Supporting Information

$K_2S_2O_8$ promoted alkynylation of alkylboronic acids/boronates

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General Considerations

Chemicals

All the chemicals were purchased from commercial sources (Sigma-Aldrich, Merck, TCI, ACROS Organics, Spectrochem, BLDpharm) and directly used as received without additional purification. Solvents (DMF, DCM, DMSO, acetone, Tolune, EtOAc, CH_3CN) purchased from Thermo Scientific Chemicals and used as received

Chromatography

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminum 60 F-254 plates. Visualization of TLC was achieved by using a UV lamp (254 nm). Column chromatography was carried out with silica gel (60-100 mesh, 100-200 mesh, and 220-400 mesh) to purify products using proper solvents as the eluent system. All the yields of the products are referred to as chromatography pure compounds.

Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra were recorded at 500 MHz for ^{1}H NMR spectra, 125 MHz for ^{13}C {1H} NMR spectra, and 471 M Hz for ^{19}F NMR spectra. The sample to be analyzed was dissolved in a chloroform-*d* solvent. Chemical shifts are quoted in parts per million referenced to the appropriate solvent peak. For ^{13}C {1H} NMR and ^{1}H NMR, chemical shifts are reported in parts per million referenced to the center of a triplet at 77.16 ppm and 7.26 ppm of chloroform-*d* respectively. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; sext = sextet; sept = septet; m = multiplet; brs = broad singlet. Coupling constants, *J* are reported in hertz.

Fourier Transform Infrared Spectroscopy

Infrared spectra were recorded with a Bruker-Alpha (ATR-ZnSe) spectrometer and are reported as wavenumber (cm^{-1}).

High-Resolution Mass Spectrometry (HRMS)

HRMS was recorded on the Thermo Scientific Q Exactive TM Benchtop LC-HRMS (ESI-TOF) instrument.

Melting point apparatus

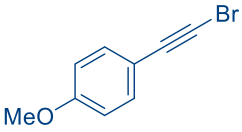
Melting points (mp) were uncorrected and recorded on a Thomas-Hoover Unimelt capillary melting point apparatus.

EPR

EPR Experiments were conducted on Bruker A200, with the following measure conditions Frequency 9.8546 GHz, Centre Field 340 mT, Sweep Width 500 mT, Sweeps Time10.49 Sec.

Synthesis of Starting materials:

Substrate scope of Alkynyl bromide: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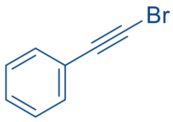
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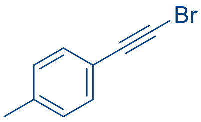
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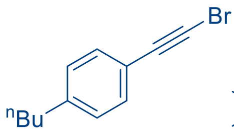
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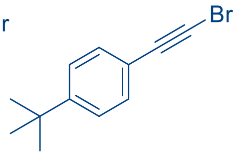
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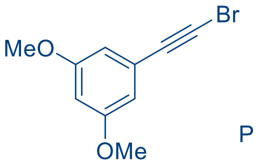
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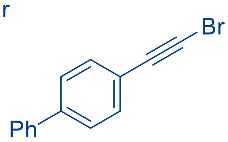
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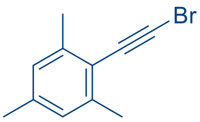
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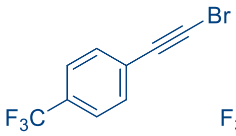
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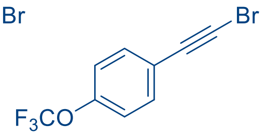
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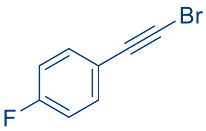
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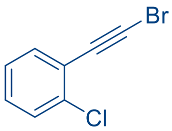
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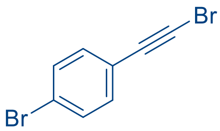
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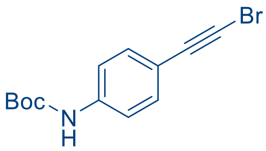
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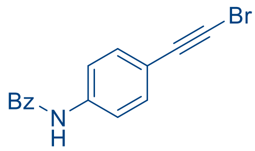
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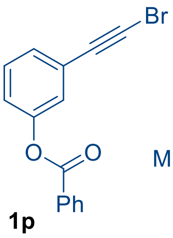
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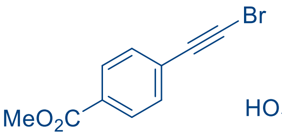
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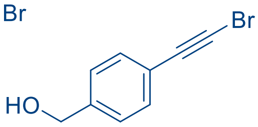
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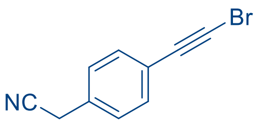
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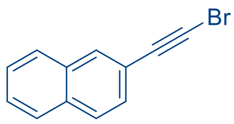
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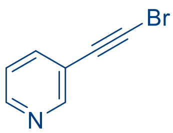
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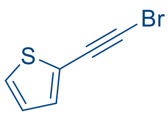
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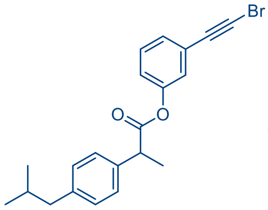
All the above alkynyl bromides were prepared according to the literature procedure.[1]



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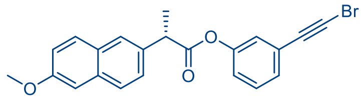
From Ibuprofen



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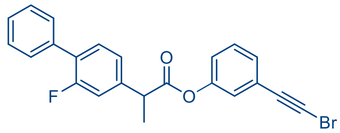

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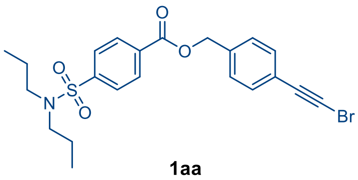

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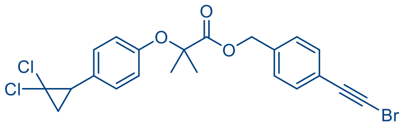

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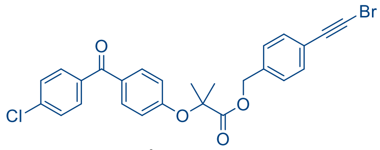

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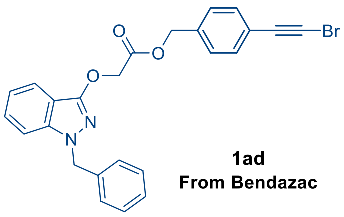
From Finofibric acid



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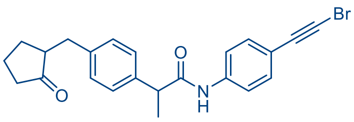

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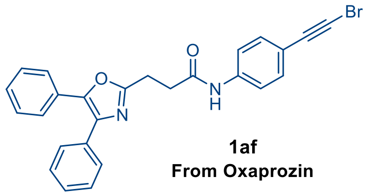

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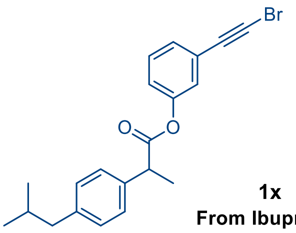
From Oxaprozin

All the above alkynyl bromides were prepared according to the literature procedure.[3]

Characterization of new starting material:



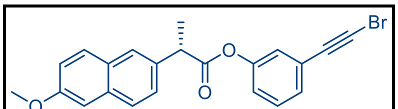
1x
From Ibuprofen

Following the procedure from previous literature, by taking 3-ethynylphenol and 2-(4-isobutylphenyl) propanoic acid, the product **1x** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc 24:1) afforded as a yellowish thick liquid (79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 4H), 7.15-7.07 (m, 3H), 6.99-6.96 (m, 1H), 3.94-3.88 (m, 1H), 2.46 (d, *J*=7.16 Hz, 2H), 1.91-1.81 (m, 1H), 1.58 (d, *J*=7.12 Hz, 3H), 0.90 (d, *J*= 6.6 Hz, 6H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.1, 150.7, 141.0, 137.1, 129.7, 129.5, 129.4, 127.3, 125.1, 123.9, 122.3, 79.2, 51.0, 45.3, 45.1, 30.3, 22.5, 18.5.

HRMS (ESI-TOF): m/z calculated for $C_{21}H_{22}BrO_2^+$(M+H)$^+$:385.0798, found: 385.0803.



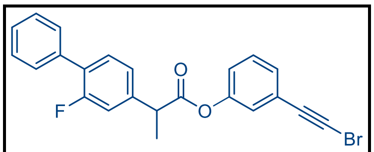
1y
From **Naproxen**

Following the procedure from previous literature, by taking 3-ethynylphenol and (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid, the product **1y** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 19:1) afforded as a white solid (74%). **M.P**: 100-104°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.75 (m, 3H), 7.52-7.50 (m, 1H), 7.28-7.26 (m, 2H), 7.21-7.11 (m, 3H), 7.02-6.99 (m, 1H), 4.14-4.08 (m, 1H), 3.93 (s, 3H), 1.71 (d, *J*=5.68 Hz, 3H).

^{13}C {1H} NMR (100 MHz, CDCl3) δ 173.0, 157.9, 150.7, 135.0, 134.0, 129.6, 129.5, 129.4, 129.1, 127.6, 126.3, 126.2, 125.1, 124.0, 122.3, 119.3, 105.8, 79.2, 55.4, 51.1, 45.7, 18.6.

HRMS (ESI-TOF): m/z calculated for $C_{22}H_{18}BrO_3^+(M+H)^+$:409.0434, found: 409.0432.



1z
From Flurbiprofen

Following the procedure from previous literature, by taking 3-ethynylphenol and 2-(2-fluoro-[1,1'-biphenyl]-4-yl) propanoic acid, the product **1z** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 19:1) afforded as a white amorphous solid (70%). **M.P.**: 94-98°C

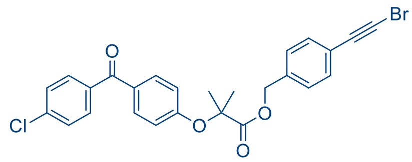
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.56 (m, 2H), 7.47-7.44 (m, 3H), 7.40-7.36 (m, 1H), 7.31-7.29 (m, 2H), 7.25-7.20 (m, 3H), 7.13(s, 1H), 7.05-7.03 (m, 1H), 3.99 (d, *J*=7.08 Hz, 1H), 1.66 (d, *J*=7.16 Hz, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 172.33, 159.7 (d, $^1J_{C-F}$ =247.07 Hz), 150.57, 141.2 (d, $^3J_{C-F}$ =7.75 Hz), 135.5, 131.2 (d, $^3J_{C-F}$ =4.06 Hz), 129.7, 129.5, 129.1 (d, $^4J_{C-F}$ =2.87 Hz), 128.6, 128.4, 127.9, 125.1, 124.1, 123.7 (d, $^3J_{C-F}$ =3.4 Hz), 122.2, 115.4 (d, $^2J_{C-F}$ =23.5 Hz), 79.1, 51.24, 45.24, 18.49.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.16.

IR (neat, cm^{-1}): 2925, 2864, 1760, 1589, 1479, 1423, 1261, 1154, 1076, 779, 695

HRMS (ESI-TOF): m/z calculated for $C_{23}H_{17}BrFO_2^+(M+H)^+$: 423.0390, found: 423.0394.



1ac
From Finofibric acid

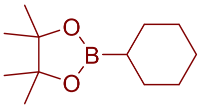
Following the procedure from previous literature, by taking (4-ethynylphenyl) methanol and 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid, the product **1ac** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 19:1) afforded as a yellowish white semi solid (78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H), 7.47-7.45 (m, 2H), 7.37-7.35 (m, 2H), 7.19-7.17 (m, 2H), 6.79-6.76 (m, 2H), 5.17 (s, 2H), 1.67 (s, 6H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 194.2, 173.5, 159.5, 138.5, 136.4, 135.7, 132.2, 132.0, 131.2, 130.5, 128.6, 128.4, 122.9, 117.2, 79.5, 79.5, 66.8, 50.9, 25.5.

HRMS (ESI-TOF): m/z calculated for $C_{26}H_{21}BrClO_4^+$(M+H)$^+$: 513.0286, found: 513.0287.

List of alkyl Bpin and alkyl boronic acid:



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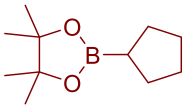

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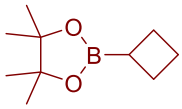

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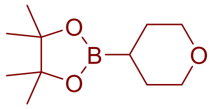

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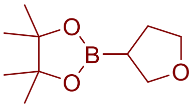

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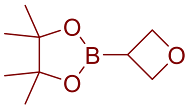

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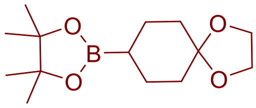

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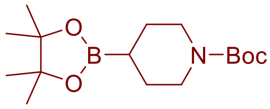

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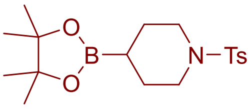

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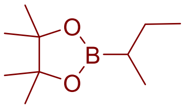

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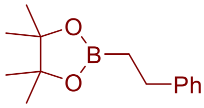

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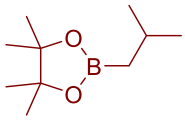

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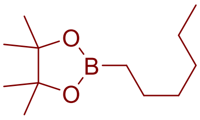

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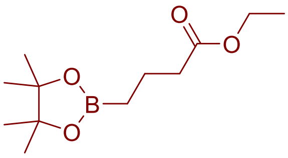

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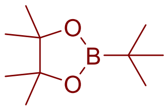

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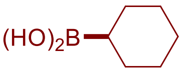

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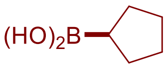

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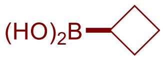

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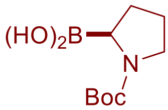

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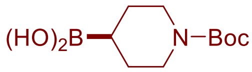

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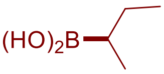
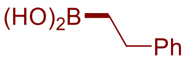


2u



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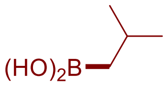
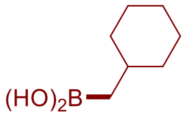
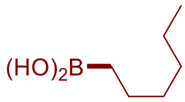


2w



2x



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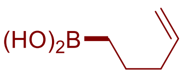
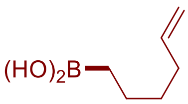
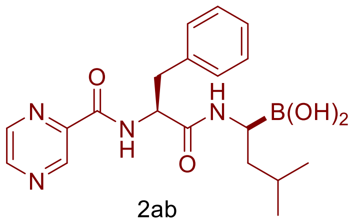


2z



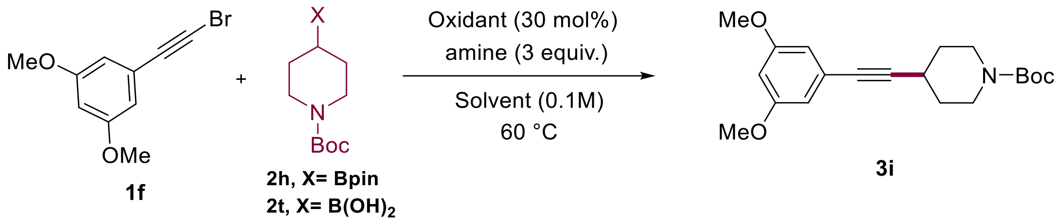
2aa



2ab

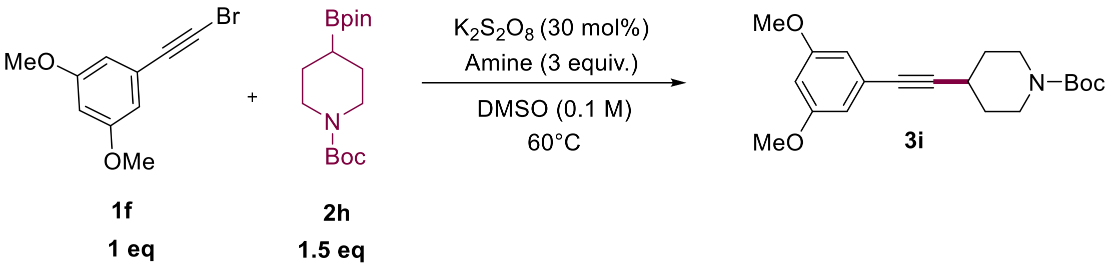
Optimization details

General procedure for the optimization



An oven-dried 10 mL glass vial was charged with **1f** (0.1 mmol), **2h** or **2t** (0.15 mmol), oxidant (30 mol%), Amine (3 mmol), and a PTFE coated magnetic bar. The glass vial was degassed with argon balloon for 2 min and sealed with a PTFE septum. Then solvent (0.1 M) was added to the reaction vial. The reaction vials were placed on the in the oil bath and stirred at 60 °C. After 6 h, a sample of this solution was analyzed by ^{1}H NMR using benzyl benzoate as the internal standard to determine the yield of the reaction.

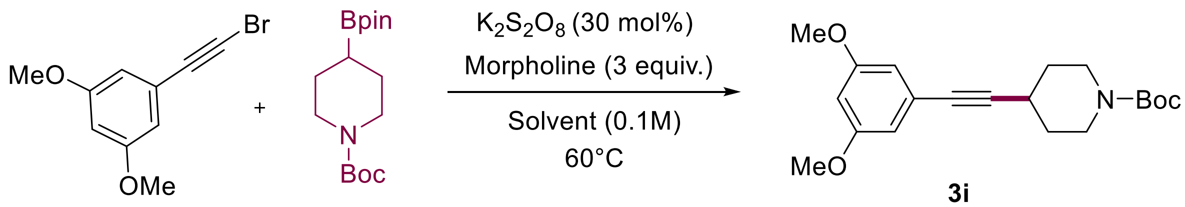
Table S1: Screening of activator:



Entry	Base	yield (%)
1	No Amine	00
2	Pyrollidine	39
3	Piperidine	73
4	Morpholine	94
5	DIPA	43
6	N-methyl morpholine	00
7	Tetramethyl Piperidine	00
8	1 eq of Morpholine	63
9	2 eq of Morpholine	78

Optimization of the reaction conditions. **1f** (0.1 mmol), **2h** (0.15 mmol) NMR yields using benzyl benzoate (0.1 mmol) as internal standard.

Table S2: Screening of solvents:



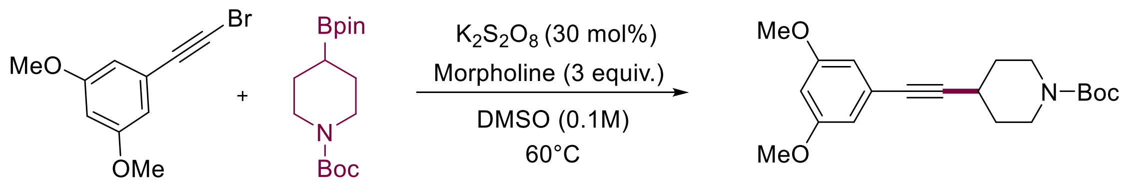
1f **2h** **3i**

1 eq **1.5 eq**

Entry	Solvent	Yield %
1	MeOH	36
2	CH_3CN	69
3	EtOAc	75
4	DMF	42
5	DMSO	94
6	Acetone	47
7	DCM	53

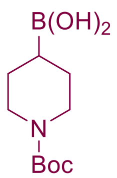
Optimization of the reaction conditions. **1f** (0.1 mmol), **2h** (0.15 mmol)
NMR yields using benzyl benzoate (0.1 mmol) as internal standard.

Table S3: Screening of other reaction condition



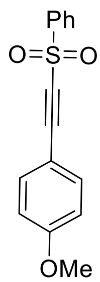
1f **2h** **3i**

1 eq **1.5 eq**



2t

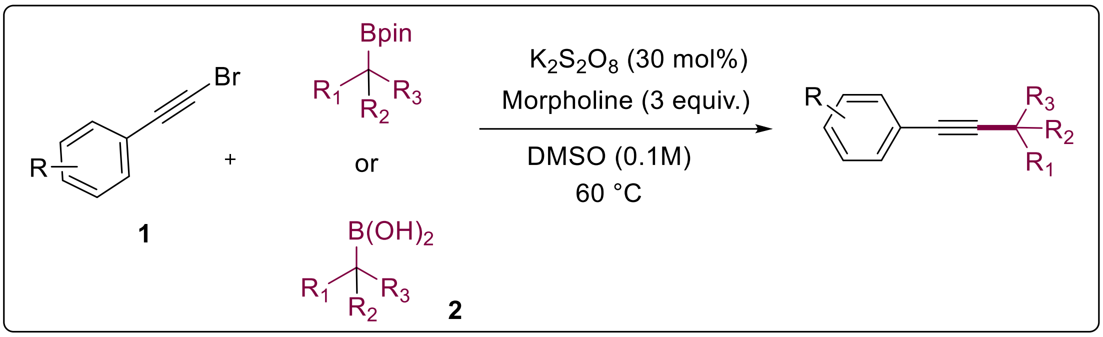
Entry	Deviation from standard condition	yield **(11)** (%)
1	10 mol% of $K_2S_2O_8$	68
2	20 mol% of $K_2S_2O_8$	81
3	$(NH)_4S_2O_8$	86
4	PIDA	63
5	**2t** instead of **2h**	82
6	**1aa'** instead of **1f**	trace
7	1 equive of **2h**	74
8	50°C	78
9	No Heating	67



1aa'

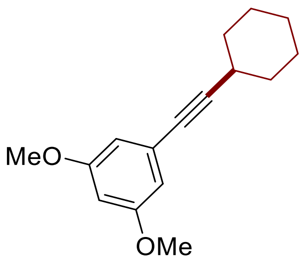
Optimization of the reaction conditions. **1f** (0.1 mmol), **2h** (0.15 mmol)
NMR yields using benzyl benzoate (0.1 mmol) as internal standard.

General procedure for Alkynylation of Alkyl boron compounds with Alkynylbromides:



General Procedure: An oven-dried 10 mL glass vial was charged with **1** (0.2 mmol, 1 equiv.), **2** (0.3 mmol, 1.5 equiv.), $K_2S_2O_8$ (30 mol%, 0.3 equiv.), Morpholine [(0.6 mmol, 3 equiv.) and a PTFE-coated magnetic bar. The glass vial was degassed with argon balloon for 2 min and sealed with a PTFE septum. Then DMSO (0.1 M) was added to the reaction vial. The reaction vials were placed in the oil bath and stirred at 60 °C. After 6 h, the product was confirmed by TLC. The reaction mixture was concentrated under reduced pressure. Product **3a-3aw** were purified by column chromatography on silica using hexane and EtOAc.

Characterization data:



3a

1-(cyclohexylethynyl)-3,5-dimethoxybenzene (3a): Following the general procedure, a reaction of **1f (**0.2 mmol, 42 mg) and Alkyl Bpin **2a** (0.3 mmol, 63 mg) or Alkyl-B(OH)$_2$ **2p** (0.3 mmol, 38 mg) and was set for 6 h. The product **3a** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane:EtOAc = 99:1), affording a colourless liquid.

For alkyl-Bpin: 46.3 mg, 95%

For alkyl-B(OH)$_2$: 43.9 mg, 90%

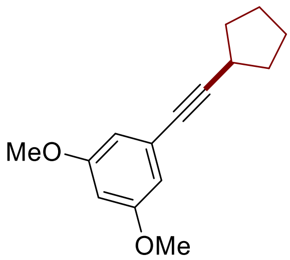
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J= 2.36 Hz, 2H), 6.40-6.39 (m, 1H), 3.77 (s, 6H), 2.61-2.54 (m, 1H), 1.89-1.86 (m, 2H), 1.79-1.72 (m, 2H), 1.57-1.49 (m, 3H), 1.37-1.32 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.5, 125.5, 109.5, 101.2, 94.2, 80.6, 55.5, 32.8, 29.7, 26.0, 25.0.

IR (neat, cm^{-1}): 2920, 2860, 1592, 1458, 1375, 1201, 1157

HRMS (ESI-TOF): m/z calculated for $C_{16}H_{21}O_2^+$ $(M+H)^+$: 245.1536, found: 245.1534.

Large-scale reaction: In an argon atmosphere of a glovebox, an oven-dried 25 ml round-bottom flask was charged with **1f** (4.2 mmol) **2a** (6.3 mmol), $K_2S_2O_8$ (1.25 mmol), morpholine (12.5 mmol) and a PTFE-coated magnetic bar. The round-bottom flask was sealed with a PTFE septum. Under the positive pressure of argon, degassed DMSO (12 mL) was added to the reaction vial. The reaction vials were placed in the oil bath and stirred at 60 °C. After 20 h, the product was confirmed by TLC. The reaction mixture was extracted with ethyl acetate (EtOAc), followed by washing with a brine solution. The organic layer was concentrated under reduced pressure, and the product was purified by column chromatography (0.8 g, 81%).



3b

1-(cyclopentylethynyl)-3,5-dimethoxybenzene (3b): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl Bpin **2b** (0.3 mmol, 59 mg) Alkyl-B(OH)$_2$ or **2q** (0.3 mmol,34 mg) and was set for 6 h. The product **3b** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane:EtOAc = 99:1), affording a colourless liquid.

For alkyl-Bpin: 42.3 mg, 92%

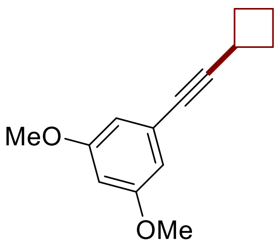
For alkyl-B(OH)$_2$: 40 mg, 87%

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, J= 2.36 Hz, 2H), 6.39-6.38 (m, 1H), 3.77 (s, 6H), 2.85-2.77 (m, 1H), 2.03-1.96 (m, 2H), 1.81-1.66 (m, 4H), 1.64-1.59 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.5, 125.6, 109.4, 101.2, 94.4, 80.1, 55.5, 34.0, 30.8, 25.2.

IR (neat, cm^{-1}): 2952, 2917, 2863, 1592, 1458, 1373, 1200,1157, 1069, 842

HRMS (ESI-TOF): m/z calculated for $C_{15}H_{19}O_2^+$ $(M+H)^+$: 231.180, found: 231.1377.



3c

1-(cyclobutylethynyl)-3,5-dimethoxybenzene (3c): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl Bpin **2c** (0.3 mmol, 54 mg) or Alkyl-B(OH)$_2$ **2r** (0.3 mmol,30 mg) and was set for 6 h. The product **3c** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane:EtOAc = 99:1), affording a colourless liquid.

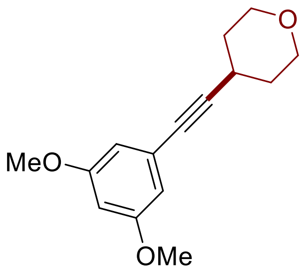
For alkyl-Bpin: 37 mg, 86%

For alkyl-B(OH)$_2$: 34.9 mg, 81%

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.56 (d, J= 2.36 Hz, 2H), 6.40-6.39 (m, 1H), 3.77 (s, 6H), 3.27-3.18 (m, 1H), 2.37-2.29 (m, 2H), 2.28-2.17 (m, 2H), 2.00-1.91 (m, 2H).

^{13}C {1H} NMR (100 MHz, CDCl$_3$) δ 160.6, 125.4, 109.42, 101.3, 93.7, 81.3, 55.5, 30.1, 25.7, 19.3.

IR (neat, cm^{-1}): 2917, 2860, 1459, 1376, 1196, 1085, 854



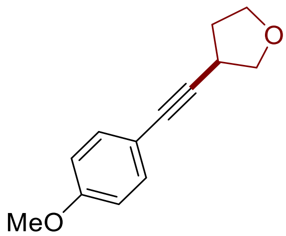
3d

4-((3,5-dimethoxyphenyl)ethynyl)tetrahydro-2H-pyran (3d): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl Bpin **2d** (0.3 mmol, 63 mg) and was set for 6 h. The product **3d** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1), affording it as a colourless liquid. (44.3 mg, 90%)

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.56-6.56 (m, 2H), 6.42-6.41 (m, 1H), 3.97-3.92 (m, 2H), 3.78-3.77 (m, 6H), 3.57-3.52 (m, 2H), 2.86-2.80 (m, 1H), 1.94-1.87 (m, 2H), 1.80-1.71 (m, 2H).

^{13}C {1H} NMR (100 MHz, CDCl$_3$) δ 160.6, 125.0, 109.5, 101.4, 91.9, 81.6, 66.5, 55.5, 32.4, 26.9.

The analytical data are consistent with published ones.[2]



3e

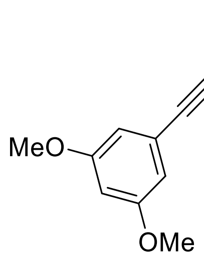
(R)-3-(phenylethynyl)tetrahydrofuran (**3e**): Following the general procedure, a reaction of **1a** (0.2 mmol, 42 mg) and Alkyl Bpin **2e** (0.3 mmol, 59 mg) and was set for 6 h. The product **3e**

was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) affording a colourless liquid (35 mg, 87%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 6.83-6.79 (m, 2H), 4.09-4.05 (m, 1H), 3.98-3.93 (m, 1H), 3.90-3.84 (m, 1H), 3.80 (s, 3H), 3.72-3.69 (m, 1H), 3.22-3.14 (m, 1H), 2.31-2.23 (m, 1H), 2.10-2.01 (m, 1H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 159.4, 133.0, 115.6, 113.9, 88.5, 81.5, 73.5, 68.1, 55.4, 33.8, 31.0.

The analytical data are consistent with published ones.[1]



3f

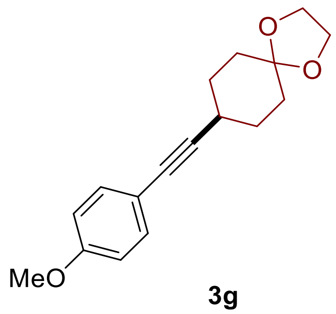
3-((3,5-dimethoxyphenyl)ethynyl)oxetane (**3f**): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl Bpin **2f** (0.3 mmol, 55 mg) and was set for 6 h. The product **3f** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless liquid (86%, 37.4 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, J= 2.36 Hz, 2H), 6.44-6.43 (m, 1H), 4.89-4.79 (m, 4H), 4.10-4.02 (m, 1H), 3.78 (s, 1H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.6, 124.4, 109.5, 101.7, 87.9, 84.2, 77.2, 55.5, 26.6.

IR (neat, cm^{-1}): 2916, 1593, 1459, 1374, 1202, 1157, 1063, 981, 843

HRMS (ESI-TOF): m/z calculated for $C_{13}H_{15}O_3^+$ (M+H)$^+$: 219.1016, found: 219.1018.



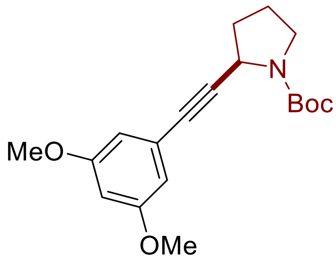
3g

8-((4-methoxyphenyl)ethynyl)-1,4-dioxaspiro[4.5]decane (**3g**): Following the general procedure, a reaction of **1a (**0.2 mmol, 42 mg) and Alkyl Bpin **2g** (0.3 mmol, 80 mg) and was set for 6 h. The product **3g** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 15:1) afforded as a colourless liquid (83%, 45 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 6.81-6.78 (m, 2H), 3.95-3.94 (m, 4H), 3.78 (s, 3H), 2.69-2.64 (m, 1H), 1.96-1.77 (m, 6H), 1.63-1.56 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 159.1, 133.0, 116.1, 113.9, 108.4, 91.2, 80.8, 64.3, 55.3, 33.0, 29.9, 28.1.

The analytical data are consistent with published ones.[1]



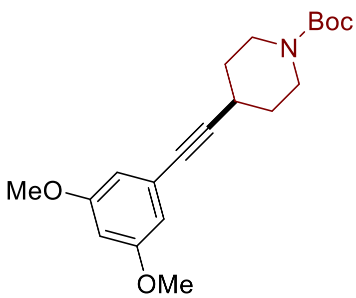
3h

tert-butyl (R)-2-((3,5-dimethoxyphenyl)ethynyl)pyrrolidine-1-carboxylate (3h): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl-B$(OH)_2$ **2s** (0.3 mmol, 64 mg) and was set for 6 h. The product **3h** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid. (56 mg, 85%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (brs, 2H), 6.40 (brs, 1H), 4.73-4.60 (m, 1H), 3.75 (s, 6H), 3.50-3.34 (m, 2H), 2.09-1.90 (m, 4H), 1.48 (s, 9H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.5, 154.2, 124.6, 109.5, 101.5, 89.5, 81.6, 79.7, 55.4, 48.7, 45.7, 33.8, 28.6, 23.9.

The analytical data are consistent with published ones.[3]



3i

tert-butyl 4-((3,5-dimethoxyphenyl)ethynyl)piperidine-1-carboxylate (3i): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl-Bpin **2h** (0.3 mmol,93) or Alkyl-B$(OH)_2$ **2t** (0.3 mmol,69 mg) and was set for 6 h. The product **3i** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid.

For alkyl-Bpin: 61.4 mg, 89%

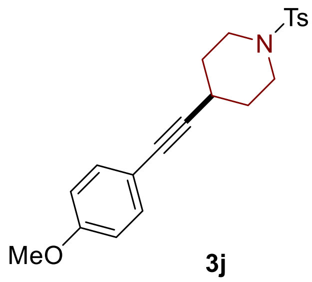
For alkyl-$B(OH)_2$: 57 mg, 83%

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, J= 2.36 Hz, 2H), 6.41-6.40 (m, 1H), 3.77-3.72 (m, 8H), 3.30-3.21 (m, 2H), 2.81-2.75 (m, 1H), 1.87-1.82 (m, 2H), 1.71-1.63 (m, 2H), 1.46 (s, 9H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.6, 154.9, 124.9, 109.5, 101.4, 91.5, 82.0, 79.6, 55.5, 42.7, 42.0, 31.5, 28.5, 27.7.

IR (neat, cm^{-1}): 2916, 2861, 1459, 1376, 1164, 1083, 852

HRMS (ESI-TOF): m/z calculated for $C_{20}H_{28}NO_4{}^+$ (M+H)$^+$: 346.2013, found: 346.2010.



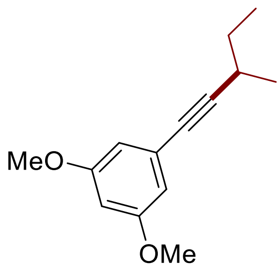
3j

4-((4-methoxyphenyl) ethynyl)-1-tosylpiperidine (3j): Following the general procedure, a reaction of **1a (**0.2 mmol, 42 mg) and Alkyl-Bpin **2i** (0.3 mmol, 109 mg) and was set for 6 h. The product **3j** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 9:1) afforded as crystalline solid. (62.7 mg, 85%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.65 (m, 2H), 7.34-7.32 (m, 2H), 7.19-7.17 (m, 2H), 6.79-6.76 (m, 2H), 3.79 (s, 3H), 3.35-3.29 (m, 2H), 2.92-2.86 (m, 2H), 2.66-2.60 (m, 1H), 2.44 (s, 3H), 1.98-1.91 (m, 2H), 1.84-1.75 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 159.4, 143.5, 133.2, 132.9, 129.7, 127.8, 115.4, 113.9, 89.3, 82.5, 55.4, 44.5, 31.0, 26.8, 21.6.

The analytical data are consistent with published ones.[1]



3k

(R)-1,3-dimethoxy-5-(3-methylpent-1-yn-1-yl)benzene (3k): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl-Bpin **2j** (0.3 mmol,55) Alkyl-$B(OH)_2$ **2u** (0.3 mmol,30 mg) and was set for 6 h. The product **3k** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid.

For alkyl-Bpin: 40 mg, 92%

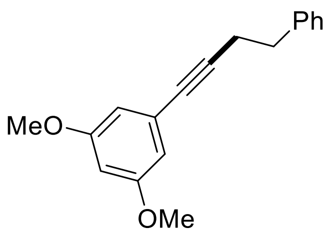
For alkyl-B(OH)$_2$: 39 mg, 90%

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.57, 6.56 (d, J= 2.36 Hz, 2H), 6.40-6.39 (m, 1H), 3.77 (s, 6H), 2.62-2.54 (m, 1H), 1.61-1.52 (m, 2H), 1.25 (d, J= 6.92 Hz, 2H), 1.05 (d, J= 7.36 Hz, 2H).

^{13}C {1H} NMR (100 MHz, CDCl$_3$) δ 160.5, 125.5, 109.5, 101.1, 94.4, 80.9, 55.4, 30.0, 28.2, 20.7, 11.9.

IR (neat, cm^{-1}): 2920, 1593, 1458, 1370, 1211, 1156, 1066, 843, 748

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{19}O_2^+$ (M+H)$^+$: 219.1380, found: 219.1382.



3l

1,3-dimethoxy-5-(4-phenylbut-1-yn-1-yl)benzene (3l): Following the general procedure, a reaction of **1f** (0.2 mmol, 48 mg) and Alkyl-Bpin **2k** (0.3 mmol,69 mg) or Alkyl-B(OH)$_2$ **2v** (0.3 mmol,45 mg) and was set for 6 h. The product **3l** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid.

For alkyl-Bpin: 45.2 mg,85%

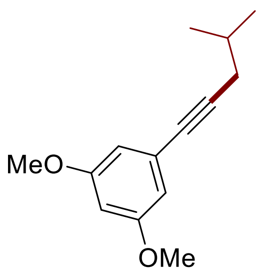
For alkyl-B(OH)$_2$: 44.1 mg, 83%

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34-7.22 (m, 5H), 6.55 (d, J= 2.36 Hz, 2H), 6.42-6.41 (m, 1H), 3.77 (s, 6H), 2.95-2.92 (m, 2H), 2.71-2.68 (m, 2H).

^{13}C {1H} NMR (100 MHz, CDCl$_3$) δ 160.6, 140.8, 128.7, 128.5, 126.4, 125.3, 109.5, 101.3, 89.3, 81.4, 55.4, 35.2, 21.7.

IR (neat, cm^{-1}): 2922, 2849, 1586, 1452, 1420, 1334, 1197, 1149, 1060, 829,688

HRMS (ESI-TOF): m/z calculated for $C_{18}H_{19}O_2^+$ (M+H)$^+$: 267.1380, found: 267.1381.



3m

1,3-dimethoxy-5-(4-methylpent-1-yn-1-yl)benzene (3m): Following the general procedure, a reaction of **1f (**0.2 mmol, 42 mg) and Alkyl-Bpin **2l** (0.3 mmol,55 mg) Alkyl-B(OH)$_2$ **2w** (0.3 mmol,30 mg) and was set for 6 h. The product **3m** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid.

For alkyl-Bpin: 37.9 mg, 87%

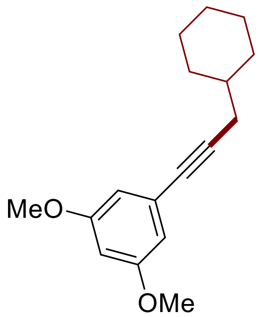
For alkyl-B(OH)$_2$: 36.1 mg, 83%

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.56 (d, J= 2.3 Hz, 2H), 6.41-6.39 (m, 1H), 3.77 (s, 6H), 2.29 (d, J= 6.56 Hz, 2H), 1.96-1.86 (m, 1H), 1.04 (d, J= 6.64 Hz, 6H).

^{13}C {1H} NMR (100 MHz, CDCl$_3$) δ 160.6, 125.6, 109.5, 101.1, 89.2, 81.6, 55.5, 28.7, 28.3, 22.2.

IR (neat, cm^{-1}): 2917, 1592, 1459, 1370, 1201, 1156, 1066, 840

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{19}O_2^+$ (M+H) $^+$: 219.1380, found: 219.1383.



3n

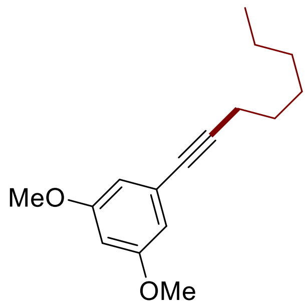
1-(3-cyclohexylprop-1-yn-1-yl)-3,5-dimethoxybenzene (3n): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl-B(OH)$_2$ **2x** (0.3 mmol,42 mg) and was set for 6 h. The product **3n** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid. (42.3 mg, 82%)

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.56 (d, J= 2.36 Hz, 2H), 6.40-6.39 (m, 1H), 3.77 (s, 6H), 2.29 (d, J= 6.68 Hz, 2H), 1.89-1.85 (m, 2H), 1.77-1.72 (m, 2H), 1.69-1.65 (m, 1H), 1.60-1.52 (m, 1H), 1.33-1.22 (m, 2H), 1.21-1.10 (m, 1H), 1.07-1.00 (m, 2H).

^{13}C {1H} NMR (100 MHz, CDCl$_3$) δ 160.6, 125.6, 109.5, 101.1, 89.2, 81.5, 55.5, 37.6, 32.9, 27.3, 26.4, 26.3.

IR (neat, cm^{-1}): 2922, 2850,1591, 1455, 1345, 1201, 1155, 1064, 839

HRMS (ESI-TOF): m/z calculated for $C_{17}H_{23}O_2^+$ (M+H)$^+$: 259.1693, found: 259.1693.



3o

1,3-dimethoxy-5-(oct-1-yn-1-yl)benzene (3o): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl-Bpin **2m** (0.3 mmol,63 mg) or Alkyl-B(OH)$_2$ **2y** (0.3 mmol,39 mg) and was set for 6 h. The product **3o** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid.

For alkyl-Bpin: 43.2 mg,88%

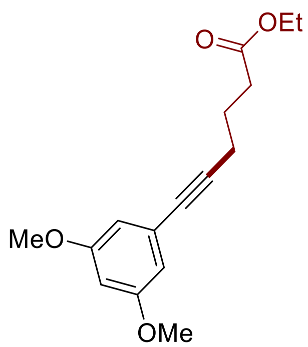
For alkyl-B(OH)$_2$: 41.8 mg, 85%

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J= 2.36 Hz, 2H),6.40-6.39 (m, 1H), 3.77 (s, 6H), 2.41-2.37 (m, 2H), 1.64-1.56 (m, 2H), 1.48-1.41 (m, 2H), 1.34-1.31 (m, 4H), 0.92-0.89 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.6, 125.5, 109.5, 101.1, 90.3, 80.6, 55.5, 31.5, 28.8, 28.7, 22.7, 19.5, 14.2.

IR (neat, cm^{-1}): 2922, 2859, 1592, 1459, 1366, 1202, 1156, 1066, 841

HRMS (ESI-TOF): m/z calculated for $C_{16}H_{23}O_2^+$ $(M+H)^+$: 247.1693, found: 247.1693.



3p

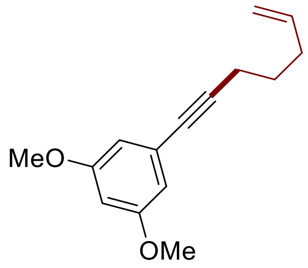
ethyl 6-(3,5-dimethoxyphenyl)hex-5-ynoate (3p): Following the general procedure, a reaction of **1f (**0.2 mmol, 48 mg) and Alkyl-Bpin **2n** (0.3 mmol,72 mg) and was set for 6 h. The product **3p** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid. (45.8 mg, 83%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (m, 2H), 6.40-6.39 (m, 1H), 4.13 (q, J=7.16 Hz, 2H), 3.76 (s, 6H), 2.50-2.45 (m, 4H), 1.96-1.88 (m, 2H), 1.27-1.23 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 160.5, 125.1, 109.4, 101.3, 88.7, 81.4, 60.5, 55.4, 33.3, 24.0, 18.9, 14.3.

IR (neat, cm^{-1}): 2938, 1731, 1591, 1456, 1321, 1200, 1154, 1061, 839

HRMS (ESI-TOF): m/z calculated for $C_{16}H_{21}O_4{}^+$ (M+H)$^+$: 277.1434, found: 277.1436.



3q

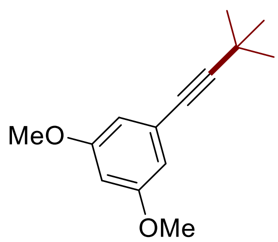
1-(hept-6-en-1-yn-1-yl)-3,5-dimethoxybenzene (3q): Following the general procedure, a reaction of **1f** (0.2 mmol, 48 mg) and Alkyl-B(OH)$_2$ **2z** (0.3 mmol,34 mg) and was set for 5 h. The product **3q** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid. (36.8 mg, 80%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J= 2.36 Hz, 2H), 6.41-6.40 (m, 1H), 5.88-5.78 (m, 1H), 5.10-4.99 (m, 2H), 3.77 (s, 6H), 2.43-2.40 (m, 2H), 2.25-2.19 (m, 2H), 1.74-1.67 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.6, 138.0, 125.4, 115.3, 109.5, 101.2, 89.8, 81.0, 55.5, 33.0, 28.0, 18.9.

IR (neat, cm^{-1}): 2930, 2850, 1591, 1457, 1341, 1201, 1155, 1064, 918, 838

HRMS (ESI-TOF): m/z calculated for $C_{15}H_{19}O_2{}^+$ (M+H)$^+$: 231.1380, found: 231.1382.



3r

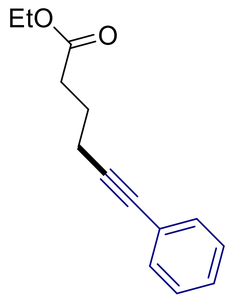
1-(3,3-dimethylbut-1-yn-1-yl)-3,5-dimethoxybenzene (3r): Following the general procedure, a reaction of **1f** (0.2 mmol, 48 mg) and Alkyl-Bpin **2o** (0.3 mmol,47 mg) and was set for 5 h. The product **3r** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 99:1) afforded as a colourless liquid. (39.6 mg, 91%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55(d, J= 2.36 Hz, 2H), 6.39-6.38 (m, 1H), 3.77 (s, 6H), 1.32 (s, 9H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.5, 125.5, 109.4, 101.2, 98.3, 79.1, 55.5, 31.1, 28.0.

IR (neat, cm^{-1}): 2922, 1734, 1592, 1458, 1372, 1243, 1156, 1048, 750

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{19}O_2^+$ (M+H)$^+$: 219.1380, found: 219.1382.



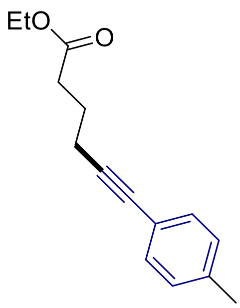
3s

ethyl 6-phenylhex-5-ynoate (**3s**): Following the general procedure, a reaction of **1b** (0.2 mmol, 36 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3s** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless thick liquid (30.6 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.28-7.25 (m, 3H), 4.13 (q, J=7.16 Hz, 2H), 2.51-2.46 (m, 4H), 1.96-1.88 (m, 2H), 1.27-1.23 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 131.6, 128.3, 127.7, 123.8, 89.0, 81.5, 60.5, 33.3, 24.0, 19.0, 14.3.

IR (neat, cm^{-1}): 2930, 1733, 1374, 1218, 1161, 1032, 757



3t

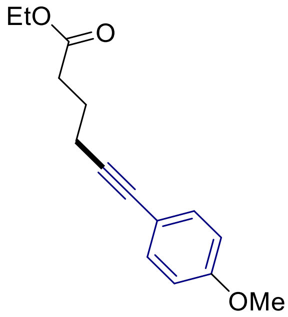
ethyl 6-(p-tolyl)hex-5-ynoate (**3t**): Following the general procedure, a reaction of **1c (**0.2 mmol, 38 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3t** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless liquid (35.4 mg, 77%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.27 (m, 2H), 7.09-7.08 (m, 2H), 4.14 (q, J=7.16 Hz, 2H), 2.51-2.46 (m, 4H), 2.33 (s, 3H), 1.96-1.89 (m, 2H), 1.28-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.4, 137.7, 131.5, 129.1, 120.8, 88.2, 81.5, 60.5, 33.3, 24.1, 21.5, 19.0, 14.3.

IR (neat, cm^{-1}): 2924, 2861, 1735, 1455, 1375, 1162, 1033, 817

HRMS (ESI-TOF): m/z calculated for $C_{15}H_{19}O_2$ + (M+H) + : 231.1830, found: 231.1382.



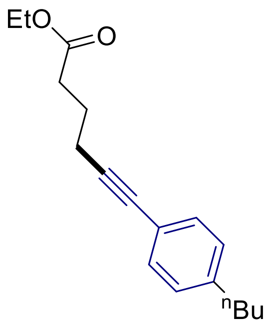
3u

ethyl 6-(4-methoxyphenyl)hex-5-ynoate (**3u**): Following the general procedure, a reaction of **1a (**0.2 mmol, 42 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3u** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless liquid (40.3 mg, 82%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2H), 6.83-6.79 (m, 2H), 4.14 (q, J=7.16 Hz, 2H), 3.79 (s, 3H), 2.51-2.45 (m, 4H), 1.95-1.88 (m, 2H), 1.28-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.4, 159.2, 133.0, 116.0, 113.9, 87.3, 81.2, 60.4, 55.3, 33.3, 24.1, 19.0, 14.3.

The analytical data are consistent with published ones.[4]



3v

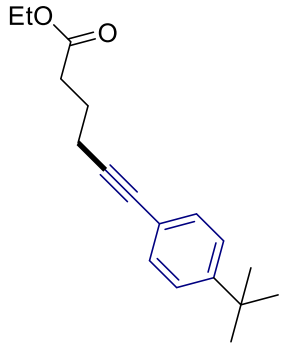
ethyl 6-(4-butylphenyl)hex-5-ynoate (**3v**): Following the general procedure, a reaction of **1d** (0.2 mmol, 47 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3v** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless liquid (43.5 mg, 80%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2H), 7.10-7.08 (m, 2H), 4.14 (q, J=7.16 Hz, 2H), 2.60-2.56 (m, 2H), 2.51-2.46 (m, 4H), 1.96-1.88 (m, 2H), 1.61-1.53 (m, 2H), 1.38-1.29 (m, 2H), 1.26 (t, J=7.16 Hz, 3H), 0.93-0.90 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.40, 142.81, 131.57, 128.45, 120.99, 88.20, 81.61, 60.49, 35.64, 33.55, 33.34, 24.15, 22.41, 19.04, 14.37, 14.05.

IR (neat, cm^{-1}): 2931, 2863, 1734, 1454, 1374, 1314, 1223, 1161, 1032, 832

HRMS (ESI-TOF): m/z calculated for $C_{18}H_{25}O_2^+$ $(M+H)^+$: 273.1849, found: 273.1851.



3w

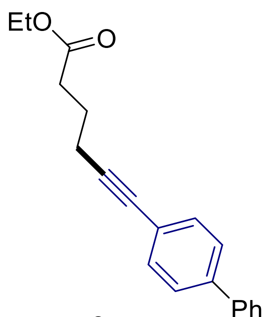
ethyl 6-(4-(tert-butyl)phenyl)hex-5-ynoate (**3w**): Following the general procedure, a reaction of **1e** (0.2 mmol, 47 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3w** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as white solid (40.8 mg, 75%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (m, 4H), 4.14 (q, J=7.16 Hz, 2H), 2.51-2.46 (q, J=7.32 Hz, 4H), 1.96-1.89 (m, 2H), 1.30 (s, 9H), 1.28-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.4, 150.9, 131.3, 125.3, 120.8, 88.2, 81.5, 60.4, 34.8, 33.3, 31.3, 24.1, 19.0, 14.3.

IR (neat, cm^{-1}): 2918, 1738, 1459, 1375, 11161, 838

HRMS (ESI-TOF): m/z calculated for $C_{18}H_{25}O_2^+$ $(M+H)^+$: 273.1849, found: 273.1850.



3x

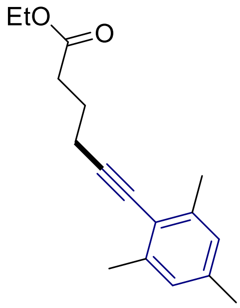
ethyl 6-([1,1'-biphenyl]-4-yl)hex-5-ynoate (3x): Following the general procedure, a reaction of **1g (**0.2 mmol, 51 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3x** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless liquid. (40.8 mg, 70%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H), 7.54-7.52 (m, 2H), 7.48-7.41 (m, 4H), 7.37-7.33 (m, 1H), 4.16 (q, J=6.32 Hz, 2H), 2.54-2.50 (m, 4H), 1.99-1.92 (m, 2H), 1.29-1.26 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 140.5, 140.5, 132.1, 128.9, 127.6, 127.1, 127.0, 122.8, 89.7, 81.4, 60.5, 33.3, 24.0, 19.1, 14.3.

IR (neat, cm^{-1}): 2922, 1720, 1478, 1373, 1313, 1155, 1026, 837, 759

HRMS (ESI-TOF): m/z calculated for $C_{20}H_{21}O_2^+$ $(M+H)^+$: 293.1536, found: 293.1537.



3y

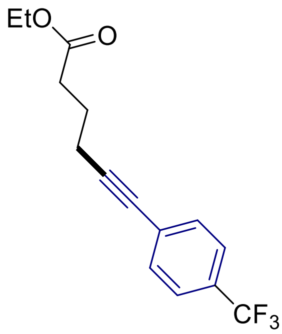
ethyl 6-mesitylhex-5-ynoate (3y): Following the general procedure, a reaction of **1h (**0.2 mmol, 44 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3y** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless liquid. (40.2 mg, 78%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 2H), 4.15 (q, J=7.16 Hz, 2H), 2.59-2.51 (m, 4H), 2.37 (s, 6H), 2.26 (s, 3H), 1.99-1.92 (m, 2H), 1.28-1.25 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.42, 140.04, 137.01, 127.56, 120.59, 96.56, 79.15, 60.47, 33.31, 24.48, 21.35, 21.15, 19.31, 14.36.

IR (neat, cm^{-1}): 2925, 2860, 1735, 1455, 1374, 1314, 1225, 1160, 1032, 853

HRMS (ESI-TOF): m/z calculated for $C_{17}H_{23}O_2^+$ $(M+H)^+$: 259.1693, found: 259.1694.



3z

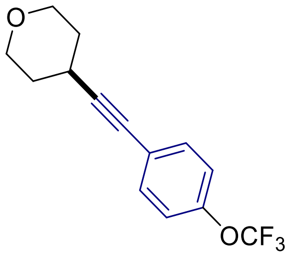
ethyl 6-(4-(trifluoromethyl)phenyl)hex-5-ynoate (3z): Following the general procedure, a reaction of **1i (**0.2 mmol, 49 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3z** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 24:1) afforded as a colourless liquid. (38 mg, 67%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.47 (m, 4H), 4.15 (q, J=7.16 Hz, 2H), 2.53-2.47 (m, 4H), 1.98-1.91 (m, 2H), 1.28-1.25 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.2, 131.9, 129.6 (q, $^2J_{C-F}$=32.5 Hz), 127.7, 125.3 (q, $^3J_{C-F}$=3.7 Hz), 123.5 (q, $^1J_{C-F}$=270.4 Hz), 91.9, 80.4, 60.6, 33.3, 23.8, 19.0, 14.3.

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.76.

HRMS (ESI-TOF): m/z calculated for $C_{15}H_{16}F_3O_2^+$ $(M+H)^+$: 285.1097, found: 285.1100.



