Cross-Coupling Reactions of 5-Bromo-1,2,3-triazines

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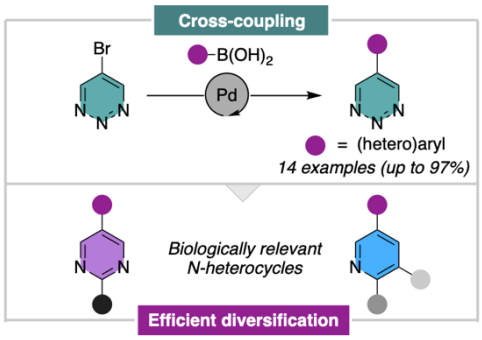
Supporting Information Placeholder



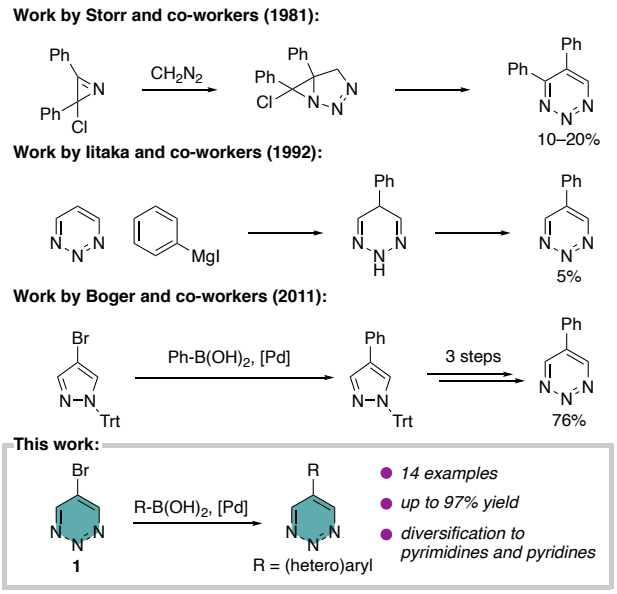
ABSTRACT: An efficient Pd catalyzed cross-coupling method for 5-bromo-1,2,3-triazine is described. Optimization of the reaction conditions allowed for the preparation of a representative scope of (hetero)aryl-1,2,3-triazines (14 examples, up to 97% yield). Additionally, diversification of the resulting products enabled the preparation of pyrimidines and pyridines in yields of up to 80% and in only two steps.

Nitrogen containing aromatic heterocycles are among the most common motifs in pharmaceutically relevant molecules.[1] Among them, triazines have become a popular *N*-heteroaromatic subclass and their potential application as drug molecules has been extensively studied and demonstrated.[2–8] Furthermore, triazines are known to undergo various transformations with suitable substrates (inverse-electron demand Diels–Alder reactions,[9] addition/elimination/cyclization reactions[10,11]), which allows their conversion into other *N*-heterocycles of interest, *e.g.* pyridines,[12,13] pyrimidines,[10] and pyridazines.[14] Taken together, methods for the preparation of triazines do not only allow for direct access to molecules of potential pharmaceutical interest, but also provide a platform for the synthesis of additional N containing heterocycles.

We recently developed a Pd catalyzed cross-coupling reaction for the coupling of the strongly electron deficient monosubstituted 3-bromo-1,2,4,5-tetrazine.[15] The use of increasingly electron deficient ferrocene-based ancillary ligands enabled the efficient cross-coupling of the tetrazine with a variety of boronic acids.[15b] Eager to investigate the generality of this finding, we turned our attention to the pharmaceutically more relevant triazines. As substrates for the cross-coupling reaction, we envisioned the use of various bromotriazines. Syntheses for the 5-bromo-1,2,3-triazine (**1**) and 6-bromo-1,2,4-triazine (**2**) have been developed by the groups of Boger[16] and Prescher[17] respectively. For 2-bromo-1,3,5-triazine, on the other hand, no efficient synthesis has been reported yet. While Suzuki cross-coupling of **2** has been reported by Prescher and co-workers, their conditions require excess of the triazine, due to its volatility.[17]

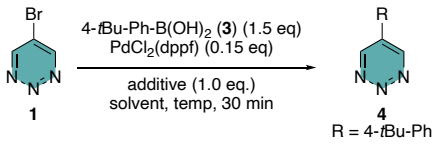
Other reports of cross-coupling reactions between bromo-1,2,4-triazines with boronic acids are generally limited to triazines with electron donating substituents at the 3-position.[17–20] In contrast to the volatile **2**, the 1,2,3-triazine **1** can be isolated and used in stoichiometric fashion as demonstrated by Boger and co-workers.[14,16] Furthermore, for **1** no general method for the cross-coupling with boronic acids has been reported. 5-Aryl- or heteroaryl substituted 1,2,3-triazines can be prepared by cross-coupling of the pyrazole precursor,[16] low yielding addition of aryl Grignard reagents to the minimal 1,2,3-triazine,[21] or ring expansion of chloroazirines with diazomethane (Scheme 1).[22] However, none of these methods allow for facile access to a wide variety of 5-(hetero)aryl-1,2,3-triazines. The respective precursors require custom synthesis, hence impeding an efficient workflow. At the same time, a plethora of structurally diverse boronic acids is commercially available for Suzuki cross-coupling. With this in mind, we set out to develop an efficient method for the Pd catalyzed cross-coupling of triazine **1**, enabling facile access to a wide array of 5-(hetero)aryl substituted 1,2,3-triazines from a common precursor (Scheme 1).

Scheme 1. Previous and current strategies for the synthesis of 5-(hetero)aryl-1,2,3-triazines



Our investigation commenced with the cross-coupling of **1** with 4-*tert*-butylphenylboronic acid (**3**) in the presence of 15 mol-% Pd(dppf)Cl_2 (dppf = 1,1'-bis(diphenylphosphino)ferrocene) and 1.0 eq of Ag_2CO_3 in MeCN at 80 °C (Table 1, entry 1).[15] Under these conditions the desired cross-coupling product **4** was isolated in 81% yield after 30 min. Intrigued by this result, we analyzed the product distribution of the reaction by NMR at various temperatures between 25 °C and 100 °C (see SI) and found that at all temperatures product is formed. However, over the course of 30 min the reactions at 25 °C and 40 °C did not proceed to full conversion. Additionally, with increasing temperature less of the homocoupling byproduct was observed, resulting in a cleaner overall reaction. Based on these results, we opted to continue our optimization at 100 °C (Table 1, entry 2). Next, we investigated the effect of the solvent, especially those with suitable boiling points. Among classically used solvents for cross-coupling reactions (DMF, toluene, 1,4-dioxane, 1,2-DME) EtCN promoted the cleanest conversion with barely any homocoupling product, while affording **4** in a yield of 81% (Table 1, entry 3). Analogously to previous reports of cross-coupling reactions of electron deficient aryl bromides, we expected the additive to occupy a crucial role (see SI).[15,23] No conversion was obtained in the absence of Ag_2CO_3 (Table 1, entry 4). When K_2CO_3, Na_2CO_3, or Cs_2CO_3 was used, the productivity of the reaction was partly restored, furnishing triazine **4** in analytical yields of 35%, 15%, and 53% respectively (see SI).

Table 1. Optimization of the Temperature, Solvent, and Additive



entry	temp	solvent	additive	yield
1	80 °C	MeCN	Ag_2CO_3	81%[a]
2	100 °C	MeCN	Ag_2CO_3	75%[a]
3	100 °C	EtCN	Ag_2CO_3	81%[a]
4	100 °C	EtCN	–	0%
5	100 °C	EtCN	AgOAc	40%[b]
6	100 °C	EtCN	Ag_3PO_4	69%[a]
7	100 °C	EtCN	K_3PO_4	84%[b]
8	100 °C	EtCN + 5% H_2O	Ag_2CO_3	84%[a]
9[c]	100 °C	EtCN + 5% H_2O	Ag_2CO_3	91%[a]

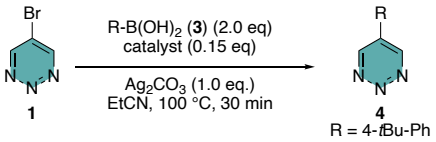
[a]Yields refer to isolated material after column chromatography. [b]Yields refer to analytically determined amounts (^{1}H NMR). [c]Reaction was performed with 2.0 eq of boronic acid.

Due to the clear superiority of Ag_2CO_3, we screened the effect of various other silver-based additives. Besides AgOAc (40% analytical yield) and Ag_3PO_4 (69%), other silver salts exhibited inferior mediatory properties (Table 1, entries 5 and 6, see SI). Since none of these silver additives were able to improve upon the yield of the reaction with Ag_2CO_3 (81%), we turned our attention to other frequently used bases and Lewis acids (see SI). While most of these additives resulted in significantly diminished yields, the addition of K_3PO_4 promoted the reaction to a similar extent as Ag_2CO_3, however, also resulted in considerable amounts of homocoupling product (Table 1, entry 7). Valuing a clean reaction and facile isolation of the product over a slight increase (<5%), we investigated the effect of additional H_2O on the productivity of the method. In line with other Suzuki cross-coupling conditions, H_2O was well tolerated up to the maximally tested 20% (see SI).[24] The addition of 5% H_2O led to an increase in yield to 84% (Table 1, entry 8). Hence, we concluded that under these conditions, Ag_2CO_3 promotes an efficient and clean reaction. When the amount of Ag_2CO_3 was varied (0.5 eq and 2.0 eq), a decrease in yield to 63% and 75% was observed, respectively (see SI). Furthermore, the use of 2.0 eq of boronic acid **3** afforded cross-coupling product **4** in an increased yield of 91% (Table 1, entry 9).

Next, we screened different ligand systems for the transformation. Interestingly, even in the absence of dppf ligand, the reaction proceeded efficiently (80%) (Table 2, entry 1). The lack of reactivity in the absence of Pd was restored when dppf was added separately (76%) (Table 2, entries 2 and 3). The discrepancy in yield between the reactions with Pd(dppf)Cl_2 and Pd(MeCN)$_2Cl_2$ + dppf might be due to incomplete ligation of Pd under the reaction conditions and competitive ligand free catalysis. When other frequently used ligand systems were used (PPh_3, DPEphos, BINAP), efficient coupling of **1** was observed (68–95%) (see SI). When the electron-rich boronic acid **3** was exchanged for the electron-poorer 4-fluorophenylboronic acid (**5**) and the Pd(MeCN)$_2Cl_2$ + dppf catalytic system was used,

this resulted in a decrease in isolated coupling product (**6**, 62%) (Table 2, entry 4). This is in line with our previous report on the cross-coupling of tetrazines.[15] Hence, we investigated the more electron-poor ancillary ligands dppf-CF_3 (1,1'-bis(di(4-CF_3-phenyl)phosphino)ferrocene) and dppf-3,5-CF_3 (1,1'-bis(di(3,5-CF_3-phenyl)phosphino)ferrocene) regarding their ability to promote the reaction. The dppf-CF_3 ligand performed excellently, and the coupling products of the boronic acids **3** and **5** was isolated in yields of 97% (**4**) and 72% (**6**) respectively (Table 2, entries 5 and 6). The electron-poorer dppf-3,5-CF_3 ligand completely failed to produce any cross-coupling product (Table 2, entries 7 and 8), which could be the result of triazine N binding to Pd, leading to a resting off-cycle intermediate, and thus preventing catalysis. A screening of catalyst loading for the coupling between triazine **1** and boronic acid **3** resulted in lower yields at loadings of 10 mol-% (86%) and 5 mol-% (69%) (Table 2, entry 9, see SI). For the latter entry, the reaction time was extended to 2 h, since the conversion of **1** was found incomplete after 30 min. While this partially alleviated the decrease in yield, the isolated yield 79% of **4** were still lower than the almost quantitative outcome (97%) at 15 mol-% catalyst loading (Table 2, entry 10). Additionally, the extended reaction times and lower catalyst loading resulted in larger amounts of homocoupling product.

Table 2. Screening of the catalyst system

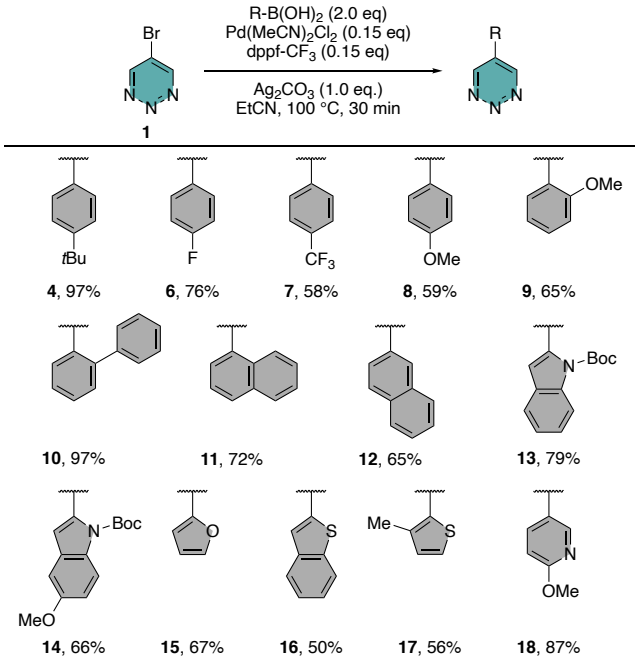


entry	catalyst	R	yield[a]
1	$Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph	80%
2	dppf	4-*t*Bu-Ph	0%
3	dppf, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph	76%
4	dppf, $Pd(MeCN)_2Cl_2$	4-F-Ph	62%
5	dppf-CF_3, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph	97%
6	dppf-CF_3, $Pd(MeCN)_2Cl_2$	4-F-Ph-	72%
7	dppf-3,5-CF_3, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph	0%
8	dppf-3,5-CF_3, $Pd(MeCN)_2Cl_2$	4-F-Ph	0%
9[b]	dppf-CF_3, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph	69%
10[b,c]	dppf-CF_3, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph	79%

[a]Yields refer to isolated material after column chromatography. [b]Reaction was performed with 5 mol-% catalyst loading. [c]Reaction time was extended to 2 h.

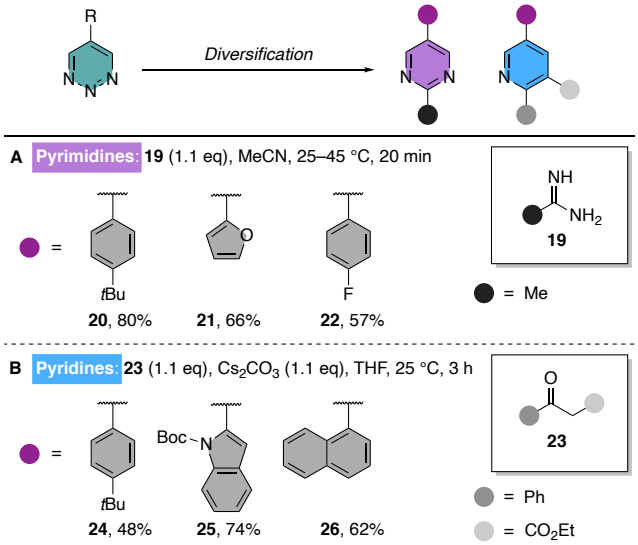
With optimized reaction conditions in hand, we explored the scope of the method (Scheme 2). Alkyl- and fluorosubstituted phenylboronic acids were already established as feasible substrates during the optimization of the method, giving rise to triazines **4** and **6** in yields of 97% and 76% respectively. The electron withdrawing *p*-CF_3 substituent was also well tolerated, producing **7** (58%). On the other hand, cross-coupling of boronic acids comprising electron donating methoxy substituents resulted in similar yields (**8**: *para*, 59%; **9**: *ortho*, 65%). Phenyl substitution in the *ortho*-position was tolerated excellently and triazine **10** was isolated in a yield of 97%. Furthermore, polyaromatic substrates were also feasible substrates, furnishing naphthyl-substituted triazines **11** and **12** in yields of 72% and 65% respectively. Of interest for the preparation of pharmaceutically active compounds is the cross-coupling with various heterocyclic boronic acids.[25] Such heteroaryl triazines have so far been elusive.[26,27] Hence, we were pleased to find that our method cleanly reacts boronic acids of indoles (**13**: 79%, **14**: 66%), furan (**15**: 67%), (benzo)thiophenes (**16**: 50, **17**: 56%), and a methoxy pyridine (**18**: 87%). Overall, the method enables the preparation of previously unattainable triazine variants, and significantly expands on the thus far rather limited 5-(hetero)aryltriazene class.[16]

Scheme 2. Conditions and scope for the cross-coupling of bromotriazine 1



We then sought to apply reported protocols to demonstrate the utility of such cross-coupling products as a basis for efficient diversification (Scheme 3). Triazines can be converted to the corresponding pyrimidines, and pyridines according to reports by the group of Boger[14,16] and Li.[12] Both of these aromatic *N*-heterocycles are frequently encountered in pharmaceutically active compounds.[1] Reaction of triazines **4**, **6**, and **15** with freshly distilled acetamidine (**19**)[28] cleanly resulted in the corresponding pyrimidines **20**–**22** in yields of 57–80% (Scheme 3, A).[16] The preparation of pyrimidines in this manner allows for full control over the substituents in 2- and 5-position, and avoids hazardous reagents such as $POCl_3$, which are otherwise used for their preparation.[29,30] Besides pyrimidines, the transformation of triazines into pyridines was also evaluated. Reaction of triazines **4**, **11**, and **13** with 1,3-ketoester **23** under basic conditions furnished the corresponding triply substituted pyridines **24**–**26** in yields of 48–74% (Scheme 3, B).[12] Hence, we were satisfied to find that our method enabled facile access to these *N*-heterocycles with control over up to three substituents and in only two steps.

Scheme 3. Diversification of triazine cross-coupling products



In conclusion, a Pd catalyzed cross-coupling method for bromotriazine **1** was presented. Thorough optimization of the reaction conditions resulted in the successful coupling of 14 structurally and electronically diverse commercially available boronic acids in yields of 50–97% yield. Diversification of various cross-coupled triazines to the corresponding pyrimidines or pyridines was used to showcase their feasibility as a platform for the efficient preparation of many unprecedented aromatic *N*-heterocycles from a common precursor. As such, the presented method provides rapid access to a diverse array of 5-(hetero)aryltriazines, thus adding a versatile tool for the preparation of six-membered *N*-heteroaromatics.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and characterization data (PDF).

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Author Contributions

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Notes

Any additional relevant notes should be placed here.

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Supporting Information

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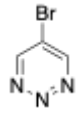
Experimental Procedures

General

All chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, TCI, or Fluka and were used without further purification. Solvents applied for chemical transformations were either puriss. quality or HPLC grade solvents. All synthetic transformations were monitored by either thin layer chromatography (TLC), ^{1}H NMR spectroscopy or UHPLC/ESI-MS. TLC was performed on Merck silica gel 60 F254 plates (0.25mm thickness) precoated with a fluorescent indicator. The developed plates were examined under UV light and stained with ceric ammonium molybdate or potassium permanganate followed by heating. Concentration under reduced pressure was performed by rotary evaporation *in vacuo* at the designated temperature and pressure. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma-Aldrich with a forced flow eluent at 0.1–0.3 bar pressure. All ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR spectra were recorded using Bruker 400 MHz (^{1}H) & 101 MHz (^{13}C) or Bruker 500 MHz (^{1}H) & 126 MHz (^{13}C) spectrometers at 25 °C. Chemical shifts (δ-values) are reported in ppm, spectra were calibrated relative to the solvents' residual proton chemical shifts ($CHCl_3$, $\delta = 7.26$) and residual carbon chemical shifts ($CDCl_3$, $\delta = 77.16$), multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and coupling constant *J* in Hz. IR spectra were recorded on a Varian 800 FT-IR ATR spectrophotometer with intensities being reported as strong (s), medium (m), and weak (w) and given in cm^{-1}. All high-resolution mass spectra (HRMS-ESI & HRMS-APCI) were recorded by the mass spectrometry service at the University of Zürich on a Dionex Ultimate 3000 UHPLC system (ThermoFischer Scientifics, Germering, Germany) connected to a QExactiveMSwith a heated ESI source(ThermoFisher Scientific, Bremen, Germany); on-flow injection of 1 µL sample (c = ca. 50 µg mL^{-1} in the indicated solvent) with an XRSauto-sampler (CTC, Zwingen, Switzerland); flow rate 120 µL min^{-1}; ESI: spray voltage 3.0 kV, capillary temperature 280 °C, sheath gas 30 L min^{-1}, aux gas 8 L min^{-1}, s-lens RF level 55.0, aux gas temperature 250 °C (N_2); full scan MS in the alternating (+)/(–)-ESI mode; mass ranges 80–1'200 m/z, 133–2'000 m/z, or 200–3'000 m/z at 70'000 resolution (full width half-maximum); automatic gain control (AGC) target of 3.00·106; maximum allowed ion transfer time (IT) 30 ms; mass calibration to <2 ppm accuracy with Pierce® ESI calibration solutions (ThermoFisher Scientific, Rockford, USA); lock masses: ubiquitous erucamide (m/z 338.34174, (+)-ESI) and palmitic acid (m/z 255.23295, (–)-ESI) or (for EI) on a DFS double-focusing (BE geometry) magnetic sector mass spectrometer (ThermoFisher Scientific, Bremen, Germany). Mass spectra were measured with electron ionization (EI) at 70 eV, solid probe inlet, a source temperature of 200°C, an acceleration voltage of 5 kV, and a resolution of 10'000. The instrument was scanned between *e.g.* m/z 300 and 350 at a scan rate of 100-200 s / decade in the electric scan mode. Perfluorokerosene (PFK, Fluorochem, Derbyshire, UK) served for calibration. Melting points (M.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected. X-ray diffraction data were recorded using a Rigaku Oxford Diffraction SuperNova area-detector diffractometer.

Synthesis of 5-bromo-1,2,3-triazine (1)[1]



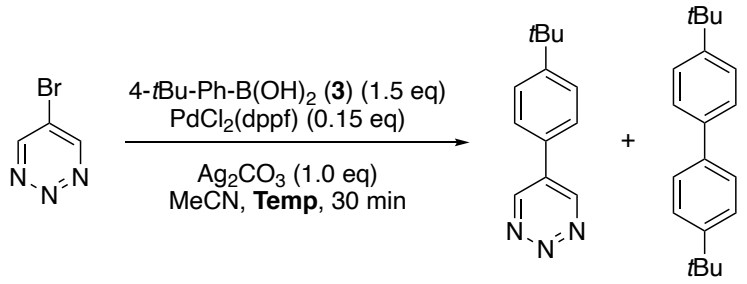
In a one-necked round-bottom flask (100 mL) equipped with a magnetic stirring bar, 4-bromo-pyrazole (2.50 g, 17.0 mmol, 1.0 eq) was dissolved in an aqueous solution of NaOH (27.3 mL, 3.7 M, 4.04 g NaOH in 27.3 mL H_2O). Hydroxylamine-*O*-sulfonic acid (5.77 g, 51.0 mmol, 3.0 eq) was added in portions to the solution, while maintaining the temperature of the mixture below 60 °C by means of an ice/H_2O bath. Upon complete addition, the mixture was stirred for 1 h, while avoiding warming of the solution above 60 °C. The aqueous solution was extracted with CH2Cl2 (3 x 10 mL), and the combined organic phases were washed with brine (25 mL), dried over anhydrous Na2SO4, filtered and concentrated *in vacuo* (45 °C, 600 to 30 mbar). The residue was dissolved in CH2Cl2 (20 mL) and H2O (7.6 mL) was added. The mixture was cooled with an ice/H2O bath, NaIO4 (6.65 g, 31.1 mmol, 1.8 eq) was added, and it was stirred for 18 h. The aqueous phase was separated and extracted with CH2Cl2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo (45 °C, 600 to 30 mbar). Drying under high vacuum afforded the desired triazine **1** (2.12 g, 13.3 mmol, 78%) as an orange/brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 2H).

Data are in agreement with reported values.

Optimization Studies

Temperature Screening



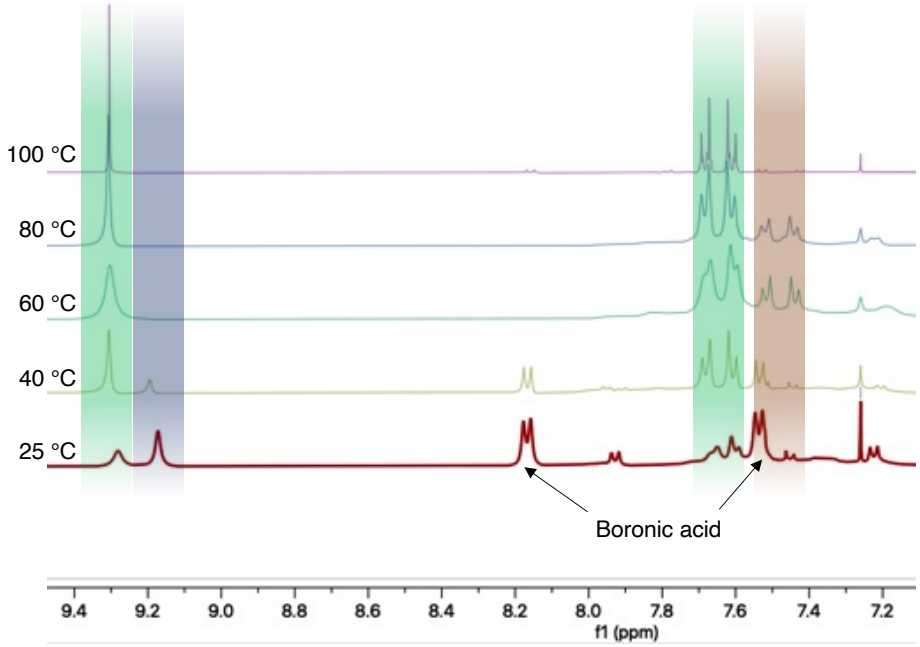
1 **4** **hc**

A Schlenk tube (10 mL) equipped with a magnetic stirring bar was charged with Pd(dppf)Cl_2 (17.1 mg, 23.4 µmol, 0.15 eq), 4-*tert*-butylphenylboronic acid (**3**, 41.7 mg, 0.234 mmol, 1.5 eq), Ag_2CO_3 (43 mg, 0.156 mmol, 1.0 eq) and 5-bromo-1,2,3-triazine (**1**, 25.0 mg, 0.156 mmol, 1.0 eq). The tube was closed with a septum, set under N_2, and MeCN (1.55 mL, 0.1 M) was added *via* syringe. The tube was immediately placed in an oil bath of designated temperature (Table S1) and the mixture was stirred (500 rpm) for 30 min. The reaction mixture was filtered over celite, eluted with CH_2Cl_2, and concentrated *in vacuo* (45 °C, 500 to 50 mbar). After purification by flash column chromatography* (SiO_2, 2x15 cm, 20% EtOAc in *n*-pentane), removal of the solvent in *vacuo* (45 °C, 500 to 10 mbar) and subsequent drying under high vacuum product distributions were determined by ^{1}H NMR.

