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Supporting Information
for

Highly diastereoselective entry to chiral spirooxindole-based 4-methyleneazetidines via formal [2+2] annulation reaction

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1. General remarks

All commercial materials (Aldrich, Fluka, TCI) were used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with ninhydrin solution in ethanol. Products were purified by flash chromatography (FC) on silica gel 60 (230–400 mesh). ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a Waters Micromass Q-ToF micro TM mass spectrometer, equipped with an ESI source. All the isatin-derived (*R*)-sulfinyl ketimines were synthesized according to reported procedures (**1a-c**, **1f**;[1] **1d**;[2] **1g**;[3] **1j-l**;[4] **1m**[5]). The alleonates **2b**[6] and **2c**[7] were also synthesized according to reported methods.

2. Experimental synthetic procedures

General procedure A for the synthesis of isatin-derived (*R*)-sulfinyl ketimines (GP-A)
To a solution of *N*-substituted isatin (1.17 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (2.9 mL, 0.4M), Ti(O*i*Pr)$_4$ (2.34 mmol, 2.0 eq) and (*R*)-2- methyl-2-propanesulfinamide (1.4 mmol, 1.2 eq) were added. The solution was refluxed until complete disappearance of the starting materials (monitored by TLC). The reaction was quenched by adding saturated aq. $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (15 mL). The biphasic solution was filtered through a pad of Celite and the organic phase washed with water (2 x 15 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude was purified by FC as indicated below.

(*R*,*E*)-2-Methyl-*N*-(1-(4-nitrobenzoyl)-2-oxoindolin-3-ylidene)propane-2-sulfinamide (1e)
Prepared according to **GP-A** using *N*-*p*-nitrobenzyl isatin.[8] FC: CH_2Cl_2:EtOAc, 49:1; obtained as a brown solid (180 mg, yield = 40%, m.p.: 104-106 °C); $[\alpha]^{D}_{25}$ = - 124.9 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 4.99 (d, *J* = 16.6 Hz, 1H), 5.05 (d, *J* = 16.6 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.37 (t, br, *J* = 7.7 Hz, 1H), 7.49 (d, br, *J* = 7.8 Hz, 2H), 8.21 (d, *J* = 7.8 Hz, 2H), 8.32-8.64 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3 (3C), 43.4, 51.6, 109.6, 123.6 (2C), 124.2, 124.3 (2C), 128.2 (2C), 135.5, 142.2 (2C), 146.5, 147.8, 162.2; HRMS-ESI: $[M+Na]^+$, calcd for $C_{19}H_{19}N_3NaO_4S^+$ 408.0988, found 408.0980.

(*R*,*E*)-*N*-(1-Allyl-2-oxoindolin-3-ylidene)-2-methylpropane-2-sulfinamide (1i)
Prepared according to **GP-A** using *N*-allyl isatin.[9] FC: CH_2Cl_2:EtOAc, 49:1; obtained as a red foam (248 mg, yield = 73%); $[\alpha]^{D}_{25}$= - 147.5 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 4.25 (d, *J* = 4.8 Hz, 2H), 5.11-5.24 (m, 2H), 5.73 (m, 1H), 6.72 (d, br, *J* = 7.7 Hz, 1H), 6.94 (t, br, *J* = 7.7 Hz, 1H), 7.31 (t, br, *J* = 7.7 Hz, 1H), 8.07-8.58 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (3C), 42.6, 66.8, 109.9, 118.4, 123.1, 123.5 (2C), 130.6, 135.4, 148.0 (2C), 160.7; HRMS-ESI: $[M+Na]^+$, calcd for $C_{15}H_{18}N_2NaO_2S^+$ 313.0981, found 313.0993.

General procedure B for diasteroselective formal [2+2] annulation reaction (GP-B)
To a solution of ketimine **1a-m** (0.15 mmol, 1.0 eq) and DABCO (0.03 mmol, 0.2 eq) in THF (1.5 mL), **2a-c** was added (0.30 mmol, 2.0 eq) and the reaction was stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure to provide an oily residue that was purified by FC as reported below.

Ethyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-tert-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3a)
Prepared according to **GP-B** using **1a** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow solid (56 mg, yield = 83%, m.p.: 126.4-127.6 °C); $[\alpha]^{D}_{25}$ = - 90.0 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.26

(t, *J* = 7.3 Hz, 3H), 3.56 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.83 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.14 (m, 2H), 4.85 (d, *J* = 15.6 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 5.55 (t, *J* = 1.9 Hz, 1H), 6.73 (d, br, *J* = 7.6 Hz, 1H), 7.07 (t, br, *J* = 7.6 Hz, 1H), 7.18-7.36 (m, 6H), 7.51 (d, br, *J* = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 14.0, 22.1 (3C), 41.3, 44.1, 59.3, 60.2, 70.7, 95.0, 110.6, 123.9, 125.9, 127.9 (2C), 128.2, 129.1 (2C), 130.4, 131.5, 136.2, 141.6, 157.3, 168.8, 173.0; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{28}N_2NaO_4S^+$ 475,1662 found 475.1655.

Ethyl (*E*)-2-((*S*)-1-((*R*)-tert-butylsulfinyl)-1'-methyl-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3b)

Prepared according to **GP-B** using **1b** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (47 mg, yield = 85%); $[\alpha]^D_{25}$= - 96.9 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 3.23 (s, 3H), 3.50 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.74 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.10 (m, 2H), 5.51 (t, *J* = 1.9 Hz, 1H), 6.83 (d, br, *J* = 7.5 Hz, 1H), 7.10 (t, br, *J* = 7.5 Hz, 1H), 7.35 (d, br, *J* = 7.5 Hz, 1H), 7.49 (d, br, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 26.6, 41.6, 58.7, 59.5, 71.0, 94.2, 108.7, 123.2, 125.1, 125.7, 130.9, 143.3, 159.47, 167.3, 173.2; HRMS-ESI: $[M+Na]^+$, calcd for $C_{19}H_{24}N_2NaO_4S^+$ 399.1349, found 399.1354.

Ethyl (*E*)-2-((*S*)-1-((*R*)-tert-butylsulfinyl)-2'-oxo-1'-tritylspiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3c)

Prepared according to **GP-B** using **1c** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (88 mg, yield = 97%); $[\alpha]^D_{25}$= - 55.2 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H), 3.55 (dd, *J* = 15.7 and 1.8 Hz, 1H), 3.81 (dd, *J* = 15.7 and 1.8 Hz, 1H), 4.11 (m, 2H), 5.48 (t, *J* = 1.8 Hz, 1H), 6.29 (d, br, *J* = 7.5 Hz, 1H), 6.82-7.08 (m, 2H), 7.06-7.37 (m, 10H), 7.31-7.52 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.5, 22.6 (3C), 42.0, 58.4, 59.5, 71.6, 75.4, 94.3, 116.4, 122.7, 124.8, 126.4, 127.1 (3C), 127.8 (6C), 129.2 (6C), 129.4, 141.6 (3C), 143.3, 159.3, 167.5, 174.8; HRMS-ESI: $[M+Na]^+$, calcd for $C_{37}H_{36}N_2NaO_4S^+$ 627.2288, found 627.2293.

(*E*)-Ethyl 3-((*S*,*E*)-1-((*R*)-tert-butylsulfinyl)-4-(2-ethoxy-2-oxoethylidene)-2'-oxospiro[azetidine-2,3'-indolin]-1'-yl)but-2-enoate (3d).

Prepared according to **GP-B** using **1d** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a brown foam (18 mg, yield = 38 %); $[\alpha]^D_{25}$= - 31.5 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.3 Hz, 3H), 2.58 (d, *J* = 0.9 Hz, 3H), 3.59 (dd, *J* = 16.1 and 2.0 Hz, 1H), 3.83 (dd, *J* = 16.1 and 2.0 Hz, 1H), 4.17 (m, 2H), 4.27 (q, *J* = 7.3 Hz, 2H), 5.55 (t, *J* = 2.0 Hz, 1H), 6.05 (q, br, *J* = 0.9 Hz, 1H), 6.99 (d, br, *J* = 7.6 Hz, 1H), 7.19 (td, br, *J* = 7.7 and 0.9 Hz, 1H), 7.38 (td, br, *J* = 7.6 and 0.9 Hz, 1H), 7.60 (d, br, *J* = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1, 17.3, 22.3 (3C), 41.8, 42.7, 56.6, 59.4, 60.3, 70.6, 93.7, 110.3, 118.4, 123.7, 125.0, 125.4, 130.6, 141.2, 147.7, 159.2, 165.3, 171.8, 171.9; HRMS-ESI: $[M+Na]^+$, calcd for $C_{24}H_{30}N_2NaO_6S^+$ 497.1717, found 497.1724.

Ethyl (*E*)-2-((*S*)-1-((*R*)-tert-butylsulfinyl)-1'-(4-nitrobenzoyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3e)

Prepared according to **GP-B** using **1e** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (27 mg, yield = 36%); $[\alpha]^D_{25}$= - 70.4 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.58 (dd, *J* = 15.8 and 1.9 Hz, 1H), 3.82 (dd, *J* = 15.8 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.92 (d, *J* = 16.6 Hz, 1H), 5.15 (d, *J* = 16.6 Hz, 1H), 5.53 (t, *J* = 1.9 Hz, 1H), 6.64 (d, br, *J* = 7.1 Hz, 1H), 7.12 (t, br, *J* = 7.2 Hz, 1H), 7.25 (t, br, *J* = 7.2 Hz, 1H), 7.47 (d, br, *J* = 8.8 Hz, 2H), 7.55 (d, br, *J* = 7.1 Hz, 1H), 8.18 (d, br, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.6, 43.6, 59.1, 59.7, 70.8, 94.6, 109.3, 121.7, 123.8, 124.2 (2C), 125.4, 128.2 (2C), 130.9, 141.8, 142.5, 147.8, 159.1, 167.3, 175.0; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}N_3NaO_6S^+$ 520.1513, found 520.1521.

Ethyl (*E*)-2-((*S*)-1-((*R*)-tert-butylsulfinyl)-1'-(4-methoxybenzyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3f)

Prepared according to **GP-B** using **1f** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (37 mg, yield = 51%); $[\alpha]^D_{25}$= - 87.7 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.53 (dd, *J* = 15.9 and 1.8 Hz, 1H), 3.76 (s, 3H), 3.80 (dd, *J* = 15.9 and 1.8 Hz, 1H), 4.14 (m, 2H), 4.77 (d, *J* =

15.6 Hz, 1H), 4.94 (d, *J* = 15.6 Hz, 1H), 5.54 (t, *J* = 1.8 Hz, 1H), 6.75 (d, br, *J* = 7.3 Hz, 1H), 6.82 (d, br, *J* = 8.7 Hz, 2H), 7.06 (t, br, *J* = 7.3 Hz, 1H), 7.18-7.33 (m, 3H), 7.49 (d, br, *J* = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.6, 43.7, 55.3, 58.7, 59.6, 71.0, 94.3, 109.8, 114.2 (2C), 123.1, 125.1, 125.8, 127.2, 128.9 (2C), 130.7, 142.4, 159.2, 159.3, 167.4, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{26}H_{30}N_2NaO_5S^+$ 505.1768 found 505.1759.

Ethyl (*E*)-2-((*S*)-1'-(4-bromobenzyl)-1-((*R*)-tert-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3g).

Prepared according to **GP-B** using **1g** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (59 mg, yield = 95%); $[\alpha]^D_{25}$= - 70.7 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.25 (t, *J* = 7.0 Hz, 3H), 3.54 (dd, *J* = 16.6 and 1.9 Hz, 1H), 3.81 (dd, *J* = 16.6 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 5.53 (t, *J* = 1.9 Hz, 1H), 6.69 (d, br, *J* = 7.1 Hz, 1H), 7.08 (t, br, *J* = 7.2 Hz, 1H), 7.18 (d, br, *J* = 8.8 Hz, 2H), 7.25 (t, br, *J* = 7.2 Hz, 1H), 7.42 (d, br, *J* = 8.8 Hz, 2H) , 7.51 (d, br, *J* = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.6, 43.6, 58.9, 59.6, 70.9, 94.6, 109.6, 121.9, 123.5, 125.3, 125.8, 129.3 (2C), 130.9, 132.0 (2C), 134.2, 142.1, 159.1, 167.4, 173.4; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}BrN_2NaO_4S^+$ 553.0767 found 553.0769.

Ethyl (*E*)-2-((*S*)-1'-allyl-1-((*R*)-tert-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3i)

Prepared according to GP-B using **1i** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (40 mg, yield = 66%); $[\alpha]^D_{25}$= - 62.3 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 3.49 (dd, *J* = 15.6 and 1.9 Hz, 1H), 3.76 (dd, *J* = 15.6 and 1.9 Hz, 1H), 4.11 (m, 2H), 4.29 (dd, *J* = 16.6 and 4.9 Hz, 1H), 4.42 (dd, *J* = 16.6 and 4.9 Hz, 1H), 5.16-5.29 (m, br, 2H), 5.50 (m, br, 1H), 5.80 (m, 1H), 6.82 (d, br, *J* = 7.6 Hz, 1H), 7.09 (t, br, *J* = 7.7 Hz, 1H), 7.31 (t, br, *J* = 7.7 Hz, 1H), 7.50 (d, br, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.7, 42.7, 58.8, 59.6, 70.9, 94.2, 109.7, 118.2, 123.2, 125.1, 125.8, 130.9 (2C), 142.5, 159.6, 167.4, 173.0; HRMS-ESI: $[M+Na]^+$, calcd for $C_{21}H_{26}N_2NaO_4S^+$ 425.1505, found 425.1513.

Ethyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-tert-butylsulfinyl)-5'-methoxy-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3j).

Prepared according to **GP-B** using **1j** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (57 mg, yield = 81%); $[\alpha]^D_{25}$= - 79.6 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.53 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.74 (s, 3H), 3.82 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.81 (d, *J* = 15.6 Hz, 1H), 4.99 (d, *J* = 15.6 Hz, 1H), 5.54 (t, *J* = 1.9 Hz, 1H), 6.60 (d, br, *J* = 8.6 Hz, 1H), 6.74 (dd, *J* = 8.6 and 2.5 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 7.21-7.35 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.8, 44.3, 55.9, 58.75, 59.6, 71.3, 94.3, 110.3, 111.9, 115.5, 127.0, 127.5 (2C), 127.8, 128.8 (2C), 135.2, 135.6, 156.4, 159.4, 167.35, 173.1; HRMS-ESI: $[M+Na]^+$, calcd for $C_{26}H_{30}N_2NaO_5S^+$ 505.1768, found 505.1757.

Ethyl (*E*)-2-((S)-1'-benzyl-1-((*R*)-tert-butylsulfinyl)-5'-chloro-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3k).

Prepared according to **GP-B** using **1k** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (43 mg, yield = 59%); $[\alpha]^D_{25}$= - 29.8 (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.53 (dd, *J* = 15.9 and 1.8 Hz, 1H), 3.82 (dd, *J* = 15.9 and 1.8 Hz, 1H), 4.12 (m, 2H), 4.81 (d, *J* = 15.6 Hz, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 5.52 (t, *J* = 1.8 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, J = 8.4 and 2.1 Hz, 1H), 7.23-7.38 (m, 5H), 7.48 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.7, 44.3, 58.9, 59.7, 71.1, 94.5, 110.9, 125.4, 127.4 (2C), 128.1, 128.8, 128.9 (2C), 130.6, 134.6, 135.2, 144.3, 158.9, 167.2, 174.8; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}ClN_2NaO_4S^+$ 509.1272, found 509.1279.

Ethyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-tert-butylsulfinyl)-5'-fluoro-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3l).

Prepared according to **GP-B** using **1l** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (33 mg, yield = 47%); $[\alpha]^D_{25}$= - 82.4 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 3.57 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.86 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.18 (m, 2H), 4.87 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 5.56 (t, *J* = 1.9 Hz, 1H), 6.68 (dd, *J* = 8.6 and 3.9 Hz, 1H), 6.97 (td, *J* = 8.8 and 2.6 Hz,

1H), 7.26-7.41 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.9, 44.4, 58.9, 59.7, 70.9, 94.4, 110.6 (d, *J* = 7.7 Hz), 113.1 (d, *J* = 24.5 Hz), 117.2 (d, *J* = 23.0 Hz), 127.5 (2C), 127.6, 128.1, 129.0 (2C), 134.8, 138.2, 158.2, 159.8 (d, *J* = 150.3 Hz) , 167.2, 173.2; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}FN_2NaO_4S^+$ 493.1568, found 493.1559.

Ethyl (*E*)-2-((*S*)-1'-benzyl-6'-bromo-1-((*R*)-tert-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3m).

Prepared according to **GP-B** using **1m** and **2a**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale yellow foam (56 mg, yield = 71%); $[\alpha]^D_{25}$= - 43.7 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.52 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.81 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.81 (d, *J* = 15.6 Hz, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 5.52 (t, *J* = 1.9 Hz, 1H), 6.88 (m, br, 1H), 7.21 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.24-7.35 (m, 5H), 7.37 (d, br, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.8, 44.3, 58.8, 59.6, 70.6, 94.3, 113.2, 124.5, 124.7, 126.2, 126.4, 127.5 (2C), 128.1, 129.0 (2C), 134.6, 143.6, 159.2, 167.2, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}BrN_2NaO_4S^+$ 553.0767, found 553.0772.

Benzyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-tert-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (3n).

Prepared according to **GP-B** using **1a** and **2b**. FC: CH_2Cl_2:EtOAc, 49:1; obtained as a pale orange foam (40 mg, yield = 52%); $[\alpha]^D_{25}$= - 57.9 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 3.58 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.85 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 5.17 (s, 2H), 5.64 (t, *J* = 1.9 Hz, 1H), 6.76 (d, br, *J* = 8.1 Hz, 1H), 7.10 (td, *J* = 8.1 and 1.0 Hz, 1H), 7.27 (td, *J* = 8.2 and 1.2 Hz, 1H), 7.28-7.43 (m, 10H), 7.53 (dd, *J* = 8.1 and 1.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.7 (3C), 41.8, 44.3, 58.8, 65.6, 71.1, 93.9, 109.8, 123.2, 125.2, 125.8, 127.6-128.9 (10C), 130.8, 135.1, 136.5, 142.5, 160.0, 167.1, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{30}H_{30}N_2NaO_4S^+$ 537.1818, found 537.1811.

<u>Post-trasformation reactions</u>

Synthesis of ethyl (*S*,*E*)-2-(1'-benzyl-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (4)

To a solution of compound **3a** (0.11 mmol, 1.0 eq) in 1:1 mixture of anhydrous 1,4-dioxane and anhydrous MeOH (550 µL), HCl in dioxane (4 M solution, 0.44 mmol, 0.4 eq) was added. After the mixture was stirred at room temperature for 1 h, all volatiles were removed under reduced pressure, and the residue was dissolved in water (2 mL) and extracted with EtOAc (1 x 1 mL). The water layer was basified to pH 8 with aqueous concentrated NH_4OH and extracted with EtOAc (2 x 2 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by FC (CH_2Cl_2:EtOAc, 49:1) affording product **4** as a pale orange foam (25 mg, yield = 64%); $[\alpha]^D_{25}$= - 47.4 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.21 (d, br, *J* = 14.2 Hz, 1H), 3.44 (dd, *J* = 14.1 and 2.8 Hz, 1H), 4.15 (m, 2H), 4.80 (s, br, 1H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.95 (d, *J* = 15.6 Hz, 1H), 6.76 (m, br, 1H), 6.78 (d, br, *J* = 7.8 Hz, 1H), 7.11 (t, br, *J* = 7.7 Hz, 1H), 7.27 (td, *J* = 7.8 and 1.2 Hz, 1H), 7.29-7.37 (m, 5H), 7.56 (d, br, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.6, 41.6, 44.2, 59.0, 65.6, 83.6, 109.5, 123.4, 124.2, 127.4, 127.5 (2C), 127.9, 128.9 (2C), 130.4, 135.4, 142.6, 162.7, 169.2, 175.1; HRMS-ESI: $[M+Na]^+$, calcd for $C_{21}H_{20}N_2NaO_3^+$ 371.1366, found 371.1360.

