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Zinc–gold cooperative catalysis for the direct alkynylation of benzofurans

Yifan Li and Jérôme Waser*

Letter

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Address:
Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH4306, 1015 Lausanne, Switzerland

Email:
Jérôme Waser* - jerome.waser@epfl.ch

* Corresponding author

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Abstract

The direct alkynylation of benzofurans was achieved for the first time using the hypervalent iodine reagent 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) based on the cooperative effect between a gold catalyst and a zinc Lewis acid. High selectivity was observed for C2-alkynylation of benzofurans substituted with alkyl, aryl, halogen and ether groups. The reaction was also successful in the case of the more complex drug 8-methoxypsoralen (8-MOP).

Introduction

Benzofurans are important heterocycles frequently encountered in both bioactive compounds and organic materials (Figure 1). For example, members of the furocoumarin class of natural products including psoralen (**1**), 8-methoxypsoralen (**2**) and angelicin (**3**) can cross-link with DNA upon light irradiation. They have consequently been used for the treatment of skin diseases such as cancer or psoriasis [1-4]. The natural product coumestrol (**4**) is found especially in soy beans and has estrogenic activity [5]. Synthetic bioactive compounds containing benzofurans are also important, as exemplified by amiodarone (**5**), as antiarrythmic drug [6,7]. Finally, benzofurans have also emerged recently as important structural elements for organic materials, such as the organic transistor **6** [8].

Due to the importance of benzofurans, the discovery of new efficient methods for their synthesis and functionalization is an intensive field of research [9-11]. Especially interesting would be methods allowing the direct and regioselective C–H functionalization of benzofurans [12]. In this context, the introduction of an alkyne would be particularly useful, as acetylenes are important building blocks in synthetic chemistry, chemical biology and materials science [13]. Nevertheless, to the best of our knowledge, the direct alkynylation of benzofurans is still an unknown process.

Since 2009, our group has developed a mild gold-catalyzed [14-17] method for the alkynylation of electron-rich aryls such as

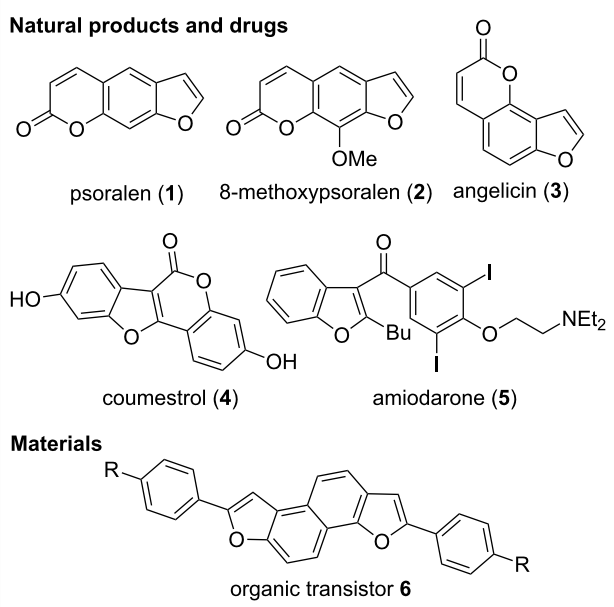


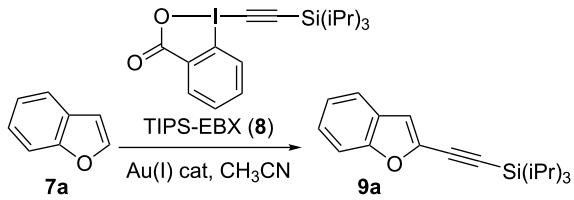
Figure 1: Benzofurans in bioactive compounds and materials.

indoles and pyrroles [18], thiophenes [19], anilines [20] and furans [21]. Key for success was the use of ethynylbenziodoxolones, which are cyclic hypervalent iodine reagents [22,23]. Nevertheless, the conditions we have used for other heterocycles gave only very low yields in the case of benzofurans. Herein, we would like to report the first catalytic direct C2-alkynylation of benzofurans **7** based on a cooperative effect between a gold catalyst and a zinc Lewis acid using 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **8**) as reagent (Scheme 1). The reaction proceeded under mild conditions (60 °C under air) and could also be used to alkynylate the more complex polycyclic natural product 8-methoxypsoralen (**2**).

Findings

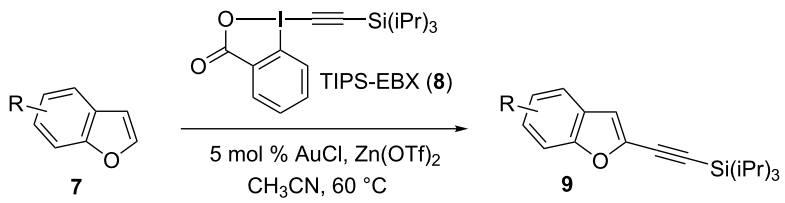
Benzofuran (**7a**) is less reactive then furans and indeed no product was observed under the conditions optimized for the latter [21] at room temperature or at 60 °C using the commercially available electrophilic alkynylation reagent TIPS-EBX (**8**) (Table 1, entries 1 and 2) [24-27]. Fortunately, benzofuran (**7a**) was also more stable in the presence of acidic additives, and co-activation became possible, whereas $Zn(OTf)_2$ was superior to trifluoroacetic acid (TFA) at 60 °C (Table 1, entries 3 and 4) [19,28]. No product was observed in the absence of AuCl, demonstrating the cooperative effect of the two metals (Table 1, entry 5). Lower or higher temperatures did not increase the yield (Table 1, entries 6 and 7). Finally, using a larger excess of TIPS-EBX (**8**) and $Zn(OTf)_2$ gave 75% yield of alkynylation product **9a** (Table 1, entry 8). The use of $Zn(OTf)_2$ in catalytic amount led to a lower yield (Table 1, entry 9), and a larger excess resulted in decomposition of the starting material only (Table 1, entry 10). Although other Lewis acids could also be used (Table 1, entries 11 and 12) [29], no better results than with $Zn(OTf)_2$ were obtained (Table 1, entry 7). Importantly, in contrast to our previous work with benzothiophenes [19], high selectivity for C2 alkynylation was observed.

Table 1: Optimization of the alkynylation of benzofuran (**7a**).



Entry[a]	Equiv **8**	Additive[b]	*T* [°C]	Yield
1	1.2	–	23	<5%
2	1.2	–	60	<5%
3	1.2	TFA	60	42%
4	1.2	$Zn(OTf)_2$	60	56%
5	1.2	$Zn(OTf)_2$[c]	60	<5%
6	1.2	$Zn(OTf)_2$	40	48%
7	1.2	$Zn(OTf)_2$	82	36%
8	2	$Zn(OTf)_2$	60	75%
9	2	$Zn(OTf)_2$[d]	60	37%
10	2	$Zn(OTf)_2$[e]	60	0%
11	2	$Zn(NTf)_2$	60	57%
12	2	$Yb(OTf)_3$	60	62%

[a]Reaction conditions: **7a** (0.20 mmol) and AuCl (0.01 mmol) in acetonitrile (0.8 mL) under air for 26 h, isolated yield; [b]same amount as **8**; [c]without gold catalyst; [d]0.2 equiv; [e]4.0 equiv.

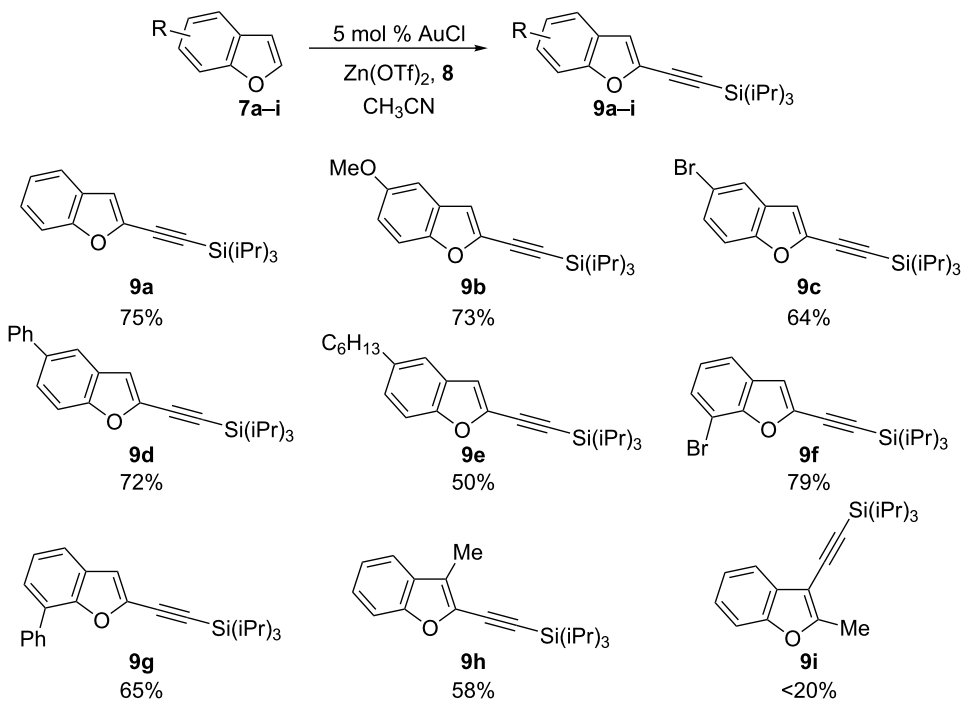


Scheme 1: Zinc–gold catalyzed C2-alkynylation of benzofurans.

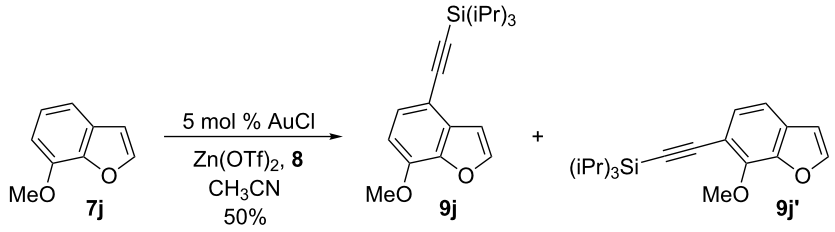
The scope of the reaction was then investigated (Scheme 2). Substitution by diverse functional groups was first examined on the C5 position. An electron-rich methoxy group was well tolerated, giving the desired alkynylation product **9b** in 73% yield. The reaction was also successful with a bromide substituent (product **9c**), making the method orthogonal to classical cross-coupling chemistry [30]. In presence of an aryl or an alkyl substituent, alkynylation was also obtained in 72% and 50% respectively (products **9d** and **9e**). Benzofurans substituted at the C7 position could also be used, as demonstrated by the efficient formation of alkynes **9f** and **9g**. In contrast, when 7-methoxybenzofuran (**7j**) was used, no C2 alkynylation product could be isolated. Instead, a mixture of C4 and C6 alkynylated benzofurans **9j** and **9j**' was obtained (Scheme 3) [31]. Substitution on the furan ring was also possible at the C3 position (product **9h**), but the use of 2-methylbenzofuran (**7i**) led to very a low yield in the alkynylation reaction.

Finally, we wondered if the alkynylation method could also be successful in the case of more complex benzofuran-containing natural products and drugs. We were pleased to see that the alkynylation of 8-methoxypsoralen (**2**) was indeed possible. The major product **10** bearing the acetylene group at the C5' position was obtained in 37% yield (Scheme 4) [32]. Although the yield was still moderate, this was one of the first examples of direct alkynylation of a marketed drug. It also gave access in a single step to an interesting furocoumarin derivative with an extended chromophore, which could be important for phototherapy.

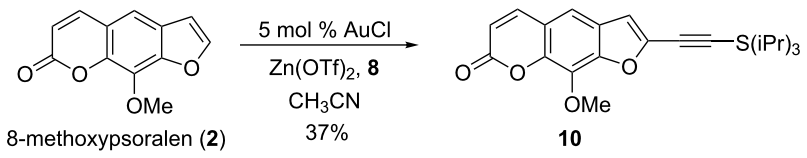
Mechanistically, the reaction could proceed either via π-activation of the triple bond by the gold catalyst followed by conjugate addition of the benzofuran, α-elimination and 1,2-shift, or oxidative addition of TIPS-EBX (**8**) onto the gold catalyst (either at the Au(I) or Au(0) oxidation level) followed by elec-



Scheme 2: Scope of the reaction.



Scheme 3: Alkynylation of 7-methoxybenzofuran (**7j**) [31].



Scheme 4: Alkynylation of 8-methoxypsoralen (**2**).

trophilic auration and reductive elimination [33]. The role of the zinc Lewis acid is not completely clear at this stage, but it may act by complexing the carboxylate group of the hypervalent iodine reagent, enhancing its electrophilic reactivity [19,34]. In fact, a complete shift of the ^{1}H NMR signals of TIPS-EBX (**8**) was observed when $Zn(OTf)_2$ was added, whereas no signal shift was observed when mixing the Lewis acid and benzofuran (**7a**) [35].

In conclusion, the first direct alkynylation method of benzofurans has been developed. Key for success was a cooperative effect between a gold catalyst and a zinc Lewis acid, together with the use of the hypervalent iodine reagent TIPS-EBX (**8**). Preliminary results obtained with 8-methoxypsoralen (**2**) demonstrated that the reaction could also be applied to more complex furocoumarin natural products.

Experimental

General procedure for the alkynylation of benzofurans: TIPS-EBX (**8**, 342 mg, 0.800 mmol, 2.0 equiv), AuCl (4.6 mg, 0.020 mmol, 0.050 equiv), $Zn(OTf)_2$ (289 mg, 0.800 mmol, 2.0 equiv) and benzofuran **7** (0.40 mmol, 1.0 equiv) were added into CH_3CN (2.0 mL) under air. The mixture was stirred for 26 hours at 60 °C. Then the mixture was concentrated in presence of silica gel and purified directly by column chromatography.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-204-S1.pdf]

Acknowledgements

The EPFL and F. Hoffmann-La Roche Ltd are acknowledged for financial support.

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See for a review on electrophilic alkynylation.
28. Wang, Y.; Liu, L.; Zhang, L. *Chem. Sci.* **2013,** *4,* 739. doi:10.1039/c2sc21333h
See for a recent example of cooperative gold-zinc catalysis.
29. See Supporting Information for a full list of tested Lewis acids.
30. No product was obtained with strongly electron-withdrawing substituents, such as cyanide.
31. A 5:1 mixture of non-separable products was obtained, which prevented complete assignment of the structure of the major regioisomer.
32. The regiochemistry of the alkynylation was determined by 2D NMR experiments after removal of the silyl protecting group on alkyne **10**. One other non-identified isomer was observed in the crude mixture by 1H NMR (yield < 5%).
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35. See Figure S1 in the Supporting Information File 1.

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Supporting information

Zinc-Gold Cooperative Catalysis for the Direct Alkynylation of Benzofurans

Yifan Li[1] and Jérôme Waser*[1]

Address: [1] Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH4306, 1015 Lausanne, Switzerland

Email: Jérôme Waser – Jerome.waser@epfl.ch

* Corresponding author

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1. General Methods

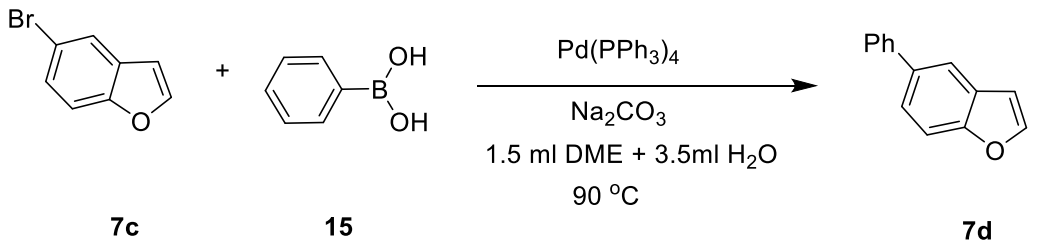
All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, *Karl-Fischer* titration). NEt_3 and pyridine were distilled under nitrogen from KOH. Gold chloride was purchased from Aldrich and kept in desiccator under anhydrous condition (decrease of reactivity has been observed for catalyst if prolonged exposition to air (*ca* 1 month). The solvents were degassed by Freeze-Pump-Thaw method when mentioned. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure.TLC was performed on Merck silica gel 60 F_{254} TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation).^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elemer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

2. Preparation of Reagents

TIPS-EBX is commercially available, or can be synthesized using a reported procedure.[1]

3. Synthesis of Starting Materials.

5-Phenylbenzofuran (7d)



A schlenk tube was charged with boronic acid **15** (152 mg, 1.25 mmol, 1.25 equiv), $Pd(PPh_3)_4$ (57.5 mg, 0.0500 mmol, 0.05 equiv) , Na_2CO_3 (265 mg, 2.50 mmol, 2.50 equiv), DME (1.5 mL) and H_2O (3.5 mL). After degassing the mixture, 5-bromobenzofuran **(7c)** (196 mg, 1.00 mmol, 1.0 equiv) was added. The mixture was heated to 90 ^oC and stirred overnight under N_2. Then, the mixture was filtered through a plug of celite, and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with 1 M NaOH (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; Pentane) to afford **7d** as a white solid (174 mg, 0.900 mmol, 90%).

