Synthesis of 2-BMIDA 6,5-bicyclic heterocycles by cycle-specific Cu(I)/Pd(0)/Cu(II) cascade catalysis

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Contents

1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[1]

1.1 Purification of Solvents

DMF was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. CH_2Cl_2, Et_2O, EtOAc, MeCN, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification.

1.2 Drying of Inorganic Bases

Inorganic bases were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 hours before use.

1.3 Experimental Details

Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5 mL microwave vials (optimization reactions and reactions for Schemes 2, 4, and 5). The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally *ca.* 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

NOTE: (1) Sand baths were used for health and safety reasons – oil baths were avoided where possible. (2) Microwave vials were used for convenience; however, these are not necessary. Reactions can be competently completed in standard laboratory glassware.

1.4 Purification of Products

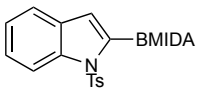
Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel. Reverse phase flash chromatography was carried out using IST Isolute C18 cartridges.

1.5 Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer at 376 MHz. ^{11}B NMR spectra were obtained on a Bruker AV 400 spectrometer at 128 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 125 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.0 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Reversed phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column. Analysis was performed using a gradient method, eluting with 5–80% MeCN/H_2O over 16 minutes at a flow rate of 2 mL/min. Samples for HPLC analysis were prepared through the addition of 2 mL of caffeine standard in MeCN to the completed reaction mixture. The resulting solution was then stirred before the removal of a 200 μL aliquot. The aliquot was diluted to 1 mL with MeCN. A 200 μL aliquot of the diluted solution was then filtered through cotton wool and further diluted with 800 μL MeCN and 500 μL H_2O for HPLC analysis against established conversion factors.

2. General Experimental Procedures

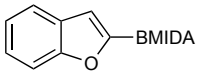
General Procedure A: Optimized reaction (indoles)



For example, synthesis of (1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester, **4a**.

To an oven dried 5 mL microwave vessel was added *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). The vessel was then capped and purged with N_2 before addition of DMF (2 mL, 0.125 M). The reaction mixture was then heated to 30 °C in a sand bath for 4 h before being heated to 55 °C for a further 14 h. The vessel was allowed to cool to room temperature, vented, and decapped. The solution was then concentrated under reduced pressure before being diluted with EtOAc (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then dried and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as a white solid (87 mg, 0.21 mmol, 82%).

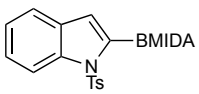
General Procedure B: Optimized reaction (benzofurans)



For example, synthesis of benzofuran-2-ylboronic acid, MIDA ester, **5a**.

To an oven dried 5 mL microwave vessel was added 2-iodophenol (55 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (2.9 mg, 0.015 mmol, 6 mol%), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 10 mol%), and K_2CO_3 (52 mg, 0.375 mmol, 1.5 equiv). The vessel was then capped and purged with N_2 before addition of DMF (2 mL, 0.125 M). The reaction mixture was then stirred at room temperature in a sand bath for 4 h before being heated to 60 °C for a further 14 h. The vessel was allowed to cool to room temperature, vented, and decapped. The solution was then concentrated under reduced pressure before being diluted with EtOAc (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then dried and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 40-80% EtOAc/Petroleum ether) to afford the title compound as a white solid (57 mg, 0.21 mmol, 83%).

General Procedure C: Mmol scale reactions



For example, synthesis of (1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester, **4a**.

To an oven dried 50 mL round bottomed flask was added *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (750 mg, 2 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (436 mg, 2.4 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol, 2 mol%), CuI (38 mg, 0.2 mmol, 10 mol%), $Cu(OAc)_2$ (109 mg, 0.6 mmol, 30 mol%), and K_3PO_4 (426 mg, 2 mmol, 1 equiv). The vessel was then sealed with a rubber septum and purged with N_2 before addition of DMF (16 mL, 0.125 M). The reaction mixture was then heated to 30 °C in a sand bath for 4 h before being heated to 55 °C for a further 14 h. The vessel was allowed to cool to room temperature before the solution was then

concentrated under reduced pressure, diluted with EtOAc (200 mL) and washed with water (2 x 100 mL) and brine (2 x 100 mL). The organics were then dried and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as a white solid (694 mg, 1.62 mmol, 81%).

General procedure D: Tosylations of anilines using TsCl

To a round bottomed flask charged with aniline (1 equiv) was added a solution of 1:1 pyridine/CH_2Cl_2 (0.7 M) and cooled to 0 °C. 4-Methylbenzenesulfonyl chloride (1 equiv) was added portion wise, and the reaction mixture was allowed to slowly warm to room temperature and then stirred for 24 h. Upon completion of the reaction, water (10 mL) and CH_2Cl_2 (10 mL) were added and the reaction mixture was separated. The organics washed with 1 N NaOH (2 ×10 mL), 1 N HCl (2 ×10 mL), and brine (2 × 10 mL). The organics were then dried and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography to afford the title compound.

General procedure E: Tosylations of anilines using Ts_2O and DMAP

To a round bottomed flask charged with aniline (1 equiv) and DMAP (0.1 equiv) was added a solution of 1:1 pyridine/CH_2Cl_2 (0.7 M) and cooled to 0 °C. 4-Methylbenzenesulfonic anhydride (1.1 equiv) was added portion wise, and the reaction mixture was allowed to slowly warm to room temperature and was stirred for 24 h. Upon completion of the reaction, water (10 mL) and CH_2Cl_2 (10 mL) were added and the reaction mixture was separated and the organics washed with 1 N NaOH (2 ×10 mL), 1 N HCl (2 ×10 mL), and brine (2 × 10 mL). The organics were then dried and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography to afford the title compound.

3. Reaction optimization data

3.1 Variation of the Pd catalyst

Reactions were carried out according to General Procedure A using *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), **Pd catalyst** (**X** mg, 0.005 mmol, 2 mol%) **Ligand** (**X** mg, 0.01 mmol, 4 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and Et_3N (105 µL, 0.25 mmol, 3 equiv).

Entry	Catalyst (mass)	Ligand (mass)	Conversion
1	$PdCl_2(PPh_3)_2$ (3.5 mg)	-	74%
2	$PdCl_2$(dppf) (4.1 mg)	-	70%
3	$PdCl_2(MeCN)_2$ (1.3 mg)	-	72%
4	$Pd(OAc)_2$ (1.1 mg)	PPh_3 (2.6 mg)	65%
5	$Pd(OAc)_2$ (1.1 mg)	SPhos (4.1 mg)	71%
6	$Pd_2(dba)_2$ (4.6 mg)	-	46%

3.2 Variation of the copper loading (indole)

Reactions were carried out according to General Procedure A using *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), **CuI** (**X** mg, **X** mmol, **X** mol%), **$Cu(OAc)_2$** (**X** mg, **X** mmol, **X** mol%), and Et_3N (105 µL, 0.75 mmol, 3 equiv).

Entry	CuI (mass, equiv)	$Cu(OAc)_2$ (mass, equiv)	Conversion
1	(2.4 mg, 5 mol%)	(9.1 mg, 20 mol%)	55%
2	(2.4 mg, 5 mol%)	(13.6 mg, 30 mol%)	63%
3	(2.4 mg, 5 mol%)	(18.1 mg, 40 mol%)	75%
4	(4.8 mg, 10 mol%)	(9.1 mg, 20 mol%)	83%
5	(4.8 mg, 10 mol%)	(13.6 mg, 30 mol%)	84%
6	(4.8 mg, 10 mol%)	(18.1 mg, 40 mol%)	68%
7	(9.6 mg, 20 mol%)	(9.1 mg, 20 mol%)	61%
8	(9.6 mg, 20 mol%)	(13.6 mg, 30 mol%)	65%
9	(9.6 mg, 20 mol%)	(18.1 mg, 40 mol%)	71%
10	(9.6 mg, 20 mol%)	(22.6 mg, 50 mol%)	67%

3.3 Variation of the base

Reactions were carried out according to General Procedure A using *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and **Base** (**X** mg, **X** mmol, **X** equiv).

Entry	Base (mass)	Equiv	Temperature (°C)	Conversion
1	Et_3N (105 µL)	3	30-70	30%
2	K_3PO_4 (159 mg)	3	30-70	27%
3	K_2CO_3 (103 mg)	3	30-70	21%
4	Cs_2CO_3 (243 mg)	3	30-70	19%
5	K_3PO_4 (53 mg)	1	30-60	81%
6	K_3PO_4 (106 mg)	2	30-60	83%
7	K_3PO_4 (159 mg)	3	30-60	67%
8	K_3PO_4 (53 mg)	1	30-50	85%
9	K_3PO_4 (106 mg)	2	30-50	74%
10	K_3PO_4 (159 mg)	3	30-50	67%

3.4 Variation of the copper loading (benzofuran)

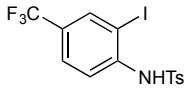
Reactions were carried out according to General Procedure B using 2-iodophenol (55 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), **CuI** (**X** mg, **X** mmol, **X** mol%), **$Cu(OAc)_2$** (**X** mg, **X** mmol, **X** mol%), and K_2CO_3 (52 mg, 0.375 mmol, 1.5 equiv).

Entry	CuI (mass, equiv)	$Cu(OAc)_2$ (mass, equiv)	Conversion
1	(1.9 mg, 4 mol%)	(4.5 mg, 10 mol%)	88%
2	(2.9 mg, 6 mol%)	(4.5 mg, 10 mol%)	91%
3	(1.9 mg, 4 mol%)	(6.8 mg, 15 mol%)	87%
4	(2.9 mg, 6 mol%)	(6.8 mg, 15 mol%)	69%
5	(1.9 mg, 4 mol%)	(9.0 mg, 20 mol%)	66%
6	(2.9 mg, 6 mol%)	(9.0 mg, 20 mol%)	68%

4. Compound characterization data

4.1 Preparation of intermediates

S1: *N*-(2-Iodo-4-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide



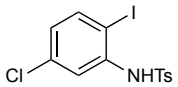
Prepared according to General Procedure E using 2-iodo-4-(trifluoromethyl)aniline (500 mg, 1.75 mmol, 1 equiv), 4-methylbenzenesulfonic anhydride (567 mg, 1.75 mmol, 1 equiv), and DMAP (17.6 mg, 0.175 mmol, 0.1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-8% EtOAc/Petroleum Ether) to afford the title compound as a yellow solid (662 mg, 1.51 mmol, 86%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (s, 1H), 7.72 (d, J = 7.5 Hz, 3H), 7.56 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.8, 140.8, 136.2 (q, $J_{C\text{-}F}$ = 3.6 Hz), 130.0, 128.0 (q, $^{2}J_{C\text{-}F}$ = 33.4 Hz), 127.4, 126.6 (q, $J_{C\text{-}F}$ = 3.4 Hz), 122.7 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz), 120.3, 90.2, 21.6.

^{19}F NMR (DMSO-d_6, 471 MHz): δ –62.35.

S2: *N*-(5-Chloro-2-iodophenyl)-4-methylbenzenesulfonamide

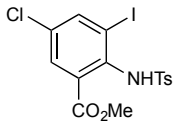


Prepared according to General Procedure D using 5-chloro-2-iodoaniline (1 g, 3.95 mmol, 1 equiv) and 4-methylbenzenesulfonyl chloride (750 mg, 3.95 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-12% EtOAc/petroleum ether) to afford the title compound as an off white solid (890 mg, 2.11 mmol, 52%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.72–7.65 (m, 3H), 7.57 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 6.88–6.80 (m, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.1, 139.1, 138.1, 135.1, 135.1, 129.4, 127.0, 126.4, 121.4, 88.3, 21.2.

S3: Methyl 5-chloro-3-iodo-2-((4-methylphenyl)sulfonamido)benzoate

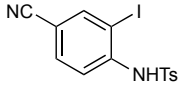


Prepared according to General Procedure E using methyl 2-amino-5-chloro-3-iodobenzoate (810 mg, 2.6 mmol, 1 equiv), 4-methylbenzenesulfonic anhydride (849 mg, 2.6 mmol, 1 equiv), and DMAP (32 mg, 0.26 mmol, 0.1 equiv). The reaction was heated to 80 °C for 24 h. After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-20% EtOAc/petroleum ether) to afford the title compound as an orange solid (263 mg, 0.57 mmol, 22%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08–8.00 (m, 2H), 7.71 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 3.58 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.7, 143.7, 143.1, 136.6, 135.3, 133.1, 130.1, 129.1, 128.2, 127.4, 101.0, 52.25, 21.0.

S4: *N*-(4-Cyano-2-iodophenyl)-4-methylbenzenesulfonamide

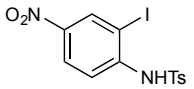


Prepared *via* two steps from 4-amino-3-iodobenzonitrile:

Step 1: To a 10 mL round bottomed flask charged with 4-amino-3-iodobenzonitrile (500 mg, 2 mmol, 1 equiv), was added a solution of 1:1 pyridine/CH_2Cl_2 (3 mL, 0.7 M) and cooled to 0 °C. 4-Methylbenzenesulfonyl chloride (389 mg, 2 mmol, 1 equiv) was added portion wise and was heated to 40 °C for 24 h. Upon completion, the reaction mixture was allowed to cool to room temperature before the subsequent addition of water (10 mL) and CH_2Cl_2 (10 mL). The reaction mixture was separated and the organics were washed with 1 N NaOH (2 x 10 mL) and 1 N HCl (2 x 10 mL). The organics were then dried and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (silica gel, 0-12 % EtOAc/petroleum ether) to afford *N*-(4-cyano-2-iodophenyl)di-4-methylbenzenesulfonamide.

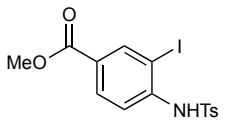
Step 2: To a 10 mL round bottomed flask charged with *N*-(4-cyano-2-iodophenyl)di-4-methylbenzenesulfonamide (200 mg, 0.36 mmol, 1 equiv) and tetrabutylammonium fluoride (1 M in THF, 725 µL, 0.72 mmol, 2 equiv), was added THF (3.6 mL, 0.1 M). The reaction mixture was then heated to 80 °C and stirred for 16 h. Upon completion, the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 0-15 % EtOAc/petroleum ether) to afford the title compound as an off white solid (65 mg, 0.36 mmol, 18% yield over two steps).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (d, *J* = 1.7 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H),
7.58 (d, *J* = 8.6 Hz, 2H), 7.46 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 2.32 (s, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.7, 141.9, 141.4, 134.9, 132.1, 128.9, 126.3, 118.6, 115.9, 107.7, 89.2, 20.6.

S5: *N*-(2-Iodo-4-nitrophenyl)-4-methylbenzenesulfonamide



Prepared according to General Procedure D using 2-iodo-4-nitroaniline (500 mg, 1.89 mmol, 1 equiv) and 4-methylbenzenesulfonyl chloride (359 mg, 1.89 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-8% EtOAc/petroleum ether) to afford the title compound as a yellow solid (660 mg, 1.57 mmol, 83%).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, *J* = 2.5 Hz, 1H), 8.16 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.77–7.68 (m, 3H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 2.41 (s, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 145.3, 143.9, 143.3, 135.3, 134.6, 130.1, 127.4, 124.9, 118.5, 88.5, 21.6.

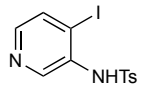
S6: Methyl 3-iodo-4-((4-methylphenyl)sulfonamido)benzoate



Prepared according to General Procedure D using methyl 4-amino-3-iodobenzoate (500 mg, 1.8 mmol, 1 equiv) and 4-methylbenzenesulfonyl chloride (342 mg, 1.8 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 10-25% EtOAc/petroleum ether) to afford the title compound as a yellow waxy solid (683 mg, 1.58 mmol, 88%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (d, *J* = 1.5 Hz, 1H), 7.86 (dd, *J* = 8.6, 1.4 Hz, 1H),
7.62 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.03 (s, 1H), 3.80 (s, 3H), 2.31 (s, 3H).

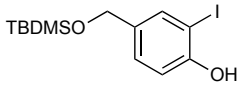
^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.0, 144.7, 141.5, 140.6, 135.6, 130.8, 129.9, 127.7, 127.4, 119.5, 89.9, 52.4, 21.6.

S7: *N*-(4-Iodopyridin-3-yl)-4-methylbenzenesulfonamide



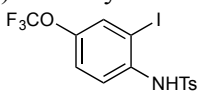
Prepared according to General Procedure E using 2-iodo-4-(trifluoromethyl)aniline (250 mg, 1.14 mmol, 1 equiv), 4-methylbenzenesulfonic anhydride (370 mg, 1.14 mmol, 1 equiv), and DMAP (13.9 mg, 0.11 mmol, 0.1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-30% EtOAc/CH_2Cl_2) to afford the title compound as an off-white solid (176 mg, 0.47 mmol, 41%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.68 (s, 1H), 7.90 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 5 Hz, 1H), 7.18 (d, *J* = 9.8 Hz, 2H), 6.60 (s, 1H), 2.33 (s, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 146.6, 144.7, 143.8, 135.7, 135.2, 133.8, 129.9, 127.5, 103.7, 21.6.

S8: 4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-iodophenol



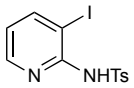
To a solution of 4-(hydroxymethyl)-2-iodophenol (200 mg, 0.8 mmol, 1 equiv) in DMF (6.4 mL, 0.125 M) at 0 °C was added imidazole (49 µL, 0.88 mmol, 1.1 equiv) and *tert*-butyldimethylsilyl (121 mg, 0.8 mmol, 1 equiv). The reaction mixture was slowly warmed to room temperature and stirred in a sandbath for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was diluted with EtOAc (10 mL) and washed with a saturated solution of sodium bicarbonate (2 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organics were dried and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography (silica gel, 0-20% EtOAc/petroleum ether) to afford the title compound as a clear oil (84 mg, 0.23 mmol, 29%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 (d, *J* = 8.1 Hz, 1H), 6.88 (s, 1H), 6.55 (dd, *J* = 8.1, 1.8 Hz, 1H), 4.56 (s, 2H), 0.84 (s, 9H), 0.00 (s, 6H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.7, 143.4, 136.9, 119.1, 111.6, 82.2, 63.1, 24.9, 17.4, -6.3.

S9: *N*-(2-Iodo-4-(trifluoromethoxy)phenyl)-4-methylbenzenesulfonamide



Prepared according to General Procedure D using 2-iodo-4-(trifluoromethoxy)aniline (500 mg, 1.65 mmol, 1 equiv) and 4-methylbenzenesulfonyl chloride (567 mg, 1.65 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-12% EtOAc/petroleum ether) to afford the title compound as a colorless wax (510 mg, 1.12 mmol, 68%).
υ_{max} (solid): 3257, 3084, 3045, 1597, 1485, 1387, 1338, 1216 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.13 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.69 (s, 1H), 2.33 (s, 3H).
^{13}C NMR ($CDCl_3$, 101 MHz): δ 145.5, 144.1, 136.0, 135.1, 130.9, 129.3, 126.9, 122.4, 121.6, 91.3, 21.1. Carbon bearing fluorine not observed.
^{19}F NMR (DMSO-d_6, 471 MHz): δ -58.15.
HRMS: exact mass calculated for $[M+Na]^+$ ($C_{14}H_{11}F_3NO_3SINa$) requires *m/z* 479.9349, found *m/z* 479.9335.

S10: *N*-(3-Iodopyridin-2-yl)-4-methylbenzenesulfonamide



Prepared according to General Procedure E using 3-iodopyridin-2-amine (250 mg, 1.14 mmol, 1 equiv), 4-methylbenzenesulfonic anhydride (179 mg, 1.14 mmol, 1 equiv) and DMAP (13.9 mg, 0.11 mmol, 0.1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 0-30% EtOAc/CH_2Cl_2) to afford the title compound as an off white solid (248 mg, 0.66 mmol, 58%).

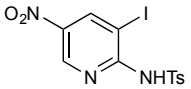
υ_{max} (solid): 3188, 3118, 1617, 1580, 1502, 1431, 1368, 1322 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz) δ 8.10 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.50 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.58 (s, 1H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.3, 147.7, 147.5, 144.2, 136.6, 129.3, 128.7, 119.7, 80.7, 21.6.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{12}H_{11}IN_2O_2SNa$) requires *m/z* 396.9476, found *m/z* 396.9476.

S11: *N*-(3-Iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide



Prepared *via* two steps from 3-iodo-5-nitropyridin-2-amine:

Step 1: To a 25 mL three-necked flask charged with 5-nitropyridin-2-amine (1 g, 7.1 mmol, 1 equiv), was added concentrated sulfuric acid (12 mL, 0.6 M). The reaction mixture was stirred at room temperature and potassium iodate (653 mg, 2.8 mmol, 0.4 equiv) was added portion wise before subsequent heating to 200 °C. Potassium iodide (1.18 g, 7.1 mmol, 1 equiv) was added dropwise as an aqueous solution (4 mL) and the reaction mixture was stirred at 200 °C. Upon completion, the reaction mixture was allowed to cool to room temperature before the slow addition of saturated sodium bicarbonate solution (20 mL) and EtOAc (20 mL). The reaction mixture was separated and the organics were washed with an aqueous solution of $Na_2S_2O_3$ (2 x 30 mL). The organics were then dried and concentrated under reduced pressure to give a yellow solid, 3-iodo-5-nitropyridin-2-amine, which was used without further purification.

Step 2: To a 100 mL round bottom flask charged with 3-iodo-5-nitropyridin-2-amine (1.29 g, 4.86 mmol, 1 equiv), was added THF (40 mL, 0.13 M) and cooled to 0 °C. Sodium hydride (224 mg, 9.72 mmol, 2 equiv) was added portion wise and the reaction mixture stirred at 0 °C for 20 minutes. 4-methylbenzenesulfonyl chloride (1.09 g, 4.86 mmol, 1 equiv) was added portion wise, and the reaction mixture was allowed to slowly warm to room temperature and was stirred for 18 h. Upon completion of the reaction, water (50 mL) and DCM (50 mL) were added and the reaction mixture was separated and the organics washed with 1 N NaOH (2 ×50 mL), 1 N HCl (2 ×50 mL) and brine (2 × 50 mL). The organics were dried and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography (silica gel, 0-30% EtOAc/petroleum ether) to afford the title compound as a yellow solid (1.43 g, 4.33 mmol, 61% yield over two steps).

υ_{max} (solid): 3581, 3268, 3064, 2919, 1571, 1444, 1320 cm^{-1}.

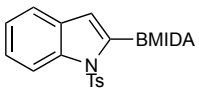
^1H NMR (DMSO-d_6, 400 MHz) δ 8.66 (d, *J* = 2.6 Hz, 1H), 8.40 (d, *J* = 2.5 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 161.9, 145.0, 142.3, 140.9, 140.7, 134.7, 128.9, 127.4, 86.7, 21.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{11}IN_3O_4S$) requires *m/z* 419.9509, found *m/z* 419.9510.

4.2 Products from Scheme 2

4a: (1-Tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester[2]

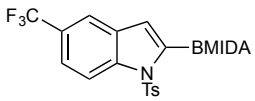


Prepared according to General Procedure A using N-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as a white solid (87 mg, 0.21 mmol, 82%).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.12 (d, J = 9.1 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 7.4 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.26 (t, J = 7.0 Hz, 1H), 7.07 (s, 1H), 4.48 (d, J = 17.4 Hz, 2H), 4.24 (d, J = 17.4 Hz, 2H), 2.97 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 172.0, 140.7, 140.2, 139.7, 139.6, 133.1, 129.7, 128.8, 127.5, 127.4, 127.4, 127.2, 127.0, 52.1, 40.9. Carbon bearing boron not observed.

4b: (1-Tosyl-5-(trifluoromethyl)-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(2-iodo-4-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide (110 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-90% EtOAc/petroleum ether) to afford the title compound as a white solid (107 mg, 0.22 mmol, 87%).

υ_{max} (solid): 2922, 2852, 1759, 1597, 1448, 1335, 1294, 1271 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.34 (d, J = 8.8 Hz, 1H), 8.11 (1, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.69 (dd, J = 8.9, 1.6 Hz, 1H) 7.42 (d, J = 8.2 Hz, 2H), 7.21 (s, 1H), 4.50 (d, J = 17.5 Hz, 2H), 4.26 (d, J = 17.5 Hz, 2H), 2.96 (s, 3H), 2.34 (s, 3H).

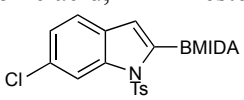
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.2, 140.6, 135.1, 130.6, 130.0, 127.2, 125.1 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 124.7 (q, $^2J_{C\text{-}F}$ = 31.8 Hz), 122.1, 119.6 (d, $^3J_{C\text{-}F}$ = 3.7 Hz), 115.6, 64.8, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.32.

^{19}F NMR (DMSO-d_6, 471 MHz): δ –59.63.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{21}H_{18}BF_3N_2O_6SNa$) requires *m/z* 517.0827, found *m/z* 517.0806.

4c: (5-Chloro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(4-chloro-2-iodophenyl)-4-methylbenzenesulfonamide (102 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica

gel, 40-80% EtOAc/petroleum ether) to afford the title compound as a white solid (105 mg, 0.23 mmol, 91%).

υ_{max} (solid): 2921, 1766, 1742, 1599, 1455, 1303 cm^{-1}.

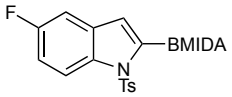
^1H NMR (DMSO-d_6, 400 MHz): δ 8.11 (d, *J* = 1.8 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.08 (s, 1H), 4.47 (d, *J* = 17.5 Hz, 2H), 4.23 (d, *J* = 17.4 Hz, 2H), 2.94 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.1, 145.6, 138.8, 134.7, 130.1, 129.9, 128.4, 126.5, 123.9, 122.9, 121.4, 113.9, 64.2, 49.4, 21.0. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.17.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{20}H_{17}O_6BClSN_2$) requires *m/z* 459.0598, found *m/z* 459.0585.

4d: (5-Fluoro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(4-fluoro-2-iodophenyl)-4-methylbenzenesulfonamide (98 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-80% EtOAc/petroleum ether) to afford the title compound as a white solid (90 mg, 0.20 mmol, 81%).

υ_{max} (solid): 2922, 1757, 1744, 1599, 1526, 1452 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ 8.12 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.22 (td, *J* = 9.2, 2.7 Hz, 1H), 7.05 (s, 1H), 4.48 (d, *J* = 17.5 Hz, 2H), 4.24 (d, *J* = 17.4 Hz, 2H), 2.96 (s, 3H), 2.33 (s, 3H).

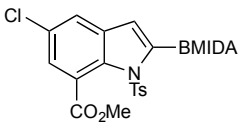
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 159.3 (d, $^1J_{C\text{-}F}$ = 238.4 Hz), 145.9, 135.4, 135.3, 131.2 (d, $^3J_{C\text{-}F}$ = 10.4 Hz), 130.4, 127.1, 121.9 (d, $J_{C\text{-}F}$ = 3.6 Hz), 116.1 (d, $^3J_{C\text{-}F}$ = 9.4 Hz), 113.5 (d, $^2J_{C\text{-}F}$ = 25.5 Hz), 107.1 (d, $^2J_{C\text{-}F}$ = 23.5 Hz), 64.8, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.44.

^{19}F NMR (DMSO-d_6, 471 MHz): δ –120.01.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{20}H_{18}BFN_2O_6SNa$) requires *m/z* 477.0859, found *m/z* 477.0854.

4e: (5-Chloro-7-(methoxycarbonyl)-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using methyl 5-chloro-3-iodo-2-((4-methylphenyl)sulfonamido)benzoate (116 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-90% EtOAc/petroleum ether) to afford a mixture of the title compound and the uncyclised product (124 mg, 96% conversion, 4/1 title compound/uncyclized intermediate).

A portion of the mixture (26 mg, 0.05 mmol, 1 equiv) was treated with $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 50 mol%) and $Pd(OAc)_2$ (2 mg, 0.01 mmol, 20 mol%) in DMF (0.4 mL, 0.125 M) at 60 °C for 16 h. The resulting mixture was filtered through celite, diluted with EtOAc, and washed with H_2O and brine. The organics were then dried through a hydrophobic frit and concentrated under reduced pressure to give the title compound as an off white solid (25 mg, 0.24 mmol, 96%).

υ_{max} (solid): 2950, 2921, 2850, 1764, 1731, 1597, 1433, 1164, 1033 cm^{-1}.

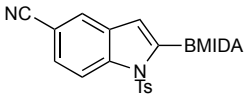
^1H NMR (DMSO-d_6, 400 MHz): δ 7.96 (d, *J* = 2.2 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.33 – 7.27 (m, 4H), 7.15 (s, 1H), 4.42 (d, *J* = 17.4 Hz, 2H), 4.16 (d, *J* = 17.3 Hz, 2H), 3.69 (s, 3H), 2.91 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 168.7, 166.6, 144.1, 135.6, 134.7, 134.0, 129.3, 128.8, 126.0, 125.5, 124.4, 124.2, 123.9, 63.6, 52.13, 48.9, 21.0. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 9.32.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{20}BClN_2O_9SNa$) requires *m/z* 541.0618, found *m/z* 541.0603.

(5-Cyano-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester, **4f**



Prepared according to General Procedure A using *N*-(4-cyano-2-iodophenyl)-4-methylbenzenesulfonamide (60 mg, 0.15 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (32 mg, 0.225 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (2.1 mg, 0.003 mmol, 2 mol%), CuI (2.9 mg, 0.015 mmol, 10 mol%), $Cu(OAc)_2$ (8.1 mg, 0.045 mmol, 30 mol%), and K_3PO_4 (32 mg, 0.15 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-80% EtOAc/petroleum ether) to afford the title compound as a white solid (62 mg, 0.14 mmol, 93%).

υ_{max} (solid): 2922, 2854, 2223, 1768, 1747, 1597, 1532, 1455 cm^{-1}.

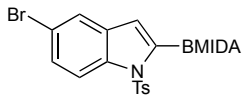
^1H NMR (DMSO-d_6, 500 MHz): δ 8.29 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 1.1 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.76 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.16 (s, 1H), 4.49 (d, *J* = 17.5 Hz, 2H), 4.25 (d, *J* = 17.4 Hz, 2H), 2.95 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.4, 140.6, 135.0, 130.6, 130.2, 128.5, 127.2, 127.1, 121.6, 119.6, 115.8, 106.5, 64.8, 50.0, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.17.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{21}H_{17}BN_3O_6S$) requires *m/z* 450.0937, found *m/z* 450.0930.

4g: (5-Bromo-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester

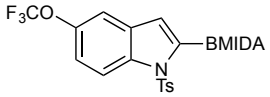


Prepared according to General Procedure A using *N*-(4-bromo-2-iodophenyl)-4-methylbenzenesulfonamide (113 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-80% EtOAc/petroleum ether) to afford the title compound as a white solid (115 mg, 0.23 mmol, 91%).

υ_{max} (solid): 3015, 2958, 1768, 1749, 1597, 1524, 1444 cm^{-1}.

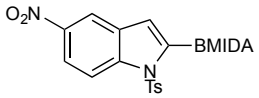
^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.51 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.07 (s, 1H), 4.49 (d, *J* = 17.5 Hz, 2H), 4.25 (d, *J* = 17.4 Hz, 2H), 2.97 (s, 3H), 2.32 (s, 3H).
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.0, 137.8, 135.2, 132.1, 130.5, 128.2, 127.1, 124.3, 121.4, 116.7, 116.6, 64.8, 49.9, 21.5. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.05.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}BBrN_2SO_6$) requires *m/z* 505.0238, found *m/z* 505.0238.

4h: (1-Tosyl-5-(trifluoromethoxy)-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(2-iodo-4-(trifluoromethoxy)phenyl)-4-methylbenzenesulfonamide (114 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-90% EtOAc/petroleum ether) to afford the title compound as a white solid (102 mg, 0.20 mmol, 80%).
υ_{max} (solid): 2953, 2924, 2854, 1747, 1766, 1599, 1532, 1452 cm^{-1}.
^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.22 (d, *J* = 9.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.36 (dd, *J* = 9.1, 1.8 Hz, 1H), 7.13 (s, 1H), 4.48 (d, *J* = 17.5 Hz, 2H), 4.24 (d, *J* = 17.4 Hz, 2H), 2.96 (s, 3H), 2.34 (s, 3H).
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.1, 144.9, 137.2, 135.2, 135.2, 130.5, 127.2, 121.8, 120.7 (q, $^{1}J_{C\text{-}F}$ = 255.9 Hz), 118.9, 116.1, 114.2, 64.8, 49.9, 21.5. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.14.
^{19}F NMR (DMSO-d_6, 471 MHz): δ –57.00.
HRMS: exact mass calculated for $[M-H]^-$ ($C_{21}H_{17}BF_3N_2O_7S$) requires *m/z* 509.0811, found *m/z* 509.0803.

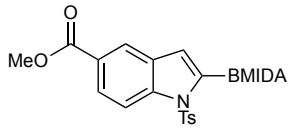
4i: (5-Nitro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(2-iodo-4-nitrophenyl)-4-methylbenzenesulfonamide (38 mg, 0.09 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (19 mg, 0.11 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (1.3 mg, 0.002 mmol, 2 mol%), CuI (1.7 mg, 0.009 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.027 mmol, 30 mol%), and K_3PO_4 (19 mg, 0.09 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-80% EtOAc/petroleum ether) to afford the title compound as a white solid (41 mg, 0.09 mmol, 97%).
υ_{max} (solid): 2956, 2922, 2854, 1766, 1747, 1597, 1517, 1455, 1338 cm^{-1}.
^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.70 (d, *J* = 2.3 Hz, 1H), 8.41 (d, *J* = 9.3 Hz, 1H), 8.29 (dd, *J* = 9.3, 2.4 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.36 (s, 1H), 4.56 (d, *J* = 17.5 Hz, 2H), 4.32 (d, *J* = 17.5 Hz, 2H), 3.02 (s, 3H), 2.40 (s, 3H).
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.5, 144.2, 141.8, 134.9, 130.7, 130.2, 127.3, 122.5, 120.5, 118.2, 115.4, 64.9, 50.0, 21.5. Carbon bearing boron not observed.

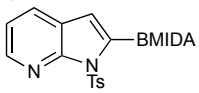
^{11}B NMR (DMSO-d_6, 128 MHz): δ 9.90.
HRMS: exact mass calculated for $[M-H]^-$ ($C_{20}H_{17}BN_3O_8S$) requires *m/z* 470.0839, found *m/z* 470.0829.

4j: (5-(Methoxycarbonyl)-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



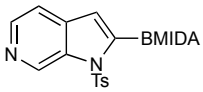
Prepared according to General Procedure A using methyl 3-iodo-4-((4-methylphenyl)sulfonamido)benzoate (107 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-90% EtOAc/petroleum ether) to afford the title compound as a white solid (98 mg, 0.20 mmol, 81%).
υ_{max} (solid): 2952, 2917, 2848, 1764, 1745, 1712, 1697, 1612, 1597, 1454, 1442, 1368 cm^{-1}.
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.29 (d, *J* = 1.2 Hz, 1H), 8.25 (d, *J* = 8.9 Hz, 1H), 8.00 – 7.91(m, 3H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.20 (s, 1H), 4.47 (d, *J* = 17.5 Hz, 2H), 4.25 (d, *J* = 17.4 Hz, 2H), 3.87 (s, 3H) 2.97 (s, 3H), 2.33 (s, 3H).
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 166.2, 145.6, 140.9, 134.7, 130.0, 129.6, 126.7, 125.8, 124.9, 123.3, 121.9, 114.4, 64.3, 52.1, 49.5, 21.0. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.04.
HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{21}BN_2O_8SNa$) requires *m/z* 507.1008, found *m/z* 507.0956.

4k: (1-Tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(3-iodopyridin-2-yl)-4-methylbenzenesulfonamide (94 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-100% EtOAc/petroleum ether) to afford the title compound as a white solid (84 mg, 0.20 mmol, 79%).
υ_{max} (solid): 3051, 3003, 2950, 1759, 1747, 1597, 1451, 1349, 1299 cm^{-1}.
^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.42 (d, *J* = 4.3 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 2H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.30 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.04 (s, 1H), 4.51 (d, *J* = 17.5 Hz, 2H), 4.29 (d, *J* = 17.5 Hz, 2H), 3.07 (s, 3H), 2.35 (s, 3H).
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.8, 150.7, 145.8, 145.4, 135.9, 130.3, 130.2, 128.2, 121.7, 119.7, 118.3, 65.2, 50.2, 21.5. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.33.
HRMS: exact mass calculated for $[M+Na]^+$ ($C_{19}H_{18}BN_3O_6SNa$) requires *m/z* 450.0902, found *m/z* 450.0888.

