Supporting Information

Selective Deuteroreduction of Alkynes by Zn/Mn with Nickel Catalysis under Mechanical Conditions

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1. General Information

Unless otherwise stated, all reagents were purchased from commercial sources, used without further purification. All solvents were purchased in their anhydrous form or dried over activated 4Å molecular sieves. Deuterium oxide (99.8% D, designated for NMR applications), nickel(II) chloride ethylene glycol dimethyl ether complex (98% purity), Zn and Mn reducing agents were used without prior drying, though they were stored in a desiccator. Prior to the experiment, all glassware was subjected to a drying procedure in a horizontal drying oven at 120 °C for 2 hours.

Ball milling was carried out using a Retsch MM 400 mixer mill. Unless otherwise stated, mechanochemical reactions were conducted in 5 mL stainless-steel jars with stainless-steel balls (10 mm in diameter). The stainless-steel jar and grinding ball were rigorously dried before use. Subsequent to the ball milling reaction, the post-treatment protocol entailed filtration through disposable short-type glass Pasteur pipettes (WITEG). These pipettes were preloaded with cotton and 200-300 mesh silica gel powder. A binary solvent system composed of ethyl acetate and petroleum ether in a 1:1 volumetric ratio (PE:EA = 1:1) was employed as the eluent during filtration.

Nuclear magnetic resonance (NMR) spectra for ^{1}H and ^{13}C were acquired using a Bruker Avance 400 spectrometer. Chemical shifts (δ) are presented in parts per million (ppm), referenced to the residual solvent peaks. Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectrometry (HRMS) analyses were performed on Agilent Technologies 6545 Q-TOF LC/MS system equipped with an ESI ion Source. Gas chromatography (GC) analyses were conducted on a SHIMADZU GC-2030AF gas chromatograph equipped with an Agilent DB-5MS capillary column (30 m in length, 0.25 mm internal diameter, and 0.25 μm film thickness). Gas chromatography-mass spectrometry (GC-MS) analyses were performed using a SHIMADAZU GC-MS QP2010 Plus instrument, equipped with an Agilent HP-5MS capillary column (30 m × 0.25 mm × 0.25 μm). X-ray powder diffraction (XRD) was performed for alloy testing using a Rigaku Mini Flex 600 instrument.

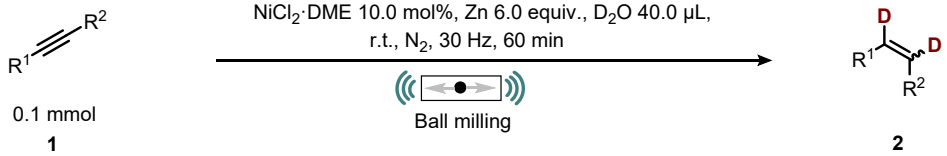
1.1 Equipment used in this Study

Retsch MM400 | **Stainless-steel balls (diameter 10 mm)** | **Stainless jar (5 mL)**

Figure S1: Equipment used in this study

2. Optimization of Reaction Condition

2.1 General procedure for semi-deuteration conditions (Zn)



Zn (39.2 mg, 6.0 equiv.) and nickel(II) chloride ethylene glycol dimethyl ether complex ($NiCl_2$·DME, 2.2 mg, 10.0 mol%) were introduced into a 5 mL stainless-steel ball milling jar. Subsequently, the jar was transferred into a glovebox purged with nitrogen. Then, 0.1 mmol of the alkyne substrate and 40 μL of deuterium oxide (D_2O) were added to the stainless-steel ball milling jar. The jar was sealed and then placed into a Retsch MM400 mixer mill, where it was milled at a frequency of 30 Hz for 60 minutes. Upon completion of the ball milling operation, the reaction mixture was diluted with a binary solvent system composed of ethyl acetate and petroleum ether at a volume ratio of 1:1 (PE:EA = 1:1). Subsequently, the mixture was filtered through a disposable WITEG short-type glass Pasteur pipette pre-packed with cotton and 200-300 mesh silica gel powder, using the aforementioned ethyl acetate/petroleum ether mixture (PE:EA = 1:1) as the eluent. The resulting filtrate was thoroughly concentrated under reduced pressure. The residue was further purified via silica gel column chromatography to yield the desired semi-deuteration products. Deuterium incorporation was determined by ^1H NMR spectroscopy.

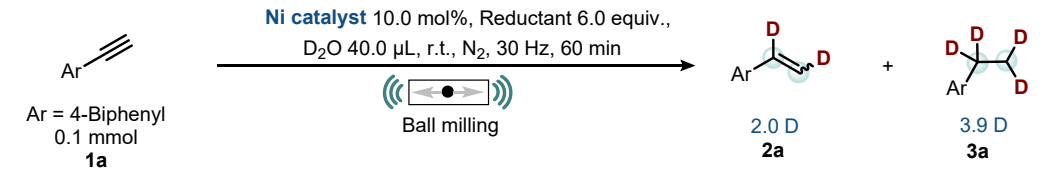
2.2 General procedure for tetra-deuteration conditions (Mn)

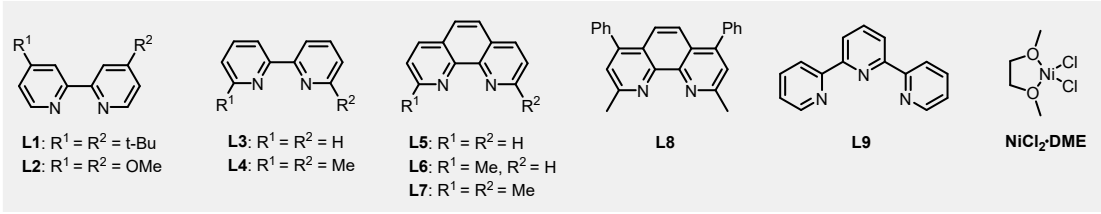
Mn (32.9 mg, 6.0 equiv.) and nickel(II) chloride ethylene glycol dimethyl ether complex ($NiCl_2$·DME, 2.2 mg, 10.0 mol%) were introduced into a 5 mL stainless-steel ball milling jar. Subsequently, the jar was transferred into a glovebox purged with nitrogen. Then, 0.1 mmol of the alkyne substrate and 40 μL of deuterium oxide (D_2O) were added to the stainless-steel ball milling jar. The jar was sealed and then placed into a Retsch MM400 mixer mill, where it was milled at a frequency of 30 Hz for 60 minutes. Upon completion of the ball milling operation, the reaction mixture was diluted with a binary solvent system composed of ethyl acetate and petroleum ether at a volume ratio of 1:1 (PE:EA = 1:1). Subsequently, the mixture was filtered through a disposable WITEG short-type glass Pasteur pipette pre-packed with cotton and 200-300 mesh silica gel powder, using the aforementioned ethyl acetate/petroleum ether mixture (PE:EA = 1:1) as the eluent. The resulting filtrate was thoroughly concentrated under reduced pressure. The residue was further purified via silica gel column chromatography to yield the desired tetra-deuteration products. Deuterium incorporation was determined by ^1H NMR spectroscopy.

2.3 Condition optimization

Table S1. Optimization of catalyst ligands under semi-deuteration conditions (Zn) / tetra-

deuteration conditions (Mn)

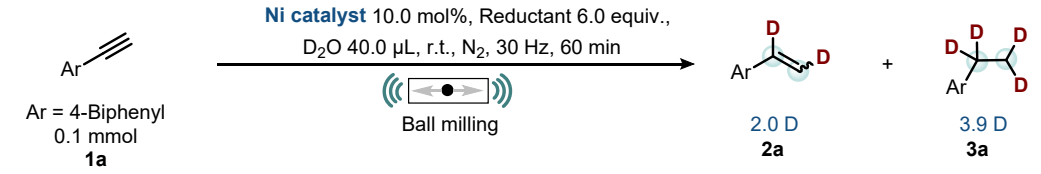




Entry	Reductant	Ni catalyst	Ligands	Yield[a] 2a	Yield[a] 3a
1	Zn	$NiCl_2$·DME	/	89%	Trace
2	Mn	NiI_2	**L1**	12%	N.D.
3	Mn	$NiBr_2$	**L1**	43%	6%
4	Mn	$NiCl_2$	**L1**	52%	16%
5	Mn	$NiCl_2$	**L2**	41%	5%
6	Mn	$NiCl_2$	**L3**	N.D.	N.D.
7	Mn	$NiCl_2$	**L4**	5%	67%
8	Mn	$NiCl_2$	**L5**	19%	N.D.
9	Mn	$NiCl_2$	**L6**	45%	9%
10	Mn	$NiCl_2$	**L7**	51%	12%
11	Mn	$NiCl_2$	**L8**	N.D.	3%
12	Mn	$NiCl_2$	**L9**	N.D.	N.D.
13	Mn	$NiCl_2$·DME	/	N.D.	97%

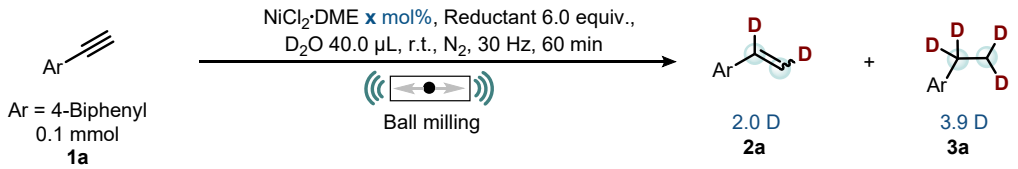
[a] GC yield was determined using *n*-dodecane as an internal standard.

Table S2. Optimization of catalyst under tetra-deuteration conditions (Mn)



Entry	Reductant	Ni catalyst	Yield[a] 2a	Yield[a] 3a
1	Mn	NiF_2	4%	71%
2	Mn	NiI_2	Trace	58%
3	Mn	$NiBr_2$	2%	52%
4	Mn	$NiCl_2$	2%	55%
5	Mn	$Ni(OAc)_2$	3%	61%
6	Mn	$Ni(acac)_2$	16%	29%
7	Mn	$NiCl_2$·DME	N.D.	97%
8	Zn	$NiCl_2$·DME	89%	N.D.

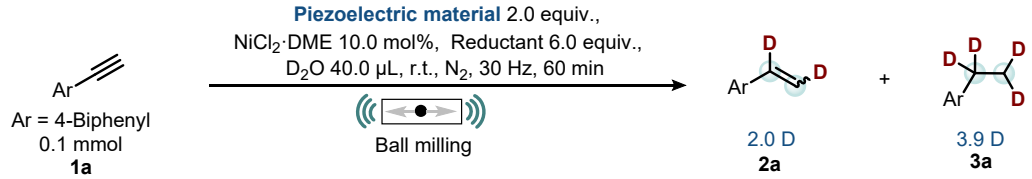
Table S3. Optimization of catalyst content under tetra-deuteration conditions (Mn)



Entry	Reductant	Ni catalyst	Yield[a] 2a	Yield[a] 3a
1	Mn	5 mol%	4%	71%
2	Mn	10 mol%	N.D.	97%
3	Mn	20 mol%	N.D.	89%
4	Mn	30 mol%	2%	83%
5	Zn	5 mol%	81%	N.D.
6	Zn	10 mol%	89%	Trace
7	Zn	20 mol%	70%	8%

[a] GC yield was determined using *n*-dodecane as an internal standard.

Table S4. Optimization of the piezoelectric material under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)

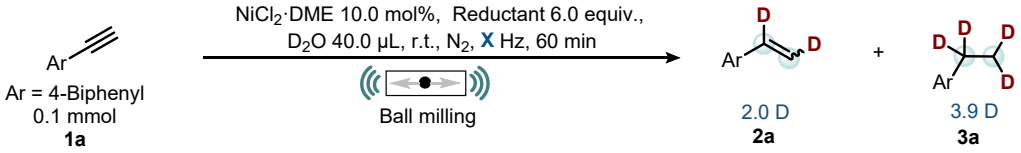


Entry	Reductant	Piezoelectric material	Yield[a] 2a	Yield[a] 3a
1	Zn	ZnO	86%	N.D.
2	Zn	$BaTiO_3$	84%	N.D.
3	Zn	$MgTiO_3$	14%	Trace
4	Zn	$SrTiO_3$	60%	Trace
5	Zn	$CaTiO_3$	51%	Trace
6	Zn	AlN	44%	Trace
7	Zn	$PbZrO_3$	6%	N.D.
8	Zn	ZnS	82%	Trace
9	Zn	Li_2TiO_3	44%	Trace
10	Zn	$LiNbO_3$	50%	Trace
11	Zn	/	89%	Trace
12	/	ZnO	N.D.	N.D.
13	/	$BaTiO_3$	N.D.	N.D.
14	Mn	ZnO	N.D.	93%
15	Mn	$BaTiO_3$	Trace	90%
16	Mn	$MgTiO_3$	N.D.	85%
17	Mn	$SrTiO_3$	2%	84%
18	Mn	$CaTiO_3$	39%	45%
19	Mn	AlN	64%	9%
20	Mn	$PbZrO_3$	53%	9%

21	Mn	ZnS	59%	11%
22	Mn	Li_2TiO_3	57%	13%
23	Mn	$LiNbO_3$	64%	19%
24	Mn	/	N.D.	97%

[a] GC yield was determined using *n*-dodecane as an internal standard.

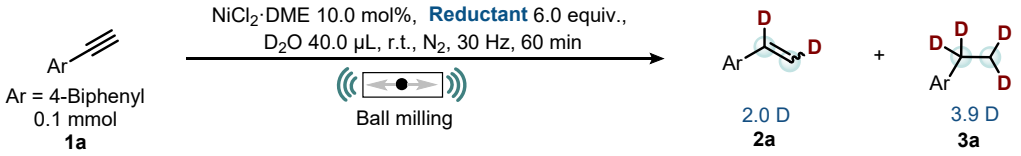
Table S5. Optimization of frequency (Hz) under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



Entry	Reductant	Frequency (Hz)	Yield[a] 2a	Yield[a] 3a
1	Zn	5	N.D.	N.D.
2	Zn	10	3%	N.D.
3	Zn	15	6%	N.D.
4	Zn	20	11%	Trace
5	Zn	25	50%	Trace
6	Zn	30	89%	Trace
7	Mn	5	5%	2%
8	Mn	10	29%	11%
9	Mn	15	53%	17%
10	Mn	20	55%	22%
11	Mn	25	7%	83%
12	Mn	30	N.D.	97%

[a] GC yield was determined using *n*-dodecane as an internal standard.

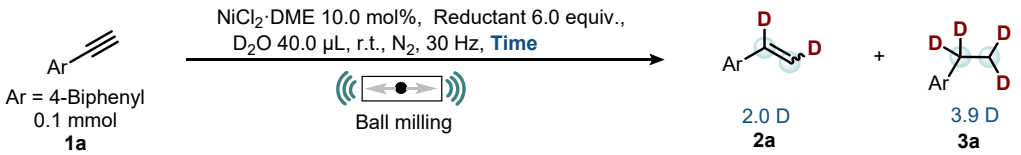
Table S6. Optimization of reductant under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



Entry	Reductant	Yield[a] 2a	Yield[a] 3a
1	Zn	89%	Trace
2	Fe	N.D.	N.D.
3	Ga	N.D.	N.D.
4	Mg	N.D.	58%
5	Mn	N.D.	97%

[a] GC yield was determined using *n*-dodecane as an internal standard.

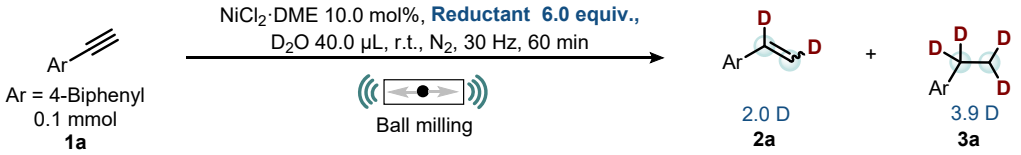
Table S7. Optimization of reaction time under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



Entry	Reductant	Reaction time (min)	Yield[a] 2a	Yield[a] 3a
1	Zn	10	3%	N.D.
2	Zn	20	18%	N.D.
3	Zn	30	32%	N.D.
4	Zn	40	44%	Trace
5	Zn	50	73%	Trace
6	Zn	60	89%	Trace
7	Zn	90	89%	Trace
8	Zn	120	87%	Trace
9	Mn	10	31%	6%
10	Mn	20	42%	8%
11	Mn	30	41%	27%
12	Mn	40	31%	41%
13	Mn	50	2%	88%
14	Mn	60	N.D.	97%

[a] GC yield was determined using *n*-dodecane as an internal standard.

Table S8. Optimization of reductant form under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



Entry	Reductant forms	Yield[a] 2a	Yield[a] 3a
1	Zn sheet	74%	N.D.
2	Zn wire	73%	N.D.
3	Zn powder (120 mesh)	80%	Trace
4	Zn powder (800 mesh)	89%	Trace
5	Without Reductant	N.D.	N.D.
6	Mn block	N.D.	79%
7	Mn sheet	N.D.	75%
8	Mn powder (100 mesh)	Trace	84%
9	Mn powder (325 mesh)	Trace	97%

[a] GC yield was determined using *n*-dodecane as an internal standard.

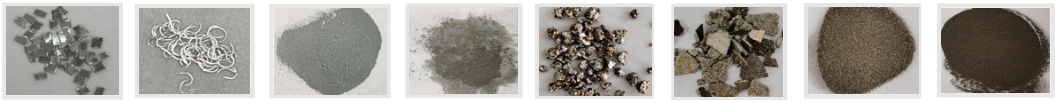
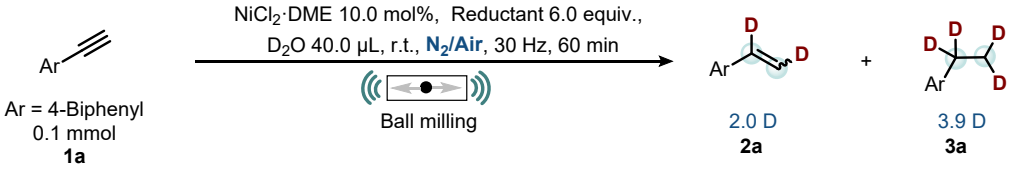


Figure S2: Different forms of reducing agents

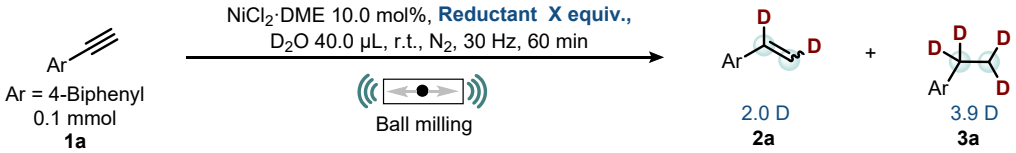
Table S9. Comparison of air and nitrogen conditions under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



Entry	Reductant	N_2/Air	Yield[a] 2a	Yield[a] 3a	Yield[a]1a
1	Zn	N_2	89%	Trace	Trace
2	Zn	Air	51%	N.D.	40%
3	Mn	N_2	N.D.	97%	N.D.
4	Mn	Air	54%	7%	26%

[a] GC yield was determined using *n*-dodecane as an internal standard.

Table S10. Optimization of reducing agent content under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



Entry	Reductant	Reductant X equiv.	Yield[a] 2a	Yield[a] 3a
1	Mn	4 equiv.	20%	65%
2	Mn	5 equiv.	Trace	77%
3	Mn	6 equiv.	N.D.	97%
4	Mn	7 equiv.	N.D.	95%
5	Mn	8 equiv.	N.D.	98%
6	Zn	4 equiv.	47%	N.D.
7	Zn	5 equiv.	73%	Trace
8	Zn	6 equiv.	89%	Trace
9	Zn	7 equiv.	88%	Trace
10	Zn	8 equiv.	90%	Trace

[a] GC yield was determined using *n*-dodecane as an internal standard.

2.3.1 Effect of milling jar materials on the reaction under semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)

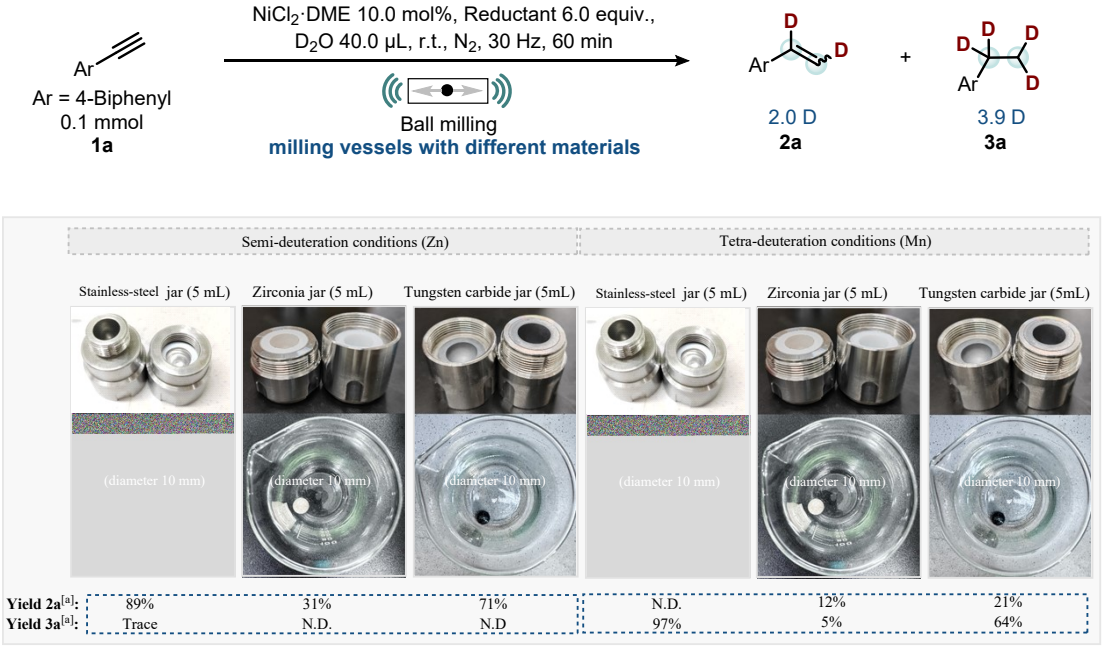
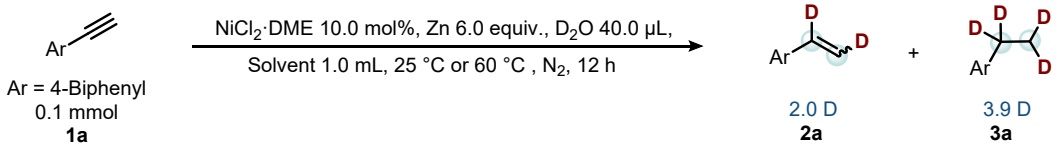


Figure S3: Effect of milling jar materials on the reaction

The experimental results clearly indicate that, under both semi-deuteration and tetra-deuteration conditions, zirconia milling media (balls and jars) afford poor reaction outcomes. In the semi-deuteration experiments, a tungsten carbide milling jar was able to give relatively moderate yields of **2a**. In the tetra-deuteration experiments, although the selectivity and yield in the tungsten carbide jar were reduced relative to those in the stainless-steel jar, the reaction was still promoted. Overall, the material of the milling jar and balls does affect the reaction. The effects of the milling jar material and composition, as well as the mass of the milling balls on the reaction, are also being further investigated in our ongoing studies.

3. Solvent Compare Experiments

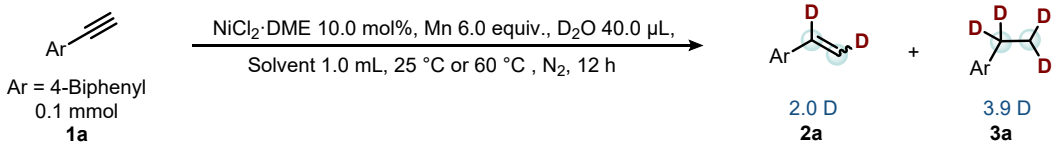
Table S11. Reactions in different solvents (under semi-deuteration conditions (Zn))



Entry	Solvent	Reductant	T(℃)	Yield[a] 2a	Yield[a] 3a
1	THF	Zn	25	5%	N.D.
2	Toluene	Zn	25	11%	N.D.
3	DCM	Zn	25	16%	N.D.
4	DMF	Zn	25	N.D.	N.D.
5	DMA	Zn	25	N.D.	N.D.
6	Xylenes	Zn	25	12%	Trace
7	Dioxane	Zn	25	6%	Trace
8	TFT	Zn	25	N.D.	N.D.
9	Benzene	Zn	25	9%	N.D.
10	CH_3CN	Zn	25	N.D.	N.D.
11	DMSO	Zn	25	N.D.	N.D.
12	$CHCl_3$	Zn	25	N.D.	N.D.
13	THF	Zn	60	39%	N.D.
14	Toluene	Zn	60	46%	4%
15	DCM	Zn	60	43%	19%
16	DMF	Zn	60	N.D.	N.D.
17	DMA	Zn	60	N.D.	N.D.
18	Xylenes	Zn	60	41%	Trace
19	Dioxane	Zn	60	43%	12%
20	TFT	Zn	60	22%	N.D.
21	Benzene	Zn	60	41%	Trace
22	CH_3CN	Zn	60	N.D.	N.D.
23	DMSO	Zn	60	N.D.	N.D.
24	$CHCl_3$	Zn	60	15%	N.D.

[a] GC yield was determined using *n*-dodecane as an internal standard.

Table S12. Reactions in different solvents (under tetra-deuteration conditions (Mn))



Entry	Solvent	Reductant	T (°C)	Yield[a] 2a	Yield[a] 3a
1	THF	Mn	25	Trace	N.D.
2	Toluene	Mn	25	Trace	6%
3	DCM	Mn	25	Trace	N.D.
4	DMF	Mn	25	N.D.	N.D.
5	DMA	Mn	25	N.D.	N.D.
6	Xylenes	Mn	25	Trace	8%
7	Dioxane	Mn	25	Trace	9%
8	TFT	Mn	25	N.D.	8%
9	Benzene	Mn	25	Trace	N.D.
10	CH_3CN	Mn	25	N.D.	N.D.
11	DMSO	Mn	25	N.D.	N.D.
12	$CHCl_3$	Mn	25	N.D.	N.D.
13	THF	Mn	60	65%	5%
14	Toluene	Mn	60	74%	14%
15	DCM	Mn	60	73%	7%
16	DMF	Mn	60	N.D.	N.D.
17	DMA	Mn	60	N.D.	N.D.
18	Xylenes	Mn	60	69%	12%
19	Dioxane	Mn	60	69%	9%
20	TFT	Mn	60	71%	11%
21	Benzene	Mn	60	32%	5%
22	CH_3CN	Mn	60	N.D.	N.D.
23	DMSO	Mn	60	N.D.	N.D.
24	$CHCl_3$	Mn	60	N.D.	N.D.

[a] GC yield was determined using *n*-dodecane as an internal standard.

Reaction conditions under 25°C / 60 °C: An 8 mL glass vial equipped with a magnetic stir bar was sequentially charged with Zn or Mn powder (6.0 equiv.), 4-ethynyl-1,1'-biphenyl (17.8 mg, 0.1 mmol), and nickel(II) chloride ethylene glycol dimethyl ether complex ($NiCl_2$·DME, 2.2 mg, 10.0 mol%). The vial was transferred to a glovebox (purged with nitrogen three times), and anhydrous solvent (1.0 mL) and deuterium oxide (D_2O, 40 μL) were then added. After sealing, the reaction mixture was stirred at 25 °C in an oil bath for 12 hours. Upon completion of the reaction, the mixture was filtered through a disposable WITEG short-type glass Pasteur pipette packed with cotton and 200-300 mesh silica gel powder, using a mixed solvent of ethyl acetate and petroleum ether (PE:EA =1:1) as the eluent. The yields were determined by GC analysis using *n*-dodecane as an internal standard.

4. Synthesis of Substrate

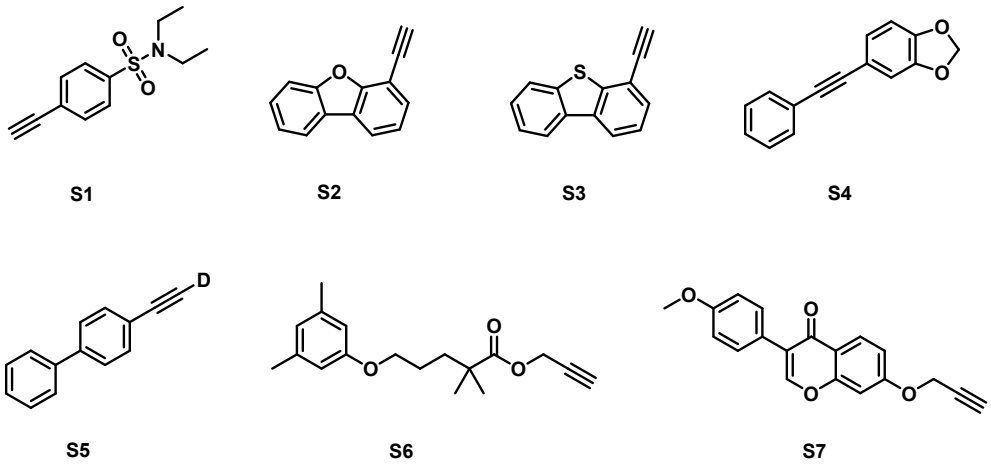
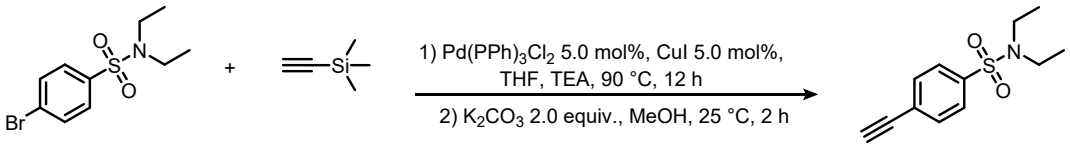


Figure S4: Substrates

Unless otherwise noted, commercial reagents were purchased from Energy Chemical, Bide Pharmatech used as received.

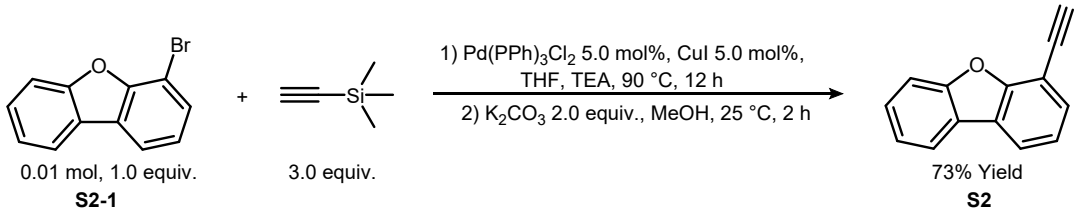
N,N-diethyl-4-ethynylbenzenesulfonamide (S1)



S1 was synthesized according to a literature procedure.[1] To a three-necked flask (equipped with magnetic stir bar and a nitrogen balloon) were added CuI (95 mg, 5.0 mol%), $PdCl_2(PPh_3)_2$ (351 mg, 5.0 mol%) and **S1-1** (2.92 g, 0.01 mol). Next, dry THF (10 mL) and dry TEA (10 mL) were introduced via a disposable syringe. After the addition of the solvents, ethynyl trimethylsilane (2.94 g, 0.03 mol) was added. The reaction mixture was stirred at 90 °C for 24 h. Upon completion of the reaction, as monitored by TLC, the reaction was quenched by the addition of water (20 mL). The mixture was then extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting concentrate was directly treated with MeOH (10 mL) and potassium carbonate (5.53 g, 0.04 mol). The reaction mixture was stirred at room temperature for 2 h. After the reaction was completed, as determined by TLC monitoring, the reaction solution was concentrated to dryness under reduced pressure. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure to produce crude product. The crude product was purified by column chromatography on silica gel (PE/EA = 20:1) to afford the pure product. The title compound was afforded as a brownish-yellow oily product (66% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 3.23 (s, 1H), 3.18 (q, *J* = 7.1 Hz, 4H), 1.07 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 140.33, 132.61, 126.86, 126.27, 82.01, 80.61, 42.03, 14.09.

5-ethynyldibenzo[b,d]furan (S2)

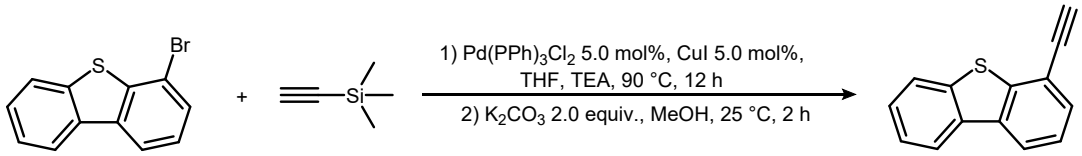


0.01 mol, 1.0 equiv. **S2-1** | 3.0 equiv. | 73% Yield **S2**

S2 was synthesized according to a literature procedure. [1] To a three-necked flask (equipped with magnetic stir bar, nitrogen balloon) was added CuI (95 mg, 5.0 mol%), $PdCl_2(PPh_3)_2$ (351 mg, 5.0 mol%) and **S2-1** (2.47 g, 0.01 mol). Next, dry THF (10 mL) and dry TEA (10 mL) were introduced via a disposable syringe. After the addition of the solvents, ethynyl trimethylsilane (2.94 g, 0.03 mol) was added. The reaction mixture was stirred at 90 °C for 24 h. Upon completion of the reaction, as monitored by TLC, the reaction was quenched by the addition of water (20 mL). The mixture was then extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting concentrate was directly treated with MeOH (10 mL) and potassium carbonate (5.53 g, 0.04 mol). The reaction mixture was stirred at room temperature for 2 h. After the reaction was completed, as determined by TLC monitoring, the reaction solution was concentrated to dryness under reduced pressure. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure to produce crude product. The crude product was purified by column chromatography on silica gel (PE/EA = 100:1) to afford the pure product. The title compound was afforded as a yellow oily product (73% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.52-7.47 (m, 1H), 7.34 (dt, *J* = 22.5, 7.6 Hz, 2H), 3.49 (s, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 156.59, 156.20, 131.08, 127.74, 124.55, 123.85, 123.19, 122.73, 121.53, 120.87, 112.10, 106.61, 82.35, 78.29.

4-bromodibenzo [b,d] thiophene (S3)



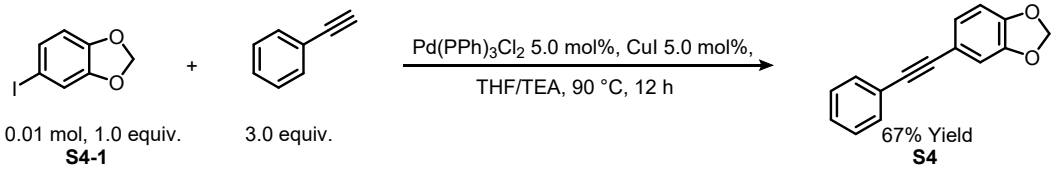
0.01 mol, 1.0 equiv. **S3-1** | 3.0 equiv. | 79% Yield **S3**

S3 was synthesized according to a literature procedure. [1] The procedure was adapted from a previously reported method. To a three necked flask (equipped with magnetic stir bar, nitrogen balloon) was added CuI (95 mg, 5.0 mol%), $PdCl_2(PPh_3)_2$ (351 mg, 5.0 mol%) and **S3-1** (2.63 g, 0.01 mol). The flask was purged with nitrogen three times. Next, dry THF (10 mL) and dry TEA (10 mL) was introduced via a disposable syringe. After the addition of the solvents, ethynyl

trimethylsilane (2.94 g, 0.03 mol) were added. The reaction mixture was stirred at 90 °C for 24 h. Upon completion of the reaction, as monitored by TLC, the reaction was quenched by the addition of water (20 mL). The mixture was then extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting concentrate was directly treated with MeOH (10 mL) and potassium carbonate (5.53 g, 0.04 mol). The reaction mixture was stirred at room temperature for 2 h. After the reaction was completed, as determined by TLC monitoring, the reaction solution was concentrated to dryness under reduced pressure. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure to produce crude product. The crude product was purified by column chromatography on silica gel (PE/EA = 100:1) to afford the pure product. The title compound was afforded as a brownish-yellow oily product (79% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 7.8 Hz, 2H), 7.92-7.86 (m, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.52-7.42 (m, 3H), 3.53 (s, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.06, 139.52, 135.68, 130.47, 127.23, 124.70, 124.52, 123.06, 122.11, 121.96, 116.89, 82.55, 81.33.

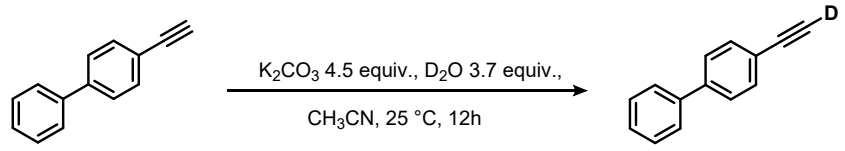
5-(phenylethynyl)benzo[d][1,3]dioxole (S4)



S4 was synthesized according to a literature procedure.[1] To a three necked flask (equipped with magnetic stir bar, nitrogen balloon) was added CuI (95 mg, 5.0 mol%), $PdCl_2(PPh_3)_2$ (351 mg, 5.0 mol%) and **S4-1** (2.48 g, 0.01 mol). Next, dry THF (10 mL) and dry TEA (10 mL) were introduced via a disposable syringe. After the addition of the solvents, ethynylbenzene (3.15 g, 0.03 mol) were added. The reaction mixture was stirred at 90 °C for 24 h. Upon completion of the reaction, as monitored by TLC, the reaction was quenched by the addition of water (20 mL). The mixture was then extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA = 20:1) to afford the pure product. The title compound was afforded as a white solid product (67% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (dd, *J* = 7.9, 2.4 Hz, 2H), 7.38-7.31 (m, 3H), 7.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.00 (d, *J* = 1.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.99 (s, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 148.00, 147.56, 131.60, 128.45, 128.19, 126.38, 123.45, 116.61, 111.66, 108.61, 101.44, 89.43, 87.90.

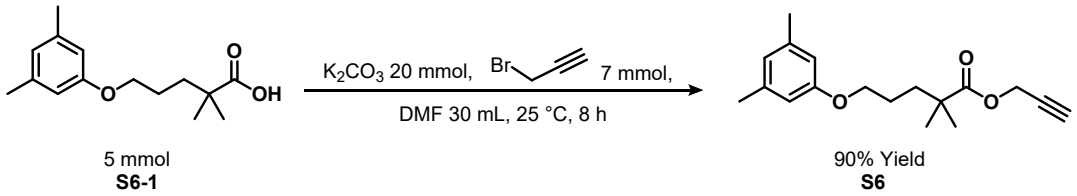
4-(Ethynyl-2-d)-1,1'-bipheny(S5)



S5 was synthesized according to a literature procedure.[2] A 50 mL round-bottom flask equipped with a magnetic stir bar was sequentially charged with **S5-1** (1.78 g, 0.01 mol), K_2CO_3 (6.22 g, 0.045 mol). The flask was transferred to a glovebox, purged with nitrogen three times, and then supplemented with anhydrous CH_3CN (2.0 mL) and deuterated water (D_2O, 40 μL). After sealing, the reaction mixture was stirred at 25 °C for 12 hours. The reaction was quenched with distilled water and extracted with dichloromethane (3 × 10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 then concentrated. The reaction was repeated three times to allow for full deuterium incorporation. The title compound was afforded as a white solid product (48% yield, 96% D).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62-7.55 (m, 6H), 7.49-7.43 (m, 2H), 7.40-7.36 (m, 1H), 3.14 (S, 0.04)H. **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.68, 140.36, 132.68, 129.00, 127.86, 127.18, 127.13, 121.08, 83.23, 83.16, 77.36 (multiplet overlapping with $CDCl_3$ signal, 1C).

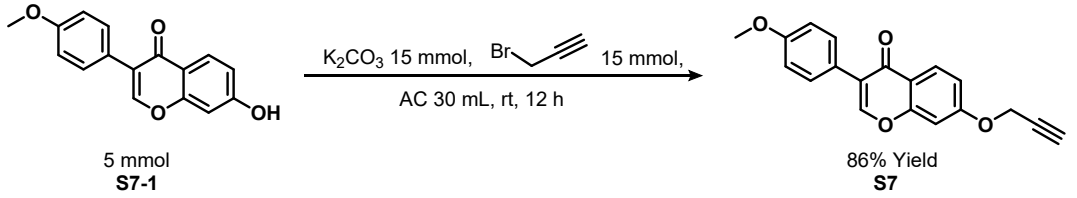
prop-2-yn-1-yl 2,2-dimethyl-5-(*m*-tolyloxy) pentanoate (S6)



S6 was synthesized according to a literature procedure.[3] A 50 mL round-bottom flask equipped with a magnetic stir bar was sequentially charged with **S6-1** (1.25 g, 5 mmol), K_2CO_3 (2.76 g, 20 mmol), DMF (30 mL), 3-bromopropyne (0.85 mL, 7 mmol). After sealing, the reaction mixture was stirred at 25 °C for 8 hours. The reaction was quenched with distilled water and extracted with dichloromethane (3 × 10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 then concentrated. The title compound was afforded as colorless oil (90% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 8 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 6.69 (s, 1H), 4.71 (m, 2H), 3.97 (m, 2H), 2.48 (m, 1H), 2.35 (s, 3H), 2.23 (s, 3H), 1.80 (m,4H), 1.30 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 177.00, 156.96, 136.47, 130.34, 123.62, 120.73, 111.95, 77.95, 74.65, 67.83, 51.95, 42.13, 37.10, 25.13, 25.09, 21.46, 15.84.

3-(4-methoxyphenyl)-7-(prop-2-yn-1-yloxy)-1λ^3,4λ^5-chromen-4-one (S7)



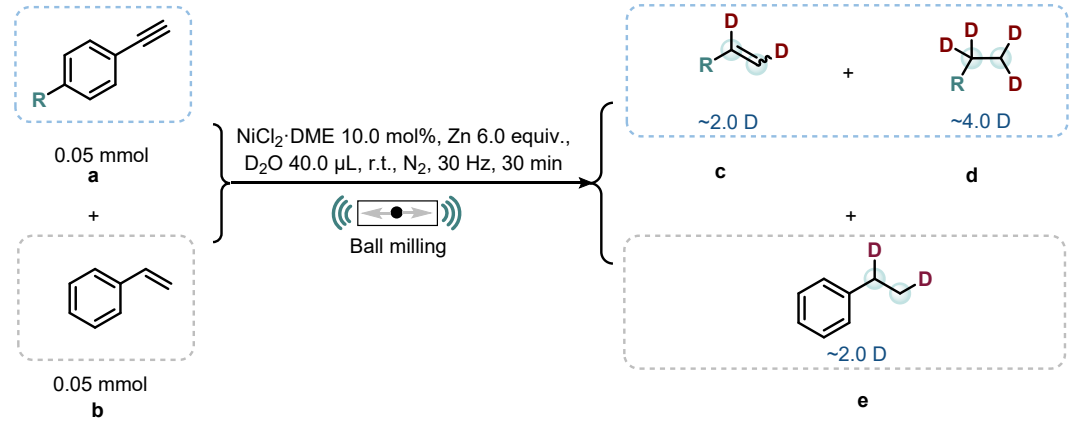
S7 was synthesized according to a literature procedure.[1] A 50 mL round-bottom flask equipped with a magnetic stir bar was sequentially charged with **S7-1** (1.34 g, 5 mmol), K_2CO_3 (2.07 g, 15 mmol), AC (30 mL). After 15 minutes, 3-bromopropyne (2.55 mL, 15 mmol) was added slowly and heated to reflux until TLC analysis indicated the disappearance of the starting material. The reaction was quenched with distilled water and extracted with dichloromethane (3 × 10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 then concentrated. The title compound was afforded as light yellow solid (86% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 8 Hz, 1H), 7.92 (s, 1H), 7.51 (d, *J* = 12 Hz, 2H), 7.06 (q, *J* = 12 Hz, 1H), 6.98 (m,3H), 4.80 (s, 2H), 3.83 (s, 3H), 2.60 (m,1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 175.84, 161.66, 159.60, 157.67, 152.19, 130.15, 127.97, 124.94, 124.12, 119.02, 114.84, 113.98, 101.52, 56.24, 55.36.

5. Mechanistic Studies

5.1 Competition experiment between alkynes and alkenes

Table S13. Competition experiment between alkynes and alkenes under semi-deuteration conditions (Zn)

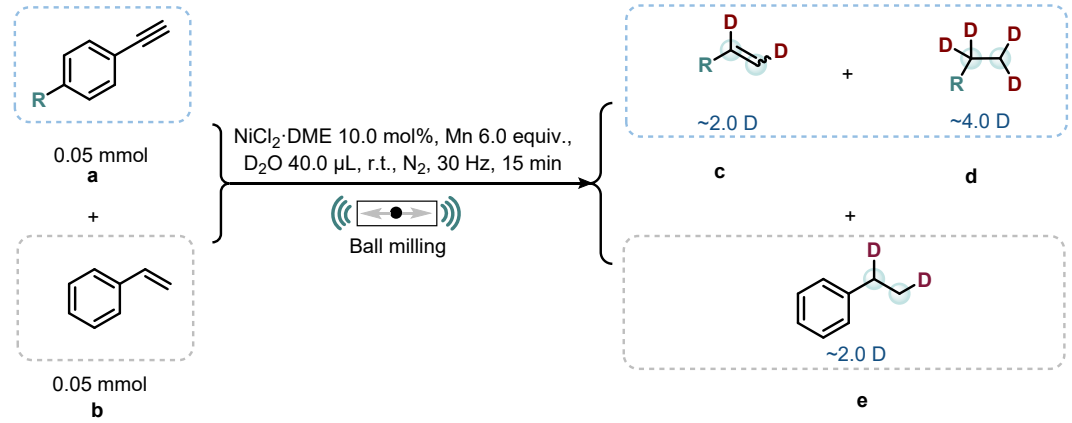


R = NMe_2[a], NH_2[b], OMe[b], t-Bu[a], Ph[b], CF_3[a], COMe[a], COOMe[b]

Entry	R groups	a	b	c	d	e
1	-NMe_2	56%	99%	28%	N.D.	N.D.
2	-NH_2	39%	98%	60%	N.D.	N.D.
3	-OMe	60%	97%	26%	N.D.	N.D.
4	-*t*-Bu	85%	99%	7%	N.D.	N.D.
5	-Ph	37%	99%	49%	N.D.	N.D.
6	-CF_3	85%	91%	12%	N.D.	N.D.
7	-COMe	1%	93%	68%	1%	N.D.
8	-COOMe	6%	91%	85%	N.D.	N.D.

[a] GC yield was determined using *n*-dodecane as an internal standard. [b] Isolated yields.

Table S14. Competition experiment between alkynes and alkenes under semi-deuteration conditions (Zn)



R = NMe_2[a], NH_2[b], OMe[b], t-Bu[a], Ph[b], CF_3[a], COMe[a], COOMe[b]

Entry	R groups	b	e	a	c	d
1	-NMe_2	9%	59%	2%	7%	53%
2	-NH_2	6%	54%	5%	1%	54%
3	-OMe	13%	53%	5%	12%	69%
4	-*t*-Bu	5%	57%	6%	5%	38%
5	-Ph	1%	92%	1%	1%	89%
6	-CF_3	16%	53%	16%	8%	46%
7	-COMe	1%	89%	1%	18%	12%
8	-COOMe	7%	58%	1%	3%	76%

[a] GC yield was determined using *n*-dodecane as an internal standard. [b] Isolated yield.

Reaction condition: A 5 mL stainless-steel ball milling jar was charged with Mn or Zn powder (6.0 equiv.), alkyne substrates (0.05 mmol), styrene (0.05 mmol), and nickel(II) chloride ethylene glycol dimethyl ether complex ($NiCl_2$·DME, 10.0 mol%). Subsequently, the jar was transferred into a nitrogen filled glovebox. Inside the glovebox, 40 μL of deuterium oxide (D_2O) were added to the jar. Afterwards, a stainless-steel grinding ball with a diameter of 10 mm was placed into the jar. The jar was sealed and then placed in a Retsch MM400 mixer mill, where it was milled at 30 Hz for 15 (30) minutes respectively. Upon completion of the ball milling process, the reaction mixture was diluted with a mixed solvent of ethyl acetate and petroleum ether at a volume ratio of 1:1 (PE:EA = 1:1). The mixture was then filtered through a disposable WITEG short-type glass Pasteur pipette packed with cotton and 200-300 mesh silica gel powder, using the same ethyl acetate and petroleum ether mixed solvent (PE:EA = 1:1) as the eluent.

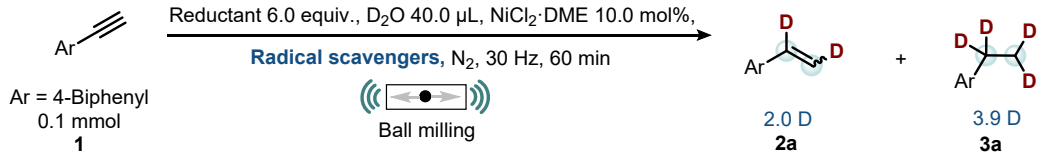
Conclusions: Competitive experiments revealed that under Zn powder conditions, the alkyne substrate **a** was reduced to the semi-deuterated alkene **c**, whereas the alkene substrate **b** remained unreacted. Under Mn conditions, the alkyne substrate **a** was reduced to both the semi-deuterated product **c** and the tetra-deuterated product **d**, while the alkene substrate **b** was further reduced to the alkane product **e**. Moreover, the electronic nature of substituents on the alkyne, whether electron-withdrawing or electron-donating, showed little influence on the reaction selectivity.

5.2 Radical capture experiments

5.2.1 Radical trapping experiments

Table S15. The influence of diverse radical scavengers on semi-deuteration conditions (Zn) /

tetra-deuteration conditions (Mn)

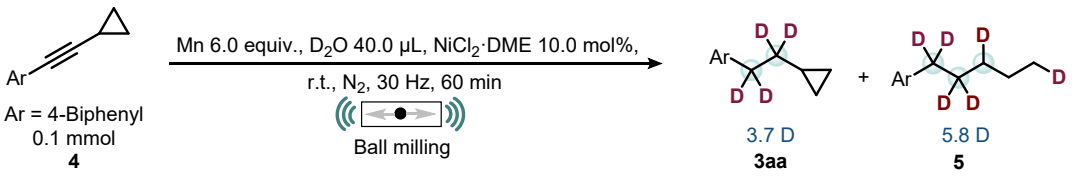


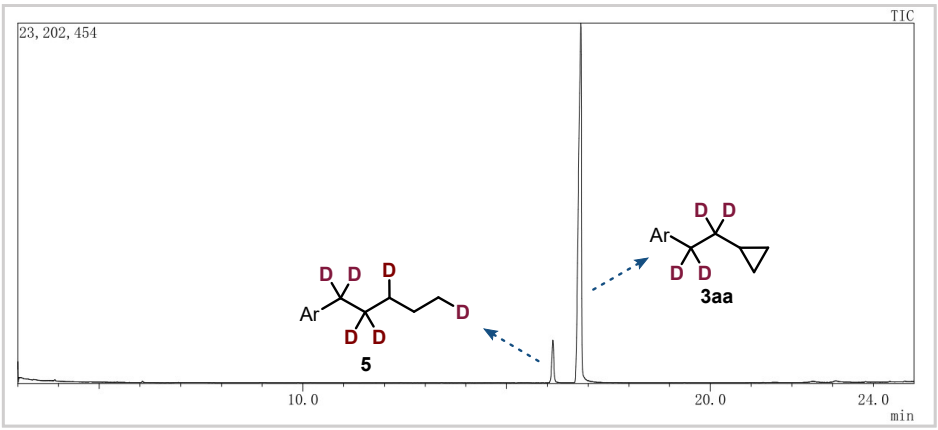
Entry	Reductant	Radical scavengers	Yield[a] 2a	Yield[a] 3a
1	Zn	TEMPO	40%	1%
2	Zn	BHT	41%	N.D.
3	Zn	1,1-Diphenylethylene	74%	N.D.
4	Mn	TEMPO	47%	5%
5	Mn	BHT	26%	3%
6	Mn	1,1-Diphenylethylene	14%	40%

[a] GC yield was determined using *n*-dodecane as an internal standard.

Data analysis: Upon completion of the reaction and standard workup procedures, no radical adduct products were detected. However, the GC yields of the reactions containing TEMPO and BHT decreased significantly. This suppression may be attributed to the oxidative nature of TEMPO, which likely oxidized the zinc powder and prematurely terminated the reaction. Similarly, the weak acidity of BHT might have compromised the reducing capacity of the zinc powder, thereby diminishing its catalytic efficacy.

5.2.2 Radical trapping experiments : (cyclopropyl ethynyl) benzene





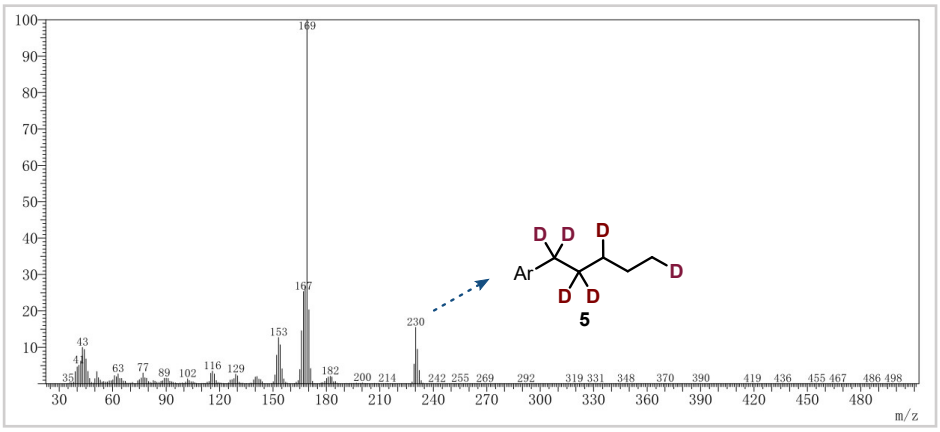
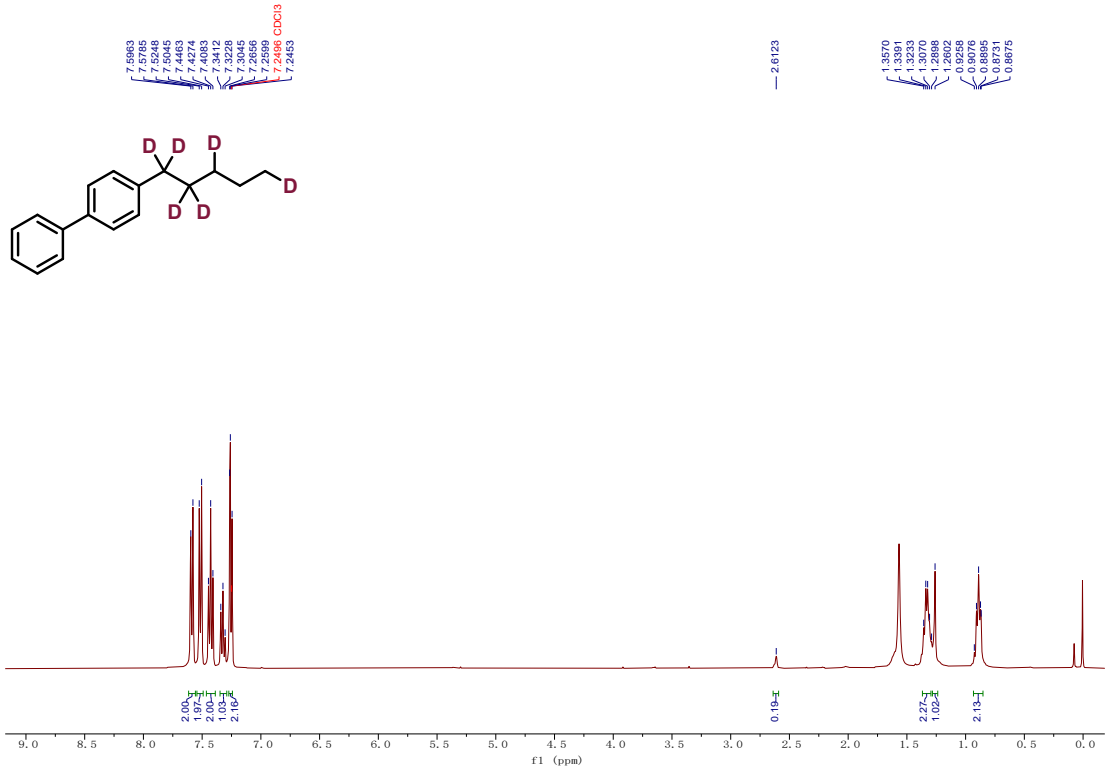


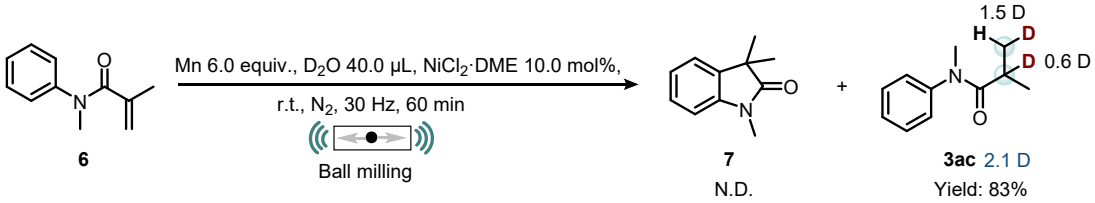
Figure S5: GC-MS of 4 reaction system



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (d, *J* = 7.1 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.27-7.24 (m, 2H), 2.61 (s, 0.19H), 1.33 (q, *J* = 6.8 Hz, 2H), 1.26 (s, 1H), 0.89 (m, 2H).