R_f (Pentane): 0.6.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 1 H, *J* = 1.4 Hz; *FuranH*), 7.68 (d, 1 H, *J* = 2.2 Hz; *ArH*), 7.65 (dd, 2 H, *J* = 8.5, 1.3 Hz, *ArH*), 7.60 (d, 1 H, *J* = 8.5 Hz; *ArH*), 7.56 (dd, 1 H, *J* = 8.6, 1.3 Hz, *ArH*), 7.48 (t, 2 H, *J* = 7.4 Hz, *ArH*), 7.38 (t, 1H, *J* = 7.4 Hz; *ArH*) 6.84 (d, 1 H, *J* = 1.4 Hz; *FuranH*) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 145.6, 141.6, 136.4, 128.7, 127.9, 127.4, 126.8, 123.9, 119.7, 111.5, 106.8. The NMR data corresponds to the literature.[2]

5-Hexylbenzofuran (7e)

[1] J. P. Brand, J. Waser, *Synthesis* **2012**, *44*, 1155.
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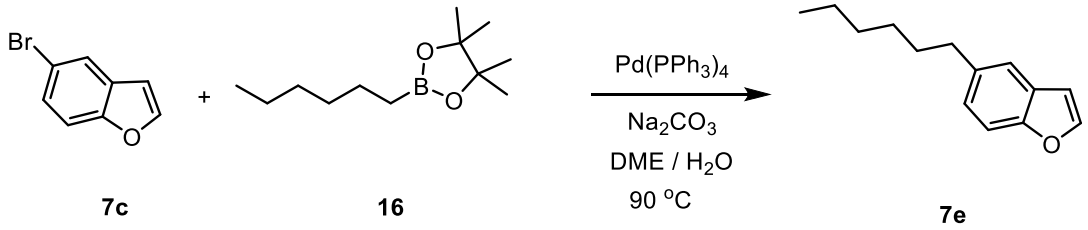
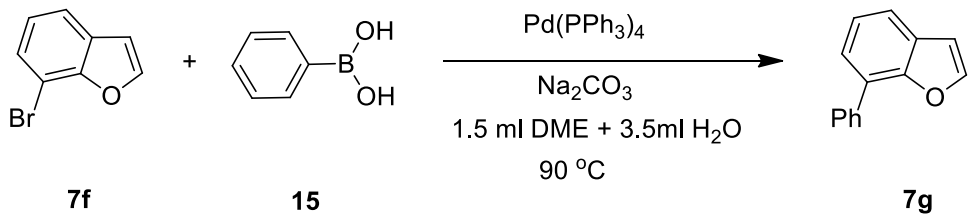


A schlenk tube was charged with boronic ester **16** (170 mg, 0.800 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (46.2 mg, 0.0500 mmol, 0.05 equiv), Na_2CO_3 (85 mg, 2.5 mmol, 1.0 equiv), DME (1.0 mL) and H_2O (2.5 mL). After degassing the mixture, 5-bromobenzofuran (**7c**) (173 mg, 0.880 mmol, 1.1 equiv) was added. The mixture was heated to 90 °C and stirred overnight under N_2. Then, the mixture was filtered through a plug of celite, and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with 1 M NaOH (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; Pentane) to afford **7e** as a colorless oil (77 mg, 0.38 mmol, 48%).

R_f (Pentane): 0.5.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 1 H, *J* = 2.2 Hz, *FuranH*), 7.41 (m, 2 H, *ArH*), 7.12 (dd, 1 H, *J* = 8.4, 1.7 Hz, *ArH*), 6.72 (dd, 1 H, *J* = 2.2, 0.8 Hz, *FuranH*), 2.70 (m, 2 H, *HexylH*), 1.65 (m, 2 H, *HexylH*), 1.40-1.26 (m, 6 H, *HexylH*), 0.90 (t, 3 H, *J* = 7.0 Hz, *HexylH*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 144.9, 137.4, 127.4, 124.9, 120.3, 110.8, 106.4, 35.9, 32.1, 31.7, 29.0, 22.6, 14.1. IR 2956 (m), 2928 (s), 2857 (m), 2362 (w), 1697 (w), 1468 (s), 1331 (w), 1263 (m), 1197 (w), 1130 (m), 1113 (w), 1034 (w), 910 (w), 885 (w), 810 (m), 764 (m), 737 (s). Anal. calcd. for $C_{14}H_{18}O$: C, 83.12%;

H, 8.97%. Found: C, 83.24%; H, 8.89%.

7-Phenylbenzofuran (7g)



A schlenk tube was charged with boronic acid (**15**) (89 mg, 0.73 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (42 mg, 0.050 mmol, 0.05 equiv) , Na_2CO_3 (77 mg, 0.73 mmol, 1.0 equiv), DME (1.0 mL) and H_2O (2.5 mL). After degassing the mixture, 7-bromobenzofuran (**7f**) (158 mg, 0.880 mmol, 1.1 equiv) was added. The mixture was heated to 90 °C and stirred overnight under N_2. Then, the mixture was filtered through a plug of celite, and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with 1 M NaOH (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; Pentane) to afford **7g** as a colorless oil (126 mg, 0.649 mmol, 89%).

R_f (Pentane): 0.3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2 H, *ArH*), 7.72 (d, 1 H, *J* = 2.2 Hz, *FuranH*), 7.63 (dd, 1 H, *J* = 7.7, 1.1 Hz, *ArH*), 7.55 (m, 2 H, *ArH*), 7.51 (dd, 1 H, *J* = 7.5, 1.1 Hz, *ArH*), 7.44 (m, 1 H, *ArH*), 7.37 (m, 1 H, *ArH*), 6.87 (d, 1 H, *J* = 2.2 Hz, *FuranH*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 145.0, 136.5, 128.6, 128.5, 128.1, 127.6, 125.6, 123.8, 123.3, 120.4, 106.7. The NMR data corresponds to the literature.[3]

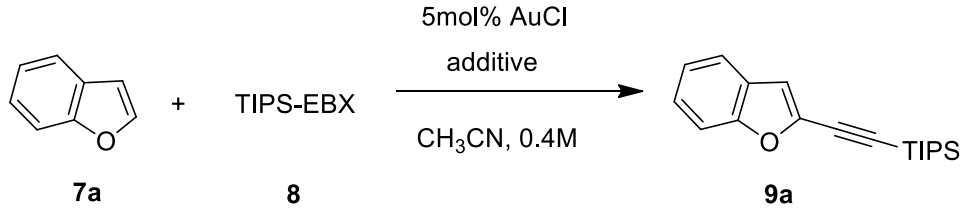
[3] Otterlo, W.; Morgans, G.; Lee, M.; Kuzvidza, S.; Moleele, S.; Thornton, N.; Koning, C. T, Teth, *Tetrahedron*, **2005** , *61*, 7746.

4. Alkynylation Reactions

Optimization of the reaction:

General procedure:

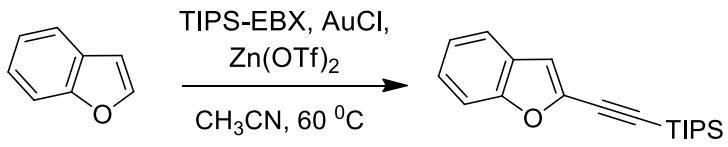
TIPS-EBX (**8**), AuCl (2.3 mg, 0.010 mmol, 0.050 equiv), additives were added into a solution of benzofuran (23.6 mg 0.200 mmol, 1.0 equiv) in CH_3CN under air. Then the mixture was concentrated with silica gel and purified by column chromatography directly.



Equiv of TIPS-EBX	Additive	Temp (°C)	Yield (%)
1.2	-	RT	0
1.2	-	60	0
1.2	1.2eq $Zn(OTf)_2$	RT	22
1.2	1.2eq $Zn(OTf)_2$	60	56
1.2	1.2eq $Zn(OTf)_2$	40	48
1.2	1.2eq $Zn(OTf)_2$	reflux	34
2	2.0eq $Zn(OTf)_2$	60	75
2	2.0eq $Zn(OTf)_2$	60 (0.1M)	34
2	2.0eq $Zn(OTf)_2$	60 (0.8M)	68
2	2.0eq TFA	60	34
2	2.0eq $Zn(BF_4)_2$	60	0
2	0.2eq $Zn(OTf)_2$	60	37
2	4.0 eq. $Zn(OTf)_2$	60	0
2	2.0eq $Zn(NTf_2)_2$	60	57
2	2.0eq $Yb(OTf)_3$	60	62
2	2.0eq $Zn(CF_3COO)_2$	60	17
2	2.0eq $ZnBr_2$	60	trace
2	2.0eq $Zn(CH_3COO)_2$	60	9

General procedure (GP): TIPS-EBX (**8**) (342 mg, 0.800 mmol, 2.0 equiv), AuCl (4.6 mg, 0.020 mmol, 0.050 equiv), $Zn(OTf)_2$ (289 mg, 0.800 mmol, 2.0 equiv) and benzofuran derivatives **7** (0.40 mmol, 1.0 equiv) were added into CH_3CN (2.0 mL) under air. The mixture was stirred for 26 hours at 60 °C. Then the mixture was concentrated with silica gel and purified by column chromatography directly.

(Benzofuran-2-ylethynyl)triisopropylsilane (9a)

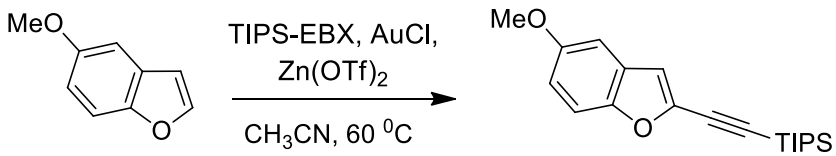


7a **9a**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane) to afford **9a** as a yellow oil (90 mg, 0.30 mmol, 75%).

R_f (Pentane): 0.6.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 1 H, *J* = 7.8 Hz, *ArH*), 7.45 (m, 1 H, *ArH*), 7.33 (m, 1 H, *ArH*), 7.21 (m, 1 H, *ArH*), 6.95 (s, 1 H, *FuranH*), 1.15 (m, 21 H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 138.7, 127.5, 125.6, 123.2, 121.2, 111.9, 111.2, 98.7, 96.2, 18.6, 11.2; IR 2943 (s), 2865 (s), 2155 (w), 2154 (w), 1558 (w), 1490 (w), 1463 (m), 1449 (m), 1261 (w), 1181 (m), 1019 (w), 997 (m), 952 (w), 922 (w), 884 (s), 818 (w), 809 (w). HRMS (ESI) calcd for $C_{19}H_{26}OSi[M]^+$ 298.1753; found 298.1749.

Triisopropyl((5-methoxybenzofuran-2-yl)ethynyl)silane (9b)

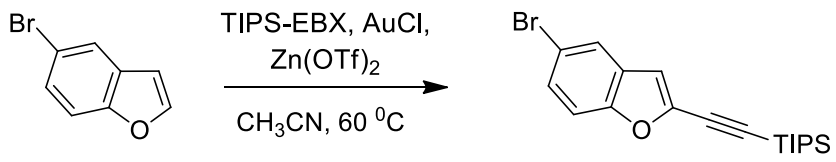


7b **9b**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane/DCM 100/1) to afford **9b** as a yellow oil (96 mg, 0.29 mmol, 73%).

R_f (Pentane/DCM 100/1): 0.2.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, 1 H, *J* = 8.8 Hz, *ArH*), 6.97 (d, 1 H, *J* = 2.5 Hz, *ArH*), 6.93 (dd, 1 H, *J* = 8.9, 2.6 Hz, *ArH*), 6.89 (s, 1 H, *FuranH*), 3.84 (s, 3 H, CH_3), 1.14 (m, 21 H, *TIPS*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.2, 149.6, 139.4, 128.0, 114.7, 112.0, 111.7, 103.0, 98.5, 96.3, 55.8, 18.6, 11.2; IR 2946 (s), 2945 (s), 2866 (m), 2363 (w), 2156 (w), 1617 (w), 1470 (s), 1299 (w), 1254 (w), 1210 (s), 1184 (m), 1032 (w), 997 (w), 956 (w), 883 (w). HRMS (ESI) calcd for $C_{20}H_{29}O_2Si^+$ $[M+H]^+$ 329.1931; found 329.1917.

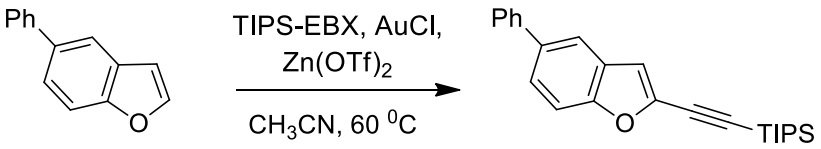
((5-Bromobenzofuran-2-yl)ethynyl)triisopropylsilane (9c)



7c **9c**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane) to afford **9c** as a yellow oil (96 mg, 0.26 mmol, 64%).

R_f (Pentane): 0.7.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1 H, *J* = 1.9 Hz, *ArH*), 7.41 (dd, 1 H, *J* = 8.7, 1.9 Hz, *ArH*), 7.31 (d, 1 H, *J* = 8.7 Hz, *ArH*), 6.88 (s, 1 H, *FuranH*), 1.15 (m, 21 H, *TIPS*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 139.9, 129.5, 128.5, 123.7, 116.3, 112.7, 111.1, 99.7, 95.6, 18.6, 11.2; IR 2945 (s), 2866 (s), 2362 (m), 2337 (w), 2159 (w), 1458 (s), 1321 (w), 1258 (w), 1206 (w), 1180 (s), 1070 (w), 1057 (w), 1015 (w), 997 (w), 952 (w), 881 (m). HRMS (ESI) calcd for $C_{38}Br_2H_{51}O_2Si_2^+$ $[M]^+$ 753.1789; found 753.1802.

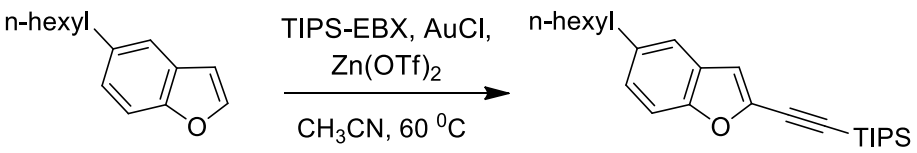


7d **9d**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane/Et_2O 100/1) to afford **9d** as a colorless oil (106 mg, 0.290 mmol, 72%).

R_f (Pentane/Et_2O 100/1): 0.7.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, 1 H, *J* = 1.8, 0.6 Hz, *ArH*), 7.60 (m, 2 H, *ArH*), 7.56 (dd, 1 H, *J* = 8.6, 1.9 Hz, *ArH*), 7.47 (m, 3 H, *ArH*), 7.34 (m, 1 H, *ArH*), 6.99 (d, 1 H, *J* = 0.9 Hz, *FuranH*), 1.17 (m, 21 H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 141.3, 139.3, 136.9, 128.8, 128.1, 127.4, 127.0, 125.4, 119.5, 112.1, 111.3, 98.9, 96.1, 18.6, 11.2; IR 2945 (s), 2866 (s), 2363 (w), 2158 (w), 1462 (s), 1257 (w), 1240 (w), 1179 (m), 1073 (w), 1015 (w), 998 (w), 954 (w), 884 (m), 814 (w). HRMS (ESI) calcd for $C_{25}H_{30}OSi$ [M+] 374.2066; found . 374.2057.

((5-Hexylbenzofuran-2-yl)ethynyl)triisopropylsilane (9e)

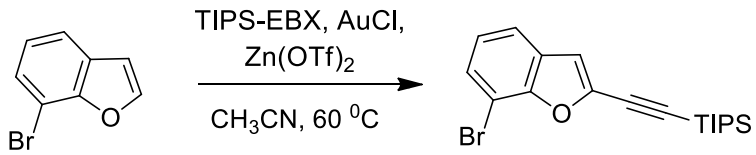


7e **9e**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane) to afford **9e** as a colorless oil (77 mg, 0.20 mmol, 50%).