4l: (1-Tosyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(3-iodopyridin-2-yl)-4-methylbenzenesulfonamide (94 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-100% EtOAc/petroleum ether) to afford the title compound as a yellow solid (71 mg, 0.17 mmol, 67%).

υ_{max} (solid): 3029, 2958, 1764, 1595, 1450, 1372, 1292, 1175 cm^{-1}.

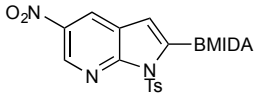
^1H NMR (DMSO-d_6, 500 MHz): δ 9.39 (s, 1H), 8.39 (d, *J* = 5.0 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 4.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.11 (s, 1H), 4.50 (d, *J* = 17.5 Hz, 2H), 4.26 (d, *J* = 17.4 Hz, 2H), 2.96 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.3, 142.8, 136.5, 135.3, 135.1, 130.6, 127.3, 120.8, 116.3, 108.9, 64.8, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.77.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}BN_3O_6S$) requires *m/z* 428.1083, found *m/z* 428.1091.

4m: (5-Nitro-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure A using *N*-(3-iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide (104 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (45 mg, 0.3 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (4.8 mg, 0.025 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the vessel was allowed to cool to room temperature, vented, and decapped. The solution was then concentrated under reduced pressure before being diluted with EtOAc (10 mL) and washed with water (2 x 20 mL) and brine (2 x 20 mL). The organics were then dried and concentrated under reduced pressure to give a yellow solid, which was triturated with cold $CHCl_3$ (2 mL) followed by cold Et_2O (2 mL) to afford the title product as a pale yellow solid (112 mg, 0.24 mmol, 95%).

υ_{max} (solid): 2956, 2924, 1747, 1587, 1521, 1455, 1376, 1340 cm^{-1}.

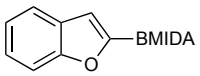
^1H NMR (DMSO-d_6, 400 MHz): δ 9.23 (d, *J* = 2.6 Hz, 1H), 8.97 (d, *J* = 2.5 Hz, 1H),
8.18 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.25 (s, 1H), 4.52 (d, *J* = 17.5 Hz, 2H), 4.31 (d, *J* = 17.5 Hz, 2H), 3.07 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.2, 151.7, 146.1, 141.1, 140.5, 134.6, 129.9, 127.9, 126.0, 120.9, 118.4, 64.8, 49.7, 21.1. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 7.76.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}BN_4O_8$) requires *m/z* 473.0936, found *m/z* 473.0933.

5a: Benzofuran-2-ylboronic acid, MIDA ester[3]

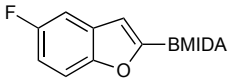


Prepared according to General Procedure B using 2-iodophenol (55 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (2.9 mg, 0.015 mmol, 6 mol%), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 10 mol%), and K_2CO_3 (52 mg, 0.375 mmol, 1.5 equiv). The vessel was then capped and purged with N_2 before addition of DMF (2 mL, 0.125 M). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-80% EtOAc/petroleum ether) to afford the title compound as a white solid (57 mg, 0.21 mmol, 83%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.60 (m, 1H), 7.58 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.35–7.26 (m, 1H), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H), 7.09 (d, *J* = 0.9, 1H), 4.44 (d, *J* = 17.2 Hz, 2H), 4.20 (d, *J* = 17.2 Hz, 2H), 2.71(s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.0, 156.7, 127.8, 124.5, 122.5, 121.3, 114.5, 111.2, 61.6, 47.3. Carbon bearing boron not observed.

5b: (5-Fluorobenzofuran-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using 4-fluoro-2-iodophenol (59 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (2.9 mg, 0.015 mmol, 6 mol%), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 10 mol%), and K_2CO_3 (52 mg, 0.375 mmol, 1.5 equiv). The vessel was then capped and purged with N_2 before addition of DMF (2 mL, 0.125 M). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-90% EtOAc/petroleum ether) to afford the title compound as a white solid (65 mg, 0.22 mmol, 89%).

υ_{max} (solid): 3015, 2958, 2924, 1760, 1563, 1470, 1448 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.60 (dd, *J* = 9.0, 4.2 Hz, 1H), 7.46 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.14 (td, *J* = 9.1, 2.6 Hz, 1H), 7.08 (s, 1H), 4.43 (d, *J* = 17.2 Hz, 2H), 4.19 (d, *J* = 17.2 Hz, 2H), 2.70 (s, 3H).

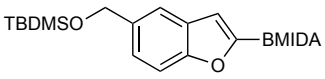
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.4, 158.9 (d, $^1J_{C\text{-}F}$ = 235.4 Hz), 153.6, 129.3 (d, $^3J_{C\text{-}F}$ = 11.0 Hz), 115.2 (d, $J_{C\text{-}F}$ = 3.6 Hz), 112.7 (d, $^3J_{C\text{-}F}$ = 9.9 Hz), 112.5 (d, $^2J_{C\text{-}F}$ = 26.5 Hz), 107.1 (d, $^2J_{C\text{-}F}$ = 24.8 Hz), 62.1, 47.8. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 8.81.

^{19}F NMR (DMSO-d_6, 471 MHz): δ –121.45.

HRMS: exact mass calculated for $[M\text{-}H]^-$ ($C_{13}H_{10}BFNO_5$) requires *m/z* 290.0642, found *m/z* 290.0638.

5c: (5-(((*tert*-Butyldimethylsilyl)oxy)methyl)benzofuran-2-yl)boronic acid, MIDA ester

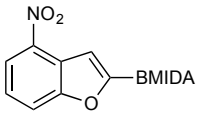


Prepared according to General Procedure B using 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-iodophenol (36 mg, 0.1 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (18 mg, 0.1 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (1.4 mg, 0.002 mmol, 2 mol%), CuI (1.1 mg, 0.006 mmol, 6 mol%), $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 10 mol%), and K_2CO_3 (21 mg, 0.15 mmol, 1.5 equiv). The vessel was then capped and purged with N_2 before addition of DMF (2 mL, 0.125 M). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 30-60% EtOAc/Petroleum Ether) to afford the title compound as an off-white solid (34 mg, 0.08 mmol, 82%).

υ_{max} (solid) 2937, 2854, 1745, 1561, 1461, 1454, 1297, 1251 cm^{-1}.

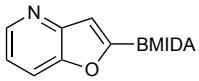
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.60 (d, J = 7.9 Hz, 1H), 7.49 (s, 1H), 7.18 (dd, J = 8.0, 1.3 Hz, 1H), 7.05 (d, J = 1.0 Hz, 1H), 4.82 (s, 2H), 4.42 (d, J = 17.2 Hz, 2H), 4.19 (d, J = 17.2 Hz, 2H), 2.70 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).
^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.0, 156.9, 138.2, 126.6, 120.9, 114.4, 108.6, 64.3, 61.6, 47.3, 25.8, 18.0, –5.3. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 9.34.
HRMS: exact mass calculated for $[M+Na]^+$ ($C_{20}H_{28}BNO_6SiNa$) requires *m/z* 440.1671, found *m/z* 440.1662.

5d: (4-Nitrobenzofuran-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using 2-iodo-3-nitrophenol (66 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (2.9 mg, 0.015 mmol, 6 mol%), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 10 mol%), and K_2CO_3 (52 mg, 0.375 mmol, 1.5 equiv). The vessel was then capped and purged with N_2 before addition of DMF (2 mL, 0.125 M). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 50-100% EtOAc/Petroleum Ether) to afford the title compound as a yellow solid (70 mg, 0.22 mmol, 88%).
υ_{max} (solid) 2919, 2850, 1773, 1757, 1524,, 1457, 1335, 1141 cm^{-1}.
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.22 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 1 Hz, 1H), 7.59 (t, J = 8.2 Hz, 1H), 4.48 (d, J = 17.3 Hz, 2H), 4.24 (d, J = 17.3 Hz, 2H), 2.76 (s, 3H).
^{13}C NMR (DMSO-d_6, 101 MHz): δ 168.9, 157.9, 139.9, 124.6, 122.9, 119.4, 118.6, 113.7, 61.9, 47.5. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 9.02.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}BN_2O_7$) requires *m/z* 319.0732, found *m/z* 319.0736.

5e: Furo[3,2-*b*]pyridin-2-ylboronic acid, MIDA ester

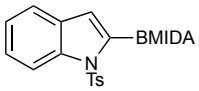


Prepared according to General Procedure B using 2-iodopyridin-3-ol (55 mg, 0.25 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (54 mg, 0.3 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol%), CuI (2.9 mg, 0.015 mmol, 6 mol%), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol, 10 mol%), and K_2CO_3 (52 mg, 0.375 mmol, 1.5 equiv). The vessel was then capped and purged with N_2 before addition of DMF (2 mL, 0.125 M). After 18 h, the vessel was allowed to cool to room temperature, vented, and decapped. The solution was then concentrated under reduced pressure before being diluted with EtOAc (10 mL) and washed with water (2 x 20 mL) and brine (2 x 20 mL). The organics were then dried and concentrated under reduced pressure to give a yellow solid, which was triturated with cold $CHCl_3$ (2 mL) to afford the title compound as a white solid (62 mg, 0.23 mmol, 91%).
υ_{max} (solid): 3093, 3004, 2948, 1777, 1686, 1411, 1279, 1147 cm^{-1}.
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.56 (br. s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.39 – 7.29 (m, 1H), 7.23 (s, 1H), 4.46 (d, J = 17.2 Hz, 2H), 4.21 (d, J = 17.2 Hz, 2H), 2.73 (s, 3H).
^{13}C NMR (DMSO-d_6, 101 MHz): δ 168.9, 147.7, 145.6, 119.4, 118.4, 115.2, 61.7, 47.3. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 128 MHz): δ 8.94.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{12}H_{10}BN_2O_5$) requires *m/z* 273.0688, found *m/z* 273.0688.

4.3 Products from scheme 3, scale up reactions

4a: (1-Tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester

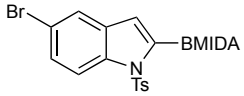


Prepared according to General Procedure C using *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (750 mg, 2 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (436 mg, 2.4 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol, 2 mol%), CuI (38 mg, 0.2 mmol, 10 mol%), $Cu(OAc)_2$ (109 mg, 0.6 mmol, 30 mol%), and K_3PO_4 (426 mg, 2 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as a white solid (694 mg, 1.62 mmol, 81%).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.12 (d, *J* = 9.1 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.42–7.33 (m, 3H), 7.26 (t, *J* = 7.0 Hz, 1H), 7.07 (s, 1H), 4.48 (d, *J* = 17.4 Hz, 2H), 4.24 (d, *J* = 17.4 Hz, 2H), 2.97 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 172.0, 140.7, 140.2, 139.7, 139.6, 133.1, 129.7, 128.8, 127.5, 127.4, 127.4, 127.2, 127.0, 52.1, 40.9.

4g: (5-Bromo-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure C using *N*-(4-bromo-2-iodophenyl)-4-methylbenzenesulfonamide (904 mg, 2 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (436 mg, 2.4 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol, 2 mol%), CuI (38 mg, 0.2 mmol, 10 mol%), $Cu(OAc)_2$ (109 mg, 0.6 mmol, 30 mol%), and K_3PO_4 (426 mg, 2 mmol, 1 equiv). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 40-80% EtOAc/Petroleum Ether) to afford the title compound as a white solid (900 mg, 1.82 mmol, 91%).

υ_{max} (solid): 3015, 2958, 1768, 1749, 1597, 1524, 1444 cm^{-1}.

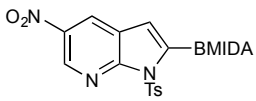
^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.51 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.07 (s, 1H), 4.49 (d, *J* = 17.5 Hz, 2H), 4.25 (d, *J* = 17.4 Hz, 2H), 2.97 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.0, 137.8, 135.2, 132.1, 130.5, 128.2, 127.1, 124.3, 121.4, 116.7, 116.6, 64.8, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.05.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}BBrN_2SO_6$) requires *m/z* 505.0238, found *m/z* 505.0238.

4m: (5-Nitro-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure C using *N*-(3-iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide (628 mg, 1.5 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (299 mg, 1.65 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (21 mg, 0.03 mmol, 2 mol%), CuI (28.5 mg, 0.02 mmol, 10 mol%), $Cu(OAc)_2$ (13.6 mg, 0.075 mmol, 30 mol%), and K_3PO_4 (53 mg, 0.25 mmol, 1 equiv). After 18 h, the vessel was allowed to cool to room temperature, vented, and decapped. The solution was

then concentrated under reduced pressure before being diluted with EtOAc and washed with water and brine. The organics were dried through a hydrophobic frit and concentrated under reduced pressure. The resulting yellow solid was then triturated with cold $CHCl_3$ (10 mL) followed by cold Et_2O (10 mL) to afford the title compound as a pale yellow solid (700 mg, 1.49 mmol, 99%).

υ_{max} (solid): 2956, 2924, 1747, 1587, 1521, 1455, 1376, 1340 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz): δ 9.23 (d, J = 2.6 Hz, 1H), 8.97 (d, J = 2.5 Hz, 1H), 8.18 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.25 (s, 1H), 4.52 (d, J = 17.5 Hz, 2H), 4.31 (d, J = 17.5 Hz, 2H), 3.07 (s, 3H), 2.35 (s, 3H).

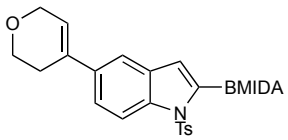
^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.2, 151.7, 146.1, 141.1, 140.5, 134.6, 129.9, 127.9, 126.0, 120.9, 118.4, 64.8, 49.7, 21.1. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 7.76.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}BN_4O_8$) requires *m/z* 473.0936, found *m/z* 473.0933.

4.4 Products from schemes 4 and 5

6: (5-(3,6-Dihydro-2*H*-pyran-4-yl)-1-tosyl-1*H*-indol-2-yl)boronic acid



To an oven-dried 5 mL microwave vial was added (5-bromo-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester (126 mg, 0.25 mmol, 1 equiv), 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (68 mg, 0.325 mmol, 1.3 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 24 h in a sandbath. Upon completion of the reaction the mixture was filtered through a pad of celite and concentrated at reduced pressure. The crude residue was diluted with EtOAc (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were dried and concentrated under reduced pressure to give a yellow oil that was purified by flash chromatography (silica gel, 40-90% EtOAc/petroleum ether) to afford the title compound as a white solid (108 mg, 0.21 mmol, 85%).

υ_{max} (solid): 2954, 2921, 2850, 1766, 1597, 1532, 1455, 1338, 1294 cm^{-1}.

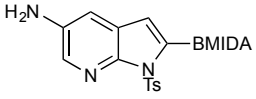
^1H NMR (DMSO-d_6, 400 MHz): δ 8.08 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 1.7 Hz, 1H), 7.50 (dd, J = 8.9, 1.9 Hz, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.04 (s, 1H), 6.27 – 6.21 (m, 1H), 4.47 (d, J = 17.5 Hz, 2H), 4.27–4.18 (m, 4H), 3.84 (t, J = 5.5 Hz, 2H), 2.96 (s, 3H), 2.48 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.1, 145.2, 137.7, 135.4, 135.0, 133.0, 129.9, 129.8, 126.5, 122.5, 122.2, 122.0, 117.1, 114.1, 65.1, 64.2, 63.6, 49.4, 26.7, 21.0. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.70.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{25}H_{25}BN_2O_7SNa$) requires *m/z* 531.1372, found *m/z* 531.1382.

7: (5-Amino-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)boronic acid, MIDA ester



An oven dried 15 mL flask was charged with (5-nitro-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)boronic acid, MIDA ester (100 mg, 0.211 mmol, 1 equiv) and 10% Pd/C (45 mg, 0.021 mmol, 10 mol%). The flask was purged with N_2 before the addition of 2.1 mL of 4:1 MeOH:EtOAc (0.1 M). The flask was then purged three times with H_2 before being left to stir at room temperature for 16 h under an atmosphere of hydrogen (balloon pressure). Upon completion of the reaction, the flask was purged with N_2 and the contents were filtered through a pad of celite and concentrated under reduced pressure to afford the title compound as a yellow solid (85 mg, 0.19 mmol, 91%).

υ_{max} (solid): 3496, 3348, 2954, 2921, 1745, 1666, 1597, 1524, 1403, 1338 cm^{-1}.

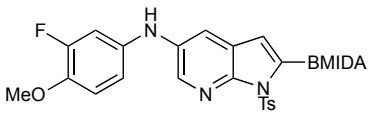
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.07 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 2.6 Hz, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 2.6 Hz, 1H), 6.80 (s, 1H), 4.48 (d, J = 17.5 Hz, 2H), 4.26 (d, J = 17.4 Hz, 2H), 3.05 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.2, 144.8, 143.4, 141.8, 135.7, 133.8, 129.5, 127.4, 121.9, 117.6, 111.6, 64.7, 49.6, 21.0. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.68.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}BN_4O_6S$) requires *m/z* 443.1192, found *m/z* 443.1176.

8: (5-((3-Fluoro-4-methoxyphenyl)amino)-1-tosyl-1*H*-pyrrolo[2,3-b]pyridin-2-yl)boronic acid, MIDA ester



A 5 mL oven dried flask was charged with (5-amino-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)boronic acid, MIDA ester (50 mg, 0.11 mmol, 1 equiv), (3-fluoro-4-methoxyphenyl)boronic acid (37 mg, 0.21 mmol, 2 equiv), and $Cu(OAc)_2$. To this, Et_3N (30 µL, 0.21 mmol, 2 equiv) and MeCN (0.4 mL, 0.25 M) were added and the reaction was left to stir at room temperature for 16 h. Upon completion of the reaction, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was diluted with EtOAc (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were dried and concentrated under reduced pressure to give a purple solid that was purified by flash chromatography (silica gel, 40-80% EtOAc/petroleum ether) to afford the title compound as an off-white solid (61 mg, 0.11 mmol, 100%).

υ_{max} (solid): 3361, 2952, 2951, 2850, 1759, 1745, 1597, 1513, 1338 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.16 (s, 1H), 8.14–8.10 (m, 3H), 7.68 (d, J = 2.6 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.93 (s, 1H), 6.89 (dd, J = 13.4, 2.6 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 4.49 (d, J = 17.5 Hz, 2H), 4.28 (d, J = 17.4 Hz, 2H), 3.78 (s, 3H), 3.06 (s, 3H) 2.36 (s, 3H).

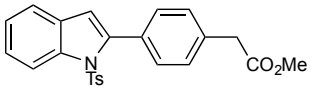
^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.3, 152.0 (d, $^1J_{C\text{-}F}$ = 243.1 Hz), 145.1, 140.8 (d, $^2J_{C\text{-}F}$ = 11.0 Hz), 137.7 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 137.0, 136.9, 135.5, 129.6, 127.5, 121.7, 117.8, 115.4 (d, $^2J_{C\text{-}F}$ = 15.5 Hz), 115.3, 112.5 (d, $J_{C\text{-}F}$ = 2.4 Hz), 105.3, 105.1, 64.7, 56.5, 49.6, 21.0. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 11.14.

^{19}F NMR (DMSO-d_6, 471 MHz): δ –133.35.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{26}H_{24}BFN_4O_7SNa$) requires *m/z* 589.1340, found *m/z* 589.1340.

9: Methyl 2-(4-(1-tosyl-1*H*-indol-2-yl)phenyl)acetate



To an oven-dried 5 mL microwave vial was added methyl 2-(4-bromophenyl)acetate (57 mg, 0.25 mmol, 1 equiv), (1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester (149 mg, 0.35 mmol, 1.4 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (8.2 mg, 0.01 mmol, 4 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was stirred at 60 °C for 24 h in a sandbath. Upon completion of the reaction, the mixture was filtered through a pad of celite and concentrated at reduced pressure. The crude residue was diluted with EtOAc (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were dried and concentrated under reduced pressure to give a brown oil that was purified by flash chromatography (silica gel, 10-20% EtOAc/petroleum ether) to afford the title compound as an off white solid (77 mg, 0.19 mmol, 74%).

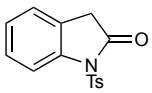
υ_{max} (solid): 2950, 2919, 2848, 1723, 1597, 1506, 1439, 1370, 1167 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.40–7.35 (m, 3H), 7.31 – 7.26 (m, 3H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.56 (s, 1H), 3.77 (s, 3H), 3.74 (s, 2H), 2.31 (s, 3H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ171.4, 144.1, 141.3, 137.8, 134.1, 134.0, 130.8, 130.1, 130.0, 128.7, 128.0, 126.3, 124.3, 123.9, 120.2, 116.2, 113.2, 51.7, 40.5, 21.0.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{24}H_{25}N_2O_4S_1$) requires *m/z* 437.1530, found *m/z* 437.1523.

10: 1-Tosylindolin-2-one[4]

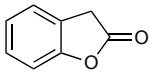


To an oven-dried 5 mL microwave vial charged with (1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester (85 mg, 0.2 mmol, 1 equiv) was added MeOH (0.8 mL) and KHF_2 solution (4.5 M in H_2O, 125 μL, 0.6 mmol, 3 equiv) and the reaction was stirred at 70 °C for 2 h. The reaction was cooled to room temperature before being concentrated at reduced pressure. The resulting white solid was dissolved in hot acetone (1 mL) and transferred to a 10 mL round bottomed flask. Oxone® (68 mg in 1 mL H_2O, 0.2 mmol, 1 equiv) was added and the reaction mixture was left to stir for 16 h at room temperature. The reaction was quenched with 1 N HCl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were filtered through a pad of silica and washed through with CH_2Cl_2 (50 mL). The organics were concentrated at reduced pressure to afford the desired product as an off white solid (45 mg, 0.16 mmol, 78%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.29–7.20 (m, 3H), 7.13 (d, *J* = 7.4, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 3.47 (s, 2H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.3, 145.2, 139.9, 134.8, 129.3, 128.1, 127.5, 124.2, 124.1, 122.7, 113.2, 35.6, 21.2.

11: Benzofuran-2(3*H*)-one[5]



To an oven-dried 5 mL microwave vial charged with benzofuran-2-ylboronic acid, MIDA ester (55 mg, 0.2 mmol, 1 equiv) was added MeOH (0.8 mL) and KHF_2 solution (4.5 M in H_2O, 125 μL, 0.6 mmol, 3 equiv) and the reaction was stirred at 70 °C for 2 h. The reaction was cooled to room temperature before the addition of Oxone® (68 mg in 1 mL H_2O, 0.2 mmol, 1 equiv), and the reaction mixture was left to stir for a further 10 min at room temperature. The reaction was quenched with 1 N HCl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were filtered through a

pad of silica and washed through with CH_2Cl_2 (50 mL). The organics were concentrated at reduced pressure to afford the desired product as colourless solid (24 mg, 0.18 mmol, 89%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26–7.19 (m, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 3.66 (s, 2H).
^{13}C NMR (DMSO-d_6, 101 MHz): δ173.6, 154.2, 128.4, 124.1, 123.6, 122.6, 110.3, 32.5.

5. References

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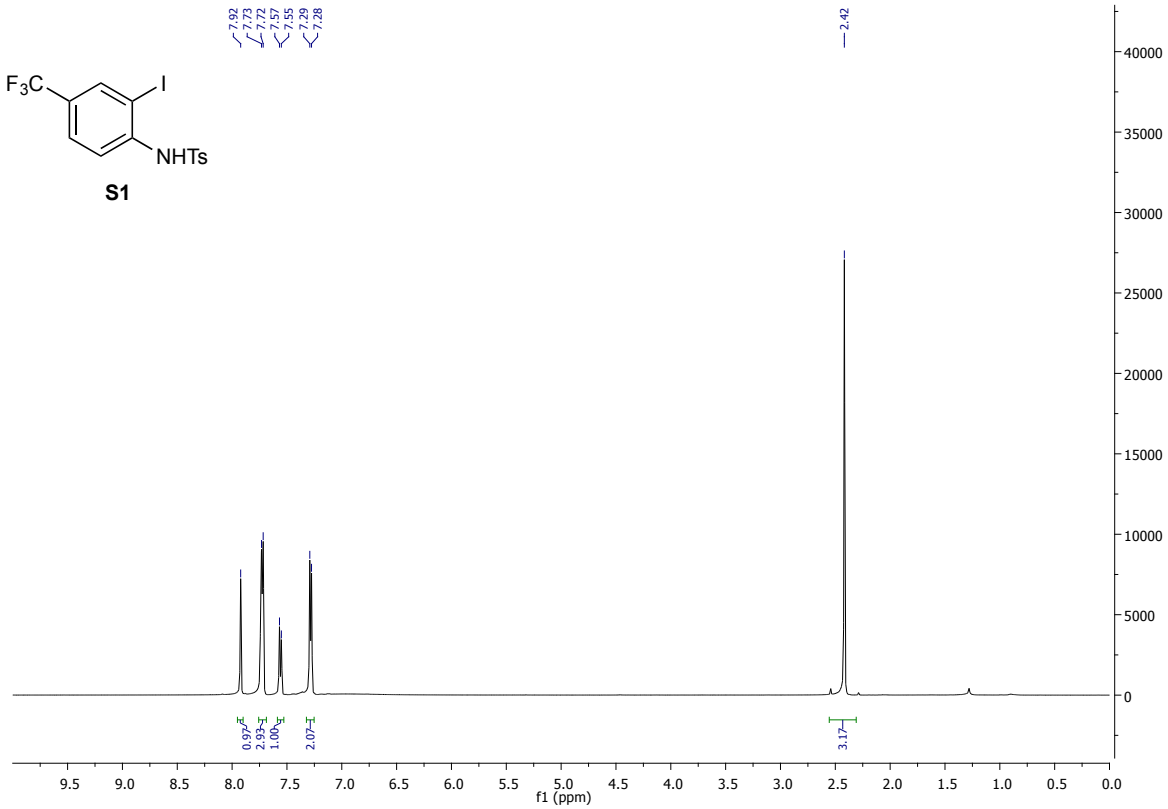
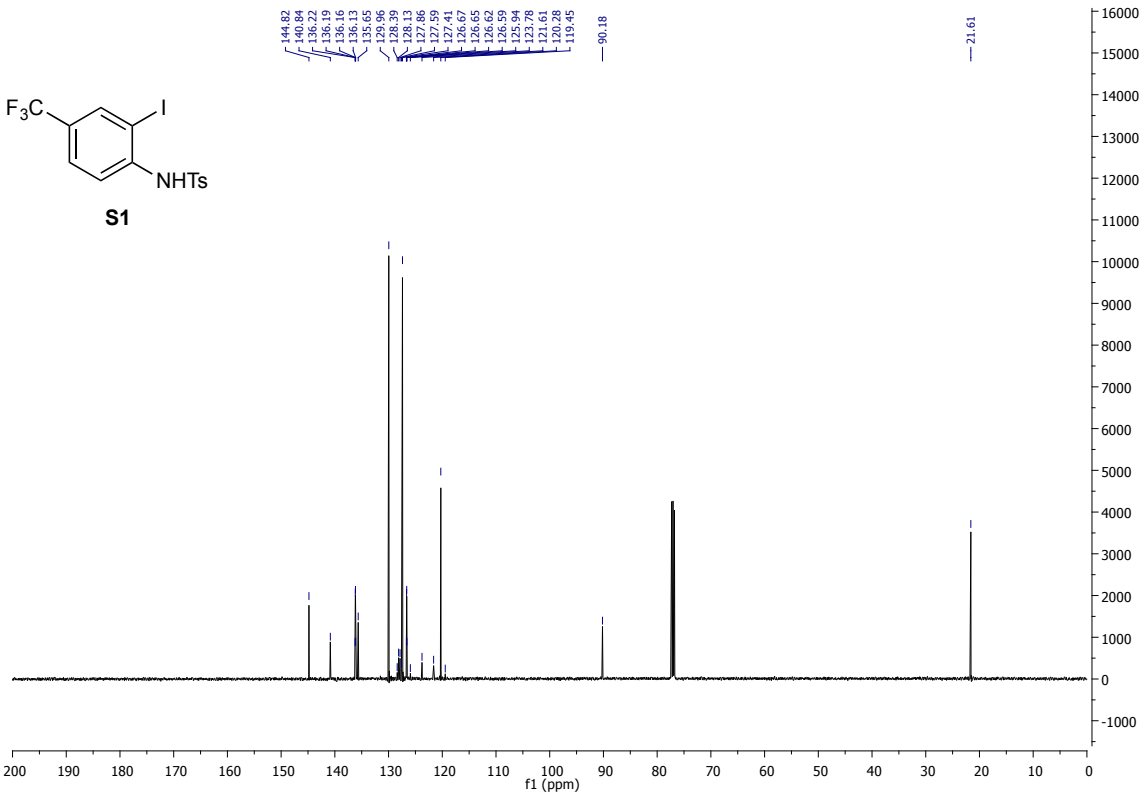
6. NMR and HRMS spectra for intermediates and products