Synthesis of (*S*,*E*)-ethyl 2-(1'-benzyl-1-(tert-butylsulfonyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (5).

A solution of compound **3a** (0.11 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (1.1 mL, 0.1M) was cooled to 0°C, and *m*CPBA (0.11 mmol, 1.0 eq) was added in small portions.

Stirring was continued for 15 min, then the solution was diluted with CH_2Cl_2 (10 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (3 x 5 mL) and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

The crude was purified by FC (CH_2Cl_2:EtOAc, 49:1) affording product **5** as a pale yellow foam (54 mg, yield = 99%); $[\alpha]^D_{25}$= + 20.5 (c 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.33 (s, 9H), 3.44 (dd, *J* = 15.6 and 1.9 Hz, 1H), 3.71 (dd, *J* = 15.6 and 1.9 Hz, 1H),4.16 (q, *J* = 7.1 Hz, 2H), 4.83 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 5.68 (s, br, 1H), 6.69 (d, br, *J* = 7.8 Hz, 1H), 7.08 (t, br, *J* = 7.7 Hz, 1H), 7.19-7.38 (m,

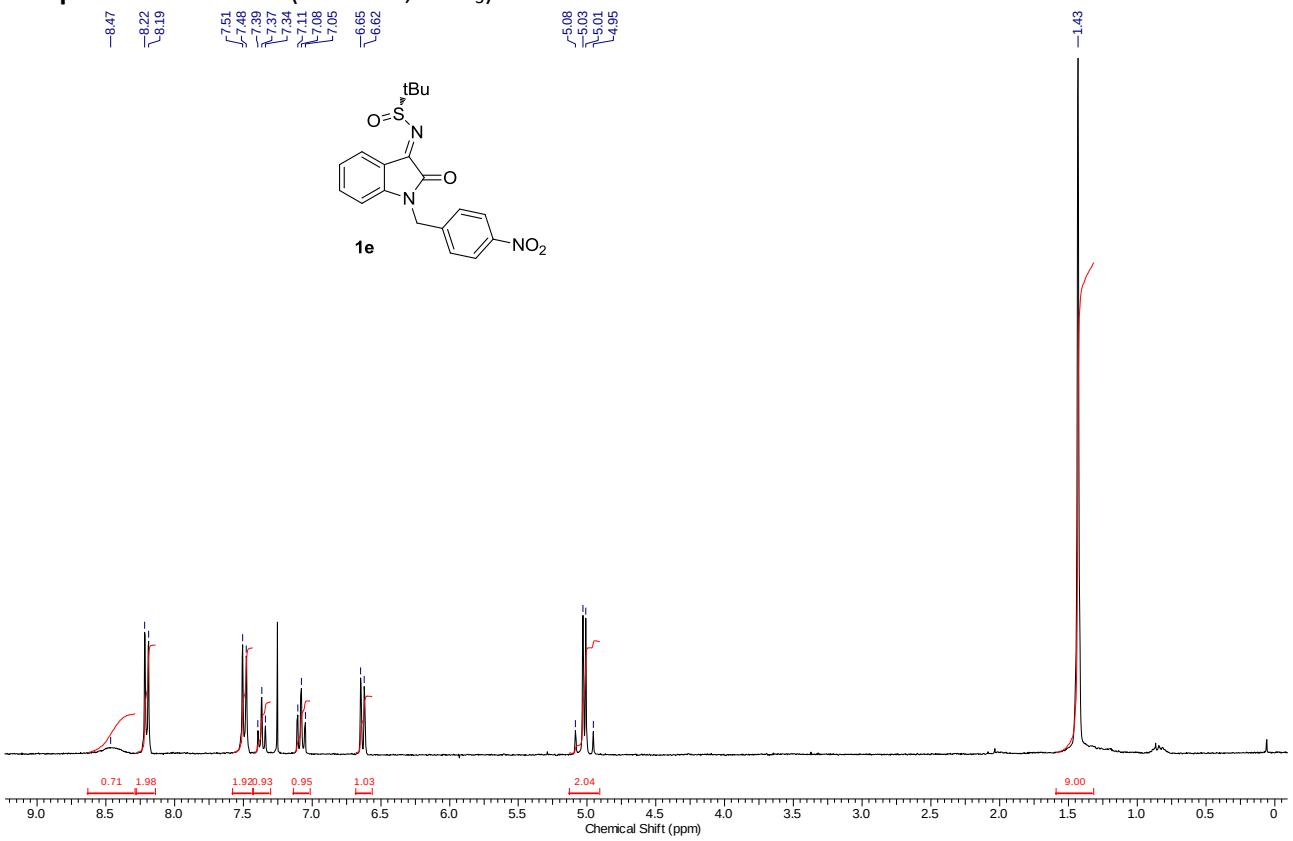
6H), 7.50 (d, br, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.5, 22.7 (3C), 41.8, 44.4, 58.9, 59.7, 70.6, 94.3, 113.2, 124.6, 126.2, 126.4, 127.5 (2C), 128.2, 129.0 (3C), 134.6, 143.6, 159.2, 167.3, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{28}N_2NaO_5S^+$ 491.1611, found 491.1604.

Synthesis of (*S*)-1'-benzyl-1-((*R*)-tert-butylsulfinyl)spiro[azetidine-2,3'-indoline]-2',4-dione (6)

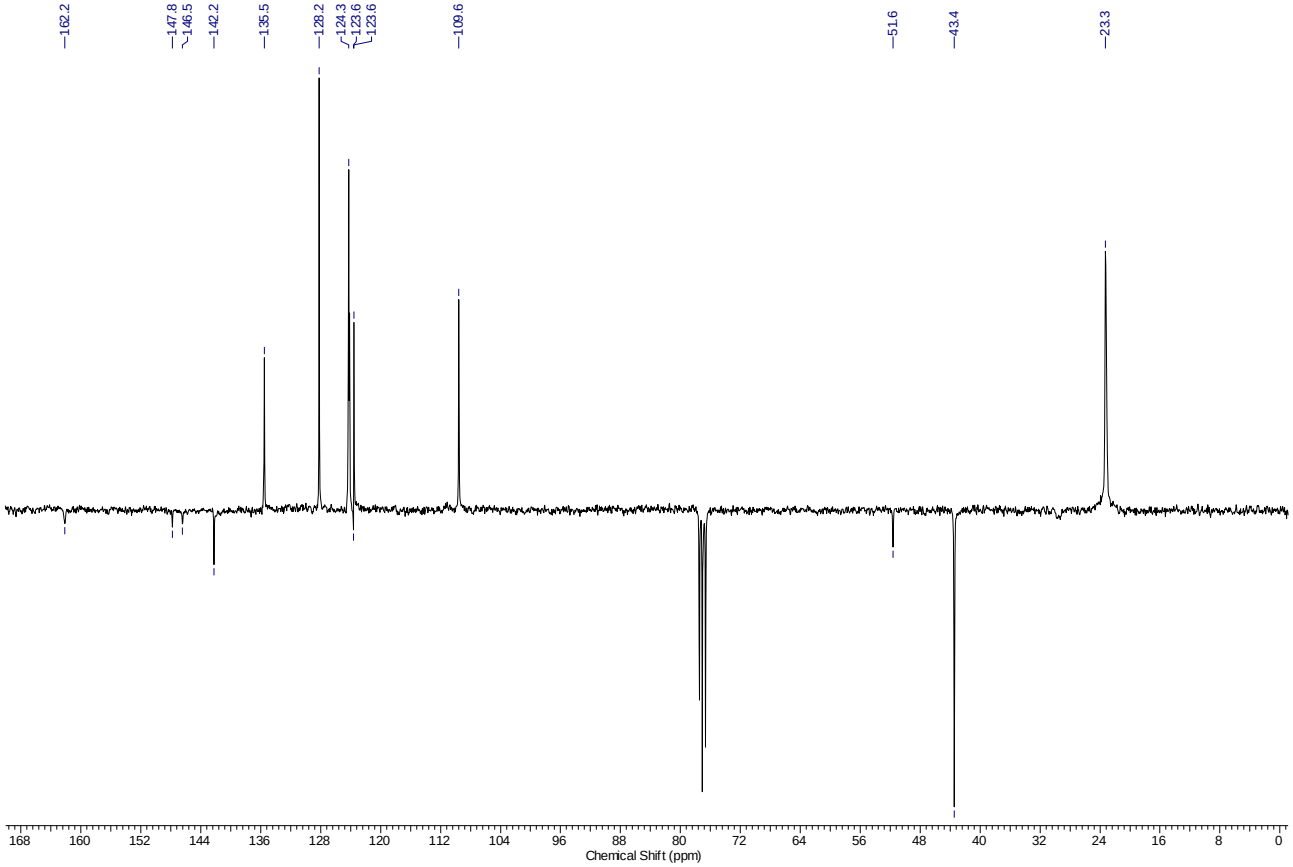
A solution of compound **3a** (0.11 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (13.75mL) was bubbled with ozone at -78°C for 10 minutes. Then Me_2S (1.21 mmol, 11.0 mmol) was added at the same temperature and the reaction was warmed up to room temperature and stirred for 10 minutes. The solvent was evaporated under reduced pressure and the residue was purified by FC (CH_2Cl_2:EtOAc, 49:1) to afford compound **6** as a pale yellow foam (45 mg, yield = 99%); $[\alpha]^D_{25}$= - 47.8 (c 0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H), 3.37 (d, *J* = 15.1 Hz, 1H), 3.69 (d, *J* = 15.1 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 6.82 (d, br, *J* = 7.6 Hz, 1H), 7.14 (t, br, *J* = 7.6 Hz, 1H), 7.23-7.39 (m, 6H), 7.50 (d, br, *J* = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.6 (3C), 44.4, 49.9, 59.2, 60.9, 109.9, 123.4, 124.3, 125.1, 127.5, 128.0 (2C), 128.9, 130.6 (2C), 135.0, 142.5, 165.7, 173.4; HRMS-ESI: $[M+Na]^+$, calcd for $C_{21}H_{22}N_2NaO_3S^+$ 405.1243, found 405.1251.

3. Copies of ^{1}H and ^{13}C NMR spectra

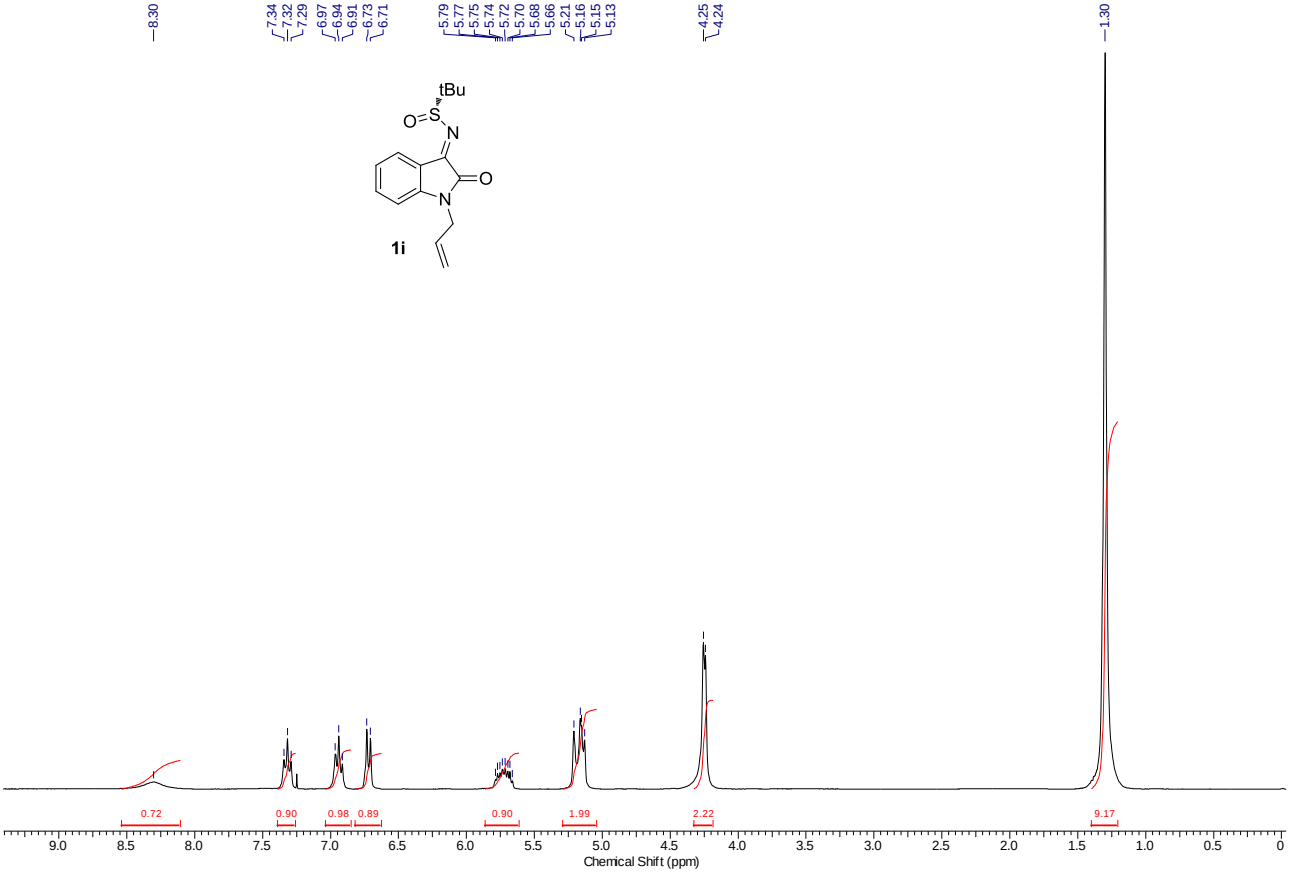
Compound 1e: ^{1}H NMR (300 MHz, $CDCl_3$)



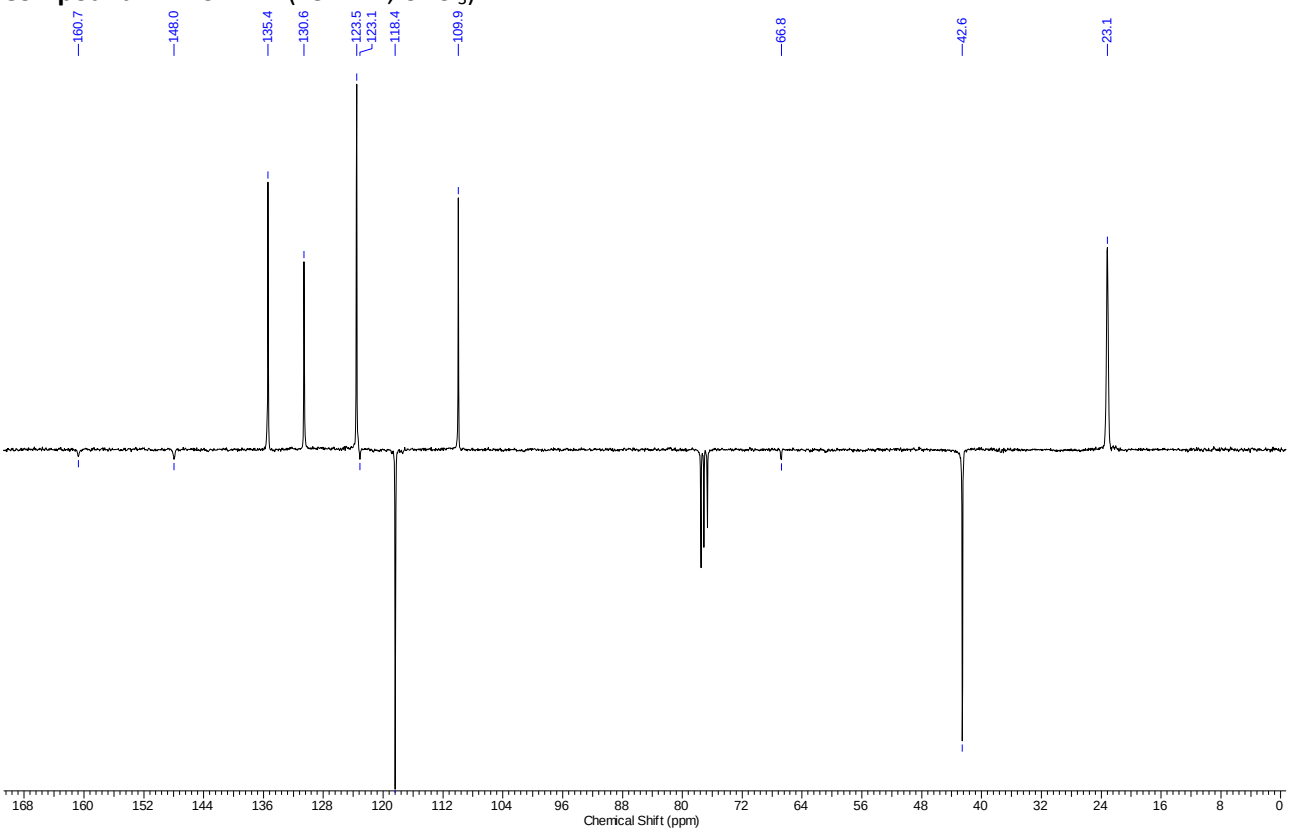
Compound 1e: ^{13}C NMR (75 MHz, $CDCl_3$)



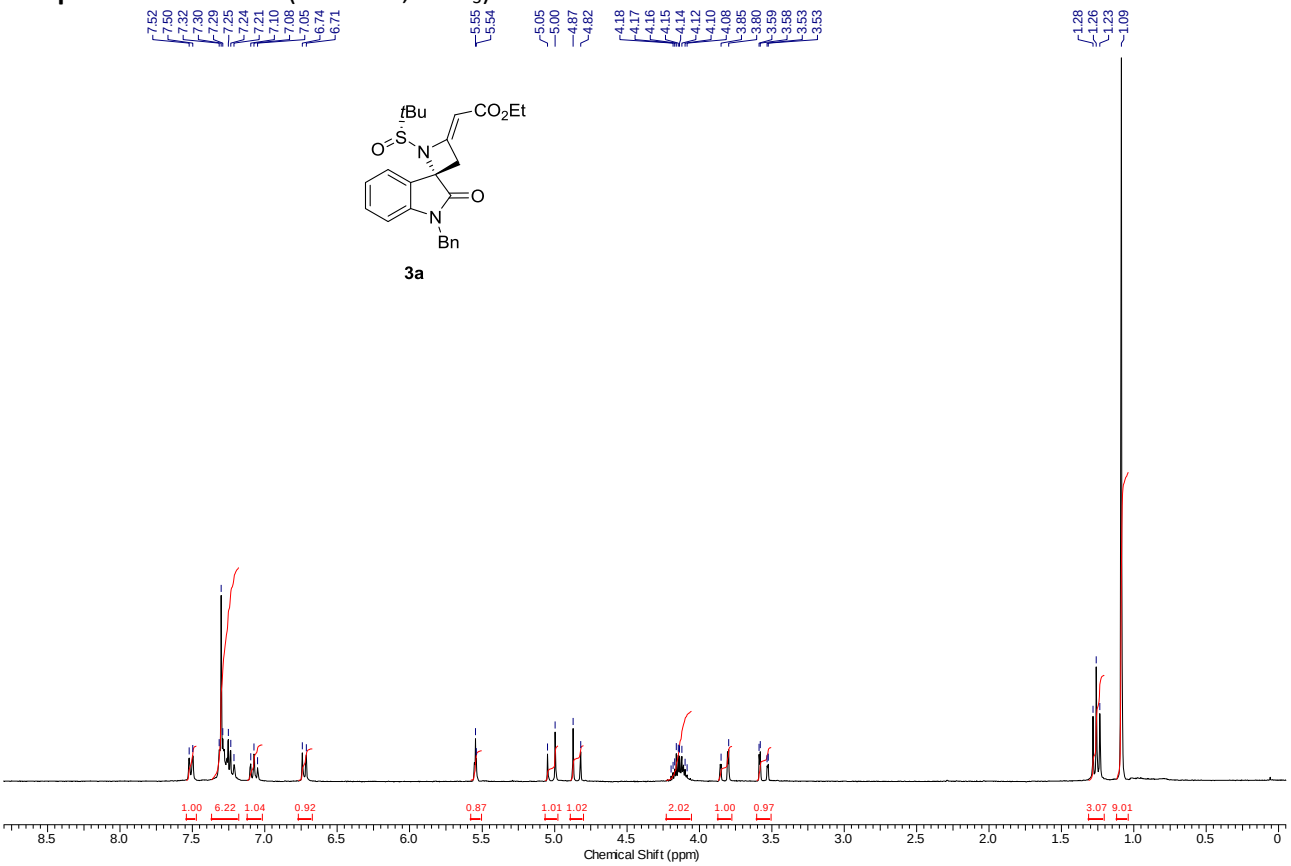
Compound 1i: ^{1}H NMR (300 MHz, $CDCl_3$)



