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Scope and limitations of a DMF bio-alternative within Sonogashira cross-coupling and Cacchi-type annulation

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Full Research Paper

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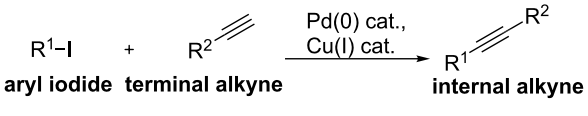
Abstract

Pd-catalysed C–C bond formation is an essential tool within the pharmaceutical and agrochemical industries. Many of these reactions rely heavily on polar aprotic solvents; however, despite their utility, these solvents are incompatible with the drive towards more sustainable chemical synthesis. Herein, we describe the scope and limitations of an alternative to DMF derived from renewable sources (Cyrene^{TM}) in Sonogashira cross-coupling and Cacchi-type annulations.

Introduction

The Sonogashira reaction [1,2] (Scheme 1) is a robust and broadly applicable Pd-catalysed bond-forming process that, alongside the Suzuki–Miyaura reaction [3], has steadily become an indispensible tool for C–C bond formation in the pharmaceutical industry [4]. While the Sonogashira reaction can be effectively carried out in a variety of media [1,2], in the general sense this process clearly relies upon the use of dipolar aprotic solvents, in particular DMF. Indeed, some 41% of all Sonogashira reactions reported using aryl iodides can be linked to the use of DMF as a solvent [5].



Scheme 1: The Sonogashira reaction.

In this context, the sustainability movement within pharmaceutical research and development strives to substitute solvents that have regulatory and environmental issues for those with a lower perceived risk. Indeed, solvent replacement has been designated a key research area with numerous pharmaceutical companies detailing their efforts towards a more sustain-

able solvent selection as part of their overall sustainability programmes [6-23].

Based on its associated regulatory issues [24], it is perhaps no surprise that DMF continues to be a priority solvent for replacement. With legislation surrounding the use of DMF becoming increasingly stringent [24], numerous efforts have been made towards the use of alternative media in the Sonogashira reaction [25-30]. However, notwithstanding its issues, DMF is an excellent solvent for the Sonogashira reaction and its replacement frequently occurs at the expense of increased temperature (and therefore potentially substrate compatibility), reaction time, catalyst loading or the requirement for non-commercial/expensive catalysts, and yield [25-30]. Consequently, poor choice of solvent replacement can result in one of industry's workhorse reactions becoming rather less predictable and robust.

In this regard, dihydrolevoglucosenone (Cyrene, Figure 1), accessed in two steps from cellulose [31,32], has been shown to possess similar physical properties to those of DMF and other dipolar aprotic solvents [31,32]. In addition to its renewability, Cyrene, as yet, has no associated pernicious effects and could potentially represent a direct and functional replacement in many of the fundamental reactions that typically employ DMF [31,32]. The replacement of solvents with regulatory issues with bio-derived alternatives has provided a series of advances within the cross-coupling arena [33], allowing efficient C–C bond formation via cornerstone Pd-based methods including Suzuki–Miyaura [34,35], Mizoroki–Heck [36,37], Sonogashira [38], Stille [39], Hiyama reactions [40], and hydroformylation reactions [41].

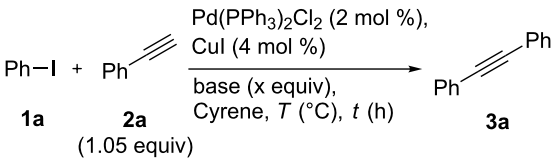
Figure 1: Cyrene vs. DMF – selected physical properties [31,32].

In the current study, we present the use of Cyrene as an alternative solvent (direct DMF replacement) for the Sonogashira reaction, as well as related Cacchi-type annulations [42,43], with an emphasis on scope and limitations of its application.

Results and Discussion

To explore the use of Cyrene in the context of the Sonogashira cross-coupling, we established a simple benchmark reaction using iodobenzene (**1a**) and phenylacetylene (**2a**) (Table 1). A typical literature-derived catalyst system was employed ($Pd(PPh_3)_2Cl_2$ with CuI additive [44,45]) and conversion to diphenylacetylene (**3a**) was monitored.

Table 1: Reaction optimisation and comparison with existing solvents.[a]



Entry	Reaction conditions	**3a** (%)[b]
1	0.1 M, Et_3N (3 equiv), 20 °C, 5 h	94
2	0.3 M, Et_3N (3 equiv), 20 °C, 5 h	98
3	0.5 M, Et_3N (3 equiv), 20 °C, 5 h	100
4	0.5 M, K_3PO_4 (3 equiv), 20 °C, 5 h	–[c]
5	0.5 M, Cs_2CO_3 (3 equiv), 20 °C, 5 h	–[c]
7	0.5 M, Et_3N (1.1 equiv), 20 °C, 5 h	98
8	0.5 M, Et_3N (1.1 equiv), 30 °C, 1 h	96
9[d]	0.5 M, Et_3N (1.1 equiv), 30 °C, 1 h	81
10[e]	0.5 M, Et_3N (1.1 equiv), 30 °C, 1 h	87

[a]**1** (1 equiv, 0.25 mmol), **2** (1.05 equiv, 0.26 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (4 mol %), base (see table), Cyrene, temperature (see table), time (see table), N_2. [b]Isolated yield. [c]Reaction mixture solidified, product was not isolated. [d]THF used as solvent. [e]DMF used as solvent.

Pleasingly, high conversion to product was immediately observed at room temperature in 5 h (94%, Table 1, entry 1). This high conversion was consistent across several reaction concentrations (Table 1, entries 2 and 3) allowing for a reduction in solvent volume, commensurate with the principles of green chemistry [46,47].

In attempts to further limit waste, we scanned a series of bases (see Supporting Information File 1); organic bases consistently performed more effectively and alternatives to Et_3N provided no significant advantages. However, during this process we identified some potential limitations of this emerging solvent. Specifically, inorganic bases such as K_3PO_4 and Cs_2CO_3 (Table 1, entries 4 and 5) resulted in the generation of a solid reaction mixture. Further analysis revealed that the aldol products **4a** and **4b** (Figure 2) were generated under specific reaction conditions.

The manufacturers note that when using Cyrene, materials to avoid are strong acids, and strong oxidising and reducing agents. Since sensitivity to base was not specified, we surveyed a range of bases at various temperatures to evaluate the limitations of Cyrene under such conditions (Table 2).

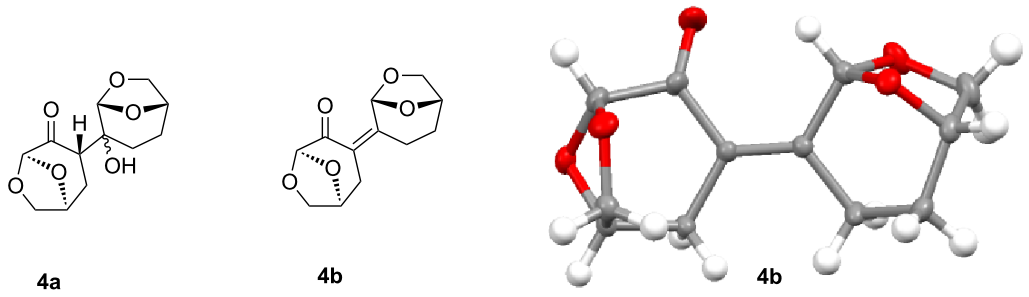


Figure 2: Aldol products **4a** and **4b** and single crystal X-ray structure of **4b**.

Table 2: Evaluation of the base sensitivity of Cyrene.[a]

Entry	Base	Temp. (°C)	Reaction (Y/N)[b]
1	KOAc	25	N
		50	Y
		100	Y
2	Pyridine	25	N
		50	Y
		100	Y
3	K_2CO_3	25	Y
		50	Y
		100	Y
4	DIPEA	25	N
		50	N
		100	Y
5	Cs_2CO_3	25	Y
		50	Y
		100	Y
6	Et_3N	25	N
		50	N
		100	Y
7	K_3PO_4	25	Y
		50	Y
		100	Y
8	DBU	25	Y
		50	Y
		100	Y
9	KOH	25	Y
		50	Y
		100	Y
10	*t*-BuOK	25	Y
		50	Y
		100	Y
11	NaH	25	Y
		50	Y
		100	Y

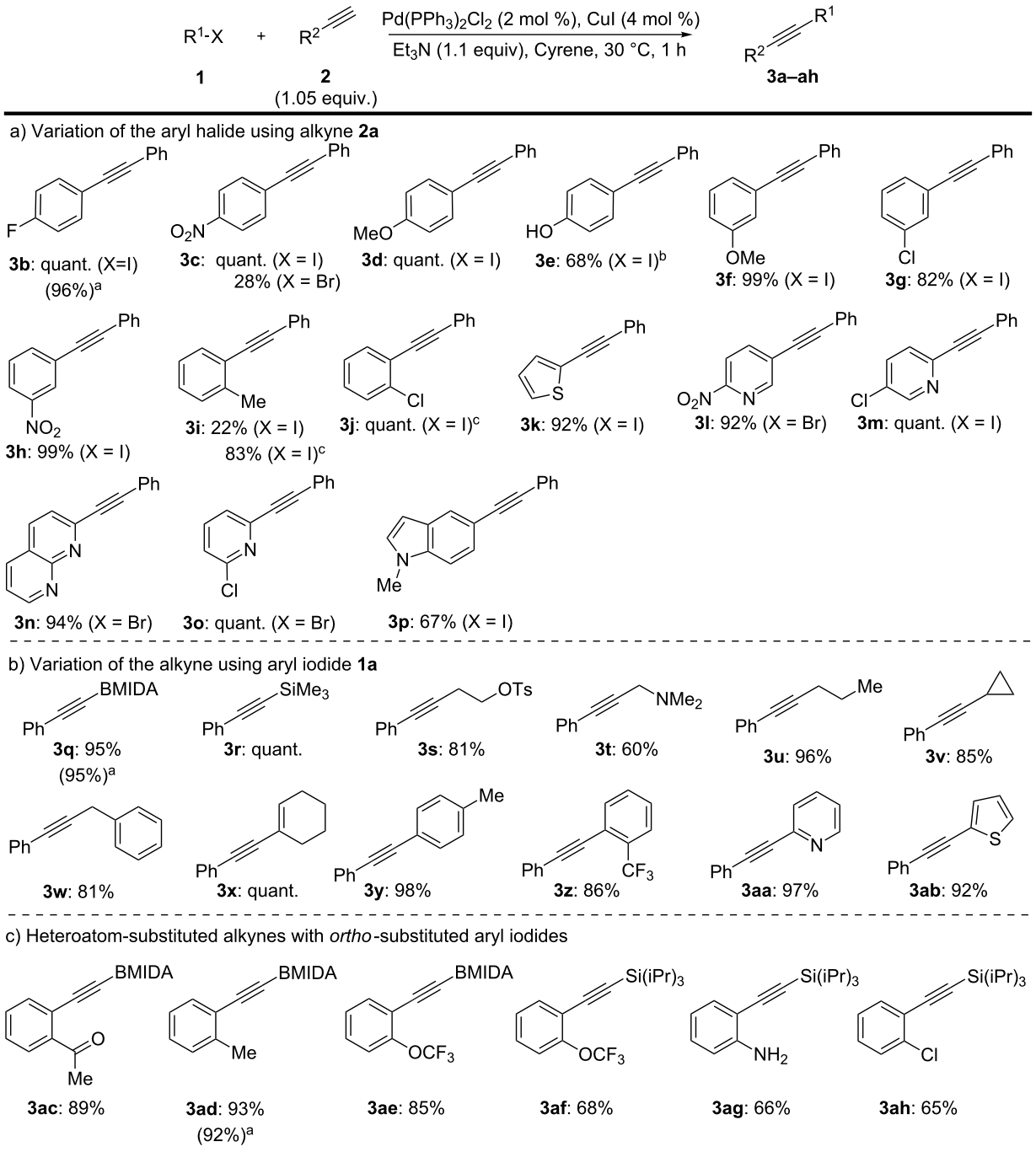
[a]Reaction conditions: base (0.07 mmol) and Cyrene (0.5 mL) stirred at the indicated temeperature for 24 h before analysis by TLC and ^{1}H NMR . [b]Y = reaction occurs, N = no reaction. See Supporting Information File 1.

Under these specific reaction conditions, with the exception of Et_3N and DIPEA, there was a clear base sensitivity displayed by Cyrene in the presence of all bases when the temperature was elevated above 25 °C. Organic bases such as pyridine (Table 2, entry 2), DIPEA (Table 2, entry 4), and Et_3N (Table 2, entry 6) were tolerated at 25 °C with DIPEA and Et_3N also tolerated at 50 °C. DBU, however, was not tolerated at any temperature (Table 2, entry 8). With the exception of KOAc (Table 2, entry 1), all inorganic bases resulted in reaction with the solvent at room temperature (Table 2, entries 3, 5, 7, and 9–11). The extent of the reaction varied from the generation of additional components, such as **4a** and **4b**, to gelation or complete solidification of the reaction mixture. However, in a moderately basic reaction mixture (e.g., using Et_3N) at mild reaction temperatures this issue could be entirely avoided. As such, optimisation of the Sonogashira process allowed complete conversion and 96% isolated yield in 1 h at 30 °C (Table 1, entry 8). Importantly, the Cyrene-based system compared very favourably upon comparison with standard solvents (THF and DMF; Table 1, entries 9 and 10, respectively).

Continuing with the primary investigation and with an optimised set of reaction conditions, we sought to explore the generality of Cyrene in the Sonogashira cross-coupling (Scheme 2). Significantly, a broad range of functionalised aryl and heteroaryl iodides were tolerated (Scheme 2a).

In addition, electron-deficient aryl bromides were accommodated, although with some variation in yield (**3c**, **3l**, **3o**, **3n**). Functionality on the alkyne component was also typically well tolerated (Scheme 2b). While **3i** and **3j** required an extended reaction time, this was a substrate-specific problem for the use of **2a** with these *ortho*-substituted aryl iodides that was not apparent for other alkyne/*ortho*-substituted iodoarene combinations (Scheme 2c).

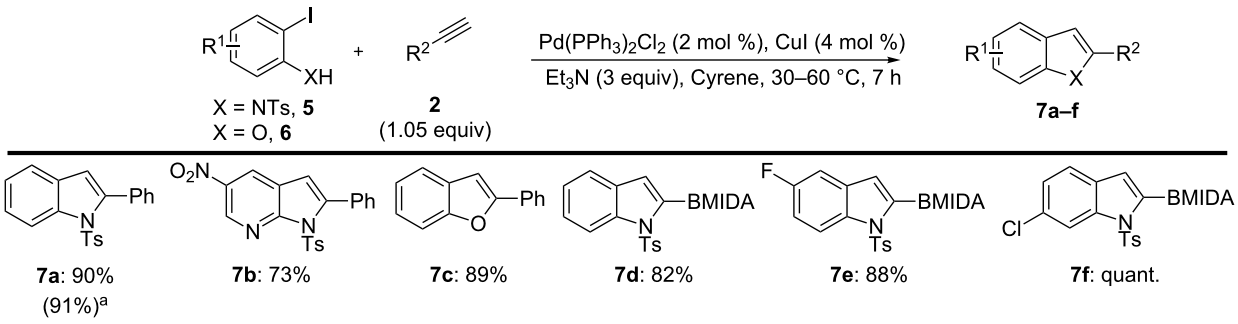
Judicious selection of reacting components also enabled the development of a useful Cacchi-type annulation (Scheme 3)



Scheme 2: Cyrene-based Sonogashira cross-coupling: Substrate scope. Isolated yields. [a]Yield using DMF as solvent. [b]2 equiv of Et_3N used. [c]24 h reaction time.

[42,43]. Specifically, employing *ortho*-amino (**5**) or *ortho*-hydroxyaryl iodides (**6**) in the Sonogashira process generated an alkyne intermediate that, upon increasing the reaction temperature from 30 °C to 60 °C, could undergo 5-*endo*-dig cyclisation to forge functionalised and pharmaceutically relevant indole, benzofuran, and aza-indole scaffolds in a single operation (**7a**–**f**) [48-52].

Finally, with the viewpoint of generality of DMF substitution by Cyrene, the base/temperature sensitivity issue may have potential implications for further applications of Cyrene within well-used organic transformations. For example, the majority of many other standard cross-coupling processes employ inorganic or organic bases and heat (e.g., Suzuki–Miyaura, Heck). Accordingly, Cyrene may be projected to be incompatible with



Scheme 3: Cacchi-type annulation of *o*-amino/hydroxy iodoarenes. Isolated yields. [a]Yield using DMF as solvent.

standard conditions for these reactions and its use would necessitate base-free or exceptionally mildly basic reaction conditions. In contrast, amide-bond formation is the most practiced reaction in the pharmaceutical industry [4] and these are routinely performed in DMF at room temperature in the presence of organic bases [53]. As such, Cyrene may offer considerable potential in this area. However, additional work will be required to validate the practicality of Cyrene as a viable DMF replacement in these applications.

Conclusion

In summary, we have developed a mild and robust method for the Sonogashira reaction, employing the bio-derived and sustainable alternative to DMF, Cyrene. In addition, we have shown the capacity for extension of the utility of this new solvent towards enabling the cascade synthesis of functionalised indoles and benzofurans via a Cacchi-type annulation. Perhaps more importantly, we have documented some of the limitations of the use of Cyrene as a solvent, providing guidance emerging in relation to the thermal and chemical (base) stabilities of this promising green solvent.

Supporting Information

Supporting Information File 1

Experimental procedures, analytical data, copies of NMR spectra, and single X-ray crystal diffraction data of **4b**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-187-S1.pdf]

Acknowledgements

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Supporting Information

for

Scope and limitations of a DMF bio-alternative within Sonogashira cross-coupling and Cacchi-type annulation

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Experimental procedures, analytical data, copies of NMR spectra, and single X-ray crystal diffraction data of 4b

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1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[1]

1.1 Purification of solvents

Cyrene was supplied directly by Circa and used as obtained. DMF was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. THF was obtained from a PureSolv SPS-400-5 solvent purification system and transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under N_2. CH_2Cl_2, Et_2O, EtOAc, MeCN, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification.

1.2 Purification and drying of bases

Et_3N was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. Inorganic bases were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 h before use.

1.3 Experimental details

Reactions were carried out using conventional glassware (preparation of **S1** and **S2**) or in sealed 5 mL microwave vials (optimization reactions and reactions for Schemes 2 and 3). The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally ca. 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

1.4 Purification of products

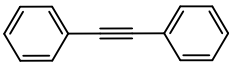
Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using a vanillin solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel. Reverse phase flash chromatography was carried out using IST Isolute C18 cartridges. Strong cation-exchange purification was carried out using an SCX cartridge.

1.5 Analysis of products

Fourier transformed infrared (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectra were obtained on a Bruker DRX 500 spectrometer (Avance III HD console, Ascend 500 MHz magnet, BBO smart probe) at 500 MHz, 126 MHz, 471 MHz and 160 MHz, respectively. ^{1}H NMR for the evaluation of the base sensitivity were obtained on a Bruker AV 400 at 400 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.0 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University or at Glasgow University's School of Chemistry Mass Spectrometry Service. Crystal data was obtained at 123(2) K using an Oxford Diffraction Gemini instrument and monochromatic Mo radiation.

2. General experimental procedures

General Procedure A: Optimized conditions



For example, synthesis of 1,2-diphenylethyne, **3a**.

To an oven-dried 5 mL microwave vessel was added $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %) and CuI (1.9 mg, 0.01 mmol, 4 mol %). The vessel was then capped and purged with N_2 before addition of Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). The reaction mixture was heated to 30 °C and maintained at this temperature with stirring for 1 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a white solid (44.5 mg, quant.).

υ_{max} (solid): 3068, 1603, 1495, 1446 cm^{-1}.

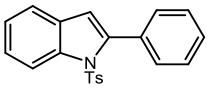
^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (dd, *J* = 7.2, 1.9 Hz, 4H), 7.36 (m, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.4, 128.3, 123.3, 89.4.

HRMS: exact mass calculated for [M] ($C_{14}H_{10}$) requires *m/z* 178.0782, found *m/z* 178.0784.

Characterisation data is consistent with literature reported values.[2]

General Procedure B: Synthesis of indoles and benzofuran



For example, synthesis of 2-phenyl-1-tosyl-1*H*-indole (**7a**).

To an oven-dried 5 mL microwave vessel was added $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), and *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv). The vessel was then capped and purged with N_2 before addition of Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). The reaction mixture was heated to 30 °C and maintained at this temperature with stirring for 1 h. The reaction was subsequently heated to 60 °C and maintained at this temperature for 6 h before the vessel was vented and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a white solid (78.4 mg, 90%).

υ_{max} (solid): 3073, 1368, 1169 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.33 (d, *J* = 8.4 Hz, 1H), 7.54–7.50 (m, 2H), 7.45 (t, *J* = 8.2 Hz, 4H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.31–7.28 (m, 3H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.56 (s, 1H), 2.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.5, 142.2, 138.3, 134.7, 132.4, 130.7, 130.4, 129.2, 128.7, 127.5, 126.8, 124.8, 124.3, 120.7, 116.7, 113.4, 21.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{18}NO_6S$) requires *m/z* 348.1058, found *m/z* 348.1061.

Characterisation data is consistent with literature reported values.[3]

3. Reaction optimization data

3.1. Variation of concentration

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (**X** M), Et_3N (104 µL, 0.75 mmol, 3 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at 20 °C for 5 h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the desired compound as a white solid.

Entry	Concentration (M)	Volume (mL)	Isolated yield (%)
1	0.3	0.83	98
2	0.1	2.5	94
3	0.5	0.5	100

3.2. Variation of the base

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), **Base** (**X** equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at 20 °C for 5 h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the desired compound as a white solid.

Entry	Base (mass)	Equiv	Isolated yield (%)
1[a]	K_3PO_4 (159 mg)	3	-
2[a]	Cs_2CO_3 (245 mg)	3	-
3	DIPEA (97 mg)	3	85
4	Pyridine (59 mg)	3	0
5	Et_3N (28 mg)	1.1	98
6	Et_3N (38 mg)	1.5	94
7	Et_3N (51 mg)	2	92

[a] Formation of solid Cyrene dimer – product was not isolated

3.3. Variation of time and temperature

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at **X** °C for **X** h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the desired compound as a white solid.

Entry	Temp. (°C)	Time (h)	Isolated yield (%)
1	20	1	86
2	20	3	94
3	20	5	98
4	25	1	91
5	30	1	96

3.4. Variation of solvent

Reactions were carried out according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), **solvent** (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at 30 °C for 1 h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the desired compound as a white solid.

Entry	Solvent	Isolated yield (%)
1	Cyrene	96
2	THF	81
3	DMF	87

4. Base sensitivity study

Base (0.07 mmol) was added to a test tube and Cyrene (0.5 mL) was added. The tube was then capped and the mixture stirred at **X** °C. After 24 h the reaction mixture was sampled and analysed by TLC (60% EtOAc in petroleum ether) and ^{1}H NMR and the resulting spectrum compared with that of Cyrene.

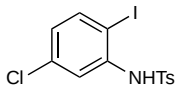
Base	Mass (mg)	Temperature (°C)	Reaction (Y/N)	Solid Formation
KOAc	7	25	N	x
		50	N	x
		100	N	x
Pyridine	6	25	N	x
		50	N	x
		100	N	x
K_2CO_3	10	25	N	x
		50	N	x
		100	Y	x
DIPEA	9	25	N	x
		50	N	x
		100	N	x
Cs_2CO_3	23	25	Y	√
		50	Y	√
		100	Y	√
Et_3N	7	25	N	x
		50	N	x
		100	N	x
K_3PO_4	15	25	Y	x
		50	Y	√
		100	Y	√
DBU	11	25	Y	√
		50	Y	√
		100	Y	√
KOH	4	25	Y	√

		50	Y	√
		100	Y	√
^{t}BuOK	8	25	Y	√
		50	Y	√
		100	Y	√
NaH	2	25	Y	√
		50	Y	√
		100	Y	√

5. Compound characterisation data

5.1. Preparation of intermediates

S1: *N*-(5-Chloro-2-iodophenyl)-4-methylbenzenesulfonamide



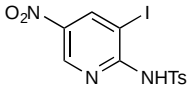
To a round-bottomed flask charged with 5-chloro-2-iodoaniline (1 g, 3.95 mmol, 1 equiv) was added a solution of 1:1 pyridine in CH_2Cl_2 (0.7 M, 40 mL) and the reaction mixture was cooled to 0 °C. 4-Methylbenzenesulfonyl chloride (750 mg, 3.95 mmol, 1 equiv) was added portionwise, and the reaction mixture was allowed to slowly warm to room temperature and then stirred for 24 h. Upon completion of the reaction, water (80 mL) and CH_2Cl_2 (80 mL) were added. The reaction mixture was separated and the organics were washed with 1 N NaOH (2 × 40 mL), 1 N HCl (2×40 mL), and brine (2 × 40 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography (silica gel, 0–12% EtOAc in petroleum ether) to afford the title compound as an off white solid (890 mg, 52%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72–7.65 (m, 3H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.88–6.80 (m, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.1, 139.1, 138.1, 135.1, 135.1, 129.4, 127.0, 126.4, 121.4, 88.3, 21.2.

Characterisation data is consistent with literature reported values.[4]

S2: *N*-(3-Iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide



Prepared in two steps from 3-iodo-5-nitropyridin-2-amine:

Step 1: To a 25 mL three-necked flask charged with 5-nitropyridin-2-amine (1 g, 7.1 mmol, 1 equiv), was added concentrated sulfuric acid (12 mL, 0.6 M) and potassium iodate (653 mg, 2.8 mmol, 0.4 equiv) portionwise, before subsequent heating to 200 °C. Potassium iodide (1.18 g, 7.1 mmol, 1 equiv) was then added dropwise as an aqueous solution (4 mL), and the reaction mixture was stirred at 200 °C for 1.5 h. Upon completion, the reaction mixture was allowed to cool to room temperature before the slow addition of saturated sodium bicarbonate solution (20 mL) and EtOAc (20 mL). The reaction mixture was separated and the organics were washed with an aqueous solution of saturated $Na_2S_2O_3$ (2 × 30 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow solid, 3-iodo-5-nitropyridin-2-amine, which was used without further purification (1.64 g, 87 %).

Step 2: To a 100 mL round-bottomed flask charged with 3-iodo-5-nitropyridin-2-amine (1.29 g, 4.86 mmol, 1 equiv) was added THF (40 mL, 0.13 M) and the reaction mixture was cooled to 0 °C.

Sodium hydride (224 mg, 9.72 mmol, 2 equiv) was added portionwise and the reaction mixture was stirred at 0 °C for 20 minutes. 4-Methylbenzenesulfonyl chloride (1.09 g, 4.86 mmol, 1 equiv) was added portion wise, and the reaction mixture was allowed to slowly warm to room temperature and was stirred for 18 h. Upon completion of the reaction, water (50 mL) and CH_2Cl_2 (50 mL) were added and the reaction mixture was separated and the organics washed with 1 M NaOH (2 × 50 mL), 1 M HCl (2 × 50 mL), and brine (2 × 50 mL). The organics were passed through a hydrophobic frit and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography (silica gel, 0–30% EtOAc in petroleum ether) to afford the title compound as a yellow solid (1.43 g, 70%).

υ_{max} (solid): 3581, 3268, 3064, 2919, 1571, 1444, 1320 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.66 (d, *J* = 2.6 Hz, 1H), 8.40 (d, *J* = 2.5 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 3.35 (bs, 1H), 2.32 (s, 3H).

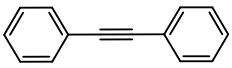
^{13}C NMR (DMSO-d_6, 126 MHz): δ 161.9, 145.0, 142.3, 140.9, 140.7, 134.7, 128.9, 127.4, 86.7, 21.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{11}IN_3O_4S$) requires *m/z* 419.9509, found *m/z* 419.9510.

Characterisation data is consistent with literature reported values.[4]

5.2. Products from Table 1

3a: 1,2-Diphenylethyne



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a white solid (44.5 mg, quant.).

υ_{max} (solid): 3068, 1603, 1495, 1446 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (dd, *J* = 7.2, 1.9 Hz, 4H), 7.36 (m, 6H).

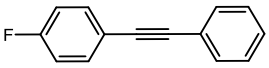
^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.4, 128.3, 123.3, 89.4.

HRMS: exact mass calculated for [M] ($C_{14}H_{10}$) requires *m/z* 178.0782, found *m/z* 178.0784.

Characterisation data is consistent with literature reported values.[2]

5.3. Products from Scheme 2a

3b: 1-Fluoro-4-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 4-fluoro-iodobenzene (28.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a white solid (48.8 mg, quant.).

Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 4-fluoro-iodobenzene (28.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv).

After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a white solid (46.9 mg, 96%).

υ_{max} (solid): 2921, 1595, 1508, 1217 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.55–7.50 (m, 4H), 7.38–7.33 (m, 3H), 7.05 (t, *J* = 8.7 Hz, 2H).

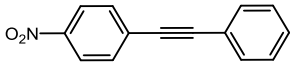
^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.5 (d, $^1J_{CF}$ = 249.6 Hz), 133.5 (d, $^3J_{CF}$ = 8.2 Hz), 131.6, 128.4, 128.4, 123.3, 119.4 (d, J_{CF} = 3.4 Hz), 115.7 (d, $^2J_{CF}$ = 22.4 Hz), 89.1, 88.3.

^{19}F NMR ($CDCl_3$, 471 MHz): δ -110.98.

HRMS: exact mass calculated for [M] ($C_{14}H_9F$) requires *m/z* 196.0688, found *m/z* 196.0689.

Characterisation data is consistent with literature reported values.[5]

3c: 1-Nitro-4-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 4-nitro-iodobenzene (62.3 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as an off white solid (48.8 mg, quant.).

Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 4-nitro-bromobenzene (50.5 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as an off white solid (14.6 mg, 28%).

υ_{max} (solid): 3107, 2926, 2217, 1593, 1511 cm^{-1}.

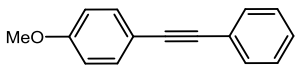
^1H NMR ($CDCl_3$, 500 MHz): δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H), 7.58–7.54 (m, 2H), 7.39 (dd, *J* = 5.3, 1.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 147.0, 132.3, 131.9, 130.4, 129.3, 128.6, 123.7, 122.1, 94.7, 87.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{10}NO_2$) requires *m/z* 224.0712, found *m/z* 224.0714.

Characterisation data is consistent with literature reported values.[5]

3d: 1-Methoxy-4-(phenylethynyl)benzene



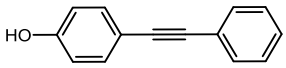
Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 4-iodoanisole (58.5 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% Et_2O in petroleum ether) to afford the title compound as an off white solid (51.9 mg, quant.).

υ_{max} (solid): 3014, 2841, 2217, 1509 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (dt, *J* = 3.9, 2.1 Hz, 2H), 7.49–7.46 (m, 2H), 7.36–7.29 (m, 3H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H).

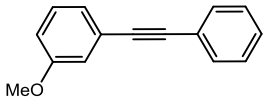
^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.6, 133.1, 131.5, 128.3, 127.9, 123.6, 115.4, 114.0, 89.4, 88.1, 55.3.
HRMS: exact mass calculated for $[2M+H]^+$ ($C_{30}H_{25}O_2$) requires *m/z* 417.1855, found *m/z* 417.1847.
Characterisation data is consistent with literature reported values.[5]

3e: 4-(Phenylethynyl)phenol



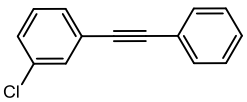
Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (70 µL, 0.5 mmol, 2 equiv), 4-iodophenol (55 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% Et_2O in petroleum ether) to afford the title compound as an off white solid (32.6 mg, 68%).
υ_{max} (solid): 3412, 3059, 1513, 1254 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.33 (m, 3H), 6.81 (d, *J* = 8.6 Hz, 2H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.7, 133.3, 131.5, 128.3, 127.9, 123.6, 115.7, 115.5, 89.2, 88.1.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{13}O$) requires *m/z* 209.0966, found *m/z* 209.1008.
Characterisation data is consistent with literature reported values.[6]

3f: 1-Methoxy-3-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 3-iodoanisole (29.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (51.4 mg, 99%).
υ_{max} (liquid film): 2937, 2838 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57–7.53 (m, 2H), 7.35 (dd, *J* = 4.9, 2.4 Hz, 3H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.91 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.83 (s, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.4, 131.7, 129.4, 128.4, 128.3, 124.3, 124.2, 123.2, 116.4, 114.9, 89.3, 89.2, 55.3.
HRMS: exact mass calculated for $[M+Na]^+$ ($C_{14}H_{11}O$) requires *m/z* 195.0810, found *m/z* 195.0813.
Characterisation data is consistent with literature reported values.[2]

3g: 1-Chloro-3-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 3-

chloro-iodobenzene (30.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a yellow oil (53.5 mg, 82%).

υ_{max} (liquid film): 3064, 2224, 884 cm^{-1}.

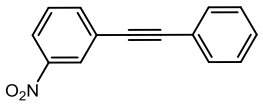
^1H NMR ($CDCl_3$, 500 MHz): δ 7.55–7.51 (m, 3H), 7.41 (dt, *J* = 7.3, 1.4 Hz, 1H), 7.36 (dd, *J* = 4.9, 1.7 Hz, 3H), 7.31 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 134.4, 131.9, 131.6, 129.9, 129.8, 128.8, 128.7, 128.6, 125.2, 122.9, 90.7, 88.1.

HRMS: exact mass calculated for [M] ($C_{14}H_9Cl$) requires *m/z* 212.0393, found *m/z* 212.0395.

Characterisation data is consistent with literature reported values.[7]

3h: 1-Nitro-3-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 3-nitro-iodobenzene (62.3 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a white solid (55.2 mg, 99%).

υ_{max} (solid): 3083, 2213, 1517, 1349 cm^{-1}.

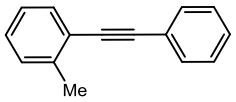
^1H NMR ($CDCl_3$, 500 MHz): δ 8.40–8.37 (m, 1H), 8.19 (m, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.56 (m, 3H), 7.40 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.2, 137.2, 131.8, 129.4, 129.1, 128.5, 126.4, 125.2, 122.9, 122.2, 91.9, 86.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{10}NO_2$) requires *m/z* 224.0712, found *m/z* 224.0710.

Characterisation data is consistent with literature reported values.[5]

3i: 1-Methyl-2-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 24 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20–65% MeCN in water) to afford the title compound as a yellow oil (40 mg, 83%).

υ_{max} (liquid film): 3023, 2924, 2855, 2217, 1496 cm^{-1}.

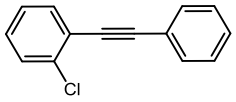
^1H NMR ($CDCl_3$, 500 MHz): δ 7.56–7.53 (m, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.35 (m, 3H), 7.24 (d, *J* = 3.9 Hz, 2H), 7.17 (m, 1H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 140.3, 131.9, 131.7, 129.6, 128.5, 128.5, 128.3, 125.7, 123.7, 123.2, 93.5, 88.5, 20.9.

HRMS: exact mass calculated for [M] ($C_{15}H_{12}$) requires *m/z* 192.0939, found *m/z* 192.0935.

Characterisation data is consistent with literature reported values.[5]

3j: 1-Chloro-2-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-chloro-iodobenzene (30.5 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 24 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20–65% MeCN in water) to afford the title compound as a yellow oil (54.9 mg, quant.).

υ_{max} (liquid film): 3060, 2926, 2224, 1495 cm^{-1}.

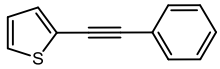
^1H NMR (DMSO-d_6, 500 MHz): δ 7.69 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.62–7.58 (m, 3H), 7.48–7.41 (m, 5H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 135.1, 133.8, 131.9, 130.9, 129.9, 129.8, 129.3, 127.9, 122.4, 122.3, 94.8, 86.4.

HRMS: exact mass calculated for [M] ($C_{14}H_9Cl$) requires *m/z* 212.0393, found *m/z* 212.0385.

Characterisation data is consistent with literature reported values.[2]

3k: 2-(Phenylethynyl)thiophene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodothiophene (27.6 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as an off white solid (41.4 mg, 92%).

υ_{max} (liquid film): 3088, 2204 cm^{-1}.

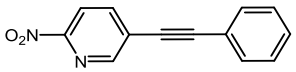
^1H NMR ($CDCl_3$, 500 MHz): δ 7.54–7.50 (m, 2H), 7.35 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.31–7.28 (m, 2H), 7.02 (dd, *J* = 5.0, 3.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.9, 131.4, 128.4, 128.4, 127.3, 127.1, 123.4, 122.9, 93.0, 82.6.

HRMS: exact mass calculated for [M] ($C_{12}H_8S$) requires *m/z* 184.0347, found *m/z* 184.0348.

Characterisation data is consistent with literature reported values.[2]

3l: 2-Nitro-5-(phenylethynyl)pyridine



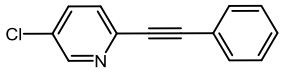
Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 5-bromo-2-nitropyridine (50.8 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% Et_2O in petroleum ether) to afford the title compound as a white solid (51.4 mg, 92%).

υ_{max} (solid): 3058, 2219, 1532, 1348 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.73 (d, *J* = 1.6 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.44 – 7.38 (m, 3H).

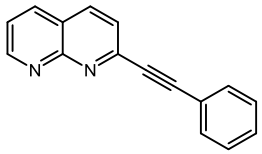
^{13}C NMR ($CDCl_3$, 126 MHz): δ 154.8, 151.1, 141.8, 131.9, 129.8, 128.7, 126.7, 121.4, 117.7, 97.9, 84.2.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_9N_2O_2$) requires *m/z* 225.0664, found *m/z* 225.0670.

3m: 5-Chloro-2-(phenylethynyl)pyridine



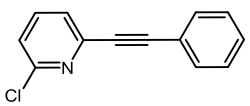
Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 3-chloro-6-iodopyridine (59.8 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et_2O in petroleum ether) to afford the title compound as a white solid (54.5 mg, quant.).
υ_{max} (solid): 3040, 2221, 1493, 1459 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.58 (d, *J* = 1.8 Hz, 1H), 7.67 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.60 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.40–7.36 (m, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.1, 141.5, 136.0, 132.1, 131.3, 129.2, 128.5, 127.7, 121.9, 90.4, 87.6.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_9NCl$) requires *m/z* 214.0418, found *m/z* 214.0421.

3n: 2-(Phenylethynyl)-1,8-naphthyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-bromo-1,8-naphthyridine (52.3 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–65% Et_2O in petroleum ether) to afford the title compound as a white solid (54.3 mg, 94%).
υ_{max} (solid): 3049, 3008, 2211, 1601, 1498 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.15 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 2H), 7.69–7.64 (m, 3H), 7.48 (dd, *J* = 7.7, 3.9 Hz, 1H), 7.43–7.37 (m, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.1, 154.3, 146.9, 137.2, 136.6, 132.4, 129.5, 128.5, 125.4, 122.3, 121.9, 91.6, 89.3. Quaternary carbon at ring junction not observed.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{11}N_2$) requires *m/z* 231.0922, found *m/z* 231.0923.

3o: 2-Chloro-6-(phenylethynyl)pyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.5 mmol, 1.1 equiv), 2-bromo-6-chloropyridine (48 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the

General Procedure (silica gel, 0–10% Et_2O in petroleum ether) to afford the title compound as an off white solid (52.3 mg, quant.).

υ_{max} (solid): 3059, 2960, 2226, 1577, 1435 cm^{-1}.

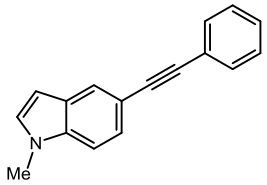
^1H NMR ($CDCl_3$, 500 MHz): δ 7.63 (t, *J* = 7.8 Hz, 1H), 7.60–7.56 (m, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.37 (q, *J* = 5.7 Hz, 3H), 7.28 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.4, 143.6, 138.7, 132.1, 129.3, 128.5, 125.7, 123.6, 121.8, 90.7, 87.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_9NCl$) requires *m/z* 214.0424, found *m/z* 214.0427.

^1H NMR and HRMS data is consistent with literature reported values.[8]

3p: 1-Methyl-5-(phenylethynyl)-1*H*-indole



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (2.6 mg, 0.004 mmol, 2 mol %), CuI (1.4 mg, 0.007 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (28 µL, 0.20 mmol, 1.1 equiv), 5-iodo-1-methyl-1*H*-indole (47 mg, 0.18 mmol, 1 equiv), and phenylacetylene (21 µL, 0.19 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% Et_2O in petroleum ether) to afford the title compound as an off white solid (27.7 mg, 67%).

υ_{max} (solid): 3051, 2926, 2208, 1597, 1496 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.85 (s, 1H), 7.57–7.54 (m, 2H), 7.41 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.49 (d, *J* = 2.7 Hz, 1H), 3.80 (s, 3H).

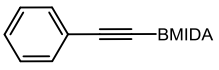
^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.4, 131.5, 129.8, 128.4, 128.3, 127.7, 125.2, 124.8, 124.1, 113.8, 109.3, 101.3, 91.2, 87.0, 32.9.

HRMS: exact mass calculated for [M] ($C_{17}H_{13}N$) requires *m/z* 231.1048, found *m/z* 231.1057.

Characterisation data is consistent with literature reported values.[9]

5.4. Products from Scheme 2b

3q: Phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (61.3 mg. 95%).

Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined

in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as an off white solid (61.2 mg. 95%).

υ_{max} (solid): 3025, 2198, 1768, 1493 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.51–7.48 (m, 2H), 7.42–7.37 (m, 3H), 4.32 (d, *J* = 17.1 Hz, 2H), 4.15 (d, *J* = 17.1 Hz, 2H), 3.08 (s, 3H).

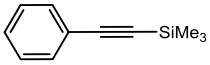
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 132.0, 129.4, 129.1, 129.1, 122.9, 99.9, 61.9, 48.4. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 6.24.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{13}H_{16}BN_2O_4$) requires *m/z* 275.1202, found *m/z* 275.1198.

Characterisation data is consistent with literature reported values.[10]

3r: Trimethyl(phenylethynyl)silane



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and ethynyltrimethylsilane (37 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (44 mg, quant.).

υ_{max} (liquid film): 2962, 2161, 1491, 1251 cm^{-1}.

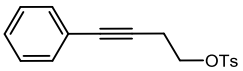
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50–7.47 (m, 2H), 7.34–7.29 (m, 3H), 0.27 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.9, 128.5, 128.2, 123.1, 105.1, 94.1, -0.01.

HRMS: exact mass calculated for [M] ($C_{11}H_{14}Si$) requires *m/z* 174.0865, found *m/z* 174.0866.

Characterisation data is consistent with literature reported values.[11]

3s: 4-Phenylbut-3-yn-1-yl 4-methylbenzenesulfonate



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 3-butynyl-*p*-toluenesulfonate (46.3 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (60.7 mg, 81%).

υ_{max} (liquid film): 2924, 2980, 1493, 1361, 1176 cm^{-1}.

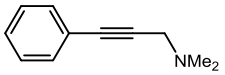
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.32–7.28 (m, 3H), 7.28–7.23 (m, 4H), 4.16 (t, *J* = 7.0 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.9, 132.9, 131.7, 129.9, 128.2, 128.2, 127.9, 122.9, 83.8, 82.7, 67.8, 21.6, 20.4.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{17}H_{16}O_3SNa$) requires *m/z* 323.0712, found *m/z* 323.0702.

Characterisation data is consistent with literature reported values.[12]

3t: *N*,*N*-Dimethyl-3-phenylprop-2-yn-1-amine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and dimethyl(prop-2-yne)amine (28 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to purification by SCX (MeOH in 3M ammonium MeOH) to afford the title compound as a yellow oil (23.6 mg, 60%).

υ_{max} (liquid film): 3058, 2941, 2824, 2775, 1690, 1493 cm^{-1}.

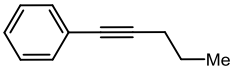
^1H NMR ($CDCl_3$, 500 MHz): δ 7.46–7.42 (m, 2H), 7.32–7.28 (m, 3H), 3.49 (s, 2H), 2.39 (s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.7, 128.3, 128.1, 123.2, 85.4, 84.4, 48.6, 44.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{14}N$) requires *m/z* 160.1126, found *m/z* 160.1125.

Characterisation data is consistent with literature reported values.[13]

3u: Pent-1-yn-1-ylbenzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 1-pentyne (25.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as a yellow oil (34.5 mg, 96%).

υ_{max} (liquid film): 3058, 2963, 2934, 2872, 2237, 1601, 1491 cm^{-1}.

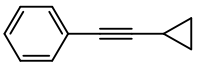
^1H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.22–7.17 (m, 3H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.56 (h, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.2, 127.5, 124.1, 90.3, 80.7, 22.2, 21.4, 13.6.

HRMS: exact mass calculated for [M] ($C_{11}H_{12}$) requires *m/z* 144.0939, found *m/z* 144.0941.

Characterisation data is consistent with literature reported values.[14]

3v: (Cyclopropylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and ethynylcyclopropane (22 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (30.3 mg, 85%).

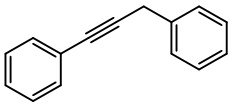
υ_{max} (liquid film): 3034, 2924, 2219, 1597, 1513 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.38 (m, 2H), 7.30–7.26 (m, 3H), 1.47 (m, 1H), 0.91–0.87 (m, 2H), 0.83 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.6, 128.1, 127.4, 123.9, 93.4, 75.8, 8.6, 0.1.

Characterisation data is consistent with values reported in the literature.[15]

3w: Prop-1-yne-1,3-diyldibenzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 3-phenyl-1-propyne (32.6 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (38.7 mg, 81%).

υ_{max} (liquid film): 3064, 3032, 2924, 1601, 1493 cm^1.

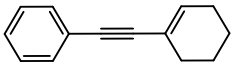
^1H NMR ($CDCl_3$, 500 MHz): δ 7.46 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.32–7.29 (m, 3H), 7.26 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.85 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.8, 131.7, 128.6, 128.3, 127.9, 127.8, 126.7, 123.7, 87.5, 82.7, 25.8.

HRMS: exact mass calculated for [M] ($C_{15}H_{12}$) requires *m/z* 192.0939, found *m/z* 192.0932.

Characterisation data is consistent with literature reported values.[14]

3x: (Cyclohex-1-en-1-ylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 1-ethynylcyclohexene (30.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as an off white solid (46.3 mg, quant.).

υ_{max} (liquid film): 3062, 2935, 2865, 2204, 1716, 1670 cm^{-1}.

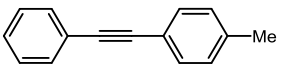
^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.28–7.23 (m, 3H), 6.20–6.16 (m, 1H), 2.20 (dd, *J* = 8.1, 6.0 Hz, 2H), 2.13–2.09 (m, 2H), 1.68–1.63 (m, 2H), 1.61–1.56 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 135.2, 131.4, 128.2, 127.7, 123.8, 120.8, 91.3, 86.8, 29.3, 25.8, 22.4, 21.6.

HRMS: exact mass calculated for [M] ($C_{14}H_{15}$) requires *m/z* 182.1095, found *m/z* 182.1102.

Characterisation data is consistent with literature reported values.[15]

3y: 1-Methyl-4-(phenylethynyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and *p*-tolylacetylene (33.2 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General

Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as an off white solid (46.9 mg, 98%).

υ_{max} (liquid film): 3032, 2921, 2219, 1597, 1511 cm^{-1}.

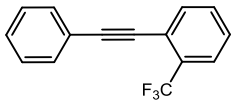
^1H NMR ($CDCl_3$, 500 MHz): δ 7.53 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 3H), 7.16 (d, *J* = 7.9 Hz, 2H), 2.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.4, 131.6, 131.5, 129.1, 128.3, 128.1, 123.5, 120.2, 89.6, 88.7, 21.5.

HRMS: exact mass calculated for [M] ($C_{15}H_{12}$) requires *m/z* 192.0939, found *m/z* 192.0942.

Characterisation data is consistent with literature reported values.[2]

3z: 1-(Phenylethynyl)-2-(trifluoromethyl)benzene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 2-ethynyltrifluorotoluene (36.5 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as a colourless oil (53 mg, 86%).

υ_{max} (liquid film): 3066, 2224, 1312 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.69 (t, *J* = 8.3 Hz, 2H), 7.57 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.40–7.35 (m, 3H).

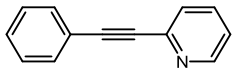
^{13}C NMR ($CDCl_3$, 126 MHz): δ 133.7, 131.7, 131.4, 128.8, 128.4, 127.9, 125.9 (q, $^3J_{CF}$ = 5.2 Hz), 123.6 (q, $^1J_{CF}$ = 273.5 Hz), 122.8, 121.6, 94.9, 85.4. Carbon bearing trifluoromethyl group not observed.

^{19}F NMR ($CDCl_3$, 471 MHz): δ -62.35.

HRMS: exact mass calculated for [M] ($C_{15}H_9F_3$) requires *m/z* 246.0656, found *m/z* 246.0654.

Characterisation data is consistent with literature reported values.[16]

3aa: 2-(Phenylethynyl)pyridine



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 2-ethynylpyridine (26.5 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a yellow oil (43.3 mg, 97%).

υ_{max} (liquid film): 3053, 2224, 1582, 1493, 1463 cm^{-1}.

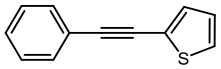
^1H NMR ($CDCl_3$, 500 MHz): δ 8.62 (d, *J* = 4.4 Hz, 1H), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H), 7.60 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.38–7.35 (m, 3H), 7.26 – 7.22 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.1, 143.5, 136.2, 132.1, 128.9, 128.4, 127.2, 122.8, 122.3, 89.2, 88.6.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{21}H_{18}BF_3N_2O_6SNa$) requires *m/z* 179.0735, found *m/z* 179.0731.

Characterisation data is consistent with literature reported values.[2]

3ab: 2-(Phenylethynyl)thiophene



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 2-ethynylthiophene (24.9 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as an off white solid (42.4 mg, 92%).

υ_{max} (liquid film): 3088, 2204 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.54–7.50 (m, 2H), 7.35 (m, 3H), 7.31–7.28 (m, 2H), 7.02 (t, *J* = 4.4 Hz, 1H).

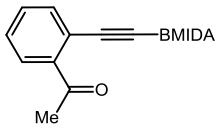
^{13}C NMR ($CDCl_3$, 126 MHz): δ 131.9, 131.4, 128.4, 128.4, 127.3, 127.1, 123.4, 122.9, 93.0, 82.6.

HRMS: exact mass calculated for [M] ($C_{12}H_8S$) requires *m/z* 184.0347, found *m/z* 184.0349.

Characterisation data is consistent with literature reported values.[2]

5.5. Products from Scheme 2c

3ac: 2-Acetyl phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodoacetophenone (35.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–100% EtOAc in petroleum ether) to afford the title compound as an off white solid (66.5 mg, 89%).

υ_{max} (solid): 2960, 2193, 1770, 1684 cm^{-1}.

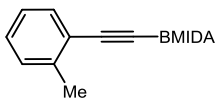
^1H NMR (DMSO-d_6, 500 MHz): δ 7.79 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.63 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H), 4.34 (d, *J* = 17.1 Hz, 2H), 4.13 (d, *J* = 17.1 Hz, 2H), 3.11 (s, 3H), 2.63 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 200.1, 169.1, 141.2, 134.6, 131.9, 129.4, 129.2, 120.7, 98.6, 61.9, 48.4, 29.9. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 6.23.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{15}H_{18}BN_2O_5$) requires *m/z* 317.1305, found *m/z* 317.1303.

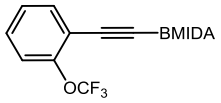
3ad: 2-Methyl-phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (62.9 mg, 93%).

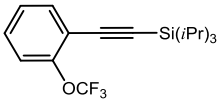
Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (62.3 mg, 92%).
υ_{max} (solid): 3019, 2191, 1770, 1290, 1247 cm^{-1}.
^1H NMR (DMSO-d_6, 500 MHz): δ 7.45 (d, *J* = 7.4 Hz, 1H), 7.31–7.27 (m, 2H), 7.22–7.18 (m, 1H), 4.33 (d, *J* = 17.1 Hz, 2H), 4.15 (d, *J* = 17.1 Hz, 2H), 3.09 (s, 3H), 2.40 (s, 3H).
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.2, 140.3, 132.4, 129.9, 129.3, 126.3, 122.7, 98.7, 61.9, 48.4, 20.8. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 160 MHz): δ 6.37.
HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{14}H_{18}BN_2O_4$) requires *m/z* 289.1355, found *m/z* 289.1354.
Characterisation data is consistent with literature reported values.[17]

3ae: 2-Trifluoromethoxy-phenylethynylboronic acid, MIDA ester



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-(trifluoromethoxy)iodobenzene (38.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (71.8 mg, 85%).
υ_{max} (solid): 3016, 2922, 2965, 2198, 1772, 1217, 1024 cm^{-1}.
^1H NMR (DMSO-d_6, 500 MHz): δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (dd, *J* = 16.7, 8.6 Hz, 2H), 4.35 (d, *J* = 17.2 Hz, 2H), 4.15 (d, *J* = 17.2 Hz, 2H), 3.09 (s, 3H).
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.0, 148.9, 134.5, 131.3, 128.3, 121.9, 120.6 (q, $^1J_{CF}$ = 257.4 Hz), 117.3, 93.5, 62.1, 48.3. Carbon bearing boron not observed.
^{11}B NMR (DMSO-d_6, 160 MHz): δ 6.29.
^{19}F NMR (DMSO-d_6, 471 MHz): δ -56.54.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{12}BF_3NO_5$) requires *m/z* 342.0763, found *m/z* 342.0767.

3af: Triisopropyl((2-(trifluoromethoxy)phenyl)ethynyl)silane



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-(trifluoromethoxy)iodobenzene (38.8 µL, 0.25 mmol, 1 equiv), and (triisopropylsilyl)acetylene (58.9 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et_2O in petroleum ether) to afford the title compound as a colouless oil (58.3 mg, 68%).

υ_{max} (liquid film): 2947, 2868, 2167, 1491, 1258, 1219, 1169 cm^{-1}.

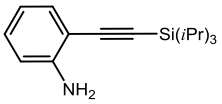
^1H NMR ($CDCl_3$, 500 MHz): δ 7.47 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.28–7.24 (m, 1H), 7.19–7.14 (m, 2H), 1.06 (s, 21H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.8, 134.1, 129.4, 126.6, 121.2, 120.6 (q, $^1J_{CF}$ = 258.1 Hz), 118.3, 100.4, 97.1, 18.5, 11.2.

^{19}F NMR (471 MHz, $CDCl_3$): δ -57.50.

HRMS: exact mass calculated for [M] ($C_{18}H_{25}F_3SiO$) requires *m/z* 342.1627, found *m/z* 342.1626.

3ag: 2-((Triisopropylsilyl)ethynyl)aniline



Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodoaniline (54.8 mg, 0.25 mmol, 1 equiv), and (triisopropylsilyl)acetylene (58.9 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% Et_2O in petroleum ether) to afford the title compound as a yellow oil (45.3 mg, 66%).

υ_{max} (liquid film): 3487, 3388, 2945, 2867, 2146, 1616, 1318 cm^{-1}.

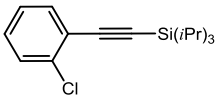
^1H NMR ($CDCl_3$, 500 MHz): δ 7.31 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.14–7.09 (m, 1H), 6.71–6.64 (m, 2H), 4.25 (s, 2H), 1.14 (s, 21H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.3, 132.4, 129.7, 117.7, 114.1, 108.3, 103.7, 95.9, 18.7, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{28}NSi$) requires *m/z* 274.1986, found *m/z* 274.1986.

Characterisation data is consistent with literature reported values.[18]

3ah: ((2-Chlorophenyl)ethynyl)triisopropylsilane

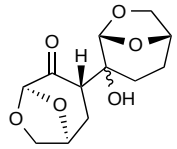


Prepared according to General Procedure A using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (38 µL, 0.275 mmol, 1.1 equiv), 2-chloro-iodobenzene (30.5 µL, 0.25 mmol, 1 equiv), and (triisopropylsilyl)acetylene (58.9 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20–100% MeCN in water) to afford the title compound as a yellow oil (47.7 mg, 65%).

υ_{max} (liquid film): 2945, 2867, 2163, 1472, 1225 cm^{-1}.
^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.23 (td, *J* = 7.7, 1.8 Hz, 1H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1H), 1.15 (s, 21H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.5, 133.9, 129.4, 126.4, 123.6, 103.3, 96.9, 18.8, 11.5.
HRMS: exact mass calculated for [M] ($C_{17}H_{25}ClSi$) requires *m/z* 292.1414, found *m/z* 292.1431.

5.6. Cyrene homo-aldol adducts, 4a and 4b

To a stirred solution of Cyrene (256 mg, 2.0 mmol, 1 equiv) was added DBU (30 mg, 0.2 mmol, 0.1 equiv) and the mixture heated to 100 °C for 10 minutes. The resulting mixture was cooled to 20 °C giving a viscous brown oil and then kept at 20 °C for 72 hours over which time the mixture began to crystallise. The mixture was then purified by flash chromatography (30% EtOAc/hexanes to EtOAc) to give **4a** as a colourless oil (40 mg, 16%).



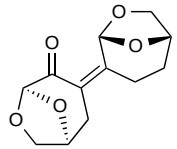
4a

υ_{max} (neat): 3470, 2962, 2895, 1731 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 5.71 (s, 1H), 5.04 (s, 1H), 4.73-4.70 (m, 1H), 4.44-4.41 (m, 1H), 4.01 (br d, *J* = 7.4 Hz, 1H), 3.91 (ddd, *J* = 7.4, 4.9, 1.6 Hz, 1H), 3.83 (d, *J* = 7.1 Hz, 1H), 3.76 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 3.35 (dd, *J* = 12.0, 7.4 Hz, 1H), 2.72 (s, 1H), 2.27 (dddd, *J* = 13.3, 12.0, 3.7, 1.8 Hz, 1H), 1.96 (ddd, *J* = 13.3, 7.4, 1.6 Hz, 1H), 1.64-1.59 (m, 3H), 1.50-1.46 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 203.7, 102.9, 101.6, 73.6, 73.2, 72.9, 68.4, 67.9, 42.7, 32.6, 26.7, 25.1.

ESI-MS: *m/z* 257 (50, [M+H]+), 279 (100, [M+Na]).



4b

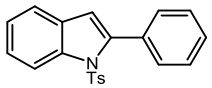
To an oven-dried 5 mL microwave vessel was added K_3PO_4 (637 mg, 3 mmol, 3 equiv). The vessel was then capped and purged with N_2 before addition of THF (4 mL, 0.25 M), and Cyrene (123 μL, 1 mmol, 1 equiv). The reaction mixture was heated to 70 °C and maintained at this temperature with stirring for 8 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (20 mL), and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give an off white solid, which was purified by flash chromatography (silica gel, 0–50% EtOAc in petroleum ether) to afford the title compound as a white solid (105 mg, 88%).

