Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

From At-line to Online NMR: Coupling Probe-based Autosampler with Benchtop-NMR

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1 General Experimental Details

Unless otherwise noted, all reactions were performed under an N_2 atmosphere.

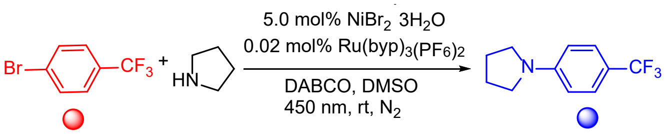
Materials: Reagents were purchased in reagent grade from commercial suppliers and used without further purification unless otherwise described.

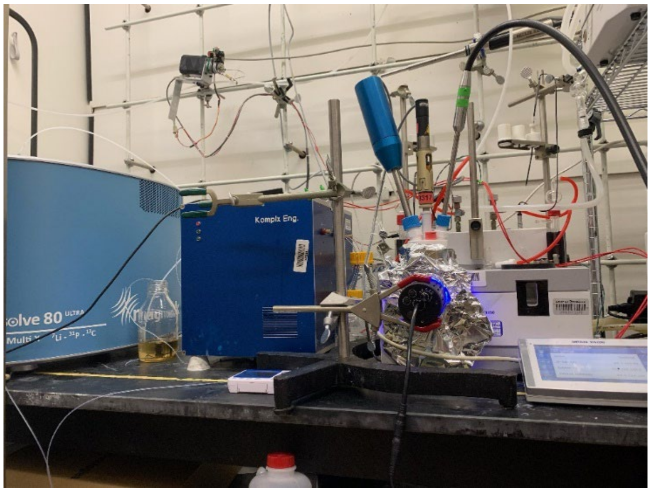
Instrumentation: All online NMR experiments were performed on a Spinsolve 80 Multi-X ULTRA (Magriteck, Inc.) benchtop NMR spectrometer using Spinsolve Reaction Monitoring (RMX) software interface for data acquisition and processing. The spectrometer operates at a ^{1}H frequency of 80.64 MHz and a sample temperature of approximately 26.5° C. The flow setup for online measurements includes a glass flow cell mounted vertically inside the bore of the magnet and connected to the reactor using 1/8" PTFE tubing.

^{1}H, ^{13}C, and ^{19}F NMR spectra were acquired on Bruker Avance III HD instrument and calibrated using solvent as an internal reference. The following abbreviations (or combinations thereof) are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad.

The autosampler used in this study was developed by Komplx Engineering LLC. Inline FTIR measurements were performed with a Mettler Toledo React IR 45m with a 6.5 mm AgX DiComp fiber conduit probe.

2 Case Study 1

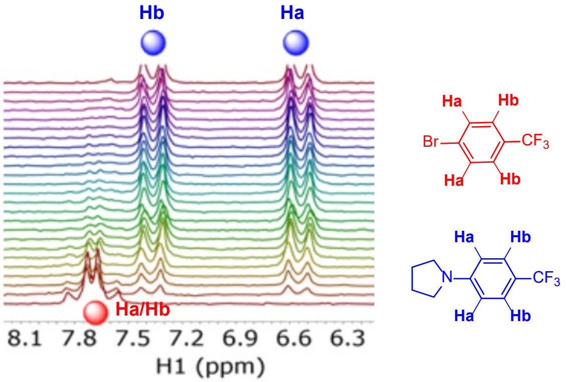




To a 100 mL volumetric flask charged 1,4-diazabicyclo[2.2.2]octane (5.05 g, 45.0 mmol) and nickel(II) bromide trihydrate (341 mg, 1.25 mmol) inside of the glovebox. DMSO (75 mL) was then added to the flask, followed by the addition of 4-bromobenzotrifluoride (3.50 mL, 25 mmol) and pyrrolidine (3.13 mL, 37.5 mmol). DMSO was then added until the desired volume of solution (100 mL) was achieved. Once everything is dissolved, 4.3 mg of the Ru catalyst was added. Then the reaction is transferred into the Easymax for reaction monitoring by IR and NMR.

2.1 *NMR Spectroscopy*

The ^{1}H spectra were collected with a 90° pulse angle, 6.55 s acquisition time, 16 scans, and 10 s repetition time. The 1D WET Solvent Suppression pulse sequence with ^{13}C decoupling and auto frequency selection was used to suppress the solvent peaks. The acquisition time per sample was approximately 3 min. Shimming on the sample was performed in between each experiment. Post-acquisition data processing was carried out using the MestReNova v14.2.0-26256 software (Mestrelab Research, Spain).



