Electronic Supplementary Material (ESI) for New Journal of Chemistry

DIAD-mediated metal-free cross dehydrogenative coupling between tertiary amines and α-fluorinated sulfones

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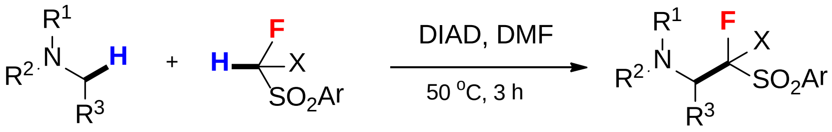
Table of Contents

1. General Information.

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. The solvent DMF were distilled from CaH_2 before being used. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz or 300 MHz NMR spectrometer. ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of the residual protonated solvent: $CDCl_3$ δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0. Data for ^{1}H, ^{13}C and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, br = broad). Melting points were uncorrected. Mass spactra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI mode.

2. Typical procedure for the coupling reaction between tertiary amines and α-fluorinated sulfones (Table 2 and Scheme 5):



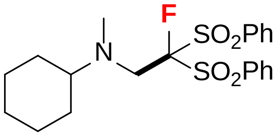
1

2a X = SO_2Ph, Ar = Ph
2b X = CO_2Et, Ar = Ph
2c X = CO_2Et, Ar = 2-Py

3

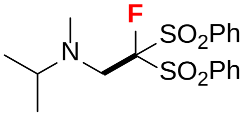
To a 25-mL Schlenk tube with *N*,*N*-dimethylcyclohexylamine **1a** (150 μL, 1.0 mmol), was dropwise added DIAD (230 μL, 1.1 mmol) in 1–2 minutes at 0 °C. The mixture was stirred in neat for 1 hour at room temperature. Then DMF (3 mL) and fluorobisphenylsulfonylmethane **2a** (157 mg, 0.5 mmol) were successively added. The resulting mixture was stirred at 50 ^{o}C for 3 hours. After cooling to room temperature, saturated brine (20 mL) was added and the mixture was extracted with ethyl acetate (15 mL × 3). The combined organic phase was dried with anhydrous $MgSO_4$ and evaporated to almost dryness under reduced pressure. Purification by flash column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1) as eluent gave product **3aa** (207 mg, 94% yield). In the case of Me_3N (**1c**), a solution of Me_3N (33 w.t.% in ethanol) was used.

N-(2-Fluoro-2,2-bis(phenylsulfonyl)ethyl)-N-methylcyclohexanamine (3aa)



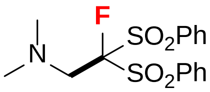
White solid. M.p.: 140–142 °C. IR (KBr): 2935, 2858, 1583, 1447, 1340, 1150, 1080 cm^{-1}. ^{1}H NMR: δ 7.96 (d, J = 7.8 Hz, 4H), 7.69 (t, J = 7.2 Hz, 2H), 7.53 (t, J = 7.8 Hz, 4H), 3.62 (d, J = 24.0 Hz, 2H), 2.19–2.28 (m, 1H), 1.93 (s, 3H), 1.44–1.72 (m, 4H), 0.95–1.14 (m, 6H). ^{19}F NMR: δ –146.3 (t, J = 24.8 Hz, 1F). ^{13}C NMR: δ 136.7, 134.8, 130.9 (d, J = 1.7 Hz), 128.5, 116.8 (d, J = 271.0 Hz), 64.3, 53.6 (d, J = 16.1 Hz), 37.0 (d, J = 2.9 Hz), 27.6, 26.0, 25.9. MS (ESI, m/z): 440.4 ($[M+H]^+$). Anal. Calcd. for $C_{21}H_{26}FNO_4S_2$: C, 57.38; H, 5.96; N, 3.19; Found: C, 57.49; H, 6.02; N, 3.11.

N-(2-Fluoro-2,2-bis(phenylsulfonyl)ethyl)-N-methylpropan-2-amine (3ba)



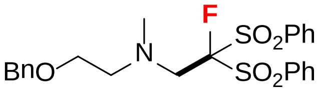
White solid. M.p.: 90–92 °C. IR (KBr): 2972, 2866, 1584, 1448, 1335, 1148, 1080 cm^{-1}. ^{1}H NMR: δ 7.96 (d, J = 7.8 Hz, 4H), 7.69 (t, J = 7.5 Hz, 2H), 7.53 (t, J = 7.8 Hz, 4H), 3.56 (d, J = 24.3 Hz, 2H), 2.70–2.79 (m, 1H), 1.89 (s, 3H), 0.78 (d, J = 6.6 Hz, 6H). ^{19}F NMR: δ –146.6 (t, J = 24.3 Hz, 1F). ^{13}C NMR: δ 136.6, 134.7, 130.8 (d, J = 1.6 Hz), 128.4, 116.7 (d, J = 271.3 Hz), 55.0, 53.3 (d, J = 11.4 Hz), 35.8, 16.9. MS (ESI, *m/z*): 400.3 ($[M+H]^+$). Anal. Calcd. for $C_{18}H_{22}FNO_4S_2$: C, 54.12; H, 5.55; N, 3.51; Found: C, 54.18; H, 5.54; N, 3.40.

2-Fluoro-N,N-dimethyl-2,2-bis(phenylsulfonyl)ethanamine (3ca)



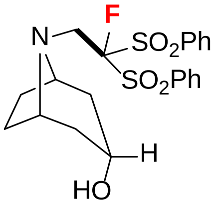
White solid. M.p.: 119–121 °C. IR (KBr): 3072, 2957, 2788, 1580, 1446, 1330, 1143, 1077, 822, 756 cm^{-1}. ^{1}H NMR: δ 7.97 (d, *J* = 7.8 Hz, 4H), 7.69 (t, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 4H), 3.45 (d, *J* = 25.2 Hz, 2H), 2.04 (s, 6H). ^{19}F NMR: δ −147.6 (t, *J* = 26.3 Hz, 1F). ^{13}C NMR: δ 136.5, 134.8, 130.9 (d, *J* = 1.1 Hz), 128.4, 116.5 (d, *J* = 270.8 Hz), 56.7 (d, *J* = 15.9 Hz), 46.1 (d, *J* = 2.2 Hz). MS (ESI, *m/z*): 372.2 ([M+H]$^+$). Anal. Calcd. for $C_{16}H_{18}FNO_4S_2$: C, 51.74; H, 4.88; N, 3.77; Found: C, 51.58; H, 4.93; N, 3.54.

N-(2-(Benzyloxy)ethyl)-2-fluoro-N-methyl-2,2-bis(phenylsulfonyl)ethanamine (3da)



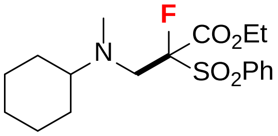
White solid. M.p.: 76–78 °C. IR (KBr): 2951, 2898, 2870, 1580, 1447, 1344, 1178, 1075, 869, 751 cm^{-1}. ^{1}H NMR: δ 7.94 (d, *J* = 8.1 Hz, 4H), 7.65 (t, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 8.1 Hz, 4H), 7.27–7.38 (m, 5H), 4.43 (s, 2H), 3.66 (d, *J* = 24.6 Hz, 2H), 3.35 (t, *J* = 5.7 Hz, 2H), 2.60 (t, *J* = 5.7 Hz, 2H), 2.03 (s, 3H). ^{19}F NMR: δ −146.1 (t, *J* = 25.4 Hz, 1F). ^{13}C NMR: δ 138.1, 136.5, 134.7, 130.9, 128.4, 128.3, 127.61, 127.57, 116.5 (d, *J* = 270.4 Hz), 73.0, 67.3, 57.4, 55.6 (d, *J* = 15.4 Hz), 42.9. MS (ESI, *m/z*): 492.3 ([M+H]$^+$). Anal. Calcd. for $C_{24}H_{26}FNO_5S_2$: C, 58.64; H, 5.33; N, 2.85; Found: C, 58.43; H, 5.43; N, 2.85.

8-(2-Fluoro-2,2-bis(phenylsulfonyl)ethyl)-8-azabicyclo[3.2.1]octan-3-ol (3ea)



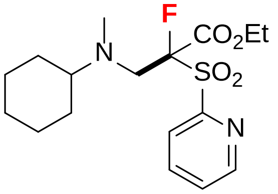
White solid. M.p.: 140–142 °C. IR (KBr): 3587, 2949, 1584, 1448, 1328, 1150, 1071, 760 cm^{-1}. ^{1}H NMR: δ 7.95 (d, *J* = 7.2 Hz, 4H), 7.69 (t, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 4H), 3.76–3.81 (m, 1H), 3.50 (d, *J* = 21.6 Hz, 2H), 2.93–2.99 (m, 2H), 1.90–1.96 (m, 2H), 1.58–1.69 (m, 4H), 1.36–1.42 (m, 2H). ^{19}F NMR: δ –148.3 (t, *J* = 20.9 Hz, 1F). ^{13}C NMR: δ 136.8, 134.7, 130.7, 128.5, 116.1 (d, *J* = 269.8 Hz), 64.1, 59.7, 50.5, 37.3, 26.2. MS (ESI, *m/z*): 454.5 ([M+H]$^+$). Anal. Calcd. for $C_{21}H_{24}FNO_5S_2$: C, 55.61; H, 5.33; N, 3.09; Found: C, 55.65; H, 5.56; N, 2.90.

Ethyl 3-(cyclohexyl(methyl)amino)-2-fluoro-2-(phenylsulfonyl)propanoate **(3ab)**



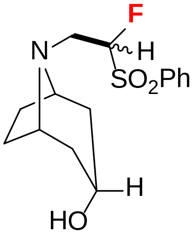
Colorless oil. IR (film): 2931, 2855, 2801, 1764, 1584, 1449, 1336, 1262, 1161, 1085, 859, 688, 604 cm^{-1}. ^{1}H NMR: δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 8.1 Hz, 2H), 4.15–4.25 (m, 2H), 3.73 (dd, *J* = 36.9 Hz, 14.7 Hz, 1H), 3.11 (t, *J* = 14.1 Hz, 1H), 2.30–2.42 (m, 1H), 2.27 (s, 3H), 1.56–1.79 (m, 4H), 1.00–1.26 (m, 9H). ^{19}F NMR: δ –158.3 (dd, *J* = 36.4 Hz, 12.7 Hz, 1F). ^{13}C NMR: δ 163.0 (d, *J* = 26.0 Hz), 134.9, 130.01, 130.00, 129.1, 108.6 (d, *J* = 235.3 Hz), 64.6, 62.8, 54.1 (d, *J* = 17.6 Hz), 38.6, 28.6, 28.3, 25.8, 25.9, 26.0, 13.9. MS (ESI, *m/z*): 372.4 ([M+H]$^+$). HRMS (ESI): calcd. for $C_{18}H_{27}FNO_4S^+$([M+H]$^+$): 372.1639; Found: 372.1649.

Ethyl 3-(cyclohexyl(methyl)amino)-2-fluoro-2-(pyridin-2-ylsulfonyl)propanoate **(3ac)**



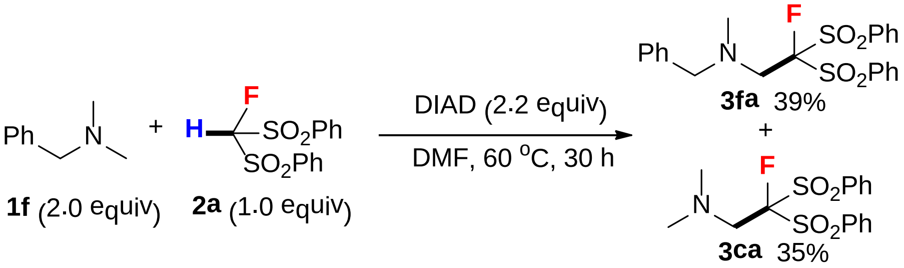
White solid. M.p.: 67–69 °C. IR (KBr): 2983, 2829, 2857, 1764, 1579, 1450, 1338, 1259, 1069, 791 cm^{-1}. ^{1}H NMR: δ 8.78 (d, *J* = 4.5 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.00 (t, *J* = 7.8 Hz, 1H), 7.62 (dd, *J* = 7.5 Hz, 4.8 Hz, 1H), 4.30–4.41 (m, 2H), 3.82 (dd, *J* = 37.8 Hz, 15.0 Hz, 1H), 3.35 (t, *J* = 14.4 Hz, 1H), 2.32–2.42 (m, 1H), 2.28 (s, 3H), 1.58–1.78 (m, 4H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.02–1.31 (m, 6H). ^{19}F NMR: δ –157.9 (dd, *J* = 39.5 Hz, 12.4 Hz, 1F). ^{13}C NMR: δ 162.6 (d, *J* = 26.5 Hz), 154.0, 150.3, 138.2, 128.3, 125.6 (d, *J* = 1.7 Hz), 108.4 (d, *J* = 234.1 Hz), 64.7, 63.0, 54.7 (d, *J* = 17.3 Hz), 38.6 (d, *J* = 3.5 Hz), 28.4 (d, *J* = 16.5 Hz), 25.8, 25.9, 26.0, 21.9, 13.9. MS (ESI, *m/z*): 373.2 ([M+H]$^+$). Anal. Calcd. for $C_{17}H_{25}FN_2O_4S$: C, 54.82; H, 6.77; N, 7.52; Found: C, 54.90; H, 6.72; N, 7.50.