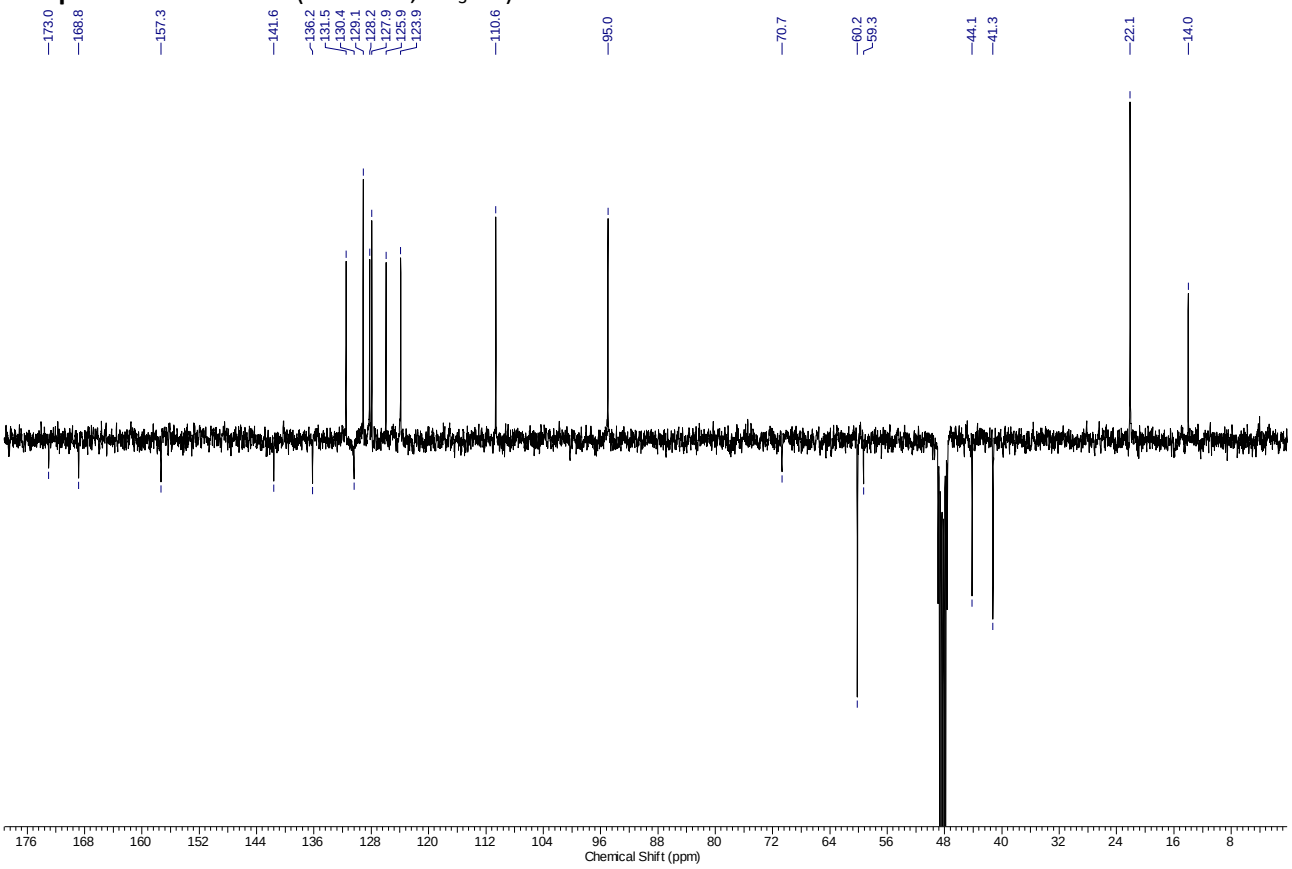
Compound 1i: ^{13}C NMR (75 MHz, $CDCl_3$)



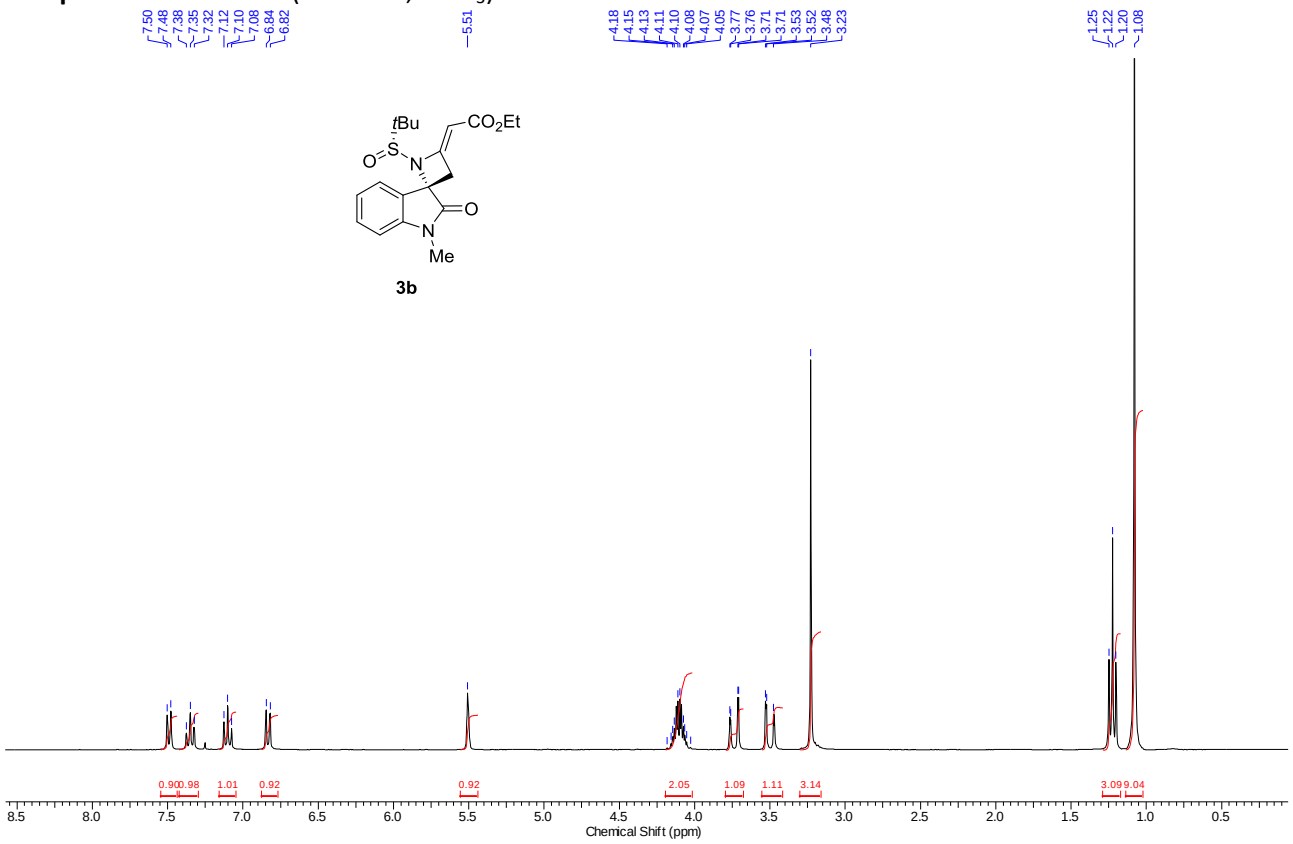
Compound 3a: ^{1}H NMR (300 MHz, $CDCl_3$)



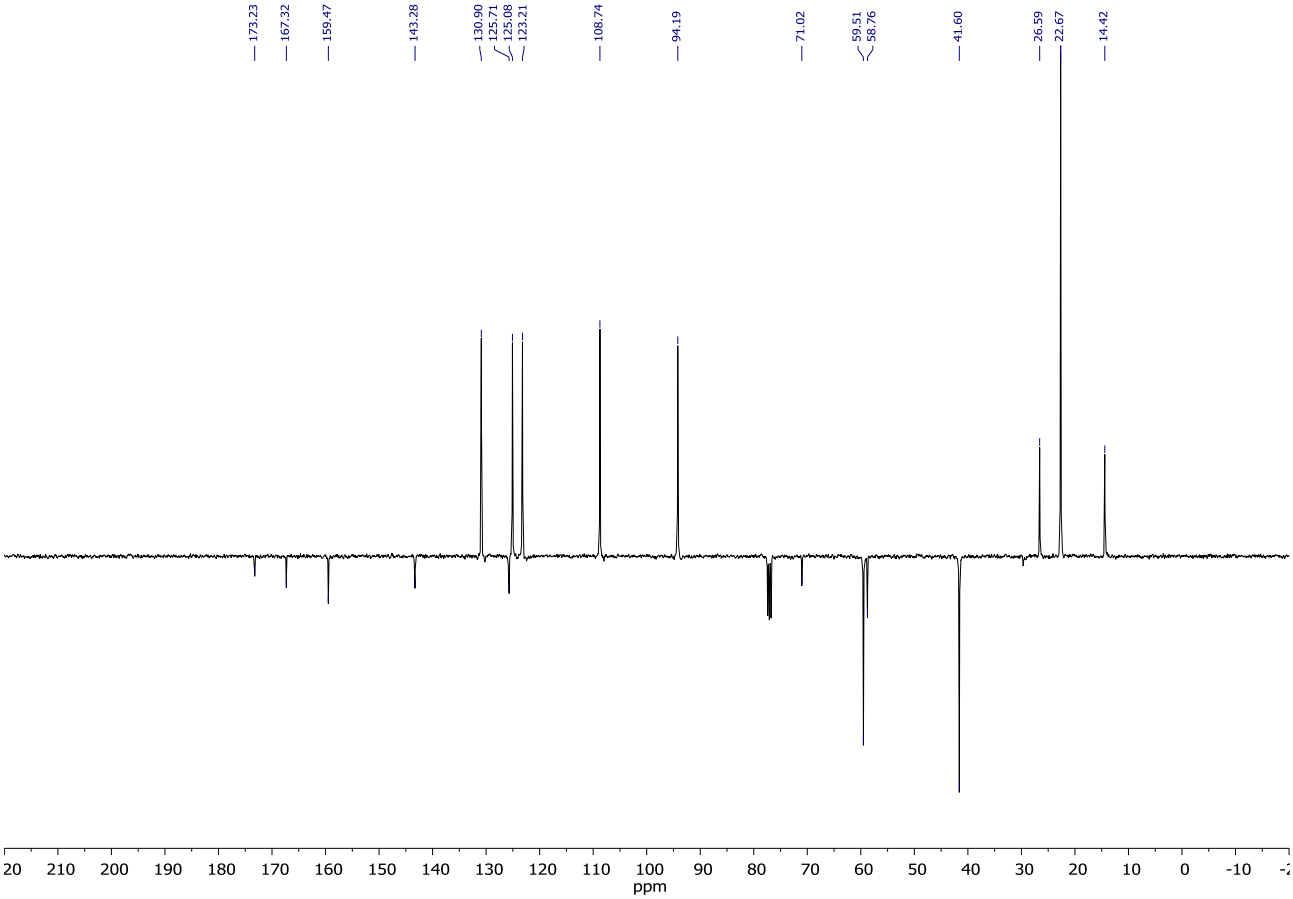
Compound 3a: ^{13}C NMR (101 MHz, CD_3OD)



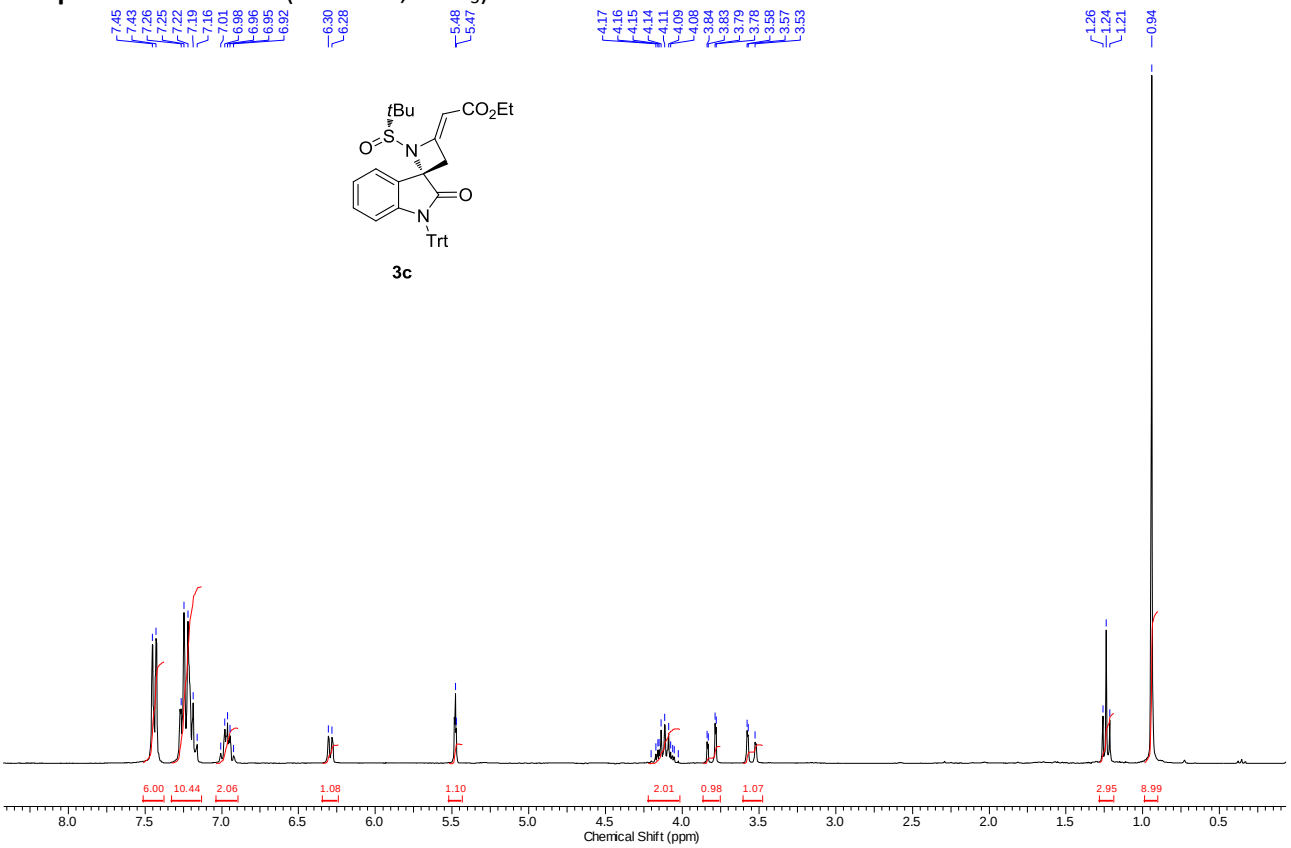
Compound 3b: ^{1}H NMR (300 MHz, $CDCl_3$)



Compound 3b: ^{13}C NMR (101 MHz, $CDCl_3$)

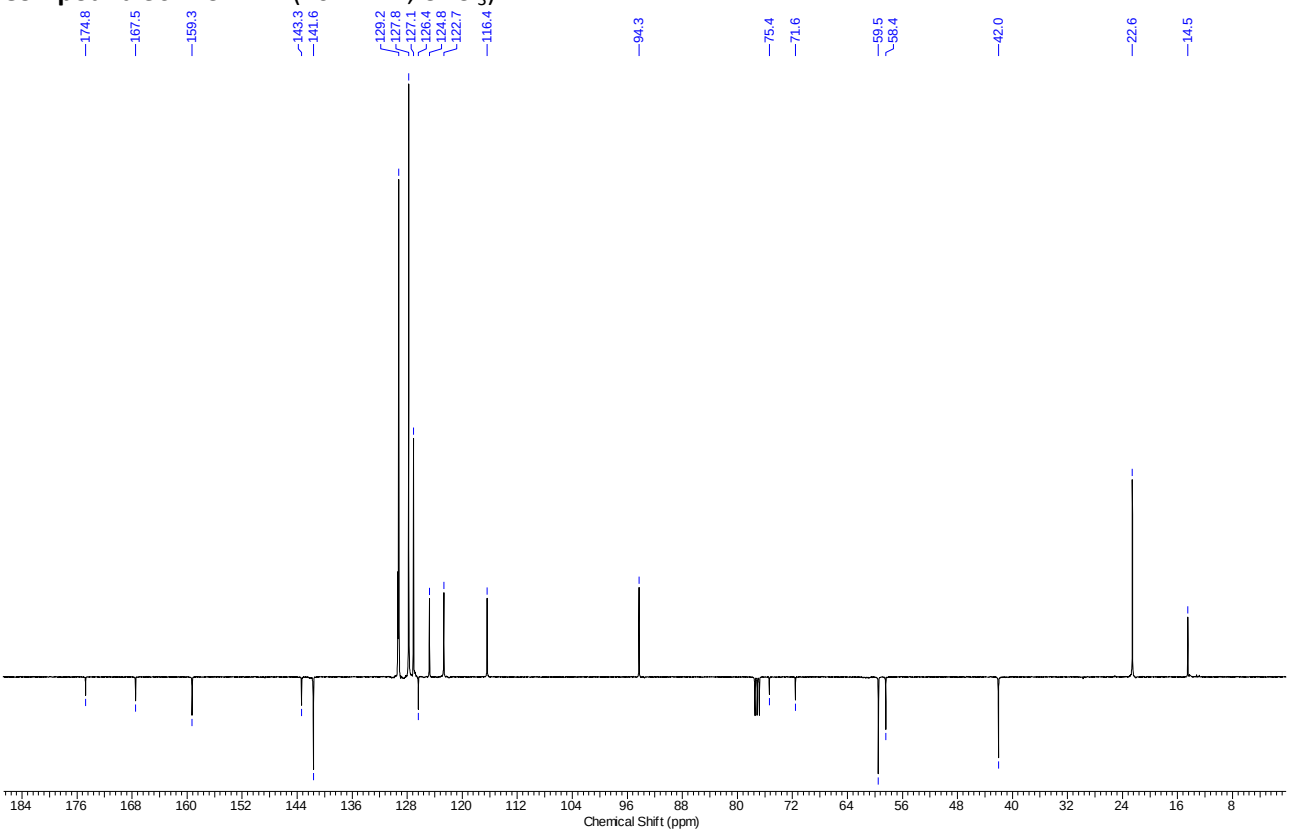


Compound 3c: ^{1}H NMR (300 MHz, $CDCl_3$)

