Ruthenium-catalyzed monodeuterium-methylenation of two indole units with vinylene carbonate as a novel methylene precursor

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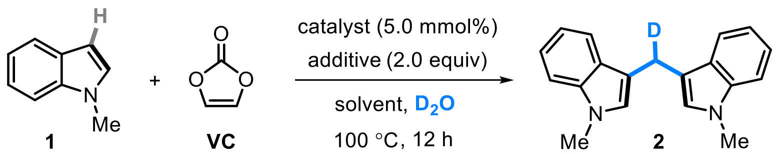
A. General information

All reagents were used from commercial received unless otherwise noted. Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (TLC Silica Gel 60 F_{254}); visualization of the developed chromatogram was performed by fluorescence. Flash Chromatography was performed with silica gel (300-400 mesh). Proton-1 nuclear magnetic resonance (^{1}H NMR) data were acquired at 400 MHz on a Bruker Ascend 400 (400 MHz) spectrometer, and chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, coupling constants *J* are quoted in Hz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) data were acquired at 100 MHz on a Bruker Ascend 400 spectrometer. High resolution mass spectra were acquired on a Bruker Daltonics MicroTof-Q II mass spectrometer.

B. Optimization of reaction

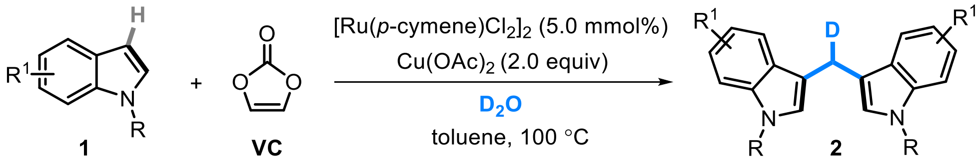
Table 1. Optimization of reaction conditions[a]



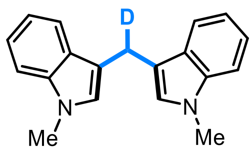
entry	catalyst	solvent	additive	yield[b]
1	$Pd(OAc)_2$	DCE	$Cu(OAc)_2$	n.d.
2	$[Cp^*RhCl_2]_2$	DCE	$Cu(OAc)_2$	n.d.
3	$[Cp^*IrCl_2]_2$	DCE	$Cu(OAc)_2$	n.d.
4	[Ru(*p*-cymene)$Cl_2]_2$	DCE	$Cu(OAc)_2$	35%
5	(indenyl)Ru$(PPh_3)_2$Cl	DCE	$Cu(OAc)_2$	20%
6	Cp*Ru$(PPh_3)_2$Cl	DCE	$Cu(OAc)_2$	10%
7	-	DCE	$Cu(OAc)_2$	n.d.
8	[Ru(*p*-cymene)$Cl_2]_2$	MeCN	$Cu(OAc)_2$	27%
9	[Ru(*p*-cymene)$Cl_2]_2$	THF	$Cu(OAc)_2$	56%
10	[Ru(*p*-cymene)$Cl_2]_2$	DMSO	$Cu(OAc)_2$	32%
11	[Ru(*p*-cymene)$Cl_2]_2$	toluene	$Cu(OAc)_2$	87%
12	[Ru(*p*-cymene)$Cl_2]_2$	toluene	AgOAc	50%
13	[Ru(*p*-cymene)$Cl_2]_2$	toluene	$Zn(OAc)_2$	n.d.
14	[Ru(*p*-cymene)$Cl_2]_2$	toluene	$CuBr_2$	n.d.
15[c]	[Ru(*p*-cymene)$Cl_2]_2$	toluene	$CuBr_2$	62%
16[d]	[Ru(*p*-cymene)$Cl_2]_2$	toluene	$CuBr_2$	58%

[a]Reaction conditions: **1a** (0.2 mmol), **VC** (0.2 mmol), catalyst (5.0 mmol%), additive (0.4 mmol), and D_2O (0.1 mL) in solvent (1.0 mL) were stirred at 100 °C for 12 h under Ar atmosphere. [b]Isolated yields (%). [c]90 °C. [d]110 °C

C. General procedure for the synthesis of products

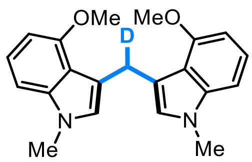


A 15.0 mL vial equipped with a stir bar was charged with substrates **1** (0.2 mmol), **VC** (17.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired products **2**.



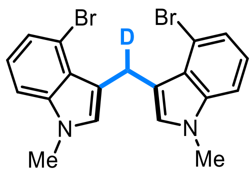
3,3'-(methylene-d)bis(1-methyl-1H-indole) (2a)

White solid (24.0 mg, 87% yield). PE:EA = 30:1, R_f = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 6.9 Hz, 2H), 7.16 (t, J = 7.8 Hz, 2H), 6.85 (s, 2H), 4.28 (d, J = 7.4 Hz, 1H), 3.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 127.9, 126.9, 121.4, 119.3, 118.5, 114.3, 114.2, 109.1, 32.5, 20.9. IR (KBr): 3078, 2932, 2817, 1474, 1336, 1236, 1013, 722 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{18}DN_2$ $[M+H]^+$ 276.1606, found 276.1611.



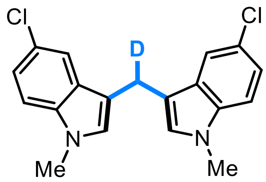
3,3'-(methylene-d)bis(4-methoxy-1-methyl-1H-indole) (2b)

White solid (20.1 mg, 60% yield). PE:EA = 20:1, R_f = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1 (s, 2H), 6.9 (d, J = 9.91 Hz, 2H), 6.6 (s, 2H), 6.5 (d, J = 9.60 Hz, 2H), 4.5 (d, J = 9.14 Hz, 1H), 3.9 (s, 6H), 3.6 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.6, 125.9, 121.8, 121.7, 121.6, 117.7, 116.5, 102.4, 98.9, 55.2, 32.7, 20.3. IR (KBr): 2925, 2840, 2280, 1551, 1451, 1412, 1328, 1221, 1105, 937 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{21}H_{22}DN_2O_2$ $[M+H]^+$ 336.1817, found 336.1825.



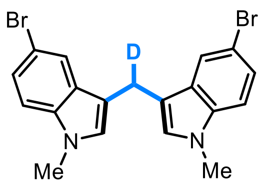
3,3'-(methylene-d)bis(4-bromo-1-methyl-1H-indole) (2c)

White solid (33.4 mg, 77% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 – 7.2 (m, 4H), 7.1 – 7.0 (m, 2H), 6.7 (d, J = 3.9 Hz, 2H), 4.8 (d, J = 8.2 Hz, 1H), 3.7 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 129.3, 125.9, 123.2, 122.1, 116.2, 114.8, 108.4, 32.8, 23.4. IR (KBr): 2939, 2855, 2380, 1551, 1467, 1298, 1052, 999, 837, 761 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{16}DBr_2N_2$ [M+H]$^+$ 431.9816, found 431.9819.



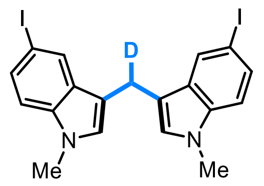
3,3'-(methylene-d)bis(5-chloro-1-methyl-1H-indole) (2d)

White solid (25.8 mg, 75% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 2H), 7.19 (q, J = 7.7, 6.7 Hz, 4H), 6.81 (s, 2H), 4.10 (d, J = 7.3 Hz, 1H), 3.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 128.7, 128.2, 124.5, 121.7, 118.6, 113.5, 113.5, 110.2, 32.8, 21.7. IR (KBr): 2939, 2863, 2403, 2249, 1789, 1474, 1412, 1367, 1183, 1075, 876, 792 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{16}DCl_2N_2$ [M+H]$^+$ 344.0826, found 344.0829.



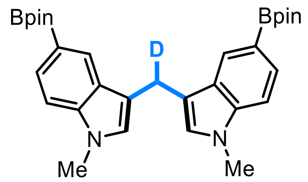
3,3'-(methylene-d)bis(5-bromo-1-methyl-1H-indole) (2e)

White solid (30.3 mg, 70% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.30 (d, J = 10.5 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 6.78 (s, 2H), 4.09 (d, J = 7.3 Hz, 1H), 3.70 (s, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 136.1, 129.6, 128.3, 124.5, 121.9, 113.7, 112.4, 110.9, 33.0, 21.7. IR (KBr): 2917, 2380, 2288, 1897, 1735, 1612, 1474, 1359, 798 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{16}DBr_2N_2$ [M+H]$^+$ 431.9816, found 431.9825.



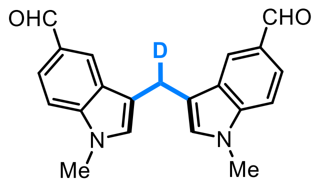
3,3'-(methylene-d)bis(5-iodo-1-methyl-1H-indole) (2f)

White solid (39.5 mg, 75% yield). PE:EA = 20:1, R_f = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.72 (s, 2H), 4.08 (d, *J* = 7.2 Hz, 1H), 3.69 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 130.3, 129.8, 128.0, 127.7, 113.2, 111.3, 82.2, 32.7, 20.9. IR (KBr): 2886, 2364, 2204, 2088, 1750, 1651, 1551, 1451, 1412, 1259, 703 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{16}DI_2N_2$ $[M+H]^+$ 527.9538, found 527.9534.



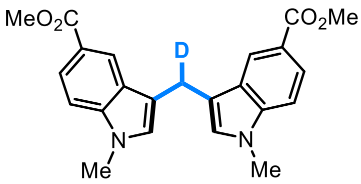
3,3'-(methylene-d)bis(1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole) (2g)

White solid (39.0 mg, 74% yield). PE:EA = 20:1, R_f = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 6.72 (s, 2H), 4.27 (d, *J* = 8.3 Hz,1H), 3.70 (s, 6H), 1.37 (s, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 127.7, 127.2, 127.0, 115.2, 108.5, 83.3, 32.6, 20.5. IR (KBr): 2978, 2902, 2395, 2257, 1805, 1498, 1382, 1221, 1083, 991, 730 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{31}H_{39}DB_2N_2O_4$ $[M+H]^+$ 527.3237, found 527.3229.



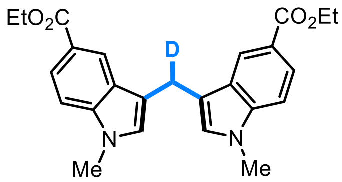
3,3'-(methylene-d)bis(1-methyl-1H-indole-5-carbaldehyde) (2h)

Yellow solid (20.9 mg, 63% yield). PE:EA = 4:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 2H), 8.14 (s, 2H), 7.79 (d, *J* = 7.0 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 6.91 (s, 2H), 4.30 (d, *J* = 7.5 Hz,1H), 3.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 140.5, 128.8, 127.6, 124.2, 122.4, 116.1, 109.8, 32.9, 20.8. IR (KBr): 2947, 2794, 2718, 2265, 1697, 1566, 1359, 1037, 768 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{21}H_{18}DN_2O_2$ $[M+H]^+$ 332.1504, found 332.1499.



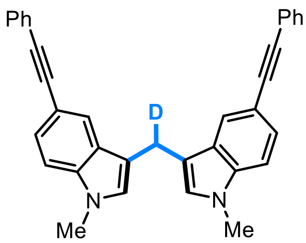
dimethyl 3,3'-(methylene-d)bis(1-methyl-1H-indole-5-carboxylate) (2i)

White solid (30.5 mg, 78% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2H), 7.95 (d, J = 8.7 Hz, 2H), 7.29 (d, 2H), 6.83 (s, 2H), 4.26 (d, J = 7.2 Hz, 1H), 3.92 (s, 6H), 3.69 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 139.5, 128.2, 127.3, 122.8, 122.1, 120.6, 115.5, 108.7, 51.7, 32.6, 20.6. IR (KBr): 2925, 2234, 1719, 1428, 1236, 1152, 1068, 899, 737 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{23}H_{22}DN_2O_4$ $[M+H]^+$ 392.1715, found 392.1721.



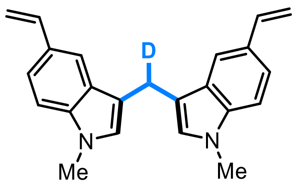
diethyl 3,3'-(methylene-d) bis (1-methyl-1H-indole-5-carboxylate) (2j)

White solid (33.6 mg, 80% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 2H), 7.95 (d, J = 7.0 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 6.84 (s, 2H), 4.39 (q, J = 7.1 Hz, 4H), 4.27 (d, J = 7.3 Hz, 1H), 3.73 (s, 6H), 1.41 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 139.5, 128.2, 127.4, 122.9, 122.1, 121.1, 115.8, 115.7, 108.7, 60.5, 32.8, 20.6, 14.4. IR (KBr): 2925, 2403, 1713, 1627, 1474, 1390, 1283, 1075, 1021, 891, 737 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{25}H_{26}DN_2O_4$ $[M+H]^+$ 420.2028, found 420.2036.



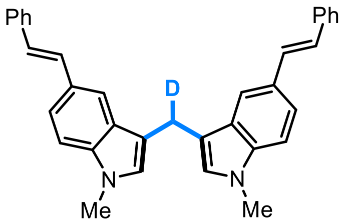
3,3'-(methylene-d)bis(1-methyl-5-(phenylethynyl)-1H-indole) (2k)

Yellow solid (39.5 mg, 83% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.52 (d, J = 6.9 Hz, 4H), 7.39 (d, J = 6.9 Hz, 2H), 7.31 (t, J = 7.2 Hz, 4H), 7.28 (d, J = 7.1 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 6.80 (s, 2H), 4.17 (d, J = 11.0 Hz, 1H), 3.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 131.4, 128.2, 127.9, 127.7, 127.6, 125.2, 124.0, 123.2, 114.4, 113.1, 109.3, 91.4, 87.0, 32.7, 20.8. IR (KBr): 2955, 2825, 2196, 1805, 1635, 1467, 1398, 1221, 1136, 891, 745 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{35}H_{26}DN_2$ $[M+H]^+$ 476.2232, found 476.2238.



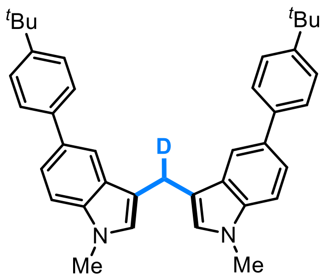
3,3'-(methylene-d)bis(1-methyl-5-vinyl-1H-indole) (2l)

White solid (24.6 mg, 75% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 2.1 Hz, 2H), 6.89 (d, *J* = 10.9 Hz, 1H), 6.85 (d, *J* = 10.9 Hz, 1H), 6.78 (s, 2H), 5.72 (d, *J* = 16.5 Hz, 2H), 5.15 (d, *J* = 11.9 Hz, 2H), 4.23 (d, *J* = 7.4 Hz, 1H), 3.73 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.1, 128.7, 128.0, 127.5, 119.6, 117.8, 114.7, 110.5, 109.2, 32.7, 22.6. IR (KBr): 2917, 2810, 2204, 1658, 1482, 1336, 1183, 1075, 891, 792 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{23}H_{22}DN_2$ $[M+H]^+$ 328.1919, found 328.1924.



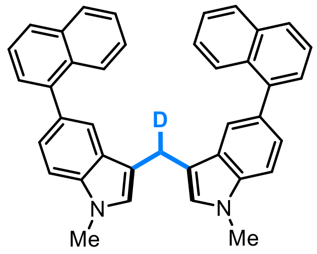
3,3'-(methylene-d)bis(1-methyl-5-((E)-styryl)-1H-indole) (2m)

White solid (27.3 mg, 57% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.51 (t, *J* = 9.3 Hz, 6H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 3.3 Hz, 2H), 7.26 (d, *J* = 3.5 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.08 (d, *J* = 16.2 Hz, 2H), 6.79 (s, 2H), 4.26 (d, *J* = 7.4 Hz, 1H), 3.72 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.1, 130.2, 128.6, 128.4, 128.2, 127.6, 126.8, 126.1, 125.7, 120.2, 118.1, 114.7, 109.5, 32.7 ,21.9. IR (KBr): 2932, 2825, 1889, 1474, 1367, 1228, 929, 768 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{35}H_{30}DN_2$ $[M+H]^+$ 480.2545, found 480.2553.



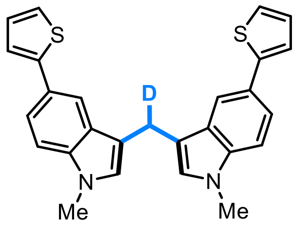
3,3'-(methylene-d)bis(5-(4-(tert-butyl)phenyl)-1-methyl-1H-indole) (2n)

White solid (37.8 mg, 70% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.63 (d, *J* = 6.3 Hz, 4H), 7.51 (dd, *J* = 16.2, 7.4 Hz, 6H), 7.36 (d, *J* = 10.8 Hz, 2H), 6.86 (s, 2H), 4.32 (d, *J* = 7.5 Hz, 1H), 3.74 (s, 6H), 1.41 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 139.8, 136.6, 132.1, 128.4, 127.6, 127.0, 125.5, 121.2, 117.6, 114.7, 114.7, 109.3, 34.4, 32.7, 31.4, 20.9. IR (KBr): 2939, 2295, 1467, 1398, 1290, 1083, 884, 722 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{39}H_{42}DN_2$ $[M+H]^+$ 540.3484, found 540.3480.



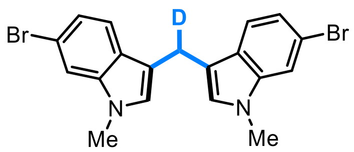
3,3'-(methylene-d)bis(1-methyl-5-(naphthalen-1-yl)-1H-indole) (2o)

White solid (41.2 mg, 78% yield). PE:EA = 20:1, R_f = 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 7.9 Hz, 2H), 7.80 (s, 2H), 7.57 – 7.46 (m, 6H), 7.44 – 7.35 (m, 6H), 6.95 (s, 2H), 4.29 (d, J = 7.4 Hz, 1H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 136.5, 133.8, 132.2, 131.2, 128.1, 127.9, 127.6, 127.3, 126.9, 126.6, 125.6, 125.5, 125.4, 124.0, 120.7, 114.6, 114.5, 108.7, 32.7, 21.0. IR (KBr): 2917, 2387, 1505, 1398, 1267, 1129, 1052, 952, 768 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{39}H_{30}DN_2$ $[M+H]^+$ 528.2545, found 528.2536.



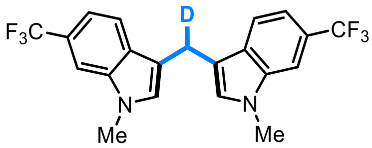
3,3'-(methylene-d)bis(1-methyl-5-(thiophen-2-yl)-1H-indole) (2p)

White solid (30.8 mg, 70% yield). PE:EA = 20:1, R_f = 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 4.8 Hz, 2H), 7.36 (dd, J = 8.6, 4.1 Hz, 4H), 7.31 (d, J = 8.5 Hz, 2H), 6.81 (s, 2H), 4.26 (d, J = 7.2 Hz, 1H), 3.72 (s, 6H). δ 143.8, 136.6, 128.2, 127.7, 127.1, 126.9, 125.7, 120.8, 118.6, 117.1, 109.4, 32.7, 21.0. IR (KBr): 2917, 2272, 1904, 1551, 1490, ,1375, 1267, 1183, 891, 776 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{27}H_{22}DN_2S_2$ $[M+H]^+$ 440.1360, found 440.1348.



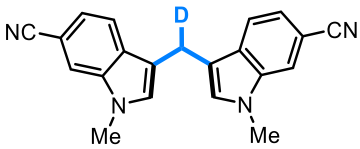
3,3'-(methylene-d)bis(6-bromo-1-methyl-1H-indole) (2q)

White solid (28.2 mg, 65% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* =7.3 Hz, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.74 (s, 2H), 4.13 (d, *J* = 7.3 Hz, 1H), 3.67 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 127.5, 126.6, 121.9, 120.5, 115.2, 114.2, 112.2, 32.7, 20.6. IR (KBr): 3025, 2886, 2395, 2241, 1766, 1566, 1490, 1328, 1013, 829 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{16}DBr_2N_2$ [M+H]$^+$ 431.9816, found 431.9824.



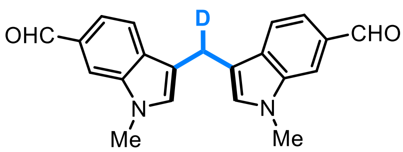
3'-(methylene-d)bis(1-methyl-6-(trifluoromethyl)-1H-indole) (2r)

White solid (32.9 mg, 80% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.57 (s, 2H), 7.30 (d, *J* = 9.6 Hz,1H), 7.26 (d, *J* = 3.5 Hz, 1H), 6.93 (d, *J* = 3.4 Hz, 2H), 4.22 (d, *J* = 4.3 Hz, 1H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 129.9, 129.6, 123.5, 119.5, 115.4, 114.3, 106.8, 106.8, 32.8, 20.8. IR (KBr): 2939, 2825, 2387, 1490, 1390, 1328, 1275, 1160, 1105, 891, 806, 753 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{21}H_{16}DF_6N_2$ [M+H]$^+$ 412.1353, found 412.1366.



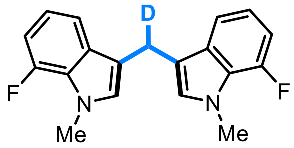
3,3'-(methylene-d)bis(1-methyl-1H-indole-6-carbonitrile) (2s)

Yellow solid (20.5 mg, 63% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 9.5 Hz, 2H), 6.98 (s, 2H), 4.19 (d, *J* = 7.0 Hz, 1H), 3.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 130.7, 130.6, 121.7, 120.7, 119.9, 114.2, 104.1, 32.9, 20.5. IR (KBr): 2986, 2241, 1658, 1275, 1052, 860, 745 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{21}H_{16}DN_4$ [M+H]$^+$ 326.1510, found 326.1517.



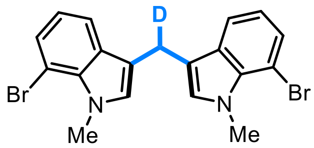
3,3'-(methylene-d)bis(1-methyl-1H-indole-6-carbaldehyde) (2t)

Yellow solid (26.5 mg, 80% yield). PE:EA = 4:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (s, 2H), 7.9 (s, 2H), 7.7 (d, *J* = 8.22 Hz, 2H), 7.6 (d, *J* = 8.19 Hz, 2H), 7.0 (s, 2H), 4.2 (d, *J* = 7.17 Hz, 1H), 3.8 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 136.7, 132.5, 131.6, 130.7, 120.2, 119.4, 114.7, 114.6, 112.0, 32.9, 20.7. IR (KBr): 2847, 2718, 2372, 1682, 1535, 1367, 1175, 806 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{21}H_{18}DN_2O_2$ $[M+H]^+$ 332.1504, found 332.1498.



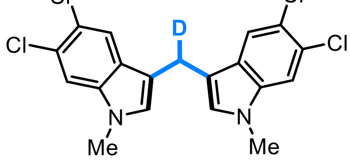
3,3'-(methylene-d)bis(7-fluoro-1-methyl-1H-indole) (2u)

White solid (23.4 mg, 75% yield). PE:EA = 20:1, R_f = 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.9 Hz, 2H), 7.01 – 6.92 (m, 2H), 6.87 (t, J = 8.2 Hz, 2H), 6.74 (s, 2H), 4.15 (d, J = 6.2 Hz, 1H), 3.93 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 149.2, 132.1 (d), 128.5 (d, J = 8.3 Hz), 125.1 (d, J = 9.6 Hz), 118.9, 116.6 – 112.5 (m), 107.0 (d, J = 17.6 Hz), 35.4 (d, J = 12.0 Hz), 20.9. IR (KBr): 2894, 2433, 2149, 1774, 1643, 1535, 1490, 1375, 1298, 1221, 1121, 1037, 929, 784, 706 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{16}DF_2N_2$ $[M+H]^+$ 312.1417, found 312.1405.



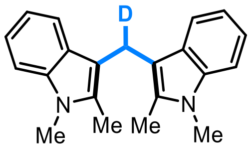
3,3'-(methylene-d)bis(7-bromo-1-methyl-1H-indole) (2v)

White solid (26.0 mg, 60% yield). PE:EA = 10:1, R_f = 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 6.90 (t, J = 7.7 Hz, 2H), 6.71 (s, 2H), 4.11 (d, J = 7.3 Hz, 1H), 4.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 130.9, 130.0, 126.5, 119.9, 118.5, 113.6, 103.9, 36.5, 20.6. IR (KBr): 2955, 2257, 1781, 1559, 1459, 1351, 1298, 1191, 1129, 837, 792, 692 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{16}DBr_2N_2$ $[M+H]^+$ 431.9816, found 431.9818.



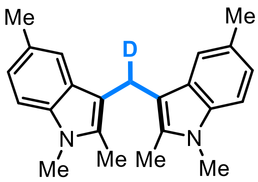
3,3'-(methylene-d)bis(5,6-dichloro-1-methyl-1H-indole) (2w)

White solid (27.7 mg, 67% yield). PE:EA = 10:1, R_f = 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2H), 7.37 (s, 2H), 6.79 (s, 2H), 4.45 (d, J = 6.2 Hz, 1H), 3.69 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 127.7, 126.6, 125.5, 122.7, 120.5, 119.4, 110.9, 32.9, 27.7. IR (KBr): 2932, 2249, 1551, 1474, 1412, 1375, 1298, 1259, 1144, 1068, 884, 792, 745 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{14}DCl_4N_2$ $[M+H]^+$ 412.0047, found 412.0054.



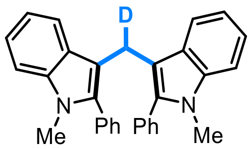
3,3'-(methylene-d)bis(1,2-dimethyl-1H-indole) (2x)

White solid (24.3 mg, 80% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 2H), 4.16 (d, *J* = 6.2 Hz, 1H), 3.65 (s, 6H), 2.43 – 2.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 132.6, 128.0, 120.2, 118.5, 118.4, 110.3, 108.3, 29.4, 19.9, 10.2. IR (KBr): 2925, 2364, 1543, 1459, 1359, 1290, 1160, 1037, 914, 730 cm^{-1}.



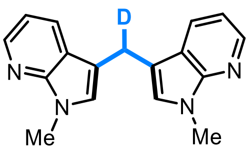
3,3'-(methylene-d)bis(1,2,5-trimethyl-1H-indole) (2y)

White solid (24.2 mg, 73% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (s, 2H), 7.1 (d, *J* = 8.21 Hz, 2H), 6.9 (d, *J* = 8.26 Hz, 2H), 4.1 (d, *J* = 7.63 Hz, 1H), 3.6 (s, 6H), 2.4 (s, 6H), 2.3 (d, *J* = 7.09 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 132.8, 128.3, 127.4, 121.7, 118.2, 109.8, 108.0, 29.4, 21.5, 19.8 ,10.5. IR (KBr): 2902, 2871, 2188, 1858, 1505, 1367, 1252, 884, 730 cm^{-1}.



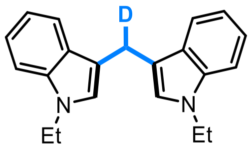
3,3'-(methylene-d)bis(1-methyl-2-phenyl-1H-indole) (2z)

White solid (36.3 mg, 85% yield). PE:EA = 20:1, Rf = 0.5.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 6.0 Hz, 6H), 7.31 (d, *J* = 7.5 Hz, 4H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.15 (t, *J* = 10.2 Hz, 2H), 6.91 (t, *J* = 9.8 Hz, 2H), 4.22 (d, *J* = 6.4 Hz, 1H), 3.56 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.2, 132.2, 130.8, 128.1, 128.0, 127.7, 121.2, 119.8, 118.8, 112.2, 112.2, 108.9, 30.7, 21.0. IR (KBr): 2732, 2464, 2104, 1789, 1520, 1380, 1252, 1075, 730 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{31}H_{26}DN_2$ $[M+H]^+$ 428.2232, found 428.2228.



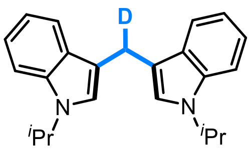
3,3'-(methylene-d)bis(1-methyl-1H-pyrrolo[2,3-b]pyridine) (2a')

White solid (21.4 mg, 77% yield). PE:EA = 2:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 6.3 Hz, 2H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.01 (dd, *J* = 7.8, 4.7 Hz, 2H), 6.93 (s, 2H), 4.17 (d, *J* = 7.3 Hz, 1H), 3.83 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 142.9, 127.2, 126.8, 120.1, 114.9, 112.2, 31.0. IR (KBr): 2939, 2234, 1498, 1482, 1398, 1344, 1275, 1205, 1160, 1044, 945, 822, 761 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{17}H_{16}DN_4$ $[M+H]^+$ 278.1510, found 278.1509.



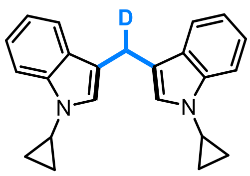
3,3'-(methylene-d)bis(1-ethyl-1H-indole) (2b')

White solid (22.8 mg, 75% yield). PE:EA = 20:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.24 (t, *J* = 6.4 Hz, 2H), 7.12 (t, *J* = 6.1 Hz, 2H), 6.90 (s, 2H), 4.11 (t, *J* = 5.9 Hz, 4H), 1.44 (d, *J* = 4.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 128.1, 125.2, 121.2, 119.4, 118.5, 114.3, 109.1, 40.7, 21.1, 15.5. IR (KBr): 2925, 2871, 2265, 1750, 1727, 1612, 1528, 1459, 1359, 1228, 1075, 745 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{21}H_{22}DN_{22}$ $[M+H]^+$ 305.1991, found 305.1984.



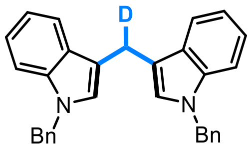
3,3'-(methylene-d)bis(1-isopropyl-1H-indole) (2c')

Yellow oil (21.5 mg, 65% yield). PE:EA = 20:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 2H), 7.07 (s, 2H), 4.76 – 4.66 (m, 2H), 4.33 (d, *J* = 7.5 Hz, 1H), 1.55 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 128.1, 121.8, 121.0, 119.4, 118.5, 114.3, 109.3, 46.8, 22.8, 21.4. IR (KBr): 2955, 2925, 2157, 1719, 1666, 1612, 1512, 1467, 1375, 1351, 1283, 1198, 745 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{23}H_{26}DN_2$ $[M+H]^+$ 331.2159, found 331.2165.



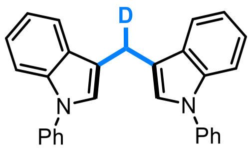
3,3'-(methylene-d)bis(1-cyclopropyl-1H-indole) (2d')

Yellow oil (21.3 mg, 65% yield). PE:EA = 20:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 2H), 6.88 (s, 2H), 4.16 (d, *J* = 7.4 Hz, 1H), 3.28 (s, 2H), 0.97 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 128.3, 126.2, 121.4, 119.3, 119.1, 114.2, 110.2, 26.7, 20.7, 6.2. IR (KBr): 2925, 2842, 2188, 1658, 1443, 1390, 1221, 983, 745 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{23}H_{22}DN_2$ $[M+H]^+$ 328.1919, found 328.1927.



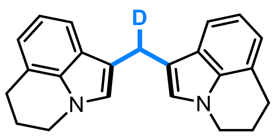
3,3'-(methylene-d)bis(1-benzyl-1H-indole) (2e')

White solid (34.2 mg, 80% yield). PE:EA = 20:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (t, *J* = 7.4 Hz, 2H), 7.3 (s, 8H), 7.2 (q, *J* = 7.0 Hz, 2H), 7.1 (d, *J* = 7.4 Hz, 6H), 6.9 (s, 2H), 5.3 (s, 4H), 4.3 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.8, 128.6, 128.2, 127.4, 126.6, 126.5, 121.6, 119.5, 118.8, 114.8, 109.6, 49.8, 21.0. IR (KBr): 3055, 2955, 2226, 1459, 1328, 1221, 1167, 999, 730 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{31}H_{26}DN_2$ $[M+H]^+$ 428.2232, found 428.2235.



3,3'-(methylene-d)bis(1-phenyl-1H-indole) (2f')

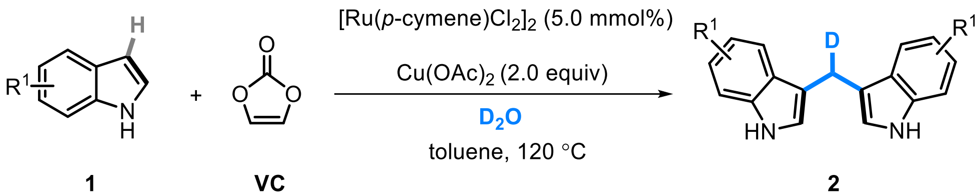
White solid (28.0 mg, 70% yield). PE:EA = 40:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (d, *J* = 7.80 Hz, 2H), 7.6 (d, *J* = 8.21 Hz, 2H), 7.5 (d, *J* = 4.29 Hz, 8H), 7.4 – 7.3 (m, 2H), 7.3 (d, *J* = 4.90 Hz, 2H), 7.2 (t, *J* = 4.01 Hz, 4H), 4.4 (d, *J* = 7.30 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 136.2, 129.5, 129.0, 126.1, 126.0, 124.1, 122.4, 119.9, 119.5, 116.3, 110.5, 21.0. IR (KBr): 2994, 2847, 2510, 2126, 1789, 1566, 1428, 1323, 1152, 745 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{29}H_{22}DN_2$ $[M+H]^+$ 400.1919, found 400.1936.



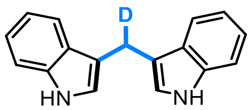
1,1'-(methylene-d)bis(5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline) (2g')

White solid (25.2 mg, 77% yield). PE:EA = 20:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 (d, *J* = 7.9 Hz, 2H), 7.0 (t, *J* = 7.5 Hz, 2H), 6.9 (d, *J* = 6.9 Hz, 2H), 6.9 (s, 1H), 4.2 (d, *J* = 7.5 Hz, 1H), 4.1 (t, *J* = 5.7 Hz, 4H), 3.0 (t, *J* = 6.2 Hz, 4H), 2.2 (p, *J* = 6.0 Hz, 4H).^{13}C NMR (100 MHz, $CDCl_3$)

δ 134.6, 125.3, 124.2, 121.5, 118.9, 118.2, 116.8, 43.8, 43.8, 24.7, 22.9, 21.5 – 21.2 (m). IR (KBr): 2939, 2855, 2180, 1674, 1498, 1436, 1344, 1259, 1167, 1021, 976, 745 cm^{-1}.

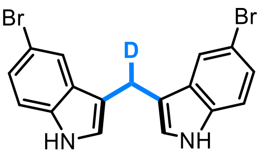


A 15.0 mL vial equipped with a stir bar was charged with substrates **1** (0.2 mmol), **VC** (17.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired products **2**.



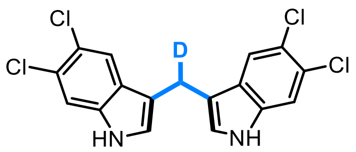
3,3'-(methylene-d)bis(1H-indole) (2h')

White solid (13.4 mg, 54% yield). PE:EA = 4:1, Rf = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 2H), 6.95 (s, 2H), 4.24 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 127.6, 122.2, 121.9, 119.2, 119.2, 115.6, 111.0, 21.2. IR (KBr): 2917, 2825, 1451, 1320, 1244, 1136, 976, 806, 737 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{17}H_{14}DN_2$ $[M+H]^+$ 248.1293, found 248.1288.



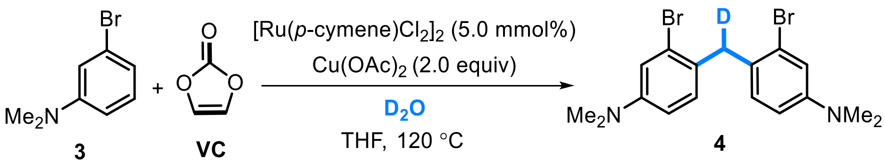
3,3'-(methylene-d)bis(5-bromo-1H-indole) (2i')

White solid (21.1 mg, 52% yield). PE:EA = 4:1, Rf = 0.5. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.99 (s, 2H), 7.65 (s, 2H), 7.39 – 7.19 (m, 4H), 7.14 (d, *J* = 8.6 Hz, 2H), 4.09 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 135.6, 129.4, 125.1, 123.7, 121.4, 114.2, 113.9, 111.3, 20.5. IR (KBr): 2932, 2832, 2241, 1498, 382, 1267, 1068,.929, 792 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{17}H_{12}DBr_2N_2$ $[M+H]^+$ 403.9503, found 403.9510.



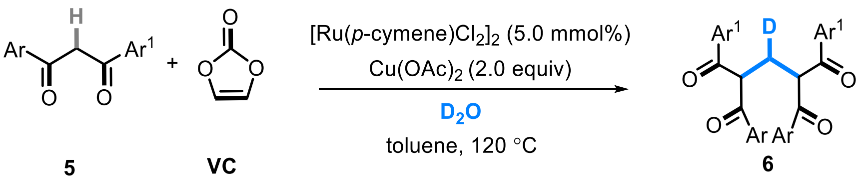
3,3'-(methylene-d)bis(5,6-dichloro-1H-indole) (2j')

White solid (18.9 mg, 49% yield). PE:EA = 4:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 2H), 7.60 (s, 2H), 7.47 (d, J = 2.3 Hz, 2H), 6.97 (s, 2H), 4.10 (d, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 127.2, 126.0, 124.1, 123.5, 120.1, 112.6. 20.8. IR (KBr): 2954, 2732, 2014, 1562, 1327, 1136, 1025, 979, 726 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{17}H_{10}DCl_4N_2$ $[M+H]^+$ 383.9734, found 383.9729.

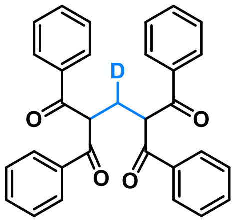


A 15.0 mL vial equipped with a stir bar was charged with compound **3** (80 mg, 0.2 mmol), $Cu(OAc)_2$ (37.2 mg, 2.0 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), **VC** (34.4 mg, 0.4 mmol), D_2O (0.1 mL) and THF (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 120 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired product **4**. Yellow solid (21.1 mg, 51% yield). PE:EA = 50:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.59 (d, J = 6.0 Hz, 2H), 3.99 (d, J = 7.9 Hz, 1H), 2.91 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 130.7, 127.1, 125.6, 116.3, 111.9, 40.5, 39.9. IR (KBr): 2885, 2763, 1520, 1429, 1292, 1247, 1079, 943, 746 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{17}H_{20}DBr_2N_2$ $[M+H]^+$ 412.0129, found 412.0130.

C(sp^3)-H compounds

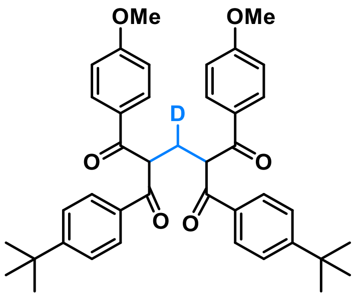


A 15.0 mL vial equipped with a stir bar was charged with substrates **5** (0.2 mmol), **VC** (17.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 120 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired products **6**.



2,4-dibenzoyl-1,5-diphenylpentane-1,5-dione-3-d (6a)

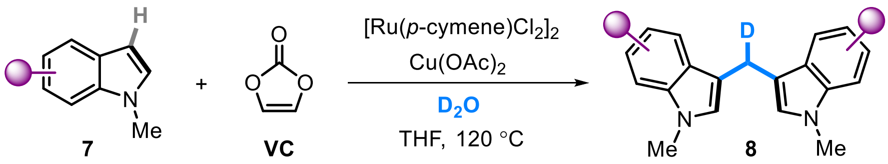
Yellow solid (27.2 mg, 59% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 5.4 Hz, 8H), 7.59 (t, *J* = 6.5 Hz, 4H), 7.48 (t, *J* = 6.7 Hz, 8H), 5.74 (d, *J* = 5.1 Hz, 2H), 2.76 (t, *J* = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 135.1, 133.6, 128.7, 128.5, 53.6, 28.6. IR (KBr): 2991, 2430, 2278, 1671, 1520, 1459, 1292, 1110, 1019. 746 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{31}H_{24}DO_4$ $[M+H]^+$ 462.1810, found 462.1823.



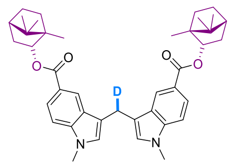
2,4-bis(4-(tert-butyl)benzoyl)-1,5-bis(4-methoxyphenyl)pentane-1,5-dione-3-d (6b)

Yellow solid (35.5 mg, 56% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 2H), 8.13 (dd, *J* = 16.2, 7.4 Hz, 4H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.47 (dd, *J* = 16.1, 8.4 Hz, 4H), 6.97 (dd, *J* = 15.5, 8.9 Hz, 4H), 5.65 (t, *J* = 7.0 Hz, 1H), 3.87 (s, 6H), 2.76 – 2.66 (m, 1H), 1.30 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 196.3, 195.4, 195.3, 164.1, 164.0, 157.5, 157.4, 133.1, 132.9, 131.4, 131.2, 128.8, 128.6, 128.6, 128.4, 126.0, 125.9, 114.2, 114.2, 55.5, 53.8, 35.1, 31.0, 29.2. IR (KBr): 2931, 2233, 1474, 1383, 1261, 1110. 974. 715 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{41}H_{44}DO_6$ $[M+H]^+$ 633.3201, found 633.3197.

D. Behavior of bioactive molecules

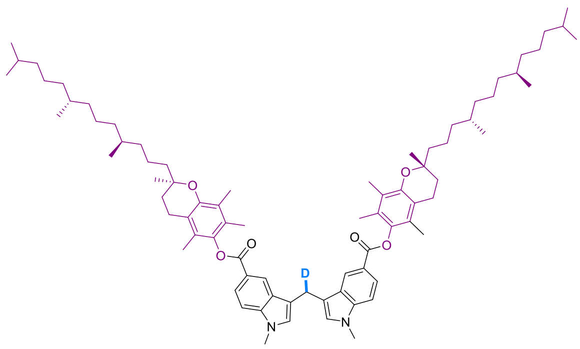


A 15.0 mL vial equipped with a stir bar was charged with compounds **7** (0.2 mmol), $Cu(OAc)_2$ (37.2 mg, 2.0 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), **VC** (34.4 mg, 0.4 mmol), D_2O (0.1 mL) and THF (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 120 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired products **8**.



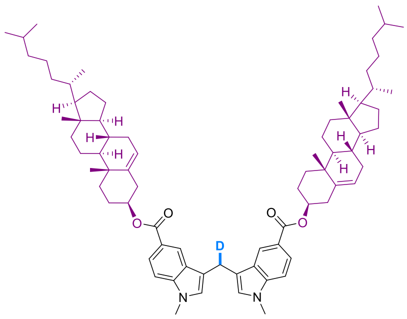
(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 1-methyl-3-((s)-(1-methyl-5-((((1R,2S,4R) -1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)carbonyl)-1H-indol-3-yl)methyl-d)-1H-indole-5 -carboxylate (8a)

White solid (41.3 mg, 65% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 6.94 (s, 2H), 5.12 (d, *J* = 9.7 Hz, 2H), 4.28 (d, *J* = 7.4 Hz, 1H), 3.74 (s, 6H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.15 (t, *J* = 8.9 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.73 (t, *J* = 4.5 Hz, 2H), 1.59 (d, *J* = 7.2 Hz, 2H), 1.44 – 1.35 (m, 2H), 1.32 – 1.27 (m, 2H), 1.13 (d, *J* = 17.2 Hz, 2H), 0.98 (s, 6H), 0.92 (d, *J* = 4.0 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 139.6, 128.1, 127.4, 122.9, 122.2, 121.4, 115.7, 108.7, 79.8, 49.1, 47.8, 45.1, 37.0, 32.8, 32.8, 28.1, 27.5, 19.8, 19.0, 13.6. IR (KBr): 2939, 2234, 1689, 1597, 1451, 1367, 1328, 1236, 1113, 1013, 884, 753 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{41}H_{50}DN_2O_4$ $[M+H]^+$ 636.3906, found 636.3902.



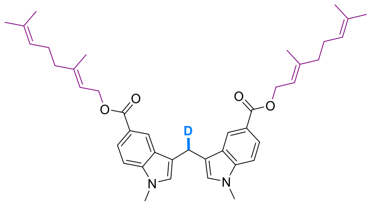
bis((R)-2,5,7,8-tetramethyl-2-((4S,8R)-4,8,12-trimethyltridecyl)chroman-6-yl) 3,3'-(methylene-d)bis(1-methyl-1H-indole-5-carboxylate) (8b)

White solid (65.4 mg, 55% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.97 (s, 2H), 4.35 (d, *J* = 7.4 Hz, 1H), 3.76 (s, 6H), 2.65 (t, *J* = 6.7 Hz, 4H), 2.15 (s, 6H), 2.10 (s, 6H), 2.06 (s, 6H), 1.91 – 1.79 (m, 4H), 1.63 – 1.53 (m, 6H), 1.49 – 1.40 (m, 8H), 1.33 – 1.27 (m, 26H), 1.18 – 1.11 (m, 8H), 0.90 (d, *J* = 6.5 Hz, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.2, 140.9, 139.9, 128.5, 127.6, 127.1, 125.3, 123.5, 123.0, 122.9, 120.1, 117.3, 115.8, 109.0, 75.0, 40.4, 39.4, 37.4, 32.8, 31.3, 29.7, 28.0, 24.8, 24.4, 23.7, 22.7, 22.6, 21.0, 20.6, 19.7, 14.1, 13.1, 12.2, 11.8. IR (KBr): 2925, 2333, 1735, 1467, 1367, 1236, 1152, 1052, 909, 706 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{79}H_{114}DN_2O_6$ $[M+H]^+$ 1188.8812, found 1188.8804.



