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One-pot gold-catalyzed synthesis of 3-silylethynyl indoles from unprotected *o*-alkynylanilines

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Letter

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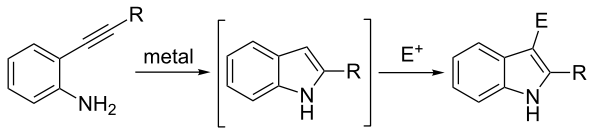
Abstract

The Au(III)-catalyzed cyclization of 2-alkynylanilines was combined in a one-pot procedure with the Au(I)-catalyzed C3-selective direct alkynylation of indoles using the benziodoxolone reagent TIPS-EBX to give a mild, easy and straightforward entry to 2-substituted-3-alkynylindoles. The reaction can be applied to unprotected anilines, was tolerant to functional groups and easy to carry out (RT, and requires neither an inert atmosphere nor special solvents).

Introduction

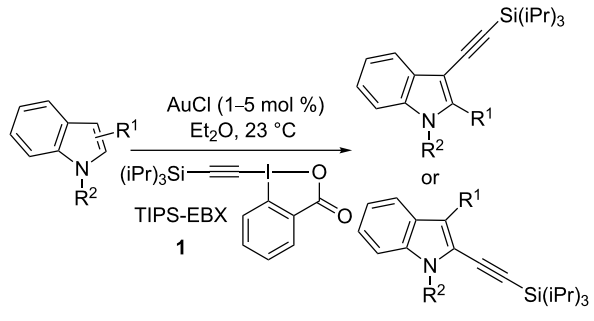
Indoles are widespread in both natural products and synthetic drugs [1,2] and as a result, their synthesis and functionalization have been extensively studied [3,4]. Among the numerous syntheses of indoles, the cyclization of 2-alkynylanilines has the advantage that the resulting products, 2-substituted indoles, are easily functionalized by electrophilic aromatic substitution at position 3. Traditionally, this transformation has been achieved in two separate steps, with isolation and purification of the 3-unsubstituted indole intermediate. Domino or one-pot processes constitute a more efficient access to organic molecules, as they avoid the use of time and resource consuming work-up, and purification procedures [5-7]. When considering the importance of multi-functionalized indoles, it is therefore not surprising that the aniline cyclization–electrophilic substitution sequence has been achieved by means of several metal-catalyzed domino processes (Scheme 1) [8-10].



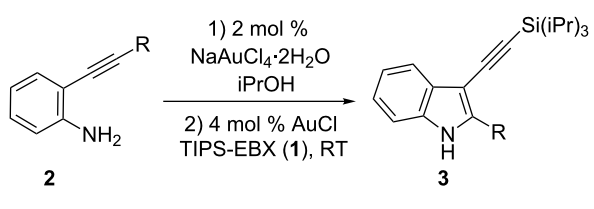
Scheme 1: Domino cyclization–substitution reactions of 2-alkynylanilines.

Among the different π-activating metals capable of promoting nucleophilic attack on acetylenes, gold has recently attracted interest from the synthetic chemistry community [11-14]. Gold catalysts have also been used in domino sequences starting from *o*-alkynylanilines. Arcadi and Marinelli reported that gold-catalyzed cyclization of 2-alkynylanilines can be followed by 1,4-addition to enones [15,16], iodination [17] or reaction with 1,3-dicarbonyl compounds [18]. Perumal recently demonstrated that aldehydes and nitroalkenes can be used as electrophilic partners [19,20]. Triple bonds can also serve as a second electrophile for the construction of tetrahydrofurans [21] and aryl-annulated[*a*]carbazoles [22]. Nakamura examined the cyclization of *N*-tosyl-*o*-alkynylanilines and observed an internal transfer of the sulfonyl group to the 3-position of the formed indoles [23,24]. Similar transformations were also achieved for the transfer of carbonyl groups, but using platinum catalysts [25-28].

To date, there are no gold- or platinum-catalyzed methods for the introduction of acetylenes as electrophiles. However, Cacchi developed a palladium-catalyzed domino sequence including cyclization of *o*-alkynyltrifluoroacetanilides and alkynylation with bromoacetylenes [29]. New methods are needed to expand the scope of this transformation and Au catalysis appears especially promising, due to its broad functional groups tolerance, which could allow the direct use of unprotected anilines.



Scheme 2: Gold-catalyzed direct alkynylation of indoles with TIPS-EBX (**1**).



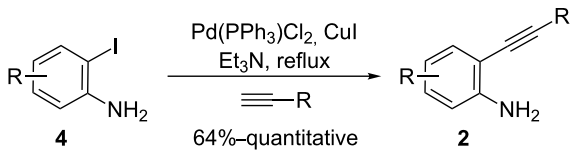
Scheme 3: One-pot alkynylaniline cyclization/direct alkynylation.

Recently, the direct alkynylation of preformed heterocycles has been intensively investigated [30-34]. Most of the developed methods involve the use of haloacetylenes. In contrast, our group has focused on the use of more reactive alkynyl hypervalent iodine reagents in order to expand the scope of direct alkynylation methods under milder conditions. We recently reported a mild procedure for the C3-selective alkynylation of indoles using AuCl and the commercially available benziodoxolone TIPS-EBX (1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**1**)) (Scheme 2) [35-40]. This methodology allowed the ethynylation of a wide range of indoles, including 2-substituted indoles.

In this letter we would like to report the one-pot combination of the cyclization of 2-alkynylanilines using $NaAuCl_4$ as catalyst [15] followed by C3-alkynylation with AuCl and TIPS-EBX (**1**) (Scheme 3). This method offers an operationally simple access to 3-silylalkynyl indoles. To the best of our knowledge, this is the first example of a one-pot process combining a Au(III) and a Au(I) catalyst.

Findings

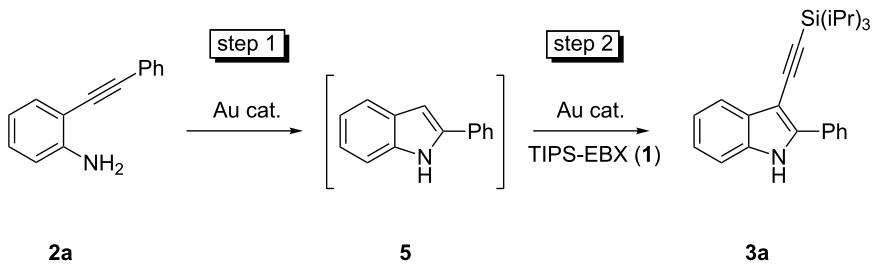
2-Alkynylanilines **2** can be efficiently prepared from 2-iodoanilines **4** and terminal alkynes via Sonogashira reaction with Et_3N as solvent (Scheme 4) [41,42]. The reaction was complete in less than 2 h and did not require aniline protection, solvent degassing or drying.



Scheme 4: Synthesis of 2-alkynylanilines **2**.

Our first investigations were focused on the cyclization of 2-(phenylethynyl)aniline (**2a**) into 2-phenylindole (**5**) with AuCl as the catalyst at room temperature (Scheme 5, step 1). Since AuCl has been shown to be the best catalyst for the alkynylation reaction [35], its use would allow a domino process with a single catalyst.

Despite the fact that the use of AuCl has been reported for step 1 [19,20], in our hands the reaction was not reproducible at room temperature in a variety of solvents (EtOH, CH_3CN, Et_2O). A black precipitate was observed after catalyst addition, which we postulate was due to the stochastically degradation of AuCl under these conditions. $NaAuCl_4$ has also been reported to be successful for the cyclization of 2-(phenylethynyl)aniline



2a 5 3a

Scheme 5: Domino cyclization–alkynylation of aniline **2a**.

(**2a**) [15]. This catalyst was next examined in different solvents in order to maximize the chance of finding conditions suitable for both steps of the process. Aniline **2a** was fully converted into 2-phenylindole (**5**) in EtOH, iPrOH and Et_2O after 3 h at room temperature using 2 mol % of $NaAuCl_4$ and there was no problem of reproducibility. Unfortunately, $NaAuCl_4$ was not an efficient catalyst for the direct alkynylation of indole, as no reaction was observed when TIPS-EBX (**1**) was added to the reaction mixture.

We then investigated the successive addition of $NaAuCl_4$ and AuCl in the same pot. Interestingly, one-pot sequential processes using both Au(I) and Au(III) have not yet been reported. AuCl and TIPS-EBX (**1**) were added when full conversion of the $NaAuCl_4$-catalyzed cyclization was observed. When 2 mol % of $NaAuCl_4$ and 2 mol % AuCl were added, the second step was unsuccessful. However, with 2 mol % of $NaAuCl_4$ and 4 mol % of AuCl, full conversion was observed after 30 h at room temperature in iPrOH (compared with 60% in EtOH and 40% in Et_2O). A basic work-up allowed the removal of the 2-iodobenzoic acid and column chromatography afforded the product in 96% yield (average of two reactions). Unfortunately, no reaction was observed when AuCl and TIPS-EBX (**1**) were added at the beginning of the reaction.

The scope of the reaction was then investigated (Scheme 6). Methyl- and fluoro groups were tolerated on the 2-aryl substituent to give products **3b** and **3c** in good yields. The low solubility of the indole intermediate in the synthesis of **3d** led to a low yield for the direct alkynylation step. The addition of CH_2Cl_2 overcame this problem. Chloro substitution in para-position of the aniline was also tolerated (**3e**, **3f**). Nevertheless, when the strongly electron-withdrawing cyano group was present, the cyclization step was too slow at room temperature. However, the use of 4 mol % of $NaAuCl_4$ and a reaction temperature of 80 °C led to the formation of the desired indole, which could then be alkynylated at room temperature to give **3g**. *o*-Hexynyl aniline (**2h**) was efficiently transformed into **3h** in 85% yield. In order to access 2-silyl indoles, the synthesis of the 2-trimethylsilylacetylene substituted compound **3i** was attempted. Unfortunately, only traces of the indole intermediate were observed in this case. The reaction with 2-ethynylaniline to give (**3j**) was also unsuccessful as previously reported [16].

These first results on the direct alkynylation reaction combined in a one-pot procedure with gold-catalyzed indole ring formation are promising, and analogous strategies combining palladium-catalyzed synthesis of indoles [3] and gold-catalyzed alkynylation could also be envisaged. The next step will be to attempt a one-pot 3-steps synthesis of alkynyl indoles starting directly from iodoaniline.

In conclusion, an efficient access to 2-substituted 3-silylalkynyl indoles is reported. 2-Alkynylanilines underwent a sequential one-pot Au(III)-catalyzed annulation and Au(I)-mediated direct alkynylation. Importantly, this transformation did not require prior aniline protection and proceeded under mild conditions. This methodology represents the first example of the sequential addition of Au(III) and Au(I) catalysts for a one-pot process.

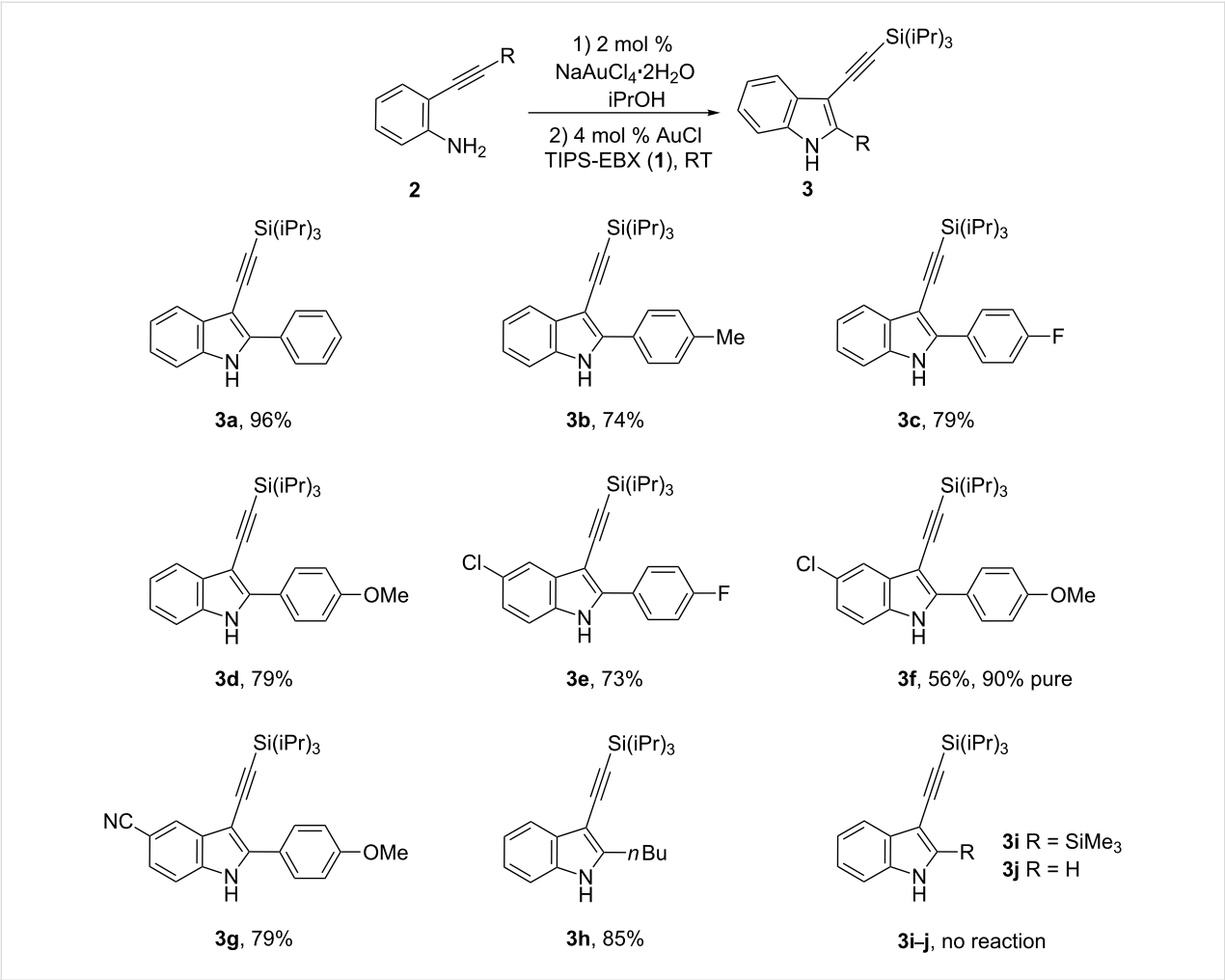
Experimental

General procedure for the synthesis of 2-alkynylanilines **2**

A solution of 2-iodoaniline (**4**) (1 equiv), terminal alkyne (1.2–1.3 equiv), $PdCl_2(PPh_3)_2$ (10 mol %) and CuI (10 mol %) was heated under reflux in Et_3N (15 mL) for 1.5–2 h under a nitrogen atmosphere. The resulting mixture was filtered through Celite®, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography.

General procedure for the synthesis of 2-substituted 3-alkynyl indoles **3**

$NaAuCl_4$ (2–4 mol %) was added to a stirred solution of 2-alkynylaniline **2** (0.40 mmol, 1 equiv) in iPrOH (3 mL) under an ambient atmosphere. The reaction was stirred at RT (80 °C for **3g**) until full conversion (3 h). TIPS-EBX (**1**) (1.2–2.4 equiv) and then AuCl (4–8 mol %) were added. The reaction was stirred until full conversion (4–30 h) and then concentrated



Scheme 6: Scope of the reaction.

under vacuum. Et_2O (20 mL) was added and the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed successively with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography.

Supporting Information

Supporting Information File 1

Experimental details and spectra of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-65-S1.pdf]

Acknowledgements

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License and Terms

Supporting information

One-pot gold-catalyzed synthesis of 3-silylethynyl indoles from unprotected *o*-alkynylanilines

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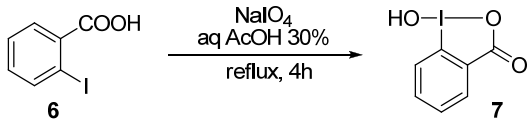
Table of contents

General procedures

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). $NaAuCl_4$ and AuCl was purchased from Aldrich and kept in desiccator under anhydrous condition (decrease of reactivity has been observed for catalyst when prolonged exposed to air (*ca* 1 month)). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem, Maybrige, TCI 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 corrected. ^{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.

TIPS-EBX (1) synthesis

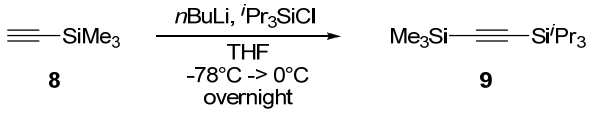
1-Hydroxy-1,2-benziodoxol-3(*1H*)-one (7)



Following a reported procedure [1], $NaIO_4$ (6.7 g, 31 mmol; 1.0 equiv) and 2-iodobenzoic acid (**6**) (7.4 g, 30 mmol, 1.0 equiv) were suspended in 30% (v:v) aq. AcOH (45 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (120 mL) and allowed to cool to room temperature, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 30 mL) and acetone (3 x 30 mL), and air-dried in the dark to give the pure product **7** (7.3 g, 19 mmol, 92% yield) as a colorless solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1 H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1

H, Ar*H*). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m). The characterization data for compounds **7** corresponded to the reported values [1].

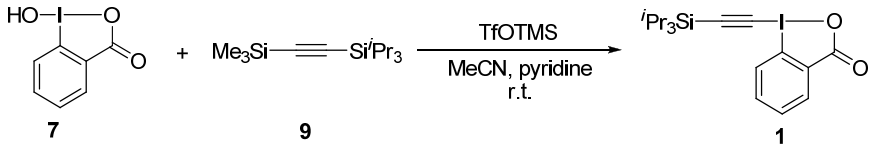
Tri*iso*propylsilyl trimethylsilylacetylene (9)



8 **9**

Following a reported procedure [2], *n*-butyllithium (2.5 M in hexanes, 12.0 mL, 29.9 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**8**) (3.0 g, 30 mmol, 1.0 equiv) in THF (48 mL) at -78 °C. The mixture was then warmed to 0 °C and stirred for 5 min. The mixture was then cooled back to -78 °C and chlorotri*iso*propylsilane (6.4 mL, 30 mmol, 1.0 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (40 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 60 mL). The organic layer was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by Kugelrohr distillation (56-57°C/0.25 mmHg) to yield **9** (7.16 g, 28.0 mmol, 92% yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.08 (m, 21 H, TIPS), 0.18 (s, 9 H, TMS). IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m). Characterization data of **16** corresponded to the literature values [2].