8-(2-Fluoro-2-(phenylsulfonyl)ethyl)-8-azabicyclo[3.2.1]octan-3-ol (**14**)



White solid. M.p.: 115–117 °C. IR (KBr): 3311, 2952, 2890, 1584, 1448, 1332, 1162, 1048, 915, 750 cm^{-1}. ^{1}H NMR: δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 5.25 (ddd, *J* = 49.5 Hz, 8.4 Hz, 1.8 Hz, 1H), 3.98 (t, *J* = 4.8 Hz, 1H), 3.05–3.22 (m, 3H), 2.77–2.91 (m, 1H), 1.97–2.14 (m, 4H), 1.83–1.90 (m, 2H), 1.60–1.66 (m, 2H). ^{19}F NMR: δ –179.1 (m, 1F). ^{13}C NMR: δ 135.7, 134.5, 129.3, 129.2, 103.0 (d, *J* = 220.0 Hz), 64.3, 59.6, 59.5, 50.3 (d, *J* = 18.9 Hz), 38.96, 38.95, 26.2, 26.0. MS (ESI, *m/z*): 314.2 ([M+H]$^+$). Anal. Calcd. for $C_{15}H_{20}FNO_3S$: C, 57.49; H, 6.43; N, 4.47; Found: C, 57.32; H, 6.64; N, 4.67.

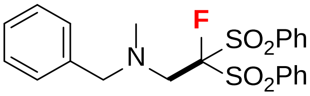
3. Coupling reaction between *N,N*-dimethylbenzyl amine (1f) and fluorobisphenylsulfonylmethane (2a)



To a Schlenk tube with *N*,*N*-dimethylcyclohexylamine **1a** (406 mg, 3.0 mmol), was dropwise added DIAD (667 mg, 3.3 mmol) in 5 minutes at 0 °C. The mixture was stirred in neat for 1 hour at room temperature. Then DMF (6 mL) and fluorobisphenylsulfonylmethane **2a** (471 mg, 1.5 mmol) were successively added. The resulting mixture was stirred at 60 ^{o}C for 30 hours. After cooling to room temperature, the yields of the fluoroalkylated products (39% + 35%) were determined by ^{19}F NMR with the remaining $(PhSO_2)_2CHF$ as the internal standard. The mixture was extracted with ethyl acetate (30 mL × 3) from brine (30 mL). The combined organic phase was dried with anhydrous $MgSO_4$ and evaporated to almost dryness under reduced pressure. After flash column chromatography (PE/EA 6:1) and recrystalization (PE/EA), the analytically pure samples **3fa** and **3ca** were obtained for characterization.

When *N*,*N*-dimethyl-1-(naphthalen-2-yl)methanamine was used instead of **1f**, 2-naphthaldehyde was isolated in 79% yield (based on **2a**) after aqueous workup (flash column chromatography, PE/EA 10:1).

N-Benzyl-2-fluoro-N-methyl-2,2-bis(phenylsulfonyl)ethanamine (**3fa**)

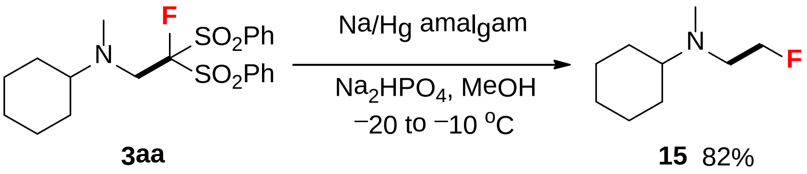


White solid. M.p.: 151–153 ^{o}C. IR (KBr): 2923, 2853, 1580, 1446, 1331, 1144, 1077, 867, 757 cm^{-1}. ^{1}H NMR: δ 7.97 (d, *J* = 7.2 Hz, 4H), 7.70 (t, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 8.1 Hz, 4H), 7.21–7.24 (m, 3H), 6.97–7.01 (m, 2H), 3.64 (d, *J* = 21.9 Hz, 2H), 3.50 (s, 2H), 2.00 (s, 3H). ^{19}F NMR: δ –147.7 (t, *J* = 21.2 Hz, 1F). MS (ESI, *m/z*): 448.3 ($[M+H]^+$). HRMS (ESI): calcd. for $C_{22}H_{22}FNO_4S_2Na^+$($[M+Na]^+$): 470.0867; Found: 470.0875.

2-Naphthaldehyde

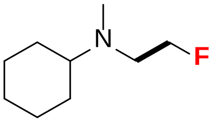
^{1}H NMR: δ 7.54–7.70 (m, 2H), 7.88–7.97 (m, 3H), 8.02 (d, *J* = 7.9 Hz, 1H), 8.35 (s, 1H), 10.17 (s, 1H). The spectrum was identical to that of an authentic sample.

4. Reductive desulfonylation



Under N_2 atmosphere, into a 25-mL Schlenk flask containing Na_2HPO_4 (575 mg, 4 mmol) and anhydrous MeOH (6 mL) was added **3aa** (220 mg, 0.5 mmol) at –20 °C. The reaction mixture was stirred at –20 °C to –10 °C for 1 h. The liquid phase was decanted, and most of the organic phase was removed under vacuum. Then brine (10 mL) was added, followed by extracting with EtOAc (15 mL × 3). The combined organic phase was dried over anhydrous $MgSO_4$. The volatile solvents were removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (8:1) as eluent to give product **15** (65 mg, 82% yield)

N-(2-Fluoroethyl)-N-methylcyclohexanamine (**15**)

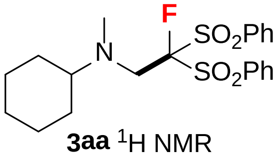


Pale yellow oil. IR (film): 2927, 2854, 2224, 1599, 1455, 1258, 1232, 1034, 757 cm^{-1}. ^1H NMR: δ 4.52 (dt, *J* = 47.4 Hz, 5.4 Hz, 2H), 2.79 (dt, *J* = 25.5 Hz, 5.4 Hz, 2H), 2.37–2.47 (m, 1H), 2.35 (s, 3H), 1.79–1.85 (m, 4H), 1.18–1.28 (m, 6H). ^{19}F NMR: δ –219.8 (tt, *J* = 47.4 Hz, 25.4 Hz, 1F). ^{13}C NMR: δ 82.7 (d, *J* = 167.0 Hz), 63.2, 53.2 (d, *J* = 20.5 Hz), 38.4, 28.5, 26.2, 25.9. MS (ESI, *m/z*): 160.1 ($[M+H]^+$). HRMS (ESI): calcd. for $C_9H_{19}FN^+$ ($[M+H]^+$): 160.1496; Found: 160.1500.

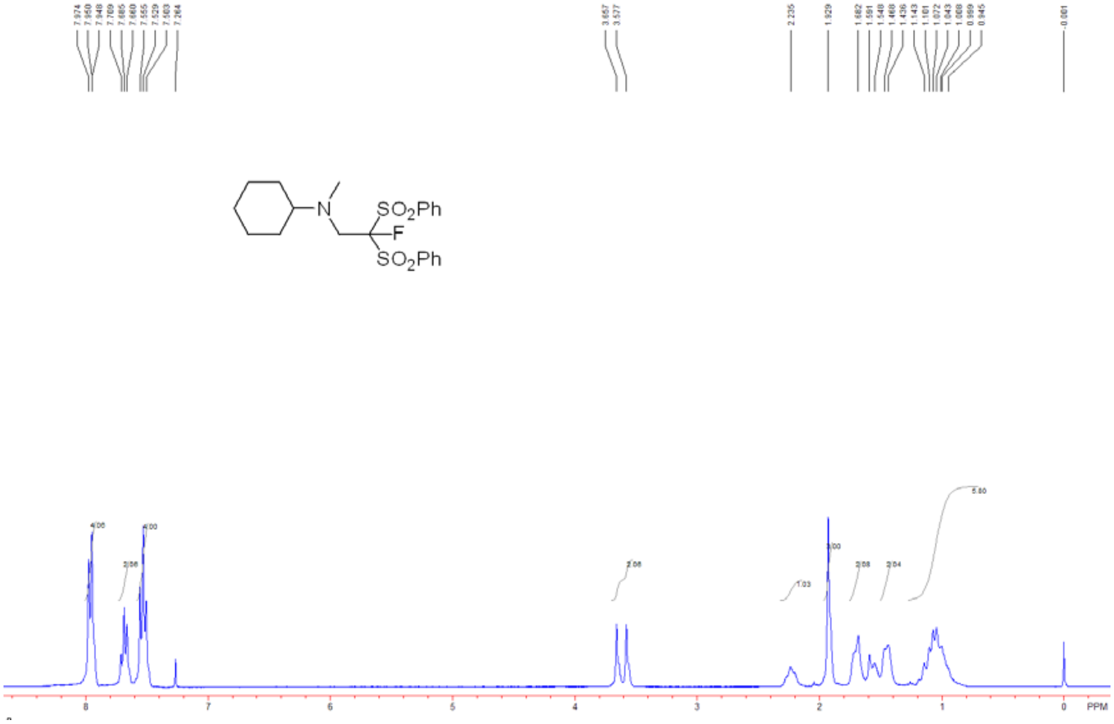
References:

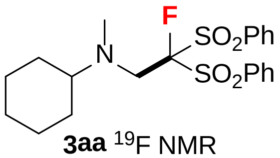
1. D. Simoni, M. Rossi, V. Bertolasi, M. Roberti, D. Pizzirani, R. Rondanin, R. Baruchello, F. P. Invidiata, M. Tolomeo, S. Grimaudo, S. Merighi, K. Varani, S. Gessi, P. A. Borea, S. Marino, S. Cavallini, C. Bianchi and A. Siniscalchi, *J. Med. Chem*. **2005**, *48*, 3337.
2. G. B. Petrović, R. N. Saičić and Z. M. Čeković, *Helv. Chim. Acta*, **2003**, *86*, 3179.

5. ^{1}H, ^{19}F and ^{13}C NMR Spectra

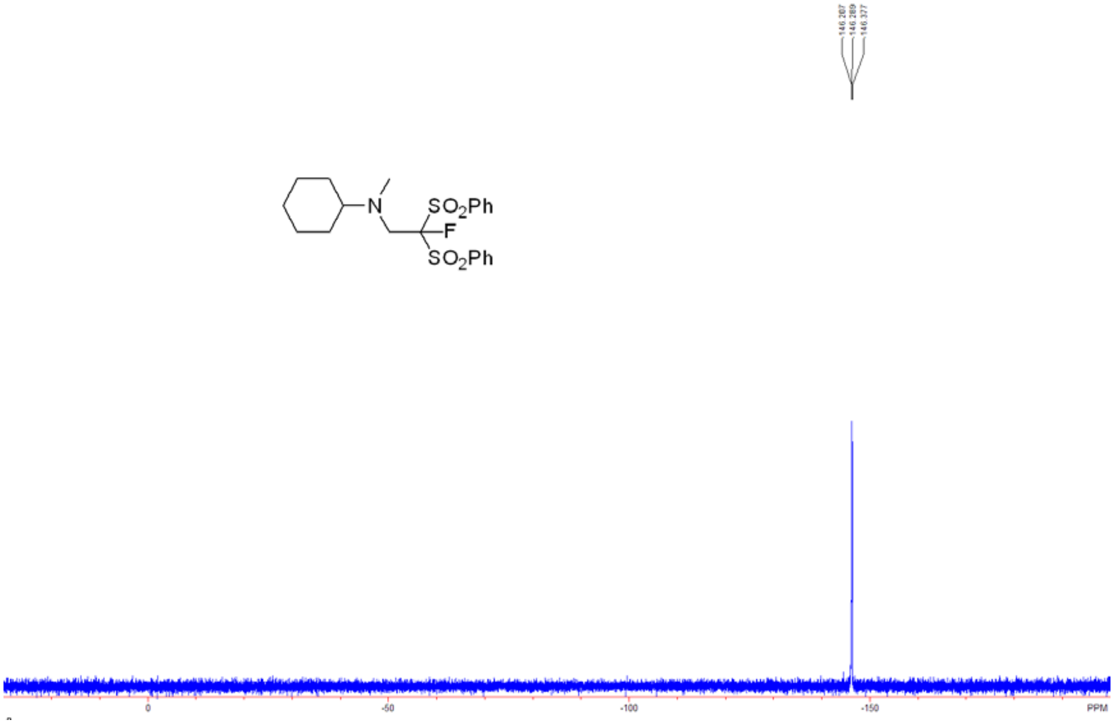


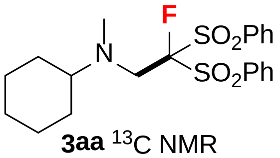
3aa ^{1}H NMR
($CDCl_3$, 300 MHz)