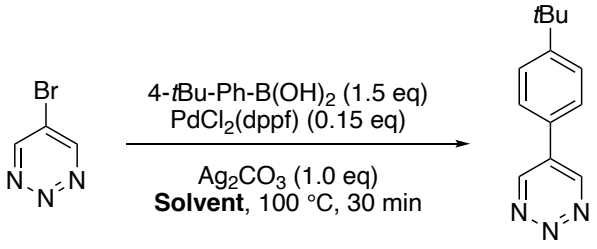
*Fractions containing starting material **1**, product **4**, and homocoupling **hc** product were collected together.

Entry	Temp	Starting material : Product : Side product	Yield
1	25°C	33 : 29 : 38	–
2	40°C	13 : 65 : 22	–
3	60°C	0 : 79 : 21	–
4	80°C	0 : 83 : 17	27.1 mg, 81%
5	100°C	0 : 87 : 13	24.9 mg, 75%

Table S1: Temperature screening.



Solvent Screening



1 **4**

A Schlenk tube (10 ml) equipped with a magnetic stirring bar was charged with $Pd(dppf)Cl_2$ (17.1 mg, 23.4 µmol, 0.15 eq), 4-*tert*-butylphenyl boronic acid (**3**, 41.7 mg, 0.234 mmol, 1.5 eq), Ag_2CO_3 (43.0 mg, 0.156 mmol, 1.0 eq) and 5-bromo-1,2,3-triazine (**1**, 25.0 mg, 0.156 mmol, 1.0 eq). The tube was sealed with a septum, set under N_2, and solvent (Table 2) (1.55 mL, 0.1 M) was added *via* syringe. The tube was directly placed in a preheated oil bath (100 °C) and the mixture was stirred (500 rpm) for 30 min. The reaction mixture was filtered over celite, eluted with CH_2Cl_2, and concentrated *in vacuo* (45 °C, 500 to 50 mbar). After purification by flash column chromatography (SiO_2, 2x15 cm, 20% EtOAc in *n*-pentane),

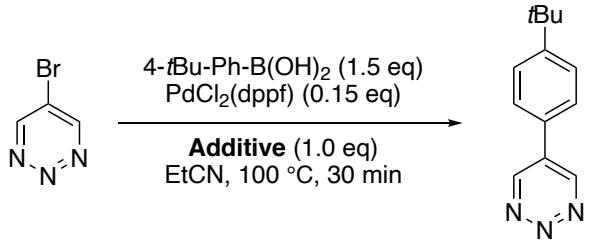
removal of the solvent *in vacuo* (45 °C, 500 to 10 mbar), and subsequent drying under high vacuum the yields were determined. In cases where this procedure afforded impure product, an analytical yield was determined by ^{1}H NMR.

Entry	Solvent	Analytical Yield	Yield
1	Acetonitrile	–	24.9 mg, 75%
2	DMF	–	13.9 mg, 42%
3	Toluene	–	–
4	1,4-Dioxane	64%	–
5	Propionitrile	–	26.8 mg, 81%
6	1,2-DME	65%	–

Table S2: Solvent screening.

Screening of Additives and Reagent Amounts

A Schlenk tube (10 mL) with a stirring bar was charged with Pd(dppf)Cl_2 (17.1 mg, 23.4 µmol, 0.15 eq), 4-*tert*-butylphenyl boronic acid (**3**, 41.7 mg, 0.234 mmol, 1.5 eq), the additive (Table 3, 1.0 eq unless otherwise stated) and 5-bromo-1,2,3-triazine (**1**, 25.0 mg, 0.156 mmol, 1.0 eq). The tube was sealed with a septum, set under N_2, and EtCN (1.55 mL, 0.1 M) was added *via* syringe. The tube was immediately placed in a preheated oil bath (100 °C) and the mixture was stirred (500 rpm) for 30 min. The reaction mixture was filtered over celite, eluted with CH_2Cl_2, and concentrated *in vacuo* (45 °C, 500 to 50 mbar). After purification by flash column chromatography (silica, 2x15 cm, 20% EtOAc in *n*-pentane), removal of the solvent *in vacuo* (45 °C, 500 to 10 mbar) and subsequent drying at high vacuum the yields were determined. In cases where this procedure afforded impure product, an analytical yield was determined by ^{1}H NMR.



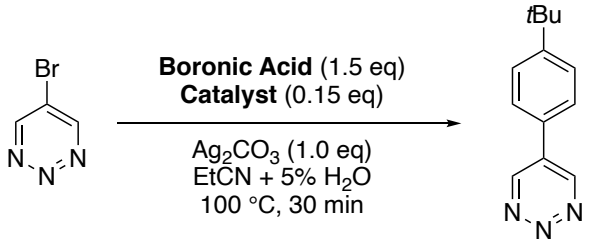
1 **4**

Entry	Additive	Analytical Yield	Yield
1	Ag_2CO_3	–	26.8 mg, 81%
2	none	–	–
3	K_2CO_3	35%	–
4	Na_2CO_3	15%	–
5	Cs_2CO_3	53%	–
6	Ag_2O	–	–
7	AgF	–	9.1 mg, 27%
8	$AgPF_6$	–	–
9	$AgBF_4$	–	–
10	$AgNO_3$	12%	–

11	AgOAc	40%	–
12	Ag_3PO_4	–	23.1 mg, 69%
13	KO*t*Bu	51%	–
14	CsF	–	9.0 mg, 27%
15	$BF_3{\cdot}OEt_2$	–	traces
16	Al_2O_3	–	traces
17	Cu_2O	24%	–
18	K_3PO_4	84%	–
19	$FeCl_3$	–	–
20	Ag_2CO_3, 5% H_2O	–	27.8 mg, 84%
21	Ag_2CO_3, 20% H_2O	–	27.0 mg, 81%
22	0.5 eq Ag_2CO_3, 5% H_2O	–	21.2 mg, 63%
23	2 eq Ag_2CO_3, 5% H_2O	–	25.3 mg, 76%
24*	Ag_2CO_3, 5% H_2O	–	30.3 mg, 91%

Table S3: Additive screening. *Reaction was performed with 2 eq of boronic acid.

Catalyst Screening



1 **4**

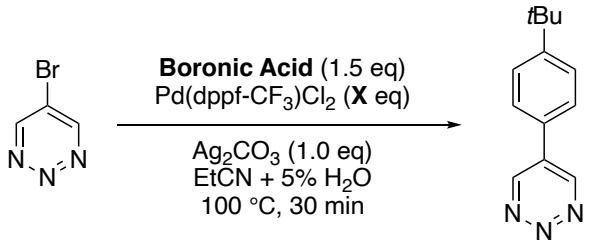
A Schlenk tube (10 mL) equipped with a stirring bar was charged consecutively with catalyst (23.4 µmol, 0.15 eq) (Table 4), boronic acid (0.312 mmol, 2 eq) (Table S4), Ag_2CO_3 (43.0 mg, 0.156 mmol, 1.0 eq) and 5-bromo-1,2,3-triazine (**1**, 25.0 mg, 0.156 mmol, 1.0 eq). The tube was sealed with a septum, set under N_2, and dry EtCN (1.55 mL, 0.1 M) with 5% H_2O was added *via* syringe. Subsequently, the tube was placed in an oil bath (100 °C) and the mixture was stirred (500 rpm) for 30 min. The reaction mixture was filtered over celite, eluted with CH_2Cl_2, and concentrated *in vacuo* (45 °C, 500 to 50 mbar). Yields were determined after purification by flash column chromatography (silica, 2x15 cm, 20% EtOAc in *n*-pentane), removal of the solvent in *vacuo* (45 °C, 500 to 10 mbar) and subsequent drying at high vacuum.

Entry	Catalyst	Boronic Acid	Yield
1	$Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph-$B(OH)_2$	80%
2	dppf	4-*t*Bu-Ph-$B(OH)_2$	0%
3	dppf, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph-$B(OH)_2$	76%
4	$Pd(PPh_3)2Cl_2$	4-*t*Bu-Ph-$B(OH)_2$	95%
5	DPEphos, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph-$B(OH)_2$	94%
6	BINAP, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph-$B(OH)_2$	68%
7	dppf, $Pd(MeCN)_2Cl_2$	4-F-Ph-$B(OH)_2$	62%
8	dppf-CF_3, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph-$B(OH)_2$	97%

9	dppf-CF_3, $Pd(MeCN)_2Cl_2$	4-F-Ph-$B(OH)_2$	72%
10	dppf-3,5-CF_3, $Pd(MeCN)_2Cl_2$	4-*t*Bu-Ph-$B(OH)_2$	0%
11	dppf-3,5-CF_3, $Pd(MeCN)_2Cl_2$	4-F-Ph-$B(OH)_2$	0%

Table S4: Catalyst screening.

Screening of Catalyst Loading



1 **4**

A Schlenk tube (10 mL) equipped with a stirring bar was charged consecutively with Pd(dppf-CF_3)Cl_2 (Table 5), boronic acid (0.312 mmol, 2 eq) (Table 5), Ag_2CO_3 (43 mg, 0.156 mmol, 1.0 eq) and bromo triazine (25.0 mg, 0.156 mmol, 1.0 eq). The tube was sealed with a septum and dry EtCN (1.55 mL, 0.1 M) was added *via* syringe. Subsequently, the tube was placed in an oil bath (100 °C) and the mixture was stirred (500 rpm) for 30 min. The reaction mixture was filtered over celite, eluted with CH_2Cl_2, and concentrated *in vacuo* (45 °C, 500 to 50 mbar). Yields were determined after purification by flash column chromatography (SiO_2, 2x15 cm, 20% EtOAc in *n*-pentane), removal of the solvent *in vacuo* (45 °C, 700 to 10 mbar) and subsequent drying at high vacuum.

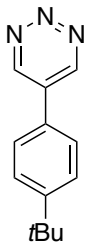
Entry	Catalyst loading	Boronic Acid	Yield
1	15 mol-%	4-*t*Bu-Ph-$B(OH)_2$	97%
2	15 mol-%	4-F-Ph-$B(OH)_2$	72%
3	10 mol-%	4-*t*Bu-Ph-$B(OH)_2$	86%
4	5 mol-%	4-*t*Bu-Ph-$B(OH)_2$	69%
5*	5 mol-%	4-*t*Bu-Ph-$B(OH)_2$	79%

Table S5: Catalyst loading screening.

General Procedure for Bromo Triazine Cross-Coupling

A Schlenk tube (10 mL) equipped with a stirring bar was charged consecutively with $Pd(MeCN)_2Cl_2$ (6.07 mg, 23.4 µmol, 0.15 eq), dppf-CF_3 (19.3 mg, 23.4 µmol, 0.15 eq), boronic acid (0.312 mmol, 2 eq), Ag_2CO_3 (0.156 mmol, 1.0 eq) and bromo triazine **1** (25 mg, 0.156 mmol, 1.0 eq). The tube was sealed with a septum and EtCN + 5% H_2O (1.55 mL, 0.1 M) was added *via* syringe. Subsequently, the tube was placed in a preheated oil bath (100°C) and the mixture was stirred (500 rpm) for 30 min. The reaction mixture was filtered through a pad of celite, eluted with CH_2Cl_2, concentrated in *vacuo* (45 °C, 600 to 30 mbar), and purified by flash column chromatography (SiO_2, 2x15 cm, designated solvent system). Removal of the solvent *in vacuo* (45 °C, 700 to 10 mbar) and subsequent drying at high vacuum, afforded the desired product.

5-(4-(*tert*-Butyl)phenyl)-1,2,3-triazine (4)



Yield: 97%, 32.4 mg

R_f = 0.333 (EtOAc/n-pentane = 1:4)

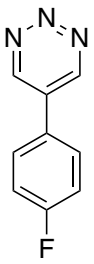
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 2H), 7.71 – 7.66 (m, 2H), 7.63 – 7.59 (m, 2H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 147.2, 129.6, 128.0, 127.2, 127.0, 35.1, 31.2.

IR (neat): 2962m, 2906m, 2869m, 1608m, 1566m, 1511m, 1477m, 1464m, 1403m, 1366m, 1322m, 1305m, 1270m, 1202w, 1169w, 1116m, 1088m, 1062m, 1017w, 993m, 924m, 834s, 768m, 732w, 695w, 667m, 576s cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{13}H_{15}N_3^{+\cdot}$ 213.1261; Found 213.1259.

5-(4-Fluorophenyl)-1,2,3-triazine (6)



Yield: 76%, 20.7 mg

R_f = 0.148 (EtOAc/n-pentane = 1:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 2H), 7.74 (dd, *J* = 8.6, 5.0 Hz, 2H), 7.30 (t, *J* = 8.2 Hz, 2H).

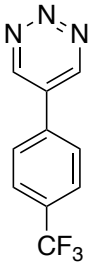
^{13}C NMR: (101 MHz, $CDCl_3$) δ 166.1, 163.6, 147.2, 129.4, 129.4, 128.8, 127.2, 127.1, 117.6, 117.4.

^{19}F NMR (377 MHz, CDCl3) δ -107.9.

IR (neat): 3064m, 1884w, 1602s, 1561m, 1507s, 1414w, 1399w, 1359s, 1323m, 1309m, 1230s, 1164s, 1132m, 1107m, 1093m, 1063m, 1016w, 995w, 947m, 923w, 846s, 832m, 764m, 749m, 717w, 668m, 602w, 568s, 554m, 486w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_9H_6N_3F^{+\cdot}$ 175.0540; Found 175.0541.

5-(4-(Trifluoromethyl)phenyl)-1,2,3-triazine (7)



Yield: 58%, 20.2 mg

R_f = 0.222 (EtOAc/n-pentane = 1:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 2H), 7.88 – 7.85 (m, 4H).

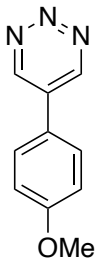
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 134.8, 133.3 (q, *J* = 33.1 Hz), 128.6, 127.1 (q, *J* = 3.6 Hz), 125.0 (q, *J* = 272.5 Hz).

^{19}F NMR (377 MHz, CDCl3) δ -63.1.

IR (neat): 3383w, 3068w, 3044w, 1618w, 1583w, 1567m, 1517w, 1414m, 1367w, 1359m, 1318s, 1285m, 1190w, 1169m, 1153m, 1110s, 1069s, 1063s, 1015m, 994m, 941m, 909m, 858m, 831s, 768m, 750m, 733m, 667m, 633w, 605m, 543w, 482w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{10}H_6N_3F_3^{+\cdot}$ 225.0508; Found 225.0511.

5-(4-Methoxyphenyl)-1,2,3-triazine (8)



Yield: 59%, 17.1 mg

R_f = 0.093 (EtOAc/n-pentane = 1:4)

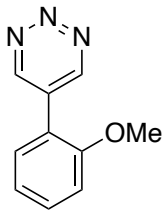
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 3.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 146.8, 129.2, 128.6, 122.8, 115.7, 55.7.

IR (neat): 3027w, 2968w, 2934w, 2831w, 1607s, 1566m, 1513s, 1457m, 1432w, 1359m, 1322m, 1295m, 1256s, 1185s, 1171m, 1126m, 1094m, 1063m, 1025m, 1008m, 990m, 946w, 918w, 830s, 822m, 765w, 742w, 669m, 581m, 552m, 492w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{10}H_9ON_3^{+\cdot}$ 187.0740; Found 187.0737.

5-(2-Methoxyphenyl)-1,2,3-triazine (9)



Yield: 65%, 19.0 mg

R_f = 0.32 (EtOAc/n-pentane 1:2)

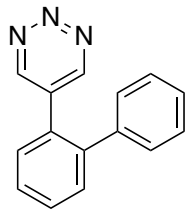
^{1}H NMR (400 MHz, CDCl3) δ 9.30 (s, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 157.5, 149.4, 132.7, 130.2, 128.5, 121.9, 120.0, 111.9, 55.8.

IR (neat): 2941w, 2840w, 1599m, 1581m, 1559m, 1508w, 1490m, 1460m, 1435m, 1361m, 1311m, 1270s, 1248s, 1166m, 1130m, 1087m, 1052m, 1019m, 991m, 926m, 809w, 753s, 666m, 628m, 578w, 566w, 498w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\bullet}$ Calcd for $C_{10}H_9ON_3^{+\bullet}$ 187.0740; Found 187.0738.

5-([1,1'-Biphenyl]-2-yl)-1,2,3-triazine (10)



Yield: 97%, 35.2 mg

R_f = 0.25 (EtOAc/n-pentane = 1:4)

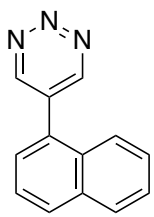
^{1}H NMR (400 MHz, CDCl3) δ 8.80 (s, 2H), 7.64 – 7.46 (m, 4H), 7.35 – 7.27 (m, 3H), 7.13 – 7.06 (m, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 149.8, 141.7, 139.0, 131.6, 131.5, 130.8, 130.2, 130.2, 129.9, 129.0, 128.7, 128.1.

IR (neat): 3055w, 1595w, 1562m, 1509w, 1476m, 1448m, 1436m, 1362m, 1351m, 1323m, 1167w, 1129m, 1075w, 1062m, 1008m, 989m, 925m, 845w, 760s, 744s, 727m, 702s, 665m, 635w, 616w, 569w, 557w, 518m cm^{-1}.

HRMS (EI) m/z: $[M]^{+\bullet}$ Calcd for $C_{15}H_{11}N_3^{+\bullet}$ 233.0948; Found 233.0944.

5-(Naphthalen-1-yl)-1,2,3-triazine (11)



Yield: 72%, 23.2 mg

R_f = 0.241 (EtOAc/n-pentane = 1:4)

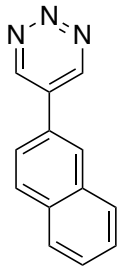
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 2H), 8.05 (d, *J* = 8.3 Hz, 1H), 8.02 – 7.97 (m, 1H), 7.77 – 7.73 (m, 1H), 7.66 – 7.55 (m, 3H), 7.49 (dd, *J* = 7.0, 1.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 134.0, 131.2, 130.8, 130.4, 129.7, 129.2, 128.4, 128.1, 127.1, 125.7, 123.7.

IR (neat): 3050w, 1589w, 1559m, 1495m, 1400w, 1369m, 1346m, 1325m, 1254m, 1192w, 1168m, 1130m, 1061m, 1043m, 1017w, 960m, 931m, 865w, 838w, 802s, 775s, 733m, 669m, 633m, 602w, 574w, 559w, 486w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{13}H_9N_3^{+\cdot}$ 207.0791; Found 207.0796.

5-(Naphthalen-2-yl)-1,2,3-triazine (12)



Yield: 65%, 15.7 mg

R_f = 0.185 (EtOAc/n-pentane = 1:4)

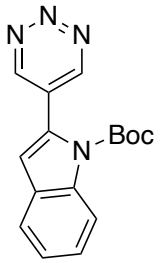
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 2H), 8.25 – 8.22 (m, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 8.02 – 7.96 (m, 1H), 7.96 – 7.90 (m, 1H), 7.78 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.71 – 7.57 (m, 2H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 147.5, 134.4, 133.5, 130.3, 129.7, 128.8, 128.4, 128.2, 128.1, 127.8, 127.7, 123.3.

IR (neat): 3034m, 1852w, 1626m, 1598m, 1558m, 1515m, 1498m, 1471m, 1388m, 1371m, 1352m, 1326m, 1300m, 1275m, 1237m, 1199m, 1148m, 1132m, 1084m, 1063m, 1019m, 1004m, 960m, 943m, 933m, 899m, 867s, 825s, 770m, 755s, 669m, 653m, 565m, 546w, 484s, 473m cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{13}H_9N_3^{+\cdot}$ 207.0791; Found 207.0795.

tert-Butyl 2-(1,2,3-triazin-5-yl)-1H-indole-1-carboxylate (13)



Yield: 79%, 36.5 mg

R_f = 0.304 (EtOAc/n-pentane = 1:4)

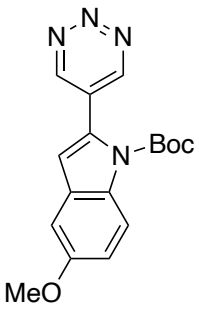
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 2H), 8.20 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.38 – 7.29 (m, 1H), 6.92 (s, 1H), 1.49 (s, 9H)..

^{13}C NMR: (101 MHz, $CDCl_3$) δ 149.5, 148.1, 138.4, 130.6, 128.8, 126.9, 125.3, 124.1, 121.8, 116.1, 115.4, 86.1, 28.0.

IR (neat): 2981w, 1727s, 1583m, 1568m, 1545m, 1500m, 1472w, 1446m, 1388m, 1372m, 1356m, 1316s, 1291s, 1277m, 1261m, 1224s, 1201m, 1151s, 1127s, 1075m, 1064m, 1039m, 1024m, 1009m, 949w, 928m, 910m, 874w, 857m, 845m, 828m, 769m, 755s, 730s, 672m, 656m, 632m, 608m, 571w, 473m cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{16}H_{16}O_2N_4^{+\cdot}$ 296.1268; Found 296.1269.

tert-Butyl 5-methoxy-2-(1,2,3-triazin-5-yl)-1H-indole-1-carboxylate (14)



Yield: 66%, 33.8 mg

R_f = 0.15 (EtOAc/n-pentane = 1:4)

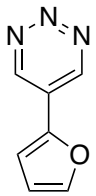
^{1}H NMR (400 MHz, CDCl3) δ 9.11 (s, 2H), 8.10 – 8.04 (m, 1H), 7.07 – 7.02 (m, 2H), 6.83 (s, 1H), 3.86 (s, 3H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, CDCl3) δ 156.7, 149.5, 148.1, 133.1, 131.0, 129.6, 125.3, 116.9, 116.1, 115.2, 103.4, 85.9, 55.8, 28.0.

IR (neat): 2980w, 2936w, 2836w, 1730s, 1613w, 1570m, 1543w, 1504m, 1474m, 1448m, 1371m, 1359m, 1310s, 1274m, 1260m, 1230s, 1158s, 1124s, 1076m, 1068m, 1033m, 1009m, 926w, 894w, 846m, 810m, 765m, 736m, 673w, 649w, 615w, 466w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{17}H_{18}O_3N_4^{+\cdot}$ 326.1373; Found 326.1370.

5-(Furan-2-yl)-1,2,3-triazine (15)



Yield: 67%, 15.4 mg

R_f = 0.093 (EtOAc/n-pentane = 1:4)

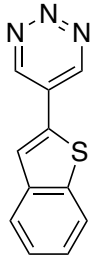
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 2H), 7.72 (d, *J* = 1.7 Hz, 1H), 7.20 (d, *J* = 3.5 Hz, 1H), 6.66 (dd, *J* = 3.6, 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 145.2, 143.5, 120.2, 113.8, 113.3.

IR (neat): 3395w, 3144m, 3129m, 3109m, 3086m, 3036m, 1870w, 1734w, 1661w, 1593s, 1552s, 1522m, 1512m, 1477s, 1398m, 1355m, 1324m, 1307m, 1234w, 1163m, 1132m, 1101m, 1064m, 1017s, 965w, 941m, 928m, 906s, 892m, 883m, 848m, 770s, 734m, 714m, 703m, 665m, 591m, 567w, 479w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_7H_5ON_3^{+\cdot}$ 147.0427; Found 147.0430.

5-(Benzo[*b*]thiophen-2-yl)-1,2,3-triazine (16)



Yield: 50%, 16.7 mg

R_f = 0.17 (EtOAc/n-pentane 1:4)

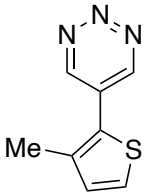
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 2H), 8.00 (s, 1H), 7.92 (dt, *J* = 6.0, 2.8 Hz, 2H), 7.54 – 7.41 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 141.0, 139.8, 133.1, 127.2, 125.9, 125.8, 125.2, 124.7, 122.9.

IR (neat): 3065w, 2928m, 1727m, 1648m, 1563s, 1520m, 1502m, 1452m, 1428m, 1398m, 1366m, 1323s, 1258m, 1241m, 1173m, 1133m, 1075m, 1062m, 1016m, 994m, 950m, 929m, 872m, 840s, 777m, 766m, 760m, 727m, 714m, 705m, 661m, 607m, 580m, 463m cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{11}H_7N_3S^{+\cdot}$ 213.0355; Found 213.0355.

5-(3-Methylthiophen-2-yl)-1,2,3-triazine (17)



Yield: 56%, 15.4 mg

R_f = 0.17 (EtOAc/n-pentane 1:4)

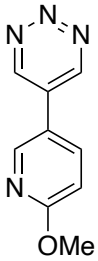
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 2H), 7.53 (d, *J* = 5.1 Hz, 1H), 7.06 (d, *J* = 5.0 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 147.4, 140.1, 133.1, 129.1, 127.2, 125.7, 15.9.

