

Supporting Information

Ligand-promoted Alkynylation of Aryl ketones: A Practical Tool for Structural Diversity in Drugs and Natural Products

Hui Xu,^{1,4} Biao Ma,^{1,4} Zunyun Fu,^{3,4} Han-Yuan Li,¹ Xing Wang,¹ Zhen-Yu Wang,³ Ling-Jun Li,¹ Tai-Jin Cheng,¹ Mingyue Zheng,^{2*} Hui-Xiong Dai^{1*}

¹Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, University of Chinese Academy of Sciences, Shanghai 201203, China.

²Drug Discovery and Design Center, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.

³School of Chinese Materia Medica, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210023, China.

⁴These authors contributed equally: Hui Xu, Biao Ma and Zunyun Fu.

Email: myzheng@simm.ac.cn; hxdai@simm.ac.cn.

Content

1. General Information	2
2. Experimental Procedures.....	2
2.1 Preparation of Arylketones.....	2
2.2 Preparation of Alkynylsilane	5
2.3 Reaction Optimization.....	5
2.4. Typical Procedure for One-pot Alkynylation of Arylketone.....	9
2.5. Typical Procedure for the Preparation of Terminal Alkynylation.....	9
2.6 Procedure for the Diversification of Drug and Natural product.....	10
3 Analytical Data.....	15
3.1 Characterization of Starting Material	15
3.2 Characterization of Product.....	18
4. DFT Calculations	34
5. References	43
6. NMR Spectra.....	49
6.1 NMR Spectra for New Starting Material.....	49
6.2 NMR Spectra for Product.....	59

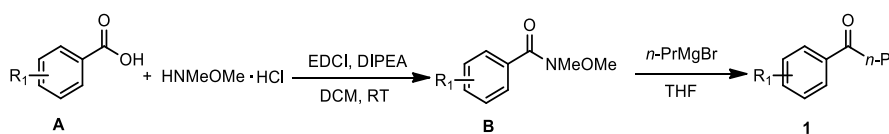
1. General Information

All reagents were purchased from TCI, J&k, STREM, Sigma-Aldrich, Adamas-beta, 9-Ding chemistry, and Energy Chemical of the highest purity grade, and used directly without further purification. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker 400 and 500 MHz spectrometer. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double of doublets, td = triple doublet, dt = double triplet, and br = broad. HRMS were recorded at the Center for Mass Spectrometry, Shanghai Institute of Material Medica. Solvents were purified prior to use according to conventional procedures. The starting material arylketones and alkynylsilane were commercially available or readily prepared according to the known method. Abbreviations in the SI: EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), DIPEA (N,N-diisopropyl ethylamine), DCM (Dichloromethane), DCE (1,2-Dichloroethane), NaBAR_F (Sodium tetrakis[3,5-bis(trifluoromethyl) phenyl]borate), TBAF (Tetrabutylammonium fluoride).

2. Experimental Procedures

2.1 Preparation of Arylketones

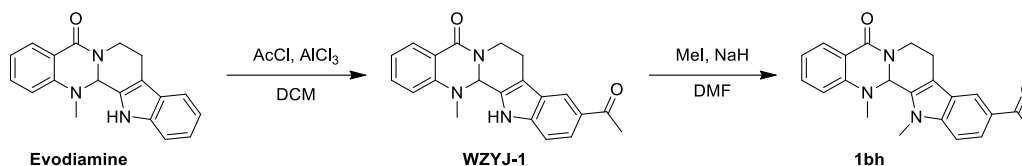
2.1.1 Preparation of 1-Arylbutan-1-one



To a 50 ml flask was added acid **A** (10 mmol), EDCI (15 mmol, 2.87 g), DIPEA (20 mmol, 2.58 g), and DCM 20 ml. The mixture was stirred for 10 min, and then N-methoxymethanamine hydrochloride (20 mmol, 1.95 g) was added. The solution was stirred at room temperature overnight. After the reaction completion, the mixture was washed with brine twice. The organic layers were dried by Na₂SO₄ and then filtered. The organic solvent was removed under vacuum to give the Weinreb amide **B** without further purification.

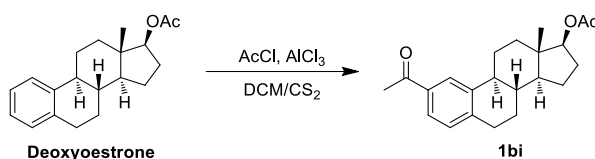
The Weinreb amide **B** was dissolved in 15 mL anhydrous THF. Then *n*-PrMgBr (6 mL, 2 M in THF) was added dropwise at 0 °C. Then the mixture was stirred at room temperature overnight. After the reaction completion, the mixture was quenched with water (20 mL) and the mixture was extracted with ethyl acetate. The organic layers were dried by Na₂SO₄ and then filtered. The organic solvent was removed under vacuum to give the crude product which was then purified by flash column chromatography on silica gel with a gradient eluent of hexane/ethyl acetate to give the ketone **1**.

2.1.2 Preparation of Arylethanone from Drug and Natural Product

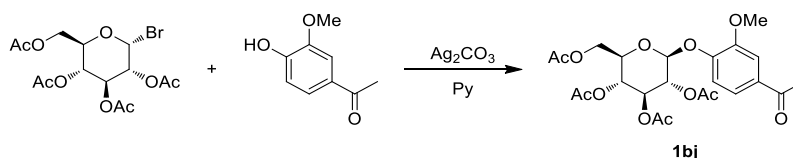


Anhydrous AlCl₃ (1.5 g, 11.25 mmol) was added to a solution of Evodiamine (0.9 g, 3 mmol) and AcCl (1.17 g, 15mmol) in DCM (20 mL) slowly. After stirring for 0.5 h at rt, the reaction mixture was poured into cold dil. HCl (2 M) and extracted with DCM. The organic phase was washed with H₂O and brine, dried with anhydrous Na₂SO₄. After evaporation of solvent, the crude product was obtained (640 mg, 62% yield) as a yellow solid without further purification. To a solution of **WZYJ-1** (345 mg) in dry DMF (5 mL) was added NaH (50 mg, 1.2 mmol), After stirring for 0.5 h at rt, MeI (170 mg, 1.2 mmol) was added slowly, and the mixture was stirred for another 2 h at rt. The reaction mixture was diluted with DCM, then washed with H₂O and brine, dried over Na₂SO₄. The solvent was removed under vacuum to give the crude product, which was recrystallized from EtOAc to give desired compound **1bh** (250 mg, 70% yield) as a yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.33 (d, *J* = 1.6 Hz, 1H), 7.96-7.91 (m, 1H), 7.86 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.56 (td, *J* = 7.8, 1.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.17 (s, 1H), 4.74-4.59 (m, 1H), 3.86 (s, 3H), 3.13-3.08 (m, 2H), 2.90-2.80 (m, 1H), 2.63 (s, 3H), 2.43 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 197.9, 164.1, 150.9, 140.3, 133.5, 129.5, 128.6, 125.1, 123.8, 122.5, 121.5, 114.5, 110.3, 67.6, 40.5, 40.3, 40.1, 30.8,

27.1, 20.3; HRMS-EI calcd for C₂₂H₂₁O₂N₃ [M]⁺, 359.1628; found 359.1628.



Anhydrous AlCl₃ (4 g, 30 mmol) was dissolved in CS₂ (30 mL) containing AcCl (6 mL, 84.4 mmol) by stirring for 10 min. To this solution was added a solution of deoxyoestrone (3 g, 10.1 mmol) in DCM (30 mL) over a period of 10 min and stirred for 1h at rt. The reaction mixture was poured into cold dil. HCl and extracted with DCM. The organic phase was washed with H₂O and brine, dried with anhydrous Na₂SO₄. After evaporation of solvent, the crude product obtained was recrystallized from MeOH to give desired compound **1bi** (2.63 g, 77% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 4.77-4.62 (m, 1H), 2.94-2.90 (m, 2H), 2.58 (s, 3H), 2.44-2.40 (m, 1H), 2.34-2.16 (m, 2H), 2.07 (s, 3H), 1.97-1.88 (m, 2H), 1.82-1.71 (m, 1H), 1.54-1.51 (m, 1H), 1.50-1.37 (m, 3H), 1.34-1.23 (m, 3H), 0.84 (s, 3H).¹



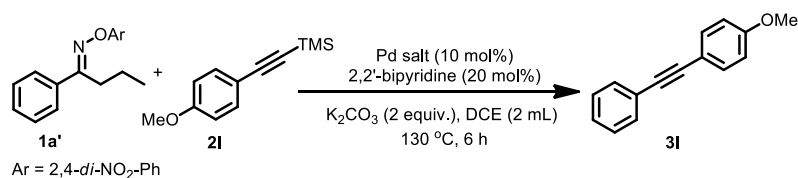
Ag₂CO₃ (5.5 g, 20 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide (4.7 g, 11.5 mmol) and acetovanillone (830 mg, 5 mmol) in Pyridine (20 mL). After stirring for 18h at rt in the dark. The reaction mixture was poured into cold dil. HCl and extracted with DCM. The organic phase was washed with H₂O and brine, dried with anhydrous Na₂SO₄. After evaporation of solvent, the crude product obtained was subjected to column chromatography for isolation (gradient eluent: petroleum ether/ethyl acetate 3:1-1:1) to give the desired product **1bj** (1.5 g, 61% yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.53 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 5.34-5.25 (m, 2H), 5.21-5.13 (m, 1H), 5.07 (d, *J* = 6.3 Hz, 1H), 4.26 (dd, *J* = 12.3, 5.0 Hz, 1H), 4.18 (dd, *J* = 12.4, 2.3 Hz, 1H), 3.87 (s, 3H), 3.84-3.79 (m, 1H), 2.56 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 6H).²

2.2 Preparation of Alkynylsilane

To a 100 mL flask was added $\text{Zn}(\text{OTf})_2$ (0.5 mmol, 0.18 g), dry CH_2Cl_2 (50 mL), NEt_3 (15 mmol, 2.09 mL), the alkyne (10 mmol), and TMSOTf (15 mmol, 2.7 mL). Then the reaction was stirred overnight and then quenched with saturated NH_4Cl . The mixture was extracted with ethyl ether and the combined organics were dried by Na_2SO_4 and then filtered. The organic solvent was removed under vacuum to give the crude product which was then purified by flash column chromatography on silica gel with a gradient eluent of hexane/ethyl acetate to give the alkynylsilane **2**.

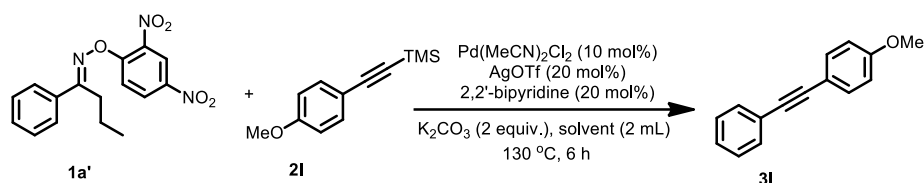
2.3 Reaction Optimization

Table S1. Screening of the palladium catalyst^a

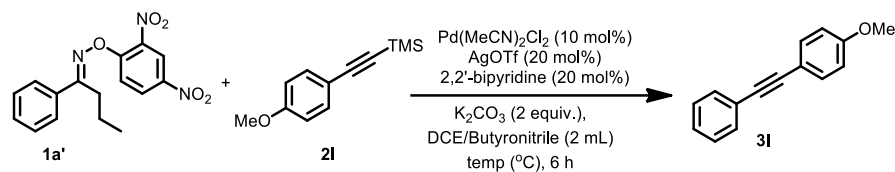


entry	Pd salt	Yield (%) ^b
1	$\text{Pd}(\text{dba})_2$	trace ^c
2	$\text{Pd}(\text{dba})_2$	14
3	$\text{Pd}(\text{dba})_2$	5 ^d
4	$\text{Pd}(\text{PPh}_3)_4$	19
5	$\text{Pd}(\text{OAc})_2$	15
6	$\text{Pd}(\text{MeCN})_2\text{Cl}_2$	15
7	$\text{Pd}(\text{TFA})_2$	23
8	$\text{Pd}(\text{MeCN})_2(\text{OTf})_2$	25
9	$\text{Pd}(\text{MeCN})_2\text{Cl}_2 + \text{AgOTf}$	30

^aReaction conditions: **1a'** (0.1 mmol), **2** (2 eq), Pd salt (10 mol%), K_2CO_3 (2.0 eq), 2,2'-bipyridine (20 mol%), DCE (2 mL), 130 °C, 6 h. ^bYield was determined by GC-MS using diphenylacetylene as internal standard. ^cNo ligand. ^dTerminal alkyne was used as the alkylation reagent.

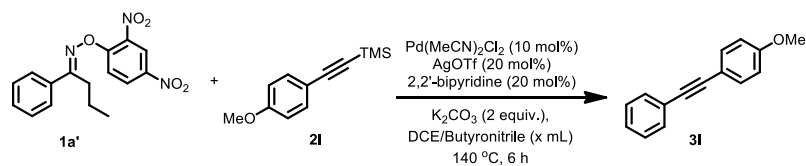
Table S2. Screening of the solvent^a

entry	sovent	Yield (%) ^b
1	THF	trace
2	dioxane	trace
3	DMSO	trace
4	toluene	trace
5	MeCN	11%
6	DMF	trace
7	Butyronitrile	9%
8	DCE	30%
9	DCE/MeCN (5/1)	32%
10	DCE/Butyronitrile (5/1)	35%
11	DCE/DMF(5/1)	25%

Table S3. Screening of the temperature^a

entry	temp (°C)	Yield (%) ^b
1	110	22
2	120	26
3	130	35
4	140	38

^aReaction conditions: **1a'** (0.1 mmol), **2I** (2 eq), Pd(MeCN)₂Cl₂(10 mol%), AgOTf (20 mol%), K₂CO₃ (2.0 eq), 2,2'-bipyridine (20 mol%), DCE/Butyronitrile (2 mL), temp (°C), 6 h. ^bYield was determined by GC-MS using diphenylacetylene as internal standard.

Table S4. Screening of the concentration^a

entry	DCE/Butyronitrile (x mL)	Yield (%) ^b
1	1	35
2	2	38
3	3	39
4	4	40
5	5	42

^aReaction conditions: **1a'** (0.1 mmol), **2I** (2 eq), Pd(MeCN)₂Cl₂(10 mol%), AgOTf (20 mol%), K₂CO₃ (2.0 eq), 2,2'-bipyridine (20 mol%), DCE/Butyronitrile (x mL), 140 (°C), 6 h. ^bYield was determined by GC-MS using diphenylacetylene as internal standard.

Table S5. Screening of the ligand loading^a

entry	2,2'-bipyridine (x mol%)	Yield (%) ^b
1	10	38
2	20	42
3	30	46
4	40	44

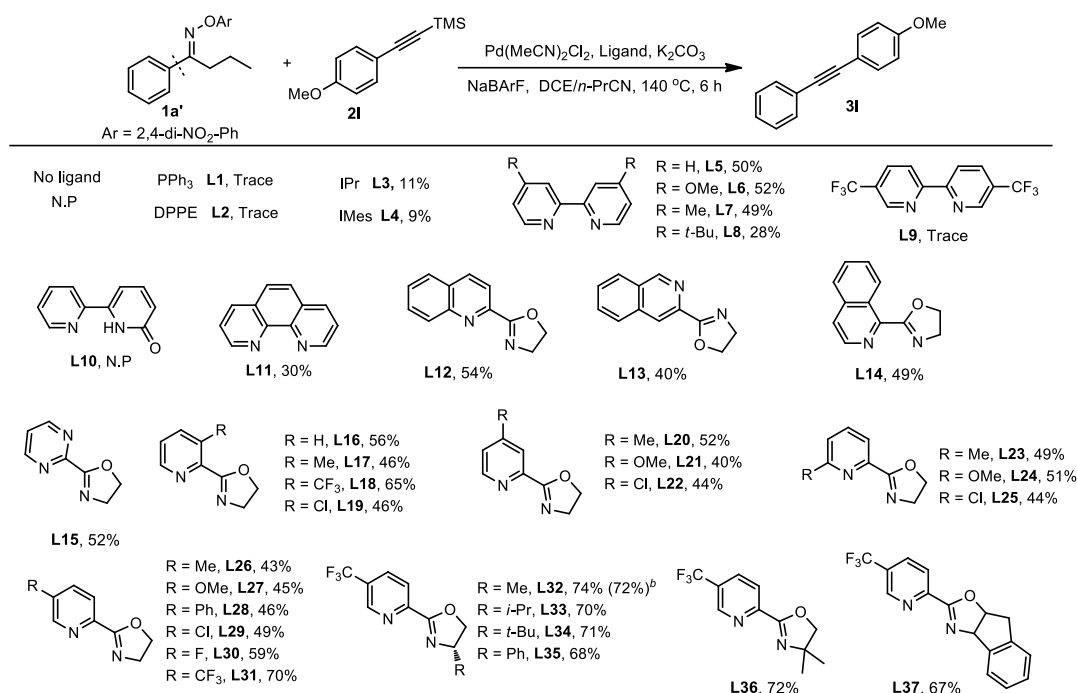
^aReaction conditions: **1a'** (0.1 mmol), **2I** (2 eq), Pd(MeCN)₂Cl₂ (10 mol%), AgOTf (20 mol%), K₂CO₃ (2.0 eq), 2,2'-bipyridine (x mol%), DCE/Butyronitrile (5 mL), 140 °C, 6 h. ^bYield was determined by GC-MS using diphenylacetylene as internal standard.

Table S6. Screening of the additives^a

entry	Additive (20 mol%)	Yield (%) ^b
1	AgBF ₄	41
2	AgSbF ₆	35
3	AgTFA	38
4	Ag ₃ PO ₄	47
5	Ag ₂ SO ₄	43
6	AgOTf	49
7	NaBAR _F	50

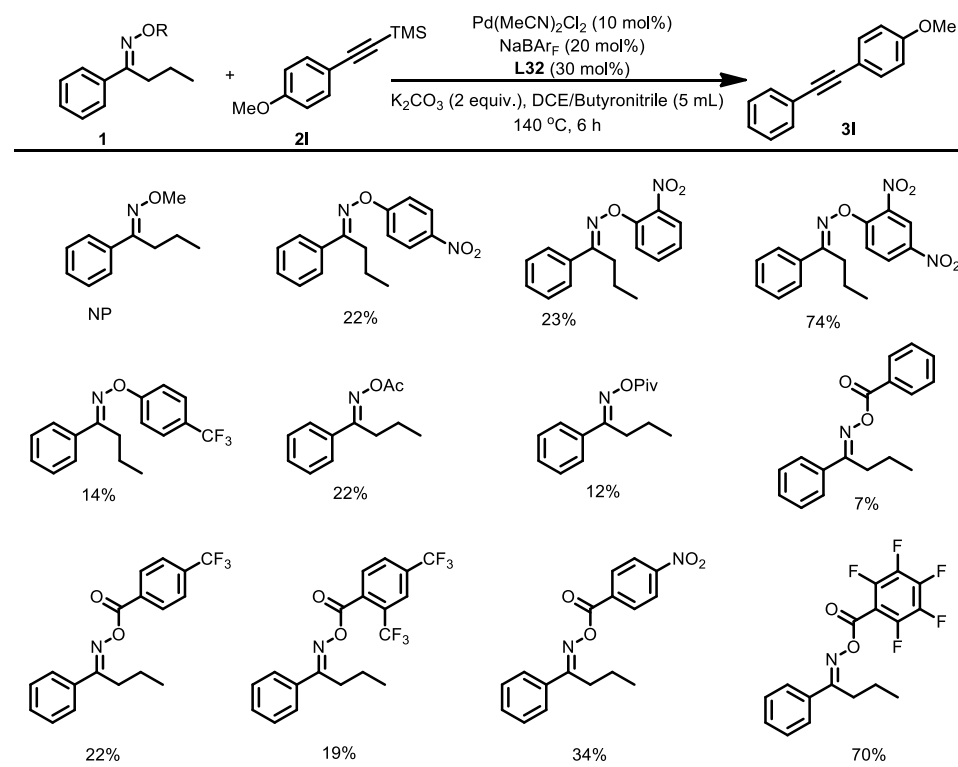
^aReaction conditions: **1a'** (0.1 mmol), **2I** (2 eq), Pd(MeCN)₂Cl₂ (10 mol%), Additive (20 mol%), K₂CO₃ (2.0 eq), 2,2'-bipyridine (30 mol%), DCE/Butyronitrile (5 mL), 140 °C, 6 h. ^bYield was determined by GC-MS using diphenylacetylene as internal standard.

Table S7. Ligand screening for the preparation of internal alkyne ^a



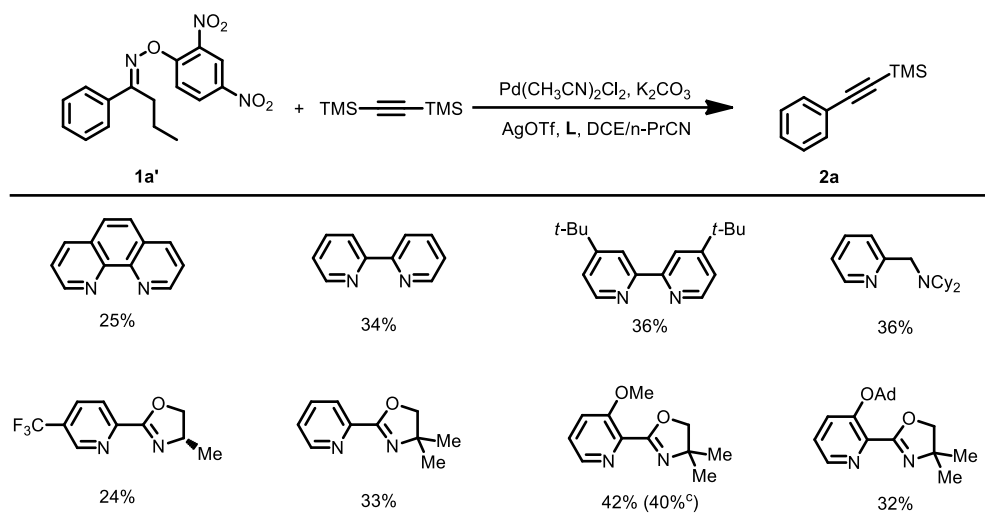
^aReaction conditions: **1a'** (0.1 mmol), **2I** (3 eq), Pd(MeCN)₂Cl₂ (10 mol%), K₂CO₃ (2.0 eq), ligand (0.3 eq), NaBAR_F (20 mol%), DCE/*n*-PrCN = 5/1 (5 mL), 140 °C, 6 h. Yield was determined by GC-MS using diphenylacetylene as internal standard. DPPE: 1,2-bis(diphenylphosphino)ethane. IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. ^bThe reaction was performed in one-pot fashion.

Table S8. Screening of various oxime esters and oxime ether ^a



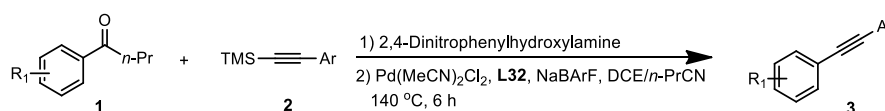
^aReaction conditions: **1a'** (0.1 mmol), **2I** (2 eq), Pd(MeCN)₂Cl₂ (10 mol%), Additive (20 mol%), K₂CO₃ (2.0 eq), **L32** (30 mol%), DCE/Butyronitrile (5 mL), 140 °C, 6 h. Yield was determined by GC-MS using diphenylacetylene as internal standard.

Table S9. Ligand screening for the preparation of terminal alkyne^a



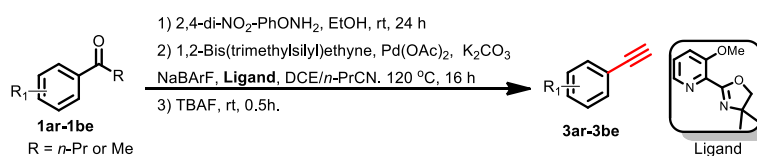
^aReaction conditions: **1a'** (0.1 mmol), Bis(trimethylsilyl)acetylene (5 eq), $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (0.1 eq), K_2CO_3 (2 eq), **L** (0.35 eq), NaBAR_4 (0.2 eq), DCE (5 mL), $n\text{-PrCN}$ (1 mL), N_2 , 130 °C, 16 h. ^bYield determined by GCMS analysis of crude reaction mixture. ^c isolated yield.

2.4. Typical Procedure for One-pot Alkylation of Arylketone



Ketone **1** (0.1 mmol), 2,4-*di*-NO₂-PhONH₂ (1.1 eq), hydrochloric acid in EtOH (2.0 mL) were added to a 15 mL sealed vials and stirred for 24 h. After completion, the solvent was evaporated to give the crude oxime ether. To the crude oxime ether were added alkynylsilane (3 eq), $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ (10 mol%, 2.6 mg), K_2CO_3 (2.0 eq, 27.6 mg), **L32** (0.3 eq, 6.9 mg), NaBAR_F (20 mol%, 17.7 mg) and $\text{DCE}/n\text{-PrCN} = 5/1$ (5 mL), then the reaction mixture was stirred at 140 °C for 6 h. After completion, the mixture and then filtered through Celite. The filtrate was evaporated to give the crude product which was then purified by flash column chromatography on silica gel with a gradient eluent of hexane/ethyl acetate to give the alkyne product **3**.

2.5. Typical Procedure for the Preparation of Terminal Alkylation

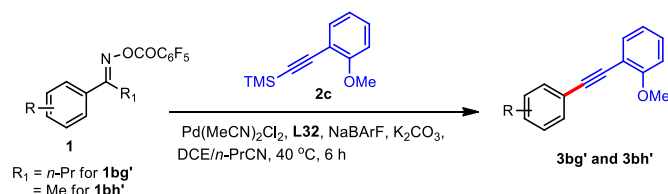


A solution of arylketone **1** (0.1 mmol) and 2,4-*di*-NO₂-PhONH₂ (21.9 mg, 0.11 mmol) in EtOH (containing 2% HCl) was stirred at rt for overnight. The reaction mixture

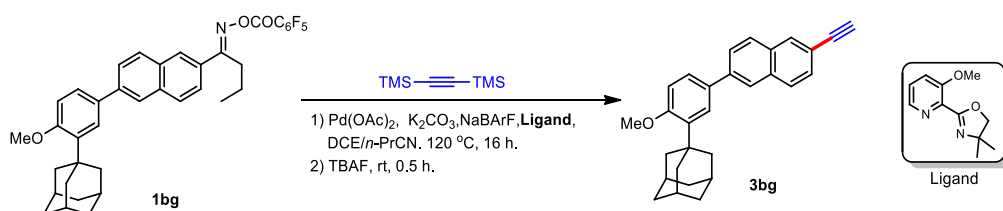
was concentrated under vacuum to give crude oxime ether without further purification. Under N₂ atmosphere, a mixture of oxime ether, 1,2-bis(trimethylsilyl)ethyne (85 mg, 0.5 mmol), Pd(OAc)₂ (2.3 mg, 10 mol%), ligand (7.2 mg, 35 mol%), NaBARF (17.7 mg, 20 mol%) and K₂CO₃ (27.6 mg, 0.2 mmol) in DCE (5 mL)/*n*-PrCN (1 mL) was stirred at 120 °C for 16 h. The reaction mixture was cooled down to rt, and then TBAF (1 mL, 1 M in THF) was added. After stirring at rt for 0.5 h, the reaction mixture was diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄. Solvent and other volatile components were removed on a rotary evaporator under reduced pressure, and the residue was subjected to column chromatography for isolation (gradient eluent: petroleum ether/ethyl acetate 20:1-3:1) to give product **3ar-3be**.

2.6 Procedure for the Diversification of Drug and Natural product.

2.6.1 Procedure for the Preparation of **3bg**, **3bg'**, and **3bh'**.



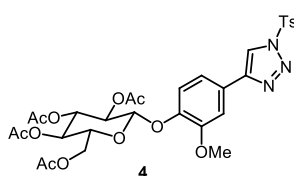
To the 25 mL tube were added **1bg'** or **1bh'** (0.1 mmol), alkyne **2c** (0.3 mmol, 61.2 mg), Pd(MeCN)₂Cl₂ (10 mol%, 2.6 mg), K₂CO₃ (2.0 eq, 27.6 mg), L32 (0.3 eq, 6.9 mg), NaBARF (20 mol%, 17.7 mg) and DCE/*n*-PrCN = 5/1 (5 mL), then the reaction mixture was stirred at 140 °C for 6 h. After completion, the mixture was then filtered through Celite. The filtrate was evaporated to give the crude product which was then purified by flash column chromatography on silica gel with a gradient eluent of hexane/ethyl acetate to give the alkyne product **3bg'** or **3bh'** in 64% and 52% yields, respectively.



Under N₂ atmosphere, a mixture consisting of oxime ester **1bg** (64.7 mg, 0.1 mmol), 1,2-bis(trimethylsilyl) ethyne (64.7 mg, 0.1 mmol), Pd(OAc)₂ (2.3 mg, 10 mol%),

ligand (7.2 mg, 35 mol%), NaBAR_F (17.7 mg, 20 mol%) and K₂CO₃ (27.6 mg, 0.2 mmol) in DCE (5 mL)/*n*-PrCN (1 mL) was stirred at 120 °C for 16 h. The reaction mixture was cooled down to room temperature, and then TBAF (1 mL, 1 M in THF) was added. After stirring at rt for 0.5 h, the reaction mixture was diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄. Solvent and other volatile components were removed on a rotary evaporator under reduced pressure, and the residue was subjected to column chromatography to give product **3bg** (20.0 mg, 51%).

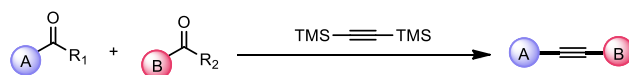
2.6.2 Click Reaction for the Preparation of **4**



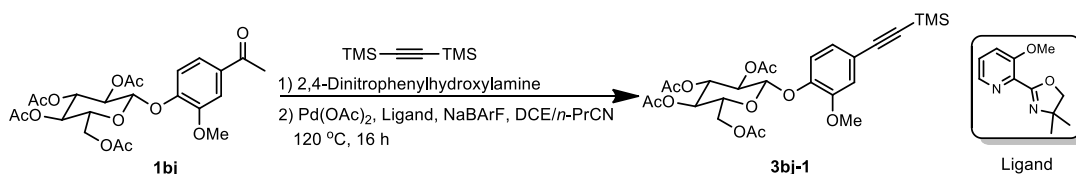
Under N₂ atmosphere, a mixture consisting of **3bj** (23.9 mg, 0.05 mmol), CuTC (1.0 mg, 0.005 mmol), and TsN₃ (19.7 mg, 0.1 mmol) in toluene (1 mL) was stirred at rt for 6 h.

The reaction mixture concentrated under reduced pressure, and the residue was subjected to column chromatography for isolation (gradient eluent: petroleum ether/ethyl acetate 1:1) to give the desired product **4** (31.4 mg, 93% yield) as a white solid.

2.6.3 Sequential Alkylation of Two Different Drugs/Natural products for the Preparation of **5a** and **5b**

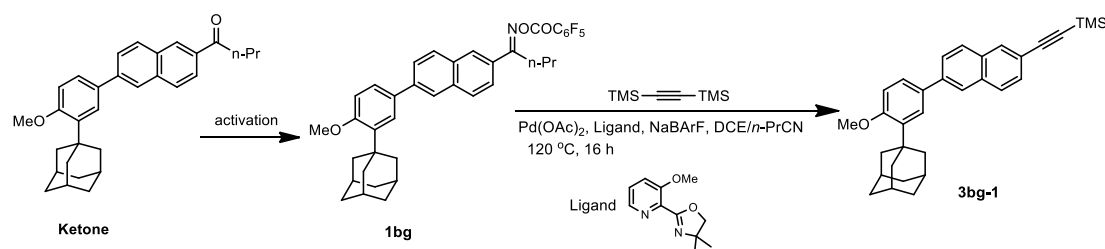


Step 1 : The preparation of alkyne from arylketone



Ketone **1bj** (0.1 mmol, 49.6 mg), 2,4-di-NO₂-PhONH₂ (1.1 eq, 21.9 mg), 2% hydrochloric acid in EtOH (2.5 mL) were added to a 15 mL sealed vials and stirred for 24 hours. After completion, the solvent was evaporated to give the crude product. To the crude product were added bis(trimethylsilyl)acetylene (85 mg, 0.5 mmol), Pd(OAc)₂ (10 mol%, 2.3 mg), K₂CO₃ (27.6 mg, 2.0 eq), ligand (7.2 mg, 35 mol%),

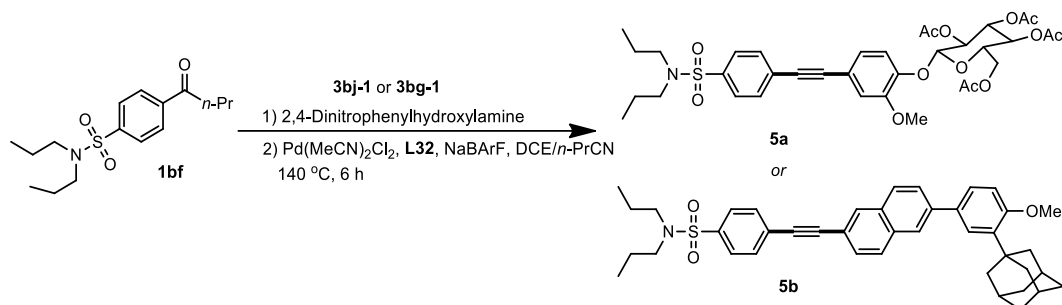
NaBARF (17.7 mg, 20 mol%) and DCE/n-PrCN = 5/1 (6 mL), then the reaction mixture was stirred at 120 °C for 16 h. After completion, the mixture and then filtered through Celite. The filtrate was evaporated to give the crude product which was then purified by flash column chromatography on silica gel with a gradient eluent of hexane/ethyl acetate or hexane/acetone to give the alkyne product **3bj-1** (30.8 mg, 56% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.03-7.00 (m, 2H), 6.99-6.97 (m, 1H), 5.34-5.22 (m, 2H), 5.19-5.11 (m, 1H), 4.99-4.92 (m, 1H), 4.26 (dd, *J* = 12.3, 5.2 Hz, 1H), 4.15 (dd, *J* = 12.3, 2.5 Hz, 1H), 3.81 (s, 3H), 3.77 (ddd, *J* = 10.0, 5.2, 2.5 Hz, 1H), 2.07 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H), 0.24 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 170.3, 169.4, 169.3, 150.1, 146.5, 124.9, 119.5, 115.9, 104.5, 100.5, 93.6, 72.5, 72.1, 71.1, 68.3, 61.9, 56.0, 20.6, -0.1; HRMS-ESI calcd for HRMS-ESI calcd for C₂₆H₃₄NaO₁₁Si [M+H]⁺, 573.1763; found 573.1773.



To 25 mL tube were added oxime ester **1bg** (0.1 mmol, 64.7 mg), bis(trimethylsilyl)acetylene (85 mg, 0.5 mmol), Pd(OAc)₂ (10 mol%, 2.3 mg), K₂CO₃ (27.6 mg, 2.0 eq), ligand (7.2 mg, 35 mol%), NaBARF (17.7 mg, 20 mol%) and DCE/n-PrCN = 5/1 (6 mL), then the reaction mixture was stirred at 120 °C for 16 h. After completion, the mixture and then filtered through Celite. The filtrate was evaporated to give the crude product which was then purified by flash column chromatography on silica gel with a gradient eluent of hexane/ethyl acetate or hexane/acetone to give the alkyne product **3bg-1** (26.0 mg, 56% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 7.94 (s, 1H), 7.81 (t, *J* = 8.0 Hz, 2H), 7.73 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.19 (d, *J* = 2.8 Hz, 6H), 2.11 (s, 3H), 1.81 (d, *J* = 3.0 Hz, 6H), 0.30 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 158.7, 139.9, 138.9, 133.3, 132.8, 131.8, 131.6, 128.9, 128.1, 128.0, 126.3, 125.9, 125.6, 124.8, 119.9, 112.1, 105.6, 94.5, 55.2, 40.6, 37.2, 37.1, 29.1, 0.0; HRMS-EI calcd for C₃₂H₃₆OSi [M]⁺, 464.2530; found

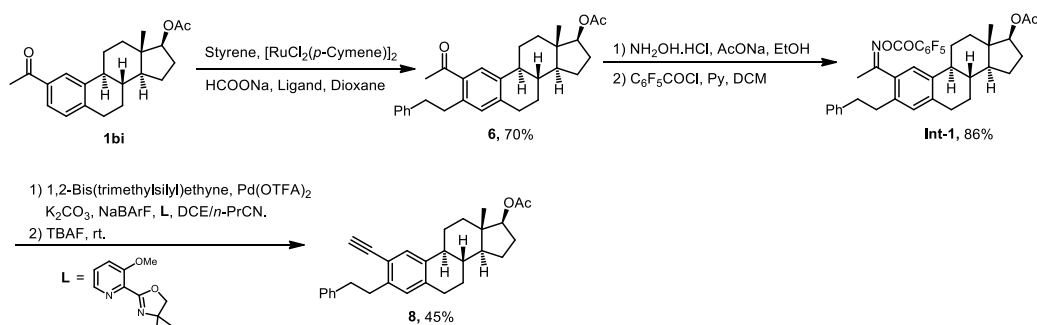
464.2522.

Step 2: Connection of two different drugs/natural products via a second alkylation



Ketone **1bf** (0.1 mmol, 31.1 mg), 2,4-di-NO₂-PhONH₂ (1.1 eq, 21.9 mg), 0.5% hydrochloric acid in EtOH (2.5 mL) were added to a 15 mL sealed vials and stirred for 24 hours. After the reaction completion, the solvent was evaporated to give the crude product. To the crude product were added **3bj-1** or **3bg-1** (3 eq), Pd(MeCN)₂Cl₂ (10 mol%, 2.59 mg), K₂CO₃ (2.0 eq, 27.6 mg), **L32** (0.3 eq, 6.9 mg), NaBARF (20 mol%, 17.7 mg) and DCE/*n*-PrCN = 5/1 (6 mL), then the reaction mixture was stirred at 140 °C for 6 h. After completion, the mixture was then filtered through Celite. The filtrate was evaporated to give the crude product which was then purified by flash column chromatography on silica gel with a gradient eluent of hexane/ethyl acetate or hexane/acetone to give the alkyne product **5a** and **5b** in 63% and 48% yields, respectively.

2.6.4 Procedure for the Bifunctionalization of Deoxyoestrone by Merging C-H/C-C Activation



A solution of arylketone **1bi** (34.0 mg, 0.1 mmol), [RuCl₂(*p*-cymene)]₂ (6.1 mg, 0.01 mmol), styrene (52 mg, 0.5 mmol), HCO₂Na (6.8 mg, 0.1 mmol) and P(4-CF₃Ph)₃ (23.0 mg, 0.05 mmol) in dioxane (1 mL) was stirred at 110 °C for 12 h. The reaction mixture was concentrated under vacuum, and the residue was subjected to column

chromatography for isolation (gradient eluent: petroleum ether/ethyl acetate 20:1) to give product **6** (31.1 mg, 70% yield) as white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.64 (s, 1H), 7.31-7.27 (m, 4H), 7.20-1.17 (m, 1H), 6.96 (s, 1H), 4.71 (dd, *J* = 9.2, 7.7 Hz, 1H), 3.11-3.07 (m, 2H), 2.93-2.80 (m, 4H), 2.55 (s, 3H), 2.38-2.32 (m, 1H), 2.29-2.20 (m, 2H), 2.07 (s, 3H), 1.95-1.90 (m, 2H), 1.80-1.74 (m, 1H), 1.59-1.51 (m, 2H), 1.51-1.41 (m, 3H), 1.40-1.35 (m, 1H), 1.34-1.25 (m, 2H), 0.85 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 201.5, 171.2, 142.3, 140.9, 139.5, 137.9, 135.0, 132.1, 128.6, 128.3, 127.0, 125.8, 82.6, 49.8, 43.8, 42.8, 38.3, 36.8, 36.3, 29.5, 29.4, 27.5, 26.9, 26.0, 23.2, 21.2, 12.1; HRMS-EI calcd for C₃₀H₃₆O₃ [M]⁺, 444.2659; found 444.2662.

To a mixture of hydroxylamine hydrochloride (278 mg, 4 mmol), NaOAc (320 mg, 4 mmol), EtOH (10 mL) was added arylketone **6** (0.5 mmol), and the mixture was stirred at 60 °C for 5 h. The reaction mixture was cooled down to room temperature, and then EtOH was removed under reduced pressure. The resulting mixture was extracted with EtOAc. The organic layer was then washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum to give oxime without further purification. To a mixture of oxime (0.5 mmol) and DCM (10 mL) was slowly added pentafluorobenzoyl chloride (140 mg, 0.6 mmol), pyridine (55 mg, 0.7 mmol) at 0 °C. After a special time, aq. HCl (1 M) was added to the above solution, and the aqueous phase was discarded. The organic portion was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was isolated by column chromatography (petroleum ether/ethyl acetate 20:1) to give product **Int-1** (281 mg, 86% yield) as white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.26 (m, 2H), 7.22-7.16 (m, 4H), 7.02 (s, 1H), 4.70 (dd, *J* = 9.1, 7.8 Hz, 1H), 2.99-2.84 (m, 6H), 2.30 (s, 3H), 2.27-2.19 (m, 2H), 2.07 (s, 3H), 1.95-1.89 (m, 2H), 1.80-1.73 (m, 1H), 1.61-1.49 (m, 2H), 1.48-1.36 (m, 4H), 1.35-1.23 (m, 2H), 0.84 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 171.2, 167.8, 156.5, 146.4 (m), 144.4 (m), 141.76, 138.8(m), 138.6, 138.4, 136.8, 131.8, 130.7, 128.5, 128.3, 125.9, 125.3, 82.6, 49.8, 43.9, 42.8, 38.2, 36.8, 35.3, 29.2, 27.5, 27.0, 25.9, 23.2, 21.2, 18.9, 12.0. HRMS-EI calcd for C₃₇H₃₆O₄NF₅ [M]⁺, 653.2559; found 653.2566.

Under N₂ atmosphere, a mixture consisting of **Int-1** (32.7 mg, 0.05 mmol), 1,2-bis(trimethylsilyl)ethyne (42.5 mg, 0.25 mmol), Pd(OTFA)₂ (1.7 mg, 10 mol%), ligand (3.6 mg, 35 mol%), NaBARF (8.9 mg, 20 mol%) and K₂CO₃ (14 mg, 0.2 mmol) in DCE (2.5 mL)/*n*-PrCN (0.5 mL) was stirred at 120 °C for 16 h. The reaction mixture was cooled down to rt, and then TBAF (0.5 mL, 1 M in THF) was added. After stirring at rt for 0.5 h, the reaction mixture was diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄. Solvent and other volatile components were removed on a rotary evaporator under reduced pressure, and the residue was subjected to column chromatography for isolation (gradient eluent: petroleum ether/ethyl acetate 20:1-3:1) to give product **8** (9.6 mg, 45% yield) as white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.43 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 6.6 Hz, 2H), 7.23-7.18 (m, 1H), 6.91 (s, 1H), 4.69 (dd, *J* = 9.2, 7.8 Hz, 1H), 3.23 (s, 1H), 3.05-2.96 (m, 2H), 2.94-2.88 (m, 2H), 2.84-2.82 (m, 2H), 2.34-2.29 (m, 1H), 2.25-2.15 (m, 2H), 2.06 (s, 3H), 1.95-1.85 (m, 2H), 1.78-1.72 (m, 1H), 1.56-1.47 (m, 2H), 1.47-1.36 (m, 2H), 1.35-1.22 (m, 3H), 0.83 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.2, 142.1, 141.4, 138.1, 137.9, 130.0, 129.4, 128.4, 128.3, 125.9, 118.6, 82.8, 82.6, 79.6, 49.8, 43.8, 42.8, 38.2, 37.1, 36.8, 36.4, 29.4, 27.5, 27.1, 25.9, 23.2, 21.2, 12.0; HRMS-EI calcd for C₃₀H₃₄O₂ [M]⁺, 426.2553; found 426.2564.

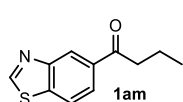
3 Analytical Data

3.1 Characterization of Starting Material

3.1.1 Characterization of ketone substrates

Ketone substrates **1a-1al**, **1aq-1av**, **1ax-1ay**, **1ba-1bc**, **1be** are all known products.³⁻¹⁰

These ketones were commercially available or readily prepared according to the general procedure in section 2.1.



1-(Benzo[d]thiazol-5-yl)butan-1-one (1am) ¹H NMR (500 MHz,

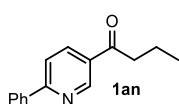
CDCl₃) δ 9.08 (s, 1H), 8.72 (dd, *J* = 1.6, 0.6 Hz, 1H), 8.09 (dd, *J* =

8.5, 1.6 Hz, 1H), 8.04 (dd, *J* = 8.5, 0.7 Hz, 1H), 3.06 (t, *J* = 7.3 Hz, 2H), 1.83 (h, *J* =

7.4 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 199.8, 155.3,

153.2, 138.3, 135.6, 124.7, 123.8, 122.1, 40.7, 17.9, 13.9. HRMS-EI calcd for

C₁₁H₁₁NOS [M]⁺, 205.0556; found 205.0556.



1-(6-phenylpyridin-3-yl)butan-1-one (1an) ¹H NMR (500 MHz,

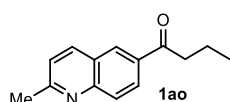
CDCl₃) δ 9.24 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.30 (dd, *J* = 8.3, 2.3 Hz, 1H),

8.09-8.03 (m, 2H), 7.84 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.56-7.42 (m, 3H), 2.99 (t, *J* = 7.3

Hz, 2H), 1.82 (h, *J* = 7.4 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (125 MHz,

CDCl₃) δ 198.9, 160.7, 149.8, 138.2, 136.3, 130.5, 130.0, 128.9, 127.3, 120.2, 40.8,

17.6, 13.8. HRMS-EI calcd for C₁₅H₁₅NO [M]⁺, 225.1148; found 225.1147.



1-(2-Methylquinolin-6-yl)butan-1-one (1ao) ¹H NMR (500

MHz, CDCl₃) δ 8.40 (d, *J* = 2.0 Hz, 1H), 8.23 (dt, *J* = 8.5, 1.5

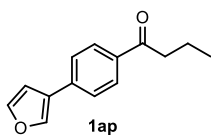
Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.35 (dd, *J* = 8.5, 1.0 Hz,

1H), 3.09-3.05 (m, 2H), 2.77 (d, *J* = 1.0 Hz, 3H), 1.83 (q, *J* = 7.5 Hz, 2H), 1.04 (td, *J*

= 7.5, 1.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 199.8, 161.6, 149.8, 137.5, 134.1,

129.1, 129.0, 127.8, 125.7, 122.9, 40.7, 25.6, 17.8, 13.9. HRMS-EI calcd for

C₁₄H₁₅NO [M]⁺, 213.1148; found 213.1149.



1-(4-(Furan-3-yl)phenyl)butan-1-one (1ap) ¹H NMR (500 MHz,

CDCl₃) δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.82 (dd, *J* = 1.5, 1.0 Hz, 1H),

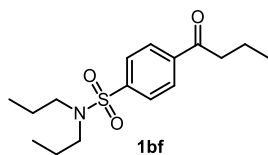
7.57 (d, *J* = 8.5 Hz, 2H), 7.51 (t, *J* = 1.5 Hz, 1H), 6.75 (dd, *J*

= 2.0, 1.0 Hz, 1H), 2.98-2.91 (m, 2H), 1.79 (q, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 199.8, 144.1, 139.6, 137.0, 135.6, 128.8, 125.8, 125.7,

108.6, 40.5, 17.9, 13.9. HRMS-EI calcd for C₁₄H₁₄O₂ [M]⁺, 214.0988; found

214.0988.



4-butyl-N,N-dipropylbenzenesulfonamide (1bf) ¹H NMR

(500 MHz, CDCl₃) δ 8.08 – 8.03 (m, 2H), 7.91-7.87 (m, 2H),

3.15-3.04 (m, 4H), 2.97 (t, *J* = 7.2 Hz, 2H), 1.78 (h, *J* = 7.4 Hz,

2H), 1.59-1.51 (m, 4H), 1.01 (td, *J* = 7.4, 0.6 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 6H). ¹³C

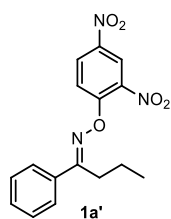
NMR (125 MHz, CDCl₃) δ 199.2, 144.0, 139.7, 128.6, 127.2, 49.9, 40.8, 21.95, 17.5,

13.8, 11.1. HRMS-EI calcd for C₁₆H₂₅NO₃S [M]⁺, 311.1550; found 311.1552.

3.1.2 Characterization of oxime ether and oxime ester

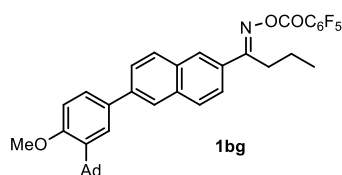
Oxime ester and oxime ether substrates were synthesized according to the

literature.^{11,12}



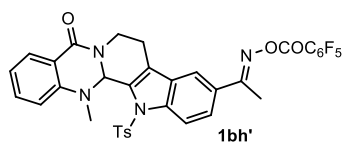
(E)-1-Phenylbutan-1-one O-(2,4-dinitrophenyl) oxime (1a') ¹H NMR (500 MHz, CDCl₃) δ 8.93 (d, *J* = 2.5 Hz, 1H), 8.45 (dd, *J* = 9.5, 3.0 Hz, 1H), 8.08 (d, *J* = 9.5 Hz, 1H), 7.78-7.73 (m, 2H), 7.54-7.44 (m, 3H), 3.08-2.99 (m, 2H), 1.76-1.65 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 167.4, 157.6, 140.7, 136.0, 133.3, 131.0, 129.5, 128.9, 127.2, 122.1, 117.3, 30.5, 20.4, 14.2. HRMS-EI calcd for C₁₆H₁₅O₅N₃ [M]⁺ 329.1006; found 329.1035.



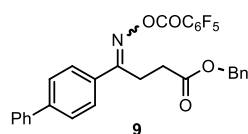
(E)-1-(6-(3-((3*r*,5*r*,7*r*)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)butan-1-one O-perfluoro benzoyl oxime (1bg): 1bg is known compound and synthesized

according to the literature.¹¹



(E)-14-methyl-10-(1-(((perfluorobenzoyl)oxy)imino)ethyl)-13-tosyl-7,8,13*b*,14-tetrahydroindolo[2',3':3,4]pyridof[2,1-*b*]quinazolin-5(13*H*)-one (1bh') ¹H NMR (500

MHz, CDCl₃) δ 8.37 (d, *J* = 8.5 Hz, 1H), 8.11 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 7.91-7.85 (m, 3H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.35 (s, 1H), 4.89 (ddd, *J* = 12.5, 5.0, 1.5 Hz, 1H), 3.16-3.09 (m, 1H), 3.05-2.97 (m, 1H), 2.85-2.75 (m, 1H), 2.55 (s, 3H), 2.42 (s, 3H), 2.11 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 165.0, 164.4, 156.4, 150.7, 145.6, 138.9, 135.6, 133.2, 130.4, 129.9, 129.7, 129.0, 128.2, 127.10, 124.90, 123.8, 123.5, 123.1, 120.9, 118.7, 115.4, 67.7, 38.3, 35.4, 21.7, 20.9, 15.3. HRMS-EI calcd for C₃₅H₂₅F₅N₄O₅S [M]⁺ 708.1453; found 708.1460.



Benzyl 4-([1,1'-biphenyl]-4-yl)-4-(((perfluorobenzoyl)oxy)imino)butanoate (9) ¹H NMR (500 MHz, CDCl₃) δ 7.85-7.81 (m, 2H), 7.69-7.64 (m, 2H), 7.61 (dt, *J* = 8.0, 1.5 Hz, 2H),

7.49-7.44 (m, 2H), 7.40-7.37 (m, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.27 (dd, *J* = 8.5, 7.0 Hz, 2H), 2.68 (dd, *J* = 8.5, 7.0 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 171.4,

166.7, 156.4(m), 144.2(m), 139.9(m), 135.5(m), 131.1, 130.4, 129.0, 128.6, 128.4, 124.90, 128.3, 128.1, 128.0, 127.6, 127.2, 127.1, 66.9, 31.0, 23.9. HRMS-EI calcd for $C_{30}H_{20}F_5NO_4$ $[M]^+$ 553.1307; found 553.1313.

3.1.3 Characterization of alkynylsilane substrates

Alkynylsilane substrates **2a-2q**, **2ah**, **2ai** are all known products.¹³⁻¹⁹ These alkynylsilanes were commercially available or readily prepared according to the general procedure in section 2.2.

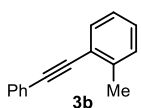
3.2 Characterization of Product



1,2-diphenylethyne (3a)²⁰, 12.1 mg, 68% yield; 0.25% hydrochloric acid

in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ :

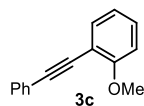
7.57-7.52 (m, 4H), 7.38-7.34 (m, 6H).



1-methyl-2-(phenylethynyl)benzene (3b)²⁰, 13.4 mg, 70% yield; 0.25%

hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz,

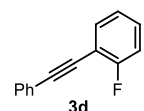
CDCl₃) δ 7.59-7.57 (m, 2H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.40-7.38 (m, 3H), 7.29-7.27 (m, 2H), 7.23-7.19 (m, 1H), 2.56 (s, 3H).



1-Methoxy-2-(phenylethynyl)benzene (3c)²¹, 15.4 mg, 74% yield; 0.25%

hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz,

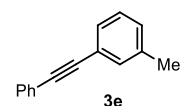
CDCl₃) δ : 7.57 (dd, $J = 7.5, 1.5$ Hz, 2H), 7.51 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.36-7.30 (m, 4H), 6.95 (t, $J = 7.5$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 1H), 3.92 (s, 3H).



1-Fluoro-2-(phenylethynyl)benzene (3d)²⁰, 12.7 mg, 65% yield; 0.25%

hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz,

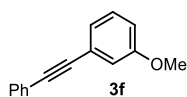
CDCl₃) δ 7.59-7.56 (m, 2H), 7.53 (td, $J = 7.5, 2.0$ Hz, 1H), 7.39-7.35 (m, 3H), 7.34-7.30 (m, 1H), 7.15-7.09 (m, 2H).



1-Methyl-3-(phenylethynyl)benzene (3e)²⁰, 13.1 mg, 68% yield; 0.25%

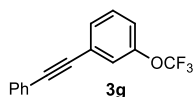
hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500

MHz, CDCl₃) δ : 7.56-7.54 (m, 2H), 7.39-7.32 (m, 5H), 7.25 (t, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H), 2.37 (s, 3H).