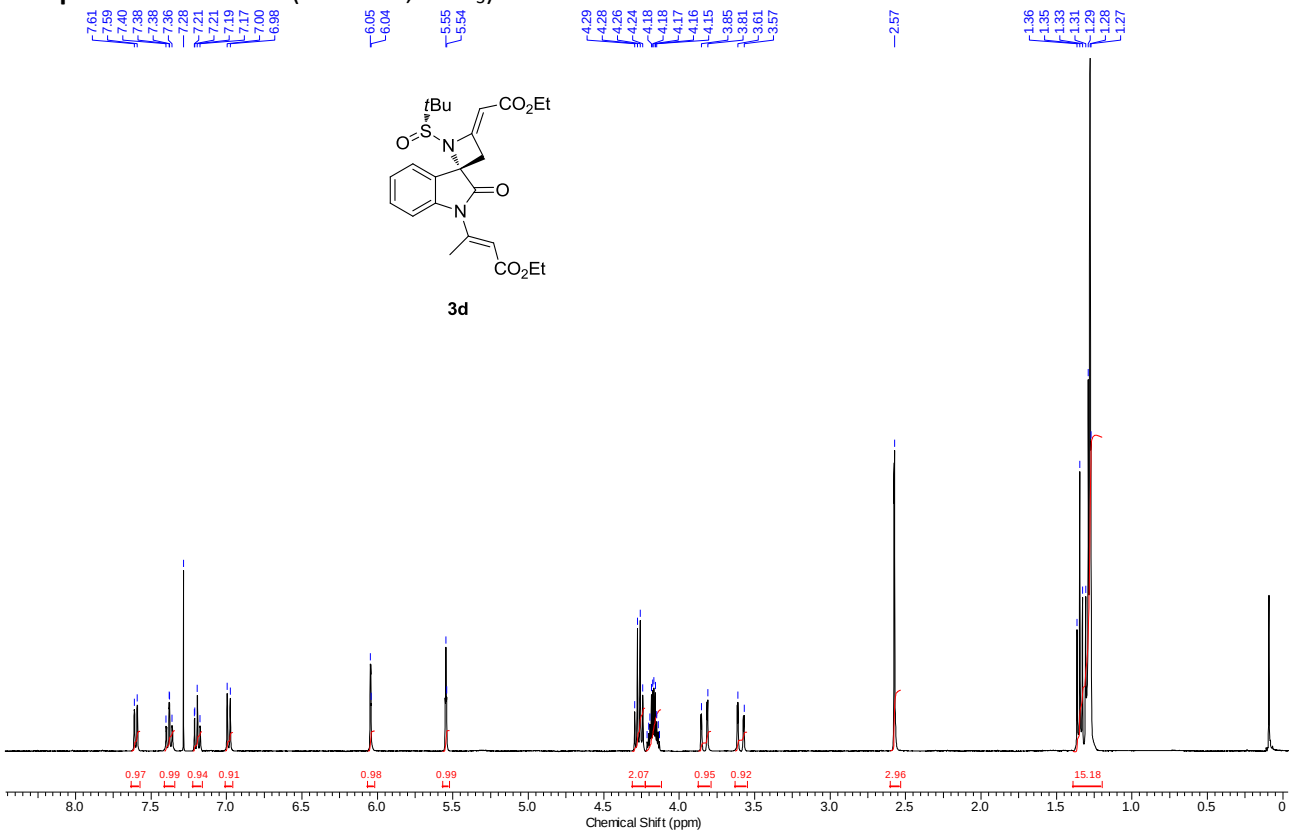


3c

Compound 3c: ^{13}C NMR (101 MHz, $CDCl_3$)

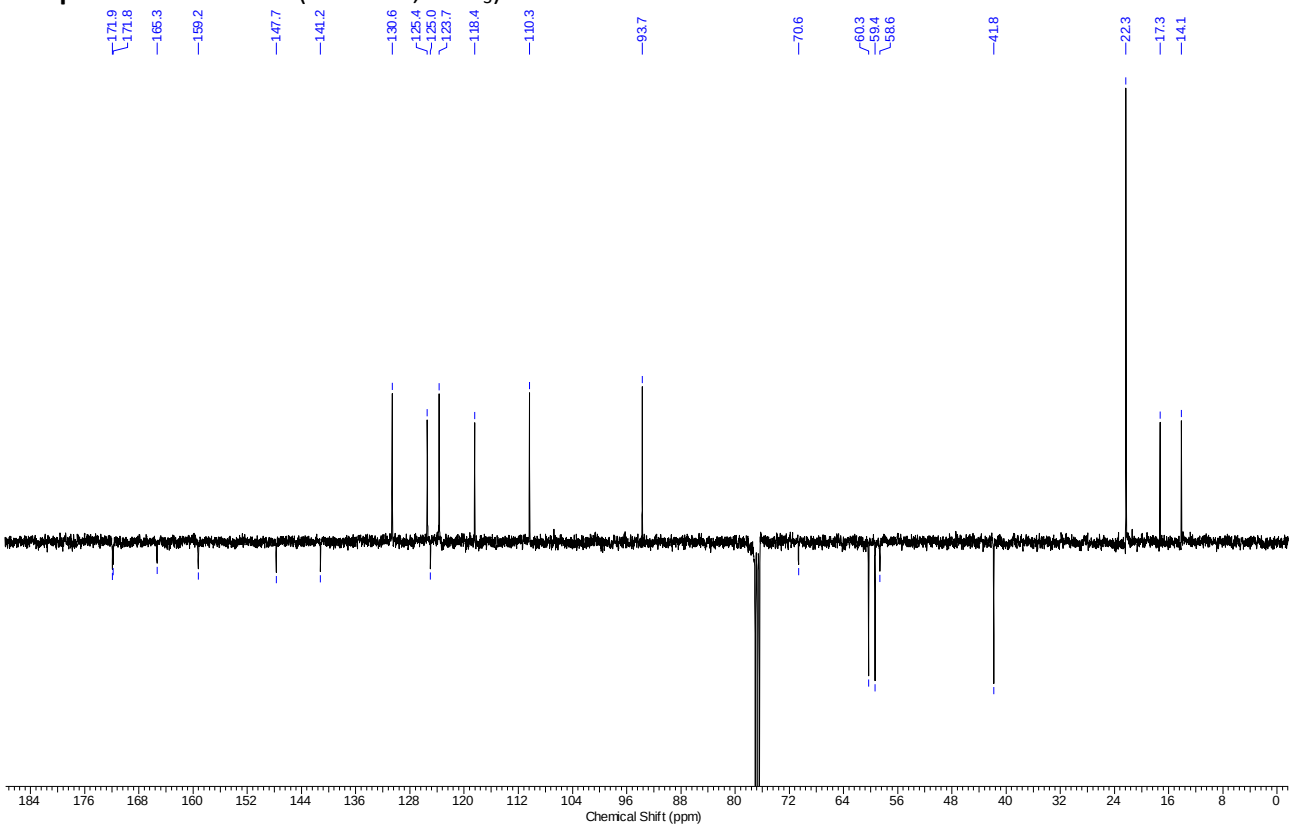


Compound 3d: ^{1}H NMR (400 MHz, $CDCl_3$)

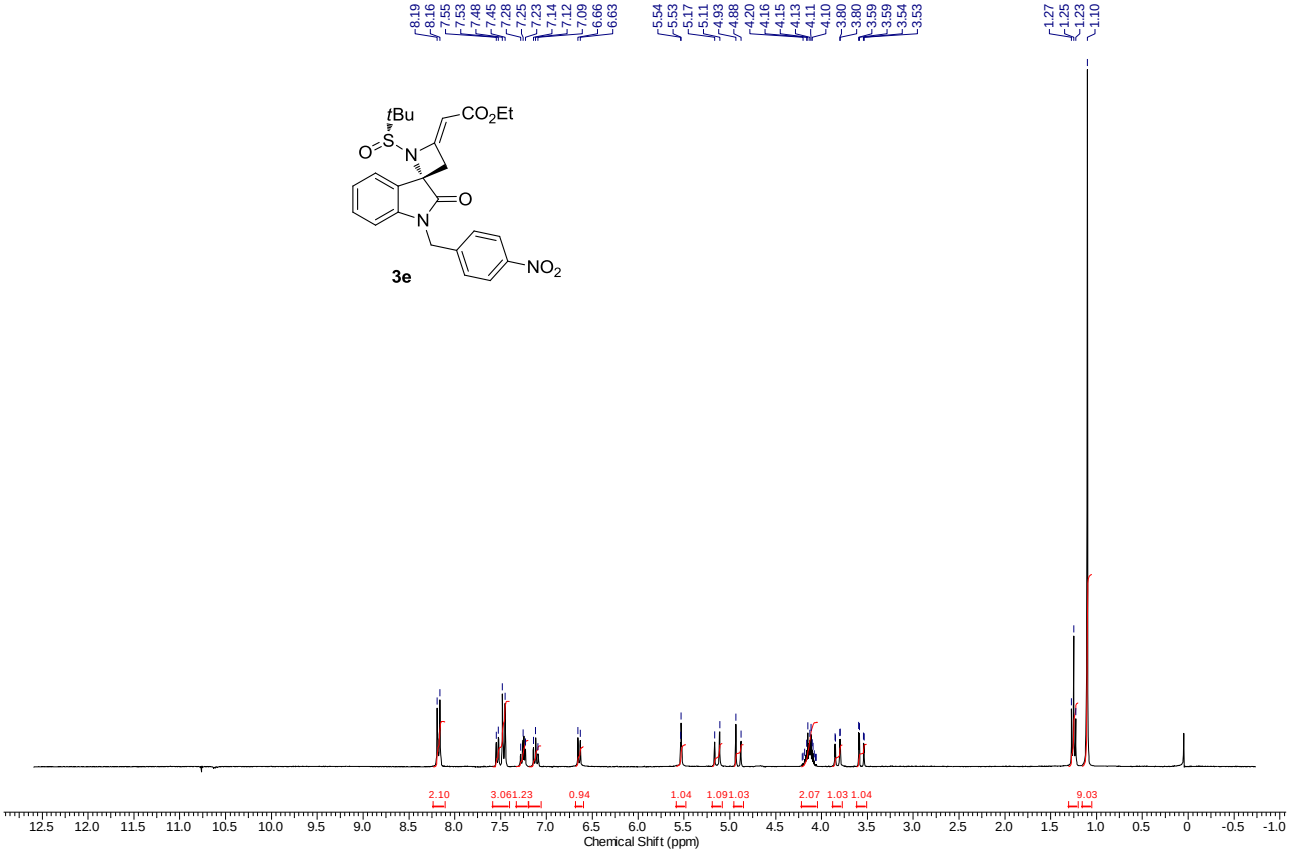


3d

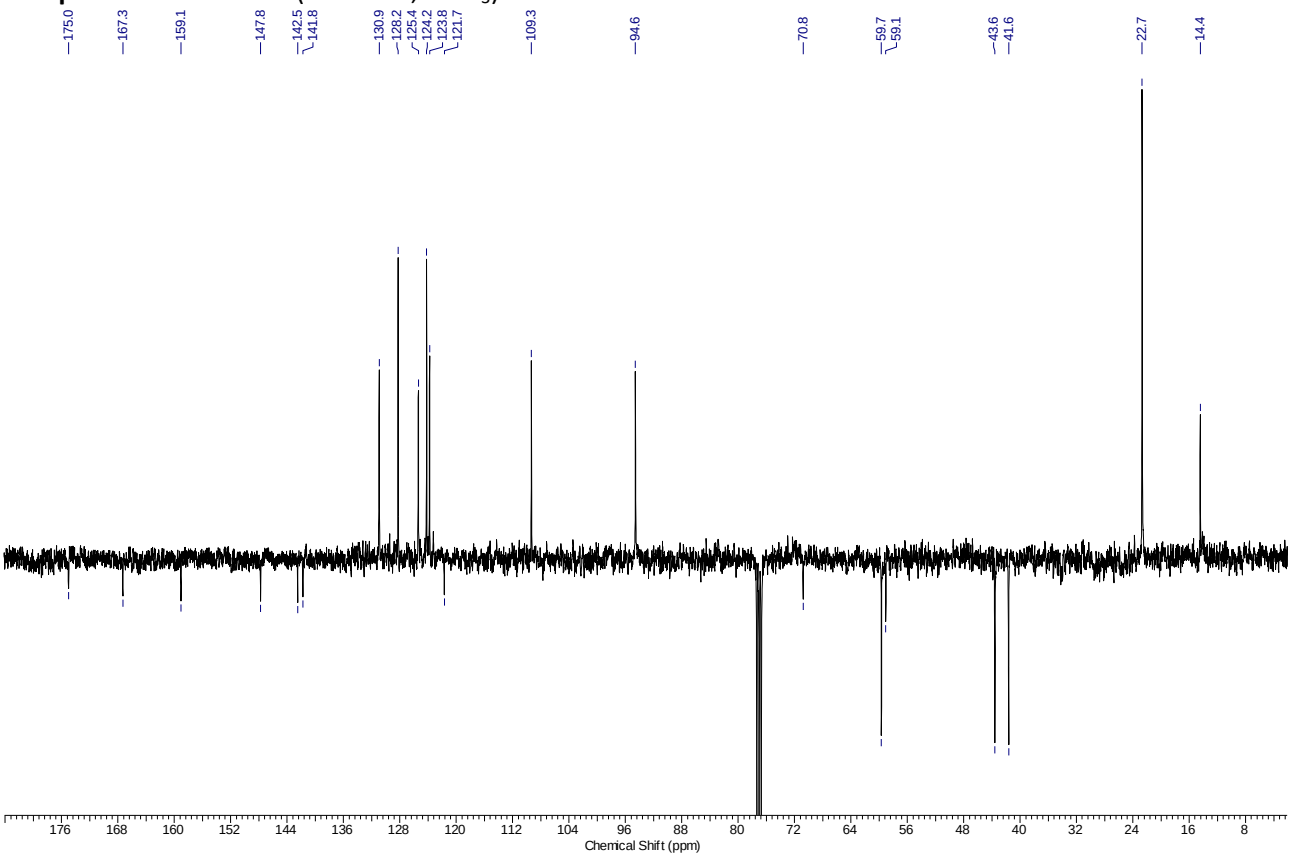
Compound 3d: ^{13}C NMR (101 MHz, $CDCl_3$)



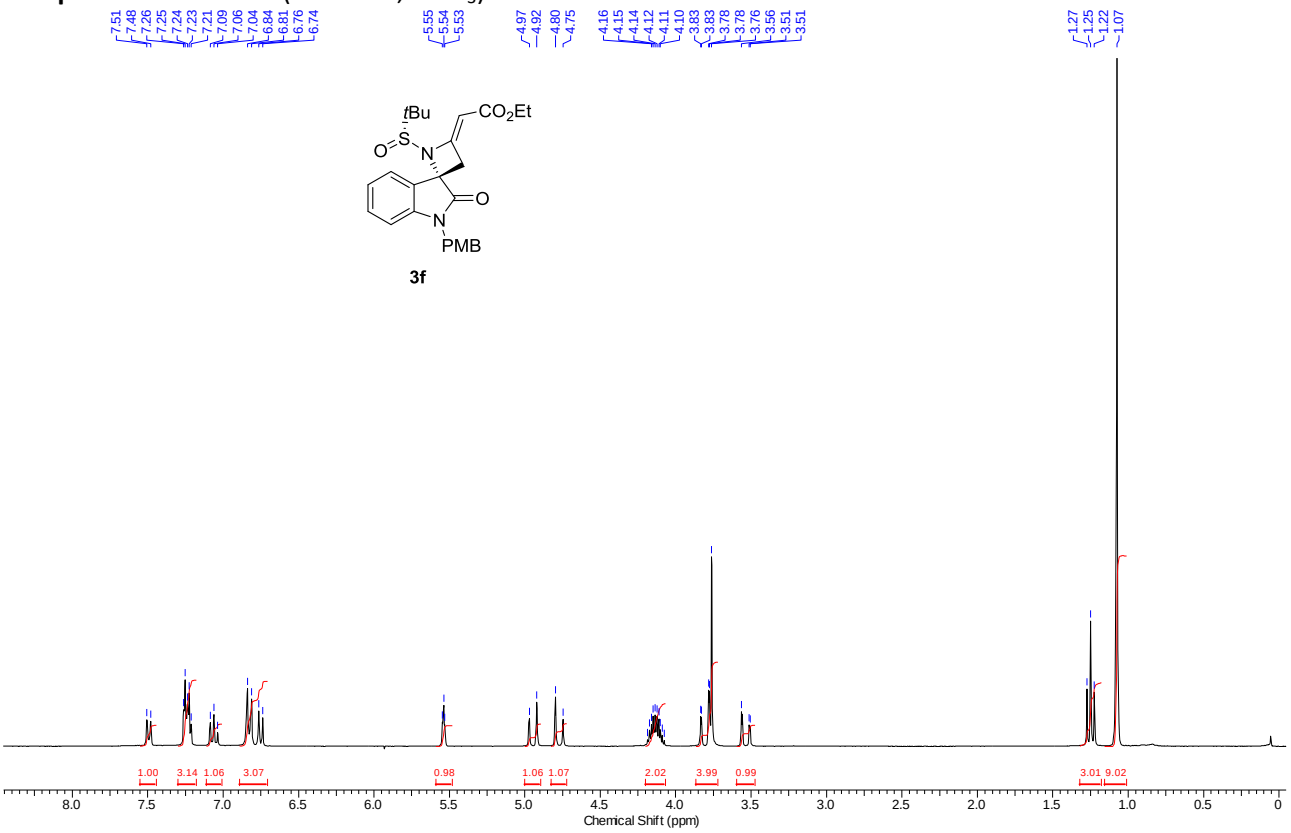
Compound 3e: ^{1}H NMR (300 MHz, $CDCl_3$)



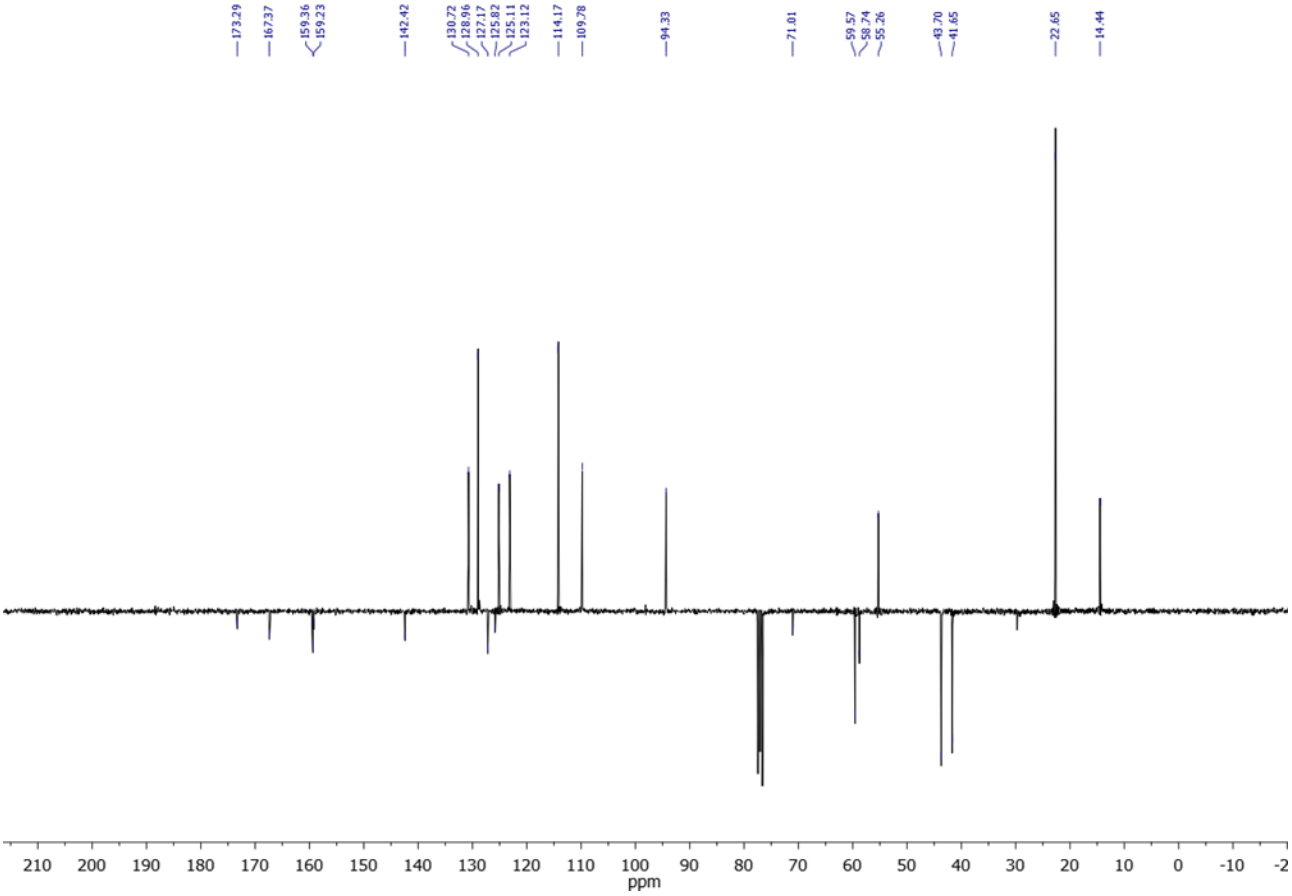
Compound 3e: ^{13}C NMR (101 MHz, $CDCl_3$)



