Exploring the Catalytic Radical Reactivity of Diazaphospholenes

by

Robert D. Riley

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Abstract

A subset of *N*-heterocyclic phosphines known as 1,3,2 diazaphospholenes (DAPs) have amassed significant attention over recent years. DAPs are excellent reduction catalysts for carbonyls, imines, pyridines, and enoates by virtue of being a strong hydride donors. *N*-heterocyclic phosphines are also known to engage in radical reactions such as carbon-carbon bond formation, hydrodehalogenations, and deoxygenation chemistry by hydrogen atom transfer. This thesis will present the first catalytic C-C bond forming intramolecular cyclization by diazaphospholene hydrides (DAP-H) generated in-situ from diazaphospholene bromides (DAP-Br). The catalysis is done without requiring a radical initiator, at room temperature, with 10% catalyst loading, and with the use of LED lights. A substrate scope examined using this chemistry showed that product formations were tolerant of some common functional groups. This work was followed by attempts at intermolecular alkylation chemistry, using the same conditions as in the former.

List of Abbreviations and Symbols Used

σ	Sigma (bonding orbital)
σ*	Sigma star (anti-bonding orbital)
Δ	Delta (heat)
δ	Delta (chemical shift)
λ	Lambda (wavelength)
Å	Angstrom
°C	Degrees Celsius
Ac	Acyl
ACN	Acetonitrile
Ad	Adamantyl
AIBN	Azobisisobutyronitrile
aq	Aqueous
Ar	Aryl
br	Broad
calc'd	Calculated
cm	Centimetre
d	Doublet
DAP	Diazaphospholene
DCM	Dichloromethane
dd	Doublet of doublets
DMF	N,N-Dimethylformamide
dq	Doublet of quartets
dt	Doublet of triplets
eq	Equivalent
ESI	Electrospray ionization

g	Grams
H	Hours
HB(pin)	Pinacol borane
HRMS	High resolution mass spectrometry
Hz	Hertz
iPr	Isopropyl
J	Coupling constant
K	Kelvin
LED	Light emitting diode
m	Multiplet
Me	Methyl
mL	Millilitre
mol	Molar
Mp	Melting point
NHP	*N*-heterocyclic phosphine
nm	Nanometre
NMR	Nuclear magnetic resonance
OMe	Methoxy
P	Pentet
Ph	Phenyl
ppm	Parts per million
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
RT	Room temperature
s	Singlet
T	Triplet
t-Bu	*Tert*-butyl
td	Triplet of doublets

THF	Tetrahydrofuran
TMS	Trimethylsilane
X	Halogen

Acknowledgements

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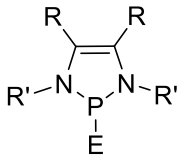
Last, I would like to acknowledge my friends and family. I want to thank them for their infinite love and support during my journey here at Dalhousie University, and my path in pursuing chemistry.

Chapter 1: Introduction

1.1 Diazaphospholenes, Synthesis and Applications

N-heterocyclic phosphines (NHPs), phosphorus analogues of the heavily utilized *N*-heterocyclic carbenes, are used as ligands in organometallic chemistry.[1] Most recently they have been used as metal-free catalysts for a number of reductive transformations.[2,3] Diazaphospholenes (DAPs) are a sub-class of *N*-heterocyclic phosphine catalysts, increasingly studied for their ability to catalyze organic transformations. DAPs have a five membered cyclic structure with a N-P-N bonded framework, and an unsaturated carbon backbone. The groups bonded on the nitrogen can be alkyl or aryl substituents, and these influence the reactivity of DAPs (Figure 1.1).



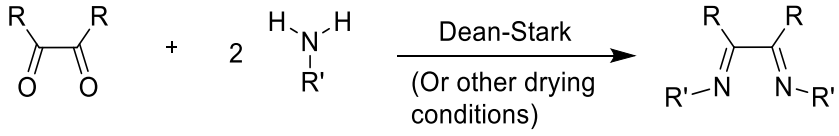
R= alkyl, aryl, H
R'= alkyl, aryl
E= heteroatom, halogen, H

Figure 1.1: General structure of a diazaphospholene, a substituted five membered NHP with an unsaturated backbone.

A bulky N substituent creates steric hinderance, potentially slowing reactions, while conversely an electron withdrawing/donating substituent can be added to alter the electronics of the DAP. Chiral substituents that produce an enantiopure DAP have been added to control enantioselectivity in DAP reductions.[4,5] Although NHPs with a saturated backbone

(diazaphospholidines) exist, unsaturation of the carbon backbone of the DAP enhances the hydride donor properties. When the backbone is saturated, the NHP halides tend to be more soluble in organic solvents, indicating that they have greater covalent character. The carbon backbone can also be altered by adding a wide range of substituents to change the reactivity.[6] The phosphorus atom of the cyclic catalyst is in oxidation state III, and it is usually bonded to an exocyclic halogen when initially prepared.

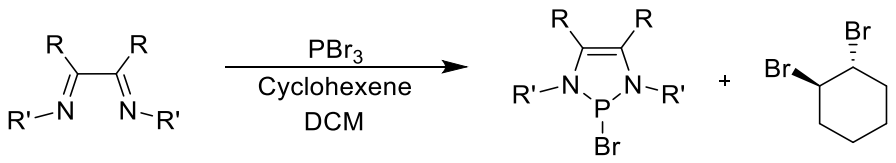
Diazaphospholenes are conveniently prepared from diimines. There are several methods in the literature for synthesizing the diimine precursor. One of the more effective syntheses begins from a functionalized 1,2-diketone or dialdehyde (glyoxal) species, to which is added two equivalents of a primary amine under drying conditions (Scheme 1.1). Sodium sulfate is commonly used as the drying agent for the glyoxal/amine condensation reactions. The R' substituent may be an alkyl or aryl group.[7]



Scheme 1.1: General synthesis of the diimine precursor for diazaphospholenes.

There are several possible pathways to transform the diimine to a DAP product. The most convenient method to form DAPs involves cyclization of the diimine with a phosphorus halide species. When PI_3 is used, the cyclization occurs spontaneously, with elimination of the triiodide anion, while use of PBr_3 requires a halogen scavenger. The Macdonald Cyclization is a convenient synthesis to form DAP bromides from the diimine, phosphorus (III) bromide and cyclohexene,

added as the bromine scavenger, providing clean product formation in good yields (Scheme 1.2).[8] However, applying these cyclizations to the formation of DAPs with small alkyl R' groups on the nitrogen is not very clean, potentially due to further intermolecular reactions that are blocked in the case of larger alkyl or aryl groups. In addition, other researchers in the Speed group have found that these conditions result in decomposition when both the R' and R groups are alkyl groups, due to enamine formation at the R groups. The cyclization is successful when the R groups are alkyl groups, and the R' groups are aryl groups.

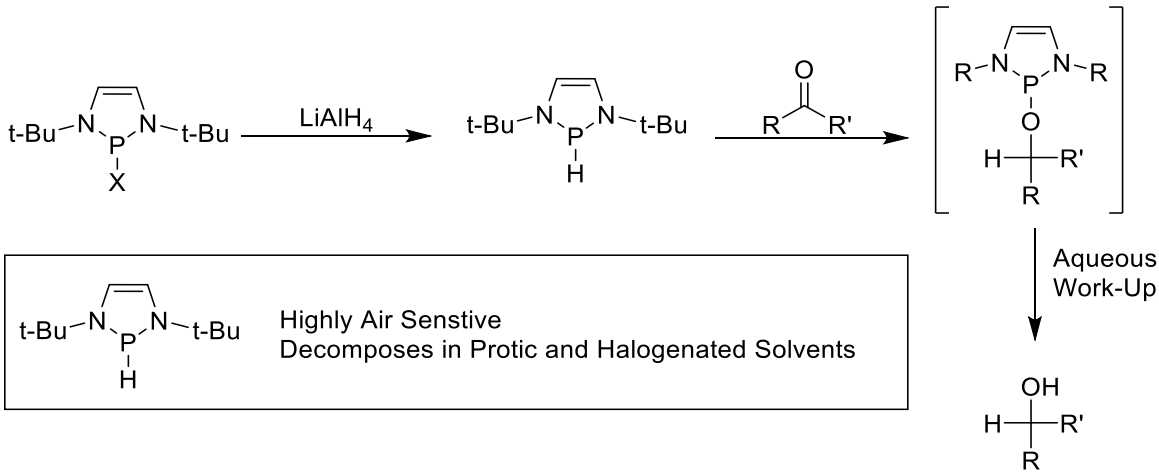


Scheme 1.2: The general reaction scheme of the MacDonald Cyclization using a diimine, phosphorus (III) bromide, and cyclohexene.

The phosphorus halide bond on the DAP is prone to nucleophilic attack, enabling synthesis of several P-bond substituted DAPs, each of which has its own application.

The P-X environment of DAPs has been studied by Gudat and his colleagues using a combination of computational and experimental methods.[9] In their work it was found that the P-X bond of the diazaphospholene compounds is unusually long (1.51 Å for the DAP-Cl bearing mesityl N substituents). This lengthening is due to stereo-electronic effects experienced on the σ* orbital of the P-X bond. The carbon nitrogen backbone of the diazaphospholene donates electron density (by hyperconjugation) to the σ* orbital. This in turn increases the ionic character of the

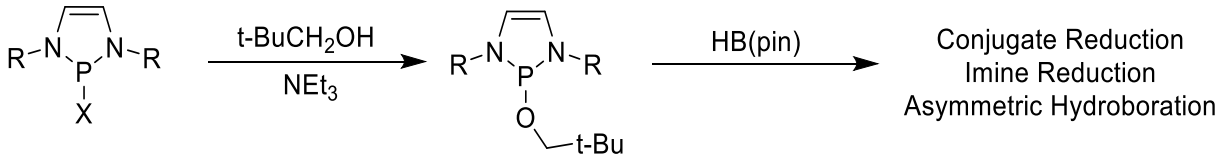
P-X bond due to the energy increase from the accepting P-X σ* orbital polarizing the bond between the phosphorus atom and its substituent. The aromaticity of the phosphenium stabilizes the partially cationic phosphorus. These factors in turn lower the P-X bond heterolytic dissociation energy, meaning that DAP halides have significant ionic character.



Scheme 1.3: Synthesis of the DAP hydride followed by its application in reduction chemistry to afford the alcohol after aqueous work-up.

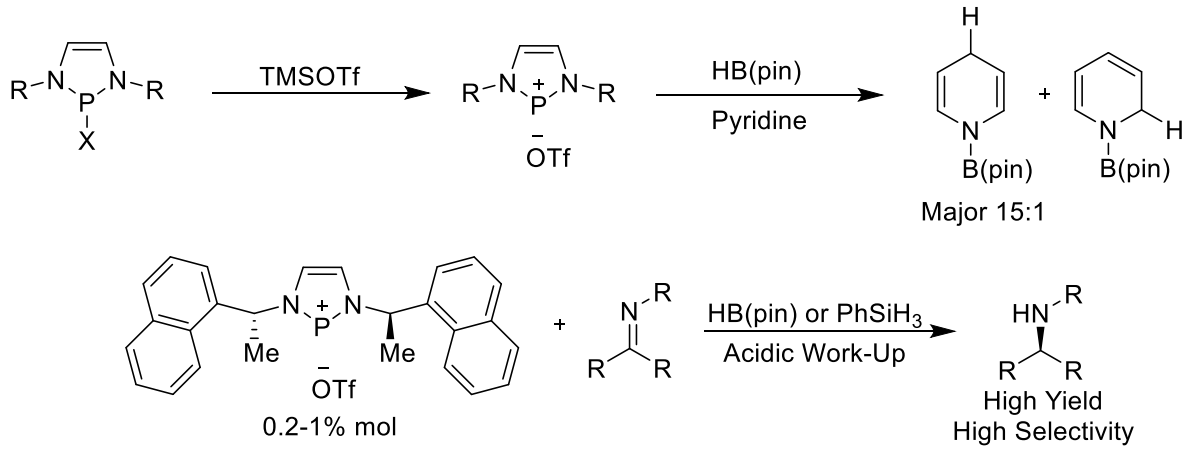
This bond polarization is also observed when there are other substituents on the DAP phosphorus, including the P-H of the DAP hydride. The same rationale of electron donation into the P-X antibonding orbital is used to explain why DAP hydrides are very strong hydride donors. This is very intriguing reactivity due to the similar electronegativity exhibited by phosphorus (2.19) and hydrogen (2.20). Most common hydride reductants such as boron hydrides or aluminum hydrides have the hydride bound to a more electropositive metal. DAP hydrides are synthesized from DAP halides by reduction using a metal hydride donating reducing reagent such as lithium aluminum hydride. Gudat subsequently found that the complex hydride Red-Al (Sodium bis(2-methoxyethoxy)aluminum hydride) gave cleaner formation of the P-H compound.

Applications of DAP hydrides were first shown in Gudat and Burck's work, where aldehydes and ketones were reduced upon addition of DAP-H followed by an aqueous work-up (Scheme 1.3).[10] This is noteworthy, because typically secondary phosphines would add to aldehydes or ketones in a reversed manner, where the phosphorus would be the most nucleophilic site.



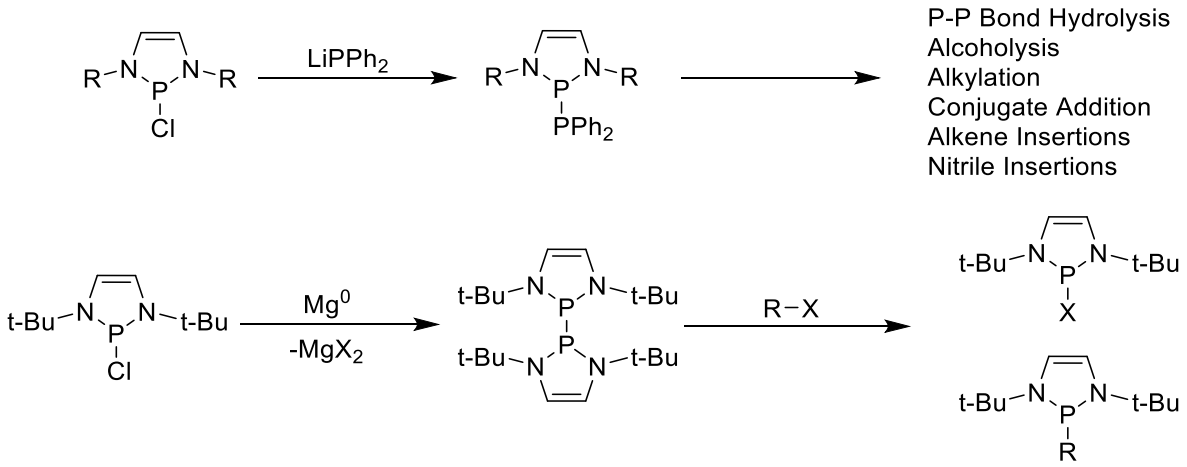
Scheme 1.4: DAP alkoxide synthesis and utilization in conjugate reductions, imine reductions, and asymmetric hydroborations.

Kinjo et al. discovered that the DAP alkoxide intermediate originally generated by Gudat could react with HB(pin) to re-form DAP-H, showing the potential for catalytic turnover in reduction chemistry. The catalytic activity and isolation of DAP alkoxides was originally discovered by the Speed group, where reaction of the alkoxide with HB(pin) generated the DAP hydride in situ; further catalytic activity was then observed. This DAP alkoxide variant has been used as an air-stable pre-catalyst for imine reductions, conjugate reductions, and asymmetric hydroborations (Scheme 1.4). [7, 11, 12, 13] These methods of using DAP alkoxides proved to be excellent alternatives to the previously utilized platinum group complexes required for similar imine reductions and to the tin complexes used for conjugate reductions.[14,15]



Scheme 1.5: Synthesis of the diazaphospholene triflate salt, followed by its use in the hydroboration of pyridines.

DAP phosphenium triflates had not been utilized in catalysis before 2018, but their electronic and structural properties were subjects of interest in the 1980s and 90s along with those of similar cyclic diazaphosphophosphenium compounds.[16, 17] DAP alkoxides were shown to be promisingly robust pre-catalysts in work published in 2017 and 2018. The Kinjo group then developed an alternative system using a DAP phosphenium triflate salt catalyst for pyridine reduction. This DAP phosphenium catalyst was shown to be more active in reducing pyridines than the neutral catalyst developed in the Speed group, which was applied to pyridine reduction in the same time frame.[18] In mid 2019, the Speed group published work with chiral DAP phosphenium triflate catalysts, which were shown to selectively reduce imines with high yield and high enantioselectivity when applied to a large scope of cyclic imines (Scheme 1.5).[19]



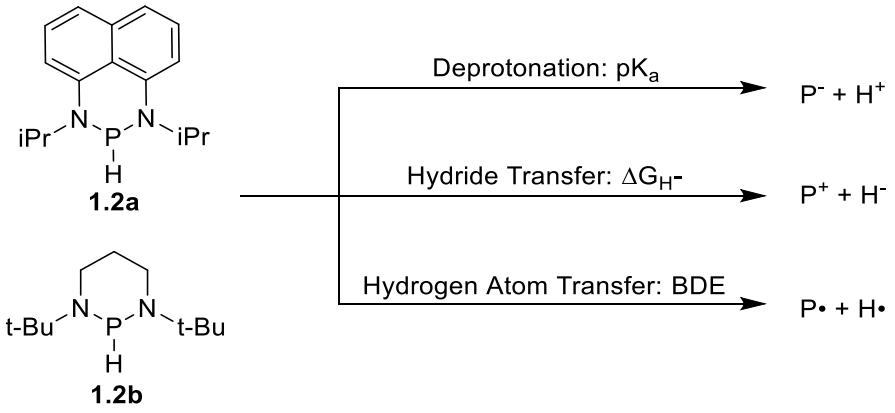
Scheme 1.6: Top - Synthesis of P-P DAP diphenylphosphine followed by its application in synthesis (P-P bond hydrolysis, alcoholysis, alkylation, conjugate addition, alkene insertions). Bottom - Synthesis of bis-diazaphospholene followed by its application of self-functionalization with electrophiles.

The addition of nucleophiles other than H have been explored at the phosphorus. Phosphorus-phosphorus bonded species involving DAPs were first isolated by reaction of DAP chlorides with lithiated phosphanides and phospholides. These compounds later showed activity towards conjugate addition, alkylation, insertion reactions and more due to the intense nucleophilicity of the phosphorus.[20] Despite this interesting reactivity, no catalytic reactions have yet been reported for phosphorus nucleophile addition from a DAP.

A distinct class of DAPs bearing P-substituents on the P are DAP dimers. These dimers are formed by reduction of DAP chlorides or bromides with magnesium dust. The tert-butyl DAP dimer variant has been shown to react with a variety of electrophiles to form functionalized diazaphospholenes (scheme 1.6).[21]

1.2 NHP Radical Reactivity

In 2020, the group of Yang and Cheng published a series of papers exploring the radical activity of diazaphospholanes, and few diazaphospholenes, focusing on hydrogen atom transfers. In their first paper, the reactivity of the P-H bond in the *N*-heterocyclic diazaphospholanes **1.2a** and **1.2b** were investigated in three fashions: deprotonation, hydride transfer, and hydrogen atom transfer (Scheme 1.7).

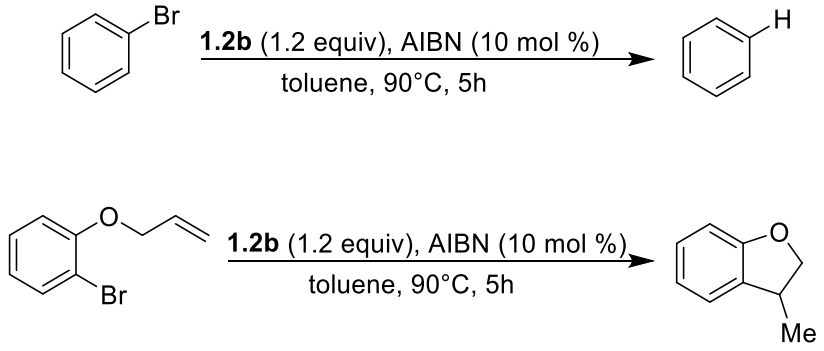


Scheme 1.7: Diazaphospholanes **1.2a** and **1.2b** used in Yang and Cheng's work on the release of hydrogen.

Hydrogen donor abilities were quantified using oxidation potentials from cyclic voltammetry results, and from a series of deprotonation reactions used to measure acidity. It was concluded that hydride donation in diazaphospholanes was effective and limiting results from the deprotonation experiments led them to determine that diazaphospholanes are not very acidic. What was surprising, given the strong hydricity of the DAPS, was that their investigation into compounds **1.2a** and **1.2b** also showed their ability to donate a hydrogen atom. Yang and Cheng demonstrated this hydrogen atom donor ability by reacting the diazaphospholanes with

the stable oxygen-centred 2,4,6-tri-butyl-phenoxyl radical O•, generating the corresponding phenol, and the aryloxy diazaphospholene.[22]

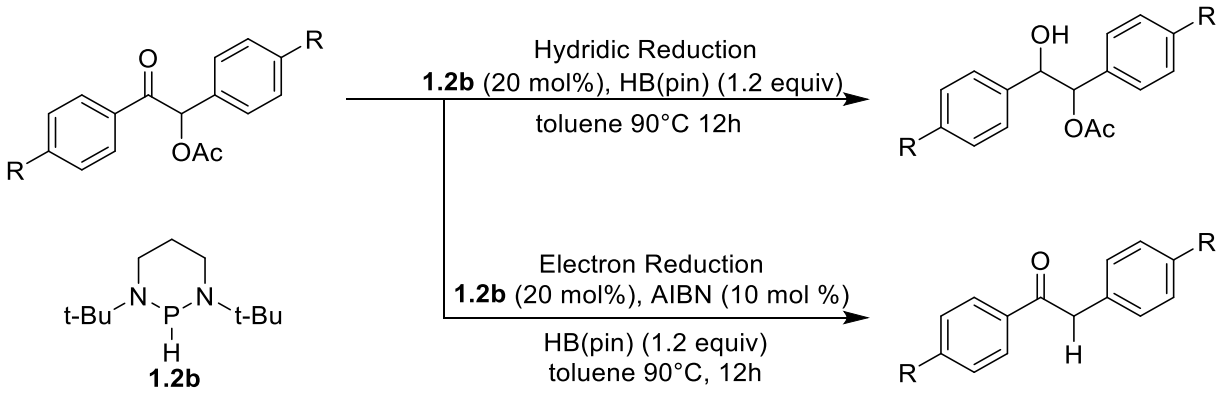
After finding out that these classes of *N*-heterocyclic phosphine hydrides were capable of participating in radical chemistry via donation of a hydrogen atom or an electron, they were subsequently applied in hydrodehalogenations, and intramolecular cyclizations, reactions known to occur by radical mechanisms. Several *N*-heterocyclic phosphines were tested in this work, including diazaphospholenes, though the DAP results were not superior to the saturated diazaphosphinanes. Using 1.2 eq of diazaphospholane catalyst **1.2b**, with a 10 mol % of radical initiator AIBN with heating, a series of halogenated compounds, mostly aromatic, were hydrodehalogenated (Scheme 1.8). Using the same conditions, aryl halide ether substrates were also found to undergo intramolecular cyclization with several substrates (Scheme 1.8).



Scheme 1.8: Hydrodehalogenation (top) and intramolecular cyclization (bottom) using a stoichiometric amount of 1.2b and a catalytic amount of AIBN.[23]

The last project in Yang and Cheng's radical *N*-heterocyclic phosphine series involved deoxygenation of α-acyloxy ketones that undergo deoxygenation at the position alpha to the ketone through a radical mechanism (Scheme 1.9). The same method and reagents mentioned

in the previous project were used to perform the cleavage. The versatility of catalyst **1.2b** was also demonstrated, since the hydridic reductions could be performed using only a terminal reductant and diazaphosphinane, without the radical initiator. These conditions reduced the carbonyl group of the substrate, instead of cleaving the acetyl function.[24]



Scheme 1.9: Diazaphospholane **1.2b** used in hydridic reductions (top), and electron-transfer reduction (bottom).[24]

1.3 Overview of Thesis

The following chapters in this thesis present the two main projects that I worked on during my MSc program at Dalhousie University under the supervision of Professor Alex Speed. The completed first project focuses on screening experiments leading to the optimal reaction conditions for the intramolecular radical cyclization reactions of aryl ether and thioether alkenyl substrates, catalyzed by diazaphospholene bromides. Screening of reaction conditions and substrate scope results are discussed. The incomplete second project focuses on intermolecular alkylation reactions, where conditions similar to those used in the intramolecular cyclization reactions were applied to form carbon-carbon bonds from aryl halides and alkene radical acceptors.

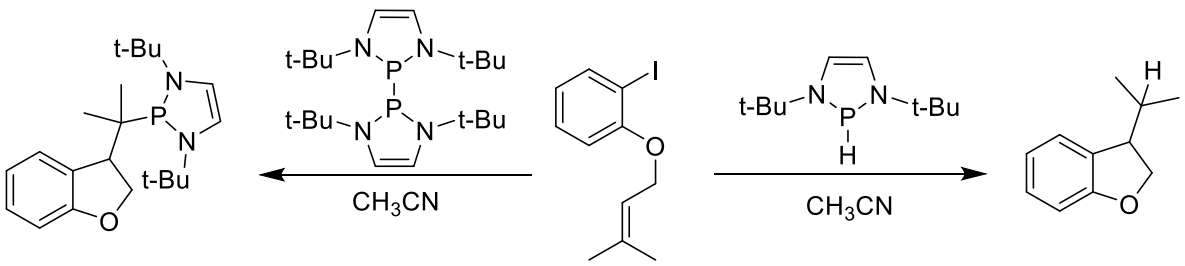
Chapter 2 : Intramolecular Cyclizations Catalyzed by Diazaphospholenes

2.1 Contributions

Dr. Alex Speed is thanked for the synthesis of compound **2.2e**. Dr. Blake Huchenski is thanked for the synthesis of compound **2.2F**. Mr. Xiao Feng is also thanked for acquiring the HRMS data for this project.

2.2 Introduction

The work presented in this chapter was inspired by a recent publication from the Speed group disclosing the previously mentioned functionalization of diazaphospholene dimers.[21] During the substrate scope of the functionalization, an aryl iodide ether containing a prenyl group was reacted with the diazaphospholene dimer system as a probe for the intermediacy of radicals. The result obtained showed that the substrate cyclized, along with the functionalization of the alkene with a DAP group. The unexpectedly observed cyclization had already been reported in the literature, with the 5-exo-trig process known as a radical clock reaction.[25] Separately, a DAP hydride was reacted with this substate, and an intramolecular cyclization was observed, where the radical addition terminated with the donation of an H atom. In both cases, a DAP iodide was the other product formed (Scheme 2.1).



Scheme 2.1: An aryl iodide ether prenyl substrate reacted under the DAP dimer functionalization protocol. The product from the dimer reaction shows functionalization and intramolecular cyclization from the substrate (left). The product from the hydride reaction shows intramolecular cyclization alone (right).

Since the reactions occurred without a radical initiator, and without heating, we saw the potential to make the reaction catalytic in phosphorus. The DAP halide product is a precursor to the P-H compound, however existing conditions for the conversion required the use of harsh aluminum-based reductants. The inspired project envisioned the creation of a cost effective, safe, and synthetically simpler way of producing these intramolecular cyclization products under the catalytic action of DAPs. Metal free catalysts such as DAPs have proven to be competitive compared to metal catalysts. Since metal-free organocatalysts are finding increasing use in industry, discovery of these radical processes adds to the toolbox of such reactions. Previously reported methods of achieving carbon-carbon bond formation in this class of substrate, via 5-exo-trig intramolecular cyclization, require expensive and/or toxic reagents, often used in excess.[26, 27] On top of using metal catalysts, the reaction conditions with these reagents require energy-intensive processes involving heating at high temperatures. Previously mentioned models have been applied to study DAPs' catalytic ability in radical deoxygenation reactions by Yang and Cheng. However, they have not yet studied catalytic transformations on aryl halides, other than fluoride. A model for such transformations is presented in this thesis; it requires only a small catalyst loading of the DAP hydride donor, short reaction times, and can be done without the use of heat and without a radical initiator.

It is known that diazaphospholene halides are precursors to diazaphospholene hydrides since they can be reduced with reagents such as $LiAlH_4$ and Red-Al. These are harsh reductants, and in excess will reduce the DAP halides to phosphine (PH_3), so we recognized we needed to employ milder terminal reductants. With the use of a nucleophilic activator and a terminal reductant, to ideally turn over the catalyst making it catalytic, a potential cycle was proposed for these radical reactions. (Figure 2.1)

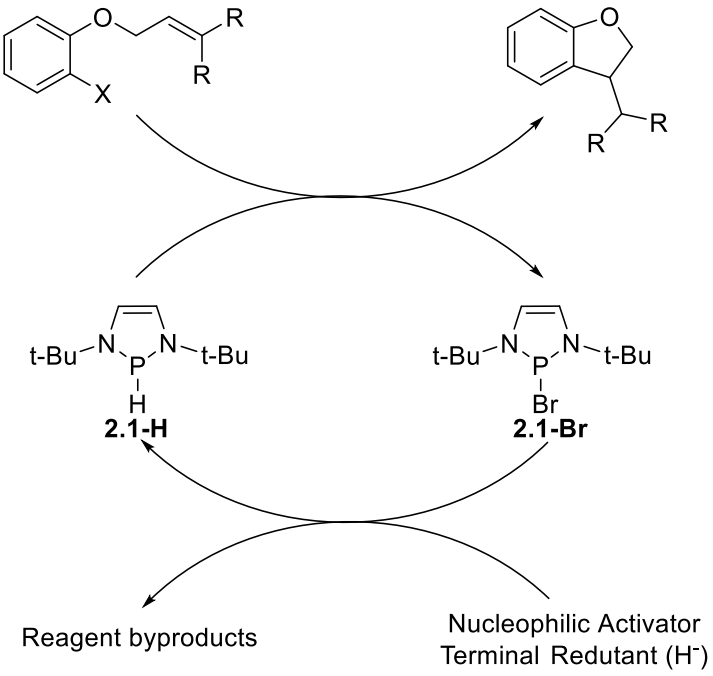


Figure 2.1: The proposed catalytic cycle for the intramolecular cyclization catalyzed by **2.1-H**.