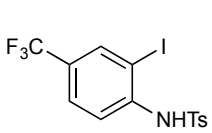
^{1}H NMR of S1



^{13}C NMR of S1



^{19}F NMR of S1

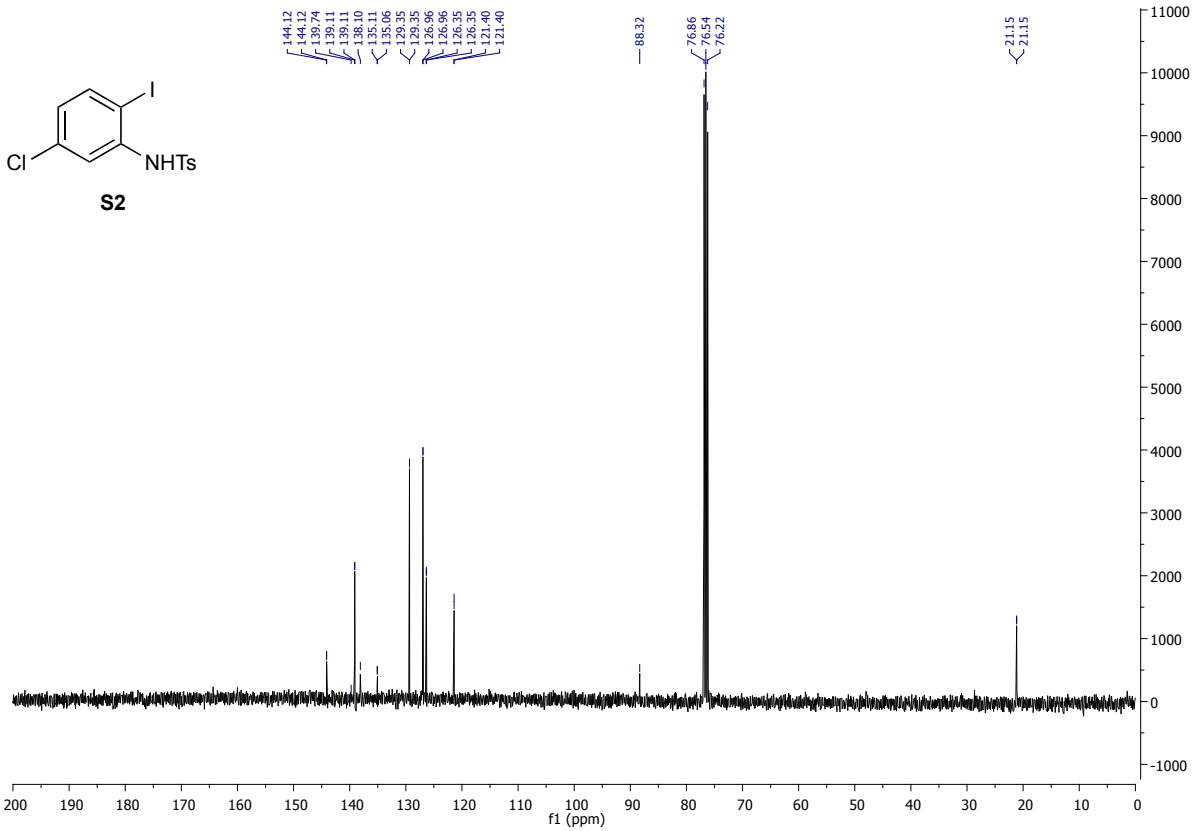


S1

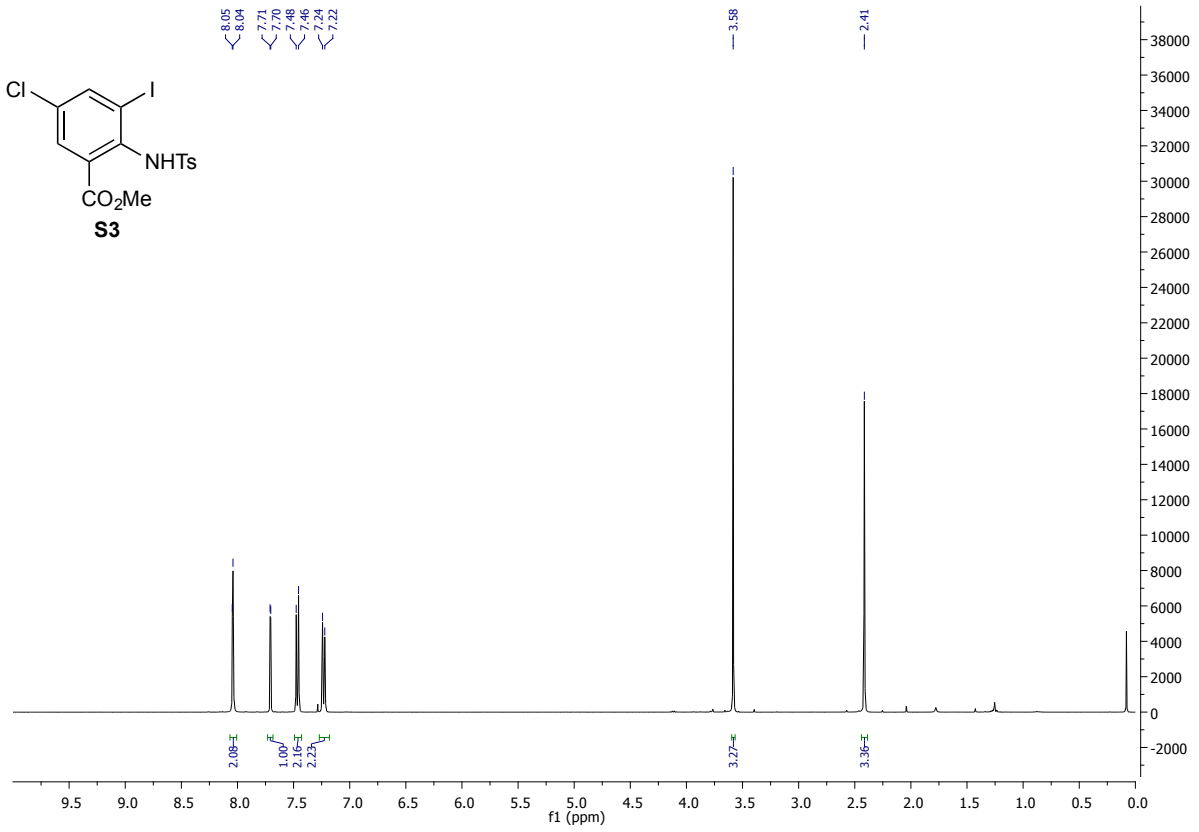
^{1}H NMR of S2

S2

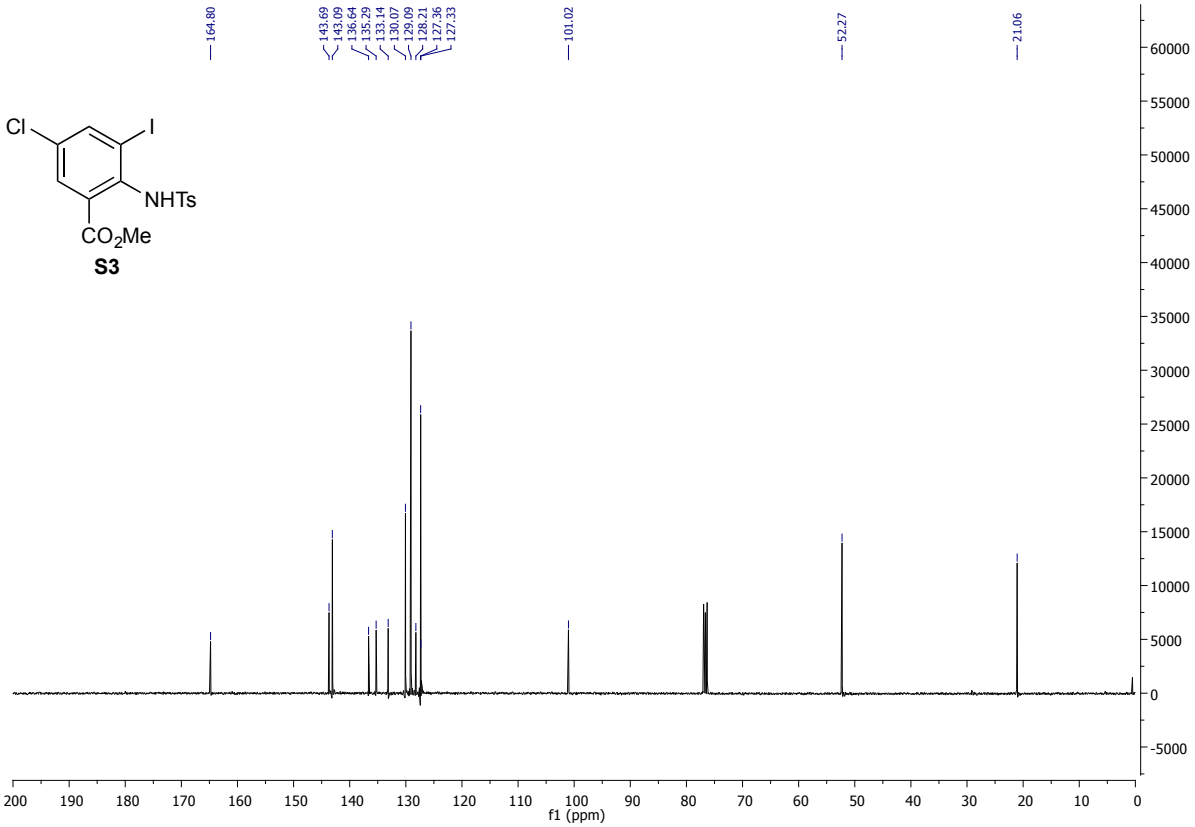
^{13}C NMR of S2



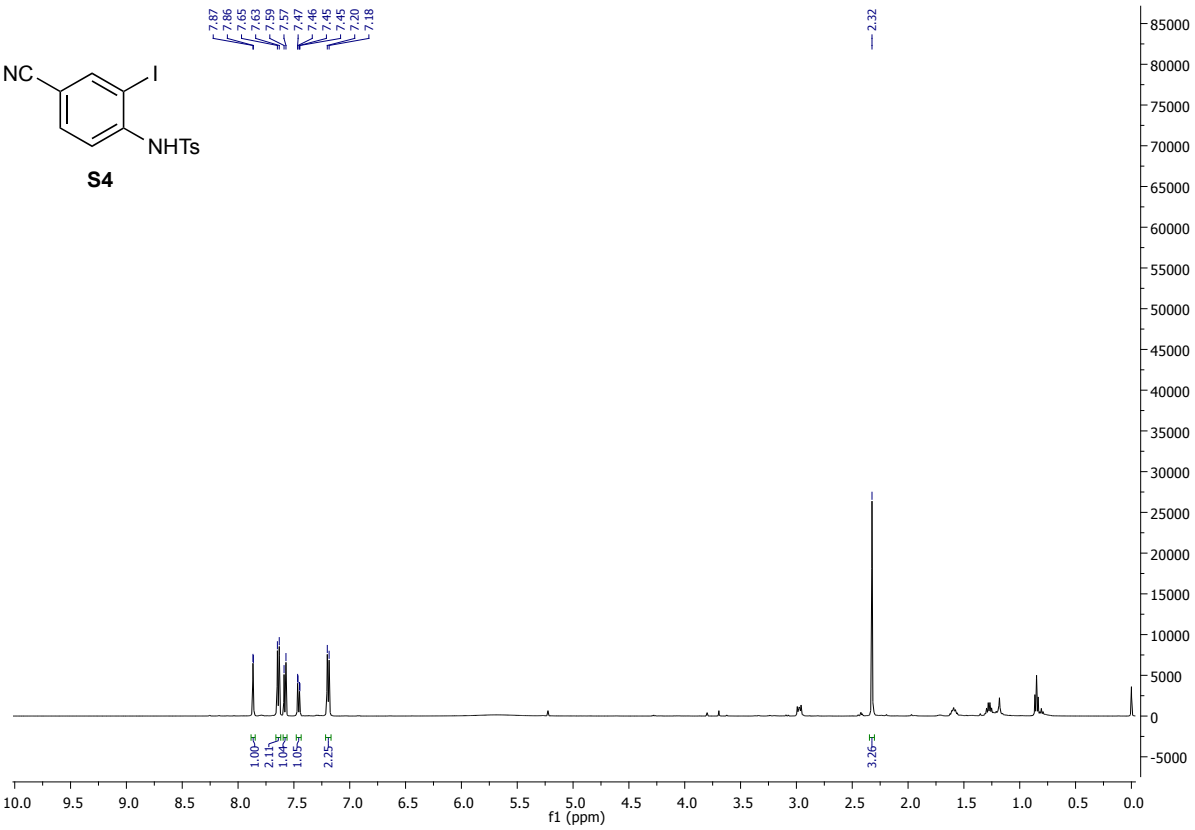
^{1}H NMR of S3



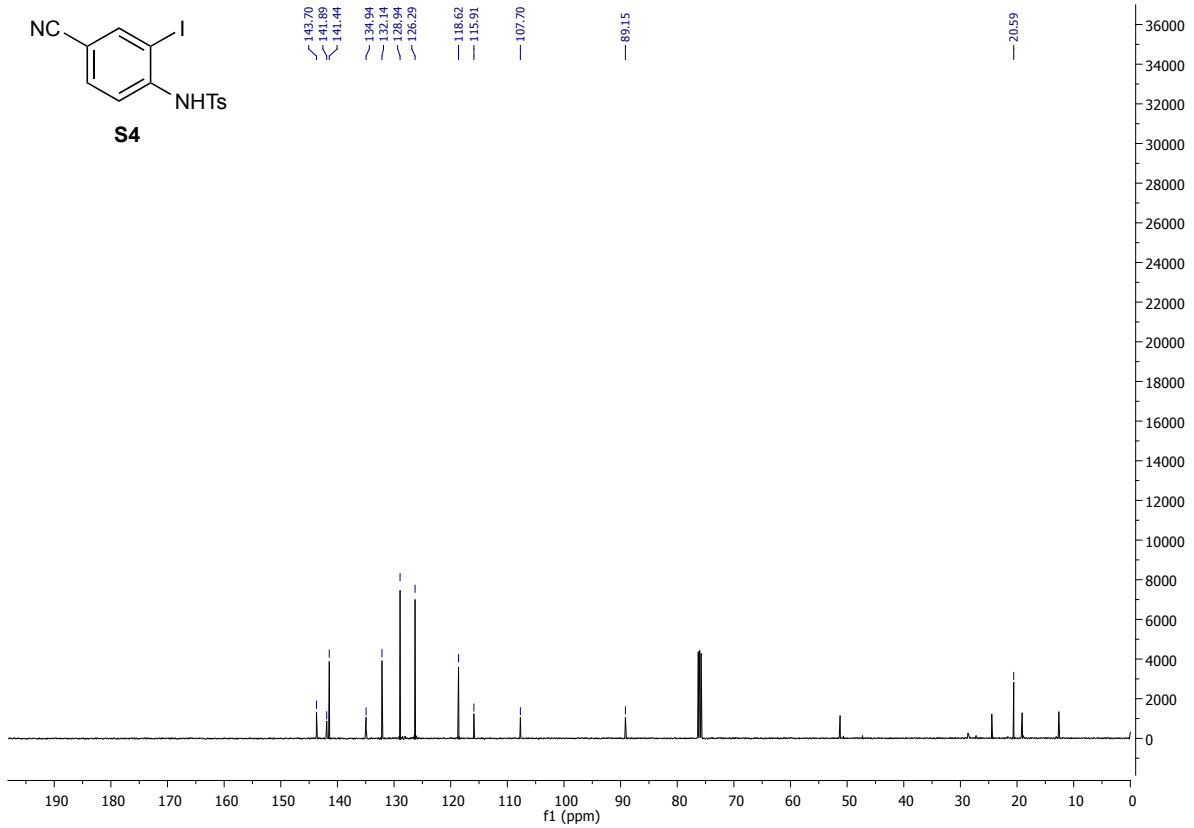
^{13}C NMR of S3



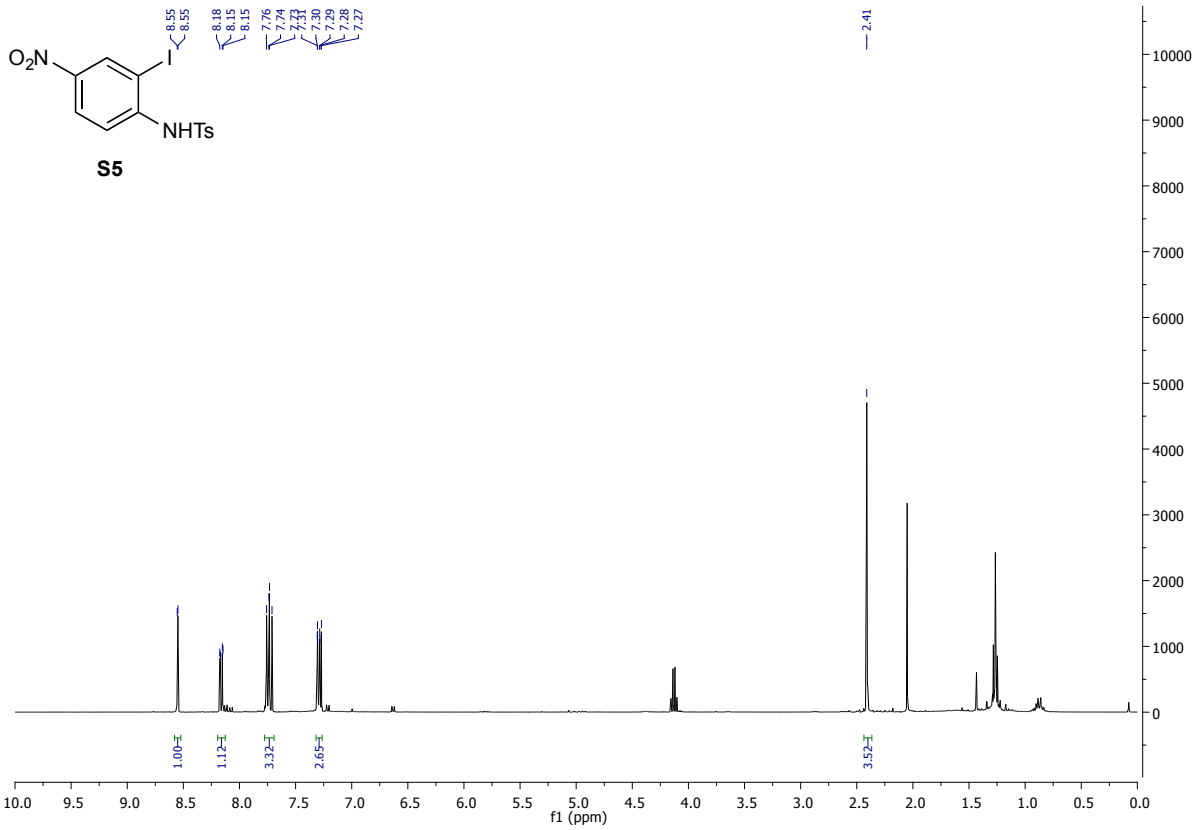
^{1}H NMR of S4



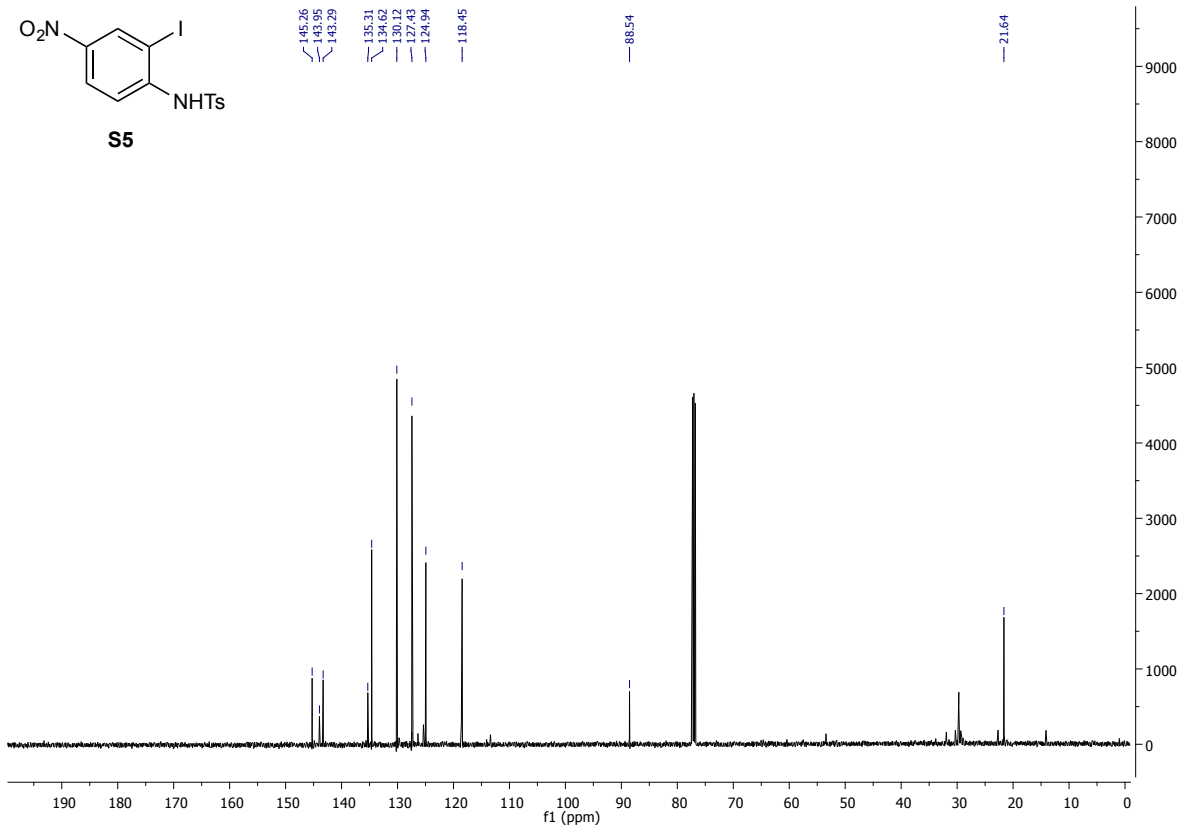
^{13}C NMR of S4



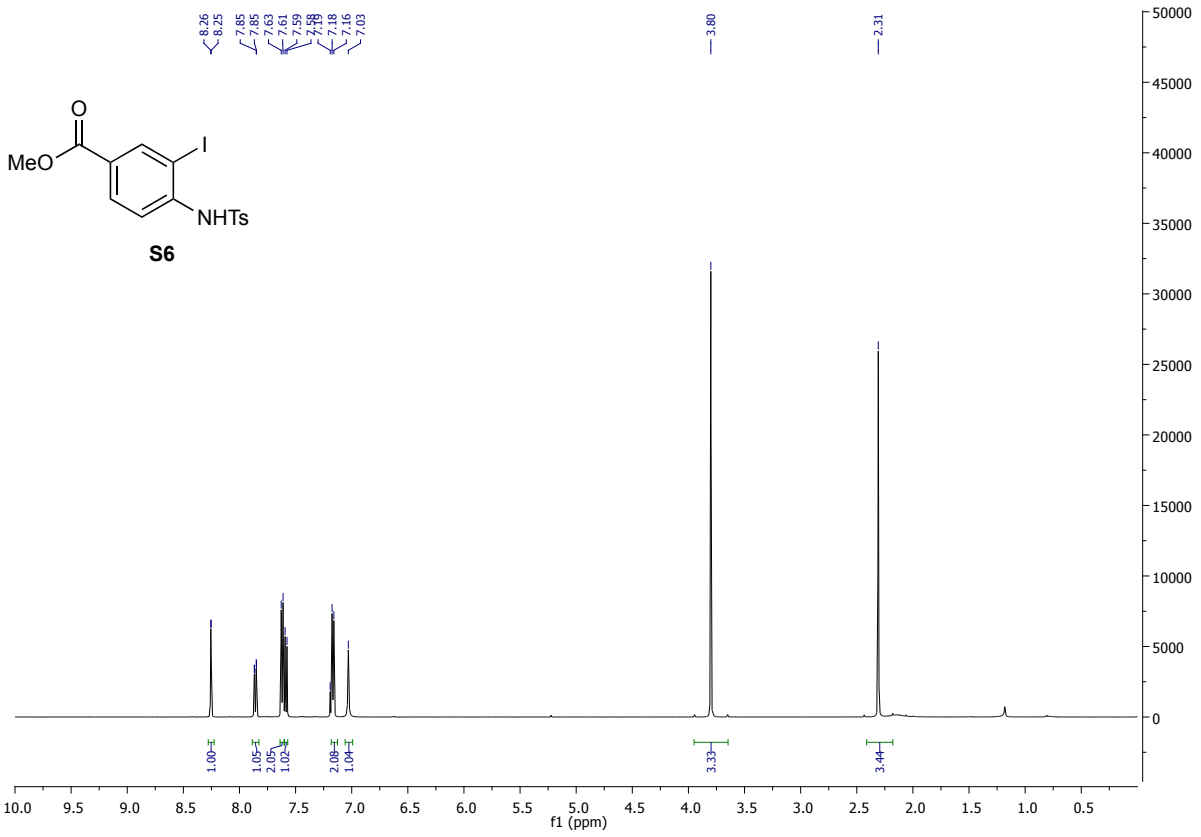
^{1}H NMR of S5



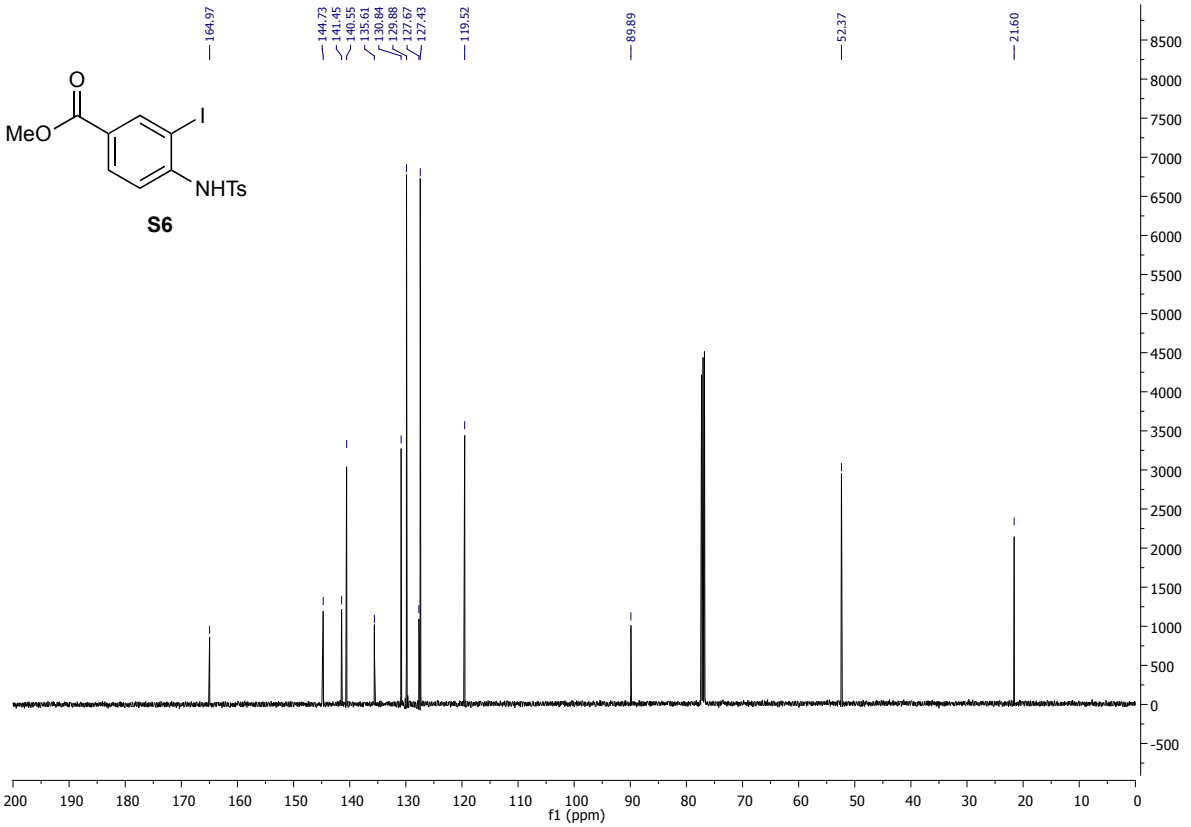
^{13}C NMR of S5



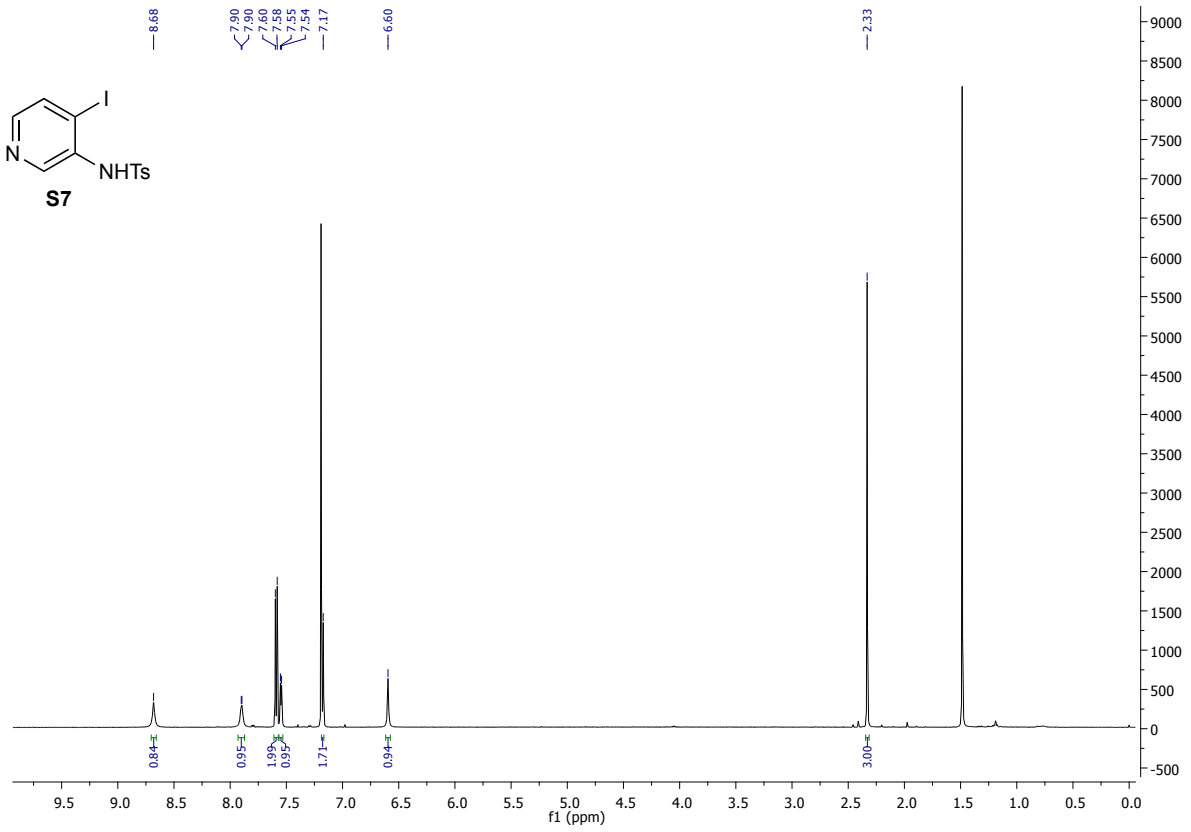
^{1}H NMR of S6



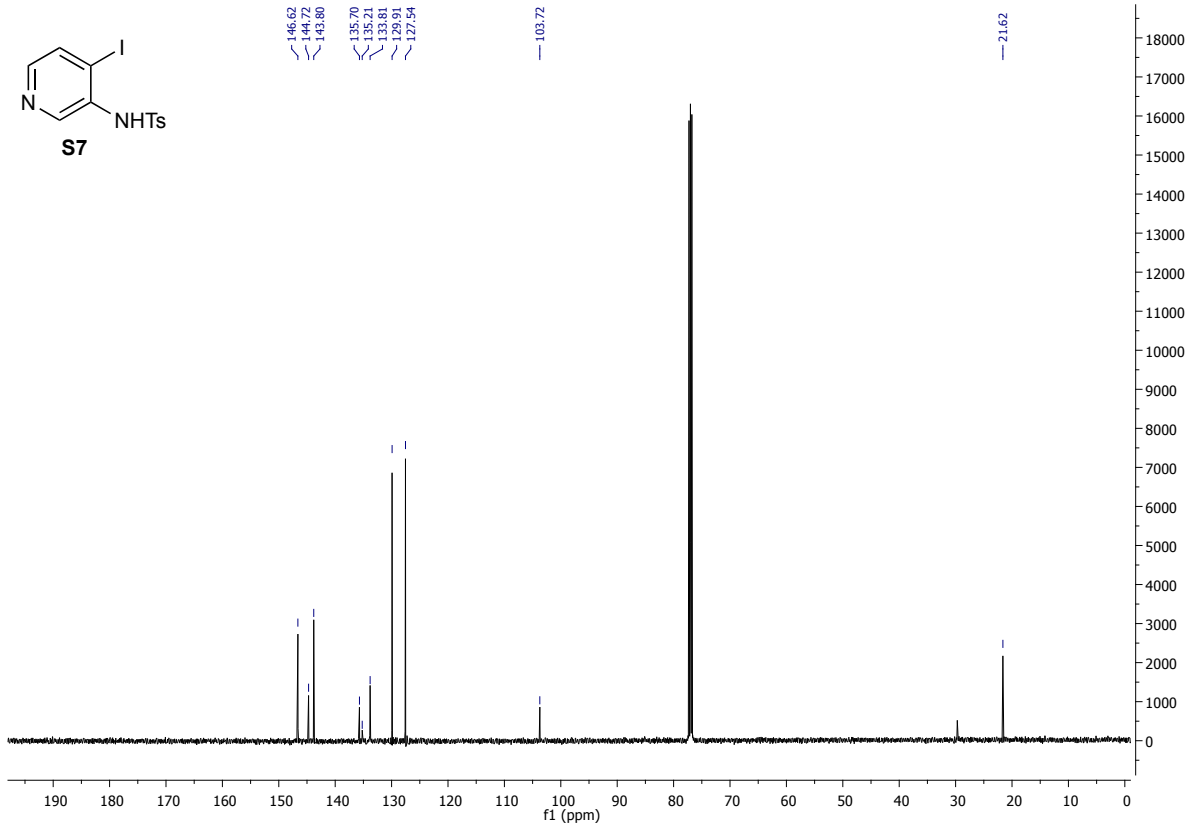
^{13}C NMR of S6



