

## Supporting Information

### Regiocontrolled aerobic oxidative coupling of indoles and benzene using Pd catalysts with 4,5-diazafluorene ligands

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#### General Considerations

All commercially available compounds were obtained from Sigma Aldrich and used as received except for Pd(OAc)<sub>2</sub> and 4,5-diazafluorenone which were donated by Eli Lilly and 6-methoxy-1*H*-indole which was purchased from Matrix Scientific. *N*-pivalyl indole<sup>1</sup> and 9,9'-dimethyl-4,5-diazafluorene (**2**)<sup>2</sup> were prepared according to literature procedures.

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AC-300 MHz or a Varian Mercury-300 MHz spectrometer. The chemical shifts (δ) are given in parts per million and referenced to residual solvent peaks or a TMS internal standard. Flash column chromatography was performed on an Isco Combiflash system using silica gel 60 (Silicycle) and eluted with ethyl acetate/hexanes or diethyl ether/hexanes. High resolution mass spectra were obtained by the mass spectrometry facility at the University of Wisconsin. Elemental analyses were performed by Robertson Microlit Laboratories. Gas chromatography/mass spectrometry (GC/MS) was performed on a Shimadzu QP2010S using an RTX-5MS column.

CAUTION: The combination of organic solvents and O<sub>2</sub> creates the risk of an explosion. To minimize risks, all reactions carried out at pressures above 1 atm of pressure should utilize a dilute oxygen gas mixture (9% O<sub>2</sub> in N<sub>2</sub>) to ensure that the O<sub>2</sub> content remains below the lower explosive limit of O<sub>2</sub>/organic mixtures.<sup>3</sup> All reactions should be performed with care and carried out behind a blast shield.

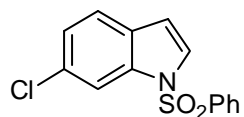
#### **Preparation of phenylsulfonyl protected indoles:**

To a solution of indole (3.3 mmol) in THF (20 mL) at 0 °C was added NaH (86.4 mg, 3.6 mmol). The reaction was warmed to RT and stirred for 1 h. Benzenesulfonyl chloride (0.46 mL, 3.6 mmol) was added dropwise and the reaction stirred for 1 h at RT. The mixture was poured into dilute NaHCO<sub>3</sub> and extracted with EtOAc (3x). The combined organics were dried over MgSO<sub>4</sub>, filtered and the solvent removed by rotatory evaporation. The residue was then purified by silica gel column chromatography (EtOAc/hexanes).

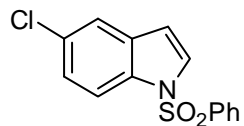
<sup>1</sup> D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* 2007, **129**, 12072.

<sup>2</sup> H. Ohru, A. Senoo, K. Tetsuya, U.S. Pat. Appl. 0161574, 2008.

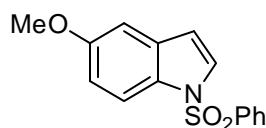
<sup>3</sup> (a) In *Perry's Chemical Engineers' Handbook*; 7th ed.; R. H. Perry, D. W. Green, Eds.; McGraw-Hill: 1997, p 51-57. (b) P. B. Laut, D. Johnstone, *Chem. Eng.* 1994, **101**, 96.



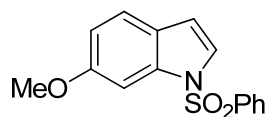
Prepared as described above to give the desired material in 89% yield (856 mg, 2.94 mmol) as a white solid. NMR data match previously reported data.<sup>4</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.03 (s, 1H), 7.91-7.87 (m, 2H), 7.60-7.42 (m, 5H), 7.21 (dd, 1H, *J* = 8.7, 1.8 Hz), 6.63 (d, 1H, *J* = 3.9 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 138.3, 135.4, 134.3, 130.9, 129.6, 129.4, 127.1, 127.0, 124.3, 122.4, 113.9, 109.1. MP = 92-93 °C.



Prepared as described above to give the desired material in 90% yield (865 mg, 2.97 mmol) as a white solid. NMR data match previously reported data.<sup>4</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.94-7.84 (m, 3H), 7.59-7.42 (m, 5H), 7.27 (dd, 1H, *J* = 2.1, 9.0 Hz), 6.61 (dd, 1H, *J* = 0.90, 3.6 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 138.1, 134.2, 133.4, 132.1, 129.5, 129.4, 127.8, 126.9, 125.1, 121.2, 114.7, 108.8. MP = 65-66 °C.



Prepared as described above to give the desired material in 90% yield (852 mg, 2.97 mmol) as a white solid. NMR data match previously reported data.<sup>5</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.90-7.83 (m, 3H), 7.52 (m, 2H), 7.41 (m, 2H), 6.97-6.91 (m, 2H), 6.59 (d, 1H, *J* = 3.6 Hz), 3.8 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 156.7, 138.4, 133.9, 131.9, 129.7, 129.4, 127.3, 126.8, 114.6, 113.9, 109.6, 103.9, 55.8. MP = 98-99 °C.



Prepared as described above to give the desired material in 92% yield (871 mg, 3.04 mmol) as a white solid. NMR data match previously reported data.<sup>6</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.88-7.84 (m, 2H), 7.53-7.51 (m, 2H), 7.46-7.37 (m, 4H), 6.86 (dd, 1H, *J* = 8.7, 2.4 Hz), 6.58 (dd, 1H, *J* = 3.6, 0.6 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 158.1, 138.4, 136.0, 133.9, 129.4, 126.8, 125.2, 124.6, 121.9, 112.7, 109.3, 98.0, 55.9. MP = 140-141 °C.

### **General Procedure for Ligand Screening and Catalyst Optimization**

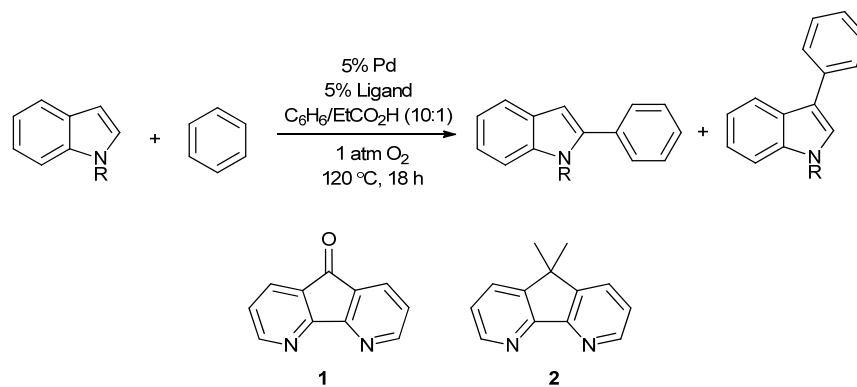
To a disposable 10 mm thick-walled culture tube was added Pd (0.0075 mmol), ligand (0.00375-0.015 mmol), indole (0.15 mmol), benzene (9.9 mmol, 0.85 mL) and acid (0.90 mmol). The tubes were placed in a HEL CAT-24 pressure vessel mounted on a custom Glas-Col large capacity mixer. The vessel was sealed and placed under 11 atm of 9% O<sub>2</sub> in N<sub>2</sub> (1 atm O<sub>2</sub> partial pressure) and the system was heated to 120 °C with shaking. After 18-24 h, the reactions were concentrated under vacuum, taken up in CDCl<sub>3</sub> and analyzed by <sup>1</sup>H NMR with tetrachloroethane as an internal standard.

<sup>4</sup> S. Komoriya, N. Haginoya, S. Kobayashi, T. Nagata, A. Mochizuki, M. Suzuki, T. Yoshino, H. Horino, T. Nagahara, M. Suzuki, Y. Isobe, T. Furugoori, *Bioorg. Med. Chem.* 2005, **13**, 3927.

<sup>5</sup> S. Mahboobi; A. Uecker; A. Sellmer; C. Cenac; H. Hocher; H. Pongratz; E. Eichhorn; H. Hufsky; A. Trumpler; M. Sicker; F. Heidel; T. Fischer; C. Stocking; S. Elz; F. D. Bohmer; S. Dove, *J. Med. Chem.*, 2006, **49**, 3101.

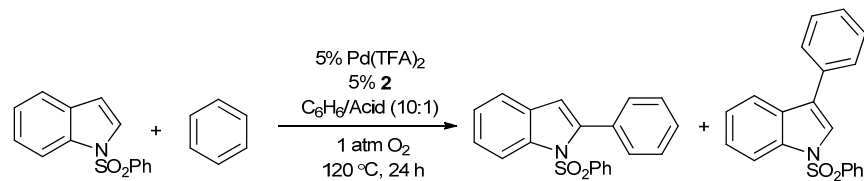
<sup>6</sup> G. Dupeyre; G. G. Chabot; S. Thoret; X. Cachet; J. Seguin; D. Guenard; F. Tillequin; D. Scherman; M. Koch; S. Michel, *Bioorg. Med. Chem.*, 2006, **14**, 4410.

**Table S1.** Results from protecting group screen<sup>a</sup>



Entry	Pd	Ligand	R	Yield <sup>b</sup>	C2:C3 Selectivity <sup>c</sup>
1	Pd(TFA) <sub>2</sub>	<b>2</b>	SO <sub>2</sub> Ph	87%	1:5.2
2	Pd(OPiv) <sub>2</sub>	<b>1</b>	SO <sub>2</sub> Ph	80%	2:1
3	Pd(TFA) <sub>2</sub>	<b>2</b>	Piv	69%	1:4.4
4	Pd(OPiv) <sub>2</sub>	<b>1</b>	Piv	58%	4.3:1
5	Pd(TFA) <sub>2</sub>	<b>2</b>	Ac	52%	1:1.6
6	Pd(OPiv) <sub>2</sub>	<b>1</b>	Ac	62%	1.5:1
7	Pd(TFA) <sub>2</sub>	<b>2</b>	Benzyl	17%	16:1
8	Pd(OPiv) <sub>2</sub>	<b>1</b>	Benzyl	39%	10:1
9	Pd(TFA) <sub>2</sub>	<b>2</b>	SEM	0%	-
10	Pd(OPiv) <sub>2</sub>	<b>1</b>	SEM	49%	3.9:1
11	Pd(TFA) <sub>2</sub>	<b>2</b>	Me	0%	-
12	Pd(TFA) <sub>2</sub>	<b>2</b>	CONEt <sub>2</sub>	40%	1:1.9

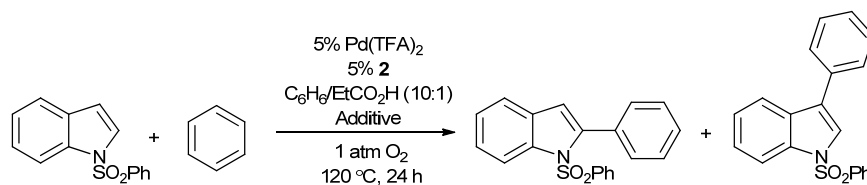
**Table S2.** Results from acid screen<sup>a</sup>



Acid	Yield <sup>b</sup>	C2:C3 Selectivity <sup>c</sup>
PivOH	77%	1:5
EtCO <sub>2</sub> H	89%	1:5.8
AcOH	76%	1:4.4
PhCO <sub>2</sub> H	87%	1:4.4
4-NO <sub>2</sub> -PhCO <sub>2</sub> H	67%	1:5
TFA	22%	1:>10
PivOH <sup>d</sup>	82%	1:3.3
PivOH <sup>e</sup>	76%	1:4.1
None	22%	1:4.5

<sup>a</sup> 5% Pd(TFA)<sub>2</sub> (2.5 mg, 0.0075 mmol), 5% **2** (1.5 mg, 0.0075 mmol), indole (38.6 mg, 0.15 mmol), 6 equiv acid (0.90 mmol), benzene (0.85 mL, 9.9 mmol), 1 atm O<sub>2</sub>, 120 °C, 24h. <sup>b</sup> By <sup>1</sup>H NMR with tetrachloroethane as internal standard. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> 12 equiv PivOH (1.8 mmol) <sup>e</sup> 3 equiv PivOH (0.45 mmol)

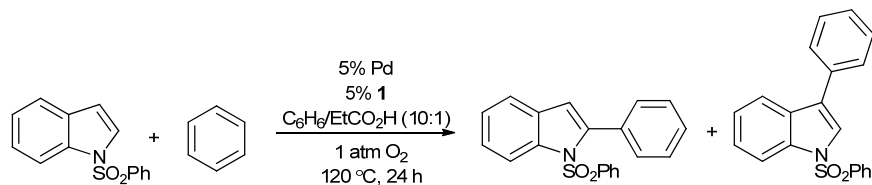
**Table S3.** Results from base additive screen<sup>a</sup>



Additive	Yield <sup>b</sup>	C2:C3 Selectivity <sup>c</sup>
None	89%	1:5.8
20% CsOPiv	55%	1:1.4
100% CsOPiv	24%	1:1.1
100% CsOPiv <sup>d</sup>	49%	1:3.5
100% NaOAc	69%	1:1.3
100% LiOAc	58%	1.1:1
10% AgOAc	58%	1:2.9
10% Cu(OAc) <sub>2</sub>	72%	1:4.5

<sup>a</sup> 5% Pd(TFA)<sub>2</sub> (2.5 mg, 0.0075 mmol), 5% **2** (1.5 mg, 0.0075 mmol), indole (38.6 mg, 0.15 mmol), 6 equiv EtCO<sub>2</sub>H (270 μL, 0.90 mmol), benzene (0.85 mL, 9.9 mmol), 1 atm O<sub>2</sub>, 120 °C, 24h. <sup>b</sup> By <sup>1</sup>H NMR with tetrachloroethane as internal standard. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> No EtCO<sub>2</sub>H was added

**Table S4.** Results from palladium source screen<sup>a</sup>

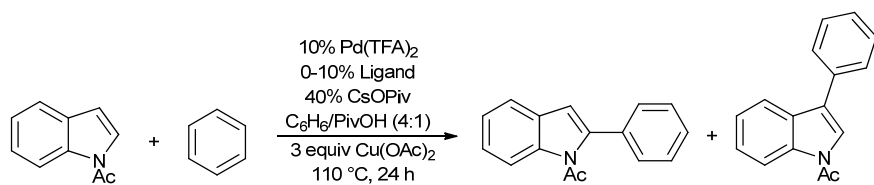


Pd	Yield <sup>b</sup>	C2:C3 Selectivity <sup>c</sup>
Pd(TFA) <sub>2</sub>	45%	1:1.7
Pd(OAc) <sub>2</sub>	64%	1:4.3
Pd(OPiv) <sub>2</sub>	58%	4.3:1
PdCl <sub>2</sub>	0%	-
PdBr <sub>2</sub>	0%	-
(MeCN) <sub>2</sub> PdCl <sub>2</sub>	0%	-
[(MeCN) <sub>4</sub> Pd][BF <sub>4</sub> ]	0%	-

<sup>a</sup> 5% Pd (0.0075 mmol), 5% **1** (1.4 mg, 0.0075 mmol), indole (38.6 mg, 0.15 mmol), 6 equiv EtCO<sub>2</sub>H (270 μL, 0.90 mmol), benzene (0.85 mL, 9.9 mmol), 1 atm O<sub>2</sub>, 120 °C, 24h. <sup>b</sup> By <sup>1</sup>H NMR with tetrachloroethane as internal standard. <sup>c</sup> Determined by <sup>1</sup>H NMR.