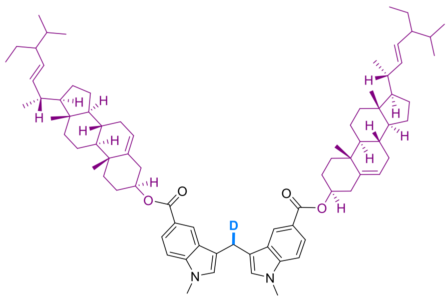
bis((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((S)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl) 3,3'-(methylene-d)bis(1-methyl-1H-indole-5-carboxylate) (8c)

White solid (66.0 mg, 60% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.29 (s, 2H), 6.84 (s, 2H), 5.42 (s, 2H), 4.85 (s, 2H), 4.27 (d, *J* = 7.3 Hz, 1H), 3.73 (s, 6H), 2.48 (d, *J* = 8.2 Hz, 4H), 2.02 (t, *J* = 7.7 Hz, 6H), 1.92 – 1.70 (m, 6H), 1.58 (s, 6H), 1.53 – 1.45 (m, 6H), 1.33 (t, *J* = 7.4 Hz, 6H), 1.24 (d, *J* = 15.1 Hz, 6H), 1.19 – 1.11 (m, 8H), 1.08 (s, 8H), 1.04 – 0.97 (m, 6H), 0.92 (d, *J* = 6.3 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 12H), 0.69 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 140.0, 139.5, 128.2, 127.4, 123.0, 122.5, 122.1, 121.4, 115.8, 108.7, 56.7, 56.1, 50.1, 42.3, 39.8, 39.5, 38.4, 37.1, 36.7, 36.2, 35.8, 32.8, 32.0, 31.9, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 20.4, 19.4, 18.7, 11.9. IR (KBr): 2932,2372, 1705, 1443, 1367, 1313, 1259, 1136, 1083, 999, 784 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{75}H_{106}DN_2O_4$ $[M+H]^+$ 1100.8288, found 1100.8293.



bis((E)-3,7-dimethylocta-2,6-dien-1-yl) 3,3'-(methylene-d)bis(1-methyl-1H-indole-5-carboxylate) (8d)

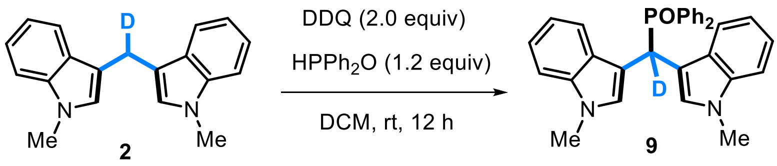
White solid (42.6 mg, 67% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 2H), 7.96 (d, J = 7.0 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 6.84 (s, 2H), 5.54 (t, J = 7.2 Hz, 2H), 5.14 (t, J = 7.4 Hz, 2H), 4.84 (d, J = 7.2 Hz, 4H), 4.27 (d, J = 7.2 Hz, 1H), 3.74 (s, 6H), 2.20 (q, J = 7.1, 6.0 Hz, 4H), 2.13 (q, J = 7.3 Hz, 4H), 1.81 (s, 6H), 1.68 (s, 6H), 1.62 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 142.0, 139.5, 132.1, 128.2, 127.4, 123.7, 123.0, 122.2, 121.1, 119.8, 115.8, 115.7, 108.7, 61.3, 32.8, 32.3, 26.7, 25.7, 23.5, 21.2, 17.7. IR (KBr): 2947, 2855, 2226, 1689, 1459, 1406, 1228, 1113, 1060, 960, 730 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{41}H_{50}DN_2O_4$ $[M+H]^+$ 635.8671, found 635.8675.



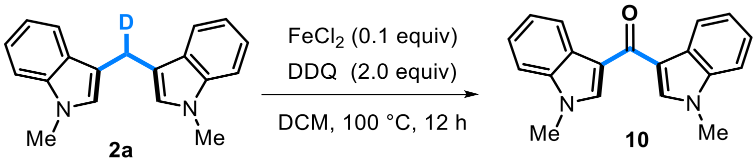
bis((3S,8S,9S,10R,13R,14S,17R)-17-((2R,E)-5-ethyl-6-methylhept-3-en-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl) 3,3'-(methylene-d)bis(1-methyl-1H-indole-5-carboxylate) compound with methane (1:1) (8e)

White solid (66.6 mg, 57% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 22.7 Hz, 2H), 7.92 (t, 2H), 7.28 (d, 2H), 6.85 (s, 2H), 5.42 (s, 2H), 5.30 (s, 1H), 5.16 (dd, J = 15.1, 8.4 Hz, 2H), 5.02 (dd, J = 15.2, 8.3 Hz, 2H), 4.85 (s, 2H), 4.27 (d, J = 7.3 Hz, 1H), 3.73 (s, 6H), 2.48 (d, J = 7.8 Hz, 4H), 2.00 (t, J = 13.1 Hz, 6H), 1.91 (d, J = 12.0 Hz, 2H), 1.72 (t, J = 12.8 Hz, 4H), 1.60 – 1.44 (m, 18H), 1.28 – 1.15 (m, 10H), 1.05 (t, 17H), 0.87 – 0.78 (m, 18H), 0.71 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 140.0, 139.7, 139.5, 138.3, 129.2, 128.2, 127.4, 127.2, 123.0, 122.9, 122.6, 122.5, 122.1, 121.4, 115.8, 108.6, 74.1, 56.8, 55.9, 51.2, 50.1, 42.2, 40.5, 39.6, 38.3, 37.1, 36.7, 32.8, 31.9, 31.9, 28.9, 28.0, 25.4, 24.4, 21.2, 21.1, 21.0, 19.4, 19.0, 12.2, 12.0. IR (KBr): 3009, 2817, 2173, 1835, 1474, 1398, 1298, 973, 798 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{80}H_{114}DN_2O_4$ $[M+H]^+$ 1169.8156, found 1169.8151.

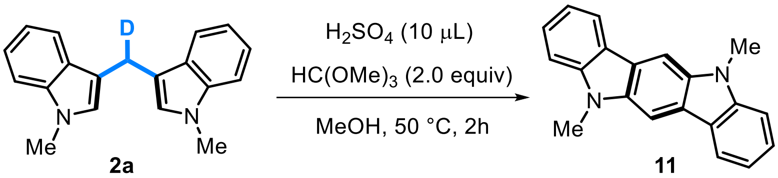
E. Scale-up reaction and derivatizations



A 15.0 mL vial equipped with a stir bar was charged with **2a** (55.1 mg, 0.2 mmol), DDQ (90.8mg, 2.0 equiv), $HPPh_2O$ (48.5 mg, 1.2 equiv) and DCM (2.0 mL). The reaction mixture was stirred at room temperature for 12 h. The reaction was then quenched with saturated aqueous Na_2SO_3 solution (2.0 mL) and extracted with DCM (2.0 mL x 3). The extracts were combined and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was then purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford the desired product **9**. Red solid (68.5 mg, 72% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, *J* = 7.7 Hz, 4H), 7.48 (s, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.14 (m, 6H), 7.09 (t, *J* = 7.5 Hz, 2H), 6.93 (t, *J* = 7.5 Hz, 2H), 5.44 (d, *J* = 9.5 Hz, 1H), 3.67 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 133.7, 132.7, 131.2, 131.1, 129.4, 129.3, 128.1, 128.0, 127.5, 127.4, 121.2, 118.8, 118.2, 110.5, 110.5, 109.0, 33.6, 32.8. IR (KBr): 3086, 2932, 2303, 1474, 1382, 1191, 1144, 921, 730, 692 cm^{-1}.

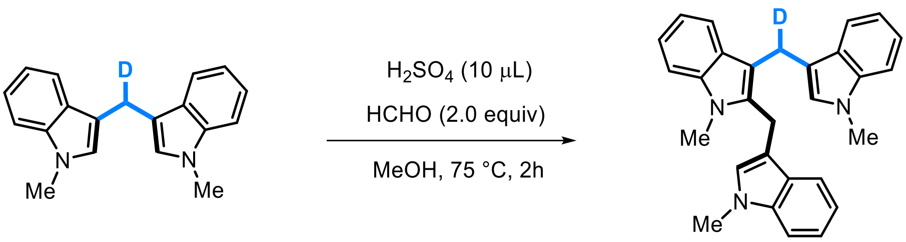


A 15.0 mL vial equipped with a stir bar was charged with **2a** (55.1 mg, 0.2 mmol), DDQ (90.8mg, 2.0 equiv), $FeCl_2$ (2.5 mg, 0.1 equiv) and DCM (2.0 mL). The reaction mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction was then quenched with saturated aqueous Na_2SO_3 solution (2.0 mL) and extracted with DCM (2.0 mL x 3). The extracts were combined and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was then purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford the desired product **10**. Yellow solid (38.1 mg, 66% yield). PE:EA = 10:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.5 Hz, 2H), 7.55 (s, 2H), 7.31 (s, 6H), 3.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 137.4, 134.5, 127.2, 123.1, 122.4, 121.8, 117.4, 109.4, 33.3. IR (KBr): 2909, 2840, 2249, 1512, 1382, 1359, 1221, 1099, 837, 714 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1335, found 289.1319.



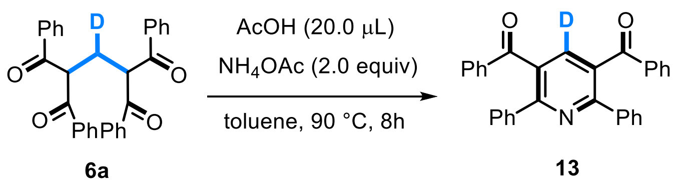
2a **11**

A 15.0 mL vial equipped with a stir bar was charged with **2a** (55.1 mg, 0.2 mmol), $HC(OMe)_3$ (42.4mg, 2.0 equiv), H_2SO_4 (10.0 μL) and MeOH (2.0 mL). The reaction mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. Then the mixture was redissolved with ethyl acetate and neutralized with saturated NaOH aqueous solution. Then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford the desired product **11**. Red solid (34.7 mg, 61% yield). PE:EA = 20:1, R_f = 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.7 Hz, 2H), 8.02 (s, 2H), 7.53 (t, J = 7.1 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H), 3.96 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 136.8, 125.7, 122.8, 122.7, 120.1, 118.0, 108.1, 98.5, 29.4. IR (KBr): 3123, 2804, 2450, 2015, 1892, 1799, 1235, 989, 746 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{20}H_{17}N_2$ $[M+H]^+$ 284.1313, found 284.1321.

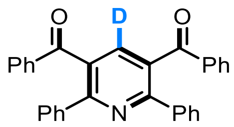


2a **12**

A 15.0 mL vial equipped with a stir bar was charged with **2a** (55.1 mg, 0.2 mmol), HCHO (12.1 mg, 2.0 equiv), H_2SO_4 (10.0 μL) and MeOH (2.0 mL). The reaction mixture was stirred at 75 °C for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. Then the mixture was redissolved with ethyl acetate and neutralized with saturated NaOH aqueous solution. Then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford the desired product **12**. White solid (41.9 mg, 50% yield). PE:EA = 20:1, R_f = 0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (q, J = 7.6 Hz, 3H), 7.31 (t, J = 8.2 Hz, 1H), 7.20 (q, J = 8.8, 7.9 Hz, 4H), 7.10 (q, J = 7.3 Hz, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.59 (s, 1H), 6.30 (s, 1H), 4.27 (d, J = 4.9 Hz, 3H), 3.61 (s, 3H), 3.56 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 136.9, 135.7, 128.1, 127.7, 127.2, 127.0, 121.6, 121.2, 120.6, 119.1, 118.9, 118.8, 118.7, 118.6, 118.4, 114.9, 111.9, 110.5, 109.2, 108.9, 108.7, 32.5, 32.4, 29.8, 20.8, 20.1. IR (KBr): 3001, 2878, 2280, 1512, 1382, 1252, 1068, 730 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{29}H_{27}DN_3$ $[M+H]^+$ 418.2268, found 418.2273.

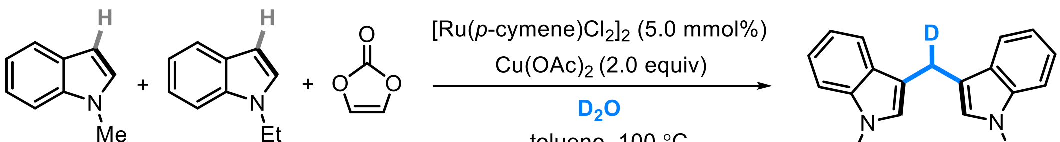


A 15.0 mL vial equipped with a stir bar was charged with **6a** (92.3 mg, 0.2 mmol), NH_4OAc (61.7 mg, 2.0 equiv), AcOH (20.0 μL) and toluene (2.0 mL). The reaction mixture was stirred at 90 °C for 8 h. After cooling to room temperature, the reaction was neutralized with saturated NaOH aqueous solution, then extracted with ethyl acetate (2.0 mL x 3) The organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford the desired product **13**.

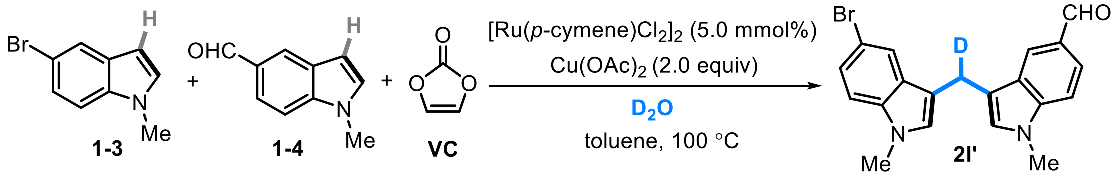


(2,6-diphenylpyridine-3,5-diyl-4-d)bis(phenylmethanone) (13)

Yellow solid (70.5 mg, 80% yield). PE:EA = 20:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.78 (d, *J* = 7.0 Hz, 4H), 7.72 (dd, *J* = 6.6, 2.9 Hz, 4H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 4H), 7.32 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 158.0, 138.8, 138.6, 136.4, 133.5, 131.9, 129.9, 129.6, 129.4, 128.5, 128.4. IR (KBr): 2403, 2295, 1674, 1543, 1443, 1298, 1244, 1183, 1006, 906, 730 cm^{-1}.



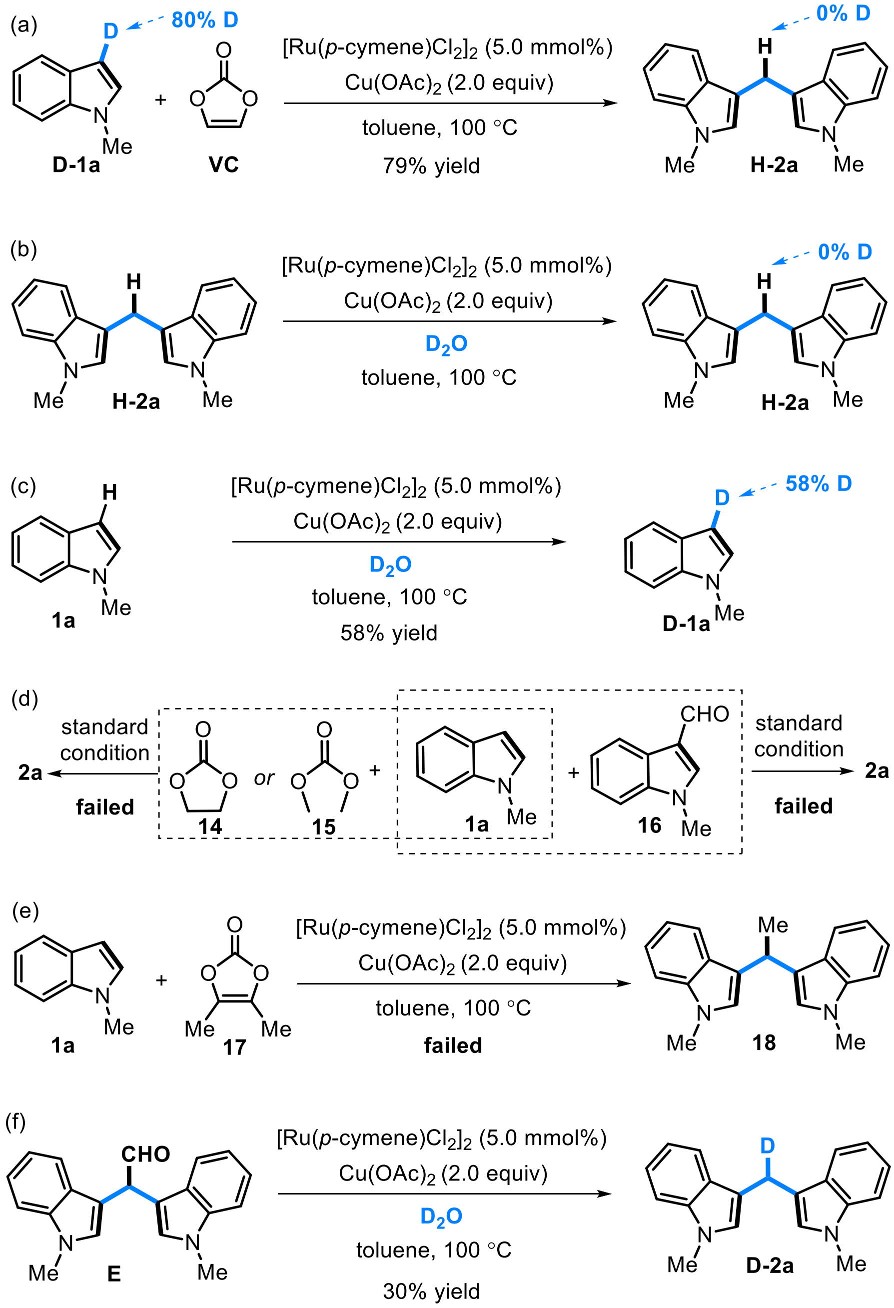
A 15.0 mL vial equipped with a stir bar was charged with substrate **1-1** (13.1 mg, 0.1 mmol), **1-2** (14.5mg, 0.1 mmol), **VC** (17.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired products (**2a**, 8.3mg, 30% yield; **2b'**, 7.6mg, 25% yield; **2k'**, 8.7 mg, 30% yield). Product **2k'**, white solid, PE:EA = 30:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.18 – 7.10 (m, 2H), 6.93 (s, 1H), 6.85 (s, 1H), 4.28 (d, *J* = 7.4 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 1.46 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.1, 128.0, 127.9, 127.0, 125.2, 121.3, 121.2, 119.4, 119.3, 118.5, 118.5, 114.2, 114.2, 109.1, 109.0, 40.7, 32.6, 21.0, 15.5. IR (KBr): 3010, 2674, 2281, 1417, 1382, 1255, 1168, 690 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{20}H_{20}DN_2$ $[M+H]^+$ 290.4076, found 290.4082.



A 15.0 mL vial equipped with a stir bar was charged with substrate **1-3** (21.0 mg, 0.1 mmol), **1-4** (15.9 mg, , 0.1 mmol), **VC** (17.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired products **2l'**. Yellow solid (13.4 mg, 35% yield). PE:EA = 5:1, R_f = 0.5. (**2e**, 8.7mg, 20% yield; **2h**, 8.9 mg, 27% yield; **2l'**, 13.4 mg, 35% yield). Product **2l'**, yellow solid, PE:EA = 5:1, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.13 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.71 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 6.84 (d, *J* = 15.5 Hz, 2H), 4.19 (d, *J* = 7.1 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 140.4, 135.8, 129.3, 128.7, 128.6, 128.1, 127.6, 124.5, 124.3, 122.1, 121.6, 116.3, 113.0, 112.1, 110.7, 109.7, 32.9, 32.8, 20.7. IR (KBr): 2920, 2480, 2253, 1758, 1735, 1523, 1434, 1327, 898 cm^{-1}. HRMS (ESI) m/z Calcd for $C_{20}H_{17}DBrN_2O$ $[M+H]^+$ 383.2866, found 383.2873.

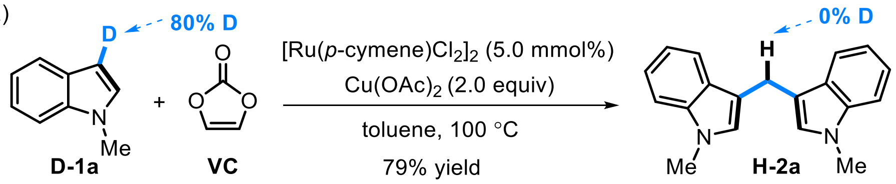
F. Reaction mechanistic studies

Mechanistic studies



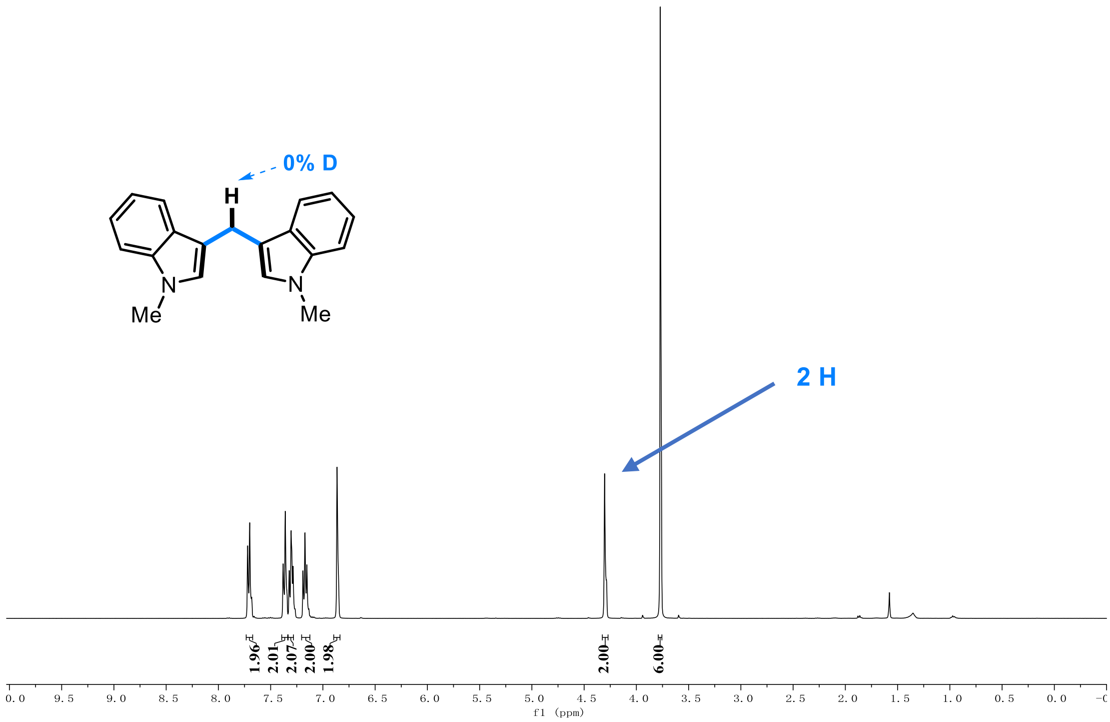
(g) Tentative reaction mechanism

(a)

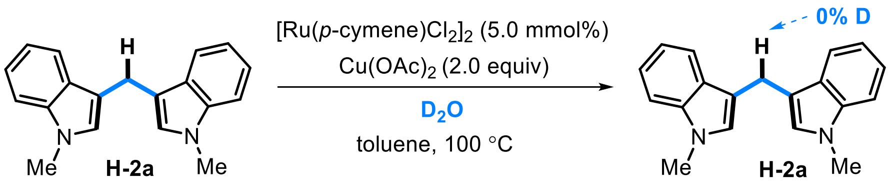


A 15.0 mL vial equipped with a stir bar was charged with substrates **D-1a** (0.2 mmol), **VC** (17.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired product **H-2a** (21.6 mg, 79% yield).

^{1}H NMR of **H-2a** (400 MHz, $CDCl_3$)



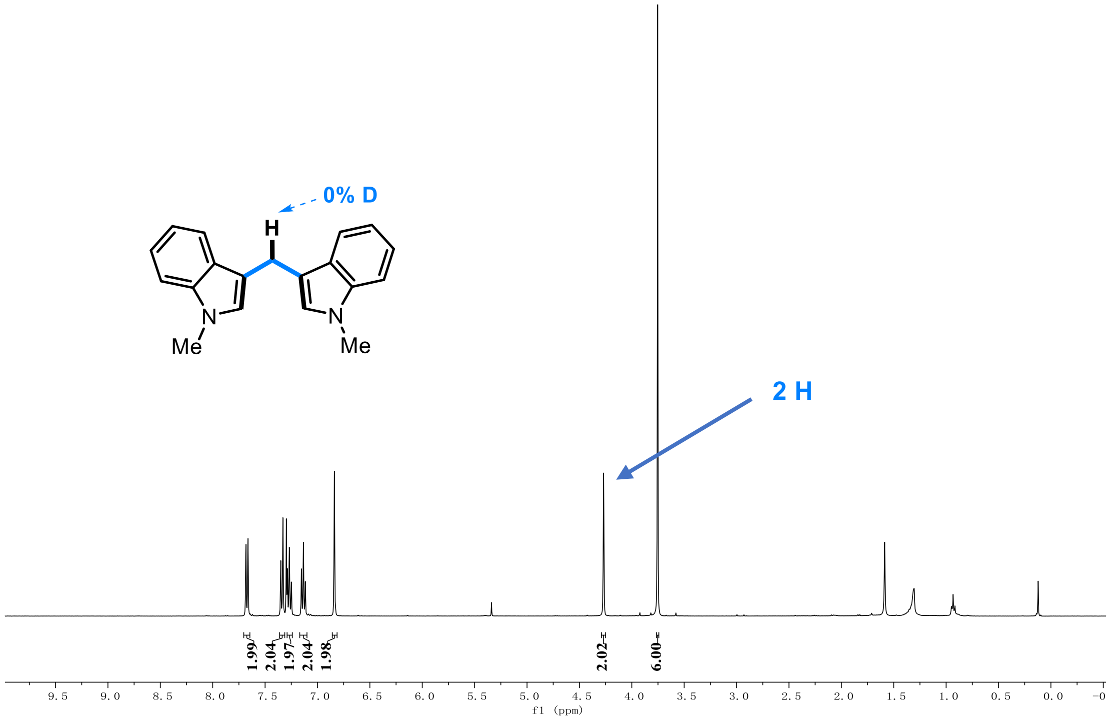
(b)



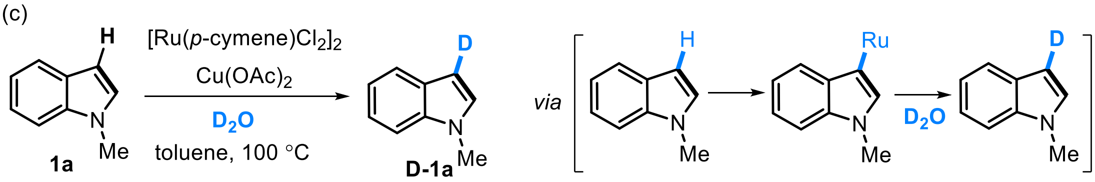
A 15.0 mL vial equipped with a stir bar was charged with substrate **H-2a** (54.9 mg, 0.2 mmol),

VC (17.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to recycle the **H-2a** substrate.

^{1}H NMR of **H-2a** (400 MHz, $CDCl_3$)



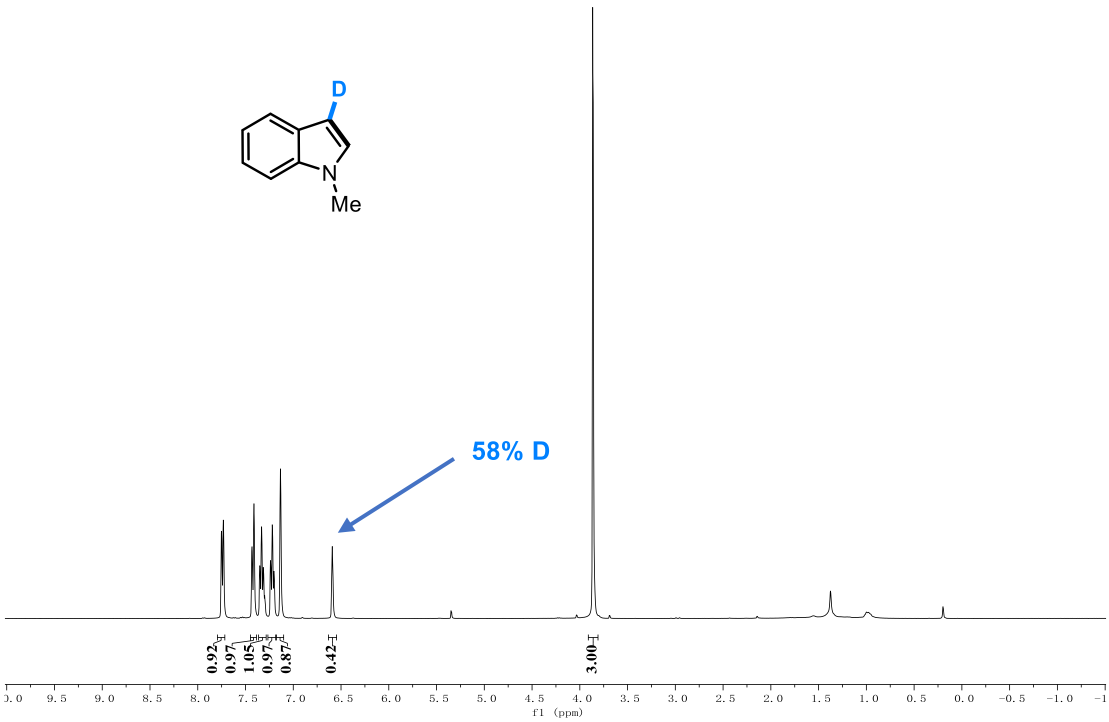
(c)

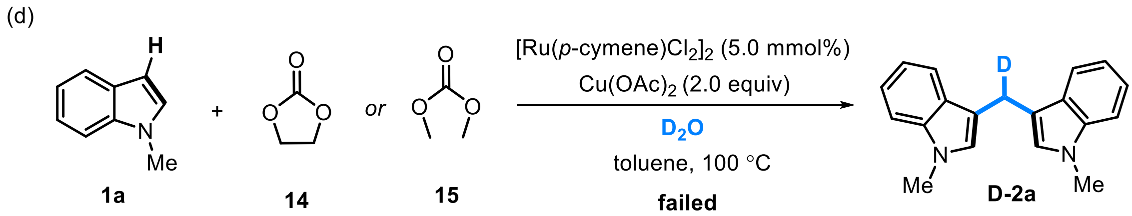


A 15.0 mL vial equipped with a stir bar was charged with substrate **1a** (26.2 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydros $MgSO_4$

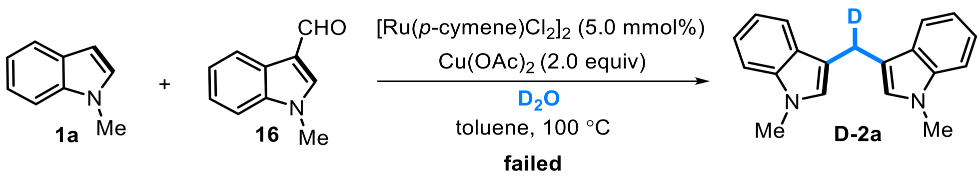
and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the mixed **H-1a** and **D-1a**.

^{1}H NMR of **D-1a** (400 MHz, $CDCl_3$)

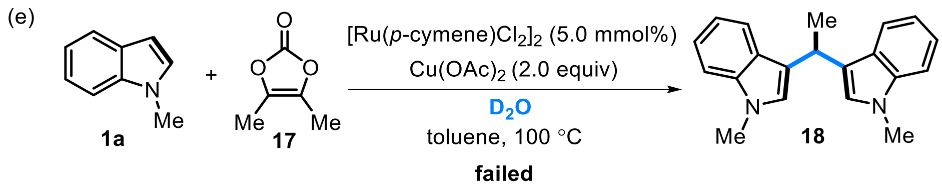




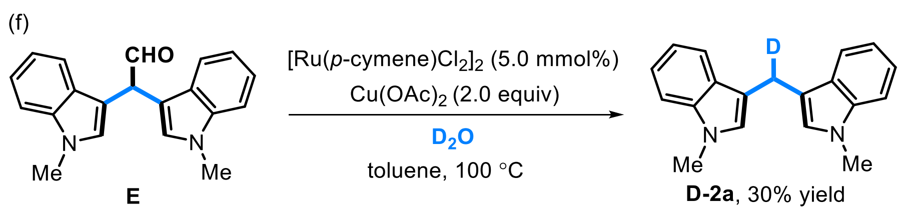
A 15.0 mL vial equipped with a stir bar was charged with substrate **1a** (0.2 mmol), compounds **14** or **15** (0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, where the substrate **1a** was fully recovered and the product **D-2a** failed to be obtained.



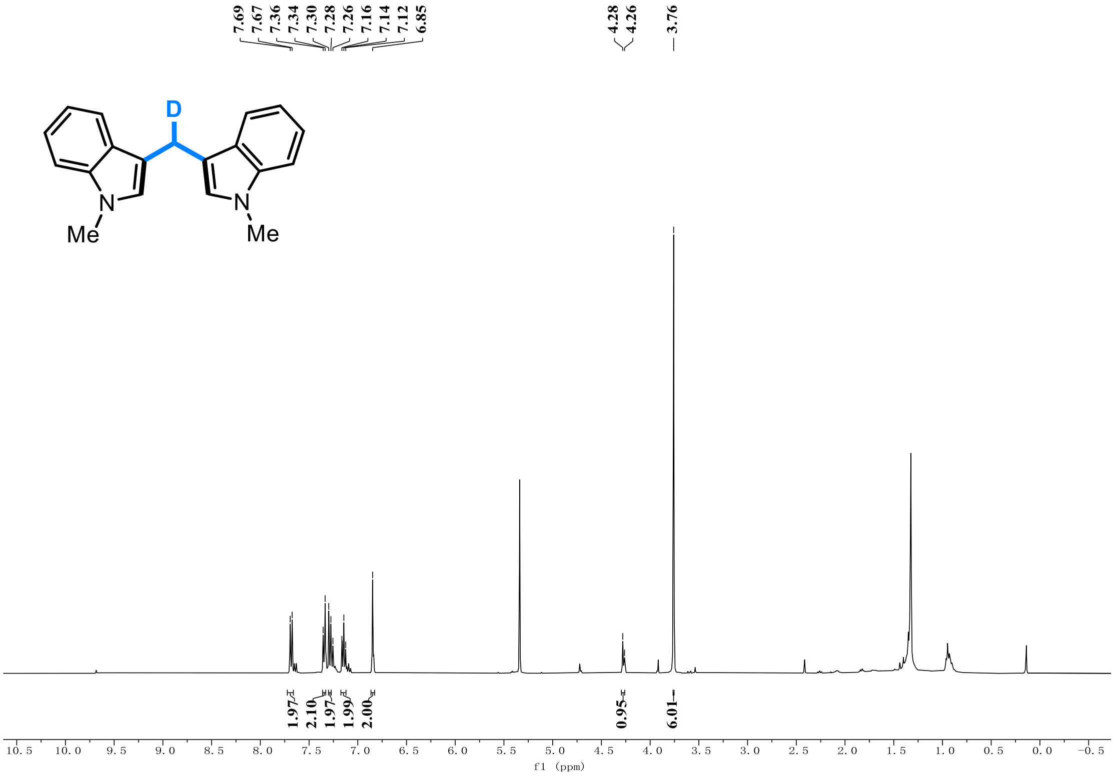
A 15.0 mL vial equipped with a stir bar was charged with substrate **1a** (13.2 mg, 0.1 mmol), compound **16** (15.9 mg, 0.1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, where the product **D-2a** failed to be obtained.



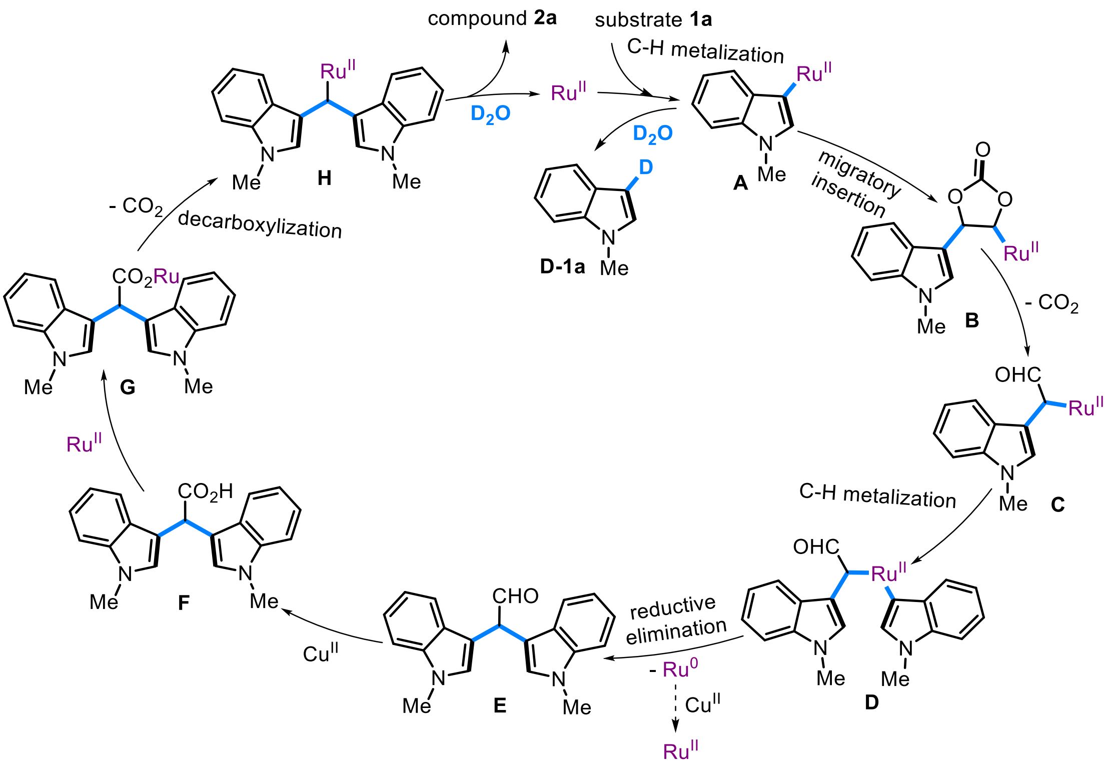
A 15.0 mL vial equipped with a stir bar was charged with substrate **1a** (0.2 mmol), compound **17** (22.8 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.1 mL) and toluene (1.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, where the product **18** failed to be obtained.



A 15.0 mL vial equipped with a stir bar was charged with substrate **E** (60.5 mg, 0.2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 5.0 mol%), $Cu(OAc)_2$ (37.2 mg, 0.4 mmol), D_2O (0.2 mL) and toluene (2.0 mL) was then added under argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After cooling to room temperature, the mixture was diluted with ethyl acetate (2.0 mL) and washed with saturated aqueous $NaHCO_3$ (2.0 mL x 3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired product **D-2a** (16.5 mg, 30% yield).