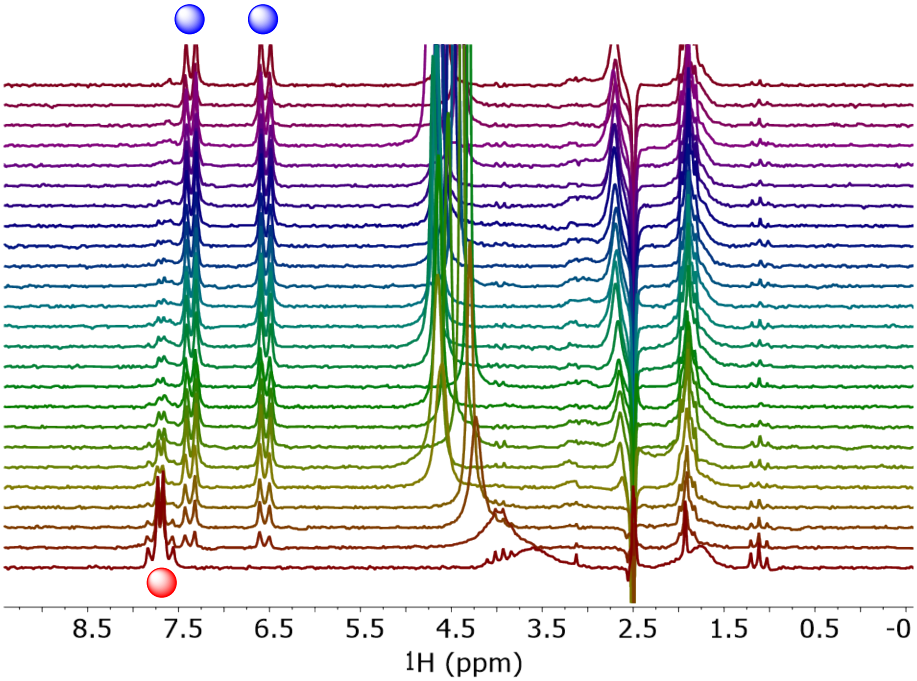
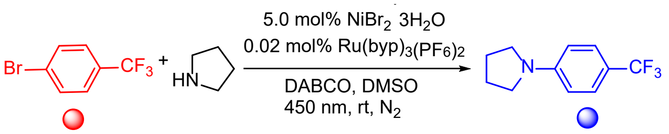


Figure S1. Stacked plot showing the ^1H NMR spectra collected during the reaction at discrete timings.

2.2 *FTIR Spectroscopy*



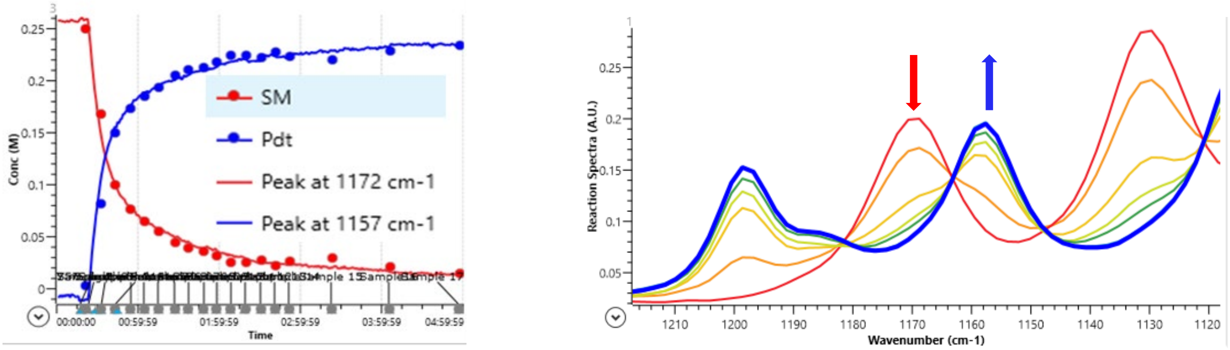


Figure S2. IR trends (left) and stacked spectra (right) showing the concomitant disappearance and disappearance of starting material and product infrared frequencies (1172 cm^{-1} and 1157 cm^{-1}, respectively) under reaction conditions.

2.3 *Linear Regression*

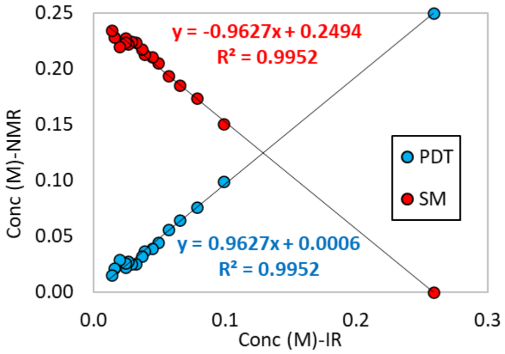
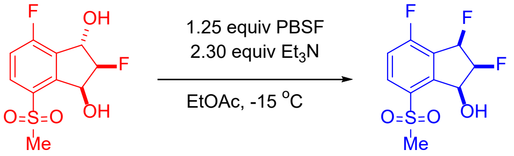
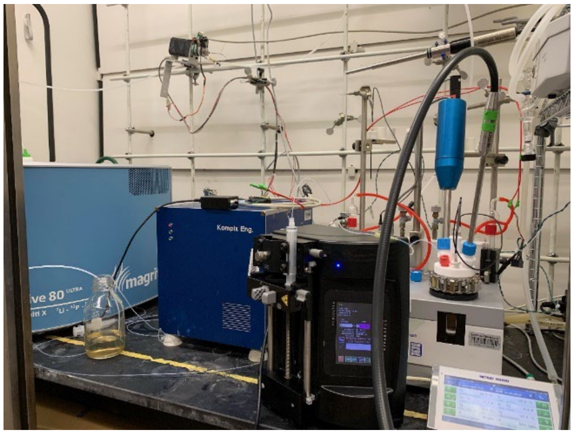