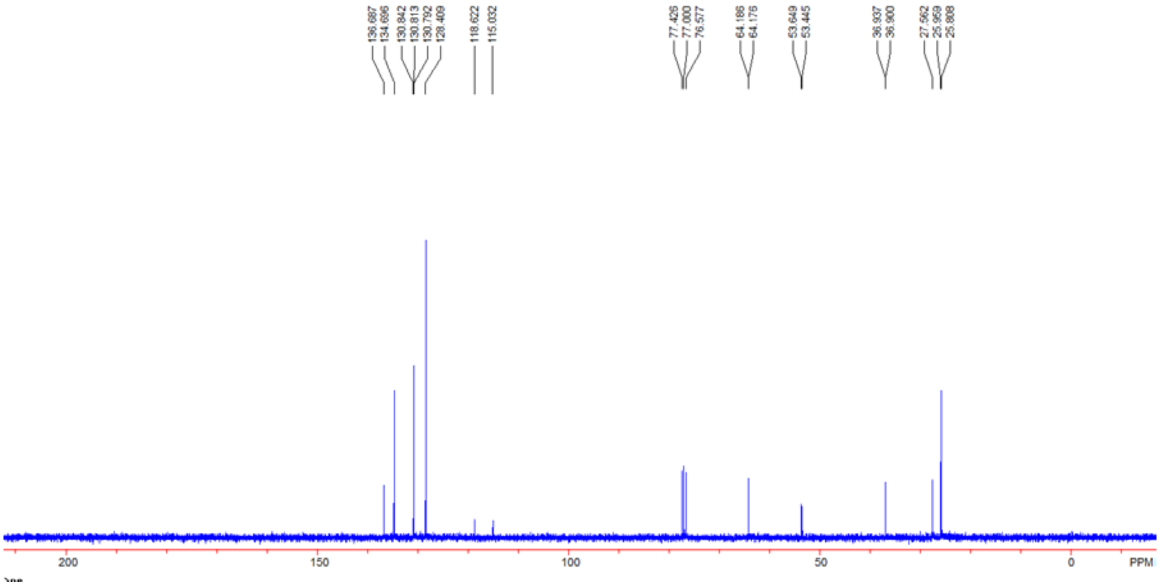


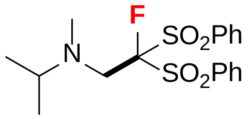
3aa ^{19}F NMR
(CDCl$_3$, 282 MHz)



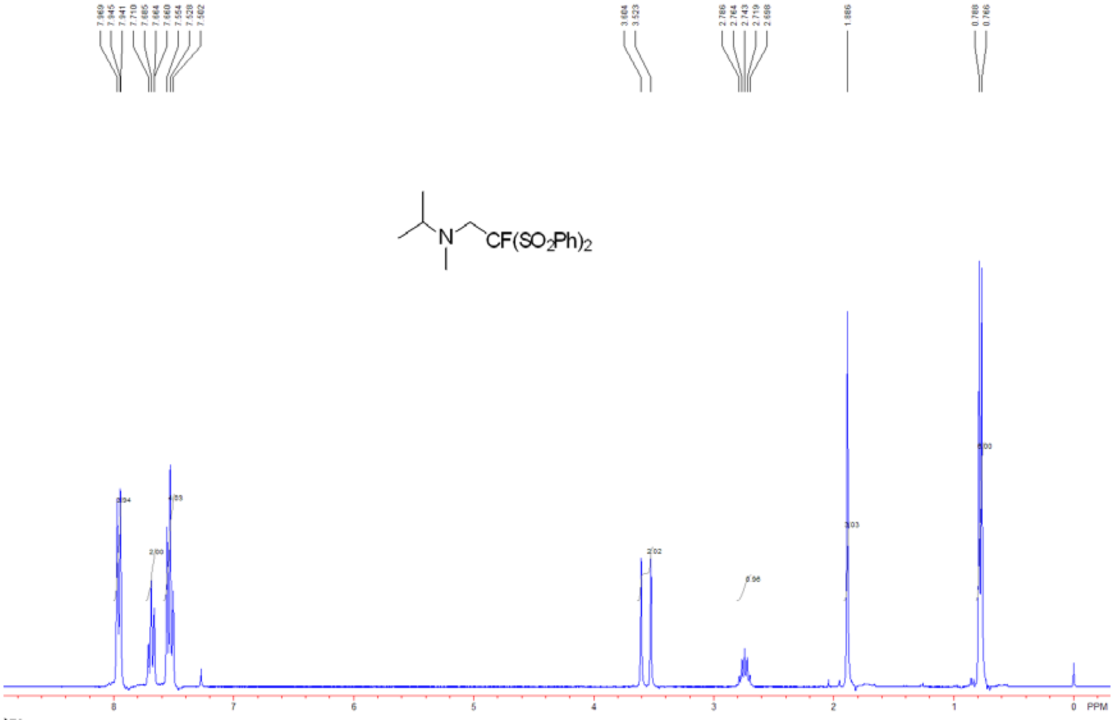


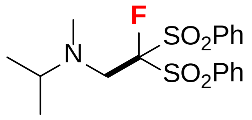
3aa ^{13}C NMR
(CDCl$_3$, 75 MHz)



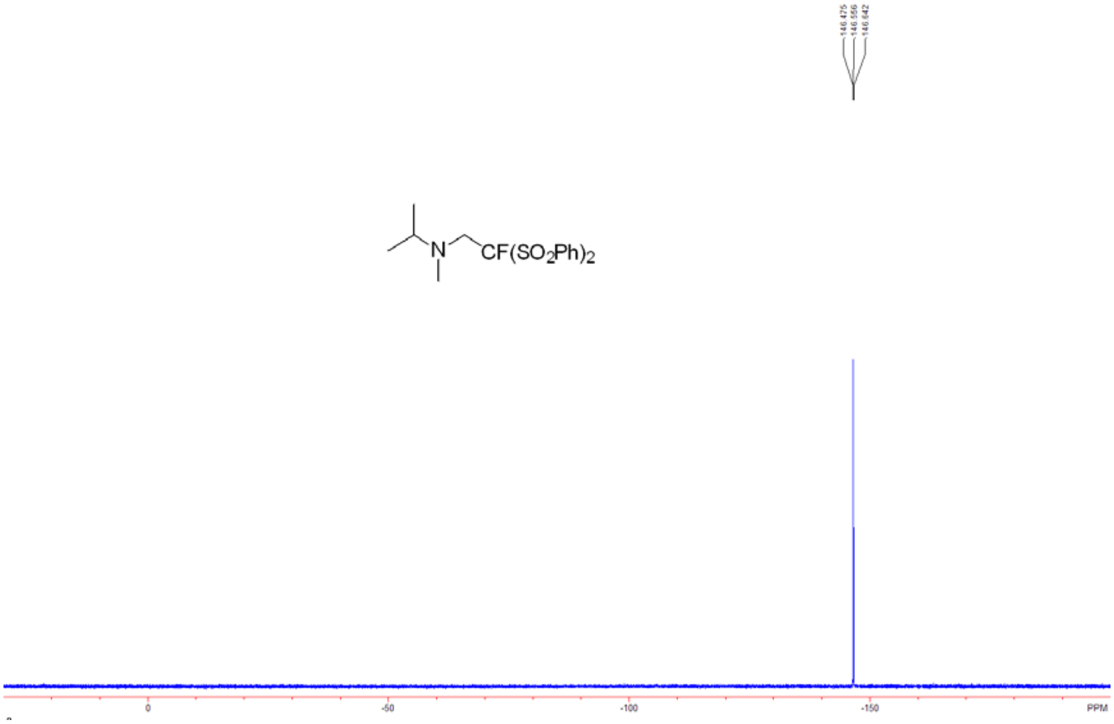


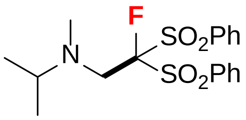
3ba ^{1}H NMR
($CDCl_3$, 300 MHz)



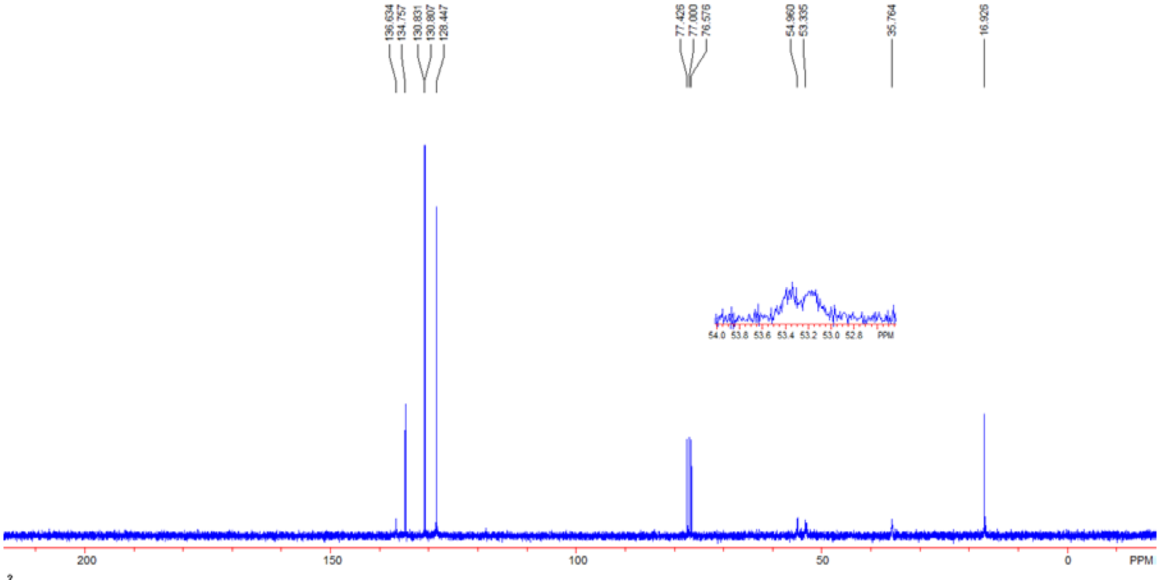


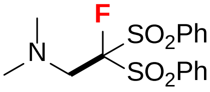
3ba ^{19}F NMR
(CDCl$_3$, 282 MHz)



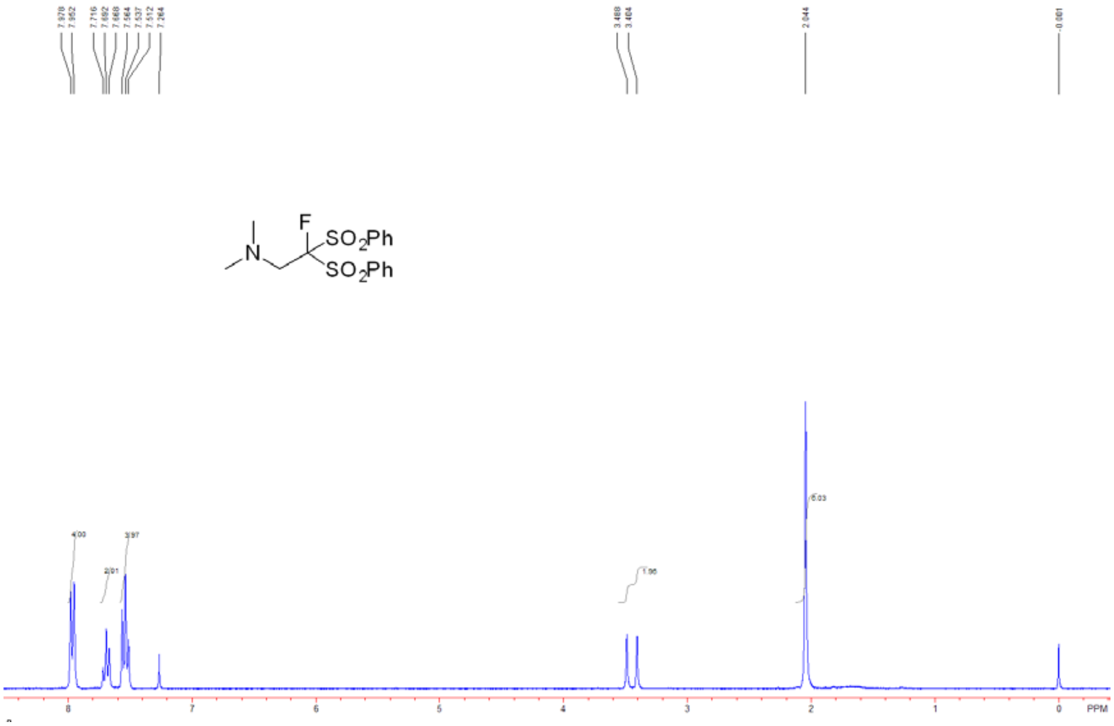


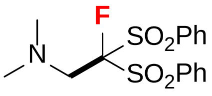
3ba ^{13}C NMR
($CDCl_3$, 75 MHz)