IR (neat): 3088m, 1555s, 1497m, 1460m, 1425s, 1383m, 1356m, 1324w, 1283w, 1131w, 1105w, 1078w, 1062w, 963m, 929w, 911w, 840w, 757m, 665m, 533w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_8H_7N_3S^{+\cdot}$ 177.0355; Found 177.0352.

5-(6-Methoxypyridin-3-yl)-1,2,3-triazine (18)



Yield: 87%, 25.6 mg

R_f = 0.4 (CH_2Cl_2 + 10% acetone)

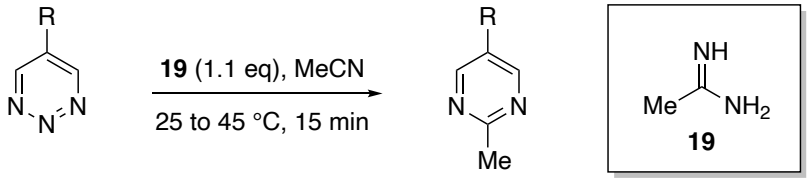
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 2H), 8.58 (d, *J* = 2.7 Hz, 1H), 7.93 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 4.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 146.6, 146.3, 136.8, 127.3, 119.9, 112.7, 54.3.

IR (neat): 2922m, 2852m, 1605s, 1565m, 1497s, 1461m, 1397m, 1363m, 1321s, 1304s, 1265m, 1170m, 1132m, 1096m, 1062m, 1028m, 1014s, 987m, 944m, 925m, 835s, 756m, 712m, 667m, 619m, 567m cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_9H_8ON_4^{+\cdot}$ 188.0693; Found 188.0693.

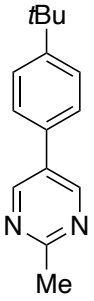
Diversification of triazines to pyrimidines[1]



A one-necked pear-shaped flask (5 mL) equipped with a magnetic stirring bar under air was charged with triazine (1.0 eq) and MeCN (~0.5 M). To this solution, freshly distilled free-based acetamidine[2] (**19**, 1.1 eq) was added and the mixture was stirred for 5 min at 25 °C. It was then warmed to 45 °C for 15 min,* concentrated *in vacuo* (40 °C, 300 to 30 mbar) and purified by column chromatography (SiO_2, CH_2Cl_2 + 0–10% acetone gradient) to afford the desired pyrimidines after removal of the solvent and drying under high vacuum.

*Note: If after the first 5 min at 45 °C there was still significant amounts of triazine observed by TLC, additional amidine **19** (0.5 eq) was added.

5-(4-(*tert*-Butyl)phenyl)-2-methylpyrimidine (20)



The reaction was performed using triazine **4** (50.0 mg, 0.234 mmol, 1.0 eq) and amidine **19** (15.0 mg, 0.257 mmol, 1.1 eq) in MeCN (0.5 mL) and afforded the product as an off-white solid. Additional amidine **19** (6.81 mg, 0.117 mmol, 0.5 eq) was added to achieve complete conversion of the triazine.

Yield: 80%, 42.6 mg

R_f = 0.31 (CH_2Cl_2 + 5% acetone)

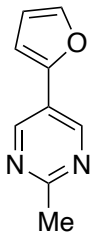
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 2H), 7.55 – 7.46 (m, 4H), 2.77 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 154.9, 152.0, 131.6, 131.0, 126.6, 126.4, 34.8, 31.3, 25.8.

IR (neat): 2961m, 2904w, 2867w, 1587m, 1567w, 1537m, 1473m, 1461m, 1442s, 1407w, 1375m, 1364m, 1278w, 1268m, 1203w, 1175w, 1114m, 1047w, 1001m, 908m, 835m, 751m, 732s, 655m, 575m, 525w cm^{-1}.

HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{15}H_{18}N_2^{+\cdot}$ 226.1465; Found 226.1467.

5-(Furan-2-yl)-2-methylpyrimidine (21)



The reaction was performed using triazine **15** (9.4 mg, 63.9 μmol, 1.0 eq) and amidine **19** (4.08 mg, 70.3 μmol, 1.1 eq) in MeCN (0.15 mL) and afforded the product as an off-white solid. Additional amidine **19** (1.85 mg, 32.0 μmol mmol, 0.5 eq) was added to achieve complete conversion of the triazine.

Yield: 66%, 6.7 mg

R_f = 0.36 (CH_2Cl_2 + 5% acetone)

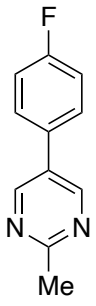
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 2H), 7.55 (d, J = 1.8 Hz, 1H), 6.77 (d, J = 3.4 Hz, 1H), 6.52 (dd, J = 3.4, 1.8 Hz, 1H), 2.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 152.1, 148.5, 143.7, 122.2, 112.1, 107.2, 25.9.

IR (neat): 3109w, 2927w, 1574m, 1548m, 1495m, 1444m, 1400m, 1365m, 1323w, 1295w, 1270w, 1220m, 1166w, 1134w, 1077w, 1063w, 1028w, 1008m, 935w, 907m, 886w, 815w, 748s, 652m, 596m, 464m cm^{-1}.

HRMS (EI) m/z: $[M]^{+\bullet}$ Calcd for $C_9H_8ON_2^{+\bullet}$ 160.0631; Found 160.0632.

5-(4-Fluorophenyl)-2-methylpyrimidine (22)



The reaction was performed using triazine **7** (20.0 mg, 0.114 mmol, 1.0 eq) and amidine **19** (7.28 mg, 0.125 mmol, 1.1 eq) in MeCN (0.25 mL) and afforded the product as an off-white solid. Additional amidine **19** (3.31 mg, 57.0 μmol mmol, 0.5 eq) was added to achieve complete conversion of the triazine.

Yield: 57%, 12.3 mg

R_f = 0.32(CH_2Cl_2 + 5% acetone)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 2H), 7.55 – 7.49 (m, 2H), 7.19 (t, *J* = 8.5 Hz, 2H), 2.78 (s, 3H).

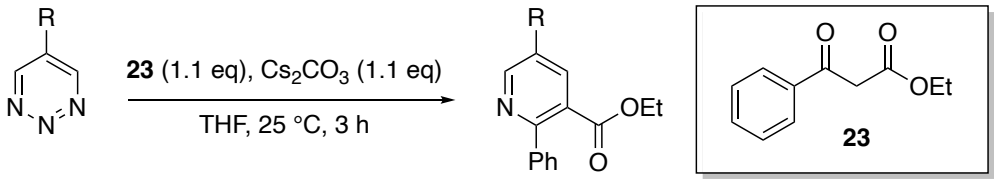
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 164.6, 162.1, 155.0, 130.8, 130.8, 130.4, 128.8, 128.7, 116.7, 116.5, 25.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.0.

IR (neat): 3047w, 3016w, 1611w, 1593m, 1547m, 1518m, 1485w, 1445m, 1379w, 1323w, 1311w, 1280w, 1266w, 1238m, 1175w, 1163m, 1140w, 1101w, 1063w, 1040w, 1006w, 907s, 844w, 830m, 808w, 731s, 679m, 656m, 546m, 510m cm^{-1}.

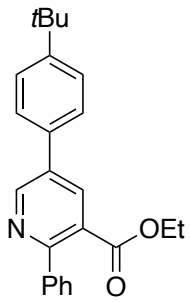
HRMS (EI) m/z: $[M]^{+\cdot}$ Calcd for $C_{11}H_9N_2F^{+\cdot}$ 188.0744; Found 18.0745.

Diversification of triazines to pyridines[3]



A one-necked pear-shaped flask (10 mL) equipped with a magnetic stirring bar was charged with triazine (1.0 eq), Cs_2CO_3 (1.1 eq), and THF (~0.5 M). Ketoester **23** (1.1 eq) was added to the mixture, and it was stirred for 3 h (or until reaction control by UHPLC-(+)-MS showed full consumption of the triazine) at 25 °C. The solvent was removed *in vacuo* (40 °C, 500 to 50 mbar), and the residue was purified by column chromatography (SiO_2, Et_2O/*n*-pentane 1:4) to afford after removal of the eluent and drying under high vacuum the desired pyridine.

Ethyl 5-(4-(*tert*-butyl)phenyl)-2-phenylnicotinate (24)



The reaction was performed using triazine **4** (25.0 mg, 0.117 mmol, 1.0 eq), Cs_2CO_3 (41.9 mg, 0.129 mmol, 1.1 eq), and ketoester **23** (24.7 mg, 0.129 mmol, 1.1 eq) in THF (0.5 mL) and afforded the product as an off-white solid.

Yield: 48%, 20.1 mg

R_f = 0.27 (Et_2O/*n*-pentane = 1:4)

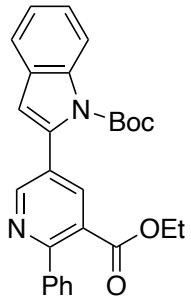
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 – 8.94 (m, 1H), 8.32 – 8.25 (m, 1H), 7.66 – 7.50 (m, 6H), 7.44 (m, 3H), 4.23 – 4.14 (m, 2H), 1.42 – 1.35 (m, 9H), 1.12 – 1.03 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 157.2, 151.9, 149.5, 140.1, 136.0, 134.6, 133.7, 128.7, 128.7, 128.3, 127.4, 126.9, 126.4, 61.7, 34.8, 31.4, 13.8.

IR (neat): 2961m, 2903w, 2868w, 1716s, 1596w, 1538w, 1445s, 1417w, 1393w, 1382w, 1364m, 1319m, 1250s, 1204m, 1105m, 1095m, 1076w, 1056m, 1040w, 1016m, 922w, 863w, 834m, 802w, 774m, 746m, 728w, 698s, 560m, 527w cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}NO_2^+$ 360.1958; Found 360.1954.

tert-Butyl 2-(5-(ethoxycarbonyl)-6-phenylpyridin-3-yl)-1*H*-indole-1-carboxylate (25)



The reaction was performed using triazine **13** (32.0 mg, 0.108 mmol, 1.0 eq), Cs_2CO_3 (38.7 mg, 0.119 mmol, 1.1 eq), and ketoester **23** (22.8 mg, 0.119 mmol, 1.1 eq) in THF (0.5 mL) and afforded the product as a colorless oil.

Yield: 74%, 35.5 mg

R_f = 0.29 (Et_2O/*n*-pentane = 1:4)

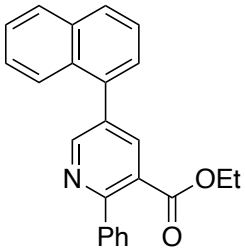
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.2 Hz, 1H), 8.27 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 7.65 – 7.54 (m, 3H), 7.50 – 7.43 (m, 3H), 7.39 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.30 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 (d, *J* = 0.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.42 (s, 9H), 1.08 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 157.7, 150.5, 150.0, 140.0, 137.8, 137.8, 135.6, 129.2, 129.1, 128.9, 128.7, 128.3, 126.5, 125.3, 123.5, 120.9, 115.8, 112.0, 84.5, 61.7, 27.9, 13.8.

IR (neat): 2980w, 2934w, 1727s, 1561w, 1537w, 1475m, 1439m, 1394w, 1368m, 1321s, 1280m, 1257s, 1220m, 1209m, 1157s, 1131s, 1104m, 1094m, 1076m, 1050m, 1018m, 951w, 913m, 851m, 819m, 803m, 768m, 739s, 698m, 649m cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{27}H_{27}N_2O_4^+$ 443.1965; Found 443.1960.

Ethyl 5-(naphthalen-1-yl)-2-phenylnicotinate (26)



The reaction was performed using triazine **11** (18.7 mg, 90.2 μmol, 1.0 eq), Cs_2CO_3 (32.3 mg, 99.2 μmol, 1.1 eq), and ketoester **23** (19.1 mg, 99.2 μmol, 1.1 eq) in THF (0.5 mL) and afforded the product as a colorless oil.

Yield: 62%, 19.8 mg

R_f = 0.33 (Et_2O/*n*-pentane = 1:4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 2.2 Hz, 1H), 8.25 (d, J = 2.2 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.91 – 7.87 (m, 1H), 7.68 – 7.64 (m, 2H), 7.62 – 7.46 (m, 7H), 4.21 (q, J = 7.1 Hz, 2H), 1.09 (t, J = 7.1 Hz, 3H).

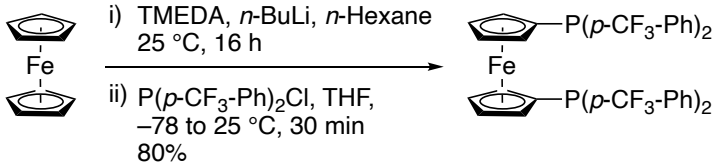
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 157.7, 152.0, 140.0, 139.0, 135.2, 134.6, 133.9, 131.5, 129.1, 128.9, 128.8, 128.7, 128.4, 127.7, 127.2, 127.0, 126.4, 125.6, 125.2, 61.8, 13.8.

IR (neat): 3056w, 2980w, 2932w, 1715s, 1596w, 1537m, 1509w, 1466m, 1445m, 1395m, 1364m, 1313m, 1264s, 1243s, 1204m, 1184m, 1104m, 1094m, 1063w, 1041m, 1018m, 991w, 916w, 863w, 802m, 777s, 742m, 698s, 671w, 625w cm^{-1}.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}NO_2^+$ 354.1489; Found 354.1489.

Ligand synthesis

1,1'-Bis(di-para-(trifluoromethyl)phenylphosphino)ferrocene (dppf-CF_3)[4]

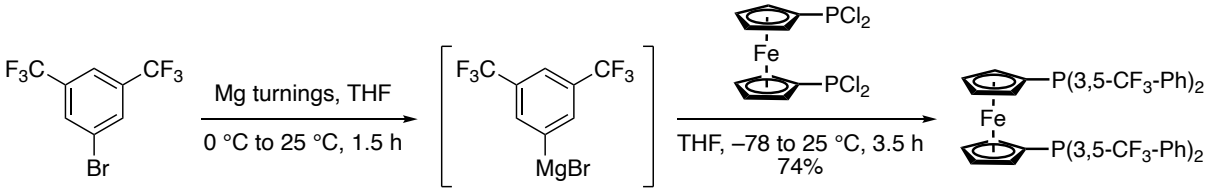


A flame-dried one-necked flask (25 mL) equipped with a stirring bar was charged under N_2 with ferrocene (569 mg, 3.06 mmol, 1.0 eq) and dry hexane (6.0 mL). TMEDA (1.11 mL, 7.34 mmol, 2.4 eq) and *n*-BuLi (4.2 mL, 1.6 M in hexane, 6.73 mmol, 2.2 eq) were added consecutively and dropwise resulting in complete dissolution of the ferrocene. The solution

was stirred for 16 h at room temperature, during which an orange solid precipitated. Stirring was stopped and after the precipitate had settled, the hexane was removed by syringe. The solid was washed once with hexane (3 mL) and was subsequently dissolved in dry THF (6.0 mL). The red solution was cooled to –78 °C with acetone/dry ice and P(*p*-CF_3-Ph)$_2$Cl (2.89 g, 8.10 mmol, 2.65 eq) was added dropwise by syringe. After stirring for 15 min at the previous temperature, cooling was removed and the mixture was allowed to warm to room temperature. After 30 min, the reaction was quenched with H_2O (6 mL), then H_2O (6 mL) and CH_2Cl_2 (15 mL) were added to achieve proper separation of the phases. Extraction of the aqueous phase with CH_2Cl_2 (4 x 10 mL) and subsequent drying of the combined organic phases over anhydrous Na_2SO_4 afforded, after removal of solvent *in vacuo* (40 °C, 600 to 50 mbar), a brownish yellow oil. After purification of the residue by flash column chromatography (SiO_2, 15 x 5 cm, CH_2Cl_2) and drying under high vacuum, the desired dppf-CF_3 (2.02 g, 2.45 mmol, 80%) was obtained as an orange foam.

Yield: 80%. **TLC:** R_f = 0.91 (CH_2Cl_2). **M.p.** (CH_2Cl_2): 68.2 – 70.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 – 7.53 (m, 8H), 7.40 – 7.35 (m, 8H), 4.35 – 4.30 (m, 4H), 4.02 – 3.96 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.1 (d, *J* = 13.6 Hz), 133.8 (d, *J* = 19.9 Hz), 131.1 (q, *J* = 32.6 Hz), 125.2 (dq, *J* = 7.4, 3.7 Hz), 124.1 (q, *J* = 272.4 Hz), 75.0 (d, *J* = 7.5 Hz), 74.0 (d, *J* = 15.2 Hz), 72.9 (d, *J* = 3.8 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ –62.8. **^{31}P NMR** (162 MHz, $CDCl_3$): δ –17.2. **IR** (neat): 1607w, 1396m, 1322s, 1164m, 1124m, 1105m, 1060m, 1031w, 1016m, 957w, 830m, 737w, 696m, 635w, 599w, 499w cm^{-1}. **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{38}H_{25}F_{12}FeP_2^+$ 827.0584; Found 827.0584.

1,1'-Bis(di-3,5-(trifluoromethyl)phenylphosphino)ferrocene (dppf-3,5-CF_3)[5]



A one-necked round bottom flask equipped with a magnetic stirring bar was charged with magnesium turnings (250 mg, 10.2 mmol, 5 eq) and sealed with a septum. The flask was evacuated, thoroughly flame dried, and flushed with N_2. In a second flame-dried flask (25 mL) 3,5-bis(trifluoromethyl)bromobenzene (1.76 mL, 10.2 mmol, 5 eq) was dissolved in dry THF (20 mL). This mixture was slowly added to the magnesium turnings while cooling with an ice/water bath (0 °C) and while stirring. After complete addition, cooling was removed, and the suspension was allowed to warm to ambient temperature and stir for 1 h. The greyish mixture

was cooled to –78 °C by dry ice/acetone bath and a solution of bis(dichlorophosphino)ferrocene (791 mg, 2.04 mmol, 1.0 eq) in dry THF (15 mL) was added dropwise over 20 min by syringe. The mixture was allowed to warm slowly to ambient temperature over 3 h. It was quenched by addition of water (15 mL) and was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* (40 °C, 600 to 50 mbar). The crude brown yellowish oil was purified by column chromatography (SiO_2, *n*-pentane then CH_2Cl_2) and the desired ligand dppf-3,5-CF_3 (1.65 g, 1.50 mmol, 74%) was obtained as a yellow solid.

Yield: 74%. **TLC:** R_f = 0.95 (CH_2Cl_2). **M.p.** (CH_2Cl_2): 153.5 – 155.2 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (s, 4H), 7.73 – 7.66 (m, 8H), 4.44 (t, *J* = 1.8 Hz, 4H), 4.00 (q, *J* = 1.9 Hz, 4H); (400 MHz, CD_3CN) δ 8.01 (s, 1H), 7.84 – 7.77 (m, 2H), 4.50 – 4.45 (m, 1H), 4.13 – 4.07 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.5 (d, *J* = 12.6 Hz), 133.1 (d, *J* = 15.5 Hz), 132.2 (q, *J* = 33.6 Hz), 123.6 (p, *J* = 3.8 Hz), 123.1 (q, *J* = 273.1 Hz), 73.9, 73.7 (d, *J* = 10.2 Hz), 73.4. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -63.0. **^{31}P NMR** (162 MHz, $CDCl_3$): δ –17.2. **IR** (neat): 1352m, 1274s, 1168m, 1116s, 1094s, 896m, 843w, 828w, 704m, 681m, 464w cm^{-1}. **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{42}H_{21}F_{24}FeP_2^+$ 1099.0079; Found 1099.0070.

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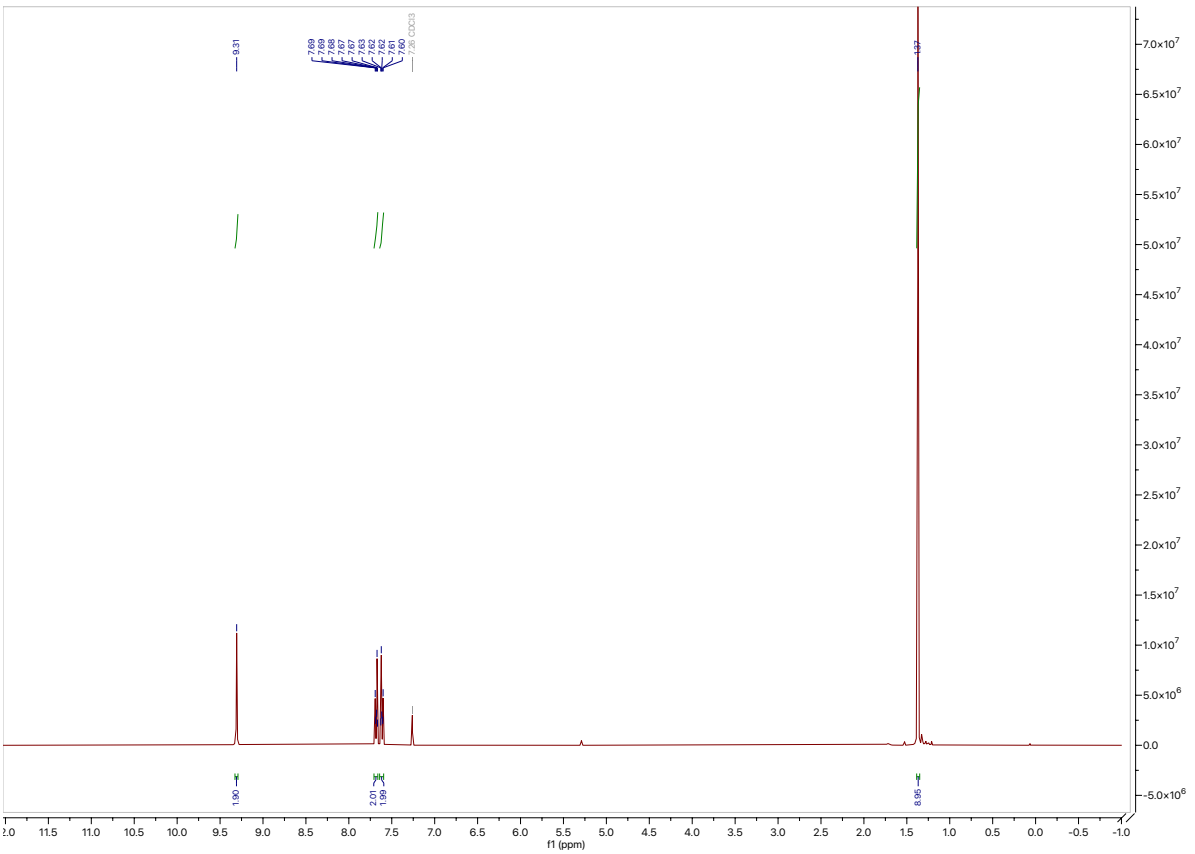
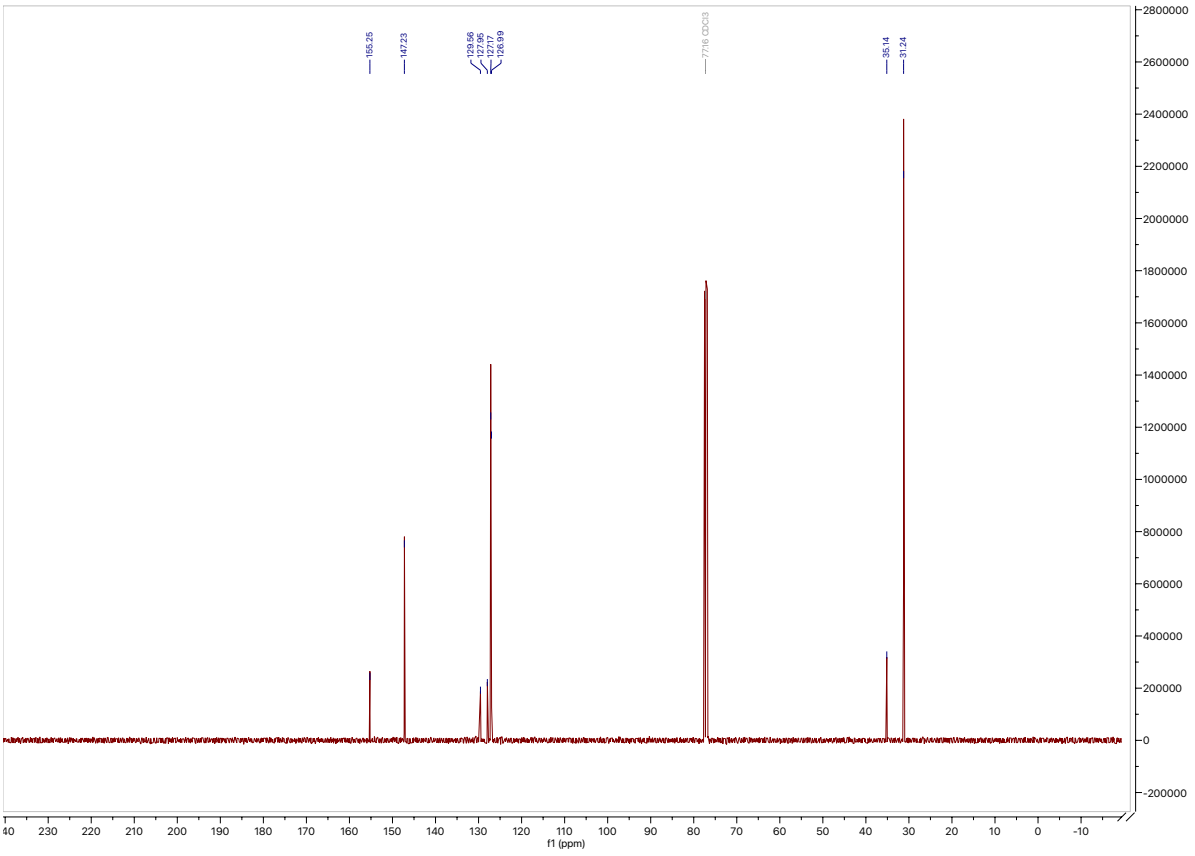
(5) Hoff, L. V.; Chesnokov, G. A.; Linden, A.; Gademann, K. Mechanistic Studies and Data Science-Guided Exploration of Bromotetrazine Cross-Coupling. *ACS Catal.* **2022**, https://doi.org/10.1021/acscatal.2c01813.