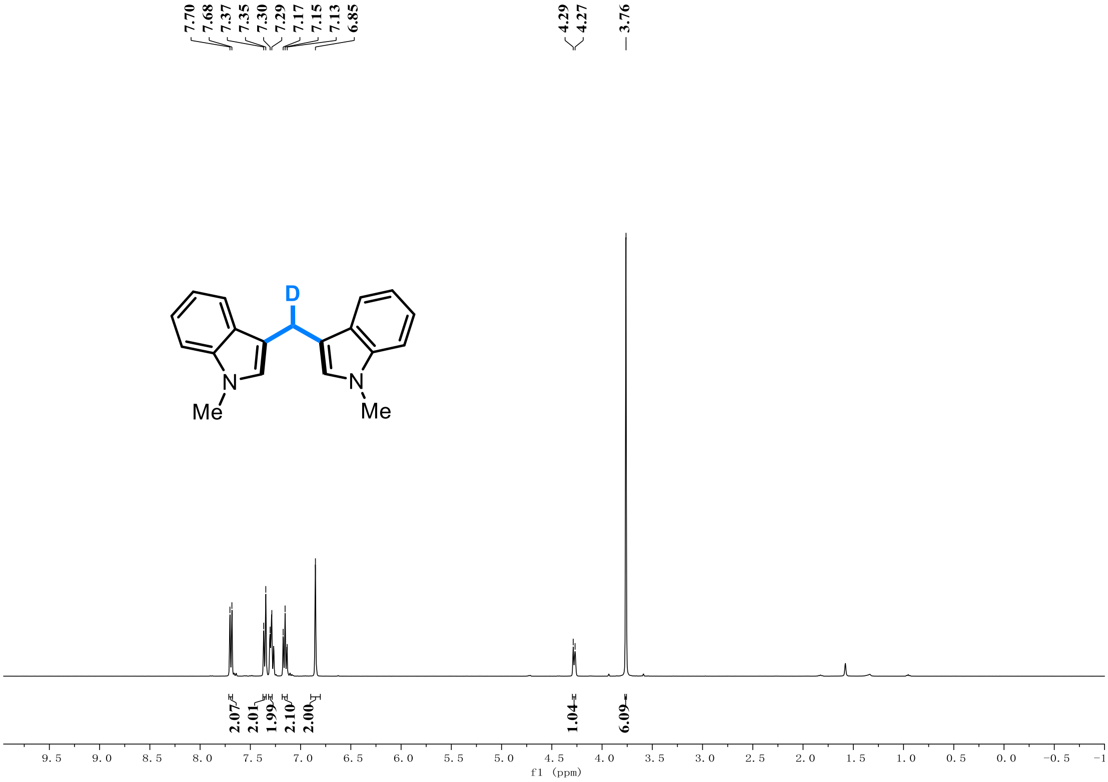


(g) Tentative reaction mechanism

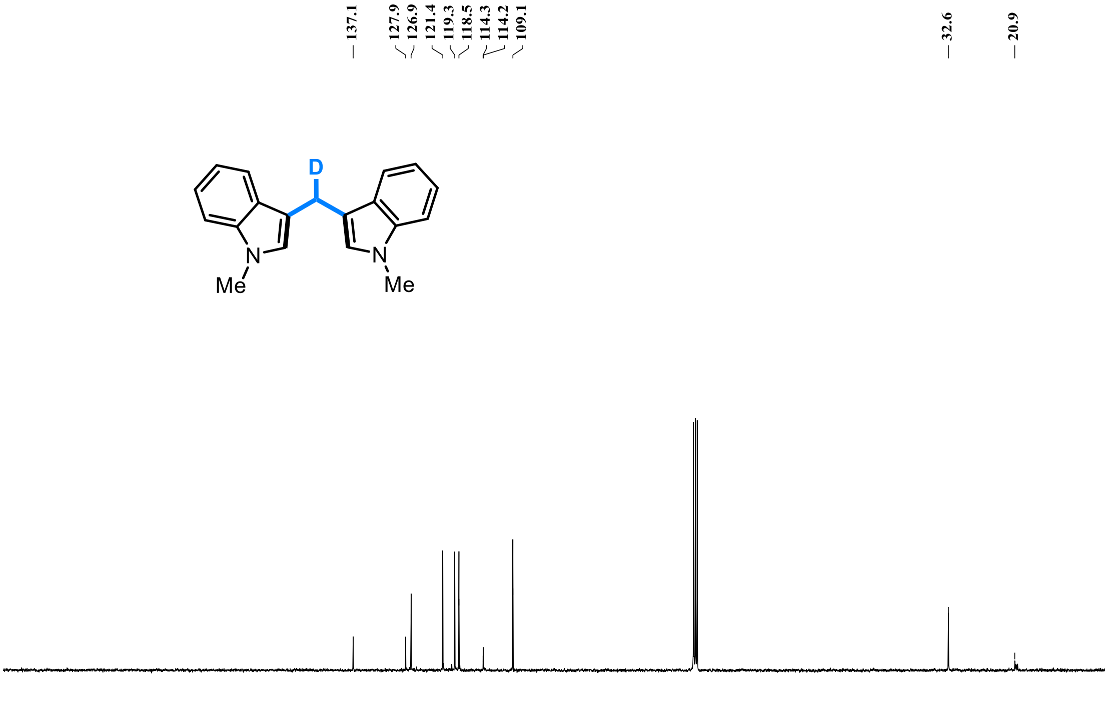


G. NMR spectra

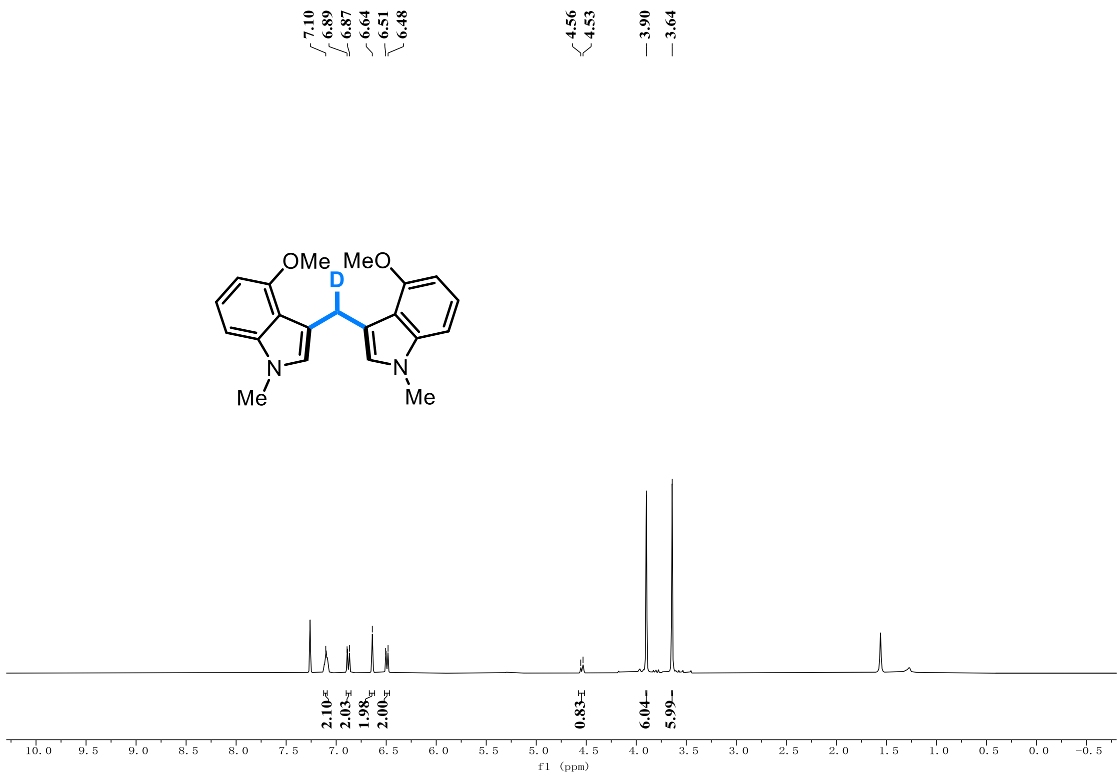
^{1}H NMR of **2a** (400 MHz, $CDCl_3$)



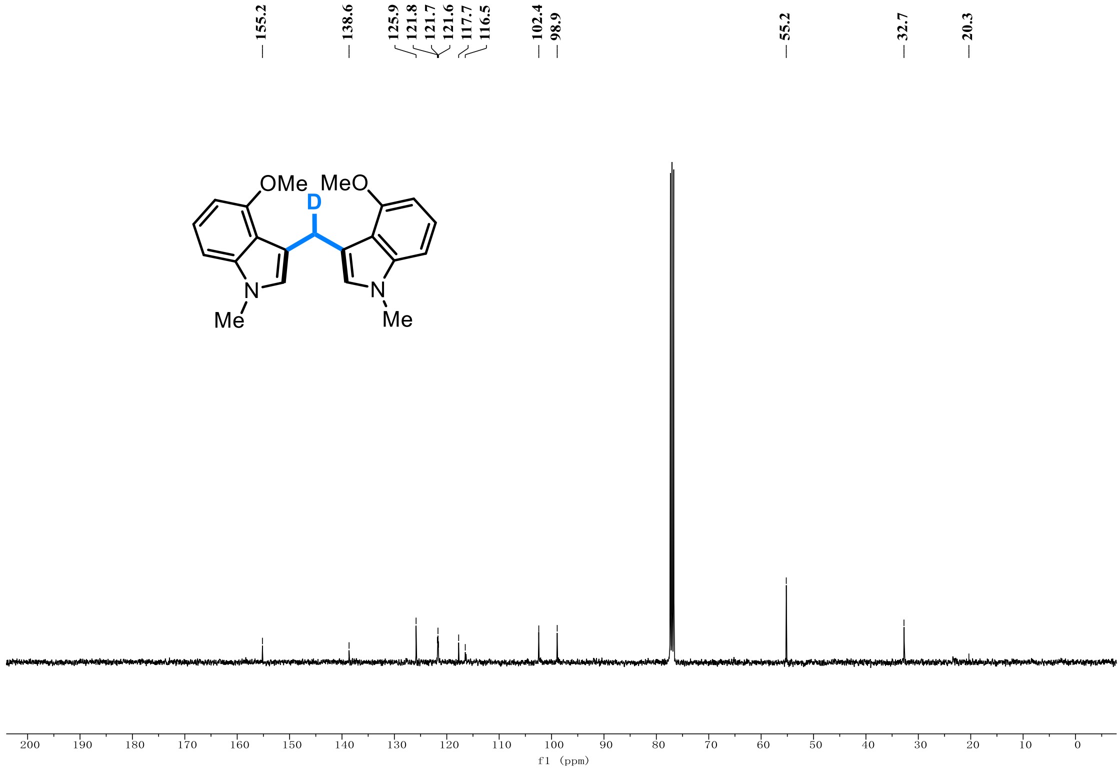
^{13}C NMR of **2a** (100 MHz, $CDCl_3$)



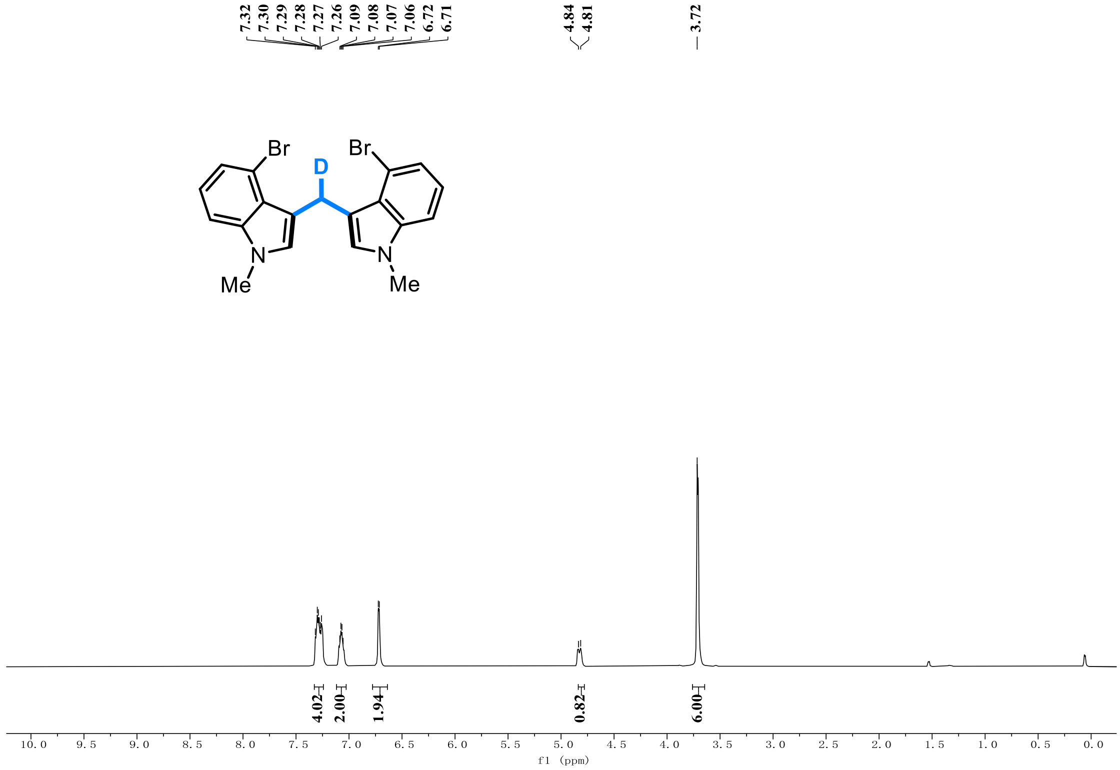
^{1}H NMR of **2b** (400 MHz, $CDCl_3$)



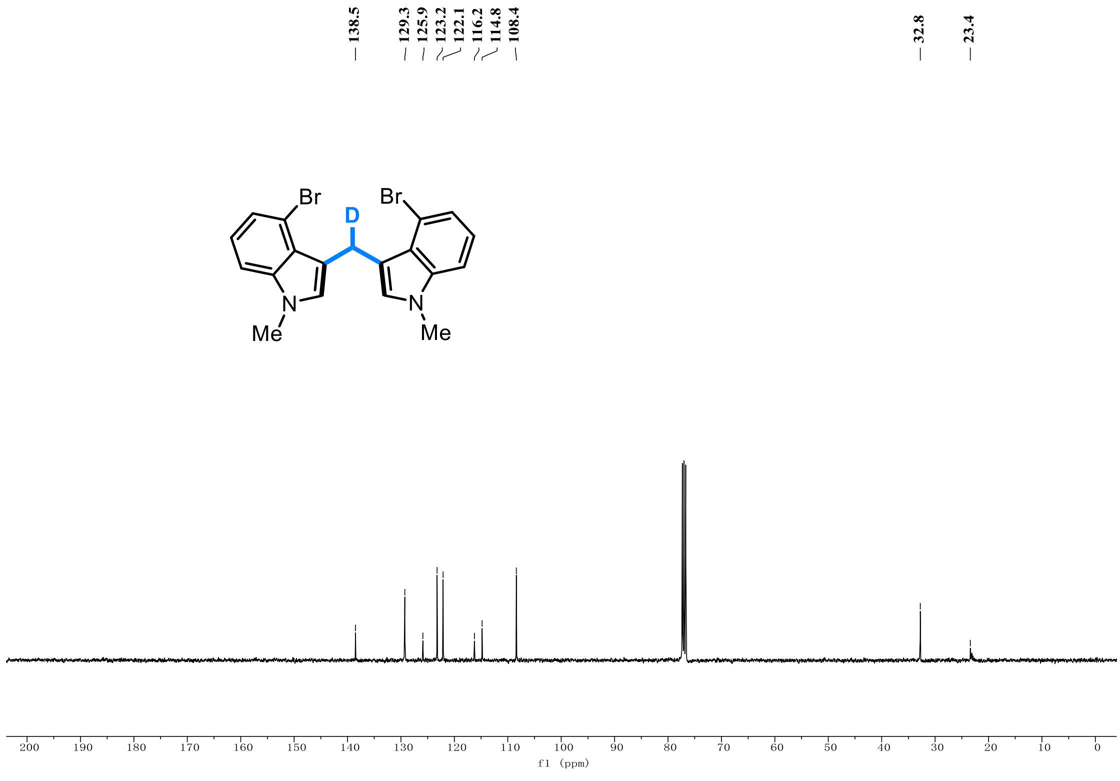
^{13}C NMR of **2b** (100 MHz, $CDCl_3$)



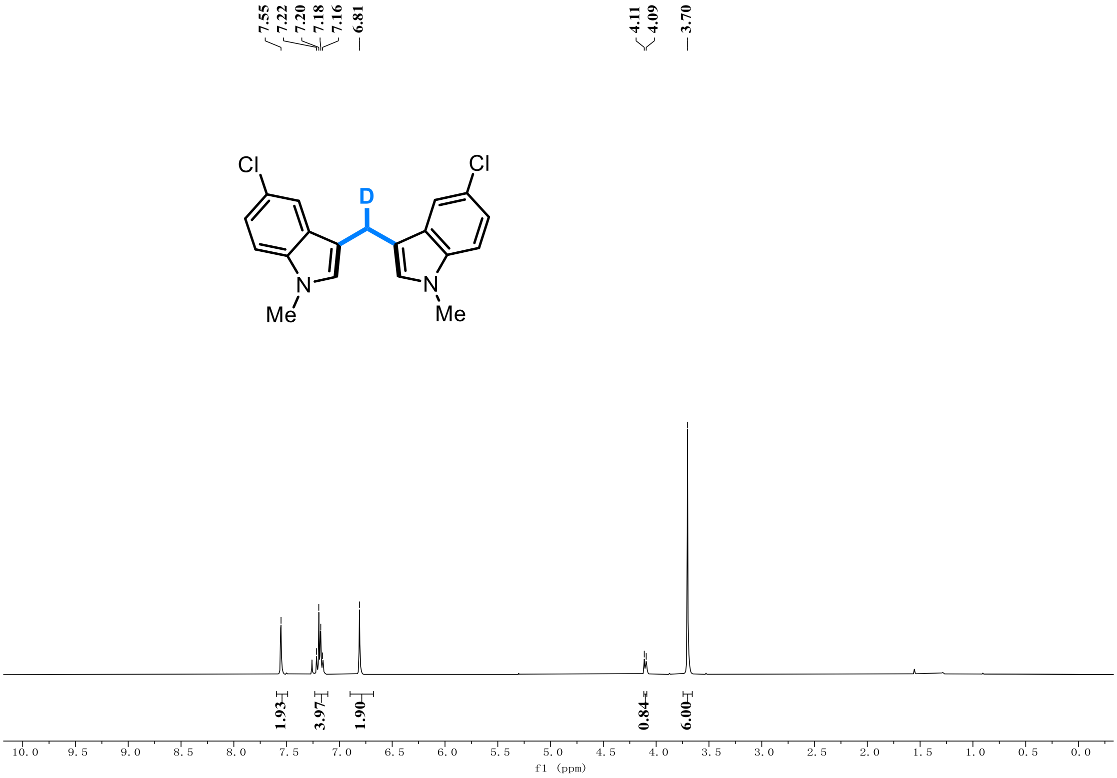
[1]H NMR of **2c** (400 MHz, $CDCl_3$)



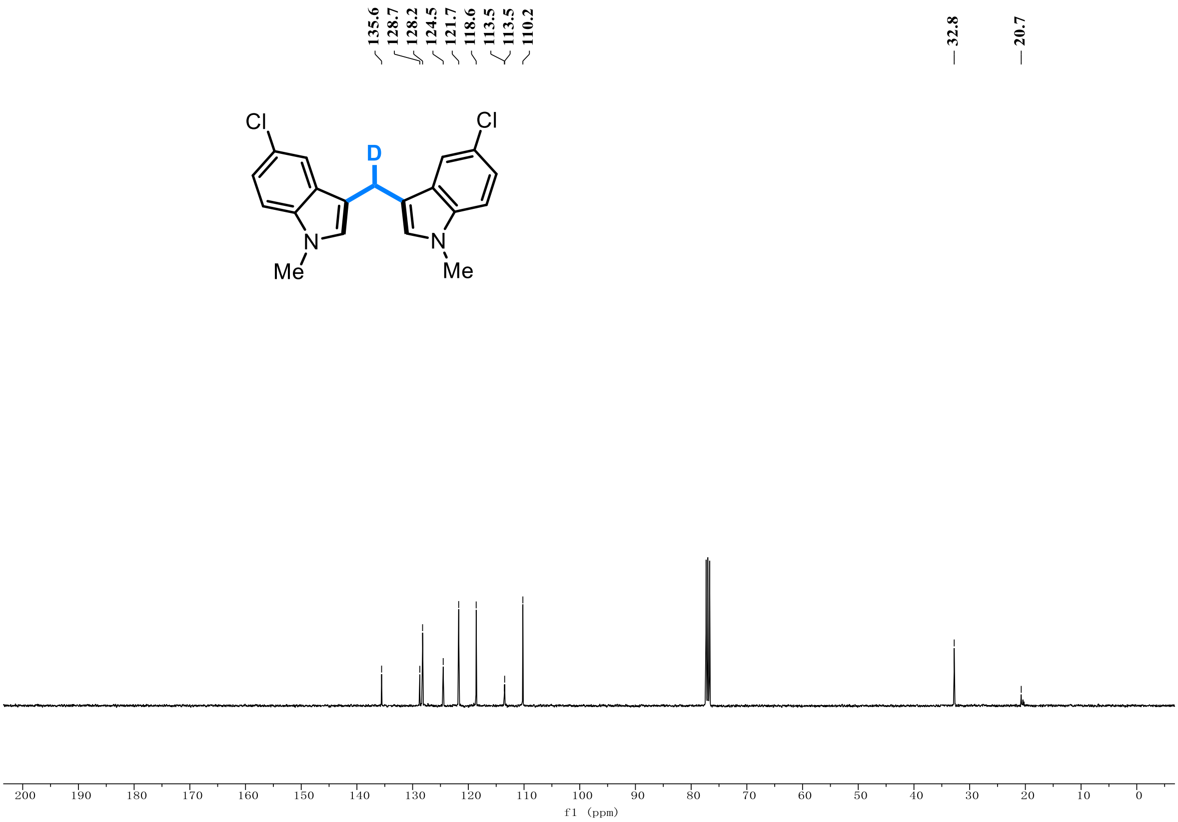
[13]C NMR of **2c** (100 MHz, $CDCl_3$)



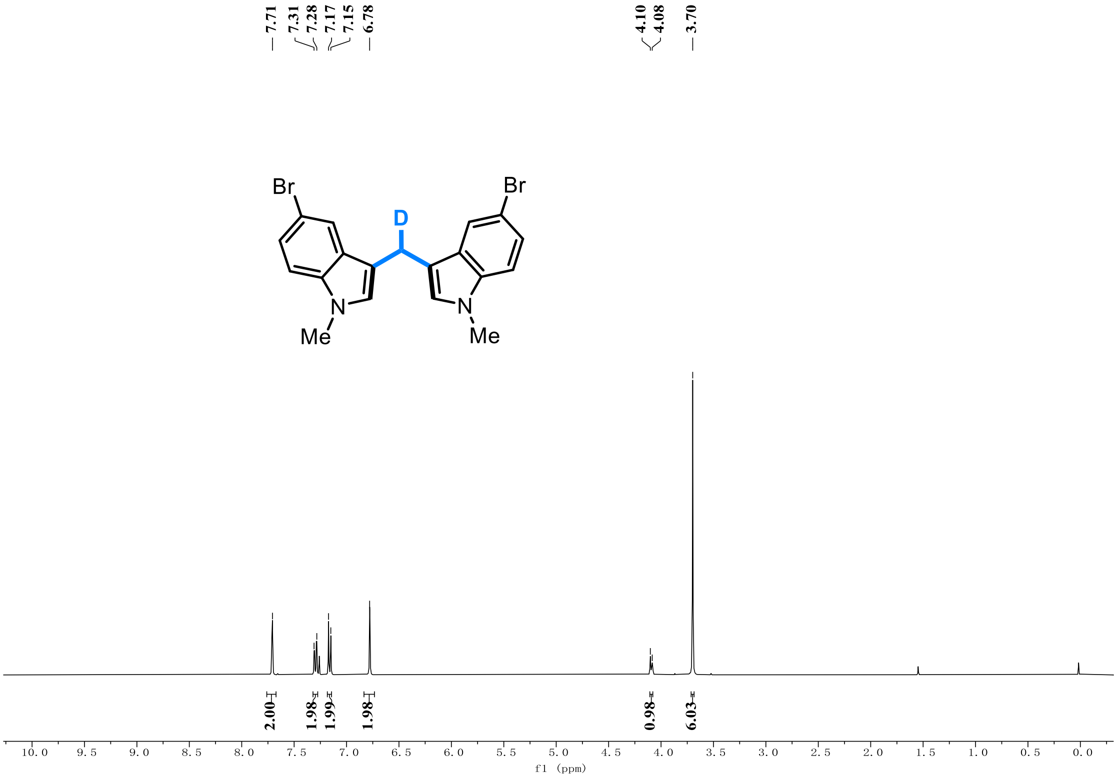
^{1}H NMR of **2d** (400 MHz, $CDCl_3$)



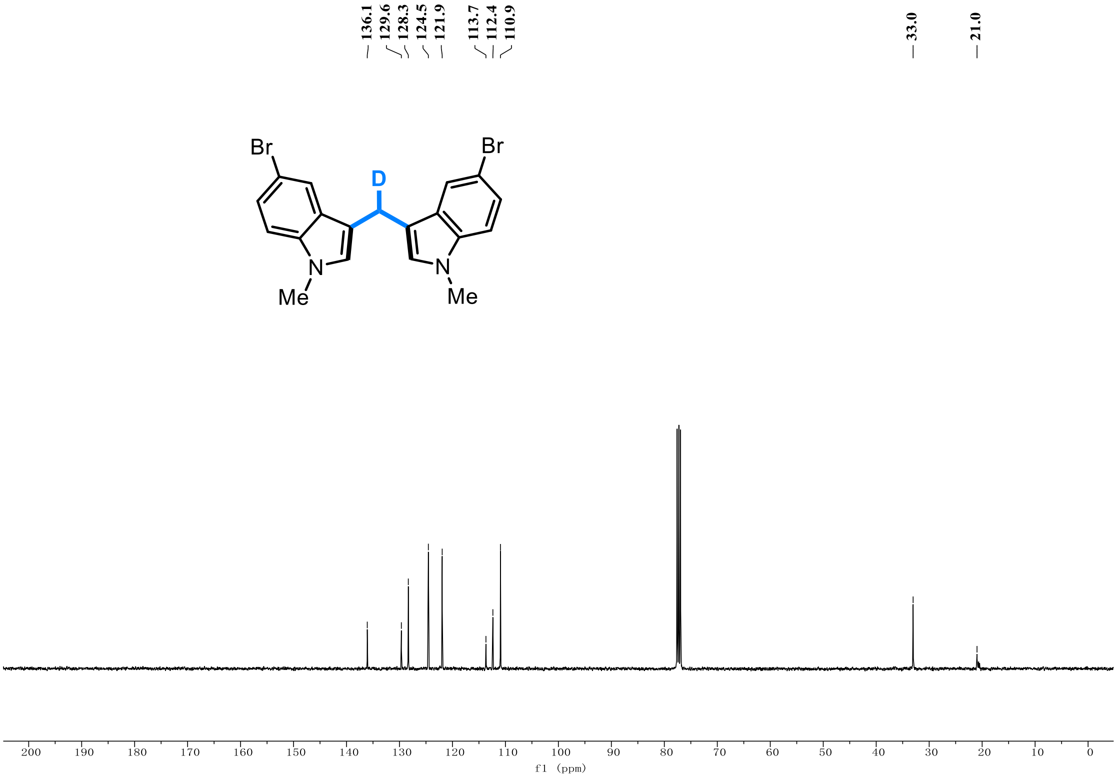
^{13}C NMR of **2d** (100 MHz, $CDCl_3$)



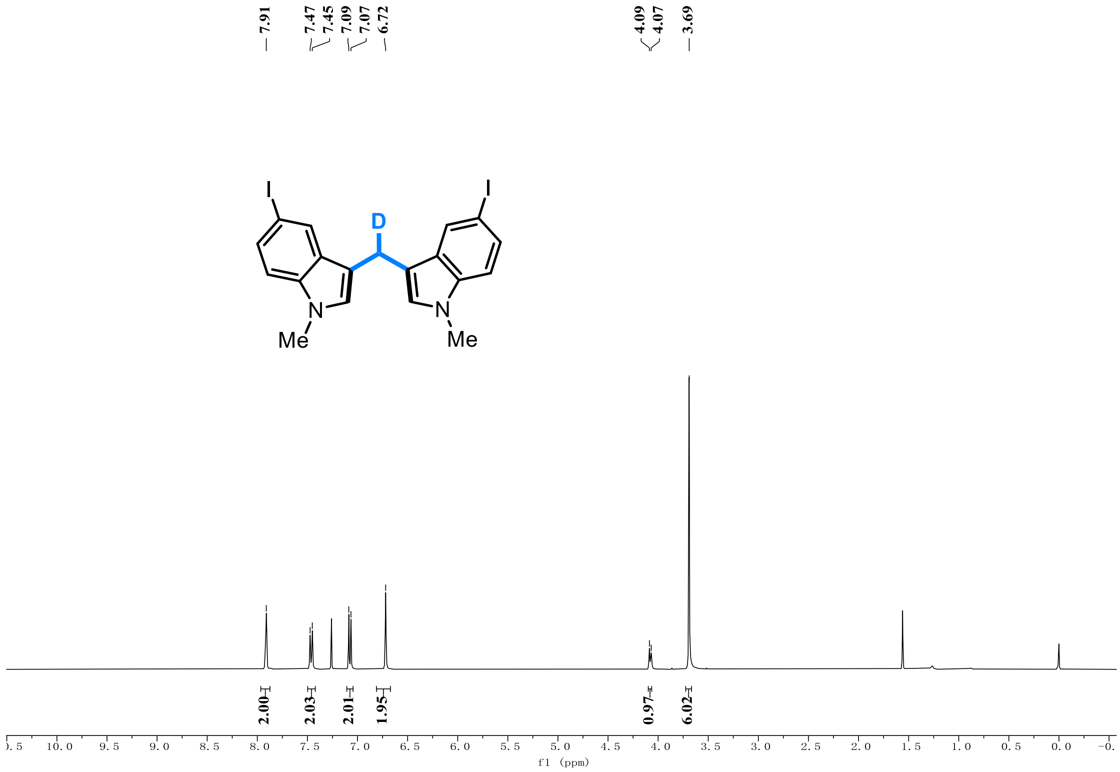
^{1}H NMR of **2e** (400 MHz, $CDCl_3$)



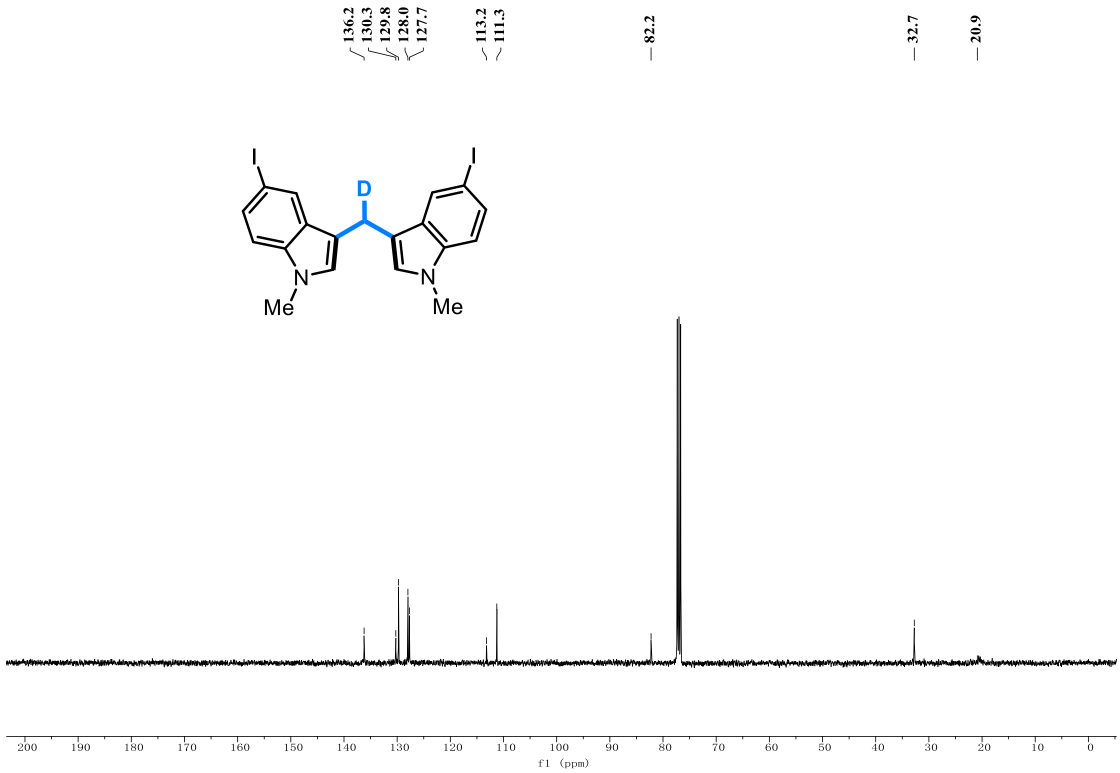
^{13}C NMR of **2e** (100 MHz, $CDCl_3$)



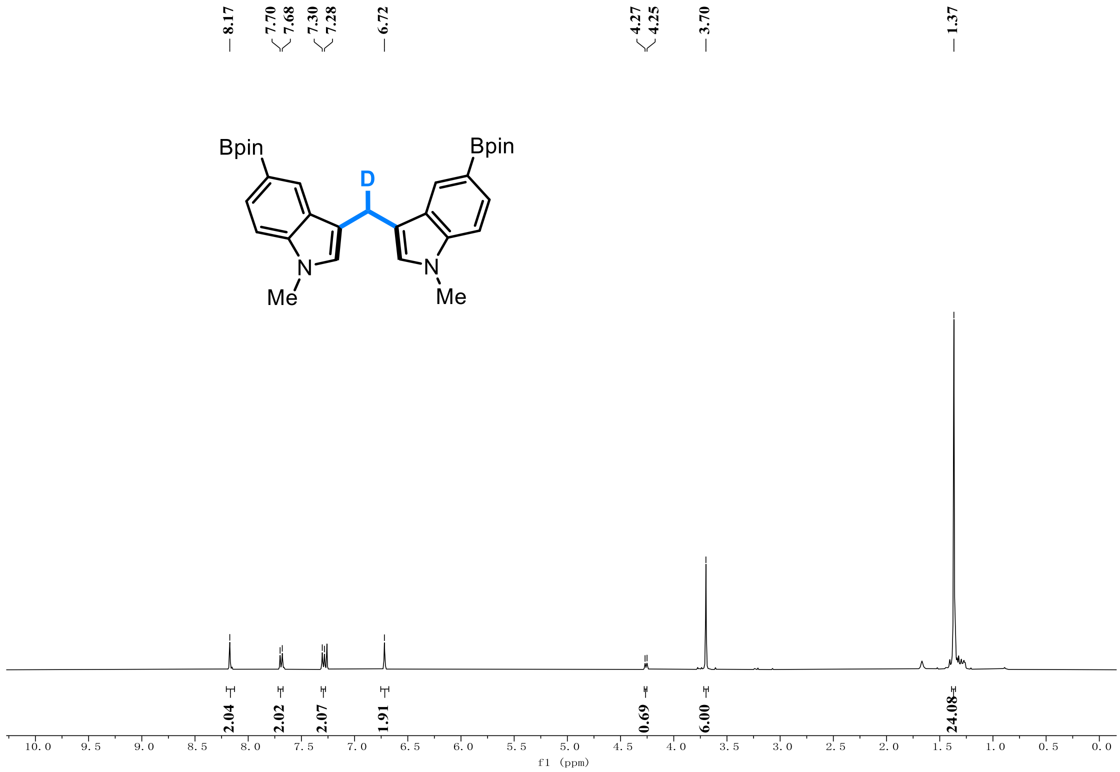
[1]H NMR of **2f** (400 MHz, $CDCl_3$)



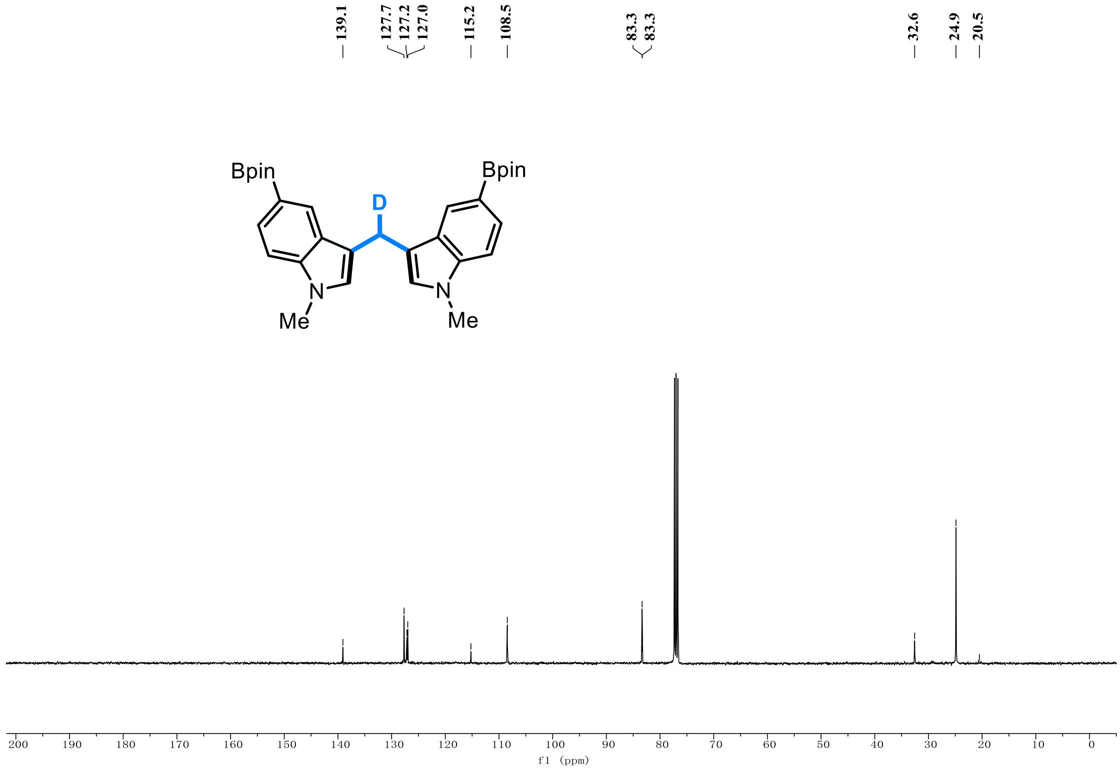
[13]C NMR of **2f** (100 MHz, $CDCl_3$)



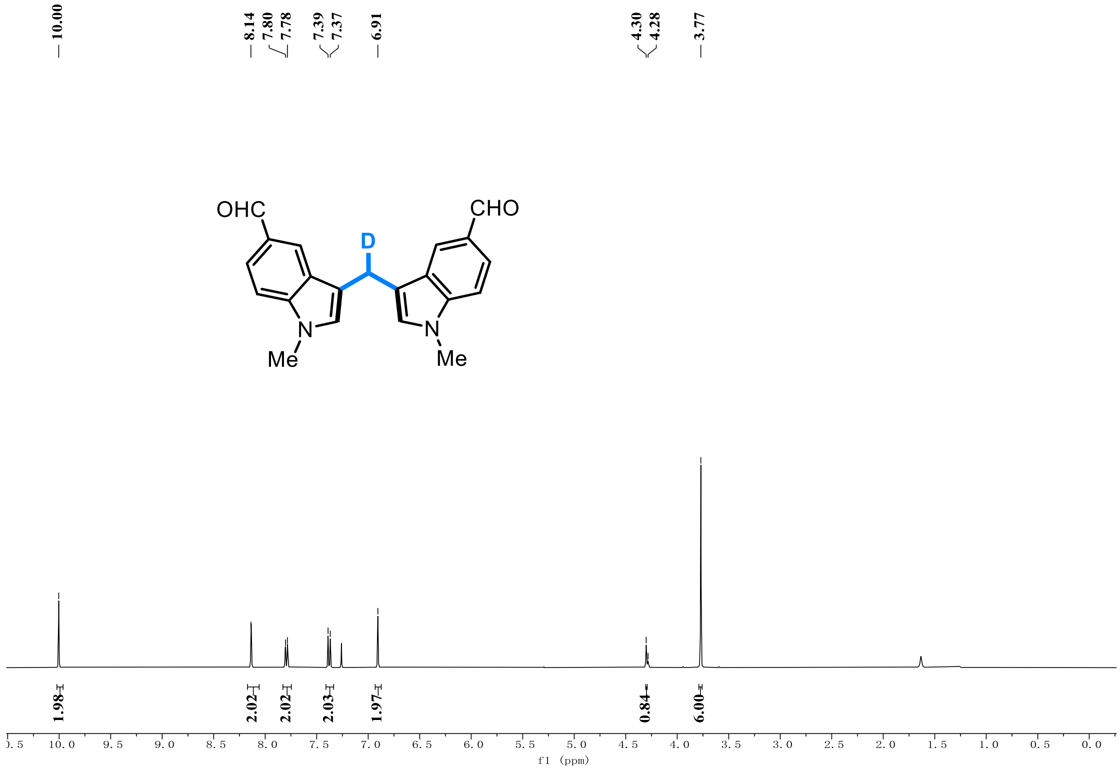
[1]H NMR of **2g** (400 MHz, $CDCl_3$)



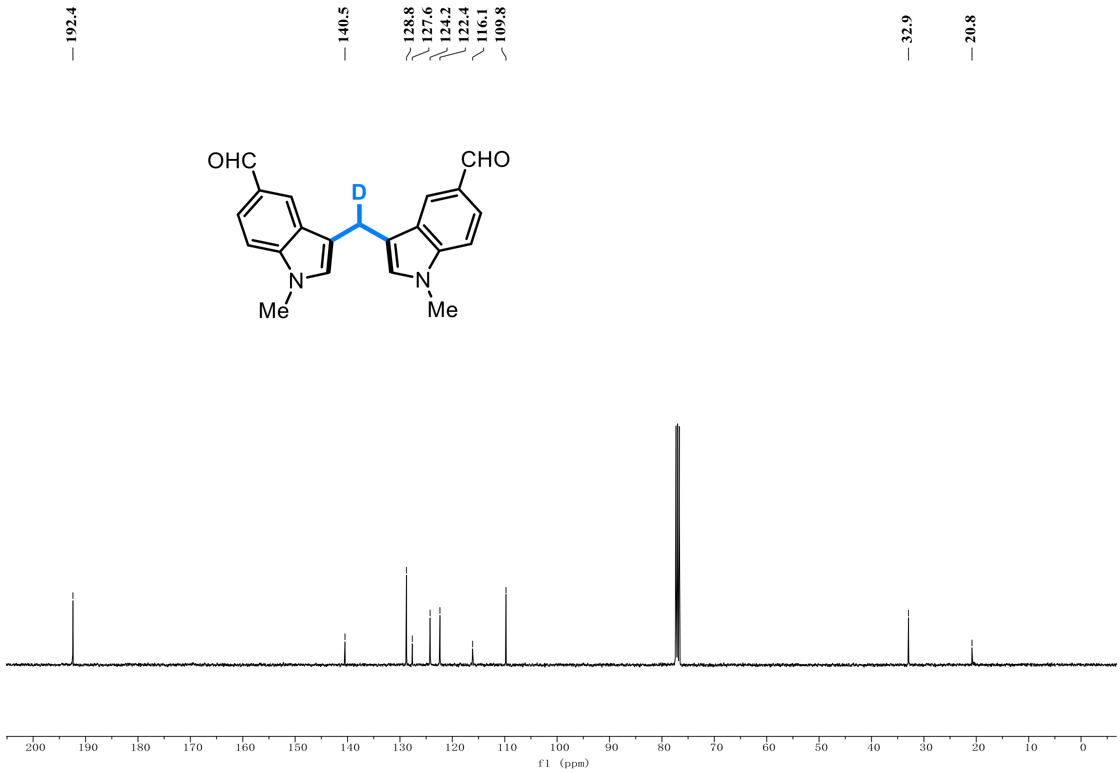
[13]C NMR of **2g** (100 MHz, $CDCl_3$)



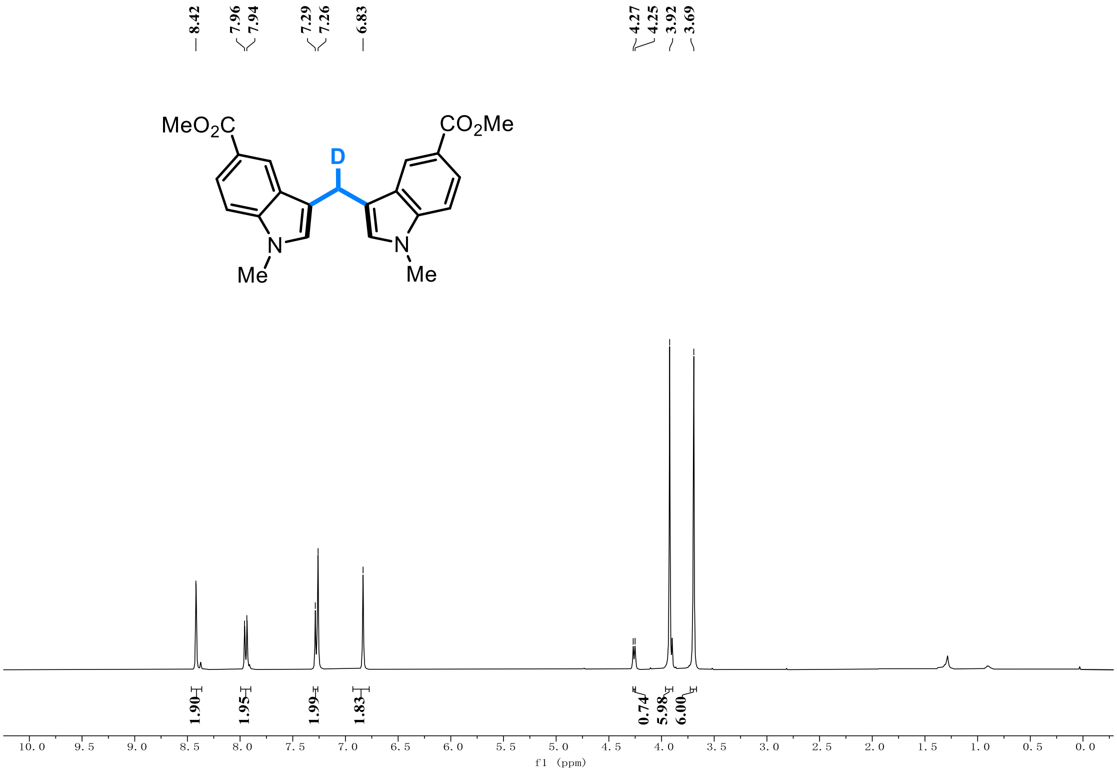
^{1}H NMR of **2h** (400 MHz, $CDCl_3$)



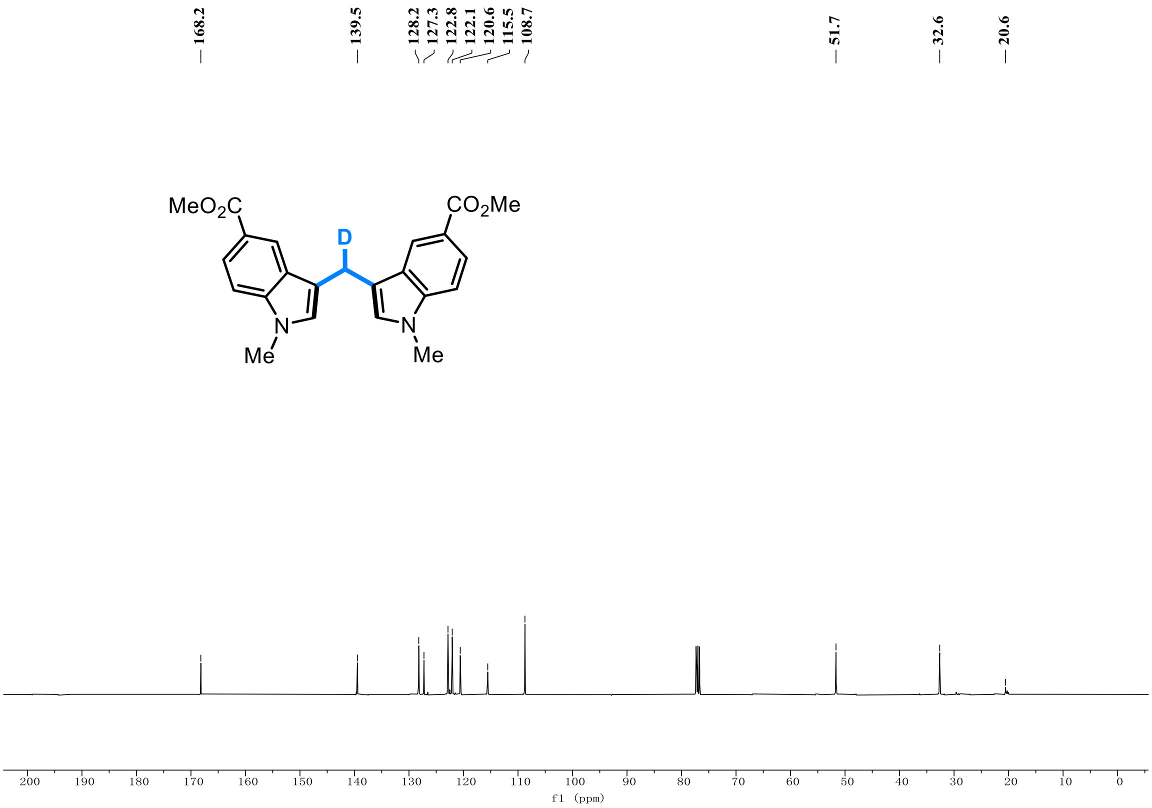
^{13}C NMR of **2h** (100 MHz, $CDCl_3$)



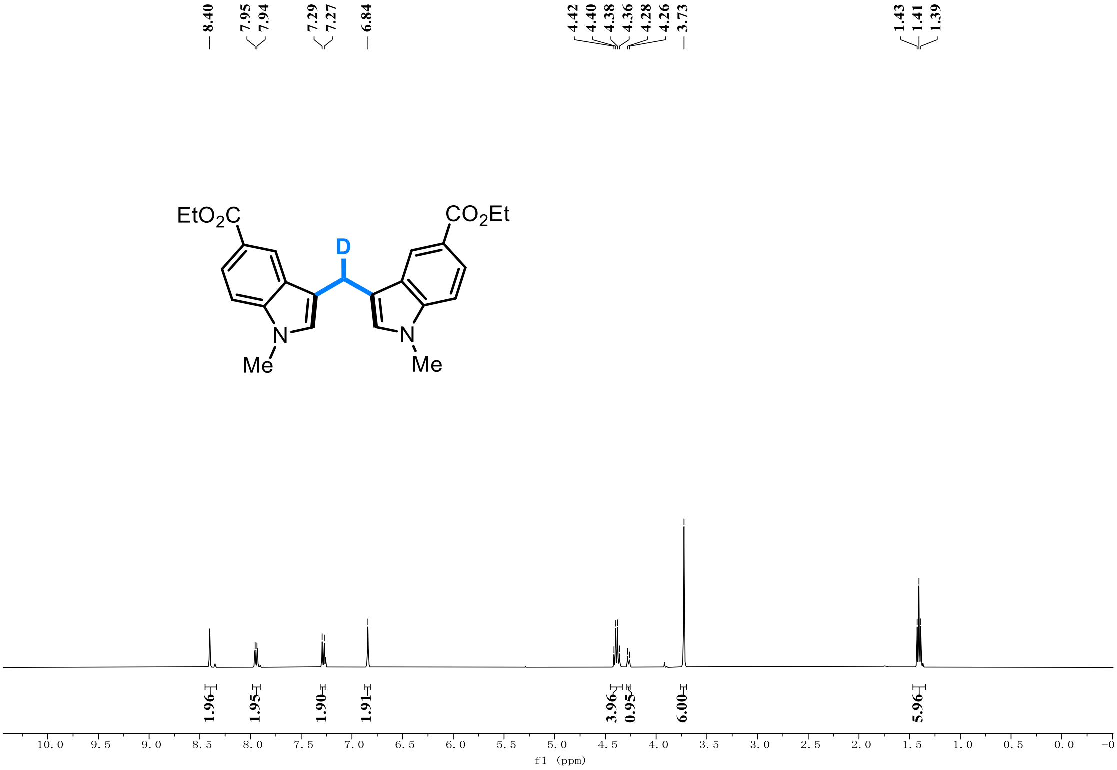
^{1}H NMR of **2i** (400 MHz, $CDCl_3$)