### Comparison of Ligands with Cu(OAc)<sub>2</sub> as the Oxidant

**Table S5.** Results from Screen with Cu(OAc)<sub>2</sub> as the Oxidant<sup>a</sup>



Ligand	Yield <sup>b</sup>	C2:C3 Selectivity <sup>c</sup>
None	43%	1:26
3-nitropyridine	41%	1:14
<b>2</b>	85%	1:1.3

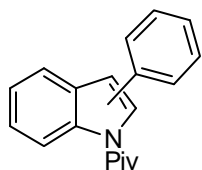
<sup>a</sup> 10% Pd(TFA)<sub>2</sub> (0.015 mmol), 10% ligand (0.015 mmol), indole (0.15 mmol), 40% CsOPiv (0.06 mmol), 3 equiv Cu(OAc)<sub>2</sub> (0.45 mmol), benzene (0.4 mL), PivOH (0.1 mmol) 110 °C, 24h. <sup>b</sup> By <sup>1</sup>H NMR with tetrachloroethane as internal standard. <sup>c</sup> Determined by <sup>1</sup>H NMR.

Procedure was adapted from the literature.<sup>7</sup> To a 9 mL pressure tube was added Pd(TFA)<sub>2</sub> (0.015 mmol, 5.0 mg), ligand (0.015 mmol), *N*-acetylindole (0.15 mmol, 22.9 mg), CsOPiv (0.06 mmol, 14 mg), Cu(OAc)<sub>2</sub> (0.45 mmol, 82 mg), benzene (0.4 mL) and PivOH (0.1 mL). The tubes were sealed and heated to 110 °C for 24 h with stirring. The reactions were then filtered, concentrated under vacuum, taken up in CDCl<sub>3</sub> and analyzed by <sup>1</sup>H NMR with tetrachloroethane as an internal standard. Results are reported in Table S5 as an average of two experiments.

### **Catalytic Oxidative Cross-Coupling**

**Oxidative cross-coupling procedure A:** A pressure tube fitted with a plunger valve was charged with Pd(TFA)<sub>2</sub> (10 mg, 0.030 mmol), **2** (5.9 mg, 0.030 mmol), indole (0.60 mmol), EtCO<sub>2</sub>H (270 μL, 3.6 mmol) and arene (39.6 mmol). The tube was evacuated and backfilled with O<sub>2</sub> (3x), sealed and heated to 120 °C for 24h with vigorous stirring. The reaction mixture was then cooled to room temperature, diluted with EtOAc and washed with sat'd. NaHCO<sub>3</sub>. The organic layer was separated and the aqueous layer washed with EtOAc (2x). The combined organics were dried over MgSO<sub>4</sub>, filtered and concentrated by rotatory evaporation. The crude product was purified by silica gel column chromatography (0-3% Et<sub>2</sub>O in hexanes) to yield the product as a mixture of two isomers.

**Oxidative cross-coupling procedure B:** A pressure tube fitted with a plunger valve was charged with Pd(OPiv)<sub>2</sub> (9.3 mg, 0.030 mmol), **1** (5.5 mg, 0.030 mmol), indole (0.60 mmol), EtCO<sub>2</sub>H (270 μL, 3.6 mmol) and arene (39.6 mmol). The tube was evacuated and backfilled with O<sub>2</sub> (3x), sealed and heated to 120 °C for 24 h with vigorous stirring. The reaction mixture was then cooled to room temperature, diluted with EtOAc and washed with sat'd. NaHCO<sub>3</sub>. The organic layer was separated and the aqueous layer washed with EtOAc (2x). The combined organics were dried over MgSO<sub>4</sub>, filtered and concentrated by rotatory evaporation. The crude product was purified by silica gel column chromatography (0-3% Et<sub>2</sub>O in hexanes) to yield the product as a mixture of two isomers.



Prepared as described above by both methods A and B except that the regioisomers were separated by column chromatography.

Method A: Following aqueous workup, the ratio of regioisomers was 1:4.4 (C2:C3). Purification by column chromatography yielded the 16 mg of the C2 isomer as a pale yellow oil and 69 mg of the C3 isomer as a white solid, giving a total yield of 52%.

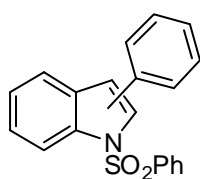
C2 isomer<sup>8</sup>: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.61 (d, 1H, *J* = 7.5 Hz), 7.53 (m, 2H), 7.45-7.35 (m, 4H), 7.25-7.18 (m, 2H), 6.68 (s, 1H), 0.96 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 187.5, 139.6, 137.4, 134.1, 129.2, 128.4, 128.0, 123.6, 121.7, 120.8, 111.4, 104.8, 45.3, 28.1. C3 isomer<sup>1</sup>: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.62 (d, 1H, *J* = 8.4 Hz), 7.81 (m, 2H), 7.67 (m, 2H), 7.54-7.49 (m, 2H), 7.46-7.32 (m, 3H), 1.58 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 177.2, 137.7, 133.7, 129.1, 128.3, 128.2, 127.6, 125.7, 124.0, 123.3, 122.7, 119.6, 117.8, 41.5, 28.9. MP = 138-139 °C.

Method B: Following aqueous workup, the ratio of regioisomers was 4.8:1 (C2:C3). Purification by column chromatography yielded the 90 mg of the C2 isomer as a pale yellow oil and 20 mg of the C3

<sup>7</sup> D. R. Stuart, K. Fagnou, *Science*. 2007, **316**, 1172.

<sup>8</sup> A. Yasuhara; Y. Kanamori; M. Kaneko; A. Numata; Y. Kondo; T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1*, 1999, 529.

isomer as a white solid, giving a total yield of 66%. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra and melting point data match those given for the compounds obtained by method A.



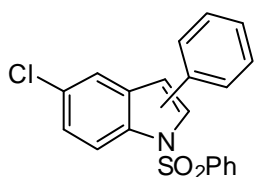
Prepared as described above by both methods A and B.

Method A: Following aqueous workup, the ratio of regioisomers was 1:6 (C2:C3). After purification by column chromatography, the product was isolated in 66% yield (131 mg, 0.40 mmol) as a pale yellow solid with a 1:4.9 ratio of regioisomers (C3:C2).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (d, 1H,  $J = 8.4$  Hz, C2), 8.06 (d, 1H,  $J = 8.4$  Hz, C3), 7.93 (m, 1H, C3), 7.91 (m, 1H, C3), 7.77 (d, 1H,  $J = 7.8$  Hz, C3), 7.70 (s, 1H, C3), 7.62-7.21 (m, C2 + C3), 6.54 (s, 1H, C2).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 142.2, 138.4, 138.3, 137.6, 135.7, 134.0, 133.6, 133.1, 132.4, 130.6, 130.5, 130.4, 129.4, 129.0, 128.8, 128.7, 128.0, 127.7, 127.6, 126.9, 126.8, 125.1, 125.0, 124.5, 124.3, 123.8, 123.0, 120.8, 120.6, 116.7, 113.9, 113.8.

Method B: Following aqueous workup the ratio of regioisomers was 2.5:1 (C2:C3). After purification by column chromatography, the product was isolated in 76% yield (152 mg, 0.46 mmol) as a pale yellow solid with a 2.4:1 ratio of regioisomers (C3:C2).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (d, 1H,  $J = 8.4$  Hz, C2), 8.06 (d, 1H,  $J = 8.1$  Hz, C3), 7.92 (m, 2H, C3), 7.77 (d, 1H,  $J = 8.1$  Hz, C3), 7.70 (s, 1H, C3), 7.62-7.24 (m, C2+C3), 6.54 (s, 1H, C2).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 142.2, 138.4, 138.3, 137.6, 135.7, 134.0, 133.6, 133.1, 132.4, 130.6, 130.5, 130.4, 129.4, 129.0, 128.8, 128.7, 128.0, 127.7, 127.6, 126.9, 126.8, 125.1, 125.0, 124.5, 124.3, 123.8, 123.0, 120.8, 120.6, 116.7, 113.9, 113.8.

These data match that reported for both regioisomers.<sup>9,10</sup>



Prepared as described above by both methods A and B.

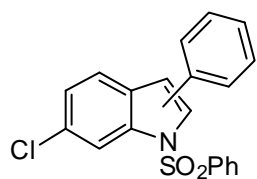
Method A: Following aqueous workup, the ratio of regioisomers was 1:1.3 (C2:C3). After purification by column chromatography, the product was isolated in 71% yield (156 mg, 0.43 mmol) as a pale yellow solid with a 1:1.4 ratio of regioisomers (C3:C2).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (d, 1H,  $J = 8.7$  Hz, C2), 7.99 (d, 1H,  $J = 8.7$  Hz, C3), 7.90 (m, 2H, C3), 7.72 (d, 1H,  $J = 2.1$  Hz, C3), 7.70 (s, 1H, C3), 7.58-7.24 (m, C2+C3), 6.47 (s, 1H, C2).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 143.6, 138.0, 137.5, 136.7, 134.3, 134.0, 133.9, 132.4, 132.2, 131.8, 130.7, 130.5, 130.3, 129.9, 129.6, 129.2, 128.8, 128.0, 127.9, 127.7, 127.5, 126.9, 126.8, 125.4, 125.1, 124.3, 123.9, 120.5, 120.3, 117.8, 115.0, 112.8. HRMS (ESI)  $[\text{M} + \text{Na}^+]/z$  calcd. 390.0326, found 390.0333. Anal found: C, 65.25; H, 3.70; N, 3.65. Calc. for  $\text{C}_{20}\text{H}_{14}\text{ClNO}_2\text{S}$ : C, 63.30; H, 3.84; N, 3.81%.

Method B: Following aqueous workup the ratio of regioisomers was 5:1 (C2:C3). After purification by column chromatography, the product was isolated in 68% yield (150 mg, 0.41 mmol) as a white solid with a 4:1 ratio of regioisomers (C3:C2).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (d, 1H,  $J = 9.0$  Hz, C2), 7.98 (d, 1H,  $J = 8.7$  Hz, C3), 7.89 (d, 2H,  $J = 6.9$  Hz, C3), 7.71 (d, 1H,  $J = 1.8$  Hz, C3), 7.70 (s, 1H, C3), 7.54-7.2 (m, C2+C3), 6.45 (s, 1H, C2).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  143.6, 138.0, 137.4, 136.7, 134.2, 133.9, 132.4, 131.8, 130.5, 130.4, 130.2, 129.8, 129.5, 129.2, 129.1, 128.9, 128.8, 128.0, 127.9, 127.7, 126.9, 126.8, 126.7, 125.4, 125.1, 124.2, 123.8, 120.4, 120.3, 117.7, 115.0, 112.8. HRMS (ESI)  $[\text{M} +$

<sup>9</sup> Y. Yin; W. Y. Ma; Z. Chai; G. Zhao, *J. Org. Chem.*, 2007, **72**, 5731.

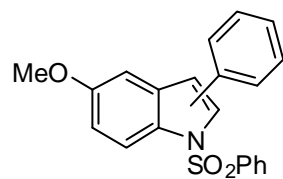
<sup>10</sup> T. Sakamoto; Y. Kondo; N. Takazawa; H. Yamanaka, *Tet. Lett.*, 1993, **34**, 5955.

$\text{Na}^+/\text{z}$  calcd. 390.0326, found 390.0316. (Found: C, 65.05; H, 4.08; N, 3.64. Calc. for  $\text{C}_{20}\text{H}_{14}\text{ClNO}_2\text{S}$ : C, 63.30; H, 3.84; N, 3.81%.)