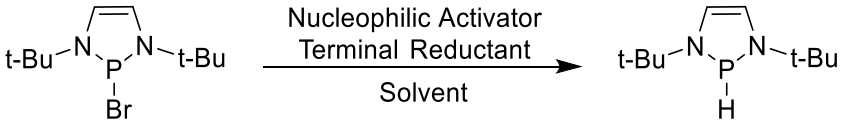
Starting with the DAP bromide bearing tert-butyl N-substituents (**2.1-Br**), the nucleophilic activator could potentially bind to the phosphorus catalyst displacing a bromide anion. This would make the substituent on the phosphorus atom more nucleophilic than the halide to promote hydride donation from the reductant. The activated DAP would then be reduced by the reductant forming the DAP-H (**2.1-H**), which would then react with the key substrate, under the

same reaction that was already disclosed as being stoichiometric. The cyclization might begin with an electron transfer from the DAP, resulting in cleavage of the Ar-X bond of the substrate, forming a halide ion, and aryl radical. The aryl radical could then add to the least substituted end of the alkene, generating another radical in the more substituted environment. The DAP-H would then donate a hydrogen atom to quench the final radical and to complete the formation of the bicyclic product. The resultant phosphenium cation could then recombine with the halide ion formed in the earlier step.

2.3: Results and Discussion

A base set of conditions was explored to observe formation of the DAP hydride (**2.1-H**) in situ from the DAP bromide precatalyst (**2.1-Br**). A nucleophilic activator, a terminal reductant, and a suitable solvent are needed for the DAP hydride intermediate to form. The chosen conditions must also produce an appropriate catalyst lifespan. DAP compounds are susceptible to over reduction, resulting in decomposition to PH_3, and also hydrolysis. In considering the activating reagent, we sought compounds that were dry, or could be readily dried, and that were relatively soluble in THF or acetonitrile, two common solvents for DAP chemistry. For practical reasons, we used commercially available salts as activators, and while we bought materials that were advertised as anhydrous, we did not take special care to dry these substances. Acetates were chosen because they are sufficiently nucleophilic to react with DAPs, but also mild, to maximize substrate compatibility. Table 2.1 shows the screening results for the formation of the DAP P-H intermediate from the bromide after 30 minutes of stirring at room temperature.

Table 2.1: Optimization screening for the generation of DAP hydride **2.1-H** from **2.1-Br**.



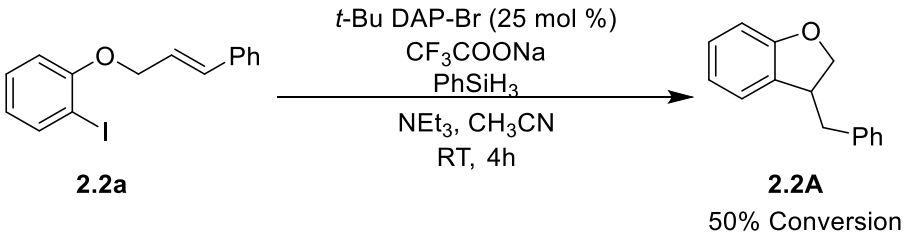
Generated in Solution

Entry	Conditions	Result of Phosphorus Environment (^{31}P NMR)
1	1 (1 eq), THF, HB(pin), CF_3COONa	Generation of P-H
2	1 (1 eq), THF, $PhSiH_3$, CF_3COONa	Generation of P-H
3	1 (1 eq), ACN, HB(pin), CF_3COONa	Generation of P-H
4	1 (1 eq), ACN, $PhSiH_3$, CF_3COONa	Generation of P-H
5	1 (1 eq), THF, HB(pin), AcONa	No Reaction (P-Br)
6	1 (1 eq), THF, HB(pin), $AcON(Bu)_4$	Decomposition of Catalyst
7	1 (1 eq), THF, HB(pin), (t-Bu)COOCs.	Decomposition of Catalyst

The status of the catalyst was monitored using ^{31}P NMR spectroscopy, focusing on the single phosphorus environment of the DAP. P-H catalyst generation was followed by monitoring the characteristic doublet (57 ppm in THF and 58 ppm in acetonitrile) in the proton coupled ^{31}P NMR spectra. The addition of sodium trifluoroacetate and phenylsilane in acetonitrile (Entry 1 of Table 2.1), showed the best catalyst conversion and the longest catalyst lifespan (1 h) before decomposition. Entries 2, 3 and 4 using HB(pin) or phenylsilane with sodium trifluoroacetate in either THF or acetonitrile generated the target P-H catalysts, but their corresponding spectra were not as clean, as they contained either a mixture of decomposition products and/or starting materials. Entries 5-7 were unsuccessful, leading either to catalyst decomposition or showing no activity. These entries involved the use of different nucleophilic activators such as sodium acetate, tetrabutyl ammonium acetate, and cesium pivalate with HB(pin) in THF. We speculate that the lack of reaction with sodium acetate was due to poor solubility, while the decomposition

with tetrabutylammonium acetate or cesium pivalate may have been due to the presence of water in these reagents.

With the conditions to make the DAP hydride catalyst from the bromide optimized, an aryl halide ether substrate (**2.2a**) containing radical donor (aryl halide) and acceptor (alkenyl ether) sites was tested to observe formation of the cyclized product **2.2A** (compounds numbered with lower case lettering, are the starting material substrates, and compounds numbered with upper case lettering are the corresponding products.). The latter transformation was successful using the compounds from the best screening for the generation of **2.1-H**. To track the conversion of the substrate to product, reactivity was observed by acquiring NMR spectra of crude product mixtures using ^{1}H NMR, and measuring by integration (no internal standard or deuterated solvent) the ratio of a starting material signal to a product signal. While this presumes clean conversion, it was a convenient and relatively accurate way to assess the reaction efficiency. Scheme 2.2 shows the optimized conditions, where **2.2a** can be converted into the bicyclic product **2.2A** using 25 mol % of the *tert*-butyl DAP bromide **2.1-Br** as the precatalyst, sodium trifluoroacetate as the nucleophilic activator, triethylamine as a catalyst stabilizer, and acetonitrile as the solvent. The DAP hydride is prone to decomposition in mild acidic environments, and triethylamine had previously been observed to stabilize the DAP hydride by creating a basic medium (discovered in work by Blake Huchenski).



2.2a **2.2A**

50% Conversion

Scheme 2.2: The intramolecular cyclization of **2.2a** to **2.2A**.

The reaction showed a conversion to 50 % product after 4 hours of stirring at room temperature. The diazaphospholene catalyst **2.1-H** which was formed in situ showed decomposition at the end of this time frame by ^{31}P NMR. Formation of PH_3 was observed, leading to the conclusion that longer stir times would not lead to higher conversions in the reaction.

This transformation is known to occur by a radical mechanism, which inspired the thought that exposure to an LED light might enhance reactivity by lowering the activation barrier of initiation (that being, the promotion of electron donation from the DAP hydride to the aryl halide C-X bond). To set up an experiment to effectively expose the reaction to LED irradiation, the sealed reaction vessel was set on a stir plate, and an LED system was initially set 3 cm away from it (Figure 2.2). Blake Huchenski's previous work on functionalization of DAP dimers with aryl halides had shown the importance of irradiation for reactivity in certain solvents.[21]

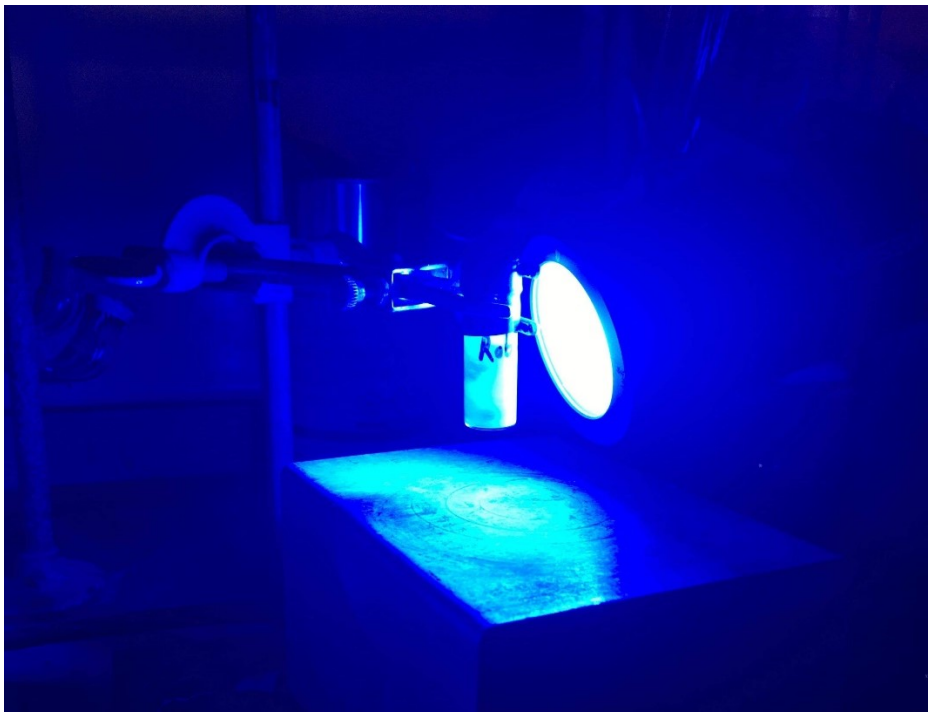


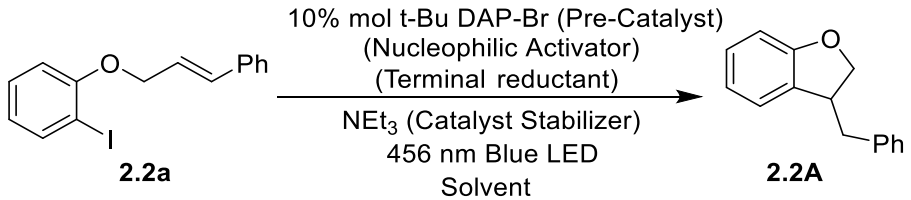
Figure 2.2: The experimental set up for the LED reactions described in this work. The reaction vial is clamped above a stir plate, and the LED light is placed at a certain distance from the reaction vial.

When the same base reaction was attempted again using a 456 nm blue LED, the reaction conversion to product increased from the previous 50% to 85%, without decomposition of the **2.1-H**. A reaction time of 4 hours was enough to give peak conversion. Times below 4 hours led to incomplete reaction, and times above 4 hours typically led to decomposition of the desired product and catalyst.

Although 85% conversion was adequate for this reaction, the goal was to achieve full conversion to the bicyclic product **2.2A**, as separation of the halogenated aryl ether from the bicyclic product could not be achieved by column chromatography and filtration methods. To find the optimal conditions for this reaction, reagents (solvent, terminal reductant, and

nucleophilic activator) were re-screened in efforts to achieve a higher conversion. Table 2.2 summarizes the results.

Table 2.2: The screening of reagents to optimize the cyclization.



2.2a **2.2A**

Entry	Conditions	Catalyst Status (^{31}P NMR)	Product Conversion
1	ACN, $PhSiH_3$, Cs_2CO_3	No decomposition, P-H remaining	100%
2	THF, $PhSiH_3$, Cs_2CO_3	Decomposition of catalyst	--
3	ACN, $PhSiH_3$, CF_3COONa	Decomposition of catalyst	85%
4	THF, $PhSiH_3$, CF_3COONa	DAP-Br only	--
5	ACN, HB(pin), Cs_2CO_3	Decomposition of catalyst	30%
6	THF, HB(pin), Cs_2CO_3	DAP-Br + Decomposition of catalyst	--
7	ACN, HB(pin), CF_3COONa	DAP-Br only	--
8	THF, HB(pin), CF_3COONa	No signal	--
9	ACN, Hantzsch ester, Cs_2CO_3	Decomposition of catalyst	--
10	ACN, ammonia borate, Cs_2CO_3	Decomposition of catalyst	--

Switching the activator to cesium carbonate, which is likely more basic than the sodium trifluoroacetate, proved fruitful. The first entry, showing use of cesium carbonate as the nucleophilic activator, phenylsilane as the terminal reductant, and acetonitrile as the solvent was the only combination of reagents that gave complete conversion to the bicyclic product. In fact, the results for this entry were so good that the pre-catalyst loading of **2.1-Br** could be reduced from 25 mol % to 10 mol %. A loading of 10 mol % was then used in the rest of the screenings. Use of THF, any terminal reductant, and sodium trifluoroacetate showed promising results in the P-H catalyst generation, but these conditions were not efficient in cyclization of the aryl-ether

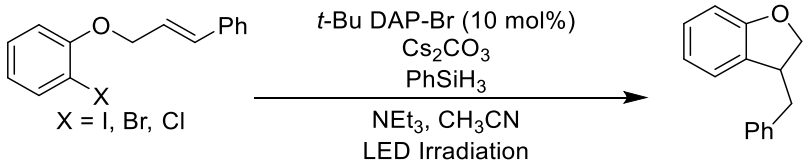
substrate. Entries involving HB(pin) also gave inferior results, with only 30% conversion at best. It is possible that HB(pin) promotes catalyst decomposition to PH_3 more readily than $PhSiH_3$.[7] Keeping the best conditions but changing the terminal reductant to Hantzsch ester or ammonia borane did not provide any conversion, showing that phenysilane was the only suitable reductant.

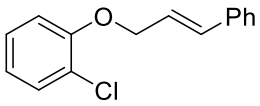
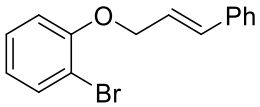
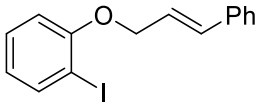
After the optimal set of conditions was established to provide full conversion, the crude products were worked up by aqueous extraction using ether. This was followed by filtration with hexanes to give a yellow oil corresponding to the pure bicyclic product **2.2A** after removal of volatiles. The catalyst residues, salts, and phenylsilane halides were poorly soluble in the hexanes, allowing separation.

Before a larger substrate scope was examined, we investigated the use of other aryl halides. It was discovered that the brominated and chlorinated substrates did not give the same results as the iodide substrate. Aryl ethers **2.2b** and **2.2c** were reacted using the best previous set of conditions, and these bromide and chloride substrates did not show consistent clean conversions, as had been observed with the iodide substrate **2.2a**.

Changing the reagents was not yet taken into consideration, but instead the previous reaction conditions were screened using sources of light of differing wavelength. We speculated that shorter wavelengths might increase the energy available to the system. We screened a 456 nm blue LED, a 427 nm violet LED, and the shortest wavelength 370 nm violet LED. Results of this screening are shown in Table 2.3.

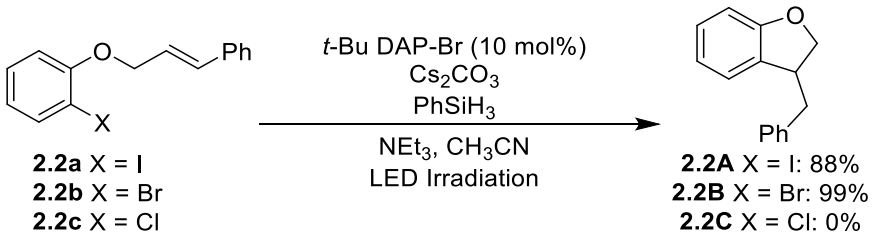
Table 2.3: Results from the optimization of the intramolecular cyclization of **2.2a**, **2.2b**, and **2.2c** using LED lights of differing wavelengths. Temperature of these screenings were not monitored.



Substrate	LED used in Experiment	Reaction Time	Light Travel Distance	Result
 **2.2c**	456 nm (Blue)	24 h	Point blank	No Reaction, starting material
	427 nm (Violet)	24 h	Point blank	No Reaction, starting material
	370 nm (Violet)	24 h	Point blank	No Reaction, starting material
 **2.2b**	456 nm (Blue)	24 h	7 cm	90% conversion, clean spectrum
	427 nm (Violet)	24 h	11 cm	Full conversion, clean spectrum
	370 nm (Violet)	24 h	7 cm	Full conversion, messy spectrum
 **2.2a**	456 nm (Blue)	4 h	3 cm	Full conversion, clean spectrum
	427 nm (Violet)	4 h	3 cm	Full conversion, clean spectrum
	370 nm (Violet)	4 h	3 cm	Decomposition of substrate

The chlorinated aryl ether substrate **2.2c** showed no reactivity in all sources of light, and did not show any reactivity even in an ultra-violet photobox. Aryl chlorides are generally less reactive in radical reactions, so work with this substrate was stopped. Unlike the aryl iodide, preliminary work showed that the aryl bromide substrate **2.2B** was not fully converted to product after 4 hours, regardless of the wavelength of light used. Though conversion was only 15%, the presence of P-H catalyst **2.1-H** could still be observed in the ^{31}P NMR spectrum, suggesting that

longer reaction times might result in completion of the reaction. It was found that 24 hours was sufficient for the reaction to reach complete conversion without decomposition. Irradiation of **2.2b** with the 370 nm LED to complete conversion of the aryl ether substrate to the bicyclic product. However, the spectrum was messy, containing small minor decomposition signals. A light travel distance (from the LED source to the reaction) of 11 cm was suitable for the bromide cyclizations, whereas any distance above 11 cm often led to discrepancies and variability in the conversion results. Substrate **2.2a** showed complete conversions when irradiated with the 427 nm LED or the 456 nm LED. However, the lower energy 456 nm LED was used in later reactions due to its more consistent conversion results. A light travel distance of 3 cm was also found to be the most suitable for the latter reactions. With a similar theme to the bromide cyclizations, any distance above 3 cm for the iodide substrates often led to discrepancies in the conversion results. Irradiation of **2.2a** with the 370 nm LED simply led to decomposition of the substrate. Isolation yields of these substrates after work up are shown in Scheme 2.3.



Scheme 2.3: The optimized substrate scope results for the isolation of compounds **2.2A**-**2.2C**.

With the intramolecular cyclization reaction optimized for iodide and bromide substrates, a substrate scope was examined.

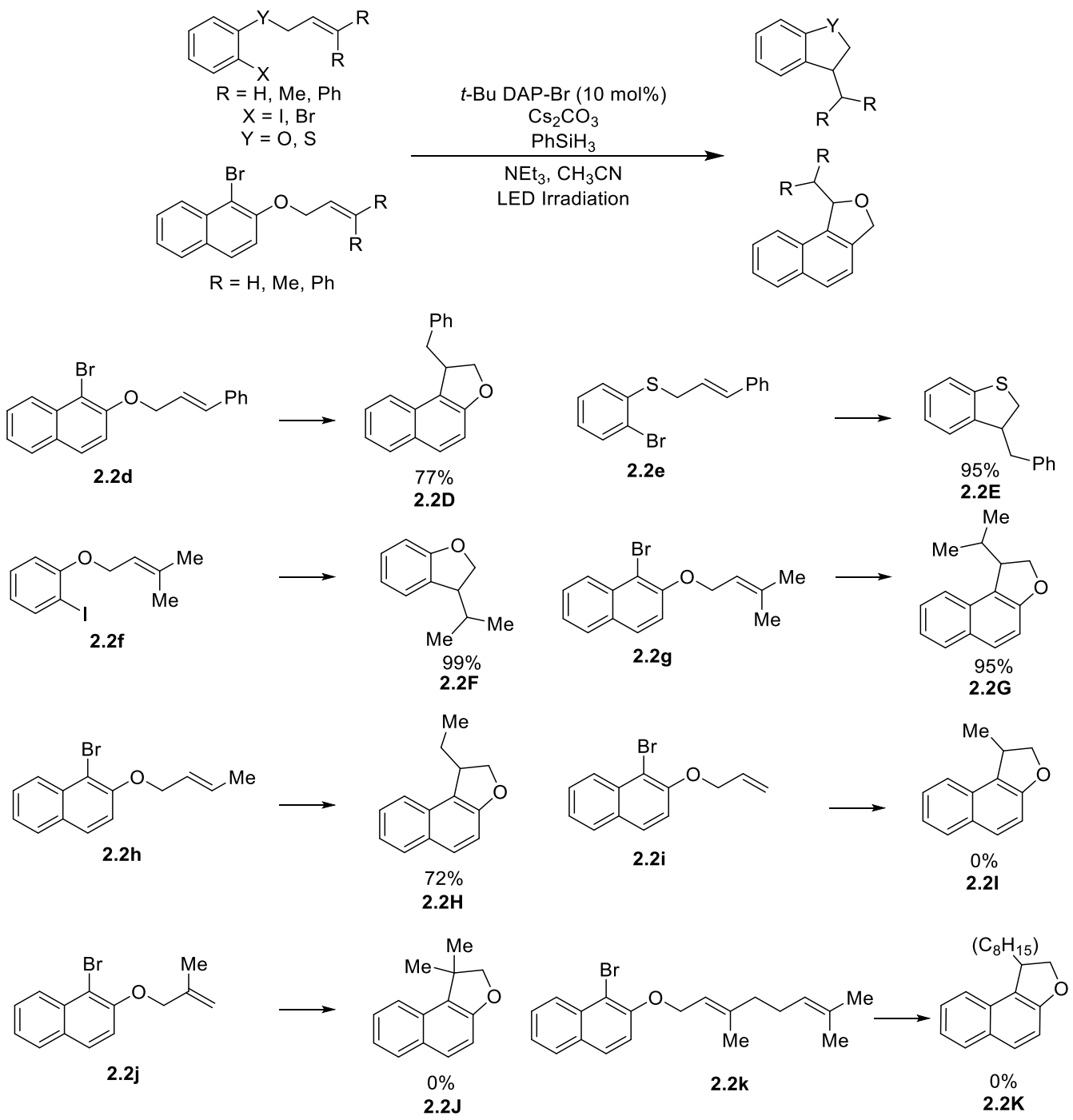


Figure 2.3: Substrate scope results for the product compounds (**2.2D**-**2.2K**).

The beginning of this scope used simple functionalized aryl ethers differing by one or both groups on the sides of the ether (Figure 2.3). Naphthyl cinnamyl ether **2.2d**, and napthyl crotyl ether **2.2h**

cyclized to give their bicyclic products **2.2D and 2.2H** at 77% and 72% yields, respectively. Phenyl cinnamyl thioether **2.2e**, and phenyl prenyl ether **2.2f** all cyclized to give their respective products in high yield. **2.2g** successfully converted to product **2.2G** under the set conditions. Naphthyl allyl ether **2.2i** showed signs of activity, with evidence of the polycyclic product **2.2I** in the crude NMR, but it also showed evidence of many side products that could not be separated from the target product. Naphthyl ether alkene **2.2j** also showed signs of activity, but in the end no product could be observed. The geranyl functionalized substrate **2.2k** did show reactivity forming side products, but clean conversion to product was not observed.

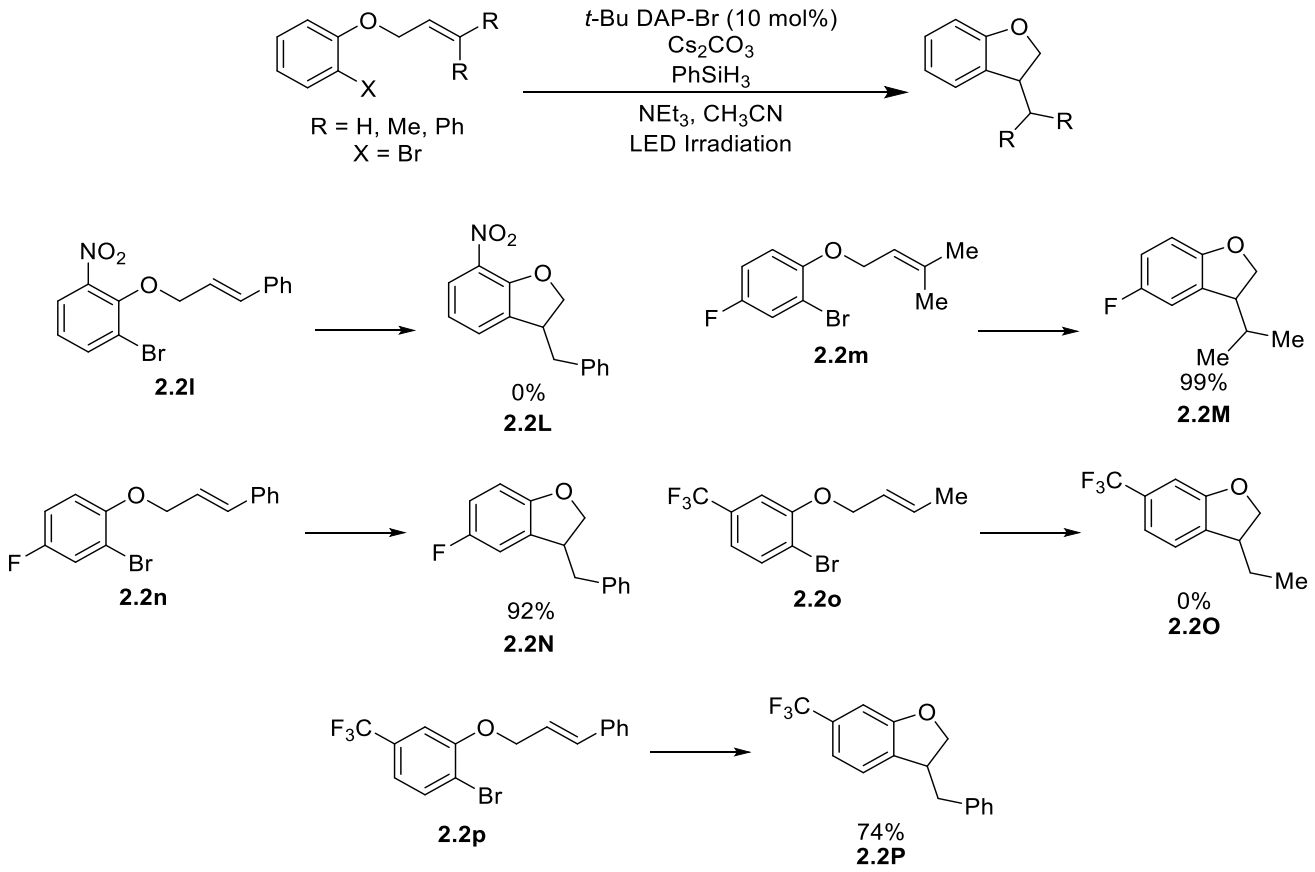


Figure 2.4: Substrate scope results for the functionalized aryl ethers (**2.2L**-**2.2P**)

Figure 2.4 continues the scope, focusing on aryl substrates with substituents on the ring. Formation of the nitro functionalized bicyclic compound **2.2L** was unsuccessful, and the substrate showed no reactivity under the established conditions. The fluoro substituted aryl ethers, both prenyl **2.2m** and cinnamyl **2.2n**, gave high yields of product. Crotyl aryl ether **2.2o**, with a CF_3 group in the 5 position, did not lead to the cyclic product **2.2O,** unlike the similar naphthyl crotyl substrate conversion of **2.2h**. It appears that the addition of such an electron withdrawing group inhibits the cyclization with the crotyl group, but not with a prenyl or cinnamyl group. Switching the crotyl group for a cinnamyl **2.2p** gave a satisfactory 74% yield.

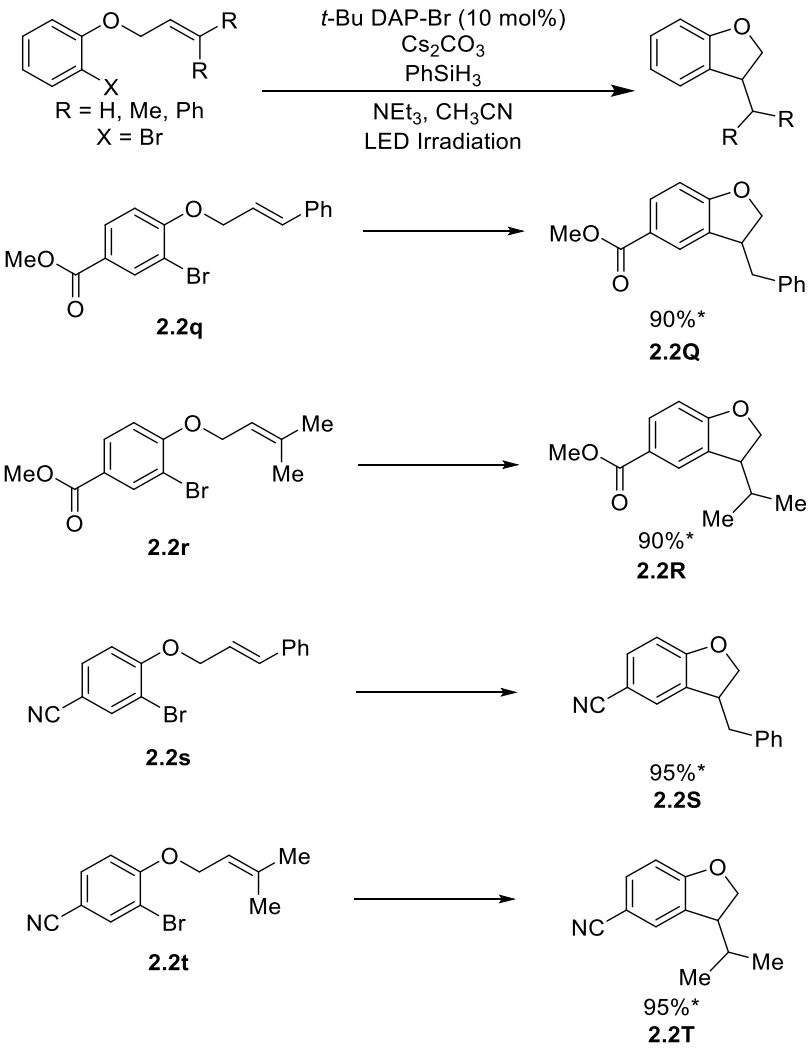


Figure 2.5: Substrate scope results for the functionalized aryl ethers (**2.2Q**-**2.2T**). * These are not isolated yields, but are conversion percentages observed by ^{1}H NMR.

Figure 2.5 shows substrate products containing esters (**2.2Q**, **2.2R**), or containing the cyano functional group (**2.2S**, **2.2T**). With these substrates conversions between 90% and 95% were obtained, but these products could not be separated from other materials in the reaction mixture. Analysis of the corresponding ^{31}P NMR spectra after these reactions gave evidence of P-C bond formation. This suggests that the DAP is interacting with the electrophilic carbon atoms of the functional groups in this series which may remove it from the catalytic cycle.

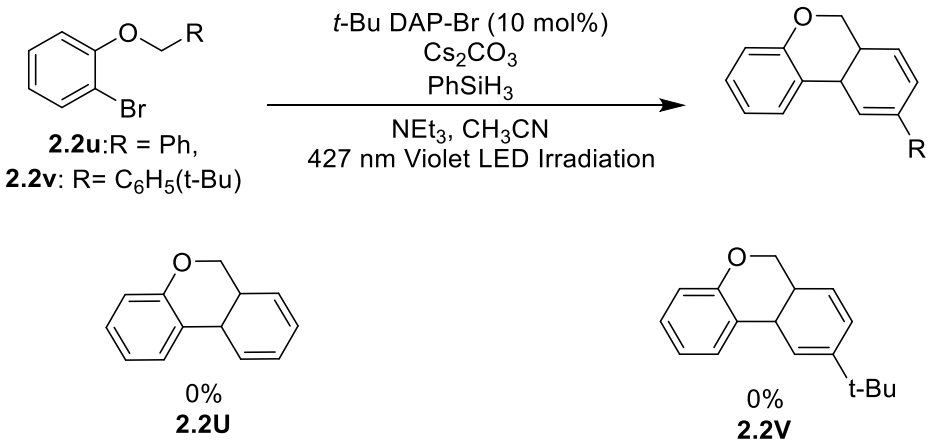


Figure 2.6: Substrate scope results for the aryl ether benzyl substrates **2.2U** and **2.2V**.

