Metal-free C-C cross-coupling reactions using simple and cheap organic additives

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Certificate of Examination

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Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. Debashis Adhikari at the Indian Institute of Science Education and Research Mohali.

I declare that this written submission represents my ideas in my own words and where others' ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

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In my capacity as the supervisor of the candidate’s project work, I certify that the above statements by the candidate are true to the best of my knowledge.

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Notations and Abbreviations

NMR	Nuclear Magnetic Resonance
δ	Chemical Shift
^{o}	Degree
SET	Single electron transfer
THF	Tetra hydro furan
Ar	Aryl
aq.	Aqueous
br	broad
BHAS	Base promoted homolytic aromatic substitution
d	doublet
DCM	dichloromethane
dd	doublet of doublet
eq.	equation
equiv.	equivalent
HRMS	High resolution mass spectrometry
KO^{t}Bu	Potassium tert-butoxide
m	milli/mutiplet
μ	micro
Me	methyl
mg	milli-gram
mL	milli-litre
PLY	Phenlenyl
mmol	millimole
mol	mole
Ph	phenyl
Ppm	parts per million
q	quartet
rt	room temperature
rxn	reaction
s	singlet
t	triplet
^{t}Bu	tert-butyl

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Abstract

Transition-metal-catalysed reactions have been explored from the starting of the last century and illustrate an evolution in organic chemistry. Over the last 50 years, it becomes elegant and direct methods for C-C bond formation.[1] Many name-reactions have been designated in the text books and are familiar now days for instance, Heck coupling, Suzuki coupling, Negishi coupling, Stille coupling and several others. Great utility and importance of these metal catalyzed reactions were focused by the Noble Prize in the field of Chemistry in 2010.[2]

However, transition-metal-catalysed coupling reactions have some limitations in terms of applications and difficulties. Firstly, most of these metal-catalysts are generally very costly. Secondly, a large number of transition-metal-catalysis are toxic to various proportions and removal of impurity from the required products is quite expensive and challenging, particularly for pharmaceutical industries.

Finally, these catalysts are significantly oxygen and moisture sensitive. Transition-metal-catalysts are very difficult to handle.

Certainly, suitable methods to form C-C bonds using without any metal to satisfy the common transition-metal-catalysed reactions are highly demanding.[3]This shows the excitement about the article of coupling of iodobenzene to pyridine derivatives without any transition-metal-catalysts by Itami *et al*.[4] in 2008. Since then several additives were reported for instance, 1,10-phenanthrolines, 1,2-diamines, 1,2-diols, N-methyl anilines, indoline derivatives are several others.

In chapter 1, metal-free Carbon-Carbon cross-coupling reactions of several diazonium salts using super cheap 3,5-dimethyl Pyrazole molecule, optimization, substrate scope and possible mechanism have been discussed.

In chapter 2, aromaticity driven metal-free cross-coupling reaction, a comparative study among three simple organic additives, plausible mechanism and substrate scope have been discussed.

Key words: cross-coupling reactions, metal-free, additive, Pyrazole, aromaticity.

Chapter 1

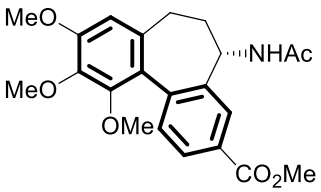
Introduction

1.1 General

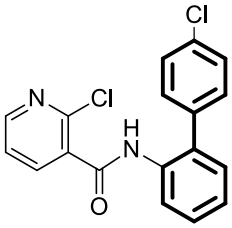
The bi-aryl moiety, which is commonly observed in several drugs and natural products, displays significant bio-activities across a variety of diseases, which includes antitumor, anti-inflammatory, antirheumatic and antifungal drugs (figure 1).[5] Due to above mentioned significance of bi-aryl scaffolds, their preparation has obtained great attraction to the organic community.

The classic procedures to their synthesis covers famous name reaction for instance Stille, Kumada, Suzuki, Negishi, and Ullmann coupling reactions, that involve late metal catalysts.

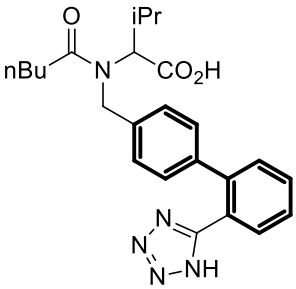
But, some problems due to the toxicity and price of these metal catalysts and compounds. Moreover, almost all of the afore-mentioned synthesis utilize difficult conditions and substituted reagents like mesylate, halide, silane, boronic acid and triflate were used. So, the advancement of environmental friendly and elegant bi-aryl synthesis reactions are highly demanding.



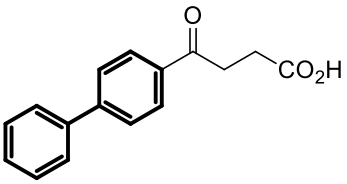
Allocolchicine: pharmaceutically important natural product



Boscalid: pesticide property



Valsartan: angiotensin receptor antagonist

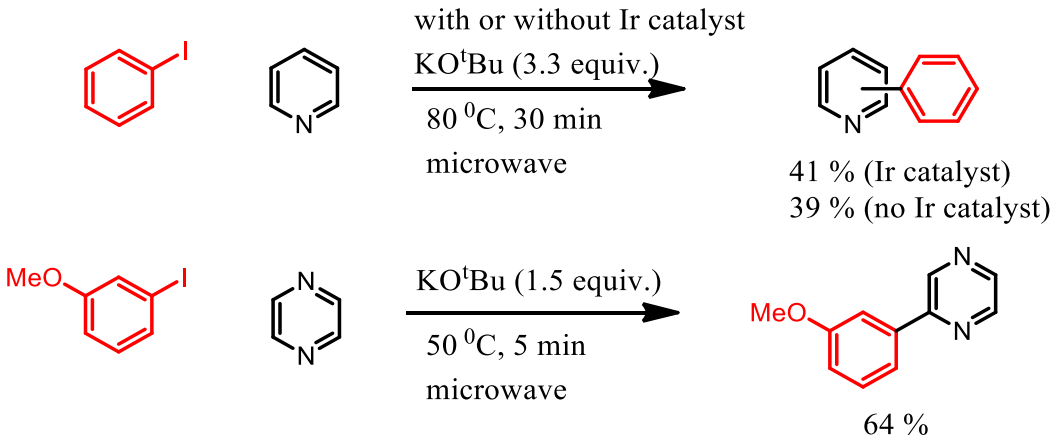


Fenbufen: anti-inflammatory property

Figure 1: Bio-active molecules containing a bi-aryl moiety.

Metal-free cross-coupling reactions

Itami explored iridium-complex-catalysed coupling of iodobenzenes using potassium tert-butoxide. At the time of the research, they claims a strange observation, that this reaction goes equally well without any iridium catalyst (**scheme 1**). That encouraged several investigations lead to the invention of a different class of reaction mechanism for biaryl synthesis, using the common methods of initiation.



Scheme 1 reactions explored by Itami *et al.*[4]

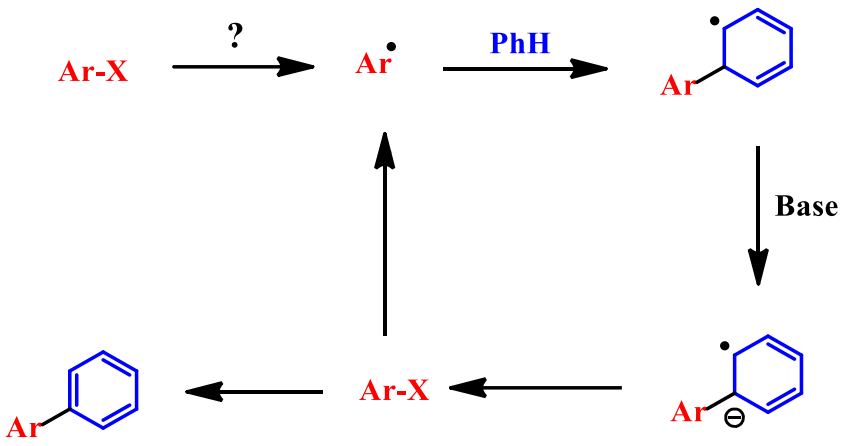
Moreover, they also observed that radical scavengers shut down the reaction completely. Shi, Shirakawa and Hayashi used phenanthroline, on the other hand Kwong and Lei used 1,2-diamine and 1,2-diols in stoichiometric amount potassium and sodium tert-butoxide for the cross-coupling reactions. Shi *et a*[6]. Explained that radicals were important intermediates in these reactions however, that was not cleared about the generation of radicals and exact mechanism lead to the coupling product.

In 2011, Studer and Curran[7] further put some light on the mechanism for base mediated electron transfer reactions. They explained the important role of KO^{t}Bu for the base-promoted homolytic aromatic substitution (BHAS) mechanism presented in **scheme 2**
which is recently majorly used.

In the latter years, several researchers reported as promoters that were capable of promoting of

the coupling reactions.

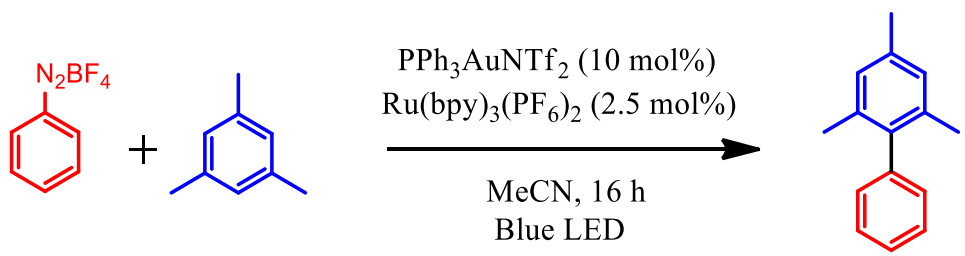
One thing we should remember that an additive is not a catalyst. A catalyst remains unchanged after the reaction and actively participate in all the steps of the reactions while, promoters only initiate the reactions, it becomes different compound after the initiation and does not take part in mechanistic cycle.



Scheme 2 Studer and Curran's BHAS cycle

Now, it's time to talk about carbon-carbon cross-coupling reaction using benzene diazonium salts. I will talk about recent reports where scientists used metal catalyst to complex organic additive for the above transformation.

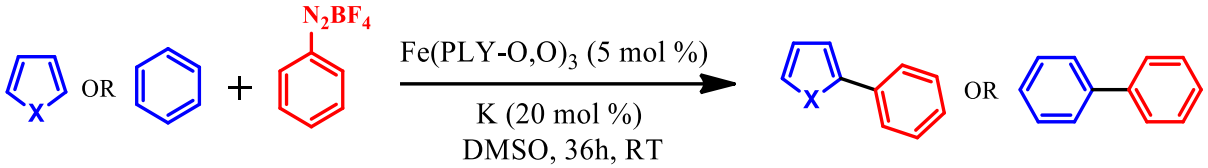
Lee *et al.*[8] explored that both of an aryldiazonium salt with PPh_3AuNTf_2 and a photo-redox catalyst should evolve an electrophile arylAu(III) species which activates C-H bonds of a corresponding haloarene to form desire cross-coupled product (**scheme 3**). They initiated with mesitylene as the arene and $Ru(bpy)_3(PF6)_2$ as the photo-redox catalyst and obtained promising yield.



Scheme 3 dual catalyst based C-H activation of arenes by Lee.

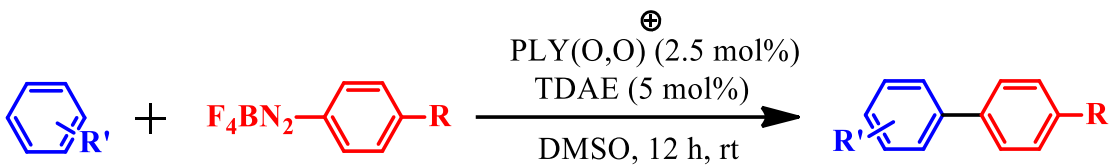
In 2018, Mandal and his co-workers[9] reported C-H activation of thiophene with p-chloro

diazonium tetrafluoroborate as a coupling partner by Fe(PLY-O,O)$_3$ catalyst (**scheme 4**). They got best result by using 5 mol% of catalyst in DMSO and stirred for 36 h at room temperature with 20 mol% K to reduce the catalyst. They got approximately 85 % yield using the above conditions.



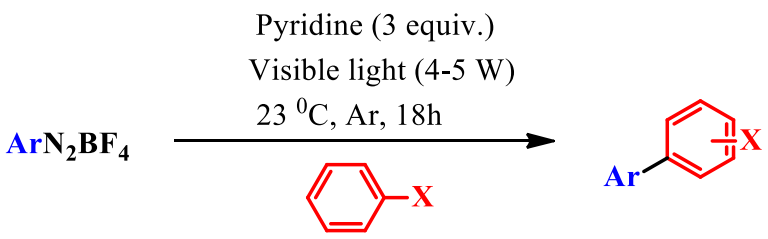
Scheme 4 coupling reactions using Fe(PLY-O,O) as a catalyst.

Same group reported carbon-carbon cross-coupling reaction in metal-free fashion[10] (**scheme 5**). The authors investigated redox activity as well as Lewis acidity of phenalenyl cation. After reduction of the cation by one electron produce the phenalenyl based radical, that involves in a single electron transfer processes (SET) to form highly reactive aryl radical from substituted benzene diazonium tetrafluoroborate. Moreover after SET processes it reproduce the phenalenyl cation that can activate arene molecule as a lewis acid similar to common Lewis acid $AlCl_3$ in Friedel Craft reaction.



Scheme 5 cross-coupling reaction by phenalenyl cation as a additive.

Very recently in 2019 Lee *et al.*[11] reported biaryl synthesis from benzene diazonium salt and suitable arene partner photo catalytically in presence of pyridine as a catalyst (**scheme 6**). They carried out the reaction for 18h at room temperature in argon atmosphere. The authors proposed that electron donor acceptor (EDA) complex is responsible for the single electron



(X = H or halogen)

Scheme 6 metal free Gomberg reaction.

Transfer from the pyridine molecule.

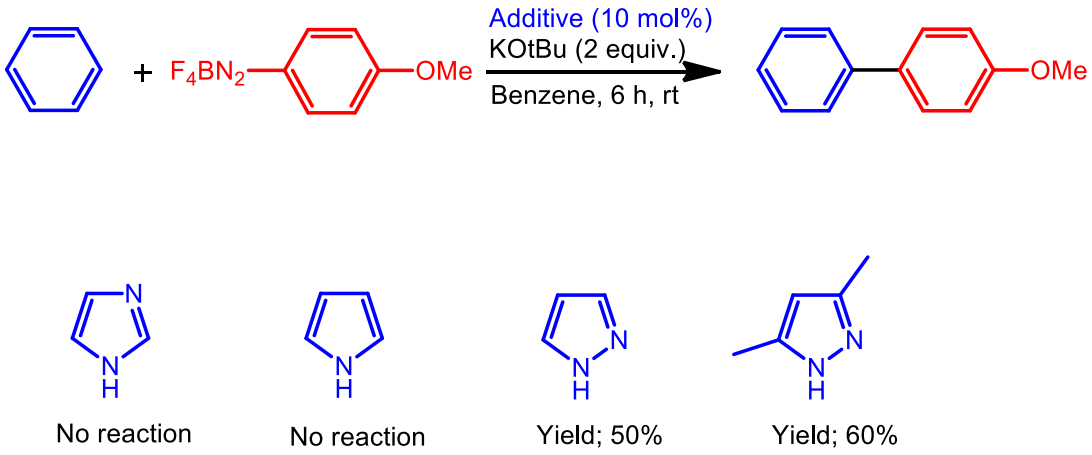
1.2 3,5- dimethyl pyrazole

-

All though there are several reports for carbon-carbon cross-coupling reactions using organoadditives. Most of them are complex in structure, synthetically challenging and quite costly. In addition to that, the reaction time is quite long and sacrificial reagents are also used. So, simple and super cheap promoters are highly desirable that will not require any sacrificial agents and the reaction time will be less in time.

We started our investigations by optimizing the reaction condition for the C-H arylation of arenes with 4-methoxy phenyl diazonium tetrafluoroborate using different organic promoters (**scheme 7**).

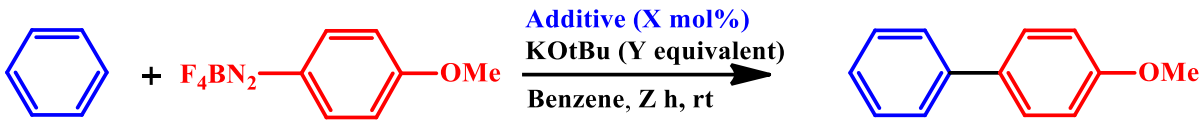
We found that 3,5-dimethyl pyrazole gives promising results for substituted biaryl synthesis.



Scheme 7 screening of additives

We optimized the reaction conditions using 10 mol% of the additive 3,5-dimethyl pyrazole, 2 equiv. potassium tert butoxide for 6 h at room temperature in presence of inert atmosphere using 10 equiv. arene partner (**table 1**). We observed 60 % of the desired bi-aryl using the above conditions. We found that with increasing the promoters mol% from 5 mol% to 7.5 mol% to finally 10 mol% resulted increase in yield from 15%, 30% and maximum 60% yield. One interesting fact that using additive as a half stoichiometric amount plummeted the % of yield from 60% to 40%. We will explain later this unusual experimental results. We also reduced the amount of base from 2 equiv. to 1 equiv. resulted less product formation. It

implies that 2 equiv. potassium tert butoxide involves in the BHAS reaction mechanism. The increase in temperature from room temperature to 80^{o}C also declines the desire product formation. We also put the reaction for prolonged time (12 hrs) but the yield was not further improved.

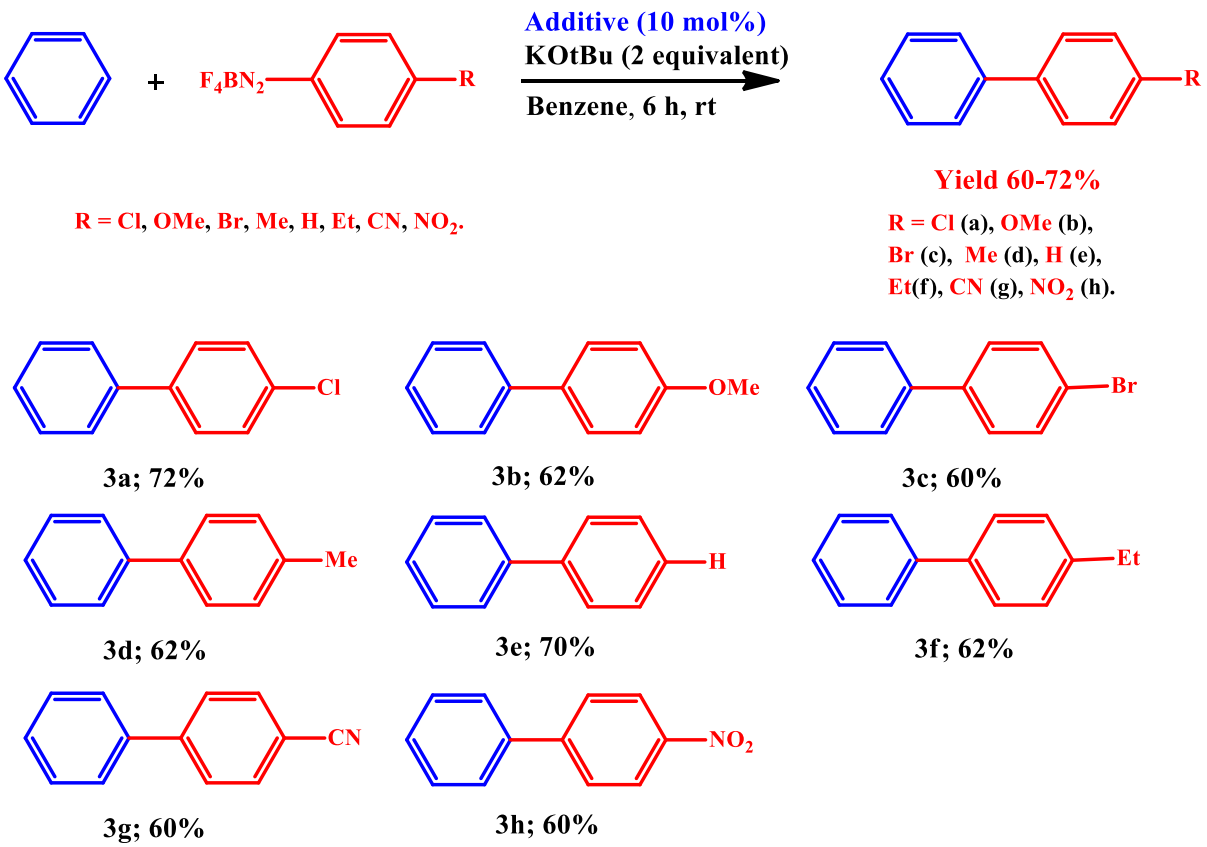


Entry No.	Additive Loading (X mol %)	Base (Y equiv.)	Time (Z hrs)	Temperature (^{0}C)	Product (Yield %)
1	5	2	6	RT	15
2	7.5	2	6	RT	30
3	10	2	6	RT	60
4	20	2	6	RT	52
5	50	2	6	RT	40
6	10	1	6	RT	20
7	10	2	12	RT	62
8	10	2	6	80	30

Table 1 optimization table

1.3 Substrate scope

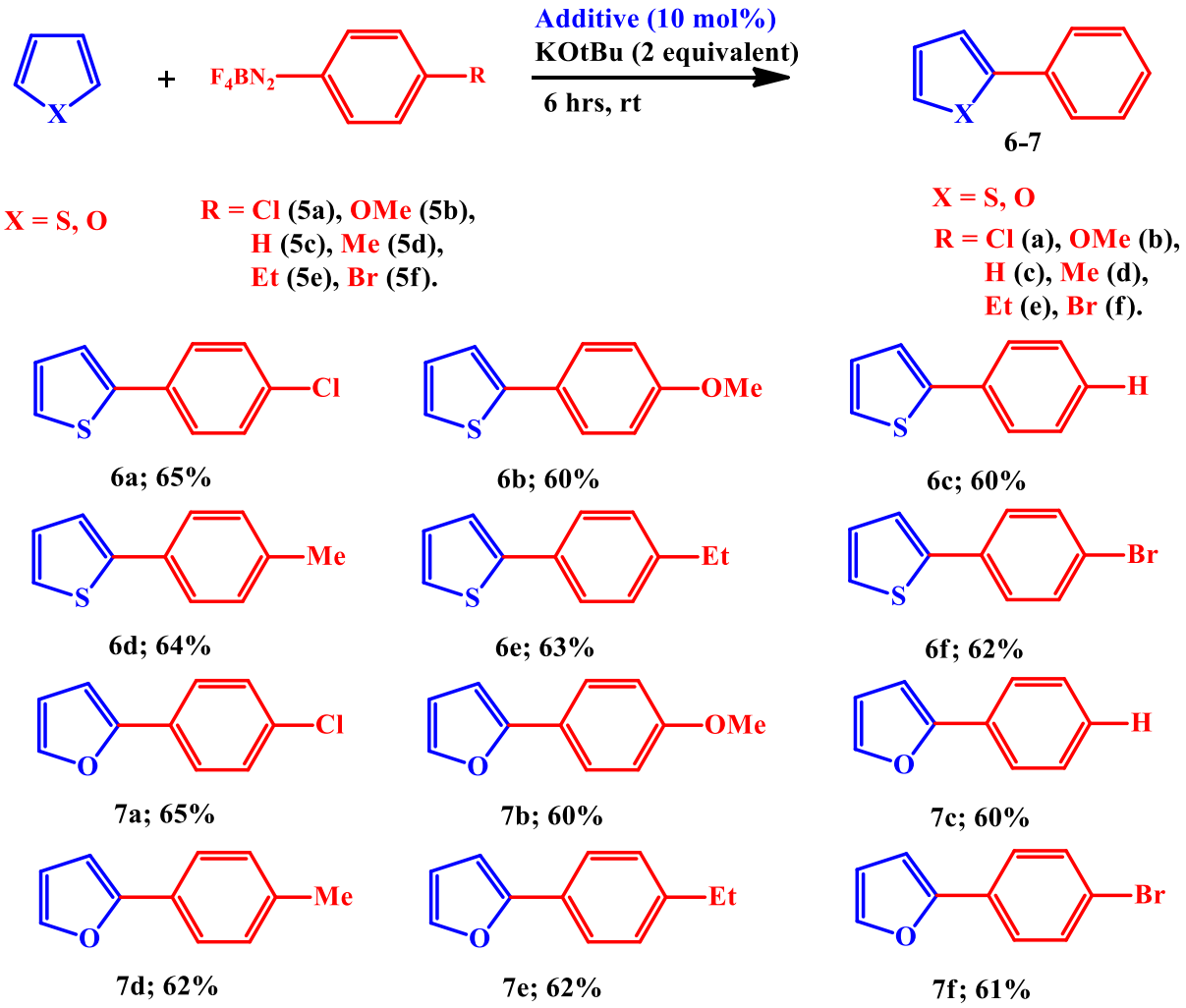
After optimizing different reaction conditions, the span of C-H activation of several arenes was tested with different substrates. The unsubstituted arene such as benzene was carried out with several substituted benzene diazonium and obtained a variety of biaryl products in moderate to good yield (**60-72%**, Scheme 8, **3a-3h**). Various substituted diazonium salts including both electron donating and electron withdrawing substrates gives decent yields.