Conclusions: Employing 4-(cyclopropylethynyl)-1,1'-biphenyl (65.5 mg, 0.3 mmol, purchased from Bide Pharmatech) as the substrate, we conducted radical clock experiments under tetra-deuteration. Under tetra-deuteration conditions, with prolonged reaction time, GC-MS results showed a small amount of ring-opening product with an isolated yield of only 5%. Through ^{1}H NMR spectroscopy and high-resolution mass spectrometry, the structure of the ring-opening product was confirmed to be correct.[4] However, the yield of the tetra-deuterated target product was as high as 79%. After a literature survey, we tend to attribute this trace amount of ring opening to the homolysis of the carbon-metal bond.[5]

5.2.3 Radical trapping experiments: N-methyl-N-benzylpropionamide



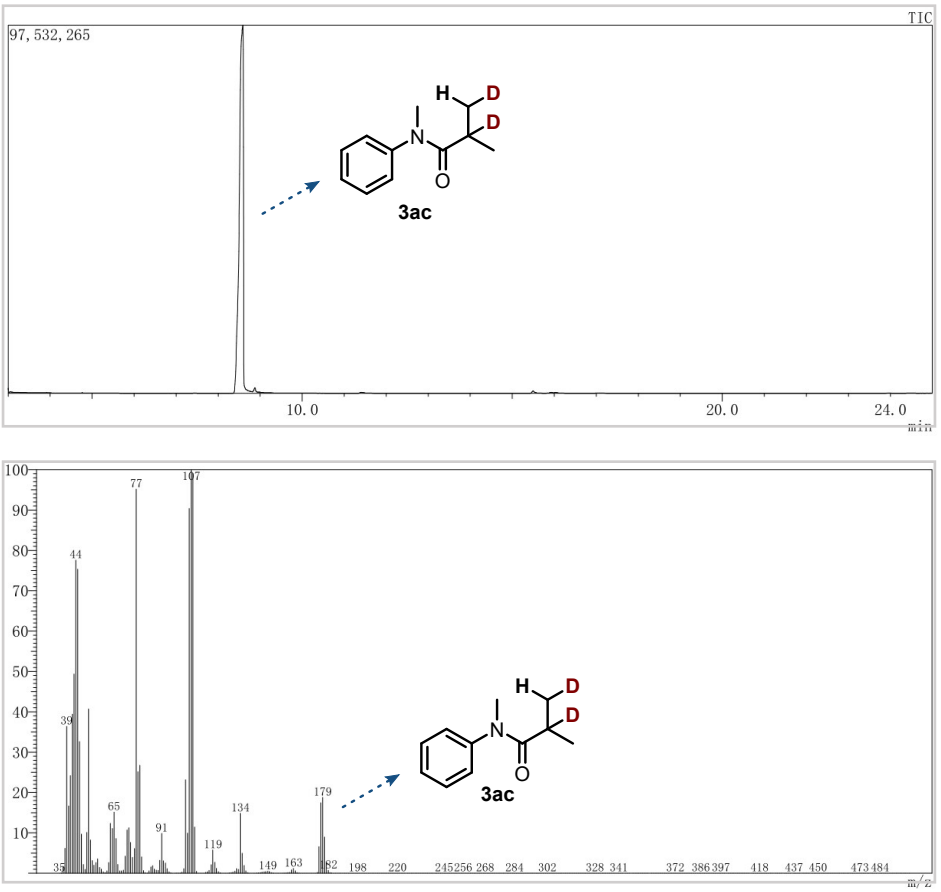
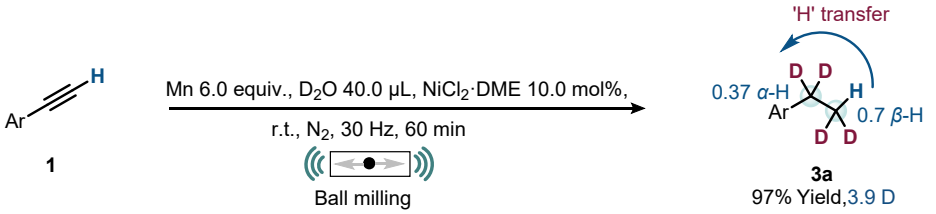
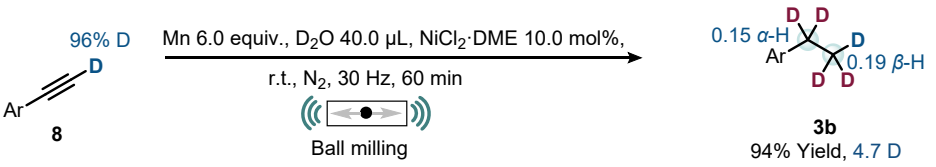


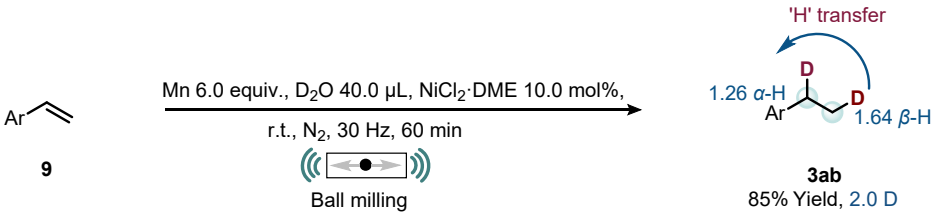
Figure S6: GC-MS of 6 reaction system

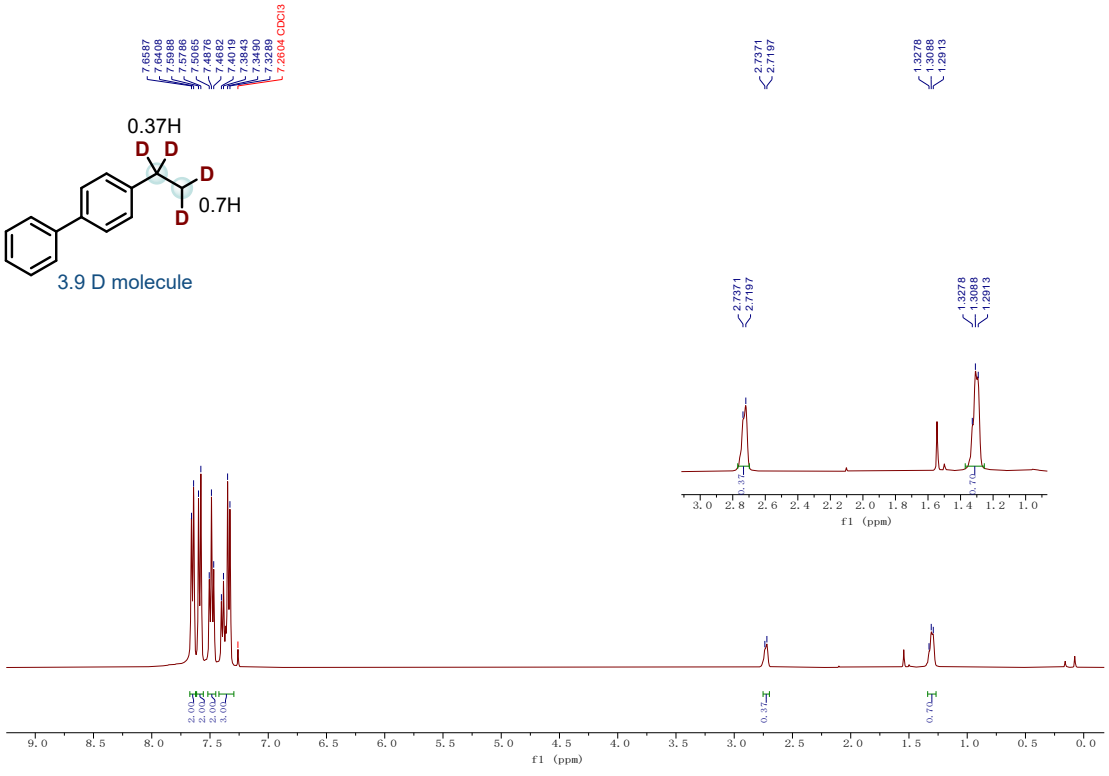
Conclusions: To further verify the potential involvement of radical pathways, we employed N-methyl-N-phenylmethacrylamide (17.5 mg, 0.1 mmol, purchased from Bide Pharmatech) as a radical clock probe under tetra-deuteration conditions. If an alkyl radical is generated, intramolecular cyclization at the α-position of the aniline moiety would afford cyclized product **7**. Notably, no formation of **7** was observed. In contrast, the yield of the reduced product **3ac** was 83%. This evidence further rules out the radical mechanism.[6]

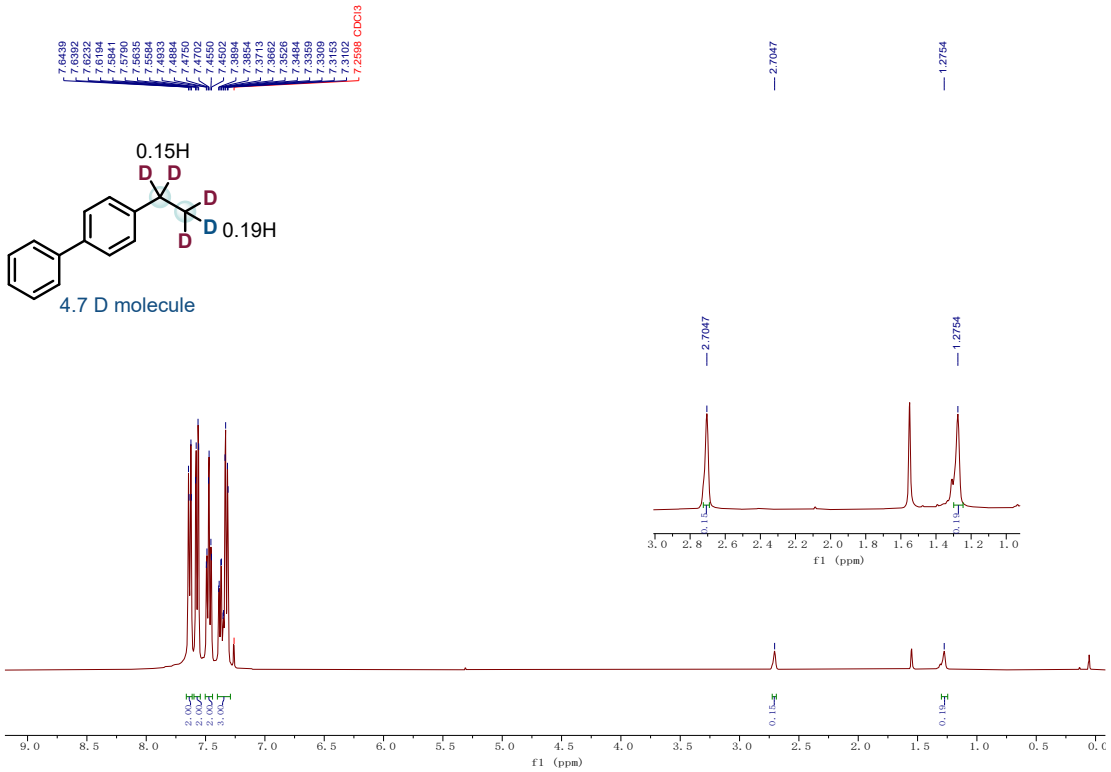
5.3 Terminal site hydrogen atom transfer experiment

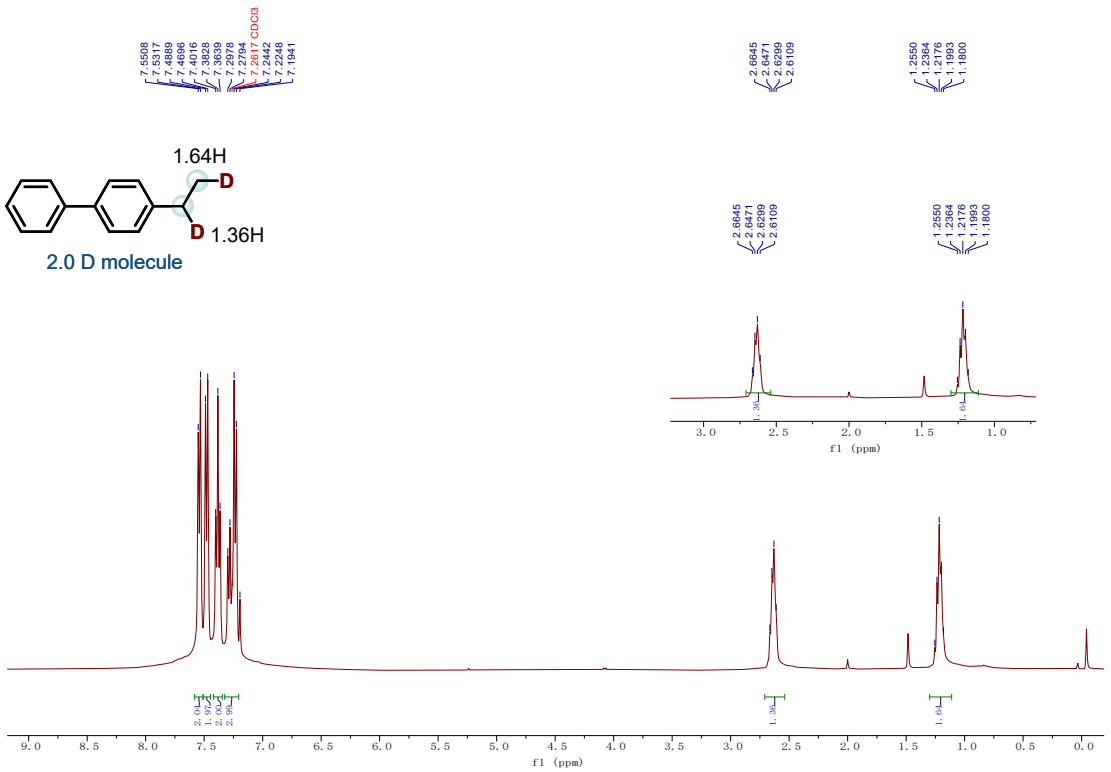

'H' transfer
Ar
H
1
Mn 6.0 equiv., D_2O 40.0 μL, $NiCl_2$·DME 10.0 mol%,
r.t., N_2, 30 Hz, 60 min
Ball milling
D D
0.37 α-H
H
Ar
0.7 β-H
D D
3a
97% Yield,3.9 D


96% D
D
Ar
8
Mn 6.0 equiv., D_2O 40.0 μL, $NiCl_2$·DME 10.0 mol%,
r.t., N_2, 30 Hz, 60 min
Ball milling
D D
0.15 α-H
D
Ar
0.19 β-H
D D
3b
94% Yield, 4.7 D


'H' transfer
Ar
9
Mn 6.0 equiv., D_2O 40.0 μL, $NiCl_2$·DME 10.0 mol%,
r.t., N_2, 30 Hz, 60 min
Ball milling
D
1.26 α-H
D
Ar
1.64 β-H
3ab
85% Yield, 2.0 D


7.6587
7.6408
7.5988
7.5786
7.5665
7.4876
7.4682
7.4019
7.3843
7.3490
7.3289
7.2604 CDCl3
2.7371
2.7197
1.3278
1.3088
1.2913
0.37H
D D
D
0.7H
D
3.9 D molecule
f1 (ppm)





Conclusions: Experimental observations indicate that the integration of the terminal alkyne proton, initially expected to be around 1.31 ppm, did not reach the theoretical value of **1**, and part of the hydrogen signal migrated to 2.72 ppm. This phenomenon was also observed in 3ad. When using deuterium-substituted **9** as the substrate, the hydrogen at 2.72 ppm decreased significantly, further supporting that the H at the α-position originates from migration from the β-position. Supported by literature research, we propose that Ni−H migration causes this phenomenon.[7]

5.4 Control experiments using $Ni(COD)_2$

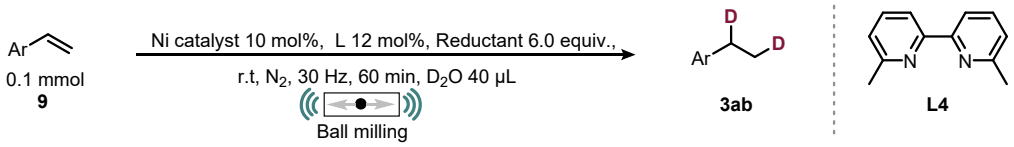


Table S16. Control experiments using $Ni(COD)_2$

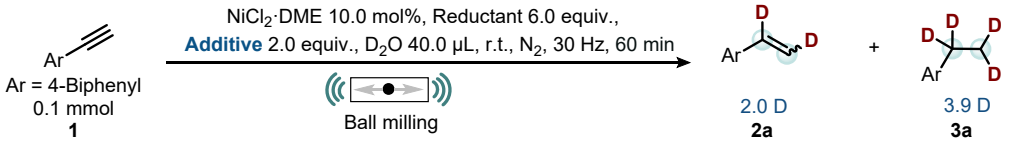
Entry	Reductant	L	Ni catalyst 10 mol%	Yield[a] 3ab
1	Zn	/	$NiCl_2$·DME	N.D.
2	Zn	/	$Ni(COD)_2$	N.D.
3	Mn	/	$NiCl_2$·DME	85%
4	Mn	/	$Ni(COD)_2$	81%
5	/	/	$Ni(COD)_2$	N.D.
6	/	L4	$Ni(COD)_2$	N.D.
7	Zn	L4	$Ni(COD)_2$	N.D.
8	Mn	L4	$Ni(COD)_2$	99%

[a] GC yield was determined using *n*-dodecane as an internal standard.

Conclusions: We wondered whether a Ni^0 species might underlie the observed selectivity differences. However, when $Ni(COD)_2$ was used alone, no alkane product was formed. We considered whether this was due to the lack of a ligand, as **L4** was the most effective ligand in the ligand screening. Therefore, we added $Ni(COD)_2$ + **L4**, but after the reaction, only the starting material remained. However, when a combination of Mn and $Ni(COD)_2$ achieved full conversion from alkene to deuterated alkane **3ab**, while the combination of Zn and $Ni(COD)_2$ did not promote the reaction. Based on the experimental results, we suspect that under the Mn condition, $NiCl_2$·DME and $Ni(COD)_2$ may play similar roles, with $NiCl_2$·DME more likely to reduce to the zero-valent nickel state.

5.5 The effect of divalent Zn and Mn on the system

Table S17. The influence of divalent Zn and Mn on semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



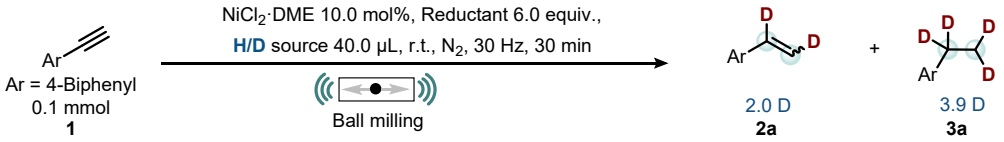
Entry	Reductant	Additive	Yield[a] 2a	Yield[a] 3a
1	Mn	$ZnCl_2$	87%	6%
2	Mn	$ZnBr_2$	71%	15%
3	Mn	$MnCl_2$	1%	91%
4	Mn	$MnBr_2$	N.D.	93%
5	Zn	$ZnCl_2$	70%	N.D.
6	Zn	$MnCl_2$	77%	3%

[a] GC yield was determined using *n*-dodecane as an internal standard.

Conclusions: The reaction results show that the addition of $ZnCl_2$ in the system inhibits the significant formation of alkanes, whereas $MnCl_2$ exerts no substantial effect on the reaction. This provides another possibility for the retention of semi-deuteration under Zn conditions.

5.6 Control experiment: comparison between H_2O and D_2O

Table S18. Influence of H_2O/D_2O on semi-deuteration conditions (Zn) / tetra-deuteration conditions (Mn)



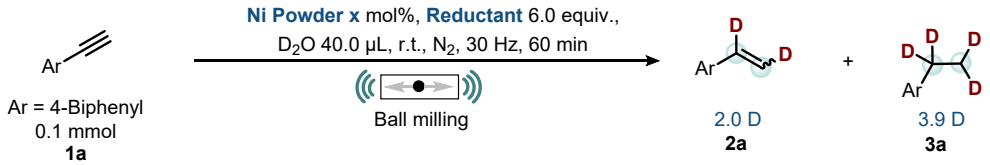
Entry	Reductant	H/D source	Yield[a] 2a	Yield[a] 3a
1	Zn	H_2O	30%	N.D.
2	Zn	D_2O	26%	N.D.
3	Mn	H_2O	30%	3%
4	Mn	D_2O	56%	17%

[a] GC yield was determined using *n*-dodecane as an internal standard.

Conclusions: Under Zn powder reduction, the yields with H_2O and D_2O were comparable, indicating that deuterium incorporation is not the rate determining step under semi-deuteration conditions. Under Mn powder reduction, however, the yield with D_2O was significantly higher than with H_2O, suggesting that D_2O addition plays a more critical role under tetra-deuteration conditions. These results further highlight the marked difference between the Zn and Mn reduction systems.

5.7 Control experiments: monometallic and bimetallic catalysis (Zn powder, Mn powder, Ni powder)

Table S19. Impact of monometallic versus bimetallic catalysis on product selectivity



Entry	Reductant	Ni powder	Yield[a] 2a	Yield[a] 3a
1	Mn	10 mol%	31%	3%
2	Mn	50 mol%	54%	20%
3	Mn	100 mol%	N.D.	80%
4	Zn	10 mol%	91%	N.D.
5	Zn	50 mol%	81%	N.D.

6	Zn	100 mol%	31%	41%
7	/	200 mol%	N.D.	N.D.
8	/	400 mol%	N.D.	N.D.
9	/	600 mol%	N.D.	N.D.
10	Zn	/	54%	N.D.
11	Mn	/	52%	N.D.

[a] GC yield was determined using *n*-dodecane as an internal standard.

Conclusions: The experimental results show that Ni powder alone failed to promote the reaction, while Zn or Mn individually afforded small amounts of the semi-deuterated product with low yields, and no tetra-deuterated product was detected. When Zn powder was combined with Ni powder, the yield of the semi-deuterated product increased significantly; when Mn powder was combined with Ni powder, complete conversion to the tetra-deuterated product was achieved, further highlighting the catalytic effect of the bimetallic system.

5.8 X-ray diffraction (XRD) analysis of alloy formation under ball-milling conditions

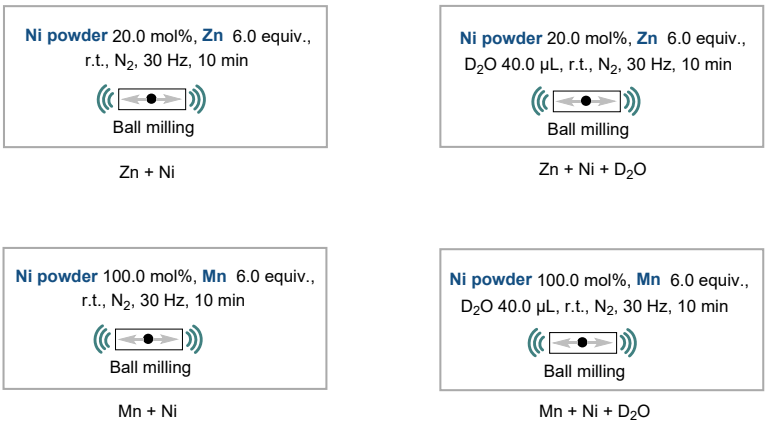


Figure S7: Experimental conditions for alloy formation

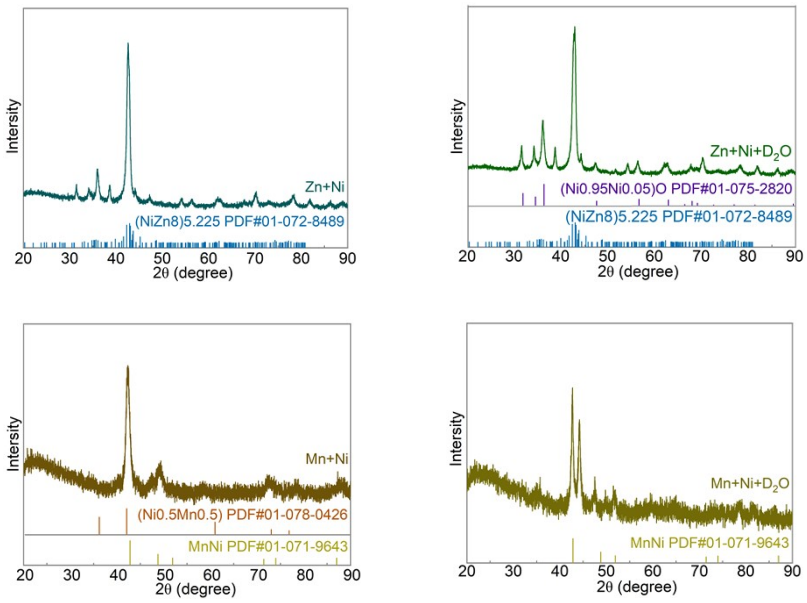


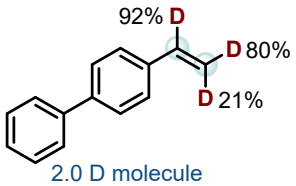
Figure S8: XRD analysis of alloy formation[8]

Figure S9: Impact of alloy composition on product selectivity

Conclusions: Interestingly, we detected the formation of the corresponding Zn-Ni and Mn-Ni alloys under ball-milling conditions. Unfortunately, when the substrate was added to the pre-milled alloy samples, the yields remained very low and did not improve significantly. Thus, we hypothesize that these alloys may not be the key determinants of selectivity. Under Zn conditions, 20 mol% of Ni powder was selected because, as shown in Table S16, using 10 mol% of Ni powder already afforded 91% yield of the semi-deuterated product (Entry 4); therefore, 20 mol% was added to compensate for possible nickel loss during the reaction. Under Mn conditions, 100 mol% of Ni powder was used because Table S16 indicates that a full conversion to the alkane product could only be achieved when 100 mol% of nickel powder was employed.

6. Characterization Data

4-(vinyl-1,2-d_2)-1,1'-biphenyl (2a)

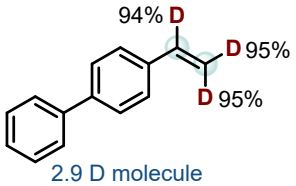


2a

Synthesized from 4-ethynyl-1,1'-biphenyl (17.8 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-(vinyl-1,2-d_2)-1,1'-biphenyl (**2a**) as a white solid (89% yield).[9]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64-7.57 (m, 4H), 7.51-7.43 (m, 4H), 7.36 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 17.4 Hz, 0.08H), 5.79 (t, *J* = 2.4 Hz, 0.79H), 5.27 (t, *J* = 1.6 Hz, 0.20H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 140.85, 140.70, 136.63, 128.92, 127.45, 127.36, 127.10, 126.76, 113.61.

4-(vinyl-d_3)-1,1'-biphenyl (2b)

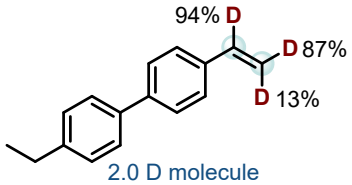


2b

Synthesized from 4-(ethynyl-d)-1,1'-biphenyl (17.9 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-(vinyl-d_3)-1,1'-bipheny (**2b**) as a white solid (85% yield).[9]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63-7.57 (m, 4H), 7.49-7.43 (dd, *J* = 22.9, 8.1 Hz, 4H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.76 (t, *J* = 2.4 Hz, 0.04H), 5.78 (t, *J* = 2.6 Hz, 0.05H), 5.27 (t, *J* = 1.4 Hz, 0.05H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 140.86, 140.69, 136.63, 136.33, 128.92, 127.45, 127.36, 127.10, 126.76, 113.47.

4-ethyl-4'-(vinyl-1,2-d_2)-1,1'-biphenyl (2c)

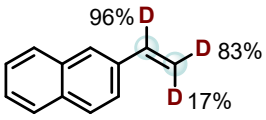


2c

Synthesized from 4-ethyl-4'-ethynyl-1,1'-biphenyl (20.6 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-ethyl-4'-(vinyl-1,2-d_2)-1,1'-biphenyl (**2c**) as a white solid (93% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58-7.48 (m, 6H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 17.6 Hz, 0.06H), 5.78 (t, *J* = 2.5 Hz, 0.87H), 5.26 (d, *J* = 2.5 Hz, 0.13H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.63, 140.67, 138.22, 136.15, 128.45, 127.18, 127.01, 126.73, 126.71, 113.40, 28.66, 15.75. **MS** (EI): $C_{16}H_{13}D_2$, Exact mass: 210.05.

2-(vinyl-1,2-d_2)naphthalene (2d)

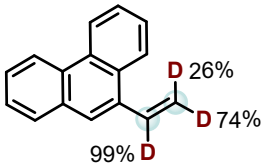


2d

Synthesized from 2-ethynylnaphthalene (15.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 2-(vinyl-1,2-d_2)naphthalene (**2d**) as a white solid (82% yield).[9]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83-7.76 (m, 4H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.50-7.40 (m, 2H), 6.88 (d, *J* = 17.5 Hz, 0.04H), 5.88 (t, *J* = 2.6 Hz, 0.83H), 5.34 (d, *J* = 6.0 Hz, 0.17H) **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 136.94, 135.04, 133.67, 133.26, 128.29, 128.18, 127.80, 126.49, 126.37, 126.04, 123.26, 113.89.

9-(vinyl-1,2-d_2)phenanthrene (2e)



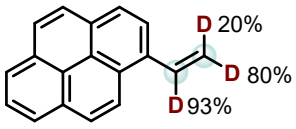
2e

Synthesized from 9-ethynylphenanthrene (20.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel

balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 9-(vinyl-1,2-d_2)phenanthrene (**2e**) as a white solid (84% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 7.5 Hz, 1H), 8.68 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.91-7.86 (m, 2H), 7.66 (tt, *J* = 15.8, 7.1 Hz, 4H), 5.86 (t, *J* = 2.6 Hz, 0.74H), 5.53 (s, 0.26H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 134.69, 131.91, 130.67, 130.44, 130.38, 128.82, 126.90, 126.87, 126.80, 126.76, 126.64, 126.60, 124.75, 123.19, 122.64, 117.25. **MS** (EI): $C_{16}H_9D_2$, Exact mass: 206.00.

1-(vinyl-1,2-d_2)pyrene (2f)



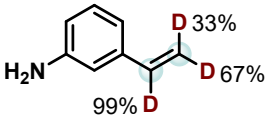
1.9 D molecule

2f

Synthesized from 1-ethynylpyrene (22.8 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 ml stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 1-(vinyl-1,2-d_2) pyrene (**2f**) as a yellow solid (81% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 9.3 Hz, 1H), 8.31-7.98 (m, 8H), 5.98 (s, 0.8H), 5.81 (s, 0.07H), 5.60 (d, *J* = 4.9 Hz, 0.20H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 134.24, 132.40, 131.60, 131.09, 131.03, 128.23, 127.71, 127.57, 127.41, 126.08, 125.38, 125.17, 125.14, 125.05, 125.02, 123.79, 123.15, 116.90. **MS** (EI): $C_{18}H_9D_2$, Exact mass: 230.10.

3-(vinyl-1,2-d_2)aniline (2g)



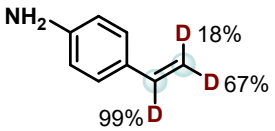
2.0 D molecule

2g

Synthesized from 3-ethynylaniline (11.7 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give 3-(vinyl-1,2-d_2) aniline (**2g**) as a colorless oil (83% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.74 (s, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 5.71-5.66 (m, 0.67H), 5.21 (d, *J* = 4.7 Hz, 0.33H), 3.85-3.46 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 146.37, 138.72, 136.98, 129.55, 117.20, 115.03, 113.63, 112.96. **HRMS** (ESI): Calcd for $C_{18}H_{13}D_3Na$ $[M+Na]^+$ 145.0816, found: 245.0818.

4-(vinyl-1,2-d_2)aniline (2h)



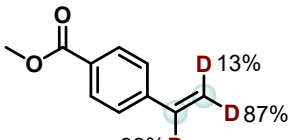
1.9 D molecule

2h

Synthesized from 4-ethynylaniline (11.7 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give 4-(vinyl-1,2-d_2) aniline (**2h**) as a colorless oil (85% yield).[10]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27-7.24 (m, 2H), 6.66-6.63 (m, 2H), 5.60-5.54 (m, 0.82H), 5.09-5.05 (m, 0.33H), 3.70 (s, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 146.29, 136.63, 135.97, 128.65, 127.43, 127.41, 115.08, 109.55.

Methyl-4-(vinyl-1,2-d_2)benzoate(2i)



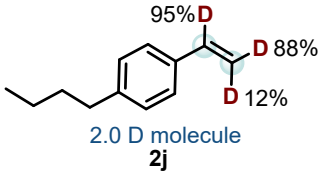
2.0 D molecule

2i

Synthesized from Methyl 4-ethynylbenzoate (11.7 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give methyl-4-(vinyl-1,2-d_2)benzoate (**2i**) as a colorless oil (90% yield).[9]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00-7.97 (m, 2H), 7.46-7.43 (m, 2H), 5.86-5.81 (m, 0.87H), 5.37-5.35 (m, 0.13H), 3.90 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.96, 141.94, 135.92, 129.98, 129.36, 126.18, 116.38, 52.15.

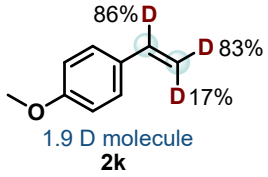
1-butyl-4-(vinyl-1,2-d_2)benzene (2j)



Synthesized from 1-butyl-4-ethynylbenzene (15.8 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 1-butyl-4-(vinyl-1,2-d_2)benzene (**2j**) as a colorless oil (75% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 17.5 Hz, 0.05H), 5.69-5.67 (m, 0.88H), 5.18 (d, *J* = 5.3 Hz, 0.12H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.62-1.55 (m, 2H), 1.38 (q, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.84, 136.45, 135.09, 128.72, 126.23, 112.49, 35.53, 33.74, 22.48, 14.10. **MS** (EI): $C_{12}H_{13}D_2$, Exact mass: 162.15.

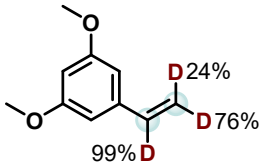
1-methoxy-4-(vinyl-1,2-d_2)benzene (2k)



Synthesized from 1-ethynyl-4-methoxybenzene (13.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 1-methoxy-4-(vinyl-1,2-d_2)benzene (**2k**) as a colorless oil (84% yield).[10]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 17.4 Hz, 0.14H), 5.61-5.57 (m, 0.83H), 5.12 (d, *J* = 5.6 Hz, 0.17H), 3.81 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 159.45, 135.89, 130.45, 127.48, 114.00, 111.27, 55.40.

1,3-dimethoxy-5-(vinyl-1,2-d_2)benzene (2l)

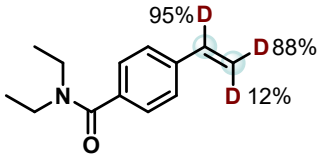


2l

Synthesized from 1-ethynyl-3,5-dimethoxybenzene (16.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 50:1) to give 1,3-dimethoxy-5-(vinyl-1,2-d_2)benzene (**2l**) as a colorless oil (71% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.57 (d, *J* = 2.4 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.71 (t, *J* = 2.5 Hz, 0.76H), 5.25 (d, *J* = 5.9 Hz, 0.24H), 3.81 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 160.92, 160.53, 139.55, 136.77, 114.22, 104.29, 100.06, 55.42, 55.33. **HRMS** (ESI): Calcd for $C_{10}H_{11}D_2O_2$ $[M+H]^+$ 167.1036, found: 167.1032.

N,N-diethyl-4-(vinyl-1,2-d_2)benzamide (2m)

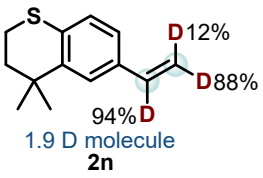


2m

Synthesized from N,N-diethyl-4-ethynylbenzamide (20.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 50:1) to give N,N-diethyl-4-(vinyl-1,2-d_2)benzamide (**2m**) as a colorless oil (88% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 17.6 Hz, 0.05H), 5.74 (s, 0.88H), 5.27 (d, *J* = 5.8 Hz, 0.12H), 3.35-3.24 (d, *J* = 109.0 Hz, 4H), 1.20 (d, *J* = 45.9 Hz, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.11, 138.30, 136.53, 135.99, 126.68, 126.19, 114.79, 43.33, 39.31, 14.29, 12.96. **HRMS** (ESI): Calcd for $C_{13}H_{16}D_2NO$ $[M+H]^+$ 206.1508, found: 206.1510.

4,4-dimethyl-6-(vinyl-1,2-d_2)thiochromane (2n)

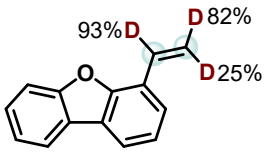


2n

Synthesized from 6-ethynyl-4,4-dimethylthiochromane (20.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 4,4-dimethyl-6-(vinyl-1,2-d_2)thiochromane (**2n**) as a yellow oil (77% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.66 (d, *J* = 17.5 Hz, 0.06H), 5.64 (s, 0.88H), 5.16 (d, *J* = 6.4Hz, 0.12H), 3.04-3.01 (m, 2H), 1.97-1.94 (m, 2H), 1.34 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 142.06, 136.41, 133.64, 131.65, 126.83, 124.90, 123.57, 111.95, 37.77, 33.11, 30.26, 23.26. **HRMS** (ESI): Calcd for $C_{13}H_{14}D_2SNa$ $[M+Na]^+$ 229.0998, found: 229.1001.

4-(vinyl-1,2-d_2)dibenzo[b,d]furan (2o)

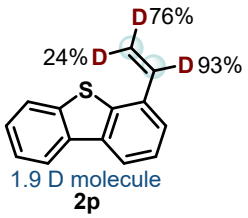


2o

Synthesized from 4-ethynyldibenzo[b,d]furan (19.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 4-(vinyl-1,2-d_2)dibenzo[b,d]furan (**2o**) as a yellow oil (86% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.48 (q, *J* = 7.9 Hz, 2H), 7.38 (dt, *J* = 14.7, 7.5 Hz, 2H), 7.13 (d, *J* = 17.8 Hz, 0.07H), 6.27 (s, 0.75H), 5.57 (d, *J* = 4.4 Hz, 0.18H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 156.24, 153.83, 131.26, 127.30, 125.45, 124.72, 124.14, 122.93, 122.62, 120.80, 119.88, 117.16 , 111.89. **HRMS** (ESI): Calcd for $C_{14}H_9D_2O$ $[M+H]^+$ 197.0930, found: 197.0921.

4-(vinyl-1,2-d_2)dibenzo[b,d]thiophene (2p)

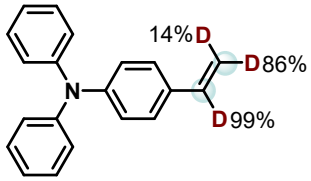


2p

Synthesized from 4-ethynyldibenzo[b,d]thiophene (20.8 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 4-(vinyl-1,2-d_2)dibenzo[b,d]thiophene (**2p**) as a yellow oil (81% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (dd, *J* = 6.2, 3.0 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.90 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.47 (dd, *J* = 8.5, 6.1 Hz, 3H), 7.04 (d, *J* = 15.6 Hz, 0.07H), 6.00 (s, 0.76H), 5.54 (s, 0.24H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 139.27, 137.83, 136.35, 135.64, 132.54, 126.95, 124.89, 124.60, 122.85, 121.79, 120.97, 116.63. **HRMS** (ESI): Calcd for $C_{14}H_9D_2S$ $[M+H]^+$ 213.0702, found: 213.0705.

N,N-diphenyl-4-(vinyl-1,2-d_2)aniline (2q)

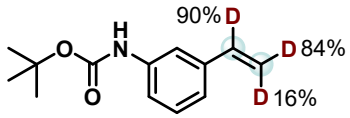


2q

Synthesized from 4-ethynyl-N,N-diphenylaniline (27.0 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give N,N-diphenyl-4-(vinyl-1,2-d_2)aniline (**2q**) as a brown solid (42% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30-7.24 (m, 6H), 7.15-7.02 (dd, *J* = 27.2, 7.7 Hz, 8H), 5.62 (s, 0.86H), 5.16 (d, *J* = 6.0 Hz, 0.14H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 147.71, 147.58, 136.22, 131.89, 129.37, 127.15, 124.48, 123.74, 123.03, 112.12. **HRMS** (ESI): Calcd for $C_{20}H_{16}D_2N$ $[M+H]^+$ 274.1559, found: 273.1552.

Tert-butyl (3-(vinyl-1,2-d$_2$)phenyl)carbamate (2r)



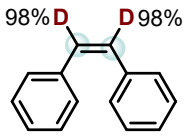
1.9 D molecule

2r

Synthesized from tert-butyl (3-ethynylphenyl) carbamate (21.8 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give tert-butyl (3-(vinyl-1,2-d$_2$) phenyl) carbamate (**2r**) as a colorless oil (43% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (s, 1H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 6.2 Hz, 1H), 6.69 (d, *J* = 17.5 Hz, 0.1H), 6.48 (s, 1H), 5.73 (s, 0.84H), 5.24 (d, *J* = 5.8 Hz, 0.16H), 1.52 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 152.84, 138.72, 138.52, 136.63, 129.22, 121.09, 118.02, 116.31, 114.29, 80.70, 28.48. **HRMS** (ESI): Calcd for $C_{13}H_{16}D_2NO_2$ $[M+H]^+$ 222.1458, found: 222.1455.

1,2-diphenylethene-1,2-d$_2$ (2s)



2.0 D molecule

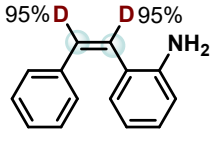
Z:E>99:1

2s

Synthesized from 1,2-diphenylethyne (17.8 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 1,2-diphenylethene-1,2-d$_2$ (**2s**) as a white solid (79% yield).[11]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28-7.17 (m, 10H), 6.61 (s, 0.04H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 137.28, 130.13, 128.99, 128.34, 127.23. **HRMS** (ESI): Calcd for $C_{14}H_{11}D_2$ $[M+H]^+$ 183.1137, found: 182.1133.

2-(2-phenylethyl-1,2-d_2)aniline (2t)

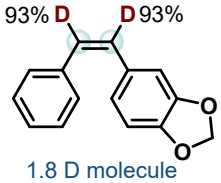


1.8 D molecule
Z:E>99:1
2t

Synthesized from 2-(phenylethynyl) aniline (19.4 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give 2-(2-phenylethyl-1,2-d_2) aniline (**2t**) as a colorless oil (81% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23-7.19 (m, 5H), 7.11 (t, *J* = 7.0 Hz, 2H), 6.73-6.68 (m, 2H), 6.54 (t, *J* = 6.6 Hz, 0.22H), 3.71 (s, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.77, 136.70, 131.74, 131.60, 129.66, 128.82, 128.52, 128.30, 127.55, 126.57, 126.32, 123.17, 118.50, 115.61. **HRMS** (ESI): Calcd for $C_{14}H_{12}D_2N$ $[M+H]^+$ 198.1246, found: 198.1243.

5-(2-phenylvinyl-1,2-d_2)benzo[d][1,3]dioxole (2u)

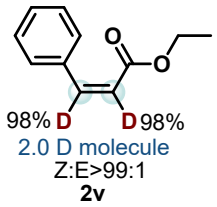


1.8 D molecule
Z:E>99:1
2u

Synthesized from 5-(phenylethynyl) benzo[d][1,3] dioxole (22.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 5-(2-phenylvinyl-1,2-d_2)benzo[d][1,3]dioxole (**2u**) as a white solid (76% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (s, 2H), 7.25-7.19 (m, 3H), 6.72 (dt, *J* = 15.9, 7.9 Hz, 3H), 6.49 (d, *J* = 9.5 Hz, 0.14H), 5.92 (s, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 147.48, 146.77, 137.36, 131.23, 129.23, 128.94, 128.41, 127.19, 123.10, 109.04, 108.32, 101.04. **HRMS** (ESI): Calcd for $C_{15}H_{11}D_2O_2$ $[M+H]^+$ 277.1036, found: 277.1034.

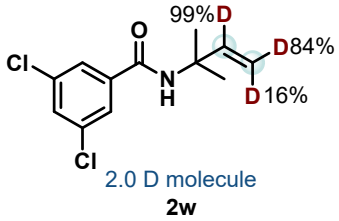
Ethenyl 3-phenylacrylate-d_2 (2v)



Synthesized from ethyl 3-phenylpropiolate (17.4 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give ethyl 3-phenylacrylate-d_2 (**2v**) as a colorless oil (61% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53-7.51 (m, 2H), 7.39-7.37 (m, 3H), 6.42 (m, 0.04H), 4.29-4.24 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.15, 144.63, 134.47, 130.35, 129.00, 128.16, 118.24, 60.63, 14.46. **HRMS** (ESI): Calcd for $C_{11}H_{11}D_2O_2$ $[M+H]^+$ 179.1036, found: 179.1040.

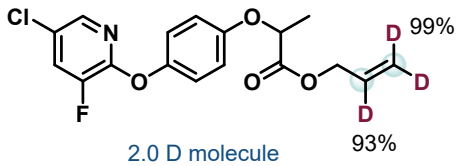
3,5-dichloro-N-(2-methylbut-3-en-2-yl-3,4-d_2)benzamide (2w)



Synthesized from 3,5-dichloro-N-(2-methylbut-3-yn-2-yl)benzamide (25.6 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 120 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give 3,5-dichloro-N-(2-methylbut-3-en-2-yl-3,4-d_2)benzamide (**2w**) as a white solid (37% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 1.9 Hz, 2H), 7.44 (s, 1H), 6.04 (s, 1H), 5.19-5.14 (m, 0.84H), 5.10 (d, *J* = 4.4 Hz, 0.16H), 1.54 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 164.19, 143.23, 142.88, 138.58, 135.48, 131.18, 125.63, 112.16, 111.92, 55.21, 27.09. **HRMS** (ESI): Calcd for $C_{12}H_{12}D_2Cl_2NO$ $[M+H]^+$ 298.0131, found: 298.0126.

Allyl-2,3,3-d_3 2-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenoxy)propanoate(2x)

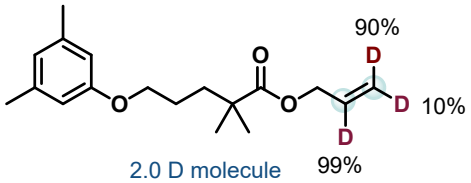


2x

Synthesized from prop-2-yn-1-yl 2-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenoxy)propanoate (34.9 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 120 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 5:1) to give allyl-2,3,3-d_3 2-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenoxy)propanoate (**2x**) as a white solid (29% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86（s, 1H）, 7.50 (d, *J* = 12 Hz, 1H), 7.08 (d, *J* = 8Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 5.88 (s, 0.16H), 5.31-5.24 (m, 0.99H) , 4.78-4.73 (m, 2H), 4.66 (s, 2H), 1.65-1.63 (m, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.80, 154.94, 151.41, 151.30, 148.31, 147.02, 145.67, 140.20, 140.13, 131.35-130.80, 125.05, 124.98, 124.87, 122.32, 118.86-116.13, 73.16, 65.74, 18.67. **HRMS** (ESI): Calcd for $C_{17}H_{12}D_3ClNaNO_4$ $[M+Na]^+$ 377.0752, found: 377.0754.

Allyl-2,3,3-d_3 5-(3,5-dimethylphenoxy)-2,2-dimethylpentanoate (2y)

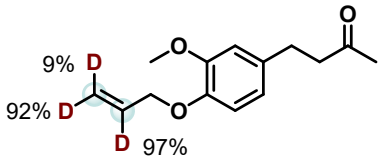


2y

Synthesized from prop-2-yn-1-yl 5-(3,5-dimethylphenoxy)-2,2-dimethylpentanoate (28.8 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 120 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give allyl-2,3,3-d_3 5-(3,5-dimethylphenoxy) -2,2-dimethylpentanoate (**2y**) as a colorless oily (68% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 (d, J =8 Hz, 1H), 6.68 (d, J = 4 Hz, 2H), 6.62(s, 1H), 5.31 (s,0.9H) 5.31 (s,0.06H), 4.60-4.59 (m, 2H), 3.94-3.92 (m, 2H), 2.32 (s, 3H), 2.19 (s, 3H), 1.77-1.75 (m, 3H), 1.26 (m, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 177.49, 156.97, 136.47, 132.31-131.77, 130.32, 130.03, 123.60, 120.70, 119.04, 117.71-117.20, 111.93, 67.90, 65.01, 64.94, 64.92, 42.16, 37.16, 25.22, 25.20, 21.44, 15.82. **HRMS** (ESI): Calcd for $C_{18}H_{24}D_2O_3K$ $[M+K]^+$ 331.1639, found: 331.1634.

4-(4-((allyl-2,3,3-d$_3$)oxy)-3-methoxyphenyl)butan-2-one(2z)

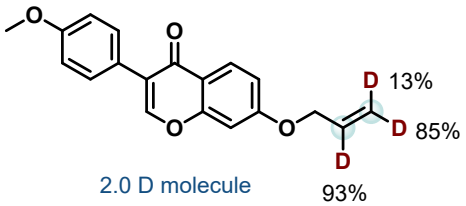


2z

Synthesized from 4-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)butan-2-one (23.2 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 120 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 50:1) to give 4-(4-((allyl-2,3,3-d$_3$)oxy)-3-methoxyphenyl)butan-2-one (**2z**) as light yellow solid (87% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.28 (d, J = 8 Hz, 1H), 6.72-6.67 (m, 2H), 6.05, 5.37-5.27 (m, 0.91H), 5.26 (m, 0.08H), 4.57 (s, 2H), 3.86 (s, 3H), 2.86-2.82 (m, 2H), 2.76- 2.72 (m,2H), 2.14 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 208.18, 149.34, 146.31, 134.05, 133.50-132.83, 120.01, 117.85-117.24, 113.59, 112.07, 69.96- 69.87, 55.88, 45.38, 30.14, 29.70, 29.38. **HRMS** (ESI): Calcd for $C_{14}H_{17}D_2O_3$ $[M+H]^+$ 273.1454, found: 273.1450.

7-((allyl-2,3,3-d$_3$)oxy)-3-(4-methoxyphenyl)-1λ^3,4λ^5-chromen-4-one (2aa)

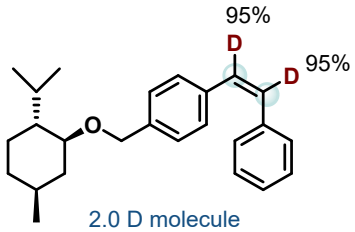


2aa

Synthesized from 3-(4-methoxyphenyl)-7-(prop-2-yn-1-yloxy)-1λ^3,4λ^5-chromen-4-one (30.6 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 120 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 3:1) to give 7-((allyl-2,3,3-d$_3$)oxy)-3-(4-methoxyphenyl) -1λ^3,4λ^5-chromen-4-one (**2aa**) as light yellow solid (75% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, J = 12 Hz, 1H), 7.91 (s, 1H), 7.50-7.48 (m, 2H), 7.02-6.95 (m, 3H), 6.86 (d, J = 4 Hz, 1H), 6.06 (m, 0.07H), 5.45 (m, 0.87H), 5.36 (m, 0.15H), 4.63 (s, 2H), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 175.88, 162.88, 159.57, 157.86, 152.10, 131.99-131.44, 130.15, 127.83, 124.87, 124.23, 118.50-117.95, 114.93, 113.97, 101.03, 69.21, 55.36. **HRMS** (ESI): Calcd for $C_{19}H_{15}D_2O_4$ $[M+H]^+$ 311.1247, found: 311.1244.

1-((((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)-4-((Z)-2-phenylvinyl-1,2-d$_2$)benzene(2ab)

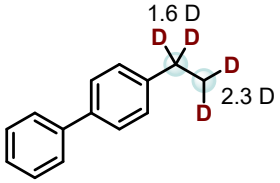


2ab

Synthesized from 1-((((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)-4- (phenyl ethynyl)benzene (35.0 mg, 0.10 mmol) following the general procedure for semi-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 120 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give 1-((((1S,2R,5S)-2-isopropyl-5-methyl cyclohexyl)oxy) methyl)-4-((Z)-2-phenylvinyl-1,2-d_2) benzene (**2ab**) as light yellow oily (78% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.38-7.32 (m, 2H), 7.30-7.29 (m, 2H), 7.26-7.24 (m, 7H), 6.62 (s, 0.10H), 4.72 (q, 1H), 4.41 (q, 1H), 3.24, 3.22-3.19 (m, 1H), 2.33 (m, 1H), 2.21-2.20 (m, 1H), 1.72-1.65 (m, 2H), 1.44-1.30 (m, 2H), 1.29-0.89 (m, 9H), 0.77-0.67 (m, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 139.49, 137.98, 137.21, 136.32, 131.63, 130.00, 129.94, 128.85, 128.24, 127.84, 127.74, 127.10, 123.35, 122.25, 89.47, 78.93, 78.69, 70.22, 48.36, 48.33, 40.32, 34.60, 34.58, 31.60, 25.58, 25.51, 23.27, 23.25, 22.43, 21.08, 16.13, 16.08. **HRMS** (ESI): Calcd for $C_{25}H_{30}D_2ONa$ $[M+Na]^+$ 373.2471, found: 373.2469.

4-(ethyl-1,1,2,2-d$_4$)-1,1'-biphenyl (3a)

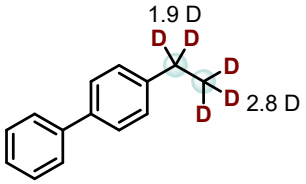


3a

Synthesized from 4-ethynyl-1,1'-biphenyl (17.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-(ethyl-1,1,2,2-d$_4$)-1,1'-biphenyl (**3a**) as a white solid (97% yield).[1a]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.37 (dd, *J* = 21.7, 7.6 Hz, 3H), 2.72 (d, *J* = 7.0 Hz, 0.39H), 1.31 (t, *J* = 7.3 Hz, 0.70H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.45, 141.31, 138.72, 128.84, 128.42, 127.21, 127.14, 127.09, 28.39, 15.37.

4-(ethyl-d_5)-1,1'-biphenyl (3b)

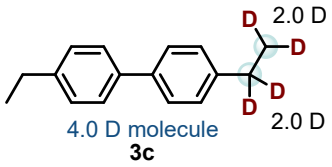


3b

Synthesized from 4-(ethynyl-d)-1,1'-biphenyl (18.7 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-(ethyl-d_5)-1,1'-biphenyl (**3b**) as a white solid (94% yield).[1a]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.57 (dd, *J* = 8.3, 2.0 Hz, 2H), 7.47 (td, *J* = 7.7, 1.9 Hz, 2H), 7.35 (ddd, *J* = 22.4, 7.8, 1.8 Hz, 3H). 2.71 (m, 0.15H), 1.28 (m, 0.19H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 143.45, 141.32, 138.72, 128.84, 128.42, 127.21, 127.15, 127.09, 27.88, 15.0.

4-ethyl-4'-(ethyl-1,1,2,2-d_4)-1,1'-biphenyl (3c)

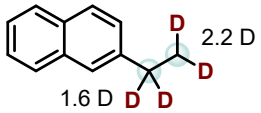


3c

Synthesized from 4-ethyl-4'-ethynyl-1,1'-biphenyl (20.6 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-ethyl-4'-(ethyl-1,1,2,2-d_4)-1,1'-biphenyl (**3c**) as a white solid (99% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.1 Hz, 4H), 7.28 (d, *J* = 7.9 Hz, 4H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.31-1.28 (m, 4H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 143.18, 143.12, 138.70, 128.37, 127.06, 28.64, 28.04, 15.74, 15.08. **MS** (EI): $C_{16}H_{14}D_4$, Exact mass: 214.10.

2-(ethyl-1,1,2,2-d$_4$)naphthalene (3d)



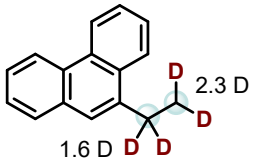
3.8 D molecule

3d

Synthesized from 2-ethynylnaphthalene (15.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 2-(ethyl-1,1,2,2-d$_4$) naphthalene (**3d**) as a colorless oil (89% yield).[1a]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90-7.78 (m, 3H), 7.67 (s, 1H), 7.48 (p, *J* = 7.1 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 2.83 (d, *J* = 7.0 Hz, 0.40H), 1.34 (d, *J* = 7.0 Hz, 0.80H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.84, 133.81, 132.04, 127.92, 127.73, 127.54, 127.21, 125.95, 125.66, 125.13, 28.86, 15.32.

9-(ethyl-1,1,2,2-d$_4$)phenanthrene (3e)



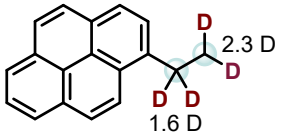
3.9 D molecule

3e

Synthesized from 9-ethynylphenanthrene (20.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 9-(ethyl-1,1,2,2-d$_4$)phenanthrene (**3e**) as a white solid (86% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.78-8.76 (m, 1H), 8.69 (d, *J* = 6.6 Hz, 1H), 8.18-8.10 (m, 1H), 7.90-7.85 (m, 1H), 7.71-7.59 (m, 5H), 3.16 (d, *J* = 7.2 Hz, 0.39H), 1.45 (d, *J* = 6.8 Hz, 0.76H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 138.30, 132.17, 131.39, 130.73, 129.69, 128.17, 126.68, 126.60, 126.21, 125.97, 125.04, 124.42, 123.32, 122.56, 25.87, 14.16. **MS** (EI): $C_{16}H_{10}D_4$, Exact mass: 210.05.

1-(ethyl-1,1,2,2-d$_4$)pyrene (3f)



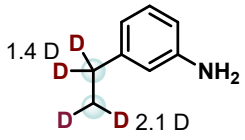
3.9 D molecule

3f

Synthesized from 6-ethynyl-1,5-dihydropyrene (22.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 1-(ethyl-1,1,2,2-d$_4$)pyrene (**3f**) as a yellow solid (83% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 9.2 Hz, 1H), 8.21-7.97 (m, 7H), 7.90 (d, *J* = 7.8 Hz, 1H), 3.37 (d, *J* = 7.6 Hz, 0.34H), 1.46 (d, *J* = 6.8 Hz, 0.73H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 138.62, 131.54, 131.04, 129.77, 128.48, 127.64, 127.23, 126.57, 126.46, 125.85, 125.16, 125.13, 125.05, 124.87, 124.73, 123.44, 26.30, 15.86. **MS** (EI): $C_{18}H_{10}D_4$, Exact mass: 234.10.

3-(ethyl-1,1,2,2-d$_4$)aniline (3g)



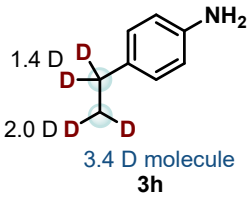
3.4 D molecule

3g

Synthesized from 3-ethynylaniline (11.7 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give 3-(ethyl-1,1,2,2-d$_4$)aniline (**3g**) as a colorless oil (94% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (t, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.56-6.50 (m, 2H), 3.60 (s, 2H), 2.53 (d, *J* = 6.6 Hz, 0.68H), 1.19 (d, *J* = 7.4 Hz, 0.90H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 146.44, 145.65, 129.34, 118.42, 114.88, 112.66, 28.88, 15.15. **HRMS** (ESI): Calcd for $C_8H_7ND_4$ $[M+H]^+$ 126.1215, found: 126.1211.

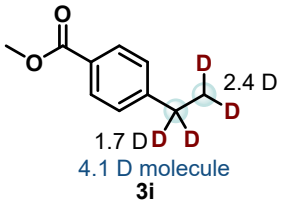
4-(ethyl-1,1,2,2-d$_4$)aniline (3h)



Synthesized from 4-ethynylaniline (12.5 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give 4-(ethyl-1,1,2,2-d$_4$)aniline (**3h**) as a colorless oil (81% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03-6.99 (m, 2H), 6.66-6.63 (m, 2H), 3.40 (s, 2H), 2.54 (m, 0.64H), 1.18 (q, *J* = 7.3 Hz, 1.03H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 144.14, 134.53, 128.69, 115.40, 28.00, 15.86. **HRMS** (ESI): Calcd for $C_8H_8ND_4$ $[M+H]^+$ 126.1215, found: 126.1211.

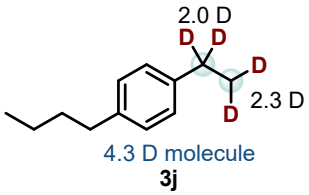
methyl 4-(ethyl-1,1,2,2-d$_4$)benzoate (3i)



Synthesized from methyl 4-ethynylbenzoate (12.5 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give methyl 4-(ethyl-1,1,2,2-d$_4$)benzoate (**3i**) as a white solid (93% yield).[12]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97-7.94 (m, 2H), 7.26-7.24 (m, 2H), 3.90 (s, 3H), 2.67(t, *J* = 7.2Hz, 0.30H), 1.21 (dd, *J* = 15.6, 8.3 Hz, 0.59H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.30, 149.79, 129.80, 127.98, 127.74, 52.03, 28.65, 14.85.

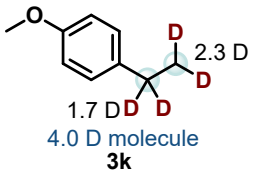
1-butyl-4-(ethyl-1,1,2,2-d_4)benzene (3j)



Synthesized from 1-butyl-4-ethynylbenzene (15.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 1-butyl-4-(ethyl-1,1,2,2-d_4)benzene (**3j**) as a colorless oil (74% yield).[1a]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 (s, 4H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.64 (p, *J* = 7.5 Hz, 2H), 1.40 (dt, *J* = 14.6, 7.4 Hz, 2H), 1.23 (d, *J* = 5.3 Hz, 0.7H), 0.97 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.45, 140.22, 128.47, 127.83, 35.39, 33.94, 28.33, 22.56, 15.55, 14.13.

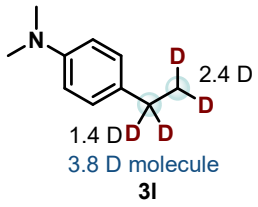
1-(ethyl-1,1,2,2-d_4)-4-methoxybenzene (3k)



Synthesized from 1-ethynyl-4-methoxybenzene (13.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 1-(ethyl-1,1,2,2-d_4)-4-methoxybenzene (**3k**) as a colorless oil (79% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.80 (s, 3H), 2.57 (d, *J* = 7.2 Hz, 0.34H), 1.17 (d, *J* = 7.0 Hz, 0.68H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 157.71, 136.46, 128.84, 113.83, 55.40, 27.97, 15.49. **HRMS** (ESI): Calcd for $C_9H_8D_4OK$ $[M+K]^+$ 179.0771, found: 179.0772.

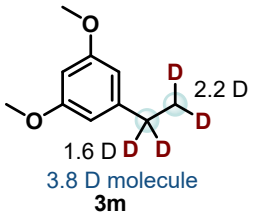
4-(ethyl-1,1,2,2-d_4)-N,N-dimethylaniline(3l)



Synthesized from 4-ethynyl-N,N-dimethylaniline (14.5 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 4-(ethyl-1,1,2,2-d_4)-N,N-dimethylaniline**(3l)** as a colorless oil (82% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12-7.10 (m, 2H), 6.75-6.73 (m, 2H), 2.94 (s, 6H), 2.57 (d, *J* = 7.2 Hz, 0.37H), 1.19 (d, *J* = 7.0 Hz, 0.63H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 149.11, 132.77, 128.53, 113.32, 41.16, 27.60, 15.68. **HRMS** (ESI): Calcd for $C_{10}H_{12}D_4N$ $[M+H]^+$ 154.1228, found: 154.1522.

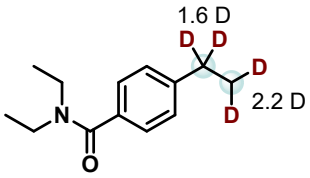
1-(ethyl-1,1,2,2-d_4)-3,5-dimethoxybenzene (3m)



Synthesized from 1-ethynyl-3,5-dimethoxybenzene (16.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 50:1) to give 1-(ethyl-1,1,2,2-d_4)-3,5-dimethoxybenzene (**3m**) as a colorless oil (78% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.38 (d, *J* = 2.3 Hz, 2H), 6.31 (t, *J* = 2.3 Hz, 1H), 3.79 (s, 6H), 2.58 (d, *J* = 7.1 Hz, 0.4H), 1.19 (d, *J* = 7.1 Hz, 0.8H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 160.86, 146.80, 106.01, 97.63, 55.34, 28.91, 15.20. **HRMS** (ESI): Calcd for $C_{10}H_{11}D_4O_2$ $[M+H]^+$ 171.1318, found: 171.1314.

N,N-diethyl-4-(ethyl-1,1,2,2-d_4) benzamide (3n)



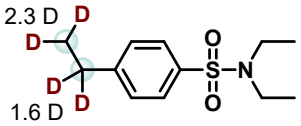
3.8 D molecule

3n

Synthesized from N,N-diethyl-4-ethynylbenzamide (20.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 50:1) to give N,N-diethyl-4-(ethyl-1,1,2,2-d_4)benzamide (**3n**) as a colorless oil (91% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 3.40 (d, *J* = 104.9 Hz, 4H), 2.63 (d, *J* = 7Hz, 0.35H), 1.26 (d, *J* = 10Hz, 0.85H), 1.24-1.08 (m, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.53, 145.32, 145.31, 134.56, 127.83, 126.39, 77.31, 43.30, 39.20, 28., 15.09, 14.25, 12.92. **HRMS** (ESI): Calcd for $C_{13}H_{16}D_4ON$ $[M+H]^+$ 210.1790, found: 210.1789.

N,N-diethyl-4-(ethyl-1,1,2,2-d_4)benzenesulfonamide (3o)



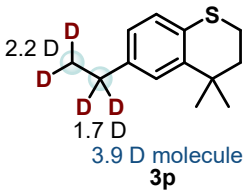
3.9 D molecule

3o

Synthesized from N,N-diethyl-4-ethynylbenzenesulfonamide (23.7 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE: EA = 100 : 1) to give N,N-diethyl-4-(ethyl-1,1,2,2-d_4)benzenesulfonamide (**3o**) as a white solid (90% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 3.22 (q, *J* = 7.1 Hz, 4H), 2.67 (d, *J* = 6.9 Hz, 0.39H), 1.20 (d, *J* = 6.9 Hz, 0.67H), 1.12 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 149.12, 137.58, 128.54, 127.21, 42.15, 28.35, 14.30. **HRMS** (ESI): Calcd for $C_{12}H_{16}D_4O_2NS$ $[M+H]^+$ 246.1460, found: 246.1457.

6-(ethyl-1,1,2,2-d$_4$)-4,4-dimethylthiochromane (3p)

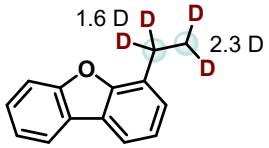


3p

Synthesized from 6-ethynyl-4,4-dimethylthiochromane (20.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 6-(ethyl-1,1,2,2-d$_4$)-4,4-dimethylthiochromane (**3p**) as a yellow oil (81% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 3.02 (s, 2H), 2.55 (d, *J* = 6.8 Hz, 0.28H), 1.96 (t, *J* = 6.1 Hz, 2H), 1.33 (s, 6H), 1.16 (d, *J* = 6.3 Hz, 0.82H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.91, 140.07, 128.39, 126.59, 126.22, 125.81, 38.08, 33.12, 30.45, 28.26, 23.18, 15.41. **HRMS** (ESI): Calcd for $C_{13}H_{15}D_4S$ $[M+H]^+$ 207.1171, found: 207.1170.

4-(ethyl-1,1,2,2-d$_4$) dibenzo[b,d]furan (3q)

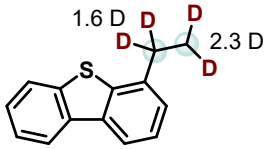


3q

Synthesized from 4-ethynyldibenzo[b,d]furan (19.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 4-(ethyl-1,1,2,2-d$_4$)dibenzo[b,d]furan (**3q**) as a yellow oil (87% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 7.7 Hz, 1H), 7.82 (dd, *J* = 6.2, 2.8 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.39-7.28 (m, 3H), 3.03 (d, *J* = 7.6 Hz, 0.41H), 1.39 (d, *J* = 6.9 Hz, 0.72H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 156.13, 154.74, 128.22, 127.00, 126.58, 124.74, 123.86, 122.89, 122.63, 120.78, 118.18, 111.76, 22.89, 14.14. **HRMS** (ESI): Calcd for $C_{14}H_8D_4ONa$ $[M+Na]^+$ 219.0749, found: 219.0749.

4-(ethyl-1,1,2,2-d_4) dibenzo[b,d]thiophene (3r)

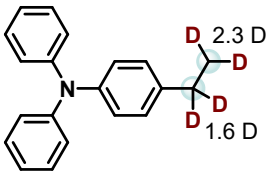


3.9 D molecule
3r

Synthesized from 4-ethynyldibenzo[b,d]thiophene (20.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 200:1) to give 4-(ethyl-1,1,2,2-d_4)dibenzo[b,d]thiophene (**3r**) as a yellow oil (84% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (dd, *J* = 5.9, 3.3 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.88 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.50-7.41 (m, 3H), 7.31 (d, *J* = 7.3 Hz, 1H), 2.91 (d, *J* = 7.1 Hz, 0.42H), 1.38 (d, *J* = 6.7 Hz, 0.66H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 139.26, 139.02, 138.36, 136.33, 135.68, 126.68, 125.35, 125.01, 124.43, 122.94, 121.84, 119.30, 27.50, 13.16. **HRMS** (ESI): Calcd for $C_{14}H_9D_4S$ $[M+H]^+$ 217.0984, found: 217.0975.