Figure S3. Linear regression used to relate FTIR and NMR concentrations for both the product and starting material.

3 Case Study 2

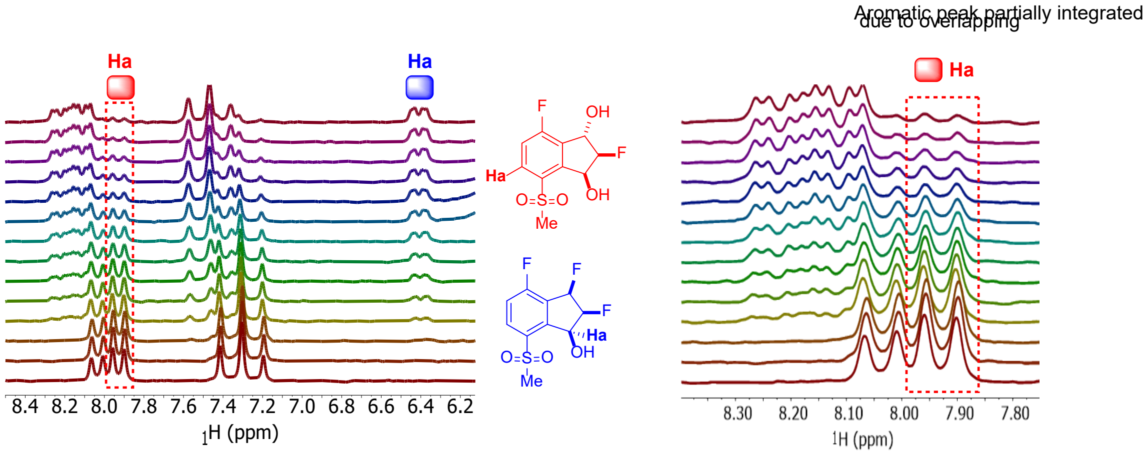




A solution of the diol starting material (9.35 g, 35.4 mmol) in ethyl acetate (81 mL) was prepared in a 100 mL reaction vessel. The solution was cooled to –15 °C followed by the addition of triethylamine (9 mL, 2.30 equiv). Perfluorobutansulfonyl fluoride (PBSF, 8 mL, 1.25 equiv) was pumped into the vessel slowly over a time span of 4 hours using a syringe pump. And the reaction was aged for 3 hours following the addition of PBSF.

3.1 *NMR Spectroscopy*

The ^{1}H spectra were collected with a 90° pulse angle, 6.55 s acquisition time, 16 scans, and 10 s repetition time. The 1D WET Solvent Suppression pulse sequence with ^{13}C decoupling and auto frequency selection was used to suppress the solvent peaks. The acquisition time per sample was approximately 3 min. Shimming on the sample was performed in between each experiment. Post-acquisition data processing was carried out using the MestReNova v14.2.0-26256 software (Mestrelab Research, Spain).