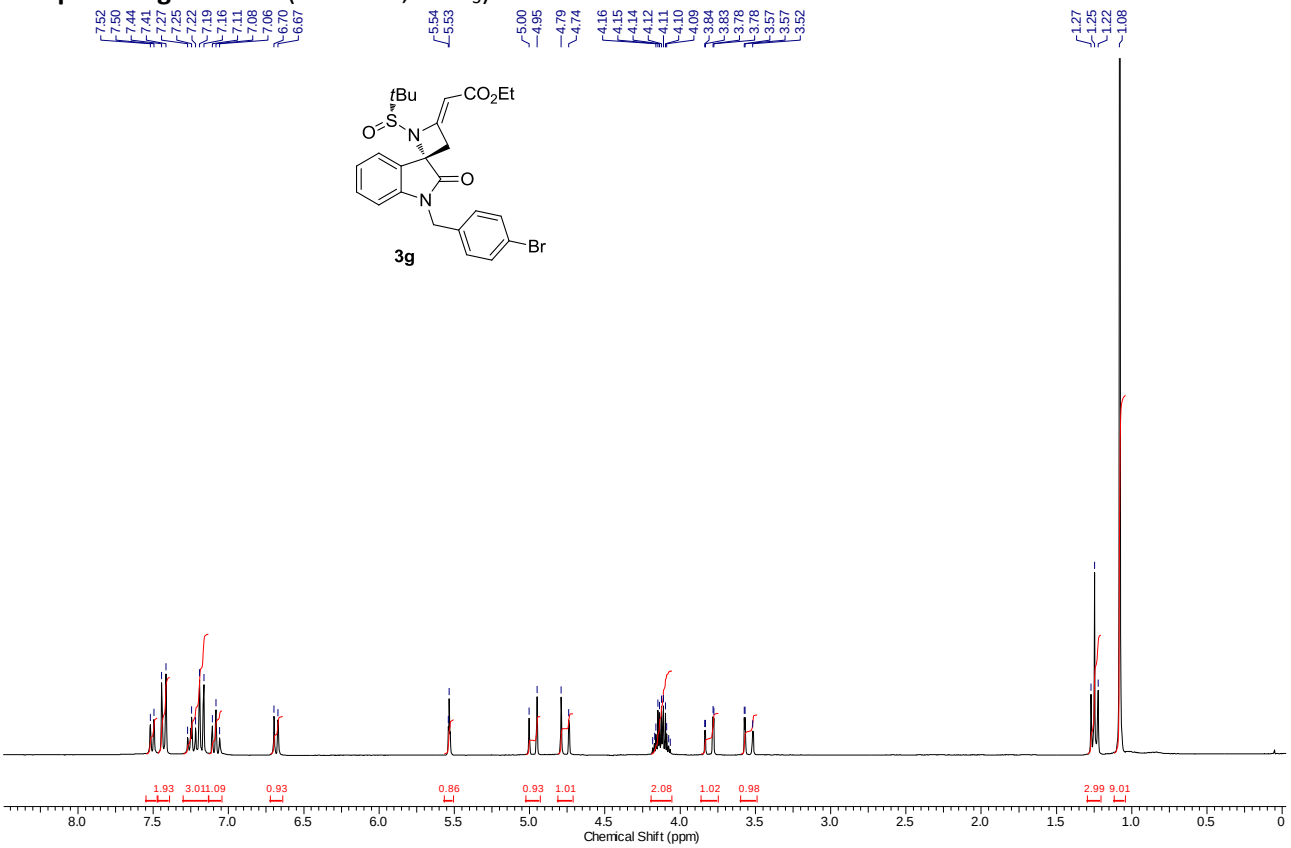
Compound 3f: ^{1}H NMR (300 MHz, $CDCl_3$)



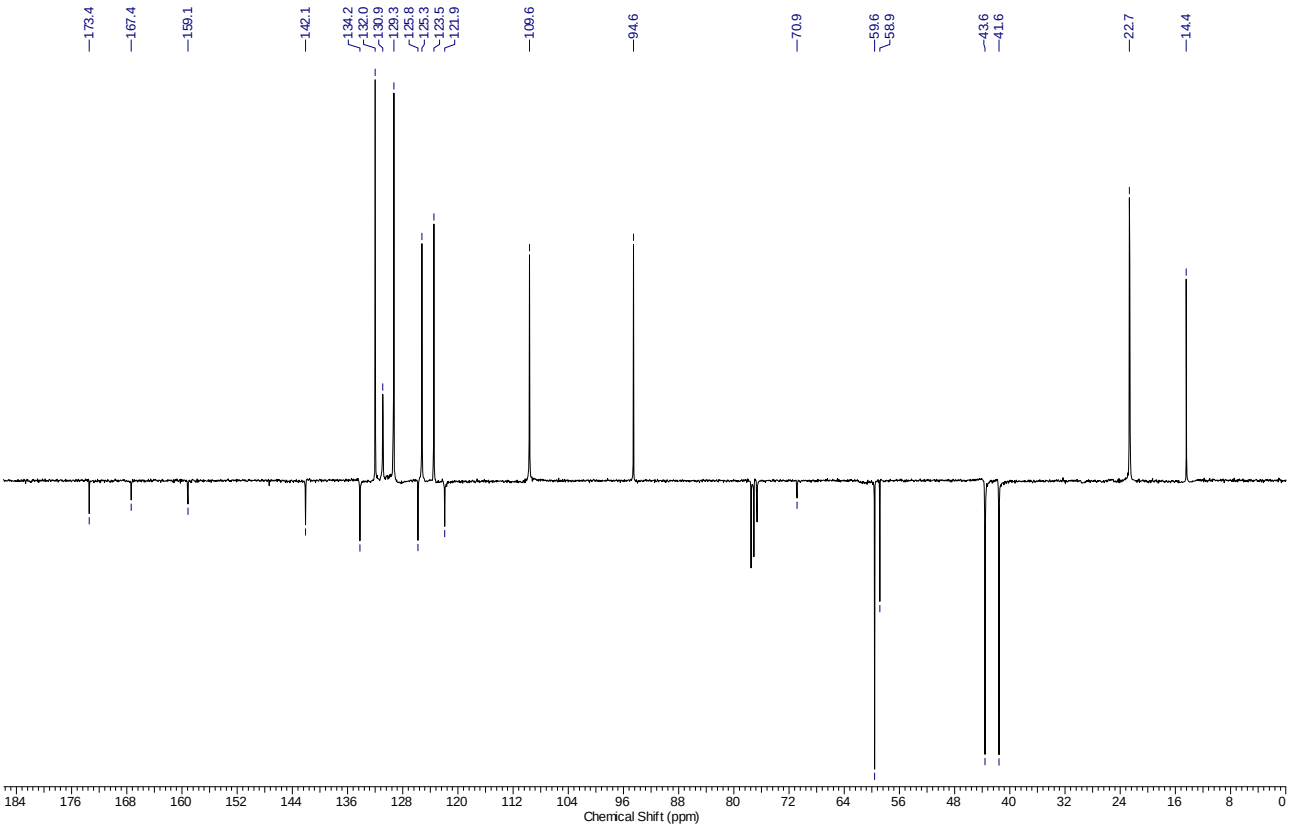
Compound 3f: ^{13}C NMR (75 MHz, $CDCl_3$)



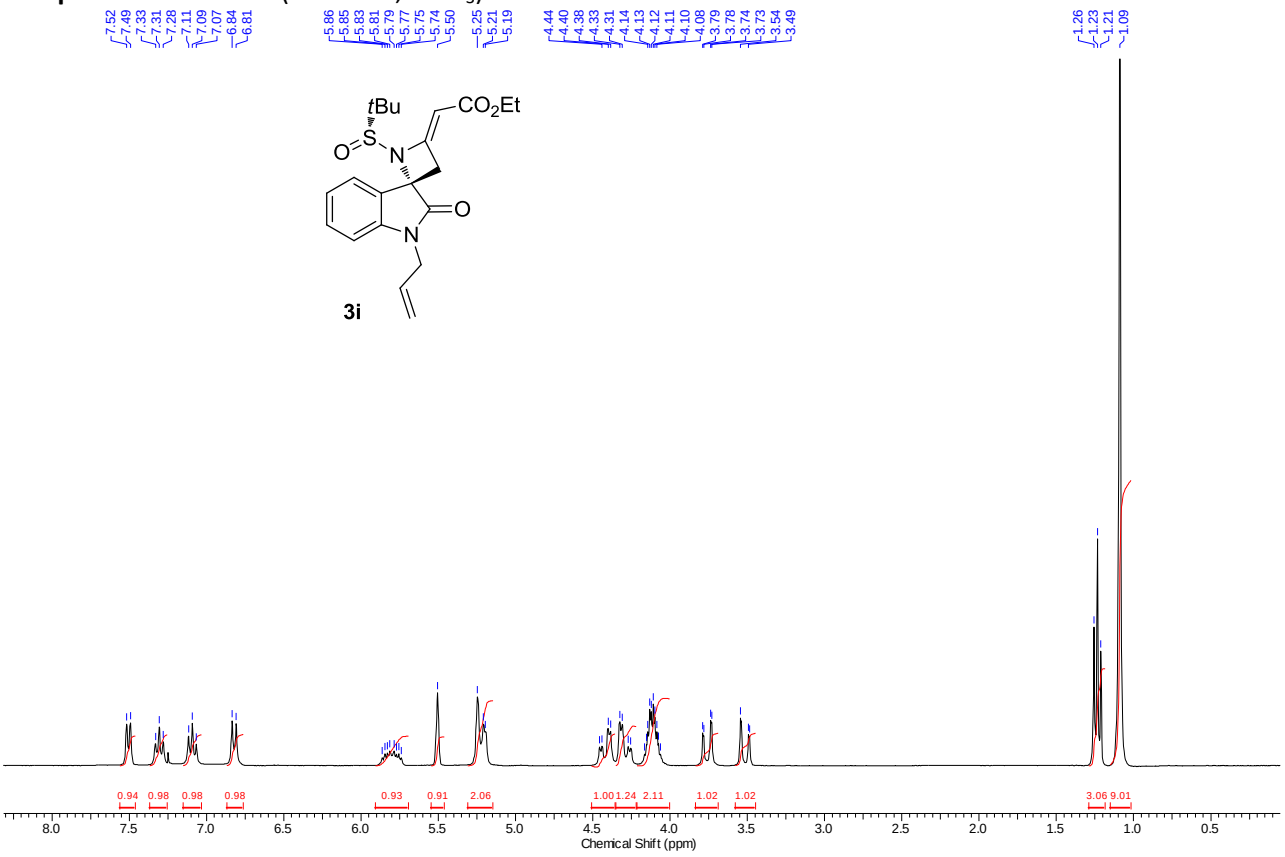
Compound 3g: ^{1}H NMR (300 MHz, $CDCl_3$)



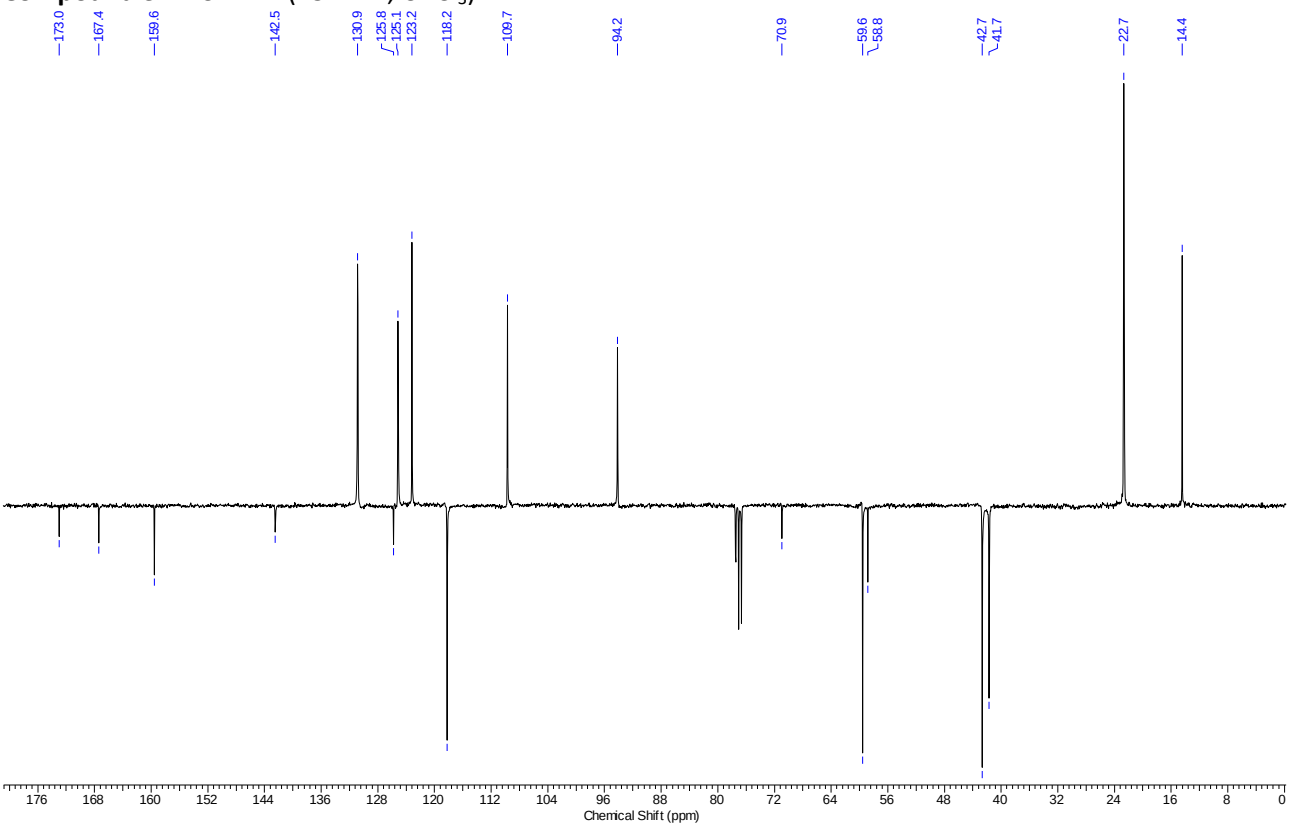
Compound 3g: ^{13}C NMR (75 MHz, $CDCl_3$)



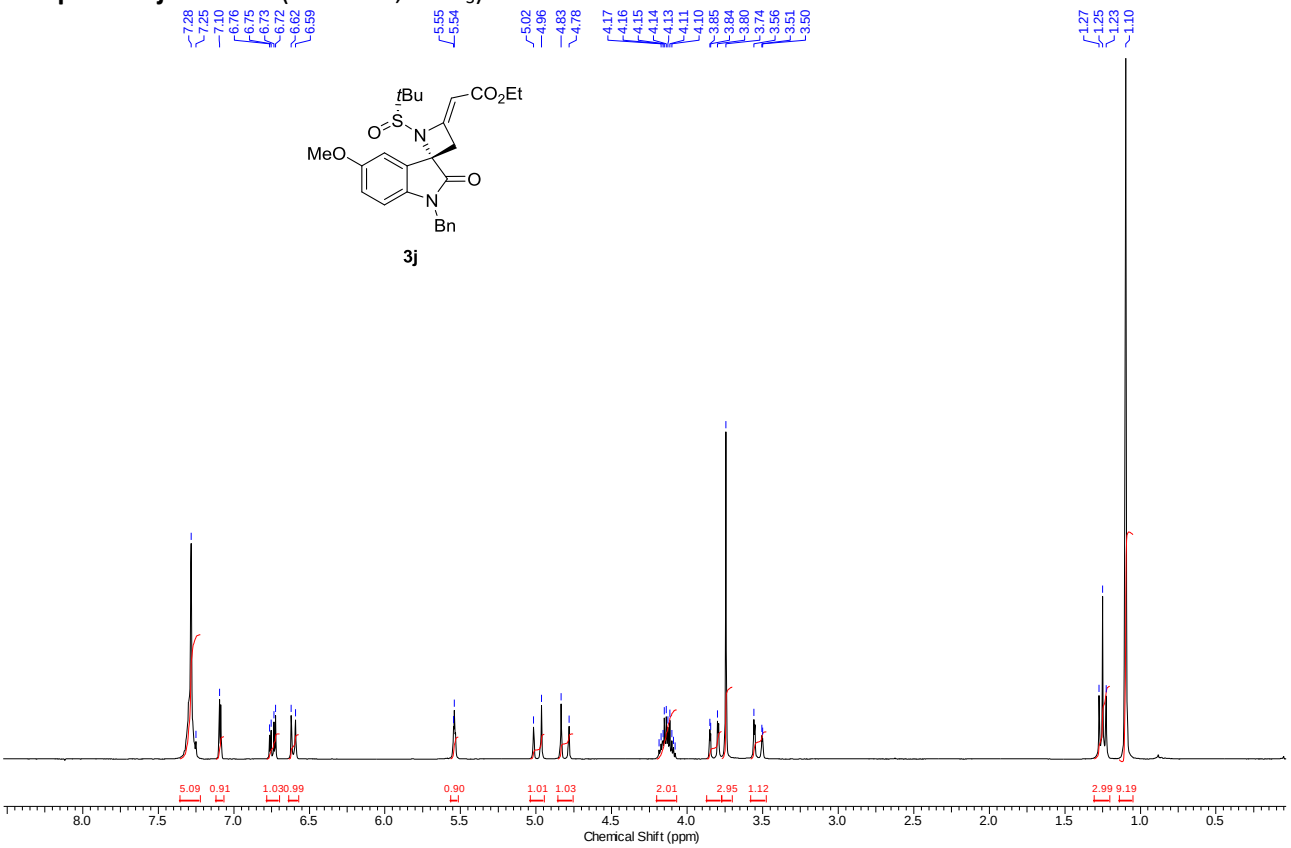
Compound 3i: ^{1}H NMR (300 MHz, $CDCl_3$)