Scheme 8 substrate scope of biaryl synthesis using benzene as a coupling partner.

After successful completion of arylation of benzene, we extended our study towards C-H activation of thiophene with several benzene diazonium salts **60-65%**, Scheme 9, **6a-6f**). For the synthesis of C-2 arylation of thiophene, various coupling partners including electron rich and electron deficient benzene diazonium salts were used. We also used furan as a hetero-arene to get heteroarene substituted biaryl from various substituted diazonium

salts partners (**60-65%**, **Scheme 9**, **7a-7f**).



Scheme 9 substrate scope of biaryl synthesis using heterocycle as a coupling partner.

1.4 Mechanistic study

Then we investigated UV-Vis spectroscopy to confirm the formation of super electron donor. We took THF as a solvent instead of benzene for better solubility. First, we took a spectra of 3,5 dimethyl pyrazole in THF and then potassium tert butoxide was added quickly to the solution and recorded the spectra (**figure 2**). We found that the peak at around 400 nm was decreased and a new peak at 275 nm was formed indicating the formation of the active

species which was responsible for single electron transfer to the diazonium salt molecule.

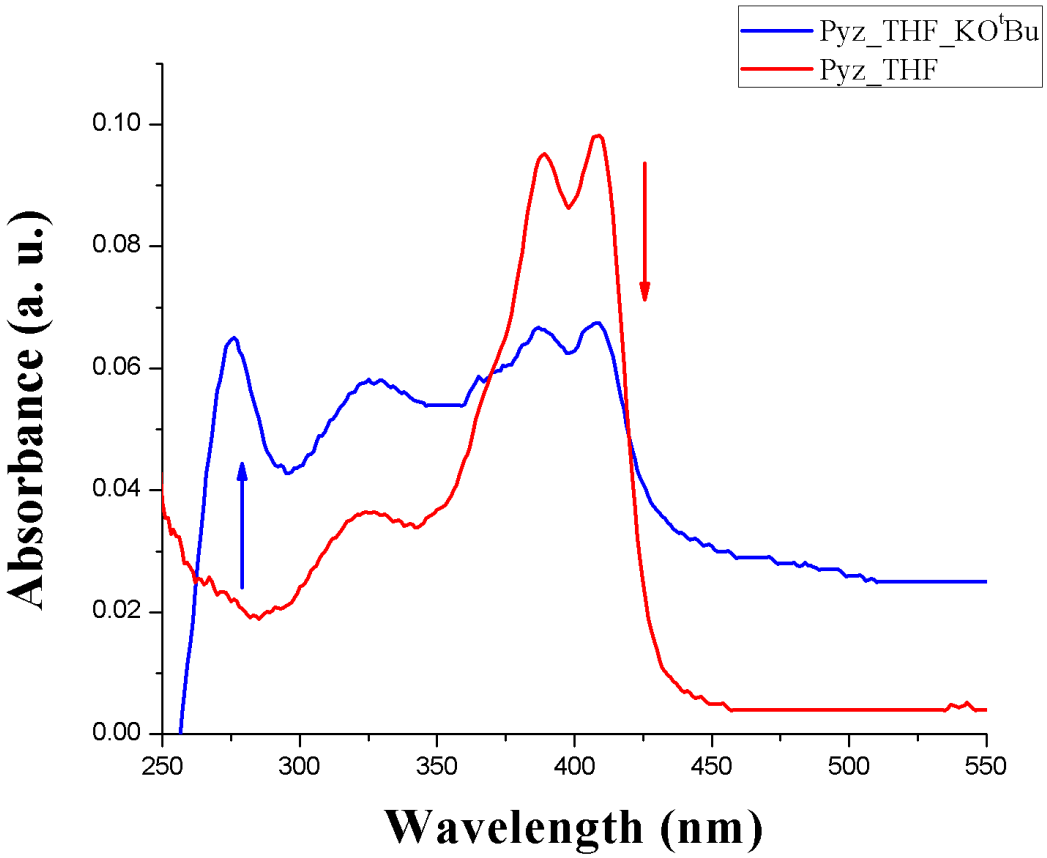


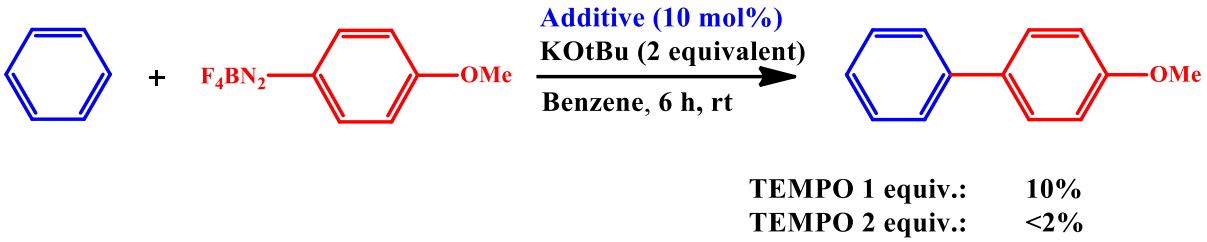
Figure 2: UV-Vis spectra of the 3,5-dimethyl pyrazole in presence of KO^{t}Bu

Next, the reaction between benzene and 4-methoxy benzene diazonium tetra fluoroborate was done with a radical scavenger 2,2,6,6-tetramethylpiperidinoxyl (TEMPO) by varying equivalents of TEMPO. When we used 1 equiv. of TEMPO, 10% of the desired product was obtained, on the other hand, the reaction was completely shut down in 2 equiv. of TEMPO (**figure 3a**). This controlled experiment confirms a mediated pathway for the arylated product.

In addition to that, the reaction between TEMPO and 4-methoxy benzene diazonium tetra fluoroborate was carried out without any arene or heteroarene coupling partner (**figure 3a**). We were able to determine the TEMPO trapped product by high resolution mass spectroscopy (HRMS) (**figure 4**). This results easily indicates a radical medicated SET process is taking

place during the reaction, further supported by previous reports on C-H arylation.

a) Reaction inhibition in presence of TEMPO



b) TEMPO trapped intermediate

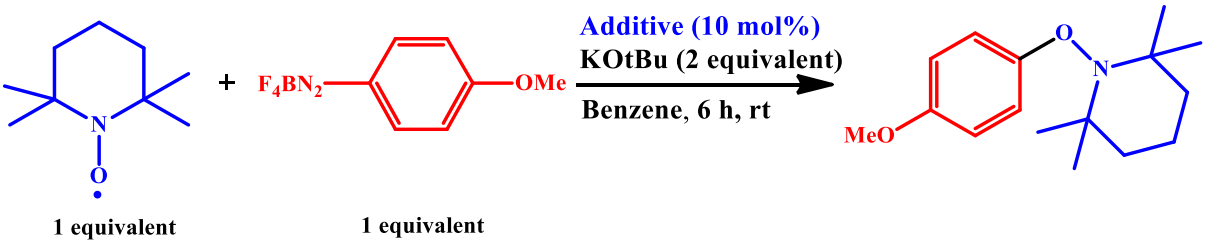


Figure 3: mechanistic investigation: a) reaction inhibition by TEMPO. **b)** TEMPO trapped aryl radical.

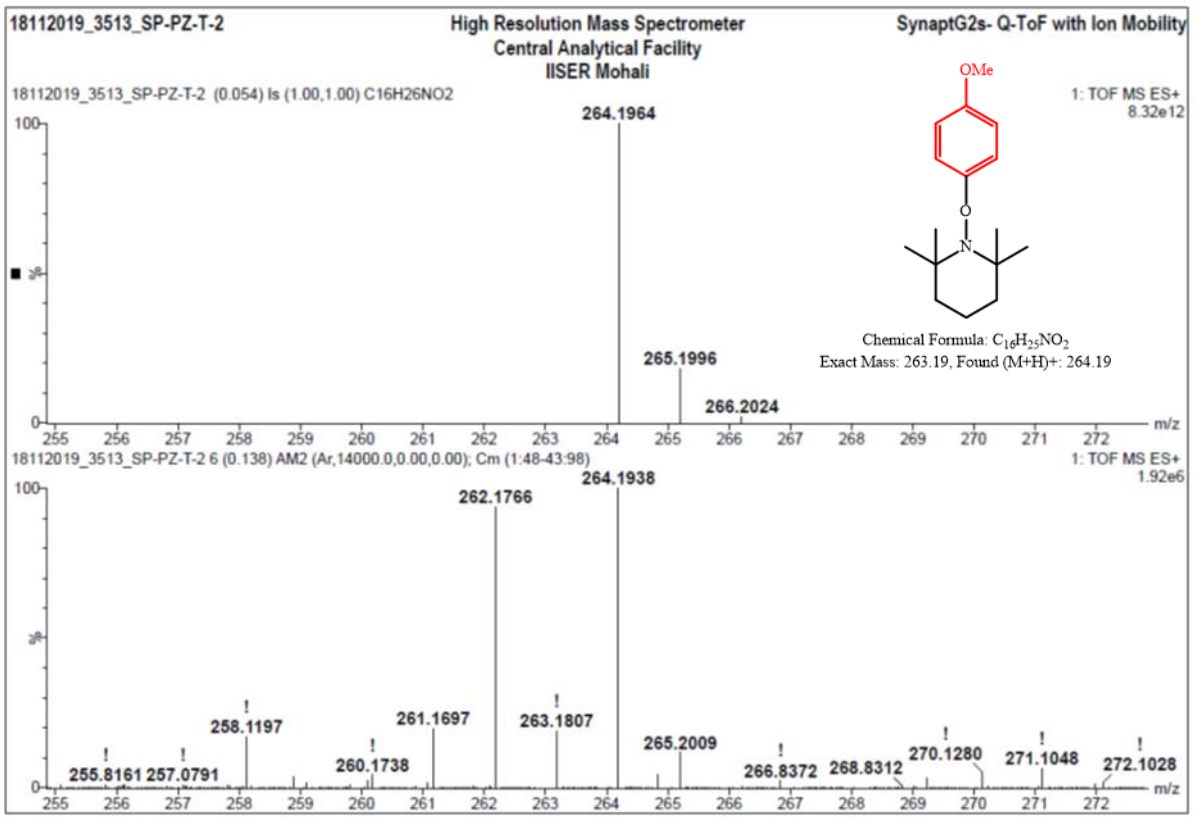
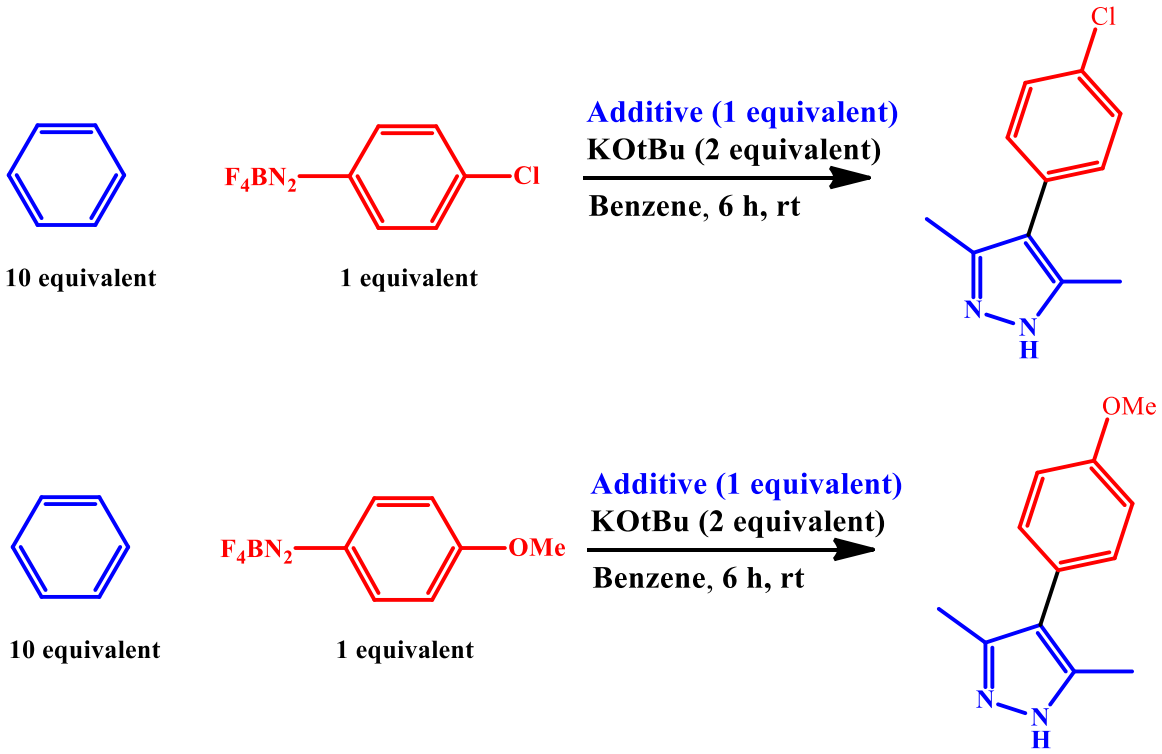


Figure 4: HRMS of TEMPO trapped aryl radical.

After that, we have done some stoichiometric reaction to know the fate of the additive after it

initiate the reaction once. We have done these reactions with our optimized reaction condition using 1 equiv. of 3,5-dimethyl pyrazole (**scheme 10**). In presence of equivalent amount additive we surprisingly recovered pyrazole arylated product along with the desired substituted biphenyl product.



Scheme 10: stoichiometric reactions using the additive.

When 4-chloro benzene diazonium tetra fluoroborate used as a substrate with coupling partner benzene in presence of equiv. amount of the additive. We were able to separate 4-(chloro phenyl) 3,5-dimethyl pyrazole and characterize by both NMR (**figure 5**) and mass spectroscopy (**figure 6**). We have done the same experiment with 4-methoxy benzene diazonium tetrafluoroborate using equiv. amount of promoter and separated 4-(methoxy phenyl) 3,5-dimethyl pyrazole and characterized by NMR spectroscopy. It confirms that pyrazole based radical was formed after it transfer an electron to the diazonium salt.

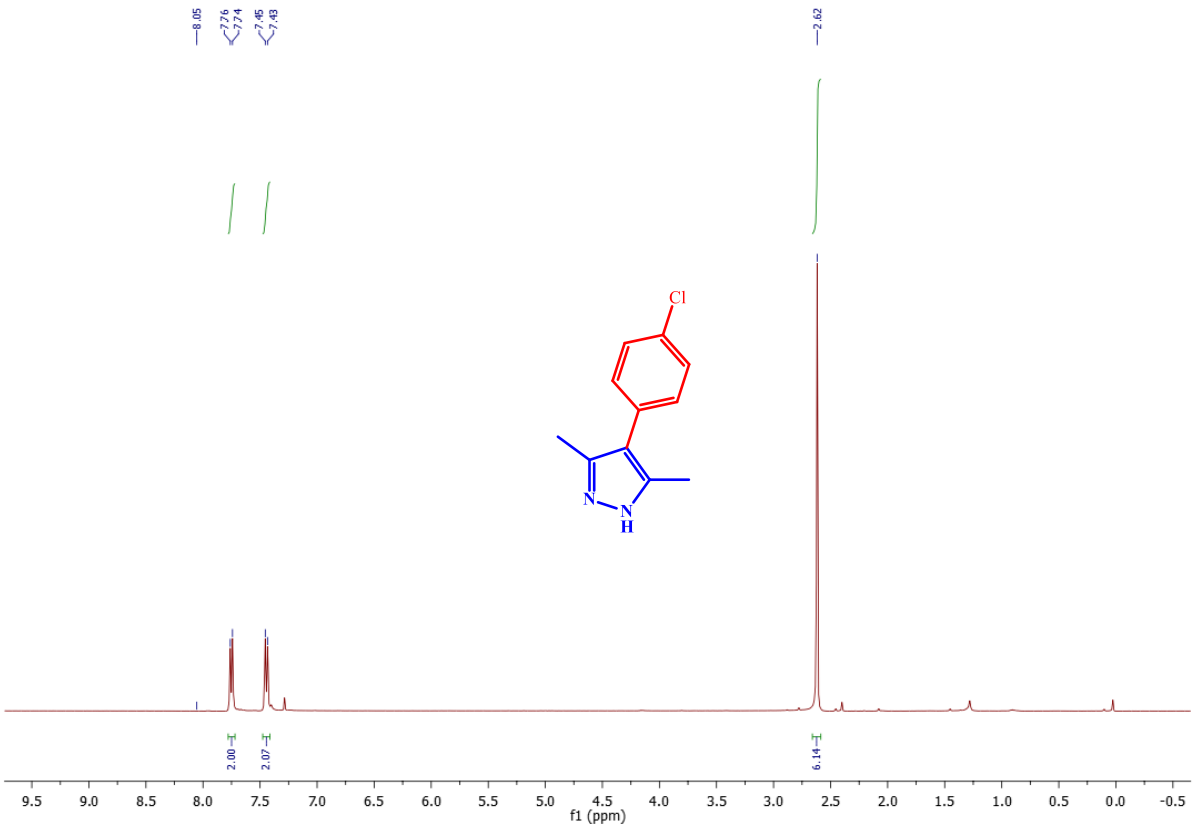


Figure 5: NMR of 4-(chloro phenyl) 3,5-dimethyl pyrazole.

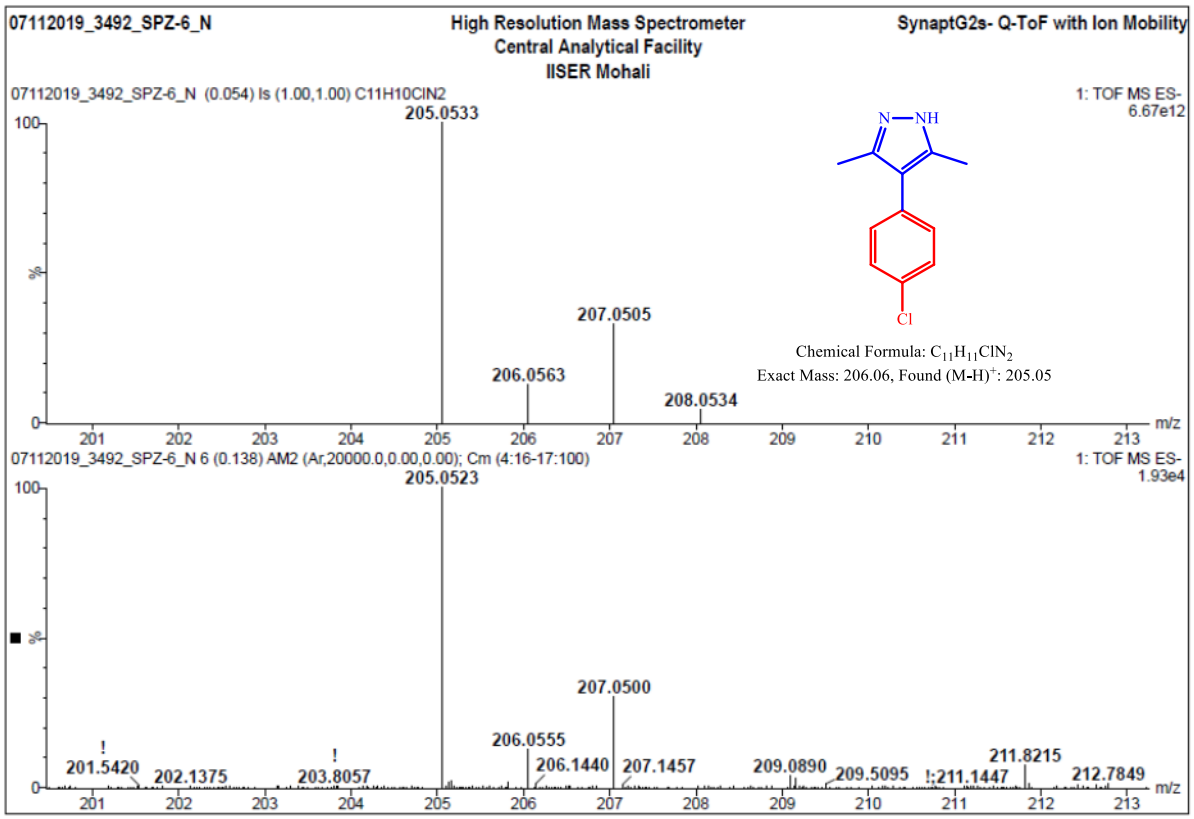


Figure 6: HRMS of 4-(chloro phenyl) 3,5-dimethyl pyrazole.

Furthermore, the dimerization product of 3,5-dimethyl pyrazole was also trapped by mass spectroscopy, that also confirms the formation of pyrazole based radical (**figure 7**). After the the formation of the radical either it can dimerize or react with the substrate diazonium salt to form pyrazole arylated product.