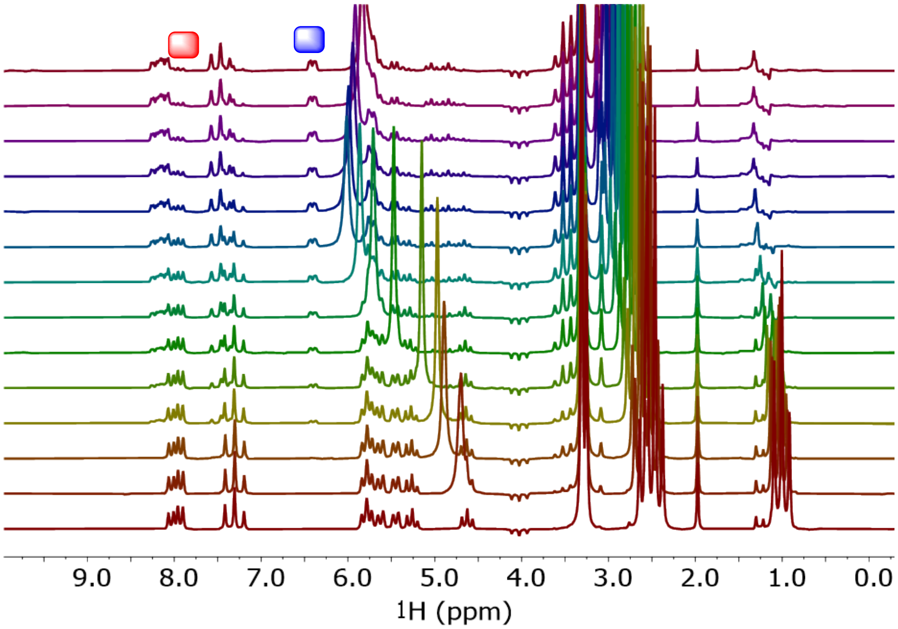


Figure S4. Stacked plot showing the ^{1}H NMR spectra collected during the reaction at discrete timings.

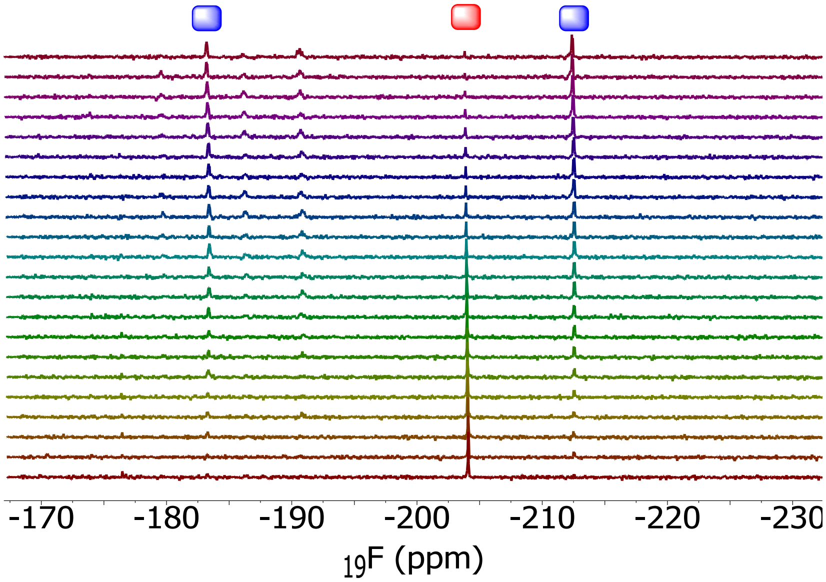


Figure S5. Stacked plot showing the ^{19}F NMR spectra collected during the reaction at discrete timings.

3.2 *FTIR Spectroscopy*

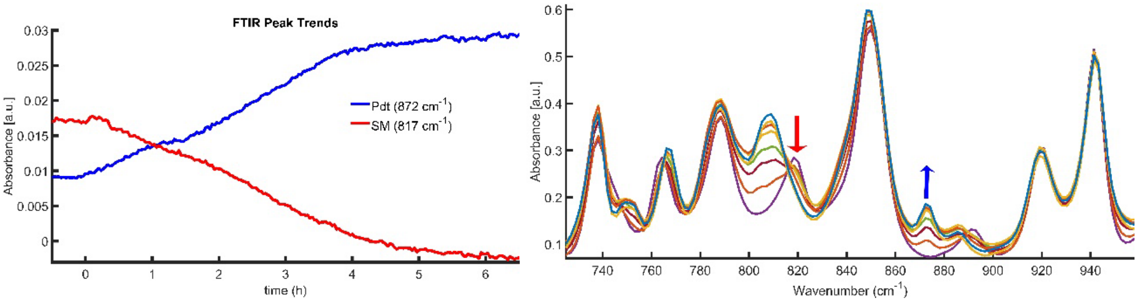


Figure S6. IR trends (left) and stacked spectra (right) showing the concomitant disappearance and appearance of starting material and product infrared frequencies (817 cm^{-1} and 872 cm^{-1}, respectively) under reaction conditions.

3.3 *Linear Regression*

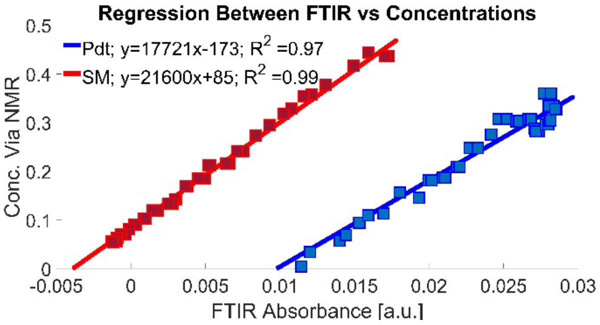
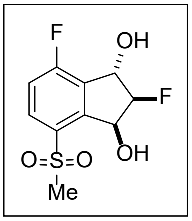
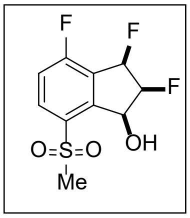


Figure S7. Regression models used to relate FTIR absorbance to NMR concentrations for both the product and starting material. The units for the y-axis is in M.