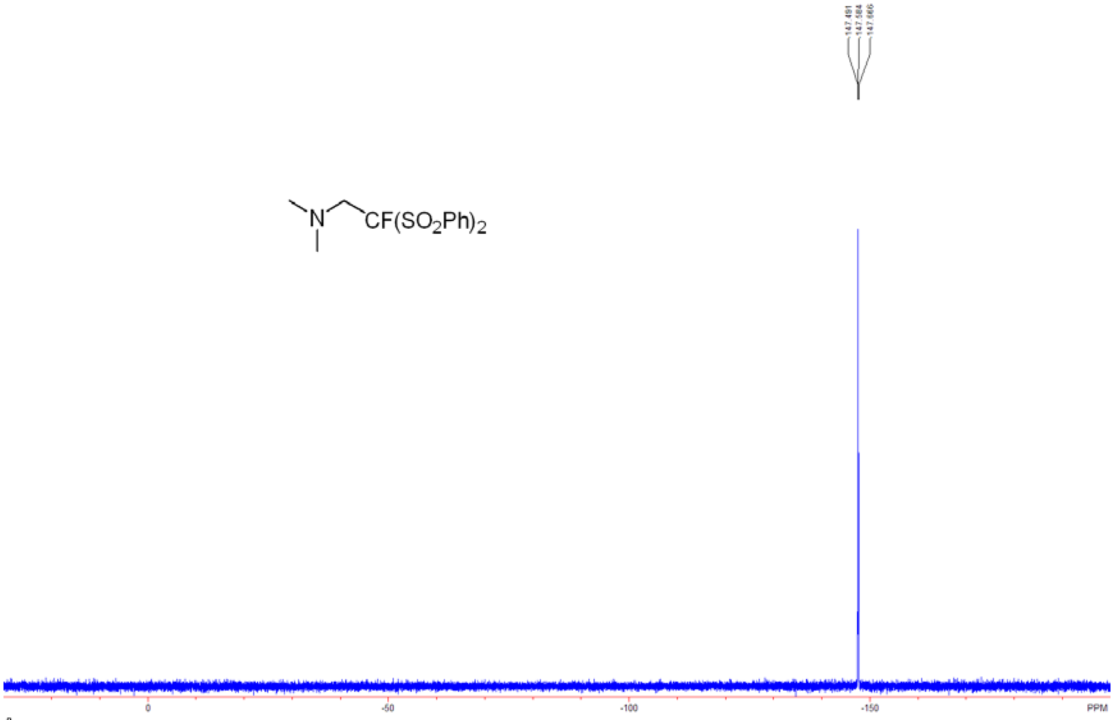
3ca ^{1}H NMR
($CDCl_3$, 300 MHz)

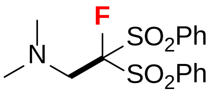




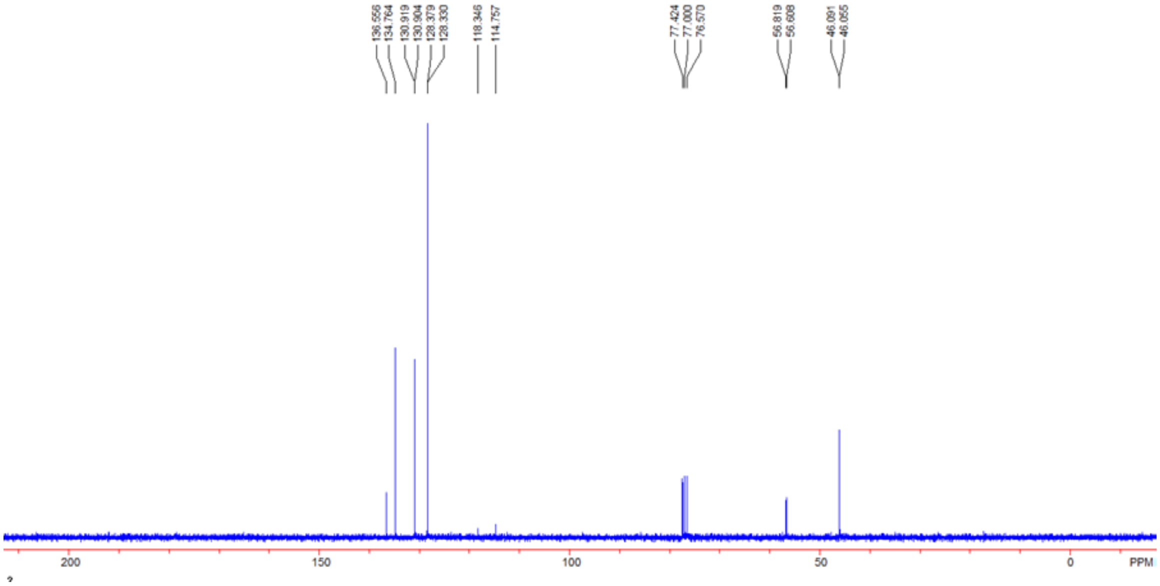
3ca ^{19}F NMR

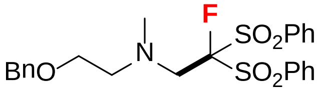
($CDCl_3$, 282 MHz)



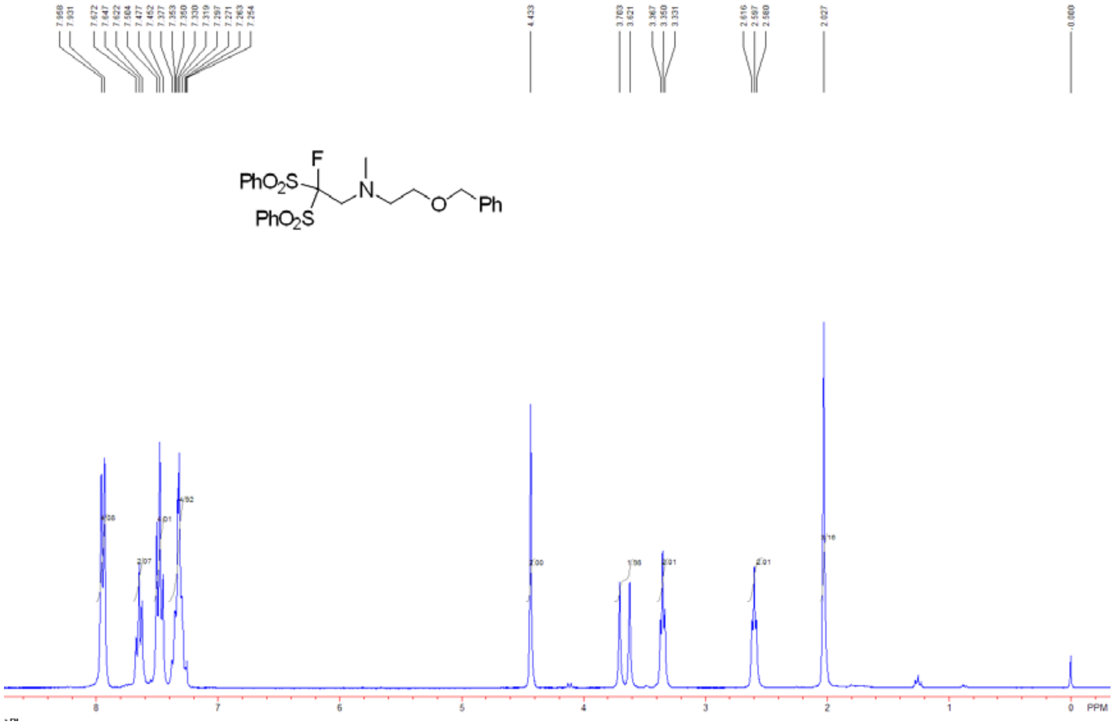


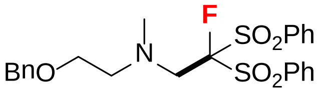
3ca ^{13}C NMR
($CDCl_3$, 75 MHz)



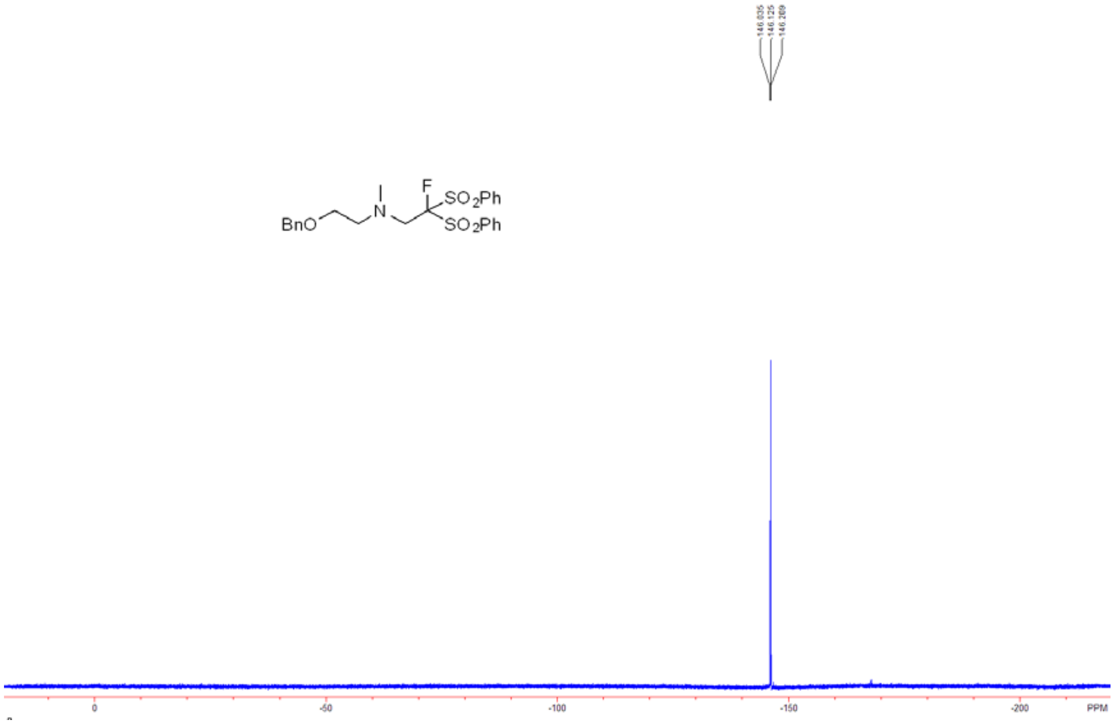


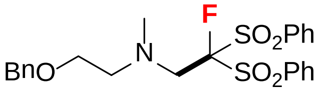
3da ^{1}H NMR
($CDCl_3$, 300 MHz)



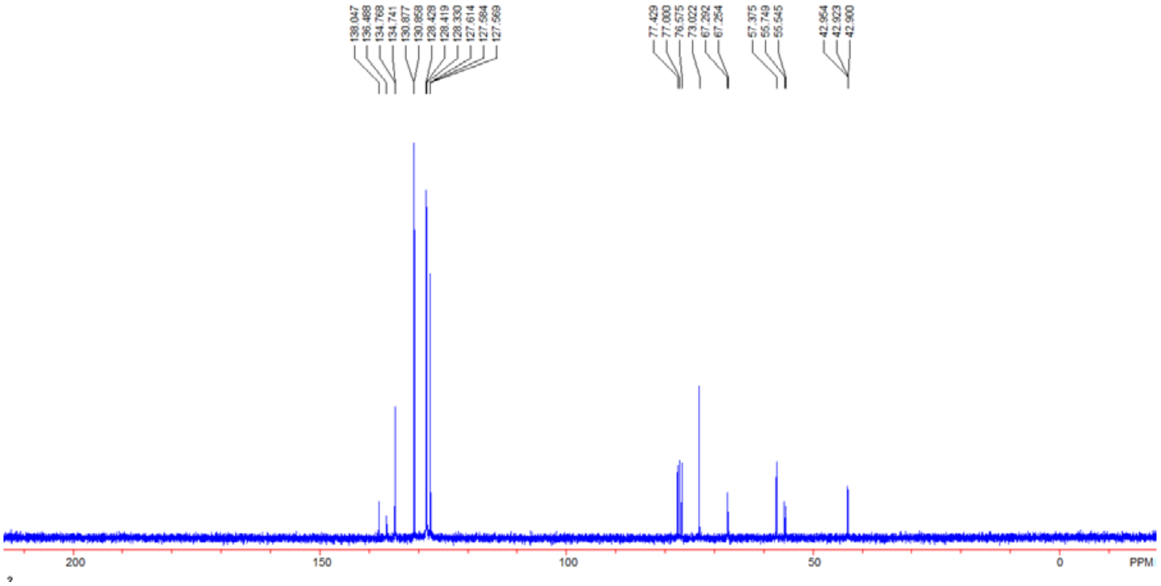


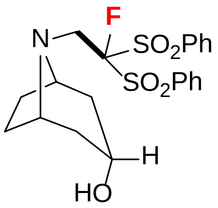
3da ^{19}F NMR
($CDCl_3$, 282 MHz)