NMR Spectra

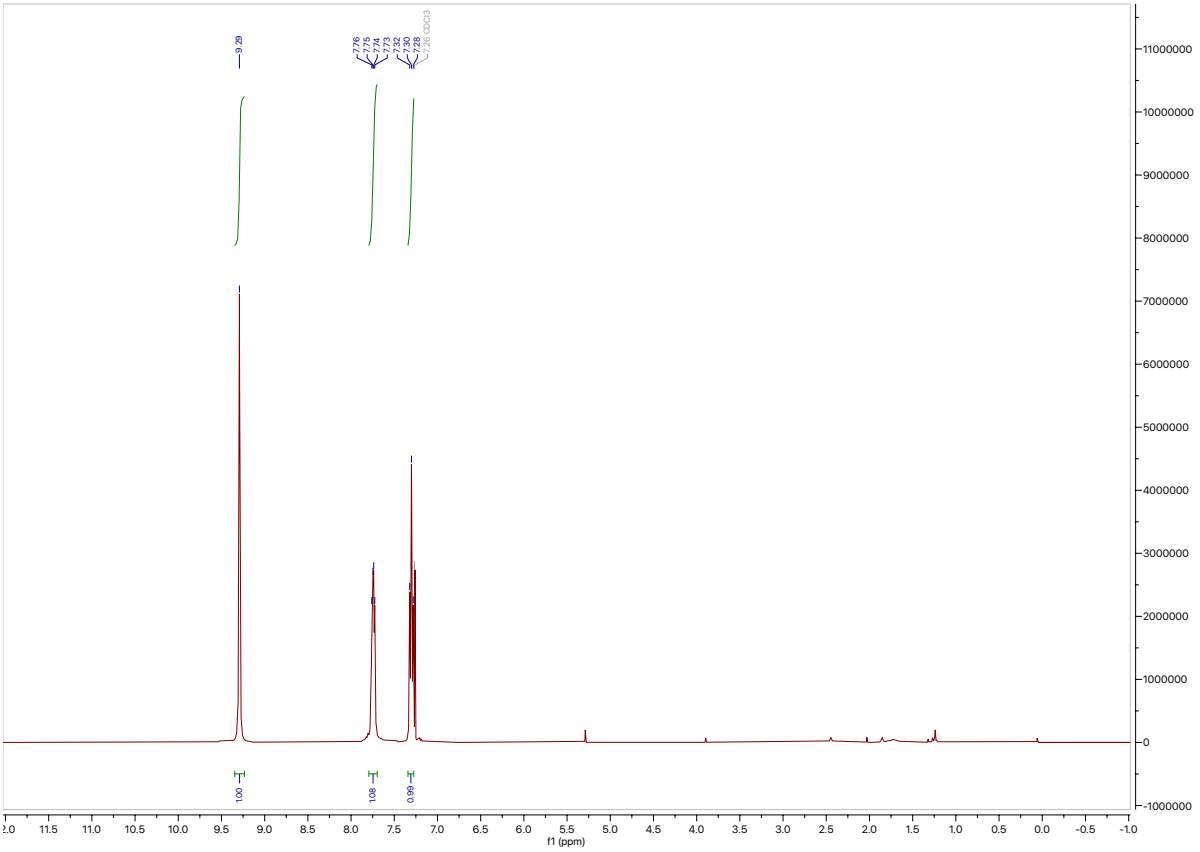
^{1}H NMR of **4** in $CDCl_3$



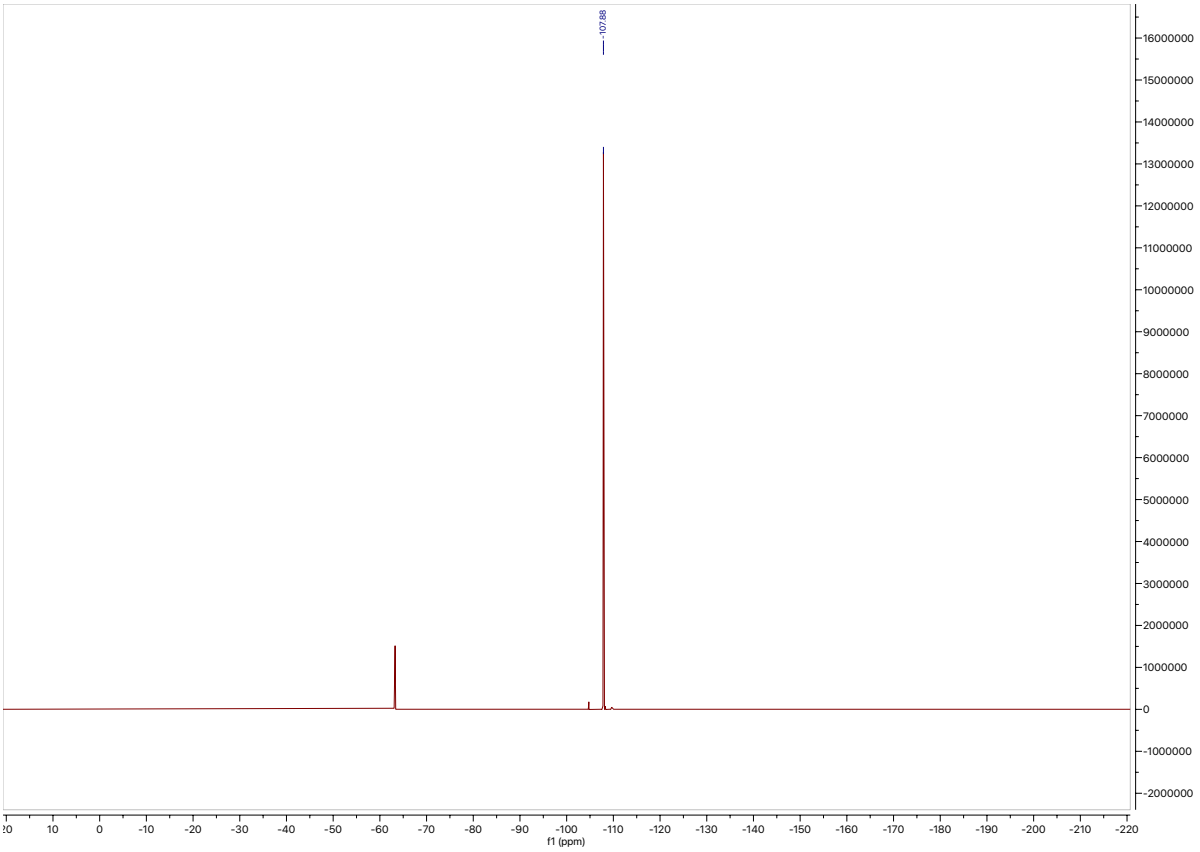
^{13}C NMR of **4** in $CDCl_3$



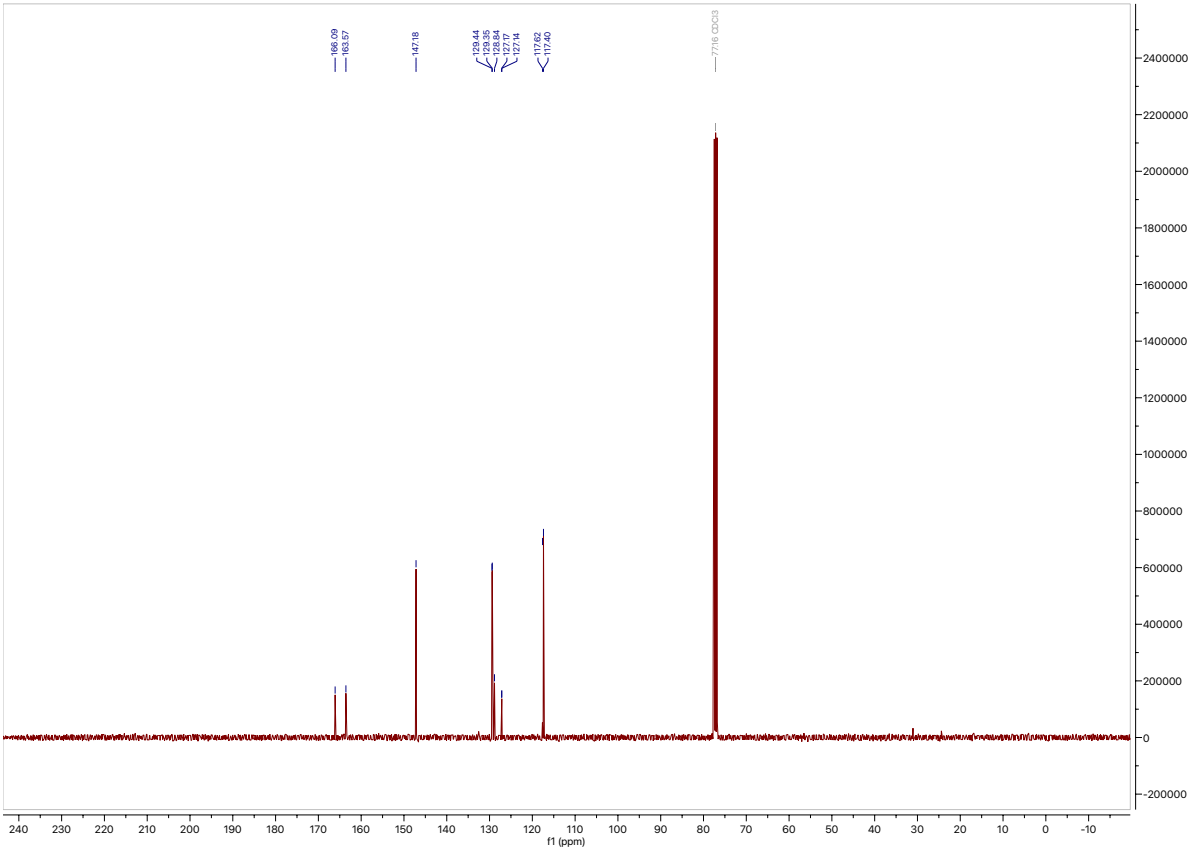
^{1}H NMR of **6** in $CDCl_3$



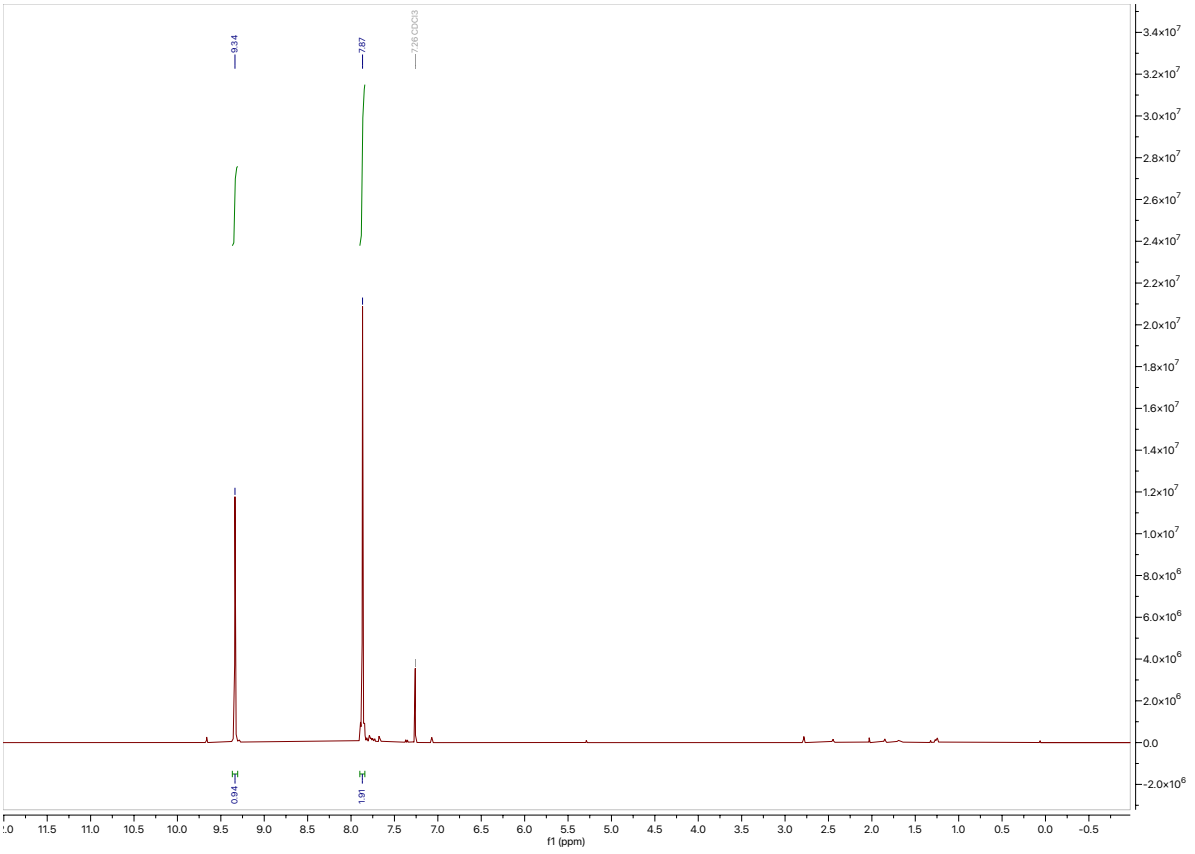
^{19}F NMR of **6** in $CDCl_3$



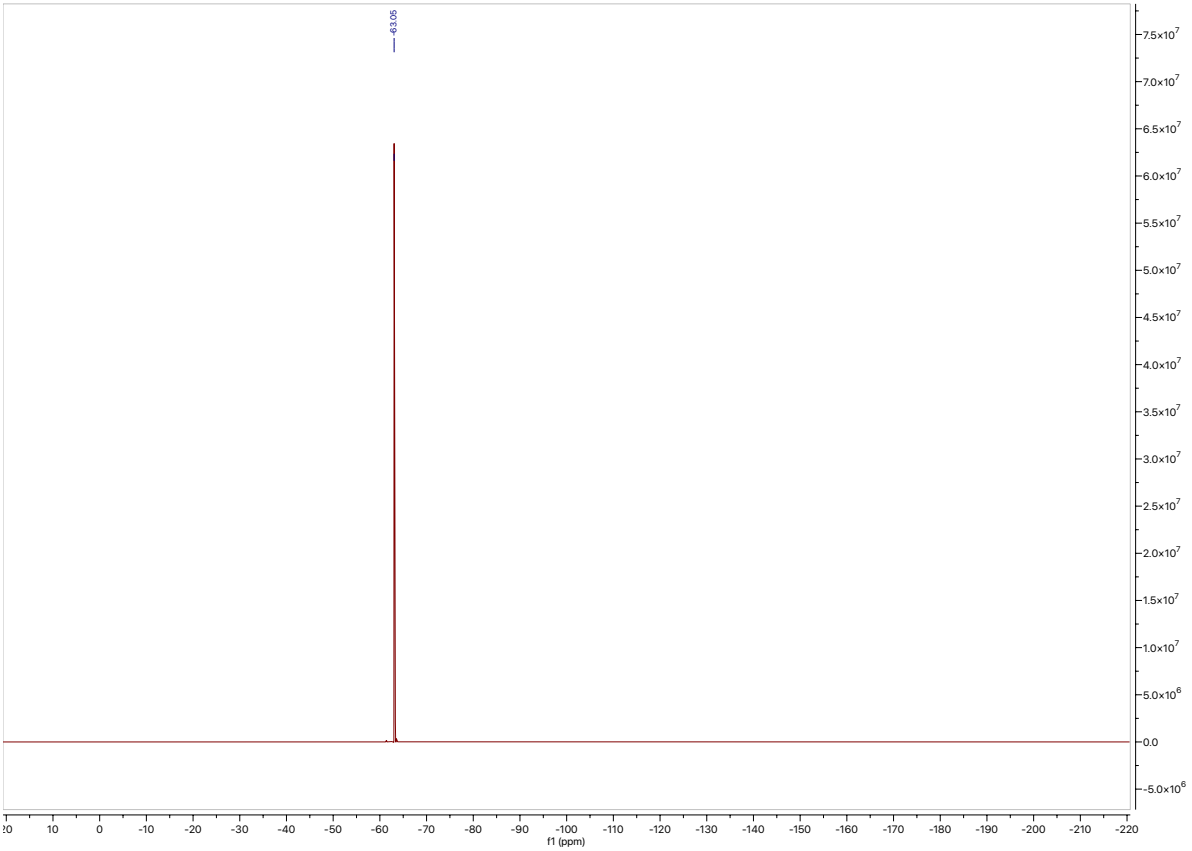
^{13}C NMR of **6** in $CDCl_3$



^{1}H NMR of **7** in $CDCl_3$



^{19}F NMR of **7** in $CDCl_3$



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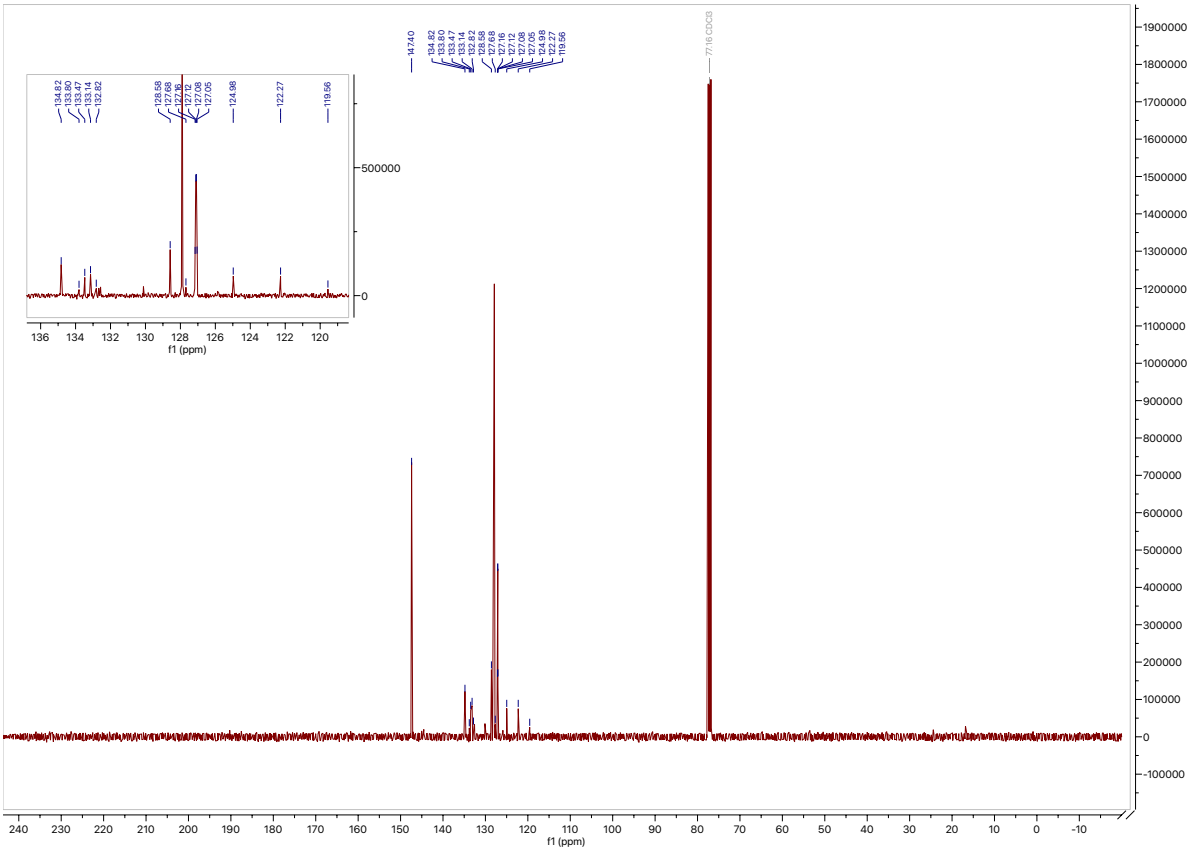
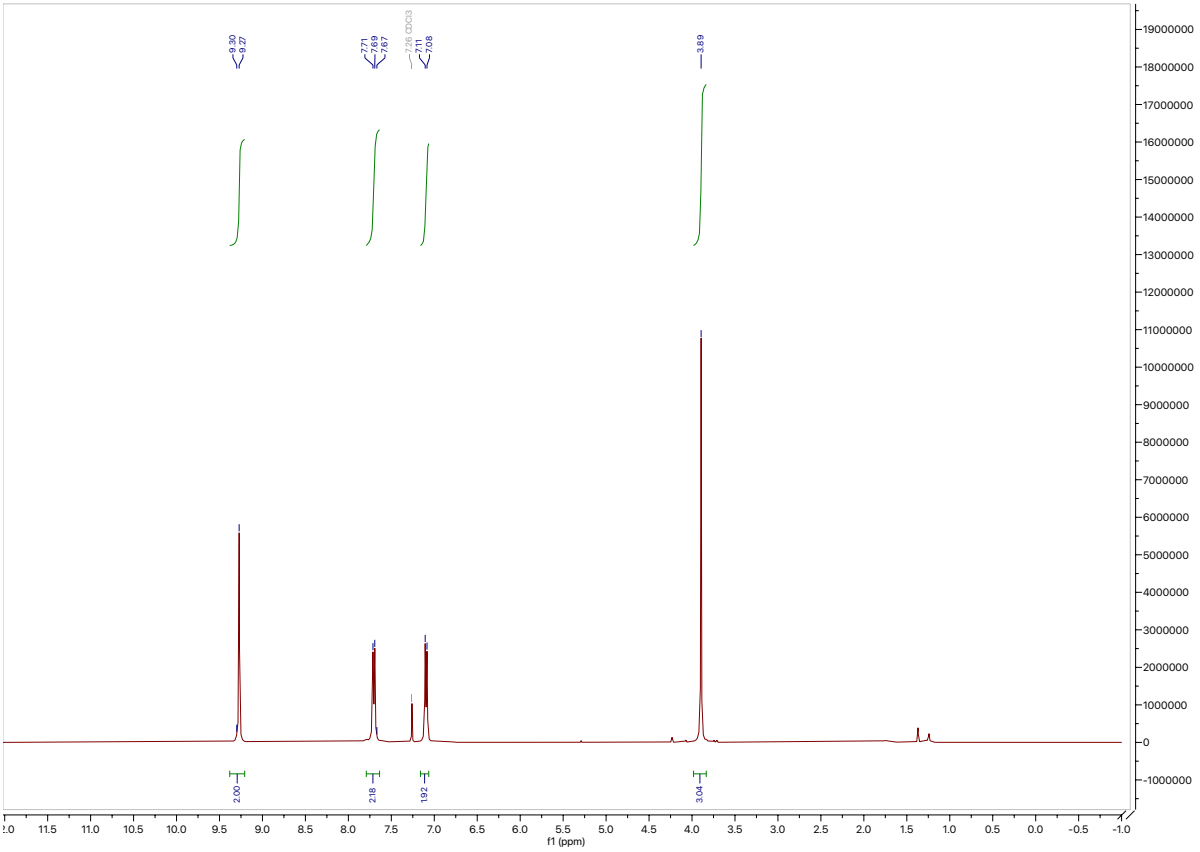
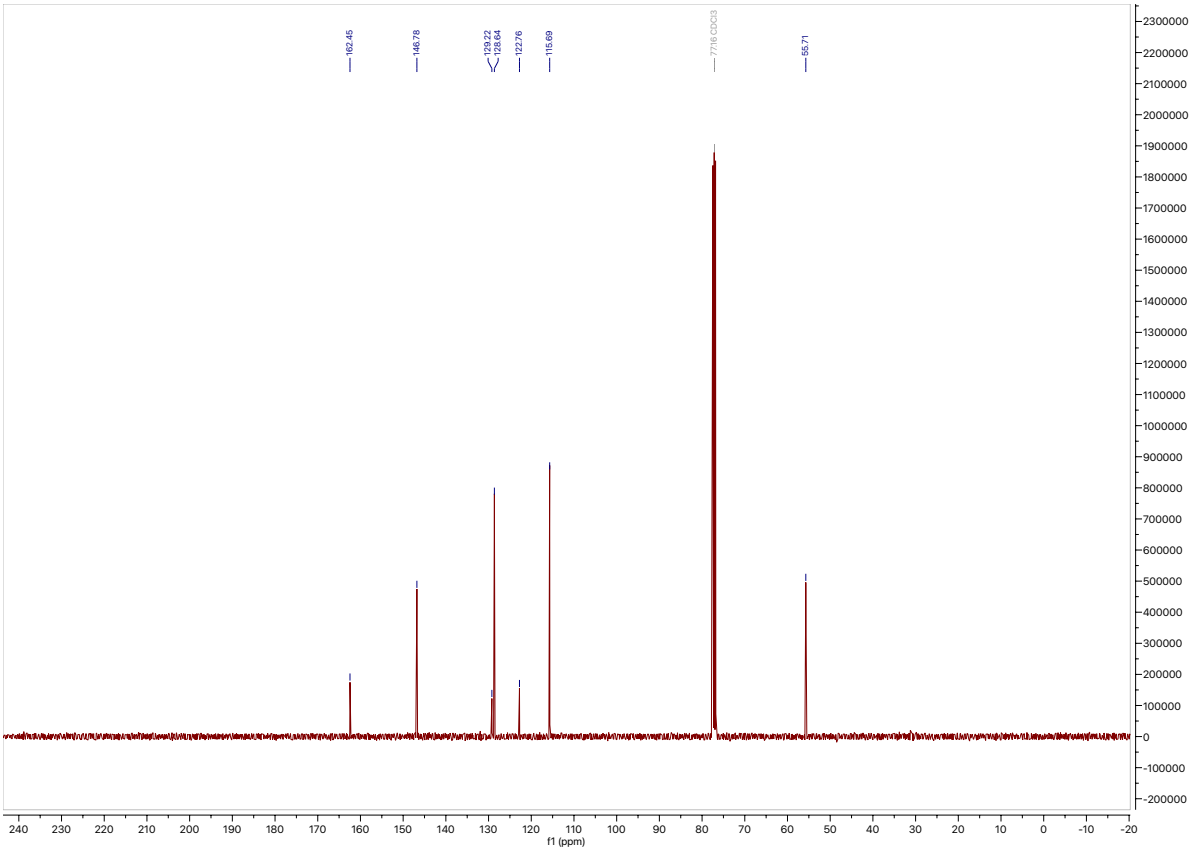