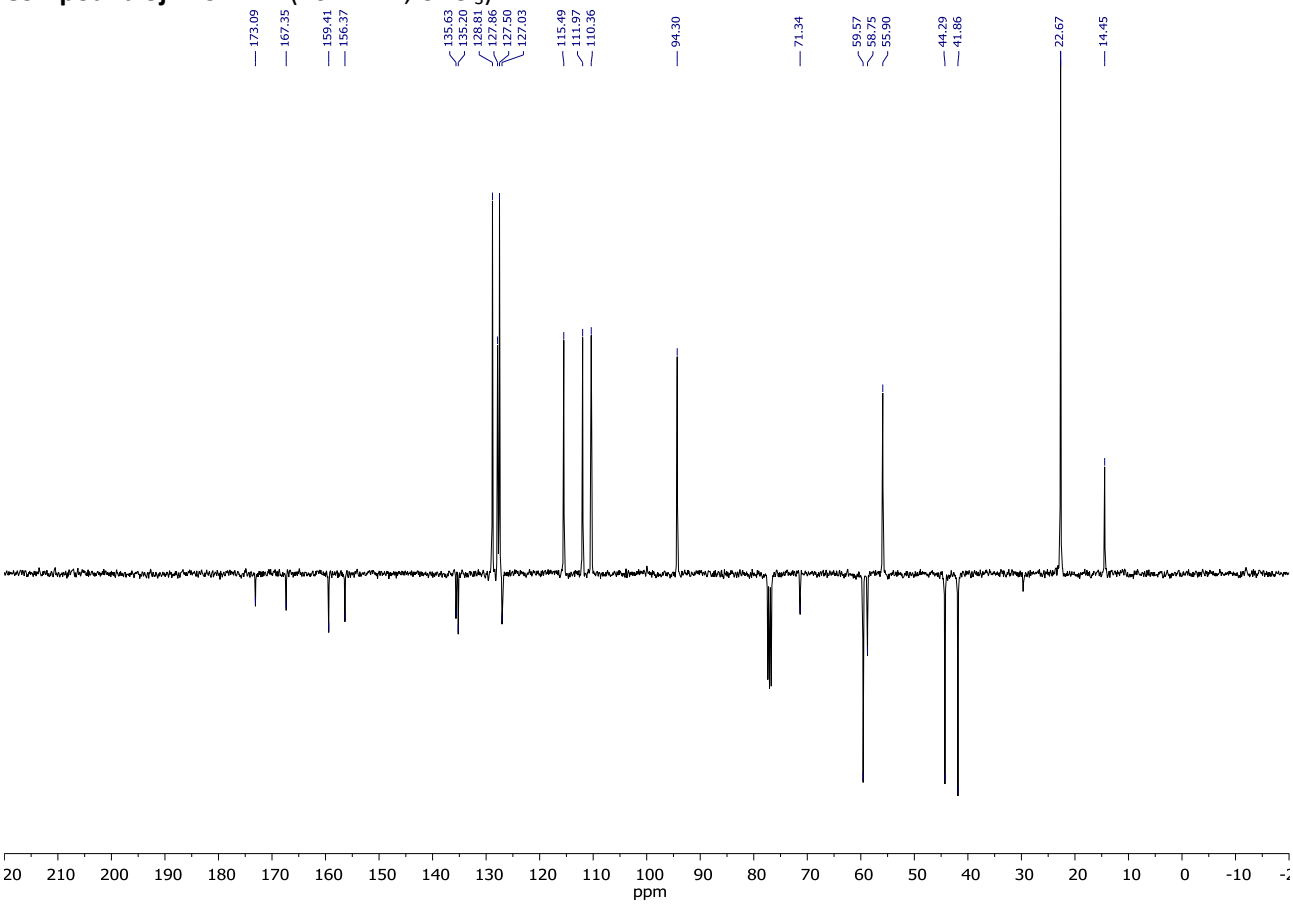
Compound 3i: ^{13}C NMR (75 MHz, $CDCl_3$)



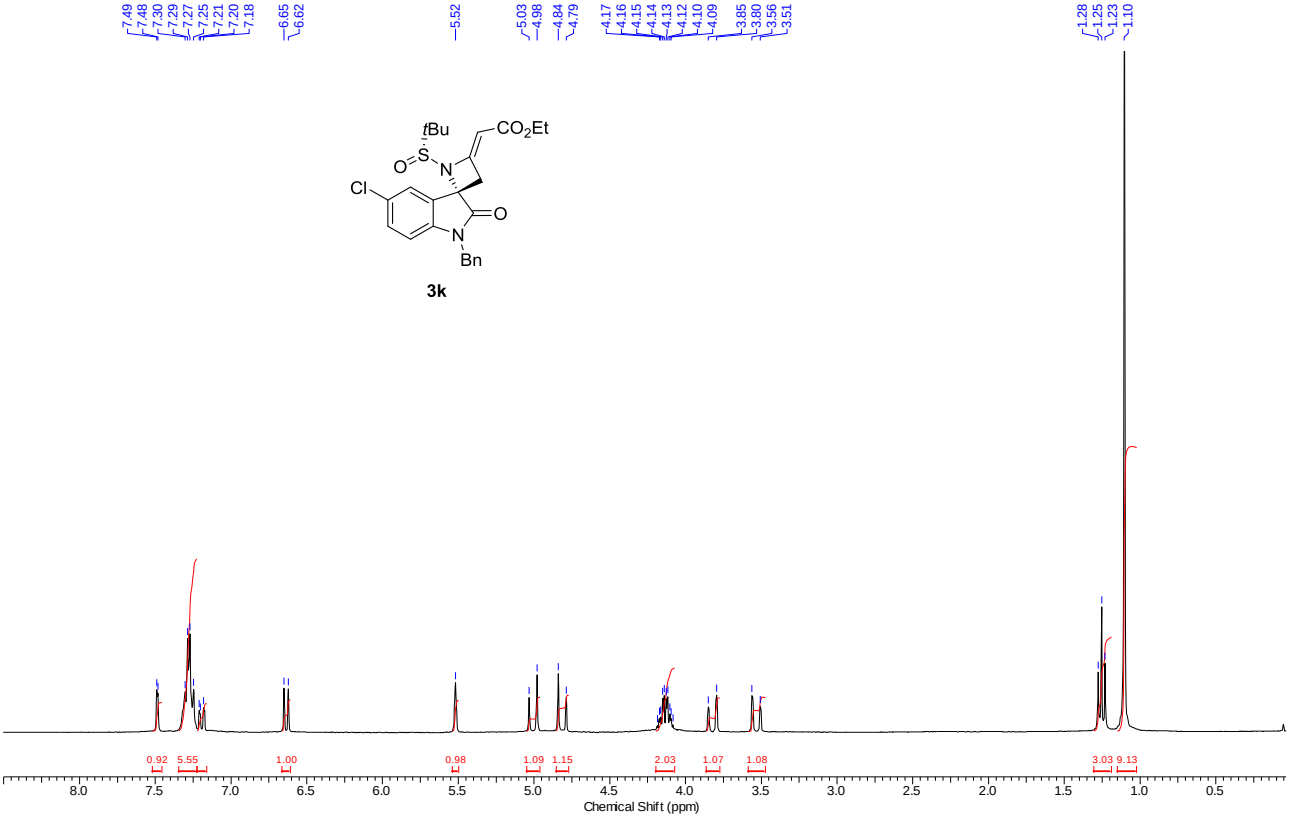
Compound 3j: ^{1}H NMR (300 MHz, $CDCl_3$)



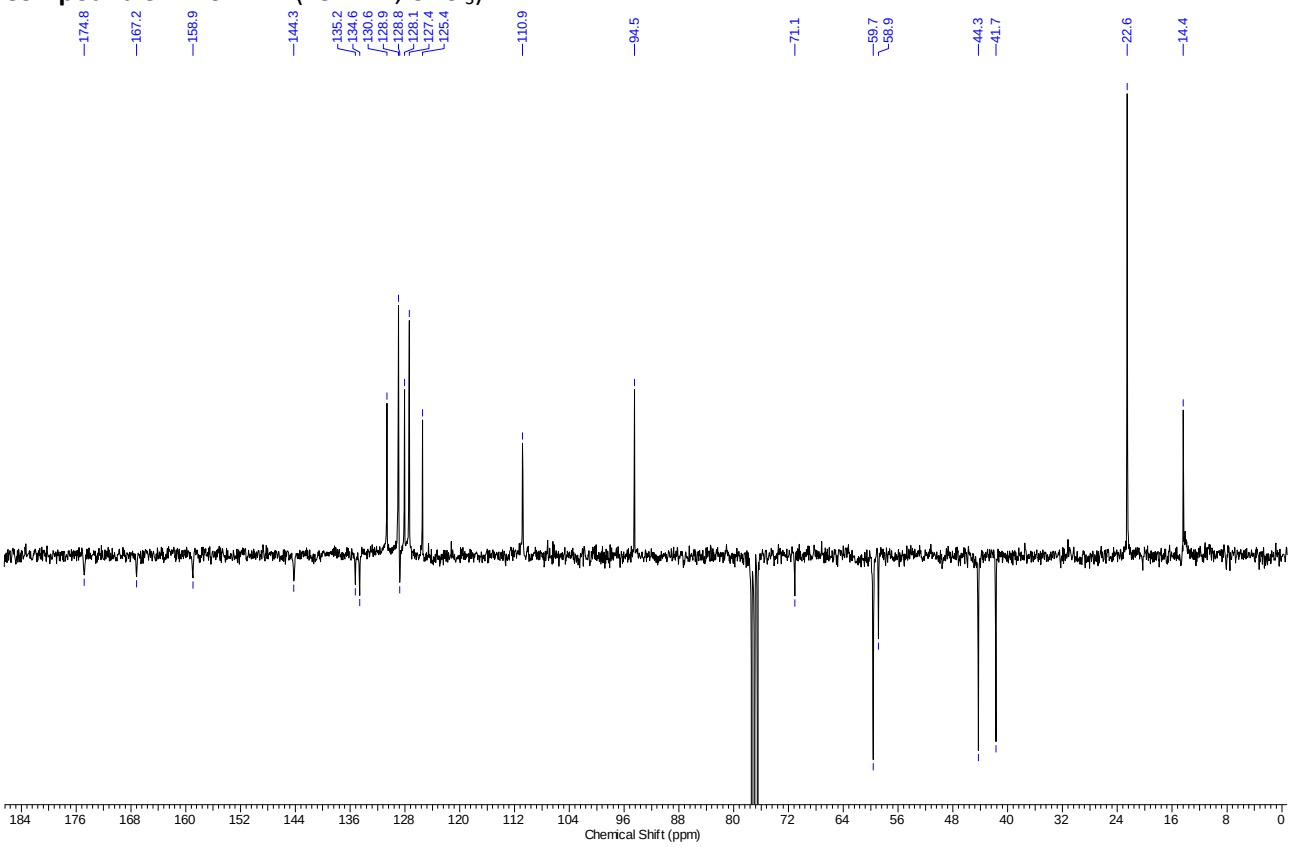
Compound 3j: ^{13}C NMR (101 MHz, $CDCl_3$)



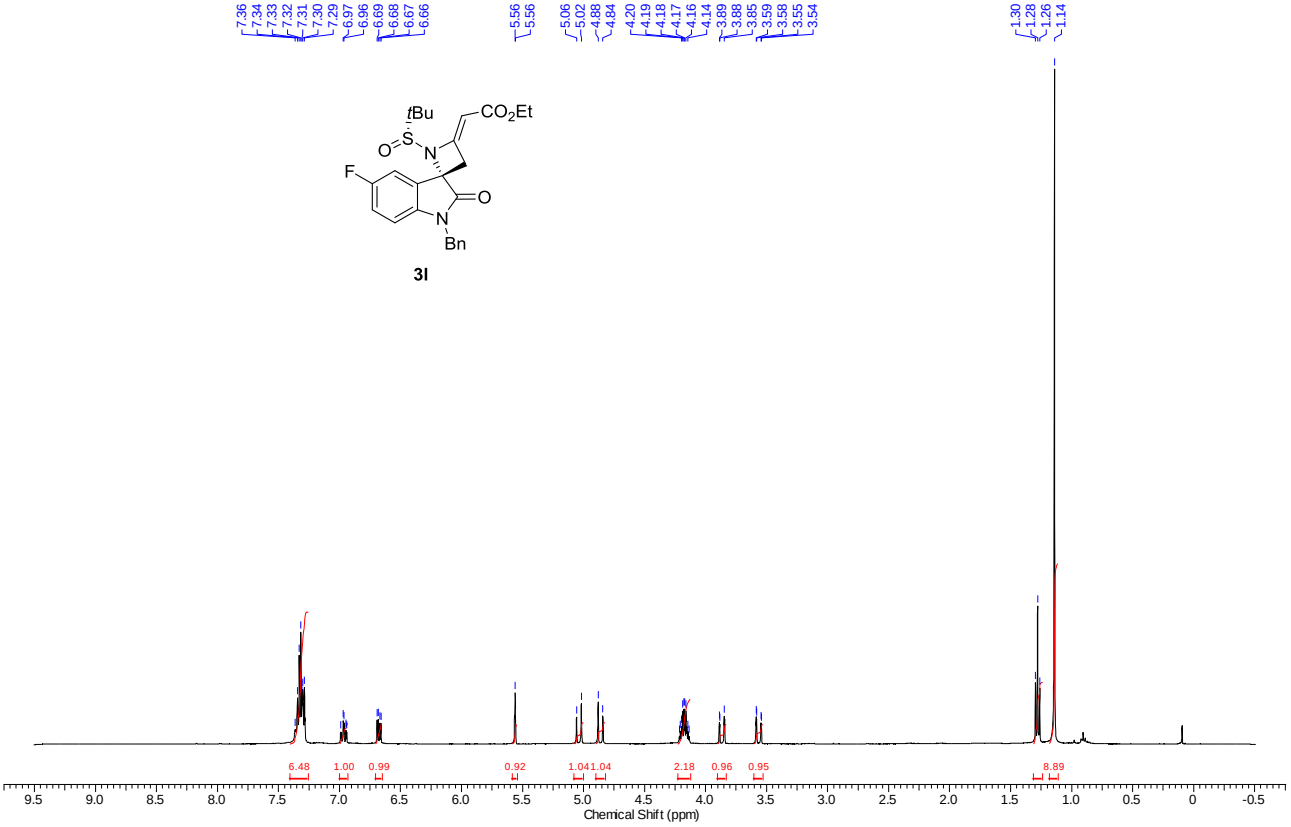
Compound 3k: ^{1}H NMR (300 MHz, $CDCl_3$)



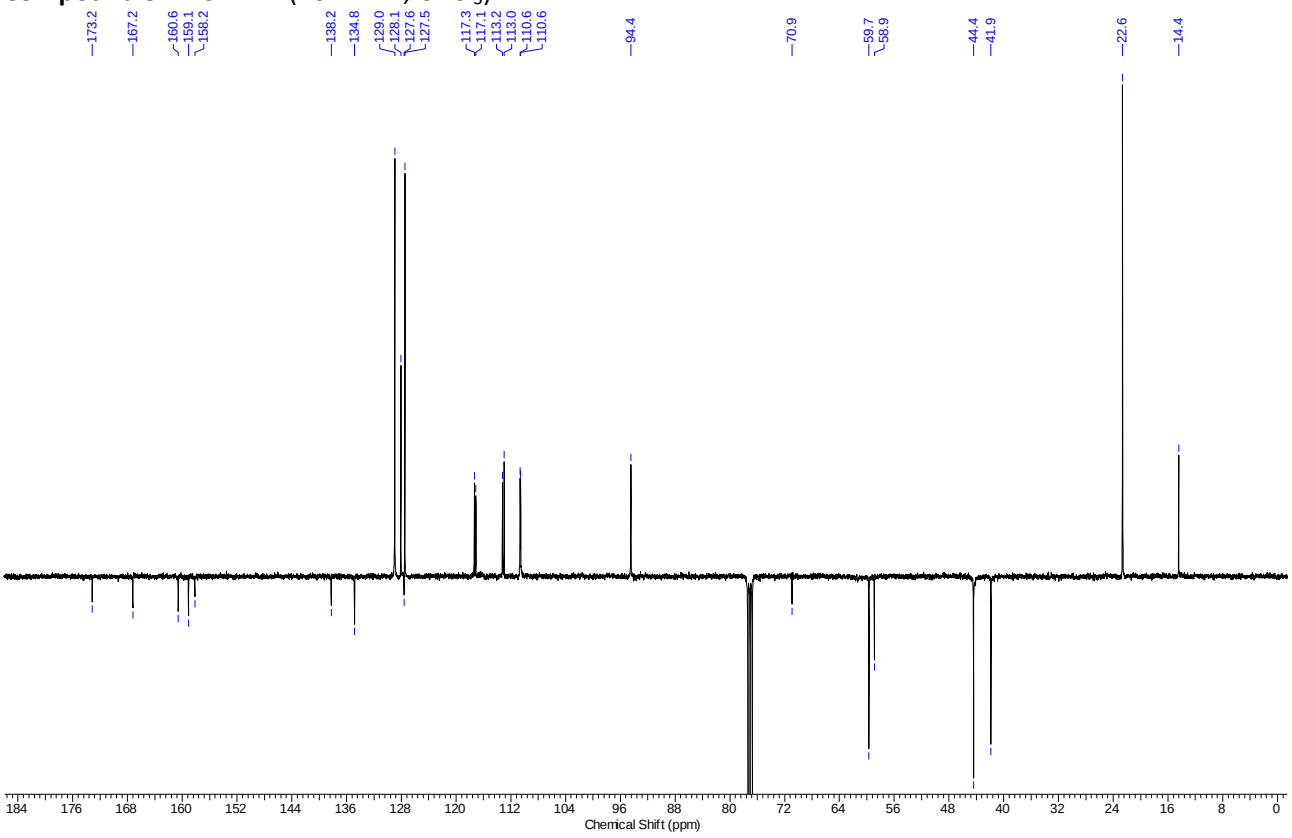
Compound 3k: ^{13}C NMR (75 MHz, $CDCl_3$)



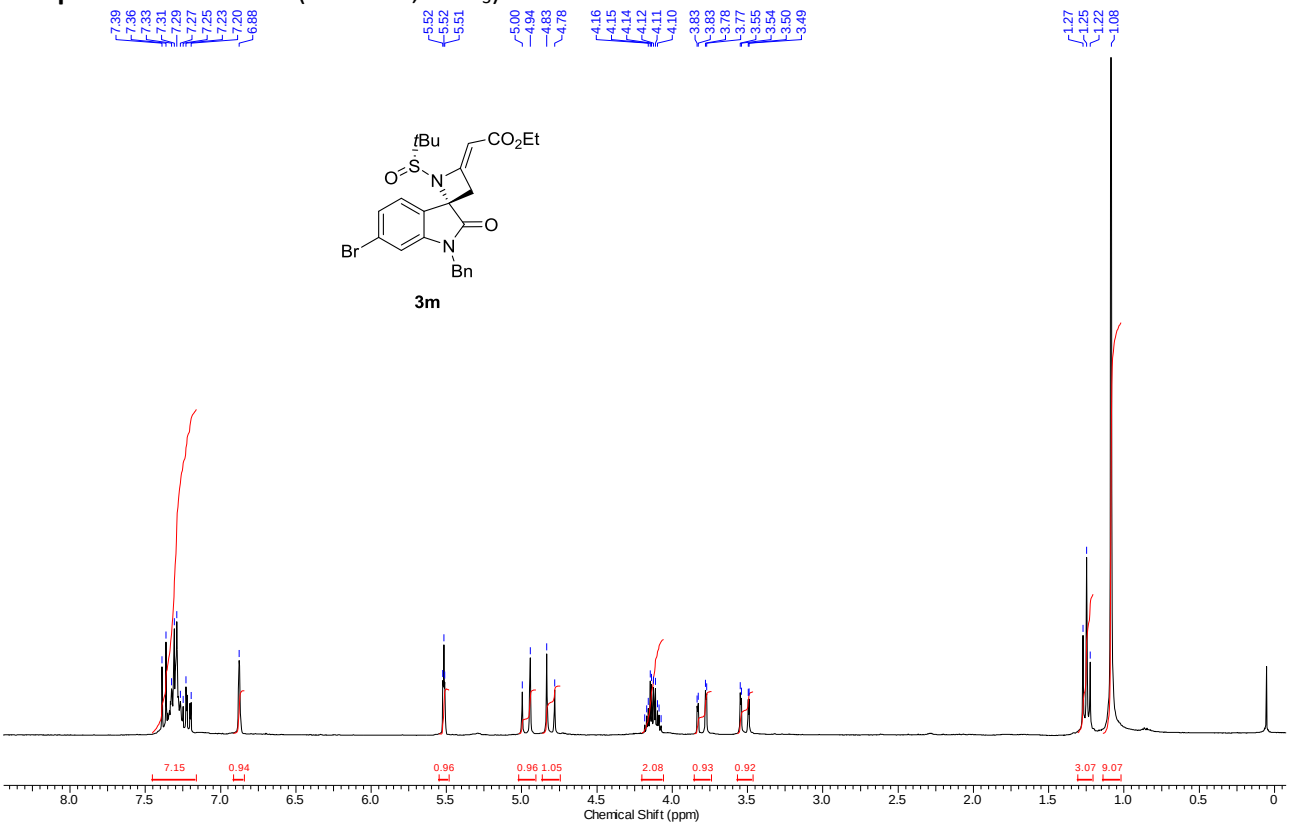
Compound 3l: ^{1}H NMR (400 MHz, $CDCl_3$)