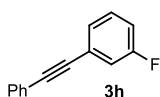
1-Methoxy-3-(phenylethynyl)benzene (3f)²¹, 12.9 mg, 62% yield;

0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ: 7.56-7.52 (m, 2H), 7.38-7.34 (m, 3H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.08-7.06 (m, 1H), 6.91 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H), 3.83 (s, 3H).



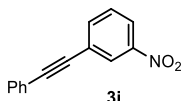
1-(Phenylethynyl)-3-(trifluoromethoxy)benzene (3g)²², 14.7 mg, 56%

yield; 0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ: 7.58-7.52 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.41-7.33 (m, 5H), 7.22-7.17 (m, 1H).



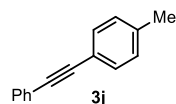
1-Fluoro-3-(phenylethynyl)benzene (3h)²³, 12.9 mg, 66% yield; 0.25%

hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ: 7.55-7.52 (m, 2H), 7.38-7.35 (m, 3H), 7.33-7.31 (m, 2H), 7.24 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.08-7.03 (m, 1H).



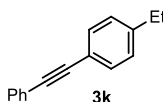
1-Nitro-3-(phenylethynyl)benzene (3i)²⁰, 11.4 mg, 51% yield; 0.25%

hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ: 8.38 (t, *J* = 2.0 Hz, 1H), 8.18 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 7.83 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.57-7.52 (m, 3H), 7.40-7.37 (m, 3H);



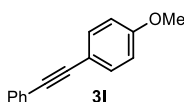
1-Methyl-4-(phenylethynyl)benzene (3j)²⁰, 13.8 mg, 72% yield; 0.25%

hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ: 7.54-7.52 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.37-7.32 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H).



1-Ethyl-4-(phenylethynyl)benzene (3k)²⁴, 14.4 mg, 70% yield; 0.25%

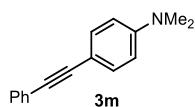
hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ: 7.57-7.55 (m, 2H), 7.50-7.48 (m, 2H), 7.39-7.36 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 2.70 (q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H).



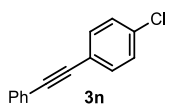
1-Methoxy-4-(phenylethynyl)benzene (3l)²⁰, 14.8 mg, 71% yield;

0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ: 7.53-7.51 (m, 2H), 7.48 (dt, *J* = 9.0, 2.5 Hz, 2H), 7.36-7.30 (m,

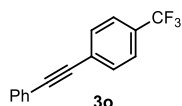
3H), 6.88 (dt, $J = 9.0, 2.5$ Hz, 2H), 3.83 (s, 3H).



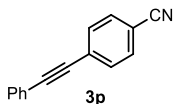
***N,N*-dimethyl-4-(phenylethynyl)aniline (3m)**²⁵, 12.2 mg, 55% yield; 0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ : 7.51-7.49 (m, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.34-7.26 (m, 3H), 6.67 (d, $J = 8.5$ Hz, 2H), 2.99 (s, 6H).



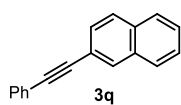
1-Chloro-4-(phenylethynyl)benzene (3n)²⁰, 15.1 mg, 71% yield; 0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ : 7.55-7.51 (m, 2H), 7.47 (dt, $J = 9.0, 2.0$ Hz, 2H), 7.38-7.35 (m, 3H), 7.33 (dt, $J = 9.0, 2.0$ Hz, 2H).



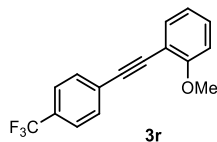
1-(Phenylethynyl)-4-(trifluoromethyl)benzene (3o)²⁰, 17.2 mg, 70% yield; 0.25% hydrochloric acid in EtOH was used in the reaction; 0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ : 7.64 (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 8.5$ Hz, 2H), 7.57-7.54 (m, 2H), 7.39-7.36 (m, 3H).



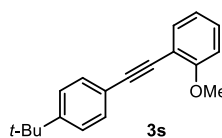
4-(Phenylethynyl)benzonitrile (3p)²⁰, 13.0 mg, 64% yield; 0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ : 7.67 (dt, $J = 9.0, 2.5$ Hz, 2H), 7.64 (dt, $J = 9.0, 2.5$ Hz, 2H), 7.59-7.57 (m, 2H), 7.43-7.40 (m, 3H).



2-(Phenylethynyl)naphthalene (3q)²³, 13.2 mg, 58% yield; 0.25% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ : 8.08 (s, 1H), 7.85-7.82 (m, 3H), 7.61-7.59 (m, 3H), 7.53-7.49 (m, 2H), 7.41-7.36 (m, 3H).

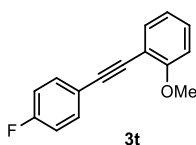


1-methoxy-2-((4-(trifluoromethyl)phenyl)ethynyl)benzene (3r)²⁶, 19.3 mg, 70% yield; 5% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, $J = 8.0$ Hz, 2H), 7.59 (d, $J = 8.0$ Hz, 2H), 7.51 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.34 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H), 6.98-6.90 (m, 2H), 3.92 (s, 3H).



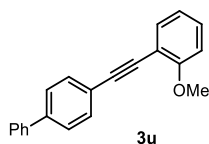
1-((4-(tert-butyl)phenyl)ethynyl)-2-methoxybenzene (3s)²⁷, 13.7

mg, 52% yield; 2% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (400 MHz, CDCl₃) δ 7.55-7.47 (m, 3H), 7.41-7.35 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.32 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.02-6.90 (m, 2H), 3.94 (s, 3H), 1.35 (s, 9H).



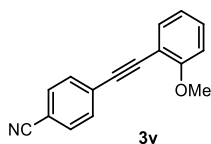
1-((4-fluorophenyl)ethynyl)-2-methoxybenzene (3t)²⁷, 9.0 mg, 40%

yield; 2% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ 7.55-7.51 (m, 2H), 7.48 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31 (ddd, *J* = 8.5, 7.5, 2.0 Hz, 1H), 7.06-7.00 (m, 2H), 6.94 (td, *J* = 7.5, 1.0 Hz, 1H), 6.90 (dd, *J* = 8.5, 1.0 Hz, 1H), 3.91 (s, 3H).



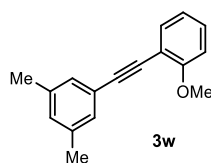
4-((2-methoxyphenyl)ethynyl)-1,1'-biphenyl (3u)²⁷, 20.4 mg, 72%

yield; ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.56 (m, 6H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.44 (td, *J* = 8.0, 1.6 Hz, 2H), 7.39-7.29 (m, 2H), 6.98-6.89 (m, 2H), 3.93 (s, 3H).



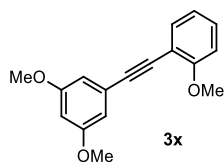
4-((2-methoxyphenyl)ethynyl)benzonitrile (3v)²⁸, 12.8 mg, 55%

yield; 2% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (500 MHz, CDCl₃) δ 7.62 (s, 4H), 7.49 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.5, 2.0 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.92 (dd, *J* = 8.5, 1.0 Hz, 1H), 3.92 (s, 3H).

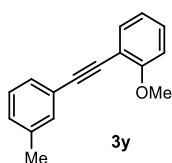


1-((2-Methoxyphenyl)ethynyl)-3,5-dimethylbenzene (3w), 14.6

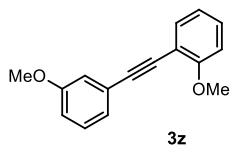
mg, 62% yield; 2% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1H), 7.21-7.18 (m, 2H), 6.96-6.87 (m, 3H), 3.91 (s, 3H), 2.30 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 159.9, 137.8, 133.6, 130.1, 129.6, 129.4, 123.2, 120.5, 112.7, 110.7, 93.8, 85.0, 55.9, 21.2. HRMS-EI calcd for C₁₇H₁₆O [M]⁺, 236.1196; found 236.1197.



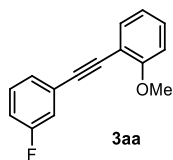
1,3-Dimethoxy-5-((2-methoxyphenyl)ethynyl)benzene (3x), 16.1 mg, 60% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.31 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H), 6.94 (td, $J = 7.6, 0.8$ Hz, 1H), 6.90 (dd, $J = 8.4, 0.8$ Hz, 1H), 6.72 (d, $J = 2.0$ Hz, 2H), 6.45 (t, $J = 2.4$ Hz, 1H), 3.92 (s, 3H), 3.80 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.5, 156.0, 133.7, 129.9, 124.8, 120.5, 112.3, 110.7, 109.4, 101.8, 93.4, 85.3, 55.9, 55.5. **HRMS**: (ESI-TOF) m/z calcd for $\text{C}_{17}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 269.1172, found: 269.1180.



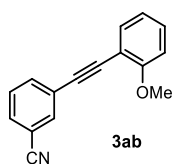
1-methoxy-2-(m-tolyethynyl)benzene (3y)²⁷, 14.2 mg, 64% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (400 MHz, CDCl_3) δ : δ 7.49 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.39 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.30 (ddd, $J = 8.4, 7.5, 1.6$ Hz, 1H), 7.22 (t, $J = 8.0$, Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.94 (td, $J = 8.0, 0.8$ Hz, 1H), 6.90 (d, $J = 8.0$ Hz, 1H), 3.91 (s, 3H), 3.35 (s, 3H).



1-Methoxy-2-((3-methoxyphenyl)ethynyl)benzene (3z)²⁷, 17.1 mg, 72% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (500 MHz, CDCl_3) δ 7.50 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.31 (ddd, $J = 8.5, 7.5, 1.5$ Hz, 1H), 7.24 (t, $J = 8.0$, Hz, 1H), 7.16 (dt, $J = 7.5, 1.0$ Hz, 1H), 7.09 (dd, $J = 2.5, 1.5$ Hz, 1H), 6.94 (td, $J = 7.5, 1.0$ Hz, 1H), 6.91-6.87 (m, 2H), 3.91 (s, 3H), 3.82 (s, 3H).



1-((3-Fluorophenyl)ethynyl)-2-methoxybenzene (3aa)²⁷, 11.8 mg, 52% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (500 MHz, CDCl_3) δ 7.49 (dd, $J = 7.5, 2.0$ Hz, 1H), 7.34-7.27 (m, 3H), 7.27-7.24 (m, 1H), 7.02 (tdd, $J = 8.5, 2.5, 1.0$ Hz, 1H), 6.94 (td, $J = 7.5, 1.0$ Hz, 1H), 6.90 (dd, $J = 8.5, 1.0$ Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.4 (d, $J = 246.1$ Hz), 160.1, 133.6, 130.1, 129.8 (d, $J = 8.6$ Hz), 127.6 (d, $J = 2.9$ Hz), 125.5 (d, $J = 9.5$ Hz), 120.5, 118.4 (d, $J = 22.9$ Hz), 115.4 (d, $J = 21.0$ Hz), 112.0, 110.7, 92.1 (d, $J = 3.1$ Hz), 86.7, 55.9. **HRMS-EI** calcd for $\text{C}_{15}\text{H}_{11}\text{OF}$ $[\text{M}]^+$, 226.0788; found 226.0788.



3-((2-Methoxyphenyl)ethynyl)benzonitrile (3ab), 14.0 mg, 60% yield;

2% hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (500

MHz, CDCl_3) δ 7.82 (t, $J = 1.5$ Hz, 1H), 7.75 (dt, $J = 8.0, 1.5$ Hz, 1H),

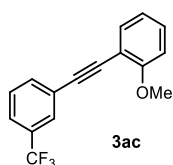
7.58 (dt, $J = 8.0, 1.5$ Hz, 1H), 7.49 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H),

7.35 (ddd, $J = 8.5, 7.5, 2.0$ Hz, 1H), 6.96 (td, $J = 7.5, 1.0$ Hz, 1H), 6.92 (dd, $J = 8.5,$

1.0 Hz, 1H), 3.92 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 160.2, 135.7, 135.0, 133.7,

131.2, 130.6, 129.2, 125.3, 120.6, 118.2, 112.8, 111.5, 110.8, 90.9, 88.4, 55.9.

HRMS-EI calcd for $\text{C}_{16}\text{H}_{11}\text{NO}$ $[\text{M}]^+$, 233.0835; found 233.0836.

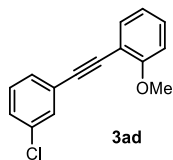


1-methoxy-2-((3-(trifluoromethyl)phenyl)ethynyl)benzene (3ac)²⁹,

16.6 mg, 60% yield; 2% hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 (s, 1H), 7.72 (d, $J = 8.0$

Hz, 1H), 7.56 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.53-7.43 (m, 2H), 7.34 (ddd, $J = 8.4, 7.6, 1.6$

Hz, 1H), 6.99-6.90 (m, 2H), 3.93 (s, 3H).

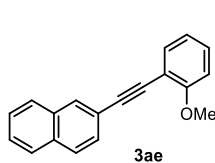


1-((3-Chlorophenyl)ethynyl)-2-methoxybenzene (3ad)²⁷, 17.9 mg, 74%

yield; 2% hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.55 (t, $J = 2.0$ Hz, 1H), 7.48 (dd, $J = 8.0,$

1.5 Hz, 1H), 7.43 (dt, $J = 8.0, 2.0$ Hz, 1H), 7.34-7.24 (m, 3H), 6.94 (td, $J = 7.5, 1.0$ Hz,

1H), 6.90 (d, $J = 8.0$ Hz, 1H), 3.91 (s, 3H).

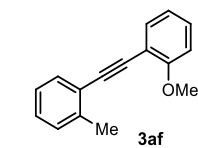


2-((2-methoxyphenyl)ethynyl)naphthalene (3ae)²⁶, 18.1 mg, 70%

yield; 2% hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.08 (s, 1H), 7.82-7.79 (m, 3H), 7.61

(dd, $J = 8.5, 1.5$ Hz, 1H), 7.54 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.51-7.45 (m, 2H), 7.33-7.30

(m, 1H), 6.96 (t, $J = 7.5$ Hz, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 3.94 (s, 3H).



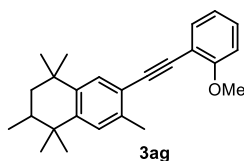
1-Methoxy-2-(o-tolyethynyl)benzene (3af)²⁶, 16.0 mg, 72% yield; 6%

hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (500

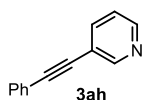
MHz, CDCl_3) δ : 7.52 (d, $J = 8.5$ Hz, 1H), 7.50 (dd, $J = 7.5, 1.5$ Hz,

1H), 7.30 (ddd, $J = 8.5, 7.5, 2.0$ Hz, 1H), 7.22-7.19 (m, 2H), 7.17-7.14 (m, 1H), 6.94

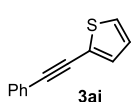
(td, $J = 7.5, 1.0$ Hz, 1H), 6.90 (dd, $J = 8.5, 1.0$ Hz, 1H), 3.91 (s, 3H), 2.54 (s, 3H).



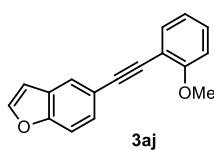
6-((2-methoxyphenyl)ethynyl)-1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydronaphthalene (3ag), 13.8 mg, 40% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (500 MHz, CDCl_3) δ 7.51 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.46 (s, 1H), 7.29 (ddd, $J = 9.0, 7.5, 1.5$ Hz, 1H), 7.21 (s, 1H), 3.92 (s, 3H), 6.96-6.90 (m, 2H), 2.49 (s, 3H), 1.91-1.84 (m, 1H), 1.65 (d, $J = 13.2$ Hz, 1H), 1.37 (dd, $J = 13.5, 2.5$ Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H), 1.07 (s, 3H), 0.99 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.9, 146.5, 142.1, 137.0, 133.3, 129.9, 129.4, 127.9, 120.6, 120.5, 113.2, 110.8, 93.0, 88.4, 55.9, 43.7, 37.8, 34.5, 34.0, 32.4, 32.0, 29.7, 28.5, 24.8, 20.5, 16.9. HRMS-EI calcd for $\text{C}_{25}\text{H}_{30}\text{O}$ $[\text{M}]^+$, 346.2291; found 346.2290.



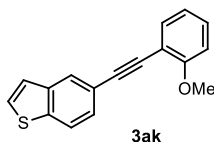
3-(Phenylethynyl)pyridine (3ah)²⁰, 7.2 mg, 40% yield; 0.25% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (500 MHz, CDCl_3) δ : 8.78 (s, 1H), 8.55 (s, 1H), 7.80 (dt, $J = 8.0, 2.0$ Hz, 1H), 7.86-7.53 (m, 2H), 7.38-7.35 (m, 3H), 7.27 (dd, $J = 8.0, 4.5$ Hz, 1H).



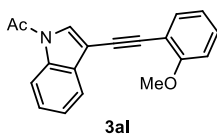
2-(Phenylethynyl)thiophene (3ai)²¹, 7.7 mg, 42% yield; 0.25% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (500 MHz, CDCl_3) δ : 7.53-7.49 (m, 2H), 7.37-7.33 (m, 3H), 7.30-7.28 (m, 2H), 7.01 (dd, $J = 5.0, 4.0$ Hz, 1H);



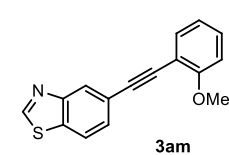
5-((2-methoxyphenyl)ethynyl)benzofuran (3aj), 15.6 mg, 63% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (m, 1H), 7.67 (d, $J = 2.0$ Hz, 1H), 7.58-7.53 (m, 2H), 7.50 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.34 (ddd, $J = 8.5, 7.5, 1.5$ Hz, 1H), 6.99 (td, $J = 7.5, 1.0$ Hz, 1H), 6.95 (dd, $J = 8.5, 1.0$ Hz, 1H), 6.79 (dd, $J = 2.0, 1.0$ Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.9, 154.6, 145.8, 133.5, 129.6, 128.2, 127.5, 124.8, 120.5, 118.2, 112.7, 111.5, 110.7, 106.6, 93.8, 84.3, 55.9. HRMS-EI calcd for $\text{C}_{17}\text{H}_{17}\text{O}_2$ $[\text{M}]^+$, 248.0832; found 248.0426.



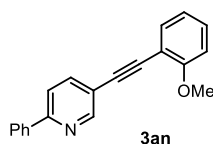
5-((2-methoxyphenyl)ethynyl)benzo[b]thiophene (3ak), 15.3 mg, 58% yield; 2% hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.15 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.90 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.73 (s, 1H), 7.61 (dt, $J = 7.5, 1.5$ Hz, 1H), 7.51 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 7.45 (ddd, $J = 8.5, 7.0, 1.5$ Hz, 1H), 7.38 (ddd, $J = 8.5, 7.5, 1.5$ Hz, 1H), 7.03-6.96 (m, 2H), 4.00 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 160.1, 139.4, 138.8, 133.5, 129.9, 129.4, 125.0, 124.7, 123.3, 122.6, 120.6, 118.8, 112.4, 110.8, 88.3, 87.1, 55.9. HRMS-EI calcd for $\text{C}_{17}\text{H}_{12}\text{OS}$ $[\text{M}]^+$, 264.0603; found 264.0606.



1-(3-((2-methoxyphenyl)ethynyl)-1H-indol-1-yl)ethanone (3al), 15.0 mg, 52% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.46 (d, $J = 8.1$ Hz, 1H), 7.85-7.82 (m, 1H), 7.71 (s, 1H), 7.58 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.44 (ddd, $J = 8.0, 7.0, 1.5$ Hz, 1H), 7.40 (td, $J = 7.5, 1.5$ Hz, 1H), 7.36 (ddd, $J = 8.5, 7.5, 1.5$ Hz, 1H), 7.00 (td, $J = 7.5, 1.0$ Hz, 1H), 6.96 (dd, $J = 8.5, 1.0$ Hz, 1H), 3.98 (s, 3H), 2.66 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 168.3, 156.0, 135.1, 133.5, 130.6, 129.9, 127.6, 126.0, 124.2, 120.6, 120.2, 116.6, 112.4, 110.8, 105.7, 90.0, 84.8, 55.9, 23.9.

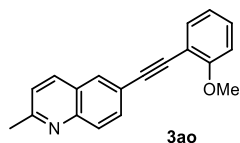


5-((2-methoxyphenyl)ethynyl)benzo[d]thiazole (3am), 17.5 mg, 66% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.02 (s, 1H), 8.17 (d, $J = 1.6$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 7.70 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.52 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.33 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H), 6.99-6.90 (m, 2H), 3.93 (s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.1, 154.8, 152.7, 133.9, 133.6, 130.0, 129.9, 125.1, 123.4, 121.2, 120.6, 112.2, 110.8, 92.9, 86.8, 55.9. HRMS: (ESI-TOF) m/z calcd for $\text{C}_{16}\text{H}_{12}\text{NOS}$ $[\text{M}+\text{H}]^+$: 266.0634, found: 266.0634.



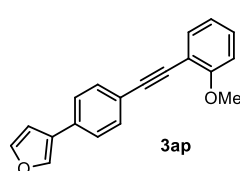
5-((2-methoxyphenyl)ethynyl)-2-phenylpyridine (3an), 17.4 mg, 61% yield; 5% hydrochloric acid in EtOH was used in the reaction;

^1H NMR (400 MHz, CDCl_3) δ 8.86 (dd, $J = 2.4, 0.8$ Hz, 1H), 8.05-8.00 (m, 2H), 7.90 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.72 (dd, $J = 8.4, 0.8$ Hz, 1H), 7.55-7.40 (m, 4H), 7.35 (ddd, $J = 8.4, 7.6, 2.0$ Hz, 1H), 7.00-6.94 (td, $J = 7.6, 1.2$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.1, 156.0, 152.2, 139.2, 138.8, 133.7, 130.3, 129.3, 128.8, 127.0, 120.6, 119.7, 119.0, 111.9, 110.8, 90.3, 89.5, 55.9. **HRMS:** (ESI-TOF) m/z calcd for $\text{C}_{20}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 286.1226, found: 286.1232.



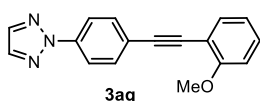
6-((2-methoxyphenyl)ethynyl)-2-methylquinoline (3ao), 14.7

mg, 54% yield; 2% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (400 MHz, CDCl_3) δ 8.03-7.95 (m, 3H), 7.82 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.54 (dd, $J = 7.6, 2.0$ Hz, 1H), 7.33 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 6.96 (td, $J = 7.6, 0.8$ Hz, 1H), 6.92 (dd, $J = 8.4, 0.8$ Hz, 1H), 3.94 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.1, 159.7, 147.3, 135.9, 133.6, 132.4, 130.8, 130.0, 128.6, 126.2, 122.6, 121.0, 120.6, 112.3, 110.7, 93.2, 86.7, 55.9, 25.4. **HRMS:** (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 274.1226, found: 274.1231.



3-(4-((2-methoxyphenyl)ethynyl)phenyl)furan (3ap), 19.2 mg,

70% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (s, 1H), 7.58-7.55 (m, 2H), 7.53-7.44 (m, 4H), 7.31 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H), 6.97-6.89 (m, 2H), 6.71 (dd, $J = 1.6, 0.8$ Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.9, 143.9, 138.9, 133.6, 132.1, 129.8, 126.0, 125.6, 122.1, 120.5, 112.5, 110.7, 108.7, 93.4, 86.2, 55.9. **HRMS-EI** calcd for $\text{C}_{19}\text{H}_{14}\text{O}$ $[\text{M}]^+$, 274.0988; found 274.0988.

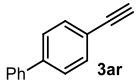


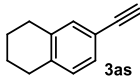
2-(4-((2-methoxyphenyl)ethynyl)phenyl)-2H-1,2,3-triazole

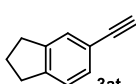
(3aq), 18.4 mg, 67% yield; 2% hydrochloric acid in EtOH was

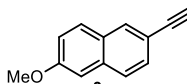
used in the reaction; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (dt, $J = 8.8, 2.0$ Hz, 2H), 7.83 (s, 2H), 7.70-7.66 (m, 2H), 7.52 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.33 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H), 6.99-6.89 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.0, 139.1,

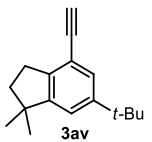
135.8, 133.6, 132.7, 130.0, 122.9, 120.6, 118.7, 112.2, 110.7, 92.6, 87.0, 55.9.
HRMS-EI calcd for C₁₇H₁₃N₃O [M], 275.1053; found 275.1058.

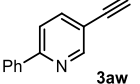
 **4-Ethynyl-1,1'-biphenyl (3ar)**³⁰, 13.5 mg, 76% yield, white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.61-7.54 (m, 6H), 7.48 -7.42 (m, 2H), 7.40-7.34 (m, 1H), 3.13 (s, 1H).

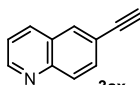
 **6-Ethynyl-1,2,3,4-tetrahydronaphthalene (3as)**³¹, 10.9 mg, 70% yield, ¹H NMR (500 MHz, CDCl₃) δ 7.21-7.18 (d, *J* = 6.4 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 1H), 2.99 (s, 1H), 2.76-2.72 (m, 4H), 1.77-1.80 (m, 4H).

 **5-Ethynyl-2,3-dihydro-1H-indene (3at)**³², 7.8 mg, 55% yield, ¹H NMR (500 MHz, CDCl₃) δ 7.35 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 3.00 (s, 1H), 2.90 (q, *J* = 7.3 Hz, 4H), 2.07 (p, *J* = 7.5 Hz, 2H).

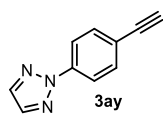
 **2-Ethynyl-6-methoxynaphthalene (3au)**³³, 12.7 mg, 70% yield, white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.95 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.49 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.16 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 3.92 (s, 3H), 3.11 (s, 1H).

 **6-(tert-Butyl)-4-ethynyl-1,1-dimethyl-2,3-dihydro-1H-indene (3av)** 19.0 mg, 84% yield, colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, *J* = 1.7 Hz, 1H), 7.15 (d, *J* = 1.7 Hz, 1H), 3.17 (s, 1H), 2.94 (t, *J* = 7.2 Hz, 2H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.32 (s, 9H), 1.26 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 152.5, 149.8, 143.0, 127.0, 119.7, 117.5, 82.9, 78.9, 44.5, 41.1, 34.6, 31.5, 29.2, 28.6; HRMS-EI calcd for C₁₇H₂₂ [M]⁺, 226.1716; found 226.1717.

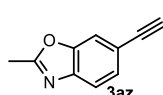
 **5-Ethynyl-2-phenylpyridine (3aw)**³⁴, 8.8 mg, 49% yield, white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.79 (d, *J* = 2.0 Hz, 1H), 8.06-7.94 (m, 2H), 7.83 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.51-7.47 (m, 2H), 7.46-7.41 (m, 1H), 3.26 (s, 1H).

 **6-Ethynylquinoline (3ax)**³⁵, 8.6 mg, 56% yield, white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.92 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.12 (ddd, *J* = 8.3, 1.8, 0.8 Hz, 1H), 8.05 (dt, *J* = 8.7, 0.8 Hz, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.76 (dd, *J* =

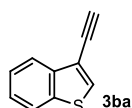
8.7, 1.8 Hz, 1H), 7.43 (dd, $J = 8.3, 4.2$ Hz, 1H), 3.19 (s, 1H).



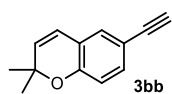
2-(4-Ethynylphenyl)-2H-1,2,3-triazole (3ay) 13.0 mg, 77% yield, white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.06 (d, $J = 8.4$ Hz, 2H), 7.82 (s, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 3.15 (s, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 139.6, 135.9, 133.2, 121.3, 118.7, 82.8, 78.3; HRMS-EI calcd for $\text{C}_{10}\text{H}_7\text{N}_3$ $[\text{M}]^+$, 169.0634; found 169.0638.



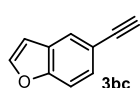
6-Ethynyl-2-methylbenzo[d]oxazole (3az)³⁶, 8.0 mg, 51% yield, white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.60 (s, 1H), 7.57 (d, $J = 8.2$ Hz, 1H), 7.44 (dd, $J = 8.1, 1.4$ Hz, 1H), 3.09 (s, 1H), 2.64 (s, 3H).



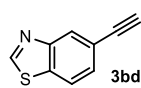
3-Ethynylbenzo[b]thiophene (3ba)³⁷, 9.6 mg, 61% yield, white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.97 (dt, $J = 7.9, 1.0$ Hz, 1H), 7.86 (dt, $J = 7.9, 0.9$ Hz, 1H), 7.70 (s, 1H), 7.46 (ddd, $J = 8.1, 7.0, 1.1$ Hz, 1H), 7.41 (ddd, $J = 8.2, 7.1, 1.3$ Hz, 1H), 3.30 (s, 1H).



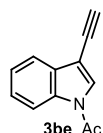
6-Ethynyl-2,2-dimethyl-2H-chromene (3bb) 7.5 mg, 41% yield, colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.24 (dd, $J = 8.3, 2.0$ Hz, 1H), 7.12 (d, $J = 2.0$ Hz, 1H), 6.70 (d, $J = 8.3$ Hz, 1H), 6.27 (d, $J = 9.8$ Hz, 1H), 5.63 (d, $J = 9.8$ Hz, 1H), 2.96 (s, 1H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.6, 133.1, 131.3, 130.1, 121.6, 121.1, 116.4, 114.0, 83.7, 75.4, 28.1; HRMS-ESI calcd for: $\text{C}_{13}\text{H}_{13}\text{O}$ $[\text{M}+\text{H}]^+$, 185.0961; found 185.0960.



5-Ethynylbenzofuran (3bc)³⁸, 9.4 mg, 66% yield, colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.80 (s, 1H), 7.68 (d, $J = 2.2$ Hz, 1H), 7.50-7.43 (m, 2H), 6.79 (dd, $J = 2.3, 0.8$ Hz, 1H), 3.06 (s, 1H).

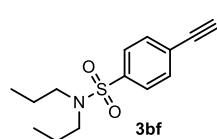


5-Ethynylbenzo[d]thiazole (3bd)³⁹, 10.8 mg, 68% yield, white solid. ^1H NMR (500 MHz, CDCl_3) δ 9.03 (s, 1H), 8.27 (s, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.55 (dd, $J = 8.3, 1.5$ Hz, 1H), 3.15 (s, 1H).

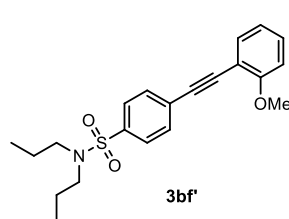


1-(3-Ethynyl-1H-indol-1-yl)ethanone (3be)⁴⁰, 10.2 mg, 56% yield, white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.41 (d, $J = 8.2$ Hz, 1H), 7.70-7.67 (m,

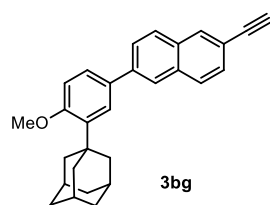
1H), 7.65 (s, 1H), 7.43-7.38 (m, 1H), 7.38-7.33 (m, 1H), 3.28 (s, 1H), 2.63 (s, 3H).



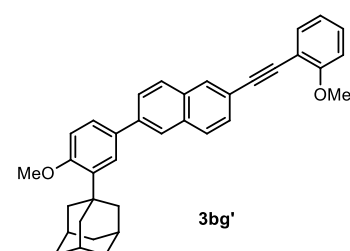
4-Ethynyl-N,N-dipropylbenzenesulfonamide (3bf) 17.2 mg, 65% yield, ¹H NMR (500 MHz, CDCl₃) δ 7.78-7.73 (m, 2H), 7.62-7.57 (m, 2H), 3.24 (s, 1H), 3.11-3.05 (m, 4H), 1.58-1.50 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 132.6, 126.9, 82.1, 80.4, 49.9, 21.9, 11.2; HRMS-ESI calcd for C₁₄H₂₀NO₂S [M+H]⁺, 266.1209; found 266.1207.



4-((2-methoxyphenyl)ethynyl)-N,N-dipropylbenzenesulfonamide (3bf'), 19.3 mg, 52% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1H), 6.99-6.90 (m, 2H), 3.92 (s, 3H), 3.13-3.04 (m, 4H), 1.60-1.49 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 160.2, 139.3, 133.7, 132.0, 130.5, 127.9, 126.9, 120.6, 111.6, 110.8, 91.9, 89.2, 55.9, 49.9, 21.9, 11.2. **HRMS:** (ESI-TOF) *m/z* calcd for C₂₁H₂₆NO₃S [M+H]⁺: 272.1628, found: 272.1634.

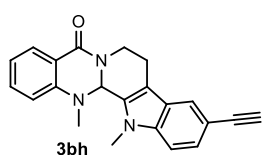


(3r,5r,7r)-1-(5-(6-ethynyl-naphthalen-2-yl)-2-methoxyphenyl)adamantane (3bg) 20.0 mg, 51% yield, white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.03 (s, 1H), 7.96 (s, 1H), 7.83 (dd, *J* = 8.5, 6.0 Hz, 2H), 7.75 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.54-7.51 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.16 (s, 1H), 2.19 (brs, 6H), 2.11 (brs, 3H), 1.81 (brs, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 158.8, 140.1, 139.0, 133.4, 132.8, 132.1, 131.6, 128.9, 128.1, 126.4, 125.9, 125.6, 124.8, 118.9, 112.1, 84.2, 77.3, 55.2, 40.6, 37.1, 29.1; HRMS-EI calcd for C₂₉H₂₈O [M]⁺, 392.2135; found 392.2132.



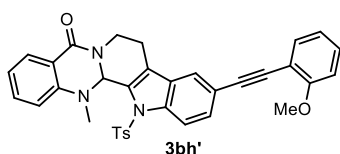
(3r,5r,7r)-1-(2-methoxy-5-(6-((2-methoxyphenyl)ethynyl)naphthalen-2-yl)phenyl)adamantane (3bg'), 31.9 mg, 64% yield; ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 1.6 Hz, 1H), 7.95 (d, *J* = 1.6 Hz, 1H), 7.84 (d, *J* = 8.4 Hz,

1H), 7.83 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.73 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.62 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H), 7.55 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.52 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.32 (ddd, $J = 8.4, 7.6, 1.6$ Hz, 1H), 7.00-6.90 (m, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 2.18 (d, $J = 2.8$ Hz, 6H), 2.10 (s, 3H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.0, 158.7, 139.7, 138.9, 133.7, 133.2, 132.9, 131.8, 131.2, 129.8, 128.9, 128.2, 128.0, 126.3, 125.9, 125.6, 124.9, 120.6, 120.5, 112.6, 112.1, 110.8, 94.1, 86.2, 55.9, 55.2, 40.7, 37.2, 29.2. HRMS-EI calcd for $\text{C}_{36}\text{H}_{34}\text{O}_2$ $[\text{M}]^+$, 498.2553; found 498.2555.



10-Ethynyl-13,14-dimethyl-7,8,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(13H)-one (3bh) 14.6 mg, 43% yield, yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.13 (dd, $J =$

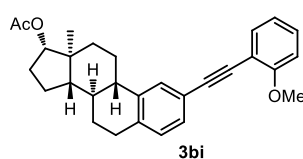
7.8, 1.6 Hz, 1H), 7.78 (dd, $J = 1.4, 0.7$ Hz, 1H), 7.50 (ddd, $J = 8.1, 7.3, 1.6$ Hz, 1H), 7.42 (dd, $J = 8.5, 1.5$ Hz, 1H), 7.31 (dd, $J = 8.5, 0.7$ Hz, 1H), 7.23 (td, $J = 7.5, 1.1$ Hz, 1H), 7.20 (dd, $J = 8.0, 1.0$ Hz, 1H), 5.95 (d, $J = 1.5$ Hz, 1H), 4.91 (ddd, $J = 12.8, 5.0, 1.8$ Hz, 1H), 3.85 (s, 3H), 3.18 (ddd, $J = 12.8, 11.7, 4.0$ Hz, 1H), 3.03 (s, 1H), 3.01-2.96 (m, 1H), 2.91-2.84 (m, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.6, 150.7, 137.7, 133.0, 129.9, 129.0, 126.5, 125.4, 124.2, 123.9, 123.5, 123.0, 109.4, 85.0, 75.1, 68.0, 39.3, 36.5, 30.2, 20.2; HRMS-EI calcd for $\text{C}_{22}\text{H}_{19}\text{ON}_3$ $[\text{M}]^+$, 341.1523; found 341.1521.



10-((2-methoxyphenyl)ethynyl)-14-methyl-13-tosyl-7,8,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(13H)-one (3bh'), 30.5 mg, 52% yield; ^1H NMR

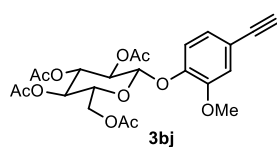
(400 MHz, CDCl_3) δ 8.27 (d, $J = 8.8$ Hz, 1H), 8.11 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 1.6$ Hz, 1H), 7.64 (dd, $J = 8.8, 1.6$ Hz, 1H), 7.53-7.47 (m, 2H), 7.36-7.25 (m, 4H), 7.18 (td, $J = 7.6, 1.2$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.98-6.89 (m, 2H), 6.33 (s, 1H), 4.90-4.85 (m, 1H), 3.93 (s, 3H), 3.14-3.07 (m, 1H), 2.96-2.90 (m, 1H), 2.82-2.71 (m, 1H), 2.40 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.4, 160.0, 150.7, 145.3, 136.9, 135.7, 133.5, 133.2, 130.0, 129.9, 129.6, 129.1, 128.1, 127.1, 123.7, 123.2, 123.0, 122.7, 120.7, 120.6, 119.4, 115.3, 112.3,

110.8, 93.1, 85.7, 67.8, 55.9, 38.3, 35.4, 21.7, 20.8. HRMS: (ESI-TOF) m/z calcd for C₃₅H₃₀N₃O₄S [M+H]⁺: 588.1952, found: 588.1936.



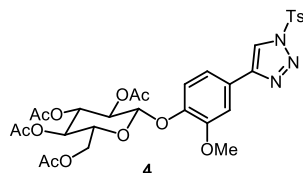
(8*R*,9*S*,13*S*,14*S*,17*S*)-2-((2-methoxyphenyl)ethynyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl acetate (3bi), 21.4 mg, 50% yield; 0.5%

hydrochloric acid in EtOH was used in the reaction; ¹H NMR (400 MHz, CDCl₃) δ 7.51-7.47 (m, 2H), 7.32-7.26 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.95-6.87 (m, 2H), 4.69 (t, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 2.89-2.85 (m, 2H), 2.37-2.33 (m, 1H), 2.29-2.16 (m, 2H), 2.06 (s, 3H), 1.94-1.86 (m, 2H), 1.81-1.70 (m, 1H), 1.60-1.22 (m, 6H), 0.84 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 159.8, 140.3, 137.1, 133.6, 129.5, 128.9, 128.9, 128.8, 120.6, 120.5, 112.7, 110.7, 94.1, 84.6, 82.7, 55.9, 49.9, 44.1, 42.9, 38.2, 36.9, 29.5, 27.6, 27.1, 25.9, 23.3, 21.2, 12.1. HRMS-EI calcd for C₂₉H₃₂O₃ [M]⁺, 428.2346; found 428.2343.



(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(4-ethynyl-2-methoxyphenoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3bj)

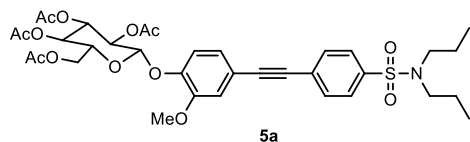
22.0 mg, 46% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.03 (m, 2H), 7.01-6.99 (m, 1H), 5.32-5.22 (m, 2H), 5.19-5.10 (m, 1H), 5.00-4.92 (m, 1H), 4.26 (dd, *J* = 12.2, 5.2 Hz, 1H), 4.15 (dd, *J* = 12.3, 2.5 Hz, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.03 (s, 1H), 2.06 (s, 6H), 2.03 (s, 3H), 2.02 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.5, 170.2, 169.4, 169.3, 150.2, 146.7, 125.1, 119.6, 118.2, 116.1, 100.4, 83.1, 77.2, 76.7, 72.5, 72.0, 71.1, 68.3, 61.9, 56.0, 20.7, 20.6, 20.5; HRMS-EI calcd for C₂₃H₂₆O₁₁ [M]⁺, 478.1470; found 478.1466.



(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-(2-methoxy-4-(1-tosyl-1*H*-1,2,3-triazol-4-yl)phenoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (4)

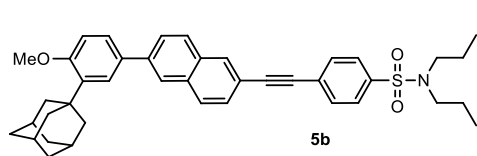
31.4 mg, 93% yield. ¹H NMR (500 MHz, CDCl₃) δ 8.26 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.40-7.36 (m, 2H), 7.26-7.23 (m, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 5.33-5.24 (m, 2H), 5.19-5.12 (m, 1H), 5.00-4.97 (m, 1H), 4.27 (dd, *J* = 12.3, 5.2 Hz, 1H), 4.16 (dd, *J* = 12.3, 2.5 Hz, 1H), 3.86 (s, 3H), 3.79 (m, 1H), 2.44 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H),

2.03 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 170.2, 169.4, 169.6, 151.0, 147.4, 146.8, 146.6, 133.0, 130.4, 128.7, 125.5, 120.3, 118.7, 118.5, 110.3, 100.6, 72.5, 72.0, 7.12, 68.3, 61.9, 56.1, 21.8, 20.7, 20.6, 20.6, 20.6; HRMS-ESI calcd for $\text{C}_{30}\text{H}_{34}\text{N}_3\text{O}_{13}\text{S}$ $[\text{M}+\text{H}]^+$, 676.1807; found 676.1816.



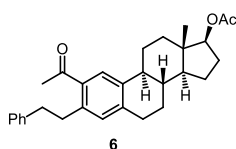
(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(4-((4-(N,N-dipropylsulfamoyl)phenyl)ethynyl)-2-methoxyphenoxy)tetrahydro-2H-pyran-3,4,5-tri

l triacetate (5a), 45.2 mg, 63% yield; 0.5% hydrochloric acid in EtOH was used in the reaction; ^1H NMR (500 MHz, CDCl_3) δ 7.80-7.78 (m, 2H), 7.66-7.61 (m, 2H), 7.11-7.10 (m, 2H), 7.08 (s, 1H), 5.33-5.30 (m, 2H), 5.21-5.16 (m, 1H), 5.04-5.01 (m, 1H), 4.30 (dd, $J = 12.5, 5.0$ Hz, 1H), 4.19 (dd, $J = 12.5, 2.5$ Hz, 1H), 3.87 (s, 3H), 3.83 (ddd, $J = 10.0, 5.0, 2.5$ Hz, 1H), 3.13-3.09 (m, 4H), 2.10 (s, 6H), 2.06 (d, $J = 1.5$ Hz, 6H), 1.61-1.52 (m, 4H), 0.89 (t, $J = 7.4$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 170.3, 169.4, 169.3, 150.4, 146.8, 139.5, 131.9, 127.4, 127.0, 124.8, 119.6, 118.5, 115.7, 100.4, 92.2, 87.4, 72.5, 72.1, 71.1, 68.3, 61.9, 56.1, 49.9, 21.9, 20.7, 20.6, 20.6, 11.2. HRMS-EI calcd for $\text{C}_{35}\text{H}_{43}\text{NO}_{13}\text{S}$ $[\text{M}]^+$, 717.2450; found 717.2455.

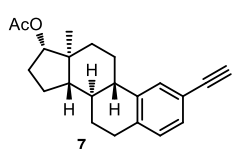


4-((6-(3-((3r,5r,7r)-Adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)ethynyl)-N,N-dipropylbenzenesulfonamide (5b) 15.1 mg, 48%

yield, white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.08 (s, 1H), 7.98 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 2H), 7.81 (d, $J = 8.1$ Hz, 2H), 7.79-7.75 (m, 1H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.61-7.57 (m, 2H), 7.54 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 3.91 (s, 3H), 3.19-3.05 (m, 4H), 2.22-2.15 (m, 6H), 2.11 (s, 3H), 1.81 (s, 6H), 1.57 (m, 4H), 0.89 (t, $J = 7.4$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.8, 140.2, 139.4, 139.0, 133.5, 132.7, 132.0, 131.7, 128.5, 128.3, 128.2, 127.6, 127.1, 126.6, 125.9, 125.6, 124.8, 119.2, 112.1, 93.3, 88.3, 55.2, 49.9, 40.6, 37.2, 37.1, 29.1, 22.0, 11.2; HRMS-EI calcd for $\text{C}_{41}\text{H}_{45}\text{O}_3\text{NS}$ $[\text{M}]^+$, 631.3115; found 631.3116.

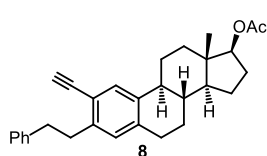


(8R,9S,13S,14S,17S)-2-acetyl-13-methyl-3-phenethyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl acetate (6) 31.1 mg, 70% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.64 (s, 1H), 7.31-7.27 (m, 4H), 7.20-1.17 (m, 1H), 6.96 (s, 1H), 4.71 (dd, $J = 9.2, 7.7$ Hz, 1H), 3.11-3.07 (m, 2H), 2.93-2.80 (m, 4H), 2.55 (s, 3H), 2.38-2.32 (m, 1H), 2.29-2.20 (m, 2H), 2.07 (s, 3H), 1.95-1.90 (m, 2H), 1.80-1.74 (m, 1H), 1.59-1.51 (m, 2H), 1.51-1.41 (m, 3H), 1.40-1.35 (m, 1H), 1.34-1.25 (m, 2H), 0.85 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 201.5, 171.2, 142.3, 140.9, 139.5, 137.9, 135.0, 132.1, 128.6, 128.3, 127.0, 125.8, 82.6, 49.8, 43.8, 42.8, 38.3, 36.8, 36.3, 29.5, 29.4, 27.5, 26.9, 26.0, 23.2, 21.2, 12.1; HRMS-EI calcd for $\text{C}_{30}\text{H}_{36}\text{O}_3$ $[\text{M}]^+$, 444.2659; found 444.2662.



(8R,9S,13S,14S,17S)-2-ethynyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl acetate (7)

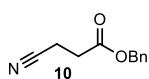
Compound 7 was synthesized according to the general procedure in Section 2.4. 21.9 mg, 68% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.43 (t, $J = 1.4$ Hz, 1H), 7.25-7.21 (m, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 4.69 (dd, $J = 9.2, 7.8$ Hz, 1H), 3.01 (s, 1H), 2.90-2.85 (m, 2H), 2.34-2.26 (m, 1H), 2.27-2.17 (m, 2H), 2.06 (s, 3H), 1.92-1.87 (m, 2H), 1.78-1.72 (m, 1H), 1.63-1.33 (m, 6H), 1.32-1.23 (m, 2H), 0.83 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.2, 140.4, 137.8, 129.2, 129.2, 128.9, 119.1, 84.2, 82.6, 76.0, 49.9, 44.0, 42.8, 38.1, 36.8, 29.4, 27.5, 27.0, 25.8, 23.2, 21.1, 12.0; HRMS-EI calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2$ $[\text{M}]^+$, 322.1927; found 322.1928.



(8R,9S,13S,14S,17S)-2-ethynyl-13-methyl-3-phenethyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl acetate (8)

^1H NMR (500 MHz, CDCl_3) δ 7.43 (s, 1H), 7.30 (t, $J = 7.5$ Hz, 2H), 7.25 (d, $J = 6.6$ Hz, 2H), 7.23-7.18 (m, 1H), 6.91 (s, 1H), 4.69 (dd, $J = 9.2, 7.8$ Hz, 1H), 3.23 (s, 1H), 3.05-2.96 (m, 2H), 2.94-2.88 (m, 2H), 2.84-2.82 (m, 2H), 2.34-2.29 (m, 1H), 2.25-2.15 (m, 2H), 2.06 (s, 3H), 1.95-1.85 (m, 2H), 1.78-1.72 (m, 1H), 1.56-1.47 (m, 2H), 1.47-1.36 (m, 2H), 1.35-1.22 (m, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.2, 142.1, 141.4, 138.1, 137.9, 130.0,

129.4, 128.4, 128.3, 125.9, 118.6, 82.8, 82.6, 79.6, 49.8, 43.8, 42.8, 38.2, 37.1, 36.8, 36.4, 29.4, 27.5, 27.1, 25.9, 23.2, 21.2, 12.0; HRMS-EI calcd for C₃₀H₃₄O₂ [M]⁺, 426.2553; found 426.2564.



Benzyl 3-cyanopropanoate (10)⁴¹, 11.0 mg, 58% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.35 (m, 5H), 5.18 (s, 2H), 2.76-2.72 (m, 2H), 2.68-2.65 (m, 2H).

4. DFT Calculations

All the DFT calculations were carried out with the Gaussian 16 package. Geometry optimizations were performed with B3LYP⁴²⁻⁴⁵ functional with the 6-31G(d) basis set^{46,47} for all nonmetal atoms and the LANL2DZ basis set^{48,49} with effective core potential (ECP) for Pd. Frequency analysis was conducted at the same level of theory to verify the stationary points to be minimum or saddle points. The single-point energies were calculated using Truhlar's M06⁵⁰ functional with the 6-311++G (d, p)⁵¹ basis set for all nonmetal atoms and the SDD^{52,53} effective core potential for Pd. The dispersion effect was included in the geometry optimization and single-point energies calculation by using the D3 correction of Grimme.⁵⁴ The solvent effects were computed by using the SMD solvation model (Solvent = Generic, eps = 12.486, epsinf = 2.0588, HBondAcidity = 0.0833, HBondBasicity = 0.1517, SurfaceTensionAtInterface = 44.675, CarbonAromaticity = 0.00, Electronegative Halogenicity = 0.4167) in all DFT calculations. And the reaction solvent used was 1,2-dichloroethane and butyronitrile (5:1), the corresponding solvent parameters were customized according to the volume ration. Optimized structures were illustrated using CYLview program⁵⁵.

Figure S1. DFT-computed Gibbs free energies for ligand-promoted alkynylation of arylketones

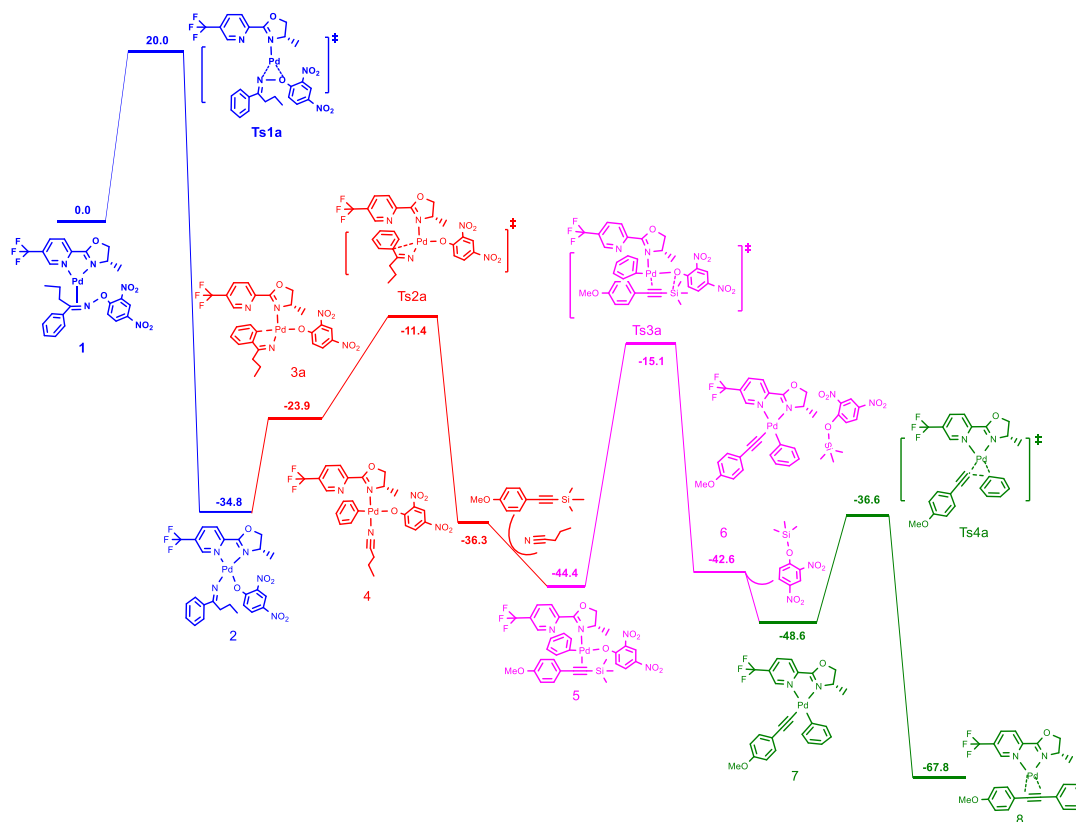
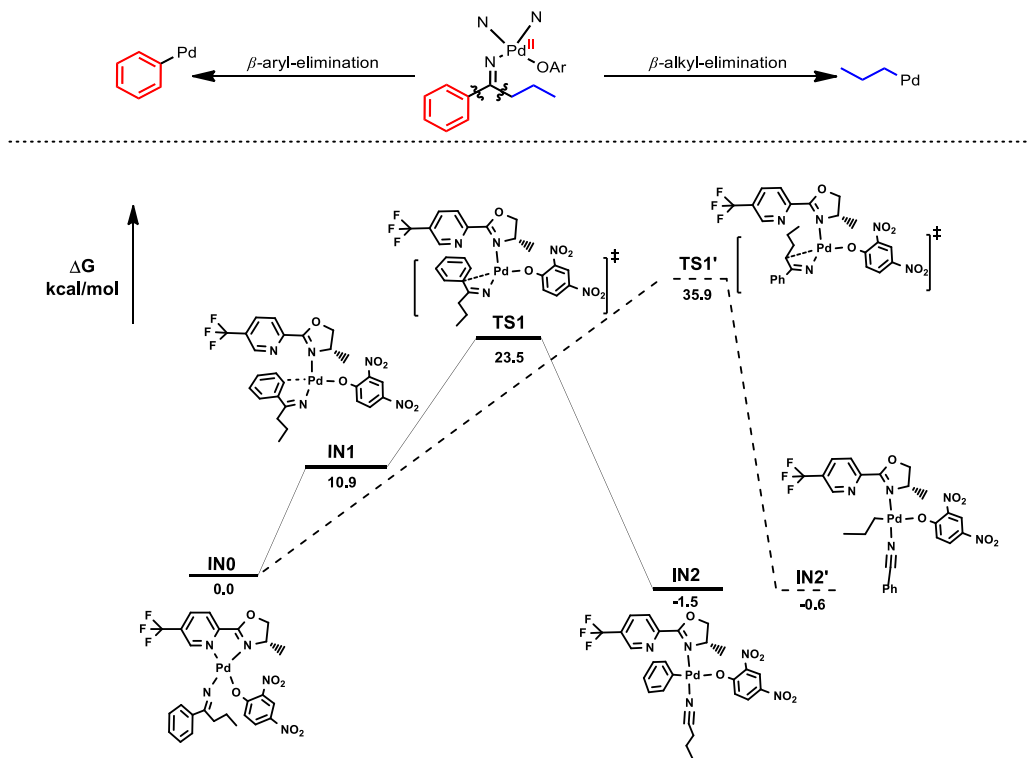


Figure S2. DFT-computed Gibbs free energies for β -carbon elimination.