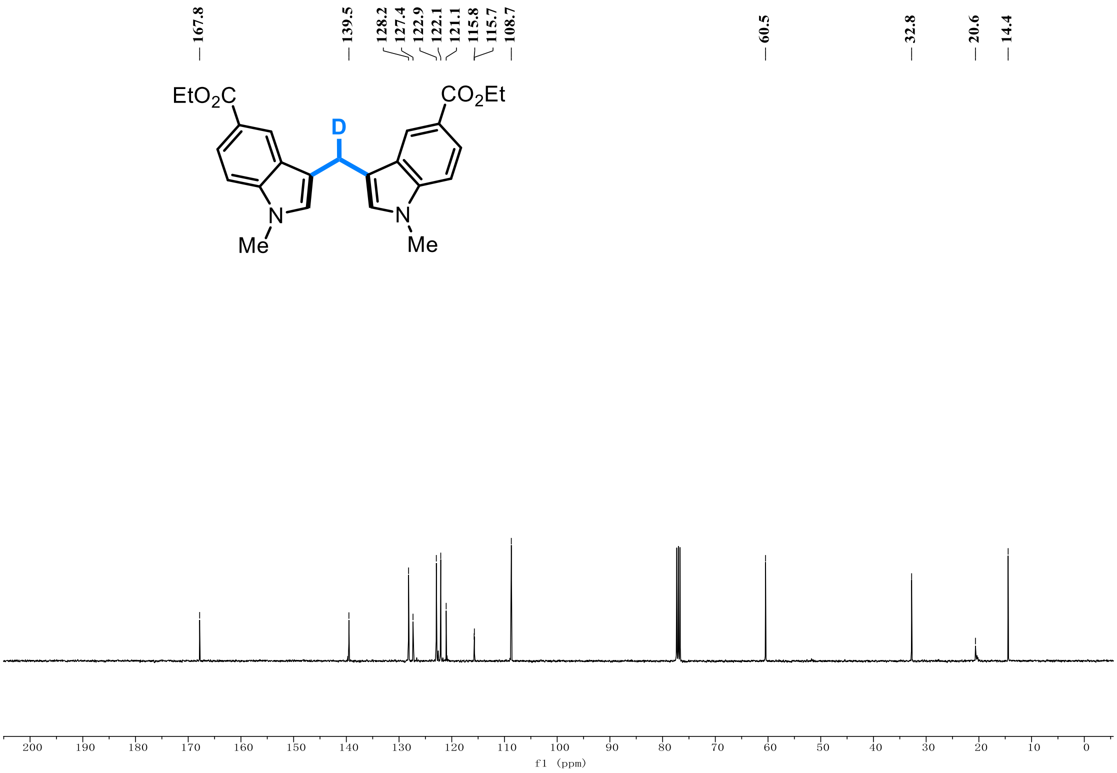
^{13}C NMR of **2i** (100 MHz, $CDCl_3$)



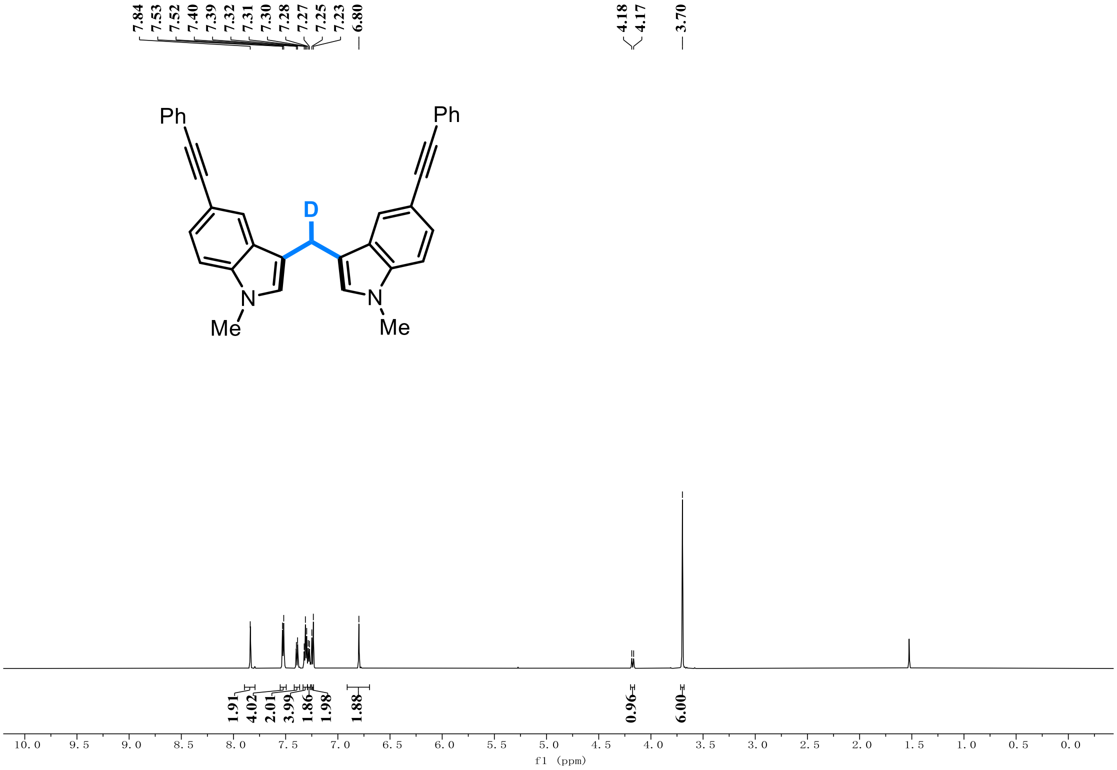
^{1}H NMR of **2j** (400 MHz, $CDCl_3$)



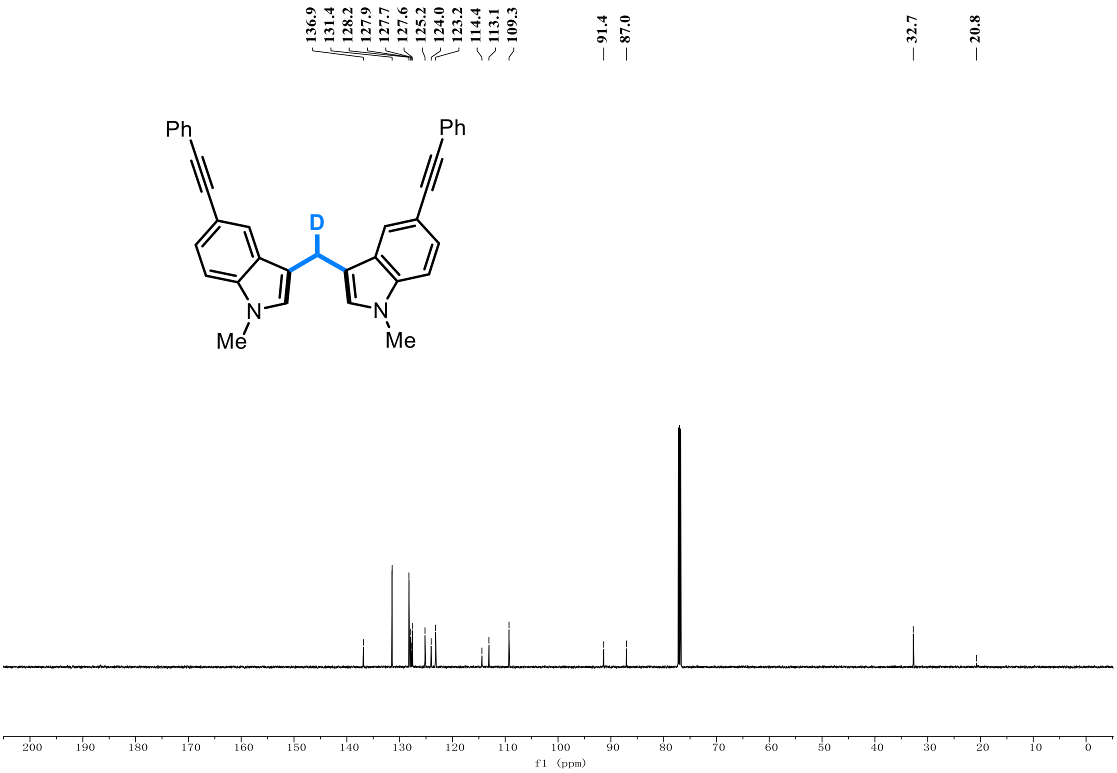
^{13}C NMR of **2j** (100 MHz, $CDCl_3$)



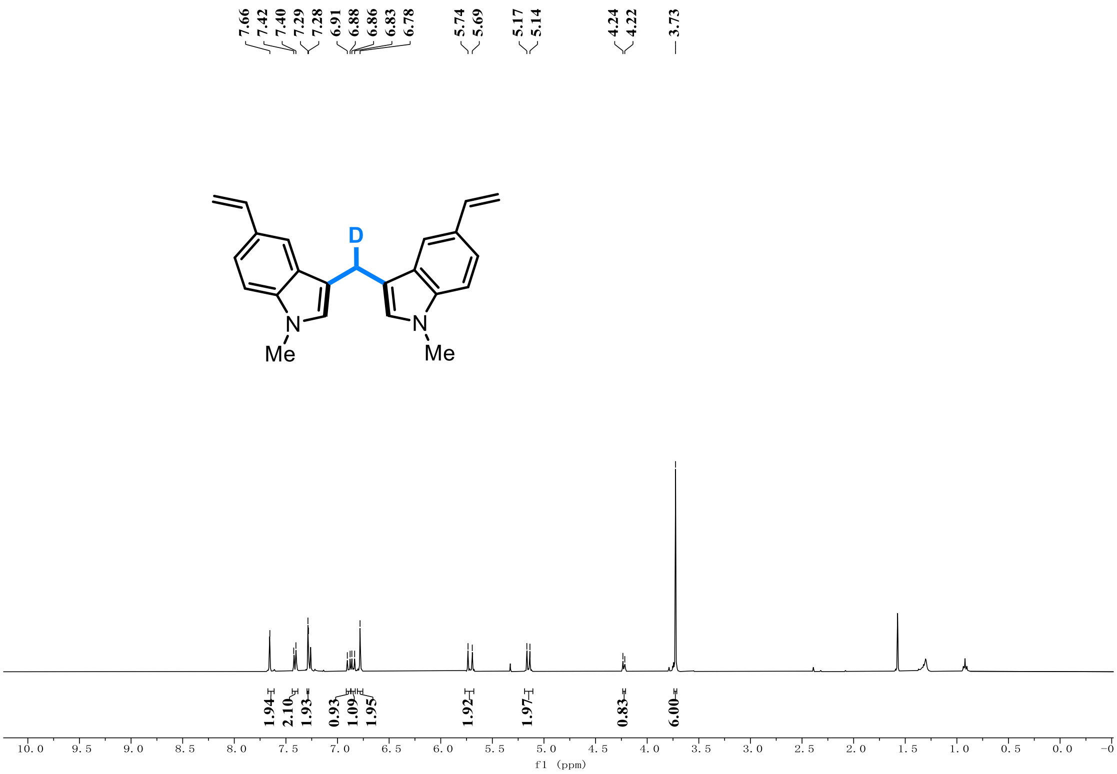
^{1}H NMR of **2k** (400 MHz, $CDCl_3$)



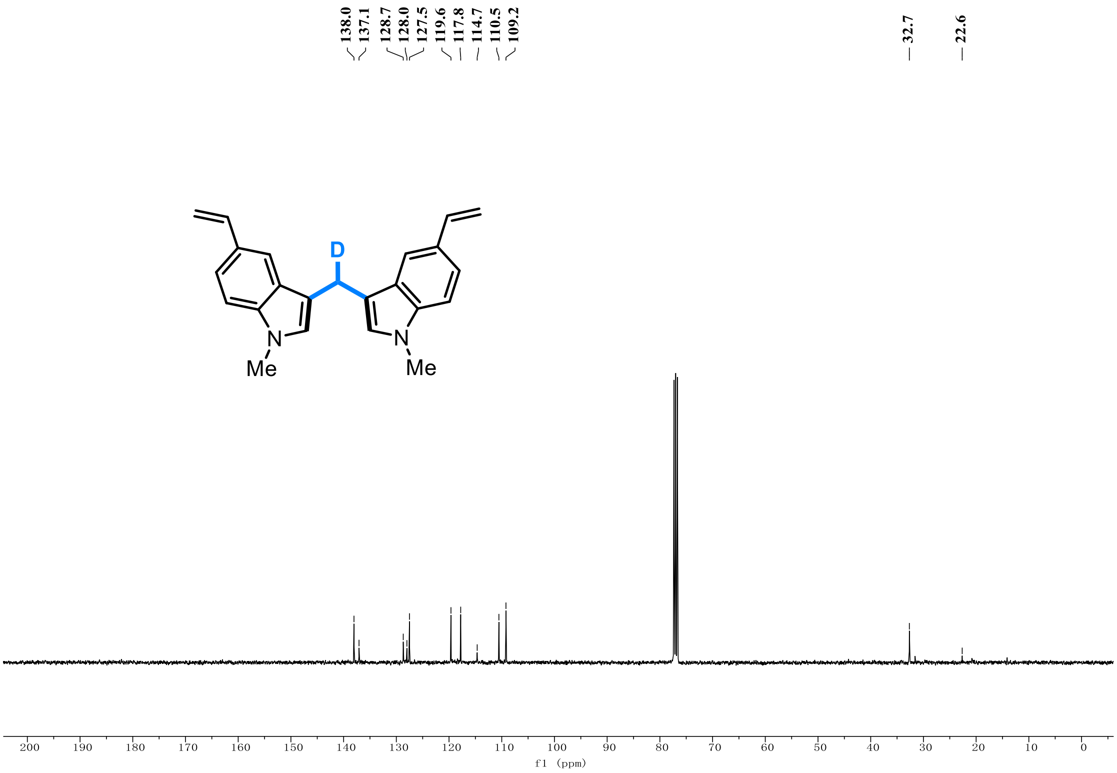
^{13}C NMR of **2k** (100 MHz, $CDCl_3$)



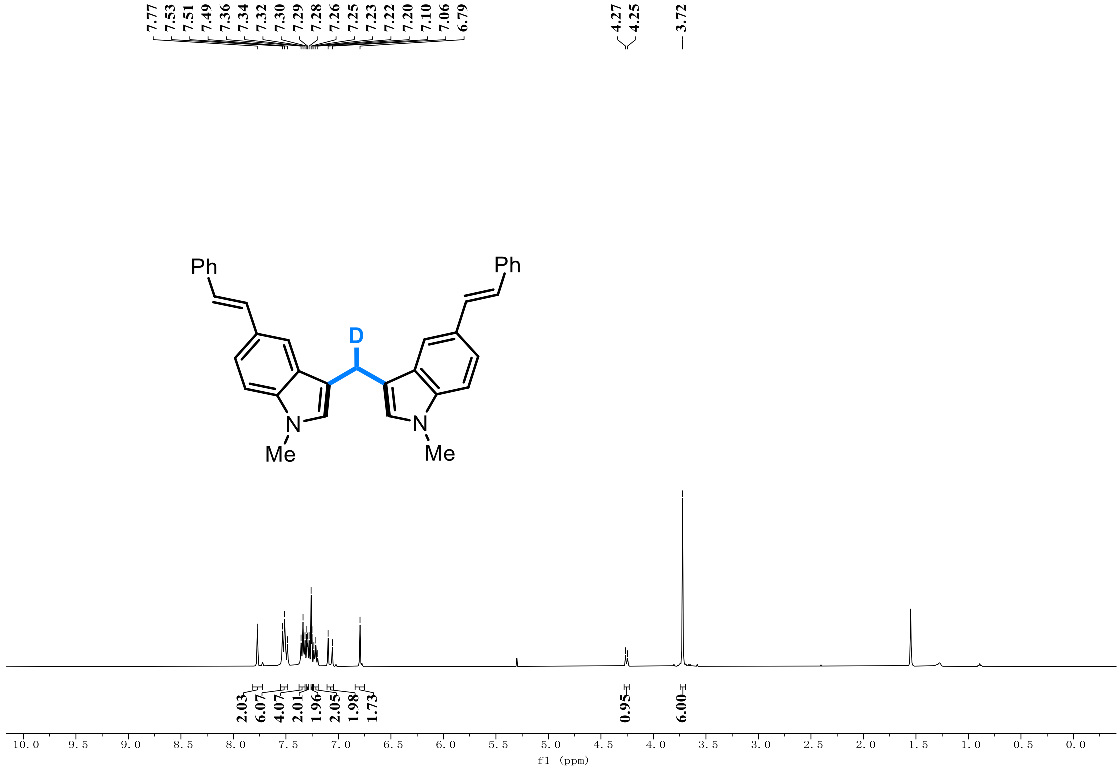
[1]H NMR of **2l** (400 MHz, $CDCl_3$)



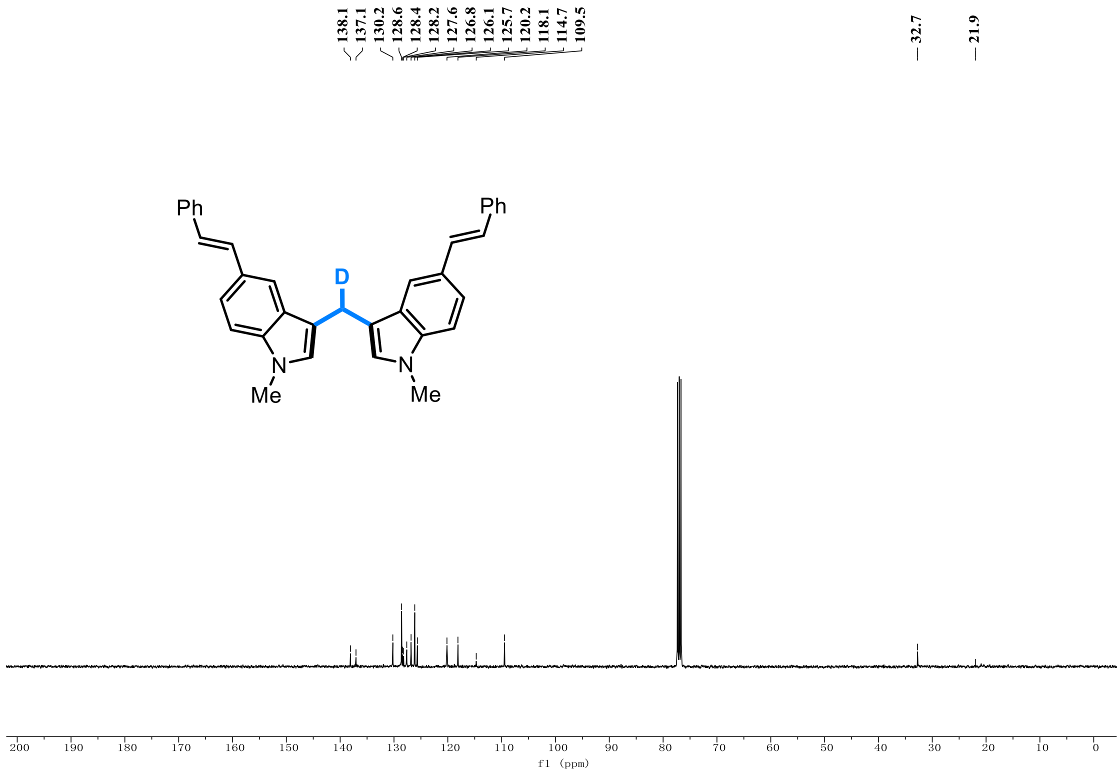
[13]C NMR of **2l** (100 MHz, $CDCl_3$)



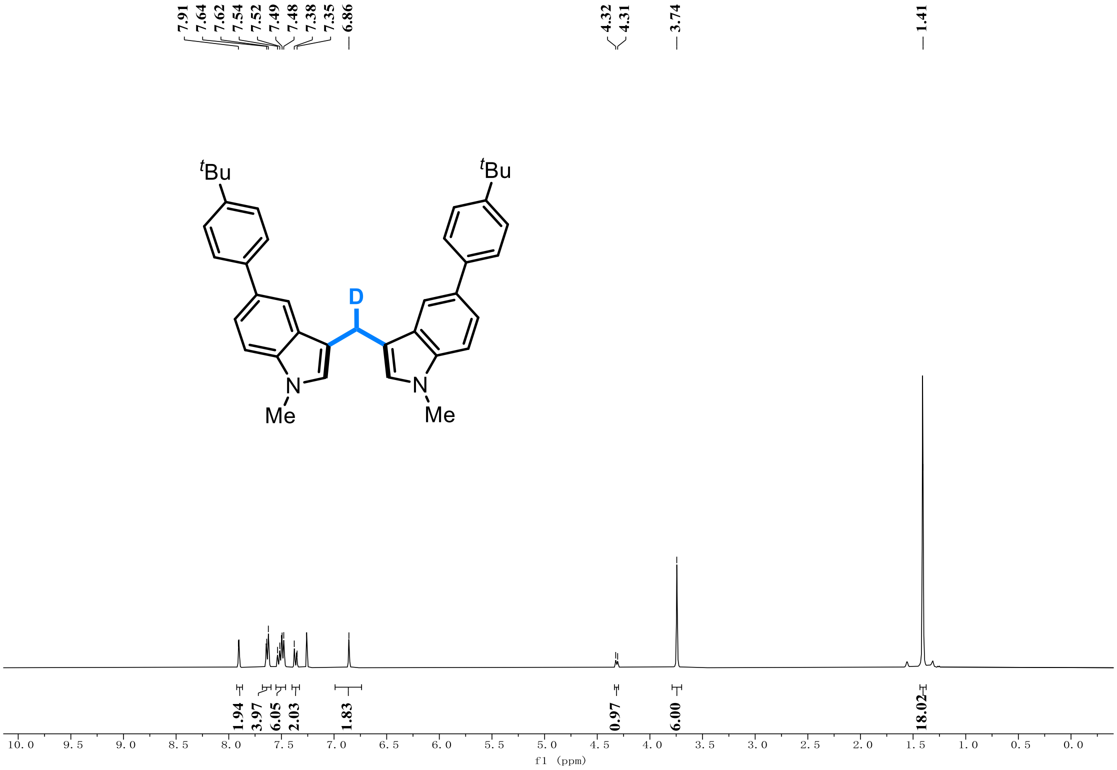
^{1}H NMR of **2m** (400 MHz, $CDCl_3$)



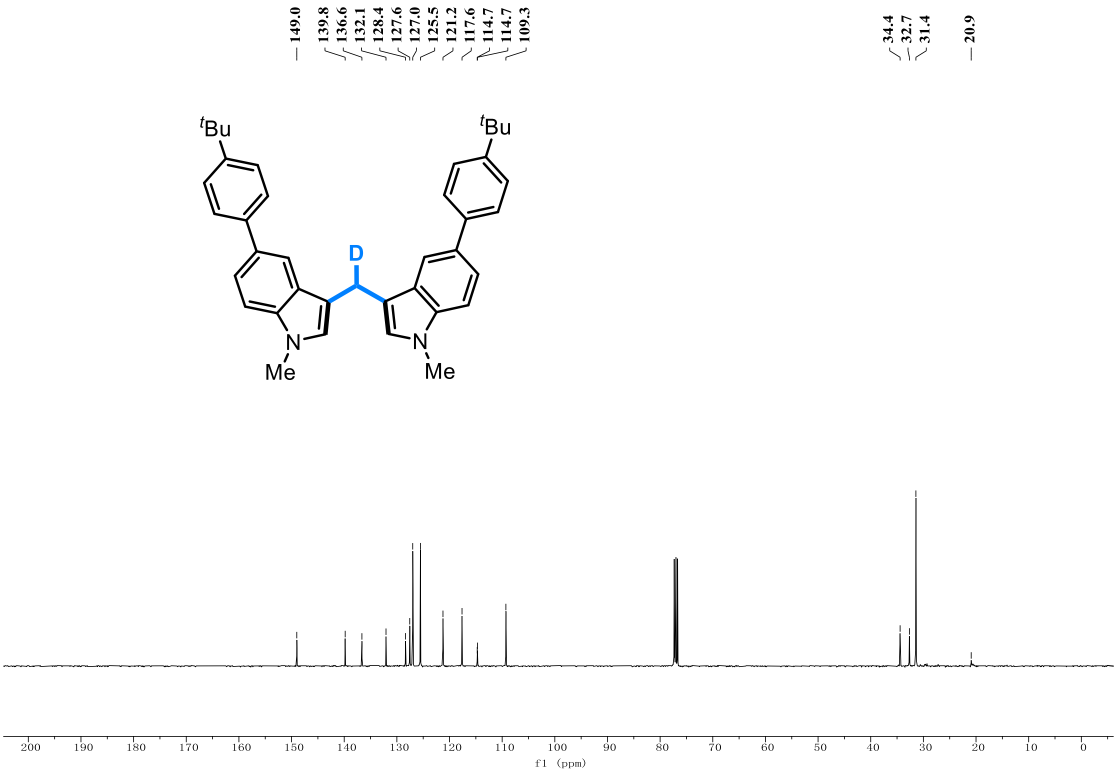
^{13}C NMR of **2m** (100 MHz, $CDCl_3$)



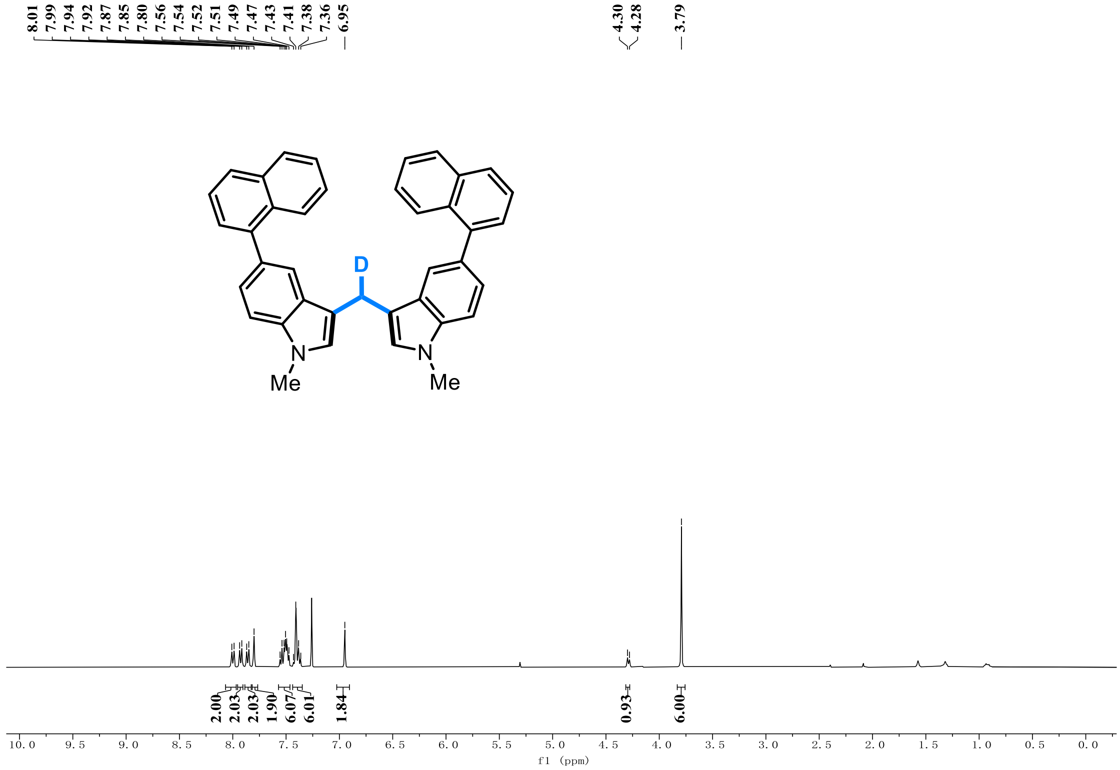
^{1}H NMR of **2n** (400 MHz, $CDCl_3$)



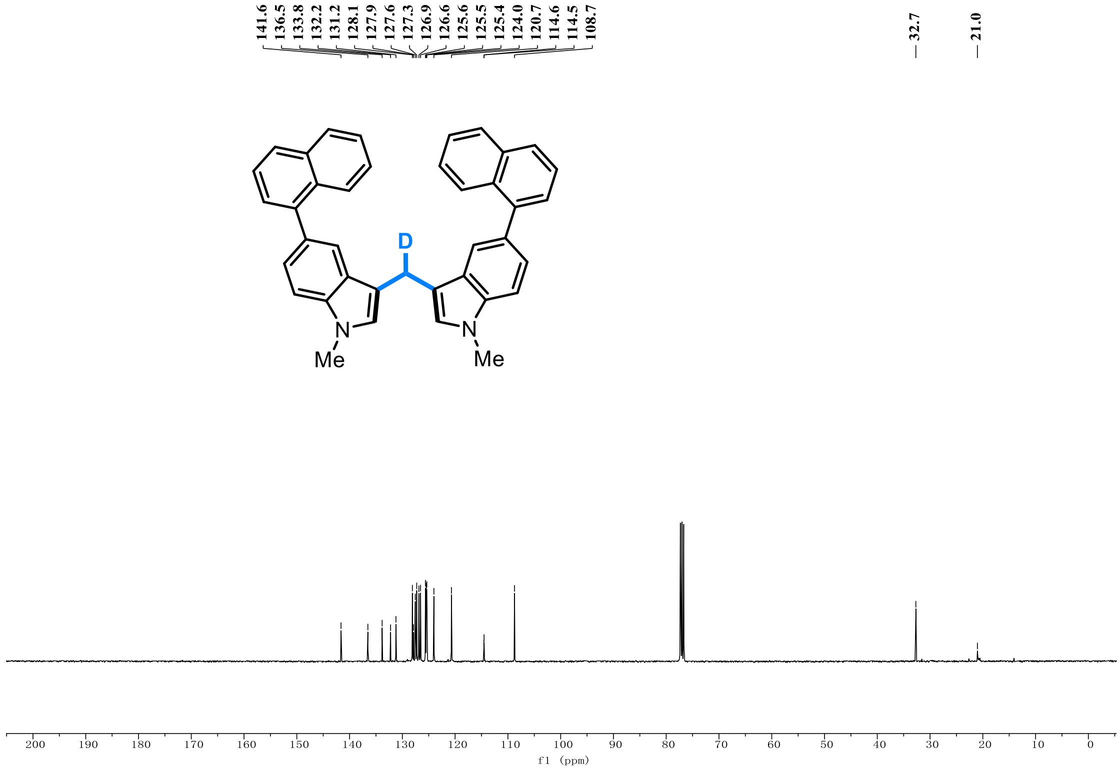
^{13}C NMR of **2n** (100 MHz, $CDCl_3$)



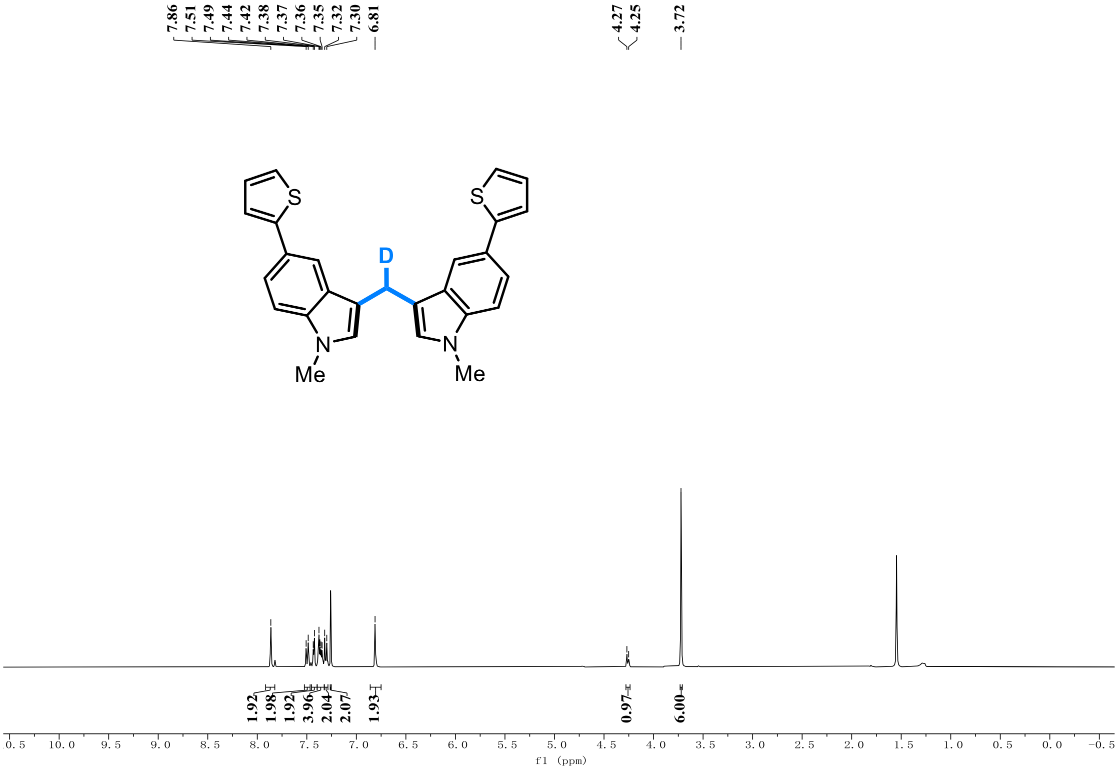
^{1}H NMR of **2o** (400 MHz, $CDCl_3$)



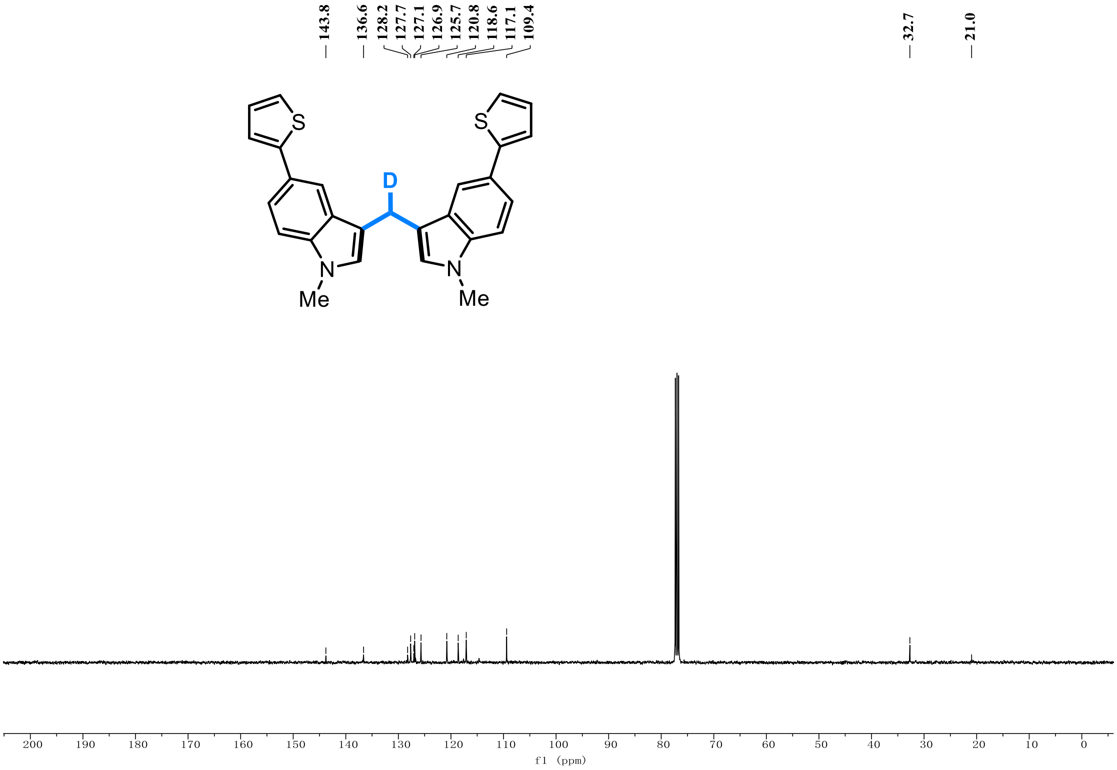
^{13}C NMR of **2o** (100 MHz, $CDCl_3$)



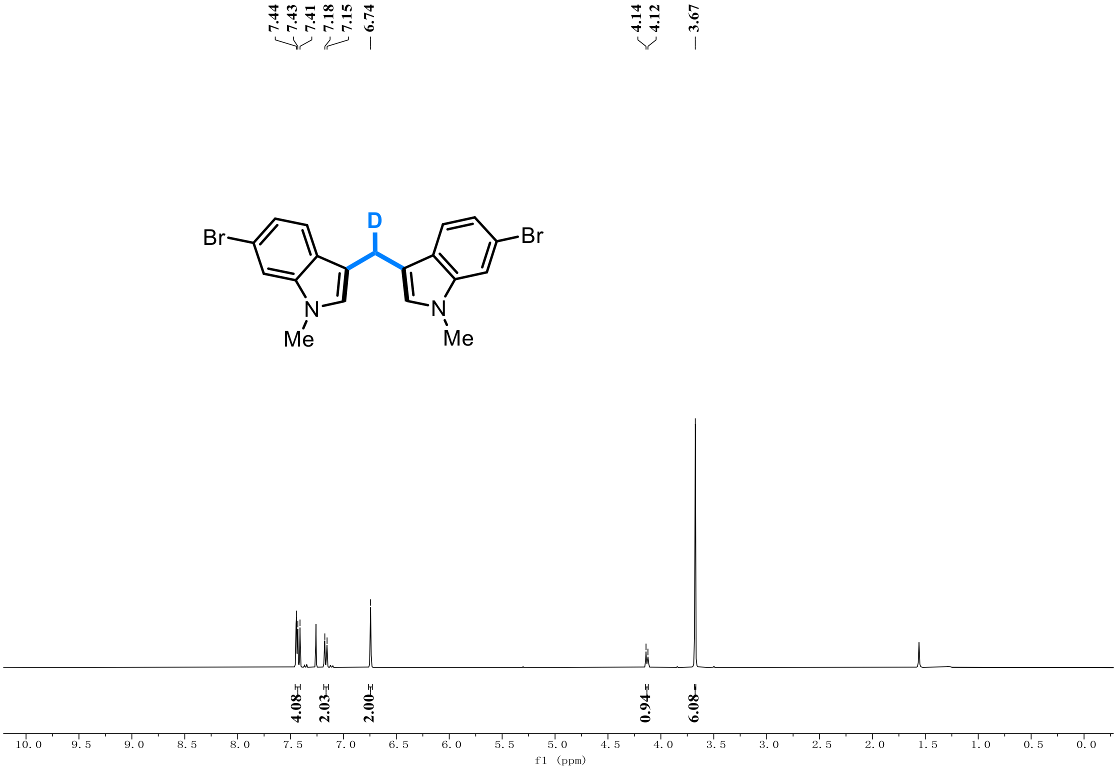
^{1}H NMR of **2p** (400 MHz, $CDCl_3$)



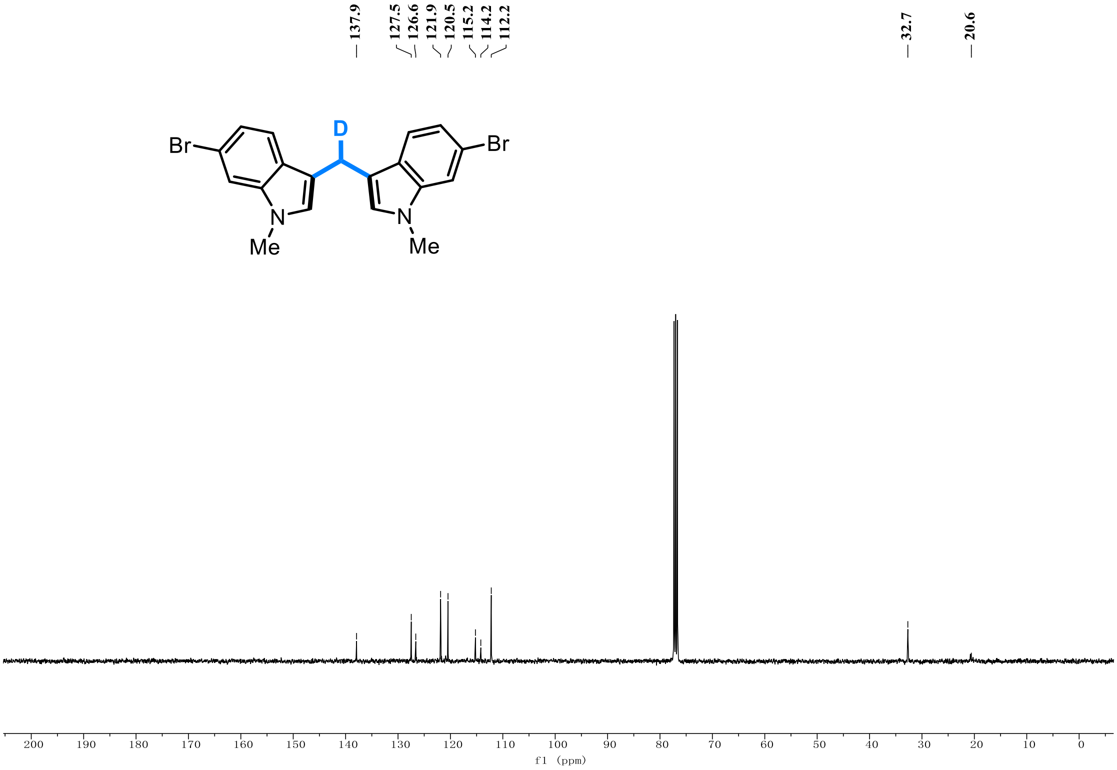
^{13}C NMR of **2p** (100 MHz, $CDCl_3$)



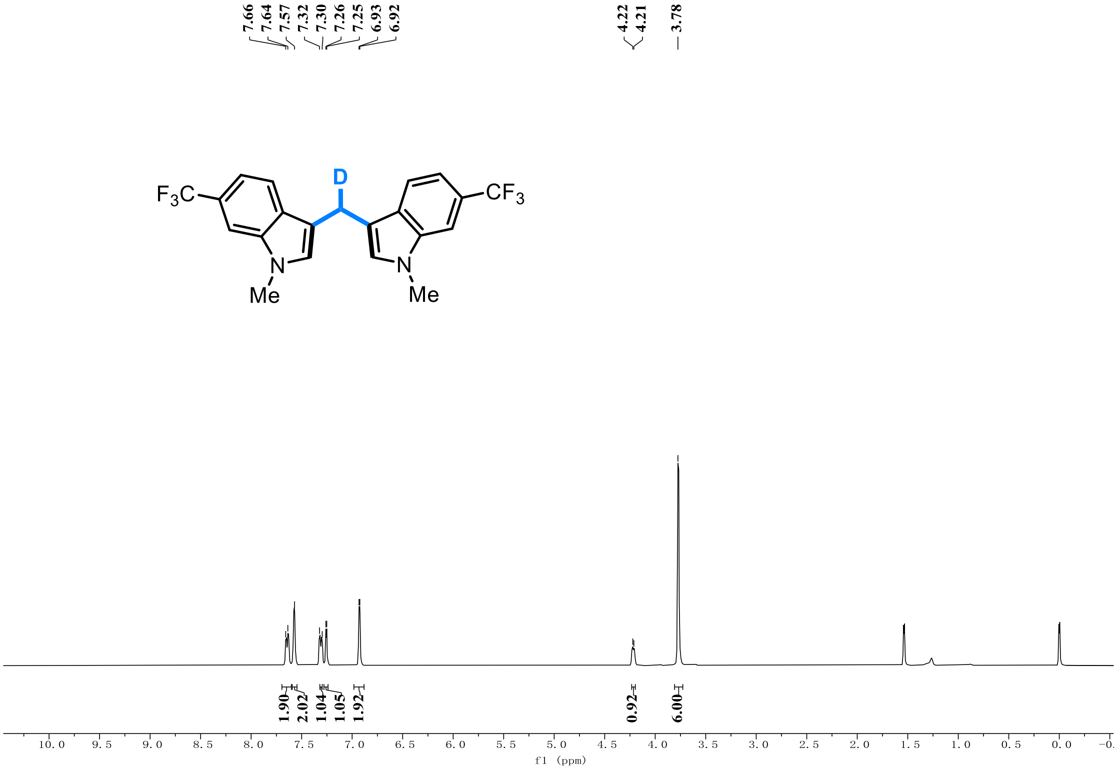
[1]H NMR of **2q** (400 MHz, $CDCl_3$)