It was thought that an aryl radical formed from the homolyzed halogen might be reactive enough to dearomatize another aryl group that would act as the radical acceptor. This was attempted with substrates **2.2u** and **2.2v** as shown in Figure 2.6. However, no reactivity was observed, even with removal of the sterically demanding *tert*-butyl group.

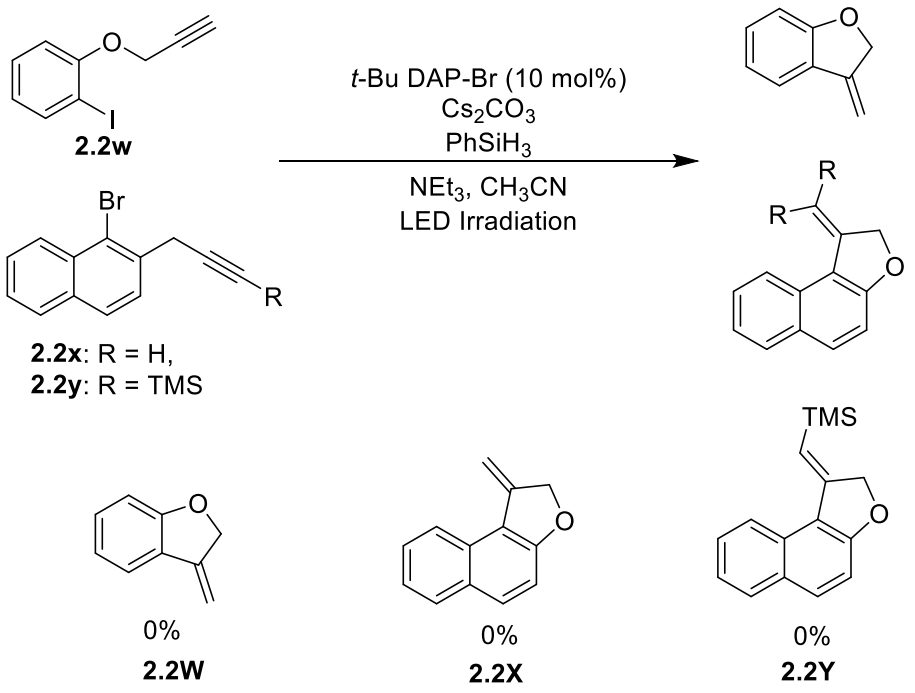


Figure 2.7: Substrate scope results for the alkyne aryl ethers (**2.2W**-**2.2Y**).

Attempted cyclizations with alkynes did not show any signs of conversion to the desired products but did show reactivity, as observed by the consumption of starting materials (Figure 2.7). First, alkyne **2.2w** was reacted under the best conditions, showing activity, but not to the desired product **2.2W**. Using a similar substrate with a naphthyl aryl group **2.2x** instead of the phenyl also did not lead to any of the desired product **2.2X**. It was thought that the aryl ether alkyne reactivity could be stabilized and improved by capping the alkyne with a trimethylsilyl group (**2.2y**), but reaction of **2.2y** did not lead to isolation of any product. The reactions with all of these alkyne substrates led to multiple side products. During these alkyne reactions, it is unclear if the desired alkenyl product is formed. If so, it is likely that alkenyl radicals (which are less stable than alkyl radicals) will form. Thus, alkenyl radical formation could be the culprit to the observed side reactions.

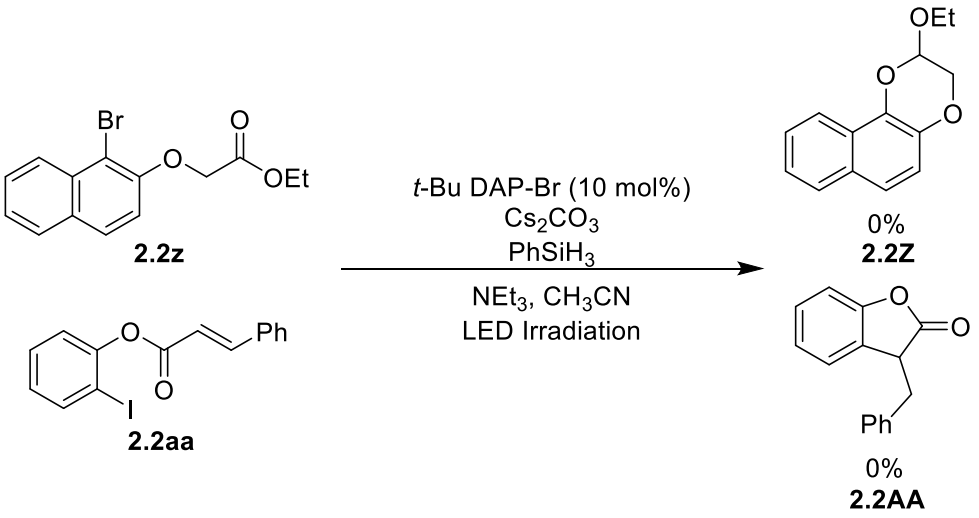


Figure 2.8: Substrate scope results for substrates (**2.2Z** and **2.2AA**).

A substrate with a terminal ester and one with an aryl ester substrate were reacted under the above conditions in hope of obtaining the heterocyclic products **2.2Z** and **2.2AA** (Figure 2.8). Both reactions did not show any signs of product formation, and unidentifiable side products were observed in their ^{1}H NMR spectra.

2.4 Conclusions and Future Work

An ideal set of conditions was determined to effectively generate **2.1-H** in situ. To study the conversion of aryl ethers containing a radical donor halide and a radical acceptor alkene, a scope of functionalized substrates was tested and completed. Many substrates in the scope could not be converted to their bicyclic products, however a number of the substrates did react. Future work of this project will focus on finding a way to intramolecularly cyclize substrates that were not active during catalysis or that did not provide clean conversions. Increasing the yield percentages would be a secondary future objective, where initial yields could have varied due to lab errors and lab technique.

2.5 Experimental Section

General Considerations

All reagents and solvents were dispensed in a 2001 issue IT Glovebox (H_2O levels varied between 2-6 ppm) unless otherwise stated. The intramolecular cyclization and related reactions were carried out in 1-dram vials equipped with magnetic stir bars. All reactions were conducted at ambient temperature unless otherwise stated. The material selected to prepare NMR samples gave homogeneous solutions unless otherwise stated. ^{1}H, ^{31}P, ^{13}C NMR data were collected at 300K on either a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR spectra are referenced to residual non-deuterated solvent from the sample ($CDCl_3$ = 7.24 ppm). ^{13}C NMR spectra are referenced as follows ($CDCl_3$ ^{13}C signal = 77.16 ppm). LED irradiation was conducted using a Kessil H150-Blue lamp centered at a wavelength of approximately 456 nm (50 W max), and a Kessil H150-Violet lamp with a maximum emission centered at a wavelength of approximately 427 nm (45 W max), and a Kessil H150-Violet lamp with a maximum emission centered at a wavelength of approximately 370 nm (52 W max). The melting points of isolated products were measured using a Fischer-Johns melting point apparatus and are uncorrected.

Solvents

Acetonitrile was purchased as anhydrous >99% ACS grade from Sigma Aldrich and used without purification but stored over 3Å molecular sieves under nitrogen.

Toluene was purchased as ACS grade from Fisher and was passed through a double column purification system (activated alumina and activated Q-5) from MBraun Inc. and stored over 3Å molecular sieves under nitrogen.

Tetrahydrofuran was purchased as anhydrous >99% ACS grade from Sigma Aldrich, free from BHT stabilizer, and stored over 3Å molecular sieves under nitrogen.

Hexanes was purchased as ACS grade from Fisher and was used as is.

Ethyl acetate was purchased as ACS grade from Fisher and was used as is.

Dimethylformamide (anhydrous) was purchased from Sigma Aldrich and was used as received.

Reagents

Potassium carbonate was purchased from ACP and was used as received.

Cesium carbonate was purchased from Sigma Aldrich, stored at ambient temperature in the glovebox, and used as received.

Diphenylsilane was purchased from Oakwood Chemical, stored at ambient temperature in the glovebox, and used as received.

Phenylsilane was purchased from Oakwood Chemical, stored at ambient temperature in the glovebox, and used as received.

Pinacolborane was purchased from Oakwood Chemical, stored at ambient temperature in the glovebox, and used as received.

Diazaphospholene (**2.1-Br**) was prepared according to literature procedures.[7]

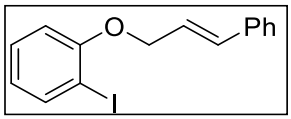
2-iodophenol, 2-bromophenol, 2-chlorophenol, 2-bromo-4-fluorophenol, 2-bromo-5-trifluoromethylphenol, 2-bromothiophenol, 1-bromo-2-naphthol, 2-bromo-4-cyanophenol, 3-bromo-4-hydroxybenzoate, 6-bromo-2-nitrophenol, 3-bromo-1-phenyl-1-propene, propargyl bromide, 3-bromo-2-methyl-2-propene (prenyl bromide), 3-bromo-1-(trimethylsilyl)-1-propyne, 3-bromo-2-methylprop-1-ene, allyl bromide, ethyl bromoacetate, cinnamoyl chloride, geranyl bromide, 4-*tert*-butylbenzyl bromide, benzyl bromide, and crotyl bromide were purchased from Sigma Aldrich and used as received.

General Procedure for the Synthesis of Aryl Ethers

In a 250 mL round bottom flask, the specified quantity of aryl alcohol was added followed by the addition of potassium carbonate and 10 mL of N,N-dimethylforamide (DMF). If solid, the alkyl halide was put into a separate stock solution with 10 mL of DMF and was added slowly to the reaction mixture. If liquid, the required amount of alkyl halide was added dropwise from a syringe. The resulting mixture was stirred overnight at room temperature unless otherwise stated in the procedure. The mixture was then diluted with water (10 mL), followed by an addition of 2M NaOH (30 mL), and everything was then transferred into a separatory funnel. The product was extracted with hexanes (50 mL) from the aqueous layer. The aqueous layer was extracted once more using hexanes (50 mL), and then the extracted organic portions were combined. The combined layers were washed with a concentrated aqueous sodium thiosulfate solution (30 mL), followed by a concentrated aqueous brine solution (30 mL). Volatiles were removed under vacuum to give the product.

Synthesis and Characterization

Synthesis of aryl ether **2.2a**



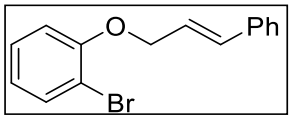
The general procedure for the synthesis of aryl ethers was followed using 2-iodophenol (4.00 g, 18.28 mmol), potassium carbonate (7.52 g, 54.8 mol, 3 eq), and 3-bromo-1-phenyl-1-propene (3.60 g, 18.28 mol). A pale-yellow oil was obtained (6.00 g, 17.8 mmol, 97% yield), Mp = oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.77 (m, Ph-H), 7.40 (d, *J* = 8.2 Hz, Ph-H) 7.31(t, *J* = 7.4 Hz, Ph-H), 7.28-7.21 (m, Ph-H), 6.85 (d, *J* = 8.2 Hz, Ph-H), 6.81 (d, *J* = 16.0 Hz, 1H) 6.70 (t, *J* = 7.6 Hz, Ph-H), 6.39 (dt, *J* = 5.4, 16.1 Hz, 1H), 4.72 (dd, *J* = 1.4, 5.4 Hz, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.40, 139.74, 136.62, 133.06, 129.60, 128.77, 128.07, 126.79, 124.11, 122.95, 112.95, 87.05, 69.90 ppm.

HRMS (ESI): calc'd for $C_{15}H_{13}INaO$ [M+] 358.990334; Found: 358.990167.

Synthesis of aryl ether **2.2b**



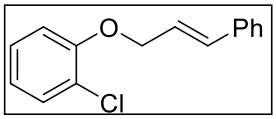
The general procedure for the synthesis of aryl ethers was followed using 2-bromophenol (4.00 g, 23.12 mmol), potassium carbonate (7.52 g, 69.36 mmol, 3 eq), and 3-bromo-1-phenyl-1-propene (4.56 g, 23.12 mmol). A bright yellow solid was obtained (6.14 g, 21.2 mmol, 92% yield), Mp = 79-80 ˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.54 (m, Ph-H), 7.35-7.30 (m, Ph-H), 7.28-7.22 (m, Ph-H), 6.96-6.93 (m, Ph-H), 6.87-6.76 (m, Ph-H), 6.43-6.38 (m, H), 4.77-4.76 (m, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 155.25, 136.63, 133.70, 133.27, 128.81, 128.65, 128.16, 126.87, 124.16, 122.33, 114.11, 112.71, 69.92 ppm.

HRMS (ESI): calc'd for $C_{15}H_{13}BrNaO$ [M+] 311.004198; Found: 311.003848.

Synthesis of aryl ether **2.2c**



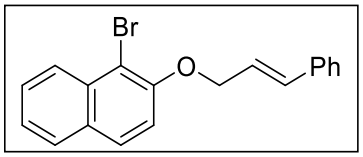
The general procedure for the synthesis of aryl ethers was followed using 2-chlorophenol (1.00 g, 7.78 mmol), potassium carbonate (3.23 g, 23.34 mmol, 3 eq) and 3-bromo-1-phenyl-1-propene (1.53 g, 7.78 mmol). A pale-yellow solid was obtained (1.43 g, 5.84 mmol, 75% yield). Mp = 45-46 ˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.95 Hz, Ph-H), 7.43-7.41 (m, Ph-H), 7.37 (t, *J* = 7.5 Hz Ph-H), 7.31-7.28 (m, Ph-H), 7.26-7.23 (m, Ph-H), 7.04 (d, *J* = 7.9 Hz, Ph-H), 6.96-6.93 (m, Ph-H), 6.82 (d, *J* = 15.8 Hz, 1H), 6.47 (dt, J = 5.9, 16.6 Hz, 1H), 4.83-4.82 (m, 2H).

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 154.4, 136.6, 133.4, 130.6, 128.8, 128.3, 128.2, 127.9, 126.9, 124.2, 121.9, 114.3, 69.9 ppm.

HRMS (ESI): calc'd for $C_{15}H_{12}ClNaO$ [M+] 243.058216; Found: 243.057896.

Synthesis of aryl ether **2.2d**



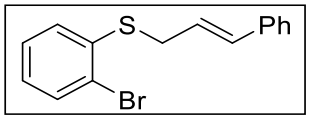
The general procedure for the synthesis of aryl ethers was followed using bromo-2-naphthol (1.00 g, 4.50 mmol), potassium carbonate (1.86 g, 13.50 mmol, 3 eq) and 3-bromo-1-phenyl-1-propene (0.89 g, 4.50 mmol). A yellow solid was obtained (0.83 g, 2.45 mmol, 54% yield), Mp = 76-78 ˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.7 Hz, Ar-H), 7.79-7.77 (m, Ar-H), 7.58-7.55 (m, Ar-H), 7.42-7.38 (m, Ar-H), 7.33-7.28 (m, Ar-H), 7.26-7.23 (m, Ar-H), 6.81 (d, *J* = 16 Hz, 1H), 6.47 (dt, *J* = 5.6 Hz, 16Hz, 1H), 4.92 (dd, *J* = 1.3 Hz, 5.8 Hz, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 153.27, 136.62, 133.43, 130.33, 129.07, 128.82, 128.25, 128.18, 127.91, 126.56, 124.76, 124.41, 115.99, 110.26, 71.07 ppm. Note, these should be 2 signals on singlet 133.43 ppm.

HRMS (ESI): calc'd for $C_{19}H_{15}BrNaO$ [M+] 361.019848; Found: 361.019635.

Synthesis of aryl thioether **2.2e**



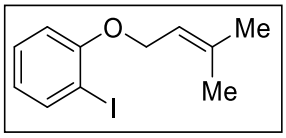
The general procedure for the synthesis of aryl ethers was followed using 2-bromothiophenol (0.5 mL, 4.15 mmol), potassium carbonate (1.14 g, 8.30 mmol, 2 eq), and 3-bromo-1-phenyl-1-propene (0.901 g, 4.56 mmol). A yellow solid was obtained (1.18 g, 3.87 mmol, 93% yield), Mp = 43-44 ˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 1.3, 8.0 Hz, Ph-H), 7.32-7.25 (m, Ph-H), 7.24-7.19 (m, Ph-H), 7.01 (td, *J* = 1.6, 7.9 Hz, Ph-H), 6.51 (d, *J* = 15.6, 1H), 6.25 (dt, *J* = 7.3, 15.8 Hz, 1H), 3.74 (dd, *J* = 1.2, 7.1 Hz, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 137.54, 136.75, 133.71, 133.19, 129.66, 128.73, 127.89, 127.87, 127.24, 126.57, 124.53, 124.14, 36.27 ppm.

HRMS (ESI): calc'd for $C_{15}H_{13}BrNaS$ [M+] 326.981354; Found: 326.981658.

Synthesis of aryl ether **2.2f**



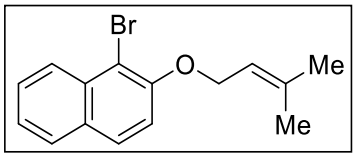
The general procedure for the synthesis of aryl ethers was followed using 2-iodophenol (1.00g, 4.50 mmol, 1 eq), potassium carbonate (1.87 g, 13.6 mmol, 3 eq), and 3-bromo-2-methyl-2-propene (0.52 mL, 4.50 mmol 1 eq). A clear yellow oil was obtained (1.17 g, 4.05 mmol, 90% yield), Mp = oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 1.4, 7.8 Hz, Ph-H), 7.34-7.30 (m, Ph-H), 6.88 (d, *J* = 8.0 Hz, Ph-H), 6.76-6.73 (m, Ph-H) 5.58-5.55 (m, 1H), 4.64 (d, *J* = 6.4 Hz, 2H), 1.84 (s, 3H), 1.80 (s, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.92, 139.89, 138.27, 129.74, 122.86, 119.99, 113.17, 87.41, 66.71, 26.19, 18.80 ppm.

HRMS (ESI): calc'd for $C_{11}H_{13}INaO$ [M+] 310.990334; Found: 310.990275.

Synthesis of aryl ether **2.2g**



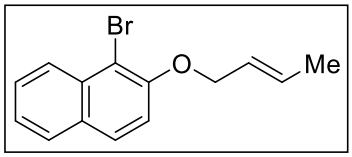
The general procedure for the synthesis of aryl ethers was followed using bromo-2-naphthol (2.00 g, 9.00 mmol, 1 eq), potassium carbonate (3.73 g, 27.0 mmol, 3 eq), and prenyl bromide (1.04 mL, 9.00 mmol). A light brown solid was obtained (2.35 g, 8.10 mmol, 90% yield), Mp = 46-47˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.5 Hz, Ph-H), 7.83-7.81 (m, Ph-H), 7.62-7.58 (m, Ph-H), 7.45-7.41 (m, Ph-H), 7.31-7.30 (m, Ph-H), 5.63 (tt, *J* = 1.3, 6.6 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 153.26, 138.31, 133.20, 129.94, 128.64, 127.94, 127.53, 126.25, 124.31, 119.66, 115.87, 109.92, 67.20, 25.77, 18.30 ppm.

HRMS (ESI): calc'd for $C_{15}H_{15}BrNaO$ [M+]: 313.0198; Found: 313.0203.

Synthesis of aryl ether **2.2h**



The general procedure for the synthesis of aryl ethers was followed using bromo-2-naphthol (1.00 g, 4.50 mmol, 1 eq), potassium carbonate (1.87 g, 13.5 mmol, 3 eq), and crotyl bromide (0.46 mL, 4.50 mmol, 1 eq). A clear olive-green oil was obtained. Material was then flash purified using 99:1 hexanes: ethylacetate. (0.95 g, 3.42 mmol, 76% yield). Mp = oil.

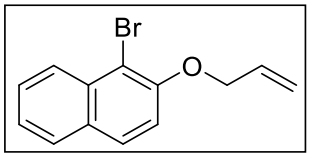
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.9 Hz, Ar-H), 7.77-7.75 (m, Ar-H), 7.56-7.75 (m, Ar-H), 7.40-7.36 (m, Ar-H) 7.25-7.21 (m, Ar-H), 5.94-5.87 (m, 1H), 5.81-5.75 (m, 1H), 4.67 (dt, *J* = 1.2, 5.9 Hz, 2H), 1.76 (dd, *J* = 1.1, 6.3 Hz, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 153.32, 139.05, 133.41, 130.69, 130.37, 130.20, 130.15, 129.21, 128.65, 127.70, 126.63, 126.06, 125.69, 124.73, 118.06, 116.44, 109.96, 78.02, 70.99, 66.24, 21.62, 18.05, 13.65 ppm.

Minor signals in the ^{13}C NMR most likely arise from E/Z isomers.

HRMS (ESI): calc'd for molecular formula $C_{14}H_{13}BrO$[M+]: 277.223; Found: 277.0219.

Synthesis of aryl ether **2.2i**



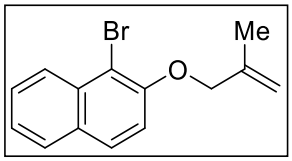
The general procedure for the synthesis of aryl ethers was followed using, bromo-2-naphthol (1.00 g, 4.50 mmol, 1 eq), potassium carbonate (1.86 g, 13.5 mmol, 3 eq) and allyl bromide (0.42 mL, 4.50 mmol). A brown crystalline solid was obtained (1.14 g, 4.37 mmol, 97% yield), Mp = 38-40˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.6 Hz, Ar-H), 7.83 (d, *J* = 9.5 Hz, Ar-H), 7.62-7.59 (m, Ar-H), 7.46-7.42 (m, Ar-H), 7.31-7.28 (m, Ar-H), 6.20 (dquintet, J = 5.0, 20.9 Hz, 1H), 5.58 (m, 5.58-5.36, 2H), 4.81-4.79 (m, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 153.16, 133.42, 133.13, 130.22, 128.98, 128.21, 127.87, 126.49, 124.68, 118.08, 115.66, 109.98, 70.94 ppm.

HRMS (ESI): calc'd for $C_{13}H_{11}BrNaO$ [M+]: 284.9885; Found: 284.9873.

Synthesis of aryl ether **2.2j**



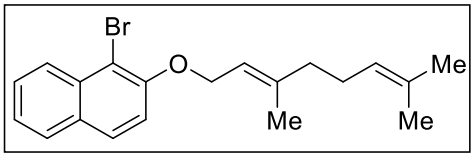
The general procedure for the synthesis of aryl ethers was followed using bromo-2-naphthol (1.00 g, 4.50 mmol), potassium carbonate (1.86 g, 13.50 mmol, 3 eq), and 3-bromo-2-methylprop-1-ene (0.50 mL, 4.95 mmol). A brown hard solid was obtained (1.17 g, 4.22 mmol, 93% yield), Mp = 47-48˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.6 Hz, Ar-H), 7.76 (d, *J* = 8.7 Hz, Ar-H), 7.56-7.53 (m, Ar-H), 7.39-7.36 (m, Ar-H), 7.23-7.20 (m, Ar-H), 5.10 (d, *J* = 87.1 Hz, 2H), 4.63 (s, 2H), 1.89 (s, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 153.21, 140.73, 133.43, 130.14, 128.93, 128.21, 127.85, 126.44, 124.59, 155.35, 133.32, 109.68, 73.63, 19.61 ppm.

HRMS (ESI): calc'd for $C_{14}H_{13}BrNaO$ [M+] 299.004198; Found: 299.003858.

Synthesis of aryl ether **2.2k**



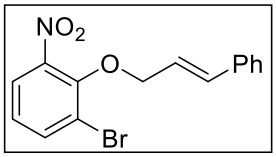
The general procedure for the synthesis of aryl ethers was followed using bromo-2-naphthol (2.00 g, 9.00 mmol, 1 eq), potassium carbonate (3.73 g, 27.0 mmol, 3 eq), and geranyl bromide (1.73 mL, 9.00 mmol 1 eq). A brown oil was obtained (1.48 g, 4.32 mmol, 48% yield), Mp = oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 9.0 Hz, Ar-H), 7.77 (d, *J* = 8.7 Hz, Ar-H), 7.56 (t, *J* = 7.5 Hz, Ar-H), 7.40 (t, *J* = 7.5 Hz, Ar-H),7.26-7.24 (m, Ar-H), 5.58-5.55 (m, 1H), 5.08-5.07 (m, 1H), 4.77 (d, *J* = 6.5 Hz, 2H), 2.14-2.09 (m, 4H), 1.76 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 153.23, 141.40, 133.18, 131.72, 129.91, 128.59, 127.92, 127.49, 126.22, 124.28, 123.71, 119.52, 115.90, 109.91, 67.21, 39.46, 26.22, 25.60, 17.65, 16.71 ppm.

HRMS (ESI): calc'd for $C_{20}H_{23}BrNaO$ [M+]: 381.0824; Found: 381.0617.

Synthesis of aryl ether **2.2l**



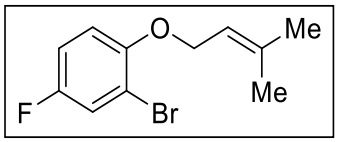
The general procedure for the synthesis of aryl ethers was followed using 6-bromo-2-nitrophenol (2.00 g, 9.20 mmol 1 eq), potassium carbonate (3.80 g, 27.5 mmol, 3 eq) and 3-chloro-1-phenyl-1-propene (1.40 g, 9.20 mmol 1 eq). The contents were stirred for one week. A dark orange crystalline solid was obtained (2.50 g, 7.45 mmol, 81% yield), Mp = 72-73˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85-7.79 (m, Ph-H), 7.47 (d, *J* = 7.2 Hz, Ph-H), 7.39-7.36 (m, Ph-H), 7.18-7.14 (m, Ph-H), 6.79 (d, *J* = 15.9 Hz, 1H), 6.54-6.49 (m, 1H), 4.89-4.87 (m, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 149.41, 145.82, 137.70, 136.10, 135.16, 128.55, 128.15, 126.76, 125.08, 124.26, 123.11, 120.18, 75.86 ppm.

HRMS (ESI): calc'd for $C_{15}H_{12}BrNNaO_3$ [M+]: 355.9893; Found: 355.9882.

Synthesis of aryl ether **2.2m**

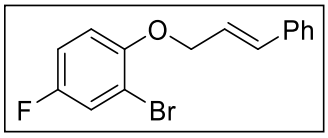


The general procedure for the synthesis of aryl ethers was followed using 2-bromo-4-fluorophenol (1.00 g, 5.00 mmol, 1 eq), potassium carbonate (2.07 g, 15.00 mmol, 3 eq), and prenyl bromide (0.58 mL, 5.00 mmol, 1 eq). A viscous bright yellow oil was obtained (1.16 g, 4.45 mmol, 89% yield), Mp = oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 3.1, 7.8 Hz, Ph-H), 6.96-6.92 (m, Ph-H), 6.84 (dd, *J* = 4.7, 9.0 Hz, Ph-H), 5.48 (tt, *J* = 1.4, 6.5 Hz, 1H), 4.54 (d, *J* = 6.5 Hz, 2H), 1,77 (s, 3H), 1.71 (s, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.83, 155.90, 152.13, 138.61, 120.68 (d, *J* = 27.04 Hz), 119.50, 114.85-114.65 (m), 112.93 (d, *J* = 15 Hz), 67.20, 25.97, 18.48 ppm.

Synthesis of aryl ether **2.2n**



The general procedure for the synthesis of aryl ethers was followed using 2-bromo-4-fluorophenol (1.00 g, 5.24 mmol), potassium carbonate (2.16 g, 15.72 mmol, 3 eq), and 3-bromo-1-phenyl-1-propene (1.03 g, 5.24 mmol). A white solid was obtained (1.25 g, 4.07 mmol, 78% yield), Mp = 75-76˚C.

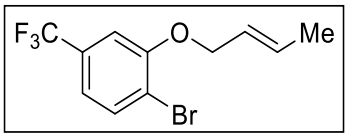
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.39 (m, Ph-H), 7.33-7.29 (m, Ph-H), 7.27-7.23 (m, Ph-H), 6.98-6.94 (m, P-H), 6.88 (dd, *J* = 4.8, 9.0 Hz, Ph-H), 6.74 (d, *J* = 16 Hz, 1H), 6.38 (dt, *J* = 5.7 Hz, 16.0 Hz), 4.71 (dd, *J* = 1.2, 5.7 Hz) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.99, 156.06, 151.89 (d, *J*= 2.5 Hz), 136.49, 133.50, 128.82, 128.23, 123.94, 120.72 (d, *J* = 25.7 Hz), 114.88 (dd, *J* = 14.3 Hz, 5.9 Hz), 112.93 (d, *J* = 9.9 Hz), 70.80 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -121.30 (dt, *J* = 4.9 Hz, 7.91 Hz, 12.6 Hz) ppm.

HRMS (ESI): calc'd for $C_{15}H_{12}BrFNaO$ [M+] 328.994776; Found: 328.995404.

Synthesis of aryl ether **2.2o**



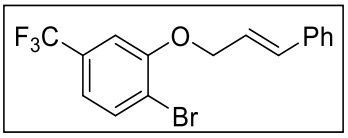
The general procedure for the synthesis of aryl ethers was followed using 2-bromo-5-trifluoromethylphenol (1.00 mL, 4.20 mmol, 1 eq), potassium carbonate (1.74 g, 12.6 mmol, 3 eq), and crotyl bromide (0.43 mL, 4.2 mmol, 1 eq). A bright lime green solid was obtained Material was then flash purified using 99:1 hexanes: ethyl acetate (0.867 g, 2.94 mmol, 70% yield), Mp = 39-41˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 1.91 Hz, Ph-H), 7.50 (dd, *J* = 1.7, 8.5 Hz, Ph-H), 6.93 (d, *J* = 8.5 Hz, Ph-H), 5.93-5.85 (m, 1H), 5.74-5.67 (m, 1H), 4.58 (dt, *J* = 1.2, 5.8 Hz, 2H), 1.77-1.75 (m, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.65, 137.81, 131.11, 130.55 (q), 129.60, 126.75, 125.71 (q), 124.75, 124.59 (q), 122.43, 120.27, 116.43, 114.66, 112.79, 112.70, 112.31, 69.89, 65.21, 17.78, 13.41 ppm.