Compound 3l: ^{13}C NMR (101 MHz, $CDCl_3$)

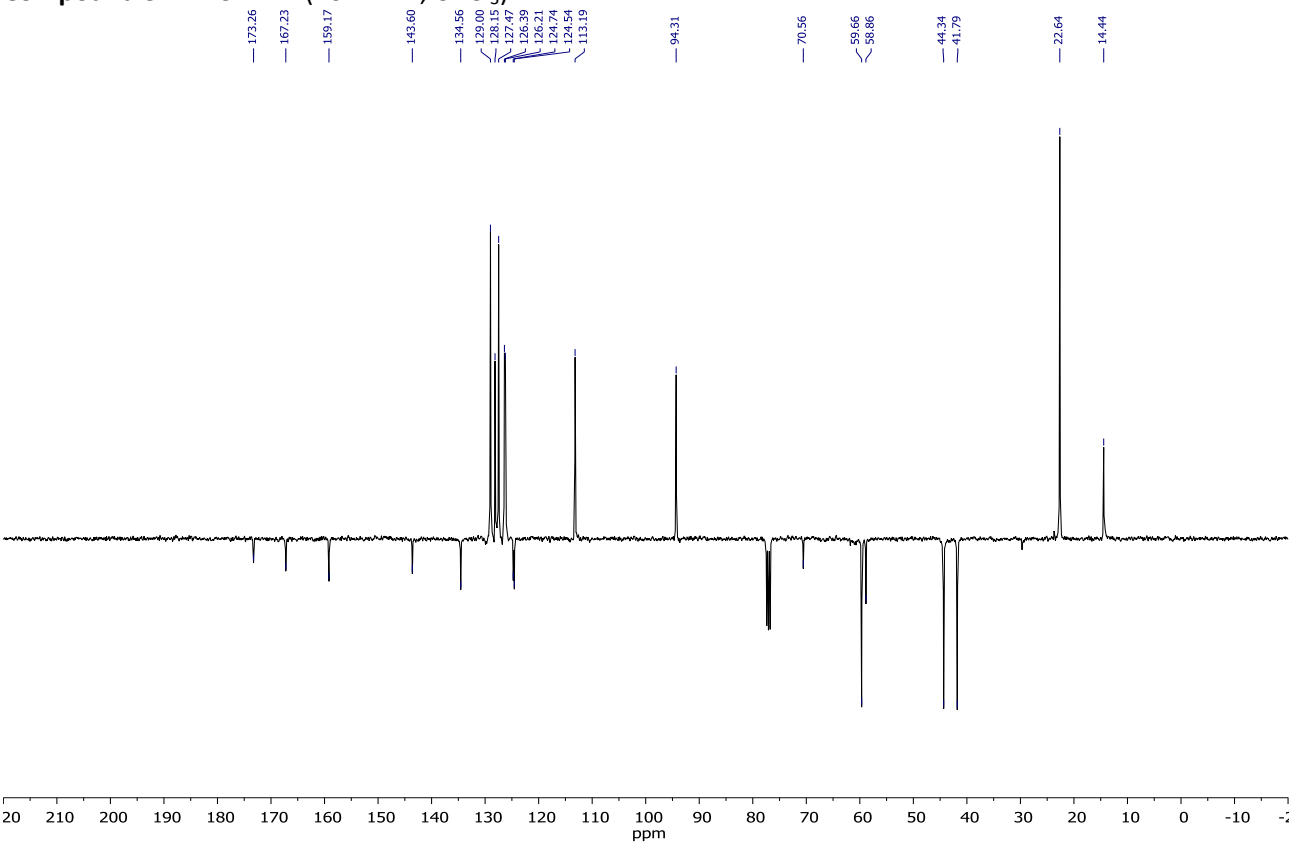


Compound 3m: ^{1}H NMR (300 MHz, $CDCl_3$)

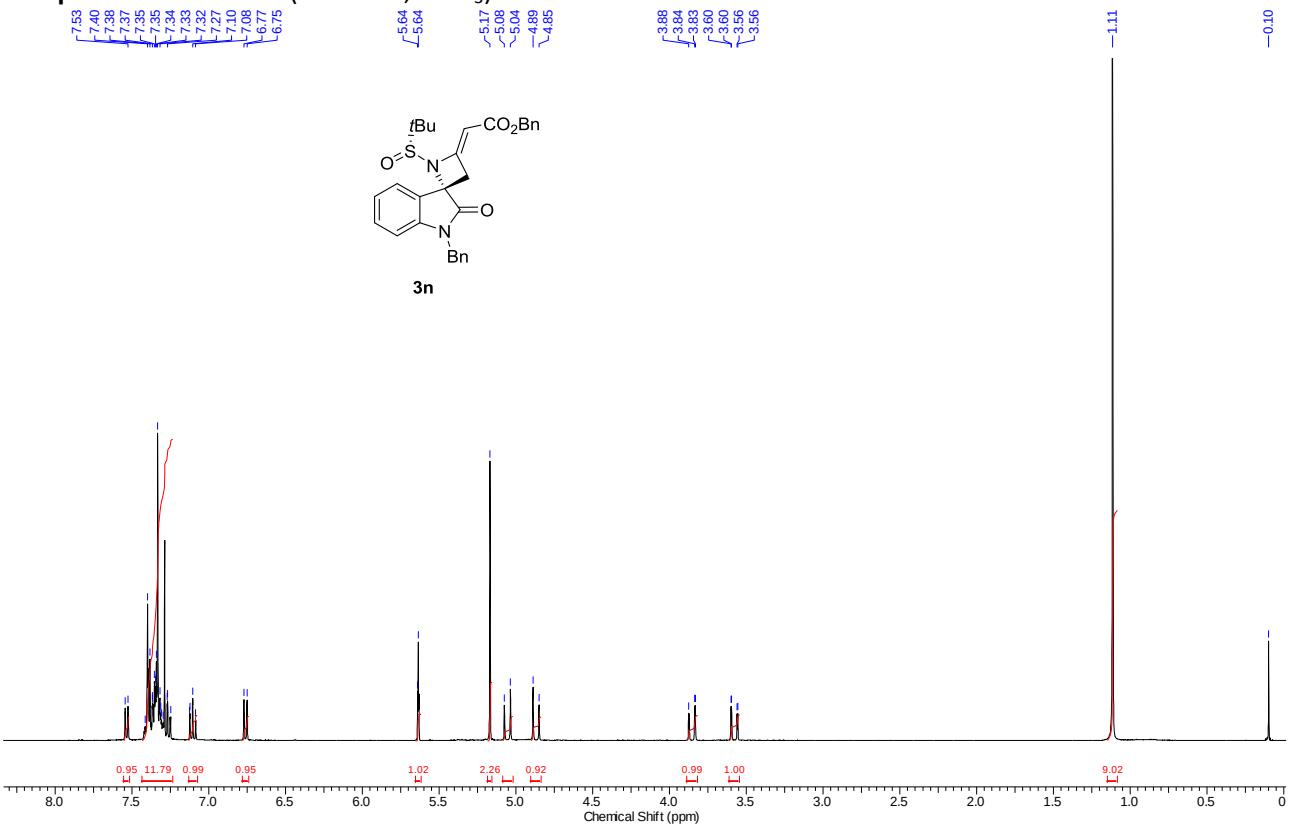


3m

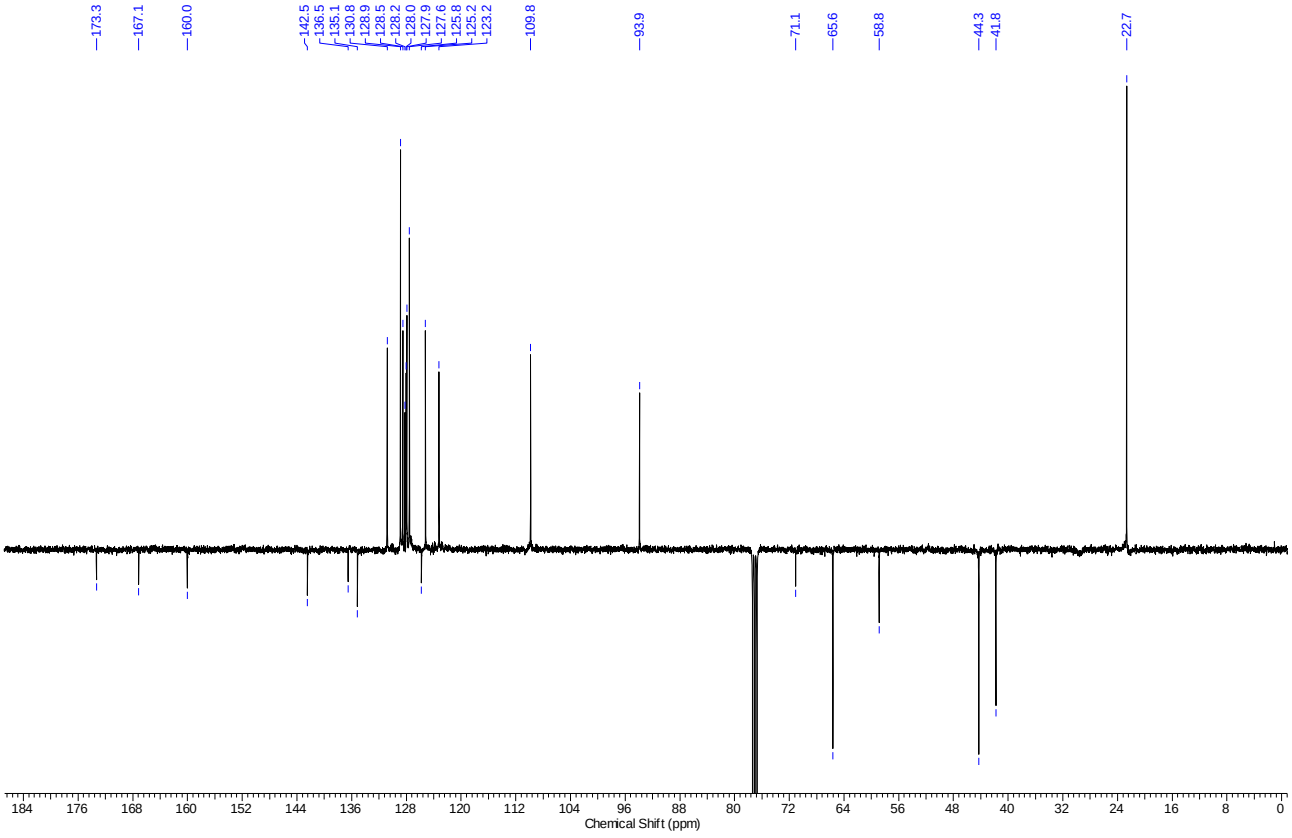
Compound 3m: ^{13}C NMR (101 MHz, $CDCl_3$)



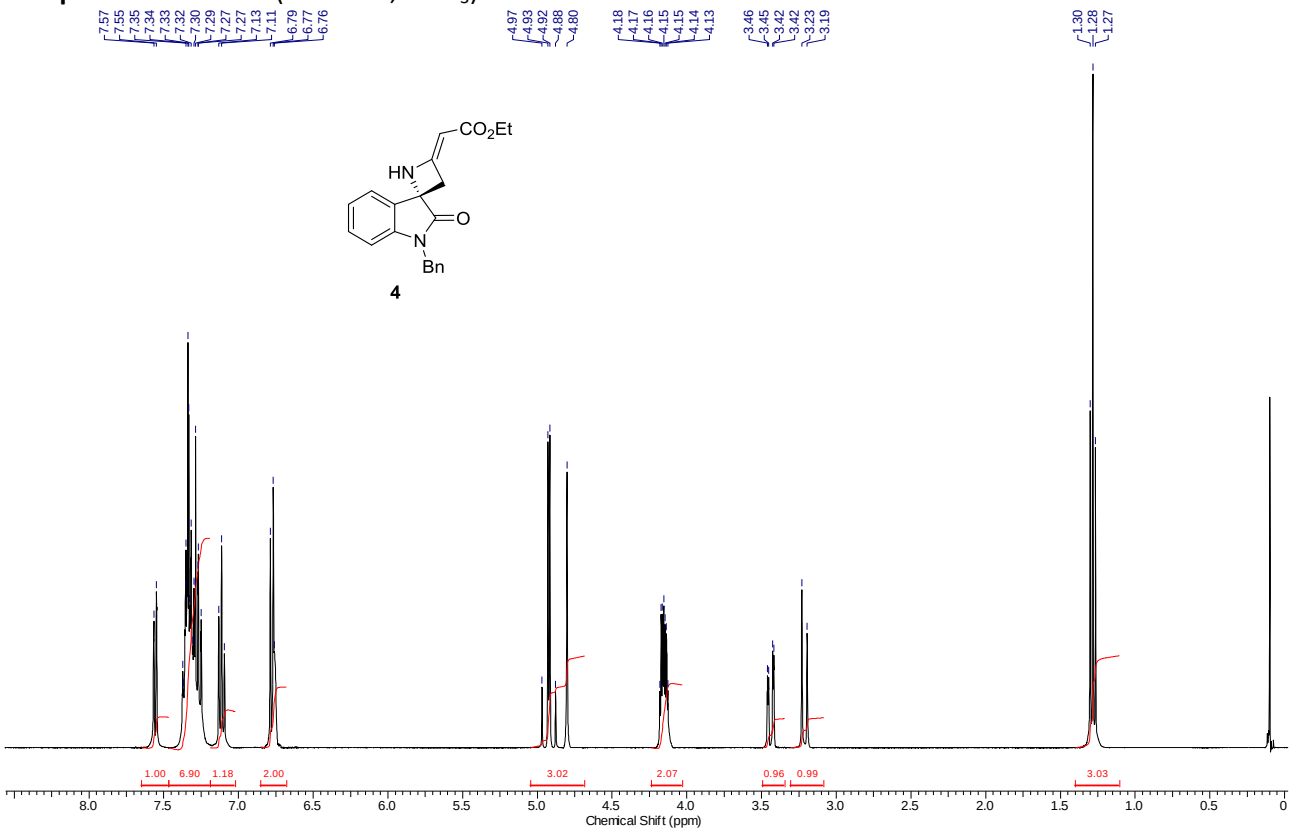
Compound 3n: ^{1}H NMR (400 MHz, $CDCl_3$)



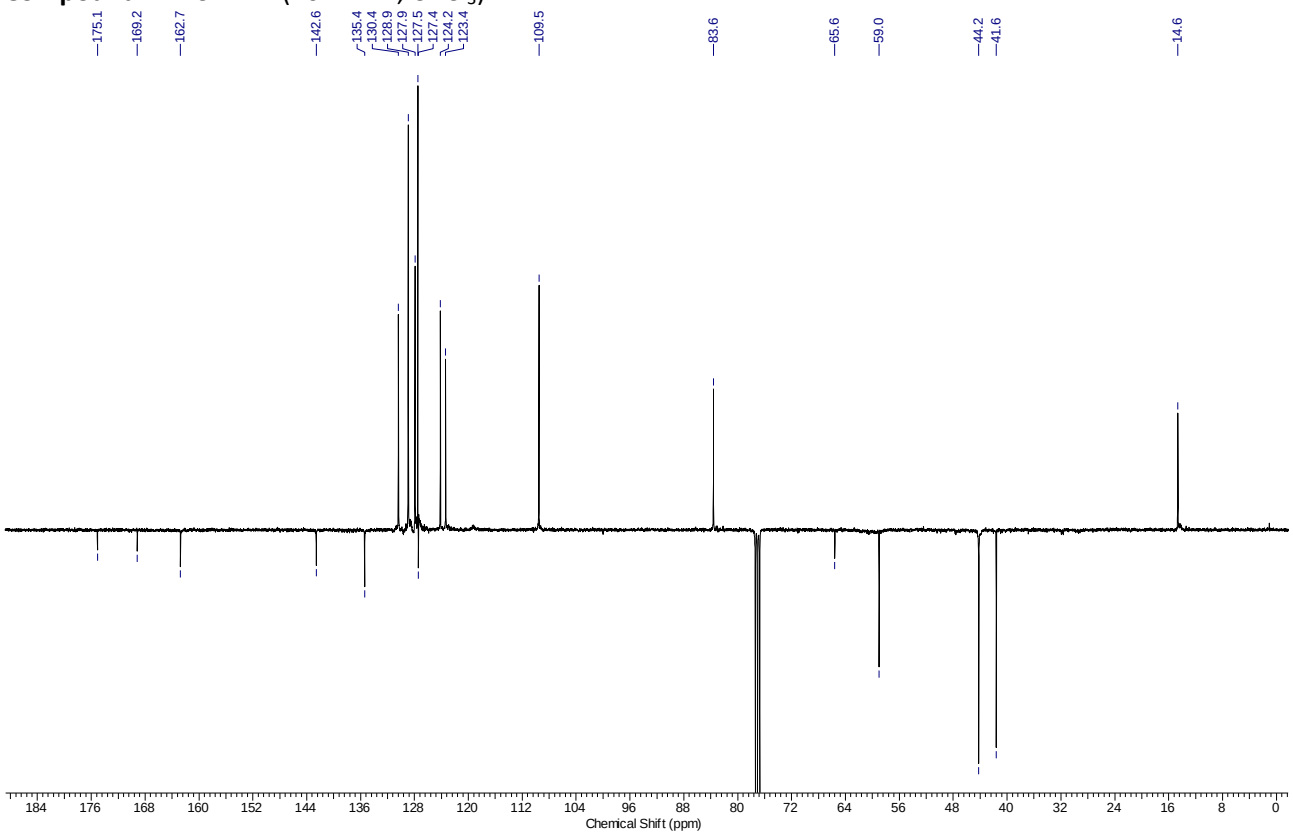
Compound 3n: ^{13}C NMR (100 MHz, $CDCl_3$)