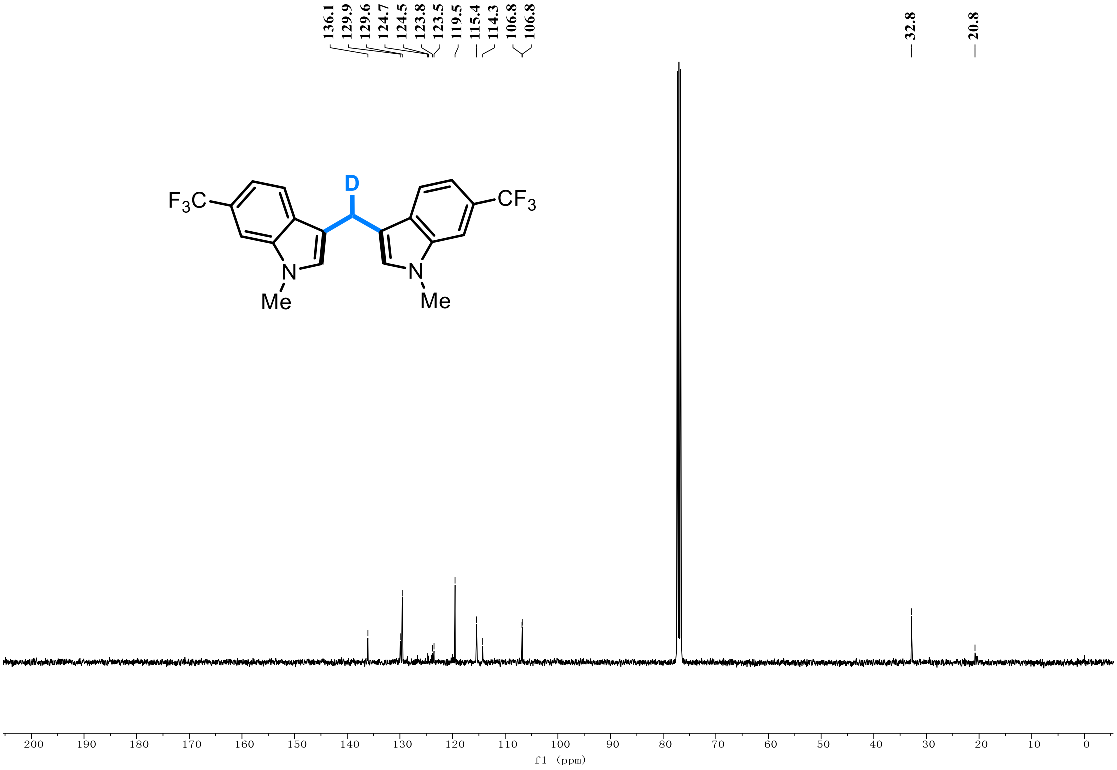
[13]C NMR of **2q** (100 MHz, $CDCl_3$)



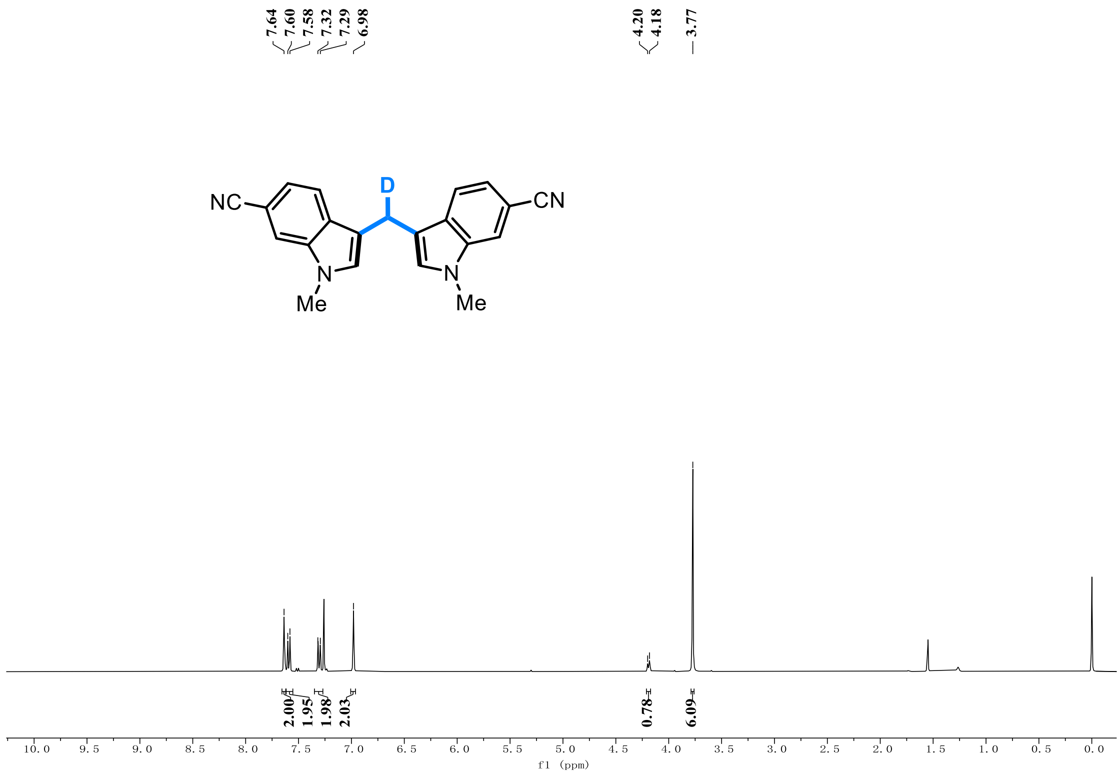
^1H NMR of **2r** (400 MHz, $CDCl_3$)



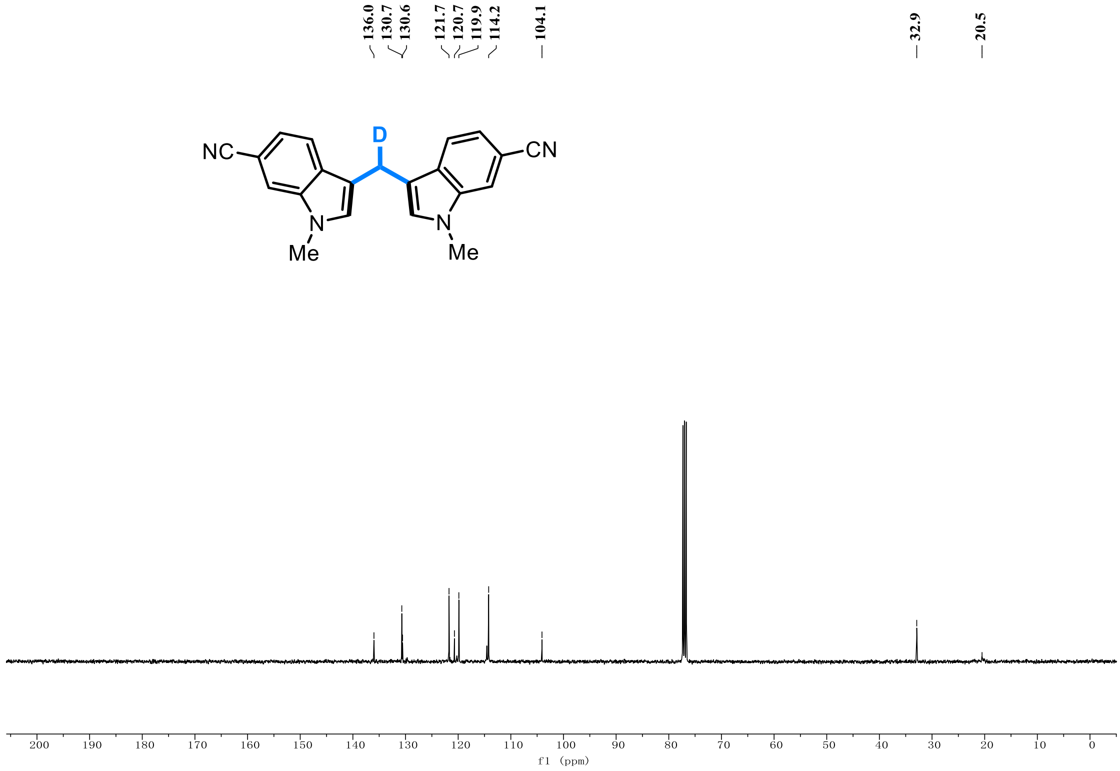
^{13}C NMR of **2r** (100 MHz, $CDCl_3$)



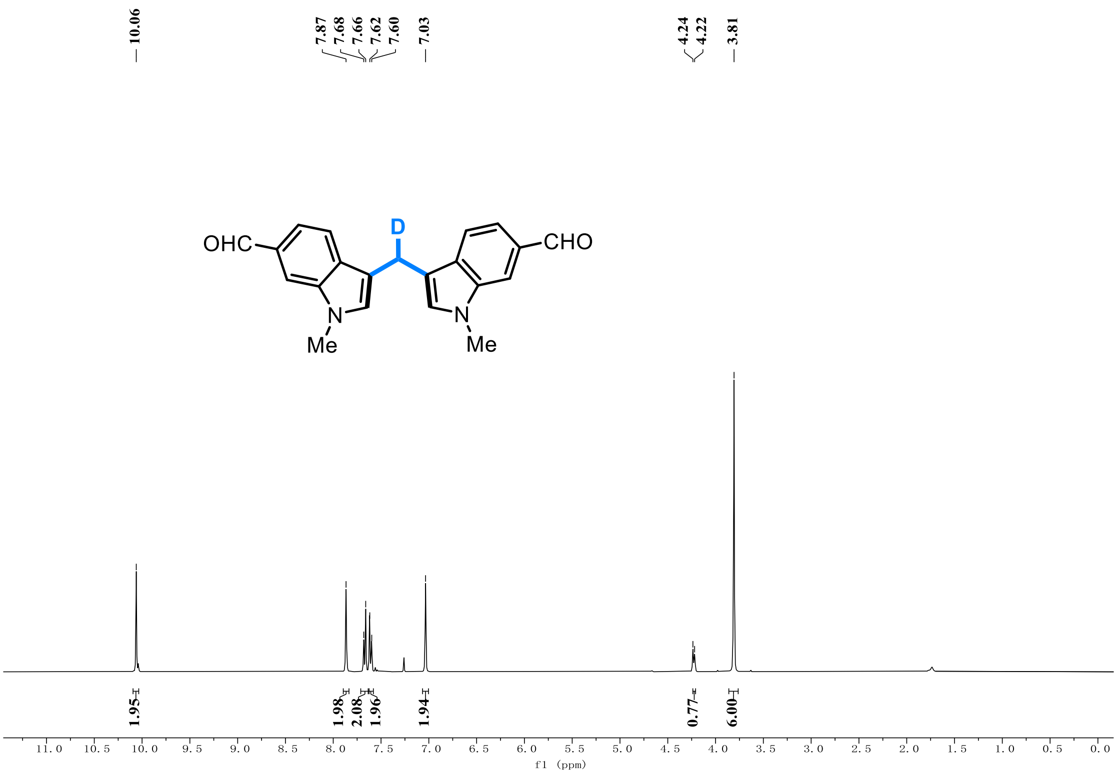
^{1}H NMR of **2s** (400 MHz, $CDCl_3$)



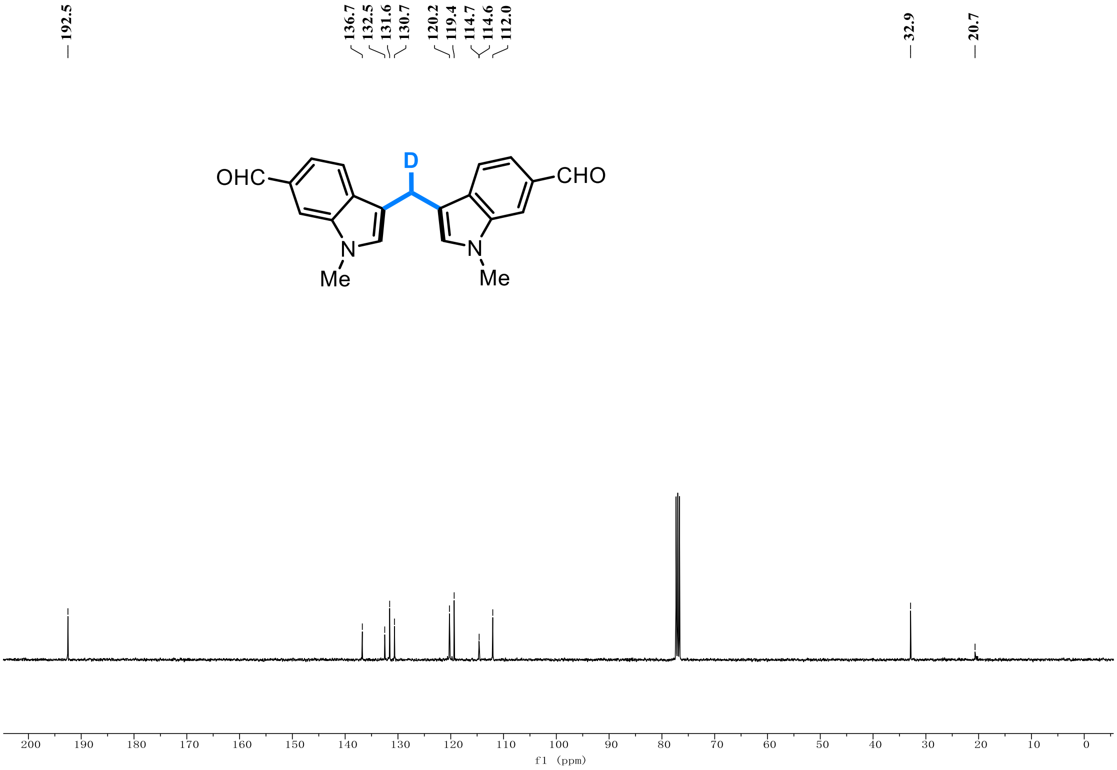
^{13}C NMR of **2s** (100 MHz, $CDCl_3$)



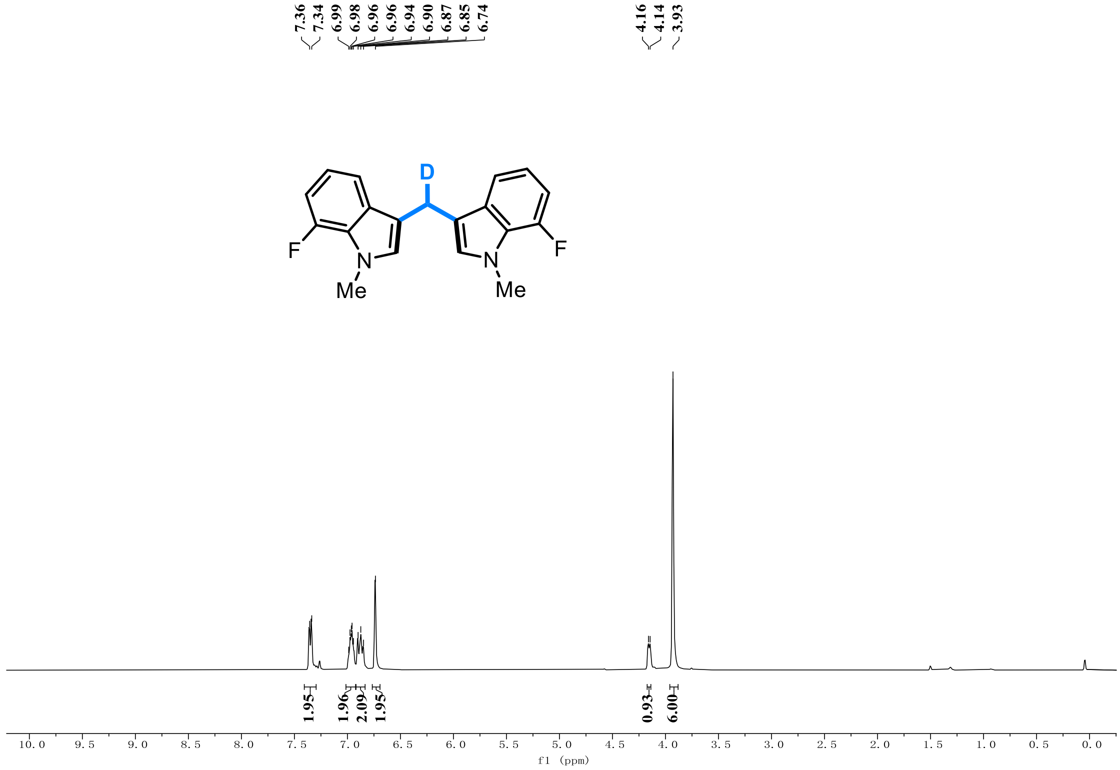
^{1}H NMR of **2t** (400 MHz, $CDCl_3$)



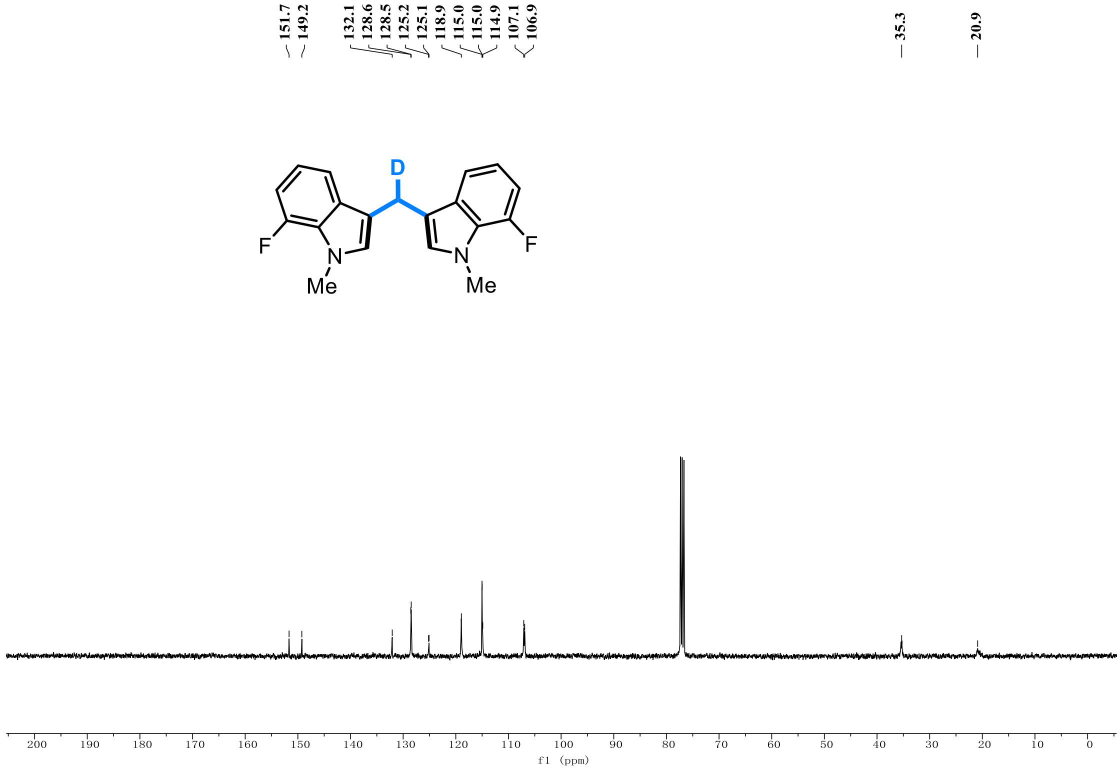
^{13}C NMR of **2t** (100 MHz, $CDCl_3$)



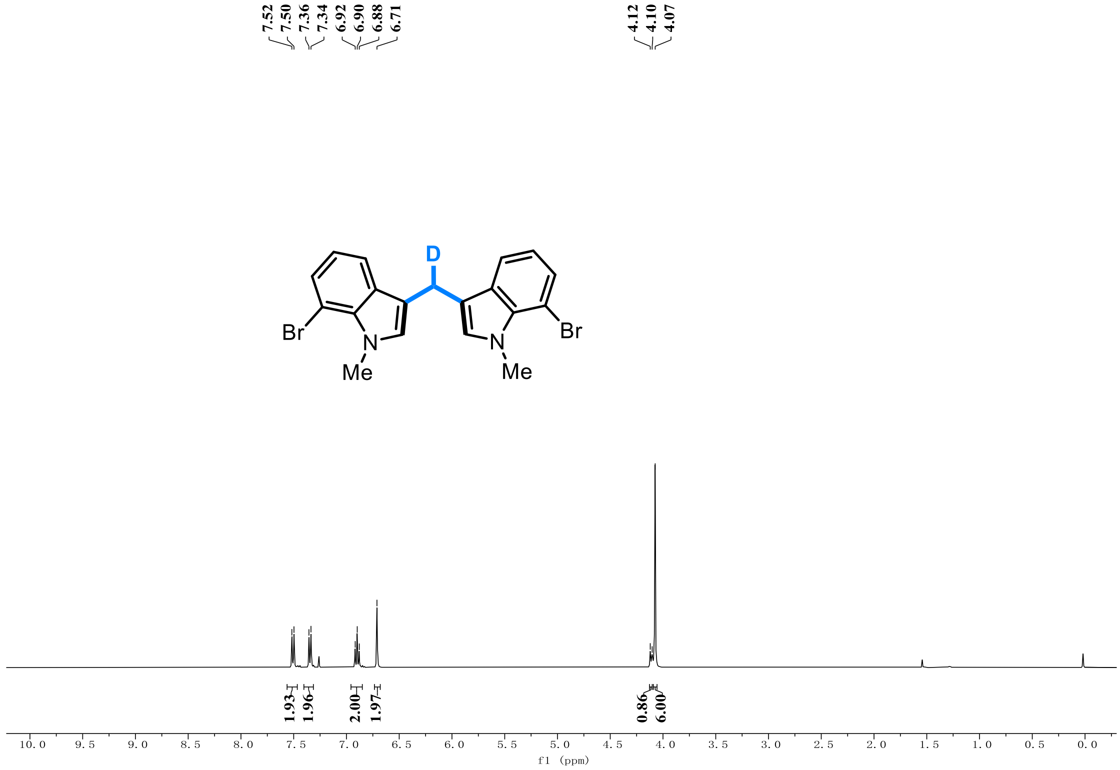
^{1}H NMR of **2u** (400 MHz, $CDCl_3$)



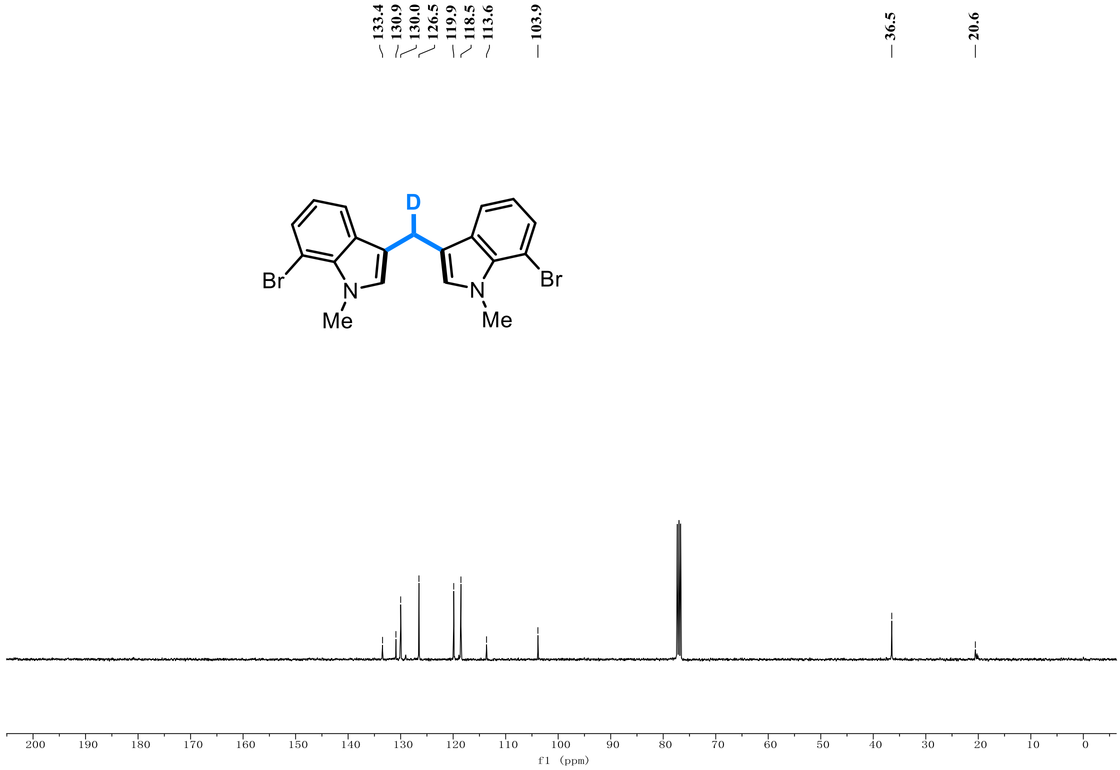
^{13}C NMR of **2u** (100 MHz, $CDCl_3$)



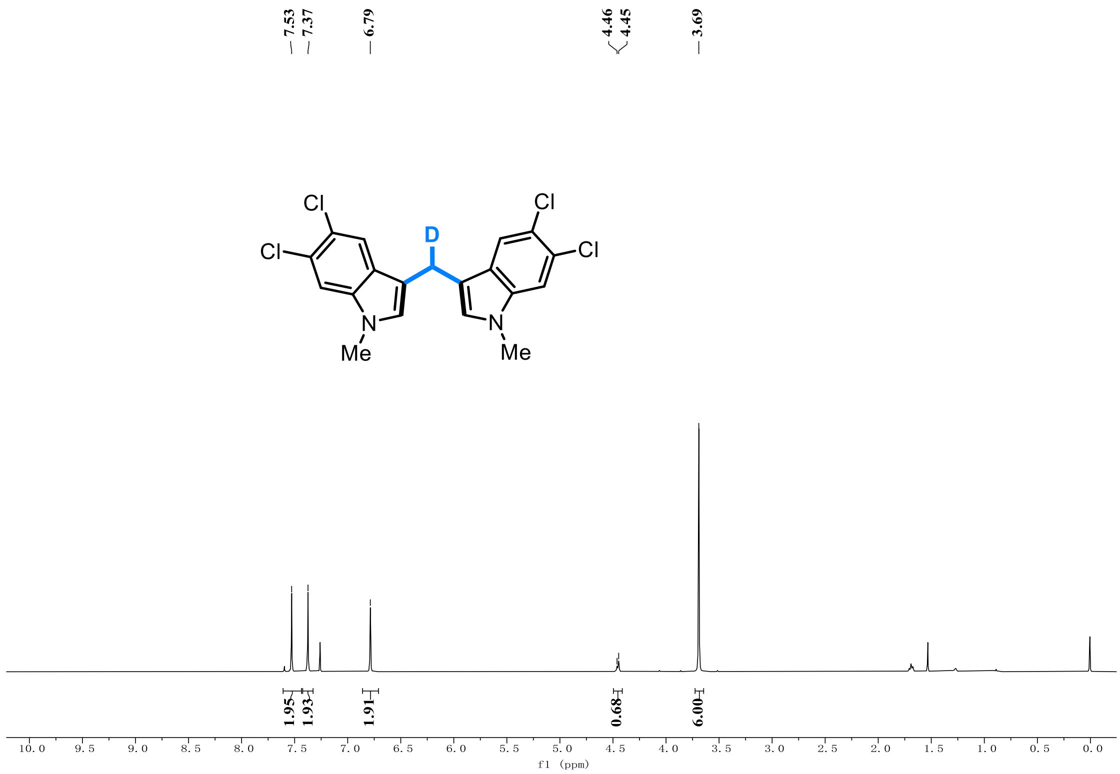
^{1}H NMR of **2v** (400 MHz, $CDCl_3$)



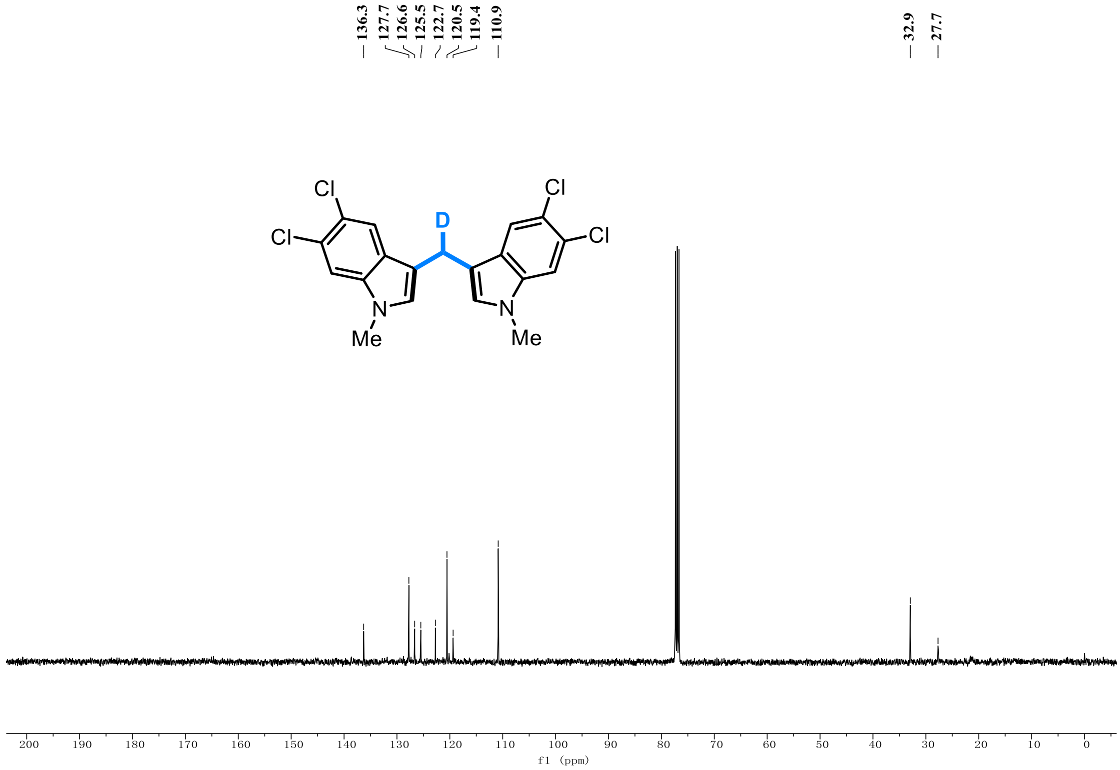
^{13}C NMR of **2v** (100 MHz, $CDCl_3$)



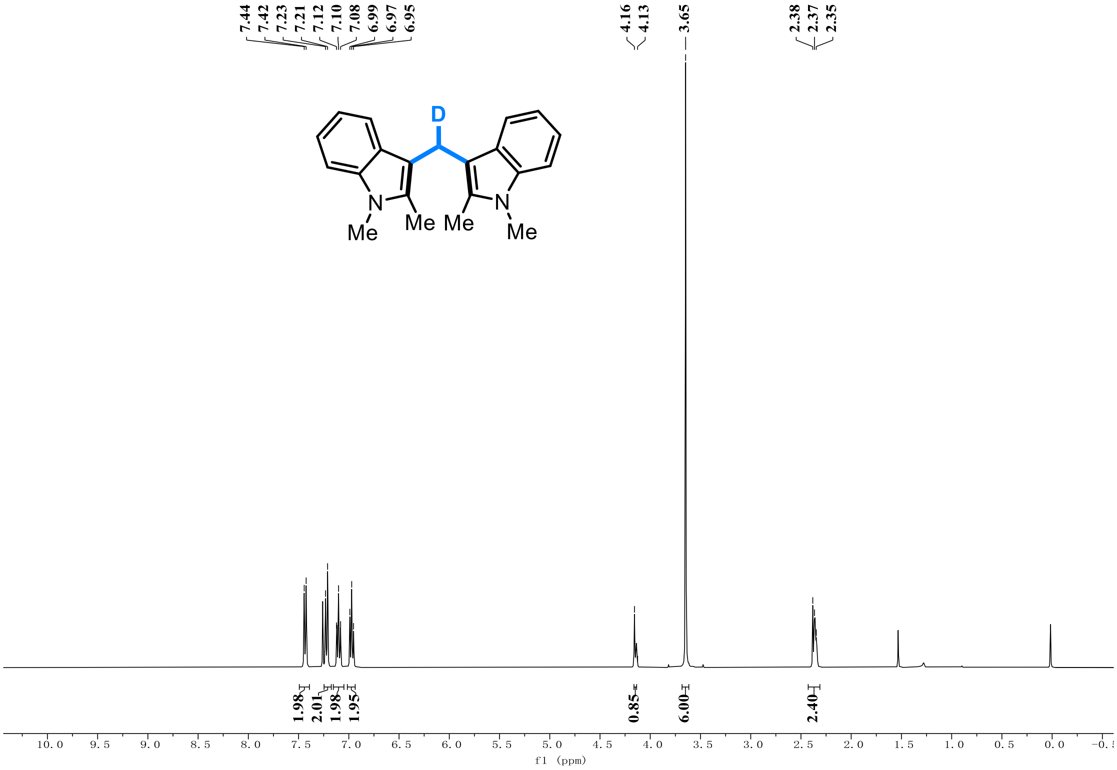
^{1}H NMR of **2w** (400 MHz, $CDCl_3$)



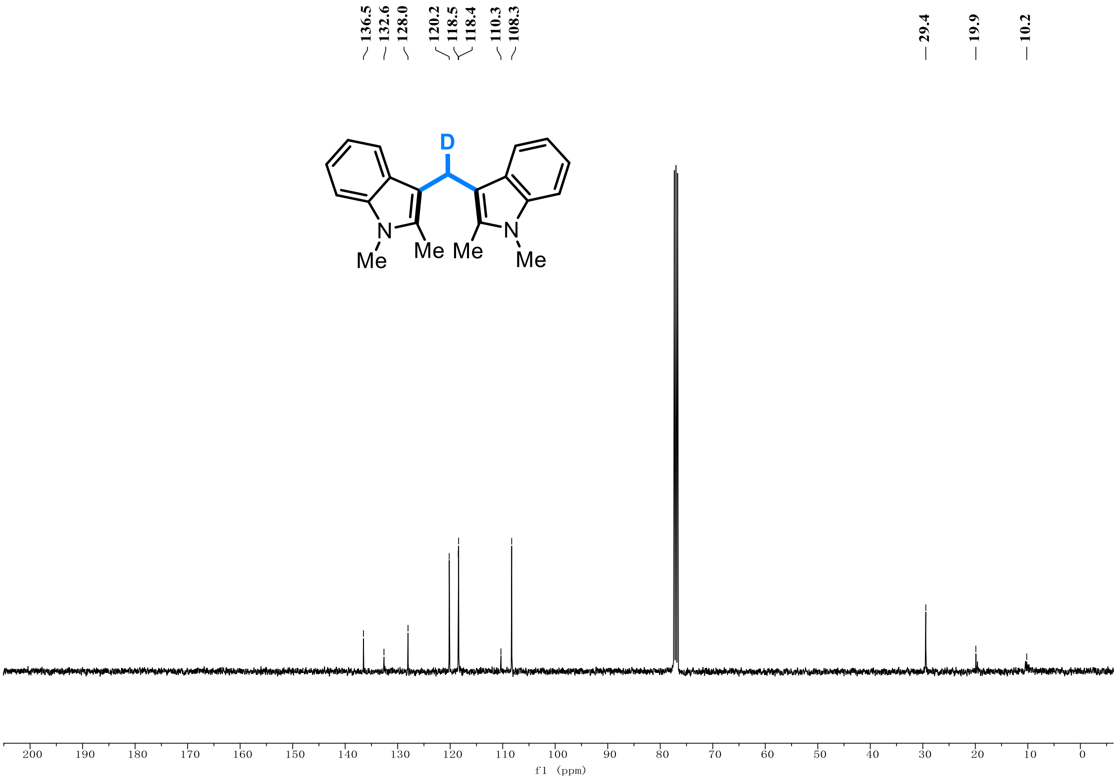
^{13}C NMR of **2w** (100 MHz, $CDCl_3$)



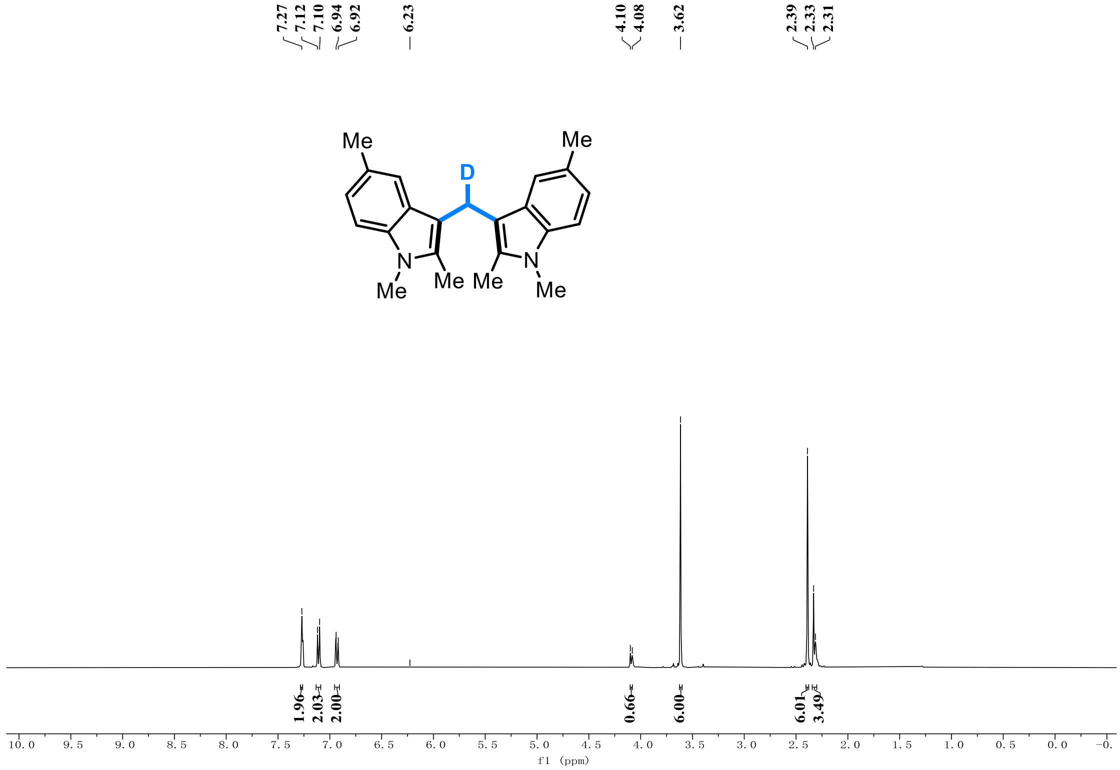
[1]H NMR of **2x** (400 MHz, $CDCl_3$)



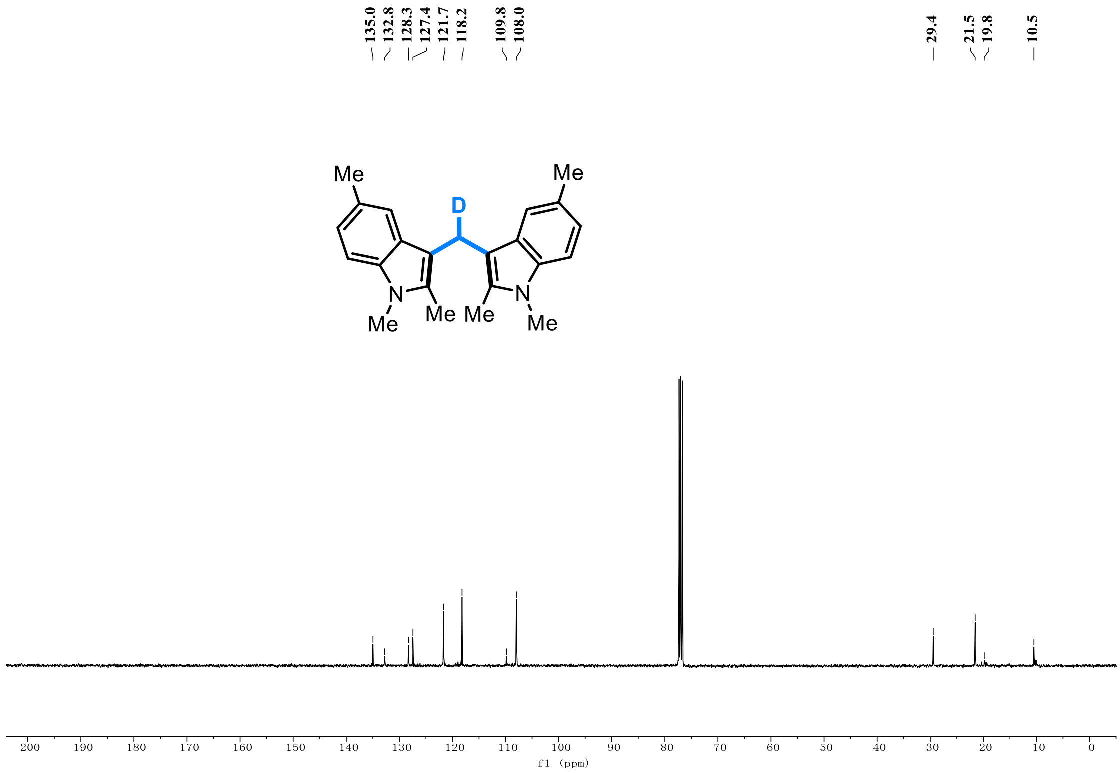
[13]C NMR of **2x** (100 MHz, $CDCl_3$)



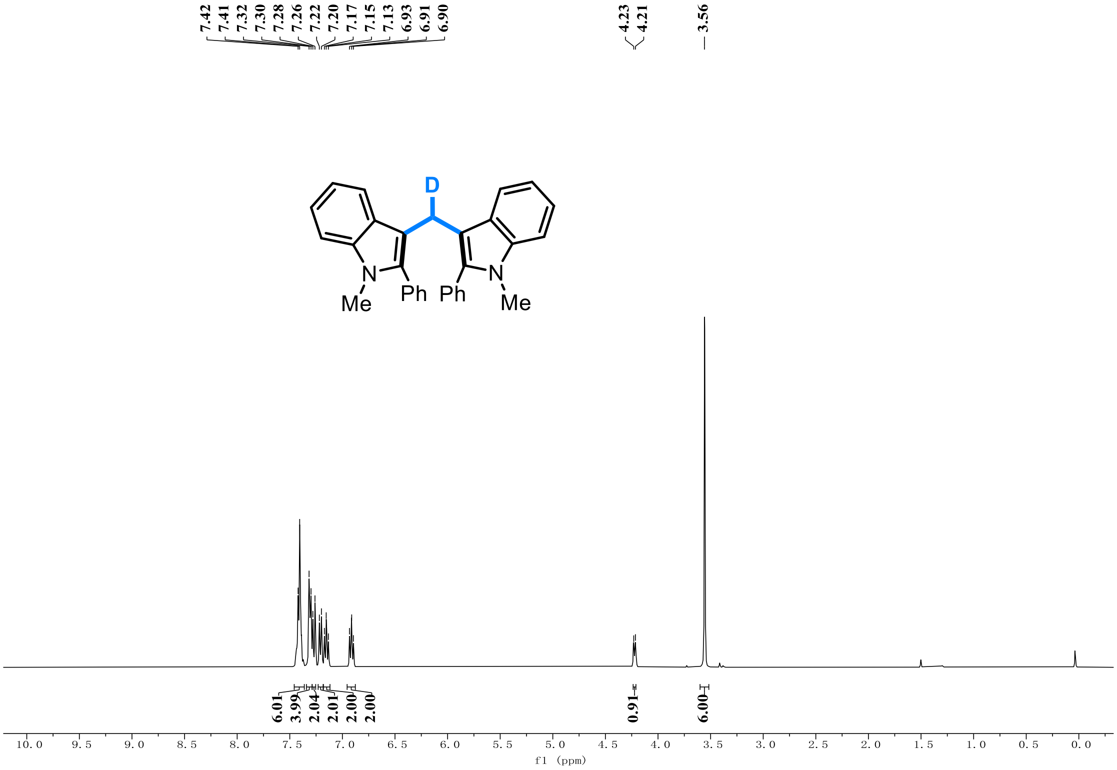
^{1}H NMR of **2y** (400 MHz, $CDCl_3$)



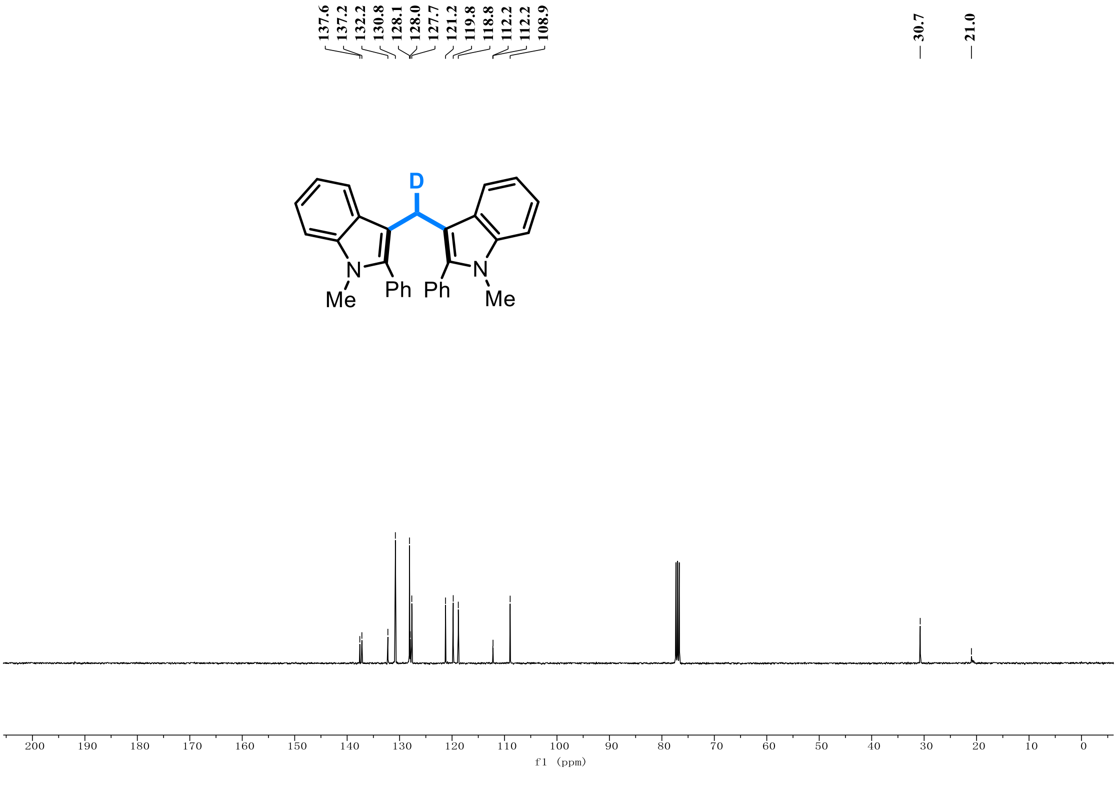
^{13}C NMR of **2y** (100 MHz, $CDCl_3$)