4-(ethyl-1,1,2,2-d_4)-N,N-diphenylaniline (3s)

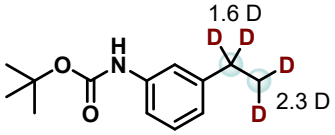


3.9 D molecule
3s

Synthesized from 4-ethynyl-N,N-diphenylaniline (27.0 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 4-(ethyl-1,1,2,2-d_4)-N,N-diphenylaniline (**3s**) as a brown solid (63% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26-7.19 (m, 4H), 7.12-6.95 (m, 10H), 2.60 (d, *J* = 7.3 Hz, 0.36H). 1.21 (d, *J* = 7.0 Hz, 0.65H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 148.15, 145.49, 139.12, 129.23, 128.78, 124.94, 123.78, 122.35, 28.03, 15.04. **HRMS** (ESI): Calcd for $C_{20}H_{15}D_4NK$ $[M+K]^+$ 316.2769, found: 316.2764.

tert-butyl (3-(ethyl-1,1,2,2-d$_4$)phenyl)carbamate (3t)



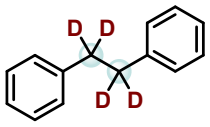
3.9 D molecule

3t

Synthesized from tert-butyl (3-ethynylphenyl)carbamate (21.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give tert-butyl (3-(ethyl-1,1,2,2-d$_4$)phenyl)carbamate (**3t**) as a colorless oil (44% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (s, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.51 (s, 1H), 2.59 (d, *J* = 7.1 Hz, 0.42H), 1.52 (s, 9H), 1.18 (d, *J* = 6.9 Hz, 0.70H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 152.93, 145.35, 138.41, 128.95, 122.72, 118.13, 115.95, 80.48, 28.56, 28.46, 15.11. **HRMS** (ESI): Calcd for $C_{13}H_{15}D_4NO_2K$ $[M+K]^+$ 264.1298, found: 264.1295.

1,2-diphenylethane-1,1,2,2-d$_4$ (3u)



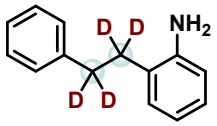
3.6 D molecule

3u

Synthesized from 1,2-diphenylethyne (17.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 1,2-diphenylethane-1,1,2,2-d$_4$ (**3u**) as a white solid (91% yield).[12]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (t, *J* = 7.6 Hz, 4H), 7.30-7.22 (m, 6H), 2.97 (d, *J* = 5.8 Hz, 0.45H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.84, 128.57, 128.47, 126.04, 37.59.

2-(2-phenylethyl-1,1,2,2-d$_4$)aniline (3v)



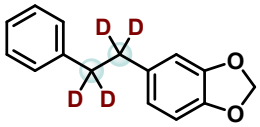
3.4 D molecule

3v

Synthesized from 2-(phenylethynyl)aniline (19.4 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give 2-(2-phenylethyl-1,1,2,2-d$_4$)aniline (**3v**) as a brown oil (89% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (t, *J* = 7.4 Hz, 2H), 7.28-7.24 (m, 3H), 7.13-7.07 (m, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 3.54 (s, 2H), 2.96 (d, *J* = 7.0 Hz, 0.28H), 2.81 (d, *J* = 6.8 Hz, 0.30H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 144.28, 141.88, 129.50, 128.56, 128.51, 127.25, 126.15, 126.02, 118.98, 115.77, 35.06, 33.16. **HRMS** (ESI): Calcd for $C_{14}H_{12}D_4N$ $[M+H]^+$ 202.1528, found: 202.1532.

5-(2-phenylethyl-1,1,2,2-d$_4$) benzo[d][1,3]dioxole (3w)



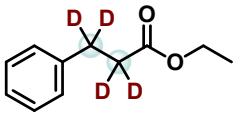
3.6 D molecule

3w

Synthesized from 5-(phenylethynyl)benzo[d][1,3]dioxole (22.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give 5-(2-phenylethyl-1,1,2,2-d$_4$)benzo[d][1,3]dioxole (**3w**) as a white solid (76% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (q, *J* = 8.4, 7.9 Hz, 2H), 7.22 (dd, *J* = 13.4, 6.9 Hz, 3H), 6.79-6.71 (m, 2H), 6.65 (d, *J* = 6.1 Hz, 1H), 5.95 (s, 2H), 2.86 (d, *J* = 14 Hz, 0.36H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 147.64, 145.78, 141.68, 135.69, 128.57, 128.46, 126.06, 121.30, 109.04, 108.24, 100.88, 37.46. **HRMS** (ESI): Calcd for $C_{15}H_{10}D_4O_2Na$ $[M+Na]^+$ 253.1137, found: 253.1140.

ethyl 3-phenylpropanoate-2,2,3,3-d_4 (3x)



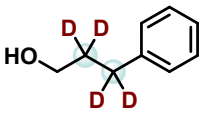
3.9 D molecule

3x

Synthesized from ethyl 3-phenylpropiolate (17.4 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give ethyl 3-phenylpropanoate-2,2,3,3-d_4 (**3x**) as a colorless oil (84% yield).[13]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (q, *J* = 6.3, 4.7 Hz, 2H), 7.29-7.21 (m, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.98 (s, 0.07H), 2.64 (s, 0.08H), 1.29 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 173.04, 140.57, 128.56, 128.39, 126.32, 60.47, 35.61, 30.61, 14.30.

3-phenylpropan-2,2,3,3-d_4-1-ol (3y)



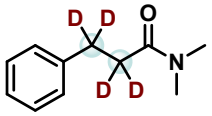
3.4 D molecule

3y

Synthesized from 3-phenylprop-2-yn-1-ol (13.2 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 10:1) to give 3-phenylpropan-2,2,3,3-d_4-1-ol (**3y**) as a colorless oil (69% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 3H), 3.67 (s, 2H), 2.70 (d, *J* = 7.4 Hz, 0.35H), 1.88 (d, *J* = 7.3 Hz, 0.30H), 1.72 (s, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.86, 128.52, 128.49, 125.95, 62.17, 33.95, 31.82. **HRMS** (ESI): Calcd for $C_9H_9D_4O$ $[M+H]^+$ 137.0930, found: 137.0936.

N,N-dimethyl-3-phenylpropanamide-2,2,3,3-d_4 (3z)

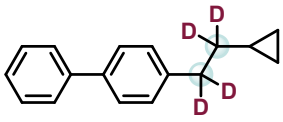


3.9 D molecule
3z

Synthesized from N,N-dimethyl-3-phenylpropiolamide (17.3 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 100:1) to give N,N-dimethyl-3-phenylpropanamide-2,2,3,3-d_4 (**3z**) as a colorless oil (90% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (t, *J* = 7.4 Hz, 2H), 7.25-7.16 (m, 3H), 2.93 (d, *J* = 9.4 Hz, 6H), 2.58 (d, *J* = 7.8 Hz, 0.16H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.31, 141.46, 128.54, 128.49, 126.17, 37.24, 35.48, 34.61, 30.79. **HRMS** (ESI): Calcd for $C_{11}H_{11}D_4NOK$ $[M+K]^+$ 220.1036, found: 220.1038.

4-(2-cyclopropylethyl-1,1,2,2-d_4)-1,1'-biphenyl (3aa)

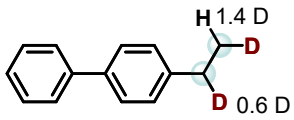


3.7 D molecule
3aa

Synthesized from 4-(cyclopropylethynyl)-1,1'-biphenyl (21.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-(2-cyclopropylethyl-1,1,2,2-d_4)-1,1'-biphenyl (**3aa**) as a white solid (79% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.59 (d, *J* = 7.1 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 12.8 Hz, 2H), 2.75 (d, *J* = 8.08 Hz, 0.17H), 1.26 (s, 0.13H), 0.73 (tt, *J* = 8.5, 5.1 Hz, 1H), 0.49-0.38 (m, 2H), 0.14-0.04 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 141.90, 141.33, 138.70, 129.00, 128.83, 127.13, 127.11, 127.09, 35.05, 10.71, 4.62.

4-(ethyl-1,2-d$_2$)-1,1'-biphenyl (3ab)

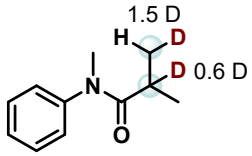


2.0 D molecule
3ab

Synthesized from 4-ethynyl-1,1'-biphenyl (17.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give 4-(ethyl-1,2-d$_2$)-1,1'-biphenyl **(3ab)** as a white solid (85% yield).[14]

^{1}H NMR data of the pure product: (400 MHz, Chloroform-d) δ 7.54 (d, *J* = 7.7 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.26 (dd, *J* = 21.7, 7.6 Hz, 3H), 2.64 (q, *J* = 7.3 Hz, 1.36H), 1.22 (t, *J* = 7.4 Hz, 1.64H).

N,2-dimethyl-N-phenylpropanamide-2,3,3-d$_3$ (3ac)

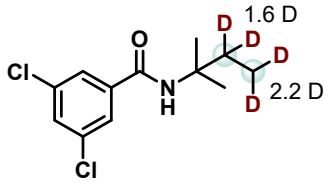


2.1 D molecule
3ac

Synthesized from N-methyl-N-phenylmethacrylamide (17.5 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 60 minutes. The product was obtained and purified by flash column chromatography on silica (PE) to give N,2-dimethyl-N-phenylpropanamide-2,3,3-d$_3$ **(3ac)** as a white solid (83% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 (dd, *J* = 8.3, 6.7 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.20-7.15 (m, 2H), 3.23 (s, 3H), 2.49 (t, *J* = 7.0 Hz, 0.42H), 1.93 (s, 0.45H), 0.99 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 177.57, 144.40, 129.84, 127.80, 127.37, 37.55, 31.09, 19.77. **HRMS** (ESI): Calcd for $C_{11}H_{13}D_2NO$ $[M+H]^+$ 181.1415, found: 181.1410.

3,5-dichloro-N-(2-methylbutan-2-yl-3,3,4,4-d$_4$) benzamide (3ad)



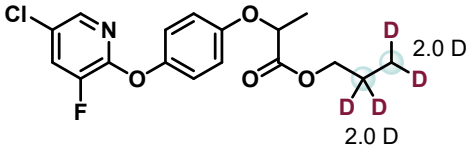
3.8 D molecule

3ad

Synthesized from 3,5-dichloro-N-(2-methylbut-3-yn-2-yl)benzamide (25.6 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 150 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give 3,5-dichloro-N-(2-methylbutan-2-yl-3,3,4,4-d$_4$)benzamide (**3ad**) as a white solid (35% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (s, 2H), 7.43 (s, 1H), 5.80 (s, 1H), 1.78 (d, *J* = 6.7 Hz, 0.36H), 1.40 (s, 6H), 0.85 (d, *J* = 6.7 Hz, 0.84H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 164.37, 139.00, 135.44, 131.01, 125.55, 54.92, 31.94, 26.52, 8.01. **HRMS** (ESI): Calcd for $C_{12}H_{11}D_4Cl_2NOK$ $[M+K]^+$ 302.0413, found: 302.0413.

Propyl-2,2,3,3-d$_4$-2-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenoxy)propanoate (3ae)



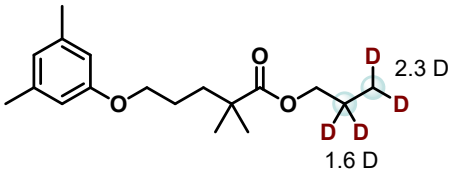
4.0 D molecule

3ae

Synthesized from prop-2-yn-1-yl 2-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenoxy)propanoate (34.9 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 120 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 5:1) to give Propyl-2,2,3,3-d4-2-(4- ((5-chloro-3-fluoropyridin-2-yl)oxy)phenoxy)propanoate (**3ae**) as a white solid (33% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.86（s, 1H）, 7.50 (d, *J* = 12 Hz, 1H), 7.07 (d, *J* = 8Hz, 2H), 6.92 (d, *J* = 8 Hz, 2H), 6.76 (m, 1H), 4.16-4.08 (m, 2H), 1.63-1.62 (m, 3H), 0.88-0.84 (m, 0.91H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.25, 155.02, 151.43, 151.31, 148.31, 146.96, 145.67, 140.19, 140.13, 125.04, 124.96, 124.85, 122.29, 116.04, 73.19, 66.79, 21.92-21.36, 18.69, 9.76-8.85. **HRMS** (ESI): Calcd for $C_{17}H_{14}D_4ClFNO_4K$ $[M+H]^+$ 358.1154, found: 358.1155.

Propyl-2,2,3,3-d_4 5-(3,5-dimethylphenoxy)-2,2-dimethylpentanoate(3af)

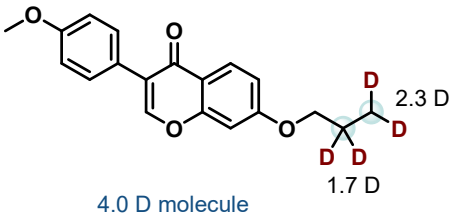


3.8 D molecule
3af

Synthesized from prop-2-yn-1-yl 5-(3,5-dimethylphenoxy)-2,2-dimethylpentanoate (28.8 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 150 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give propyl-2,2,3,3-d_4 5-(3,5-dimethylphenoxy) -2,2-dimethylpentanoate (**3af**) as a colorless oily (71% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.02 (d, *J* =8 Hz, 1H), 6.68 (d, *J* = 4 Hz, 2H), 6.62 (s, 1H), 4.04-4.03 (m, 1.6 H), 3.94-3.91 (s, 2H), 2.32 (s, 3H), 2.18 (s, 3H), 1.75-1.74 (m, 3H), 1.66 (m, 0.51H). 1.26 (m, 6H), 0.93 (m, 0.63H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 177.92, 177.48, 156.97, 156.96, 136.47, 130.30, 123.60, 120.68, 111.93, 67.96, 67.90, 65.93, 65.88, 64.92, 42.15, 42.13, 37.17, 37.15, 25.22, 25.19, 21.73, 21.43, 15.81, 15.79, 9.82-9.71. **HRMS** (ESI): Calcd for $C_{18}H_{25}D_4O_3$ $[M+H]^+$ 297.2362, found: 297.2358.

3-(4-methoxyphenyl)-7-(propoxy-2,2,3,3-d_4)-1λ^3,4λ^5-chromen-4-one(3ag)

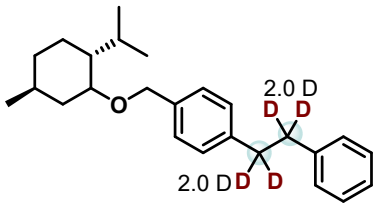


4.0 D molecule
3ag

Synthesized from 3-(4-methoxyphenyl)-7-(prop-2-yn-1-yloxy)-1λ^3,4λ^5-chromen-4-one (30.6mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 150 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 3:1) to give 3-(4-methoxyphenyl)-7- (propoxy-2,2,3,3-d_4)- 1λ^3,4λ^5-chromen-4-one (**3ag**) as light yellow solid (73% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 12 Hz, 1H), 7.90 (s, 1H), 7.51 (d, *J* = 8 Hz, 2H), 6.99-6.95 (m, 3H), 6.86 (m, 1H), 4.01 (m, 2H), 3.84 (m, 3H), 1.86-1.83 (m, 0.34H), 1.06-1.04 (m, 0.71H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 175.93, 163.56, 159.55, 157.98, 152.10, 152.07, 130.15, 127.83, 127.70, 124.82, 124.30, 118.23, 114.94, 114.90, 113.96, 101.03, 100.54, 70.03, 55.35, 21.76, 9.70. **HRMS** (ESI): Calcd for $C_{19}H_{15}D_4O_4$ $[M+H]^+$ 315.1529, found: 315.1523.

1-((((2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)-4-(2-phenylethyl-1,1,2,2-d_4)benzene(3ah)



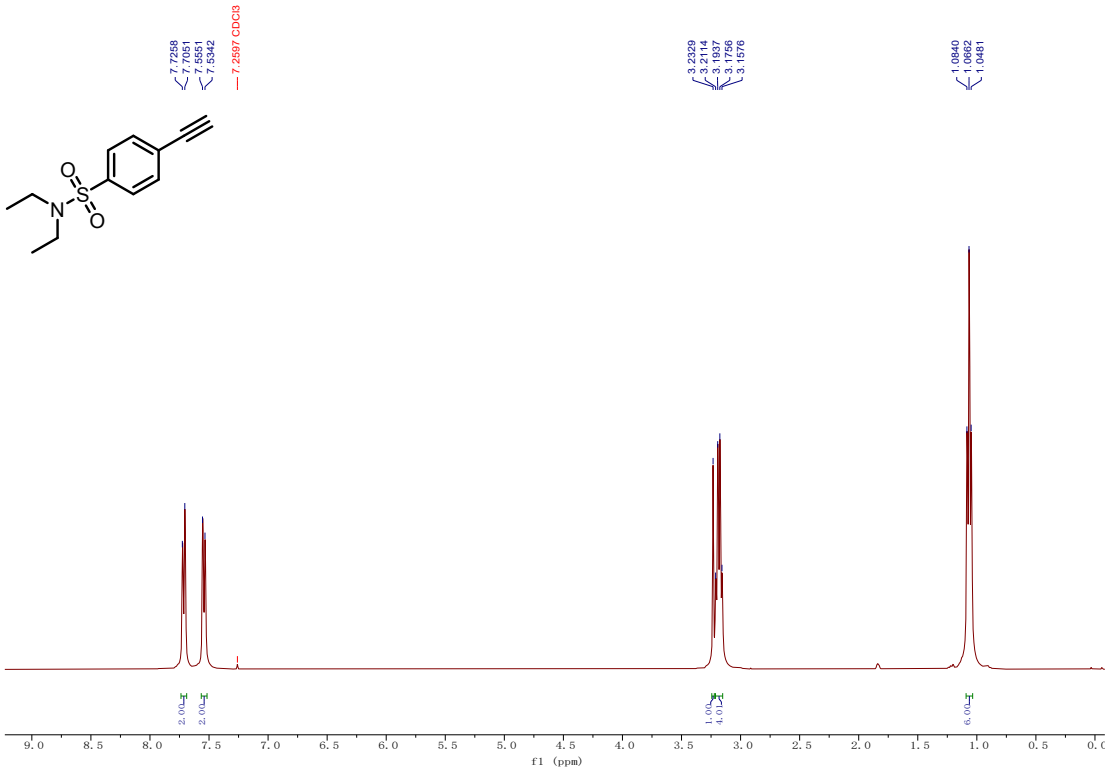
3ah

Synthesized from 1-((((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)-4- (phenyl ethynyl)benzene (35.0 mg, 0.10 mmol) following the general procedure for tetra-deuteration, the reaction was carried out in 5 mL stainless-steel jars with stainless-steel balls (diameter 10 mm) and then milled at a frequency of 30 Hz for 180 minutes. The product was obtained and purified by flash column chromatography on silica (PE:EA = 30:1) to give 1-((((2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)-4-(2-phenylethyl-1,1,2,2-d_4)benzene (**3ah**) as light yellow oily (80% yield).

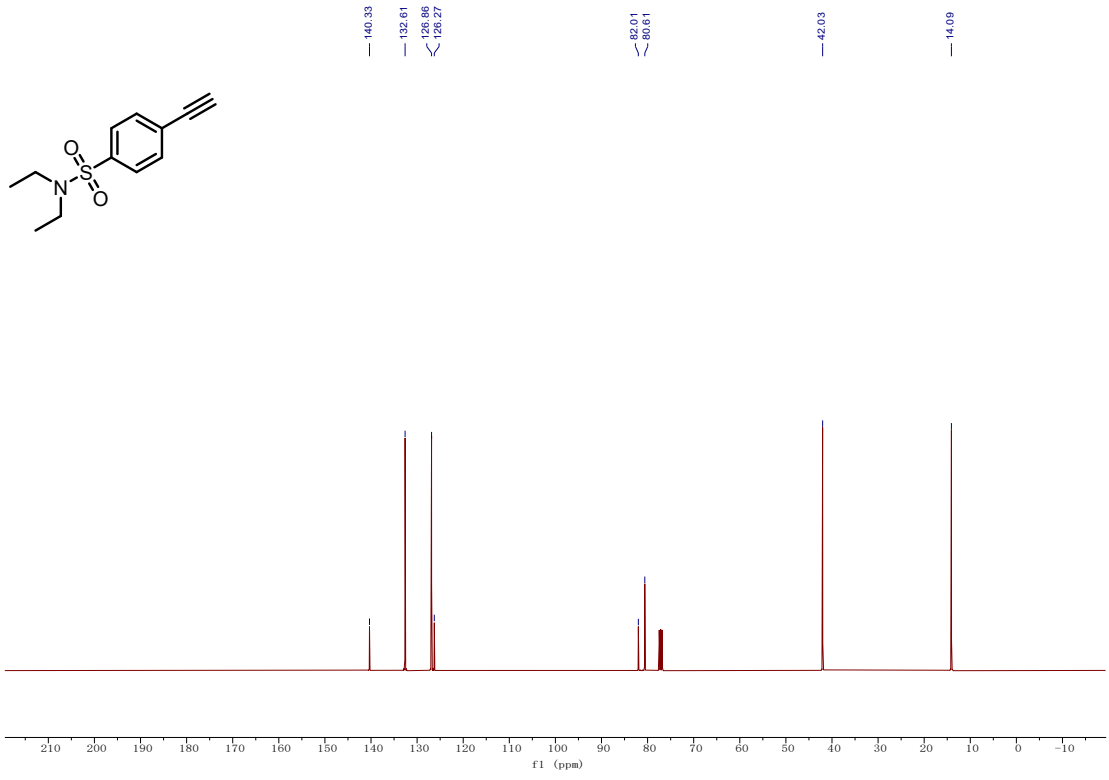
^{1}H NMR (400 MHz, Chloroform-d) δ 7.38-7.34 (m, 4H), 7.29-7.22 (m, 5H), 4.73 (d, J =12 Hz, 1H), 4.47 (d, J = 12 Hz, 1H), 3.28-3.25 (m, 1H), 2.97 (s, 0.2H), 2.41-2.37 (m, 1H), 2.27 (m, 1H), 1.77-1.69 (m, 2H), 1.42-1.36 (m, 2H), 1.04-1.00 (m, 9H), 0.83-0.79 (m, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.77, 141.01, 140.97, 136.74, 128.53, 128.46, 128.40, 128.29, 128.09, 125.97, 78.97, 78.82, 78.73, 78.66, 70.36, 70.23, 48.40, 40.40, 37.55-37.02, 36.83, 36.64, 34.68, 31.67, 25.58, 25.40, 23.34, 22.51, 21.15, 16.21, 16.17. **HRMS** (ESI): Calcd for $C_{25}H_{30}D_4ONa$ $[M+Na]^+$ 377.2753, found: 377.2756.

7. Copies of NMR Spectra

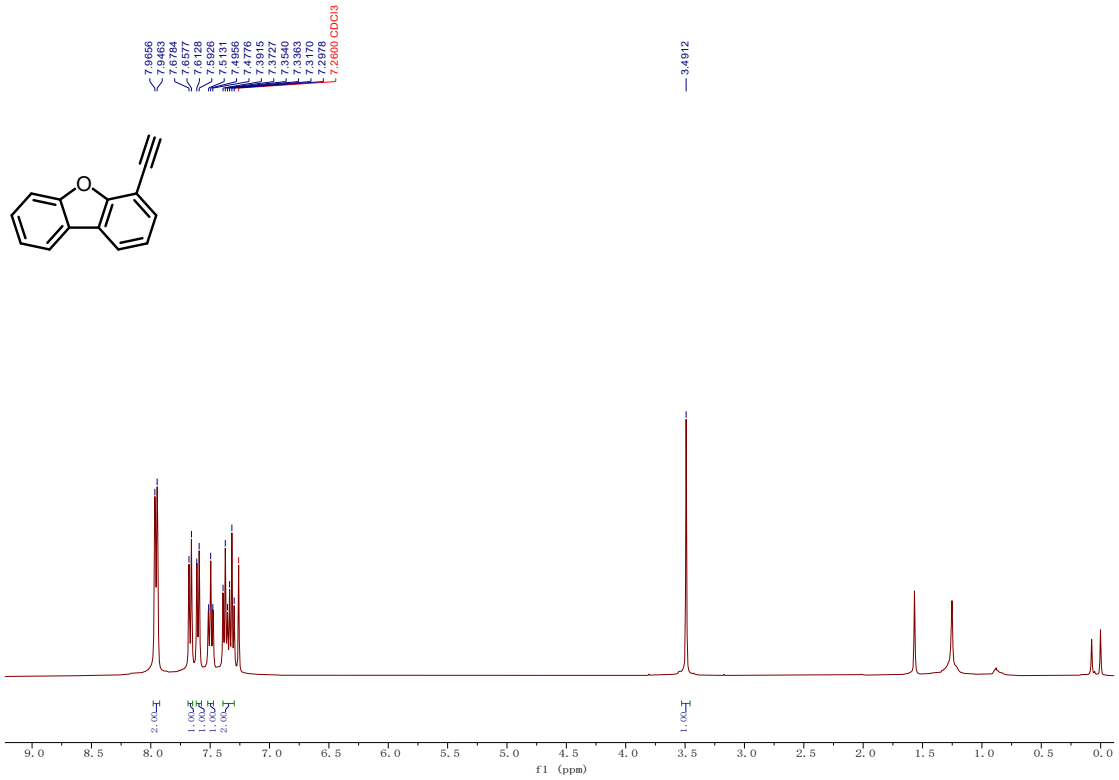
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of S1



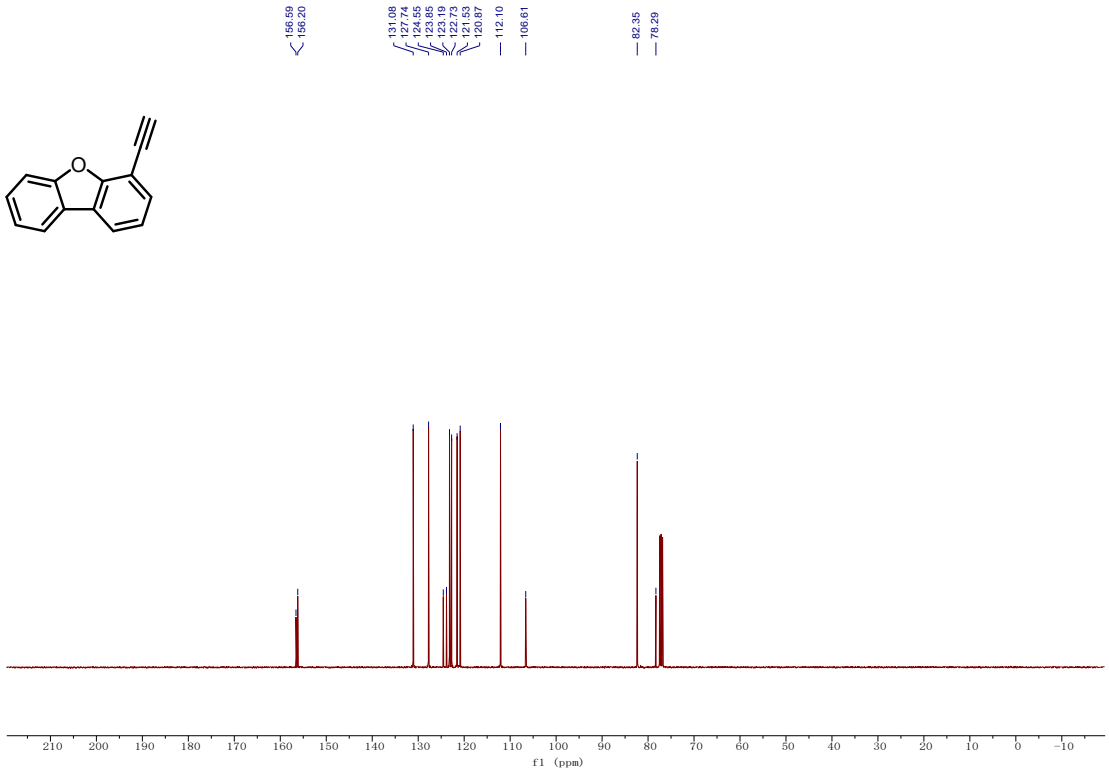
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of S1



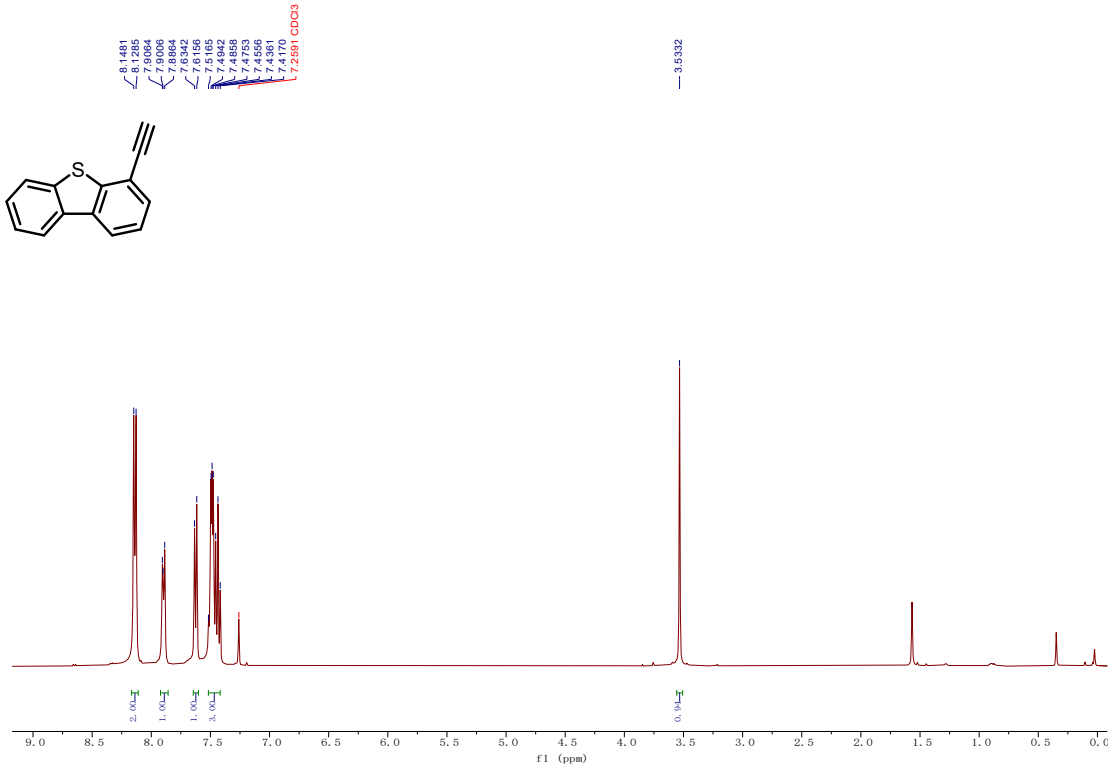
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of S2



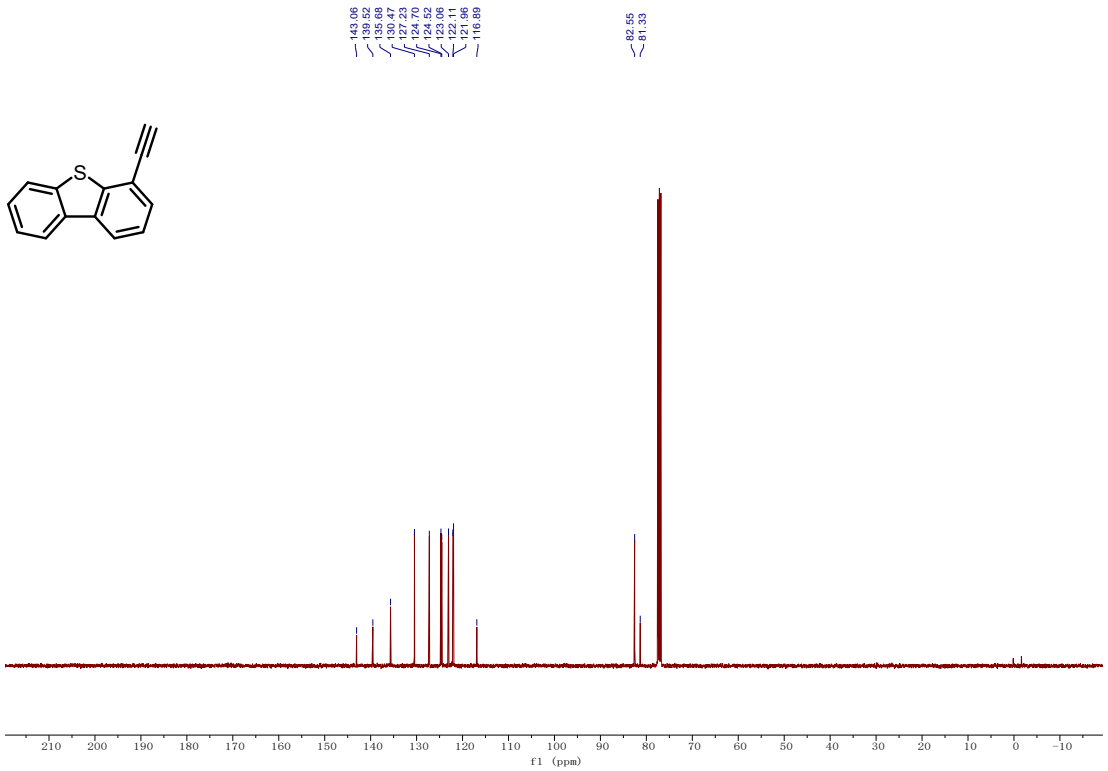
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of S2



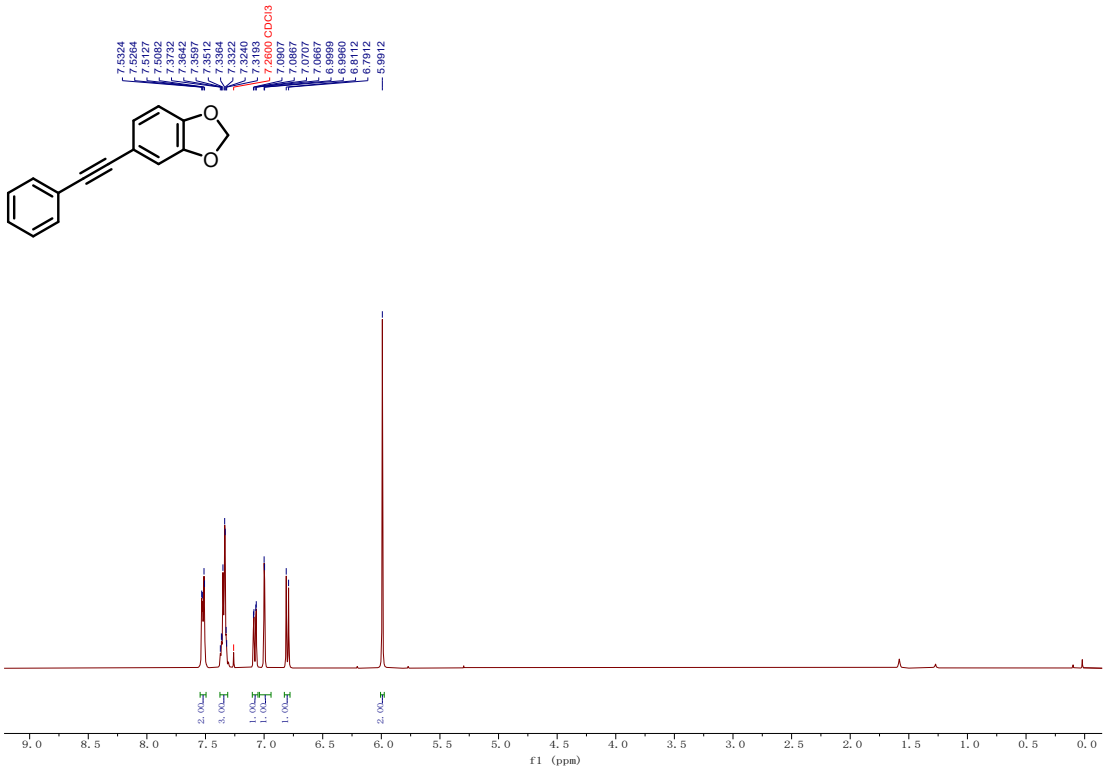
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of S3



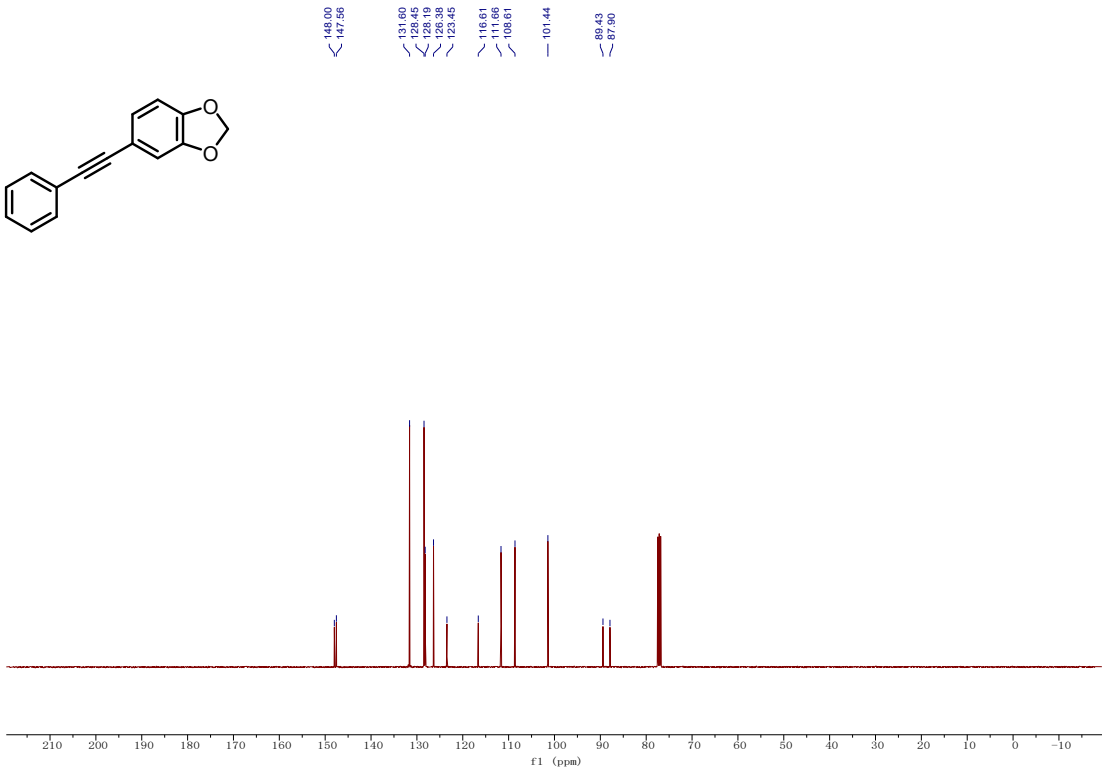
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of S3



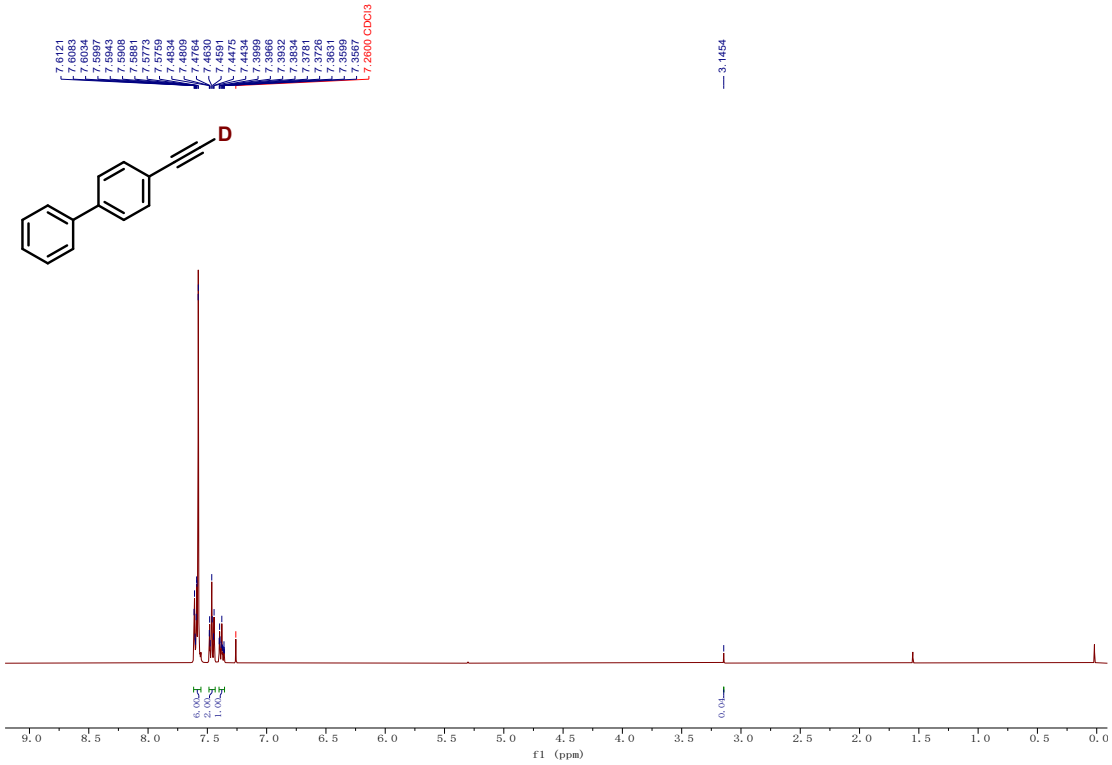
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of S4



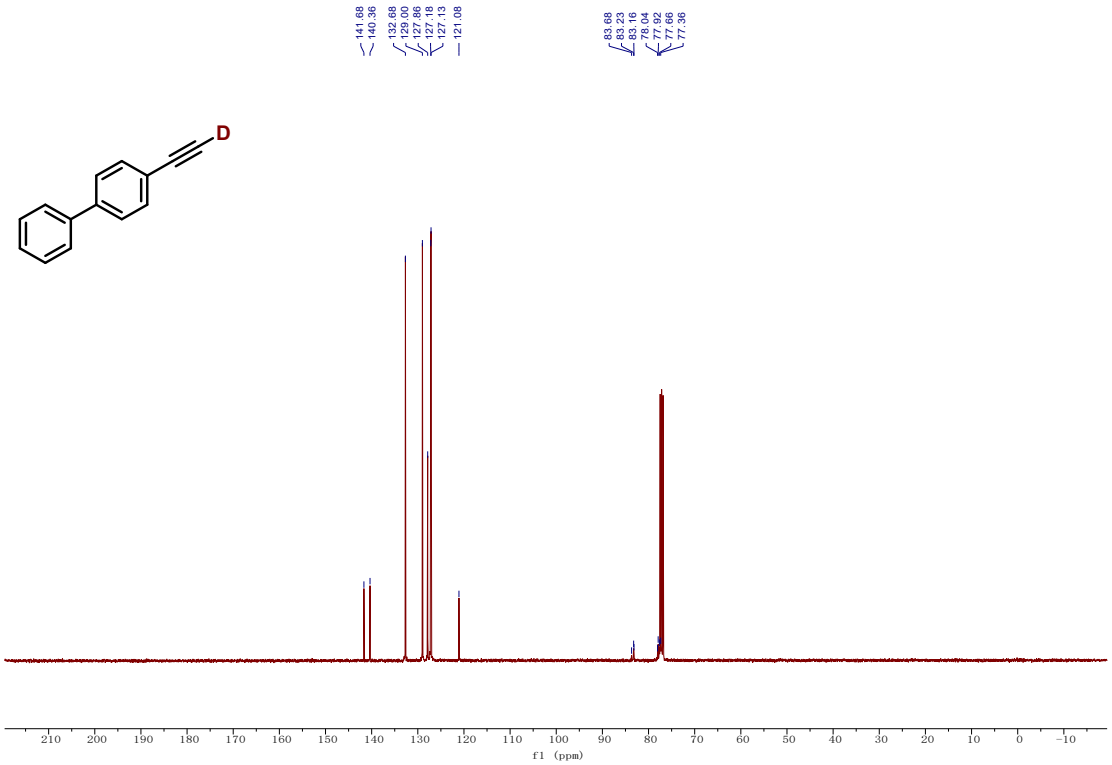
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of S4



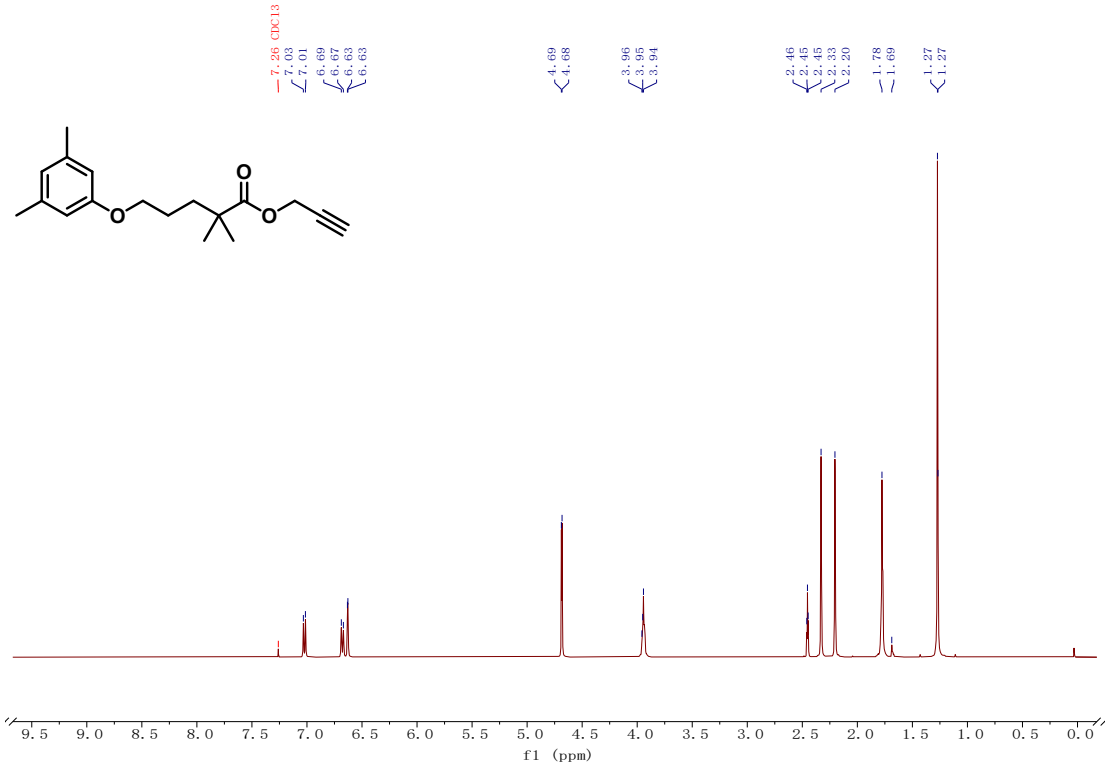
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of S5



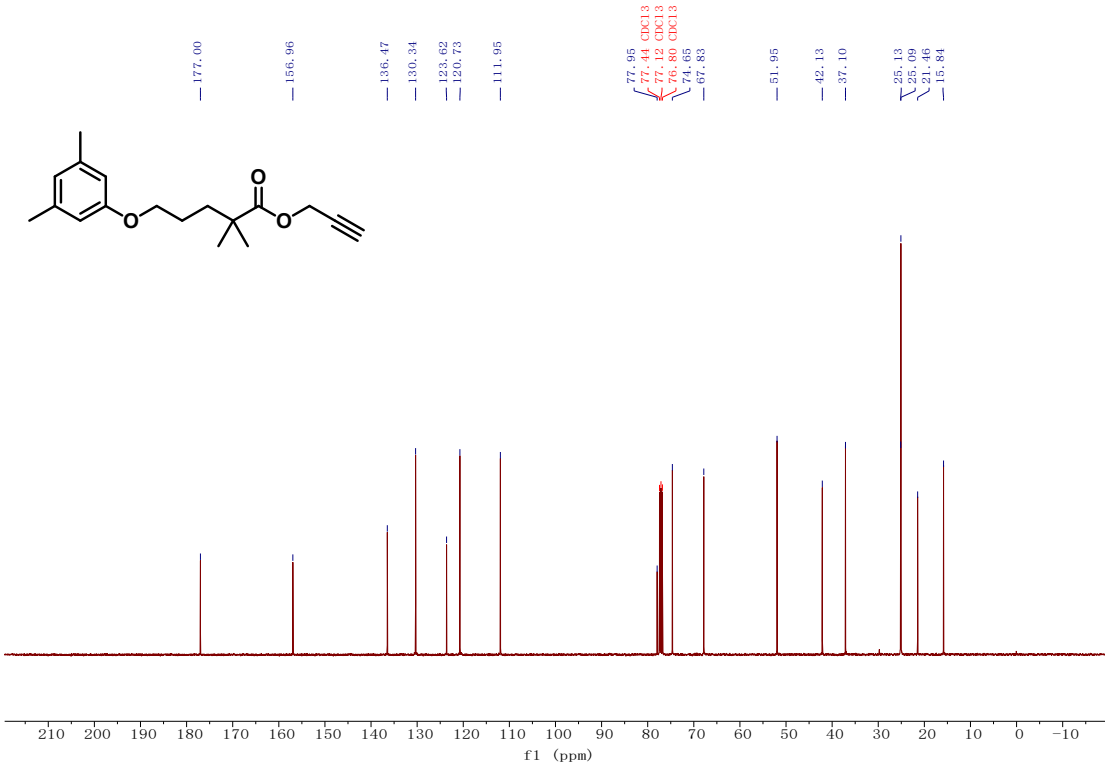
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of S5



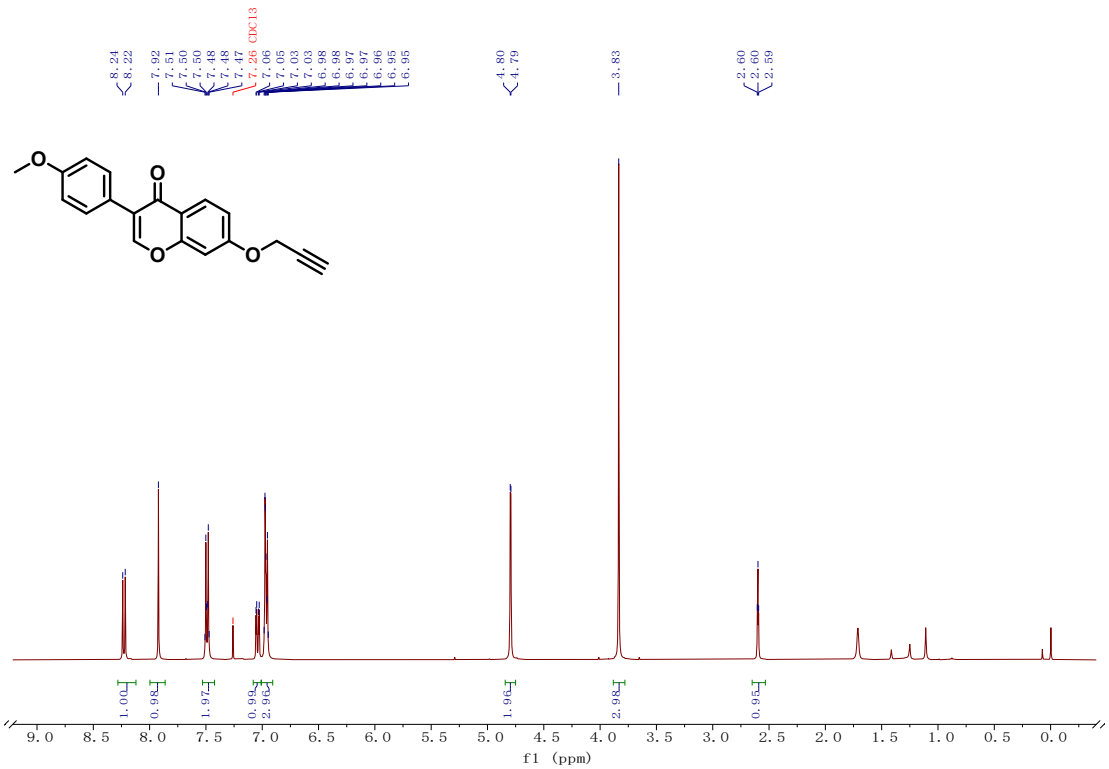
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of S6



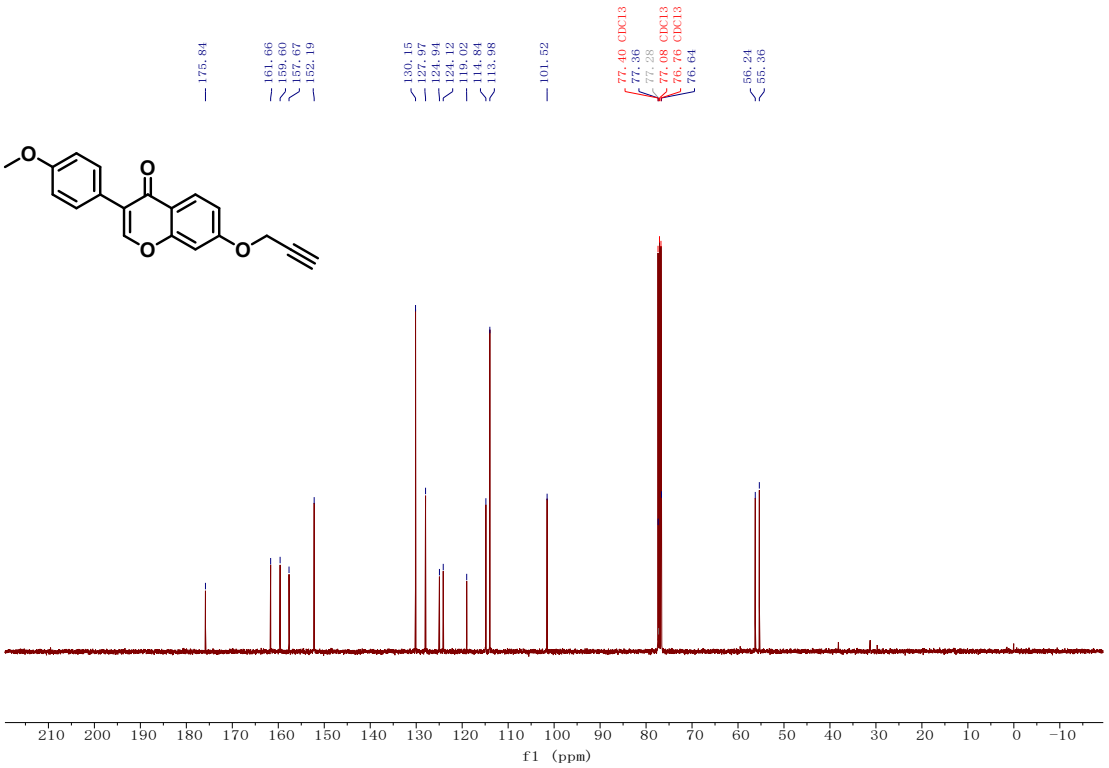
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of S6



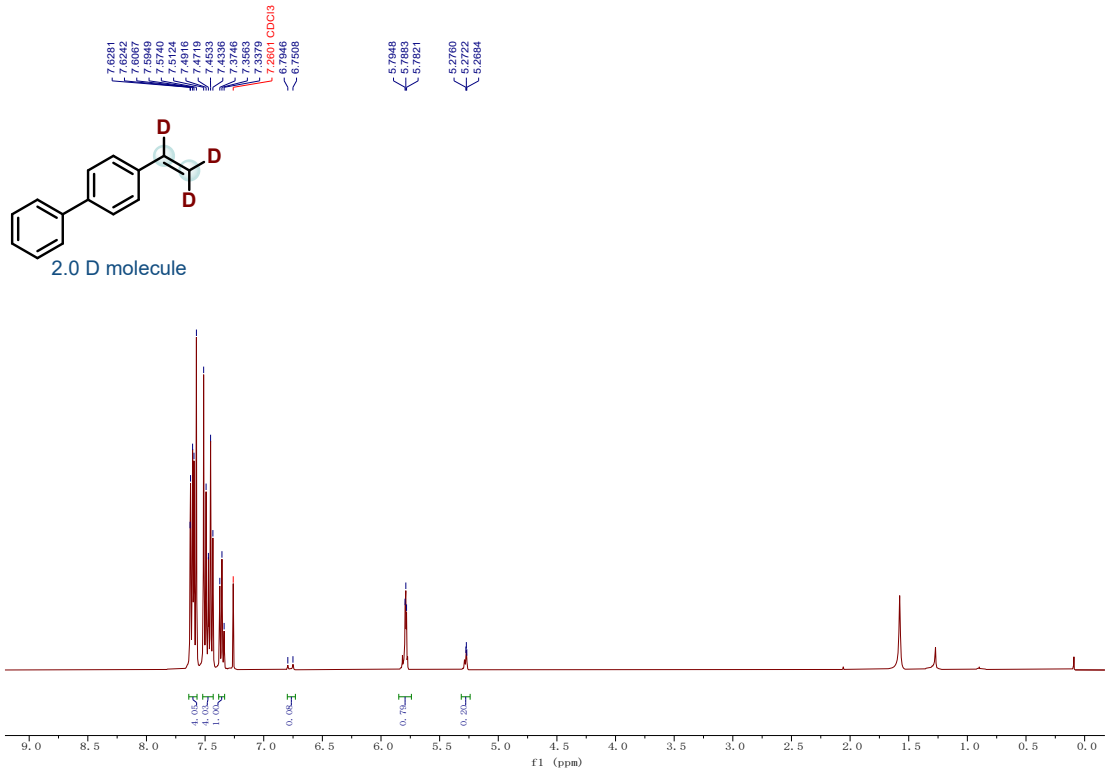
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of S7



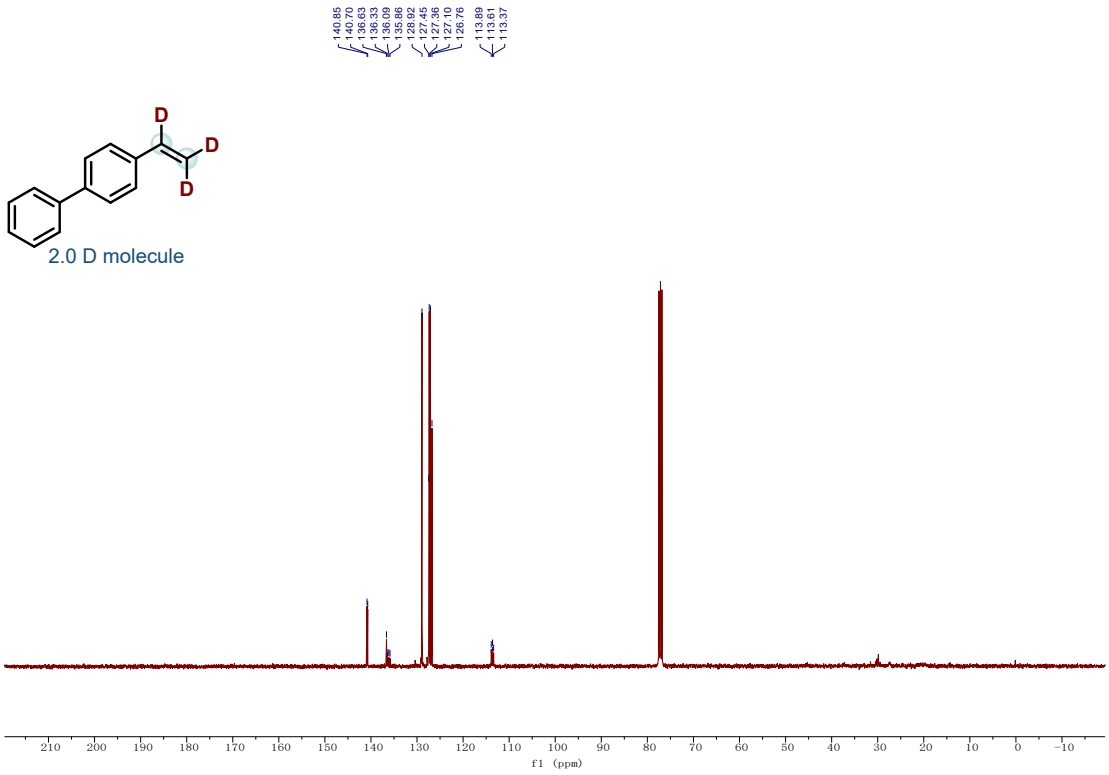
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of S7



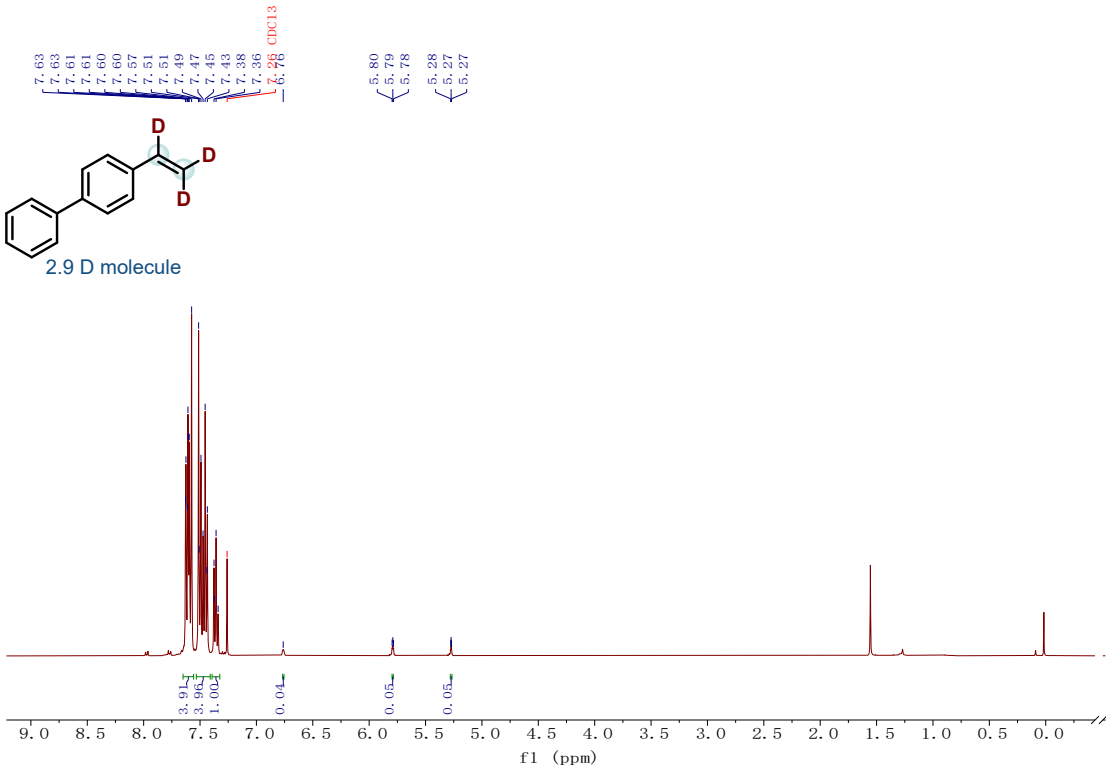
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2a