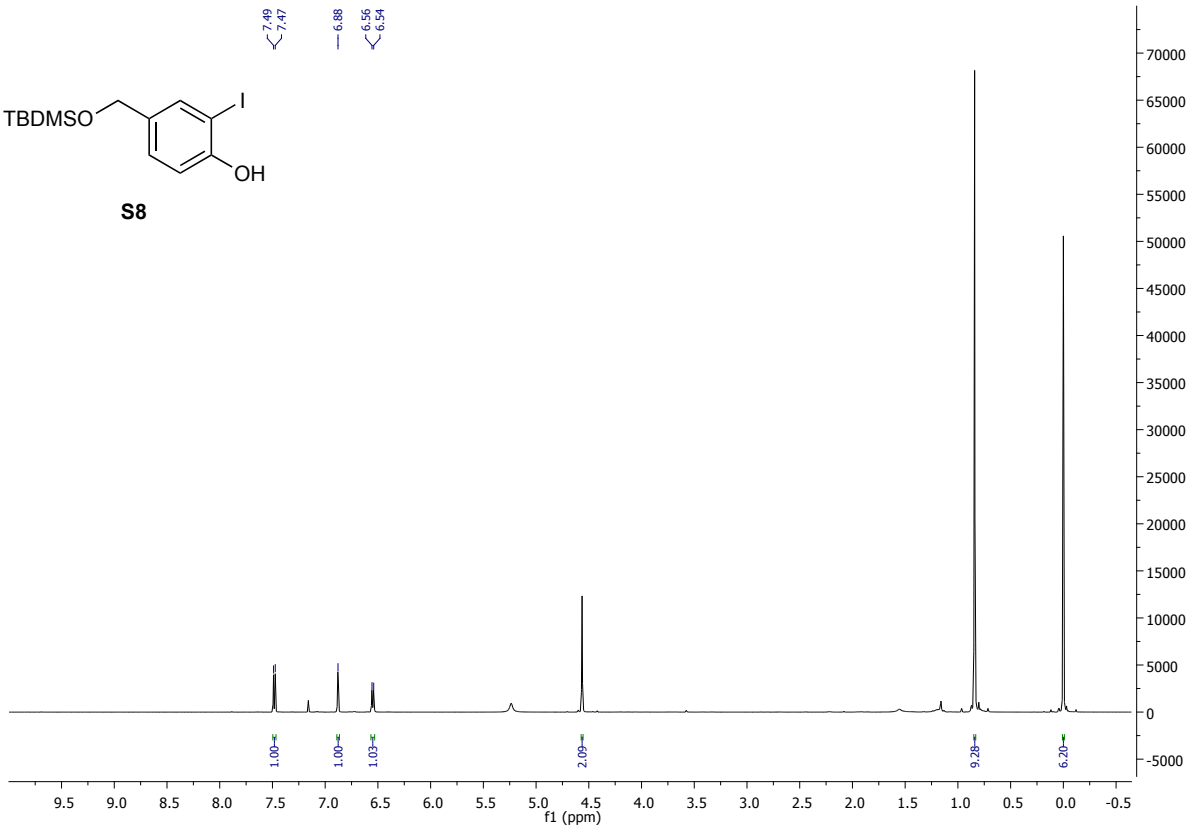
^{1}H NMR of S7



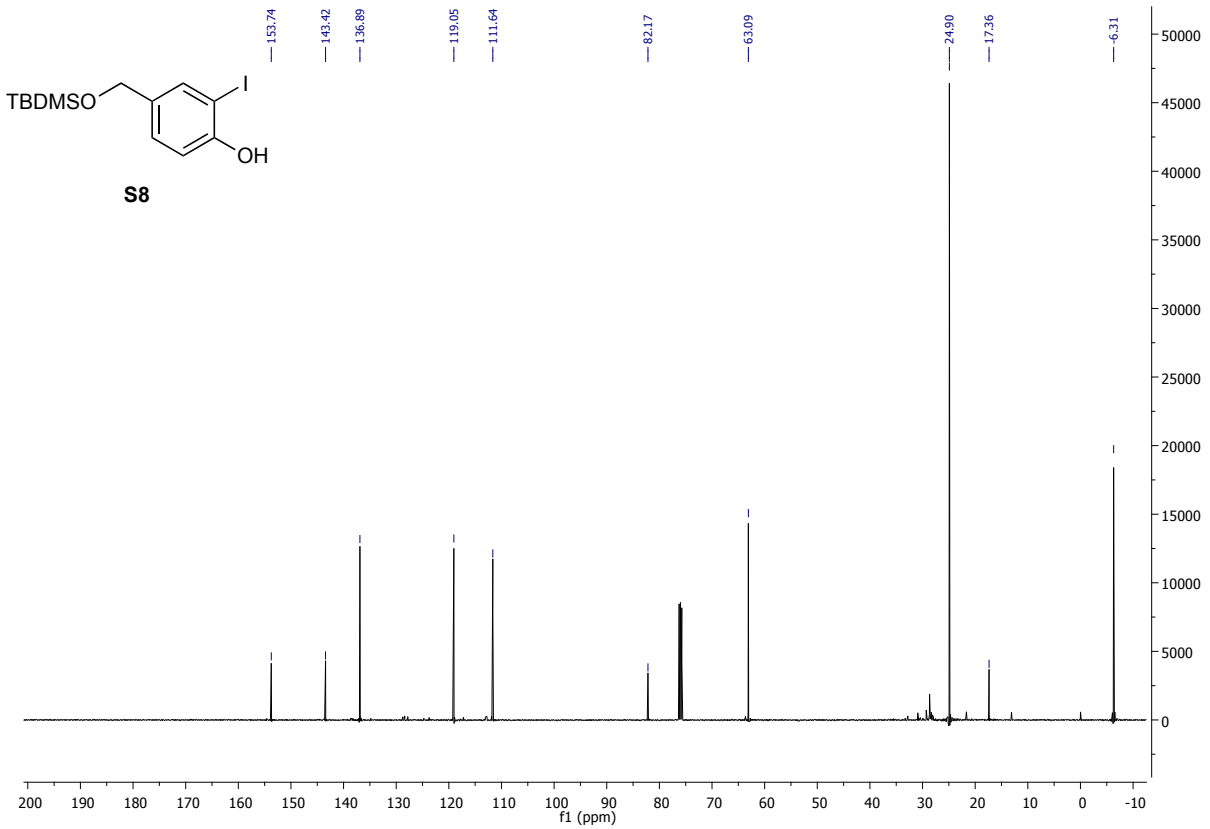
^{13}C NMR of S7



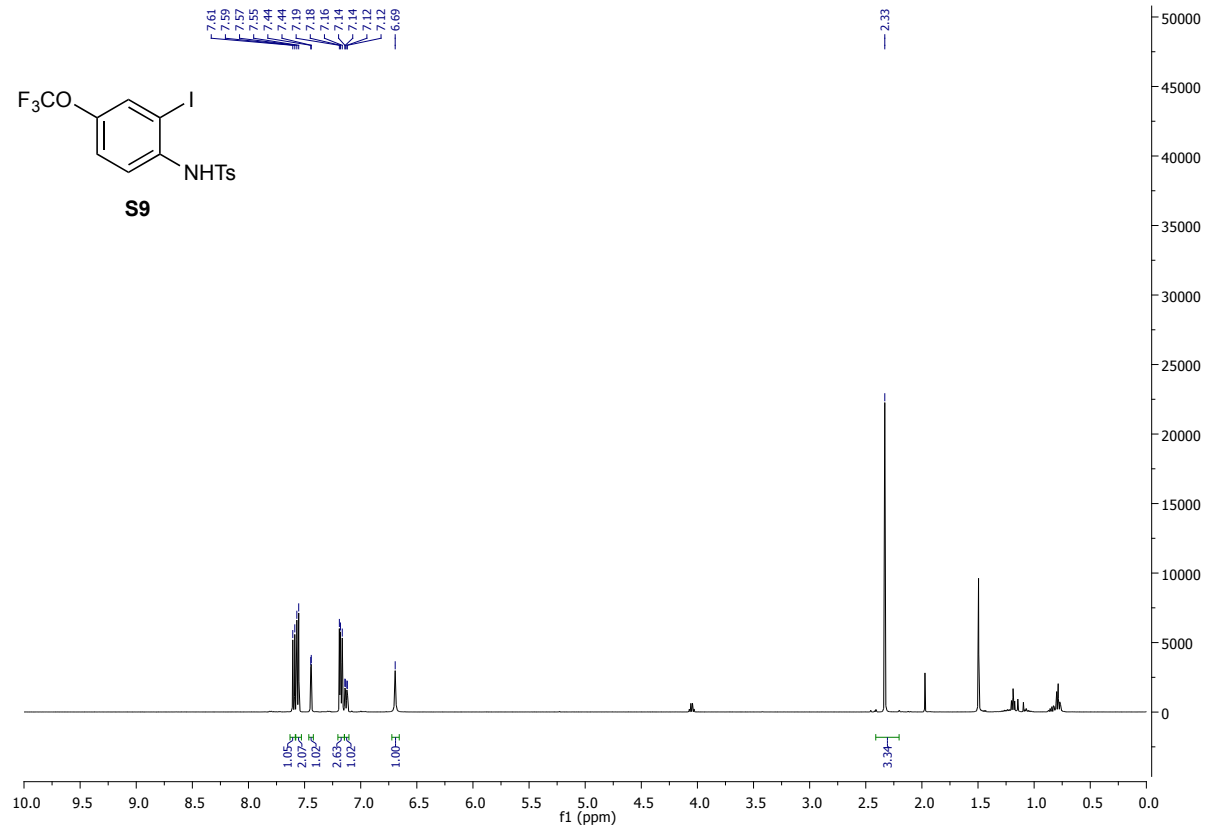
^{1}H NMR of S8



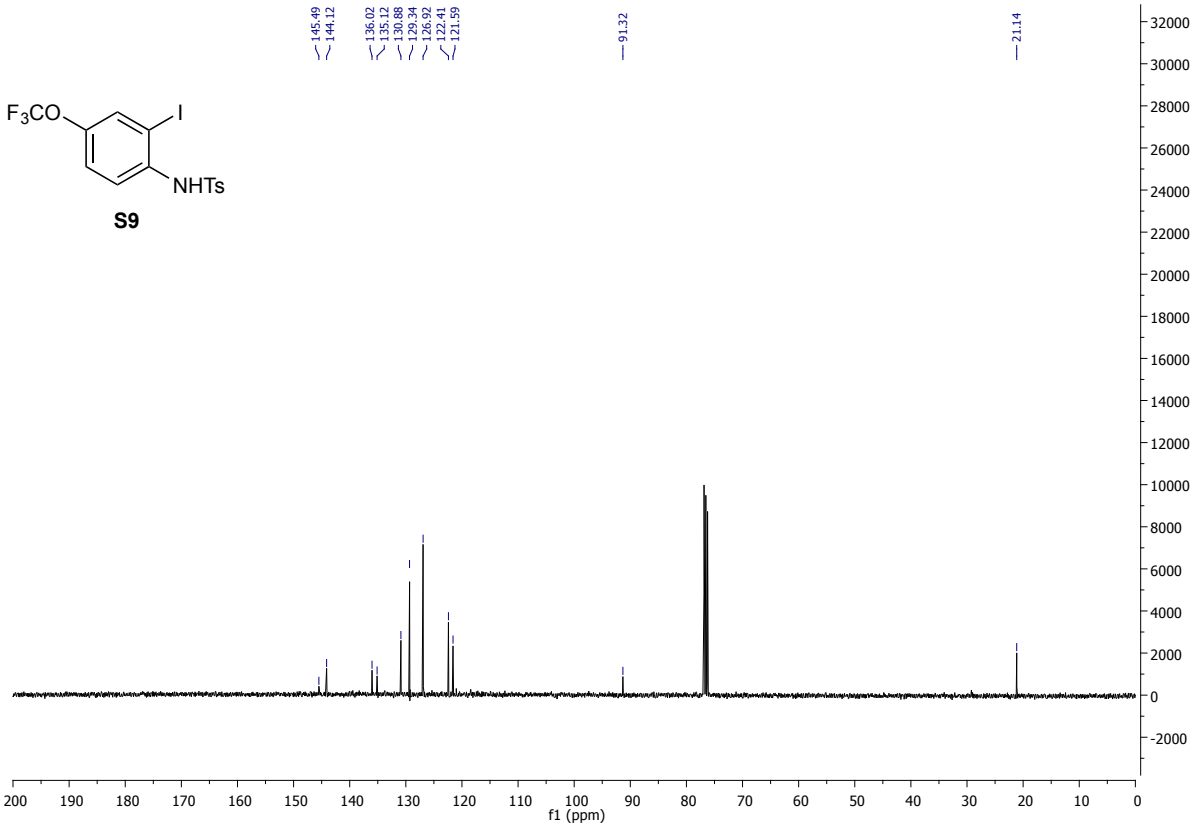
^{13}C NMR of S8



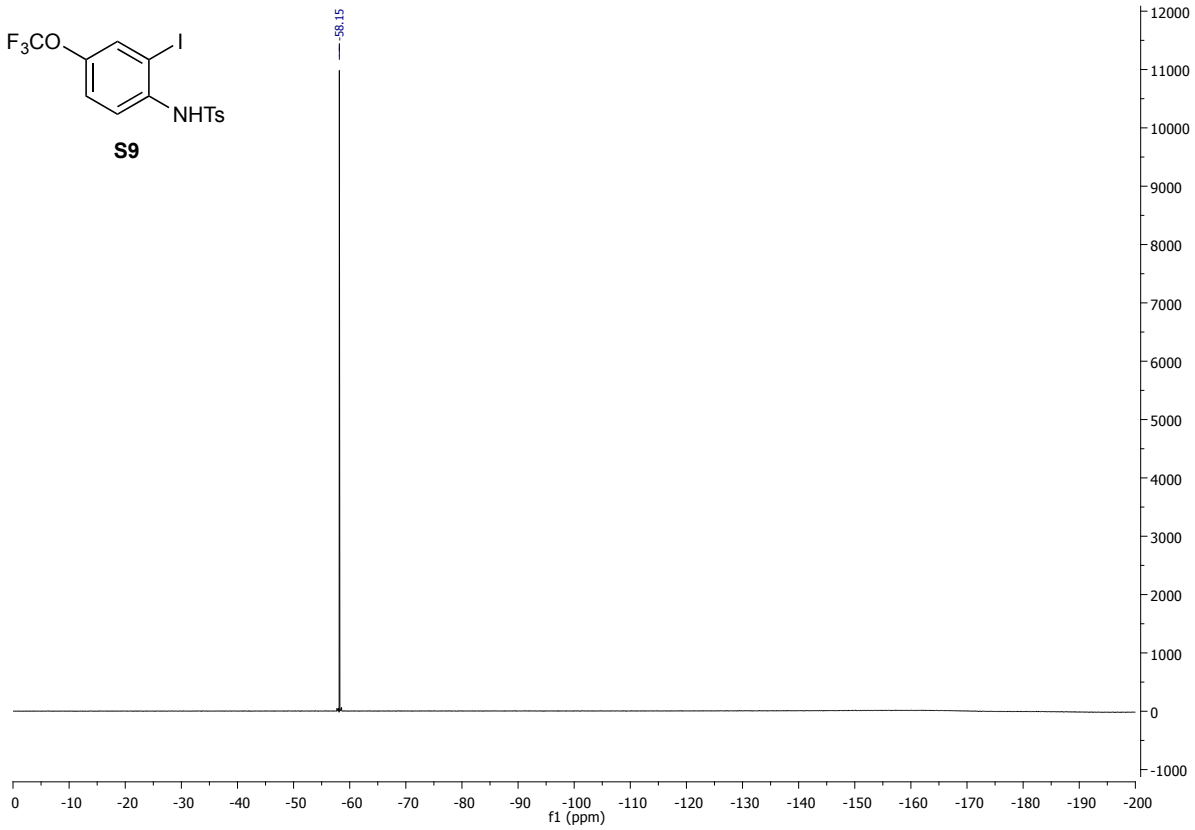
^{1}H NMR of S9



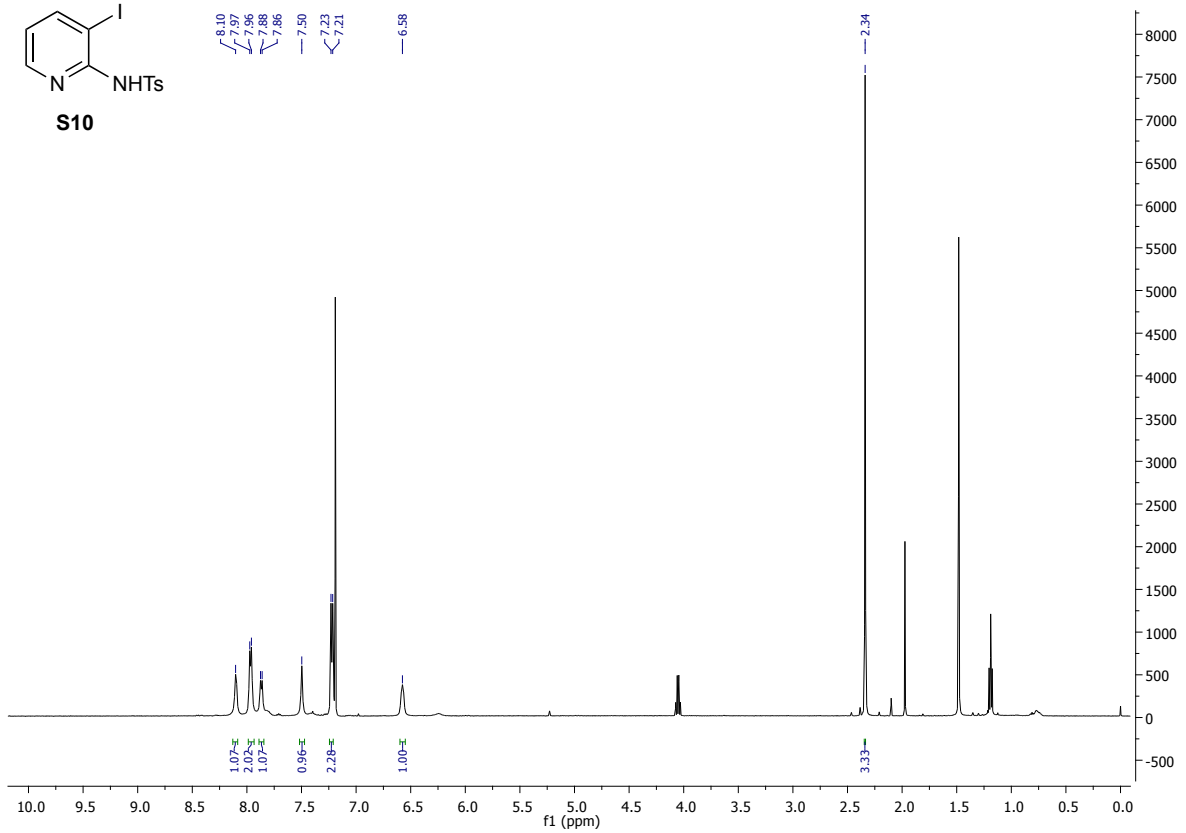
^{13}C NMR of S9



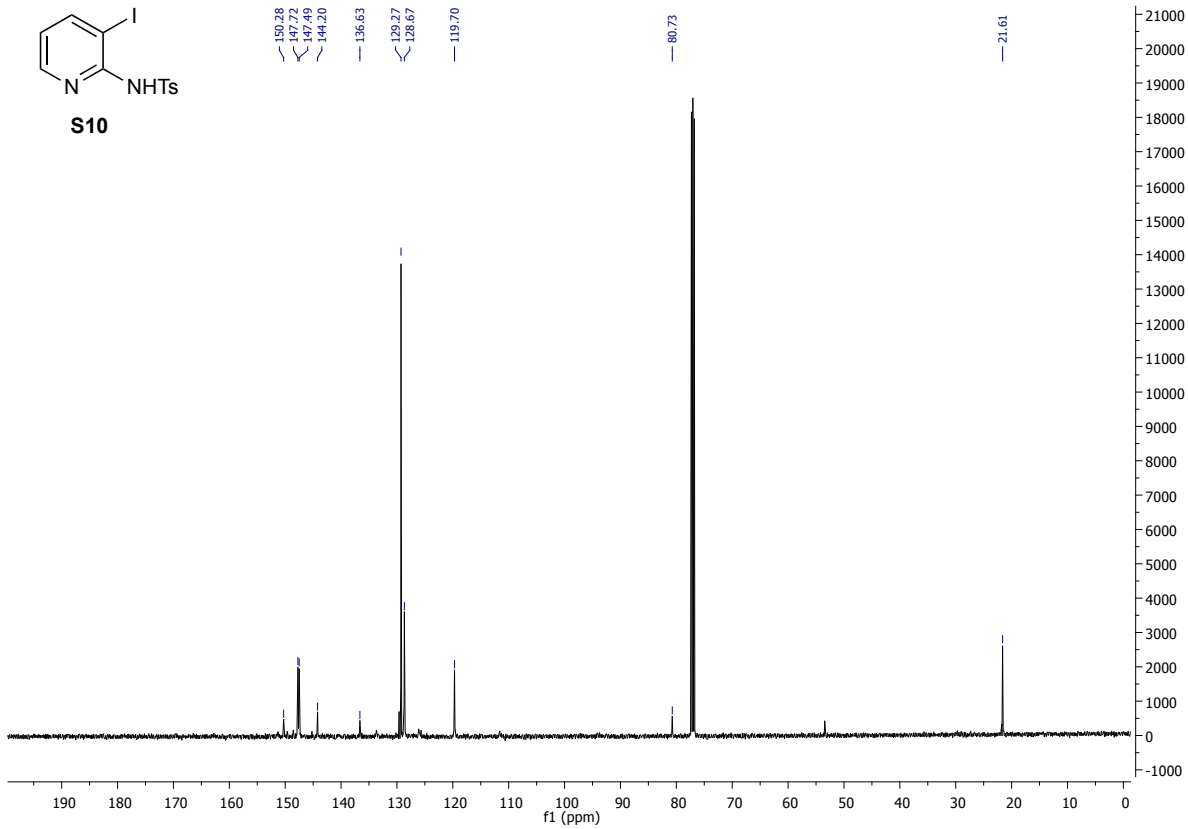
^{19}F NMR of S9



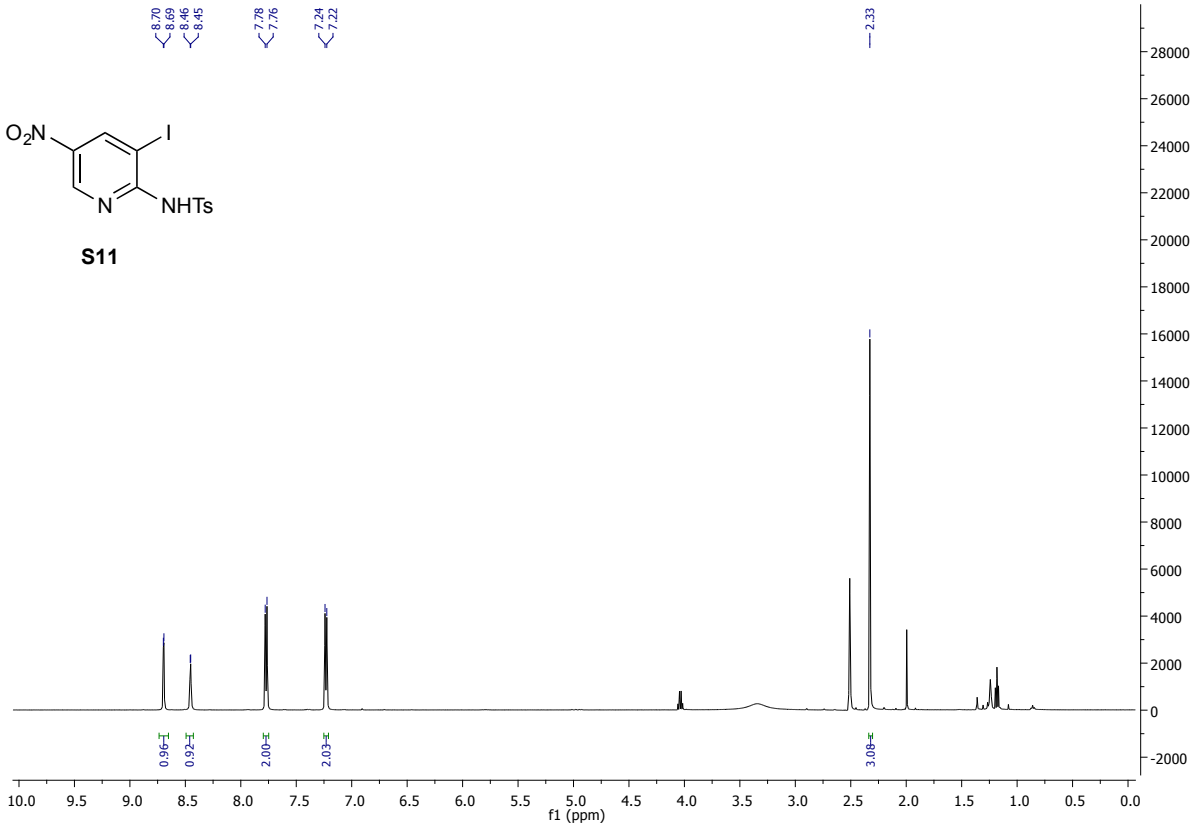
^{1}H NMR of S10



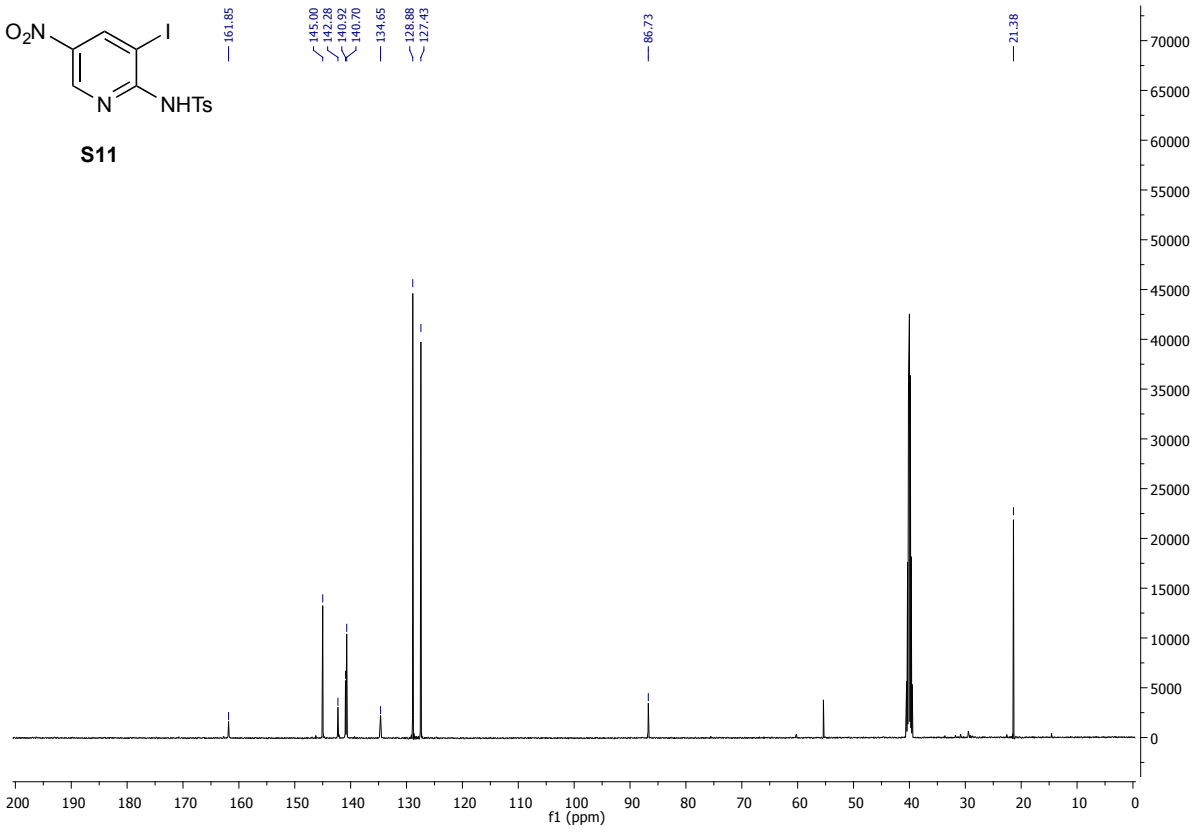
^{13}C NMR of S10



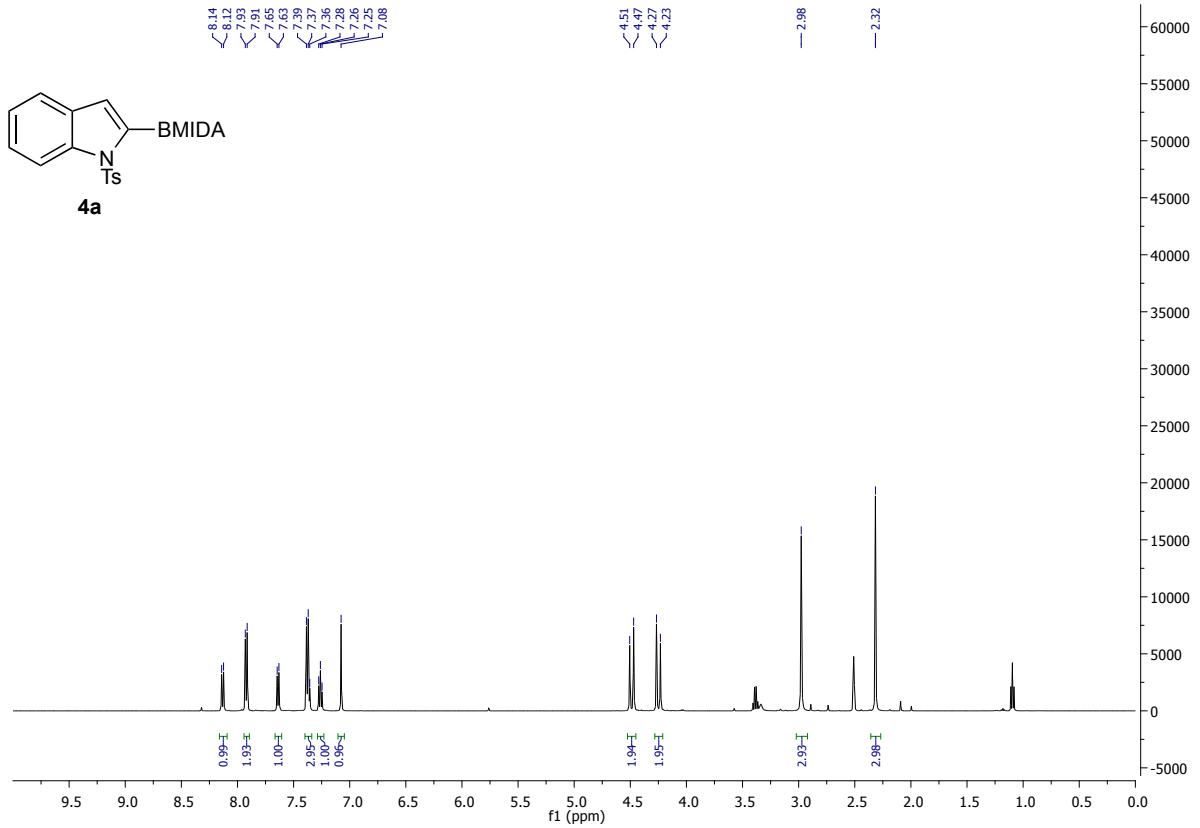
^{1}H NMR of S11



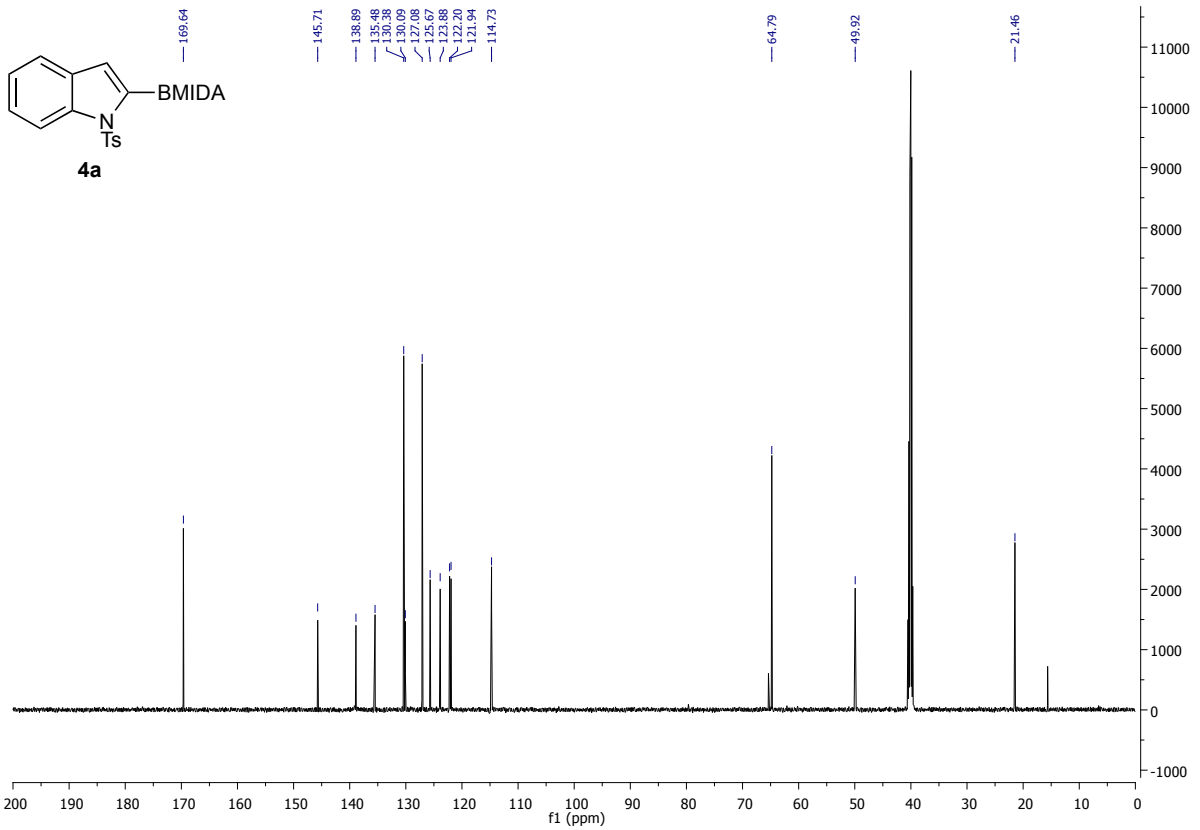
^{13}C NMR of S11



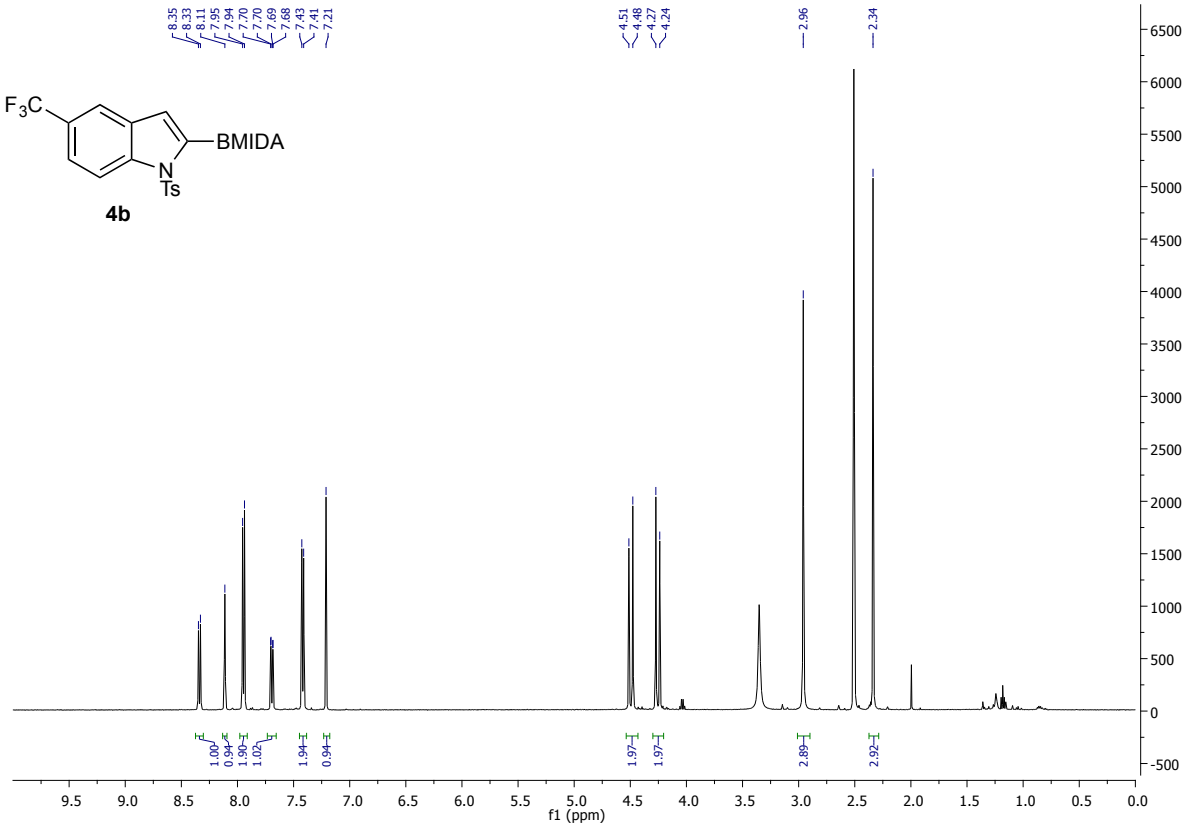
^{1}H NMR of 4a



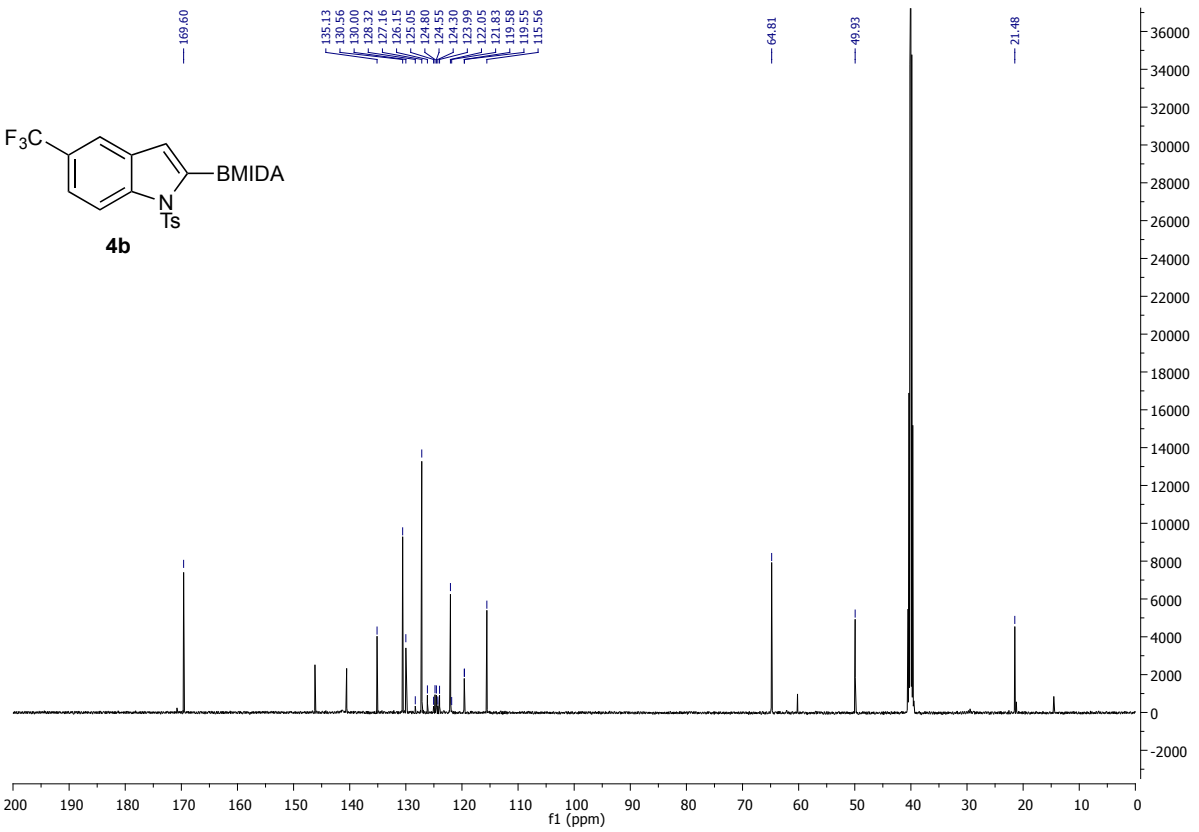