3aa

4-((4-(trifluoromethoxy)phenyl)ethynyl)tetrahydro-2H-pyran (3aa): Following the general procedure, a reaction of **1j (**0.2 mmol, 49 mg) and Alkyl Bpin **2d** (0.3 mmol, 63 mg) and was set for 6 h. The product **3aa** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 24:1) afforded as white semi solid. (41.6 mg, 77%)

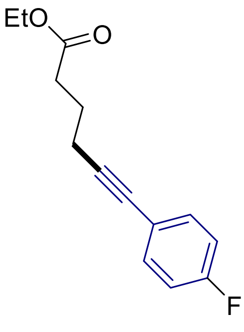
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.15-7.12 (m, 2H), 3.97-3.92 (m, 2H), 3.58-3.52 (m, 2H), 2.87-2.80 (m, 1H), 1.94-1.88 (m, 2H), 1.79-1.71 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 148.6, 133.2, 120.5 (q, $^1J_{C-F}$=270.25 Hz), 122.6, 120.9, 93.3, 80.3, 66.5, 32.3, 26.9.

^{19}F NMR (471 MHz, $CDCl_3$) δ -57.86.

IR (neat, cm^{-1}): 2919, 2857, 1458, 1376, 1257, 1213, 1171, 1084, 851

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{14}F_3O_2^+$ $(M+H)^+$: 271.0940, found: 271.0942.



3ab

ethyl 6-(4-fluorophenyl)hex-5-ynoate (3ab): Following the general procedure, a reaction of **1k (**0.2 mmol, 40 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3ab** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 24:1) crystalline solid. (30 mg, 64%)

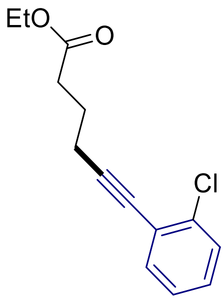
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 6.99-6.94 (m, 2H), 4.15 (q, J=7.16 Hz, 2H), 2.50-2.45 (m, 4H), 1.95-1.88 (m, 2H), 1.27-1.24 (3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 162.5 (d, $^1J_{C-F}$= 246.8 Hz), 133.5 (d, $^3J_{C-F}$= 8.3 Hz), 119.9 (d, $^4J_{C-F}$= 3.5 Hz), 115.5 (d, $^2J_{C-F}$= 21.8 Hz), 88.6, 80.4, 60.5, 33.3, 24.0, 18.9, 14.3.

^{19}F NMR (471 MHz, $CDCl_3$) δ -112.08.

IR (neat, cm^{-1}): 2919, 1737, 1506, 1459, 1375, 1227, 1160, 837

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{16}FO_2^+$ $(M+H)^+$: 235.1129, found: 235.1130.



3ac

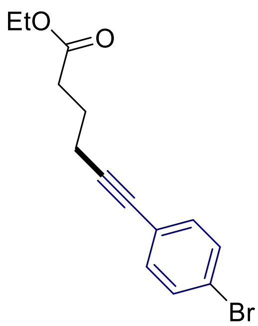
ethyl 6-(2-chlorophenyl)hex-5-ynoate (**3ac):** Following the general procedure, a reaction of **1l (**0.2 mmol, 43 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3ac** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) white solid. (30.5 mg, 61%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (m, 1H), 7.38-7.36 (m, 1H), 7.22-7.15 (m, 2H), 4.15 (q, J= 7.16 Hz, 2H), 2.57-2.52 (m, 4H), 1.99-1.92 (m, 2H), 1.28-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 135.9, 133.4, 129.2, 128.8, 126.4, 123.7, 94.7, 78.5, 60.5, 33.2, 23.9, 19.1, 14.3.

IR (neat, cm^{-1}): 2925, 2861, 1734, 1468, 1375, 1313, 1162, 1033, 755

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{16}ClO_2^+$ $(M+H)^+$: 251.0833, found: 251.0839.



3ad

ethyl 6-(4-bromophenyl)hex-5-ynoate (**3ad):** Following the general procedure, a reaction of **1m (**0.2 mmol, 51 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product

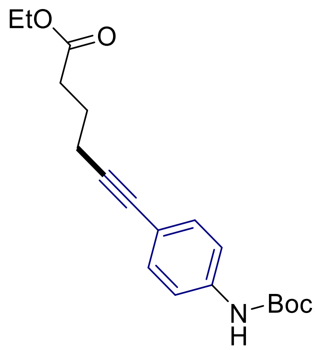
3ad was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as a colourless liquid. (44.7 mg, 76%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.25-7.23 (m, 2H), 4.15 (q, J=7.12 Hz, 2H), 2.49-2.45 (m, 4H), 1.95-1.88 (m, 2H), 1.27-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.2, 133.1, 131.5, 122.8, 121.9, 90.3, 80.5, 60.5, 33.3, 23.9, 19.0, 14.3.

IR (neat, cm^{-1}): 2930, 1733, 1482, 1376, 1315, 1221, 1161, 1070, 1023, 825

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{16}BrO_2^+$ $(M+H)^+$: 295.0328, found: 295.0329.



3ae

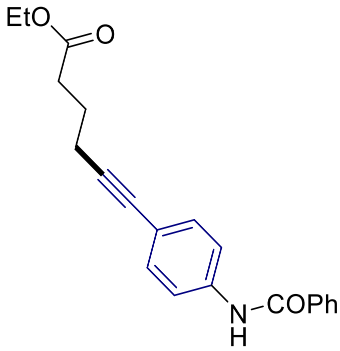
ethyl 6-(4-((tert-butoxycarbonyl)amino)phenyl)hex-5-ynoate (3ae): Following the general procedure, a reaction of **1n (**0.2 mmol, 59 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3ae** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 5:1) afforded as a colourless liquid. (49.6 mg, 75%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H), 6.54 (brs, 1H), 4.14 (q, J= 7.16 Hz, 2H), 2.50-2.44 (m, 4H), 1.95-1.87 (m, 2H), 1.50 (s, 9H), 1.27-1.23 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.4, 152.6, 138.0, 132.4, 118.2, 118.1, 88.0, 81.2, 80.8, 60.5, 33.3, 28.4, 24.1, 19.0, 14.3.

IR (neat, cm^{-1}): 2922, 1714, 1587, 1517, 1369, 1311, 1225, 1152, 1040, 832

HRMS (ESI-TOF): m/z calculated for $C_{19}H_{26}NO_4^+$ $(M+H)^+$: 332.1856, found: 332.1852.



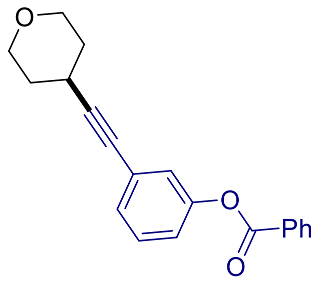
3af

ethyl 6-(4-benzamidophenyl)hex-5-ynoate (**3af):** Following the general procedure, a reaction of **1o (**0.2 mmol, 59 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3af** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 5:1) afforded as a colourless liquid. (48.2 mg, 72%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (brs, 1H), 7.86-7.83 (m, 2H), 7.60-7.58 (m, 2H), 7.55-7.52 (m, 1H), 7.48-7.44 (m, 2H), 7.39-7.37 (m, 2H), 4.14 (q, J= 7.16 Hz, 2H), 2.51-2.46 (m, 4H), 1.96-1.89 (m, 2H), 1.28-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.4, 165.8, 137.6, 134.9, 132.5, 132.0, 128.9, 127.1, 119.9, 119.8, 88.7, 81.1, 60.5, 33.3, 24.0, 19.0, 14.3.

IR (neat, cm^{-1}): 2917, 2861, 1730, 1662, 1516, 1459, 1376, 1316, 1242, 1192, 1087, 843

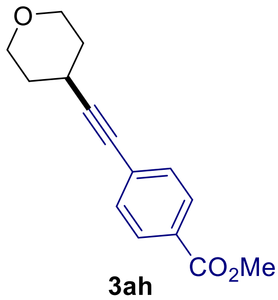


3ag

3-((tetrahydro-2H-pyran-4-yl)ethynyl)phenyl benzoate (**3ag):** Following the general procedure, a reaction of **1p (**0.2 mmol, 60 mg) and Alkyl Bpin **2d** (0.3 mmol, 63 mg) and was set for 6 h. The product **3ag** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid. (45.2 mg, 74%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.18 (m, 2H), 7.67-7.62 (m, 1H), 7.54-7.50 (m, 2H), 7.37-7.28 (m, 3H), 7.17-7.14 (m, 1H), 3.97-3.92 (m, 2H), 3.58-3.52 (m, 2H), 2.88-2.81 (m, 1H), 1.94-1.87 (m, 2H), 1.79-1.71 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 165.1, 150.8, 133.8, 130.3, 129.5, 129.4, 129.2, 128.7, 125.2, 125.0, 121.5, 93.3, 80.8, 66.5, 32.3, 26.9.



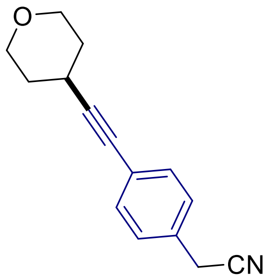
3ah

methyl 4-((tetrahydro-2H-pyran-4-yl)ethynyl)benzoate (3ah): Following the general procedure, a reaction of **1q (**0.2 mmol, 47 mg) and Alkyl Bpin **2d** (0.3 mmol, 63 mg) and was set for 6 h. The product **3ah** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid. (27.8 mg, 57%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.47-7.45 (m, 2H), 3.98-3.91 (m, 5H), 3.58-3.52 (m, 2H), 2.90-2.83 (m, 1H), 1.95-1.89 (m, 2H), 1.81-1.72 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 166.7, 131.6, 129.5, 129.2, 128.5, 95.6, 81.1, 66.5, 52.3, 32.2, 27.0.

The analytical data are consistent with published ones.[1]

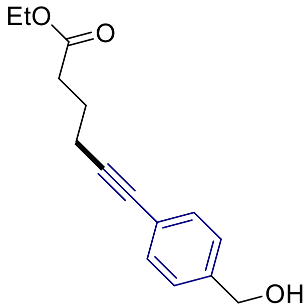


3ai

2-(4-((tetrahydro-2H-pyran-4-yl)ethynyl)phenyl)acetonitrile (3ai): Following the general procedure, a reaction of **1s (**0.2 mmol, 43 mg) and Alkyl Bpin **2d** (0.3 mmol, 63 mg) and was set for 6 h. The product **3ai** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a white semi solid. (27 mg, 60%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.40 (m, 2H), 7.26-7.24 (m, 2H), 3.97-3.92 (m, 2H), 3.73 (s, 2H), 3.58-3.52 (m, 2H), 2.87-2.81 (m, 1H), 1.94-1.88 (m, 2H), 1.79-1.71 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 132.3, 129.4, 127.9, 123.7, 117.6, 93.2, 80.8, 66.5, 32.2, 26.9, 23.6.



3aj

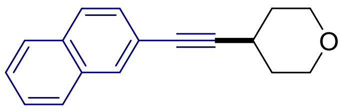
ethyl 6-(4-(hydroxymethyl)phenyl)hex-5-ynoate (**3aj**)**:** Following the general procedure, a reaction of **1r** (0.2 mmol, 42 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3aj** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 4:1) white semi solid. (36 mg, 73%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 2H), 7.27- 7.25 (m, 2H), 4.65 (s, 2H), 4.15-4.09 (m, 2H), 2.50-2.45 (m, 4H), 1.95-1.88 (m, 2H), 1.27-1.23 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 140.5, 131.8, 126.8, 123.1, 89.1, 81.3, 65.1, 60.5, 33.3, 24.0, 19.0, 14.3.

IR (neat, cm^{-1}): 2921, 2864, 1723, 1455, 1375, 1315, 1203, 1157, 1025, 818

HRMS (ESI-TOF): m/z calculated for $C_{15}H_{19}O_3^+$ $(M+H)^+$: 247.1329, found: 247.1329.



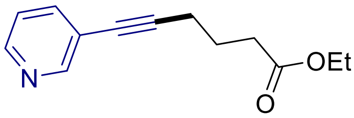
3ak

4-(naphthalen-2-ylethynyl)tetrahydro-2H-pyran (**3ak**)**:** Following the general procedure, a reaction of **1t** (0.2 mmol, 46 mg) and Alkyl Bpin **2d** (0.3 mmol, 63 mg) and was set for 6 h. The product **3ak** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 24:1) colourless liquid. (36.3 mg, 77%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.81-7.75 (m, 3H), 7.48-45 (m, 3H), 4.02-3.97 (m, 2H), 3.61-3.55 (m, 2H), 2.93-2.87 (m, 1H), 2.00-1.92 (m, 2H), 1.85-1.76 (m, 2H).

^{13}C {1H} NMR ((100 MHz, $CDCl_3$) δ 133.1, 132.7, 131.3, 128.7, 127.9, 127.8, 127.7, 126.5, 126.5, 121.0, 92.7, 82.0, 66.5, 32.4, 27.0.

The analytical data are consistent with published ones.[5]

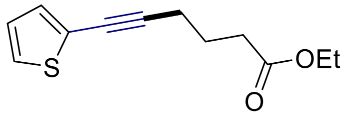


3al

ethyl 6-(pyridin-3-yl)hex-5-ynoate (3al): Following the general procedure, a reaction of **1u (**0.2 mmol, 36 mg) and **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3al** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 4:1) afforded as brownish liquid (27.3 mg, 63%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.49-8.48 (m, 1H), 7.69-7.65 (m, 1H), 7.23-7.20 (m, 1H), 4.15 (q, J=7.16 Hz, 2H), 2.53-2.47 (m, 4H), 1.98-1.91 (m, 2H), 1.28-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.1, 152.3, 148.1, 138.7 (2C), 123.1, 92.8, 78.2, 60.5, 33.2, 23.8, 19.0, 14.3.



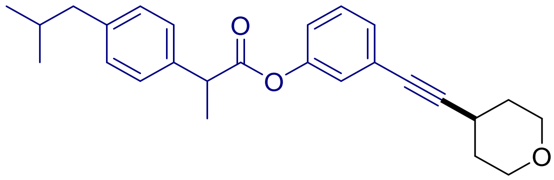
3am

ethyl 6-(thiophen-2-yl)hex-5-ynoate (**3am**): Following the general procedure, a reaction of **1v** (0.2 mmol, 37 mg) and **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3am** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 32:1) afforded as brownish liquid (32 mg, 72%,)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.16 (m, 1H), 7.12-7.11 (m, 1H), 6.94-6.92 (m, 1H), 4.14 (q, J=7.16 Hz, 2H), 2.52-2.46 (m, 4H), 1.96-1.89 (m, 2H), 1.28-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.2, 131.2, 126.9, 126.2, 123.9, 93.1, 74.6, 60.5, 33.3, 23.8, 19.2, 14.3.

IR (neat, cm^{-1}): 2924, 1729, 1434, 1373, 1310, 1158, 1030, 839, 699



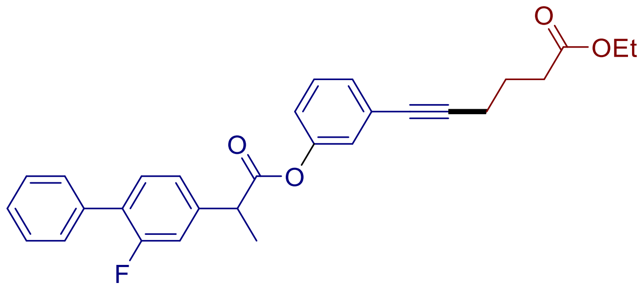
3an

3-((tetrahydro-2H-pyran-4-yl)ethynyl)phenyl 2-(4-isobutylphenyl)propanoate (3an): Following the general procedure, a reaction of **1x (**0.2 mmol, 77 mg) and Alkyl-Bpin **2d** (0.3 mmol, 63 mg) and was set for 6 h. The product **3an** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid (66.3 mg, 85%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 4H), 7.15-7.13 (m, 2H), 7.06-7.05 (m, 1H), 6.94-6.91 (m, 1H), 3.96-3.89 (m, 3H), 3.57-3.51 (m, 2H), 2.85-2.79 (m, 1H), 2.47 (d, J=7.16 Hz, 2H), 1.92-1.84 (m, 3H), 1.77-1.71 (m, 2H), 1.60 (d, J=6.36 Hz, 3H), 0.91 (d, J= 6.64 Hz, 6H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.1, 150.7, 141.0, 137.2, 129.6, 129.2, 129.1, 127.3, 125.0, 124.7, 121.2, 93.1, 80.7, 66.5, 45.3, 45.1, 32.3, 30.3, 26.9, 22.5, 18.6.

HRMS (ESI-TOF): m/z calculated for $C_{26}H_{31}O_3^+$ $(M+H)^+$: 391.2268, found: 391.2273.



3ao

ethyl 6-(3-((2-(2-fluoro-[1,1'-biphenyl]-4-yl) propanoyl)oxy)phenyl)hex-5-ynoate (**3ao**): Following the general procedure, a reaction of **1z** (0.2 mmol, 84 mg) and Alkyl Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3ao** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as colourless liquid. (75 mg, 82%)

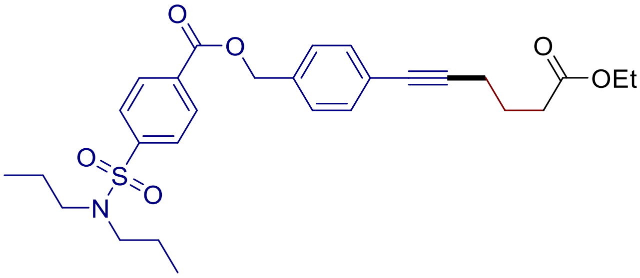
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.47-7.43 (m, 3H), 7.40-7.35 (m, 1H), 7.27-7.20 (m, 4H), 7.07 (brs, 1H), 6.98-6.95 (m, 1H), 4.14 (q, J= 7.16 Hz, 2H), 4.02-3.96 (m, 1H), 2.50-2.45 (m, 4H), 1.95-1.88 (m, 2H), 1.65 (d, J= 7.16 Hz, 3H), 1.27-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.2, 172.4, 160.0 (d, $^1J_{C-F}$= 246.9 Hz), 150.5, 141.3 (d, $^2J_{C-F}$= 7.71Hz), 135.5, 131.2(d, $^3J_{C-F}$= 2.91 Hz), 129.3, 129.1(d, $^3J_{C-F}$=2.84 Hz), 128.6 (2C), 128.3 (d, $^2J_{C-F}$= 13.5 Hz), 127.9, 125.3, 124.6, 123.7 (d, $^3J_{C-F}$= 3.36 Hz), 121.0, 115.5 (d, $^2J_{C-F}$= 23.57 Hz), 90.1, 80.5, 60.5, 45.2, 33.3, 24.0, 19.0, 18.5, 14.3.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.24.

IR (neat, cm^{-1}): 2919, 2863, 1736, 1460, 1375, 1322, 1210, 1152, 1077

HRMS (ESI-TOF): m/z calculated for $C_{29}H_{28}FO_4^+$(M+H)$^+$: 459.1966, found: 459.1964.



3ap

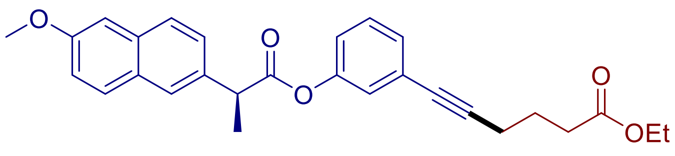
4-(6-ethoxy-6-oxohex-1-yn-1-yl) benzyl 4-(N, N-dipropylsulfamoyl) benzoate (3ap): Following the general procedure, a reaction of **1aa** (0.2 mmol, 95 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3ap** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid. (86 mg, 84%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 2H), 7.88-7.86 (m, 2H), 7.43-7.35 (m, 4H), 5.35 (s, 2H), 4.14 (d, J= 7.16 Hz, 2H), 3.11-3.07 (m, 4H), 2.51-2.47 (m, 4H), 1.97-1.90 (m, 2H), 1.56-1.49 (m, 4H), 1.28-1.24 (m, 3H), 0.88-0.84 (m, 6H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.32, 165.18, 144.57, 135.00, 133.44, 131.99, 130.47, 128.35, 127.17, 124.24, 89.90, 81.07, 67.08, 60.56, 50.05, 33.33, 24.03, 22.05, 19.04, 14.38, 11.28.

IR (neat, cm^{-1}): 2917, 2863, 1731, 1459, 1376, 1268, 1165, 1095, 750

HRMS (ESI-TOF): m/z calculated for $C_{28}H_{36}NO_6S$+ (M+H) + : 514.2258, found: 514.2261.



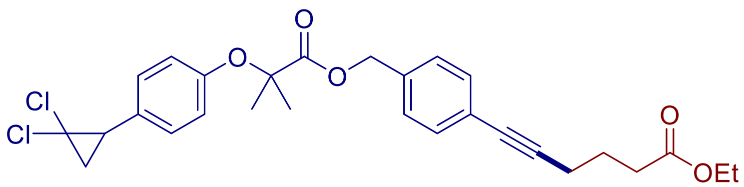
3aq

ethyl (S)-6-(3-((2-(6-methoxynaphthalen-2-yl)propanoyl)oxy)phenyl)hex-5-ynoate (3aq): Following the general procedure, a reaction of **1y (**0.2 mmol, 81 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3aq** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 19:1) afforded as colourless liquid. (70 mg, 79%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.73 (m, 3H), 7.50-7.48 (m, 1H), 7.25-7.21 (m, 2H), 7.18-7.14 (m, 2H), 7.03-7.02 (m, 1H), 6.92-6.89 (m, 1H), 4.16-4.06 (m, 3H), 3.93 (s, 3H), 2.48-2.43 (m, 4H), 1.93-1.86 (m, 2H), 1.69 (d, J= 7.12 Hz, 3H), 1.27-1.23 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 173.1, 157.9, 150.6, 135.1, 133.9, 129.4, 129.2, 129.1, 129.1, 127.5, 126.3, 126.2, 125.1, 124.6, 121.1, 119.2, 105.7, 90.0, 80.6, 60.5, 55.4, 45.6, 33.2, 23.9, 18.9, 18.6, 14.3.

HRMS (ESI-TOF): m/z calculated for $C_{28}H_{29}O_5^+$(M+H)$^+$: 445.2010, found: 445.2005.



3ar

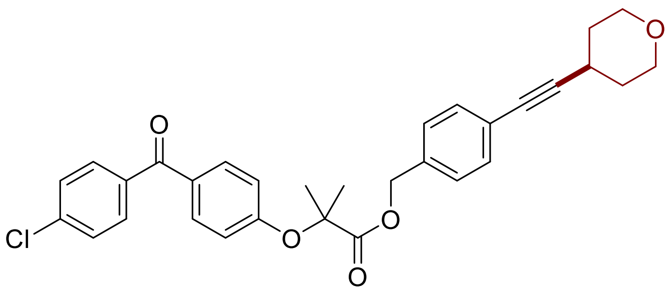
ethyl 6-(4-(((2-(4-(2, 2-dichlorocyclopropyl) phenoxy)- 2-methylpropanoyl) oxy) methyl) phenyl) hex-5-ynoate (**3ar**): Following the general procedure, a reaction of **1ac (**0.2 mmol, 96 mg) and **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3ar** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid. (78.4 mg,76%)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.32-7. 30 (m, 2H), 7.16-7.14 (m, 2H), 7.03-7.01 (m, 2H), 6.72-6.70 (m, 2H), 5.15 (s, 2H), 4.14 (q, J= 7.16 Hz, 2H), 2.84-2.79 (m, 1H), 2.51-2.47 (m, 4H), 1.97-1.89 (m, 3H), 1.79-1.75 (m, 1H), 1.60 (s,6H), 1.28-1.24 (m, 3H).

^{13}**C {1H} NMR** (100 MHz, $CDCl_3$) δ 174.1, 173.3, 154.9, 134.8, 131.8, 129.7, 128.5, 128.2, 124.0, 118.6, 89.8, 81.1, 79.2, 66.9, 61.0, 60.5, 34.9, 33.3, 25.9, 25.6, 25.5, 24.0, 19.0, 14.4.

HRMS (ESI-TOF): m/z calculated for $C_{28}H_{31}Cl_2O_5^+(M+H)^+$: 517.1543, found: 517.1542.

The analytical data are consistent with published ones.[1]



From Fenofibric acid

3as

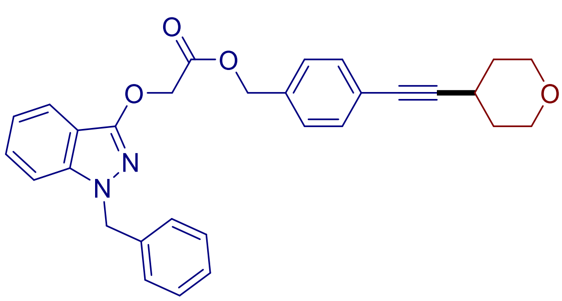
4-((tetrahydro-2H-pyran-4-yl) ethynyl) benzyl 2-(4-(4-chlorobenzoyl) phenoxy)-2-methylpropanoate (**3as**): Following the general procedure, a reaction of **1ac (**0.2 mmol, 102 mg) and Alkyl-Bpin **2d** (0.3 mmol, 63 mg)and was set for 6 h. The product **3as** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid (75.3 mg,73%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.47-7.45 (m, 2H), 7.34-7.32 (m, 2H), 7.18-7.15 (m, 2H), 6.79-6.77 (m, 2H), 5.17 (s, 2H), 3.96-3.90 (m, 2H), 3.56-3.50 (m, 2H), 2.85-2.79 (m, 1H), 1.91-1.86 (m, 2H), 1.77-1.67 (m, 2H).

^{13}**C {1H} NMR** (100 MHz, $CDCl_3$) δ 194.2, 173.5, 159.6, 138.5, 136.4, 134.7, 132.1, 131.8, 131.3, 130.5, 128.7, 128.4, 124.0, 117.3, 81.0, 79.5, 67.0, 66.5, 32.3, 26.9, 25.5.

IR (neat, cm^{-1}): 2918, 2858, 1738, 15596, 1459, 1377, 1255, 1135, 849, 750

HRMS (ESI-TOF): m/z calculated for $C_{31}H_{30}ClO_5$+ (M+H) + : 517.1776, found: 517.1782.



3at

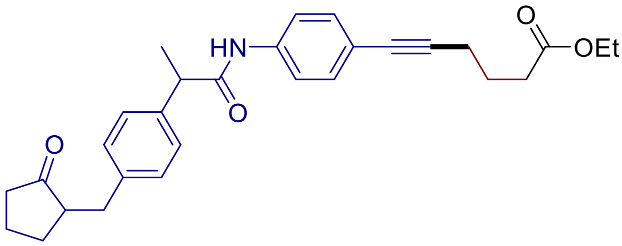
4-((tetrahydro-2H-pyran-4-yl)ethynyl)benzyl 2-((1-benzyl-1H-indazol-3-yl)oxy)acetate (**3at**): Following the general procedure, a reaction of **1ad (**0.2 mmol, 95 mg) and Alkyl Bpin **2d** (0.3

mmol, 63 mg) and was set for 6 h. The product **3at** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 12:1) afforded as a colourless liquid. (75.8 mg,79%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J= 8.08 Hz, 1H), 7.35-7.30 (m, 3H), 7.28-7.21 (m, 5H), 7.19-7.16 (m, 1H), 7.14-7.12 (m, 2H), 7.08-7.04 (m, 1H), 5.34 (s, 2H), 5.18 (s, 2H), 5.01 (s, 2H), 3.98-3.93 (m, 2H), 3.58-3.53 (m, 2H), 2.88-2.82 (m, 1H), 1.95-1.88 (m, 2H), 1.80-1.72 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.9, 154.8, 141.9, 137.4, 135.0, 131.8, 128.7, 128.1, 127.6, 127.6, 127.1, 123.7, 120.2, 119.6, 112.6, 109.0, 92.9, 81.3, 66.5, 66.4, 65.6, 52.45, 32.4, 26.9.

The analytical data are consistent with published ones.[3]



3au

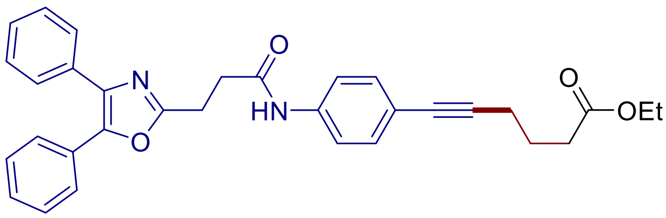
ethyl 6-(4-(2-(4-((2-oxocyclopentyl) methyl) phenyl) propanamido)phenyl)hex-5-ynoate (3au): Following the general procedure, a reaction of **1ae** (0.2 mmol, 84 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3au** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 4:1) afforded as a colourless liquid. (62.4 mg, 68%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (m, 2H), 7.29-7.22 (m, 5H), 7.17-7.15 (m, 2H), 4.12 (q, J=7.12 Hz, 2H), 3.69-3.64 (m, 1H), 3.15-3.10 (m, 1H), 2.53-2.43 (m, 5H), 2.37-2.30 (m, 2H), 2.15-2.08 (m, 2H), 2.05-1.86 (m, 3H), 1.79-1.67 (m, 2H), 1.56 (d, J=7.16 Hz, 3H), 1.24-1.23 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 220.2, 173.3, 172.4, 139.5, 138.7, 137.5, 132.2, 129.7, 127.8, 119.4, 119.3, 88.5, 81.1, 60.5, 51.0, 47.8, 38.2, 35.3, 33.3, 29.3,24.9, 24.0, 20.6, 19.0, 14.3.

IR (neat, cm^{-1}): 2917, 2859, 1734, 1458, 1376, 1168, 1085, 850

HRMS (ESI-TOF): m/z calculated for $C_{29}H_{34}NO_4$ + (M+H) + : 460.2325, found: 460.2481.



3av

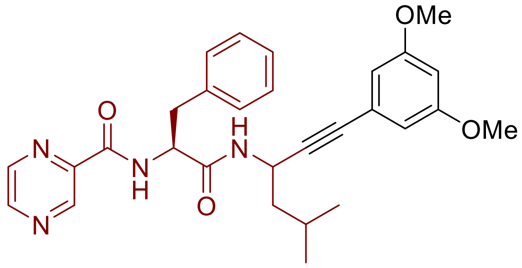
ethyl 6-(4-(3-(4,5-diphenyloxazol-2-yl)propanamido)phenyl)hex-5-ynoate (3av): Following the general procedure, a reaction of **1ag** (0.2 mmol, 94 mg) and Alkyl-Bpin **2n** (0.3 mmol, 72 mg) and was set for 6 h. The product **3av** was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 4:1) afforded as a colourless liquid. (74.8 mg, 74%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (brs, 1H), 7.64-7.61 (m, 2H), 7.57-7.54 (m, 2H), 7.44-7.42 (m, 2H), 7.38-7.29 (m, 8H), 4.14 (q, J=7.16 Hz, 2H), 3.28-3.25 (m, 2H), 2.95-2.92 (m, 2H), 2.47 (q, J=7.44 Hz, 2H), 1.95-1.87 (m, 2H), 1.27-1.24 (m, 3H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 173.3, 169.9, 162.5, 145.8, 137.7, 134.9, 132.3, 128.8, 128.4, 128.0, 126.6, 119.3, 88.4, 81.2, 60.5, 34.2, 33.3, 24.1, 24.0, 19.0, 14.3.

IR (neat, cm^{-1}): 2918, 1727, 1592, 1517, 1454, 1374, 1232, 1162, 764, 693

HRMS (ESI-TOF): m/z calculated for $C_{32}H_{31}N_2O_4^+$ $(M+H)^+$: 507.2278, found: 507.2296.



From Bortezomib

3aw

***N*-((2S)-1-((1-(3,5-dimethoxyphenyl)-5-methylhex-1-yn-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)pyrazine-2-carboxamide (3aw):** Following the general procedure, a reaction of **1f** (0.2 mmol, 48 mg) and **2ab** (0.3 mmol, 115 mg) and was set for 6 h. The product **3aw** (*dr* = 1:0.8) was purified by column chromatography of the reaction mixture on silica gel (hexane, followed by hexane: EtOAc = 3:1) afforded as a colourless liquid. (65 mg, 65%).

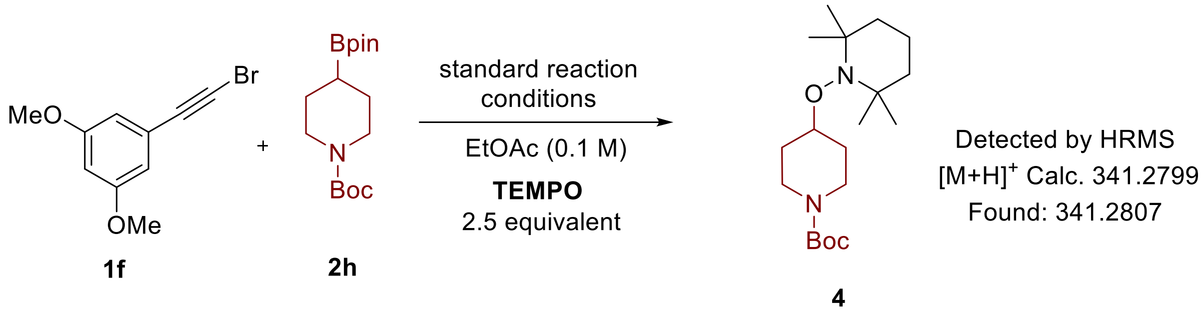
^{1}H NMR (diastereomer, *dr* = 1:0.8) (400 MHz, $CDCl_3$) δ 9.35-9.33 (m, 1H), 8.74-8.72 (m, 1.8H), 8.53-8.51 (m, 1.8 H), 8.47-8.43 (m, 1H), 7.30-7.28 (m, 5H), 7.26, 7.25-7.16 (m, 4H), 6.56-6.56 (m, 1.8H), 6.45-6.44 (m, 2.6H), 6.38-6.37 (m, 1H), 6.15 (s, 1.8H), 4.98, 4.96-4.81 (m, 3.6H), 3.79 (s, 6H), 3.72 (s, 4.8H), 3.28-3.13 (m, 3.6H), 1.75-1.70 (m, 0.8H), 1.66-1.59 (m, 1H), 1.54-1.49 (m, 1.8H), 1.42-1.40 (m, 1.8H), 0.92-0.88 (m, 10.8H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 169.2, 169.2, 163.0 (2C), 160.6, 160.5, 147.6 (2C), 144.4, 144.3, 144.0, 144.0, 142.9, 142.9, 136.4, 136.3, 129.6, 129.5, 128.8 (2C), 127.2, 127.2, 124.1, 123.9, 109.7 (2C), 109.5 (2C), 101.9, 101.8, 87.7, 87.6, 83.1, 83.1, 55.5, 55.4, 54.9, 54.8, 44.9, 44.8, 40.6 (2C), 39.0, 38.9, 29.8 (2C), 25.2, 25.1, 22.8, 22.7, 22.1, 22.0.

HRMS (ESI-TOF): m/z calculated for $C_{29}H_{33}N_4O_4^+$ $(M+H)^+$: 501.2496, found: 501.2499.

Mechanistic Studies:

Radical trapping experiments:



An oven-dried 10 mL glass vial was charged with **1f** (0.2 mmol, 1 equiv.), **2h** (0.3 mmol, 1.5 equiv.), Morpholine [(0.6 mmol, 3 equiv.), **TEMPO** (2.5 equiv.) and a PTFE-coated magnetic bar. The glass vial was degassed with argon balloon for 2 min and sealed with a PTFE septum. Then DMSO (0.1 M) was added to the reaction vial. The reaction vials were placed in the oil bath and stirred at 60°C. After 6 h, a sample of this solution was analyzed by HRMS and observed tert-butyl 4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidine-1-carboxylate) **4** : m/z calculated for $C_{19}H_{37}N_2O_3^+(M+H)^+$: 341.2799, found: 341.2807.

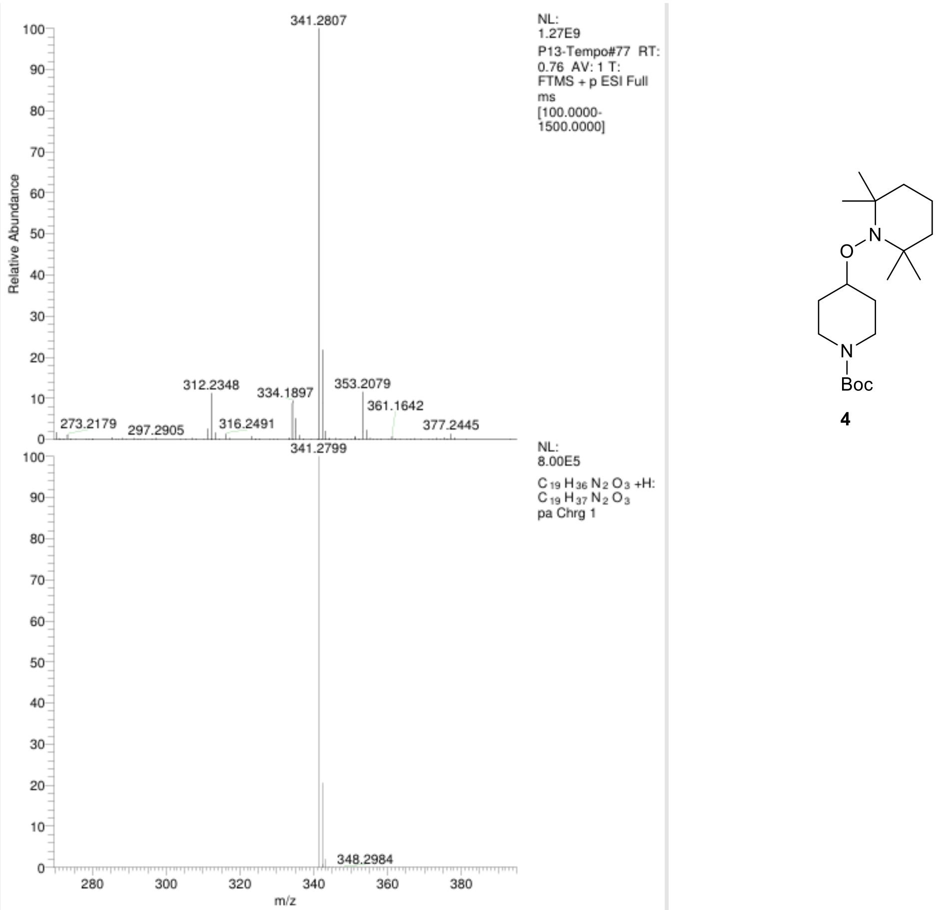
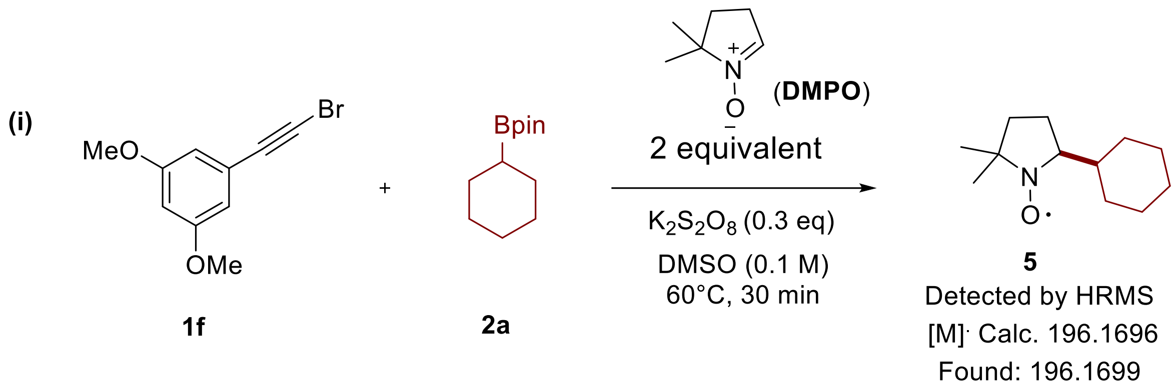


Figure S1: HRMS spectrum of reaction mixture showing **4** where the TEMPO used as a radical trapping agent.

EPR Experiment

An oven-dried 10 mL glass vial was charged with **1f** (0.2 mmol, 1 equiv.), **2a** (0.3 mmol, 1.5 equiv.), $K_2S_2O_8$ (30 mol%, 0.3 equiv.), Morpholine [(0.6 mmol, 3 equiv.), **DMPO** (2 equiv.) and a PTFE-coated magnetic bar. The glass vial was degassed with argon balloon for 2 min and sealed with a PTFE septum. Then DMSO (0.1 M) was added to the reaction vial. The reaction vials were placed in the oil bath and stirred at 60°C. and after 15 min the reaction mixture was analysed by EPR.



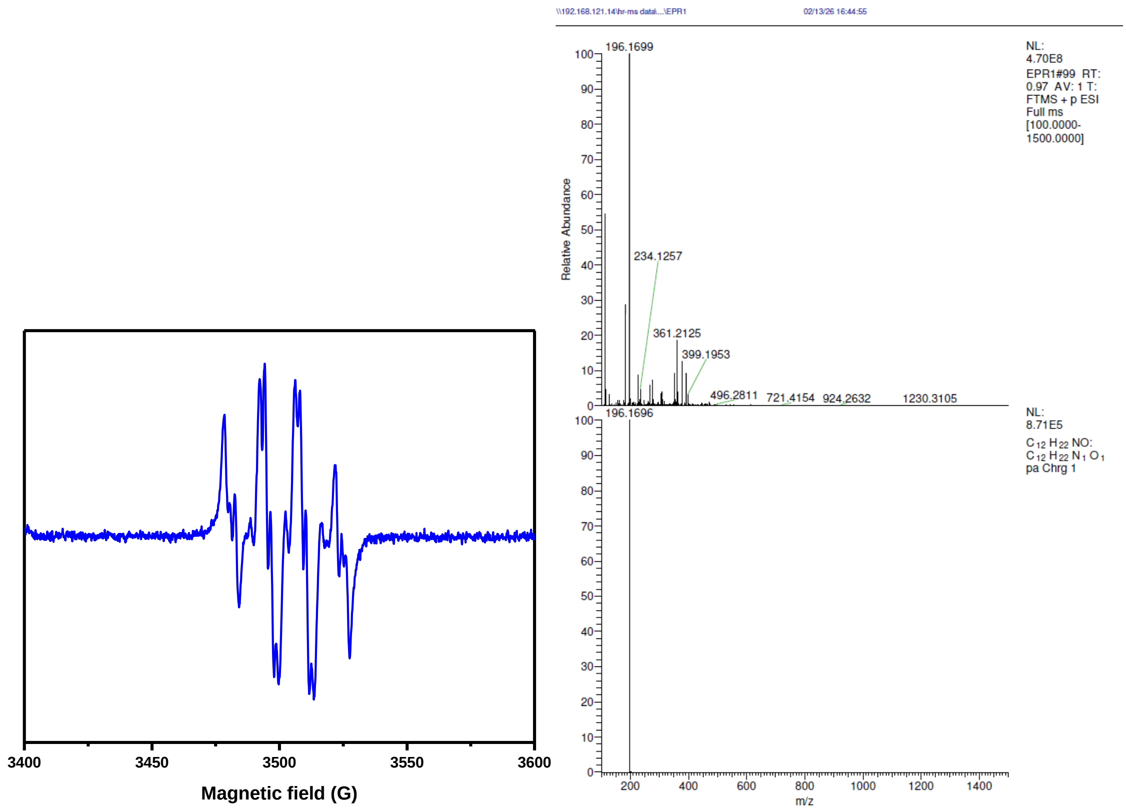
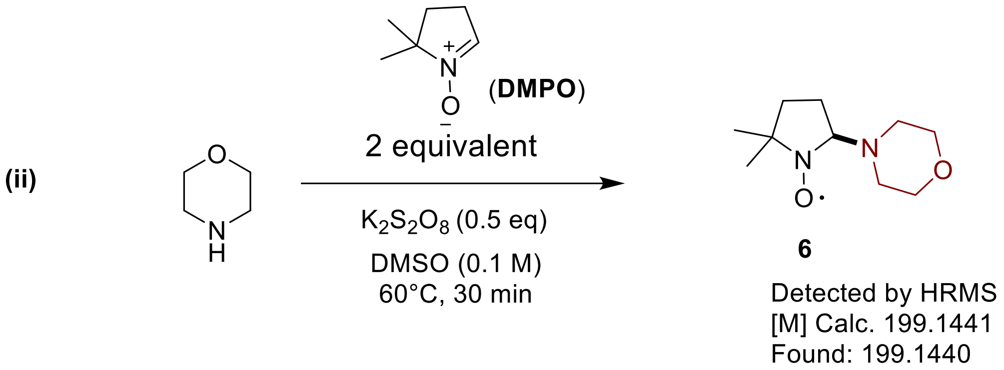
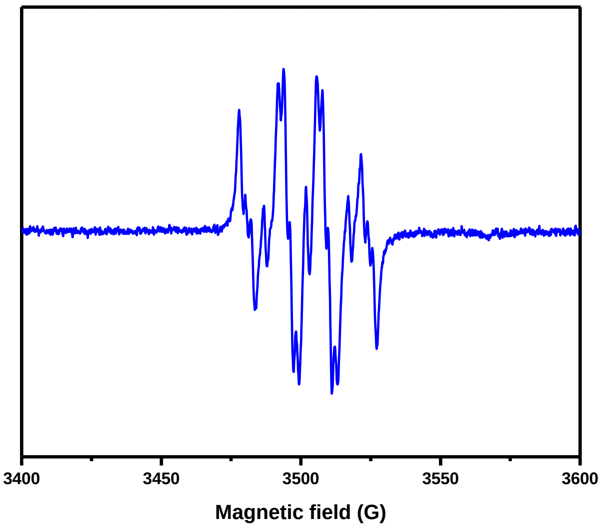


Figure S2: EPR spectrum (left) and HRMS spectrum (right) of **5**.

An oven-dried 10 mL glass vial was charged with Morpholine [(0.6 mmol, 3 equiv.), $K_2S_2O_8$ (50 mol%, 0.5 equiv.), **DMPO** (2 equiv.) and a PTFE-coated magnetic bar. The glass vial was degassed with argon balloon for 2 min and sealed with a PTFE septum. Then DMSO (0.1 M) was added to the reaction vial. The reaction vials were placed in the oil bath and stirred at 60°C. and after 15 min the reaction mixture was analysed by EPR.





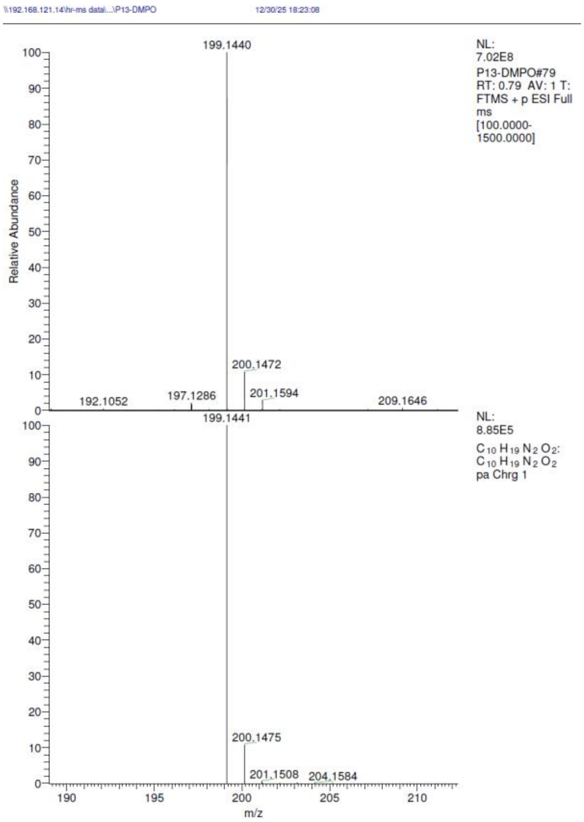
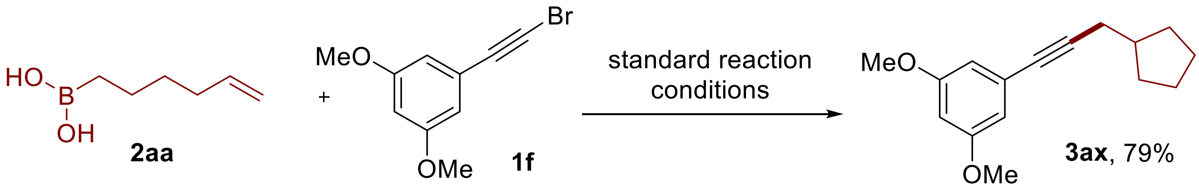


Figure S3: EPR spectrum (left) and HRMS spectrum (right) of 6.

Radical clock experiment:



An oven-dried 10 mL glass vial was charged with **1f** (47.8 mg, 0.2 mmol, 1 equiv.), alkyl-B(OH)$_2$ **2aa** (38 mg, 0.3 mmol, 1.5 equiv.), $K_2S_2O_8$ (30 mol%, 0.3 equiv.), Morpholine (52 mg, 0.6mmol, 3 equiv.) and a PTFE-coated magnetic bar. The glass vial was then degassed with argon balloon for 1-2 min and sealed with a PTFE septum. Then, DMSO (0.1 M) was added to the reaction vial. The reaction vials were placed in the oil bath and stirred at 60°C. After 6 h, the product was confirmed by TLC. The reaction mixture was concentrated under reduced pressure. Product **3ax** was purified by column chromatography on silica using hexane and afforded as colorless liquid (38 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J= 2.36 Hz, 2H), 6.40-6.39 (m, 1H), 3.77 (s, 6H), 2.40 (d, J= 6.8 Hz, 2H), 2.17-2.10 (m, 1H), 1.88-1.80 (m, 2H), 1.68-1.64 (m, 2H), 1.61-1.55 (m, 2H), 1.39-1.29 (m, 2H).

^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.6, 125.6, 109.5, 101.1, 89.8, 80.7, 55.5, 39.2, 32.2, 25.4, 25.3.

HRMS (ESI-TOF): m/z calculated for $C_{16}H_{21}O_2$ + (M+H) + : 245.1536, found: 245.1537.

[11]B NMR Experiment

For Cyclohexane Bpin

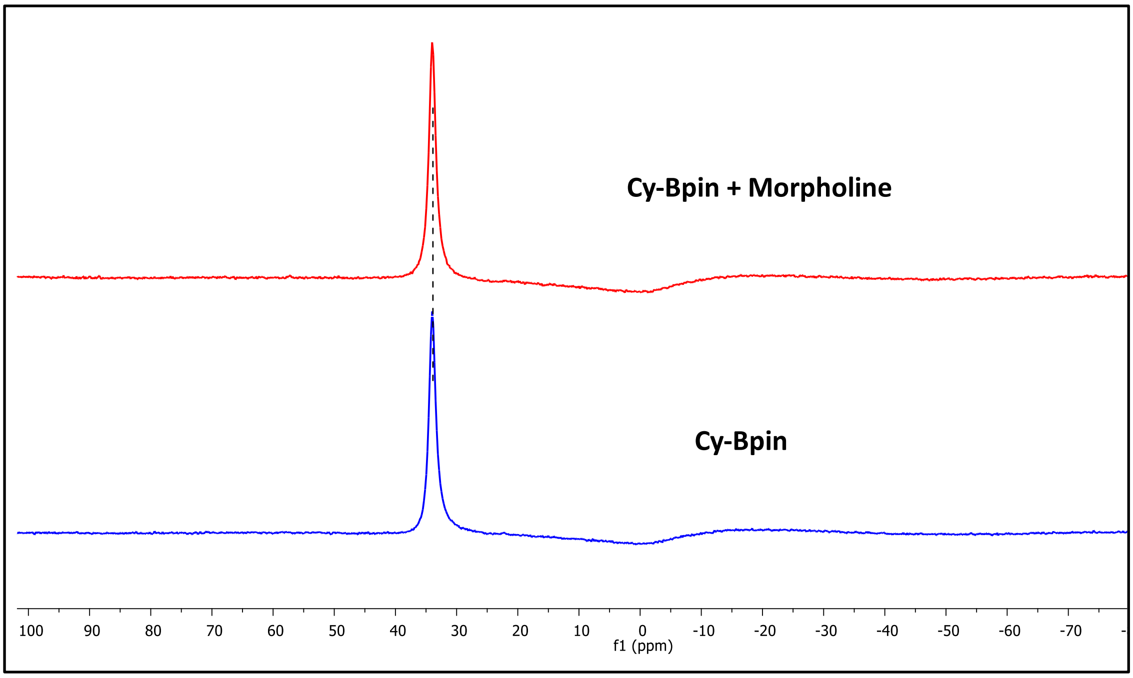
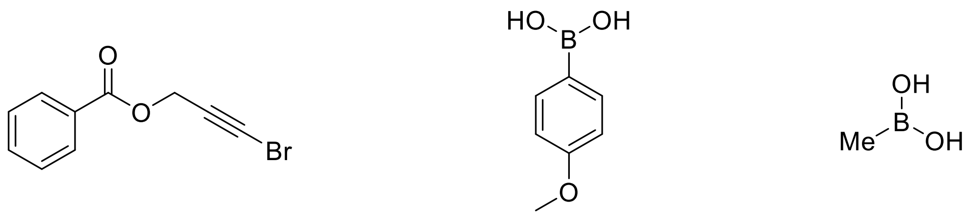
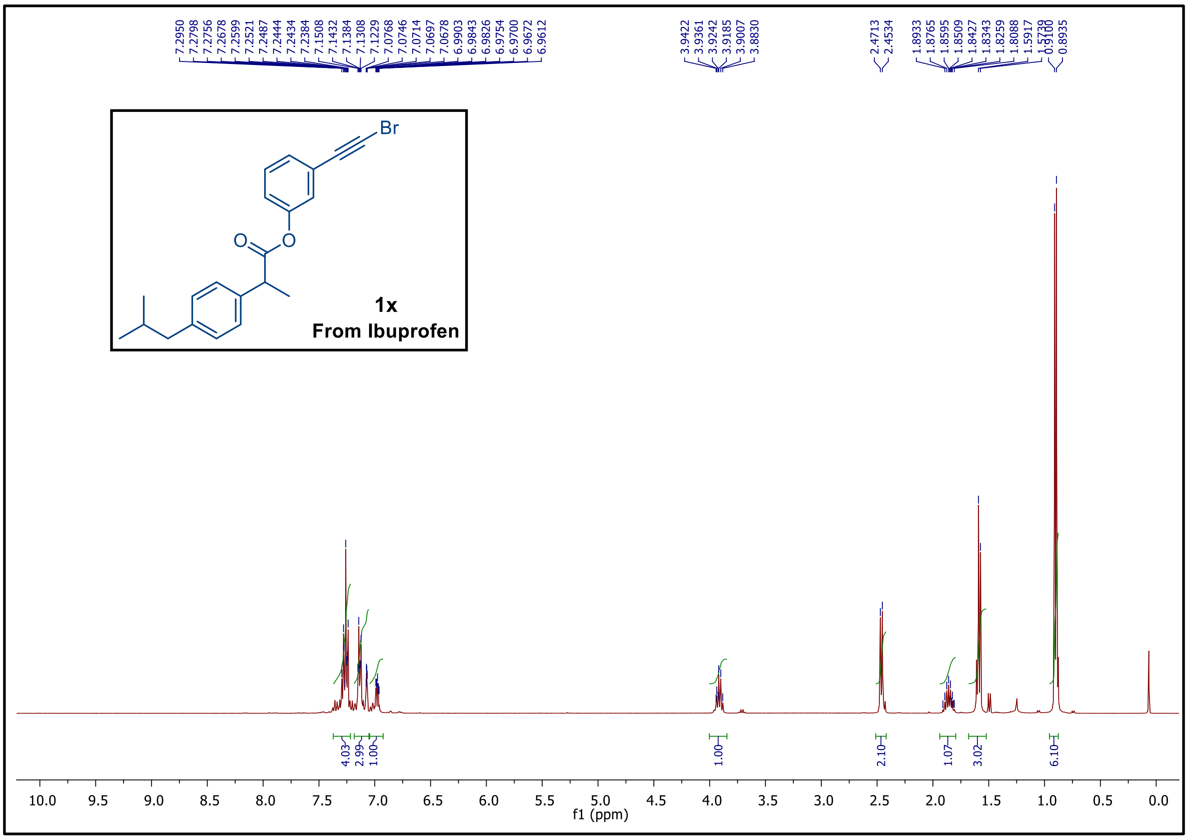


Figure S4. ^{11}B NMR (160 Mz, $CDCl_3$) for Cy-Bpin + Morpholine (top), Cy-Bpin (bottom)

Unsuccessful substrates



NMR Spectra:



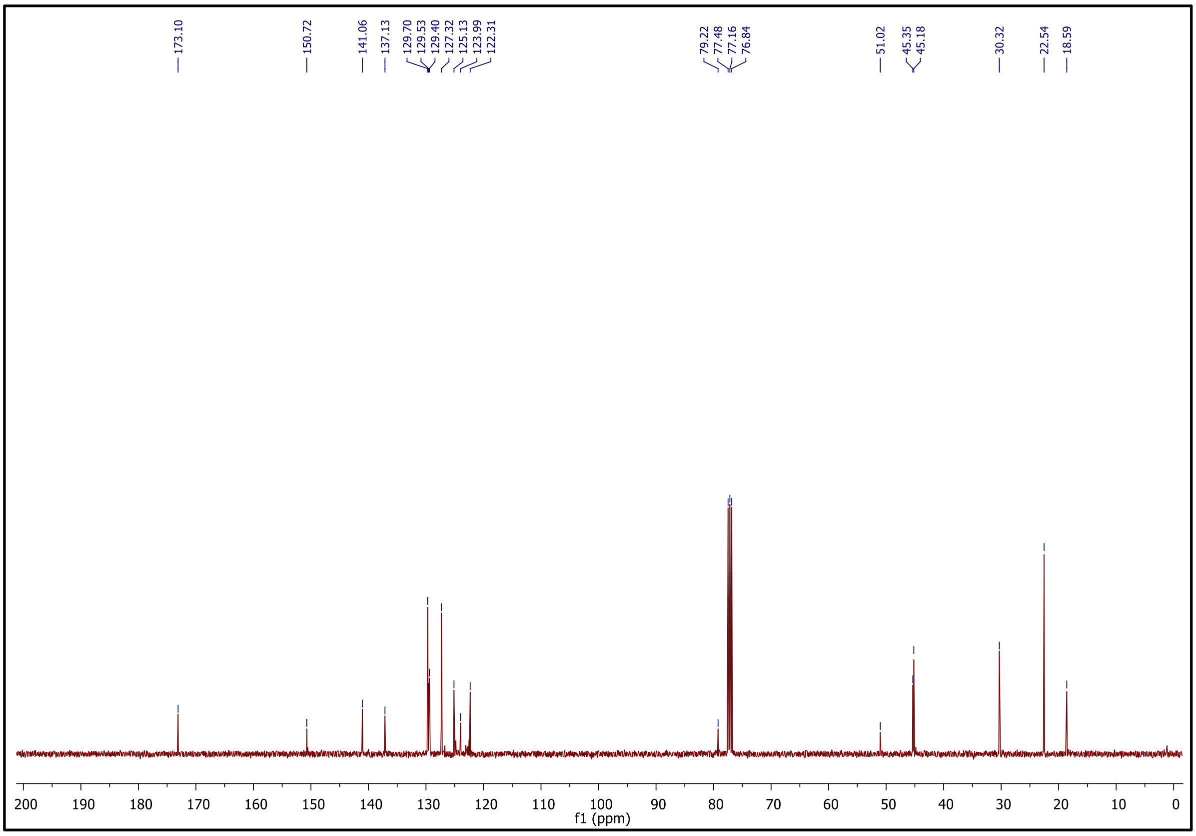


Figure S5. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **1x** in $CDCl_3$ at 298K.