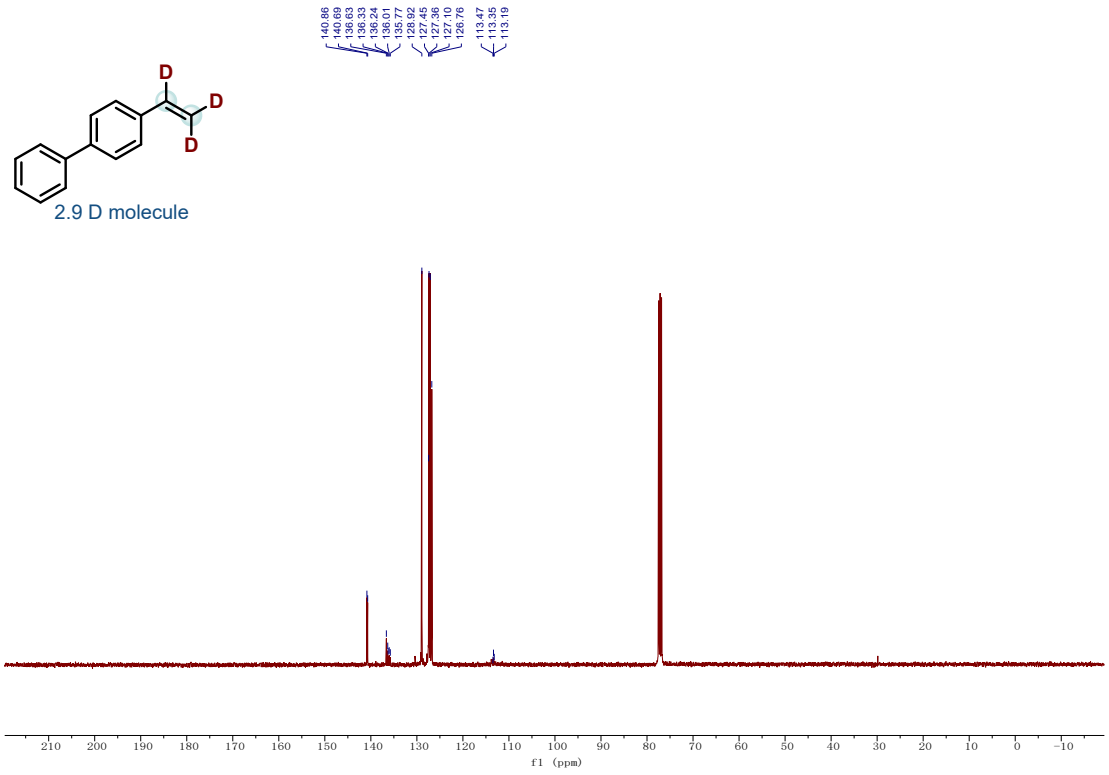
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2a



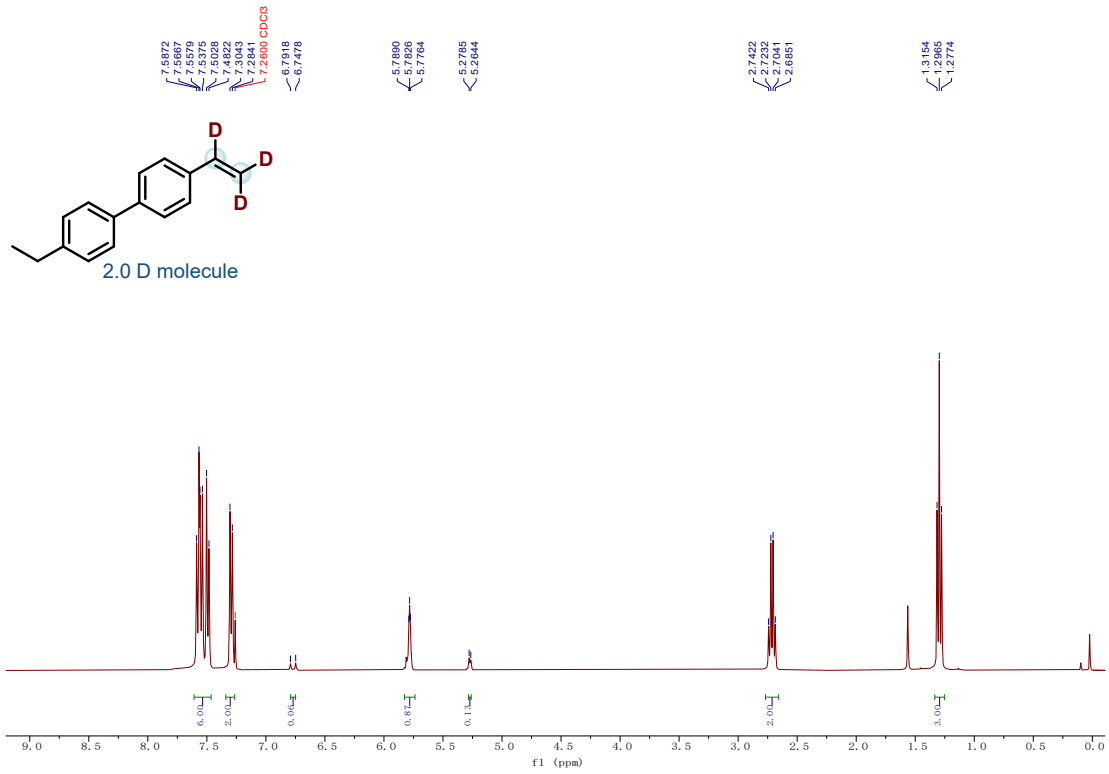
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2b



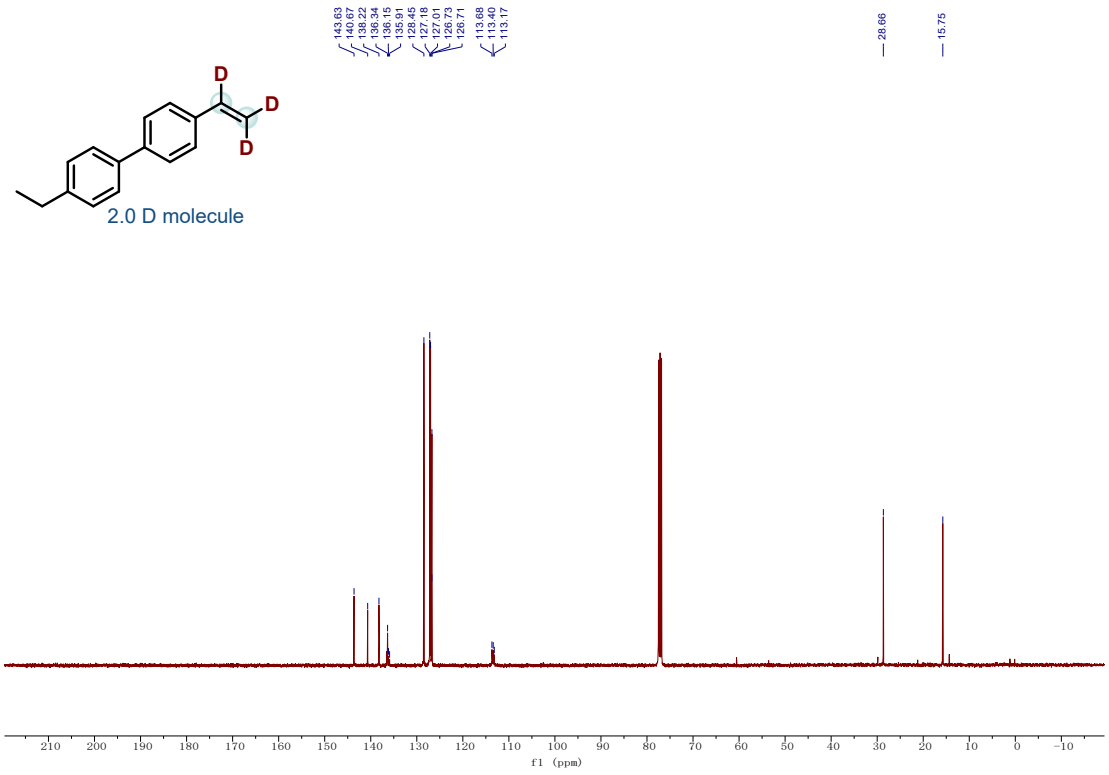
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2b



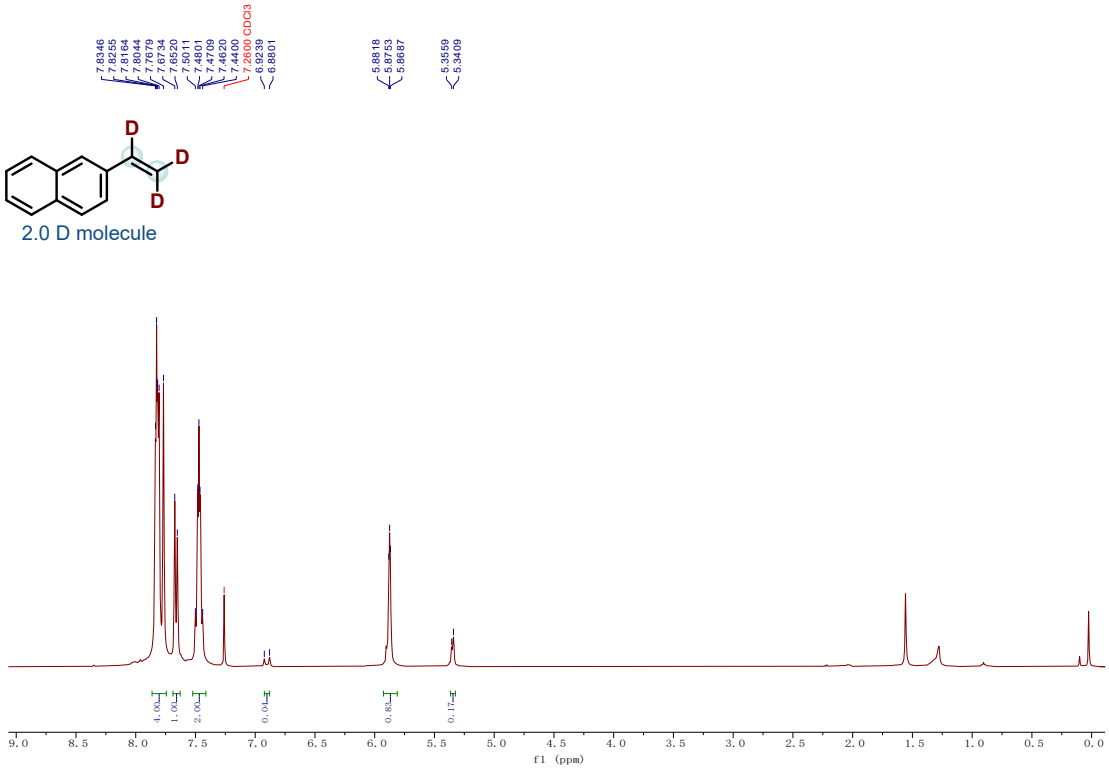
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2c



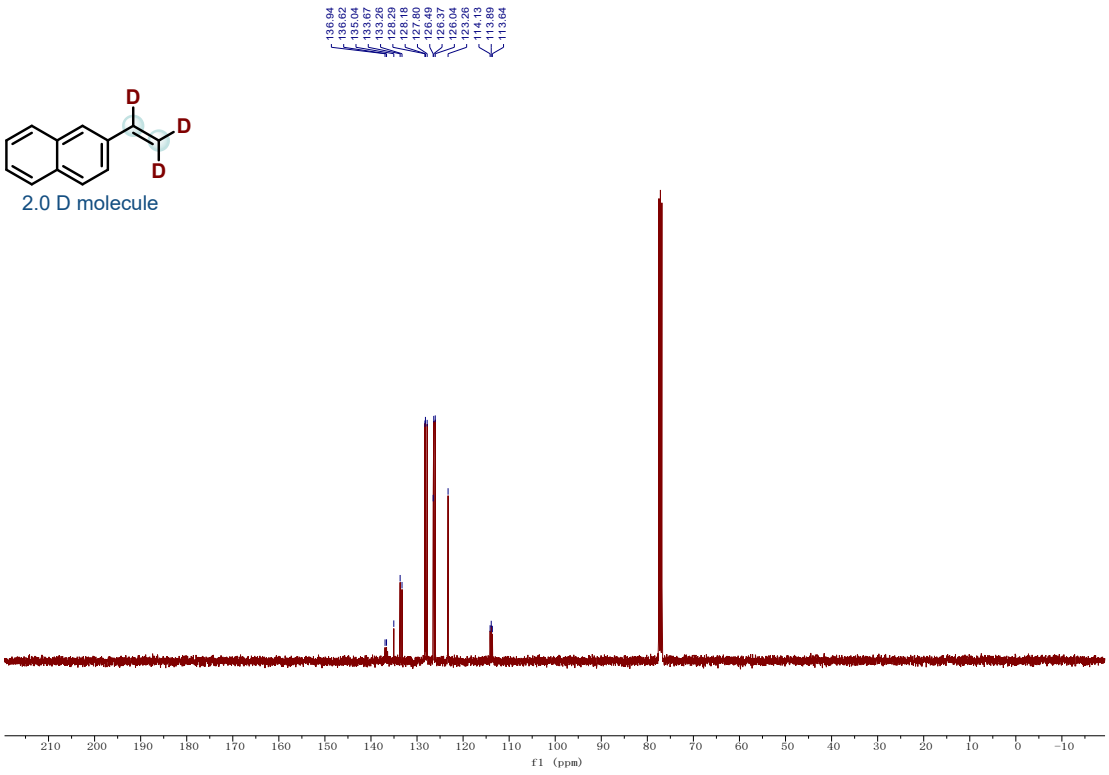
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2c



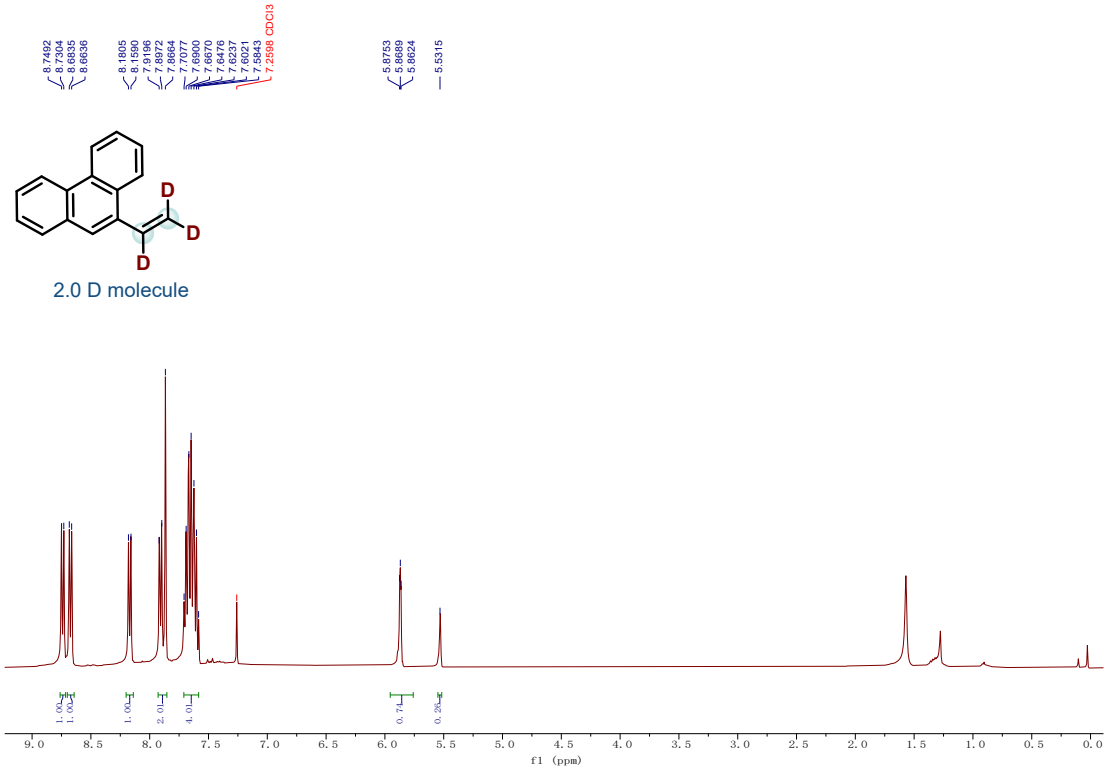
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2d



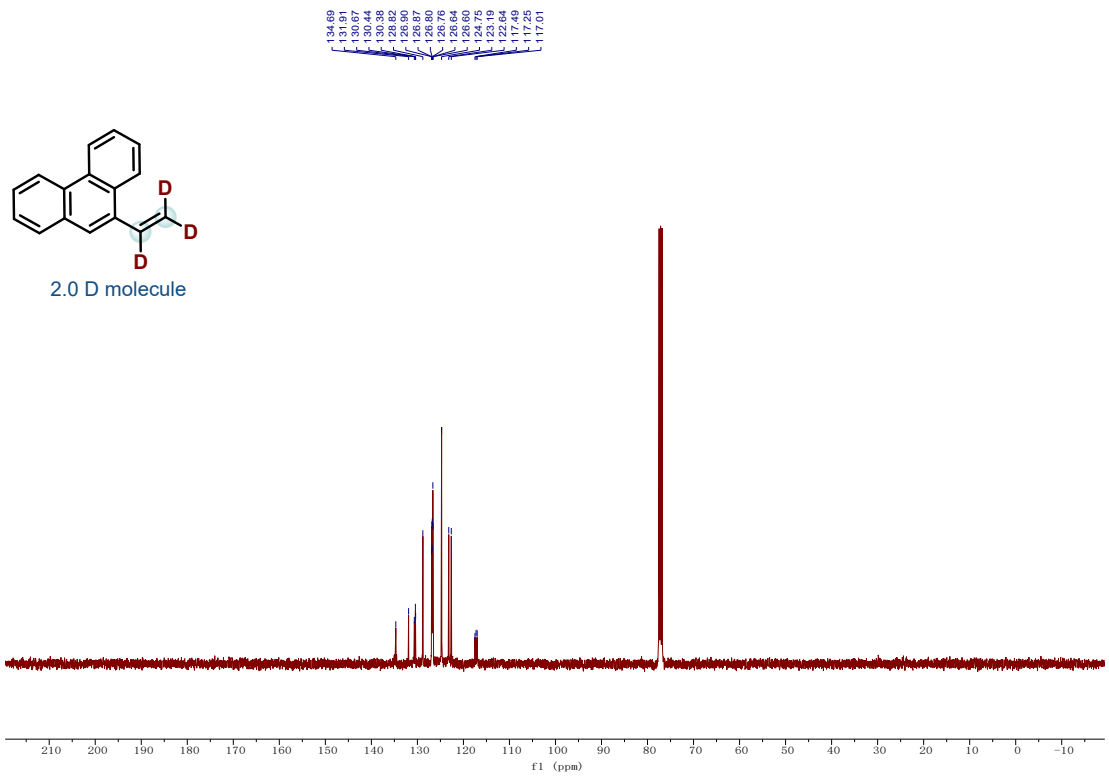
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2d



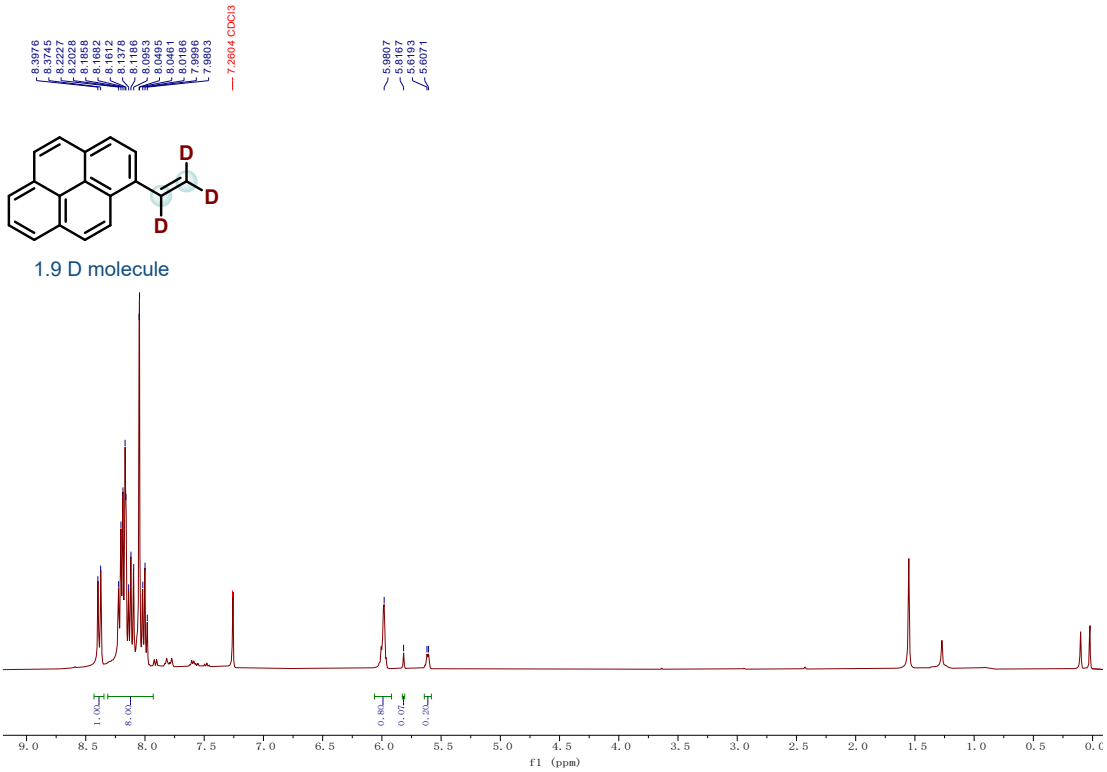
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2e



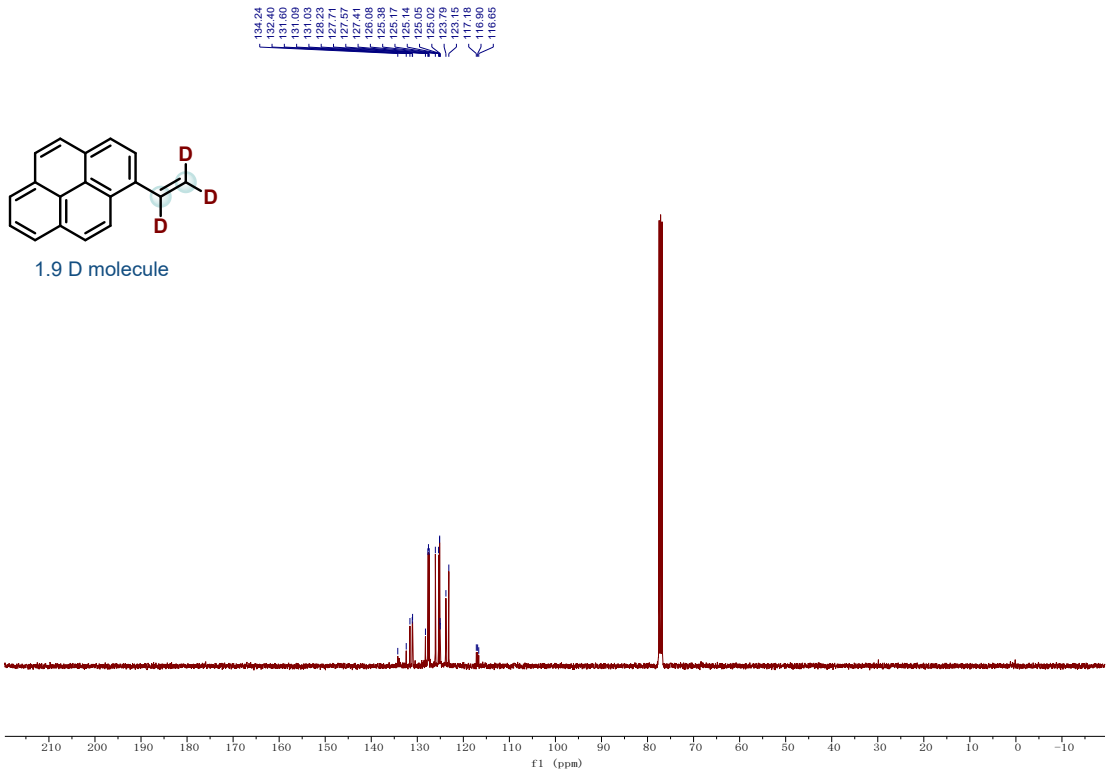
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2e



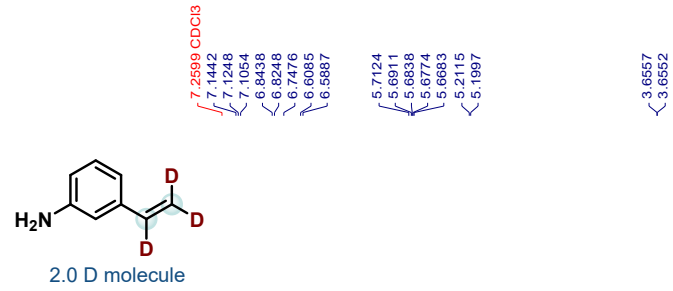
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2f



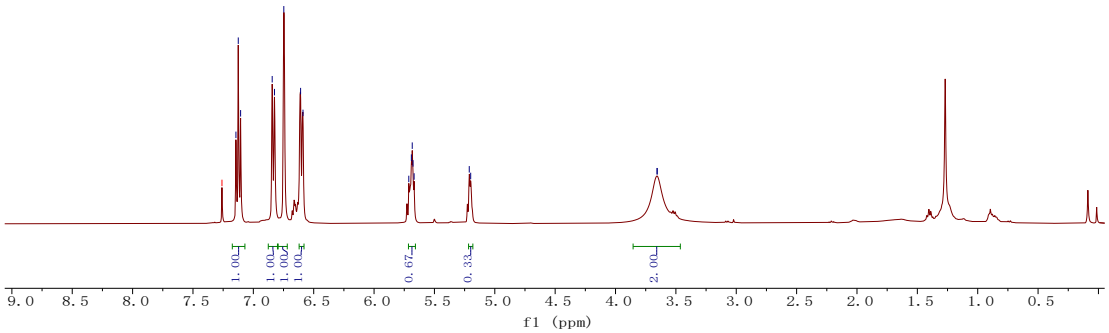
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2f



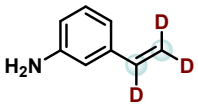
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2g



2.0 D molecule



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2g



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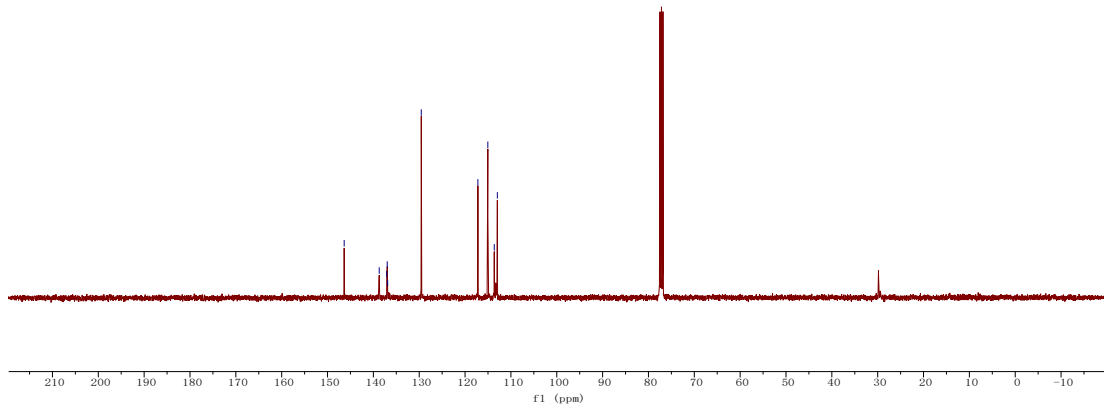
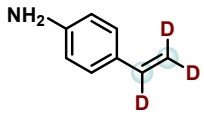
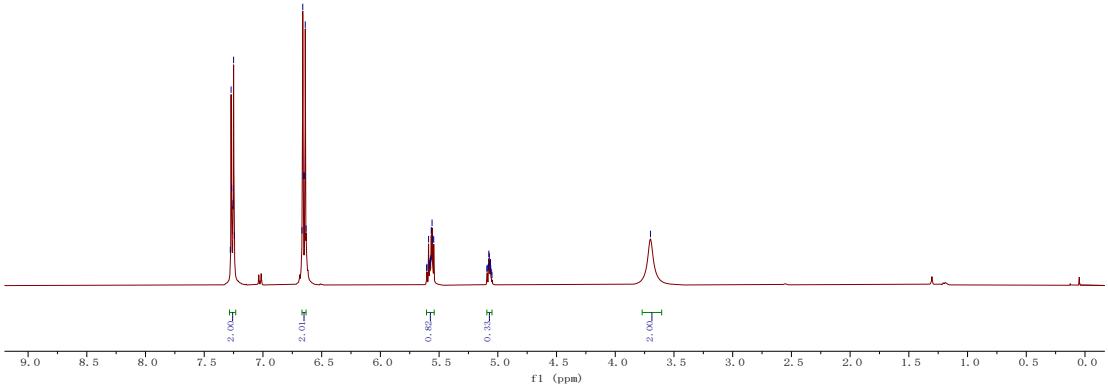


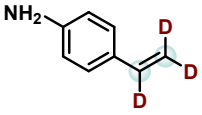
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2h



1.9 D molecule



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2h



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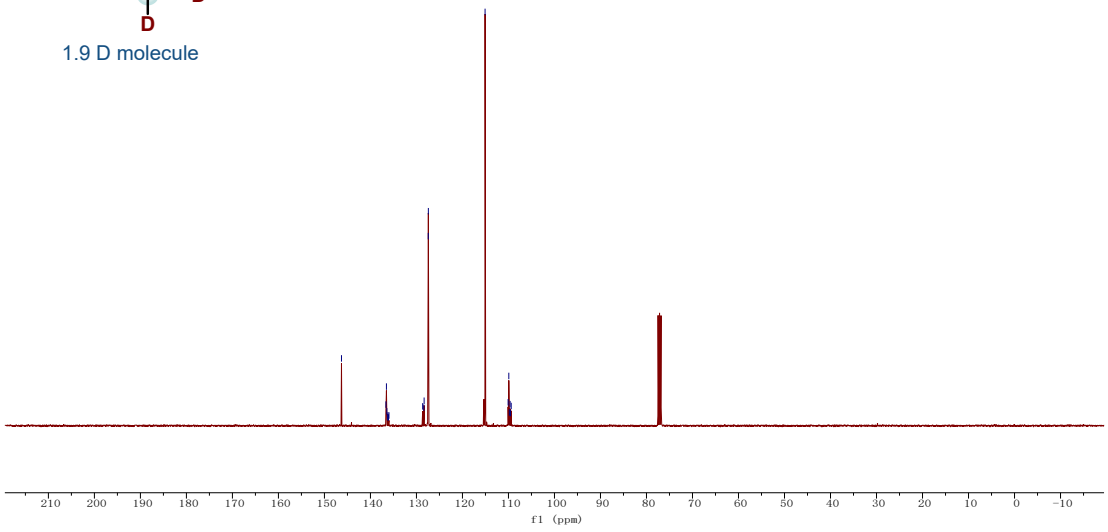
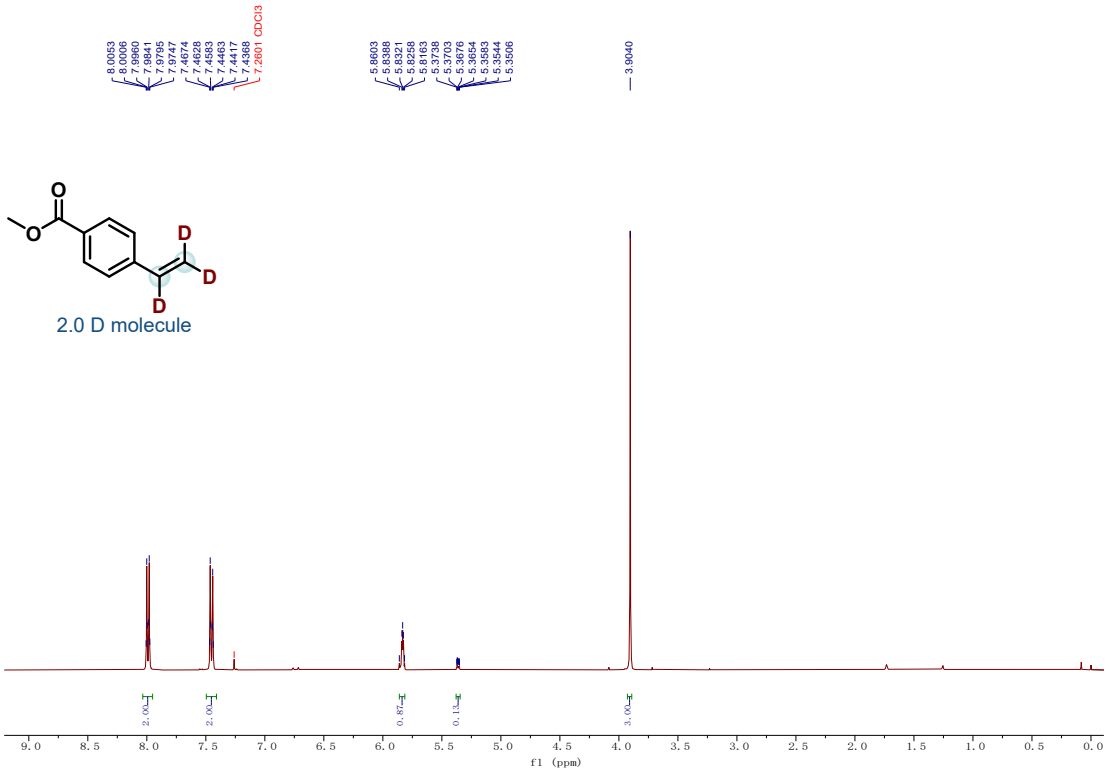
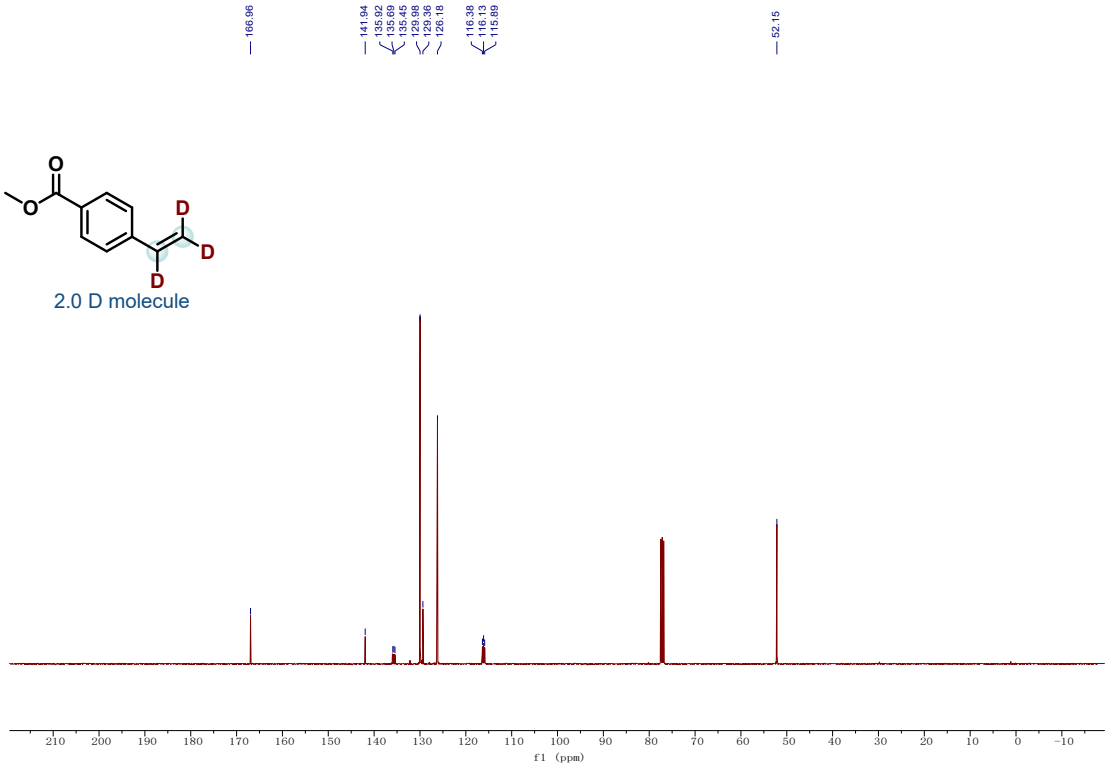


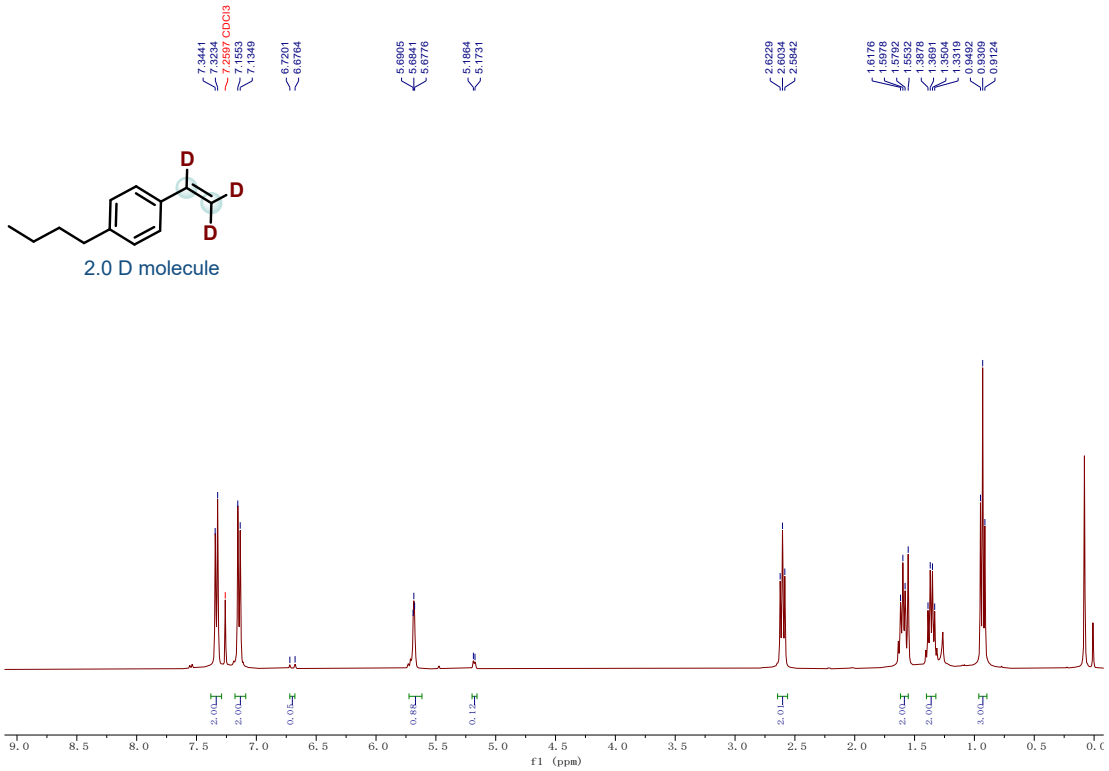
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2i



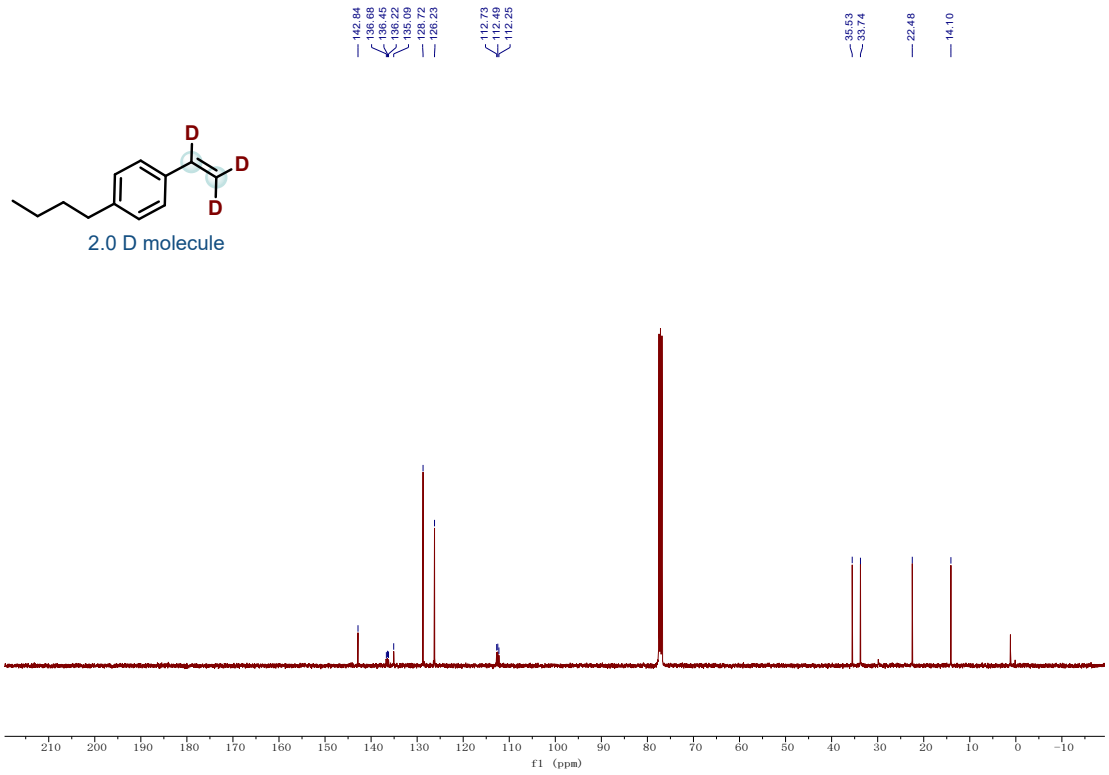
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2i



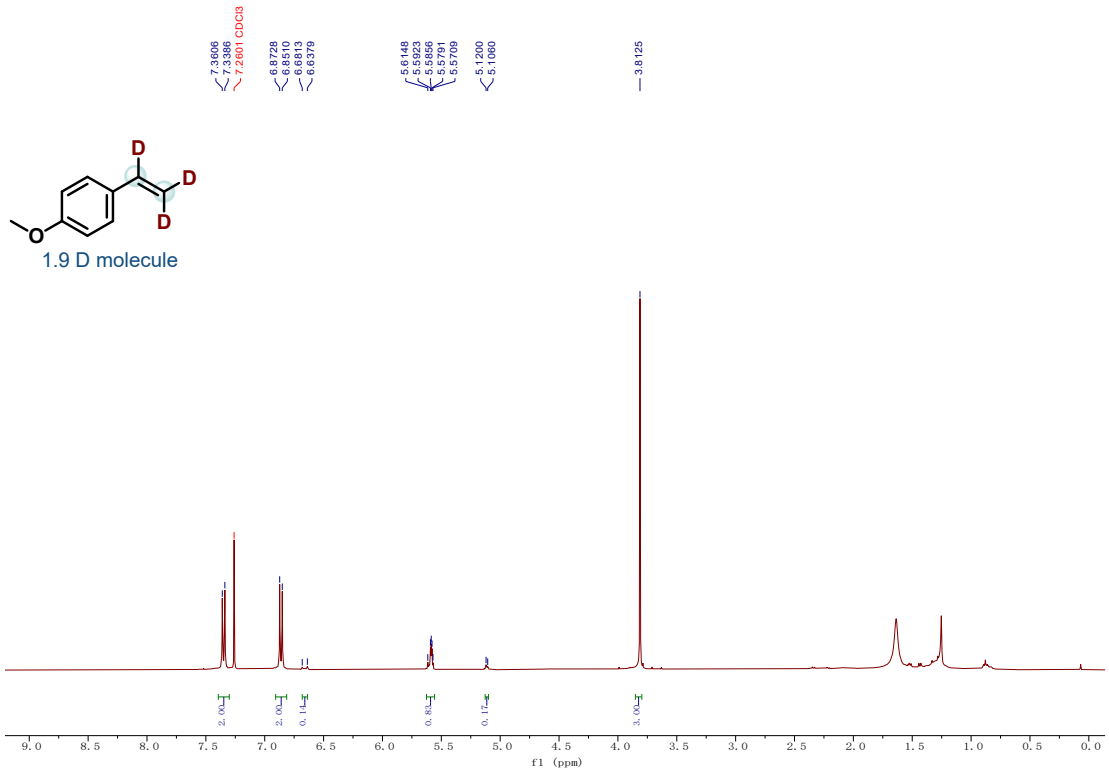
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2j



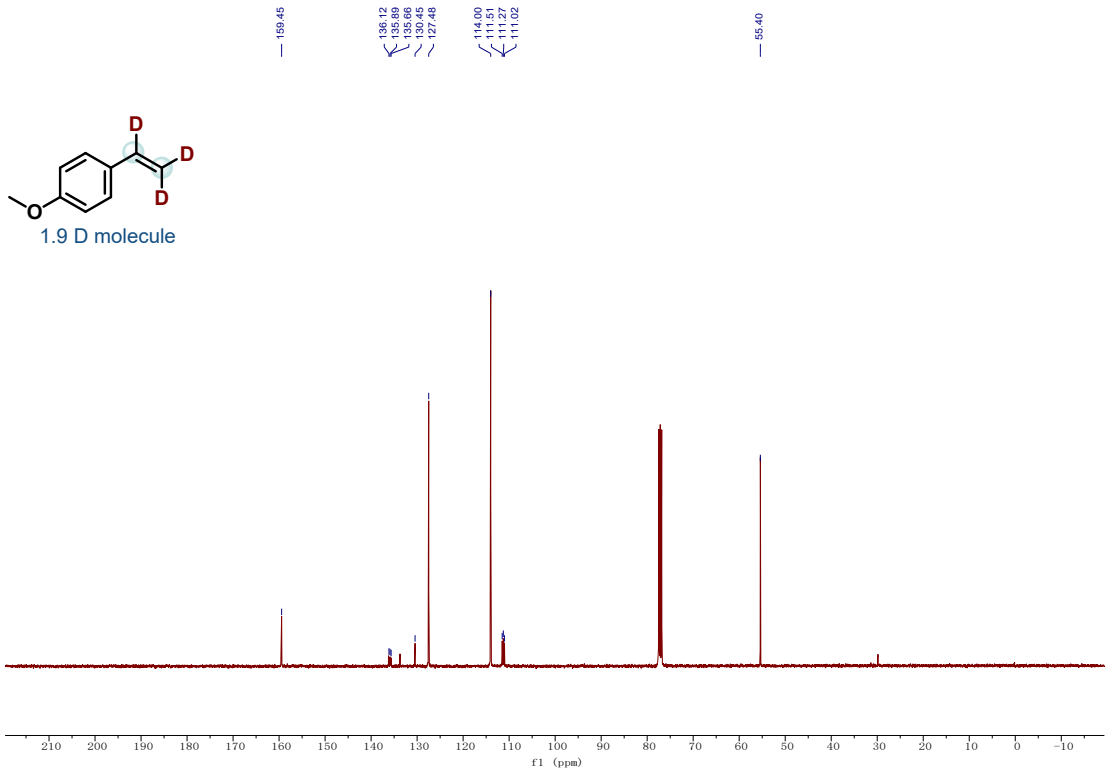
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2j



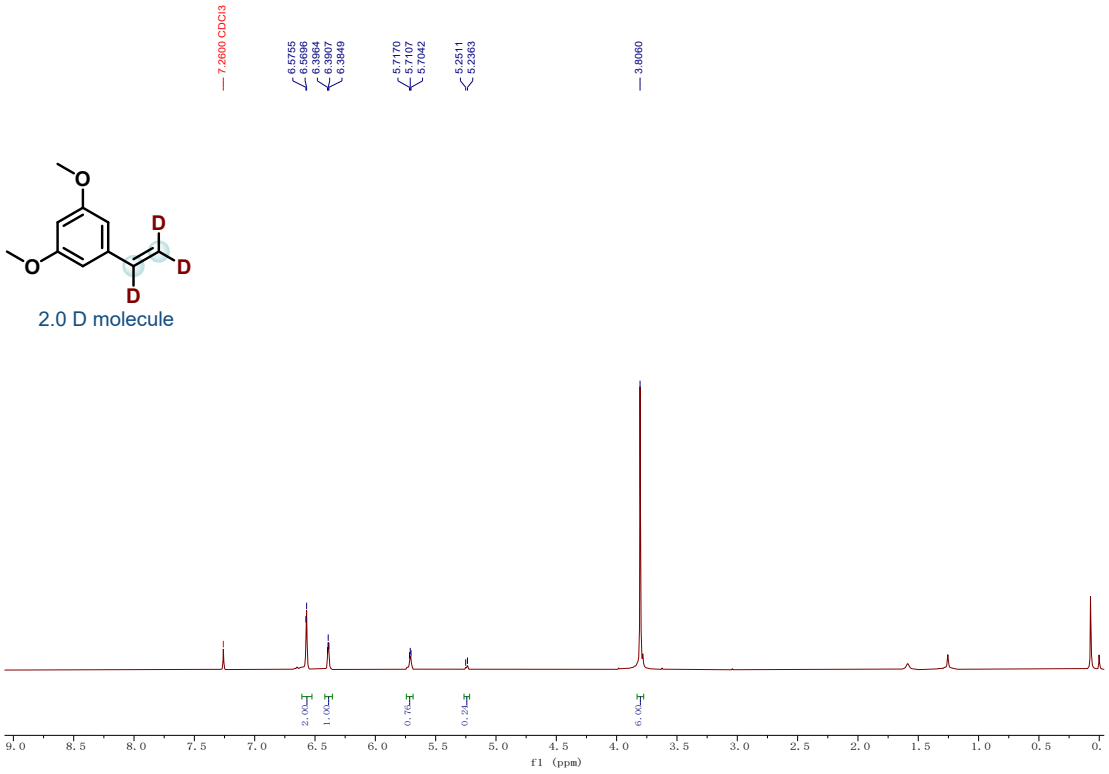
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2k



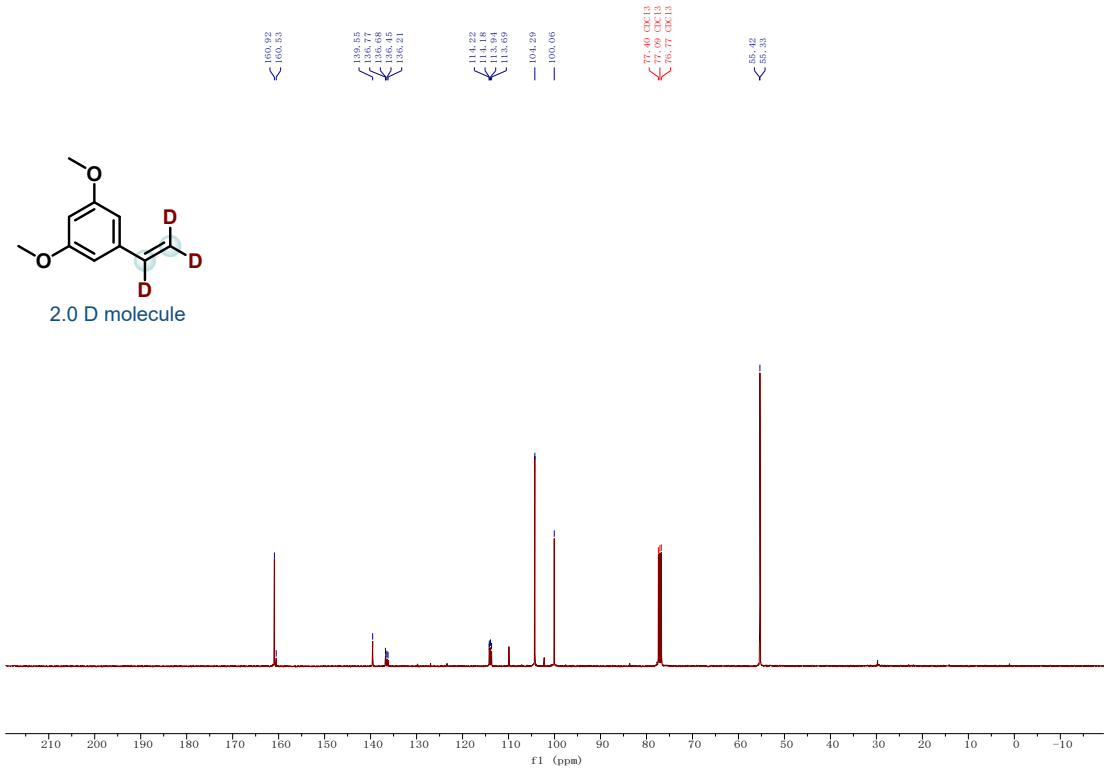
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2k



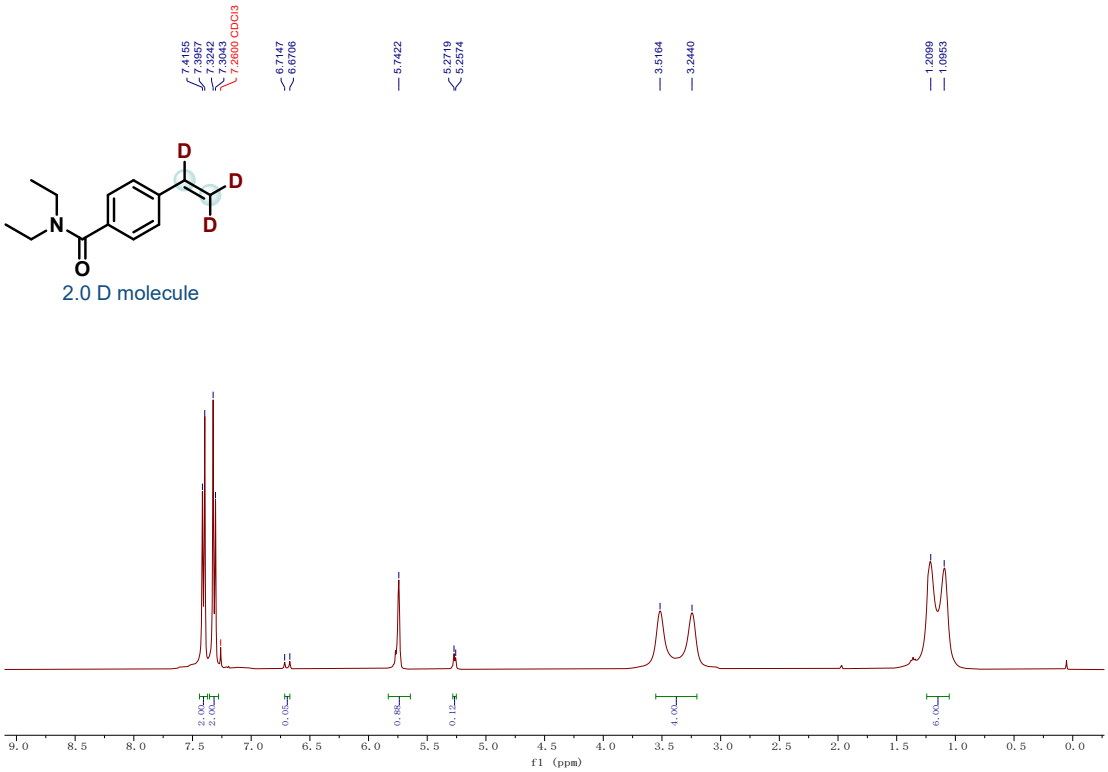
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2l



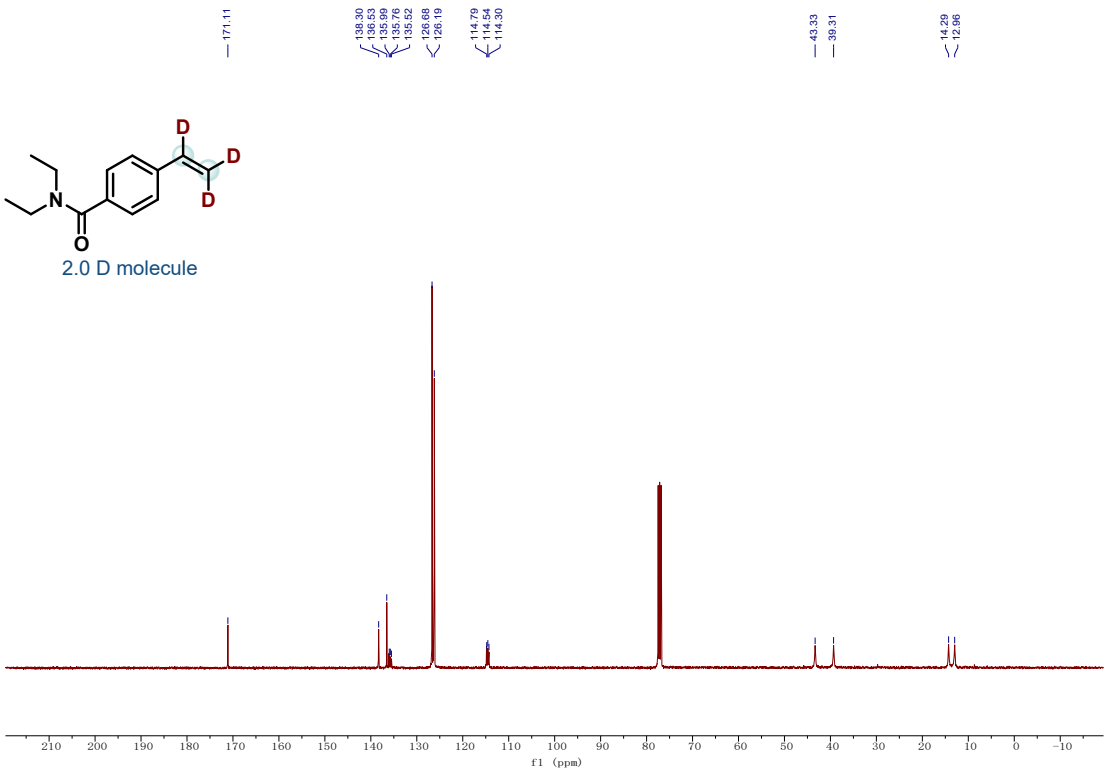
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2l



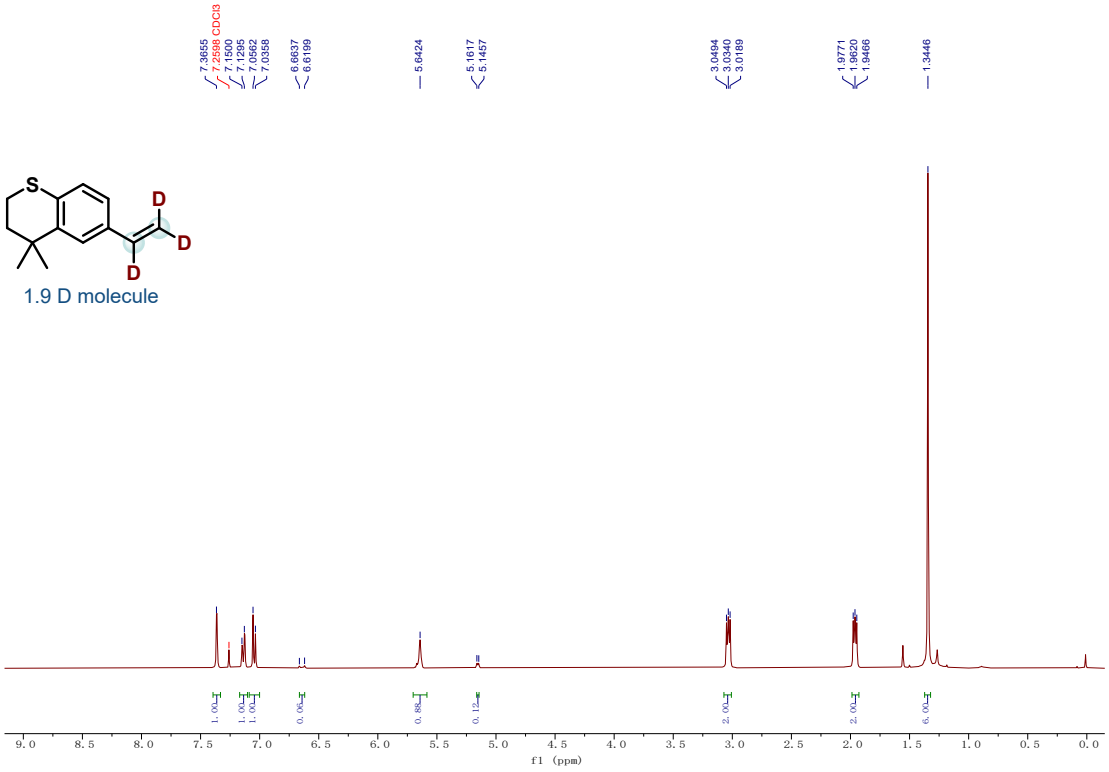
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2m



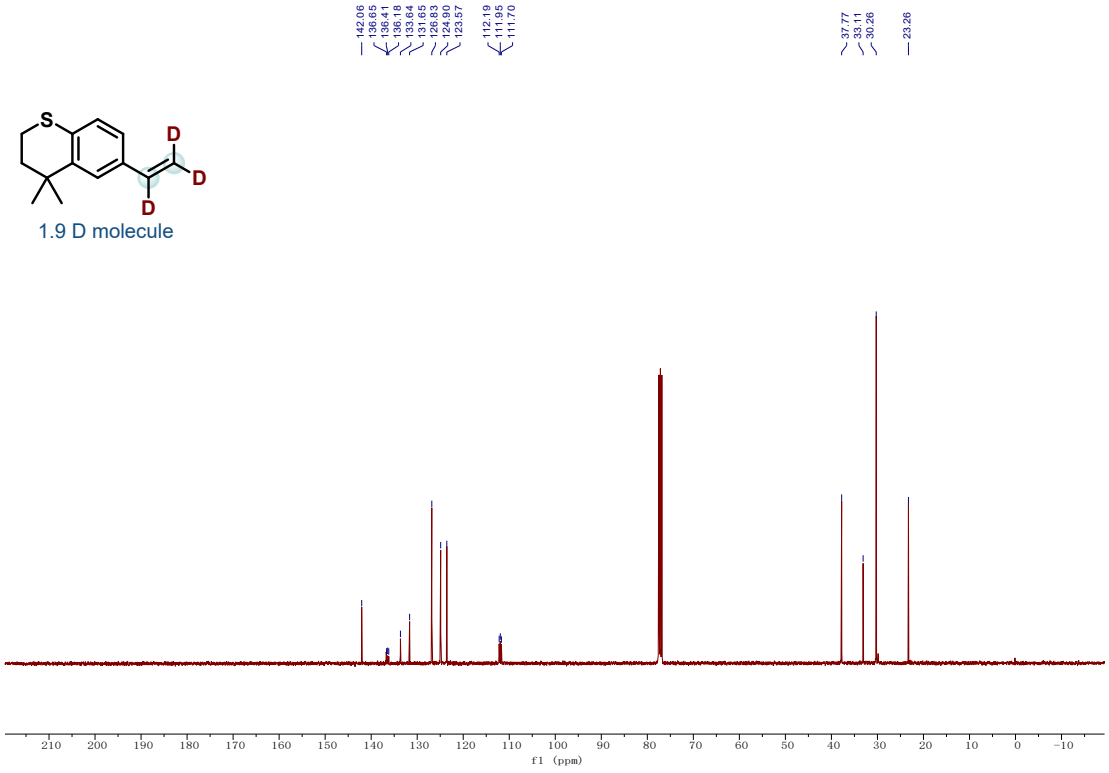
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2m