R_f (Pentane): 0.6.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 1 H, *J* = 8.4, *ArH*), 7.32 (d, 1 H, *J* = 0.9 Hz, *ArH*), 7.14 (dd, 1 H, *J* = 8.4, 1.7 Hz, *ArH*), 6.89 (d, 1 H, *J* = 0.9 Hz, *FuranH*), 2.67 (t, 2 H, *J* = 7.5 Hz, *HexylH*), 1.63 (m, 2 H, *HexylH*), 1.36-1.26 (m, 6 H, *HexylH*), 1.14 (m, 21 H, *TIPS*), 0.88 (t, 3 H, *J* = 6.8 Hz, *HexylH*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 138.7, 137.9, 127.5, 126.4, 120.2, 111.8, 110.7, 98.3, 96.4, 35.8, 32.0, 31.7, 28.9, 22.6, 18.6, 14.1, 11.2. IR 2946 (m),), 2868 (m), 2361 (s), 2157 (w), 2114 (w), 1758 (w), 1727 (w), 1467 (w), 1264 (w), 1233 (w), 1195 (w), 995 (w), 884 (w), 812 (w), 729 (m). HRMS (ESI) calcd for $C_{25}H_{39}OSi^+$ $[M+H]^+$ 383.2765; found 383.2782.

((7-Bromobenzofuran-2-yl)ethynyl)triisopropylsilane (9f)

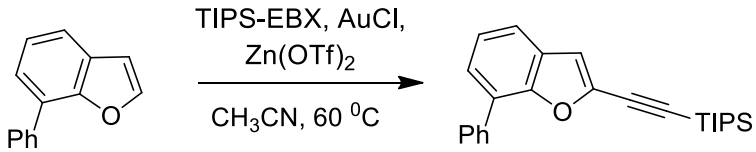


7f **9f**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane) to afford **9f** as a colorless oil (119 mg, 0.316 mmol, 79%).

R_f (Pentane): 0.4.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 4.9, 1.0 Hz, *ArH*), 7.47 (dd, 1 H, *J* = 4.9, 1.0 Hz, *ArH*), 7.11 (t, 1 H, *J* = 7.8 Hz, *ArH*), 7.00 (s, 1 H, *FuranH*), 1.19 (m, 21 H, *TIPS)*. ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 139.5, 128.8, 128.5, 124.5, 120.2, 112.6, 103.9, 99.9, 95.5, 18.6, 11.2. IR 2945 (m), 2866 (m), 2361 (w), 2158 (w), 1579 (w), 1465 (w), 1417 (w), 1304 (w), 1223 (w), 1176 (m), 1137 (w), 1018 (w), 927 (m), 912 (w), 884 (w), 815 (w), 769 (w), 737 (s). HRMS (ESI) calcd for $C_{38}Br_2H_{51}O_2Si_2^+$ $[2M+H]^+$ 753.1789; found 753.1825.

Triisopropyl((7-phenylbenzofuran-2-yl)ethynyl)silane (9g)

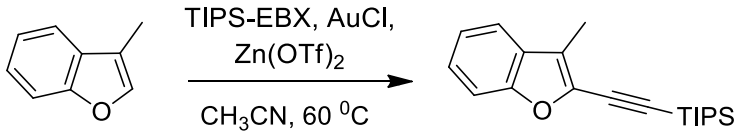


7g **9g**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane) to afford **9g** as a colorless oil (98 mg, 0.26 mmol, 65%).

R_f (Pentane): 0.3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2 H, *ArH*), 7.50 (m, 4 H, *ArH*), 7.40 (m, 1 H, *ArH*), 7.32 (t, 1 H, *J* = 7.6 Hz, *ArH*), 7.02 (s, 1 H, *FuranH*), 1.16 (m, 21 H, *TIPS*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8, 138.9, 136.2, 128.7, 128.6, 128.4, 127.7, 125.4, 125.1, 123.8, 120.2, 112.3, 98.8, 96.3, 18.6, 11.2. IR 2945 (s), 2892 (w), 2866 (s), 2361 (s), 2156 (w), 1730 (w), 1685 (w), 1564 (w), 1465 (m), 1409 (w), 1249 (w), 1210 (m), 1171 (w), 1017 (w), 998 (w), 956 (w), 912 (w), 884 (m), 820 (w), 757 (s). HRMS (ESI) calcd for $C_{25}H_{31}OSi^+$ $[M+H]^+$ 375.2139; found 375.2142.

Triisopropyl((3-methylbenzofuran-2-yl)ethynyl)silane (9h)

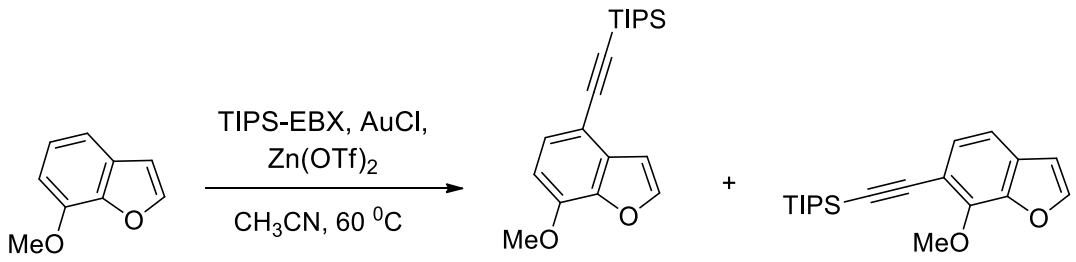


7h **9h**

Following a slightly modified version of **GP**, TIPS-EBX (**8**) (514 mg, 1.20 mmol, 3.0 equiv) and $Zn(OTf)_2$ (434 mg, 1.20 mmol, 3.0 equiv) were used. The crude product was purified by flash column chromatography (SiO_2; Pentane) to afford **9h** as a colorless oil (72 mg, 0.23 mmol, 58%).

R_f (Pentane): 0.5.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1 H, *J* = 7.7 Hz *ArH*), 7.45 (d, 1 H, *J* = 8.0 Hz *ArH*), 7.36 (t, 1 H, *J* = 8.0 Hz *ArH*), 7.29 (d, 1 H, *J* = 9.0 Hz *ArH*), 2.37 (s, 3 H, CH_3), 1.19 (m, 21 H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 136.0, 128.7, 125.6, 122.7, 121.9, 119.6, 111.2, 100.8, 95.8, 18.6, 11.2, 8.9; IR 2943 (m), 2865 (m), 2154 (w), 1745 (w), 1463 (m), 1449 (s), 1387 (w), 1353 (w), 1281 (w), 1250 (w), 1191 (s), 1116 (w), 1096 (m), 1071 (w), 1017 (w), 997 (w), 920 (w), 883 (s). HRMS (ESI) calcd for $C_{20}H_{29}OSi^+$ $[M+H]^+$ 313.1982; found 313.1981.

Triisopropyl((7-methoxybenzofuran-4-yl)ethynyl)silane (9j) + Triisopropyl((7-methoxybenzofuran-6-yl)ethynyl)silane (9j')

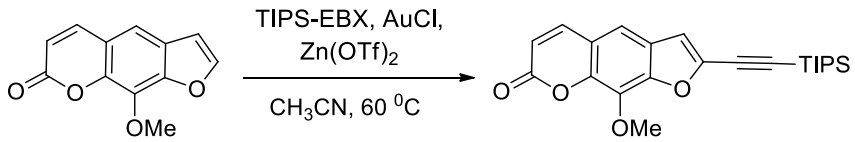


7j **9j** **9j'**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane/DCM 100/1) to afford an inseparable mixture of two isomers **9j** and **9j'** as yellow oil (66 mg, 0.20 mmol, 50%).

R_f (Pentane/DCM 100/1): 0.5.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 0.2 H, *J* = 2.1 Hz, *ArH* minor isomer), 7.58 (d, 1 H, *J* = 2.1 Hz, *ArH* major isomer), 7.32 (d, 0.2 H, *J* = 8.3 Hz, *FuranH*, minor isomer), 7.25 (d, 1 H, *J* = 8.3 Hz, *FuranH*, major isomer), 6.90 (d, 0.2 H, *J* = 2.1 Hz, *ArH* minor isomer), 6.82 (d, 1 H, *J* = 2.1 Hz, *ArH* major isomer), 6.67 (d, 0.2H, *J* = 8.3 Hz, *FuranH*, minor isomer), 6.66 (d, 1H, *J* = 8.3 Hz, *FuranH*, major isomer) 4.03 (s, 0.6 H, OCH_3, minor isomer), 4.02 (s, 3 H, OCH_3, major isomer), 1.16 (s, 21 H, *TIPS*, major isomer), 1.13 (s, 4 H, *TIPS*, minor isomer). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.8, 145.9, 145.8, 145.4, 143.4, 131.9, 131.4, 129.6, 127.9, 108.5, 106.9, 106.7, 106.5, 106.2, 104.5, 91.9, 89.7, 88.0, 76.1, 73.6, 56.2, 56.1, 29.7, 18.7, 18.6, 11.3. IR 2943 (s), 2865 (s), 2362 (m), 2147 (m), 1619 (m), 1584 (w), 1497 (s), 1464 (m), 1407 (w), 1336 (w), 1289 (s), 1258 (w), 1199 (w), 1176 (w), 1093 (m), 1044 (m), 915 (w), 882 (m). HRMS (ESI) calcd for $C_{20}H_{29}O_2Si^+$ $[M+H]^+$ 329.1931; found 329.1928.

2-((Triisopropylsilyl)ethynyl)-7H-furo[3,2-g]chromen-7-one (10)



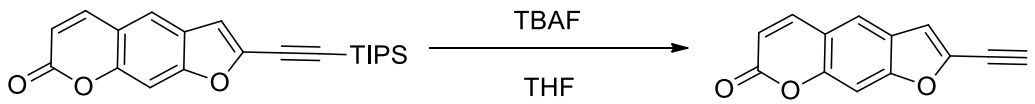
2 **10**

Following the conditions described in **GP**, the crude product was purified by flash column chromatography (SiO_2; Pentane/EA 10/1) to afford **10** as yellow oil (58 mg, 0.15 mmol, 37%).

Rf (Pentane/EA 10/1): 0.7.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 1 H, *J* = 9.7 Hz, *VinylH*), 7.71 (s, 1 H, *FuranH*), 6.94 (s, 1 H, *ArH*), 6.45 (d, 1 H, *J* = 9.7 Hz, *VinylH*), 4.33 (s, 3 H, CH_3), 1.18 (m, 21 H, *TIPS*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 146.9, 146.4, 142.9, 142.3, 133.4, 129.3, 117.8, 115.4, 106.9, 106.7, 100.4, 100.1, 61.4, 18.7, 11.2. IR 2944 (w), 2866 (w), 2146 (w), 1742 (s), 1587 (m), 1473 (m), 1423 (w), 1380 (w), 1310 (w), 1134 (s), 1046 (s), 1028 (w), 916 (w), 830 (w), 814 (w). HRMS (ESI) calcd for $C_{23}H_{28}NaO_4Si^+$ $[M+Na]^+$ 419.1649; found 419.1657.

2-Ethynyl-7H-furo[3,2-g]chromen-7-one (17)



10 **17**

290 μL TBAF (1M in THF, 0.29 mmol, 2.0 equiv) was added into a solution of **10** (53.0 mg, 0.145 mmol, 1.0 equiv) in 2 mL dry THF. The solution was kept overnight then was quenched with sat NH_4Cl (10 mL). The aqueous phase was extracted with DCM (3 × 5 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2; Pentane/EA 5/1) to afford **17** as yellow solid. The yellow solid was washed by pentane to get pure compround (8 mg, 0.04 mmol, 26%).

Rf: (Pentane/EA 10/1): 0.4

Melting point: 248-249 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 1 H, *J* = 9.6 Hz, *VinylH*), 7.32 (s, 1 H, *ArH*), 7.03 (s, 1 H, *FuranH*), 6.39 (d, 1 H, *J* = 9.6 Hz, *VinylH*), 4.30 (s, 3 H, CH_3), 3.56 (s, 1 H, *CH*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 147.4, 144.1, 144.0, 139.6, 132.5, 125.7, 117.0, 115.2, 113.0, 112.3, 84.7, 73.2, 61.4. IR 3203 (w), 2363 (w), 1713 (s), 1620 (w), 1468 (w), 1400 (w), 1324 (w), 1267 (w), 1237 (w), 1219 (w), 1164 (w), 1021 (w), 962 (w), 936 (w), 874 (w), 815 (m), 776 (w), 760 (w). HRMS (ESI) calcd for $C_{14}H_9O_4^+$ $[M+H]^+$ 241.0495; found 241.0491.

NMR Experiment

TIPS-EBX (**8**) (43 mg, 0.10 mmol) and $Zn(OTf)_2$ (36 mg, 0.10 mmol) were mixed in $CDCl_3$ (1 mL).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (m, 1 H, *ArH*), 8.20 (m, 1 H, *ArH*), 7.76 (m, 2 H, *ArH*), 1.18 (m, 21 H, *TIPS*).

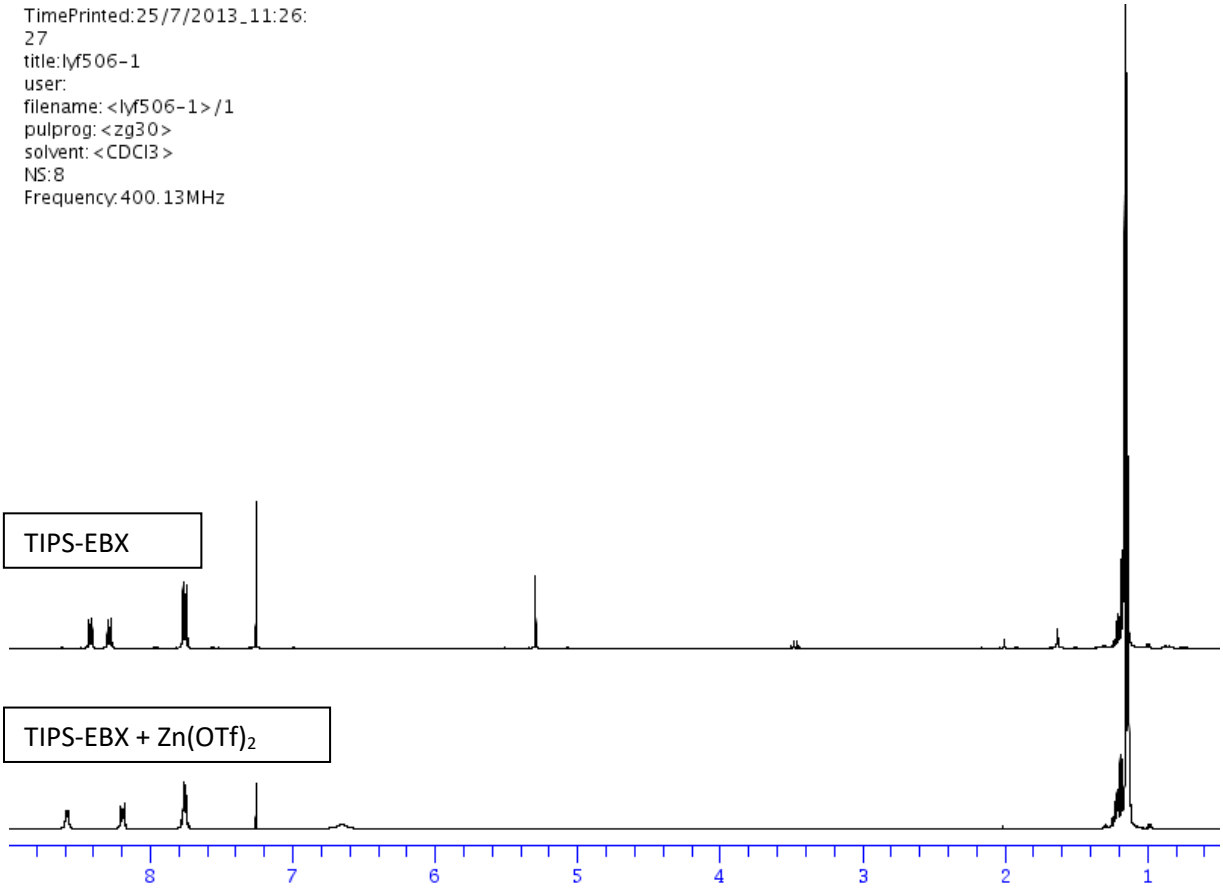


Figure S1: ^{1}H NMR spectrum of $Zn(OTF)_2$/TIPS-EBX (**8**) adduct

5. Spectra of New Compounds

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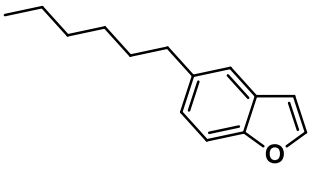
Frequency: 400.13MHz