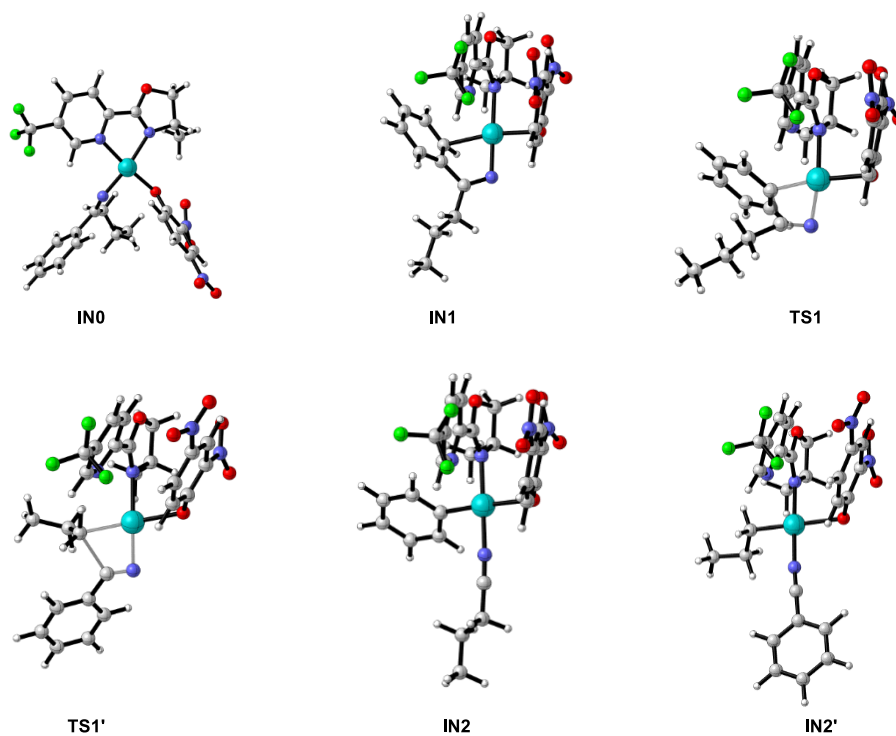


Table S10. Energies, enthalpies, and free energies of the structures calculated at the M06/SDD, 6-311++G(d,p)(SMD^{generic})/B3LYP/LANL2DZ,6-31G(d) (SMD^{generic}).

Structures	IN0	IN1	TS1	TS1'	IN2	IN2'
ZPE	0.484425	0.483173	0.480411	0.480234	0.481587	0.480868
DE	0.522805	0.521583	0.519186	0.519008	0.521216	0.520753
DH	0.523749	0.522527	0.52013	0.519952	0.52216	0.521697
DG	0.405664	0.408498	0.40442	0.403252	0.403472	0.399872
E	-2156.980408	-2156.96585	-2156.94178	-2156.920747	-2156.980528	-2156.975603
H	-2156.456659	-2156.443323	-2156.42165	-2156.400795	-2156.458368	-2156.453906
G	-2156.574744	-2156.557352	-2156.53736	-2156.517495	-2156.577056	-2156.575731
Imaginary	--	--	-368.4	-429.62	--	--
ΔG	0.0	10.9	23.5	35.9	-1.5	-0.6

Table S11. Cartesian Coordinates for the Optimized Structures.

Structure IN0				C	-3.36752900	0.41907900	-0.42293000
Pd	-0.59432100	-0.87414100	-0.03426900	C	-3.34395500	-1.90416000	-0.34272300
N	-2.68445300	-0.71754700	-0.29388000	C	-4.75496400	0.41583500	-0.59287700

H	-2.78196300	1.33290800	-0.39803800	N	5.78172100	0.48881000	-2.60760900
C	-4.71995400	-1.98224400	-0.51107000	O	6.91339200	0.36717000	-2.11809200
C	-5.44247600	-0.79423700	-0.63507900	O	5.57620000	0.98213600	-3.72562800
H	-5.20881300	-2.94864600	-0.54859200	N	4.03046700	-1.51201300	1.46427100
H	-6.51786900	-0.81512400	-0.77070800	O	3.25155600	-2.33982100	1.94611500
N	-1.18740400	-2.93418900	-0.14453700	O	5.05355100	-1.12642000	2.04784400
C	-2.46311200	-3.07391500	-0.21897000	O	1.40084200	-1.23681400	0.36704100
O	-2.96990900	-4.30511800	-0.17802500	C	0.09796900	1.74428900	0.92228900
C	-5.47945200	1.73405700	-0.67934700	C	0.21762900	3.23564800	0.75089200
F	-6.69540800	1.60179300	-1.24585400	C	0.09913000	4.11700200	1.83855900
F	-4.78148300	2.63389900	-1.40409300	C	0.44427000	3.77418600	-0.52804500
F	-5.66353900	2.27169000	0.54780800	C	0.18858700	5.49822800	1.64903300
C	-1.81439300	-5.20787400	-0.01991700	H	-0.07306800	3.73029400	2.83809500
H	-1.96280200	-5.75626900	0.91316700	C	0.54218900	5.15195600	-0.71555400
H	-1.82477000	-5.89543900	-0.86685200	H	0.55210100	3.09632700	-1.36904900
C	-0.57521100	-4.26791100	0.00981600	C	0.41123700	6.02090000	0.37297900
H	0.07070100	-4.44378700	-0.85637400	H	0.08613100	6.16486400	2.50141400
C	0.24966500	-4.34164200	1.29201700	H	0.72689200	5.54885300	-1.71055200
H	0.68835400	-5.34060900	1.39540700	H	0.48825300	7.09522400	0.22773600
H	1.05356300	-3.59957700	1.26752600	C	0.56536300	1.15498100	2.24940200
H	-0.38569400	-4.14806500	2.16449600	C	2.06007200	1.39951000	2.52936800
C	2.40124300	-0.85940300	-0.34257200	H	0.37060500	0.07976700	2.24025600
C	2.26537700	-0.27959700	-1.64725800	H	-0.03201800	1.58099200	3.06718500
C	3.75431300	-0.96417300	0.14815400	C	2.54877300	0.61416400	3.74903700
C	3.34527900	0.15007700	-2.37918500	H	2.64260800	1.10847000	1.64771300
H	1.25947900	-0.18455800	-2.04242700	H	2.23778300	2.47146700	2.67670700
C	4.84532400	-0.50626600	-0.58007900	H	3.60949800	0.80871300	3.94478300
C	4.64488100	0.03670300	-1.84247900	H	1.98259800	0.88816400	4.64881700
H	3.21111200	0.57774100	-3.36568900	H	2.43191700	-0.46433800	3.59018900
H	5.84132300	-0.58149800	-0.16495600	N	-0.36745500	1.08893500	-0.07102300

Structure IN1							
				C	2.38418600	2.11405800	1.49899700
Pd	1.80248300	-0.72208500	-0.61809300	C	3.40746700	-0.05885500	1.04970500
N	-0.49505700	0.16851900	1.00904600	C	2.10825000	1.70128100	2.79652200
C	-1.22970900	1.27419900	1.06440400	H	2.08910000	3.10304600	1.16110500
H	-0.77201900	2.18155700	0.68069500	C	3.11143200	-0.45975400	2.37137900
C	-2.53713800	1.28798500	1.56800900	H	4.08101400	-0.66146800	0.44044600
C	-3.09008700	0.10725500	2.05455600	C	2.45812600	0.40992600	3.23177000
H	-4.10336300	0.08674700	2.43939200	H	1.61022900	2.38176000	3.48171900
C	-2.32042900	-1.05401600	2.00838000	H	3.40735800	-1.44913900	2.70393800
H	-2.71523400	-2.00304000	2.34826500	H	2.22838800	0.10262800	4.24779900
C	-1.03619300	-0.97425900	1.46442200	C	3.89802600	2.83261900	-1.28492700
C	-0.23880400	-2.19910400	1.24904900	C	5.36976300	2.88597900	-0.83430700
N	0.79427100	-2.29198600	0.48744900	H	3.35830400	3.68853800	-0.85364800
O	-0.68688500	-3.32690400	1.81728500	H	3.82553000	2.91156000	-2.37553200
C	0.05860500	-4.42110900	1.19355700	C	6.04872200	4.19457100	-1.24531800
H	-0.63026600	-4.92259000	0.51075100	H	5.41941600	2.76877600	0.25611000
H	0.38031000	-5.09866100	1.98606200	H	5.90760300	2.03257800	-1.26812700
C	1.21954700	-3.71196600	0.45744500	H	7.09596600	4.21469600	-0.92111200
H	1.25712500	-4.01900700	-0.59032100	H	6.03126400	4.32366800	-2.33475300
C	2.58619300	-3.89702300	1.11298700	H	5.54132600	5.05893200	-0.79828900
H	2.88653400	-4.94901500	1.05172000	O	0.65017700	-1.28332900	-2.38324600
H	3.34316500	-3.29105800	0.60429300	C	-0.50433200	-0.72187400	-2.29981000
H	2.55205800	-3.60530500	2.16856300	C	-1.68761500	-1.38952900	-1.81081500
C	-3.30797700	2.57726200	1.56277500	C	-0.68627400	0.66017900	-2.65335700
F	-3.14264800	3.23764900	0.39242500	C	-2.87620500	-0.70898700	-1.56571300
F	-2.88830000	3.41360700	2.54248700	C	-1.87513700	1.32075700	-2.46995000
F	-4.62920800	2.38422400	1.73989500	H	0.18651400	1.17751500	-3.03741400
N	2.71481700	0.70664100	-1.65203600	C	-2.96933200	0.63519200	-1.89668400
C	3.20735400	1.56608100	-0.84543500	H	-3.71839400	-1.22725200	-1.12818900
C	3.03660500	1.24197800	0.60847900	H	-1.97972400	2.36882300	-2.72499400

N	-1.65072400	-2.79235800	-1.45583300	F	-3.76415400	2.97683700	0.21278500
O	-0.84706300	-3.53615800	-2.02399800	F	-3.20135000	3.62704000	2.20741000
O	-2.44343600	-3.19408900	-0.58556100	F	-4.84053500	2.21829100	1.94991800
N	-4.19323400	1.34567100	-1.61897000	N	2.14709200	1.04590700	-2.28697300
O	-4.34382500	2.47045700	-2.11268600	C	2.65655000	1.71521600	-1.41449400
O	-5.03593900	0.80625000	-0.88601700	C	3.13697000	0.49257400	0.07411900
Structure TS1				C	2.84269200	0.96340300	1.36908600
Pd	1.63755400	-0.47027800	-1.01142700	C	4.43261100	0.02292600	-0.21940800
N	-0.52388900	0.54064100	0.87337700	C	3.82084400	0.92679800	2.35995700
C	-1.42900500	1.51418200	0.88026100	H	1.84811500	1.33837000	1.58852000
H	-1.19382000	2.40152700	0.29842900	C	5.40490200	-0.02432200	0.78313200
C	-2.64178700	1.41825600	1.57534400	H	4.67718900	-0.29184700	-1.22976400
C	-2.91114300	0.26892400	2.31111600	C	5.09815500	0.42510400	2.06977900
H	-3.84544400	0.15994700	2.84973000	H	3.59107700	1.28134800	3.36125900
C	-1.96317400	-0.75315700	2.31466800	H	6.39925000	-0.39885600	0.55639700
H	-2.14143200	-1.67834800	2.84722400	H	5.85646700	0.39843000	2.84765400
C	-0.79347800	-0.57683300	1.56964400	C	3.03791600	3.11164700	-1.05647800
C	0.16299900	-1.69830300	1.43404200	C	4.53478000	3.33020300	-0.78566700
N	1.07711100	-1.83171100	0.53515900	H	2.45206500	3.38753800	-0.17136400
O	-0.01020000	-2.72209400	2.28169400	H	2.70182600	3.73914900	-1.89129900
C	0.78310600	-3.83065000	1.75546800	C	4.82881800	4.80696000	-0.51055300
H	0.08171700	-4.53053100	1.29632300	H	4.84261800	2.72467000	0.07181900
H	1.30256400	-4.29580700	2.59444900	H	5.11307300	2.98398900	-1.65083700
C	1.71897200	-3.15934400	0.72669800	H	5.89604000	4.95837100	-0.31280500
H	1.68012000	-3.68368100	-0.23055600	H	4.55166000	5.43587600	-1.36543900
C	3.16294700	-3.02070300	1.20156300	H	4.27049200	5.16304600	0.36431800
H	3.58697400	-4.01605500	1.37609000	O	0.23545500	-1.44095500	-2.40039500
H	3.77153900	-2.51092300	0.45157300	C	-0.96598900	-1.06367600	-2.16742400
H	3.21136100	-2.45031300	2.13607800	C	-1.89913400	-1.79802800	-1.34197900
C	-3.61987700	2.55590600	1.49163500	C	-1.46900000	0.18048100	-2.69046500

C	-3.13495000	-1.27620800	-0.97276600	H	0.51880000	-3.42423000	0.54061700
C	-2.71163900	0.66994100	-2.37663700	C	1.97360400	-3.20595000	2.11254800
H	-0.79530300	0.74139600	-3.33031500	H	2.06593200	-4.27948100	2.31321900
C	-3.54013500	-0.05429900	-1.48993900	H	2.77201300	-2.91679700	1.42178200
H	-3.77474300	-1.82459000	-0.29519300	H	2.10401300	-2.66374000	3.05573900
H	-3.05707900	1.61928200	-2.76902600	C	-3.36950200	3.73366100	0.43850300
N	-1.53757100	-3.08092900	-0.77971400	F	-3.32938200	3.79983400	-0.91532400
O	-0.70476600	-3.78183700	-1.36076600	F	-2.72191900	4.83051300	0.89609300
O	-2.09162200	-3.43066700	0.27848000	F	-4.66106400	3.83805200	0.80681800
N	-4.81122400	0.49298200	-1.08852900	N	2.68029100	0.16727900	-1.82014700
O	-5.25954600	1.46065800	-1.71709100	C	3.49480700	0.61509200	-1.03503300
O	-5.39654600	-0.01872000	-0.12143300	O	0.18987700	-1.74643400	-1.62204800
Structure TSI'				C	-1.02934700	-1.34863800	-1.64668600
Pd	1.49983000	-0.55279700	-0.37008000	C	-2.14474300	-2.19347600	-1.28606000
N	-0.70826600	1.20271100	1.17328700	C	-1.38024200	0.00940900	-1.96792800
C	-1.33776600	2.33570000	0.87723200	C	-3.44476900	-1.71050600	-1.18453300
H	-0.71685200	3.17293500	0.56875400	C	-2.66282200	0.48682700	-1.88590900
C	-2.73190500	2.46763800	0.93570500	H	-0.56434400	0.66964800	-2.24504800
C	-3.49509400	1.39288200	1.37905400	C	-3.70325500	-0.38038900	-1.48413200
H	-4.57469200	1.46528900	1.44115600	H	-4.23947900	-2.36252000	-0.84739400
C	-2.84083400	0.20684300	1.70875000	H	-2.88536400	1.52689300	-2.08935600
H	-3.39636500	-0.66368300	2.03475000	N	-1.92369700	-3.56662200	-0.88114900
C	-1.45275400	0.15054000	1.55550700	O	-0.97501900	-4.18713200	-1.36772700
C	-0.74822700	-1.13865600	1.73701700	O	-2.70158900	-4.05911700	-0.04643700
N	0.39095900	-1.46961500	1.23518100	N	-5.03030500	0.14113100	-1.28444300
O	-1.41839400	-2.07942300	2.41762100	O	-5.19510900	1.36773800	-1.37886800
C	-0.57793800	-3.27568600	2.42971600	O	-5.94601300	-0.64484700	-1.00266400
H	-1.18384800	-4.10616600	2.06691300	C	4.90658500	1.00766200	-1.01475700
H	-0.27347600	-3.44993100	3.46581400	C	5.84385800	0.06774000	-1.47673200
C	0.60771600	-2.91553600	1.50559300	C	5.33246300	2.26496400	-0.56157200

C	7.20019600	0.39003700	-1.48176900	N	0.82635200	-2.06162000	-0.08441600
H	5.50332400	-0.90395600	-1.82071900	O	-0.68200100	-3.56166600	0.60717400
C	6.69067500	2.57990300	-0.57941900	C	0.17943400	-4.31865000	-0.30024400
H	4.61112300	2.99827900	-0.21581000	H	-0.41290500	-4.52860100	-1.19296200
C	7.62494200	1.64396800	-1.03300900	H	0.46280400	-5.24210800	0.20621800
H	7.92366200	-0.33880400	-1.83539400	C	1.36105700	-3.36330100	-0.57379200
H	7.01849000	3.55753800	-0.23844700	H	1.53430500	-3.26245500	-1.64711300
H	8.68259200	1.89198800	-1.03719400	C	2.64949200	-3.76068400	0.14179100
C	2.78477700	0.85167700	0.86158400	H	2.97133000	-4.74398500	-0.21959500
H	3.02868500	1.89180300	0.63305000	H	3.44636600	-3.03909800	-0.05208200
H	1.75151600	0.92827500	1.23440100	H	2.49017100	-3.81941700	1.22418100
C	3.73085900	0.20662000	1.86053800	C	-3.82576900	1.80582600	2.27857900
C	3.99624200	1.14418900	3.04786000	F	-3.46220900	2.94852800	1.65450100
H	4.68416200	-0.05042600	1.38501000	F	-3.80028400	2.05841700	3.60871500
H	3.29472900	-0.72946900	2.22059800	F	-5.10841400	1.54875400	1.94756600
H	4.65082400	0.66266000	3.78449400	N	2.73535000	1.49240900	-0.93569000
H	4.48377200	2.06877500	2.71480100	C	3.30749900	2.48040000	-1.11930400
H	3.06181400	1.41861300	3.55313400	C	2.99424400	-0.51639500	1.04031300
Structure IN2				C	2.49421700	-0.72458900	2.33149900
Pd	1.76357000	-0.25725000	-0.51322200	C	4.38119800	-0.49736800	0.83470400
N	-0.72114500	-0.03683900	1.25949500	C	3.37398600	-0.91819200	3.40408700
C	-1.56472200	0.91565100	1.64506900	H	1.42353500	-0.73625400	2.50834900
H	-1.16045200	1.92037400	1.72636200	C	5.25626900	-0.69925800	1.90895900
C	-2.91726700	0.66692100	1.90728900	H	4.78965100	-0.33005800	-0.15834100
C	-3.40003900	-0.63470400	1.80044500	C	4.75572000	-0.91107200	3.19643700
H	-4.44556500	-0.85560100	1.98452700	H	2.97325400	-1.07811800	4.40272600
C	-2.51862200	-1.64024100	1.40855500	H	6.32995500	-0.68801200	1.73484200
H	-2.85633900	-2.66019800	1.27740500	H	5.43615000	-1.06576400	4.02991300
C	-1.19515000	-1.28581000	1.12833300	C	4.08517800	3.69797800	-1.31277100
C	-0.27540200	-2.28946800	0.54854200	C	5.51960800	3.55062900	-0.75454700

H	3.55563000	4.51850500	-0.81319600	C	-3.68029400	0.87465300	1.43977000
H	4.10449000	3.92325200	-2.38593000	H	-4.72402700	1.14729100	1.33334500
C	6.31284700	4.84331200	-0.94821600	C	-3.25267400	-0.42413900	1.16675800
H	5.46369400	3.29180900	0.30899500	H	-3.95381700	-1.18508400	0.84753100
H	6.01685900	2.71795700	-1.26511700	C	-1.88738600	-0.70854000	1.26545300
H	7.32853600	4.73287400	-0.55246400	C	-1.38929300	-2.04273700	0.85670500
H	6.39004500	5.10478800	-2.01061800	N	-0.18691700	-2.35711600	0.51249500
H	5.83569100	5.68202700	-0.42681300	O	-2.31278800	-3.00853600	0.78599000
O	0.48917600	0.05719200	-2.33394200	C	-1.64328300	-4.21773300	0.30956900
C	-0.73813200	0.34141000	-2.13597700	H	-2.13907800	-4.52215700	-0.61204200
C	-1.80765700	-0.63458600	-2.10988300	H	-1.76614100	-4.98209200	1.08084200
C	-1.15260000	1.69640000	-1.86859300	C	-0.17037100	-3.78749200	0.10561900
C	-3.11550500	-0.29778000	-1.77534100	H	0.09868300	-3.81509100	-0.95365700
C	-2.44734300	2.03583000	-1.57128500	C	0.82709700	-4.60496100	0.91814500
H	-0.37063000	2.44949000	-1.88548700	H	0.76887400	-5.65671400	0.61563000
C	-3.43668900	1.02666200	-1.51622700	H	1.84736400	-4.25224200	0.74501900
H	-3.87324600	-1.06664900	-1.71263500	H	0.60449700	-4.53697900	1.98891300
H	-2.72266000	3.06030500	-1.35088900	C	-3.08316100	3.26204100	2.02940700
N	-1.53301800	-2.03762100	-2.32822600	F	-2.46886100	4.05531300	1.11857300
O	-0.55798300	-2.36601500	-3.01041700	F	-2.67678000	3.69291100	3.24790400
O	-2.30023000	-2.86842000	-1.80751300	F	-4.40709200	3.48927500	1.93903600
N	-4.78601000	1.36212300	-1.13679400	N	3.05930000	0.08786200	-0.14070000
O	-5.05689200	2.55298500	-0.92713700	C	3.90690300	0.83572100	-0.40194300
O	-5.61738400	0.44897900	-1.02444200	O	0.70547100	-0.77816900	-1.92394200
Structure IN2'				C	-0.41955800	-0.18548400	-1.96821200
Pd	1.46348800	-1.12647700	0.20455200	C	-1.67287600	-0.83473200	-2.30556600
N	-0.97298900	0.19139400	1.66565500	C	-0.54560800	1.20516700	-1.59935800
C	-1.39056100	1.42323300	1.93796400	C	-2.89753400	-0.18046600	-2.22167900
H	-0.63346400	2.13634300	2.25483800	C	-1.74962100	1.85208600	-1.51996100
C	-2.72988400	1.81804400	1.81280900	H	0.37577200	1.71460700	-1.33406000

C	-2.93854100	1.15094200	-1.83410100	H	5.99166900	1.46399600	1.14435200
H	-3.81299200	-0.71907700	-2.42549500	C	6.97266500	3.54629800	-1.37007900
H	-1.81283800	2.88087500	-1.18705500	H	5.92458200	3.82949500	-3.23700200
N	-1.71010500	-2.24596300	-2.61650600	H	7.80178200	3.06891100	0.56610700
O	-0.70182300	-2.78917400	-3.07789800	H	7.76447200	4.24629700	-1.62083200
O	-2.76707000	-2.86544100	-2.39454800	C	2.12718500	-1.45585500	2.11302200
N	-4.21363200	1.78718800	-1.64513800	H	2.13000600	-0.45598500	2.56539700
O	-4.23290700	2.91912000	-1.13506700	H	1.36065900	-2.06287100	2.60439300
O	-5.24336700	1.17627700	-1.96968600	C	3.50082000	-2.10997900	2.19519300
C	4.94715400	1.75399300	-0.72864100	C	3.91346500	-2.35662900	3.65661700
C	4.91881500	2.41731600	-1.96992800	H	4.25230100	-1.47592900	1.70908800
C	5.98591500	1.98506900	0.19244000	H	3.50297900	-3.06696400	1.65826100
C	5.93773800	3.31312100	-2.28209300	H	4.90654500	-2.82013700	3.71390400
H	4.10987900	2.22598400	-2.66755200	H	3.94696700	-1.41583200	4.22073200
C	6.99598600	2.88443800	-0.13773400	H	3.20113800	-3.02259900	4.15985700

5. References

- (1) Nambara, T.; Honma, S.; Akiyama, S. Studies on Steroid Conjugates. III. New Syntheses of 2-Methoxyestrogens. *Chem. Pharm. Bull.* **1970**, *18*, 474-480.
- (2) Delay, D. New Syntheses of Plant Aryl Glycosides as Potential Gene Inducers. *Carbohydr. Res.* **1990**, *198*, 223–234.
- (3) Fan, P.; Zhang, C.; Zhang, L.; Wang C. Acylation of Aryl Halides and α -Bromo Acetates with Aldehydes Enabled by Nickel/TBADT Cocatalysis. *Org. Lett.* **2020**, *22*, 3875-3878.
- (4) Peng, J.-B.; Chen, B.; Qi, X.; Ying, J.; Wu, X.-F. Palladium-Catalyzed Carbonylative Coupling of Aryl Iodides with Alkyl Bromides: Efficient Synthesis of Alkyl Aryl Ketones. *Adv. Synth. Catal.* **2018**, *360*, 4153-4160.
- (5) Hsieh, J.-C.; Chen, Y.-C.; Cheng, A.-Y.; Tseng, H.-C. Nickel-Catalyzed Intermolecular Insertion of Aryl Iodides to Nitriles: A Novel Method to Synthesize Arylketones. *Org. Lett.*, **2012**, *14*, 1282-1285.

- (6) Neve, J. E.; Wijesekera, H. P.; Duffy, S.; Jenkins, I. D.; Ripper, J. A.; Teague, S. J.; Campitelli, M.; Garavelas, A.; Nikolakopoulos, G.; Le, P. V.; Leone, P. de A.; Pham, N. B.; Shelton, P.; Fraser, N.; Carroll, A. R.; Avery, V. M.; McCrae, C.; Williams, N.; Quinn, R. J. Euodenine A: A Small-Molecule Agonist of Human TLR4. *Journal of Medicinal Chemistry*, **2014**, *57*, 1252-1275.
- (7) Lo Fiego, M. J.; Badajoz, M. A.; Domini, C.; Chopra, A. B.; Lockhart, M. T. Indium-mediated Regioselective Synthesis of Ketones from Arylstannanes under Solvent-free Ultrasound Irradiation. *Ultrasonics Sonochemistry* **2013**, *20*, 826-832.
- (8) Branstrom, A.; Josyula, V. P. V. N.; Arnold, M. A.; Gerasyuto, A. I.; Karp, G.; Wang, J. Antibacterial Compounds and Methods for Use. PCT Int. Appl., 2013033258, WO 2013033258.
- (9) Ueda, S.; Su, M.; Buchwald, S. L. Highly N²-Selective Palladium-Catalyzed Arylation of 1,2,3-Triazoles. *Angew. Chem. Int. Ed.* **2011**, *50*, 8944-8947.
- (10) Lin, C.-H.; Chen, C.-C.; Wu, M.-J. Mercury(II)-Catalyzed Cyclization of 2-Alkynylphenyl Alkyl Sulfoxides Provides 3-Acylbenzo[b]thiophenes. *Chem. Eur. J.* **2013**, *19*, 2578-2581.
- (11) Li, H.; Ma, B.; Liu, Q.-S.; Wang, M.-L.; Wang, Z.-Y.; Xu, H.; Li, L.-J.; Wang, X.; Dai, H.-X. Transformations of Aryl Ketones via Ligand-Promoted C-C Bond Activation. *Angew. Chem. Int. Ed.* **2020**, *59*, 14388-14393.
- (12) Miyata, O.; Takeda, N.; Naito, T. Highly Effective Synthetic Methods for Substituted 2-Arylbenzofurans Using [3,3]-Sigmatropic Rearrangement: Short Syntheses of Stemofuran A and Eupomatenoid 6. *Org. Lett.* **2004**, *6*, 1761-1763.
- (13) Chiu, H. C.; Tonks, I. A. Trimethylsilyl-Protected Alkynes as Selective Cross-Coupling Partners in Titanium-Catalyzed [2+2+1] Pyrrole Synthesis. *Angew. Chem. Int. Ed.* **2018**, *57*, 6090-6094.
- (14) Chiu, H.-C.; See, X. Y.; Tonks, I. A. Dative Directing Group Effects in Ti-Catalyzed [2+2+1] Pyrrole Synthesis: Chemo- and Regioselective Alkyne Heterocoupling. *ACS Catal.* **2019**, *9*, 216-223.
- (15) Nozawa-Kumada, K.; Inagi, M.; Kondo, Y. Highly Chemoselective DMPU-Mediated Trialkylsilylation of Terminal Alkynes Using

- Trifluoromethyltrialkylsilane. *Asian J. Org. Chem.* **2017**, *6*, 63-66.
- (16) Lei, Y.; Hu, T.; Wu, X.; Wu, Y.; Xiang, H.; Sun, H.; You, Q.; Zhang, X. Microwave-assisted Copper- and Palladium-catalyzed Sonogashira-type Coupling of Aryl Bromides and Iodides with Trimethylsilylacetylene. *Tetrahedron Lett.* **2016**, *57*, 1100-1103.
- (17) Agejas-Chicharro, F. J.; Dressman, B. A.; Gutierrez Sanfeliciano, S.; Henry, S. S.; Martinez Perez, J. A.; Massey, S. M.; Monn, J. A.; Zia-Ebrahimi, M. S. Pyridyl Derivatives and Their Use as Mglu5 Antagonists. PCT Int. Appl., 2005094822, WO 2005094822.
- (18) Arde, P.; Reddy, V.; Anand, R. V. NHC Catalysed Trimethylsilylation of Terminal Alkynes and Indoles with Ruppert's Reagent under Solvent Free Conditions. *RSC Adv.*, **2014**, *4*, 49775-49779.
- (19) Ladouceur, S.; Soliman, A. M.; Zysman-Colman, E. One-Pot Click Synthesis of 1N-Alkyl-4-aryl-1,2,3-triazoles from Protected Arylalkynes and Alkyl Bromides. *Synthesis* **2011**, *22*, 3604-3611.
- (20) Li, P.; Wang, L.; Wang, M.; You, F. Gold(I) Iodide Catalyzed Sonogashira Reactions. *Eur. J. Org. Chem.* **2008**, 5946-5951.
- (21) Huang, H.; Liu, H.; Jiang, H.; Chen, K. Rapid and Efficient Pd-Catalyzed Sonogashira Coupling of Aryl Chlorides. *J. Org. Chem.* **2008**, *73*, 6037-6040.
- (22) Yang, Y.-M.; Yao, J.-F.; Yan, W.; Luo, Z.; Tang, Z.-Y. Silver-Mediated Trifluoromethoxylation of (Hetero)aryldiazonium Tetrafluoroborates. *Org. Lett.* **2019**, *21*, 8003-8007.
- (23) Truong, T.; Daugulis, O. Transition-Metal-Free Alkynylation of Aryl Chlorides. *Org. Lett.* **2011**, *13*, 4172-4175.
- (24) Cai, R.; Lu, M.; Aguilera, E. Y.; Xi, Y.; Akhmedov, N. G.; Petersen, J. L.; Chen, H.; Shi, X. Ligand-Assisted Gold-Catalyzed Cross-Coupling with Aryldiazonium Salts: Redox Gold Catalysis without an External Oxidant. *Angew. Chem. Int. Ed.* **2015**, *54*, 8772-8776.
- (25) Liang, B.; Dai, M.; Chen, J.; Yang, Z. Copper-Free Sonogashira Coupling Reaction with PdCl₂ in Water under Aerobic Conditions. *J. Org. Chem.* **2005**, *70*,

391-393.

(26) Torigoe, T.; Ohmura, T.; Suginome, M. Iridium-Catalyzed Intramolecular Methoxy C–H Addition to Carbon–Carbon Triple Bonds: Direct Synthesis of 3-Substituted Benzofurans from o-Methoxyphenylalkynes. *Chem. Eur. J.* **2016**, *22*, 10415-10419.

(27) Wang, W.-Y.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. One-pot Synthesis of 3-trifluoromethylbenzofurans via Tandem Iodocyclization and Trifluoromethylation of 2-alkynylanisoles. *Tetrahedron Lett.* **2014**, *55*, 1501-1503.

(28) Rubin, M.; Trofimov, A.; Gevorgyan, V. Can Polarization of Triple Bond in Tolanes Be Deduced from ¹³C NMR Shifts? Re-evaluation of Factors Affecting Regiochemistry of the Palladium-Catalyzed Hydrostannation of Alkynes. *J. Am. Chem. Soc.* **2005**, *127*, 10243-10249.

(29) Gay, R. M.; Manarin, F.; Schneider, C. C.; Barancelli, D. A.; Costa, M. D.; Zeni, G. FeCl₃-Diorganyl Dichalcogenides Promoted Cyclization of 2-Alkynylanisoles to 3-Chalcogen Benzo[b]furans. *J. Org. Chem.* **2010**, *75*, 5701-5706.

(30) Beshai, M. Terminal Alkynes from Aldehydes via Dehydrohalogenation of (Z)-1-iodo-1-alkenes with TBAF. *Tetrahedron Lett.* **2008**, *49*, 6794-6796.

(31) Campbell, A. D. The Preparation of Polycyclic Aromatic Hydrocarbons from Arylpropionic acids. *J. Chem. Soc.* **1954**, 3659-3669.

(32) Clive, D. L. J.; Sunasee, R.; Chen, Z. Formal Radical Closure onto Aromatic Rings—A General Route to Carbocycles. *Org. Biomol. Chem.* **2008**, *6*, 2434-2441.

(33) Hiyama, T. A Facile, Practical Synthesis of 2-(6-Methoxy-2-naphthyl)propenoic Acid. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 640-642.

(34) St-Pierre, G. Fraternal Twin Iridium Hemicage Chelates. *Dalton Trans.* **2011**, *40*, 11726-11731.

(35) Ames, D. E. A Convenient Synthesis of Ethynyl-N- heteroarenes. *Synthesis* **1981**, *5*, 364-365.

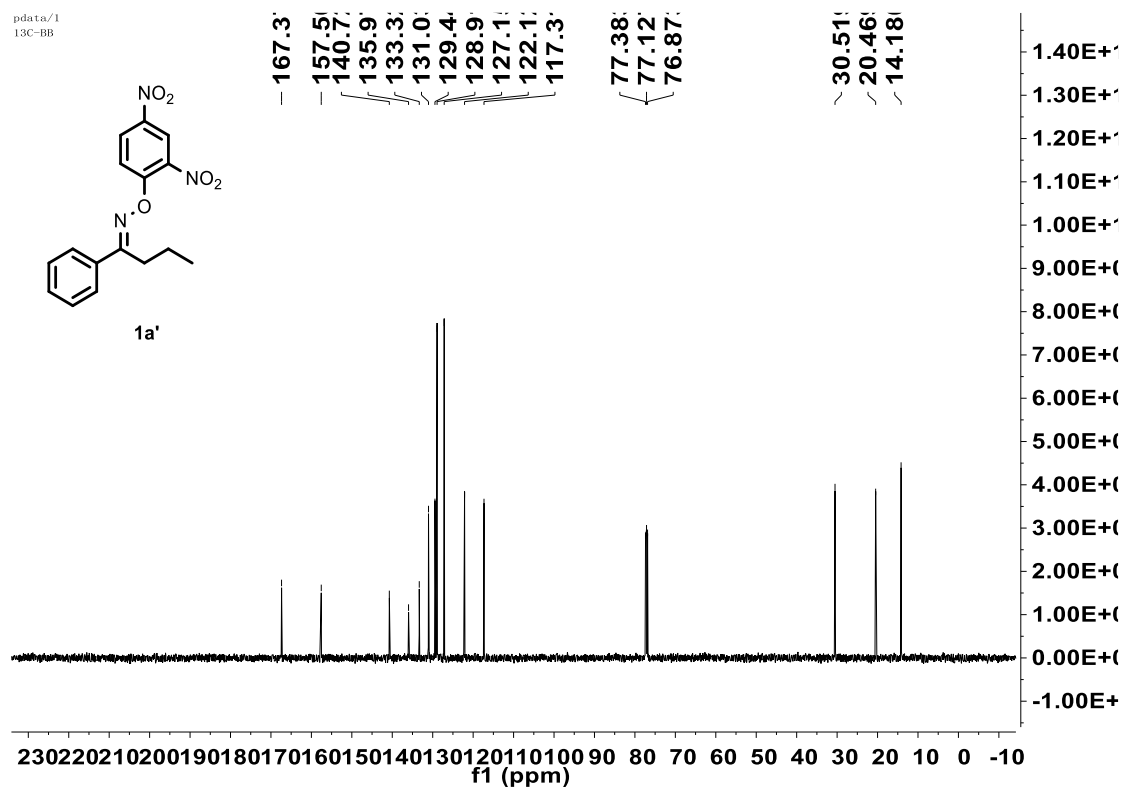
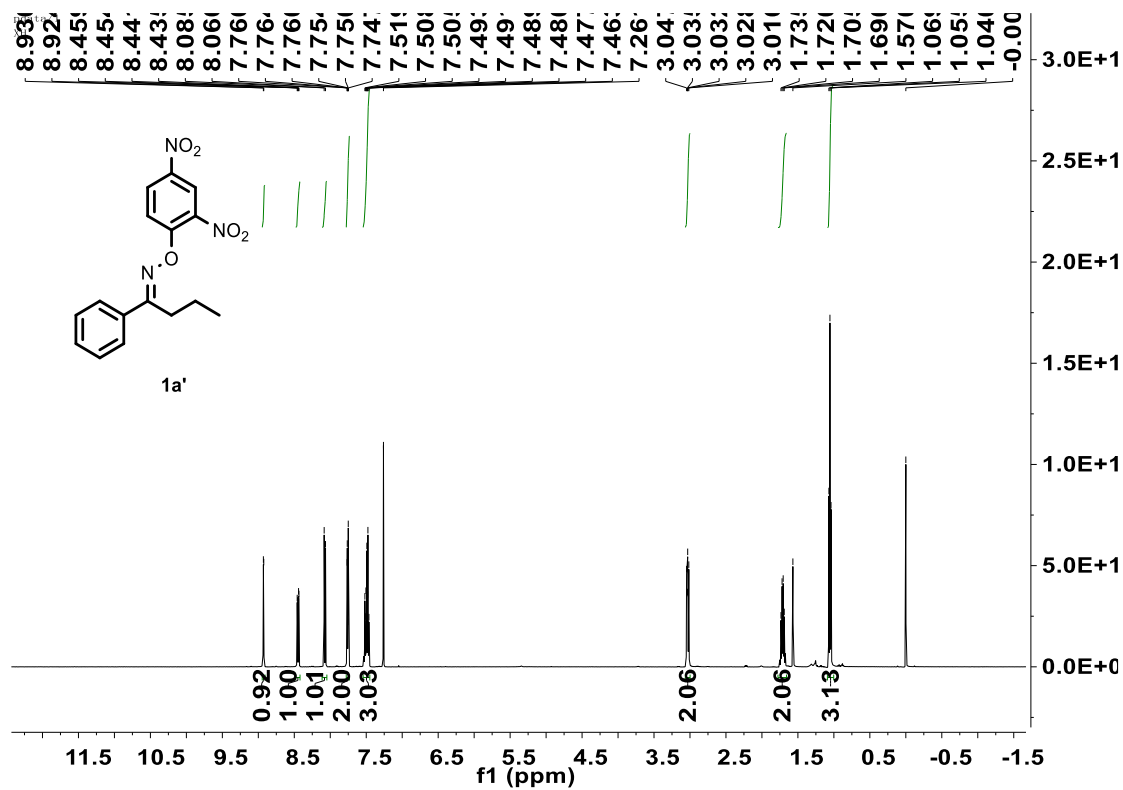
(36) Tran, G.; Pardo, D. G.; Tsuchiya T.; Hillebrand, S.; Vors, J.-P.; Cossy, J. Modular, Concise, and Efficient Synthesis of Highly Functionalized 5-Fluoropyridazines by a [2 + 1]/[3 + 2]-Cycloaddition Sequence. *Org. Lett.* **2015**, *17*, 3414-3417.

- (37) Feng, L.; Hu, T.; Zhang, S.; Xiong, H.-Y.; Zhang, G. Copper-Mediated Deacylative Coupling of Ynones via C–C Bond Activation under Mild Conditions. *Org. Lett.* **2019**, *21*, 9487-9492.
- (38) Li, C.; Zhao, P.; Li, R.; Zhang, B.; Zhao, W. Oxidation of Alkynyl Boronates to Carboxylic Acids, Esters, and Amides. *Angew. Chem. Int. Ed.* **2020**, *59*, 10913-10917.
- (39) Jalagam, P. R.; Nair, S. K.; Panda, M.; Feng, J.; Wang, W.; Liu, C.; Ellsworth, B. A.; Sarabu, R.; Swidorski, J.; Hartz, R. A. Small Molecule Inhibitors of Galectin-3. Patent Number WO2019067702A1, Apr. 04, 2019.
- (40) Sanchez-Cantalejo, F.; Priest, J. D.; Davies, P. W. A Gold Carbene Manifold to Prepare Fused γ -Lactams by Oxidative Cyclisation of Ynamides. *Chem. Eur. J.* **2018**, *24*, 17215-17219.
- (41) Donald, J. R.; Berrell, S. L. Radical Cyanomethylation via Vinyl Azide Cascade-Fragmentation. *Chem. Sci.*, **2019**, *10*, 5832-5836.
- (42) Becke, A. D. Density-Functional Thermochemistry.3. The Role of Exact Exchange. *J. Chem. Phys.*, **1993**, *98*, 5648-5652.
- (43) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into A Functional of the Electron Density. *Physical Review B*, **1988**, *37*, 785-789.
- (44) Becke, A. D. A New Mixing of Hartree-Fock and Local Density-Functional Theories. *J. Chem. Phys.*, **1993**, *98*, 1372-1377.
- (45) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab-Initio Calculation of Vibrational Absorption and Circular- Dichroism Spectra Using Density-Functional Force-Fields. *J. Phys. Chem.*, **1994**, *98*, 11623-11627.
- (46) Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-Consistent Molecular-Orbital Methods.9. Extended Gaussian-Type Basis for Molecular-Orbital Studies of Organic Molecules. *J. Chem. Phys.*, **1971**, *54*, 724-728.
- (47) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self-Consistent Molecular-Orbital Methods.12. Further Extensions of Gaussian-Type Basis Sets for Use in Molecular-Orbital Studies of Organic Molecules. *J. Chem. Phys.*, **1972**, *56*, 2257-2261.

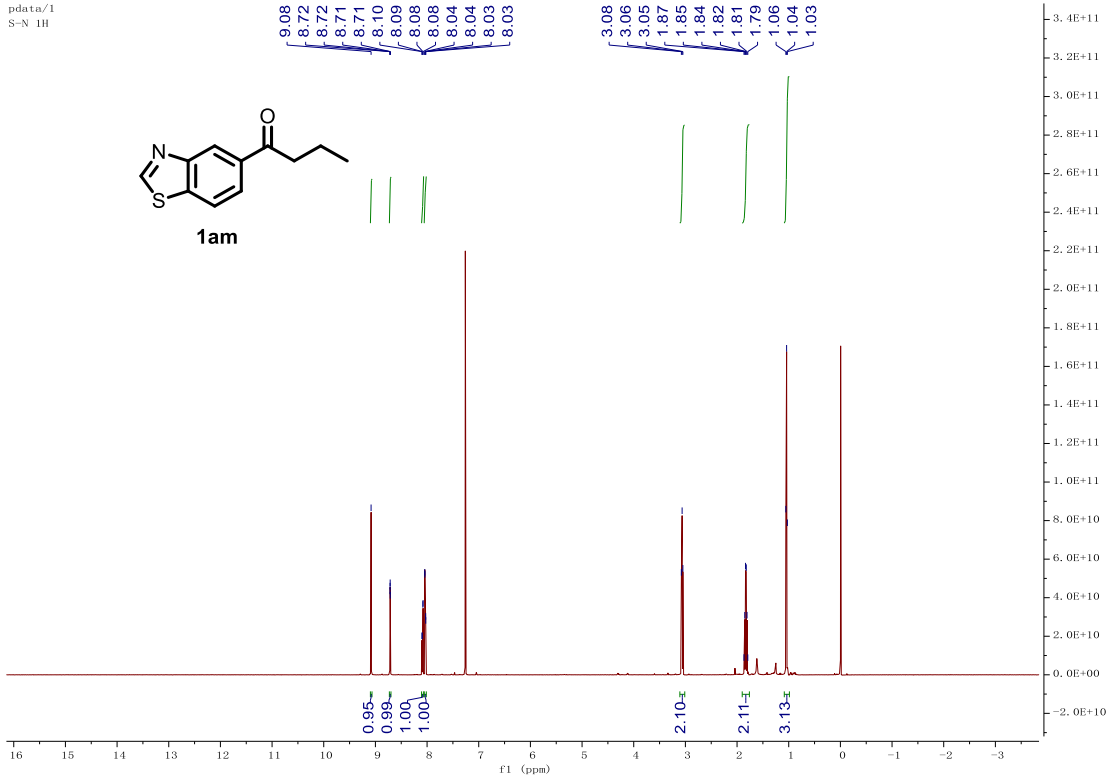
- (48) Hay, P. J.; Wadt, W. R. Abinitio Effective Core Potentials for Molecular Calculations - Potentials for K to Au Including the Outermost Core Orbitals. *J. Chem. Phys.*, **1985**, *82*, 299-310.
- (49) Roy, L. E.; Hay, P. J.; Martin, R. L. Revised Basis Sets for the LANL Effective Core Potentials. *J. Chem. Theory Comput.*, **2008**, *4*, 1029-1031.
- (50) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-class Functionals and 12 Other Functionals. *Theor. Chem. Acc.*, **2008**, *120*, 215-241.
- (51) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B*, **2009**, *113*, 6378-6396.
- (52) Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H. Energy-adjusted Ab Initio Pseudopotentials for the First Row Transition Elements. *The Journal of Chemical Physics*, **1987**, *86*, 866-872.
- (53) Andrae, D.; Haussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. Energy-Adjusted Abinitio Pseudopotentials for the 2nd and 3rd Row Transition-Elements. *Theor. Chim. Acta*, **1990**, *77*, 123-141.
- (54) S. Grimme, J. Antony, S. Ehrlich and H. Krieg, A Consistent and Accurate Ab Initio Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu, *J. Chem. Phys.*, 2010, **132**, 154104-154119.
- (55) Legault, C. Y. CYLView, 1.0b; Université de Sherbrooke, Canada, 2009; <http://www.cylview.org>.