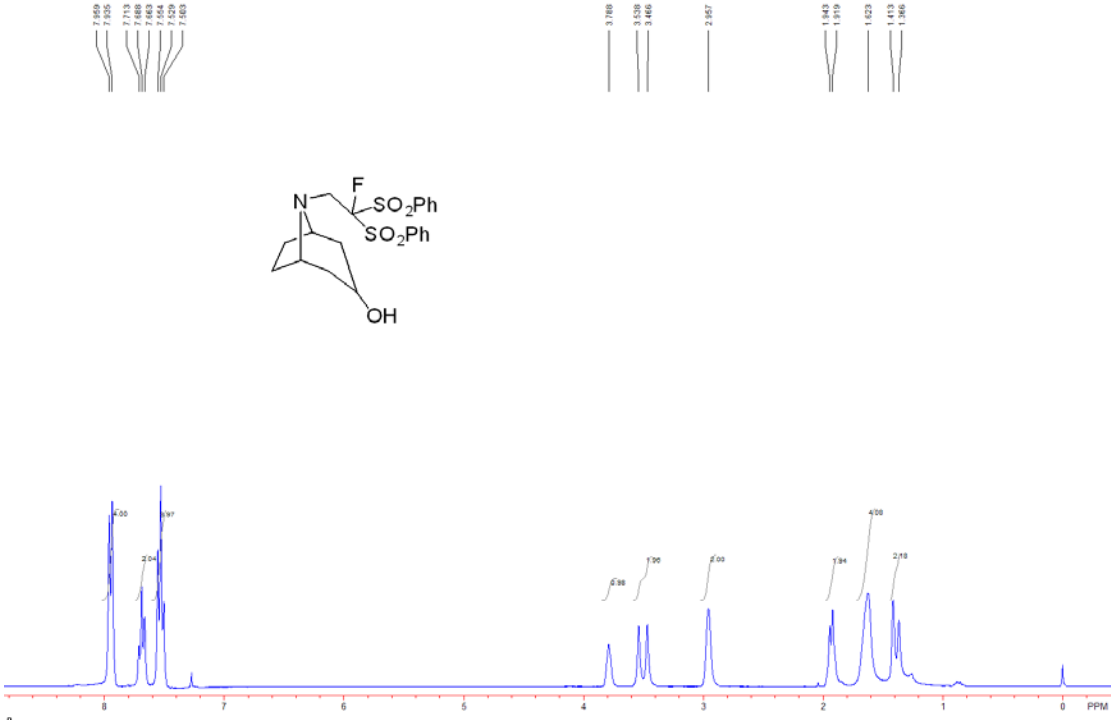


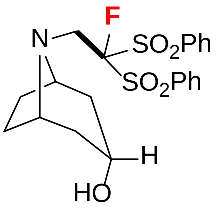
3da ^{13}C NMR
($CDCl_3$, 75 MHz)



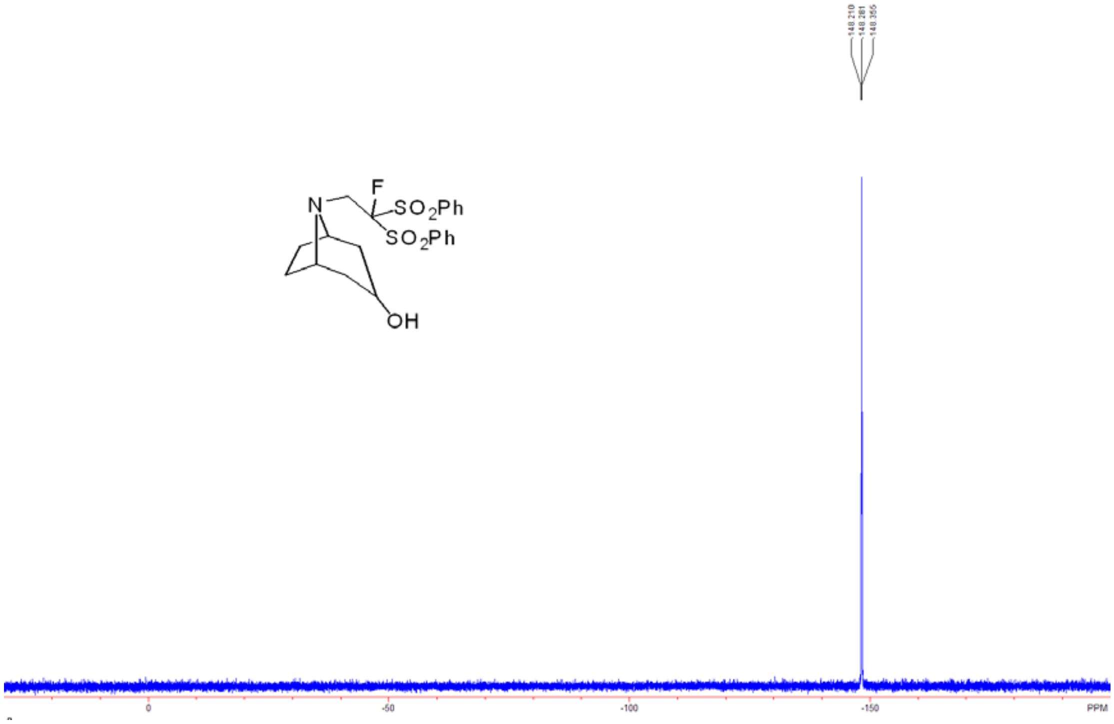


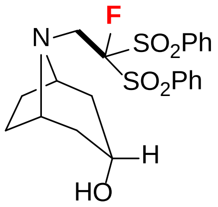
3ea ^{1}H NMR
(CDCl$_3$, 300 MHz)



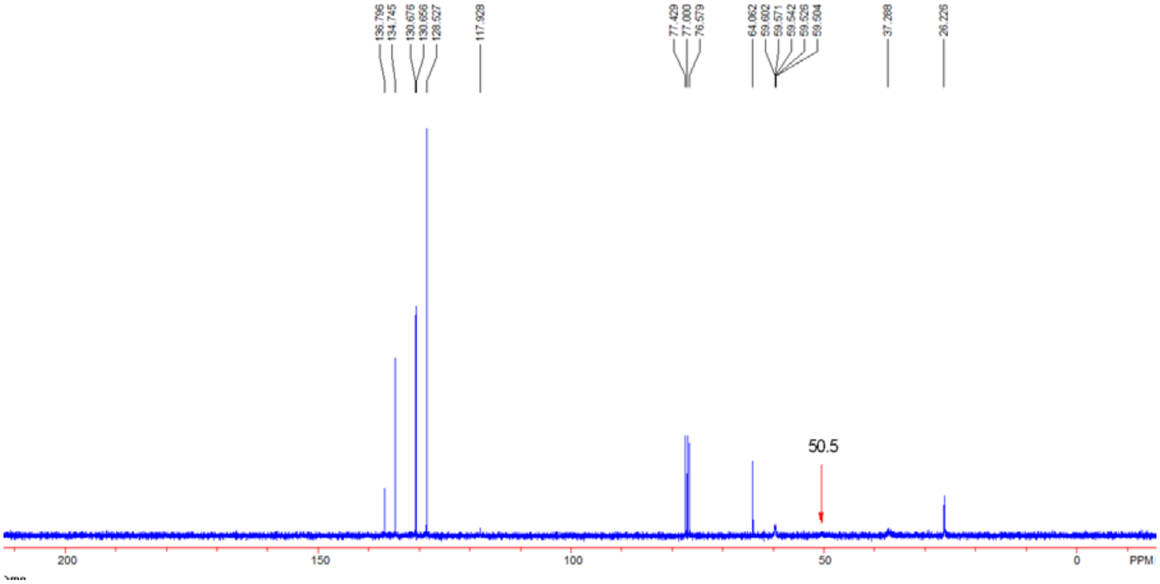


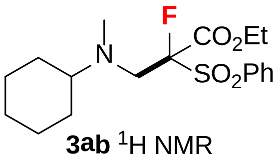
3ea ^{19}F NMR
(CDCl$_3$, 282 MHz)



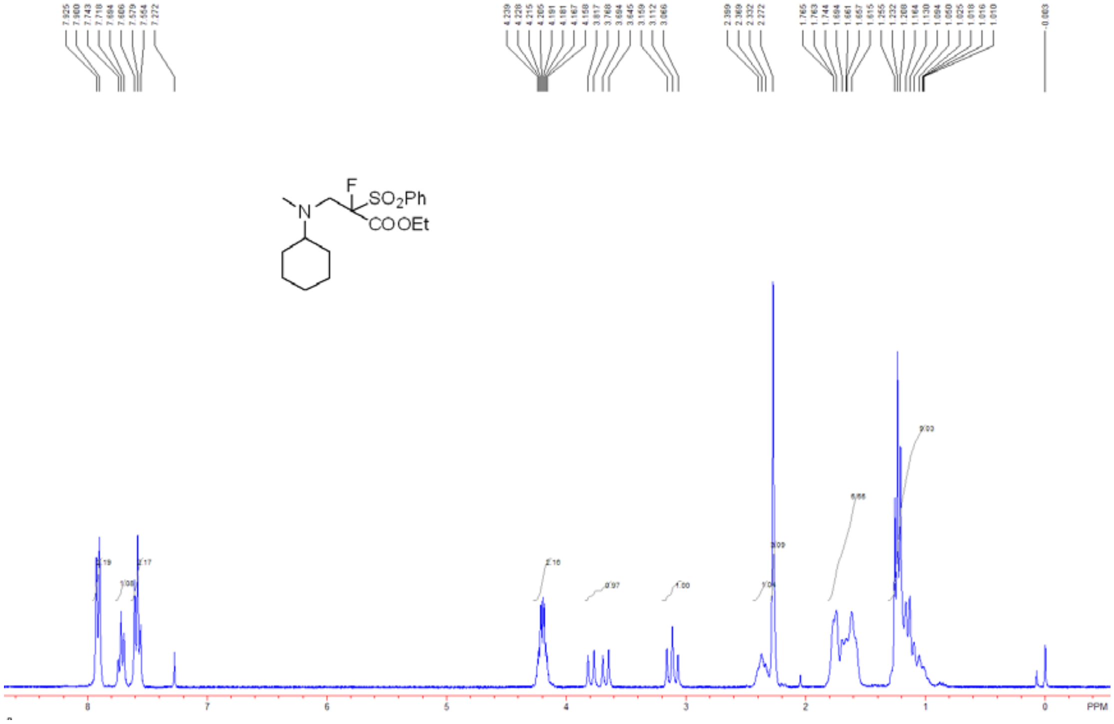


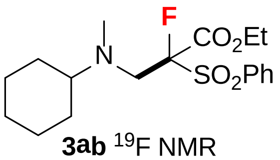
3ea ^{13}C NMR
(CDCl$_3$, 75 MHz)



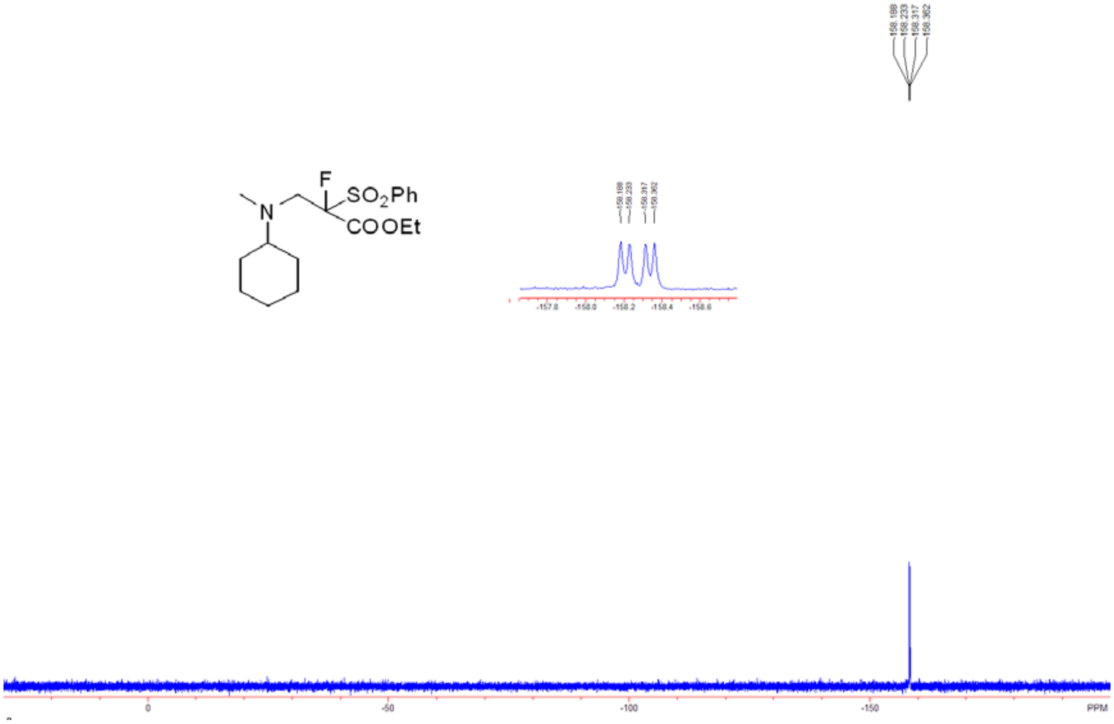


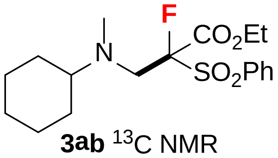
3ab ^{1}H NMR
($CDCl_3$, 300 MHz)