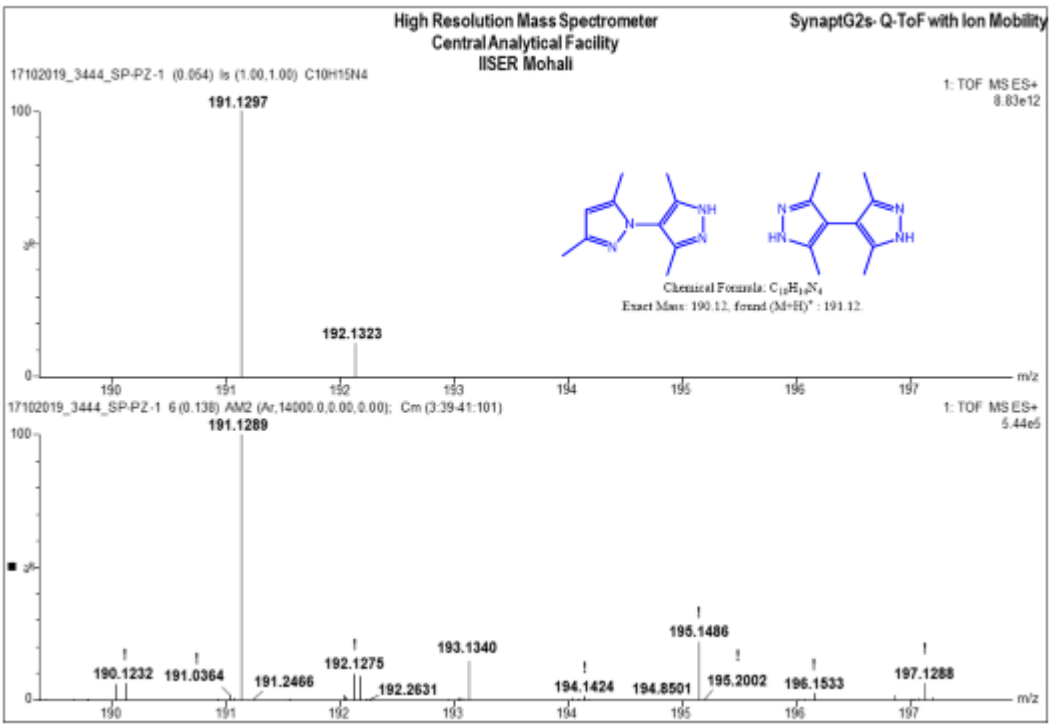


Figure 7: HRMS of dimerization product of the additive 3,5-dimethyl pyrazole.

1.5 Probable initiation:

Considering all the results from the present study and some previous reports[12], we proposed a probable initiation of the respective diazonium salts by the additive 3,5-dimethyl pyrazole (**figure 8**). First KO^{t}Bu takes a proton from the additive to form potassium salt of the pyrazole. Now, it becomes a super electron donor and donates an electron to the diazonium salt via SET processes. Now, the additive becomes pyrazolium radical and diazonium becomes radical anion. Then, the radical either can dimerize to give dimerized product or can react with the aryl radical to form 3-arylated product of pyrazole.

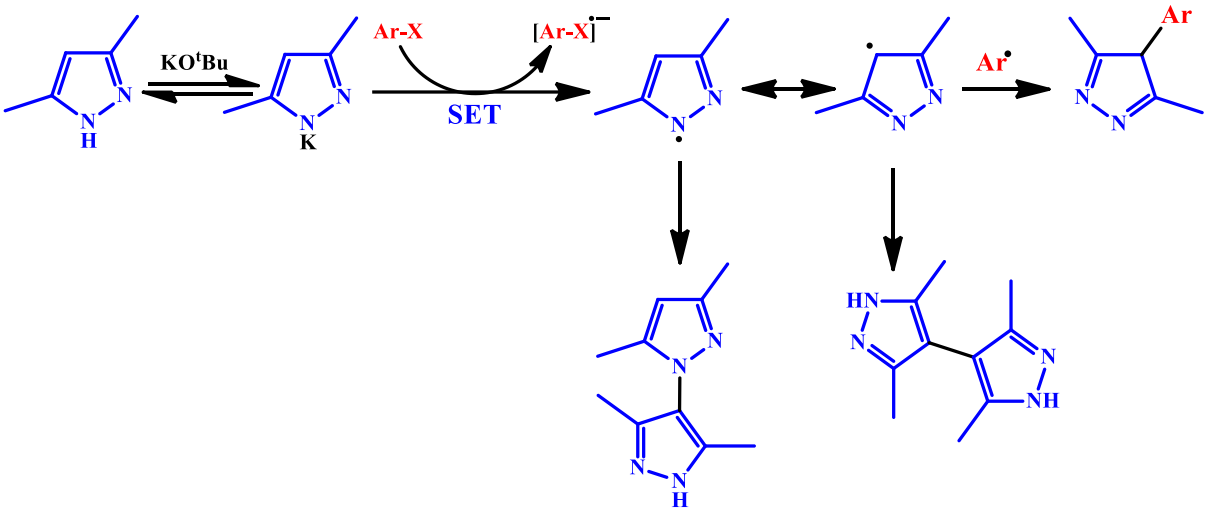


Figure 8: probable initiation of the additive 3,5-dimethyl pyrazole.

Now, we will talk about mechanistic cycle which is governed by base promoted homolytic aromatic substitution (BHAS) (**figure 9**). 3,5-dimethyl pyrazole in presence of a KO^{t}Bu

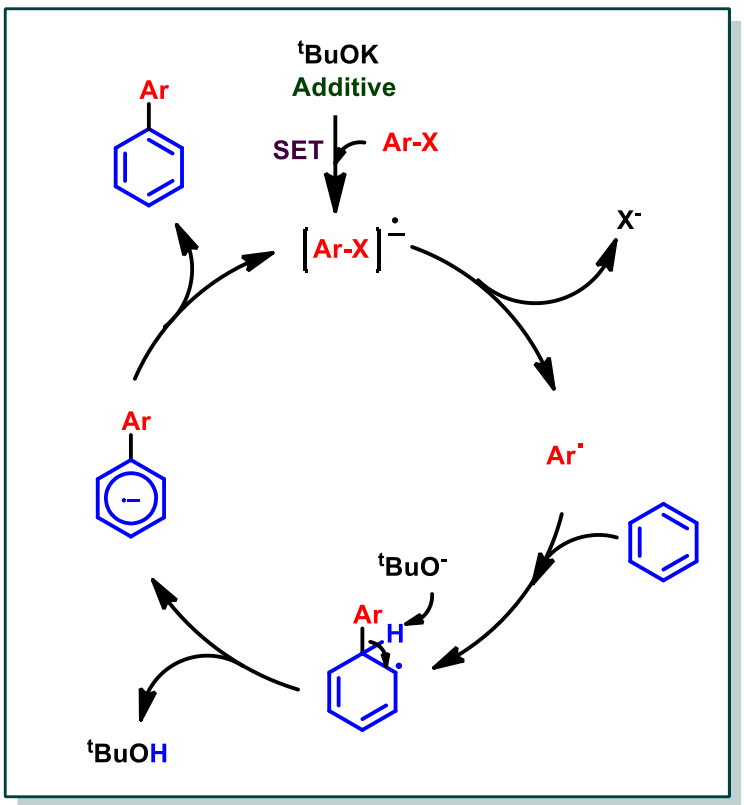


Figure 9: BHAS mechanism of benzene as coupling partner.

transfer a single electron to the substituted benzene diazonium salt to generate radical anion after that it forms aryl radical. Then that radical reacts with the benzene to form cyclohexadienyl radical. After that, another molecule of KO^tBu takes another proton from the cyclohexadienyl radical to form radical anion and this way up transfer occurs. This radical anion transfer an electron to another diazonium salts to form desired biaryl product and this way mechanistic cycle was completed.

1.6 Conclusion

To conclude, we modified a transition metal free cross-coupling reactions to synthesize several cross-coupled product. We successfully obtained desired products in absence of any metal catalyst and using mild condition. Addition to that, our method provides a straight forward way for the preparation of substituted biphenyl, that are significant for many bio active scaffolds.

1.7 Experimental Section

Common experimental Information: Reactions were done in overnight dried schlenk flask using argon atmosphere. Most of the chemicals were commercially available and used directly without purification, unless otherwise mentioned. Column chromatography was executed by silica gel 60 (100-200 mesh) using ethyl acetate/hexane mixture and DCM/hexane mixture. NMR spectra were recorded on a Bruker 400 MHz spectrometer with deuterated chloroform ($CDCl_3$) with tetrametyhlsilane (TMS) as an internal standard. Solvents were evaporated using a rotary evaporator.

General procedure for the synthesis of substituted benzene diazonium tetrafluoroborate: Substitited diazonium salts were prepared according to the reported literature[10].

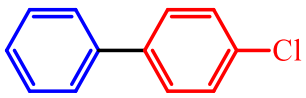
General procedure for the synthesis of biaryl: In a schlenk flask aryl diazonium salt (0.5 mmol), KO^{t}Bu (1 mmol) and 3,5-dimethyl pyrazole (5 mol%) were dried for 30 mins in a well-equipped schlenk line. After that arene (10 mmol) was introduced drop by drop to the reaction mixture at argon atmosphere. The reaction mixture was stirred for 6 hours under an argon atmosphere at room temperature. When the reaction was completed, DCM was added to mixture and extracted. Then the resulting solution was dried over Mg_2SO_4, filtered and concentrated under the reduced pressure. Purification was executed by flash column chromatography with ethyl acetate/hexane mixture to get desired products.

Usual way of the reaction inhibition by a radical scavenger TEMPO: In a schlenk flask aryl diazonium salt (0.5 mmol), KO^{t}Bu (1 mmol), 3,5-dimethyl pyrazole (5 mol%) and TEMPO were dried for 30 mins in a well-equipped schlenk line. After that arene (10 mmol) was added drop by drop to the reaction mixture at argon atmosphere. The reaction mixture was stirred for 6 hours under an argon atmosphere at room temperature. When the reaction was completed, measured by TLC, extracted the reaction mixture by adding DCM in it. After the mixture was dried over Mg_2SO_4, it was filtered and concentrated. Purification was executed by flash column chromatography with ethyl acetate/hexane mixture to get desired products.

General procedure for the stoichiometric reaction of the additive with the diazonium salts: In a schlenk flask aryl diazonium salt (0.5 mmol), KO^{t}Bu (1 mmol), 3,5-dimethyl pyrazole (0.5 mmol) and TEMPO were dried for 30 mins in a well-equipped schlenk line. After that arene (10 mmol) was added dropwise to the reaction mixture at argon atmosphere. The reaction mixture was stirred for 6 hours under an argon atmosphere at room temperature. When the reaction was completed, monitored by TLC, extracted the reaction mixture by adding DCM in it. After the mixture was dried over Mg_2SO_4, it was filtered and concentrated. Purification was executed by flash column chromatography with ethyl acetate/hexane mixture to get desired products. The biaryl product comes at pure hexane and then pyrazole arylated product comes at 10% EtOAc/hexane mixture.

1.8 Spectroscopic data

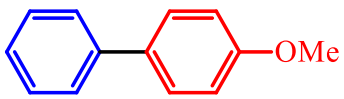
4-chlorophenylbenzene (3a)



White solid, yield: 72%.

NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.35-7.40 (m, 5H), 7.47-7.57 (m, 4H).
NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 127.57, 128.37, 128.89, 129.47, 132.29, 133.36, 139.6, 139.99.

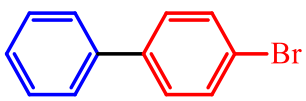
4-methoxyphenylbenzene (3b)



Pale yellow solid, yield: 62%.

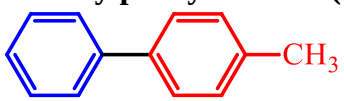
NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 3.86 (s, 3H), 6.97-6.99 (m, 2H), 7.28-7.33(m, 1H), 7.40-7.44 (q, 2H), 7.52-7.56 (m, 4H).
NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 55.3, 114.4, 126.6, 126.7, 128.1, 128.7, 133.8, 140.9, 159.4.

4-bromophenylbenzene (3c)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.34-7.40 (m, 5H), 7.43-7.53 (m, 4H).
NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 127.17, 128.26, 128.59, 129.47, 132.29, 133.16, 139.6, 139.99.

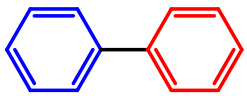
4-methylphenylbenzene (3d)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 2.34 (s, 3H), 7.29 (d, 2H), 7.33 (d, 2H), 7.51 (d, 2H), 7.52 (d, 2H), 7.41 (t, 1H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 21.4, 127.7, 127.9, 127.9, 129.2, 129.5, 137.8, 140.7

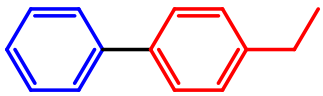
Biphenyl (3e)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.33-7.37 (m, 2H), 7.43-7.47 (m, 4H), 7.59-7.69 (m, 4H)

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 127.1, 127.2, 128.7, 141.2

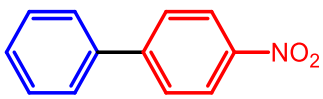
4-ethylphenylbenzene (3f)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 1.25 (t, 3H), 2.34 (q, 2H), 7.29 (d, 2H), 7.35 (d, 2H), 7.51 (d, 2H), 7.52 (d, 2H), 7.41 (t, 1H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 12.1, 21.3, 127.6, 127.8, 127.9, 129.2, 129.5, 137.8, 140.7

4-nitrophenylbenzene (3h)



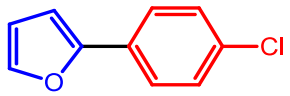
Yellow solid, yield: 60%.

NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.42-7.54 (m, 3H), 7.60-7.62 (d, 2H), 7.71-7.73 (d,

2H), 8.25-8.30 (d, 2H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 123.8, 127.1, 127.8, 128.9, 129.2, 138.5, 147.1, 147.4

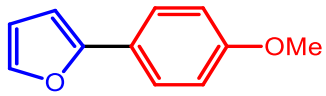
2-(4-chlorophenyl) furan (6a)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.62-7.59 (m, 2H), 7.48 (m,1H), 7.34-7.31 (m, 2H), 6.65 -6.64 (m, 1H), 6.49-6.48 (m,1H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 152.9, 142.3, 132.9, 129.3, 128.8, 125.0, 117.7, 105.4

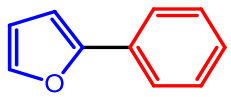
2-(4-methoxyphenyl) furan (6b)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.60 (d, 2H), 7.42 (s, 1H), 6.92 (d, 2H), 6.50 (d, 1H), 6.46-6.43 (m, 1H), 3.82 (s, 3H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 159, 154.3, 141.2, 125.2, 124, 114.1, 111.5, 103.3, 55.3.

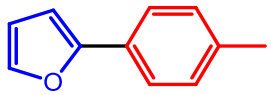
2-(phenyl) furan (6c)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm)7.70 (d, 2H), 7.49 (m, 1H), 7.41 (t, 2H), 7.30-7.25 (m, 1H), 6.69 (d, 1H), 6.50-6.48 (m, 1H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 154, 142, 131.2, 128.6, 127.3, 123.7, 111.5, 105.3.

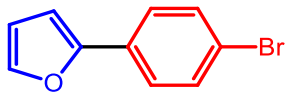
2-(4-methylphenyl) furan (6d)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.57 (d, 2H), 7.45 (d, 1H), 6.92 (d, 2H), 7.19 (d, 2H), 6.60 (d, 1H), 6.47-6.46 (m, 1H), 2.73 (s, 3H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 154.3, 141.6, 125.2, 137.1, 129.3, 128.2, 123.7, 111.5, 104.1, 21.2.

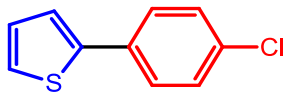
2-(4-bromophenyl) furan (6f)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm)7.55-7.47 (m, 5H), 6.65 (d, 1H), 6.48-6.47 (m, 1H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 152.9, 142.3, 131.7, 129.7, 125.2, 121.0, 111.7, 105.5.

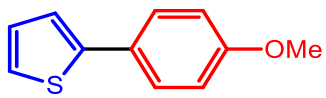
2-(4-chlorophenyl) thiophene (7a)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.55-7.53 (m, 2H), 7.36-7.34 (m, 2H), 7.30-7.29 (m, 2H), 7.07 (m, 1H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 143.3, 133.1, 132.9, 128.9, 128.1, 127.0, 125.7, 123.4

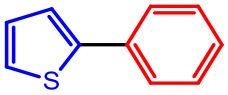
2-(4-methoxyphenyl) thiophene (7b)



NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.60 (d, 2H), 7.29-7.27 (m, 2H), 7.13-7.11 (m, 1H), 6.97 (d, 2H), 3.92 (s, 3H).

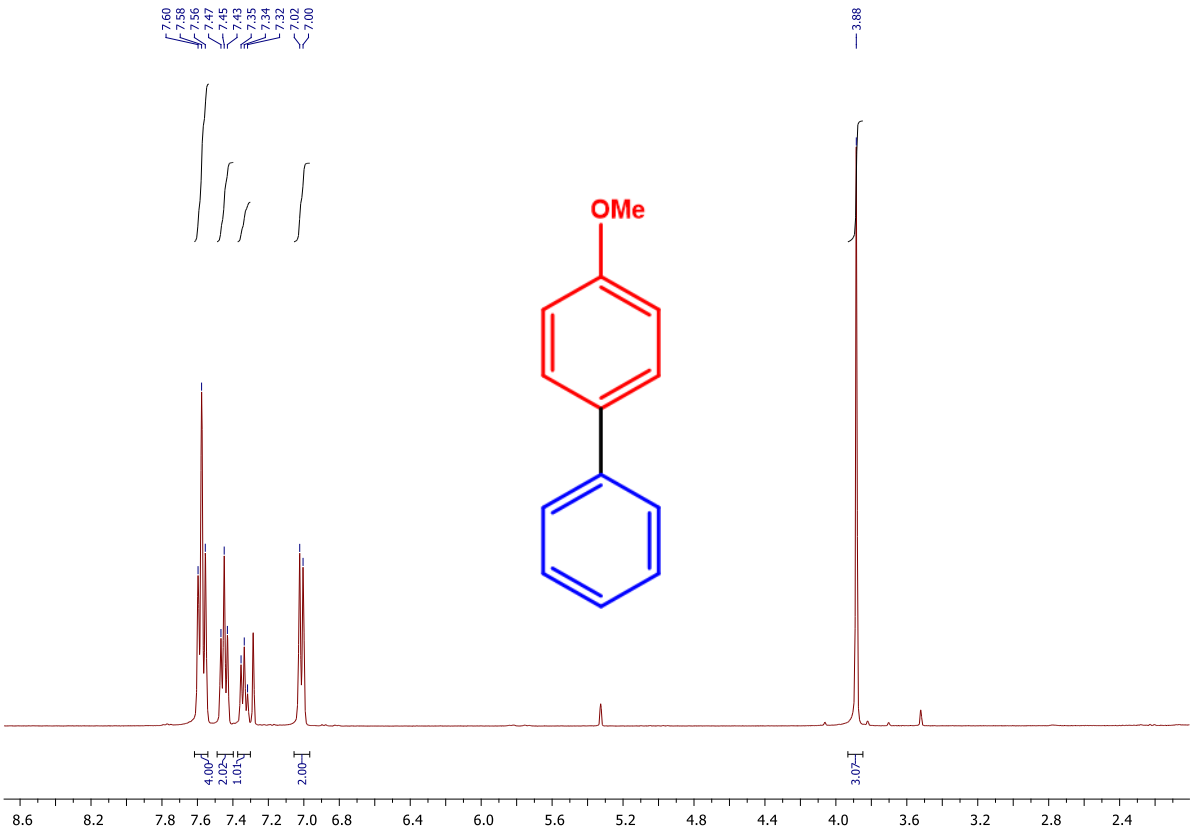
NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 159.1, 144.3, 127.9, 127.3, 127.2, 123.8, 122, 114.1, 114.5, 55.3.

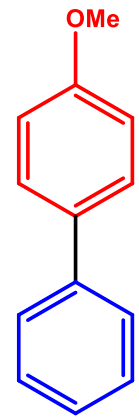
2-(phenyl) thiophene (6c)

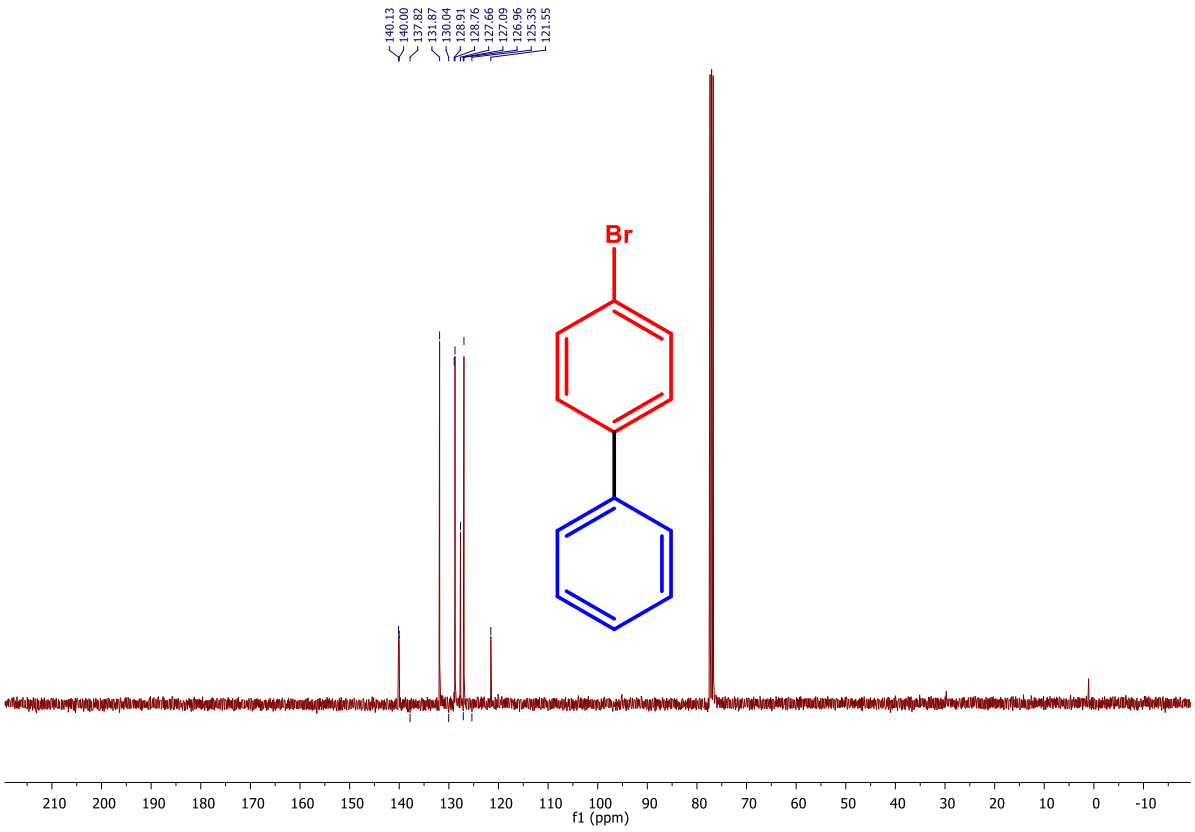


NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.66-7.60 (m, 2H), 7.42-7.38 (m, 2H), 7.30-7.26 (m, 2H), 7.28-7.27 (m, 1H), 7.12-7.09 (m, 1H).