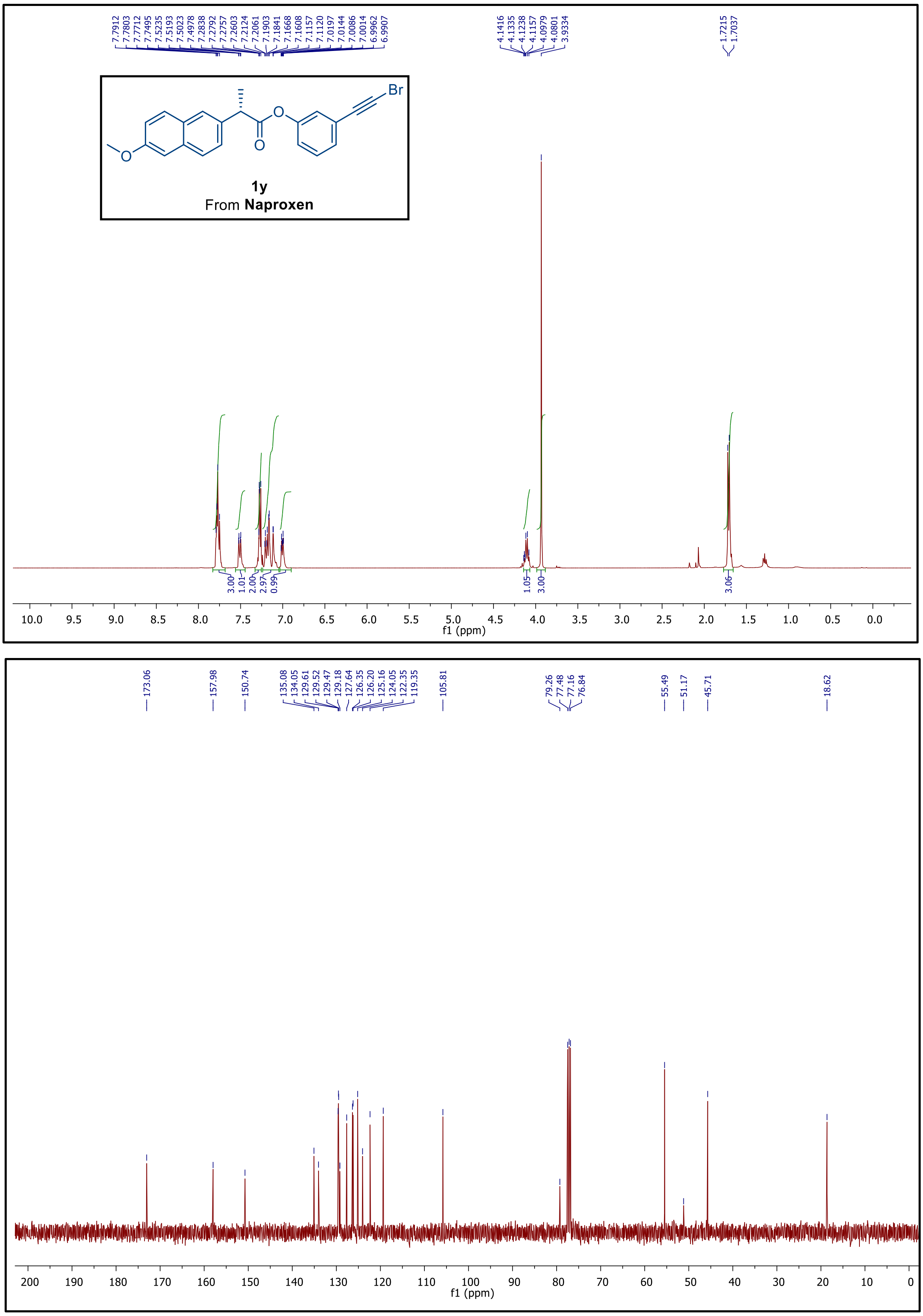
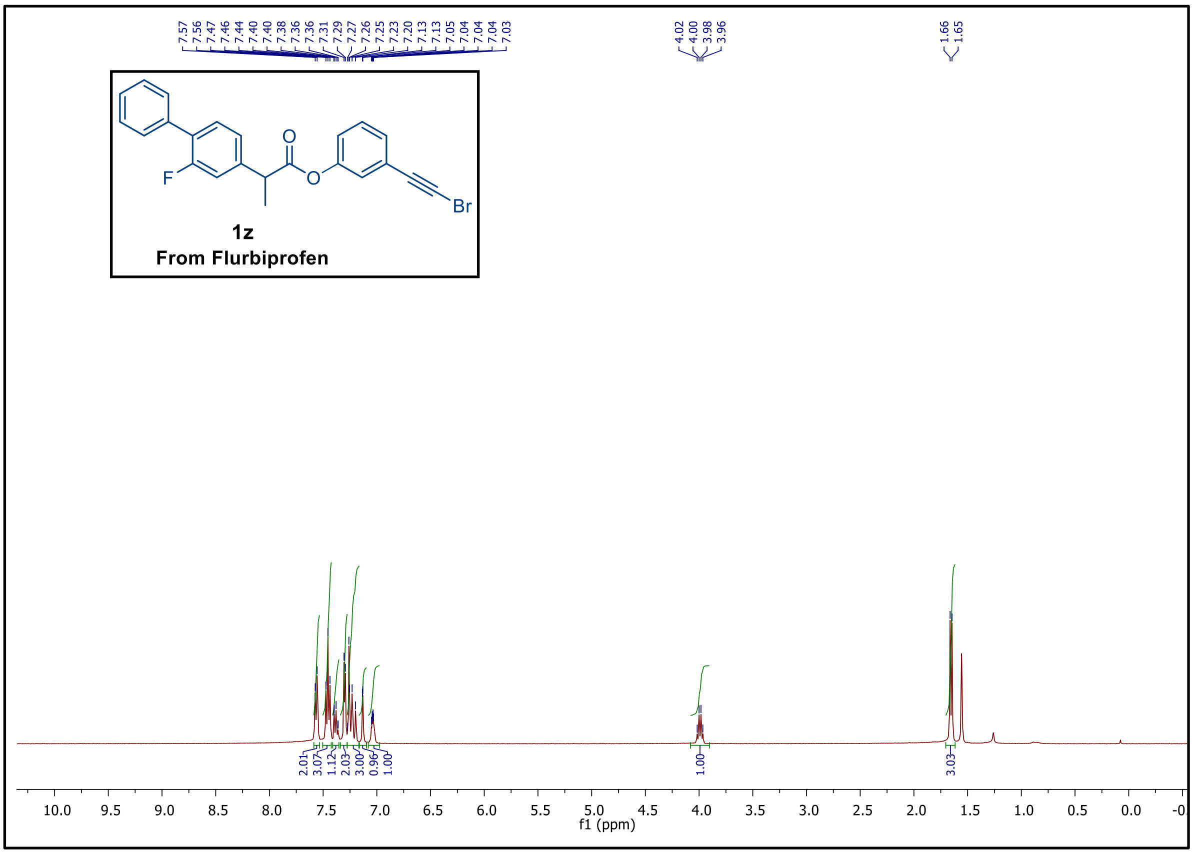


Figure S6. **¹H NMR** (400 MHz, top) and **¹³C {¹H} NMR** (100 MHz, bottom) Spectra of **1y** in $CDCl_3$ at 298K.



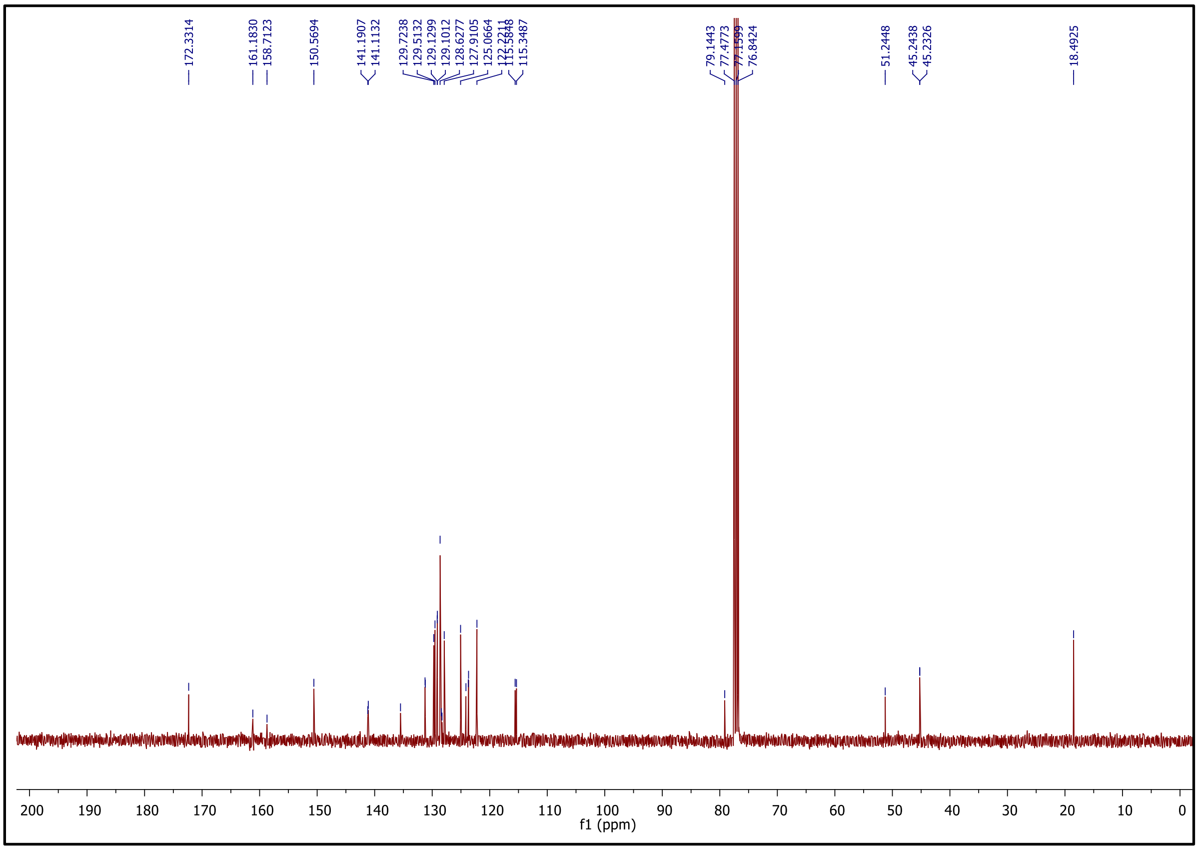


Figure S7. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **1z** in $CDCl_3$ at 298K.

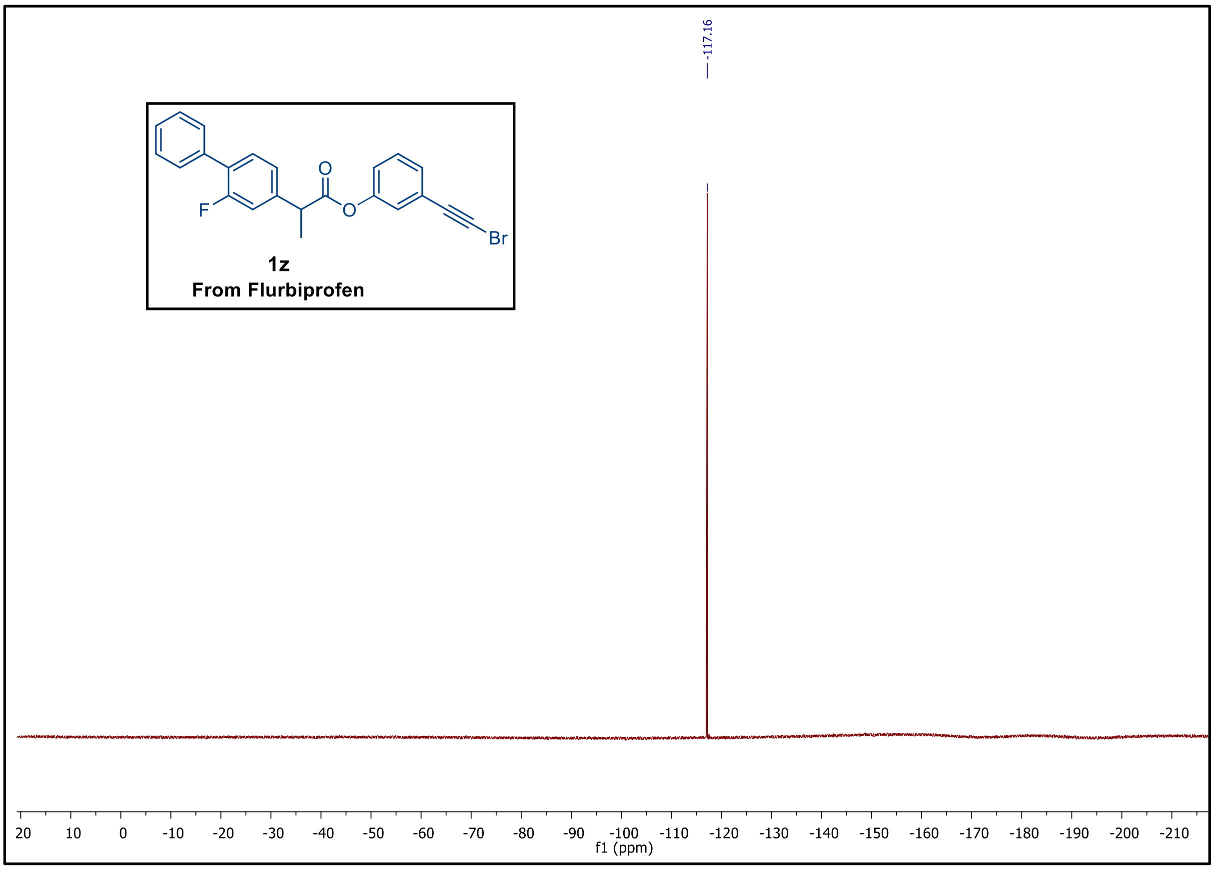
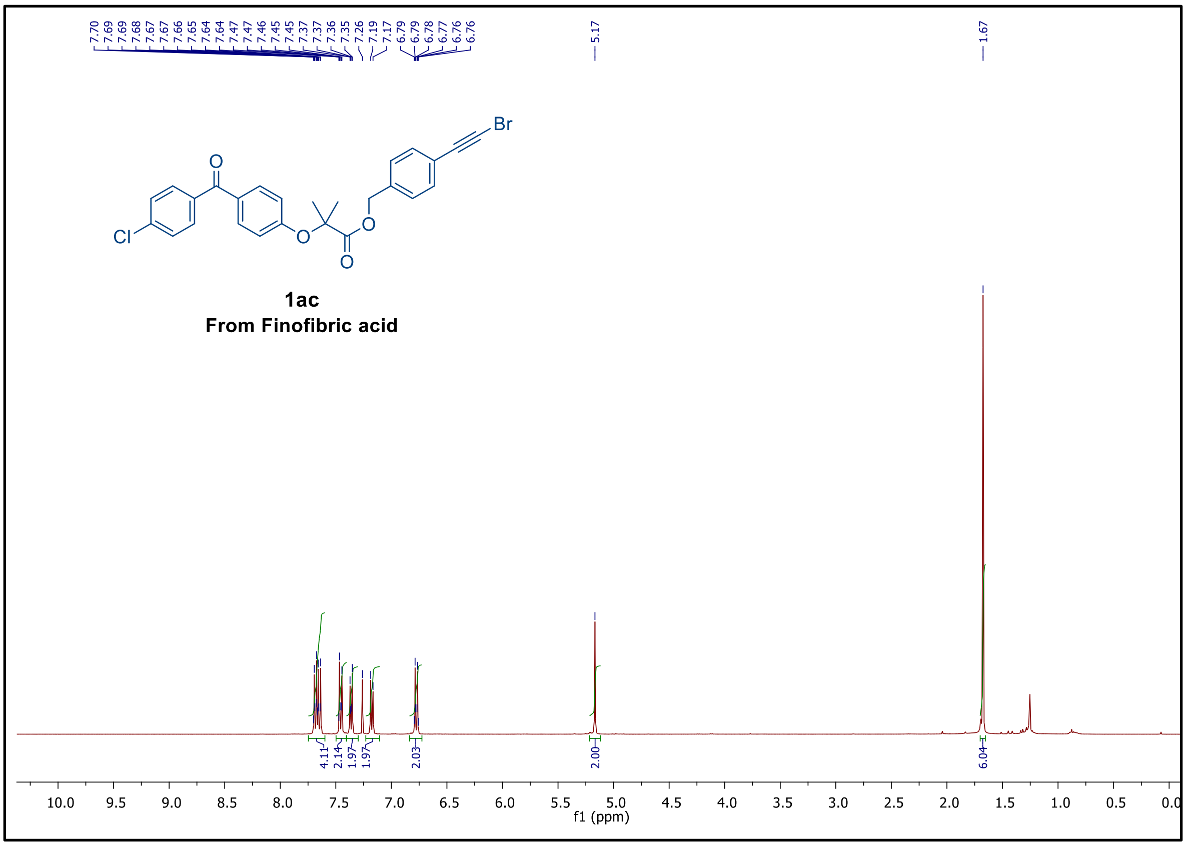


Figure S8. ^{19}**F NMR** (471 MHz) Spectra of **1z** in $CDCl_3$ at 298K.



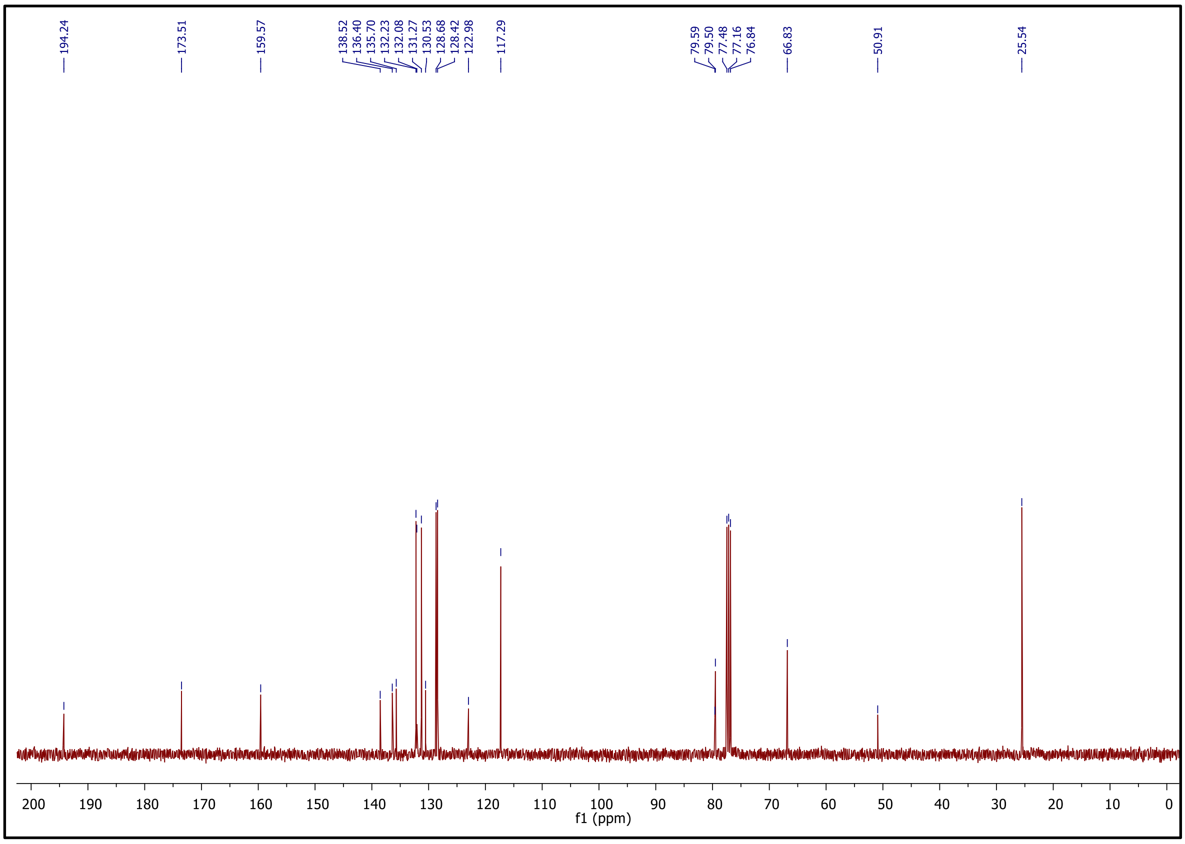
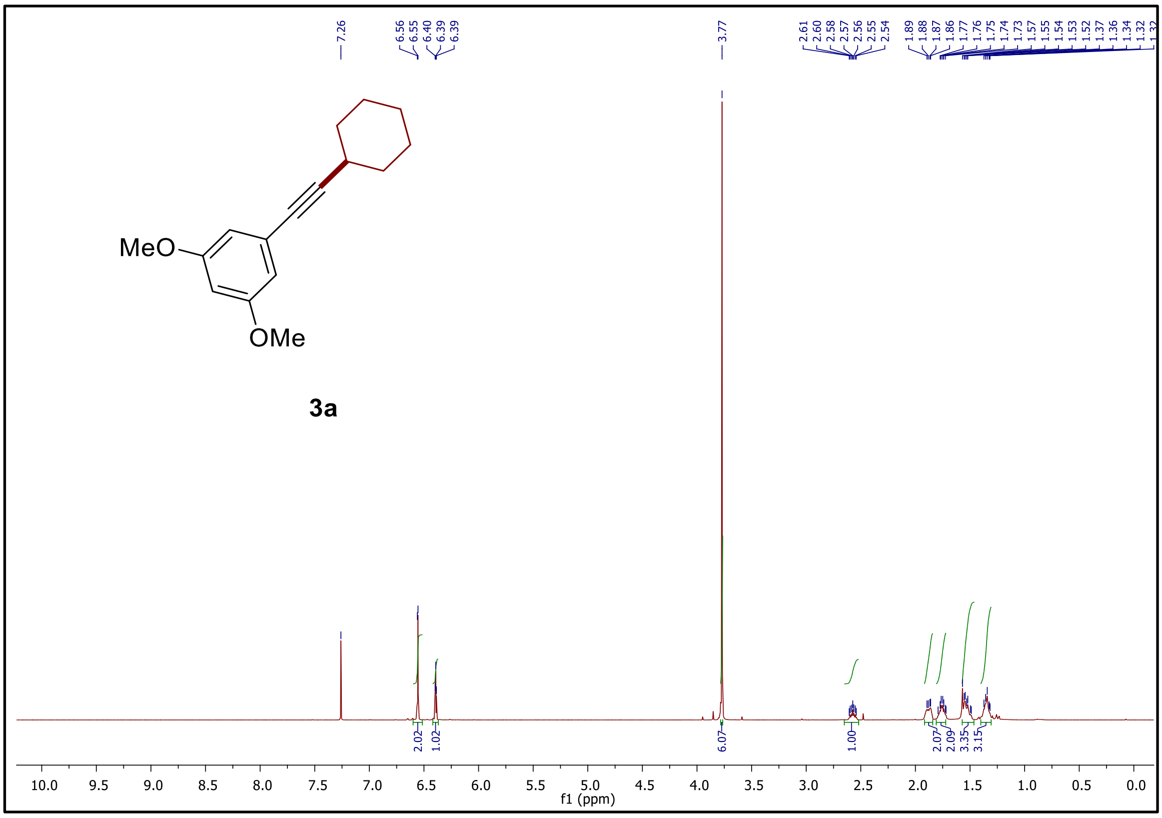


Figure S9. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **1ac** in $CDCl_3$ at 298K.



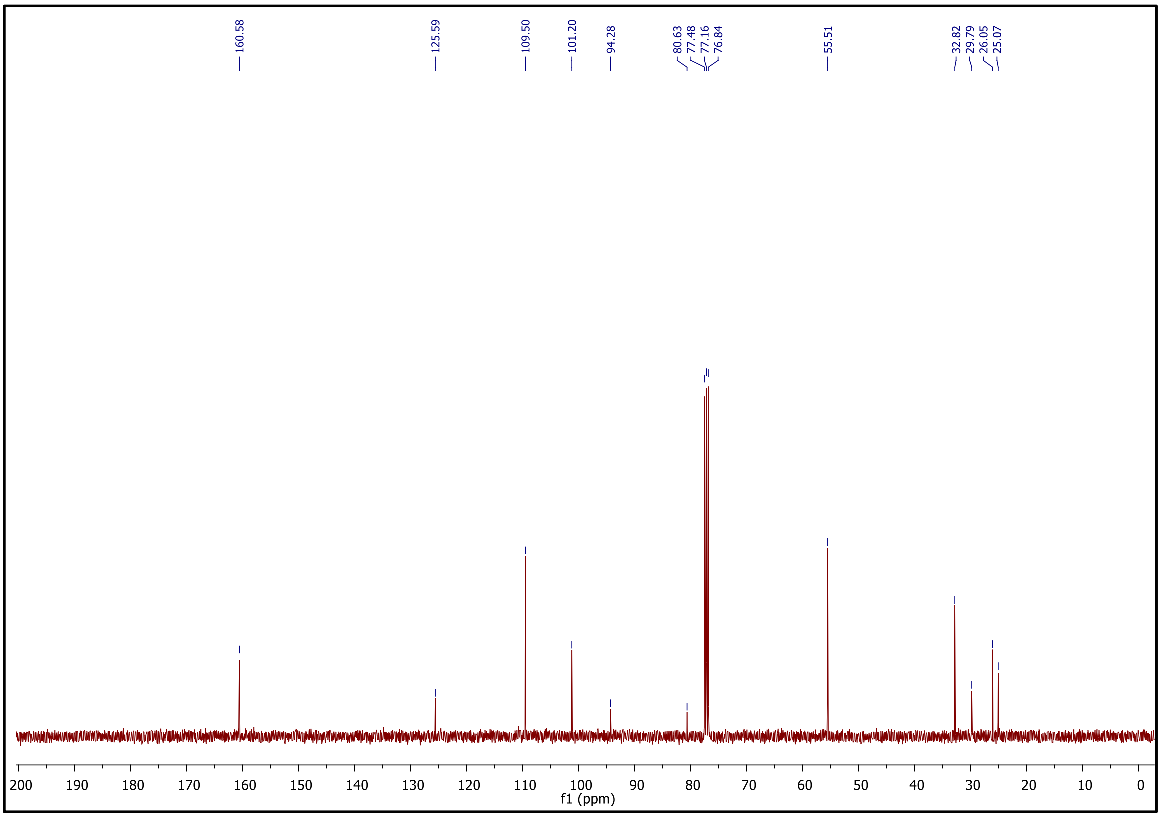
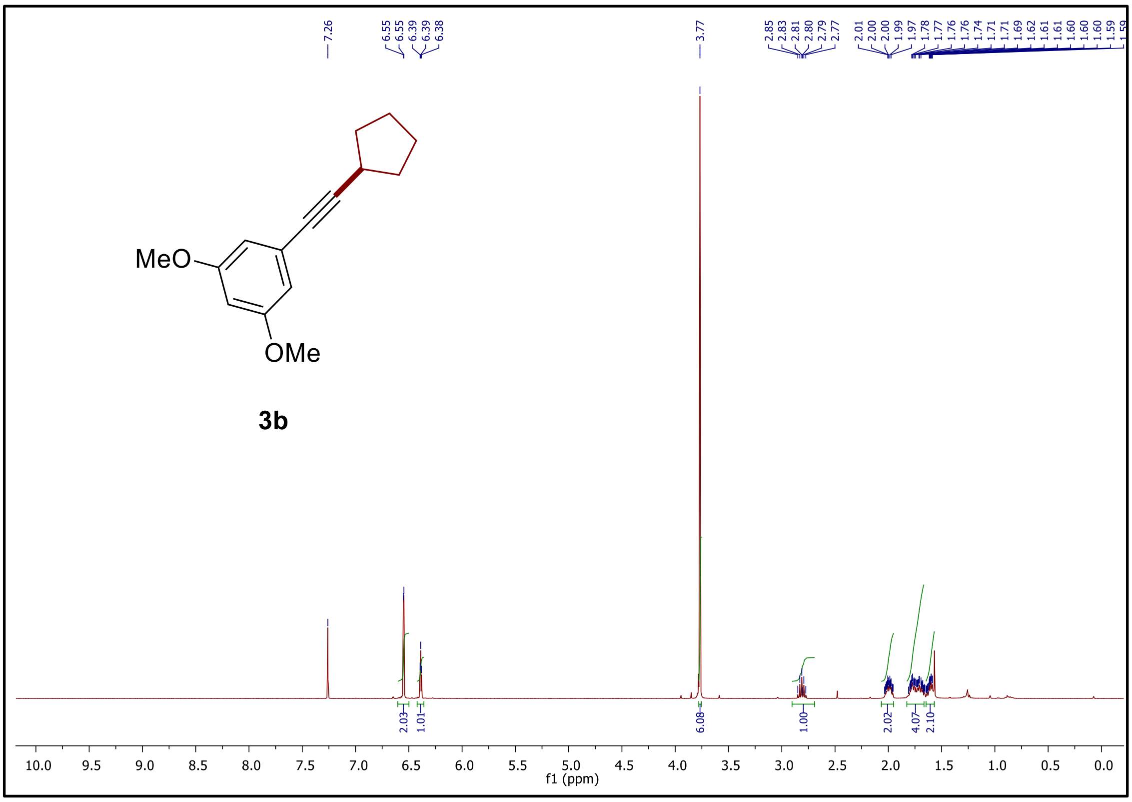


Figure S10. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3a** in $CDCl_3$ at 298K.



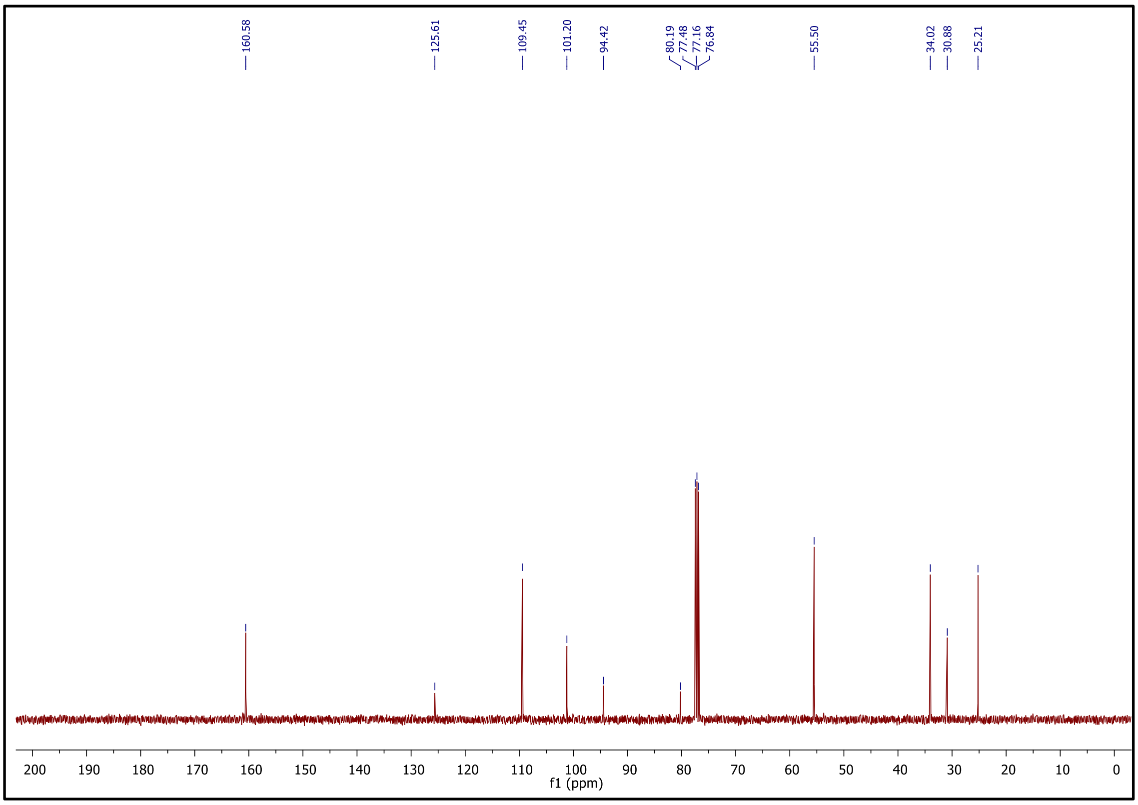
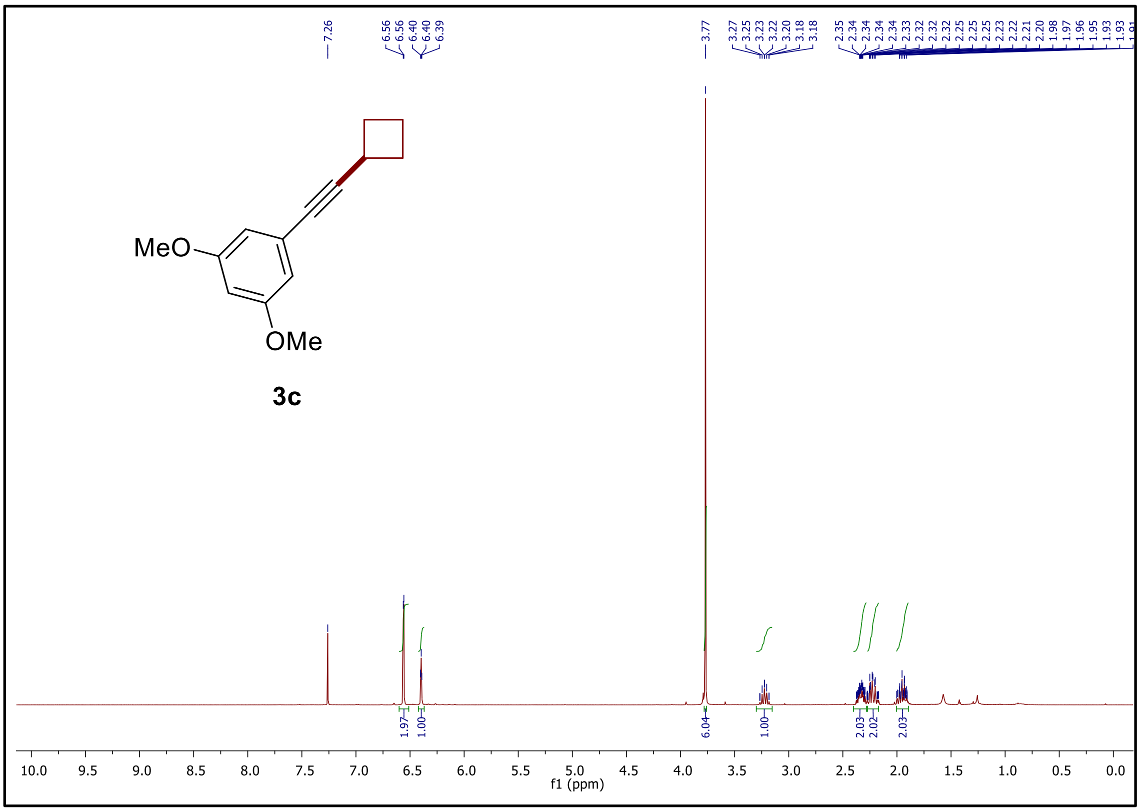


Figure S11. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3b** in $CDCl_3$ at 298K.



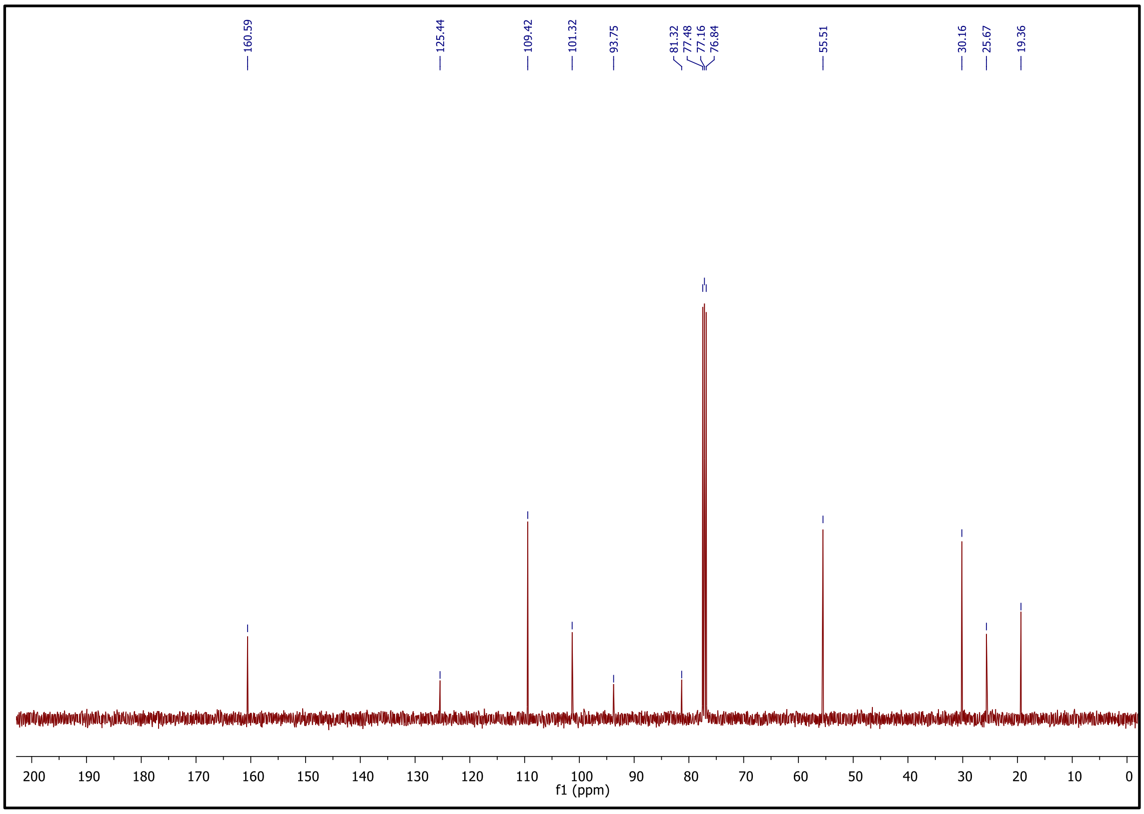
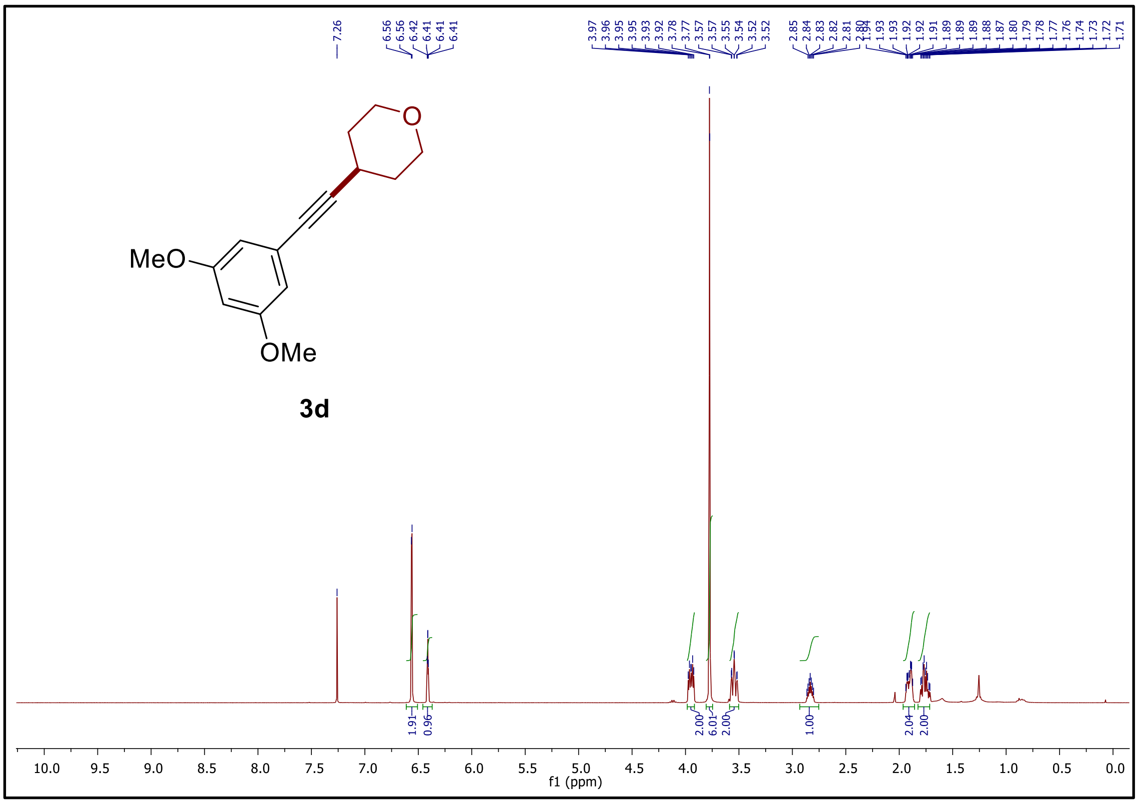


Figure S12. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3c** in $CDCl_3$ at 298K.



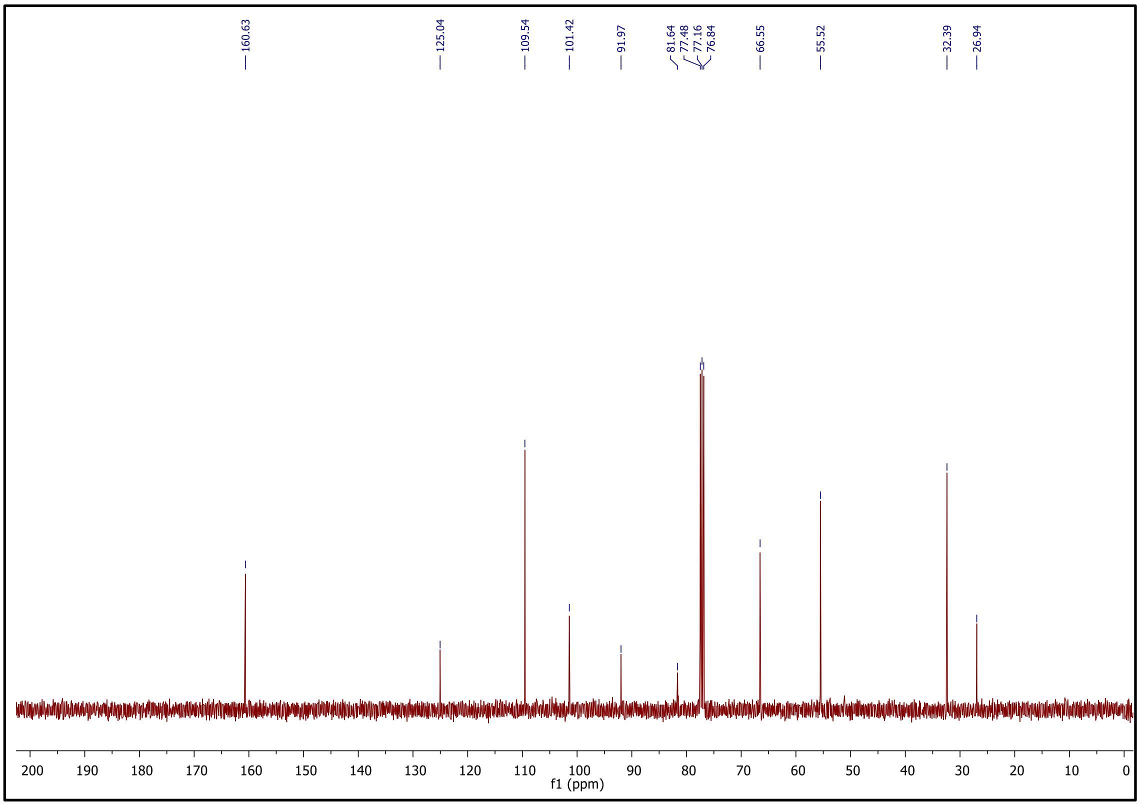
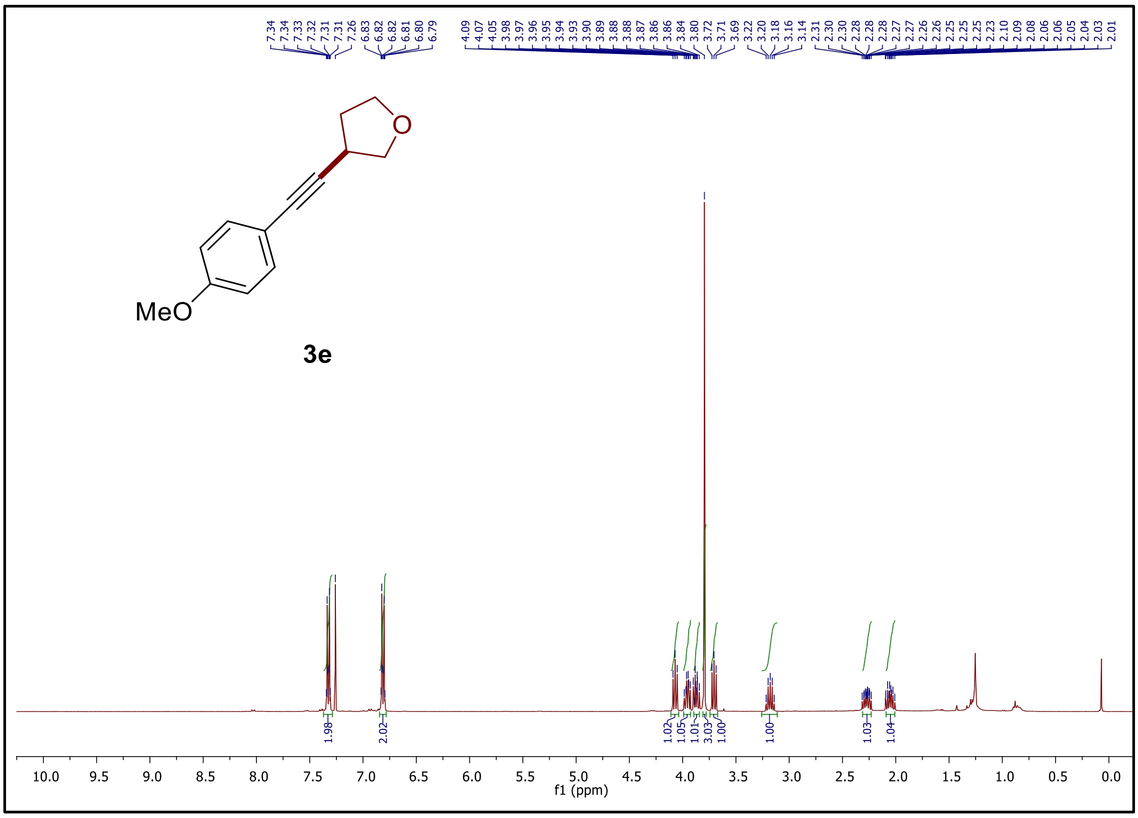


Figure S13. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3d** in $CDCl_3$ at 298K.



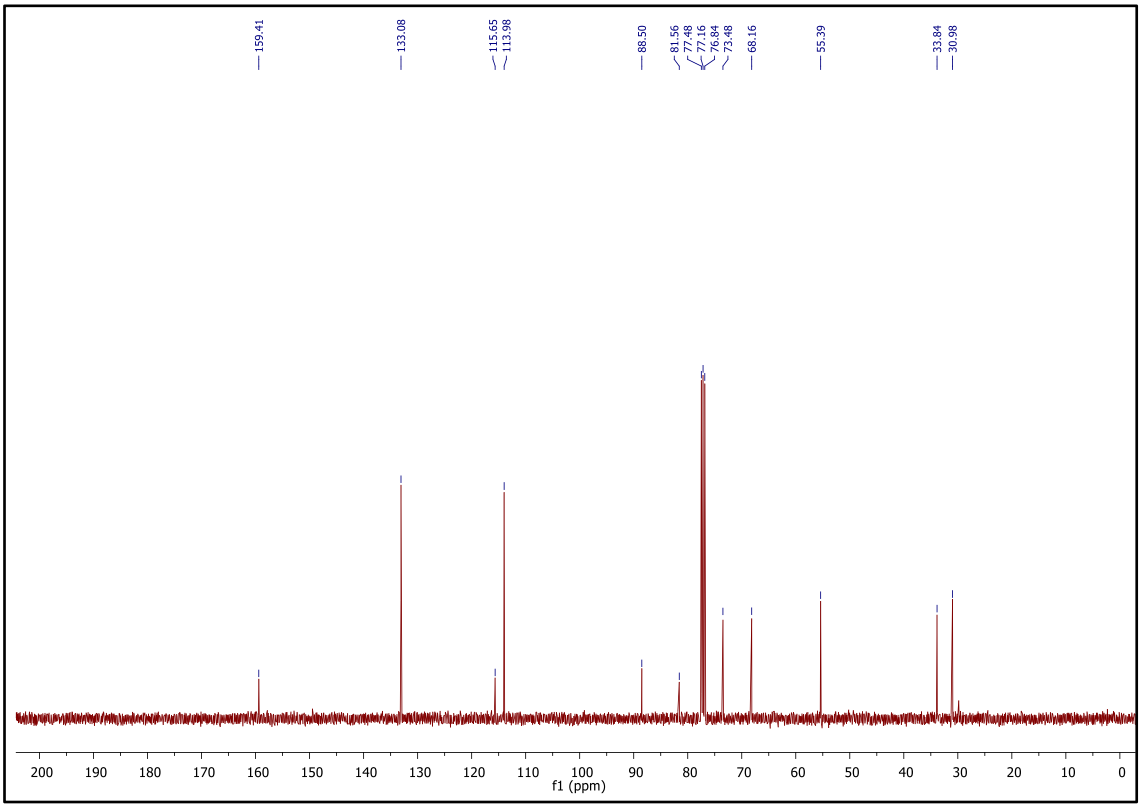


Figure S14. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3e** in $CDCl_3$ at 298K.