Prepared as described above by both methods A and B. Following aqueous workup, method A gave a 1.4:1 ratio of regioisomers (C2:C3). After purification by column chromatography, the product was isolated in 71% yield (156 mg, 0.43 mmol) as a pale yellow solid with a 2:1 ratio of regioisomers (C3:C2).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (s, 1H, C2), 8.11 (d, 1H,  $J = 1.8$  Hz, C3), 7.94 (m, 2H, C3), 7.69 (m, 1H, C3), 7.59-7.25 (m, C2+C3), 6.51 (s, 1H, C2).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  142.8, 142.4, 138.7, 138.1, 137.6, 136.0, 134.3, 133.9, 132.6, 131.9, 131.2, 130.8, 130.6, 129.8, 129.6, 129.1, 129.0, 128.9, 128.0, 127.7, 127.5, 126.9, 125.1, 124.5, 124.2, 124.1, 123.4, 121.5, 117.4, 116.8, 114.1, 113.1. HRMS (ESI)  $[\text{M} + \text{Na}^+]/\text{z}$  calcd. 390.0326, found 390.0332. Anal found: C, 65.03; H, 3.85; N, 3.73. Calc. for  $\text{C}_{20}\text{H}_{14}\text{ClNO}_2\text{S}$ : C, 63.30; H, 3.84; N, 3.81%

Following aqueous workup, method B gave a 3.7:1 ratio of regioisomers (C2:C3). After purification by column chromatography, the product was isolated in 75% yield (165 mg, 0.45 mmol) as a white solid with a 7:1 ratio of regioisomers (C3:C2).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 8.37 (s, 1H, C2), 8.11 (d, 1H,  $J = 1.8$  Hz, C3), 7.94 (m, 2H, C3), 7.69 (m, 1H, C3), 7.59-7.36 (m, C2+C3), 7.32-7.25 (m, C2+C3), 6.51 (s, 1H, C2).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  142.8, 142.4, 138.7, 138.1, 137.6, 136.0, 134.3, 133.9, 132.6, 131.9, 131.2, 130.8, 130.6, 129.8, 129.6, 129.1, 129.0, 128.9, 128.0, 127.7, 127.5, 126.9, 125.1, 124.5, 124.2, 124.1, 123.4, 121.5, 117.4, 116.8, 114.1, 113.1. HRMS (ESI)  $[\text{M} + \text{NH}_4^+]/\text{z}$  calcd. 385.0773, found 385.0763. (Found: C, 65.18; H, 3.97; N, 3.72. Calc. for  $\text{C}_{20}\text{H}_{14}\text{ClNO}_2\text{S}$ : C, 63.30; H, 3.84; N, 3.81%.)

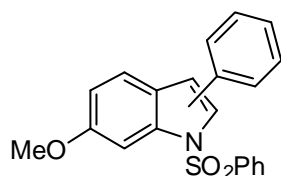


Prepared as described above by both methods A and B. Following aqueous workup, method A gave a 1:3.9 ratio of regioisomers (C2:C3). After purification by column chromatography, the product was isolated in 54% yield (93 mg, 0.32 mmol) as a white solid with a 1:4.4 ratio of regioisomers (C3:C2).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (d, 1H,  $J = 9.0$  Hz, C2), 7.96 (d, 1H,  $J = 9.3$  Hz, C3), 7.91 (m, 2H, C3), 7.66 (s, 1H, C3), 7.58-7.19 (m, C2+C3), 6.97 (m, C2+C3), 6.90 (d, 1H,  $J = 2.7$  Hz, C2), 6.49 (s, 1H, C2), 3.82 (s, 3H, C2), 3.80 (s, 3H, C3).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.3, 157.0, 143.2, 138.3, 137.4, 133.9, 133.6, 133.2, 133.0, 132.4, 132.1, 131.9, 130.5, 130.4, 129.9, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 128.0, 127.7, 126.9, 124.4, 123.9, 117.9, 114.9, 114.0, 113.7, 103.4, 103.1, 55.9, 55.7.

Following aqueous workup, method B gave a 2.3:1 ratio of regioisomers (C2:C3). After purification, method B gave 71% yield of product (154 mg, 43 mmol) in a 2.8:1 ratio of isomers (C3:C2) as a white solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.19 (d, 1H,  $J = 9.0$  Hz, C2), 7.95 (d, 1H,  $J = 9.0$  Hz, C3), 7.88 (m, 2H, C3), 7.64 (s, 1H, C3), 7.58-7.19 (m, C2+C3), 6.95 (m, C2+C3), 6.88 (d, 1H,  $J = 2.7$  Hz, C2), 6.47 (s, 1H, C2), 3.82 (s, 3H, C2), 3.80 (s, 3H, C3).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  157.3, 157.0, 143.2, 138.3, 137.4, 133.9, 133.6, 133.2, 133.0, 132.4, 132.1, 131.9, 130.5, 130.4, 129.9, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 128.0, 127.7, 126.9, 124.4, 123.9, 117.9, 114.9, 114.0, 113.7, 103.4, 103.1, 55.9, 55.7.



These data match that reported for both regioisomers.<sup>11</sup>



Prepared as described above by both methods A and B.

Method A: Following aqueous workup, the ratio of regioisomers was 1:1.3 (C2:C3). After purification by column chromatography, the product was isolated in 70% yield (120 mg, 0.42 mmol) with a 1.2:1 ratio of regioisomers (C3:C2) as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.90 (m, C2+C3), 7.62-7.20 (m, C2+C3), 6.93 (m, C2+C3), 6.46 (s, 1H, C2), 3.92 (s, 3H, C2), 3.88 (s, 3H, C3). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 158.3, 158.1, 141.0, 139.6, 138.3, 137.6, 136.8, 134.0, 133.6, 133.2, 130.3, 129.4, 129.0, 128.7, 128.5, 127.9, 127.7, 127.6, 126.9, 126.8, 124.5, 124.3, 123.2, 121.7, 121.3, 121.2, 113.7, 113.6, 112.8, 101.2, 98.3, 56.0, 55.9. HRMS (ESI) [M + Na<sup>+</sup>]/z calcd. 386.0822, found 386.0829. (Found: C, 69.19; H, 4.70; N, 3.65. Calc. for C<sub>21</sub>H<sub>17</sub>NO<sub>3</sub>S: C, 69.40; H, 4.71; N, 3.85%.)

Method B: Following aqueous workup, the ratio of regioisomers was 2.6:1 (C2:C3). After purification by column chromatography, the product was isolated in 65% yield (112 mg, 0.39 mmol) as a pale yellow solid with a 2.3:1 ratio of regioisomers (C3:C2). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.90 (m C2+C3), 7.60-7.56 (m, C2+C3), 7.47-7.21 (m, C2+C3), 6.91-6.87 (m, C2+C3), 6.45 (s, 1H, C2), 3.92 (s, 3H, C2), 3.88 (s, 3H, C3). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 158.3, 158.1, 141.0, 139.6, 138.3, 137.6, 136.8, 134.0, 133.6, 133.2, 132.6, 132.2, 130.3, 129.4, 129.0, 128.5, 128.3, 127.9, 127.6, 126.8, 124.5, 124.3, 123.2, 121.7, 121.3, 121.2, 113.7, 113.6, 112.8, 101.2, 98.3, 56.0, 55.9. HRMS (ESI) [M + Na<sup>+</sup>]/z calcd. 386.0822, found 386.0827. (Found: C, 69.15; H, 4.74; N, 3.72. Calc. for C<sub>21</sub>H<sub>17</sub>NO<sub>3</sub>S: C, 69.40; H, 4.71; N, 3.85%.)

### Intermolecular Competition Kinetic Isotope Effect

To a pressure tube fitted with a plunger valve was added Pd (0.0075 mmol), ligand (0.0075 mmol), indole (38.6 mg, 0.15 mmol), benzene (426 μL, 4.95 mmol), benzene-d<sub>6</sub> (439 μL, 4.95 mmol) and EtCO<sub>2</sub>H (67 μL, 0.90 mmol). The tube was evacuated and backfilled with O<sub>2</sub> (3x), sealed and heated to 120 °C for 24 h with vigorous stirring. The reaction mixture was then cooled to room temperature, diluted with EtOAc and filtered through a plug of silica. GC/MS analysis was used to determine the ratio of C<sub>6</sub>H<sub>6</sub> and C<sub>6</sub>D<sub>6</sub> incorporation into the product. KIE values are the amount of C<sub>6</sub>H<sub>6</sub> incorporation/C<sub>6</sub>D<sub>6</sub> incorporation.

**Table S6.** Intermolecular Competition Kinetic Isotope Effect

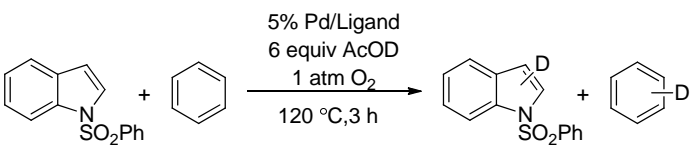
Catalyst	Product	KIE
Pd(TFA)2/2	C2	3.1
	C3	2.8
Pd(OPiv)2/1	C2	3.6
	C3	3.8

<sup>11</sup> T. C. Leboho; J. P. Michael; W. A. L. van Otterlo; S. F. van Vuuren; C. B. de Koning, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4948.

### Deuterium Incorporation into Indole and Benzene

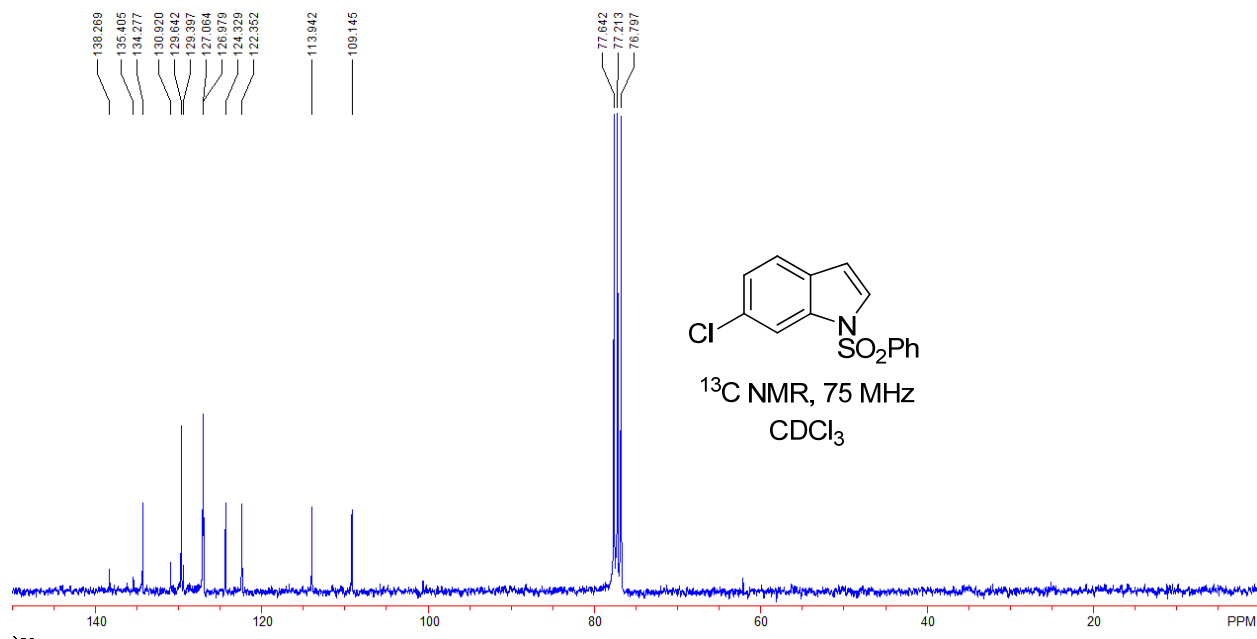
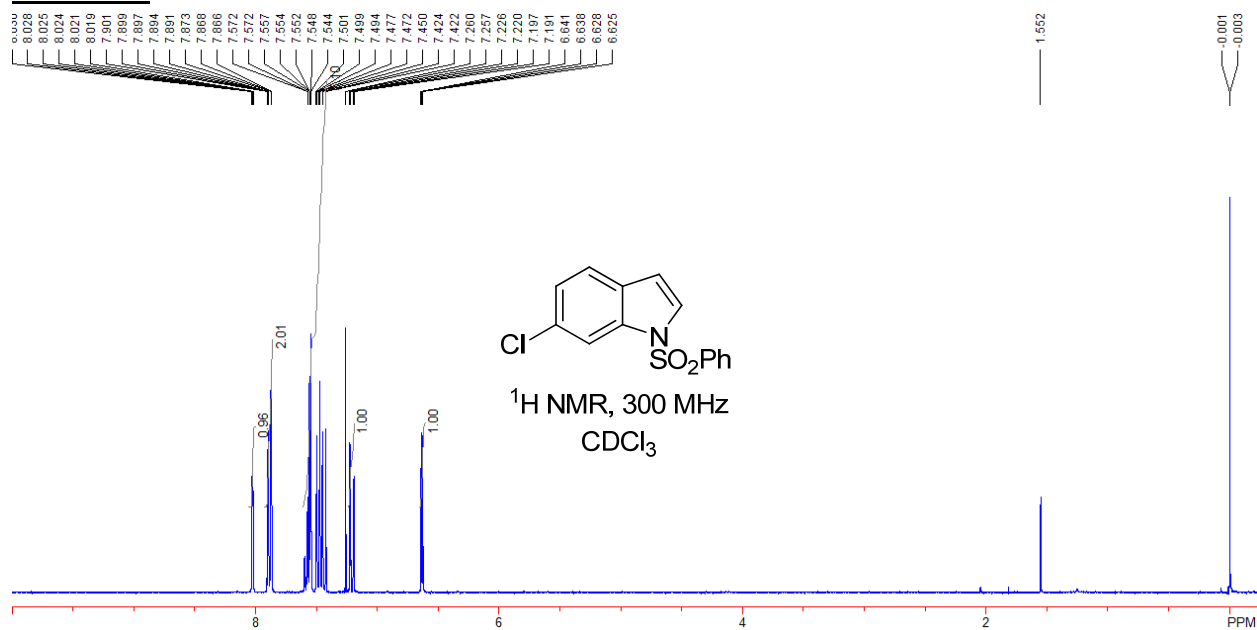
To a pressure tube fitted with a plunger valve was added Pd (0.0075 mmol), ligand (0.0075 mmol), indole (38.6 mg, 0.15 mmol), benzene (852  $\mu$ L, 9.9 mmol) and acetic acid- $d_4$  (52  $\mu$ L, 0.90 mmol). The tube was evacuated and backfilled with  $O_2$  (3x), sealed and heated to 120  $^\circ$ C for 3 h with vigorous stirring. The reaction mixture was then cooled to room temperature, diluted with EtOAc and filtered through a plug of silica. GC/MS analysis was used to determine the amount of deuterium incorporation into the substrates. A similar control experiment was carried out as described above but omitted the Pd and ligand. No deuterium incorporation was observed into the indole and < 3% of the benzene had deuterium incorporation.