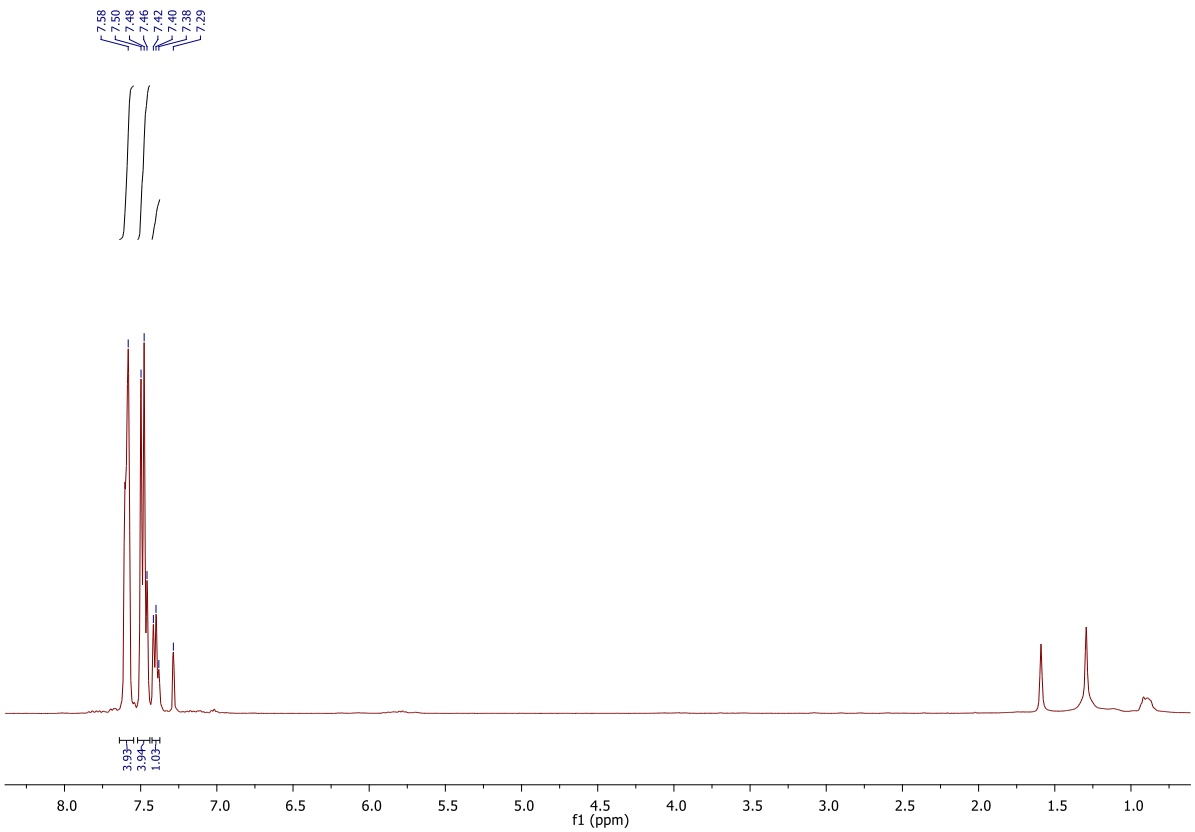
NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 144, 134.2, 128.8, 128, 127.4, 125.7, 124.5, 123.3.




OMe


140.13
140.00
137.82
131.87
130.04
128.91
128.76
127.66
127.09
126.96
125.35
121.55
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Br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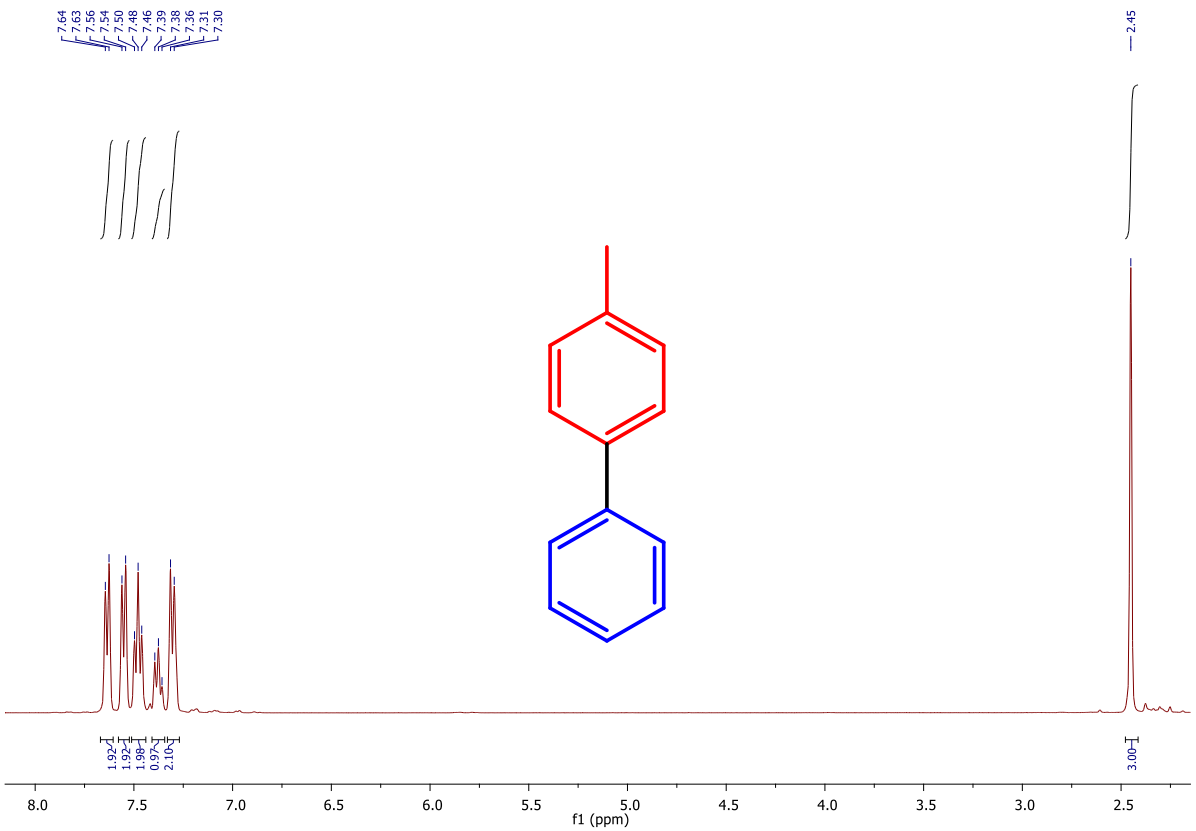
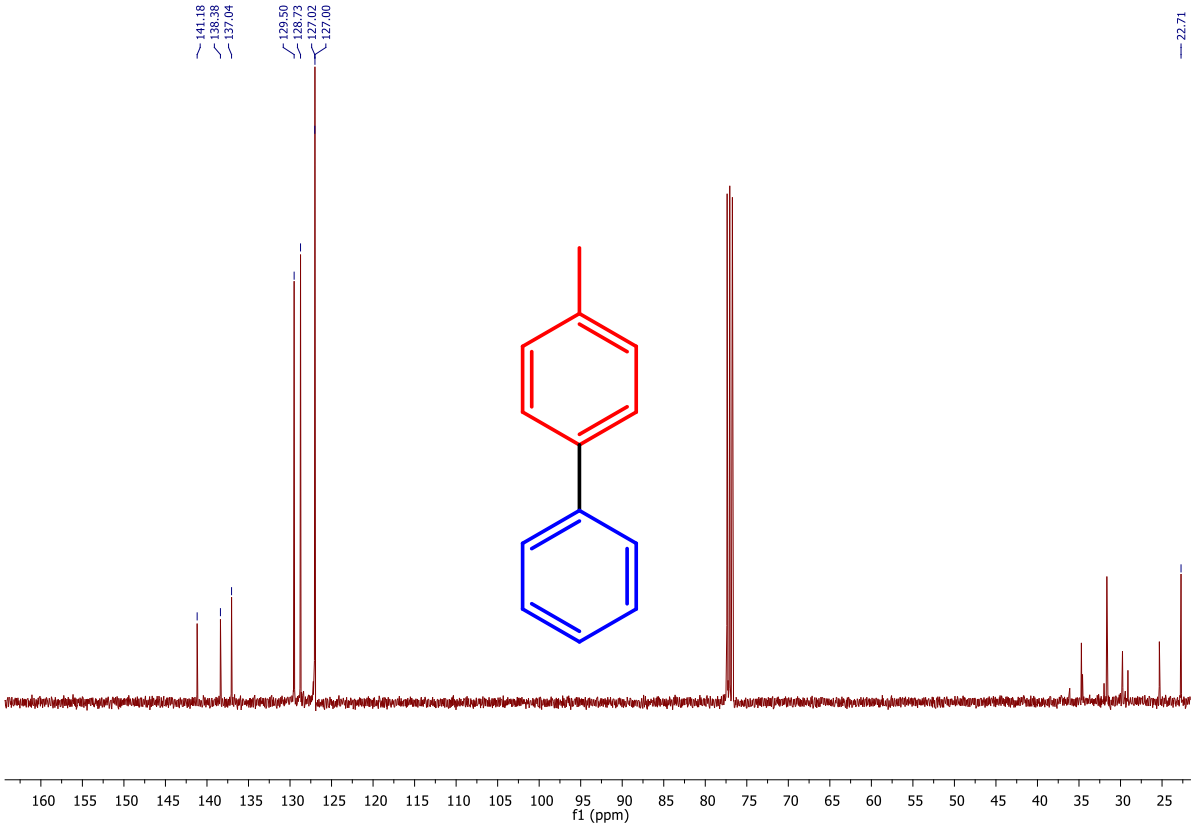
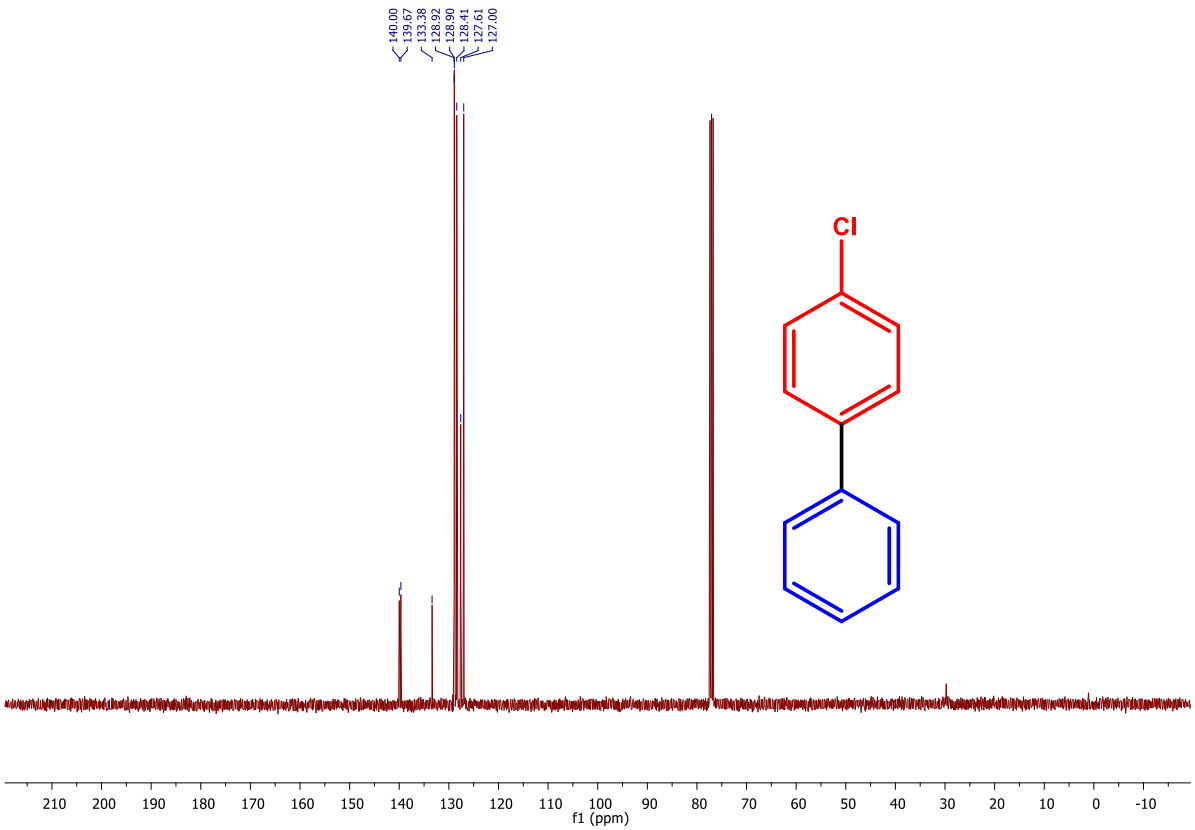
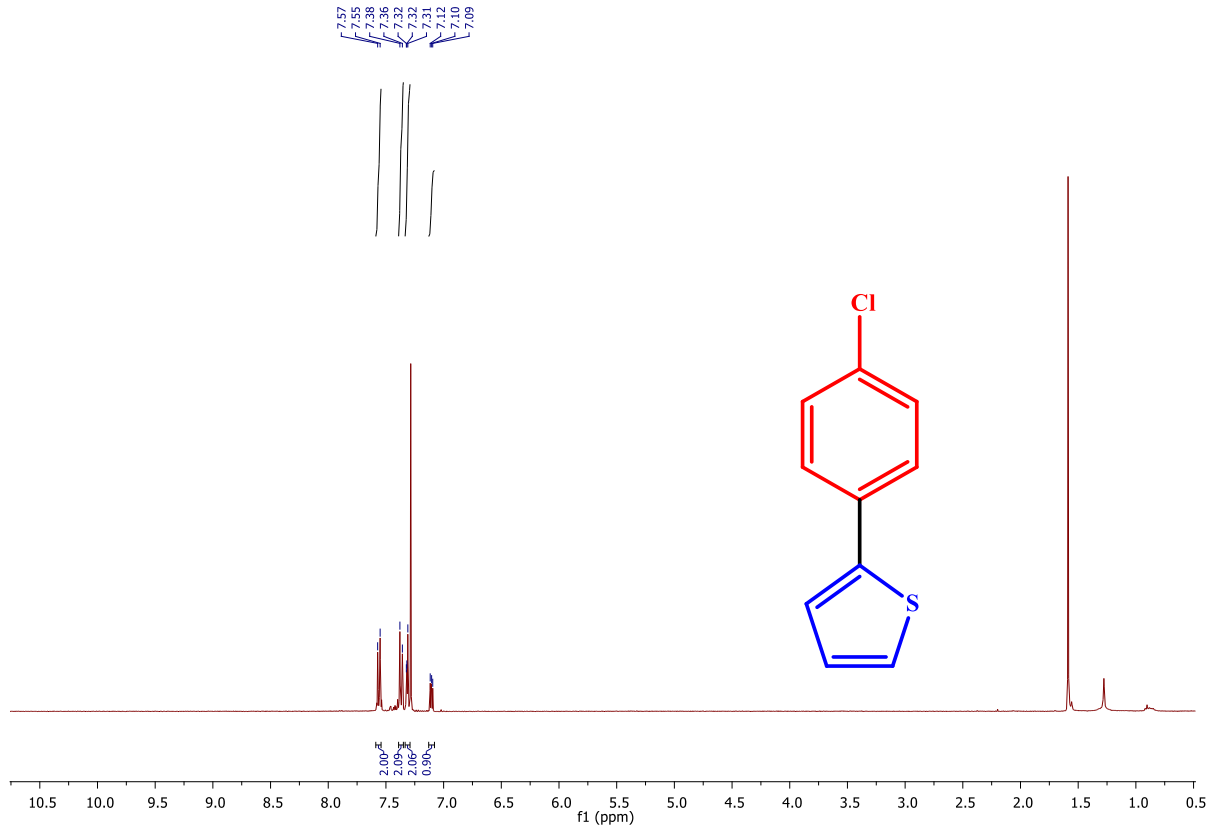
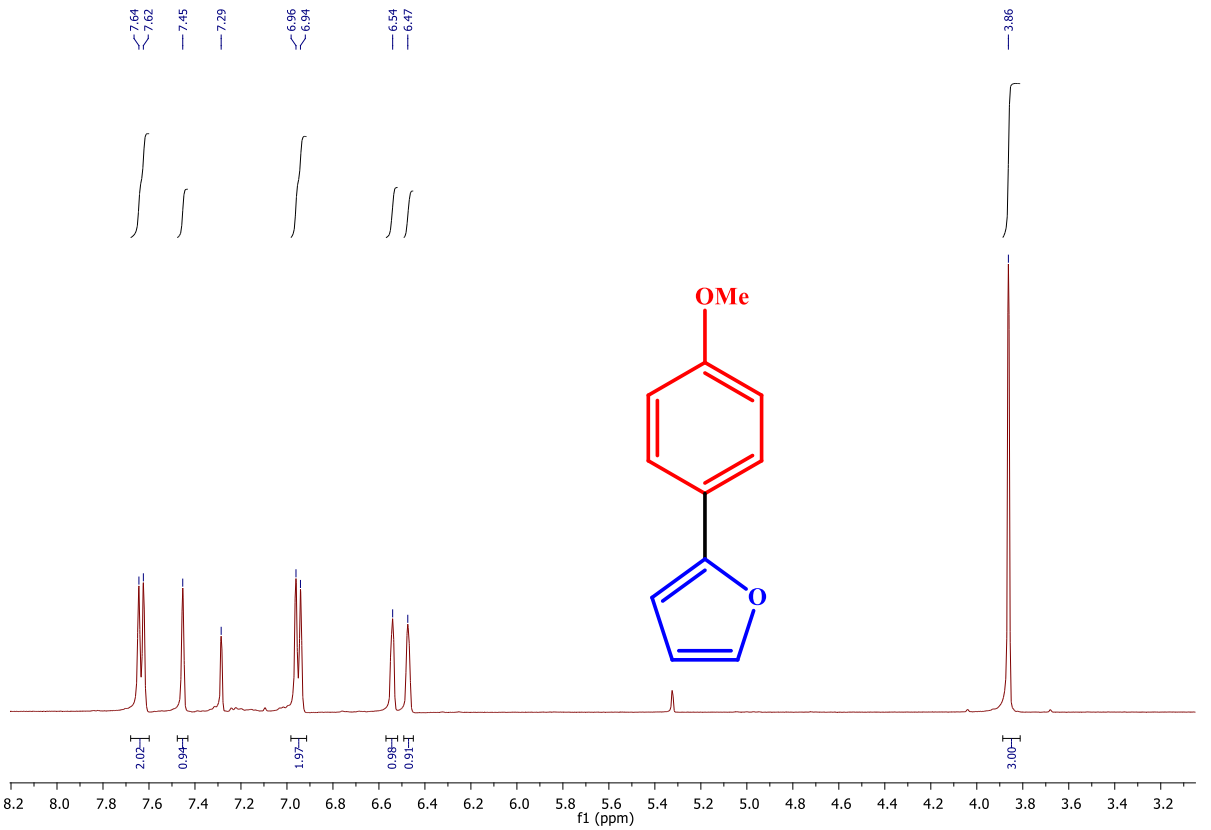
7.50
7.48
7.46
7.42
7.40
7.38
7.29
3.93
3.94
1.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


7.64
7.63
7.56
7.54
7.50
7.48
7.46
7.39
7.38
7.36
7.31
7.30
2.45
1.92
1.92
1.98
0.97
2.16
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)


141.18
138.38
137.04
129.50
128.73
127.02
127.00
22.71
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
f1 (ppm)