υ_{max} (solid): 2898, 1703, 1621, 1098 cm^{-1}.
^1H NMR ($CDCl_3$, 500 MHz): δ 6.76 (s, 1H), 5.18 (s, 1H), 4.79 (t, *J* = 5.1 Hz, 1H), 4.60 (t, *J* = 4.0 Hz, 1H), 3.94 – 3.83 (m, 4H), 2.78 (dd, *J* = 16.3, 2.6 Hz, 1H), 2.56 (d, *J* = 16.3 Hz, 1H), 2.41-2.24 (m, 2H), 2.14-2.07 (m, 1H), 1.75 (dd, *J* = 13.5, 6.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.7, 151.0, 123.4, 101.5, 97.2, 72.6, 72.5, 68.7, 67.8, 34.1, 28.8, 20.4.
HRMS: exact mass calculated for [M] ($C_{12}H_{14}$) requires *m/z* 238.0841, found *m/z* 238.0839.

5.7. Products from Scheme 3

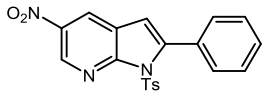
7a: 2-Phenyl-1-tosyl-1*H*-indole



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a white solid (78.4 mg, 90%).

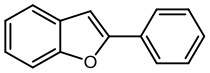
Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a white solid (78.6 mg, 91%).
υ_{max} (solid): 3073, 1368, 1169 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.33 (d, *J* = 8.4 Hz, 1H), 7.54–7.50 (m, 2H), 7.45 (t, *J* = 8.2 Hz, 4H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.31–7.28 (m, 3H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.56 (s, 1H), 2.31 (s, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.5, 142.2, 138.3, 134.7, 132.4, 130.7, 130.4, 129.2, 128.7, 127.5, 126.8, 124.8, 124.3, 120.7, 116.7, 113.4, 21.5.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{18}NO_6S$) requires *m/z* 348.1058, found *m/z* 348.1061.
Characterization data is consistent with literature reported values.[3]

7b: 5-Nitro-2-phenyl-1-tosyl-1*H*-pyrrolo[2,3-b]pyridine



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), *N*-(3-iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide (104 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as an off white solid (71.4 mg, 73%).
υ_{max} (solid): 3070, 2935, 1593, 1517, 1394, 1346, 1184 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.32 (d, *J* = 2.4 Hz, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.48 (m, 5H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.63 (s, 1H), 2.37 (s, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.3, 145.8, 145.8, 141.4, 140.3, 135.3, 131.5, 129.9, 129.6, 129.6, 128.2, 127.9, 124.3, 121.4, 108.3, 21.7.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{16}N_3O_4S$) requires *m/z* 394.0862, found *m/z* 394.0869.

7c: 2-Phenylbenzofuran



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), 2-iodophenol (55 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% EtOAc in petroleum ether) to afford the title compound as a white solid (43.3 mg, 89%).

υ_{max} (solid): 3038, 2924, 2855 cm^{-1}.

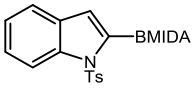
^1H NMR ($CDCl_3$, 500 MHz): δ 7.88 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.9, 154.9, 130.5, 129.2, 128.8, 128.6, 124.9, 124.3, 122.9, 120.9, 111.2, 101.3

HRMS: exact mass calculated for [M] ($C_{14}H_{10}O$) requires *m/z* 194.0732, found *m/z* 194.0737.

Characterization data is consistent with literature reported values.[19]

7d: (1-Tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–80% EtOAc in petroleum ether) to afford the title compound as a white solid (87.4 mg, 82%).

υ_{max} (solid): 2928, 1763, 1450, 1176, 1038 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.37 (dd, *J* = 13.1, 8.0 Hz, 3H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 4.47 (d, *J* = 17.5 Hz, 2H), 4.23 (d, *J* = 17.4 Hz, 2H), 2.96 (s, 3H), 2.32 (s, 3H).

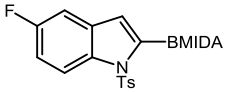
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 145.72, 138.9, 135.5, 130.4, 130.1, 127.08, 125.7, 123.9, 122.2, 122.0, 114.7, 64.8, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 10.28.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{20}BN_2O_6S$) requires *m/z* 427.1139, found *m/z* 427.1139.

Characterization data is consistent with literature reported values.[4]

7e: (5-Fluoro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), *N*-(4-fluoro-2-iodophenyl)-4-methylbenzenesulfonamide (98 mg, 0.25 mmol, 1 equiv), and ethynyl boronic

acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–80% EtOAc in petroleum ether) to afford the title compound as a white solid (98 mg, 88%).

υ_{max} (solid): 2930, 1750, 1305, 1174, 1040 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.13 (dd, *J* = 9.2, 4.3 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.22 (td, *J* = 9.2, 2.6 Hz, 1H), 7.06 (s, 1H), 4.48 (d, *J* = 17.5 Hz, 2H), 4.24 (d, *J* = 17.5 Hz, 2H), 2.96 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 159.3 (d, $^{1}J_{CF}$ = 238.2 Hz), 145.9, 135.4, 135.3, 131.2 (d, $^{3}J_{CF}$ = 10.4 Hz), 130.5, 127.1, 121.9, 116.1 (d, $^{3}J_{CF}$ = 9.4 Hz), 113.5 (d, $^{2}J_{CF}$ = 25.5 Hz), 107.1 (d, $^{2}J_{CF}$ = 23.5 Hz), 64.8, 49.9, 21.5. Carbon bearing boron not observed.

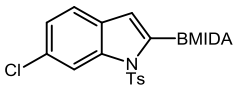
^{11}B NMR (DMSO-d_6, 160 MHz): δ 10.09.

^{19}F NMR (DMSO-d_6, 471 MHz): δ -120.04.

HRMS: exact mass calculated for [M] ($C_{21}H_{18}BF_3N_2O_6SNa$) requires *m/z* 444.2966, found *m/z* 444.0951.

Characterization data is consistent with literature reported values.[4]

7f: (6-Chloro-1-tosyl-1*H*-indol-2-yl)boronic acid, MIDA ester



Prepared according to General Procedure B using $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et_3N (104 µL, 0.75 mmol, 3 equiv), *N*-(4-chloro-2-iodophenyl)-4-methylbenzenesulfonamide (102 mg, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–80% EtOAc in petroleum ether) to afford the title compound as a white solid (116 mg, quant.).

υ_{max} (solid): 2922, 1763, 1455, 1267, 1173, 1038 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.11 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.34 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.09 (s, 1H), 4.48 (d, *J* = 17.5 Hz, 2H), 4.23 (d, *J* = 17.4 Hz, 2H), 2.94 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.6, 146.1, 139.3, 135.2, 130.6, 130.4, 128.9, 127.0, 124.4, 123.4, 121.9, 114.4, 64.7, 49.9, 21.5. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 10.21.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{20}H_{18}ClN_2O_6SB$) requires *m/z* 460.0671, found *m/z* 460.0658.

Characterization data is consistent with literature reported values.[4]

6. Crystallographic Data for Compound 4b

Single crystal diffraction measurements were made with an Oxford Diffraction Gemini S instrument. Refinement was to convergence against F^2 and used all unique reflections. Programs used were from the SHELX suite.[20] Non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were placed in idealized positions and refined in riding modes. Selected crystallographic and refinement parameters are given in Table 1. CCDC reference number CCDC 1485168 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S1 Selected crystallographic data and refinement parameters for compound **4b**.

Compound	**4**
Formula	$C_{12}H_{14}O_5$
M_r (g mol^{-1})	238.23
Crystal system	monoclinic
Space group	$P2_1$
Temperature (K)	123(2)
a (Å)	6.4668(2)
b (Å)	9.8239(3)
c (Å)	8.5963(2)
β (°)	96.341(3)
V/Å^3	542.78(3)
Z	2
Wavelength (Å)	0.71073
Measured reflections	9884
Unique reflections	3457
R_{int}	0.03024
Observed rflns [$I > 2\sigma(I)$]	3286
μ (mm^{-1})	0.114
No. of parameters	155
2ϑmax (°)	63.8
R [on *F*, obs rflns only]	0.0329
wR [on F^2, all data]	0.0852
GoF	1.043
Largest diff. peak/hole/e Å^{-3}	0.242/–0.191

7. References

1. Armarego, W.; Chai, C. *Purification of laboratory chemicals*. Elsevier: Amsterdam, 2009.
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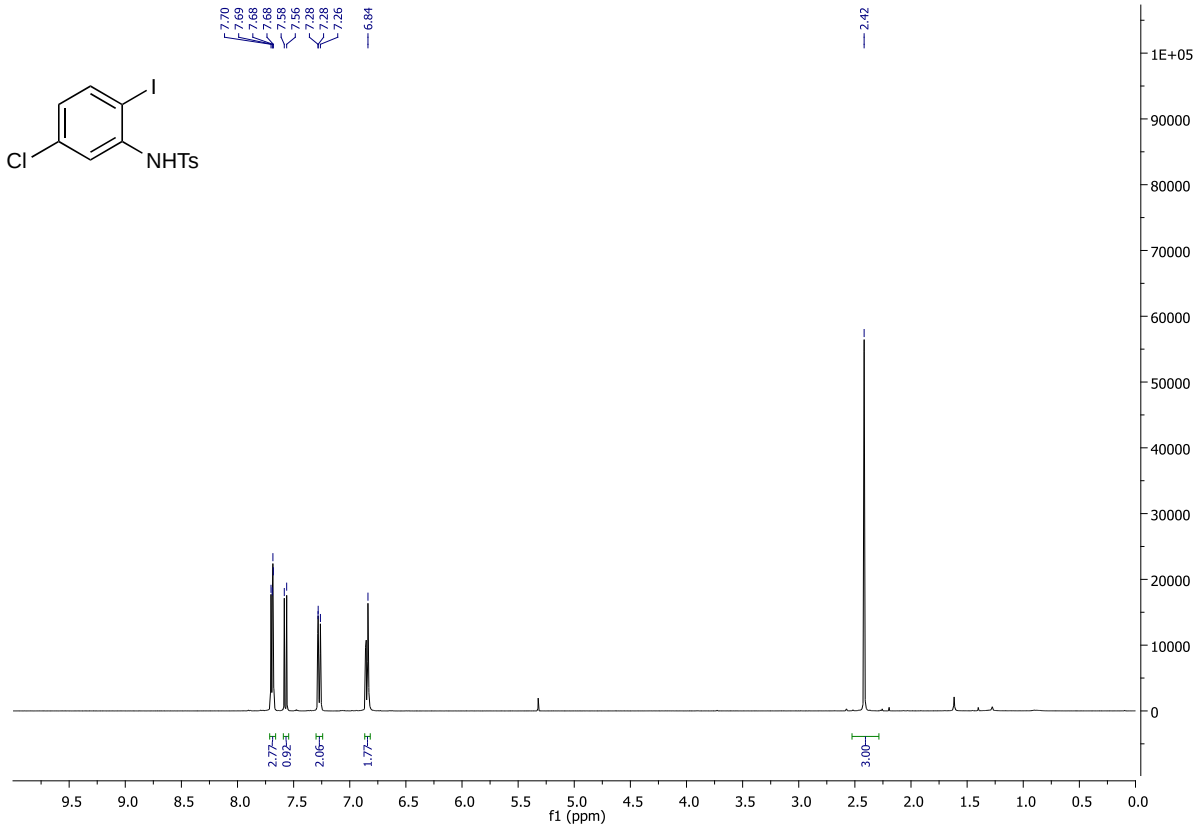
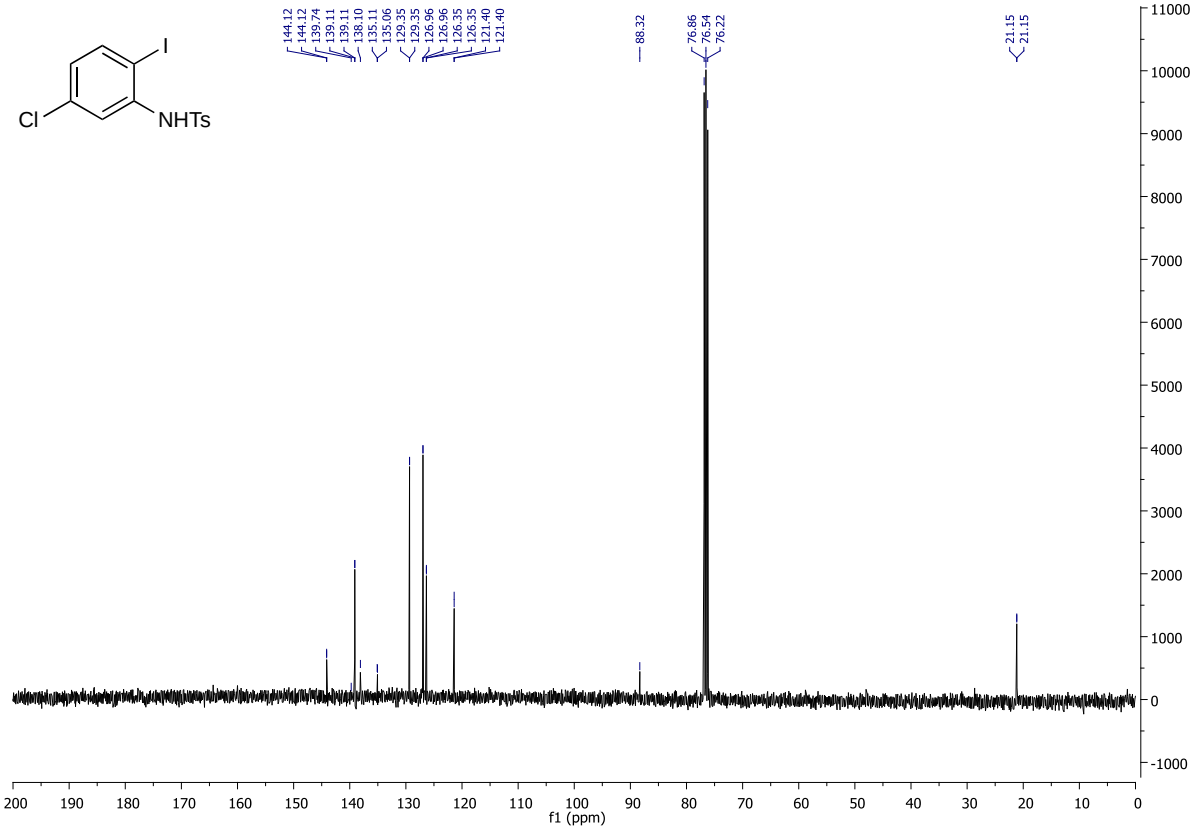
8. NMR spectra for intermediates and products

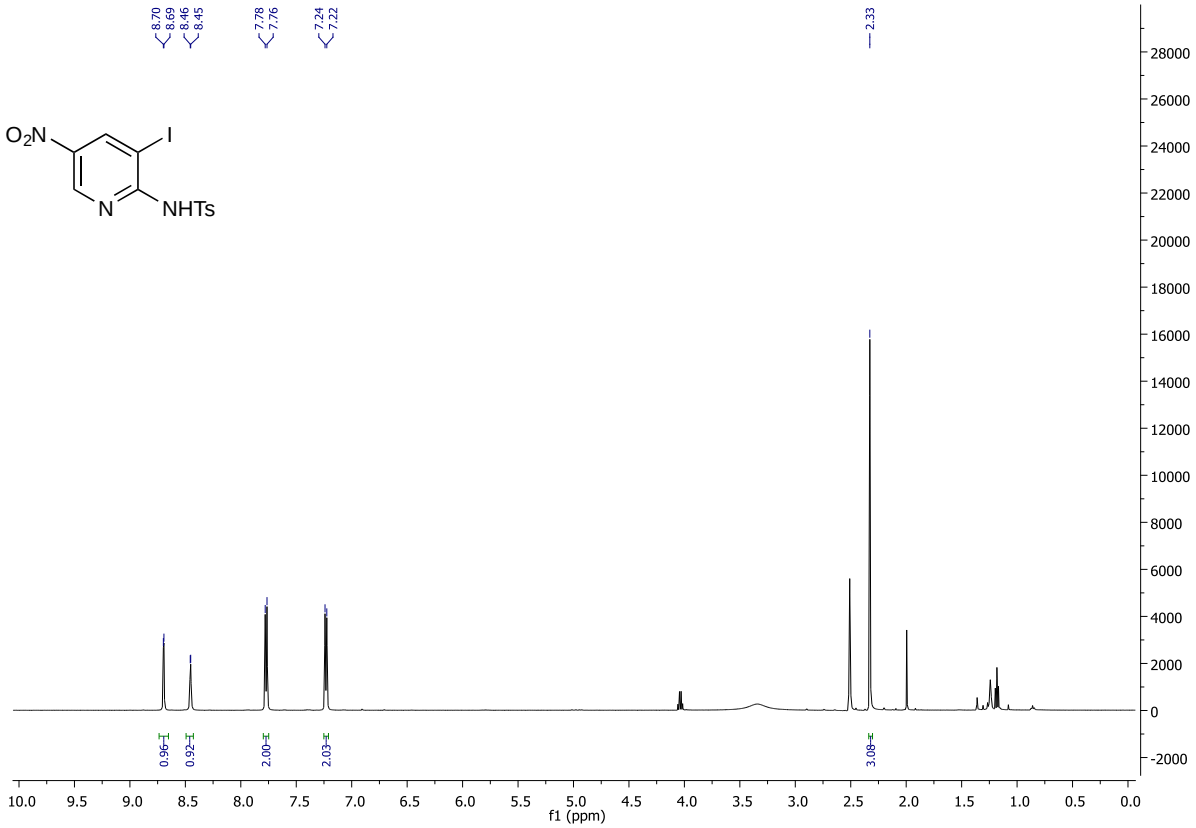
^{1}H NMR of S1



^{13}C NMR of S1



^{1}H NMR of S2



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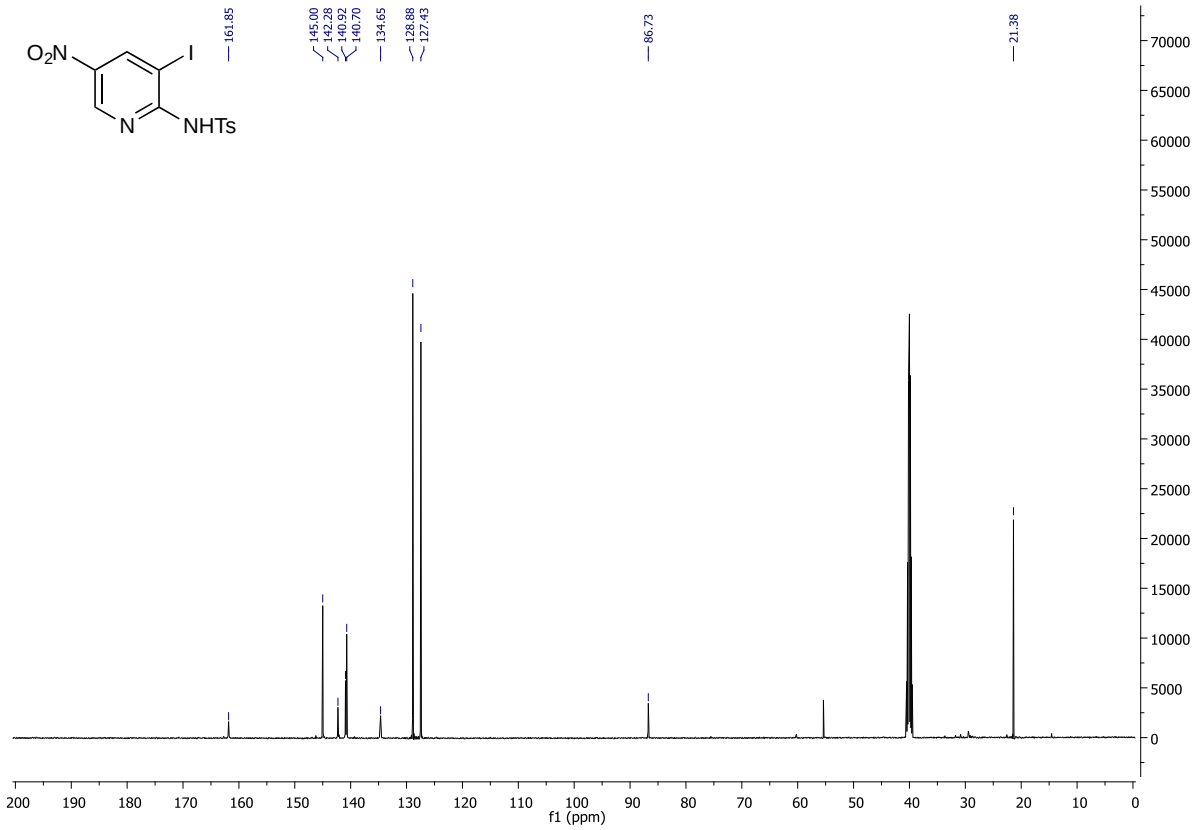

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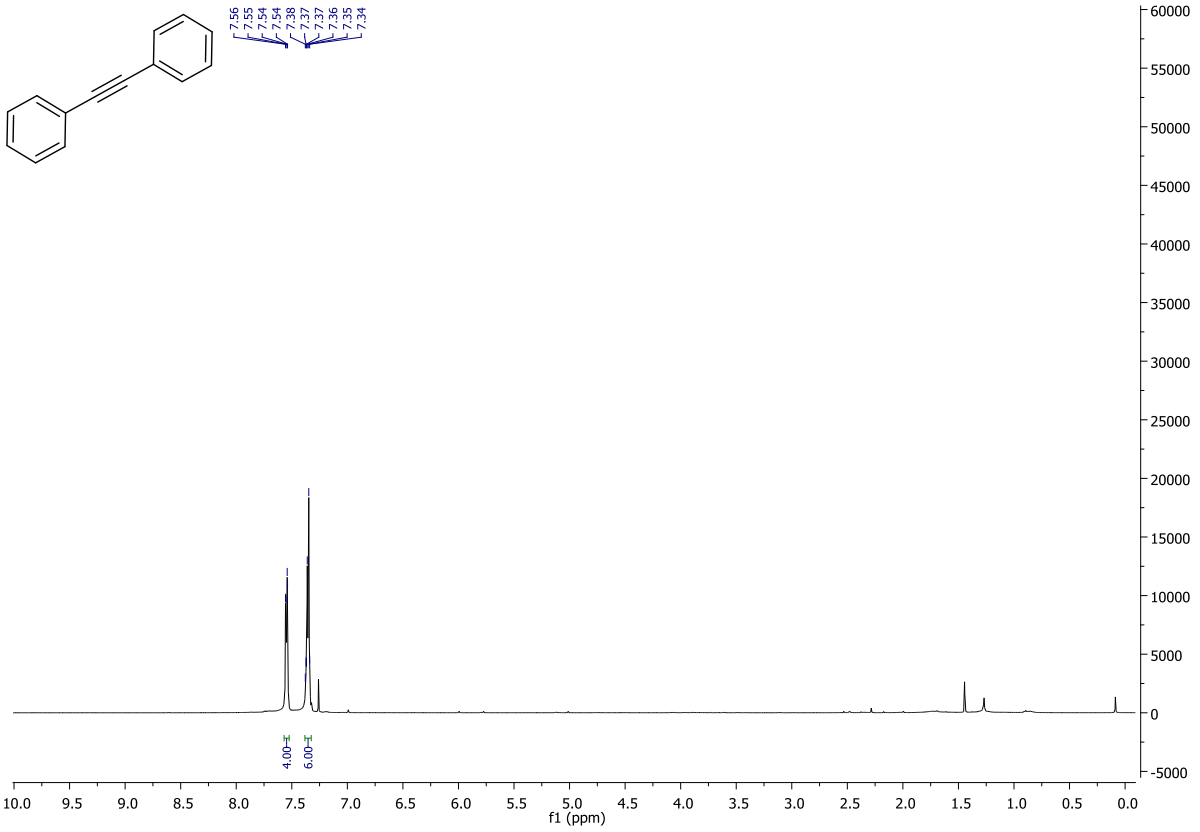
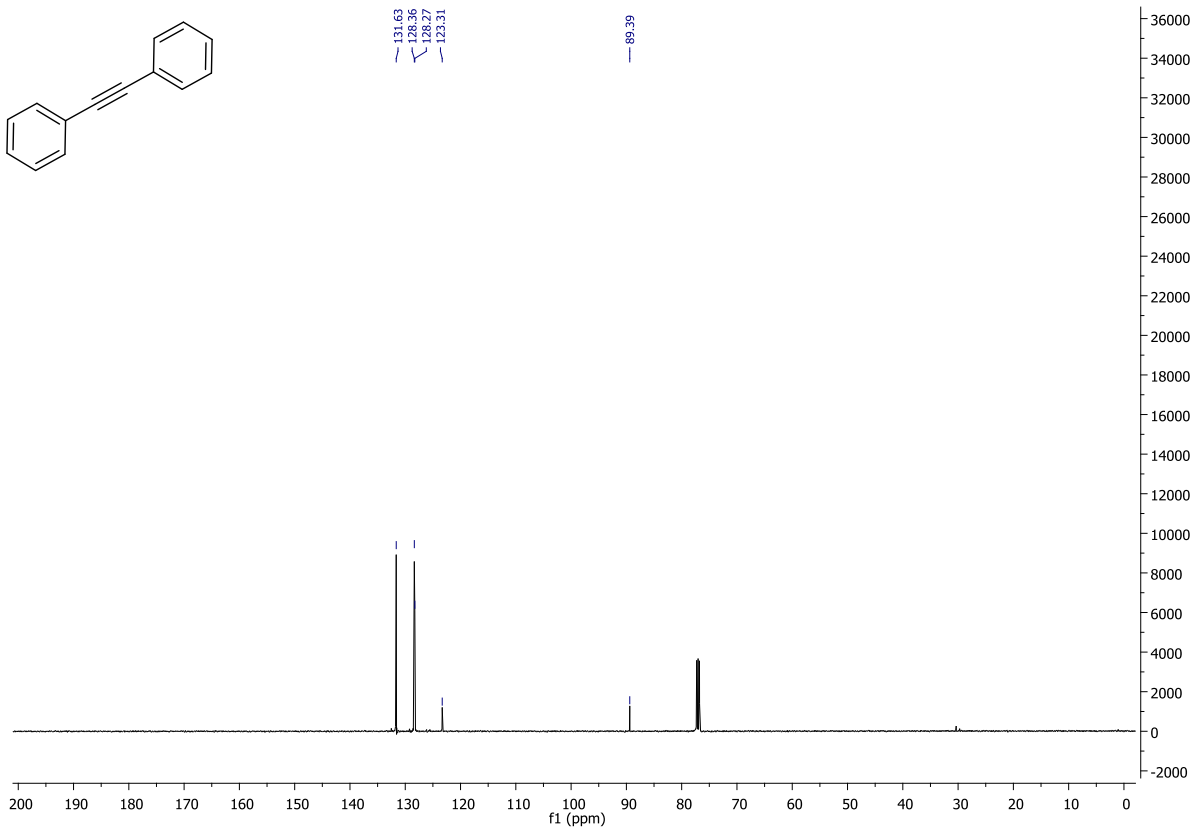
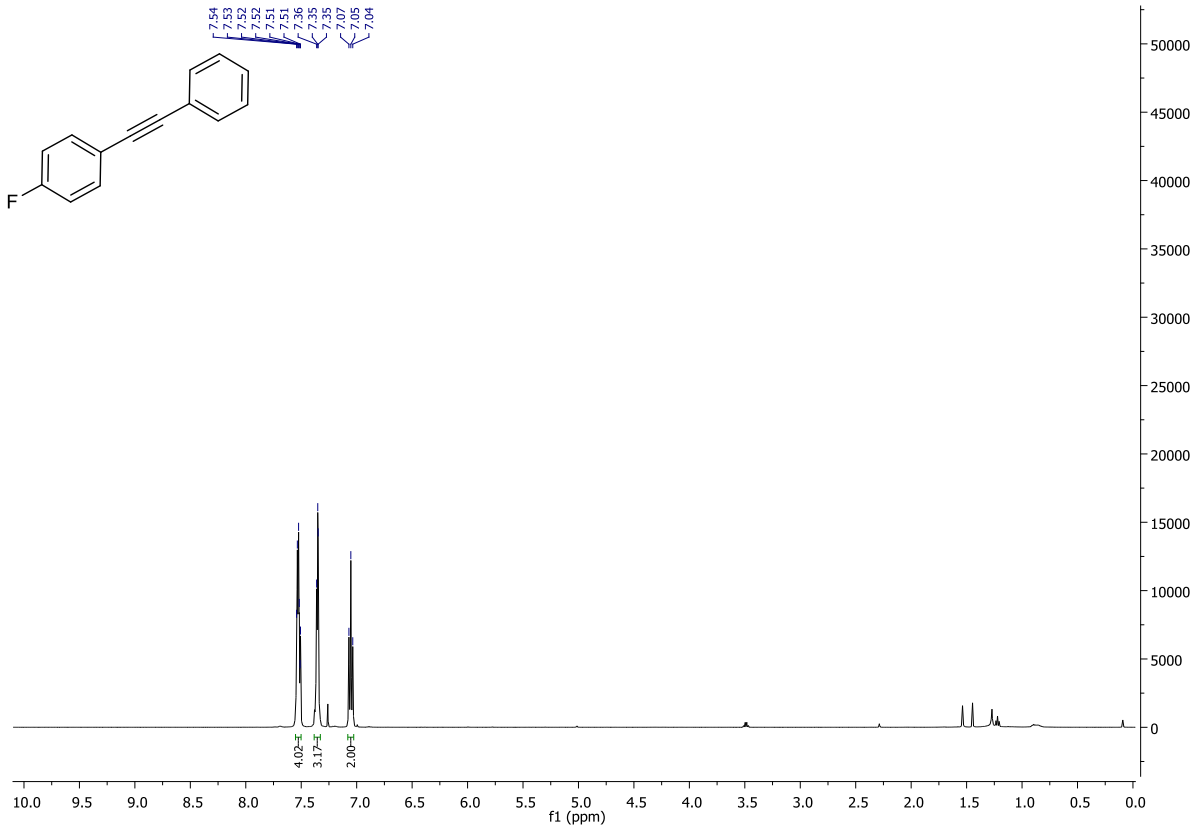


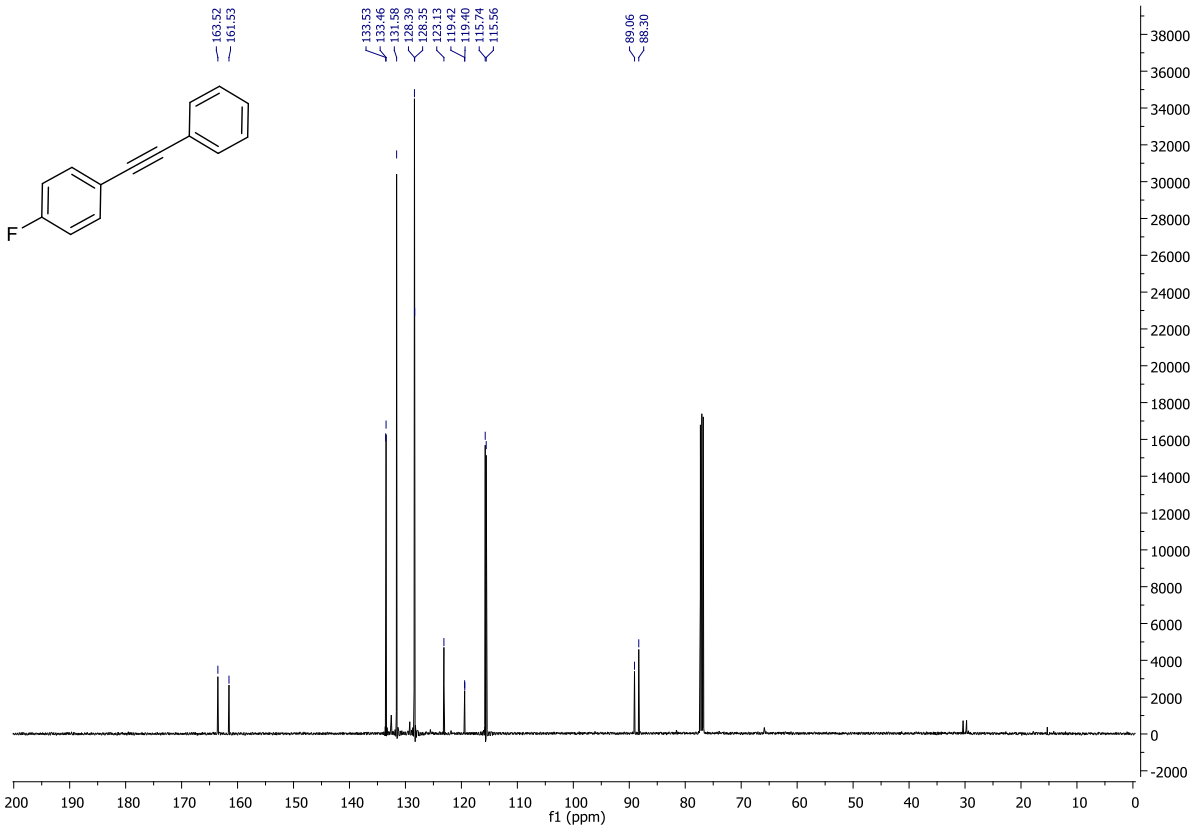
^{13}C NMR of 3a



^{1}H NMR of 3b



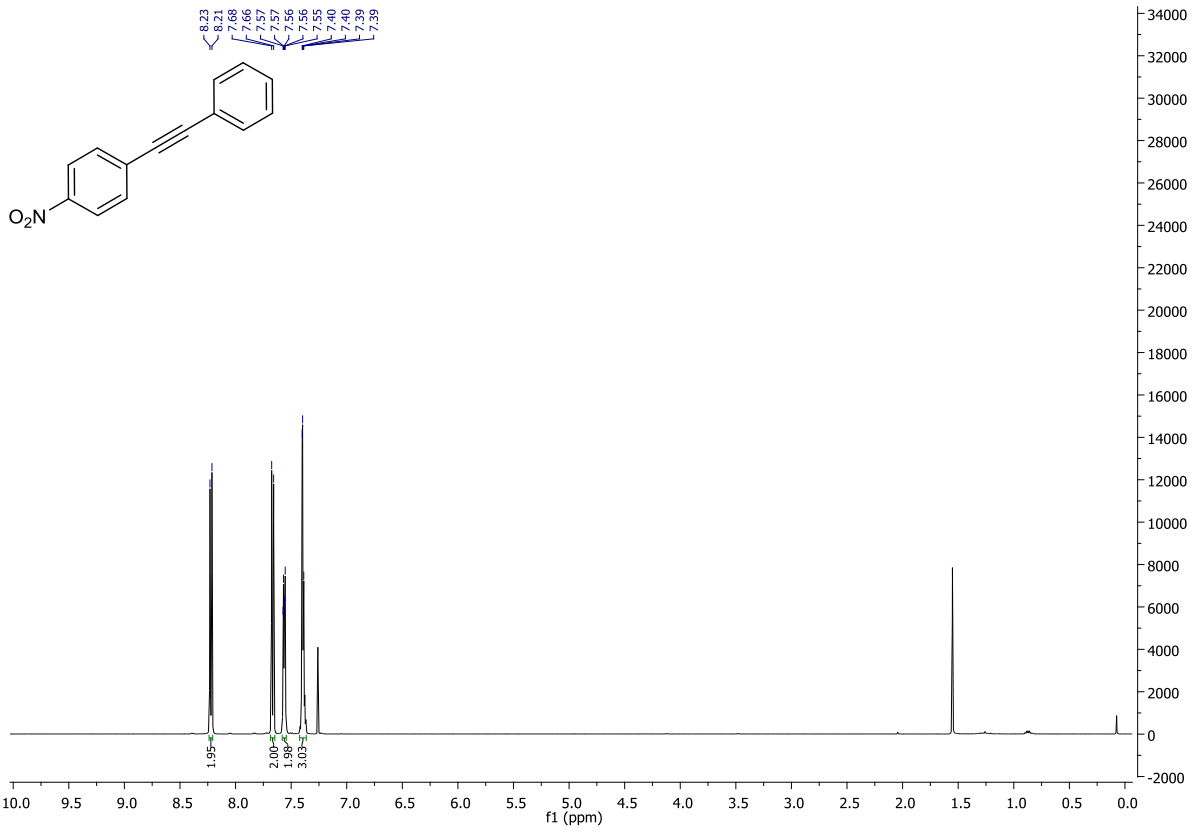
^{13}C NMR of 3b



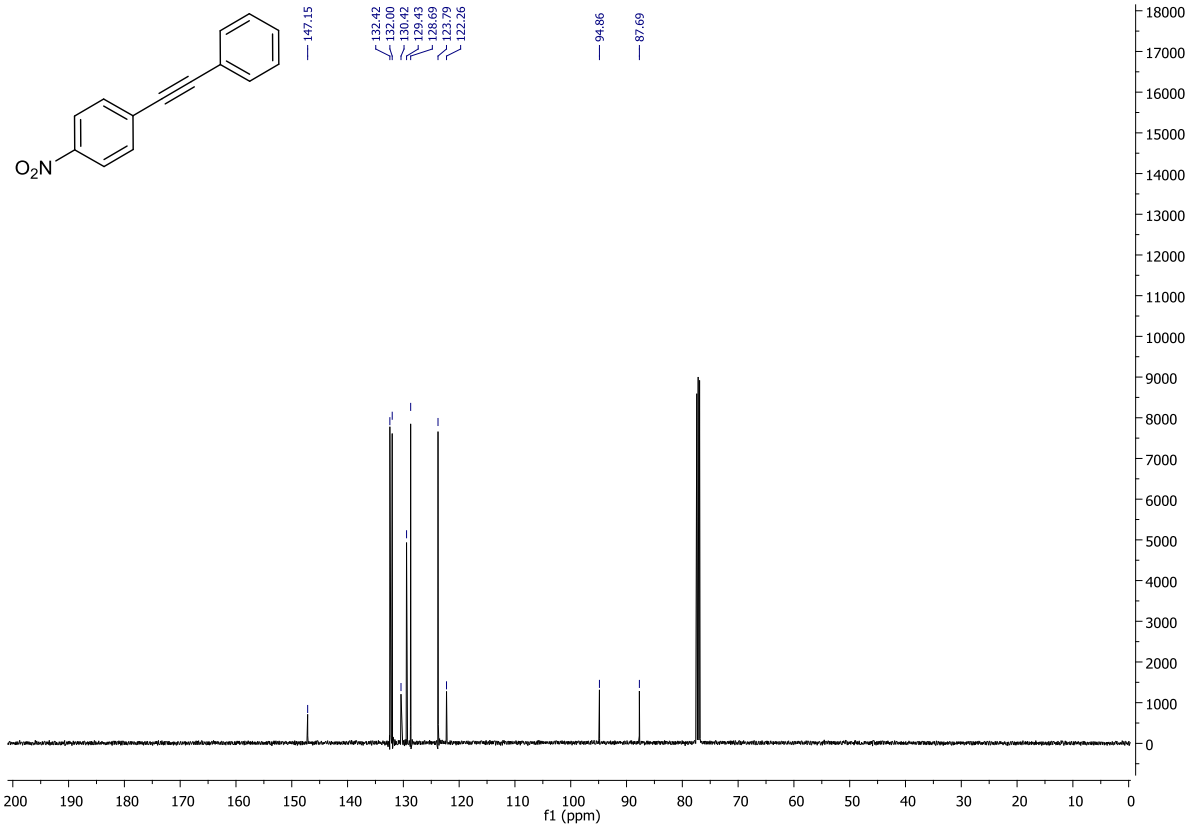
^{19}F NMR of 3b


F
-110.98
4000
3500
3000
2500
2000
1500
1000
500
0
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

^{1}H NMR 3c


8.23
8.21
7.68
7.66
7.57
7.57
7.56
7.56
7.55
7.40
7.40
7.39
7.39
O2N
1.95
2.00
1.98
3.03
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

^{13}C NMR 3c



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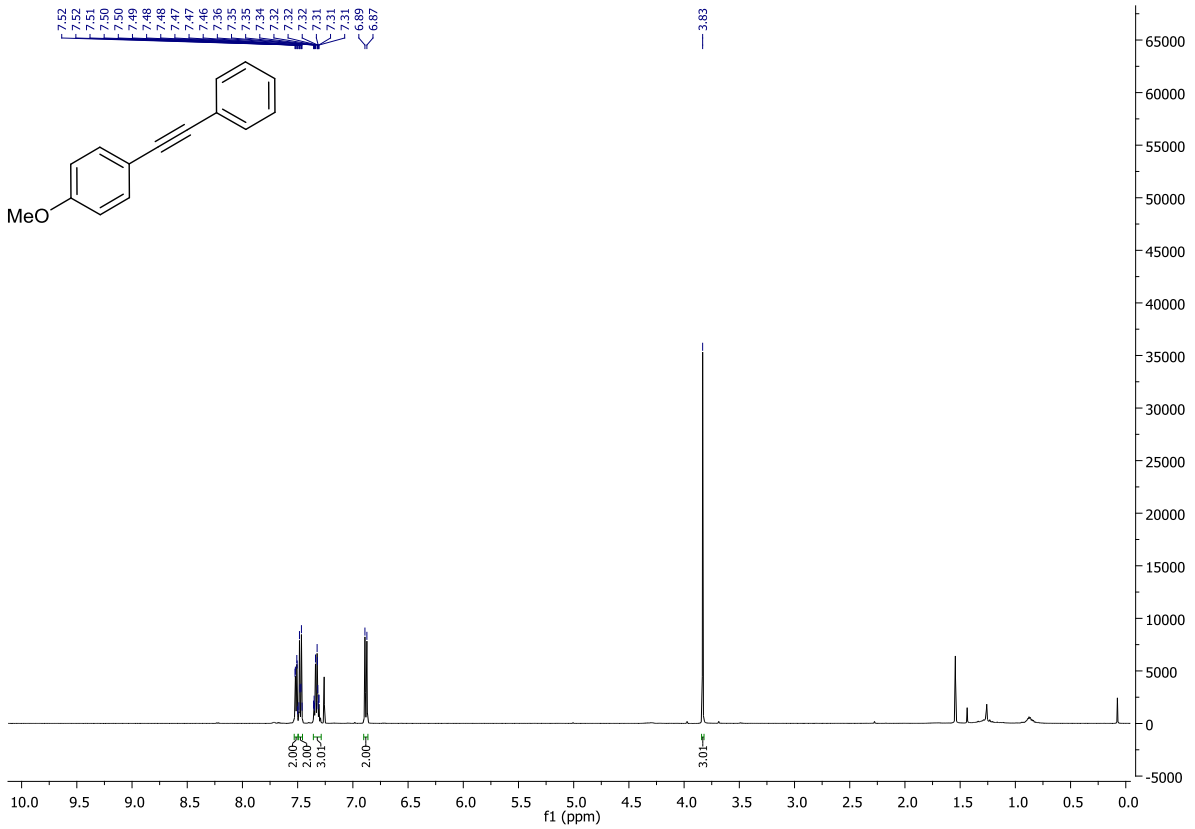

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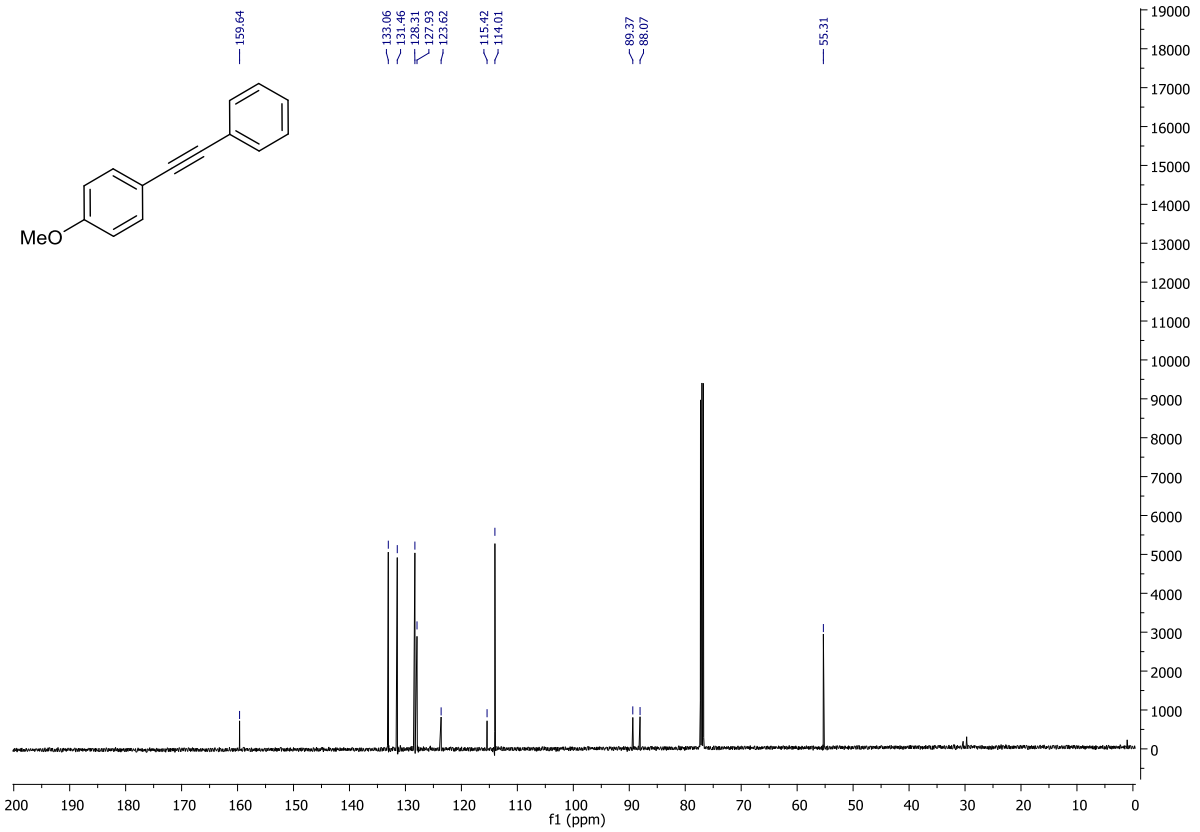
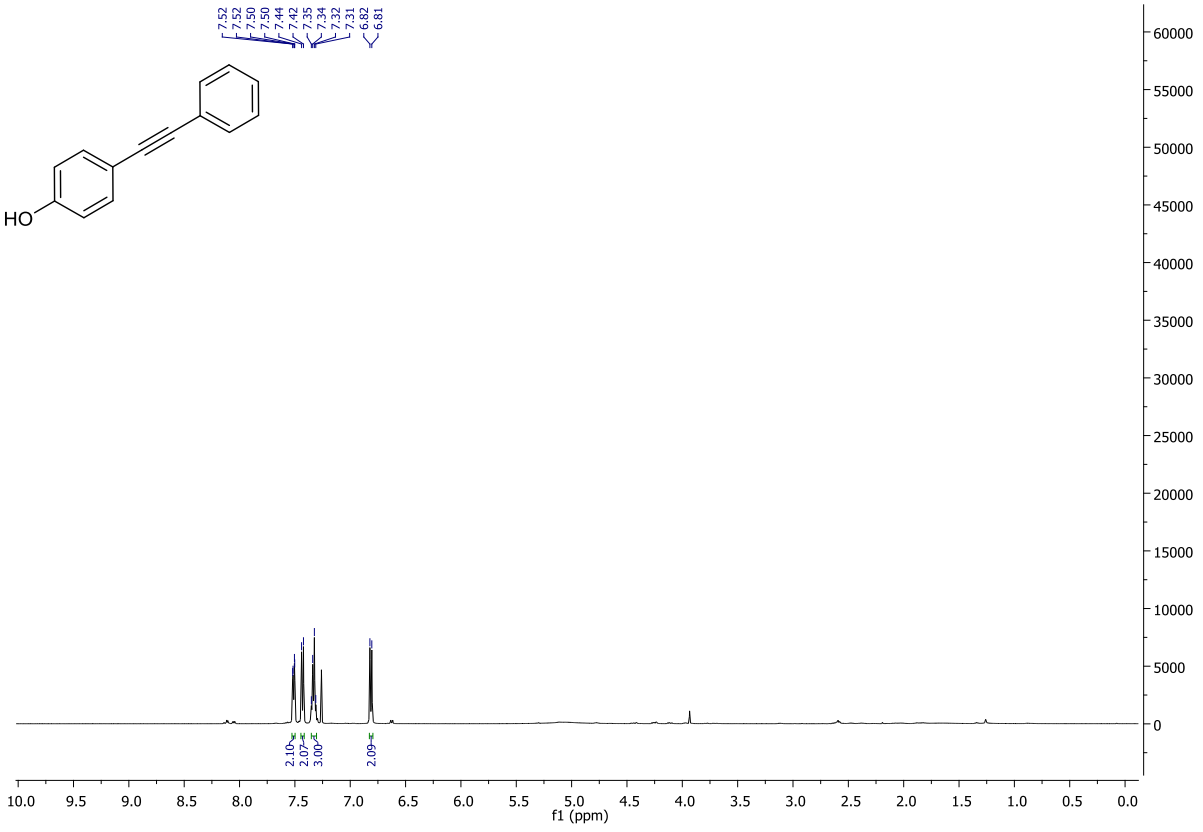


^{1}H NMR 3e



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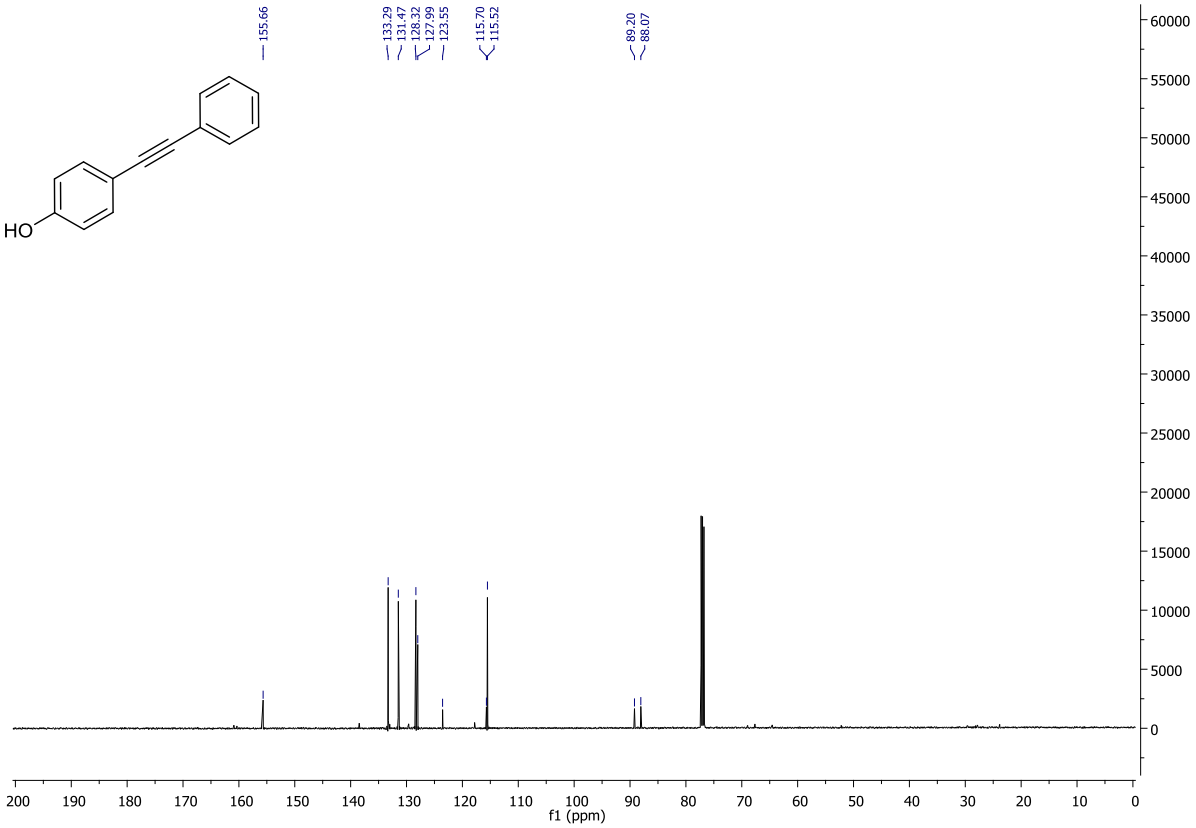
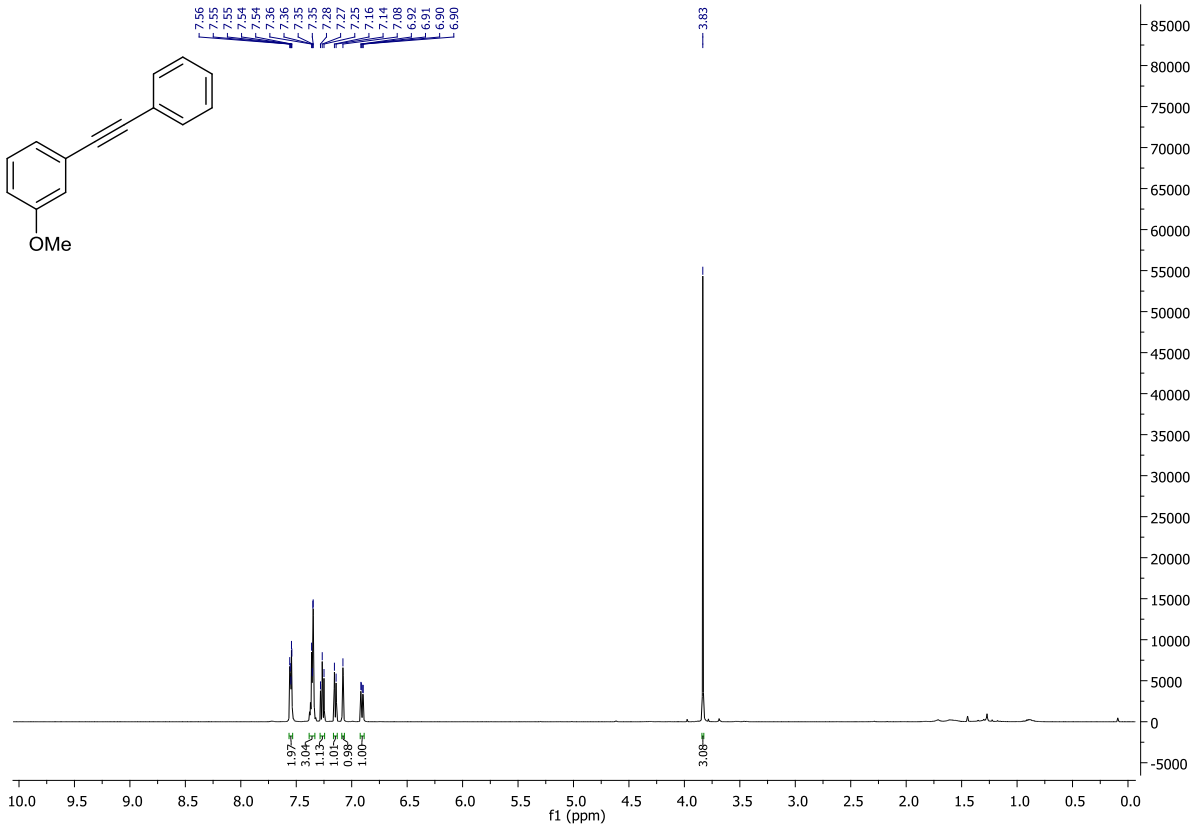


^{1}H NMR 3f



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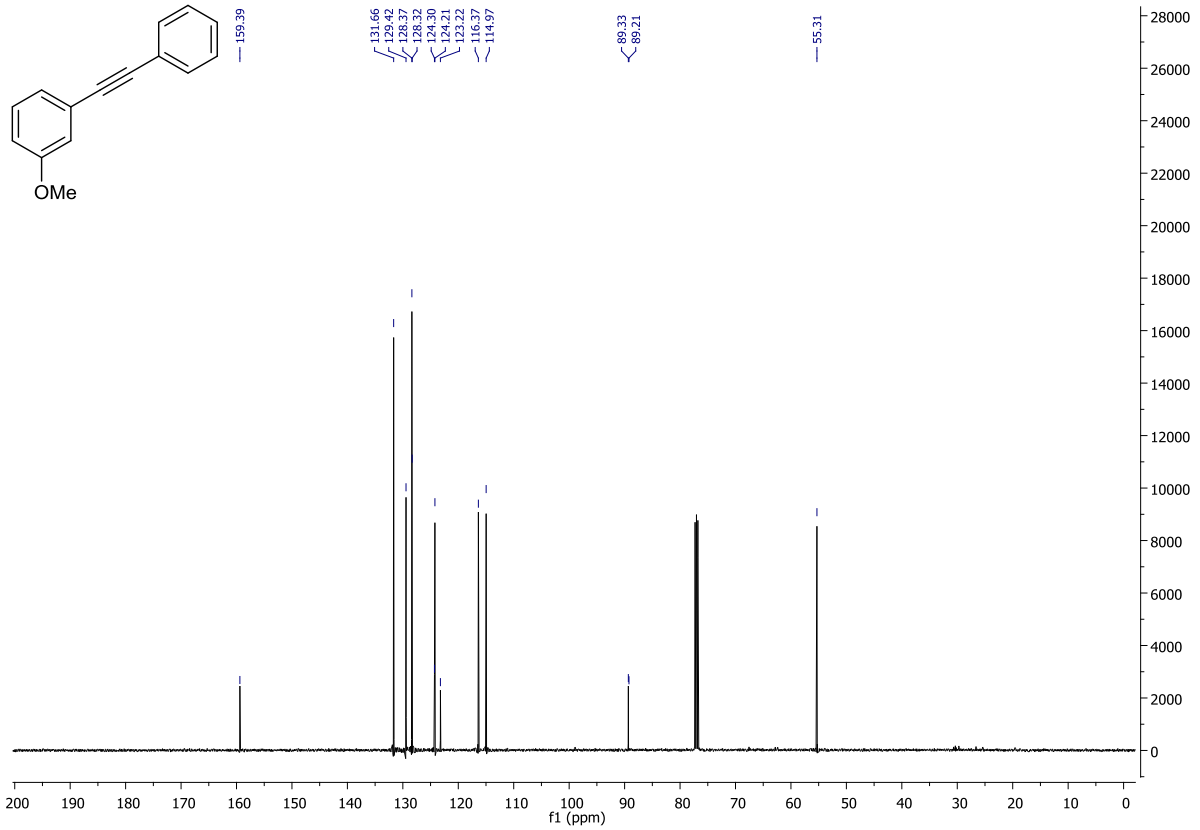