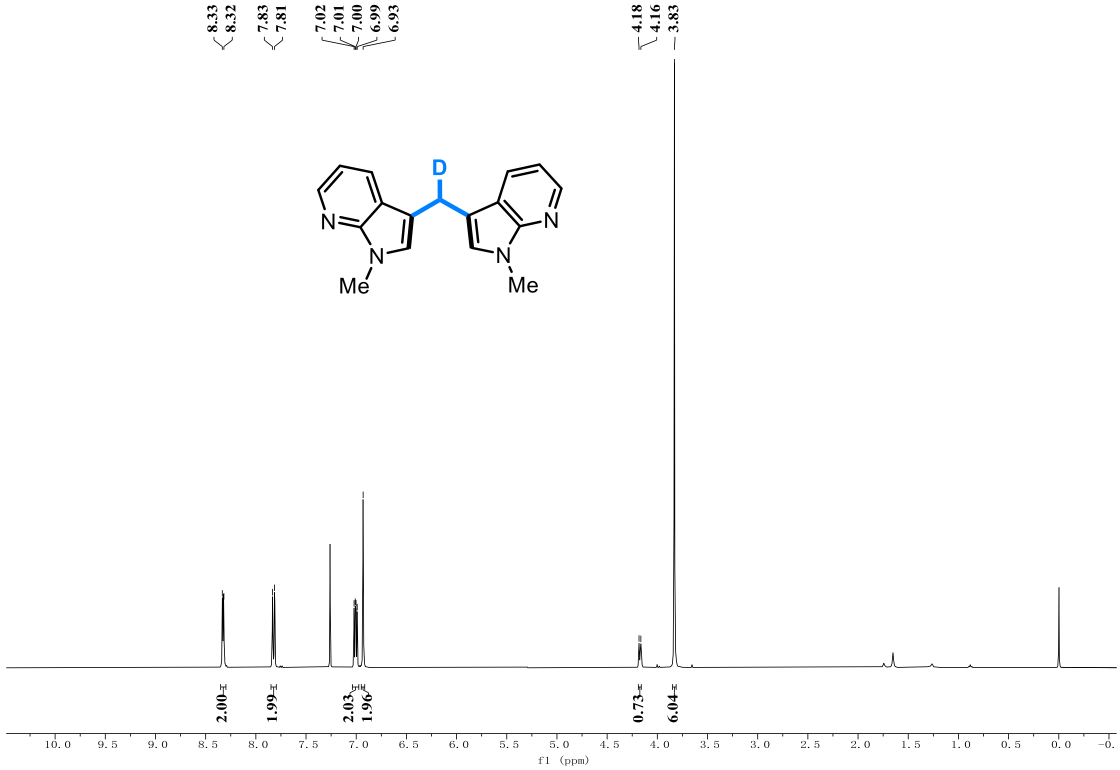
^{1}H NMR of **2z** (400 MHz, $CDCl_3$)



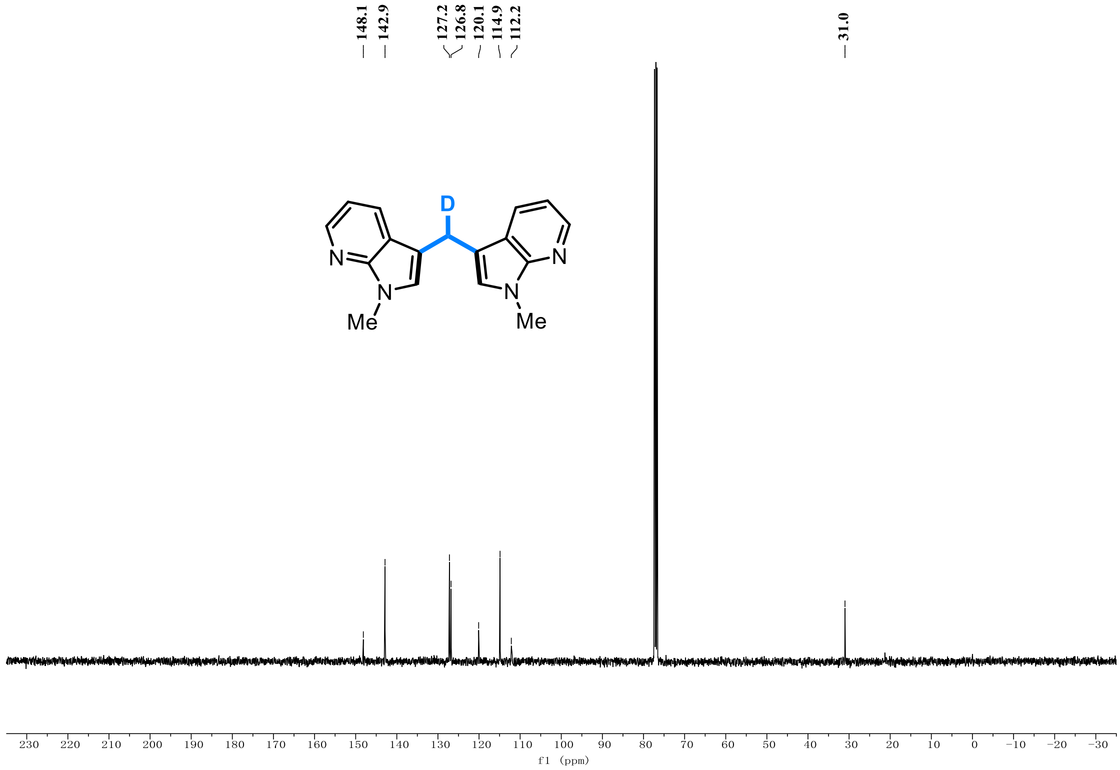
^{13}C NMR of **2z** (100 MHz, $CDCl_3$)



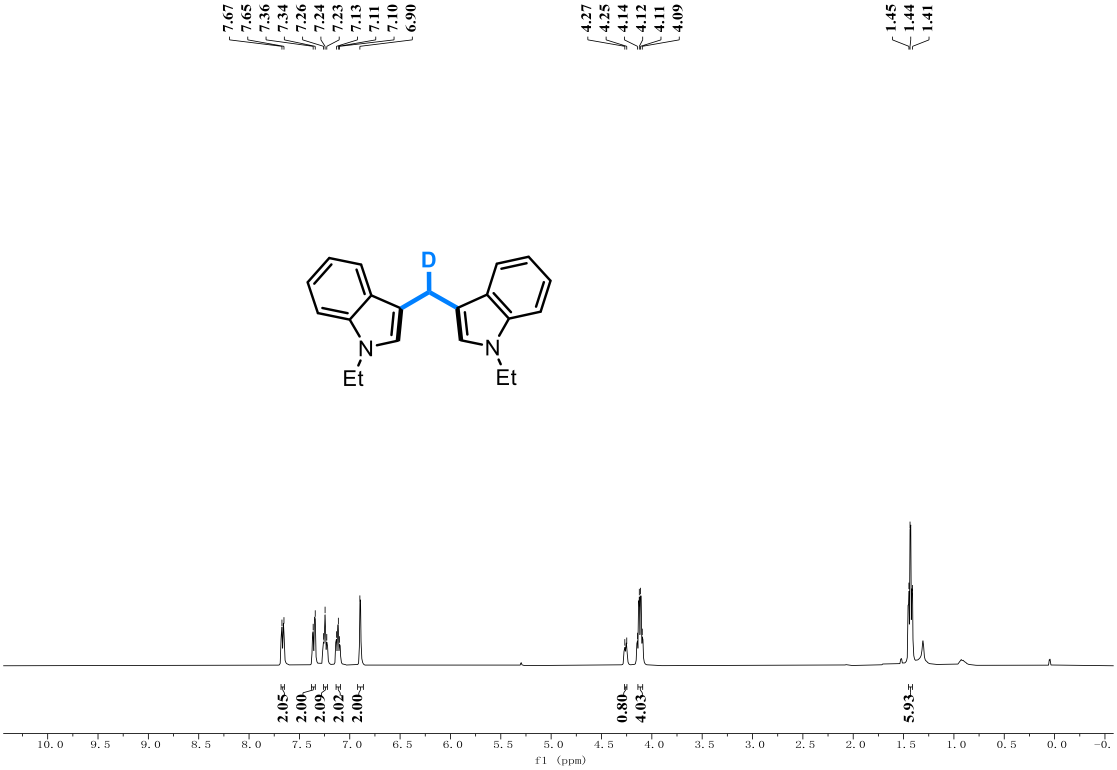
[1]H NMR of **2a'** (400 MHz, $CDCl_3$)



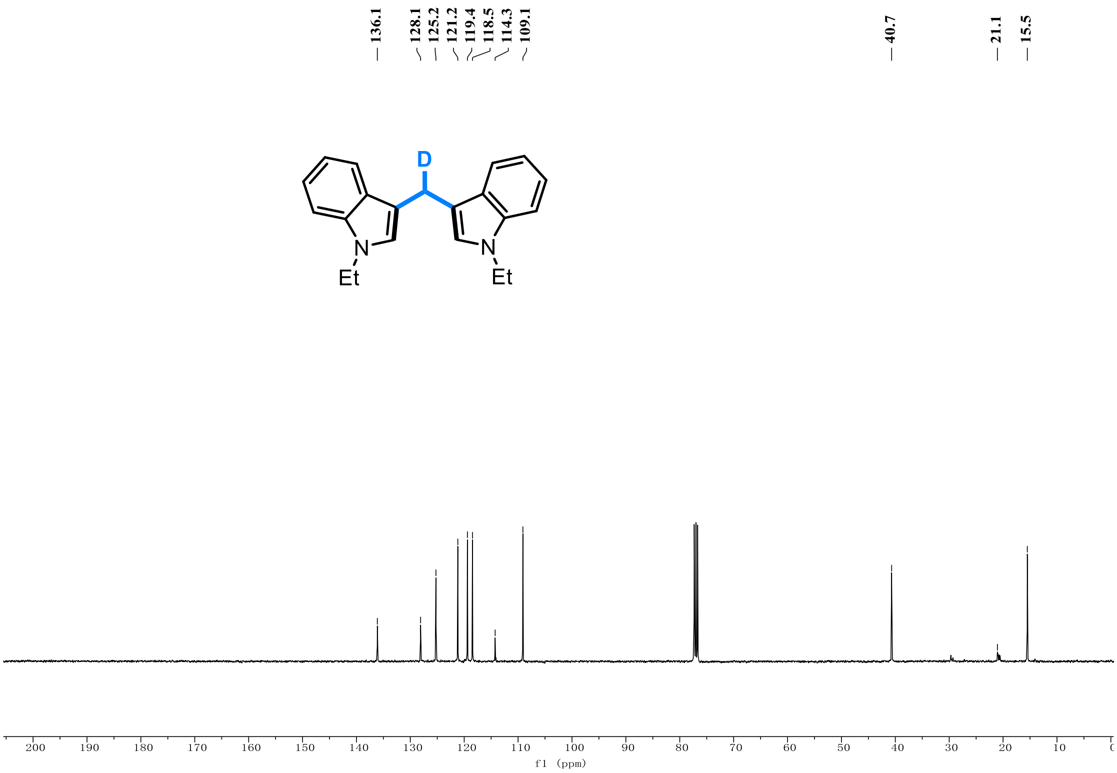
[13]C NMR of **2a'** (100 MHz, $CDCl_3$)



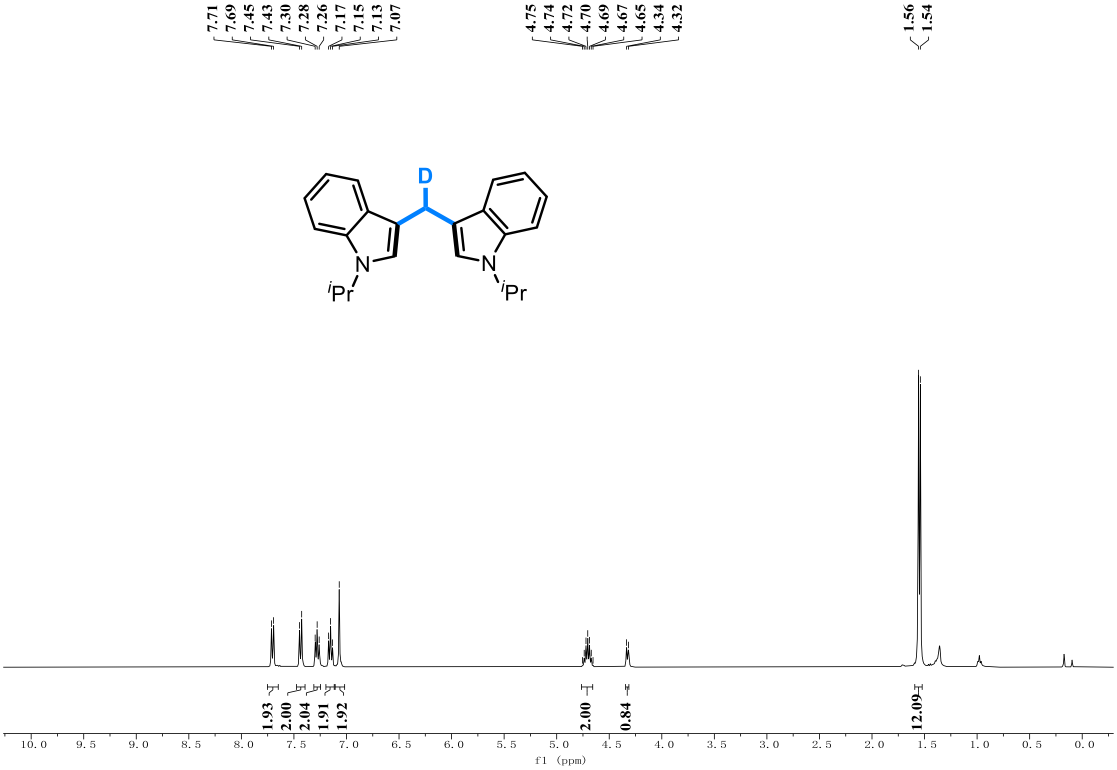
^{1}H NMR of **2b'** (400 MHz, $CDCl_3$)



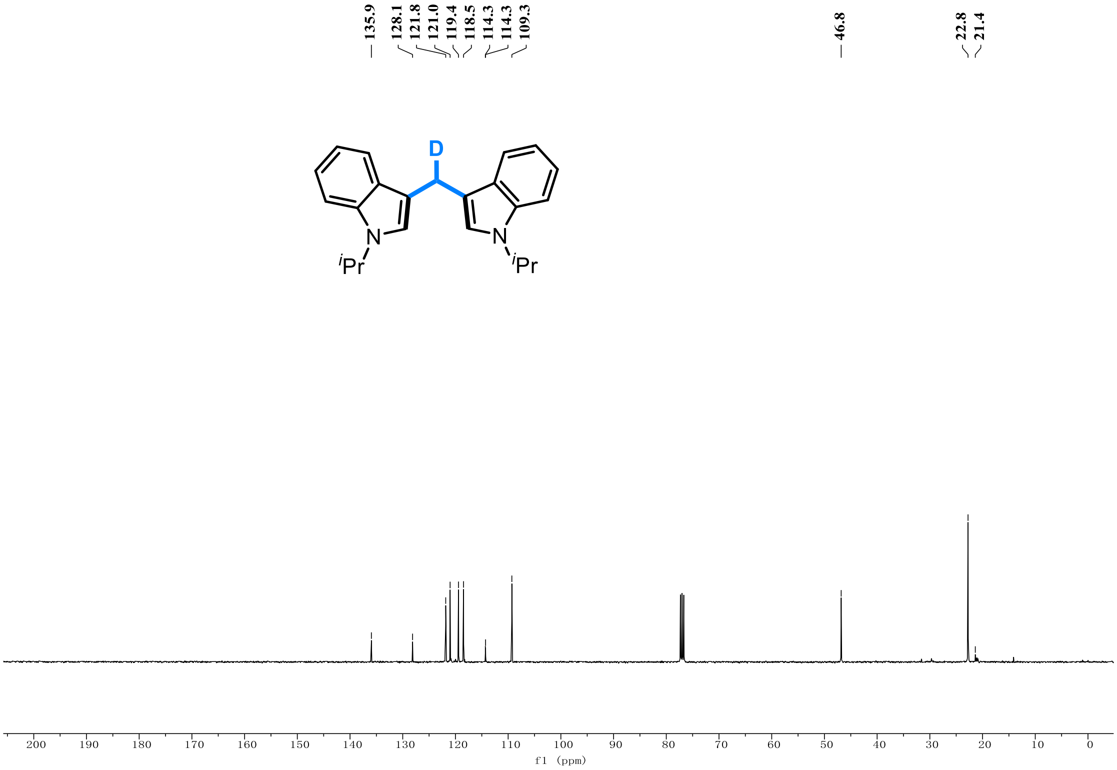
^{13}C NMR of **2b'** (100 MHz, $CDCl_3$)



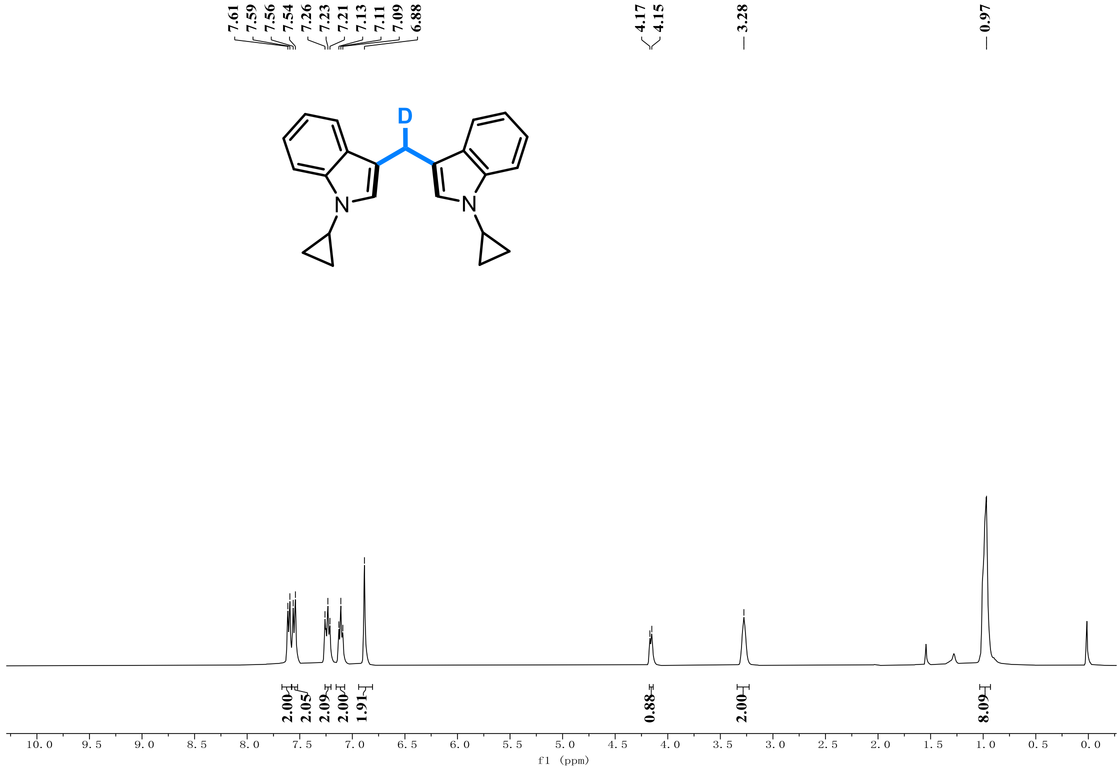
^{1}H NMR of **2c'** (400 MHz, $CDCl_3$)



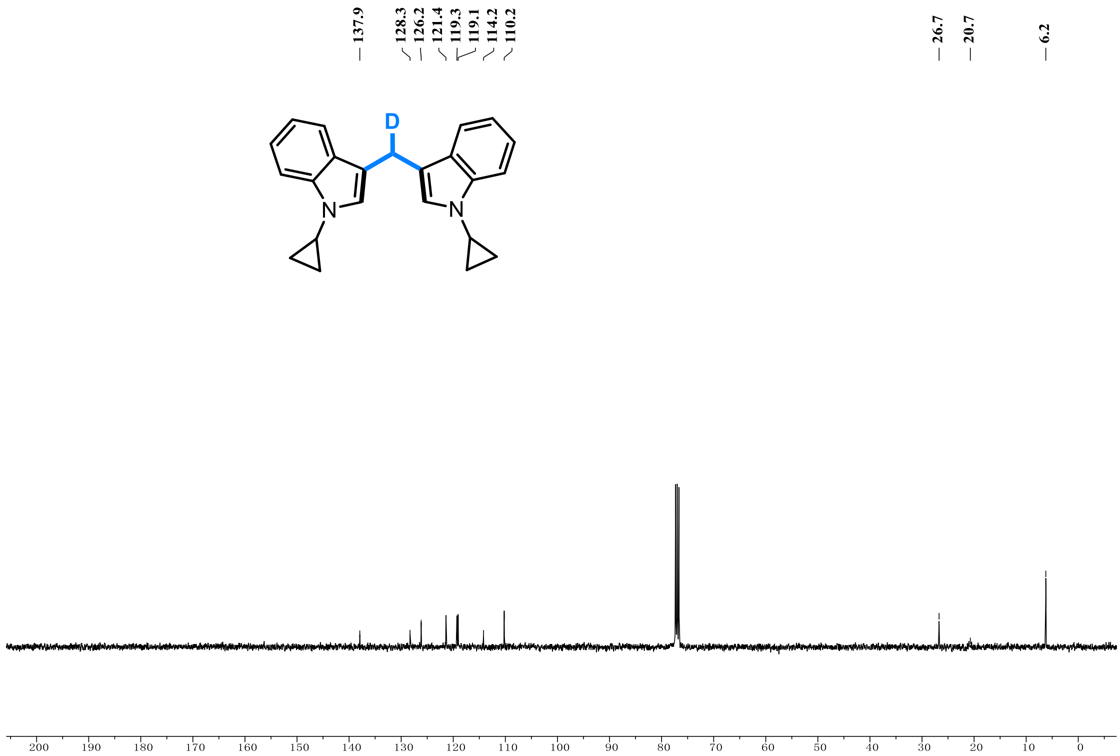
^{13}C NMR of **2c'** (100 MHz, $CDCl_3$)



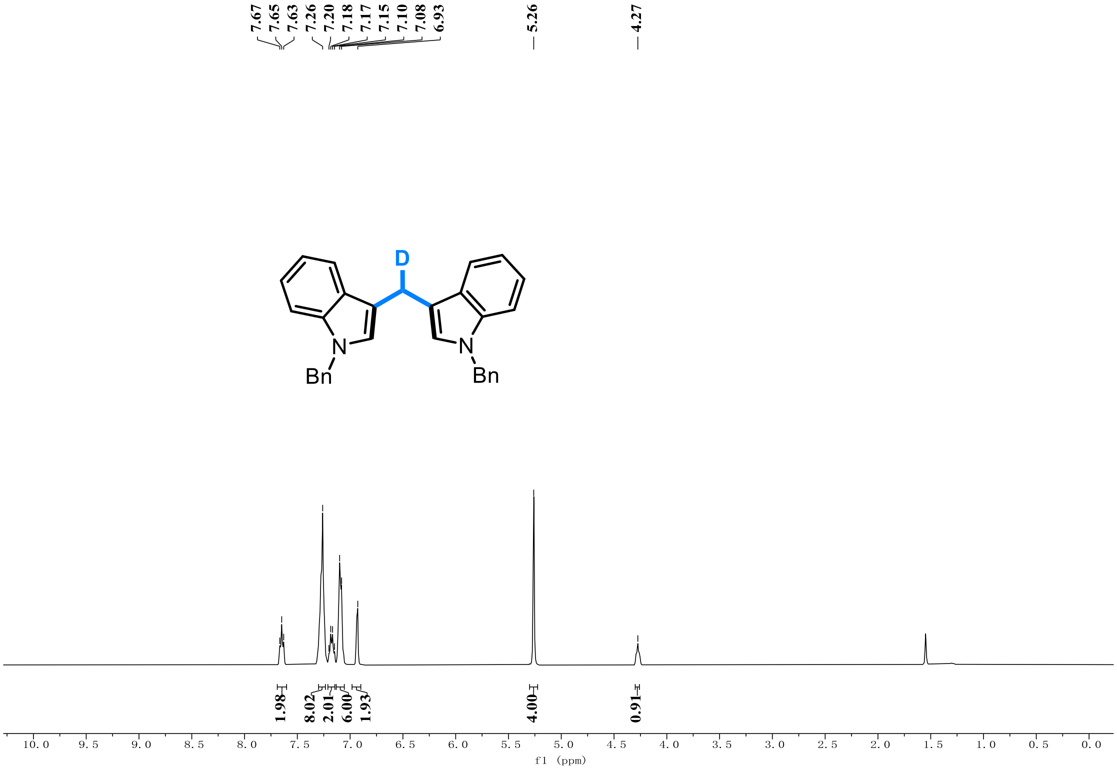
^{1}H NMR of **2d'** (400 MHz, $CDCl_3$)



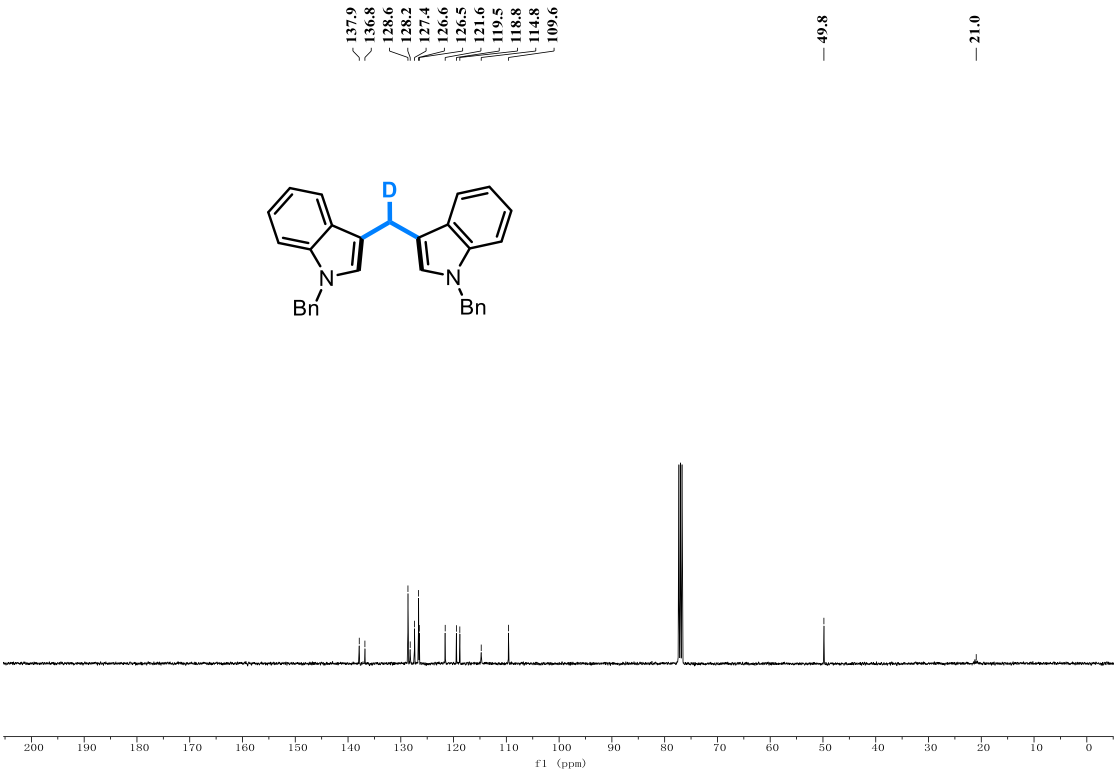
^{13}C NMR of **2d'** (100 MHz, $CDCl_3$)



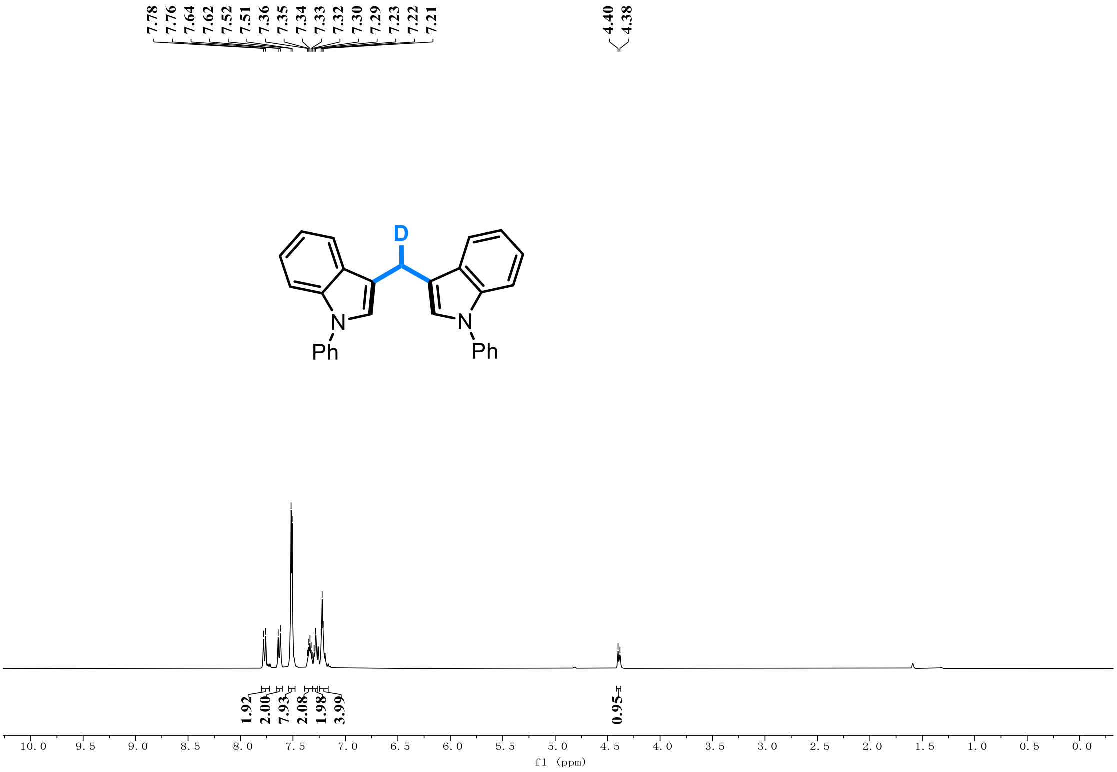
^{1}H NMR of **2e'** (400 MHz, $CDCl_3$)



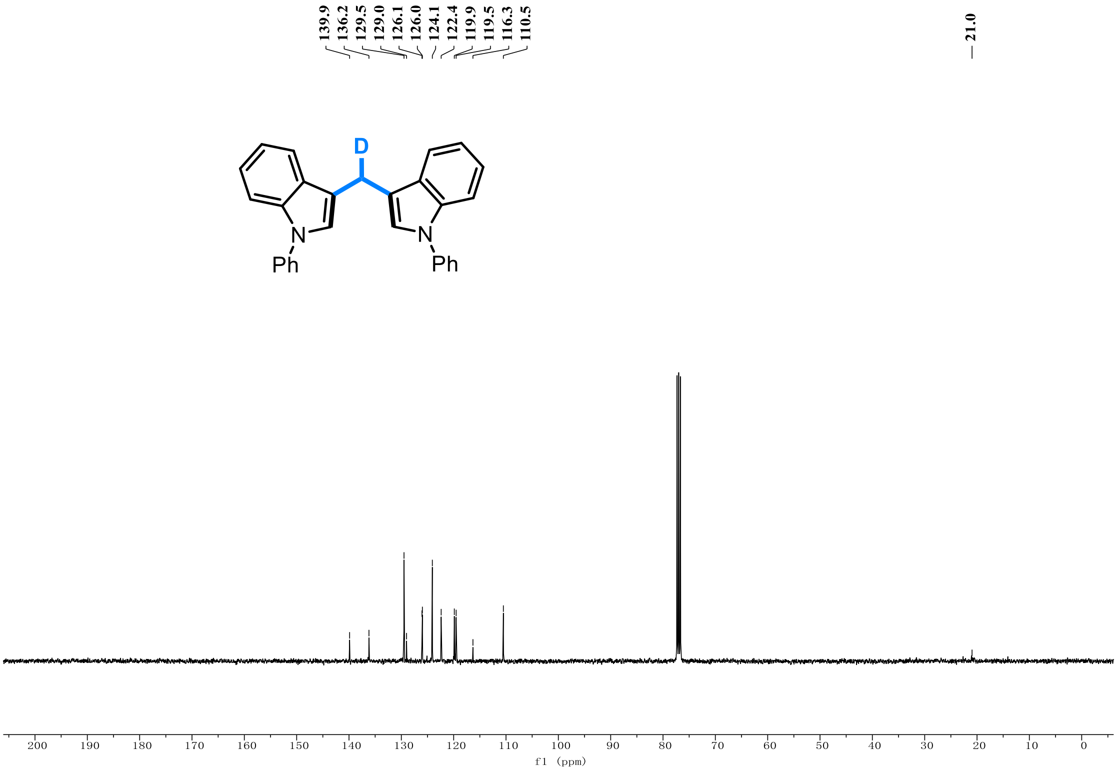
^{13}C NMR of **2e'** (100 MHz, $CDCl_3$)



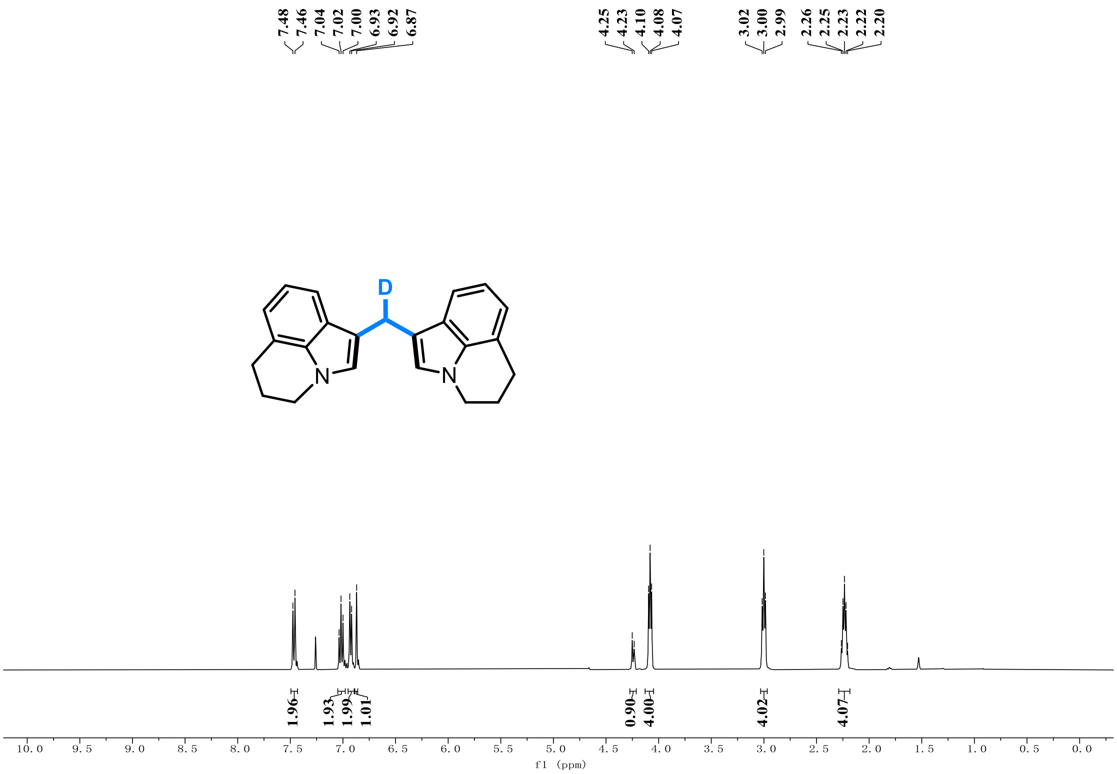
^{1}H NMR of **2f'** (400 MHz, $CDCl_3$)



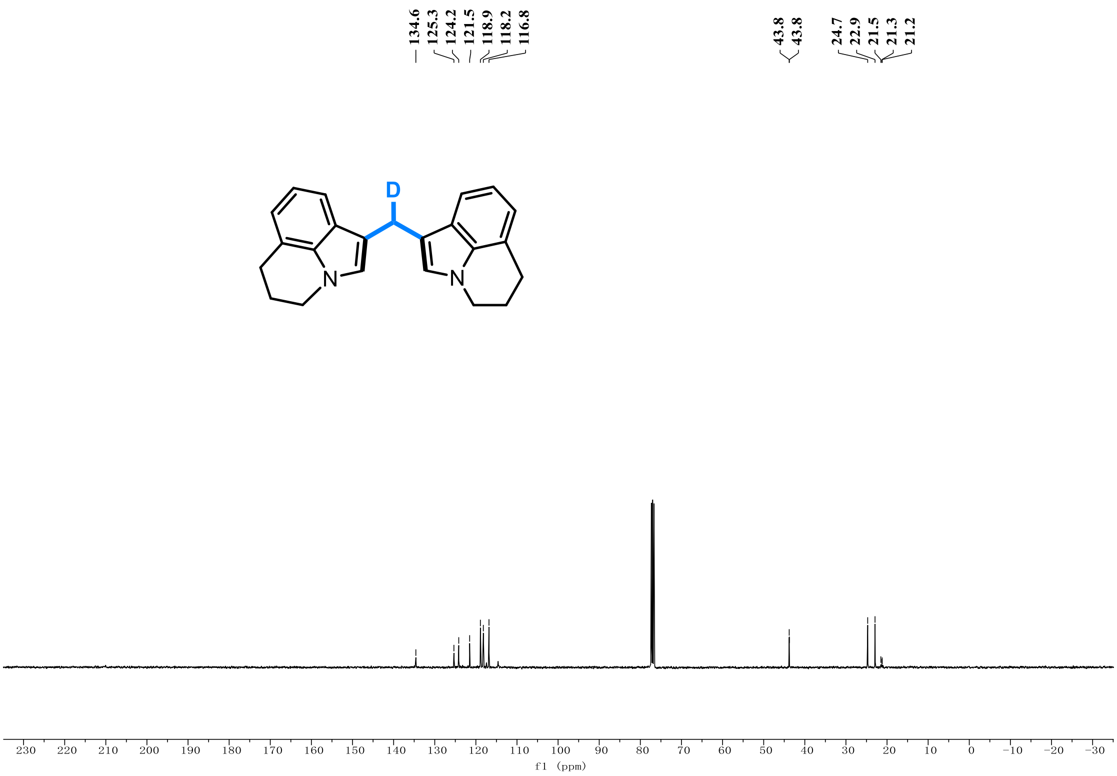
^{13}C NMR of **2f'** (100 MHz, $CDCl_3$)



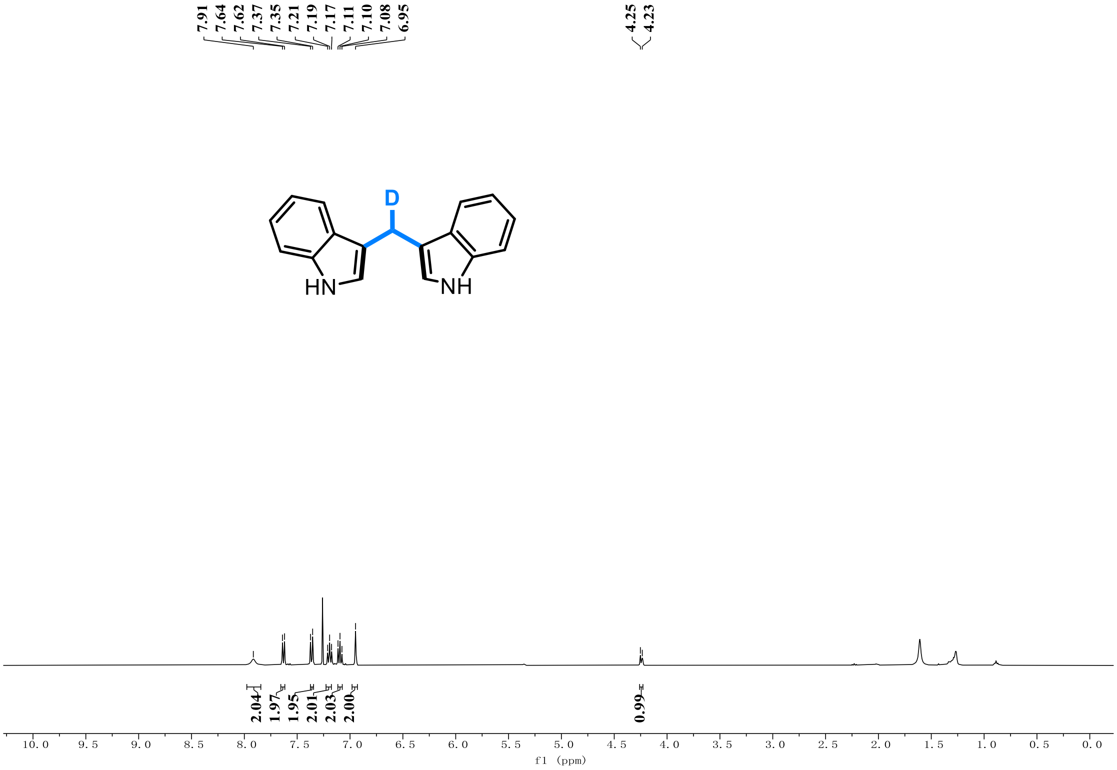
^{1}H NMR of **2g'** (400 MHz, $CDCl_3$)



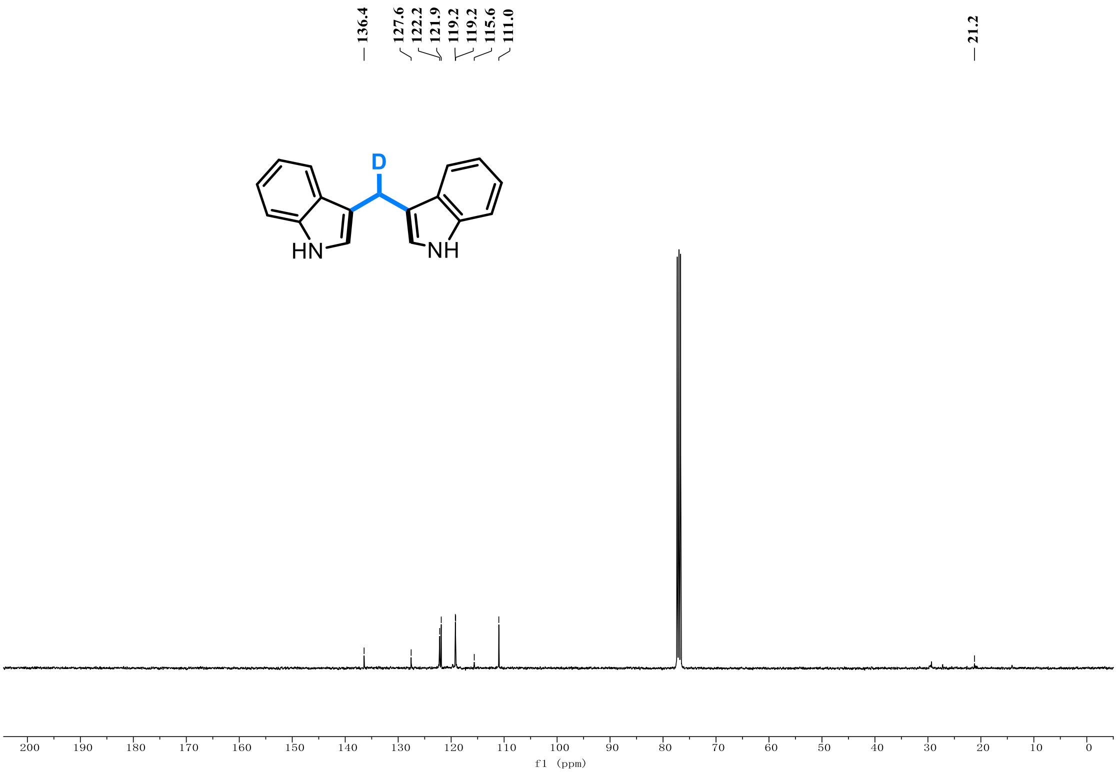
^{13}C NMR of **2g'** (100 MHz, $CDCl_3$)