140.00
139.67
133.38
128.92
128.90
128.41
127.61
127.00
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.57
7.55
7.38
7.36
7.32
7.32
7.31
7.12
7.10
7.09
Cl
S
2.00
2.09
2.06
0.90
f1 (ppm)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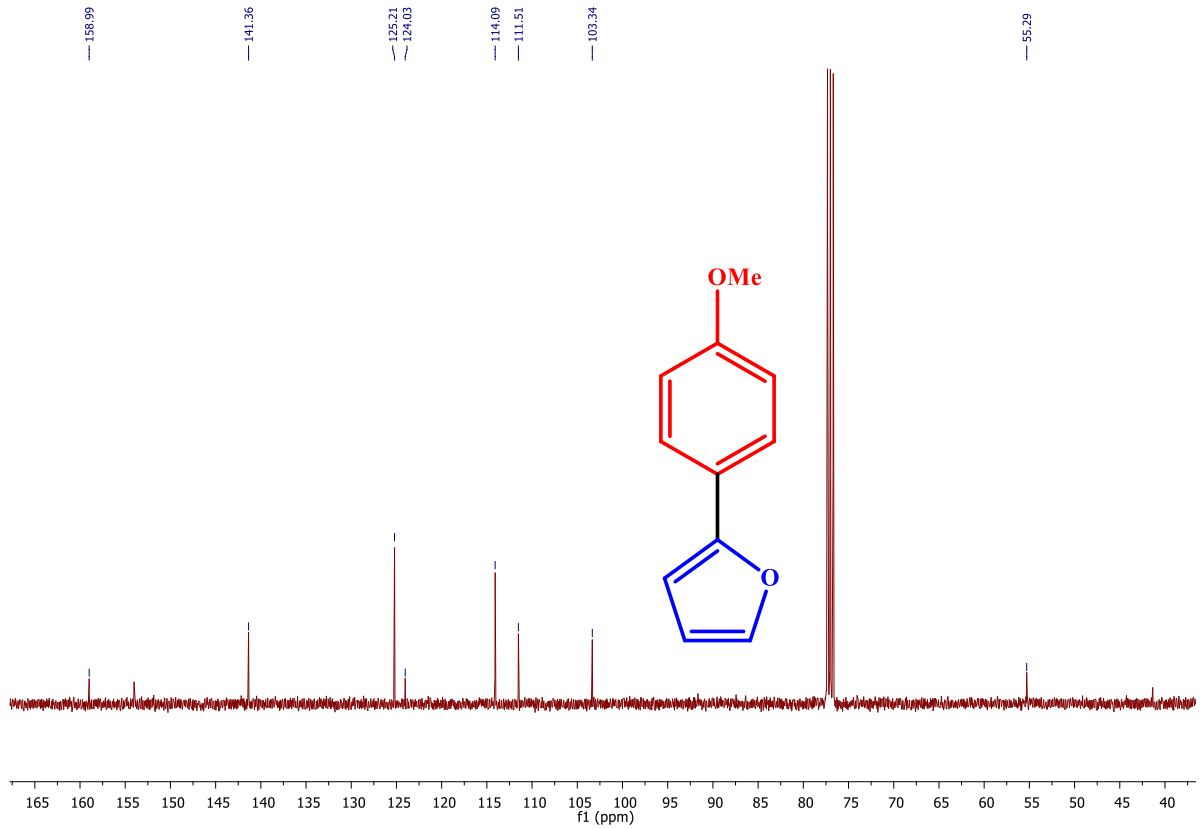
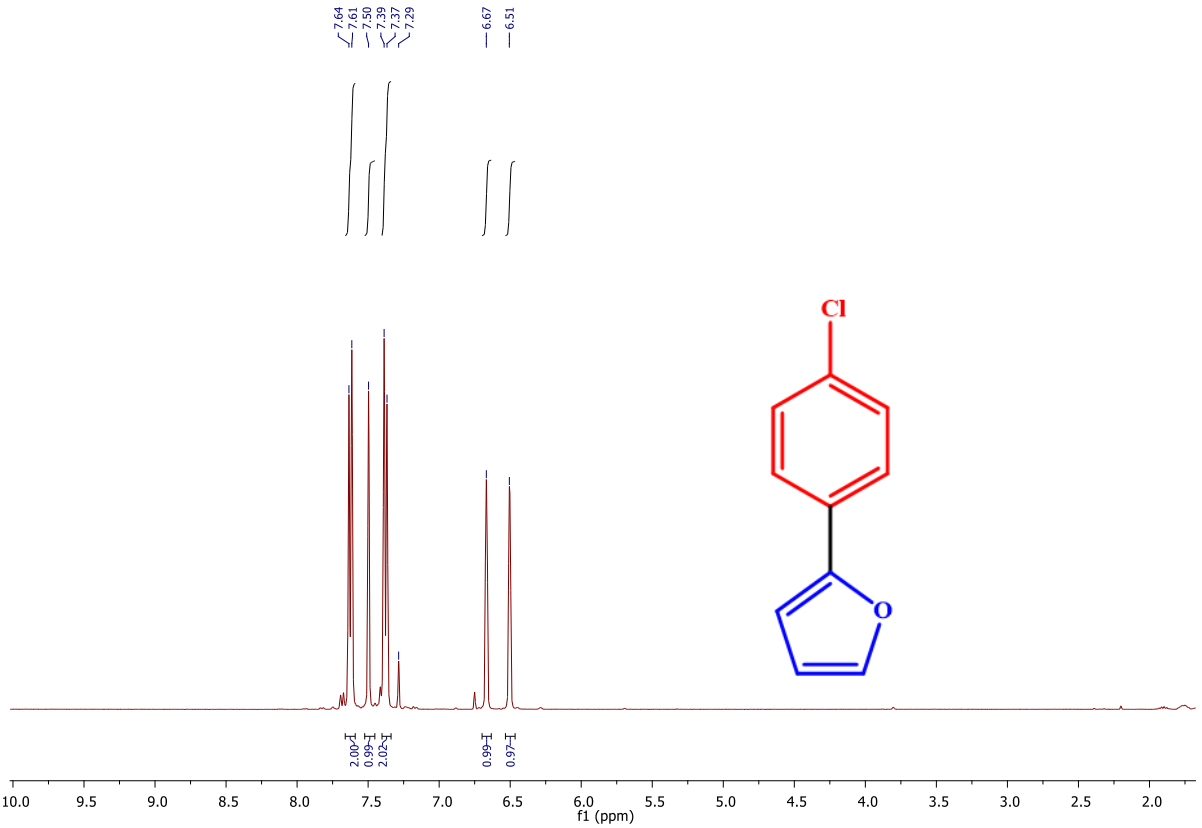
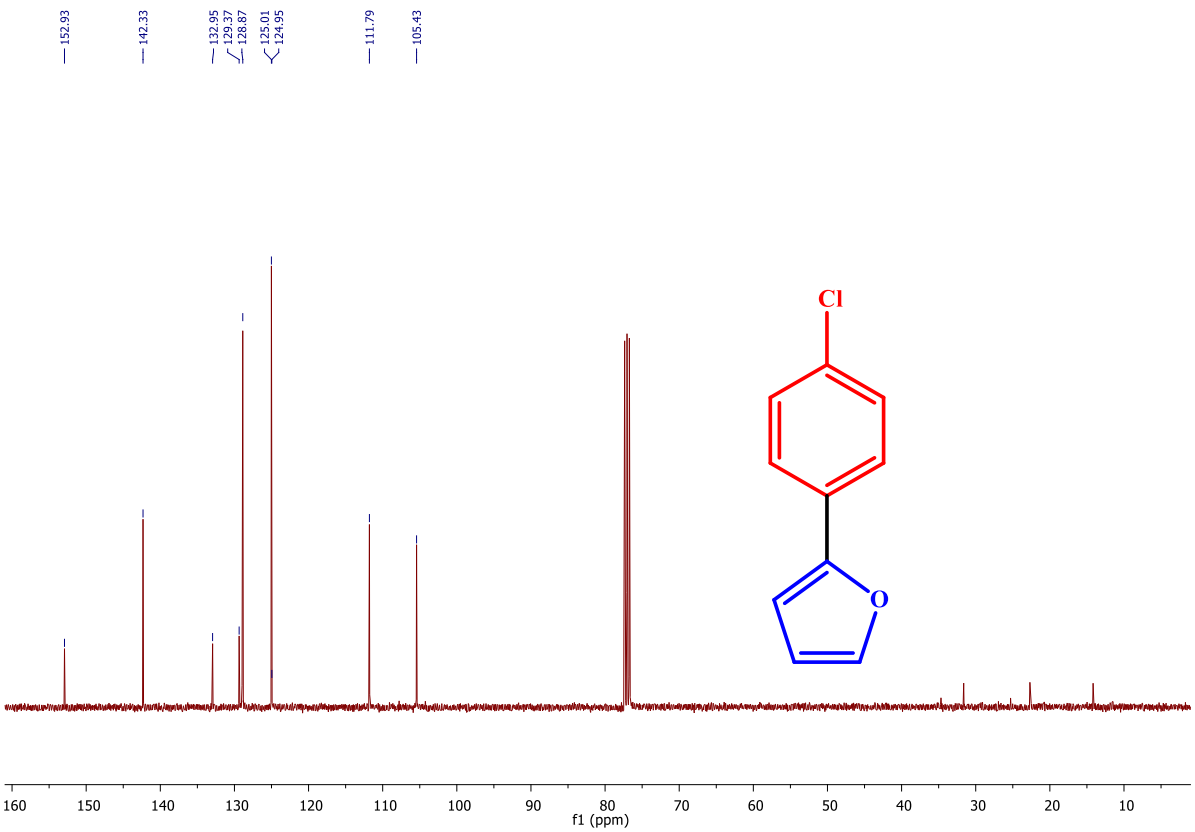
7.62
7.45
7.29
6.96
6.94
6.54
6.47
3.86
OMe
O
2.02
0.94
1.97
0.98
0.91
3.00
f1 (ppm)


158.99
141.36
125.21
124.03
114.09
111.51
103.34
55.29
OMe
O
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40
f1 (ppm)


7.64
7.61
7.50
7.39
7.37
7.29
6.67
6.51
Cl
O
2.00
0.99
2.02
0.99
0.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
f1 (ppm)


152.93
142.33
132.95
129.37
128.87
125.01
124.95
111.79
105.43
Cl
O
160
150
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130
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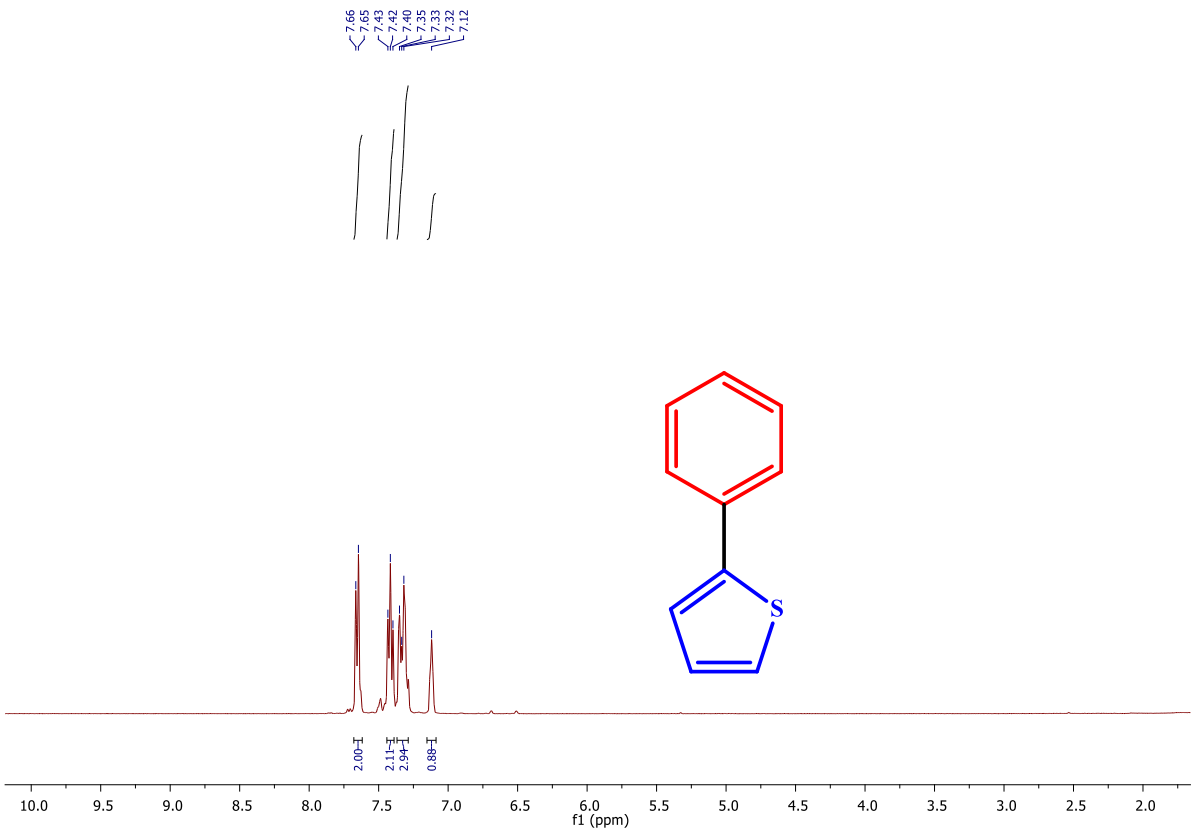
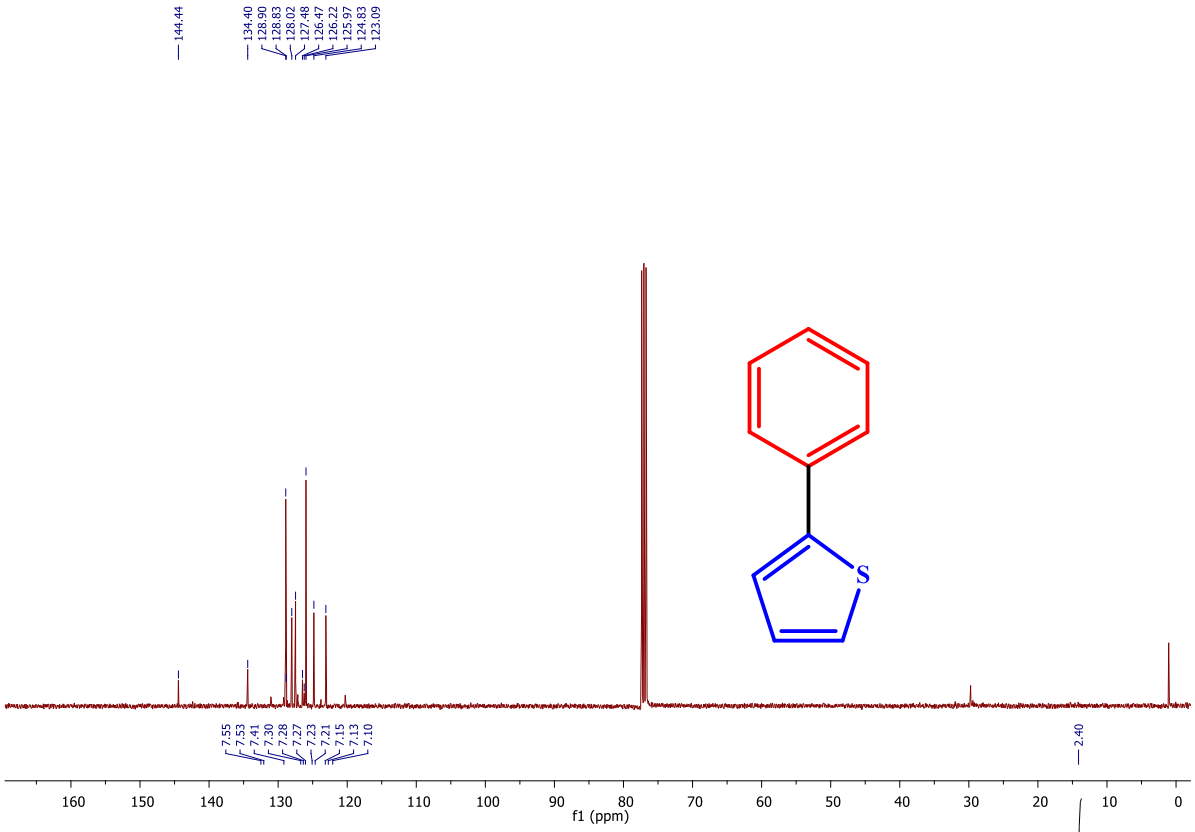
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.66
7.65
7.43
7.42
7.40
7.35
7.33
7.32
7.12
S
2.00
2.11
2.94
0.88
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)