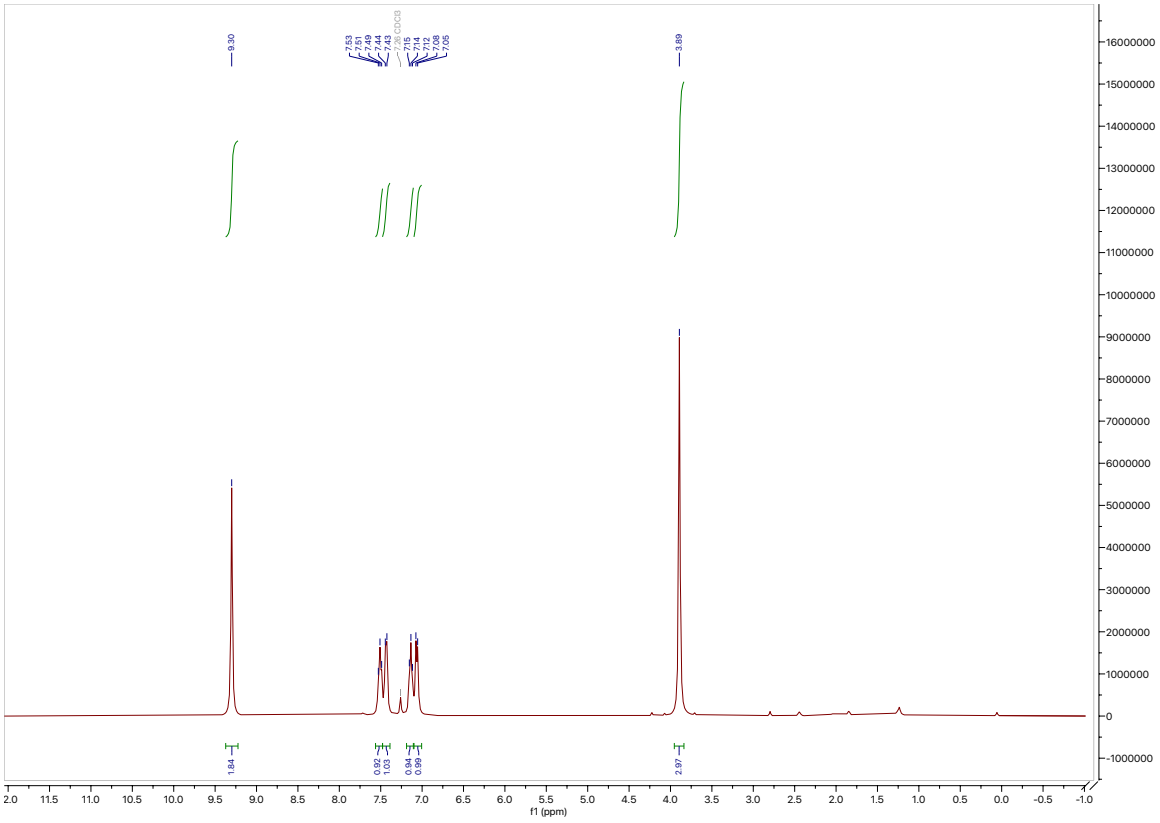
^{1}H NMR of **8** in $CDCl_3$



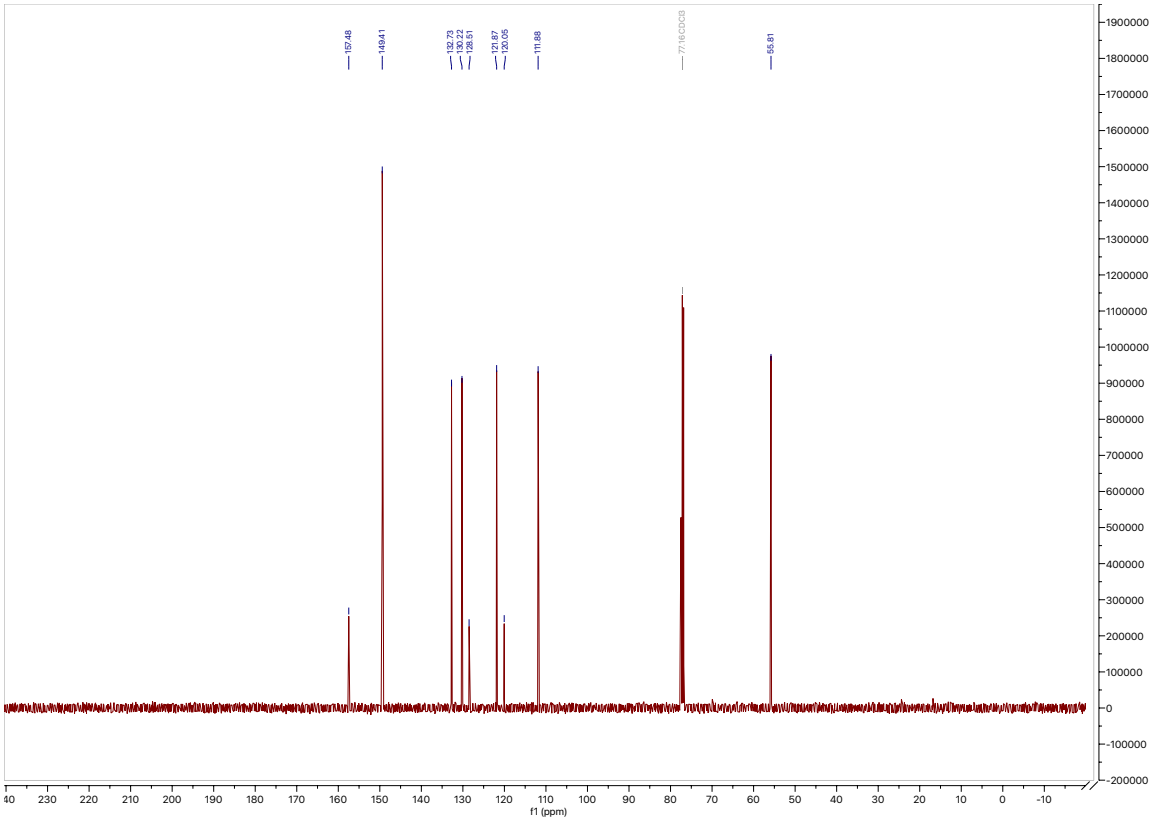
^{13}C NMR of **8** in $CDCl_3$



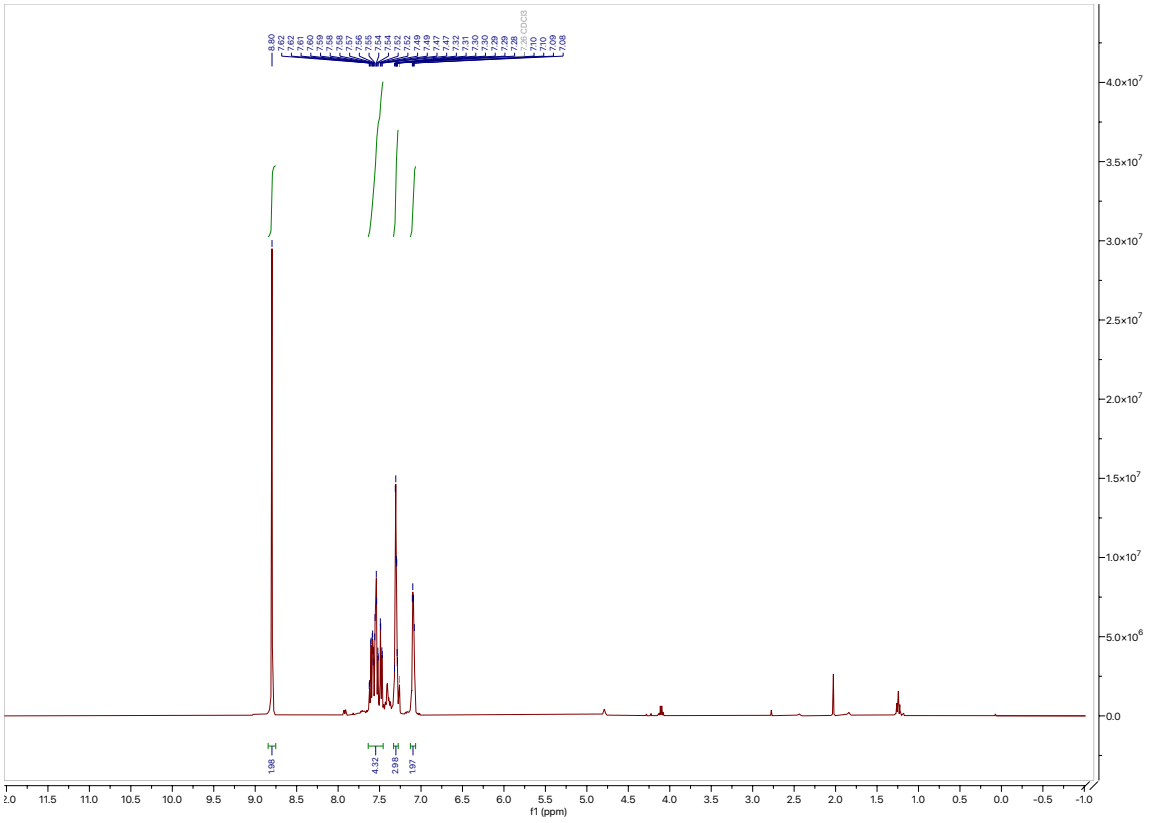
^{1}H NMR of **9** in $CDCl_3$



^{13}C NMR of **9** in $CDCl_3$



^{1}H NMR of **10** in $CDCl_3$



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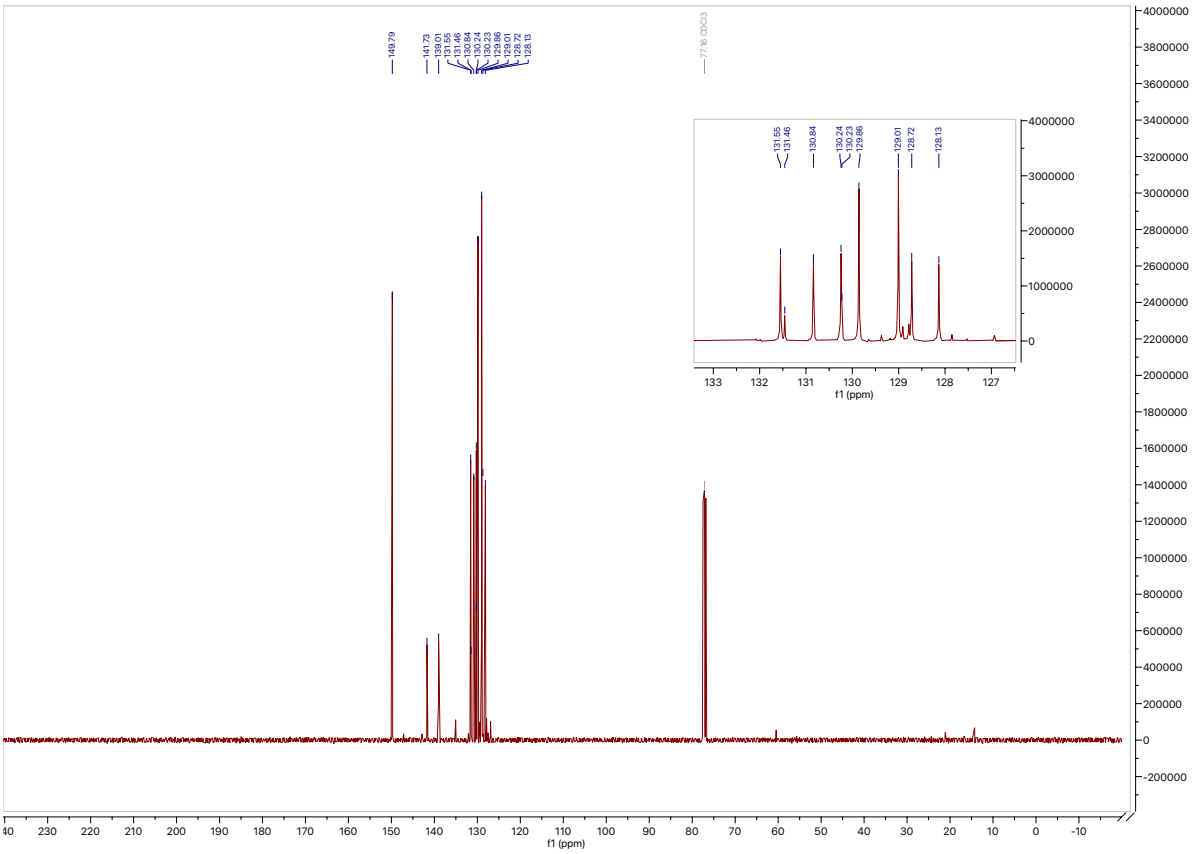

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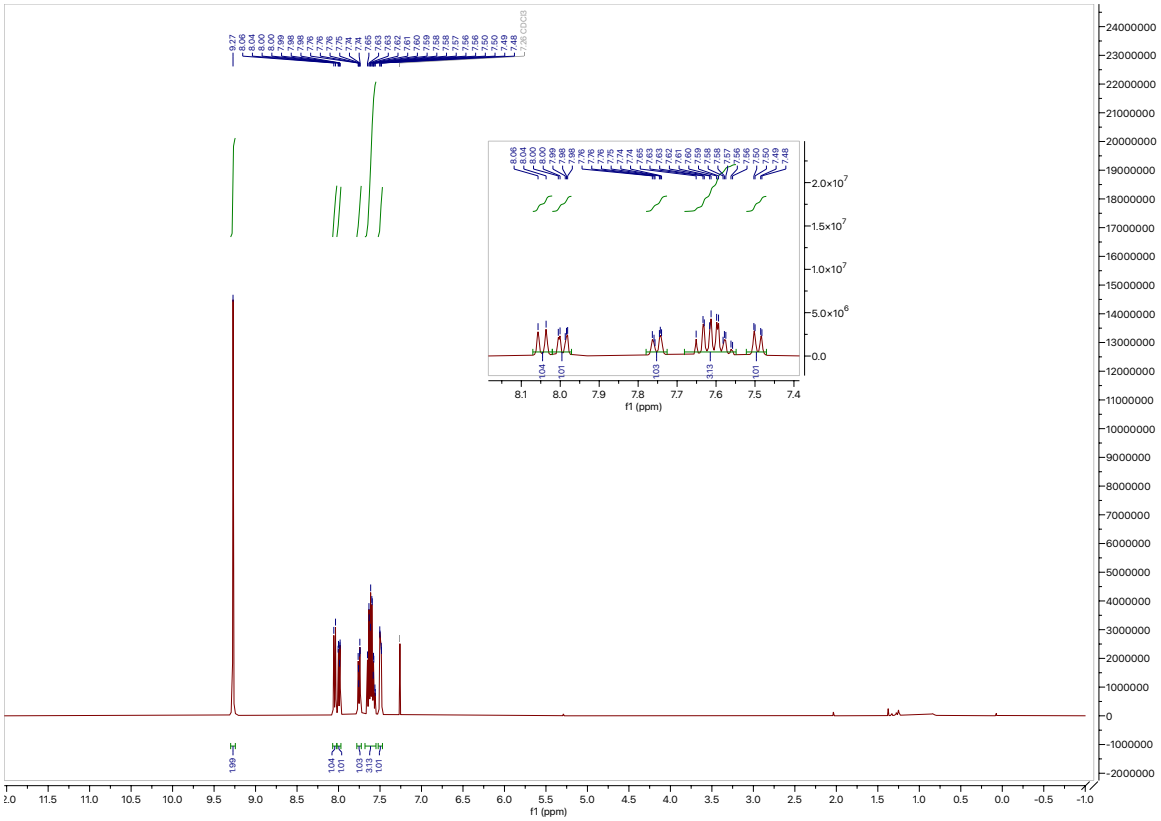

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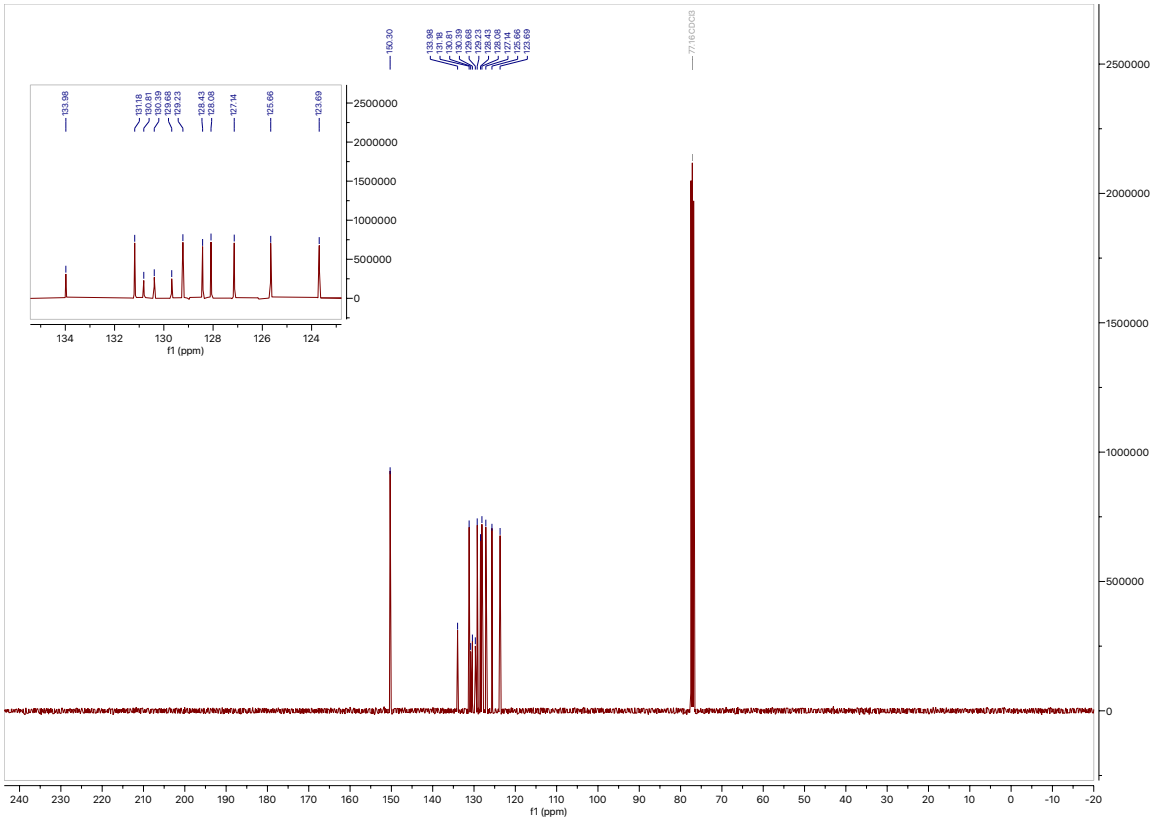

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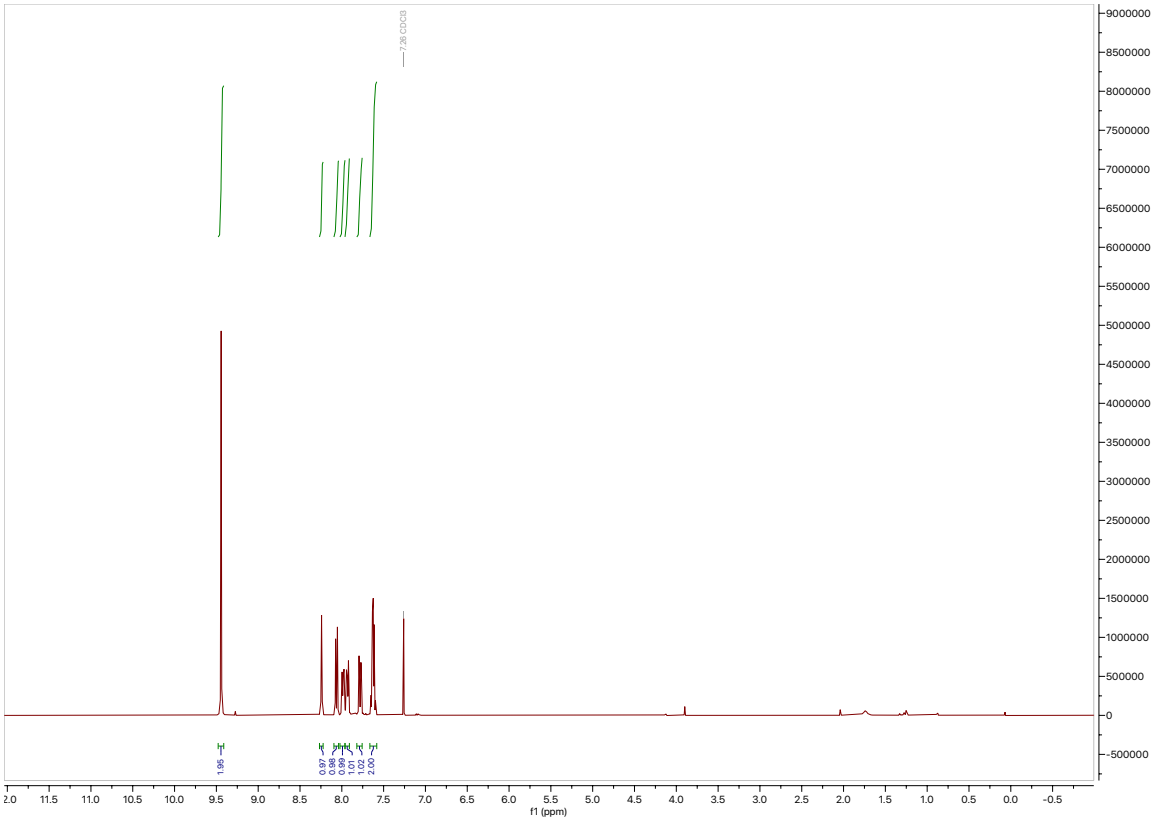

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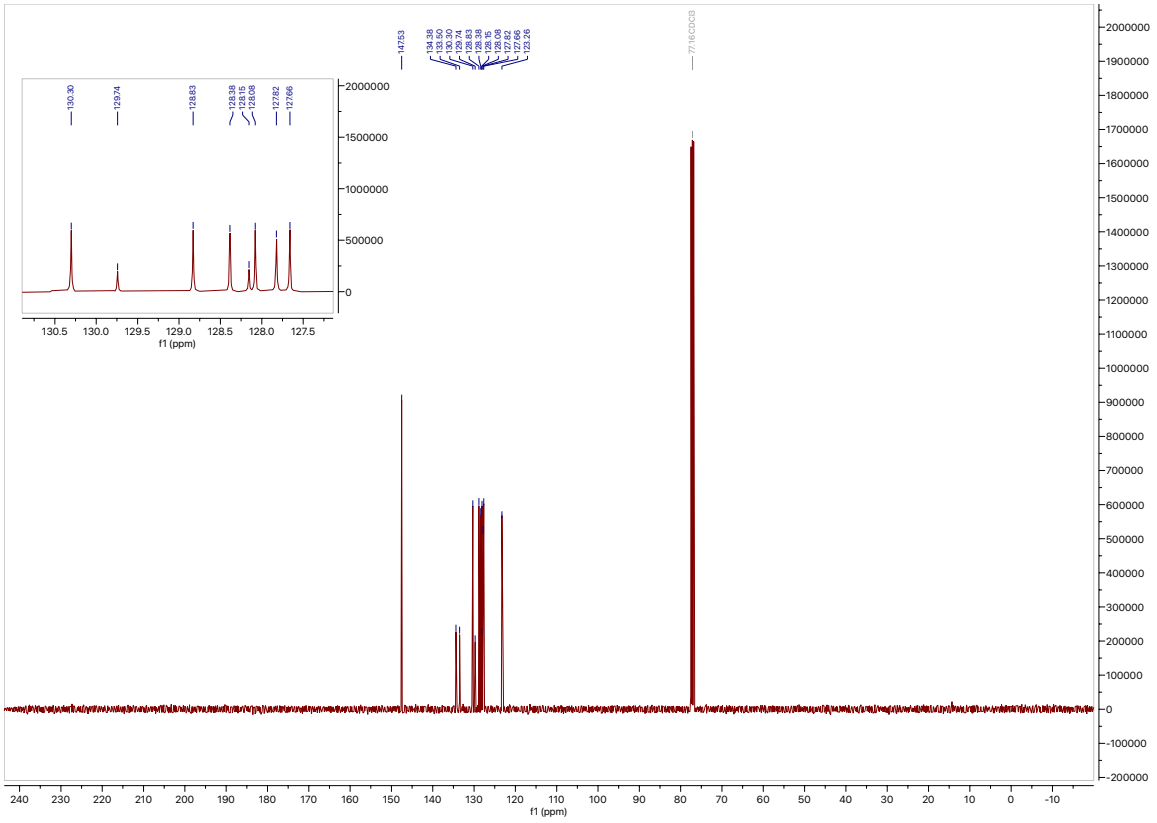