4 NMR characterization



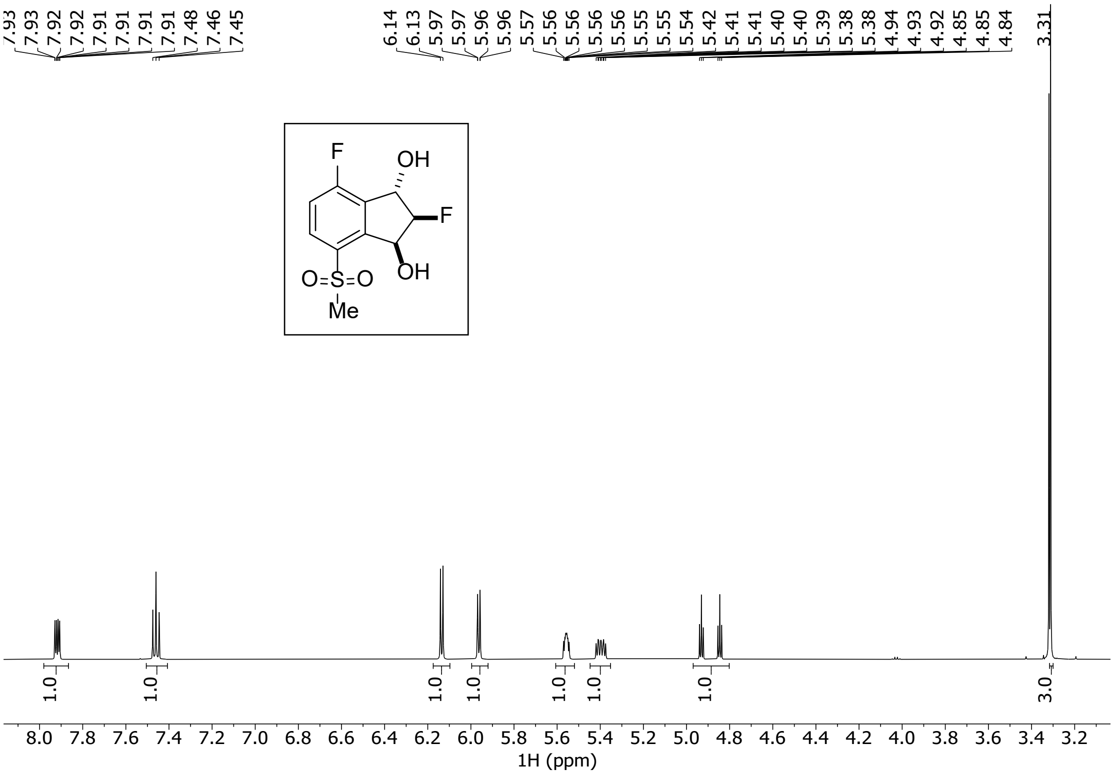
^{1}H NMR (599.90 MHz, DMSO-d_6) δ 7.92 (ddd, *J* = 8.6, 4.7 and 0.7 Hz, 1H, CH), 7.46 (t, *J* = 8.9 Hz, 1H, CH), 6.14 (d, *J* = 7.1 Hz, 1H, OH), 5.96 (d, *J* = 6.9 Hz, 1H, OH), 5.56 (dd, *J* = 6.8, 5.2 and 3.2 Hz, 1H, CH), 5.40 (ddd, *J* = 14.1, 7.0 and 5.2 Hz, 1H, CH), 4.89 (dt, *J* = 51.1 and 5.2 Hz, 1H, CH), 3.31 (s, 3H, CH3) ppm. ^{13}C{^{1}H} NMR (150.85 MHz, DMSO-d_6) δ 162.31 (d, J_{CF} = 258.7 Hz, **C**F), 142.85 (dd, J_{CF} = 6.0 and 2.9 Hz, **C**), 133.89 (d, J_{CF} = 3.4 Hz, **C**), 132.20 (d, J_{CF} = 8.9 Hz, **C**), 130.53 (dd, J_{CF} = 16.4 and 10.1 Hz, **C**H), 117.25 (d, J_{CF} = 21.4 Hz, **C**H), 97.82 (d, J_{CF} = 194.0 Hz, **C**H), 73.17 (d, J_{CF} = 25.2 Hz, **C**H), 68.95 (d, J_{CF} = 17.9 Hz, **C**H), 44.93 (s, **C**H$_3$) ppm. ^{19}F NMR (564.47 MHz, DMSO-d_6) δ -111.51 (dd, J_{HF} = 9.9 and 4.6 Hz, 1F), -203.88 (dd, J_{HF} = 51.0 and 13.9 Hz, 1F) ppm. HRMS (ESI-TOF) *m/z*: [M-H+Formate]$^-$ Calcd for $C_{11}H_{11}F_2O_6S$ 309.0244; Found: 309.0244.