1-[(Tri*iso*propyllsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, 1)

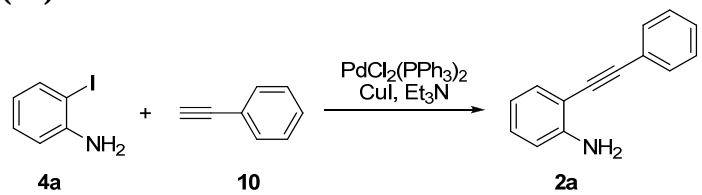


7 **9** **1**

Following a reported procedure [3], 2-iodosylbenzoic acid (**7**) (21.7 g, 82.0 mmol, 1.0 equiv) was charged in oven-dried three-neck 1L flask equipped with a magnetic stirred. After 3 vacuum/nitrogen cycles, anhydrous acetonitrile (500 mL) was added via canula and cooled to 4 °C. Trimethylsilyltriflate (16.4 mL, 90.0 mmol, 1.1 equiv) was added dropwise via a dropping funnel over 30 min (no temperature increase was observed). After 15 min, (trimethylsilyl)(tri*iso*propylsilyl)acetylene (**9**) (23.0 g, 90.0 mmol, 1.1 equiv) was added via canula over 15 min (no temperature increase was observed). After 30 min, the suspension became an orange solution. After 10 min, pyridine (7.0 mL, 90 mmol, 1.1 equiv) was added via syringe. After 15 min, the reaction mixture was transferred in a one-neck 1L flask and reduced under vacuum until a solid was obtained. The solid was dissolved in DCM (200 mL) and transferred in a 1L separatory funnel. The organic layer was added and washed with 1 M HCl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2 x 200 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (*ca* 120 mL) afforded **1** (30.1 g, 70.2 mmol, 86%) as colorless cristals. Mp (Dec.) 170-176°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (m, 1 H, Ar*H*), 8.29 (m, 1 H, Ar*H*), 7.77 (m, 2 H, Ar*H*), 1.16 (m, 21 H, TIPS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1. IR ν 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m). Characterization data of **1** corresponded to the literature values [3].

2-Alkynylanilines synthesis

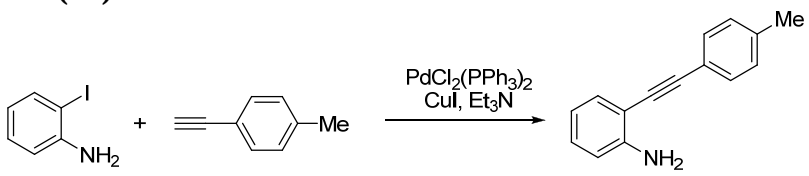
2-(Phenylethynyl)aniline (2a)



4a 10 2a

Following a slightly modified procedure [4], phenylacetylene (**10**) (1.20 ml, 11.0 mmol, 1.2 equiv) was added to a solution of 2-iodoaniline (**4a**) (2.0 g, 9.1 mmol, 1 equiv), $PdCl_2(PPh_3)_2$ (309 mg, 0.440 mmol, 0.05 equiv) and CuI (84 mg, 0.44 mmol, 0. 2 equiv) in Et_3N (50 mL).The resulting suspension was stirred for 2 h under nitrogen at RT. The resulting mixture was filtered over celite and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 8/2) to afford **2a** (1.85 g, 9.57 mmol, quant.) as a orange solid. Mp: 85-87°C (lit [4] 91-92°C). Rf (Pentane/EtOAc 8/2): 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H, ArH), 7.36 (m, 4 H, ArH), 7.15 (td, 1H, *J* = 7.7, 1.5 Hz, ArH), 6.73 (m, 2 H, ArH), 4.28 (s, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 132.1, 131.4, 129.7, 128.4, 128.2, 123.3, 118.0, 114.3, 107.9, 94.7, 85.8. ^{1}H NMR is consistent with reported values [4].

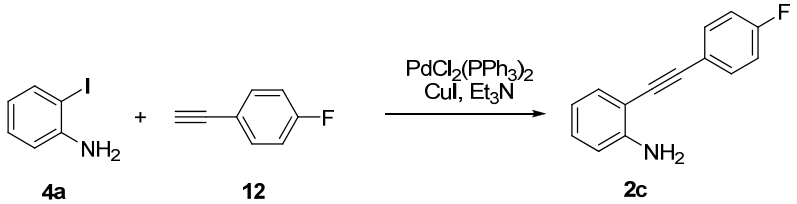
2-(p-Tolylethynyl)aniline (2b)



4a 11 2b

Following a slightly modified procedure [5], a solution of 2-iodoaniline (**4a**) (329 mg, 1.50 mmol, 1 equiv), 1-ethynyl-4-methylbenzene (**11**) (209 mg, 1.80 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (102 mg, 0.150 mmol, 0.1 equiv) and CuI (28 mg, 0.15 mmol, 0.1 equiv) were refluxed in Et_3N (15 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 95/5) to afford **2b** (276 mg, 1.33 mmol, 88%) as a yellow solid. Mp: 104-107°C. Rf (Pentane/EtOAc 95/5): 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2 H, *J* = 8.1 Hz, ArH), 7.38 (m, 1 H, ArH), 7.16 (m, 3 H, ArH), 6.74 (m, 2 H, ArH), 4.28 (s, 2 H, NH_2), 2.39 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 138.3, 132.0, 131.3, 129.5, 129.1, 120.2, 117.9, 114.2, 108.1, 94.8, 85.2, 21.5. IR 3475 (w), 3376 (w), 3056 (w), 3027 (w), 2919 (w), 2863 (w), 2207 (w), 1911 (w), 1611 (s), 1567 (w), 1509 (m), 1489 (m), 1456 (m), 1312 (m), 1258 (w), 1182 (w), 1157 (w), 1028 (w), 940 (w), 909 (w), 869 (w), 819 (s), 747 (s). HRMS (ESI) calcd for $C_{15}H_{14}N^+$ $[M+H]^+$ 208.1121; found 208.1125.

2-((4-Fluorophenyl)ethynyl)aniline (2c)

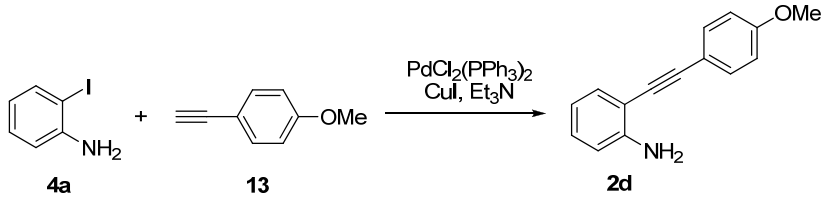


4a 12 2c

Following a slightly modified procedure [5], a solution of 2-iodoaniline (**4a**) (329 mg, 1.50 mmol, 1 equiv), 1-ethynyl-4-fluorobenzene (**12**) (216 mg, 1.80 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (105 mg, 0.15 mmol, 0.1 equiv) and CuI (28 mg, 0.15 mmol, 0.1 equiv) were refluxed in Et_3N (15 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 8/1) to afford **2c** (208 mg, 0.985 mmol, 66%) as a yellow solid. Mp: 97-98°C (lit,[5] 79-81°C). Rf (Pentane/EtOAc 8/1): 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H, ArH), 7.35 (d, 1 H, *J* = 8.1 Hz, ArH), 7.15 (td, 1H, *J* = 7.9, 1.5 Hz, ArH), 7.05 (t, 2 H, *J* = 8.7 Hz, ArH), 6.72 (m, 2 H, ArH), 4.25 (s, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, *J* =

249 Hz), 147.7, 133.2 (d, *J* = 8 Hz), 132.0, 129.7, 119.3 (d, *J* = 3 Hz), 117.9, 115.6 (d, *J* = 22 Hz), 114.3, 107.6, 93.5, 85.5. Consistent with reported values [5].

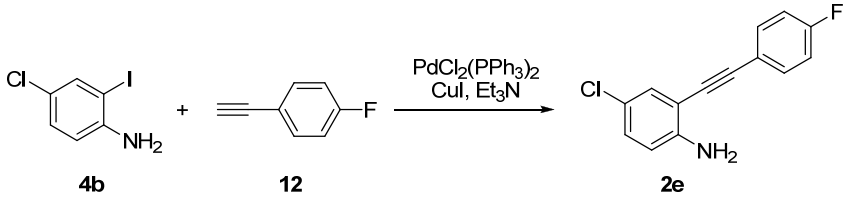
2-((4-Methoxyphenyl)ethynyl)aniline (2d)



4a 13 2d

Following a slightly modified procedure [5], a solution of 2-iodoaniline (**4a**) (329 mg, 1.50 mmol, 1 equiv), 1-ethynyl-4-methoxybenzene (**13**) (258 mg, 1.95 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (105 mg, 0.15 mmol, 0.1 equiv) and CuI (28 mg, 0.15 mmol, 0.1 equiv) were refluxed in Et_3N (15 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 8/1) to afford **2d** (330 mg, 1.48 mmol, 98%) as a yellow solid. Mp: 109-110°C. Rf (Pentane/EtOAc 8/1): 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dt, 2 H, *J* = 9.5, 2.6 Hz, ArH), 7.35 (ddd, 1 H, *J* = 7.5, 1.6, 0.6 Hz, ArH), 7.12 (ddd, 1 H, *J* = 8.1, 7.3, 1.6 Hz, ArH), 6.88 (dt, 2 H, *J* = 9.4, 2.6 Hz, ArH), 6.71 (m, 2 H, ArH), 4.25 (m, 2 H, NH_2), 3.83 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 147.6, 132.9, 132.0, 129.4, 118.0, 115.4, 114.3, 114.0, 108.3, 94.6, 84.4, 55.3. Consistent with reported values [5].

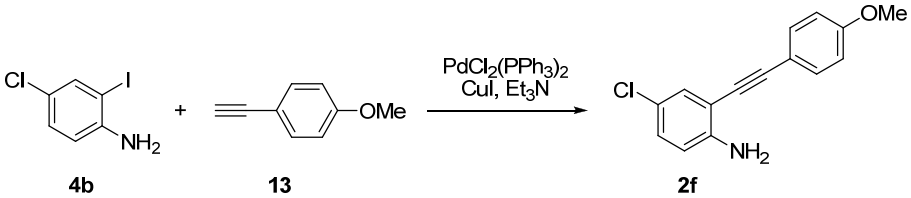
4-Chloro-2-((4-fluorophenyl)ethynyl)aniline (2e)



4b 12 2e

Following a slightly modified procedure [5], a solution of 4-chloro-2-iodoaniline (**4b**) (304 mg, 1.20 mmol, 1 equiv), 1-ethynyl-4-fluorobenzene (**12**) (173 mg, 1.44 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (84 mg, 0.12 mmol, 0.1 equiv) and CuI (23 mg, 0.12 mmol, 0.1 equiv) was refluxed in Et_3N (12 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/Et_2O 8/2 to 6/4) to afford **2e** (283 mg, 1.15 mmol, 96%) as a yellow solid. Mp: 84-86°C. Rf (Pentane/Et_2O 8/2): 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H, ArH), 7.32 (d, 1 H, *J* = 2.4 Hz, ArH), 7.07 (m, 3 H, ArH), 6.65 (d, 1 H, *J* = 8.7 Hz, ArH), 4.26 (s, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 250 Hz), 146.4, 133.5 (d, *J* = 8 Hz), 131.4, 129.8, 122.3, 119.0, 115.9, 115.8 (d, *J* = 22 Hz), 109.1, 94.5, 84.4. IR 3474 (w), 3385 (w), 3050 (w), 1890 (w), 1616 (m), 1612 (m), 1508 (s), 1486 (s), 1411 (m), 1309 (w), 1284 (w), 1229 (s), 1155 (m), 1092 (w), 901 (w), 834 (s), 810 (s), 787 (m), 741 (w), 680 (w). HRMS (ESI) calcd for $C_{14}ClFH_{10}N^+$ $[M+H]^+$ 246.0480; found 246.0484.

4-Chloro-2-((4-methoxyphenyl)ethynyl)aniline (2f)

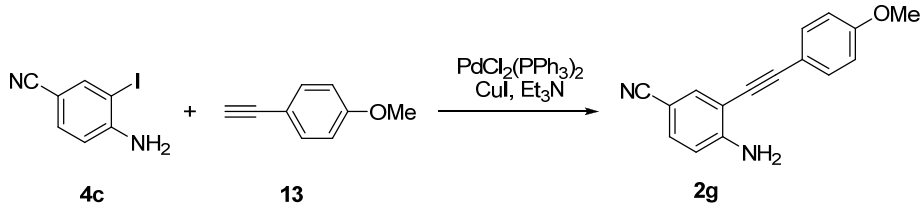


4b 13 2f

Following a slightly modified procedure [5], a solution of 4-chloro-2-iodoaniline (**4b**) (304 mg, 1.20 mmol, 1 equiv), 1-ethynyl-4-methoxybenzene (**13**) (206 mg, 1.56 mmol, 1.3 equiv), $PdCl_2(PPh_3)_2$ (84 mg, 0.12 mmol, 0.1 equiv) and CuI (23 mg, 0.12 mmol, 0.1 equiv) were refluxed in Et_3N (12 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 8/2) to afford **2f** (331 mg, 1.33 mmol, 89%) as an orange solid. Mp: 97-99°C. Rf (Pentane/EtOAc 8/2): 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2 H, ArH), 7.32 (d, 1 H, *J* = 2.5 Hz, ArH), 7.07 (dd, 1 H, *J* = 8.6, 2.5 Hz, ArH), 6.89 (m, 2 H, ArH),

6.64 (d, 1 H, J = 8.7 Hz, ArH), 4.26 (s, 2 H, NH_2), 3.83 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 146.2, 133.0, 131.2, 129.3, 122.2, 115.3, 114.8, 114.1, 109.7, 95.6, 83.3, 55.3. IR 3464 (w), 3362 (w), 3037 (w), 2932 (w), 2840 (w), 2201 (w), 1605 (s), 1567 (w), 1513 (s), 1488 (s), 1460 (w), 1410 (w), 1294 (s), 1249 (s), 1174 (m), 1152 (w), 1089 (w), 1032 (m), 901 (w), 839 (s), 818 (m), 778 (w), 737 (m). HRMS (ESI) calcd for $C_{15}ClH_{13}NO^+$ $[M+H]^+$ 258.0686; found 258.0683.

4-Amino-3-((4-methoxyphenyl)ethynyl)benzonitrile (2g)



4c **13** **2g**

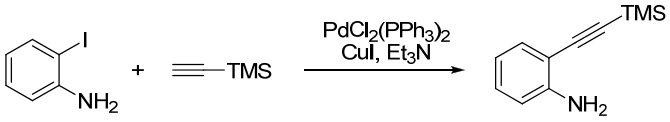
Following a slightly modified procedure [5], a solution of 4-cyano-2-iodoaniline (**4c**) (366 mg, 1.50 mmol, 1 equiv), 1-ethynyl-4-methoxybenzene (**13**) (238 mg, 1.80 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (102 mg, 0.150 mmol, 0.1 equiv) and CuI (28 mg, 0.15 mmol, 0.1 equiv) were refluxed in Et_3N (15 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 7/3) to afford **2g** (331 mg, 1.33 mmol, 89%) as an orange solid. Mp: 138-140°C. Rf (Pentane/EtOAc 7/3): 0.3. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 1 H, J = 1.5 Hz, ArH), 7.46 (d, 2 H, J = 8.7 Hz, ArH), 7.34 (dd, 1 H, J = 8.5, 1.6 Hz, ArH), 6.89 (d, 2 H, J = 8.7 Hz, ArH), 6.70 (d, 1 H, J = 8.5 Hz, ArH), 4.79 (s, 2 H, NH_2), 3.83 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 150.8, 136.1, 133.0, 132.9, 119.4, 114.3, 114.1, 113.8, 108.5, 100.0, 96.2, 82.0, 55.3. IR 3459 (m), 3354 (m), 3218 (w), 3055 (w), 2956 (w), 2838 (w), 2217 (s), 1618 (s), 1606 (s), 1559 (w), 1505 (s), 1467 (w), 1423 (w), 1337 (w), 1288 (m), 1248 (s), 1174 (m), 1158 (w), 1109 (w), 1026 (m), 907 (w), 832 (s), 787 (w), 736 (w). HRMS (ESI) calcd for $C_{16}H_{13}N_2O^+$ $[M+H]^+$ 249.1022; found 249.1014.

2-(Hex-1-yn-1-yl)aniline (2h)

4a **14** **2h**

Following a slightly modified procedure [5], a solution of 2-iodoaniline (**4a**) (438 mg, 2.00 mmol, 1 equiv), 1-hexyne (**14**) (277 µL, 2.4 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (135 mg, 0.200 mmol, 0.1 equiv) and CuI (38 mg, 0.20 mmol, 0.1 equiv) were refluxed in Et_3N (20 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 98/2) to afford **2h** (293 mg, 1.69 mmol, 85%) as a yellow liquid. Rf (Pentane/EtOAc 98/2): 0.15. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, 1 H, J = 7.5, 1.4 Hz, ArH), 7.09 (m, 1 H, ArH), 6.68 (m, 2 H, ArH), 4.17 (br s, 2 H, NH_2), 2.49 (t, 2 H, J = 7.0 Hz, CH_2), 1.62 (m, 2 H, CH_2), 1.51 (m, 2 H, CH_2), 0.97 (t, 3 H, J = 7.3 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 132.1, 128.8, 117.9, 114.2, 109.0, 95.8, 77.0, 31.1, 22.1, 19.4, 13.7. Consistent with reported values [6].