144.44
134.40
128.90
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128.02
127.48
126.47
126.22
125.97
124.83
123.09
7.55
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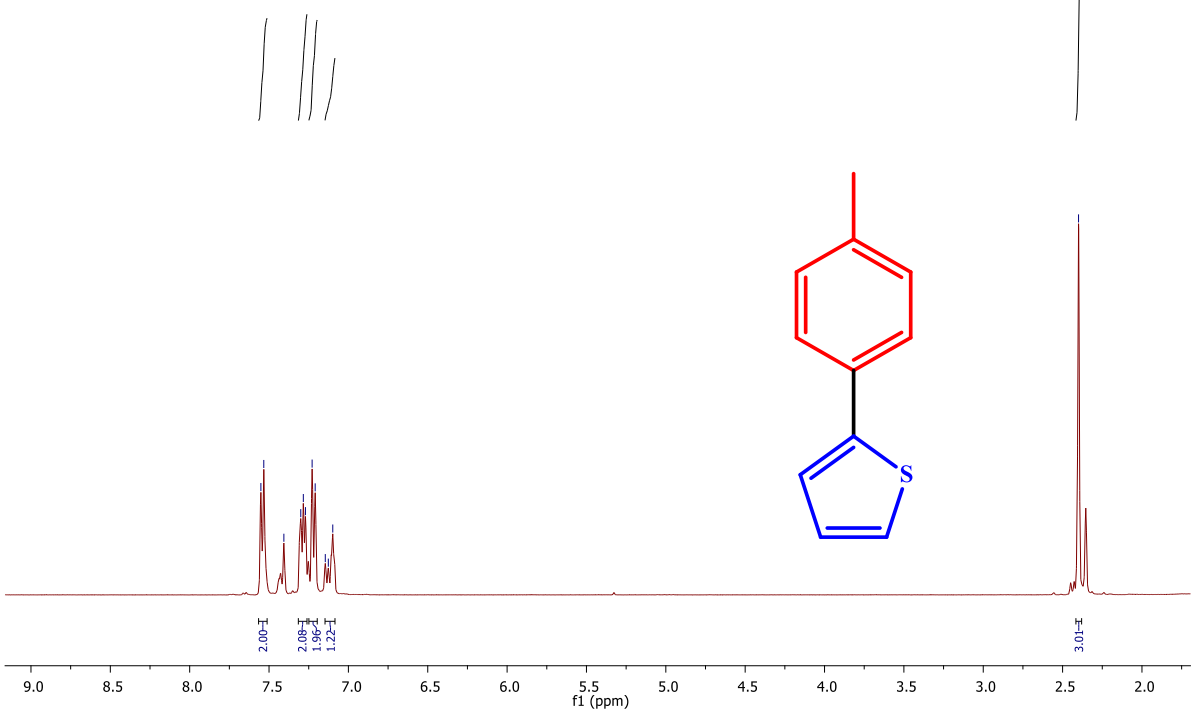
7.41
7.30
7.28
7.27
7.23
7.21
7.15
7.13
7.10
2.40
S
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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1.22
3.01
S
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8.5
8.0
7.5
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4.5
4.0
3.5
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2.0
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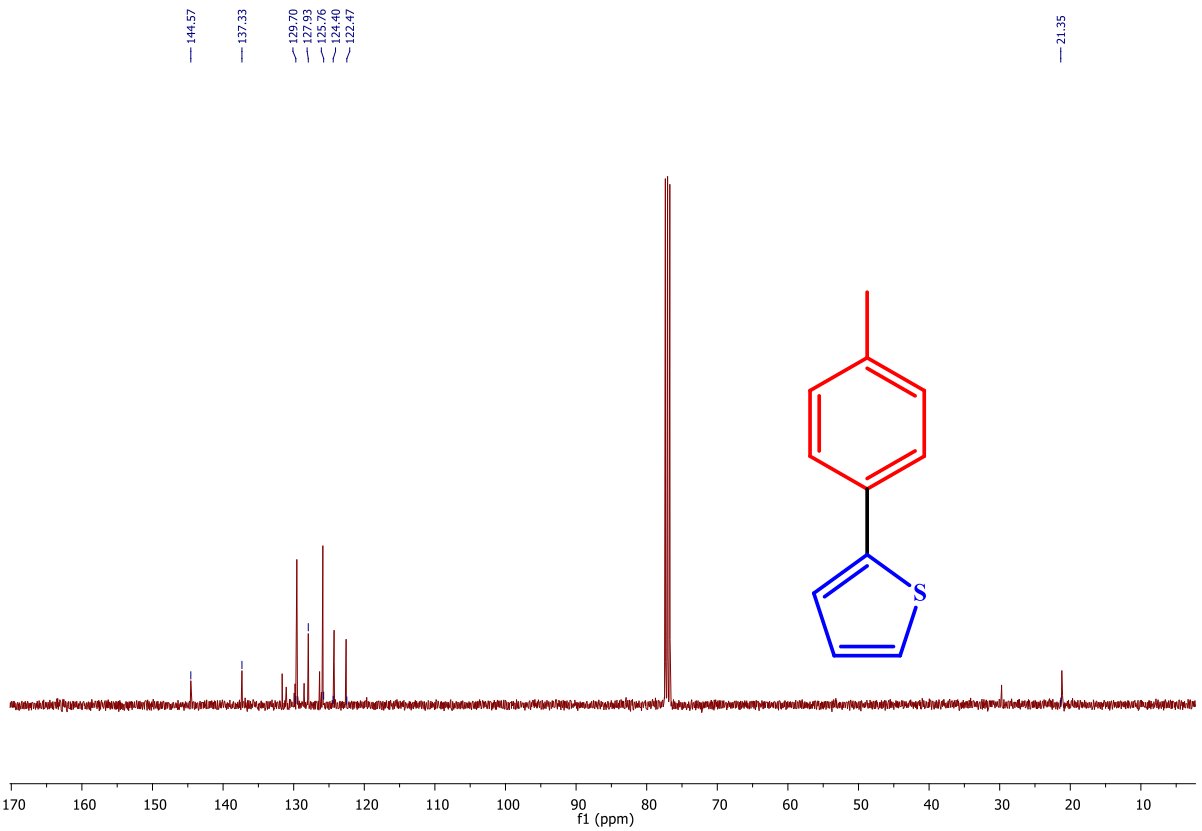
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122.47
21.35
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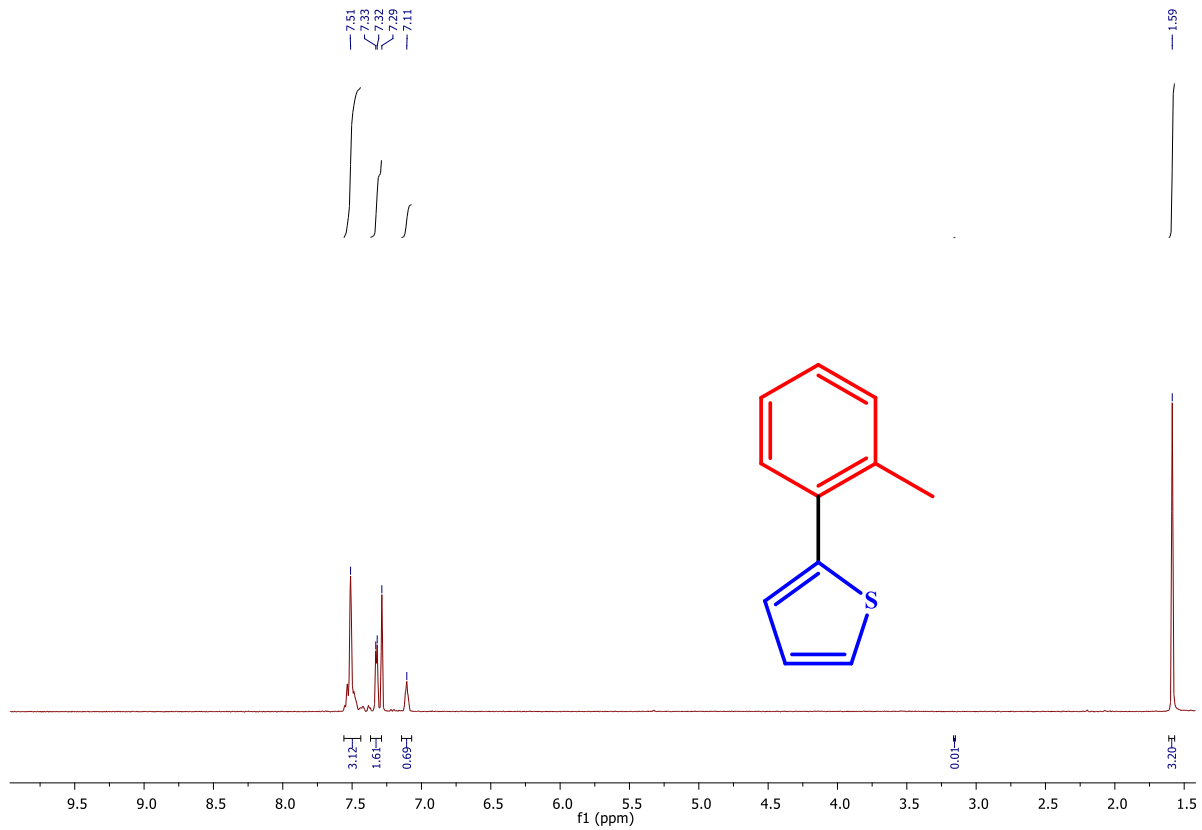
f1 (ppm)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0.01
3.20
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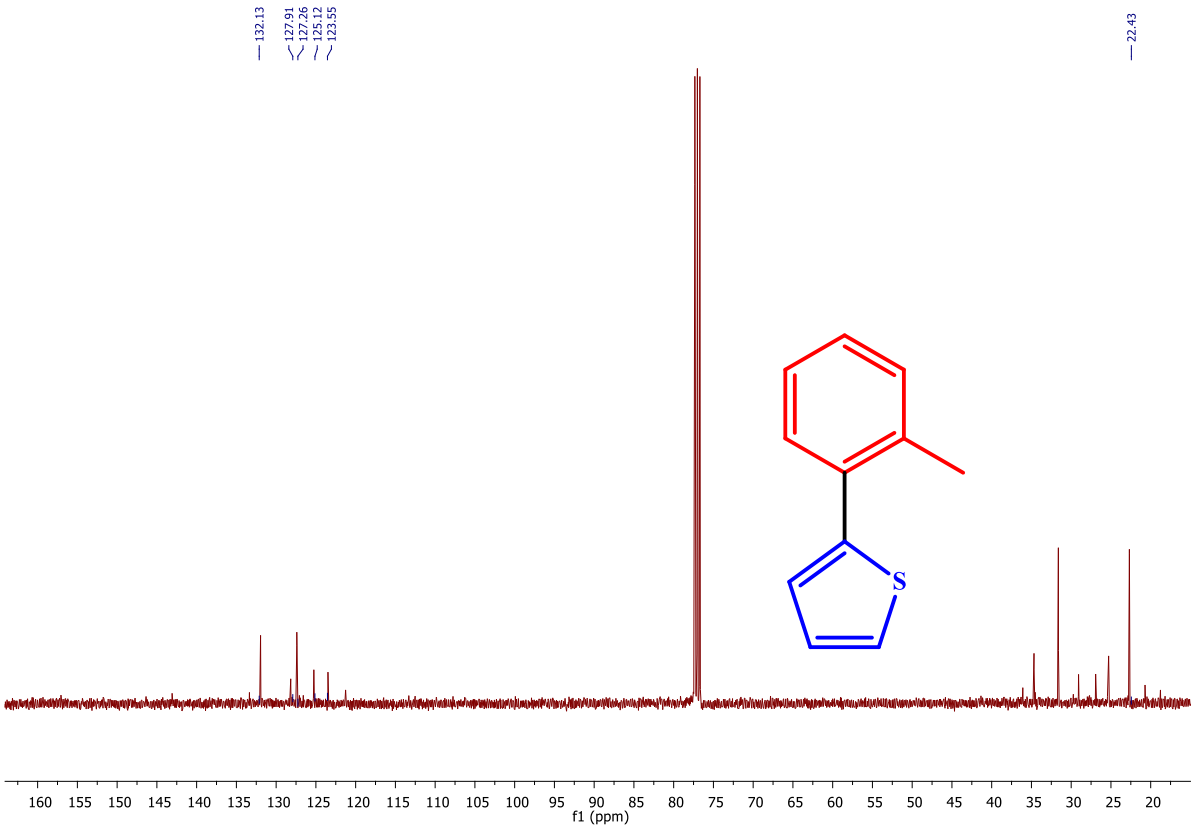
f1 (ppm)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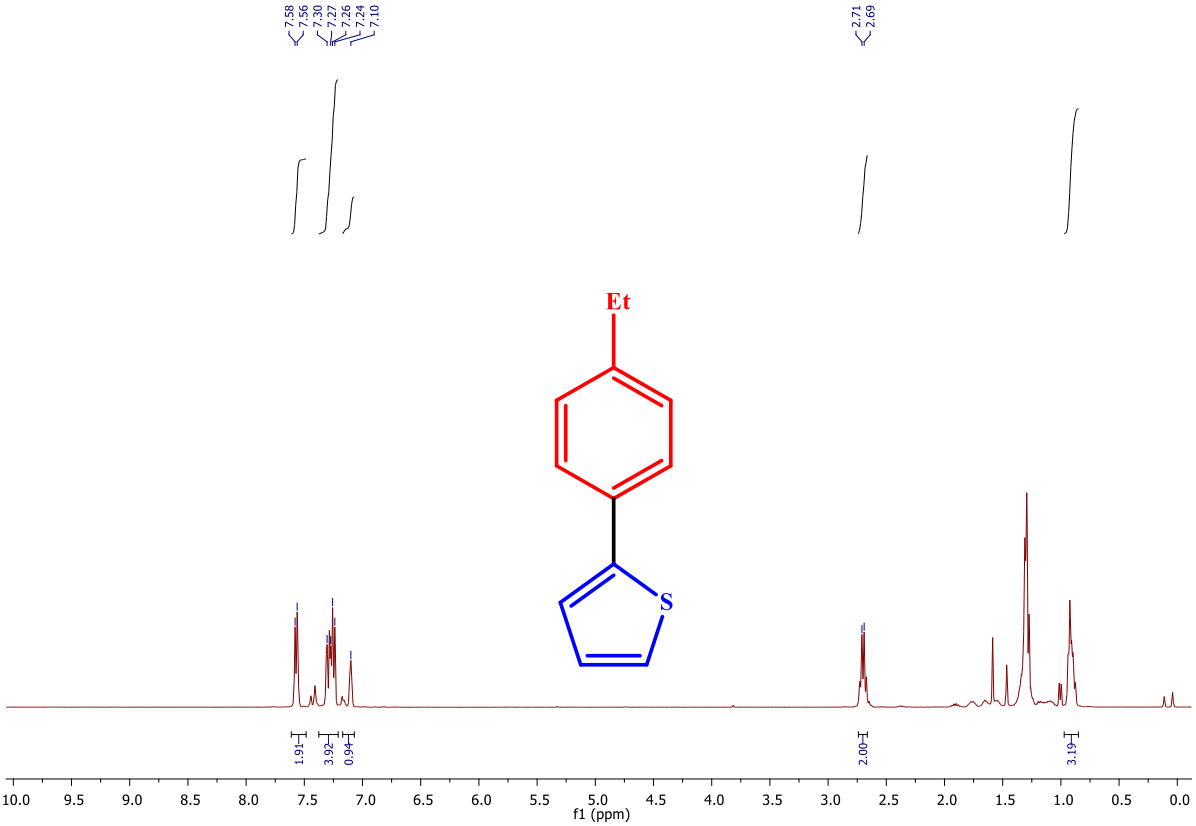
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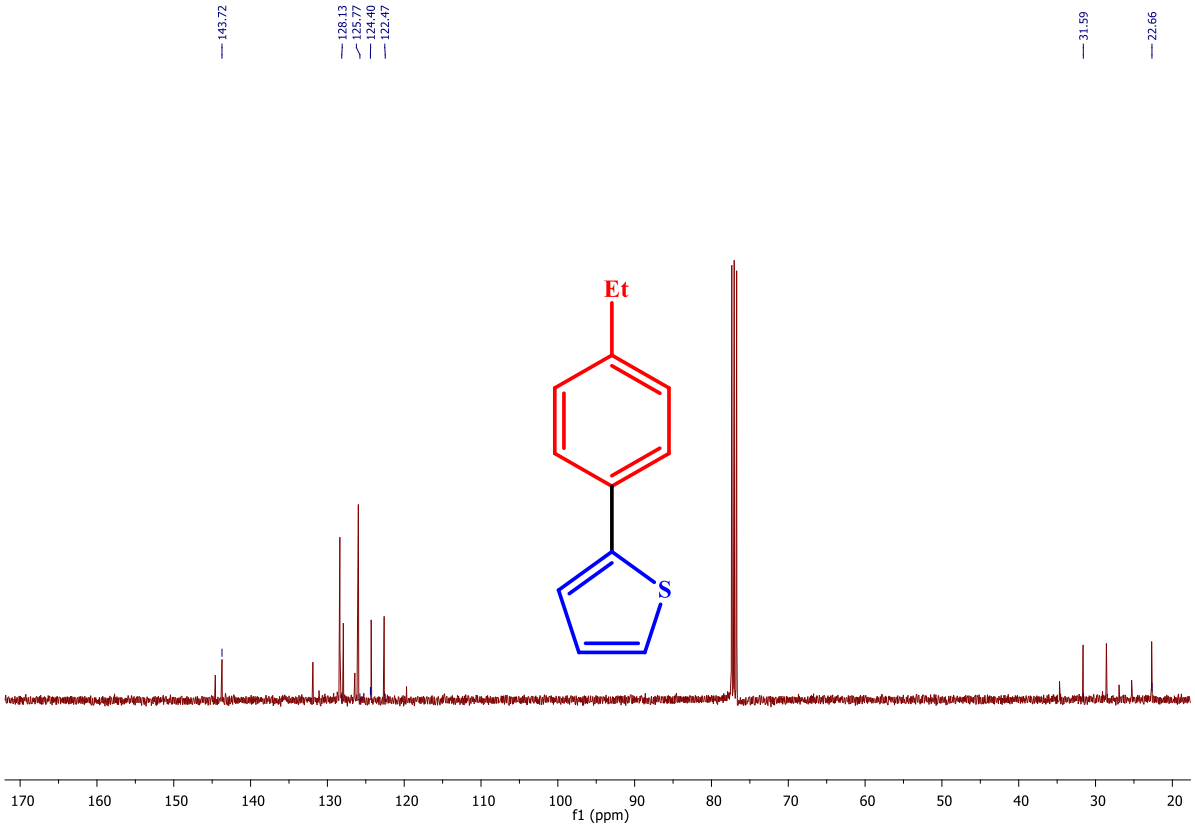
2.00
3.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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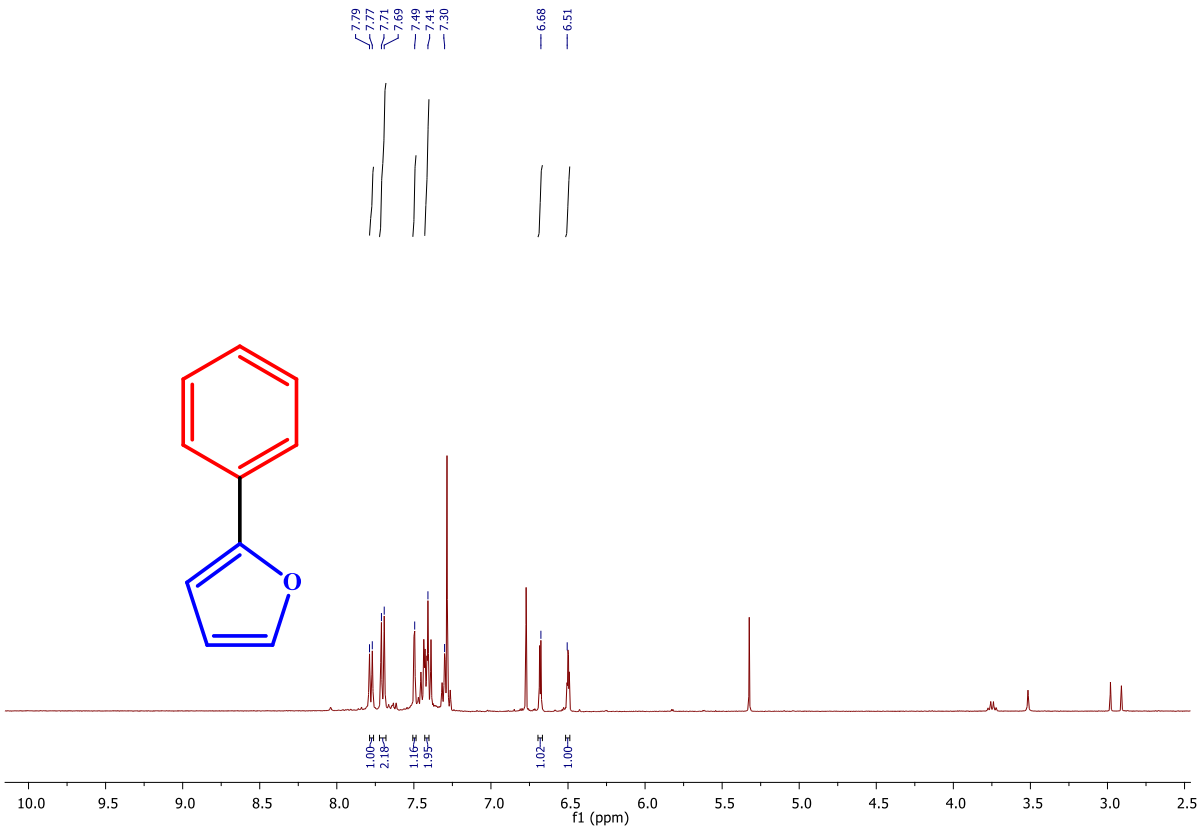
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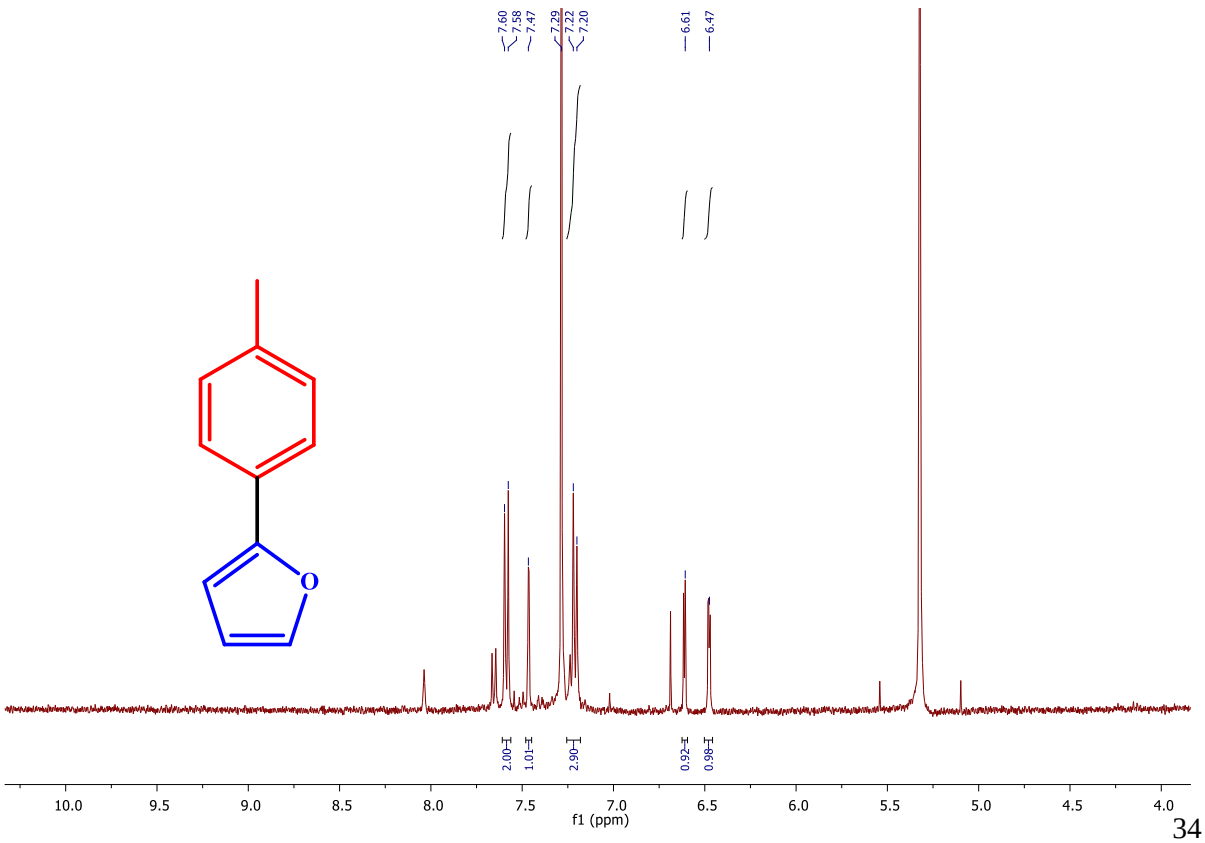
f1 (ppm)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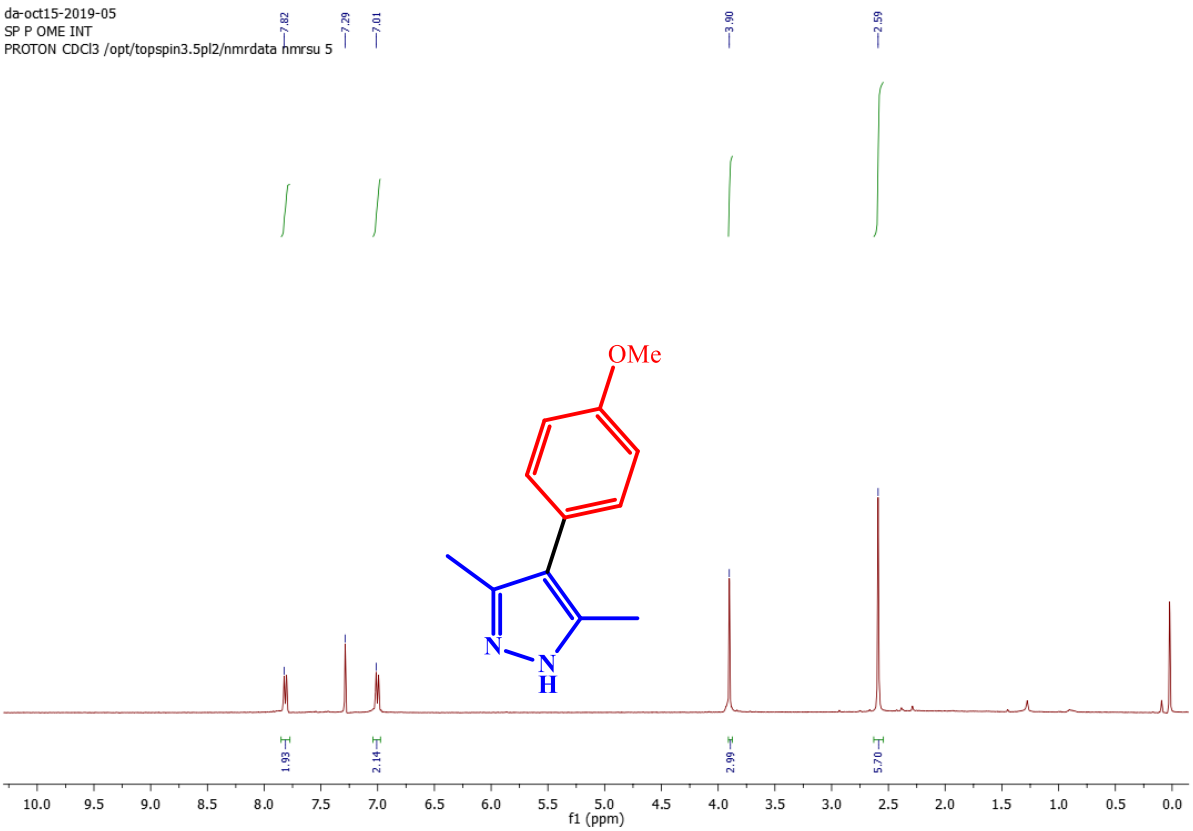
5.0
4.5
4.0
f1 (ppm)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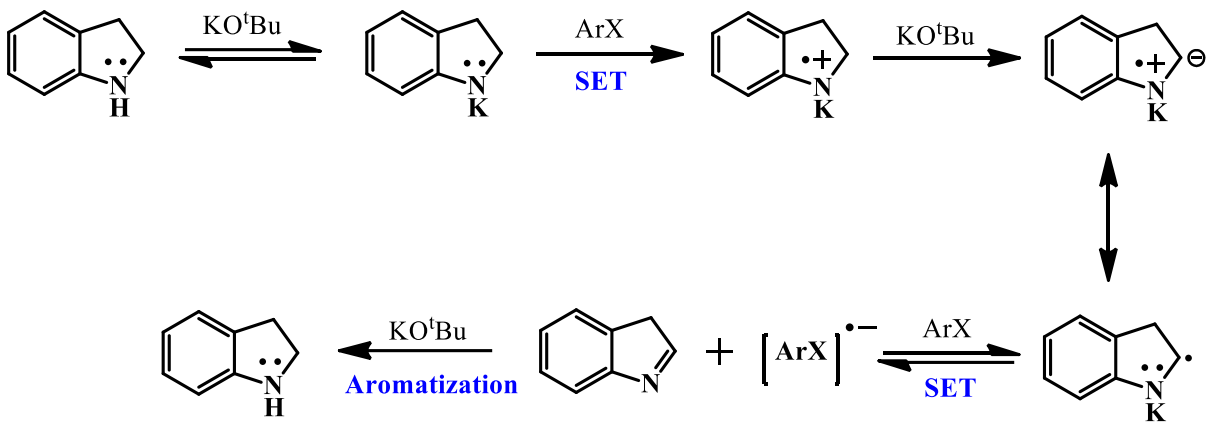
5.70
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

Chapter 2

2.1 Introduction

We know that transition metal catalysed C-X bond activation, recently C-X bond activation via small organic molecules shows hugh potential. Several of these organic molecules, such as 1,2-diamines, 1,10-phenanthrolines, 1,2-diols and N-methylanilines showed the ability to activate C-X bond in presence of a base, resulting an aryl radical intermediate that undergoes substitution reactions via BHAS mechanism. In 2018, Jiao *et al*[13] reported that aromatization of indoline plays a significant role in the activation of C-X bond, and also trace amount of oxygen also an important factor to initiate the activation processes. They also proposed an indoline promoted BHAS reaction for the initiation of the R-X bond (**Scheme 11**).

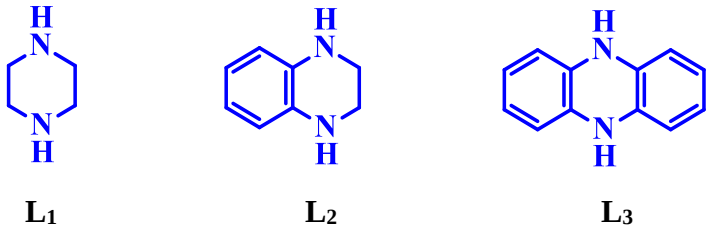


Scheme 11: direct C-H activation of arene by Jiao *et al*[13]

Firstly, KO^{t}Bu deprotonates indoline to its potassium salt. This anion either can transfer an electron to the Ar-X bond or to the oxygen molecule. Then another equiv. of base deprotonates a proton adjacent to the nitrogen atom and gives a resonating structure of a radical anion. Now, that anion transfer an electron to Ar-X bond and convert to 3-hydro indoline. It was experimentally proved that the second electron transfer was more effective than the first one. Finally, 3-hydro indoline was aromatize to indoline in presence of the KO^{t}Bu. As only one report on aromatization driven metal free cross-coupling reaction, comparative study on how aromaticity is the driving force for C-H activation of arene is highly desirable.

2.2 Optimization and substrate scope

We have taken piperazine (**L1**), 1,2,3,4 tetrahydro quinoxoline (**L2**) and 5,10-dihydrophenazine (**L3**) as additives for cross-coupling reaction for biaryl synthesis (**scheme 12**).



L1 **L2** **L3**

Scheme 12: Screening of additives.

As the number of benzene ring increases from **L1** to **L3**, we expected that the reactivity will also increase due to the aromaticity. Although the additive **L1** is commercially available, we have synthesized **L2** and **L3** according to the reported procedure[14]. For initial screening we used the additive **L3** 10 mol% with 4-chloro benzene diazonium tetrafluoroborate in presence of 2 equiv. of potassium tert butoxide with benzene as a coupling partner. We got promising 70% yield of 4-chloro biphenyl as a coupling product. After optimizing we found 80% of the product formation with 20 mol% of the additive loading. Under this optimizing condition using **L1** and **L2** as additives resulted respectively 40% and 60% of the desire product formation using 4-chloro benzene diazonium tetrafluoroborate (**figure 10**).