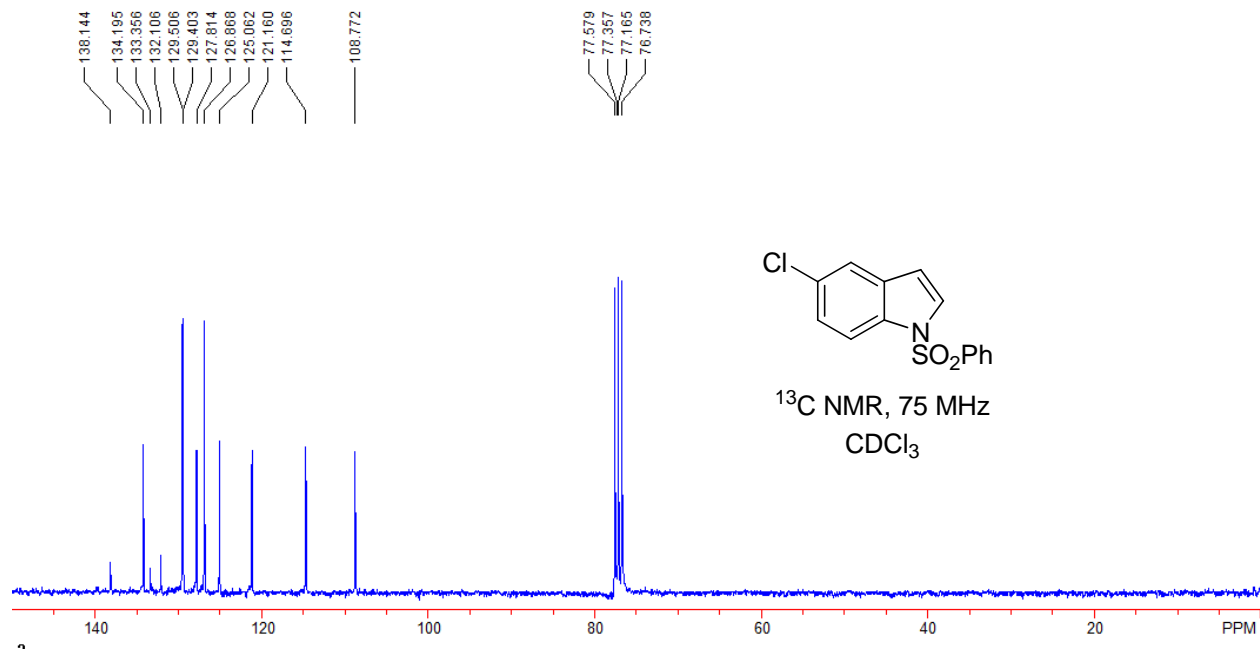
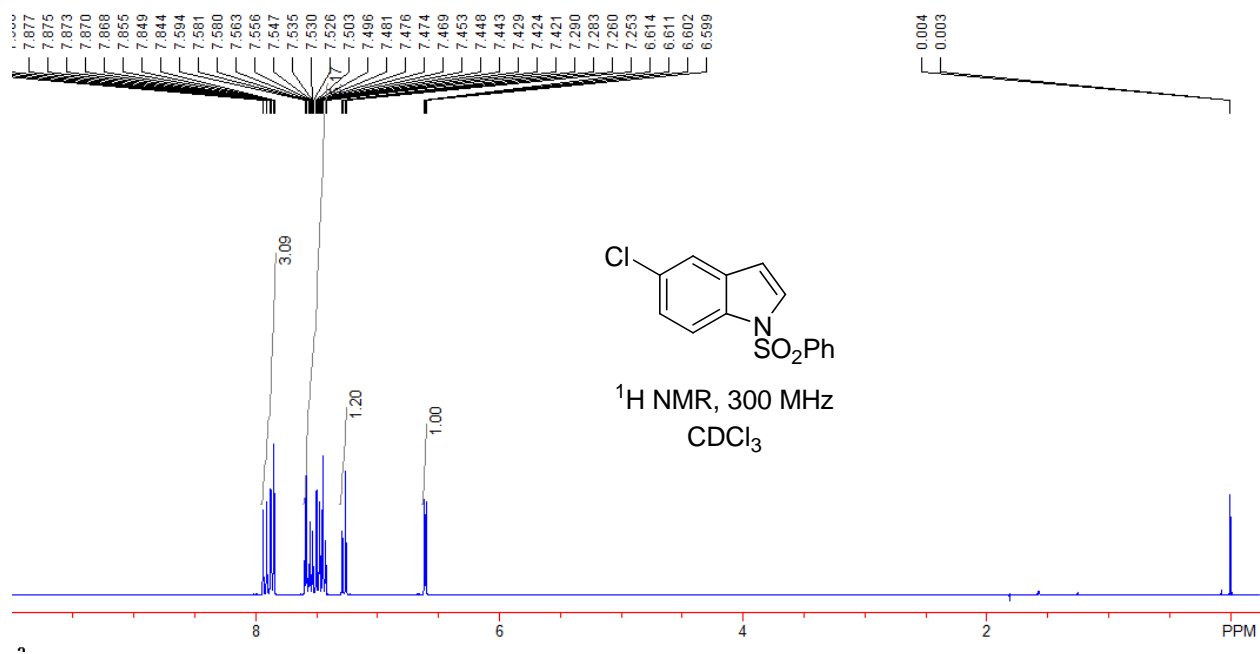
**Table S7.** Deuterium Incorporation into Indole and Benzene

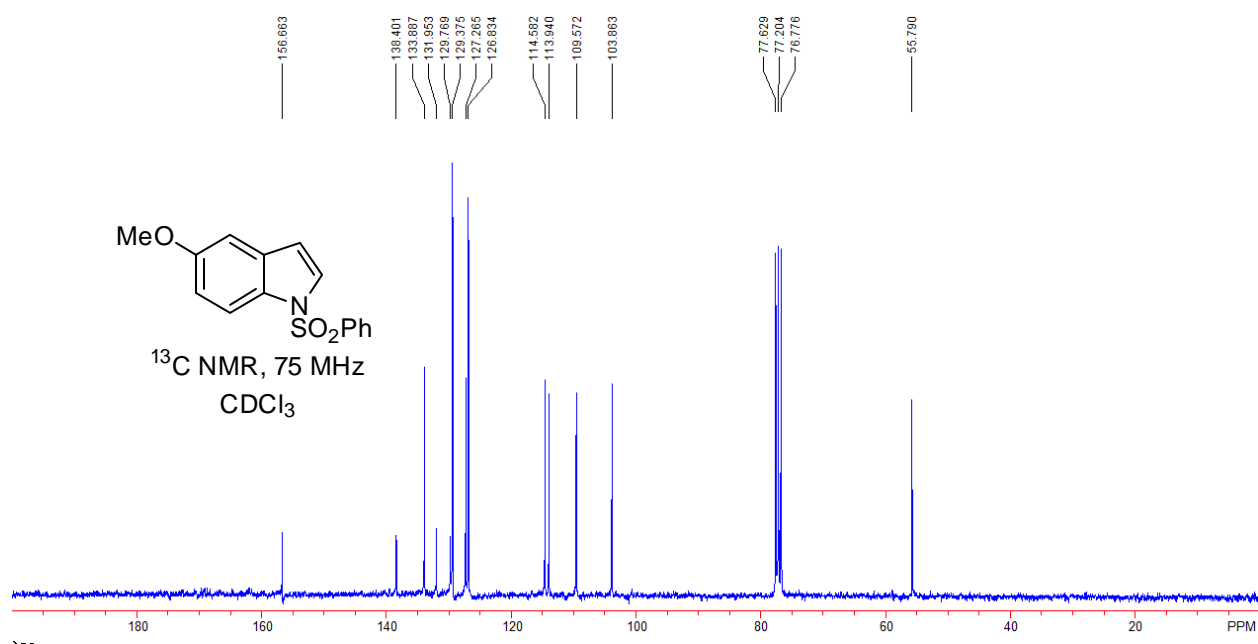


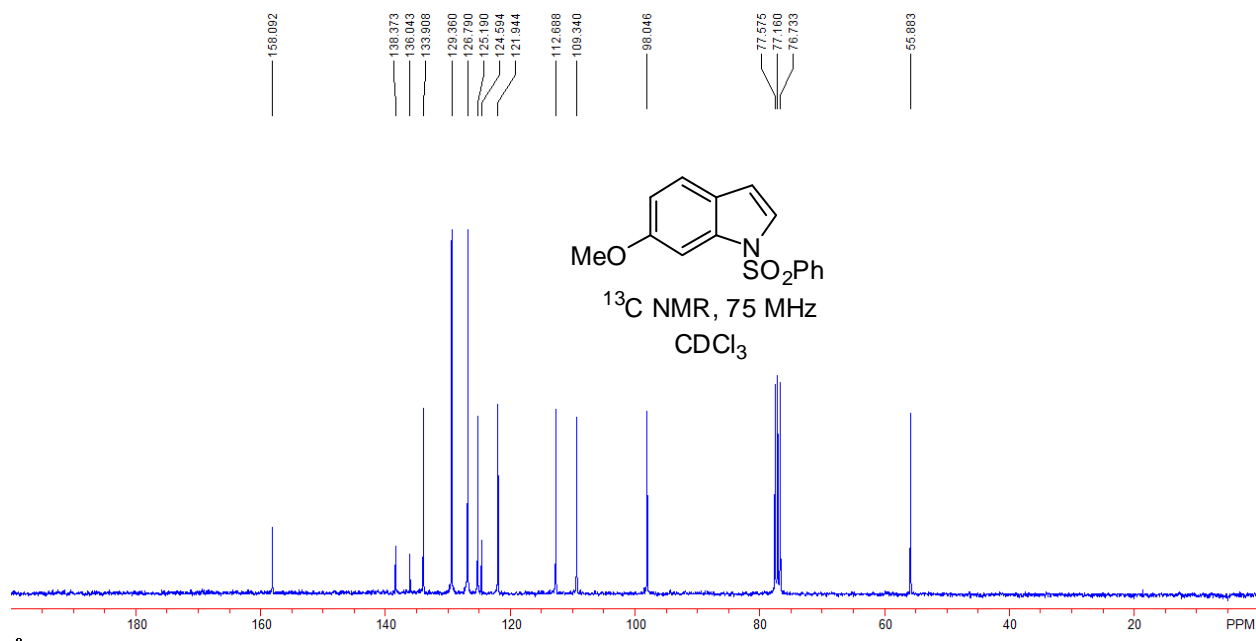
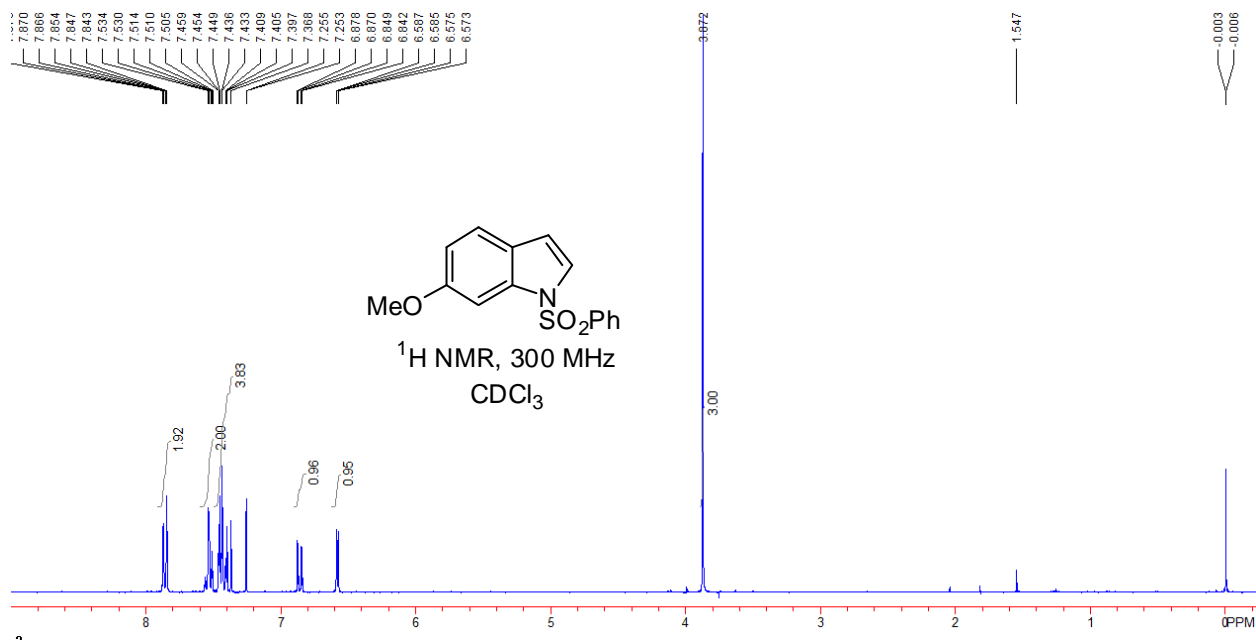
Catalyst	Substrate	% D-incorp
Pd(TFA)2/2	Indole	56%
	Benzene	22%
Pd(OPiv)2/1	Indole	48%
	Benzene	27%