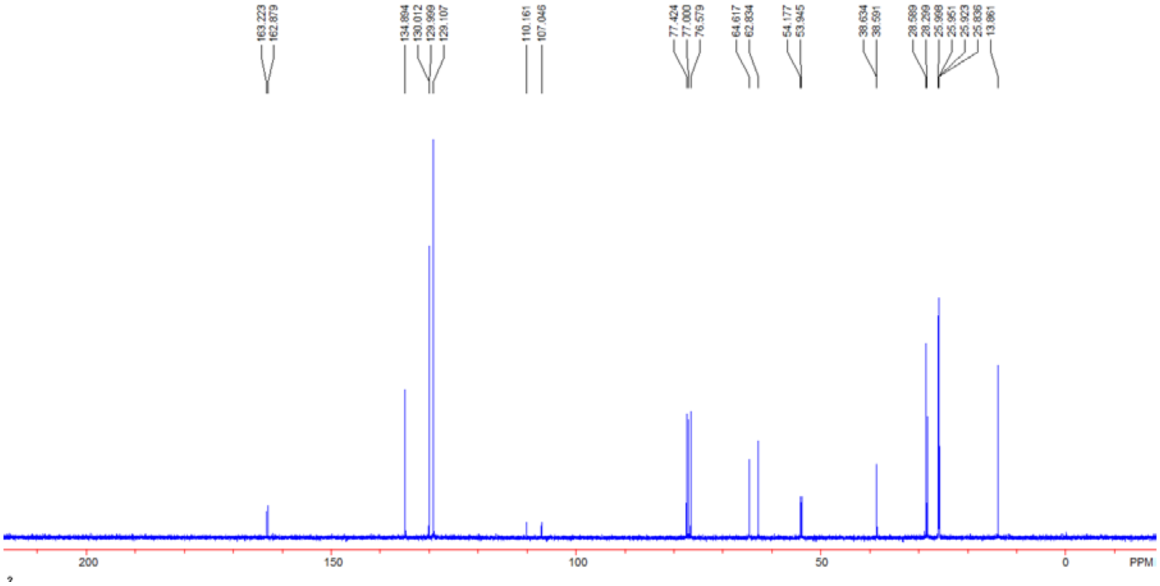


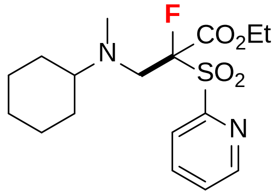
3ab ^{19}F NMR
(CDCl$_3$, 282 MHz)



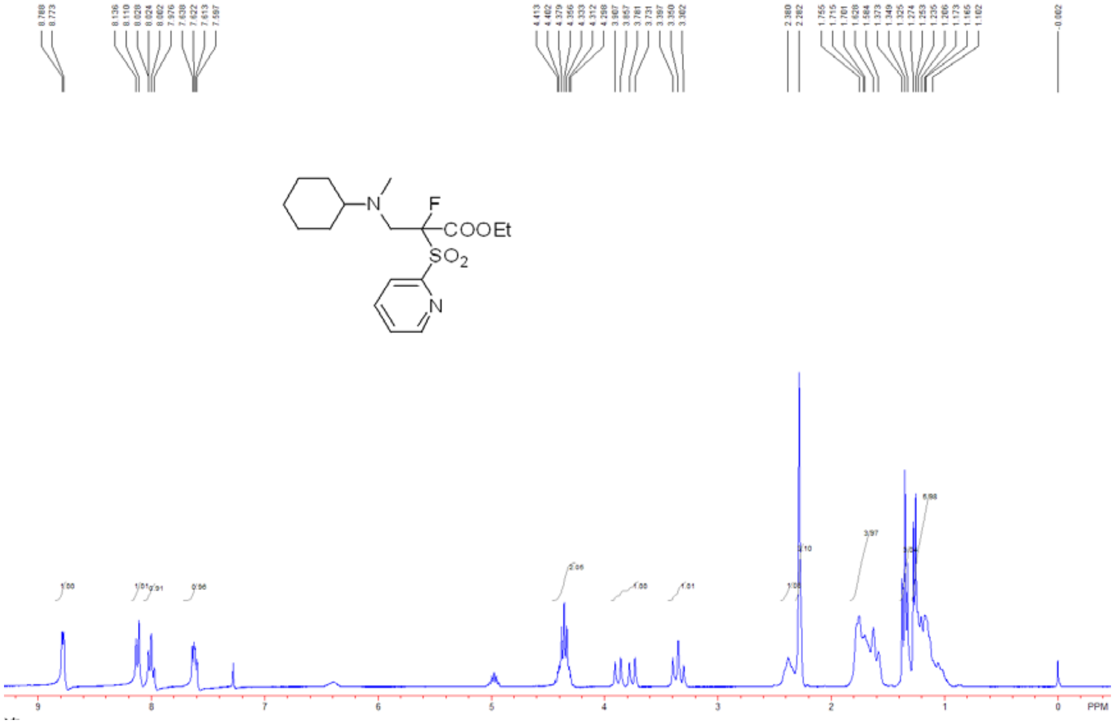


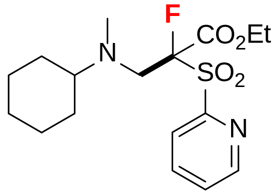
3ab ^{13}C NMR
(CDCl$_3$, 75 MHz)



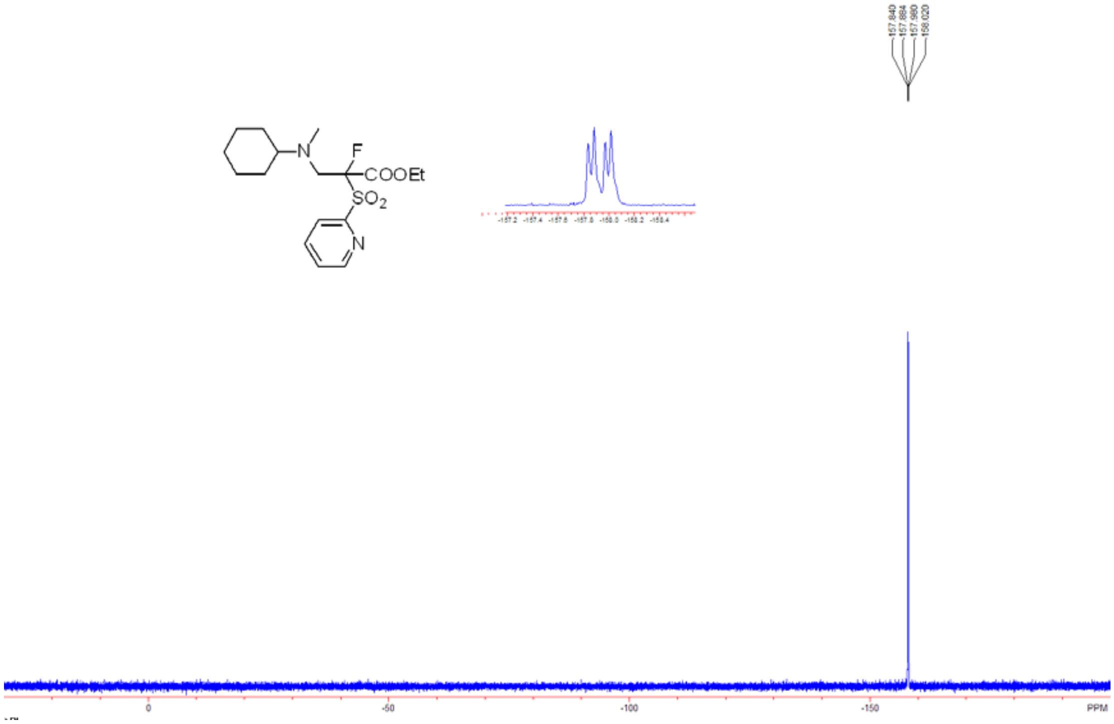


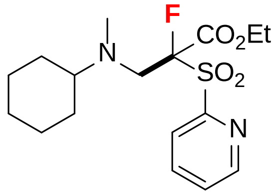
3ac ^{1}H NMR
(CDCl$_3$, 300 MHz)



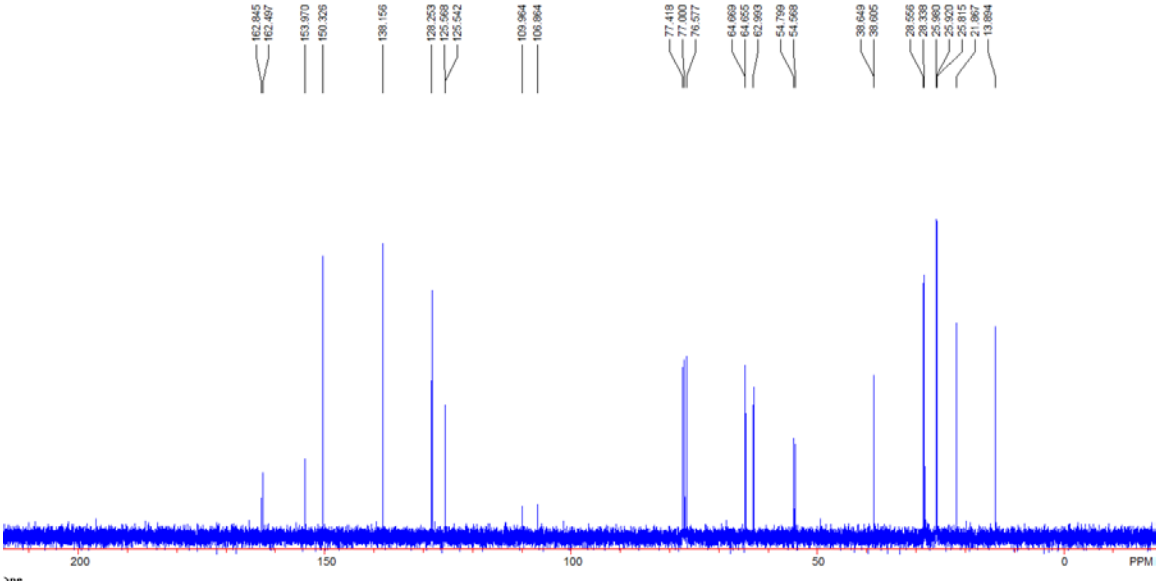


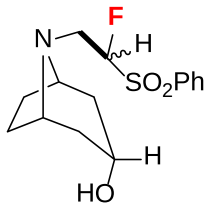
3ac ^{19}F NMR
($CDCl_3$, 282 MHz)



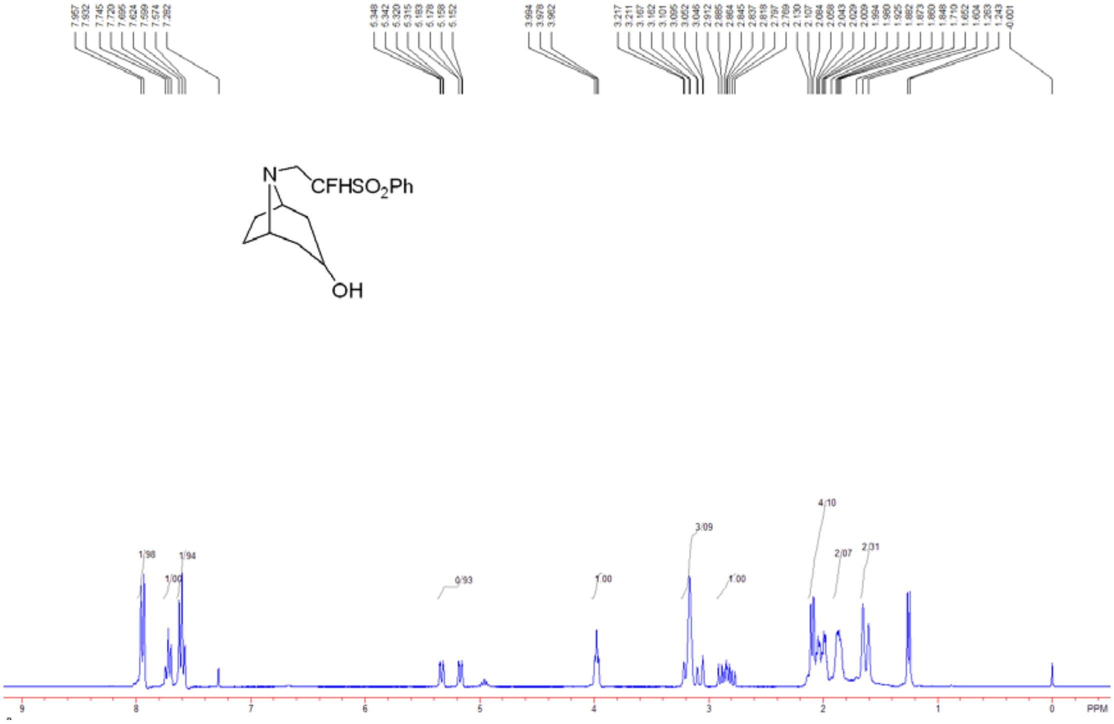


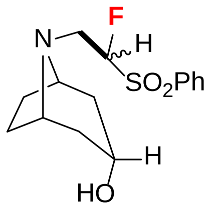
3ac ^{13}C NMR
($CDCl_3$, 75 MHz)