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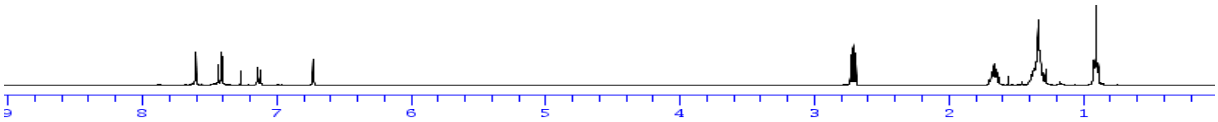

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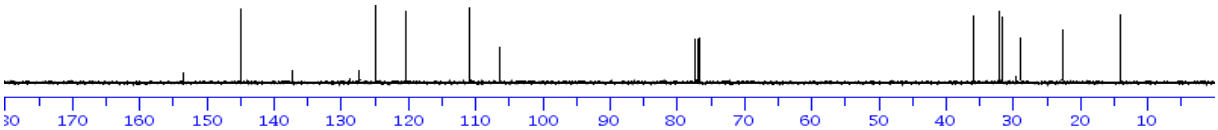

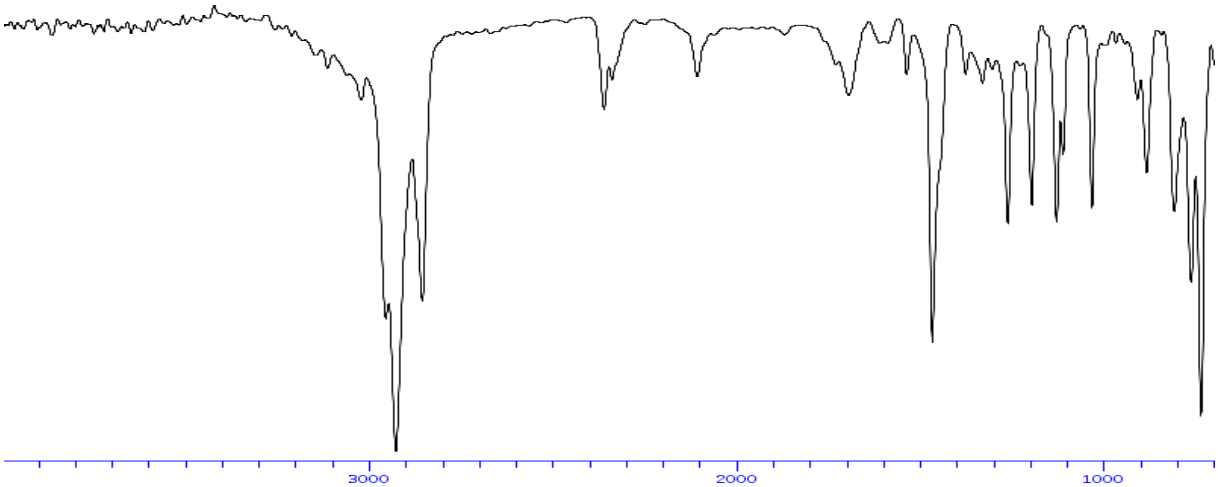

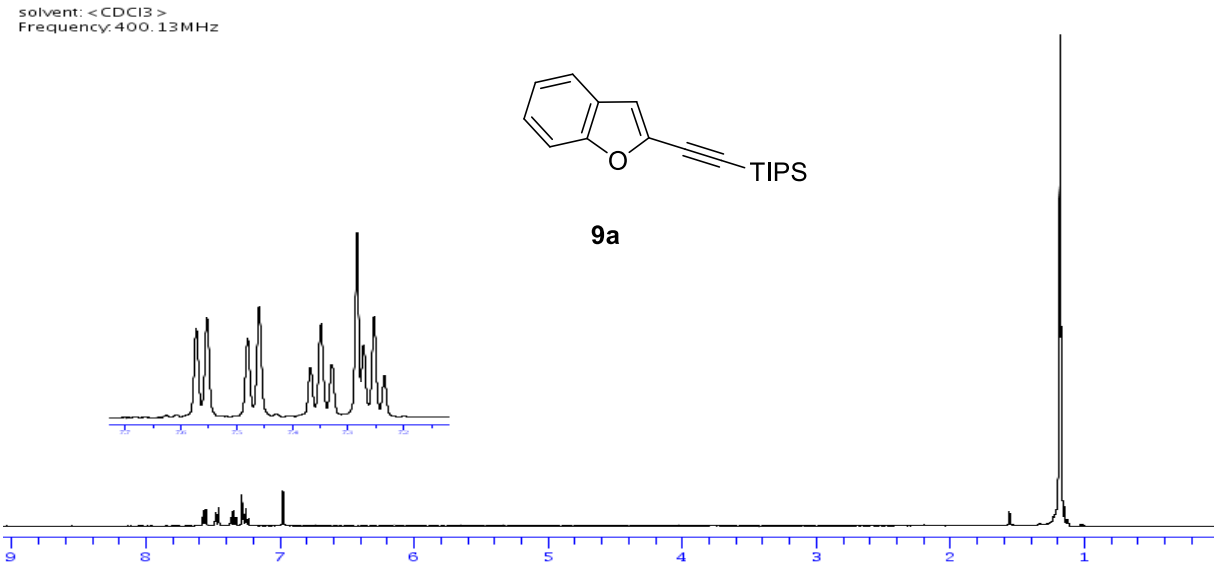
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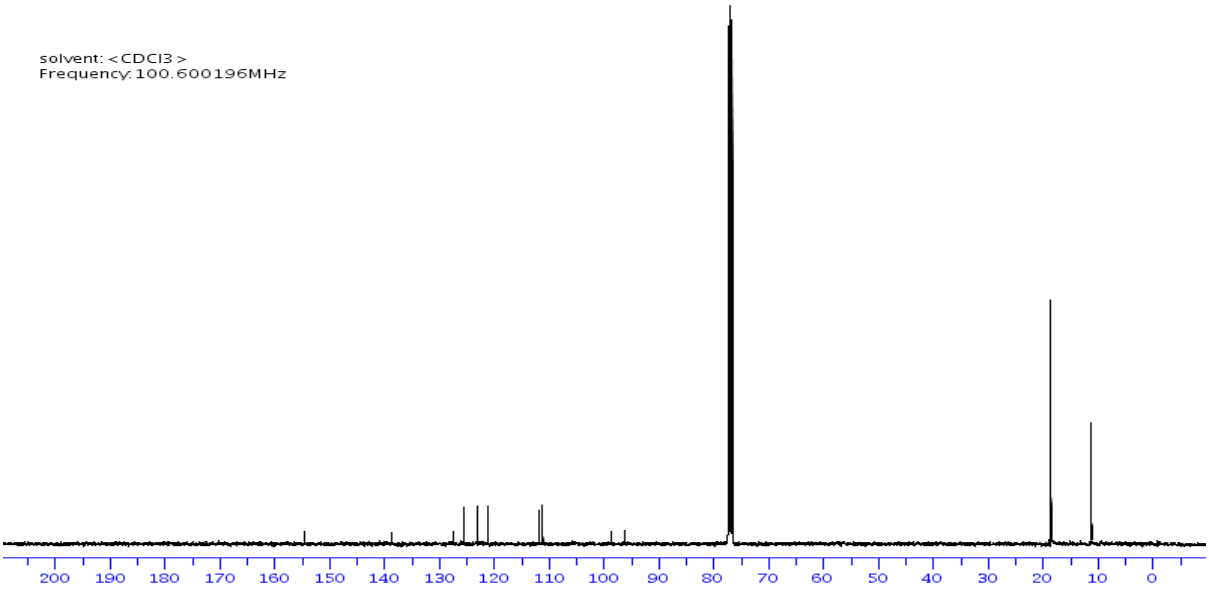
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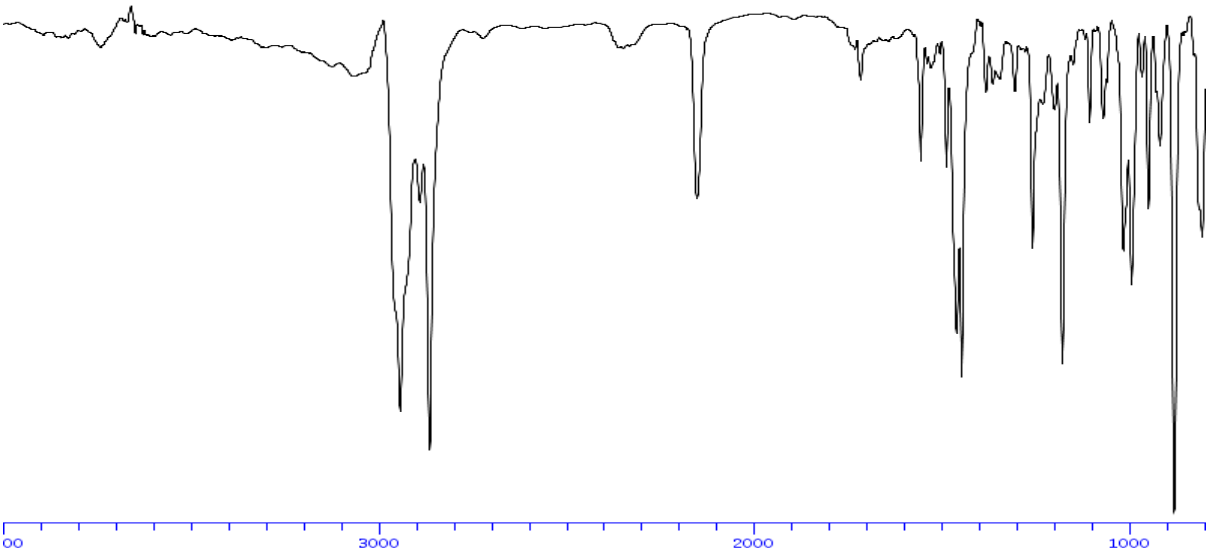
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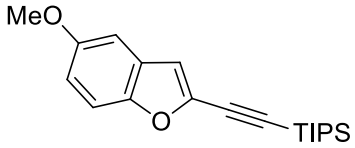

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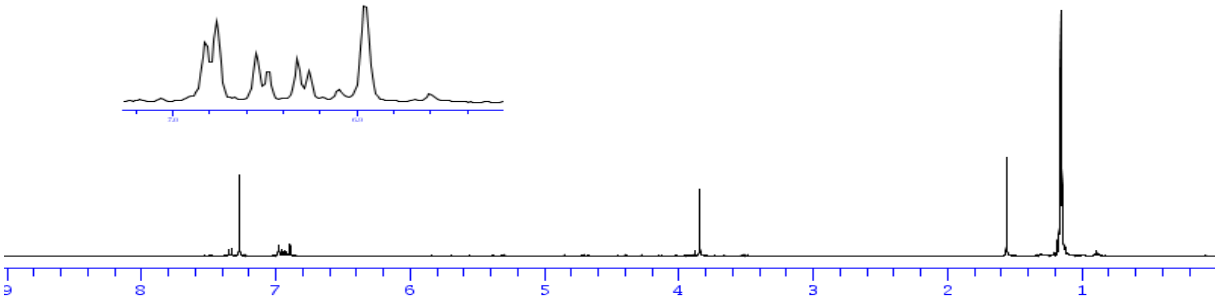

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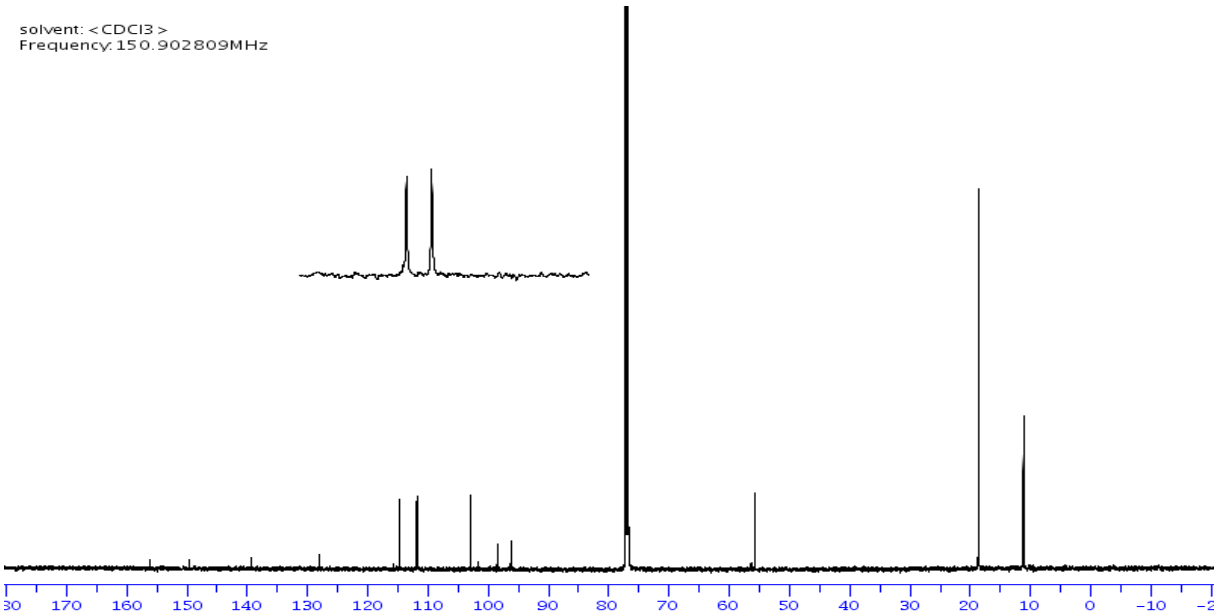