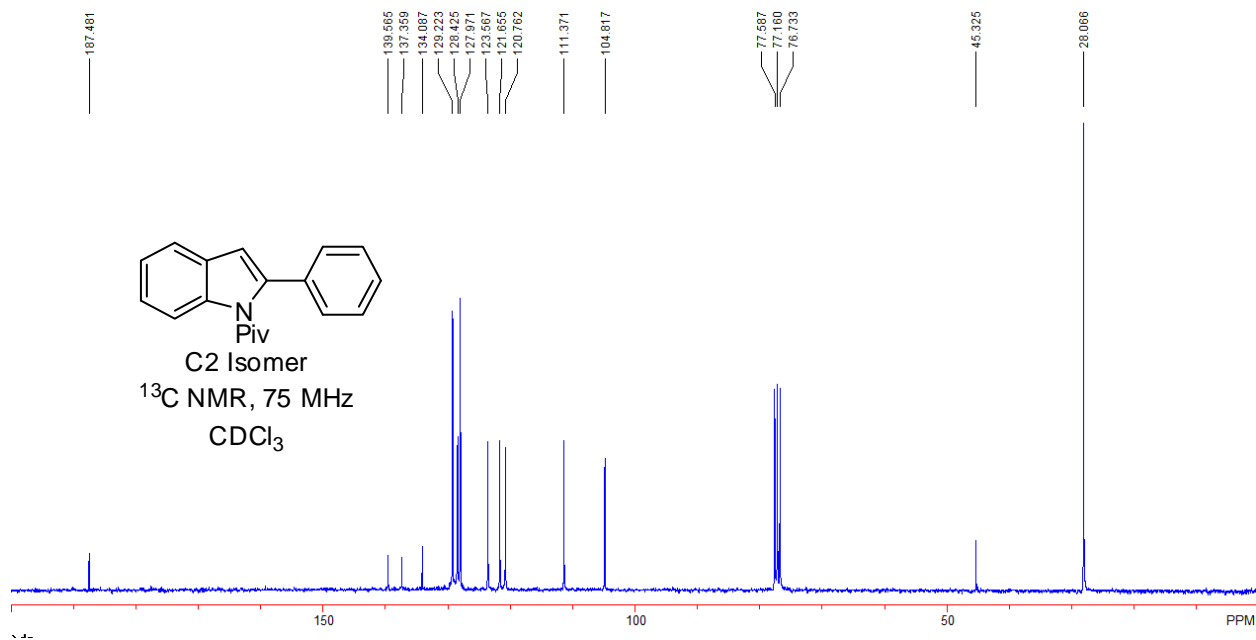
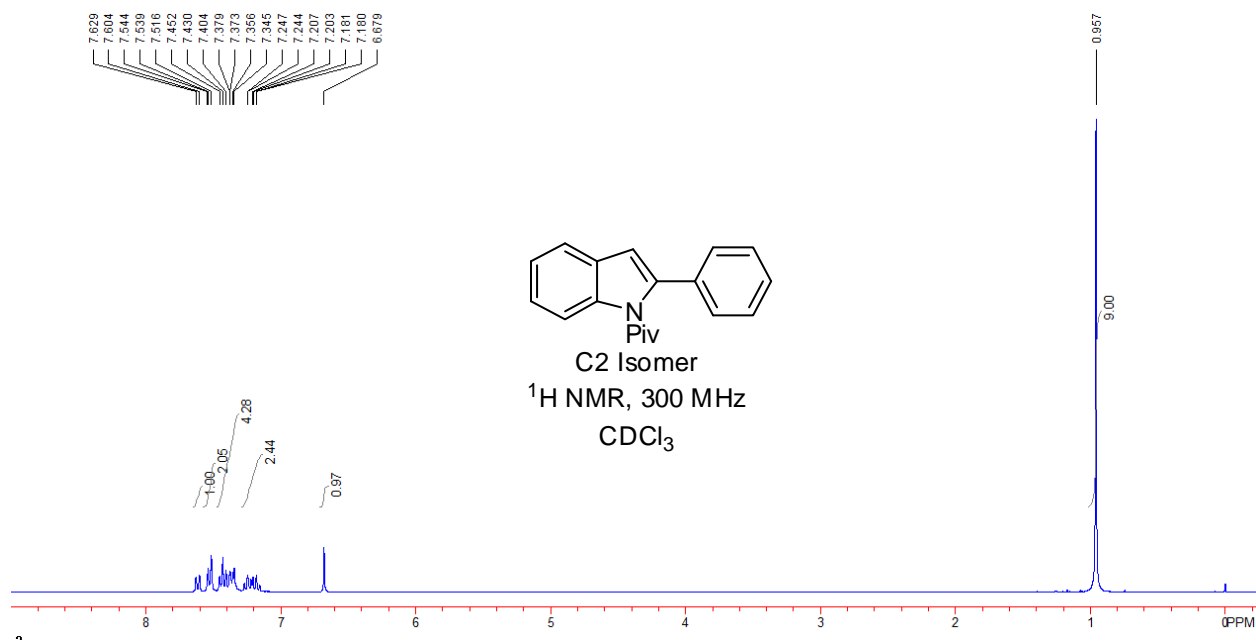
### NMR Data

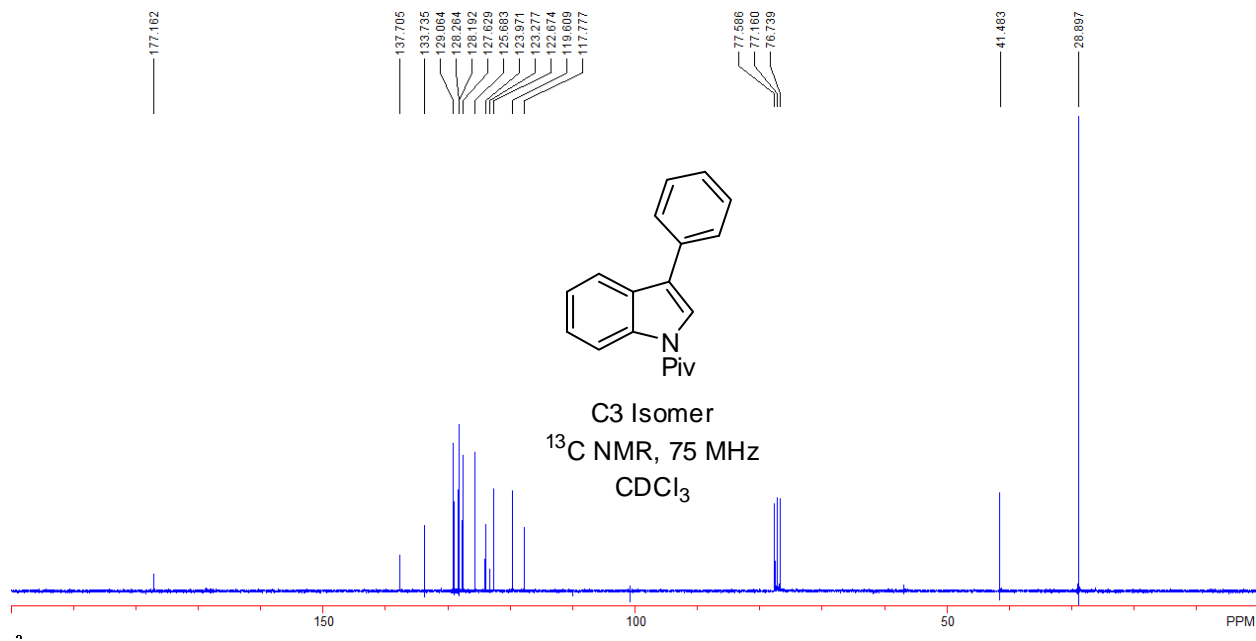
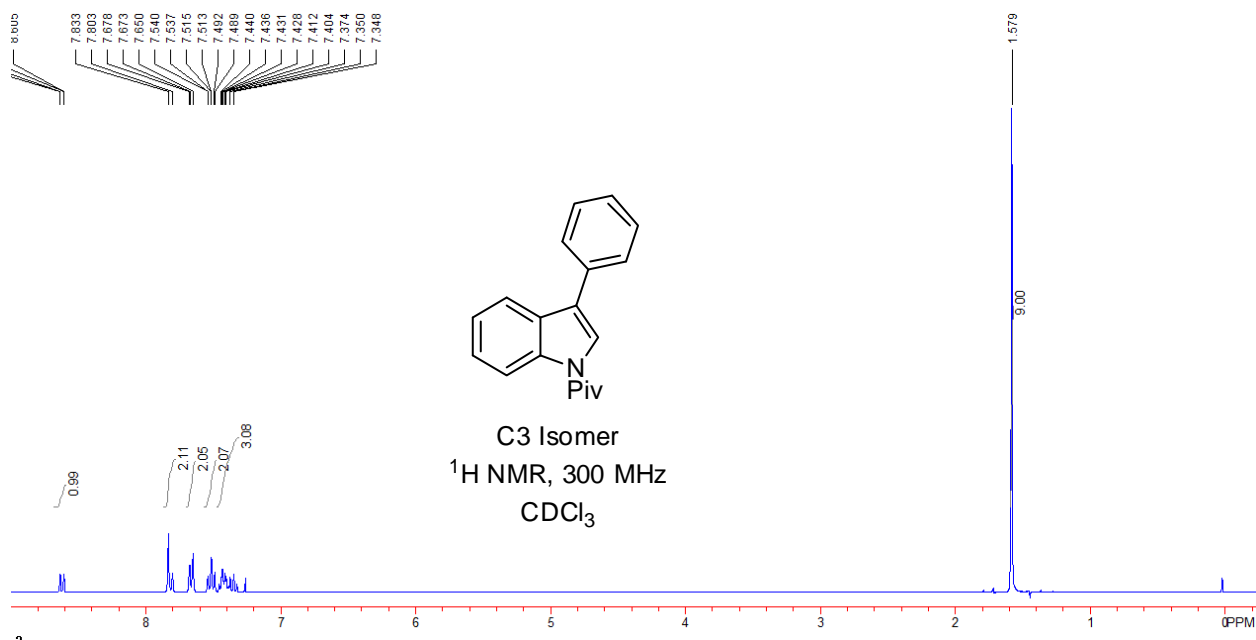




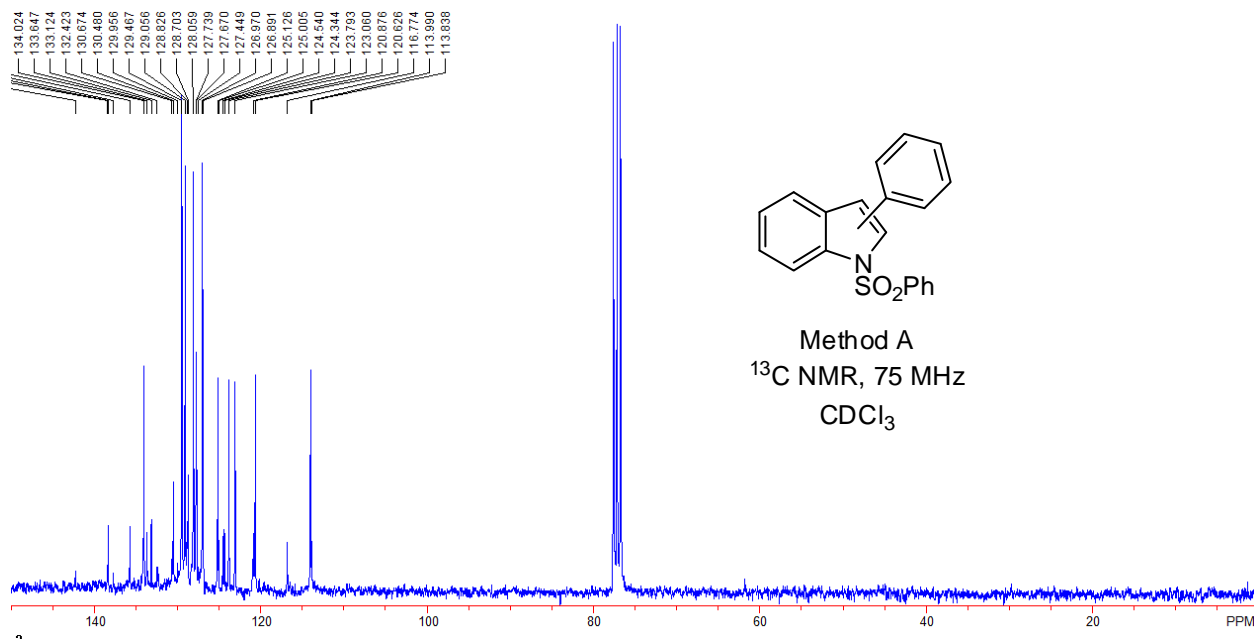
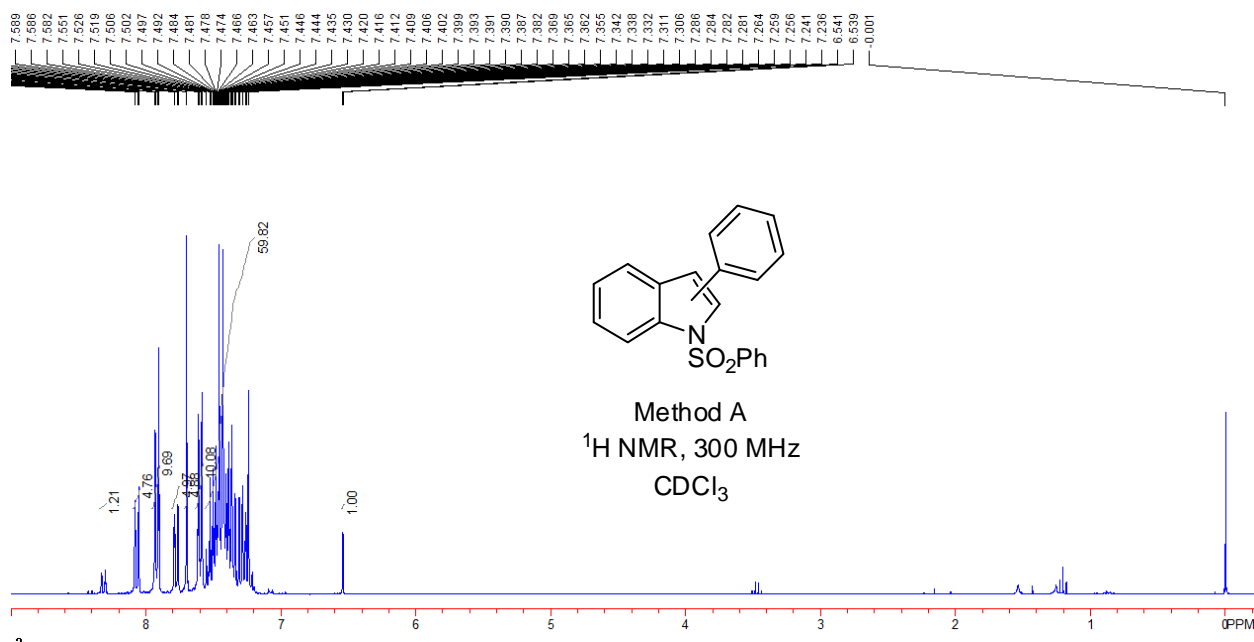