^{13}C NMR of 4a



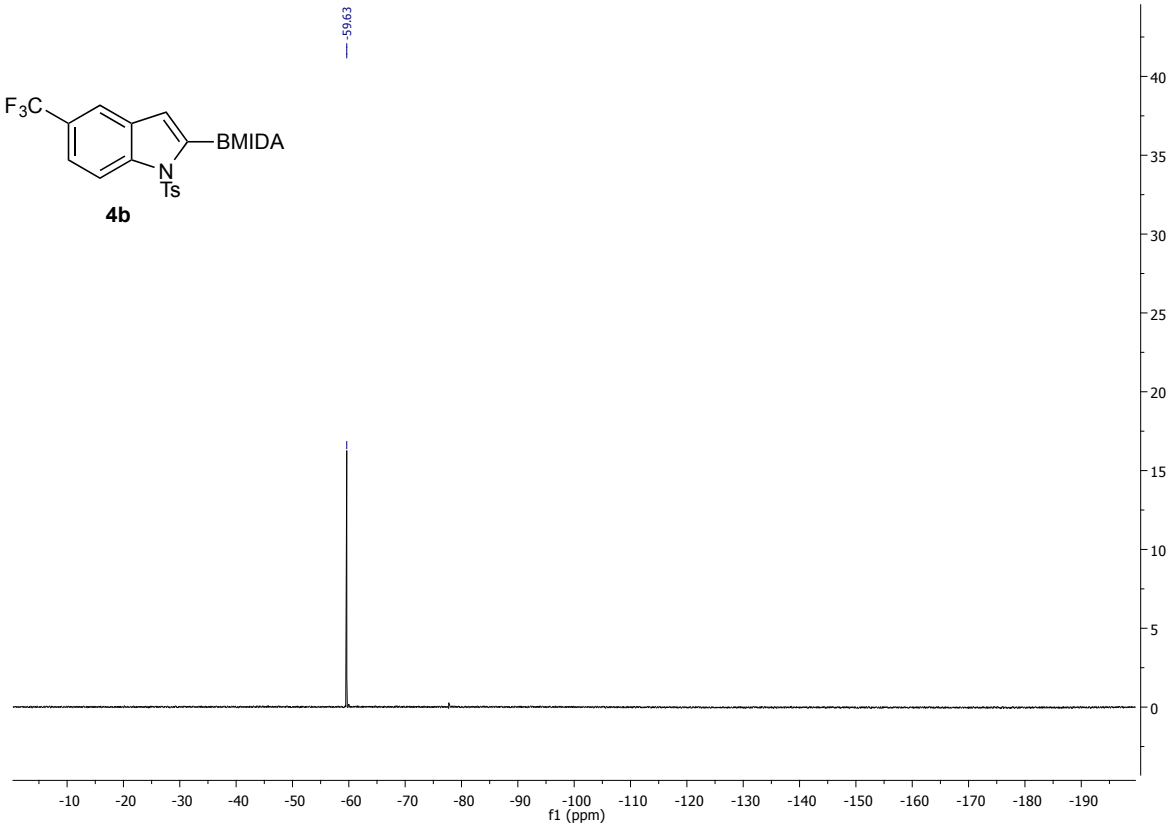
^{1}H NMR of 4b



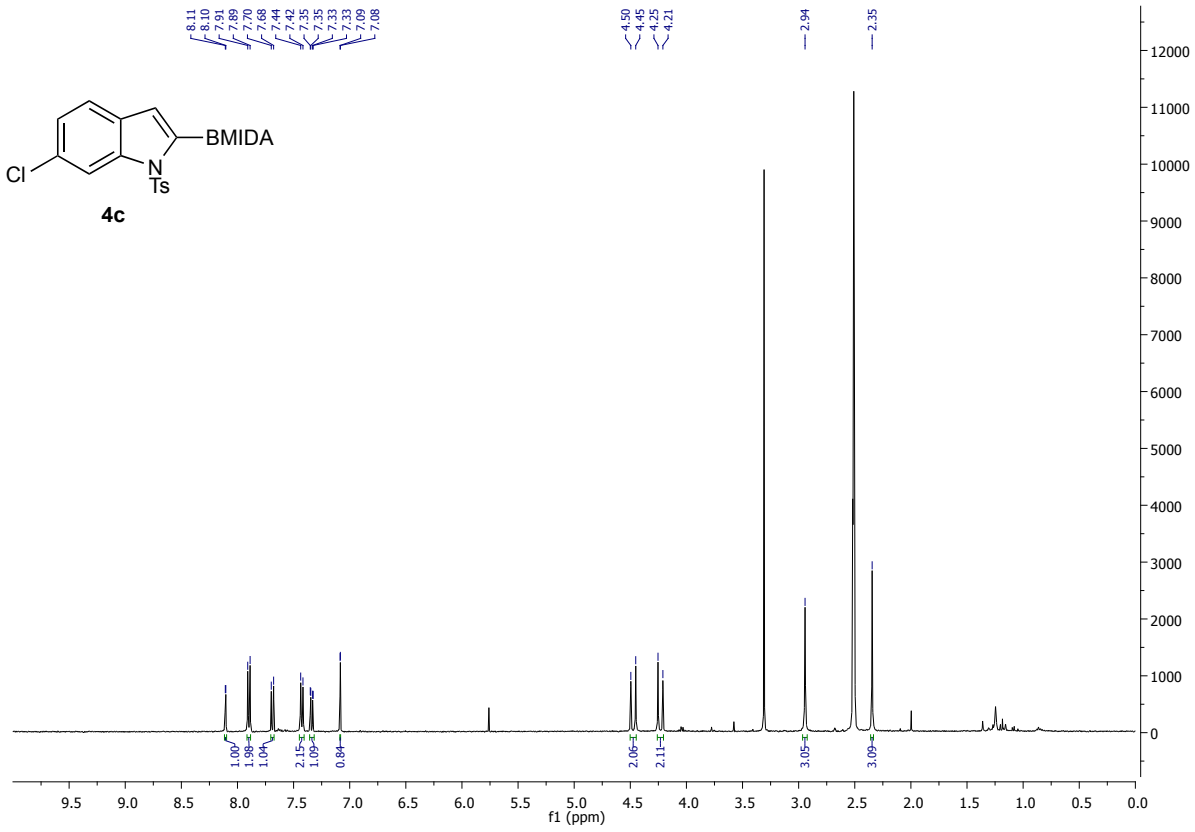
^{13}C NMR of 4b



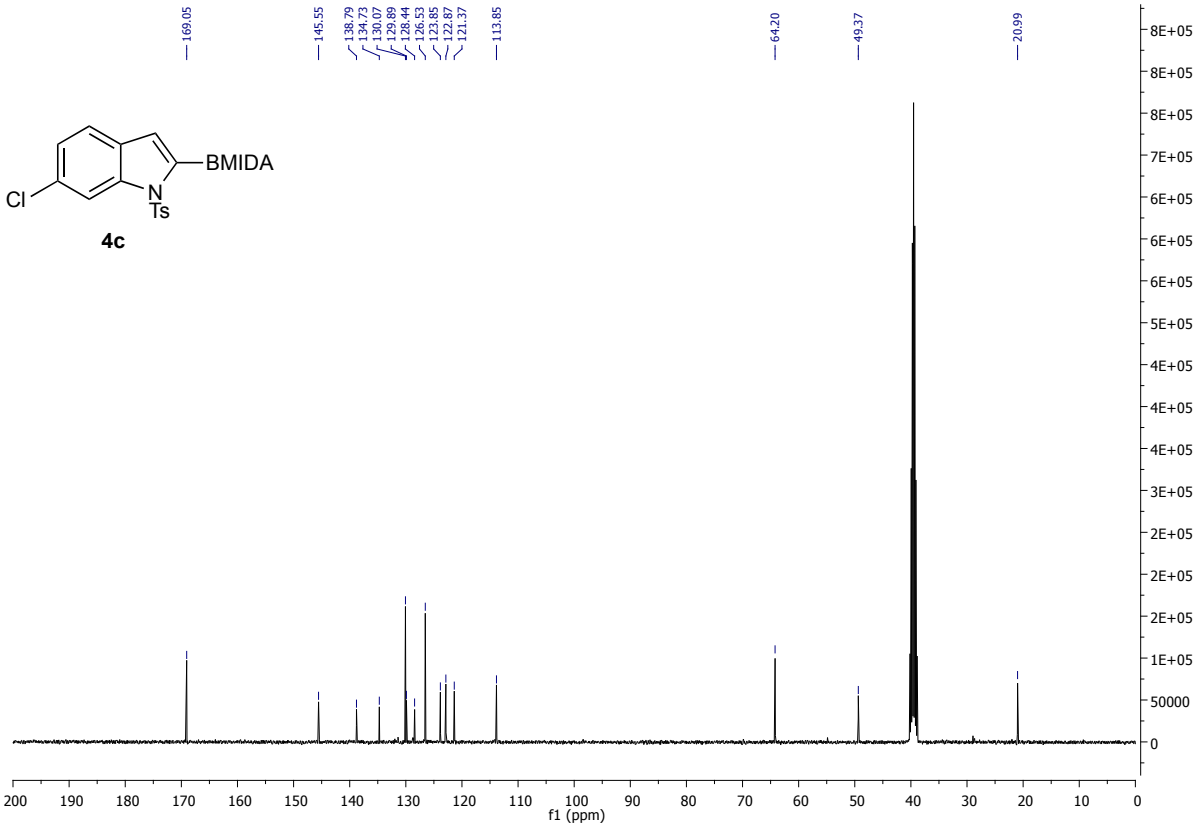
^{19}F NMR of 4b



^{1}H NMR of 4c

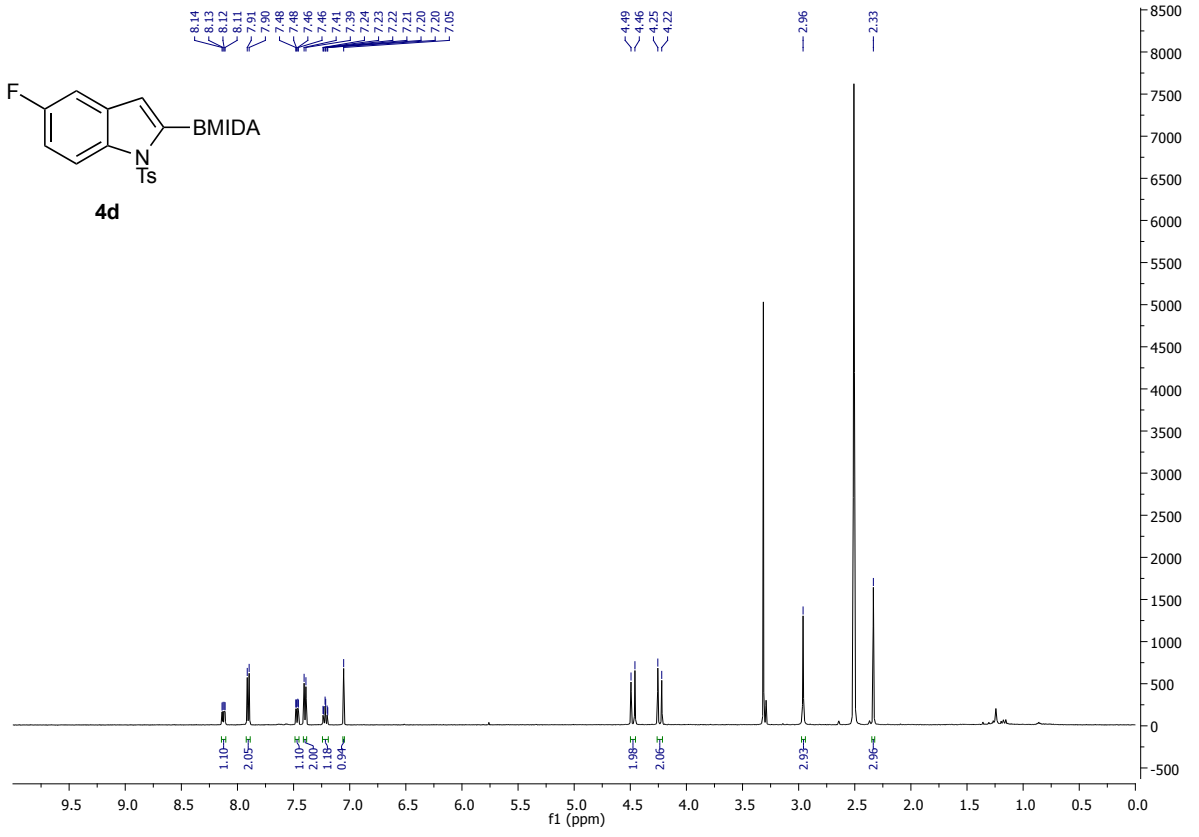


^{13}C NMR of 4c



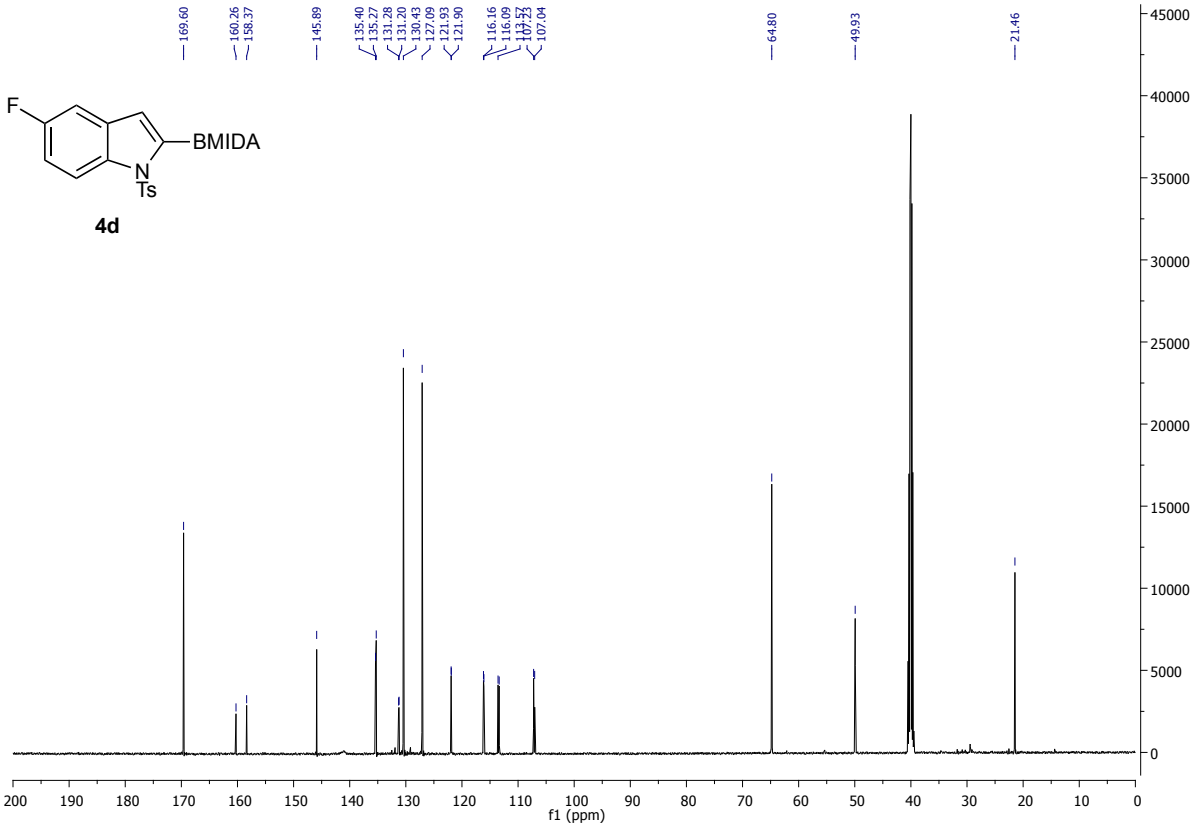
4c

^{1}H NMR of 4d

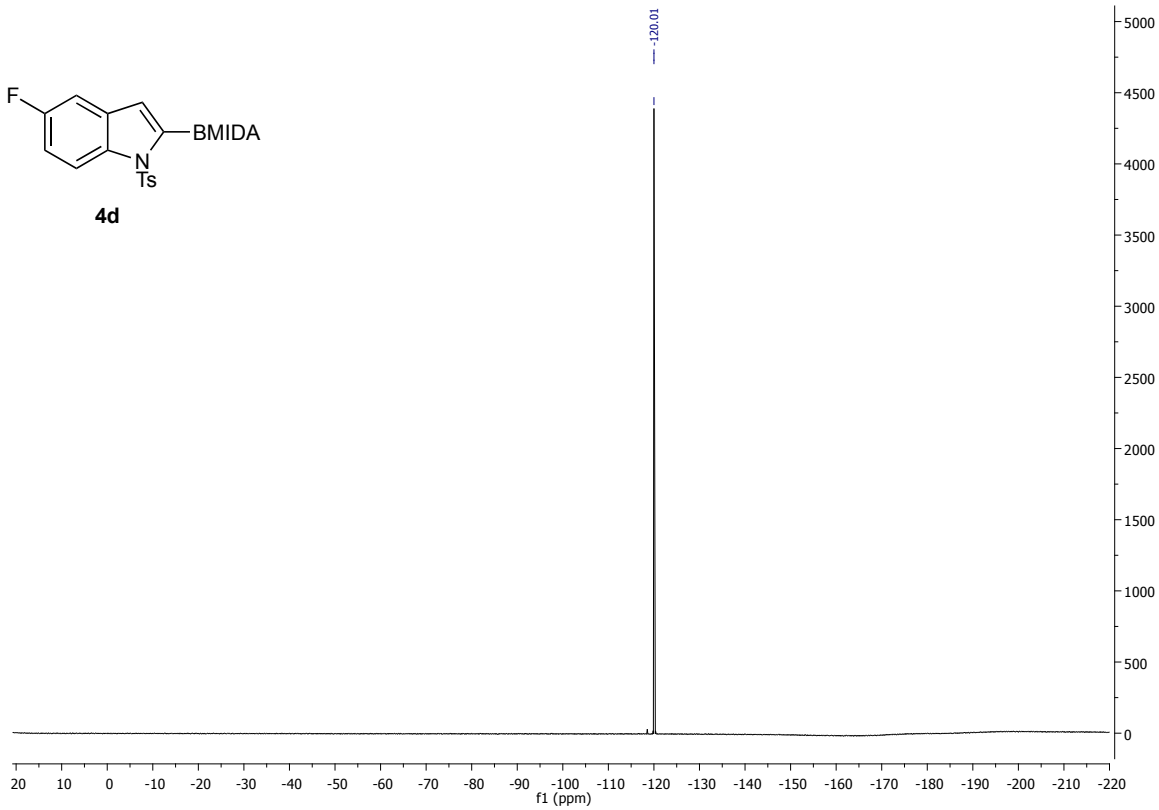


4d

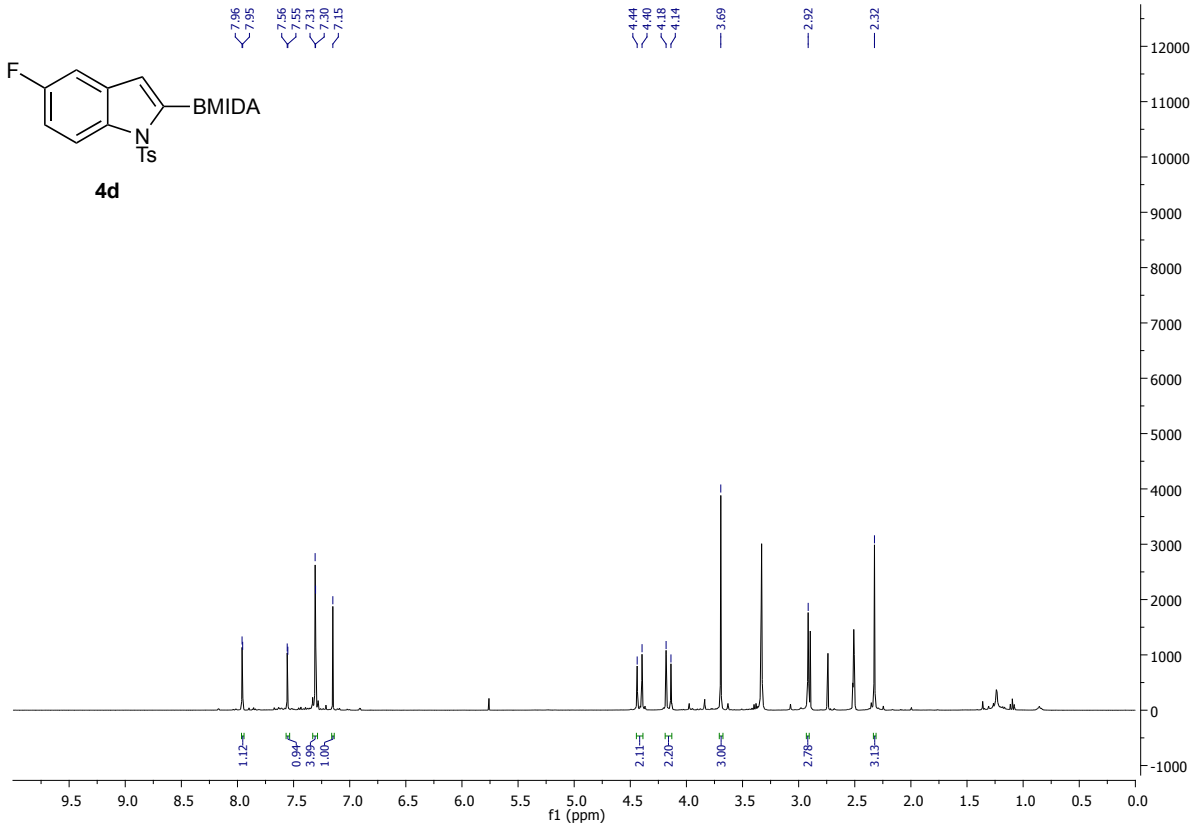
^{13}C NMR of 4d



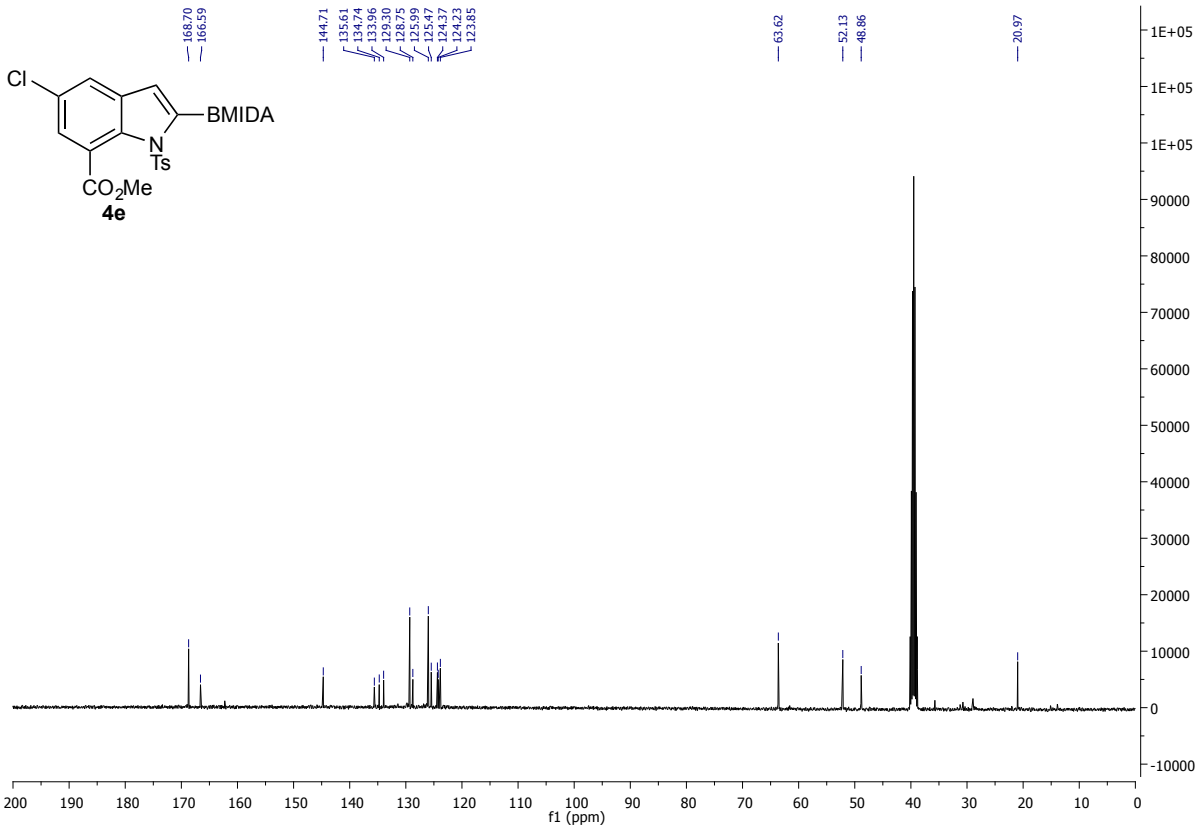
^{19}F NMR of 4d



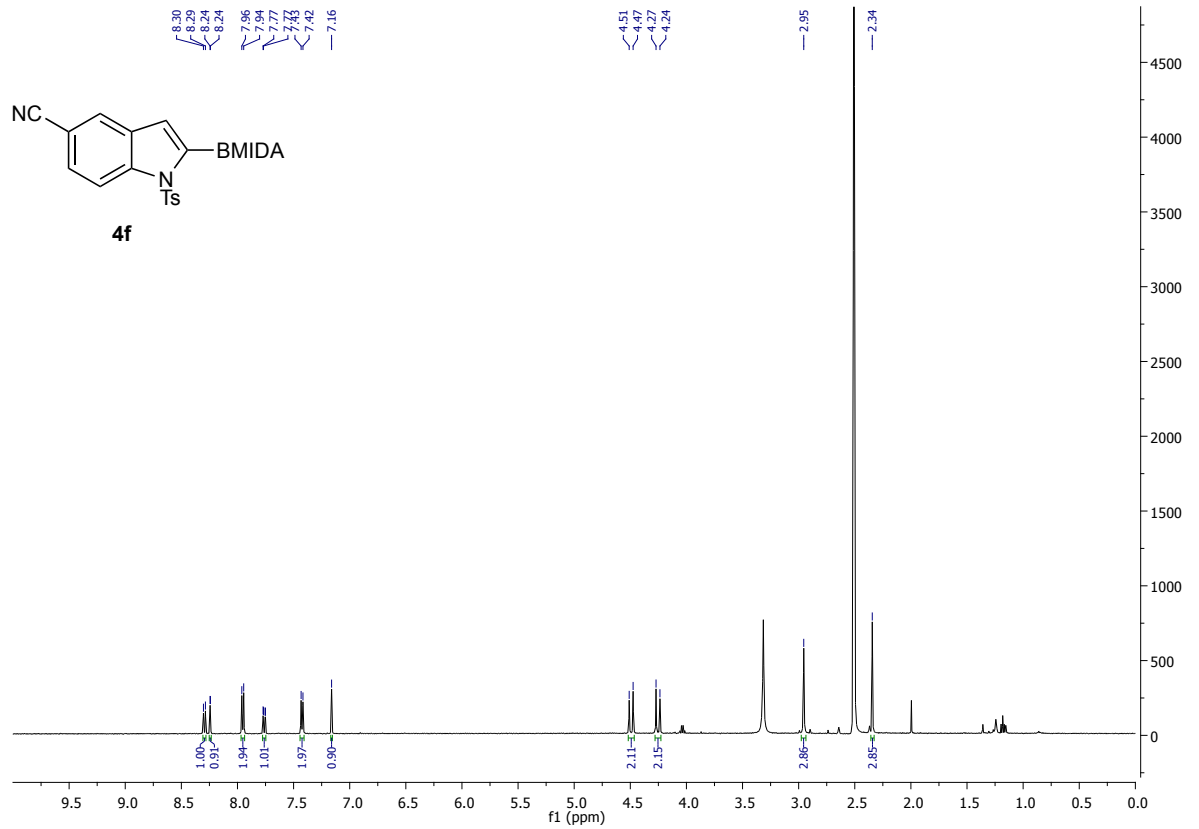
^{1}H NMR of 4e



^{13}C NMR of 4e

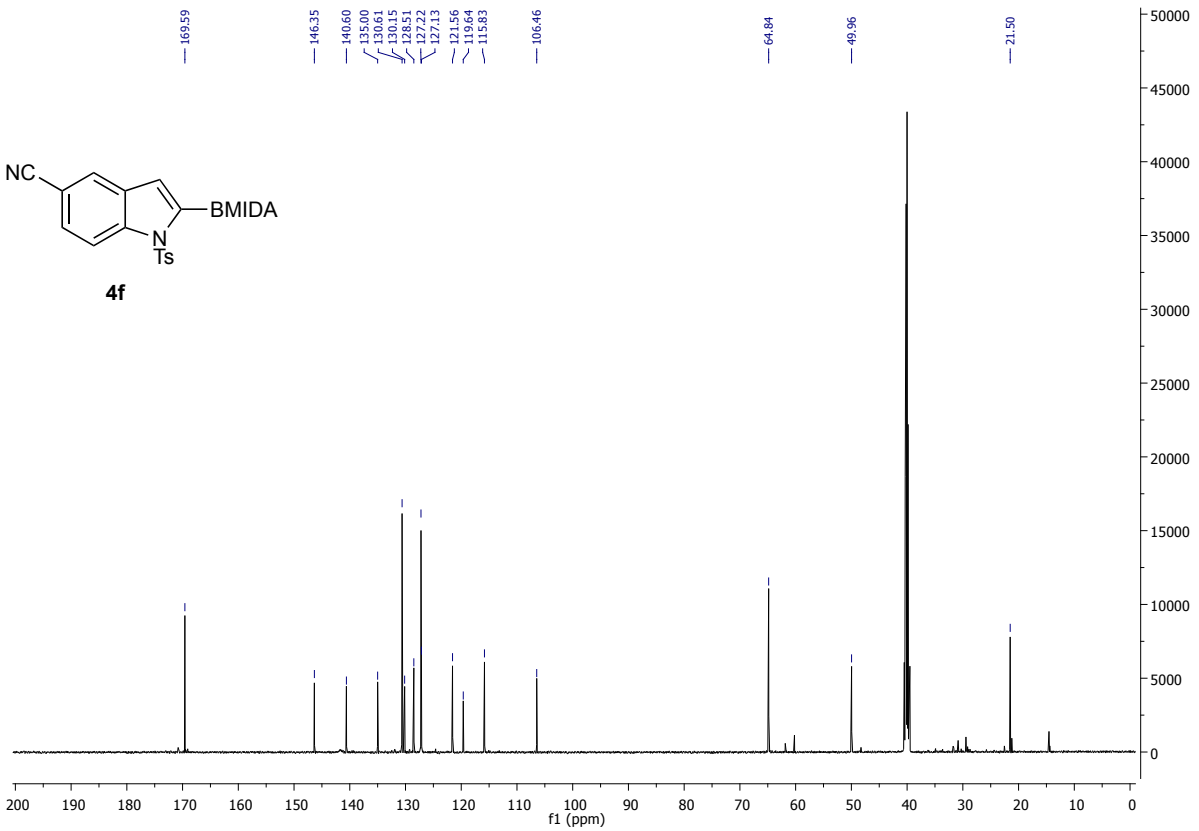


^{1}H NMR of 4f



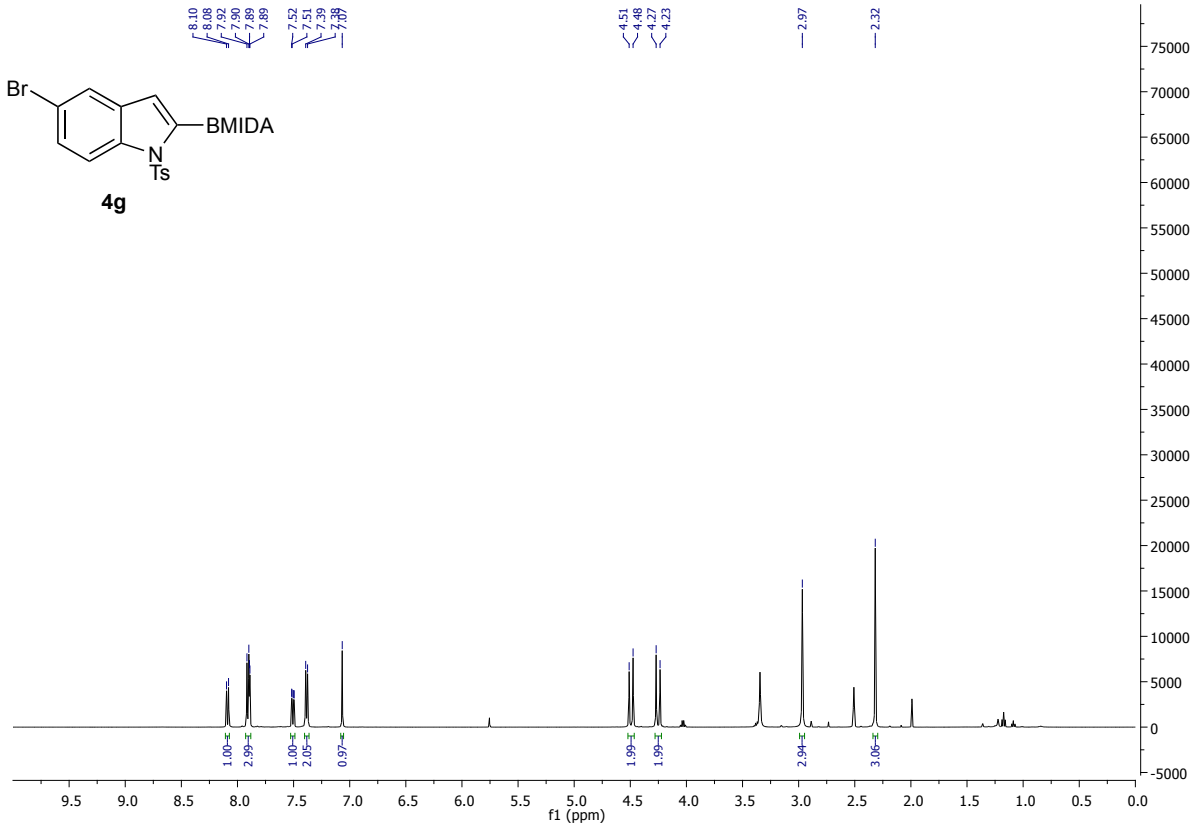
4f

^{13}C NMR of 4f

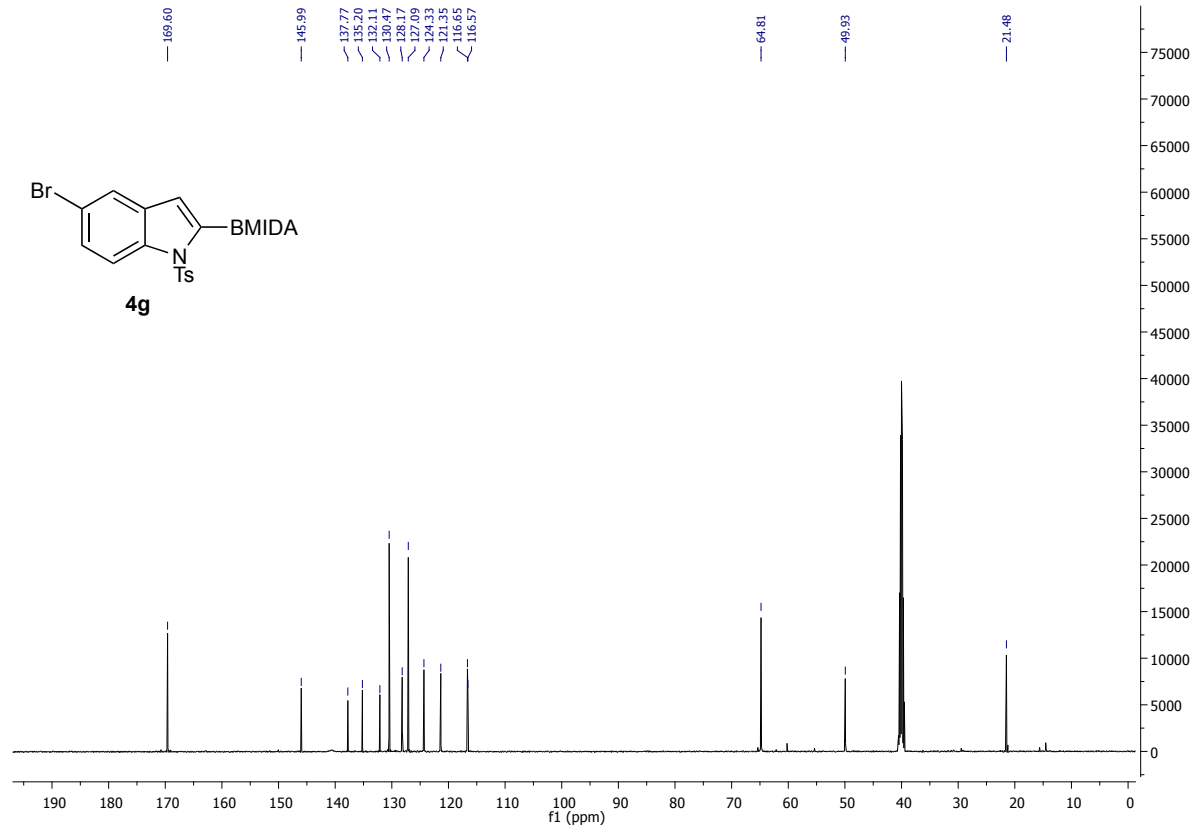


4f