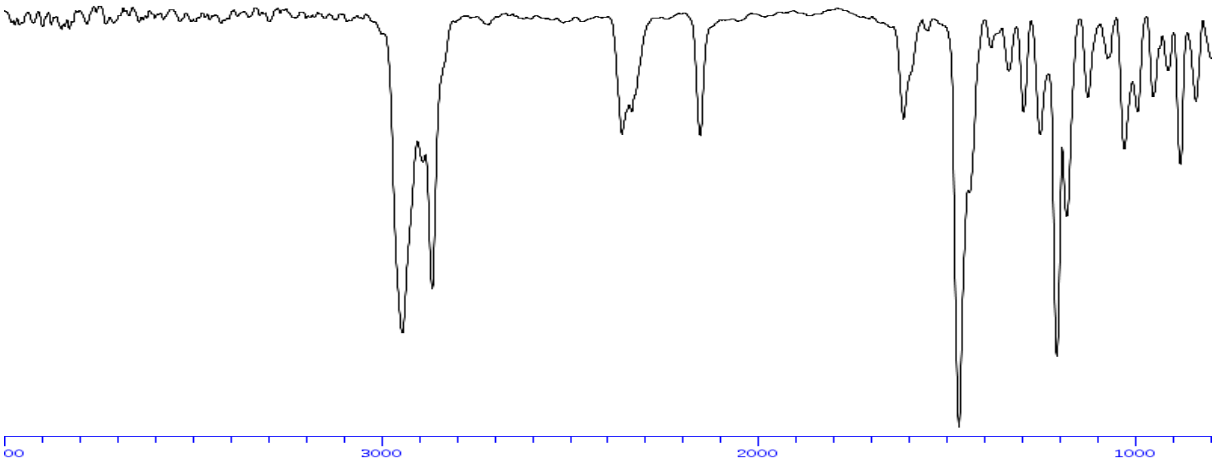

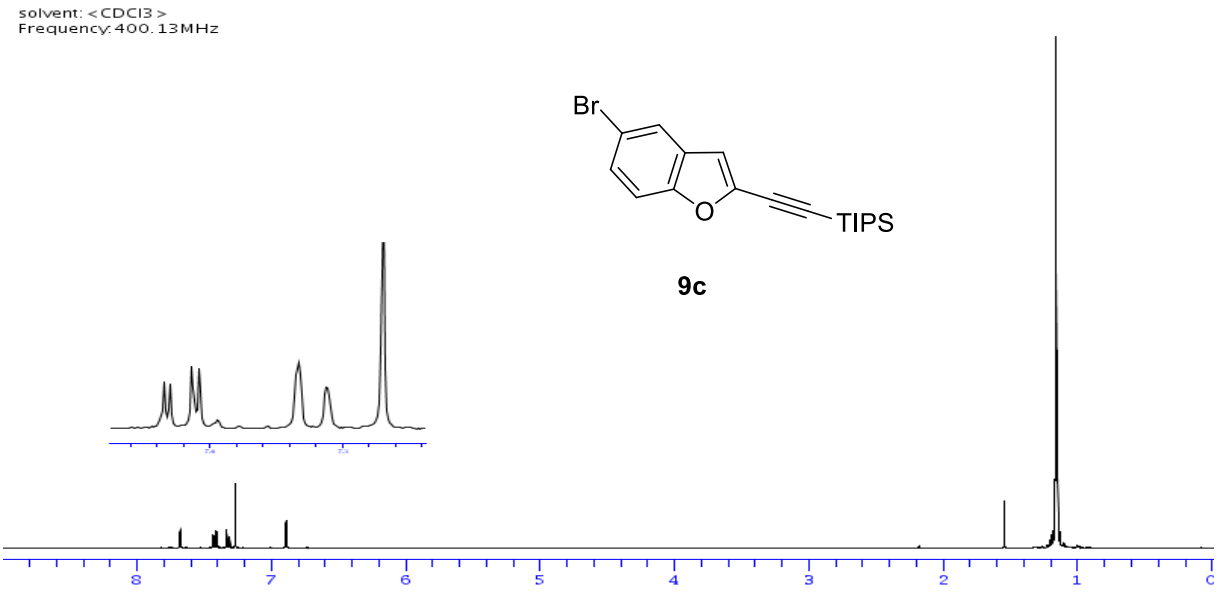
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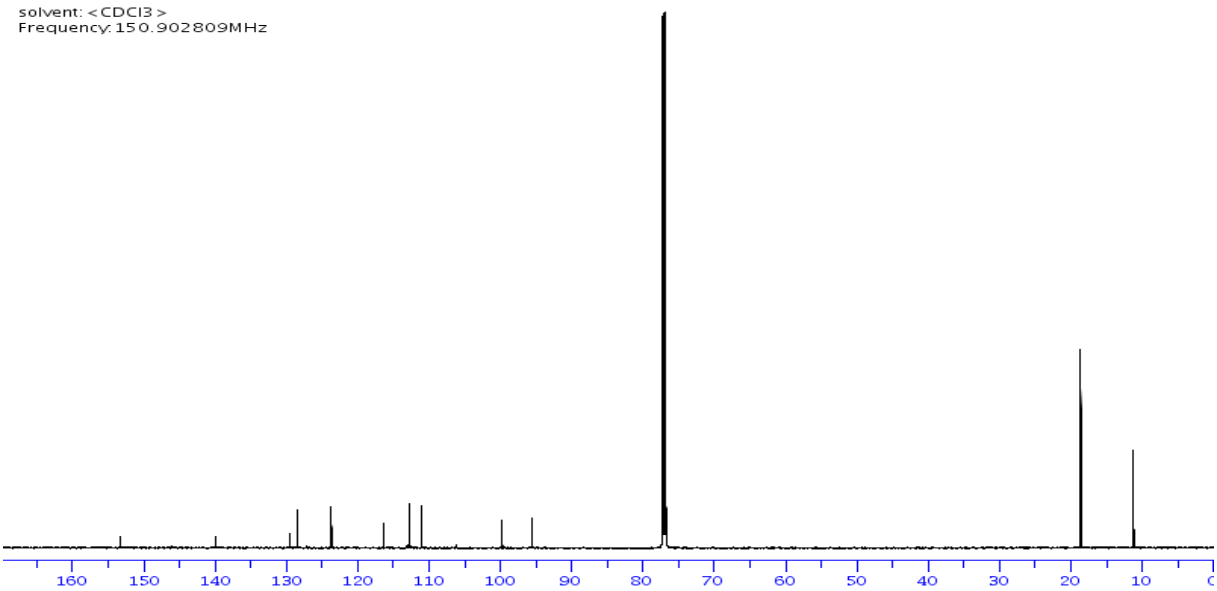
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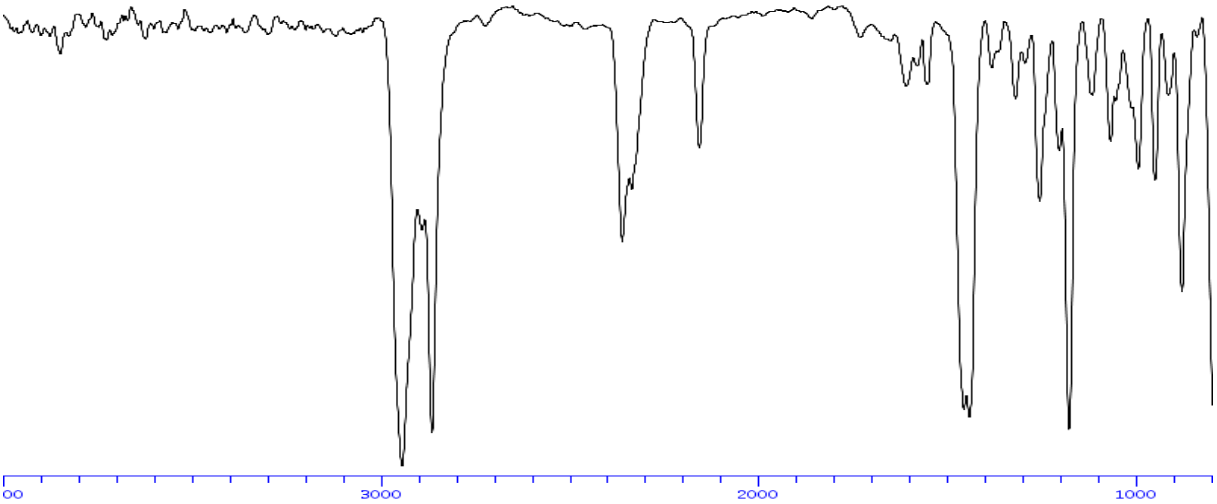
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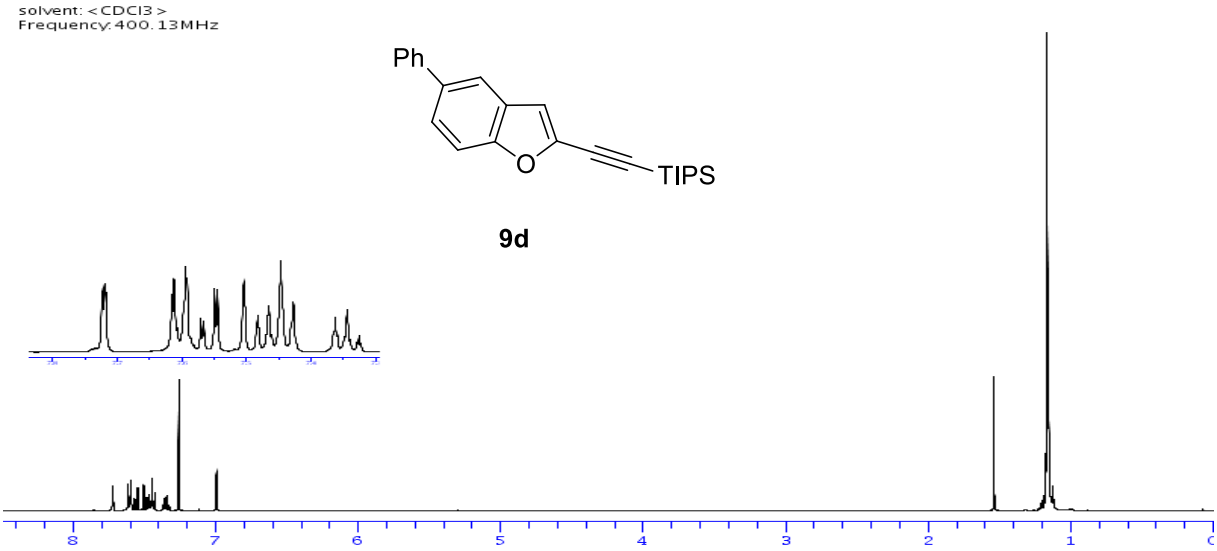
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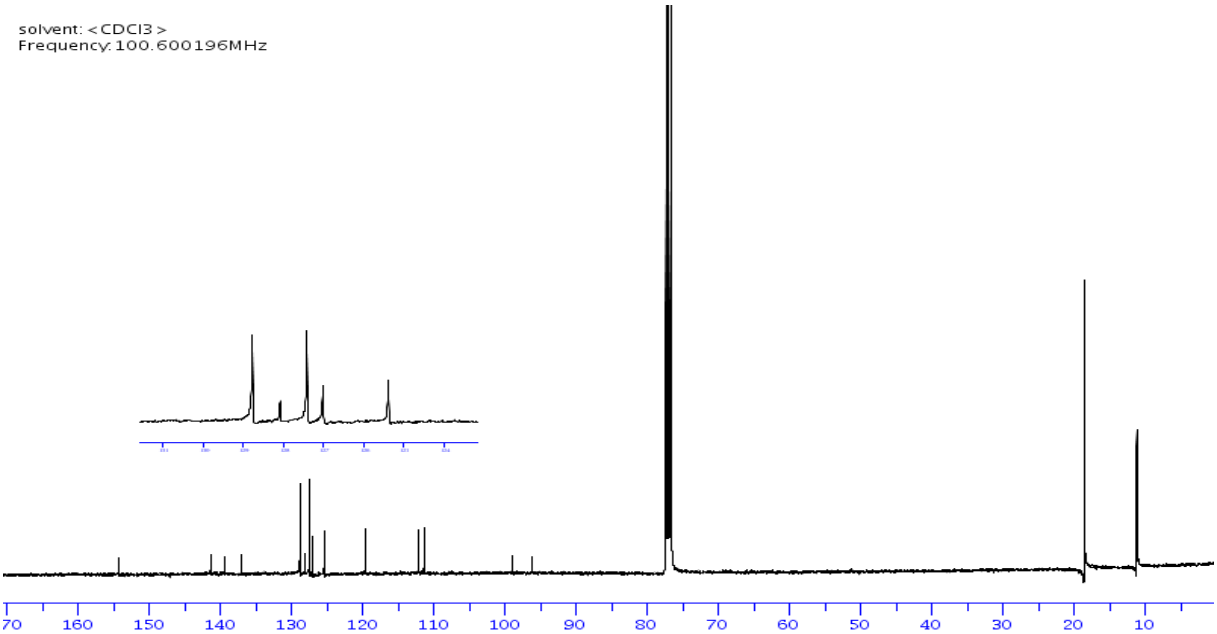
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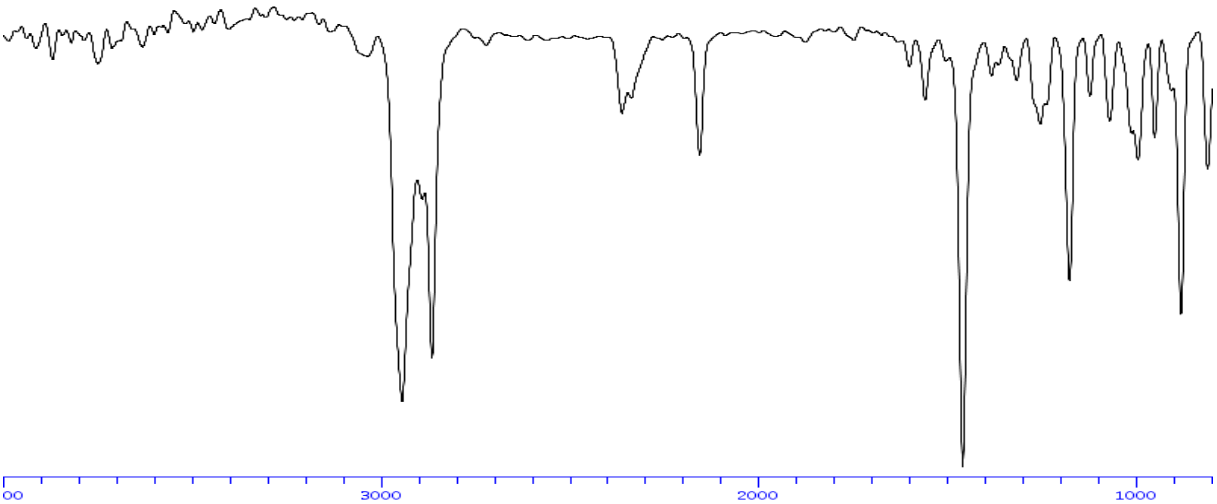
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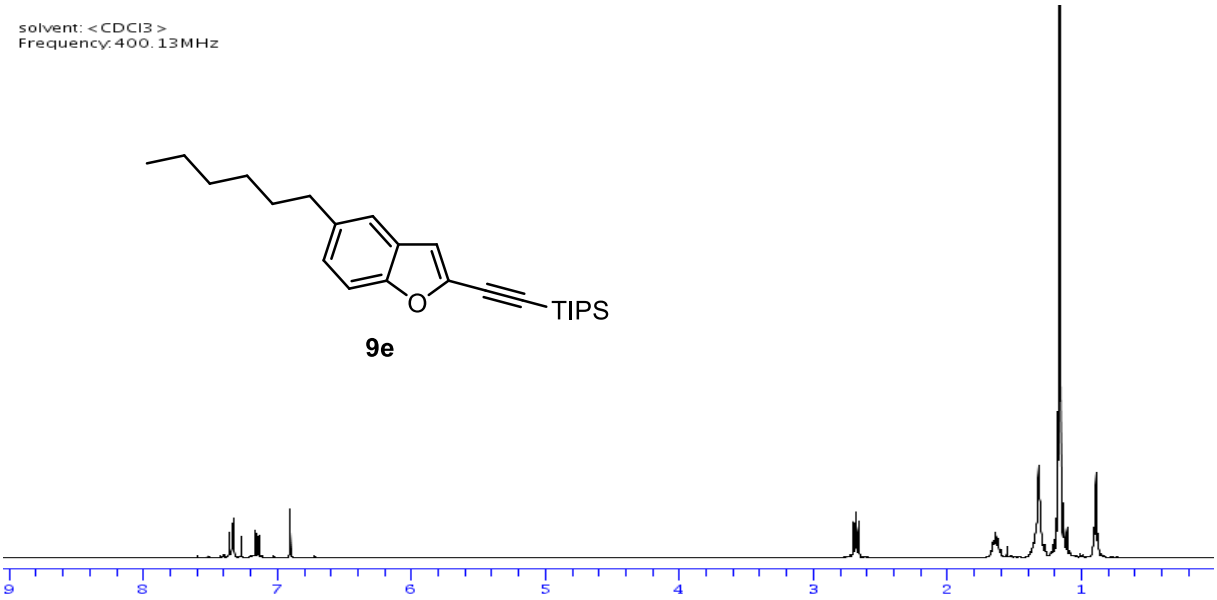
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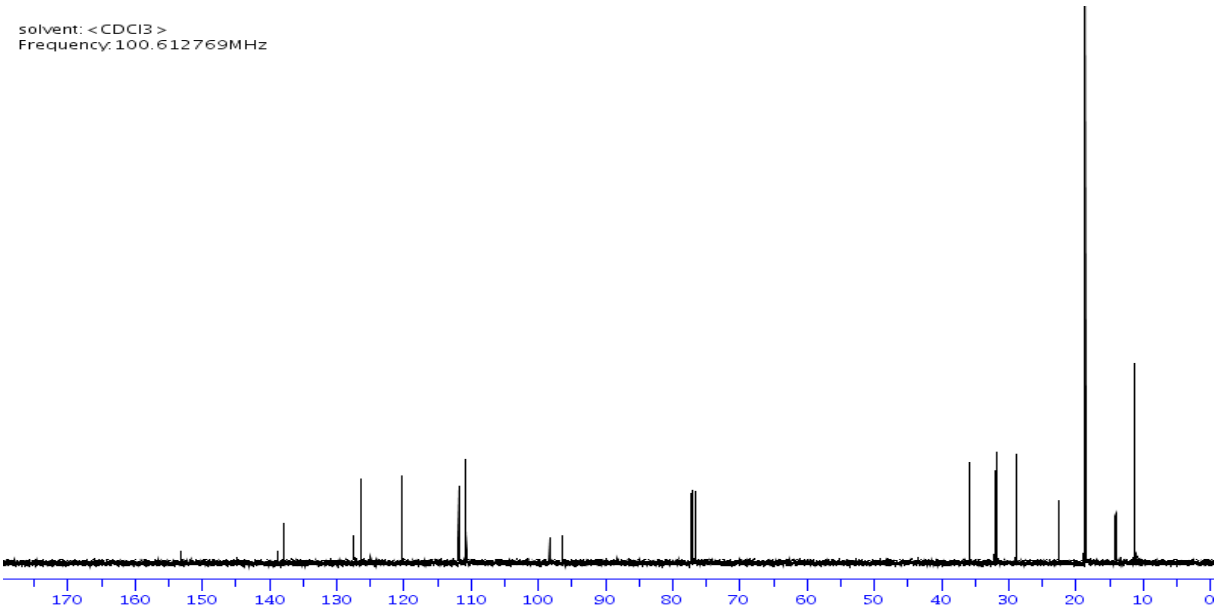
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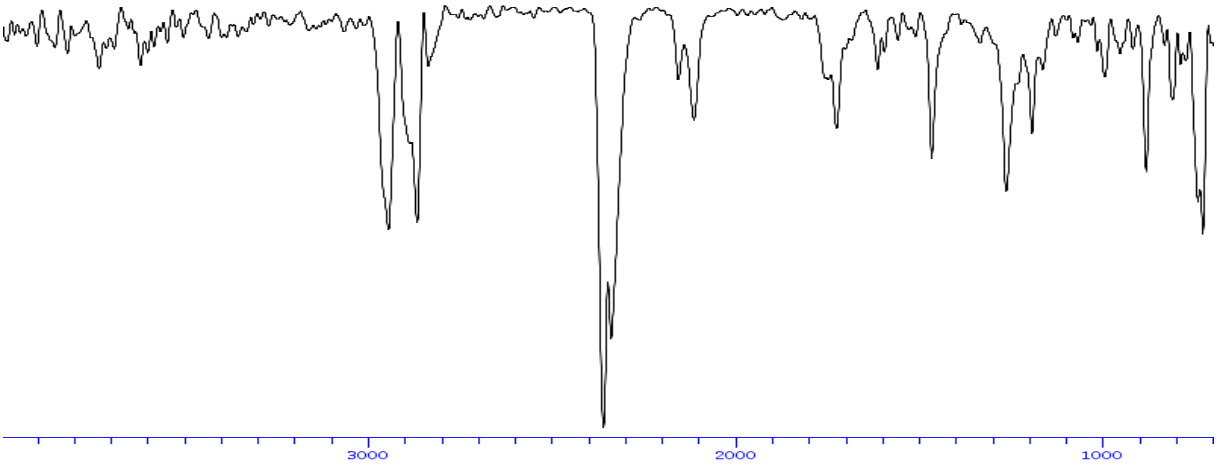