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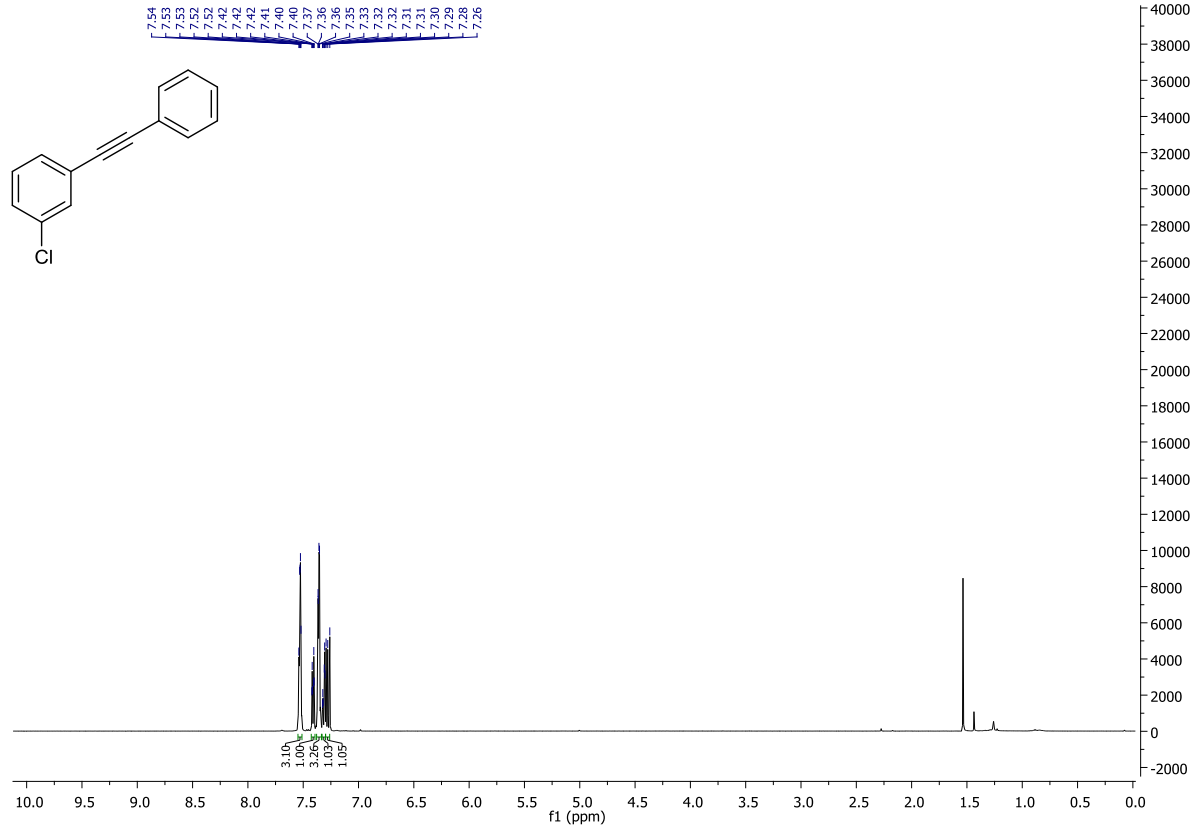

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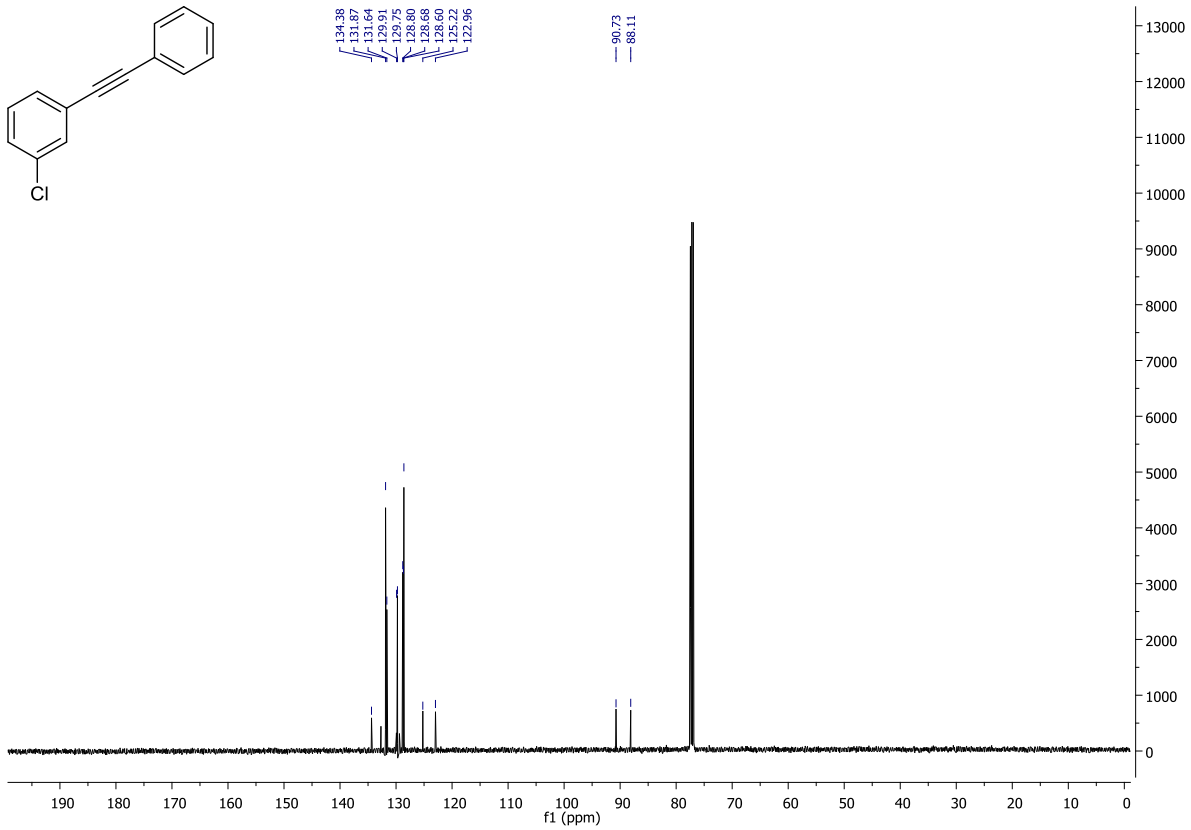

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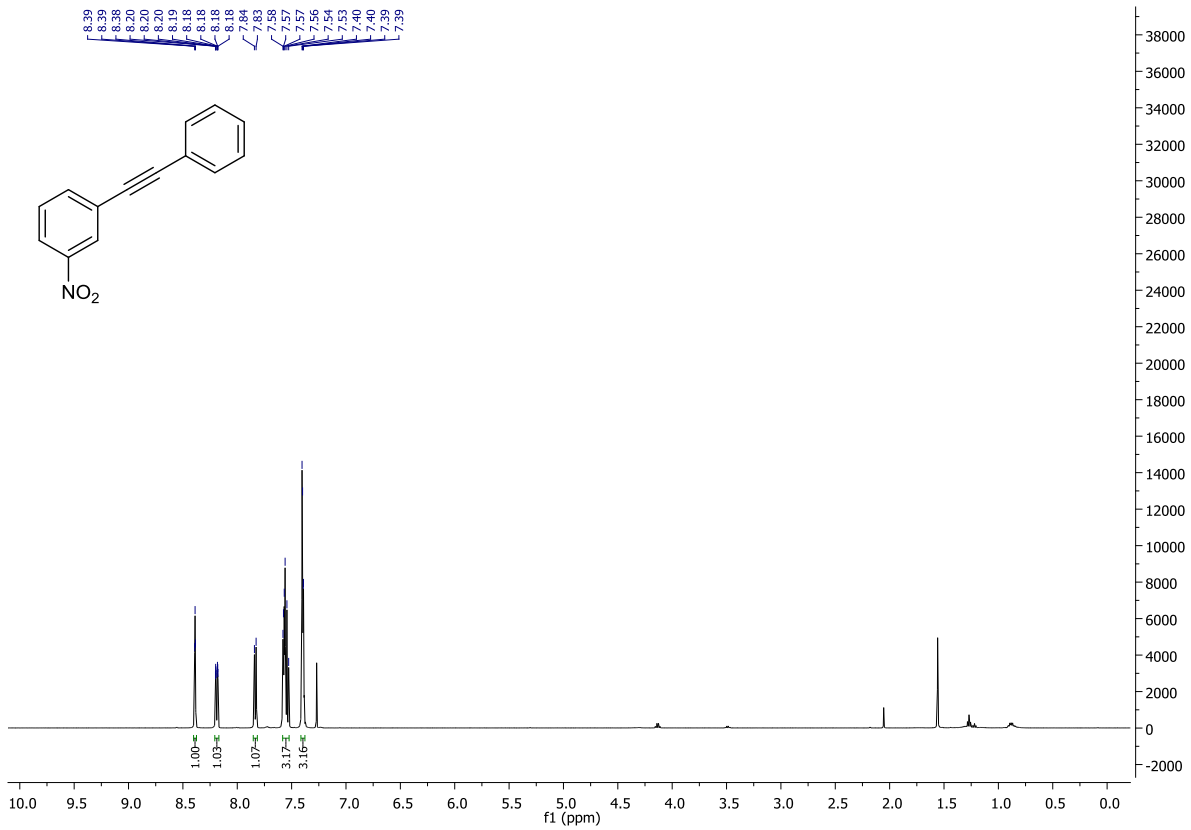

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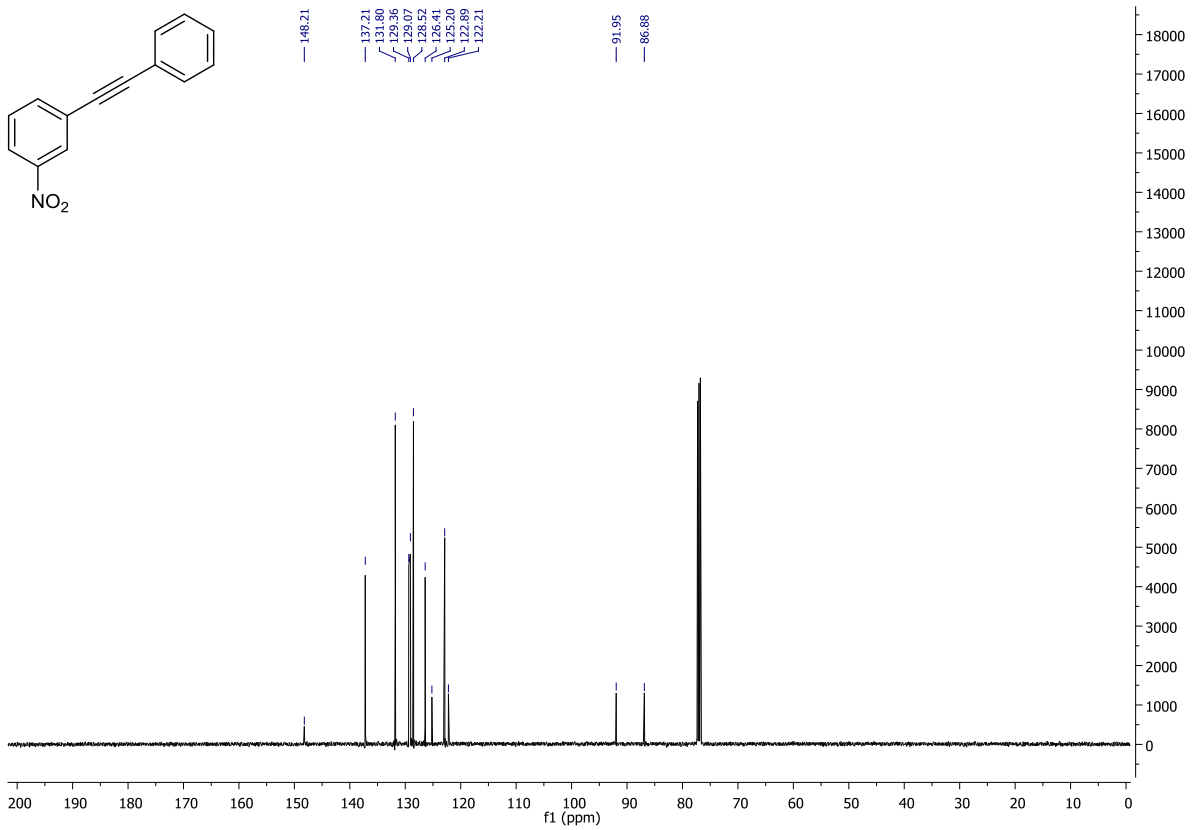

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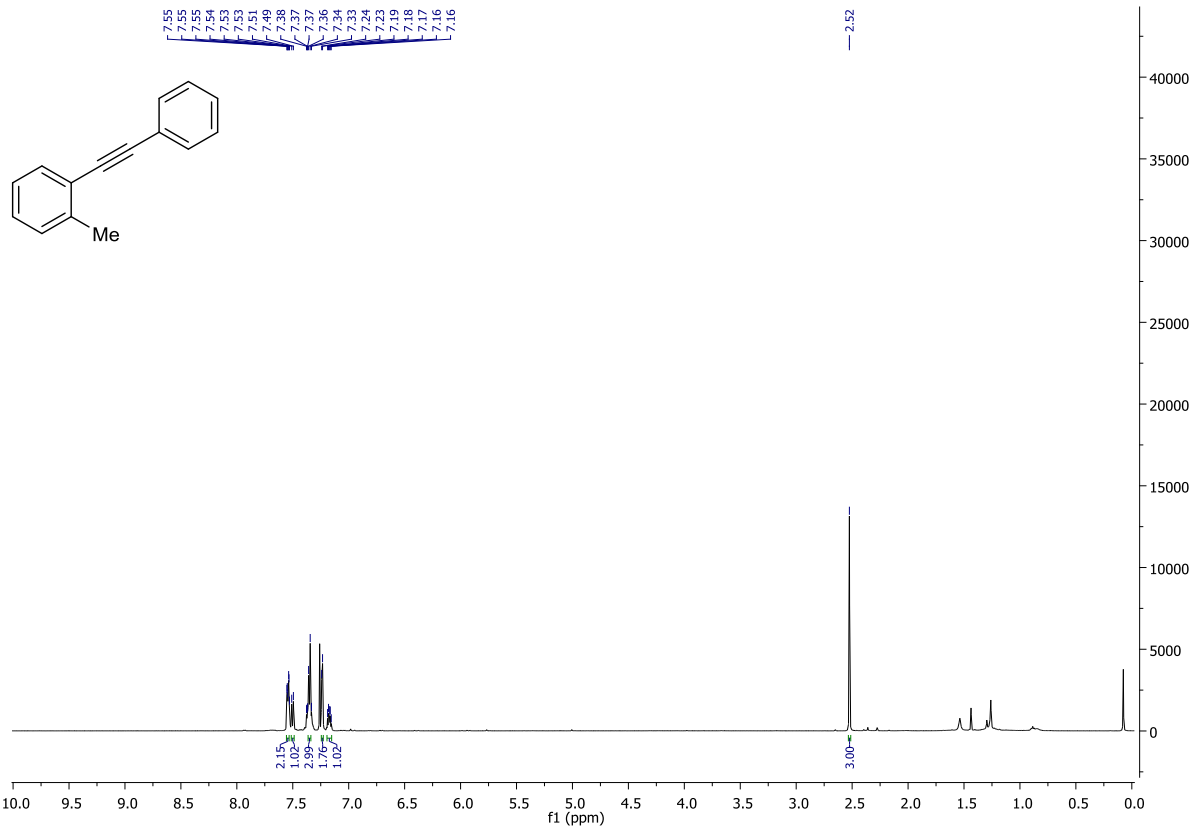

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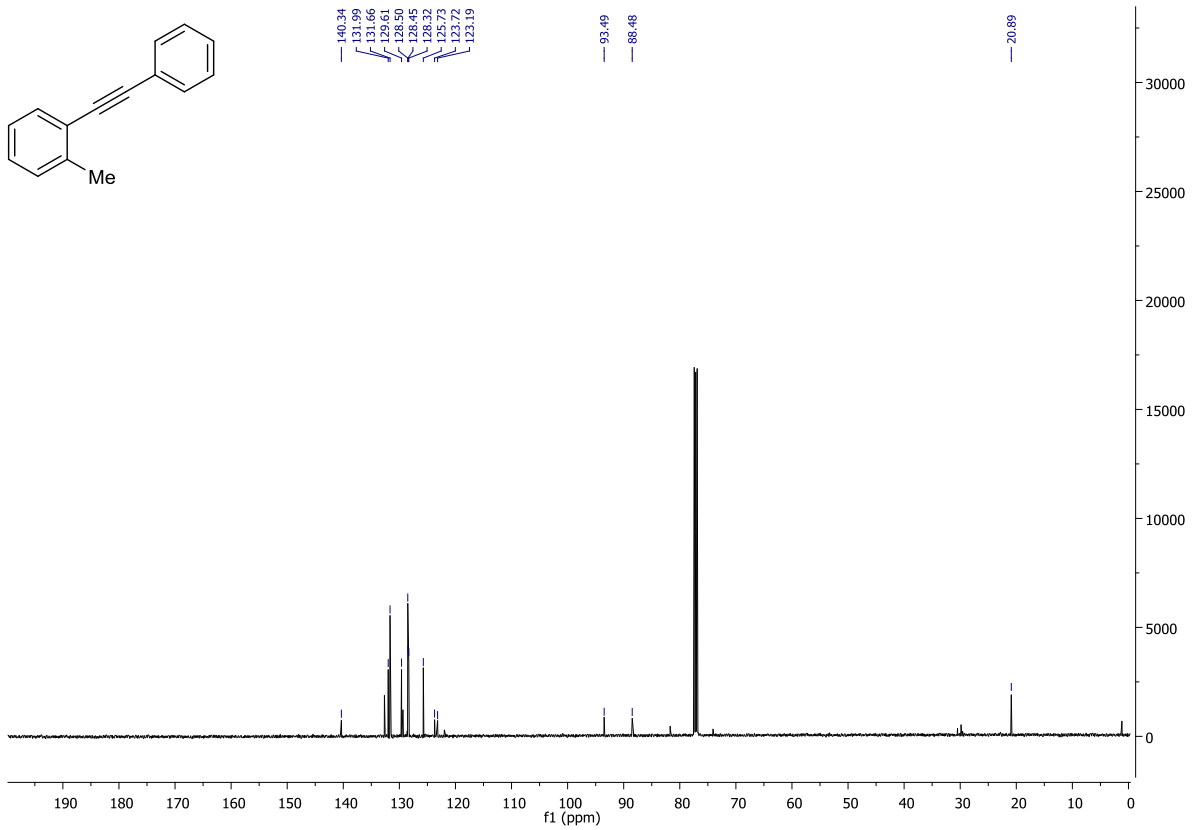

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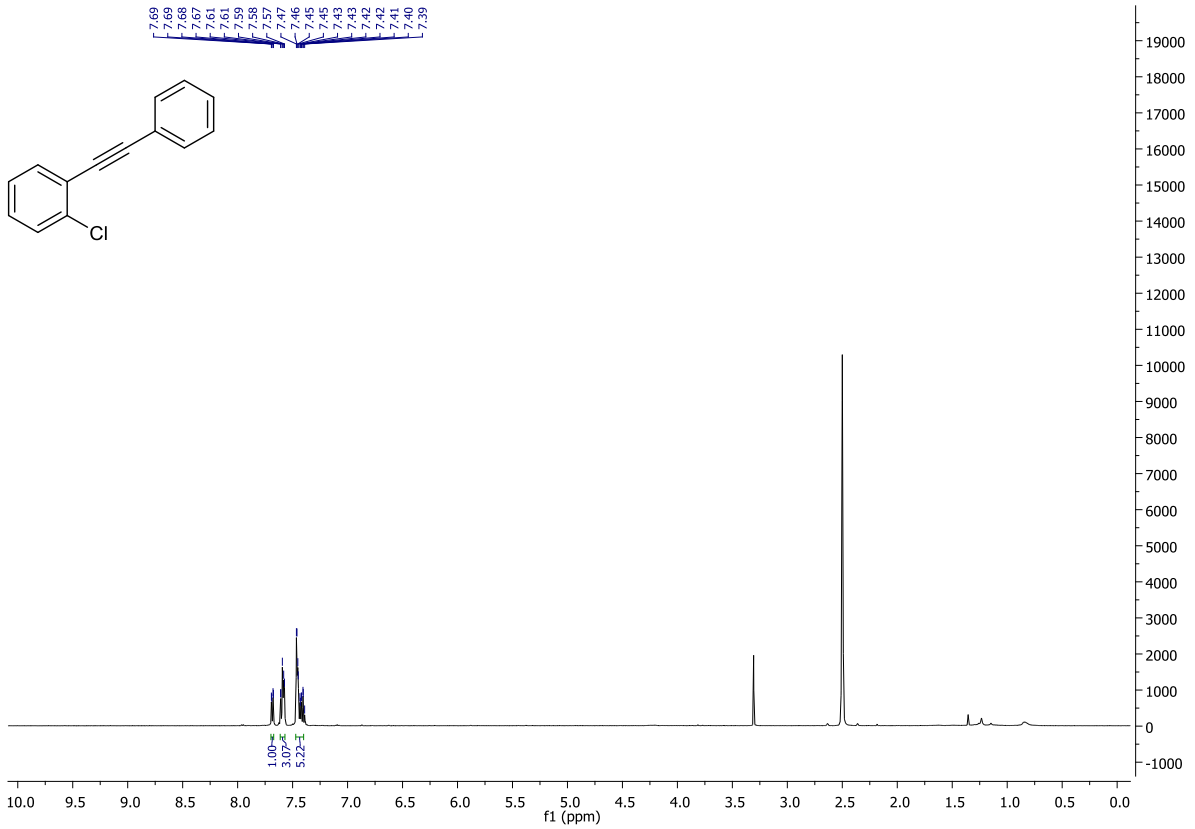

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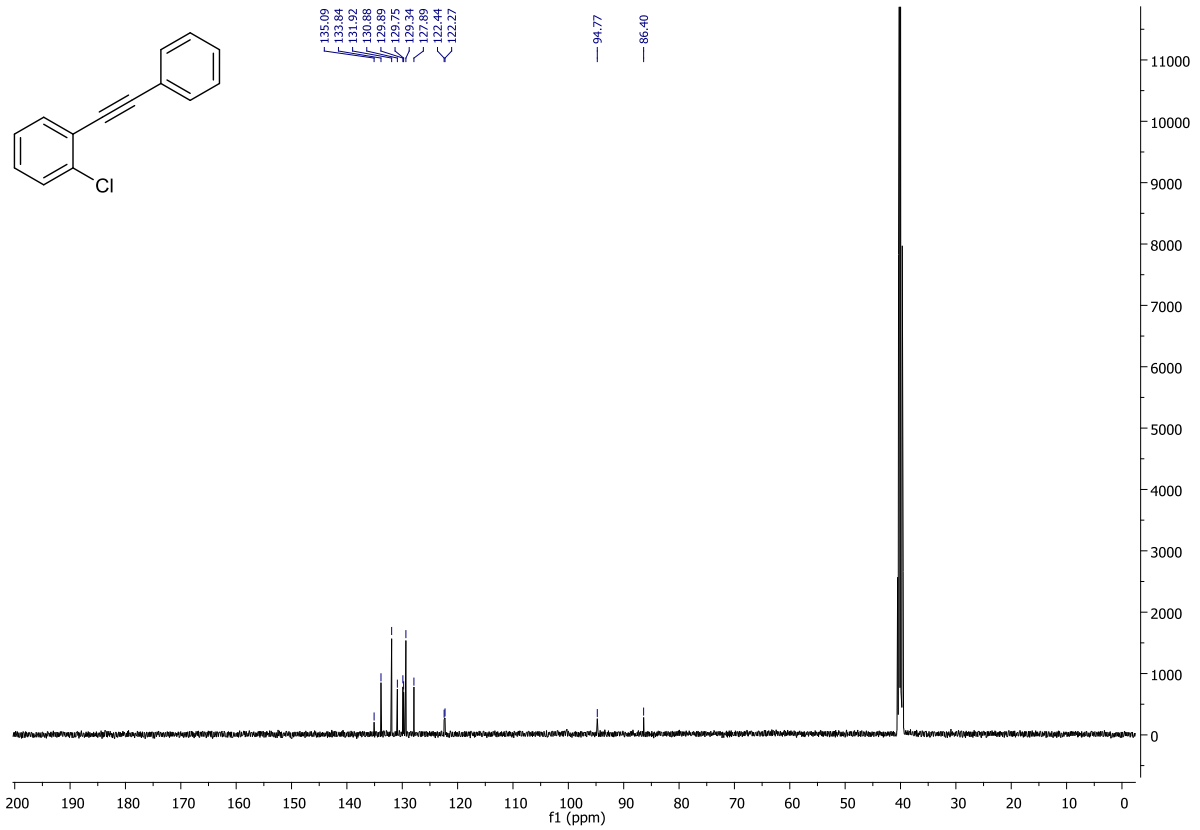

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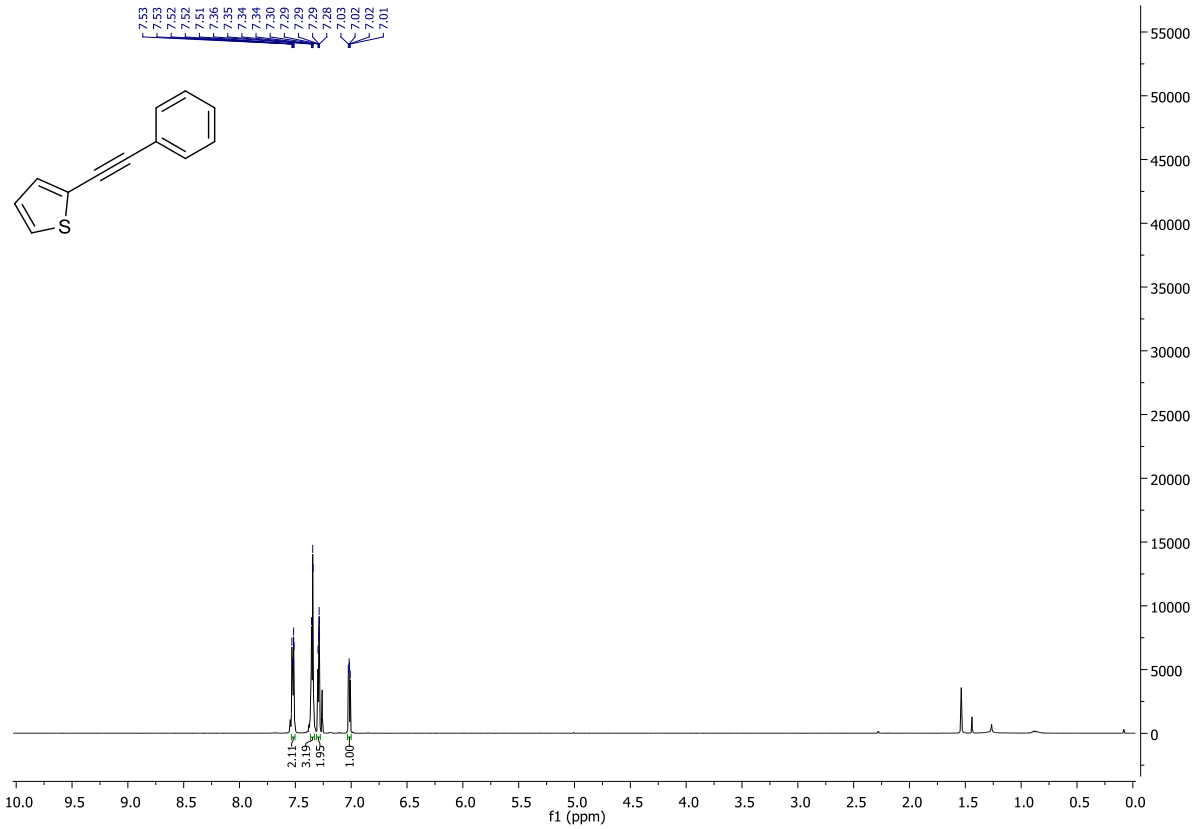

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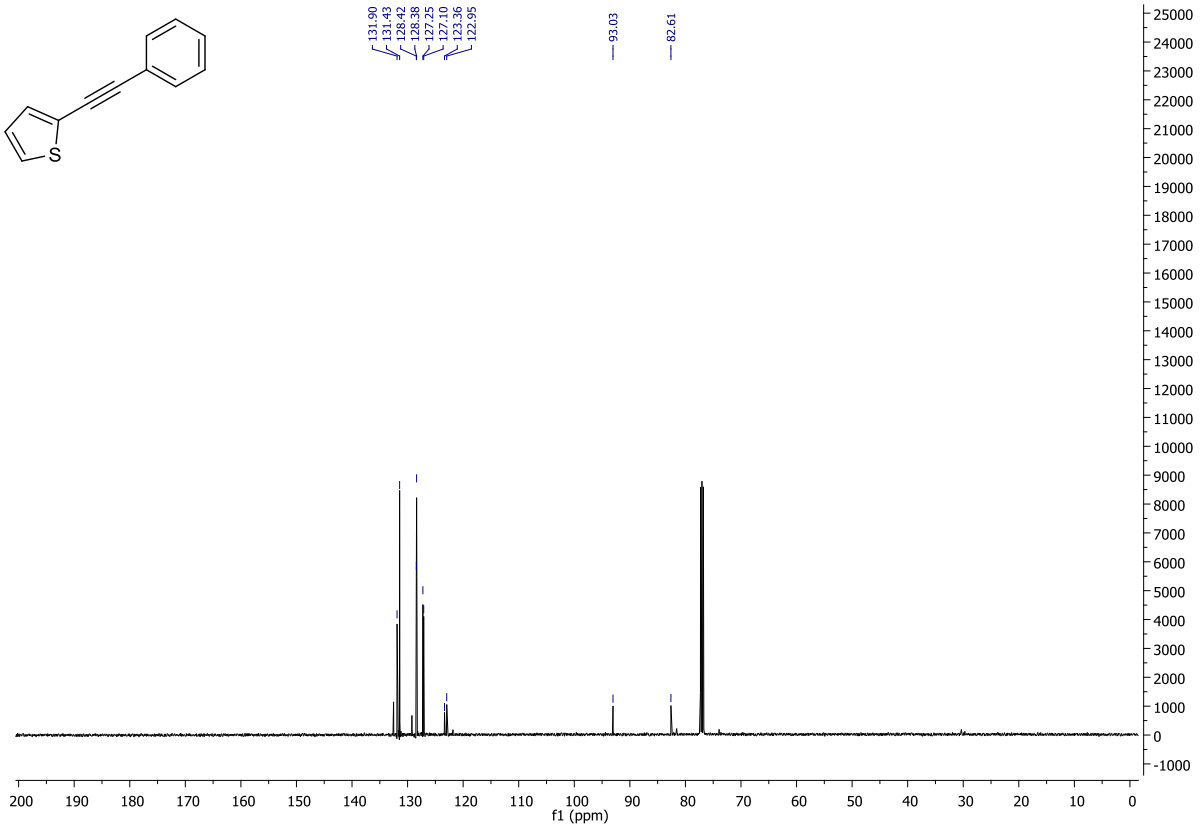

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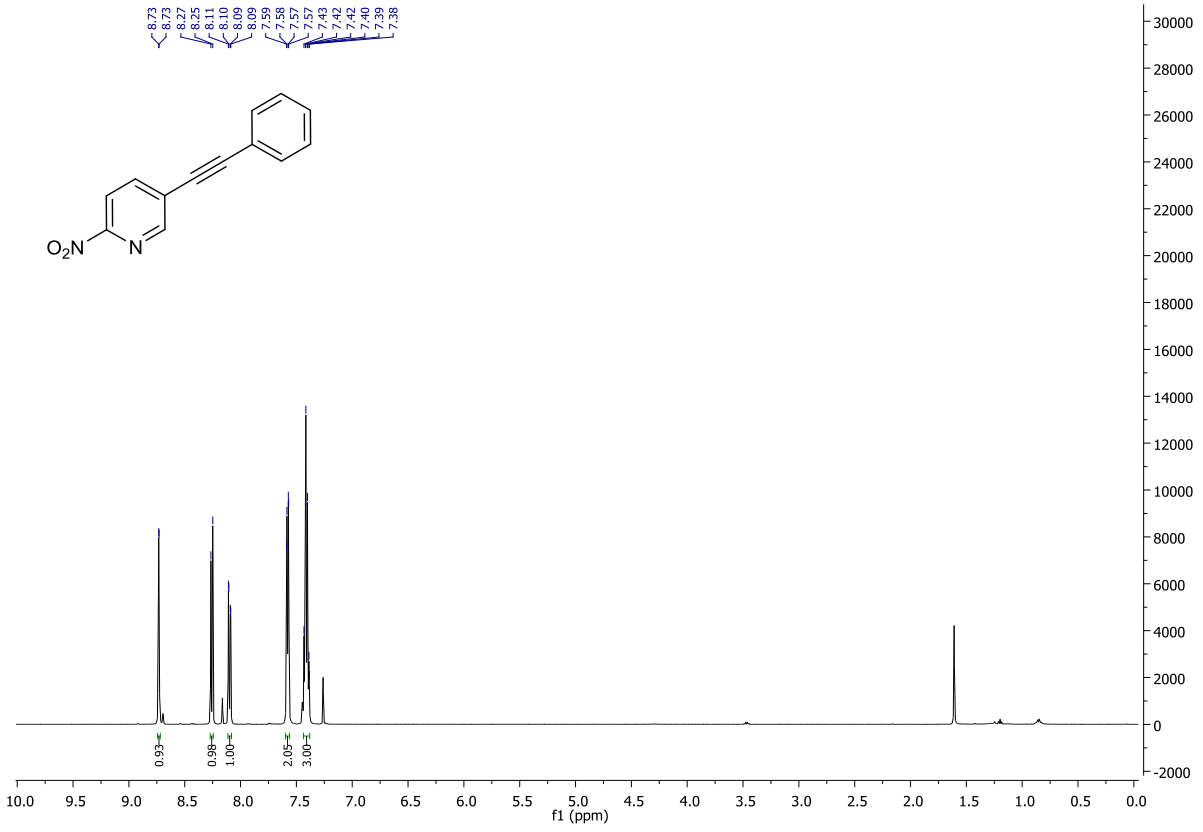

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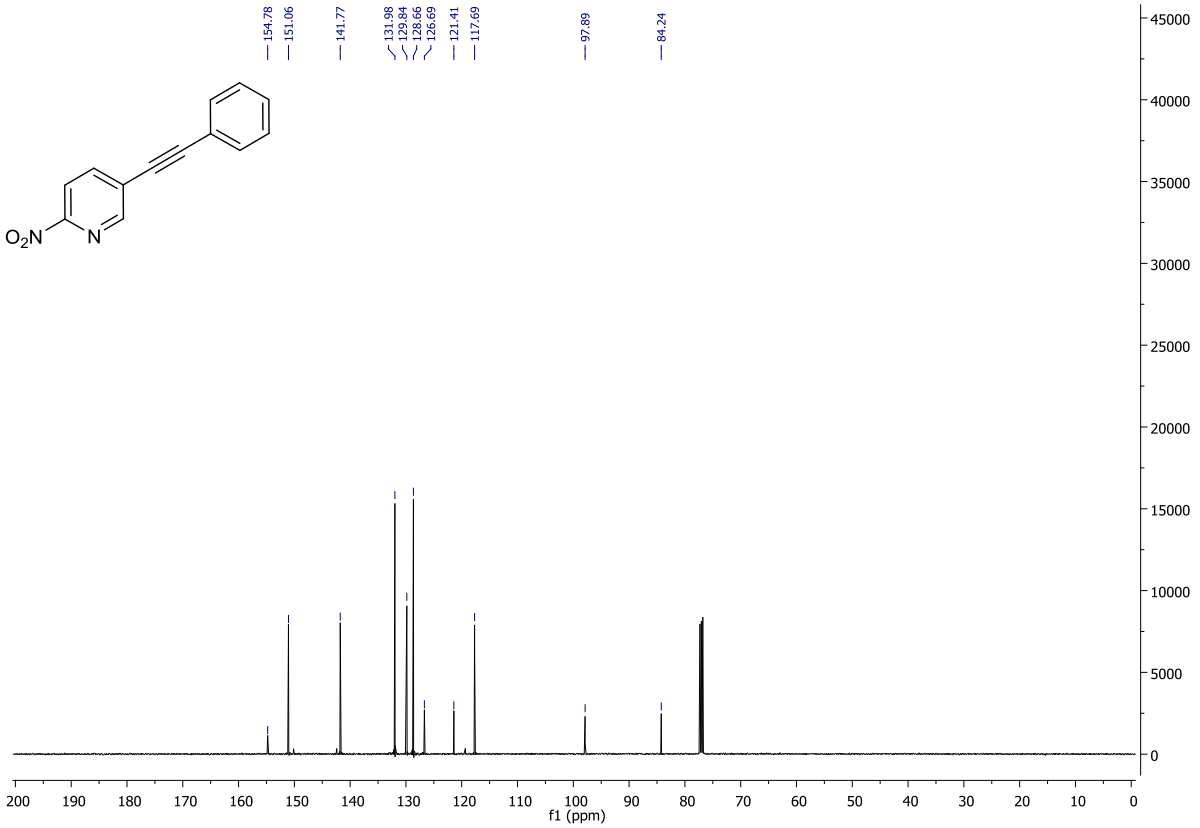

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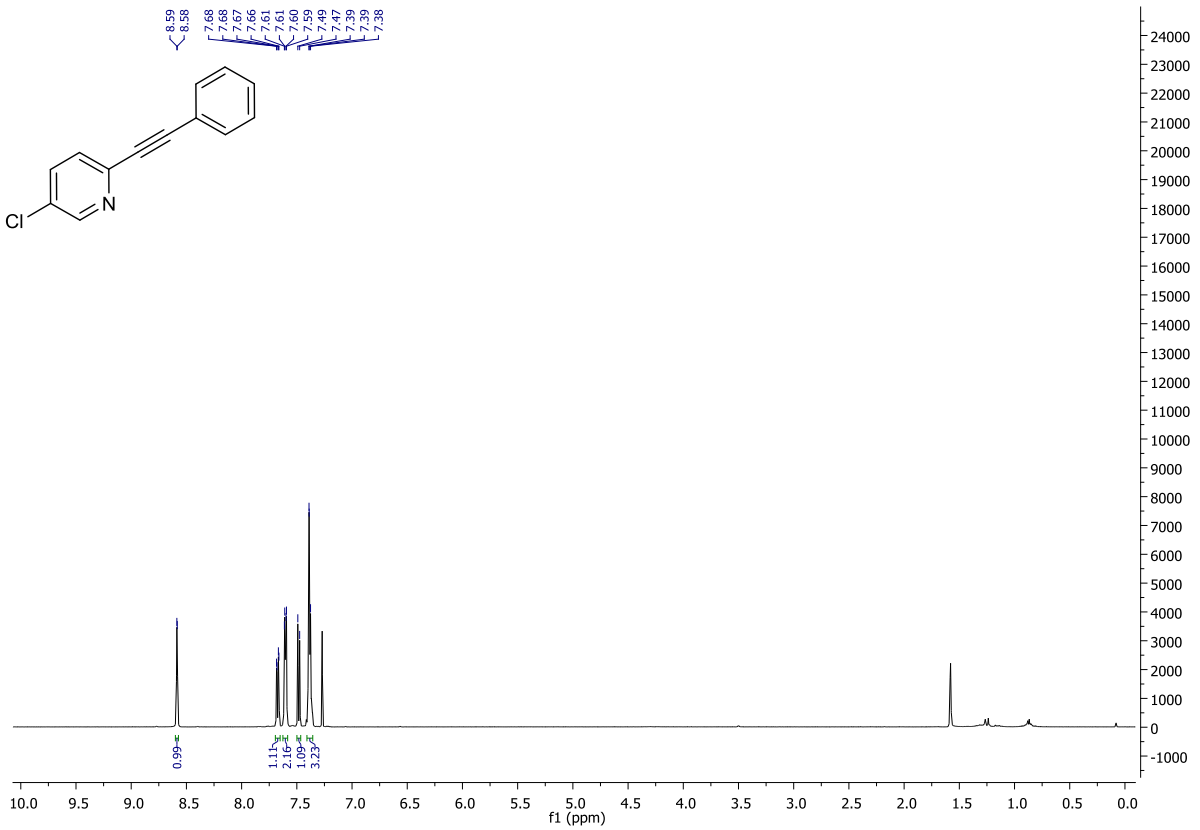

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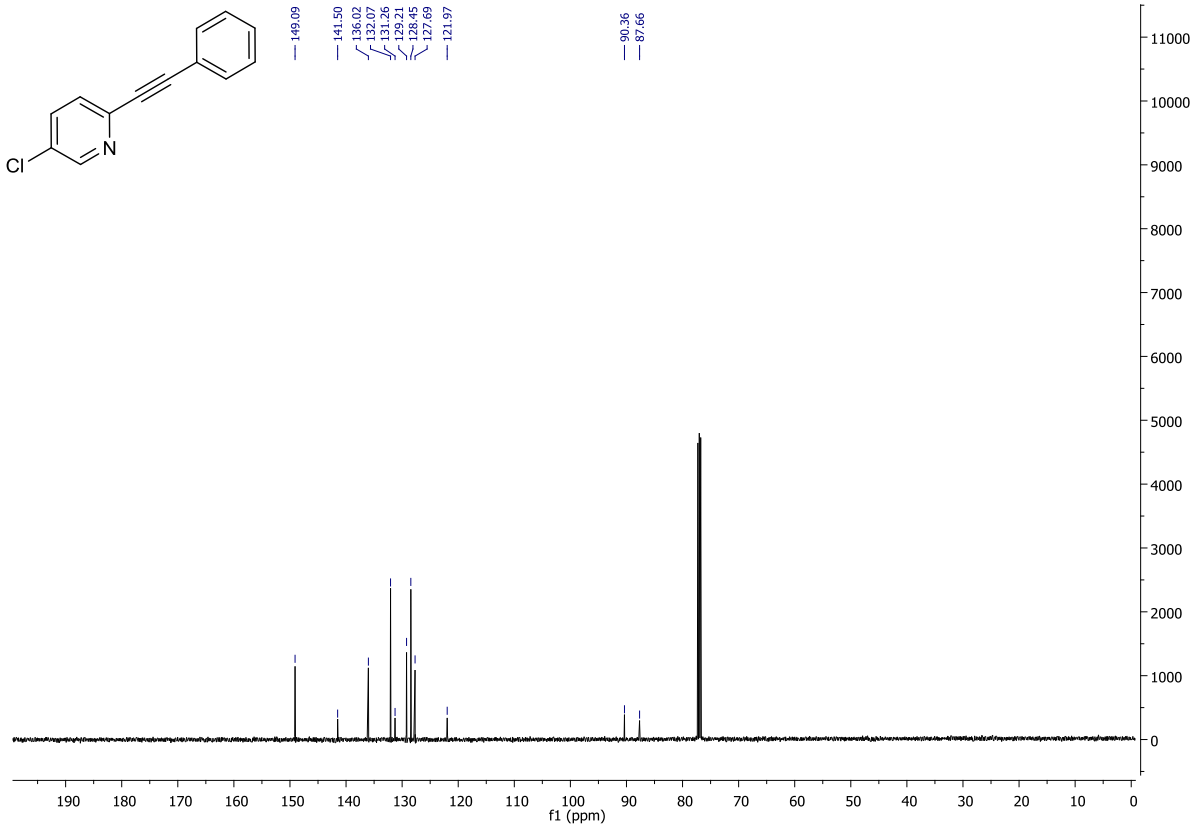

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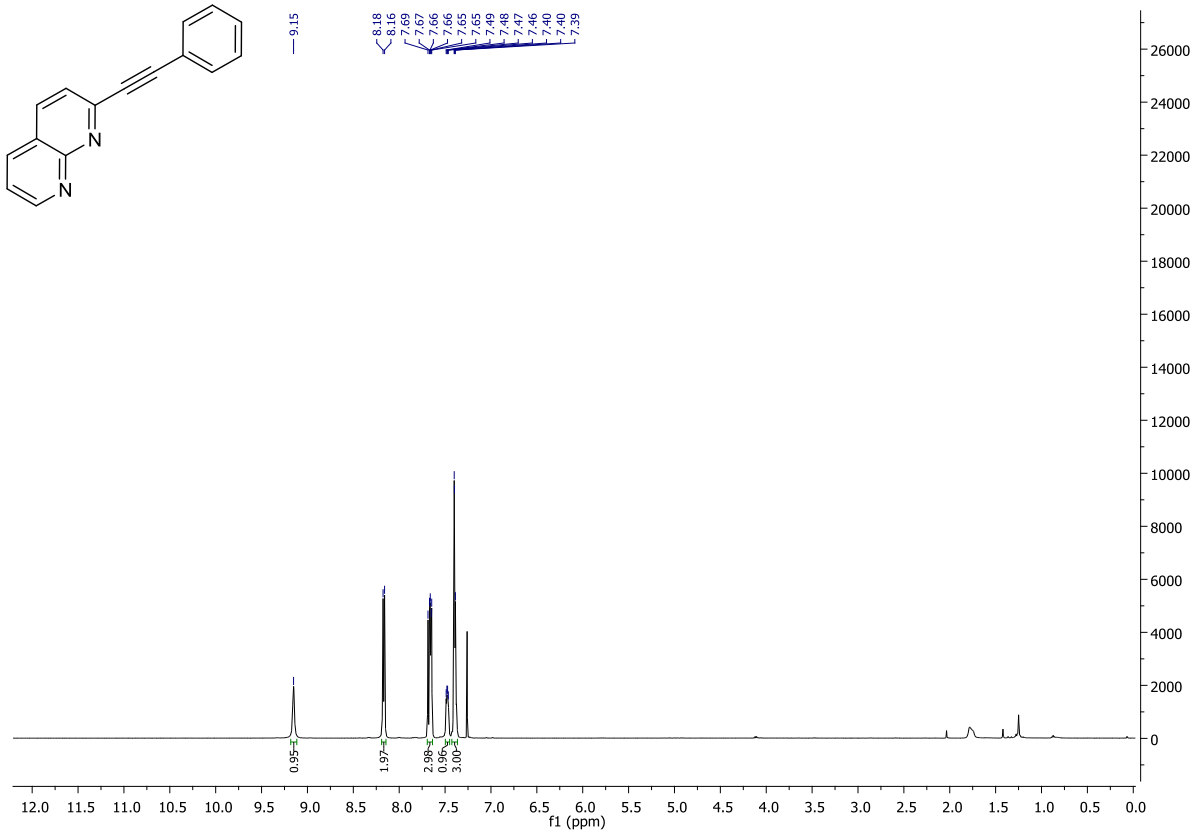

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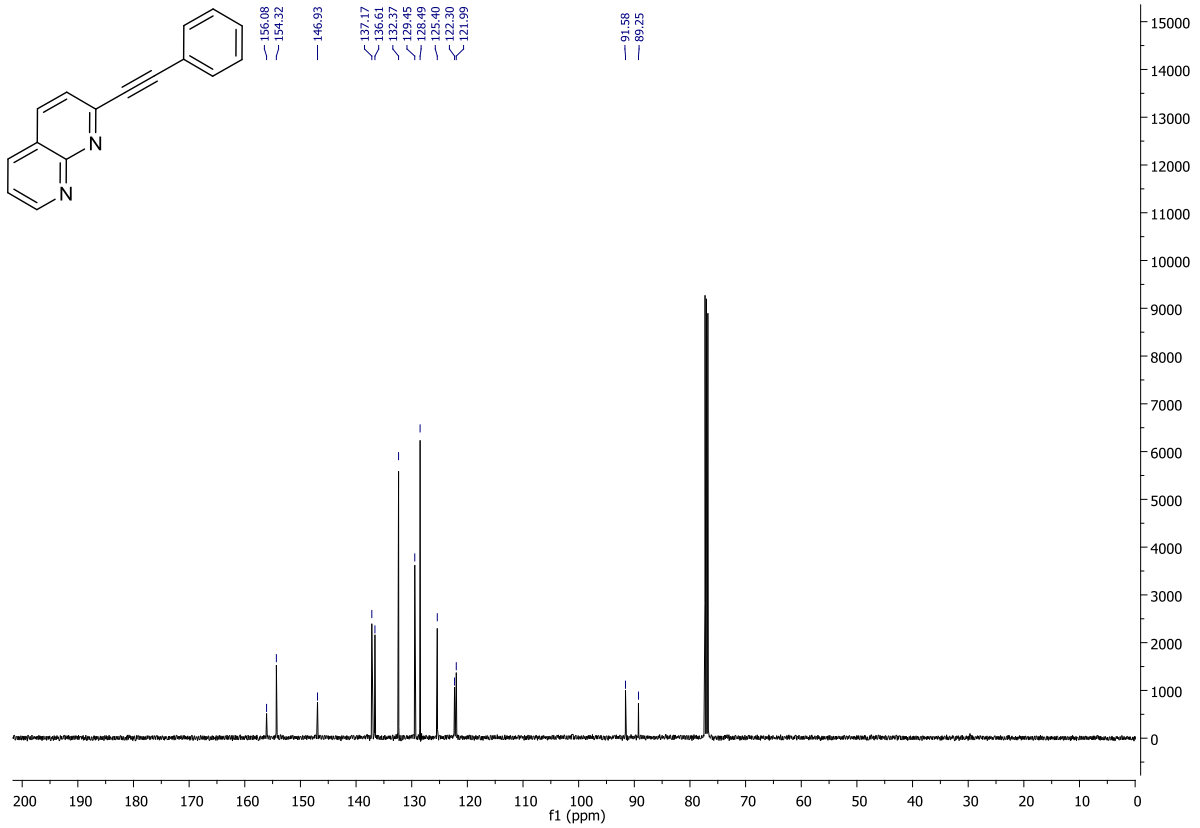

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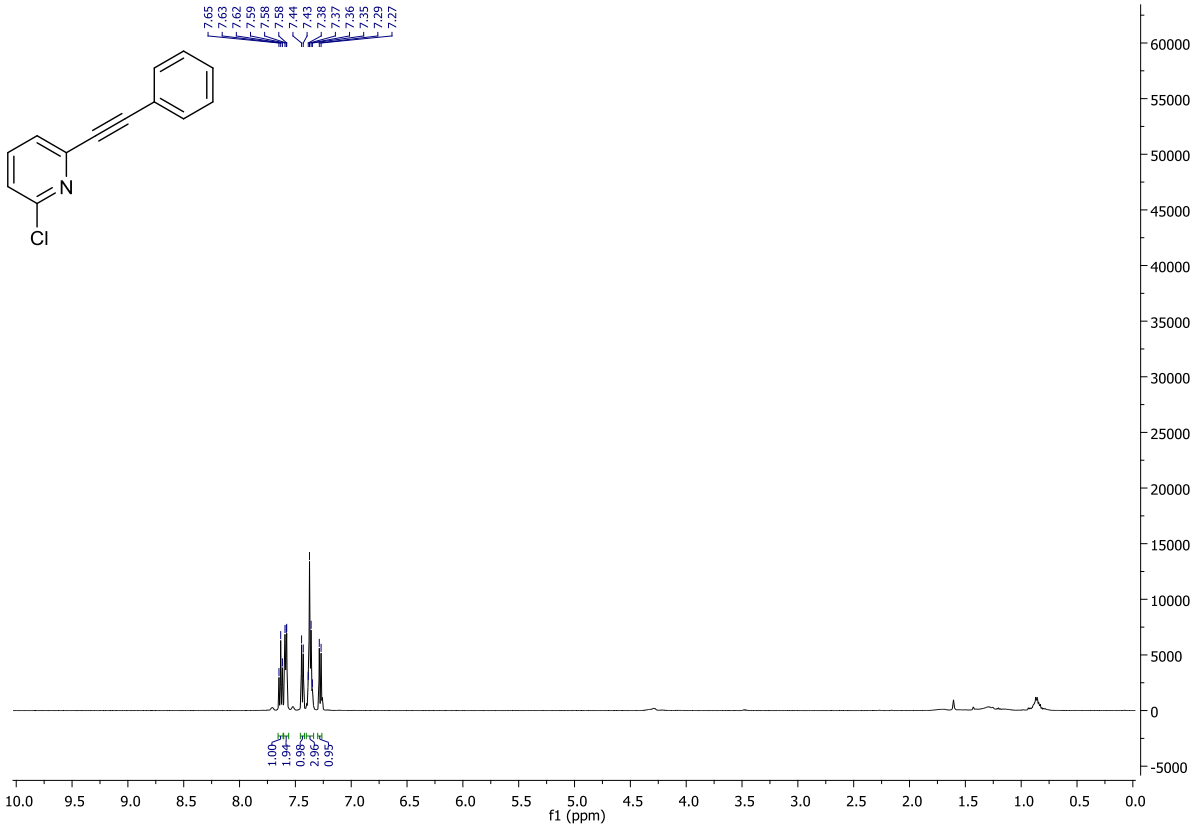

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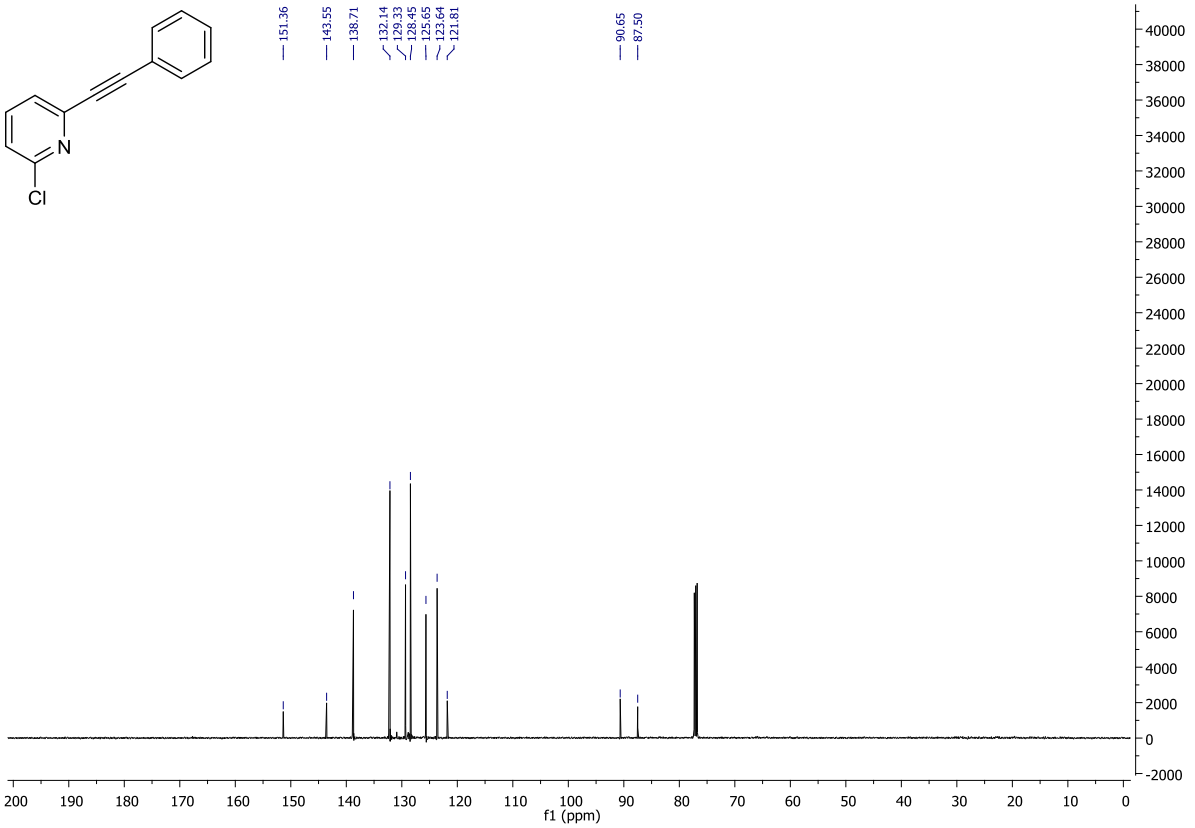

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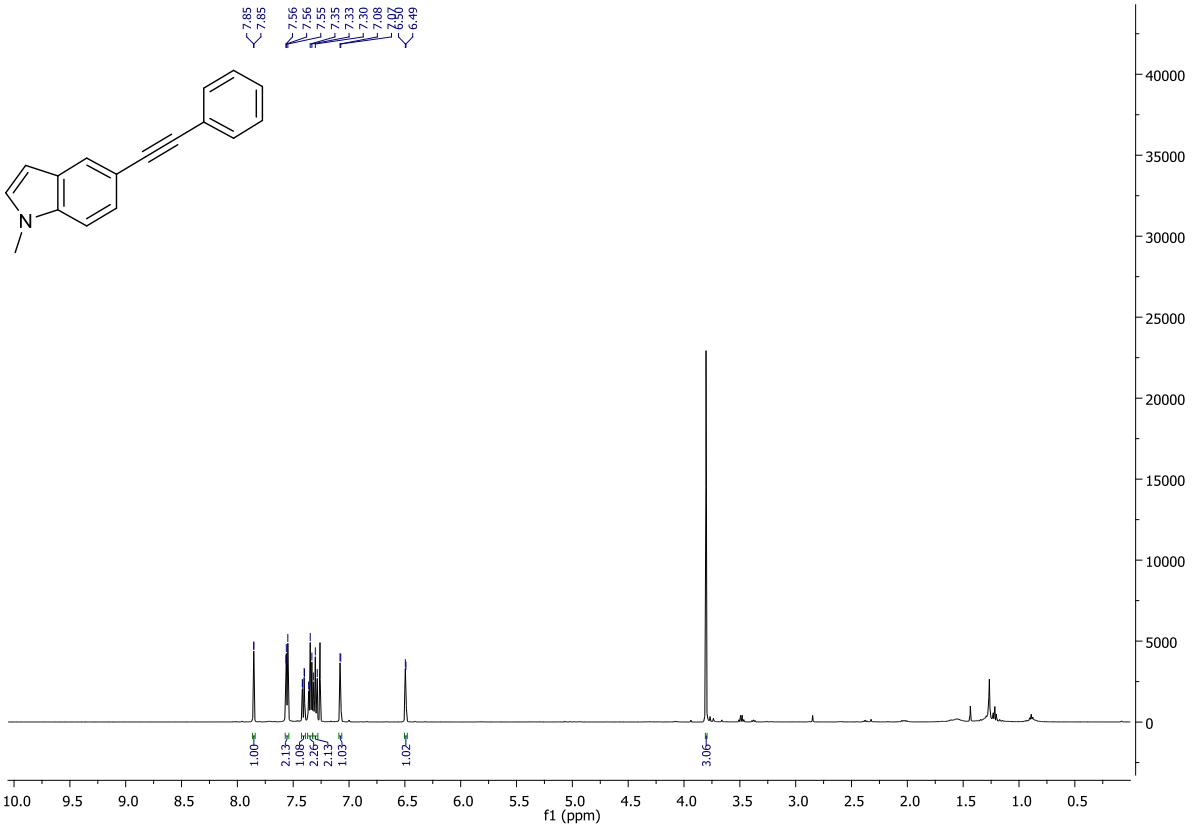