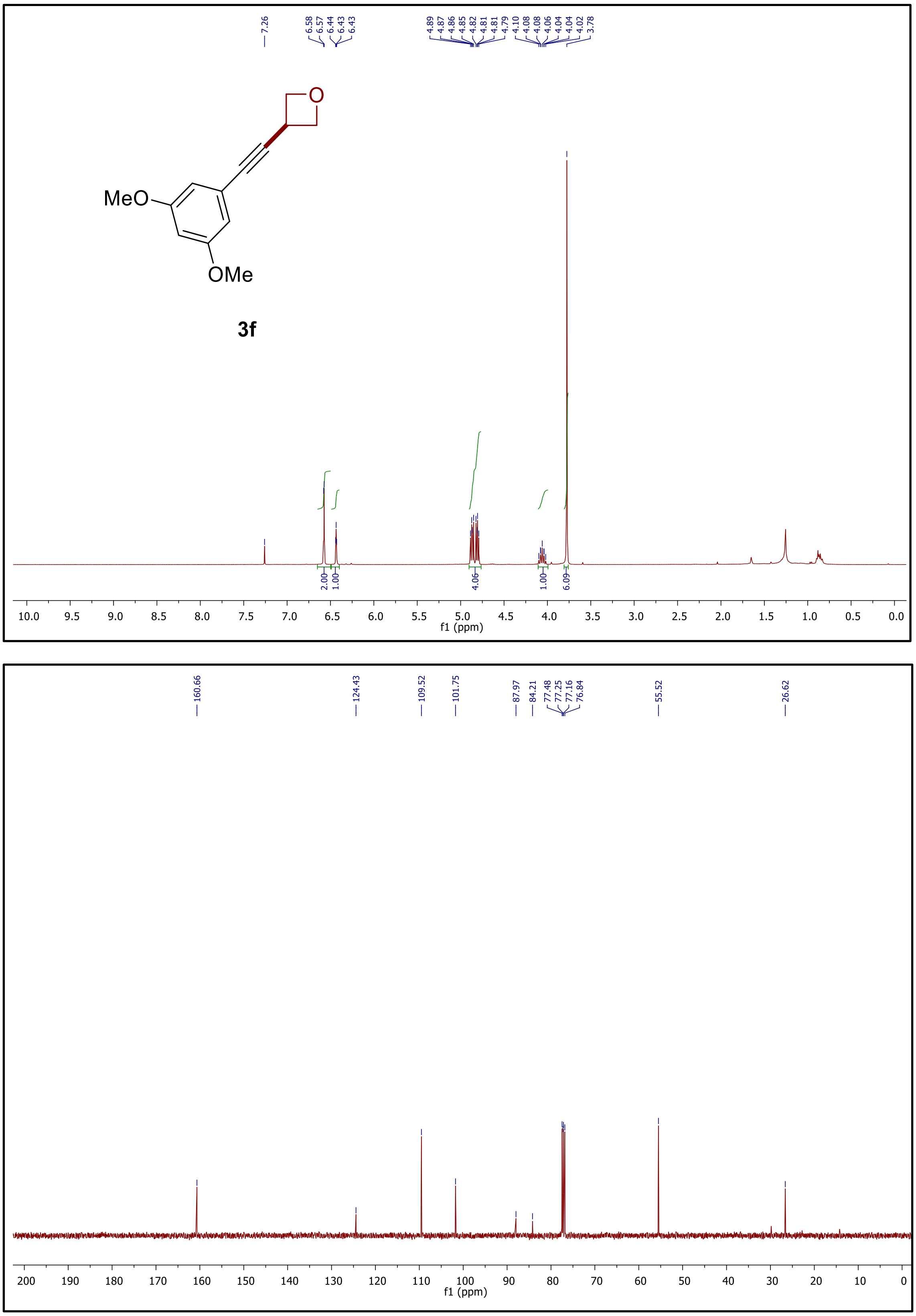


Figure S15. **[1]H NMR** (400 MHz, top) and **[13]C {[1]H} NMR** (100 MHz, bottom) Spectra of **3f** in $CDCl_3$ at 298K.

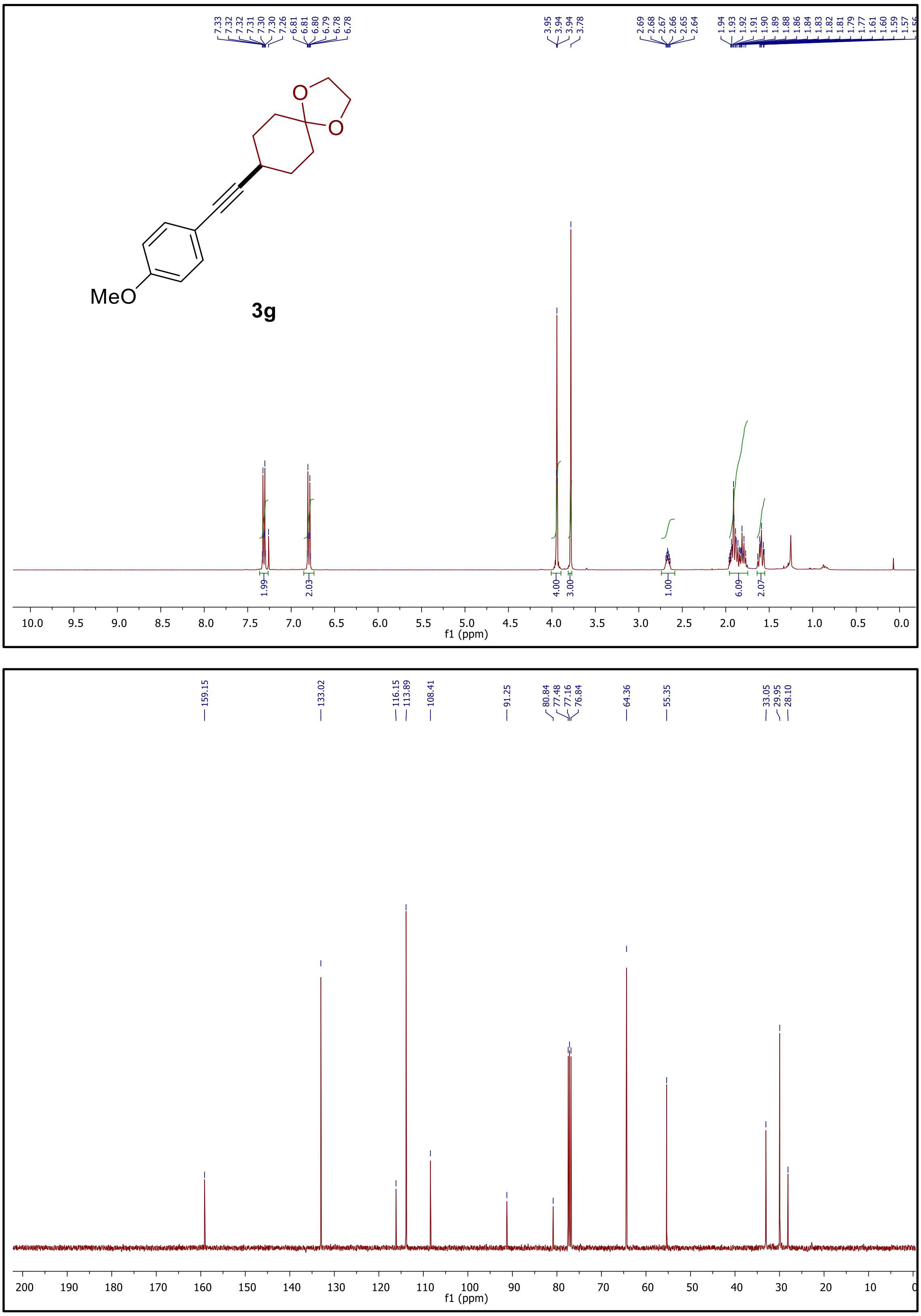
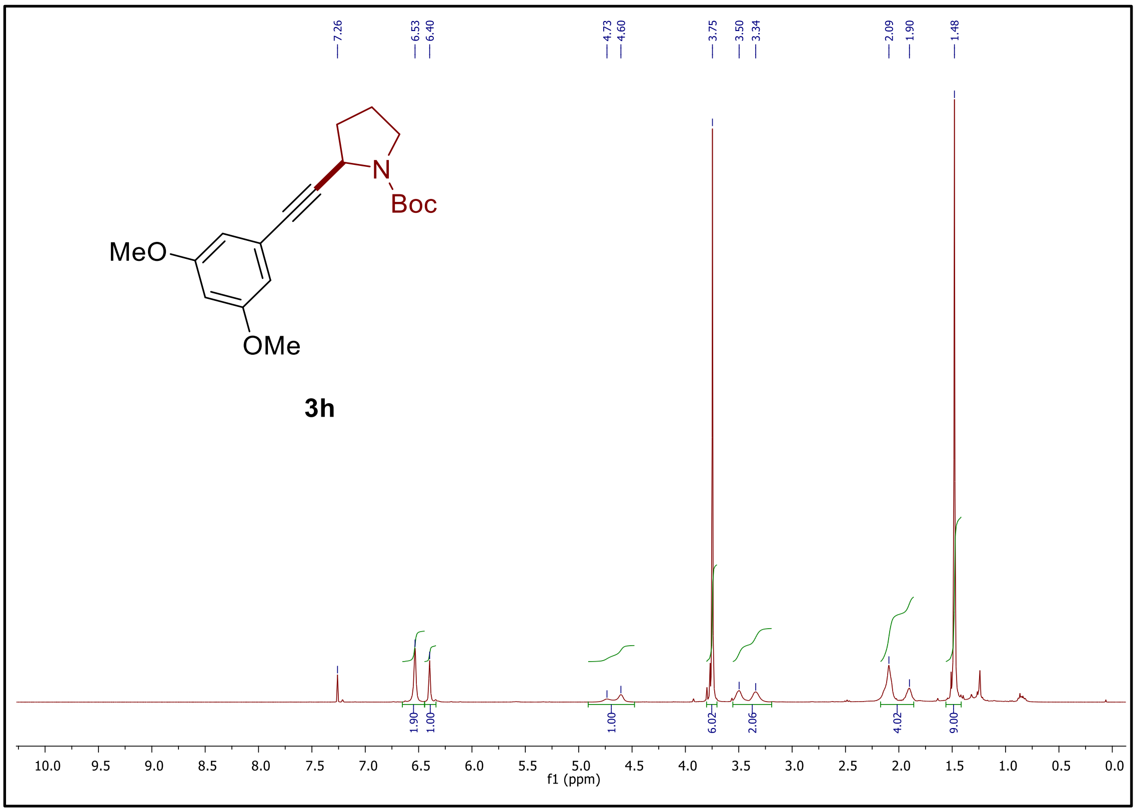


Figure S16. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3g** in $CDCl_3$ at 298K.



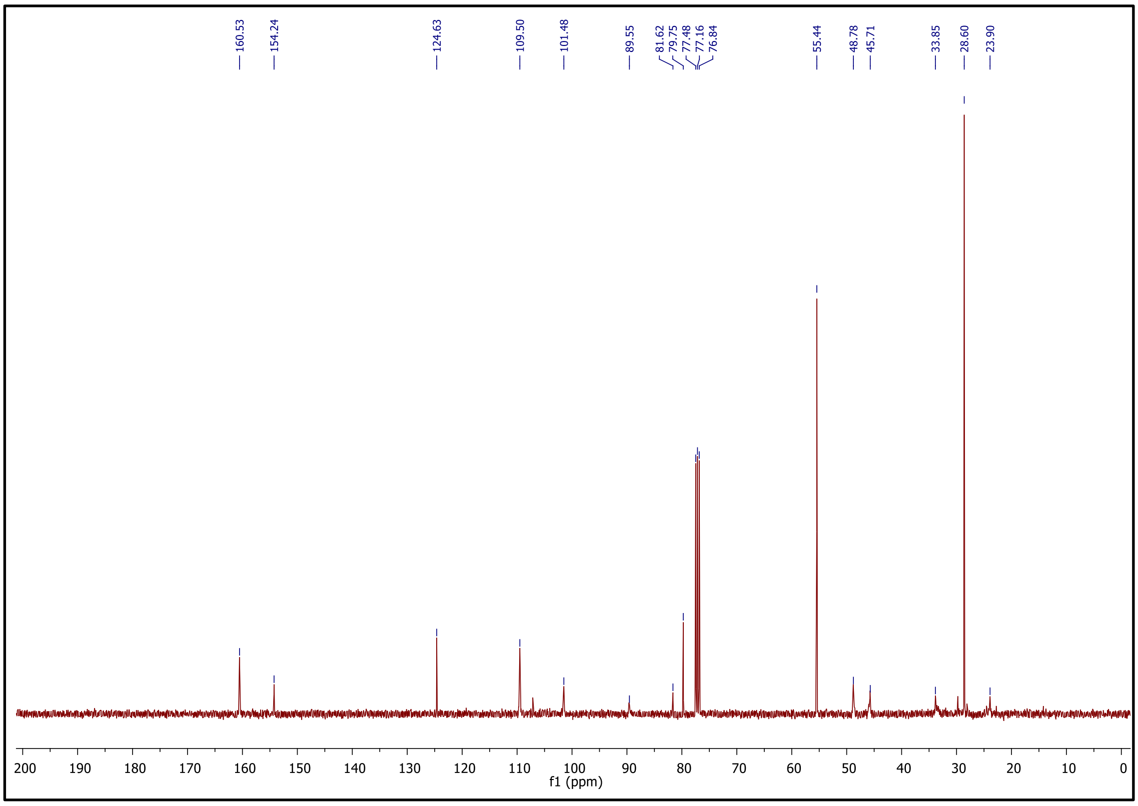
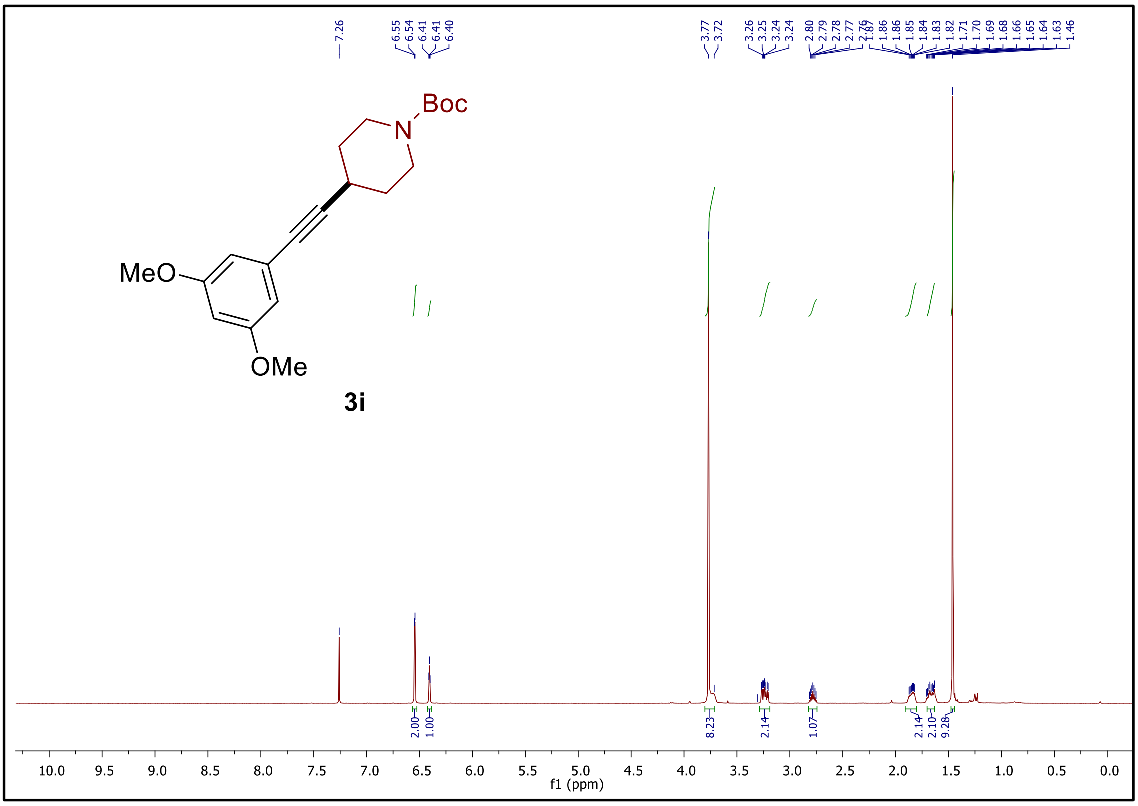


Figure S17. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3h** in $CDCl_3$ at 298K.



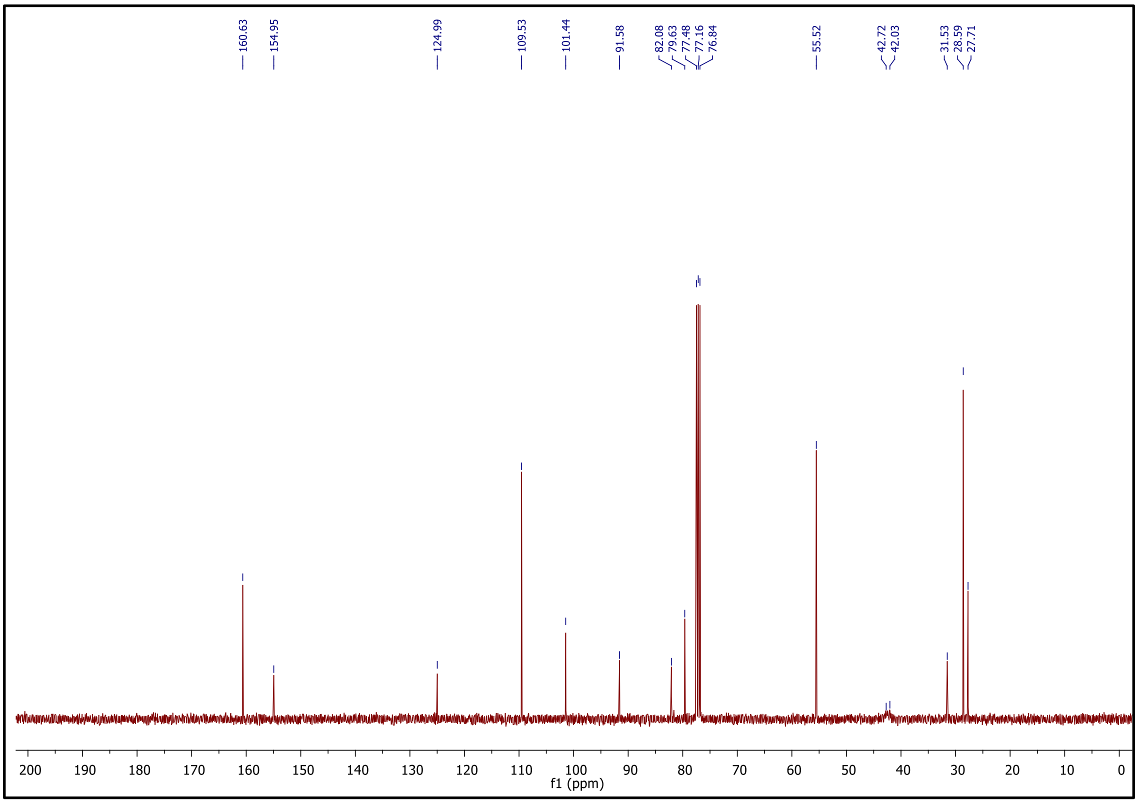
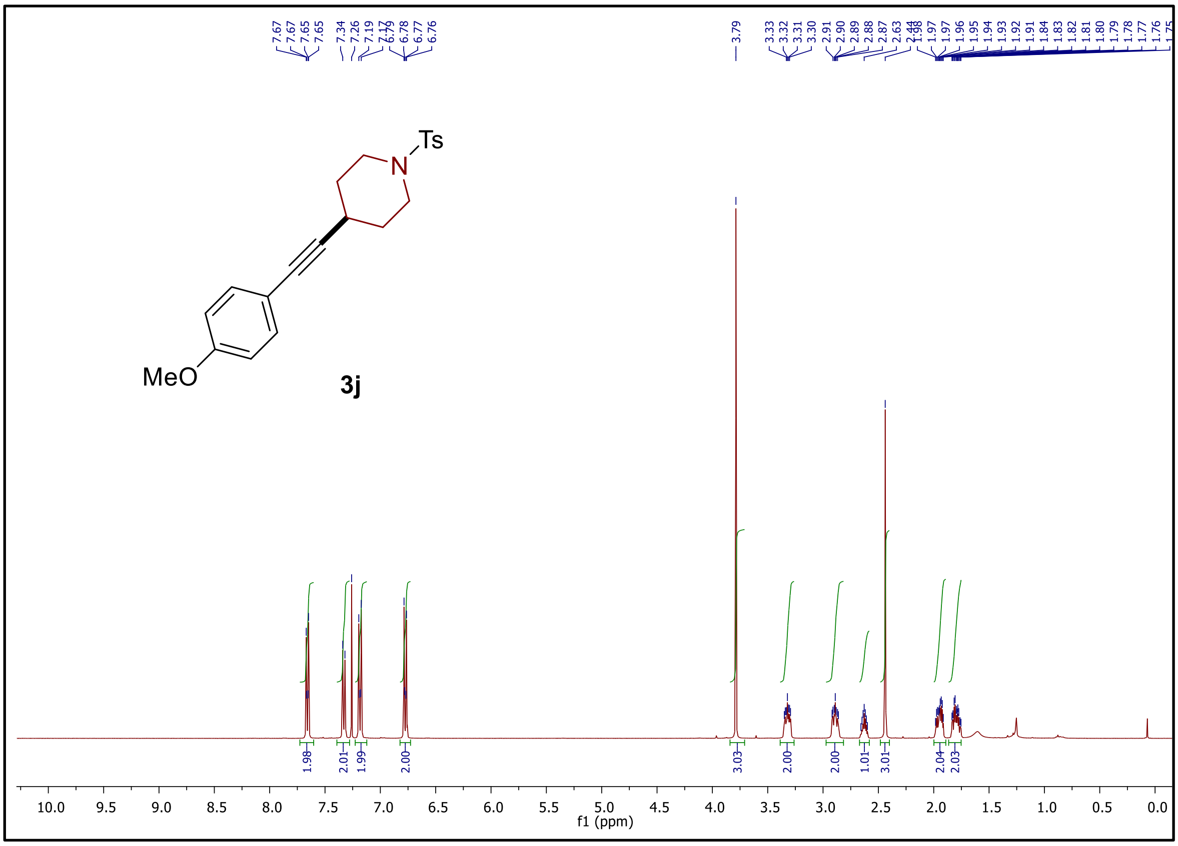


Figure S18. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3i** in $CDCl_3$ at 298K.



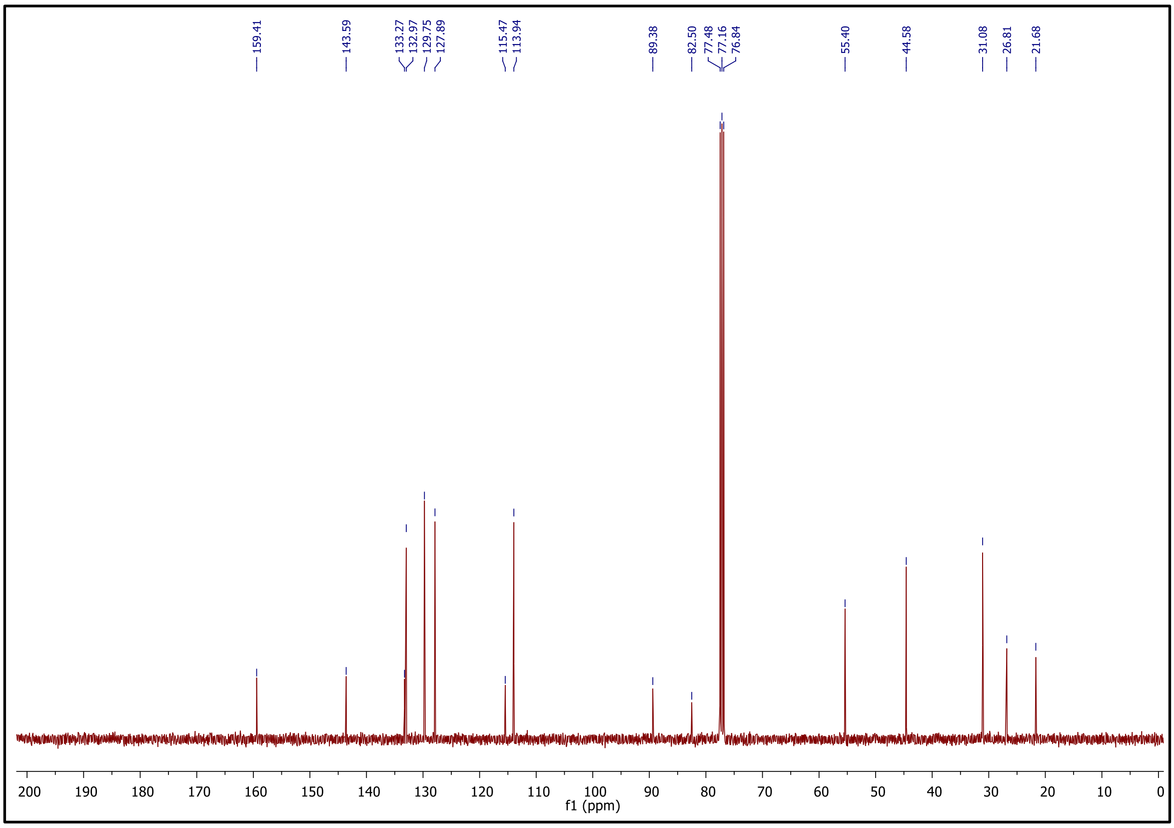
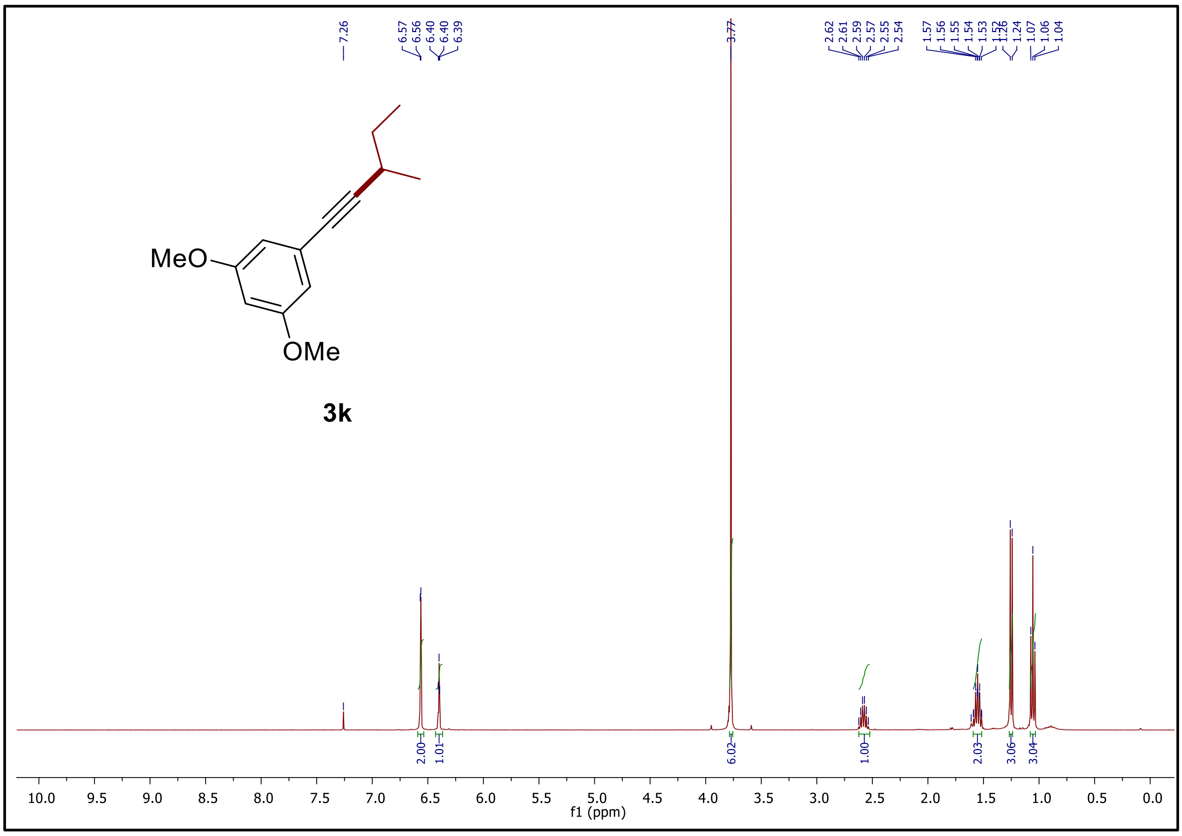


Figure S19. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3j** in $CDCl_3$ at 298K.



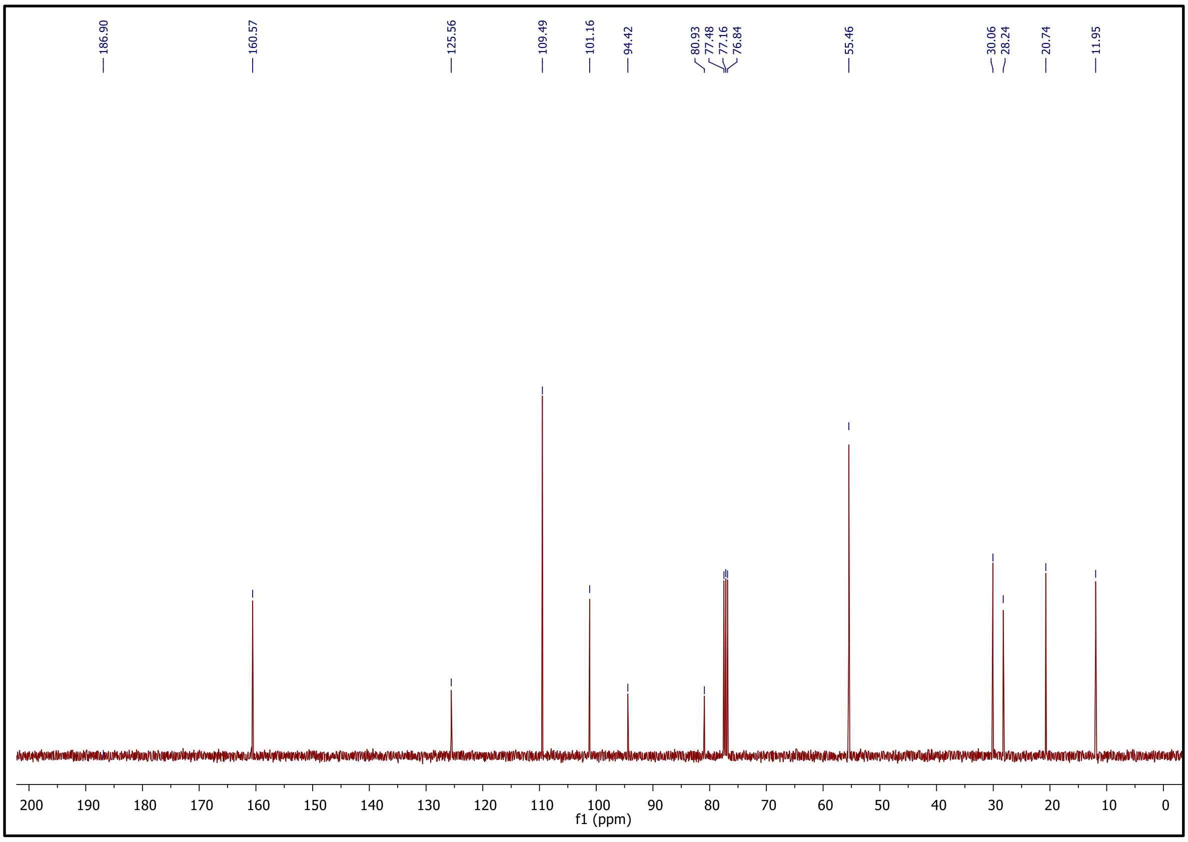
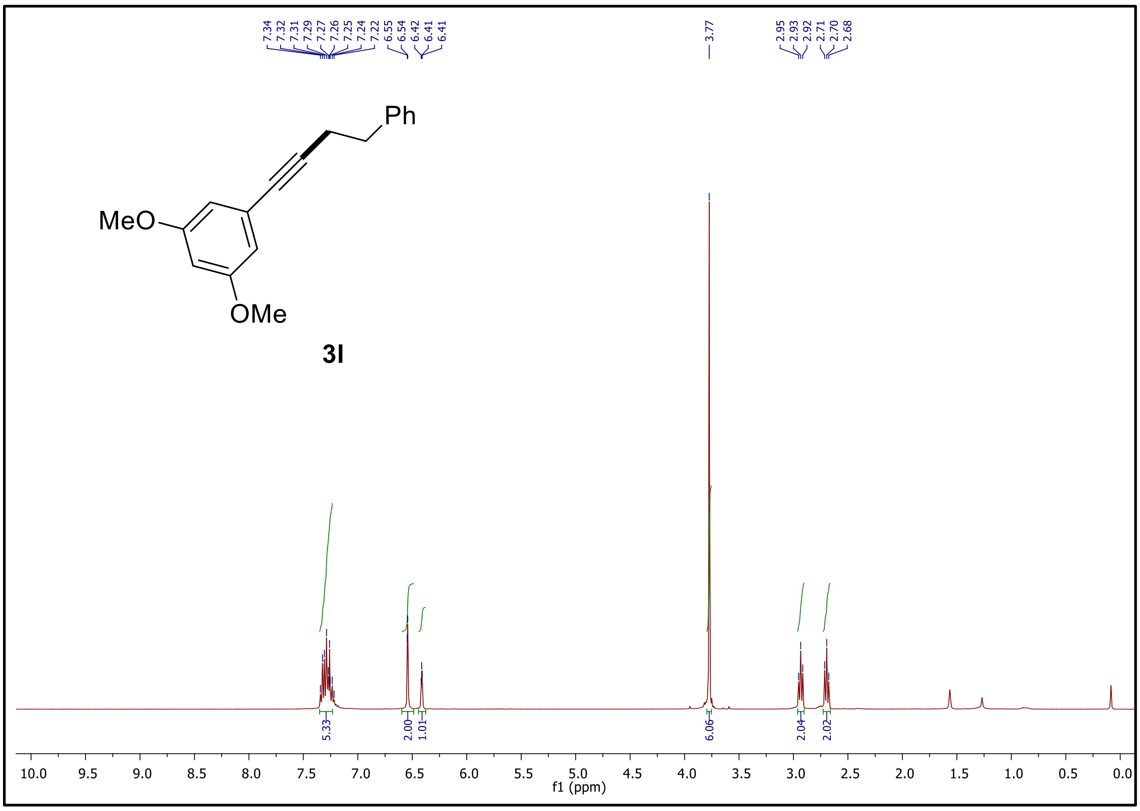


Figure S20. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3k** in $CDCl_3$ at 298K.



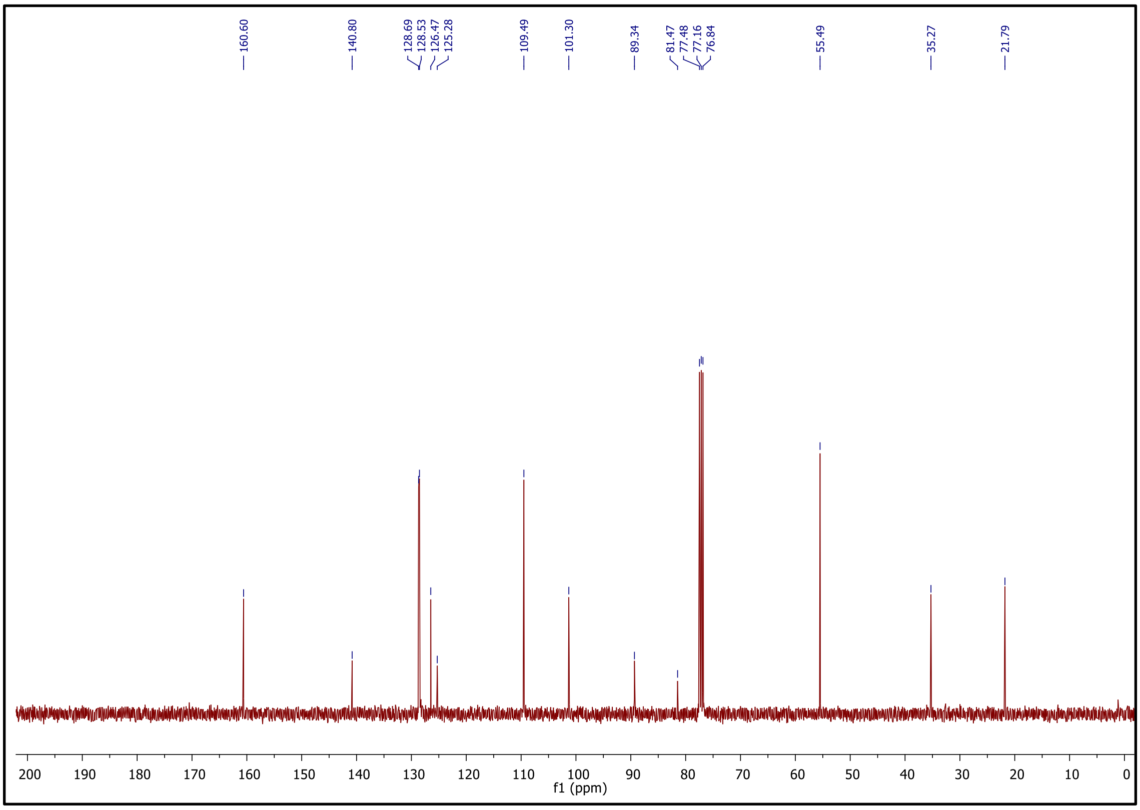


Figure S21. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3l** in $CDCl_3$ at 298K.

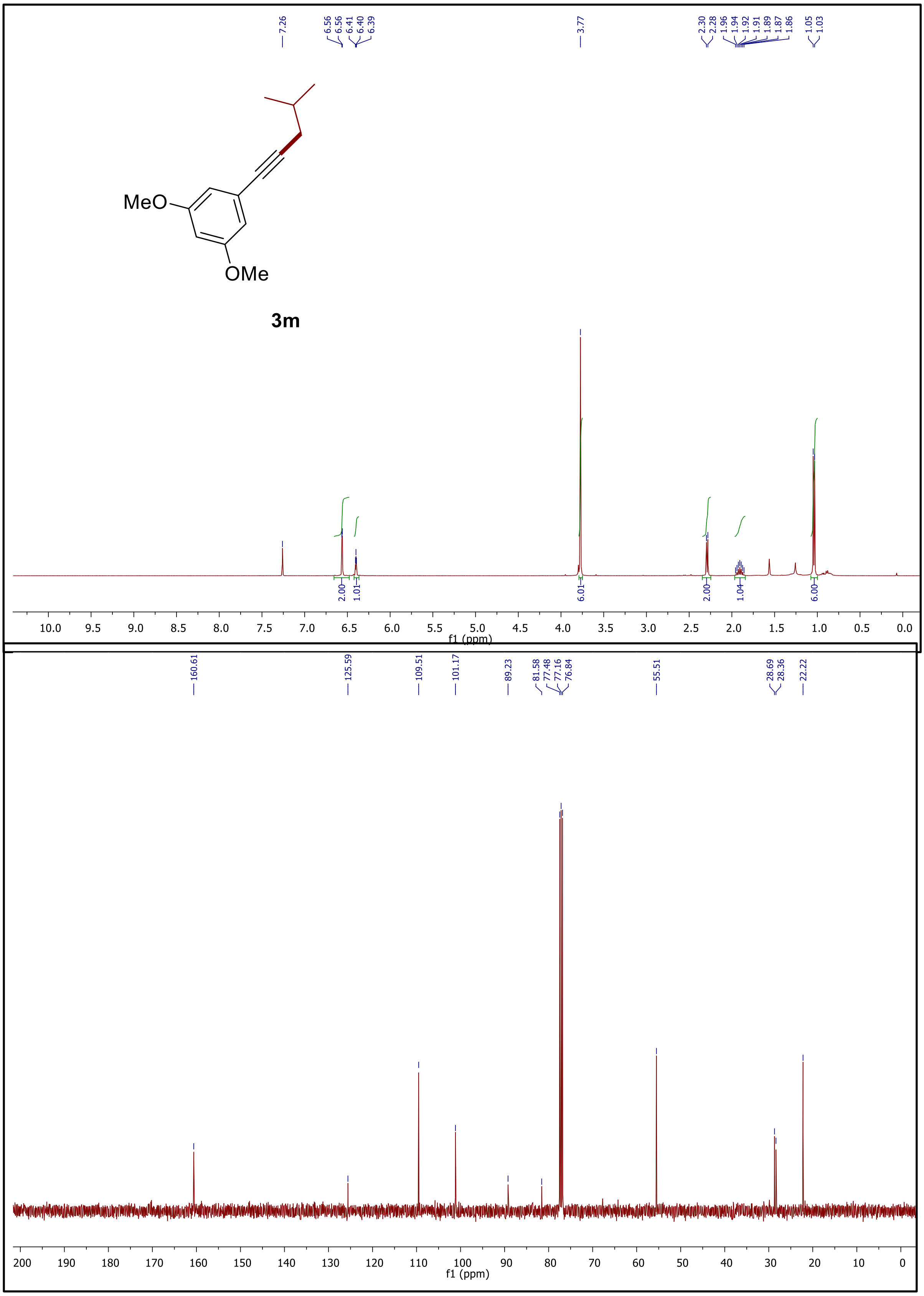
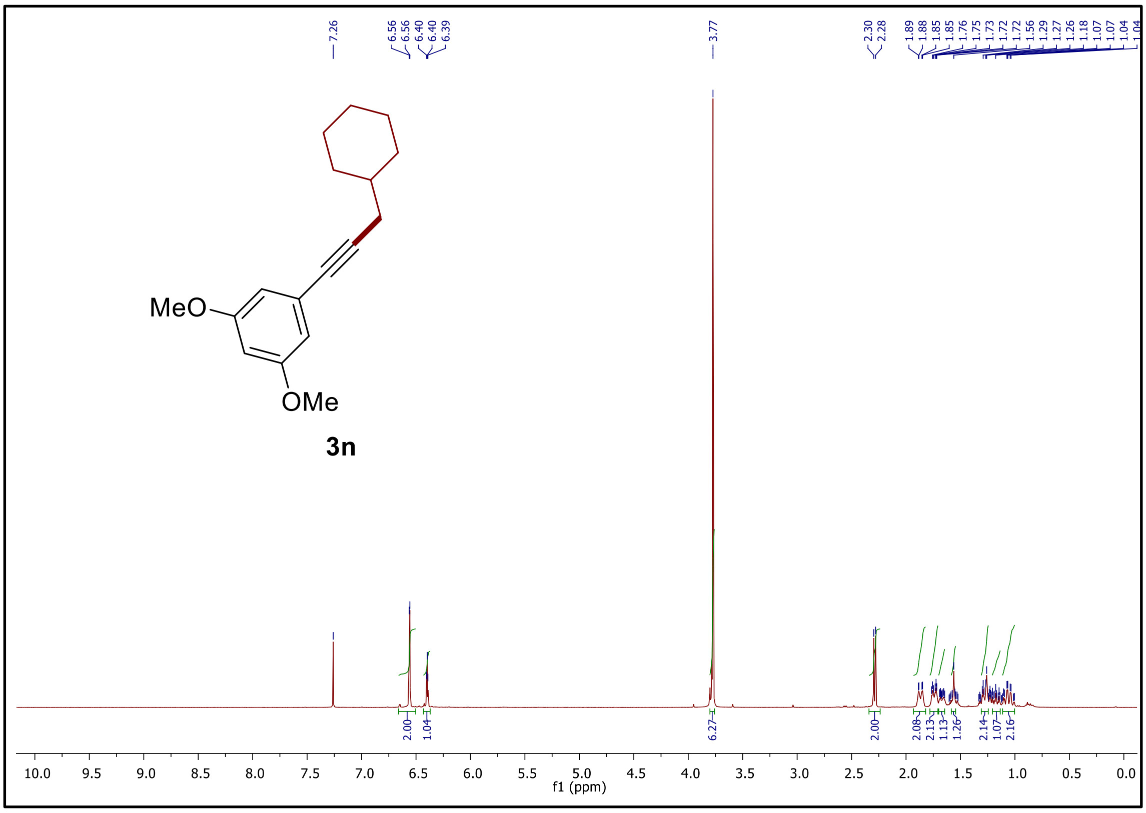


Figure S22. **[1]H NMR** (400 MHz, top) and **[13]C {[1]H} NMR** (100 MHz, bottom) Spectra of **3m** in $CDCl_3$ at 298K.



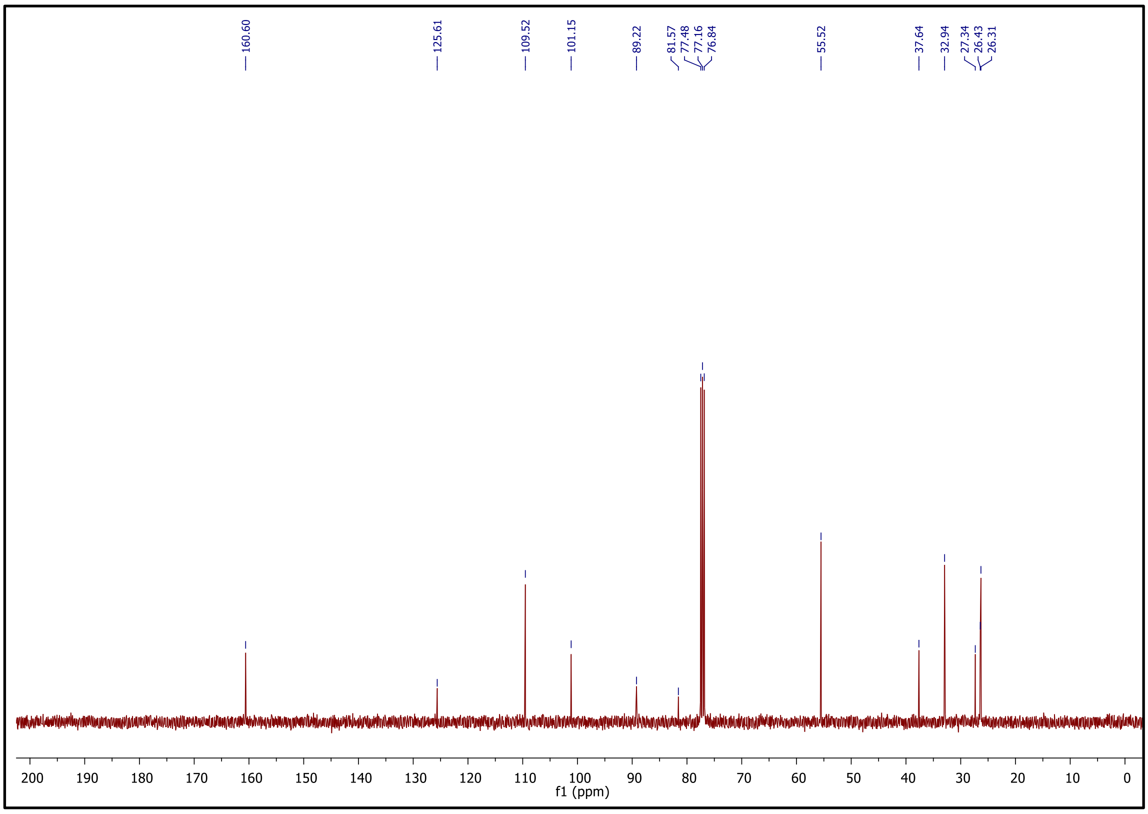


Figure S23. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3n** in $CDCl_3$ at 298K.

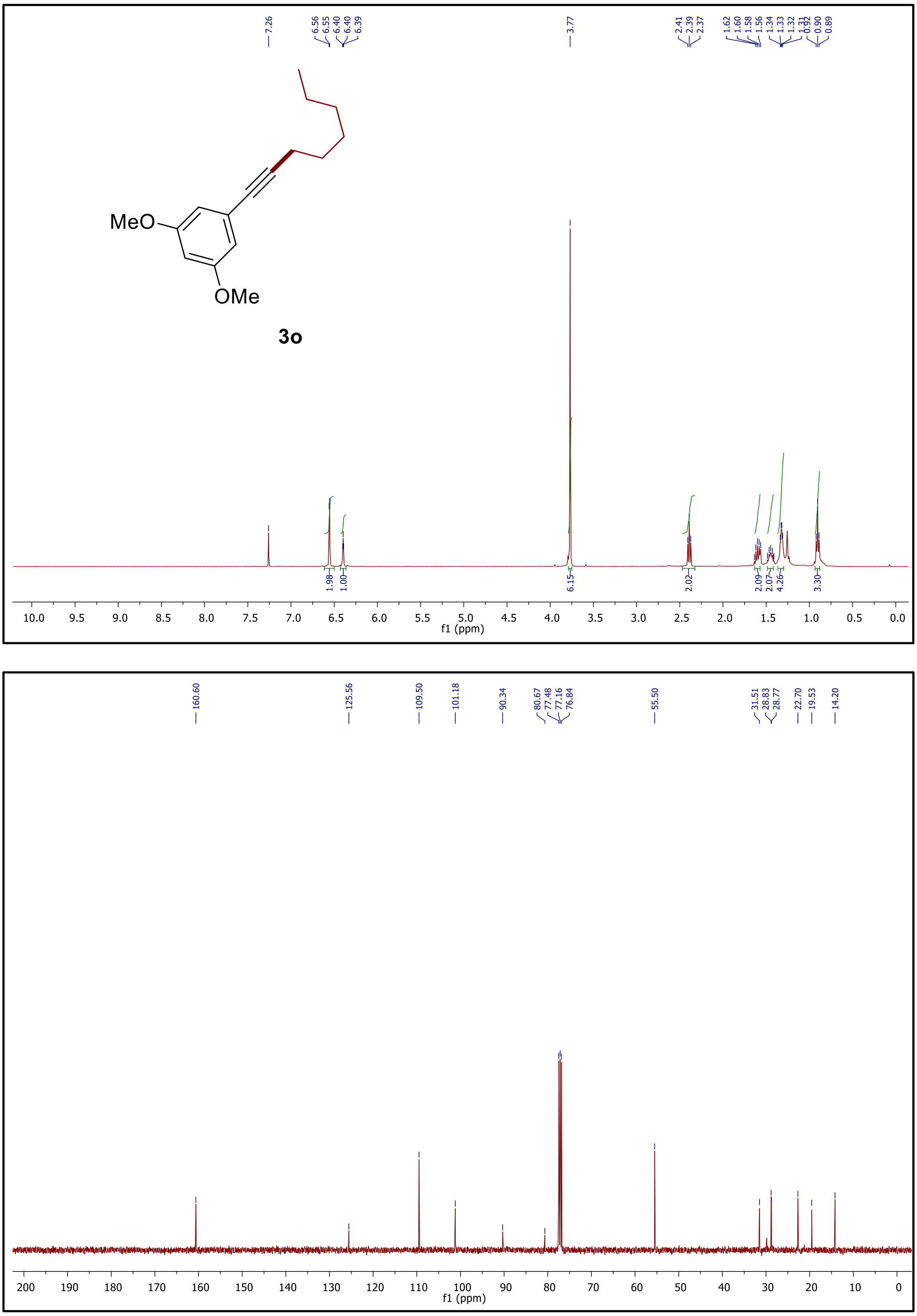
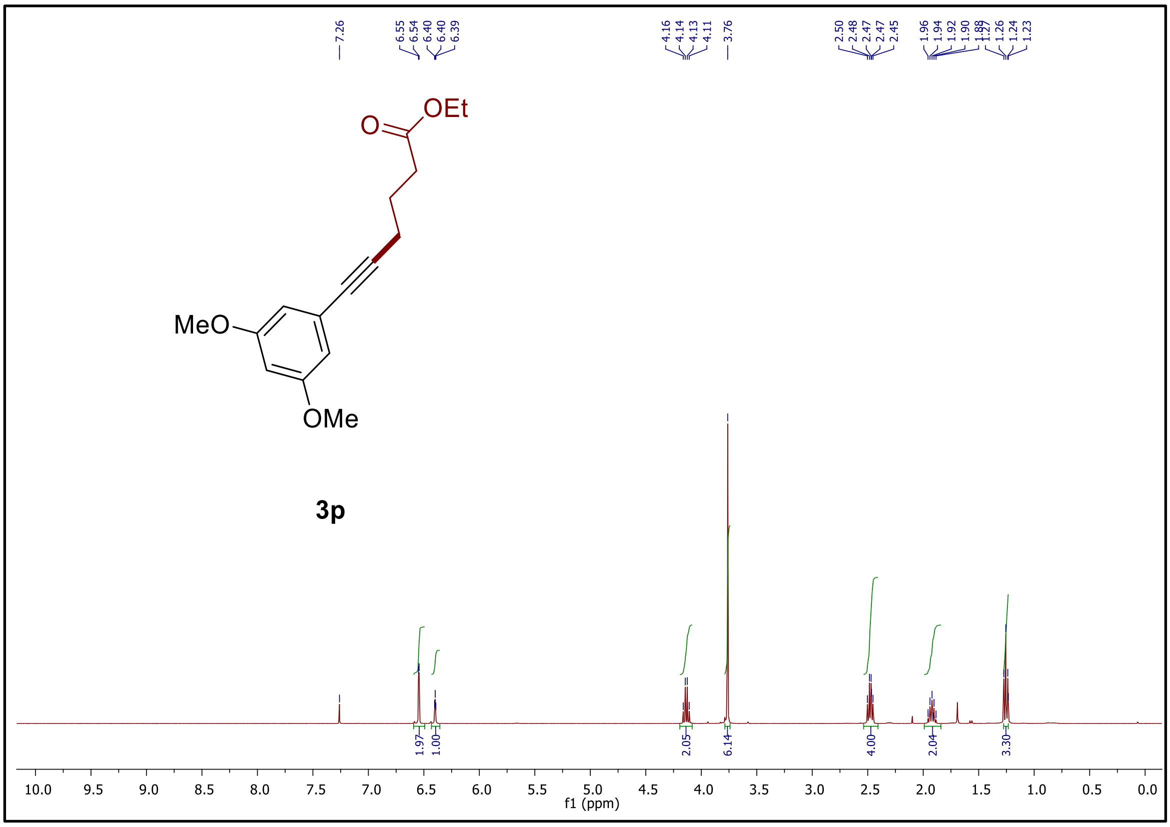


Figure S24. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3o** in $CDCl_3$ at 298K.