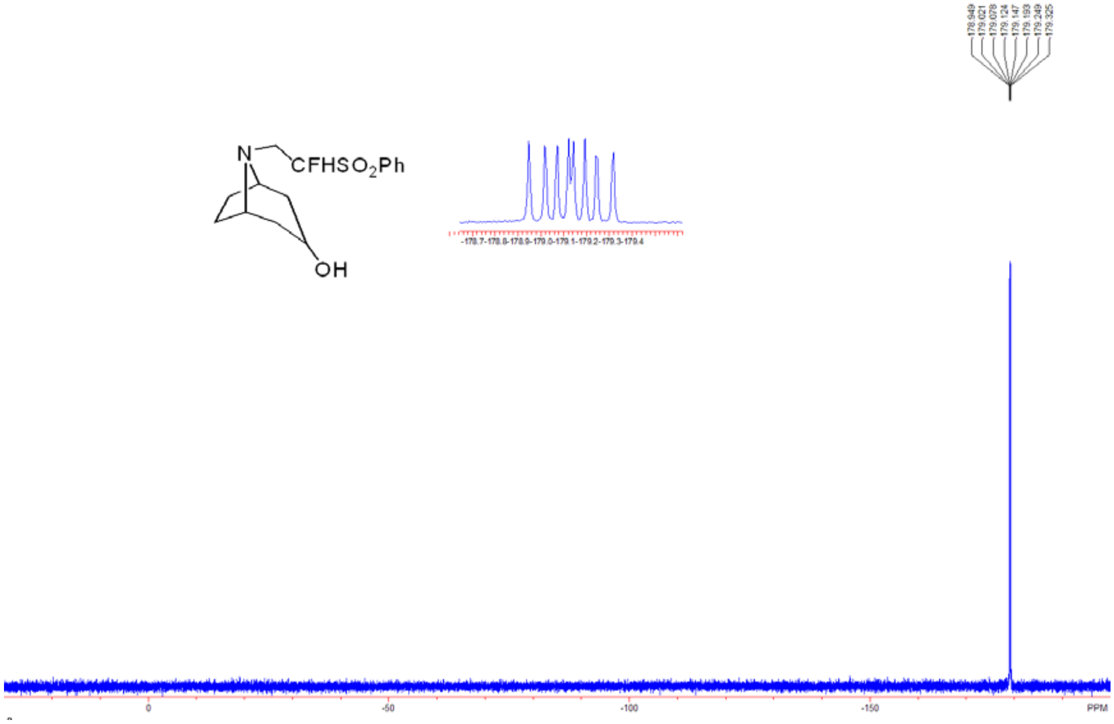


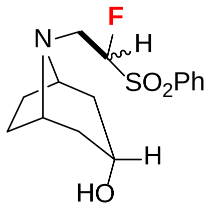
14 ^1H NMR
($CDCl_3$, 300 MHz)



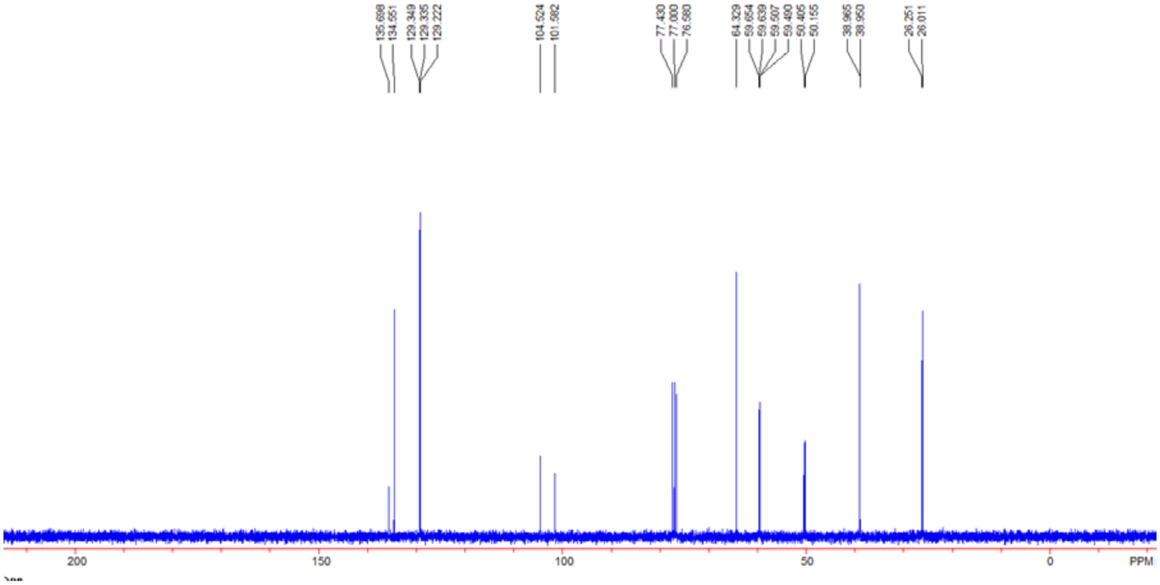


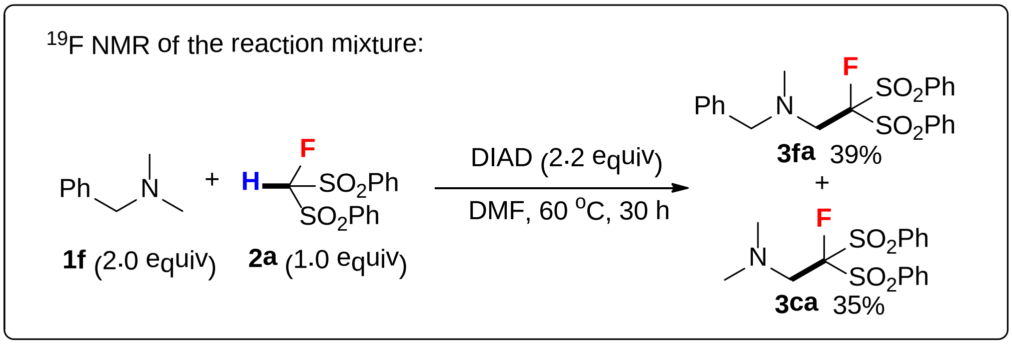
14 ^{19}F NMR
($CDCl_3$, 282 MHz)

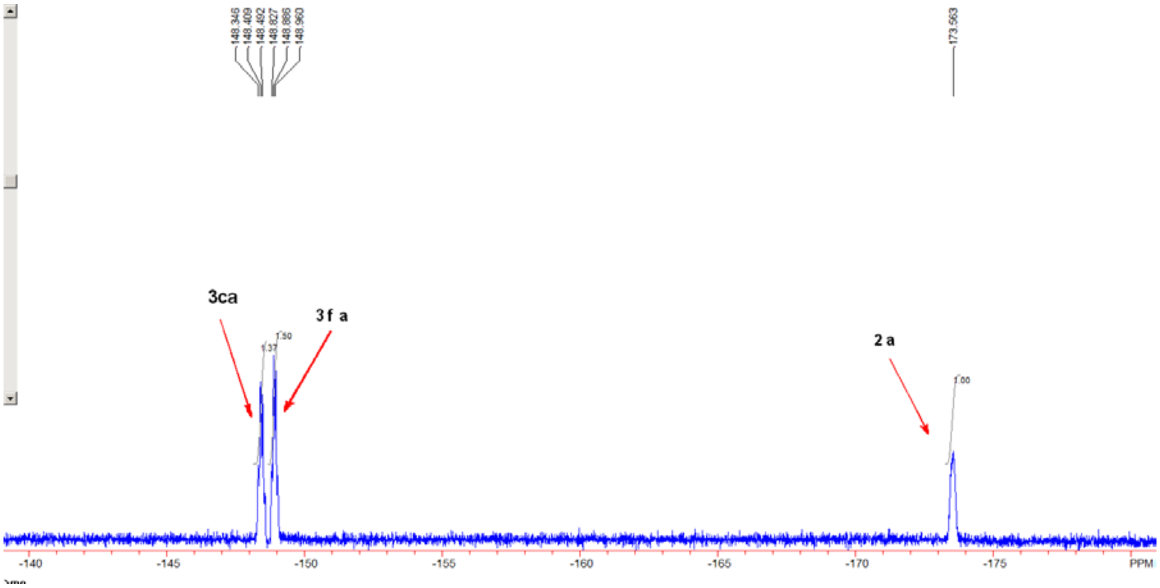


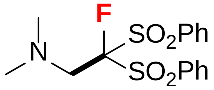


14 ^{13}C NMR
(CDCl$_3$, 75 MHz)

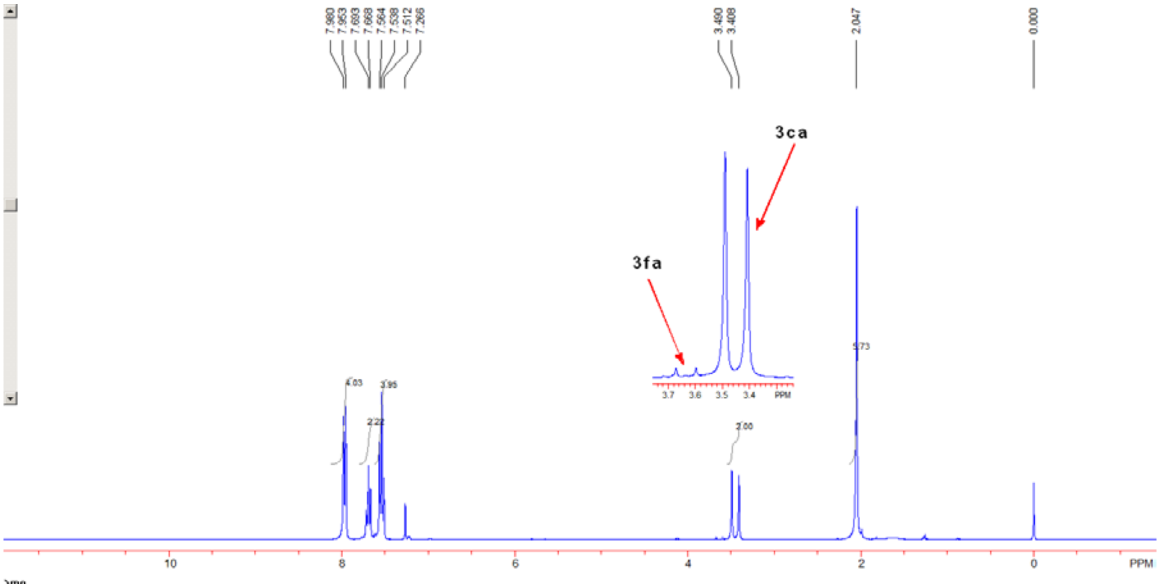


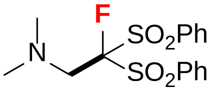

^{19}F NMR of the reaction mixture:
Ph
N
+
H
F
SO$_2$Ph
SO$_2$Ph
1f (2.0 equiv)
2a (1.0 equiv)
DIAD (2.2 equiv)
DMF, 60 °C, 30 h
3fa 39%
+
3ca 35%


148.345
148.409
148.492
148.827
148.886
148.960
173.563
3ca
3f a
2 a
1.37
1.50
1.00
-140
-145
-150
-155
-160
-165
-170
-175
PPM

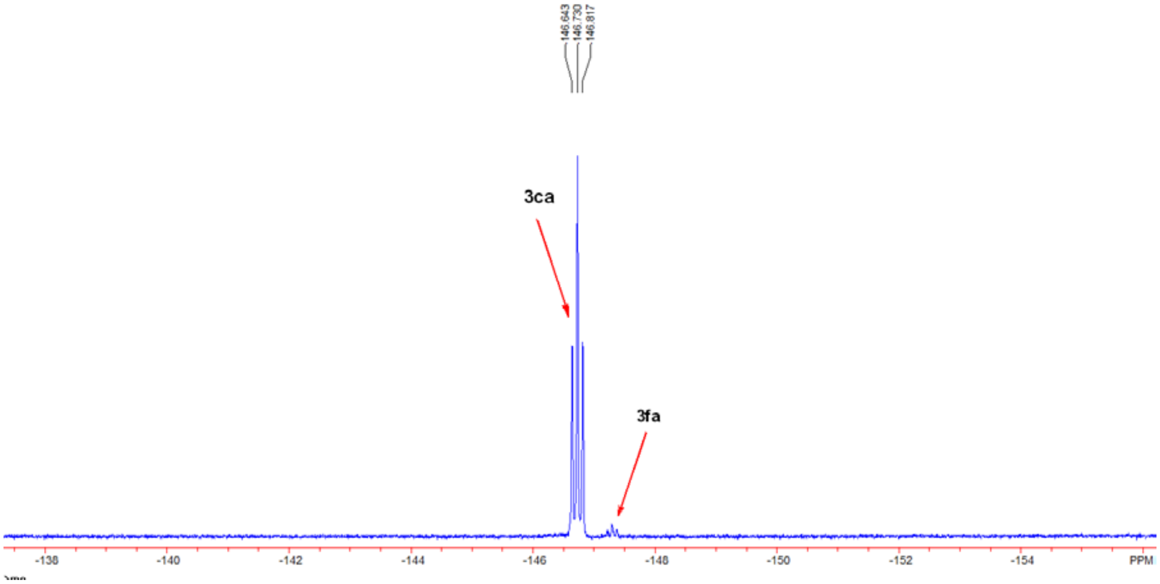


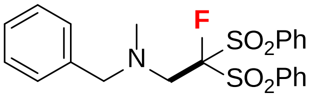
3ca in **Scheme 3** ^1H NMR ($CDCl_3$, 300 MHz)