6. NMR Spectra

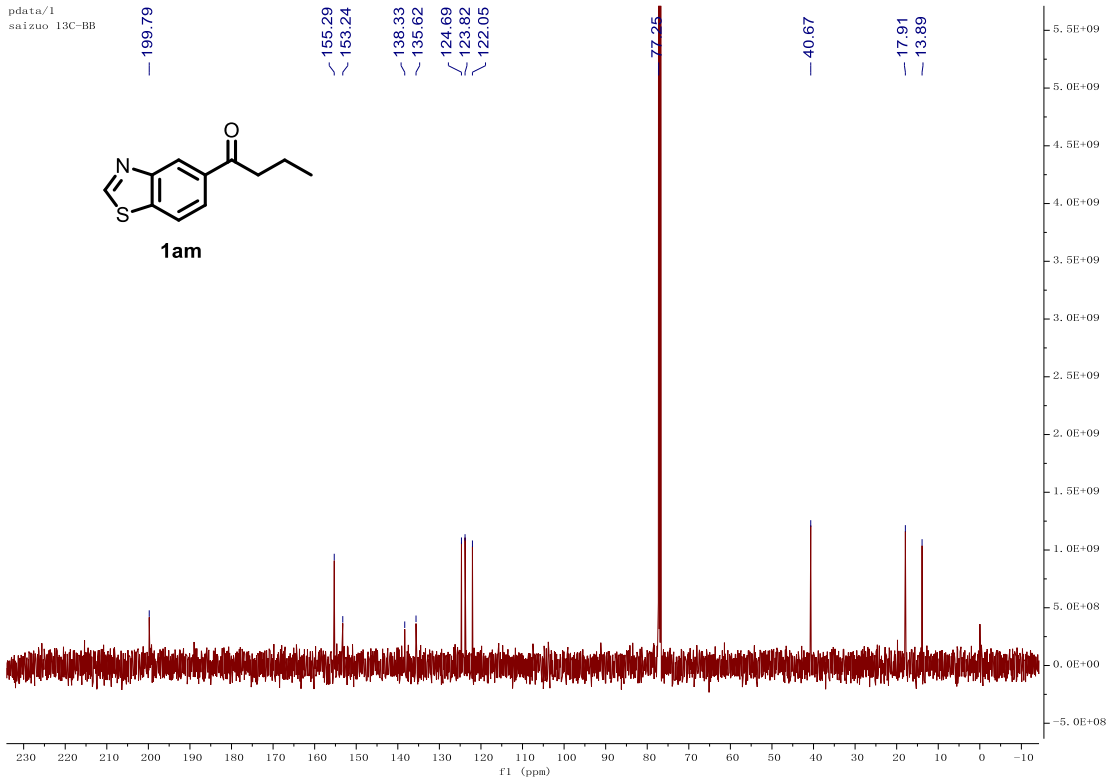
6.1 NMR Spectra for New Starting Material

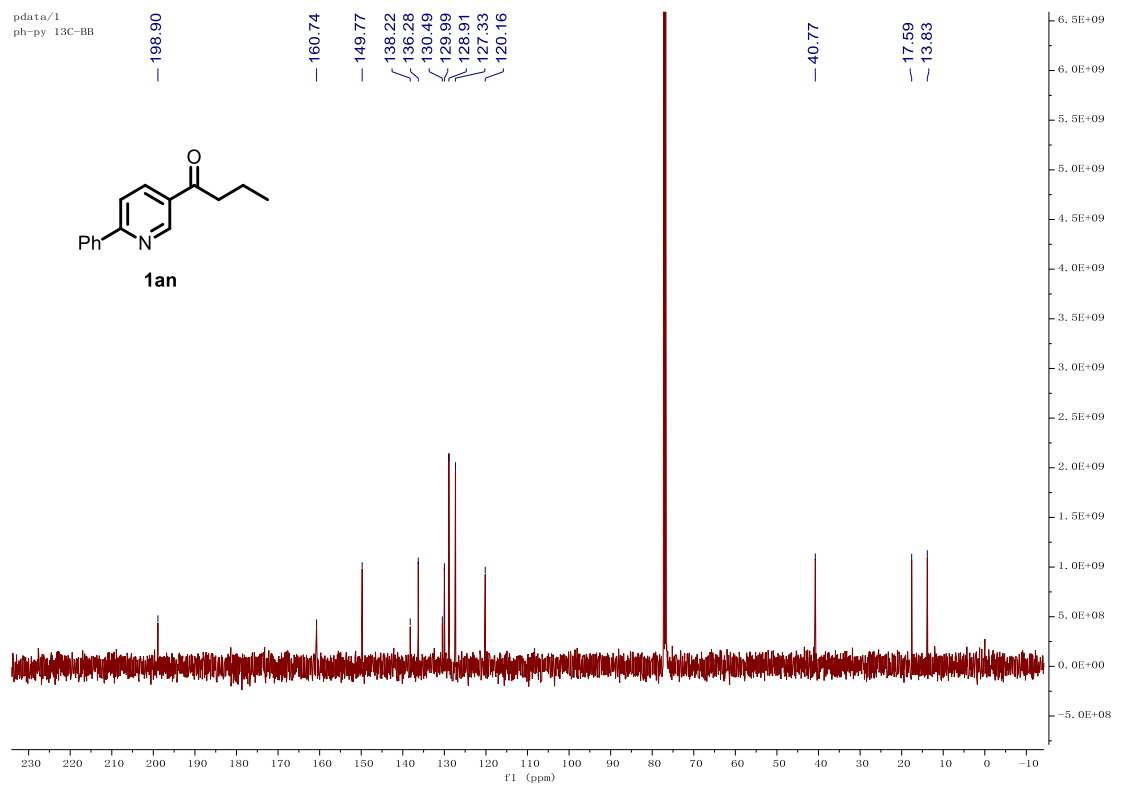
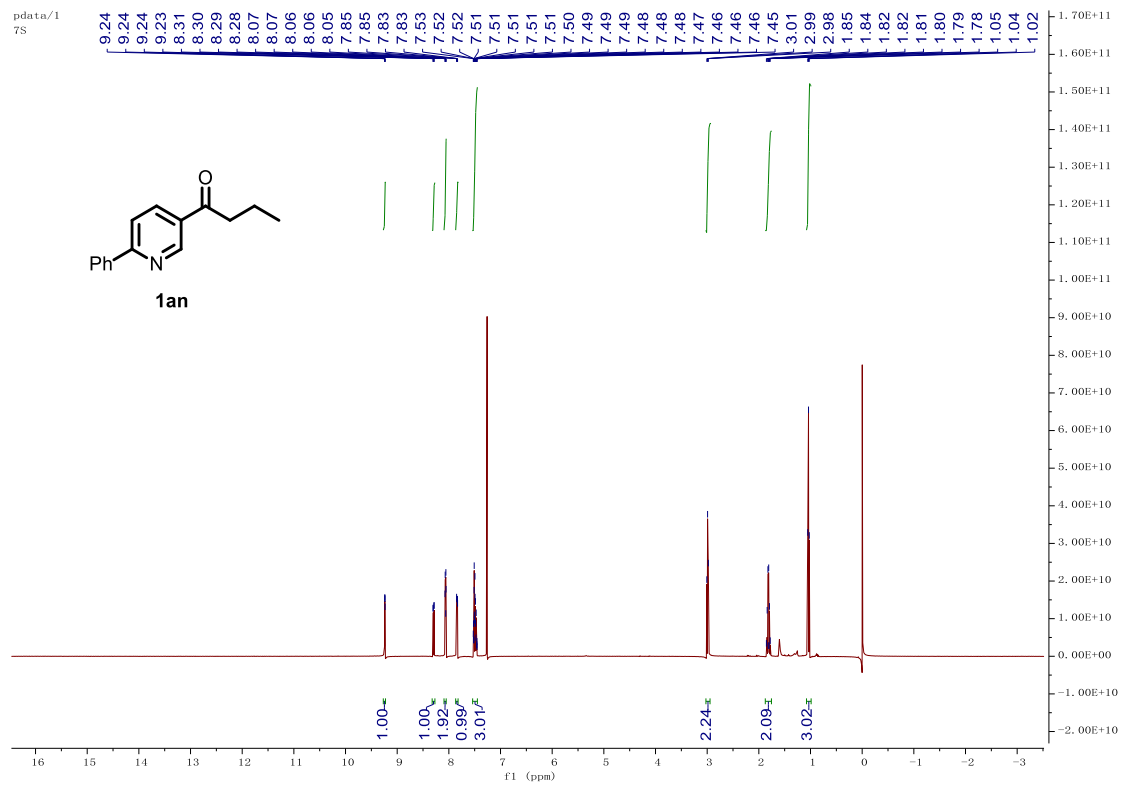


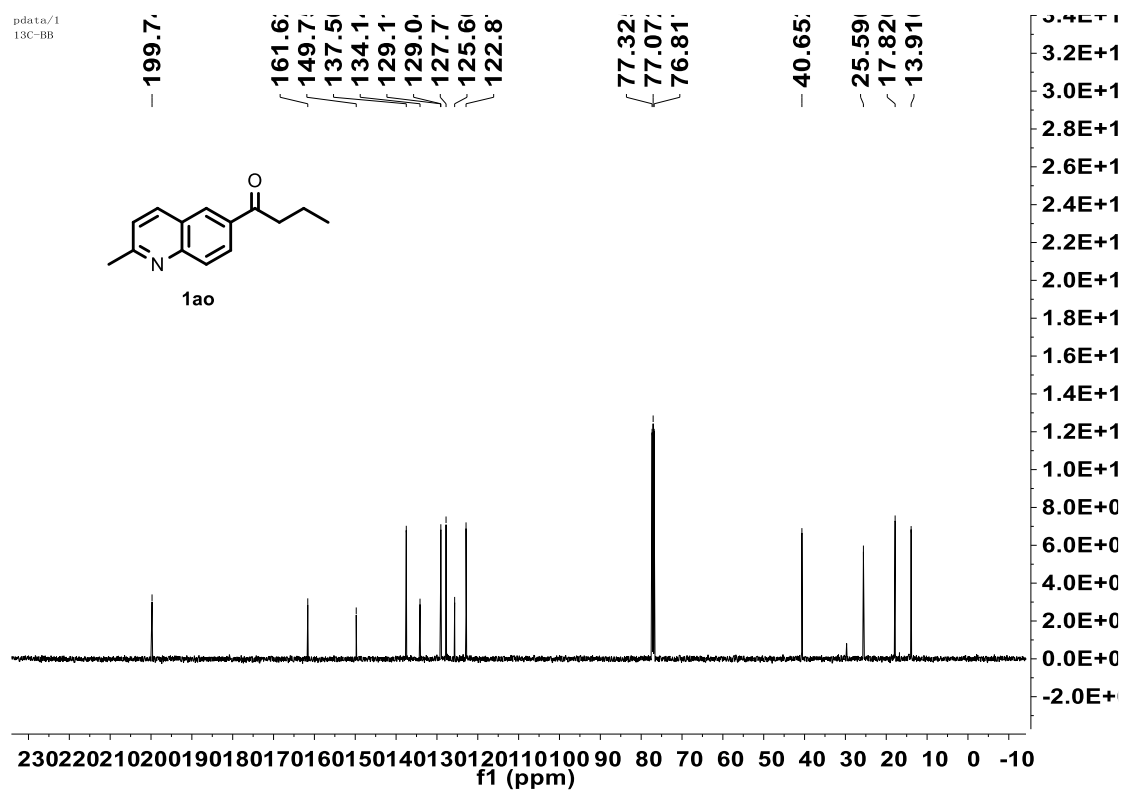
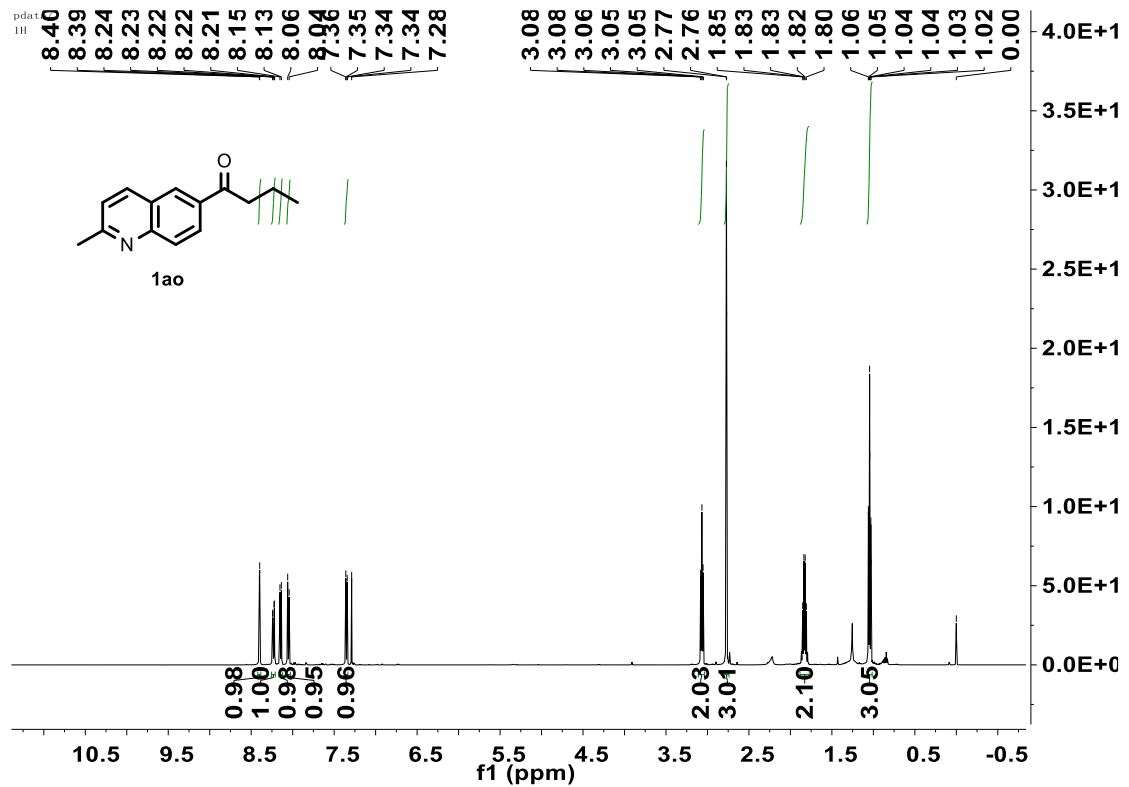
pdata/1
S-N 1H

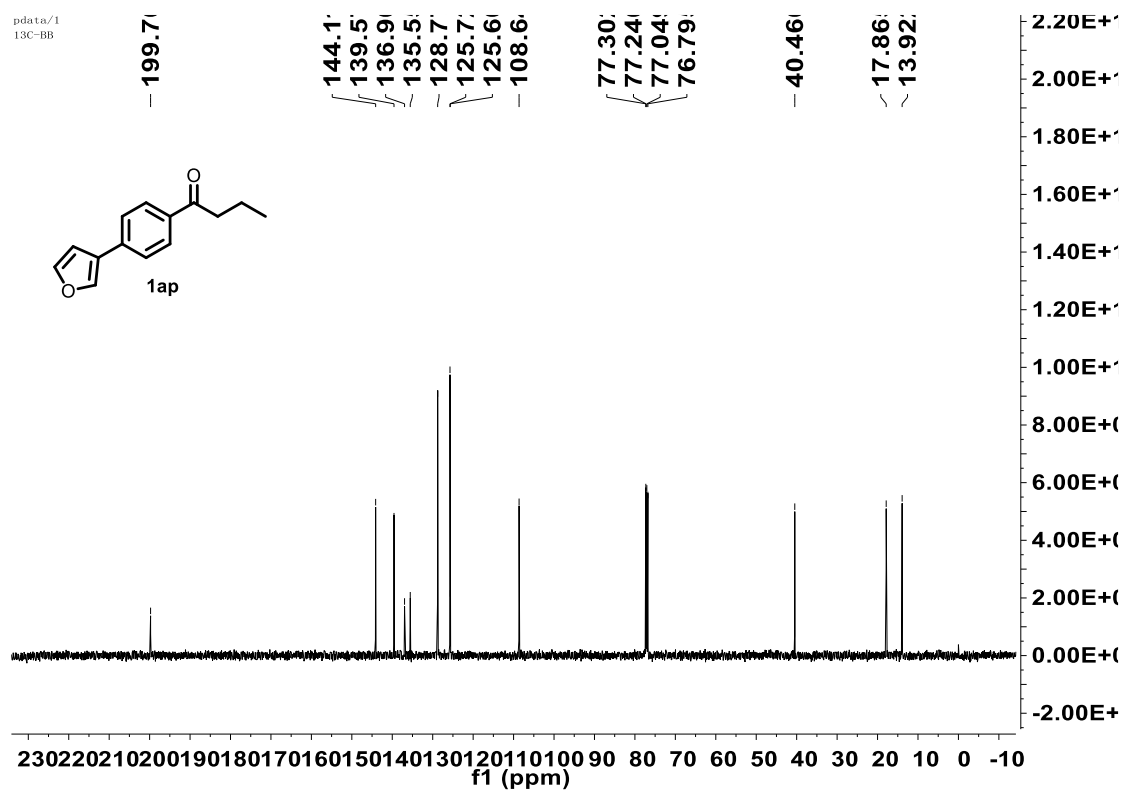
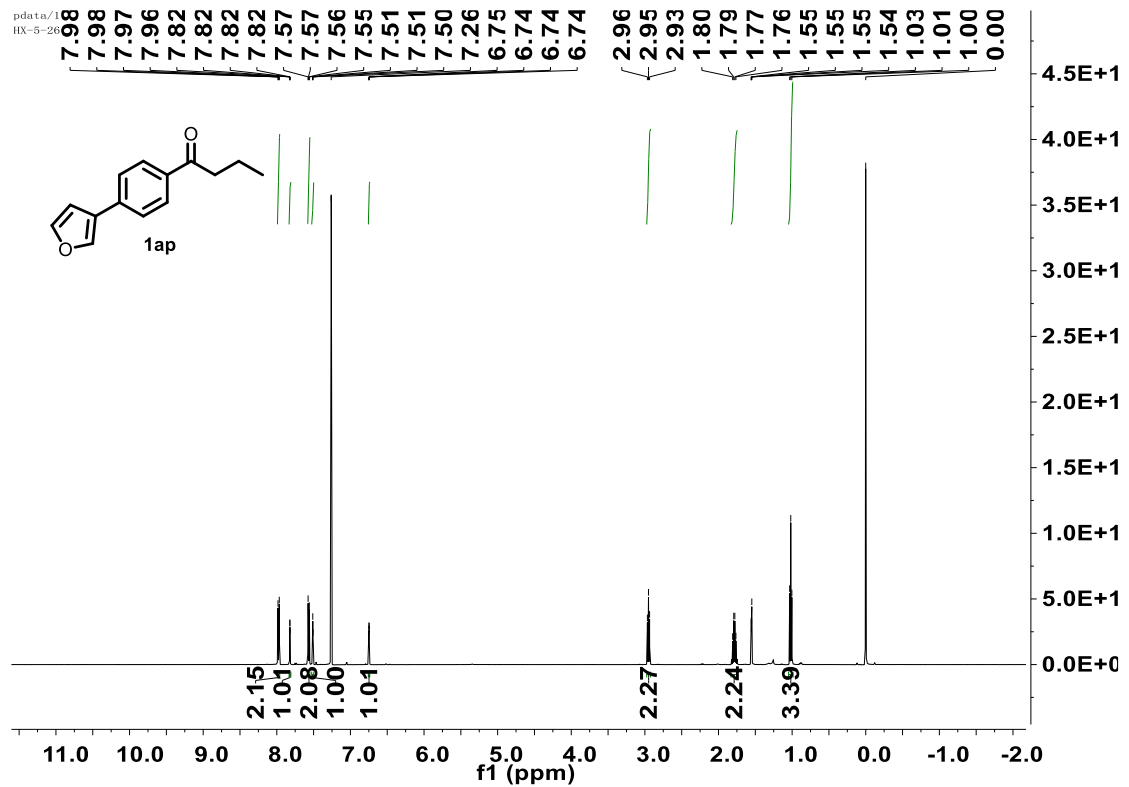


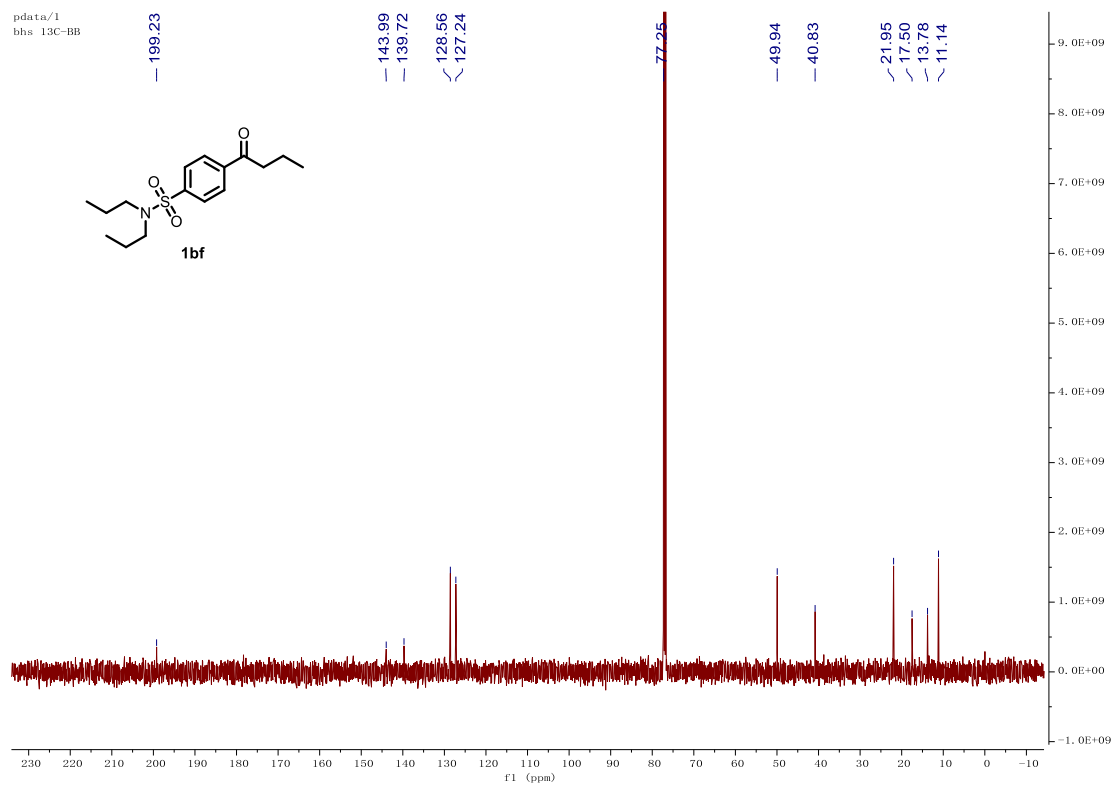
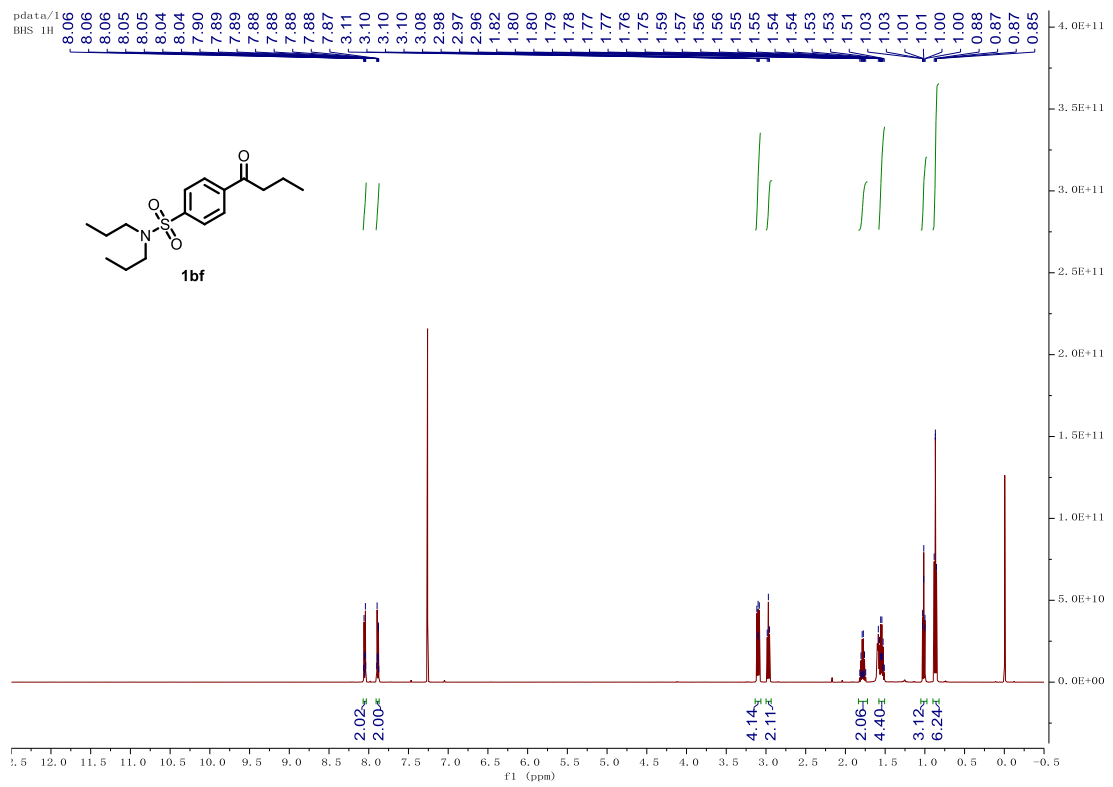
pdata/1
saizuo 13C-BB

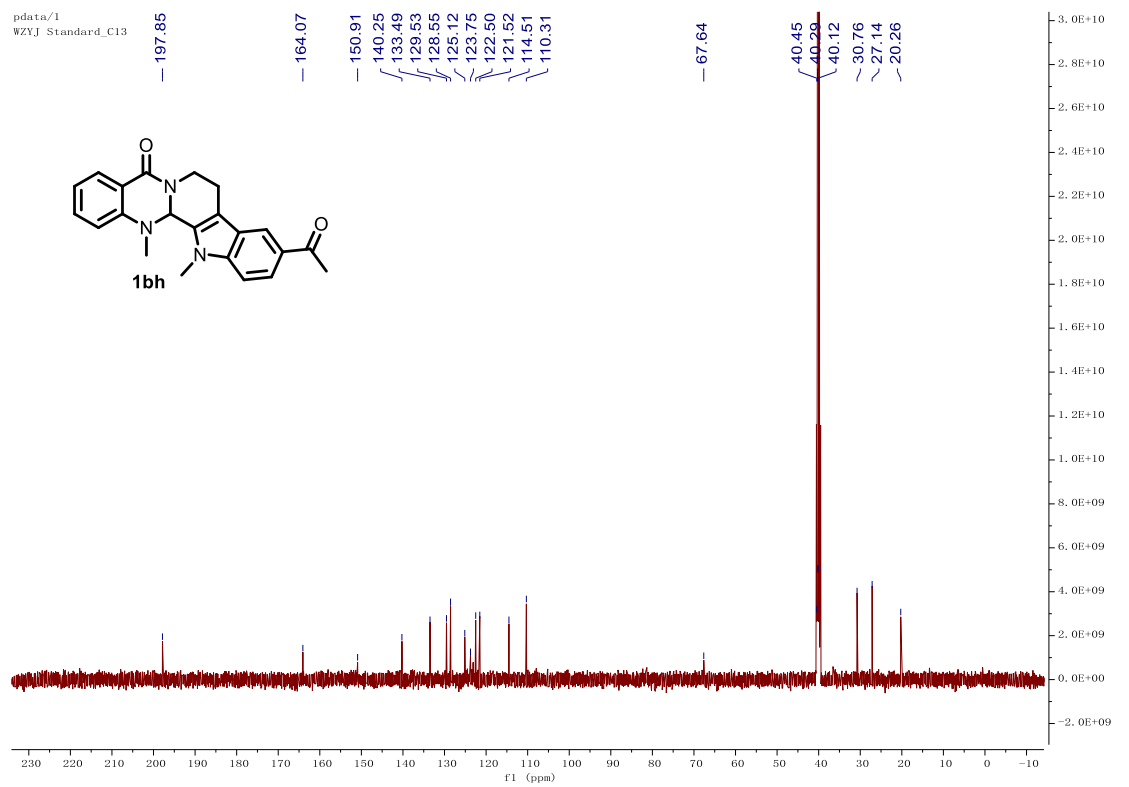
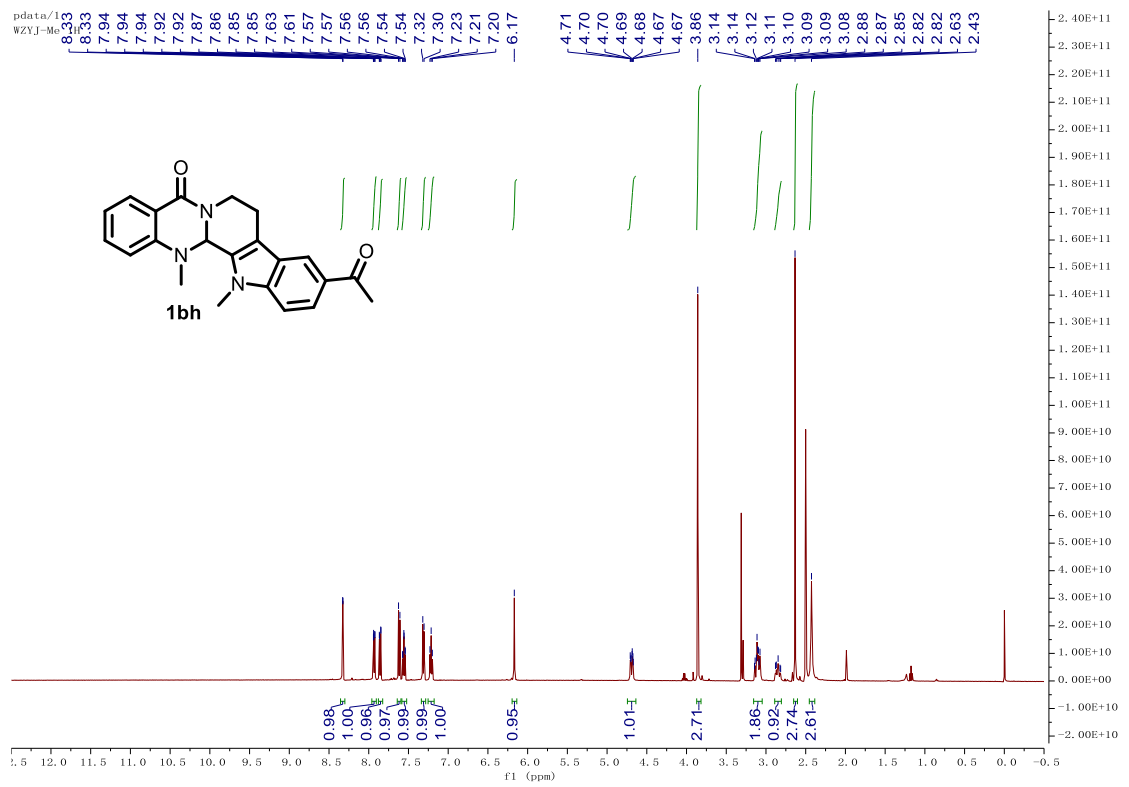


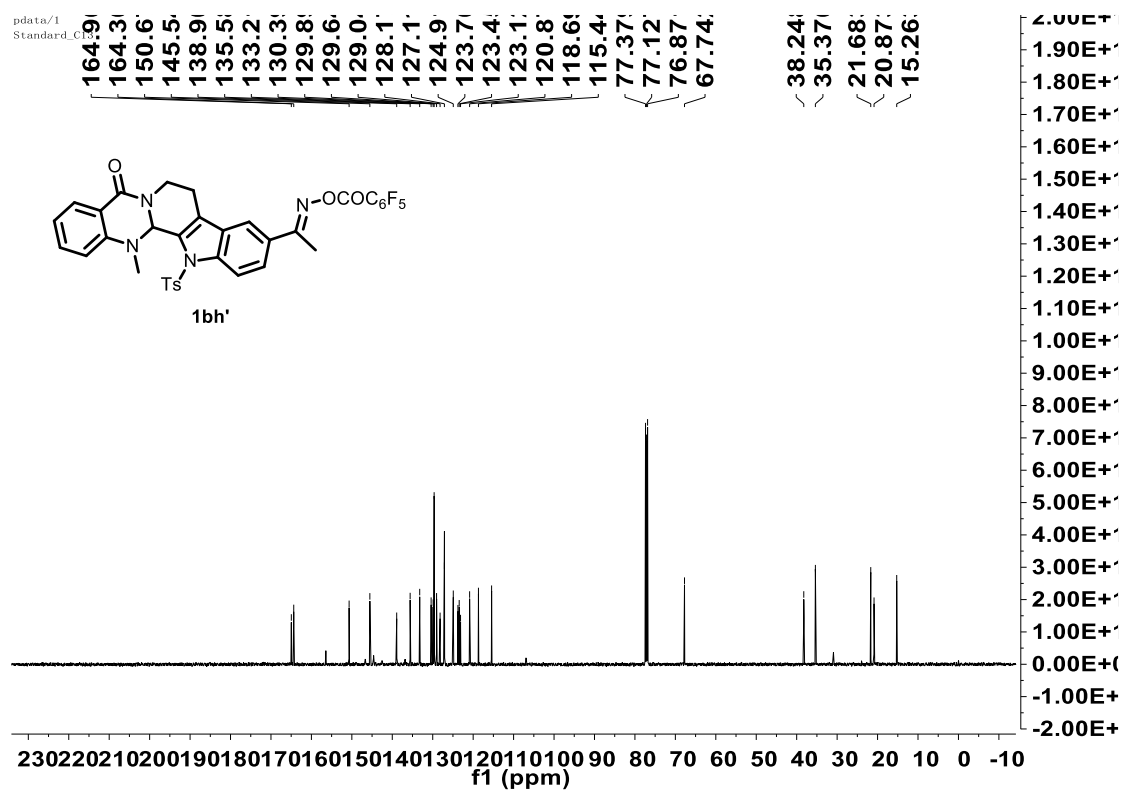
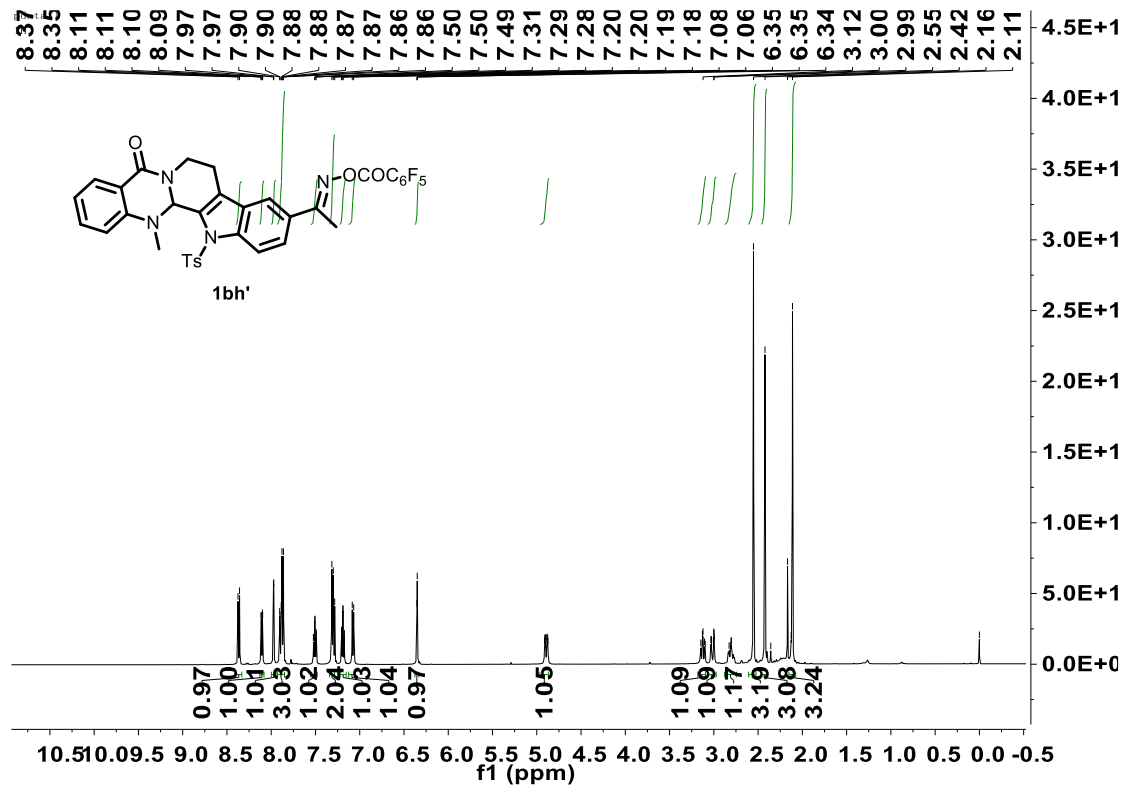


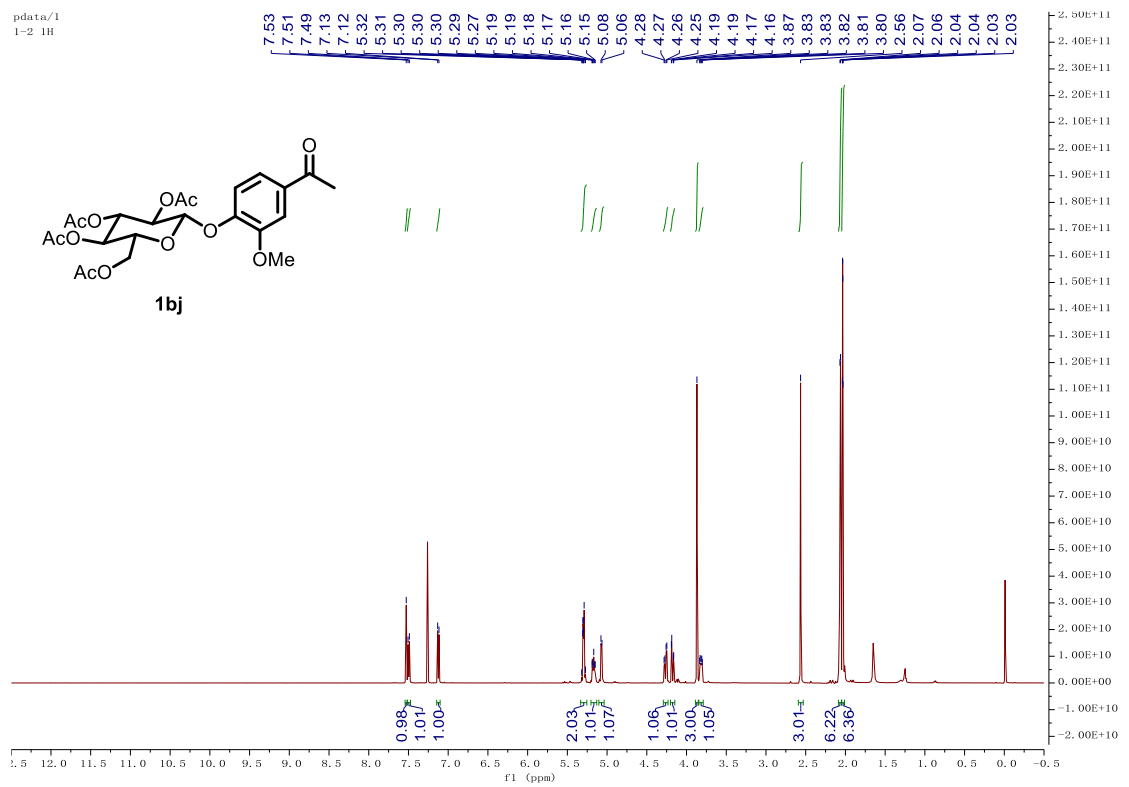
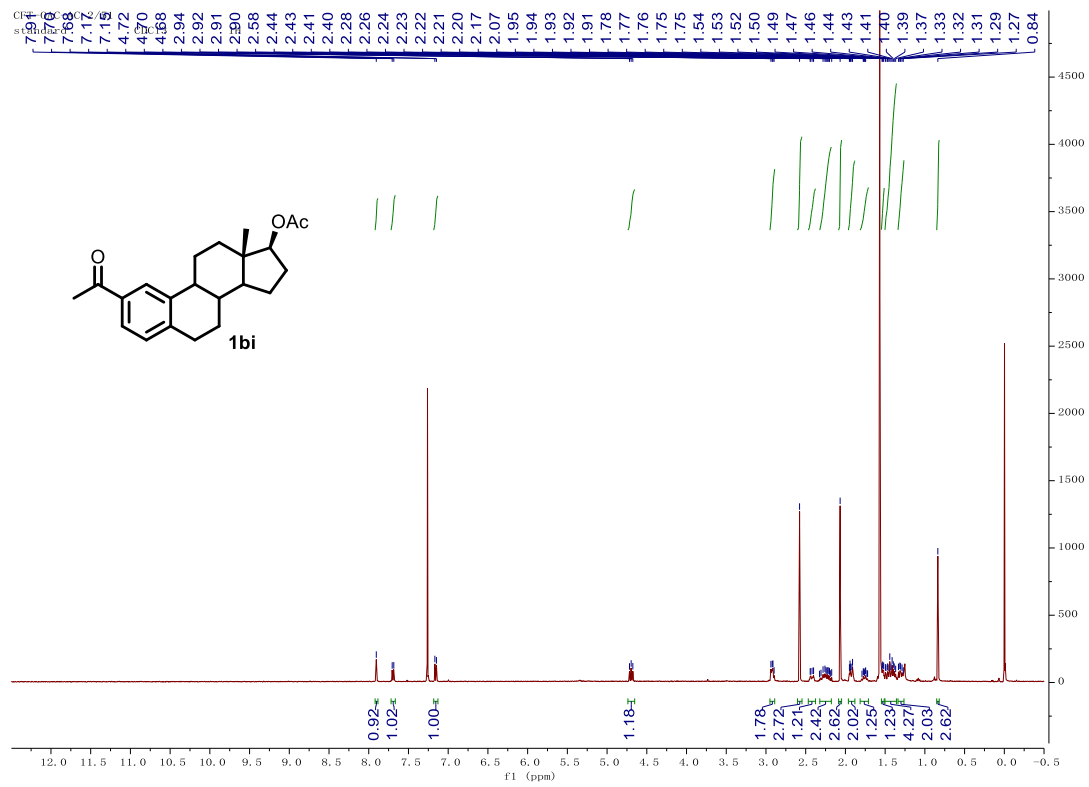


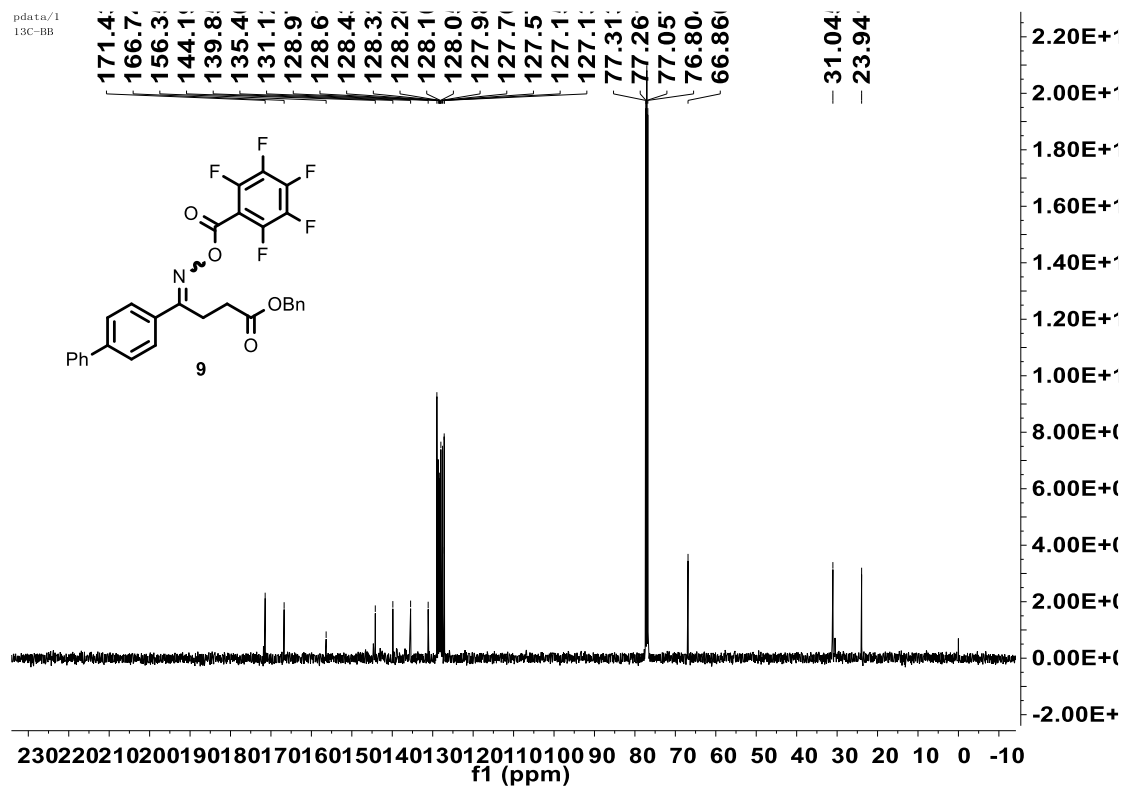
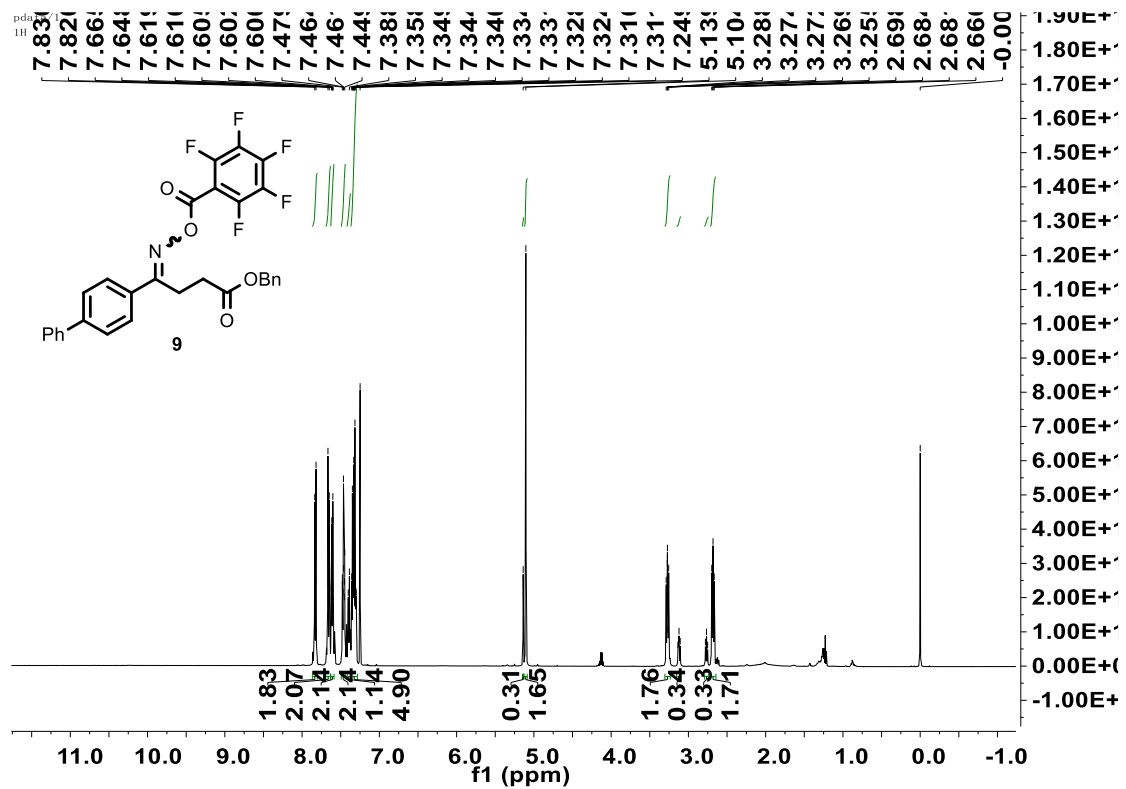




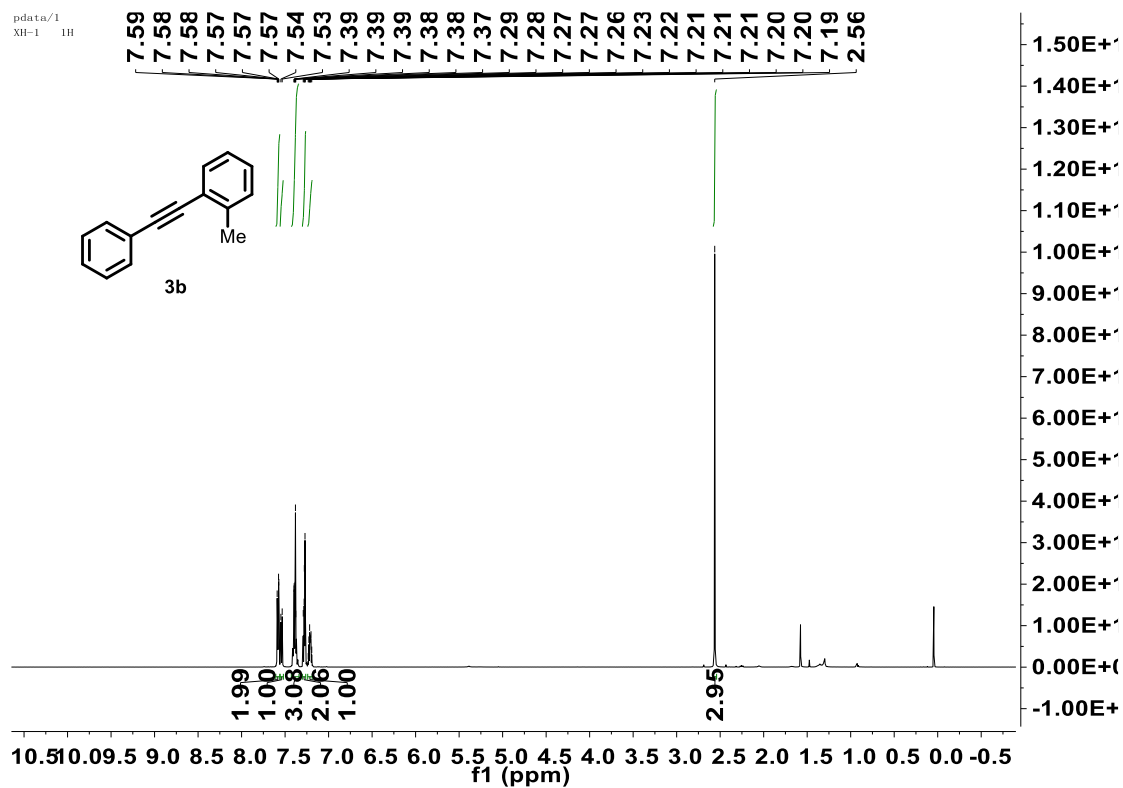
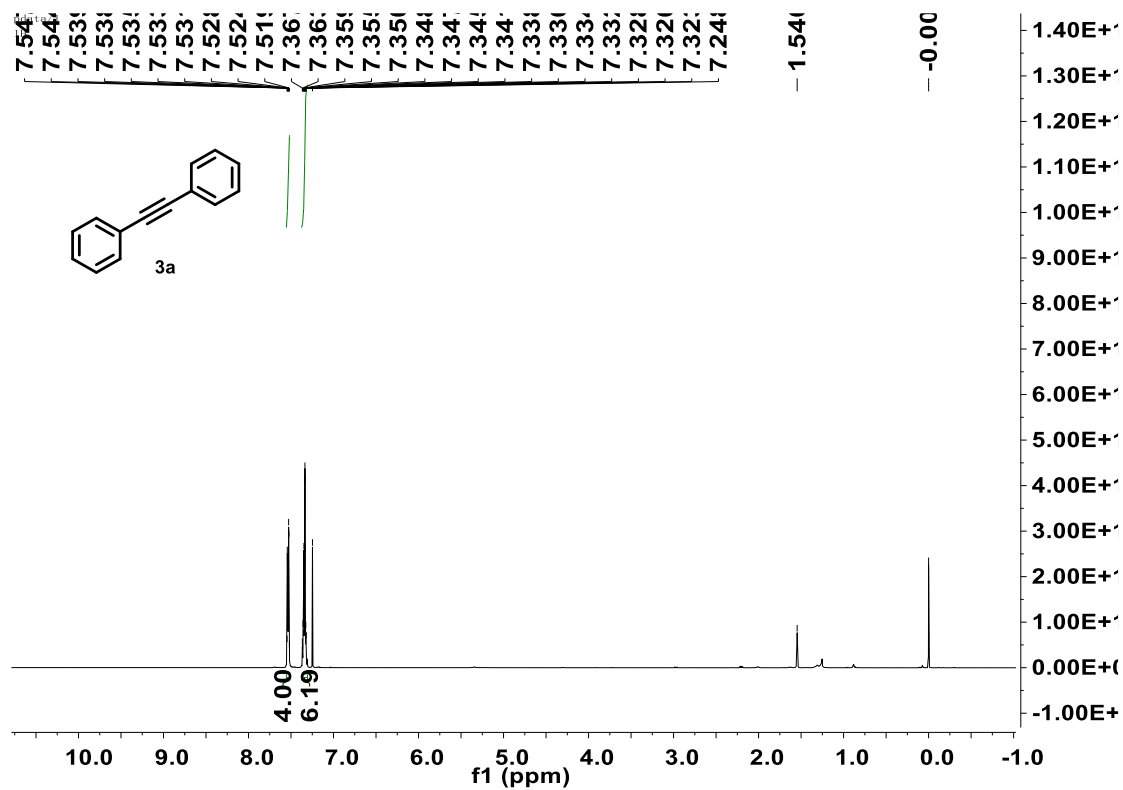


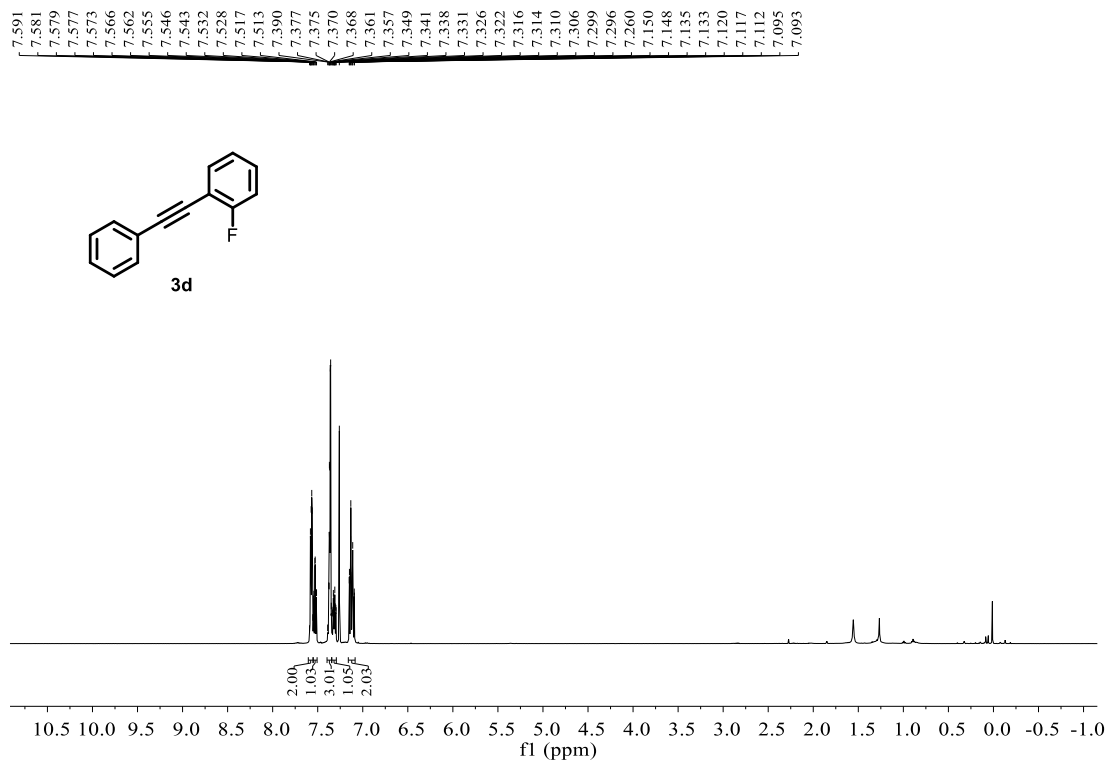
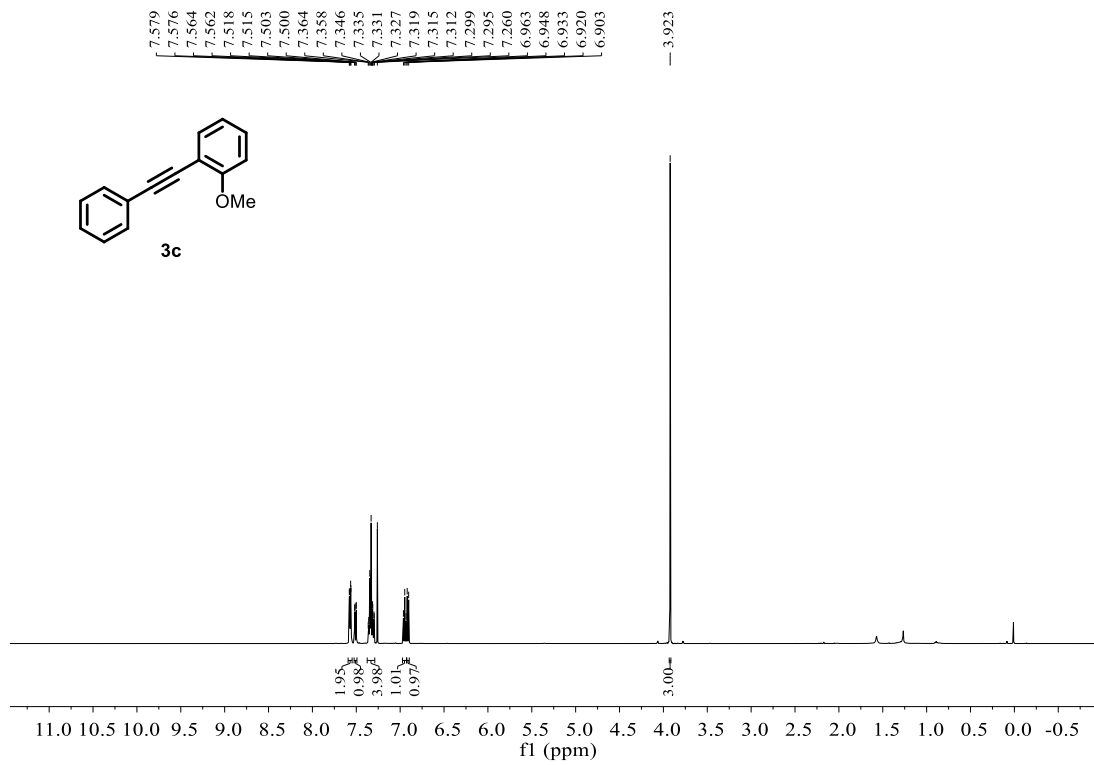


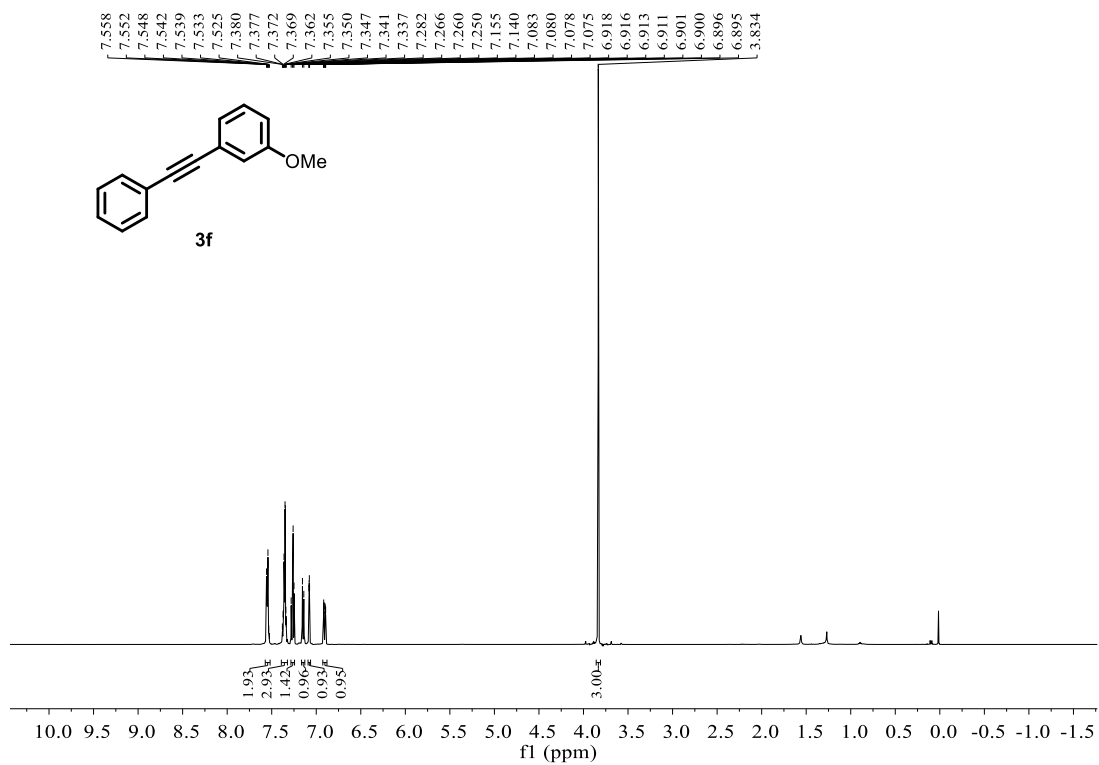
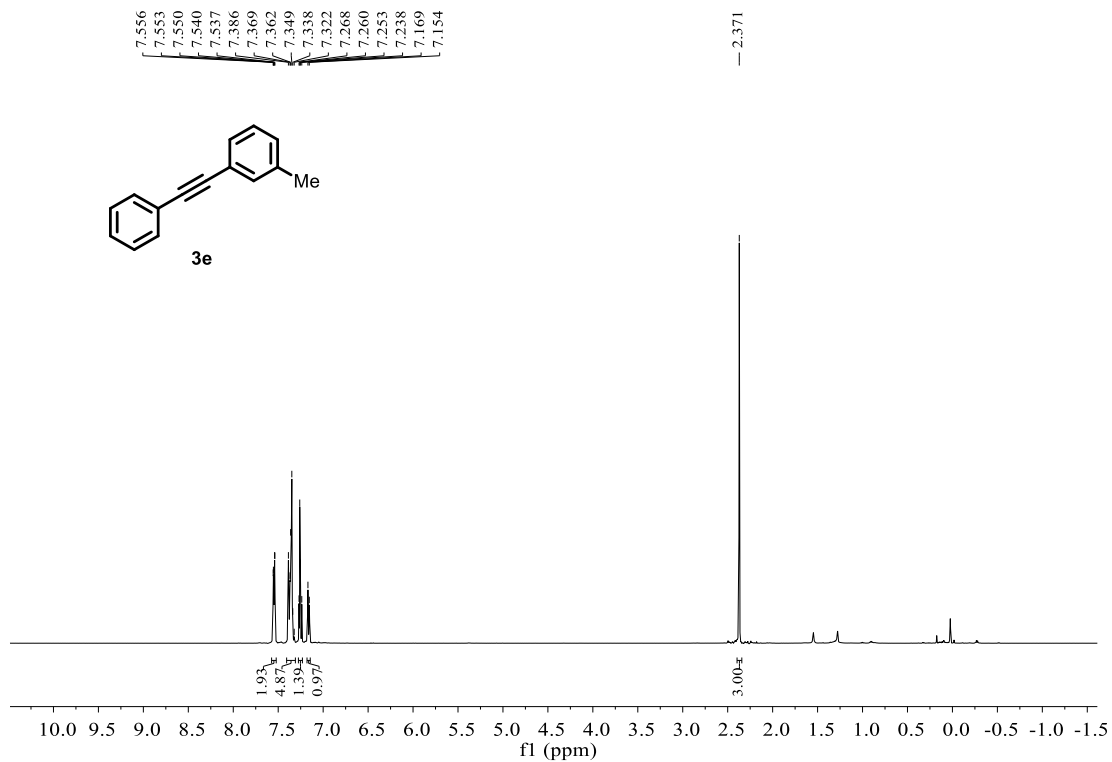