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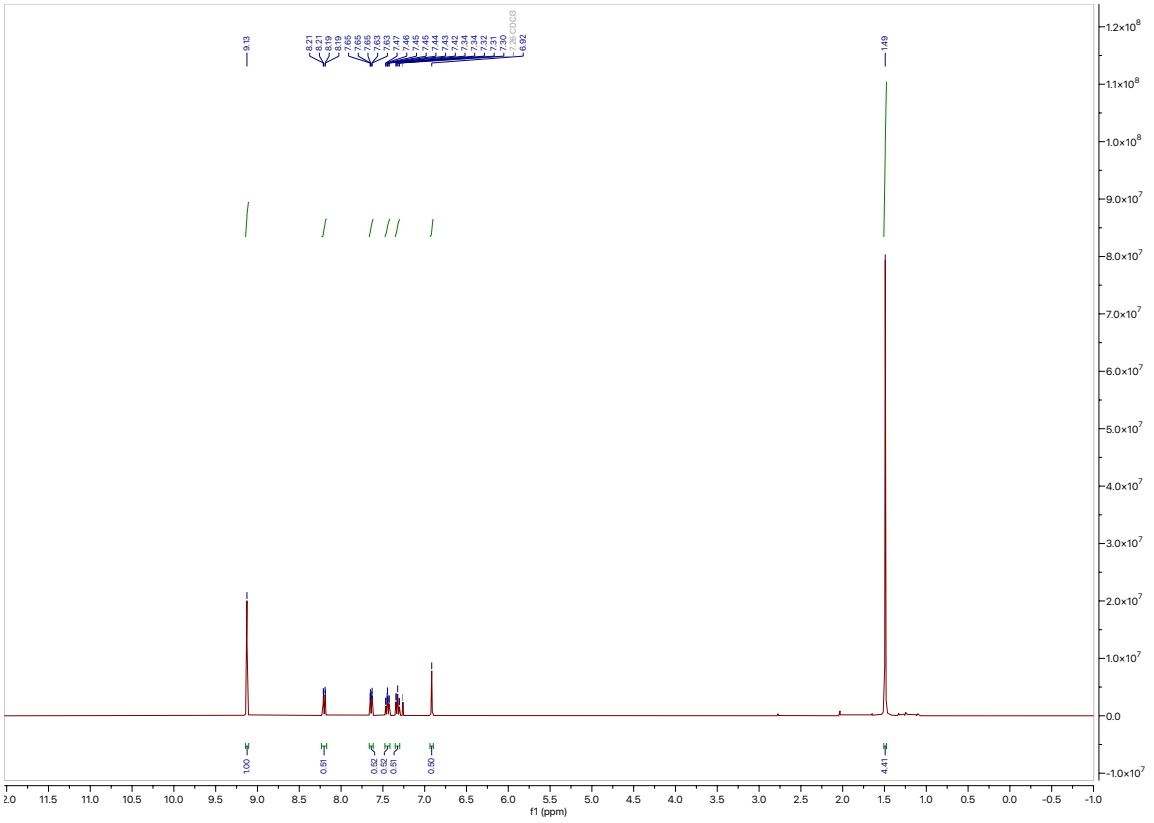

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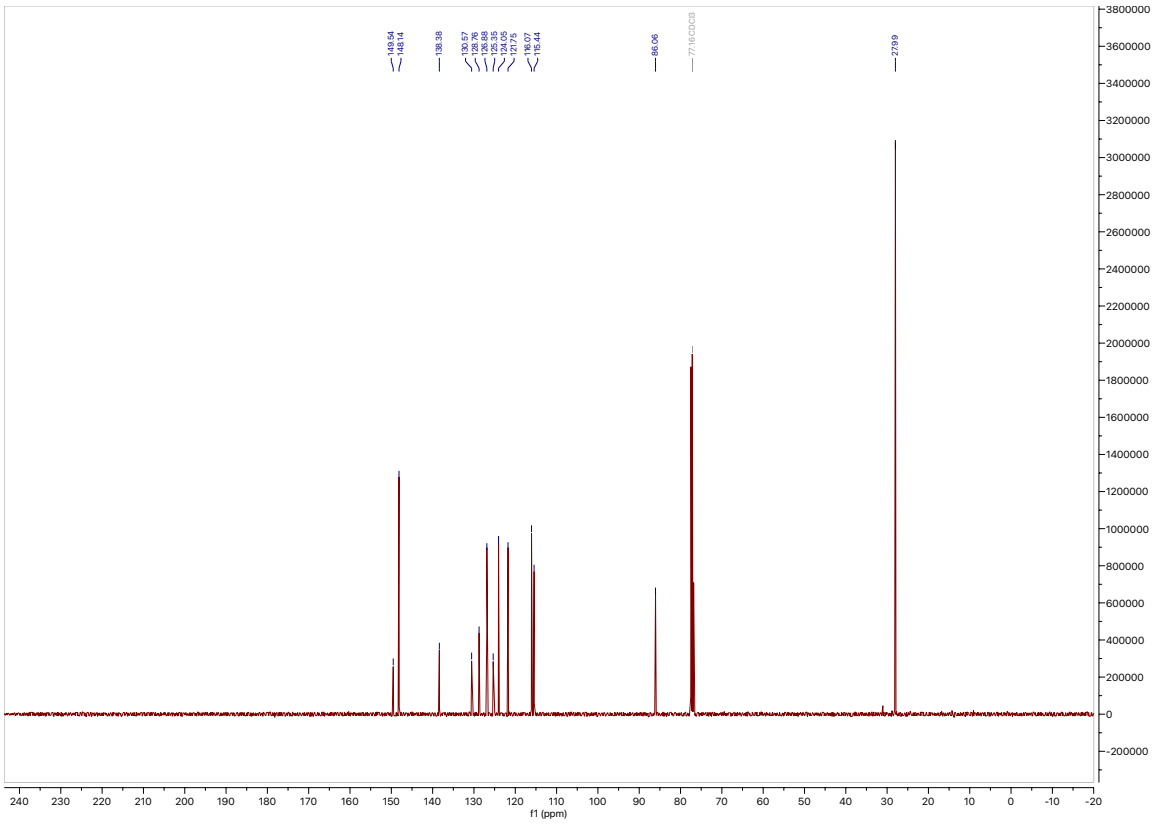

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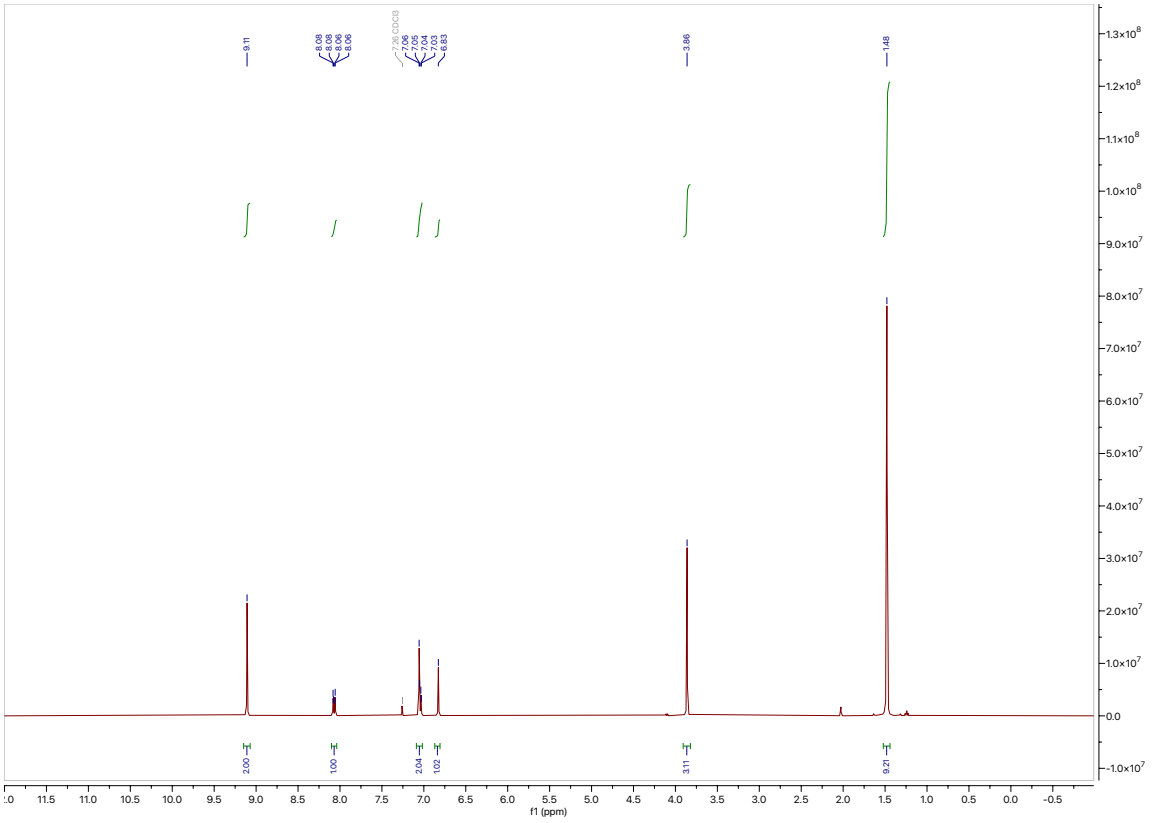

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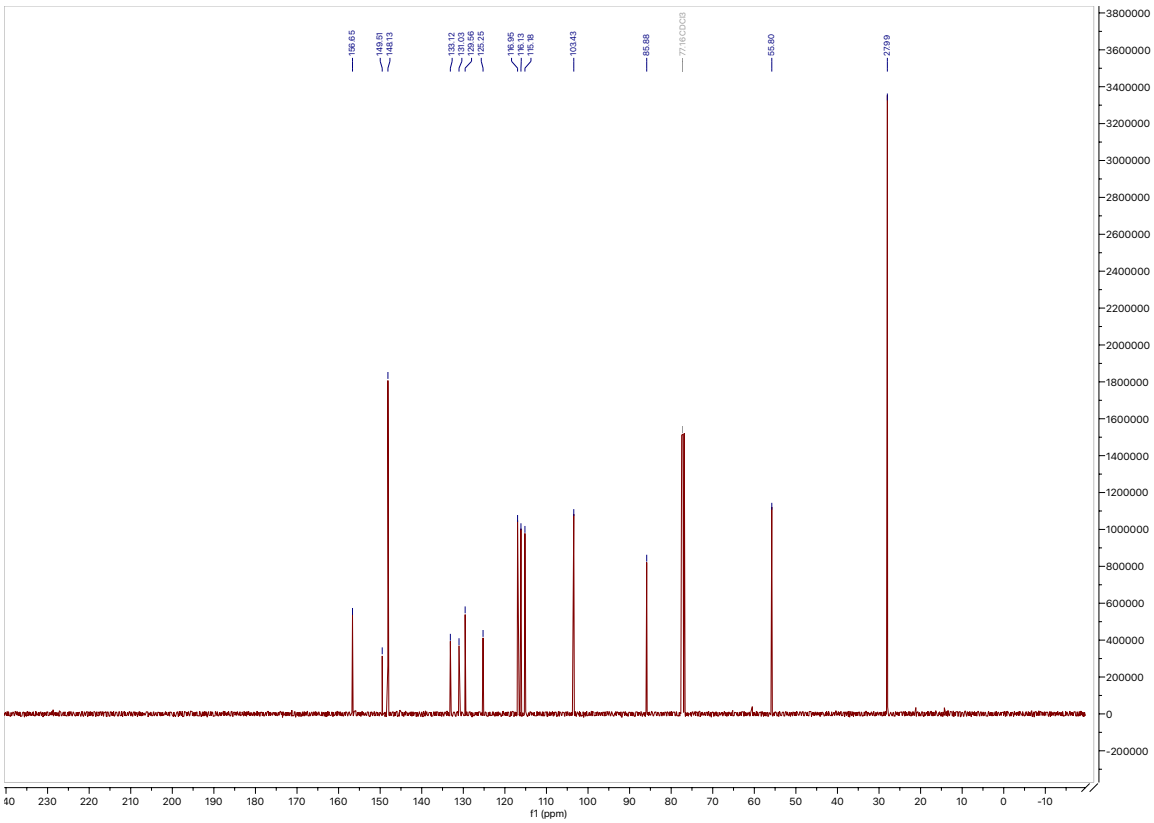

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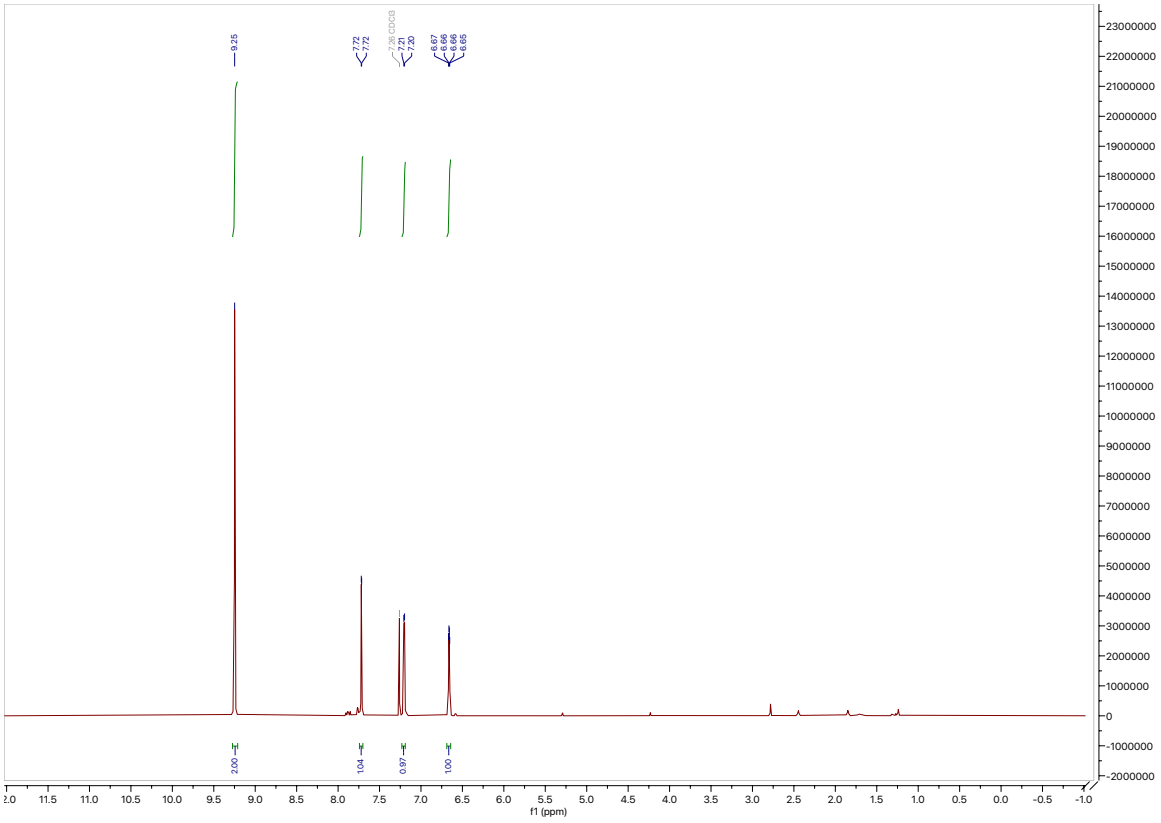

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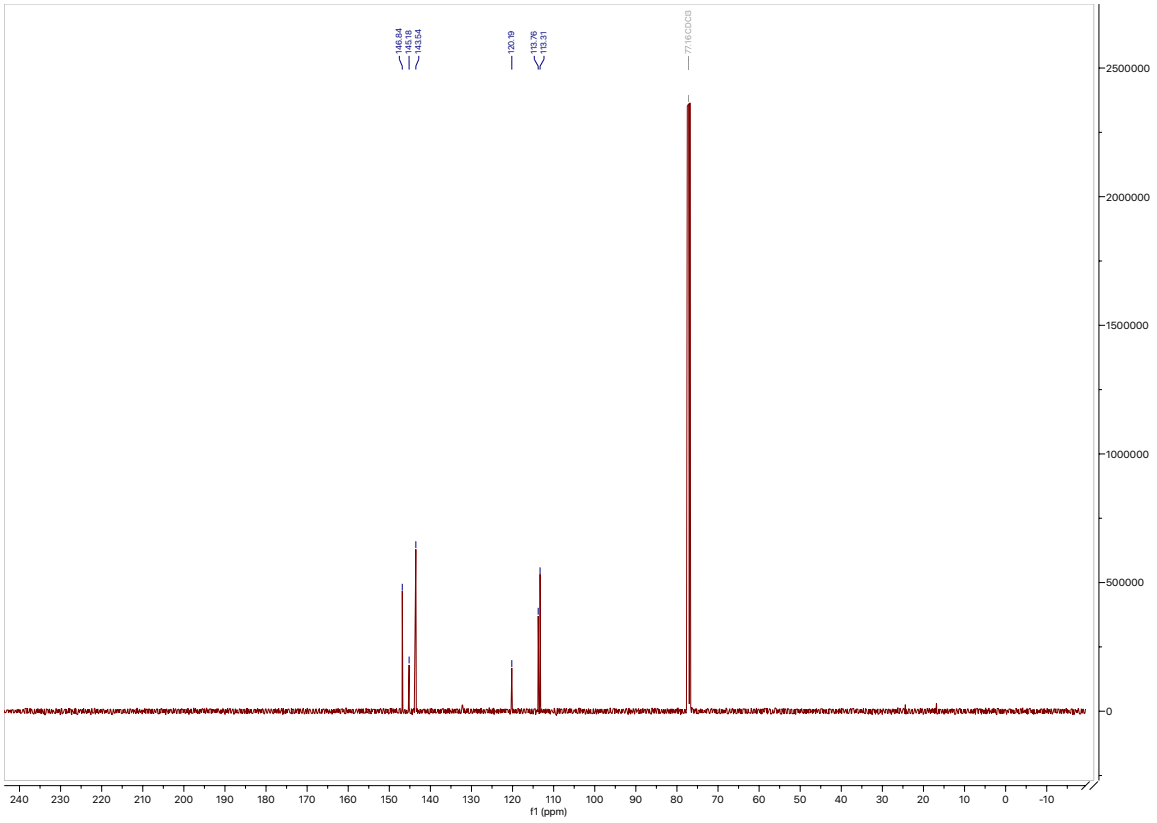

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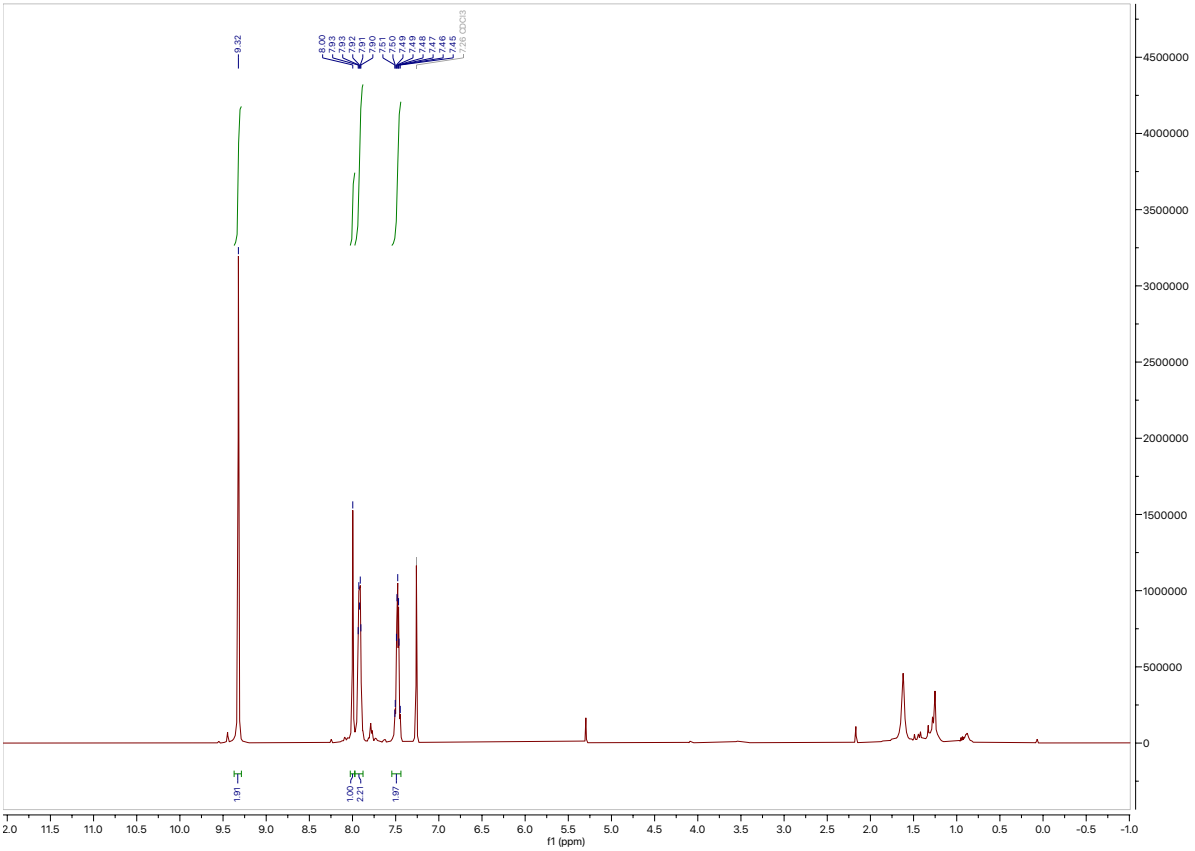

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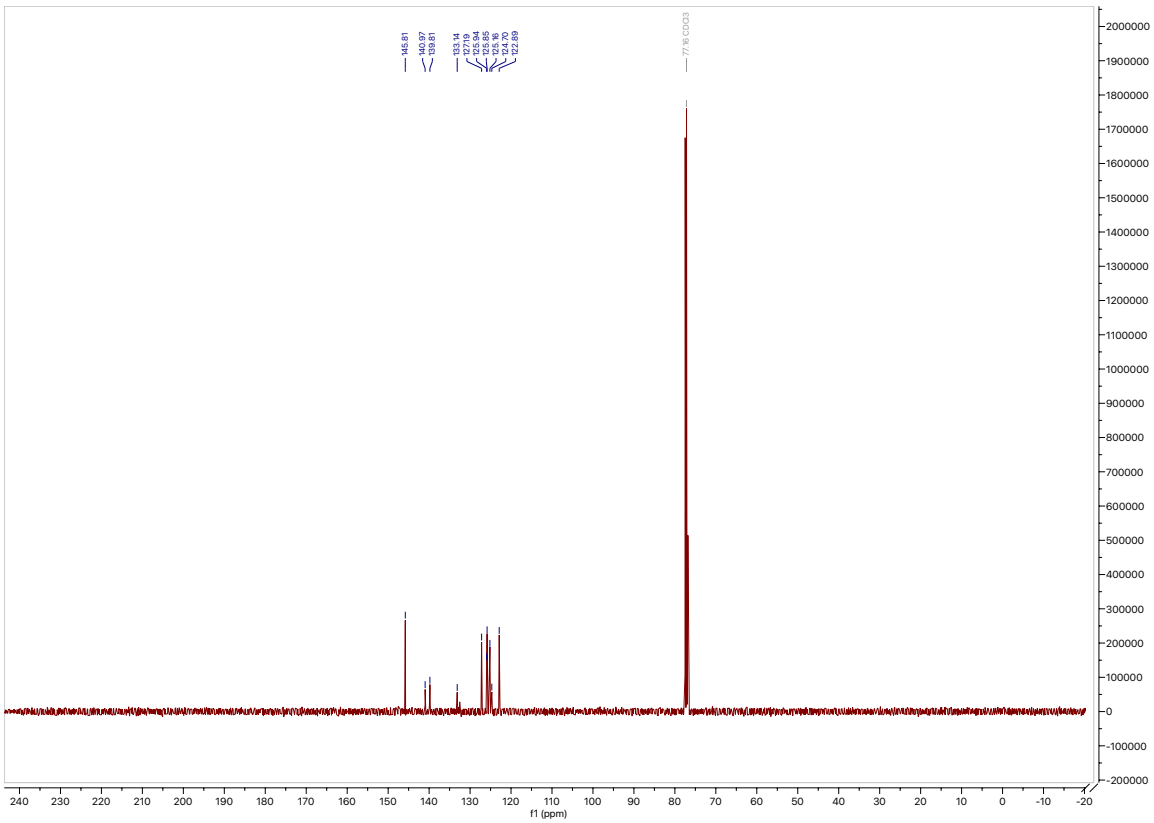