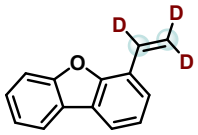
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2n



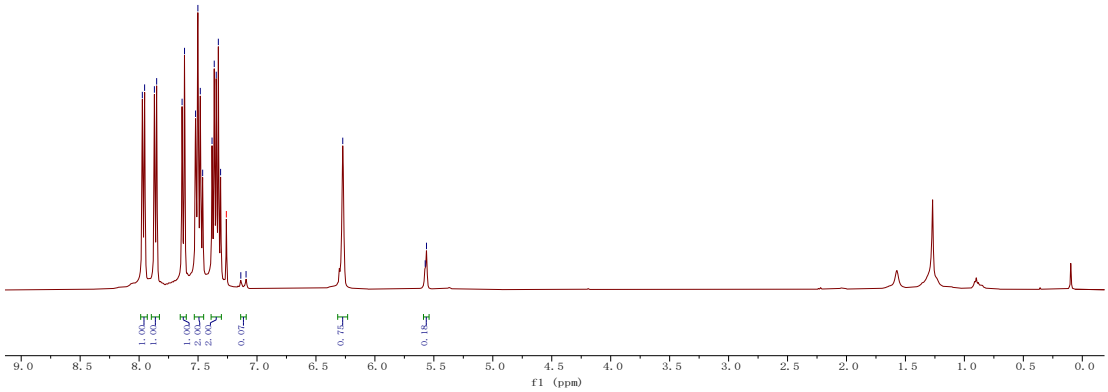
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2n



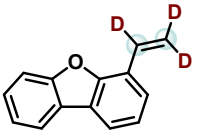
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2o



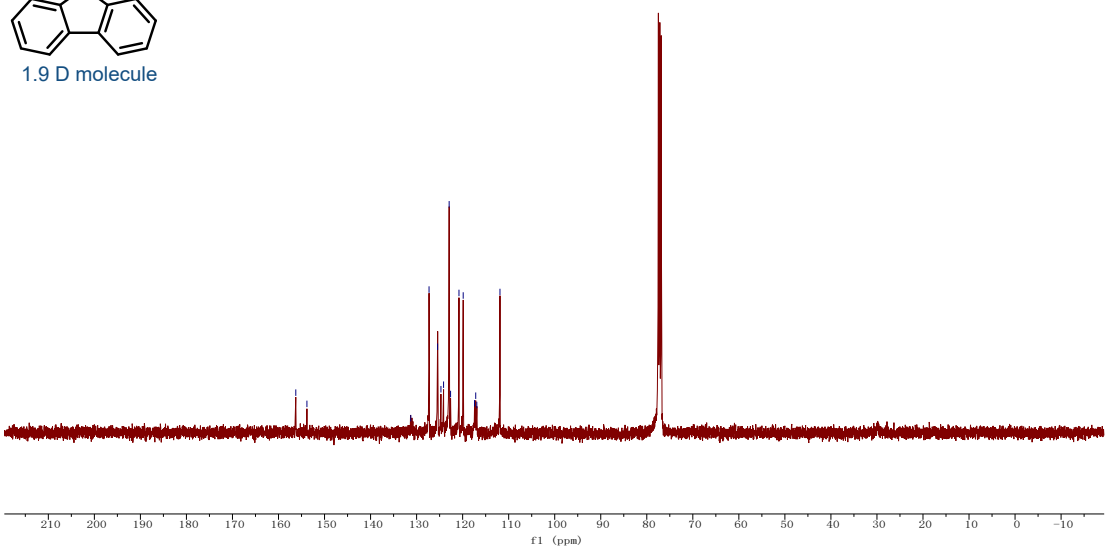
1.9 D molecule



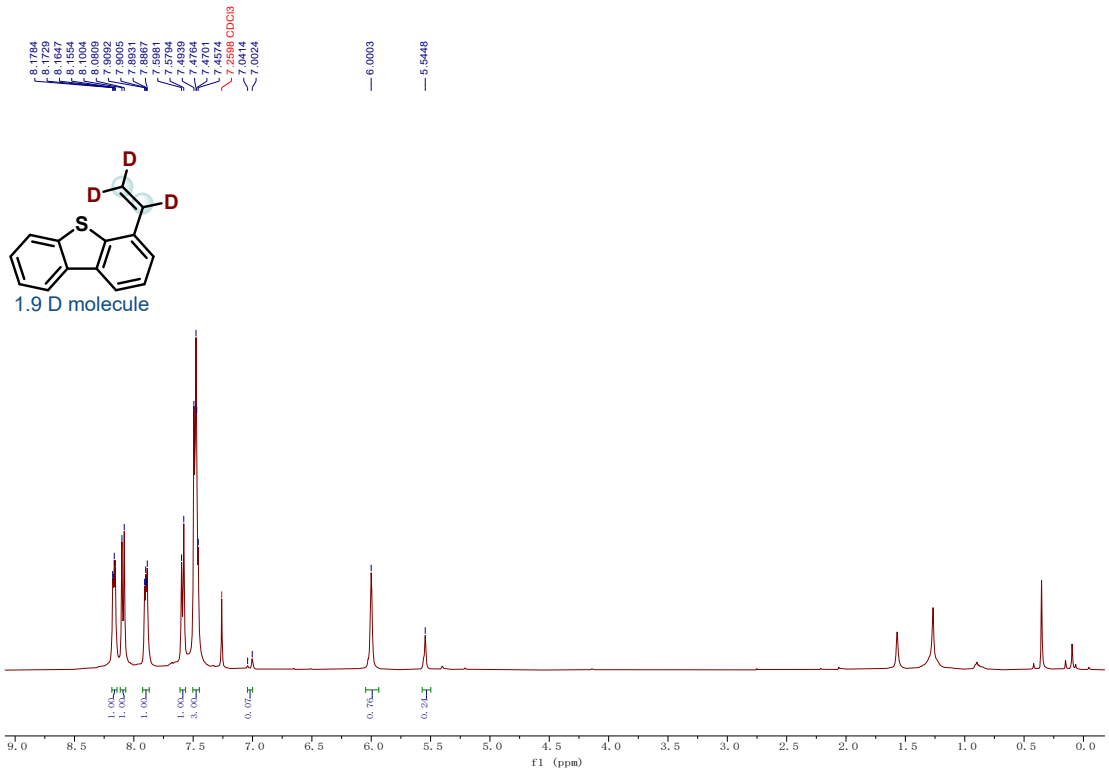
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2o



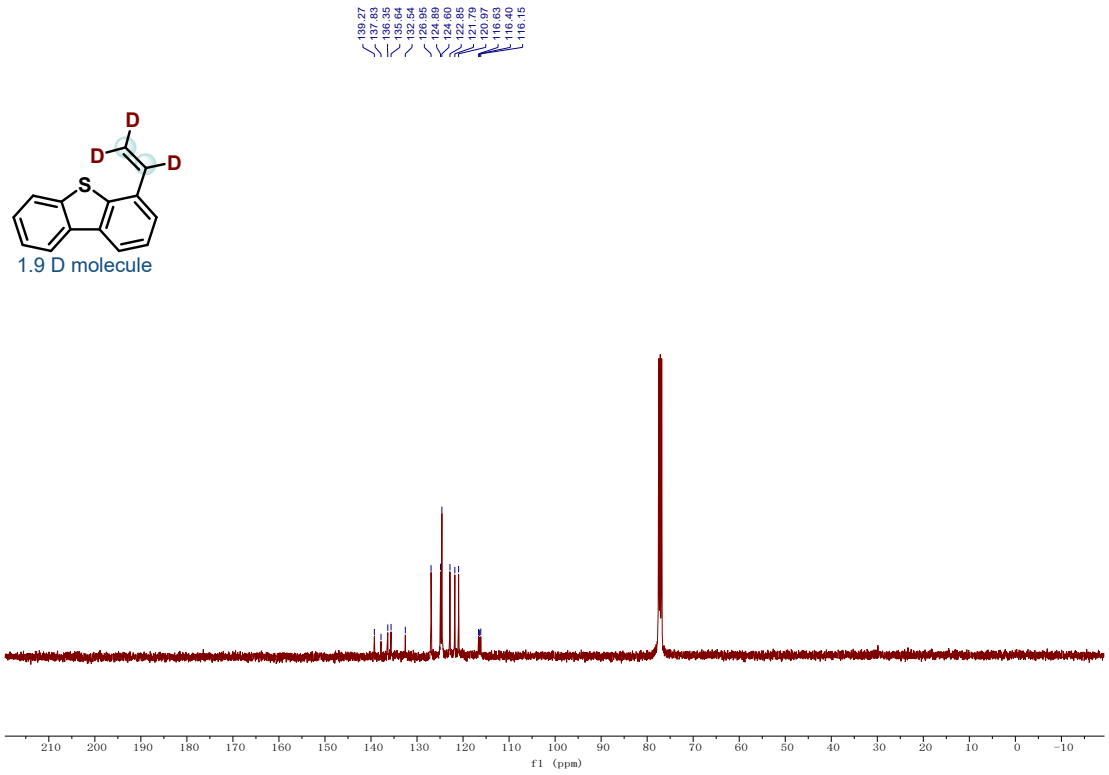
1.9 D molecule



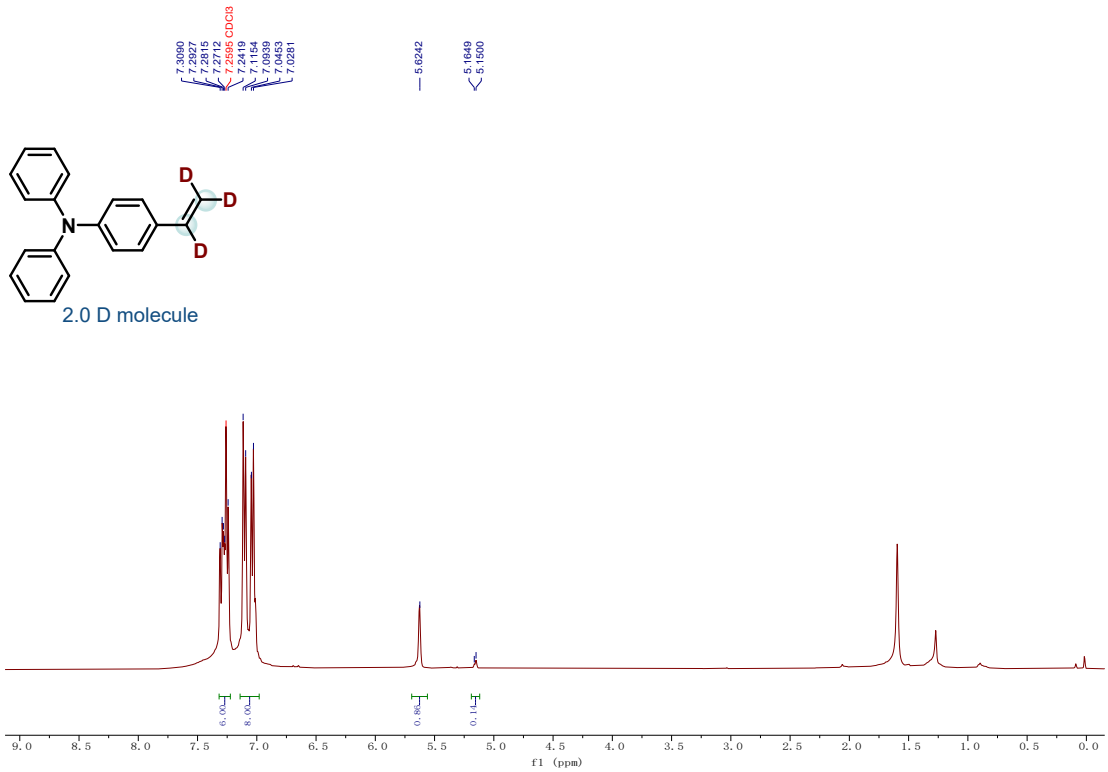
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2p



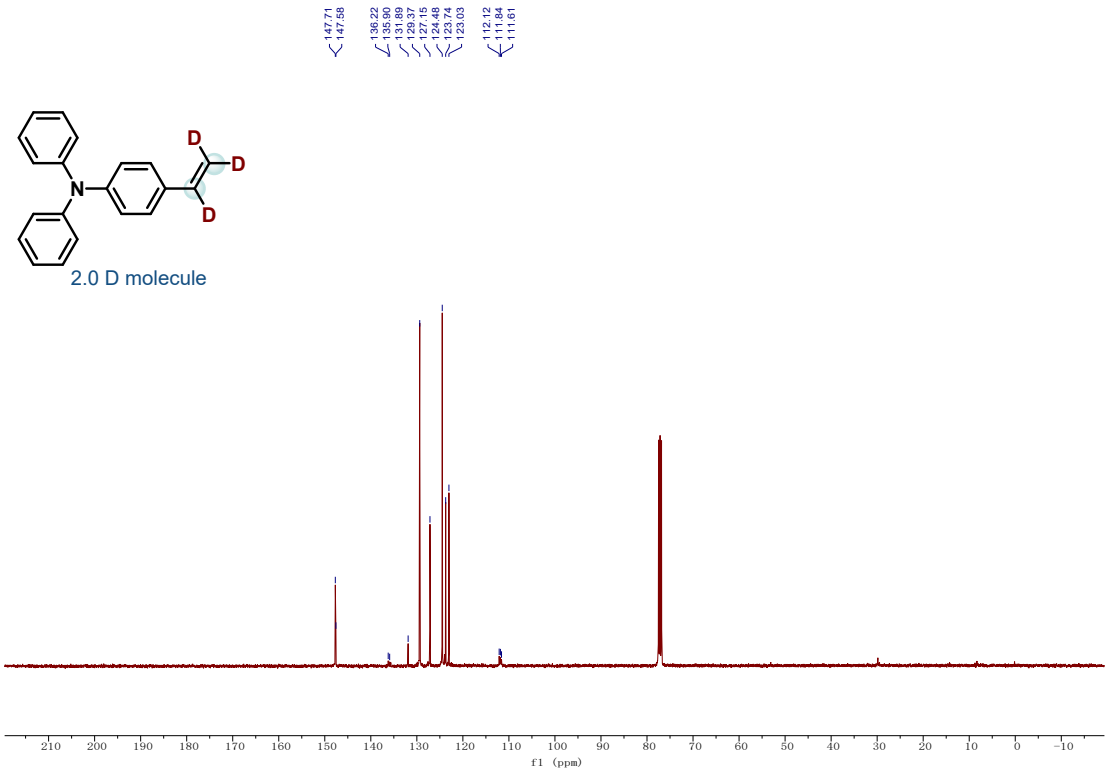
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2p



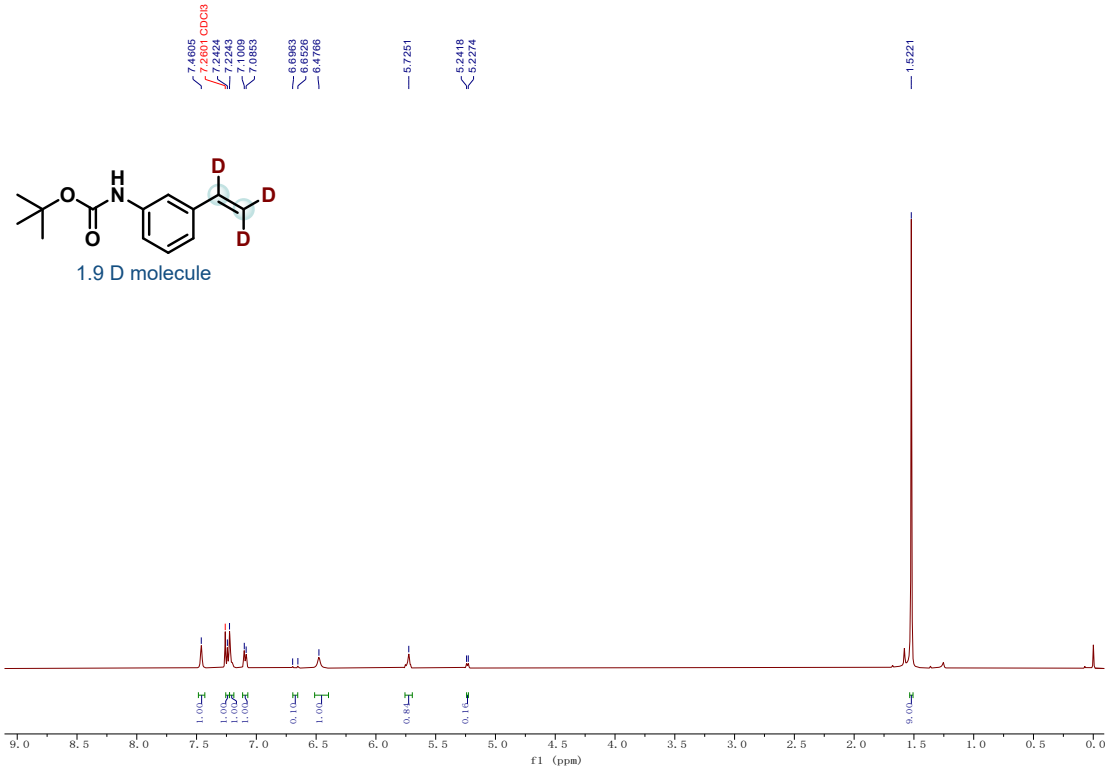
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2q



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2q

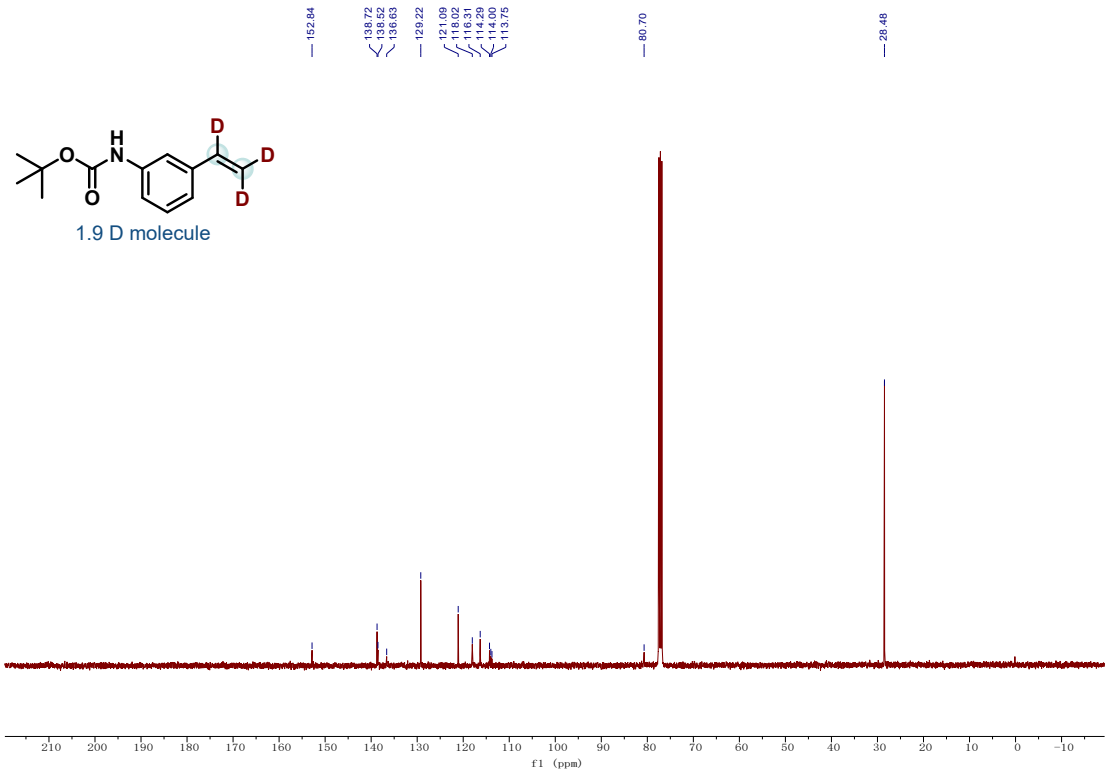


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2r



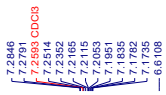
1.9 D molecule

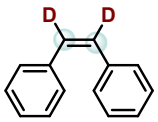
^{13}C NMR (101 MHz, CDCl3) spectrum of 2r



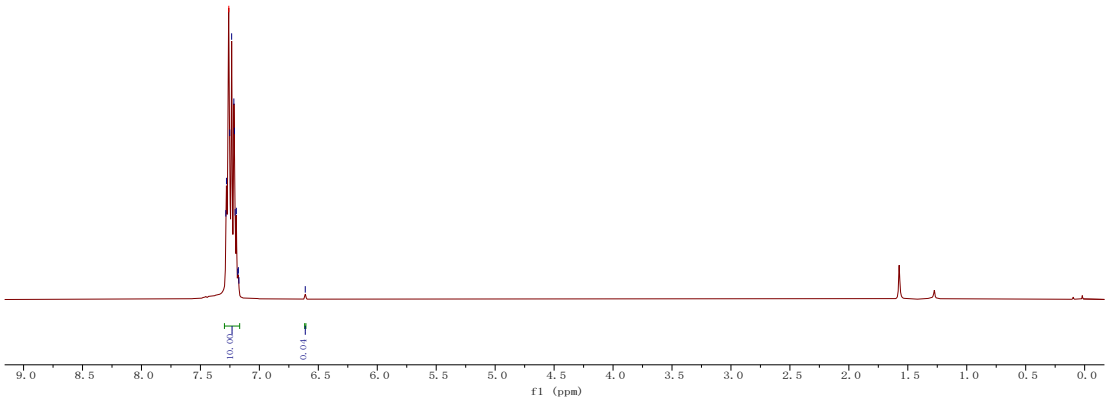
1.9 D molecule

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

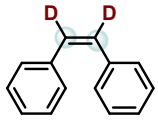




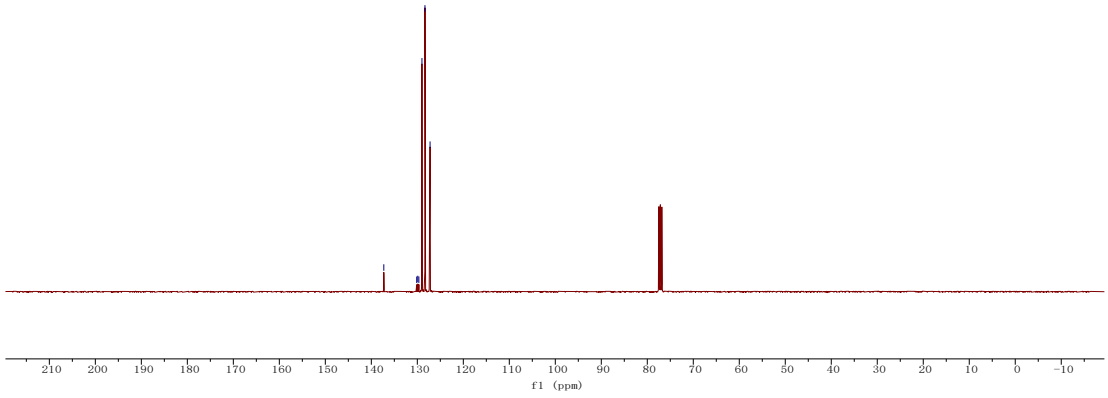
2.0 D molecule



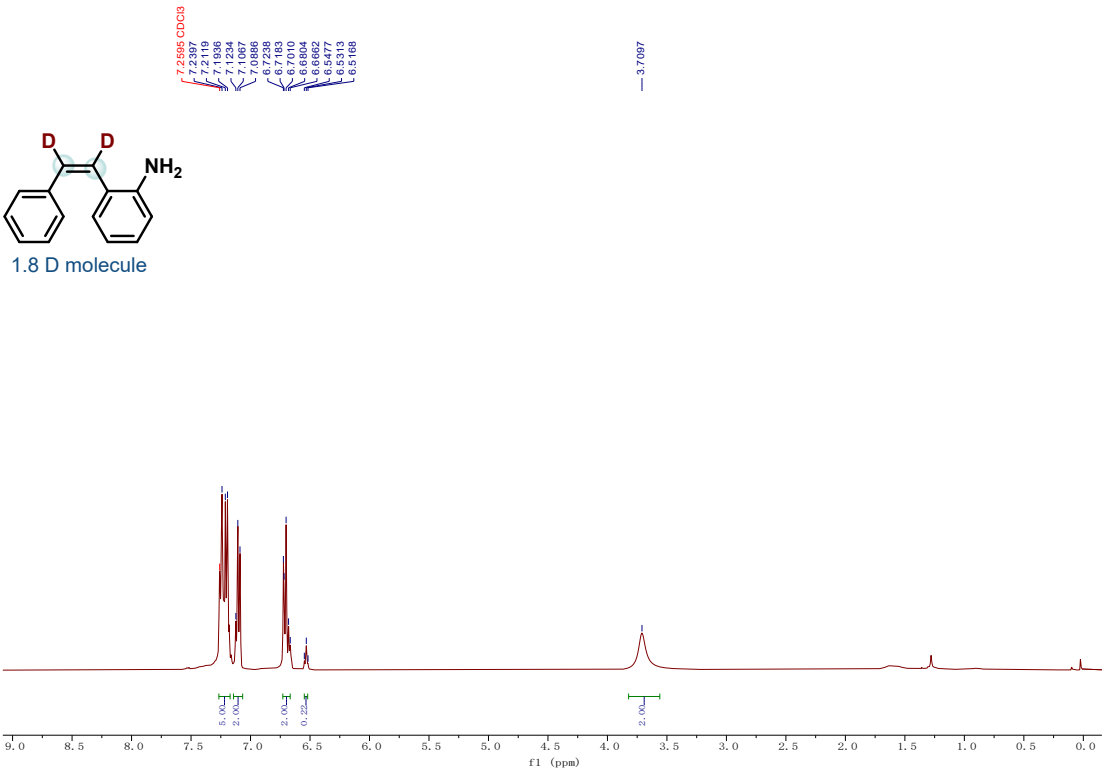
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2s



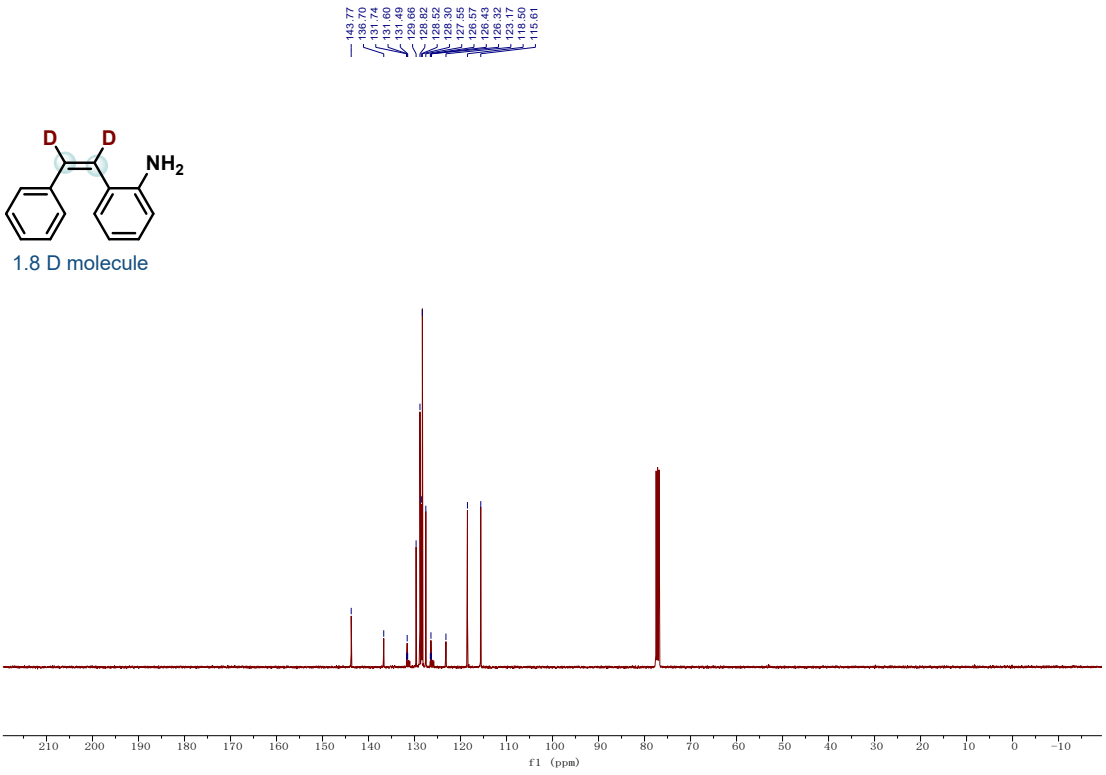
2.0 D molecule



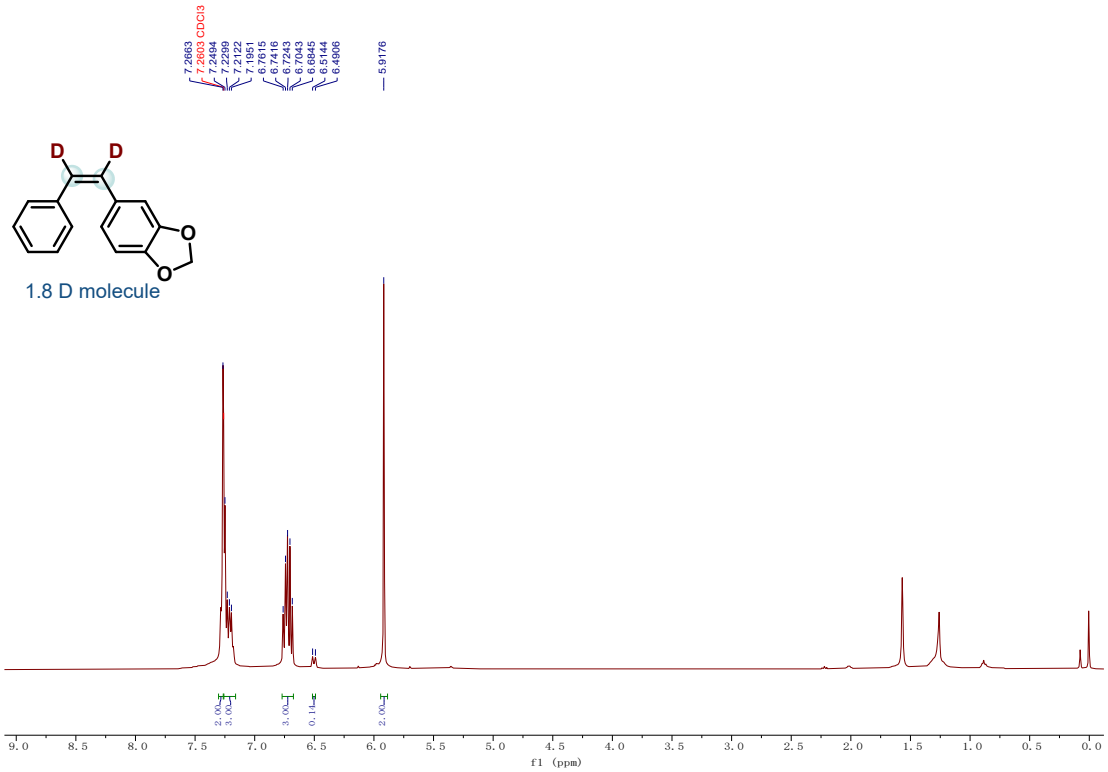
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2t



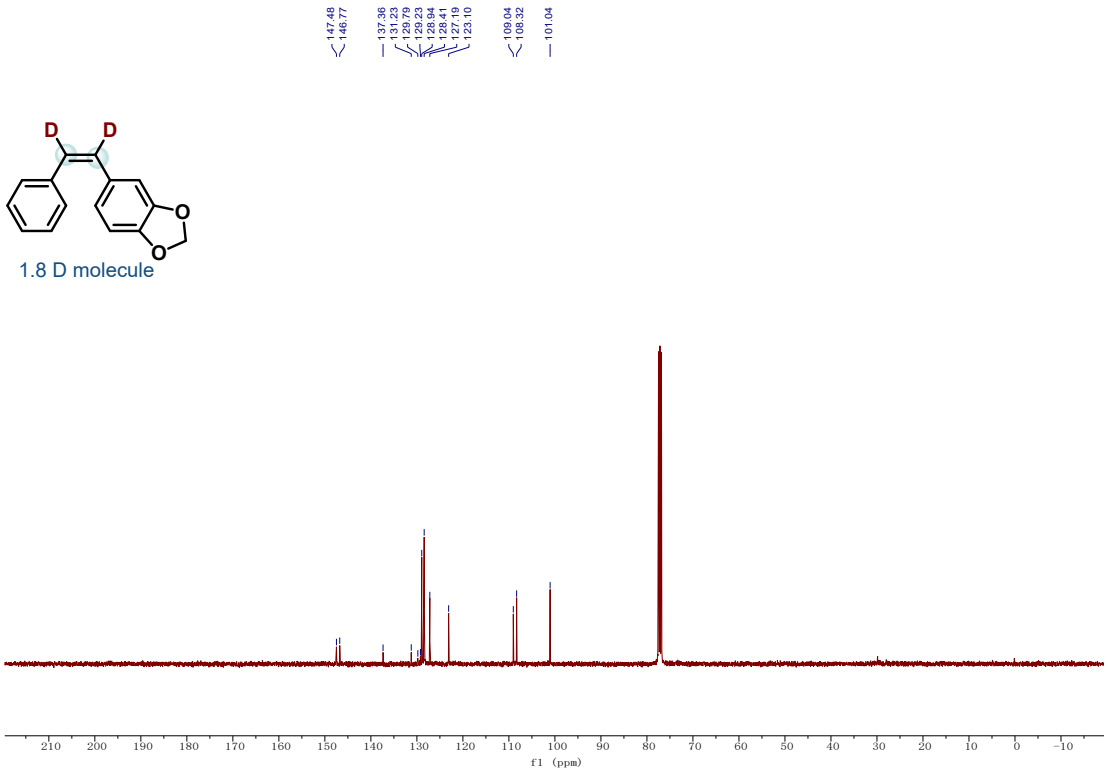
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2t



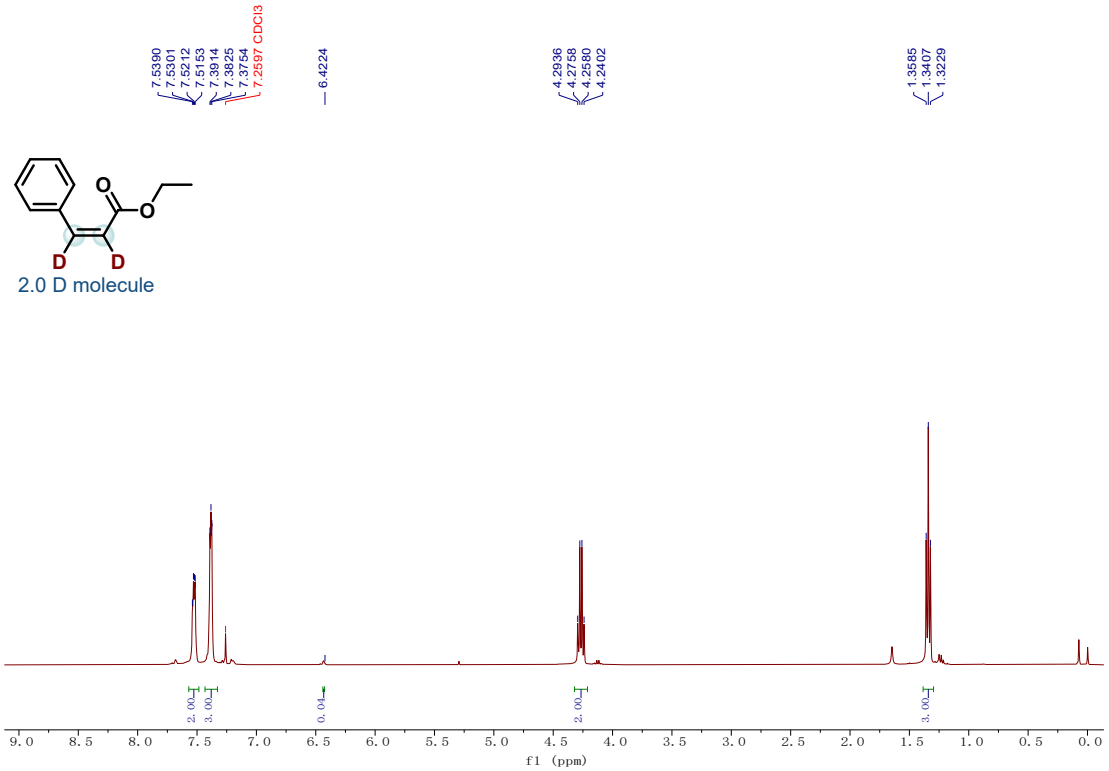
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2u



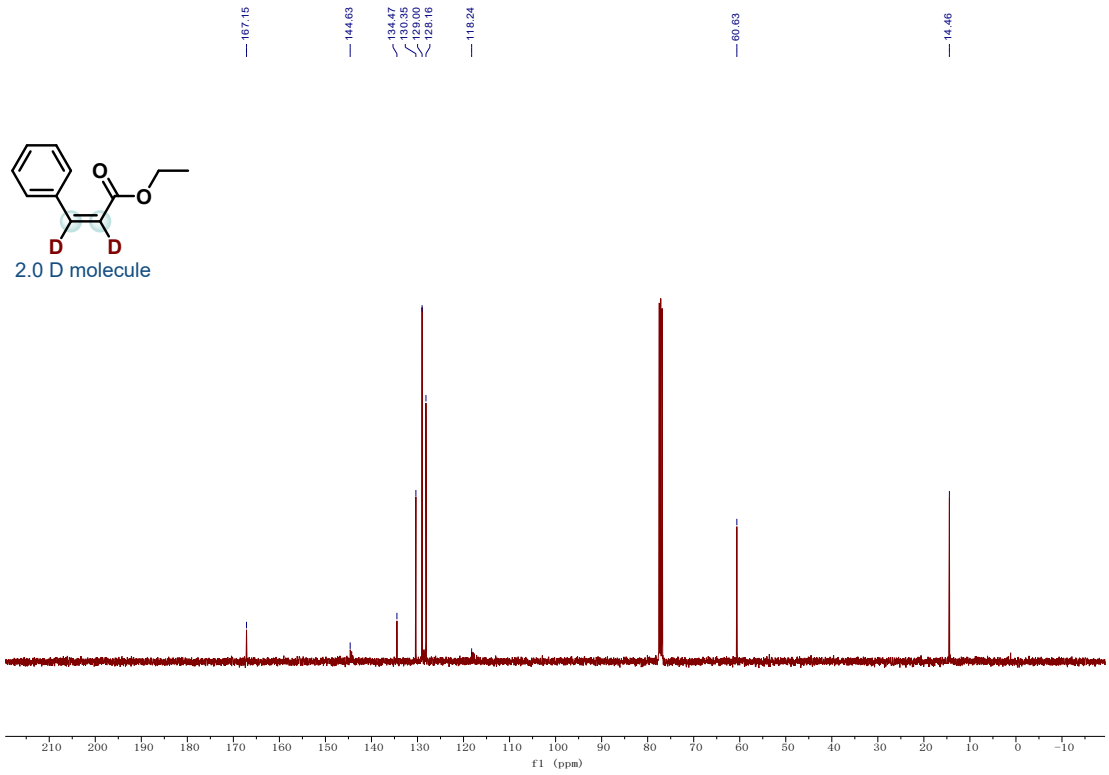
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2u



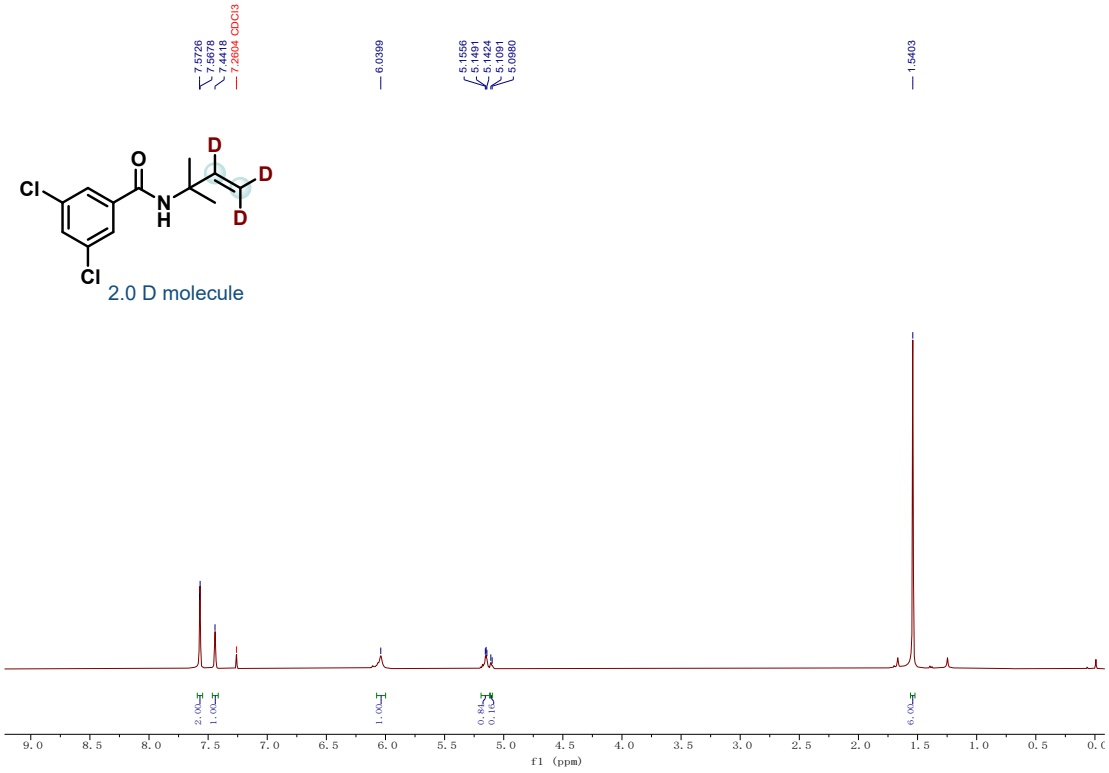
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2v



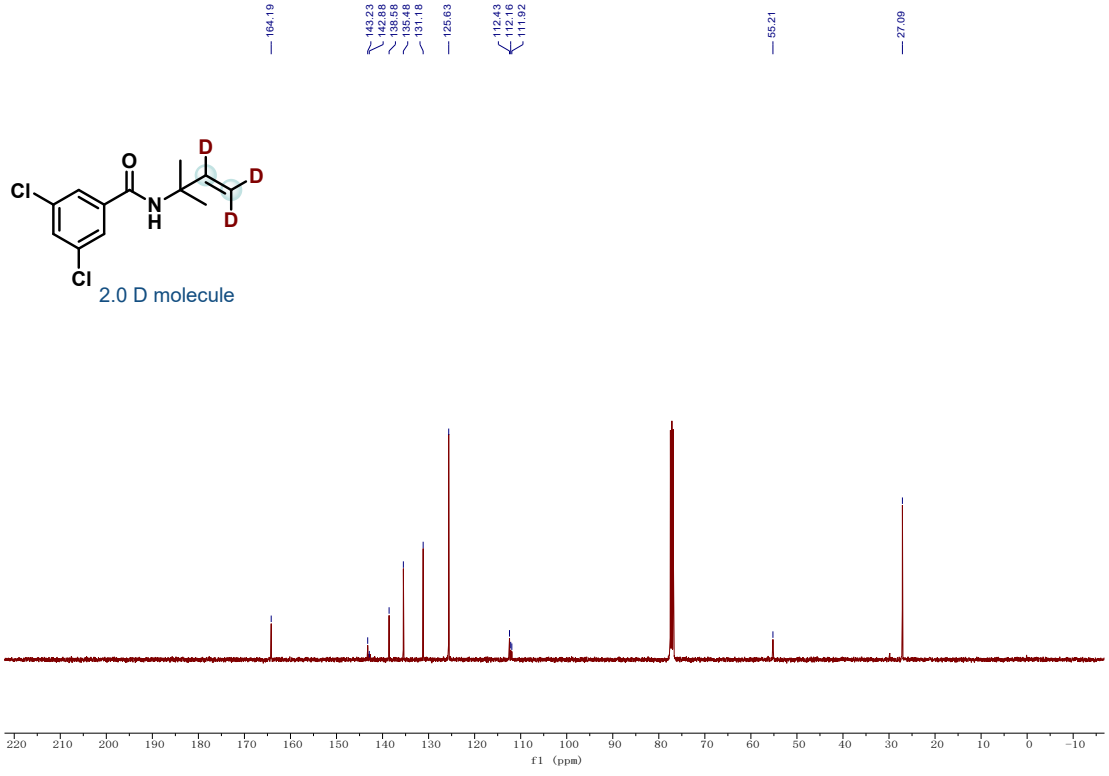
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2v



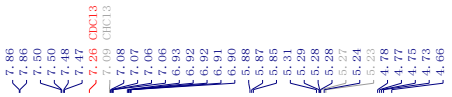
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2w

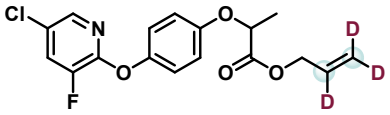


^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2w

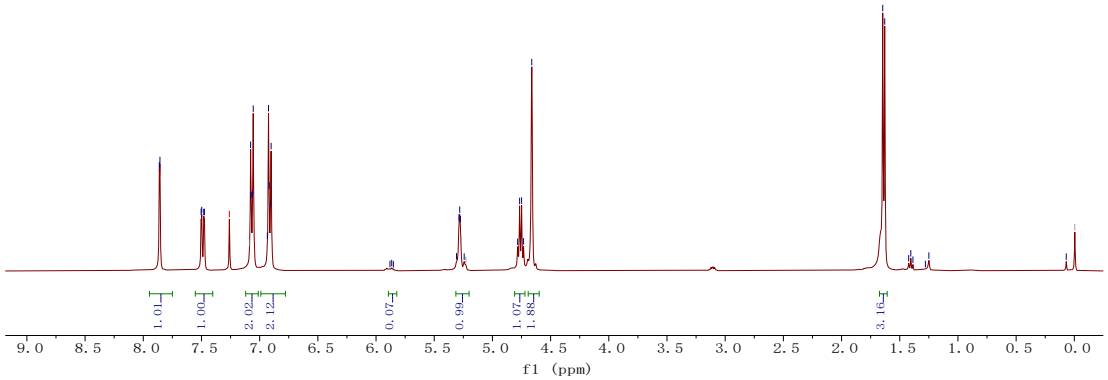


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2x

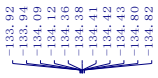


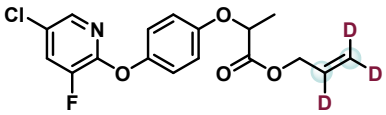


2.0 D molecule

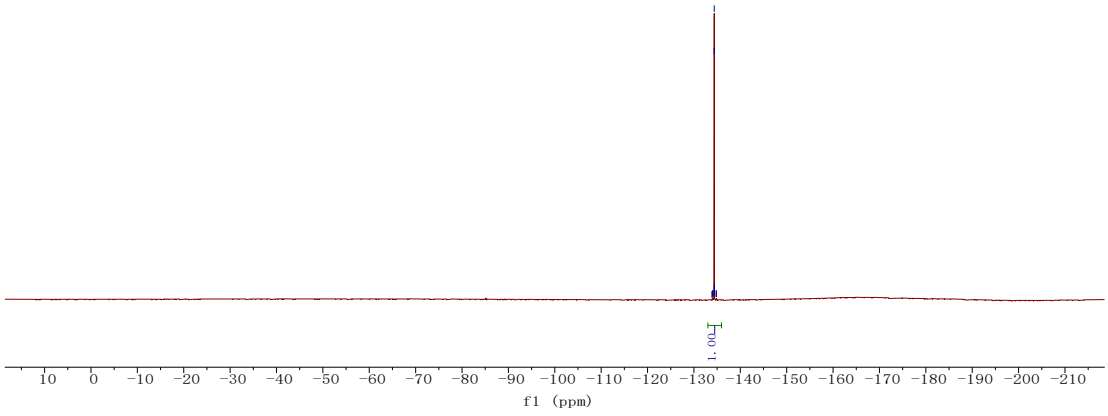


^{19}F NMR (376 MHz, $CDCl_3$) spectrum of 2x

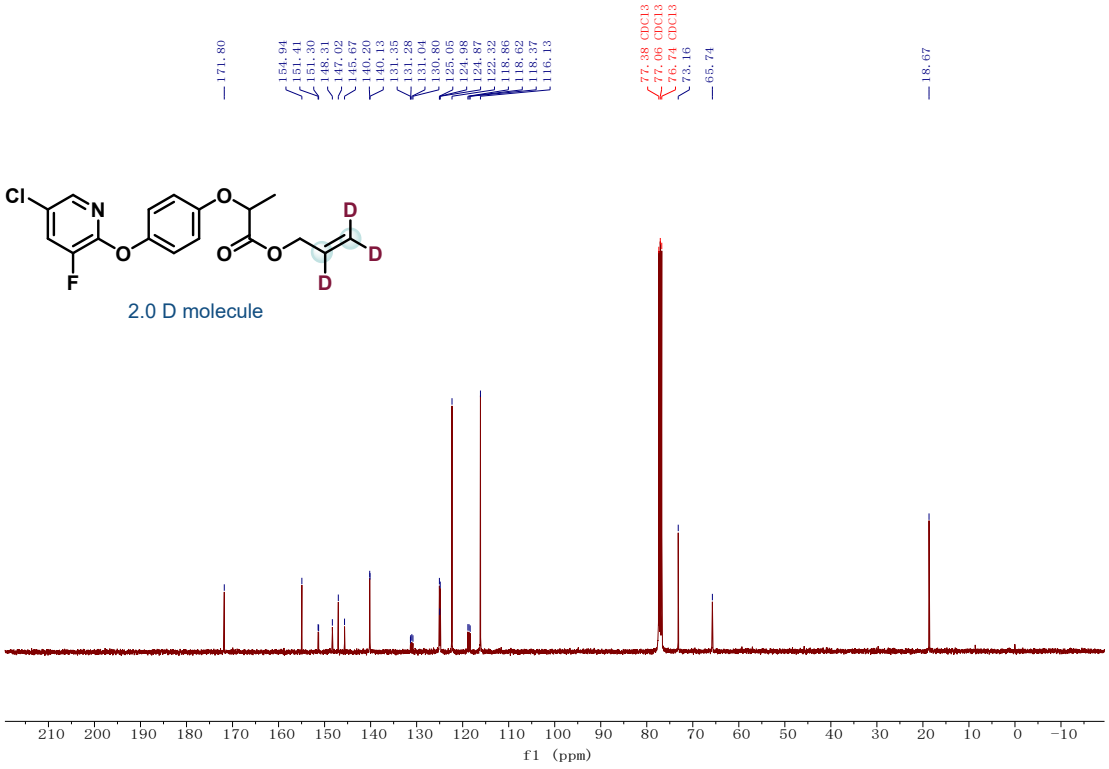




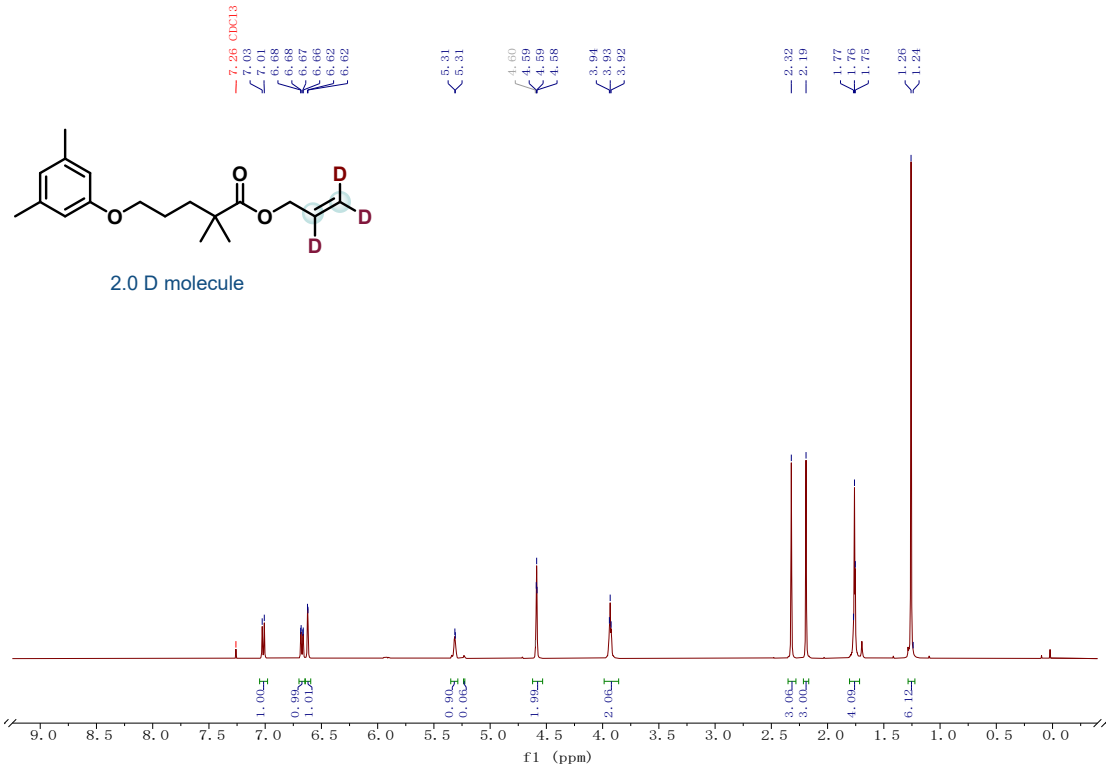
2.0 D molecule



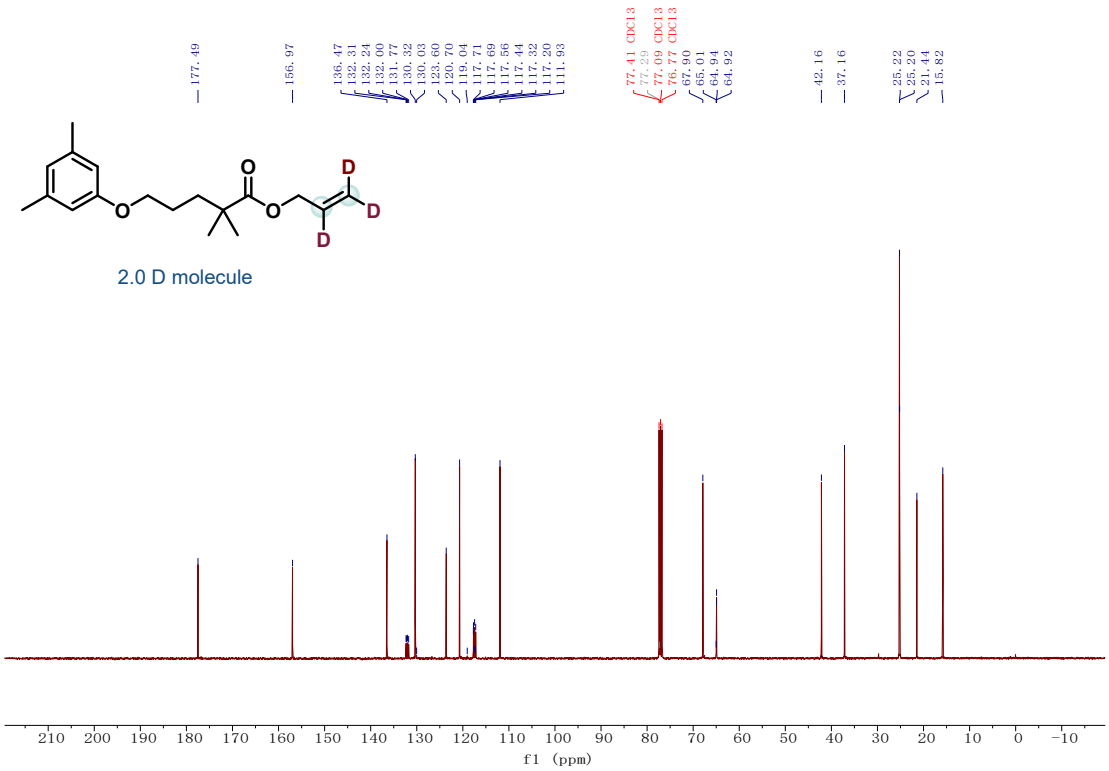
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2x



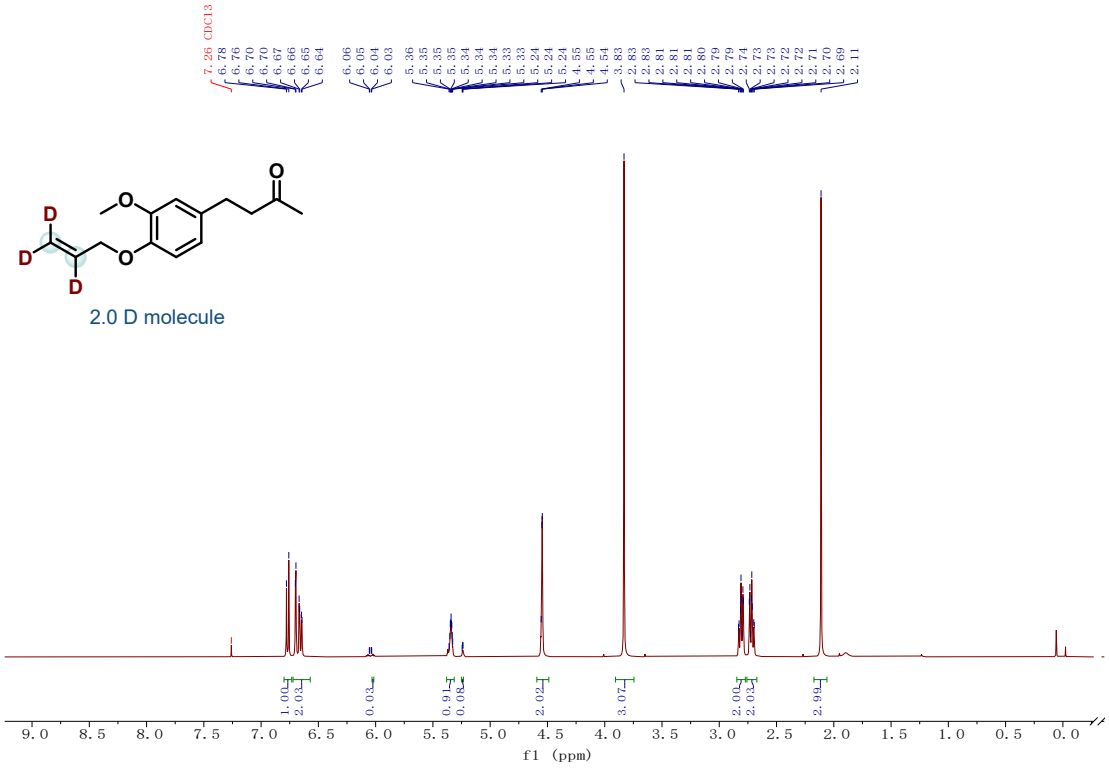
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2y



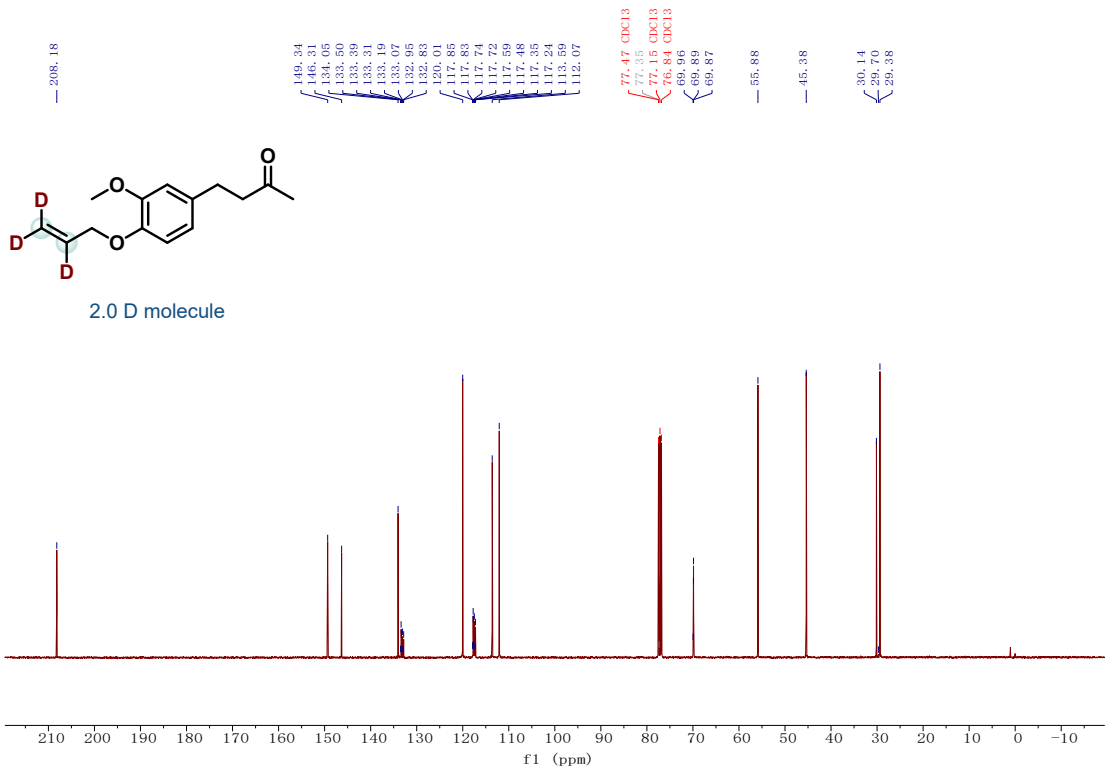
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2y



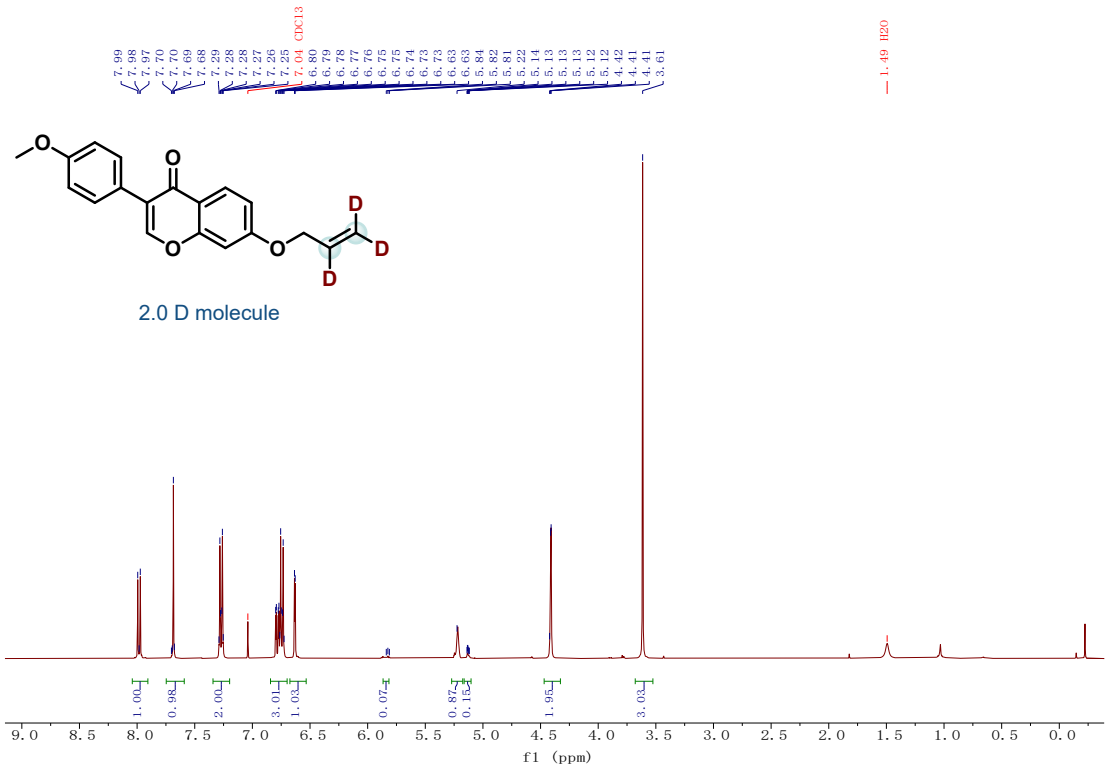
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2z