2-((Trimethylsilyl)ethynyl)aniline (2i)

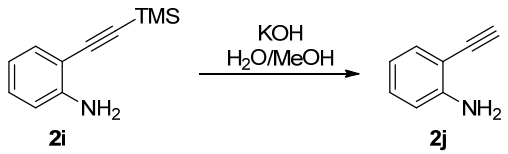


4a **15** **2i**

Following a slightly modified procedure [5], a solution of 2-iodoaniline (**4a**) (438 mg, 2.00 mmol, 1 equiv), trimethylsilyl acetylene (**15**) (342 µL, 2.40 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (135 mg, 0.200 mmol, 0.1 equiv) and CuI (38 mg, 0.20 mmol, 0.1 equiv) were refluxed in Et_3N (20 mL) for 2 h under nitrogen. The resulting mixture was filtered over celite, washed with DCM and concentrated under vacuum. The resulting solid was purified by column chromatography (Pentane/EtOAc 98/2) to afford **2i** (242 mg, 1.28 mmol, 64%) as a colorless liquid. Rf (Pentane/EtOAc 98/2): 0.25.^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.5, 1.3 Hz, 1

H, ArH), 7.12 (dt, *J* = 7.8, 1.6 Hz, ArH), 6.67 (m, 2 H, ArH), 4.24 (br s, 2 H, NH_2), 0.29 (s, 9 H, TMS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 132.2, 129.8, 117.7, 114.1, 107.7, 101.8, 99.7, 0.1. Consistent with reported values [7].

2-(Ethynyl)aniline (2j)

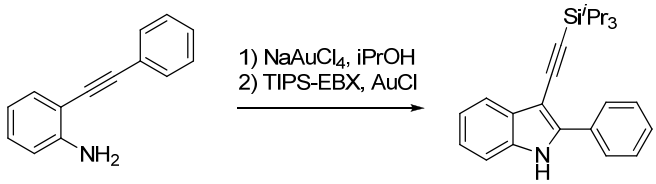


2i **2j**

KOH (1M in H_2O, 700 µL, 0.700 mmol, 1.1 equiv) was added to a stirring solution of **2i** (121mg, 0.640 mmol, 1 equiv) in MeOH (2 mL). After 1 h, the reaction was diluted in DCM (20 mL) and water (20 mL). The layers were separated and the aqueous layer extracted with DCM (20 mL). The organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to afford **2j** (69 mg, 0.59 mmol, 92%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, 1 H, *J* = 8.0, 1.6 Hz, ArH), 7.16 (td, *J* = 7.8, 1.5 Hz, 1 H, ArH), 6.70 (m, 2 H, ArH), 4.26 (br s, 2 H, NH_2), 3.40 (s, 1 H, CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 132.5, 130.1, 117.7, 114.2, 106.5, 82.4, 80.6. Consistent with reported values [8].

Sequential annulations/Direct alkynylation

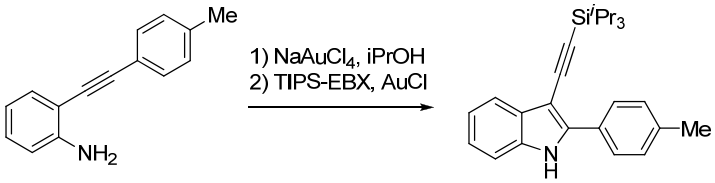
2-Phenyl-3-((triisopropylsilyl)ethynyl)-*1H*-indole (3a)



2a **3a**

$NaAuCl_4$ (3.2 mg, 0.0081 mmol, 0.02 equiv) was added to a stirring solution of **2a** (78 mg, 0.40 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at RT for 3 h. TIPS-EBX (**1**) (206 mg, 0.480 mmol, 1.2 equiv) and then AuCl (3.7 mg, 0.016 mmol, 0.04 equiv) were added. The reaction was stirred for 30 h and then concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 8/2) afforded **3a** (1. run: 145 mg, 0.388 mmol, 97 %, 2. run: 142 mg, 0.380 mmol, 95%) as brown amorphous solid. R*f* (Pentane/Et_2O 8/2): 0.4. ^1H NMR ($CDCl_3$, 400MHz) δ 8.32 (br s, 1 H; NH), 8.11 (m, 2 H; ArH), 7.80 (m, 1 H; ArH), 7.49 (m, 2 H; ArH), 7.40 (m, 2 H; ArH), 7.27 (m, 2H; ArH), 1.24 (m, 21 H; TIPS). ^{13}C NMR ($CDCl_3$, 101MHz) δ 139.7, 135.1, 131.3, 130.8, 128.7, 128.3, 126.4, 123.4, 120.9, 120.1, 110.9, 101.2, 96.5, 95.1, 18.8, 11.5. Consistent with reported values [9].

2-(*p*-Tolyl)-3-((triisopropylsilyl)ethynyl)-*1H*-indole (3b)

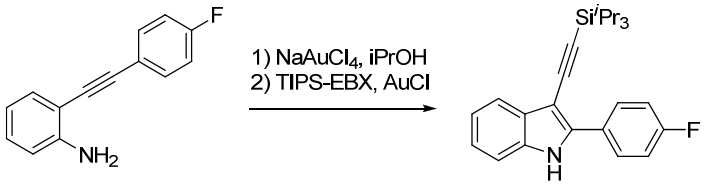


2b **3b**

$NaAuCl_4$ (3.2 mg, 0.0081 mmol, 0.02 equiv) was added to a stirring solution of **2b** (83 mg, 0.40 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at RT for 3 h. TIPS-EBX (**1**) (206 mg, 0.480

mmol, 1.2 equiv) and then AuCl (3.7 mg, 0.016 mmol, 0.04 equiv) were added. The reaction was stirred for 24 h and the concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 9/1) afforded **3b** (115 mg, 0.296 mmol, 74 %) as an orange amorphous solid. R*f* (Pentane/Et_2O 9/1): 0.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1 H, NH), 8.00 (d, 2 H, *J* = 8.2 Hz, ArH), 7.75 (d, 1 H, *J* = 6.9 Hz, ArH), 7.36 (m, 1 H, ArH), 7.25 (m, 4 H, ArH), 2.42 (s, 3 H, CH_3), 1.21 (m, 21 H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 138.4, 135.0, 130.9, 129.4, 128.6, 126.2, 123.3, 120.9, 120.0, 110.8, 101.4, 96.0, 95.0, 21.4, 18.8, 11.5. IR 3418 (m), 3063 (w), 2942 (s), 2863 (s), 2141 (s), 1676 (w), 1617 (w), 1504 (w), 1458 (s), 1382 (w), 1327 (m), 1305 (w), 1235 (m), 1175 (w), 1115 (w), 1060 (w), 1010 (w), 997 (m), 910 (m), 883 (m), 821 (m), 780 (m), 743 (s), 677 (s). HRMS (ESI) calcd for $C_{26}H_{34}NSi^+$ $[M+H]^+$ 388.2455; found 388.2459

2-(4-Fluorophenyl)-3-((triisopropylsilyl)ethynyl)-*1H*-indole (3c)



2c **3c**

$NaAuCl_4$ (3.2 mg, 0.0081 mmol, 0.02 equiv) was added to a stirring solution of **2c** (84 mg, 0.40 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at RT for 3 h. TIPS-EBX (**1**) (206 mg, 0.480 mmol, 1.2 equiv) and then AuCl (3.7 mg, 0.016 mmol, 0.04 equiv) were added. The reaction was stirred for 30 h and then concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 8/2) afforded **3c** (124 mg, 0.317 mmol, 79 %) as brown amorphous solid. R*f* (Pentane/Et_2O 8/2): 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1 H, NH), 7.93 (dd, 2 H, *J* = 8.9, 5.3 Hz, ArH), 7.65 (m, 1 H, ArH), 7.25 (m, 1 H, ArH), 7.14 (m, 2 H, ArH), 7.04 (t, 2 H, *J* = 8.6 Hz, ArH), 1.10 (m, 21 H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 249 Hz), 138.8, 135.1, 130.7, 128.4 (d, *J* = 8 Hz), 127.7 (d, *J* = 3 Hz), 123.6, 121.1, 120.1, 115.9 (d, *J* = 22 Hz), 110.9, 101.0, 96.5, 95.2, 18.8, 11.5. IR 3422 (w), 2864 (m), 1890 (w), 1546 (w), 1502 (m), 1457 (m), 1440 (m), 1367 (w), 1327 (m), 1235 (s), 1162 (m), 1153 (w), 1104 (w), 1059 (w), 996 (m), 908 (m), 883 (m), 836 (s), 781 (m), 781 (m), 742 (s), 679 (s). HRMS (ESI) calcd for $C_{25}FH_{31}NSi^+$ $[M+H]^+$ 392.2204; found 392.2195

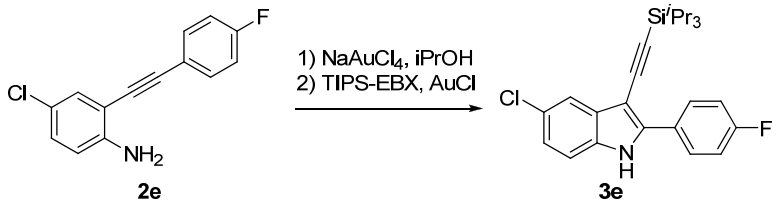
2-(4-Methoxyphenyl)-3-((triisopropylsilyl)ethynyl)-*1H*-indole (3d)

2d **3d**

$NaAuCl_4$ (3.2 mg, 0.0081 mmol, 0.02 equiv) was added to a stirring solution of **2d** (89 mg, 0.40 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at RT for 3 h. DCM (1.5 mL), TIPS-EBX (**1**) (206 mg, 0.480 mmol, 1.2 equiv) and then AuCl (3.7 mg, 0.016 mmol, 0.04 equiv) were added. The reaction was stirred for 18 h and then concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 8/2)

afforded **3d** (128 mg, 0.317 mmol, 79 %) as a brown oil. R*f* (Pentane/Et_2O 8/2): 0.4. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1 H, NH), 8.04 (m, 2 H, ArH), 7.75 (m, 1 H, ArH), 7.36 (m, 1 H, ArH), 7.24 (m, 2 H, ArH), 7.00 (m, 2 H, ArH), 3.90 (s, 3 H. CH_3), 1.22 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 139.9, 135.0, 130.9, 129.6, 127.8, 124.1, 123.1, 119.9, 114.1, 110.7, 101.5, 95.4, 94.7, 55.4, 18.8, 11.5. IR 3415 (w), 3063 (w), 2863 (m), 2140 (m), 1612 (m), 1578 (w), 1545 (w), 1504 (s), 1458 (s), 1439 (m), 1367 (w), 1328 (w), 1308 (m), 1285 (m), 1255 (s), 1184 (m), 1116 (w), 1062 (w), 1032 (m), 1019 (w), 911 (w), 883 (m), 834 (m), 790 (m), 744 (s), 678 (m), 659 (m). HRMS (ESI) calcd for $C_{26}H_{34}NOSi^+$ $[M+H]^+$ 404.2404; found 404.2423.

5-Chloro-2-(4-fluorophenyl)-3-((triisopropylsilyl)ethynyl)-*1H*-indole (3e)



2e **3e**

$NaAuCl_4$ (3.2 mg, 0.0081 mmol, 0.02 equiv) was added to a stirring solution of **2e** (98 mg, 0.40 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at RT for 3 h. TIPS-EBX (**1**) (206 mg, 0.480 mmol, 1.2 equiv) and then AuCl (3.7 mg, 0.016 mmol, 0.04 equiv) were added. The reaction was stirred for 30 h and then concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 9/1 to 7/3) afforded **3e** (124 mg, 0.291 mmol, 73 %) as grey solid. Mp: 99-100°C. R*f* (Pentane/Et_2O 9/1): 0.2. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1 H, NH), 8.03 (m, 2 H, ArH), 7.68 (d, 1 H, *J* = 1.5 Hz, ArH), 7.27 (m, 1 H, ArH), 7.18 (m, 3 H, ArH), 1.21 (m, 21 H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (d, *J* = 249 Hz), 140.1, 133.4, 131.7, 128.4 (d, *J* = 8 Hz), 127.2 (d, *J* = 3 Hz), 126.9, 123.9, 119.6, 115.9 (d, *J* = 22 Hz), 112.0, 100.1, 96.2, 95.8, 18.8, 11.4. IR 2926 (s), 2848 (s), 2106 (w), 1587 (w), 1530 (w), 1486 (m), 1433 (s), 1344 (w), 1294 (w), 1260 (m), 1200 (w), 1141 (w), 1089 (w), 1052 (w), 961 (w), 893 (s), 863 (m), 827 (m), 774 (w), 759 (m), 707 (s). HRMS (ESI) calcd for $C_{25}ClFH_{30}NSi^+$ $[M+H]^+$ 426.1815; found 426.1824.

5-Chloro-2-(4-methoxyphenyl)-3-((triisopropylsilyl)ethynyl)-*1H*-indole (3f)

2f **3f**

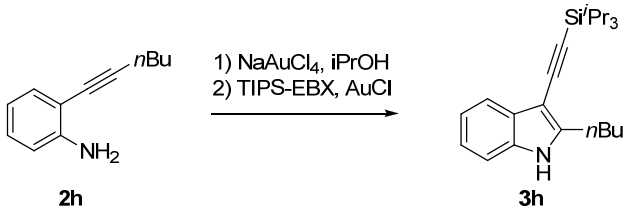
$NaAuCl_4$ (3.2 mg, 0.0081 mmol, 0.02 equiv) was added to a stirring solution of **2f** (103 mg, 0.400 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at RT for 3 h. DCM (1.5 mL), TIPS-EBX (**1**) (206 mg, 0.480 mmol, 1.2 equiv) and then AuCl (7.4 mg, 0.032 mmol, 0.08 equiv) were added. The reaction was stirred for 30 h and then concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 8/2) afforded **3f** (99 mg, 0.23 mmol, 56 %, 90% pure) as a grey solid. Analytically pure product was obtained by preparative TLC (Pentane/Et_2O 7/3). R*f* (Pentane/Et_2O 7/3): 0.2. Mp: 180-182°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1 H, NH), 8.01 (m, 2 H, ArH), 7.65 (d, 1 H, *J* = 2.0 Hz, ArH), 7.27 (m, 1 H, ArH), 7.18 (dd, 1 H, *J* = 8.5, 2.0 Hz, ArH), 6.99 (m, 2 H, ArH), 3.88 (s, 3 H, CH_3), 1.19 (m, 21 H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 141.2, 133.3, 132.0, 127.9, 126.7, 123.6, 123.4, 119.4, 114.2, 111.7, 100.6, 98.4, 95.3, 55.4, 18.8, 11.5. IR 3427 (w), 2865 (w), 2141 (w), 1545 (w), 1503 (m), 1467 (s), 1311 (w), 1288 (m),

1256 (s), 1183 (m), 1073 (w), 1033 (m), 997 (w), 910 (m), 883 (w), 837 (m), 803 (s), 735 (m), 697 (m), 667 (m). HRMS (ESI) calcd for $C_{26}ClH_{33}NOSi^+$ $[M+H]^+$ 438.2014; found 438.2018.

2-(4-Methoxyphenyl)-3-((triisopropylsilyl)ethynyl)-*1H*-indole-5-carbonitrile (3g)

$NaAuCl_4$ (6.4 mg, 0.016 mmol, 0.04 equiv) was added to a stirring solution of **2g** (99 mg, 0.40 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at 80°C for 3 h. The reaction was cooled to RT and DCM (1.5 mL), TIPS-EBX (**1**) (206 mg, 0.480 mmol, 1.2 equiv) and then AuCl (7.4 mg, 0.032 mmol, 0.08 equiv) were added. The reaction was stirred for 18 h and then TIPS-EBX (206 mg, 0.480 mmol, 1.2 equiv) was added. After 12 h the reaction was concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 5/5 to 3/7) afforded **3g** (98 mg, 0.23 mmol, 54 %, 95% pure) as a grey solid. A second batch of product **3g** (48 mg, 0.11 mmol, 25 %, 90% pure) was also obtained. Analytically pure product was obtained by recrystallization in hexanes/EtOAc. Combined yield: 79%. R*f* (Pentane/Et_2O 5/5): 0.2. Mp: 158-159°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1 H, NH), 8.04 (m, 2 H, ArH), 8.00 (m, 1 H, ArH), 7.42 (m, 2 H, ArH), 6.97 (m, 2 H, ArH), 3.85 (m, 3 H, CH_3), 1.20 (m, 21 H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 142.0, 136.7, 130.7, 128.1, 126.0, 125.0, 123.0, 120.7, 114.3, 111.7, 103.6, 99.8, 96.4, 95.7, 55.4, 18.8, 11.4. IR 3310 (m), 2941 (m), 2864 (m), 2223 (m), 2142 (m), 1707 (w), 1615 (m), 1586 (w), 1546 (w), 1504 (s), 1473 (s), 1382 (w), 1293 (m), 1255 (s), 1184 (s), 1133 (w), 1034 (m), 1025 (w), 909 (m), 884 (m), 833 (m), 805 (m), 739 (s), 672 (m), 661 (m). HRMS (ESI) calcd for $C_{27}H_{33}N_2OSi^+$ $[M+H]^+$ 429.2357; found 429.2369.

2-butyl-3-((triisopropylsilyl)ethynyl)-*1H*-indole (3h)



$NaAuCl_4$ (3.2 mg, 0.0081 mmol, 0.02 equiv) was added to a stirring solution of **2h** (69 mg, 0.40 mmol, 1 equiv) in ^{i}PrOH (3 mL) under air. The reaction was stirred at RT for 3 h. TIPS-EBX (**1**) (206 mg, 0.480 mmol, 1.2 equiv) and then AuCl (3.7 mg, 0.016 mmol, 0.04 equiv) were added. The reaction was stirred for 4 h and the concentrated under vacuum. Et_2O (20 mL) was added, the organic layer was washed twice with 0.1 M NaOH (20 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (Pentane/Et_2O 9/1) afforded **3h** (120 mg, 0.339 mmol, 85 %) as yellow oil. R*f* (Pentane/Et_2O 9/1): 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1 H, NH), 7.65 (m, 1 H, ArH), 7.27 (m, 1H, ArH), 7.16 (m, 2 H, ArH), 2.90 (t, 2 H, J = 7.5 Hz, CH_2), 1.74 (m, 2 H, CH_2), 1.41 (m, 2 H, CH_2), 1.18 (m, 21 H, TIPS), 0.95 (t, 3 H, J = 7.3 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 134.4, 129.5, 122.1, 120.5, 119.4, 110.5, 100.6, 96.7, 93.1, 31.2, 27.1, 22.3, 18.8, 13.8, 11.4. IR 3401 (m), 2958 (s), 2942 (s), 2865 (s), 2146 (s), 1617 (w), 1548 (w), 1460 (s), 1382 (w), 1330 (w), 1242 (m), 1158 (w), 1077 (w), 1000 (w), 997 (w), 920 (w), 883 (m), 778 (m), 743 (s), 677 (s), 631 (s). HRMS (ESI) calcd for $C_{23}H_{36}NSi^+$ $[M+H]^+$ 354.2612; found 354.2606.