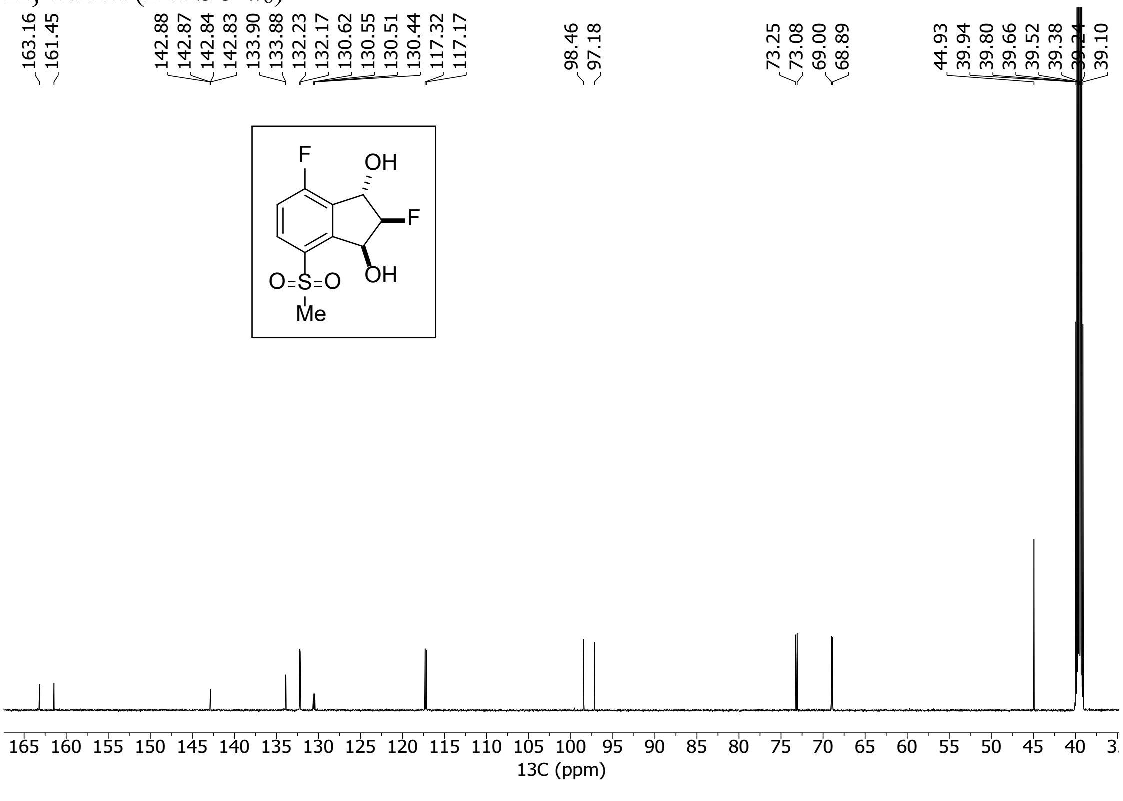
^{1}H NMR (599.90 MHz, DMSO-d_6) δ 8.11 (ddd, *J* = 8.7, 4.9 and 1.9 Hz, 1H, CH), 7.62 (td, *J* = 8.7 and 0.7 Hz, 1H, CH), 6.24 (dd, *J* = 6.2 and 0.7 Hz, 1H, OH), 6.08 (ddd, *J* = 56.0, 4.8, and 2.1 Hz, 1H, CH), 5.56 (m, 1H, CH), 5.21 (ddt, *J* = 48.1, 16.0, and 4.9 Hz, 1H, CH), 3.37 (s, 3H, CH3) ppm. ^{13}C{^{1}H} NMR (150.85 MHz, DMSO-d_6) δ 162.18 (d, J_{CF} = 259.8 Hz, **C**F), 144.85 (d, J_{CF} = 4.5 Hz, **C**), 135.01 (dd, J_{CF} = 9.3 and 2.9 Hz, **C**H), 134.54 (s, **C**), 125.71 (td, J_{CF} = 17.8 and 4.1 Hz, **C**), 117.30 (dd, J_{CF} = 20.8 and 2.3 Hz, **C**H), 88.97 (dd, J_{CF} = 198.8 and 15.5 Hz, **C**H), 86.00 (dd, J_{CF} = 188.0 and 16.6 Hz, **C**H), 69.34 (d, J_{CF} = 18.4 Hz, **C**H), 44.87 (s, **C**H$_3$) ppm. ^{19}F NMR (564.47 MHz, DMSO-d_6) δ -109.25 (br, 1F), -184.40 (ddd, J_{HF} = 55.9, 16.4 and 6.8 Hz, 1F), -212.69 (dd, J_{HF} = 47.9 and 7.3 Hz, 1F) ppm. HRMS (ESI-TOF) *m/z*: [M-H]$^-$ Calcd for $C_{10}H_8F_3O_3S$ 265.0146; Found: 265.014.