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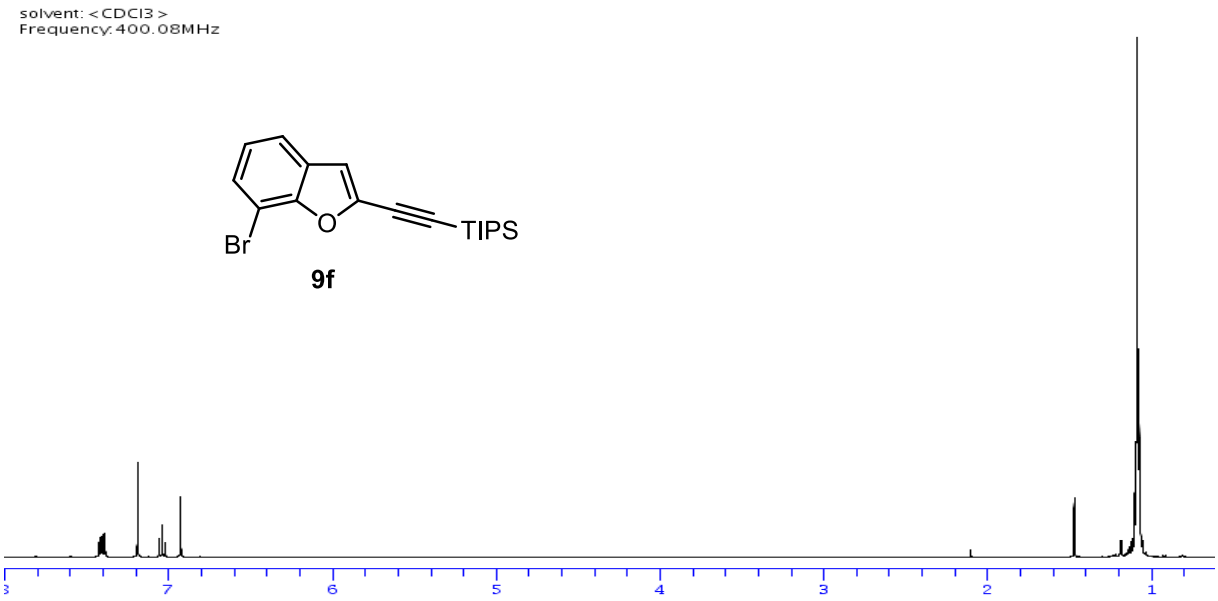
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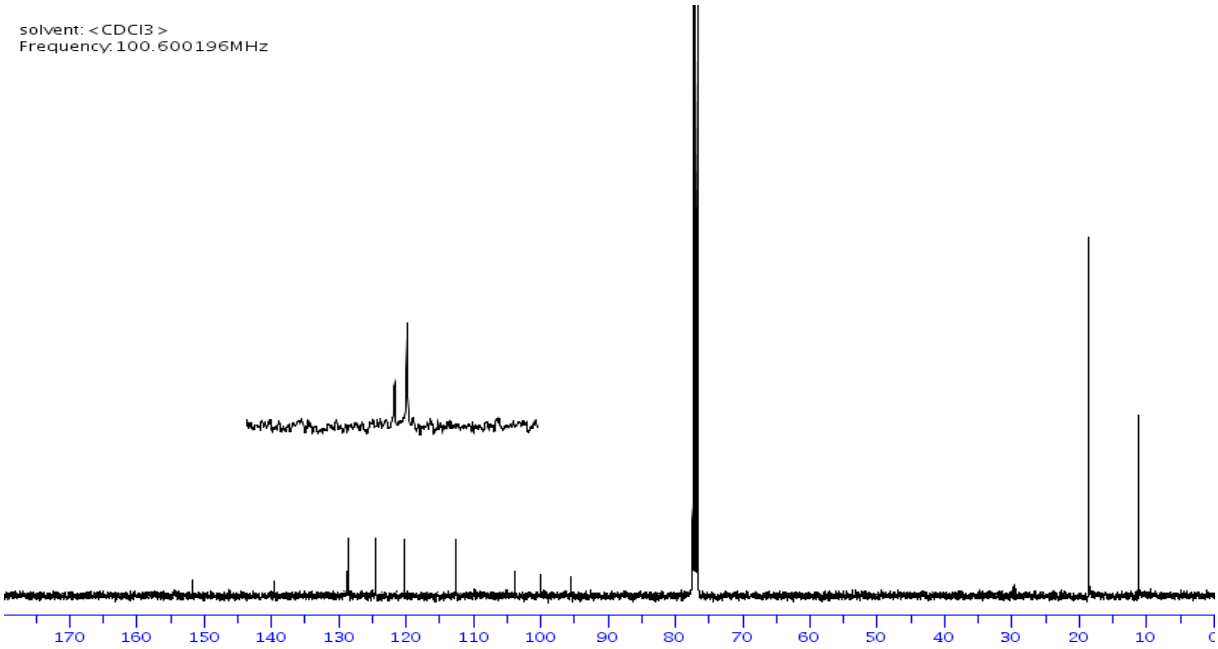
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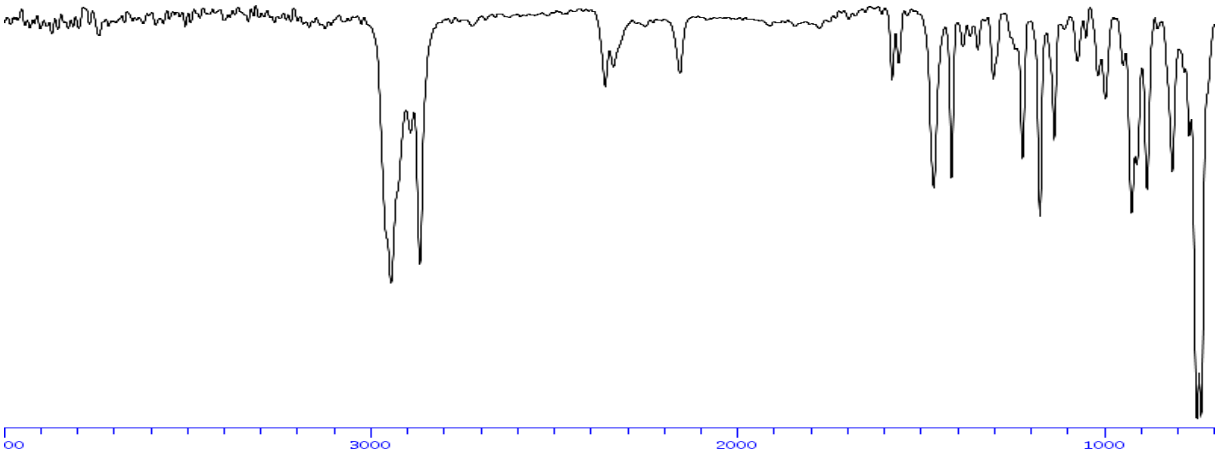
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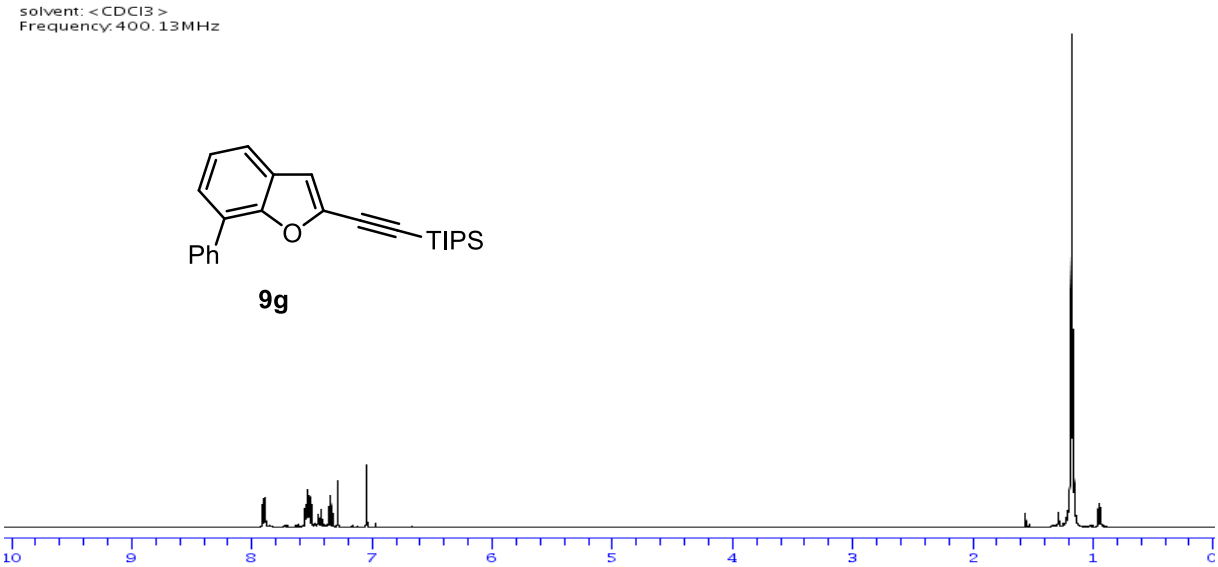
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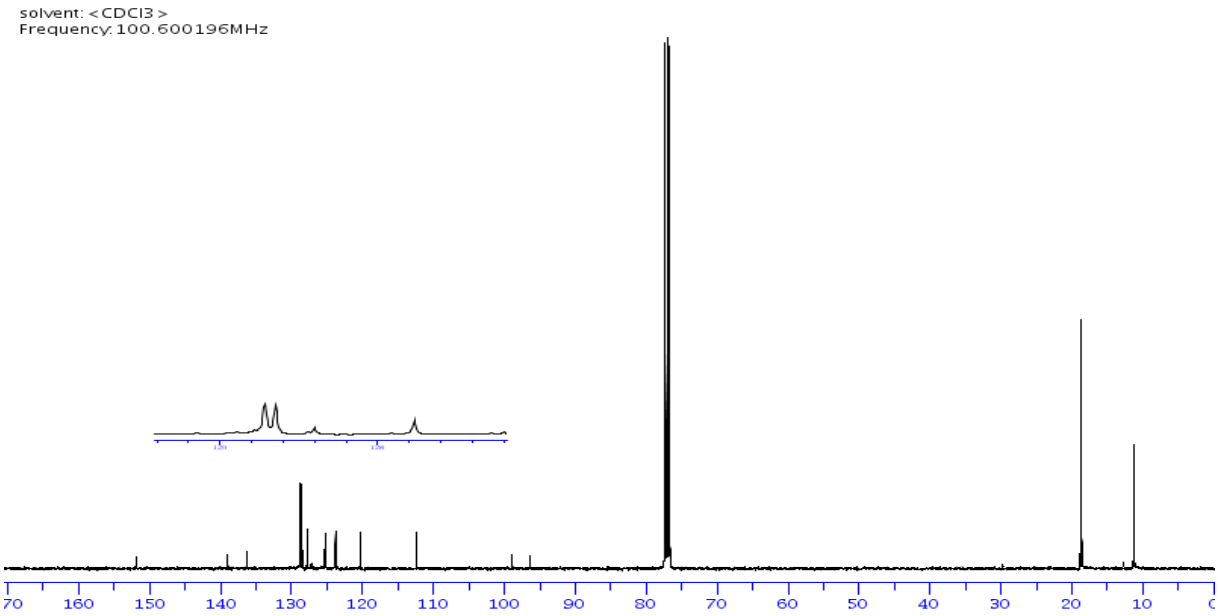
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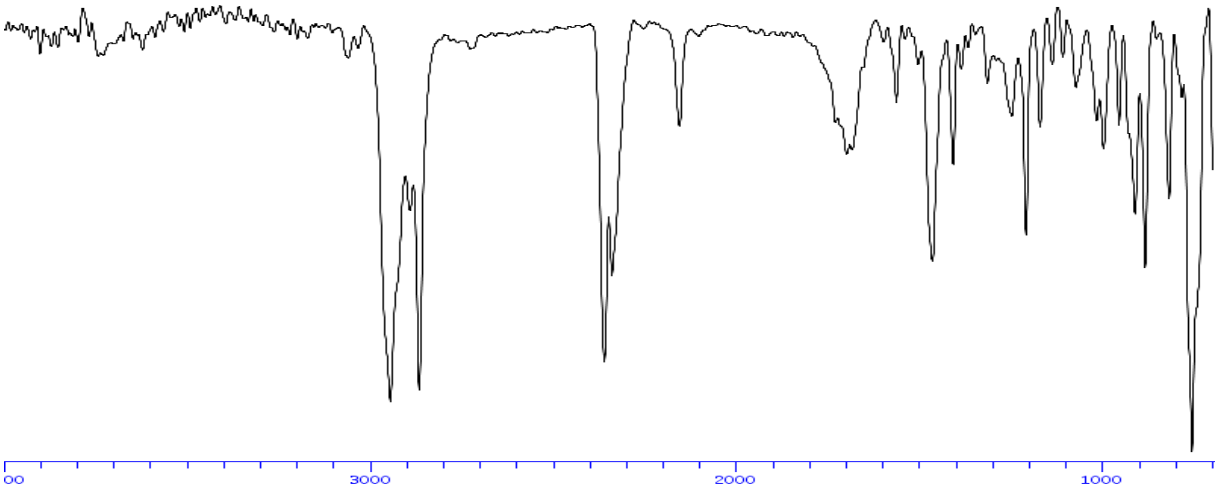
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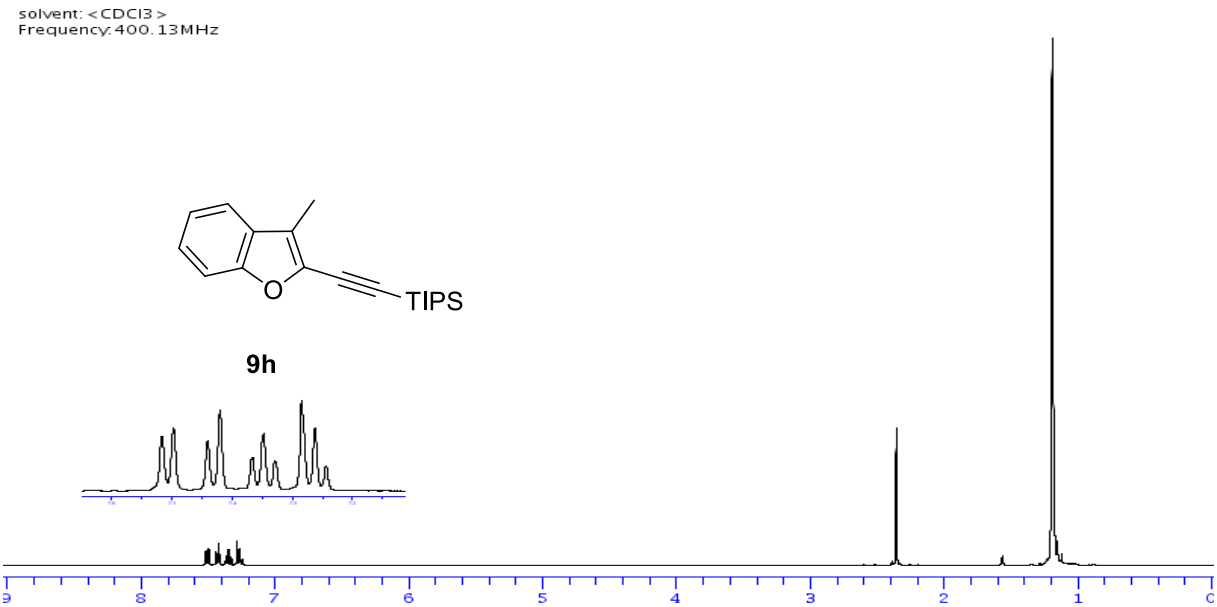
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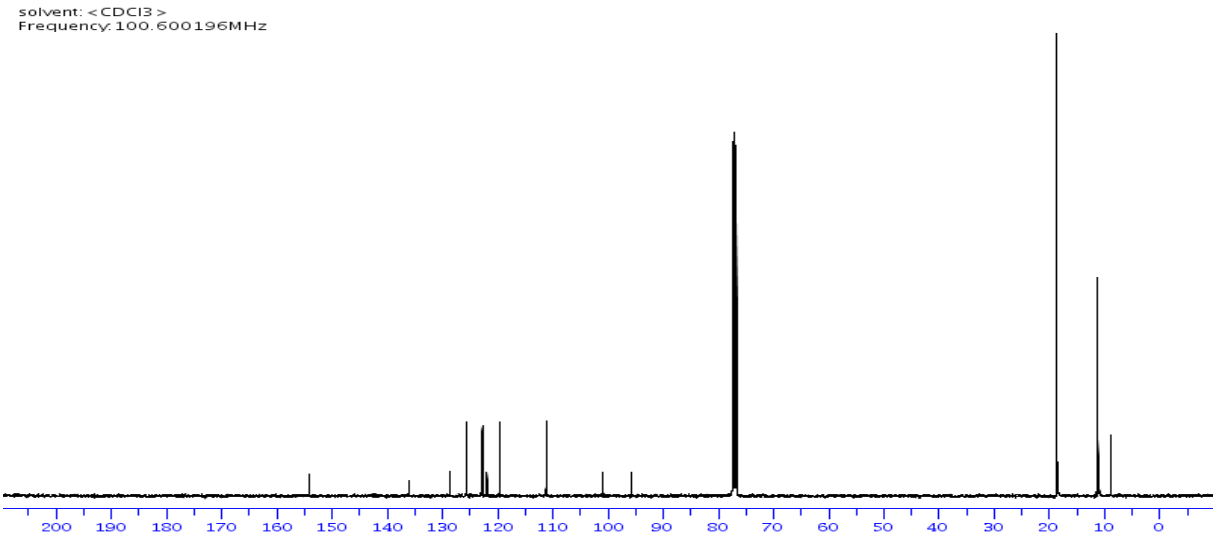
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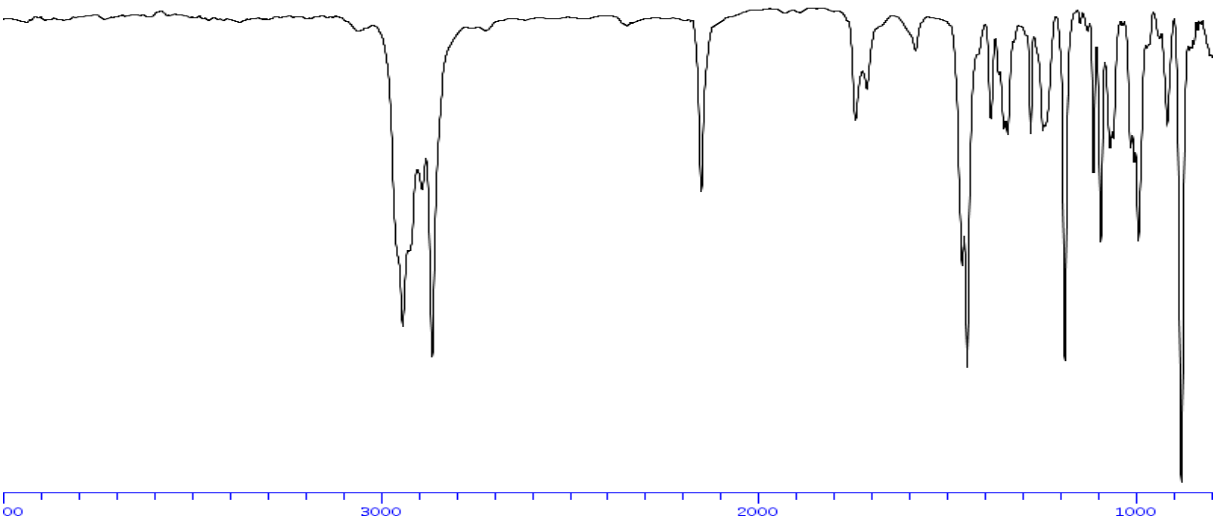