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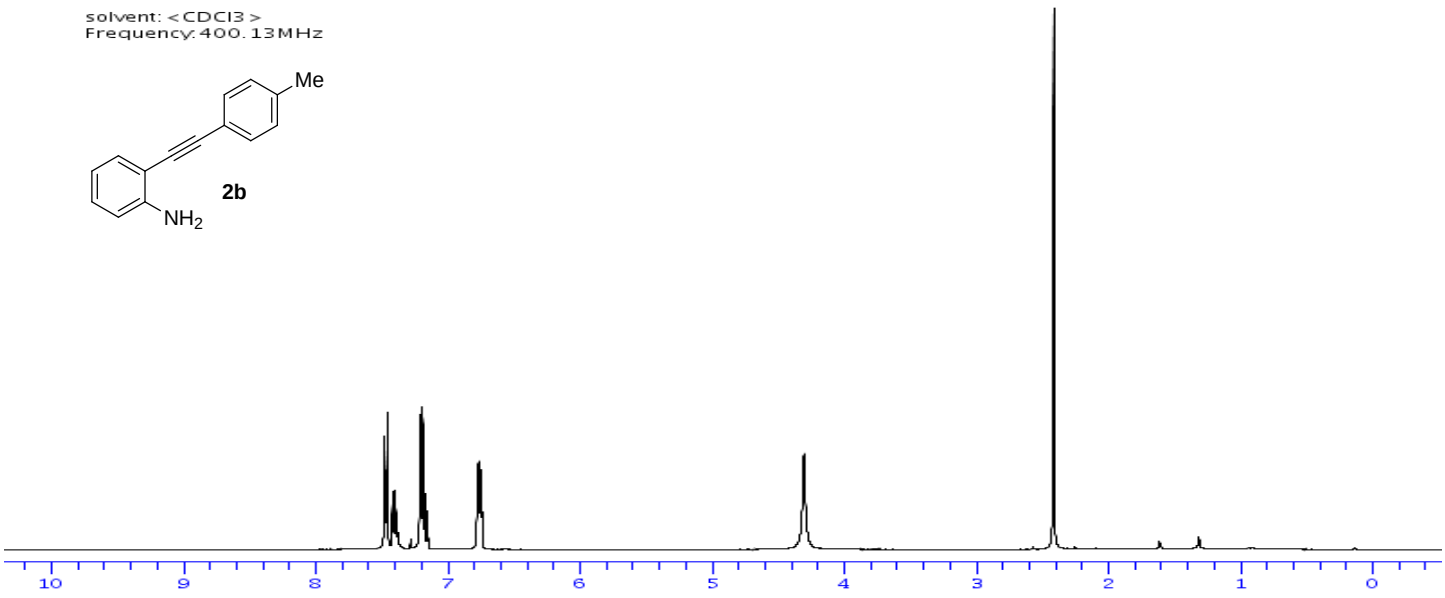
Spectra of new compounds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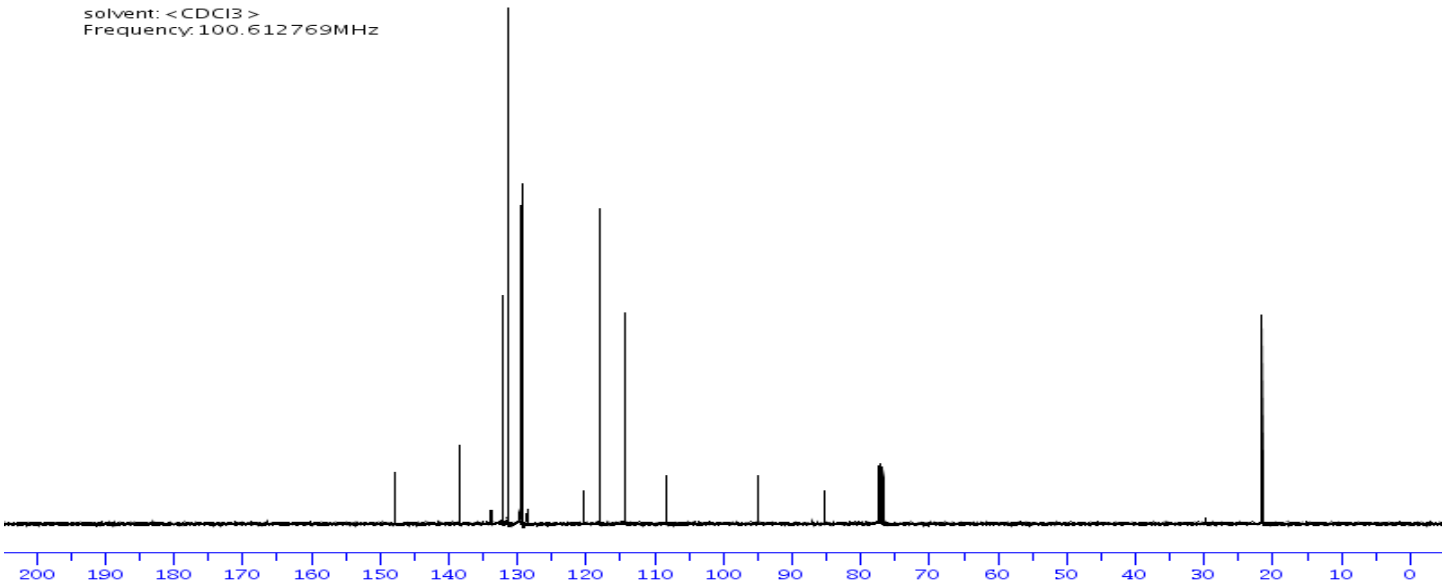
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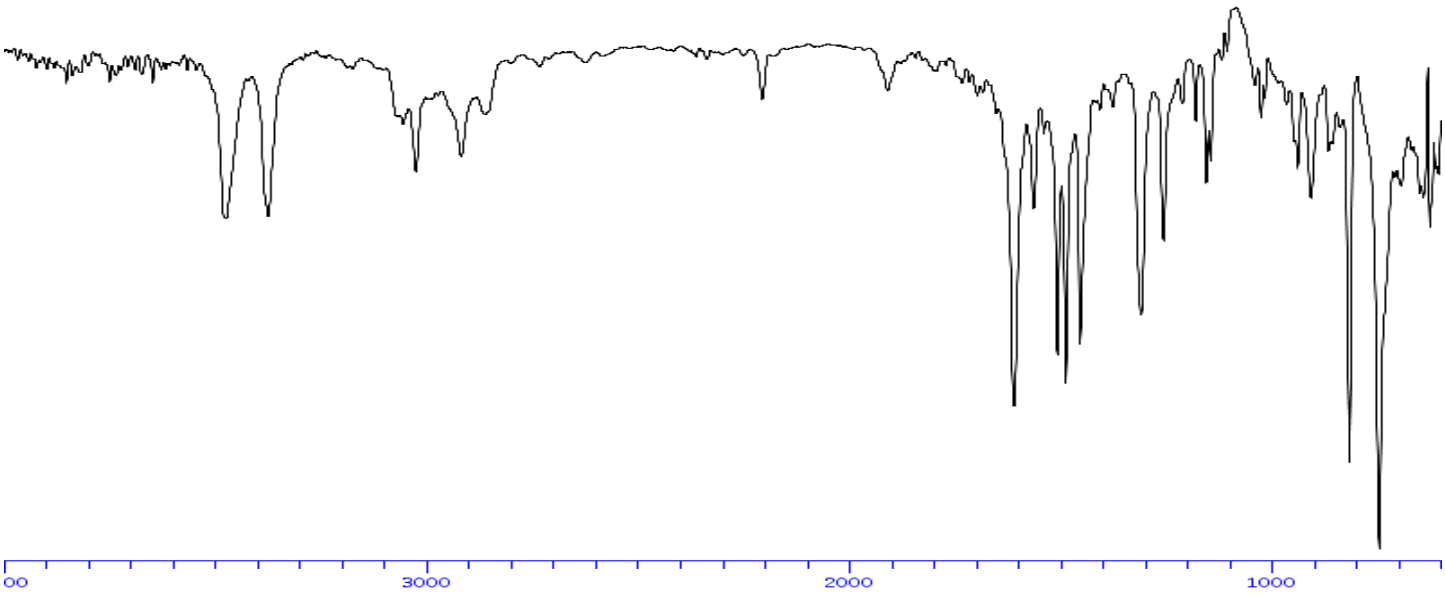
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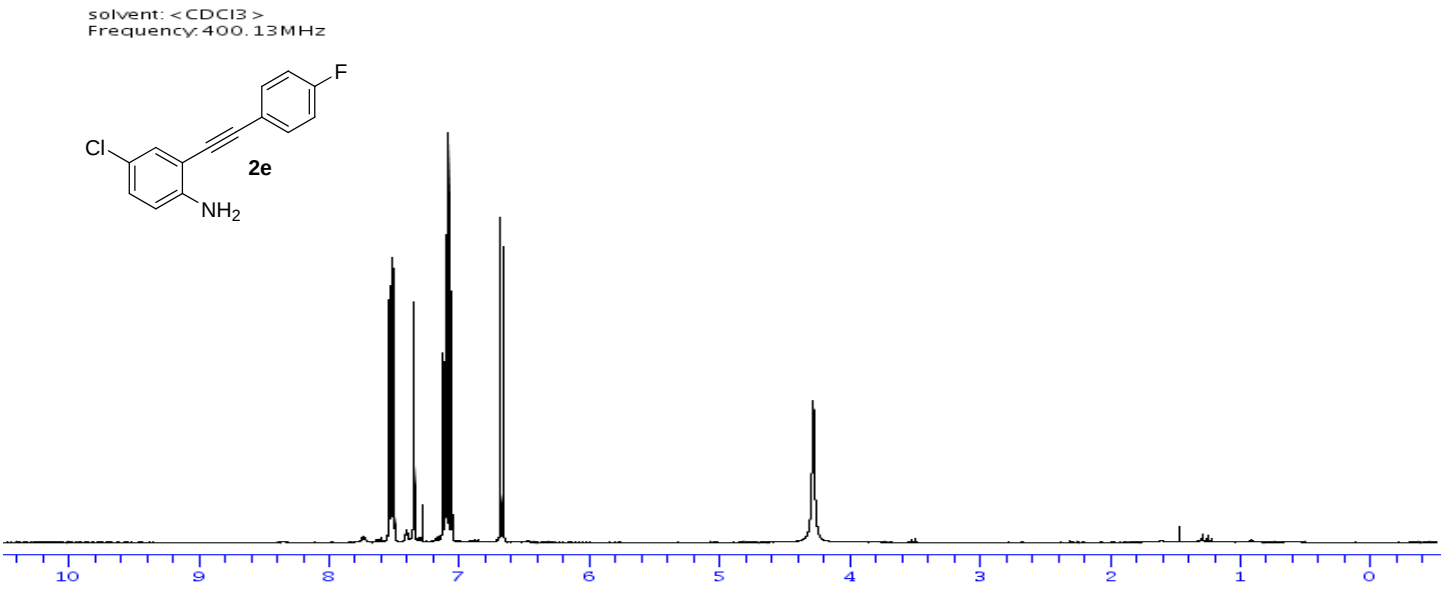
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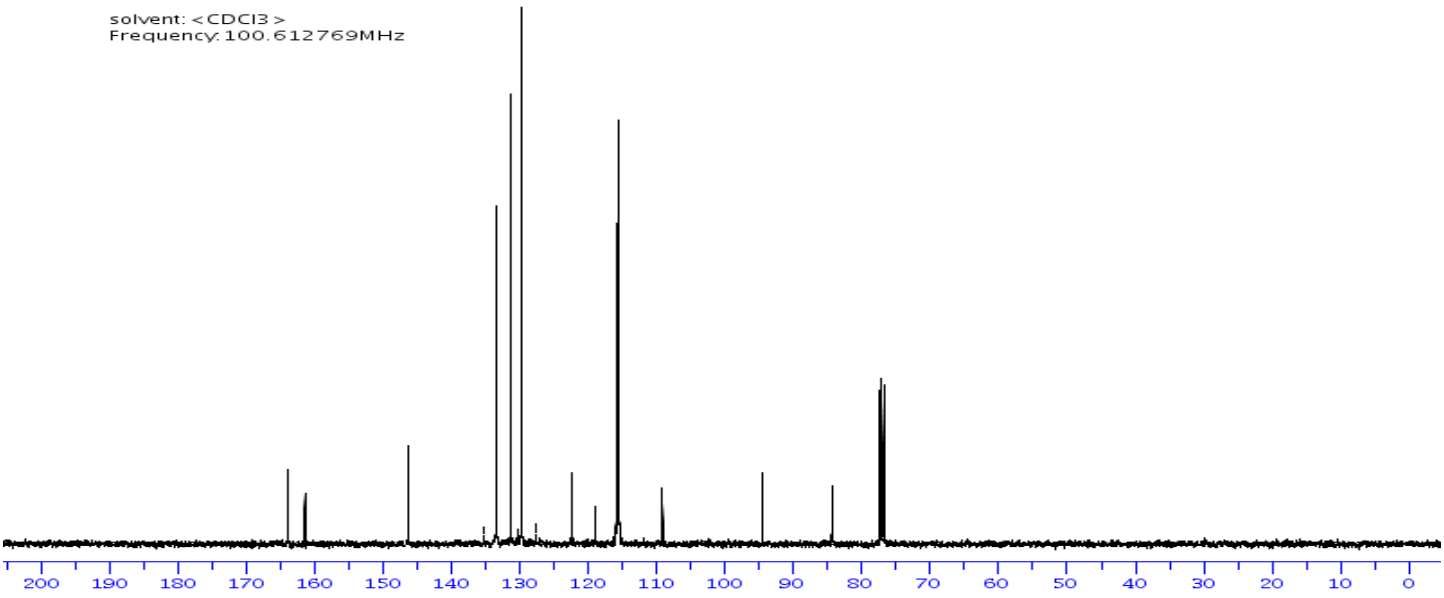
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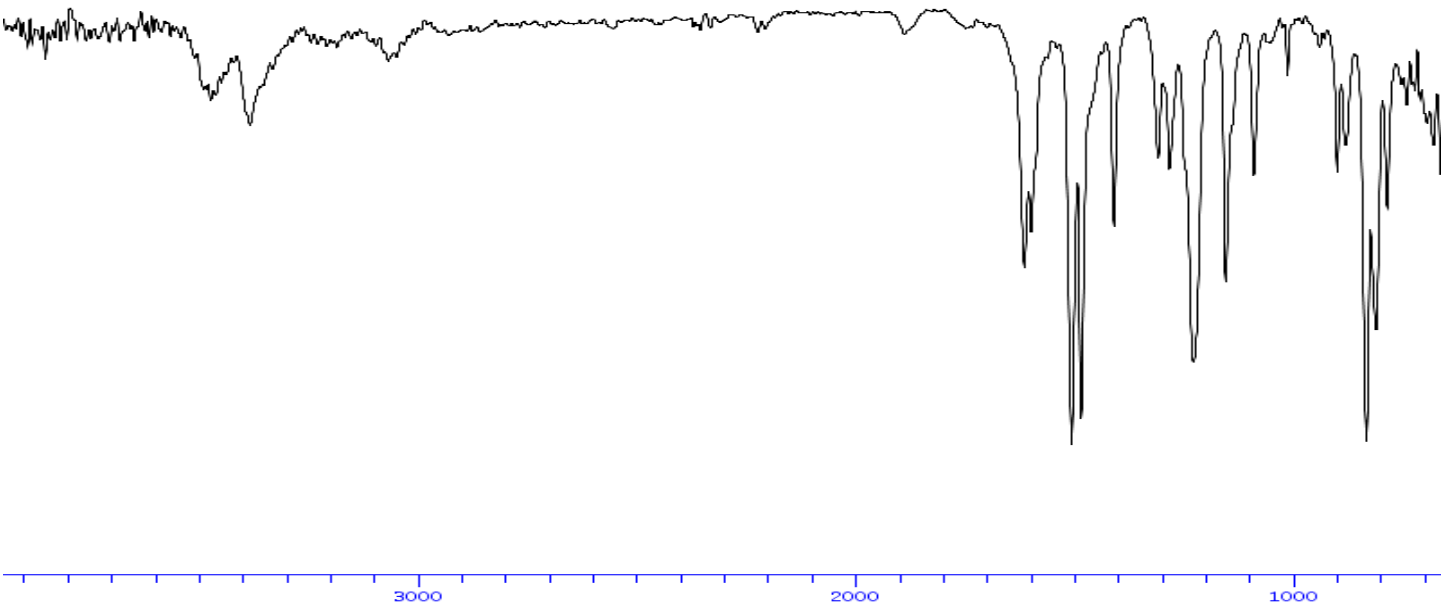
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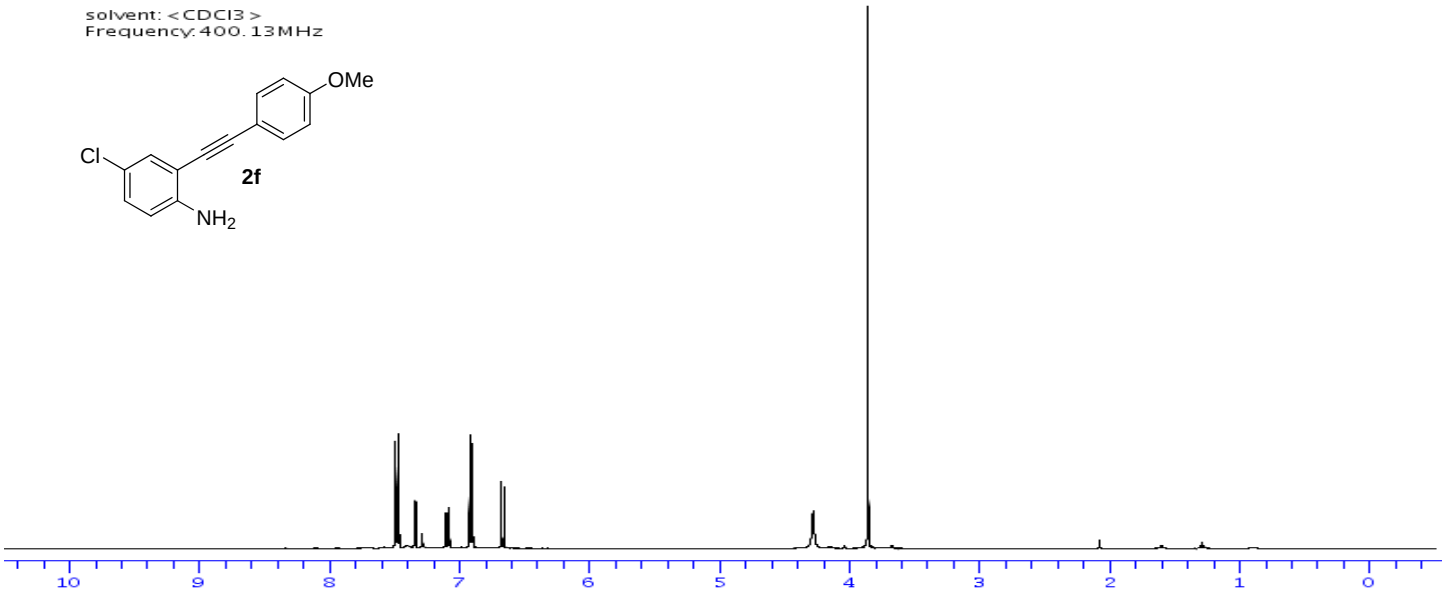
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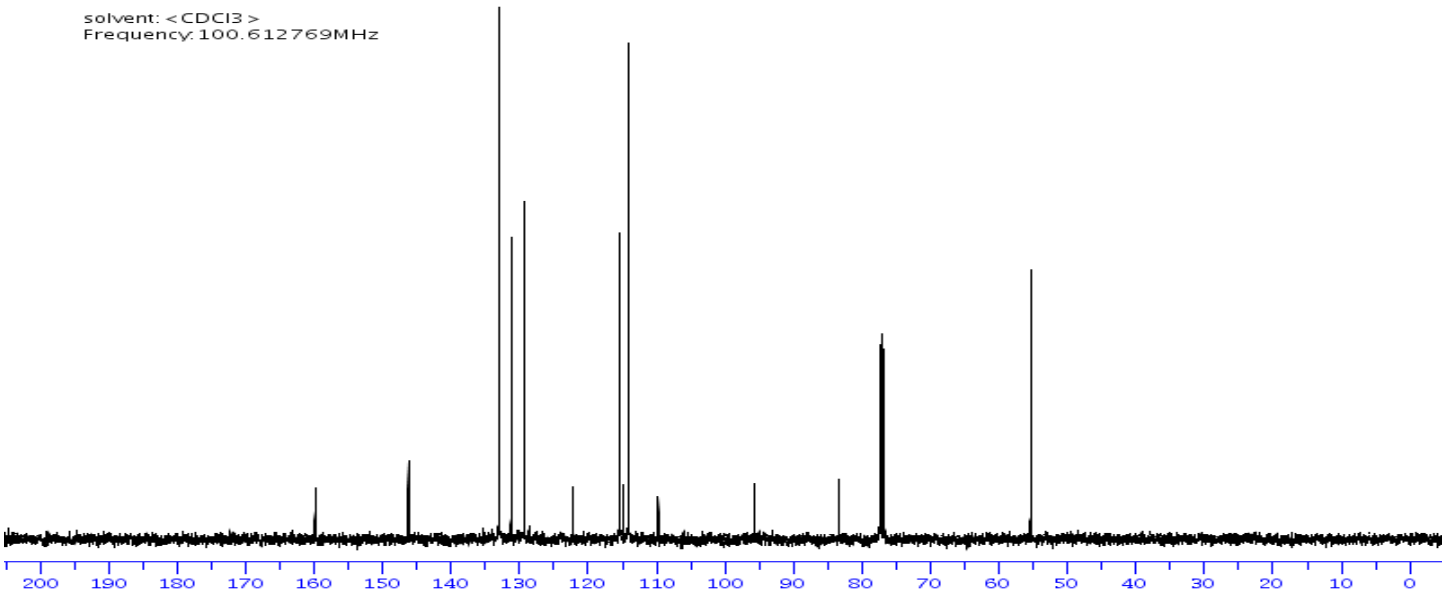
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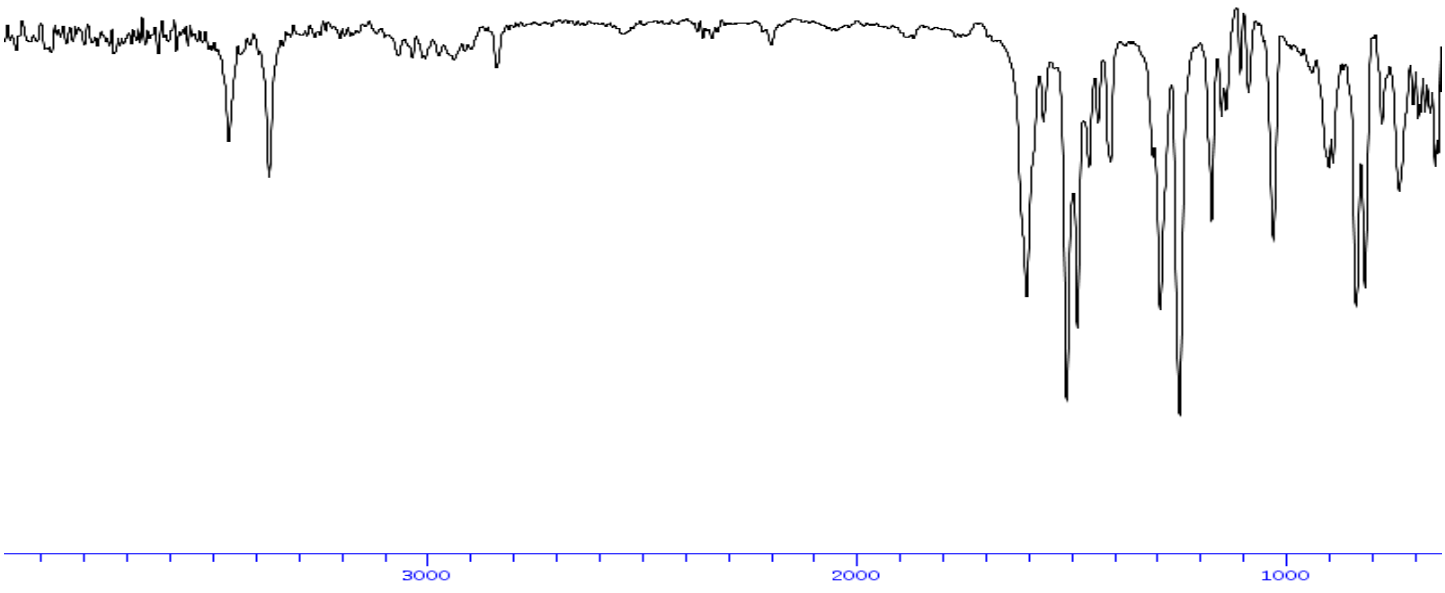
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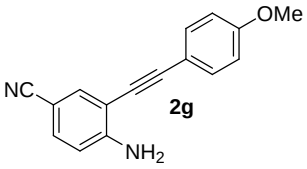