Minor signals in the ^{13}C NMR arise from E/Z isomers and short/long C-F coupling.

Synthesis of aryl ether **2.2p**



The general procedure for the synthesis of aryl ethers was followed using 2-bromo-5-trifluoromethylphenol (0.89 g, 3.86 mmol), potassium carbonate (1.60 g, 11.58 mmol, 3 eq), and 3-bromo-1-phenyl-1-propene (3.60 g, 18.28 mmol). A white fluffy solid was obtained (0.61 g, 1.71 mmol, 44% yield), Mp = 75-77˚C.

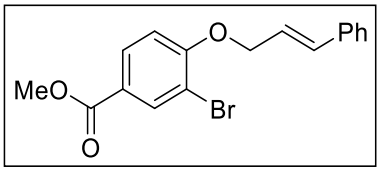
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, Ph-H), 7.42-7.40 (m, Ph-H), 7.33 (t, *J* = 7.7 Hz, Ph-H), 7.28-7.24 (m, Ph-H), 7.14 (s, Ph-H), 7.10 (d, *J* = 8.3 Hz), 6.80 (d, *J* = 15.5 Hz, 1H), 6.40 (dt, *J* = 16.0 Hz, 5.7 Hz, 1H), 4.80 (d, *J* = 5.7 Hz, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 155.54, 136.38, 134.11, 131.10 (q, *J* = 32.7 Hz), 128.86, 128. 38, 126.90, 124.99, 123.13, 122.82, 118.90-118.88 (q, J = 4.0 Hz), 116.75, 110.40 (q, *J* = 3.8 Hz), 70.24 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -62.65 ppm.

HRMS (ESI): calc'd for $C_{16}H_{12}BrF_3NaO$ [M+] 378.991582; Found: 378.992525.

Synthesis of aryl ether **2.2q**



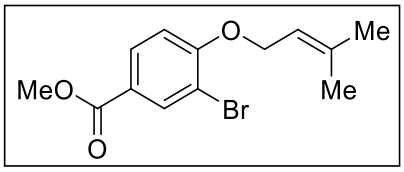
The general procedure for the synthesis of aryl ethers was followed using methyl-3-bromo-4-hydroxybenzoate (1.00 g, 4.30 mmol), potassium carbonate (1.78 g, 12.9 mmol, 3 eq) and 3-bromo-1-phenyl-1-propene (0.85 g, 4.30 mmol). A white solid was obtained (0.785 g, 2.26 mmol, 53% yield), Mp = 103-104˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 2.2 Hz, Ph-H), 7.89 (dd, *J* = 2.0 Hz, 8.6 Hz, Ph-H), 7.34 (d, *J* = 7.3 Hz, Ph-H), 7.26 (t, *J* = 7.5 Hz, Ph-H), 7.19 (t, *J* = 7.1 Hz, Ph-H), 6.90-6.88 (m, Ph-H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.34 (dt, *J* = 5.6 Hz, 16.0 Hz, 1H), 4.77 (dd, *J* = 1.3 Hz, 5.3 Hz, 2H), 3.82 (s, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 165.91, 158.84, 136.34, 135.17, 133.92, 130.69, 128.86, 128.37, 126.88, 124.15, 123.20, 122.65, 122.23, 70.01, 52.34 ppm.

HRMS (ESI): calc'd for $C_{17}H_{15}BrNaO_3$ [M+] 369.0009677; Found: 369.009689.

Synthesis of aryl ether **2.2r**

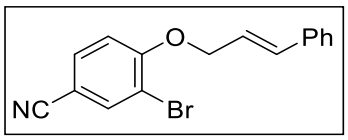


The general procedure for the synthesis of aryl ethers was followed using methyl-3-bromo-4-hydroxybenzoate (1.00 g, 4.30 mmol 1 eq), potassium carbonate (1.78 g, 12.9 mmol, 3 eq) and prenyl bromide (0.50 mL, 4.30 mmol 1 eq). A white snowflake solid was obtained (1.13 g, 3.74 mmol, 87% yield), Mp = 48-49˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27-8.26 (m, Ph-H), 8.00-7.97 (m, Ph-H), 6.94-6.92 (m, Ph-H), 5.54-5.51 (m, 1H), 4.70-4.69 (m, 2H), 3.93-3.92 (m, 3H), 1.84 (s, 3H), 1.80 (s, 3H) ppm.

HRMS (ESI): calc'd for $C_{13}H_{15}BrNaO_3$ [M+]: 321.0097; Found: 321.0094.

Synthesis of aryl ether **2.2s**



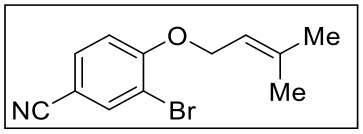
The general procedure for the synthesis of aryl ethers was followed using 2-bromo-4-cyanophenol (1.00 g, 5.00 mmol), potassium carbonate (2.07 g, 15.00 mmol, 3 eq) and 3-bromo-1-phenyl-1-propene (0.99, 5.00 mmol). A fluffy, pale yellow solid was obtained (0.856 g, 2.72 mmol, 54%), Mp = 115-116˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 2.0 Hz, Ar-H), 7.56 (dd, *J* = 2.2, 8.9 Hz, Ar-H), 7.41-7.39 (m, Ar-H), 7.34-7.31 (m, Ar-H), 7.28-7.25 (m, Ar-H), 6.96 (d, *J* = 9.2 Hz, Ar-H), 6.77 (d, *J* = 15.9 Hz, 1H), 6.37 (dt, *J* = 5.3, 16.0 Hz, 1H), 4.82 (dd, *J* = 1.4, 5.7 Hz, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 158.8, 137.1, 136.1, 134.4, 133.2, 128.9, 128.6, 126.9, 122.6, 177.9, 133.5, 133.1, 105.7, 70.2 ppm.

HRMS (ESI): calc'd for $C_{16}H_{12}BrNNaO$ [M+] 335.999447; Found: 335.999159.

Synthesis of aryl ether **2.2t**

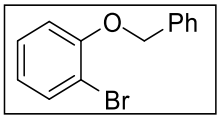


The general procedure for the synthesis of aryl ethers was followed using 2-bromo-4-cyanophenol (1.00 g, 5.0 mmol, 1 eq), potassium carbonate (2.07 g, 15 mmol, 3 eq) and prenyl bromide (0.54 mL, 5.0 mmol). A white crystalline solid was obtained (1.18 g, 4.45 mmol, 89% yield), Mp = 45-47˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86-7.85 (m, Ph-H), 7.61-7.56 (m, Ph-H), 6.97-6.94 (m, Ph-H), 5.51-5.50 (m, 1H), 4.72-4.69 (m, 2H), 1.84 (s, 3H), 1.80 (s, 3H) ppm.

HRMS (ESI): calc'd for $C_{12}H_{12}BrNNaO$ [M+]: 287.9994; Found: 287.9983.

Synthesis of aryl ether **2.2u**

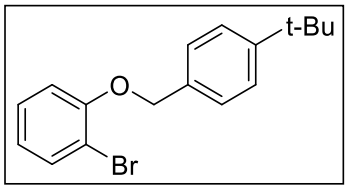


The general procedure for the synthesis of aryl ethers was followed using 2-bromophenol (0.67 mL, 5.78 mmol, 1 eq), potassium carbonate (2.40 g, 17.34 mmol, 3 eq), and benzyl bromide (0.69 mL, 5.78 mmol, 1 eq). A yellow oil was obtained (1.47 g, 5.60 mmol, 97% yield), Mp = oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 7.9 Hz, Ph-H), 7.54 (d, *J* = 7.6 Hz, Ph-H), 7.46 (t, 7.6 Hz, Ph-H), 7.39-7.36 (m, Ph-H), 7.28-7.27 (m, Ph-H), 7.00 (dd, *J* = 1.0, 8.1 Hz, Ph-H), 6.92 (td, *J* = 1.2, 7.7 Hz, Ph-H). 5.21 (s, 2H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 155.26, 136.77, 133.63, 128.77, 128.64, 128.12, 127.20, 122.37, 114.14, 112.75, 70.94 ppm.

Synthesis of aryl ether **2.2v**



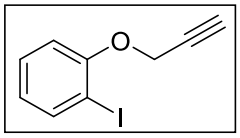
The general procedure for the synthesis of aryl ethers was followed using 2-bromophenol (0.67 mL, 5.78 mmol, 1 eq), potassium carbonate (2.40 g, 17.34 mmol, 3 eq), and 4-*tert*-butylbenzyl bromide (1.06 mL, 5.78 mmol, 1 eq). A white solid was obtained (1.75 g, 2.28 mmol, 95% yield), Mp = 44-45˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56-7.54 (m, Ph-H), 7.40 (s, Ph-H), 7.23-7.21 (m, Ph-H), 6.96 (d, *J* = 8.1 Hz, Ph-H), 6.85-6.82 (m, Ph-H), 5.12 (s, 2H), 1.32 (s, 9H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 155.18, 150.90, 133.50, 133.38, 128.35, 126.85, 125.46, 122.03, 113.92, 112.54, 70.69, 34.54, 31.32 ppm.

HRMS (ESI): calc'd for $C_{17}H_{19}BrNaO$ [M+]: 341.0511; Found: 341.0503.

Synthesis of aryl ether **2.2w**



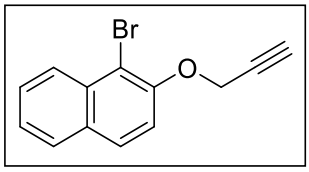
The general procedure for the synthesis of aryl ethers was followed using 2-iodophenol (1.00 g, 4.57 mmol), potassium carbonate (1.90 g, 13.71 mmol, 3 eq) and propargyl bromide in a 20% toluene solution (0.49 mL, 5.48 mmol). A viscous yellow oil was obtained (1.00 g, 3.98 mmol, 85% yield), Mp = oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (dd, *J*= 1.5, 7.8 Hz, Ph-H), 7.30 (td, *J*= 1.5, 8.2 Hz, Ph-H), 6.97 (d, *J* = 8.5 Hz, Ph-H), 6.74 (td, *J* = 1.2, 7.7 Hz, Ph-H), 4.74-4.73 (m, 2H), 2.53-2.52 (m, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.39, 140.78, 130.46, 124.56, 114.20, 87.72, 79.14, 77.25, 58.08 ppm.

HRMS (ESI): calc'd for C_9H_7INaO [M+] 280.943384; Found: 280.943342.

Synthesis of aryl ether **2.2x**



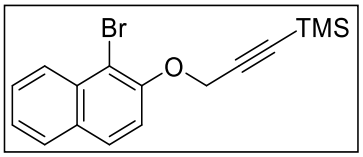
The general procedure for the synthesis of aryl ethers was followed using 1-bromo-2-naphthol (1.00 g, 4.50 mmol), potassium carbonate (1.86 g, 13.50 mmol, 3 eq), and propargyl bromide in a 20% toluene solution (0.60 mL excess, 4.95 mmol). A light brown solid was obtained (1.00 g, 3.98 mmol, 85% yield), Mp = 53-54˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.6 Hz, Ar-H), 7.85 (t, *J* = 9.3 Hz, Ar-H), 7.62-7.60 (m, Ar-H), 7.48-7.45 (m, Ar-H), 7.43 (d, *J* = 9.0 Hz, Ar-H), 4.94 (d, *J* = 2.5 Hz, 2H), 2.59 (t, *J* = 2.5 Hz, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 152.3, 133.3, 130.7, 129.0, 128.3, 128.0, 126.6, 125.0, 116.1, 110.7, 78.6, 76.4, 58.1 ppm.

HRMS (ESI): calc'd for $C_{13}H_9BrNaO$ [M+] 282.972898; Found: 282.972756.

Synthesis of aryl ether **2.2y**



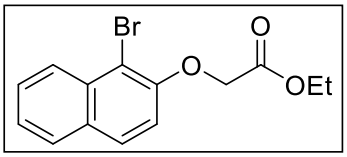
The general procedure for the synthesis of aryl ethers was followed using 1-bromo-2-naphthol (1.00 g, 4.50 mmol, potassium carbonate (1.86 g, 13.50 mmol, 3 eq), and 3-bromo-1-(trimethylsilyl)-1-propyne (0.81 mL, 4.96 mmol). The crude material was a brown solid (1.23 g, 3.70 mmol, 82% yield), Mp = 40-43 ˚C. Material was flash purified using 99:1 hexanes/ethyl acetate. Most column fractions coeluted, but some pure material was obtained (20% product recovery).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.8 Hz, Naph-H), 7.61 (dd, *J* = 3.9 Hz, 8.8 Hz, Naph-H), 7.39-7.37 (m, Naph-H), 7.24-7.22 (m, Naph-H), 4.70 (s, 2H) ppm, 0.00 (s, 9H, TMS) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 152.71, 133.41, 130.75, 128.93, 128.34, 127.96, 126.71, 125.09, 116.73, 110.27, 93.97, 59.20, 0.00 (TMS) ppm.

HRMS (ESI): calc'd for $C_{16}H_{17}BrNaOSi$ [M+] 355.012424; Found: 355.012268.

Synthesis of aryl ether **2.2z**



The general procedure for the synthesis of aryl ethers was followed using bromo-2-naphthol (1.00 g, 4.50 mmol, 1 eq), potassium carbonate (1.86 g, 13.50 mmol, 3 eq), and ethyl bromoacetate (0.50 mL, 4.50 mmol). A brown solid was obtained (1.30 g, 4.23 mmol, 94% yield), Mp = 60-61˚C.

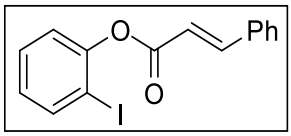
^{1}H NMR (500 MHz, $CDCl_3$): 8.30 (d, *J* = 9.0 Hz, Ar-H), 7.83 (d, *J* = 8.8 Hz, Ar-H), 7.64 (t, *J* = 7.8 Hz, Ar-H), 7.48 (t, *J* = 7.8 Hz, Ar-H), 7.23 (d, *J* = 9.0 Hz), 4.86 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 168.81, 152.73, 133.37, 130.67, 129.13, 128.24, 128.02, 126.66, 125.13, 115.52, 110.58, 67.53, 61.68, 14.34 ppm.

HRMS (ESI): calc'd for $C_{14}H_{13}BrNaO_3$ [M+]: 330.9940; Found: 330.9939.

.

Synthesis of cinnamoyl **2.2aa**



The general procedure for the synthesis of aryl ethers was followed using iodophenol (1.00 g, 4.57 mmol, 1 eq), triethylamine (0.64 mL, 4.57 mmol, 1 eq), a catalytic amount of 4-dimethylaminopyridine (0.028 g, 0.23 mmol, 0.05 eq), and cinnamoyl chloride (0.76 g, 4.57 mmol, 1 eq) in 20 mL of methylene chloride. A pale pink crystalline solid was obtained (0.75 g, 2.10 mmol, 46% yield), Mp = 53-55˚C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03-7.99 (m, 1H), 7.91 (d, *J* = 7.9 Hz, Ph-H), 7.67-7.66 (m, Ph-H), 7.49-7.48 (m, Ph-H), 7.46 (t, *J* = 7.6 Hz, Ph-H), 7.27-7.24 (m, Ph-H), 7.06 (dt, *J* = 1.1, 7.3 Hz, Ph-H), 6.75-6.71 (m, 1H) ppm.

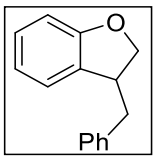
^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 139.39, 134.03, 130.80, 123.37, 129.37, 128.96, 128.38, 127.50, 123.07, 116.81, 90.48 ppm.

HRMS (ESI): calc'd for $C_{15}H_{11}INaO_2$ [M+]: 372.9701; Found: 372.9685.

General Procedure for the Radical Aryl Furan Formation Reactions

In a 1 dram vial, aryl ether (0.5 mmol, 1 eq) was added to a mixture of *t*-Bu-DAP-Br (0.014 g, 0.05 mmol, 0.1 eq) and Cs_2CO_3 (0.163 g, 0.5 mmol, 1 eq). 1 mL of acetonitrile (0.5 mL) was then added. Phenylsilane (0.05 mL, 0.45 mmol, 0.7 eq) was added followed by triethylamine (0.7 mL, 0.5 mmol, 1 eq). This was allowed to stir while being irradiated by LED light at room temperature (If the light wavelength was centered at 427 nm, stirring was overnight at a distance of 7 centimetres. If the light wavelength was centered at 456 nm, stirring was for only 5 hours at a distance of 3 centimetres.). The resulting mixture was extracted using an aqueous hexane-ethyl acetate work up, extracting the organic layer (3x20 mL). Volatiles were removed to obtain an oil. The oil was then dissolved with minimal ethyl acetate, and then 20 mL of hexane was added crashing out a white solid. The white solid was filtered from the solution using a C frit filter, and volatiles were removed to yield the final product.

Synthesis of aryl furan **2.2A**



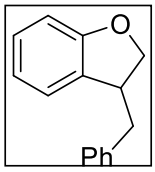
The general procedure for the radical aryl furan formation reactions was followed using **2.2a** (0.168 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 456 nm blue LED. A yellow oil was obtained (0.185 g, 0.88 mmol, 88% yield), Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.0 Hz, Ph-H), 7.13 (t, *J* = 7.0 Hz, Ph-H), 7.06 (d, *J* = 6.7 Hz, Ph-H), 7.01 (t, *J* = 8.2 Hz, Ph-H), 6.85 (d, *J* = 7.5 Hz, Ph-H), 6.70 (t, *J* = 7.5 Hz, Ph-H), 4.40 (t, *J* = 8.6 Hz, 1H), 4.16 (dd, *J* = 5.0, 8.5 Hz, 1H), 3.64-3.58 (m, 1H), 2.94 (dd, *J* = 6.3 13.8 Hz, 1H), 2.72 (dd, *J* = 9.2, 13.8 Hz, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 160.92, 140.13, 131.23, 129.93, 129.49, 129.30, 127.39, 125.48, 121.21, 110.56, 77.23, 44.35, 41.98 ppm.

HRMS (ESI): calc'd for $C_{15}H_{14}NaO$ [M+] 233.0937; Found: 233.9345.

Synthesis of aryl furan **2.2B**



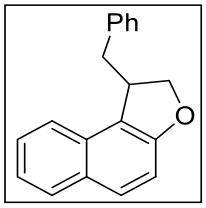
The general procedure for the radical aryl furan formation reactions was followed **2.2b** (0.145 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 violet LED. A yellow oil was obtained (0.208 g, 0.99 mmol, 99% yield), Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.22 (m, Ph-H), 7.18-7.15 (m, Ph-H), 7.12-7.10 (m, Ph-H), 7.07-7.04 (m, Ph-H), 6.90 (d, *J* = 7.2 Hz, Ph-H), 6.76-6.71 (m, Ph-H), 4.47 (t, *J* = 8.3 Hz, 1H), 4.22 (dd, *J* = 6.0, 8.8 Hz, 1H), 3.71-3.65 (m, 1H), 3.01 (dd, *J* = 6.3, 14.2 Hz, 1H), 2.80 (dd, *J* = 8.8, 14.2 Hz, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 160.18, 139.41, 130.51, 129.21, 128.77, 128.57, 126.68, 124.75, 120.49, 109.84, 76.52, 43.65, 41.27 ppm.

HRMS (ESI): calc'd for $C_{15}H_{14}NaO$ [M+] 233.0937; Found: 233.0932.

Synthesis of aryl furan **2.2D**



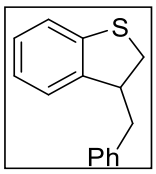
The general procedure for the radical aryl furan formation reactions was followed using **2.2d** (0.167 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427nm LED for 24 hours. Product was then flash purified with 99:1 hexanes:ethyl acetate. Clear oil was obtained (0.087 g, 0.385 mmol, 77 % yield), Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, Ar-H), 7.59 (d, *J* = 8.2 Hz, Ar-H), 7.54 (d, *J* = 8.5 Hz, Ar-H), 7.33-7.29 (m, Ar-H), 7.17-7.13 (m, Ar-H), 7.09-7.06 (m, Ar-H), 7.04 (d, *J* = 7.0 Hz, Ar-H), 6.98 (d, *J* = 8.8 Hz, Ar-H), 4.40-4.33 (m, 2H), 3.91-3.86 (m, 1H), 3.20 (dd, *J* = 3.9 Hz, 14.3 Hz, 1H), 2.63 (dd, *J* = 10.3 Hz, 14.2 Hz, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 158.47, 140.51, 131.49, 130.61, 130.59, 130.11, 130.08, 129.59, 127.73, 127.42, 123.78, 123.32, 122.90, 113.32, 77.23, 44.30, 41.04 ppm.

HRMS (ESI): calc'd for $C_{19}H_{16}NaO$ [M+] 283.1093; Found: 283.1084.

Synthesis of aryl furan **2.2E**



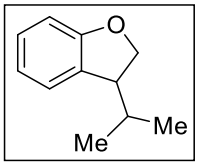
The general procedure for the radical aryl furan formation reactions was followed using **2.2e** (0.305 g, 1 mmol, 1 eq). The reaction was irradiated using a 427 nm violet LED. A yellow oil was obtained (0.107 g, 0.48 mmol, 95% yield), Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (t, *J* = 7 Hz, Ph-H), 7.35-7.29 (m, Ph-H), 7.24 (t, *J* = 7.1 Hz, Ph-H), 7.15 (t, *J* = 7.1 Hz, Ph-H), 7.12 (t, *J* = 7.3 Hz, Ph-H), 3.82-3.76 (m, 1H), 3.45 (dd, *J* = 7.43, 11.0 Hz, 1H), 3.21 (ddd, *J* = 5.5, 13.6, 25.1 Hz, 2H), 2.96 (dd, *J* = 9.7, 13.7 Hz, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 142.98, 141.54, 139.74, 129.28, 128.68, 127.91, 126.55, 124.46, 124.25, 122.62, 49.80, 39.84, 38.37 ppm.

HRMS (ESI): calc'd for $C_{15}H_{15}S$ [M+]: 227.0889; Found: 227.0893.

Synthesis of compound **2.2F**



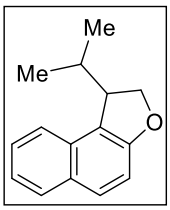
The general procedure for the radical aryl furan formation reactions was followed using **2.2f** (0.144 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 456 nm LED. A clear colourless oil was obtained (0.080 g, 0.50 mmol, 99% yield), Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.3 Hz, Ph-H), 7.13-7.10 (m, Ph-H), 6.86 (td, *J* = 0.9, 7.4 Hz, Ph-H), 6.78 (d, *J* = 8.1 Hz, Ph-H), 4.53 (t, *J* = 9.3 Hz, 1H), 4.35 (dd, *J* = 4.8, 8.8 Hz, 1H), 3.34 (dt, *J* = 5.1, 9.2 Hz, 1H), 1.99-1.93 (m, 1H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 7.3 Hz, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 160.86, 129.85, 128.56, 125.49, 120.48, 109.76, 74.25, 48.60, 32.13, 20.23, 18.86 ppm.

HRMS (ESI): calc'd for $C_{11}H_{15}O$ [M+]: 163.1117; Found: 163.1115.

Synthesis of aryl furan **2.2G**



The general procedure for the radical aryl furan formation reactions was followed using **2.2g** (0.146 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 nm violet LED. A yellow oil was obtained (0.101 g, 0.48 mmol, 95% yield), Mp= oil.

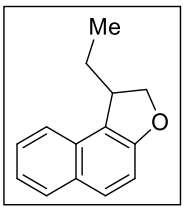
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.3 Hz, Ar-H), 7.76 (d, *J* = 8.8 Hz, Ar-H), 7.71 (d, *J* = 8.8 Hz, Ar-H), 7.48-7.45 (m, Ph-H), 7.32-7.29 (m, Ph-H), 7.14 (d, *J* = 8.8 Hz, Ph-H), 4.70 (dd, *J* = 3.0 Hz, 9.0 Hz, 1H), 4.62 (t, *J* = 9.0 Hz, 1H), 3.83 (dt, *J* = 3.2 Hz, 9.0 Hz, 1H), 2.46-2.40 (m, Ph-H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 7.0 Hz, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.86, 131.00, 129.74, 129.54, 129.18, 126.58, 122.85, 122.76, 121.38, 112.27, 73.01, 47.90, 30.37, 21.39, 16.43 ppm.

HRMS (ESI): calc'd for $C_{15}H_{15}O$ [M+]: 211.1128; Found: 211.1133.

.

Synthesis of aryl furan **2.2H**



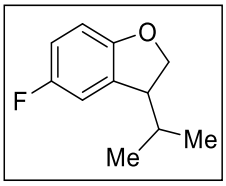
The general procedure for the radical aryl furan formation reactions was followed using **2.2h** (0.139 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 nm violet LED. A clear yellow oil was obtained (0.071 g, 0.36 mmol, 72% yield), Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.4 Hz, Ar-H), 7.80 (d, *J* = 8.7 Hz, Ar-H), 7.68 (d, *J* = 8.7 Hz, Ar-H), 7.47-7.43 (m, Ar-H), 7.31-7.27 (m, Ar-H), 7.12 (d, *J* = 8.8 Hz, Ar-H), 4.72 (t, *J* = 8.5 Hz, 1H), 4.55 (dd, *J* = 3.5, 8.9 Hz, 1H), 3.80 (sept, *J* = 3.5 Hz, 1H), 2.00-1.92(m, 1H), 1.79-1.70 (m, 1H), 0.97 (t, *J* = 7.7 Hz, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 157.85, 131.14, 129.98, 129.71, 129.43, 126.94, 123.08, 122.86, 122.38, 112.58, 77.12, 43.41, 27.30, 11.41 ppm.

HRMS (ESI): calc'd for $C_{14}H_{15}O$ [M+]: 199.1117; Found: 199.1113.

Synthesis of aryl furan **2.2M**



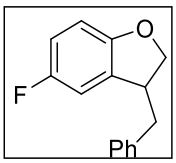
The general procedure for the radical aryl furan formation reactions was followed using **2.2m** (0.130 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 nm LED. A yellow oil was obtained (0.088 g, 0.49 mmol, 99% yield), Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (ddd, *J* = 0.6, 2.7, 8.2 Hz, Ph-H), 6.86-6.82 (m, Ph-H), 6.72 (dd, *J* = 4.1, 8.6 Hz, Ph-H), 4.60 (t, *J* = 9.3 Hz, 1H), 4.44 (dd, *J* = 5.1, 9.3 Hz, 1H), 3.37-3.33 (m, 1H), 2.04-1.95 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 158.41, 156.56, 156.53, 134.42-134.24 (m), 131.11 (d), 128.08-127.61 (m), 144.49 (d), 112.37 (d), 109.53 (d), 74.60, 48.65, 31.77, 19.88 (d) ppm.

Note: Impurity signals in the aromatic region most likely arise from phenylsilane by-product.

Synthesis of aryl furan **2.2N**



The general procedure for the radical aryl furan formation reactions was followed using **2.2n** (0.153 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 nm LED. A colourless oil was obtained (0.105 g, 0.41 mmol, 92% yield), Mp= oil.

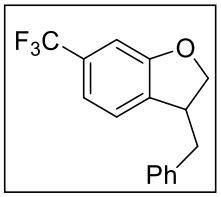
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.32 (m, Ph-H), 7.28-7.24 (m, Ph-H), 7.19-7.18 (m, Ph-H), 6.83 (td, *J* = 2.5 Hz, 9.0 Hz, Ph-H), 6.71 (dd, *J* = 4.2 Hz, 8.4 Hz, Ph-H), 6.65 (dd, *J* = 2.5 Hz, 8.0 Hz, Ph-H), 4.57 (t, *J* = 8.5 Hz, 1H), 4.32 (dd, *J* = 5.9 Hz, 8.9 Hz, 1H), 3.76-3.70 (m, 1H), 3.04 (dd, *J* = 6.6 Hz, 13.9 Hz, 1H), 2.90 (dd, *J* = 8.8 Hz, 14.0 Hz, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 158.56, 156.68 (d, *J* = 54.4 Hz), 139.024, 132.04 (d, *J* = 8.3 Hz), 129.30, 128.97, 126.98, 114.86(d, *J* = 24.8 Hz), 112.12 (d, *J* = 24.8 Hz), 110.00 (d, *J* = 8.5 Hz), 77.62 (d, *J* = 6.1 Hz) 44.03, 41.07 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -124.41– -124.46 (m) ppm.

HRMS (ESI): calc'd for $C_{15}H_{14}FO$ [M+]: 229.1023; Found: 229.1020.

Synthesis of aryl furan **2.2P**



The general procedure for the radical aryl furan formation reactions was followed using **2.2p** (0.357 g, 1.0 mmol, 1 eq). The reaction was irradiated using a 427 nm violet LED. A red oil was obtained (0.270 g, 0.97 mmol, 97% yield), Mp= oil. Product oil was flash purified using 99:1 hexanes and ethyl acetate eluent (74% recovery).

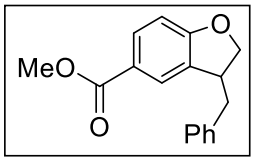
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (t, *J* = 7.4 Hz, Ph-H), 7.17 (t, *J* = 7.4 Hz, Ph-H), 7.08 (d, *J* = 7.4 Hz, Ph-H), 6.98 (d, *J* = 8.0 Hz , Ph-H) 6.92 (s, Ph-H), 6.88 (d, *J* = 8.0 Hz, Ph-H), 4.51 (t, *J* = 9.5 Hz, 1H), 4.27 (dd, *J* = 6.1, 9.0 Hz, 1H), 3.70 (quin, *J* = 7.5 Hz, 1H) 2.95 (dd, *J* = 6.9, 13.9 Hz, 1H), 2.80 (dd, *J* = 8.6, 13.9 Hz, 1H) ppm.

^{13}C{H} NMR (125 MHz, $CDCl_3$): δ 160.54, 138.75, 134.68, 131.59 (q, *J* = 32.3 Hz, CF_3), 129.24, 128.93, 126.98, 125.49, 125.08, 123.32, 117.70 (q, *J* = 3.6 Hz, Ph), 106.93 (q, *J* = 3.8 Hz, Ph), 43.43, 41.07 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -62.26 ppm.

HRMS (ESI): calc'd for $C_{16}H_{14}F_3O$ [M+]: 279.0991; Found: 279.0990.

Synthesis of aryl furan **2.2Q**

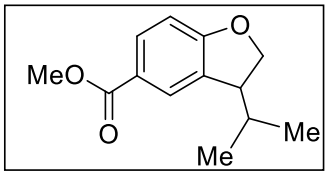


The general procedure for the radical aryl furan formation reactions was followed using **2.2q** (0.173 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 nm violet LED. A yellow oil was obtained containing an inseparable contaminant. Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 1.9 Hz, 8.5 Hz, Ph-H), 7.81 (s, Ph-H), 7.38-7.31 (m, Ph-H), 7.29-7.26 (m, Ph-H), 7.21 (d, *J* = 6.5 Hz Ph-H), 6.85 (d, *J* = 8.2 Hz, Ph-H), 4.62 (t, *J* = 8.8 Hz, 1H), 4.41 (dd, *J* = 6.0, 9.1 Hz, 1H), 3.90 (s, 3H), 3.83-3.73 (m, 1H), 3.17 (dd, *J* = 5.5, 13.5 Hz, 1H), 2.87 (dd, *J* = 9.5, 13.5 Hz, 1H) ppm.