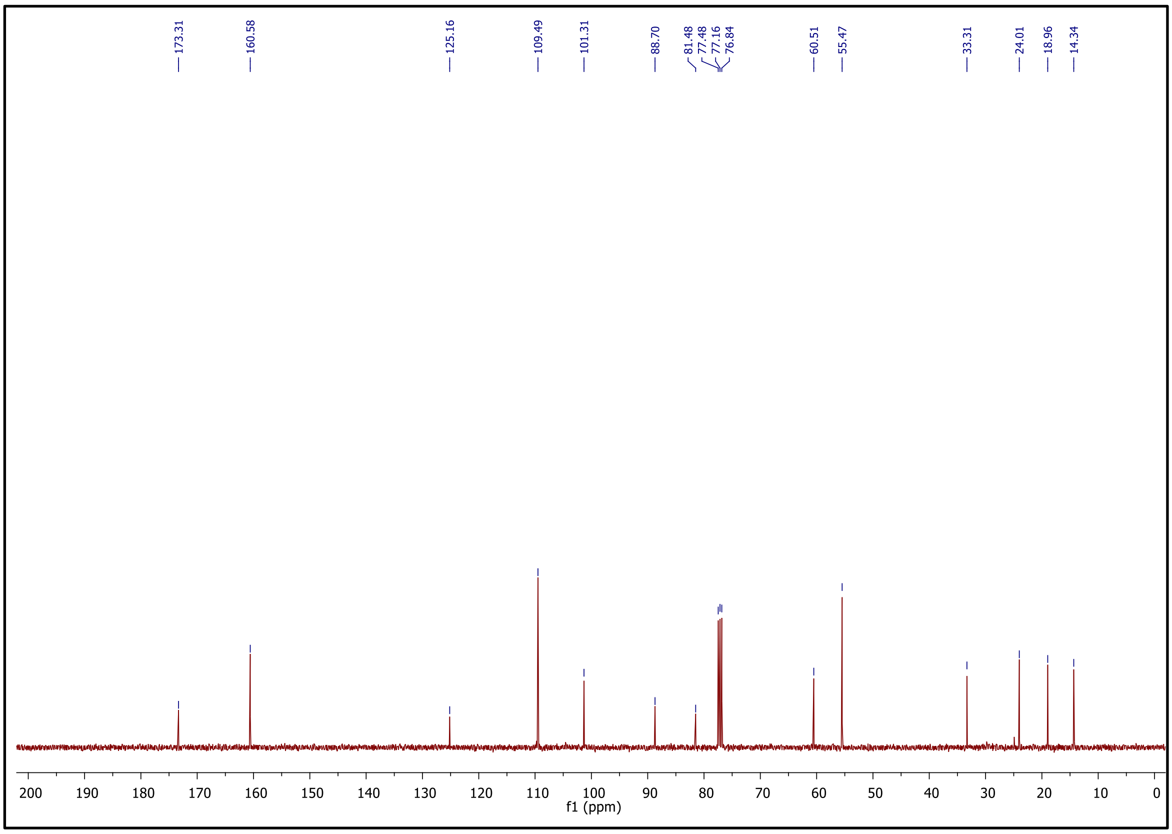
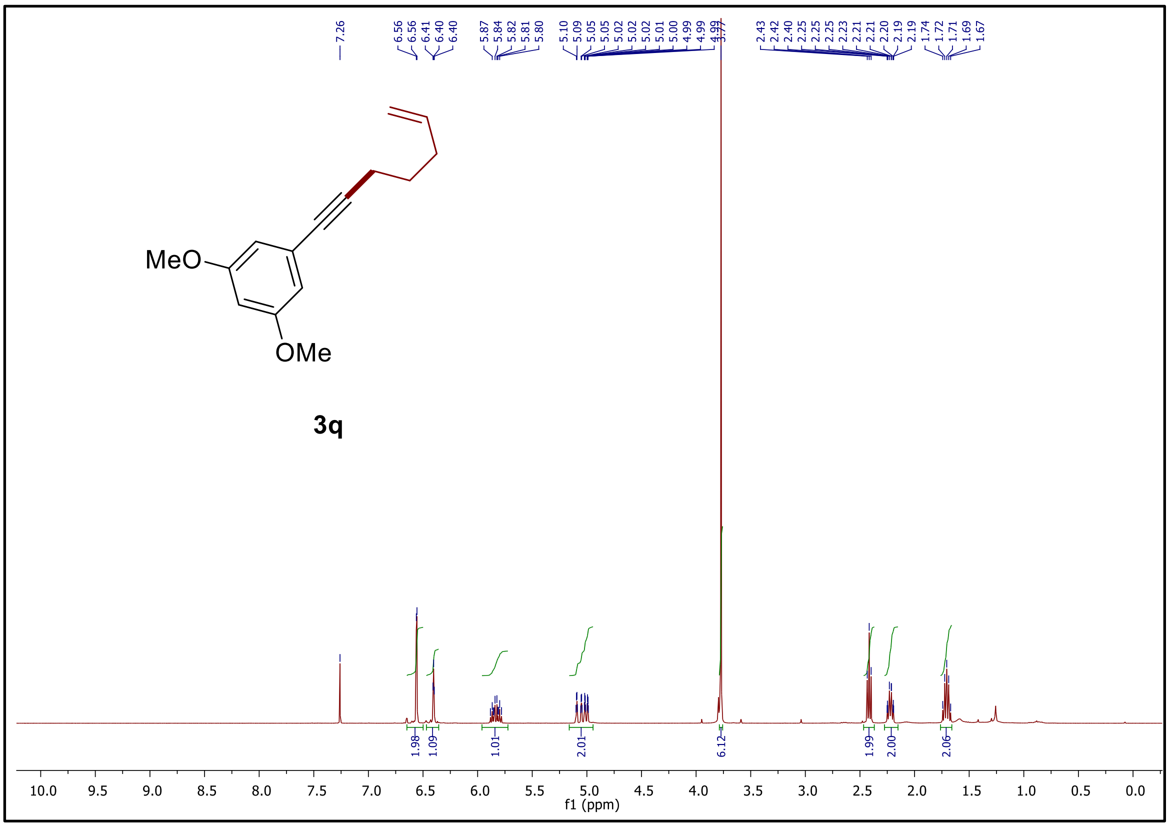


Figure S25. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3p** in $CDCl_3$ at 298K.



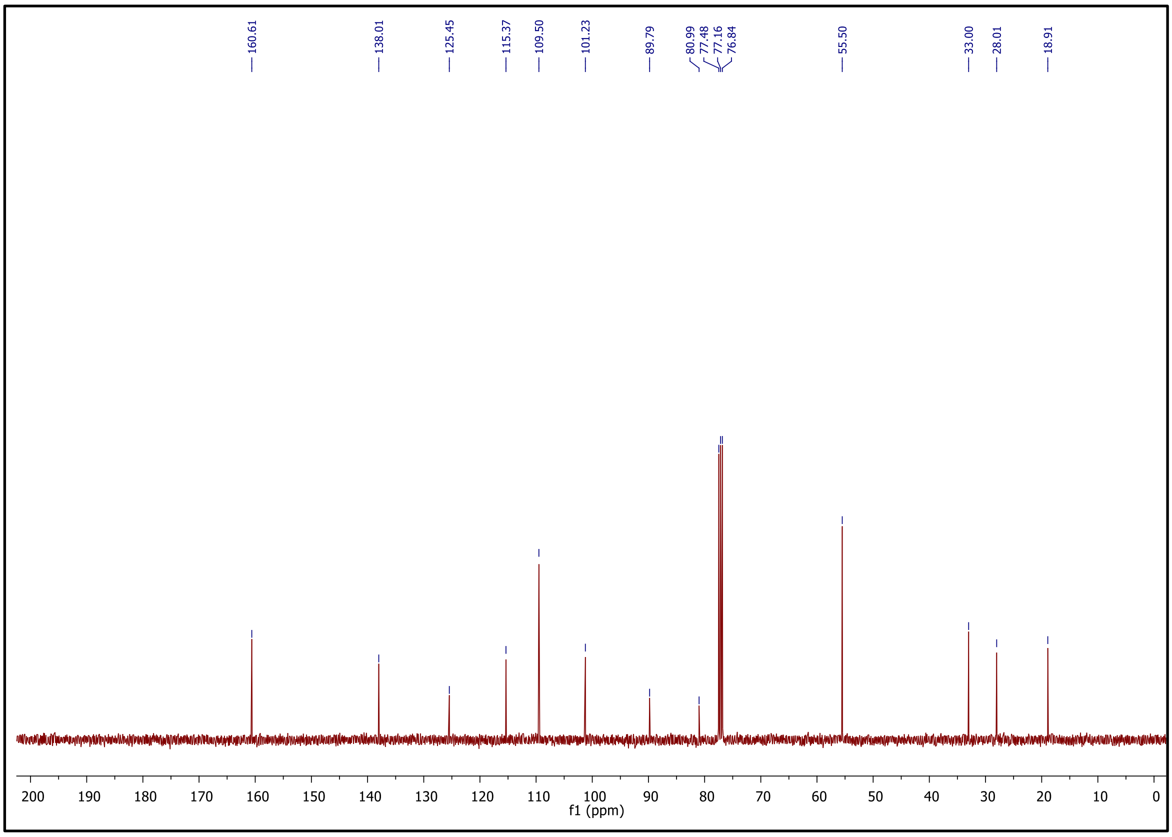
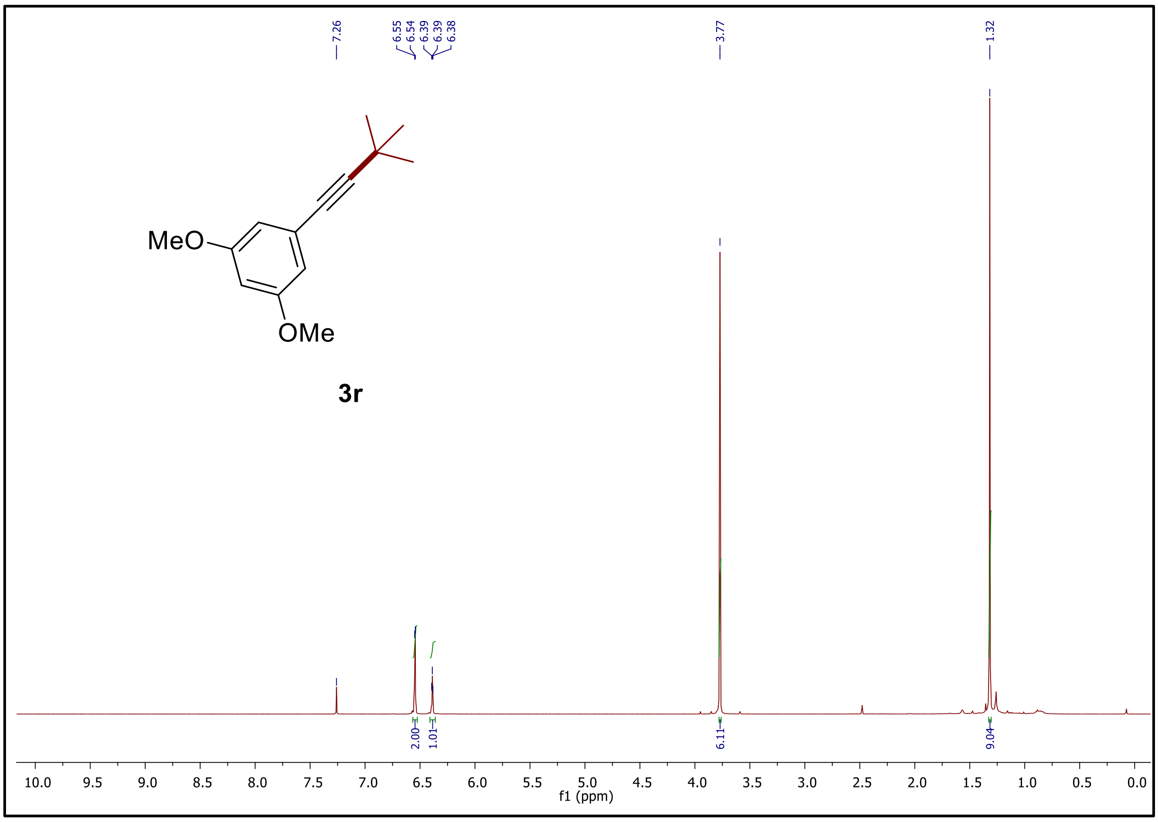


Figure S26. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3q** in $CDCl_3$ at 298K.



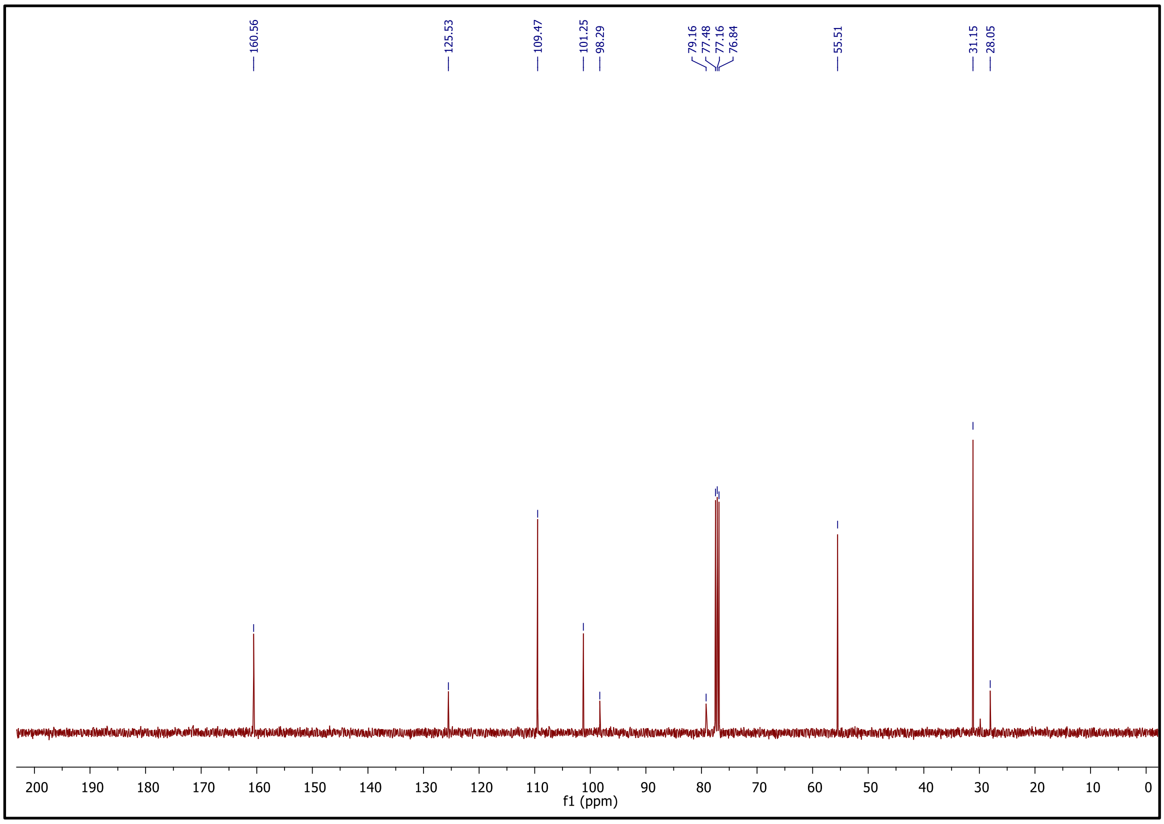
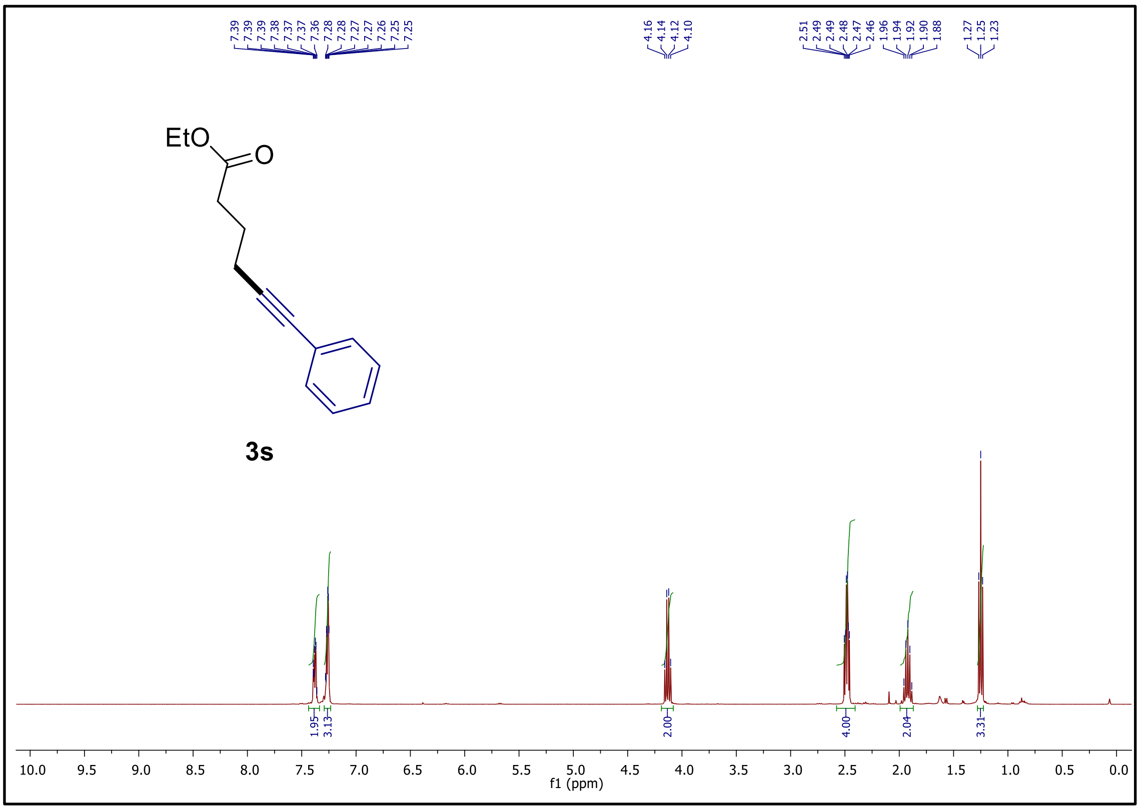


Figure S27. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3r** in $CDCl_3$ at 298K.



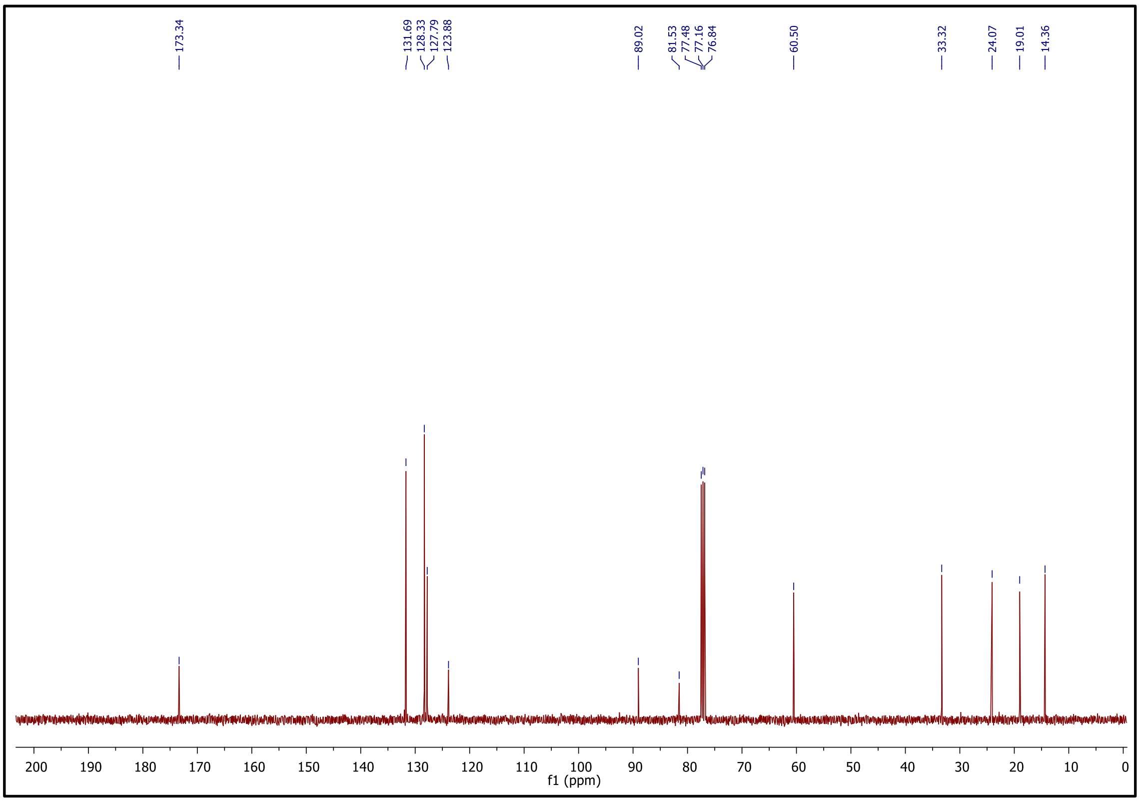
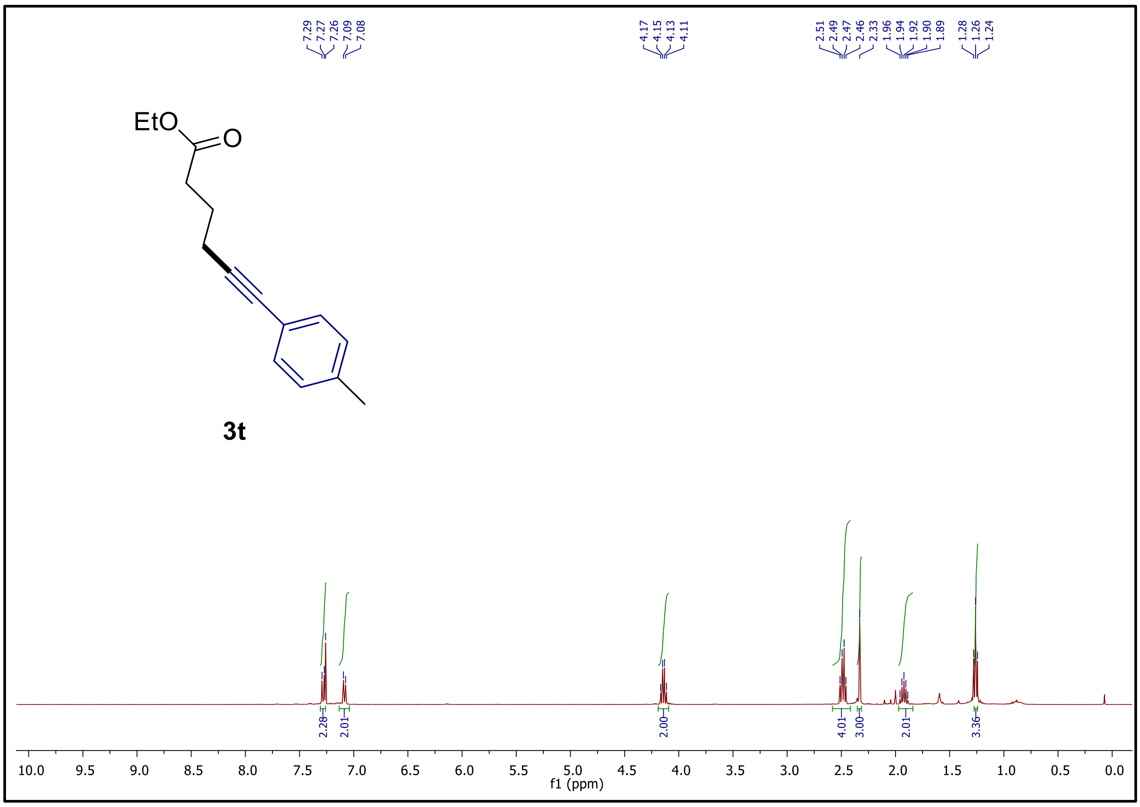


Figure S28. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3s** in $CDCl_3$ at 298K.



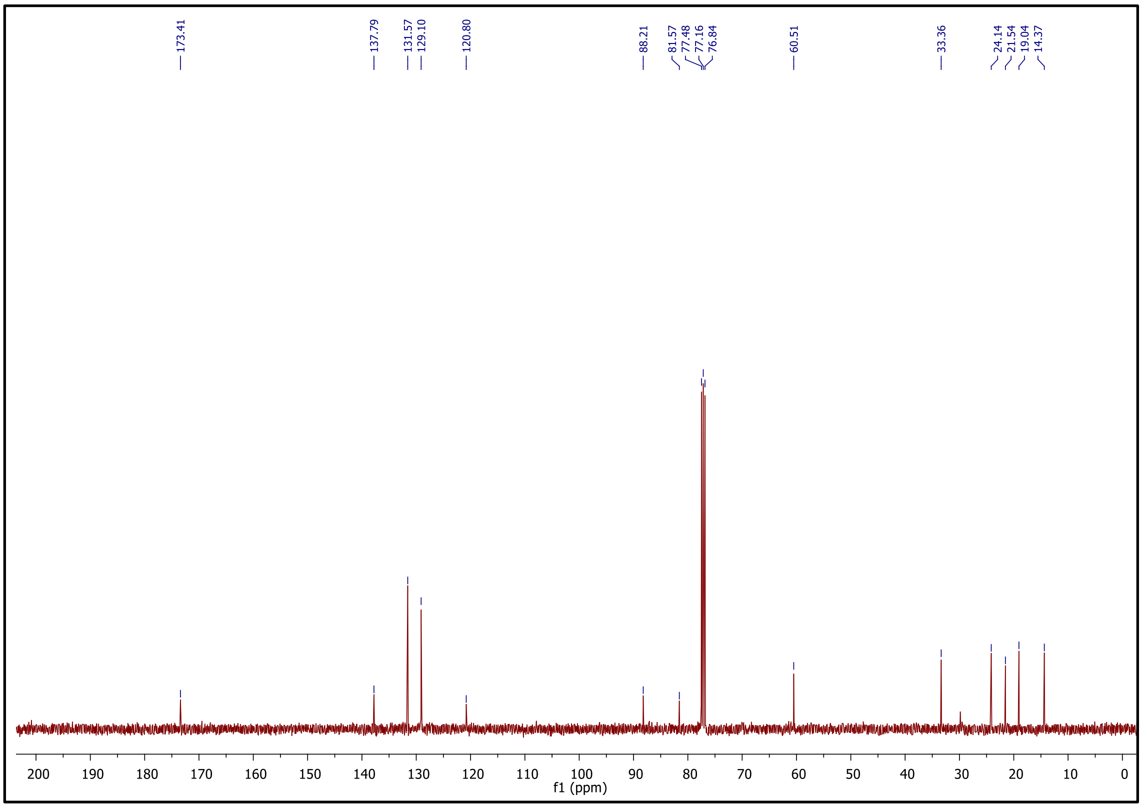
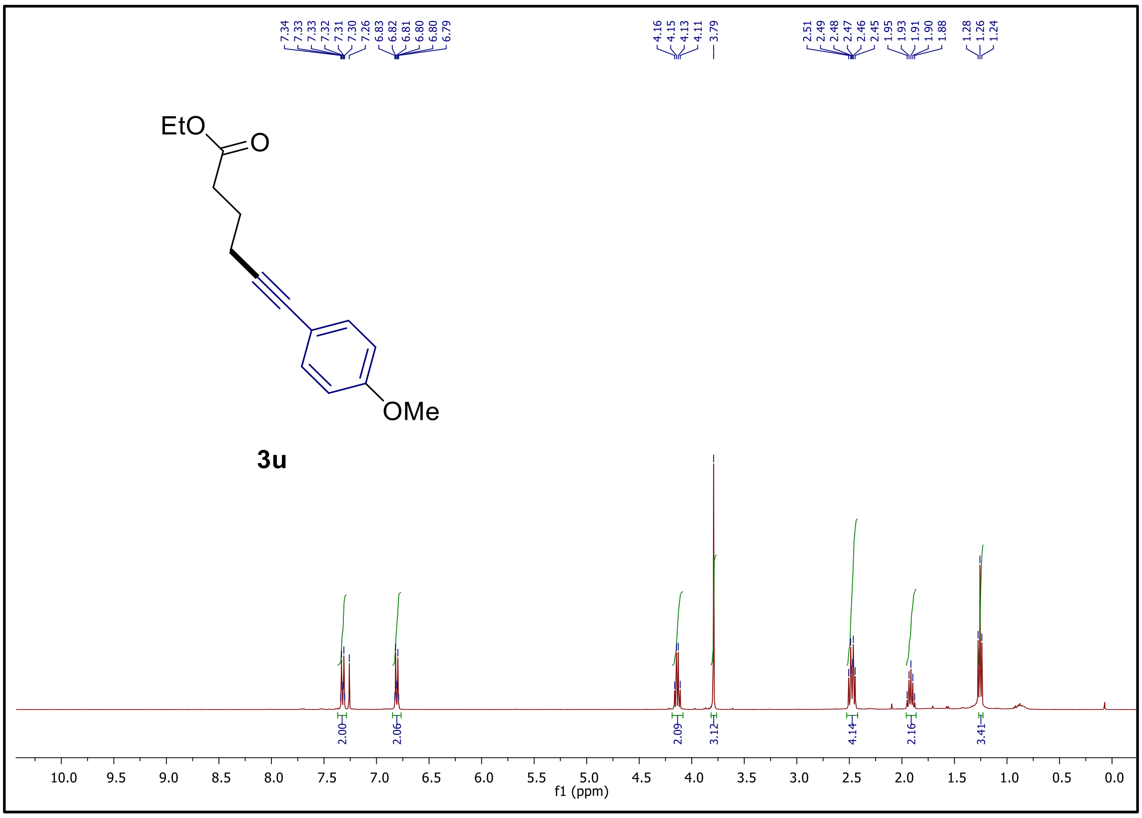


Figure S29. [1]**H NMR** (400 MHz, top) and ^{13}**C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3t** in $CDCl_3$ at 298K.



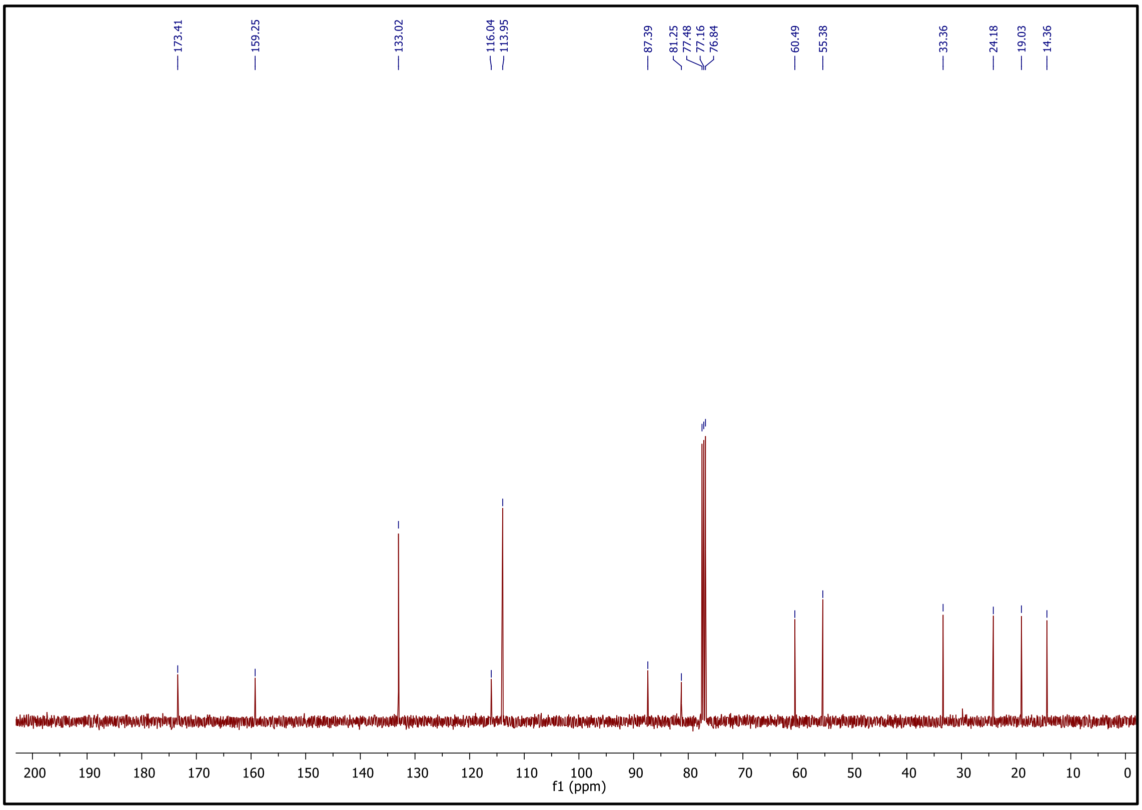
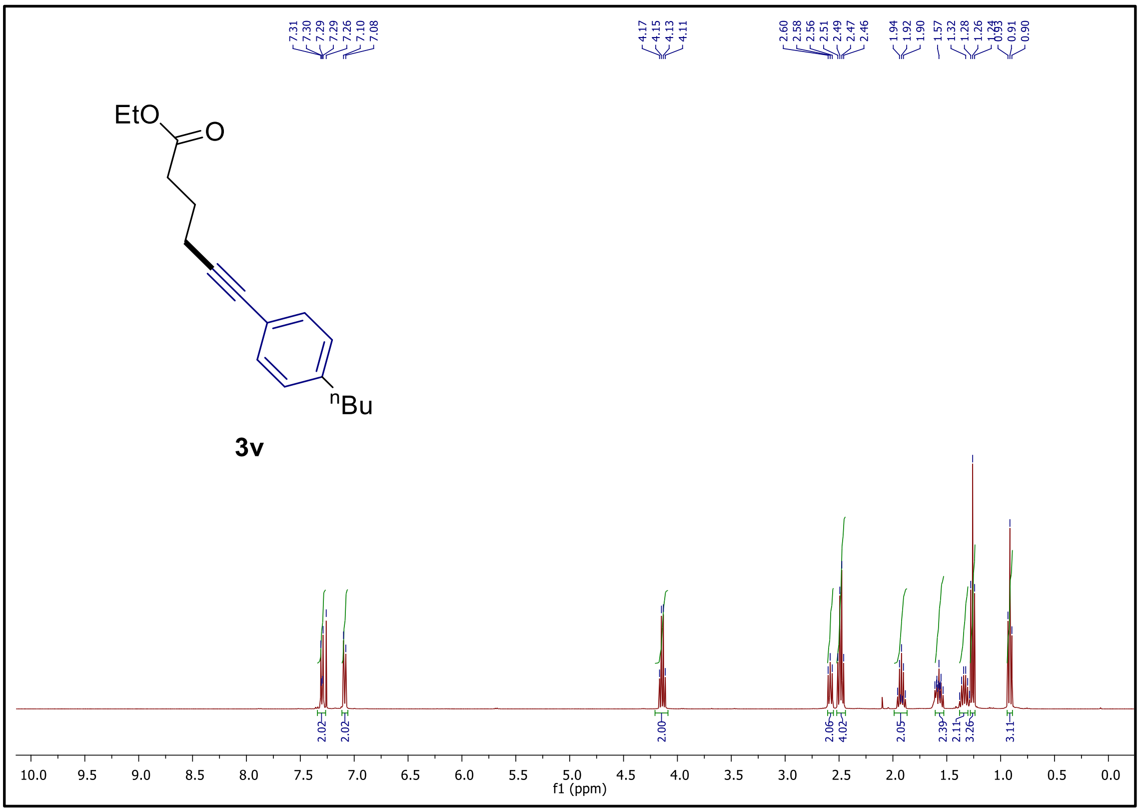


Figure S30. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3u** in $CDCl_3$ at 298K.



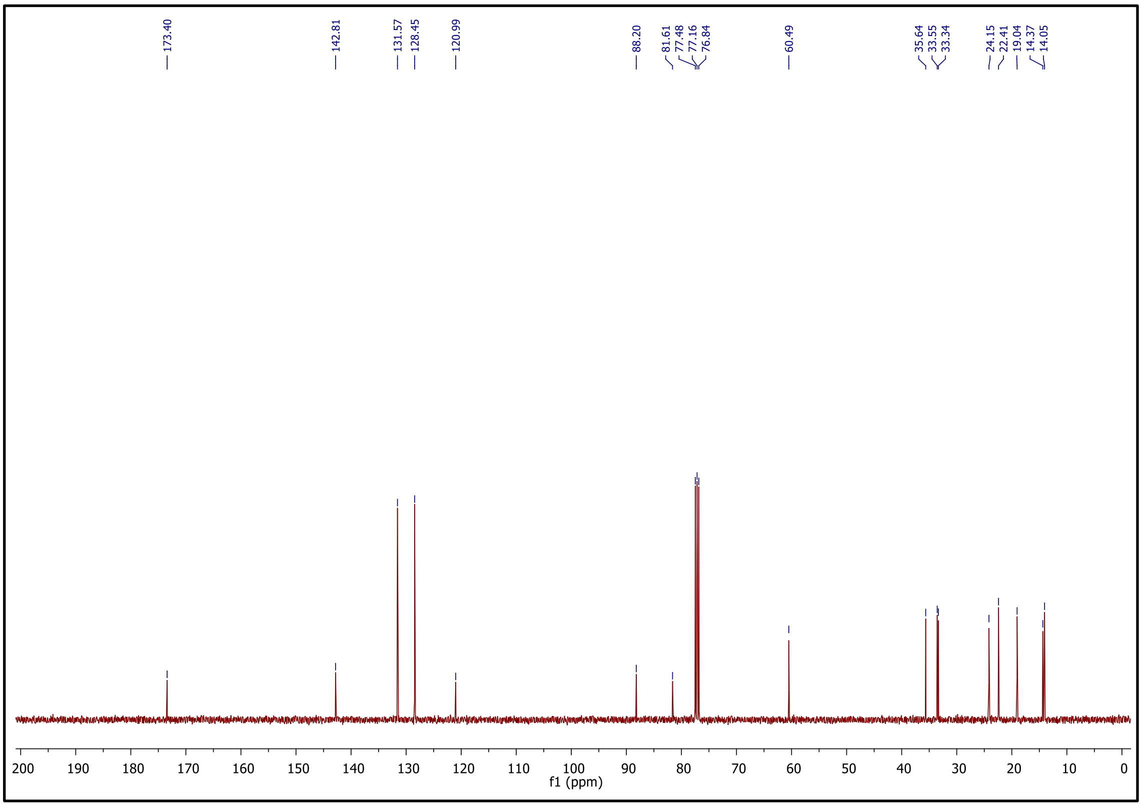
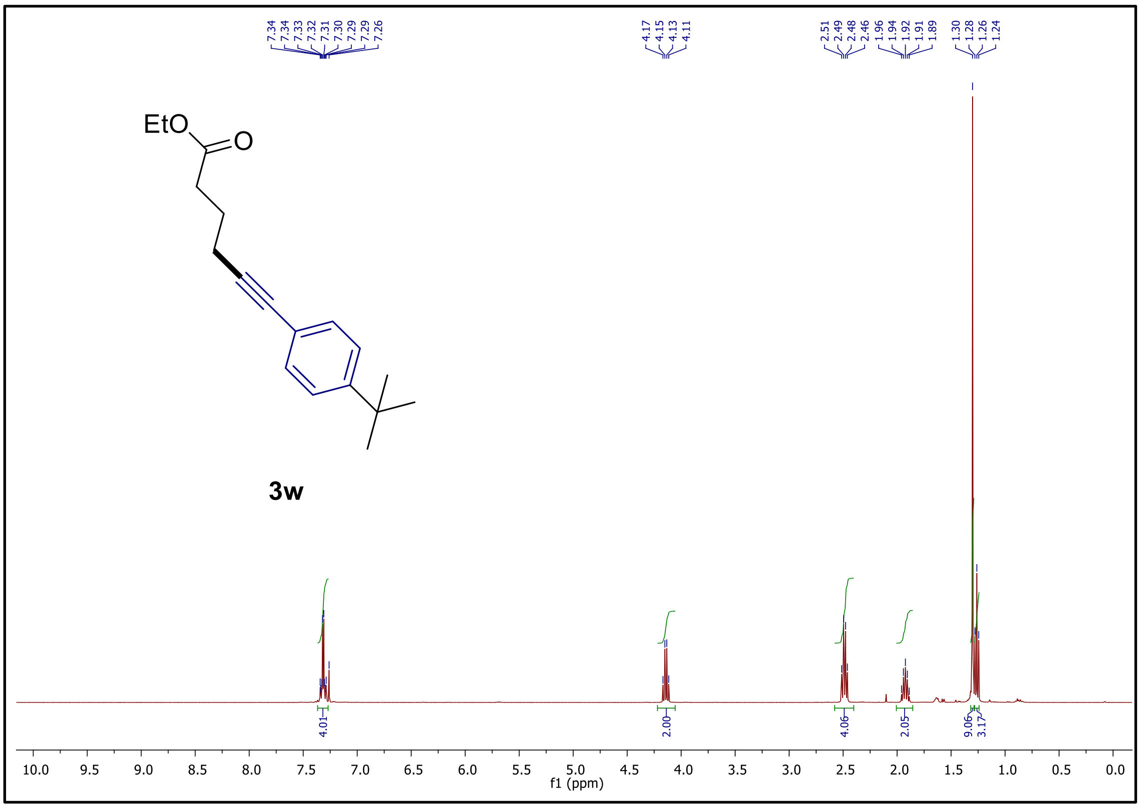


Figure S31. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3v** in $CDCl_3$ at 298K.



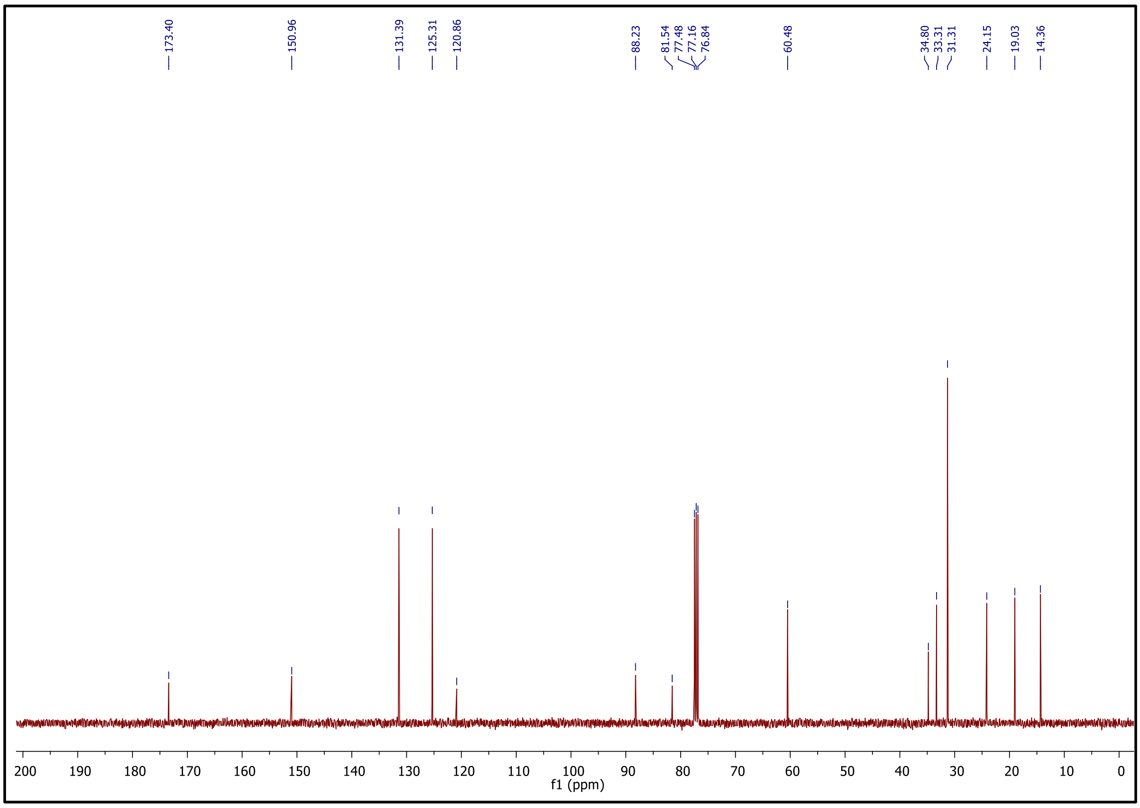


Figure S32. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3w** in $CDCl_3$ at 298K.

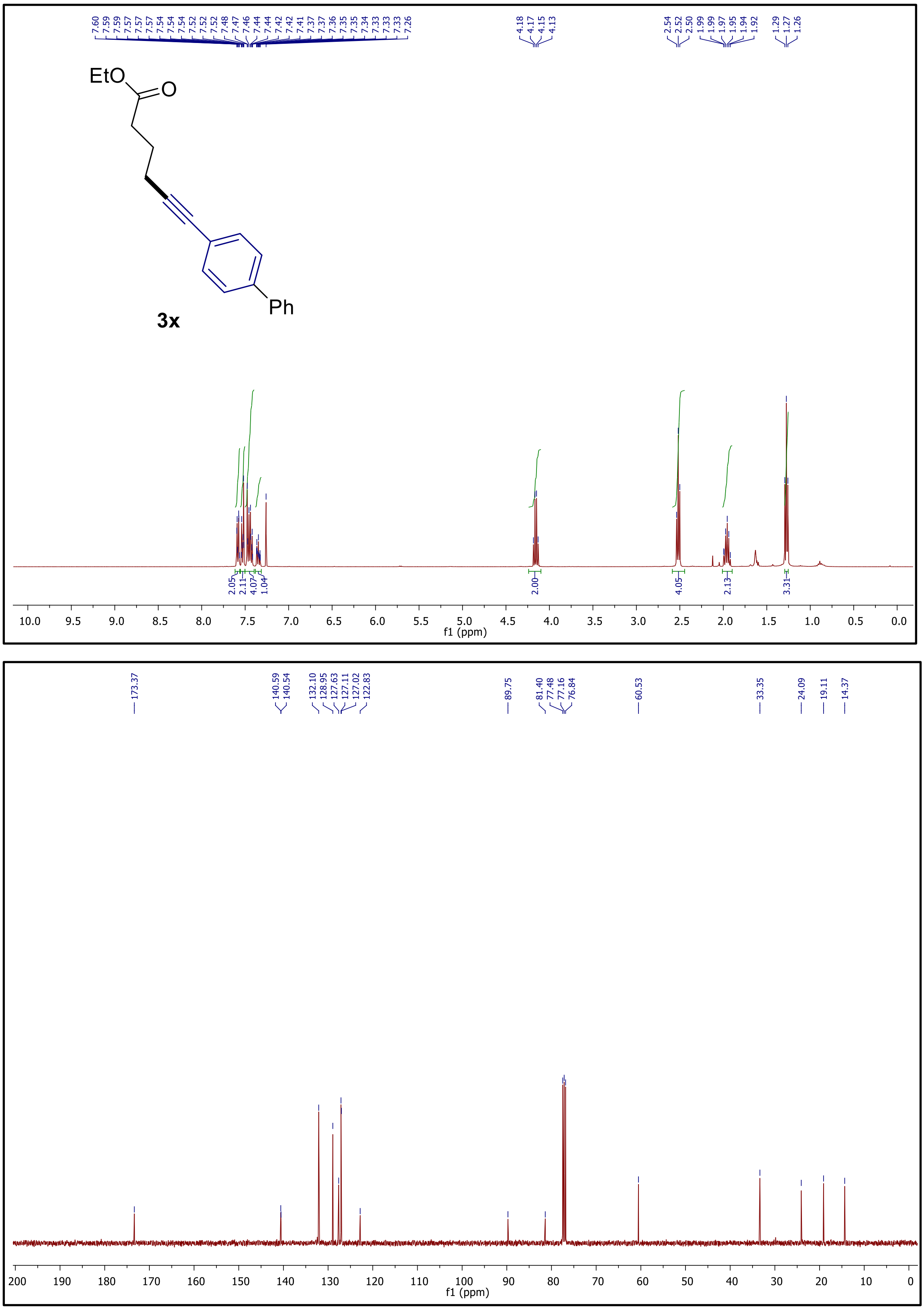
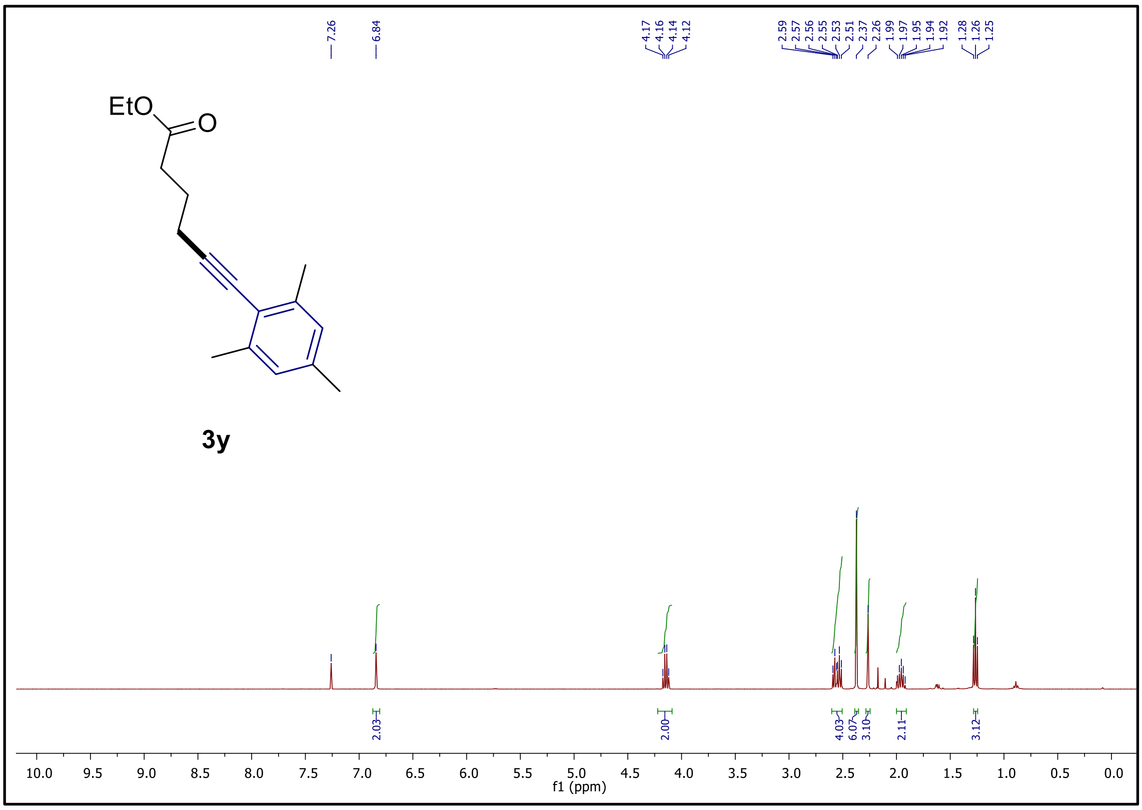


Figure S33. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3x** in $CDCl_3$ at 298K.



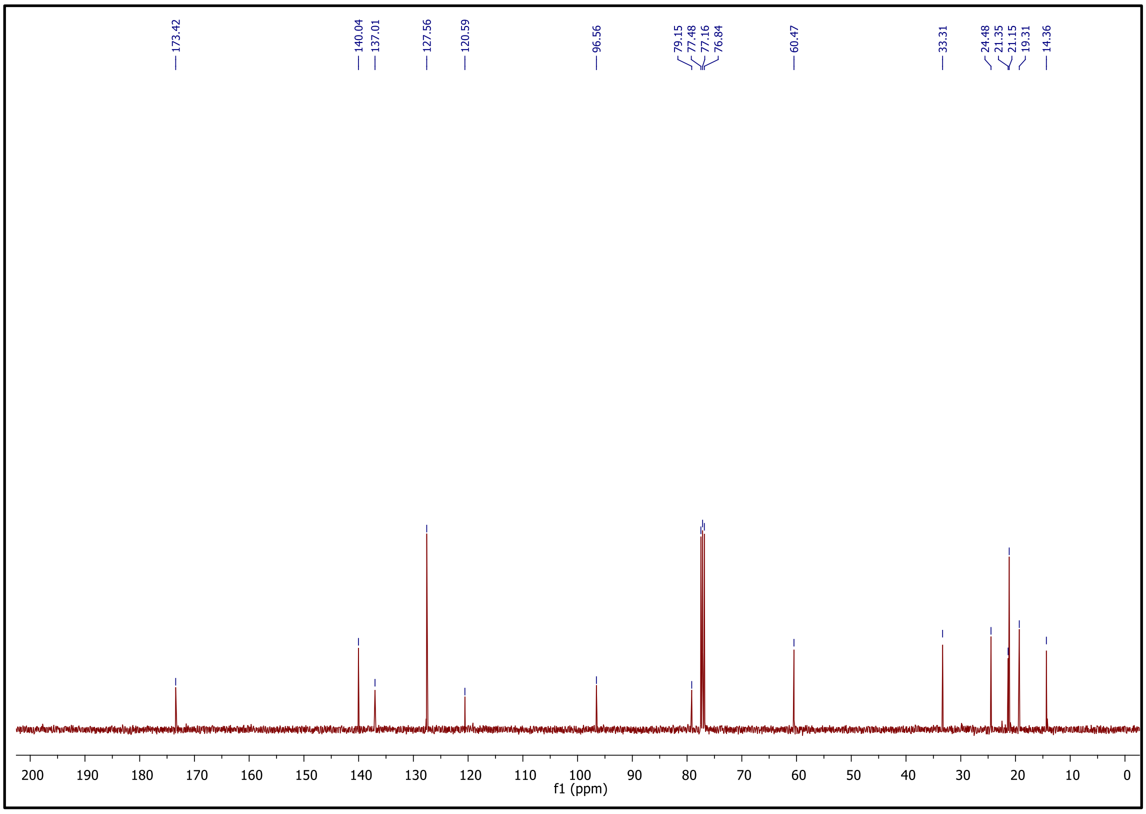
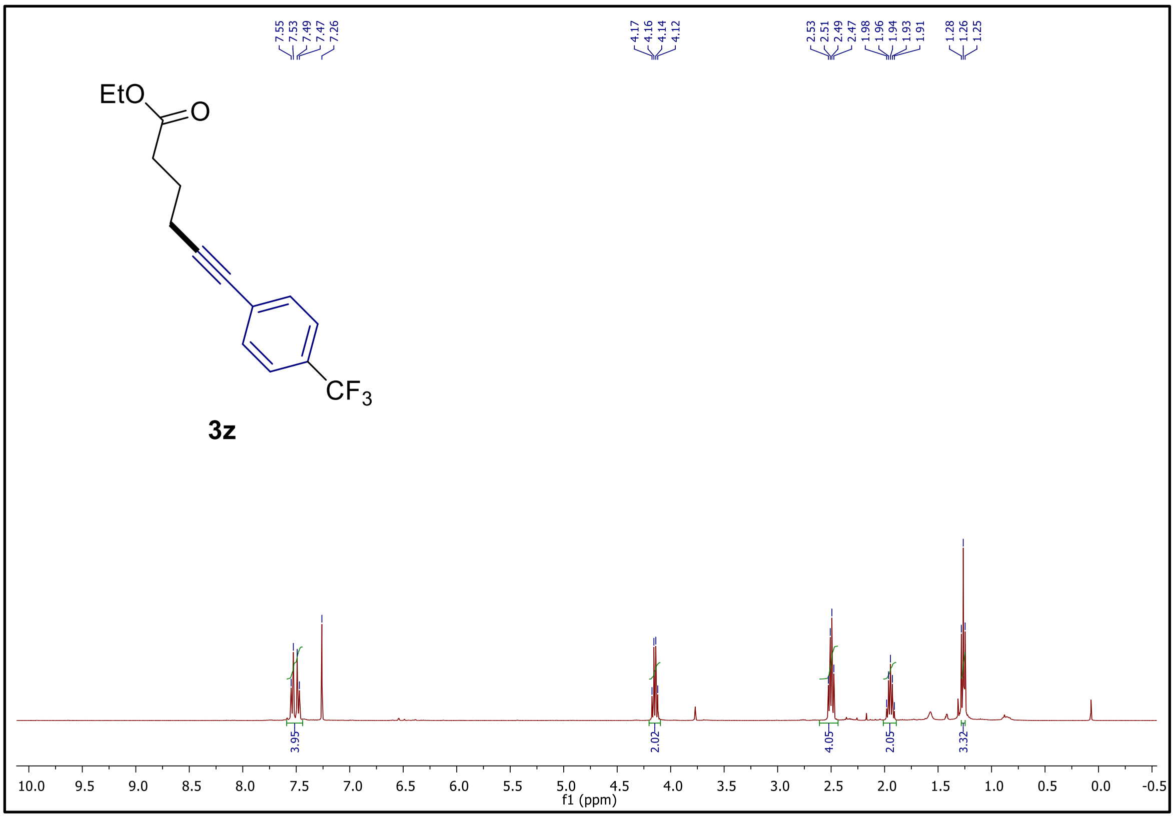


Figure S34. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3y** in $CDCl_3$ at 298K.