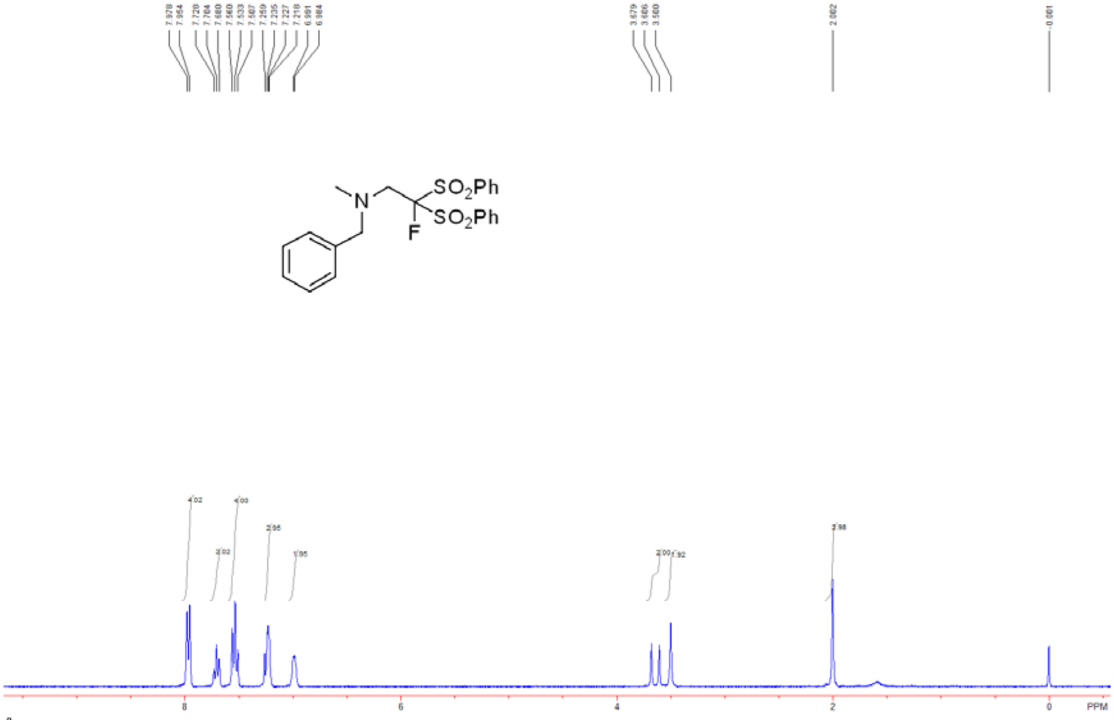


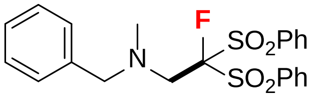
3ca in **Scheme 3** ^{19}F NMR
($CDCl_3$, 282 MHz)



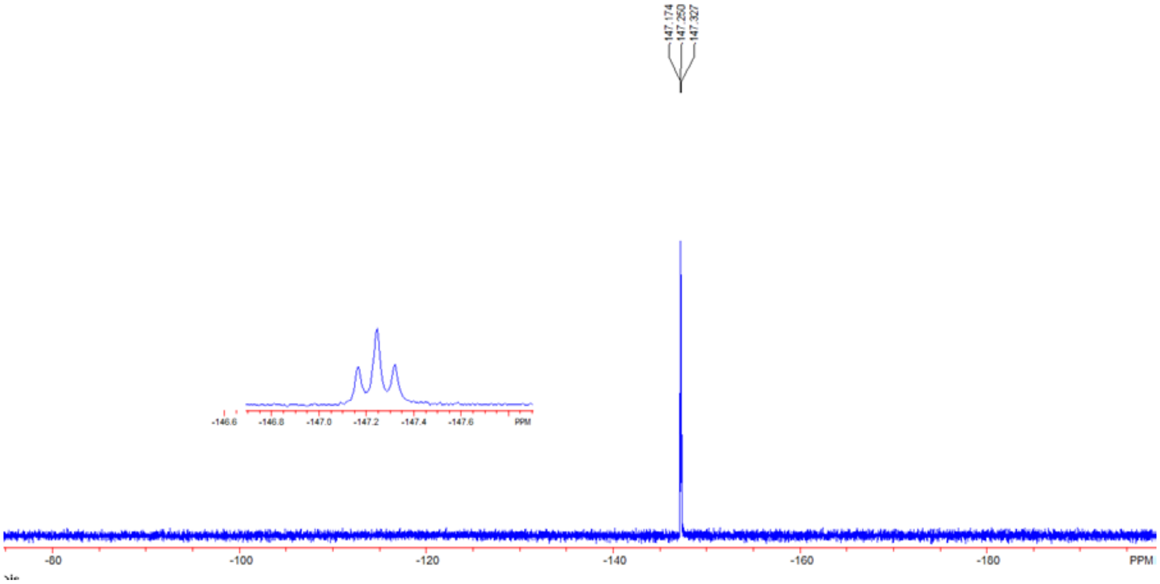


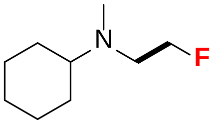
3fa in **Scheme 3** ^{1}H NMR
($CDCl_3$, 300 MHz)



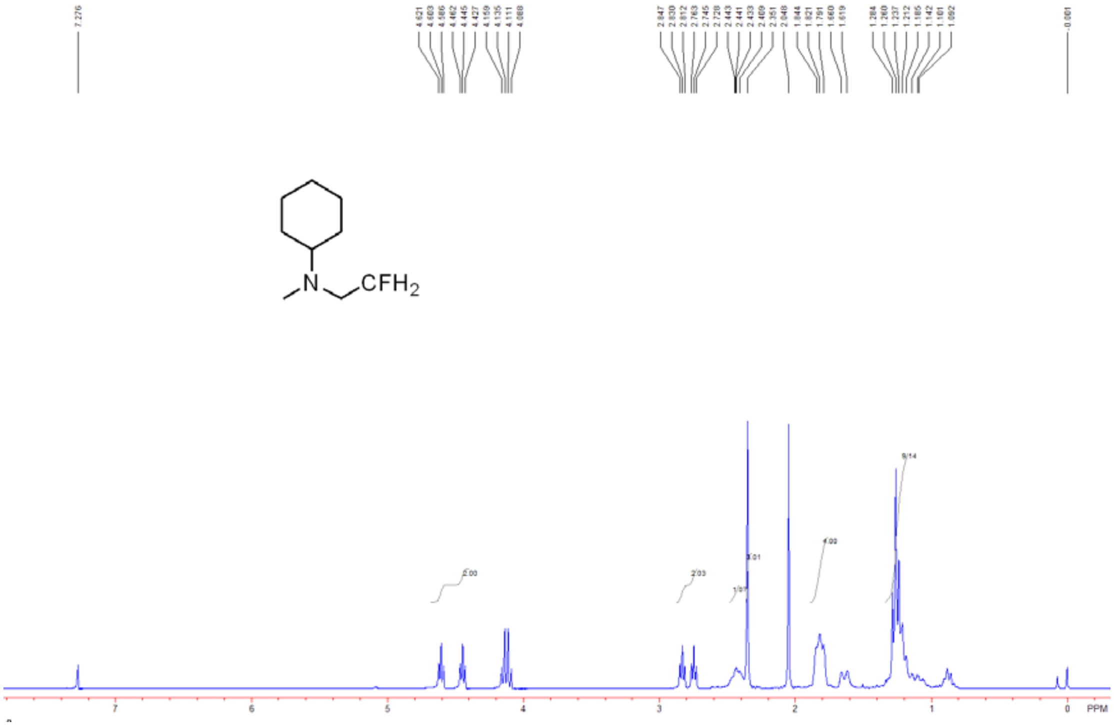


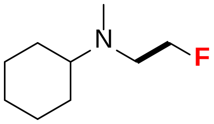
3fa in **Scheme 3** ^{19}F NMR
(CDCl$_3$, 282 MHz)





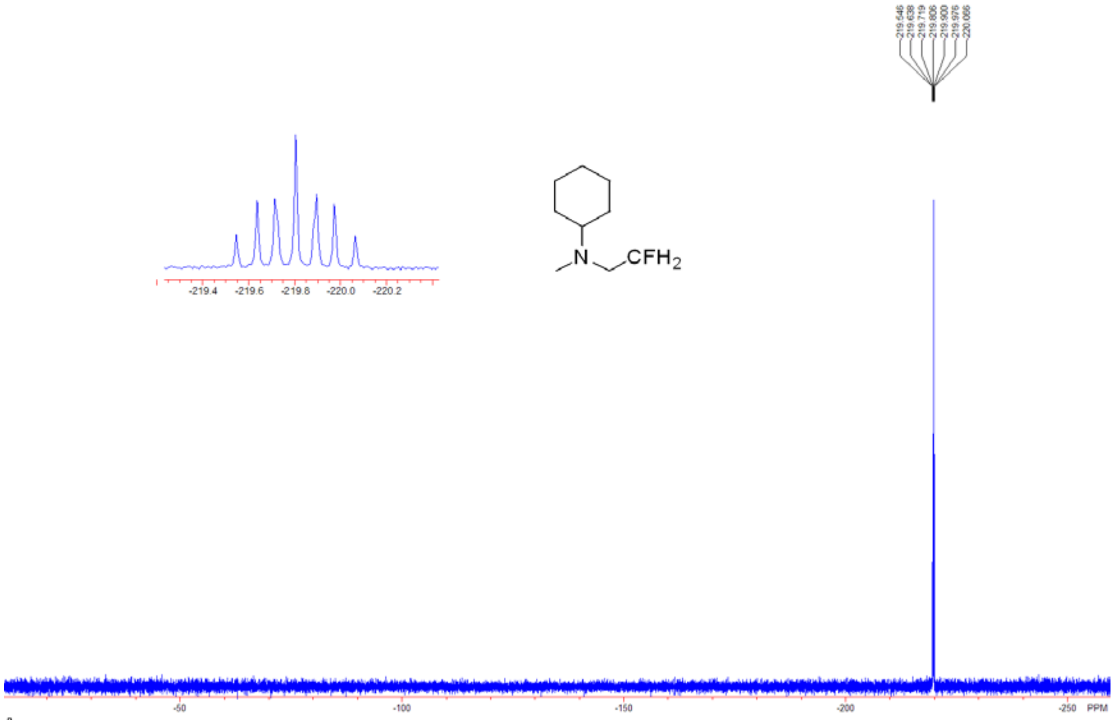
15 ^{1}H NMR
($CDCl_3$, 300 MHz)

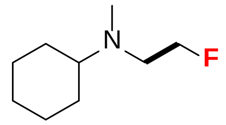




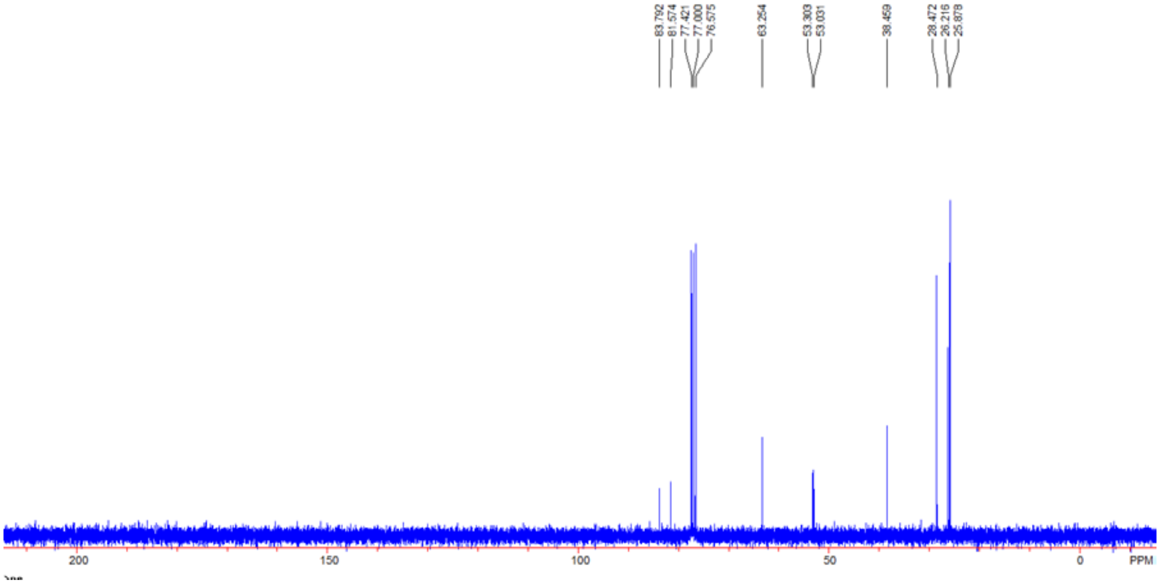
15 ^{19}F NMR

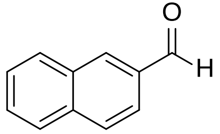
($CDCl_3$, 282 MHz)





15 ^{13}C NMR
($CDCl_3$, 75 MHz)





^{1}H NMR
($CDCl_3$, 300 MHz)