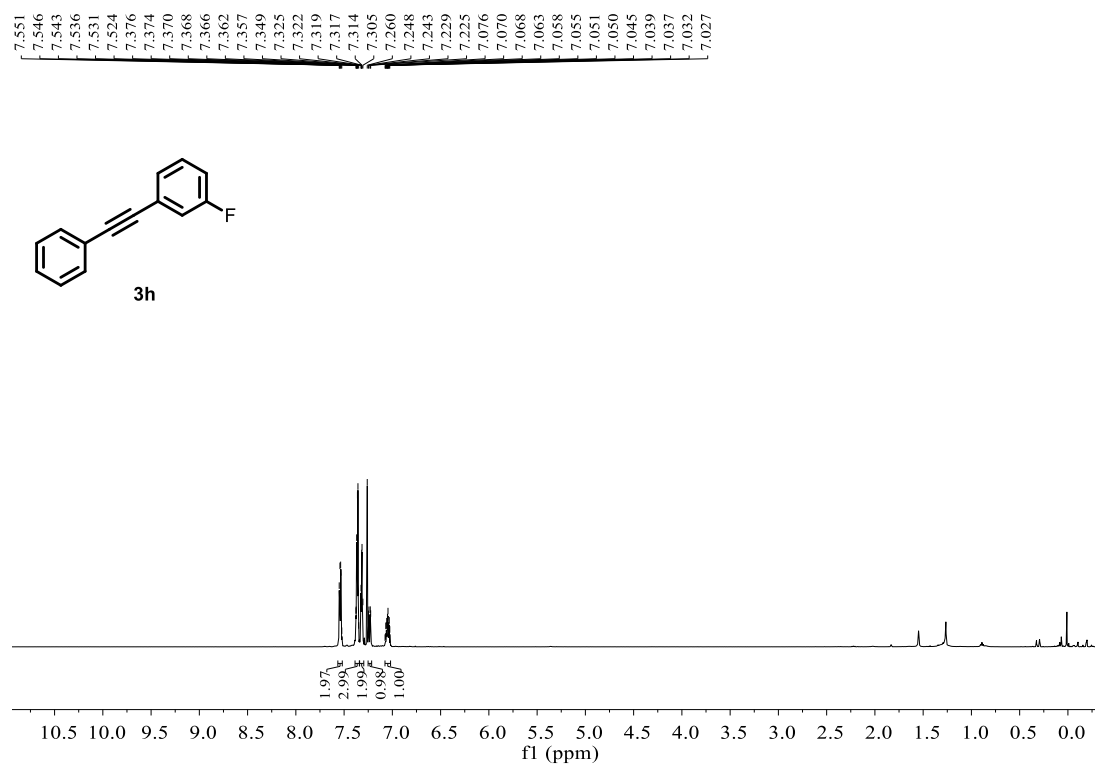
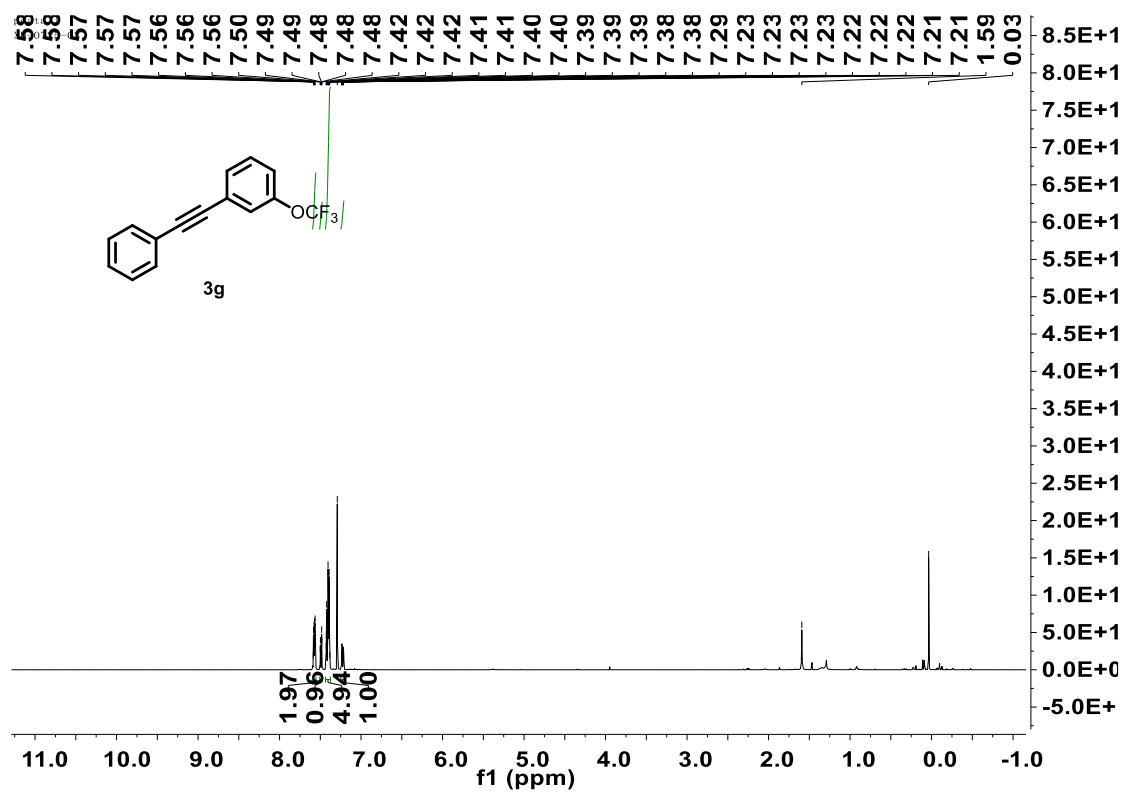


6.2 NMR Spectra for Product

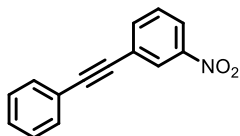




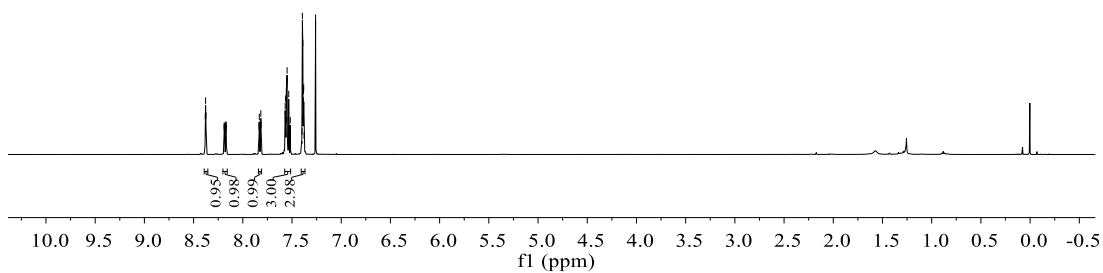




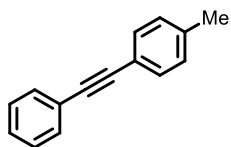
8.381
8.378
8.374
8.191
8.189
8.186
8.184
8.174
8.172
8.170
8.168
7.835
7.833
7.830
7.820
7.817
7.815
7.570
7.565
7.558
7.555
7.550
7.533
7.518
7.398
7.395
7.390
7.385
7.383
7.381
7.377
7.374
7.260



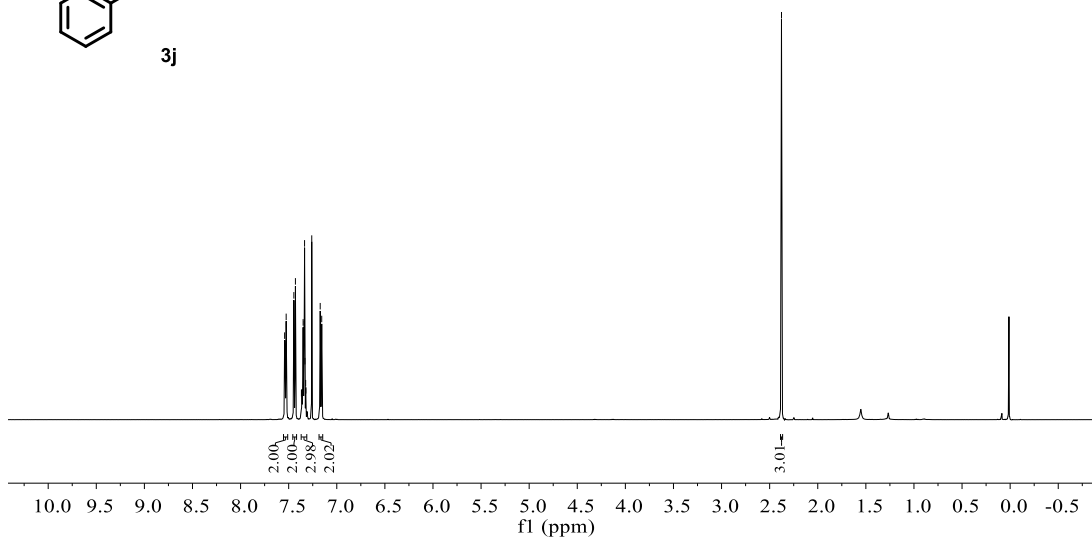
3i

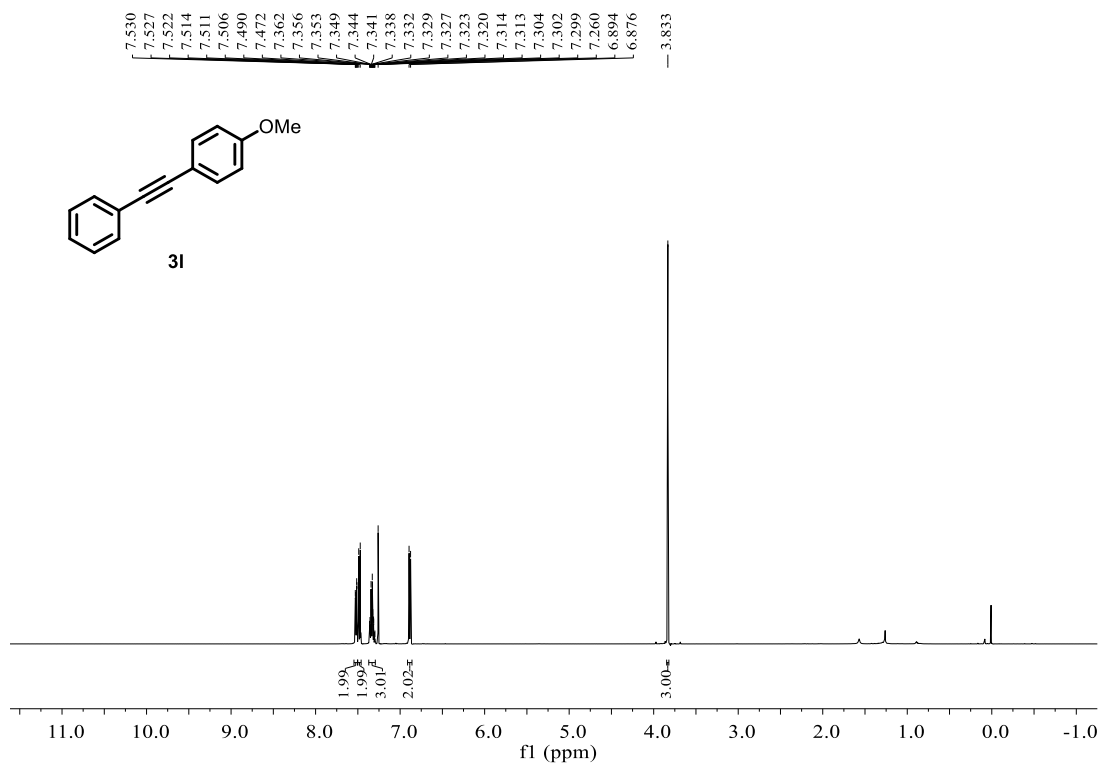
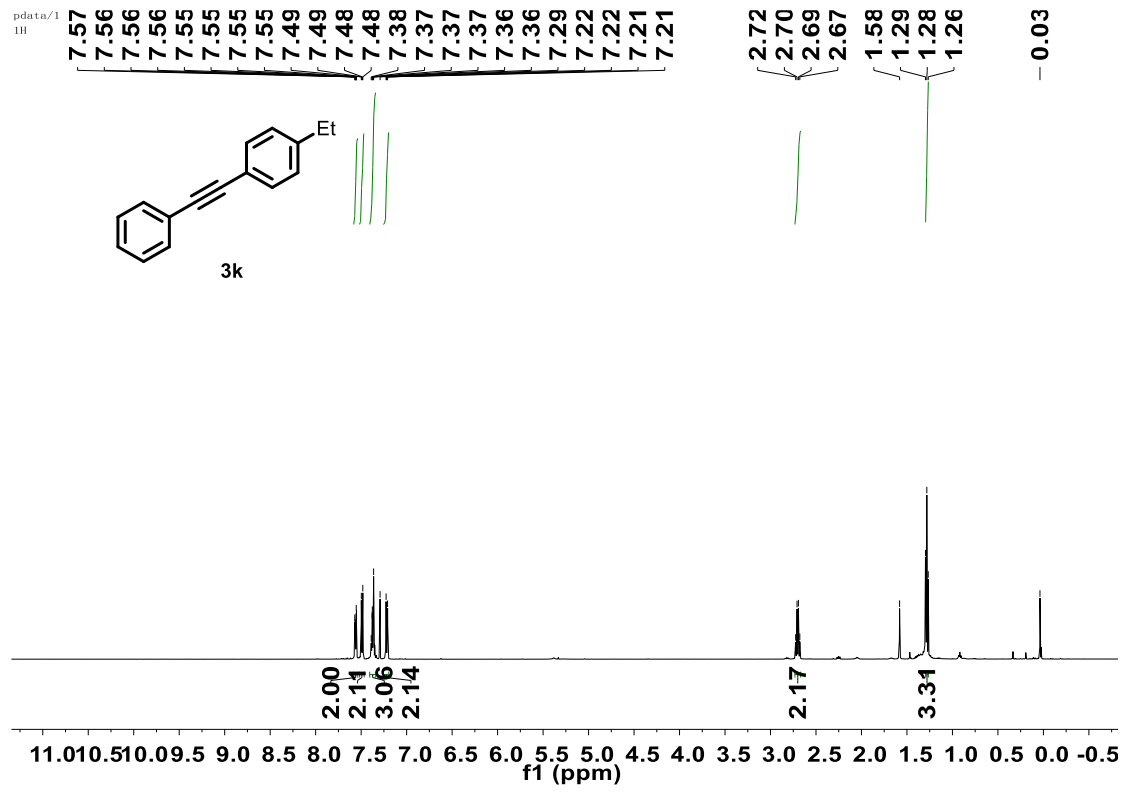


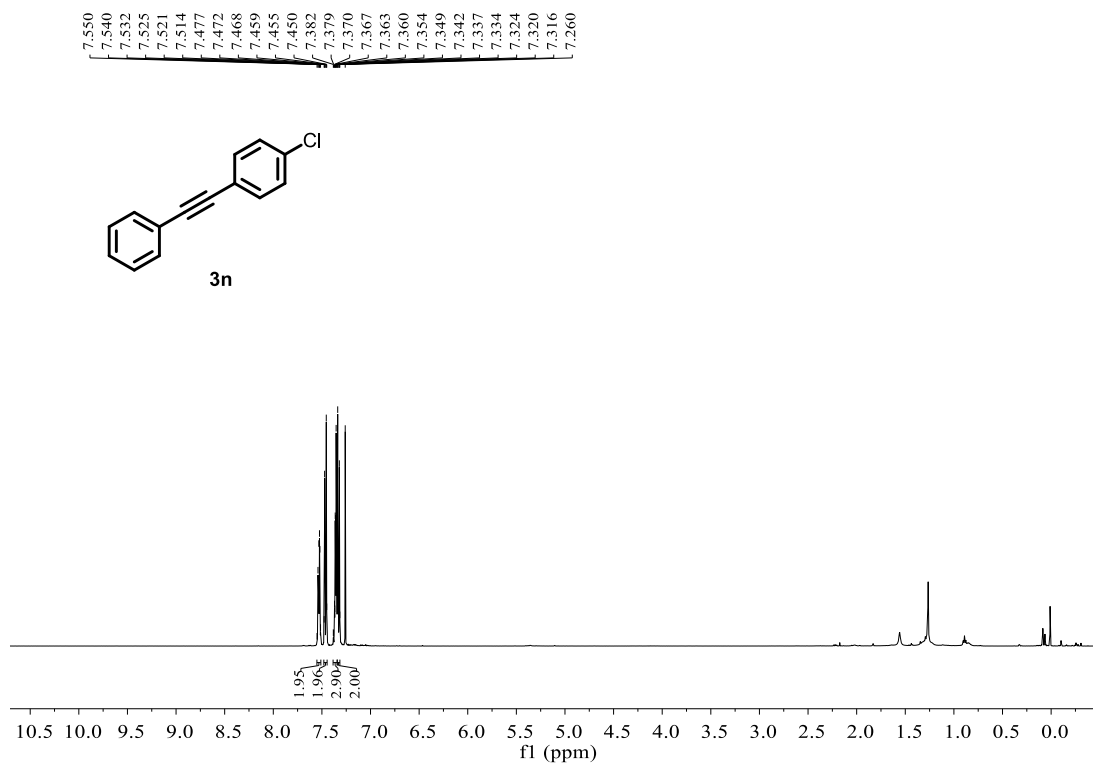
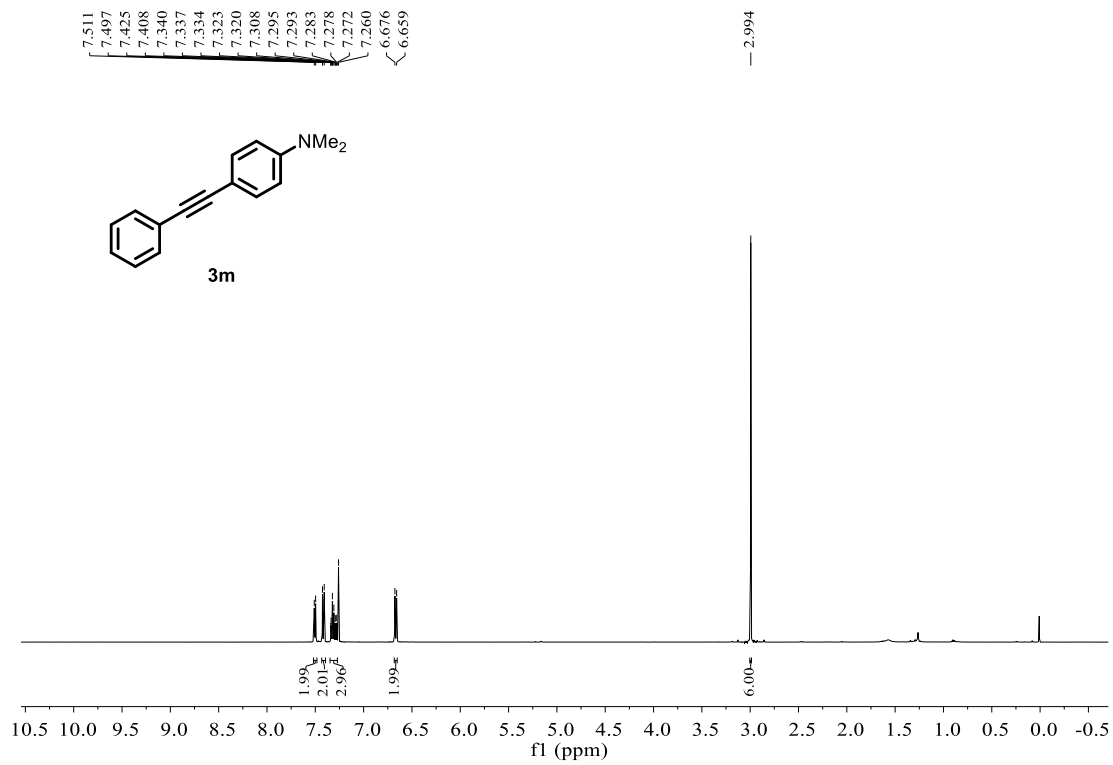
7.542
7.538
7.526
7.523
7.446
7.430
7.368
7.350
7.339
7.335
7.331
7.324
7.321
7.260
7.172
7.157

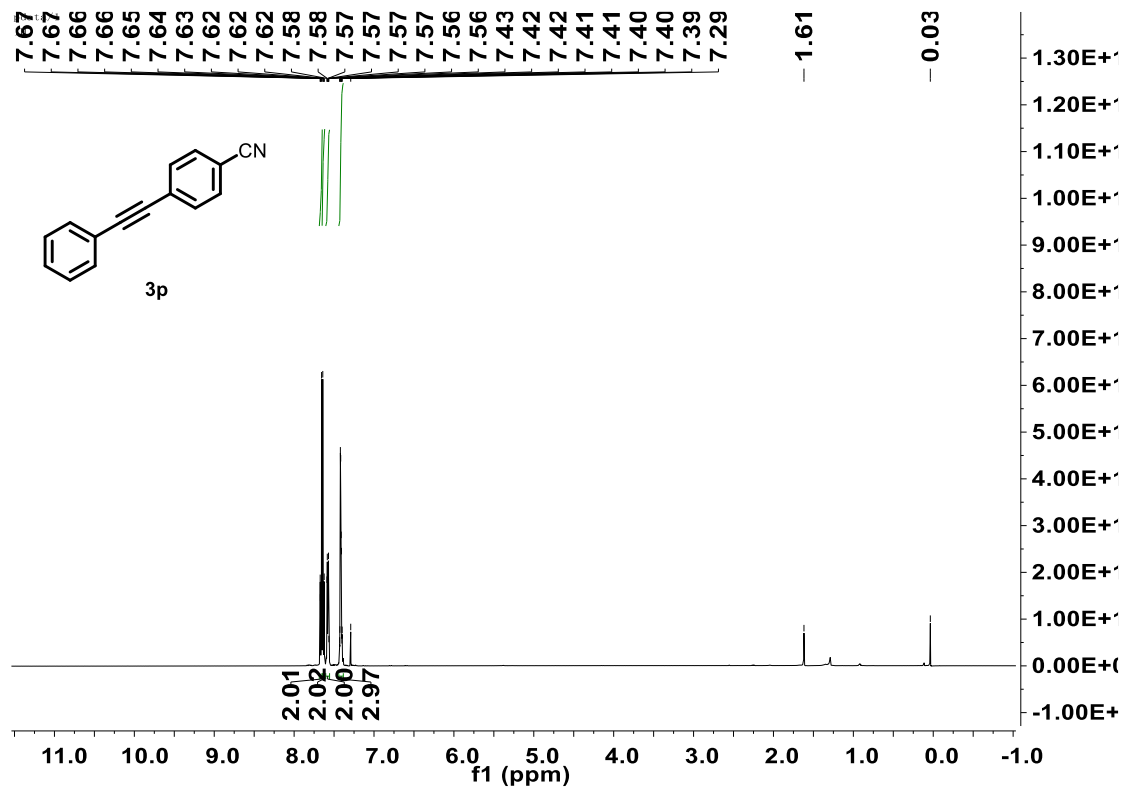
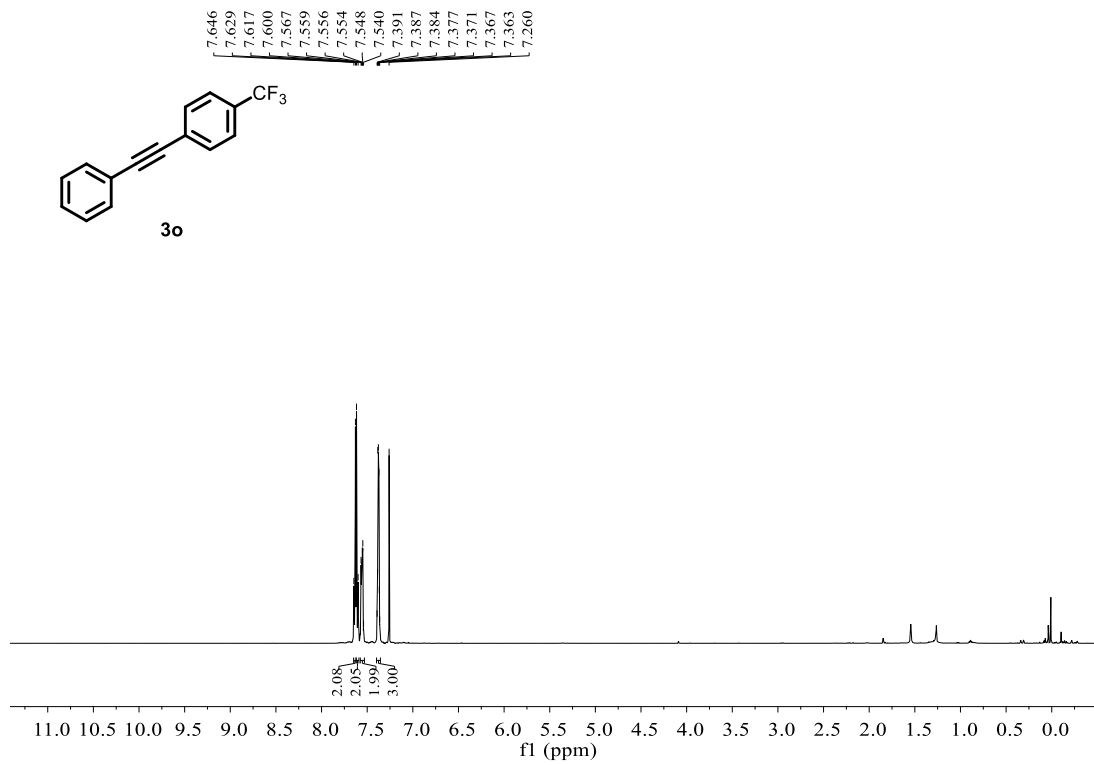


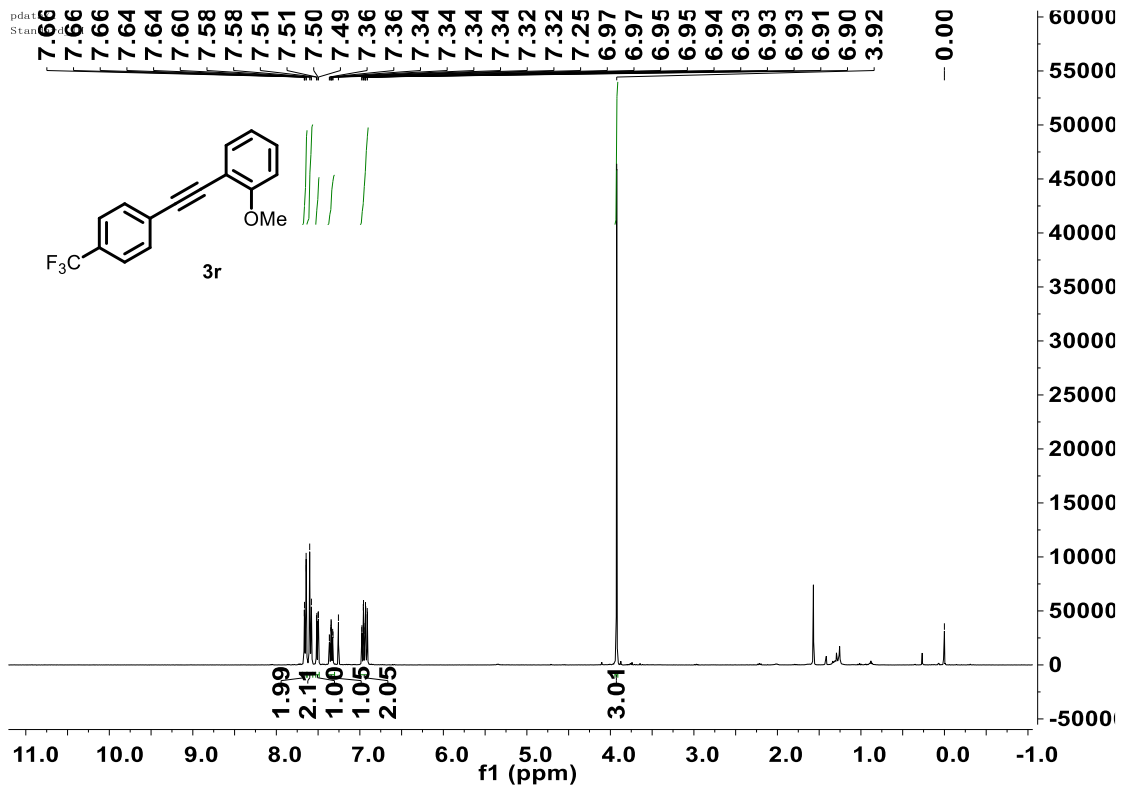
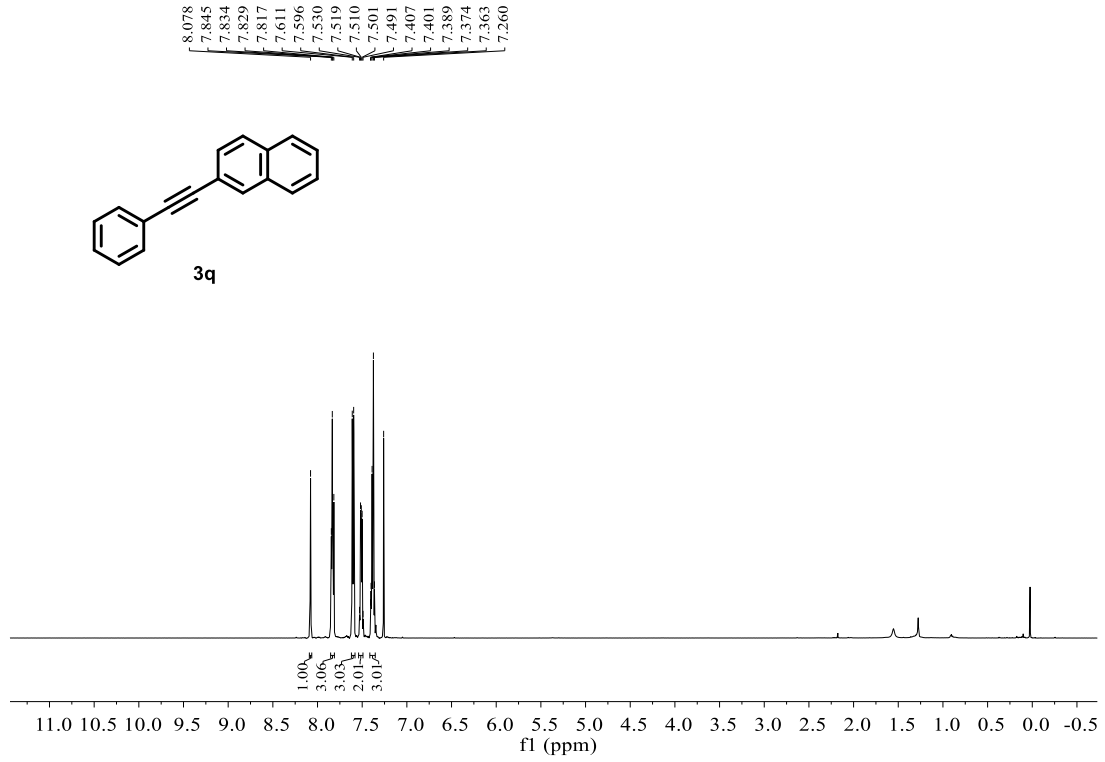
3j

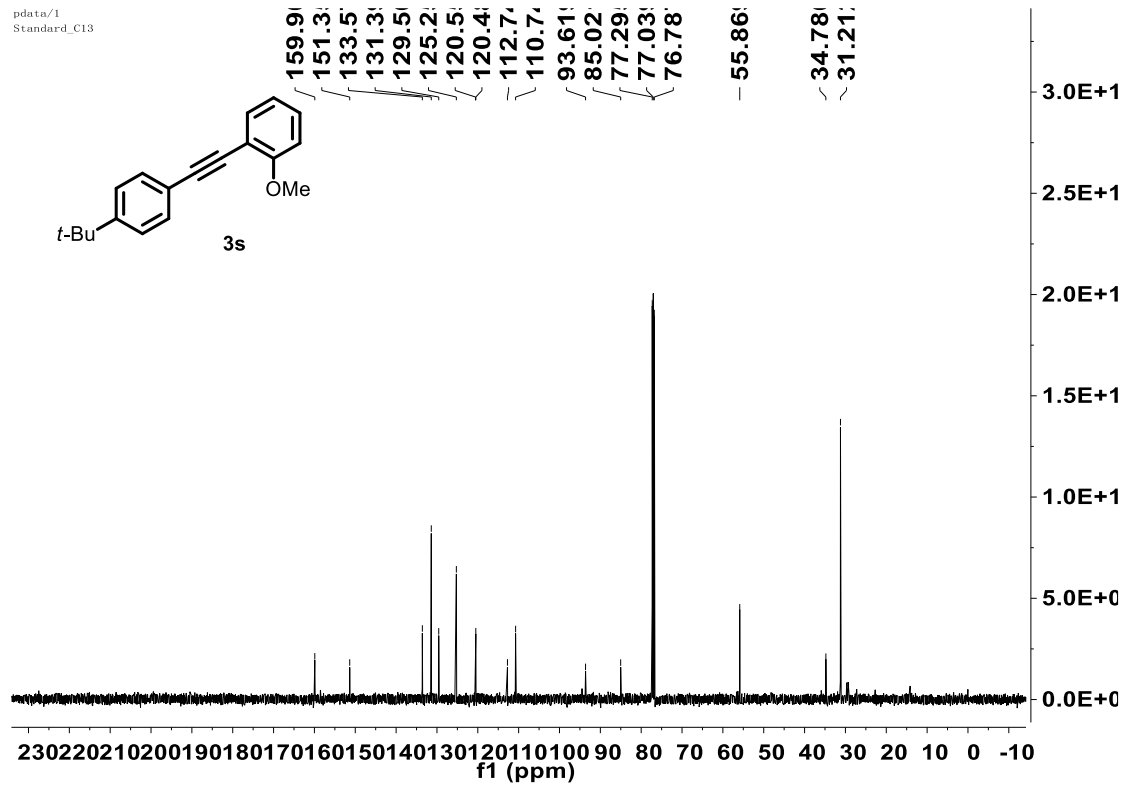
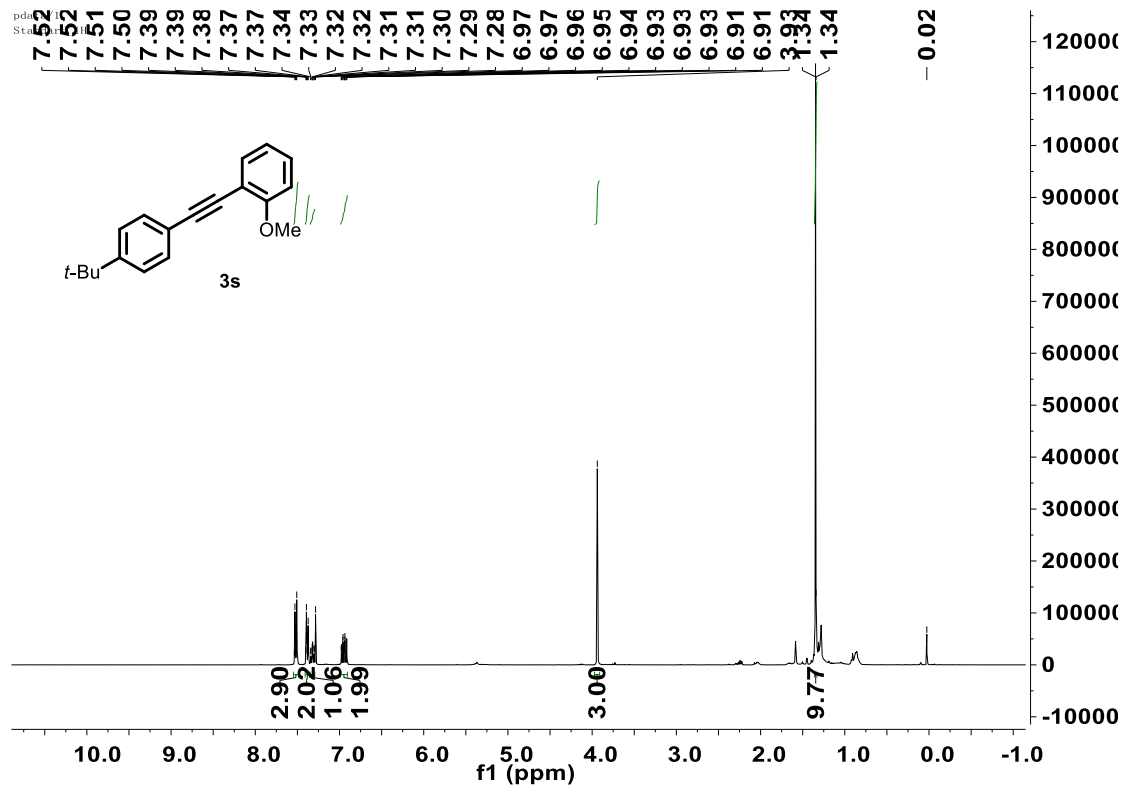


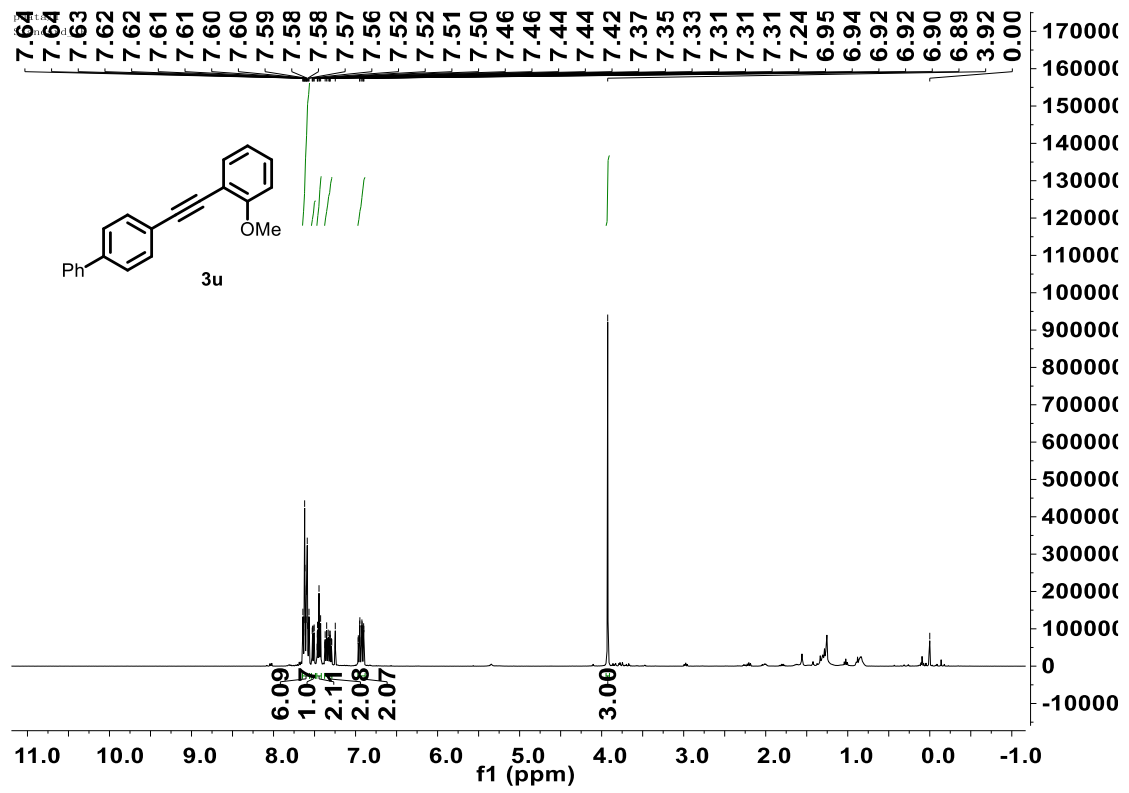
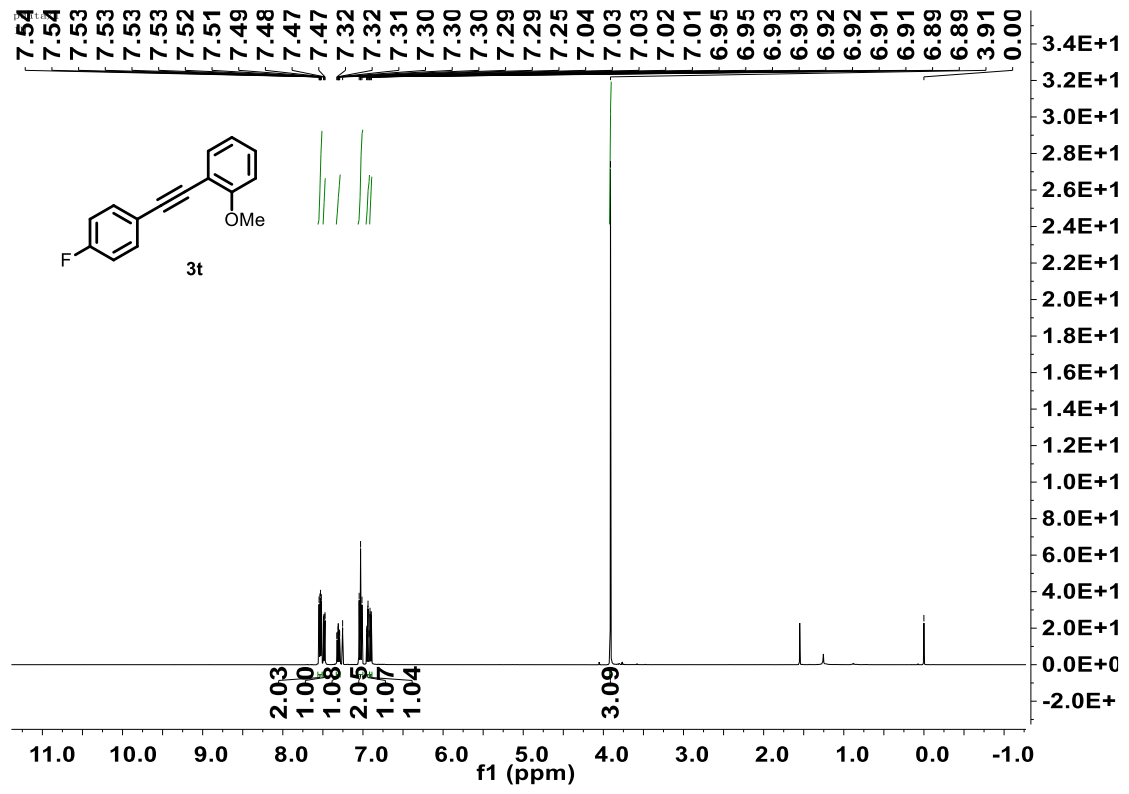


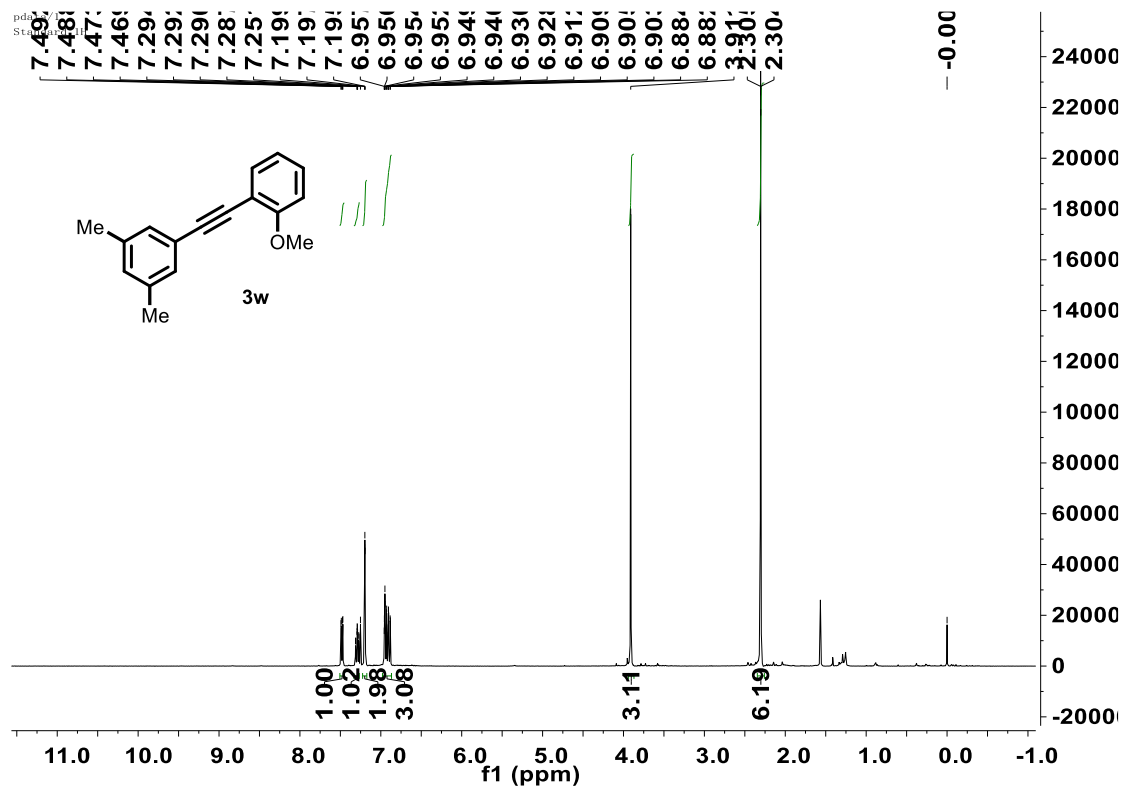
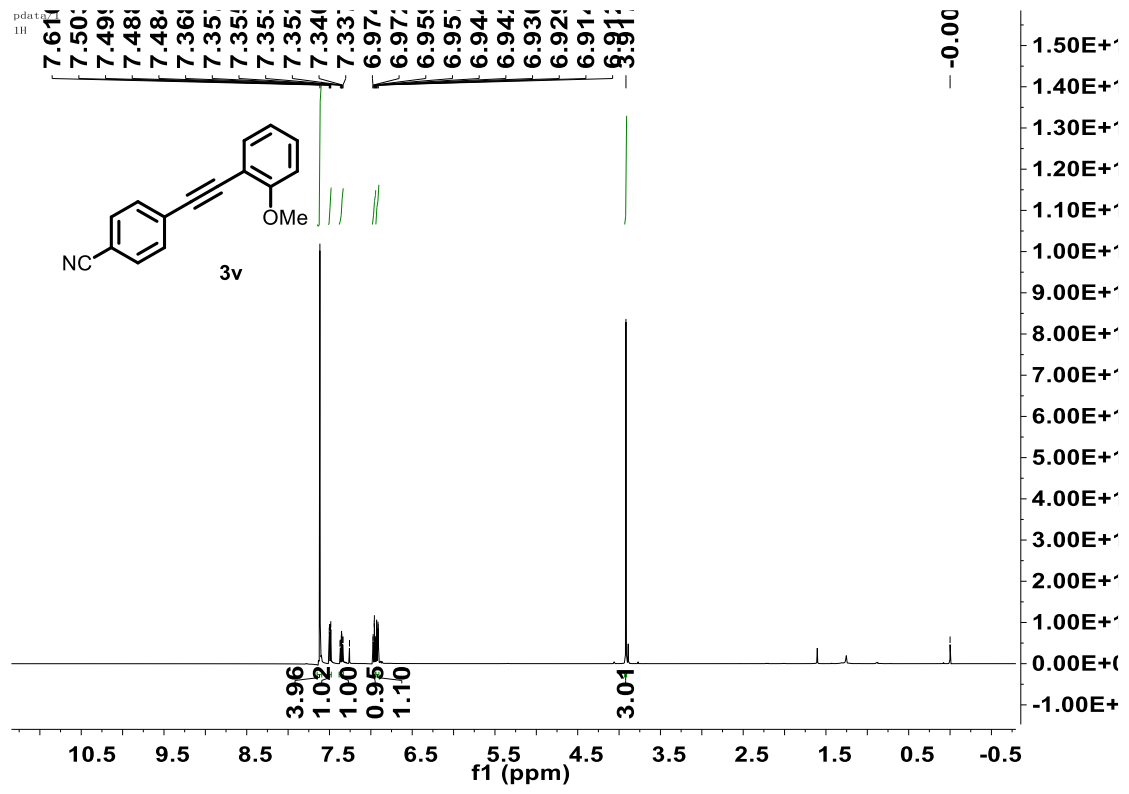




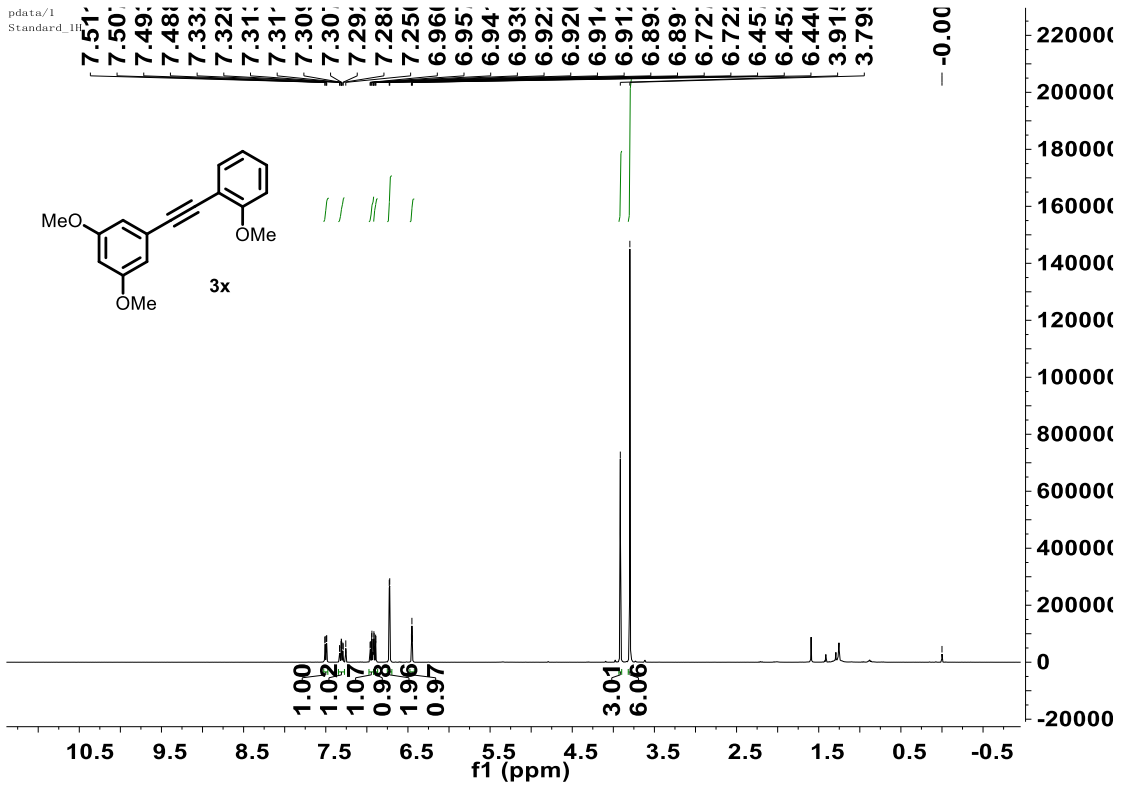
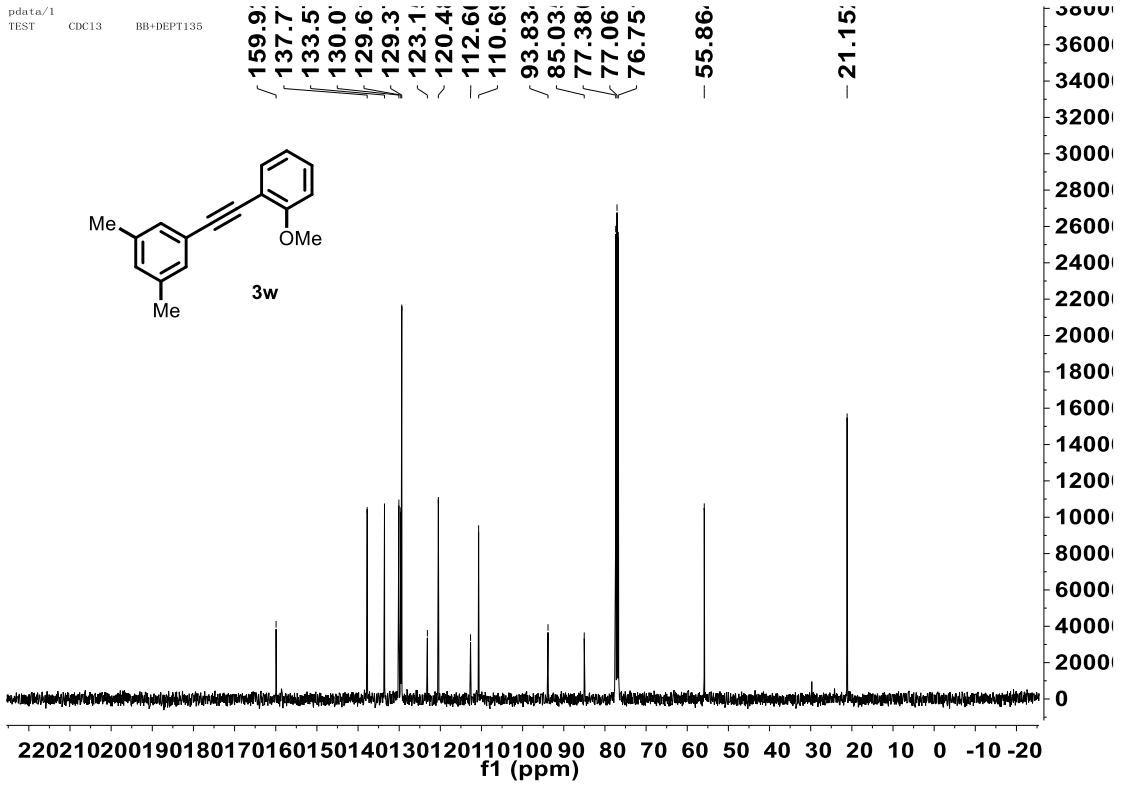