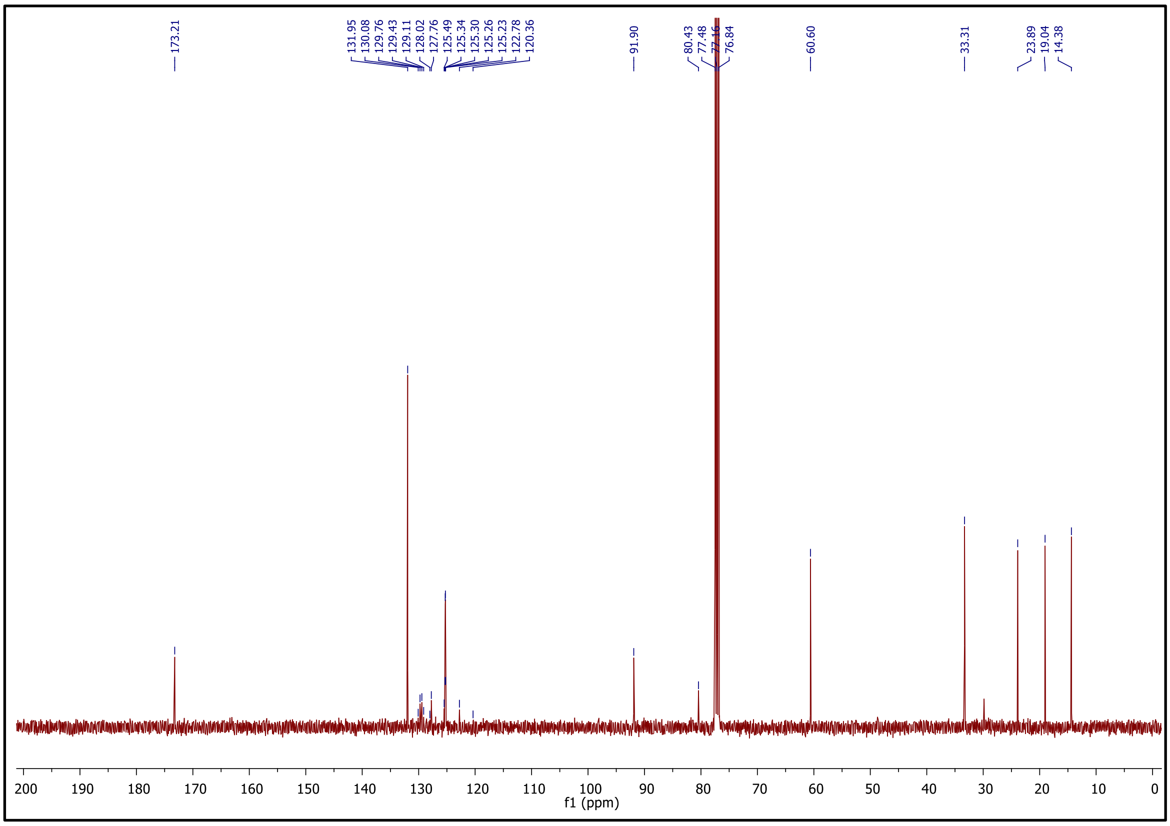


Figure S35. **¹H NMR** (400 MHz, top) and **¹³C {¹H} NMR** (100 MHz, bottom) Spectra of **3z** in $CDCl_3$ at 298K.

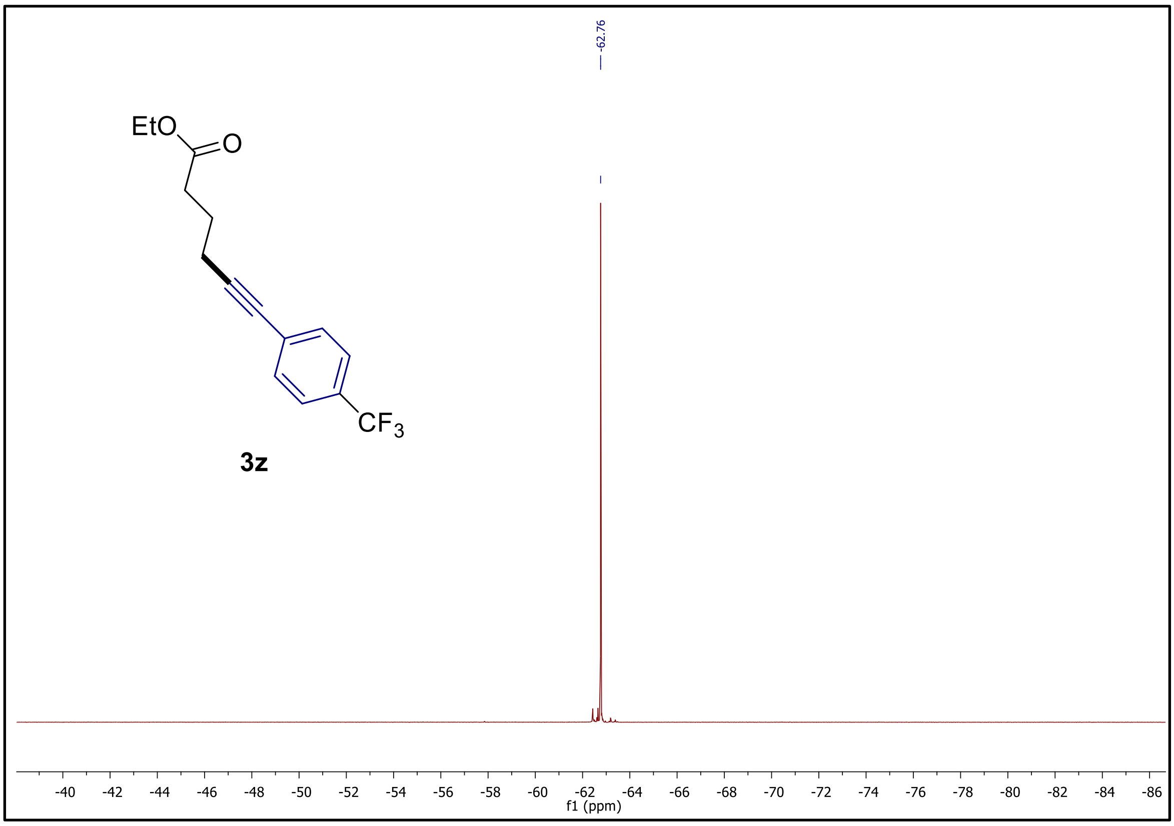
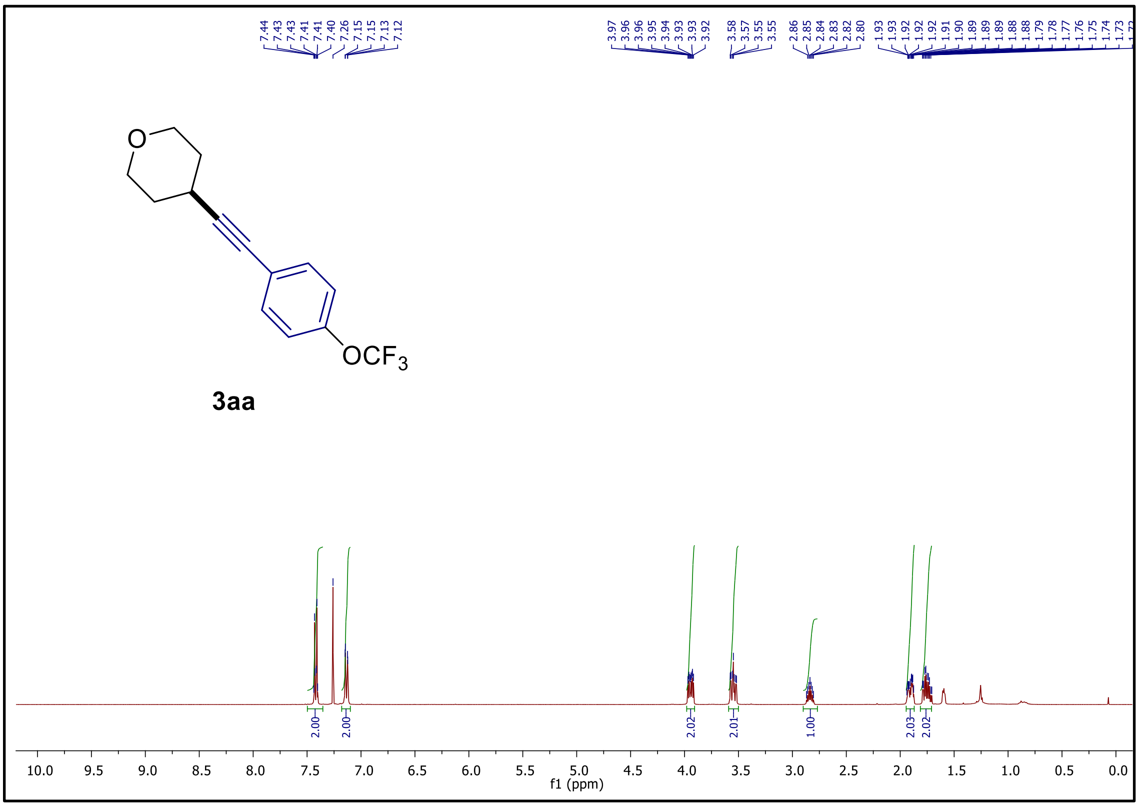


Figure S36. **^{19}F NMR** (471 MHz) Spectra of **3z** in $CDCl_3$ at 298K.



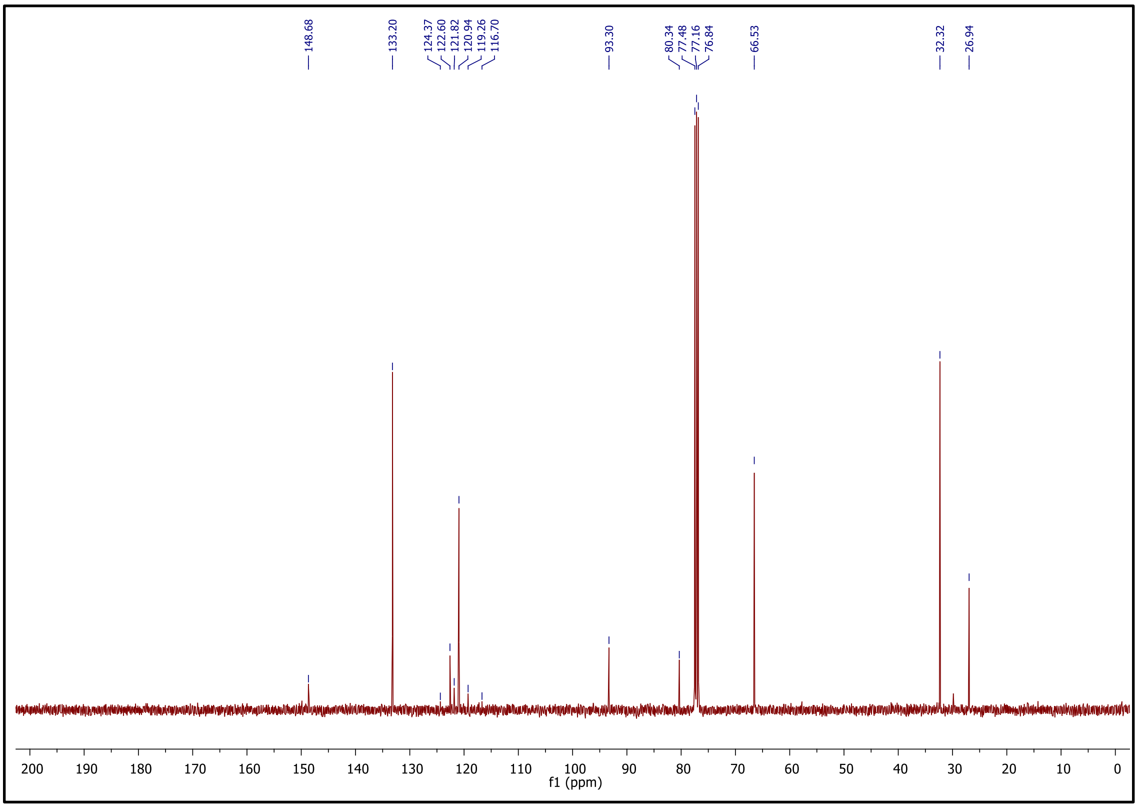


Figure S37. [1]**H NMR** (400 MHz, top) and ^{13}**C {**^{1}**H} NMR** (100 MHz, bottom) Spectra of **3aa** in $CDCl_3$ at 298K.

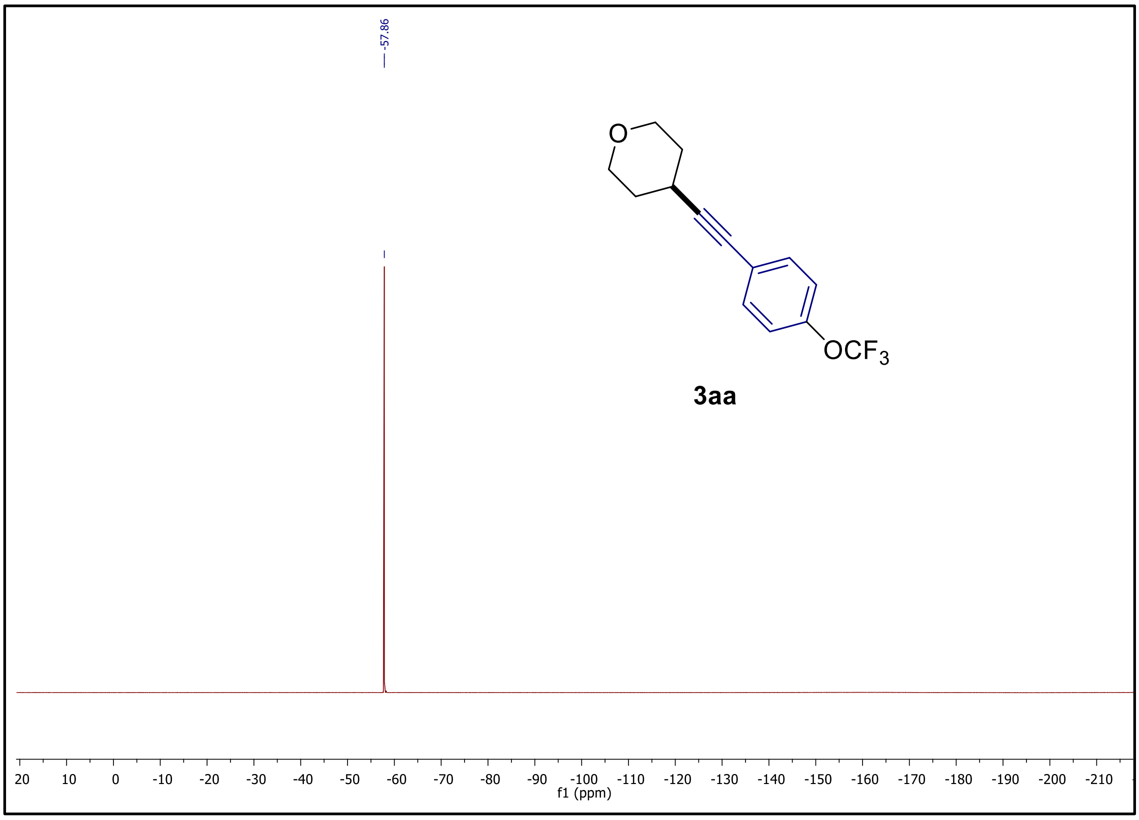
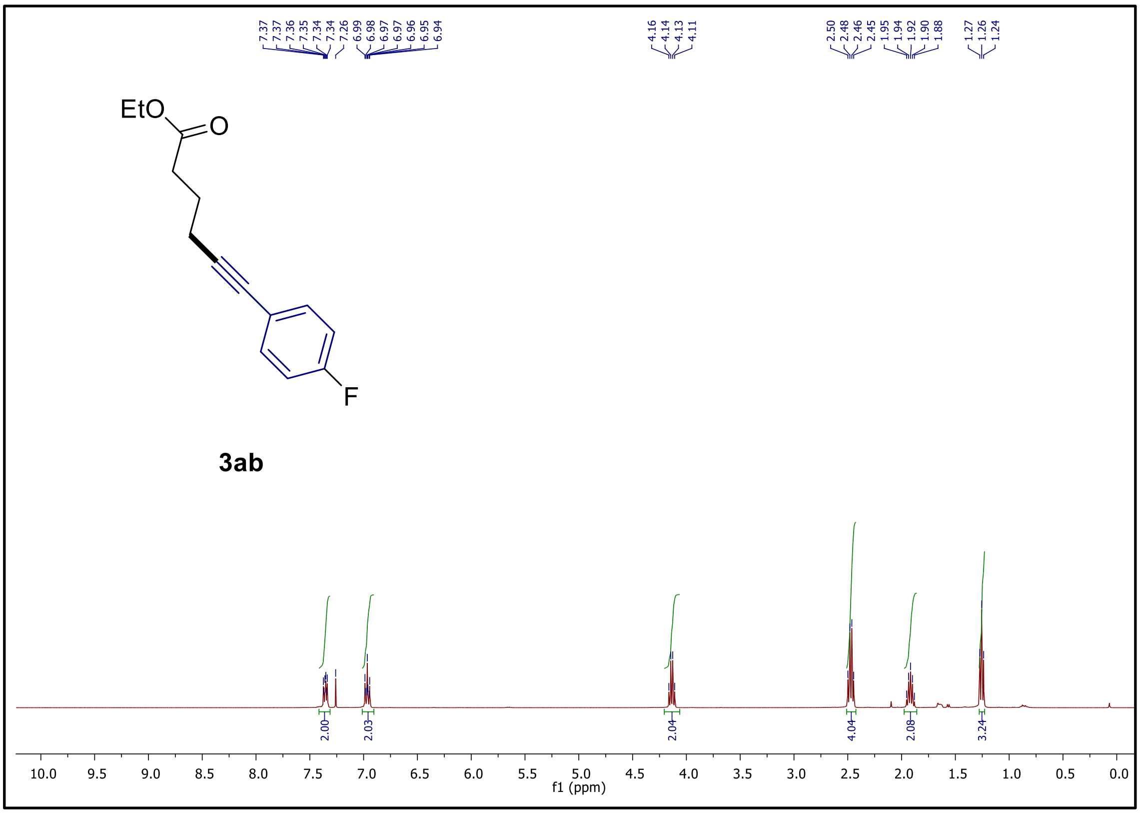


Figure S38. **^{19}F NMR** (471 MHz) Spectra of **3aa** in $CDCl_3$ at 298K.3aa



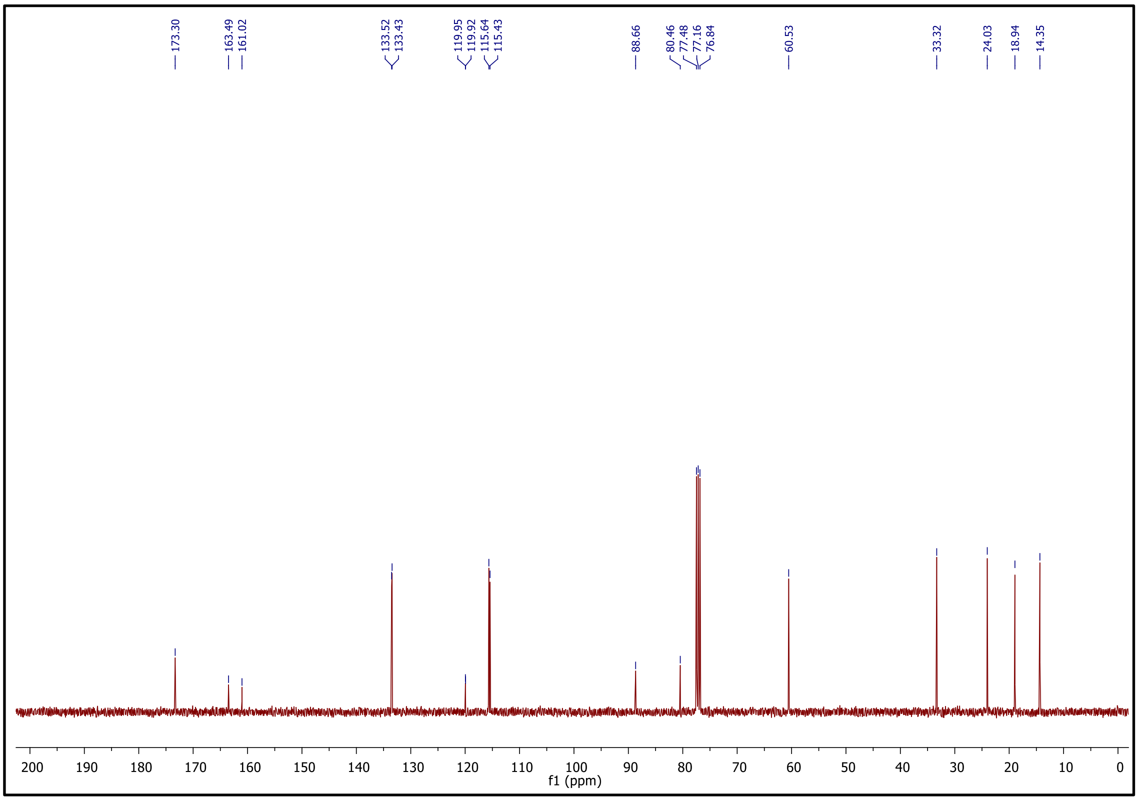


Figure S39. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ab** in $CDCl_3$ at 298K.

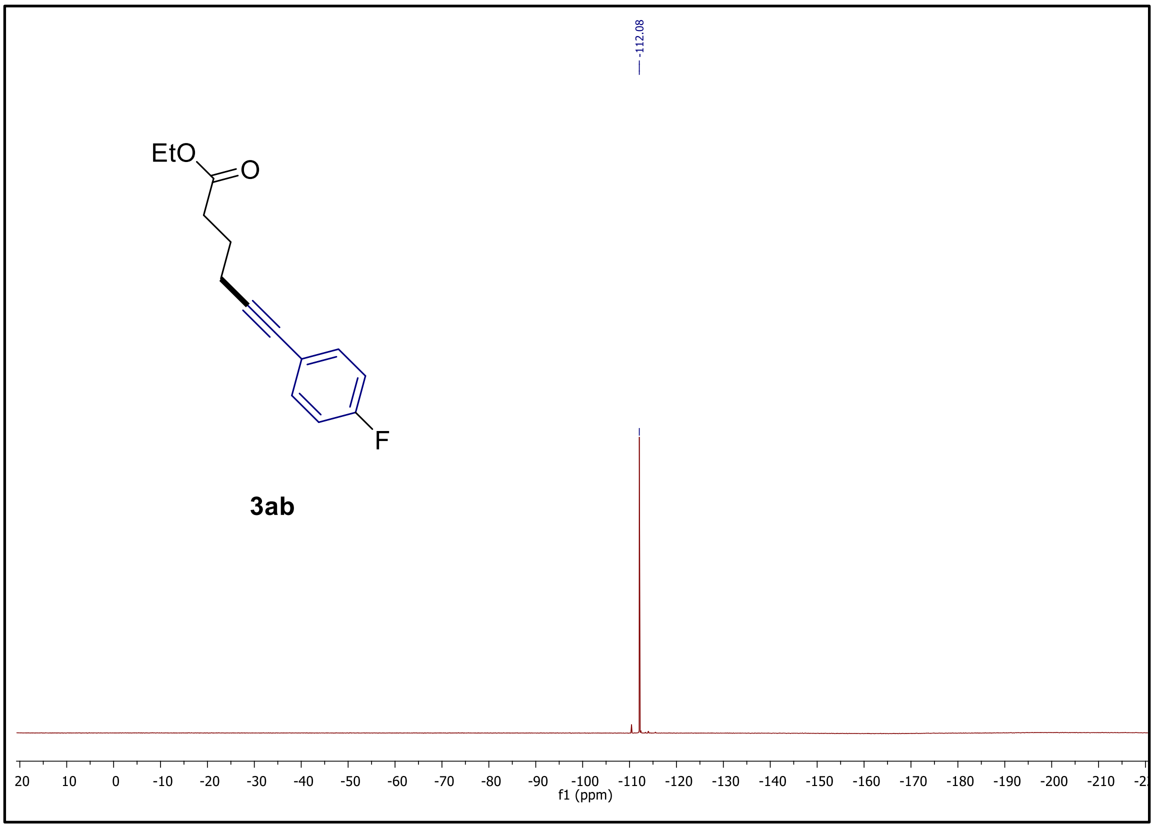
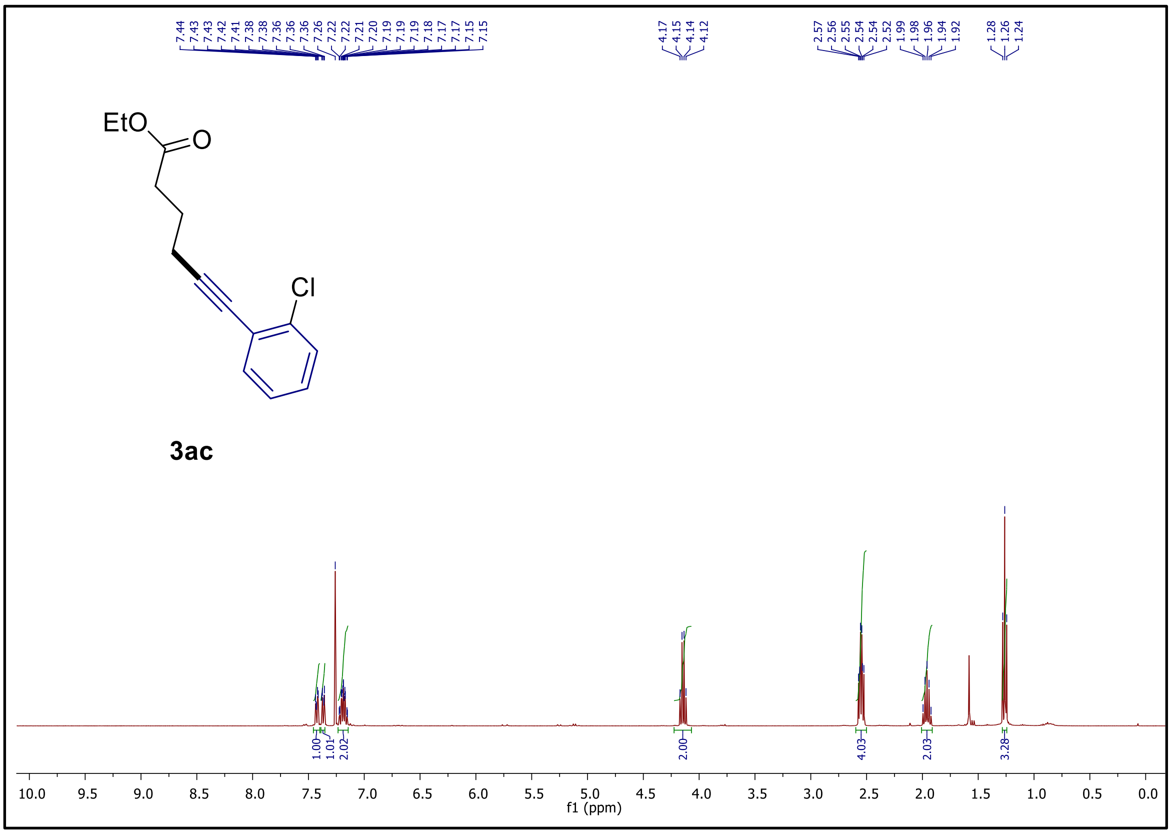


Figure S40. **^{19}F NMR** (471 MHz) Spectra of **3ab** in $CDCl_3$ at 298K.3ab



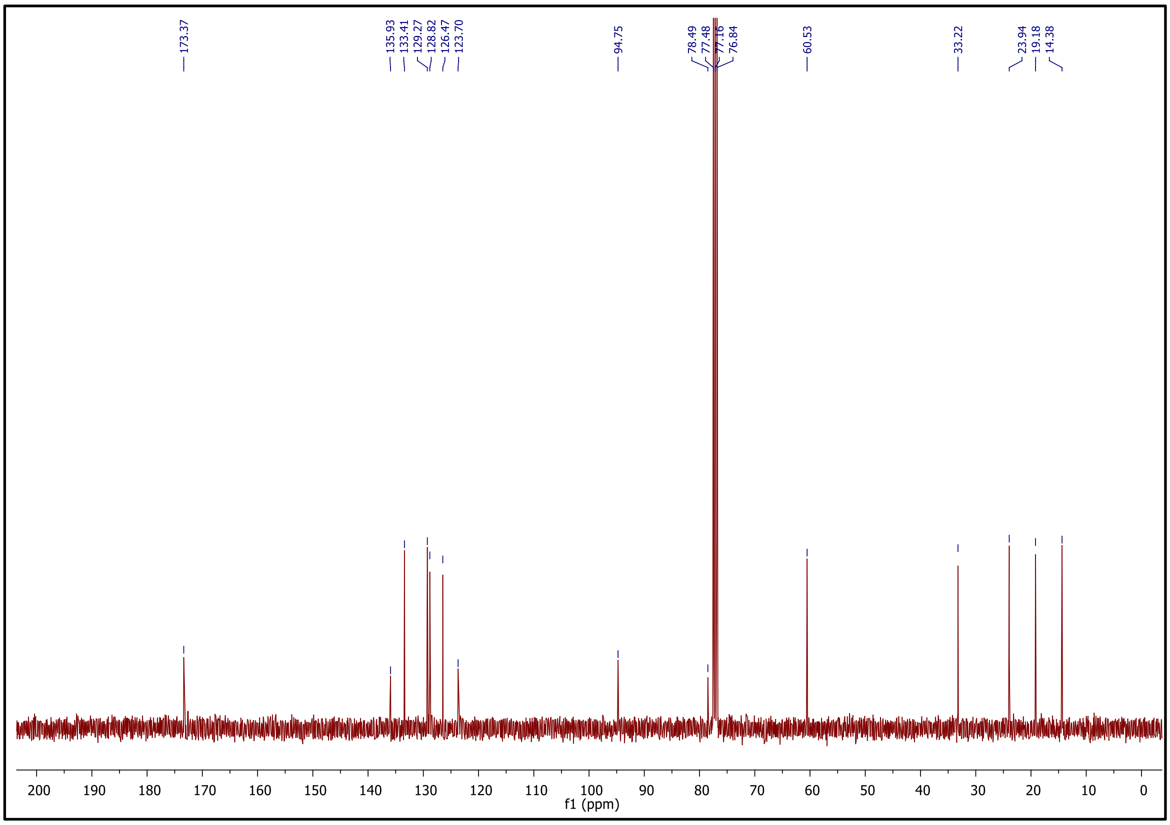
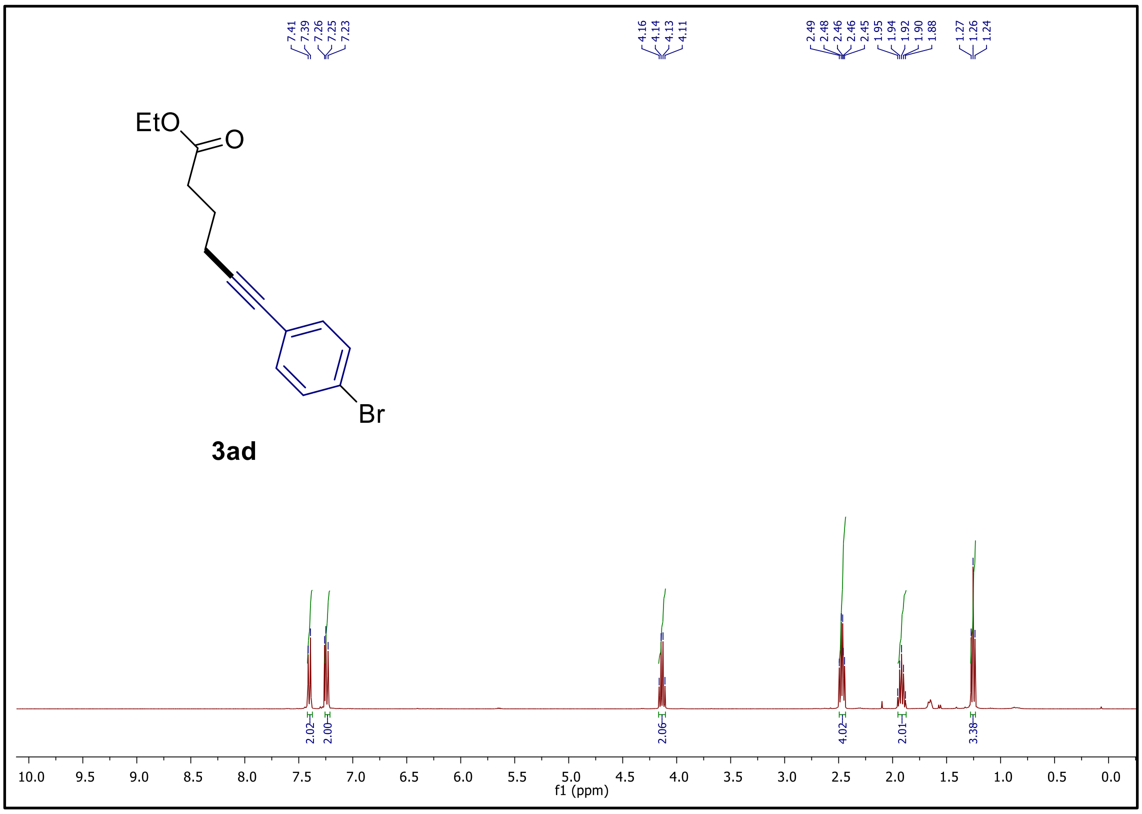


Figure S41. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ac** in $CDCl_3$ at 298K.



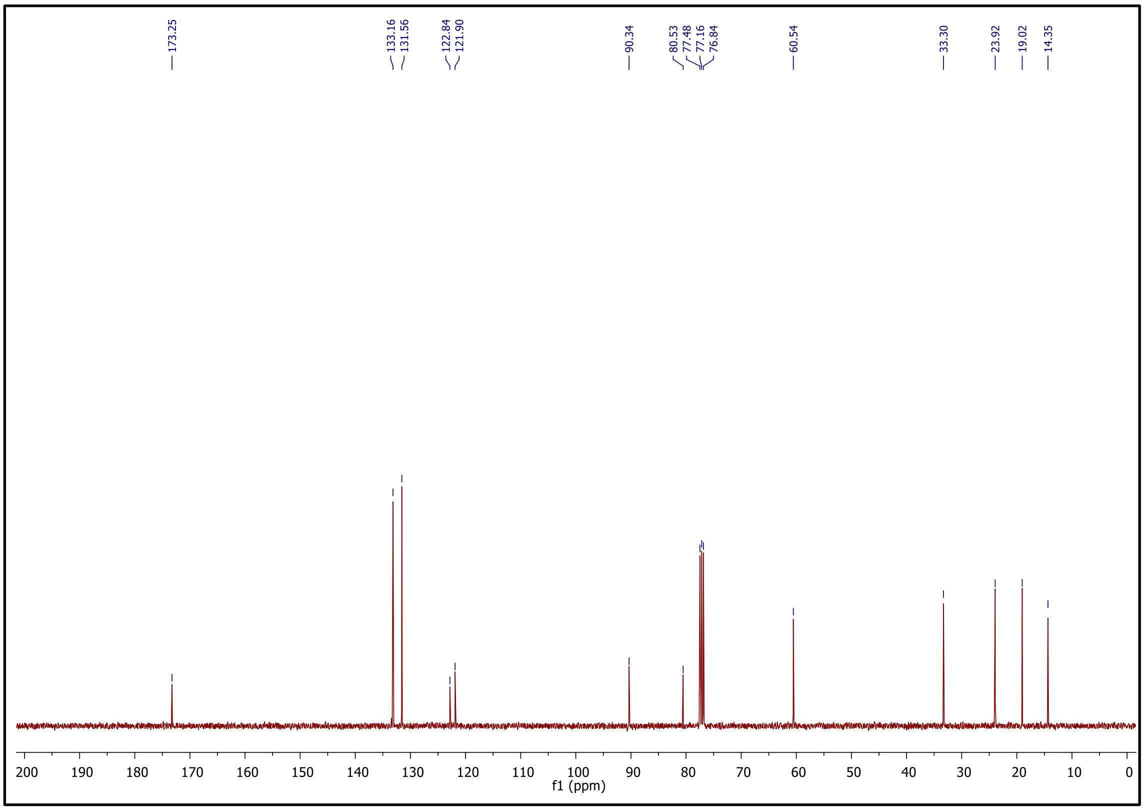
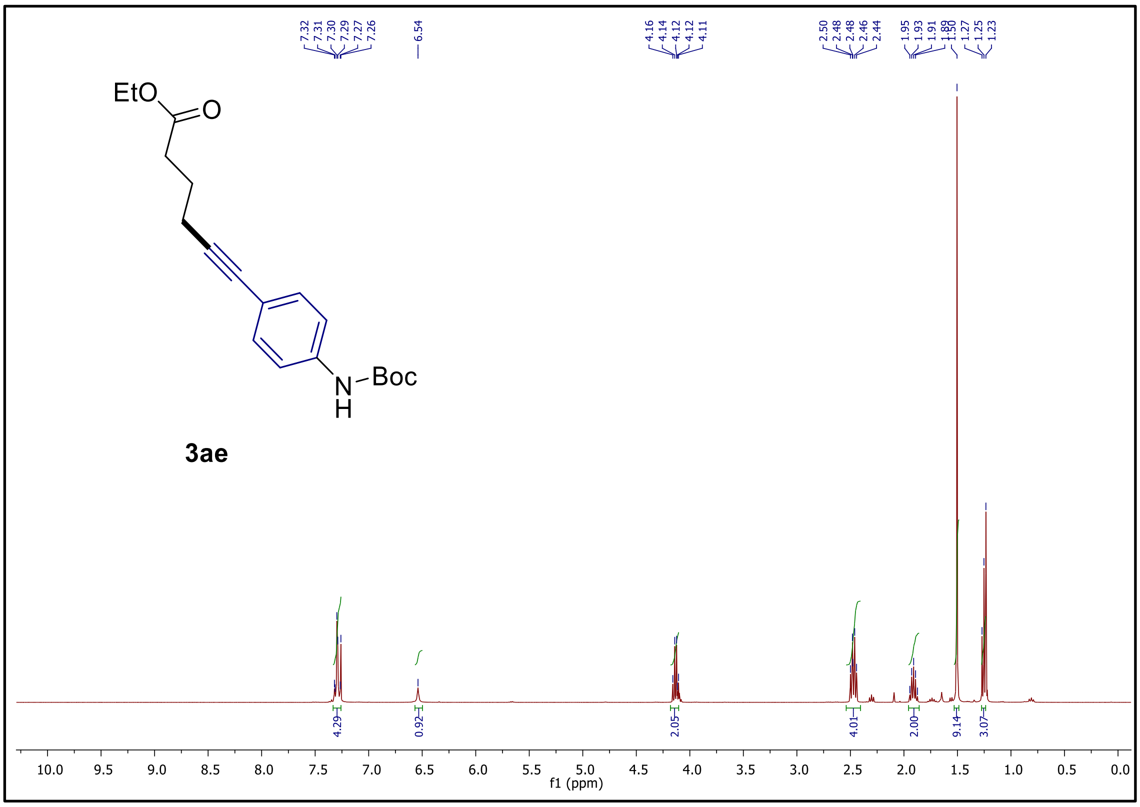


Figure S42. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ad** in $CDCl_3$ at 298K.



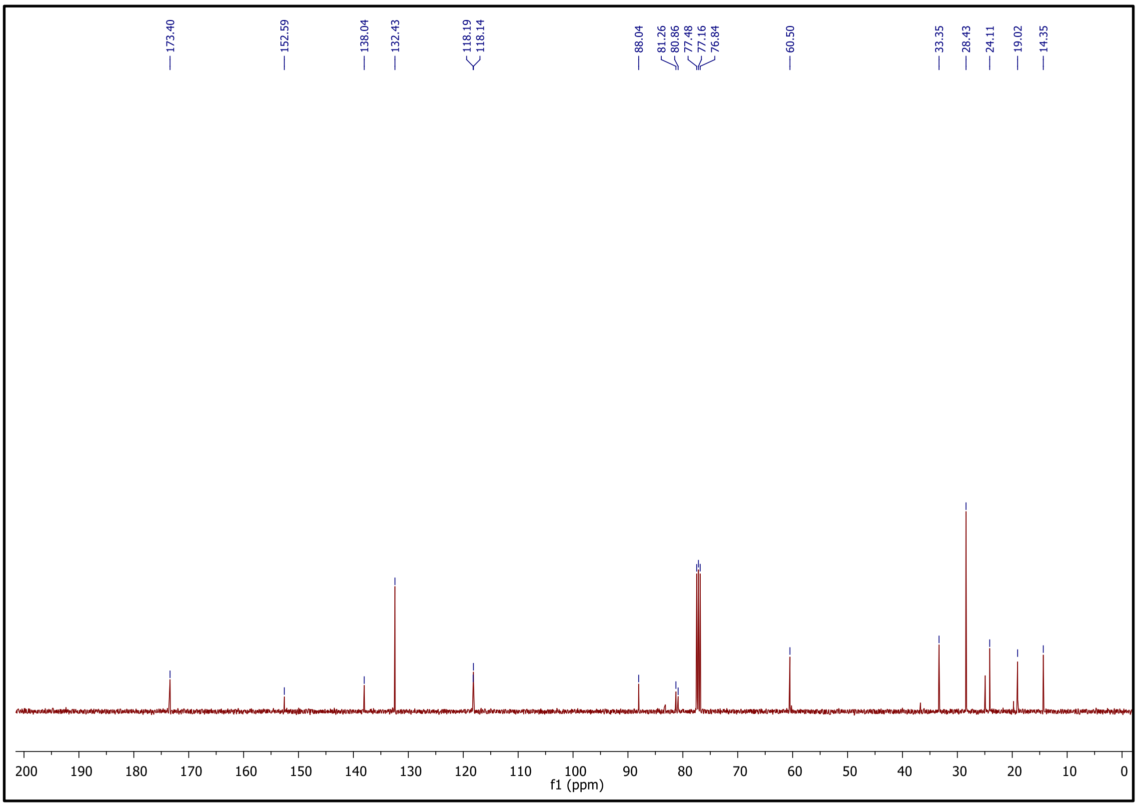
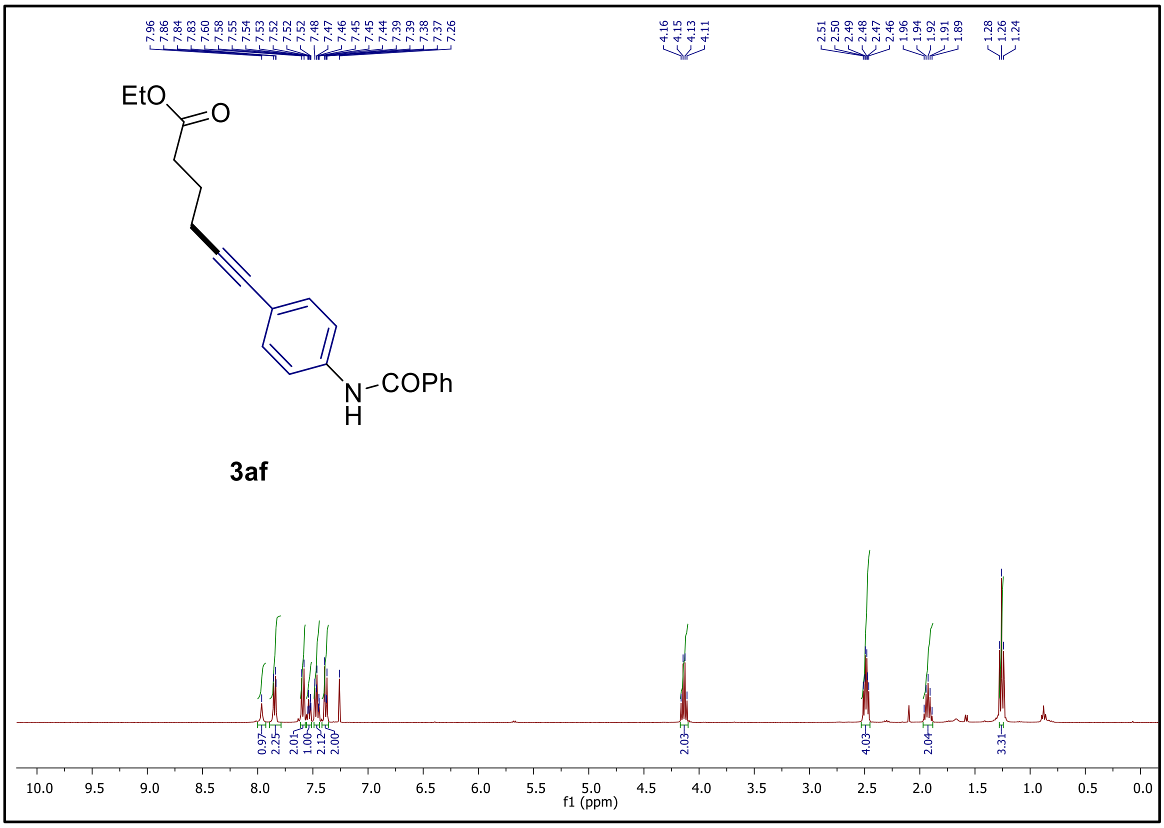


Figure S43. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ae** in $CDCl_3$ at 298K.



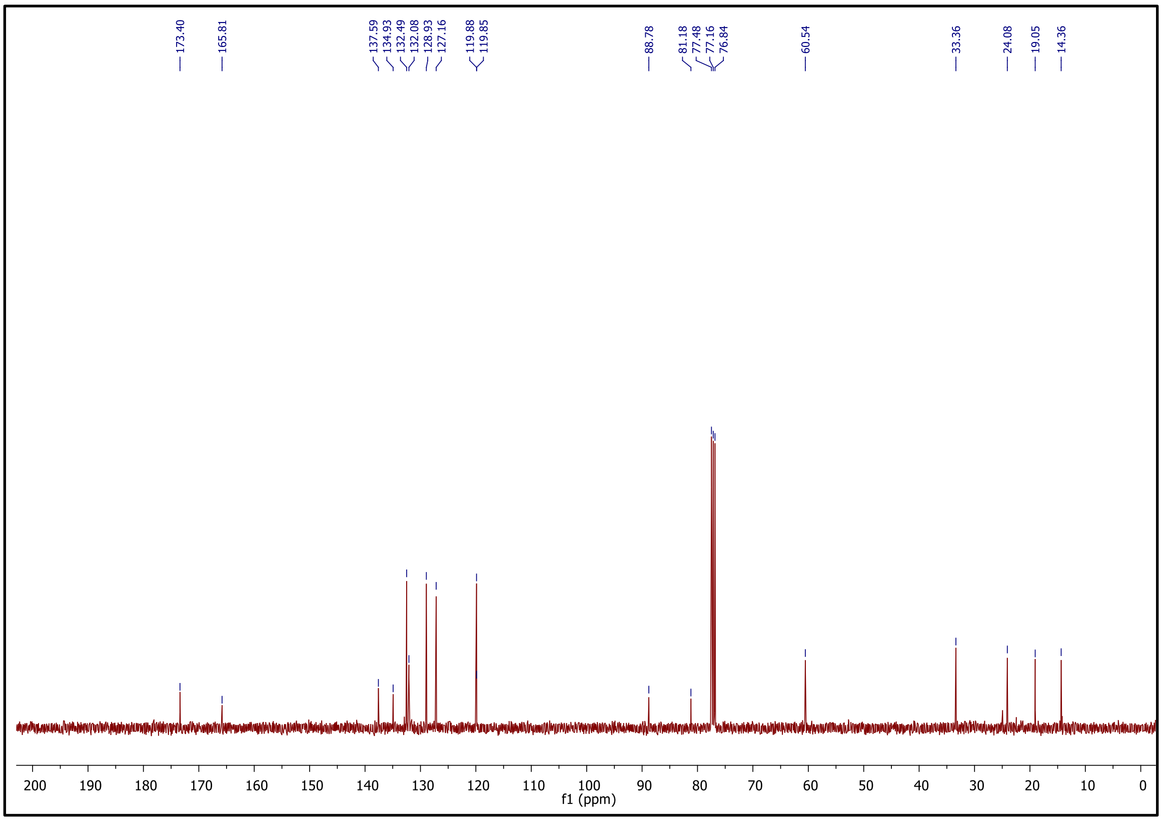
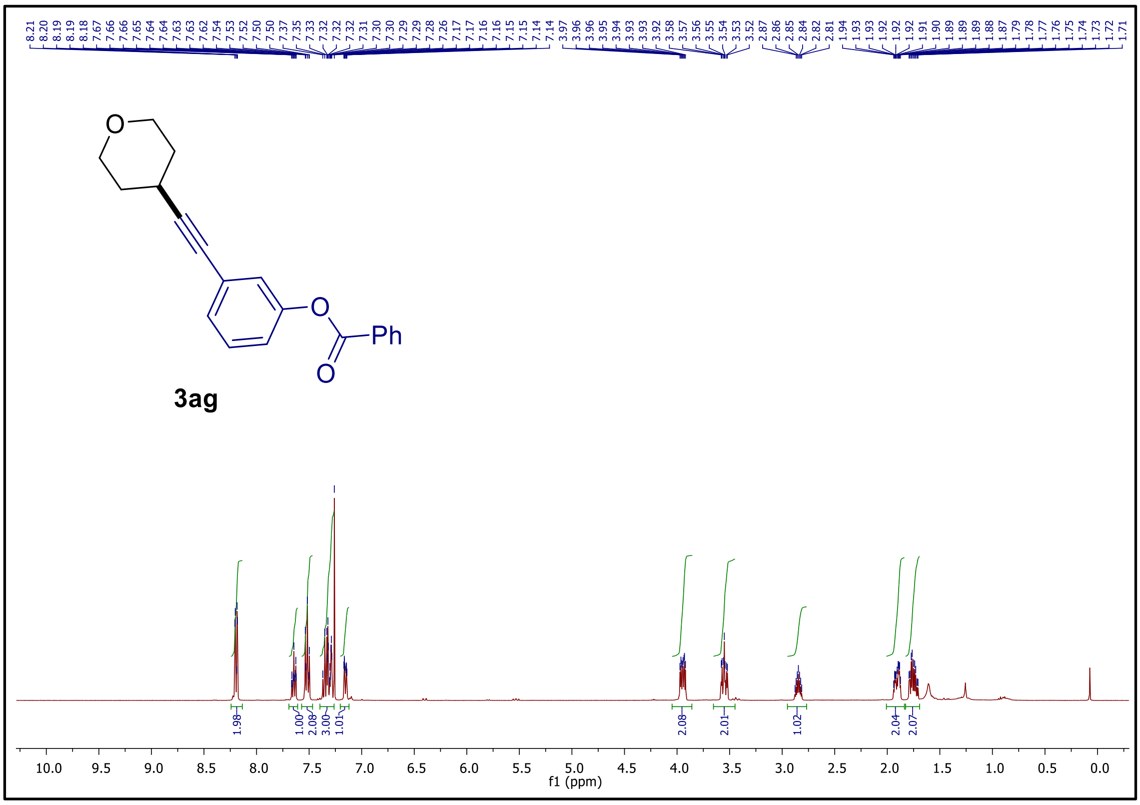


Figure S44. **[1]H NMR** (400 MHz, top) and **[13]C {[1]H} NMR** (100 MHz, bottom) Spectra of **3af** in $CDCl_3$ at 298K.



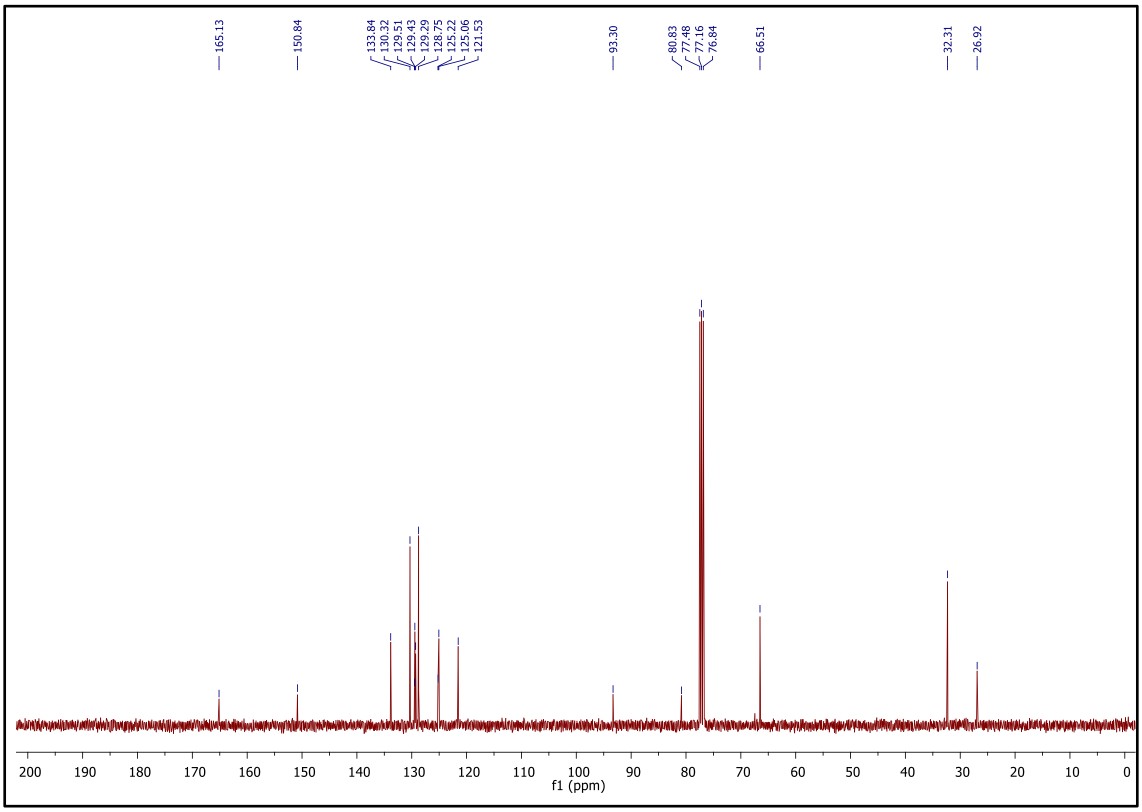


Figure S45. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ag** in $CDCl_3$ at 298K.