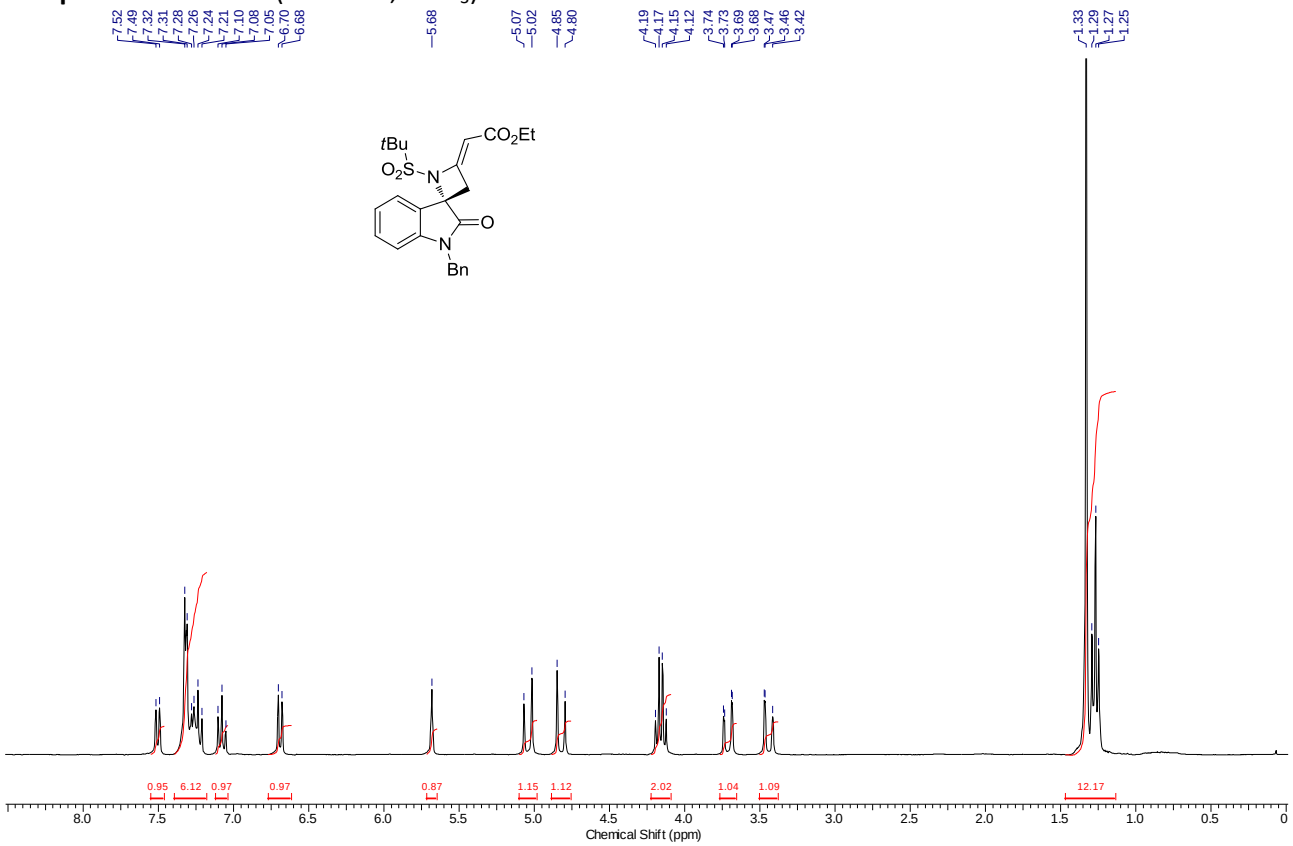
Compound 4: ^{1}H NMR (400 MHz, $CDCl_3$)



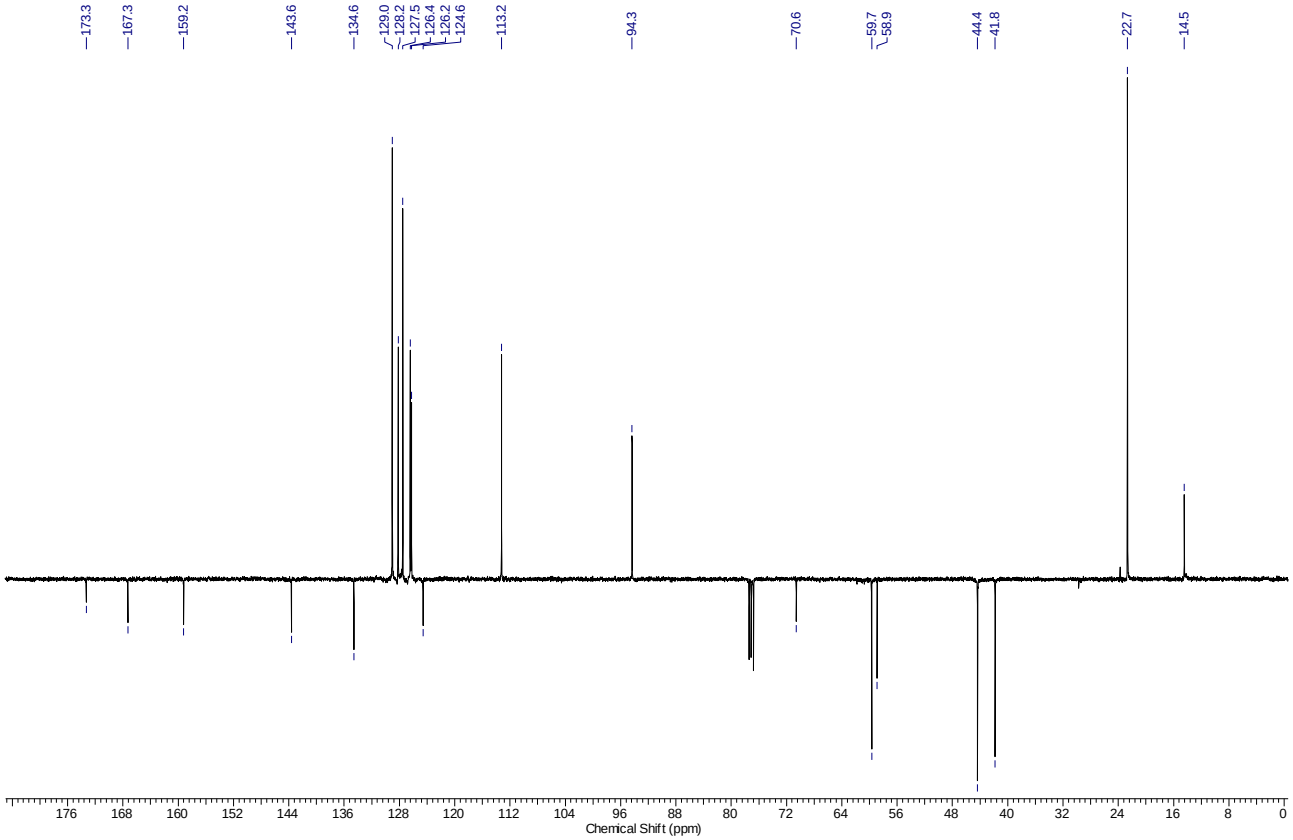
Compound 4: ^{13}C NMR (101 MHz, $CDCl_3$)



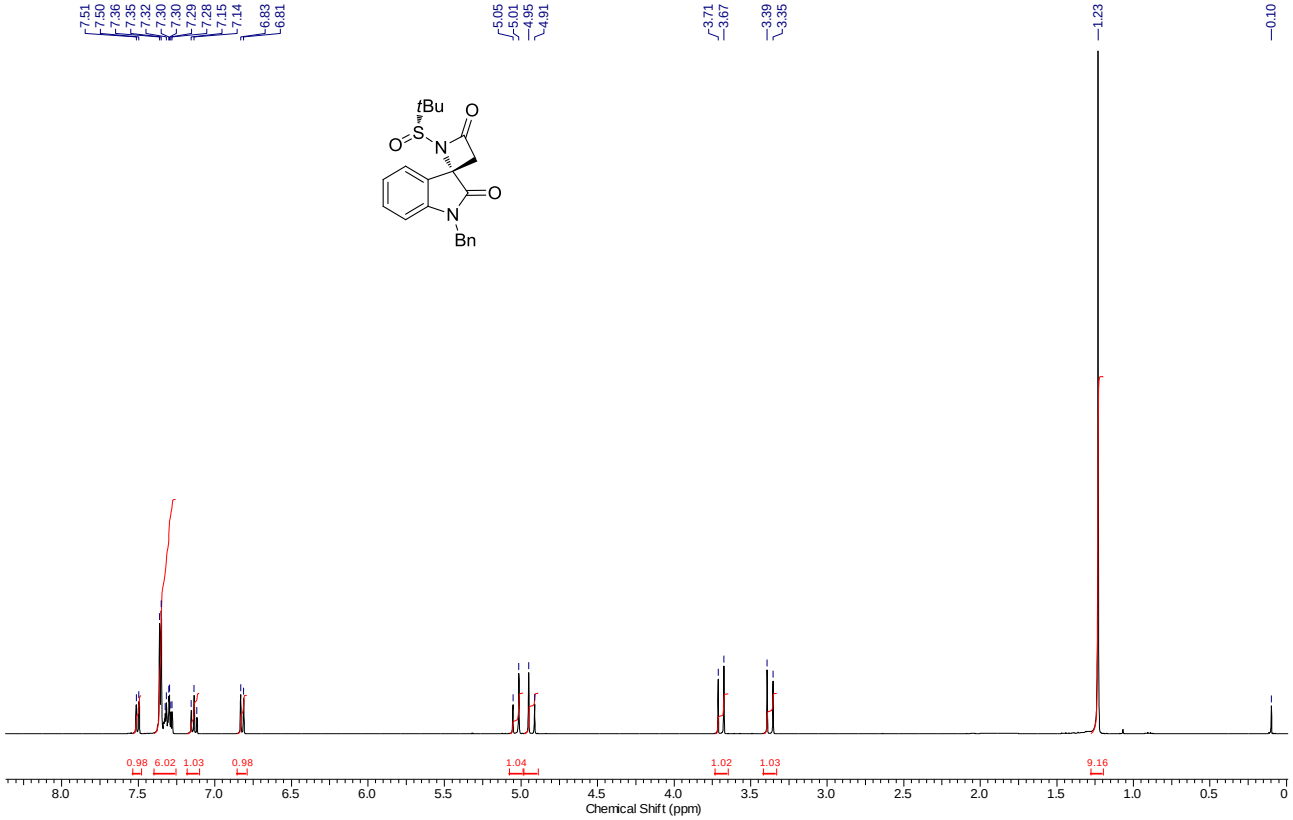
Compound 5: ^{1}H NMR (300 MHz, $CDCl_3$)



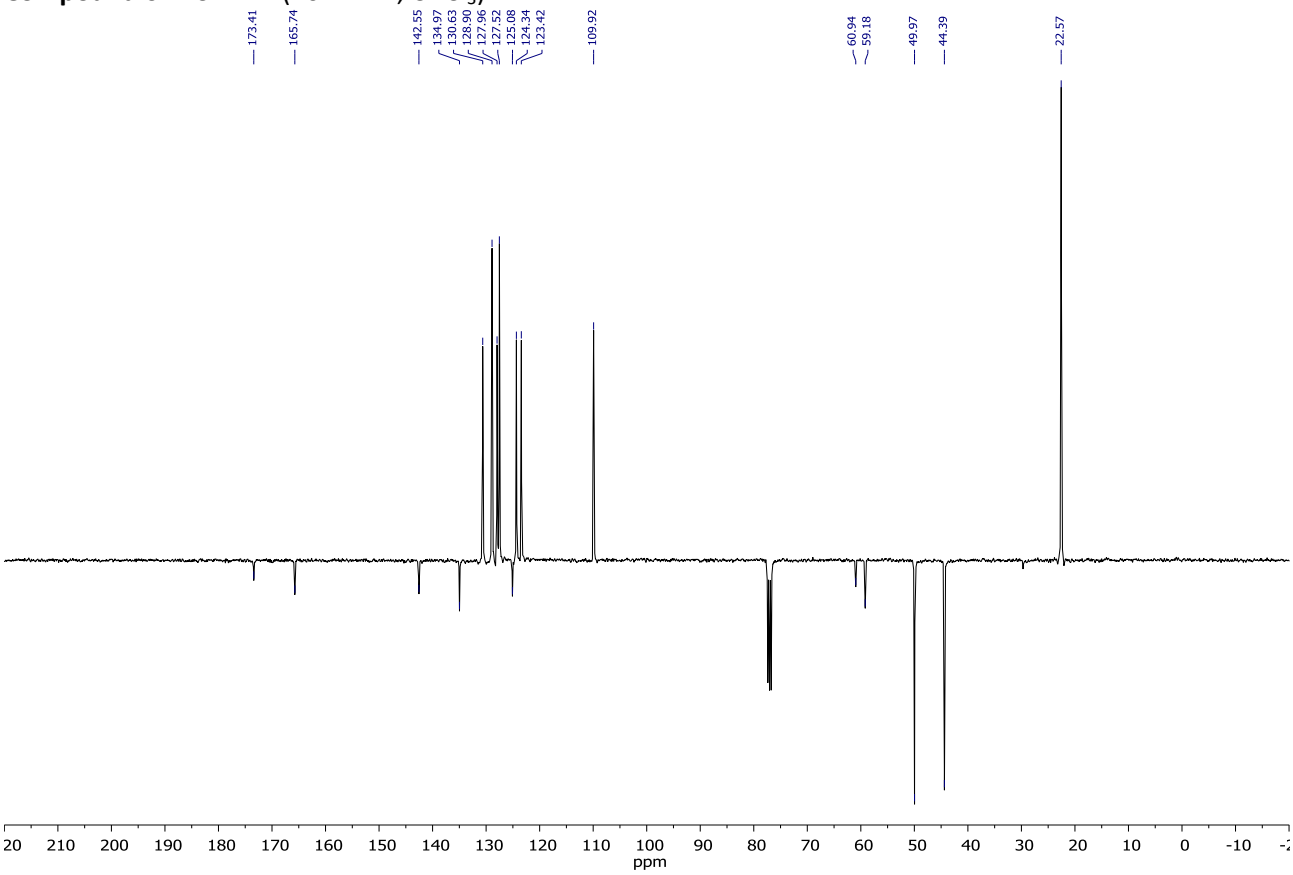
Compound 5: ^{13}C NMR (101 MHz, $CDCl_3$)



Compound 6: ^{1}H NMR (400 MHz, $CDCl_3$)



Compound 6: ^{13}C NMR (101 MHz, $CDCl_3$)



4. **Crystallographic analysis of 3a.**

Large crystals of the compound **3a** were obtained in a sample tube by slow evaporation from isopropyl ether at *T* = 4 ºC. Crystallization took approximately 4 days, after which a well formed specimen (Figure 1) was selected for the single crystal X-ray diffraction analysis.

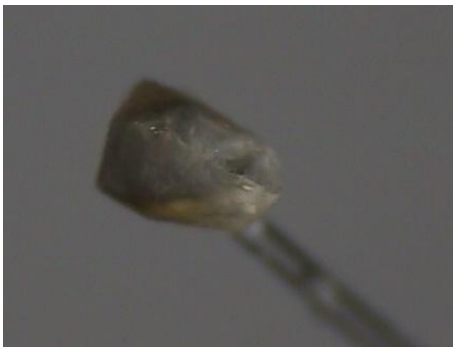


Figure 1. Sample selected for the X-ray diffraction experiment.
The brownish-white prism has dimensions ≈ 450 x 300 x 200 μm

The sample was cut from an agglomerate using a microknife and polished by mechanical ablation in a drop of perfluorinated oil. Then, it was mounted on a glass capillary fiber with perfluorinated oil as glue. The X-ray data collection was performed with a three-circle Bruker Smart APEX diffractometer equipped with an APEXII CCD detector. Graphite-monochromated Mo Kα radiation was employed throughout in conjunction with a nominal X-ray power of 50 kV x 30 mA. Raw data were processed by means of the SAINT+ software[10] and corrected for beam anisotropy and absorption by TWINABS.[11] Finally, data were scaled and analyzed by XPREP[12] to determine the correct space group symmetry.
A minor non-merohedral TLQS twin component was found to be present; the latter is rotated by roughly 142º around the [0.4, 1.0, -0.6] real direction. Roughly the 45 % of the reflections suffer a maximum of ≈ 5 % of intensity contamination due to the minority component. Therefore, twinning was explicitly considered in the shelx[13] least-squares procedure by processing data in HKLF 5 format in conjunction with a BASF scale parameter.[14] The latter refined to 4.4(3)%, meaning that the major component accounts for roughly 95% of the whole specimen mass. As for the reciprocal lattice, a 99.6% complete dataset was obtained, consisting of 29165 measured reflections belonging to both lattices. The agreement factors for the final least-squares model were R1(F) = 0.035 for 23117 intense reflections ($F_o > 4\sigma(F_o)$) and 0.0457 for all the measured data, whereas the maximum and minimum Fourier residuals in the unit cell were as low as +0.21 /–0.17 e·Å^{-3}.

Crystal data for **3a**: $C_{25}H_{28}N_2O_4S$, M = 452.55 amu, orthorhombic, space group $P2_12_12_1$, nº 19, acentric, a = 8.7820(1) Å, b = 10.8274(2) Å, c = 26.0299(4) Å, V = 2475.09(7) Å^3, Z = 4, Z'=1; ρ_{calcd}= 1.214 g·cm^{-3}, μ = 0.163 mm^{-1}. CCDC 1487568 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Comments. The compound is chiral and enantiomerically pure. It crystallizes in the acentric non-polar $P2_12_12_1$ space group with one molecule per asymmetric unit. Figures 2 shows the relative configuration of the chiral centres. The presence of an anomalous scatterer (sulphur) allows to unequivocally assess the absolute structure, with the Flack's parameter[15] being as low as 0.09(9) and the Parson's parameter[16] from 1511 selected intensity quotients equal to 0.03(5). As expected (see the main text), the sulfur S1 in the N-sulfinyl moiety has R configuration, while the unknown stereocentre at the C3 spiro carbon is S.

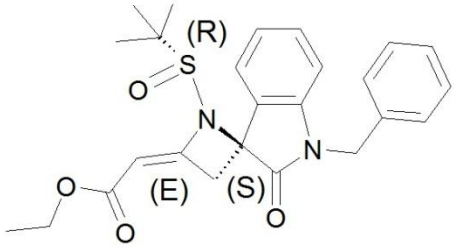


Figure 2. Molecular structure of **3a**, with configurational descriptors highlighting the experimentally determined absolute structure

It is also worth noting that the terminal –OEt group of the ester moiety is disordered. Two equiprobable conformations were detected, with occupation coefficients as large as 0.51(1) and 0.49(1). However, experiments as a function of *T* are required to assess whether the disorder is static or dynamic.

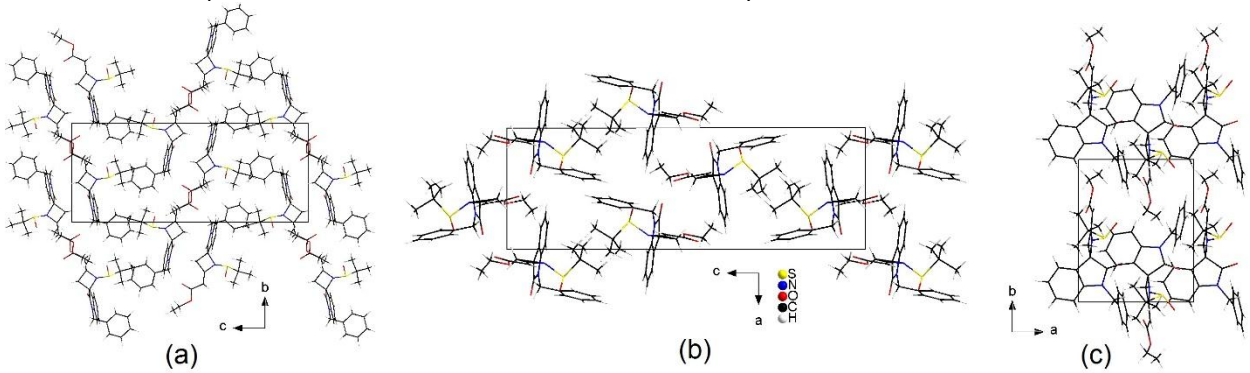


Figure 3. Crystal packing of **3a**, as seen (a) along the *a* cell axis; (b) the *b* cell axis; (c) the *c* cell axis (to the sake of clarity, just the layer close to the viewing point is shown). All the pictures showing crystallographic results in this work were realized with Diamond v. 3.2k, © K. Brandenburg 1997-2014, Crystal Impact GbR, Germany.

Figure 3 shows the main packing motifs of **3a**. No strong hydrogen bond donors are present in this structure. Least-squares planes of the azetidine and the phenyl rings are tilted by 14.2(2)º with respect to each other and they are both nearly orthogonal to the *a* cell axis. On the contrary, the indole moiety lies rougly perpendicular to them (with dihedral angles with azetidine and phenyl as high as 89.6(1)º and 88.5(1)º), being also orthogonally oriented with respect to the *c* cell axis. The molecule extends itself roughly along the *b* axis, keeping the bulky groups apart from those of other molecules to avoid steric clashes. This conformation also likely maximizes dipolar (and possibly higher-order) electrostatic interactions. No stacking motifs were detected among symmetry-related hydrocarbon rings.

5. References

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