HRMS (ESI): calc'd for $C_{17}H_{16}NaO_3$ [M+]: 291.0992; Found: 291.0995.

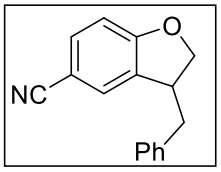
Synthesis of aryl furan **2.2R**



The general procedure for the radical aryl furan formation reactions was followed using **2.2r** (0.150 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 nm violet LED. A yellow oil was obtained containing an inseparable contaminant. Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86-7.84 (m, Ph-H), 6.75 (d, *J* = 8.51 Hz, Ph-H), 4.58 (t, *J* = 9.5 Hz, 1H), 4.43 (dd, *J* = 5.2, 9.0 Hz, 1H), 3.84 (s, 3H), 3.35 (m, 1H), 2.00-1.93 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H) ppm.

Synthesis of benzofuran **2.2S**

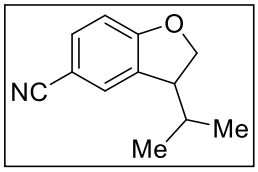


The general procedure for the radical aryl furan formation reactions was followed using **2.2s**. The reaction was irradiated using a 427 nm violet LED. A yellow oil was obtained containing an inseparable contaminant. Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 1.9, 8.3 Hz, Ph-H), 7.34-7.31 (m, Ph-H), 7.28-7.24 (m, Ph-H), 7.15-7.13 (m, Ph-H), 6.82 (d, *J* = 8.5 Hz, Ph-H), 4.64 (t, *J* = 9.8 Hz, 1H), 4.40 (dd, *J* = 5.8, 9.1 Hz, 1H), 3.79 (quin, *J* = 7.5 Hz, 1H), 3.00 (dd, *J* = 7.1, 13.9 Hz, 1H), 2.90 (dd, *J* = 8.4, 13.9 Hz, 1H) ppm.

HRMS (ESI): calc'd for $C_{16}H_{13}NNaO$ [M+]: 258.0889; Found: 258.0886.

Synthesis of aryl furan **2.2T**



The general procedure for the radical aryl furan formation reactions was followed using **2.2t** (0.133 g, 0.5 mmol, 1 eq). The reaction was irradiated using a 427 nm violet LED. A yellow oil was obtained containing an inseparable contaminant. Mp= oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.41 (m, Ph-H), 6.79 (d, *J* = 8.4 Hz, Ph-H), 4.60 (t, *J* = 8.52 Hz, 1H), 4.45 (dd, *J* = 5.2, 8.1 Hz, 1H), 3.36-3.32 (m, 1H), 1.97-1.91 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H) ppm.

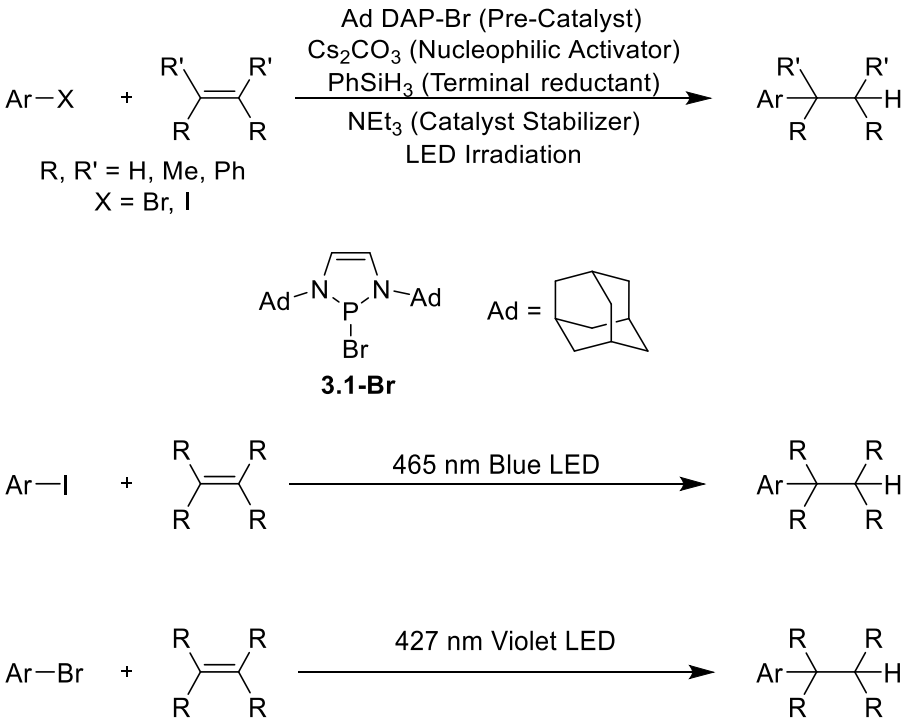
Chapter 3: Catalytic Intermolecular Alkylations

3.1 Contributions

There are no contributions to add in this section.

3.2 Introduction

The success we had with the intramolecular cyclizations inspired the thought of performing carbon-carbon bond synthesis intermolecularly. Instead of using a radical donor and an acceptor on the same substrate, the reactivity studied in this section will explore a select few alkylation reactions from one separate radical donor, and another separate radical acceptor (Scheme 3.1). This is a more challenging reaction, because in the intermolecular reaction the effective concentration of the radical trap is lower, giving the radical more time to engage in undesired reactivity.



Scheme 3.1: General reaction conditions for the intermolecular alkylation reactions. Reactions that involved use of an aryl iodide were done under the irradiation of a 456 nm blue LED. Reactions that involved use of an aryl bromide were done under the irradiation of a 427 nm violet LED.

The same radical mechanism applies in this chemistry from the intramolecular cyclizations, and the reaction reagents utilized are the same. The logic of using the 456 nm blue LED for iodide substrates, and the 427 nm violet LED for bromide substrates were applied in this chemistry as well. Intermolecular alkylations are much more challenging to achieve compared to intramolecular cyclizations. Since the active reactants in the carbon-carbon bond formation are not on the same molecule, it is much easier for the radical donor to perform side reactions, such

as dimerization, reaction with the solvent, or H atom transfer from the diazaphospholene, than to find and react with its corresponding radical acceptor in solution.

With this concept in mind, other criteria of a successful radical intermolecular alkylation can be relied on for radical carbon-carbon bond synthesis. If the C-X bond is relatively weak, the activation barrier will be lowered making the initiation of the reaction faster. For example, if the radical acceptor alkene is electrophilic, the nucleophilic radical donor will have more of an affinity to interact with the acceptor as opposed to performing a side reaction. Also, if the radical acceptor is added in excess, it will be much more likely that radical donor will react with it[28]. These three factors were considered when attempting to perform this chemistry.

3.3 Results and Discussion

A set of substrates consisting of alkene radical acceptors and aryl halide radical donors were reacted using the previously optimized conditions. Unfortunately, there was a general lack of success, which could be attributed to the nature of the chemistry, and the difficulties stated previously. Not only the radical intermediates are more likely to perform side reactions, but the diazaphospholene catalyst had an affinity to react with the radical acceptor, shutting down the catalytic cycle (Figure 3.1).

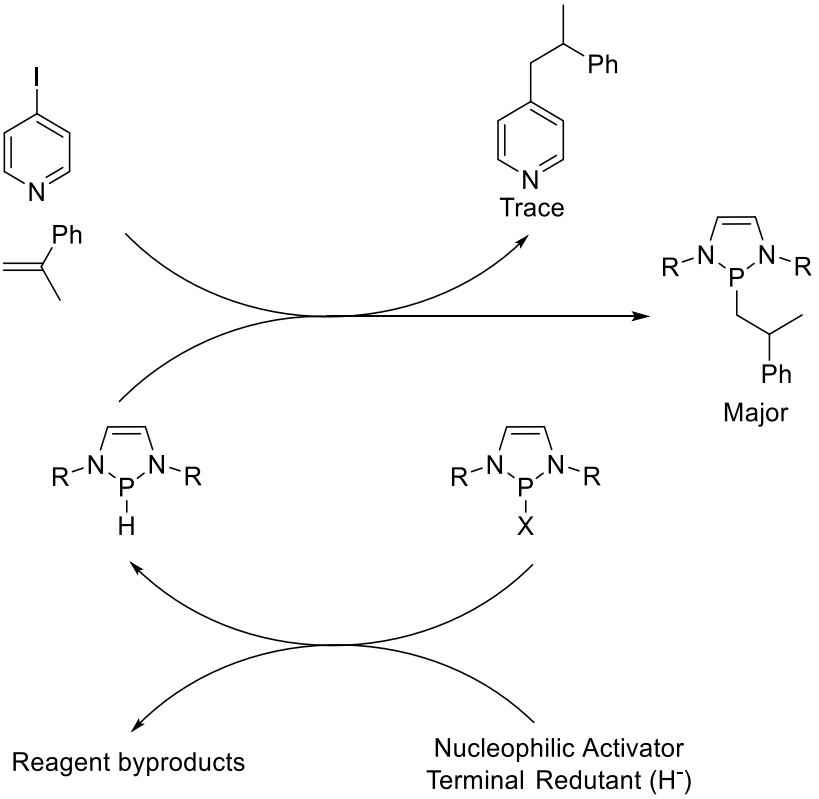
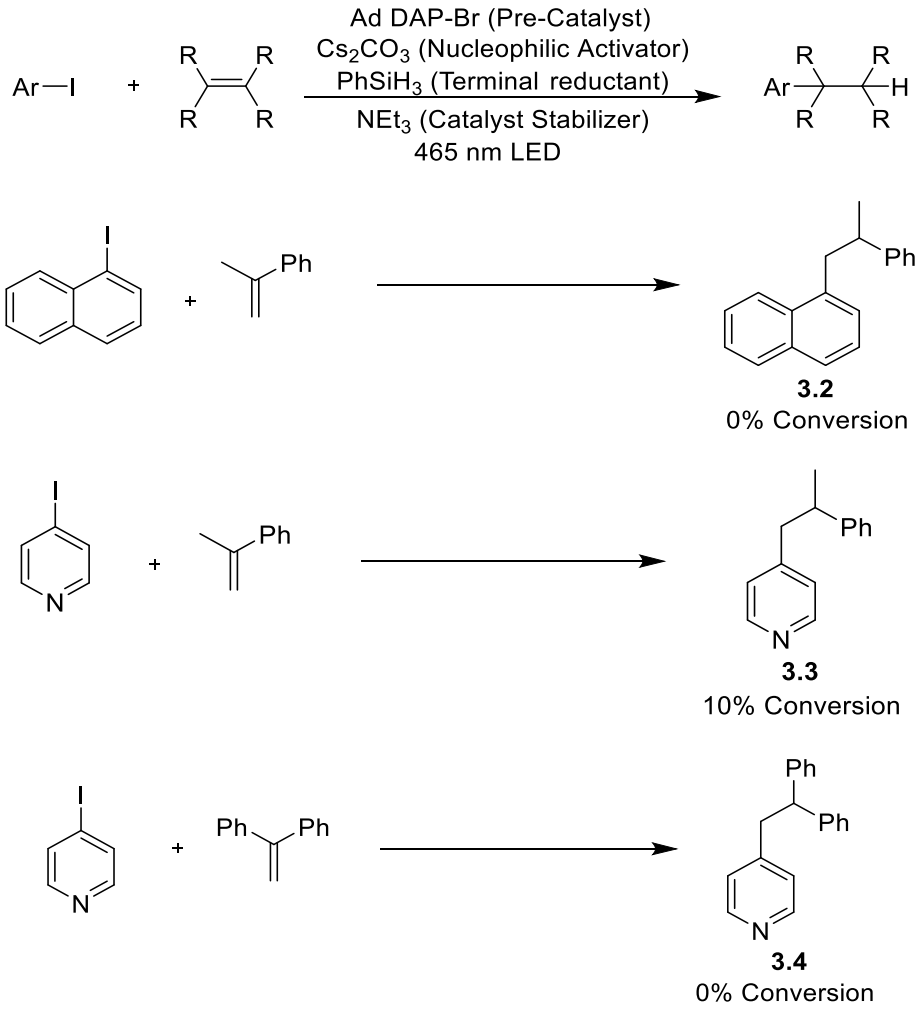


Figure 3.1: The proposed mechanism for the intermolecular alkylation.

It was later found that catalytic use of a diazaphospholene bromide bearing adamantyl substituents on the nitrogen atoms (**3.1-Br**) gave overall higher conversions than the *tert*-butyl

DAP-H. This was explained by the additional steric hinderance of the adamantyl groups slowing down the DAP reactivity of the radical acceptor.

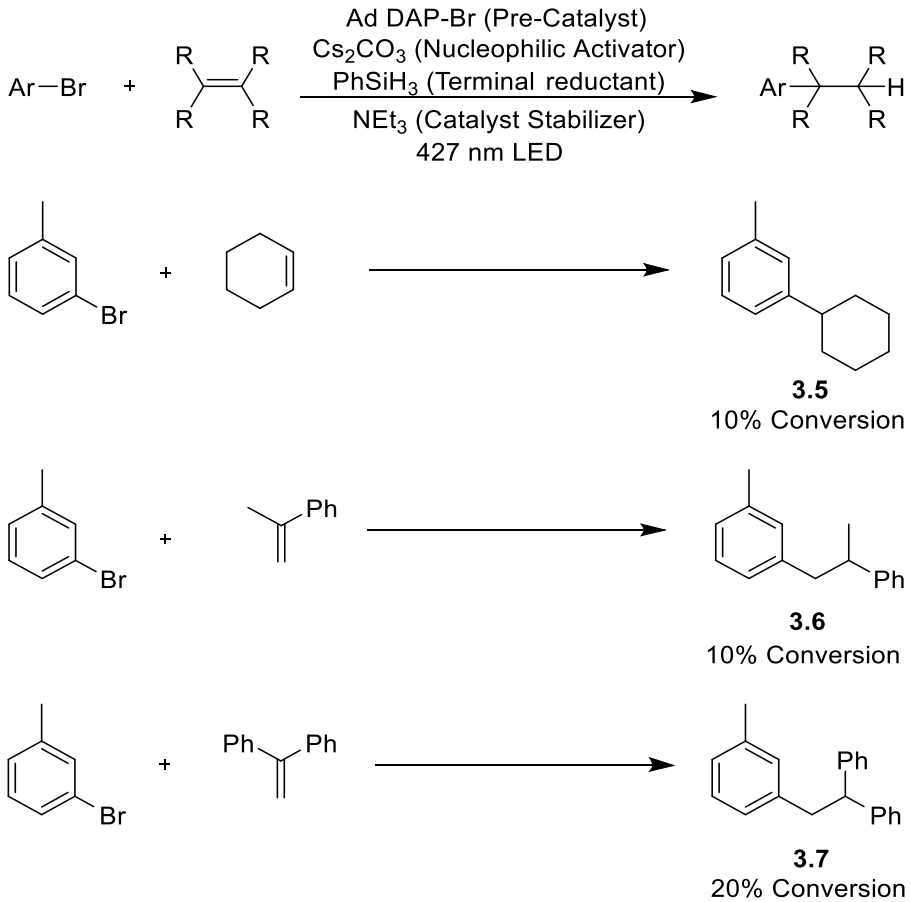
Conversions were determined by comparing ^{1}H NMR peak integration ratios of target product to starting material or undesired product.



Scheme 3.2: Intermolecular alkylations with iodide donors, showing conversion percentage by integrations of product and starting material.

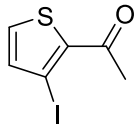
Alkylation reactions using aryl iodides showed little promise, where attempted synthesis of compound **3.2** using 1-iodonaphthalene and methyl styrene, and attempted synthesis of

compound **3.4** using 4-iodopyridine and diphenylethylene were not successful. These failed reactions did show activity, with major signals in their ^{31}P NMR indicating P-C bond forming reactions between the diazaphospholene and the alkene acceptor. Only a fraction of conversion to the alkylated product **3.3** was shown to occur upon a reaction with 4-iodopyridine and methyl styrene, giving a 12% conversion. However, alkylated product **3.3** was isolated upon aqueous workup with ethyl acetate, followed by column chromatography using 99:1 hexanes-ethyl acetate eluent. Although some of **3.3** was isolated, the yield was low (< 10%) and included a minor impurity.

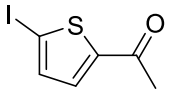


Scheme 3.3: Intermolecular alkylations with bromide donors, showing conversion percentage by integration of the product and starting material.

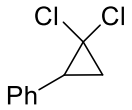
Reactions carried out with aryl bromide radical donors delivered miniscule conversion percentages but were more successful than aryl iodide radical donors (Scheme 3.3). Compound **3.5** using 1,3-bromotoluene and cyclohexene showed a trace conversion of 10%. The same conversion was observed for the generation of compound **3.6**, from 1,3-bromotoluene and methyl styrene. The best results were obtained for the generation of compound **3.7**, using diphenyl ethylene with 1,3-bromotoluene, which gave an increased alkylation conversion to 20%. The result of these bromo substrate alkylation reactions were similar to those of the iodo substrates. After the reaction was complete, the formation of P-C environments were evident in the ^{31}P NMR spectra, indicating again that some diazaphospholene functionalization had occurred. Potential radical donors **3a**, **3b**, **3c**, and **3d** (figure 3.2) were reacted with methyl styrene under the previous conditions but were shown to be inert during reaction trials.



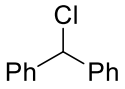
3a



3b



3c



3d

Figure 3.2: Unsuccessful intermolecular radical donors that were also reacted in this work. Methyl-3-iodothiophene (**3a**), 2-acetyl-5-iodothiophene (**3b**), cyclopropyldichlorophenyl (**3c**), chlorodiphenylmethane (**3d**).

3.4 Conclusions and Future Work

Alkylating aryl halides and radical accepting alkenes intermolecularly using **3.1-Br** is an incomplete project but one that has potential for success with more optimizing and screening of conditions. The conditions used in this work still shows some promise however, with indications of some reactivity; higher conversion could potentially be achieved for one of the substrate pairs. The testing of new substrate pairs and the optimization experiments should be investigated in the future. If higher yields were obtained, use of chiral diazaphospholenes might reveal if enantioselectivity is feasible in these radical reactions.

3.5 Experimental Section

All reagents and solvents were dispensed in a 2001 issue IT Glovebox (H_2O levels may vary between 2-6 ppm) unless otherwise stated. The intermolecular alkylation reactions and related reactions were prepared in a 1-dram vials equipped with magnetic stir bars. All reactions were conducted at ambient temperature unless otherwise stated. The material selected to prepare NMR samples gave homogeneous solutions unless otherwise stated. ^{1}H, ^{31}P, ^{13}C NMR data were collected at 300K on either a Bruker AV-300 or AV-500 spectrometer. ^{1}HNMR spectra are referenced to residual non-deuterated NMR solvent from the sample ($CDCl_3$ = 7.24 ppm). ^{13}C NMR spectra are referenced to as follows ($CHCl_3$ = 77.16 ppm). LED irradiation was conducted using a Kessil H150-Blue lamp centered at a wavelength approximately 456 nm (50 W max), and a Kessil H150-Violet lamp with a maximum emission centered at a wavelength approximately 427 nm (45 W max). The melting points of isolated products were observed using a Fischer-Johns melting point apparatus.

Solvents

Acetonitrile was purchased as anhydrous >99% ACS grade from Sigma Aldrich and used without purification.

Hexanes was purchased in a drum ACS grade from Fisher and used as is.

Ethyl acetate was purchased in a drum ACS grade from Fisher and used as is.

Reagents

Potassium carbonate was purchased from ACP and used as received.

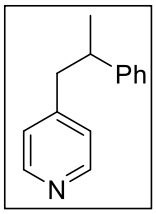
Cesium carbonate was purchased from Sigma Aldrich, stored at ambient temperature in the glovebox, and used as received.

Phenylsilane was purchased from Oakwood Chemical, stored at ambient temperature in the glovebox, and used as received.

Diazaphospholene (**3.1-Br**) was prepared according to literature methods[7].

Synthesis and Characterization

Synthesis of compound **3.3**



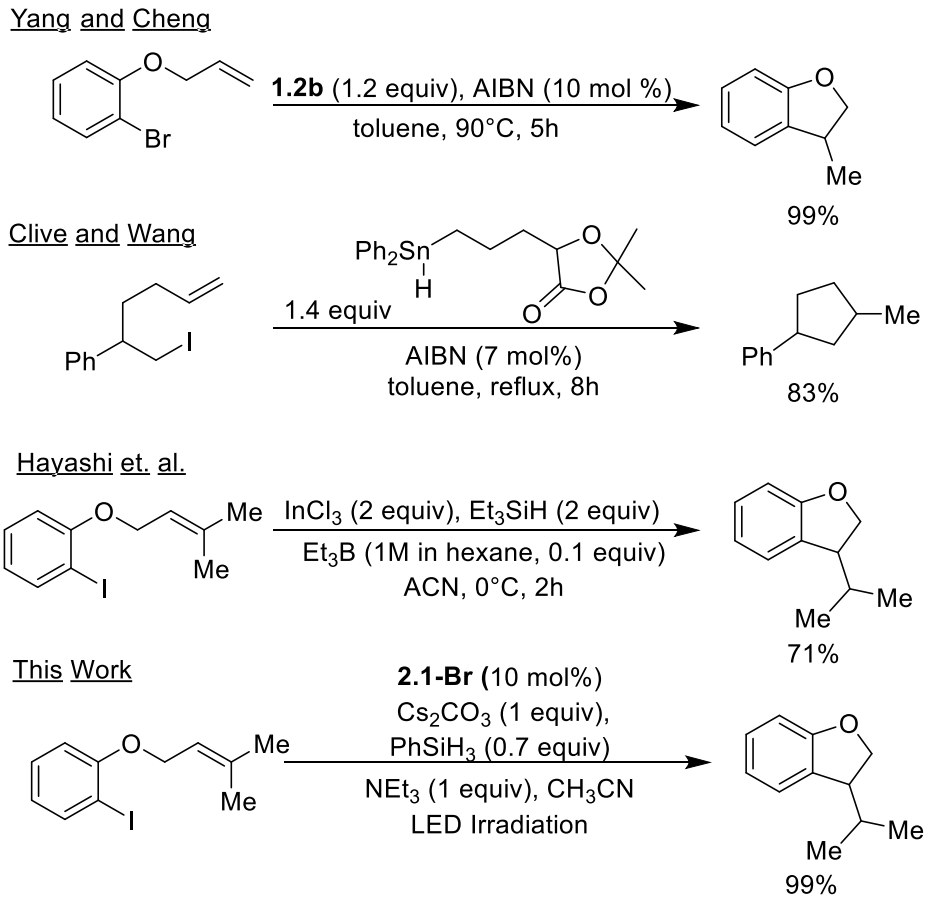
In a 1 dram vial, 4-iodopyridine (0.039 g, 0.144 mmol, 1 eq) was added to a mixture of **3.1-Br** (0.015 g, 0.036 mmol, 0.15 eq) and cesium carbonate (0.047 g, 0.114 mmol, 1 eq). Methyl styrene (0.04 mL, 0.288 mmol, 2 eq) was then added to the mixture followed by phenylsilane (0.03 mL, 0.243 mmol, 1.7 eq) and triethylamine (0.02 mL, 0.144 mmol, 1 eq). This mixture was allowed to stir for 4 hours while being irradiated by a 456 nm LED. The resulting mixture was extracted using an aqueous hexane-ethyl acetate work up, extracting the organic layer (3x 20 mL). Volatiles were removed to obtain an oil. The oil was purified using column chromatography with the eluent consisting of a 1:1 ratio of ethyl acetate and hexane. Volatiles were removed by rotatory evaporation, and the ^{1}H NMR spectra was obtained corresponding to the oil.

Note: The oil contained excess ethyl acetate which overlapped with the CH_3 signal.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, *J* = 5.6 Hz, Ar-H), 7.28-7.25 (m, Ar-H), 7.20-7.16 (m, Ar-H), 7.14- 7.12 (m, Ar-H), 6.96 (d, *J* = 5.7 Hz, Ar-H), 3.73 (q, *J* = 7.0 Hz, Impurity), 3.05 (sextet, *J* = 7.0 Hz, 1H), 2.92 (dd, *J* = 7.2 Hz, 13.4 Hz, 1H), 2.82 (dd, *J* = 7.2 Hz, 13.4 Hz, 1H) ppm.

Chapter 4: Conclusions

The work presented in this thesis expands on existing diazaphospholene radical chemistry that was done in a stoichiometric manner, by allowing it to be made catalytic. This work will also open more doors for diazaphospholene radical chemistry with the use of LED lights (Scheme 4.1). Known diazaphospholene **2.2-Br** was synthesized, and a system was successfully developed to generate catalyst **2.2-H** in situ while remaining stable under the reaction conditions for a considerable amount of time. This system was then applied to cyclizing aryl ether substrates and was successful in doing this chemistry catalytically. The metal free cyclization method is superior to previous literature systems, and even superior to similar organometallic catalysis that are stoichiometric for these substrate classes. Most aryl ether substates reacted in this scope were not successful, most having to do with the radical acceptor groups deviating from an alkene. Substrates with radical acceptors such as alkynes, and aryl groups will need more screening (potentially more aggressive reacting systems for non-reacting substrates such as aryl bearing acceptors and chloride substrates, and more mild systems for overly reactive substrates such as alkynes). Yields of these products have room for improvement as well with improved purification techniques.



Scheme 4.1: Comparison of previous intramolecular cyclization chemistry in the literature, followed by the improved method for aryl ether class substrate cyclization developed by the Speed group.

These reactions create a stereocenter, and with asymmetric chemistry being an area of expertise of the Speed group, another future objective would involve synthesizing stereochemically pure bicyclic products. This might be achieved by using a different chiral diazaphospholene catalyst, or by using a chiral auxiliary.

Developing intermolecular alkylation reactions using **3.1-Br** was a much more challenging task. It is more difficult for the radical acceptor and the radical donor to react with each other in

solution, given the limited lifetimes of aryl radicals. Only a highlight reel of this work was presented in this thesis even though results were incomplete and modest, showing conversions up to 20% at best. This incomplete project still has potential for success. Much more screening is required than previously done, with some but not all variables including reaction time, catalyst variants, catalyst loading, LED irradiation screening, and new reactants. With optimal conditions established, product conversions are sure to increase to more satisfactory values. Isolation of compound **3.3** showed that it is possible by aqueous work up and column chromatography. Other future work on this project will be doing these alkylating reactions asymmetrically with chiral DAPs. An alternate strategy to achieve asymmetric product formation could use a chiral auxiliary to aid in stereo-control.