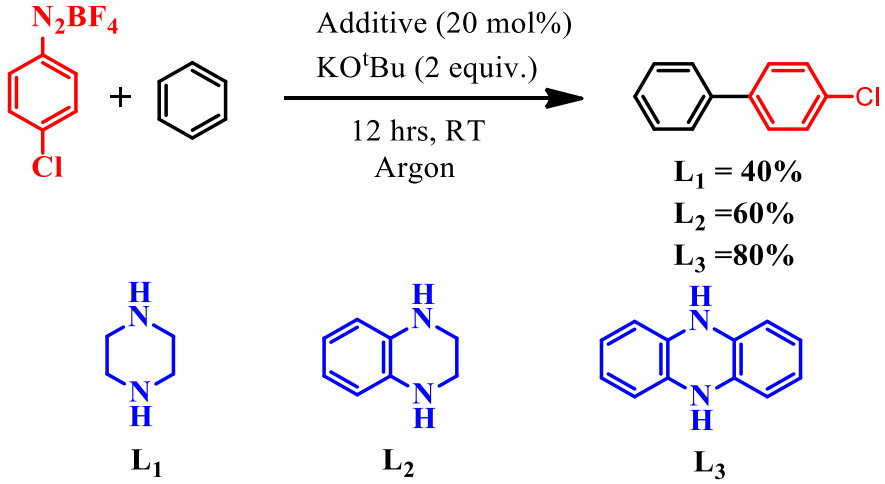
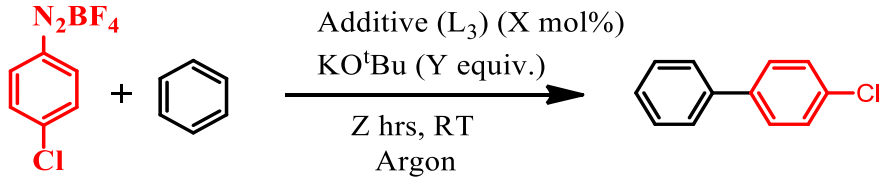


Figure 10: performance of 3 different additives using 4-chloro benzene diazonium tetrafluoroborate as a substrate.

After getting decent initial result, we optimized our reaction conditions by varying additive loading, equiv. of base and time of the reaction. Finally, it gives best results using 20 mol% of the promoter and 2 equiv. of KO^{t}Bu under Argon atmosphere at room temperature with 12 hours of the reaction time (**table 2**).



Entry No.	Additive Loading (X mol %)	Base (Y equiv.)	Time (Z hrs)	Temperature (^{0}C)	Product (Yield %)
1	5	2	12	RT	55
2	7.5	2	12	RT	65
3	10	2	12	RT	70
4	20	2	12	RT	80
5	20	1	12	RT	30
6	20	2	6	RT	50
7	20	2	12	80	75

Table 2: Optimization table

Under the optimized condition the reaction of 4-methoxy benzene diazonium tetrafluoroborate

with benzene as a coupling partner using **L_1**, **L_2** and **L_3** as additives resulting the expected product 4-methoxy biphenyl respectively 40%, 58% and 75% (**figure 11)**. The above results confirms that aromaticity in the additive is the driving force for the reactions and the yield increases with the extent of aromaticity increases in the additives.

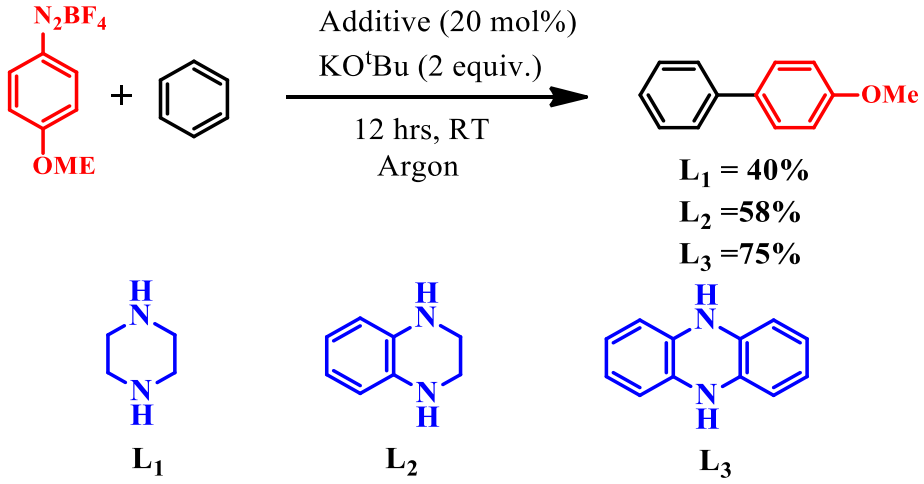
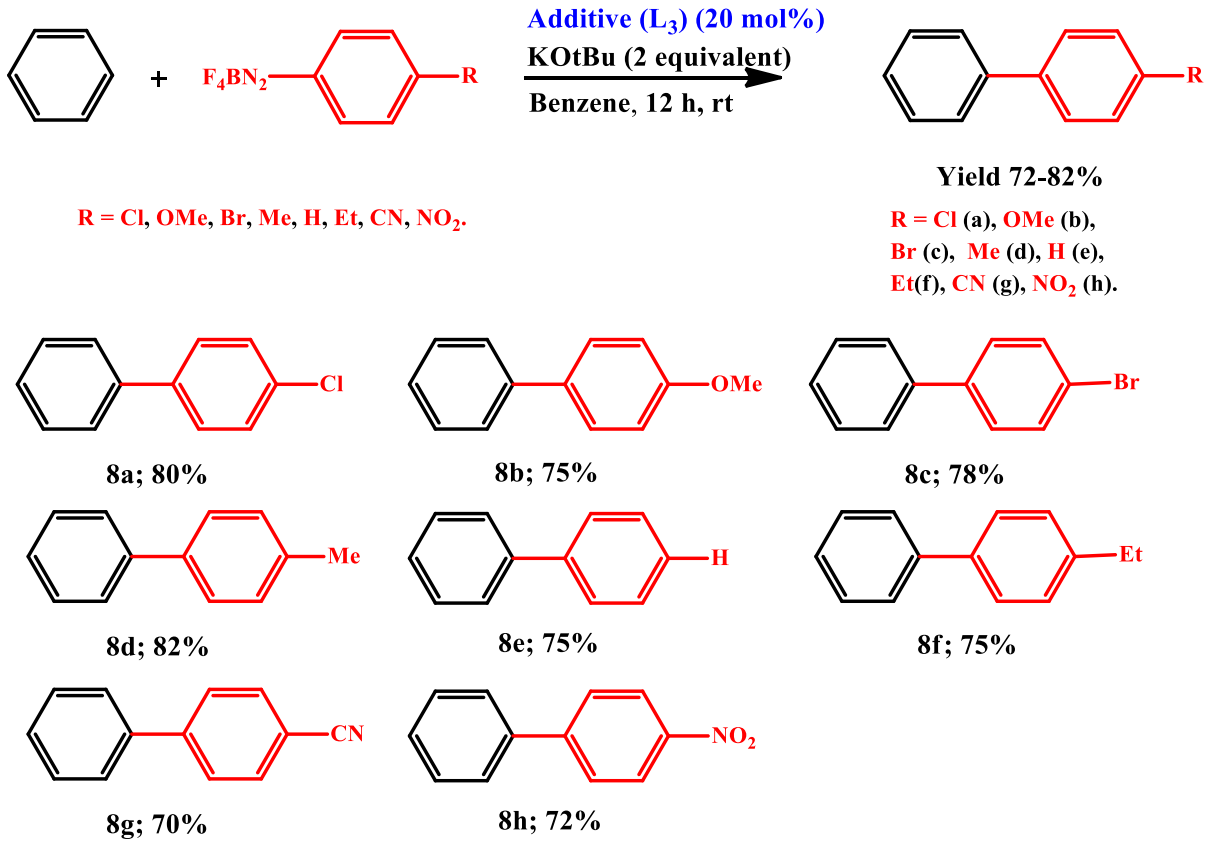


Figure 11: performance of 3 different additives using 4-methoxy benzene diazonium tetrafluoroborate as a substrate.

With the above optimizing conditions we have expanded our substrate scope using various benzene diazonium salts. The arylation of benzene was carried out with eight different benzene diazonium salts using metal free catalytic conditions that resulted in excellent yields 72%-82% of corresponding biarylated products (8a-8h, **scheme 13**). Several electron donating group on the para substituted benzene diazonium salt such as methoxy, methyl and ethyl gives excellent yield. In case of electron withdrawing groups (nitro, cyano) on benzene diazonium salt we got good yields, although it was little less than the electron rich substrates.

After that we moved to some sterically challenged substrates using L_3 as an additive under the optimized reaction condition resulted moderate to good yields. Then we moved to some hetero cycle such as furan and thiophene as coupling partner, that also gives moderate yield of the hetero-arylated product.



Scheme 13: substrates scope of several diazonium salts using benzene as a coupling partner.

2.3 mechanistic investigation

After some controlled experiments and previous reports we came up with the probable initiation followed by famous BHAS mechanism (**figure 12)**. First, potassium tert butoxide deprotonates 5,6-dihydrophenazine to its potassium salt. Then it transfer an electron to the Ar-X bond forming benzene diazonium radical anion and itself converted to a radical. After that another equiv. of KO^{t}Bu takes care of second proton resulting radical anion which resonances to give another structure. According to studer and curran this radical anion effectively participates in single electron transfer to the Ar-X bond to form aryl radical that was the active species for the desired coupling product and the additive becomes aromatic.

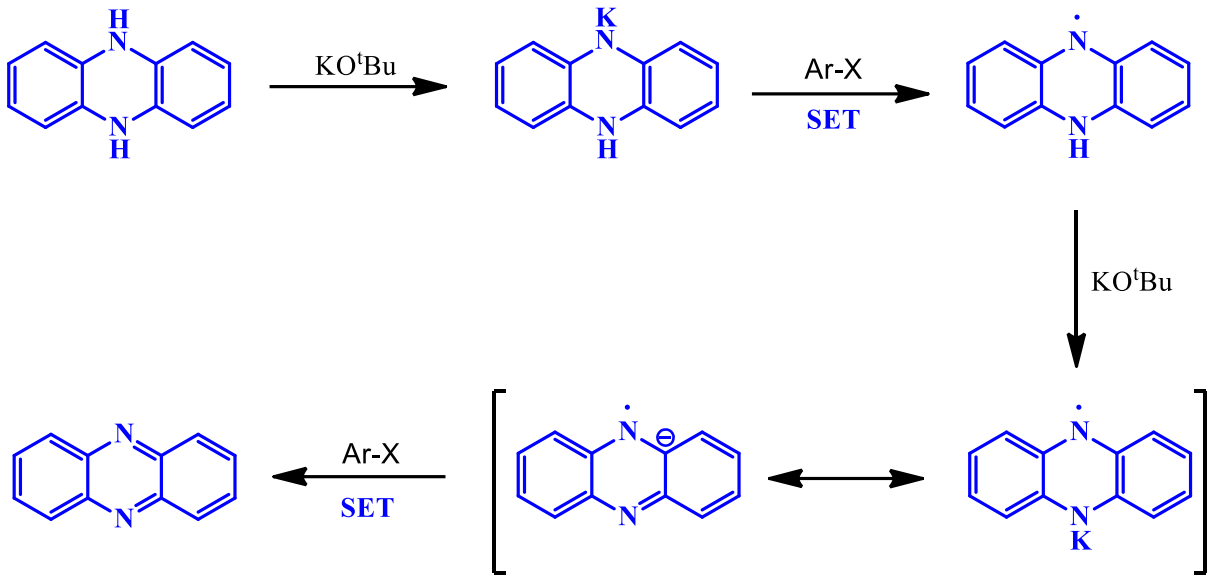


Figure 12: possible initiation of 5,6-dihydrophenazine

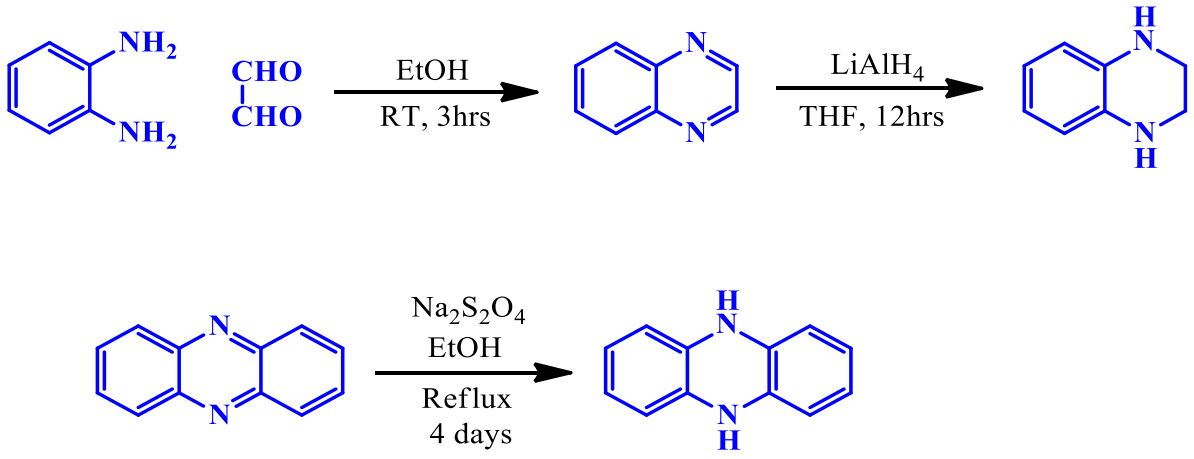
2.4 conclusion

In this work we have shown the activity of additive/KO^{t}Bu systems for C-X bond arylation in BHAS mechanism. In this case aromatization of the produced intermediate plays a important role to control the electron transfer processes. This is the second time aromatization energy is utilized to increase the activity of the small molecule additives. This idea can be used to control the electron transfer processes therein.

2.5 Experimental Section

Common experimental Information: Reactions were done in overnight dried schlenk flask using argon atmosphere. Most of the chemicals were commercially available and used directly without purification, unless otherwise mentioned. Column chromatography was executed by silica gel 60 (100-200 mesh) using ethyl acetate/hexane mixture and DCM/hexane mixture. NMR spectra were recorded on a Bruker 400 MHz spectrometer with deuterated chloroform ($CDCl_3$) with tetrametyhlsilane (TMS) as an internal standard. Solvents were evaporated using a rotary evaporator.

Synthesis of tetrahydro quinoxiline (L_2): This additive was synthesized according to the reported procedure[14]. Ortho phenyl diamine (1 equiv.) was dissolved in ethanol solution, then dropwise glyoxal (2.2 equiv.) was added to the solution with room temperature stirring condition. When the reaction was completed checked by TLC, the solution was concentrated using rotary evaporator. We purified the cyclic imine by column chromatography using 25% EtOAc/hexane mixture to get yellow liquid. Then we transferred the liquid to a schlenk flask containing dry THF and $LiAlH_4$ (2.2 equiv.) was added the flask in argon atmosphere at 0^oC. The reaction was completed after 12 hrs room temperature stirring checked by TLC. Then EtOAc was added to the mixture and extracted with water. Then the solution was concentrated in rotary evaporator to get brown colored desired product (**scheme 14**).



Scheme 14: synthesis of L_2 and L_3

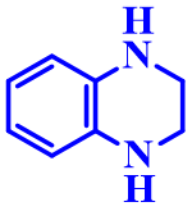
Synthesis of 5,6-dihydro phenazine (L_3): The promoter was synthesized according to the reported procedure[14]. One equiv. of phenazine was dissolved in ethanol solution, then disodium tetra thionate ($Na_2S_2O_4$) (4 equiv.) were added to the reaction mixture and it was refluxed for four days. When the reaction was completed, light green precipitate was found on the edge the flask. After it was comes to room temperature, excess distilled water was added to reaction mixture. Then the light green colored compound was collected through filtration. Finally, after drying it was directly used without purification (**scheme 14**).

General procedure for the synthesis of substituted benzene diazonium tetrafluoroborate: Substitited diazonium salts were prepared according to the reported literature[10].

General procedure for the synthesis of biaryl: In a schlenk flask aryl diazonium salt (0.5 mmol), KO^tBu (2 mmol) and Additive (20 mol%) were dried for 30 mins in a well-equipped schlenk line. After that arene (10 mmol) was added drop by drop to the reaction mixture at argon atmosphere. The reaction mixture was stirred for 12 hours under an argon atmosphere at room temperature. When the reaction was completed, DCM was added to mixture and extracted. Then the resulting solution was dried over Mg_2SO_4, filtered and concentrated under the reduced pressure. Purification was executed by flash column chromatography with ethyl acetate/hexane mixture to get desired products.

2.6 spectroscopic data

Tetra hydroquinoline (L_2)

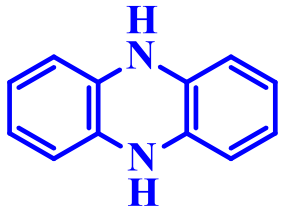


Brown solid, yield 70%.

NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 3.44 (s, 4H), 7.50-7.54 (d, 2H), 7.60-7.62 (d, 2H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 41.39, 115.30, 119.85, 134.18

Dihydro phenazine (L_3)

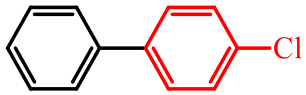


Light green solid, yield 65%.

NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.85-7.87 (d, 4H), 7.26-8.28 (d, 4H).

NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 129.68, 130.53, 143.53.

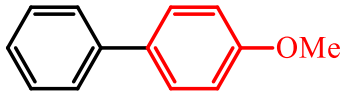
4-chlorophenylbenzene (8a)



White solid, yield: 80%.

NMR (^{1}H) ($CDCl_3$, 400 MHz) δ (ppm) 7.35-7.45 (m, 5H), 7.47-7.57 (m, 4H).
NMR (^{13}C) ($CDCl_3$, 400 MHz) δ (ppm) 127.57, 128.37, 128.89, 129.47, 132.29, 133.36, 139.6, 139.99.

4-methoxyphenylbenzene (8b)

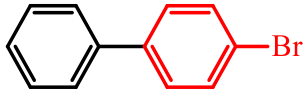


Pale yellow solid, yield: 75%.

NMR (^{1}H) ($CDCl_{3,}$ 400 MHz) δ (ppm) 3.86 (s, 3H), 6.97-6.99 (m, 2H), 7.26-7.33(m, 1H), 7.40-7.44 (m, 2H), 7.52-7.56 (m, 4H).

NMR (^{13}C) ($CDCl_{3,}$ 400 MHz) δ (ppm) 55.3, 114.4, 126.6, 126.7, 128.1, 128.7, 133.8, 140.9, 159.4.

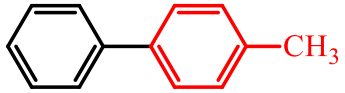
4-bromophenylbenzene (8c)



NMR (^{1}H) ($CDCl_{3,}$ 400 MHz) δ (ppm) 7.32-7.40 (m, 5H), 7.43-7.53 (m, 4H).

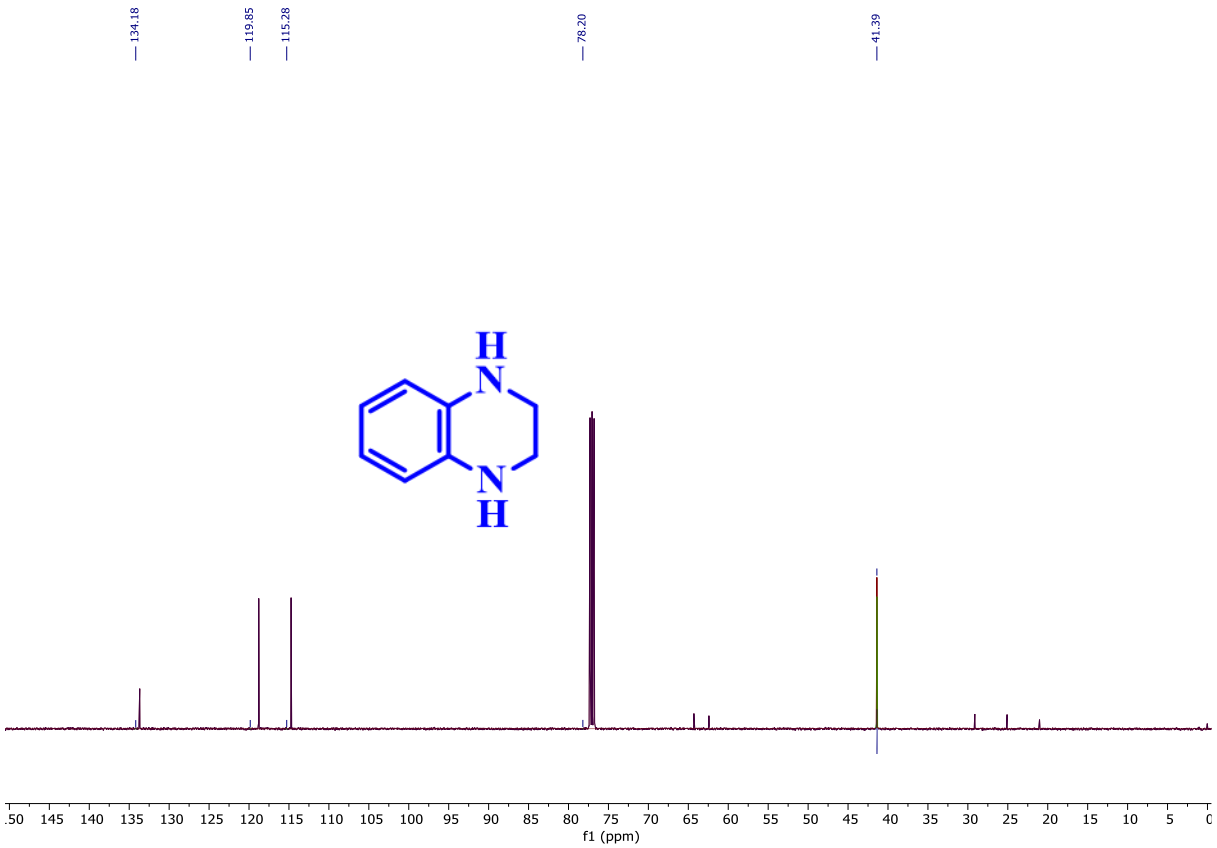
NMR (^{13}C) ($CDCl_{3,}$ 400 MHz) δ (ppm) 127.17, 128.45, 128.59, 129.47, 132.29, 133.16, 139.6, 139.99.

4-methylphenylbenzene (8d)



NMR (^{1}H) ($CDCl_{3,}$ 400 MHz) δ (ppm) 2.34 (s, 3H), 7.29 (d, 2H), 7.33 (d, 2H), 7.51 (d, 2H), 7.52 (d, 2H), 7.41 (t, 1H).