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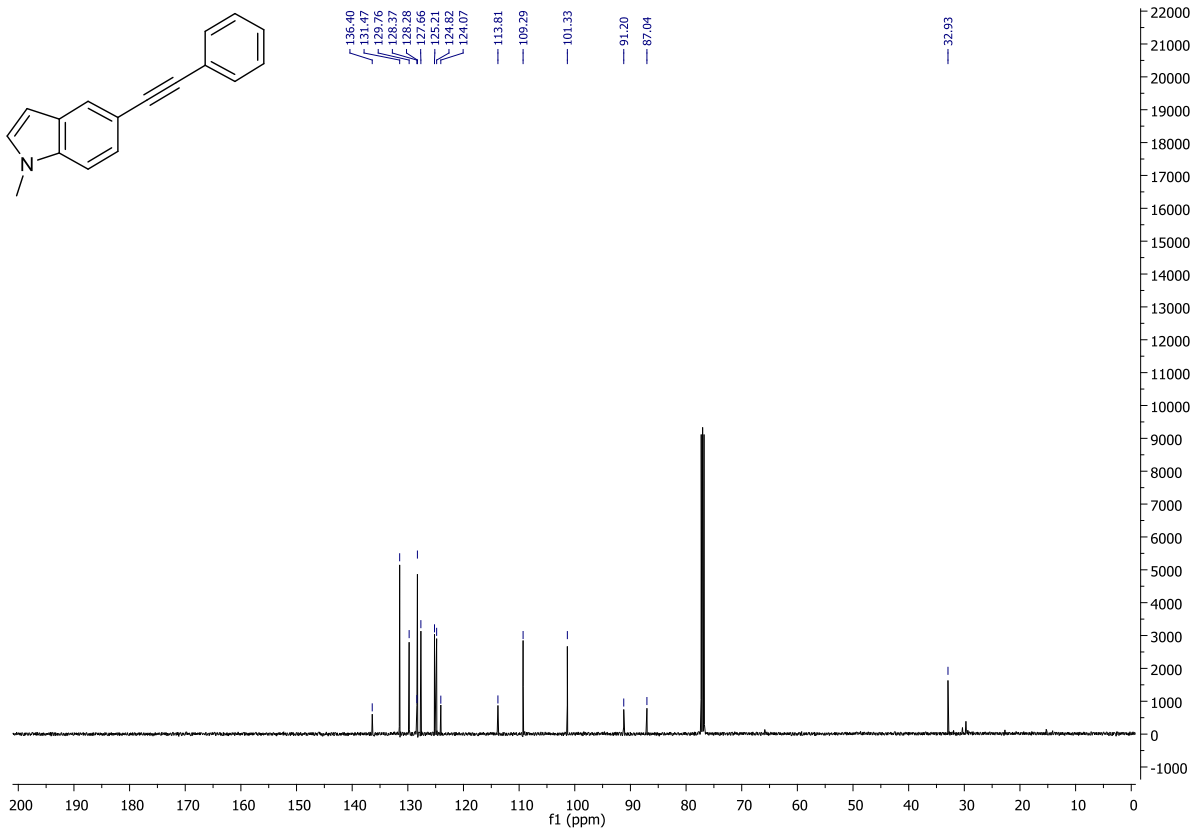

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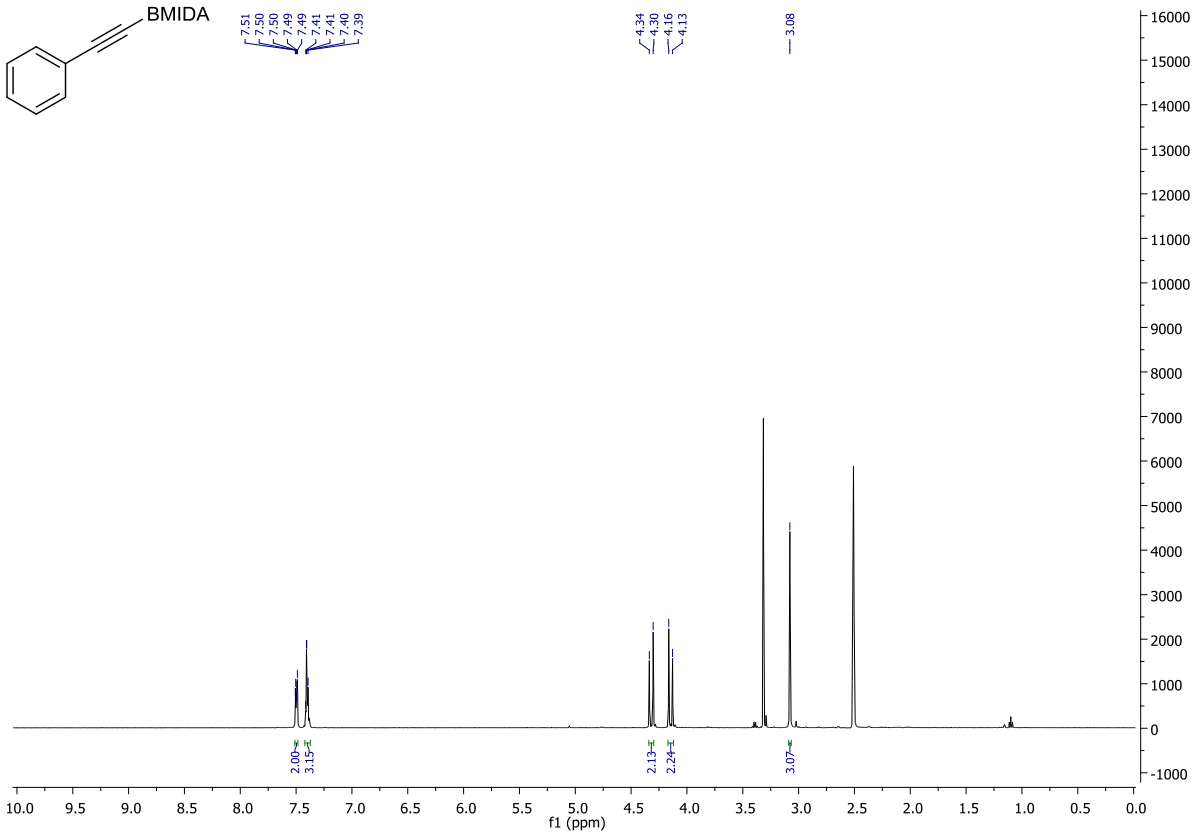

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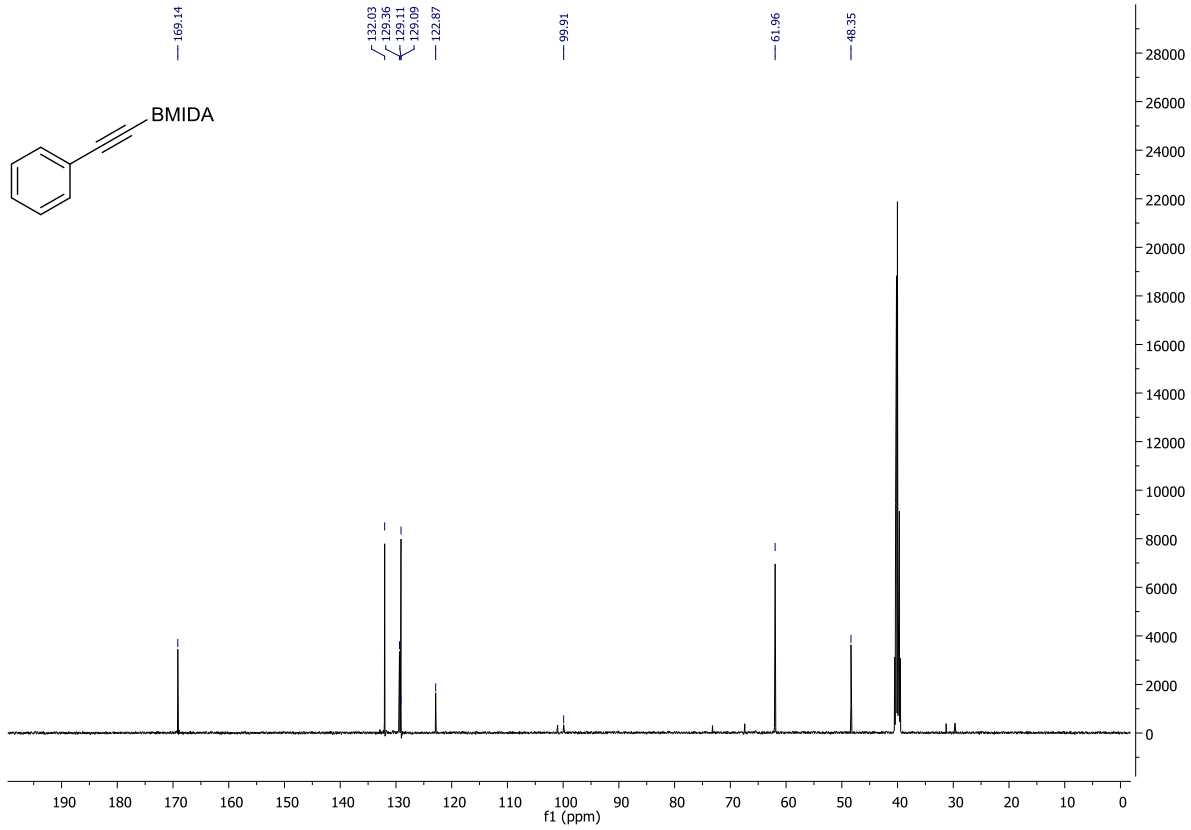

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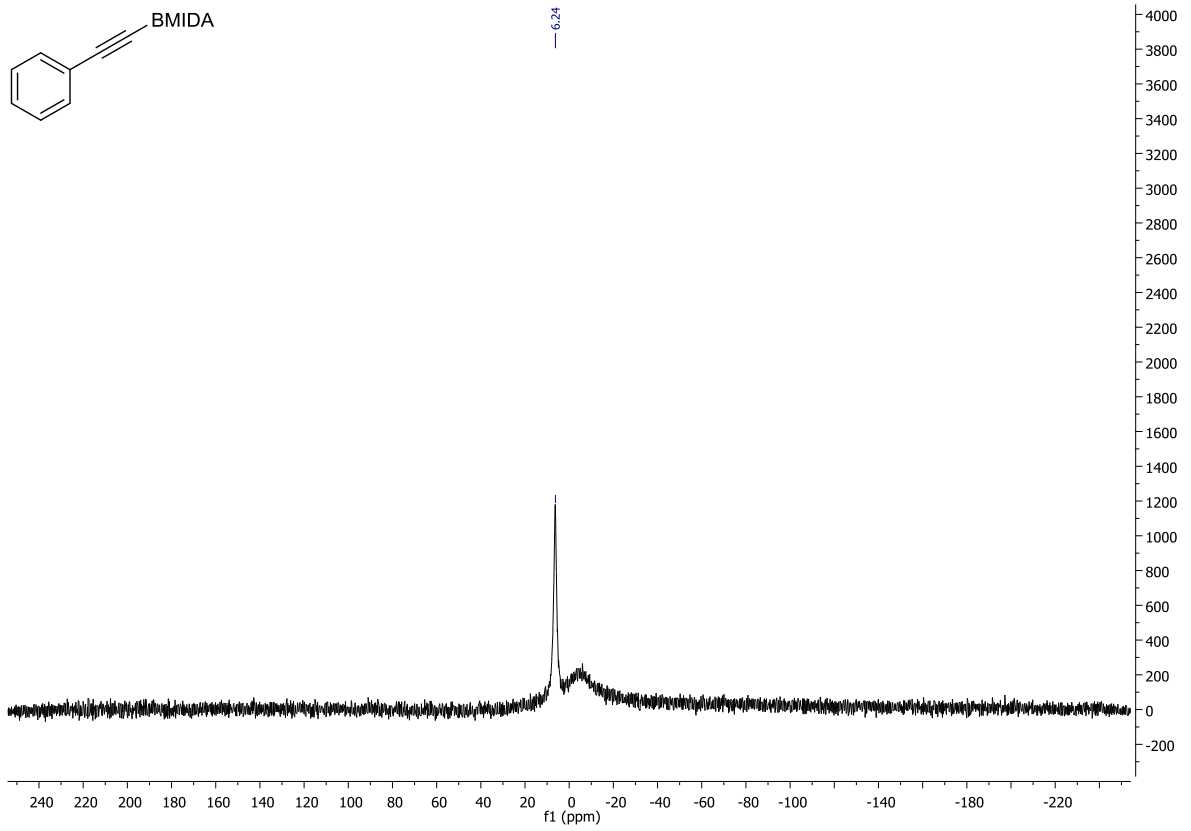

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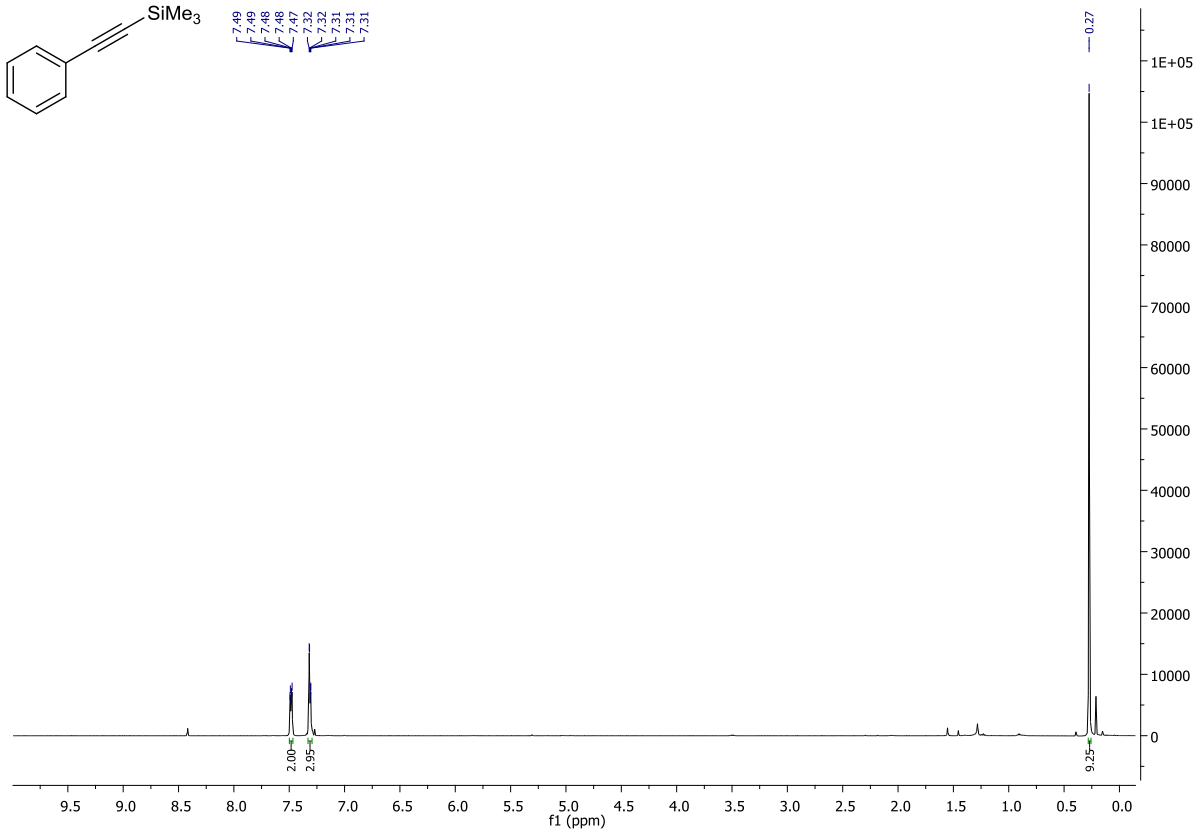

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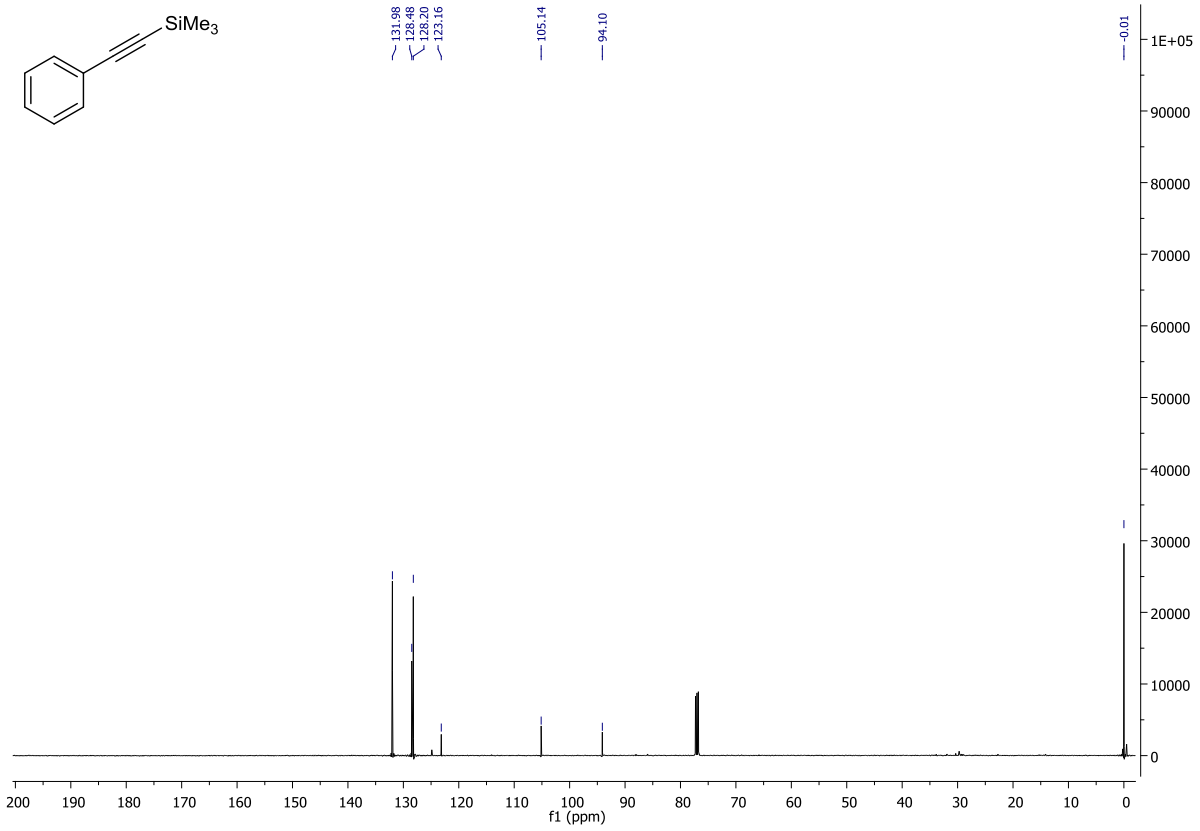

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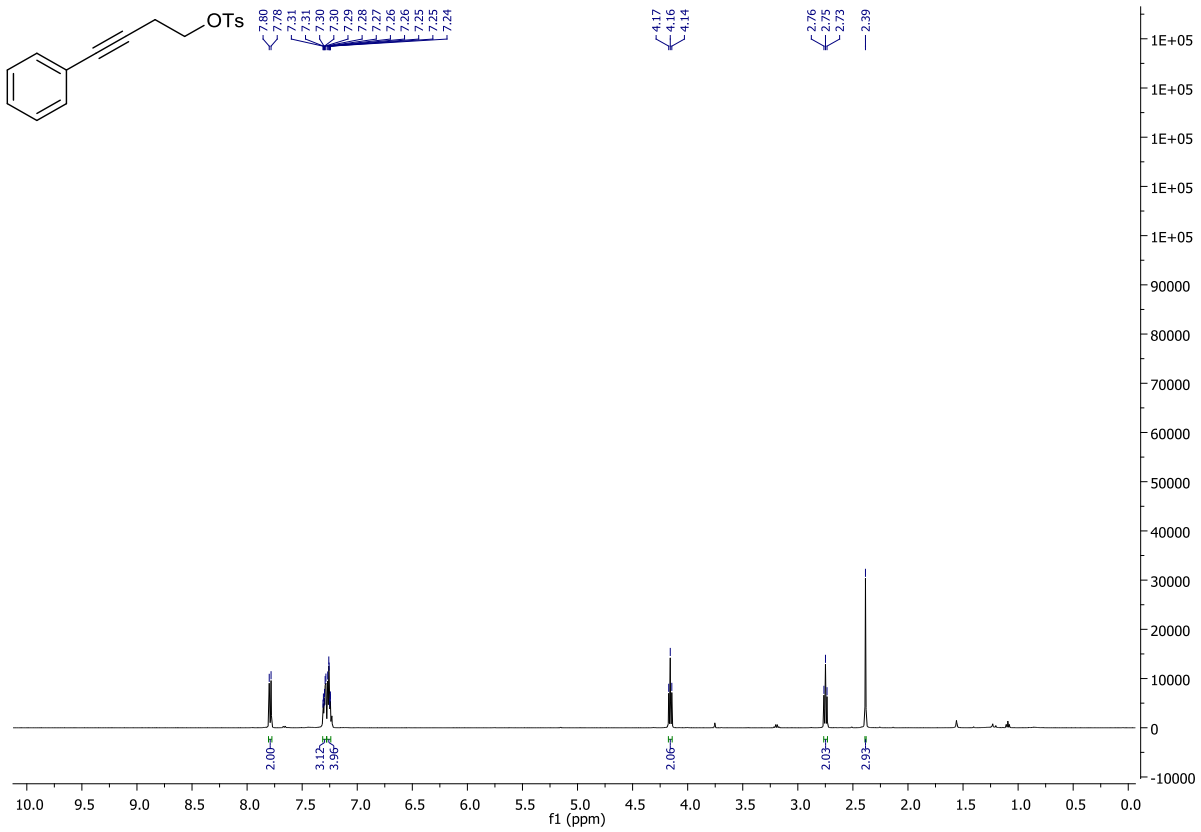

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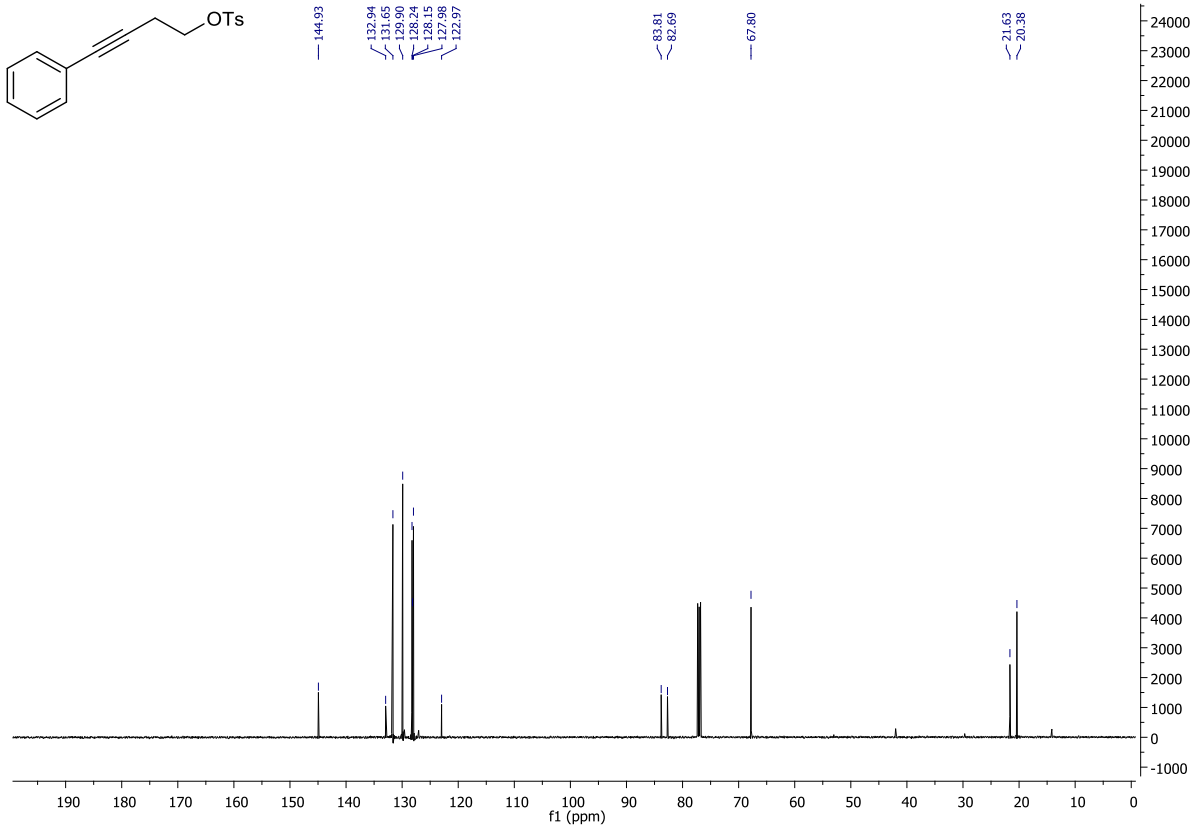

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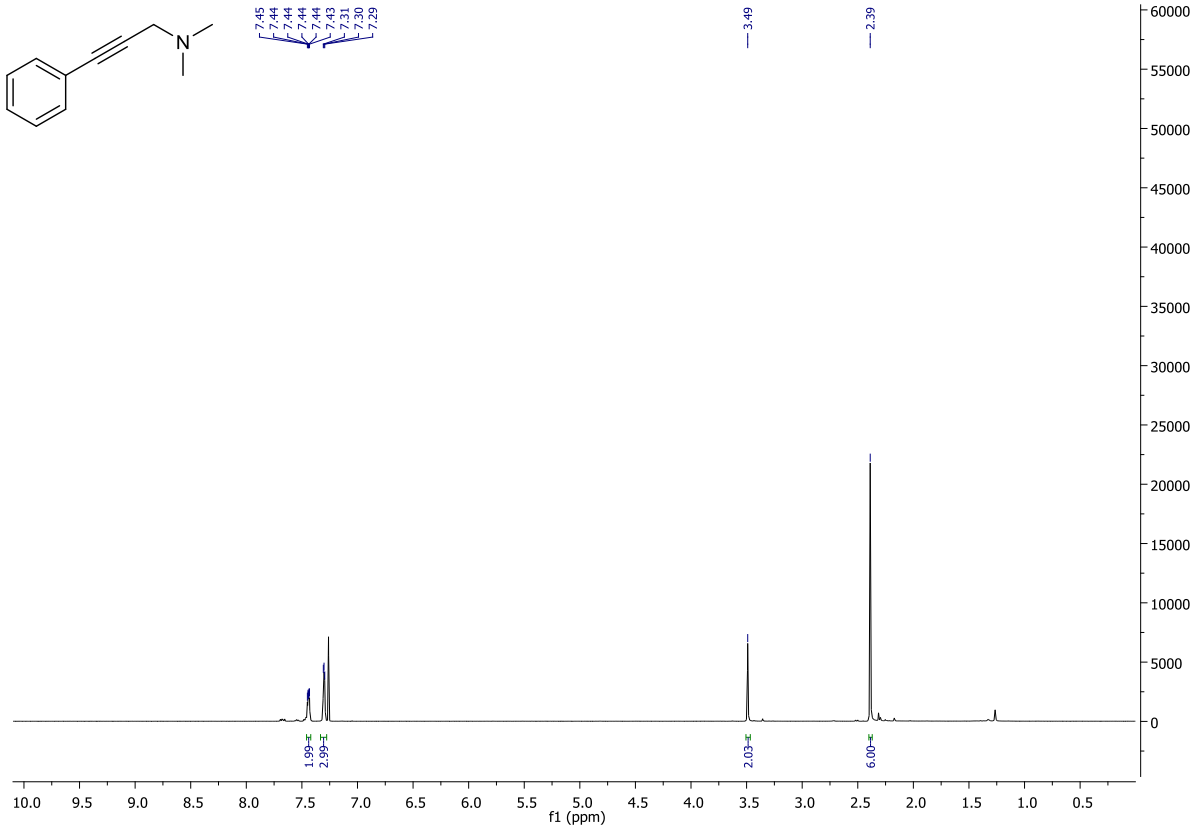

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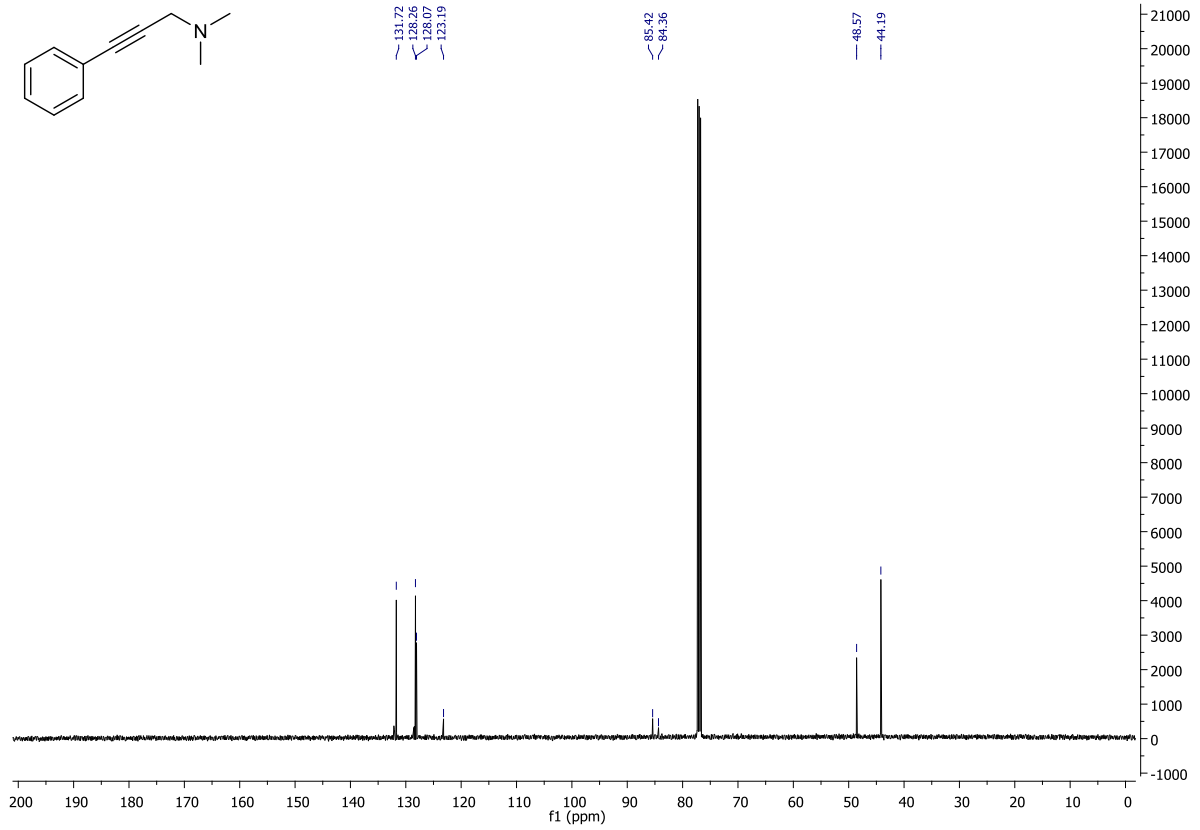

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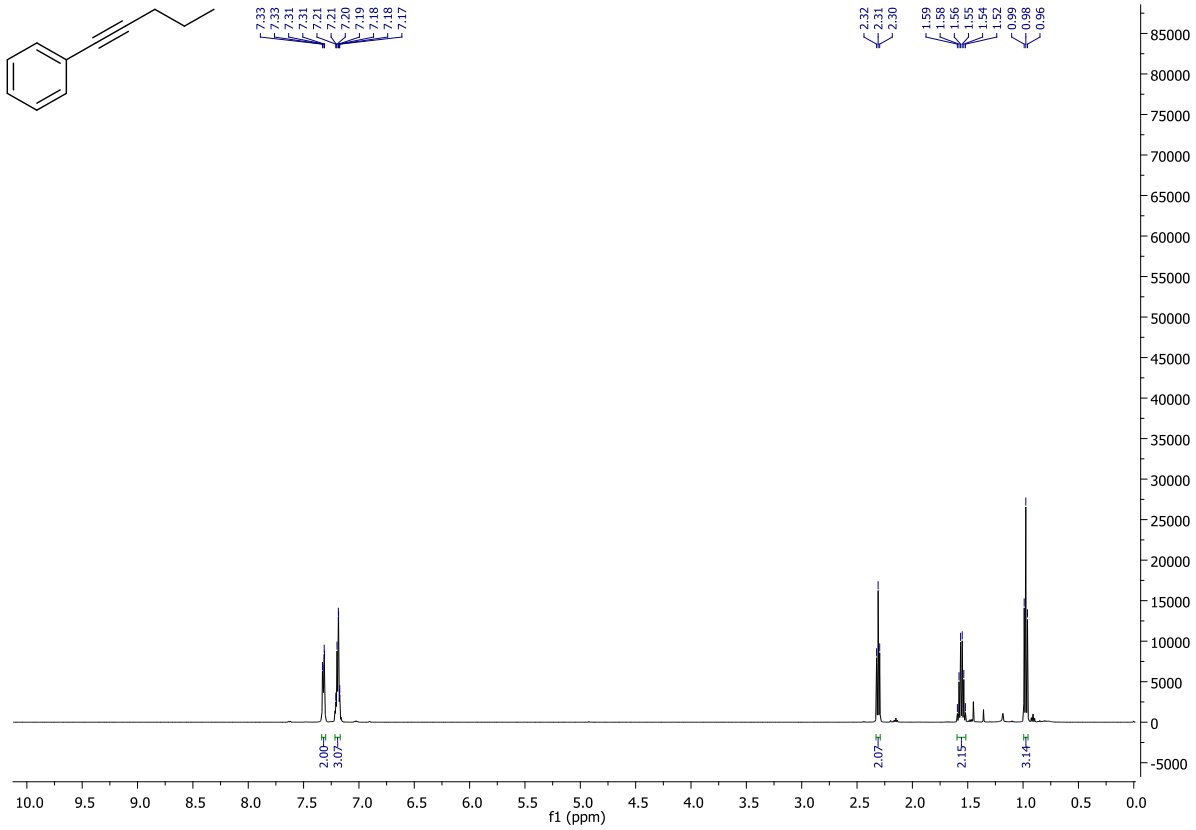

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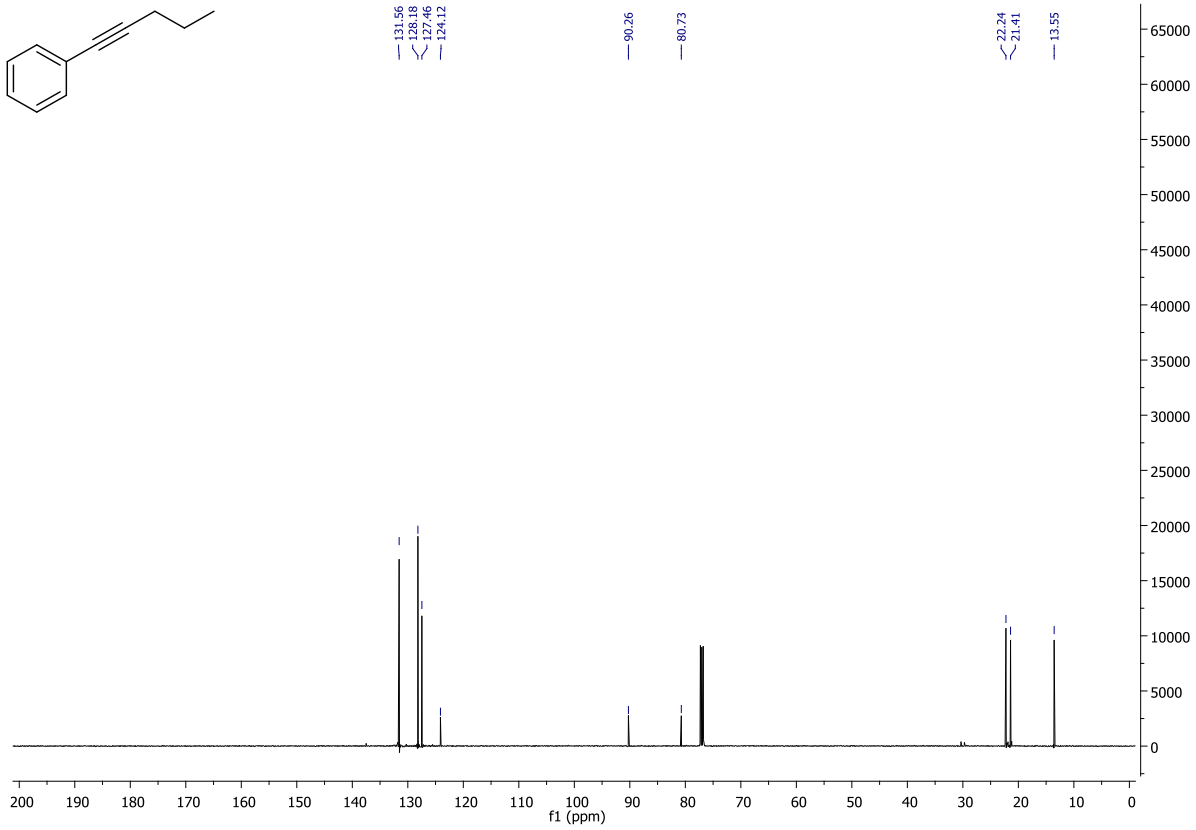

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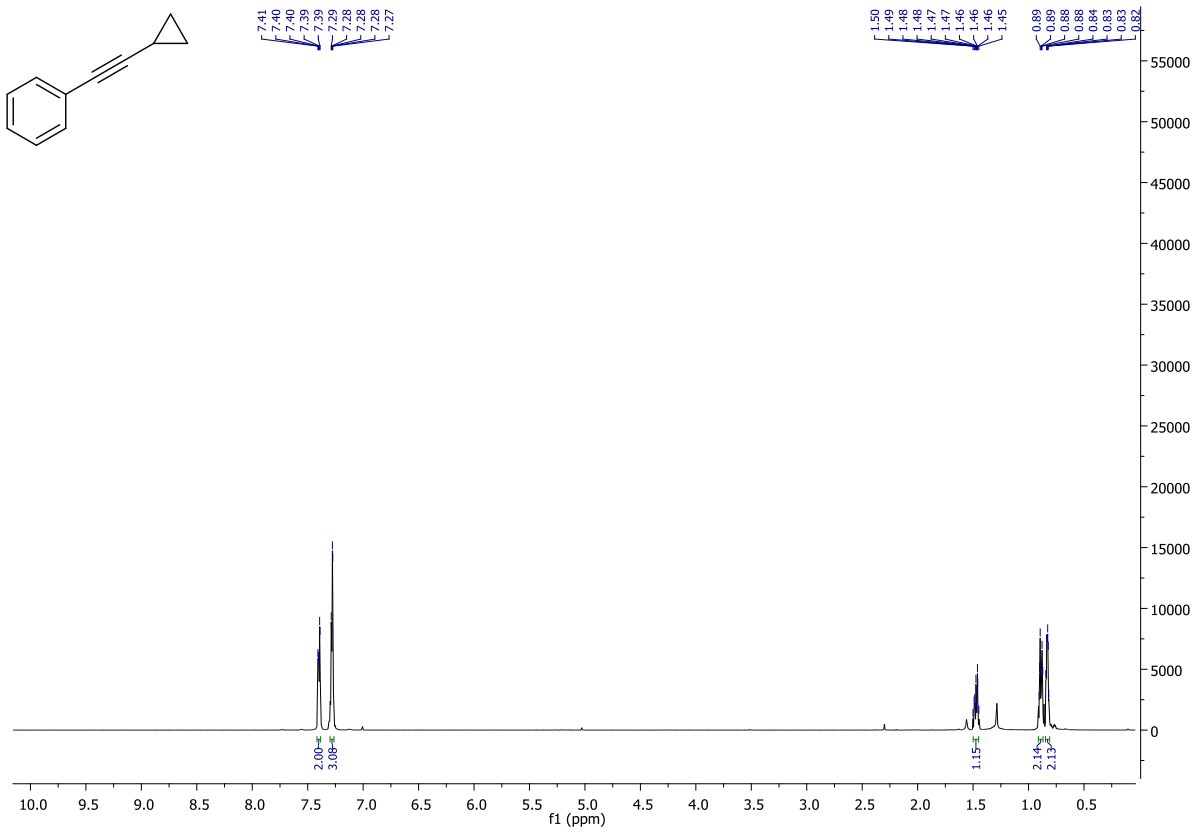
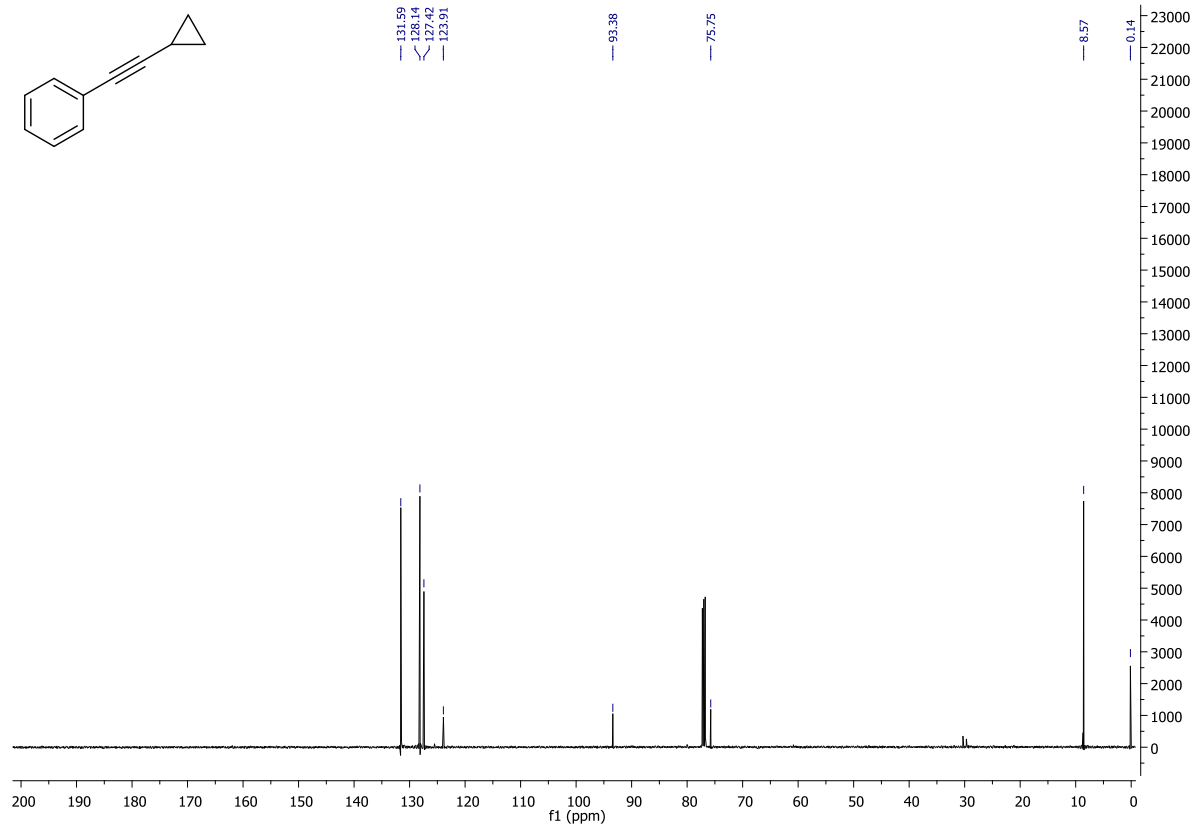
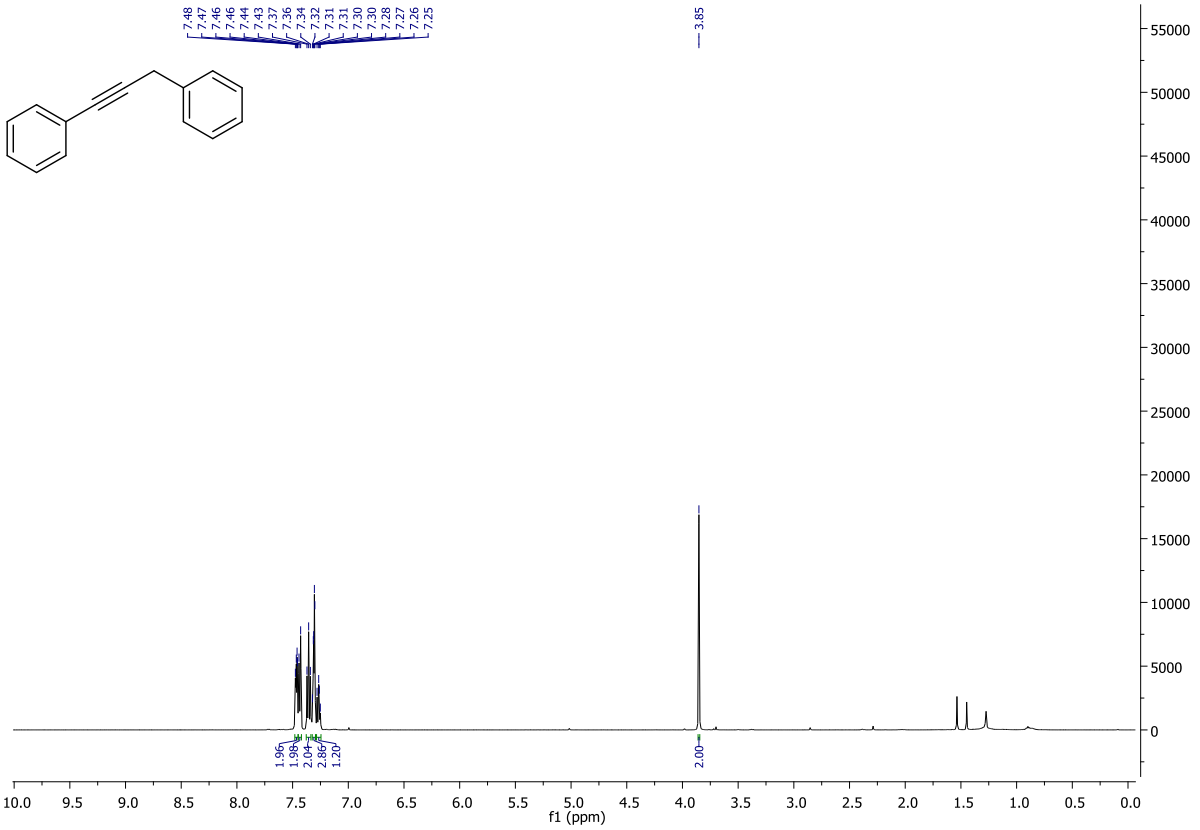