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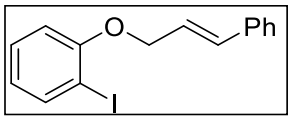
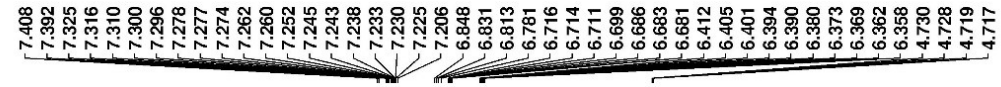
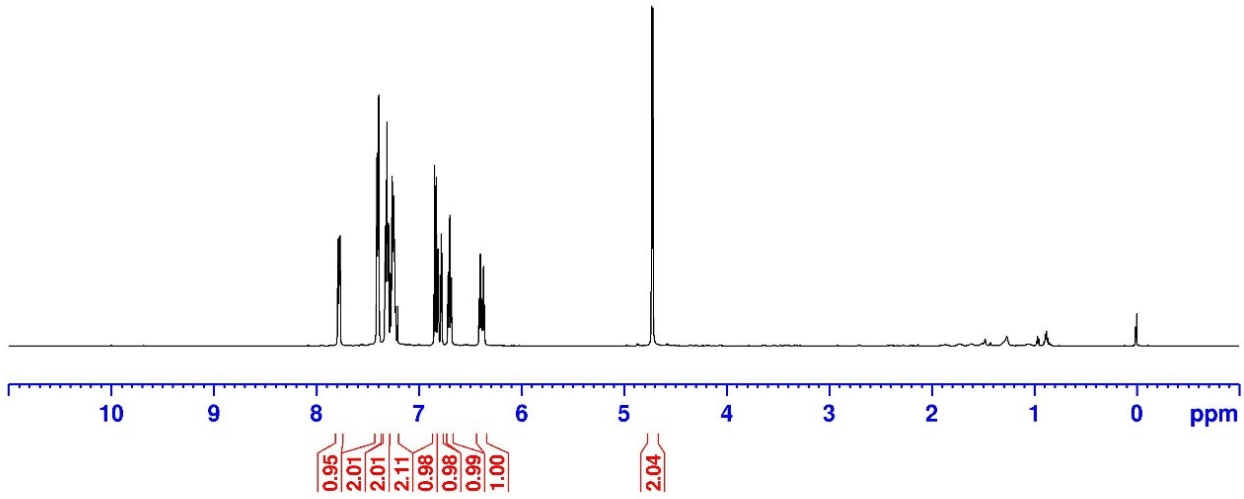
Appendix A: NMR Spectra for Chapter 2

(2.2a)

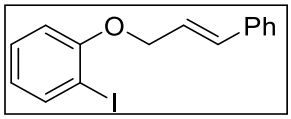
^{1}H NMR

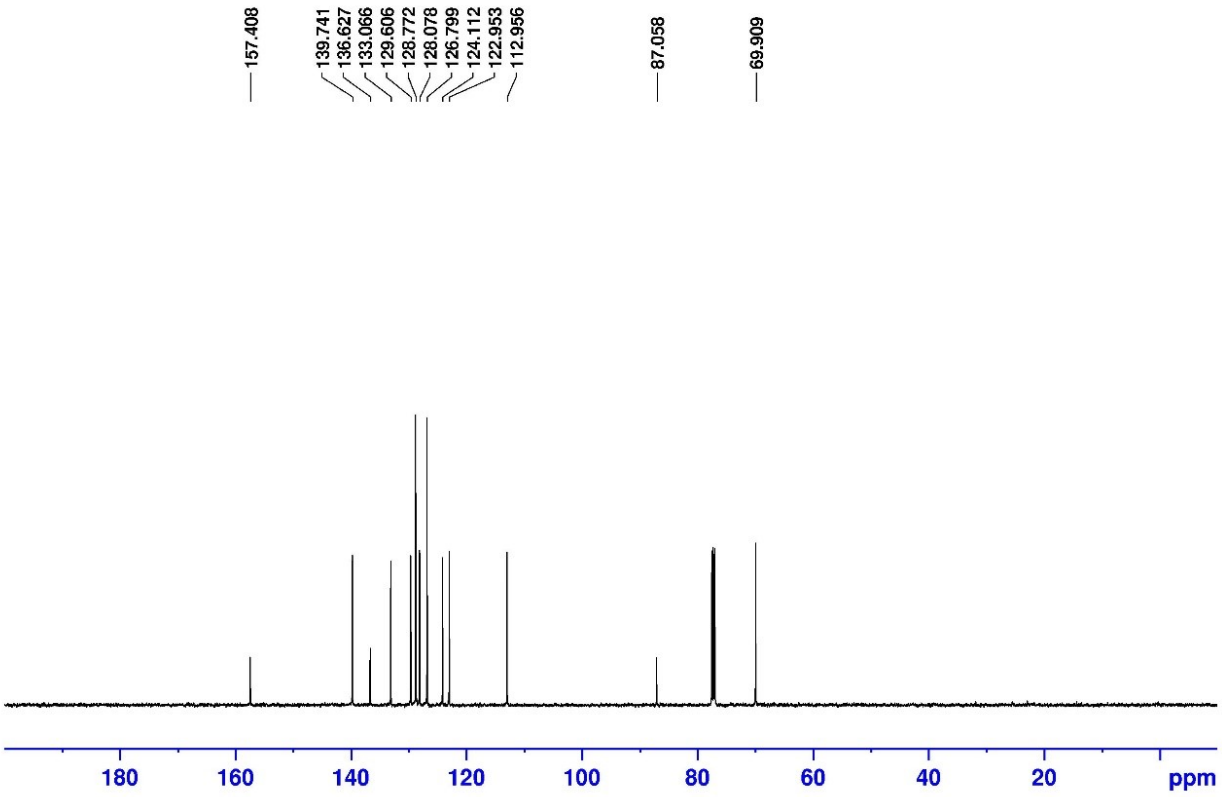






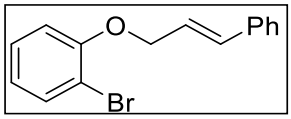
^{13}C NMR

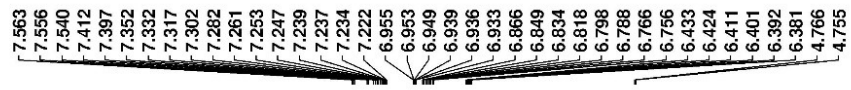

O
Ph
I


157.408
139.741
136.627
133.066
129.606
128.772
128.078
126.799
124.112
122.953
112.956
87.058
69.909
180
160
140
120
100
80
60
40
20
ppm

(**2.2b**)

^{1}H NMR


O
Ph
Br


7.563
7.556
7.540
7.412
7.397
7.352
7.332
7.317
7.302
7.282
7.261
7.253
7.247
7.239
7.237
7.234
7.222
6.955
6.953
6.949
6.939
6.936
6.933
6.866
6.849
6.834
6.818
6.798
6.788
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6.756
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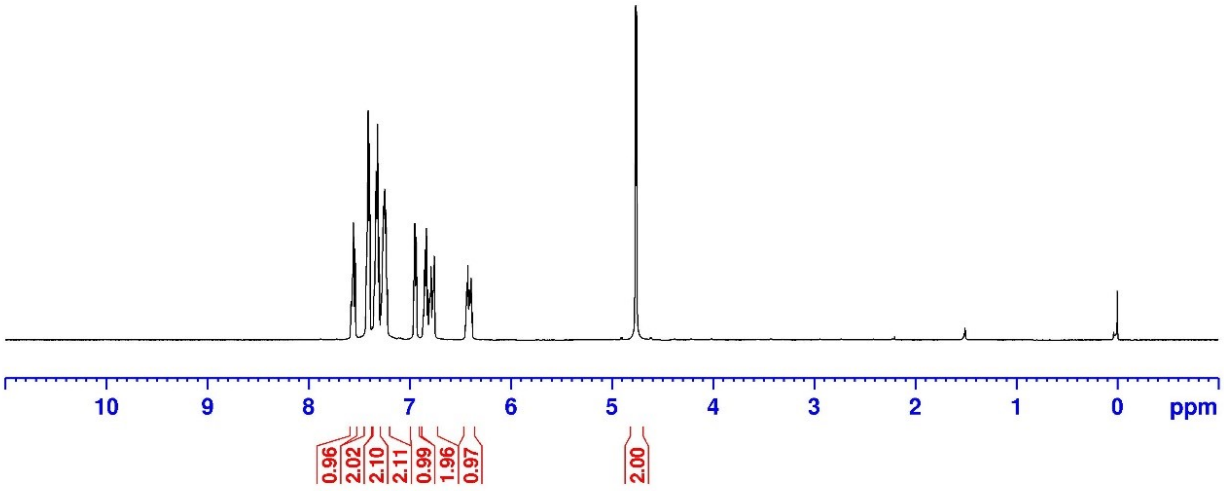
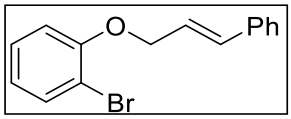
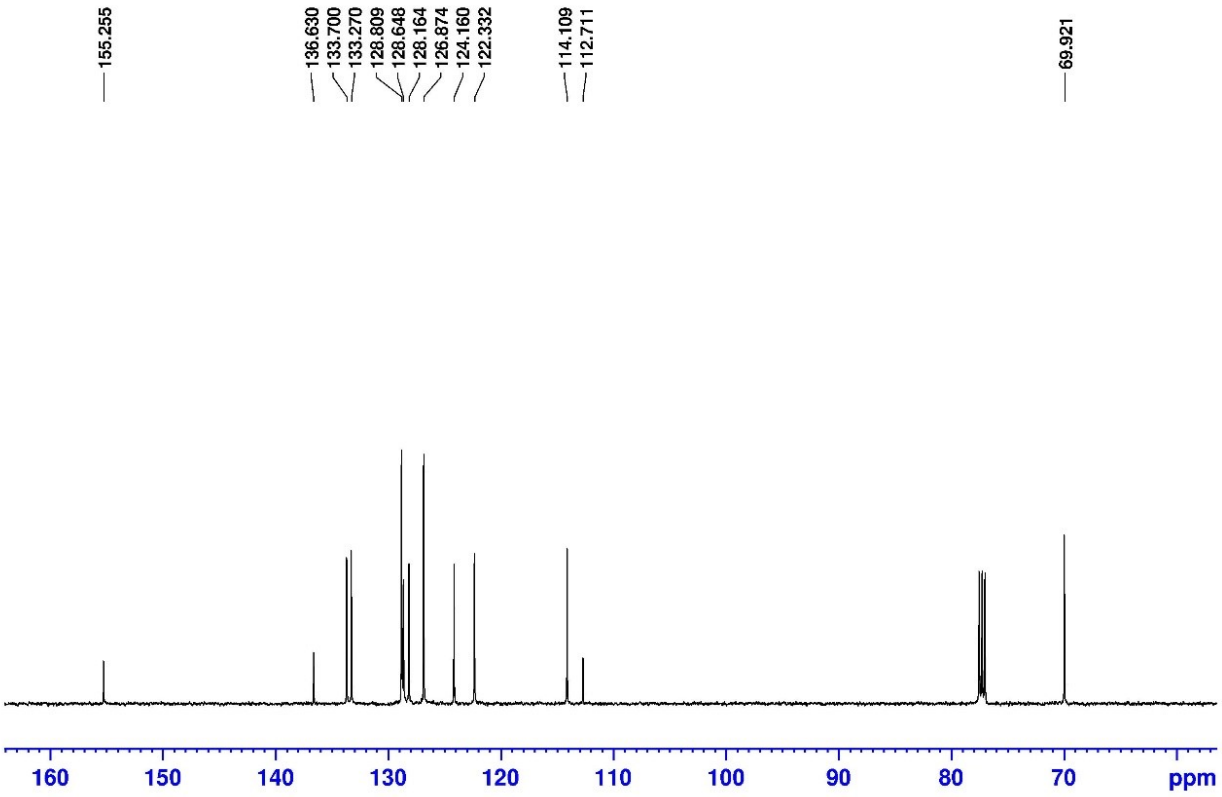
6.401
6.392
6.381
4.766
4.755


10
9
8
7
6
5
4
3
2
1
0
ppm
0.96
2.02
2.10
2.11
0.99
1.96
0.97
2.00

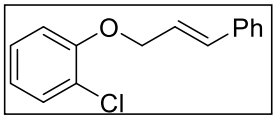
^{13}C NMR

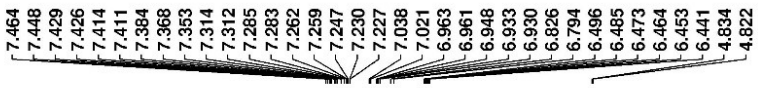

O
Ph
Br

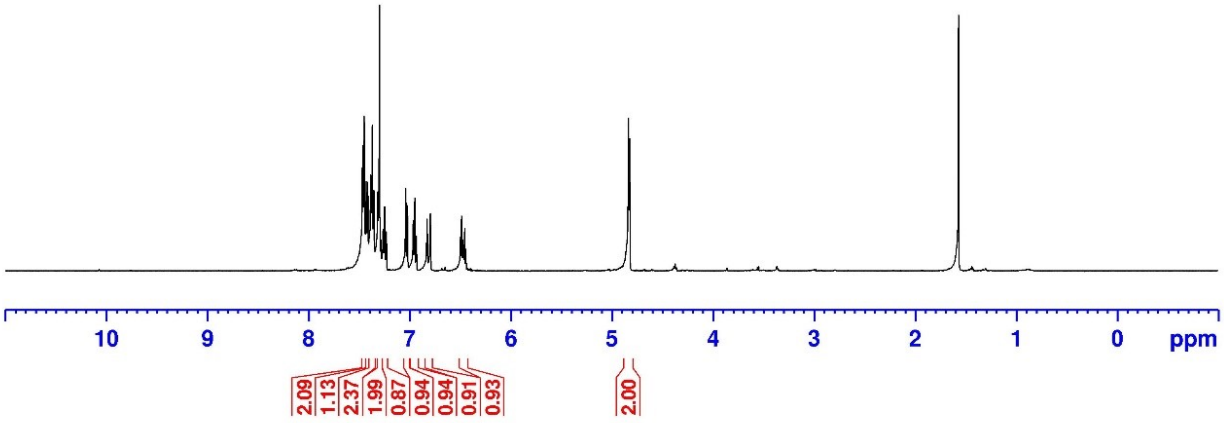

155.255
136.630
133.700
133.270
128.809
128.648
128.164
126.874
124.160
122.332
114.109
112.711
69.921
160
150
140
130
120
110
100
90
80
70
ppm

(**2.2c**)

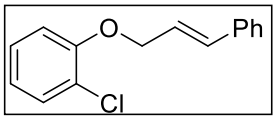
^{1}H NMR

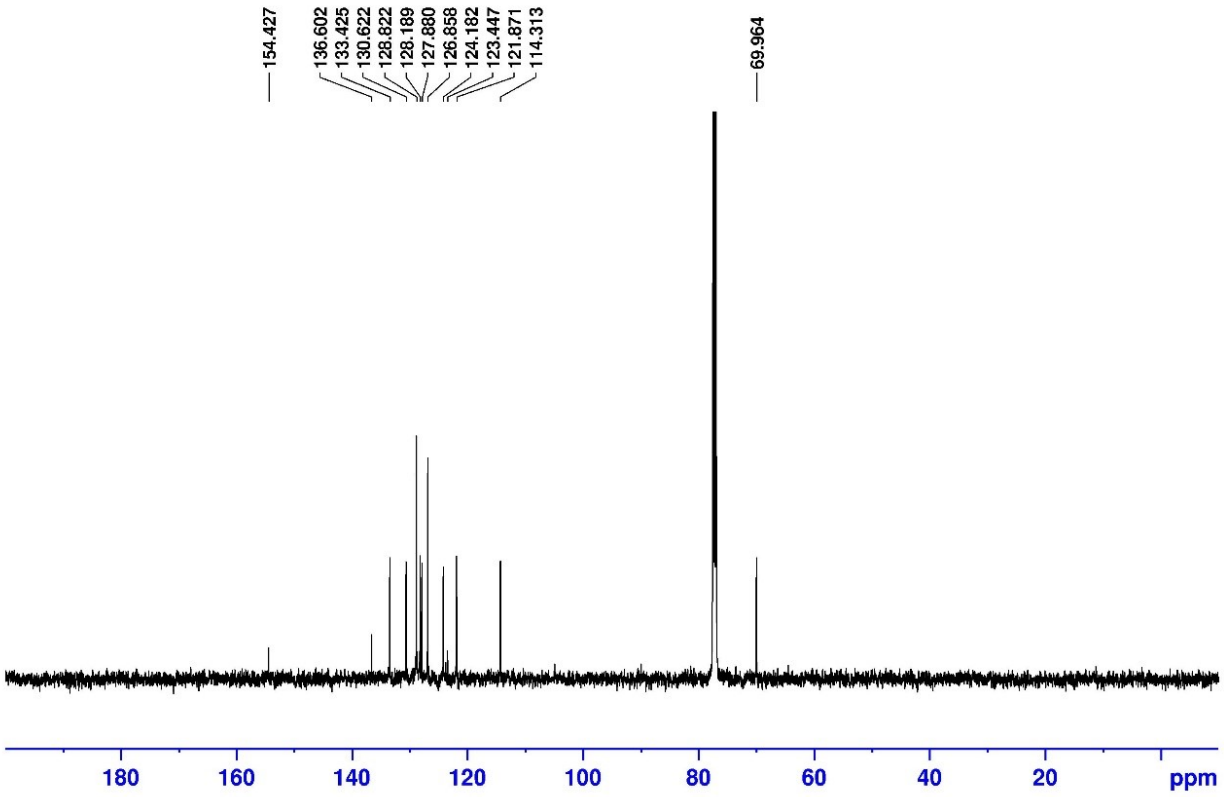

O
Ph
Cl


7.464
7.448
7.429
7.426
7.414
7.411
7.384
7.368
7.353
7.314
7.312
7.285
7.283
7.262
7.259
7.247
7.230
7.227
7.038
7.021
6.963
6.961
6.948
6.933
6.930
6.826
6.794
6.496
6.485
6.473
6.464
6.453
6.441
4.834
4.822


10
9
8
7
6
5
4
3
2
1
0
ppm
2.09
1.13
2.37
1.99
0.87
0.94
0.94
0.91
0.93
2.00

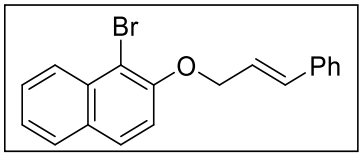
^{13}C NMR

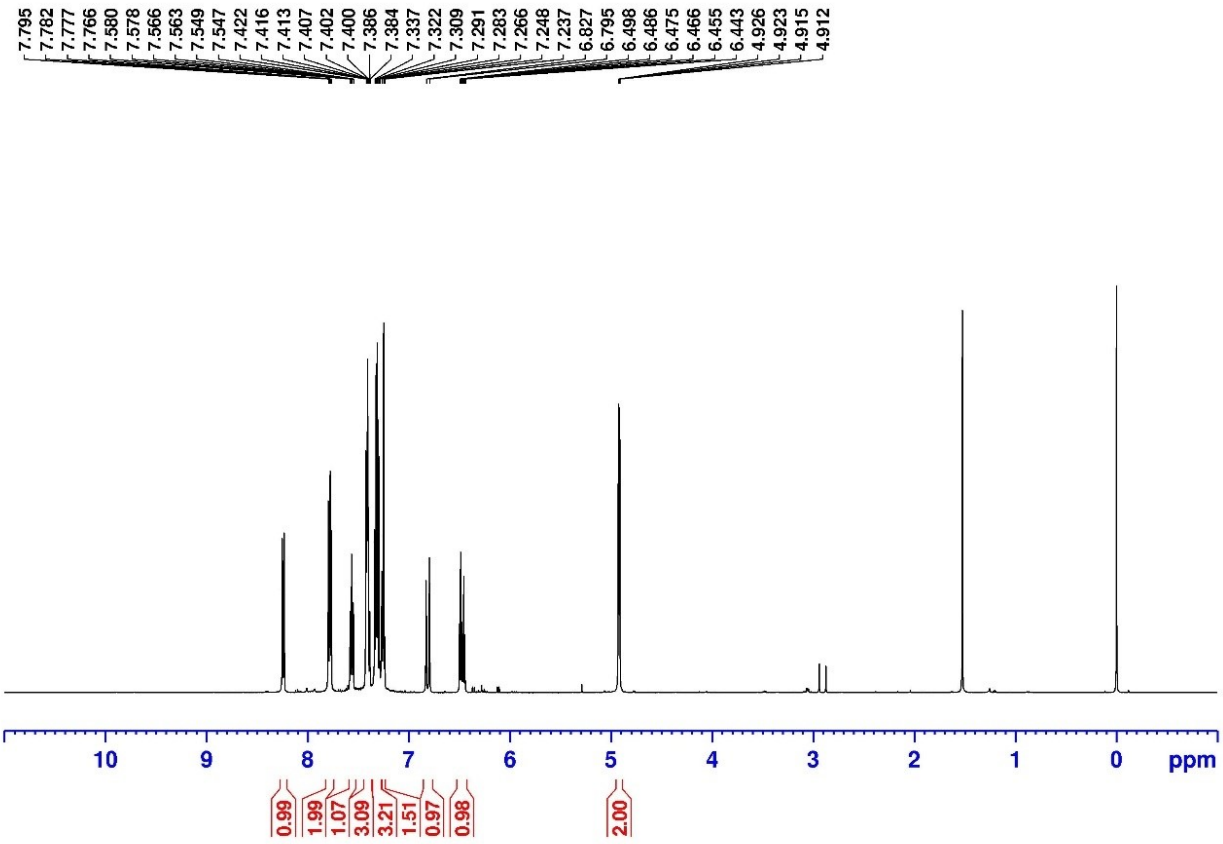

O
Ph
Cl


154.427
136.602
133.425
130.622
128.822
128.189
127.880
126.858
124.182
123.447
121.871
114.313
69.964
180
160
140
120
100
80
60
40
20
ppm

(**2.2d**)

^{1}H NMR


Br
O
Ph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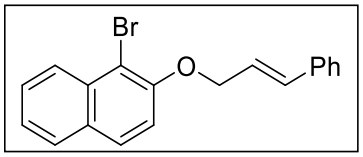
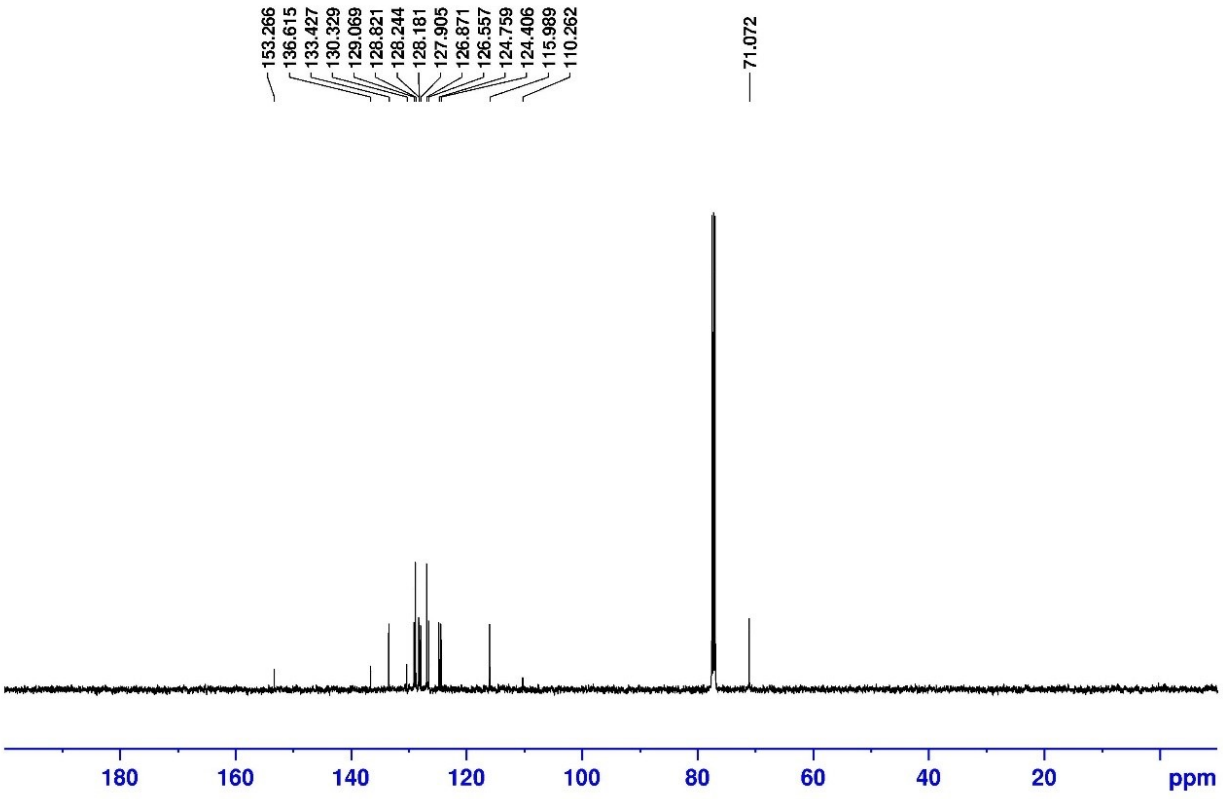
7.782
7.777
7.766
7.580
7.578
7.566
7.563
7.549
7.547
7.422
7.416
7.413
7.407
7.402
7.400
7.386
7.384
7.337
7.322
7.309
7.291
7.283
7.266
7.248
7.237
6.827
6.795
6.498
6.486
6.475
6.466
6.455
6.443
4.926
4.923
4.915
4.912
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.99
1.07
3.09
3.21
1.51
0.97
0.98
2.00

^{13}C NMR


Br
O
Ph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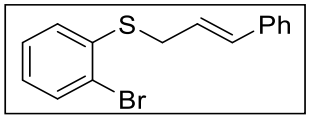
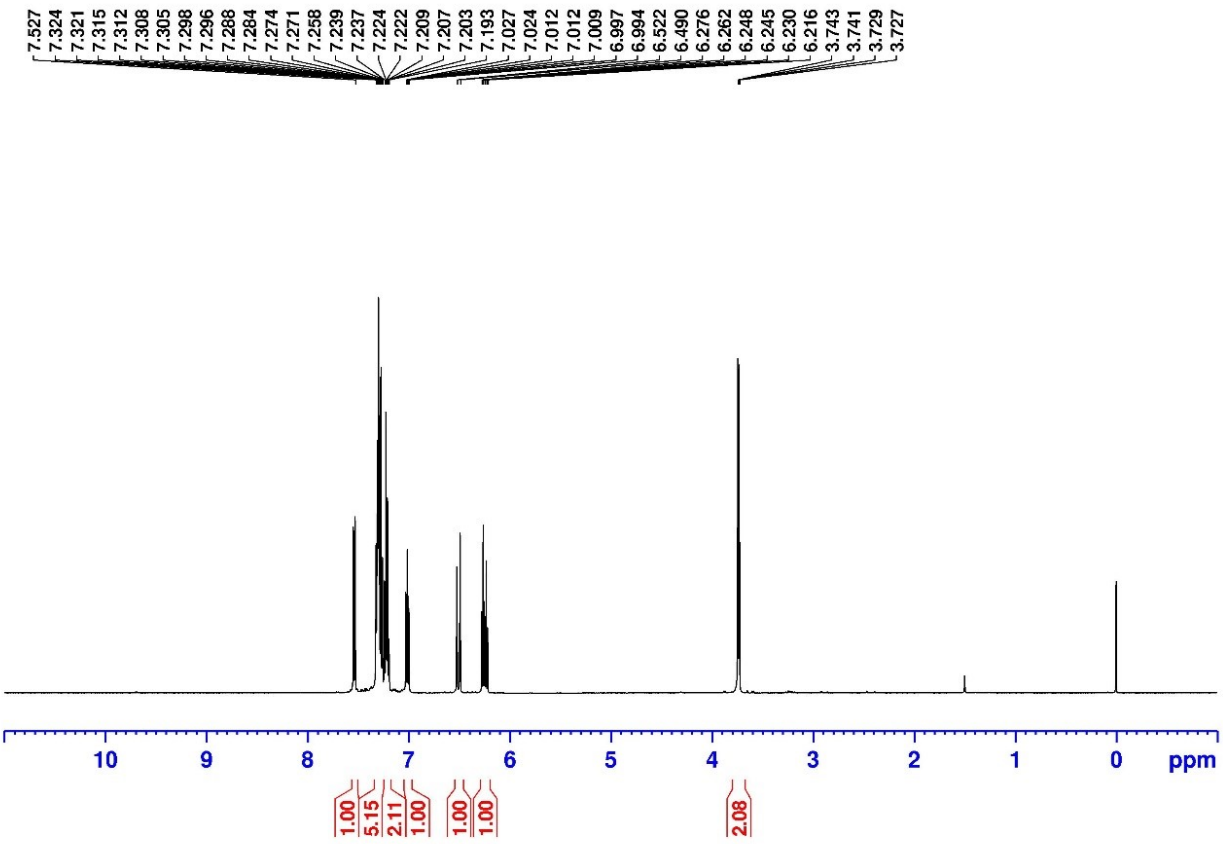
136.615
133.427
130.329
129.069
128.821
128.244
128.181
127.905
126.871
126.557
124.759
124.406
115.989
110.262
71.072
180
160
140
120
100
80
60
40
20
ppm

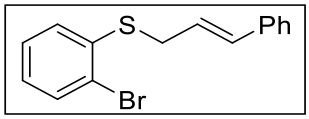
(**2.2e**)

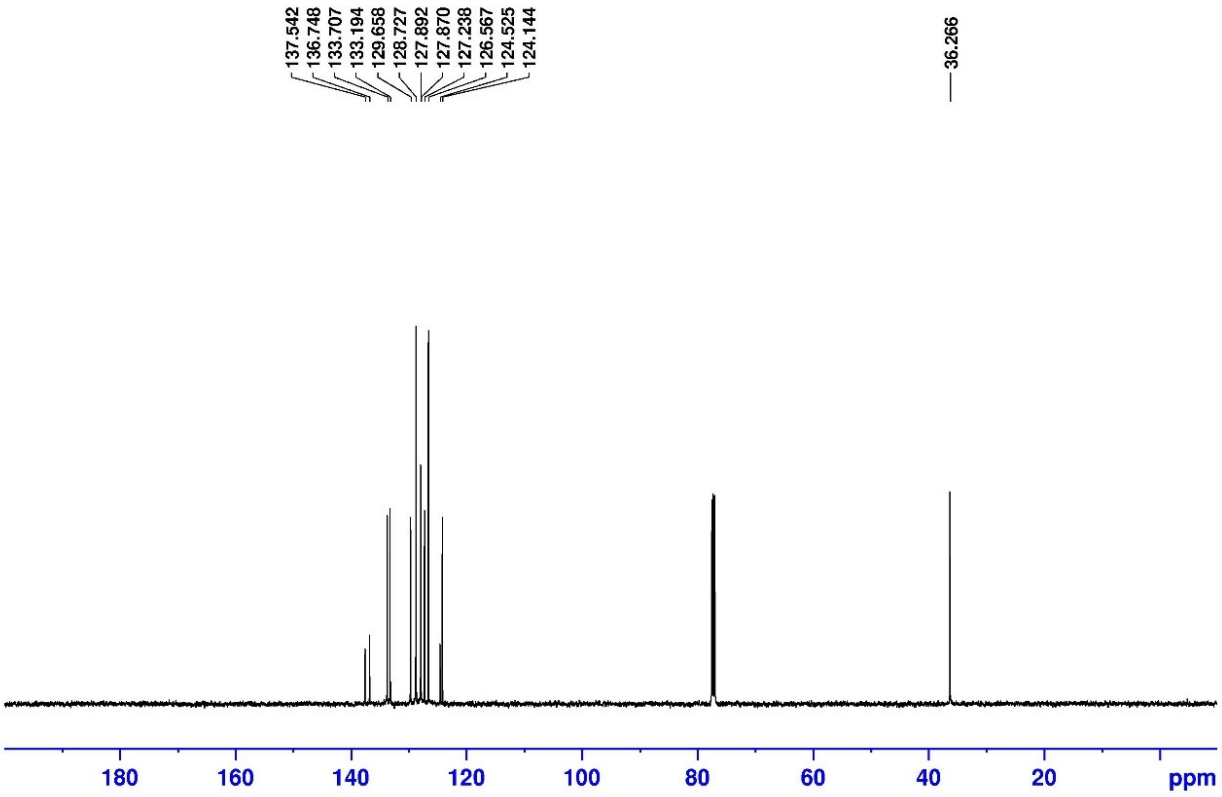
^{1}H NMR


S
Ph
Br


7.527
7.324
7.321
7.315
7.312
7.308
7.305
7.298
7.296
7.288
7.284
7.274
7.271
7.258
7.239
7.237
7.224
7.222
7.209
7.207
7.203
7.193
7.027
7.024
7.012
7.012
7.009
6.997
6.994
6.522
6.490
6.276
6.262
6.248
6.245
6.230
6.216
3.743
3.741
3.729
3.727
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
5.15
2.11
1.00
1.00
1.00
2.08