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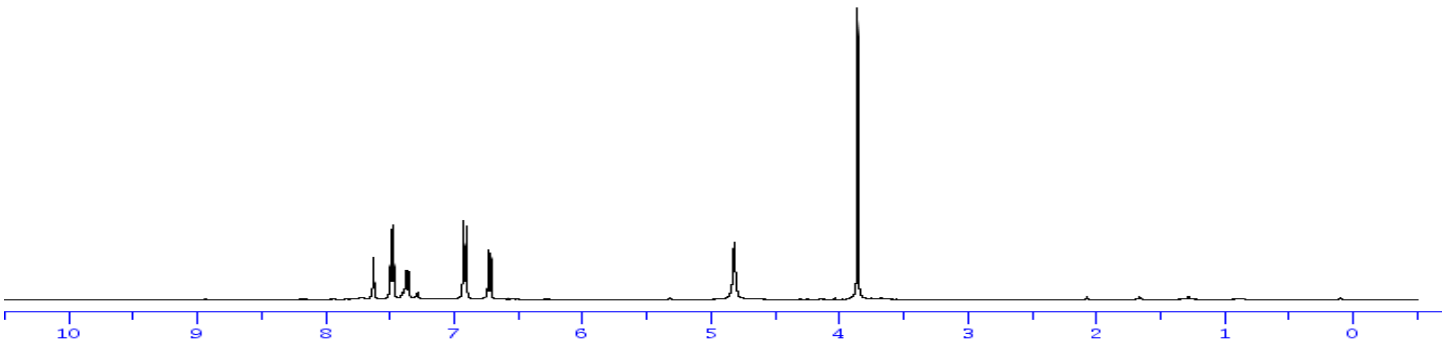

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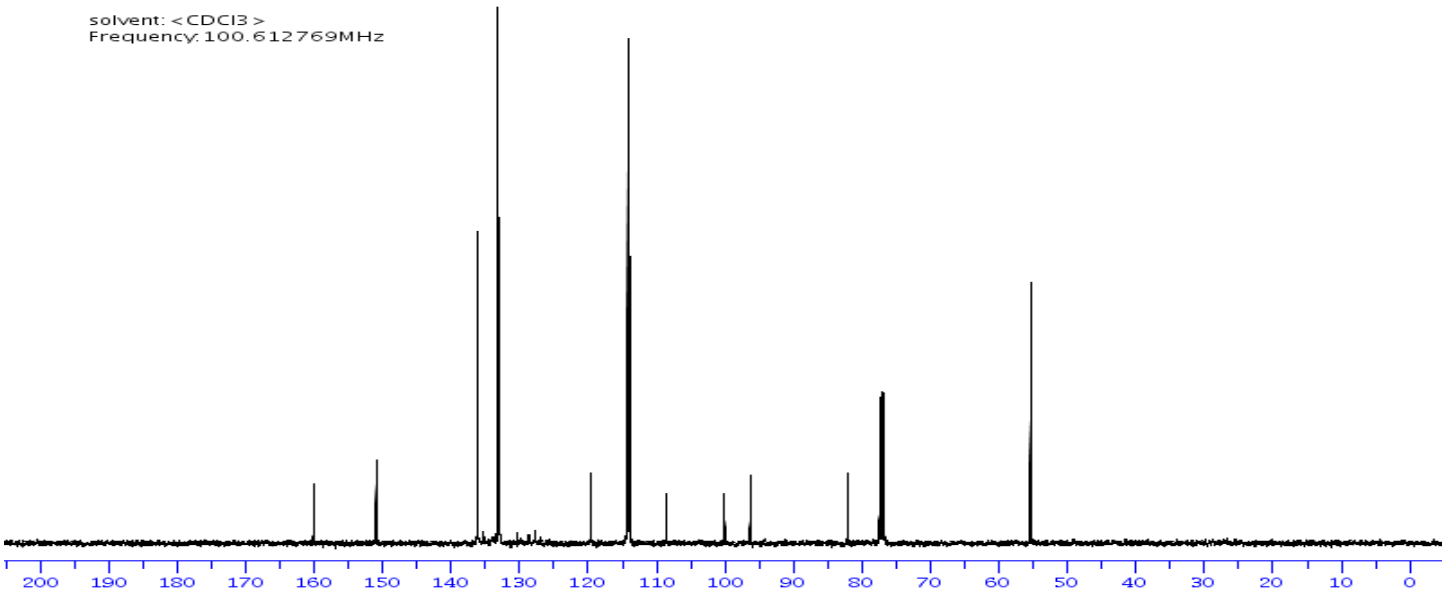