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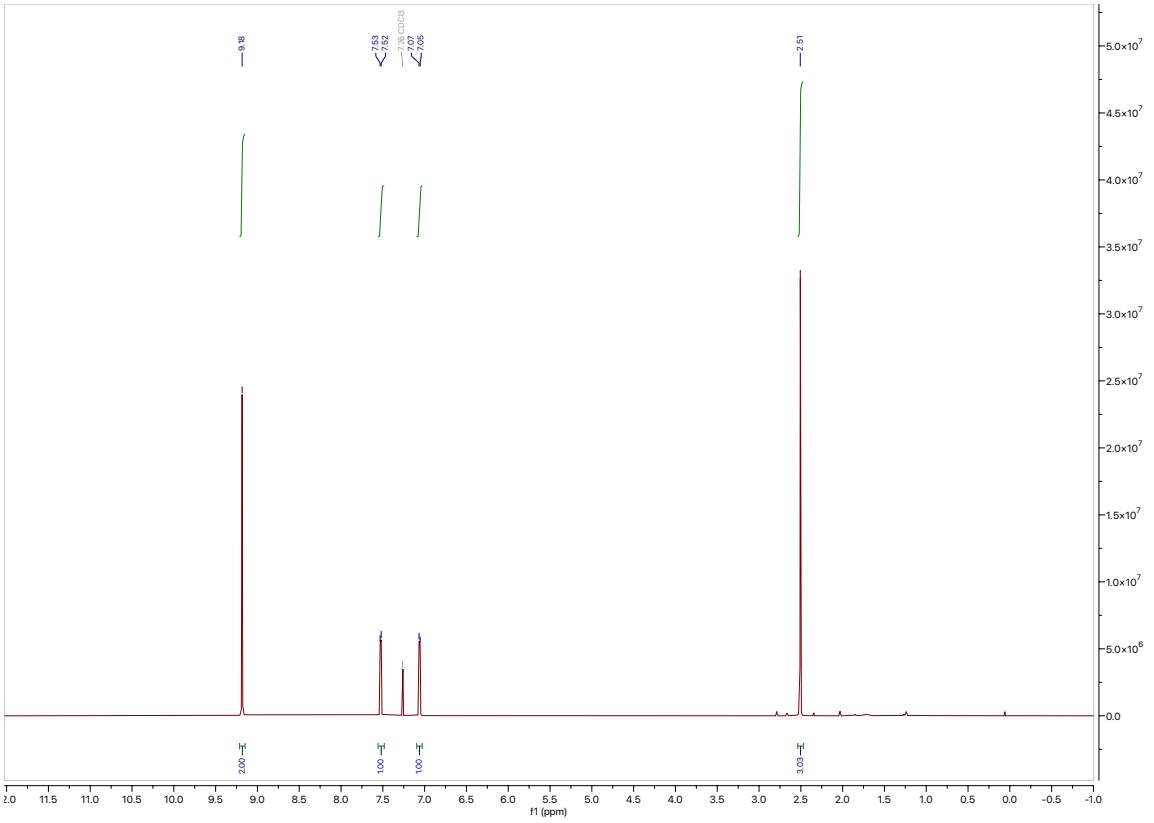

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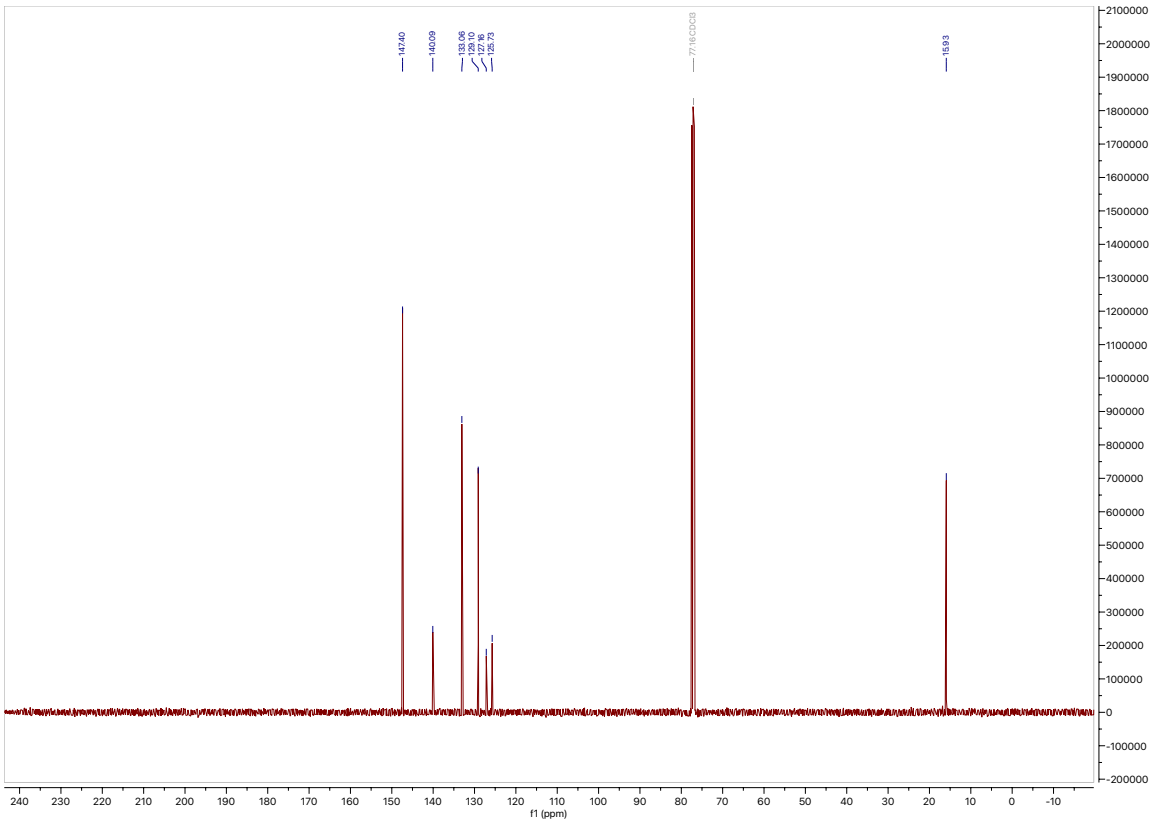
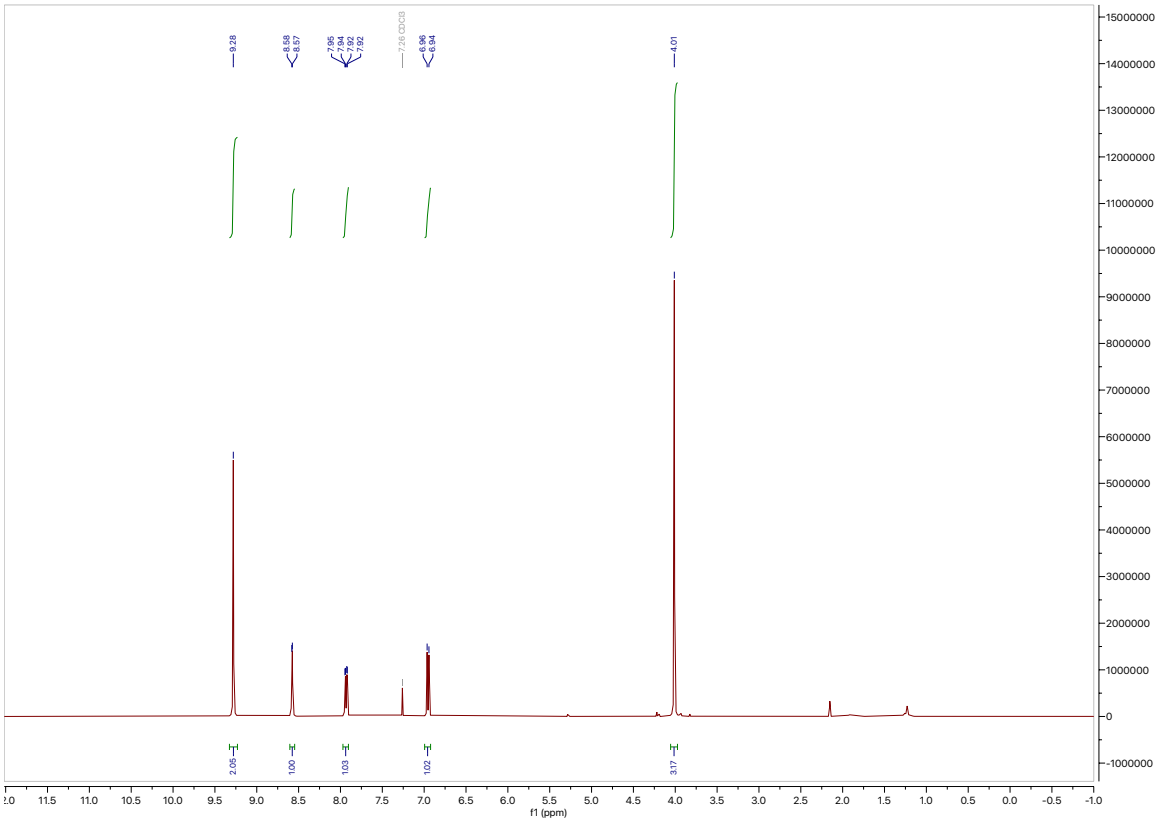
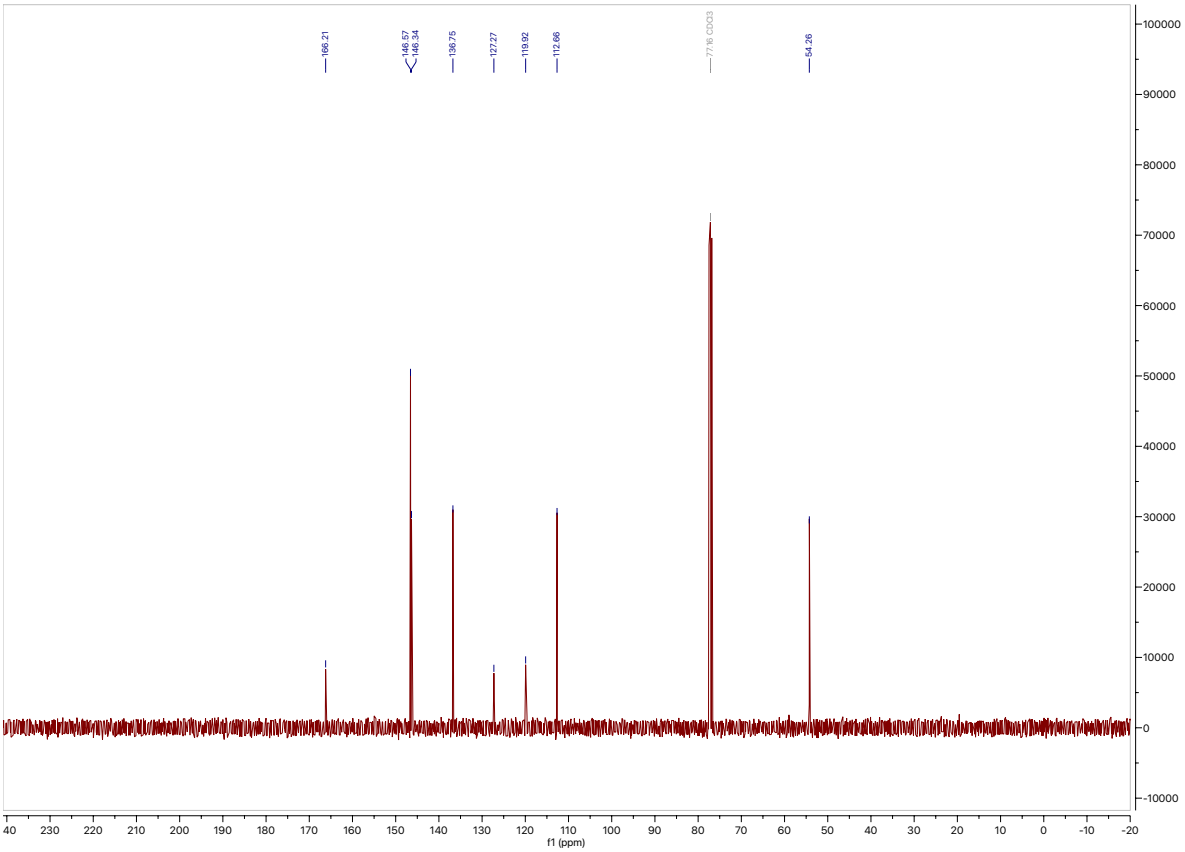