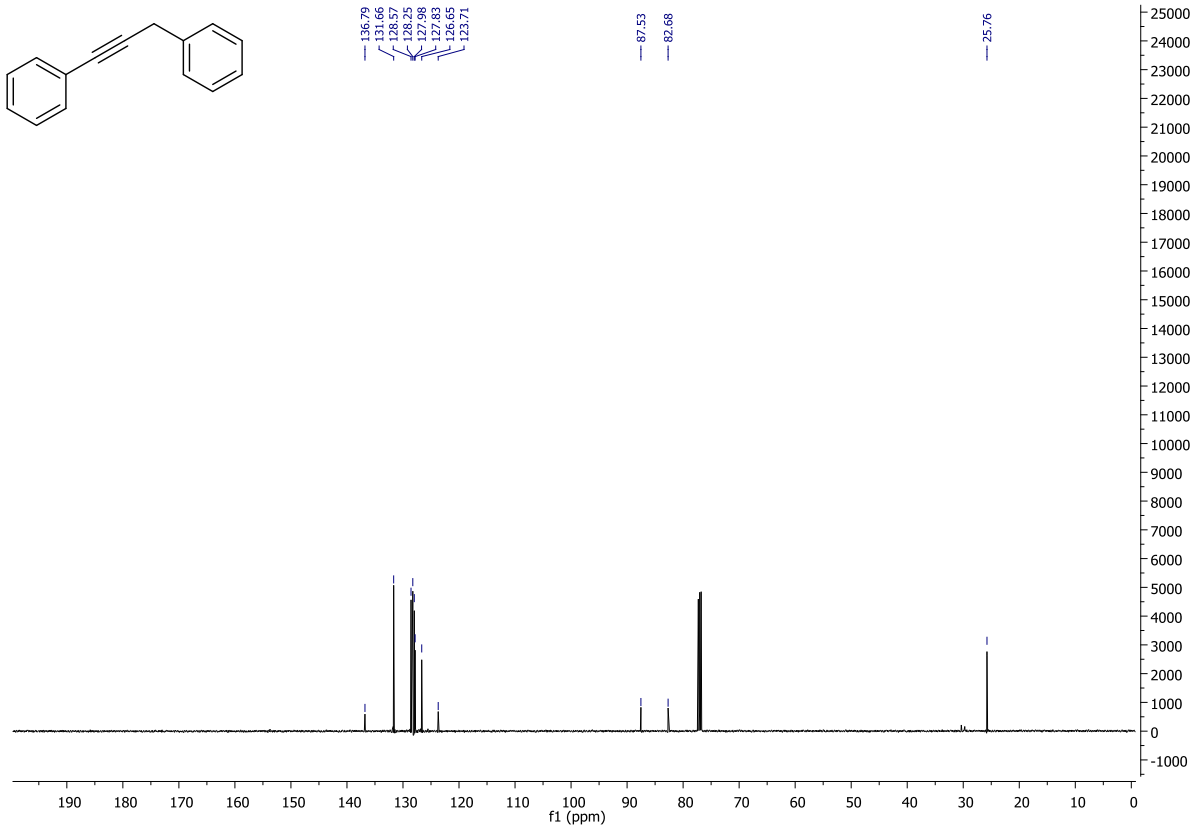
^{13}C NMR 3v



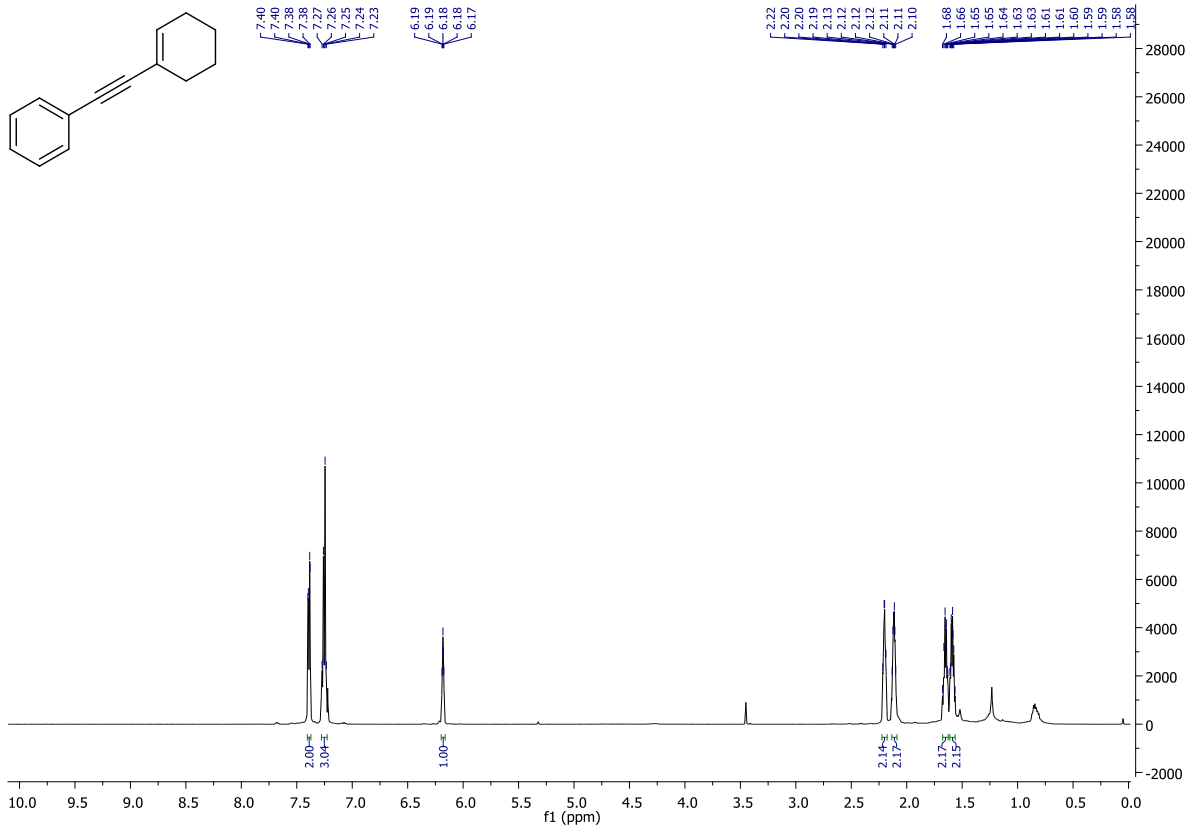
^{1}H NMR 3w



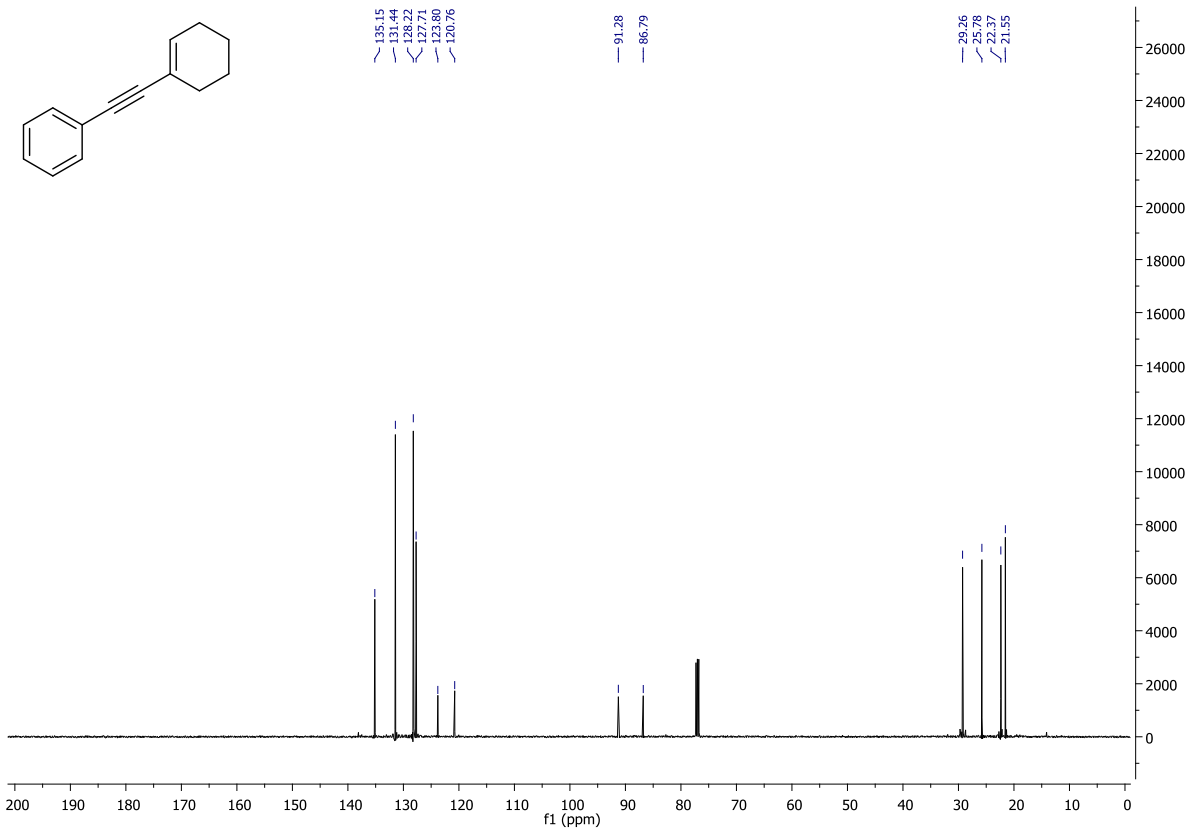
^{13}C NMR 3w



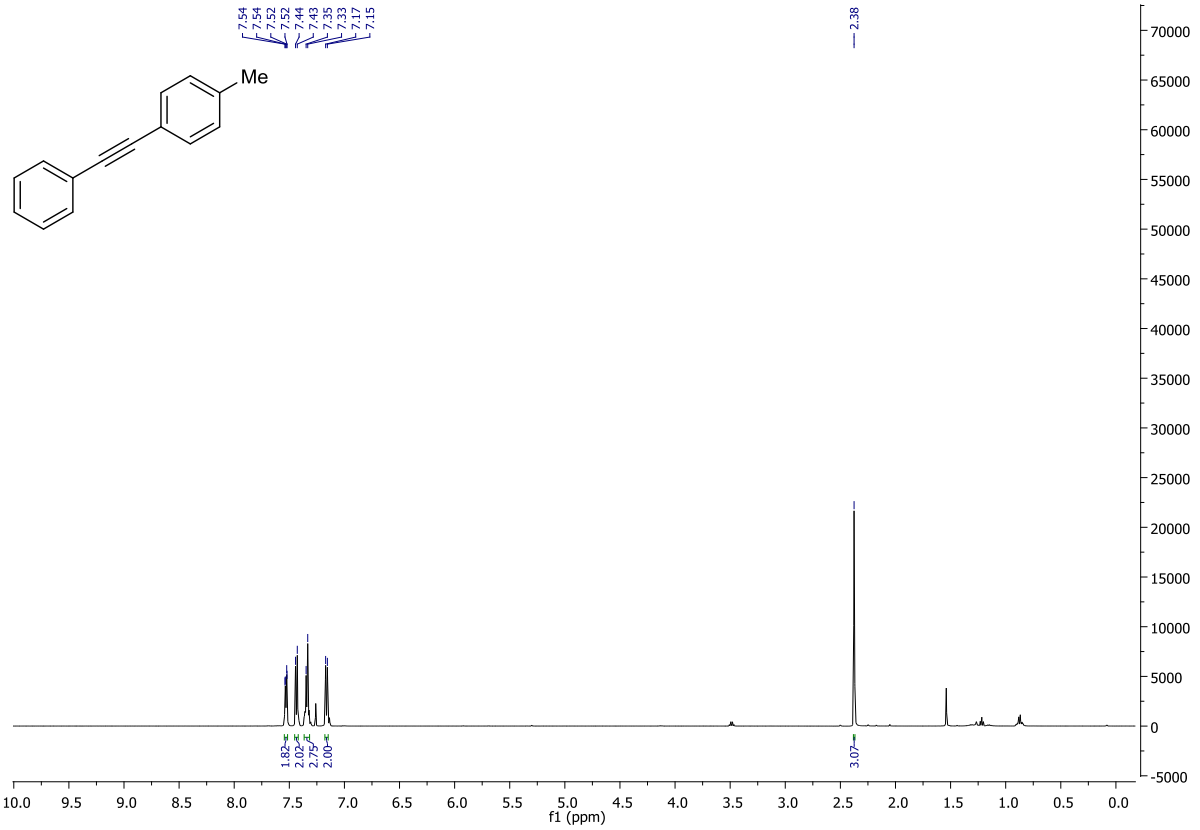
^{1}H NMR 3x



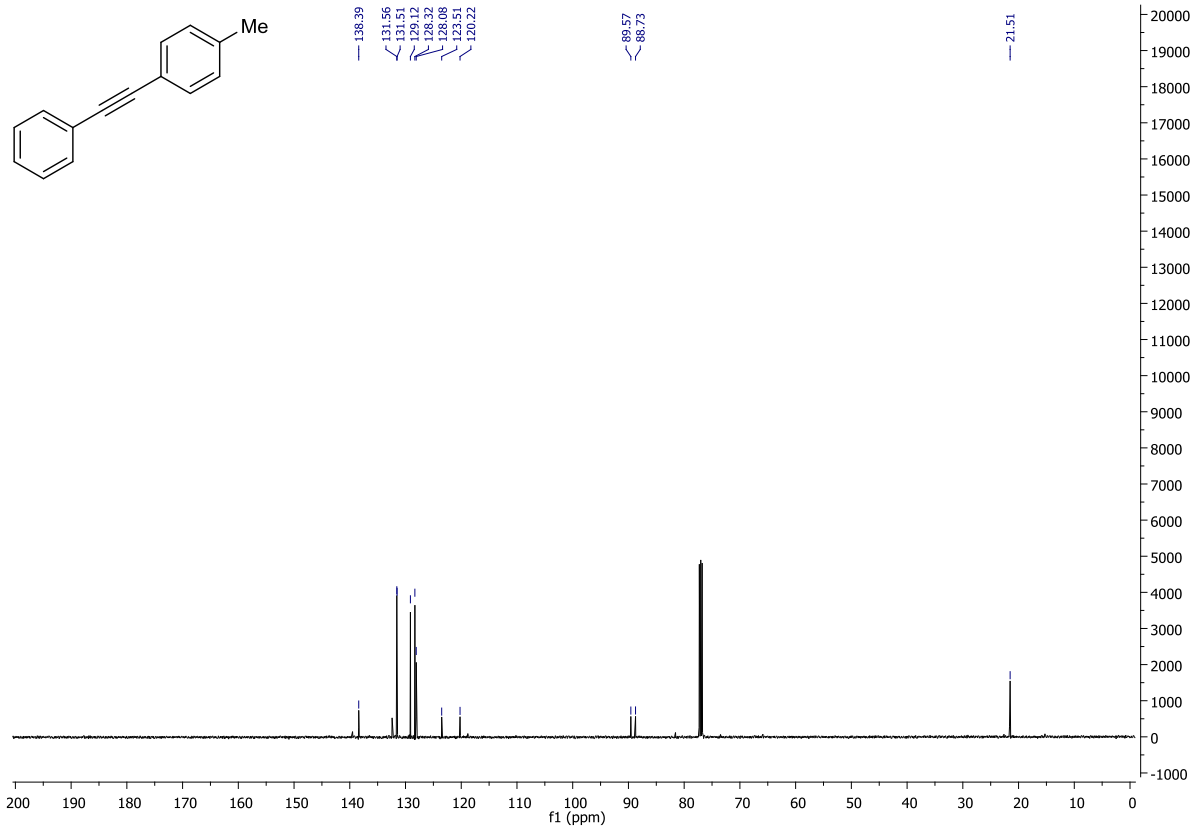
^{13}C NMR 3x



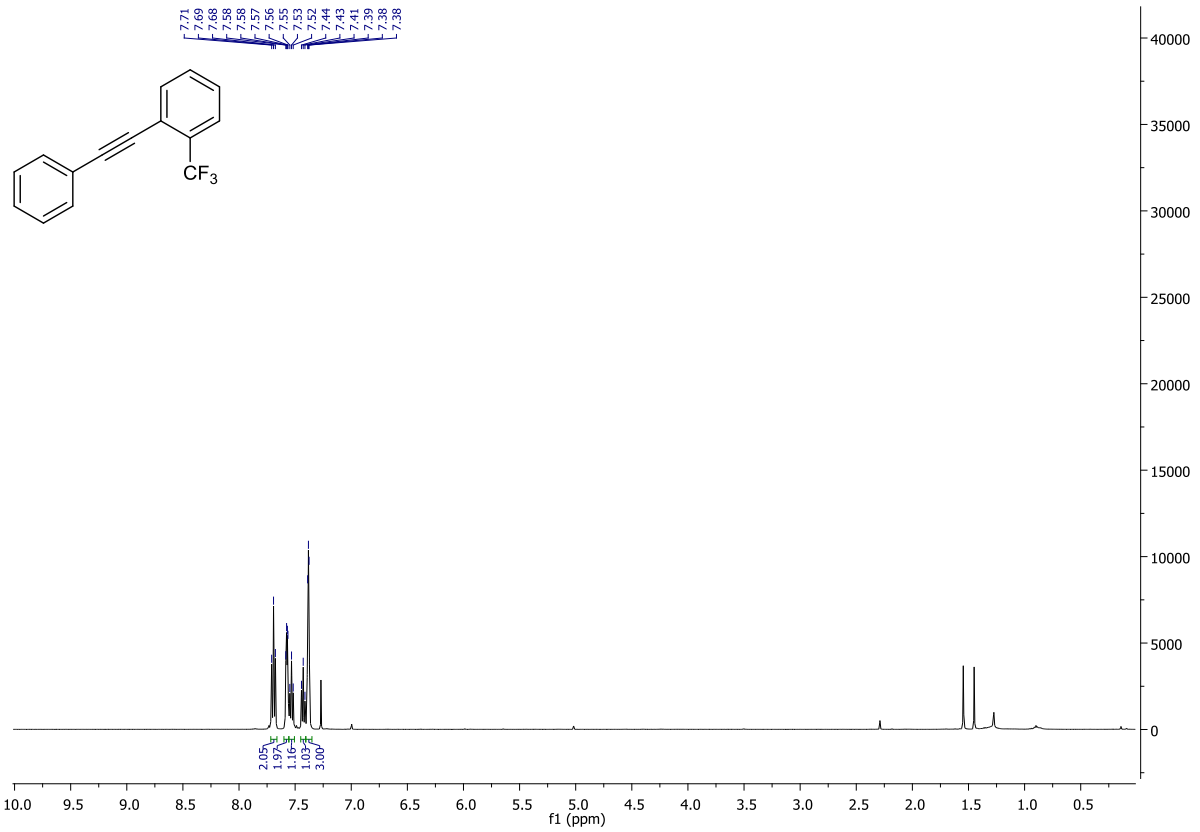
^{1}H NMR 3y



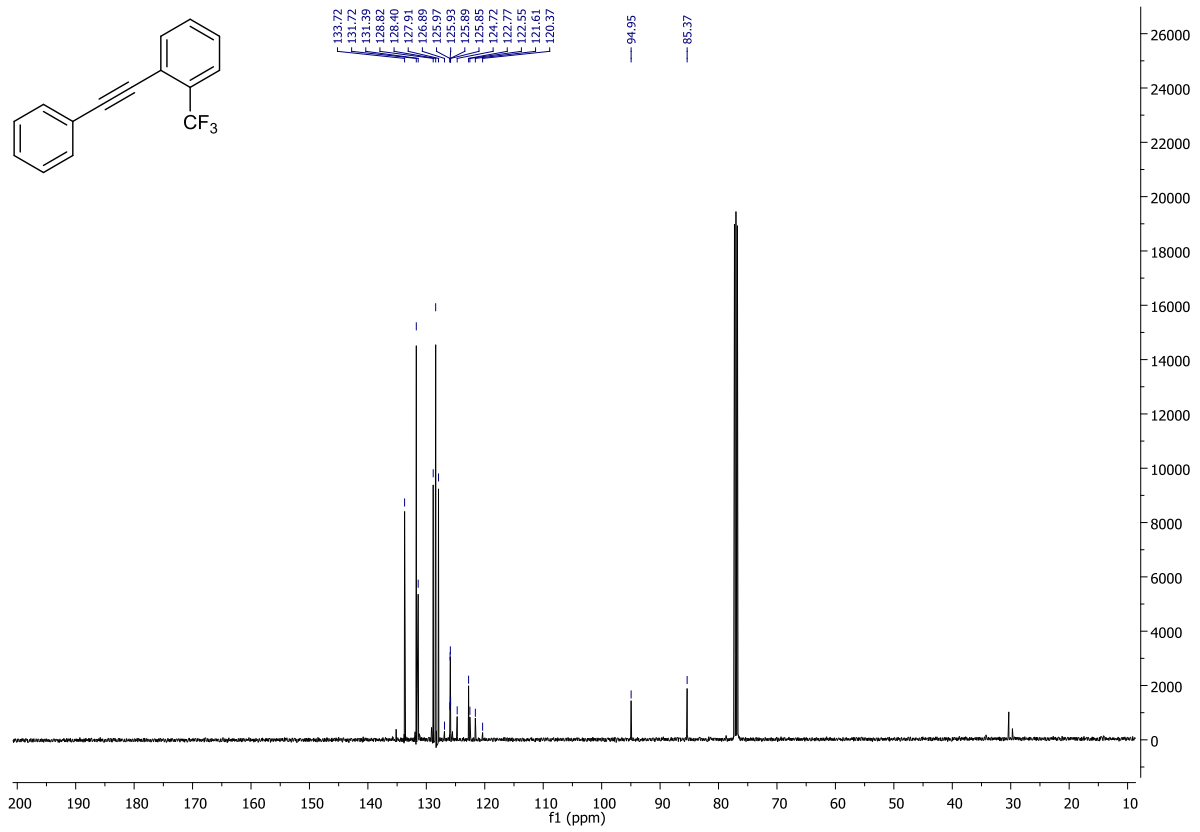
^{13}C NMR 3y



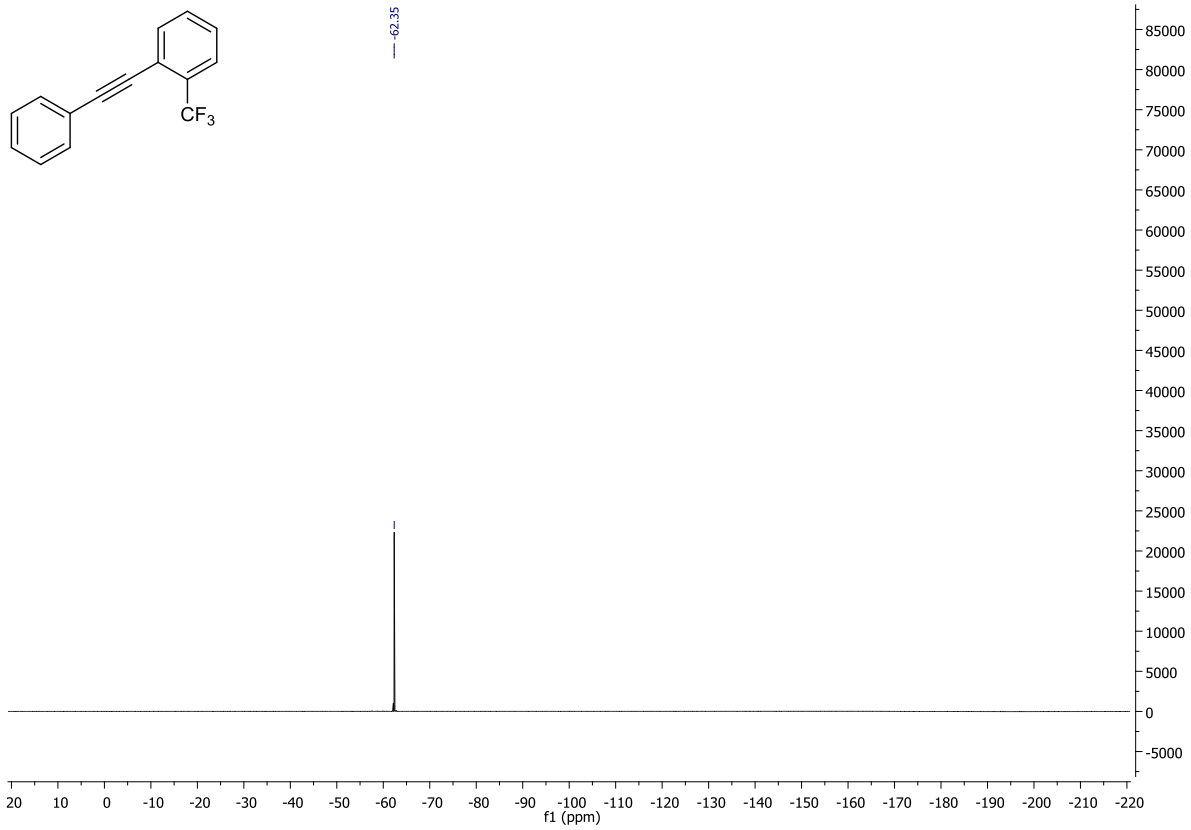
^{1}H NMR 3z



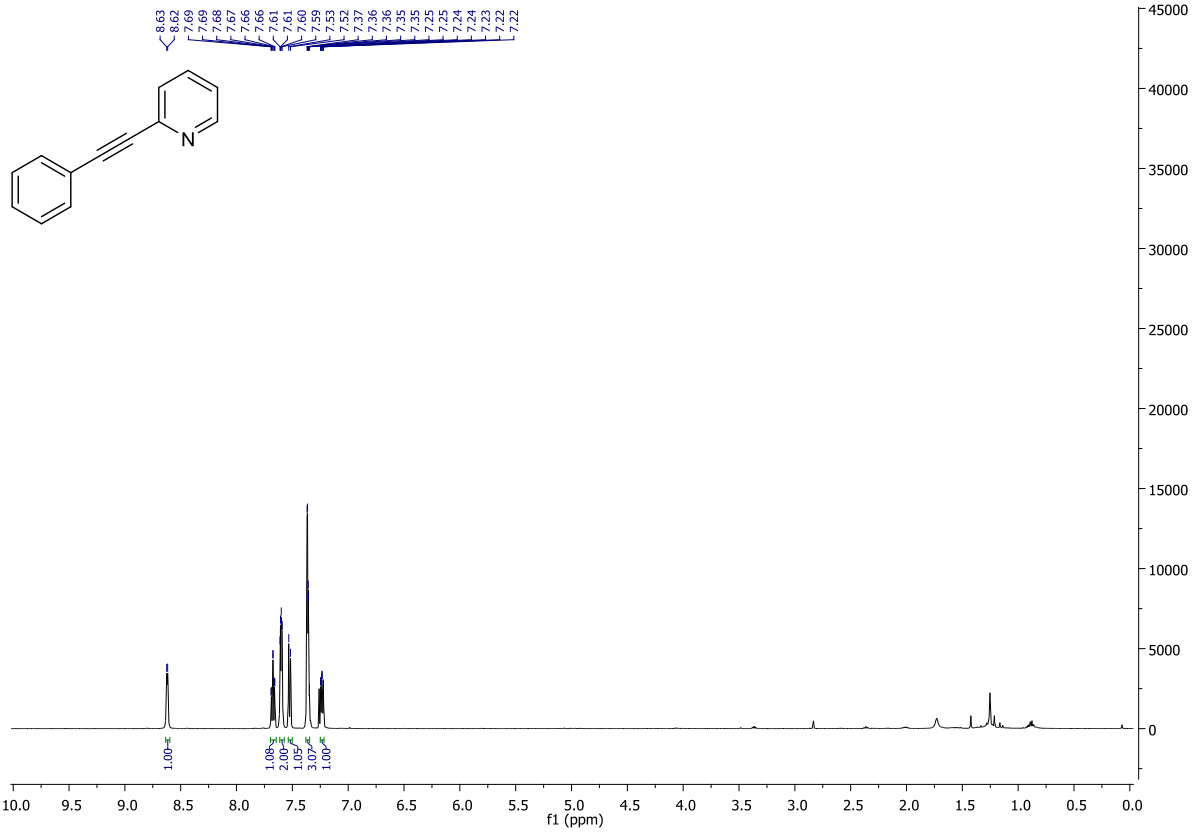
^{13}C NMR 3z



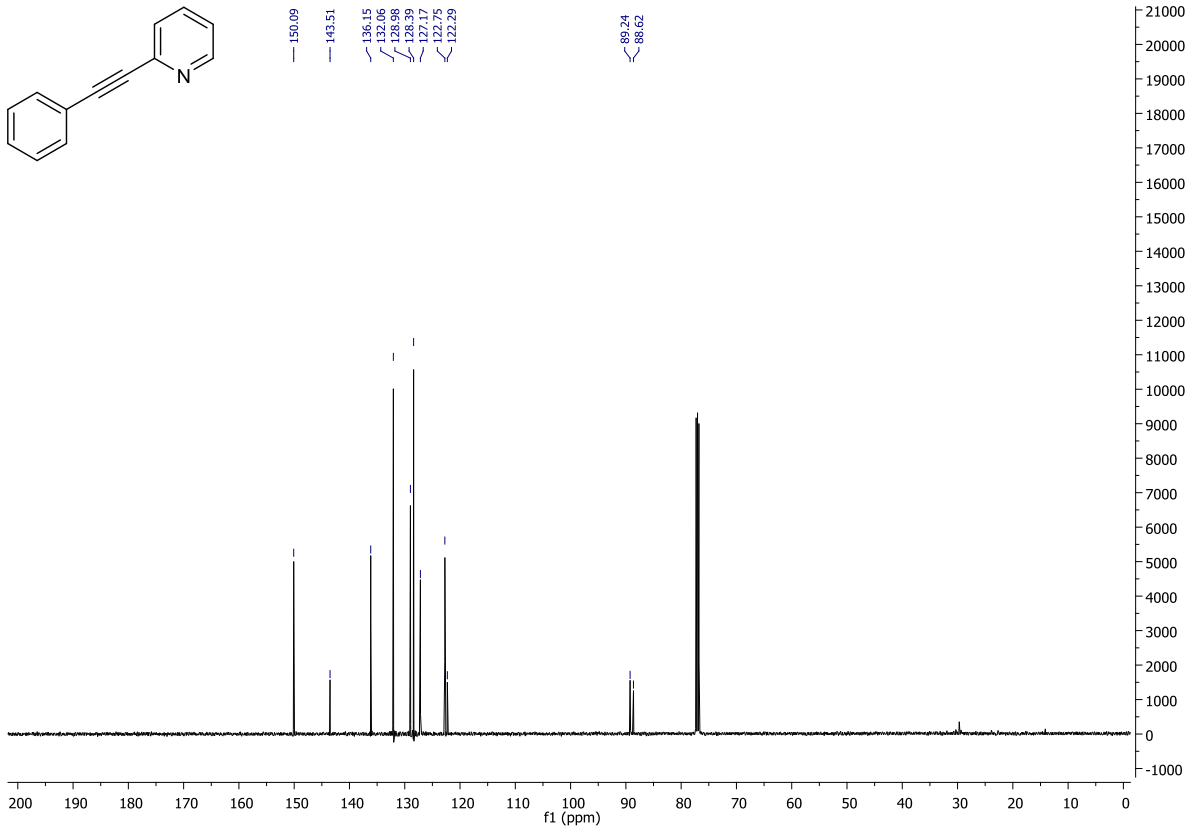
^{19}F NMR 3z



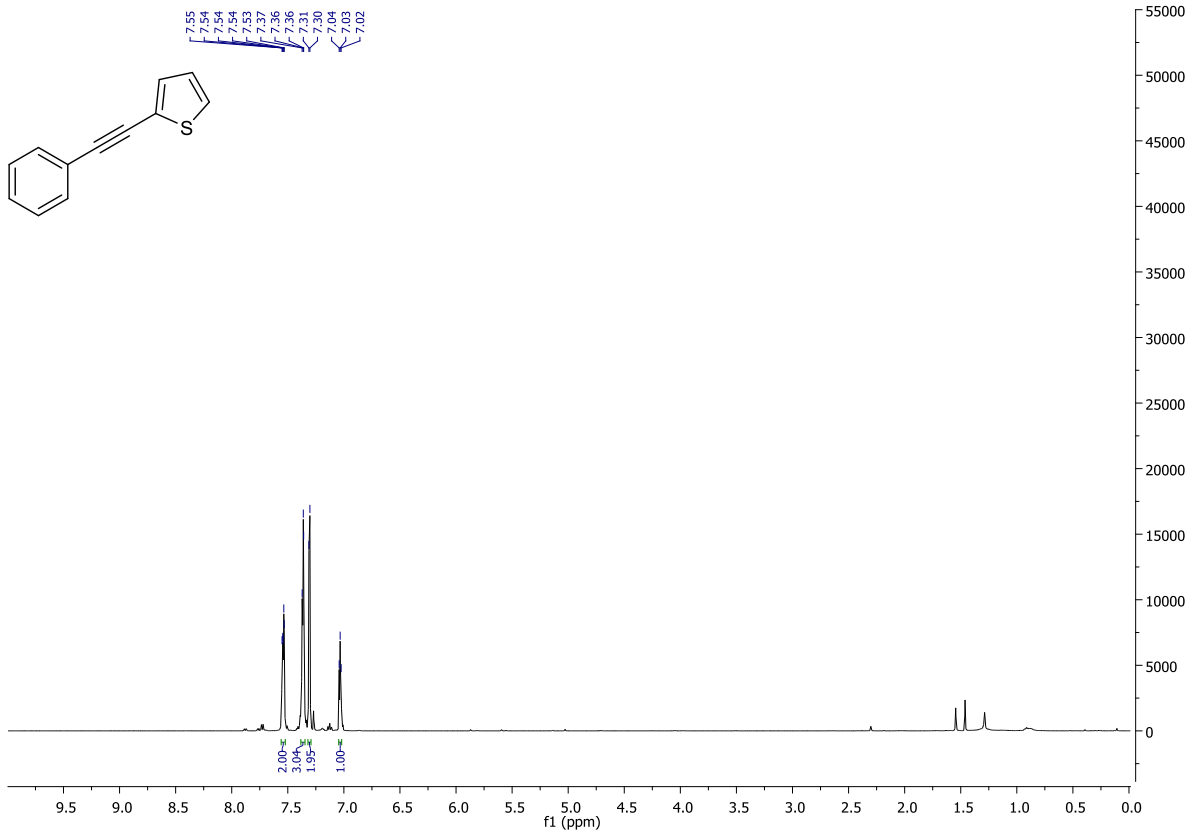
^{1}H NMR 3aa



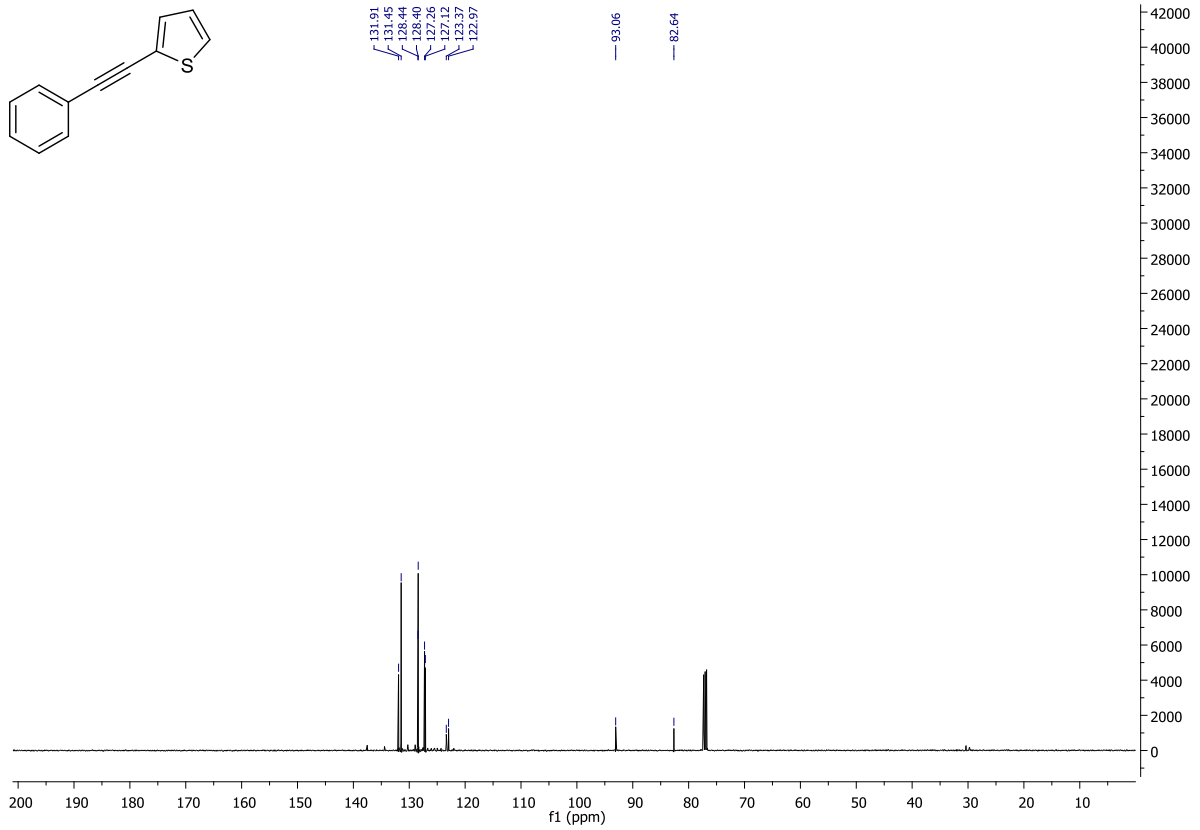
^{13}C NMR 3aa



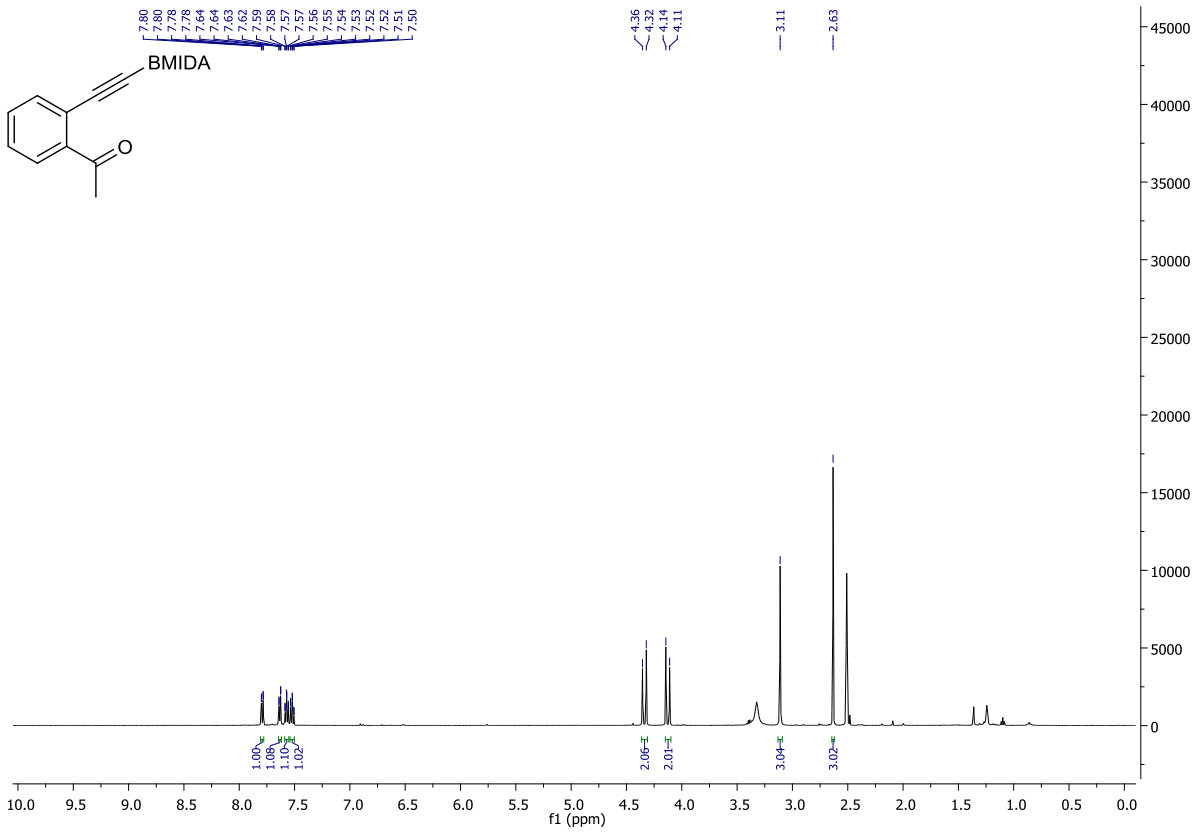
^{1}H NMR 3ab



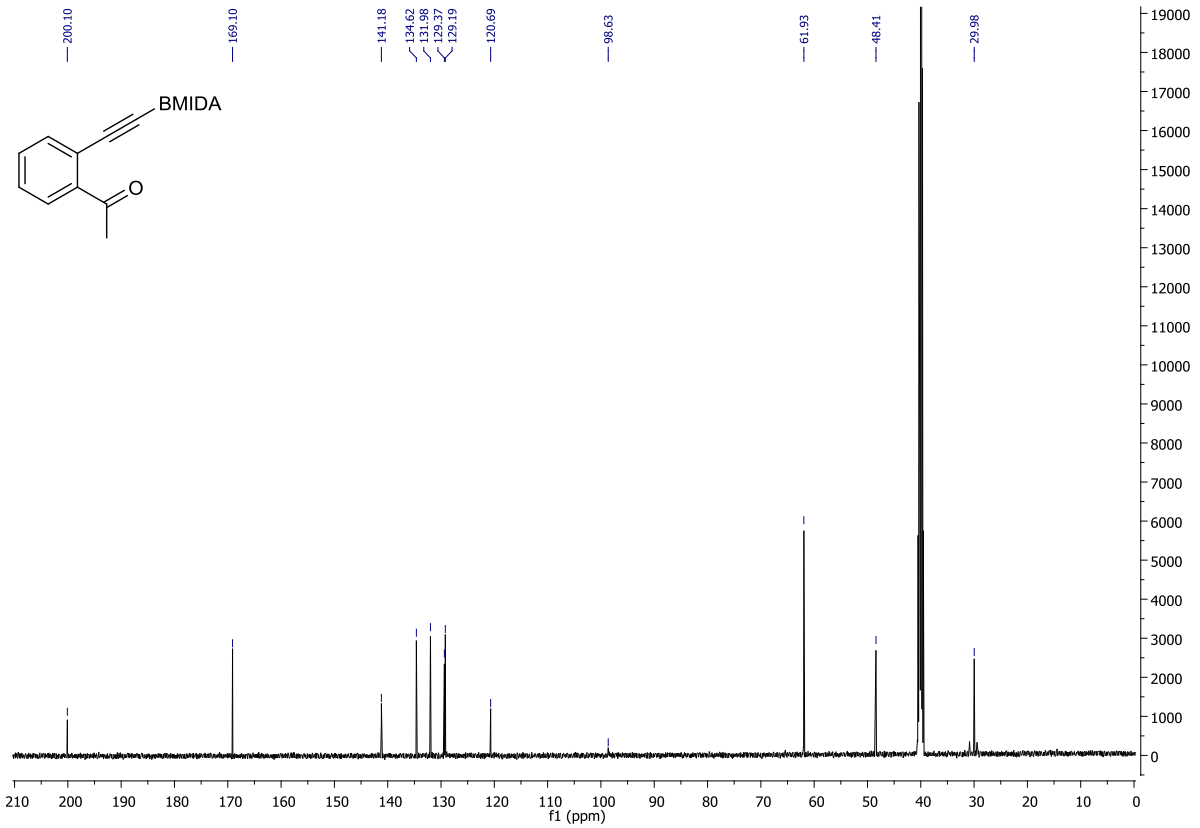
^{13}C NMR 3ab



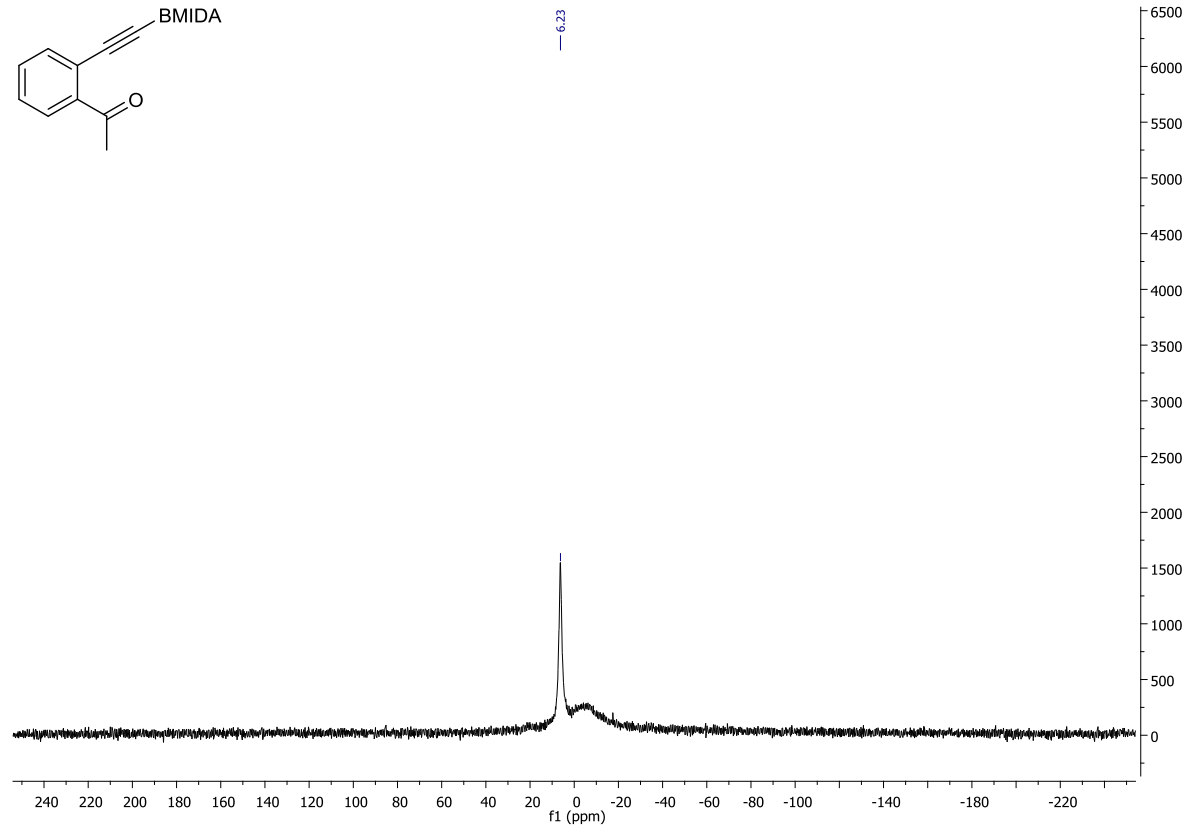
^{1}H NMR 3ac



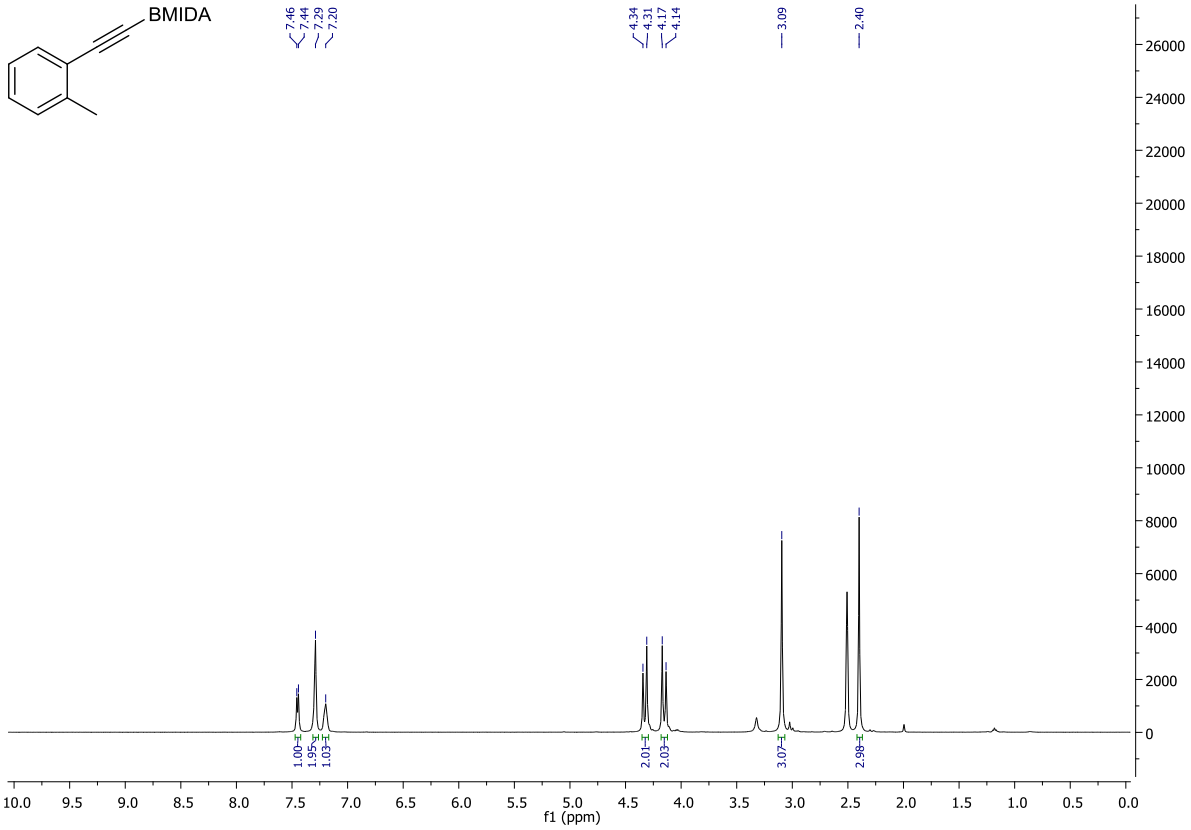
^{13}C NMR 3ac



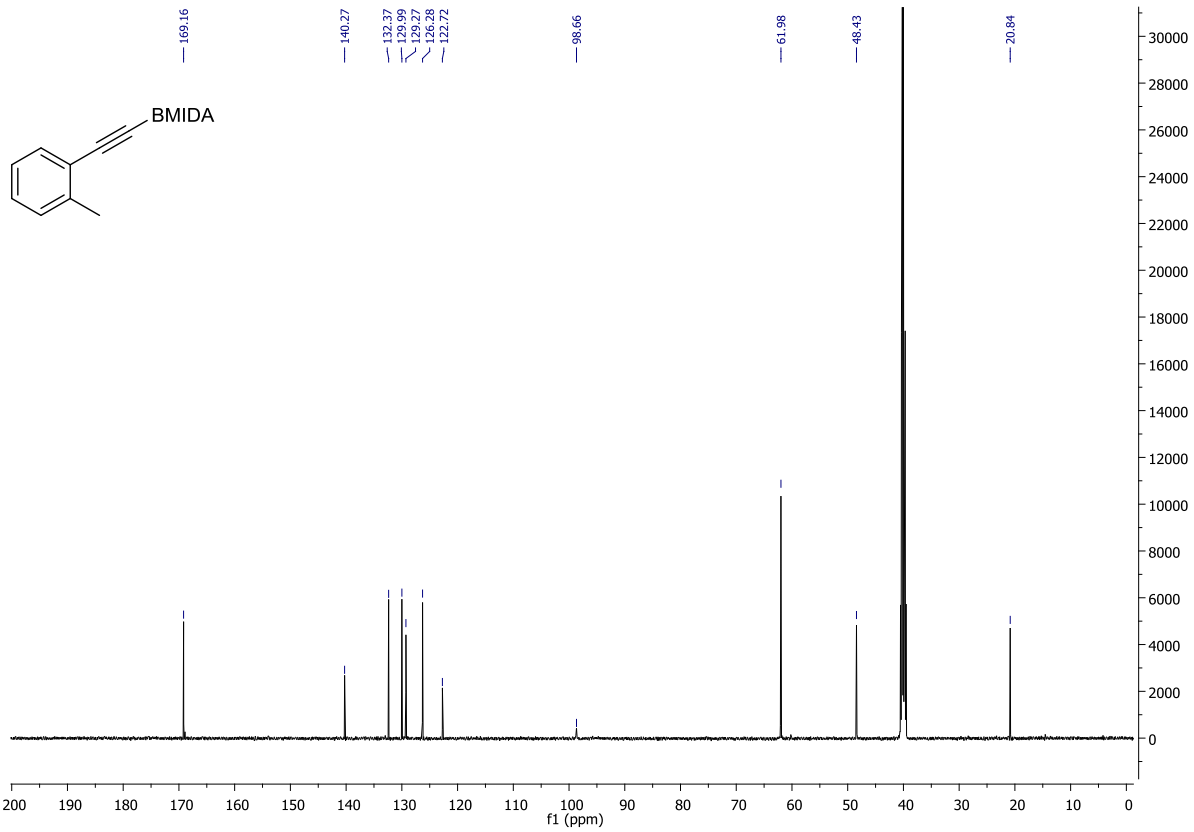
^{11}B NMR 3ac



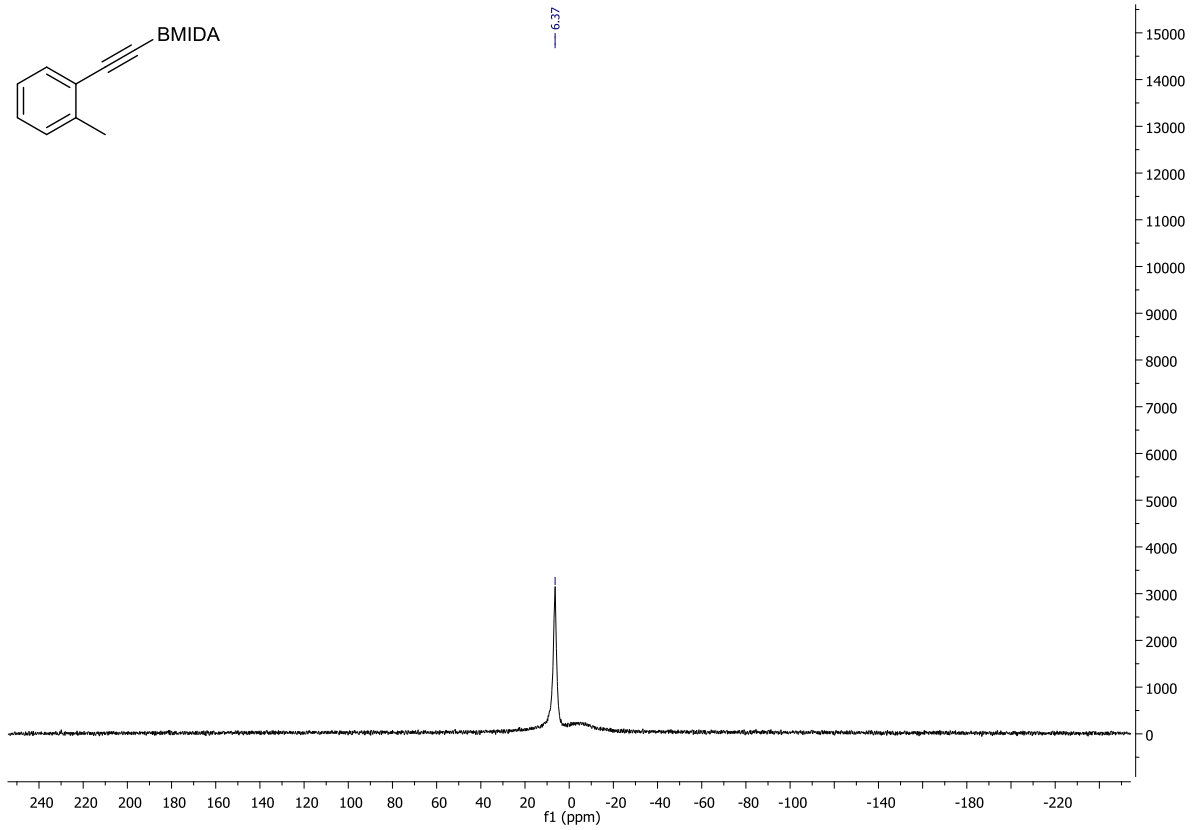
^{1}H NMR 3ad



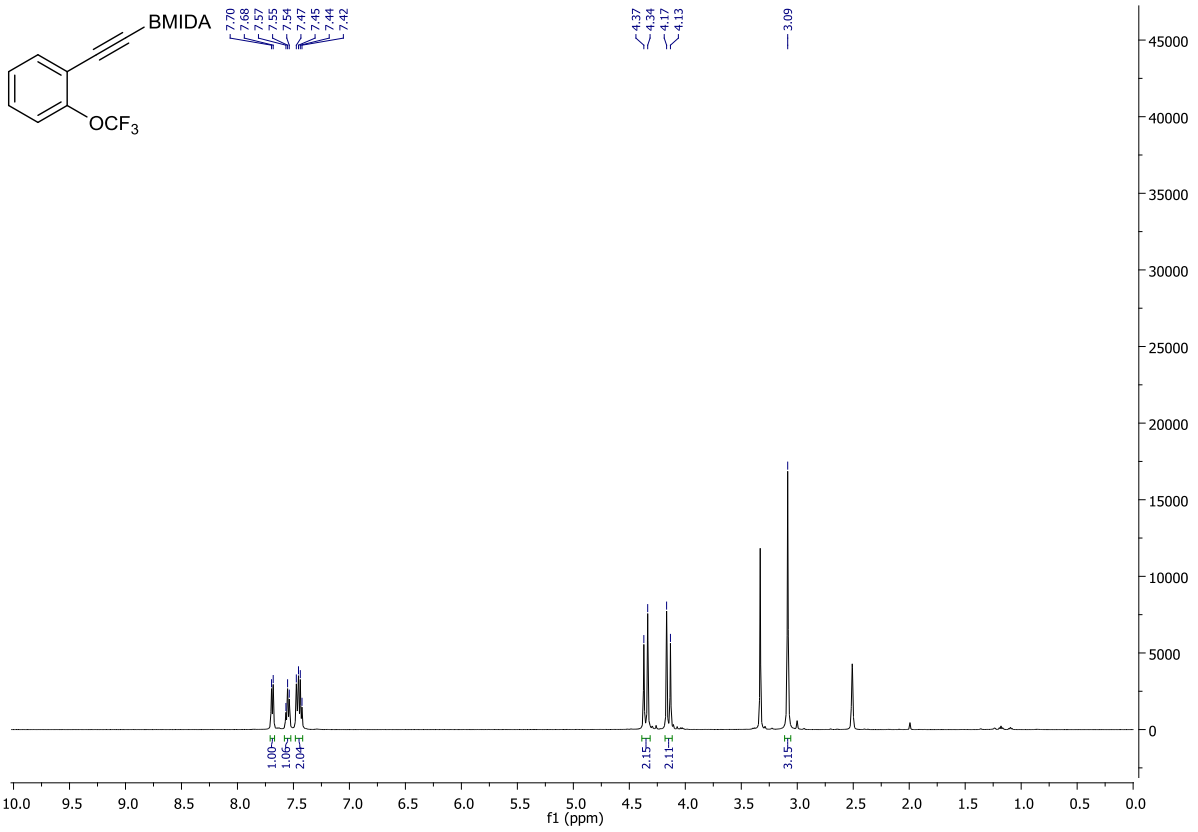
^{13}C NMR 3ad



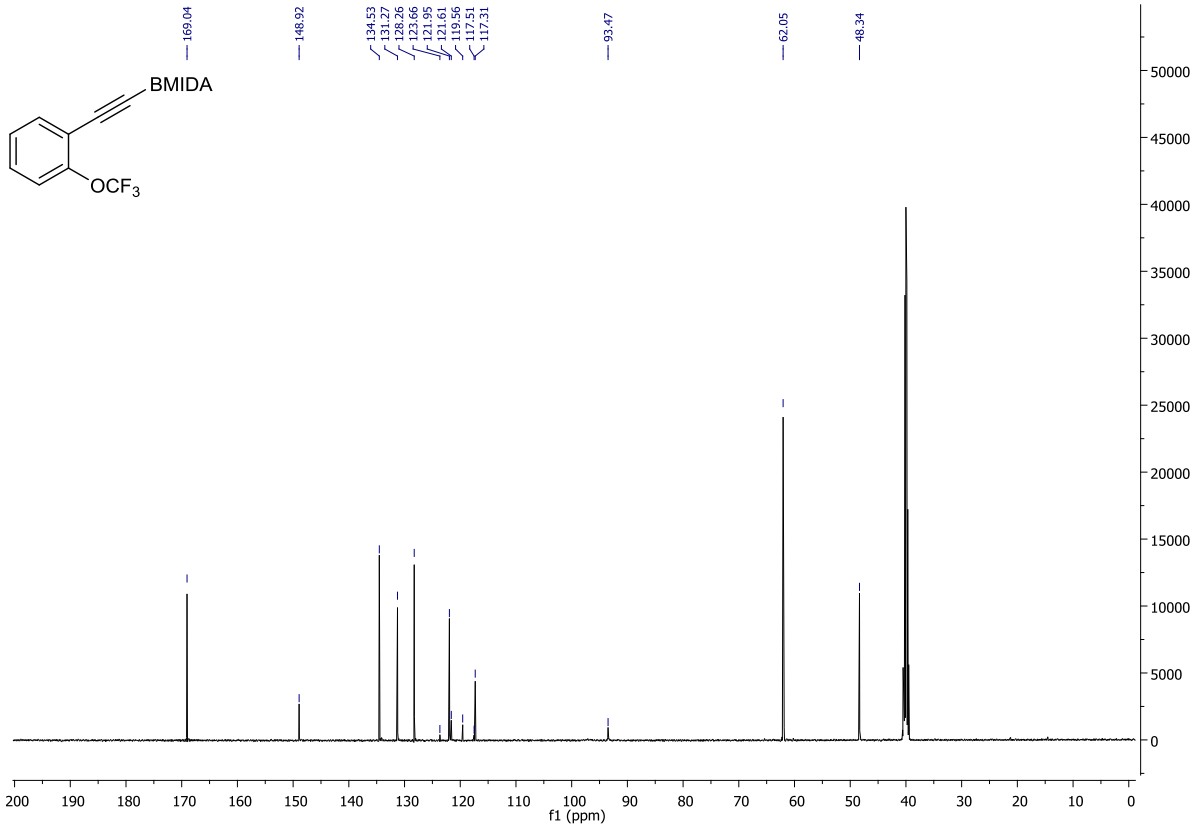
^{11}B NMR 3ad