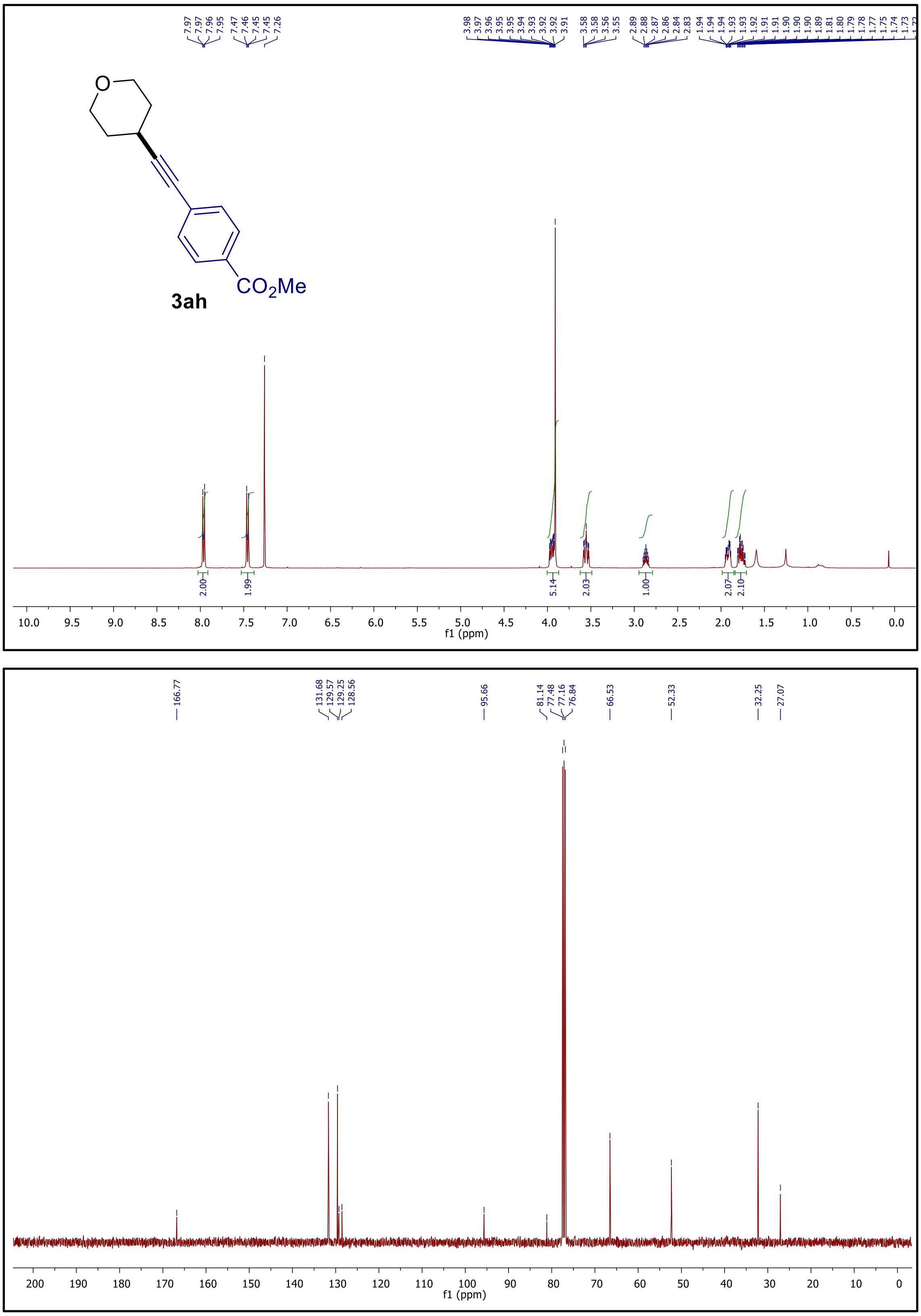
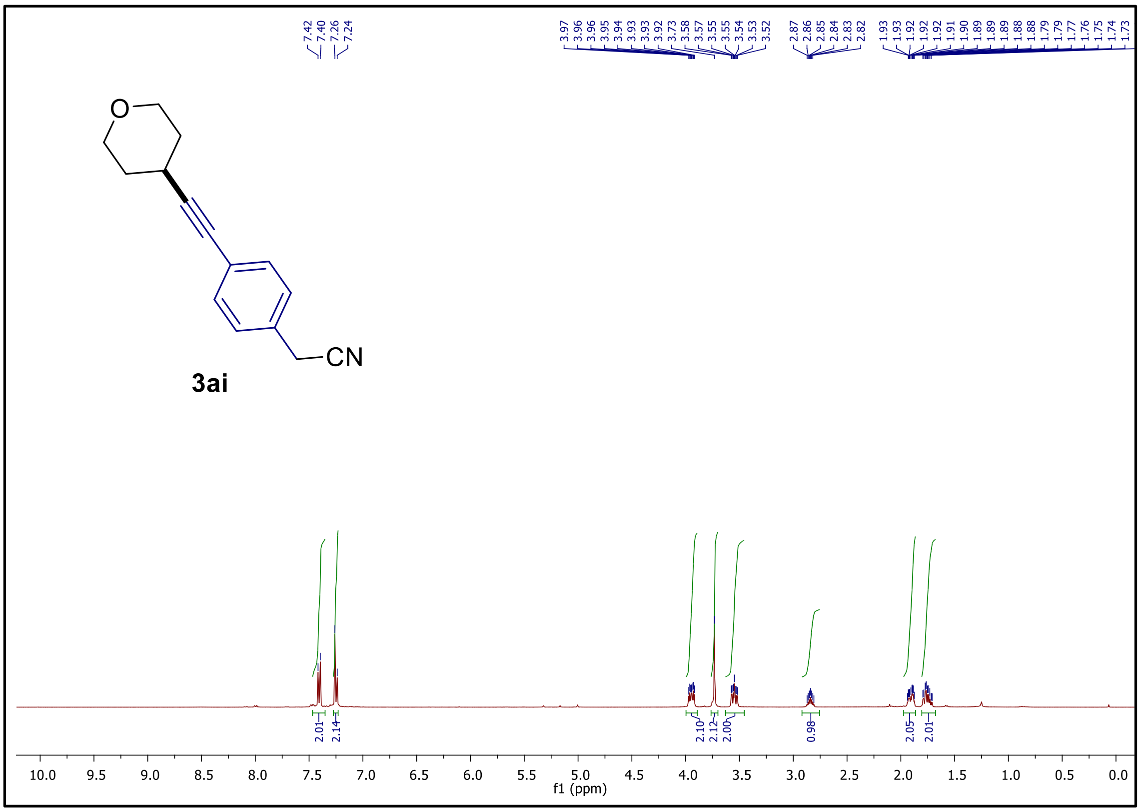


Figure S46. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ah** in $CDCl_3$ at 298K.



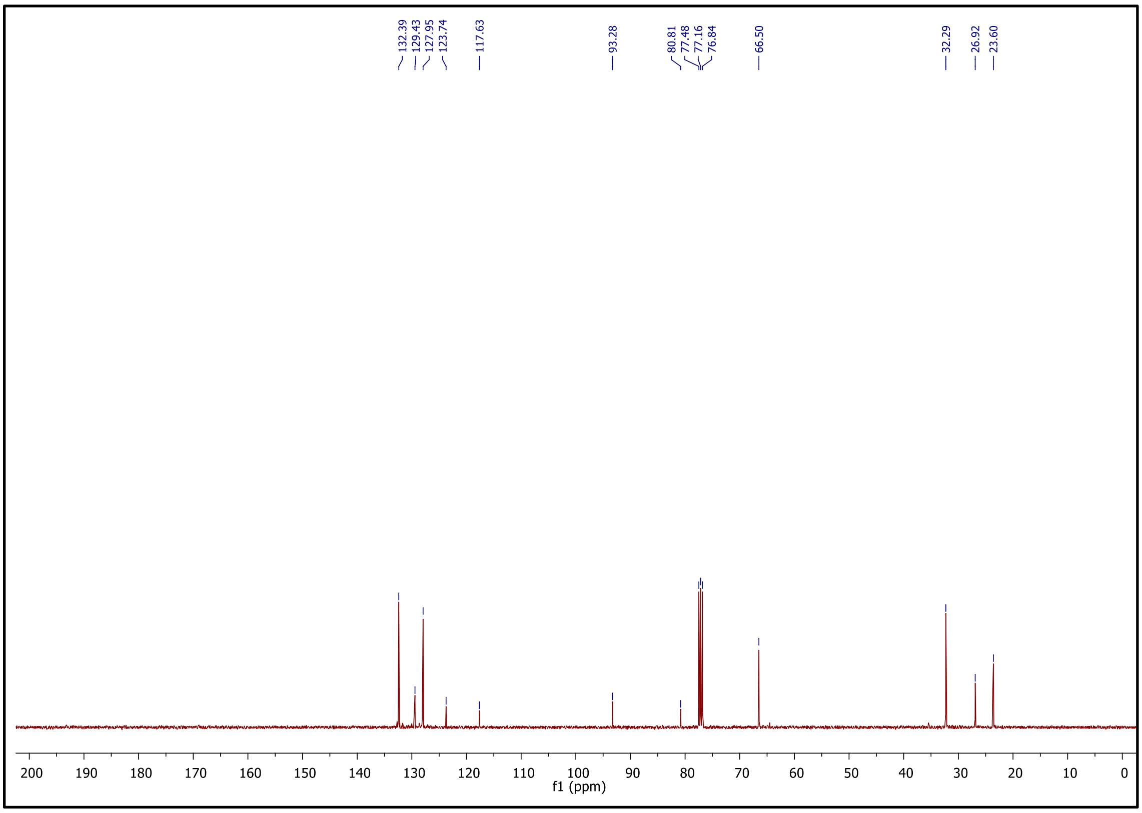
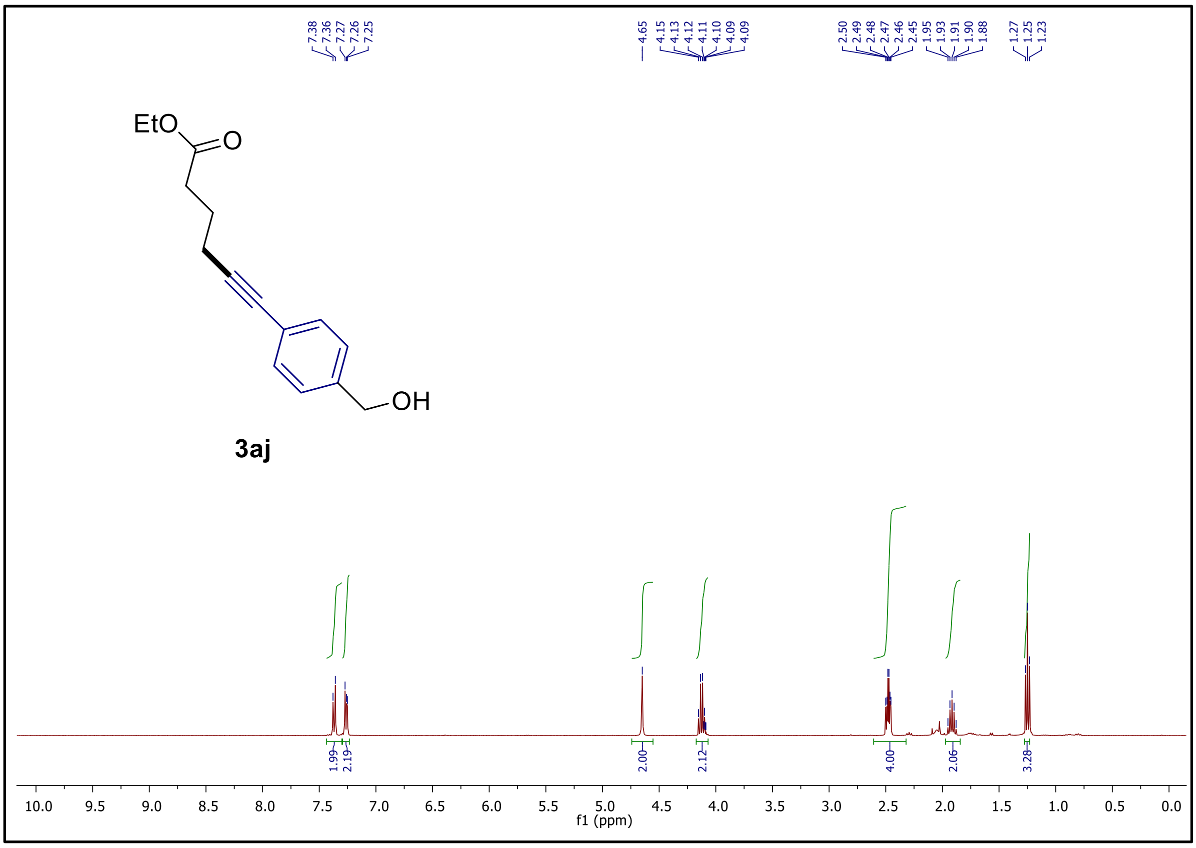


Figure S47. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ai** in $CDCl_3$ at 298K.



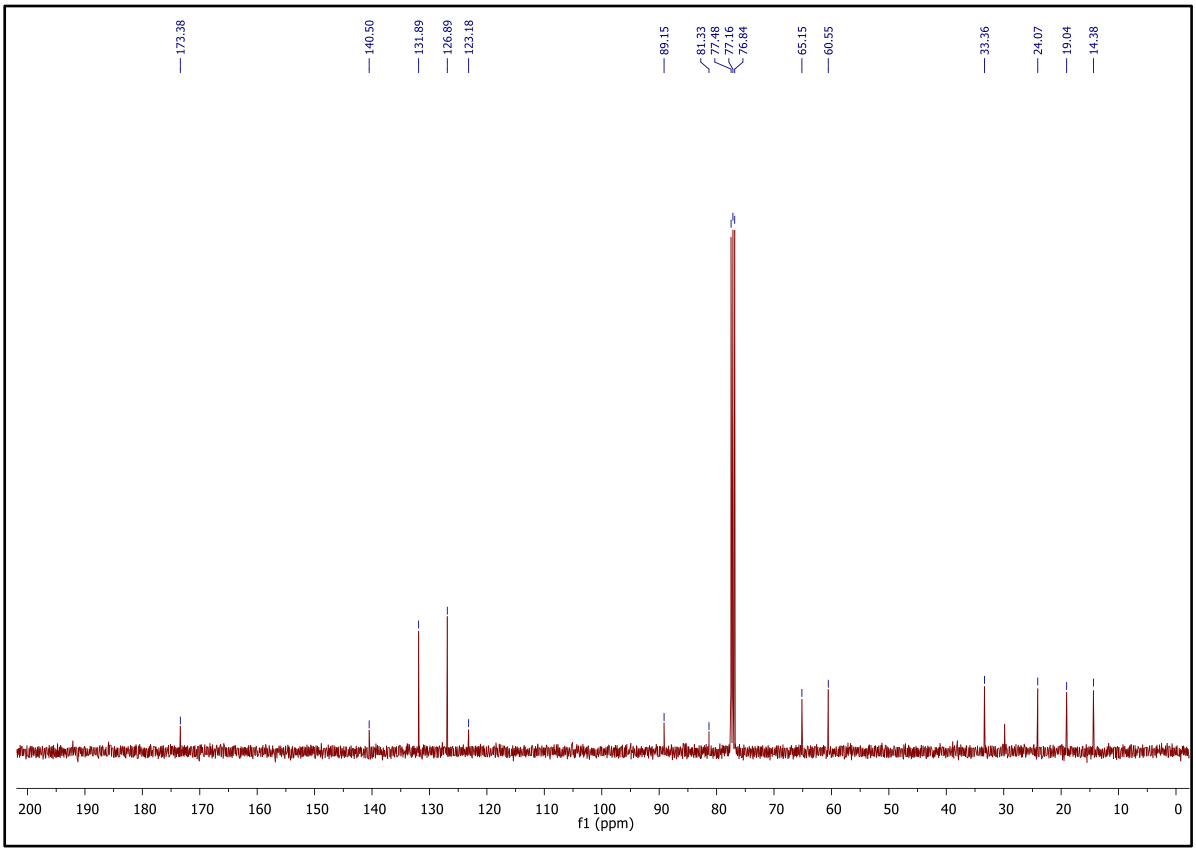
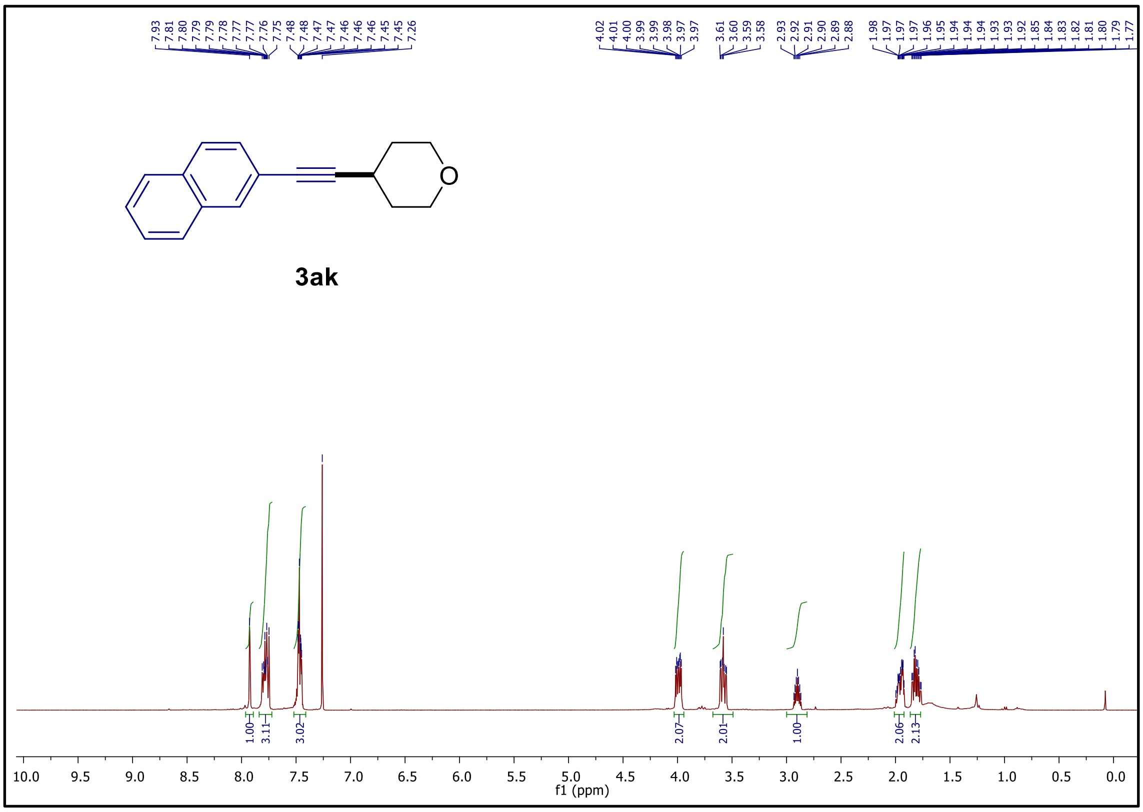


Figure S48. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3aj** in $CDCl_3$ at 298K.



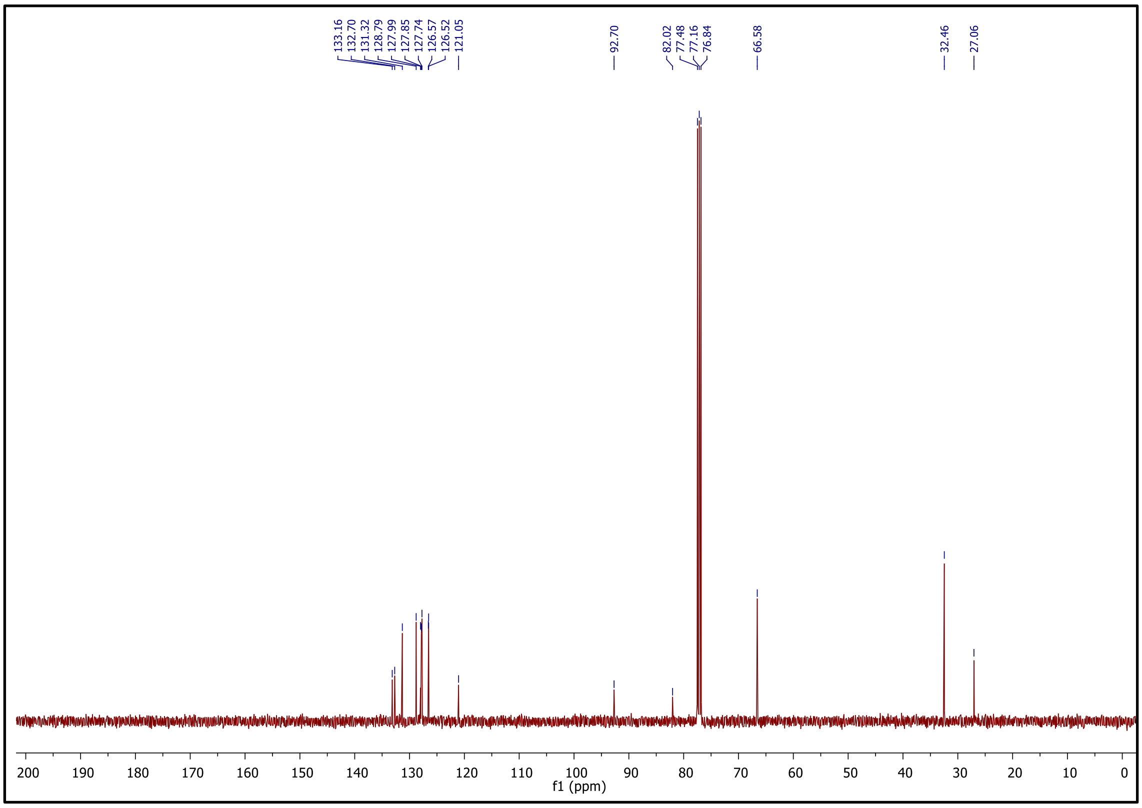
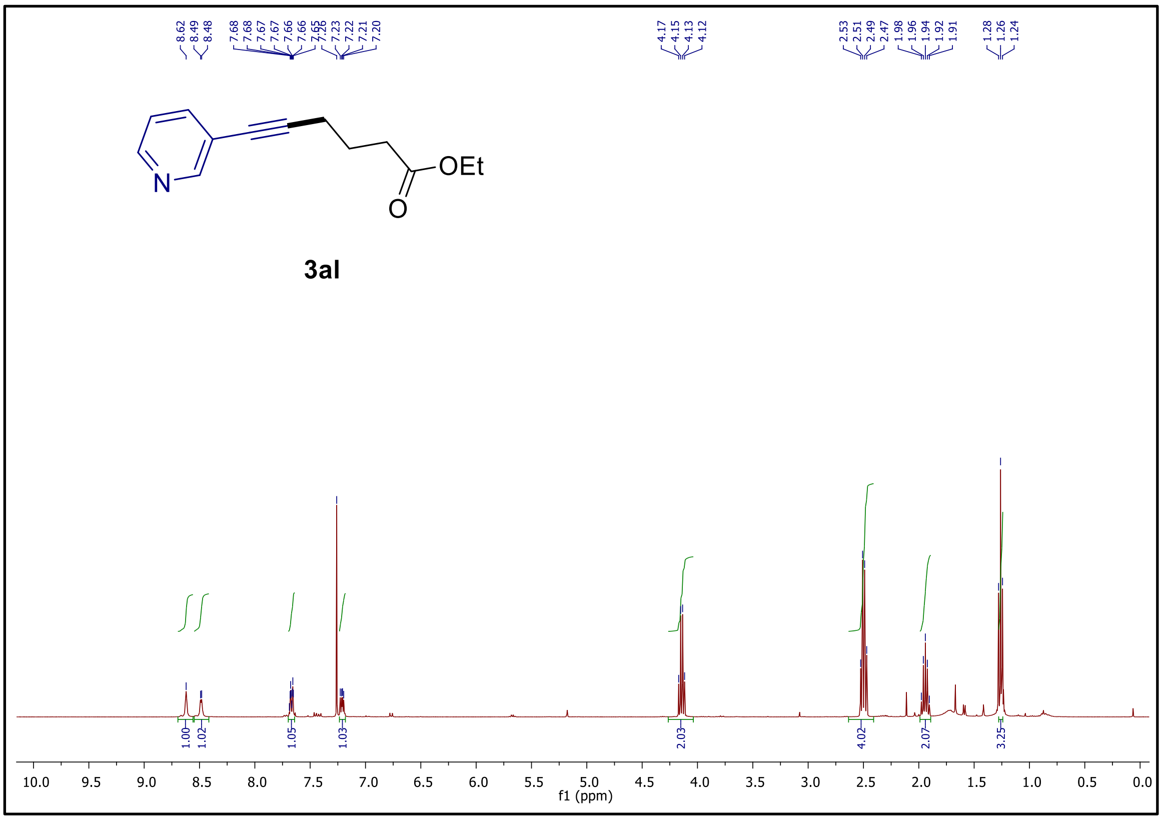


Figure S49. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ak** in $CDCl_3$ at 298K.



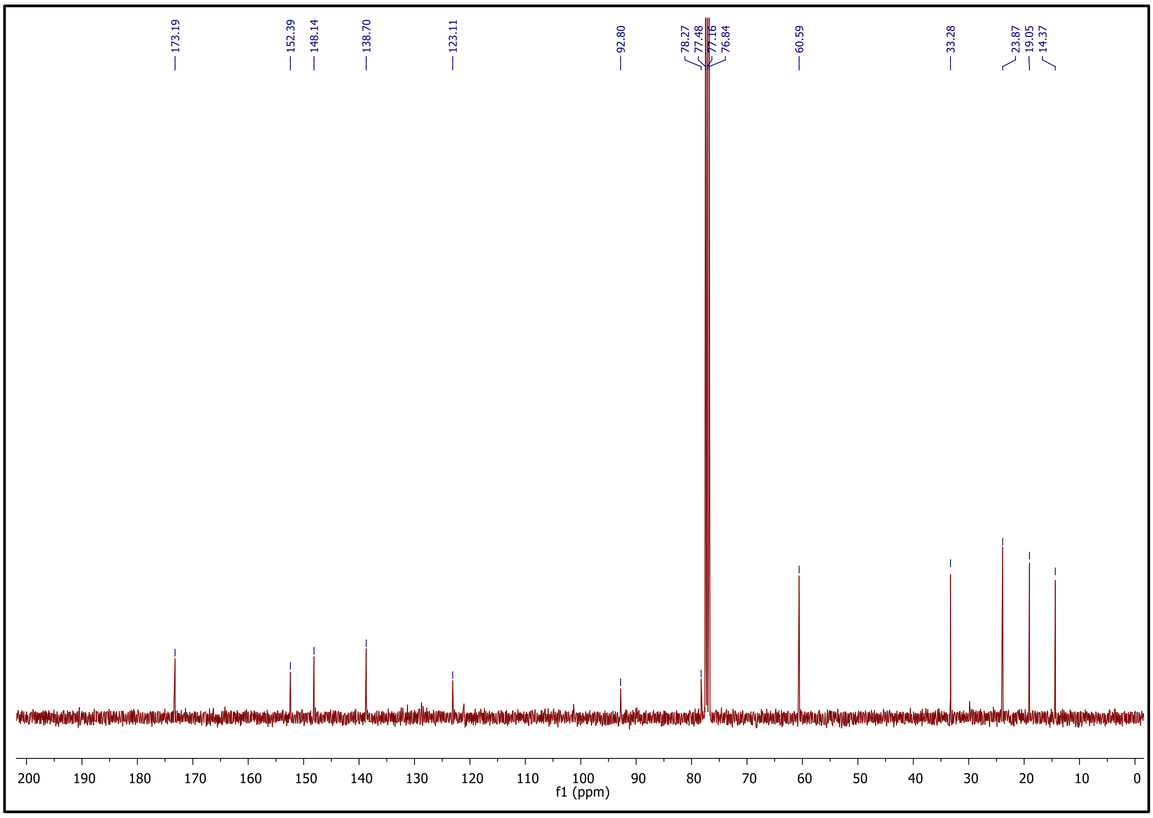
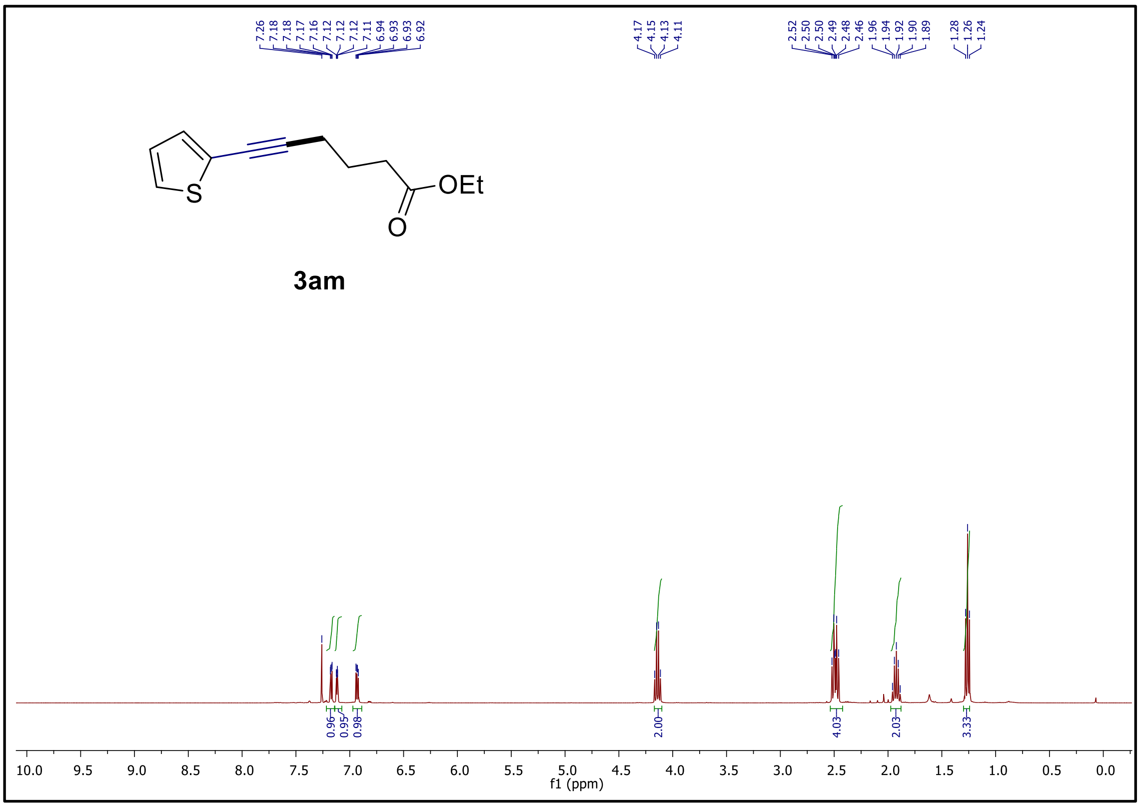


Figure S50. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3al** in $CDCl_3$ at 298K.



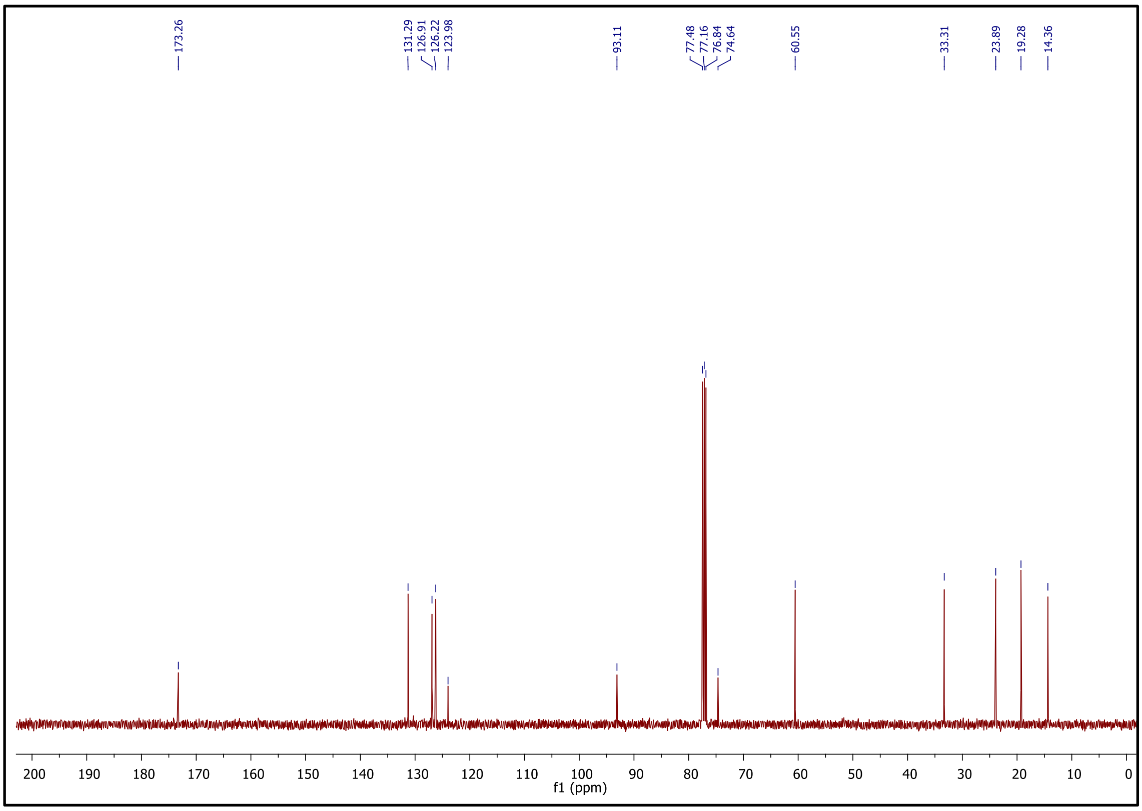


Figure S51. **¹H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3am** in $CDCl_3$ at 298K.

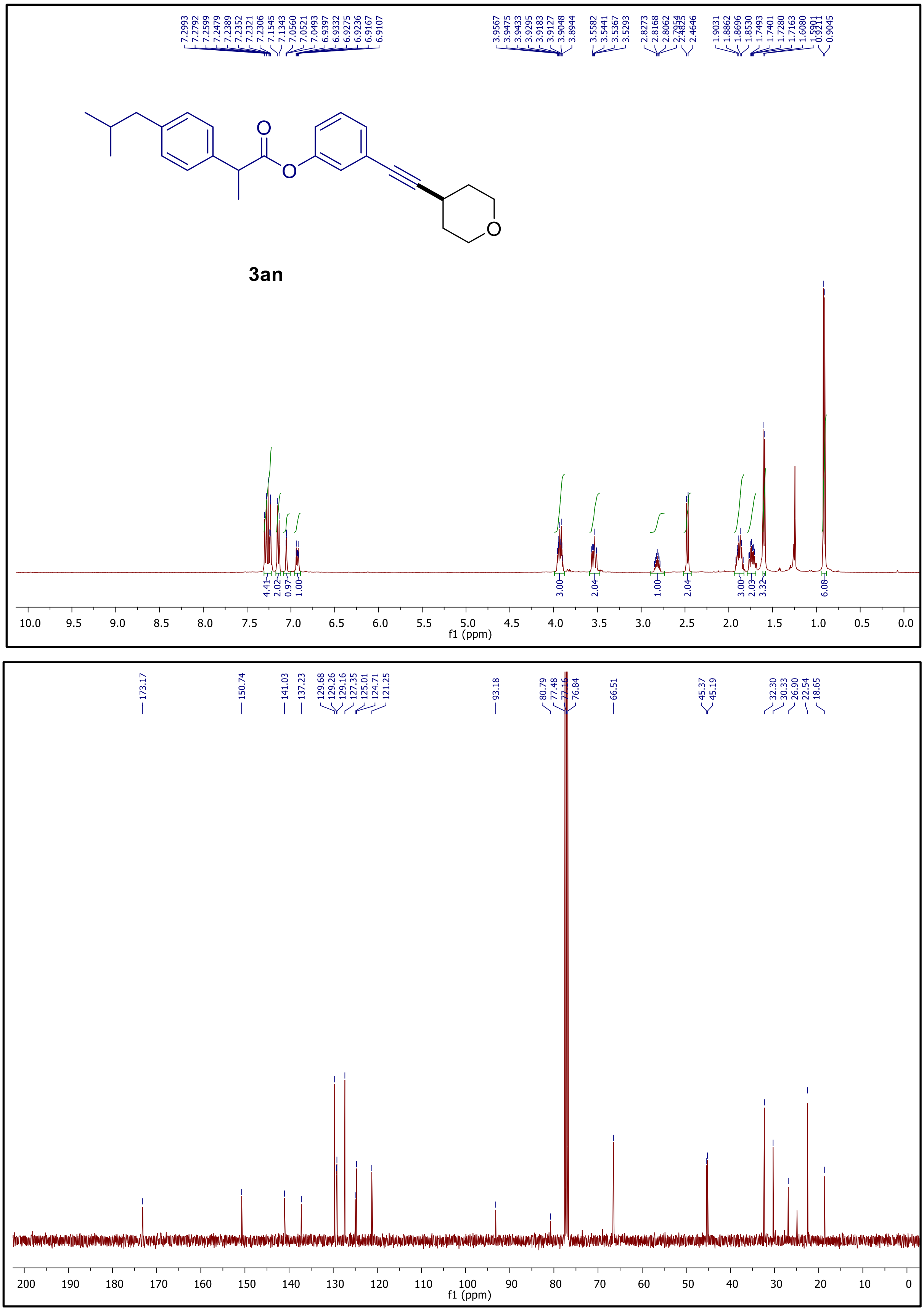
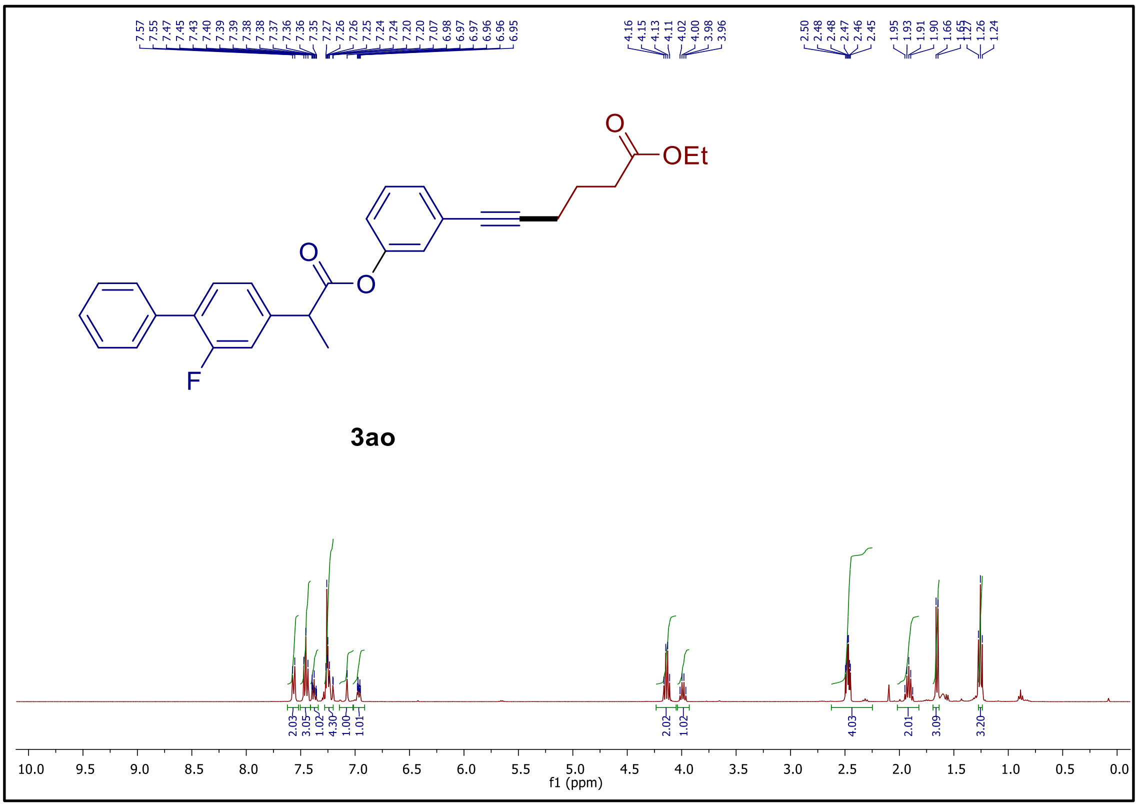


Figure S52. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3an** in $CDCl_3$ at 298K.



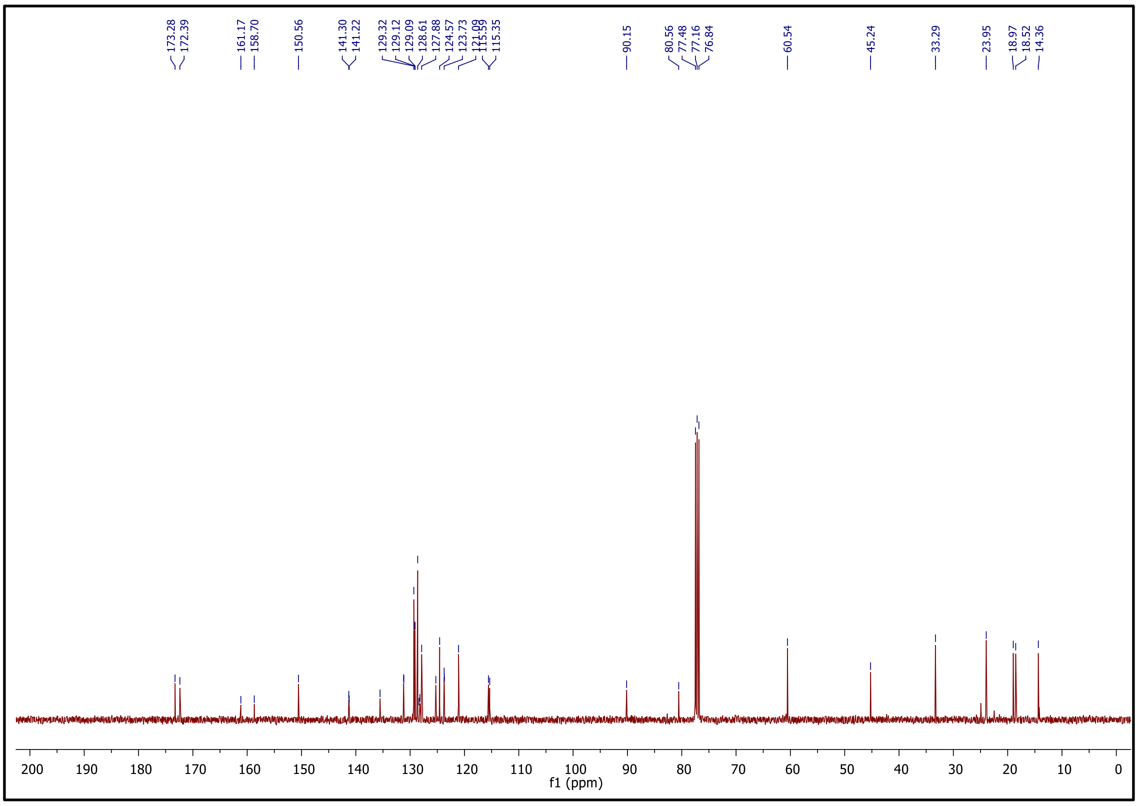
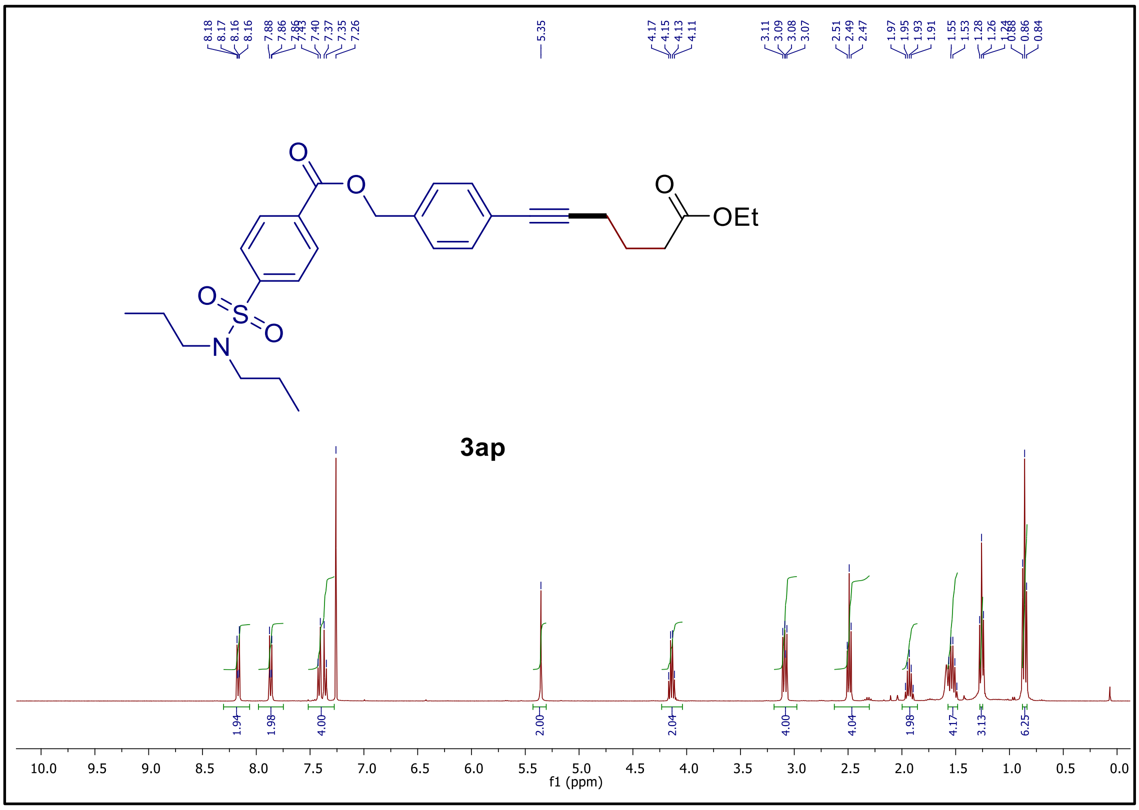


Figure S53. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ao** in $CDCl_3$ at 298K.



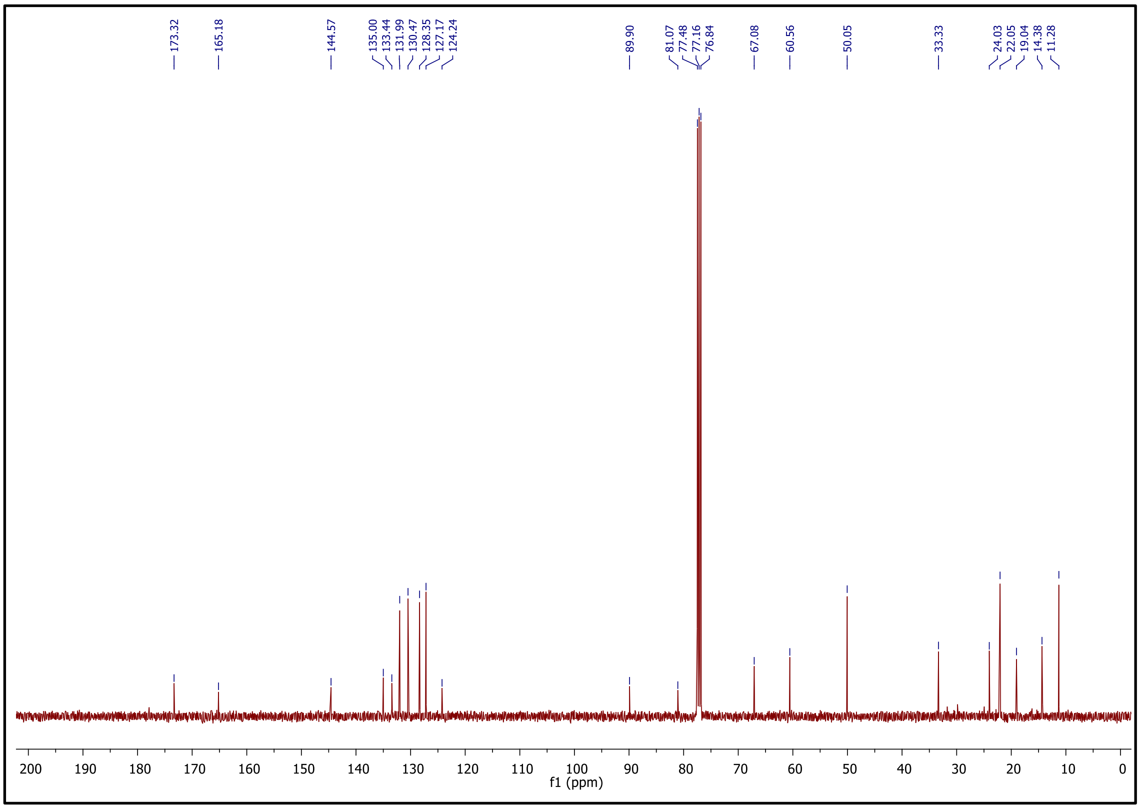
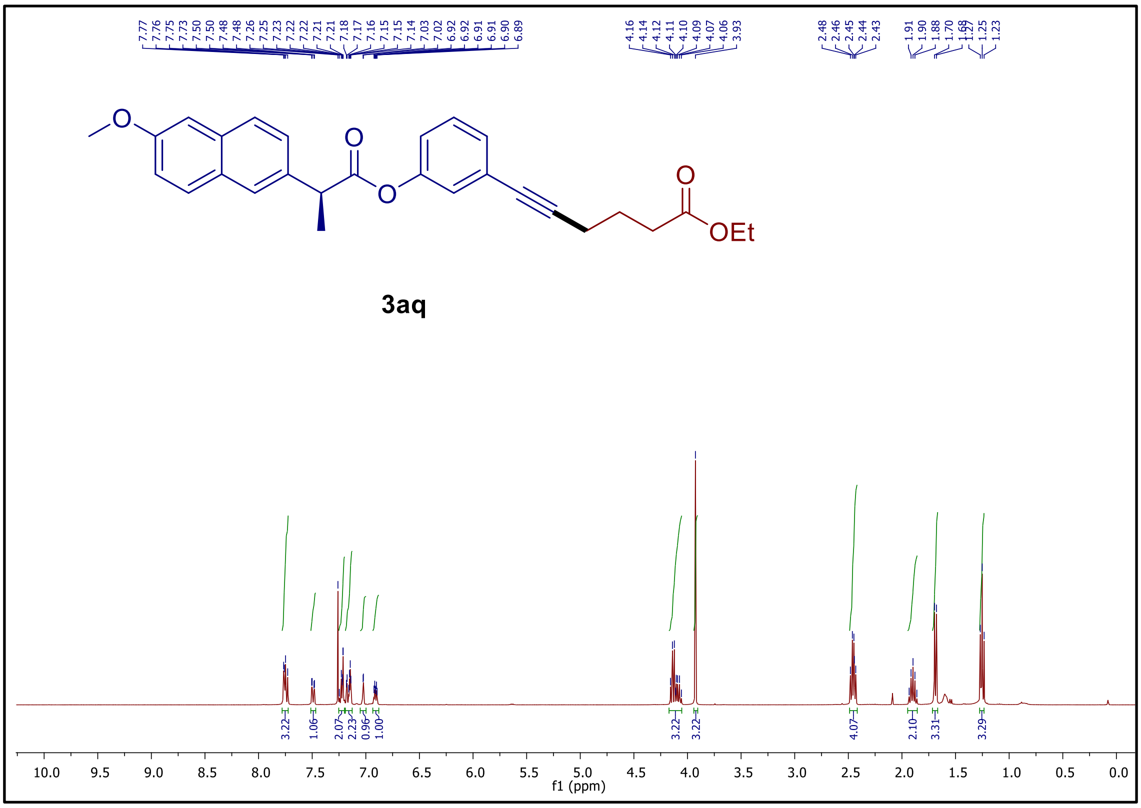


Figure S54. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ap** in $CDCl_3$ at 298K.



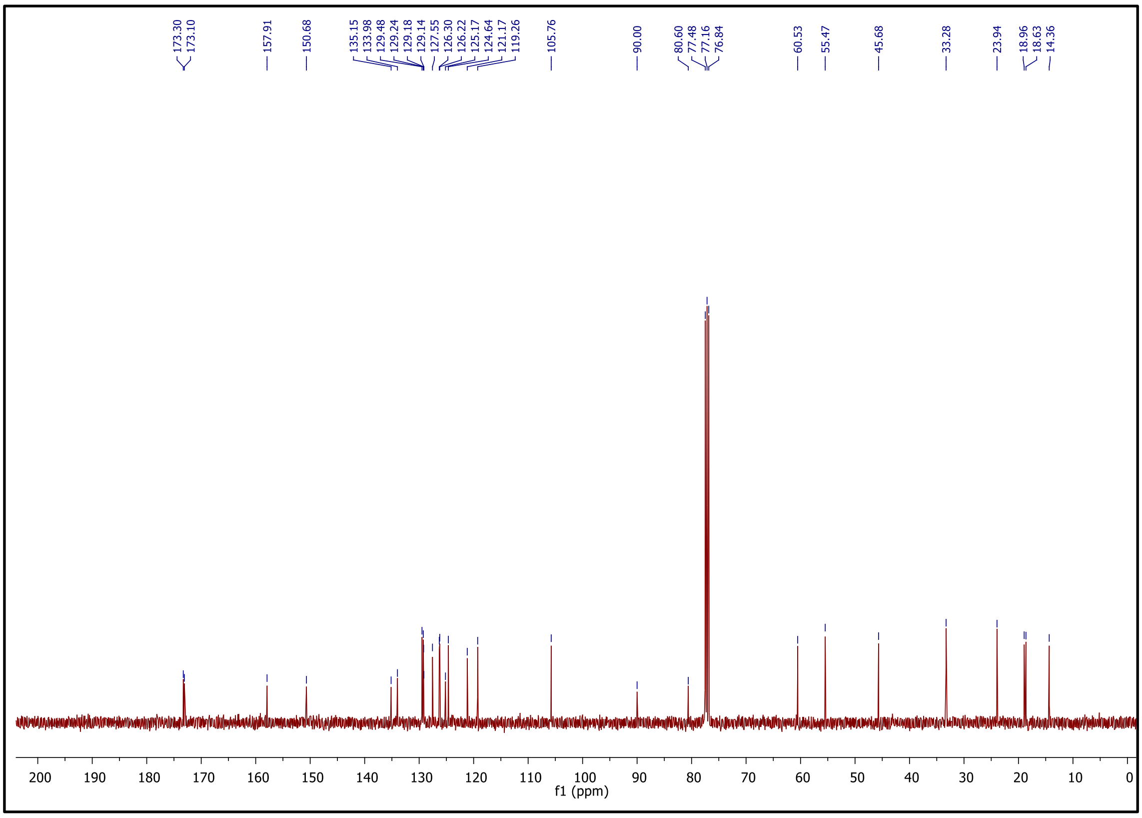


Figure S55. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3aq** in $CDCl_3$ at 298K.