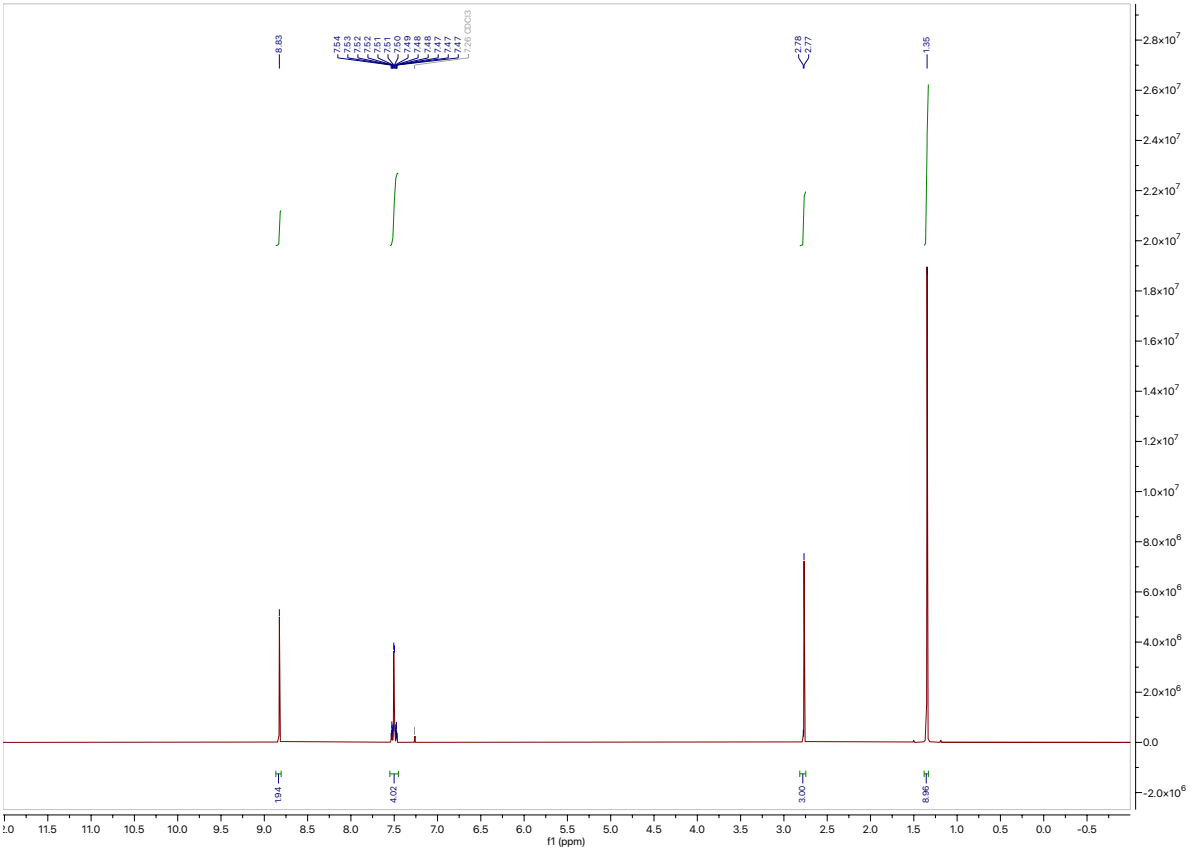
^{1}H NMR of **18** in $CDCl_3$



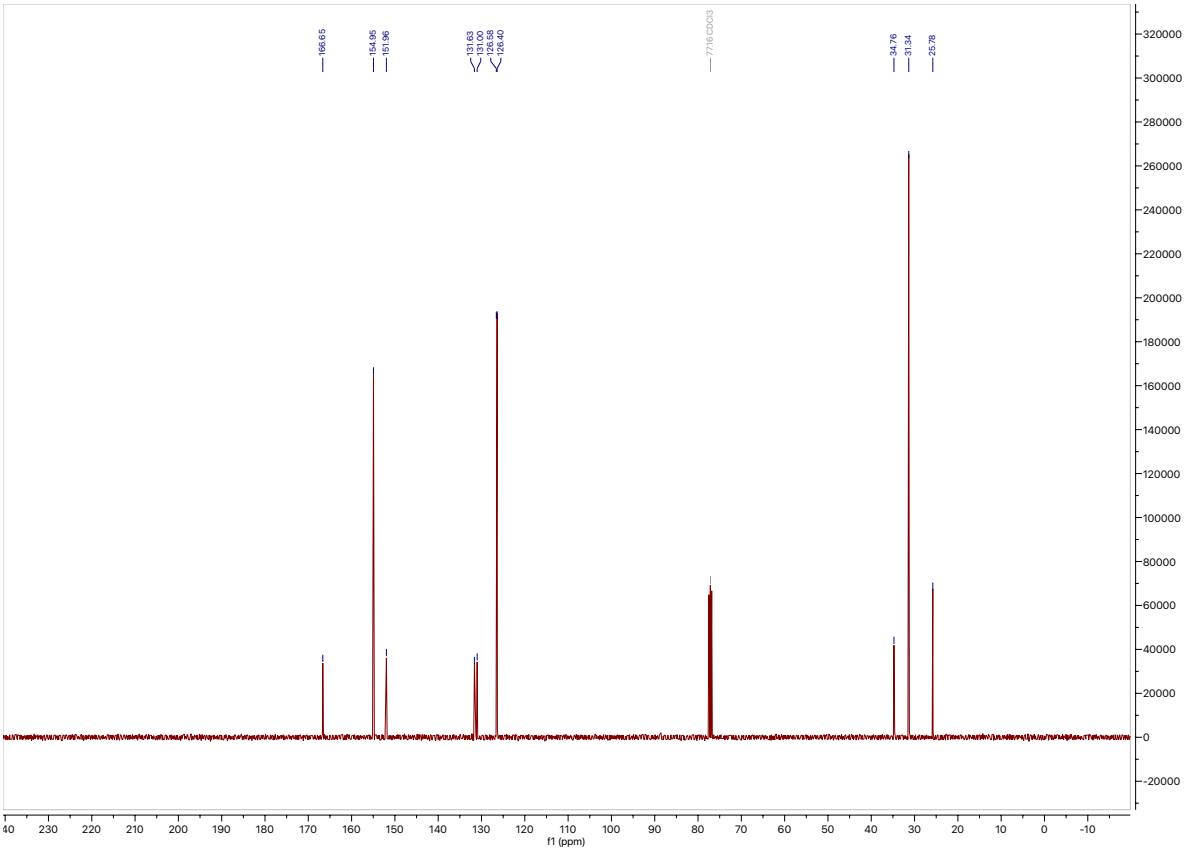
^{13}C NMR of **18** in $CDCl_3$



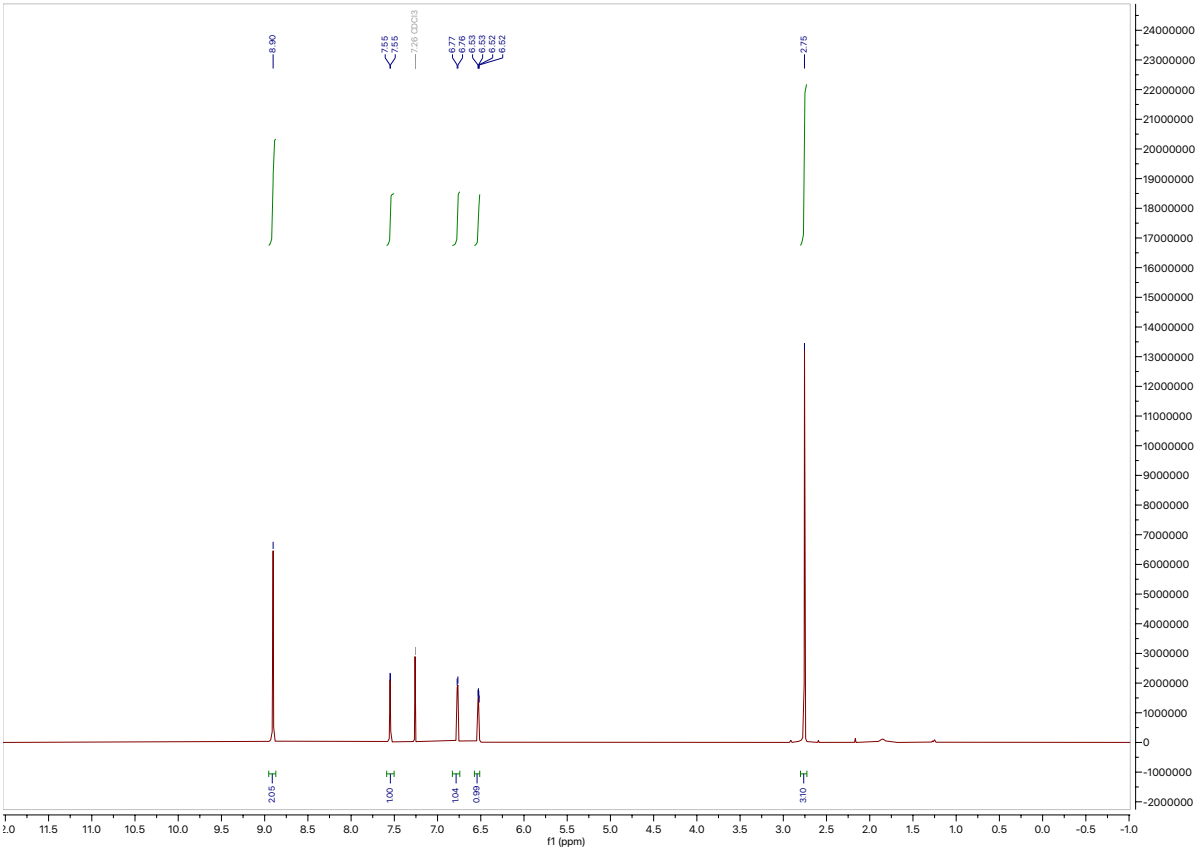
^{1}H NMR of **20** in $CDCl_3$



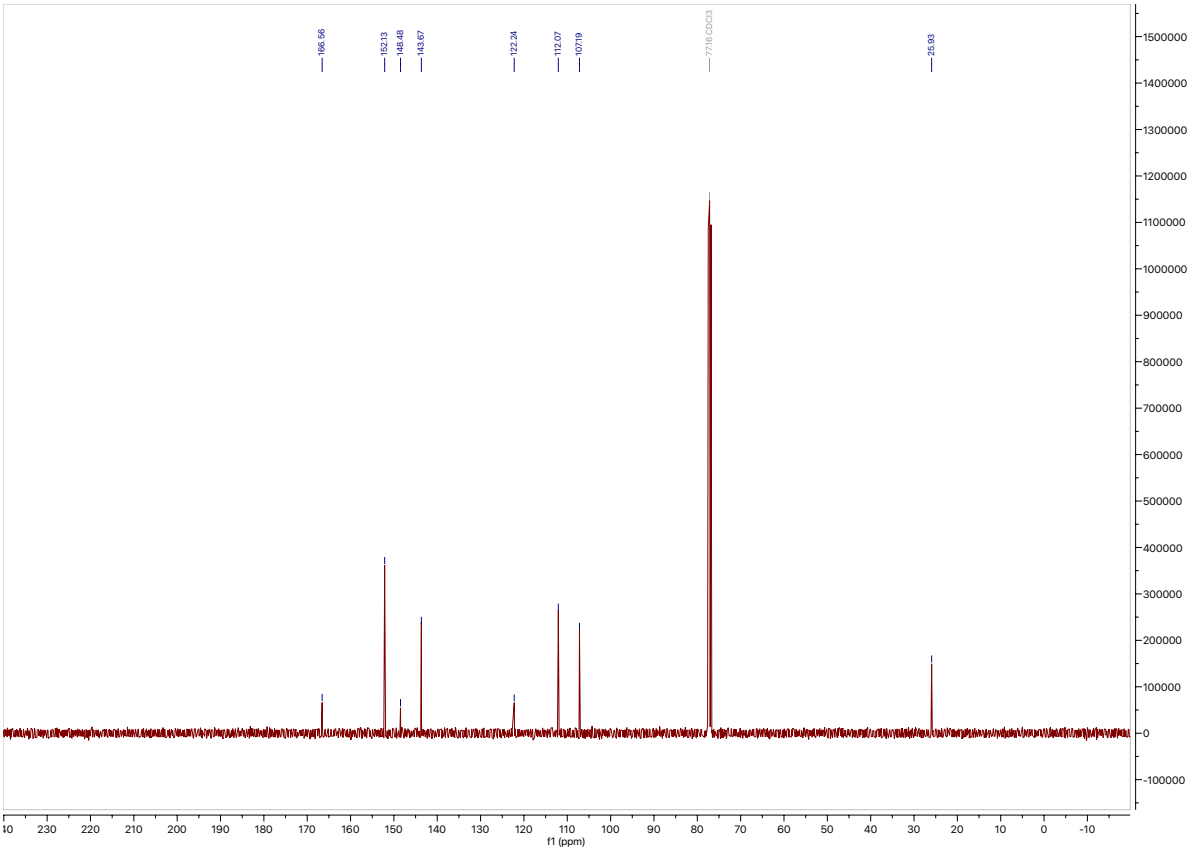
^{13}C NMR of **20** in $CDCl_3$



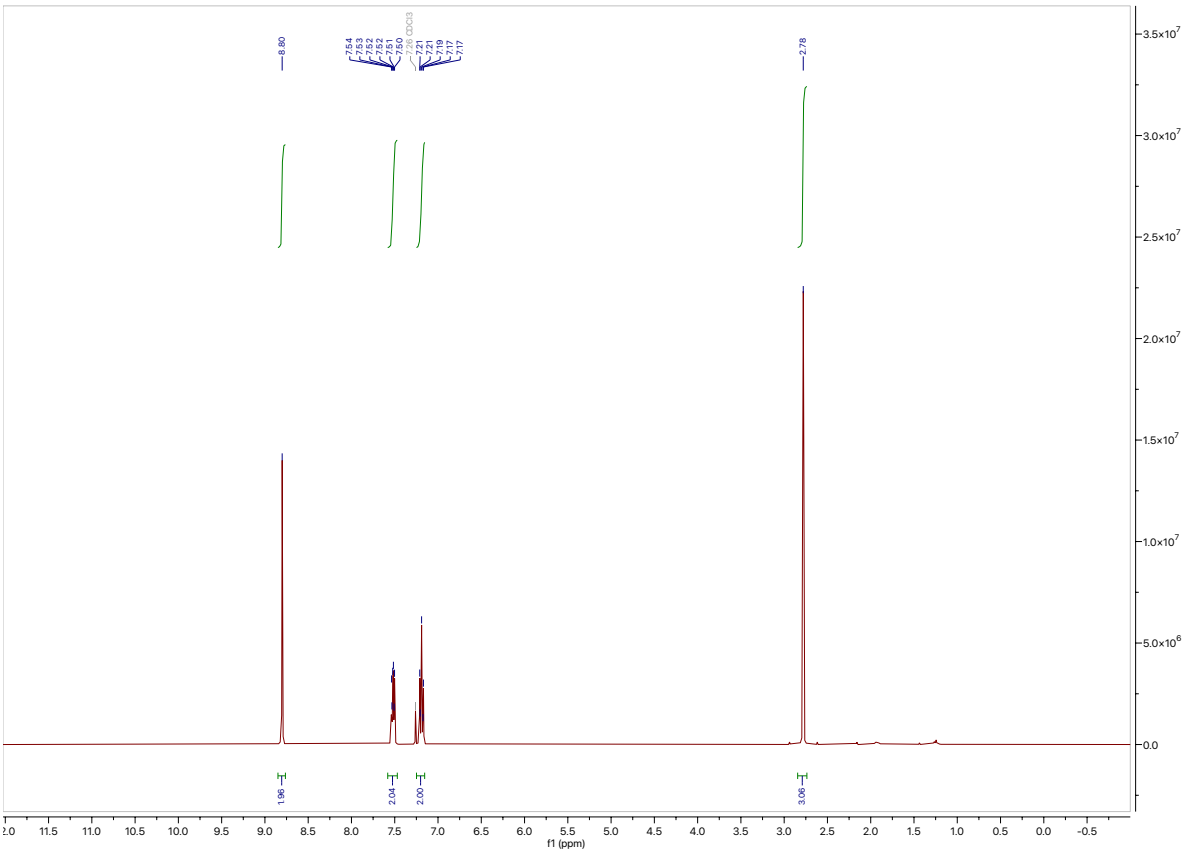
^{1}H NMR of **21** in $CDCl_3$



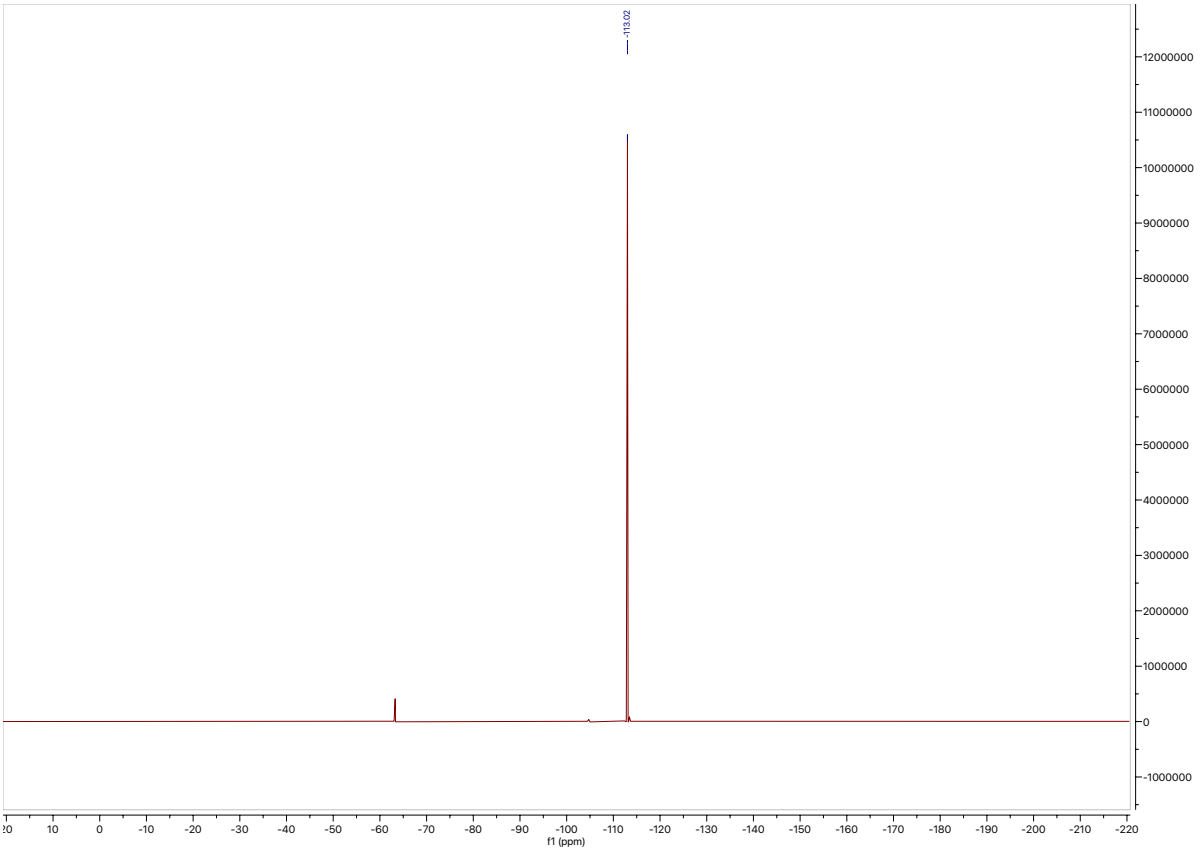
^{13}C NMR of **21** in $CDCl_3$



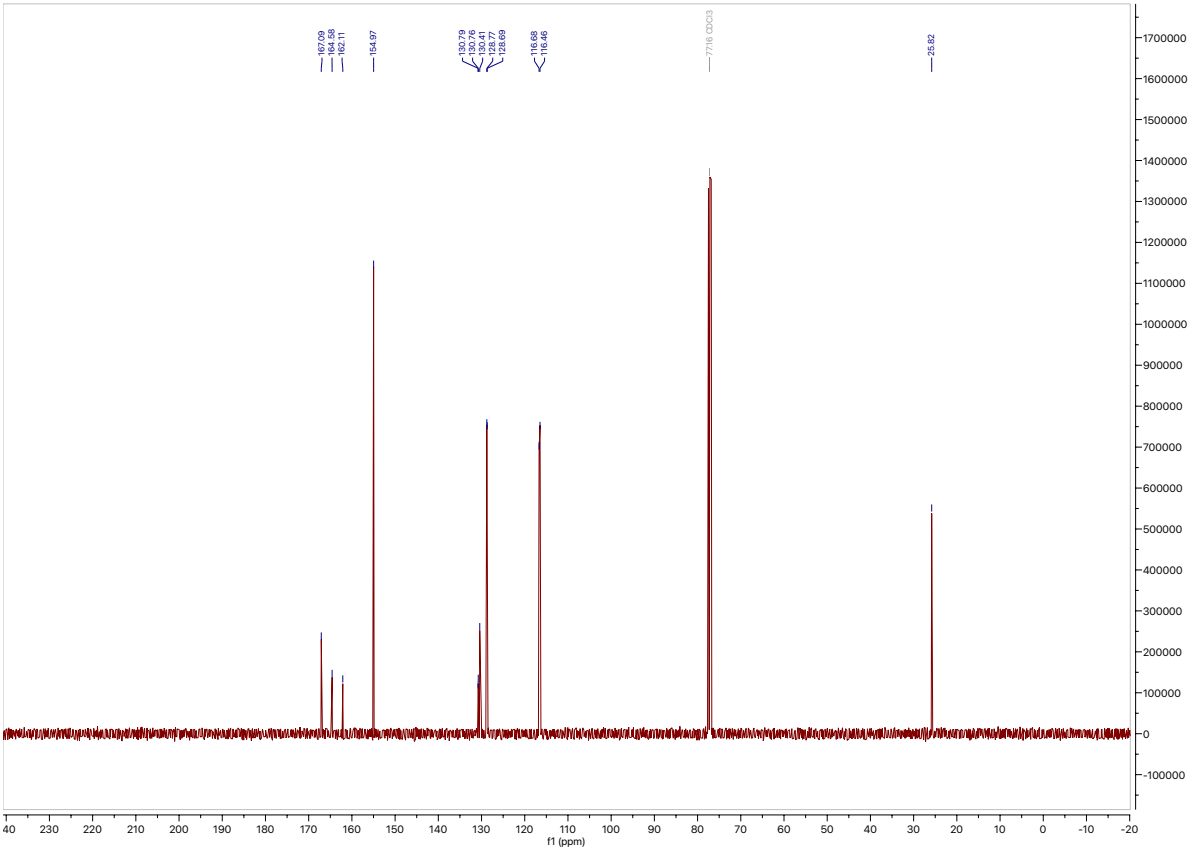
^{1}H NMR of **22** in $CDCl_3$



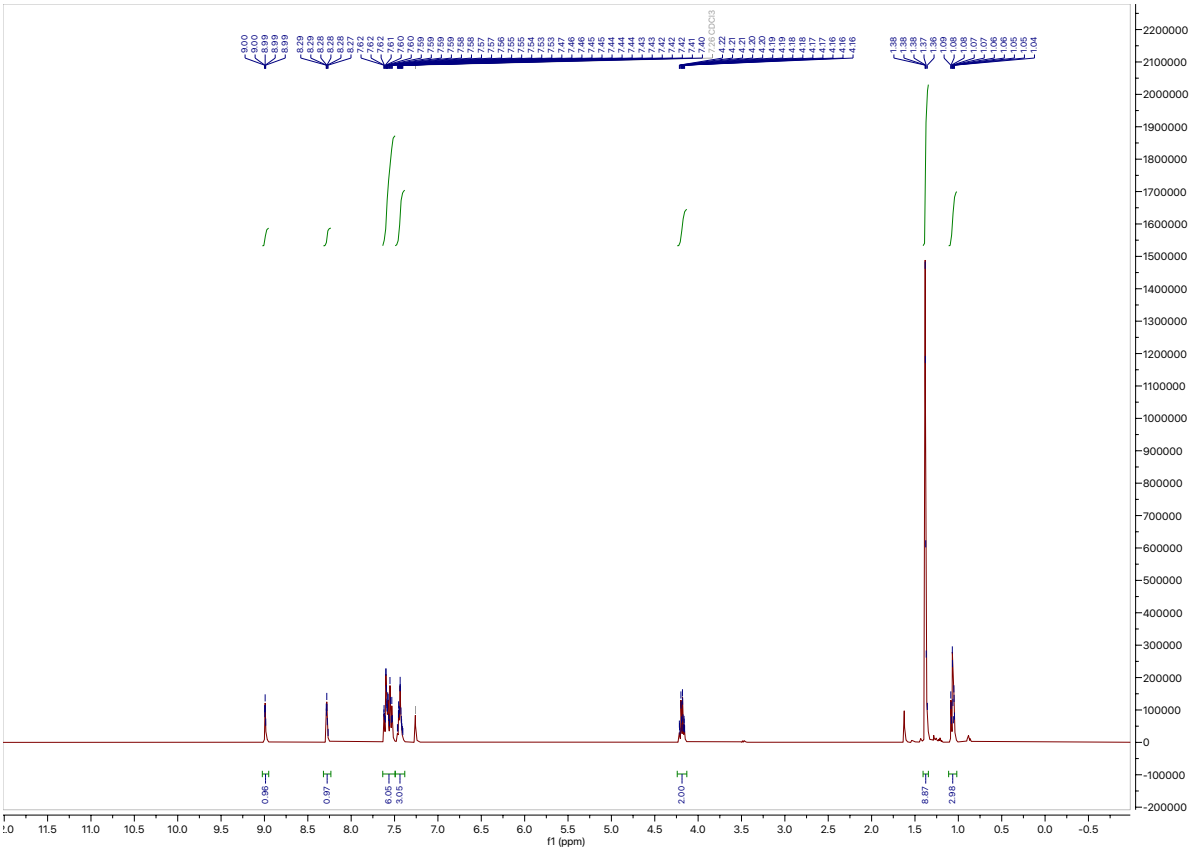
^{19}F NMR of **22** in $CDCl_3$



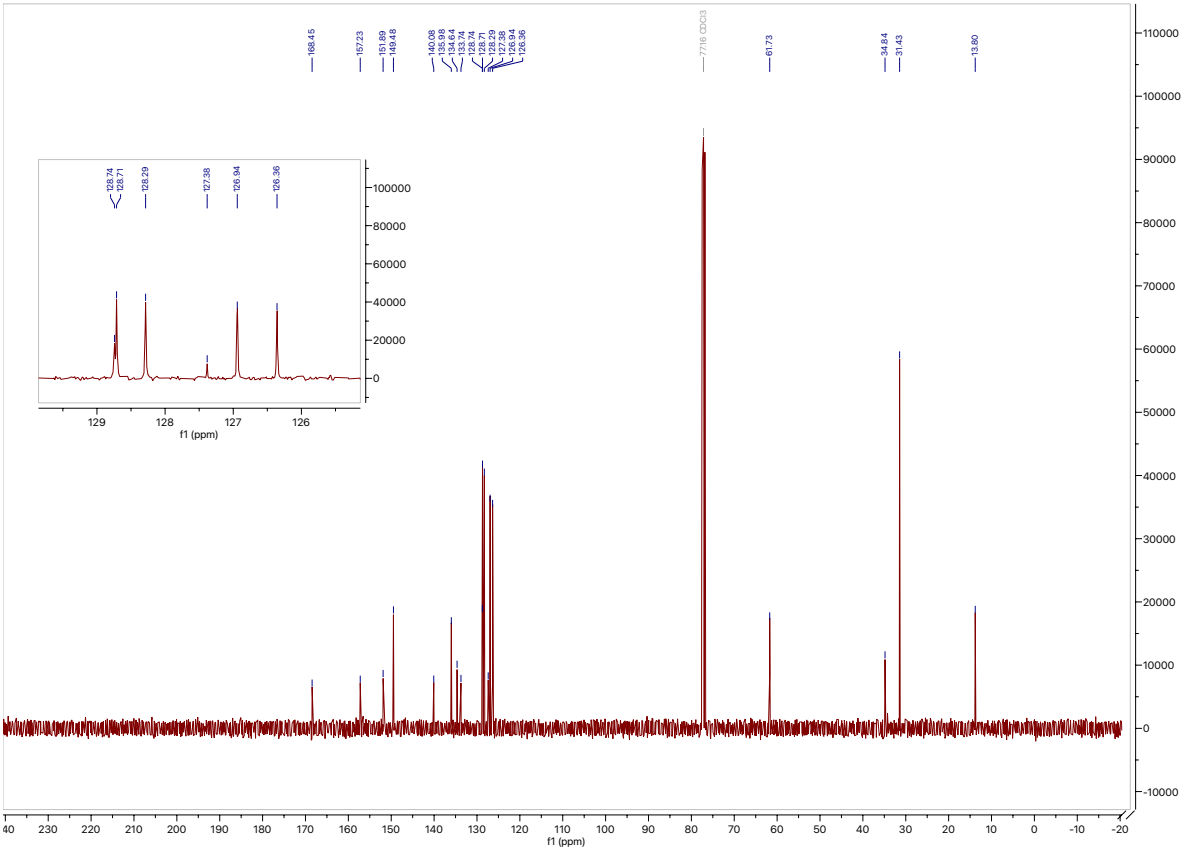
^{13}C NMR of **22** in $CDCl_3$



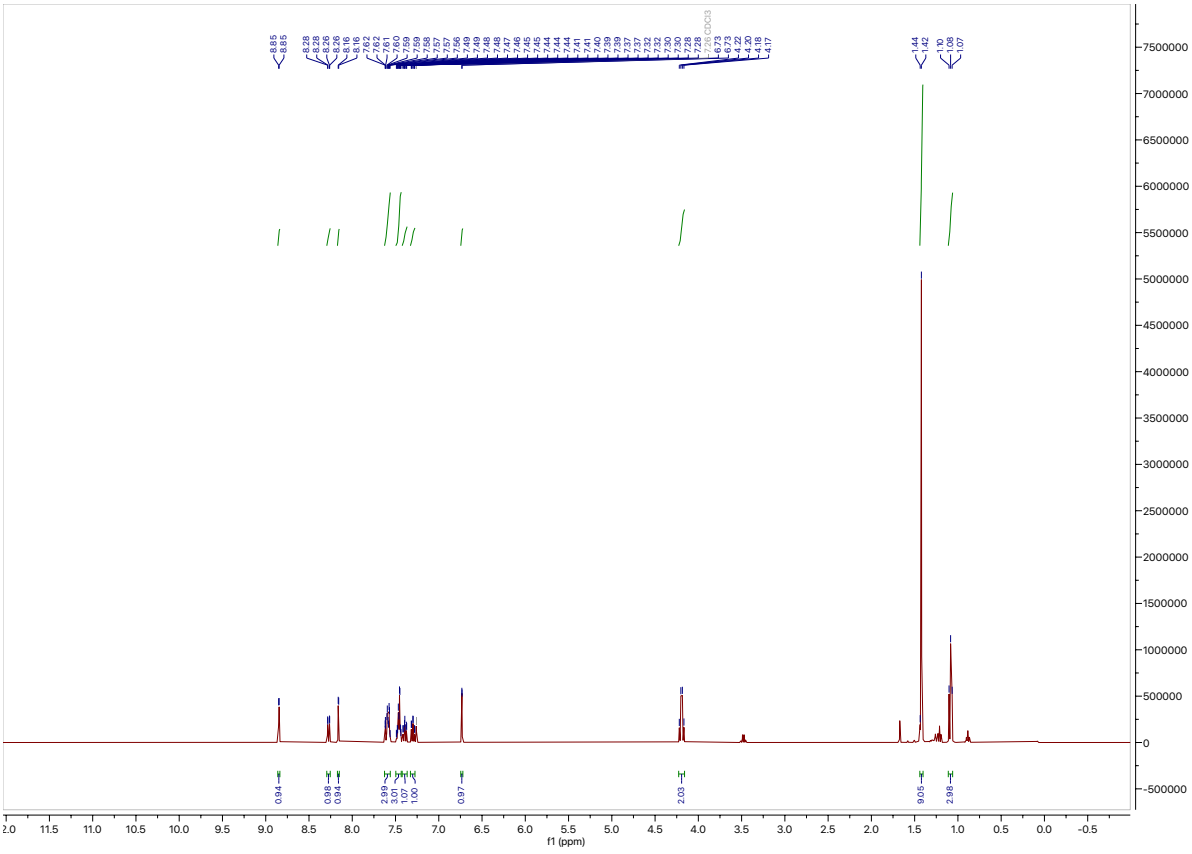
^{1}H NMR of **24** in $CDCl_3$



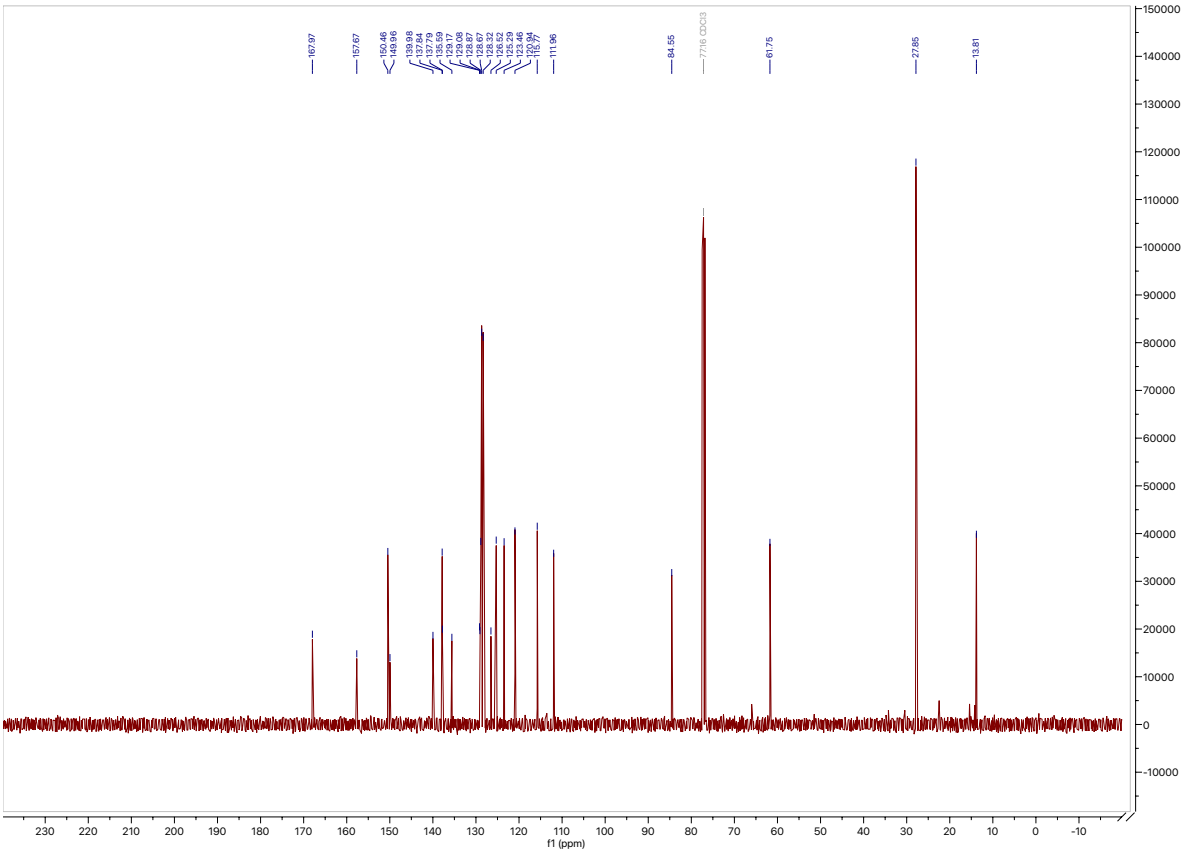
^{13}C NMR of **24** in $CDCl_3$



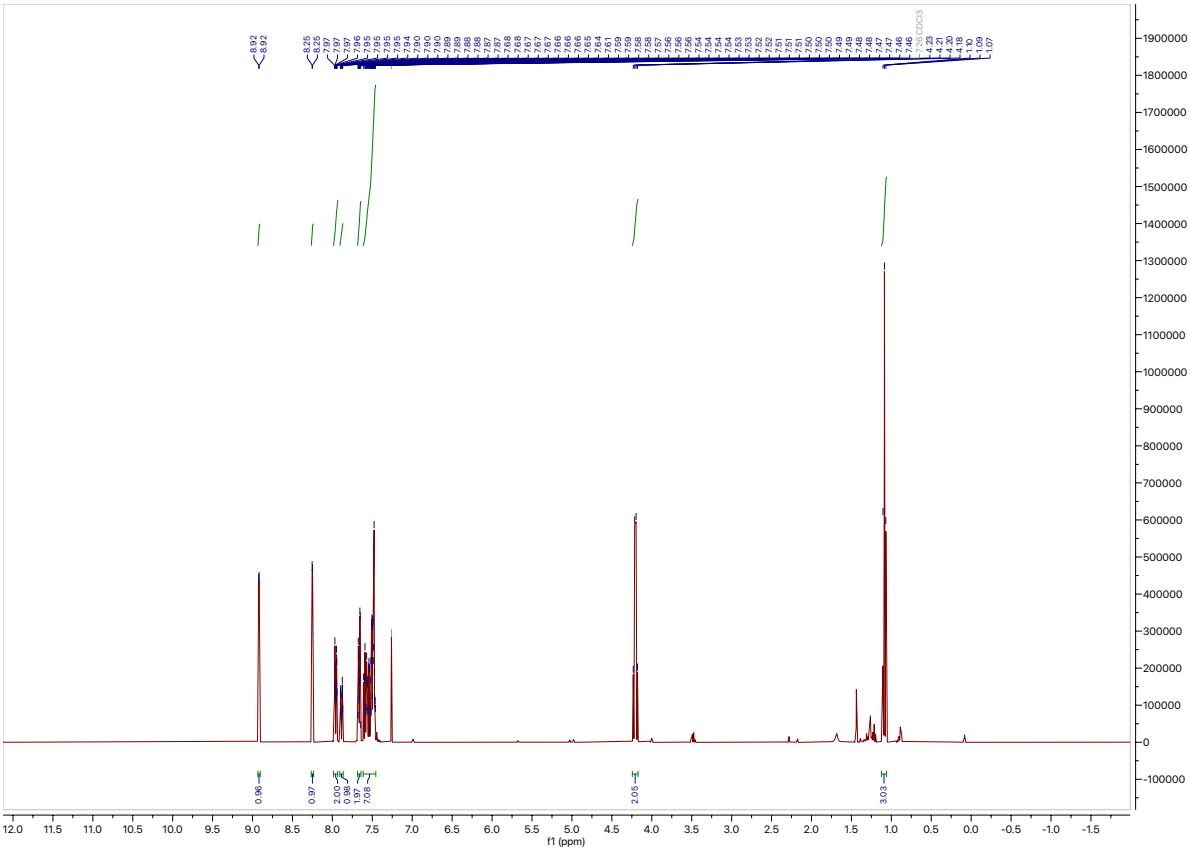
^{1}H NMR of **25** in $CDCl_3$



^{13}C NMR of **25** in $CDCl_3$



^{1}H NMR of **26** in $CDCl_3$



^{13}C NMR of **26** in $CDCl_3$