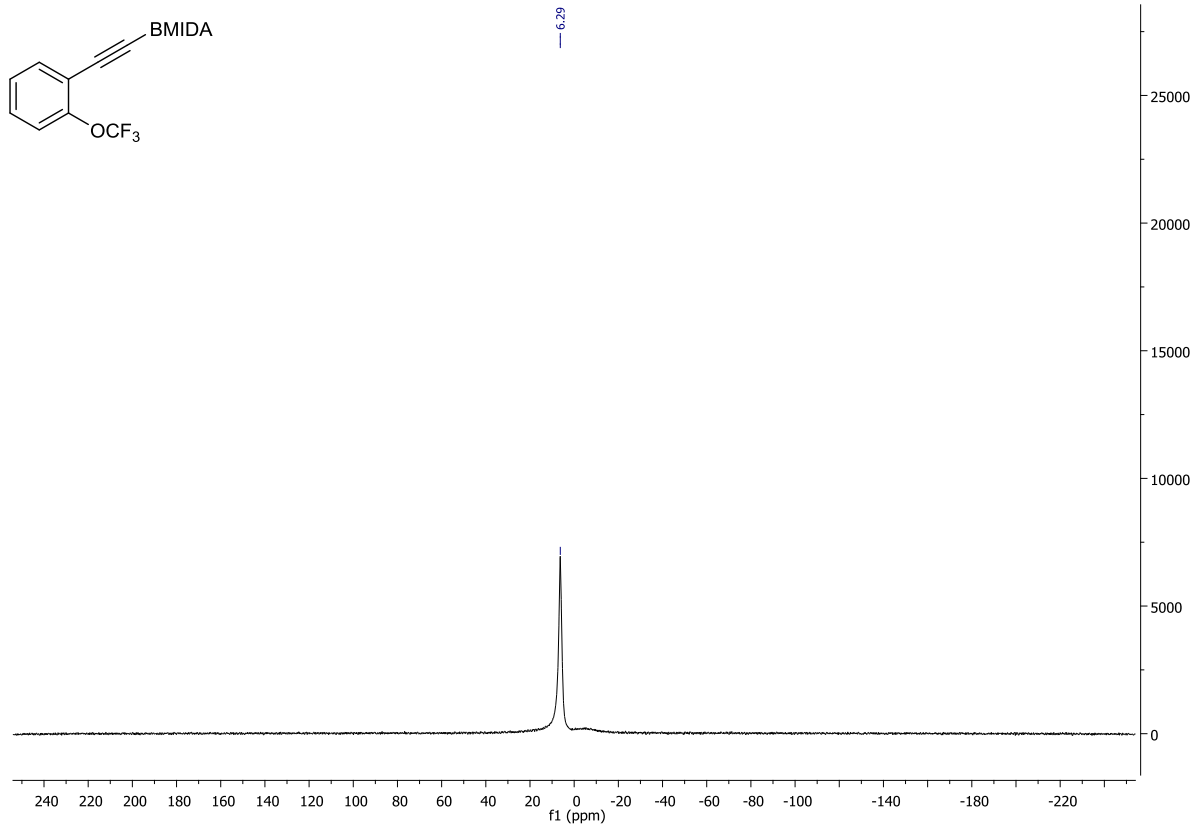
^{1}H NMR 3ae



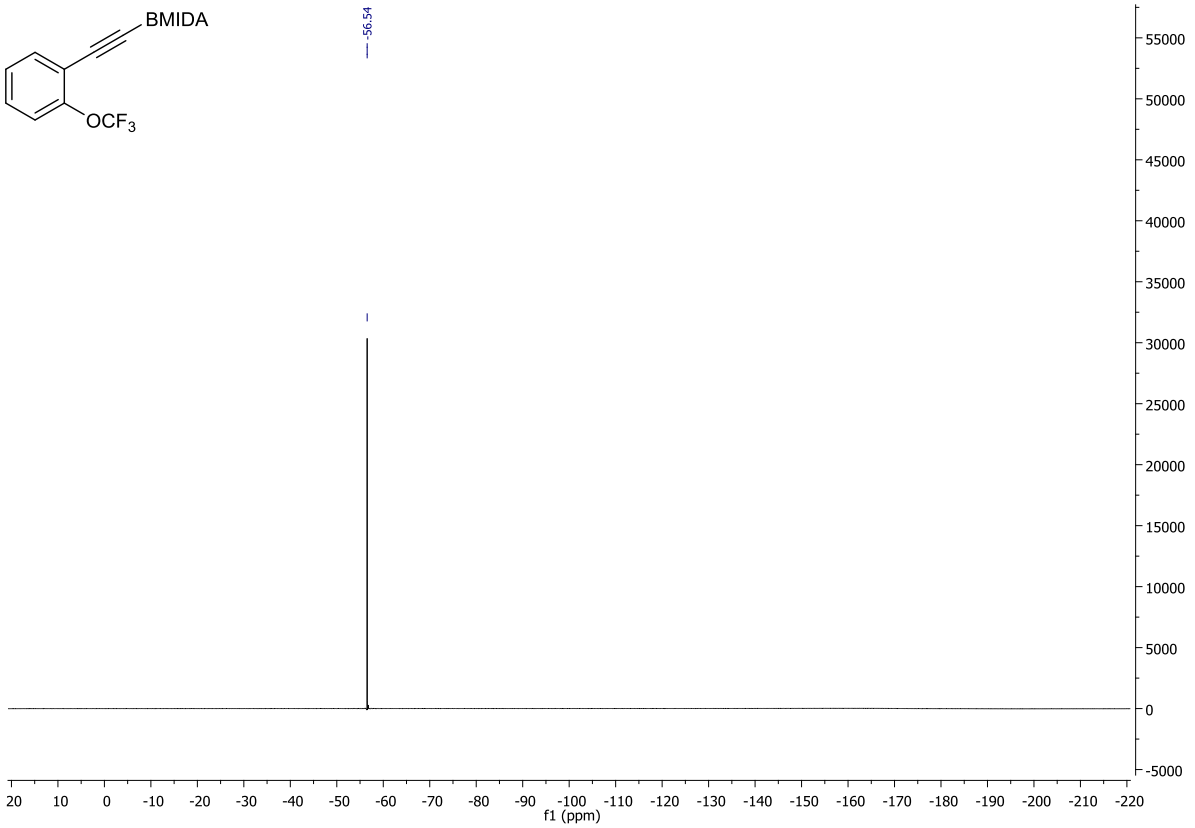
^{13}C NMR 3ae



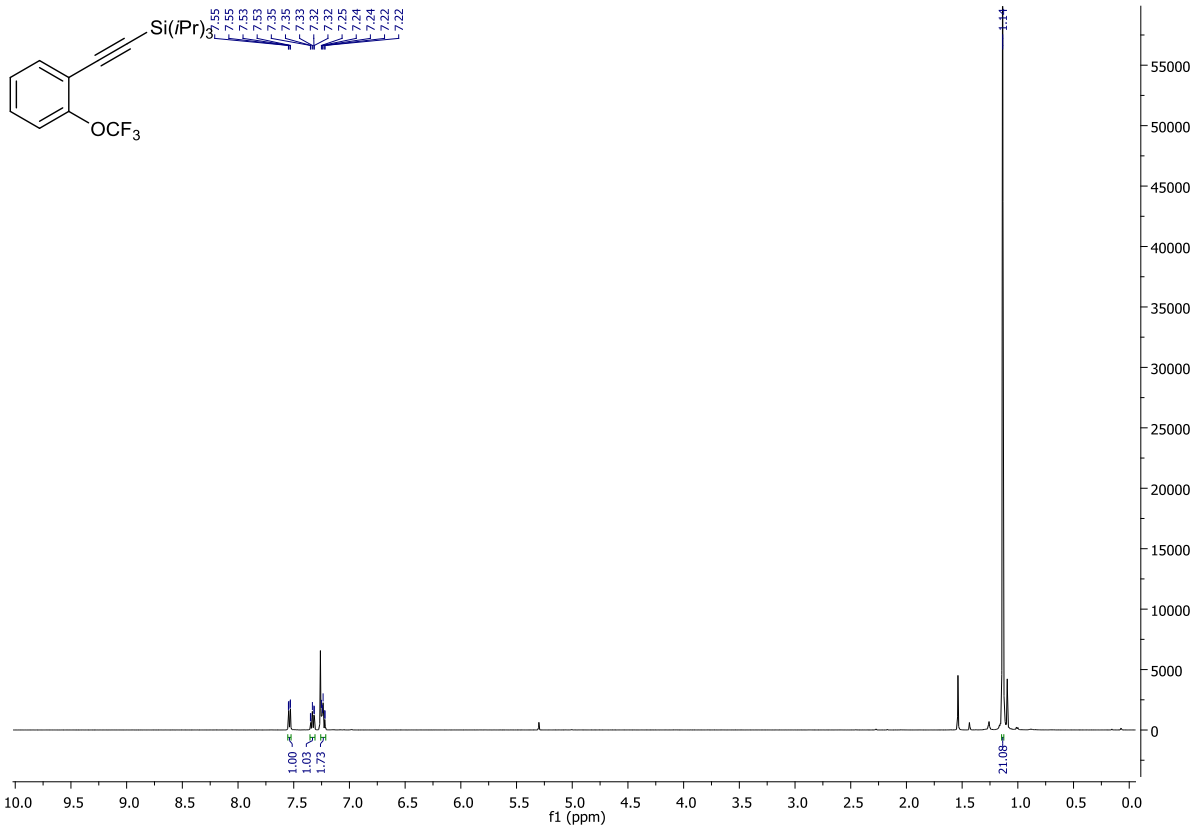
^{11}B NMR 3ae



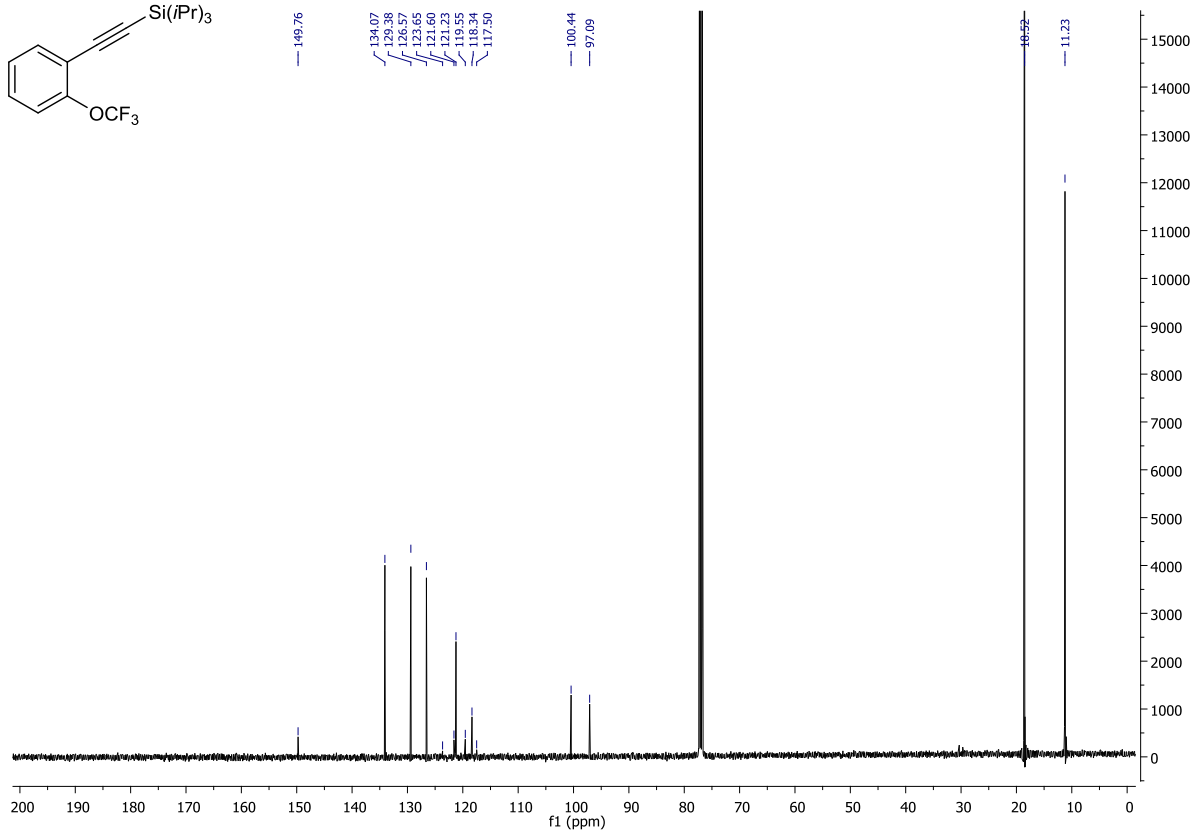
^{19}F NMR 3ae



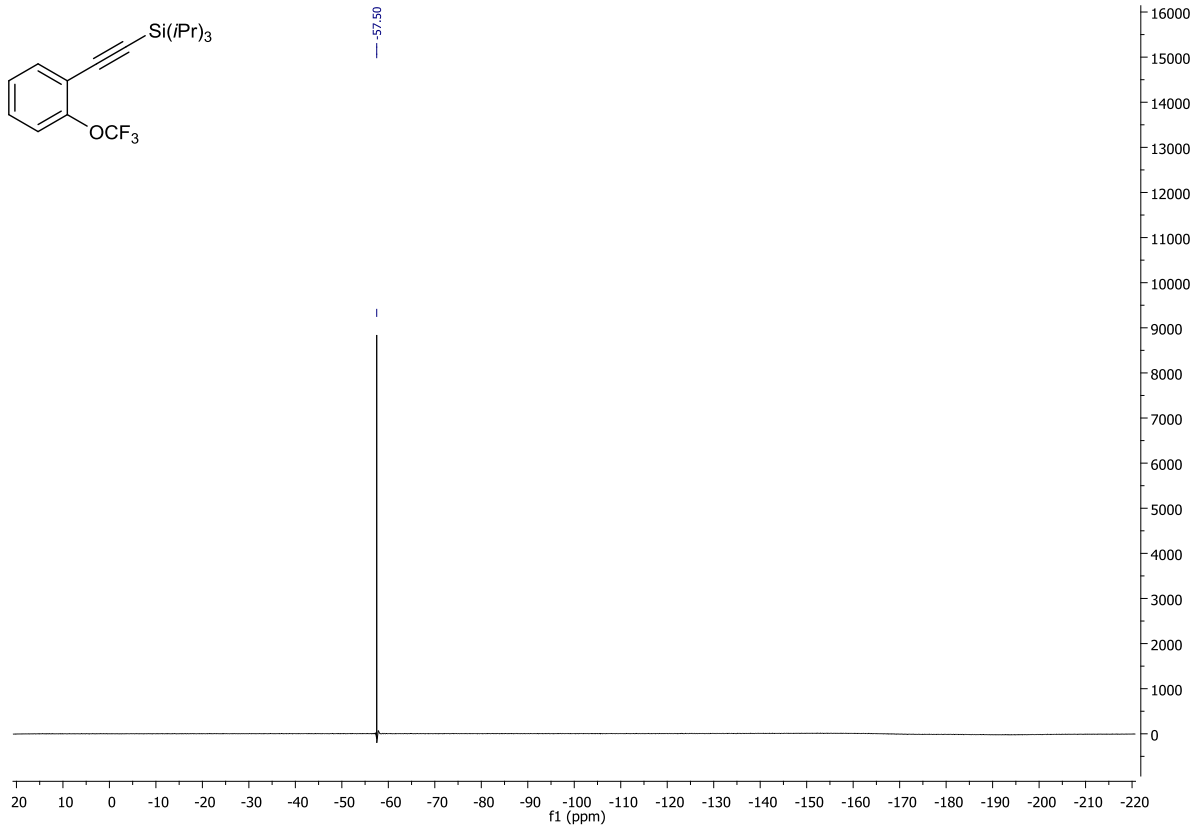
^{1}H NMR 3af



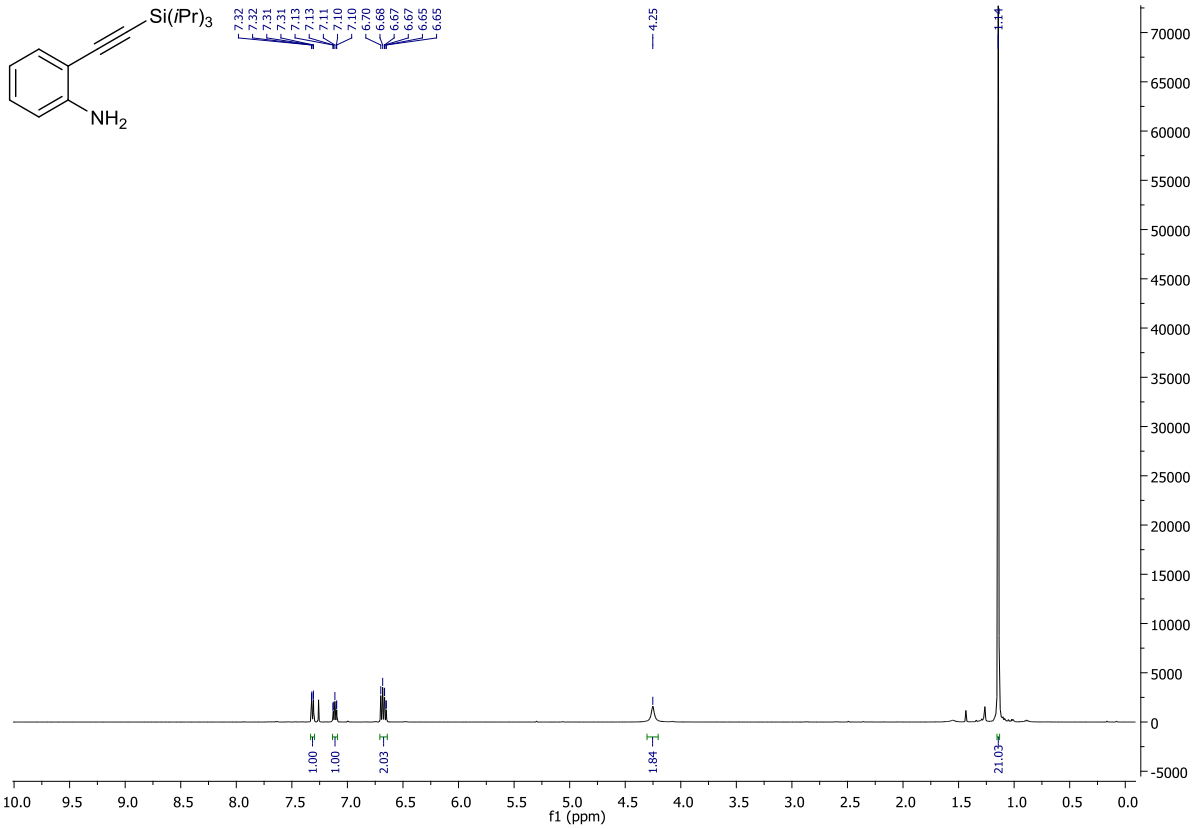
^{13}C NMR 3af



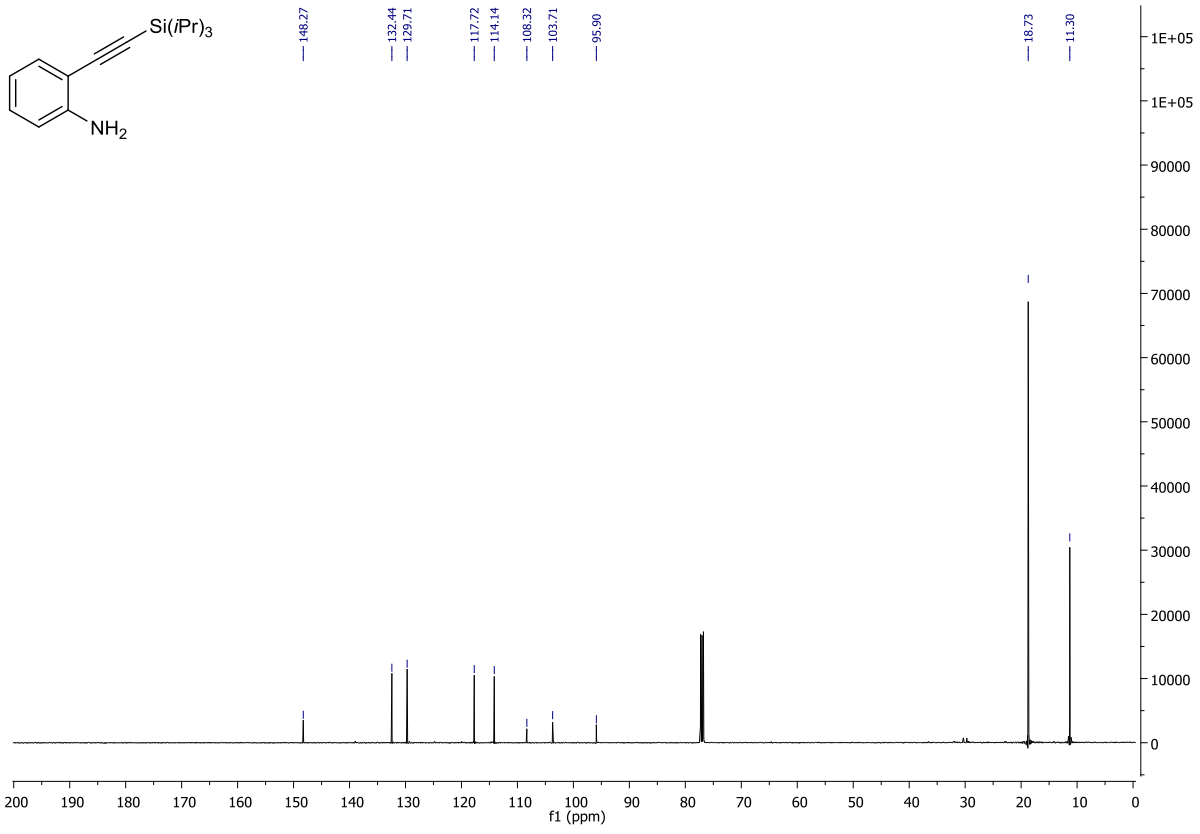
^{19}F NMR 3af



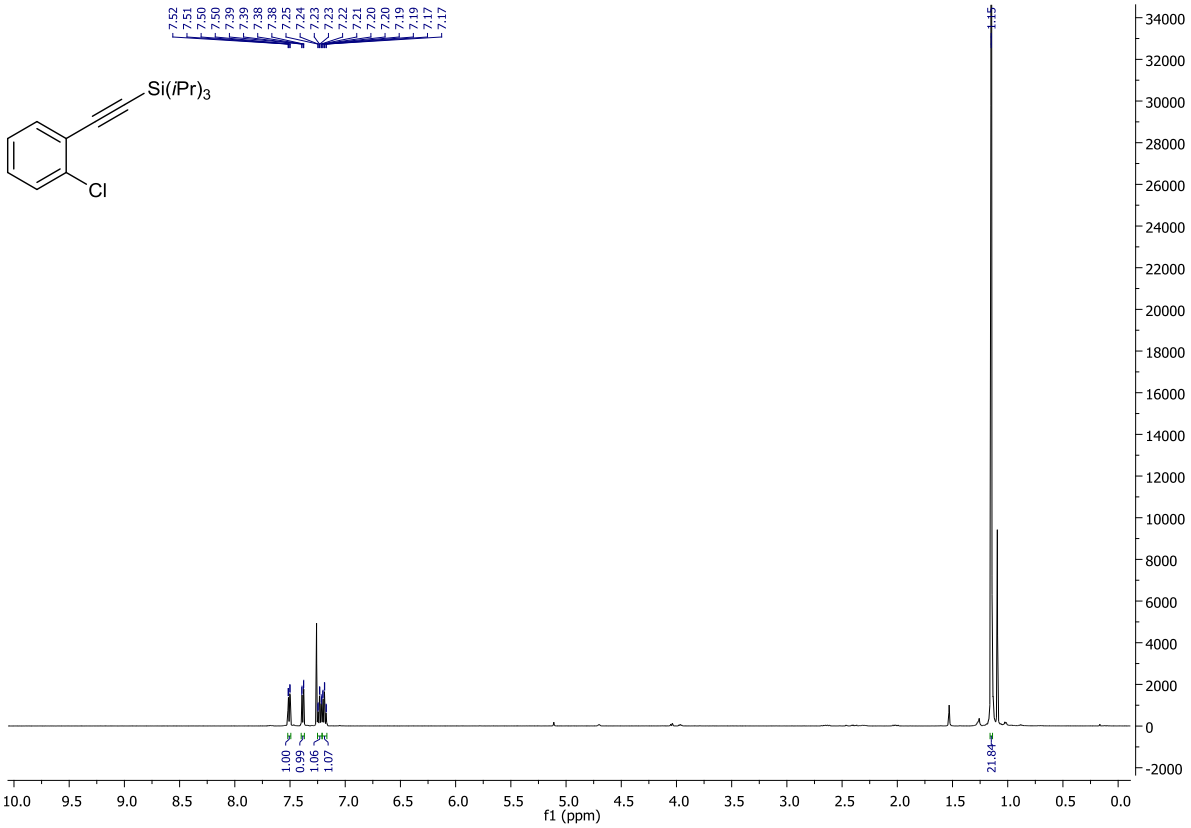
^{1}H NMR 3ag



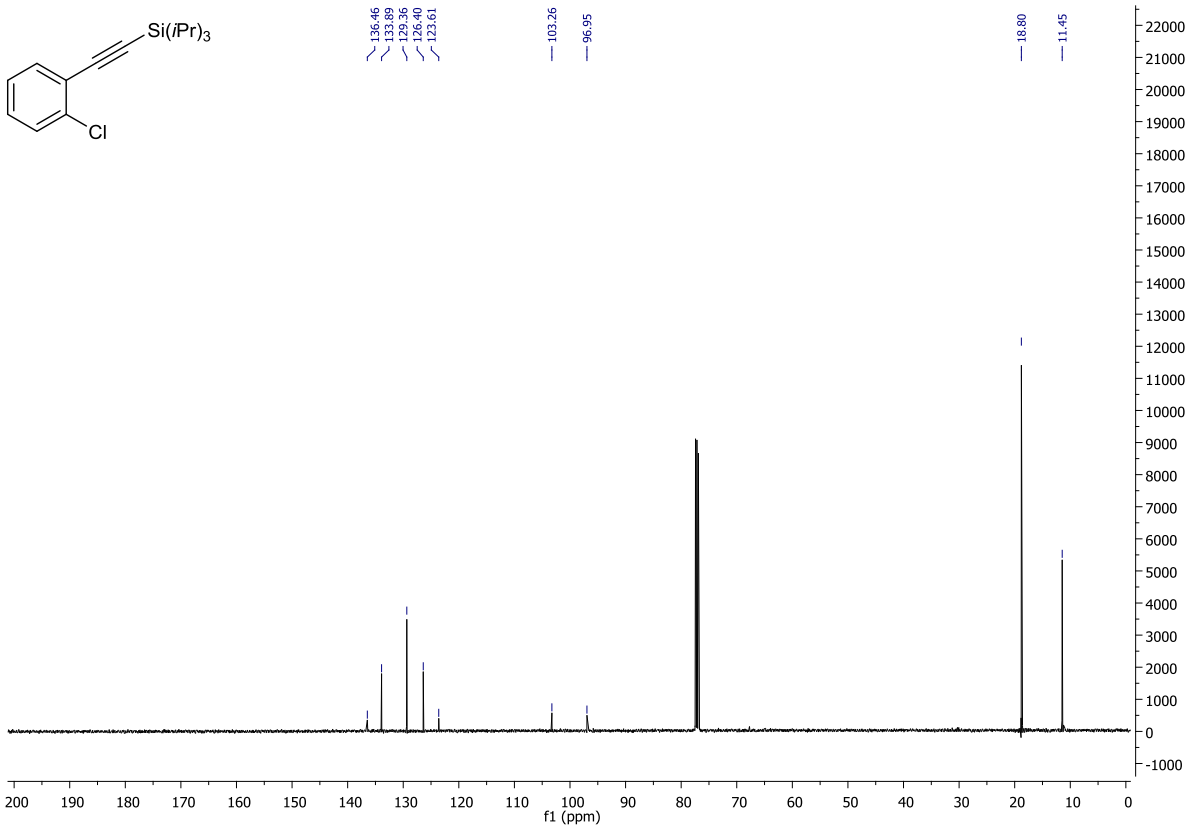
^{13}C NMR 3ag



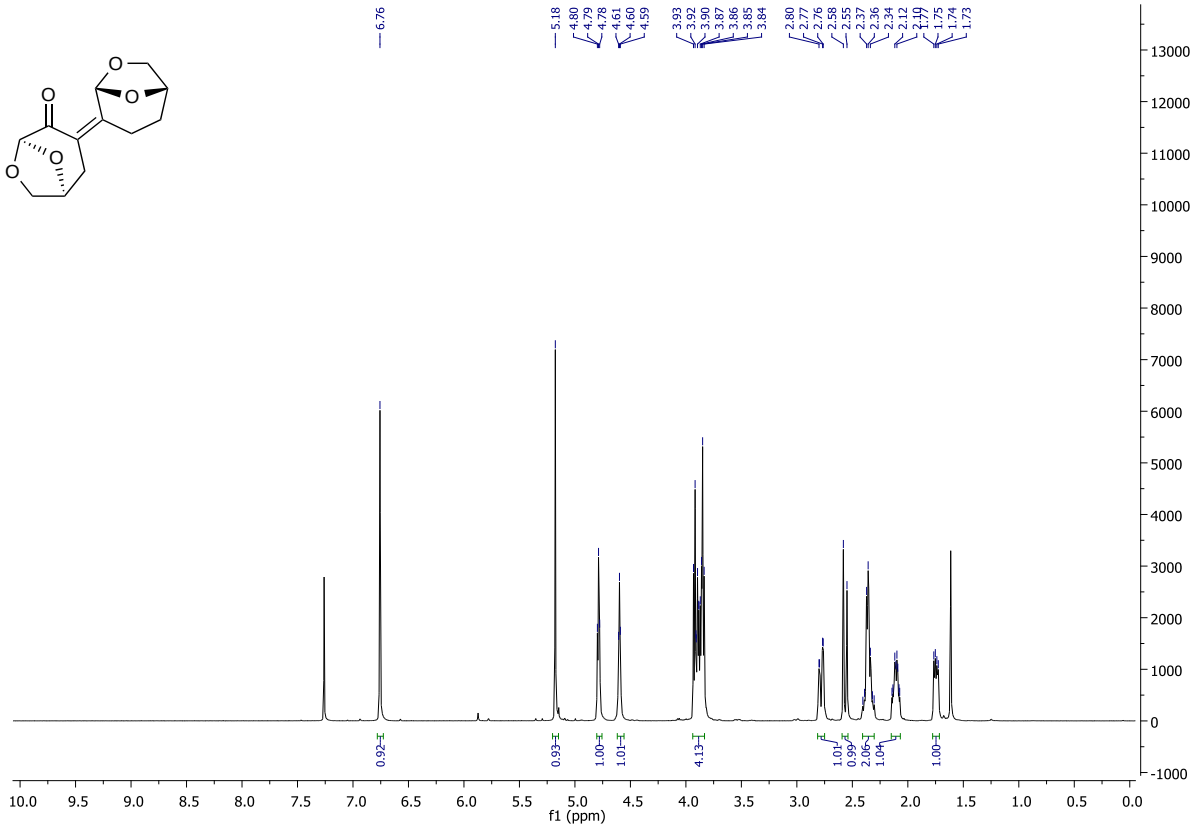
^{1}H NMR 3ah



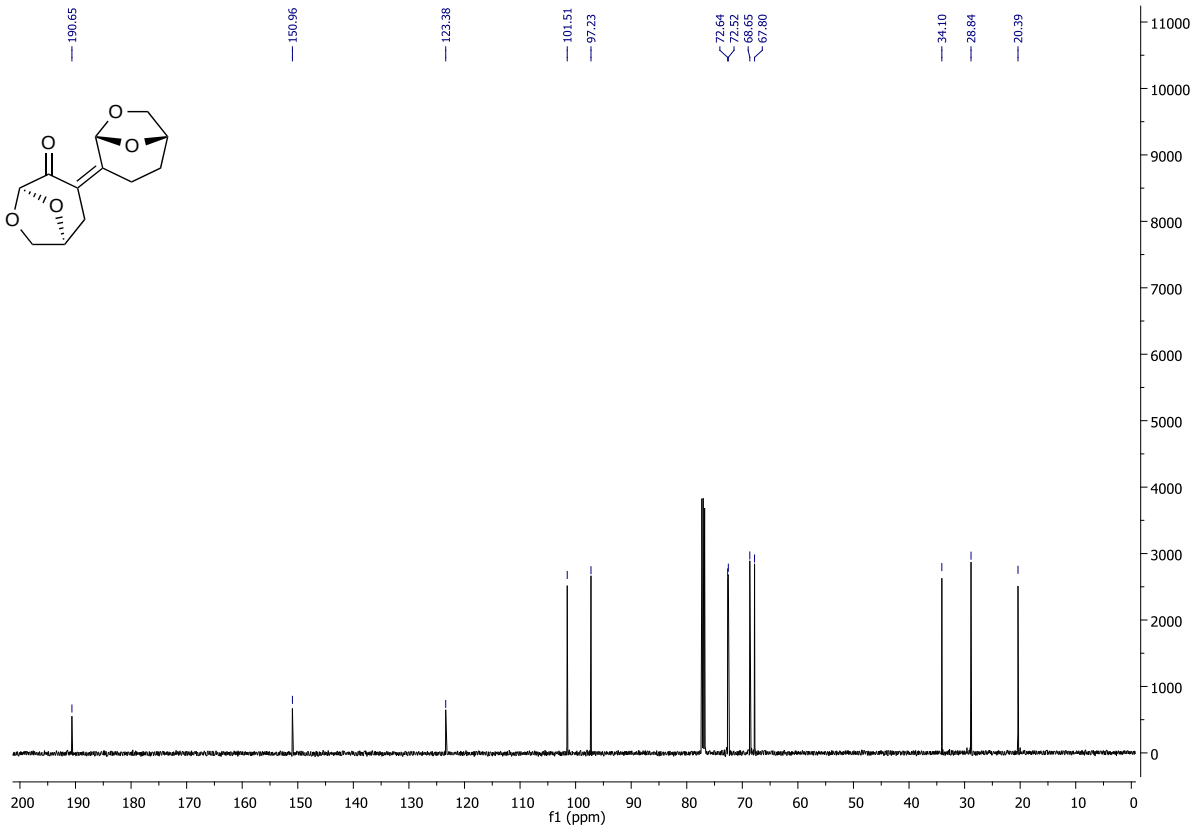
^{13}C NMR 3ah



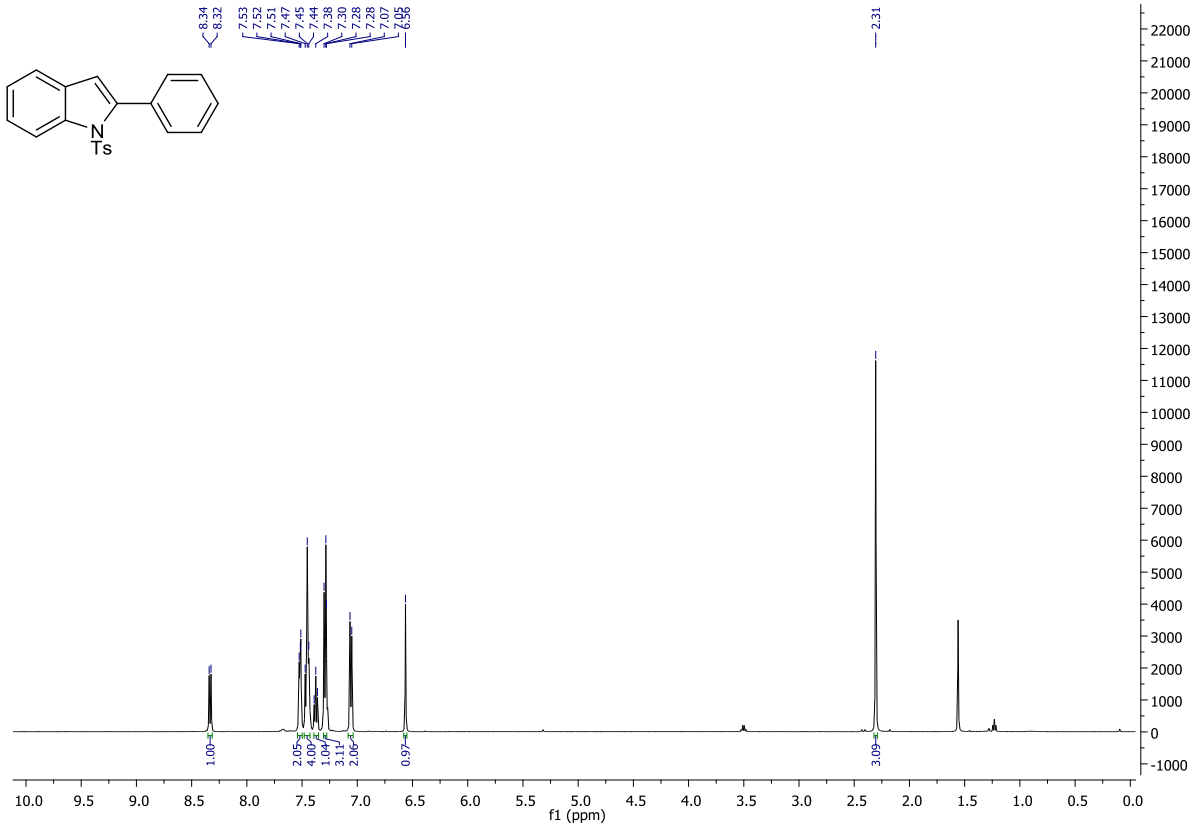
^{1}H NMR of 4a



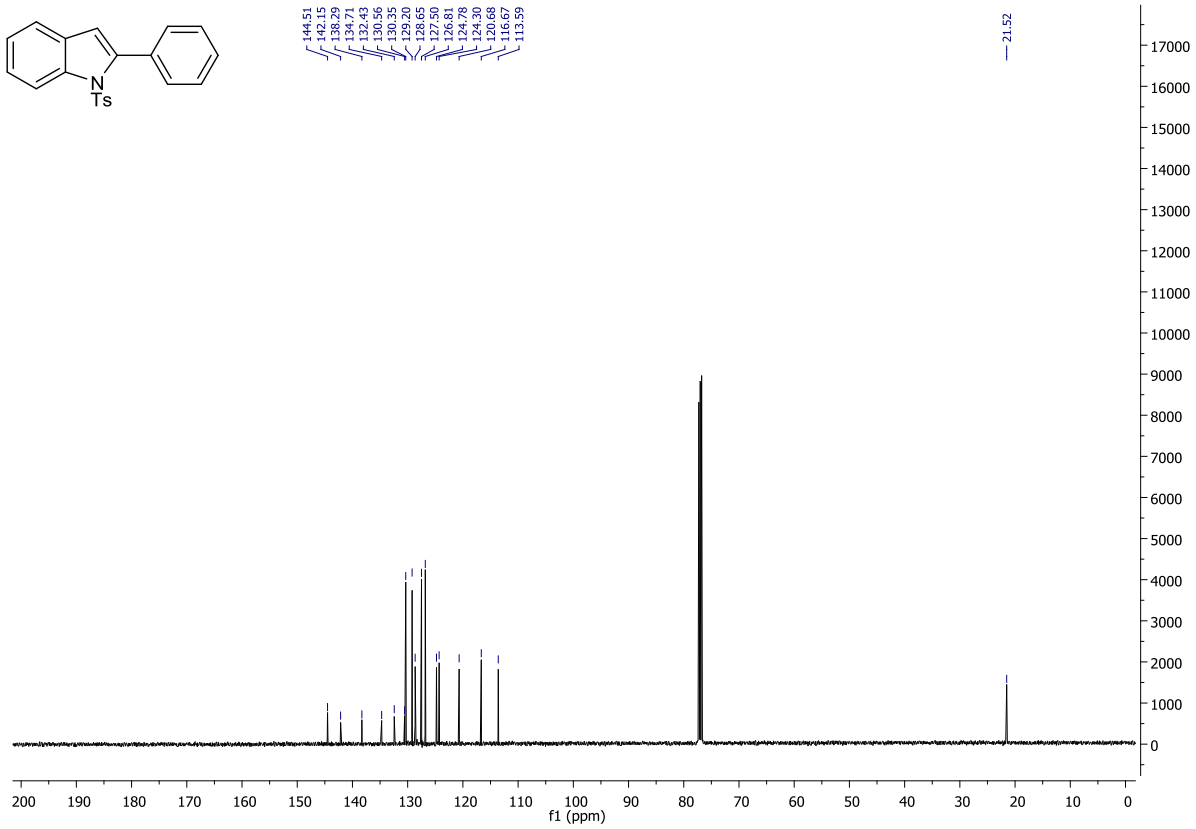
^{13}C NMR of 4a



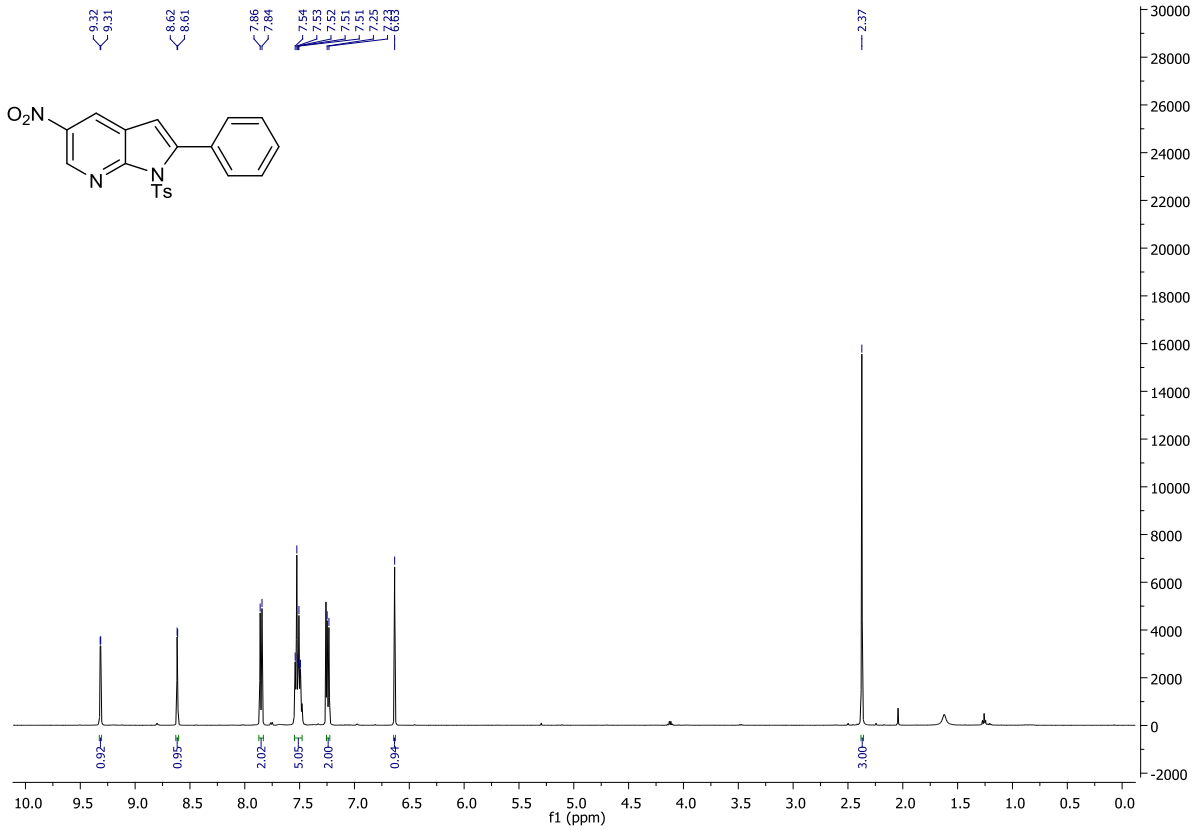
^{1}H NMR 7a



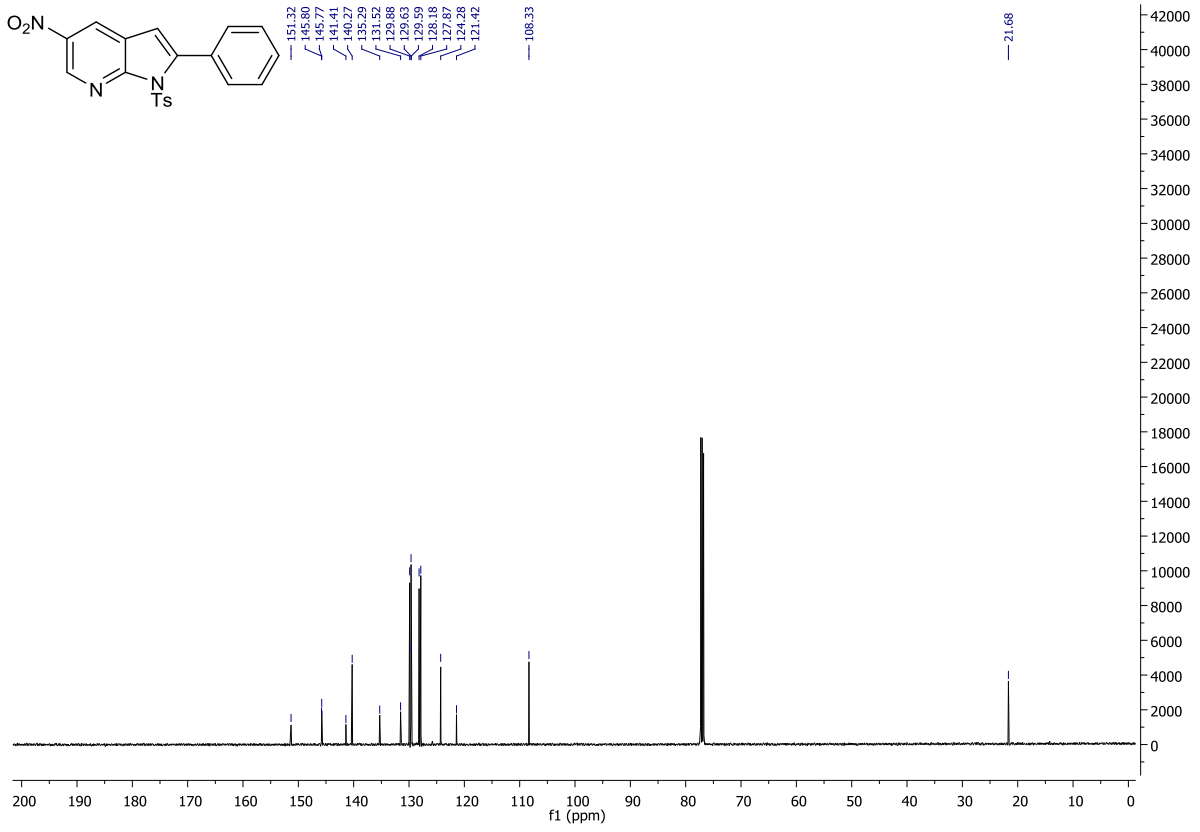
^{13}C NMR 7a



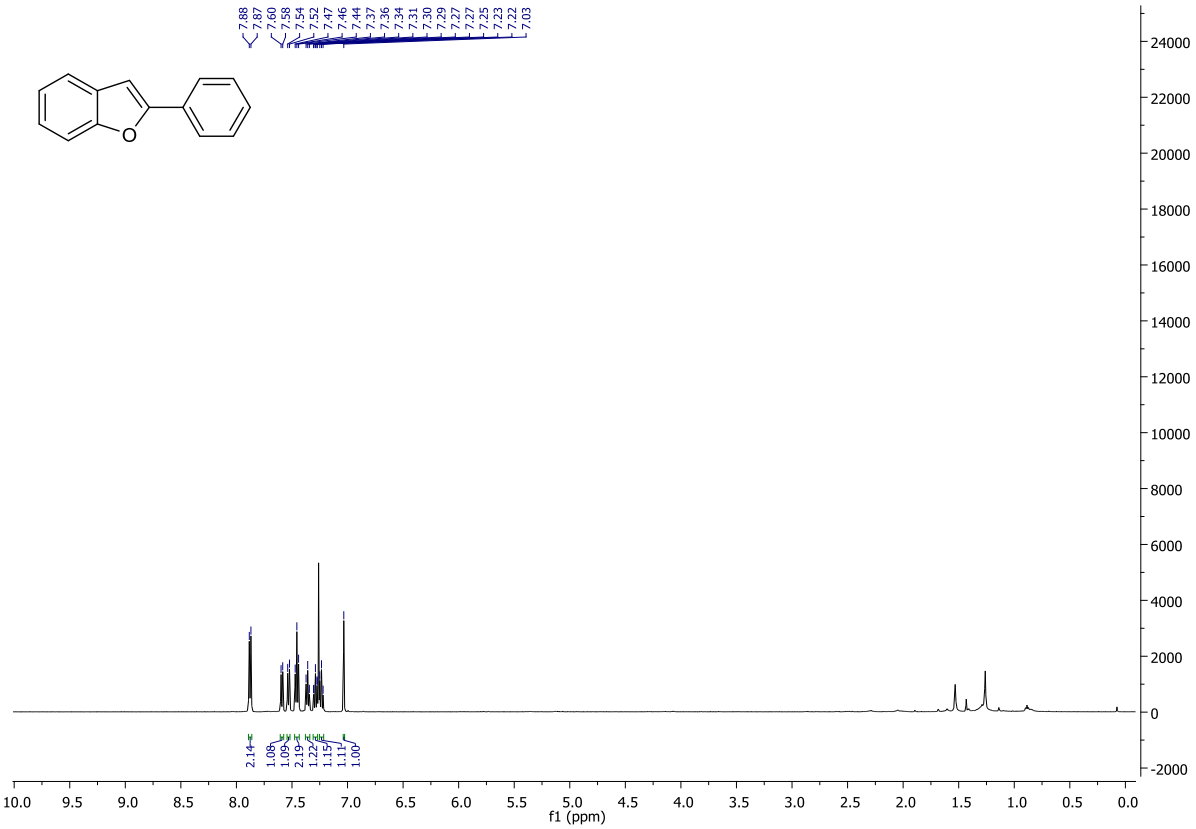
^{1}H NMR 7b



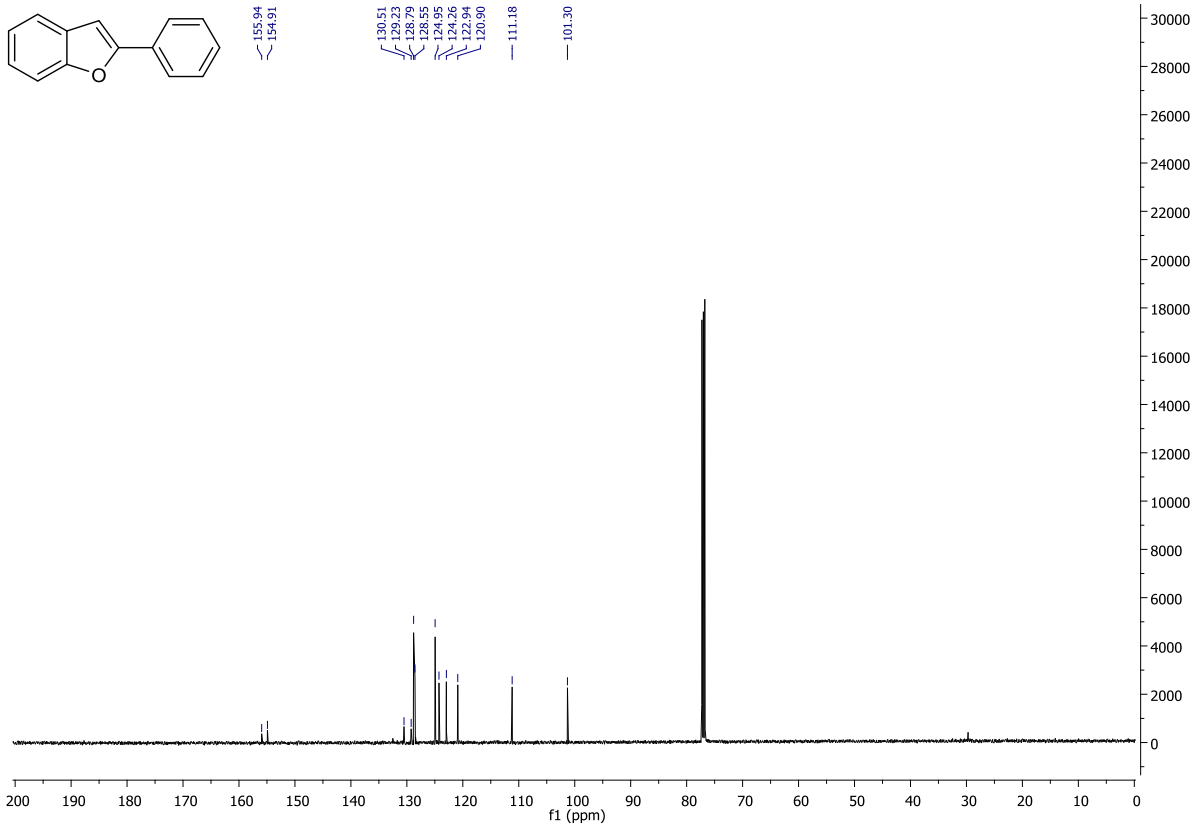
^{13}C NMR 7b



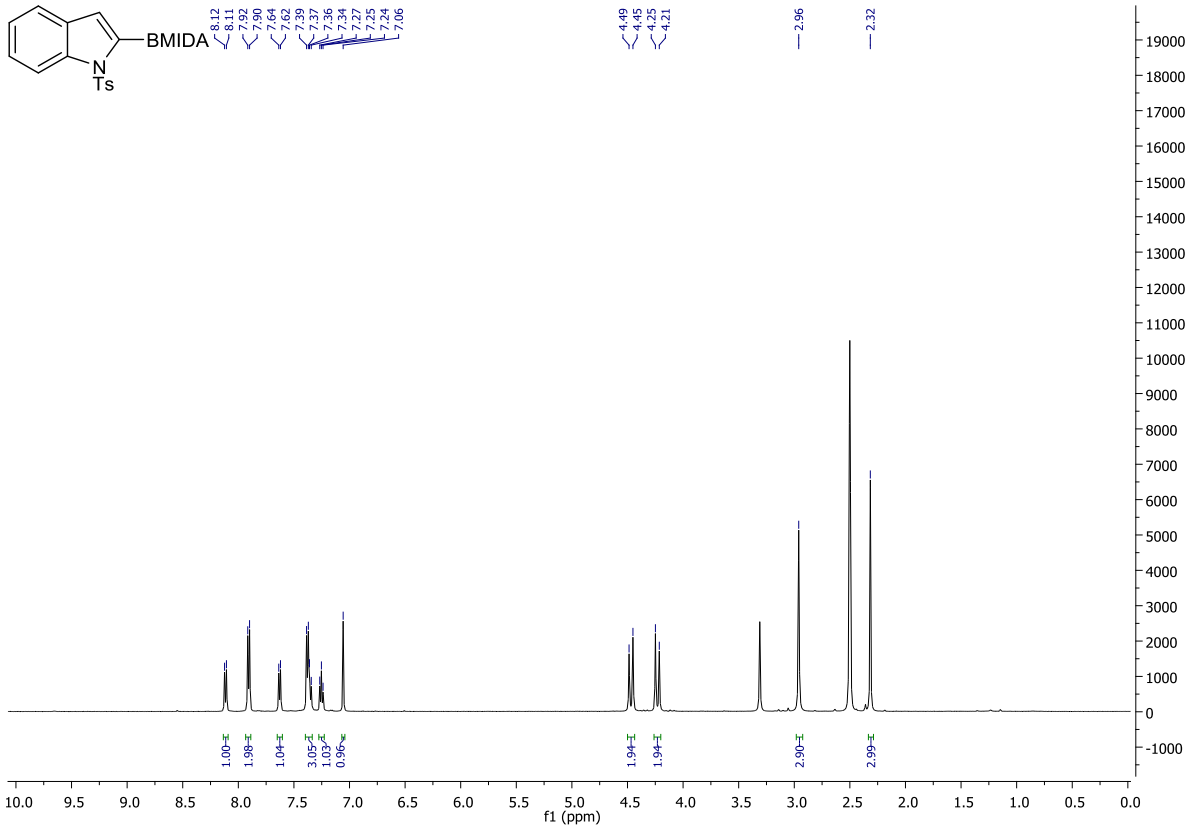
^{1}H NMR 7c



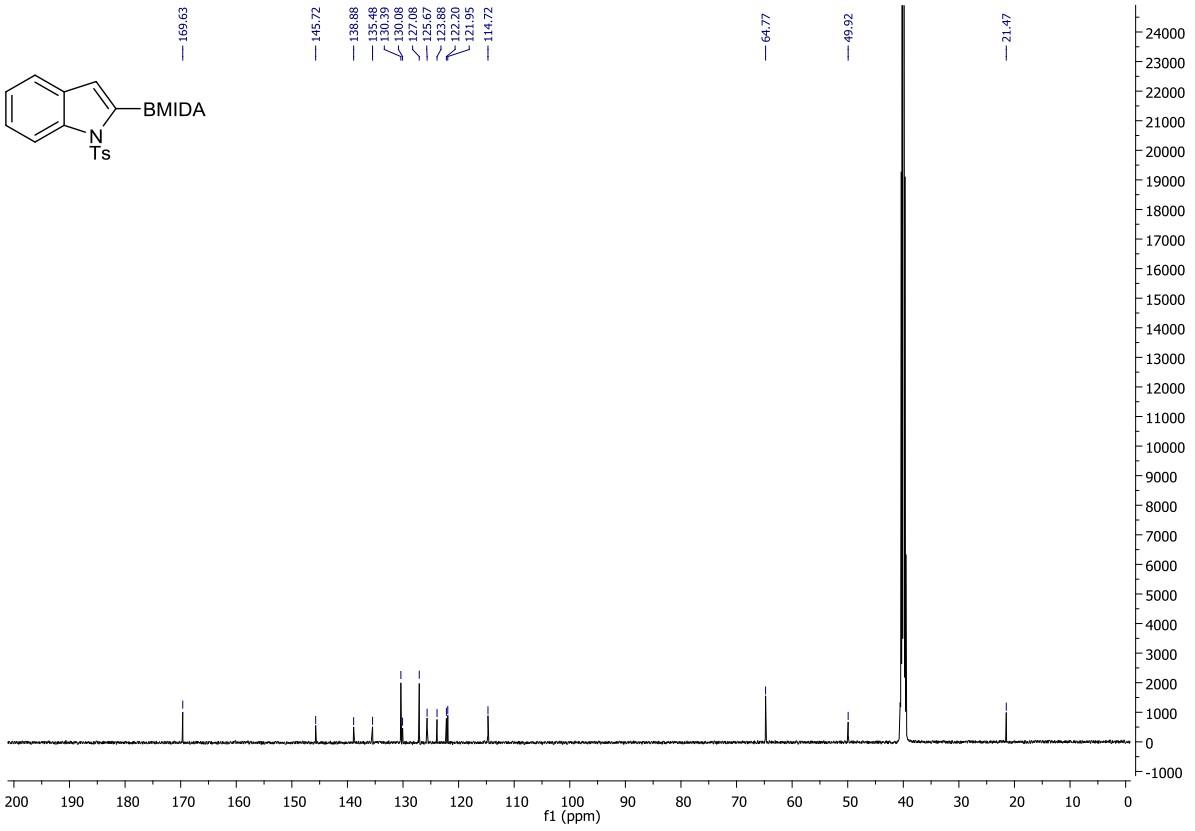
^{13}C NMR 7c



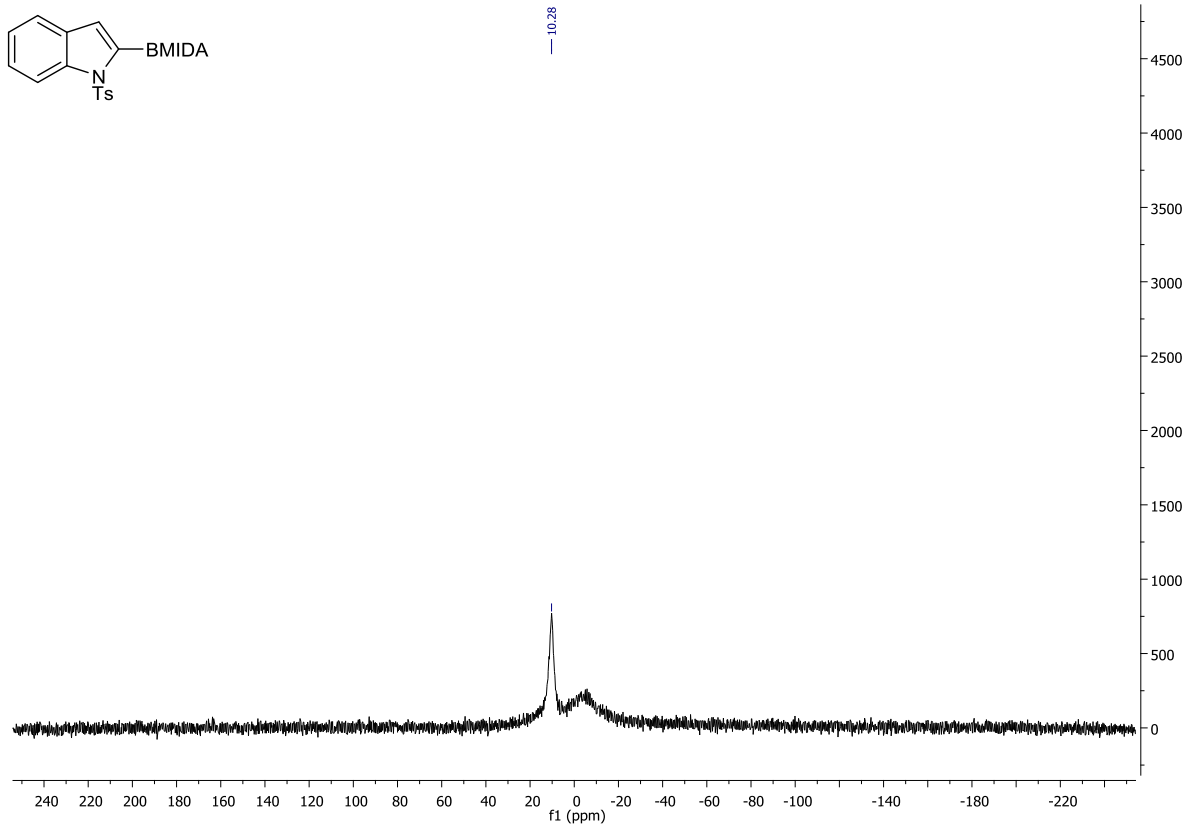
^{1}H NMR 7d



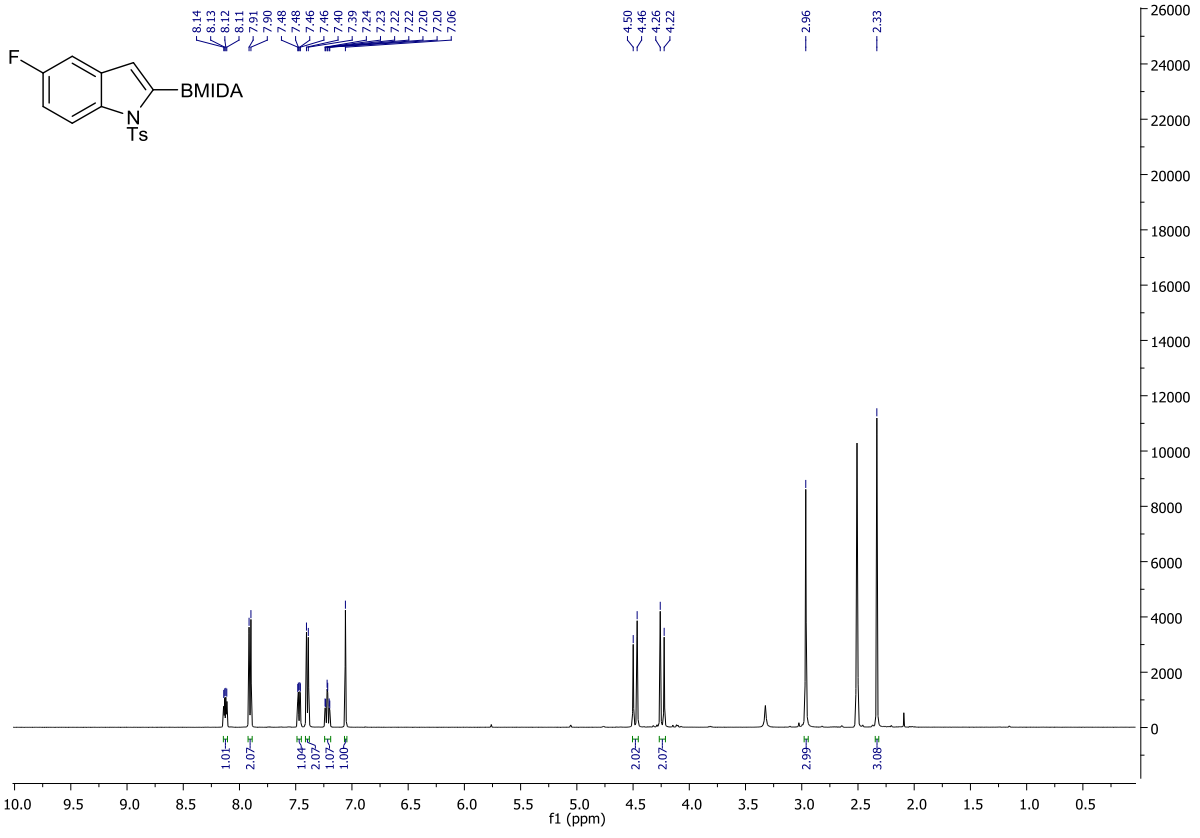