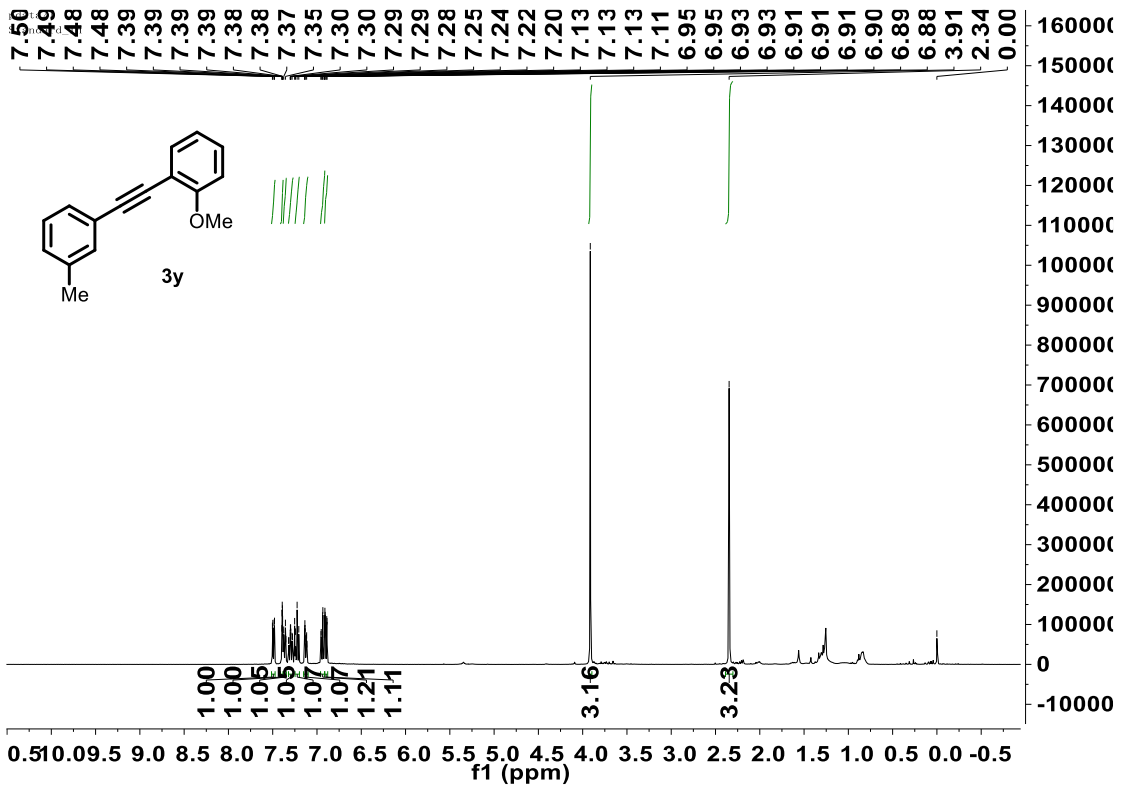
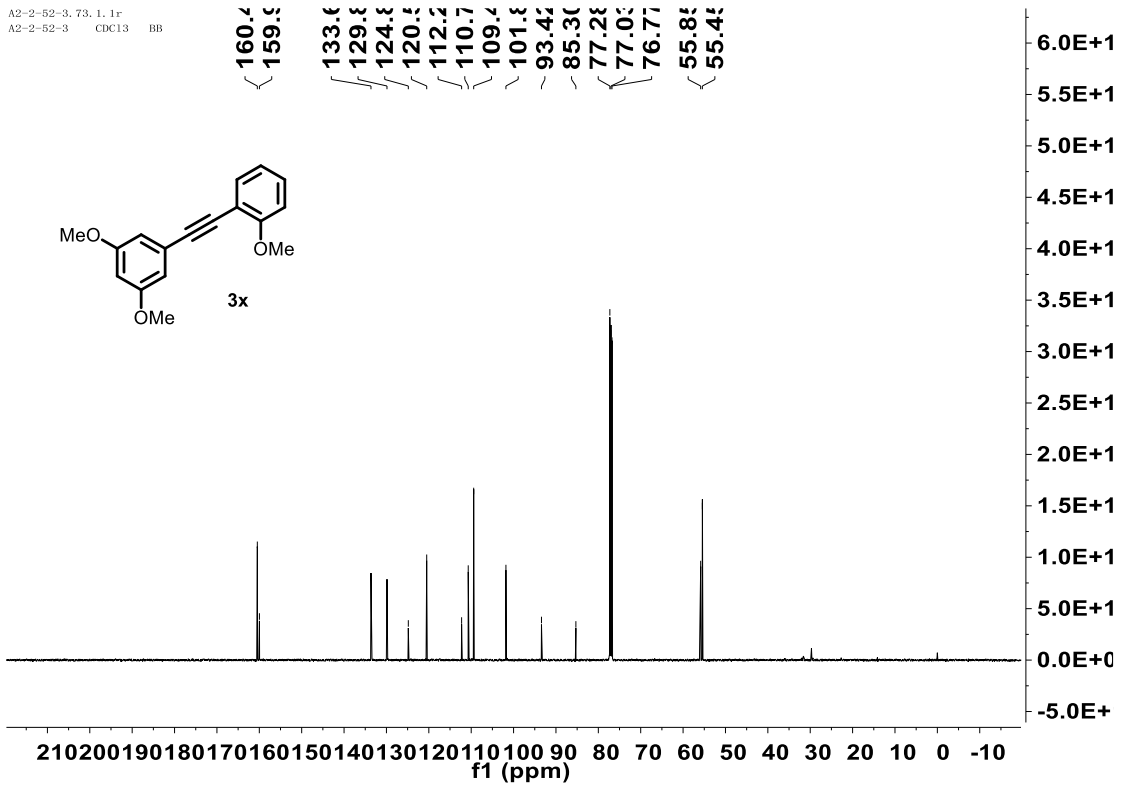


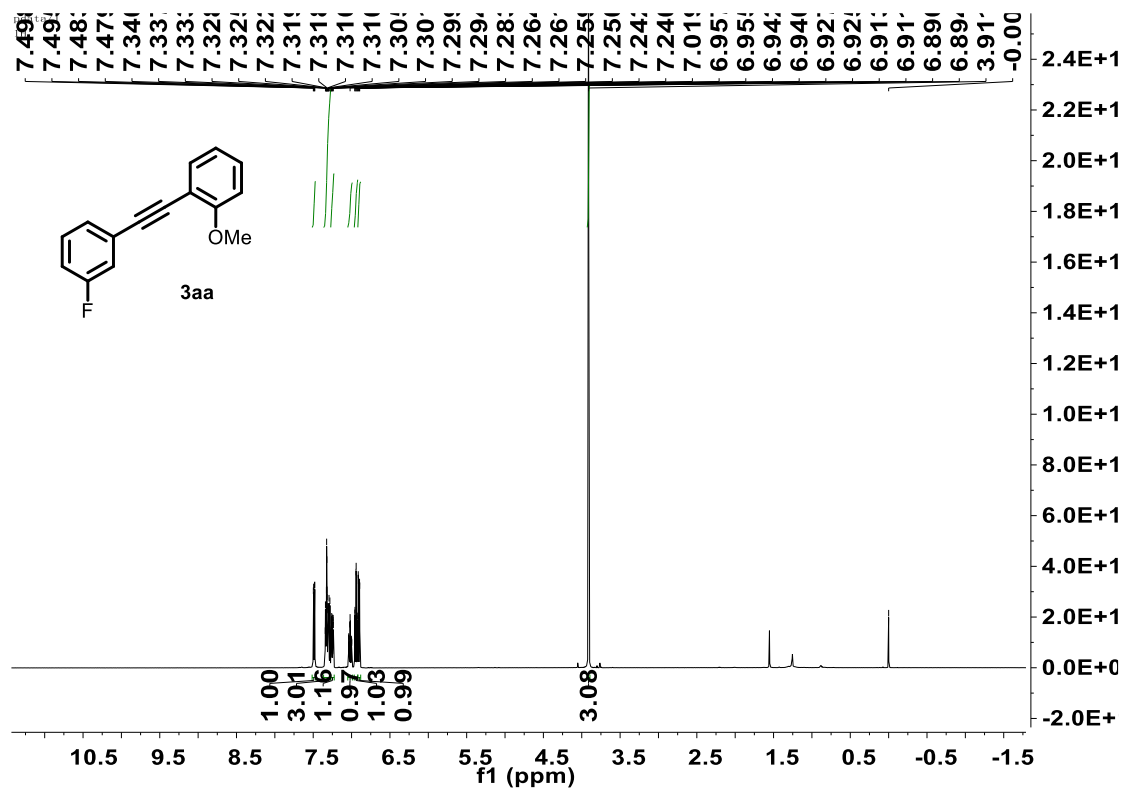
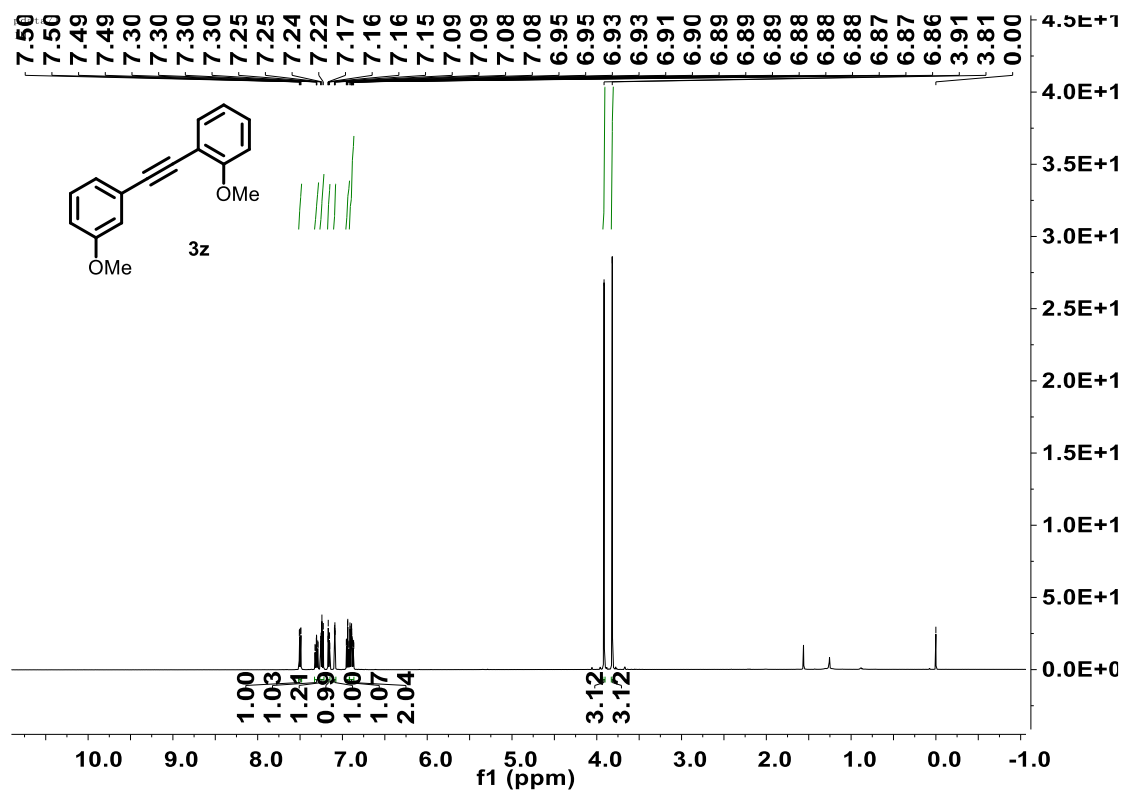


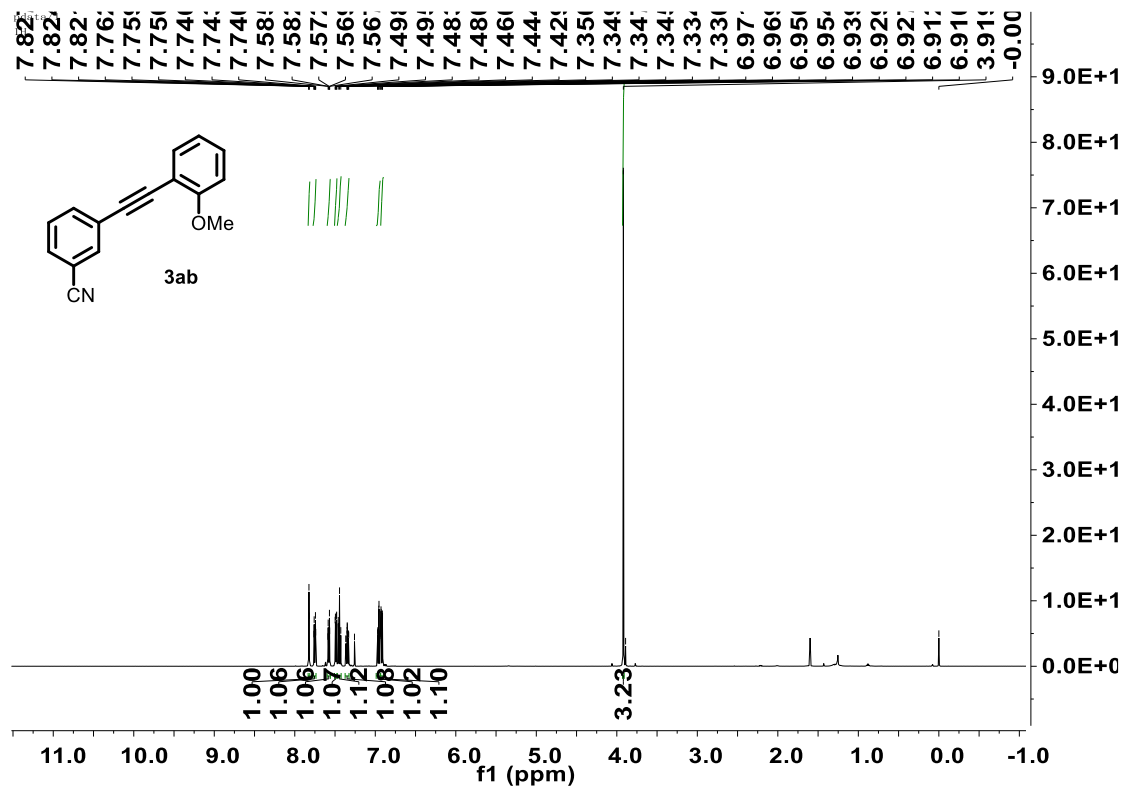
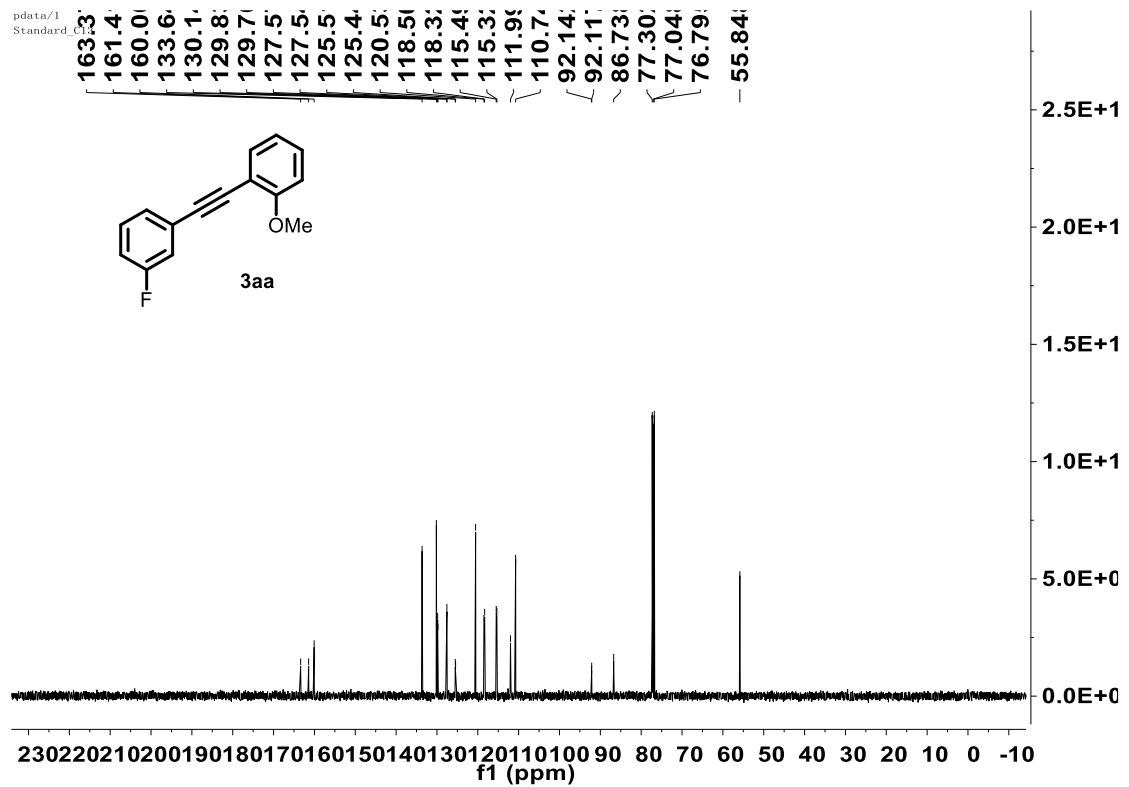
pdata/1
TEST CDC13 BB+DEPT135



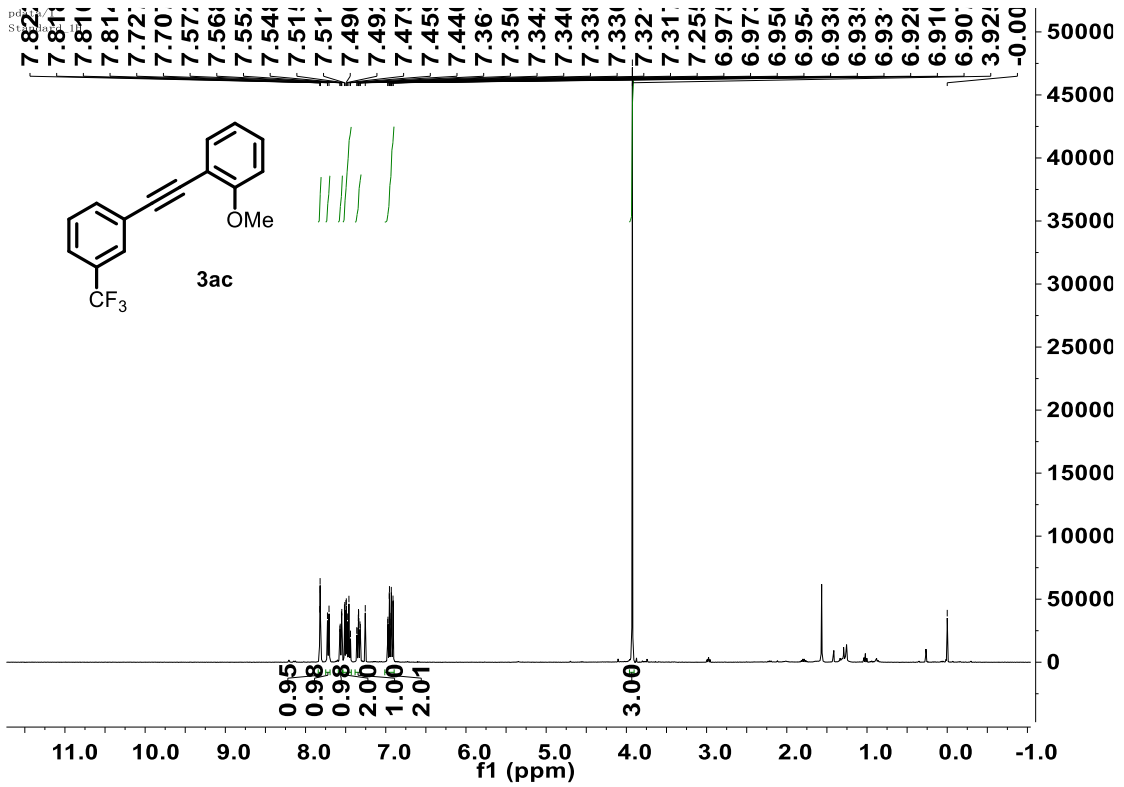
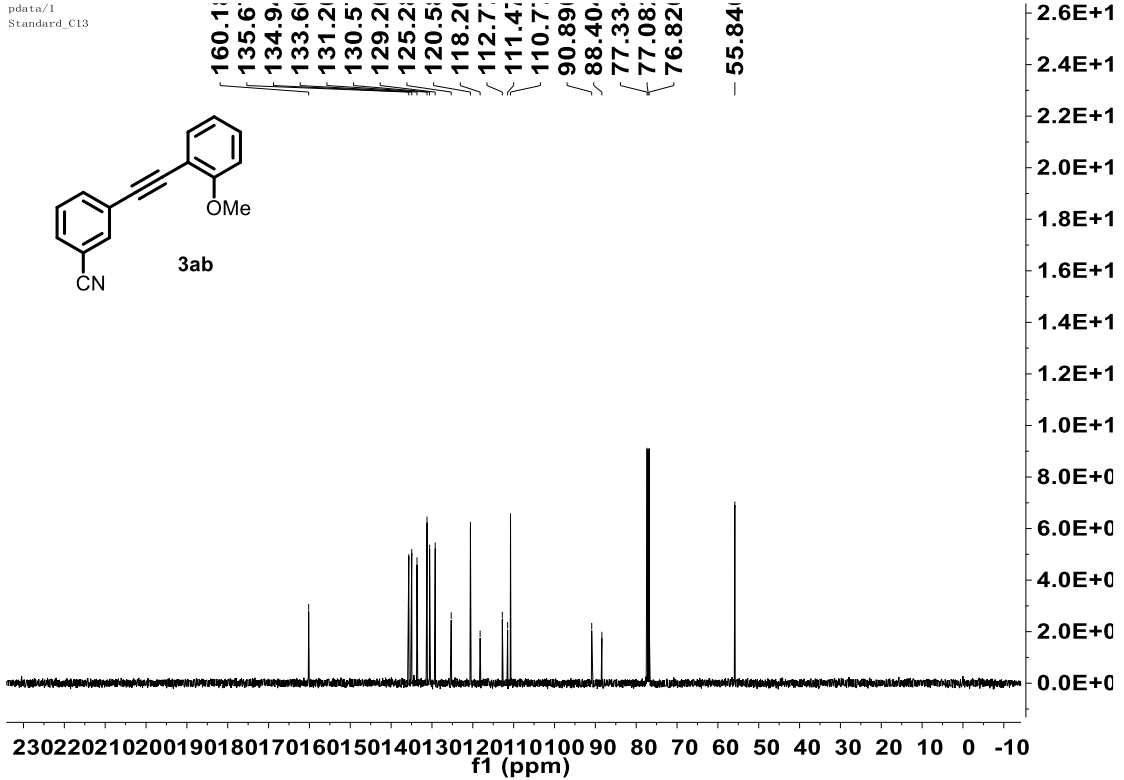
A2-2-52-3, 73.1.1r
A2-2-52-3 CDC13 BB

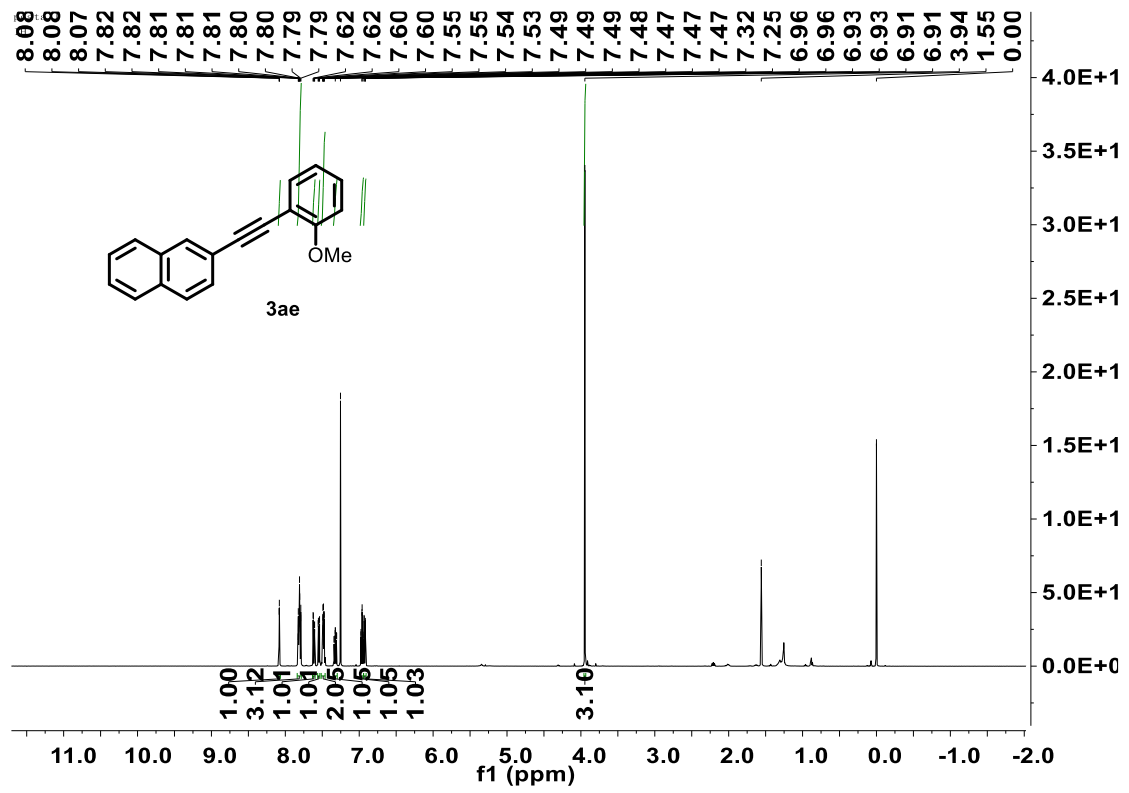
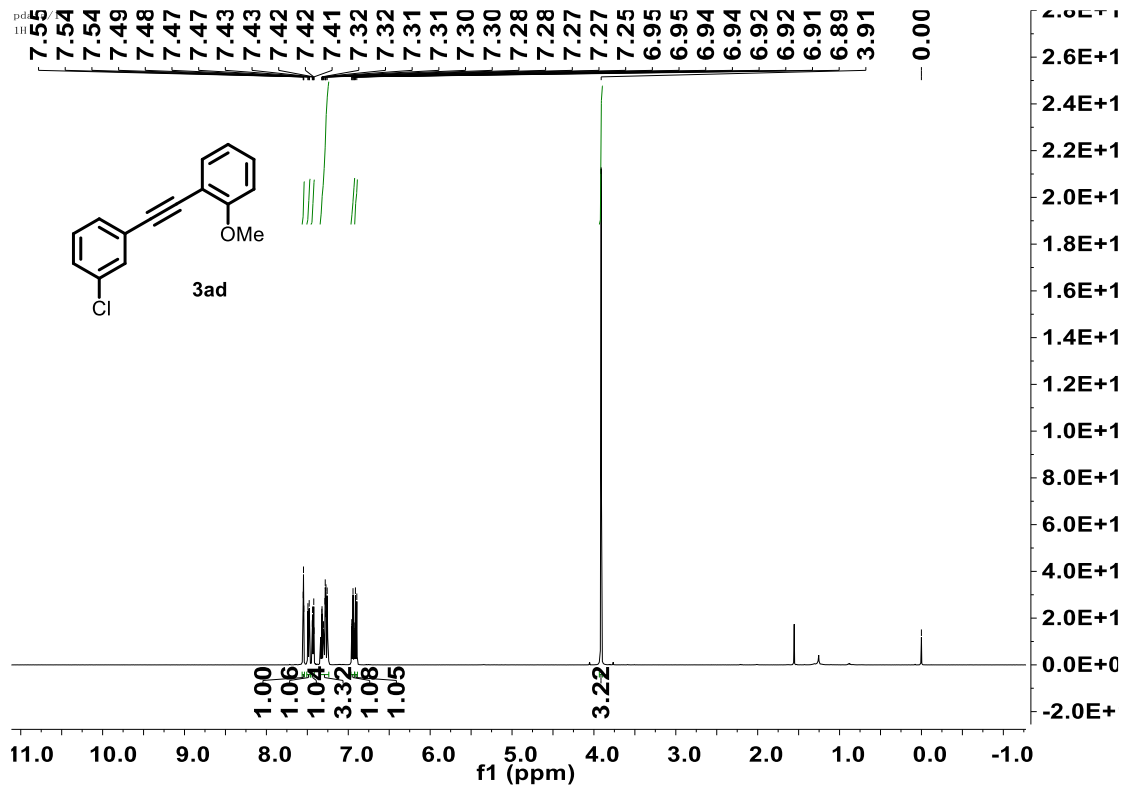


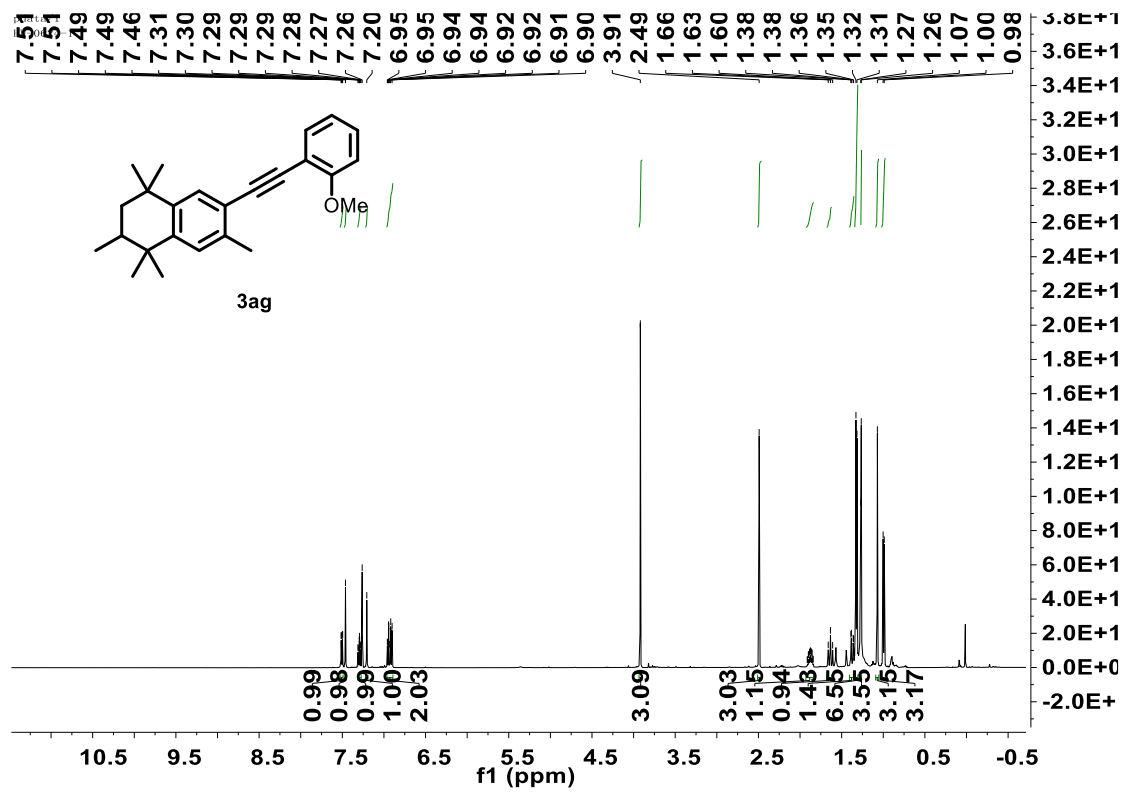
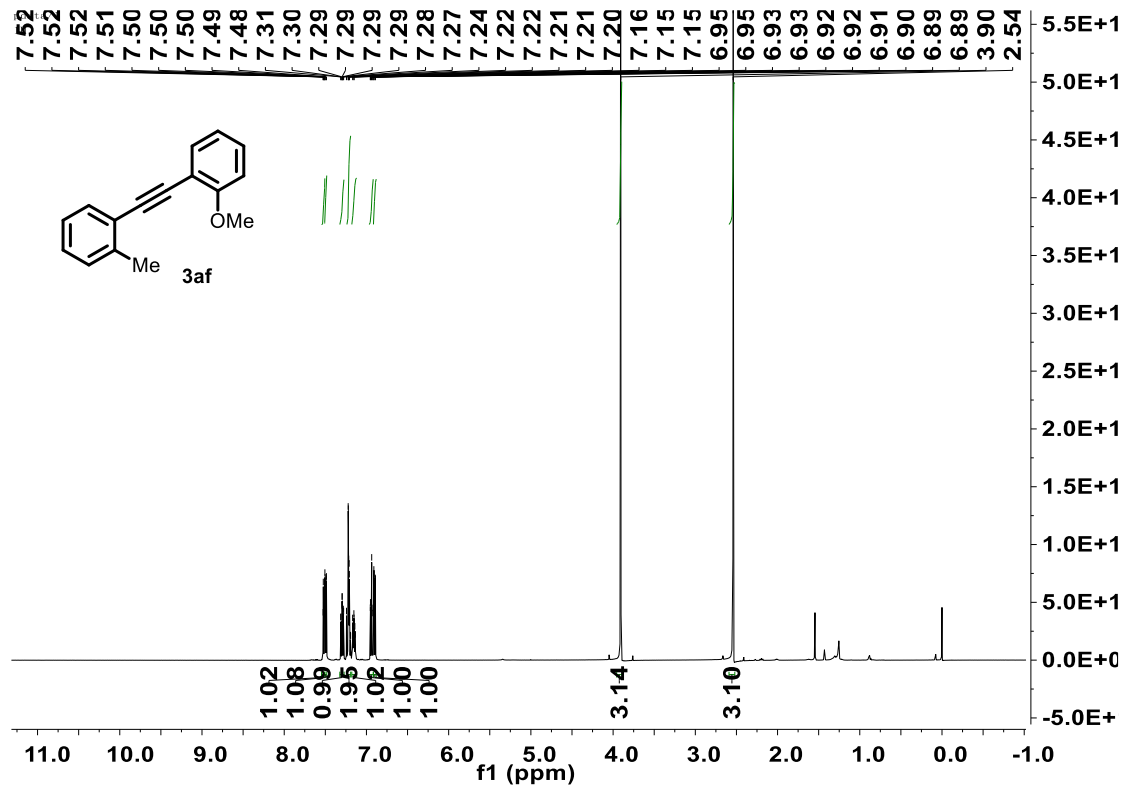




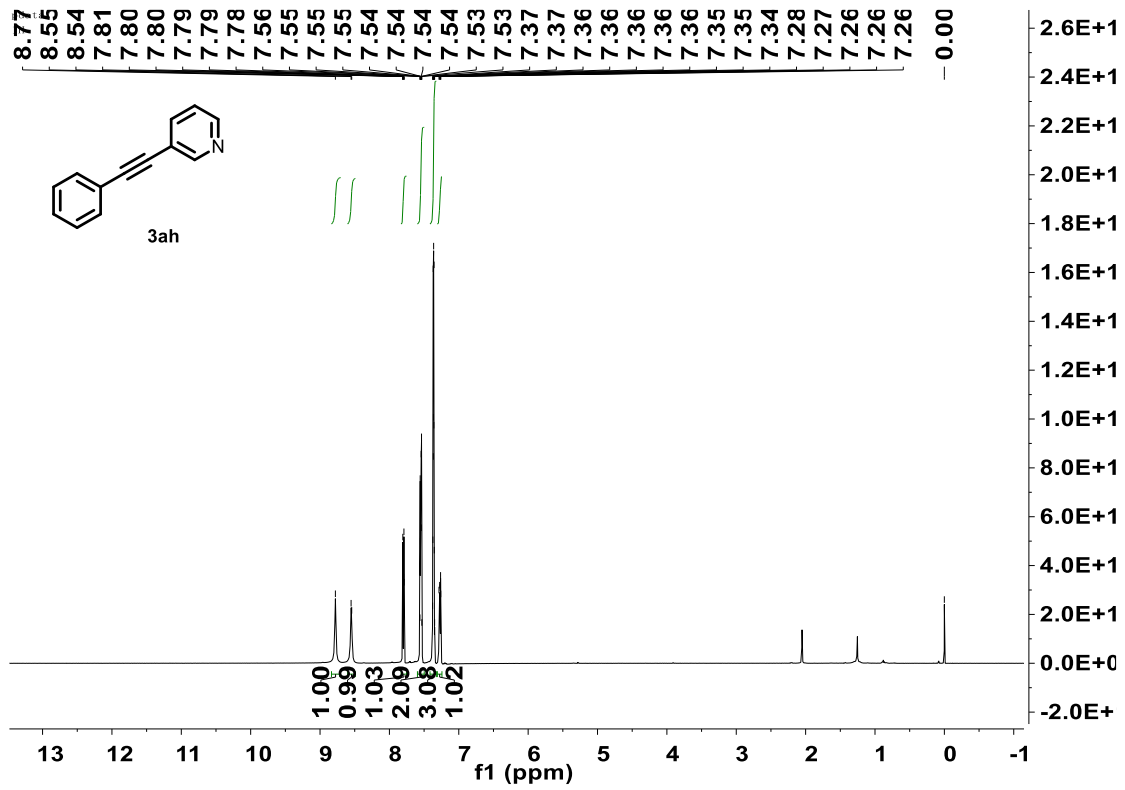
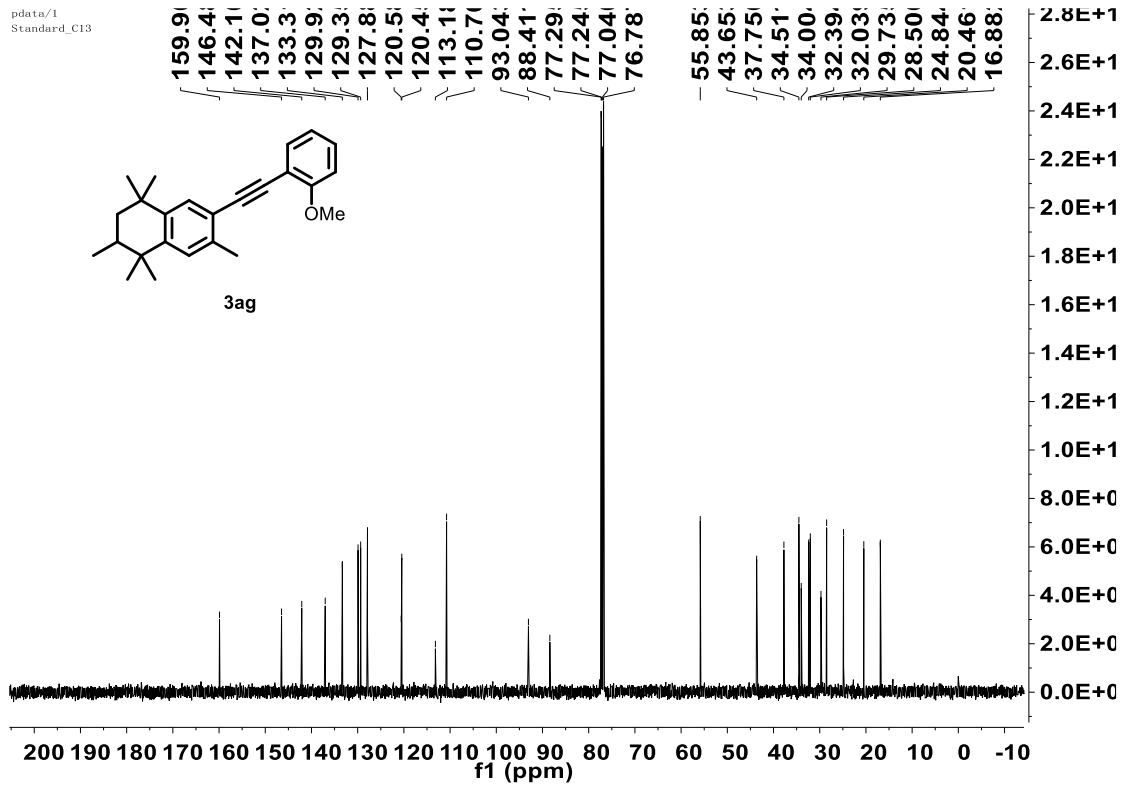
pdata/1
Standard_C13

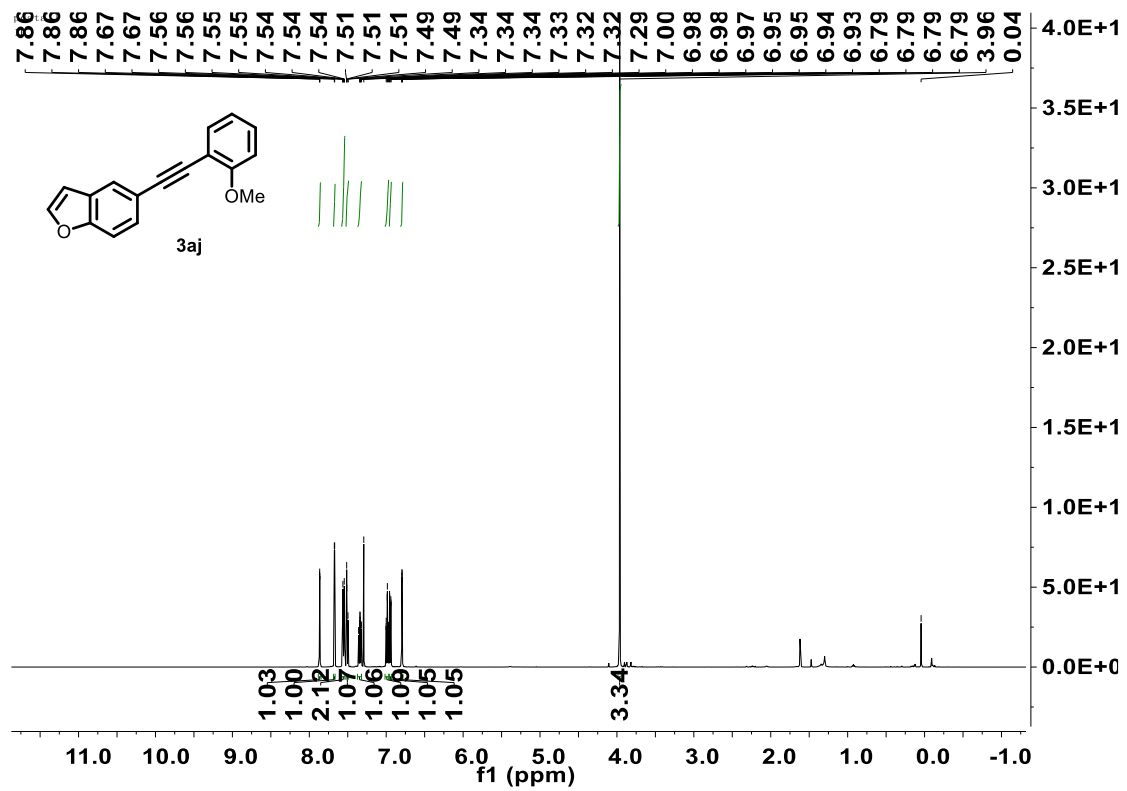
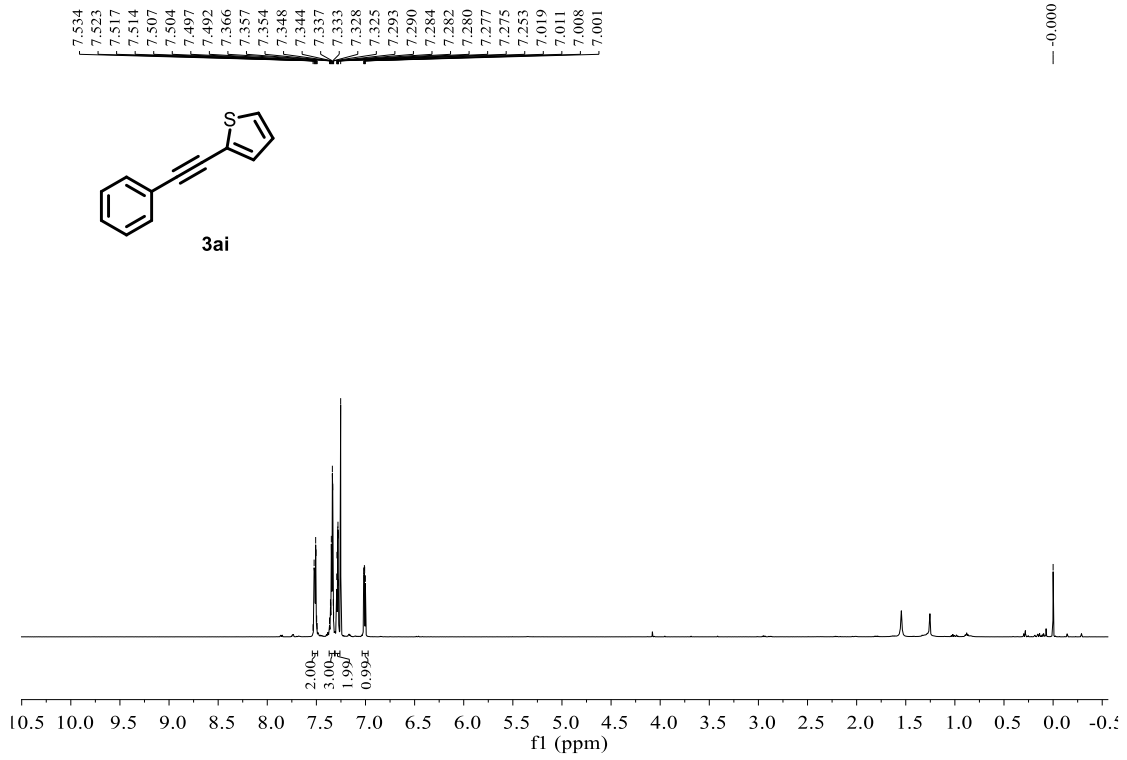




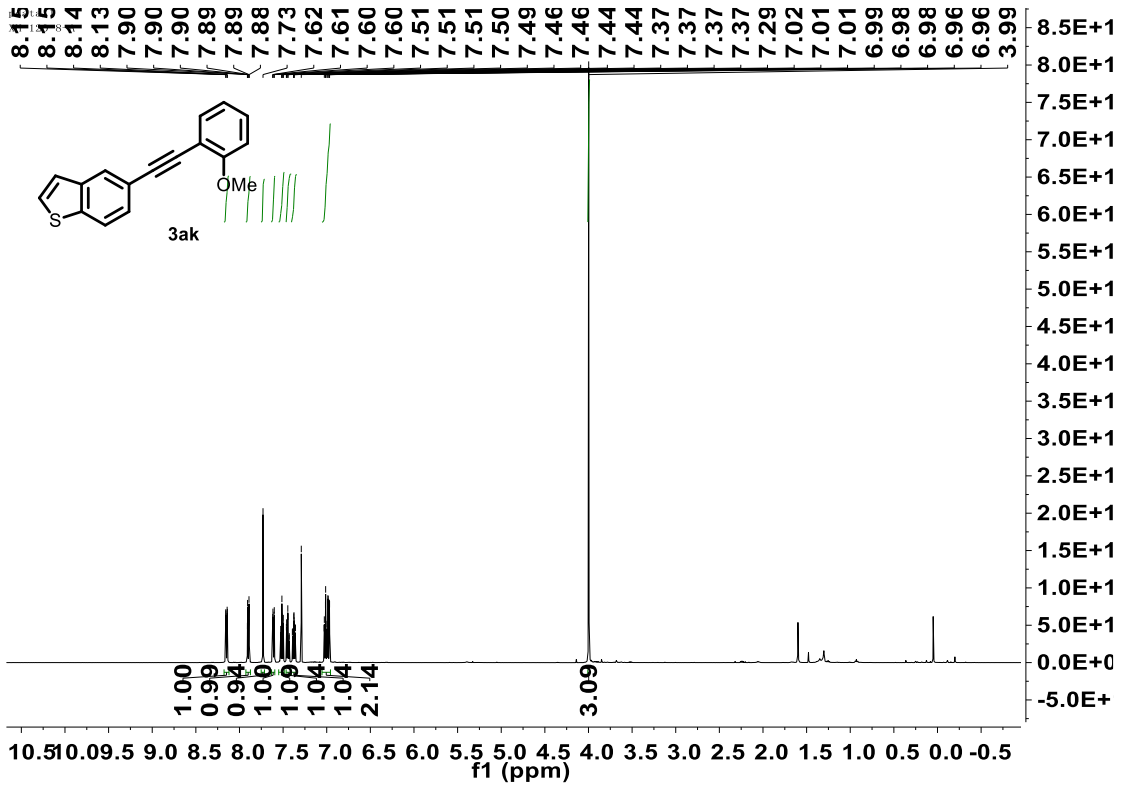
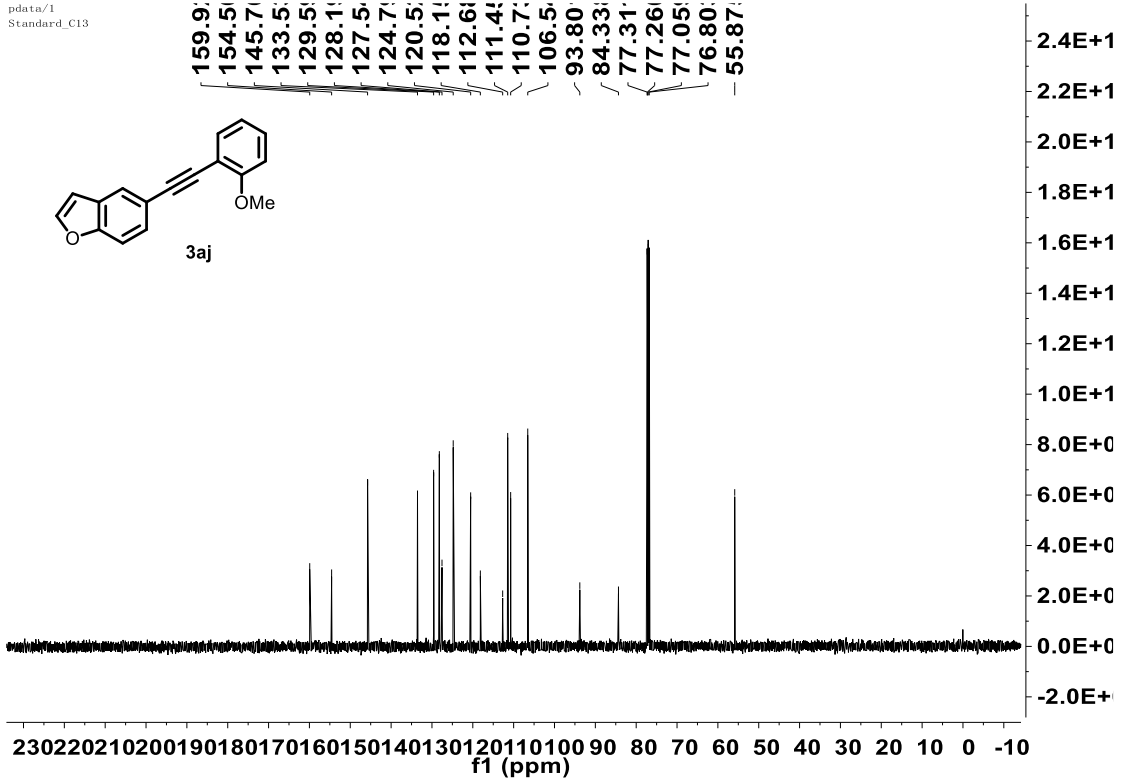


pdata/1
Standard_C13

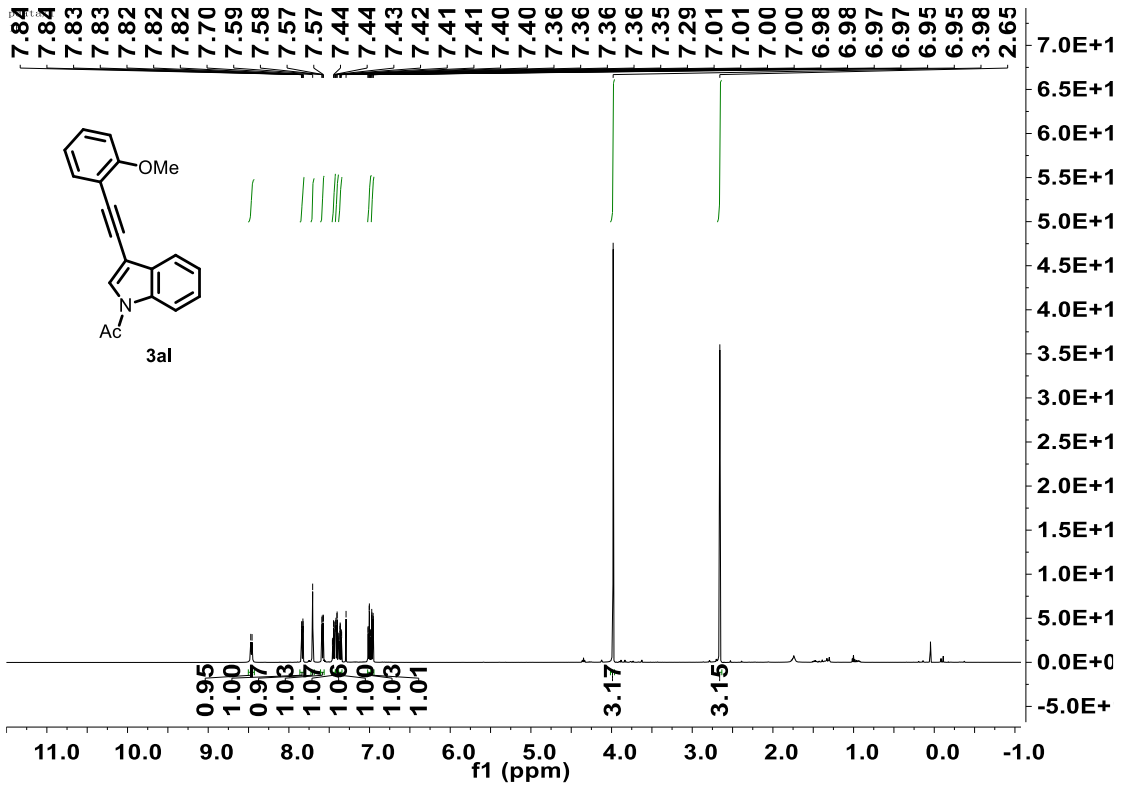
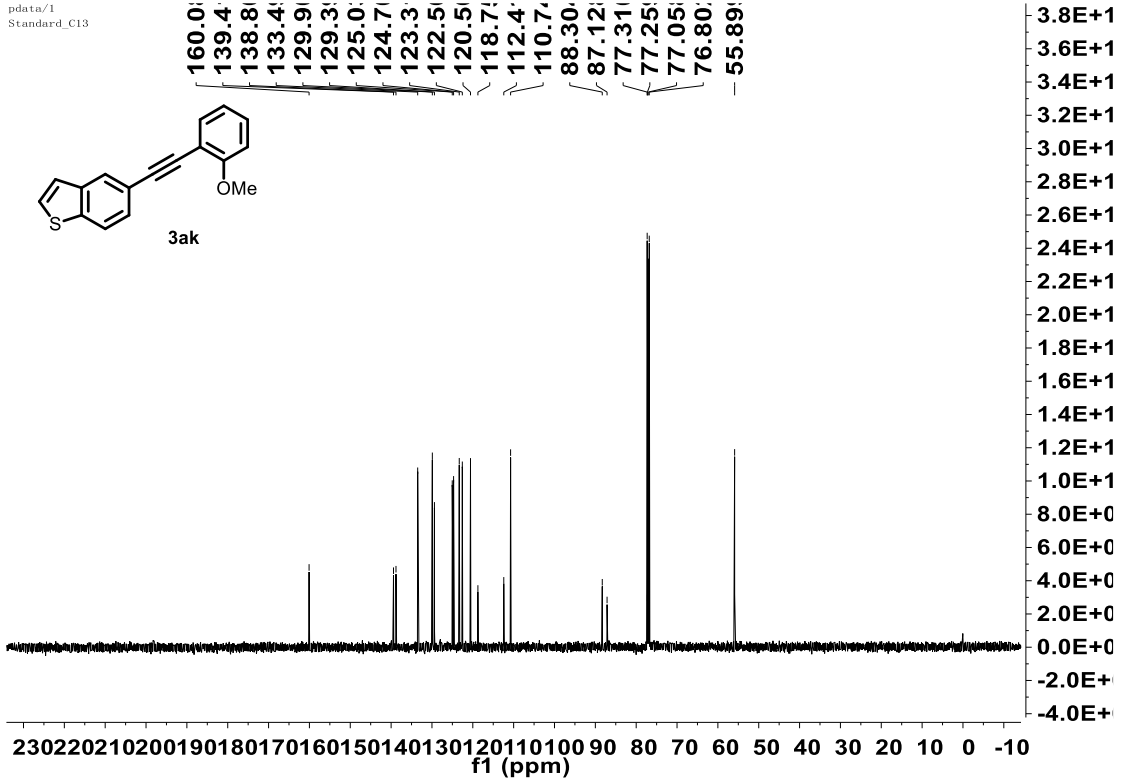