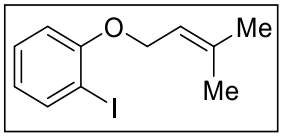
^{13}C NMR

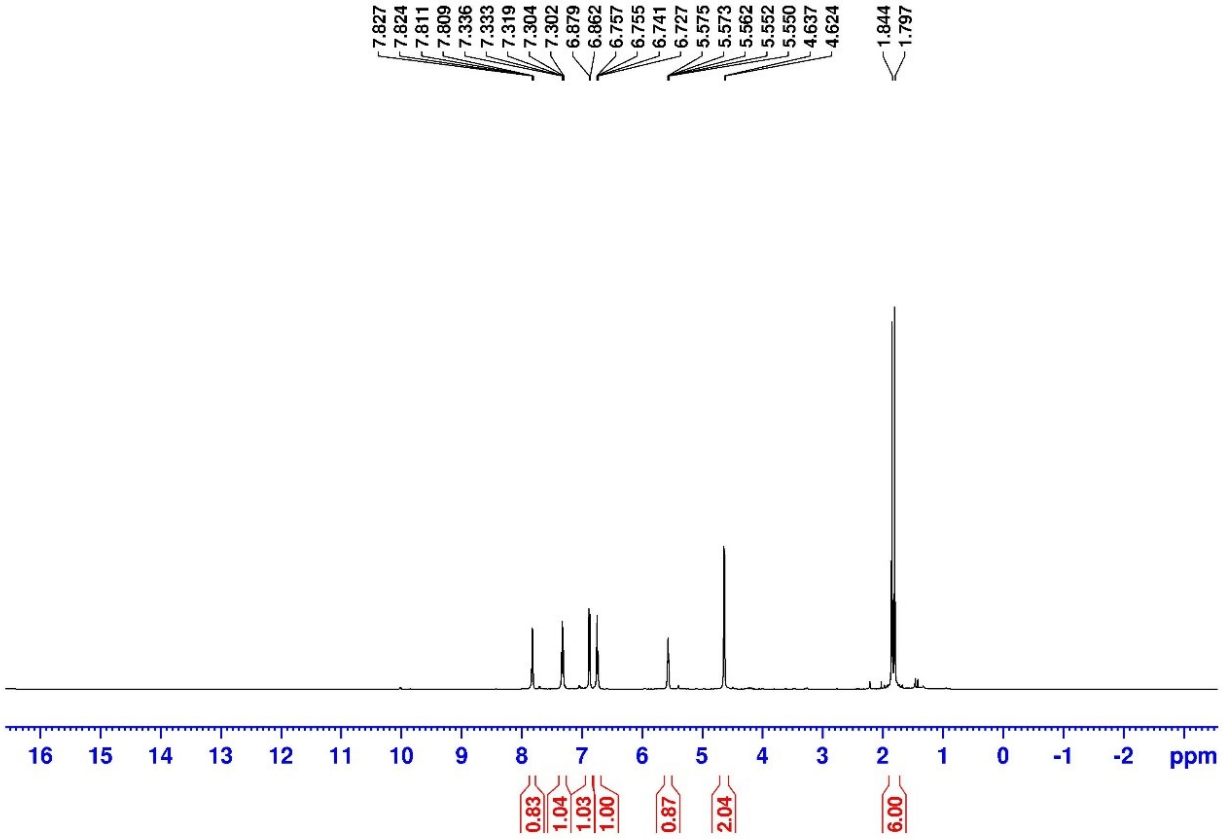

S
Ph
Br


137.542
136.748
133.707
133.194
129.658
128.727
127.892
127.870
127.238
126.567
124.525
124.144
36.266
180
160
140
120
100
80
60
40
20
ppm

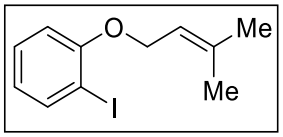
(**2.2f**)

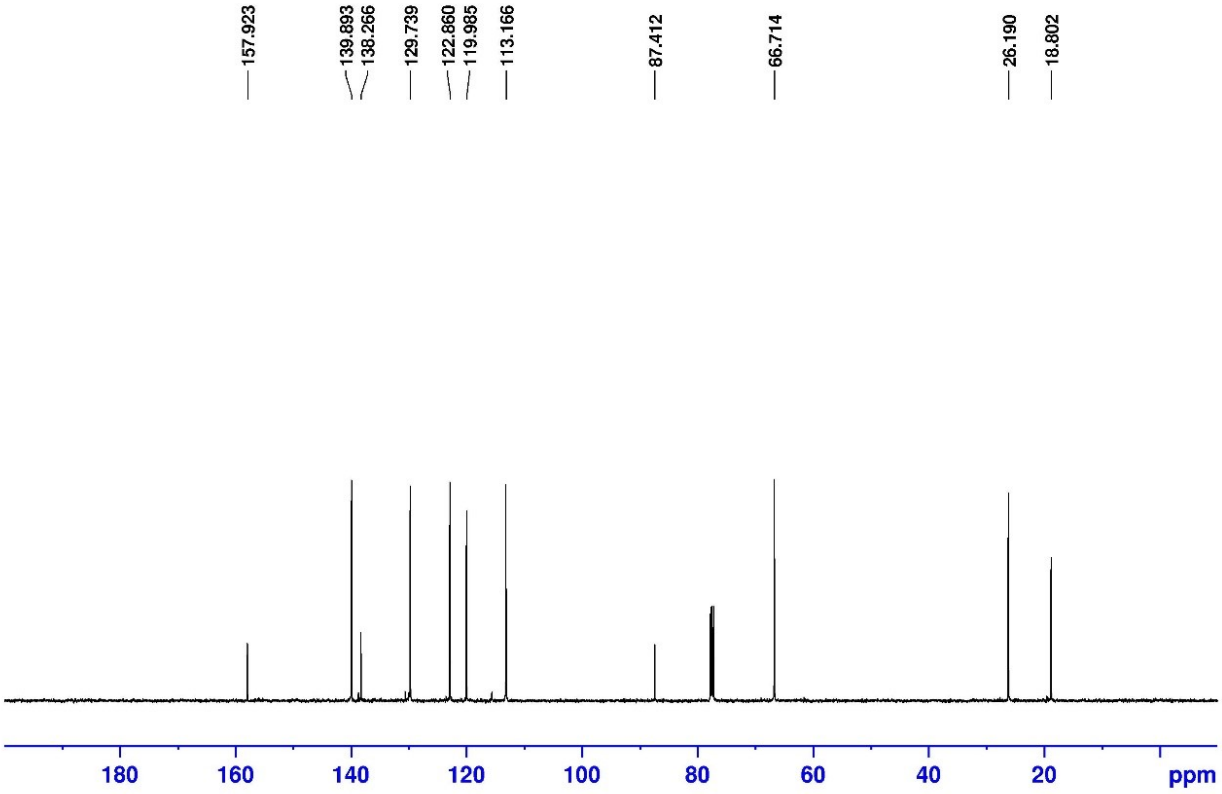
^{1}H NMR


O
Me
Me
I


7.827
7.824
7.811
7.809
7.336
7.333
7.319
7.304
7.302
6.879
6.862
6.757
6.755
6.741
6.727
5.575
5.573
5.562
5.552
5.550
4.637
4.624
1.844
1.797
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
0.83
1.04
1.03
1.00
0.87
2.04
6.00

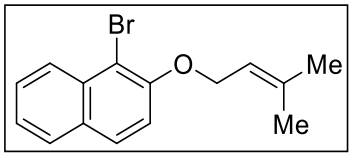
^{13}C NMR

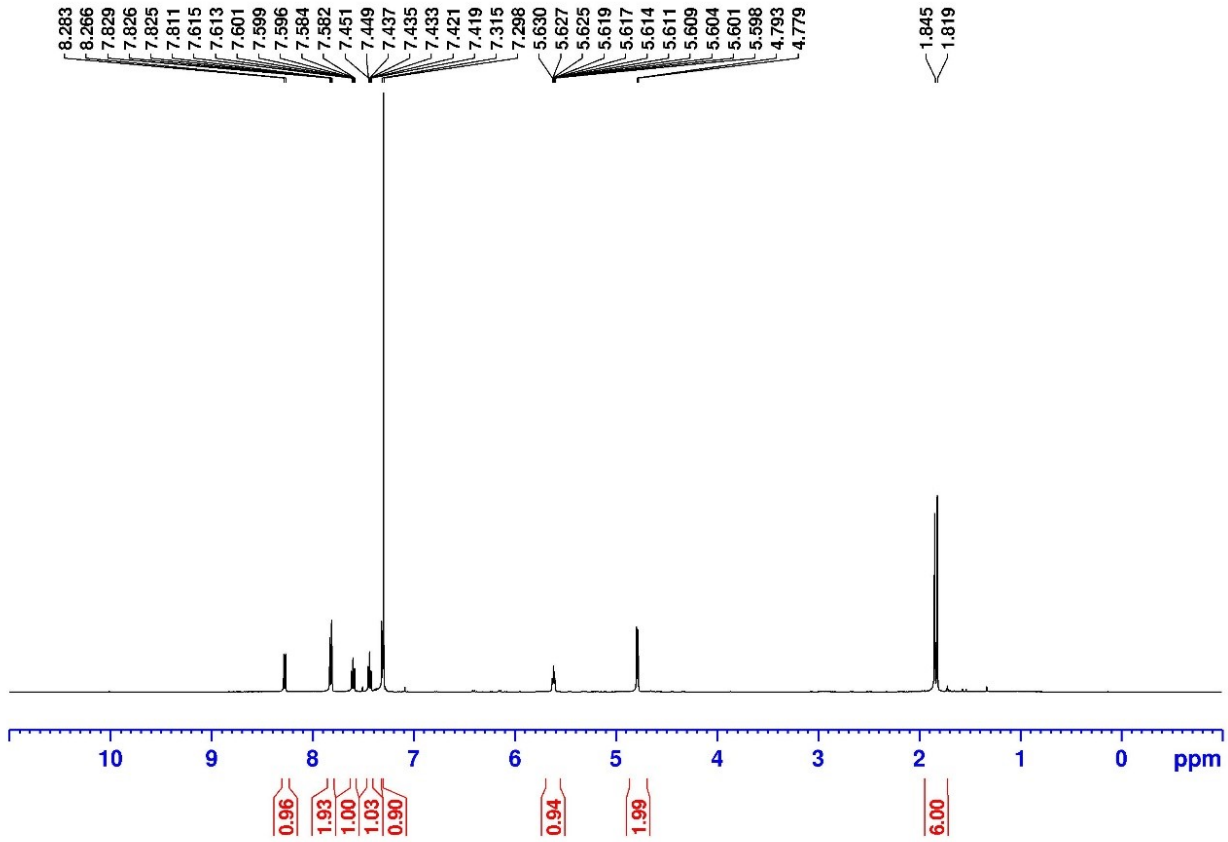

O
Me
Me
I


157.923
139.893
138.266
129.739
122.860
119.985
113.166
87.412
66.714
26.190
18.802
180
160
140
120
100
80
60
40
20
ppm

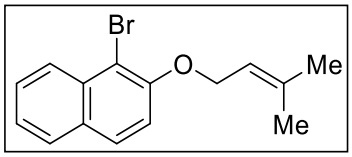
(**2.2g**)

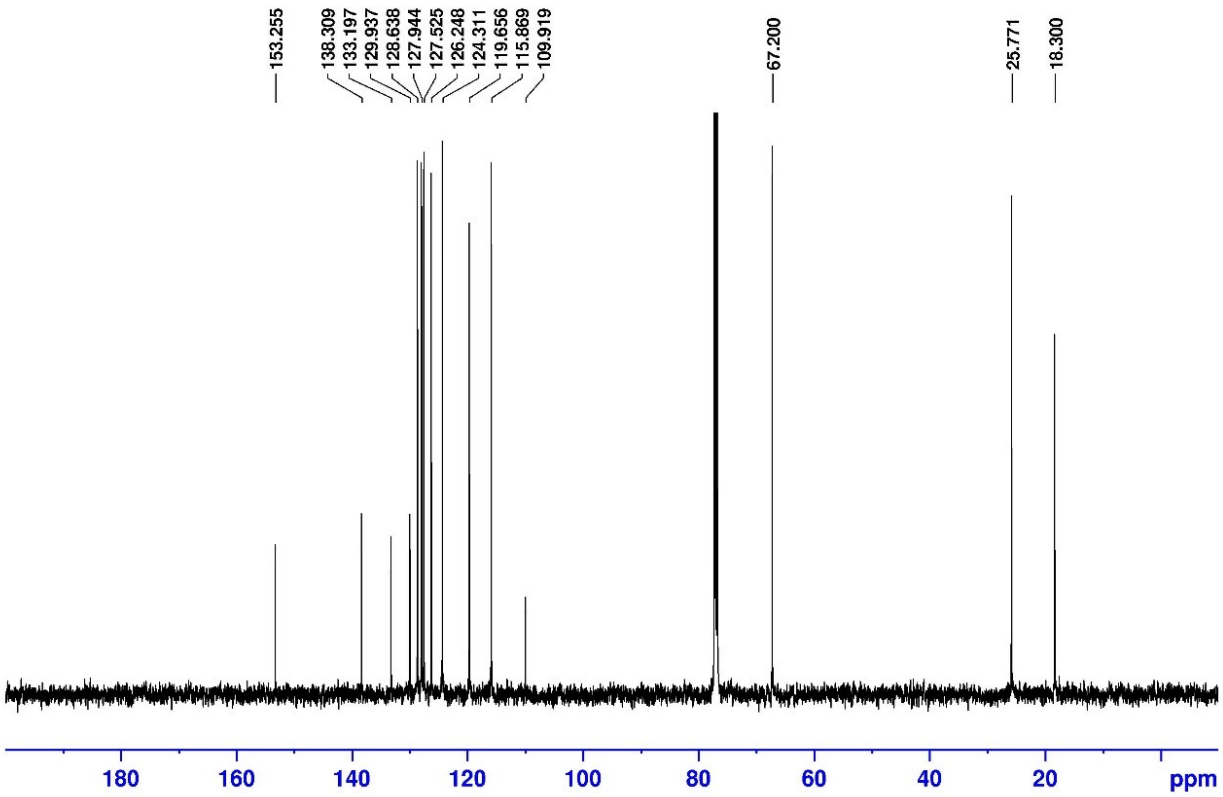
^{1}H NMR


Br
O
Me
Me


8.283
8.266
7.829
7.826
7.825
7.811
7.615
7.613
7.601
7.599
7.596
7.584
7.582
7.451
7.449
7.437
7.435
7.433
7.421
7.419
7.315
7.298
5.630
5.627
5.625
5.619
5.617
5.614
5.611
5.609
5.604
5.601
5.598
4.793
4.779
1.845
1.819
10
9
8
7
6
5
4
3
2
1
0
ppm
0.96
1.93
1.00
1.03
0.90
0.94
1.99
6.00

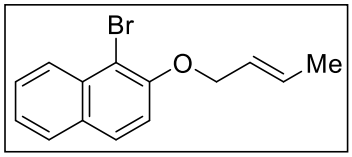
^{13}C NMR

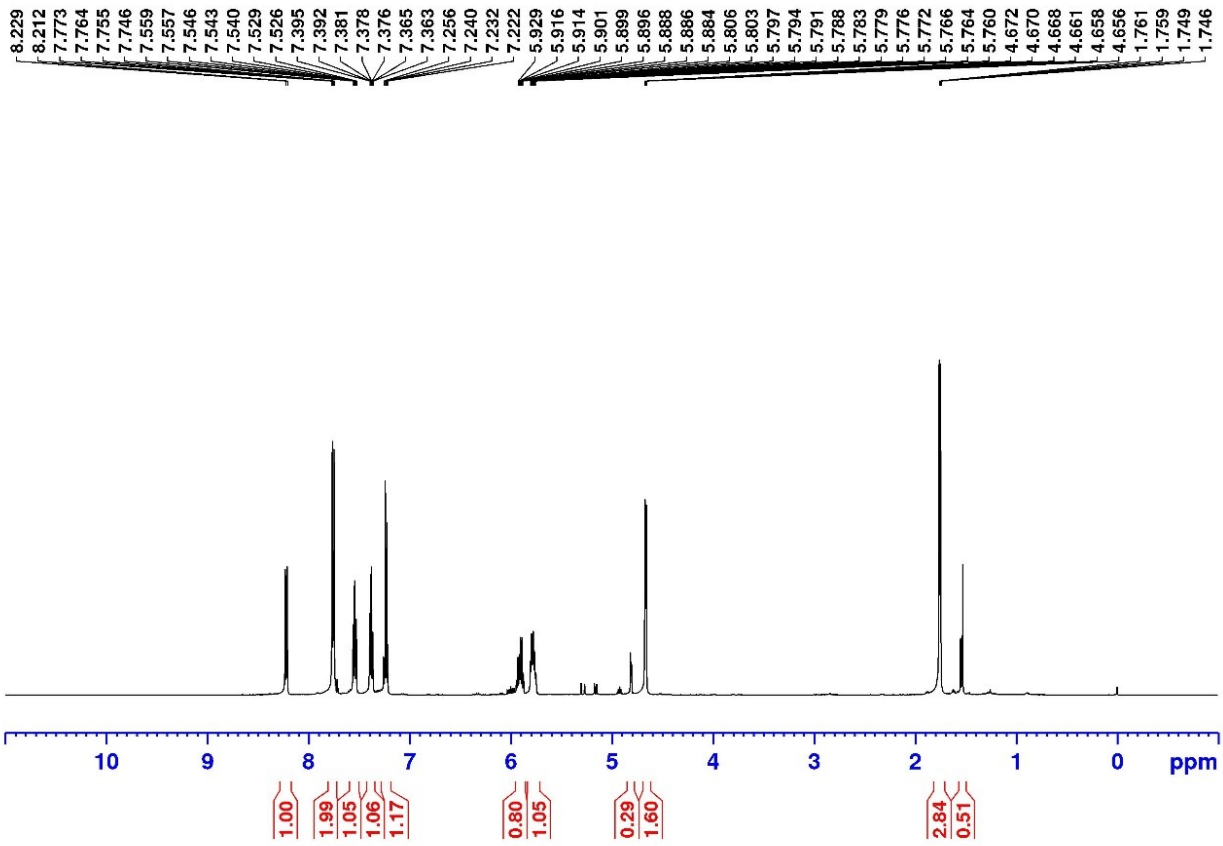

Br
O
Me
Me


153.255
138.309
133.197
129.937
128.638
127.944
127.525
126.248
124.311
119.656
115.869
109.919
67.200
25.771
18.300
180
160
140
120
100
80
60
40
20
ppm

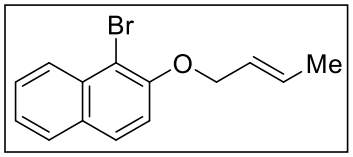
(**2.2h**)

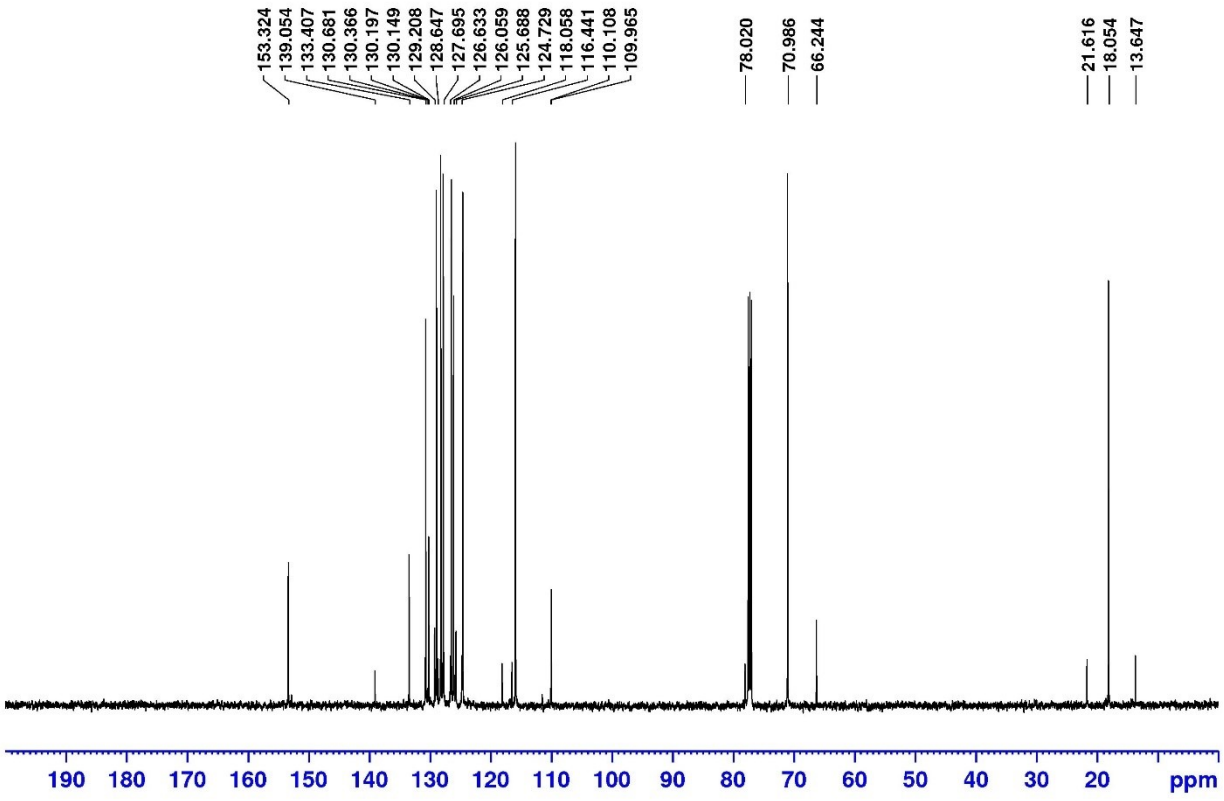
^{1}H NMR


Br
O
Me


8.229
8.212
7.773
7.764
7.755
7.746
7.559
7.557
7.546
7.543
7.540
7.529
7.526
7.395
7.392
7.381
7.378
7.376
7.365
7.363
7.256
7.240
7.232
7.222
5.929
5.916
5.914
5.901
5.899
5.896
5.888
5.886
5.884
5.806
5.803
5.797
5.794
5.791
5.788
5.783
5.779
5.776
5.772
5.766
5.764
5.760
4.672
4.670
4.668
4.661
4.658
4.656
1.761
1.759
1.749
1.746
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.99
1.05
1.06
1.17
0.80
1.05
0.29
1.60
2.84
0.51

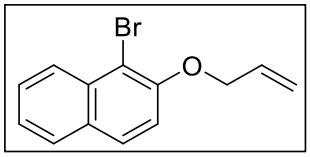
^{13}C NMR

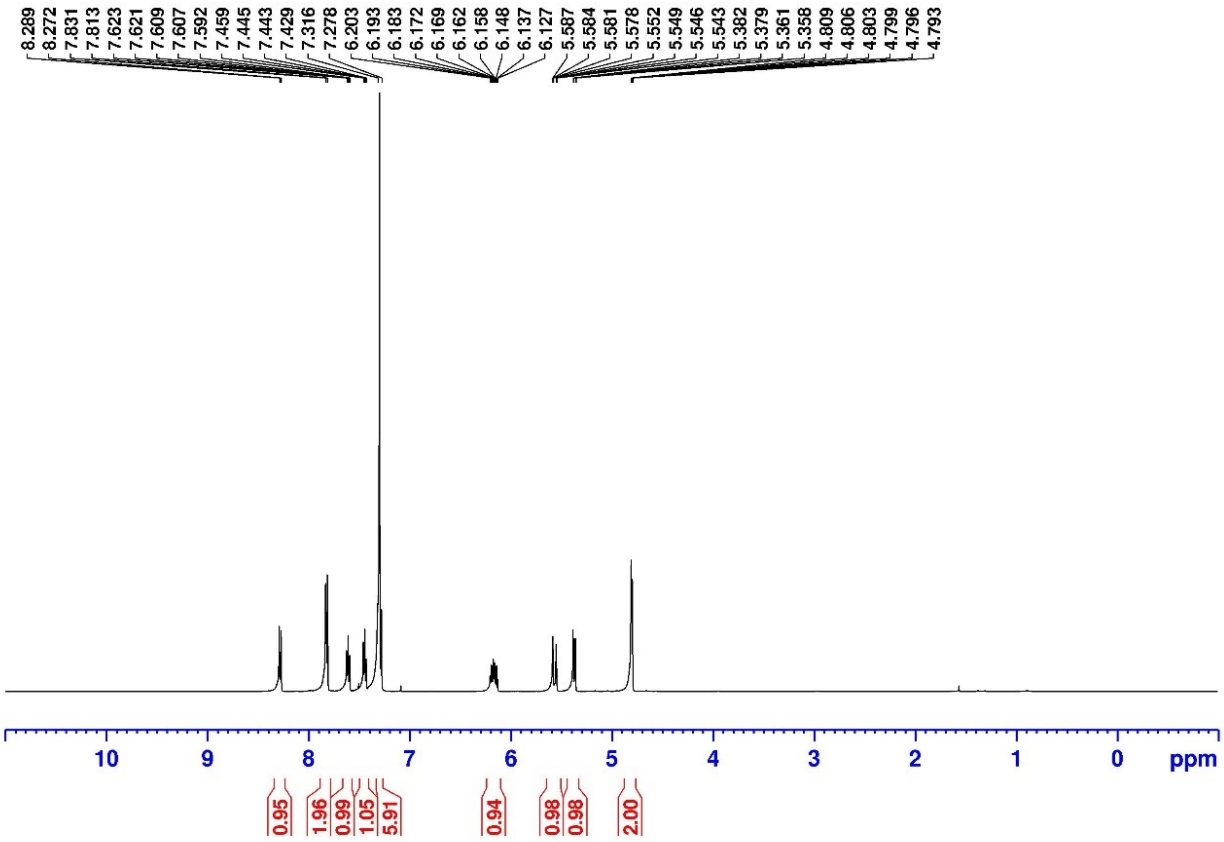

Br
O
Me


153.324
139.054
133.407
130.681
130.366
130.197
130.149
129.208
128.647
127.695
126.633
126.059
125.688
124.729
118.058
116.441
110.108
109.965
78.020
70.986
66.244
21.616
18.054
13.647
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

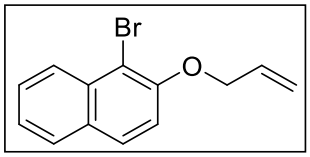
(**2.2i**)

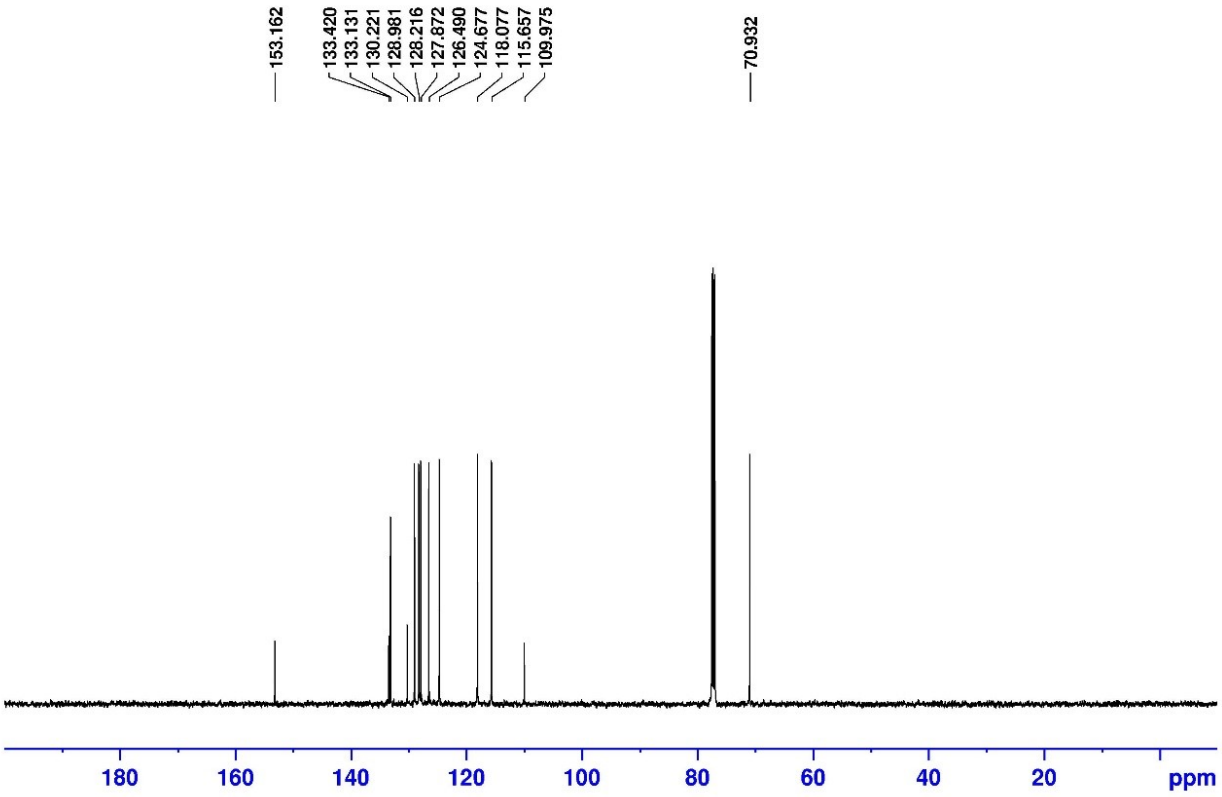
^{1}H NMR


Br
O


8.289
8.272
7.831
7.813
7.623
7.621
7.609
7.607
7.592
7.459
7.445
7.443
7.429
7.316
7.278
6.203
6.193
6.183
6.172
6.169
6.162
6.158
6.148
6.137
6.127
5.587
5.584
5.581
5.578
5.552
5.549
5.546
5.543
5.382
5.379
5.361
5.358
4.809
4.806
4.803
4.799
4.796
4.793
10
9
8
7
6
5
4
3
2
1
0
ppm
0.95
1.96
0.99
1.05
5.91
0.94
0.98
0.98
2.00

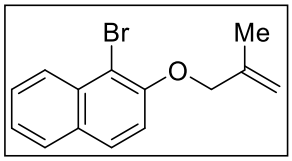
^{13}C NMR


Br
O

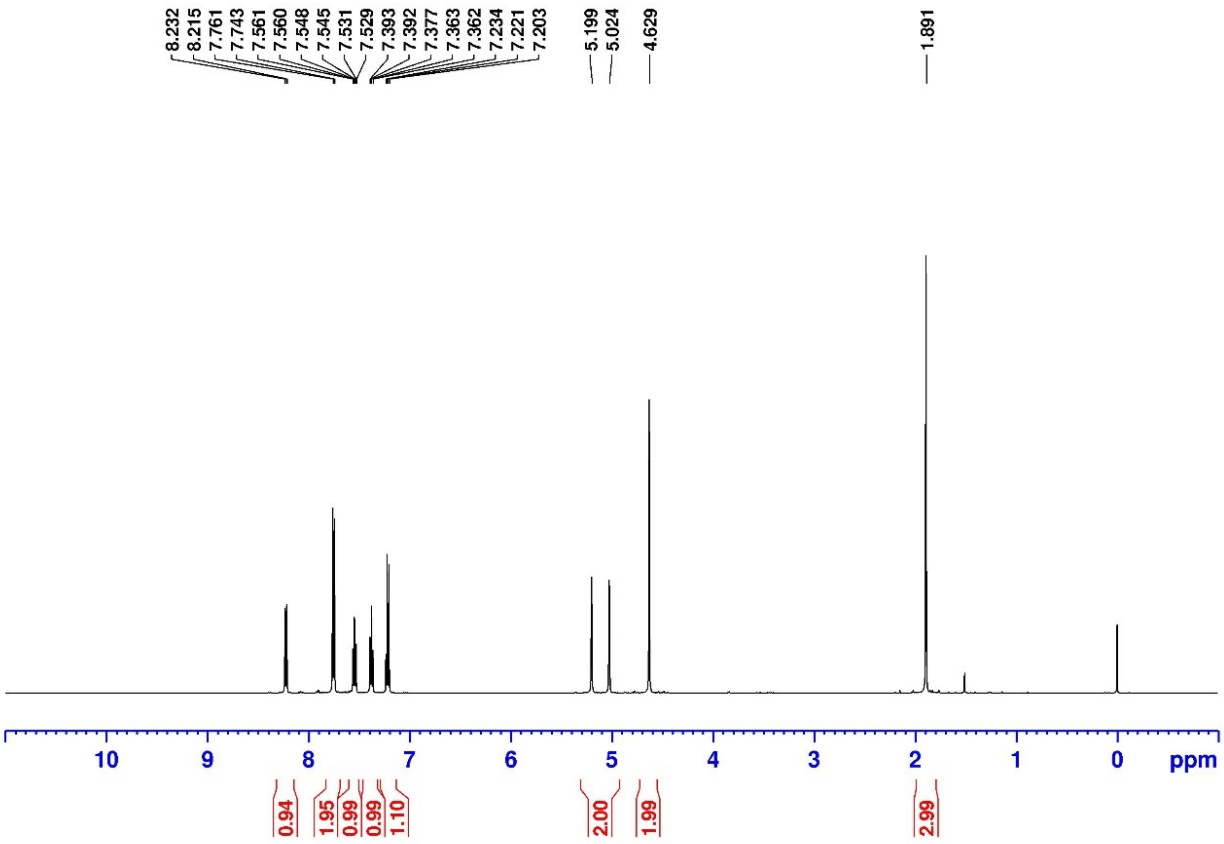

153.162
133.420
133.131
130.221
128.981
128.216
127.872
126.490
124.677
118.077
115.657
109.975
70.932
180
160
140
120
100
80
60
40
20
ppm