^{13}C NMR 7d



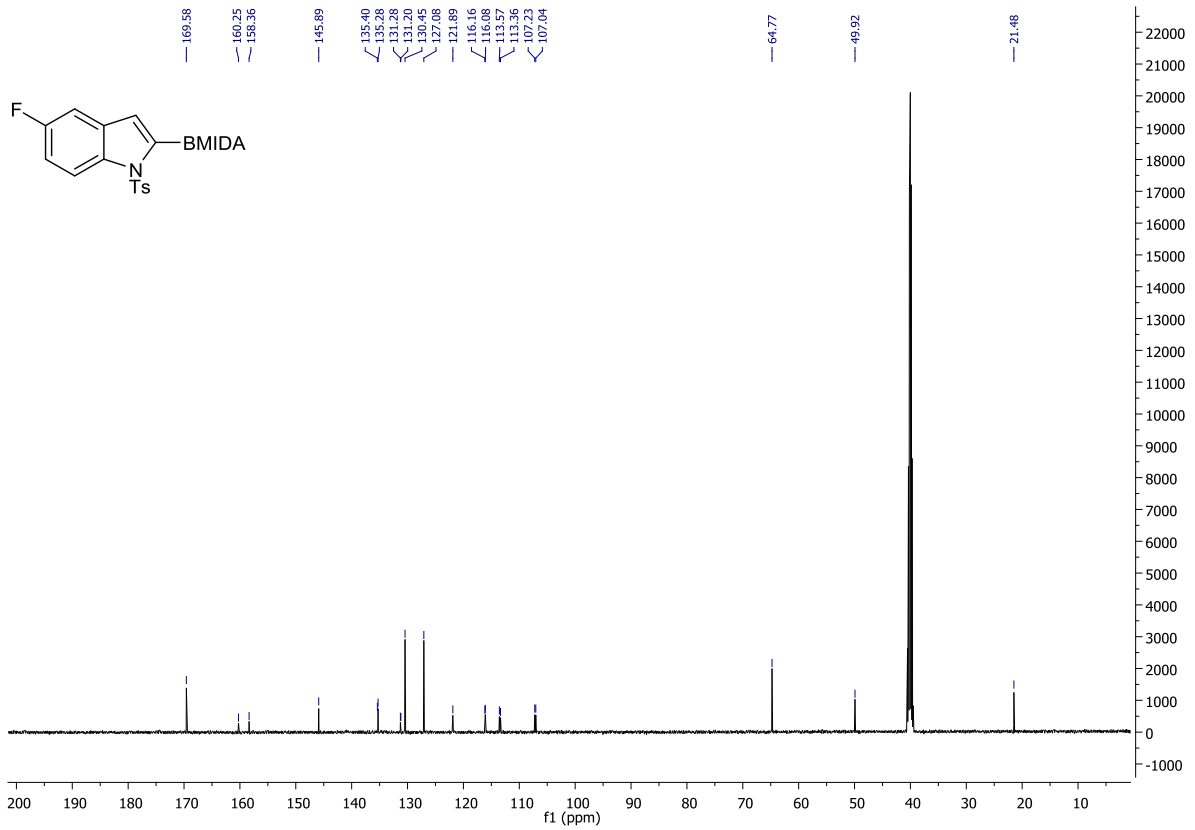
^{11}B NMR 7d



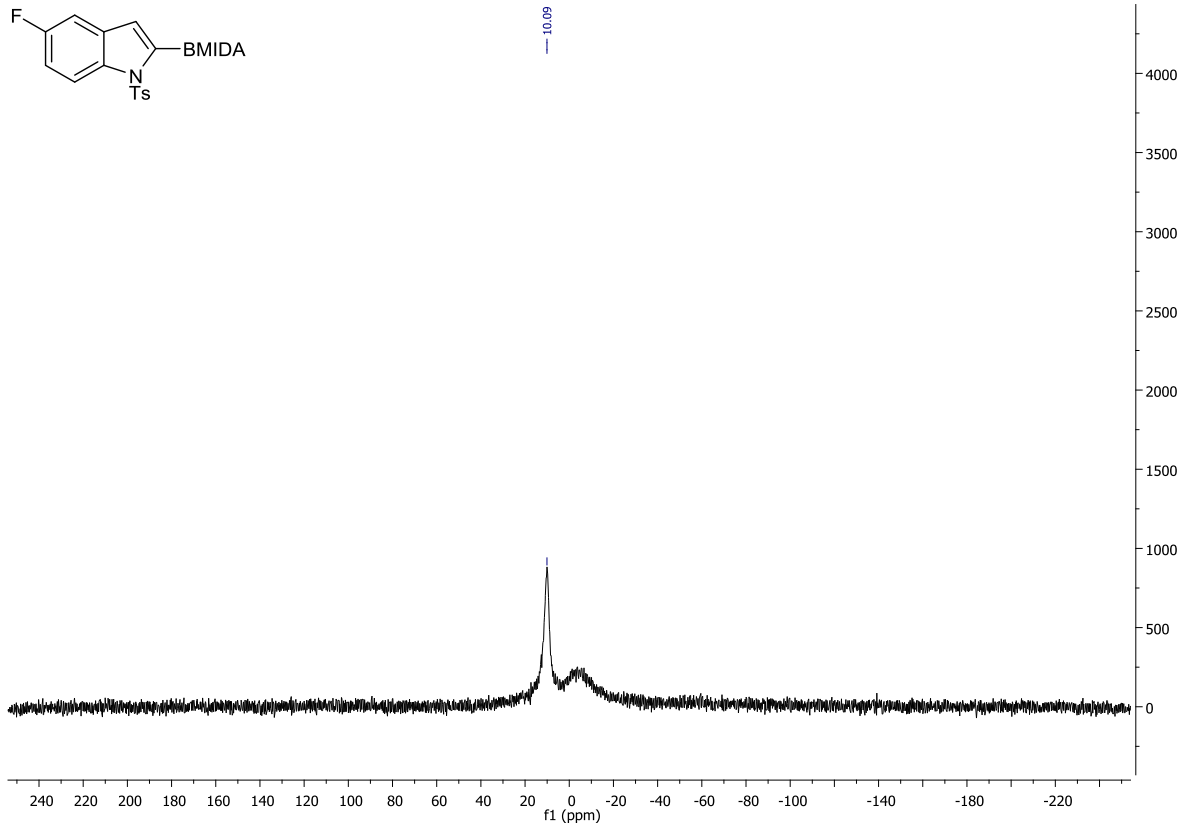
^{1}H NMR 7e



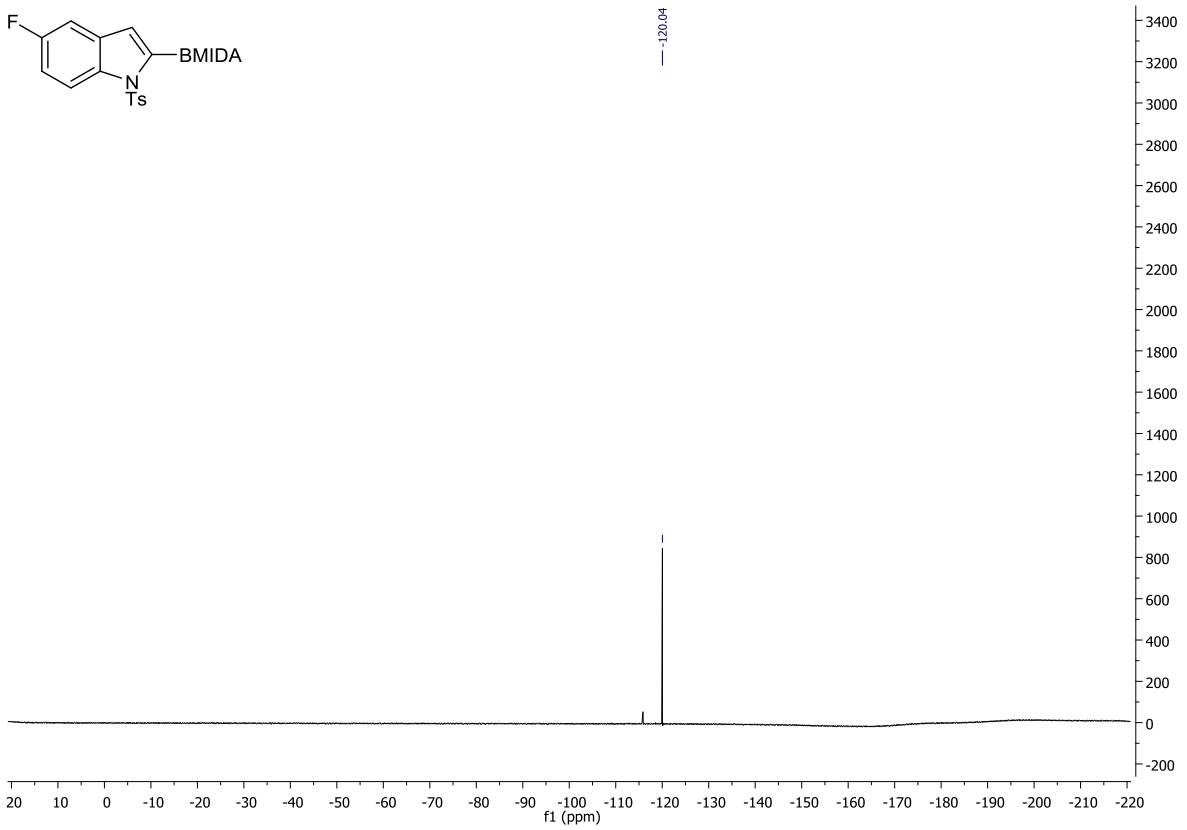
^{13}C NMR 7e



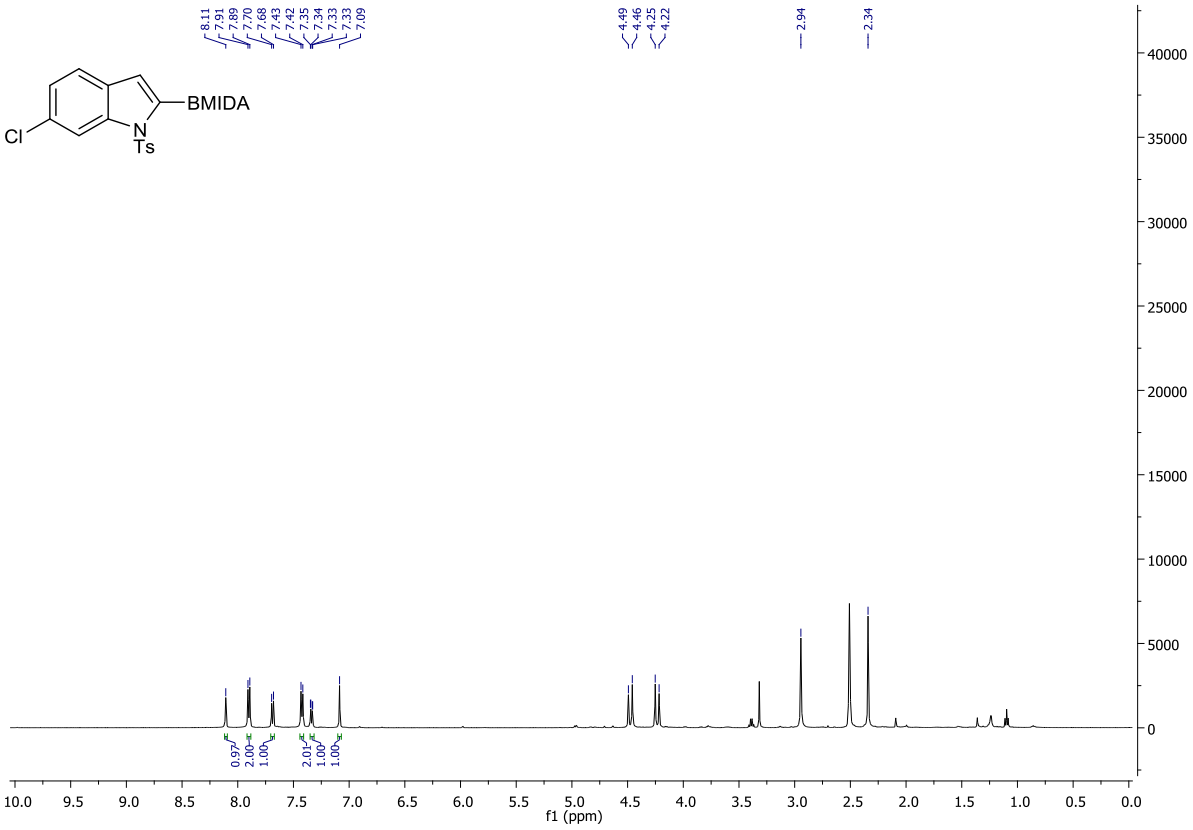
^{11}B NMR 7e



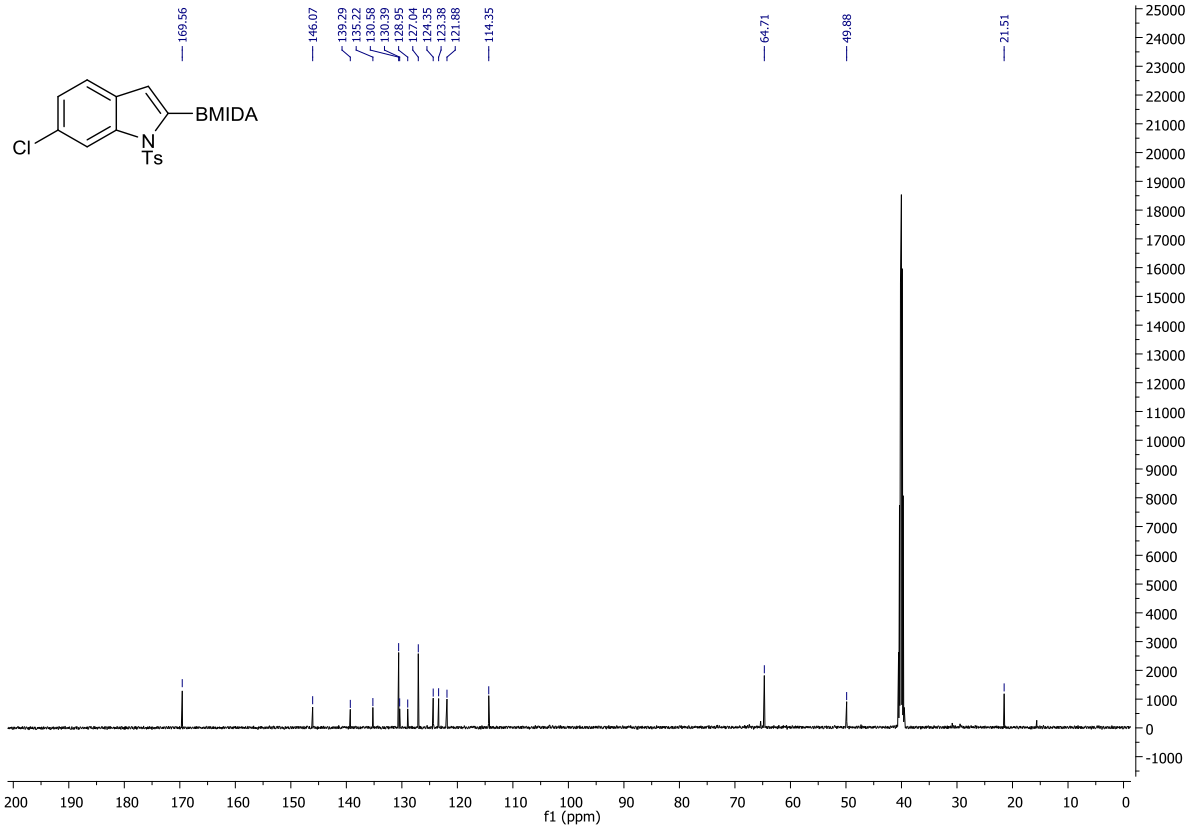
^{19}F NMR 7e



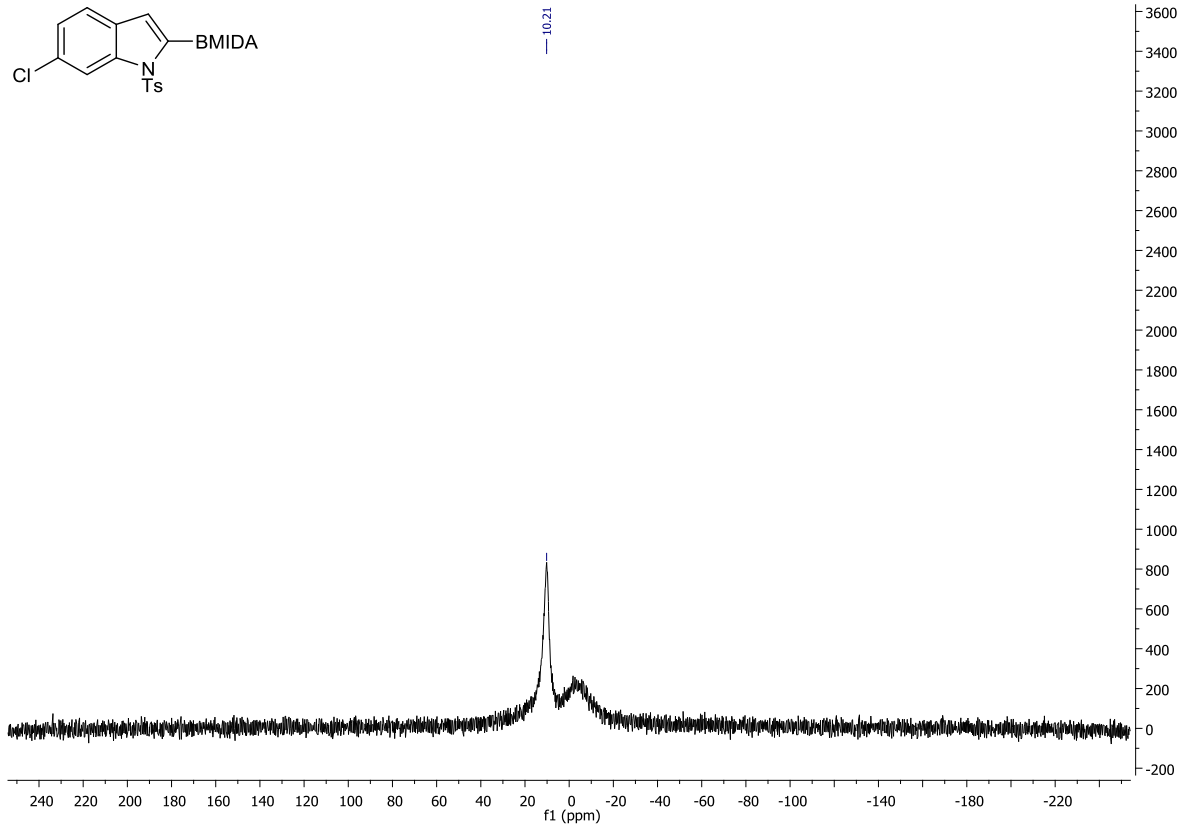
^{1}H NMR 7f



^{13}C NMR 7f

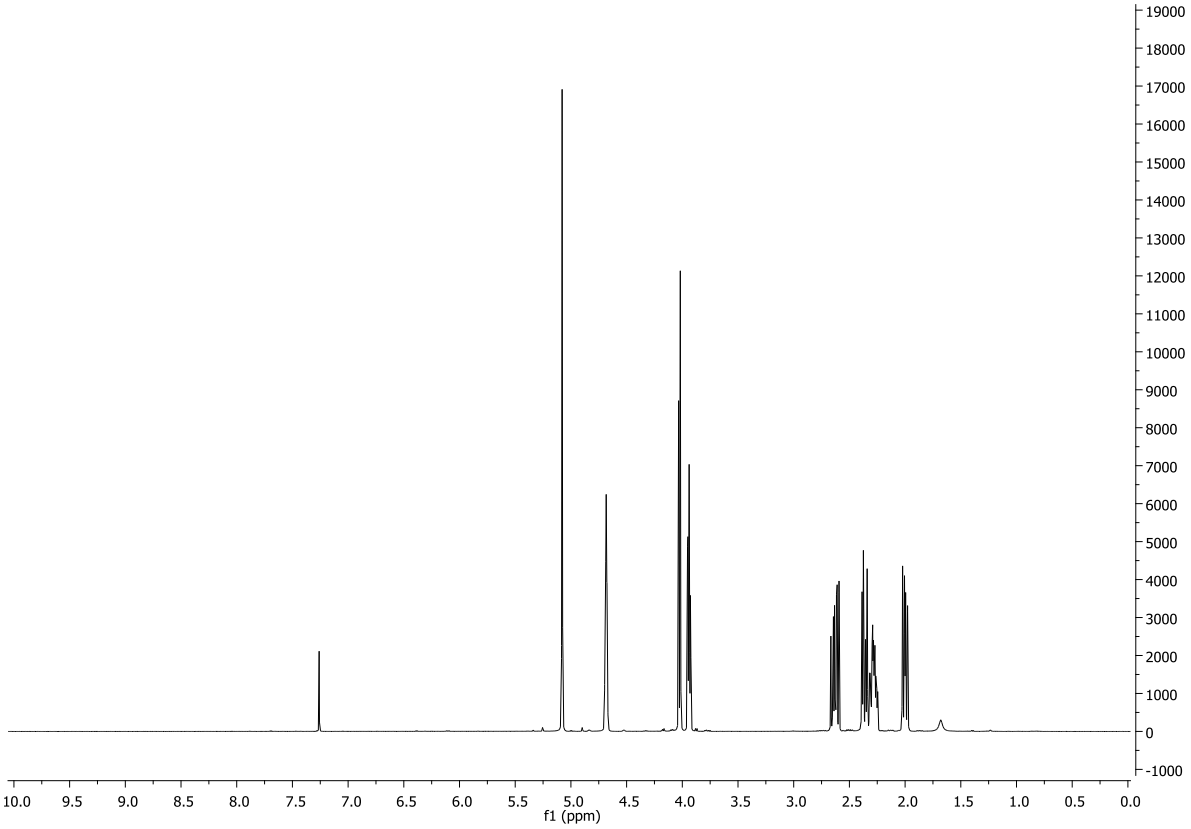


^{11}B NMR 7f

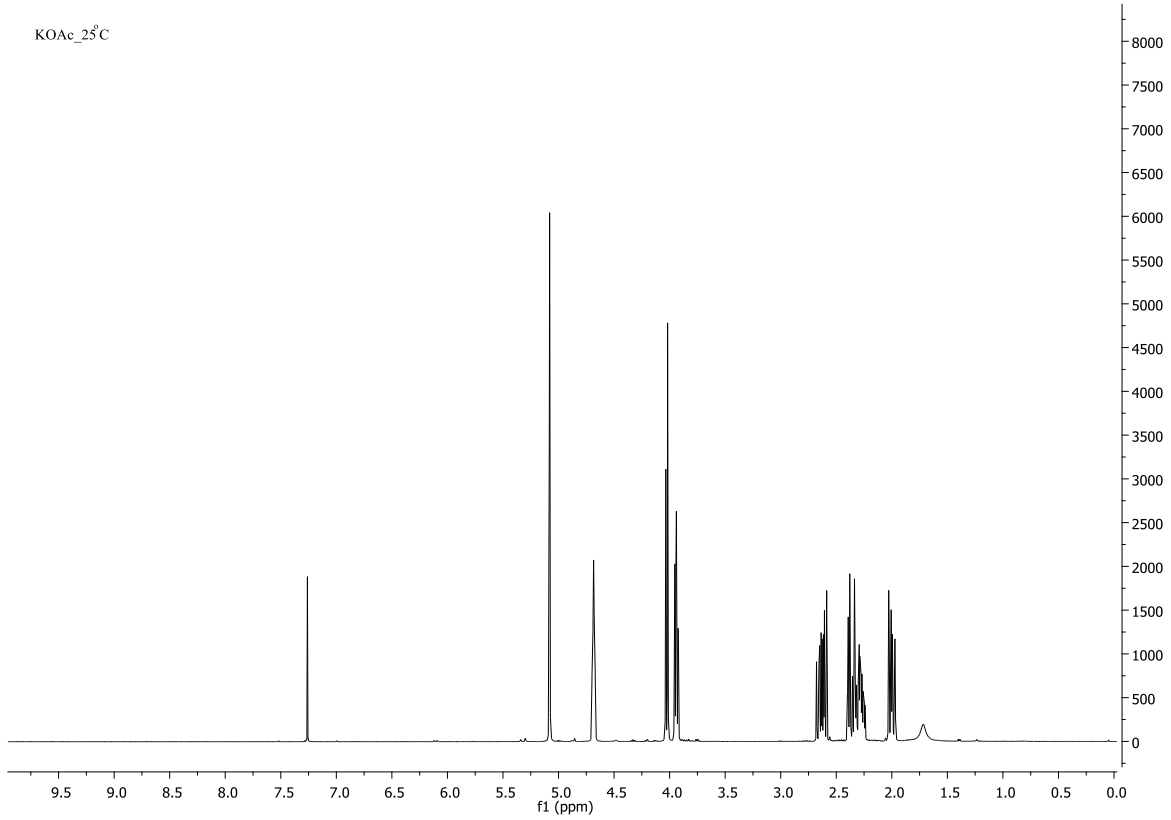


9. ^{1}H NMR Evidence for the Evaluation of the Base Sensitivity

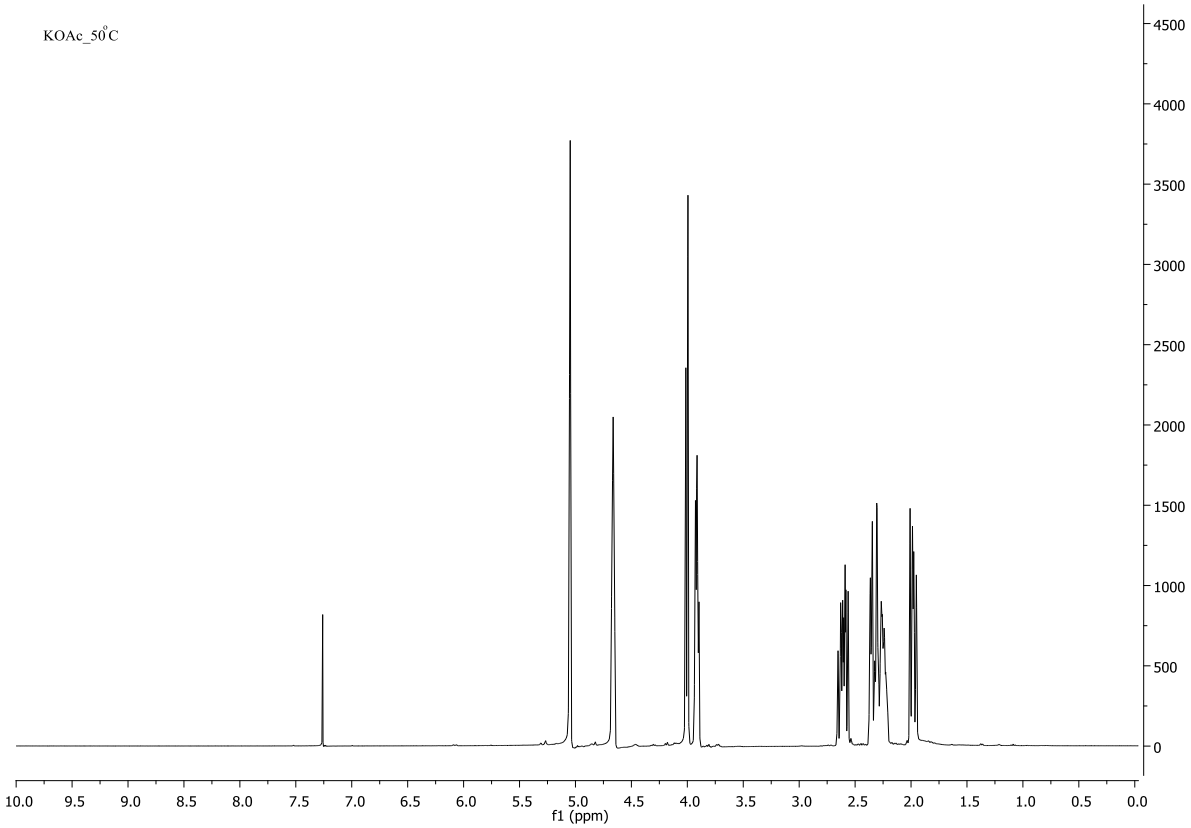
Cyrene ^{1}H NMR



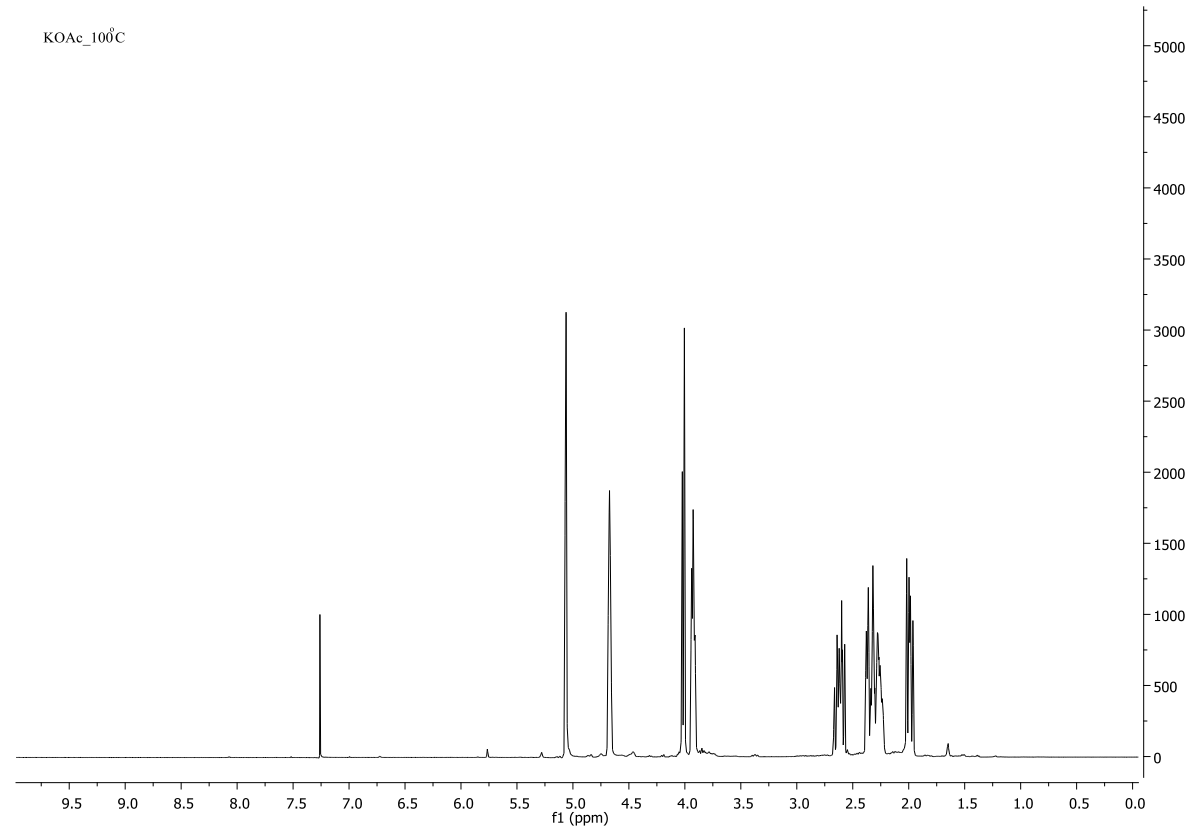
KOAc 25 °C



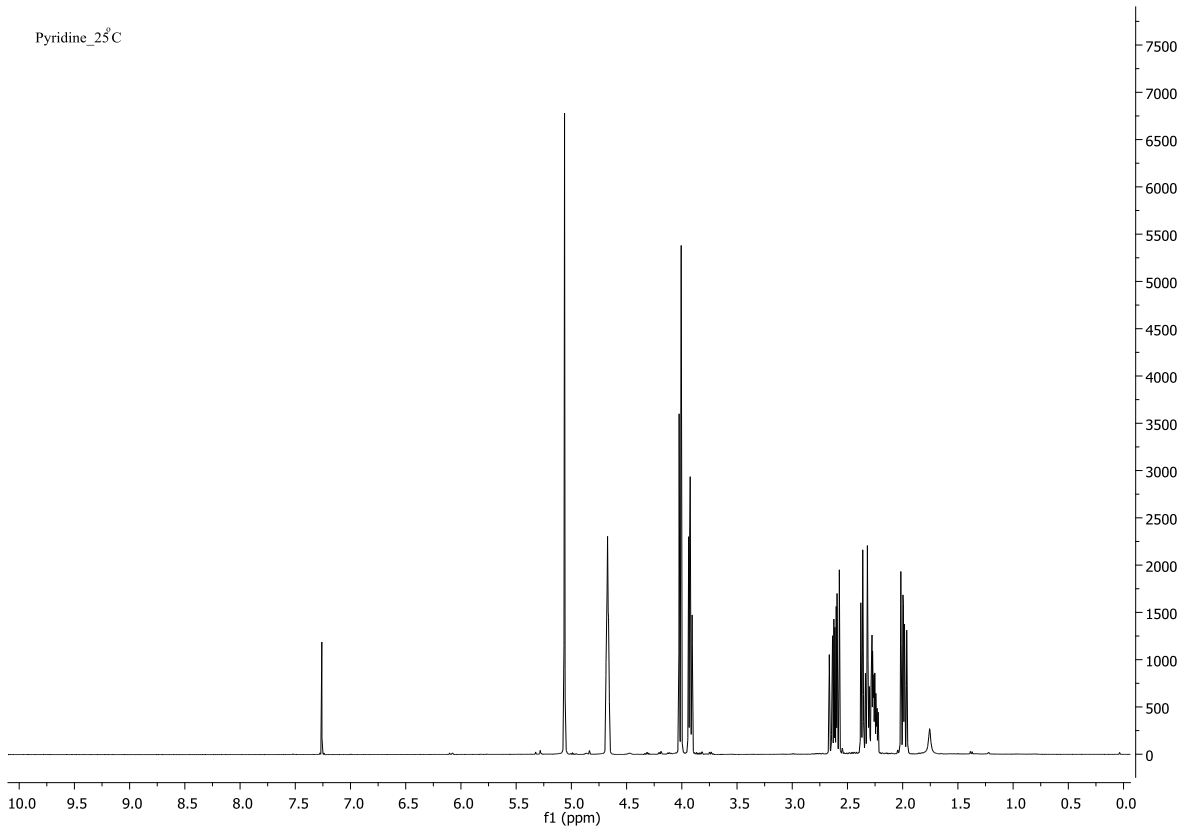
KOAc 50 °C



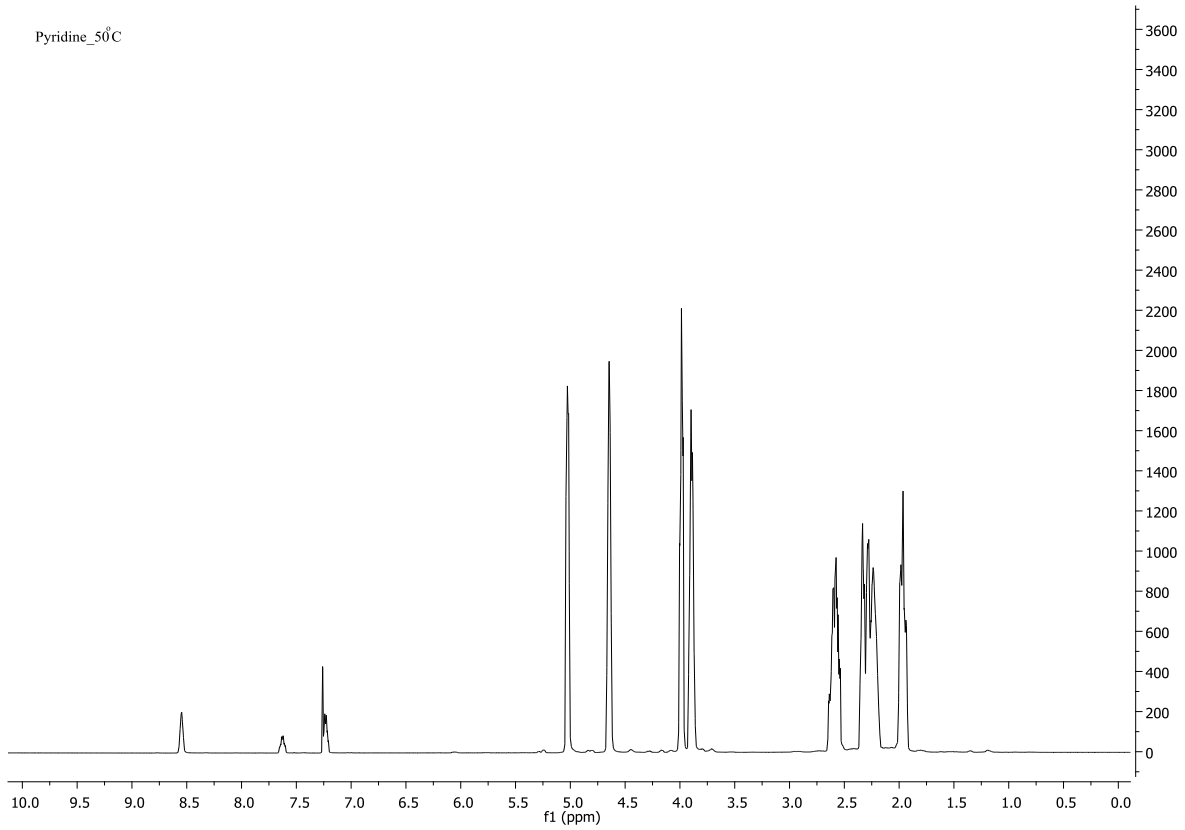
KOAc 100 °C



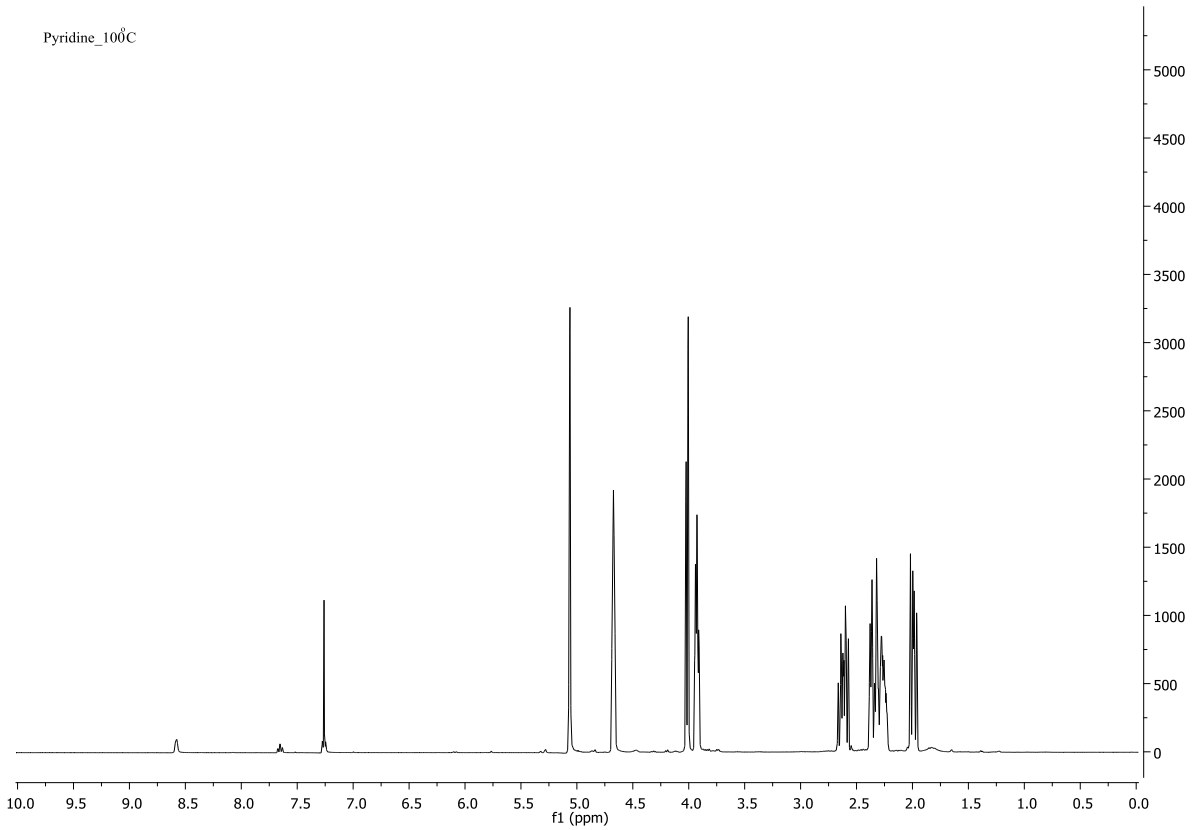
Pyridine 25 °C



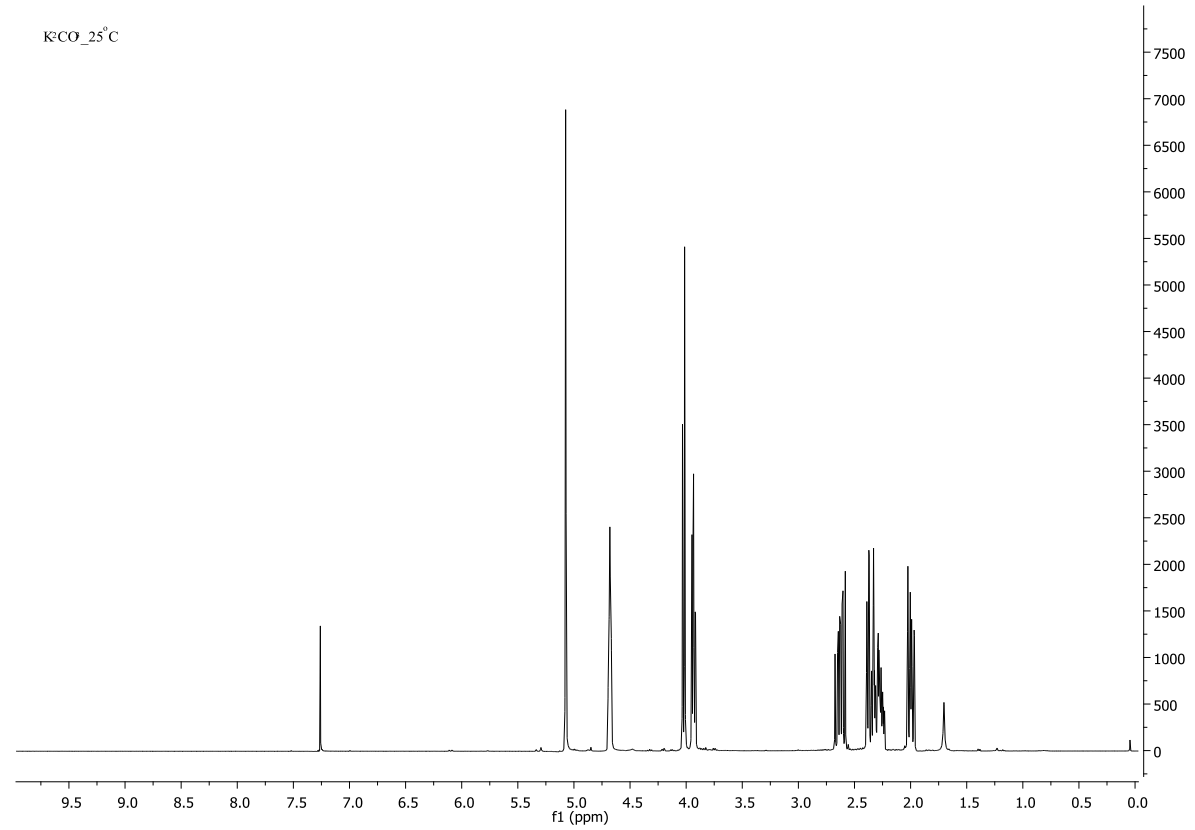
Pyridine 50 °C



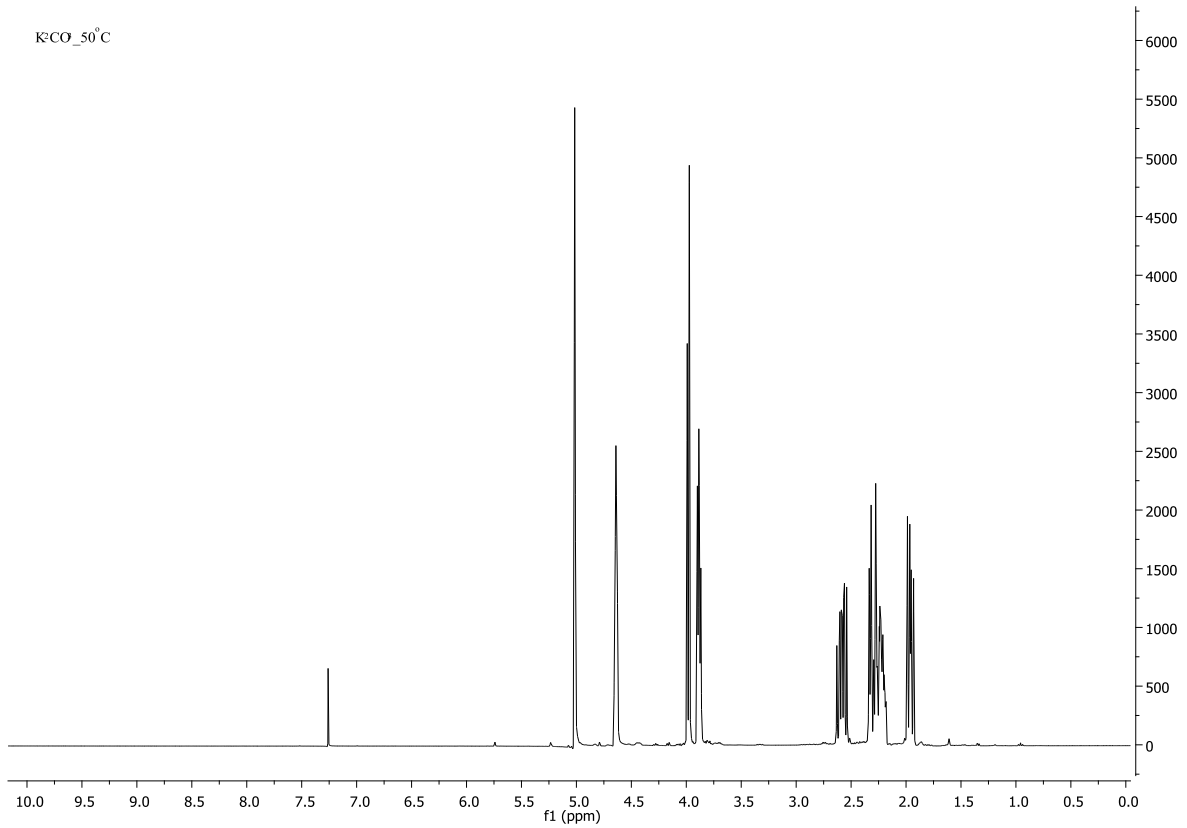
Pyridine 100 °C



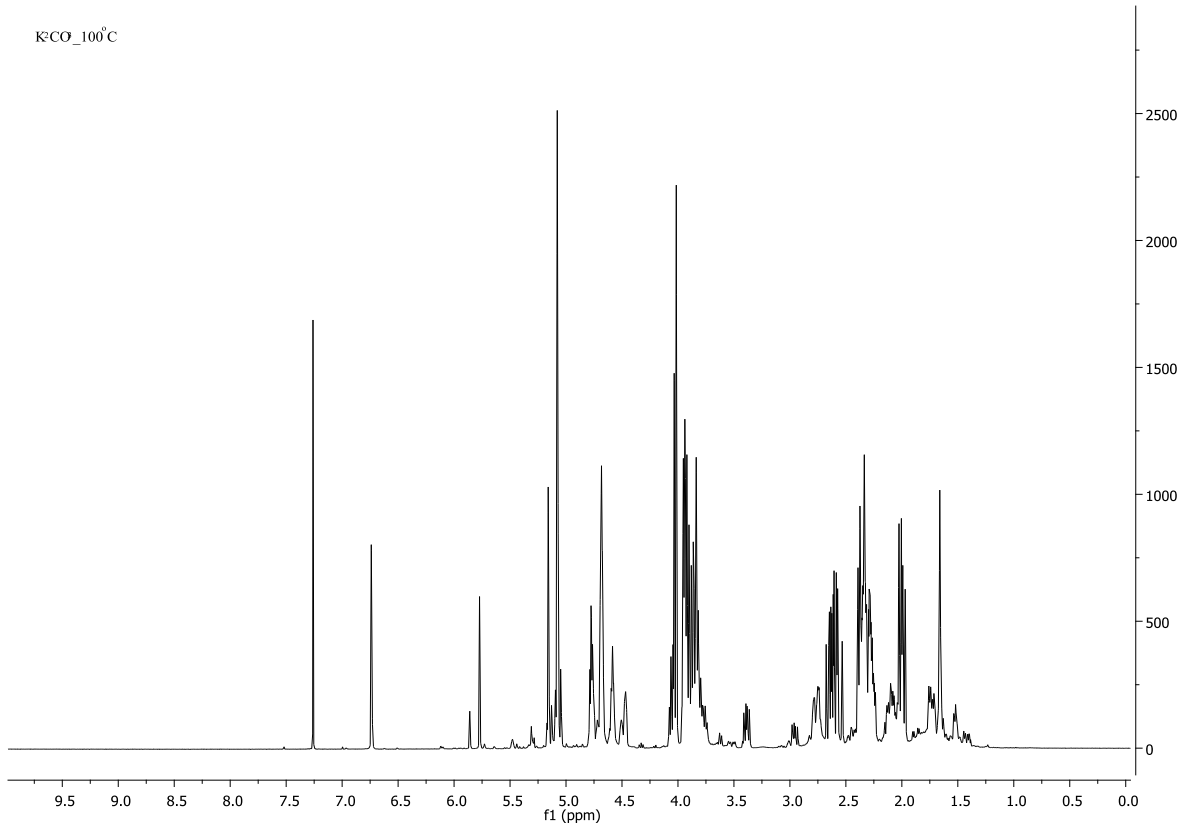
K_2CO_3 25 °C



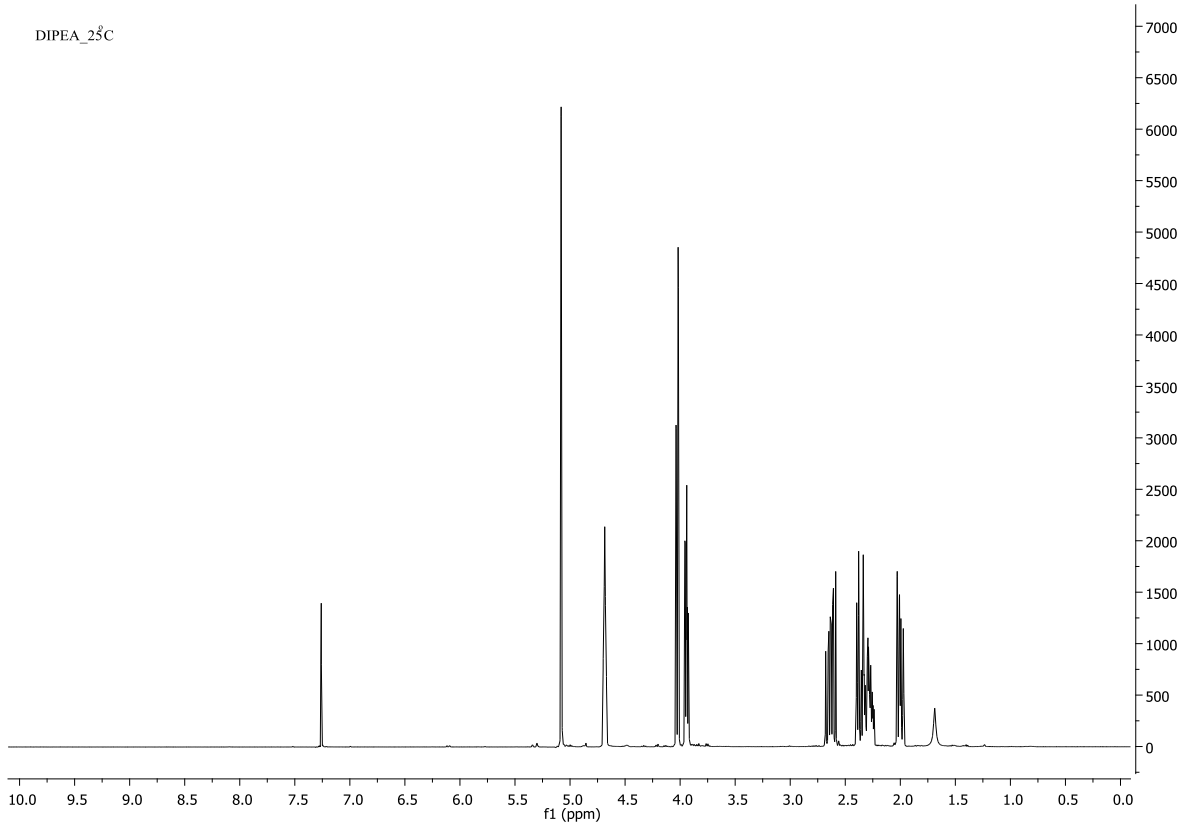
K_2CO_3 50 °C



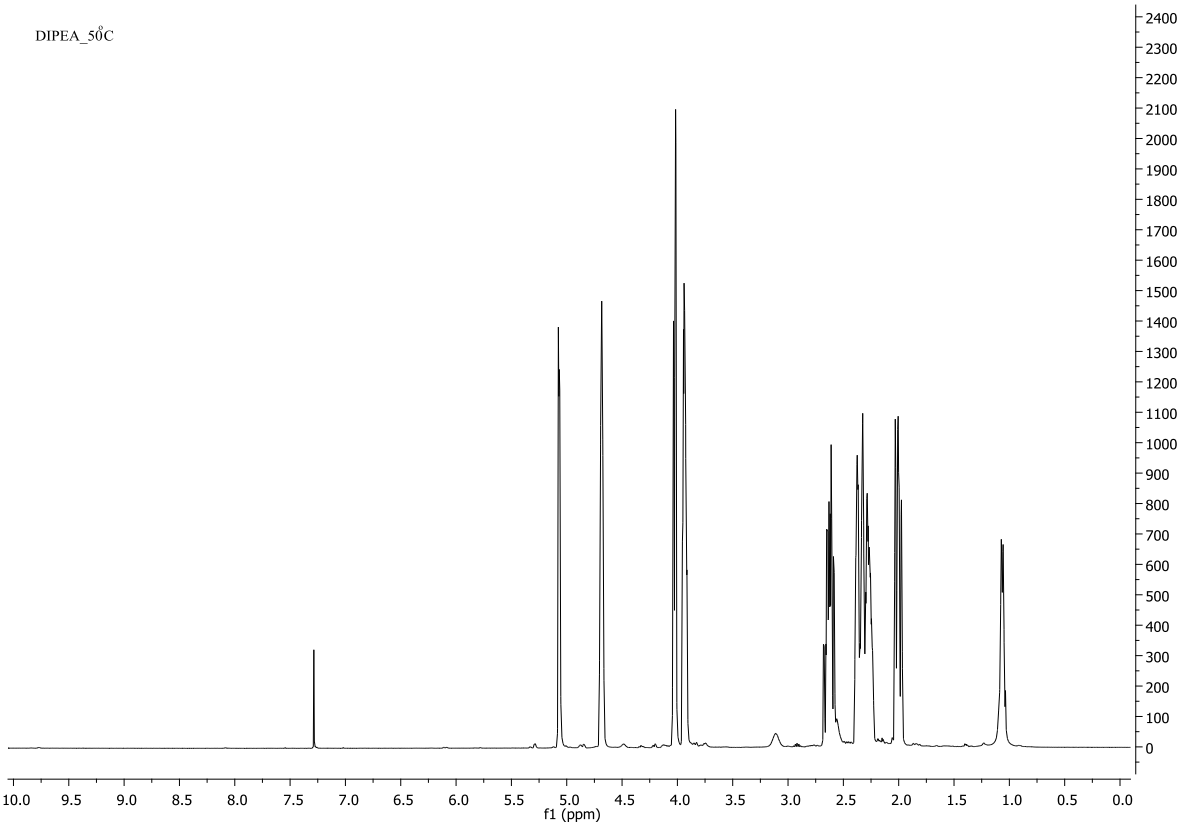
K_2CO_3 100 °C



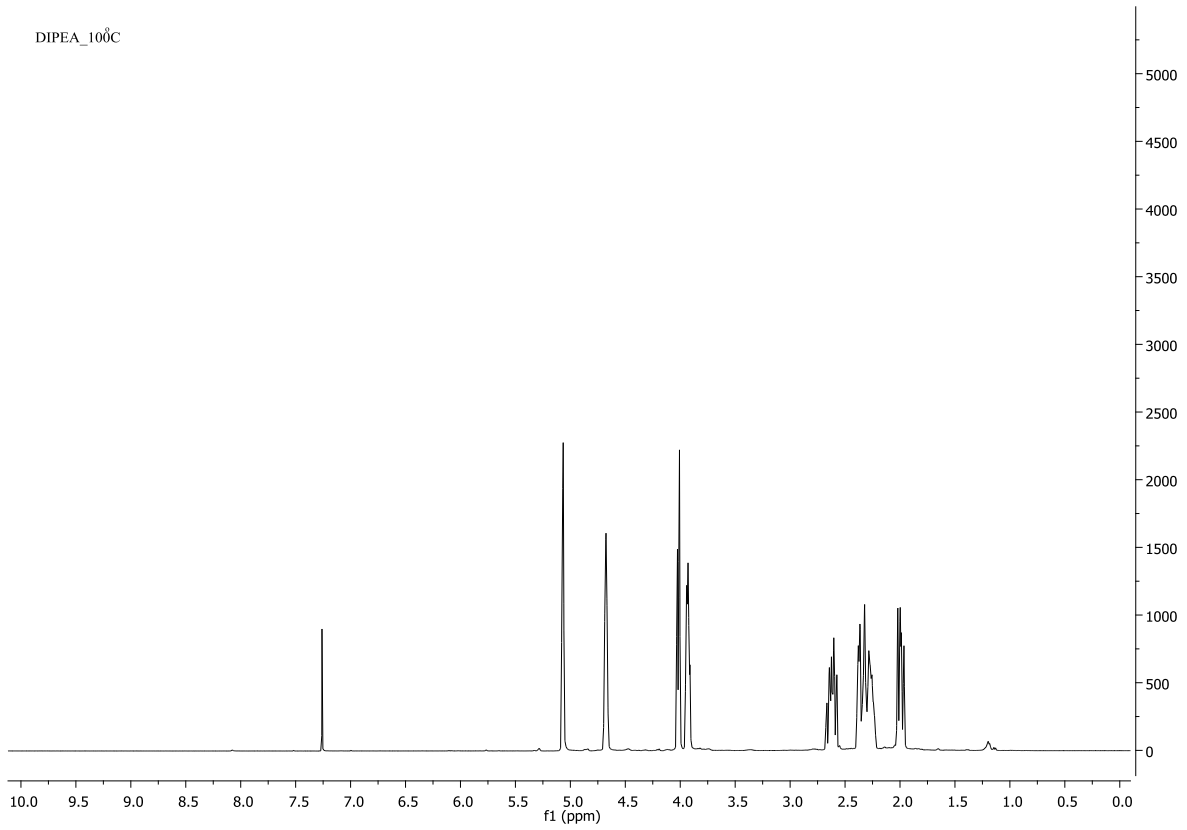