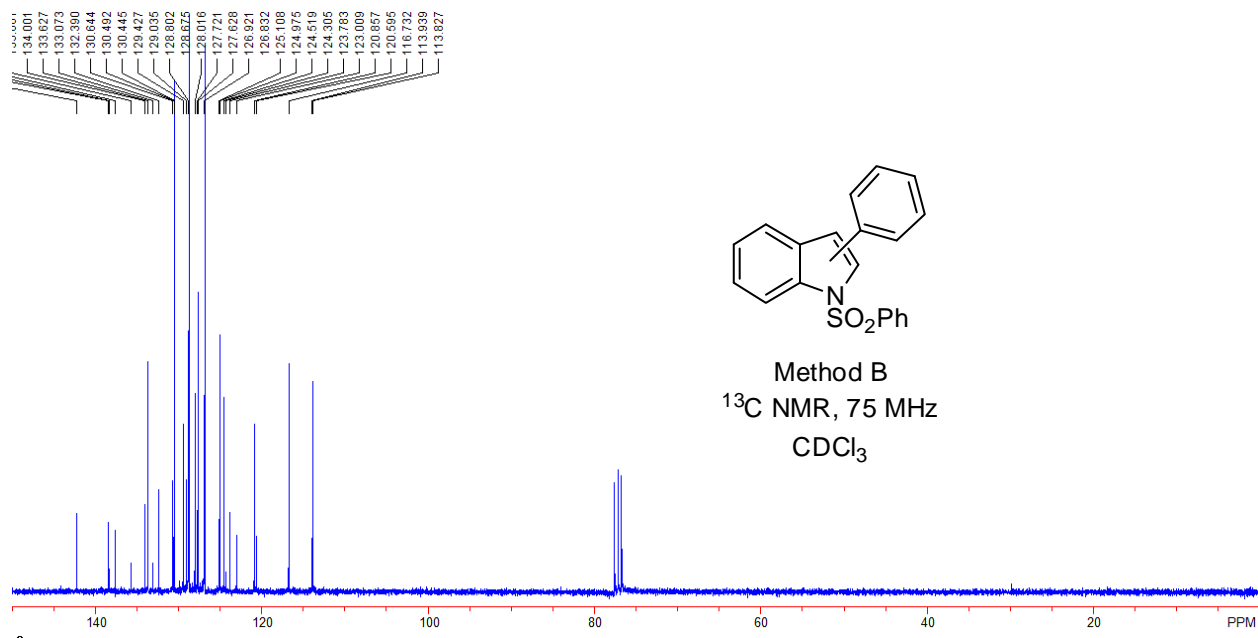
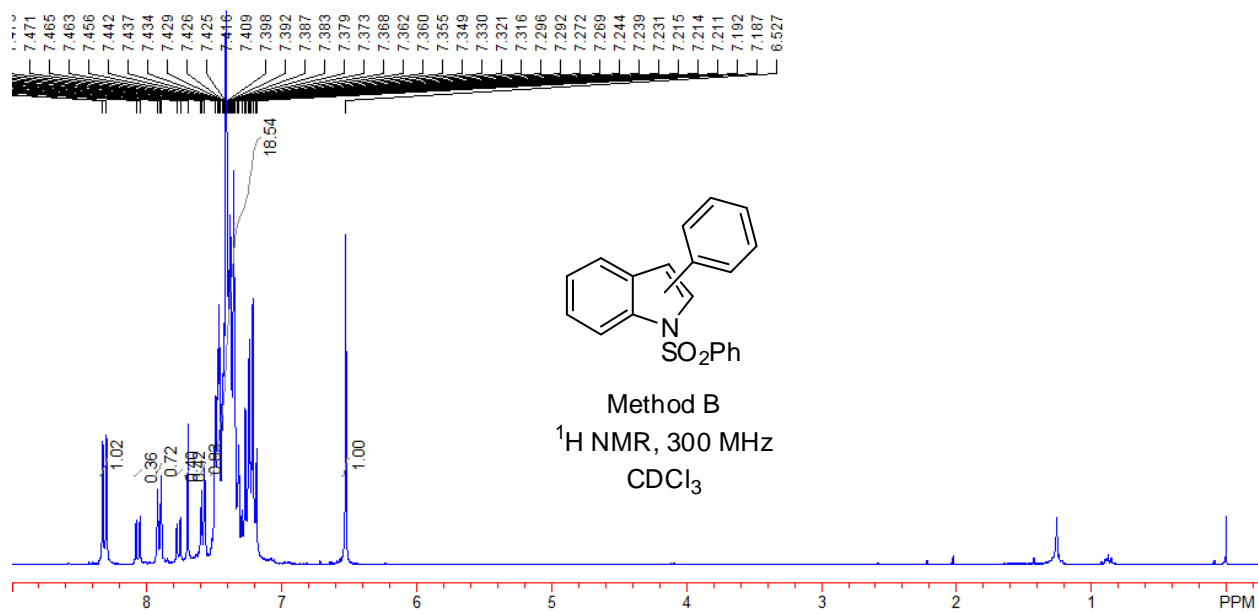


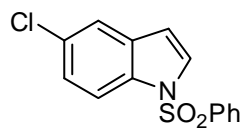
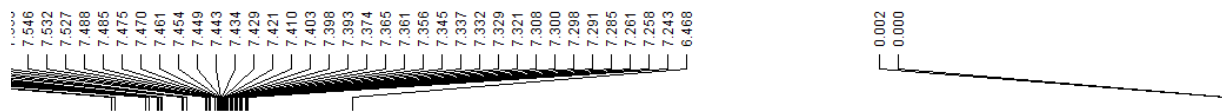




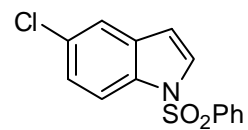
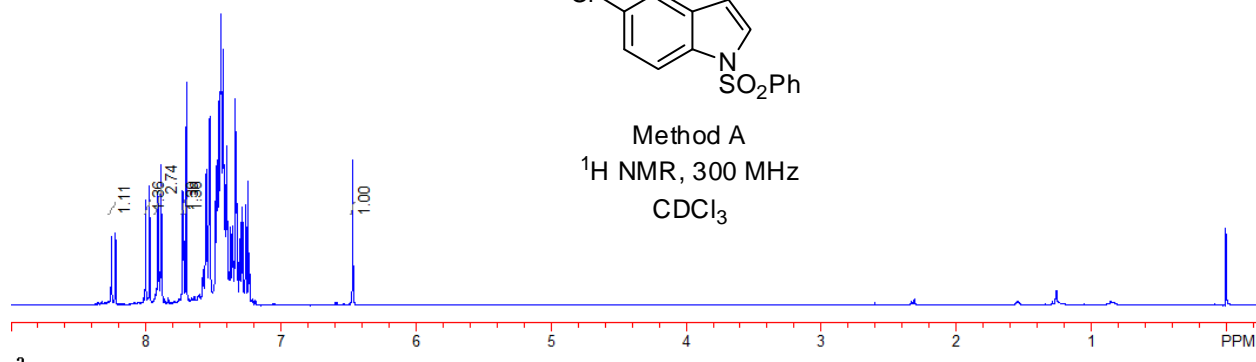