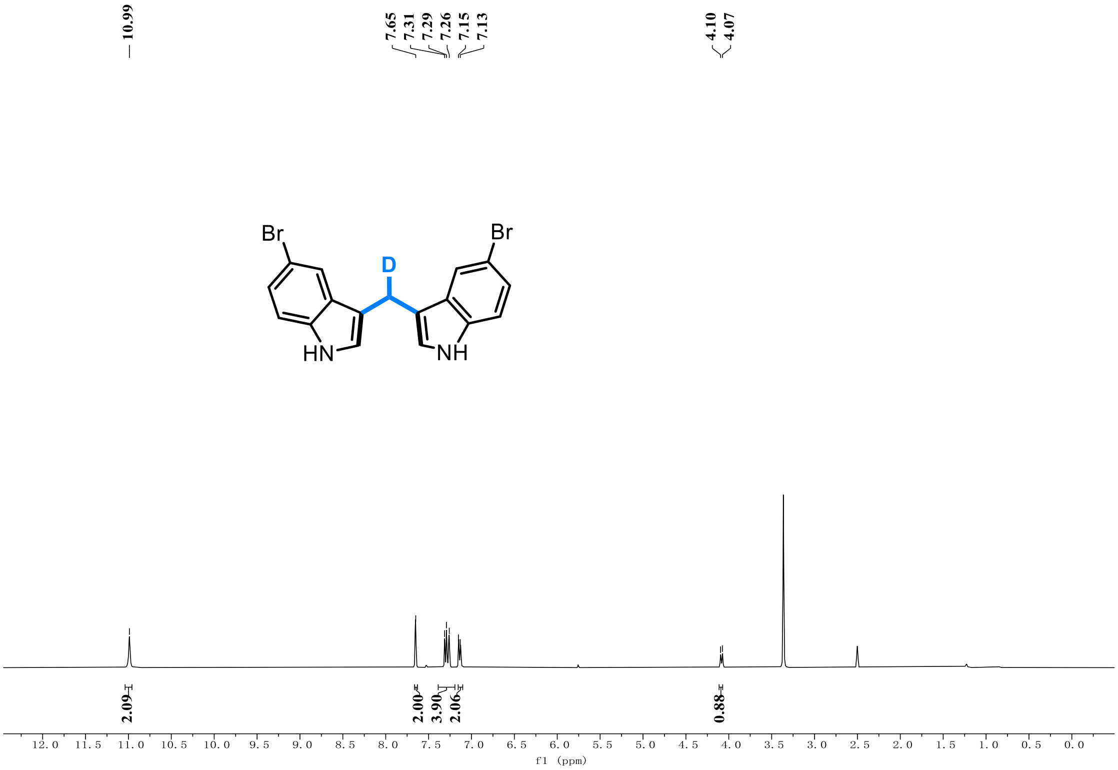
[1]H NMR of **2h'** (400 MHz, $CDCl_3$)



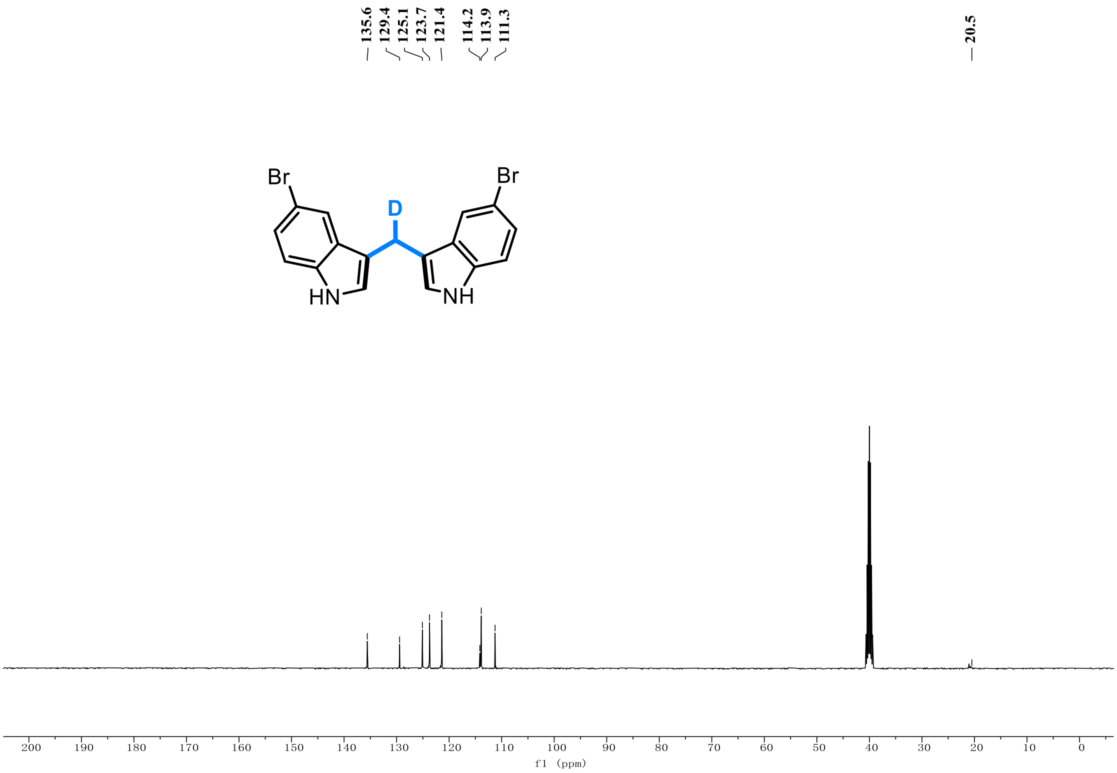
[13]C NMR of **2h'** (100 MHz, $CDCl_3$)



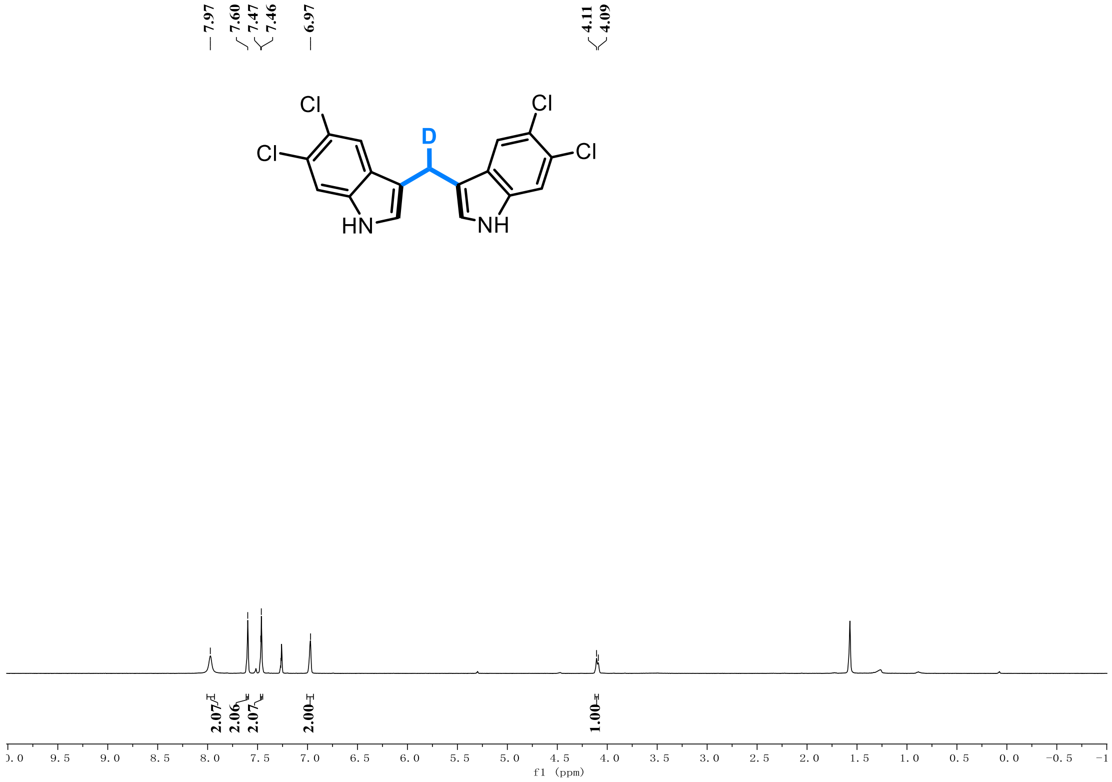
^{1}H NMR of **2i'** (400 MHz, DMSO)



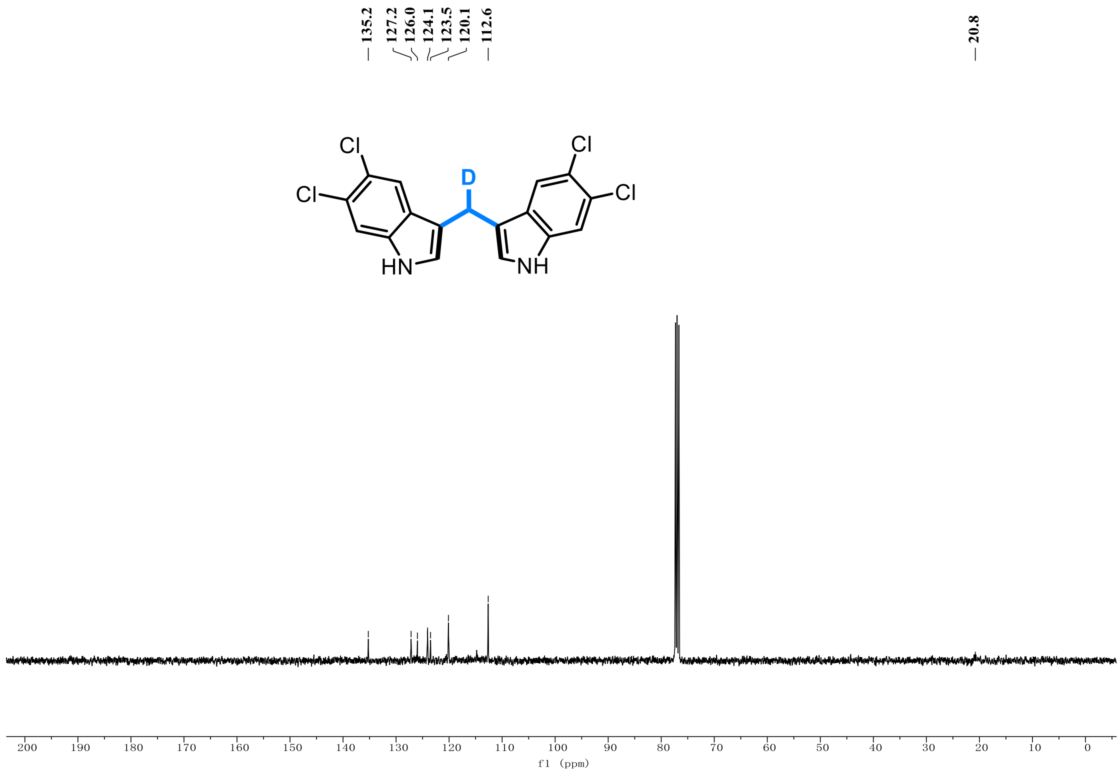
^{13}C NMR of **2i'** (100 MHz, DMSO)



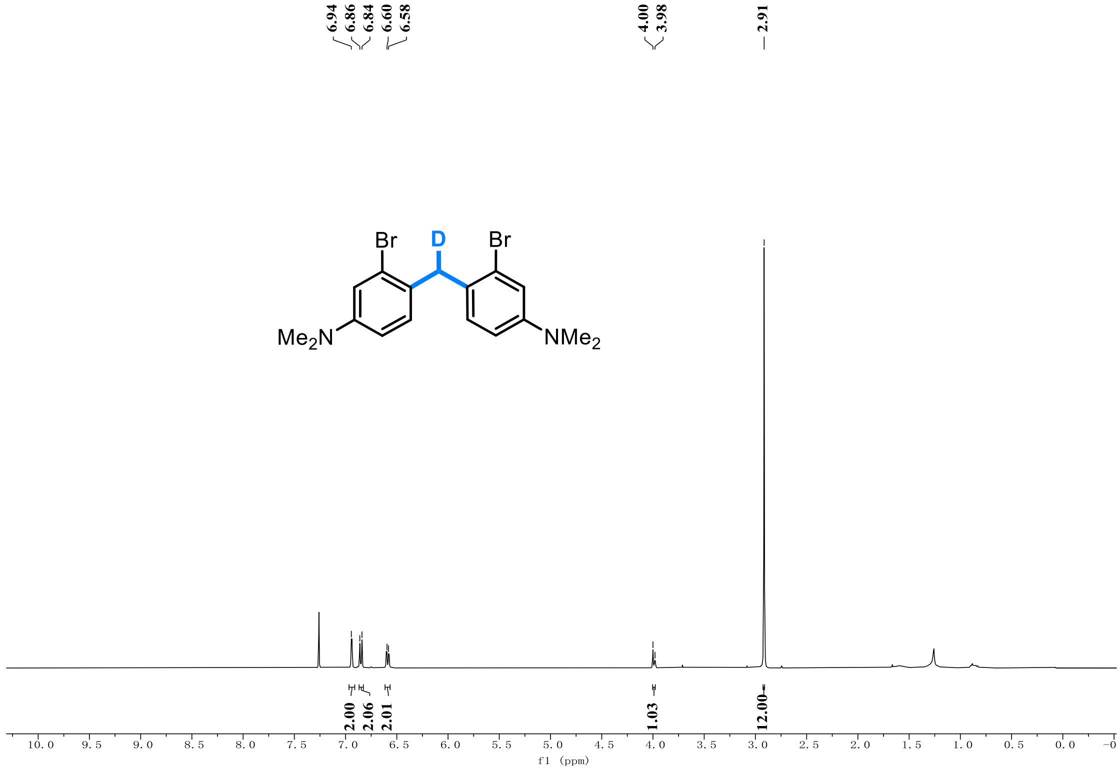
^{1}H NMR of **2j'** (400 MHz, $CDCl_3$)



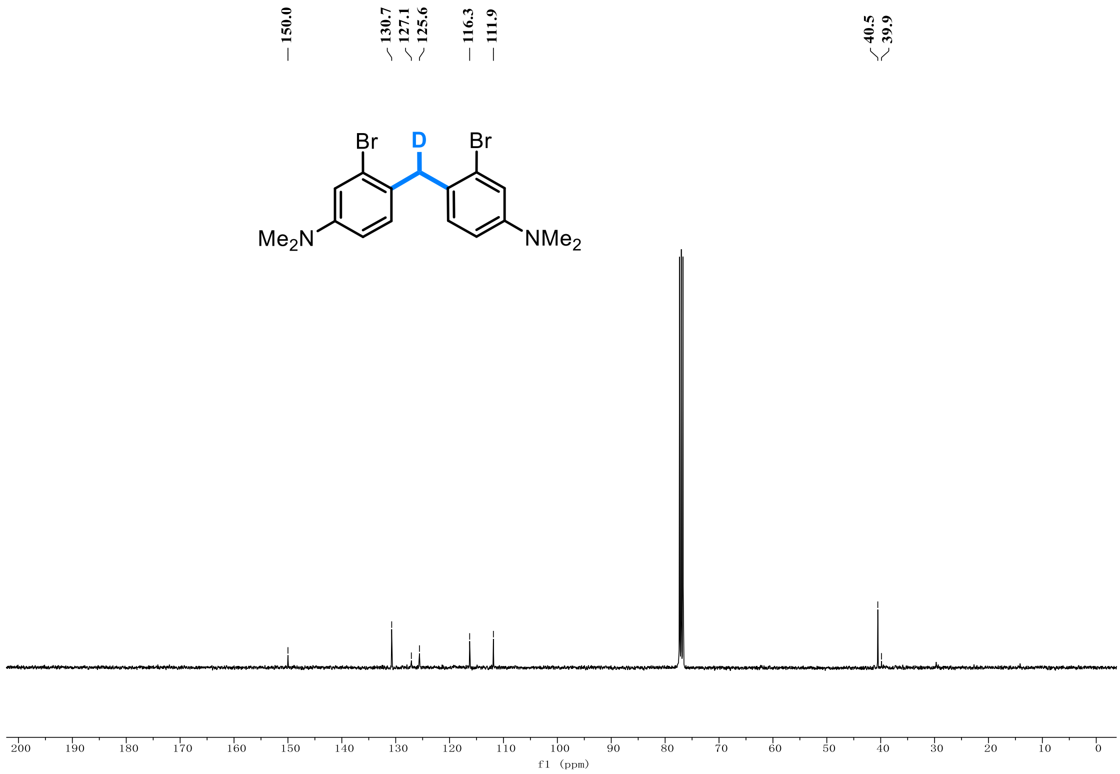
^{13}C NMR of **2j'** (100 MHz, $CDCl_3$)



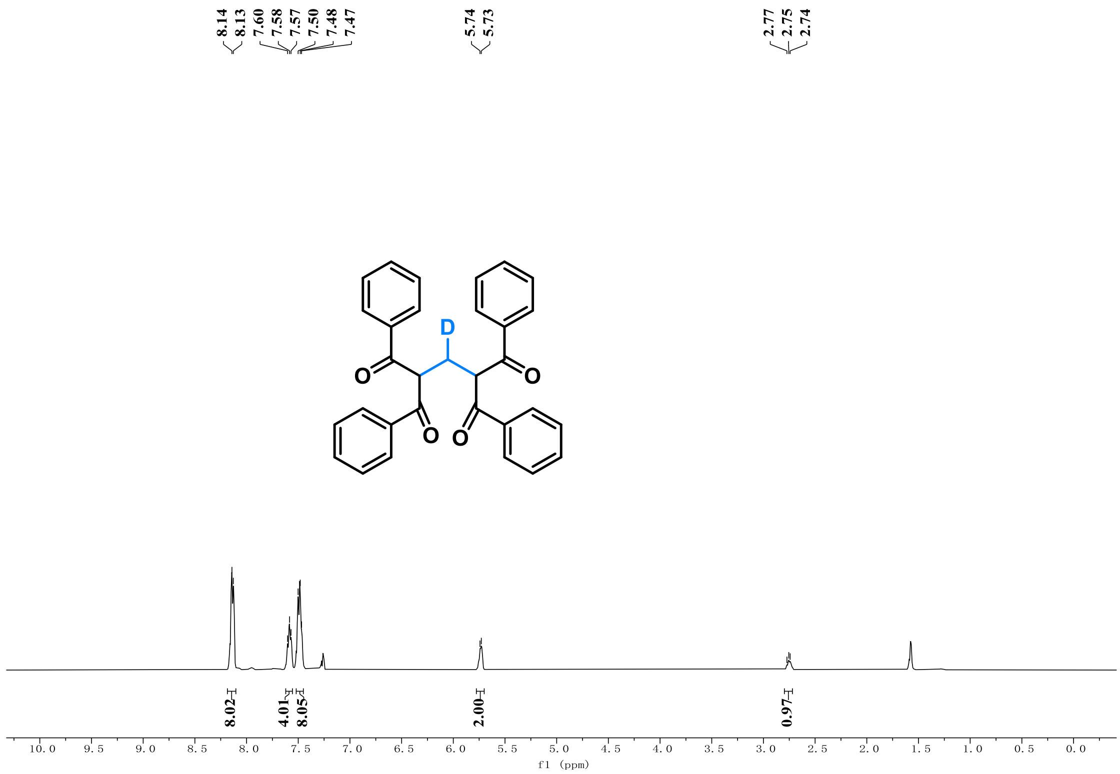
^{1}H NMR of **4** (400 MHz, $CDCl_3$)



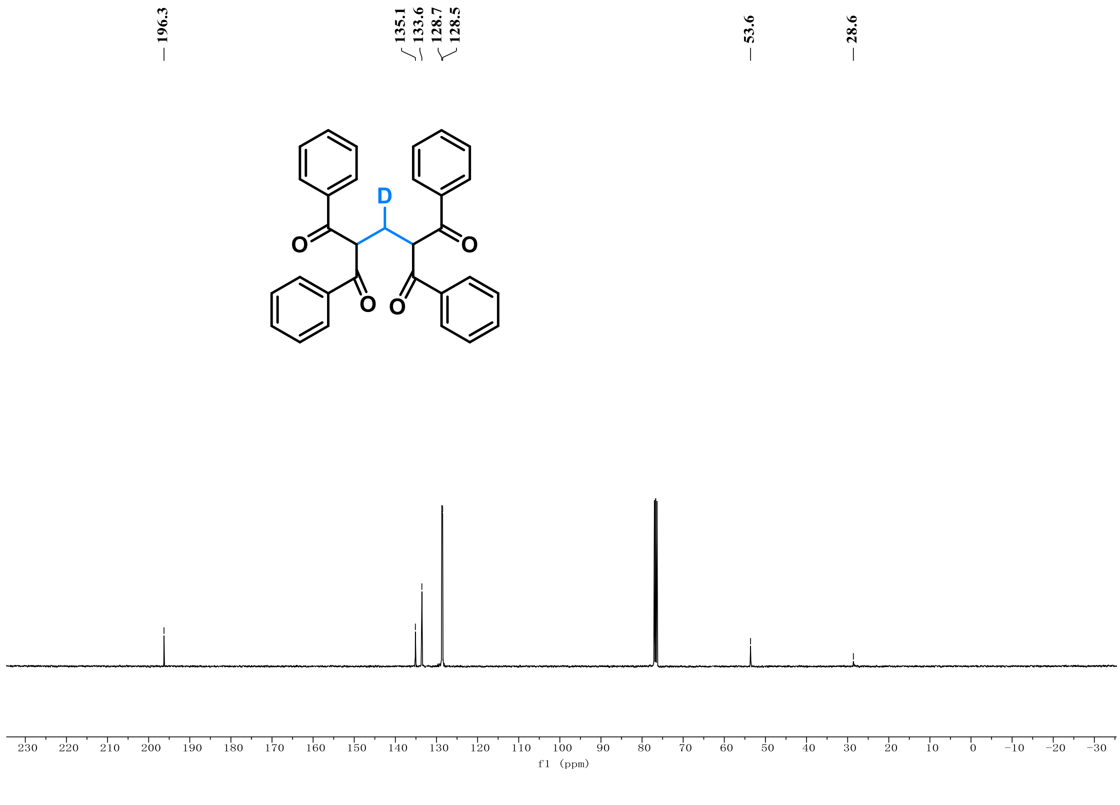
^{13}C NMR of **4** (100 MHz, $CDCl_3$)



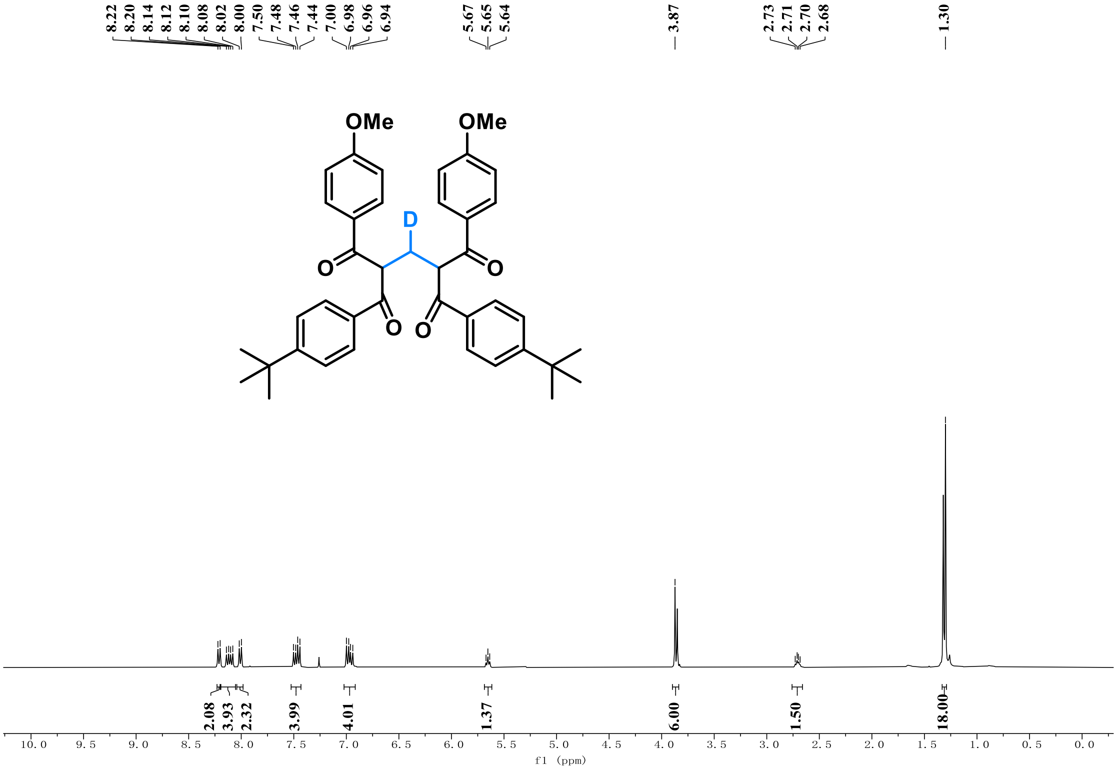
^{1}H NMR of **6a** (400 MHz, $CDCl_3$)



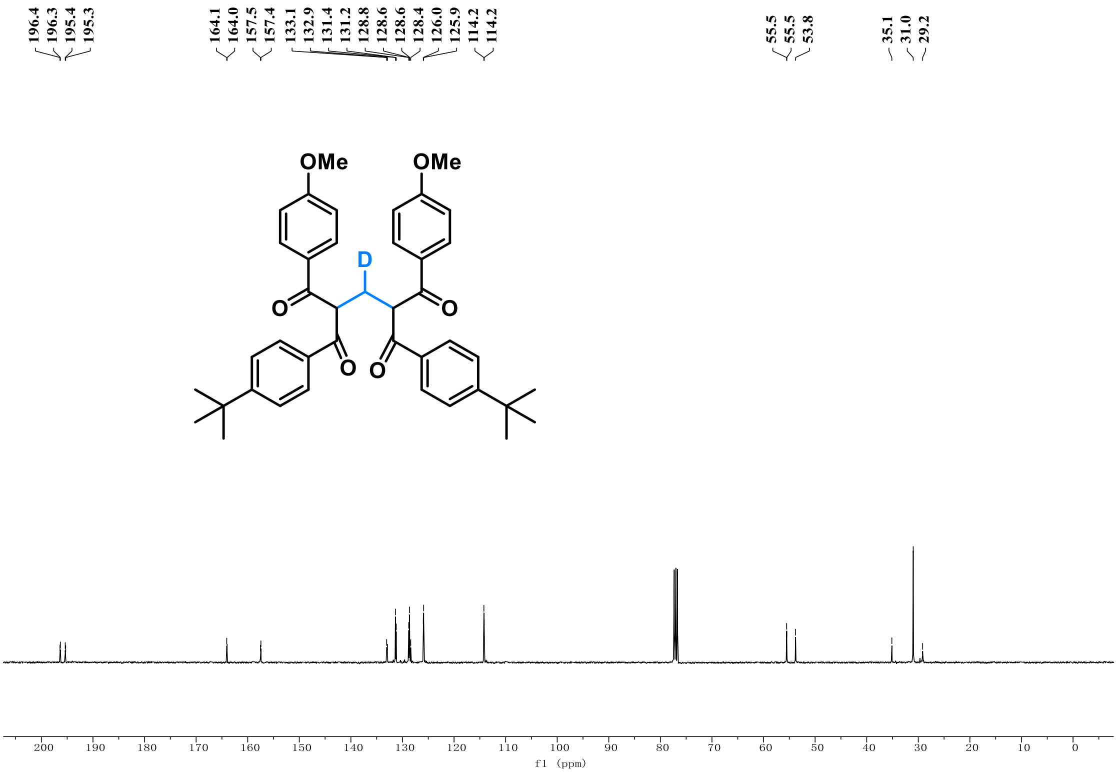
^{13}C NMR of **6a** (100 MHz, $CDCl_3$)



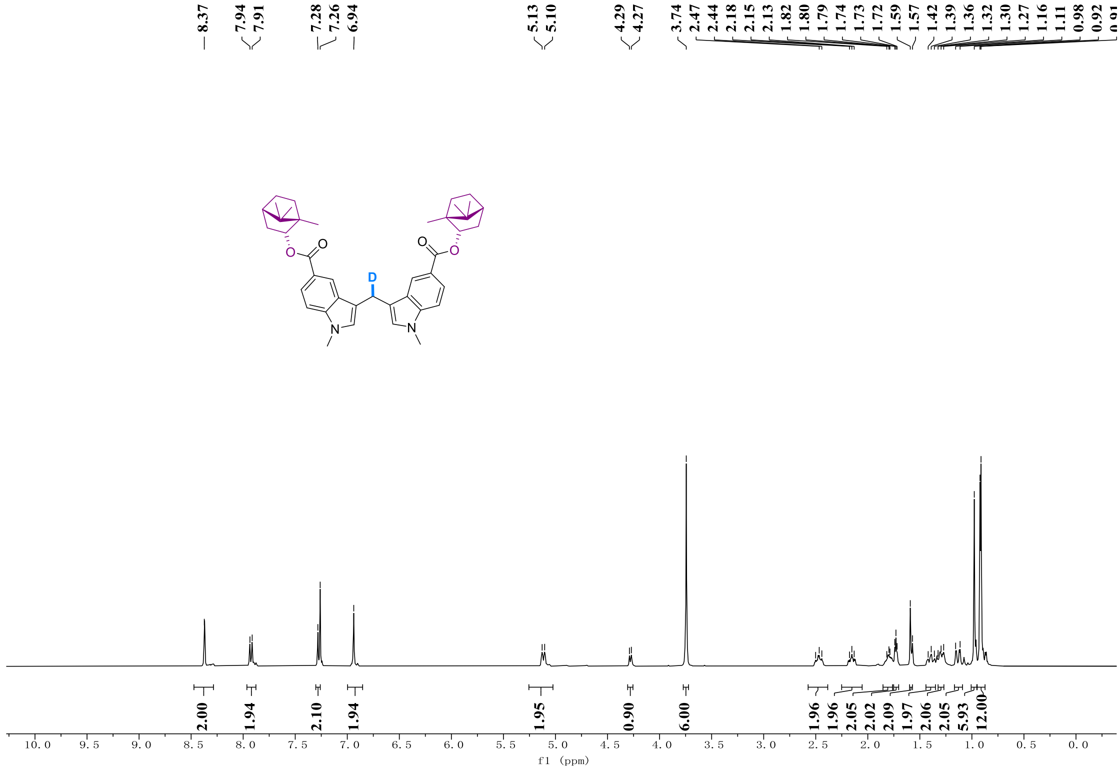
^1H NMR of **6b** (400 MHz, $CDCl_3$)



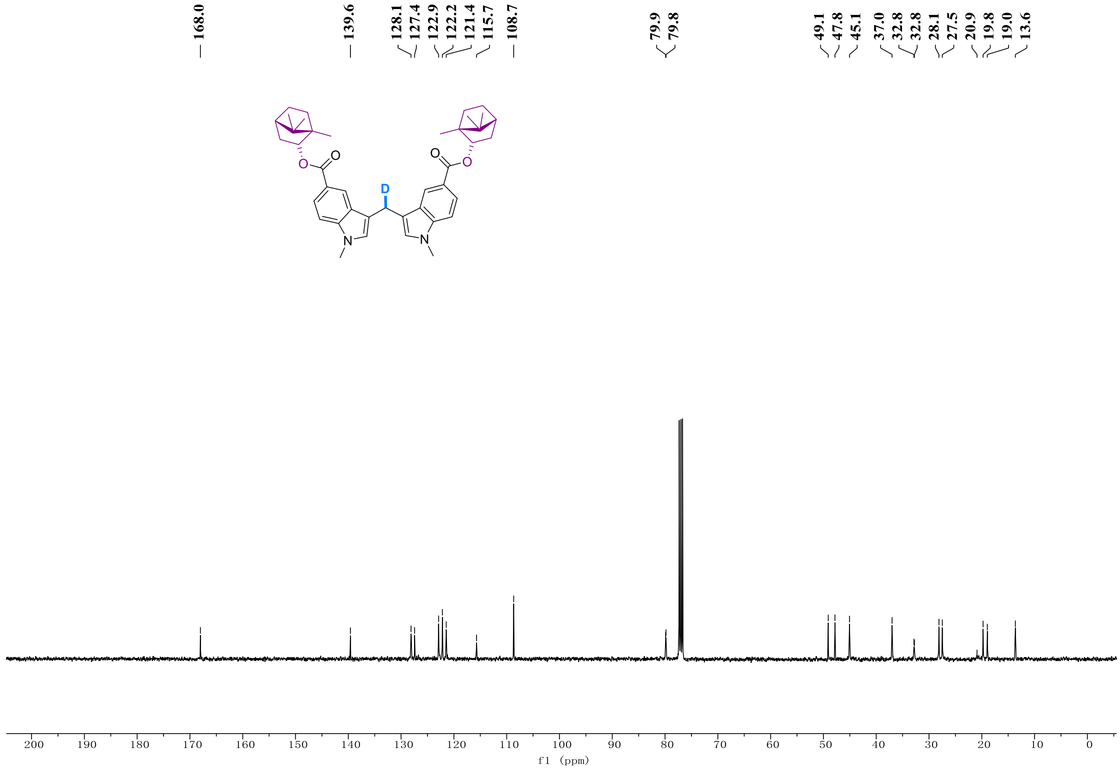
^{13}C NMR of **6b** (100 MHz, $CDCl_3$)



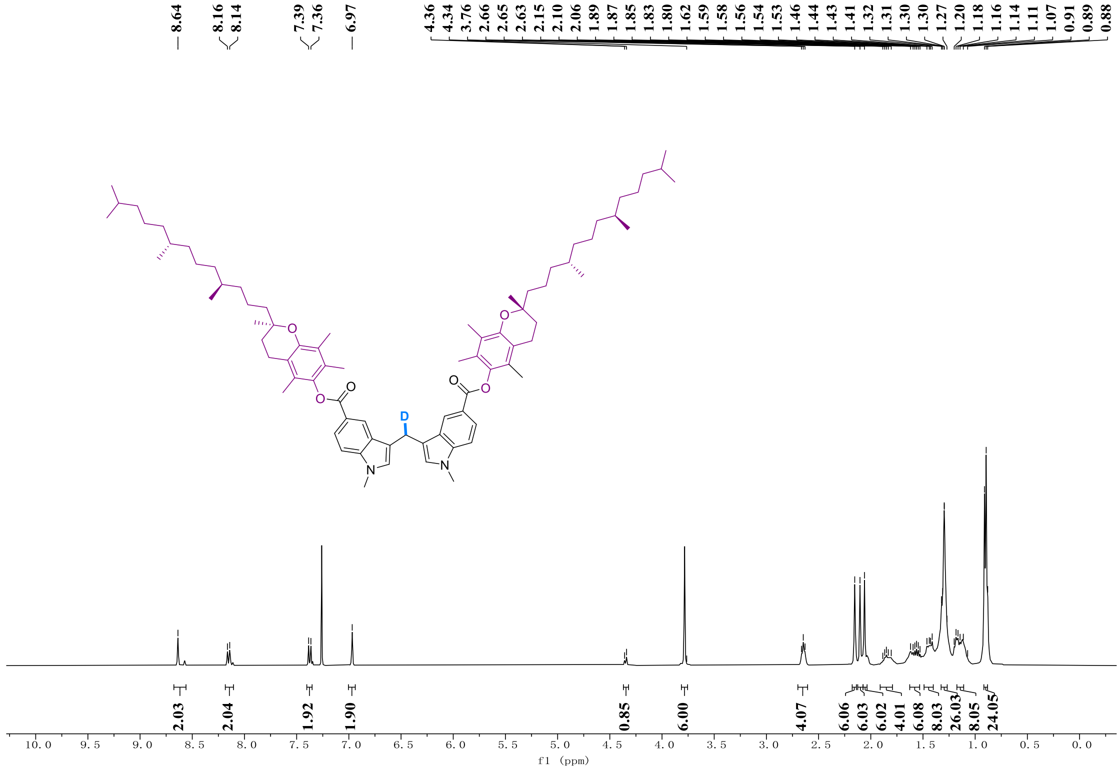
[1]H NMR of **8a** (400 MHz, $CDCl_3$)



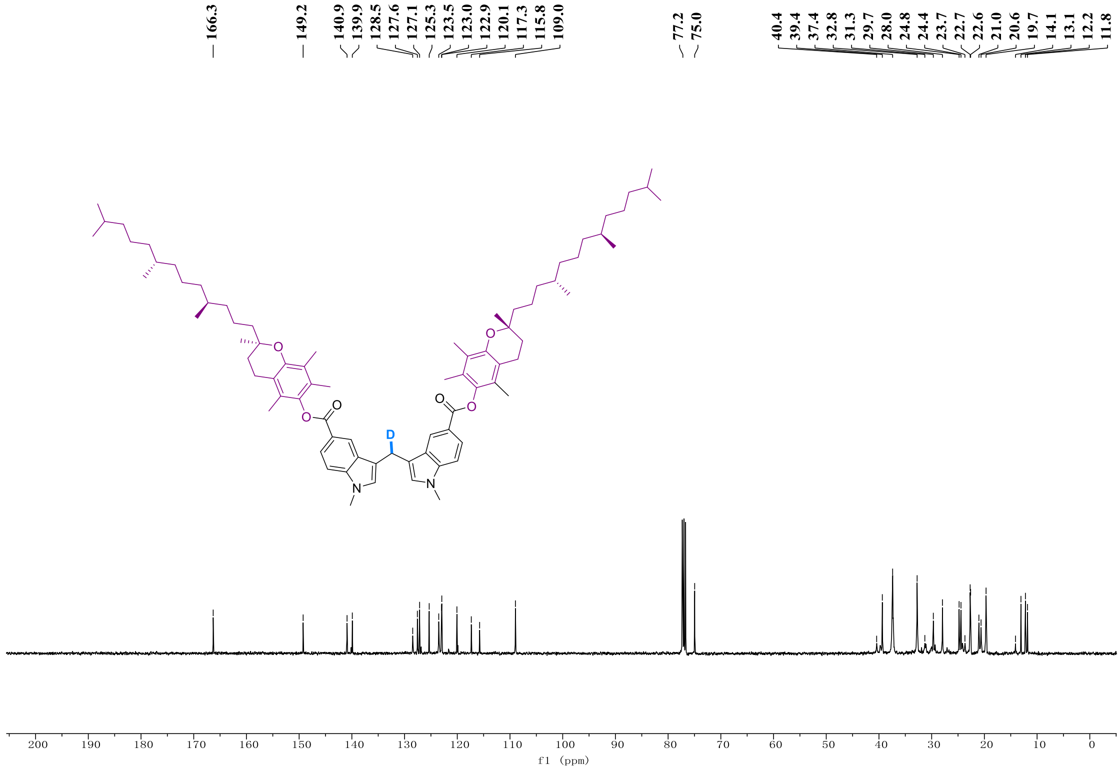
[13]C NMR of **8a** (100 MHz, $CDCl_3$)



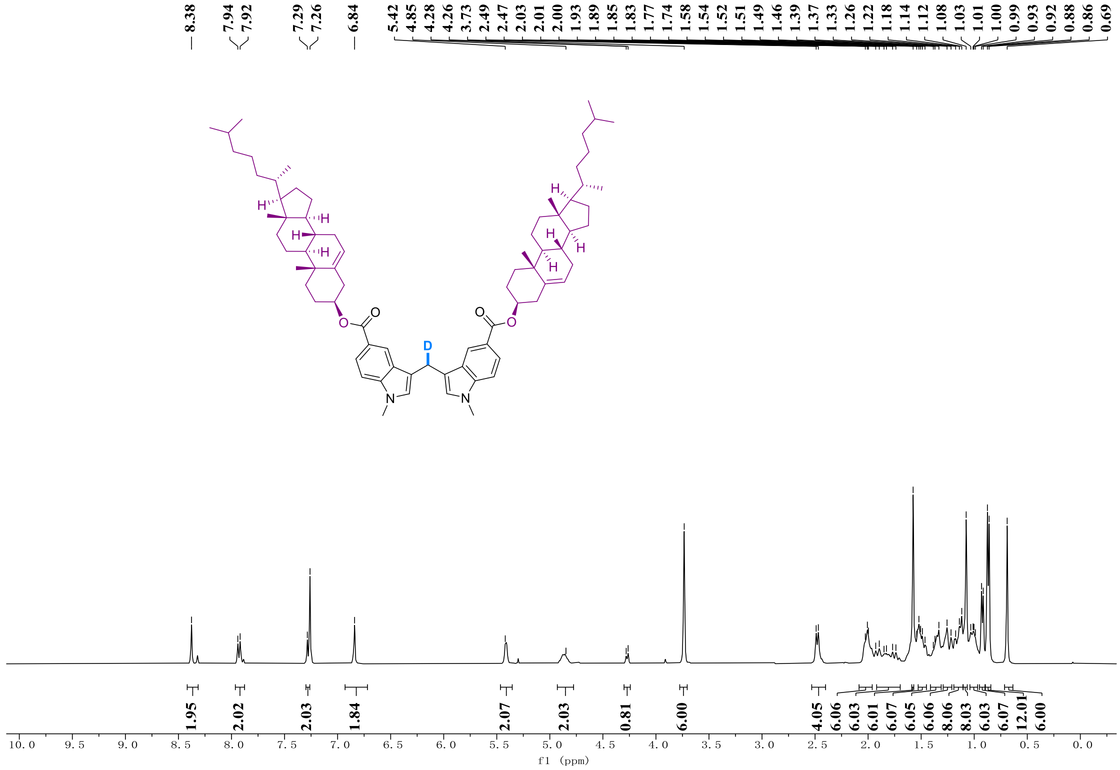
^{1}H NMR of **8b** (400 MHz, $CDCl_3$)



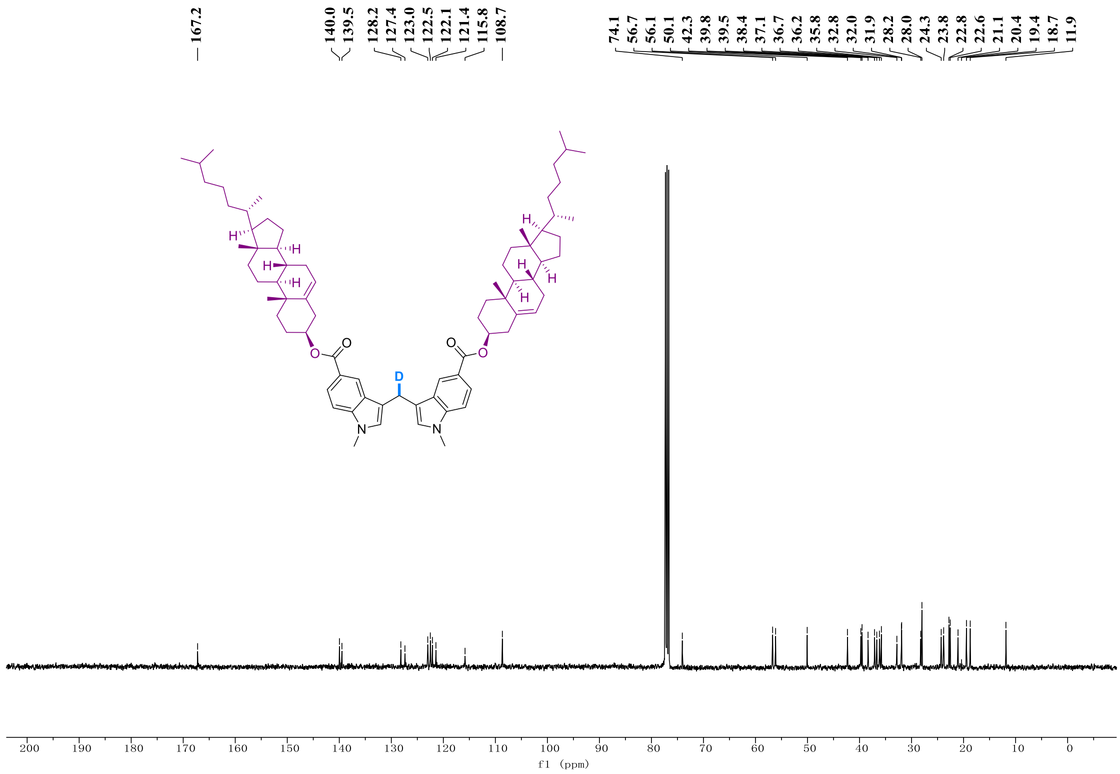
^{13}C NMR of **8b** (100 MHz, $CDCl_3$)



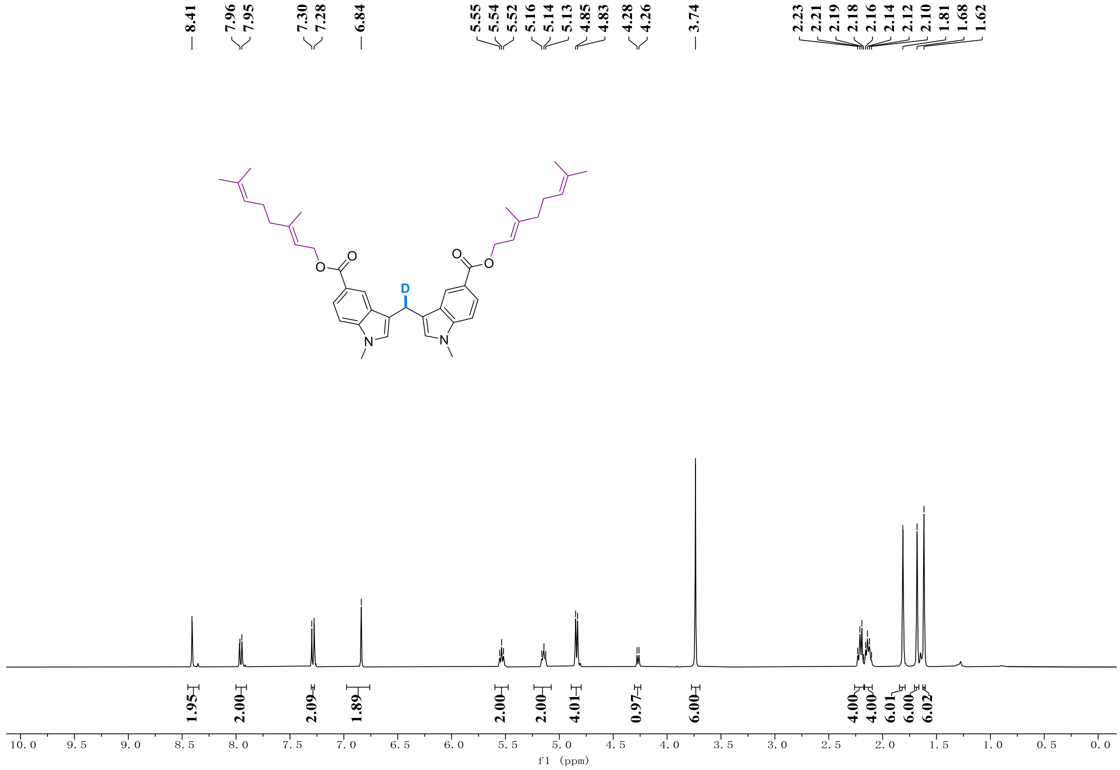
^{1}H NMR of **8c** (400 MHz, $CDCl_3$)