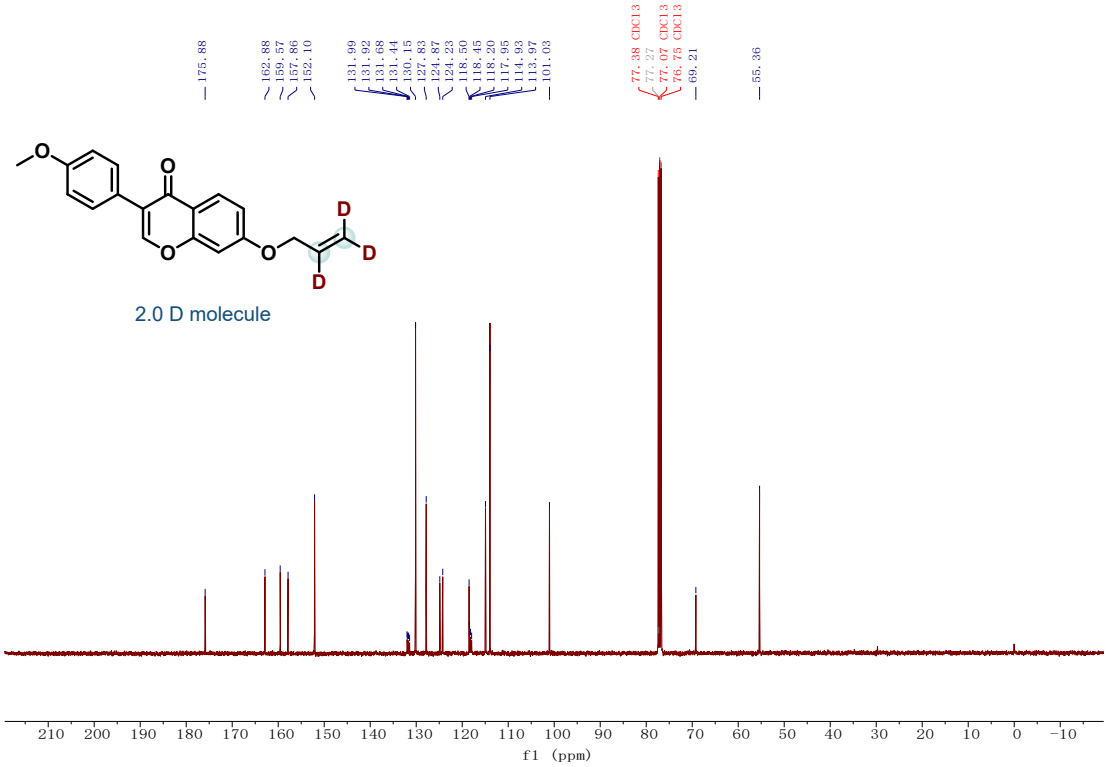
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2z



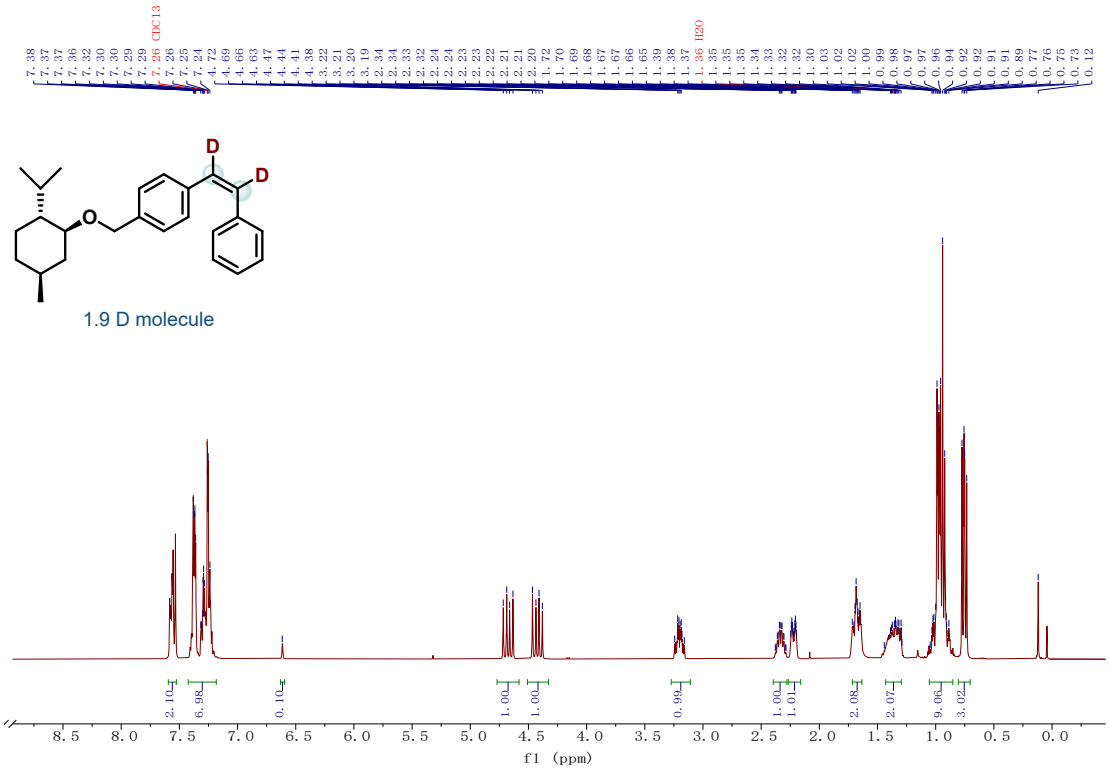
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2aa



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2aa

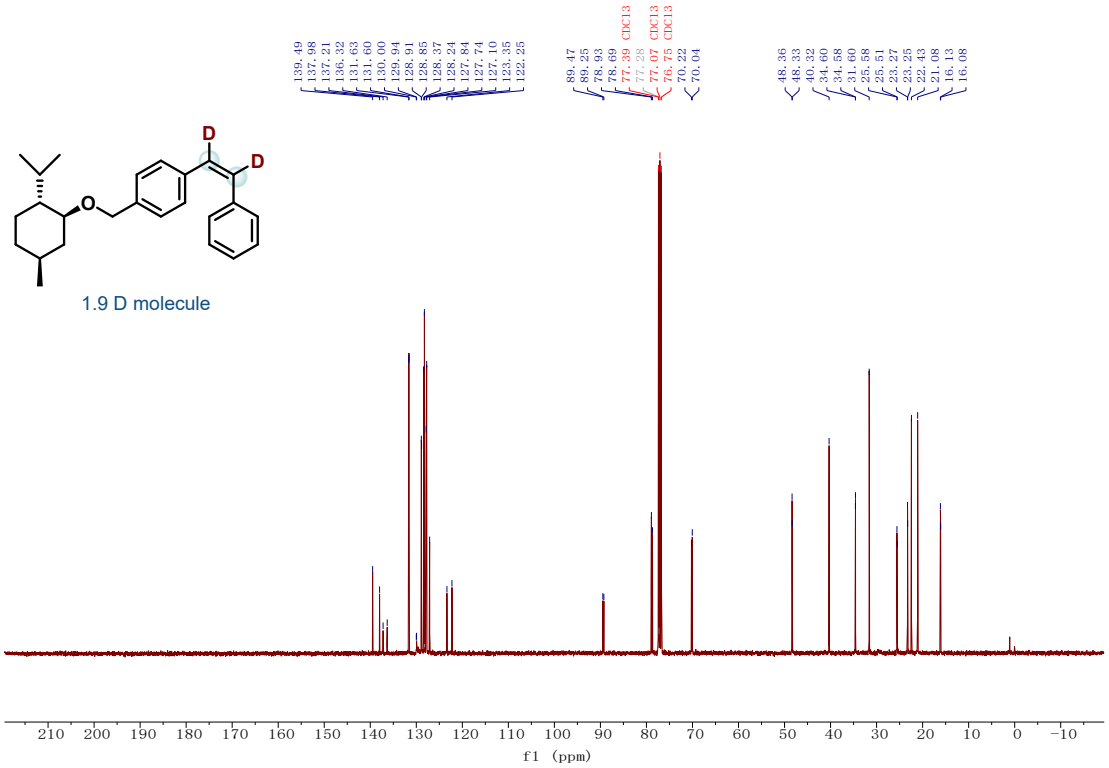


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2ab

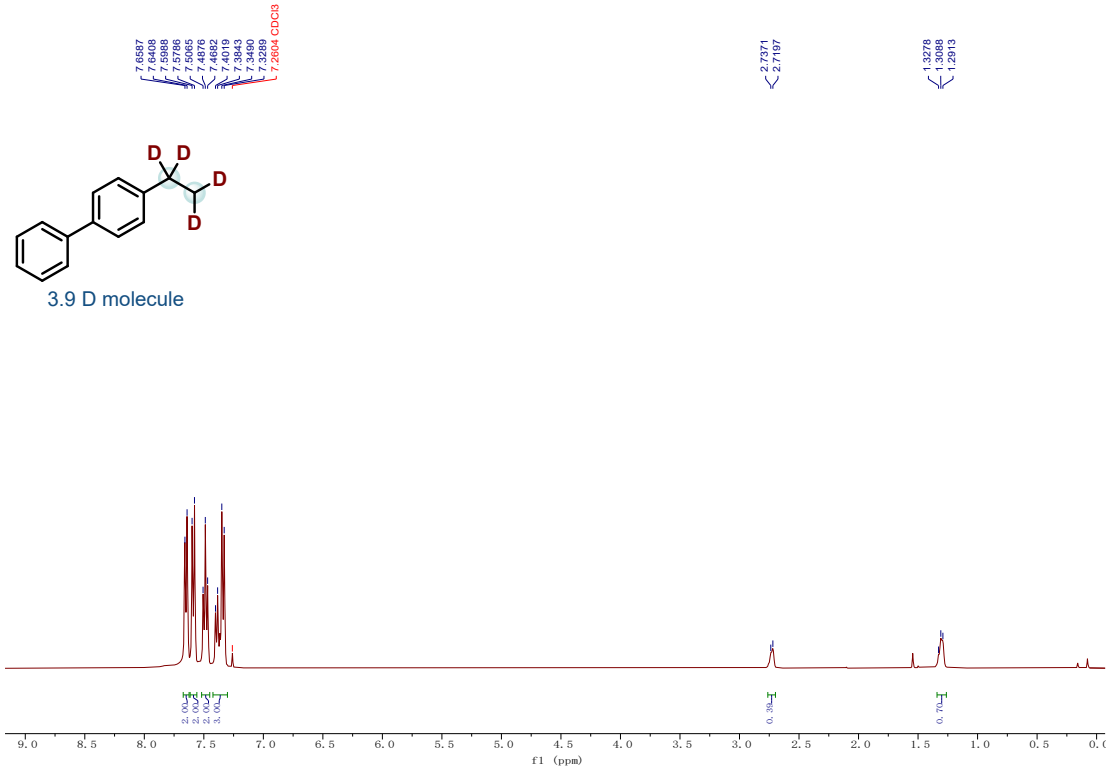


1.9 D molecule

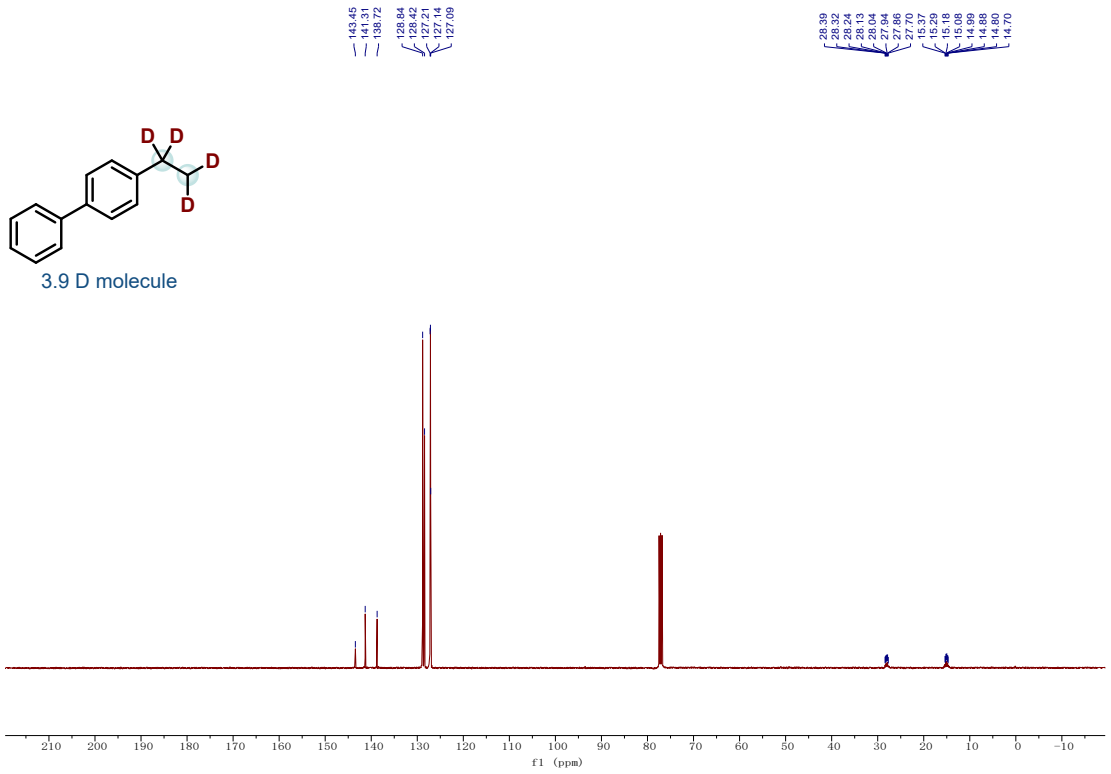
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 2ab



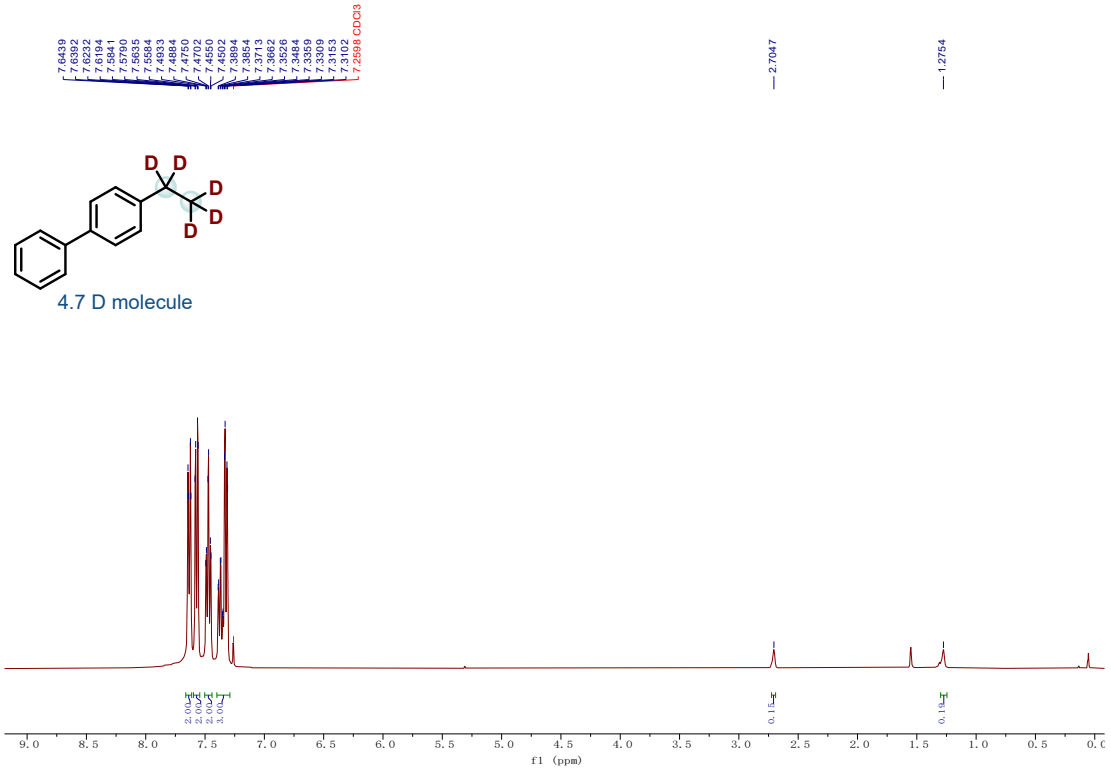
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3a



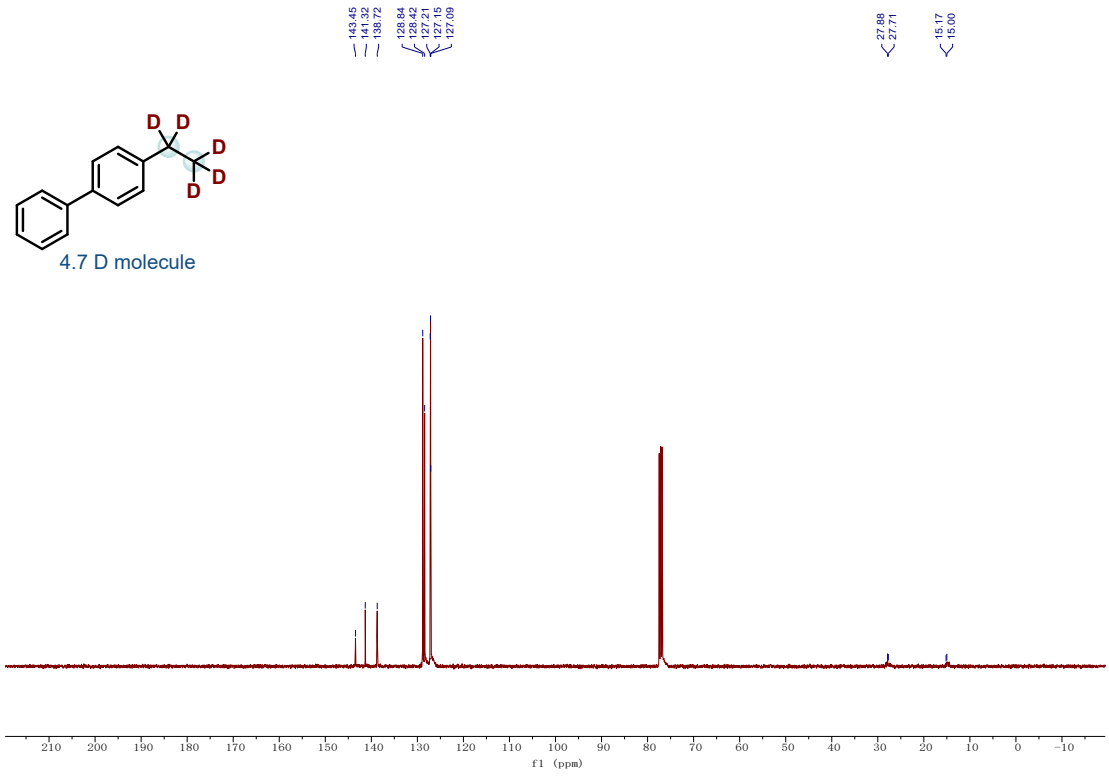
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3a



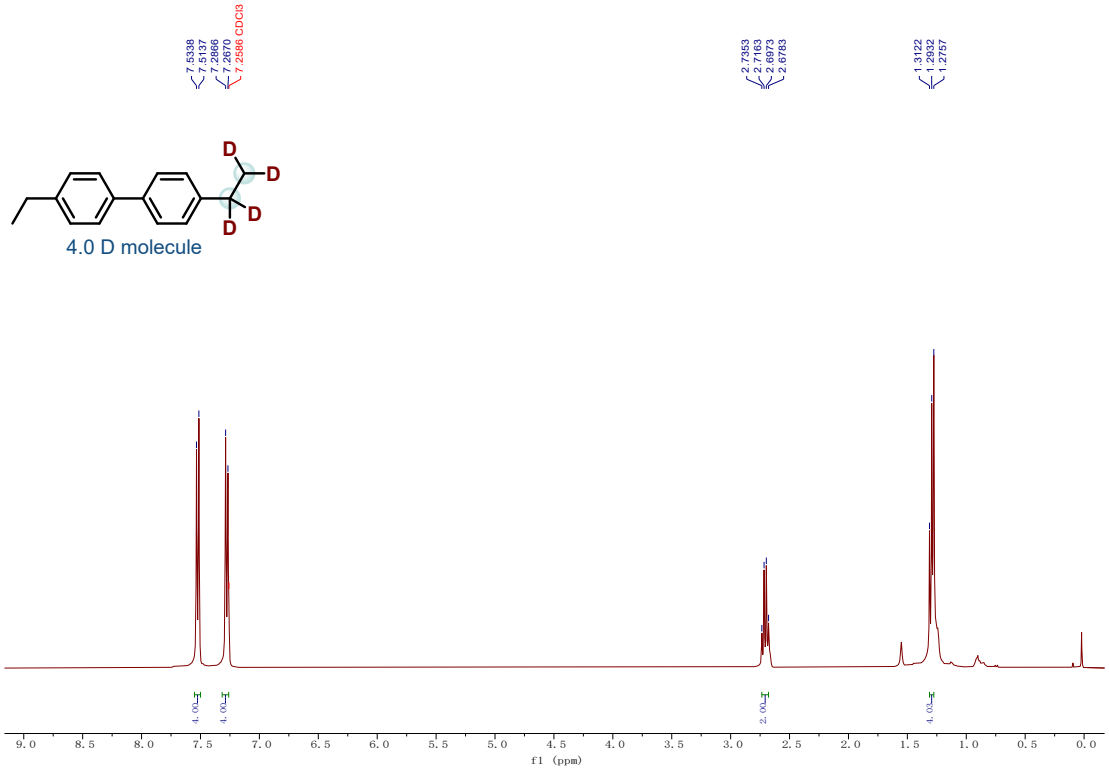
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3b



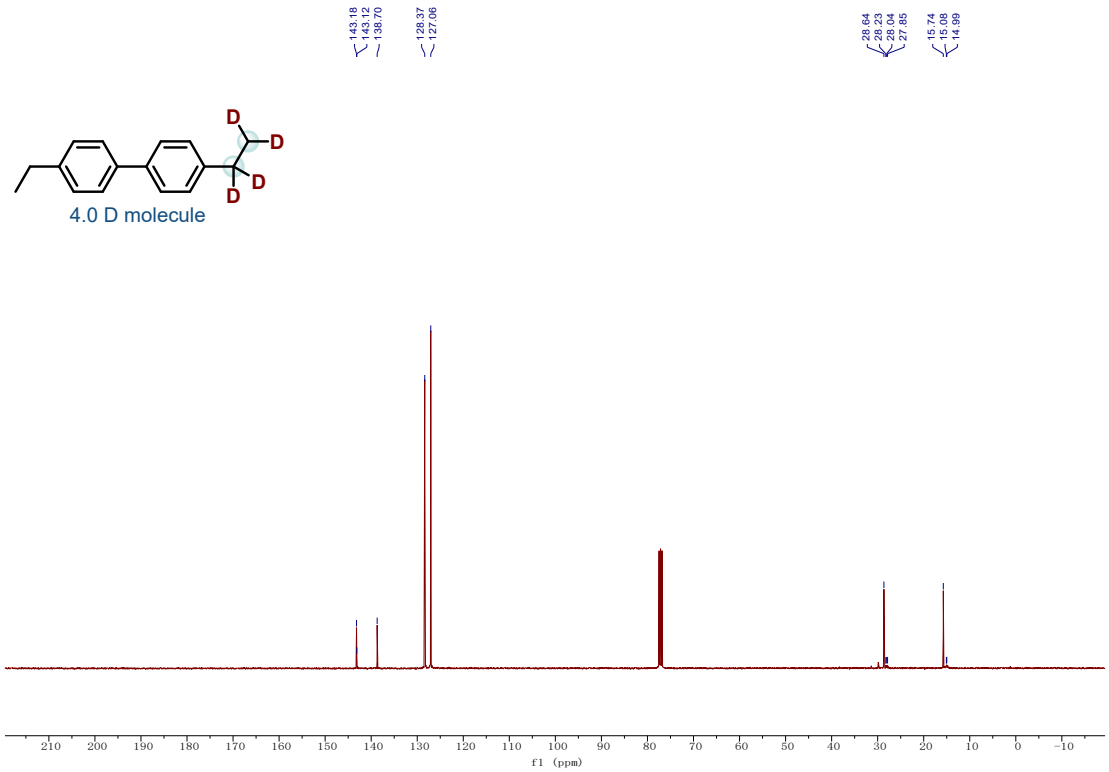
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3b



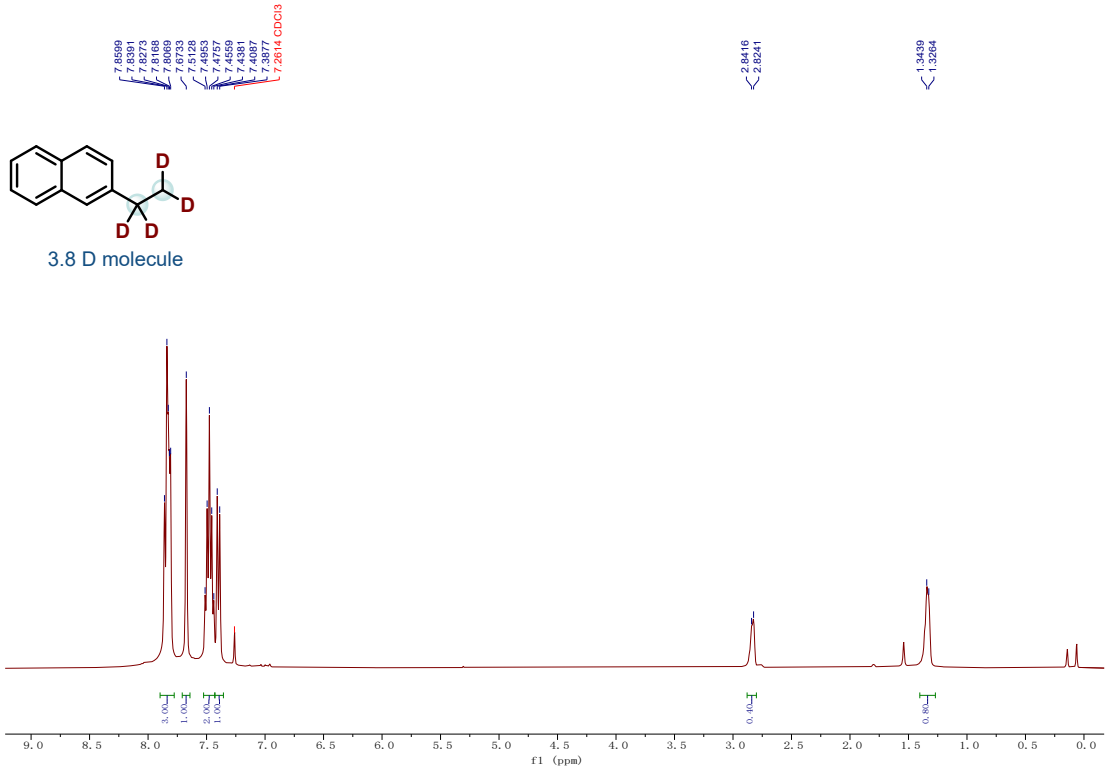
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3c



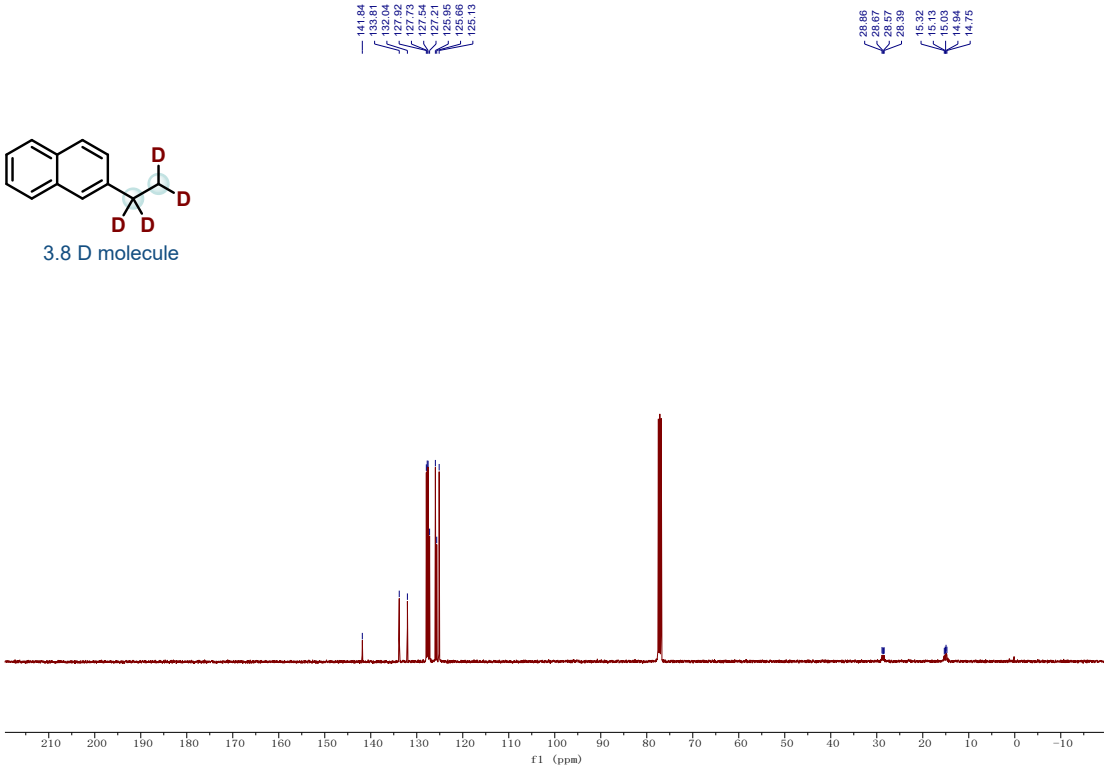
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3c



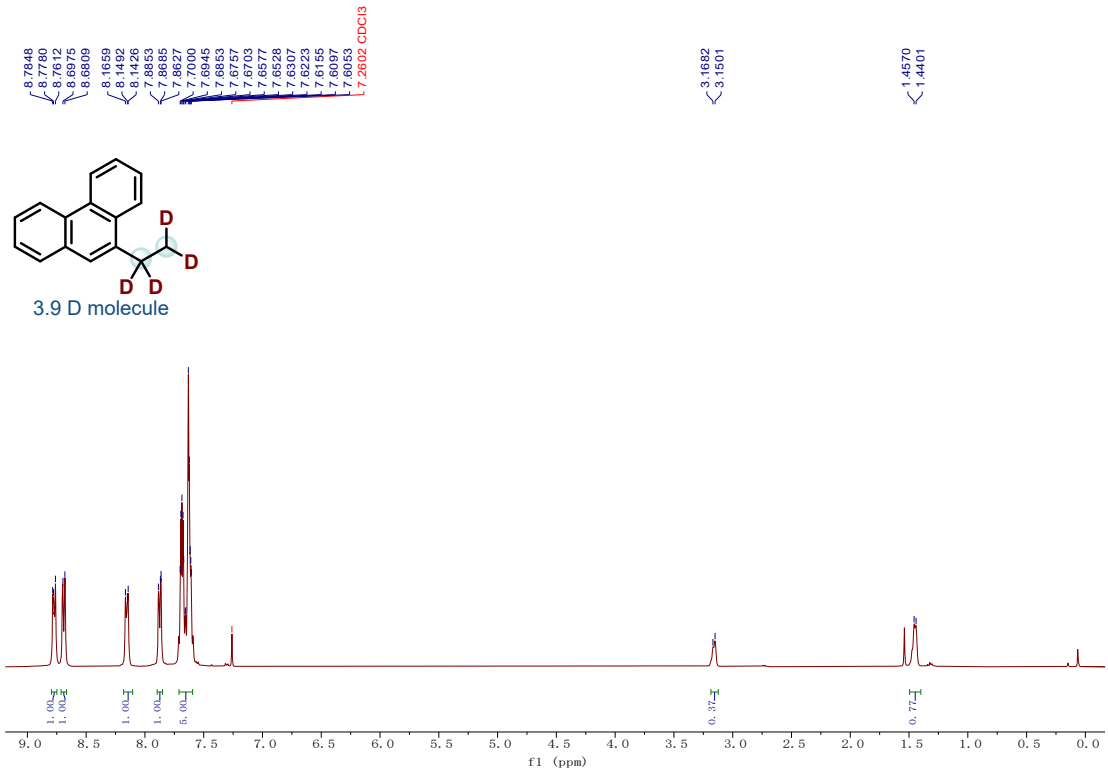
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3d



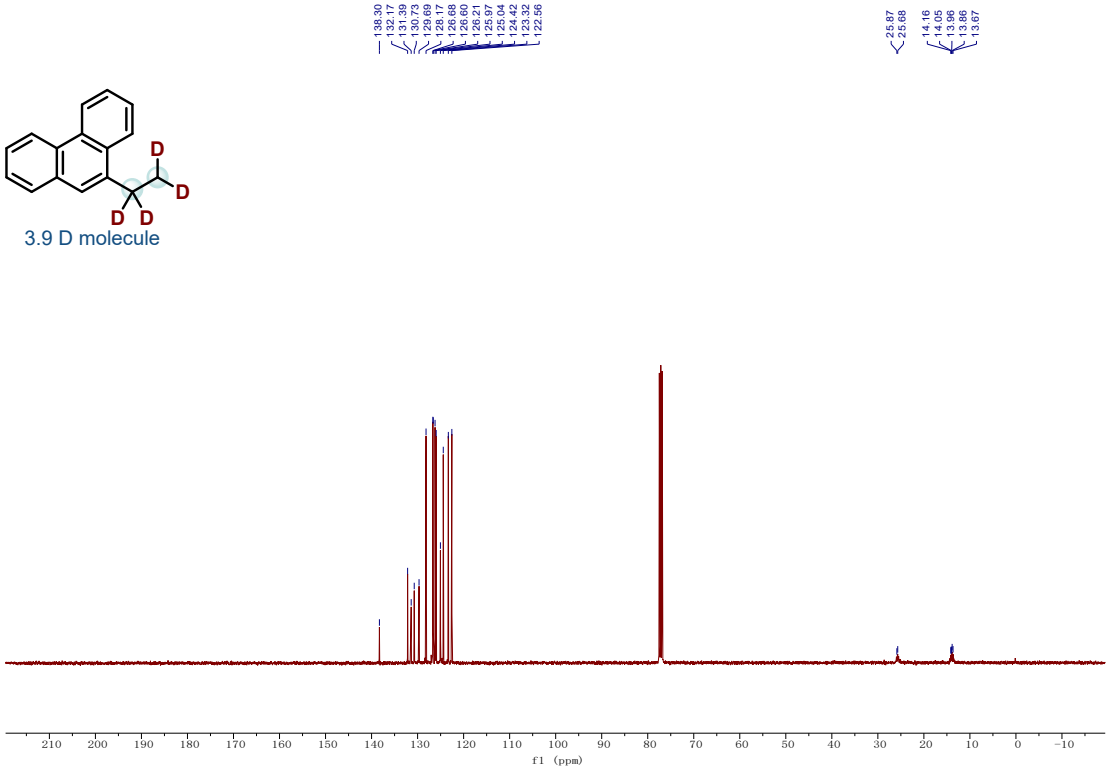
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3d



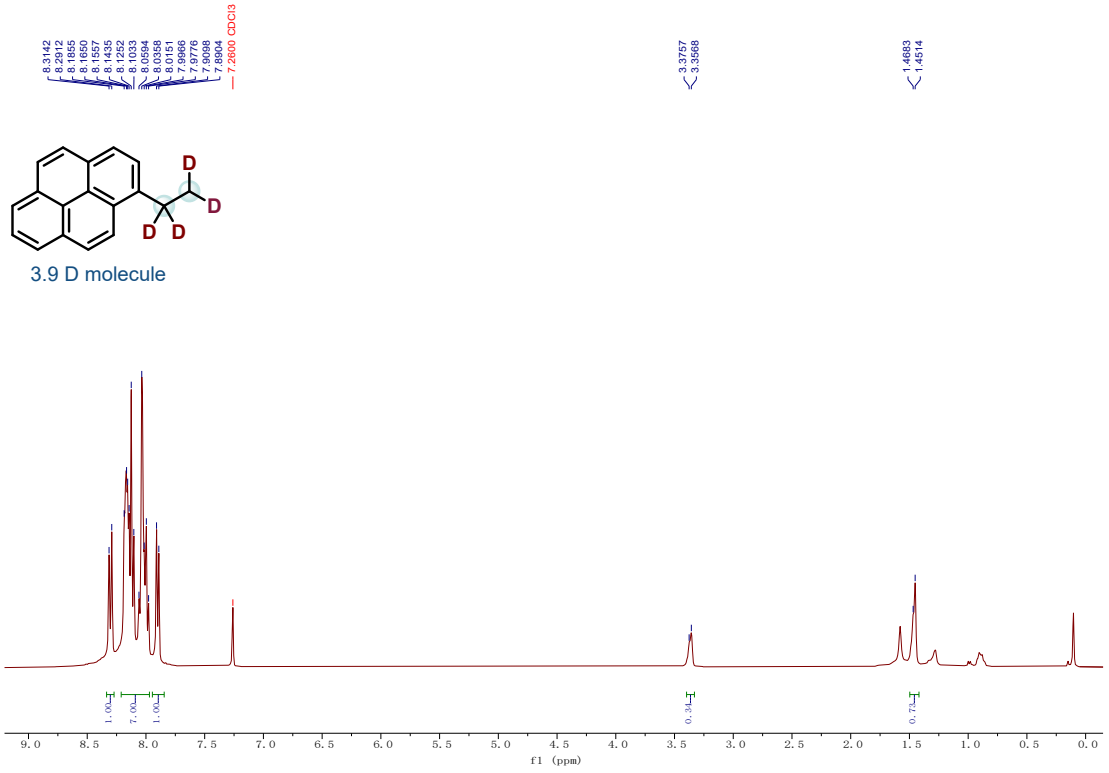
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3e



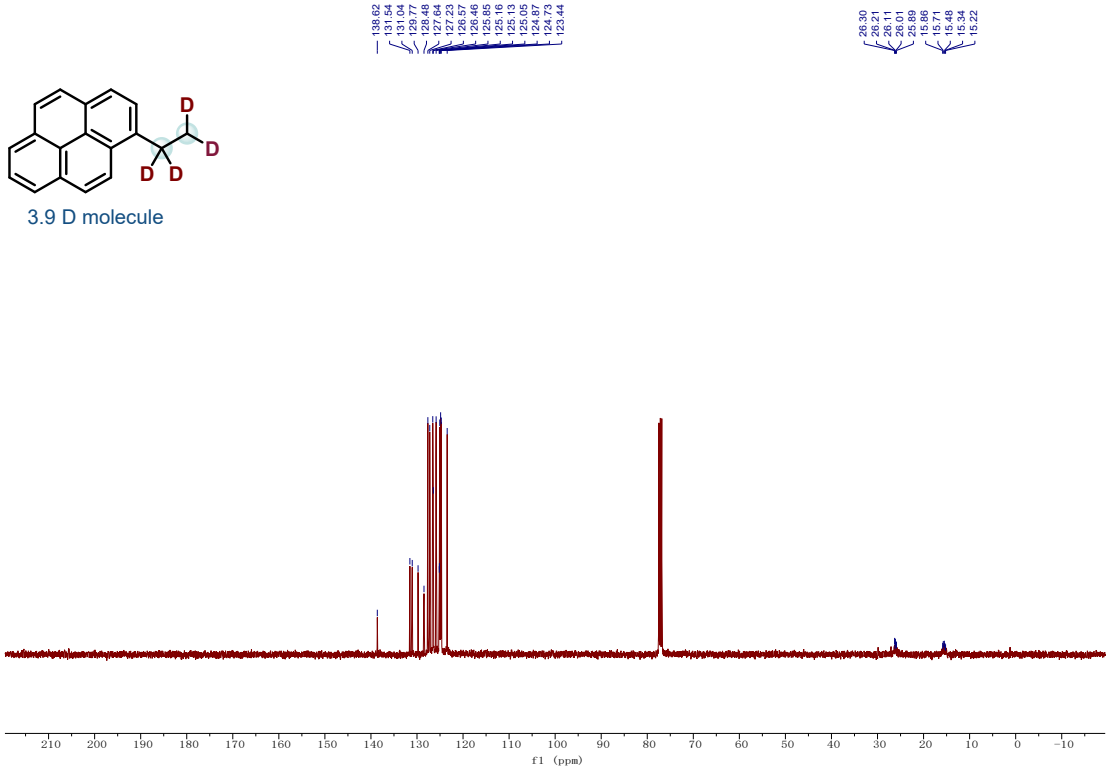
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3e



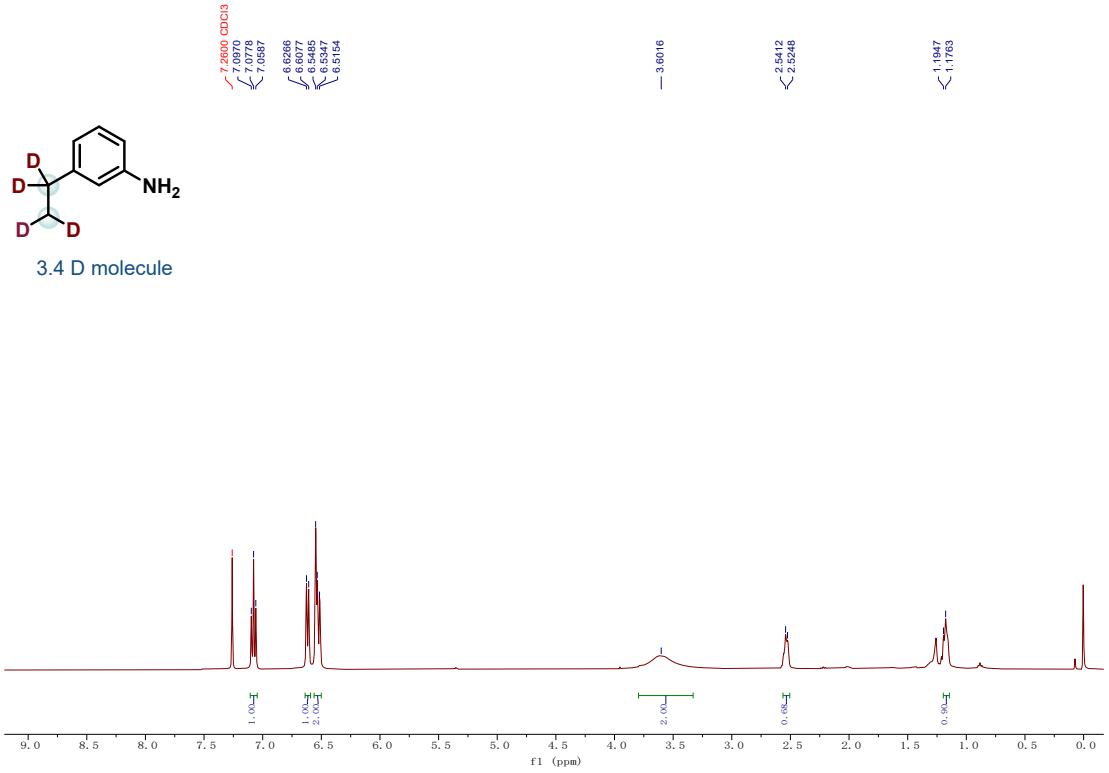
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3f



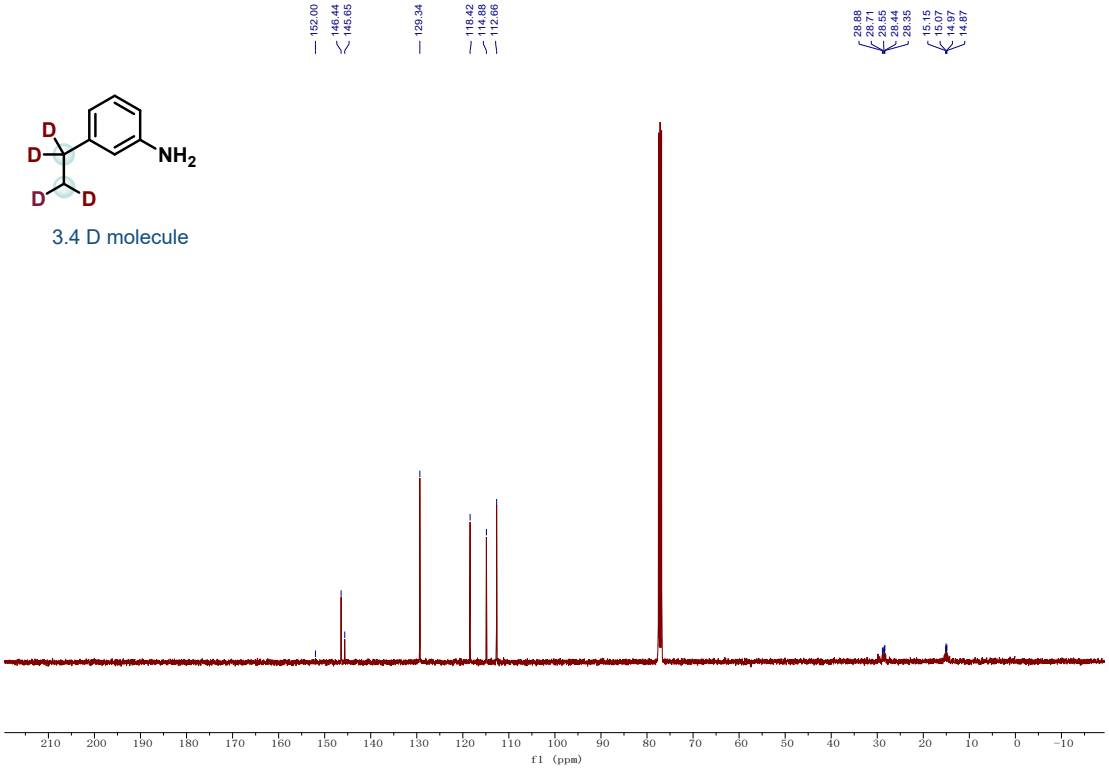
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3f



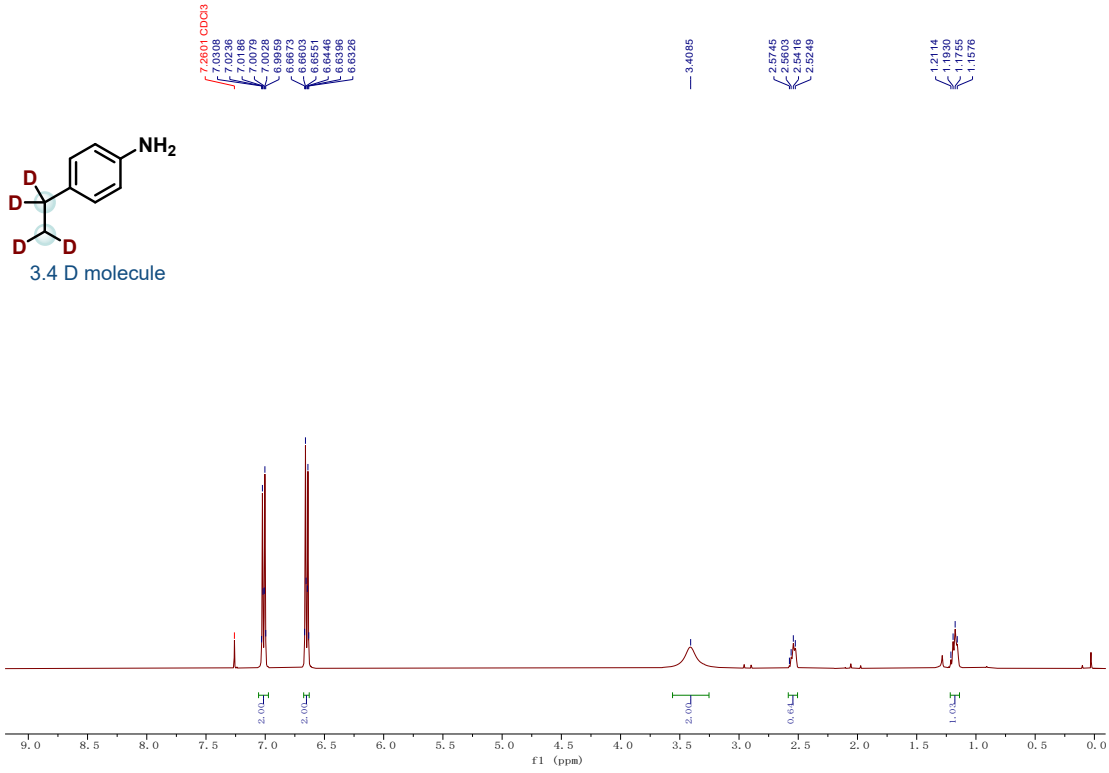
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3g



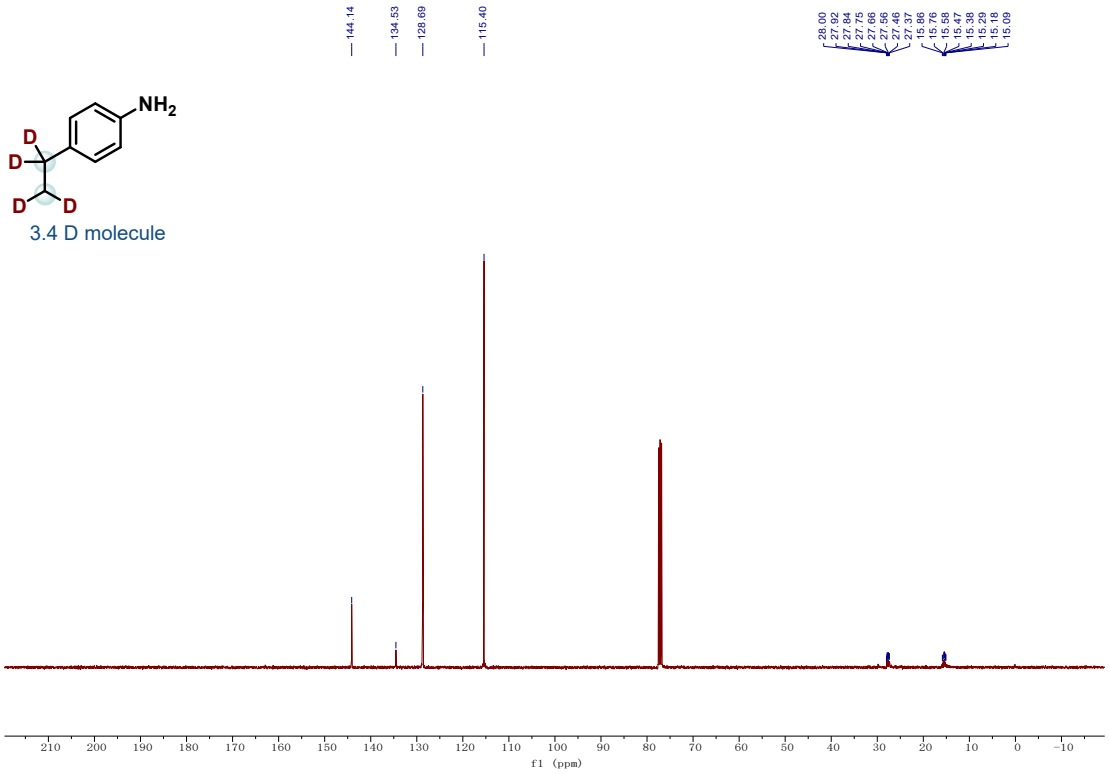
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3g



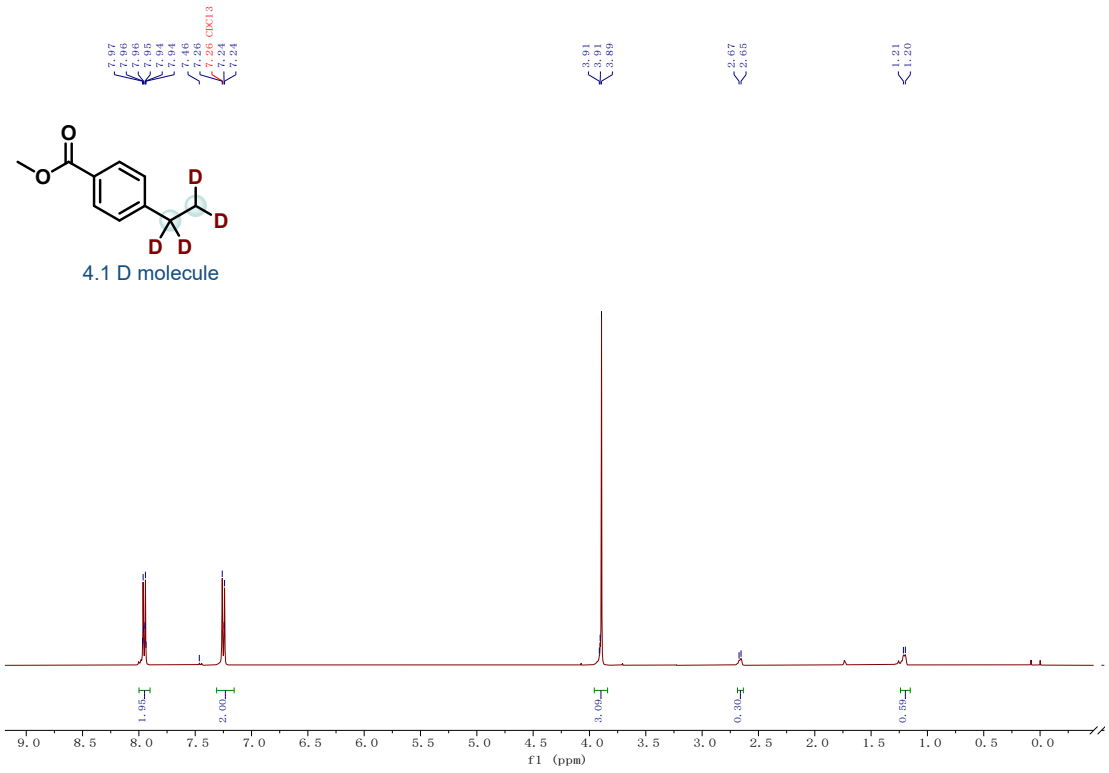
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3h



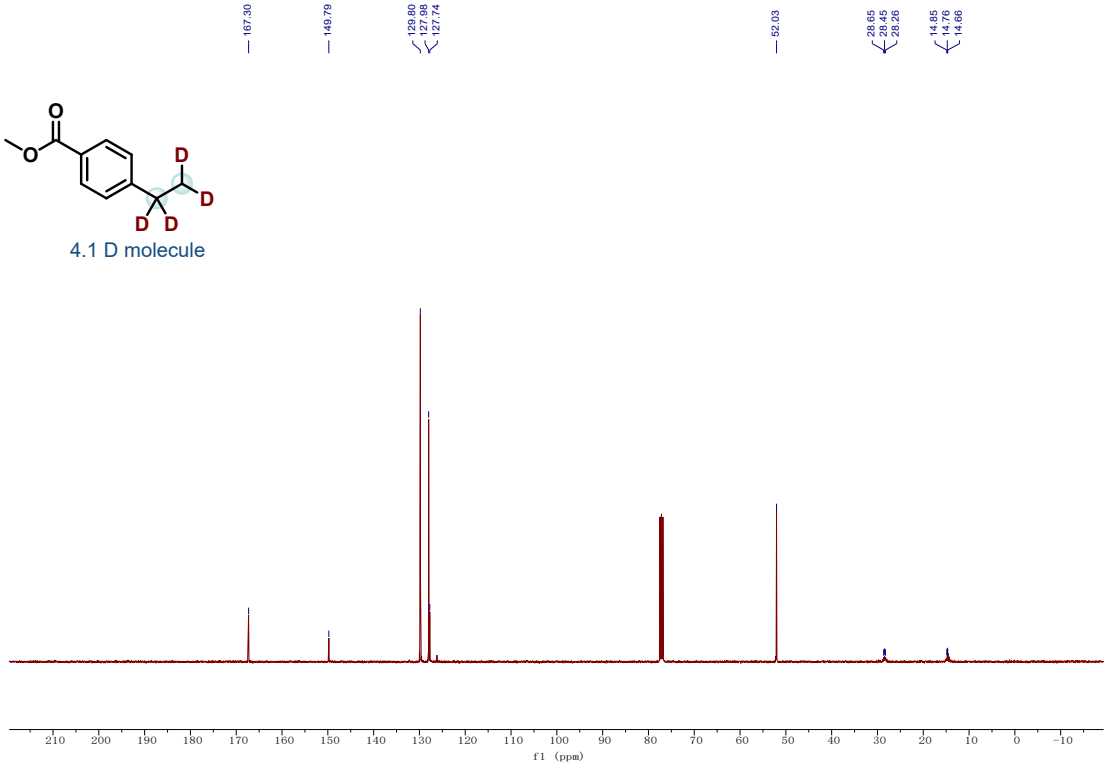
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3h



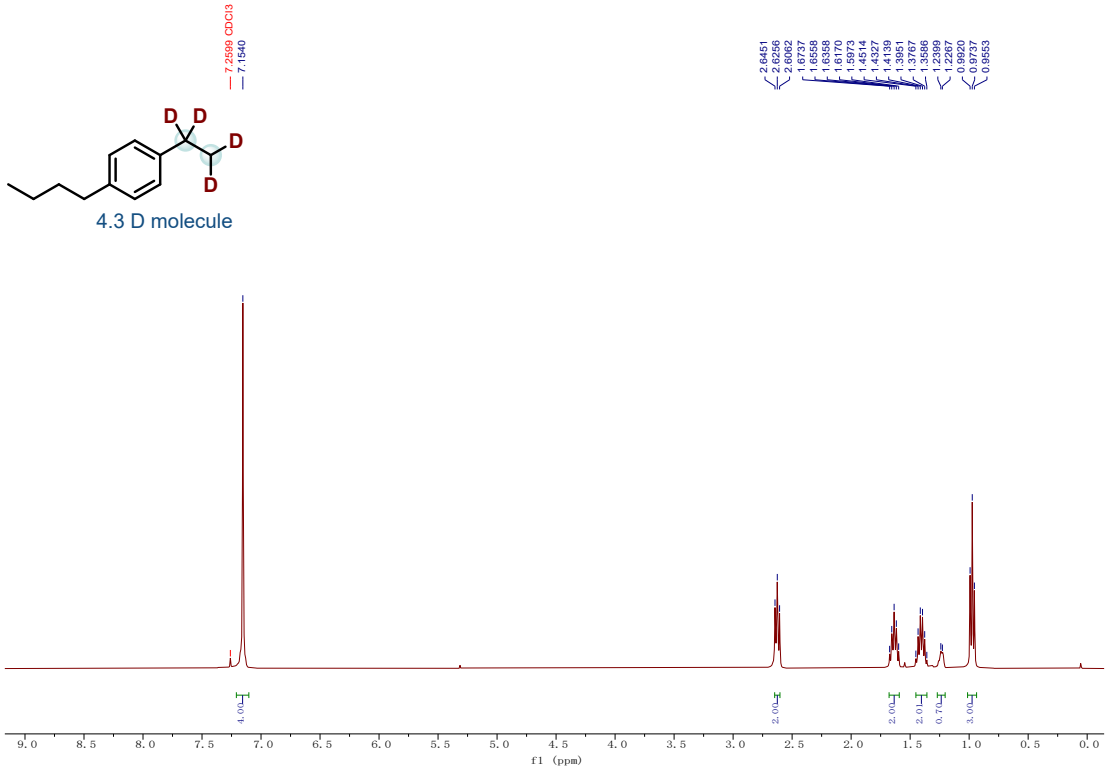
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3i



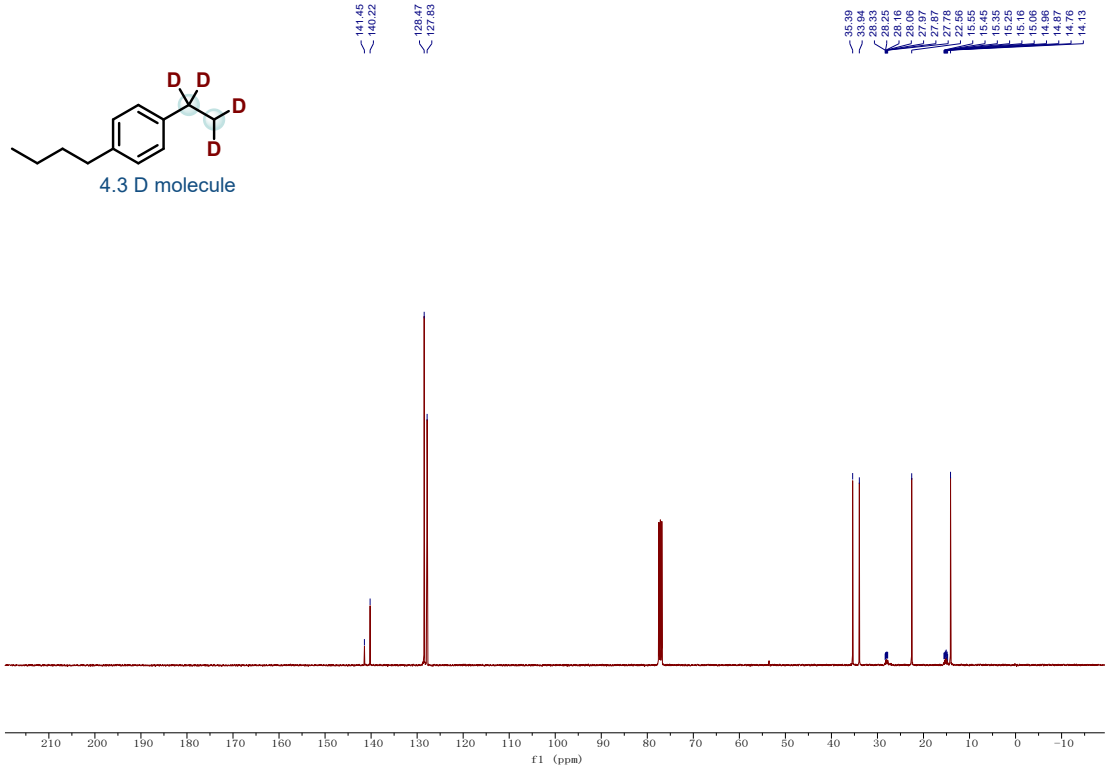
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3i