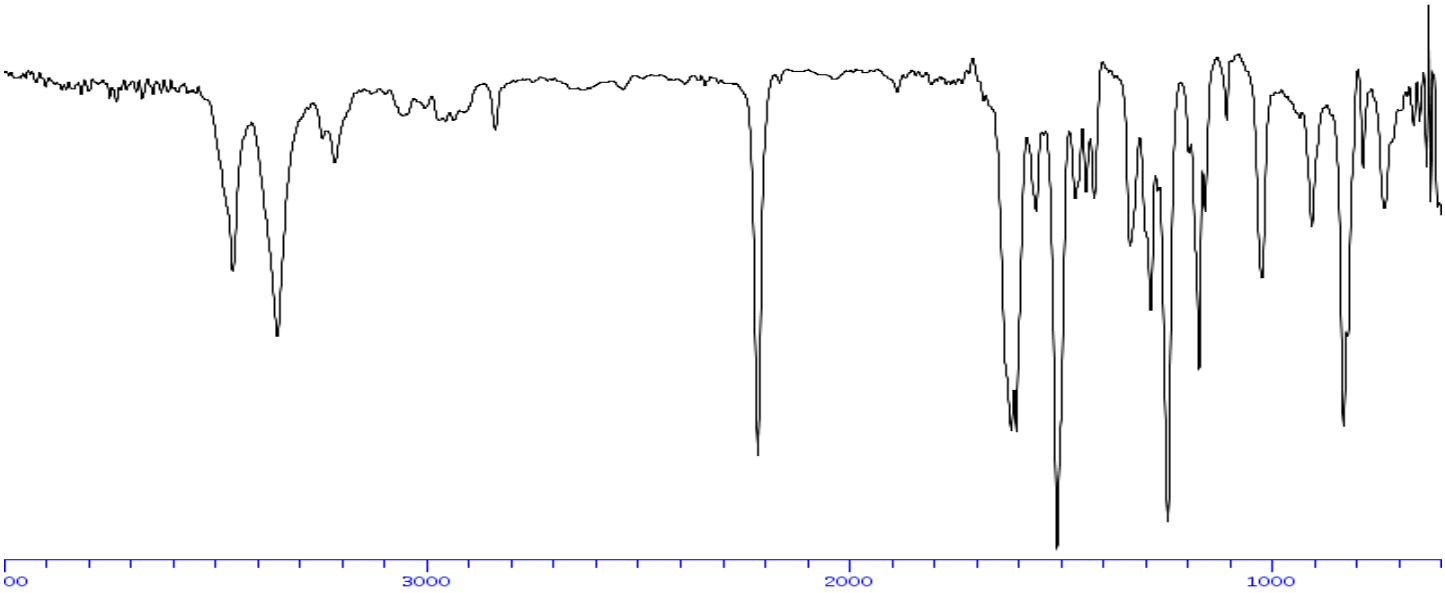

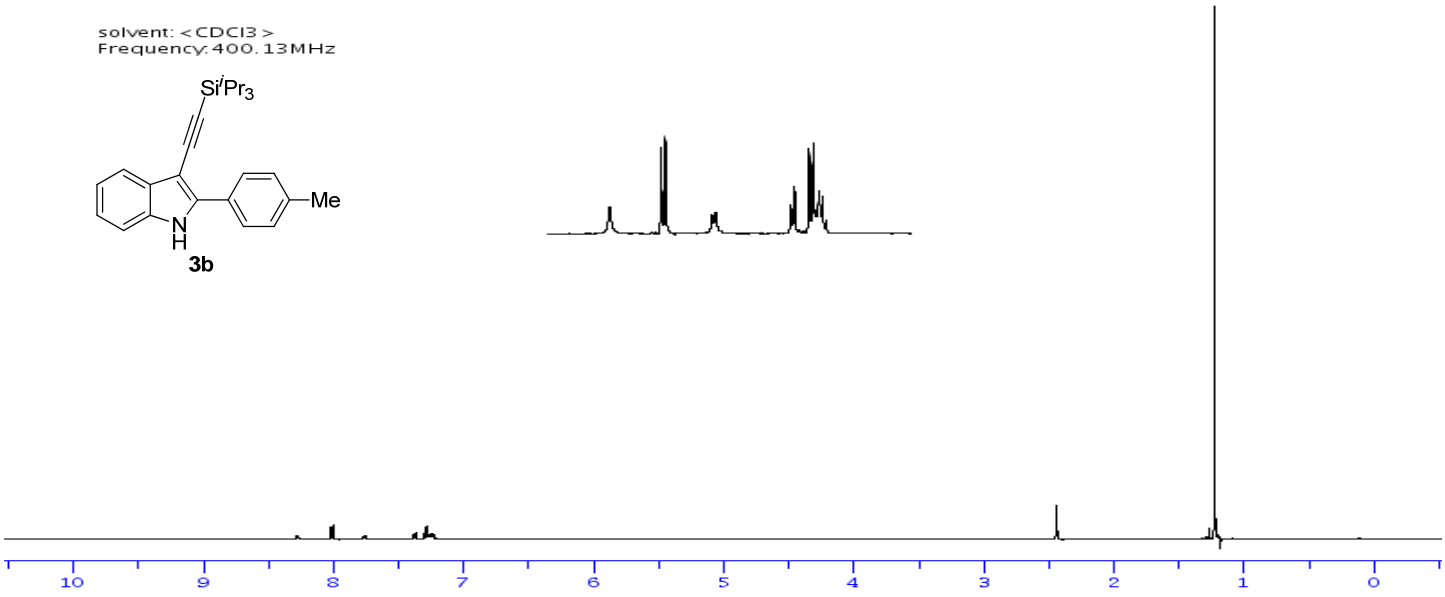
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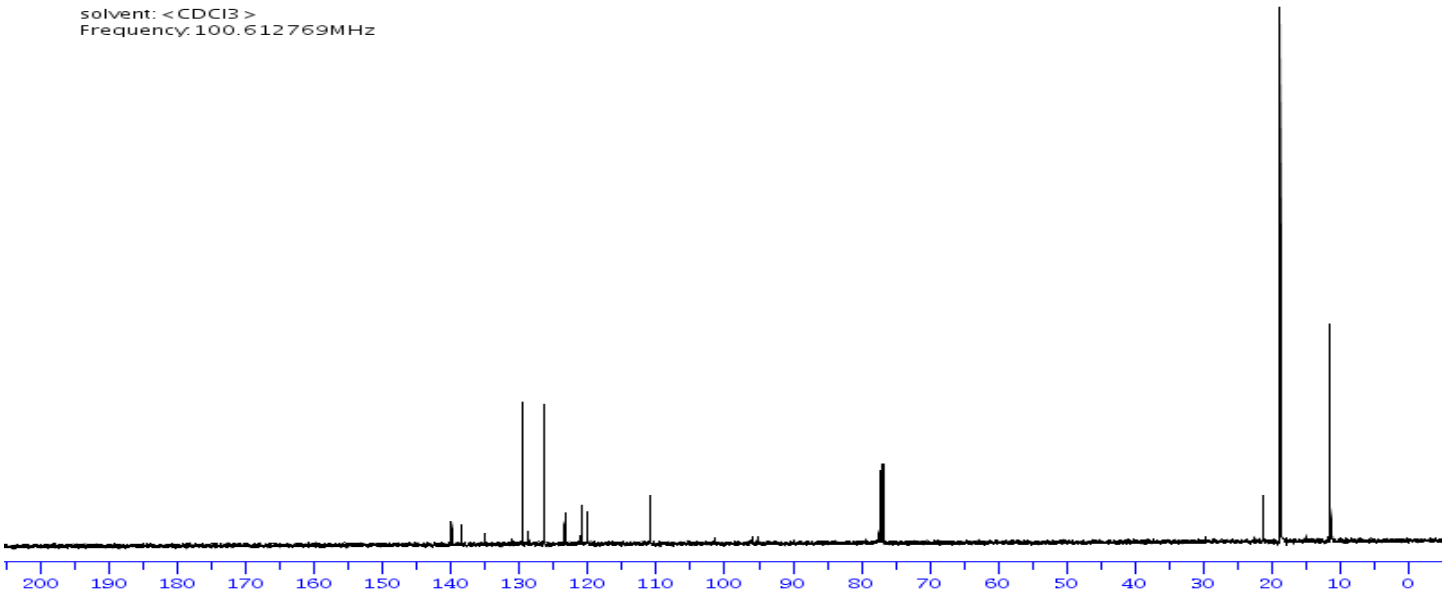
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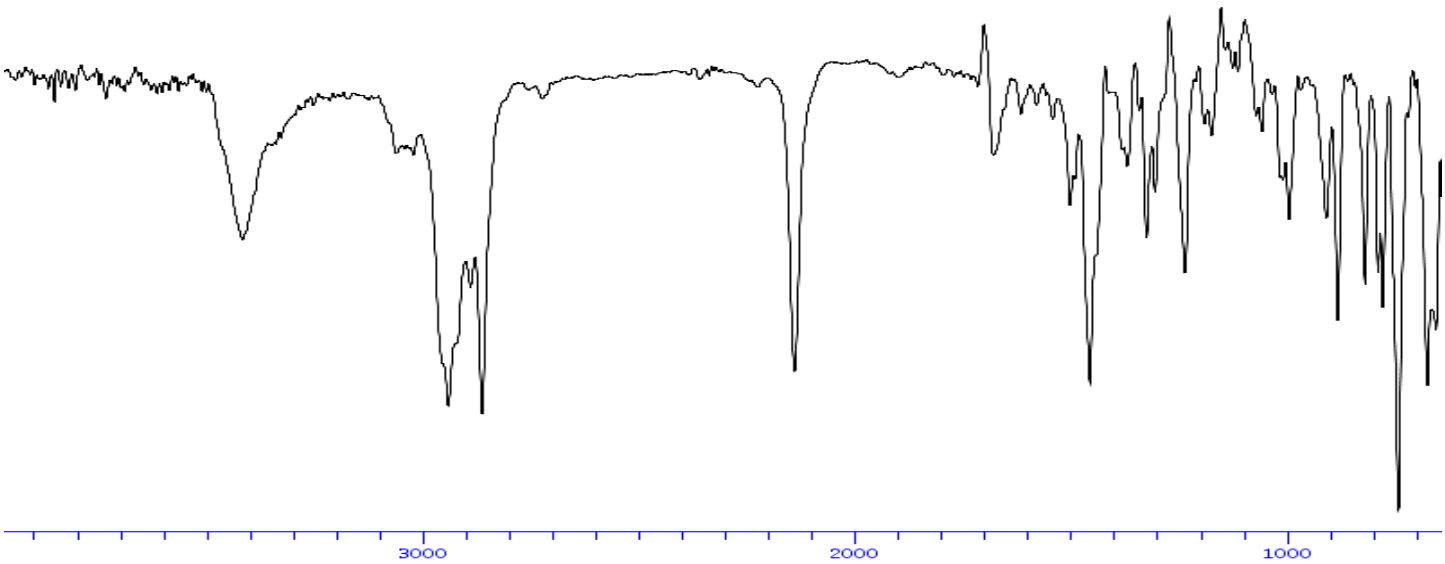
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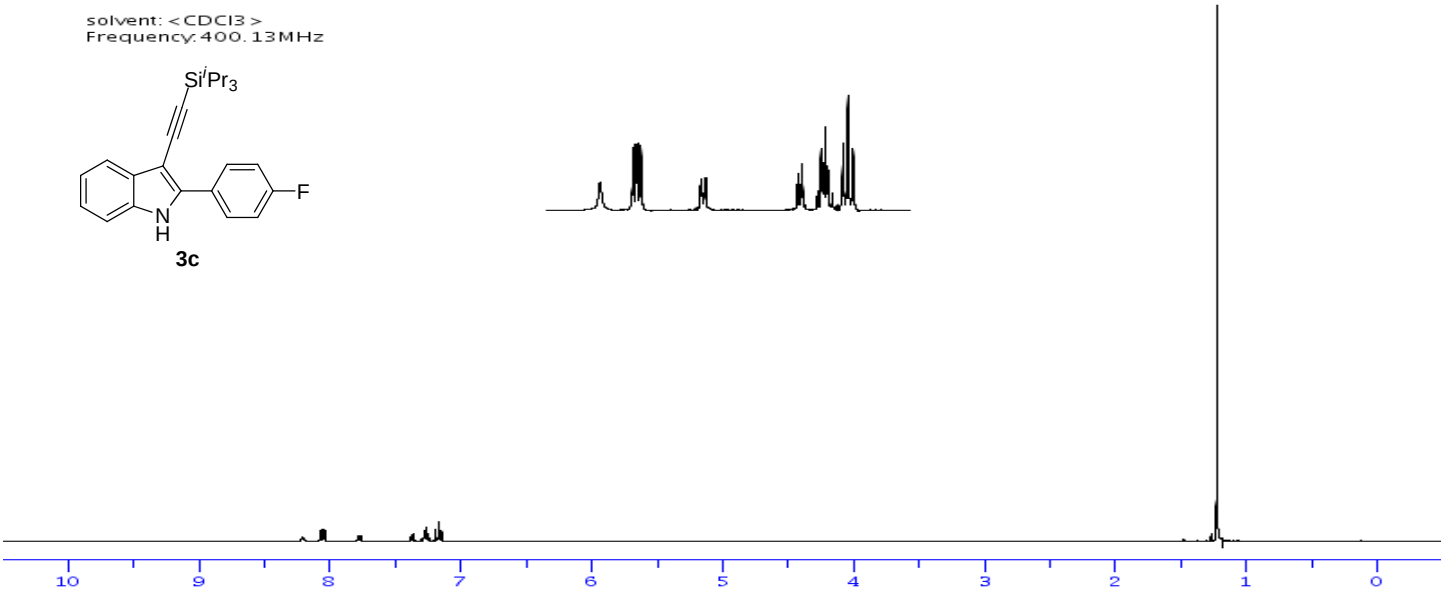
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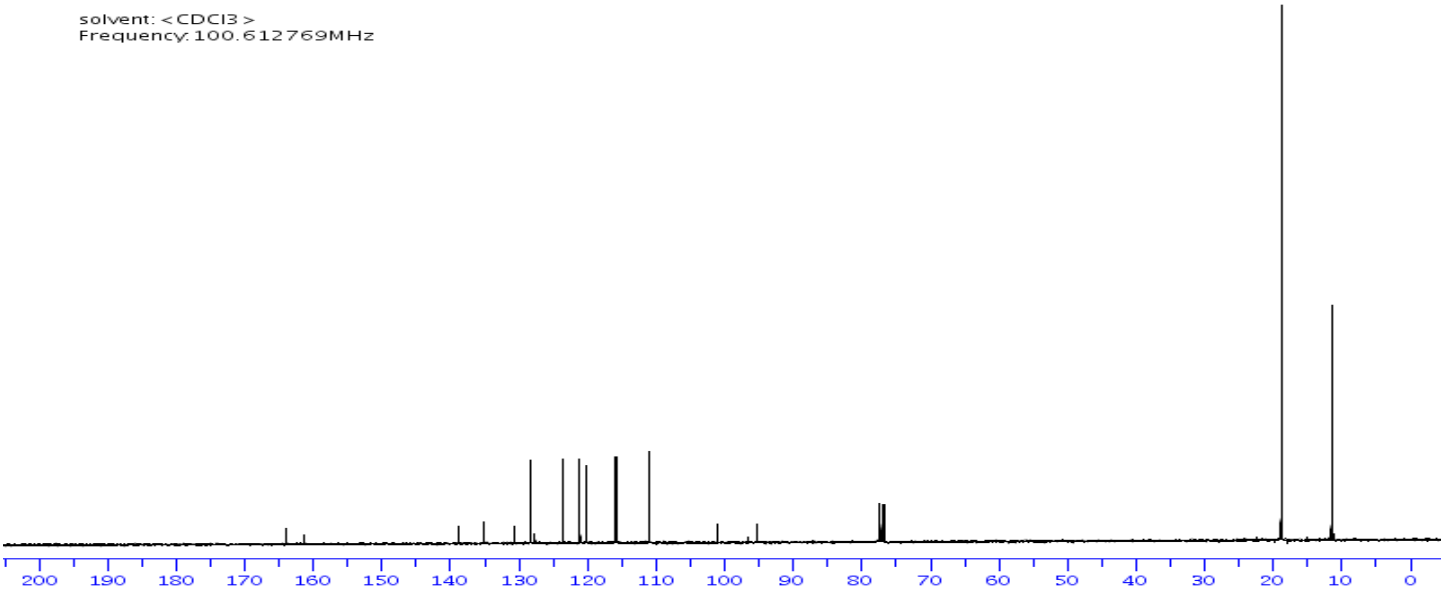
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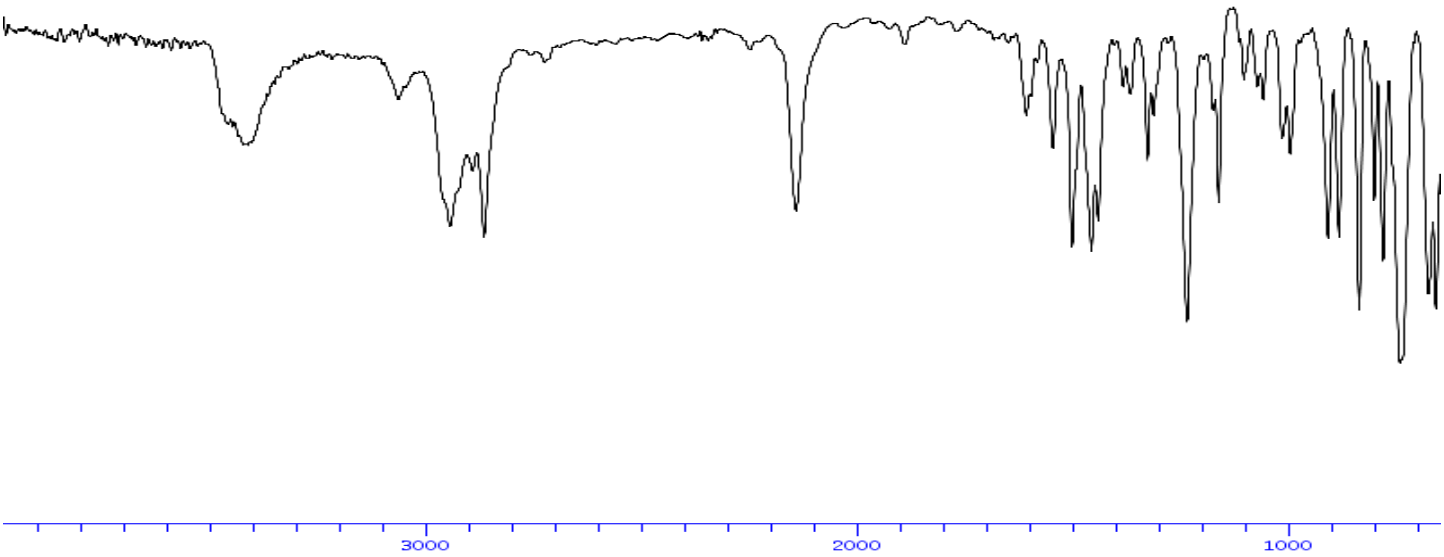
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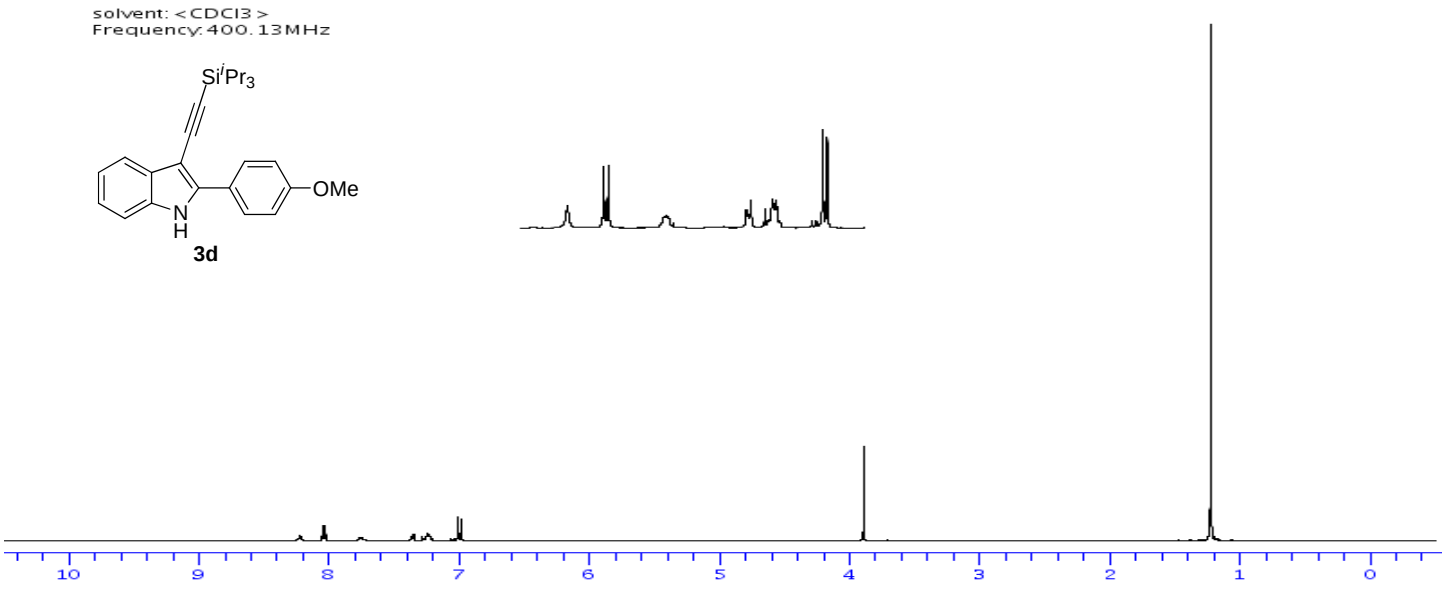