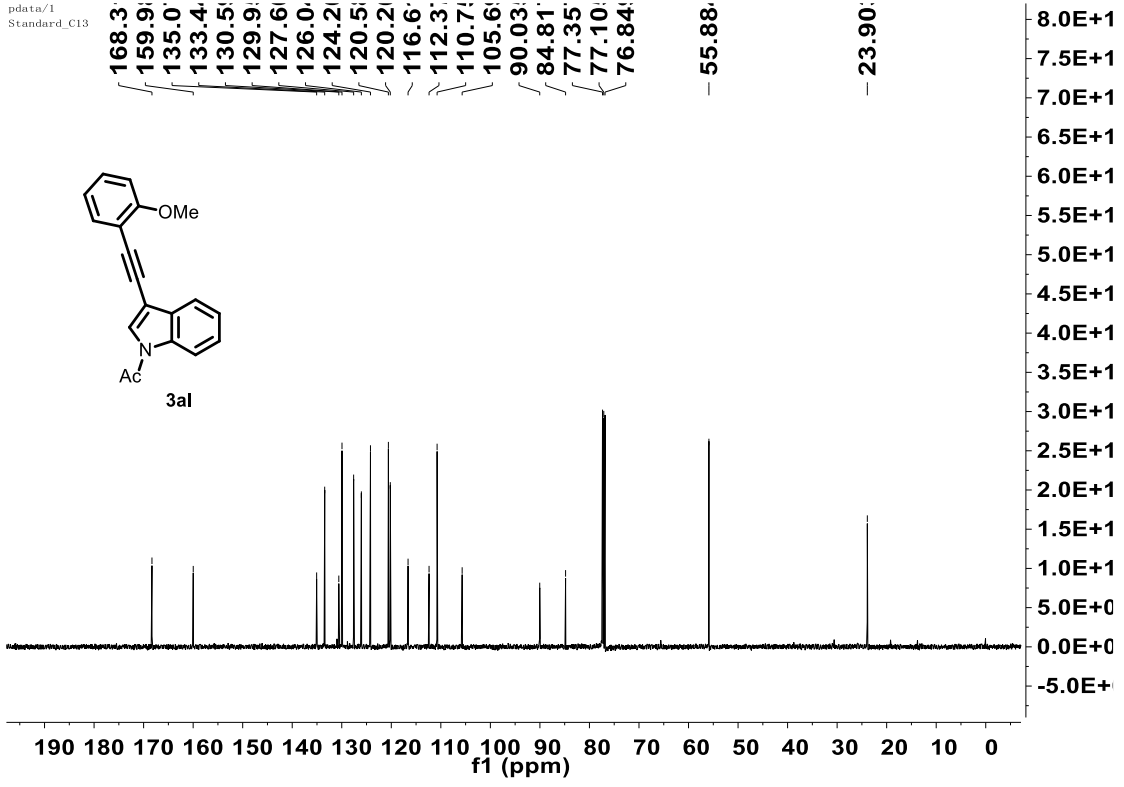
pdata/1
Standard_C13



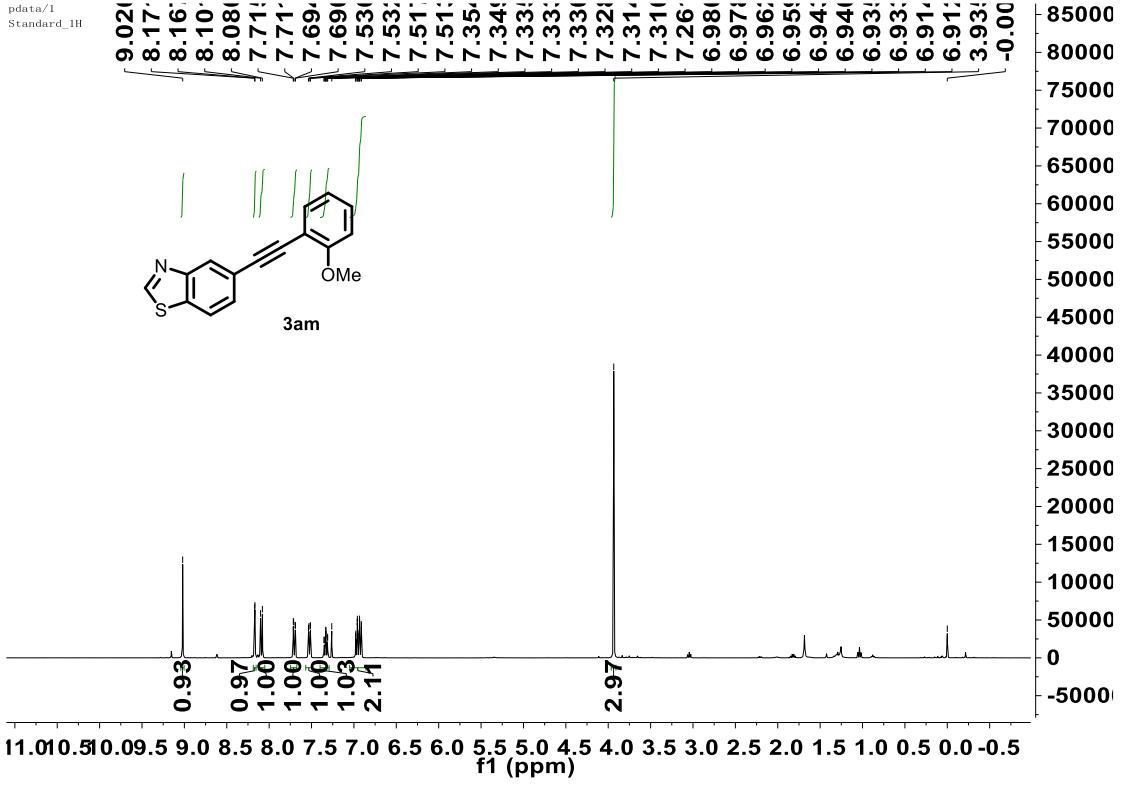
pdata/1
Standard_C13

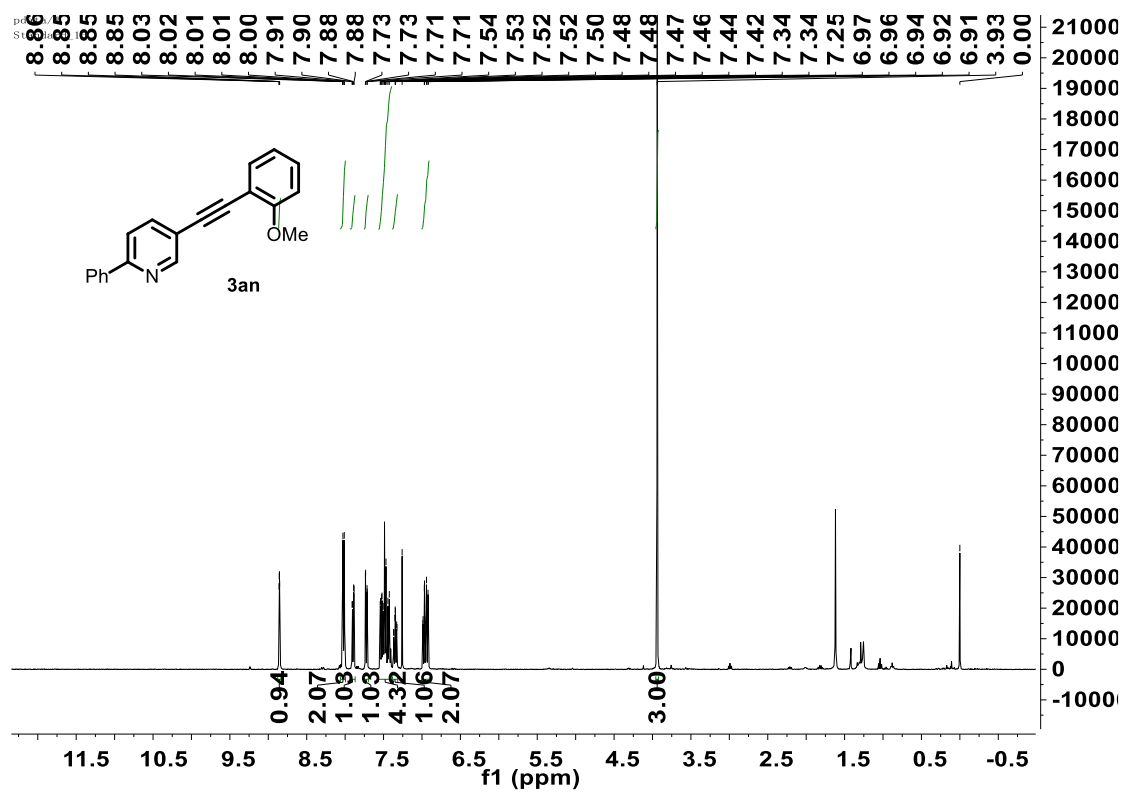
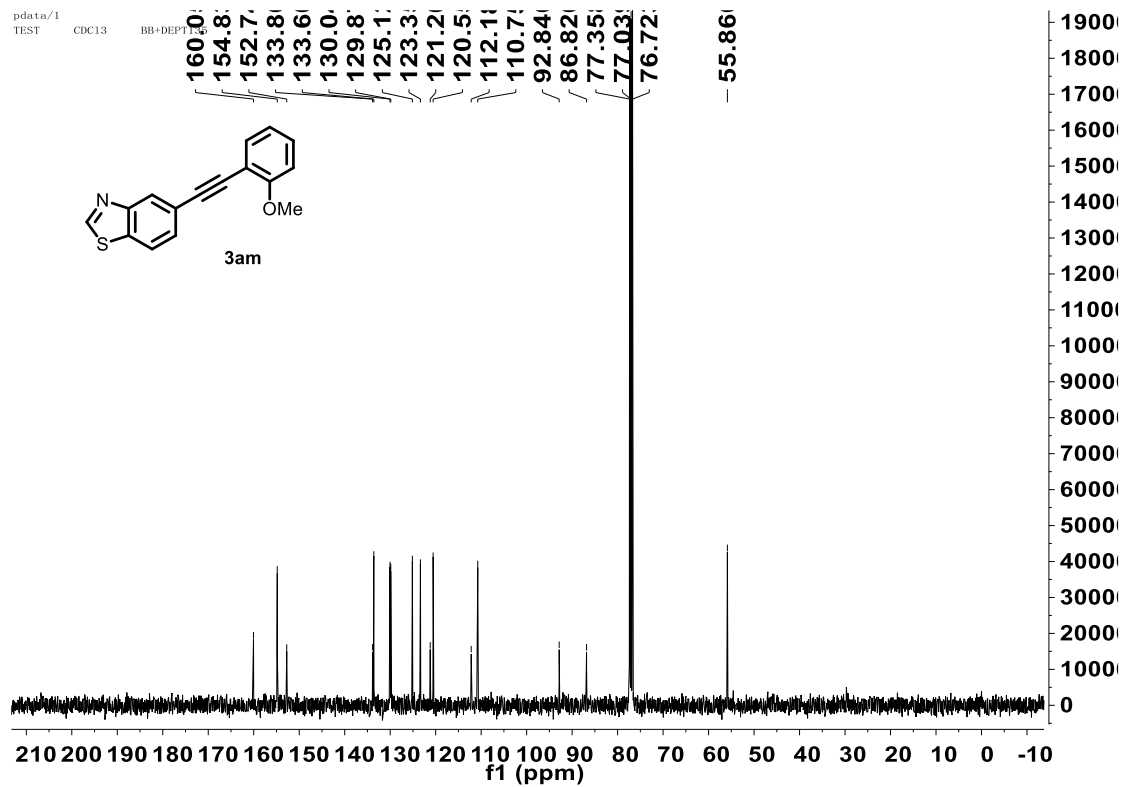


pdata/1
Standard_C13

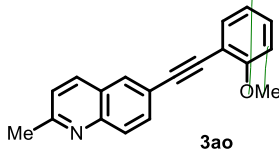
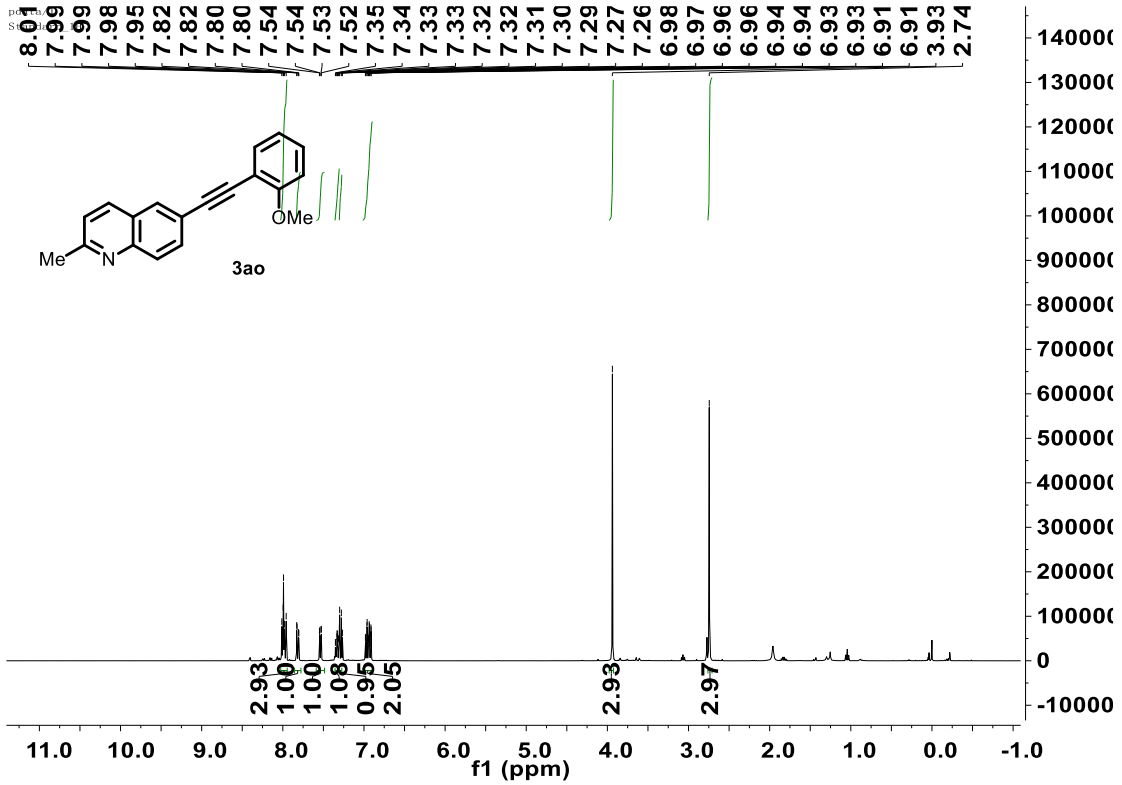
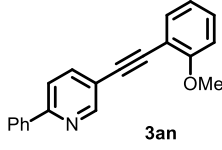
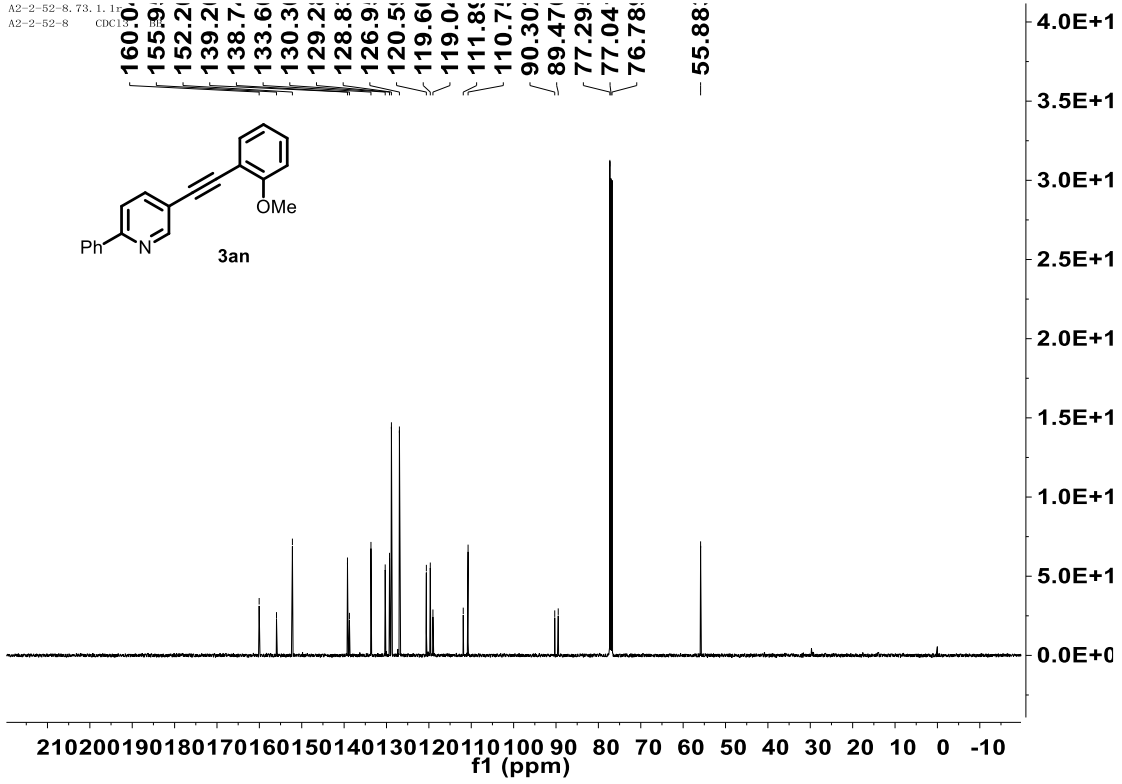


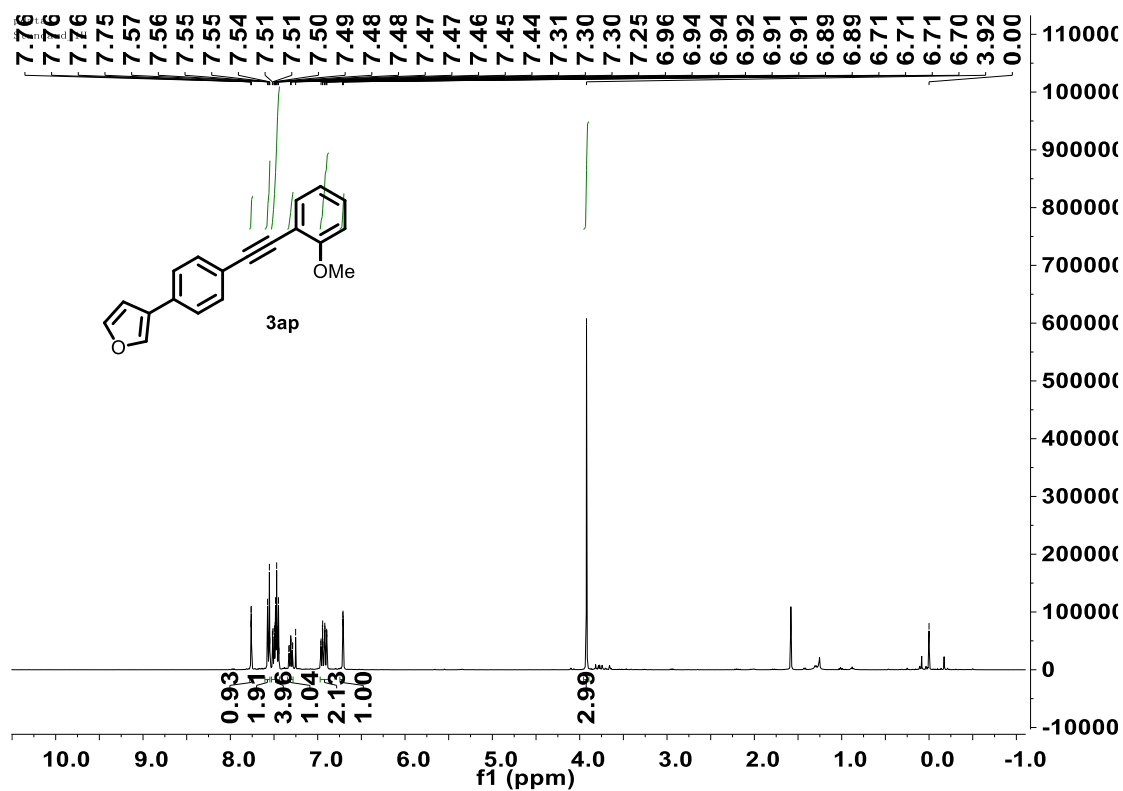
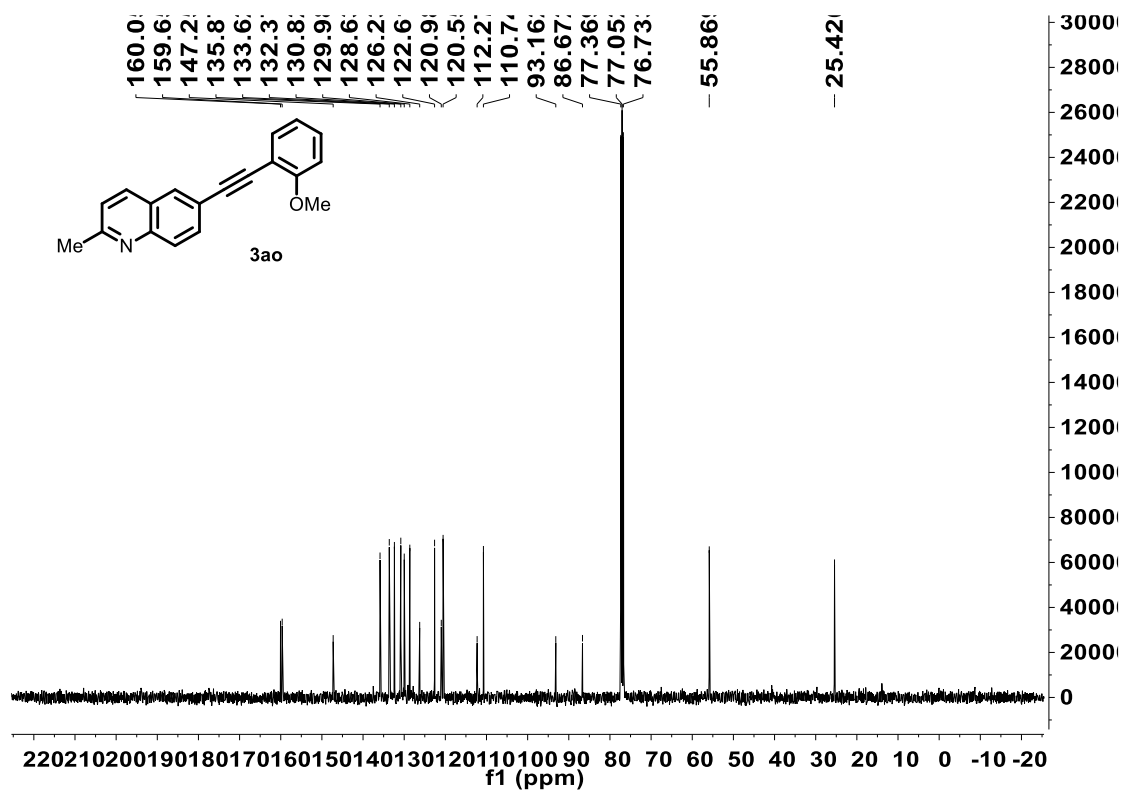
pdata/1
Standard_1H

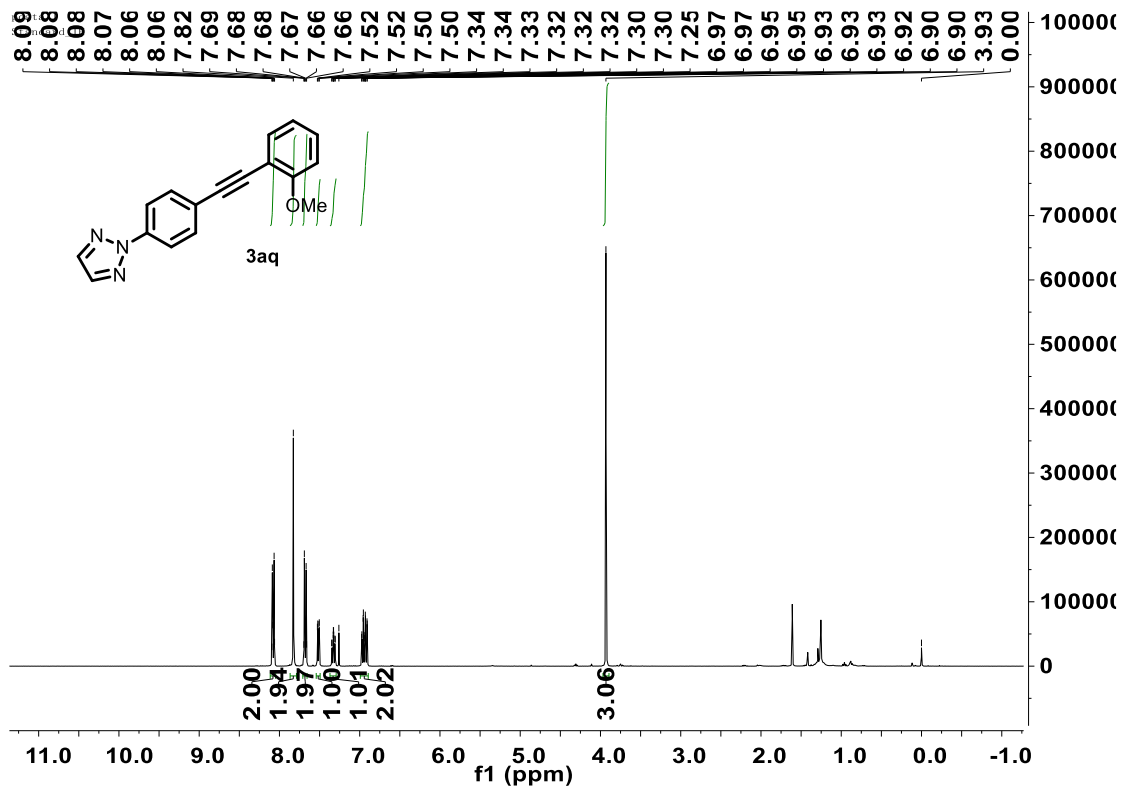
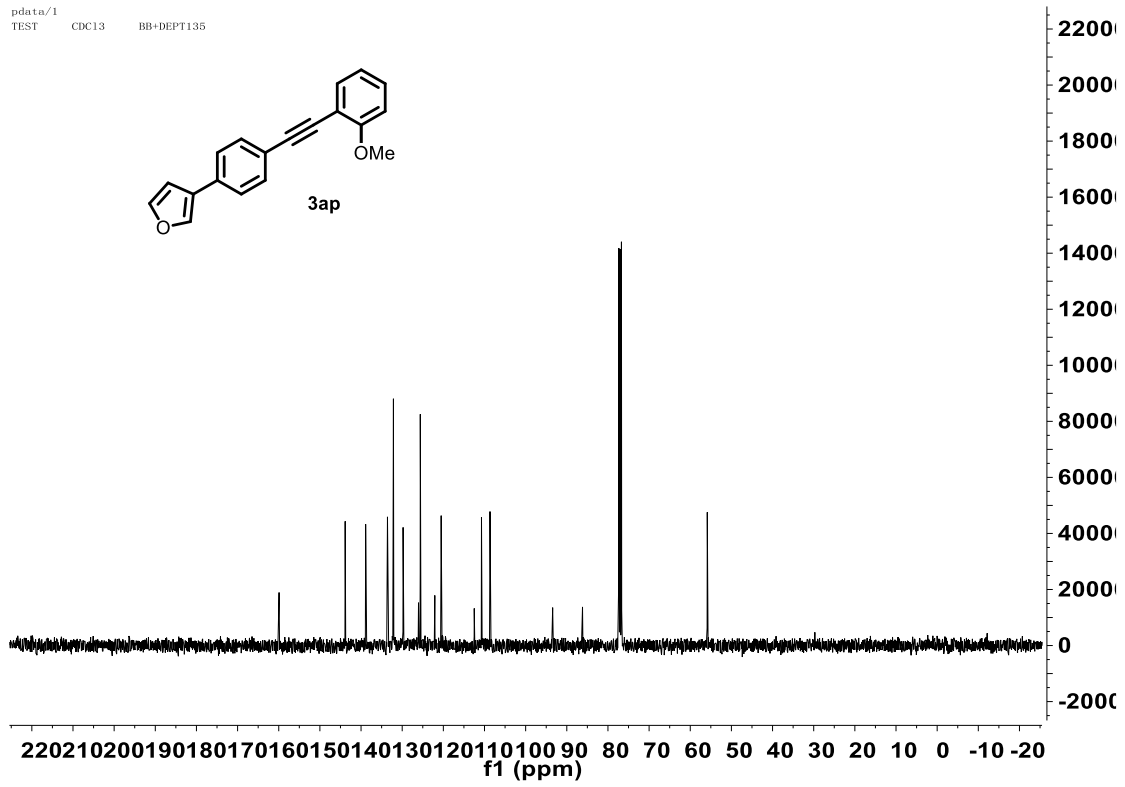




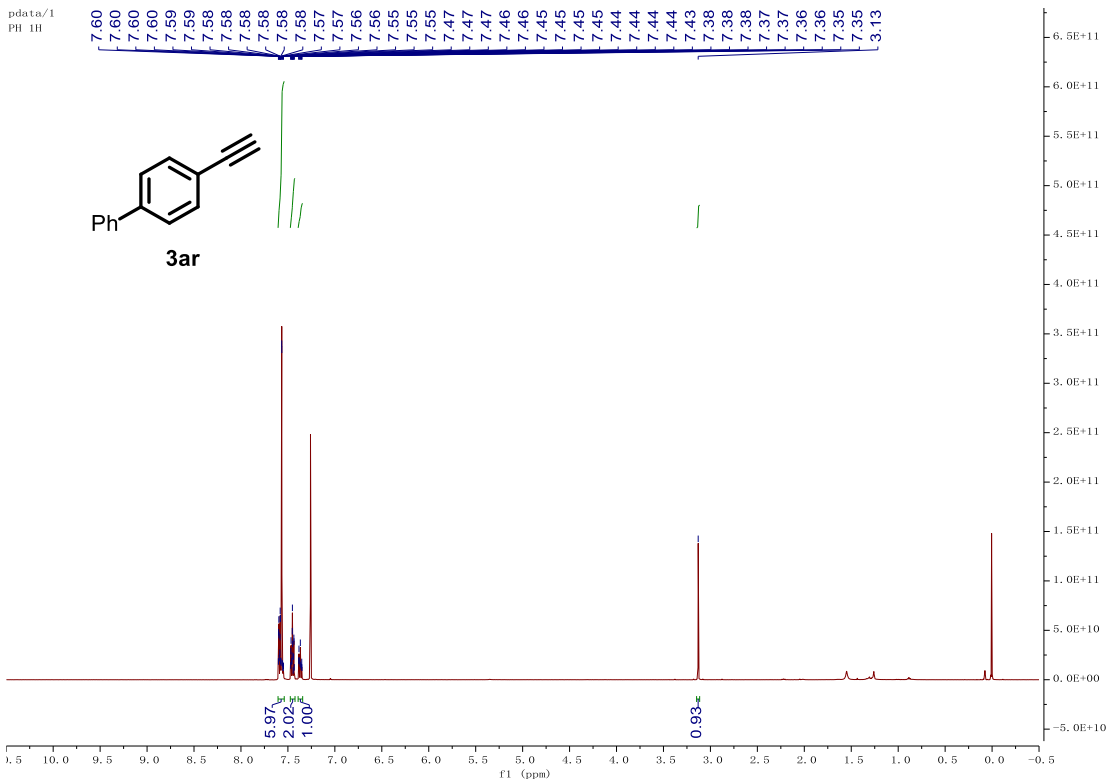
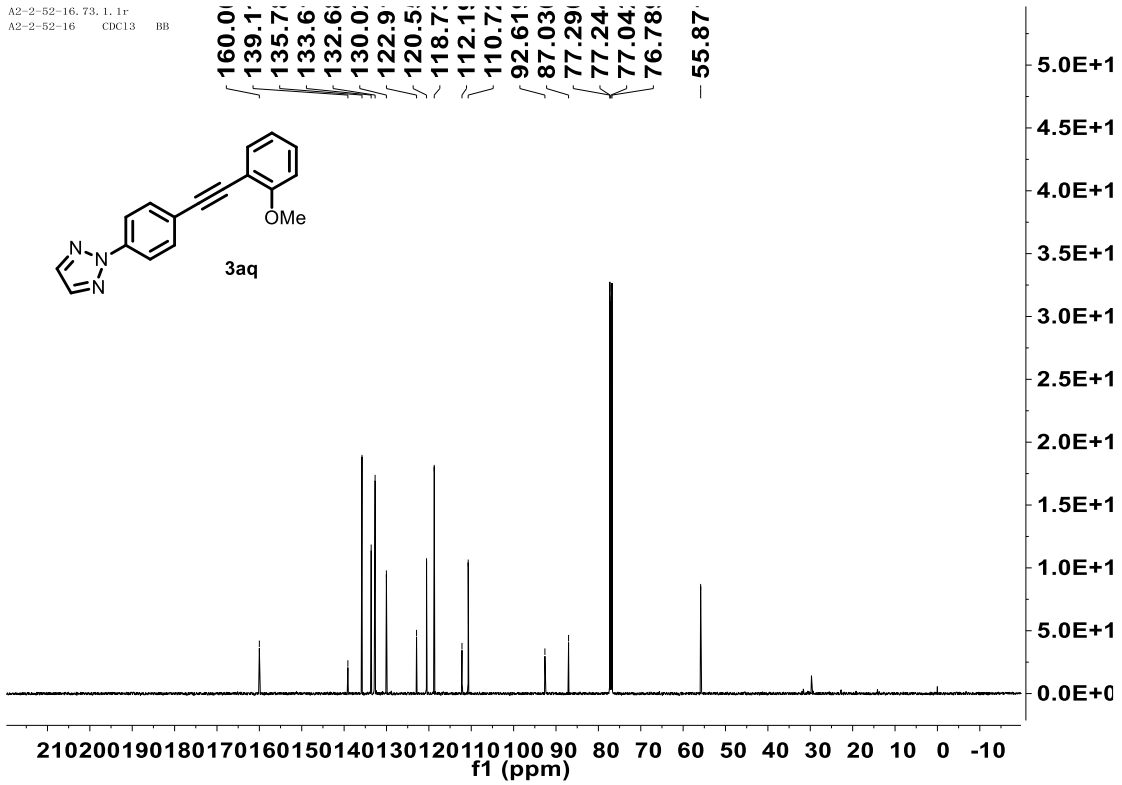
A2-2-52-8, 73.1.1h
A2-2-52-8 CDCl3



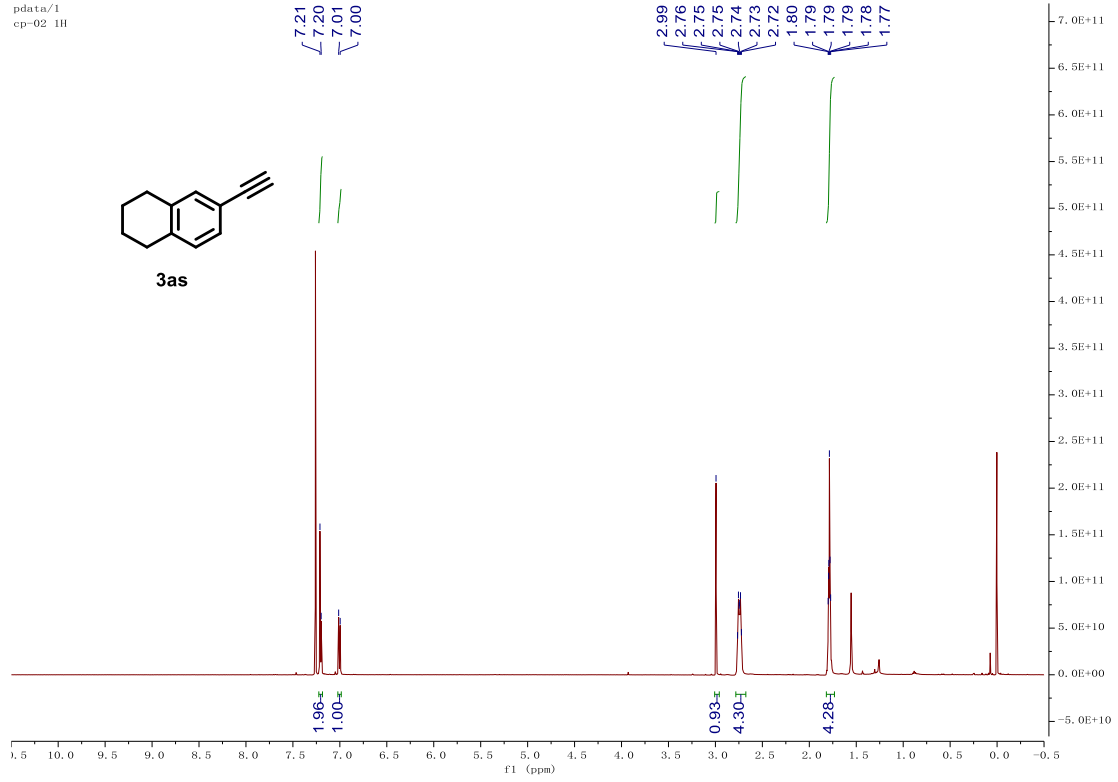




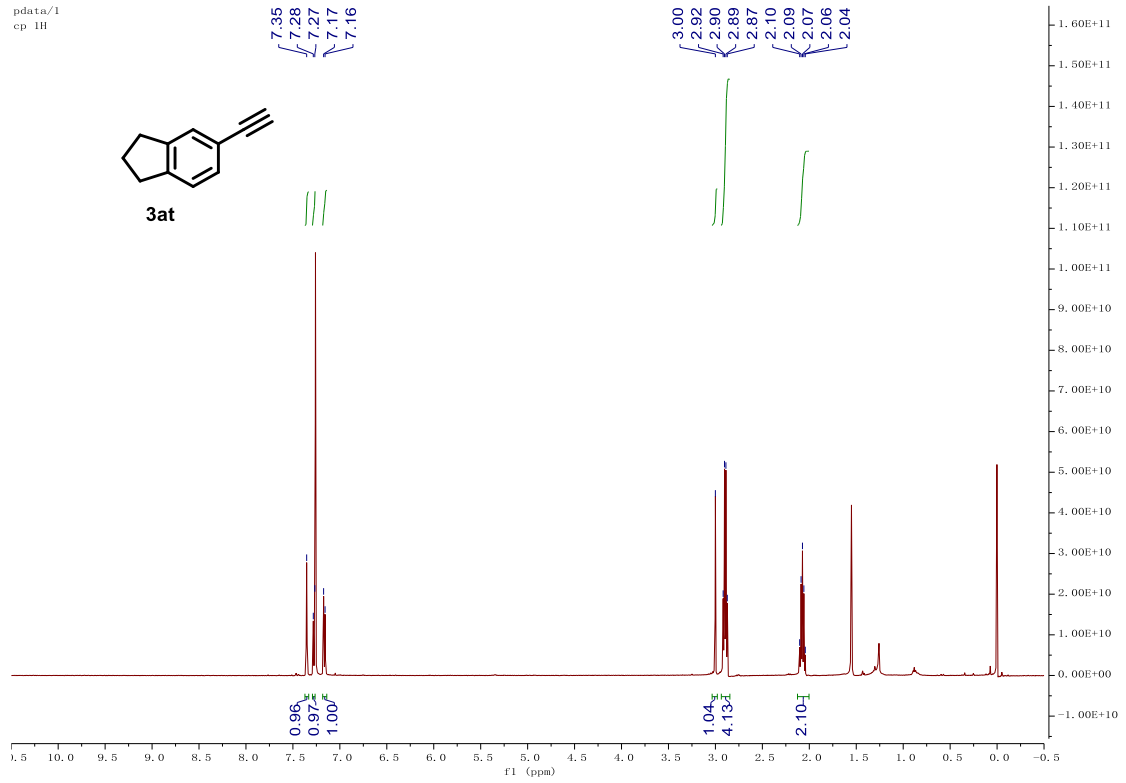
A2-2-52-16.73.1.1r
A2-2-52-16 CDC13 BB

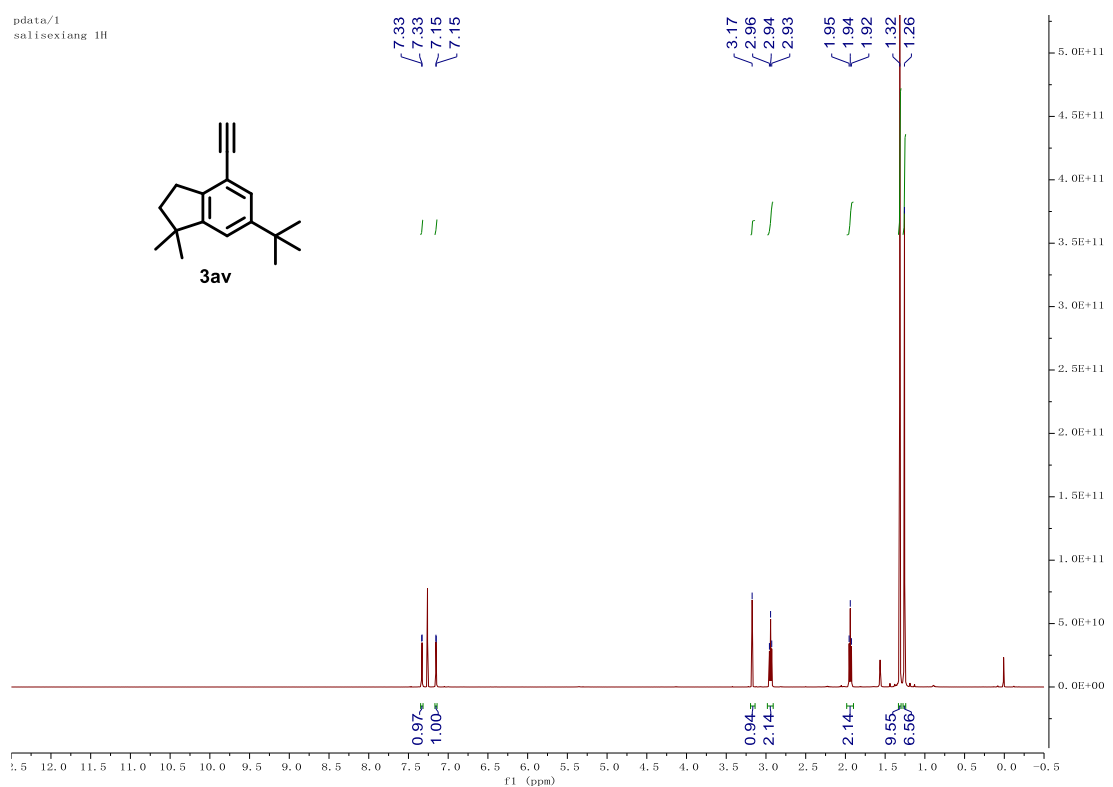
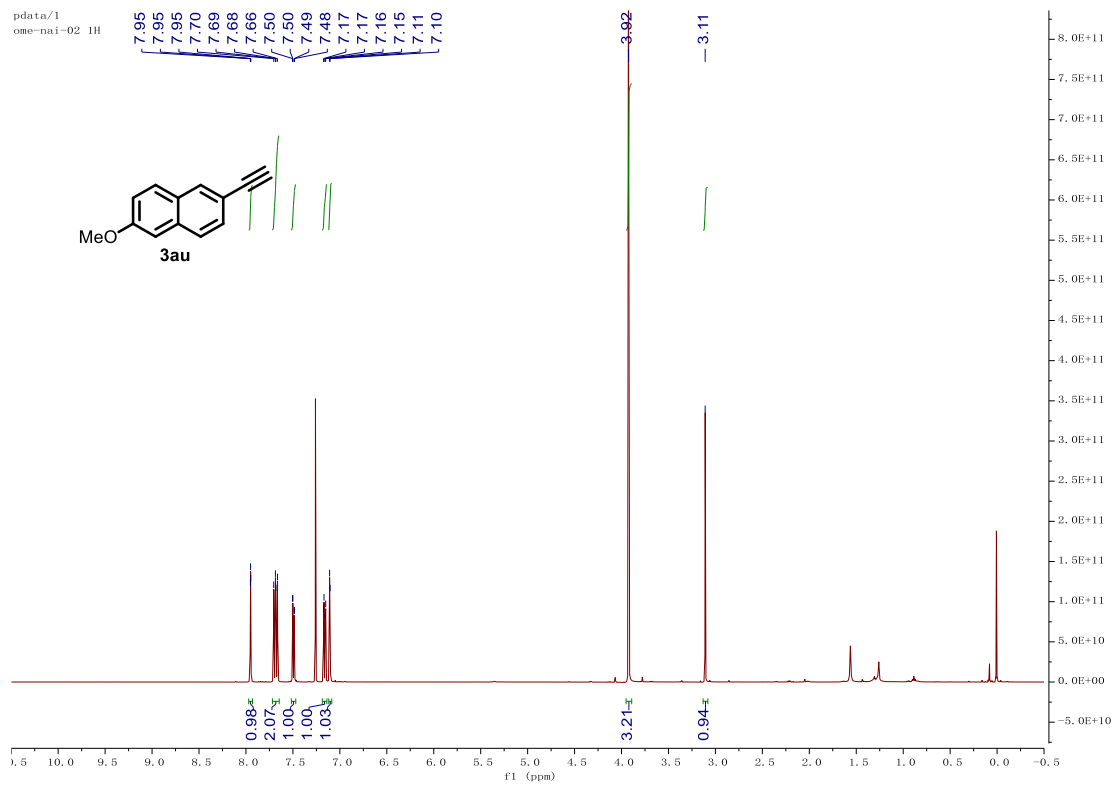


pdata/1
cp-02 1H

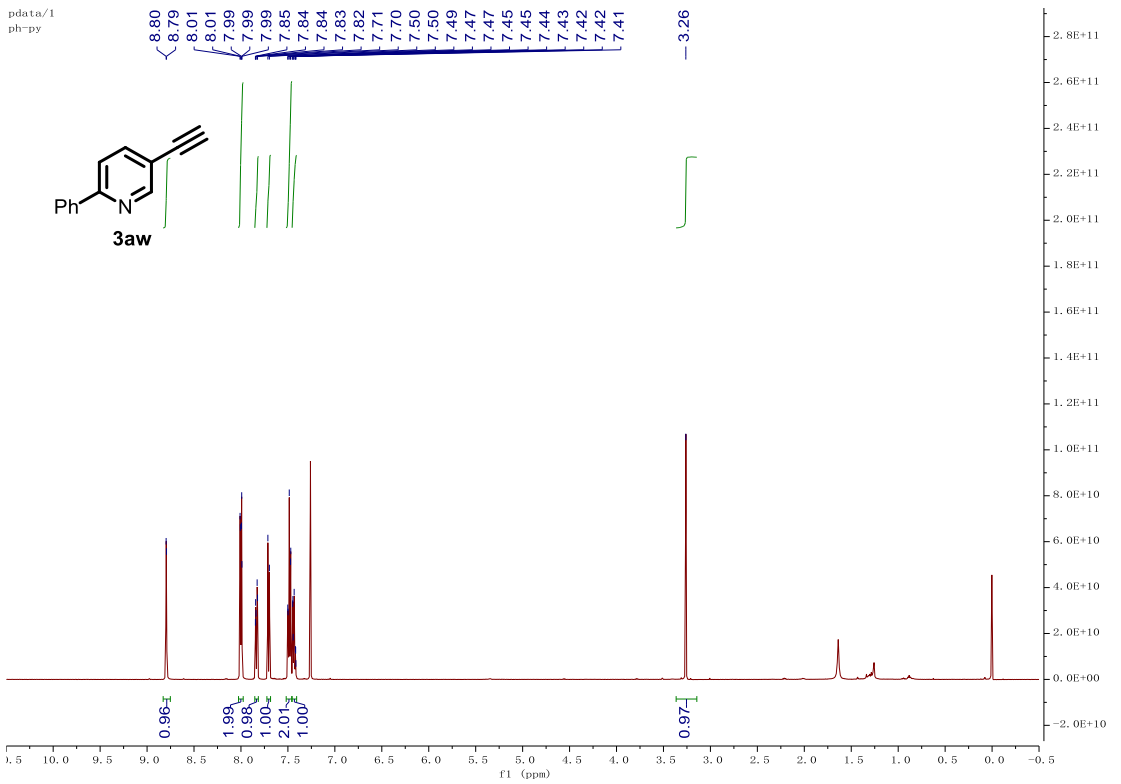
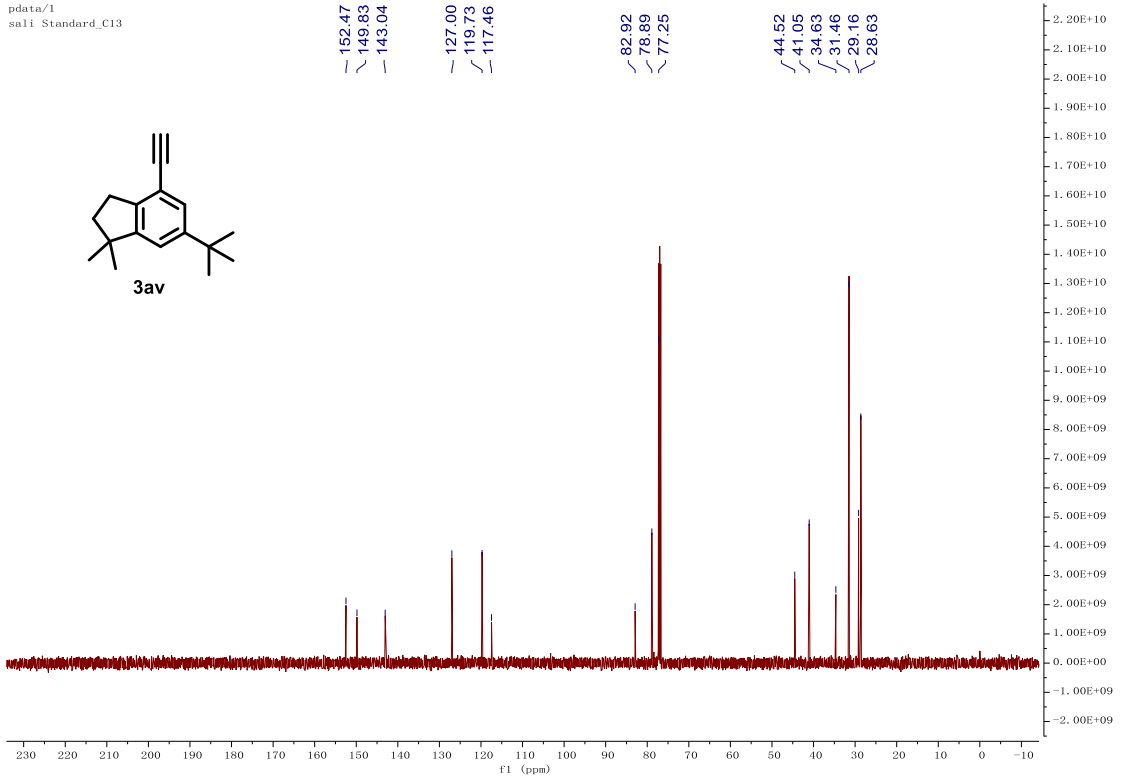