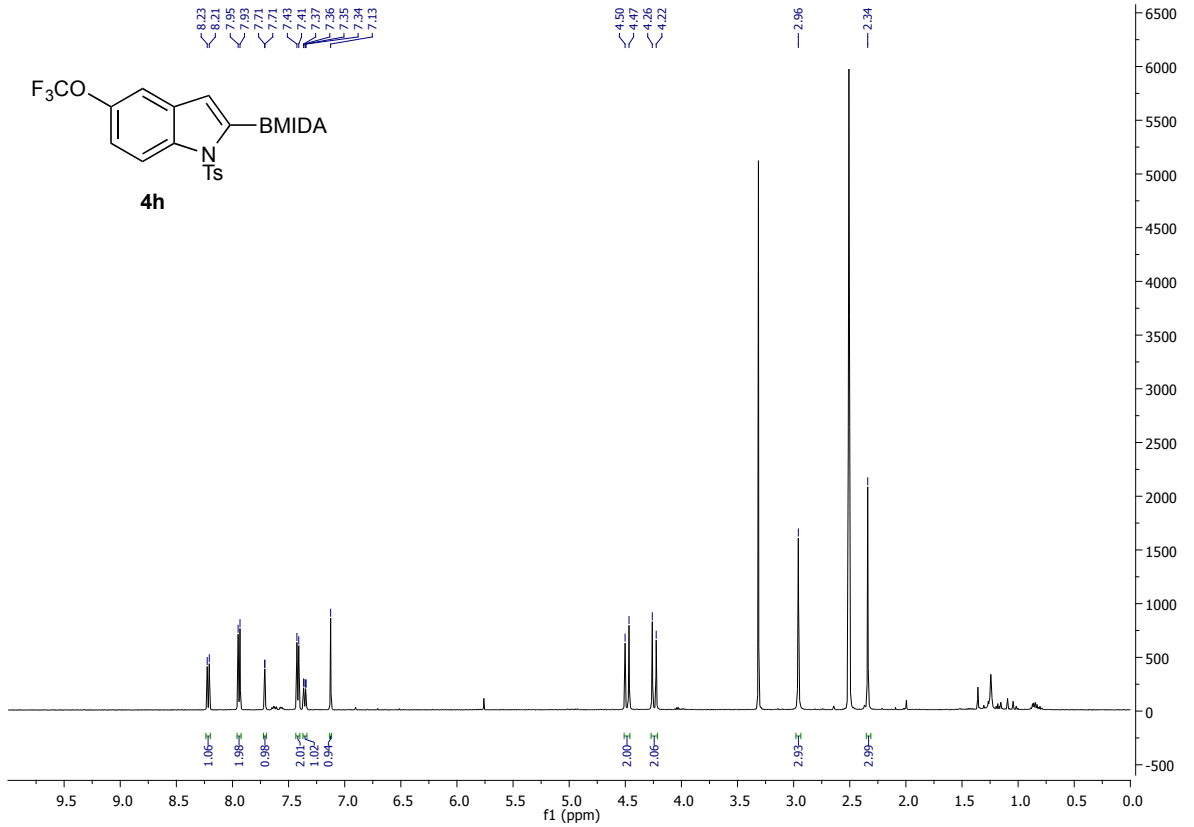
^{1}H NMR of 4g



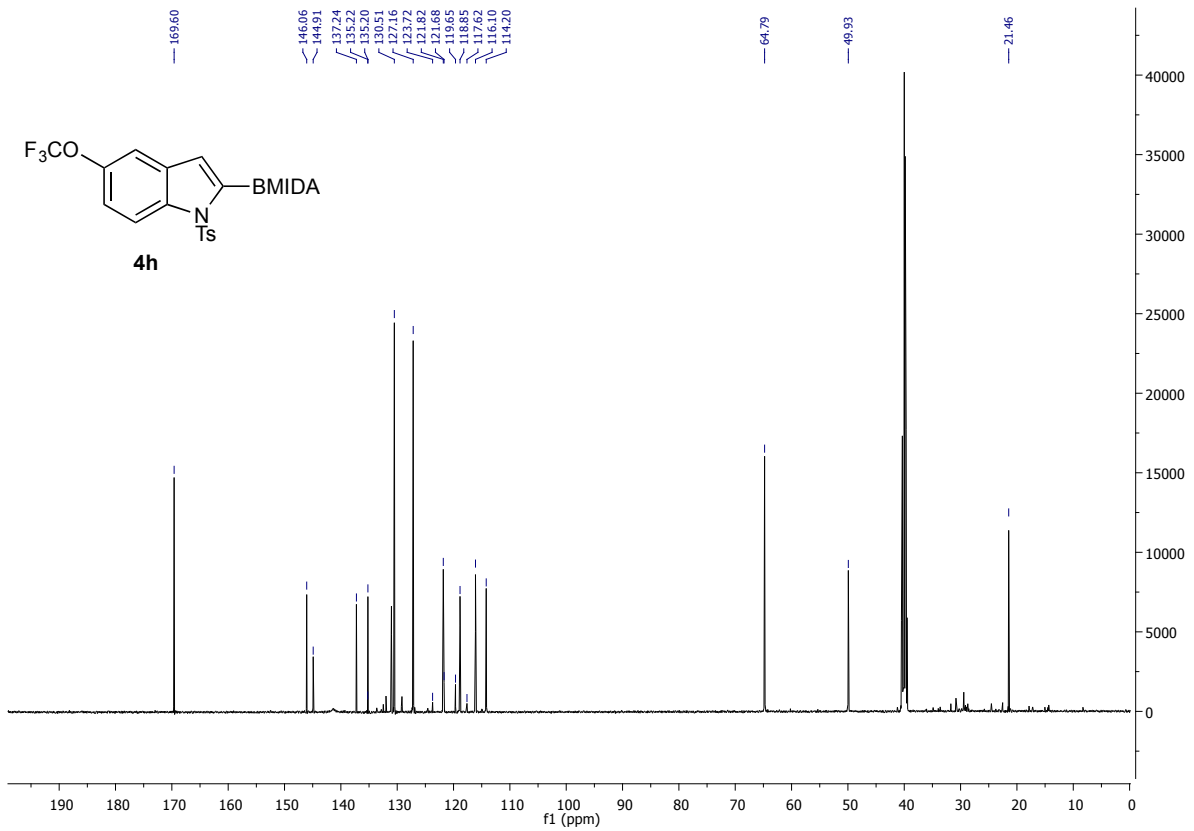
^{13}C NMR of 4g



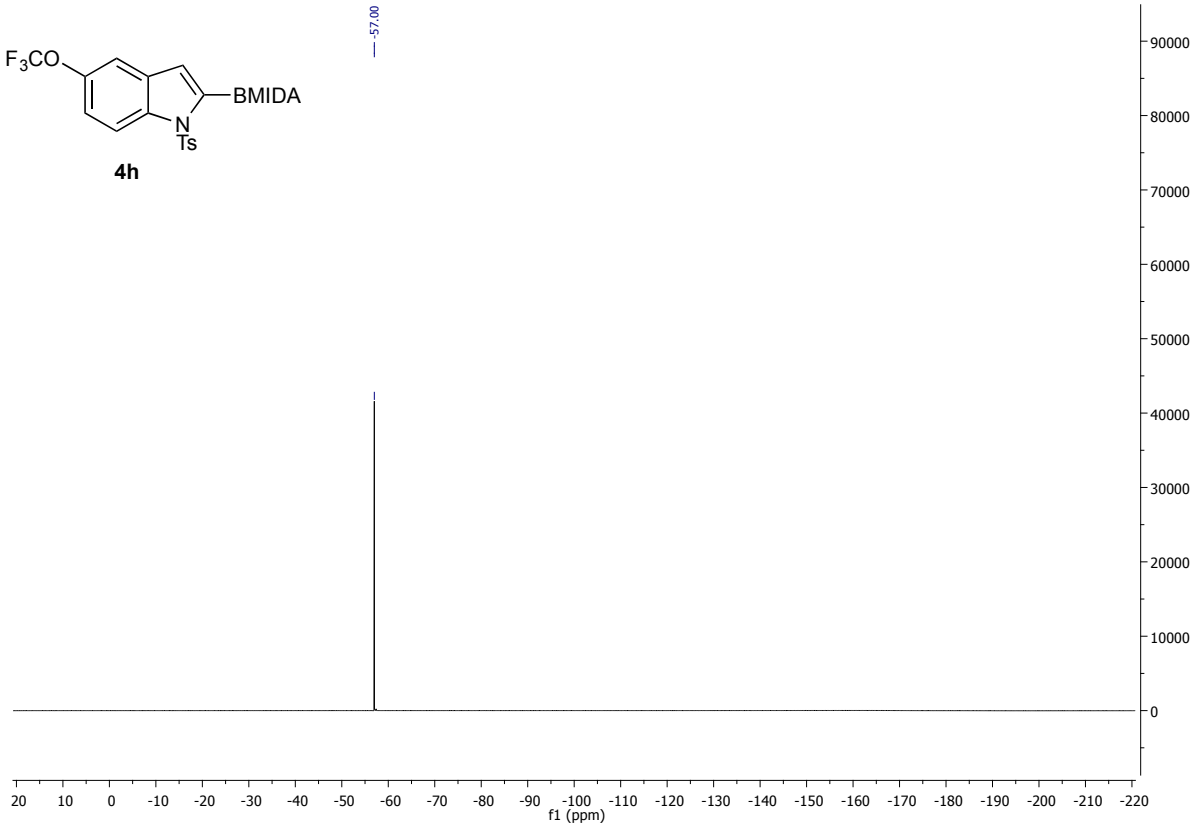
^{1}H NMR of 4h



^{13}C NMR of 4h

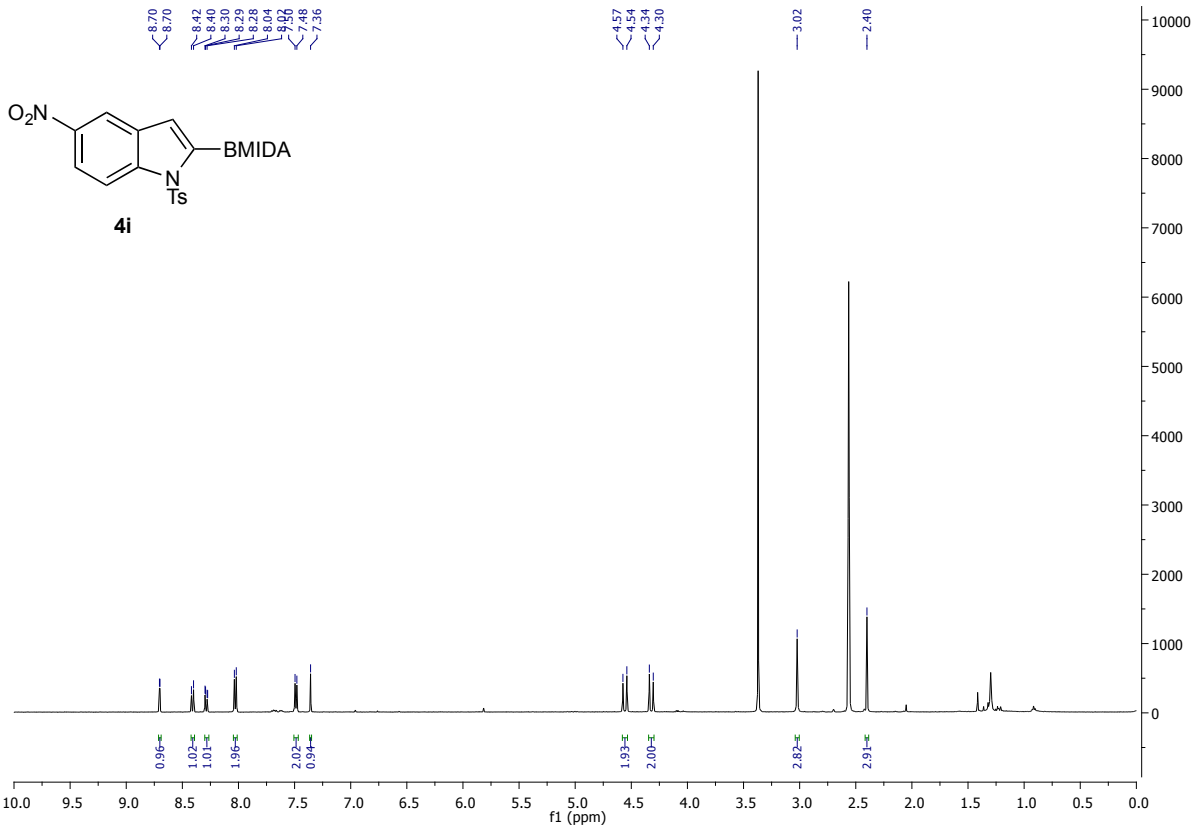


^{19}F NMR of 4h



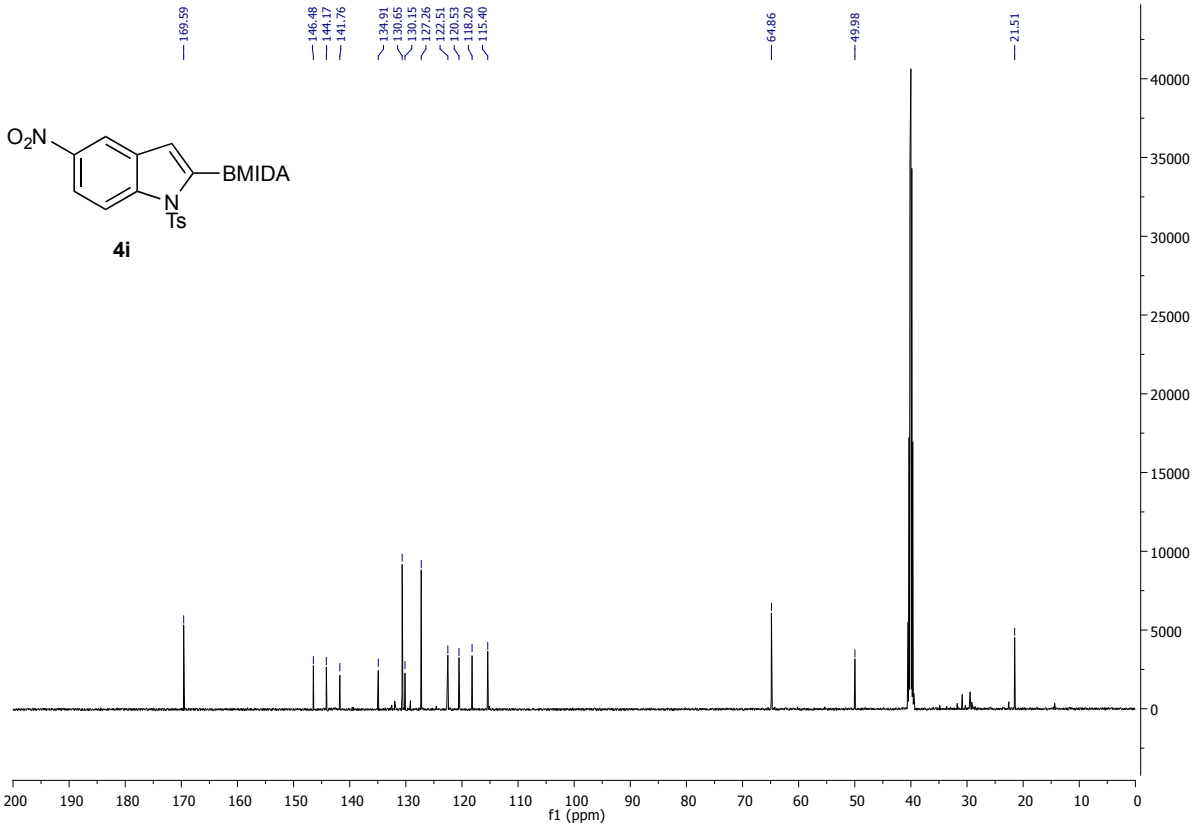
4h

^{1}H NMR of 4i



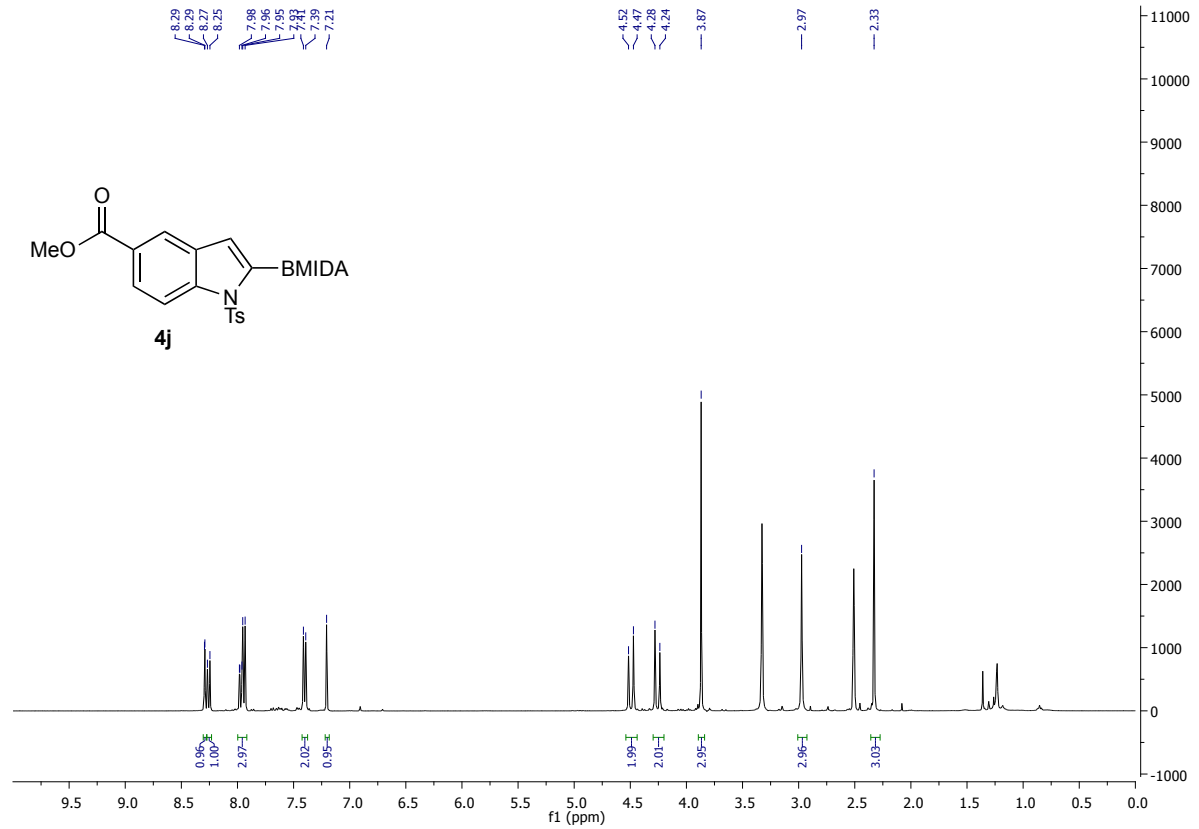
4i

^{13}C NMR of 4i



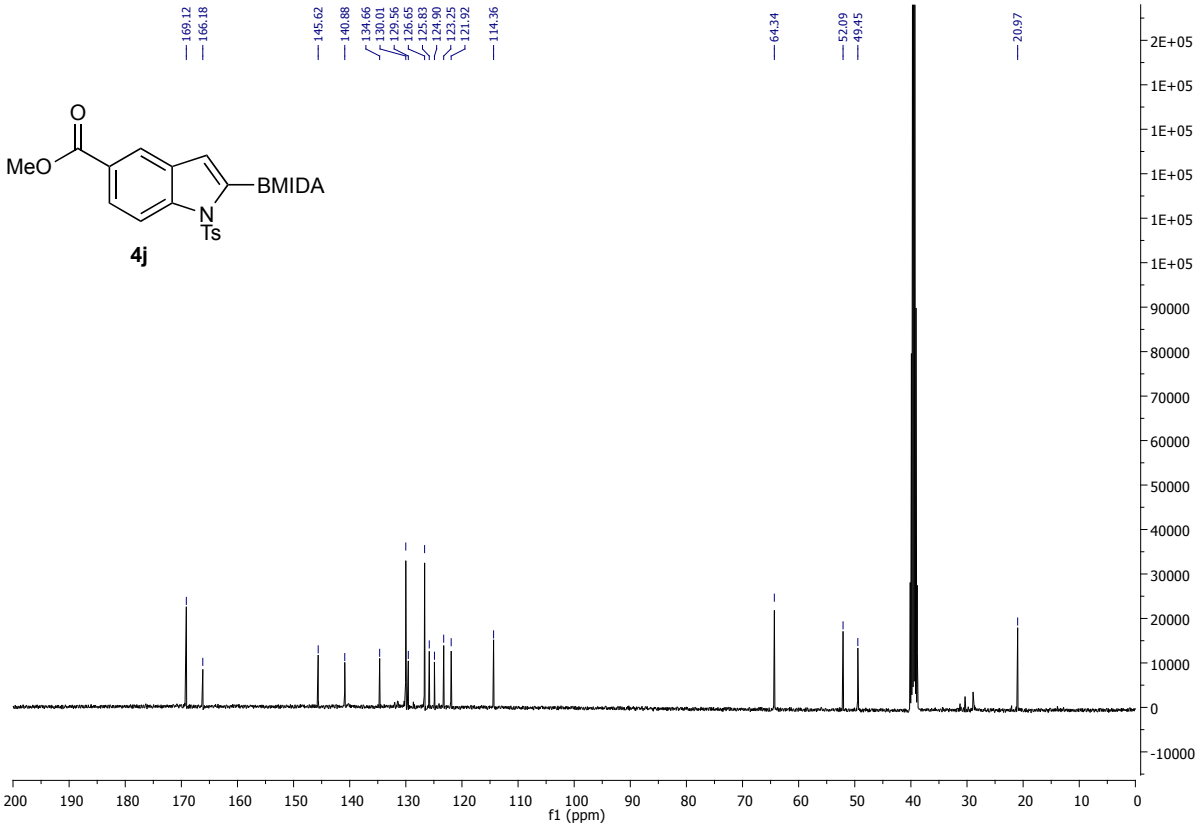
4i

^{1}H NMR of 4j



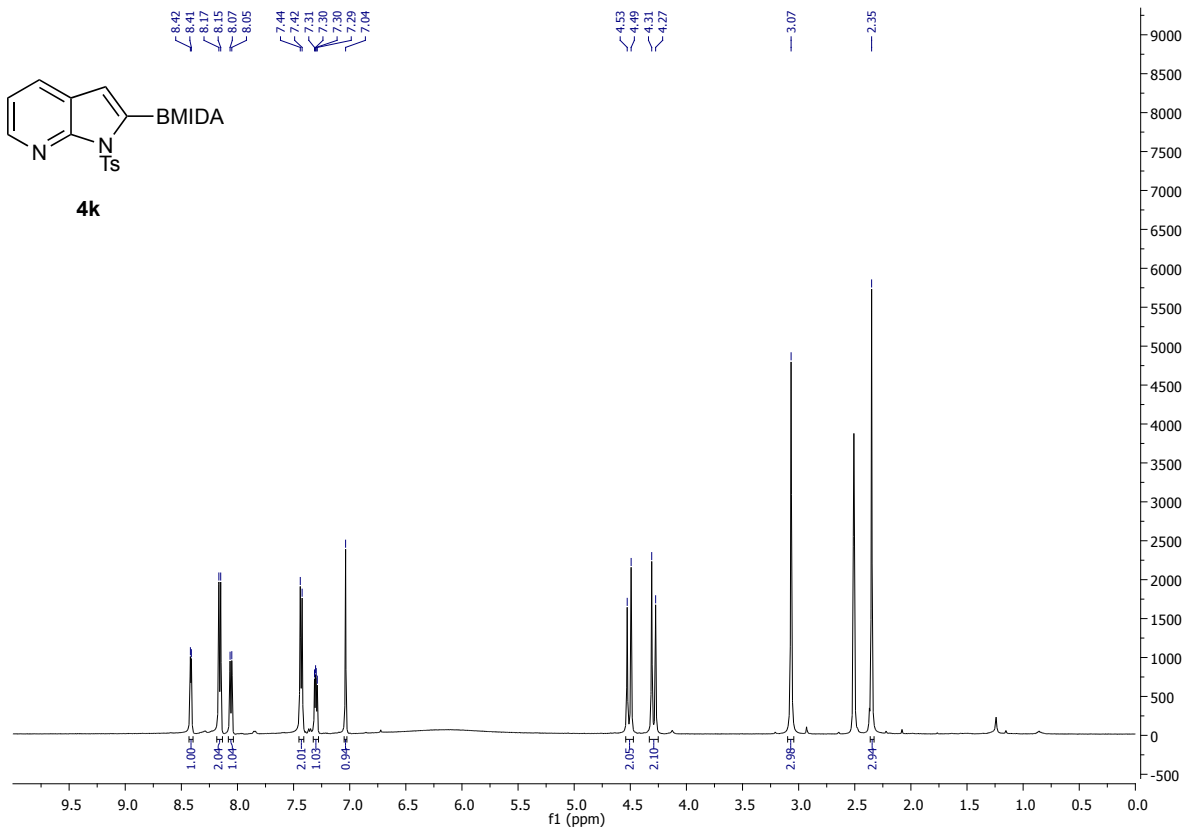
4j

^{13}C NMR of 4j



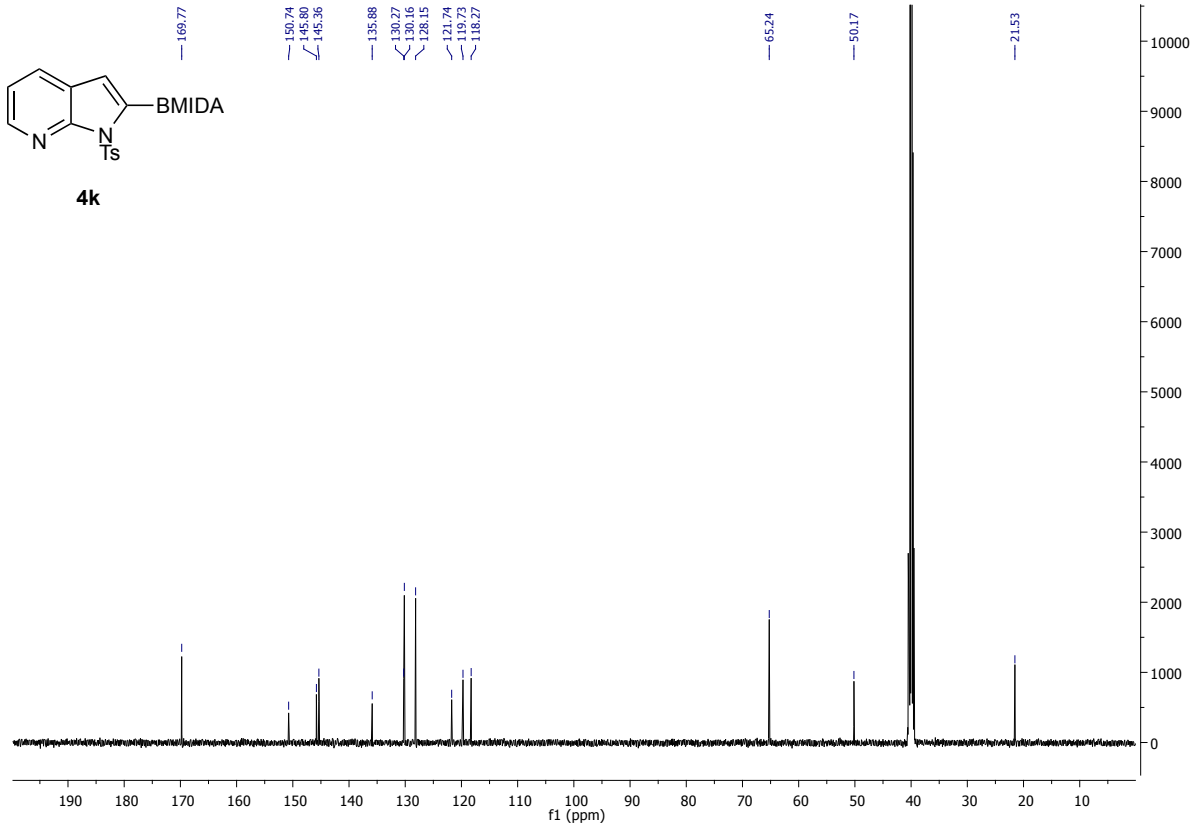
4j

^{1}H NMR of 4k



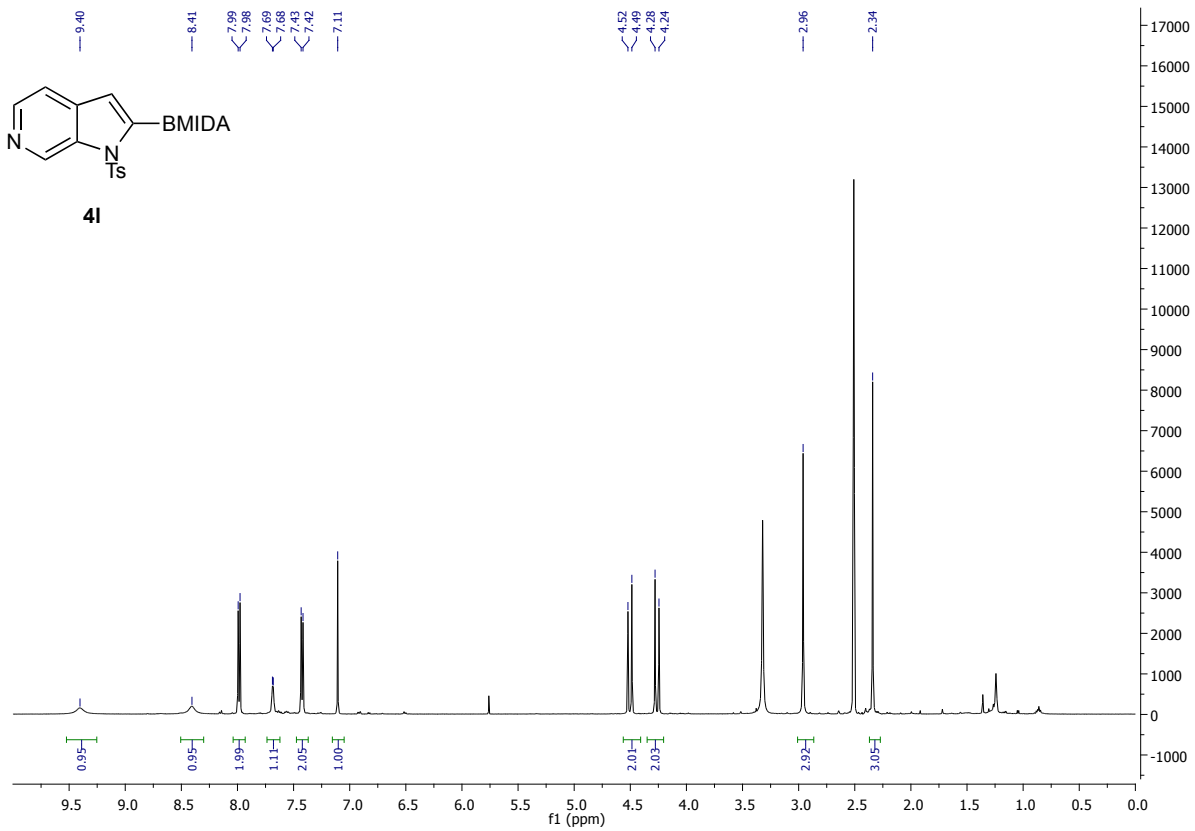
4k

^{13}C NMR of 4k



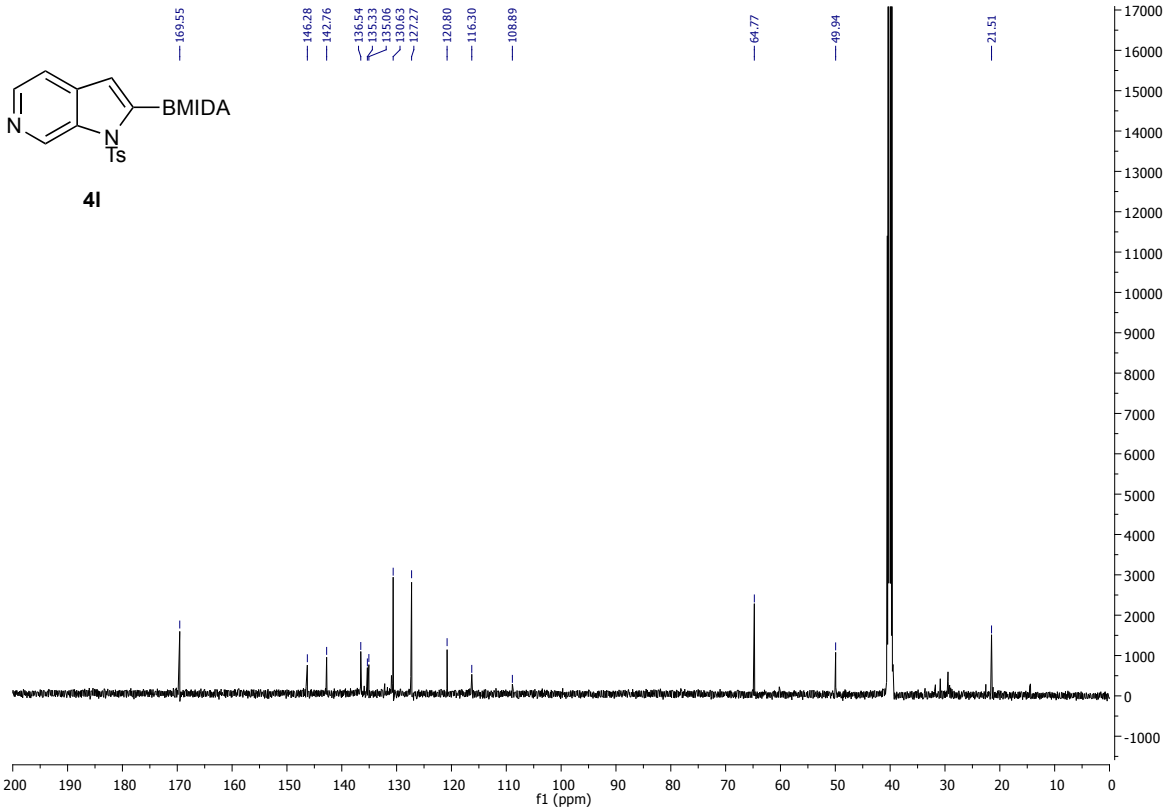
4k

^{1}H NMR of 4l



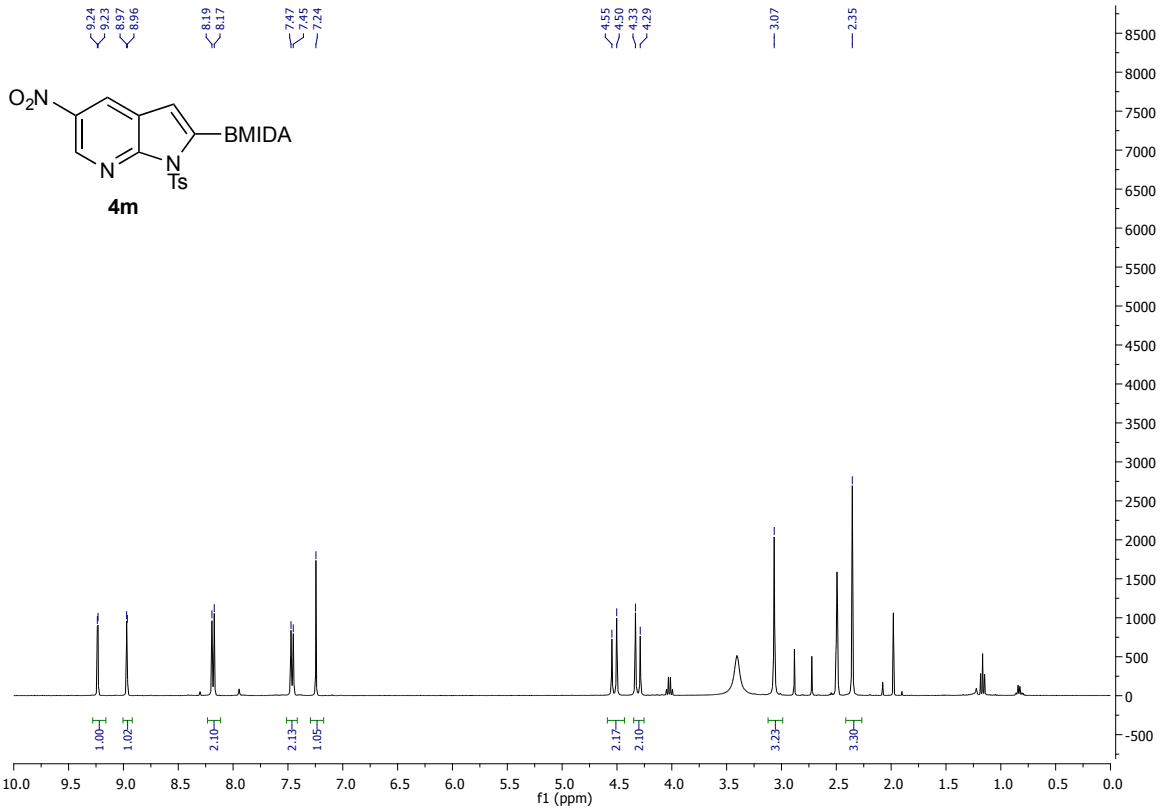
4l