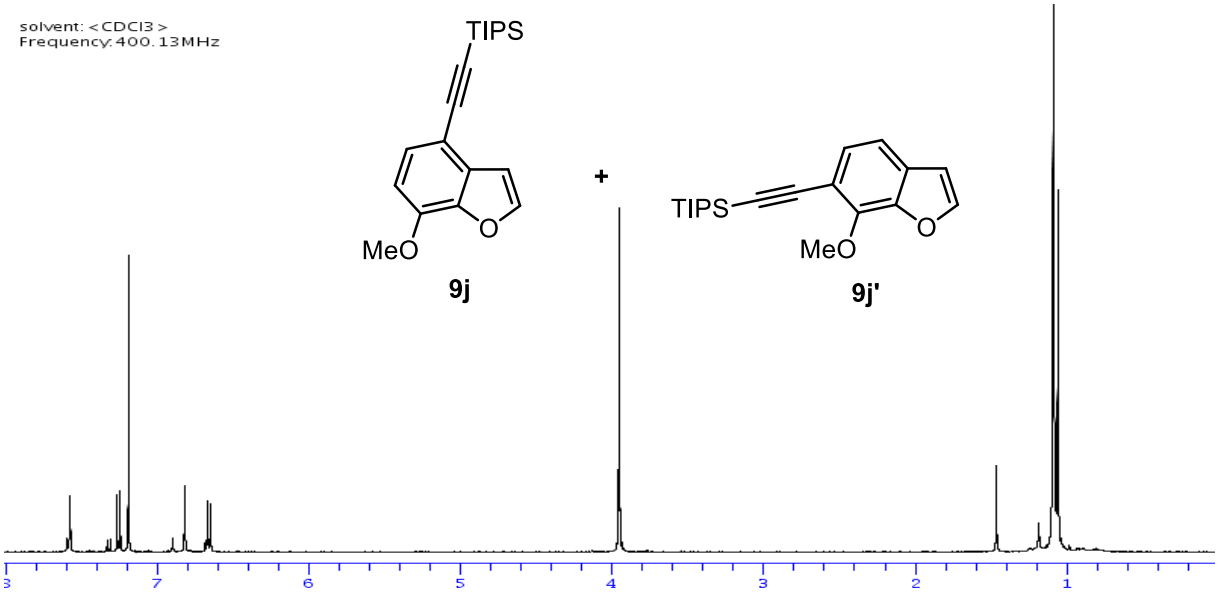
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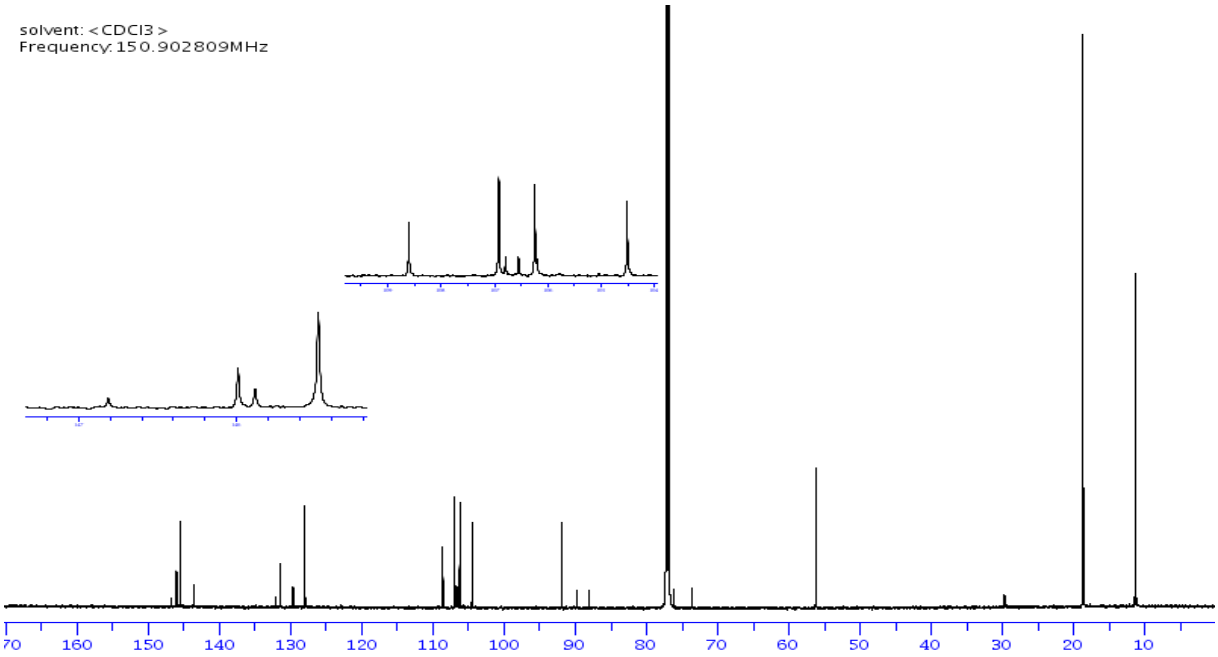
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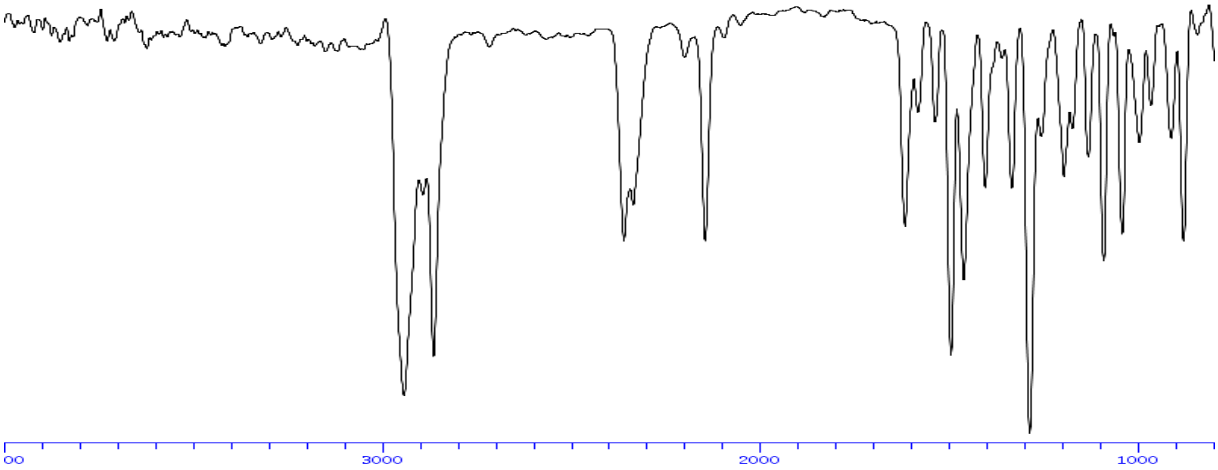