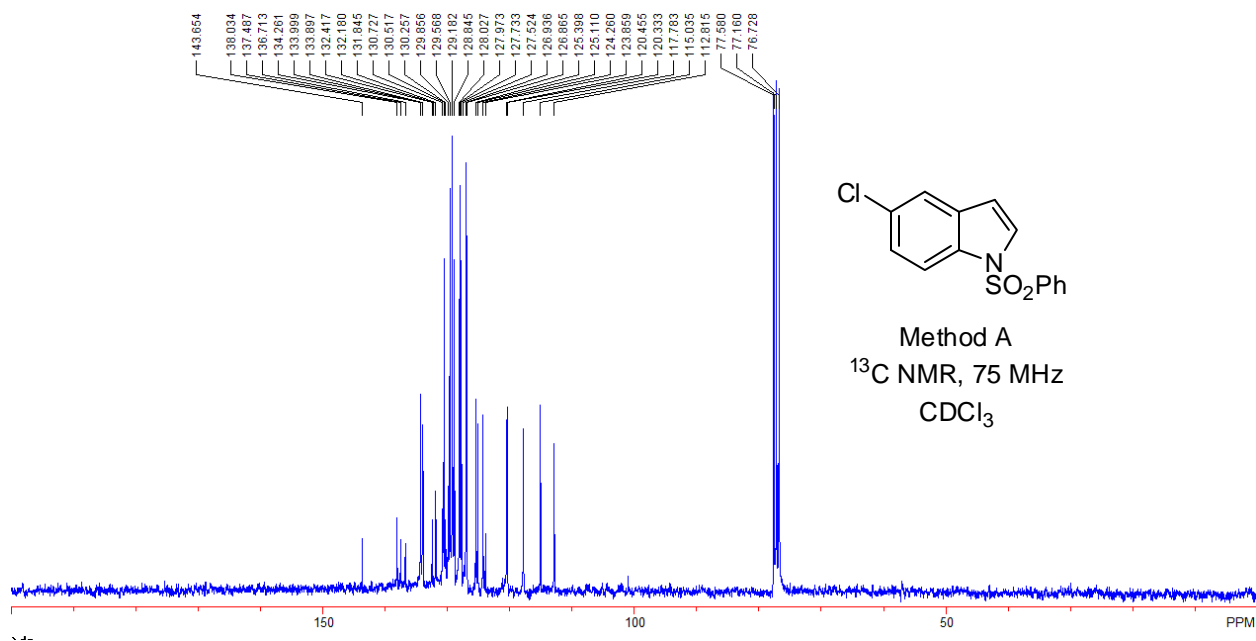


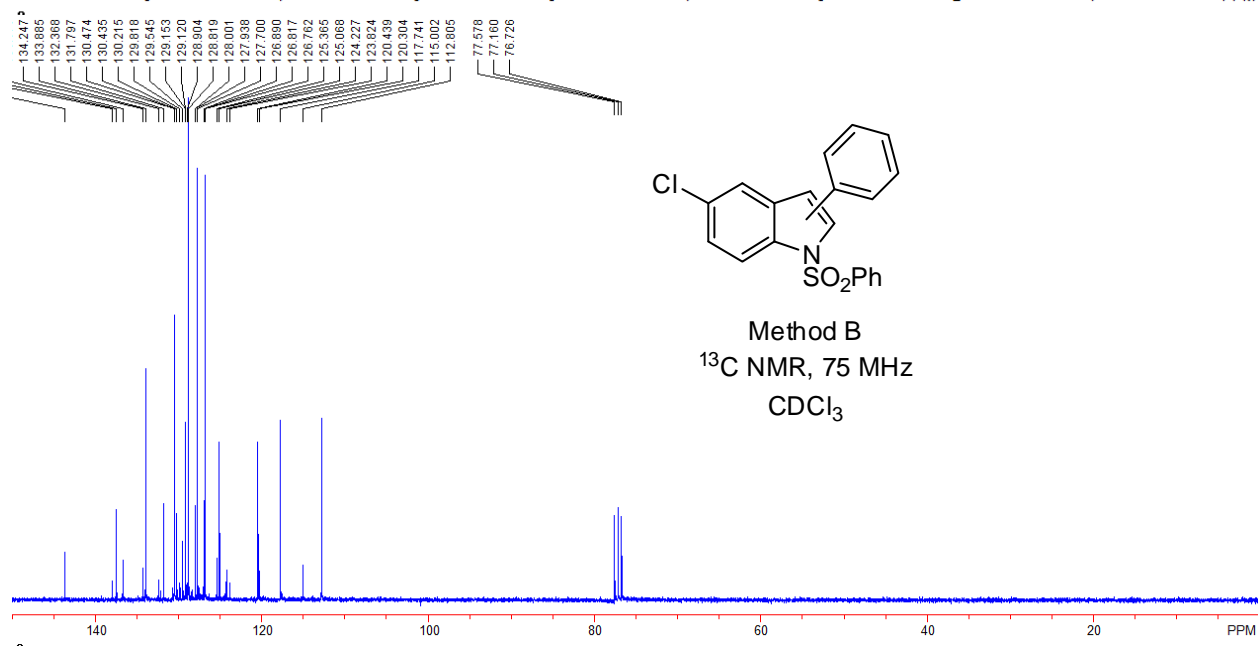
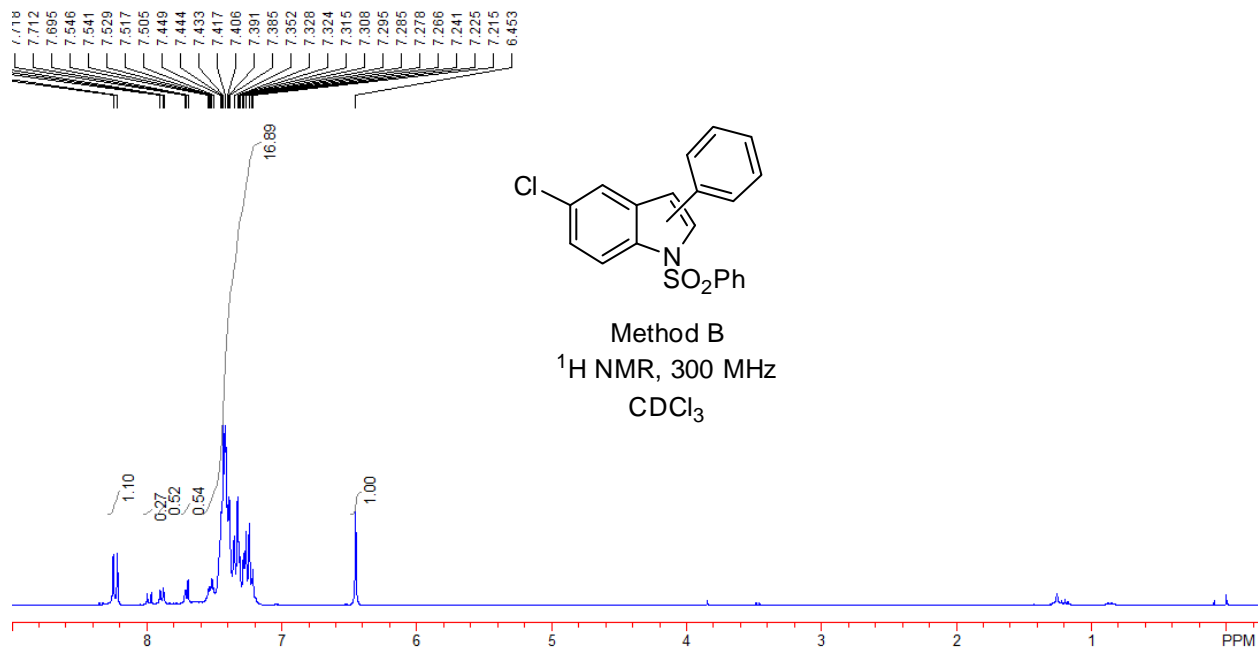


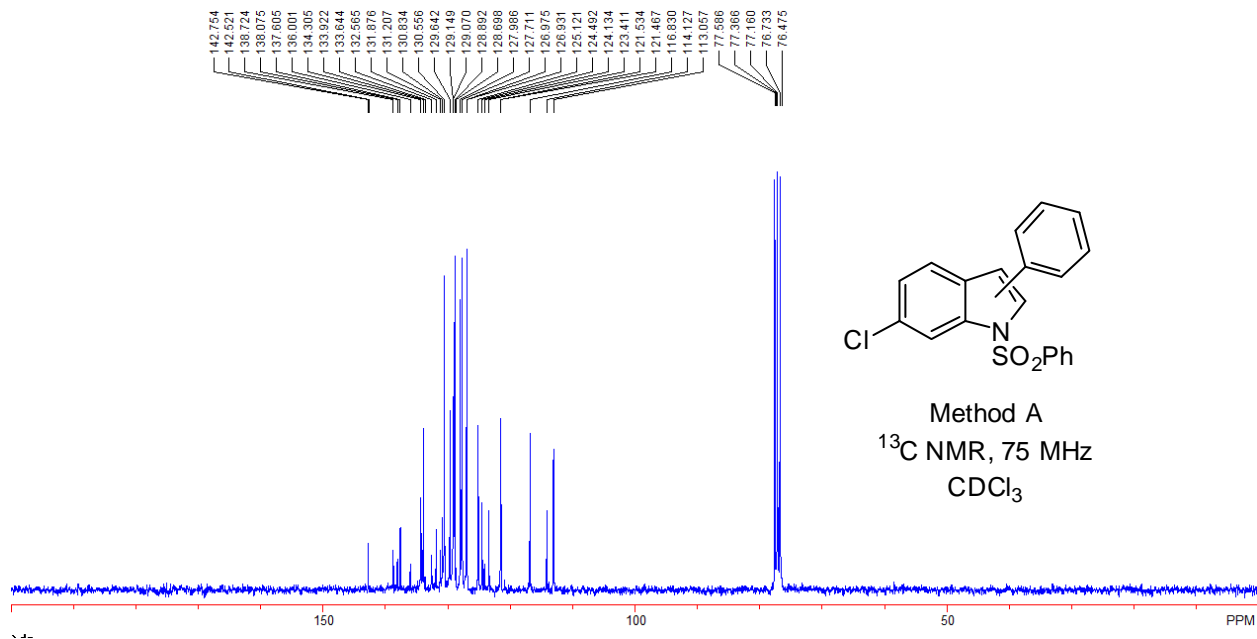
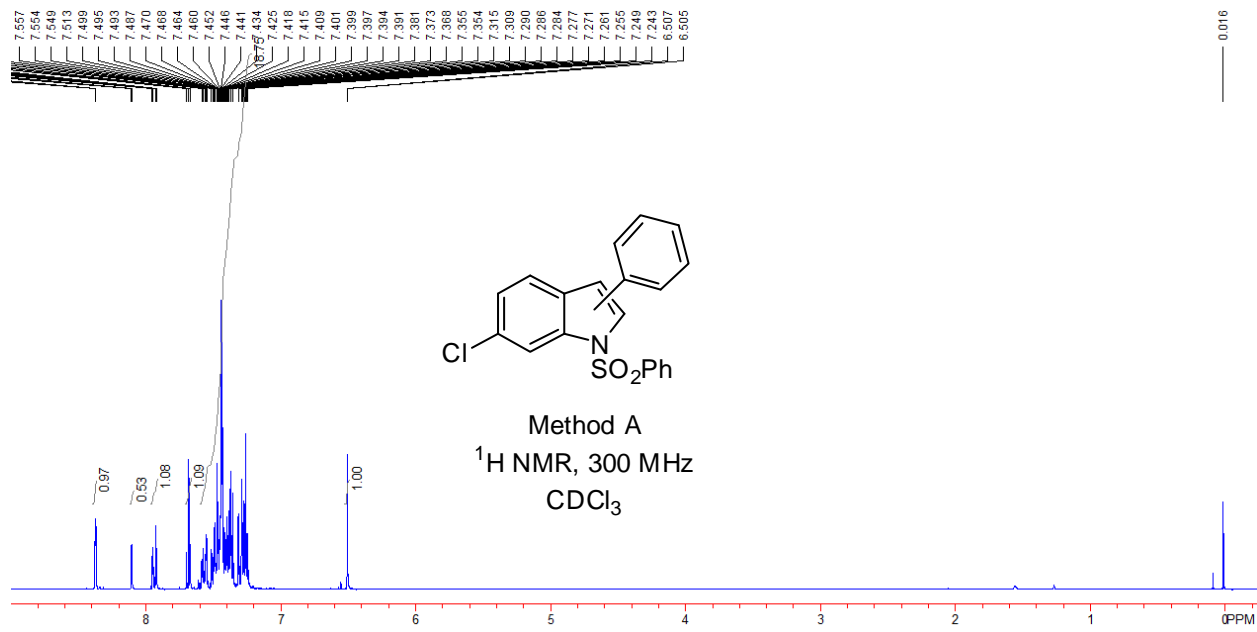
Method A  
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CDCl<sub>3</sub>

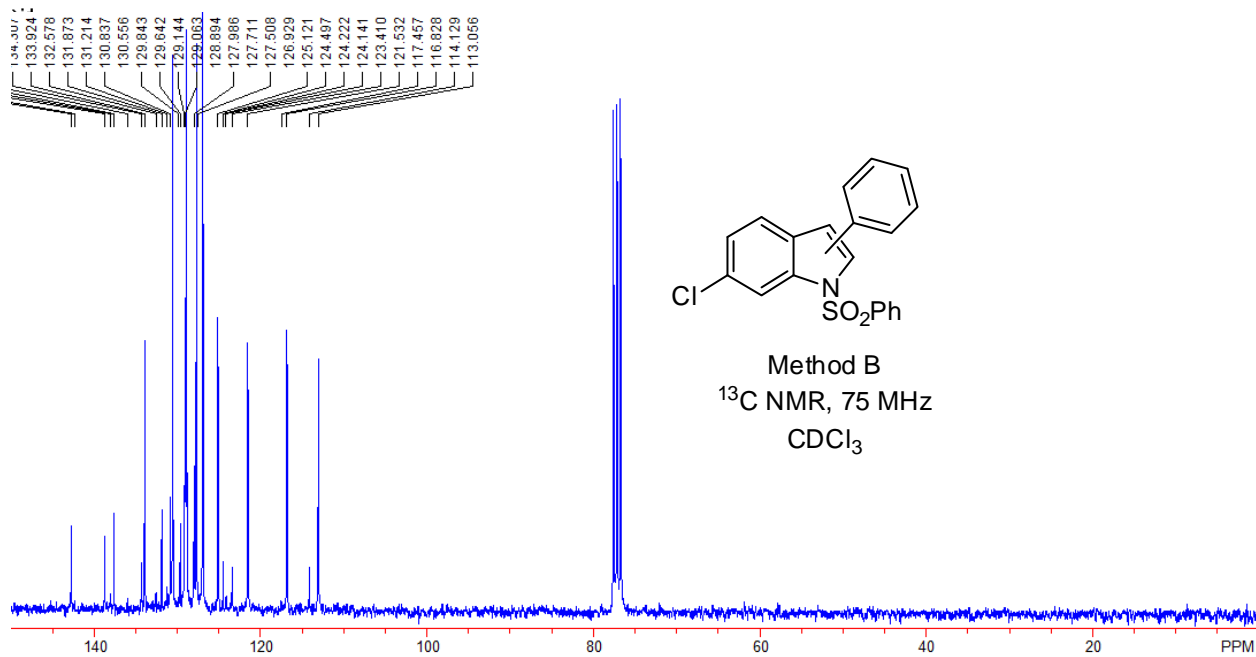
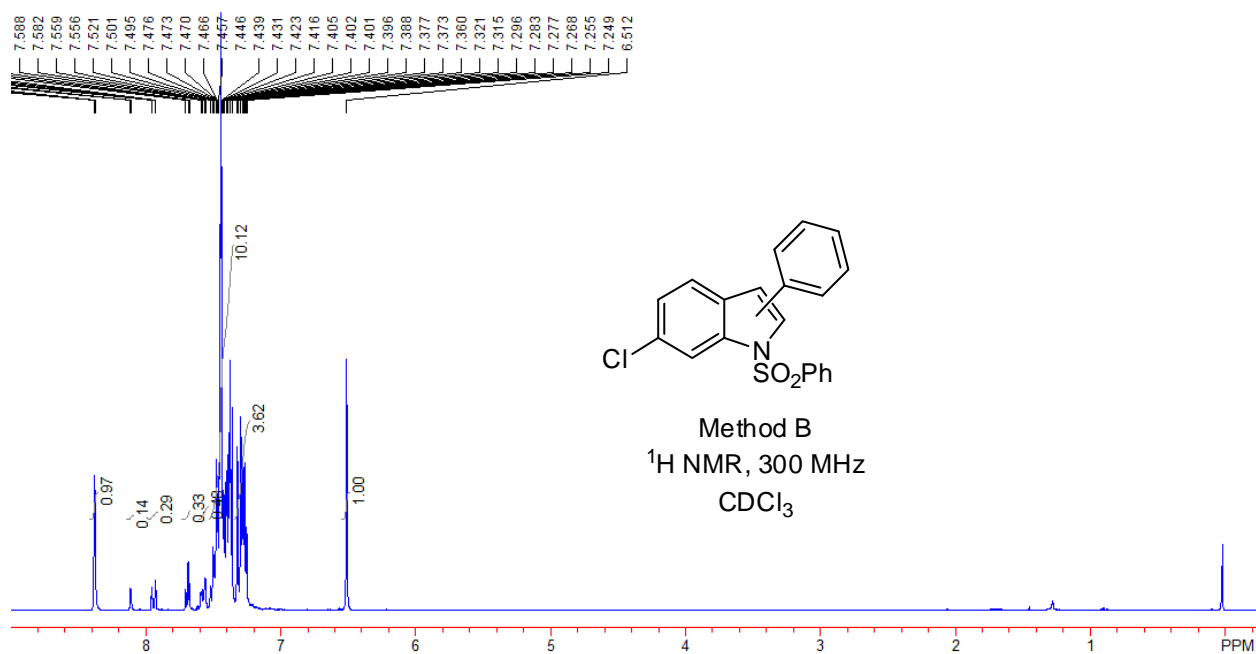