^{13}C NMR of 4l



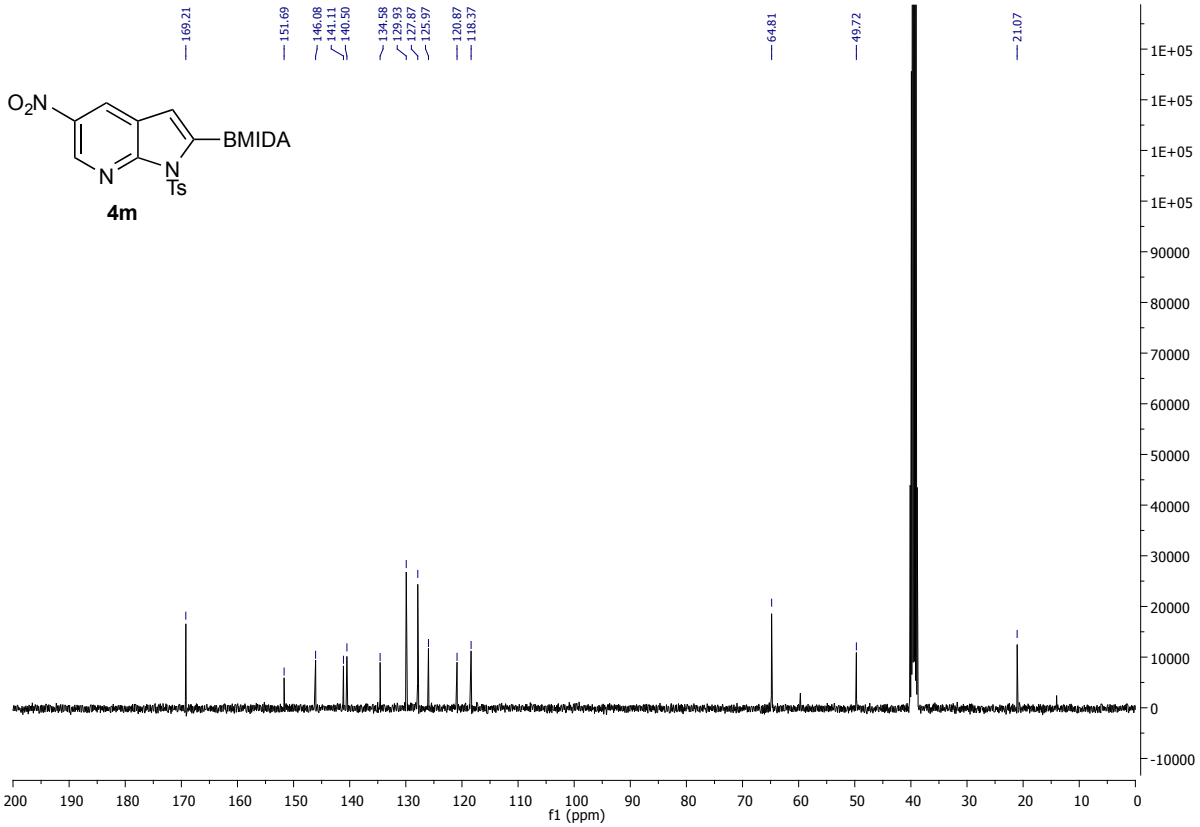
4l

^{1}H NMR of 4m

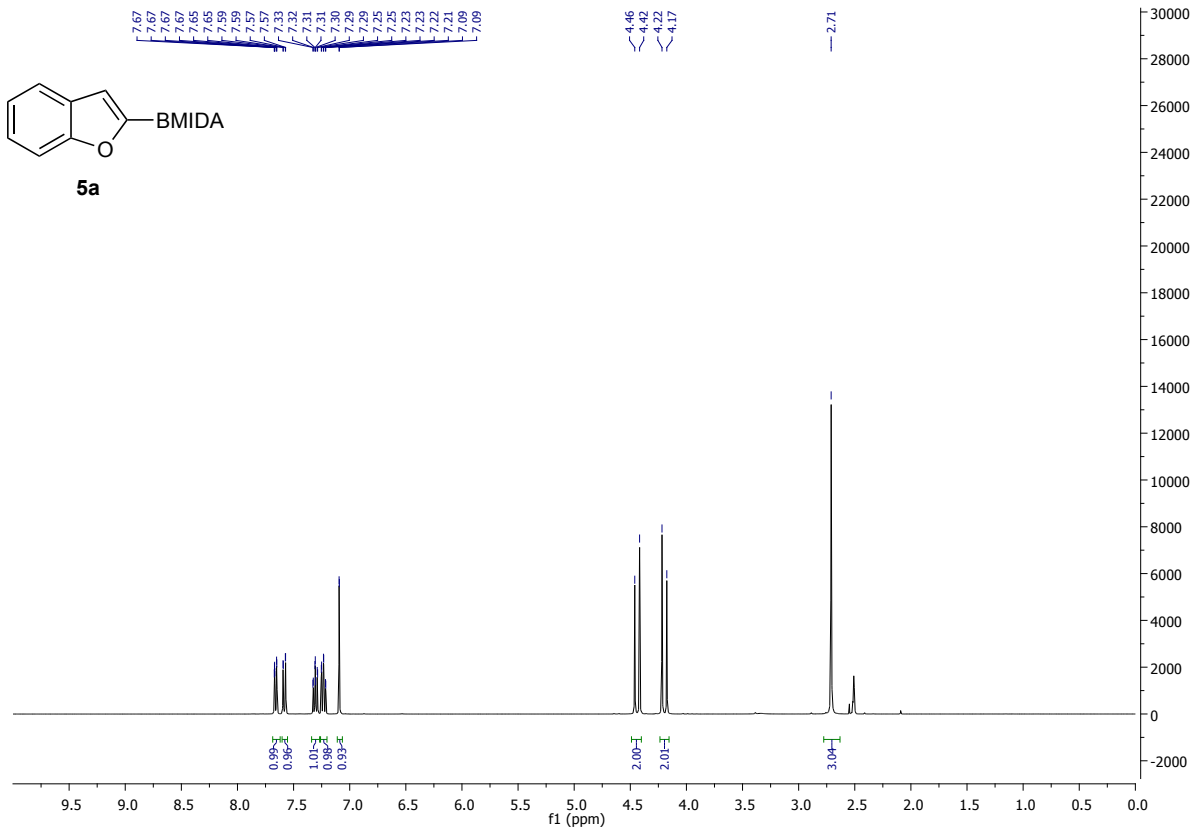


4m

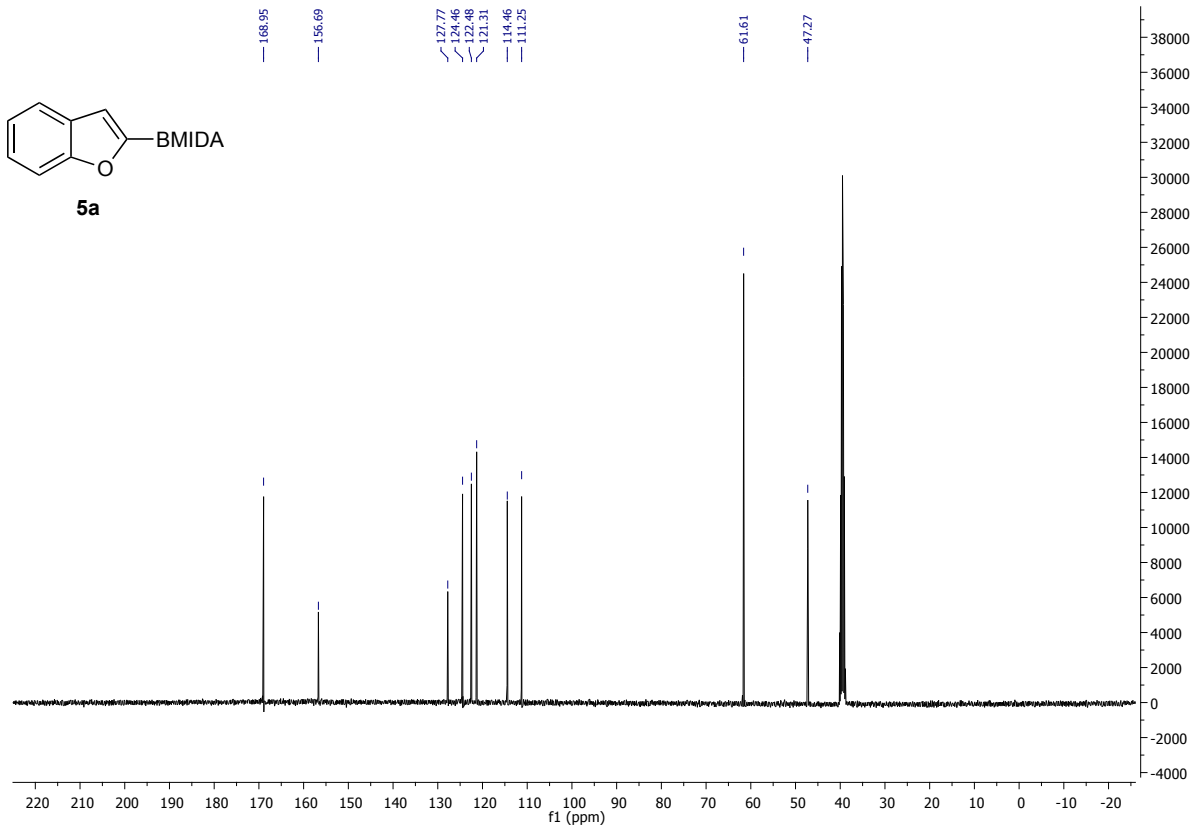
^{13}C NMR of 4m



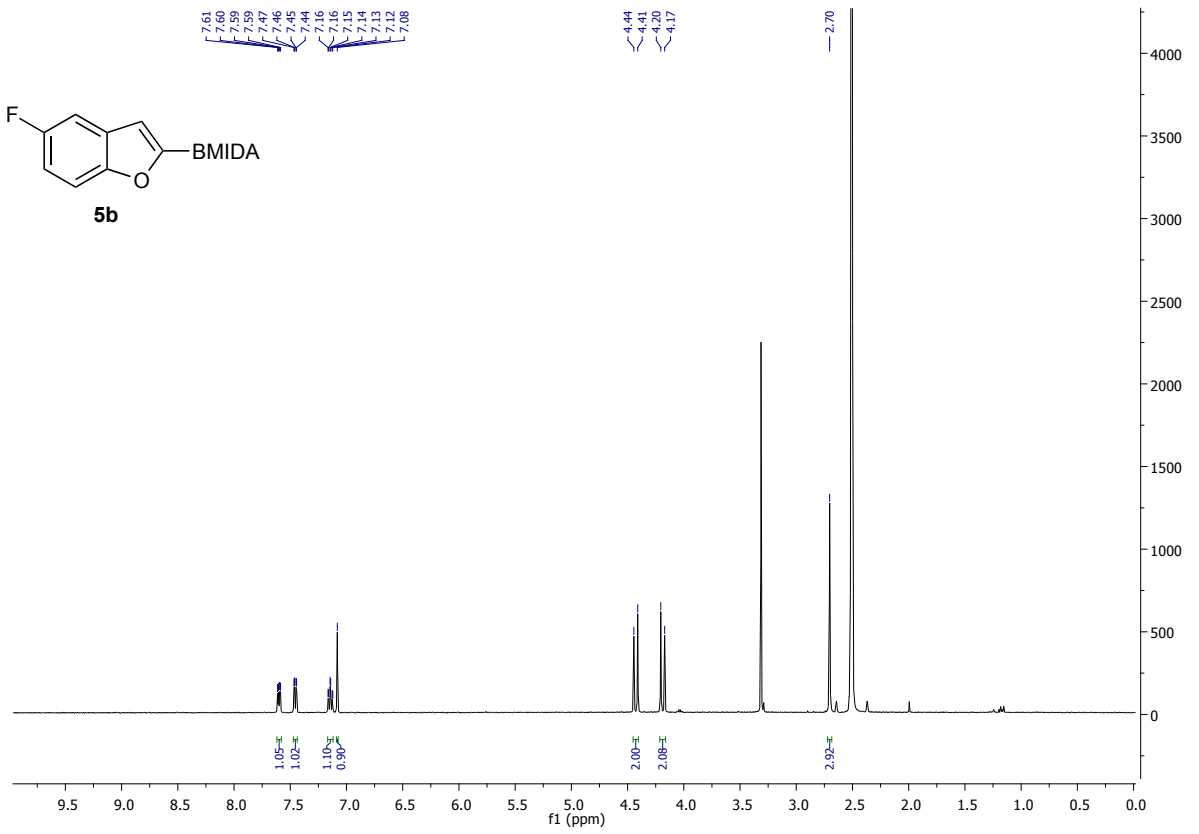
^{1}H NMR of 5a



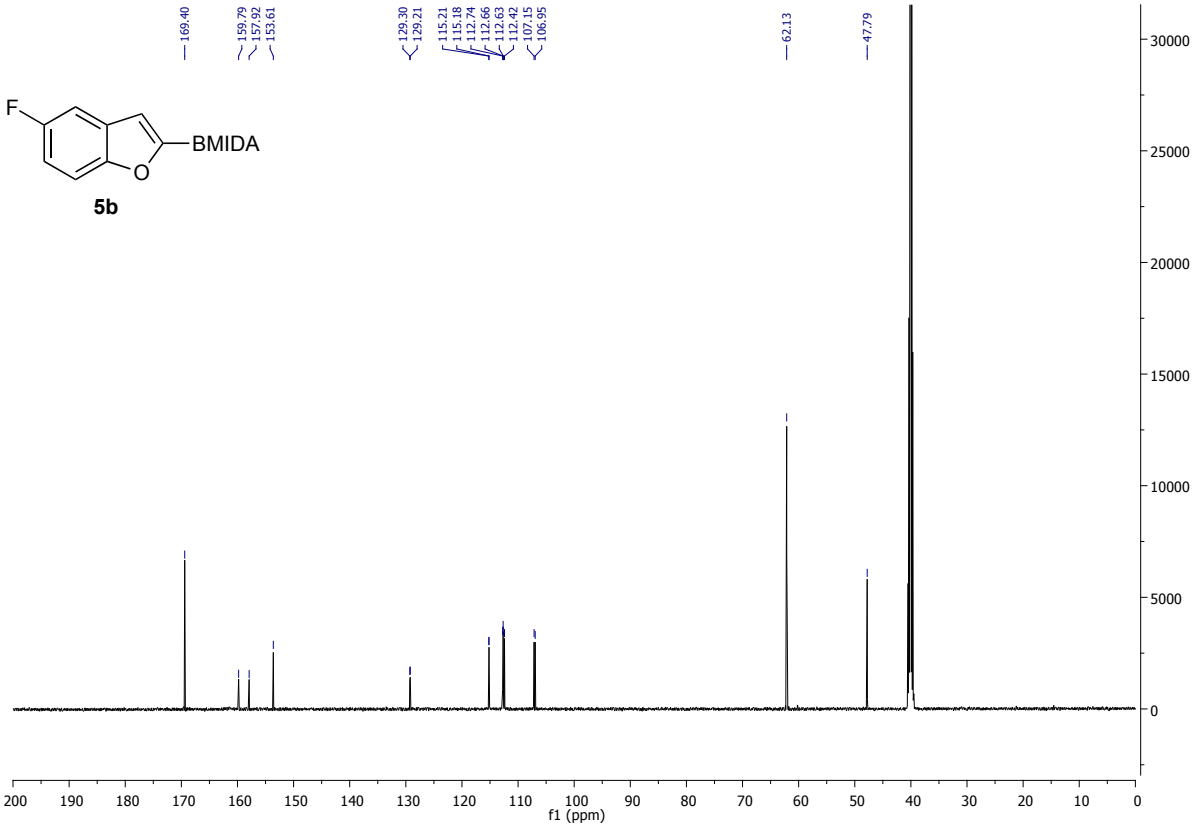
^{13}C NMR of 5a



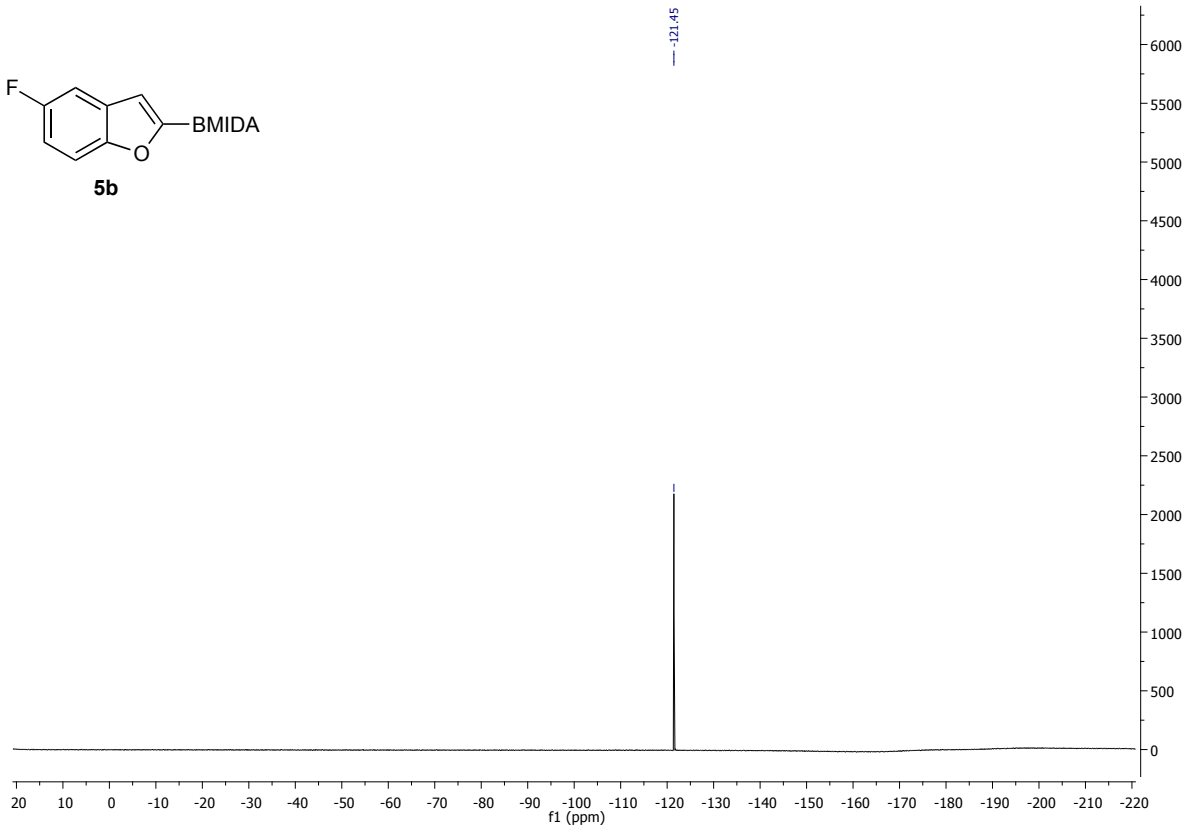
^{1}H NMR of 5b



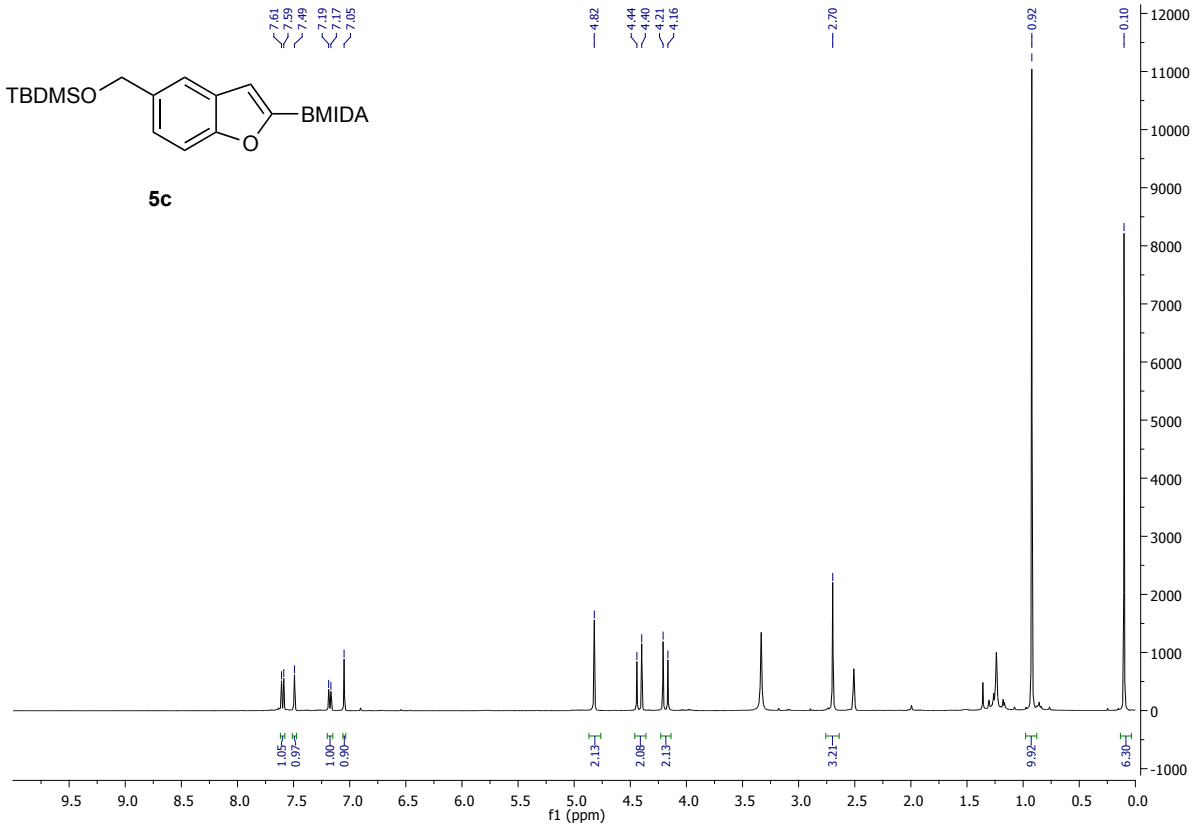
^{13}C NMR of 5b



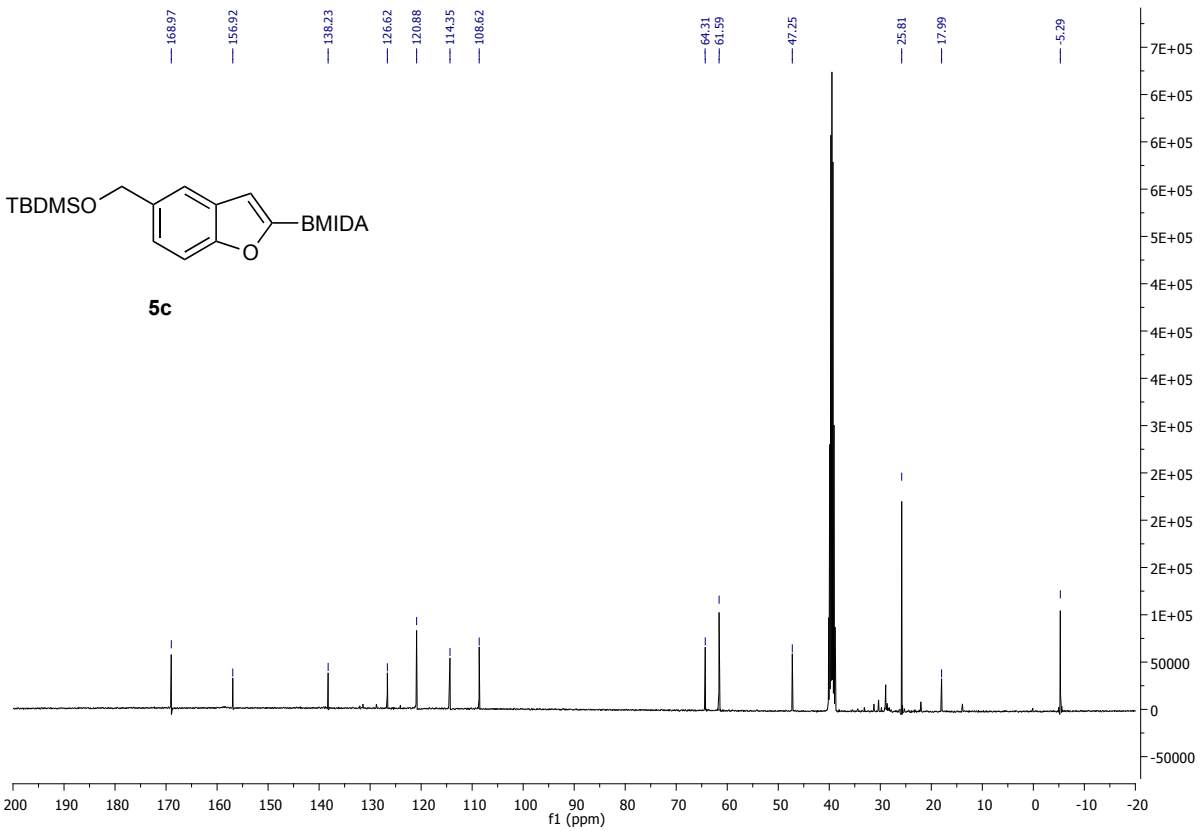
^{19}F NMR of 5b



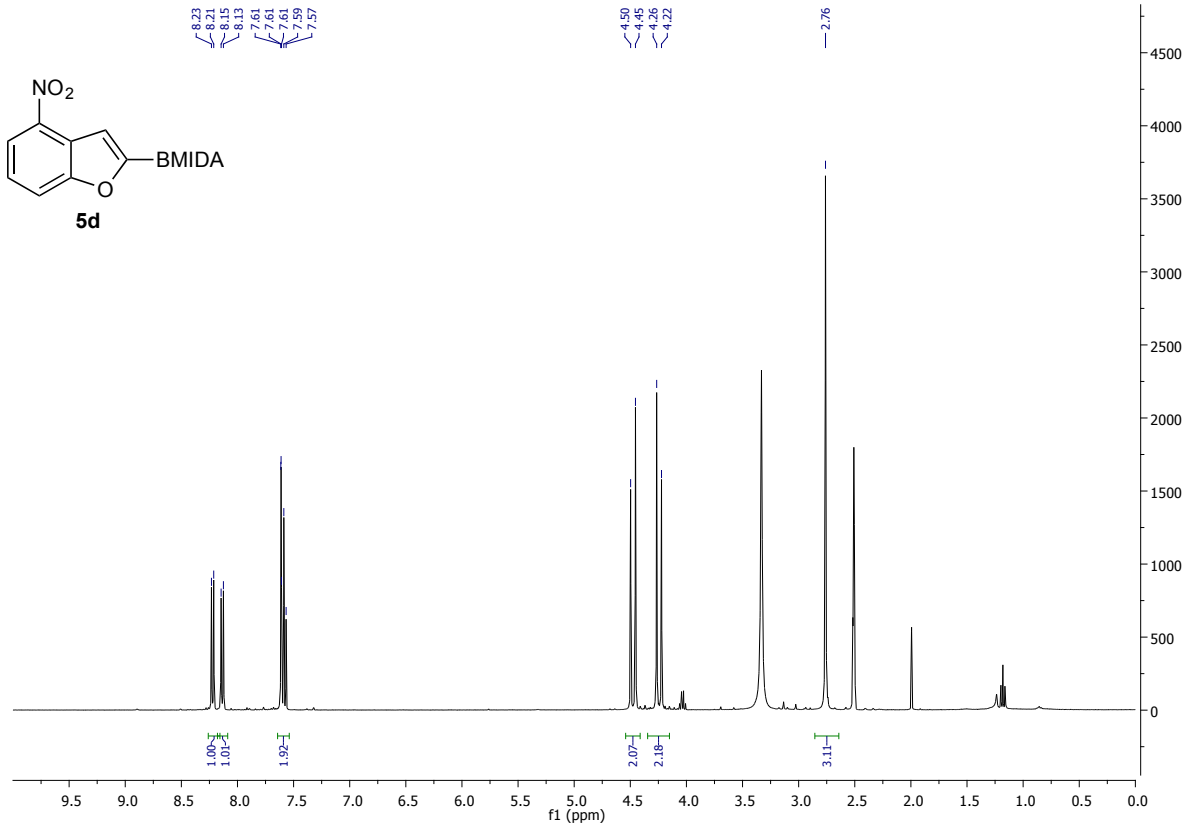
^{1}H NMR of 5c



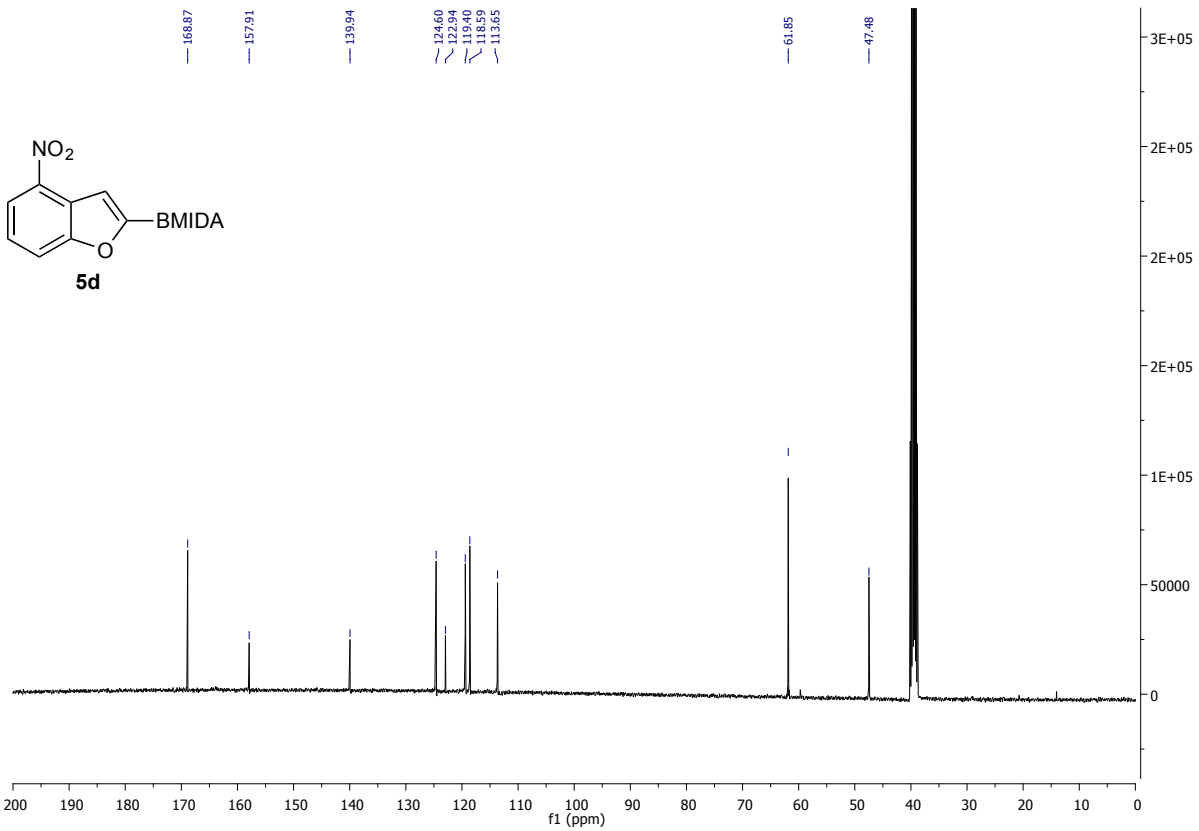
^{13}C NMR of 5c



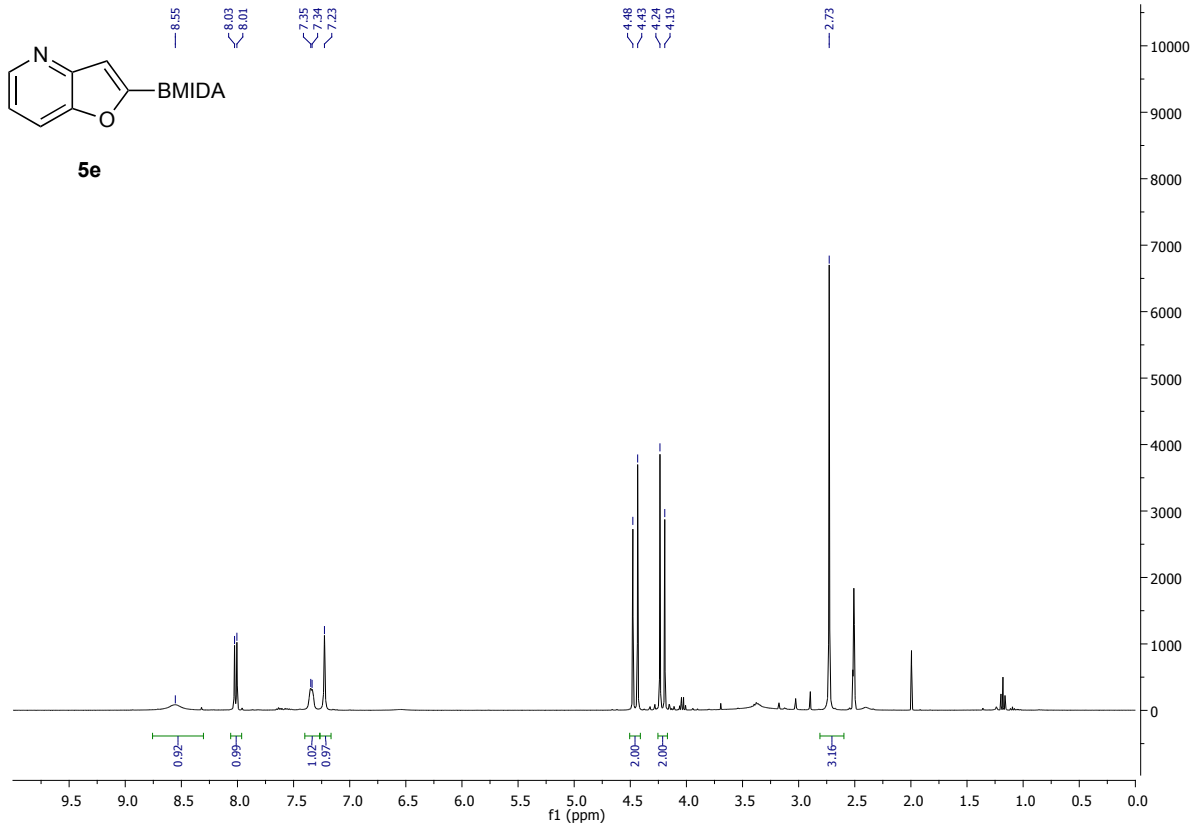
^{1}H NMR of 5d



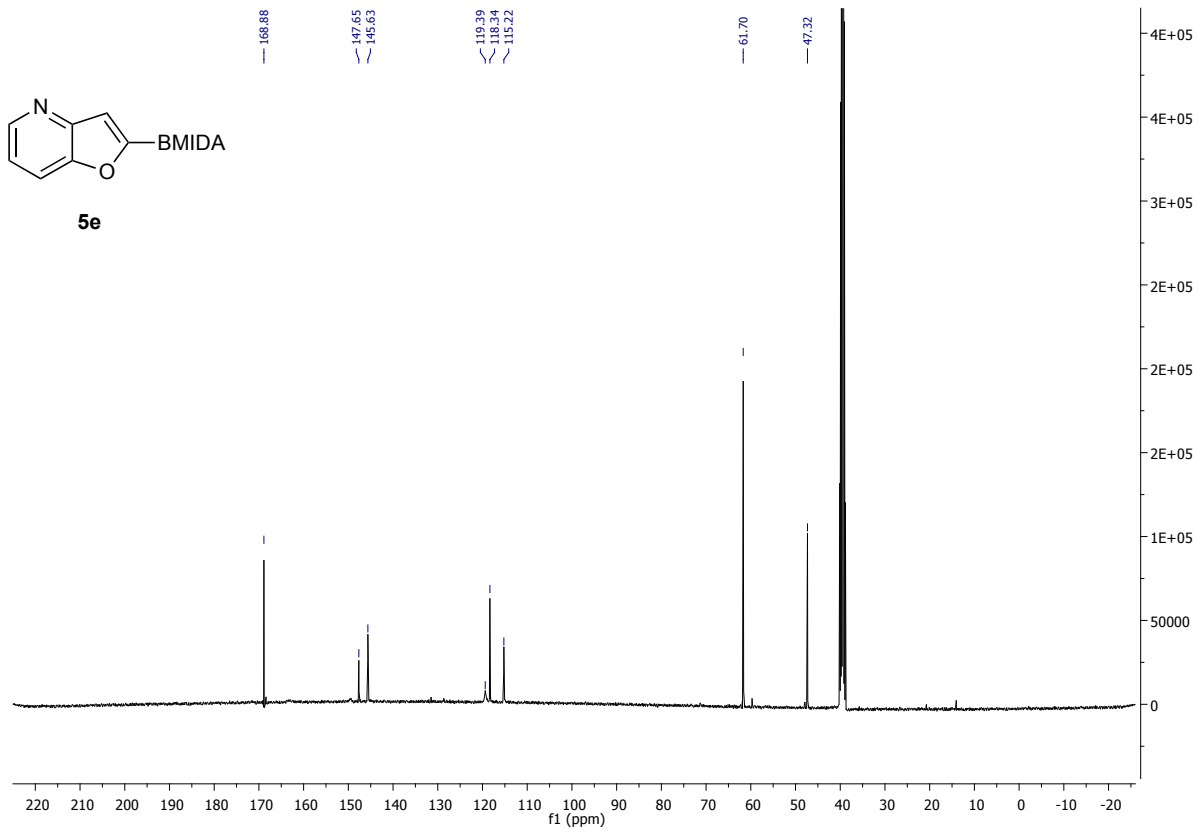
^{13}C NMR of 5d



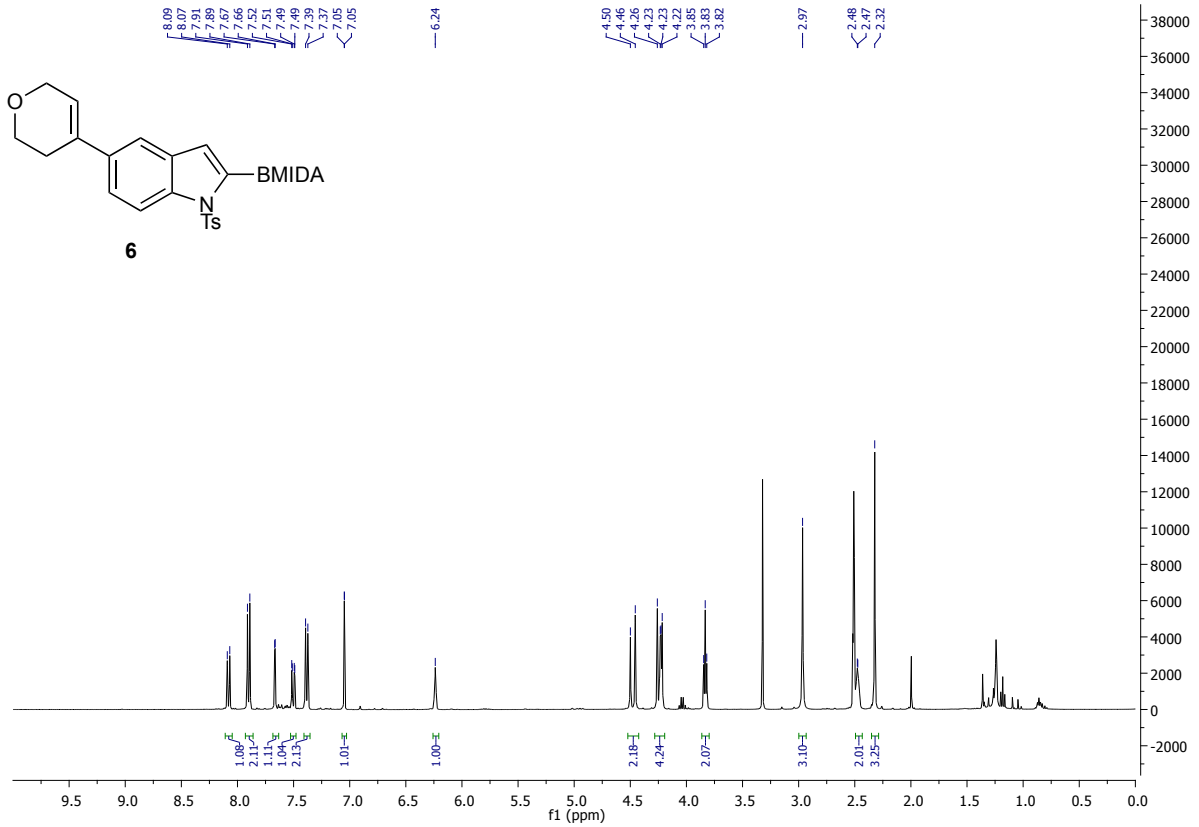