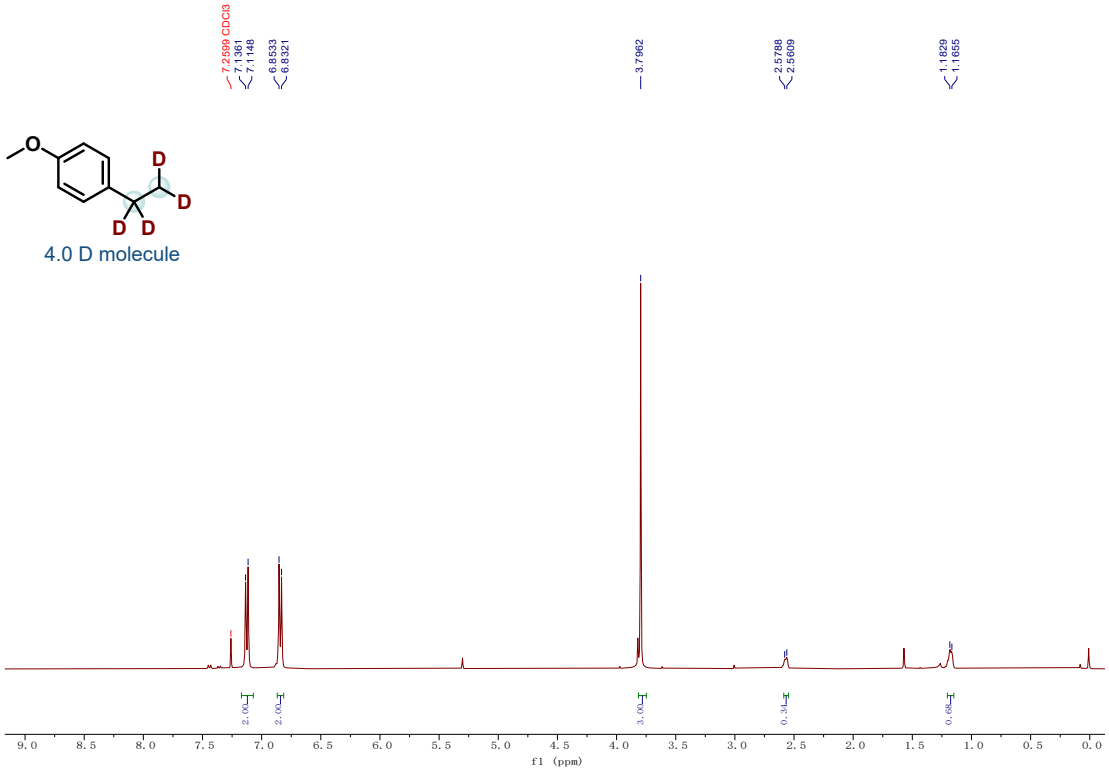
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3j



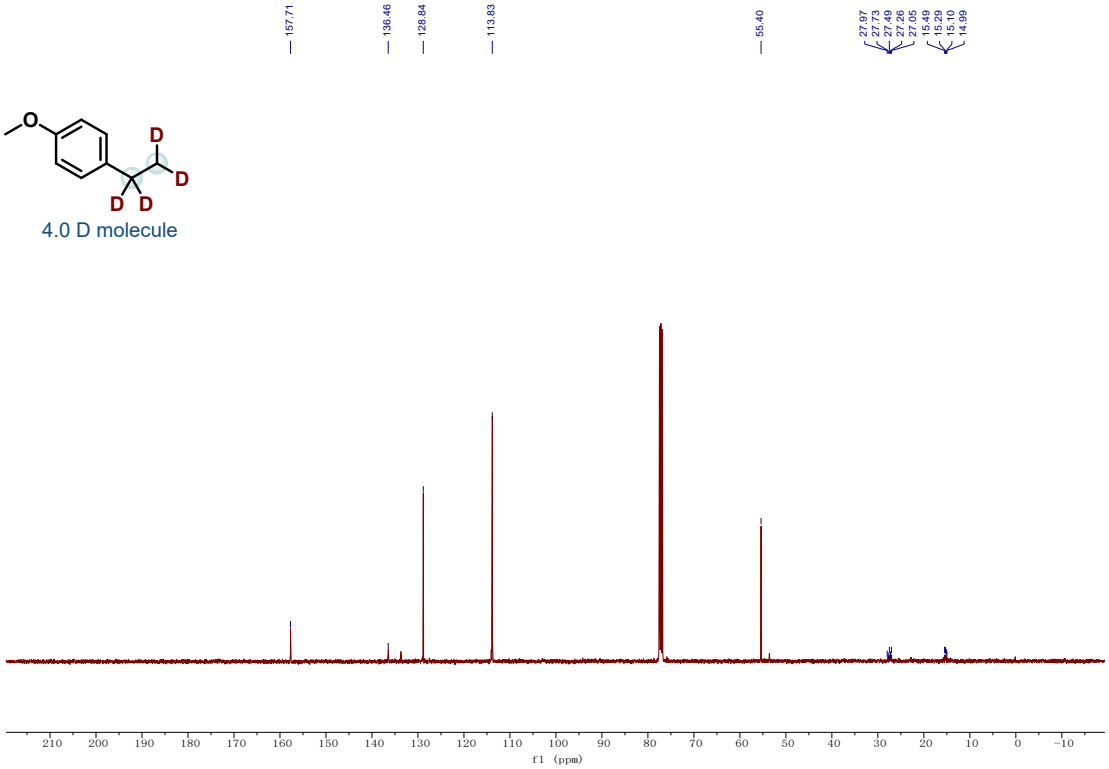
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3j



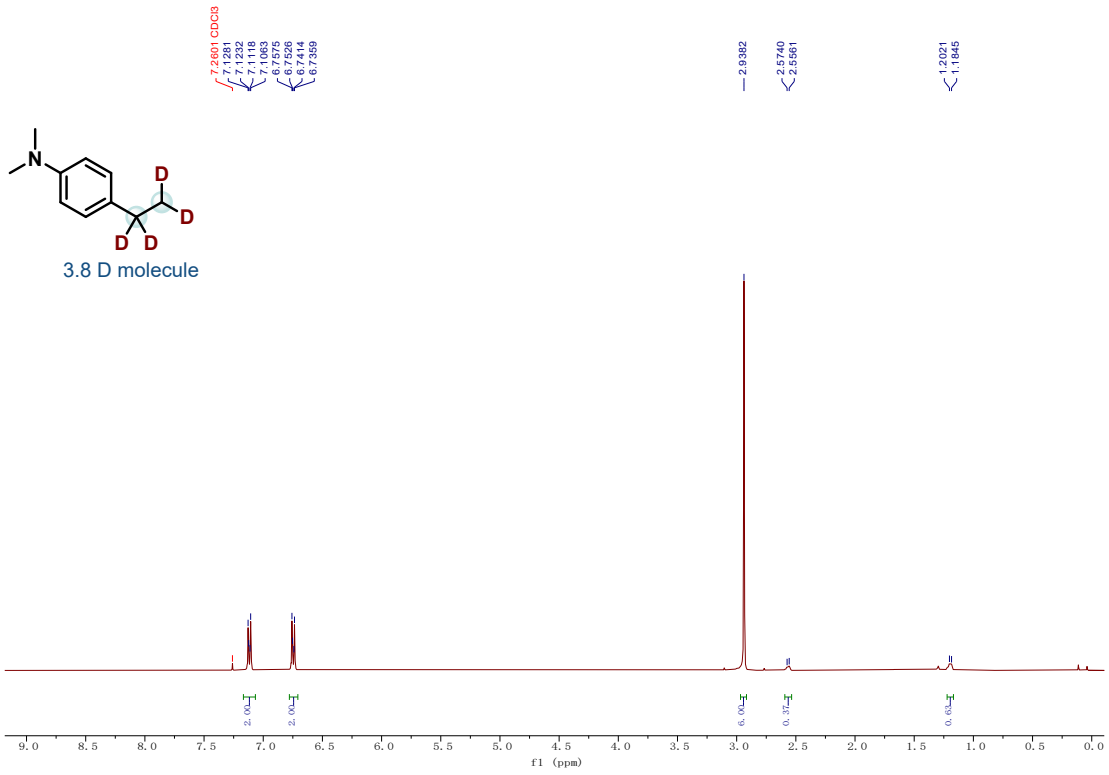
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3k



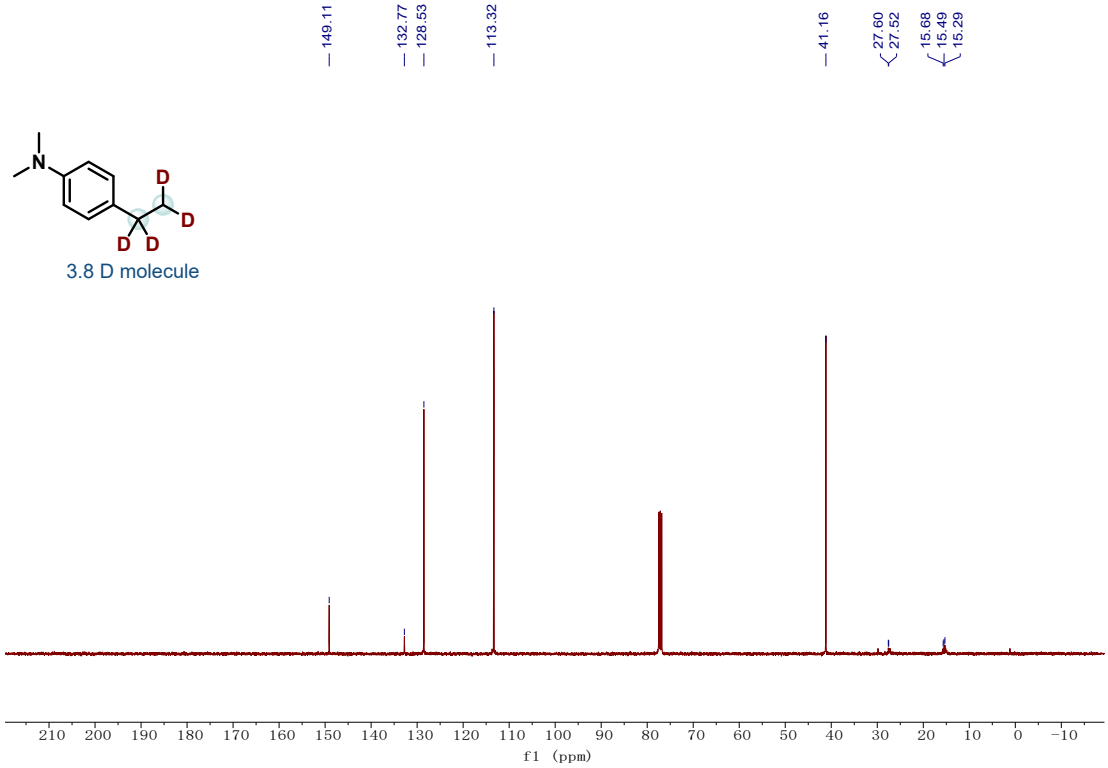
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3k



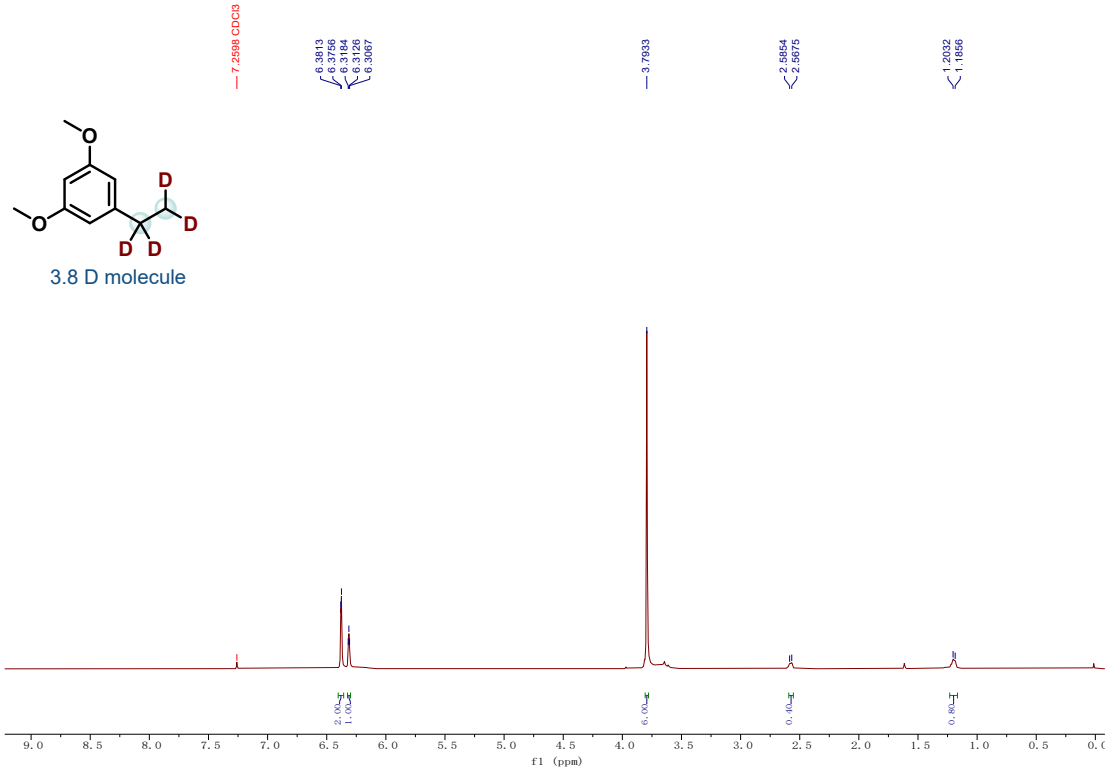
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3l



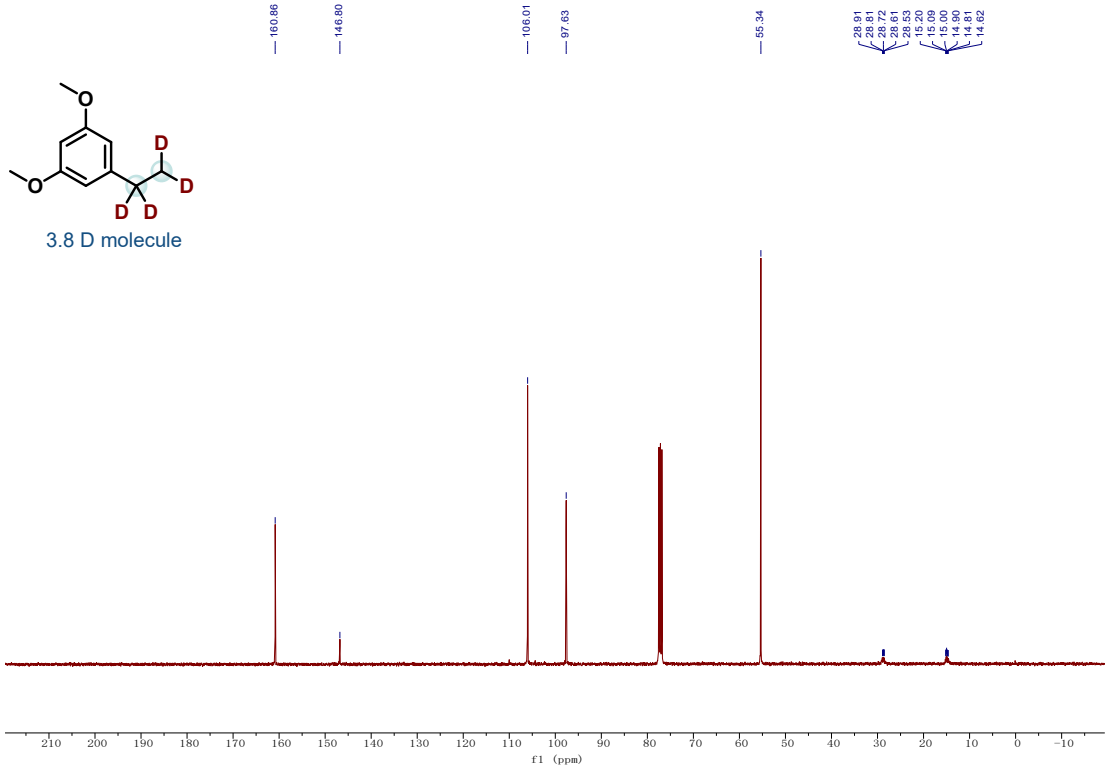
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3l



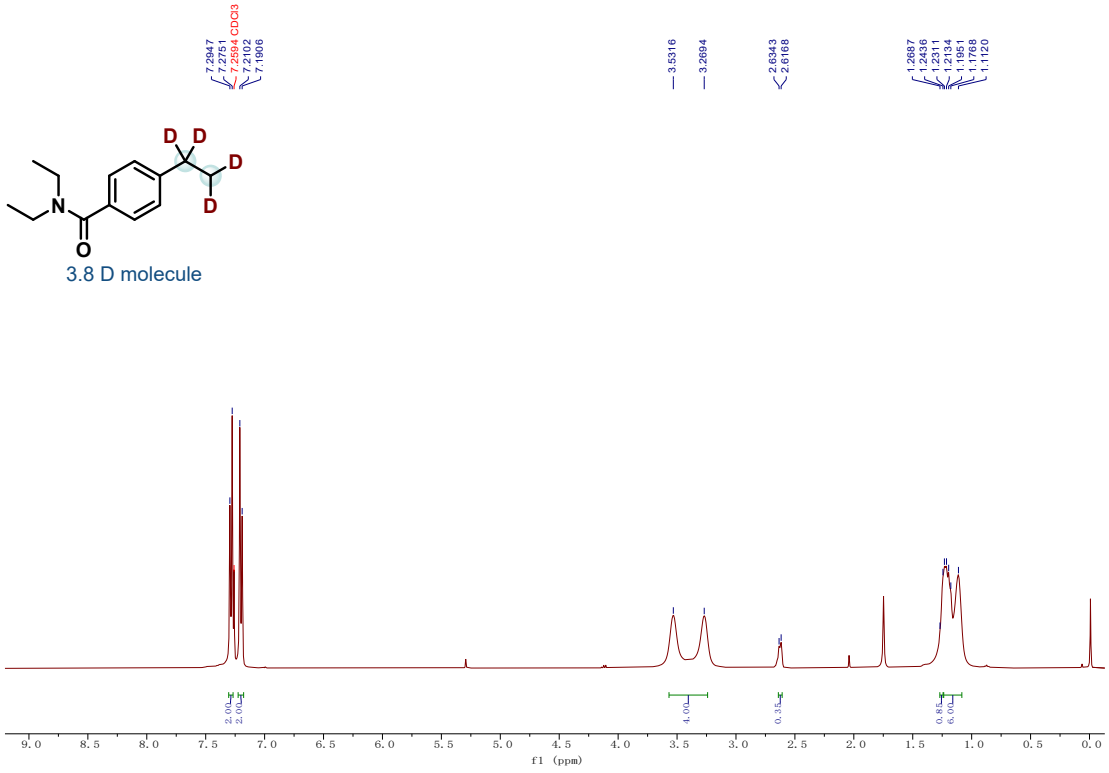
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3m



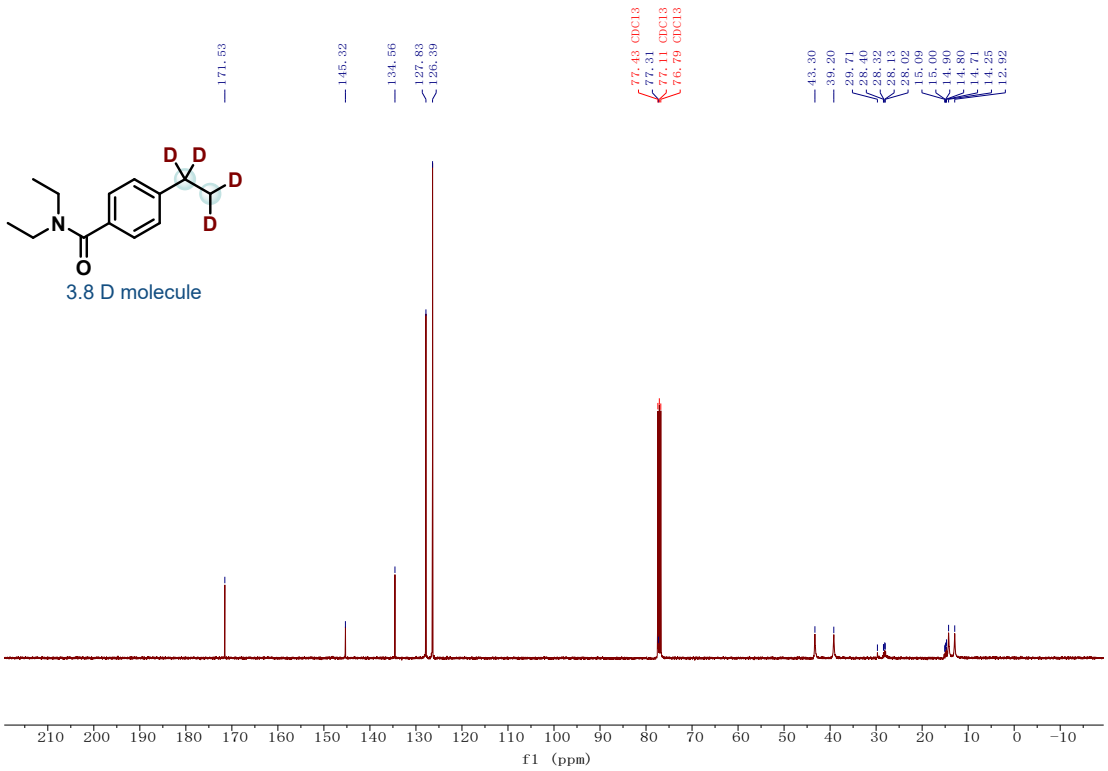
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3m



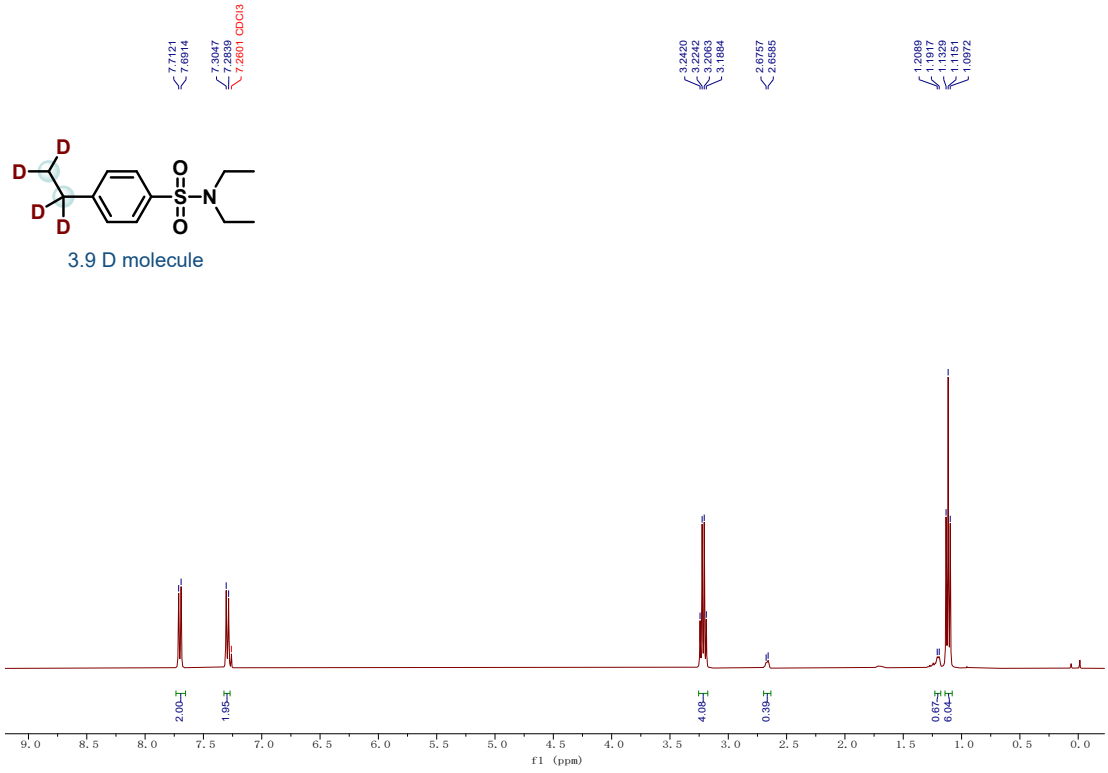
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3n



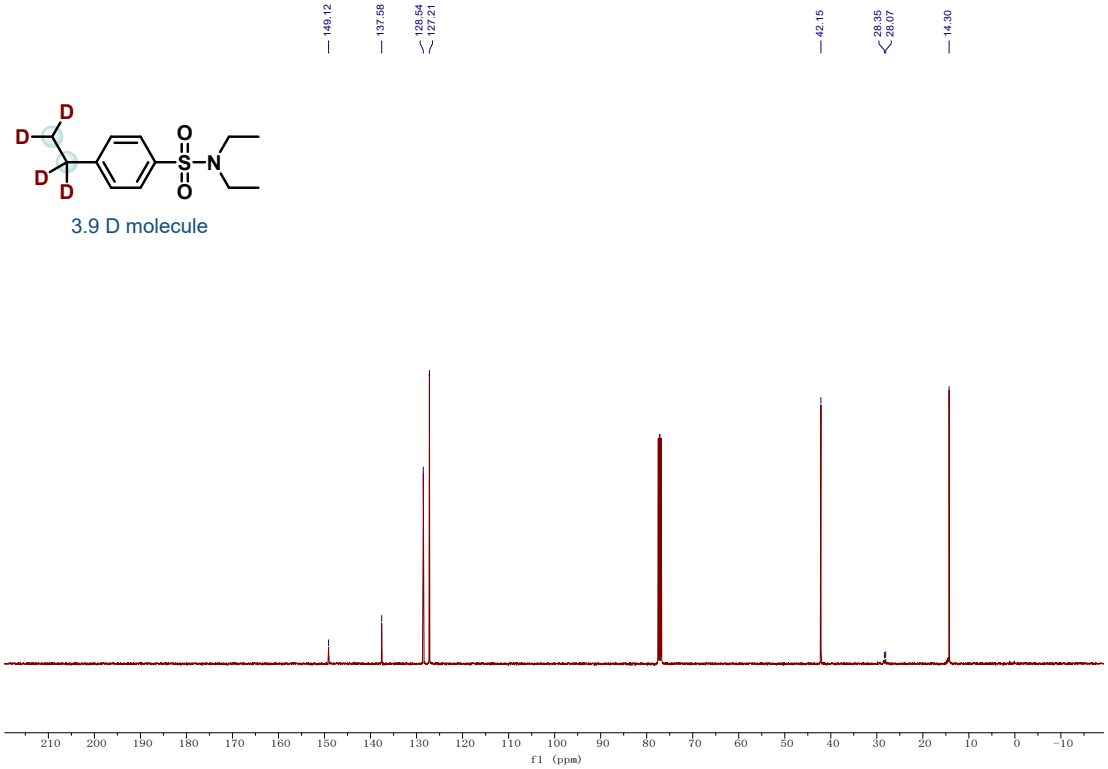
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3n



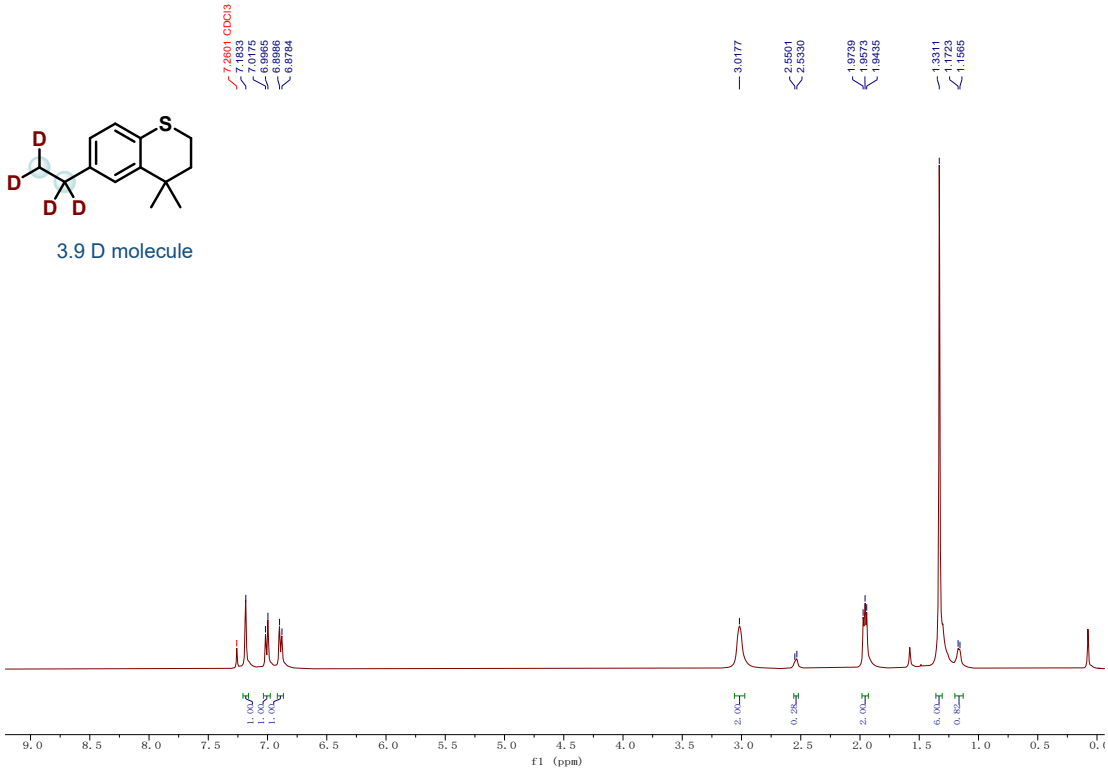
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3o



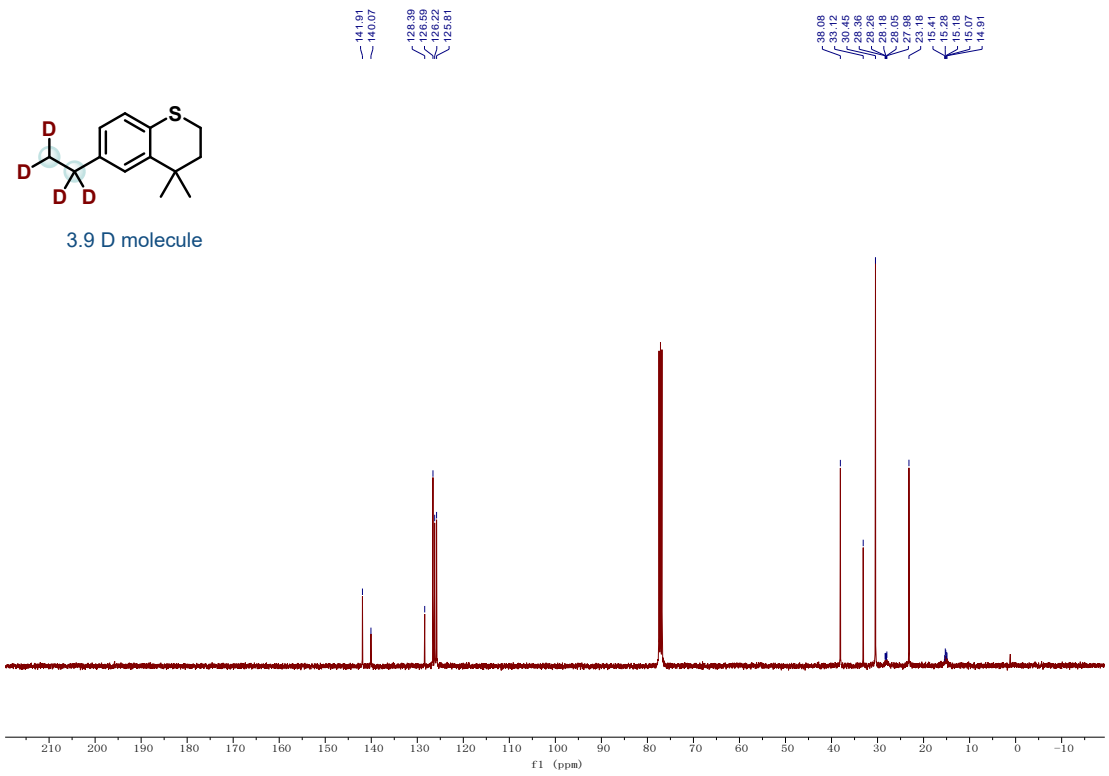
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3o



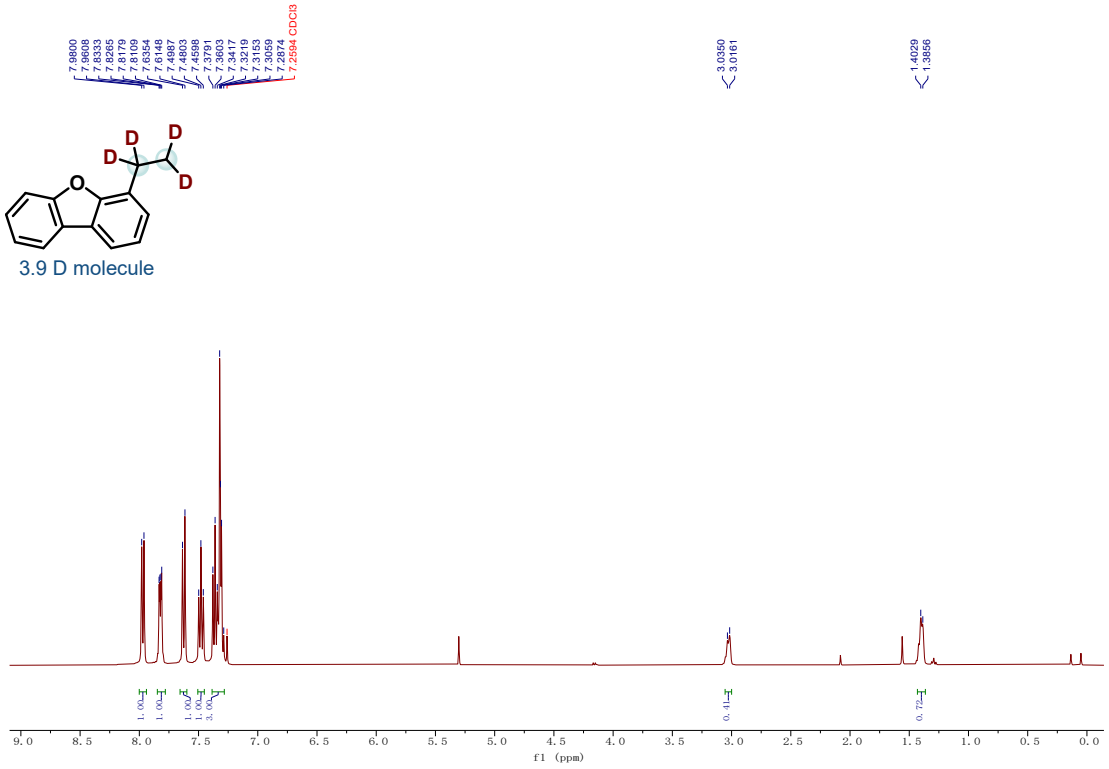
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3p



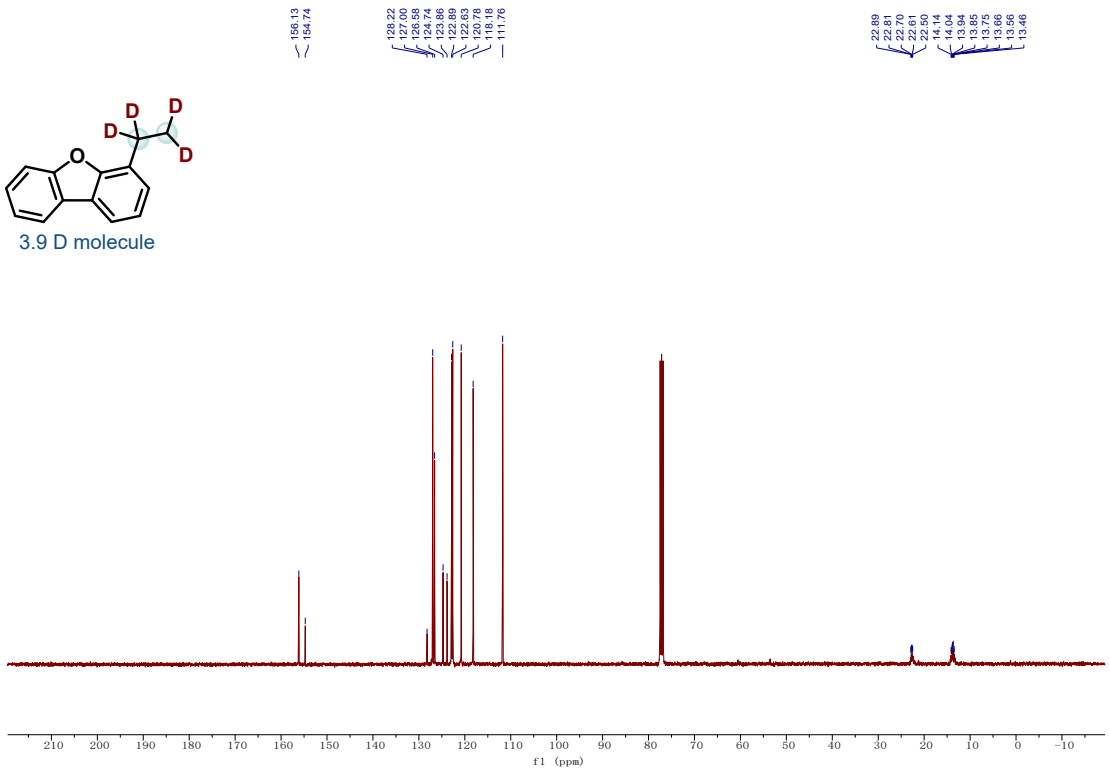
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3p



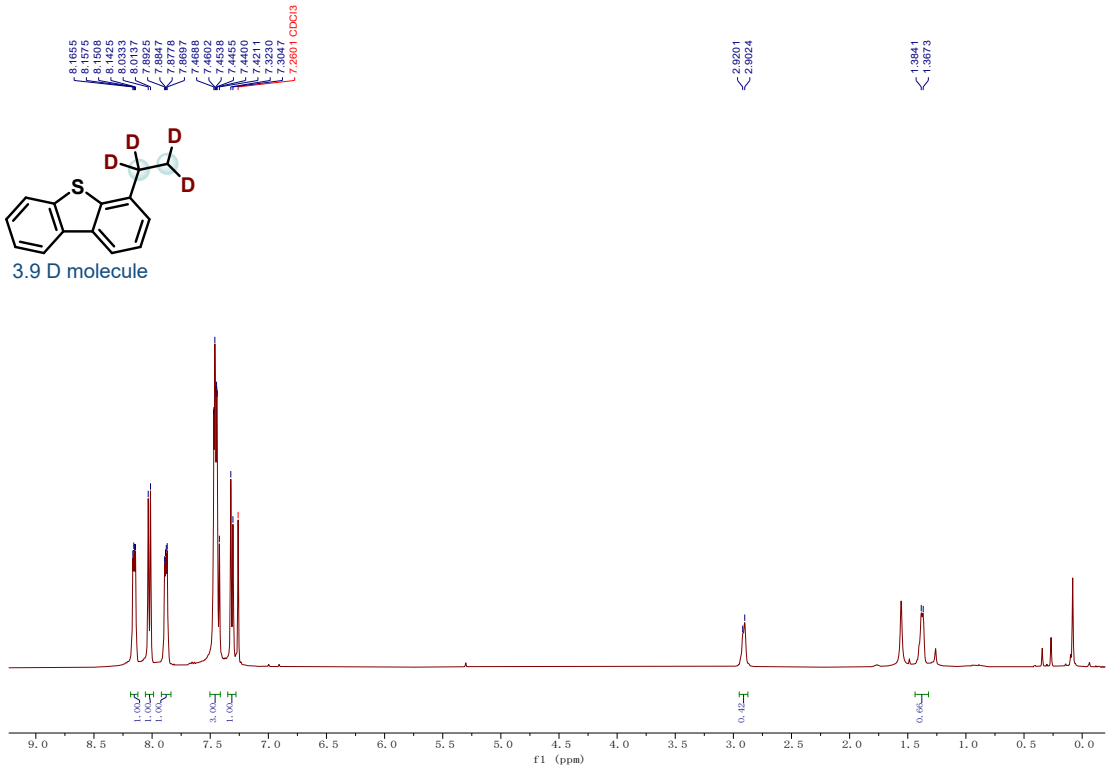
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3q



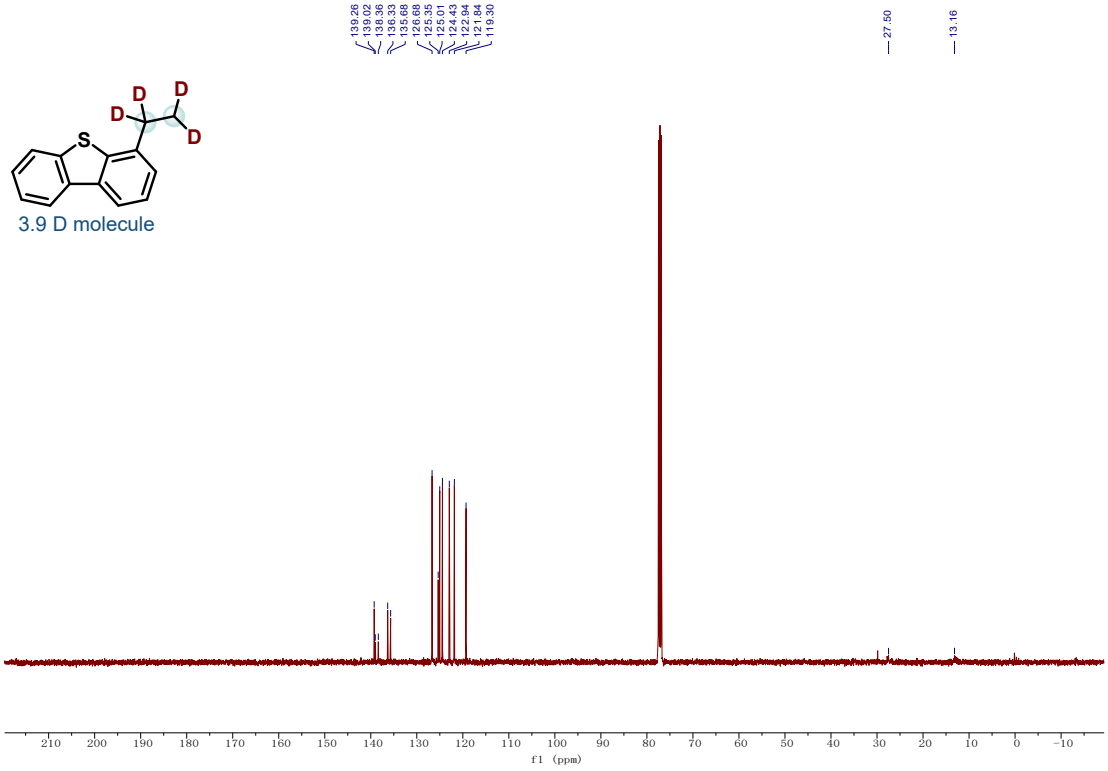
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3q



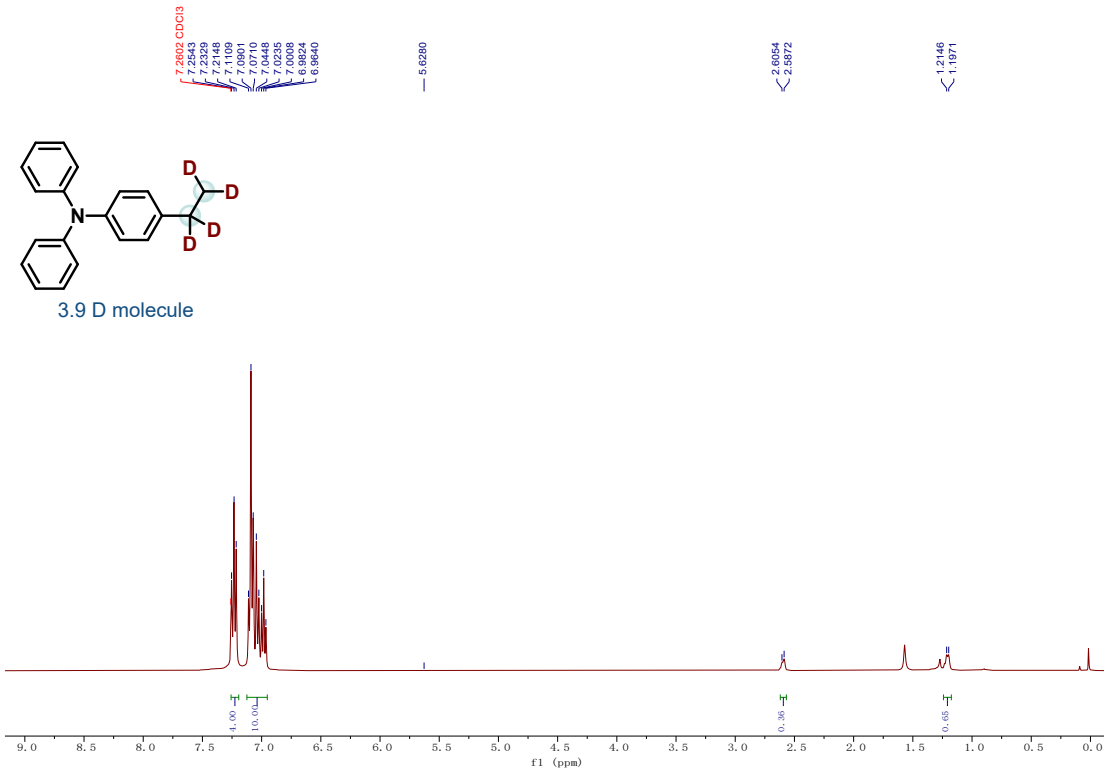
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3r



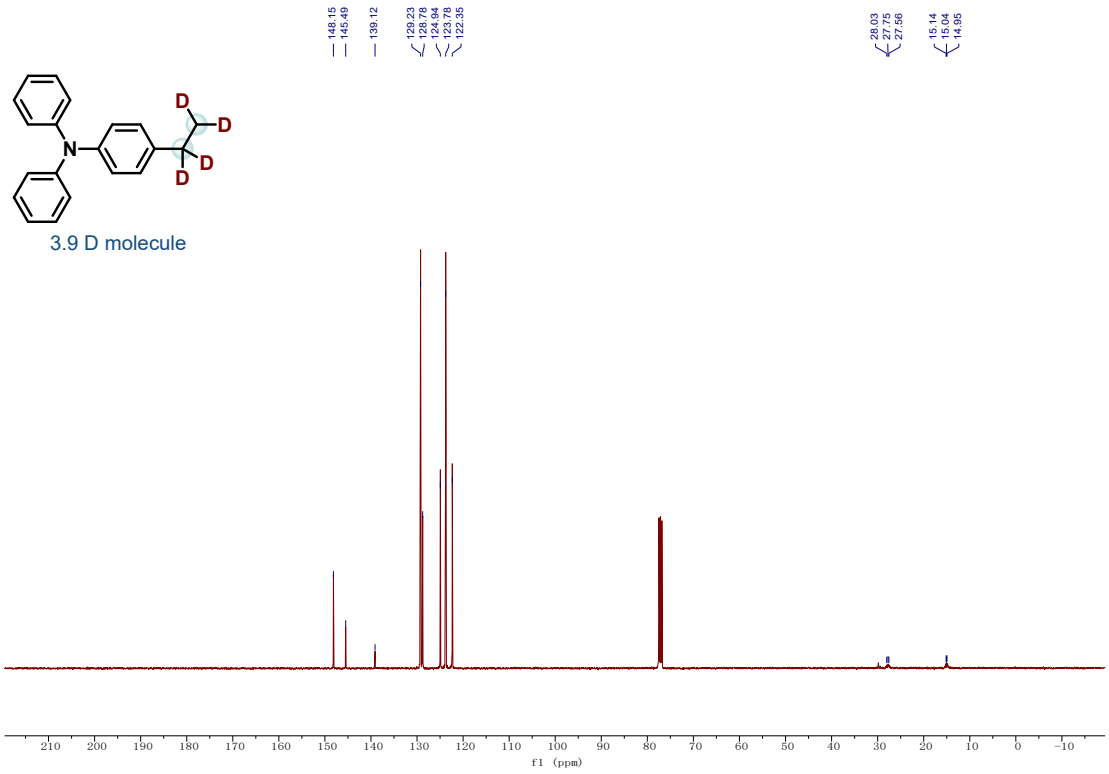
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3r



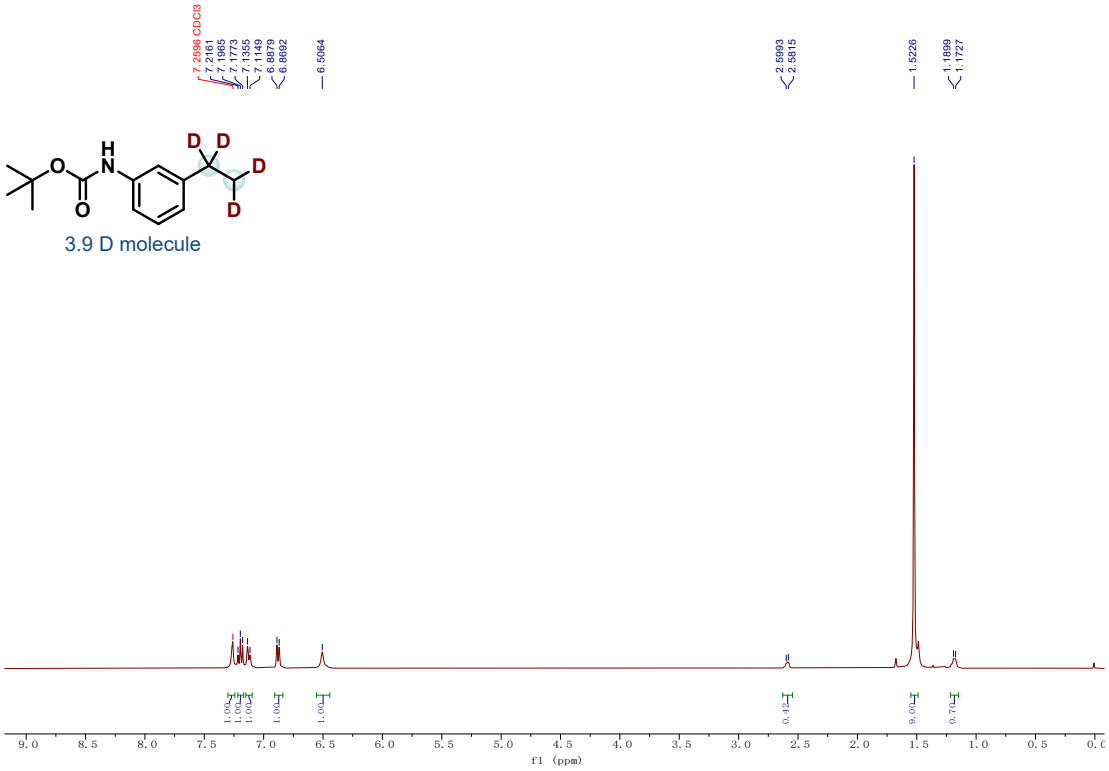
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3s



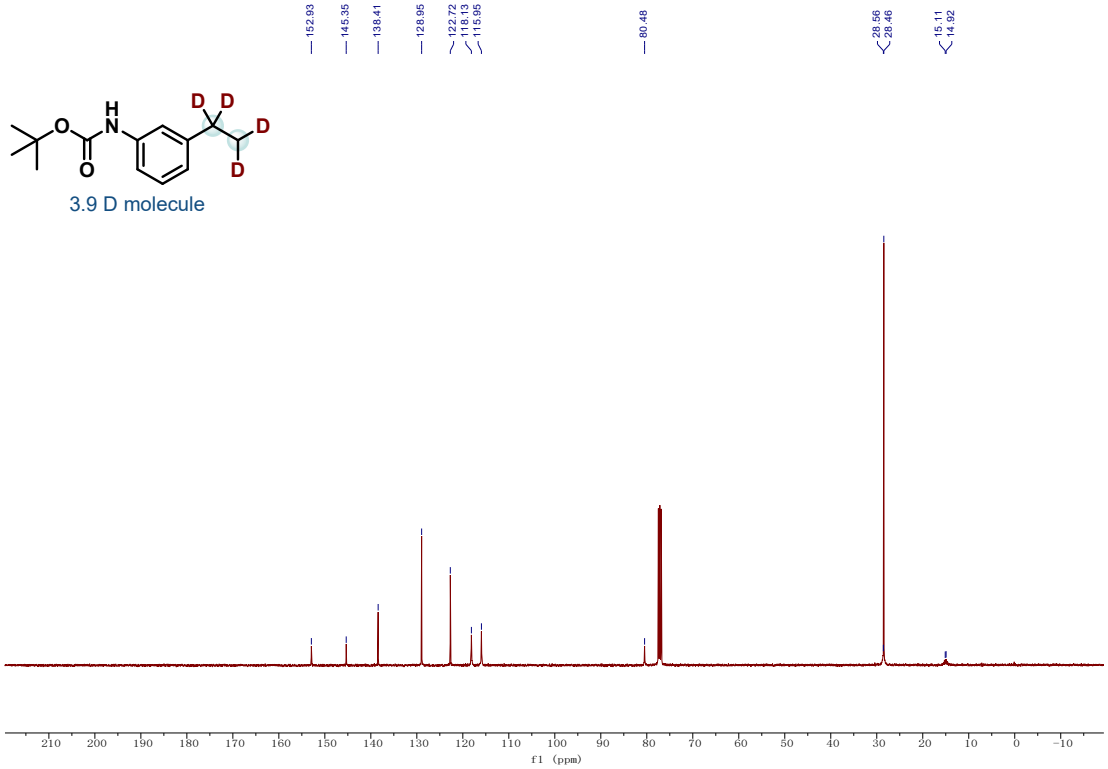
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3s



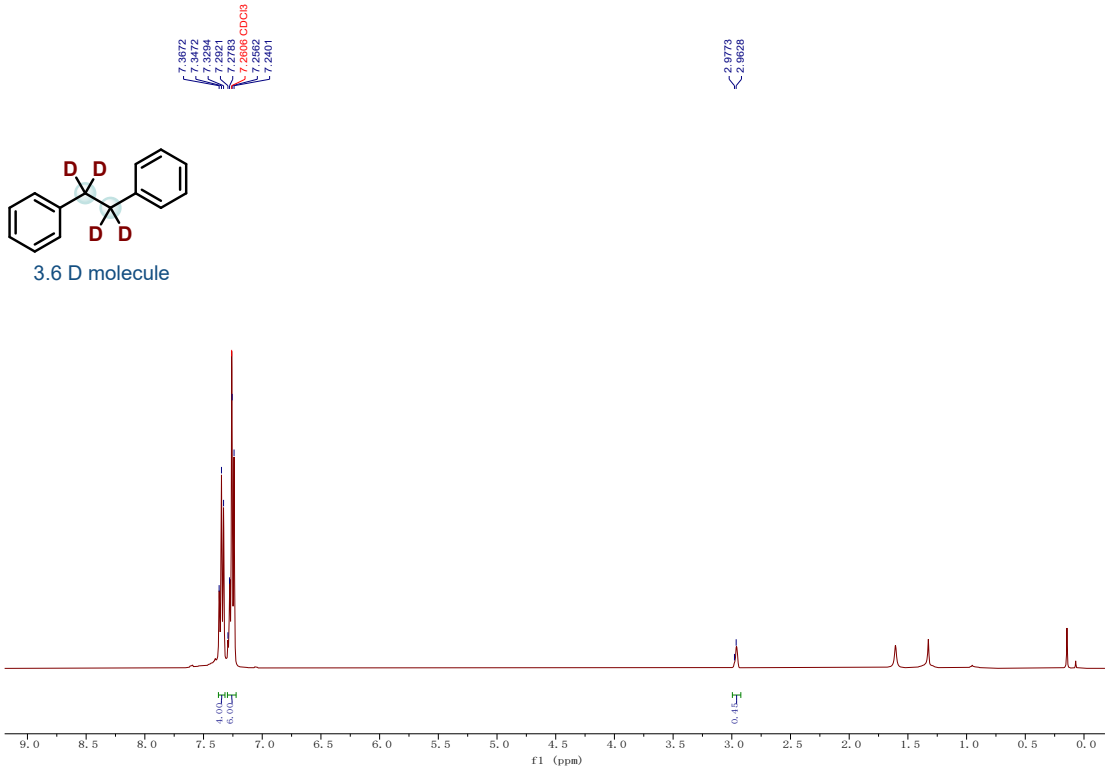
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3t



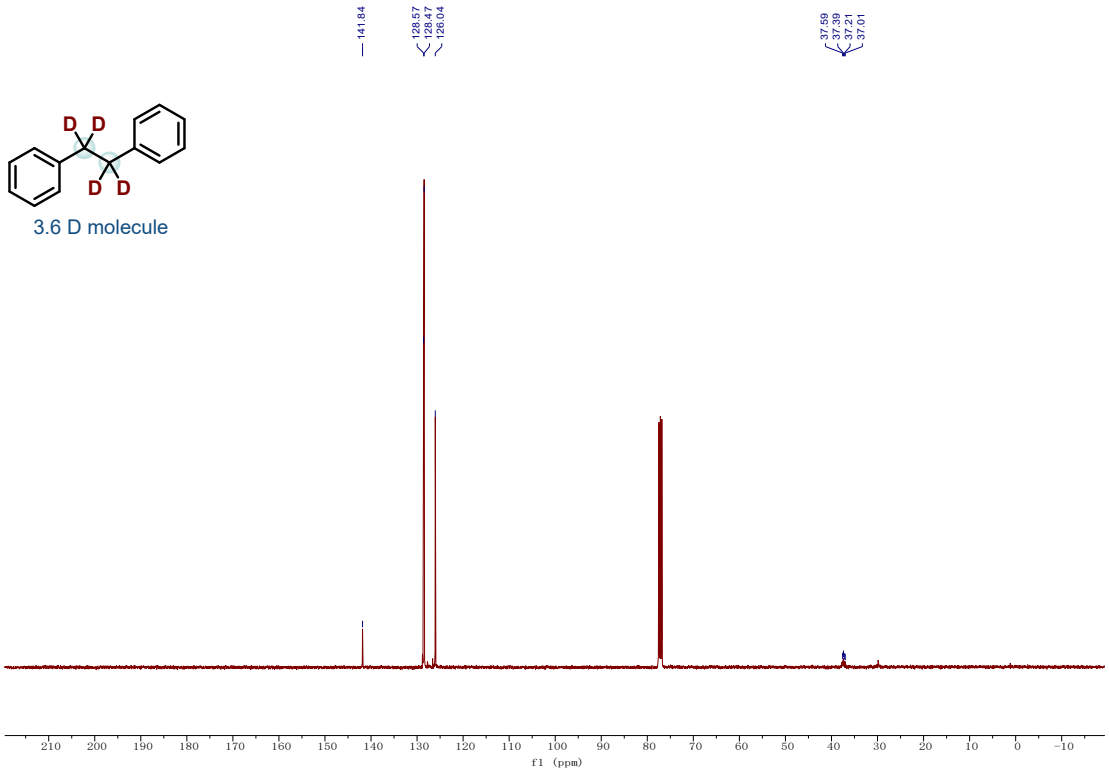
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3t



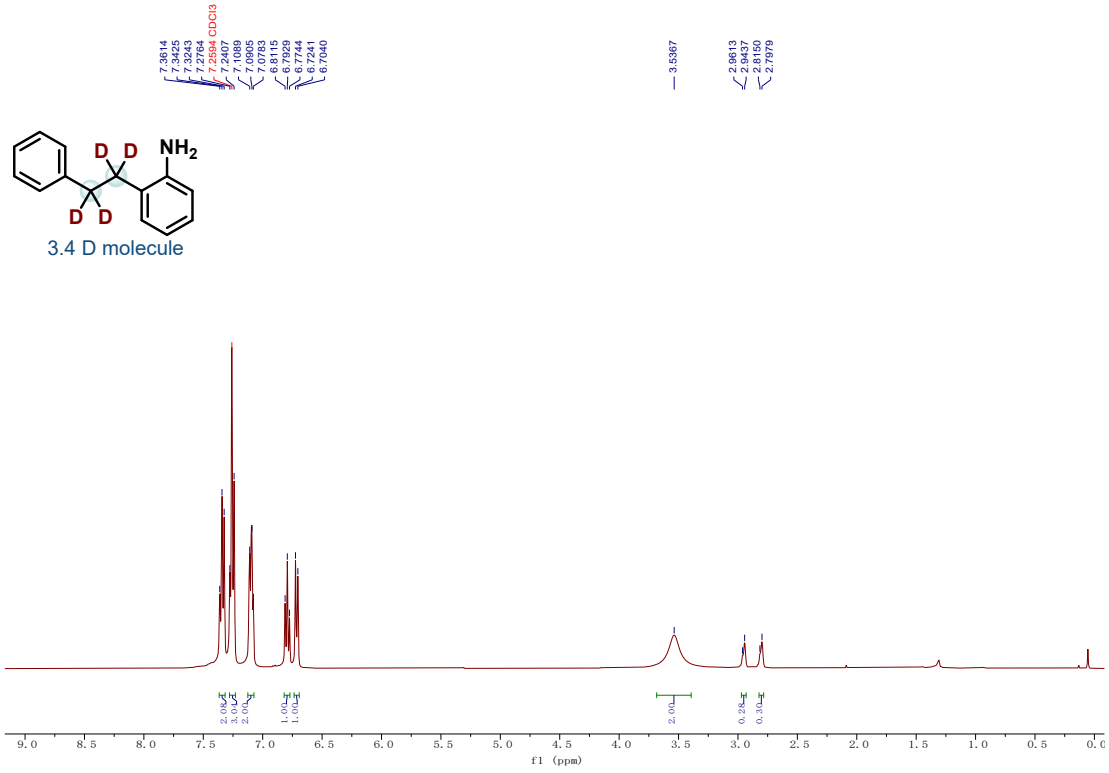
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3u



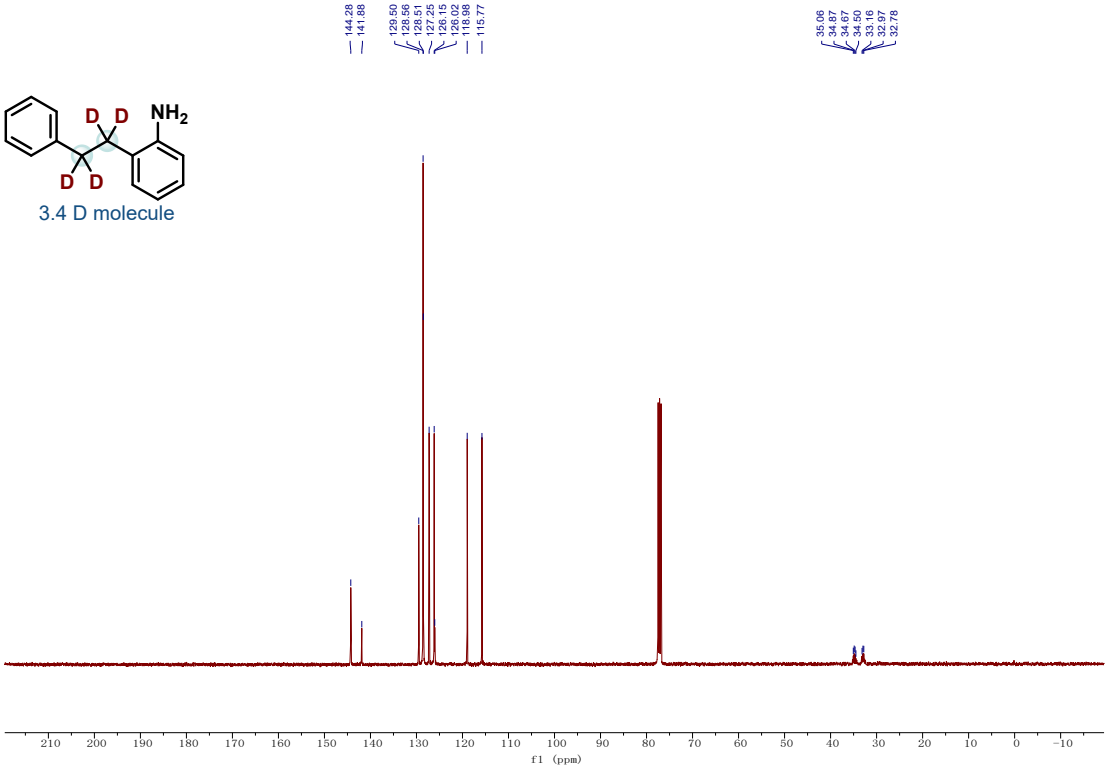
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3u