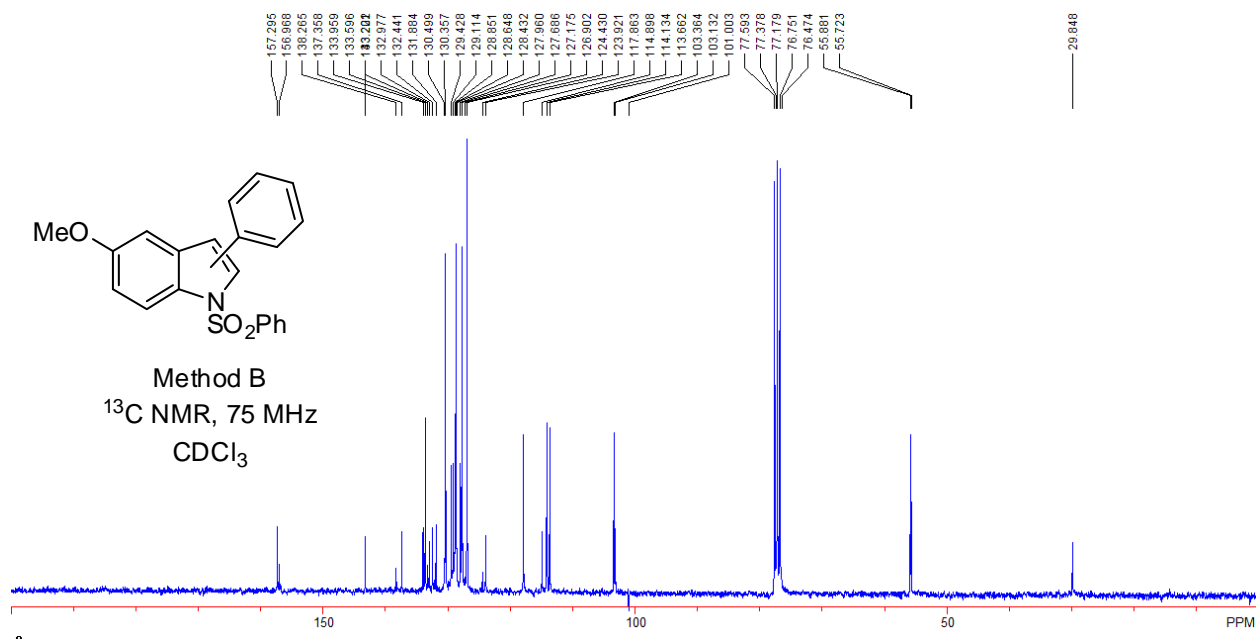
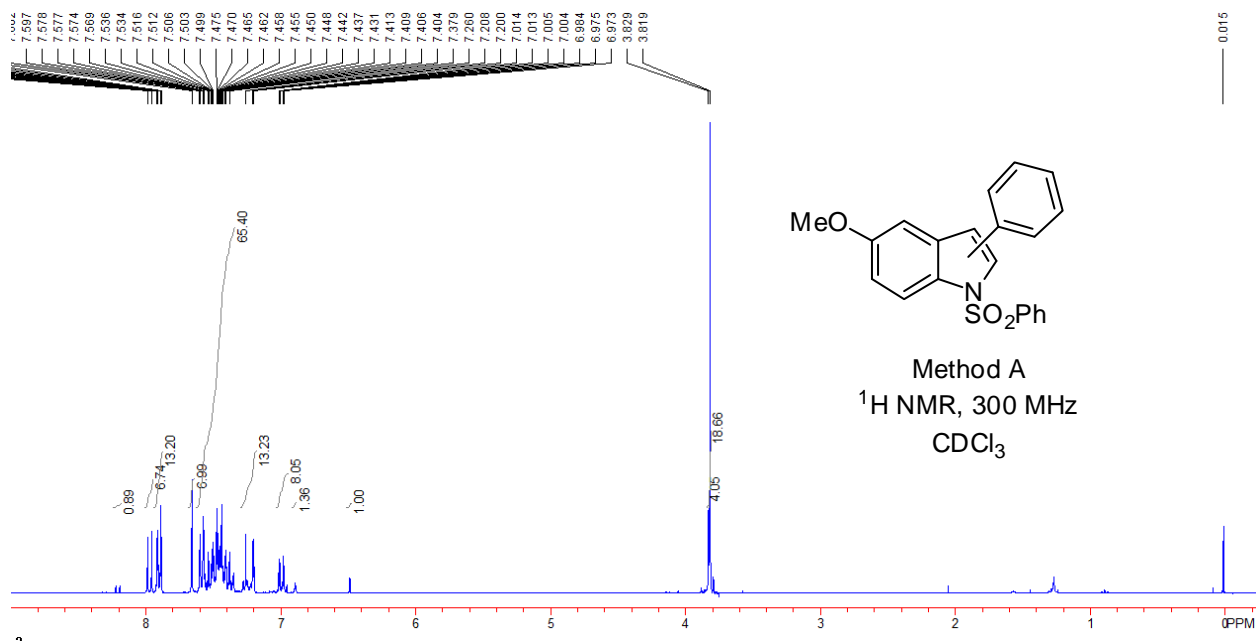
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<sup>13</sup>C NMR, 75 MHz  
CDCl<sub>3</sub>

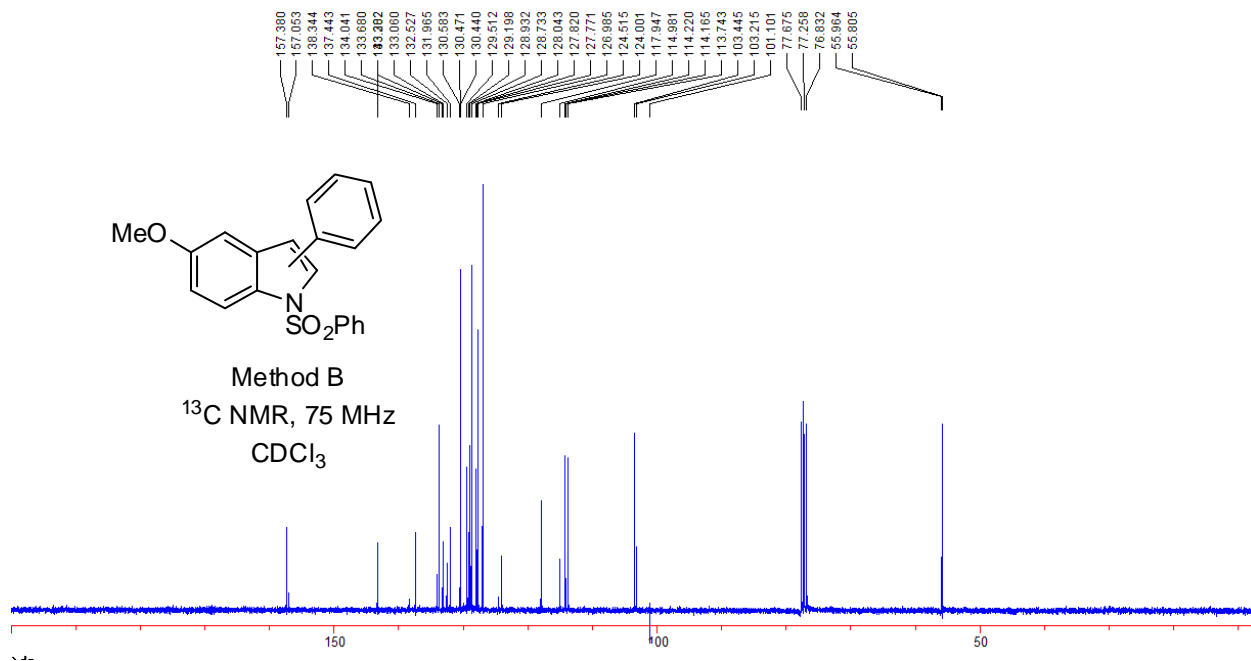
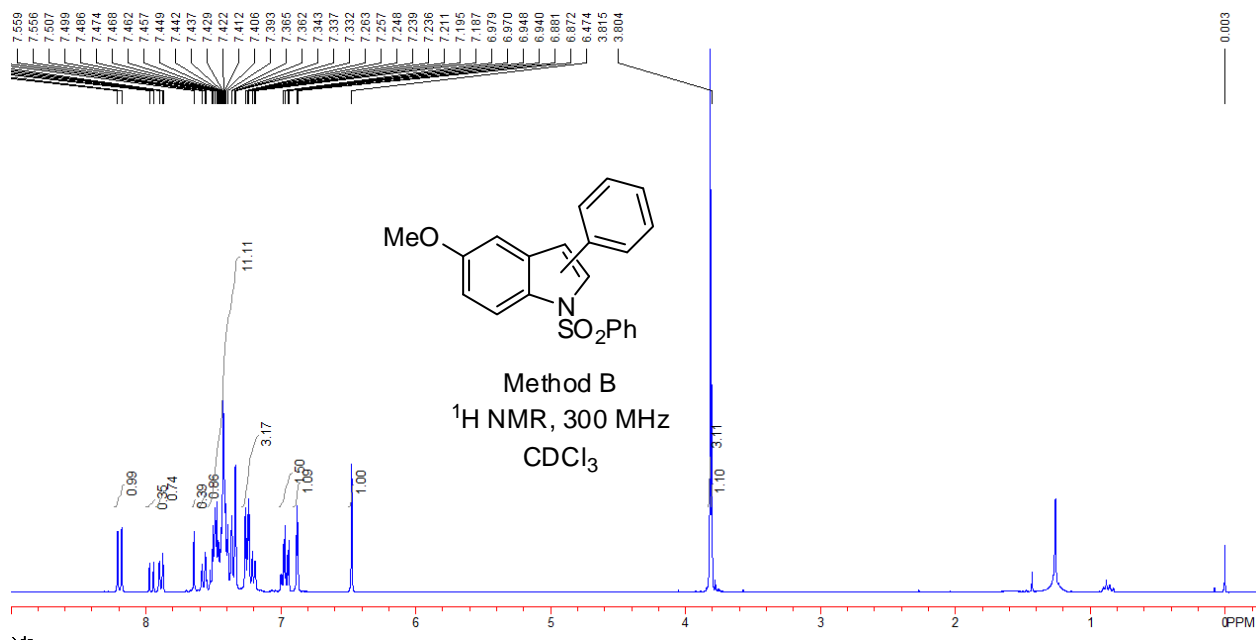




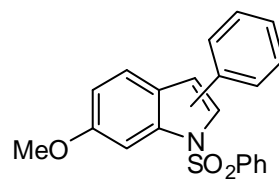
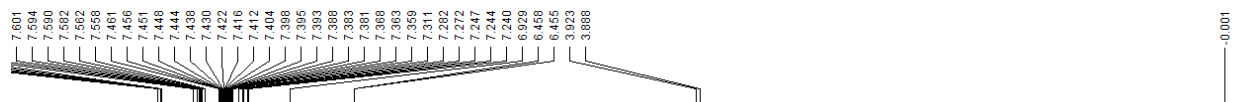




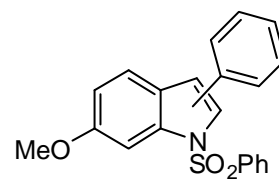
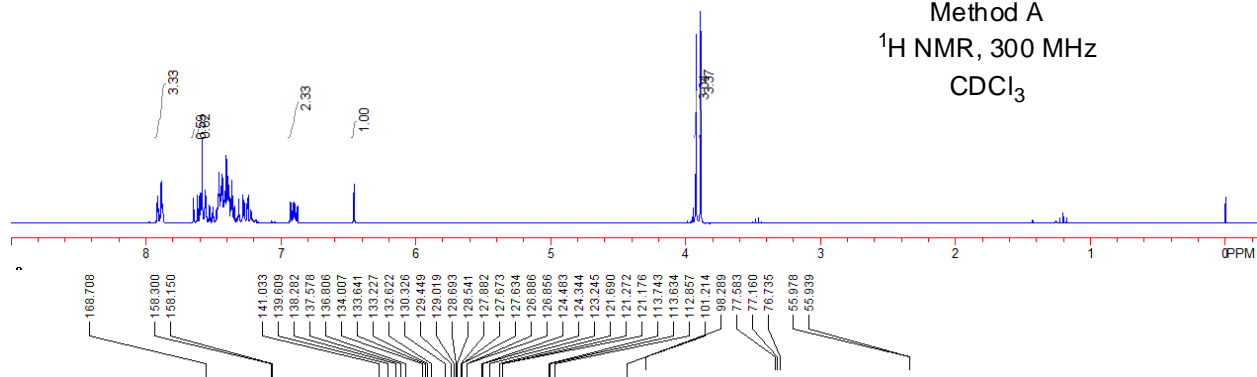








Method A  
<sup>1</sup>H NMR, 300 MHz  
CDCl<sub>3</sub>



Method A  
<sup>13</sup>C NMR, 75 MHz  
CDCl<sub>3</sub>