^{1}H NMR of 5e



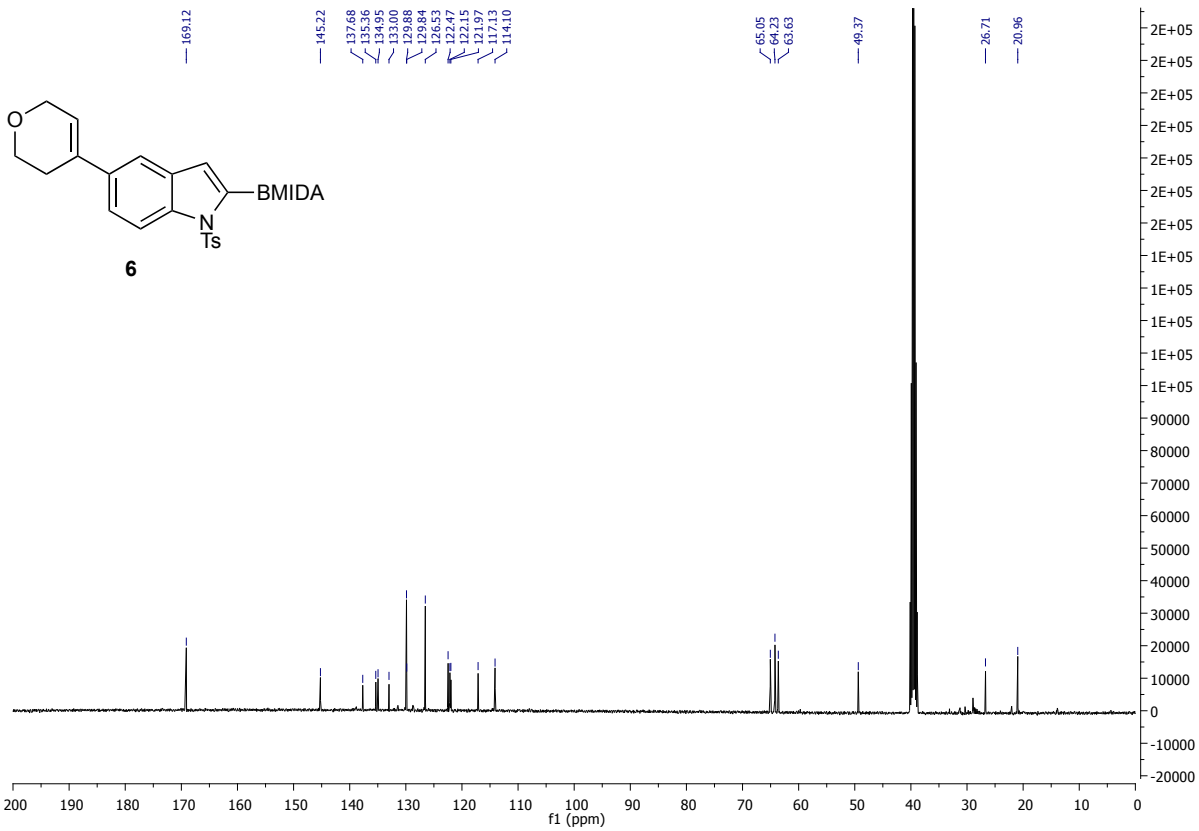
^{13}C NMR of 5e



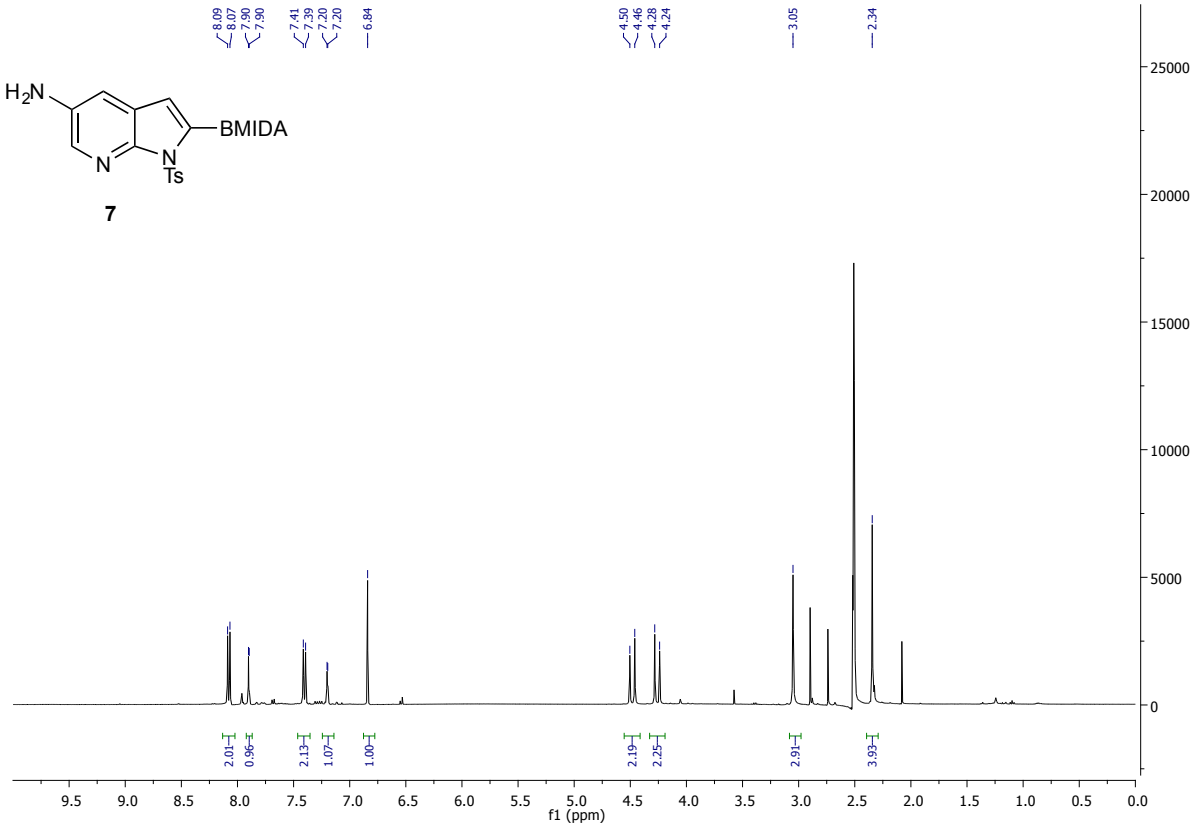
^{1}H NMR of 6



^{13}C NMR of 6

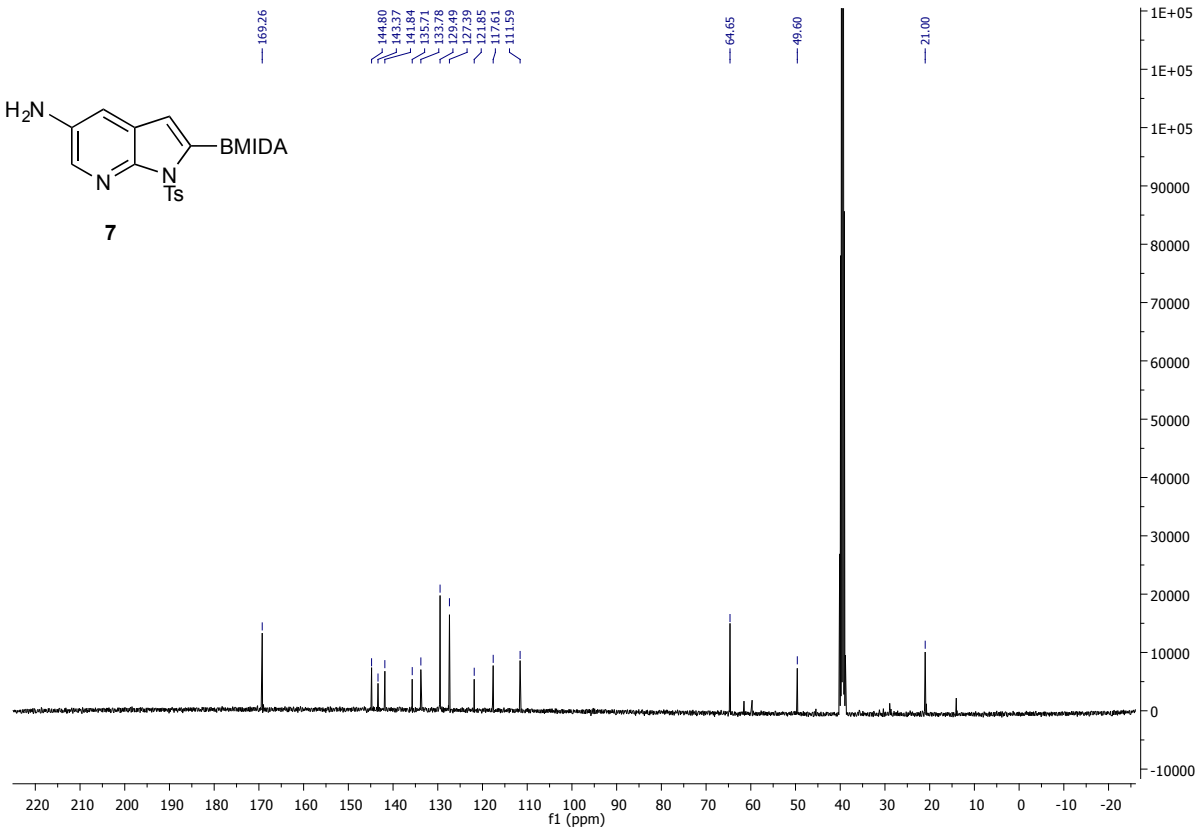


^{1}H NMR of 7



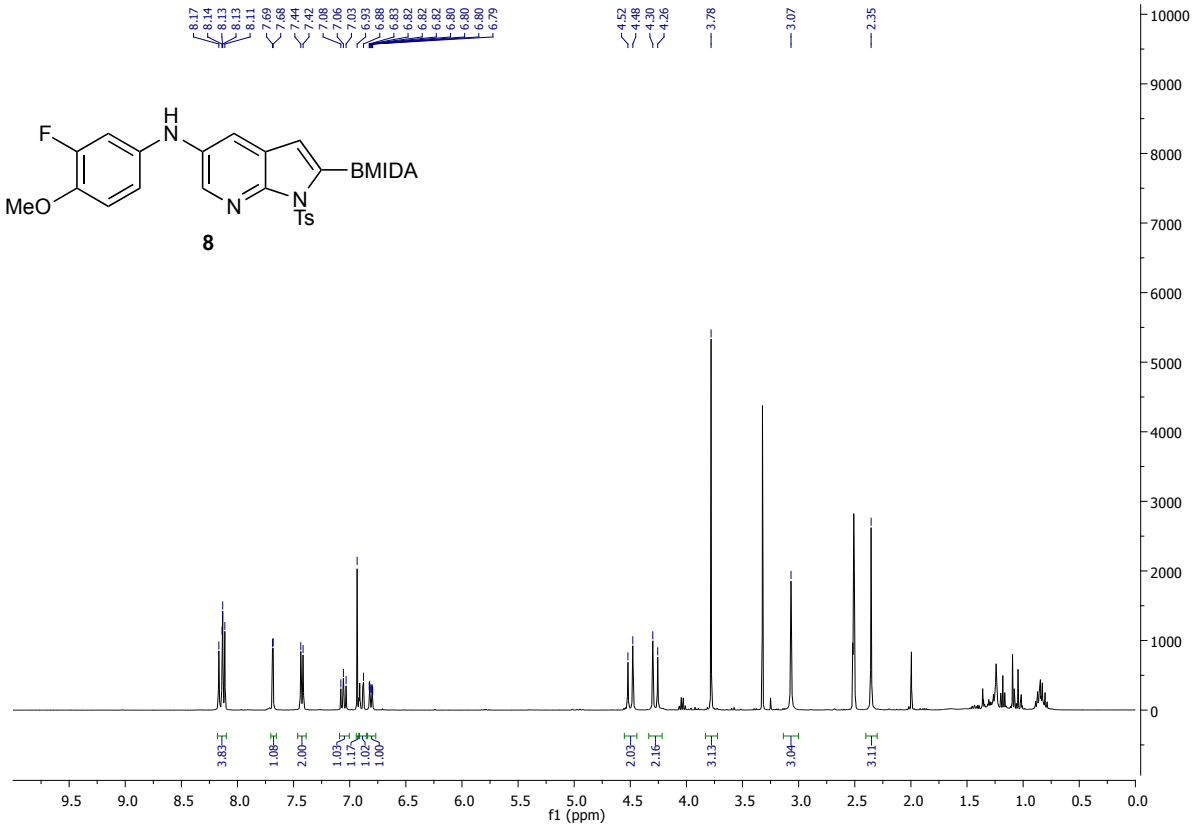
7

^{13}C NMR of 7

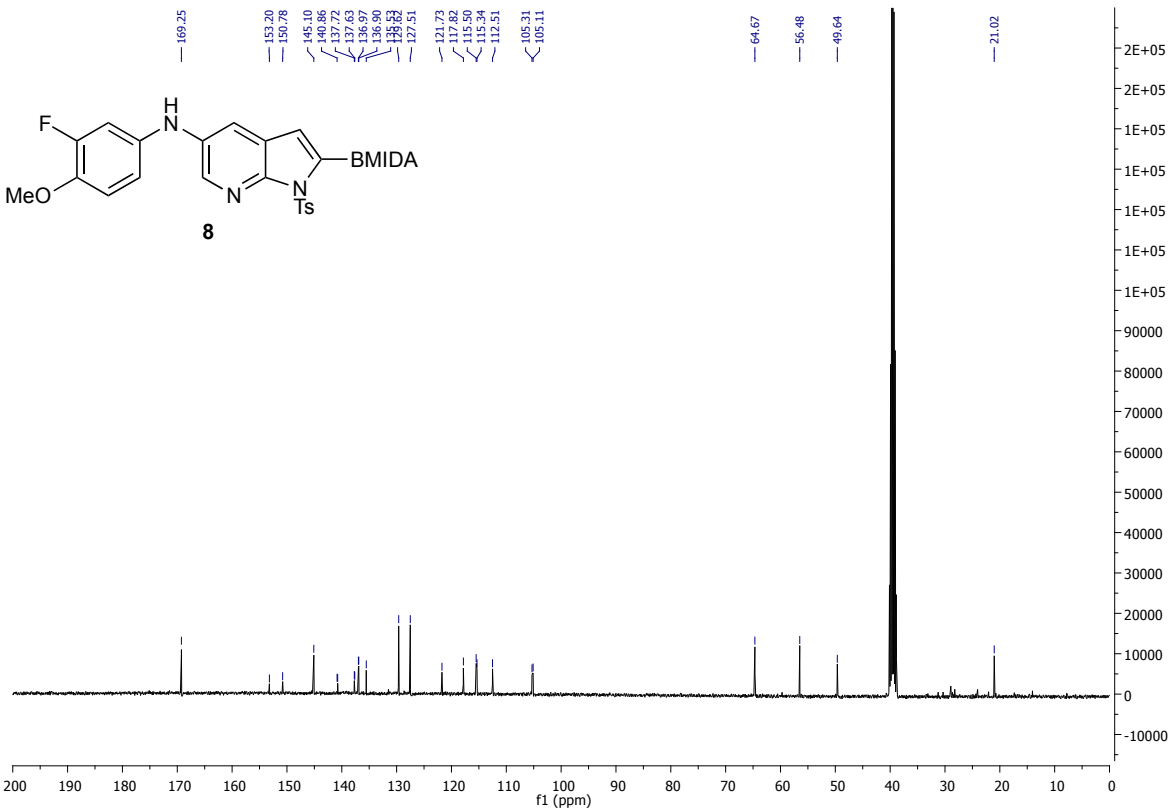


7

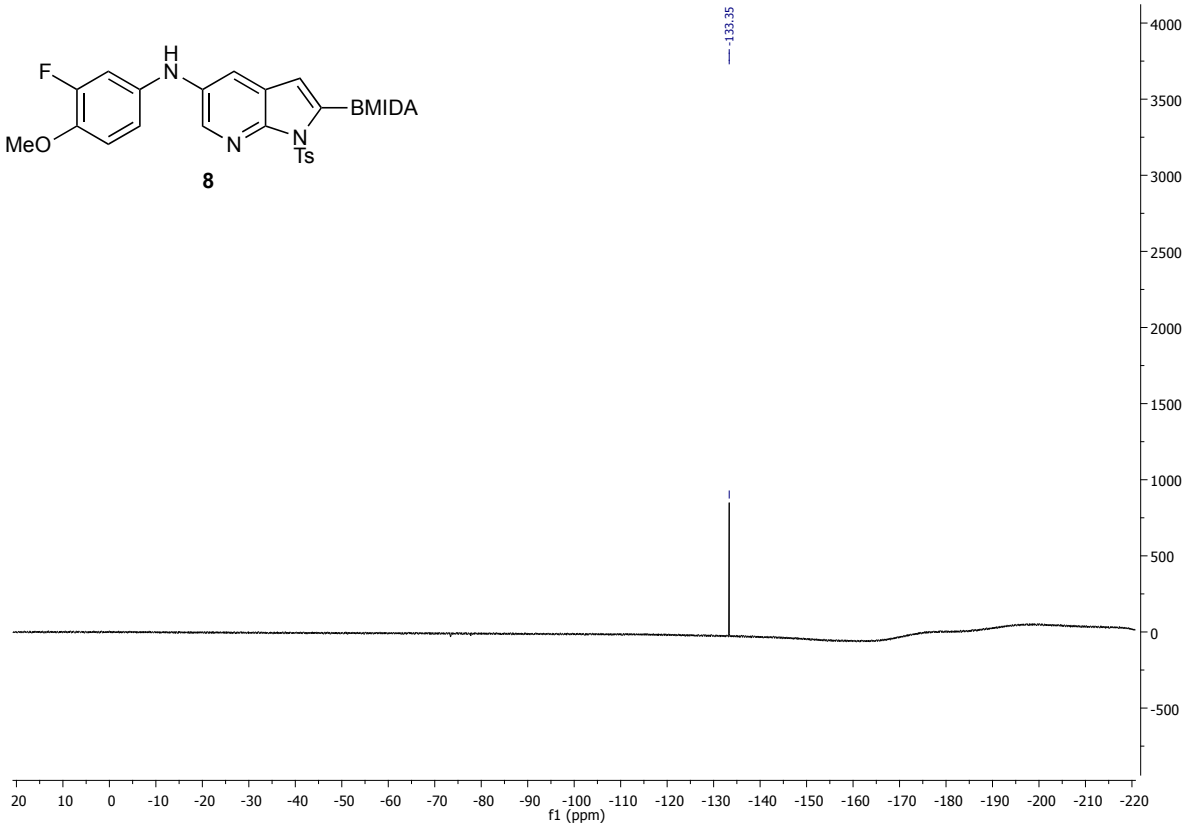
^{1}H NMR of 8



^{13}C NMR of 8

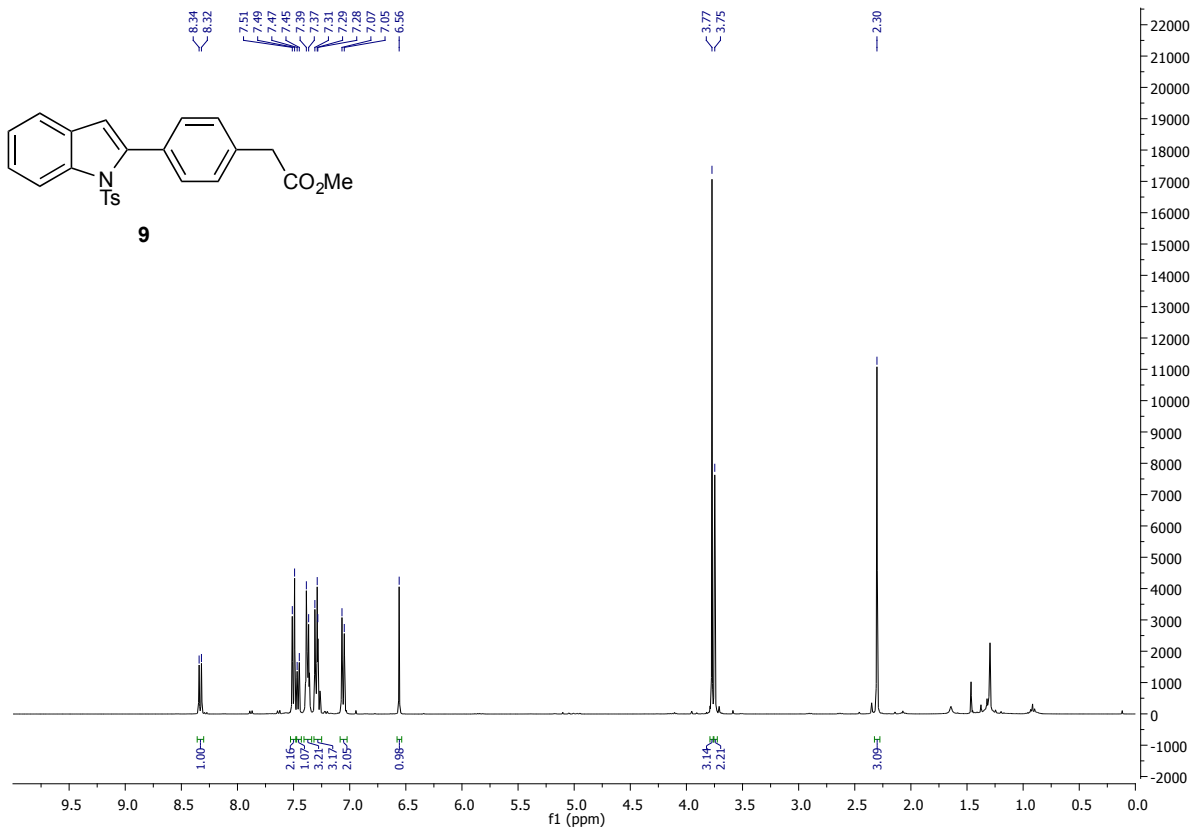


^{19}F NMR of 8



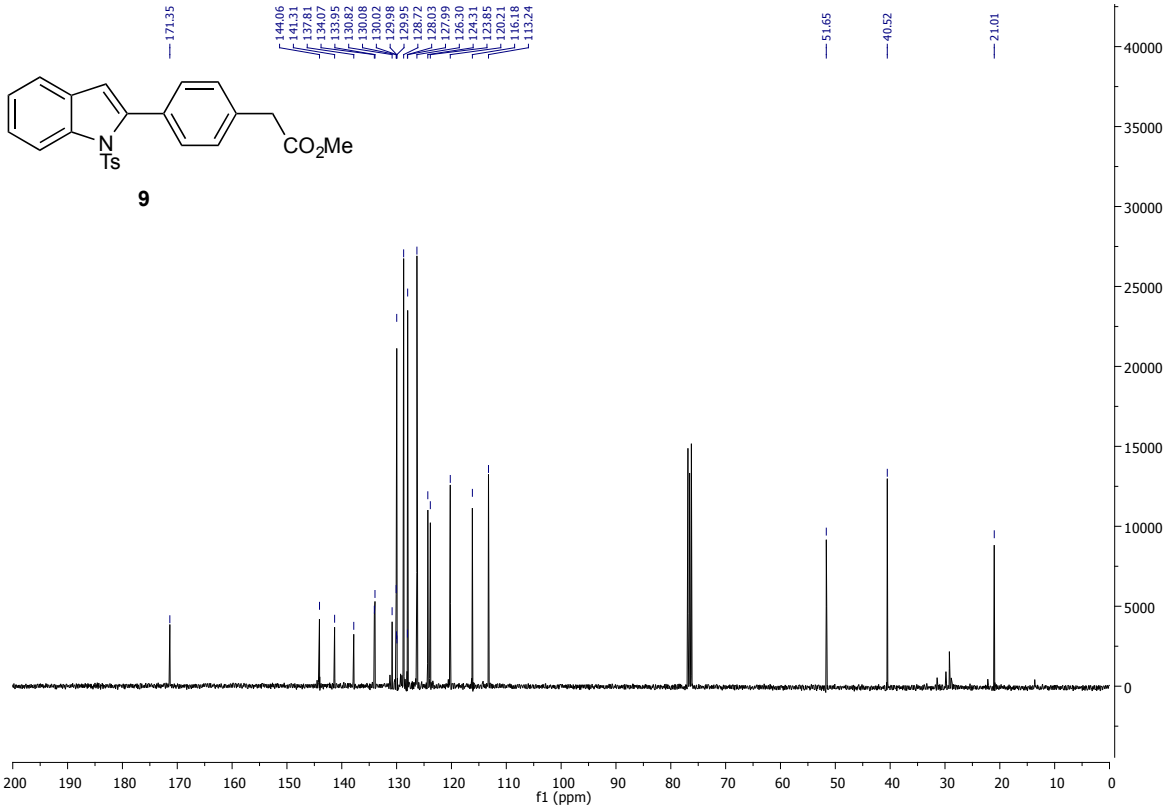
8

^{1}H NMR of 9



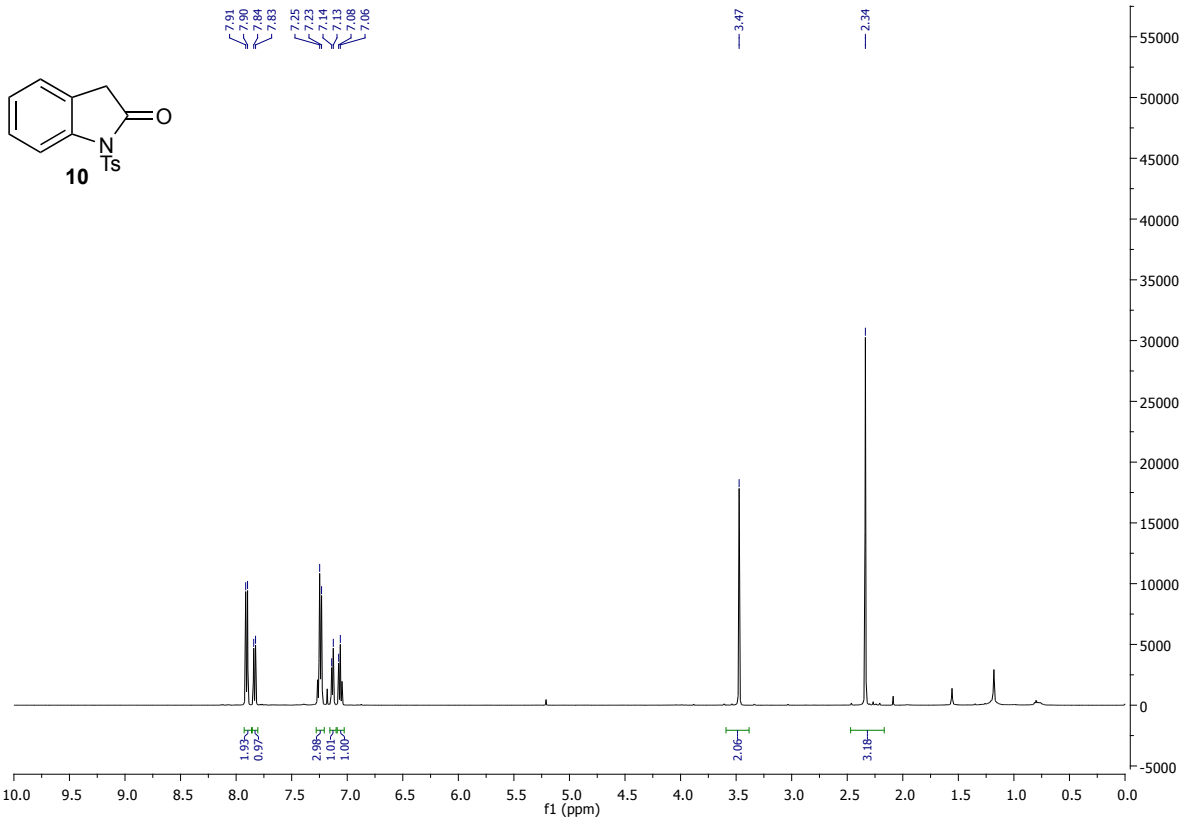
9

^{13}C NMR of 9



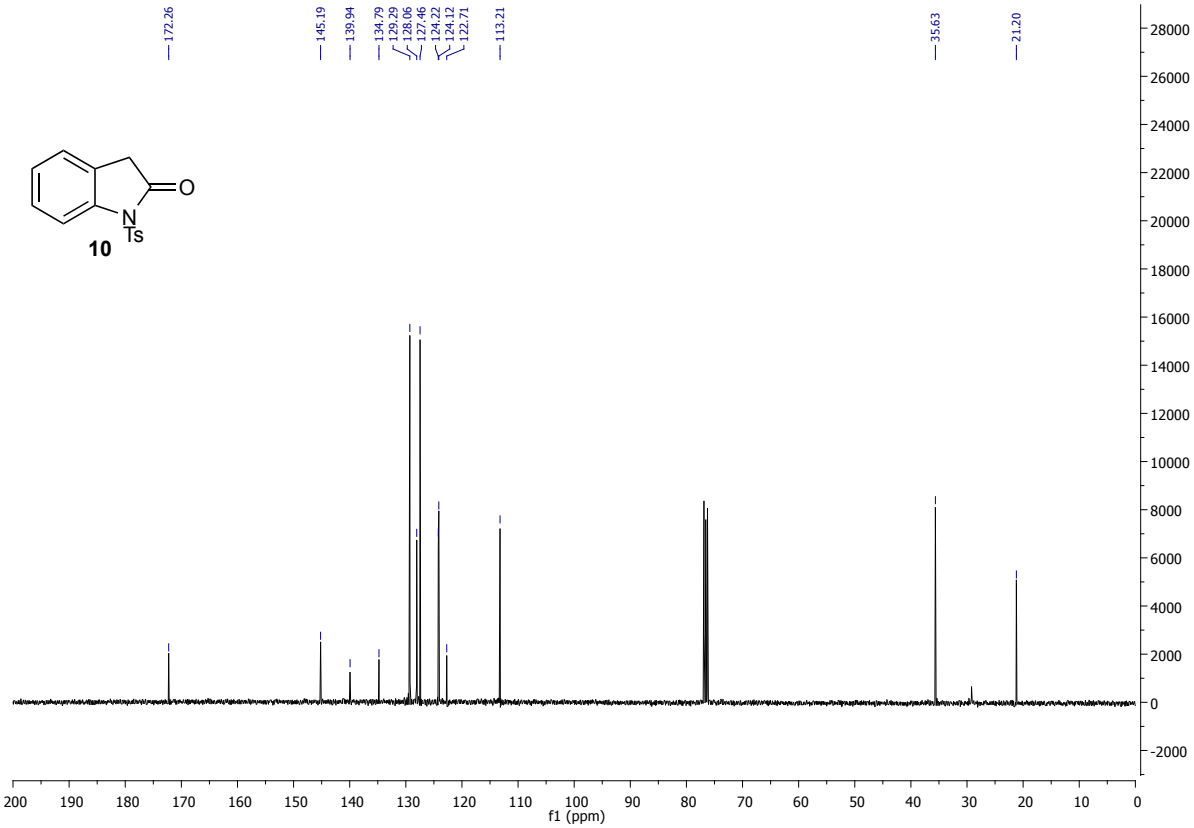
9

^{1}H NMR of 10

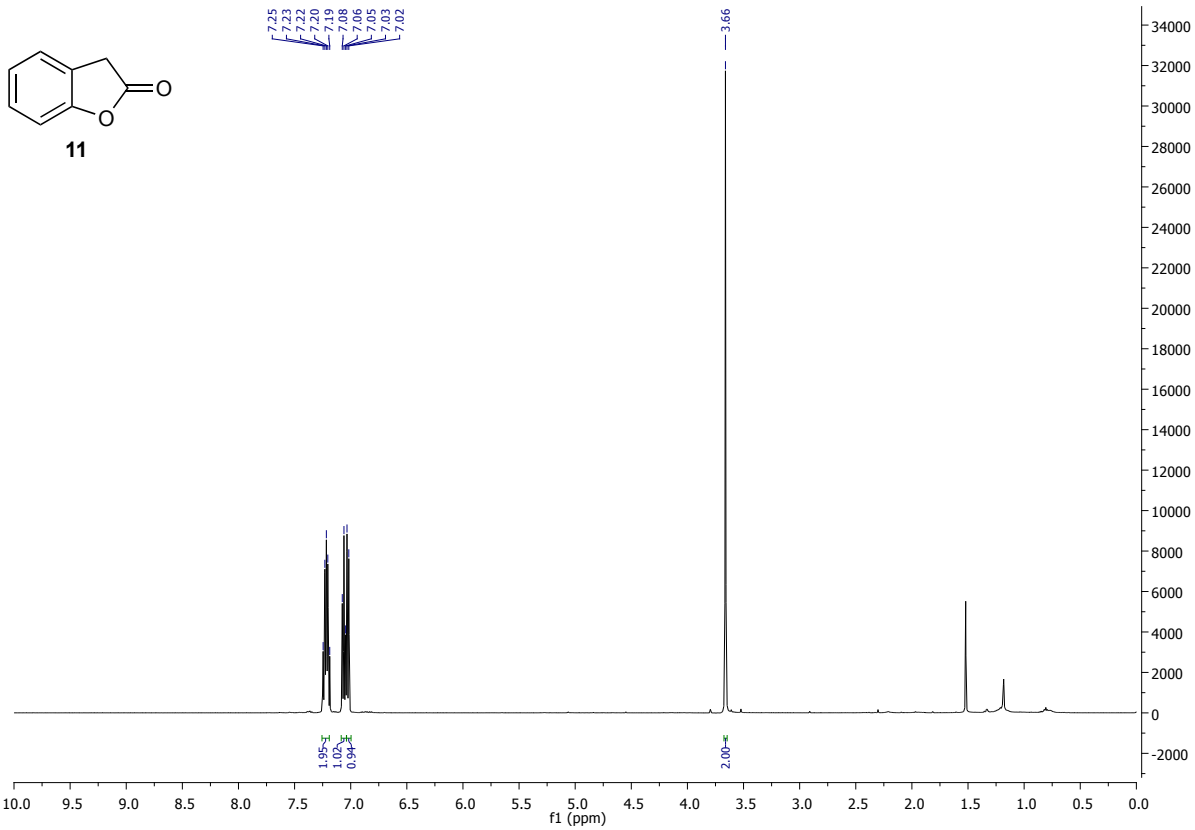


10

^{13}C NMR of 10



^{1}H NMR of 11



^{13}C NMR of 11