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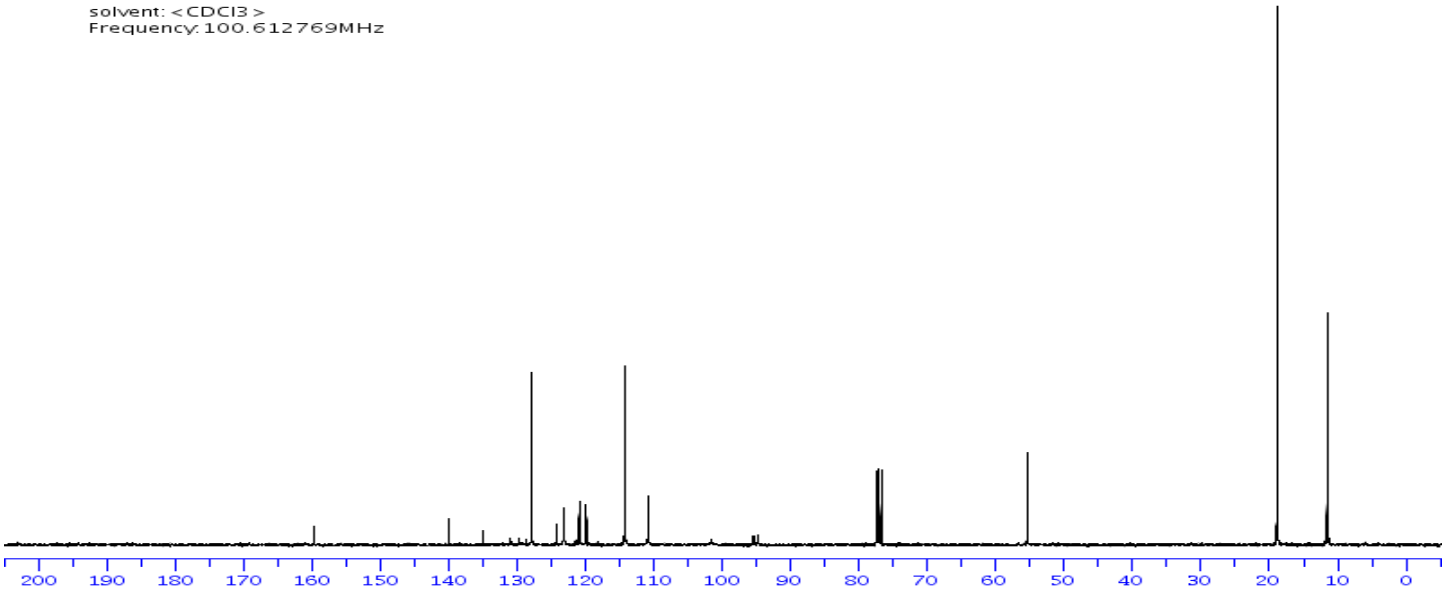
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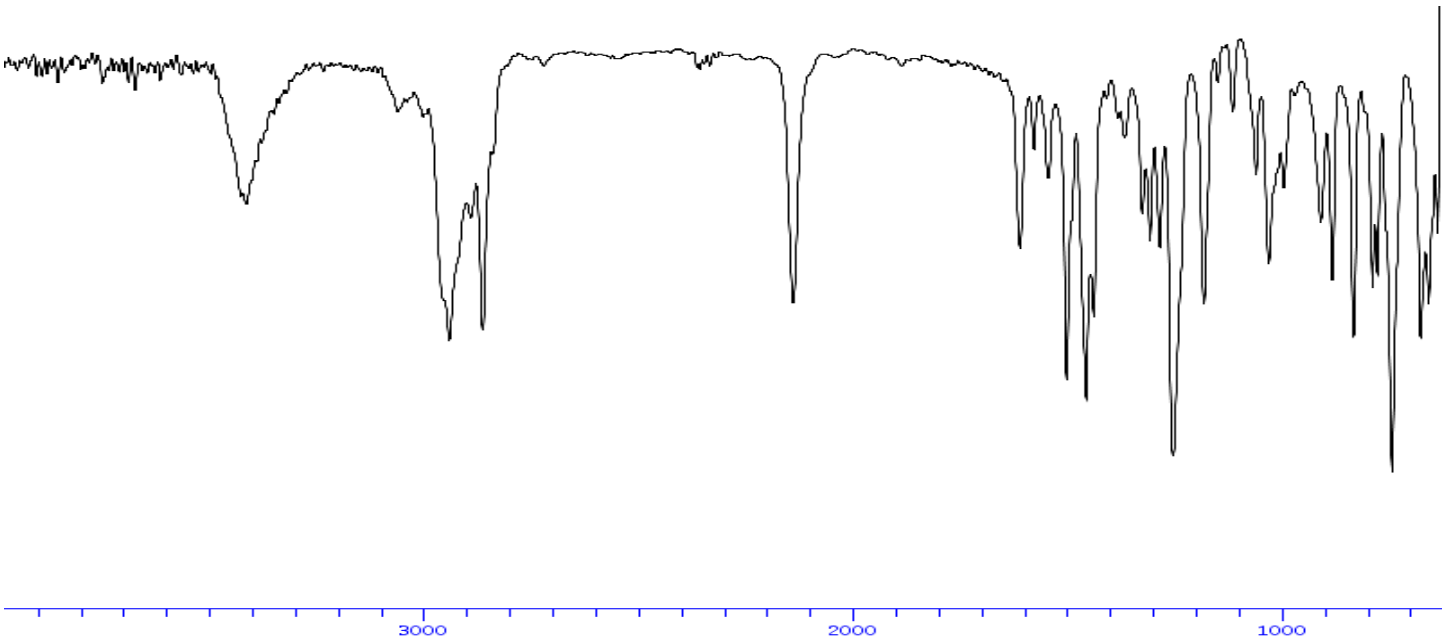
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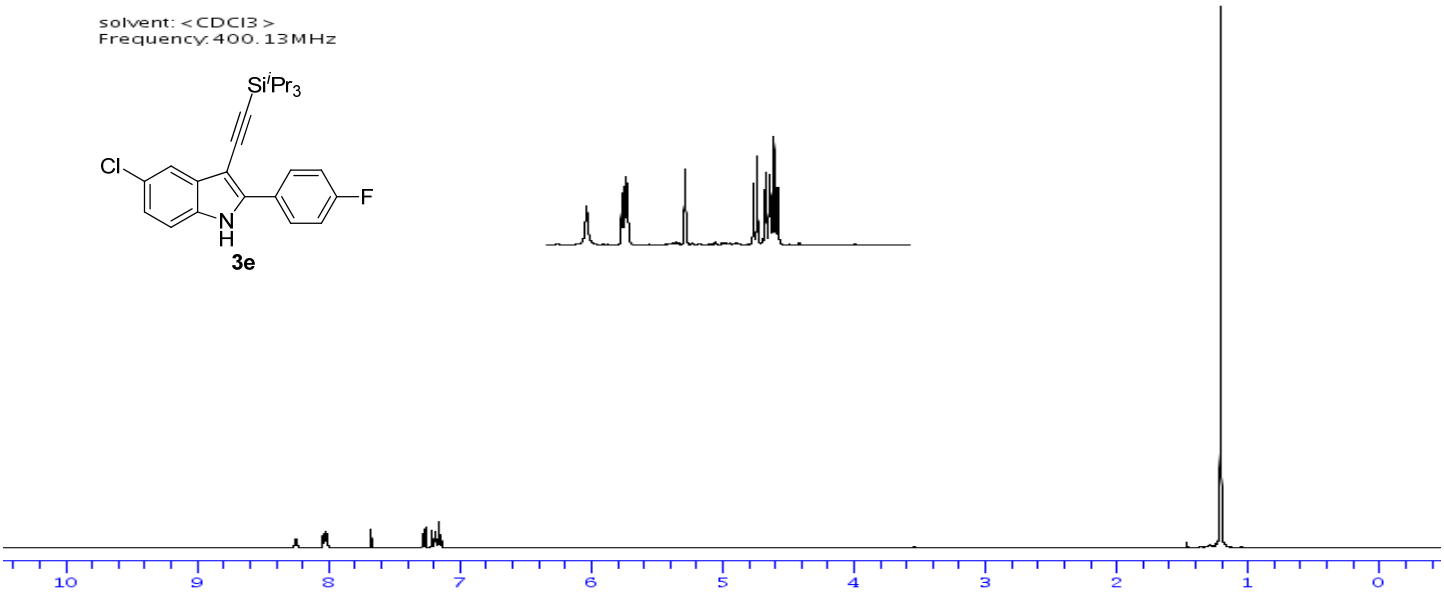
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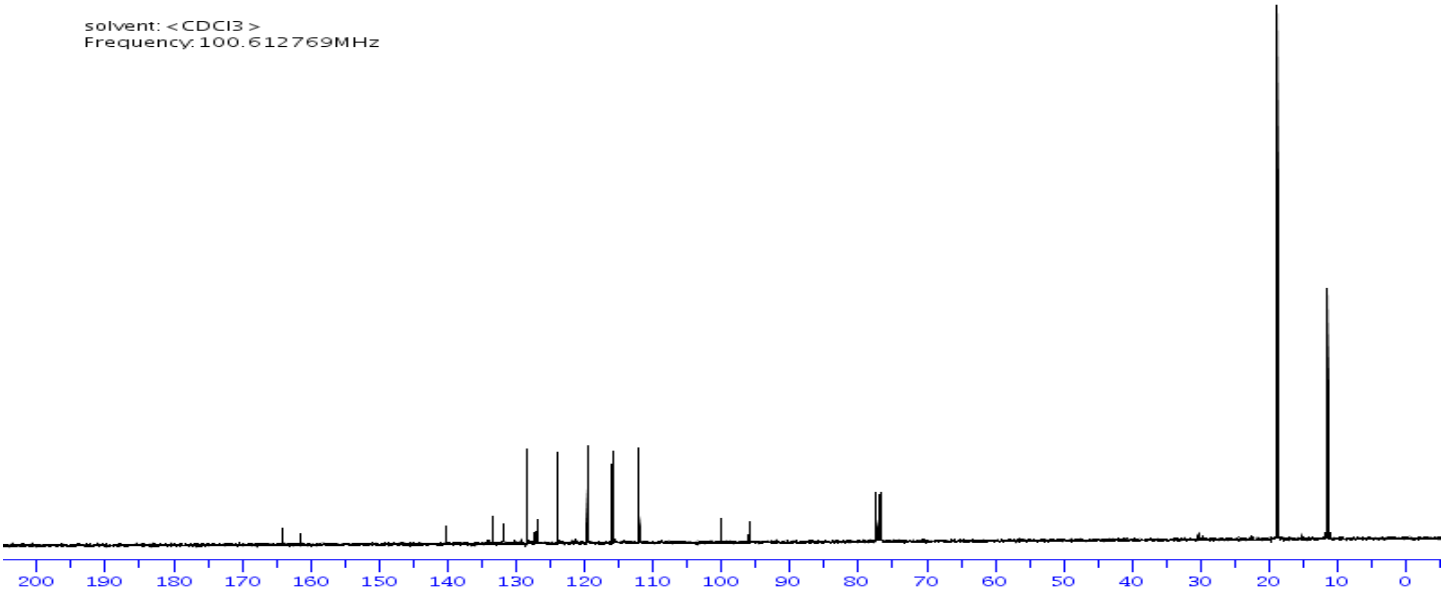
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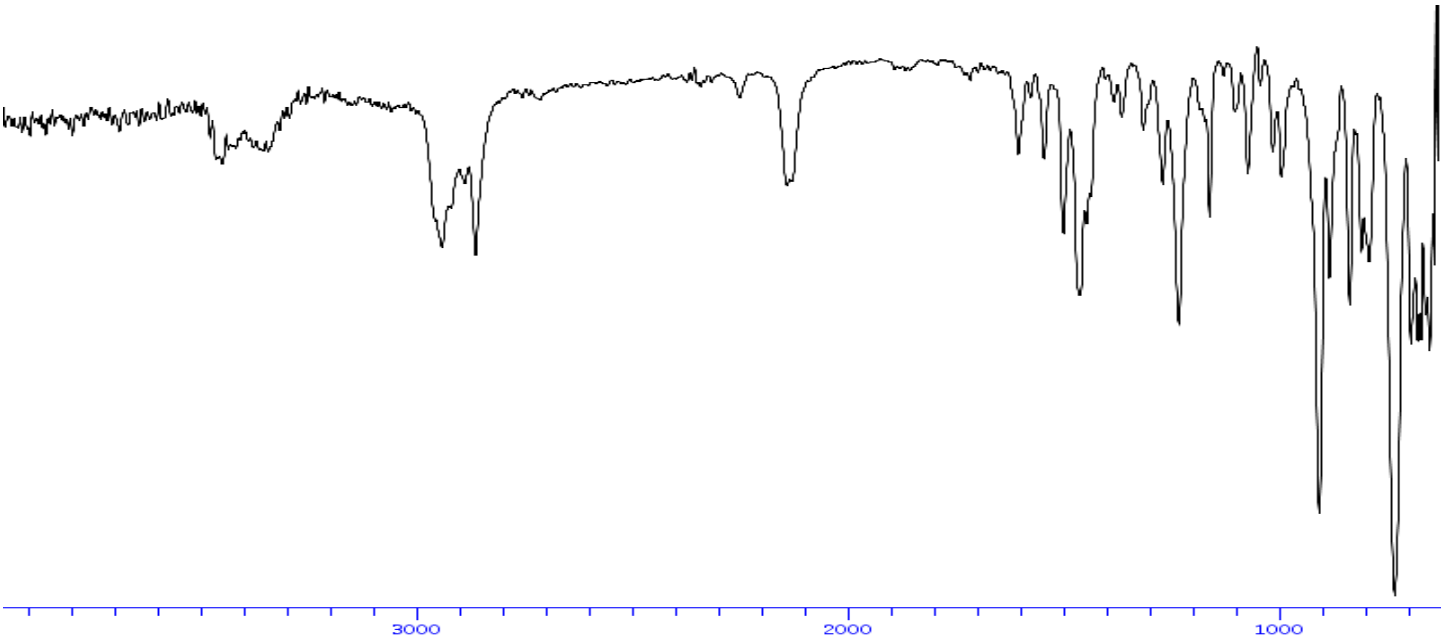
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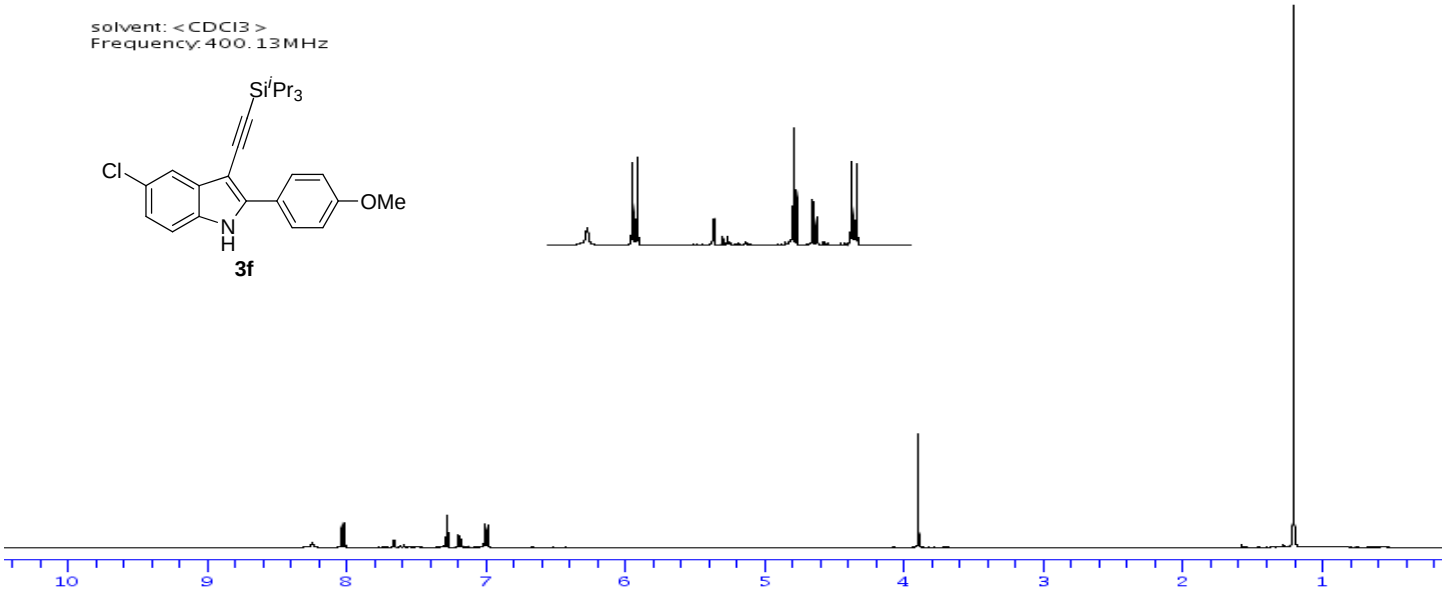
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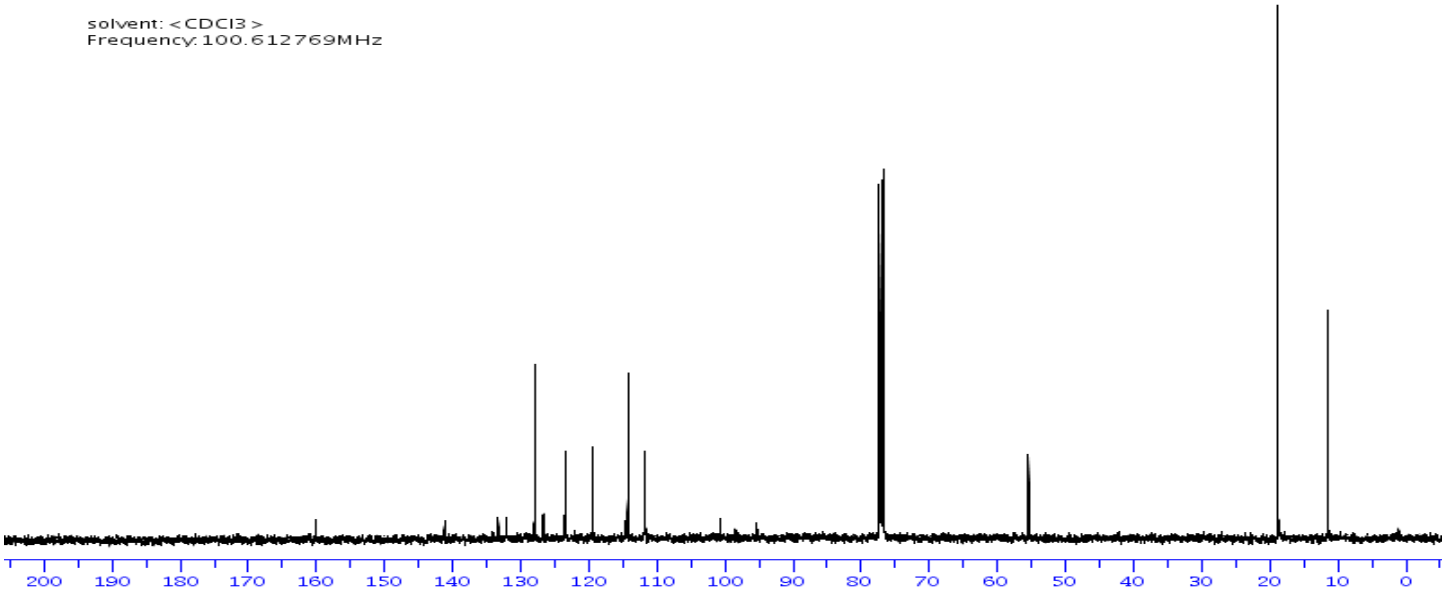