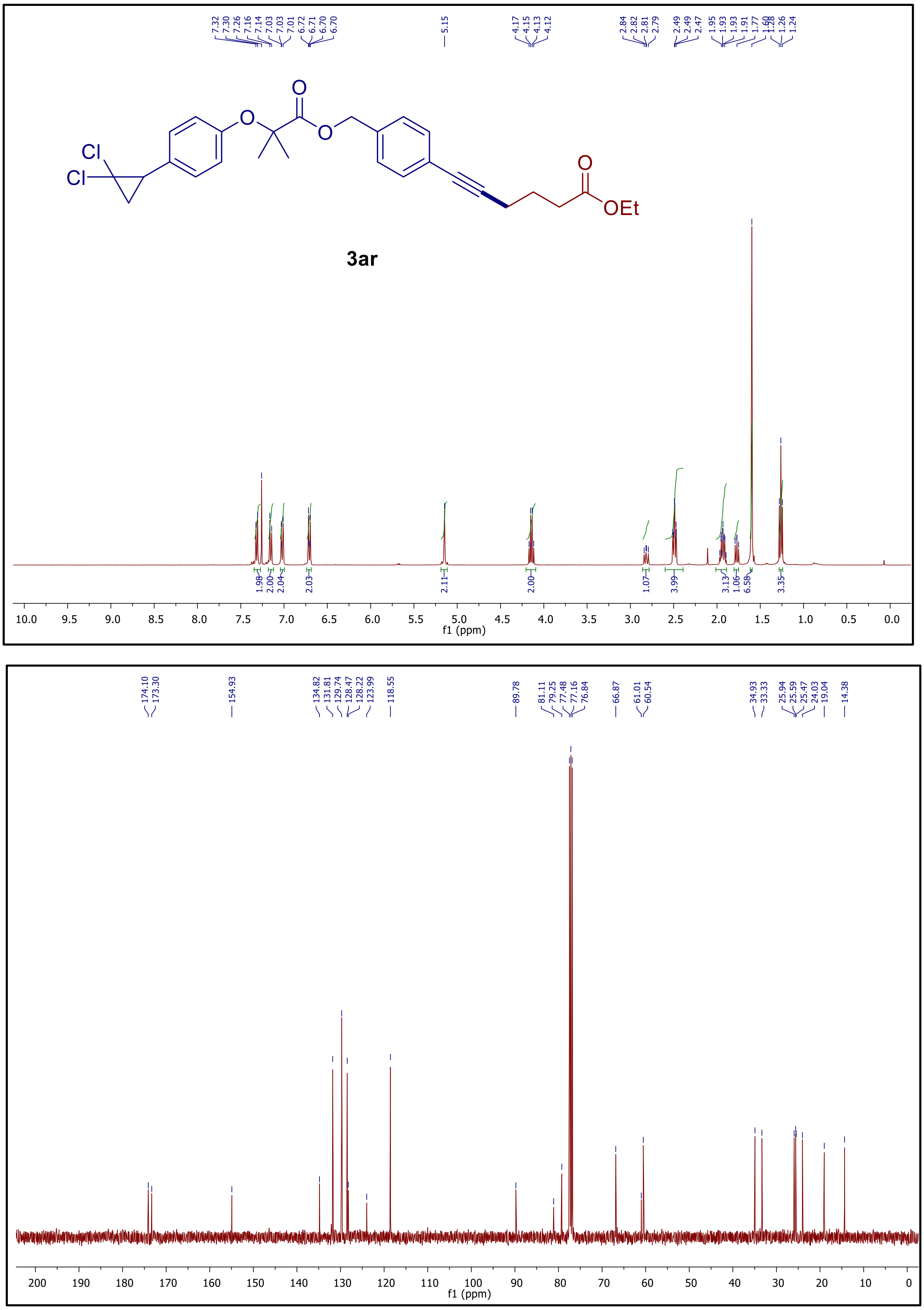
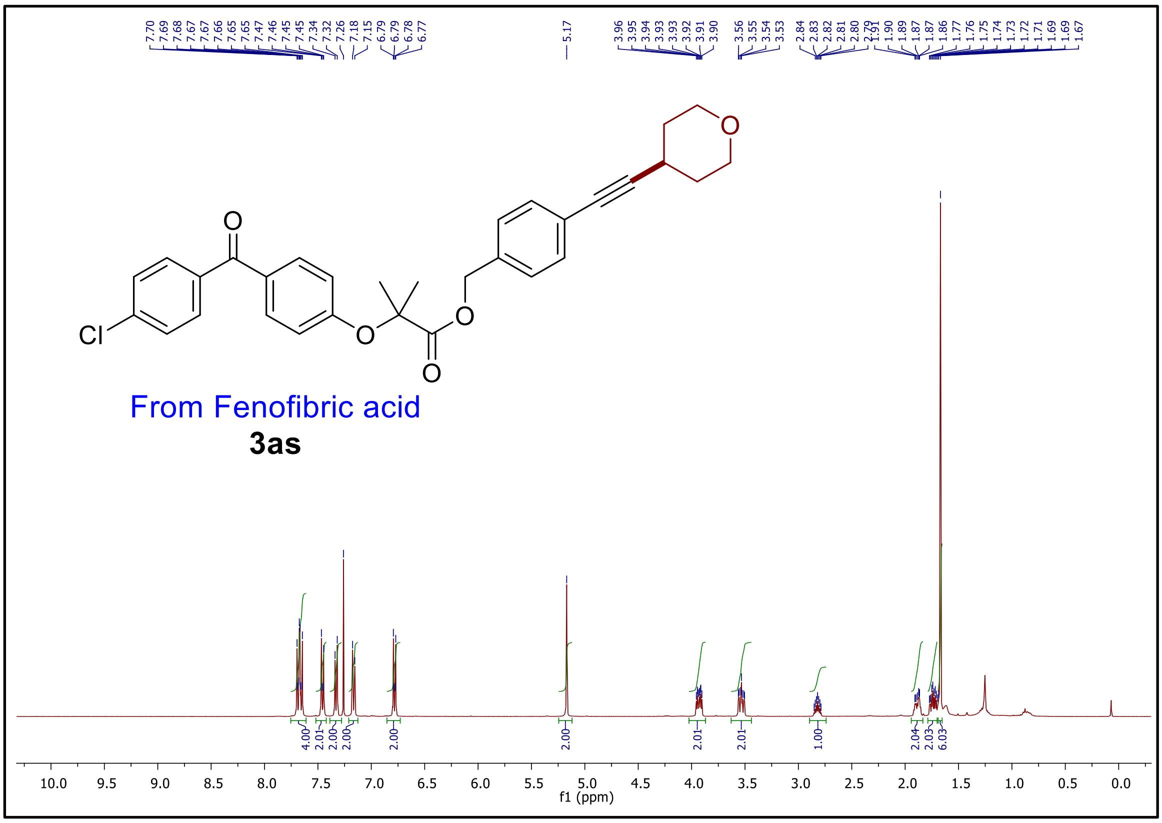


Figure S56. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ar** in $CDCl_3$ at 298K.



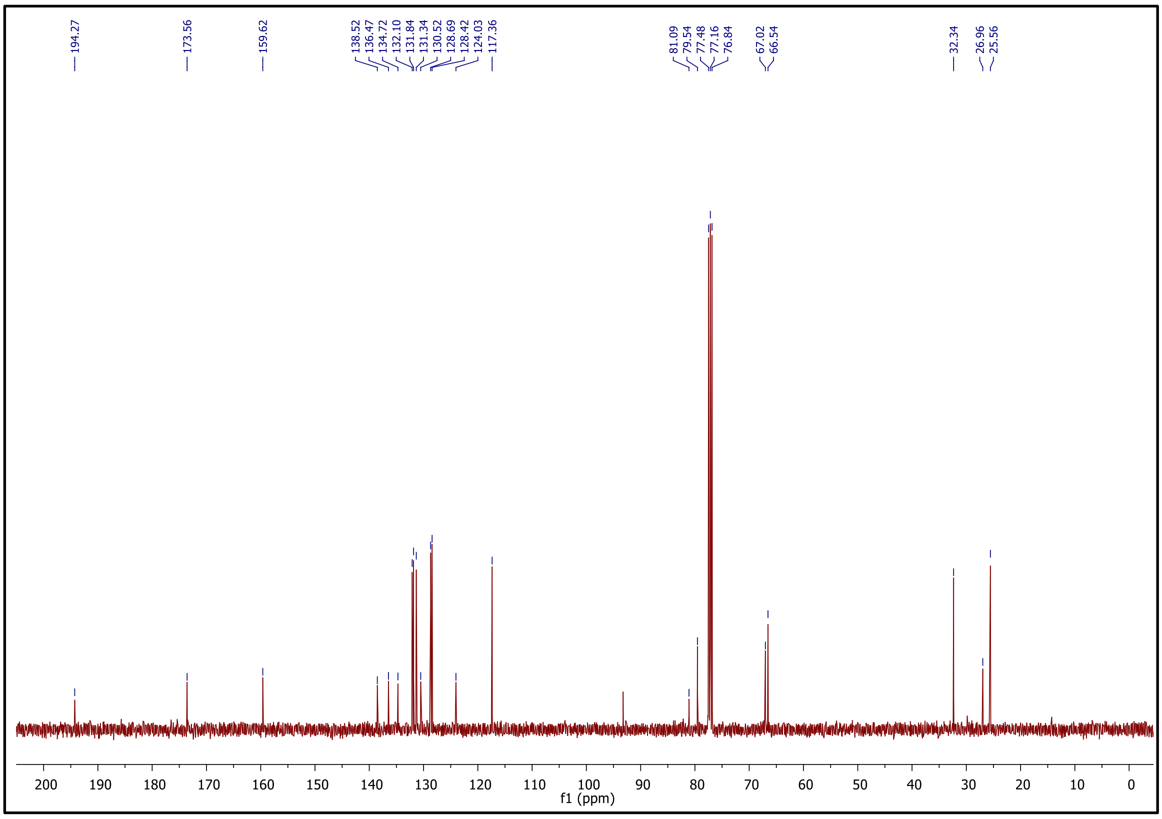


Figure S57. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3as** in $CDCl_3$ at 298K.

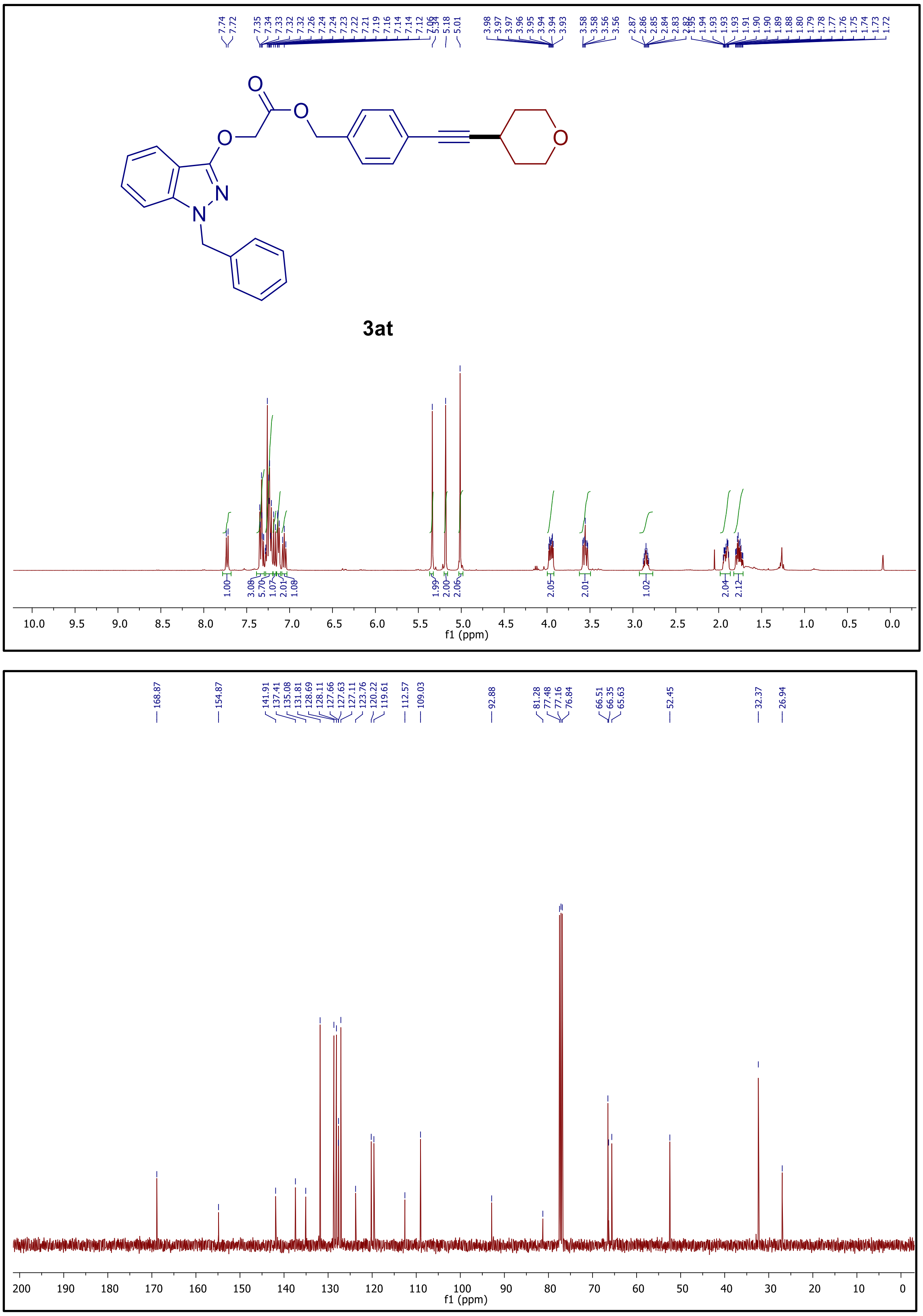
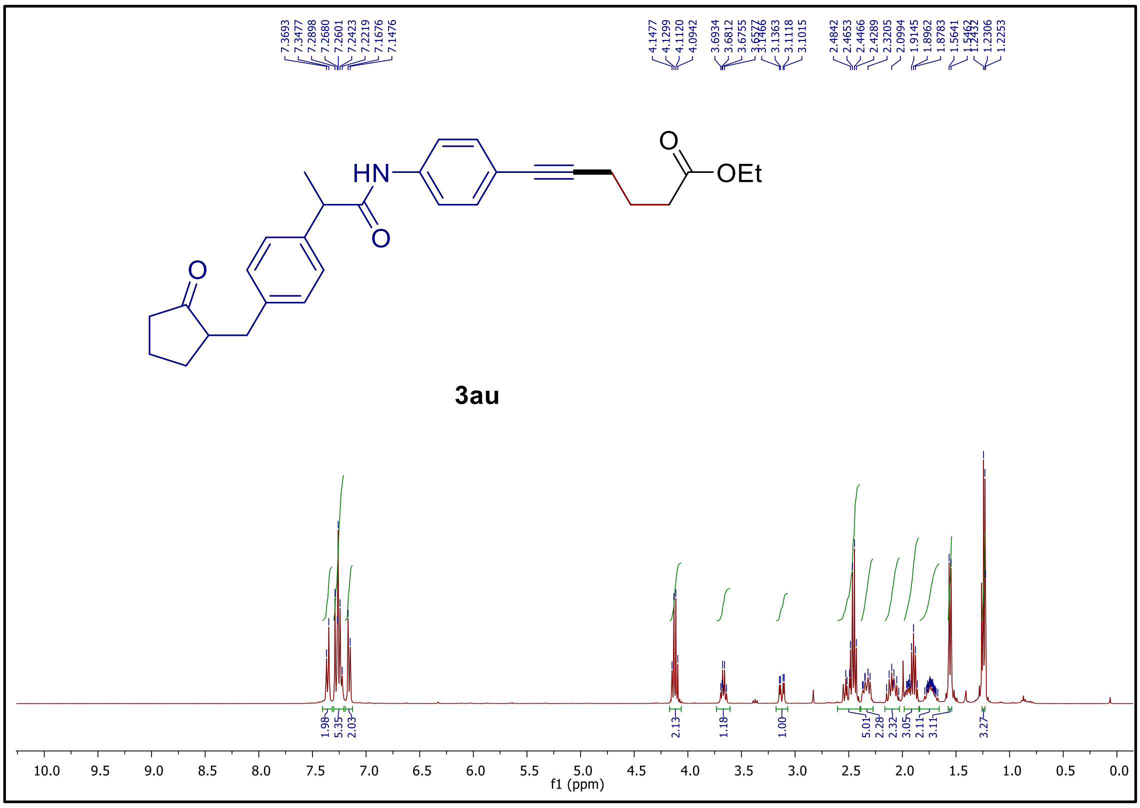


Figure S58. **¹H NMR** (400 MHz, top) and **¹³C {¹H} NMR** (100 MHz, bottom) Spectra of **3at** in $CDCl_3$ at 298K.



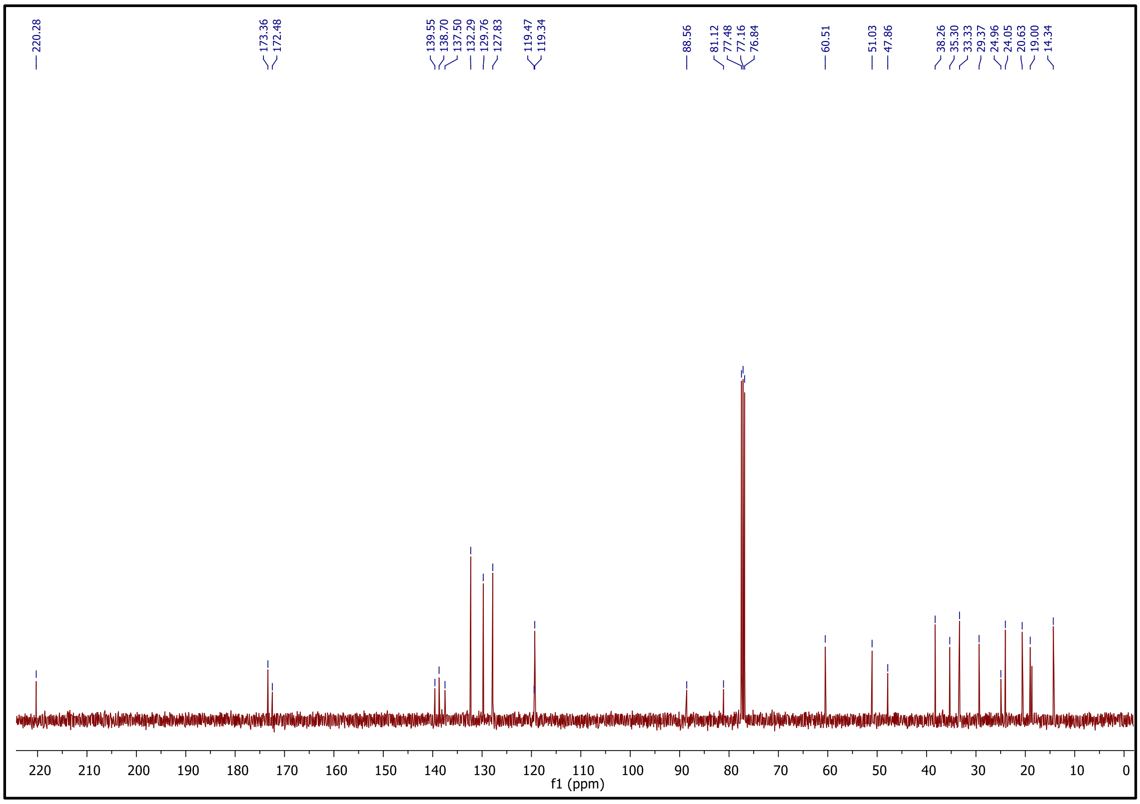


Figure S59. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3au** in $CDCl_3$ at 298K.

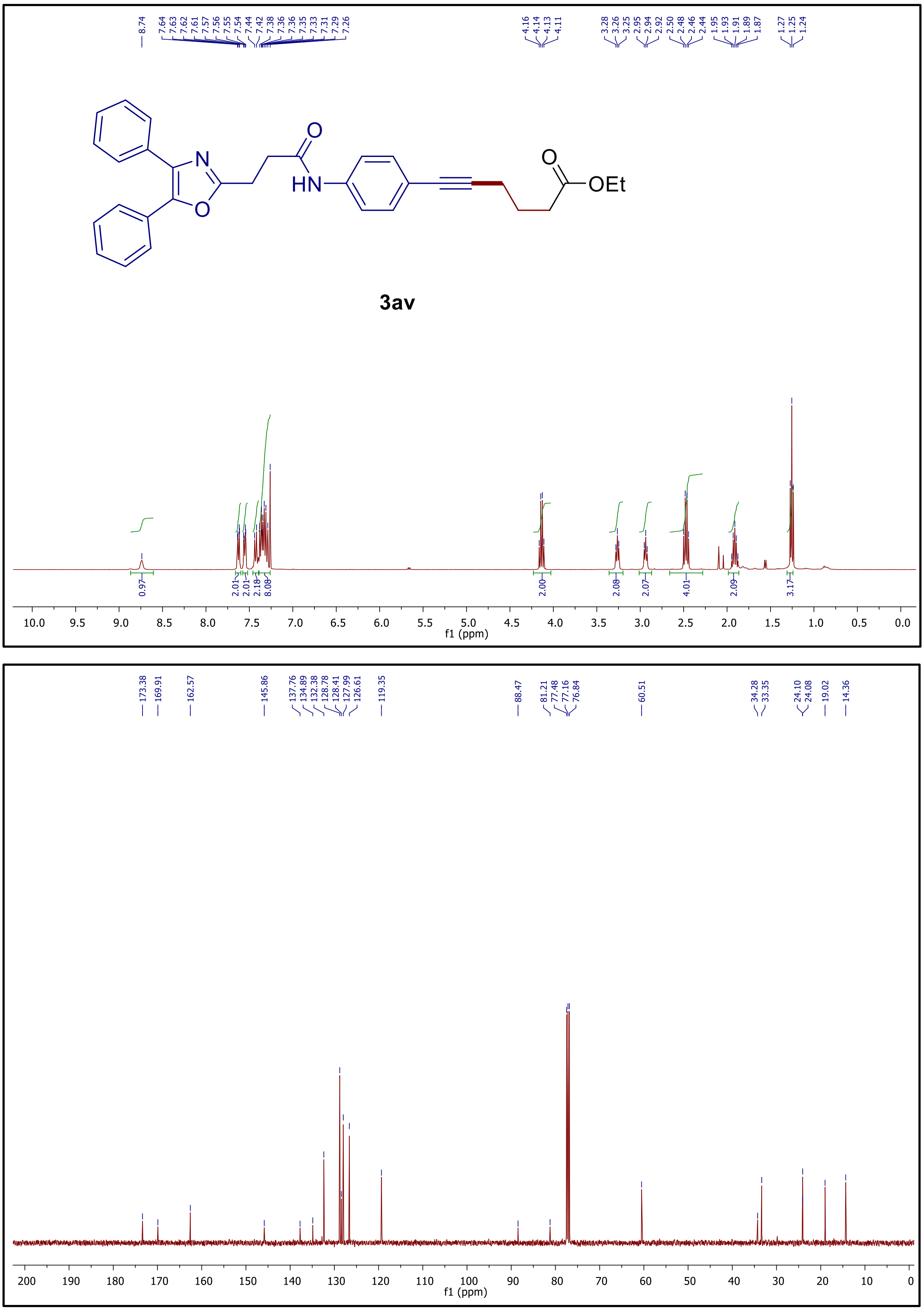
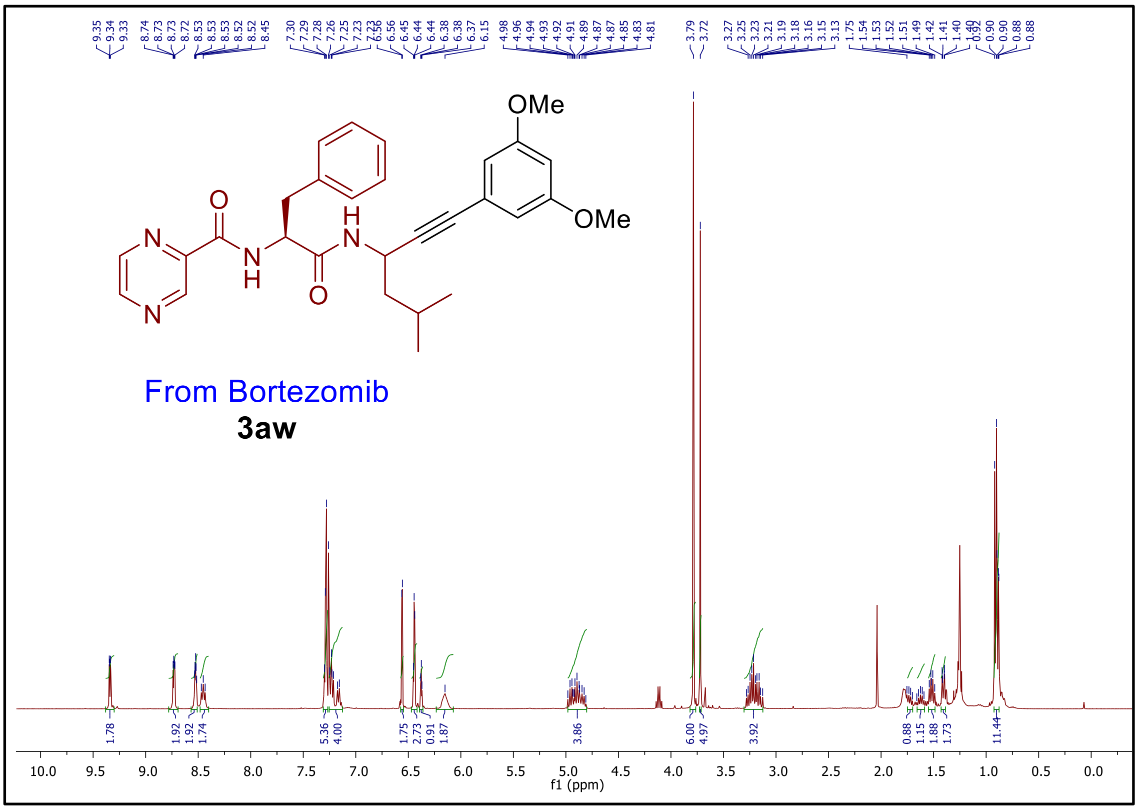


Figure S60. ^{1}**H NMR** (400 MHz, top) and ^{13}**C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3av** in $CDCl_3$ at 298K.



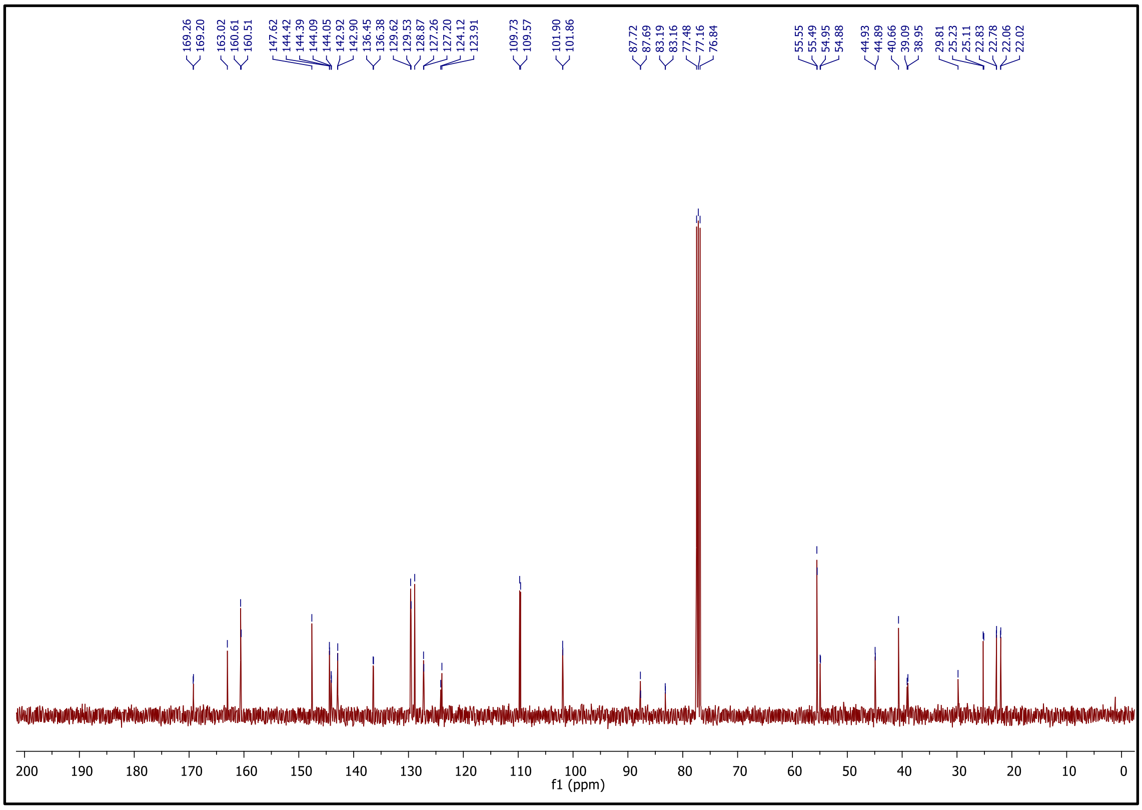
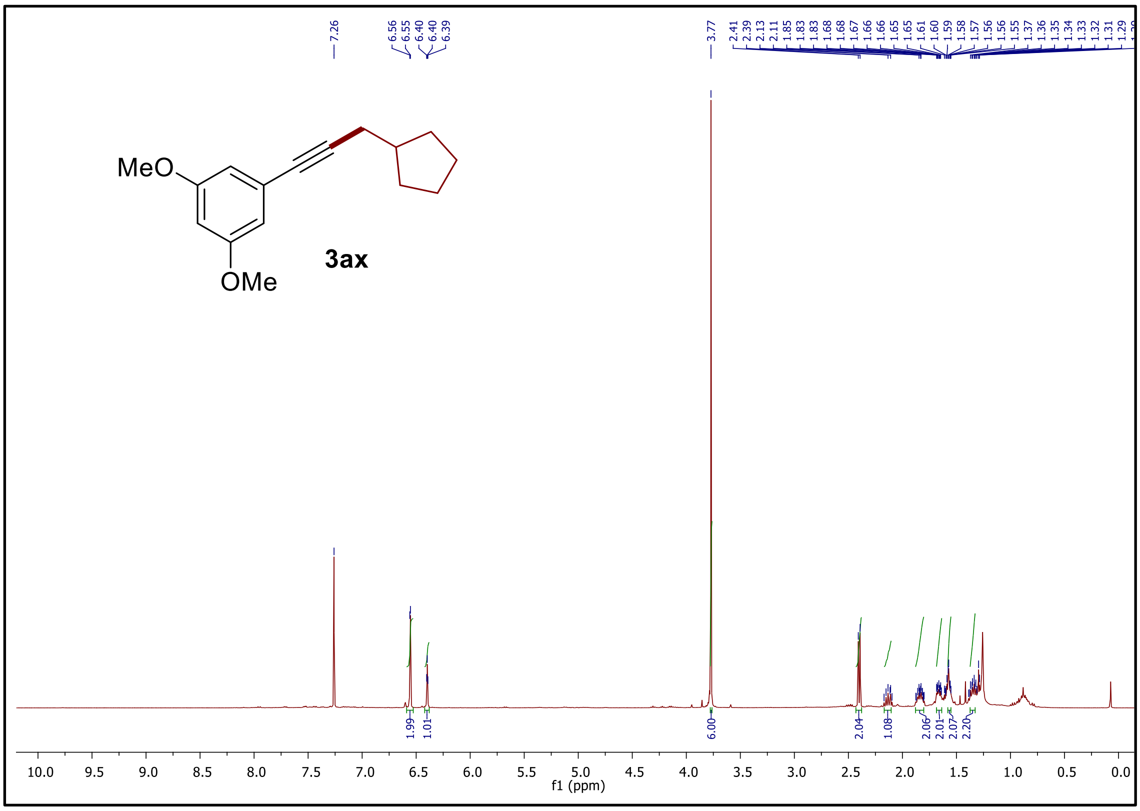


Figure S61. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3aw** in $CDCl_3$ at 298K.



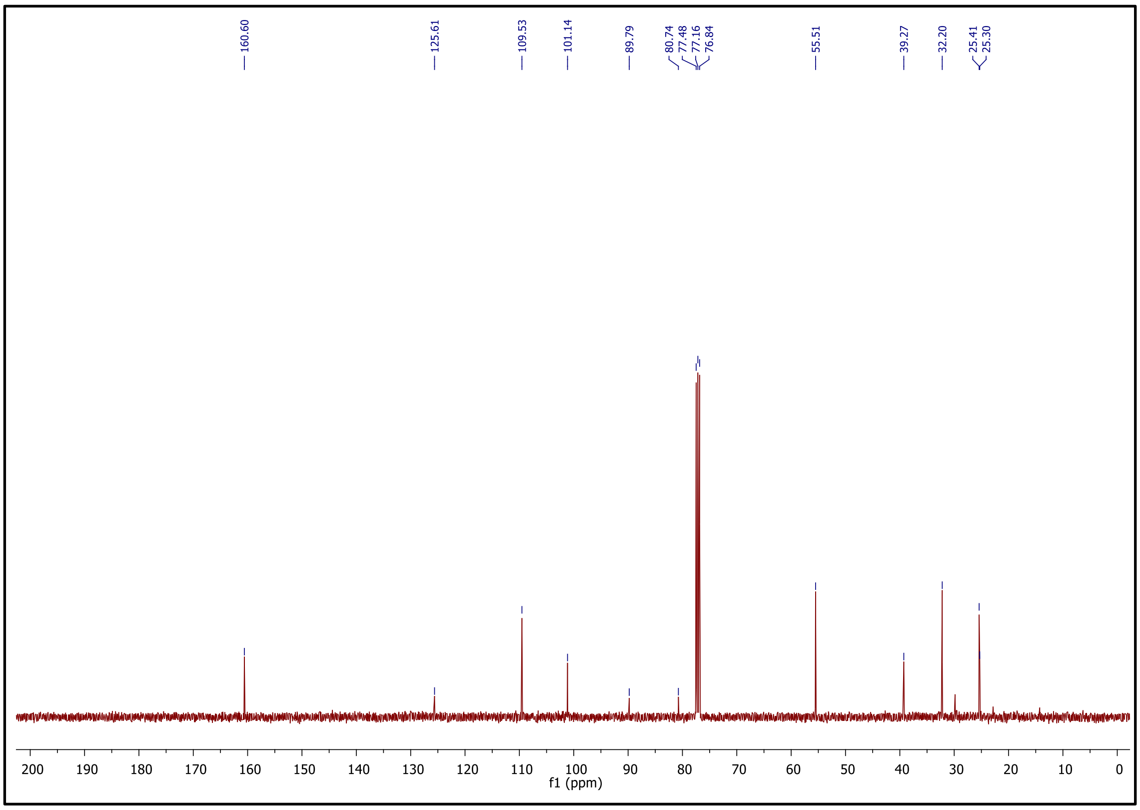


Figure S62. **^{1}H NMR** (400 MHz, top) and **^{13}C {^{1}H} NMR** (100 MHz, bottom) Spectra of **3ax** in $CDCl_3$ at 298K.

Computational Studies

All calculations were performed using the Gaussian 16 Rev. C.01 program package.[6] Geometry optimizations were carried out using the ω-B97XD functional.[7] The def2SVP (Split Valence Polarization)[8] basis set was employed for all atoms including bromine atom. All stationary points were fully optimized without symmetry constraints. Harmonic vibrational frequency calculations were performed at the same level of theory to confirm the nature of the stationary points. The transition states exhibited a single imaginary frequency (Nimag = 1) corresponding to the intended reaction coordinate. Intrinsic Reaction Coordinate (IRC) calculations were performed to ensure that each transition state properly connects the corresponding reactant and product minima.[9]

Mechanistic Interpretation of Morpholine-Assisted *N*-Centered Radical Formation

Efficient generation of the morpholine N-centered radical is best described by a cooperative two-morpholine mechanism rather than by direct hydrogen-atom abstraction from a single morpholine molecule by a free bromine radical. To evaluate the feasibility of the one-molecule pathway, extensive transition-state searches were carried out for direct HAT between bromine-radical character and one morpholine molecule using multiple computational approaches, including SCAN-based calculations. However, no viable transition state could be located, suggesting that direct abstraction from a single morpholine molecule is not favorable on the computed potential energy surface.

In contrast, when a second morpholine molecule was explicitly included, a smooth and chemically reasonable HAT transition state was successfully identified as shown in Figure S63. In this cooperative pathway, one morpholine molecule engages with bromine-radical character and serves as the radical acceptor, while the second morpholine functions as a base/proton shuttle to facilitate N–H bond cleavage and stabilize the developing HBr species through hydrogen-bonding interactions. This dual participation significantly lowers the kinetic barrier and enables formation of the morpholine N-centered radical.

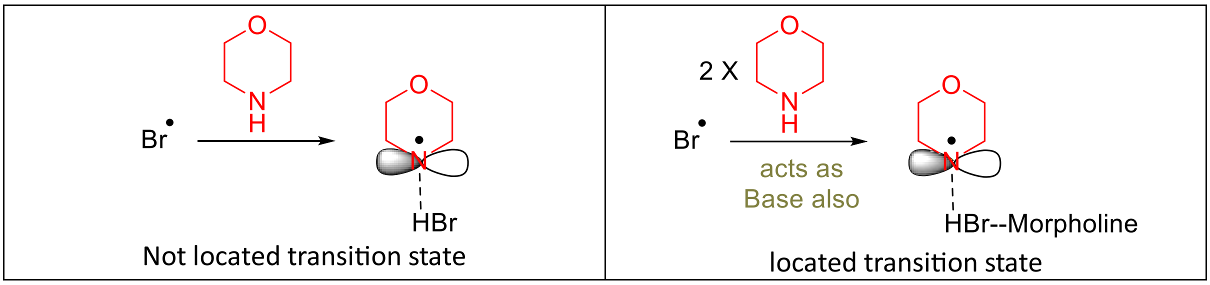


Figure S63. hydrogen atom transfer (HAT) pathways for conversion of bromine-radical character into the morpholine N-centered radical in the presence of one and two morpholine molecules.

Energy profile calculations were performed to compare the feasibility of nitrogen-centered versus carbon-centered radical formation from morpholine after interaction with bromine-radical character as shown in Figure S64. The pathway leading to the N-centered morpholine radical is both kinetically and thermodynamically favored, proceeding through a substantially lower activation barrier (ΔG‡ = 5.1 kcal mol^{-1}) and affording a more stable product state (ΔG = –2.4 kcal mol^{-1}). In contrast, formation of the corresponding carbon-centered radical requires a significantly higher barrier (ΔG‡ = 19.6 kcal mol^{-1}) and is thermodynamically unfavorable (ΔG = +13.8 kcal mol^{-1}). These results clearly indicate that transfer of radical character to nitrogen is strongly preferred over α-C–H hydrogen atom transfer, establishing the N-centered morpholine radical as the most plausible reactive intermediate under the reaction conditions.

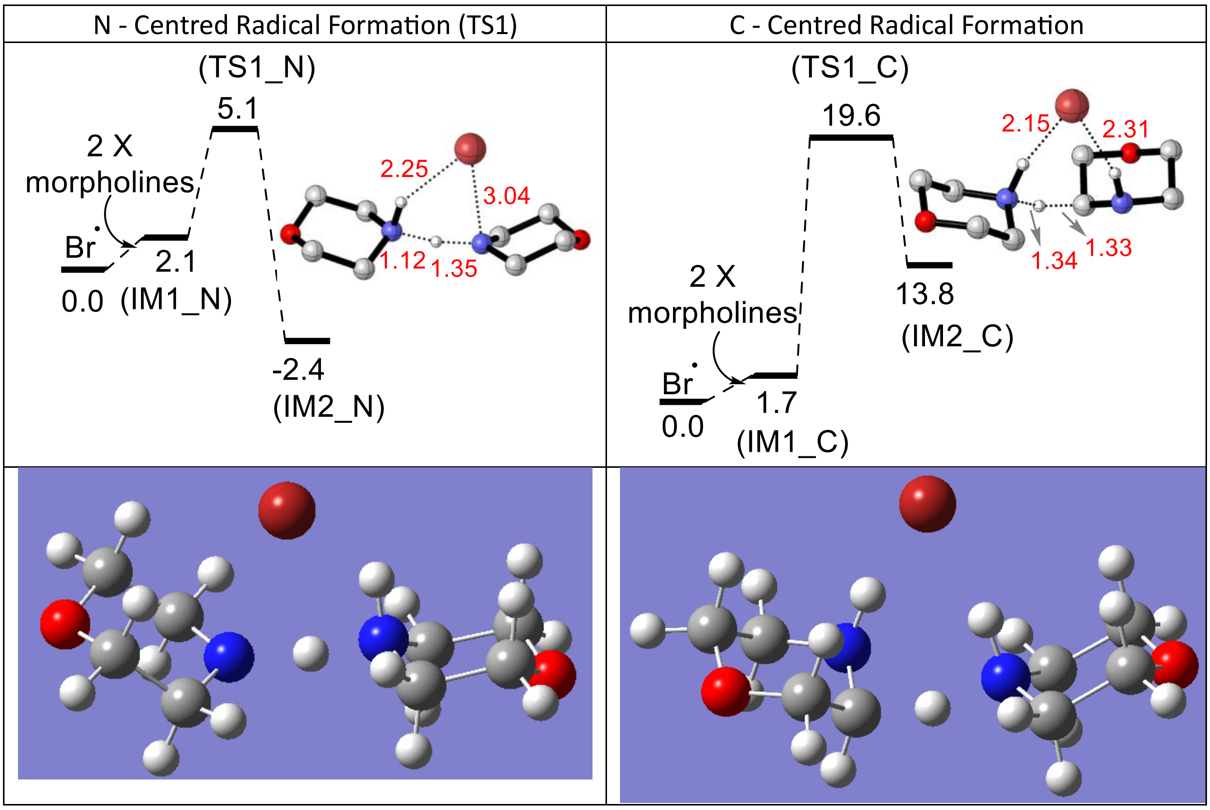


Figure S64. Relative Gibbs free energy profiles (kcal/mol) for nitrogen-centered and carbon-centered radical formation from morpholine through hydrogen atom transfer (HAT) involving bromine-radical character at the SMD(EtOAc)/ω-B97XD/def2SVP (C, H, N, O and Br) level of theory.

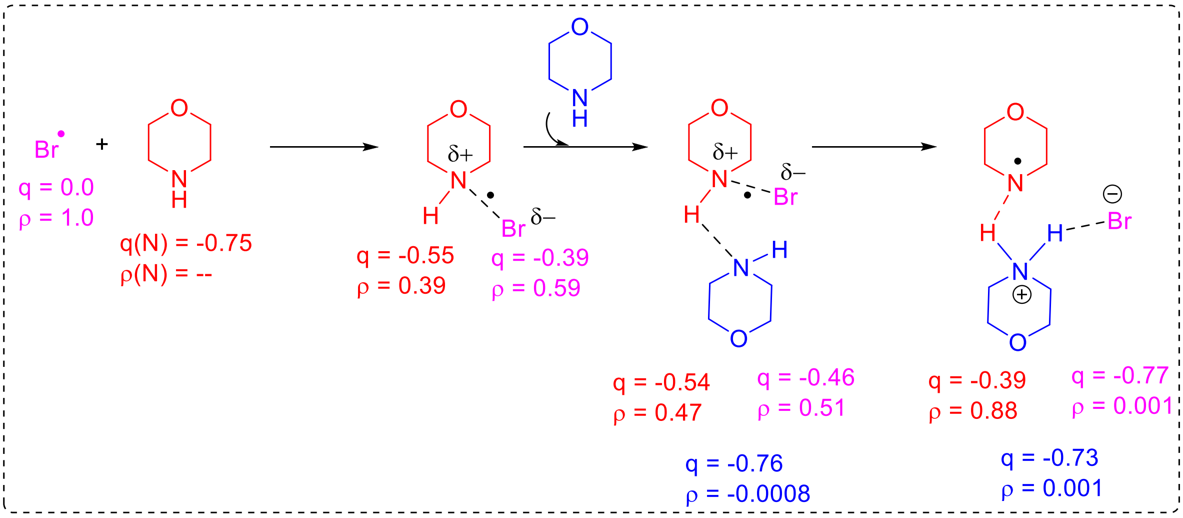


Figure S65. Spin density (ρ) and charge (q) analysis of the hydrogen atom transfer (HAT) process involving bromine-radical character in the presence of one and two morpholine molecules, highlighting formation of a polarized N···Br intermediate and cooperative generation of the N-centered morpholine radical at the SMD(EtOAc)/ω-B97XD/def2SVP (C, H, N, O and Br) level of theory.

Spin density analysis (Figure S65) of the intermediate reveals substantial delocalization between bromine and nitrogen (ρ_{Br} = 0.59; ρ_N = 0.39), consistent with formation of a polarized two-center three-electron N···Br hemibonded species. Charge distribution further shows partial positive character on nitrogen and partial negative character on bromine, supporting charge-transfer stabilization within the complex. The second morpholine molecule therefore acts as a base/proton shuttle, facilitating N–H proton removal and transfer of radical character from bromine to nitrogen. This interpretation is also consistent with the experimental observation that two or more equivalents of morpholine are required for efficient transformation, demonstrating that morpholine functions cooperatively as both a radical mediator and a base.

As a conclusion, we agree that direct hydrogen-atom abstraction by an isolated bromine radical from a single morpholine molecule is unlikely based on BDE considerations. Our DFT studies instead support a cooperative two-morpholine pathway, in which one morpholine forms a polarized N···Br intermediate while the second morpholine acts as a base/proton shuttle to enable energetically favorable formation of the N-centered morpholine radical.

XYZ Coordinates:

All the complexes were optimized using SMD(EtOAc)/ω-B97XD/def2SVP(C, H, O, N, Br) level of theory.

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Morpholine

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15

Morpholine

C	-1.198028	0.715553	0.192701
C	-1.166044	-0.756058	-0.190969
C	1.166420	-0.755501	-0.190960
C	1.197715	0.716133	0.192699
H	-2.024182	-1.290419	0.242117
H	-1.282083	0.786468	1.299425
H	-2.092828	1.188237	-0.241345
H	-0.000743	2.348913	-0.082645
H	2.024763	-1.289409	0.242298
H	1.223811	-0.844117	-1.295220
H	1.281655	0.787141	1.299402
H	2.092208	1.189294	-0.241416
H	-1.223219	-0.844537	-1.295285
N	-0.000325	1.360322	-0.320343
O	0.000314	-1.384323	0.286781

==

Bromine-radical-morpholine

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16

Bromine-radical-morpholine

Br	1.864891	0.000003	-0.196831
C	-1.081431	1.222759	0.818140
C	-1.647853	1.164676	-0.592402
C	-1.648246	-1.164091	-0.593126
C	-1.082015	-1.223283	0.817421
H	-2.305936	2.027131	-0.766695
H	-1.910087	1.332332	1.543424
H	-0.406979	2.082840	0.928952
H	-2.306671	-2.026166	-0.767941
H	-0.816129	-1.205832	-1.321853
H	-1.910747	-1.332810	1.542636
H	-0.407945	-2.083701	0.927938
H	-0.815761	1.206477	-1.321128
N	-0.346848	-0.000497	1.098836
O	-2.413718	0.000481	-0.784843
H	0.104010	-0.001121	2.010460

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HAT_Morpholine-N-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS (TS1) (N-Centered)
==
31
HAT_Morpholine-N-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS
H -1.104612 -0.559142 2.118913
C -1.705393 -1.058090 1.344482
C -3.111974 -0.459905 1.285274
H -3.021097 0.637536 1.187489
H -3.666753 -0.697169 2.203924
C -1.812644 -1.332418 -1.067917
C -3.216046 -0.725379 -1.021917
H -1.287036 -1.020939 -1.982899
H -1.906857 -2.438180 -1.081003
H -3.846607 -1.161352 -1.809518
H -3.130433 0.364591 -1.184942
H -1.790406 -2.131908 1.611575
N -1.029945 -0.951684 0.078277
O -3.832315 -1.001675 0.208984
Br -0.700887 1.814538 -0.284239
C 2.404061 -1.269205 -0.941271
C 3.814168 -0.691857 -0.981121
H 3.807369 0.259293 -1.552993
H 4.500976 -1.385115 -1.486449
C 2.086313 -0.114241 1.187517
C 3.507289 0.411741 1.049513
H 1.428224 0.629148 1.660691
H 2.081246 -1.036175 1.790824
H 3.973735 0.532831 2.036665
H 3.484486 1.405645 0.557630
H 2.426195 -2.273520 -0.488748
N 1.520661 -0.424483 -0.133094
O 4.307989 -0.480809 0.314466
H 1.984530 -1.359937 -1.953717
H 1.292266 0.468160 -0.600233
H 0.270748 -0.813434 -0.010070

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HAT_Morpholine-N-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_for (IM1) (N-Centred)
==
31
HAT_Morpholine-N-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_for
H -1.778621 -1.596330 2.081827
C -2.396148 -1.428904 1.185963
C -2.917674 0.033591 1.158315
H -2.058779 0.729109 1.194905
H -3.570134 0.207292 2.024840
C -2.397867 -1.429122 -1.184967
C -2.919485 0.033345 -1.156867
H -1.781619 -1.596657 -2.081691

H -3.280871 -2.095882 -1.230952
H -3.573342 0.206740 -2.022399
H -2.060749 0.728963 -1.195019
H -3.279113 -2.095618 1.233347
N -1.635859 -1.675013 -0.000032
O -3.676297 0.231722 0.001300
Br 0.243468 2.047419 -0.002271
C 1.801710 -1.183463 -1.230800
C 3.128124 -0.437943 -1.160933
H 2.927243 0.650120 -1.187492
H 3.756236 -0.703309 -2.021685
C 1.796230 -1.172950 1.233340
C 3.123275 -0.428600 1.163069
H 1.193824 -0.819046 2.081674
H 1.959243 -2.257583 1.329976
H 3.747669 -0.687535 2.028462
H 2.922640 0.659662 1.180321
H 1.965869 -2.268797 -1.317134
N 1.033865 -0.911859 -0.001621
O 3.832205 -0.787282 0.003907
H 1.203019 -0.837783 -2.085135
H 0.753285 0.145526 -0.005895
H 0.090515 -1.391663 -0.001238

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HAT_Morpholine-N-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_rev (IM2) (N-Centred)
==
31
HAT_Morpholine-N-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_rev
H -1.084875 -0.488482 2.043853
C -1.676148 -1.025623 1.288828
C -3.139782 -0.605379 1.349859
H -3.197466 0.498627 1.300998
H -3.594841 -0.942113 2.291376
C -1.930448 -1.225569 -1.133067
C -3.382129 -0.796156 -0.958256
H -1.516797 -0.826660 -2.070110
H -1.879939 -2.331933 -1.170635
H -4.015819 -1.273738 -1.718056
H -3.447691 0.301854 -1.078574
H -1.600087 -2.111939 1.494012
N -1.137999 -0.736068 -0.024134
O -3.870318 -1.187424 0.300070
Br -0.856554 1.808576 -0.278012
C 2.729420 -1.315386 -0.935845
C 4.109064 -0.664772 -0.892934
H 4.100725 0.258543 -1.511029
H 4.876835 -1.337523 -1.302267
C 2.167956 -0.105939 1.079490
C 3.565639 0.501796 1.053371

H	1.440338	0.611917	1.488509
H	2.173540	-0.999909	1.726630
H	3.937157	0.685122	2.071829
H	3.532226	1.476308	0.521984
H	2.780403	-2.297078	-0.435004
N	1.723499	-0.506734	-0.254982
O	4.482051	-0.362076	0.426564
H	2.415962	-1.491032	-1.976481
H	1.516974	0.338268	-0.793094
H	-0.111059	-0.852597	-0.121465

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HAT_Morpholine-C-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS (TS1-C-Centered)

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31

HAT_Morpholine-C-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS

H	0.005569	-1.380164	-0.122847
C	1.380489	-1.514249	0.054664
C	2.007184	-1.027090	-1.256383
H	1.624703	-0.023108	-1.514141
H	1.851152	-1.728154	-2.086748
C	3.088862	-0.543687	1.380382
C	3.775263	-0.140436	0.050254
H	3.290077	0.196558	2.168045
H	3.458024	-1.528348	1.708767
H	4.868845	-0.209138	0.139167
H	3.493466	0.902381	-0.187613
H	1.710269	-2.537762	0.297006
N	1.671691	-0.617407	1.085674
H	1.285827	0.322352	0.873946
O	3.395429	-1.005465	-0.987505
Br	0.040088	2.057422	-0.158267
C	-1.759887	-0.961356	1.228211
C	-3.079576	-0.198295	1.259751
H	-2.869891	0.881129	1.130162
H	-3.586311	-0.345837	2.222894
C	-2.093095	-1.263329	-1.177432
C	-3.403801	-0.491049	-1.030075
H	-1.622233	-1.056095	-2.149097
H	-2.275966	-2.346144	-1.092272
H	-4.144947	-0.856738	-1.754052
H	-3.213841	0.581390	-1.232911
H	-1.923323	-2.026266	1.457393
N	-1.178798	-0.848661	-0.112789
O	-3.943215	-0.666098	0.252679
H	-1.037670	-0.545418	1.945980
H	-0.877429	0.161501	-0.252172

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HAT_Morpholine-C-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_for (IM1_C-centered)
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31
HAT_Morpholine-C-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_for
H 0.376736 -1.480378 0.712344
C 1.475915 -1.404832 0.757485
C 2.099567 -1.801455 -0.572064
H 1.617204 -1.223061 -1.383447
H 1.936538 -2.871109 -0.760286
C 3.270767 0.250197 0.986471
C 3.804612 -0.231842 -0.357415
H 3.431629 1.331227 1.101550
H 3.802829 -0.277468 1.801729
H 4.899160 -0.141173 -0.381592
H 3.379276 0.401540 -1.159111
H 1.856166 -2.075528 1.552711
N 1.846210 -0.030021 1.063800
H 1.395349 0.341381 1.894141
O 3.489008 -1.582563 -0.570064
Br 0.646312 1.643683 -0.470573
C -2.367177 -0.064004 1.260203
C -3.526443 0.778571 0.736793
H -3.128753 1.552293 0.046507
H -4.051494 1.291331 1.556248
C -2.765338 -1.619634 -0.531336
C -3.914867 -0.731397 -1.000725
H -2.291756 -2.121146 -1.389964
H -3.170498 -2.407848 0.126896
H -4.722125 -1.327622 -1.451681
H -3.541790 -0.023338 -1.771624
H -2.738159 -0.737281 2.052743
N -1.759555 -0.871607 0.210162
O -4.475689 -0.022843 0.075771
H -1.597701 0.588493 1.701863
H -1.248889 -0.248188 -0.418819

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HAT_Morpholine-C-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_rev (IM2_C-Centred)
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31
HAT_Morpholine-C-H-atom-tranfer-to-second-N-morpholine_Br-radical-TS_rev
H -0.369915 -1.387905 -0.792447
C 1.748327 -1.481466 -0.480659
C 2.479889 -0.580730 -1.434509
H 1.979327 0.403043 -1.513934
H 2.611584 -1.014025 -2.434838
C 2.969938 -0.756284 1.391790
C 3.793902 0.103735 0.419974
H 2.894605 -0.273898 2.378298
H 3.444630 -1.742234 1.522753

H	4.846874	0.156490	0.733991
H	3.376705	1.130460	0.413660
H	2.053100	-2.538739	-0.493272
N	1.631069	-0.937116	0.813648
H	1.204709	-0.000906	0.745433
O	3.787593	-0.434571	-0.880614
Br	-0.198732	1.947264	0.071715
C	-1.649238	-1.476039	0.847762
C	-2.860817	-0.697855	1.337289
H	-2.554990	0.340575	1.566744
H	-3.257900	-1.159152	2.250866
C	-2.301653	-0.829289	-1.447275
C	-3.482841	-0.095201	-0.821854
H	-1.920490	-0.287795	-2.323939
H	-2.584123	-1.851966	-1.739598
H	-4.337650	-0.112395	-1.510809
H	-3.194089	0.957790	-0.640965
H	-1.903386	-2.535361	0.690367
N	-1.216905	-0.900748	-0.446636
O	-3.883110	-0.716869	0.371196
H	-0.793567	-1.405470	1.533733
H	-0.859848	0.122583	-0.264898

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