5 NMR spectra

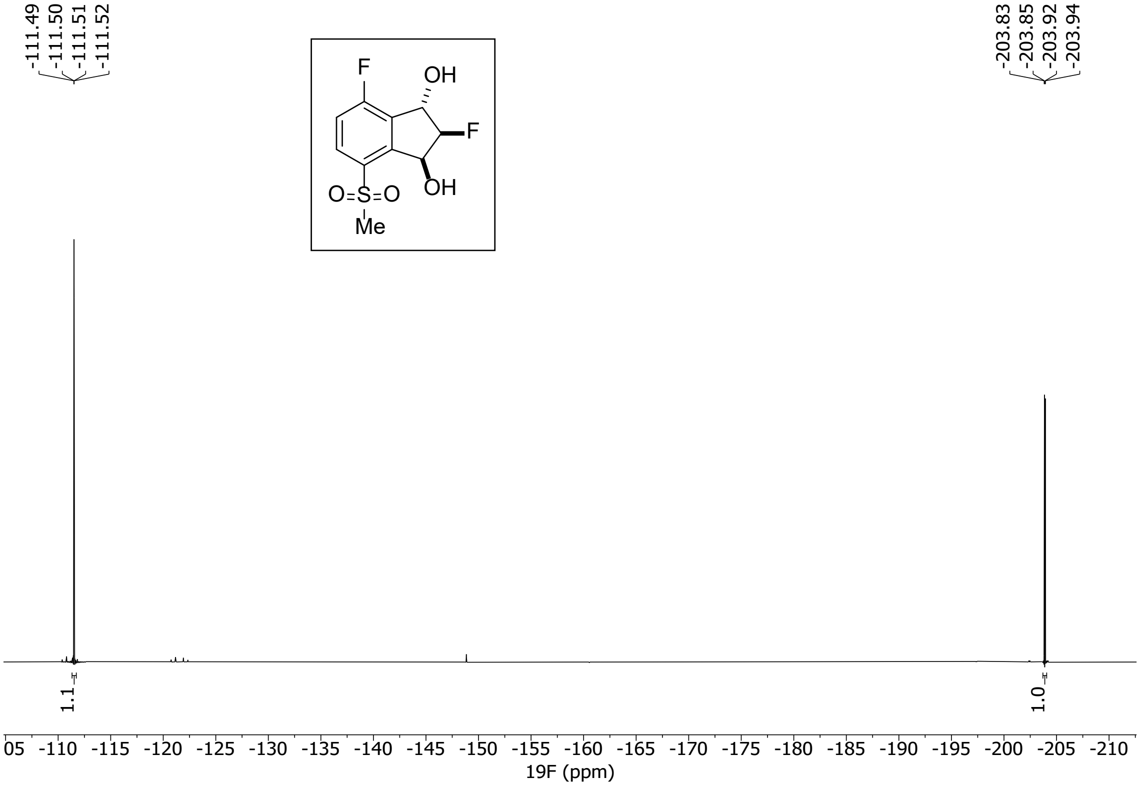
^{1}H NMR (DMSO-d_6)