DIPEA 25 °C



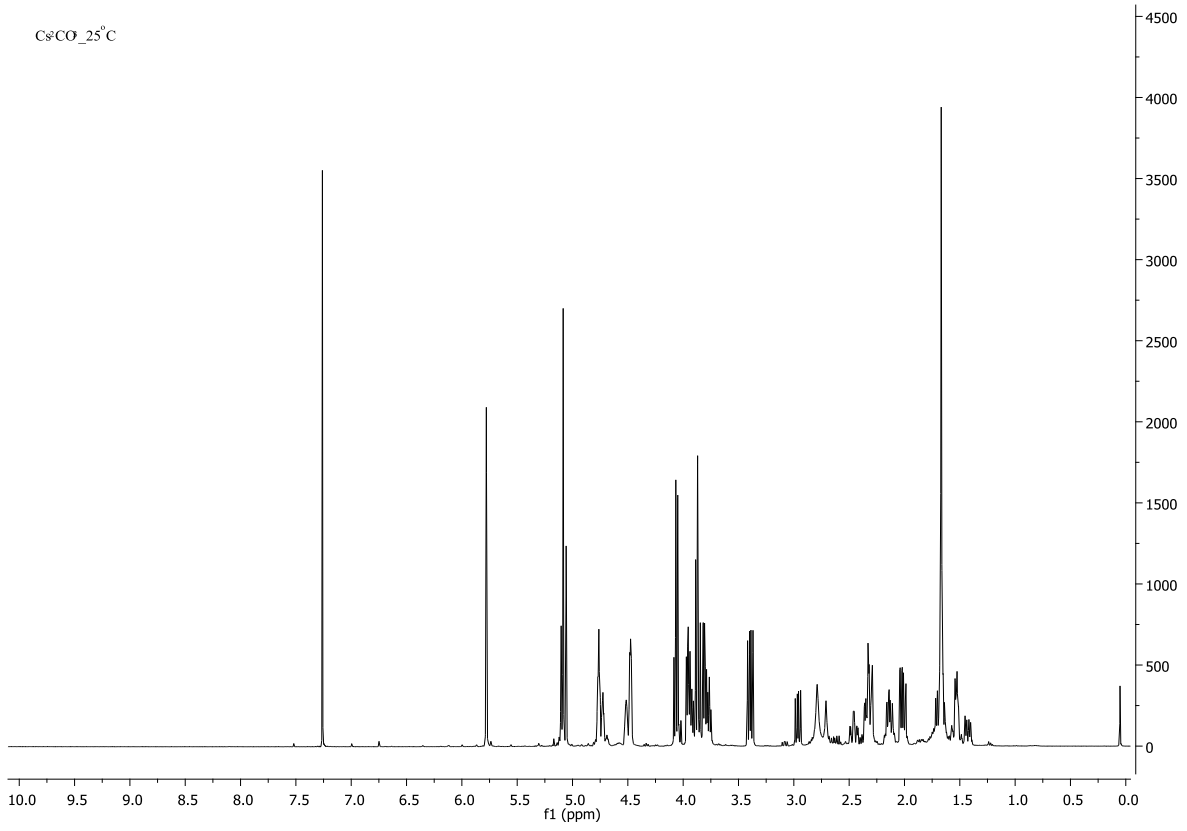
DIPEA 50 °C



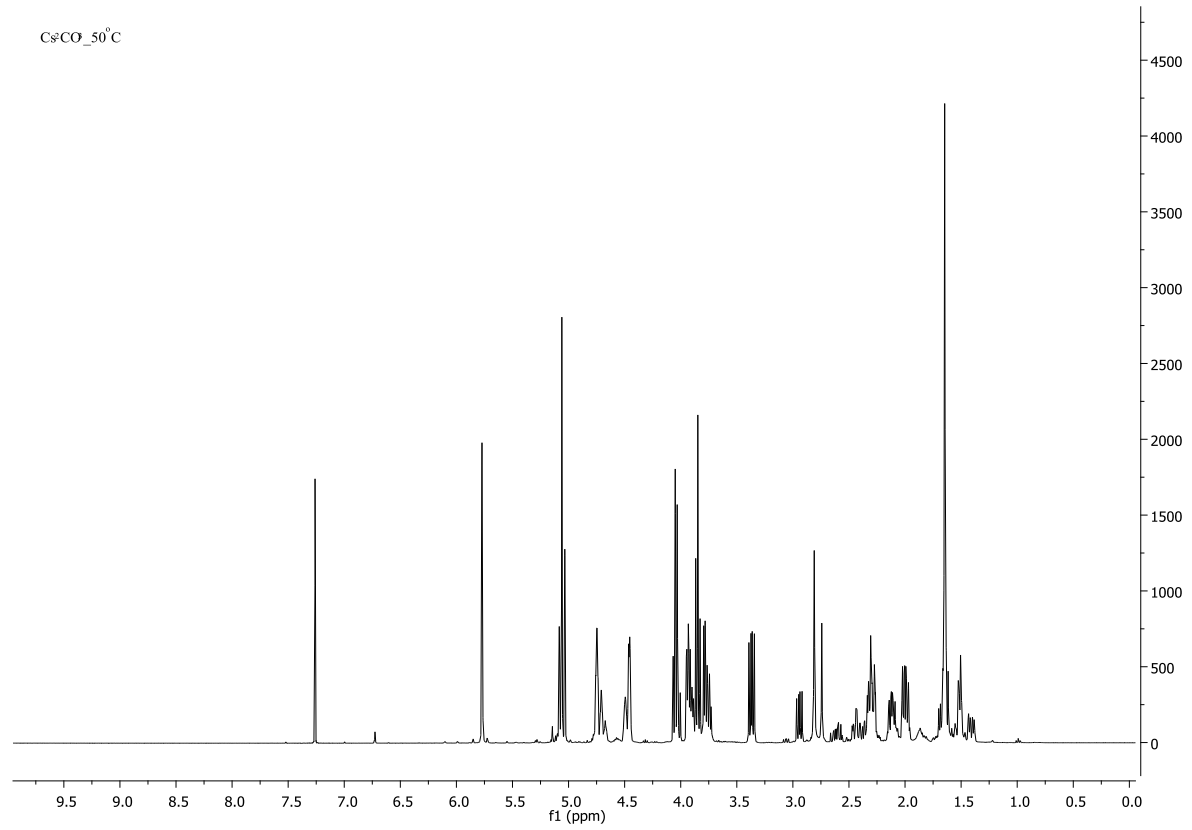
DIPEA 100 °C



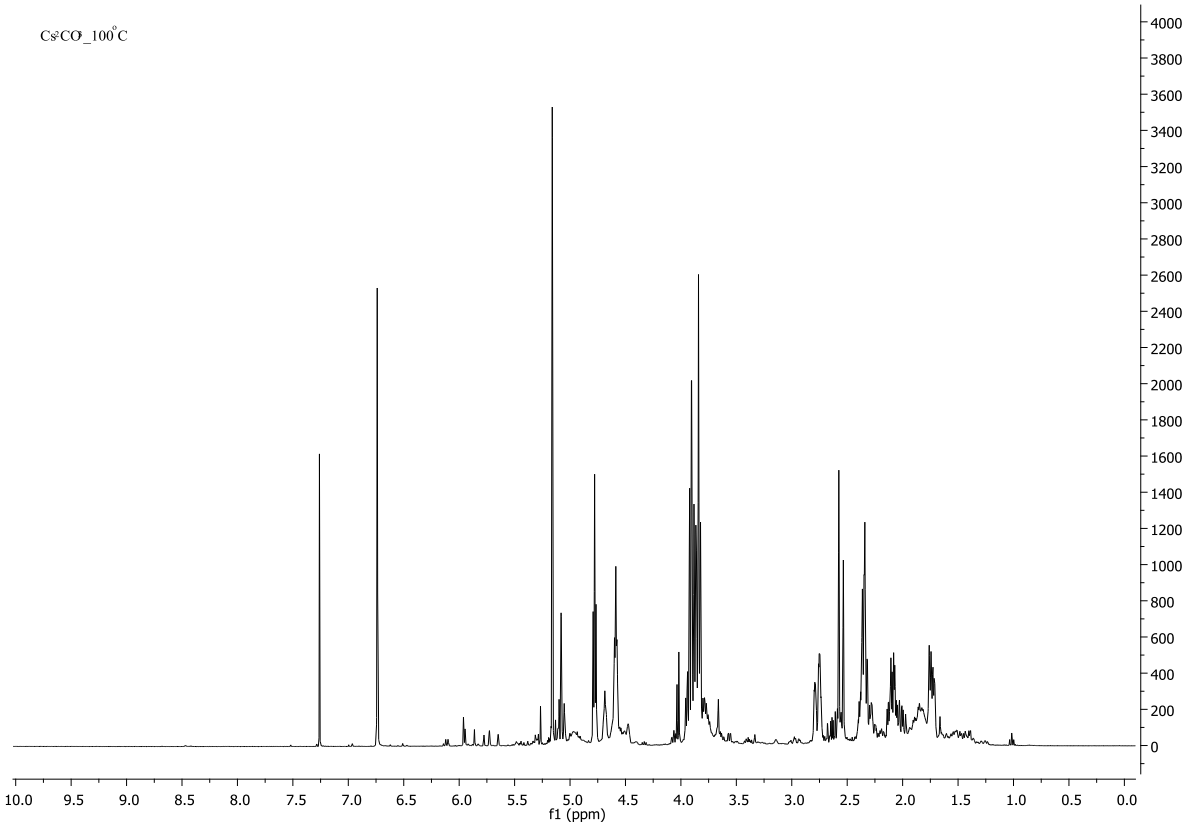
Cs_2CO_3 25 °C



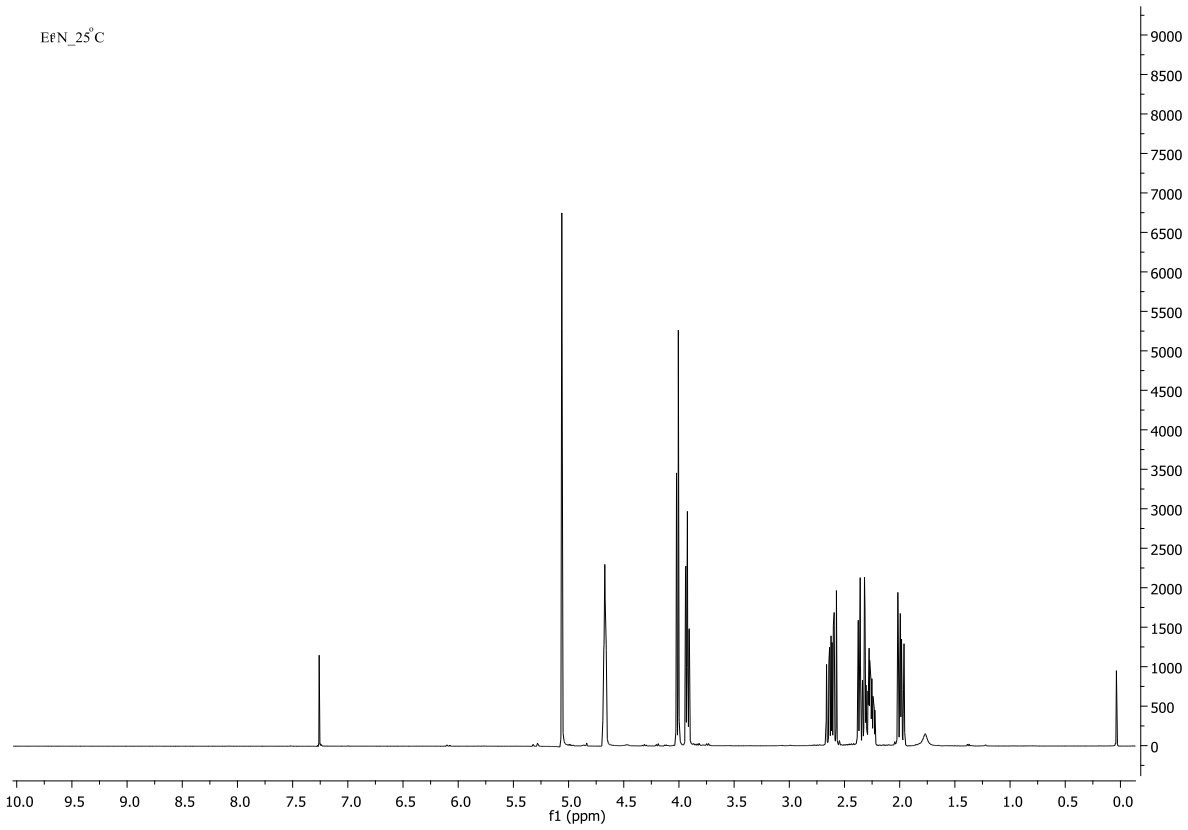
Cs_2CO_3 50 °C



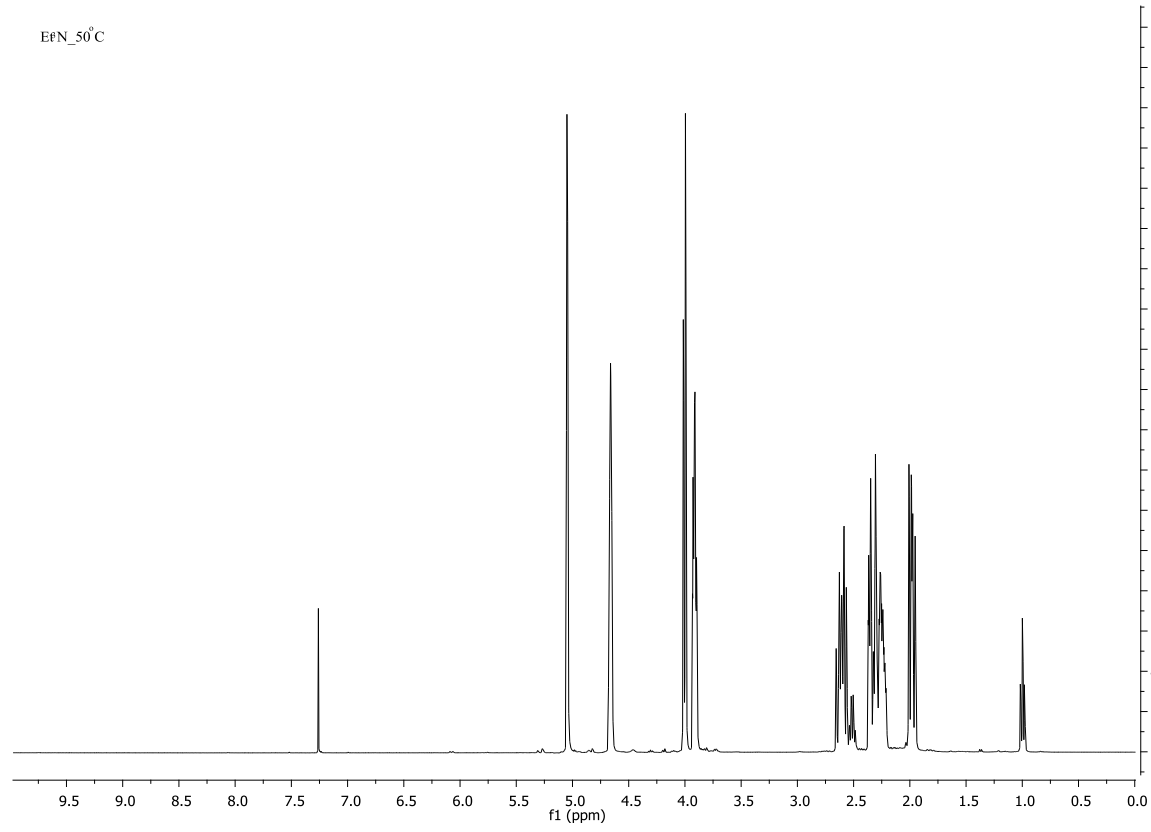
Cs_2CO_3 100 °C



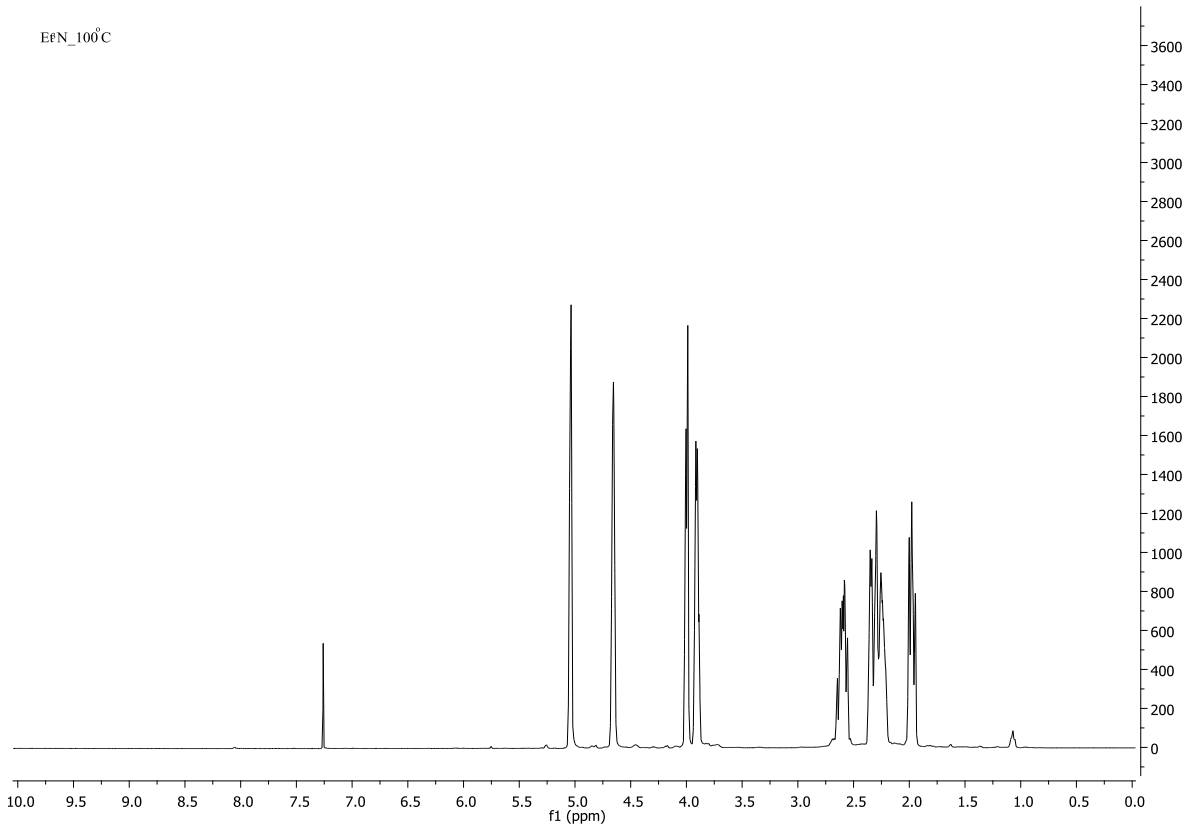
Et_3N 25 °C



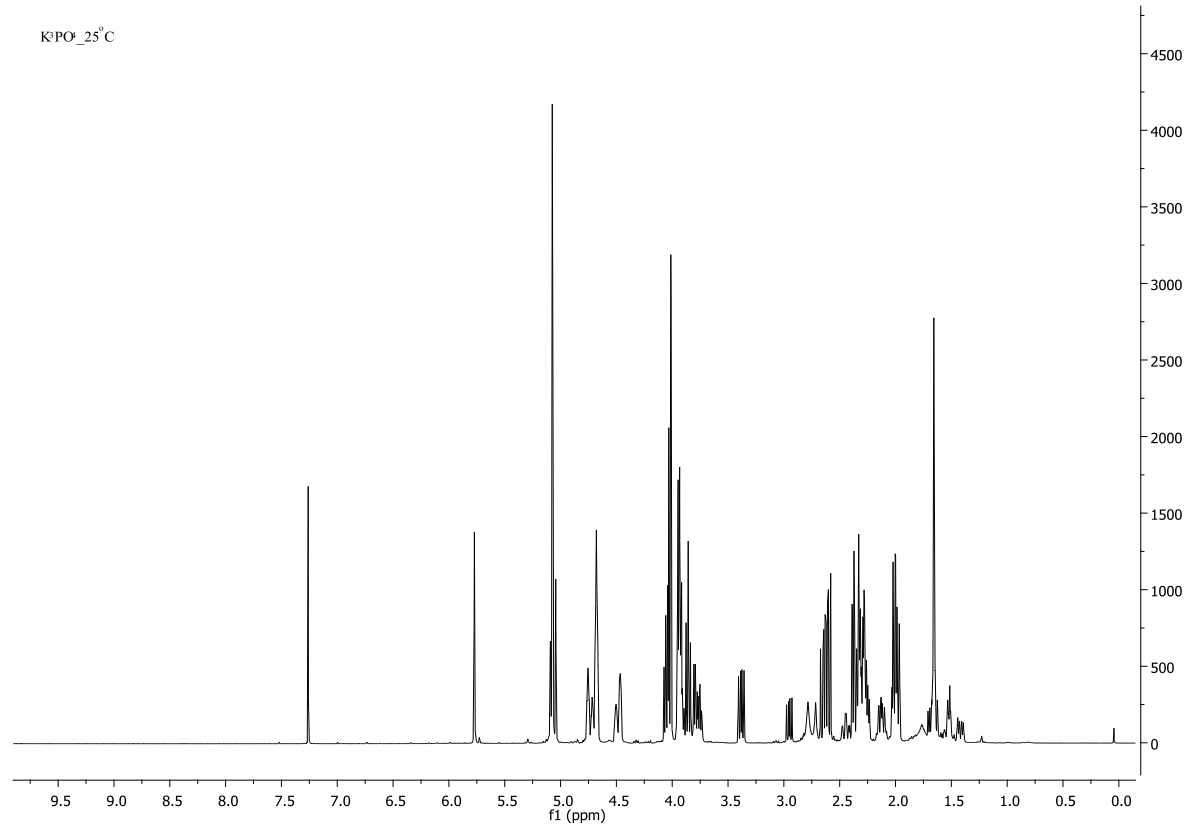
Et_3N 50 °C



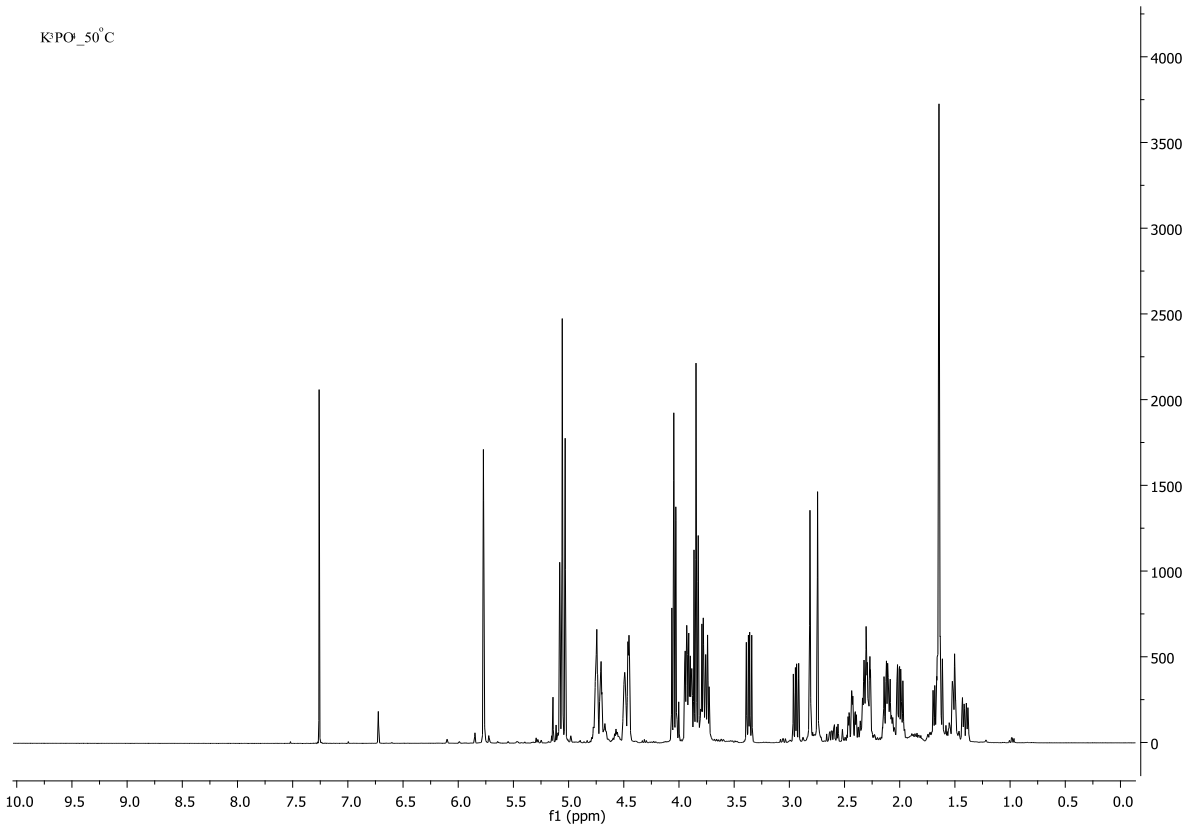
Et_3N 100 °C



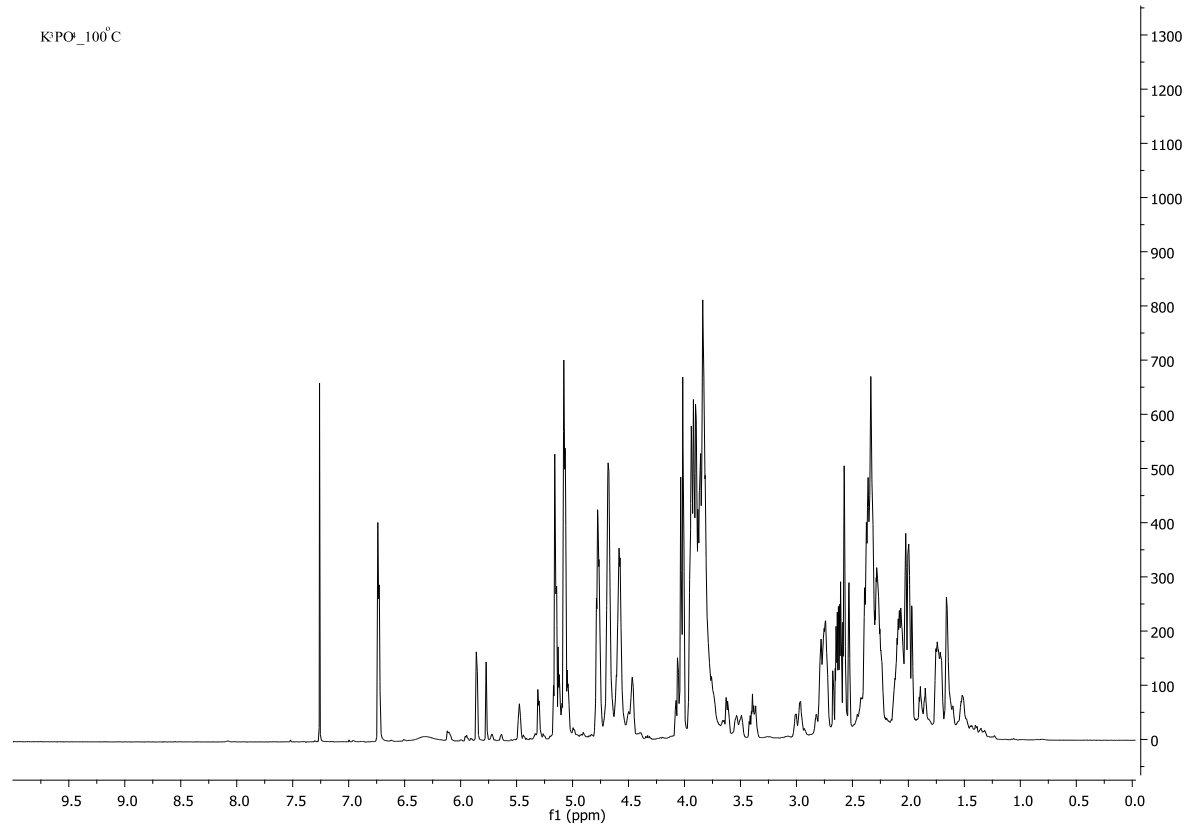
K_3PO_4 25 °C



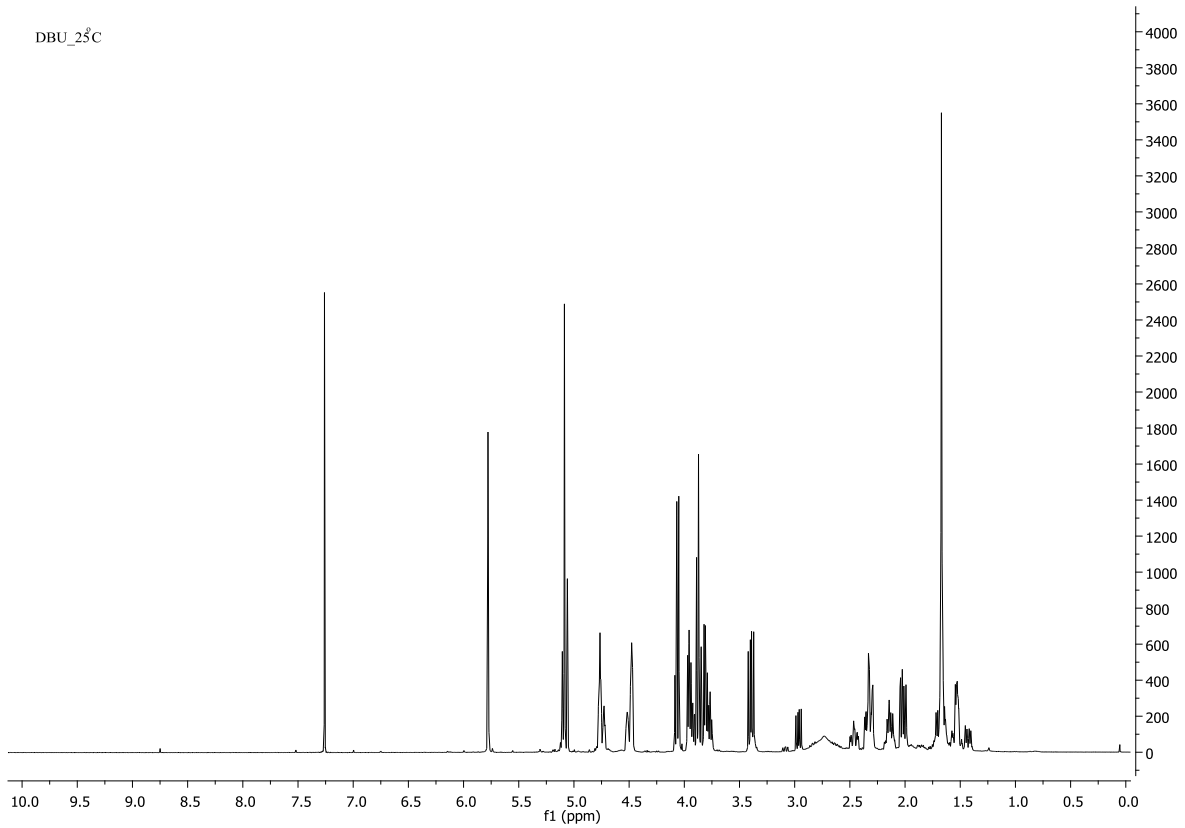
K_3PO_4 50 °C



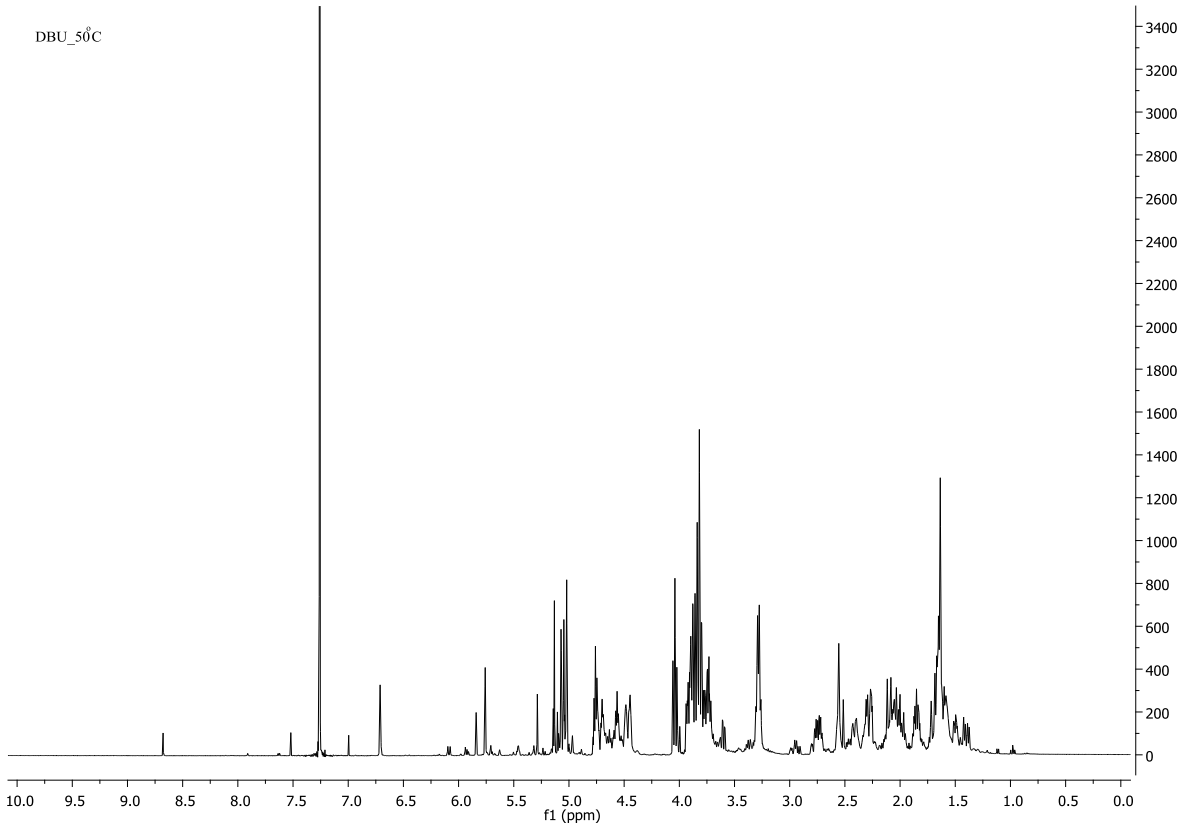
K_3PO_4 100 °C



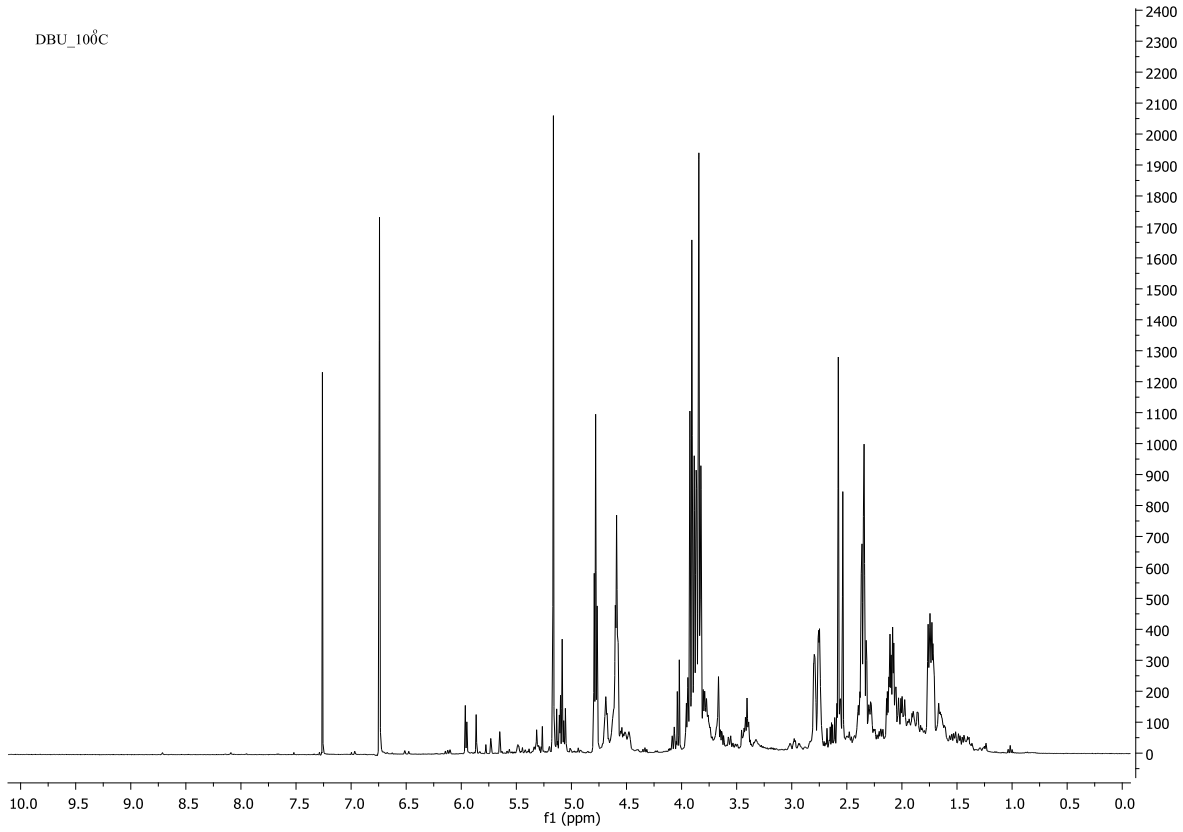
DBU 25 °C



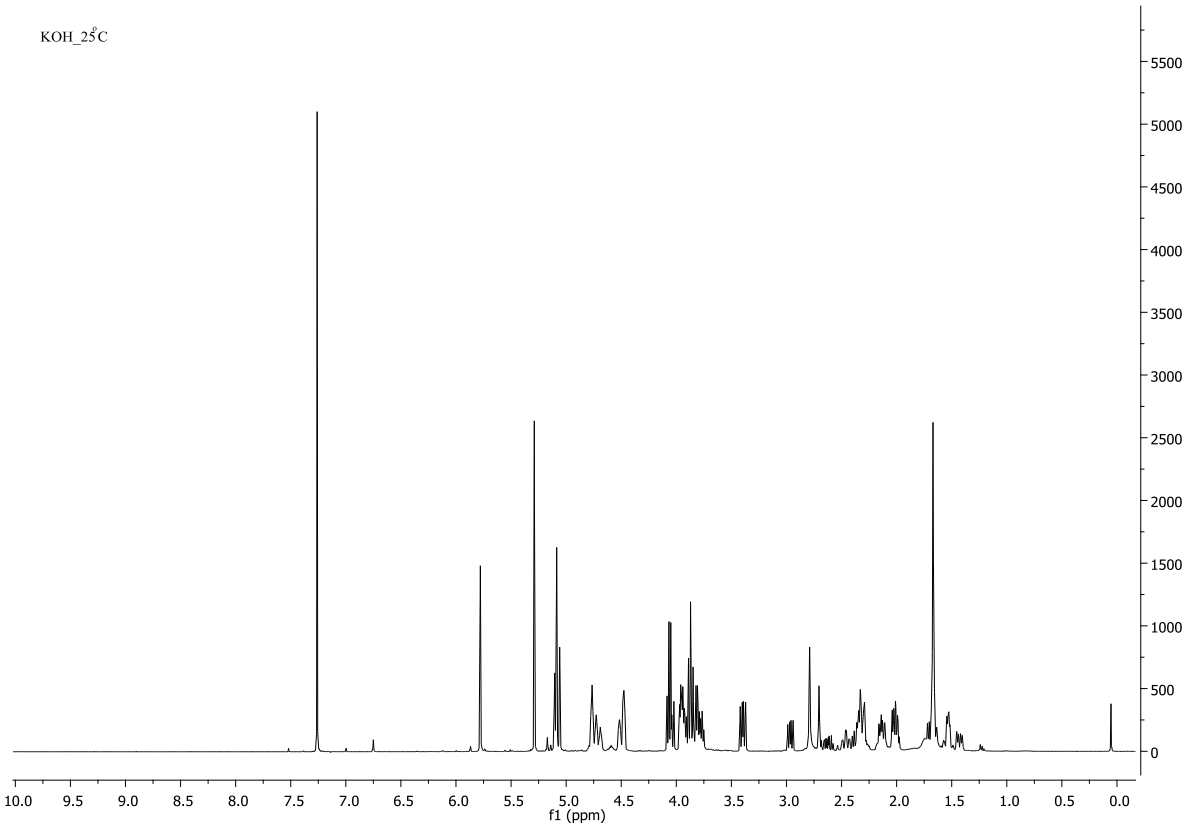
DBU 50 °C



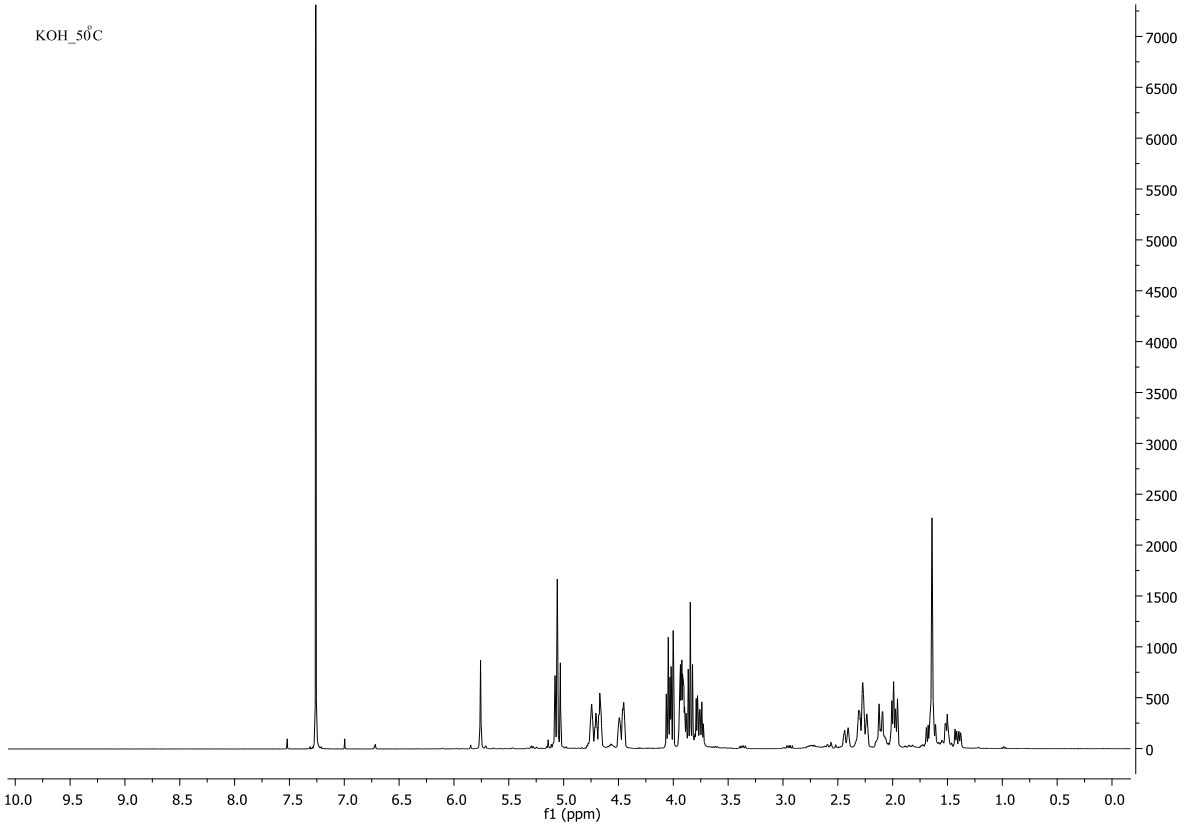
DBU 100 °C



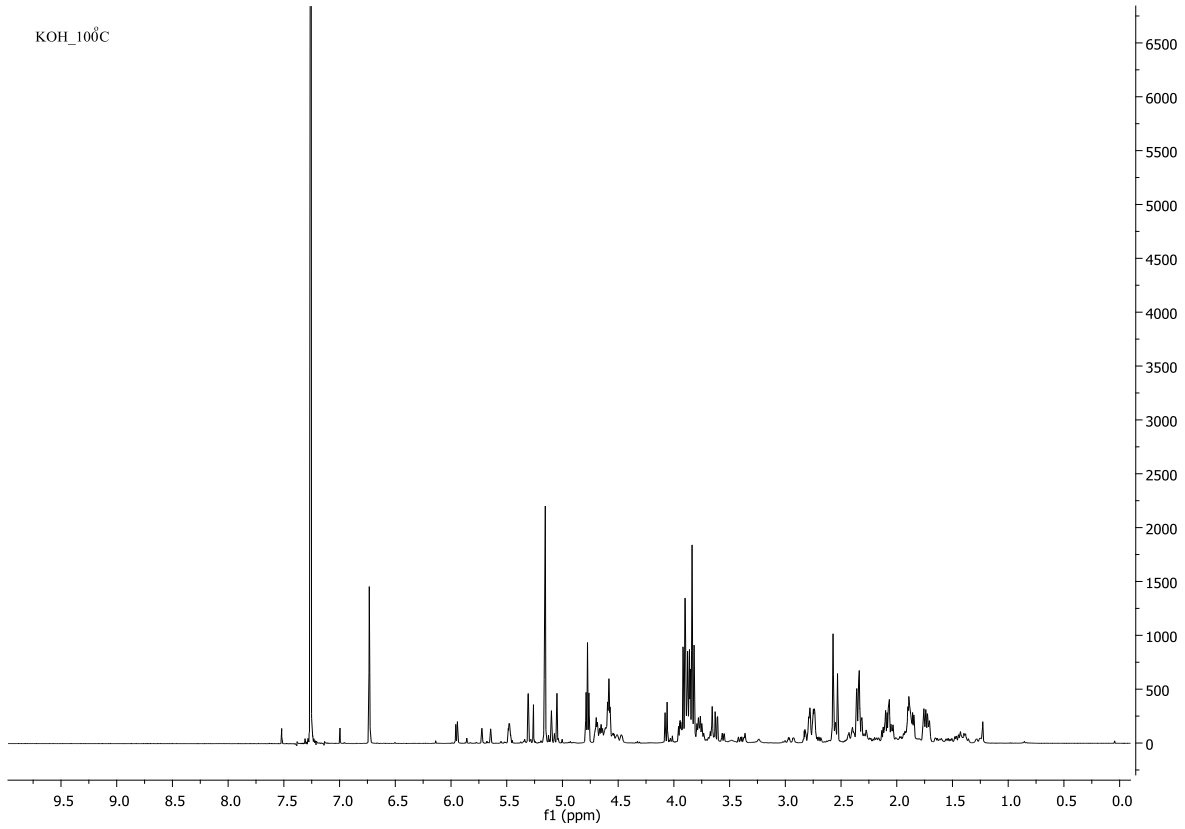
KOH 25 °C



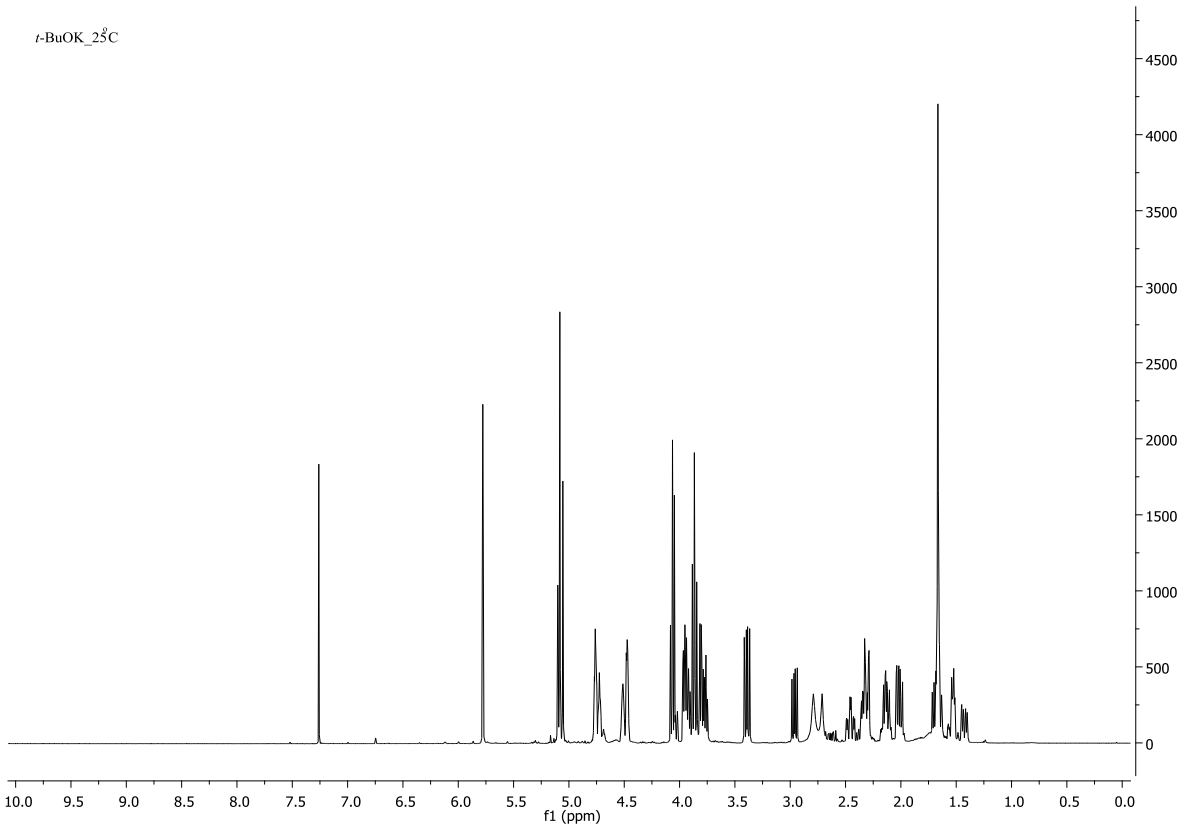
KOH 50 °C



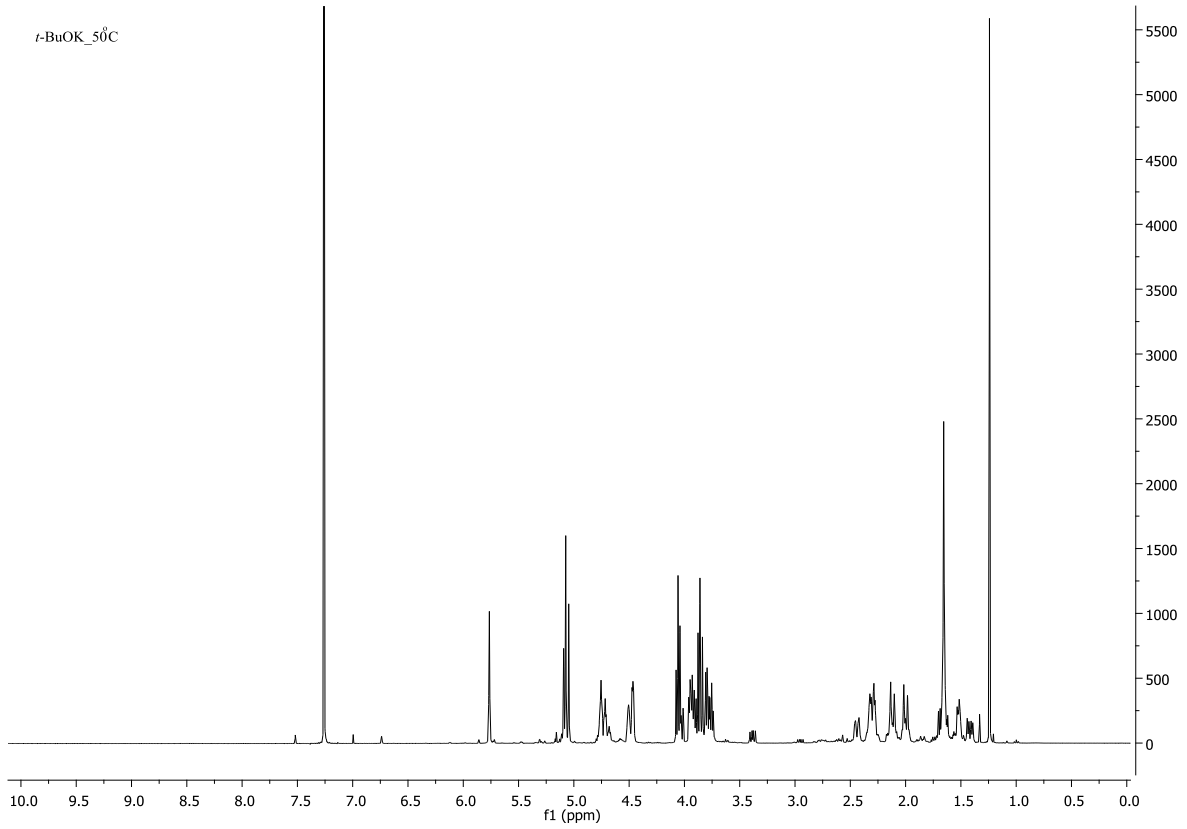
KOH 100 °C



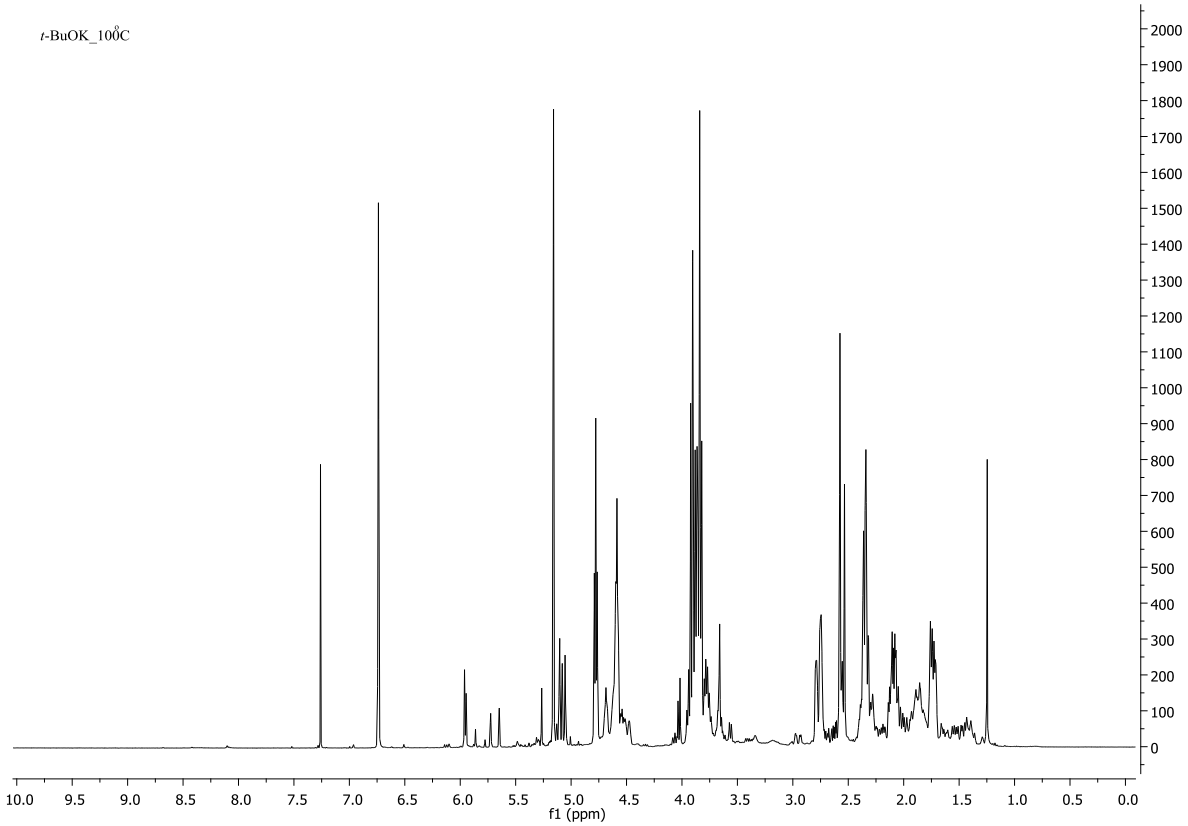
t-BuOK 25 °C



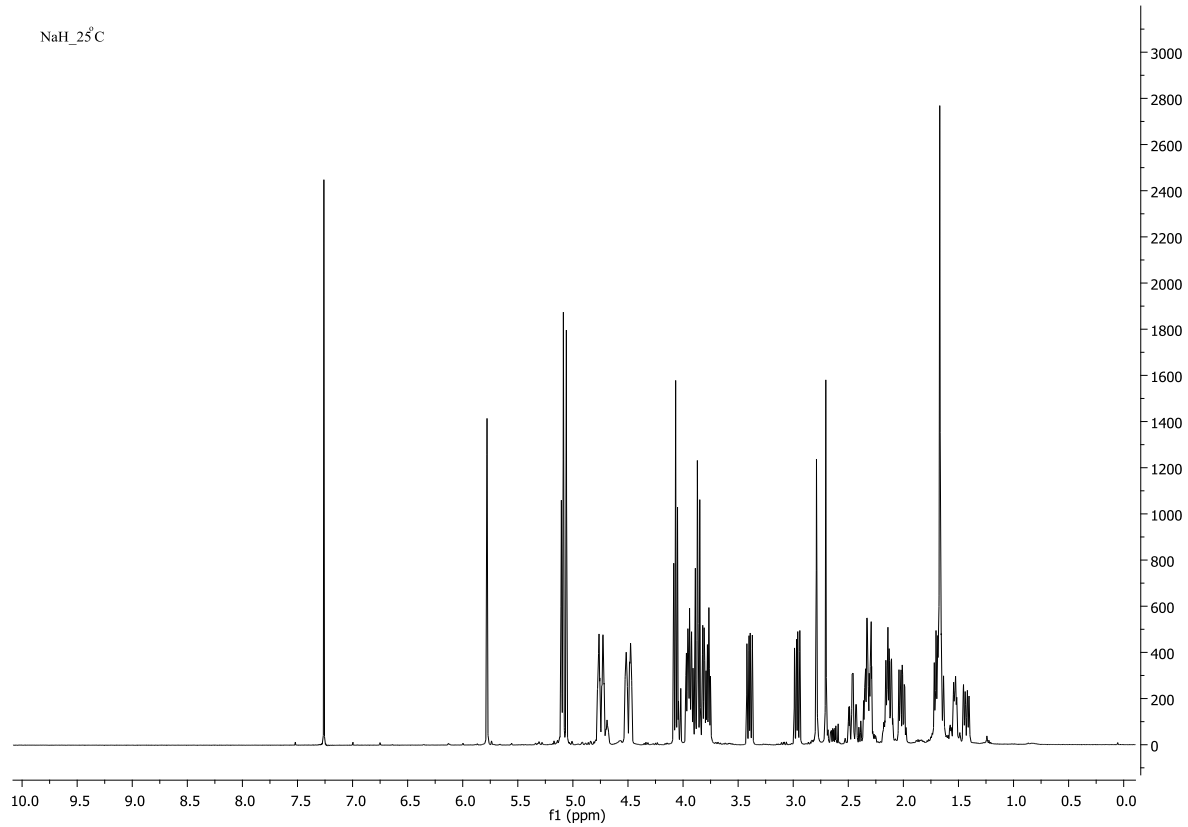
t-BuOK 50 °C



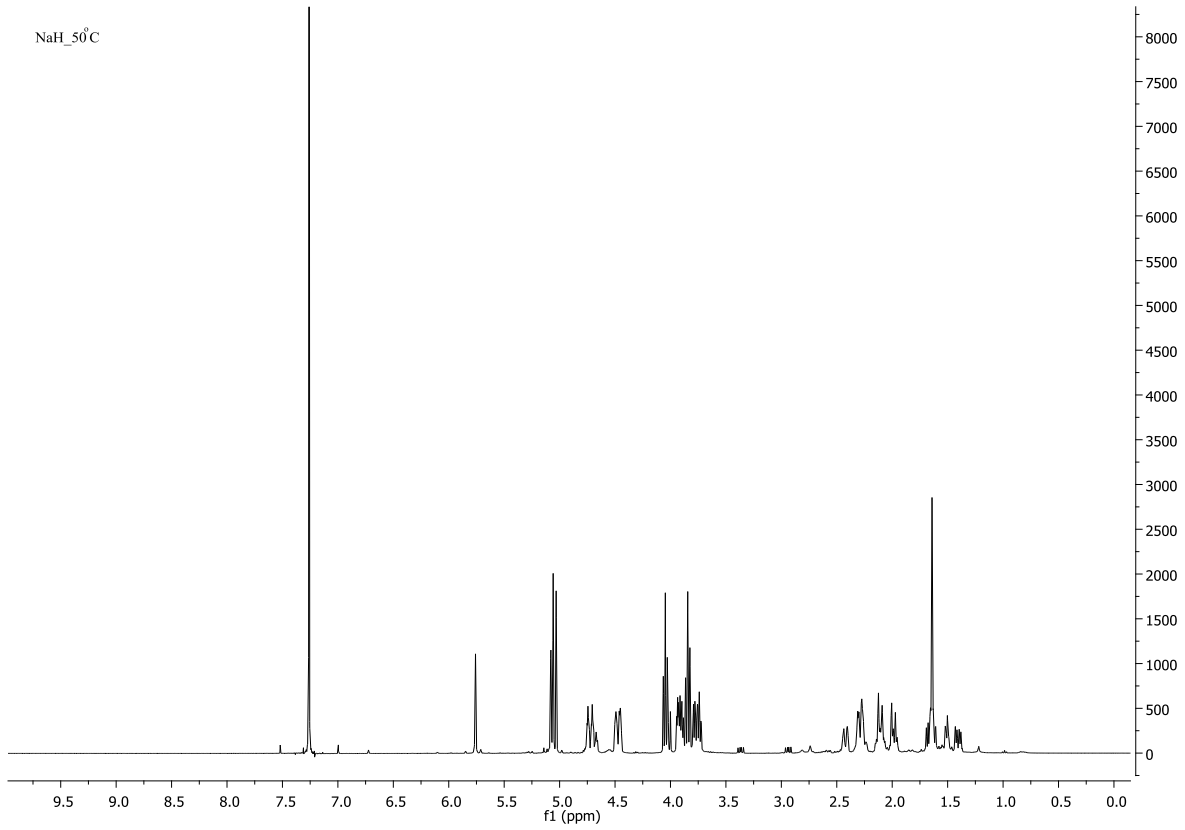
t-BuOK 100 °C



NaH 25 °C



NaH 50 °C



NaH 100 °C