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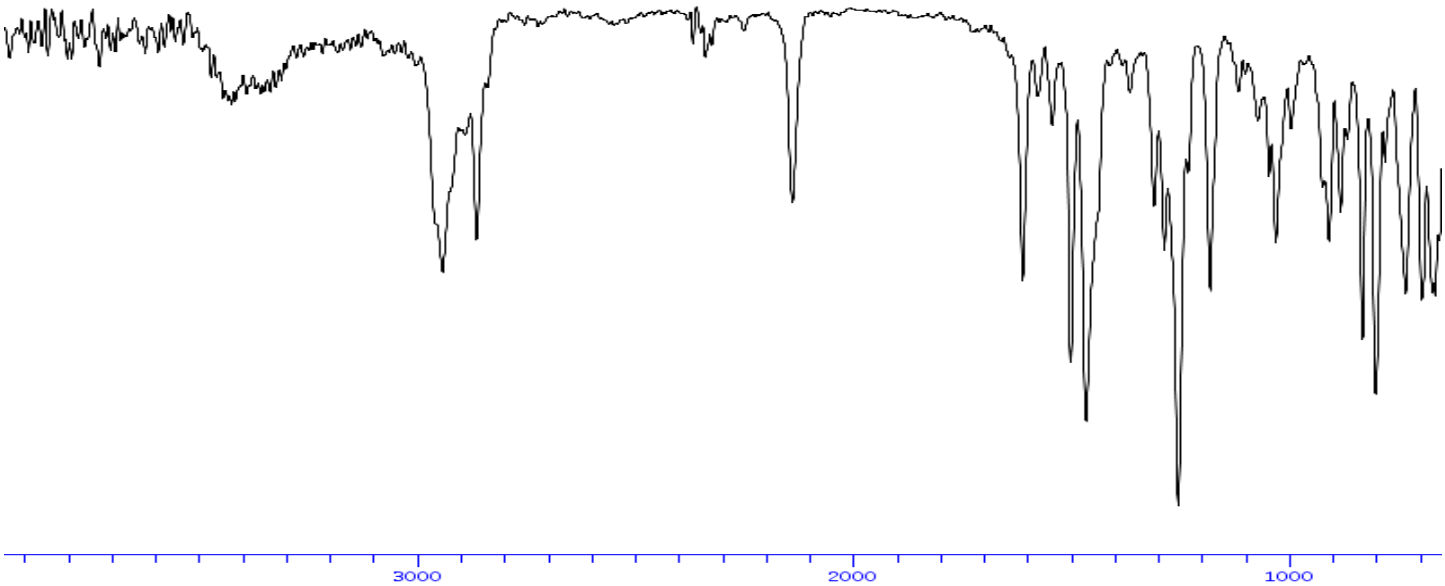
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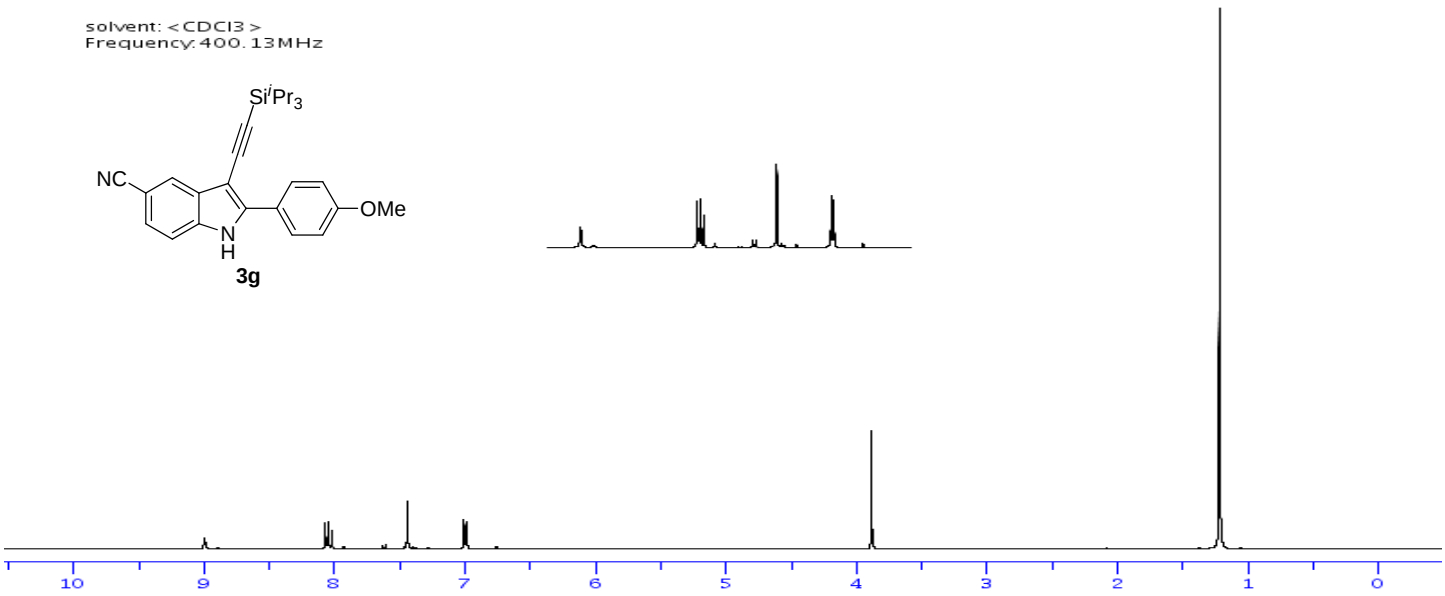
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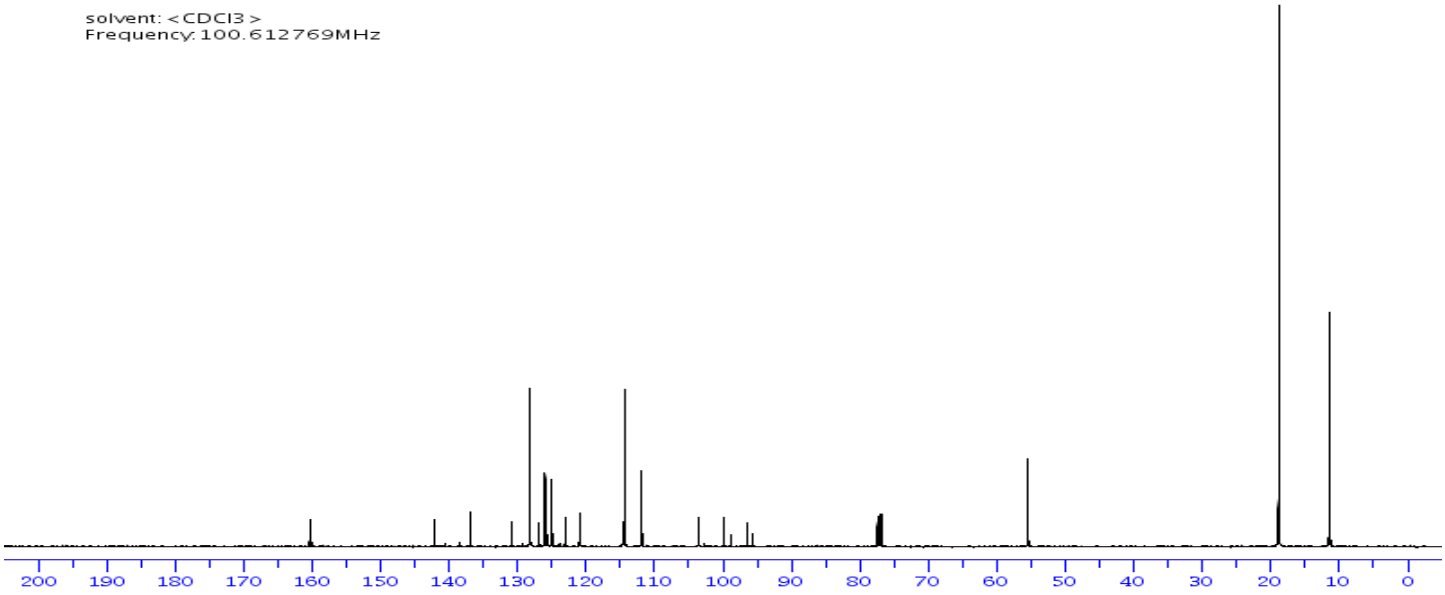
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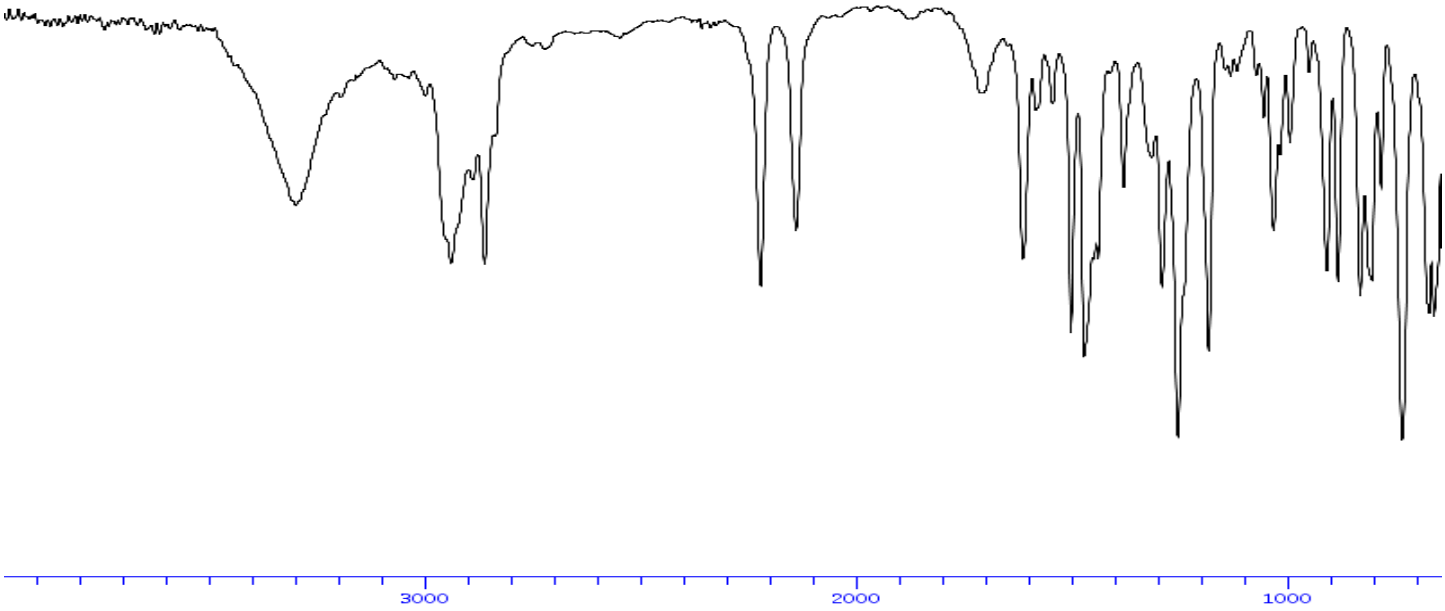
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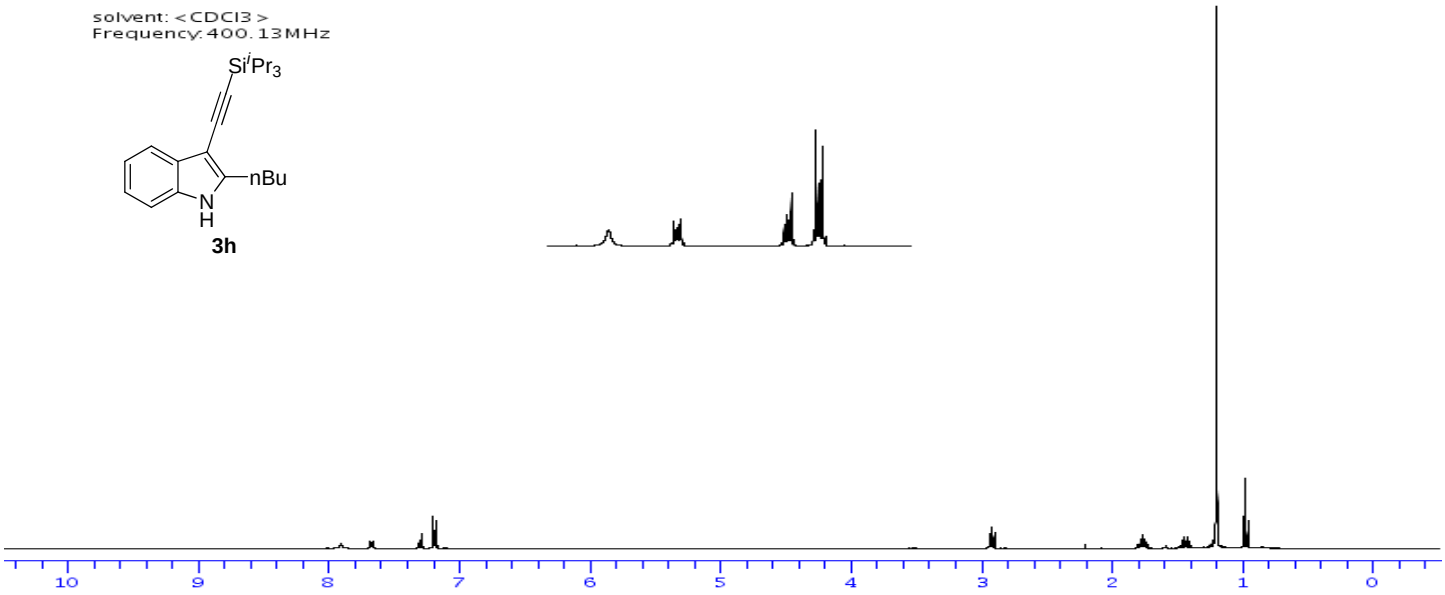
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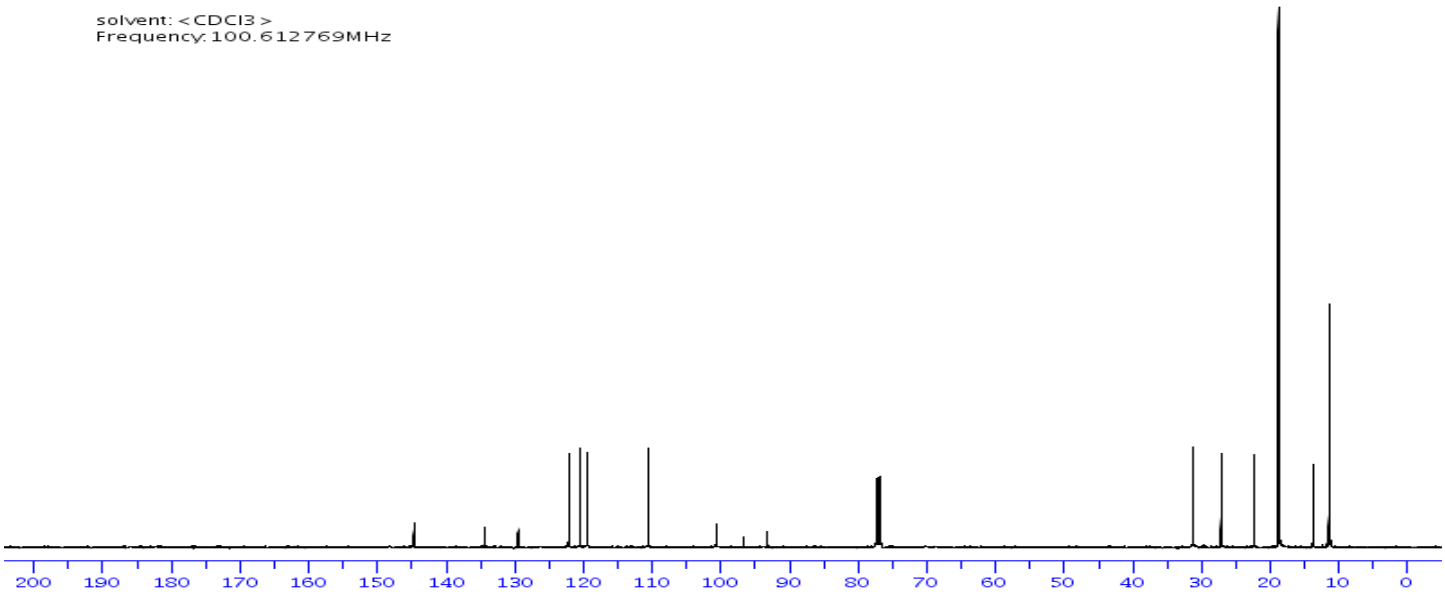
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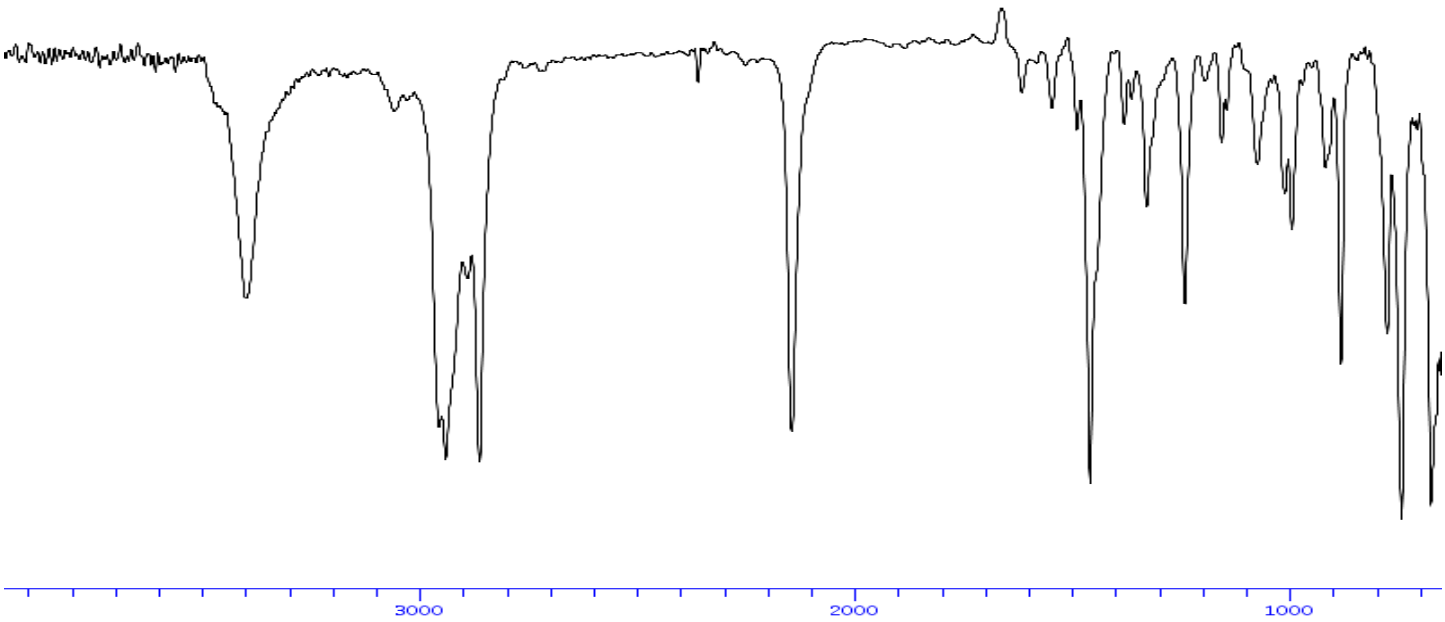
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