NMR (^{13}C) ($CDCl_{3,}$ 400 MHz) δ (ppm) 21.3, 127.6, 127.8, 127.9, 129.2, 129.5, 137.8, 140.7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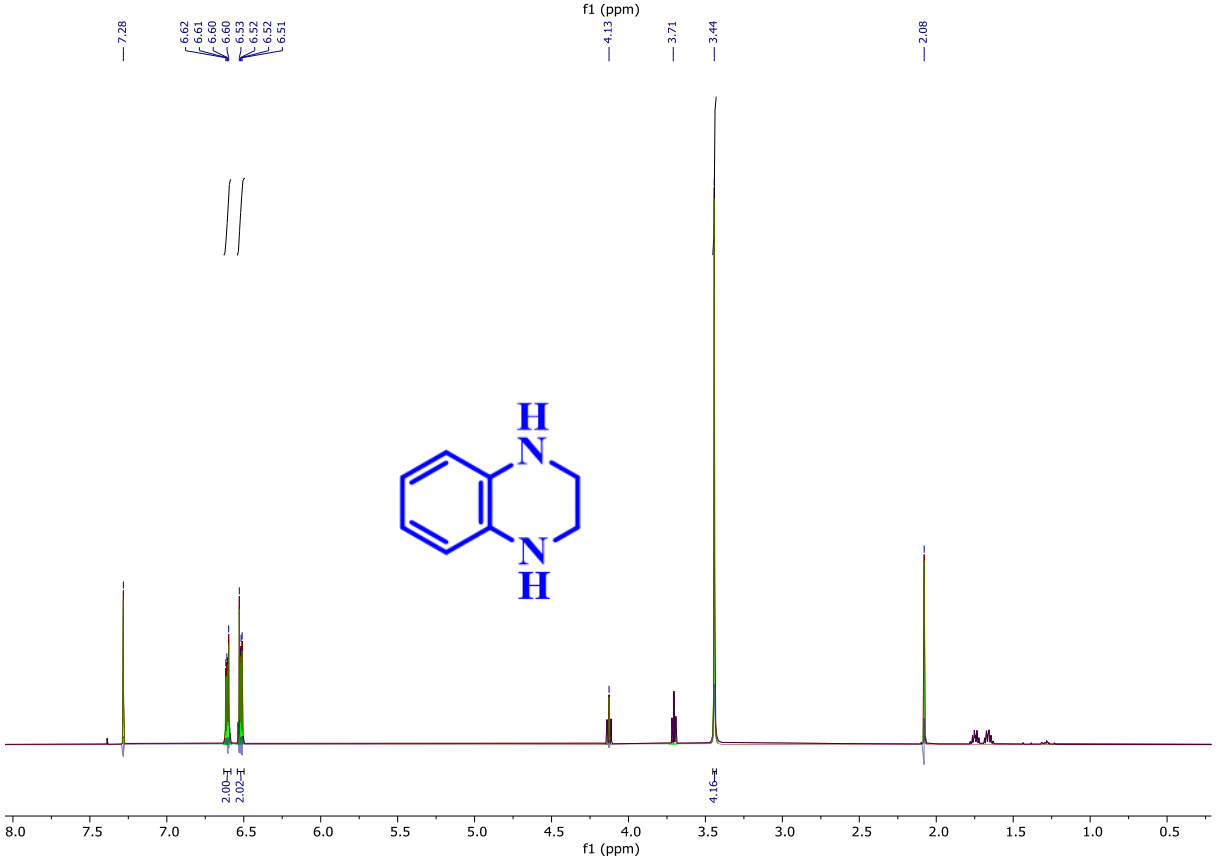
78.20
41.39
H
N
N
H
f1 (ppm)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6.52
6.52
6.51
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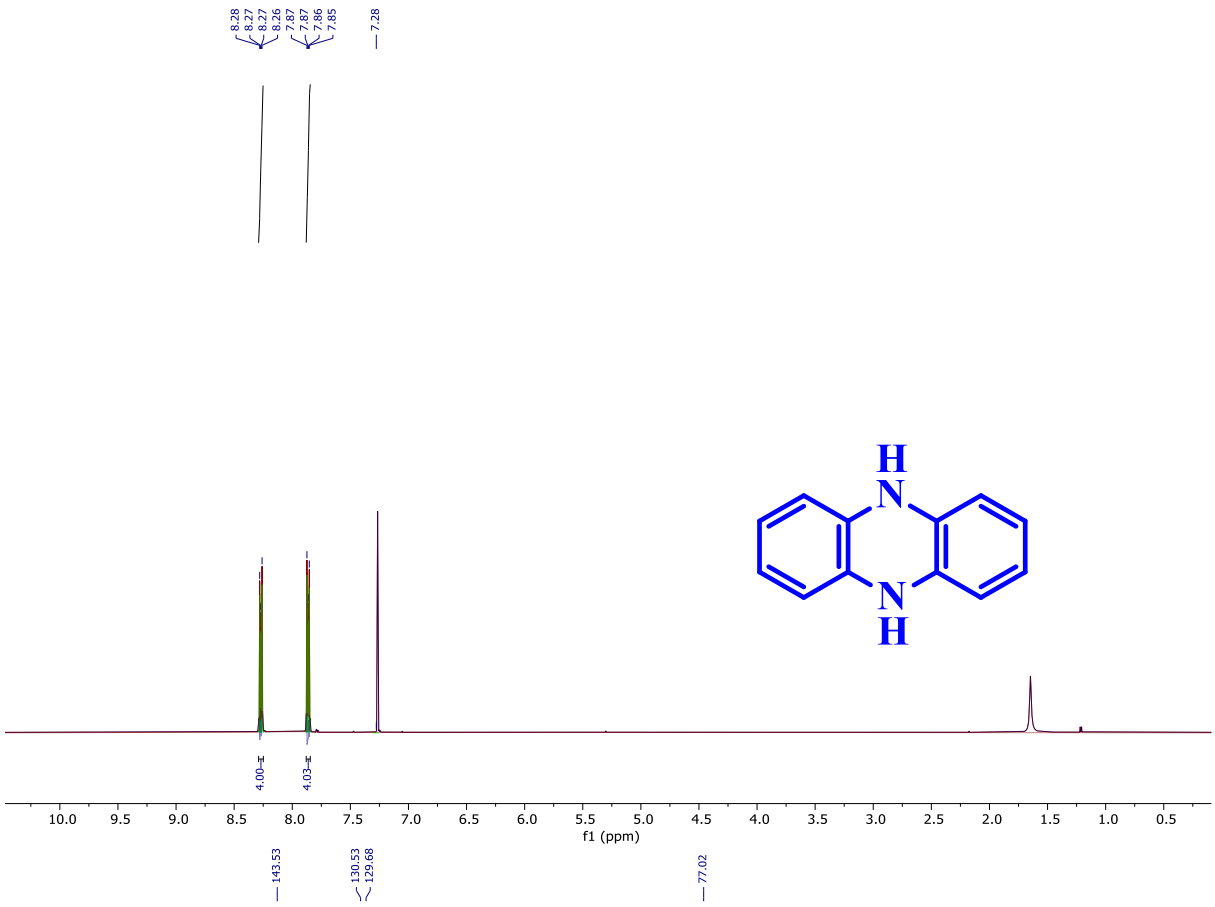
2.02
4.16
H
N
N
H
f1 (ppm)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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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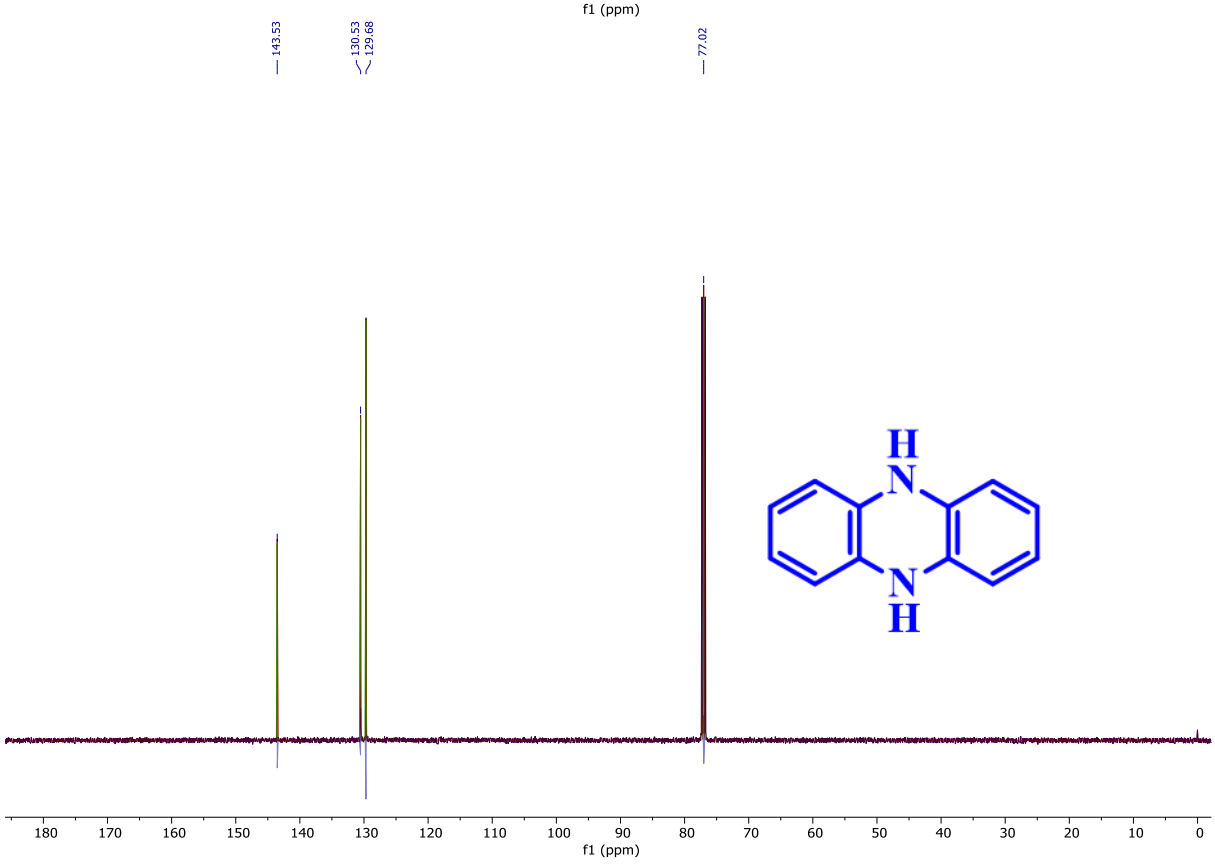
0.5
f1 (ppm)
H
N
N
H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10
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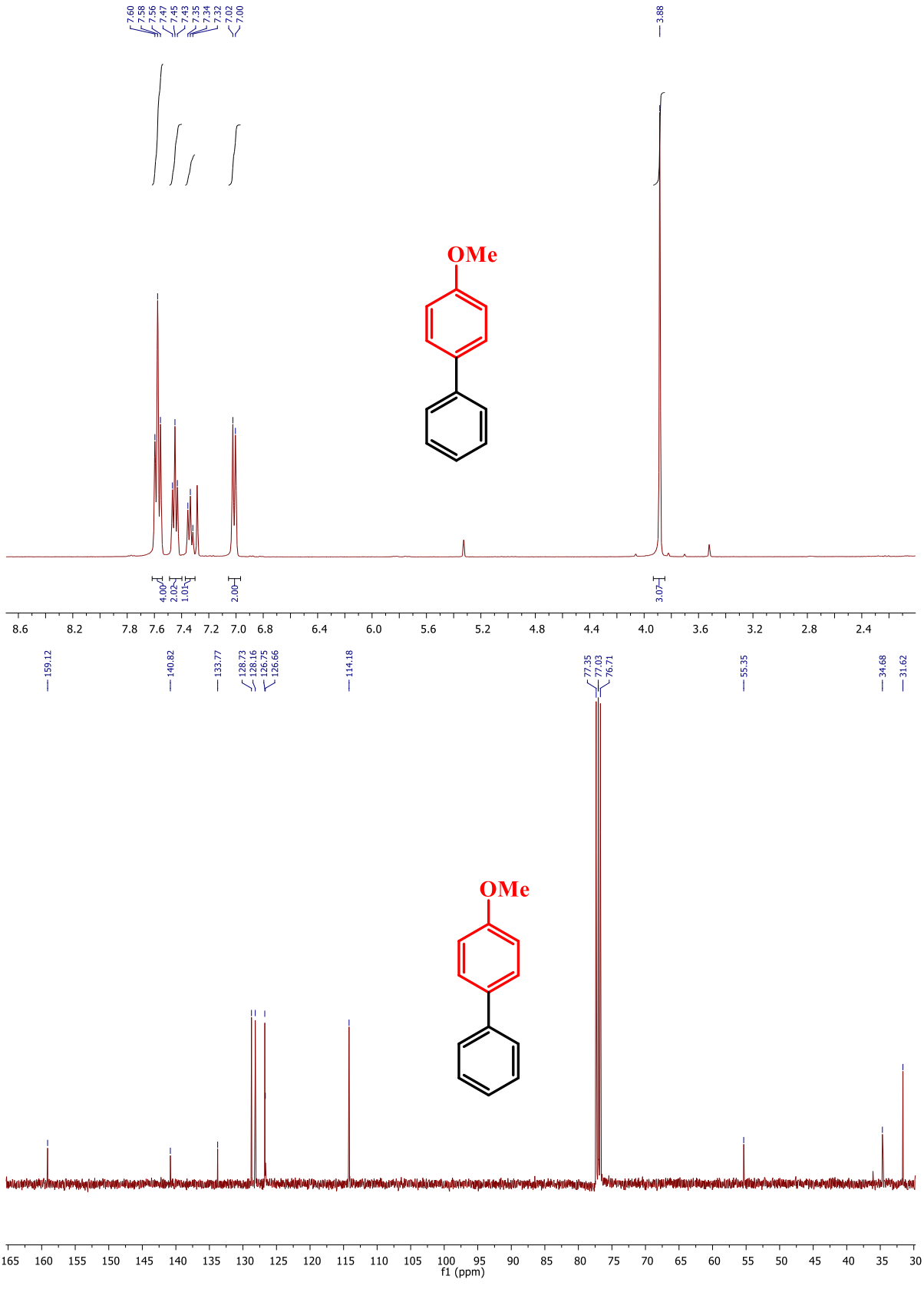
N
N
H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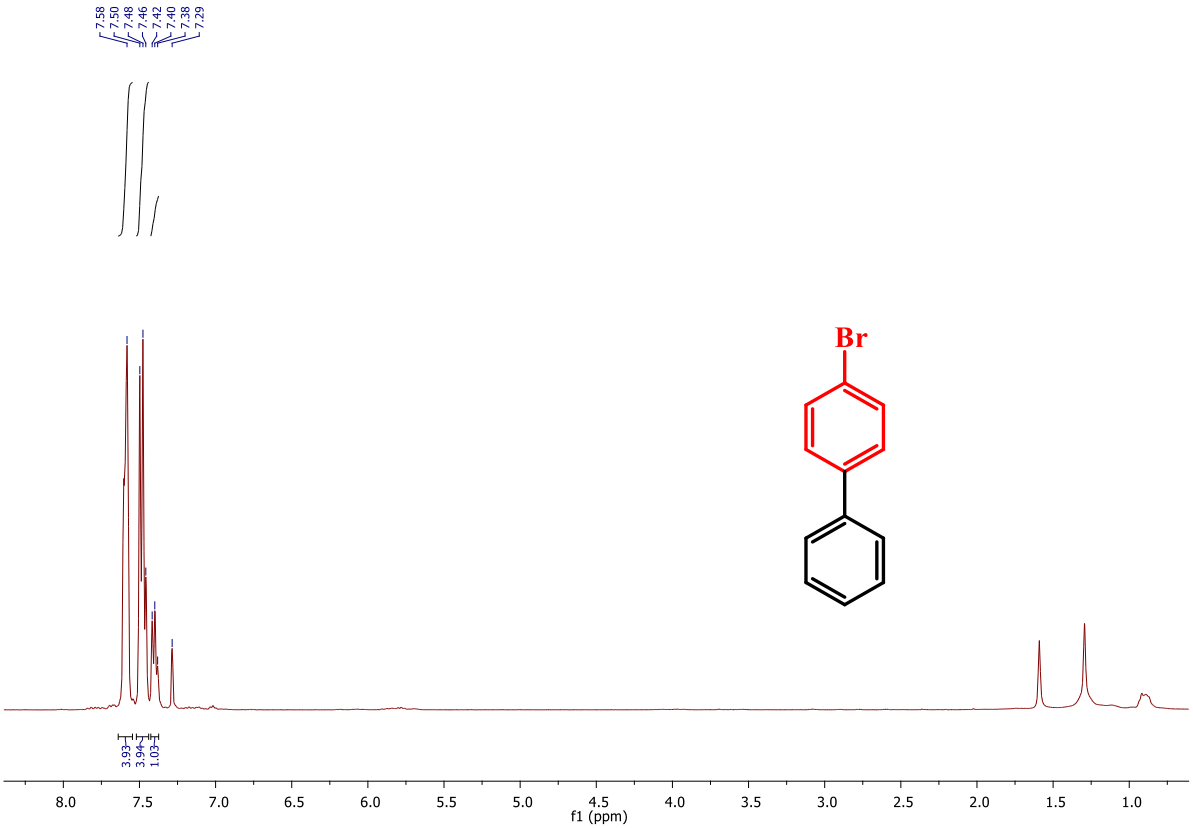
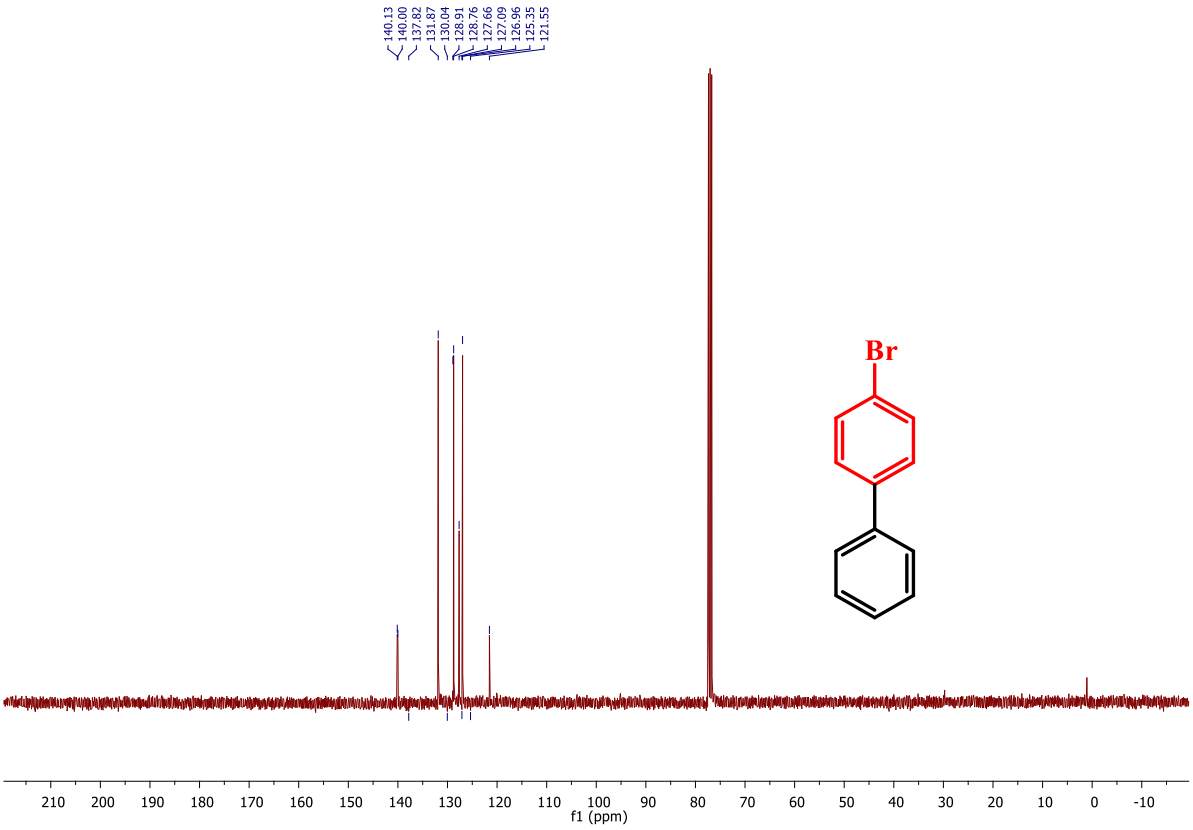
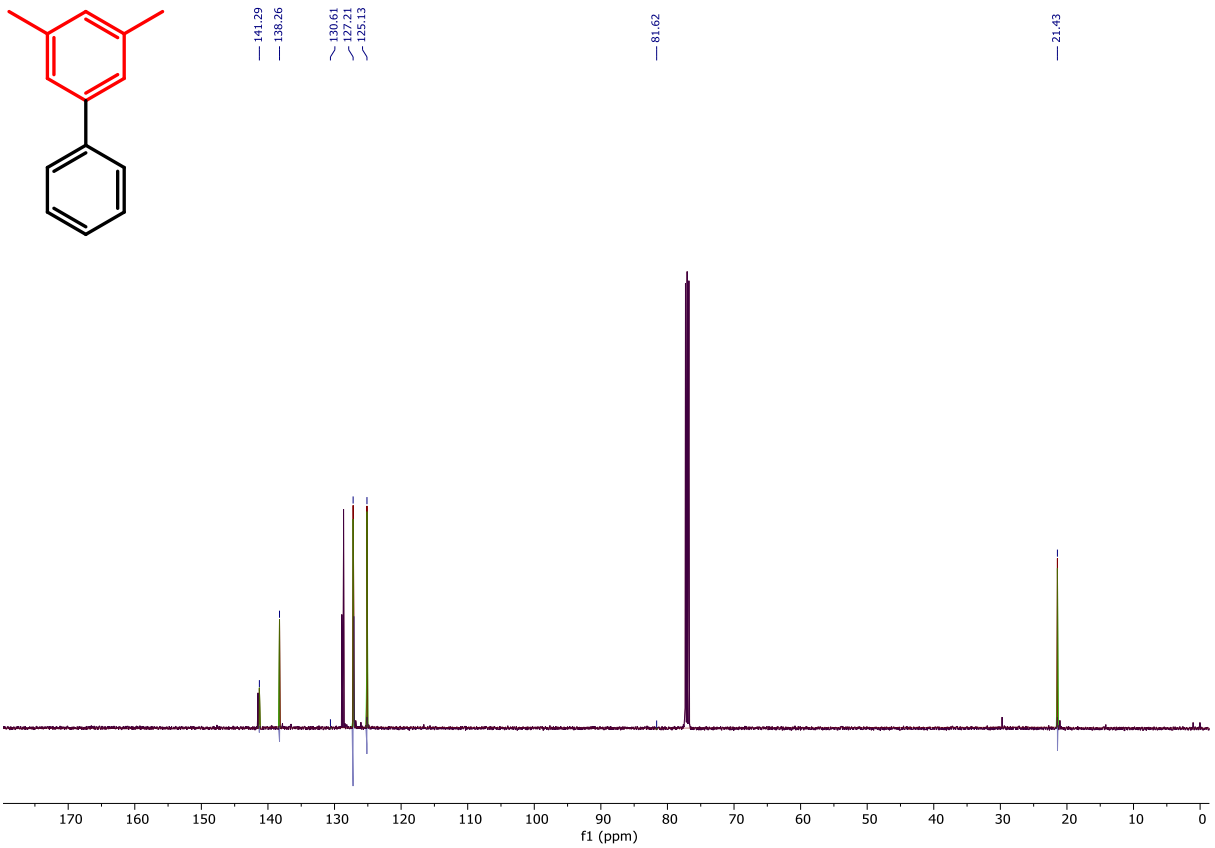
7.00
3.88
OMe
4.00
2.02
1.01
2.00
3.07
8.6
8.2
7.8
7.6
7.4
7.2
7.0
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
159.12
140.82
133.77
128.73
128.16
126.75
126.66
114.18
77.35
77.03
76.71
55.35
34.68
31.62
OMe
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
f1 (ppm)


7.58
7.50
7.48
7.46
7.42
7.40
7.38
7.29
Br
3.93
3.94
1.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


140.13
140.00
137.82
131.87
130.04
128.91
128.76
127.66
127.09
126.96
125.35
121.55
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


141.29
138.26
130.61
127.21
125.13
81.62
21.43
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

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