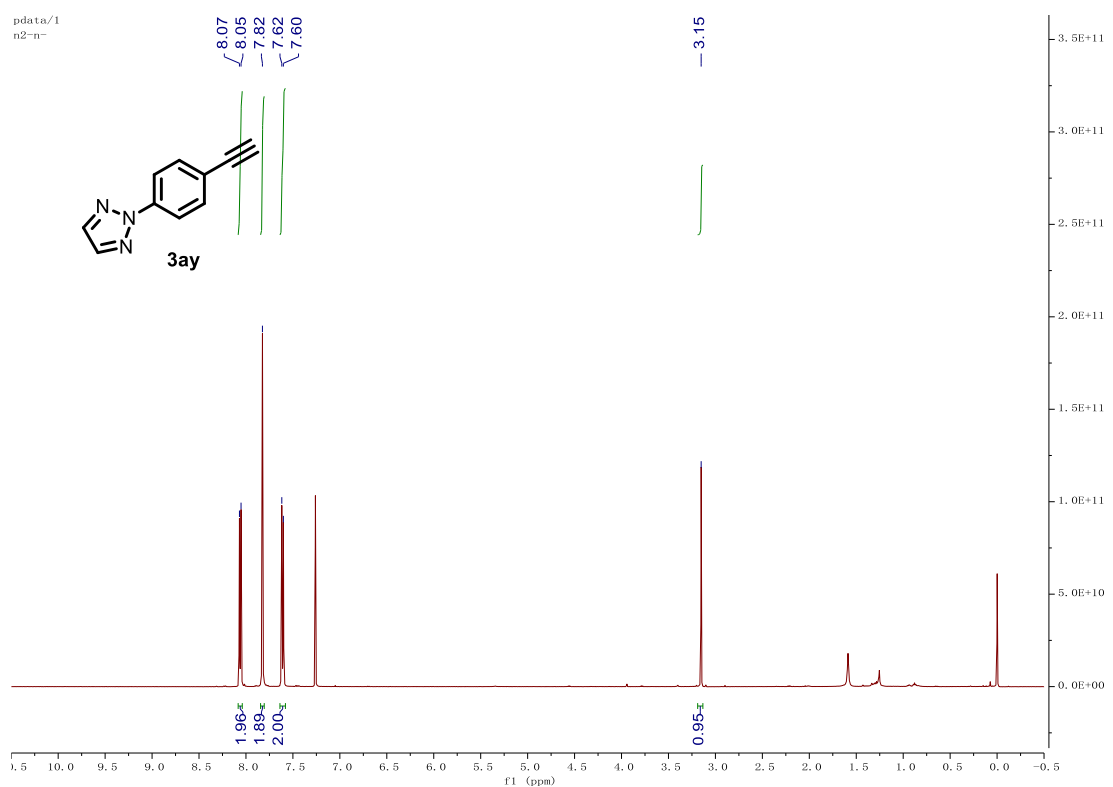
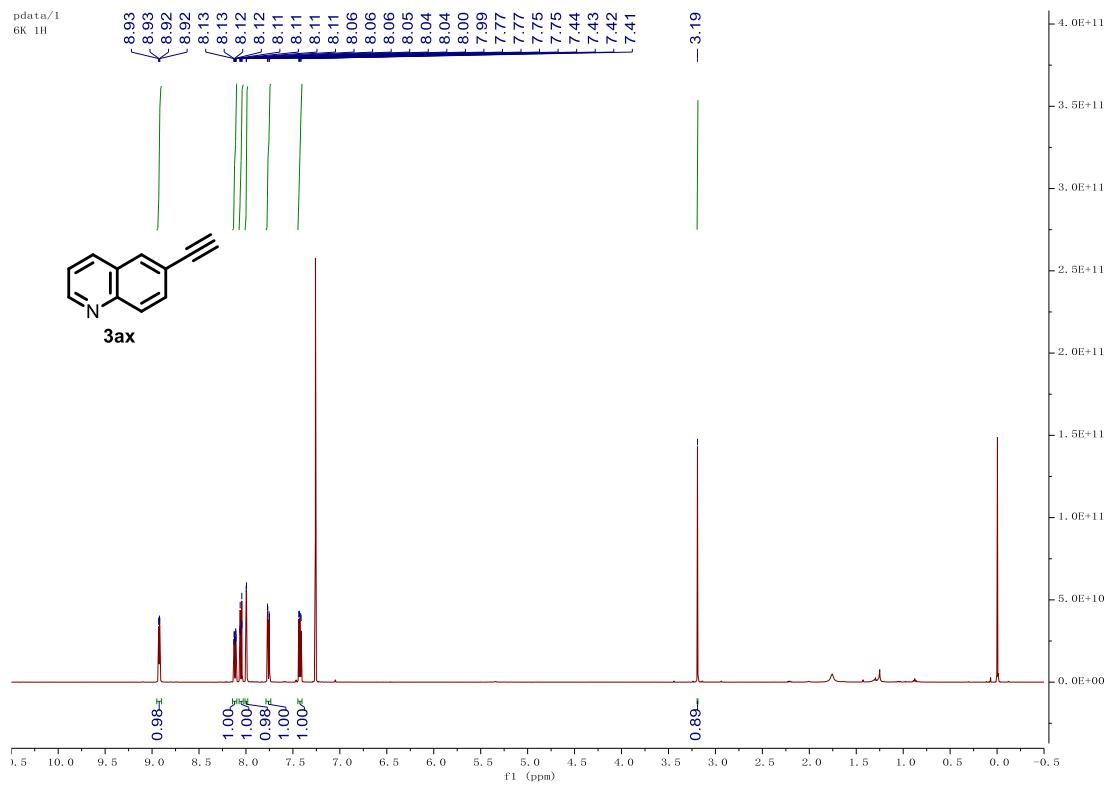
pdata/1
cp 1H



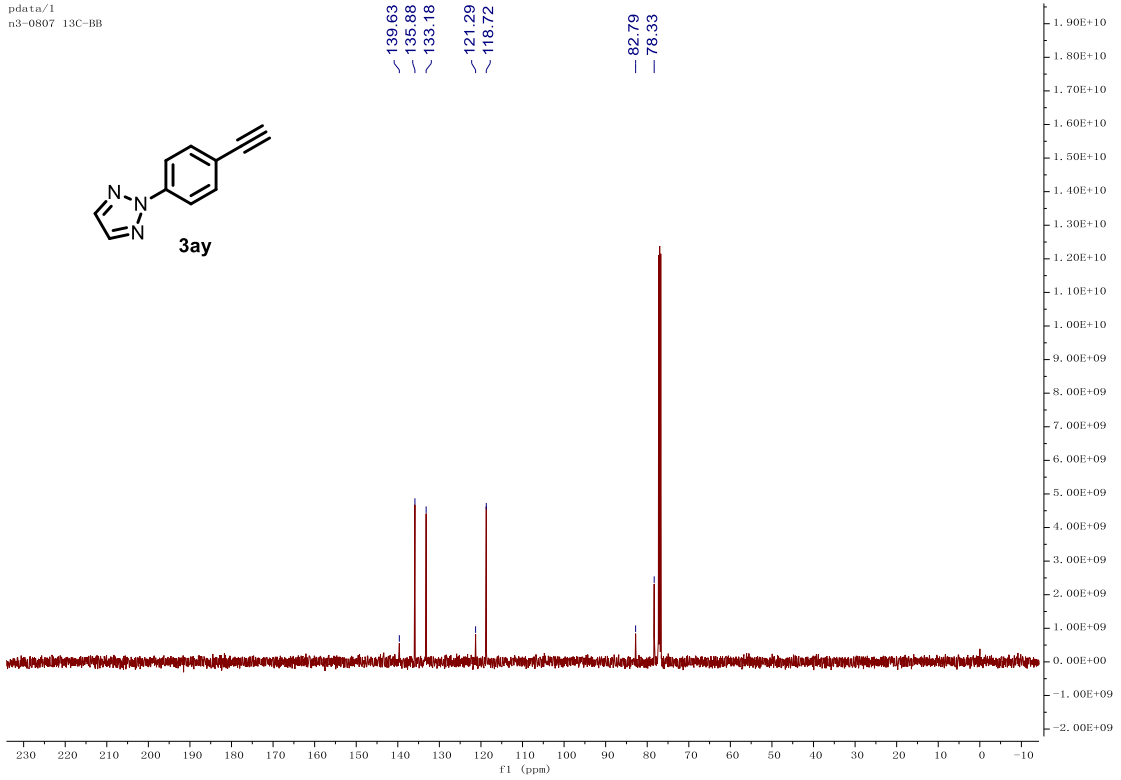


pdata/1
sali_Standard_C13

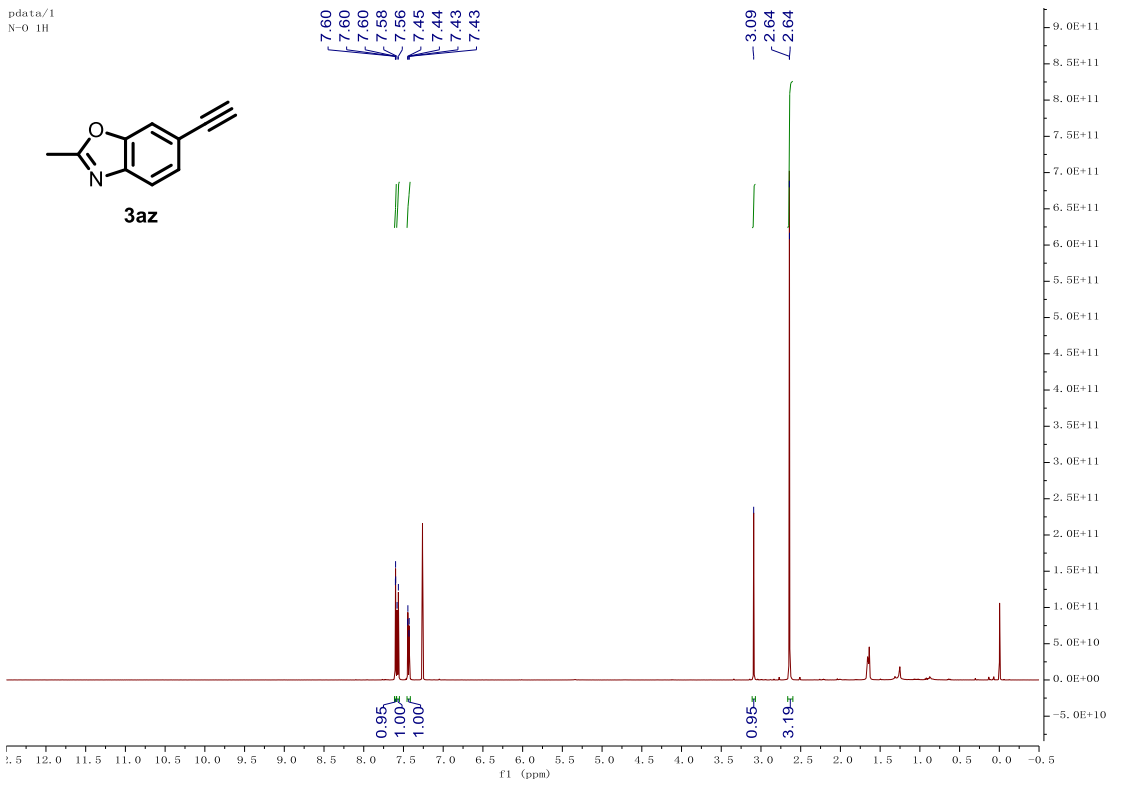


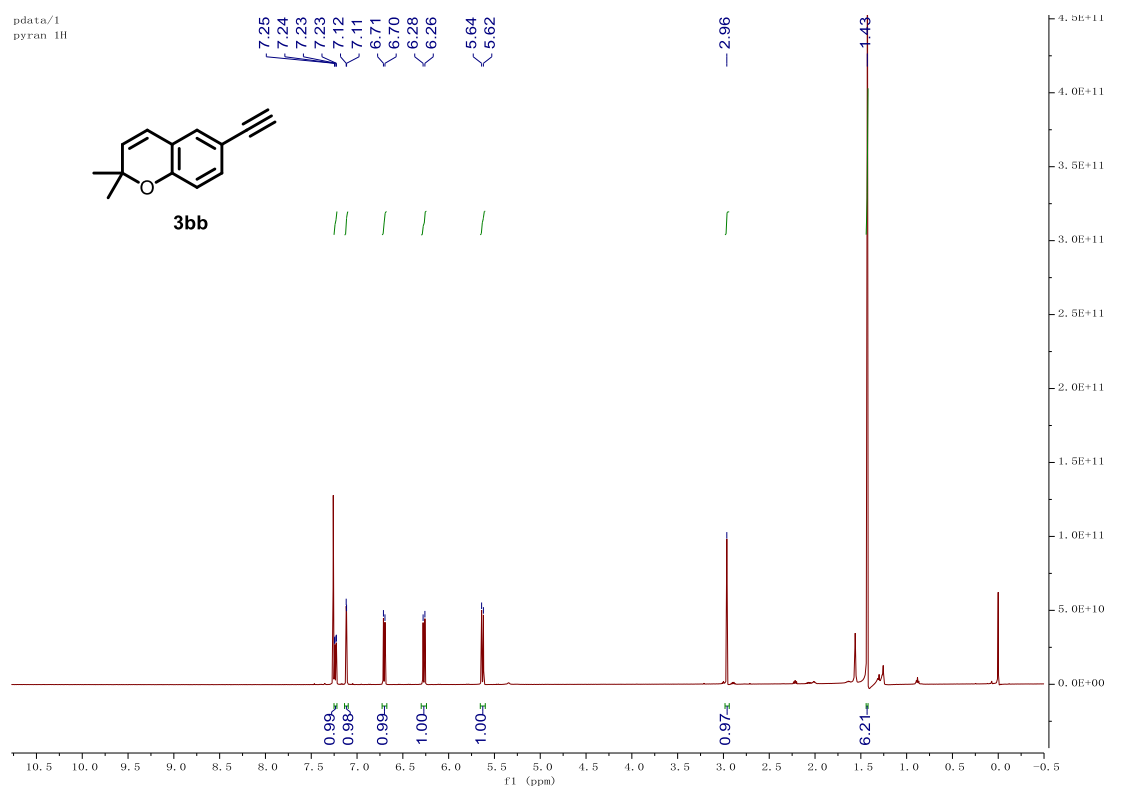
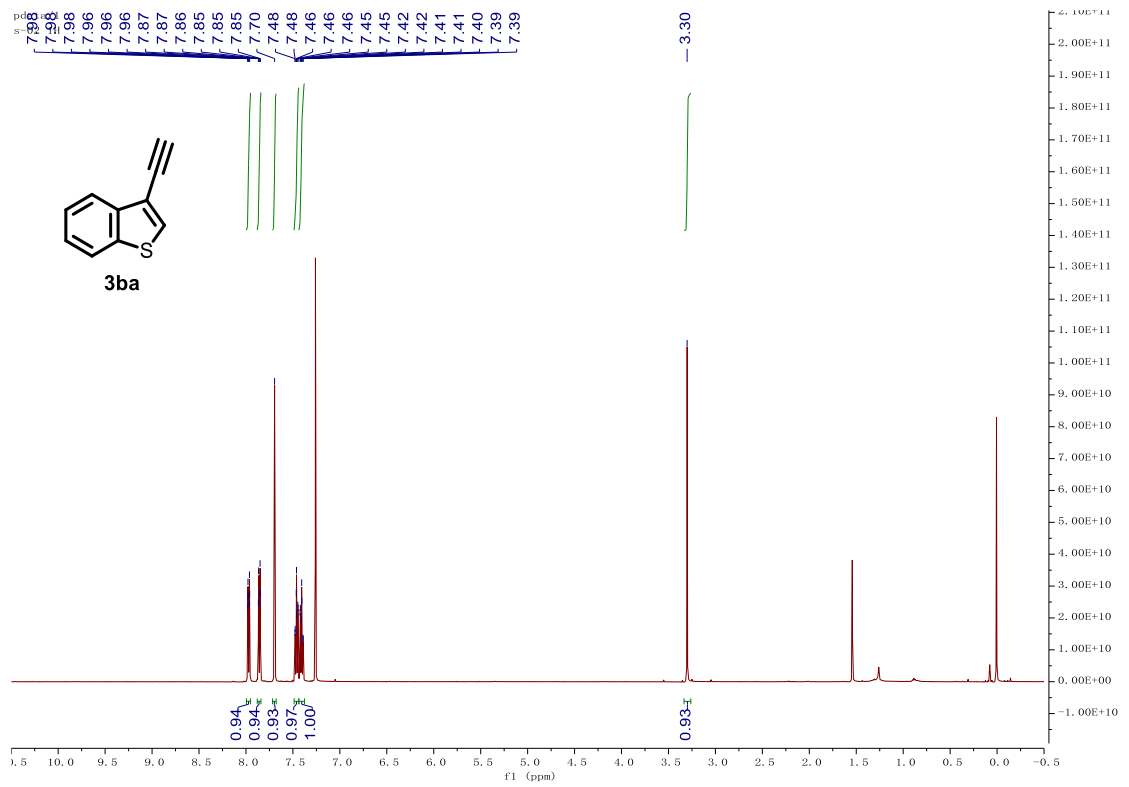


pdata/1
n3-0807 13C-BB

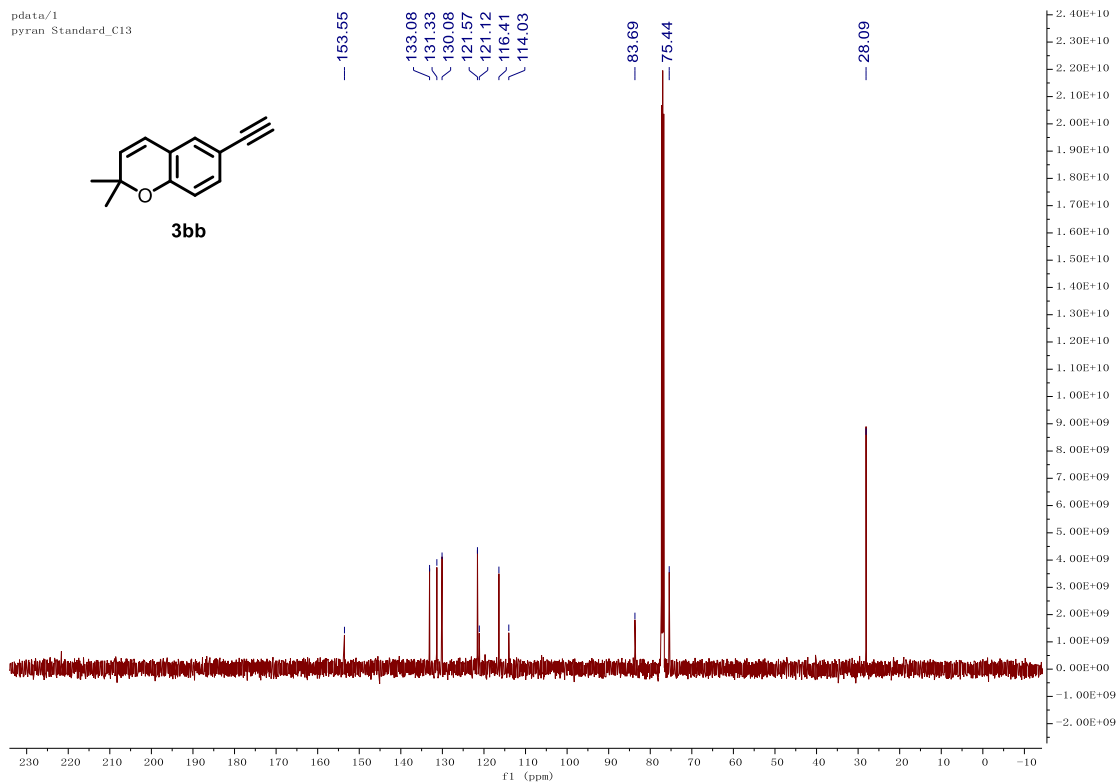


pdata/1
N-O 1H

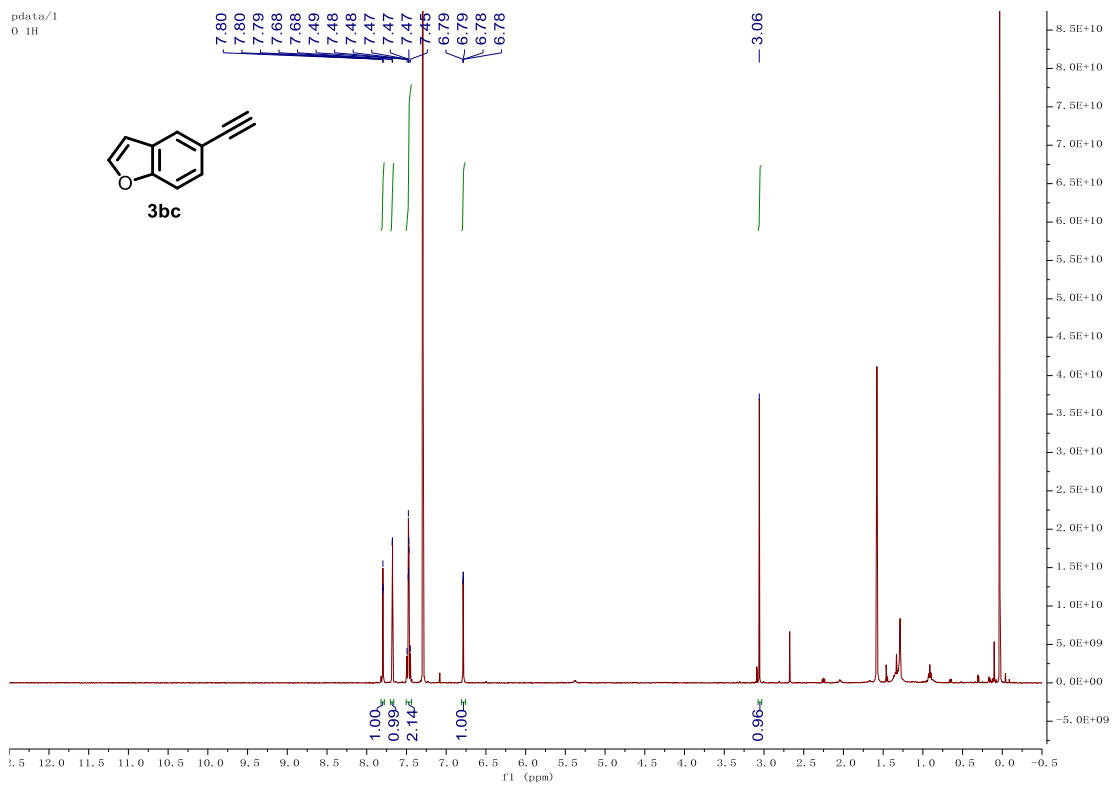


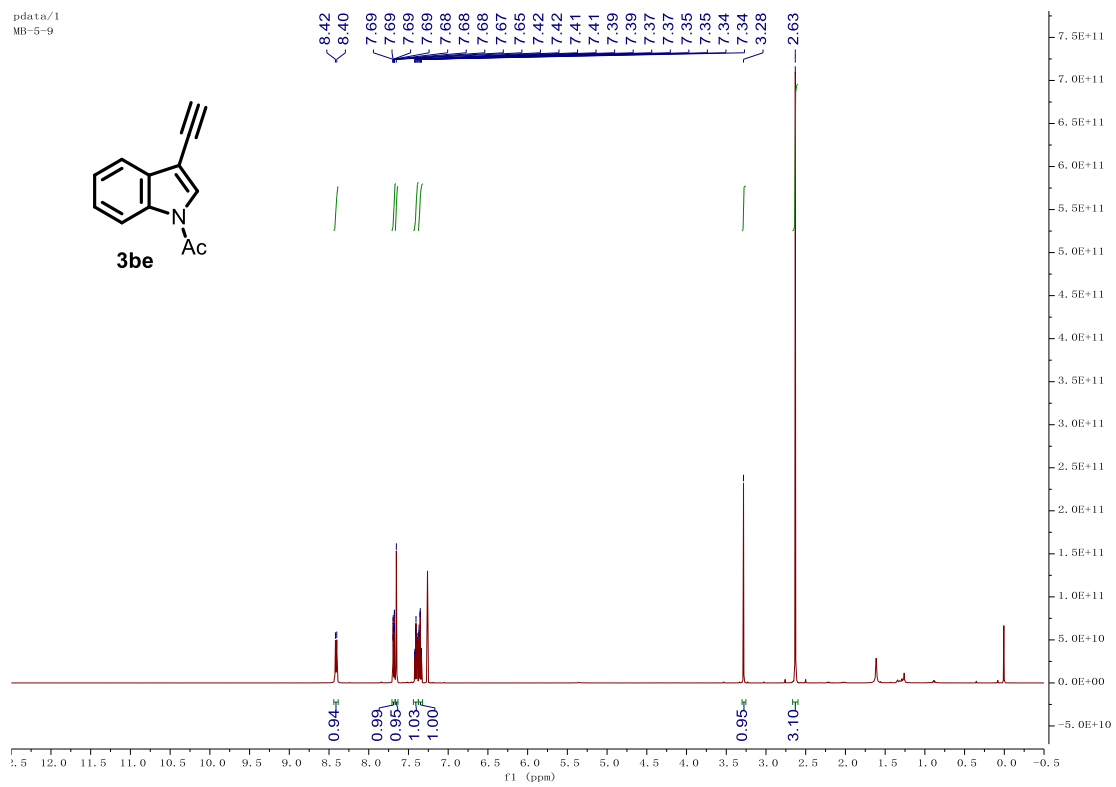
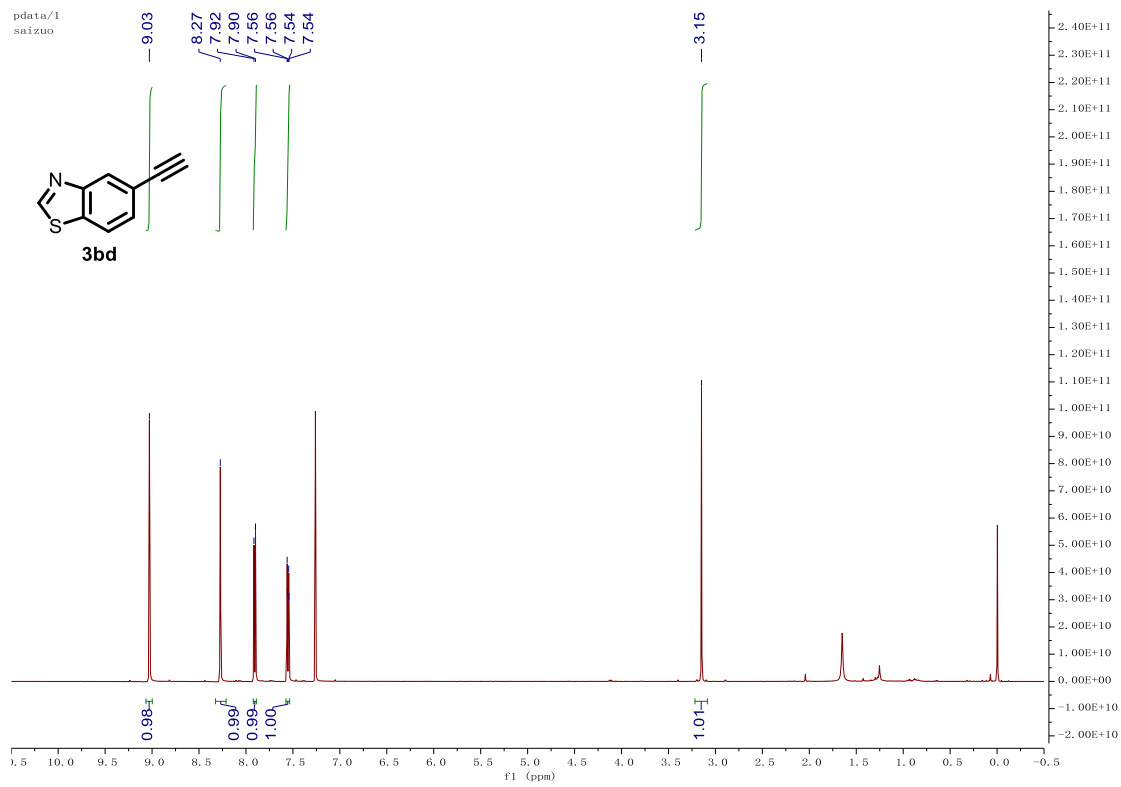


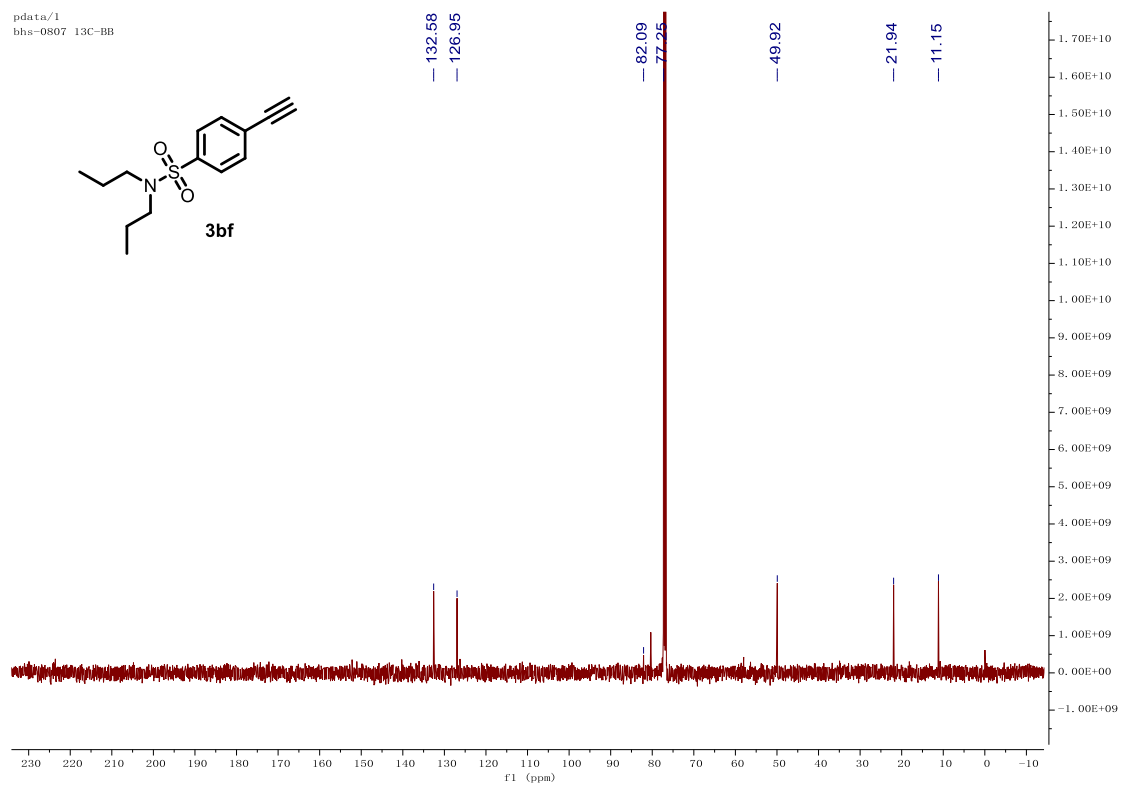
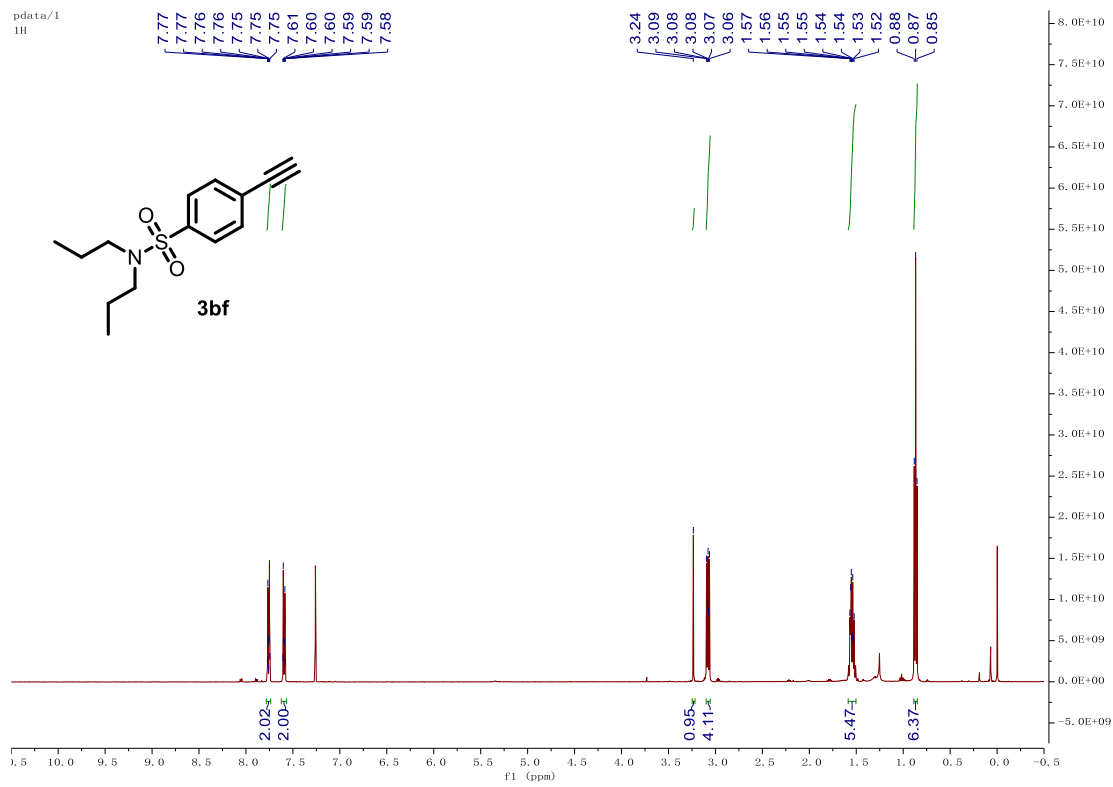
pdata/1
pyran_Standard_C13

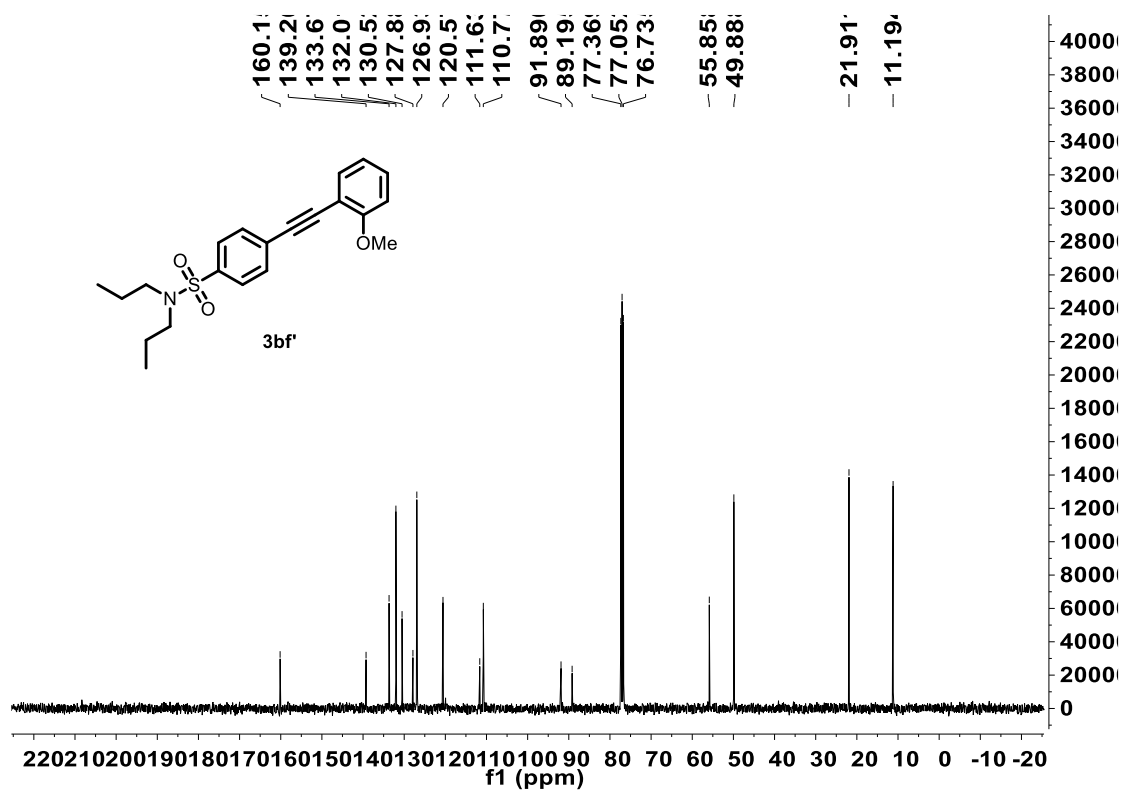
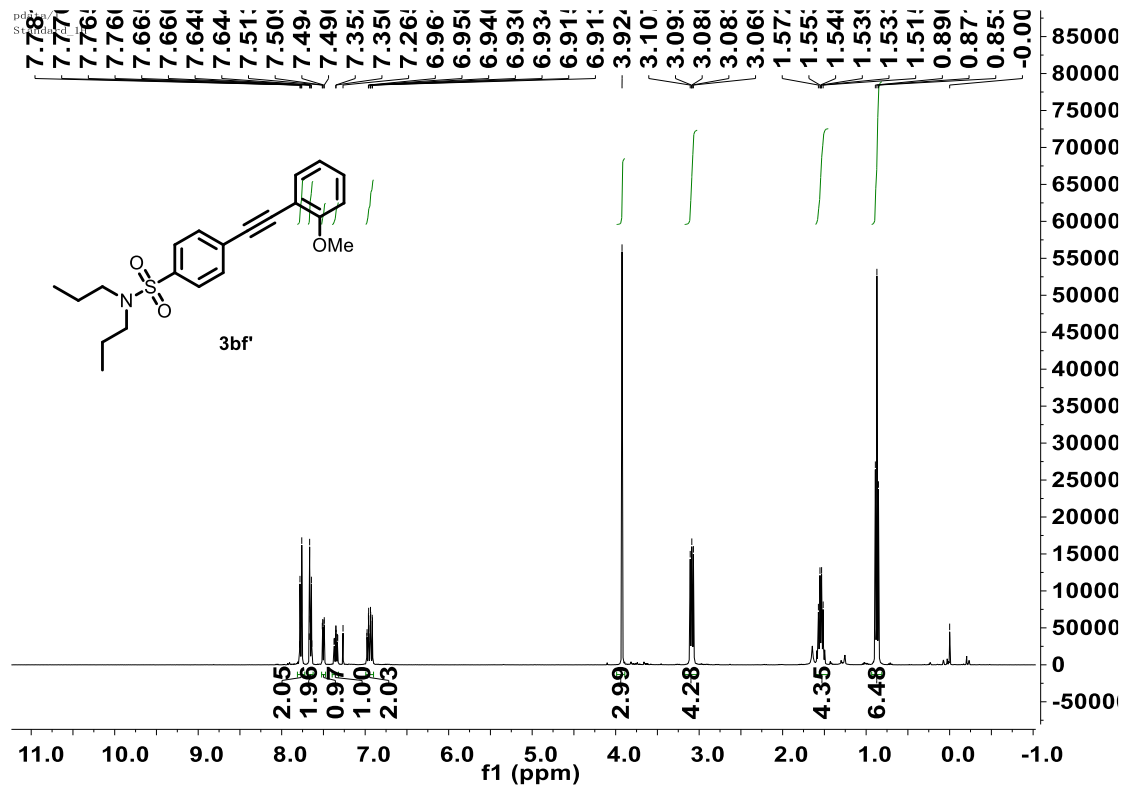


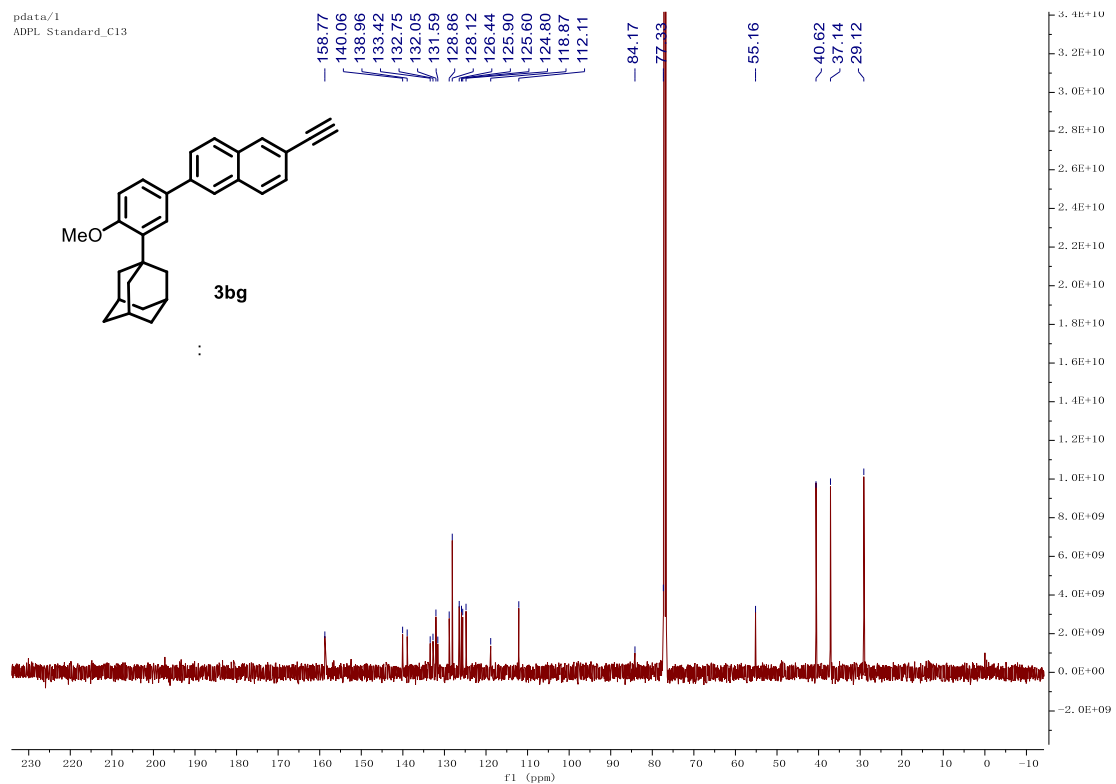
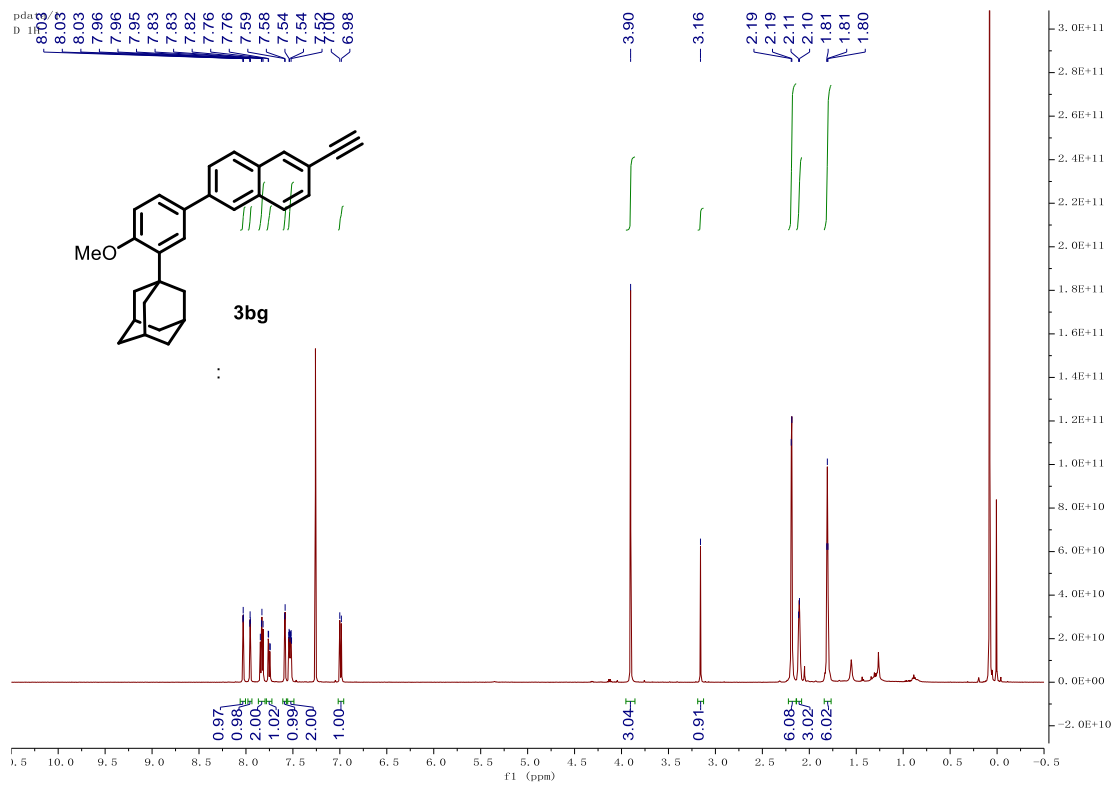
pdata/1
0 1H

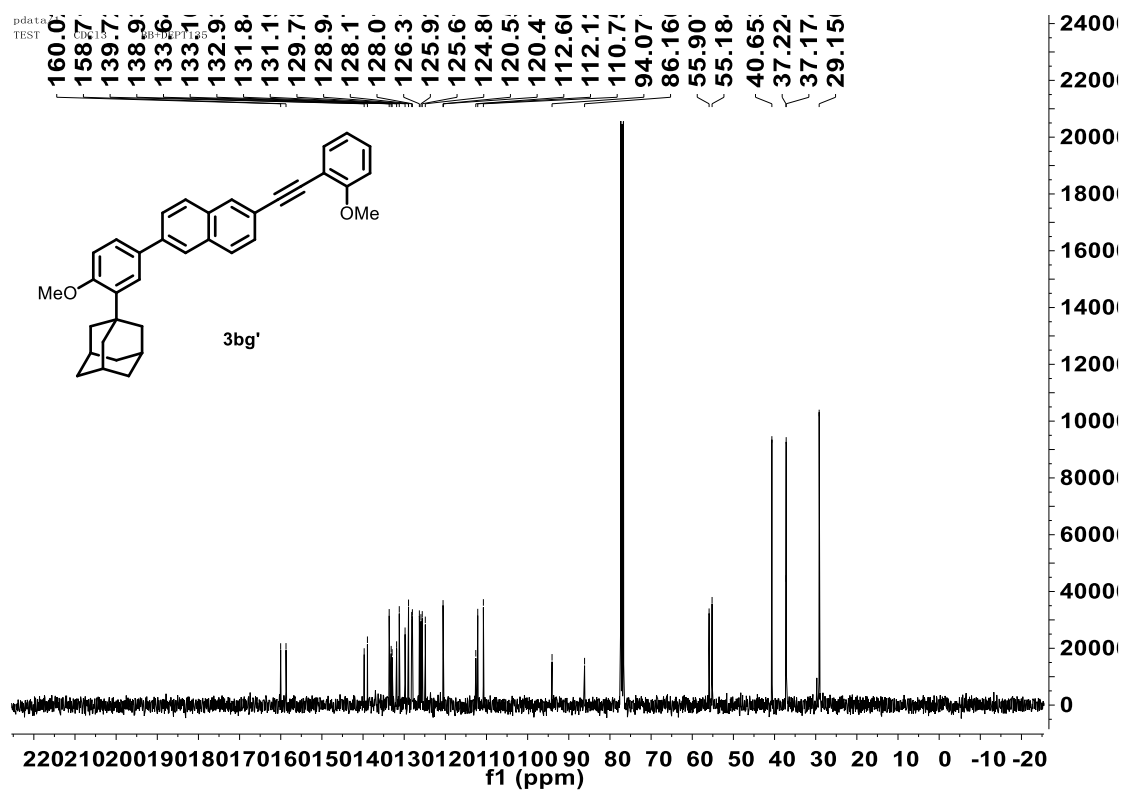
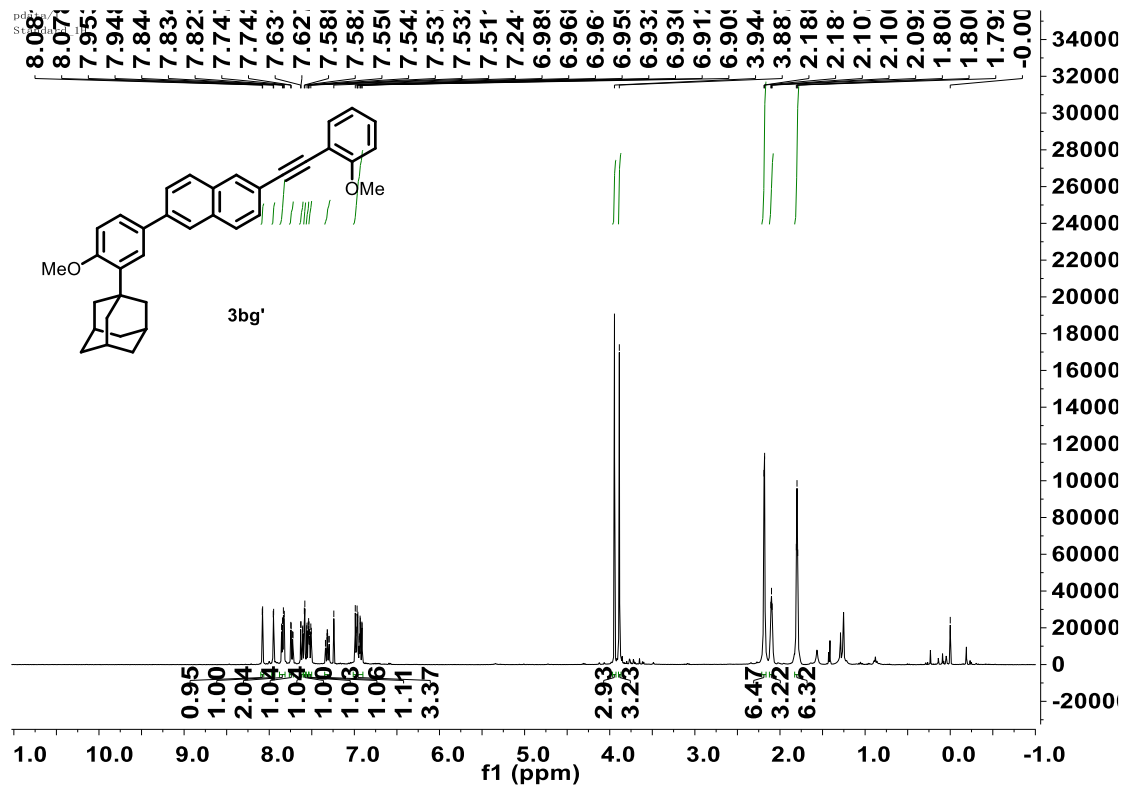




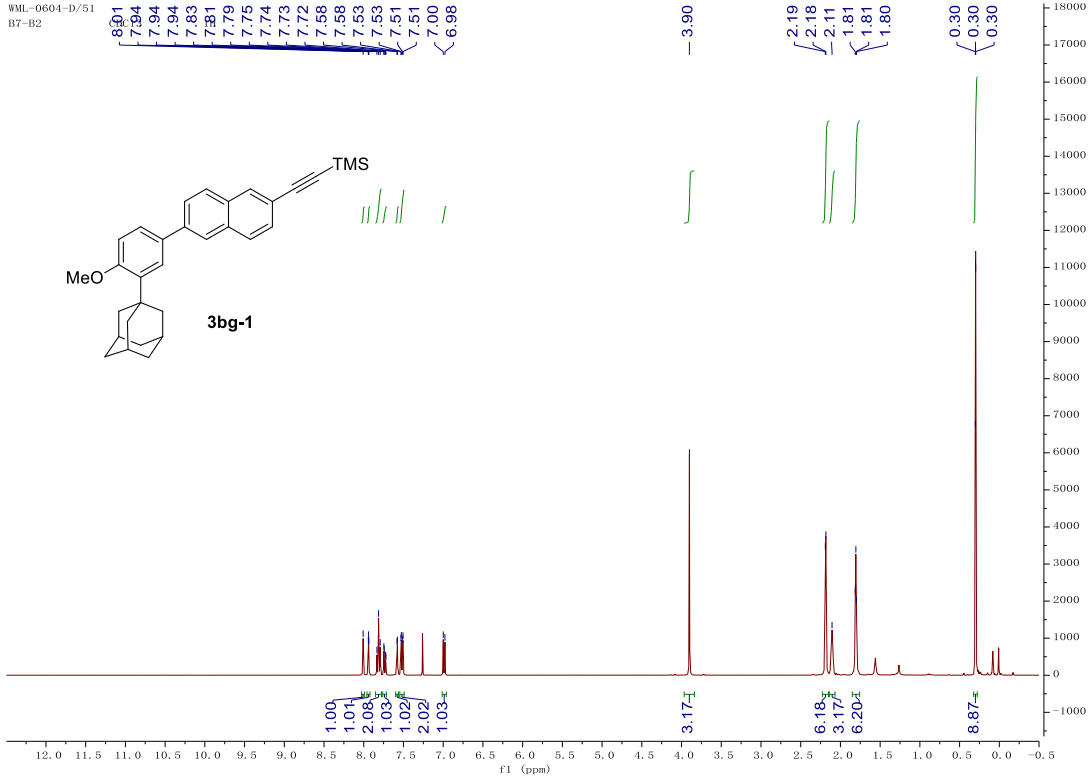








WML-0604-D/51
B7-B2



pdata/1
A2-ADPL-2 CDC13 13C-BB