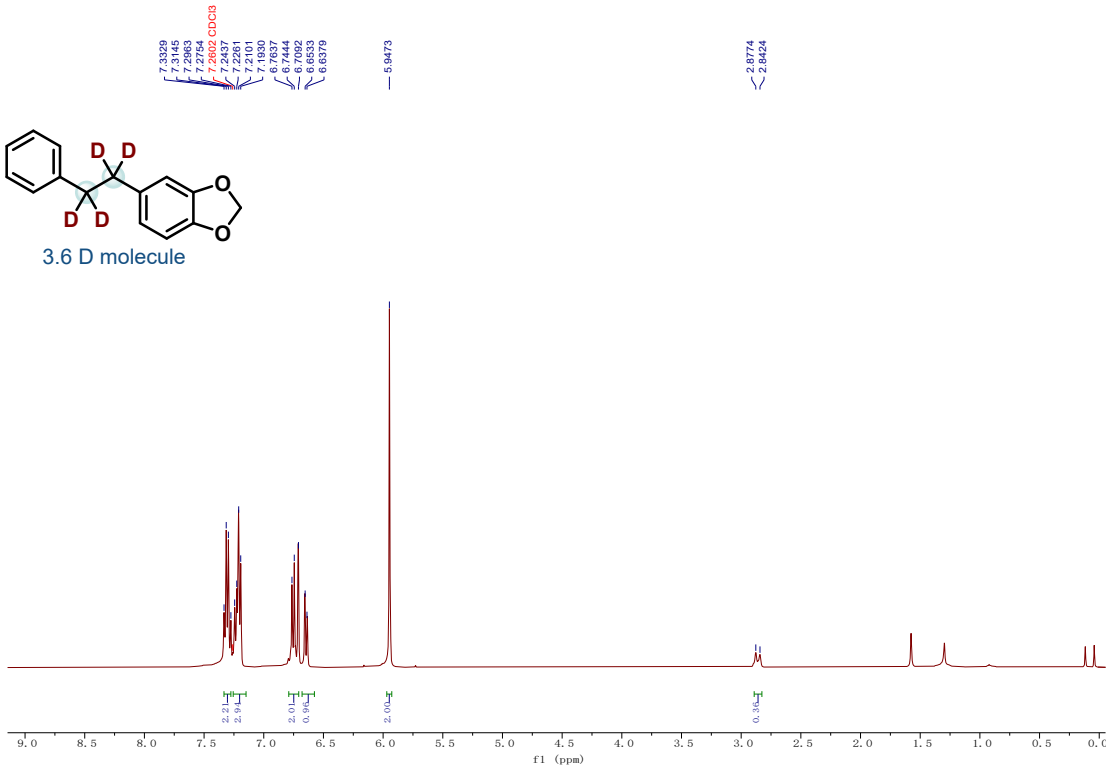
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3v



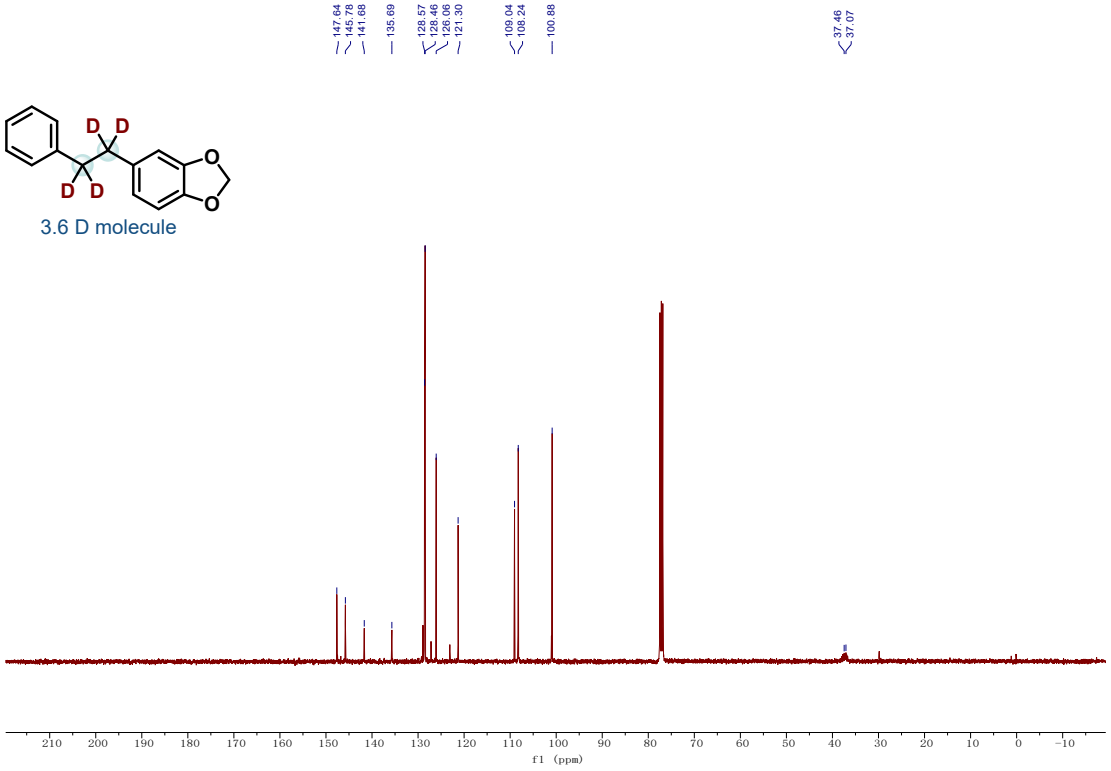
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3v



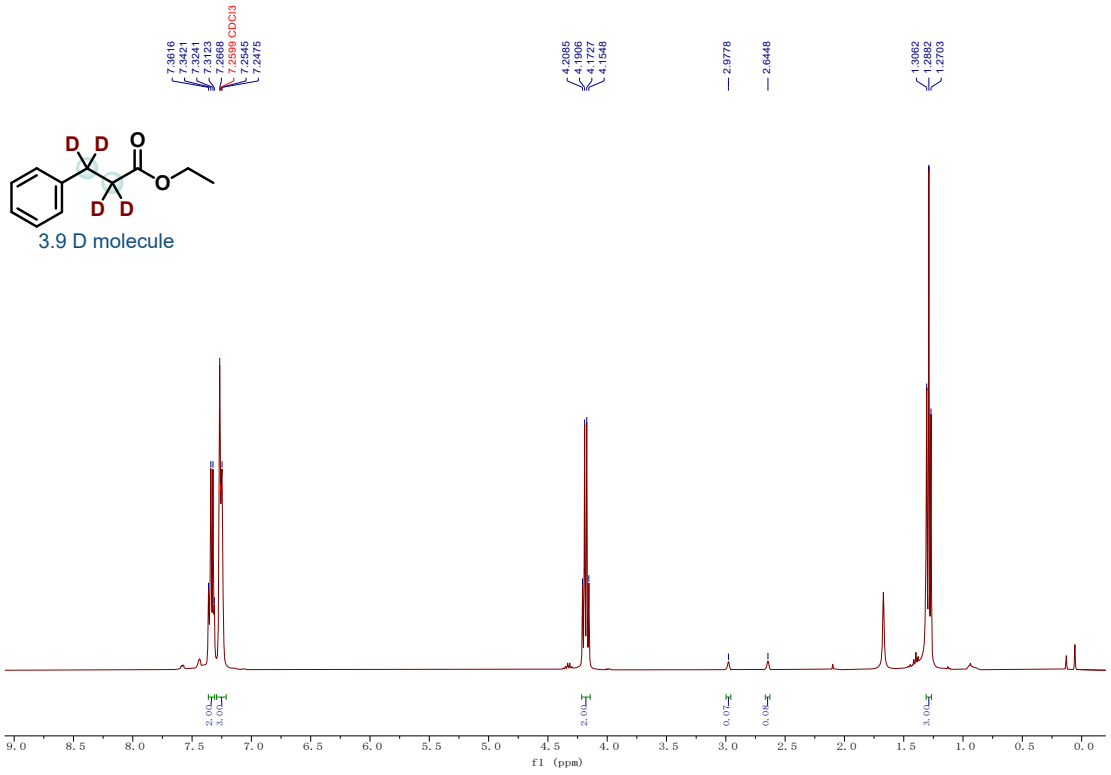
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3w



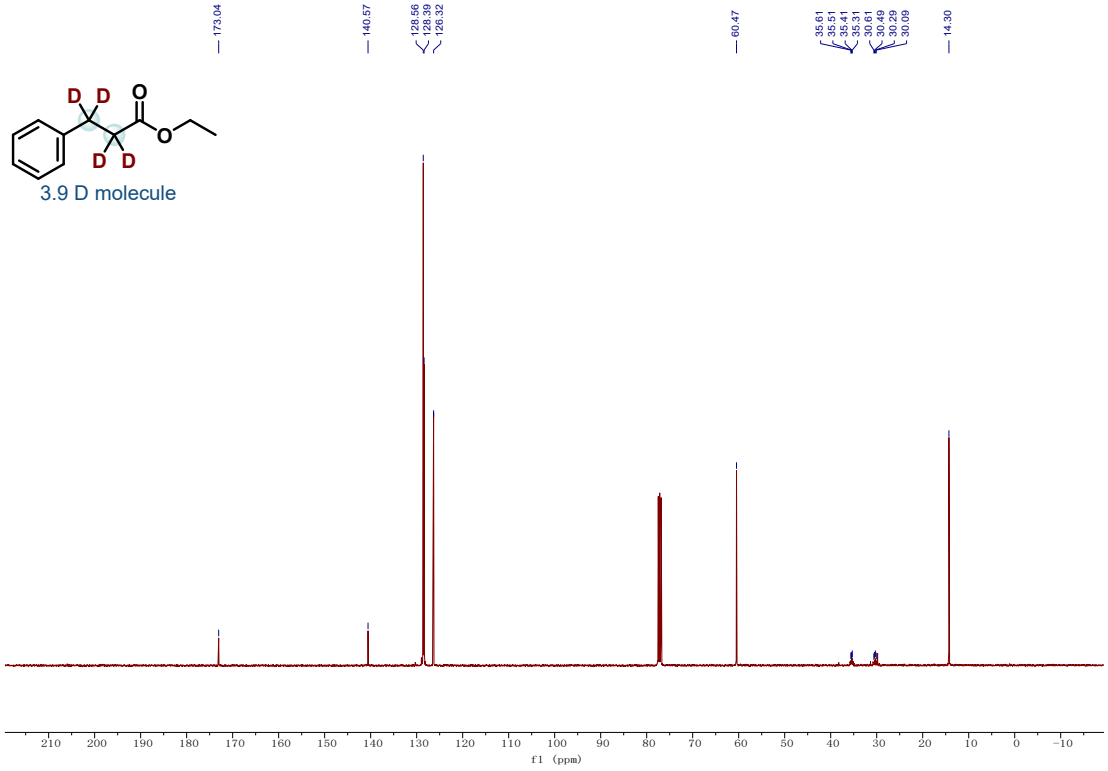
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3w



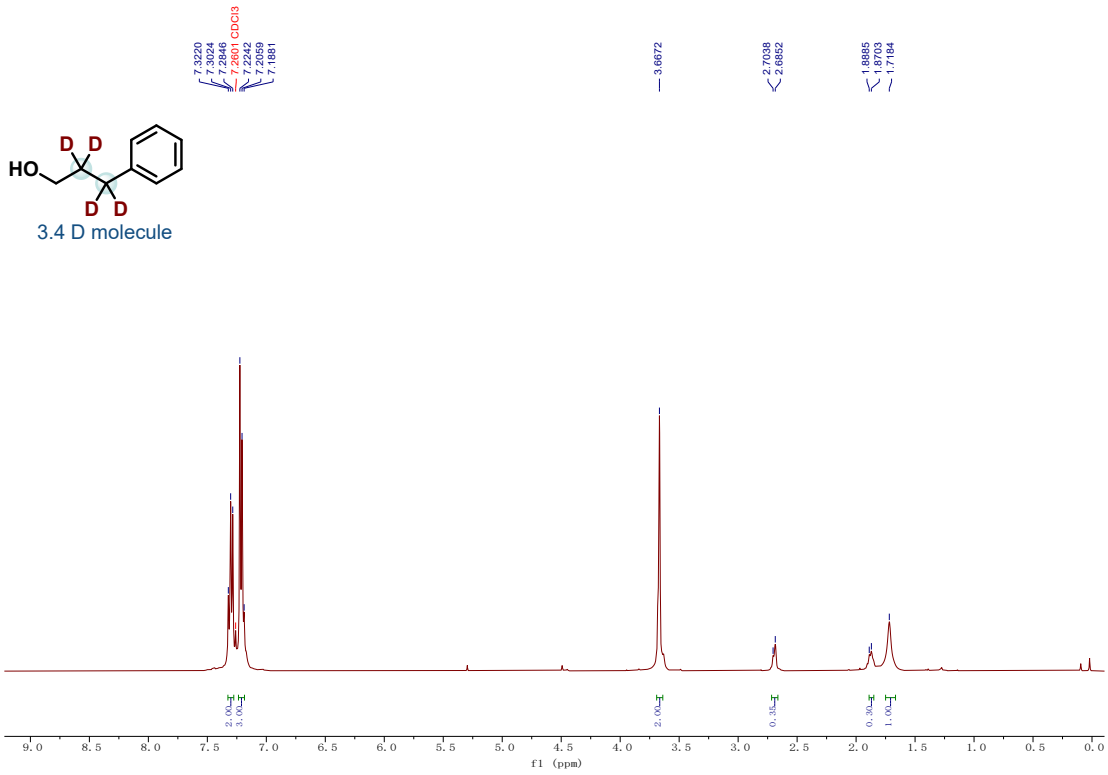
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3x



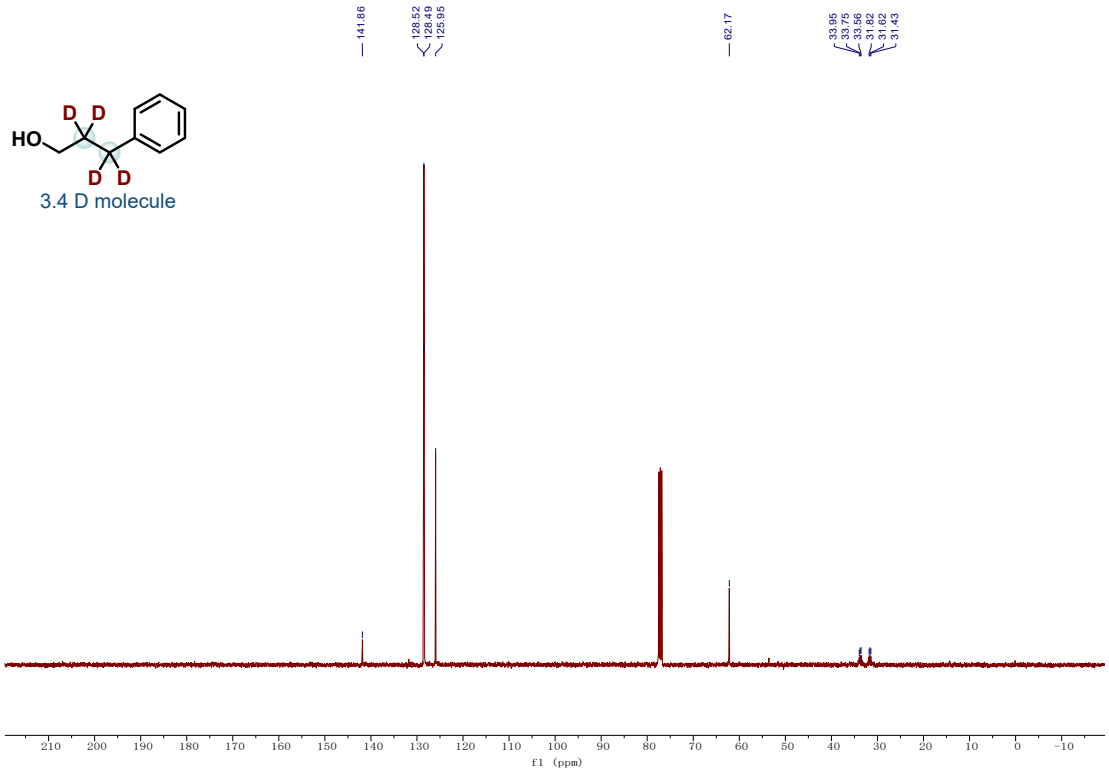
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3x



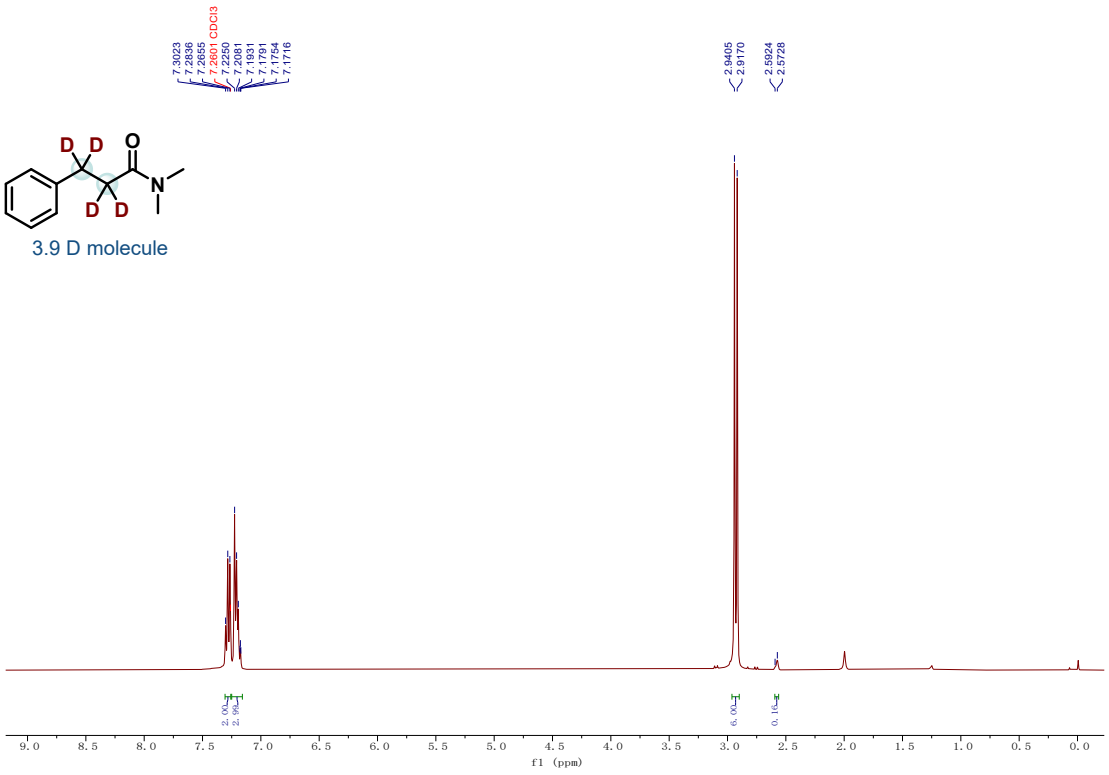
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3y



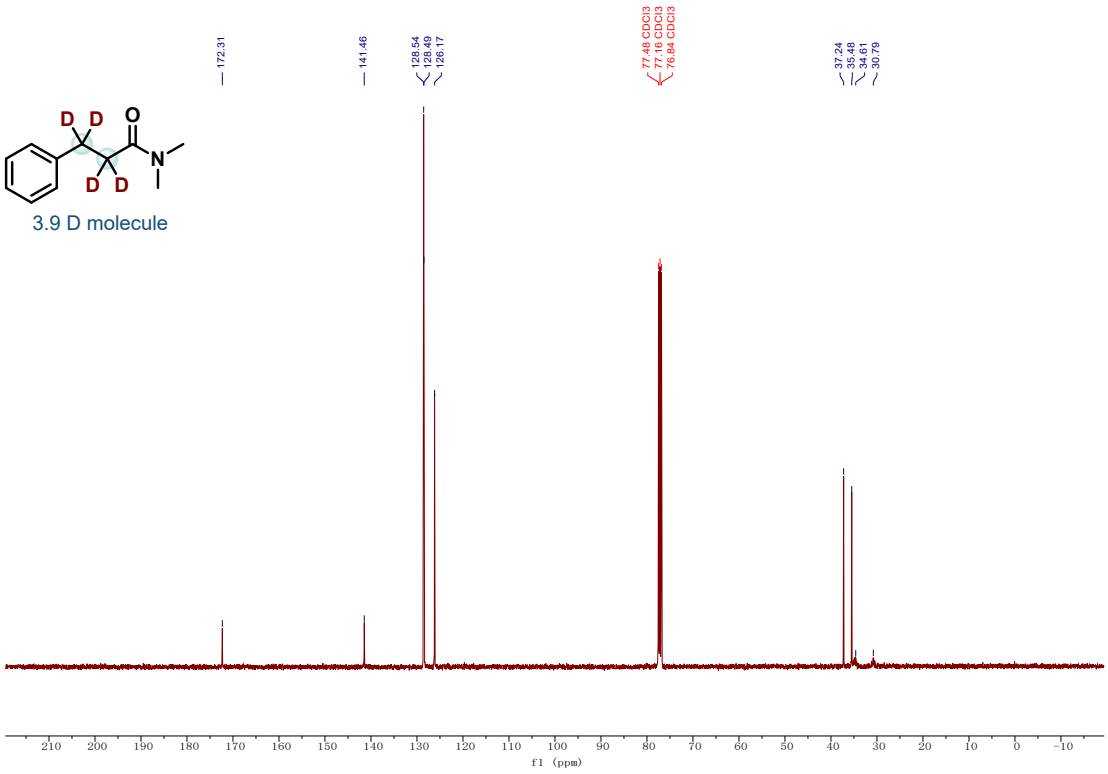
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3y



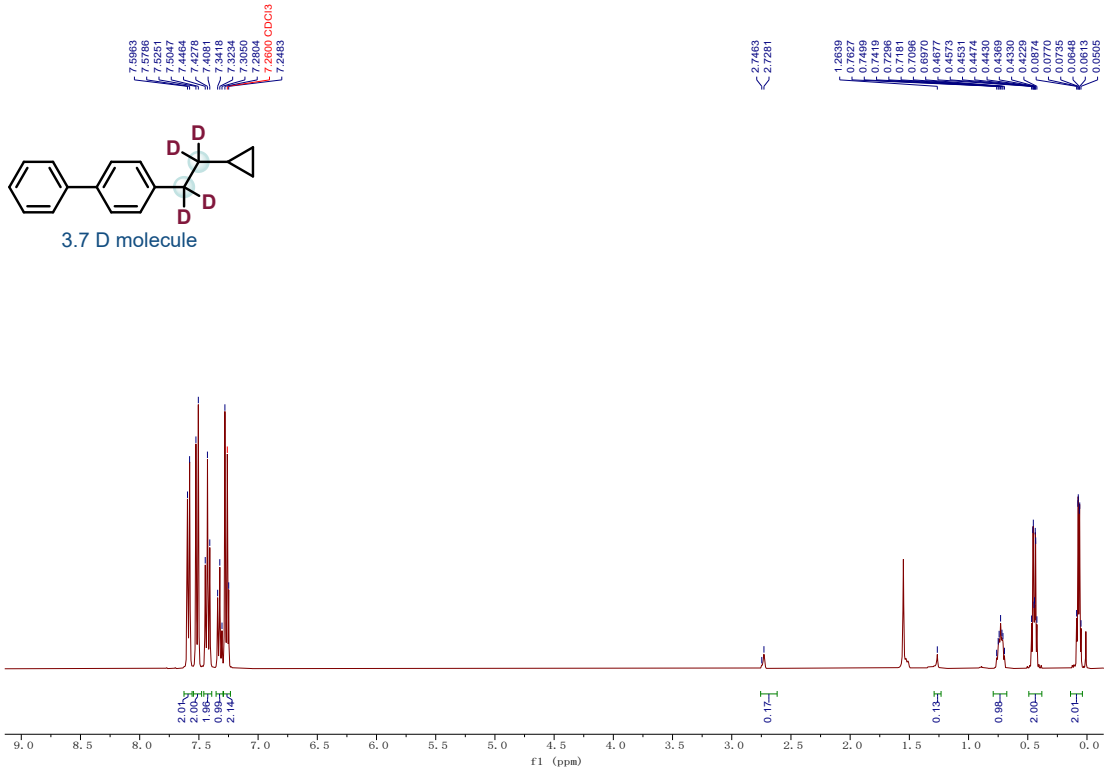
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3z



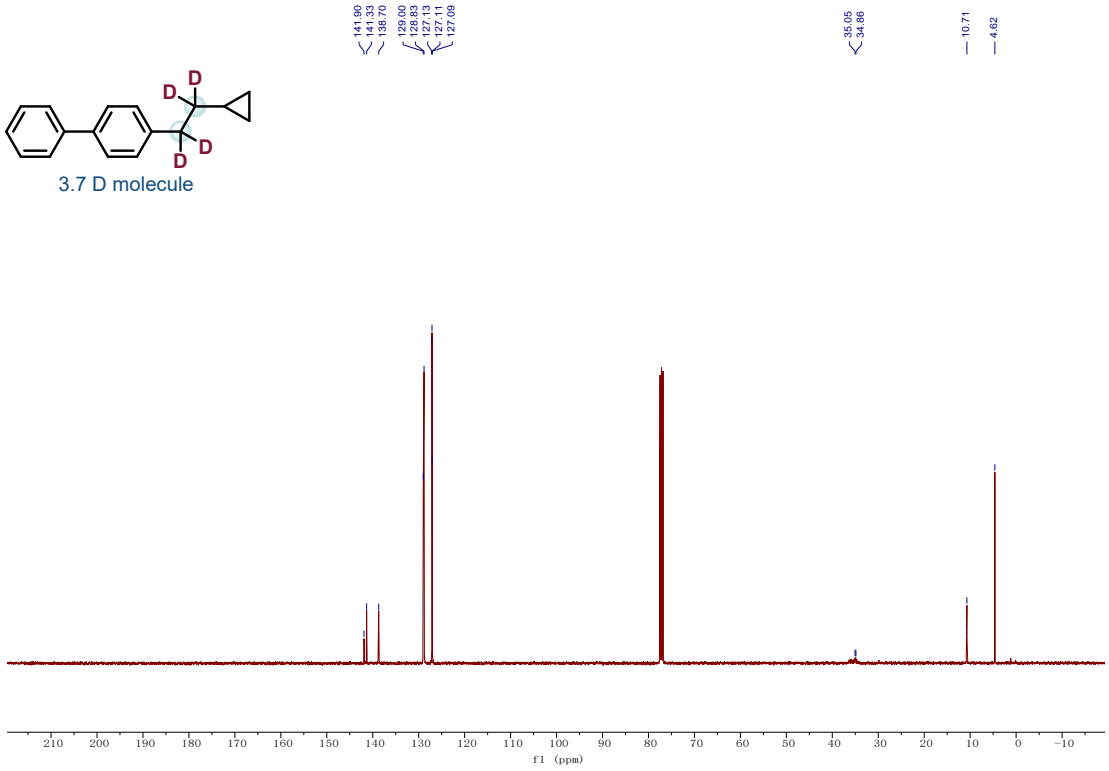
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3z



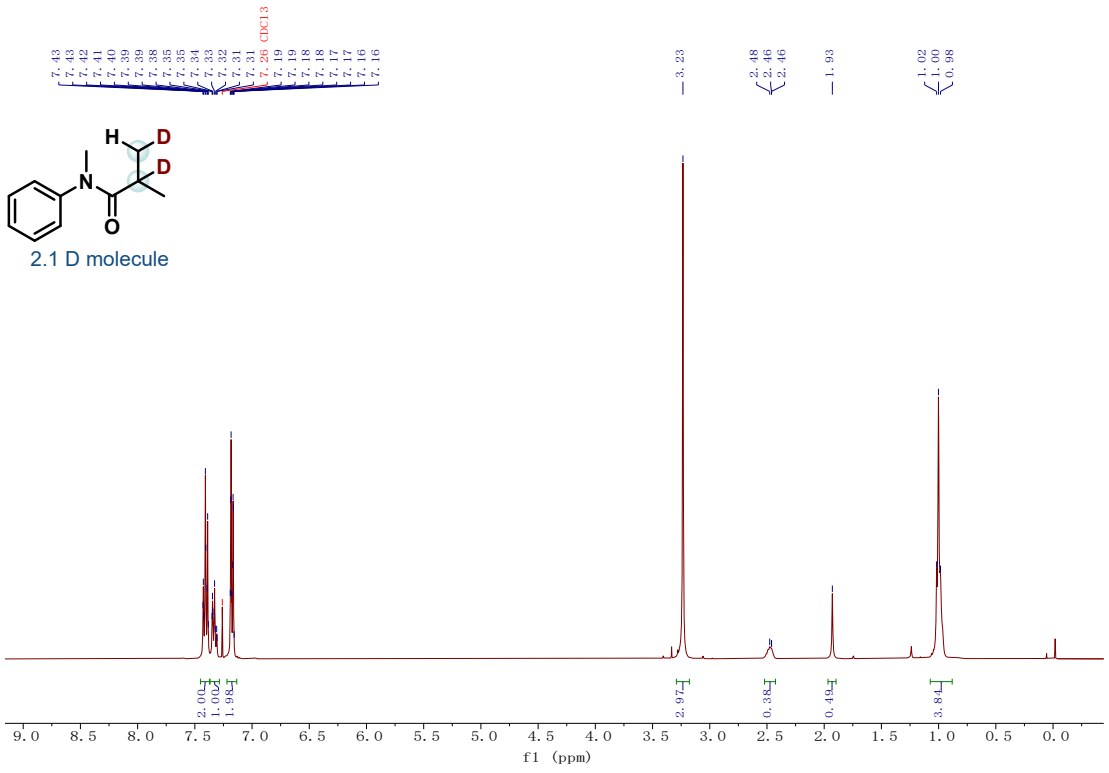
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3aa



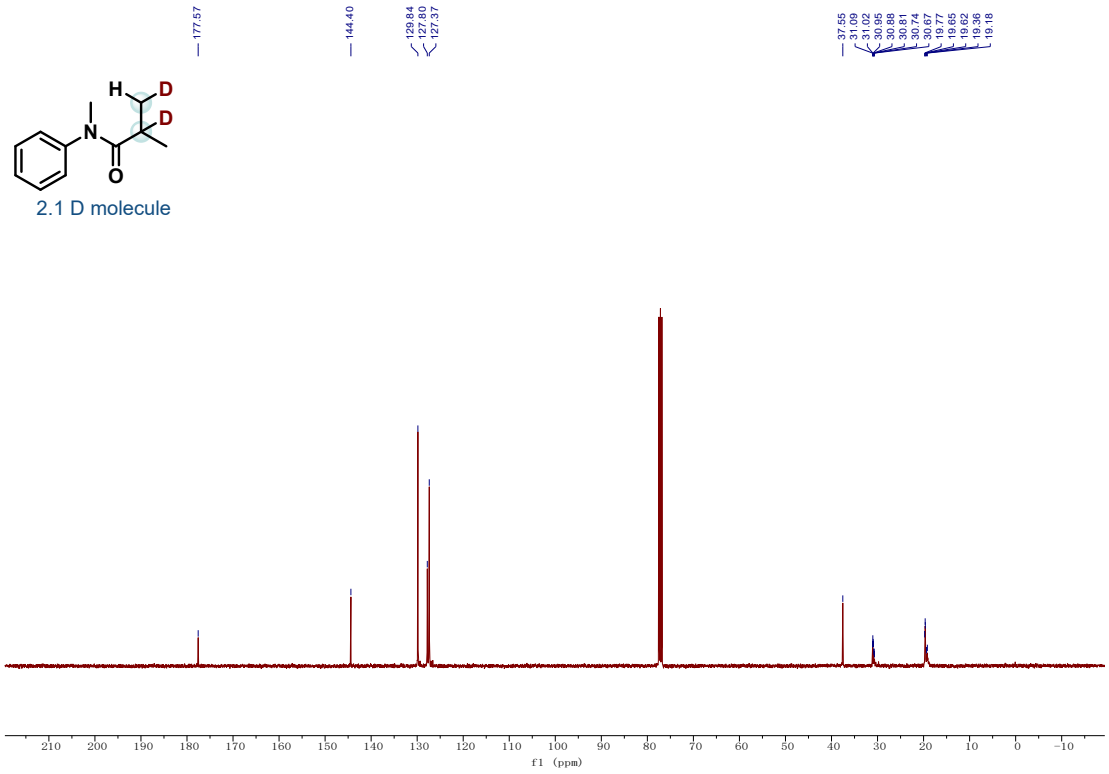
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3aa



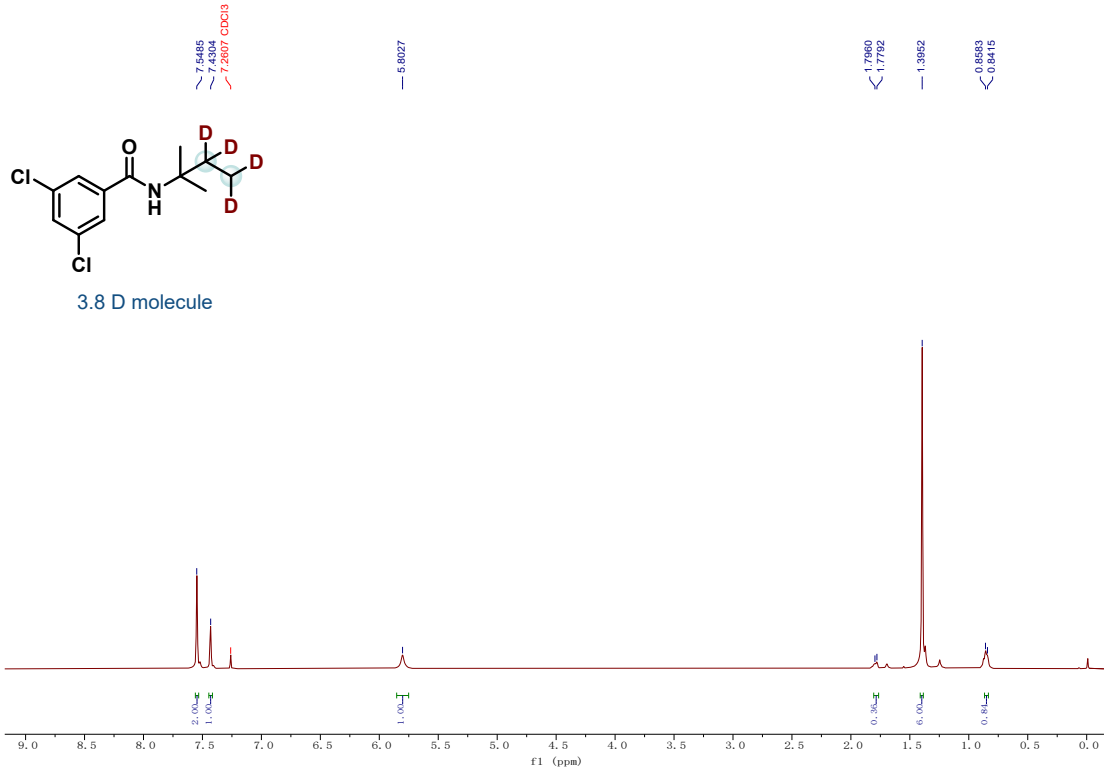
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3ac



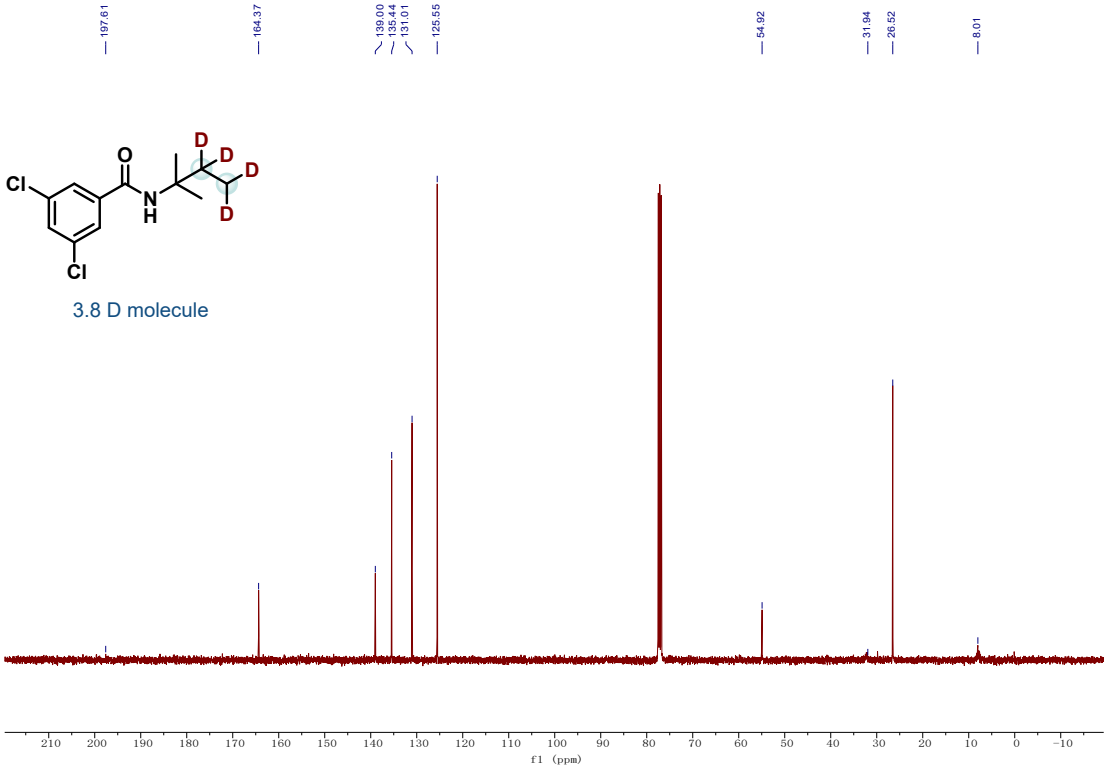
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3ac



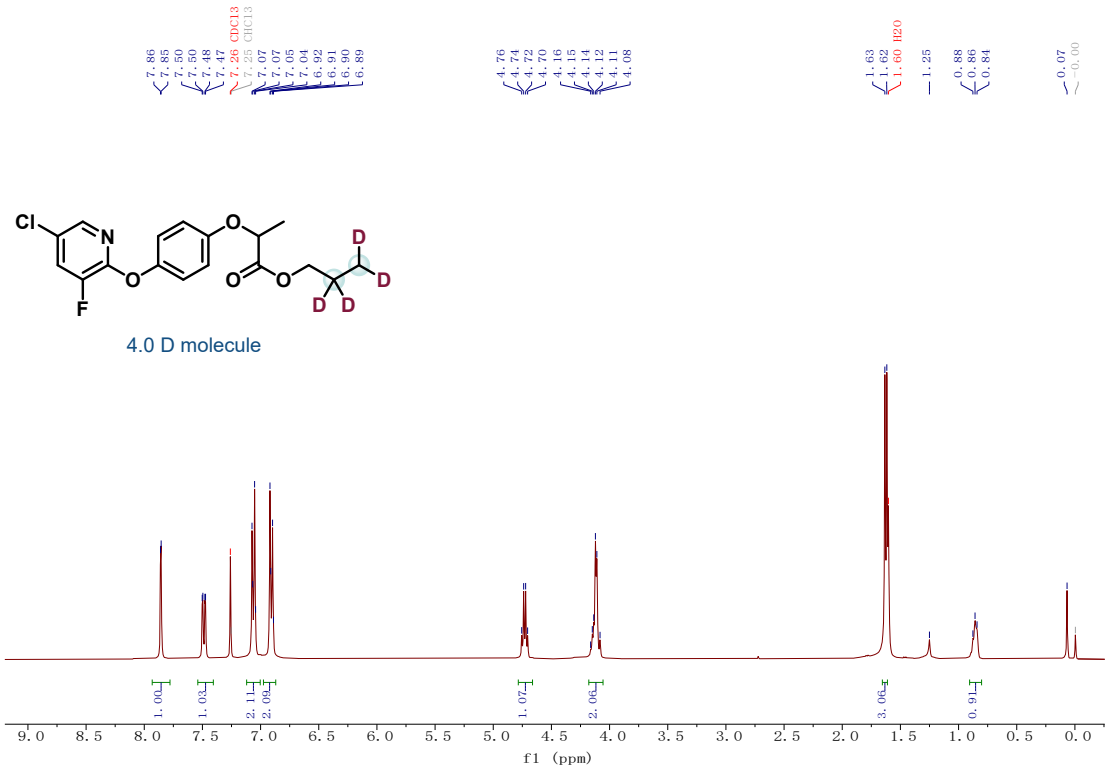
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3ad



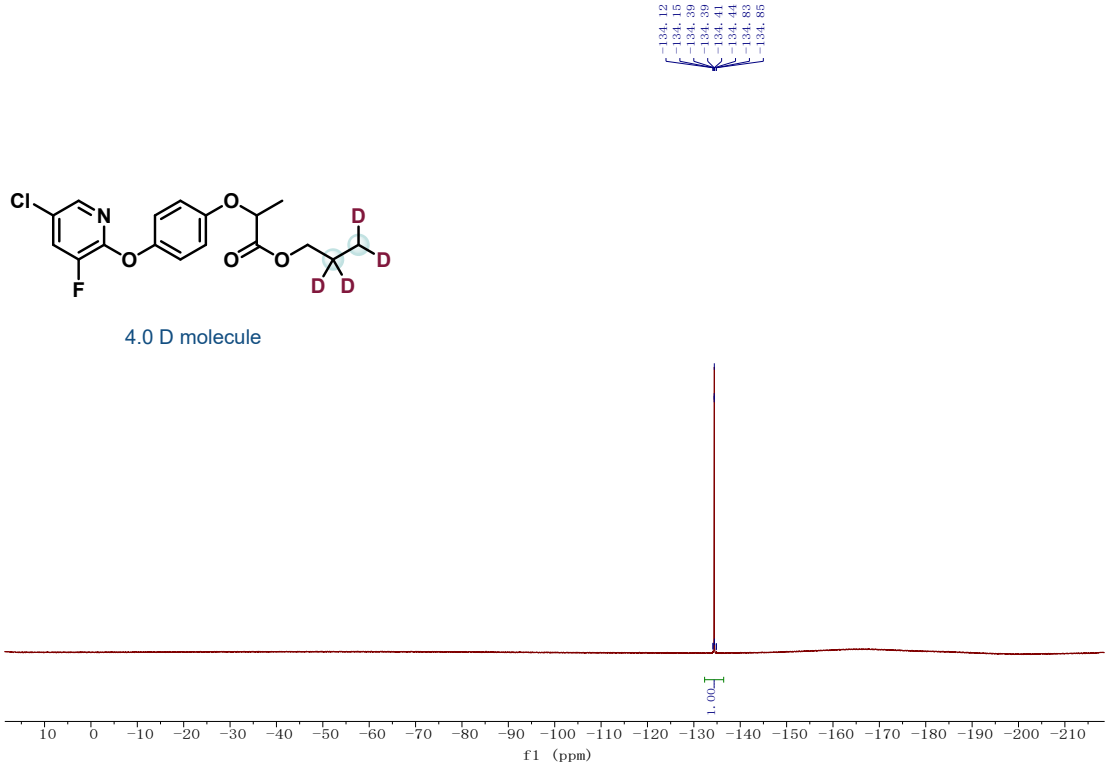
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3ad



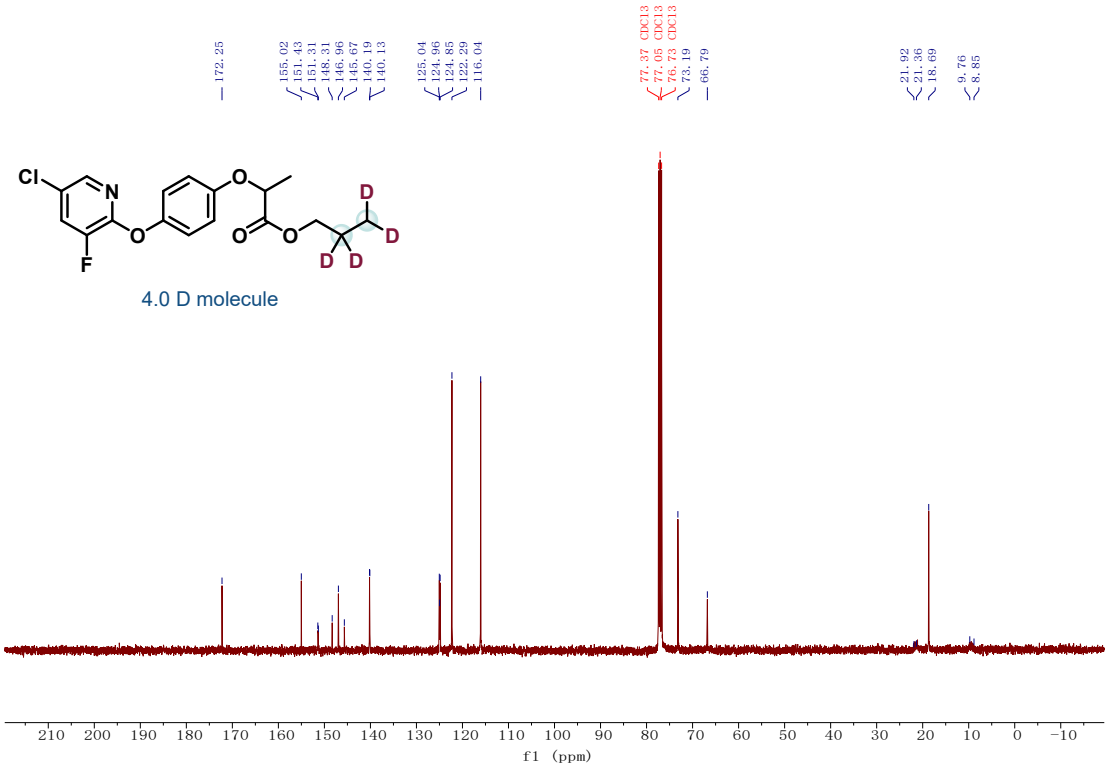
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3ae



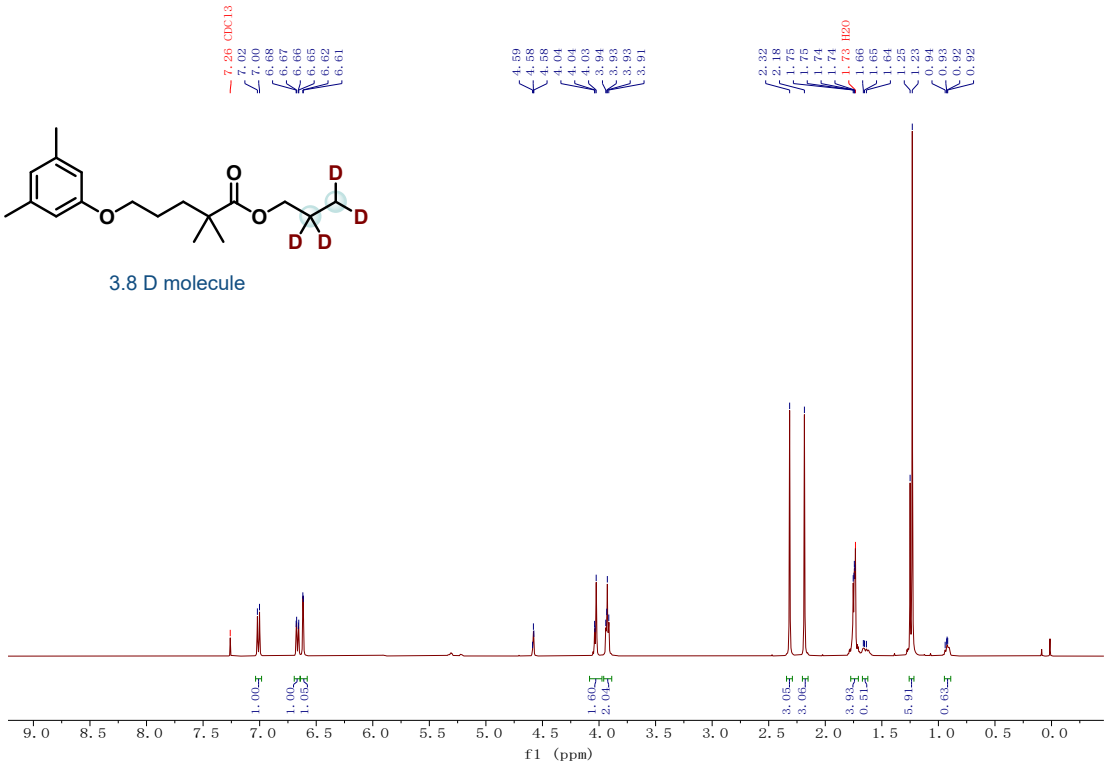
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of 3ae



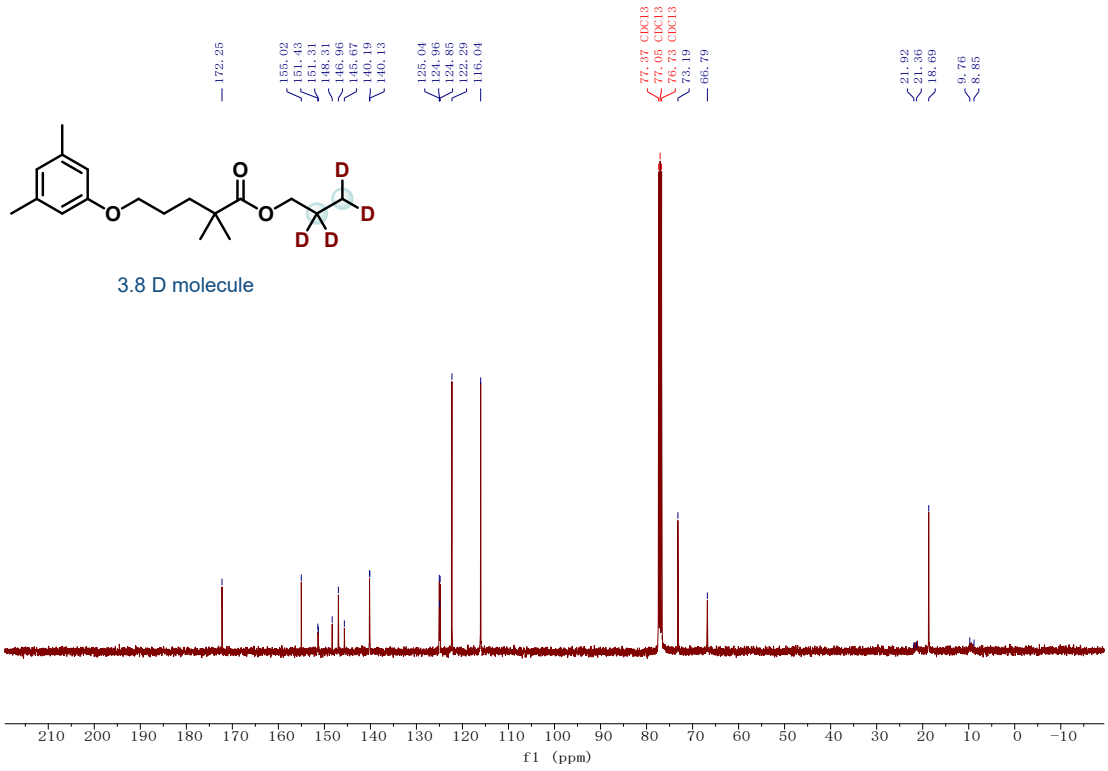
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3ae



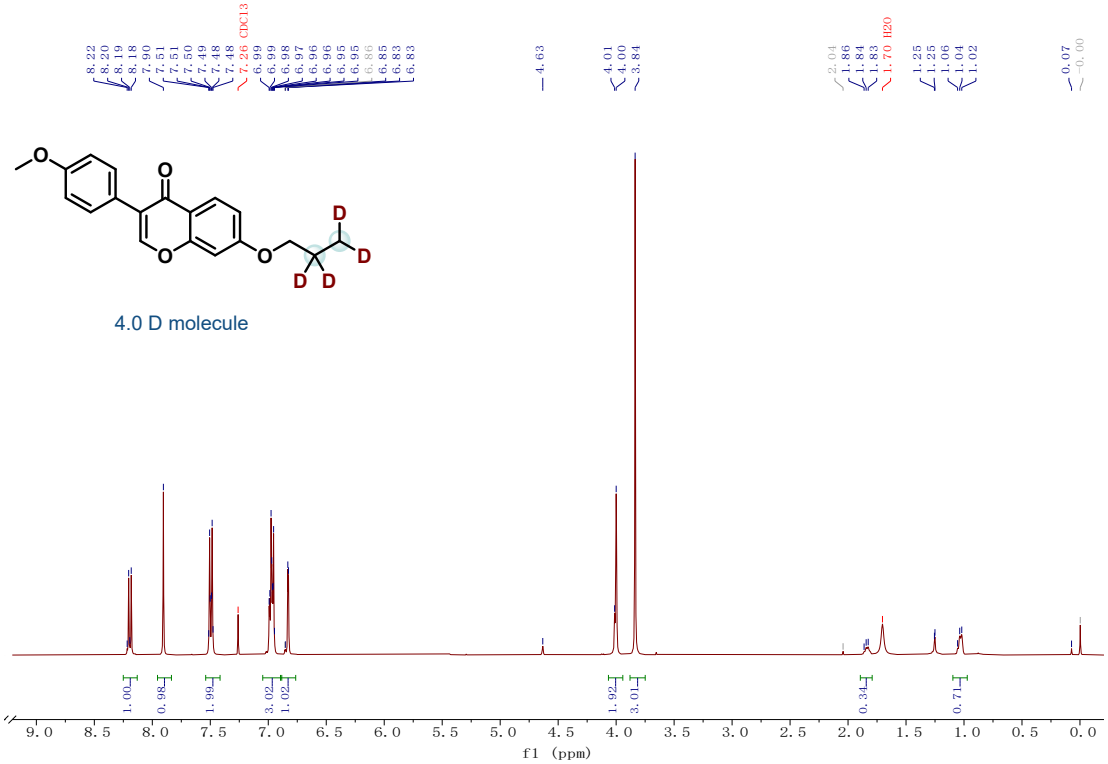
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3af



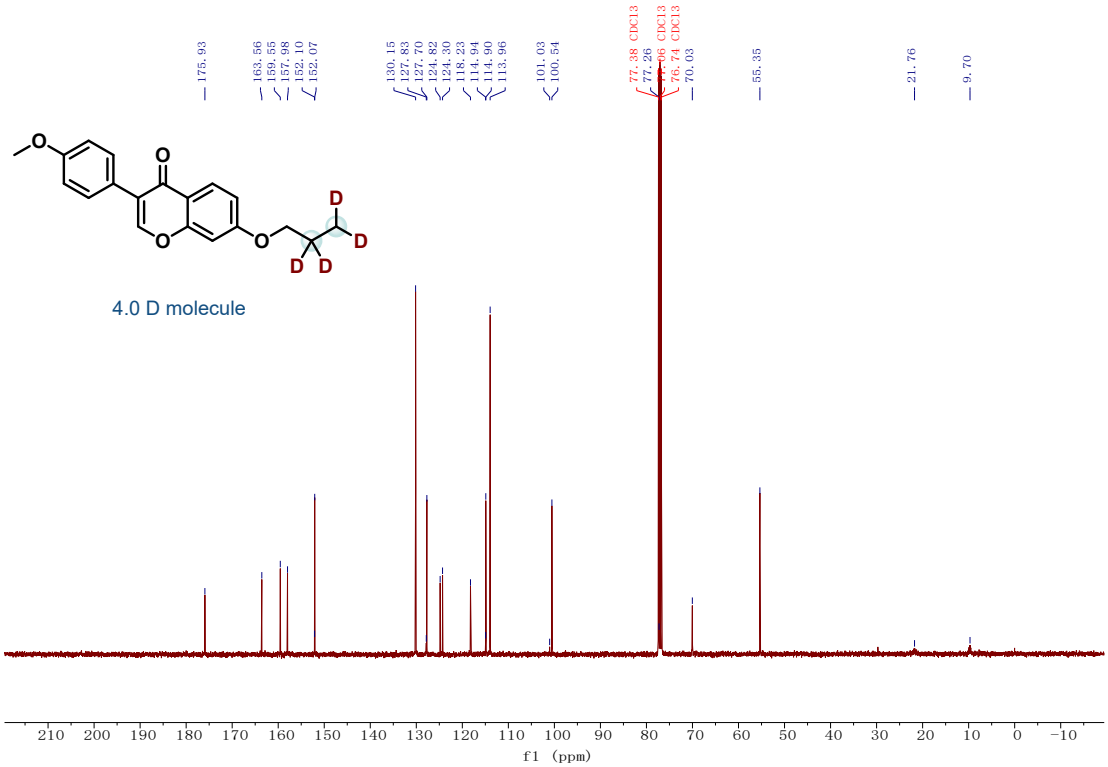
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3af



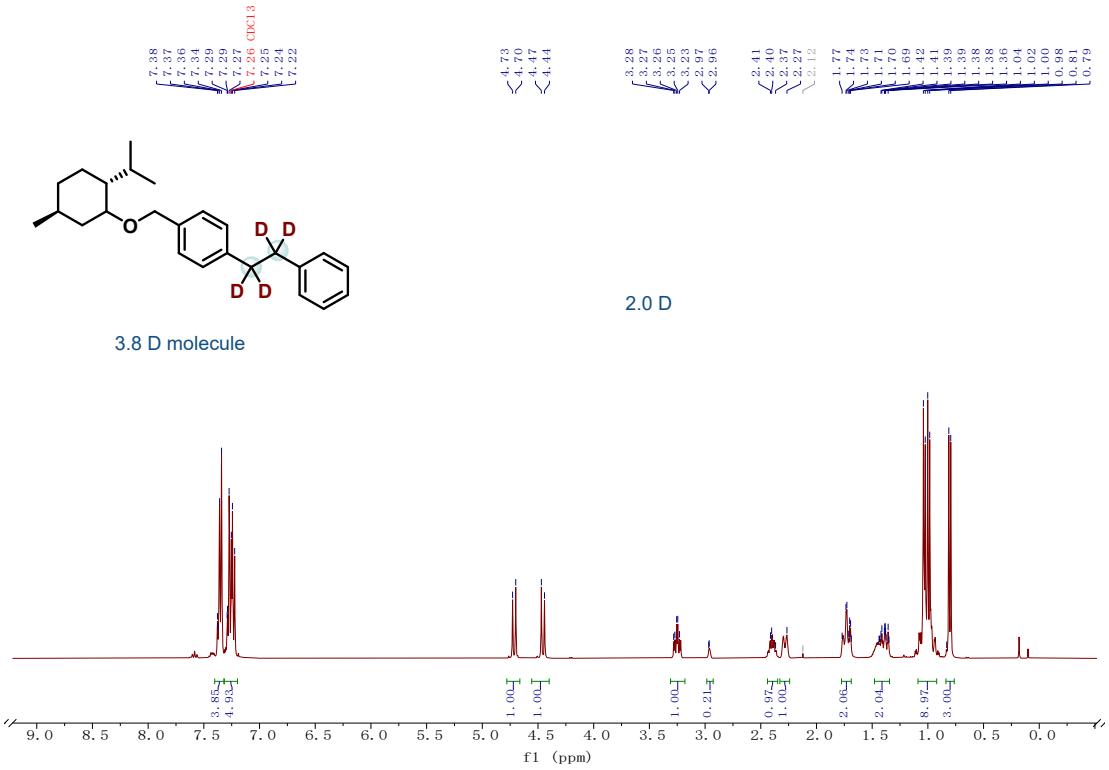
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3ah



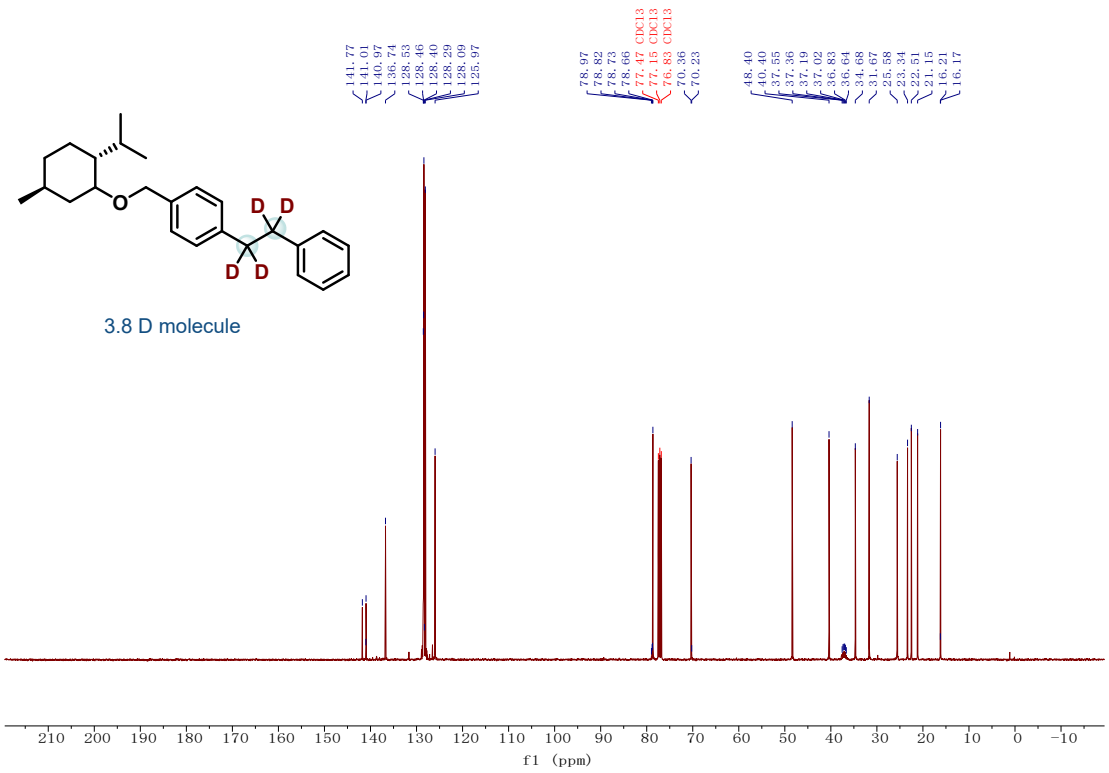
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3ah



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3ai



^{13}C NMR (101 MHz, $CDCl_3$) spectrum of 3ai



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