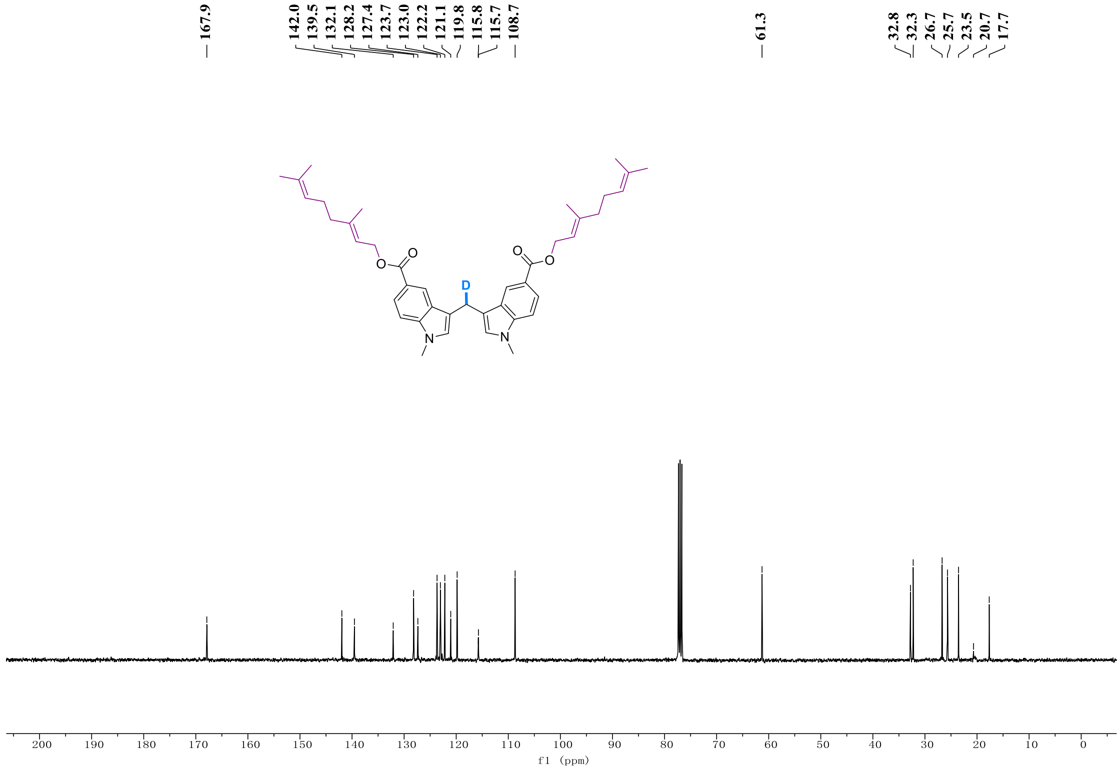
^{13}C NMR of **8c** (100 MHz, $CDCl_3$)



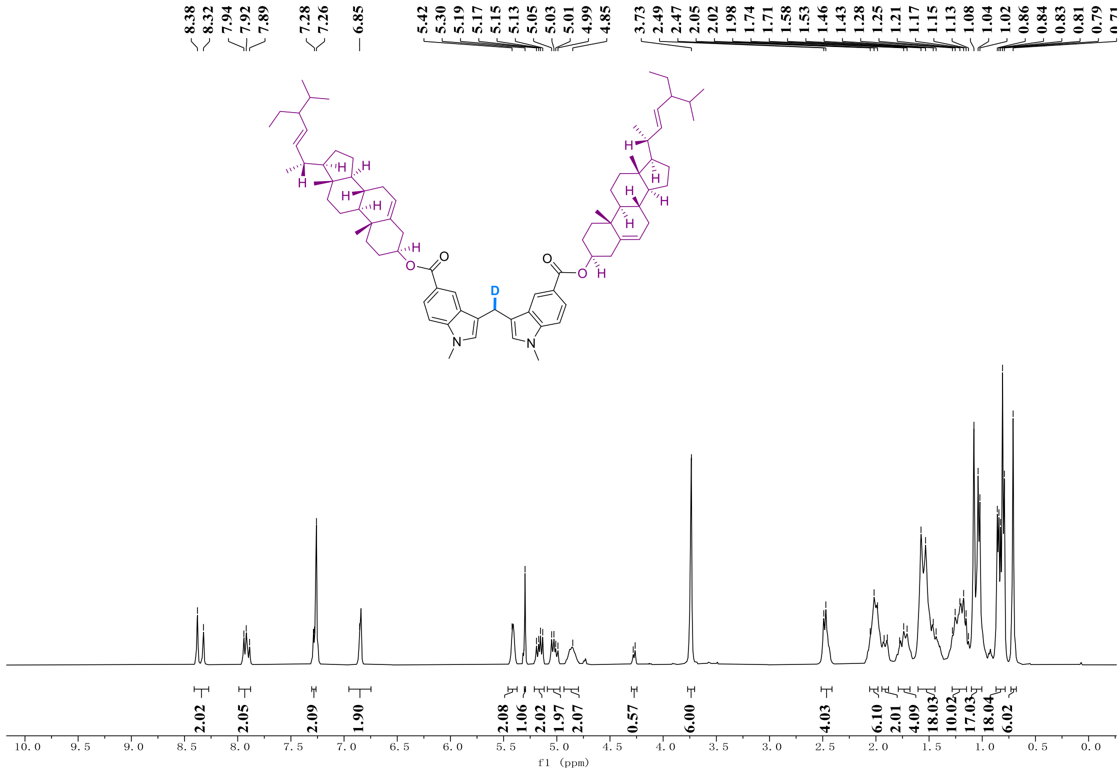
^{1}H NMR of **8d** (400 MHz, $CDCl_3$)



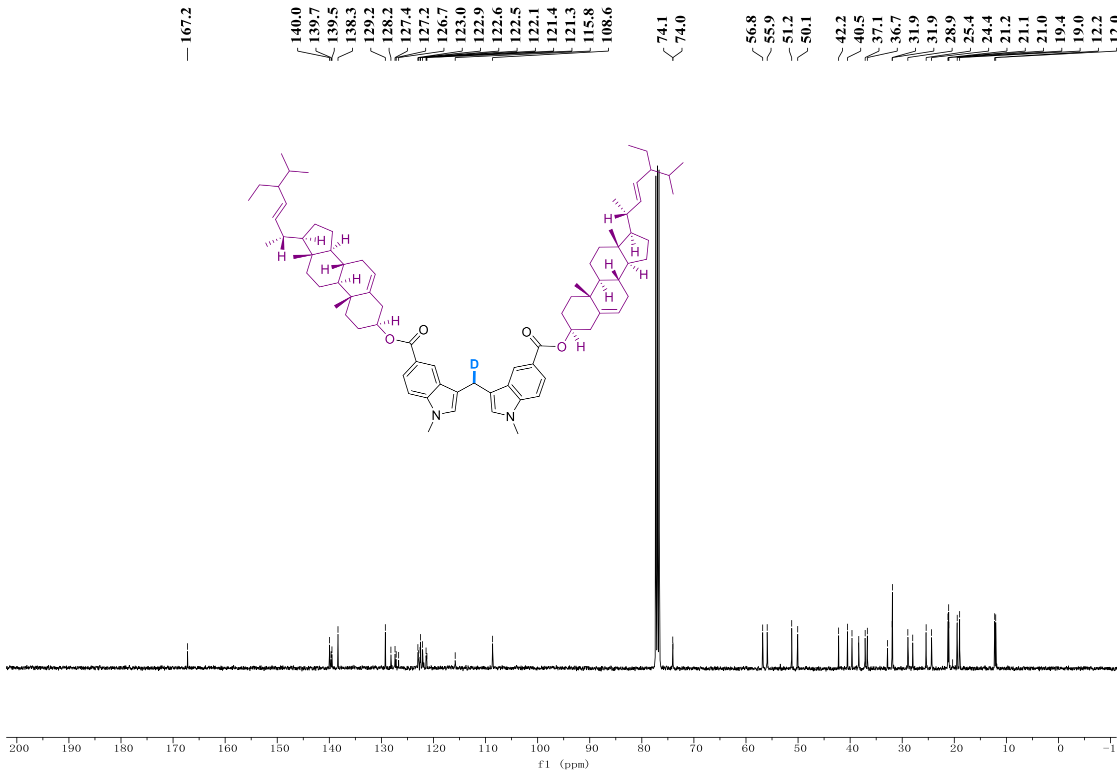
^{13}C NMR of **8d** (100 MHz, $CDCl_3$)



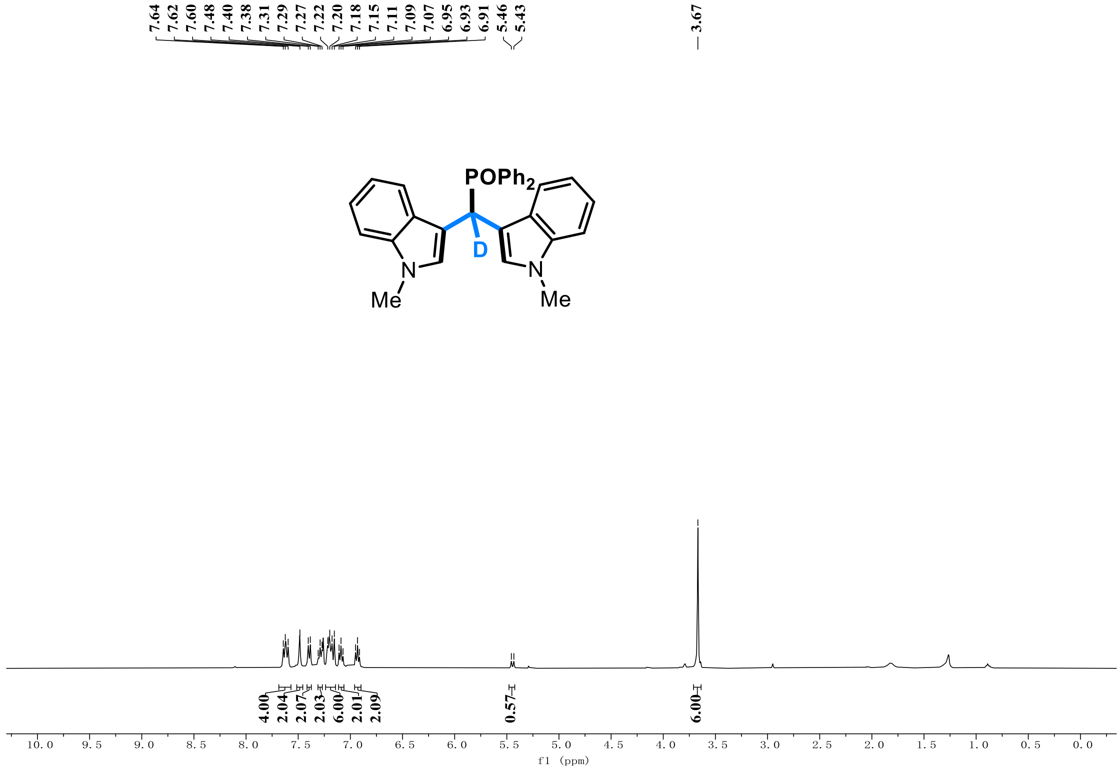
^{1}H NMR of **8e** (400 MHz, $CDCl_3$)



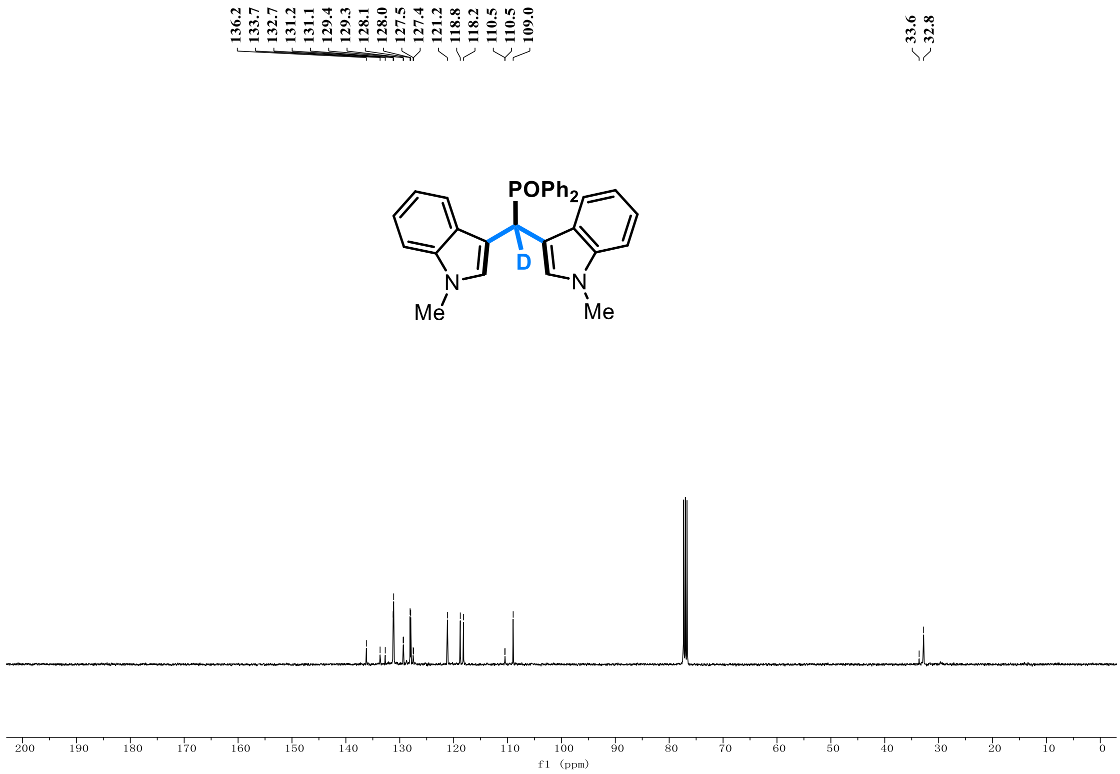
^{13}C NMR of **8e** (100 MHz, $CDCl_3$)



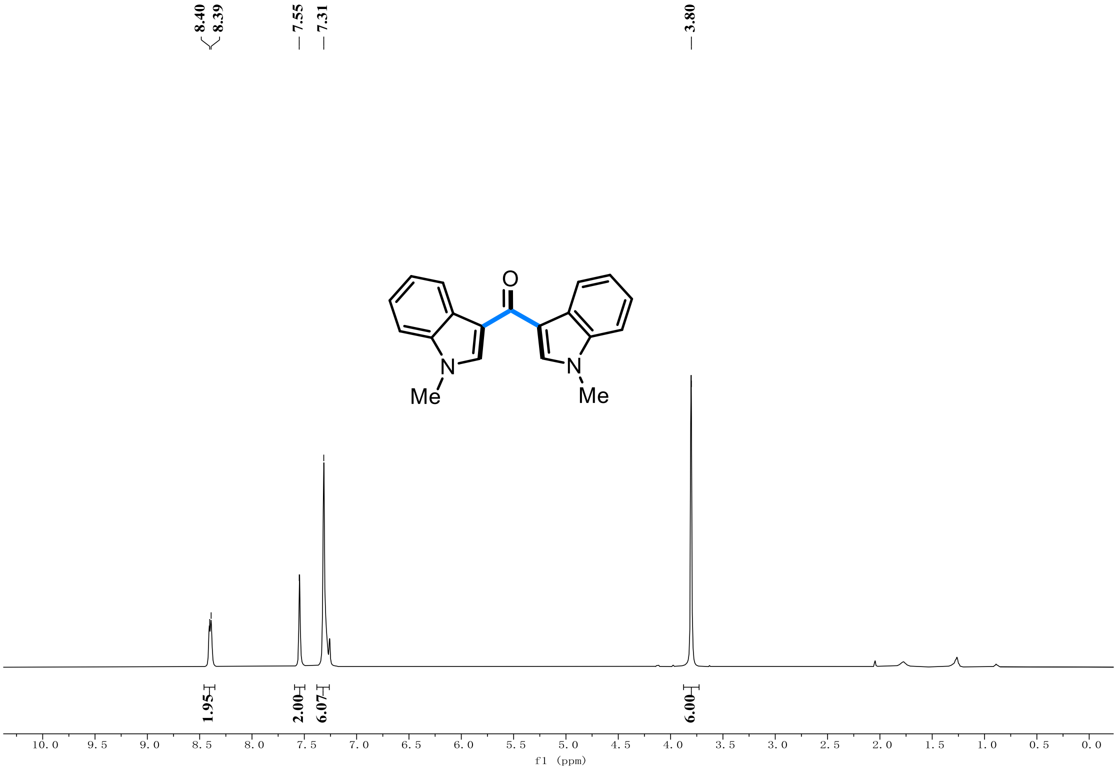
^{1}H NMR of **9** (400 MHz, $CDCl_3$)



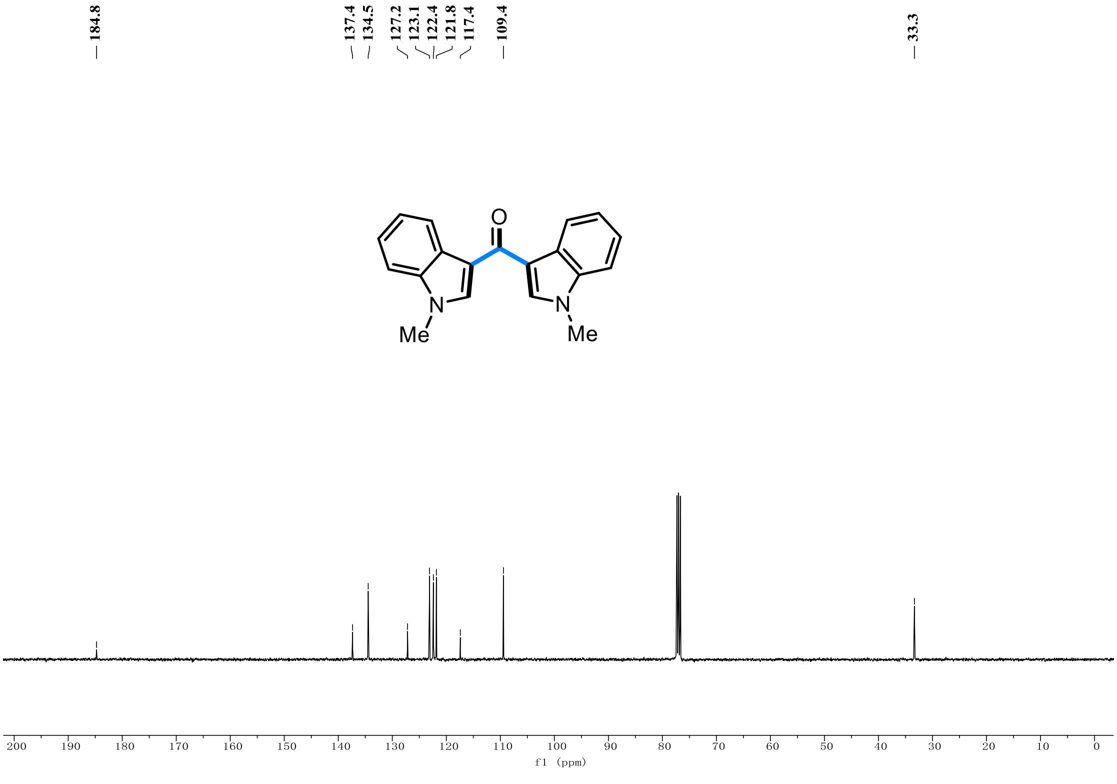
^{13}C NMR of **9** (100 MHz, $CDCl_3$)



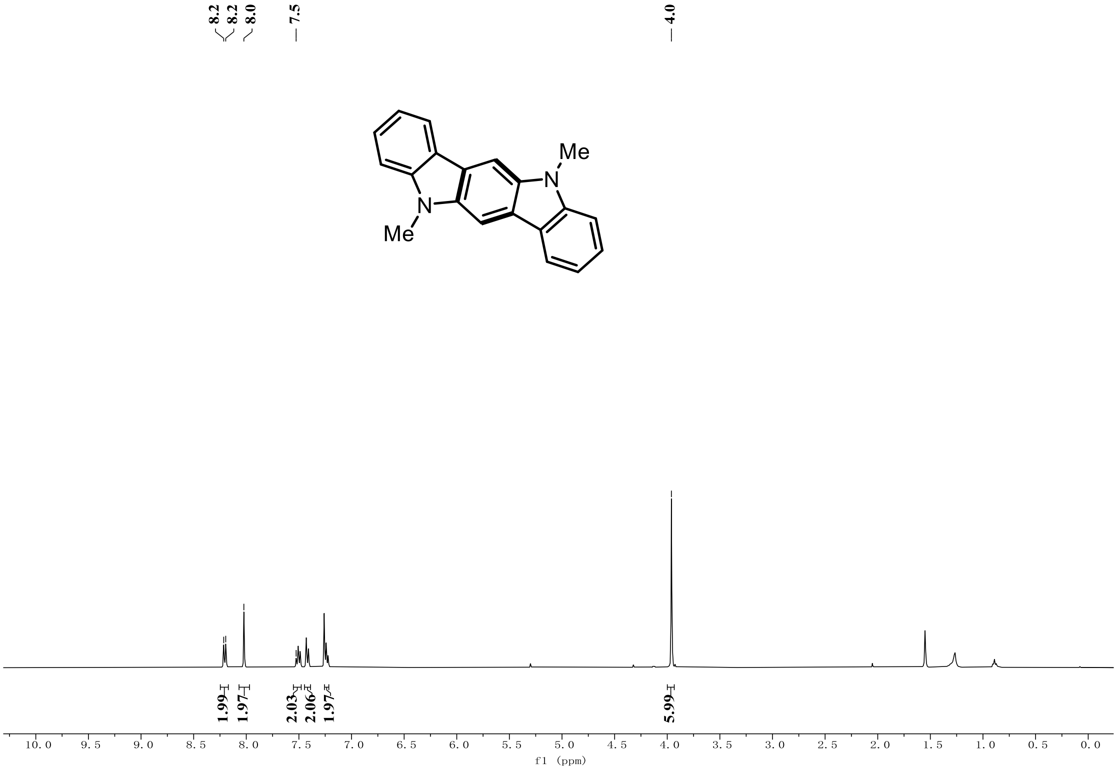
^{1}H NMR of **10** (400 MHz, $CDCl_3$)



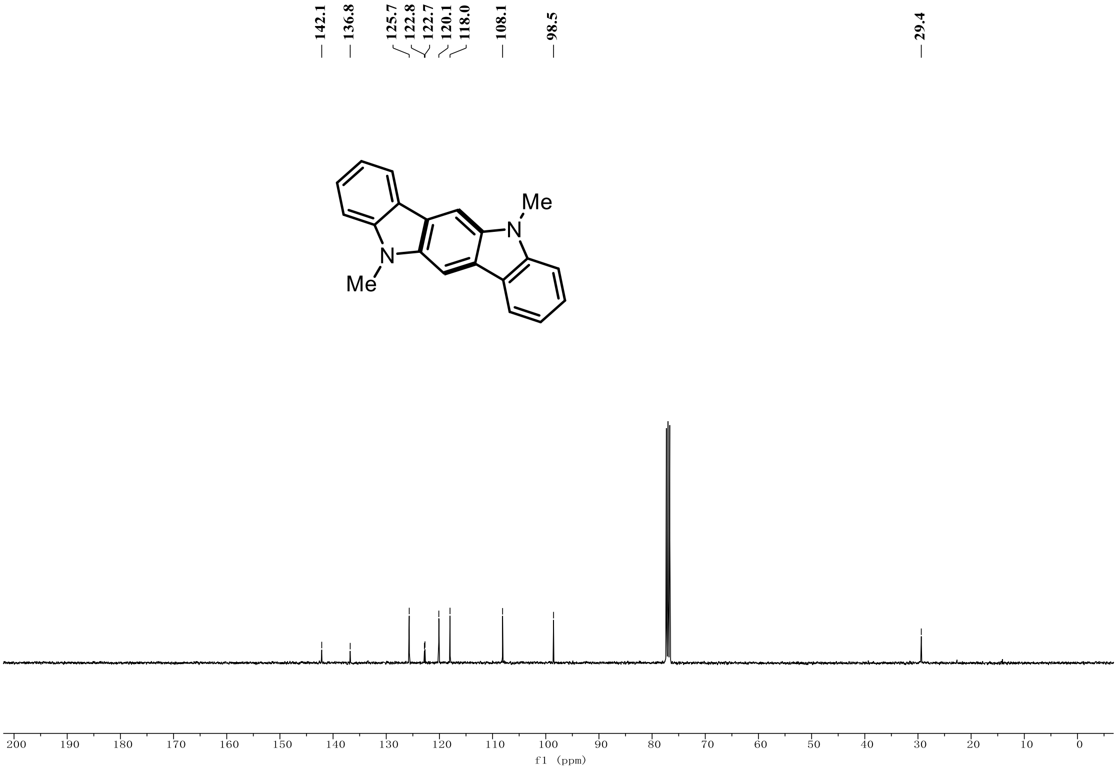
^{13}C NMR of **10** (100 MHz, $CDCl_3$)



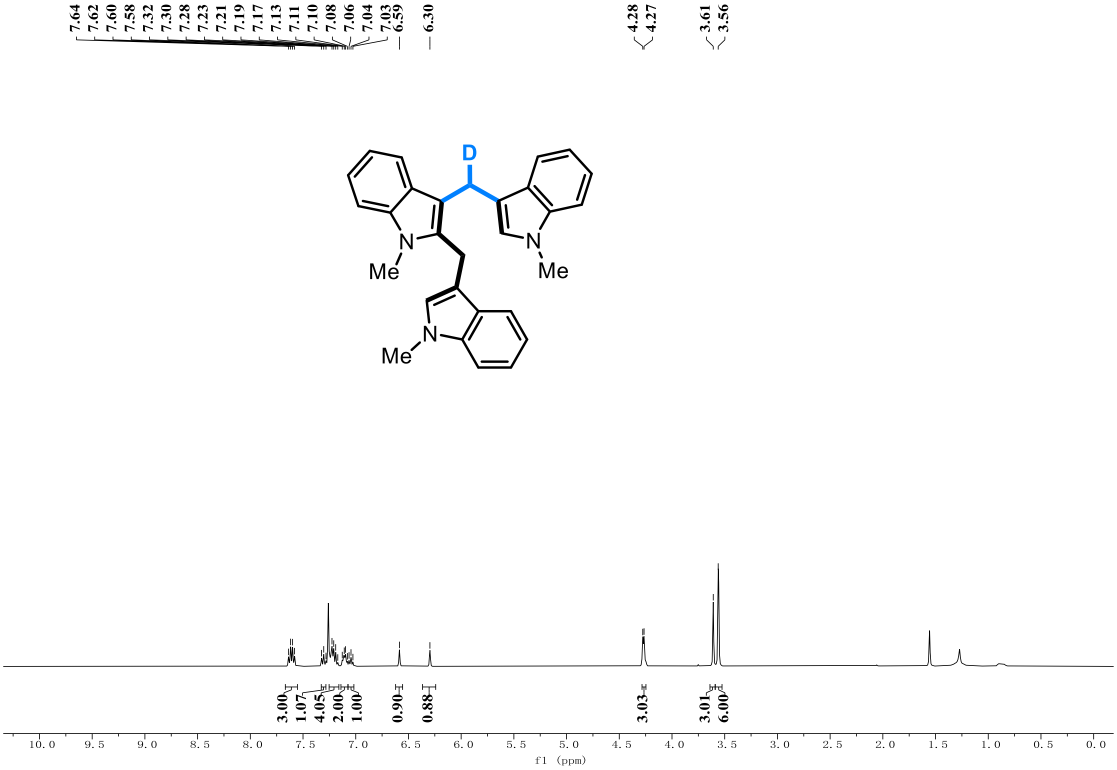
^1H NMR of **11** (400 MHz, $CDCl_3$)



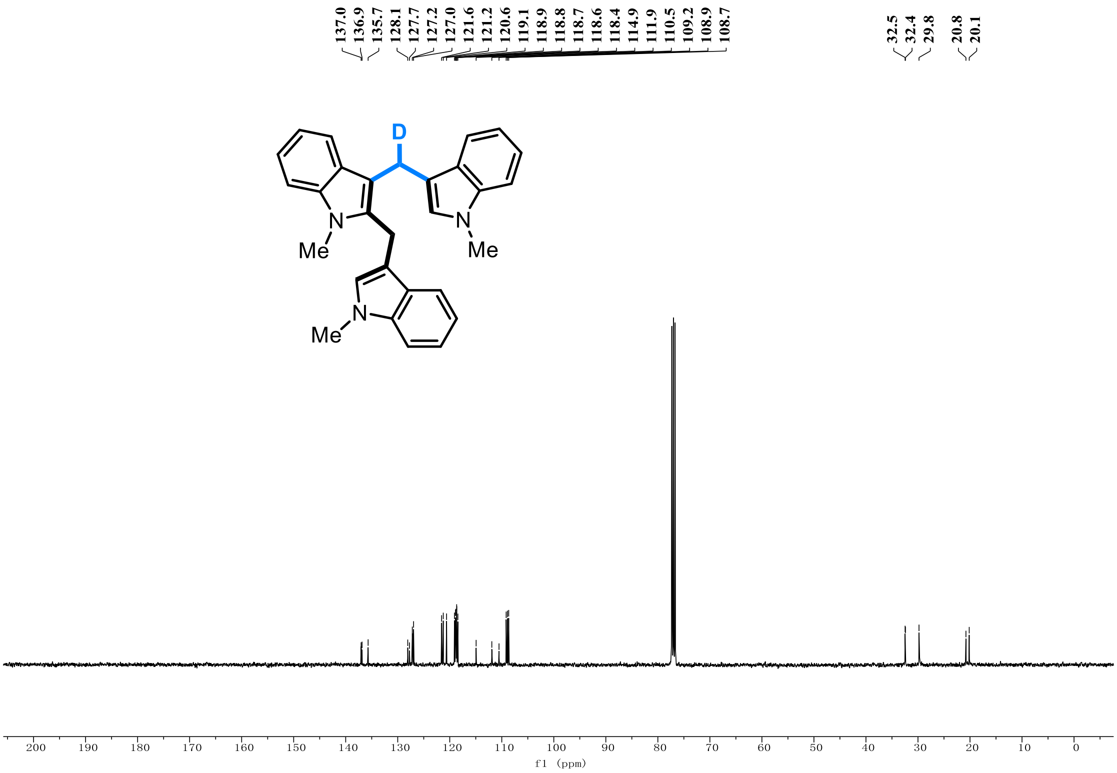
^{13}C NMR of **11** (100 MHz, $CDCl_3$)



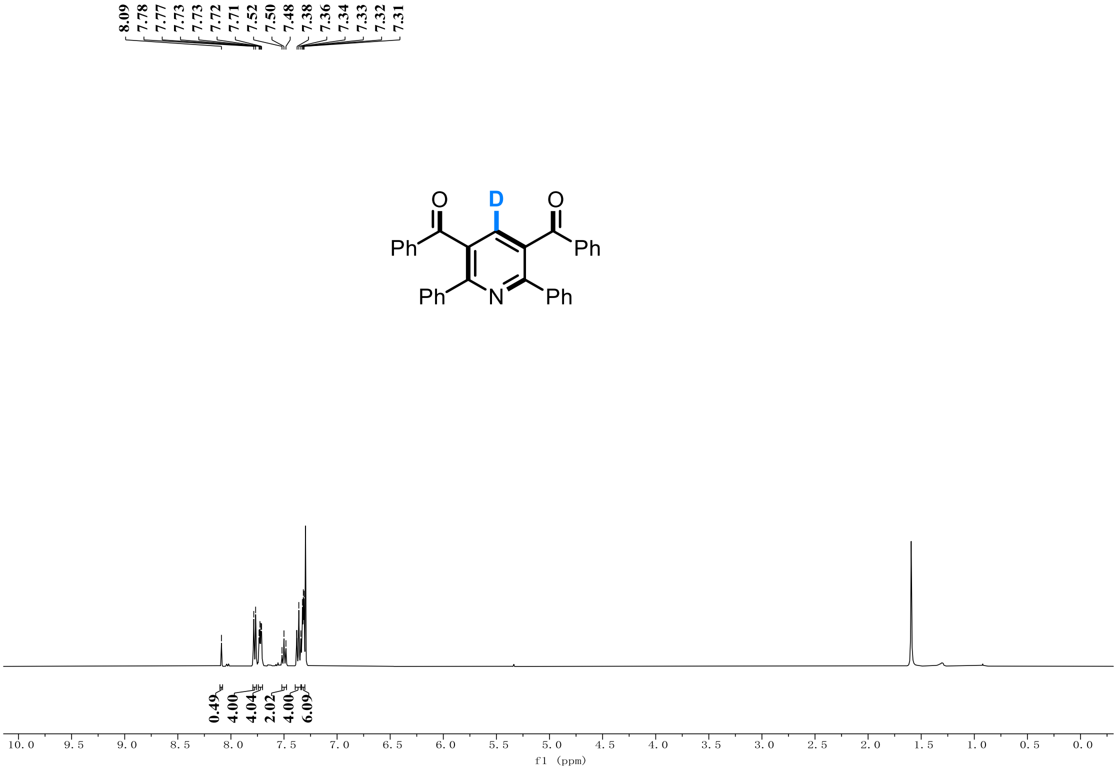
^{1}H NMR of **12** (400 MHz, $CDCl_3$)



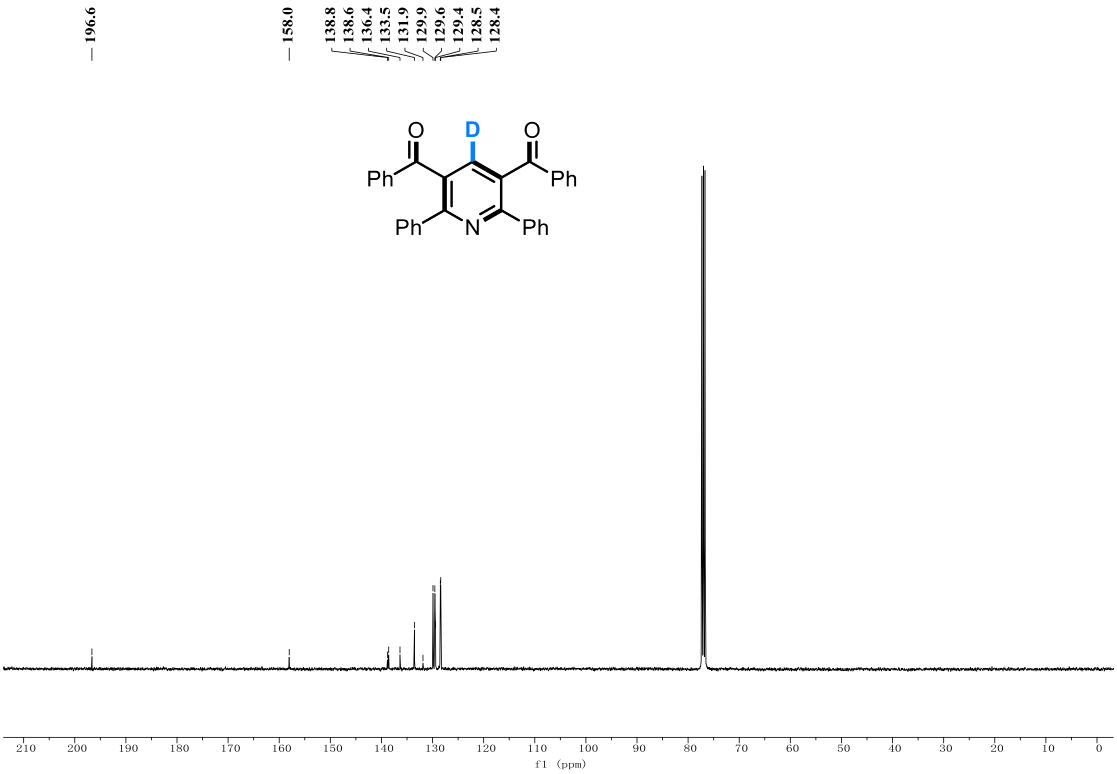
^{13}C NMR of **12** (100 MHz, $CDCl_3$)



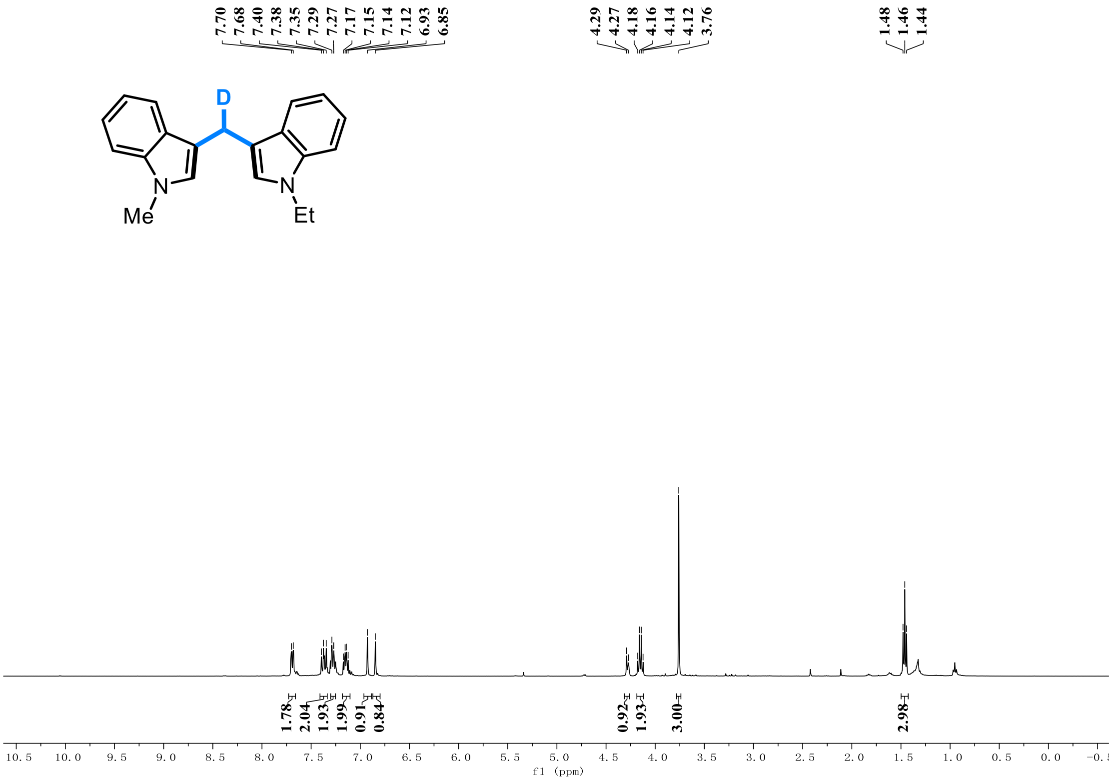
[1]H NMR of **13** (400 MHz, $CDCl_3$)



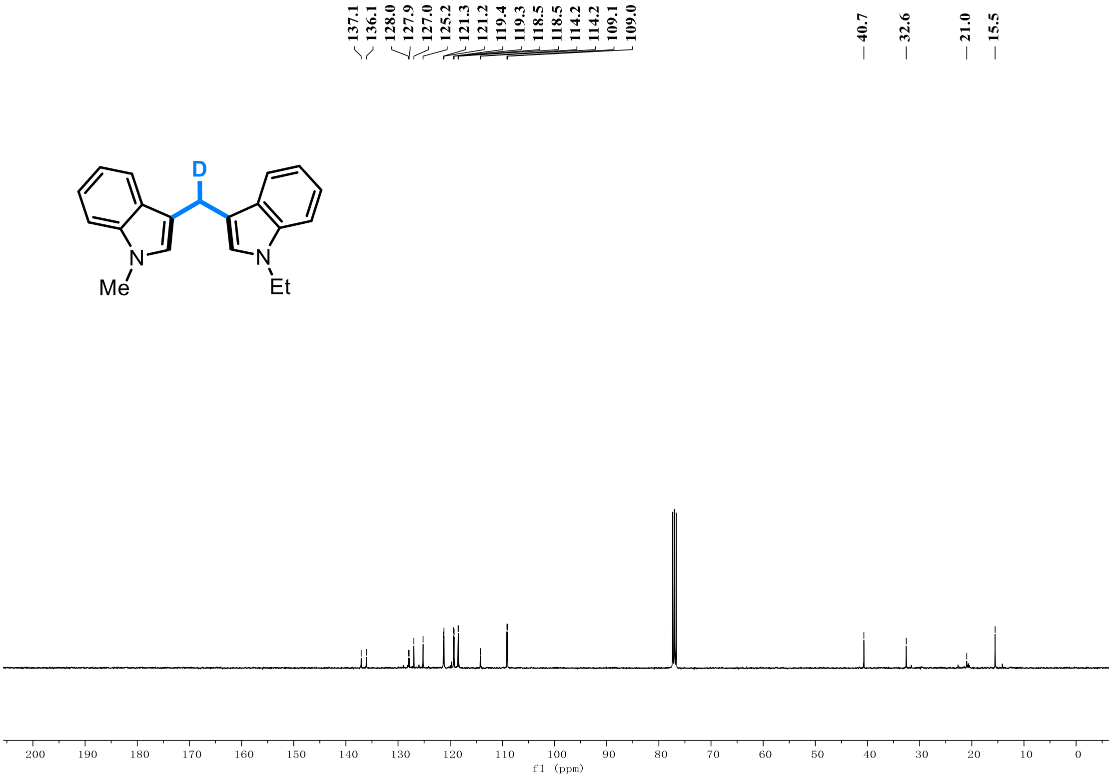
[13]C NMR of **13** (100 MHz, $CDCl_3$)



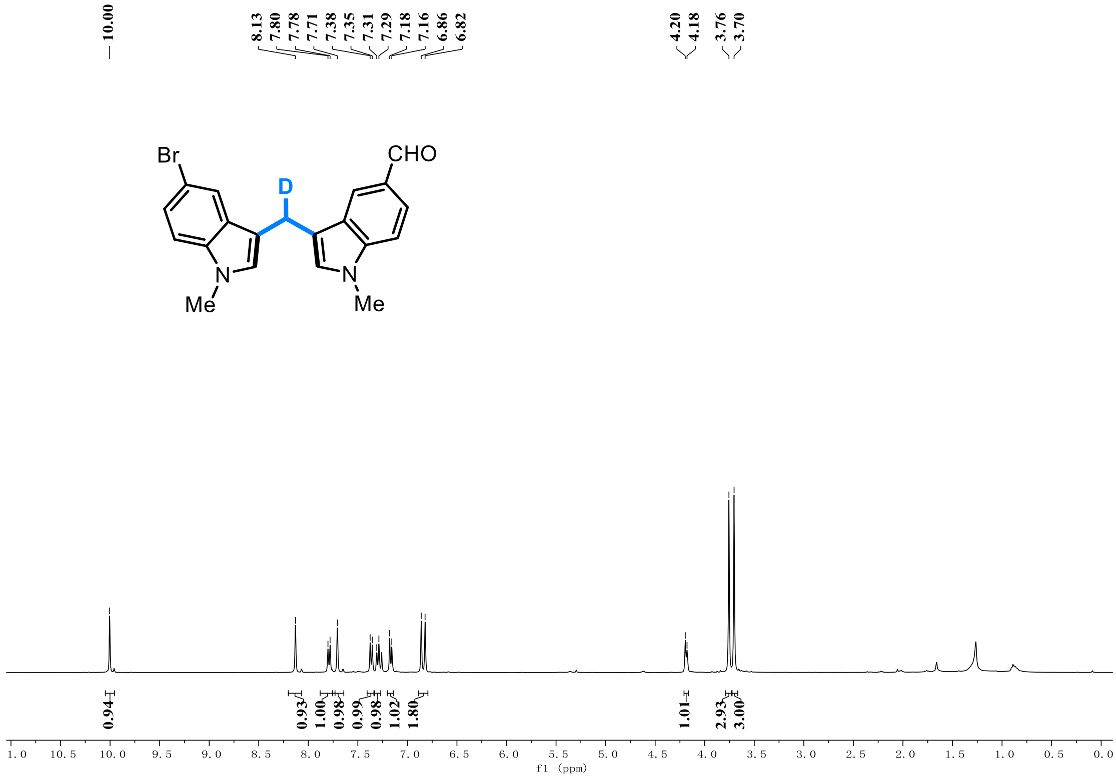
^{1}H NMR of **2k'** (400 MHz, $CDCl_3$)



^{13}C NMR of **2k'** (100 MHz, $CDCl_3$)



^{1}H NMR of **2l'** (400 MHz, $CDCl_3$)



^{13}C NMR of **2l'** (100 MHz, $CDCl_3$)