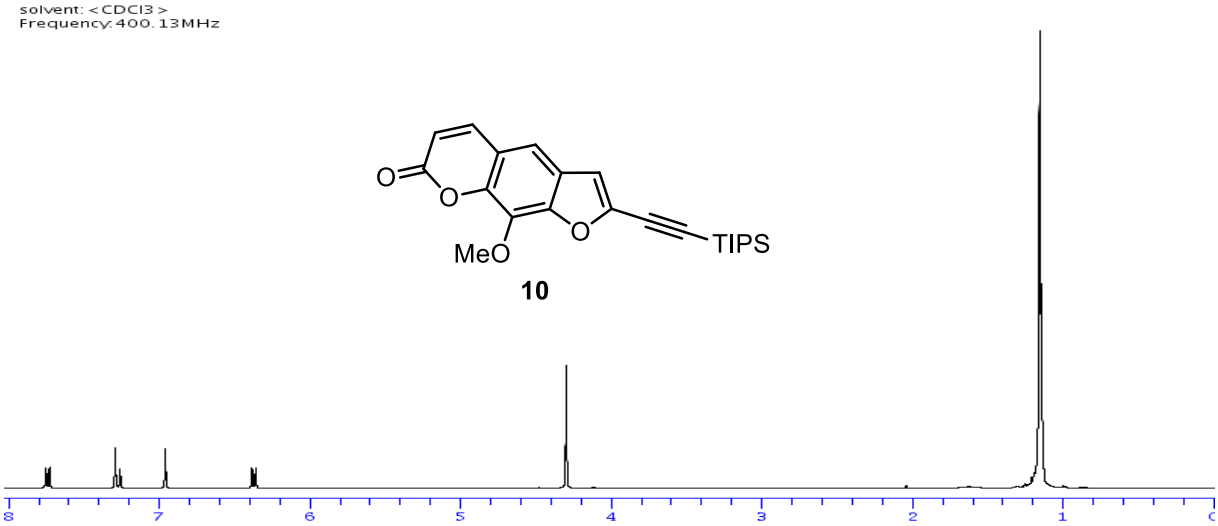
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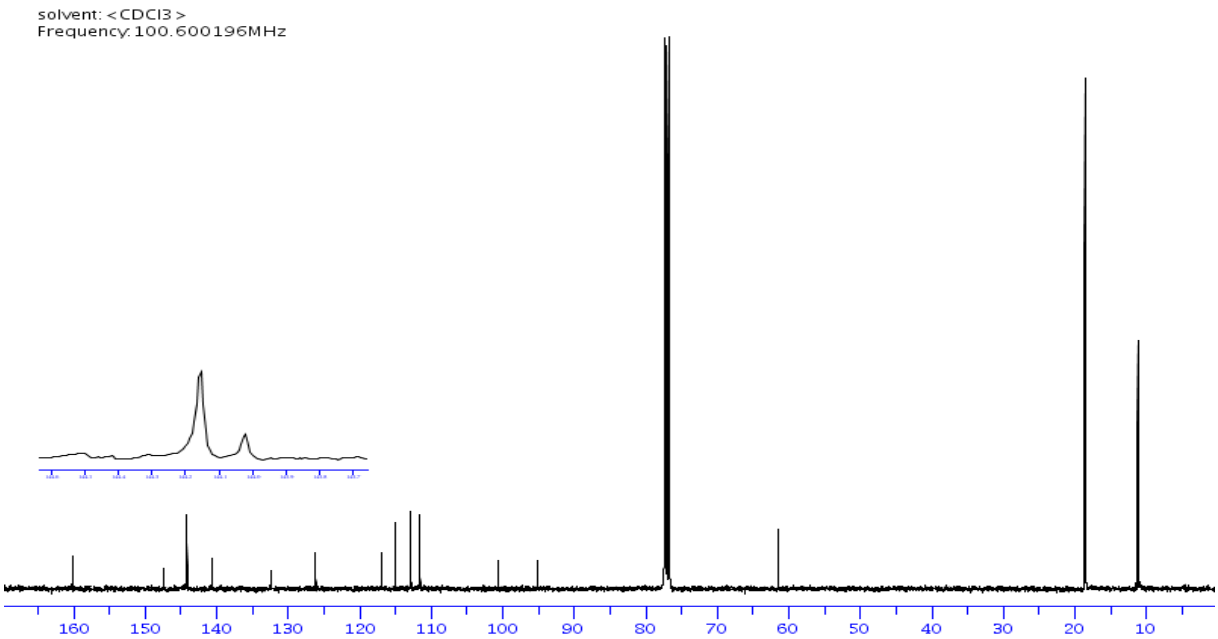
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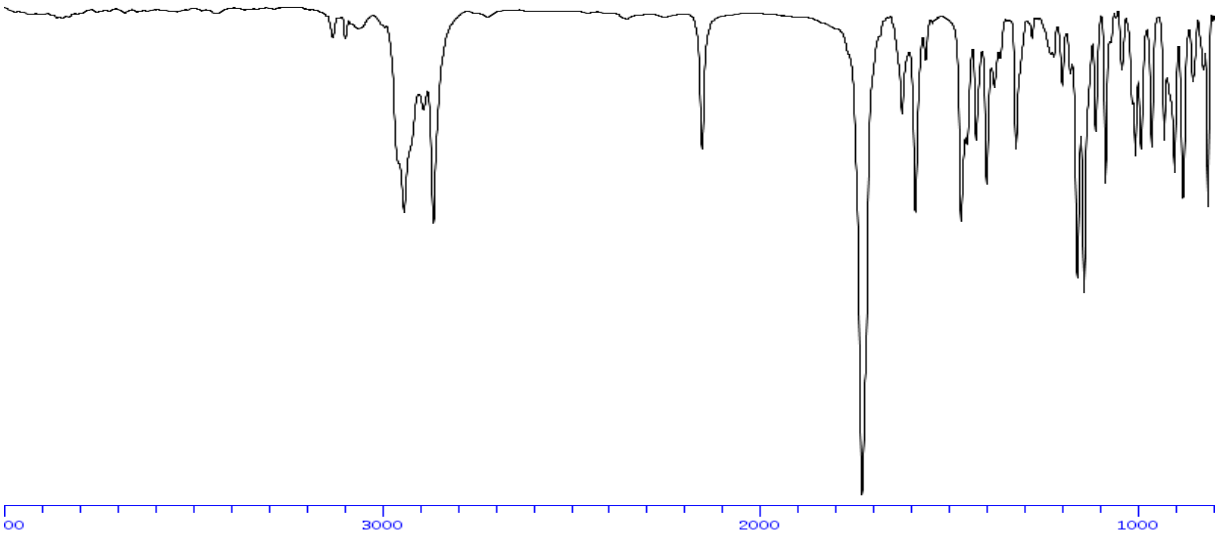
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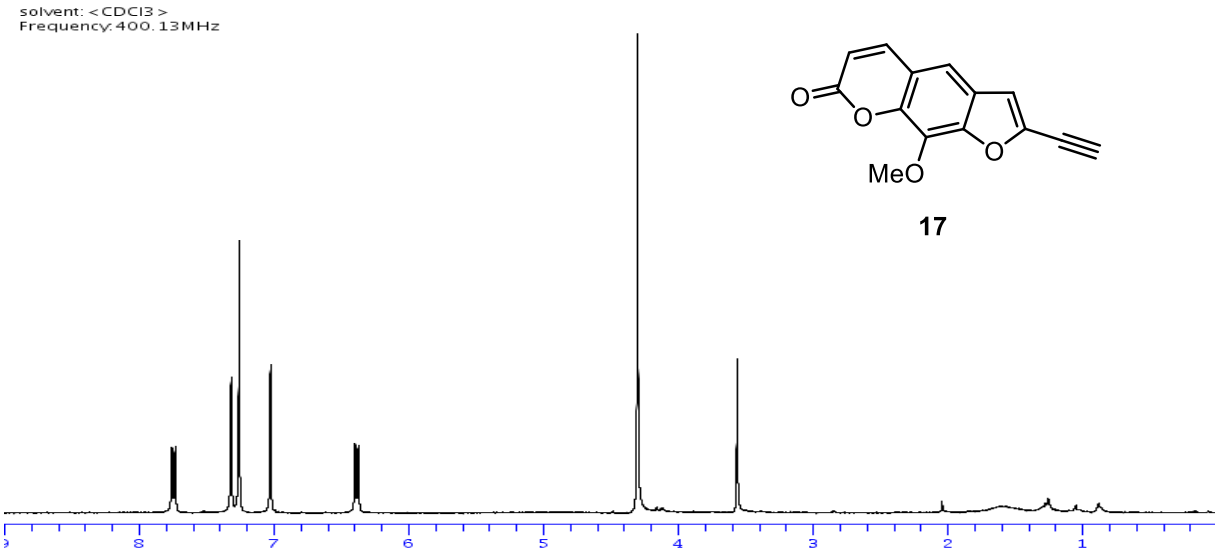
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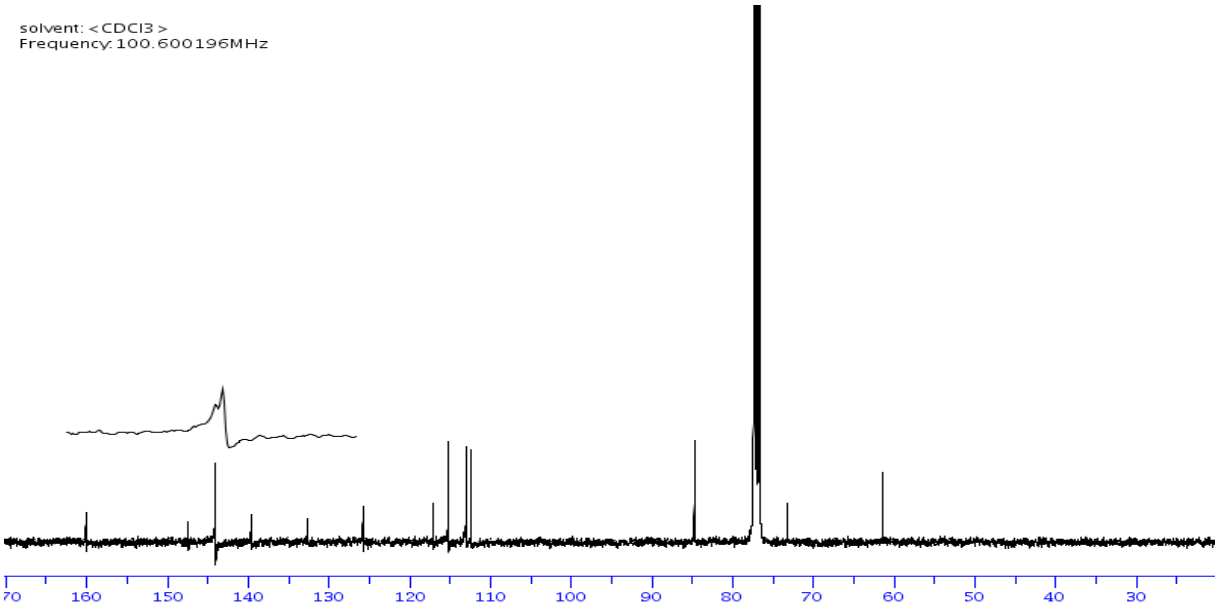
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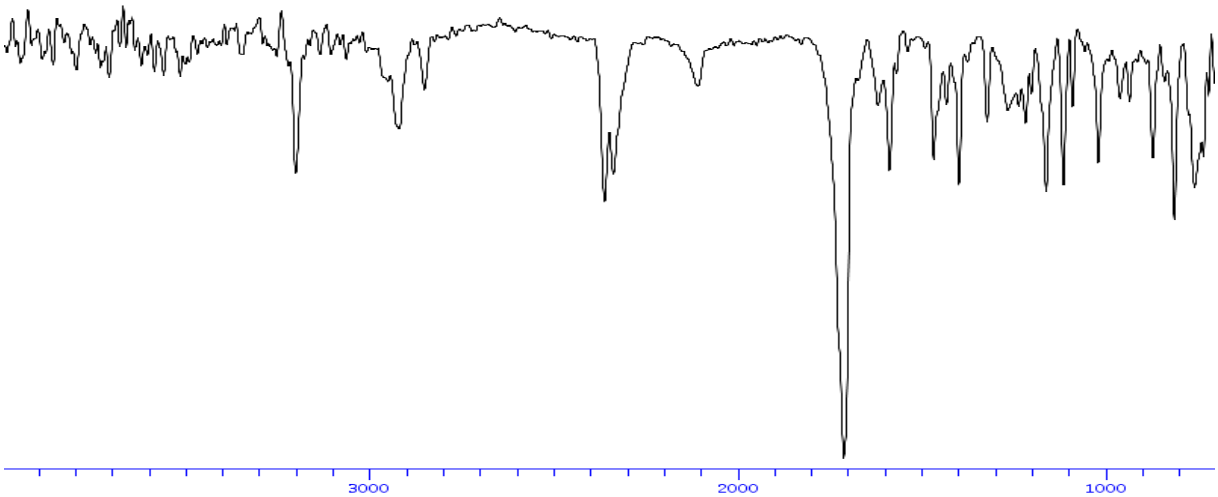
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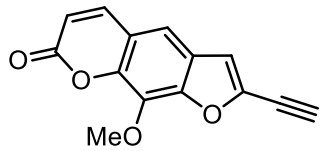
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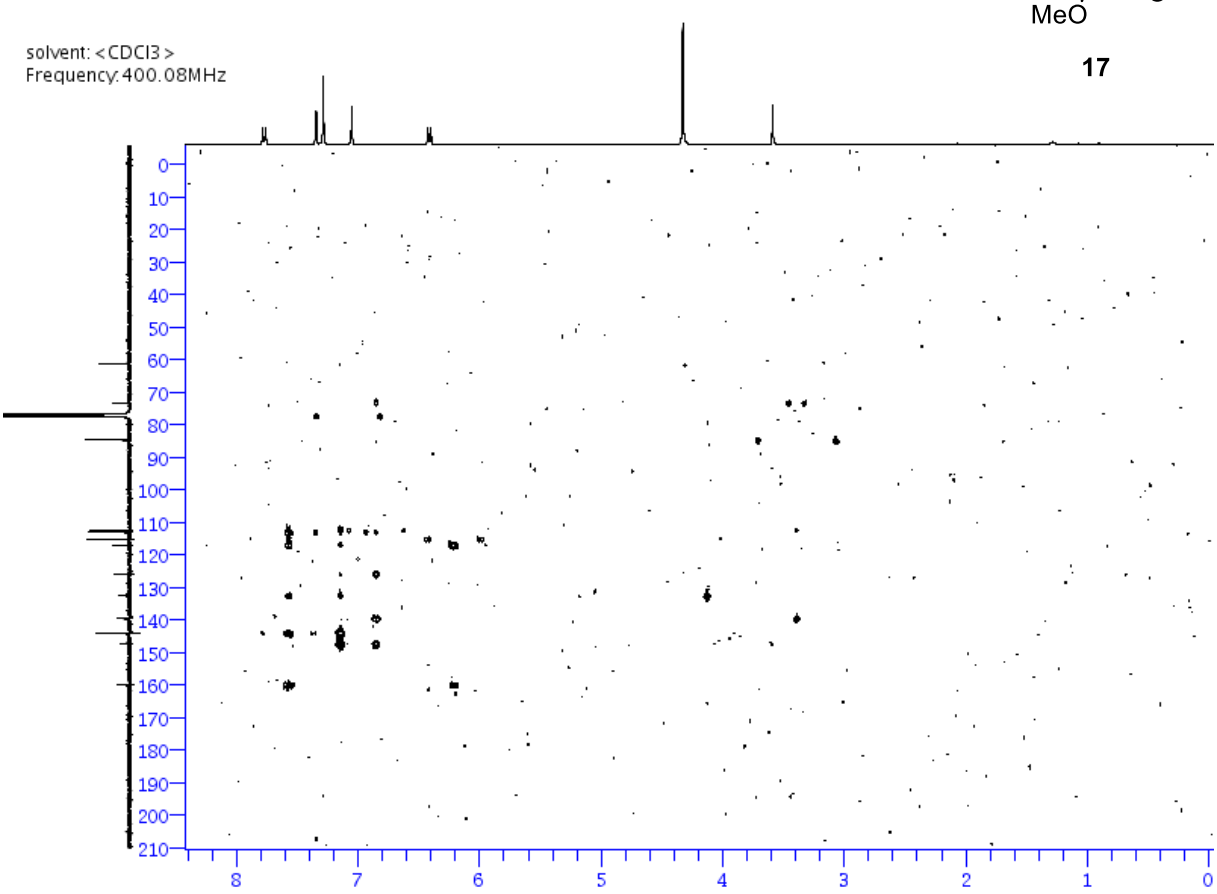
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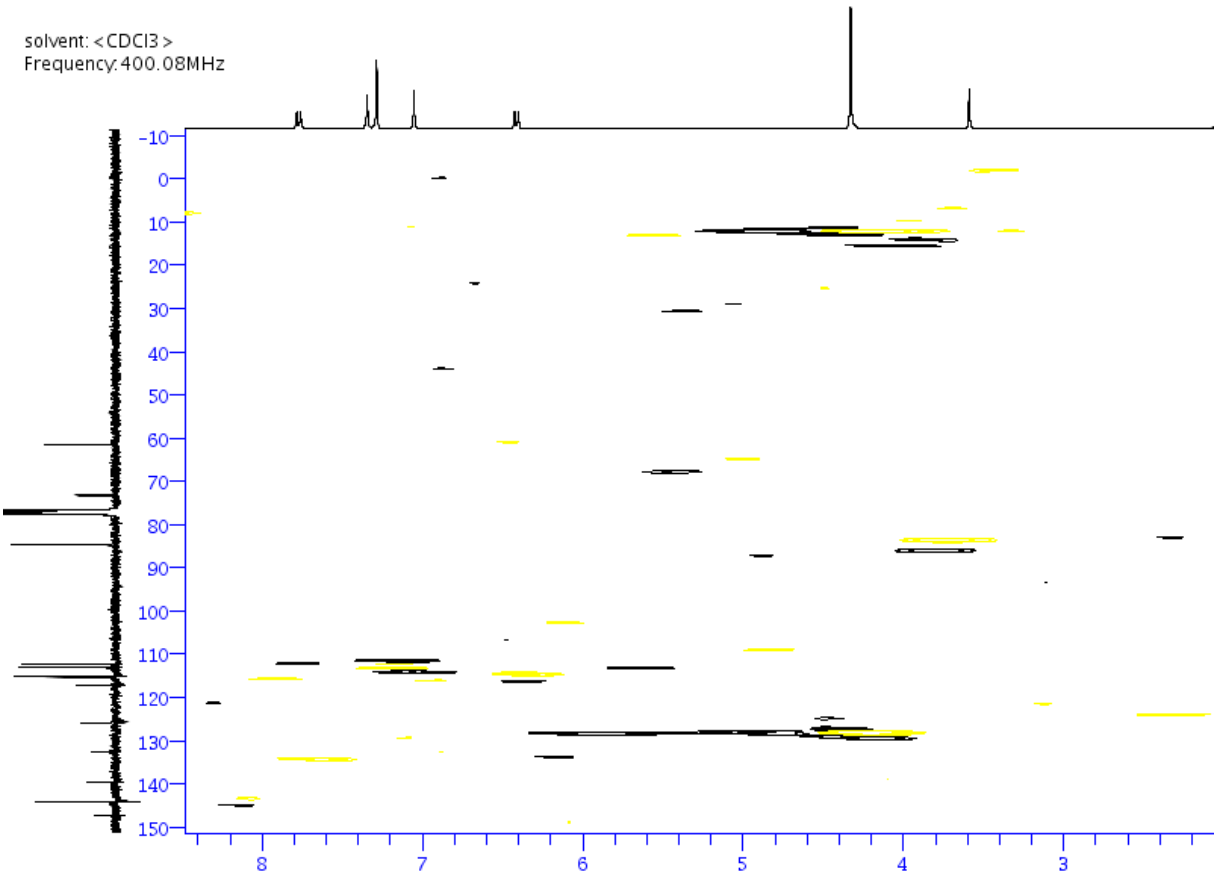
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