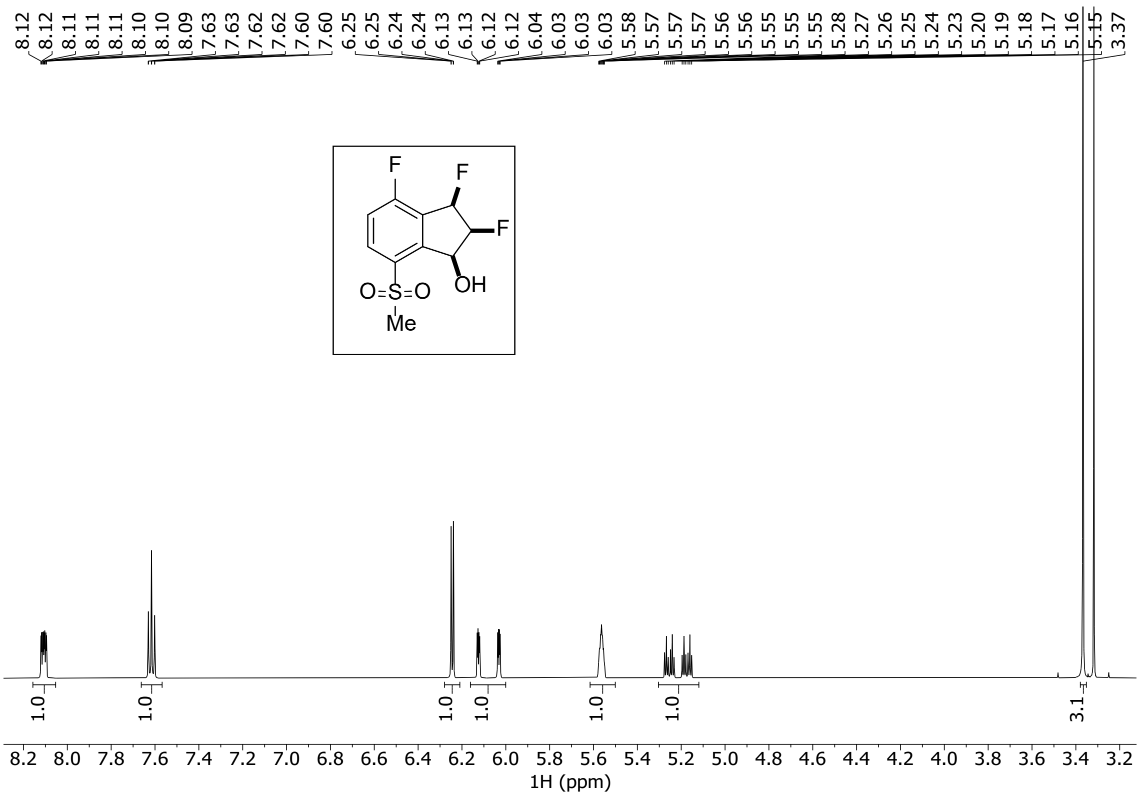
^{13}C{^{1}H} NMR (DMSO-d_6)



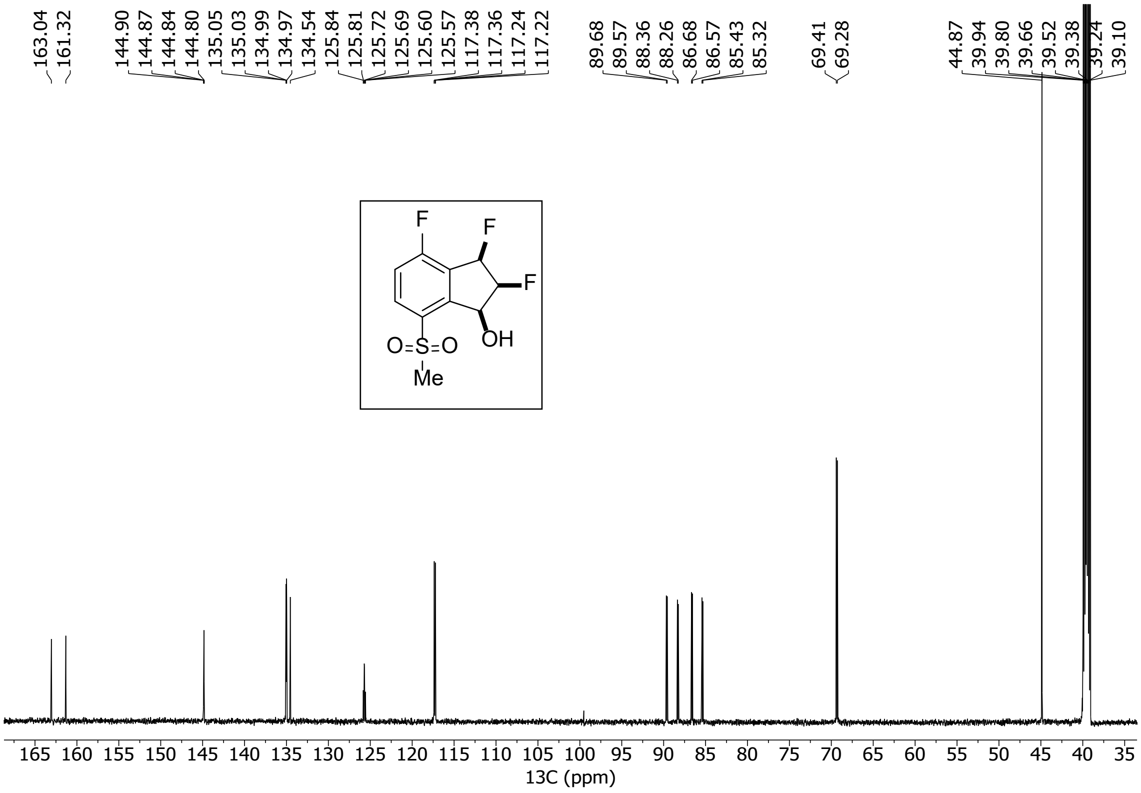
^{19}F NMR (DMSO-d_6)



^{1}H NMR (DMSO-d_6)



^{13}C{^{1}H} NMR (DMSO-d_6)



^{19}F NMR (DMSO-d_6)