(**2.2j**)

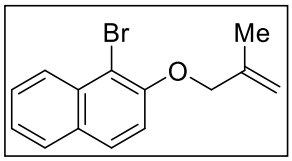
^{1}H NMR

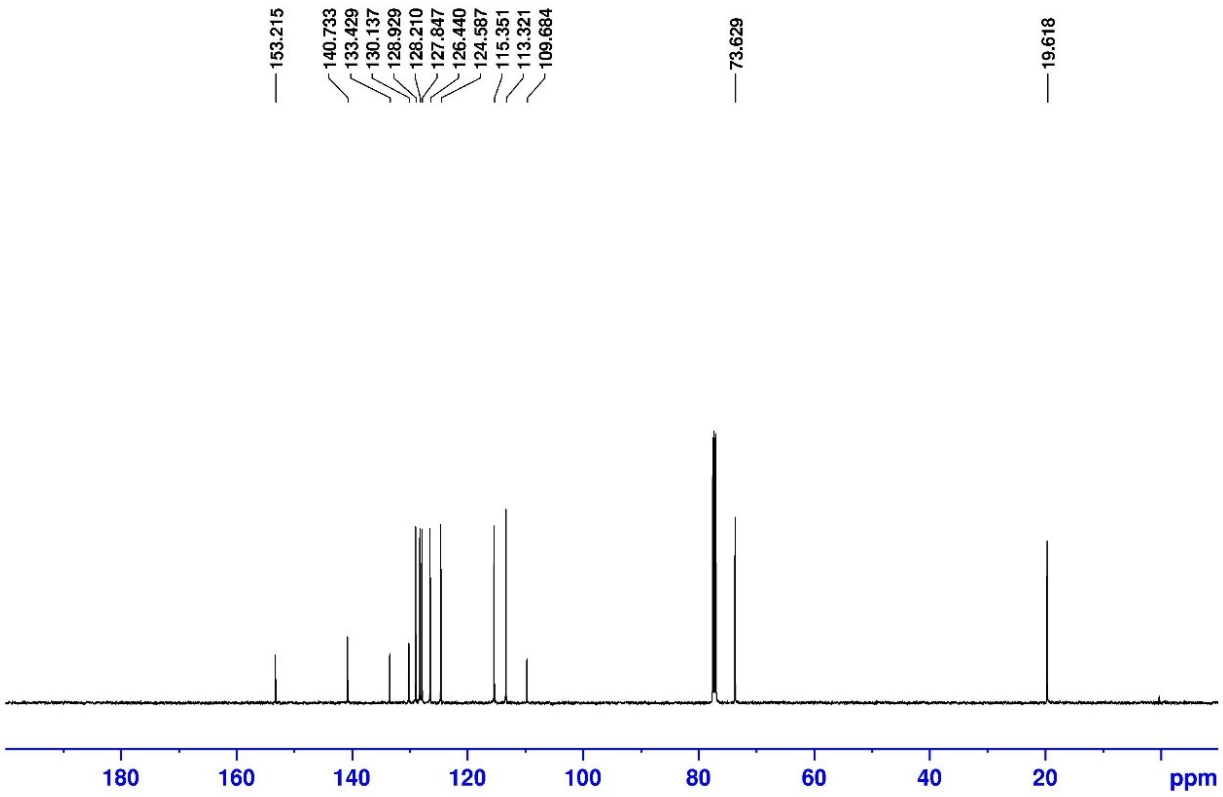

Br
Me
O

.


8.232
8.215
7.761
7.743
7.561
7.560
7.548
7.545
7.531
7.529
7.393
7.392
7.377
7.363
7.362
7.234
7.221
7.203
5.199
5.024
4.629
1.891
10
9
8
7
6
5
4
3
2
1
0
ppm
0.94
1.95
0.99
0.99
1.10
2.00
1.99
2.99

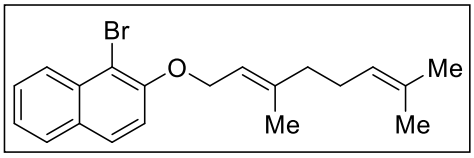
^{13}C NMR

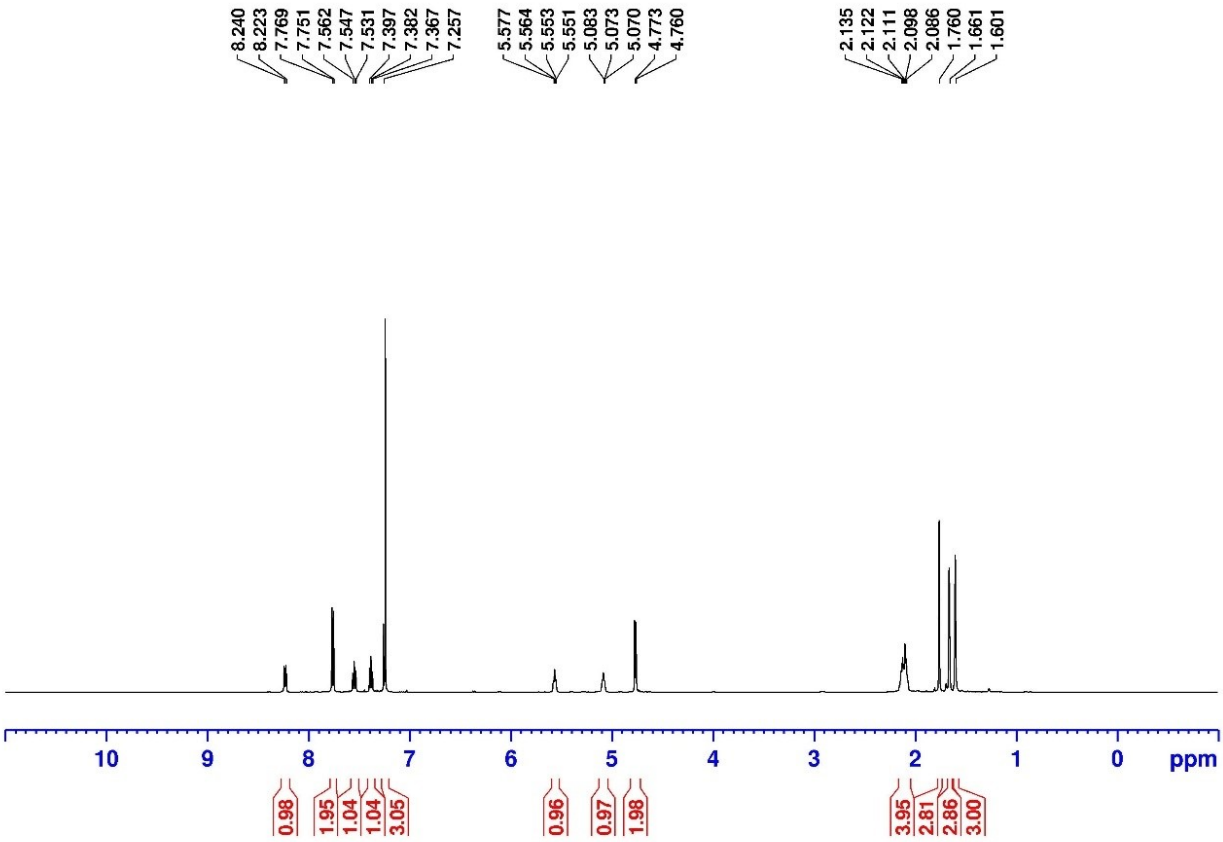

Br
Me
O


153.215
140.733
133.429
130.137
128.929
128.210
127.847
126.440
124.587
115.351
113.321
109.684
73.629
19.618
180
160
140
120
100
80
60
40
20
ppm

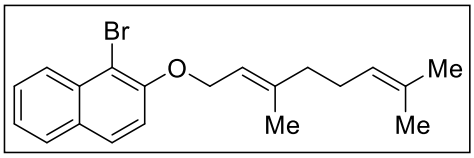
(**2.2k**)

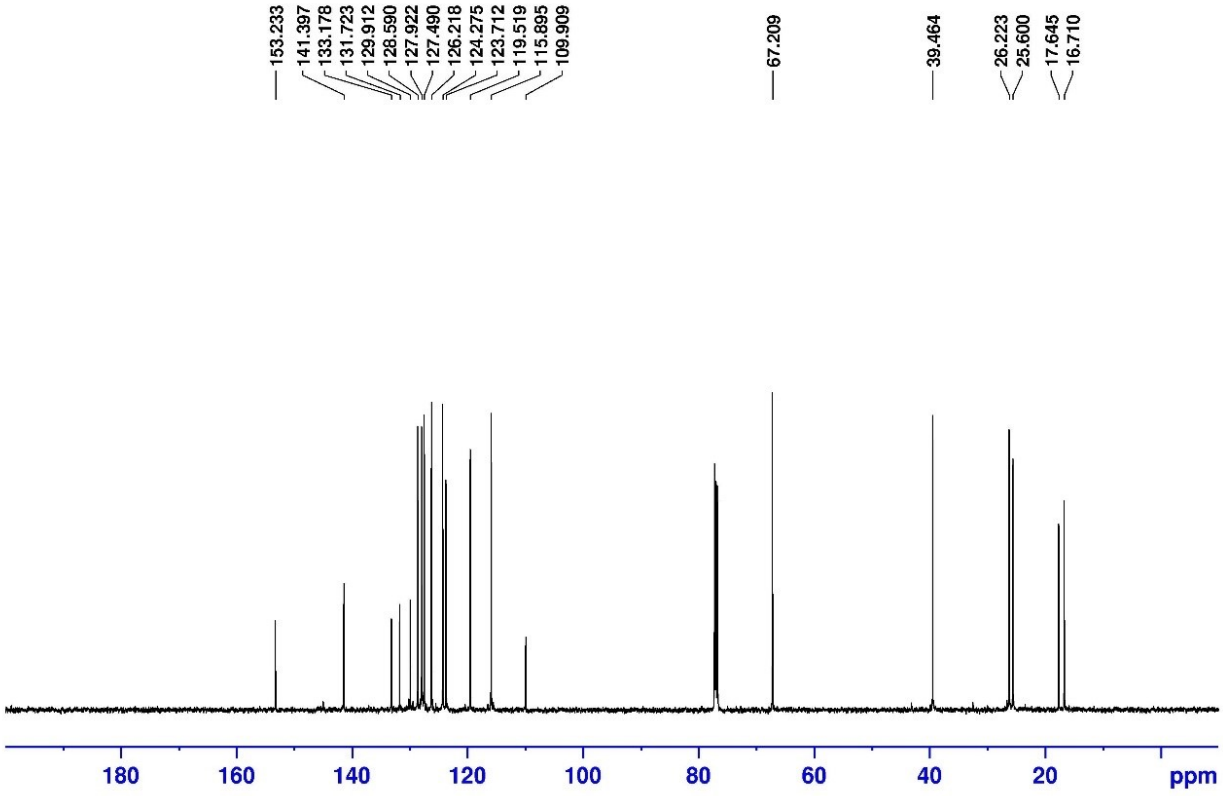
^{1}H NMR


Br
O
Me
Me
Me


8.240
8.223
7.769
7.751
7.562
7.547
7.531
7.397
7.382
7.367
7.257
5.577
5.564
5.553
5.551
5.083
5.073
5.070
4.773
4.760
2.135
2.122
2.111
2.098
2.086
1.760
1.661
1.601
10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
1.95
1.04
1.04
3.05
0.96
0.97
1.98
3.95
2.81
2.86
3.00

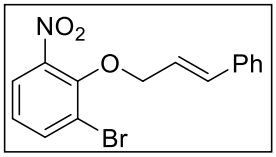
^{13}C NMR

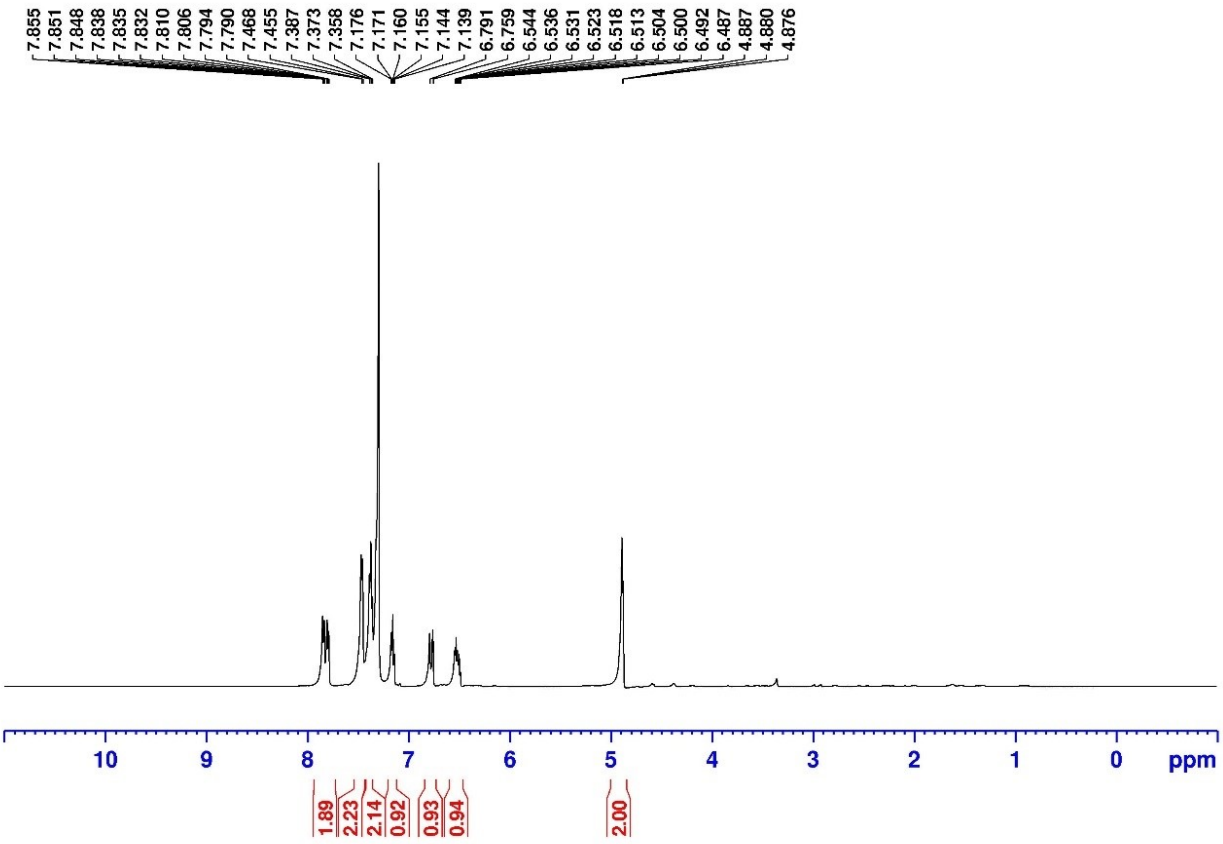

Br
O
Me
Me
Me


153.233
141.397
133.178
131.723
129.912
128.590
127.922
127.490
126.218
124.275
123.712
119.519
115.895
109.909
67.209
39.464
26.223
25.600
17.645
16.710
180
160
140
120
100
80
60
40
20
ppm

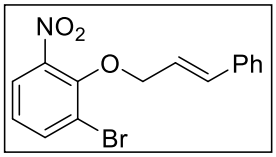
(**2.2l**)

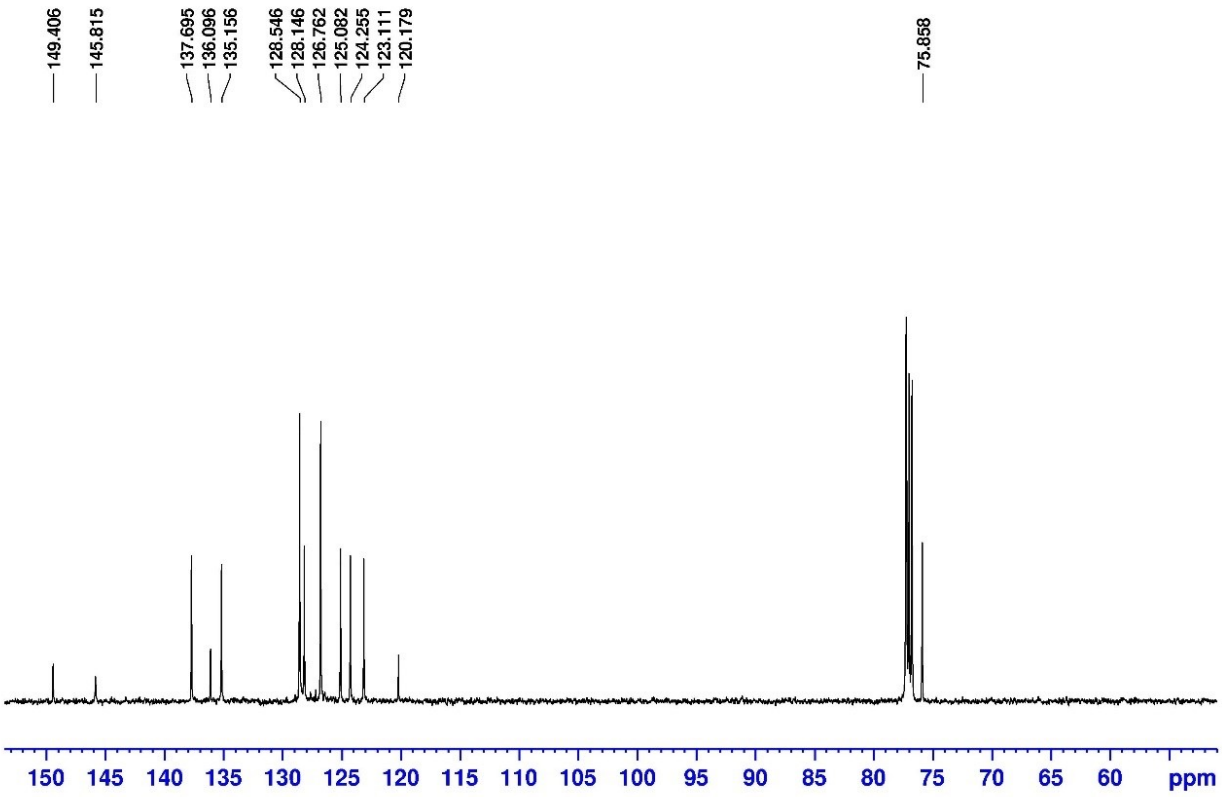
^{1}H NMR


NO2
O
Ph
Br


7.855
7.851
7.848
7.838
7.835
7.832
7.810
7.806
7.794
7.790
7.468
7.455
7.387
7.373
7.358
7.176
7.171
7.160
7.155
7.144
7.139
6.791
6.759
6.544
6.536
6.531
6.523
6.518
6.513
6.504
6.500
6.492
6.487
4.887
4.880
4.876
10
9
8
7
6
5
4
3
2
1
0
ppm
1.89
2.23
2.14
0.92
0.93
0.94
2.00

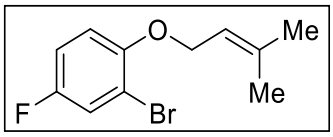
^{13}C NMR

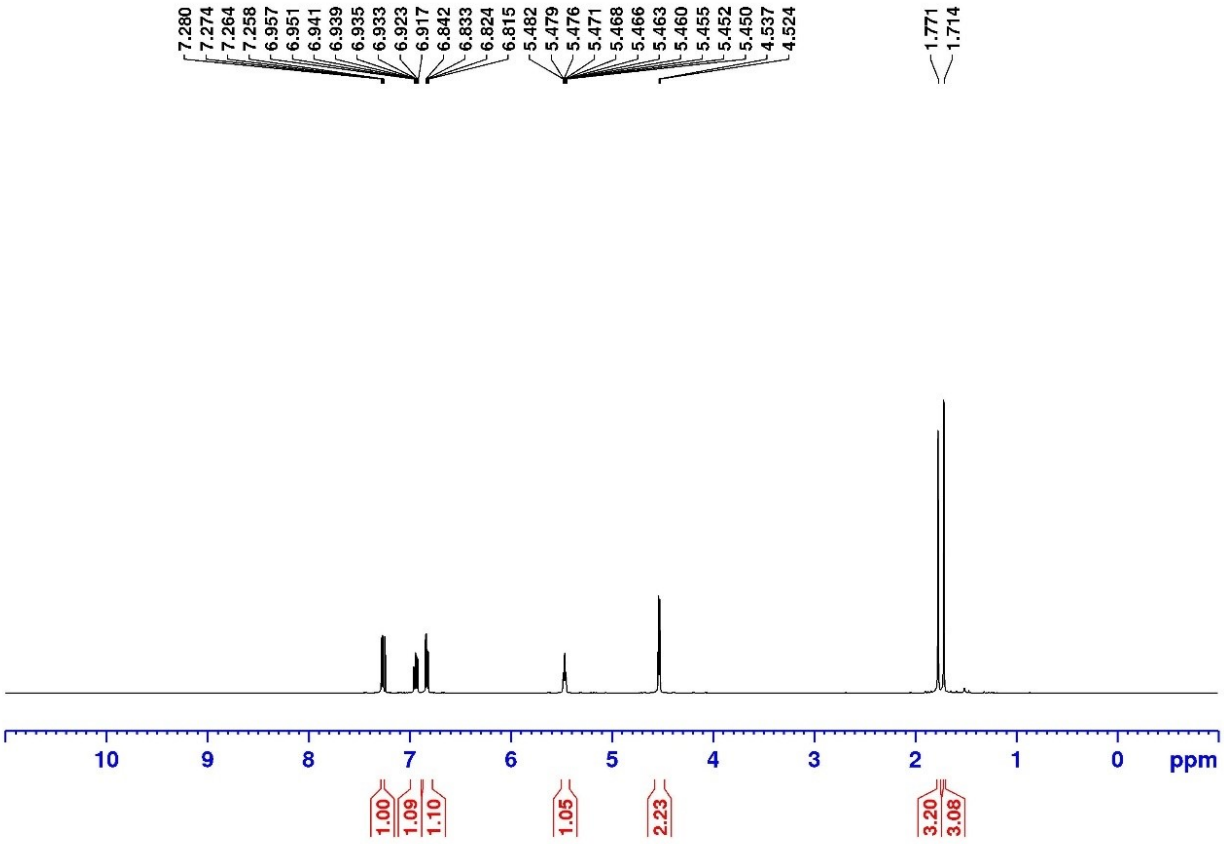

NO2
O
Ph
Br


149.406
145.815
137.695
136.096
135.156
128.546
128.146
126.762
125.082
124.255
123.111
120.179
75.858
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 ppm

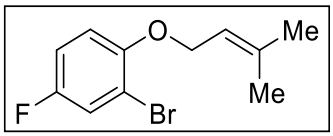
(**2.2m**)

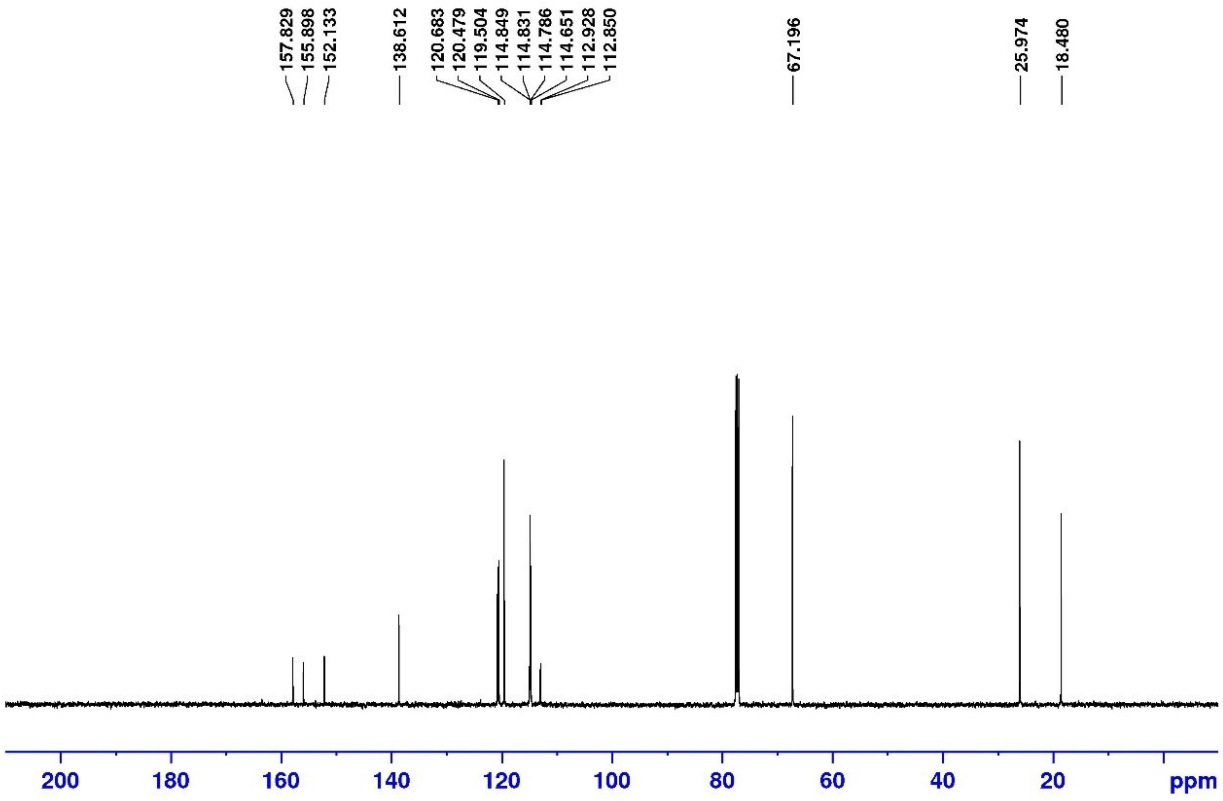
^{1}H NMR


O
Me
Me
F
Br


7.280
7.274
7.264
7.258
6.957
6.951
6.941
6.939
6.935
6.933
6.923
6.917
6.842
6.833
6.824
6.815
5.482
5.479
5.476
5.471
5.468
5.466
5.463
5.460
5.455
5.452
5.450
4.537
4.524
1.771
1.714
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.09
1.10
1.05
2.23
3.20
3.08

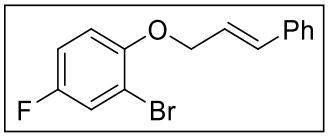
^{13}C NMR

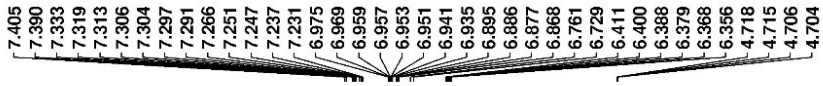

O
Me
Me
F
Br

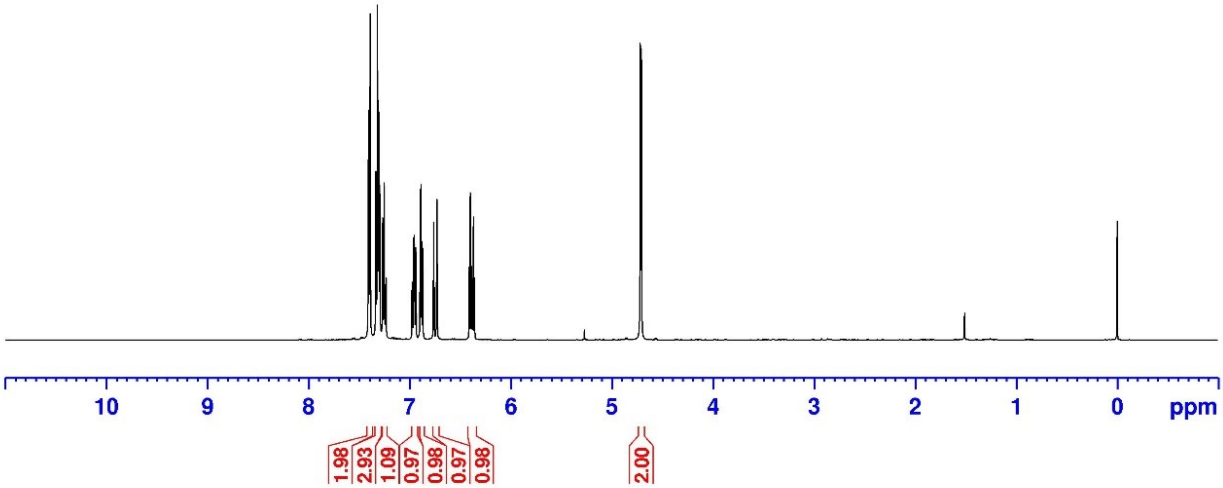

157.829
155.898
152.133
138.612
120.683
120.479
119.504
114.849
114.831
114.786
114.651
112.928
112.850
67.196
25.974
18.480
200
180
160
140
120
100
80
60
40
20
ppm

(**2.2n**)

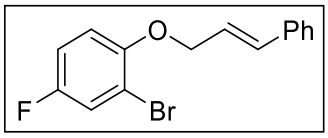
^{1}H NMR

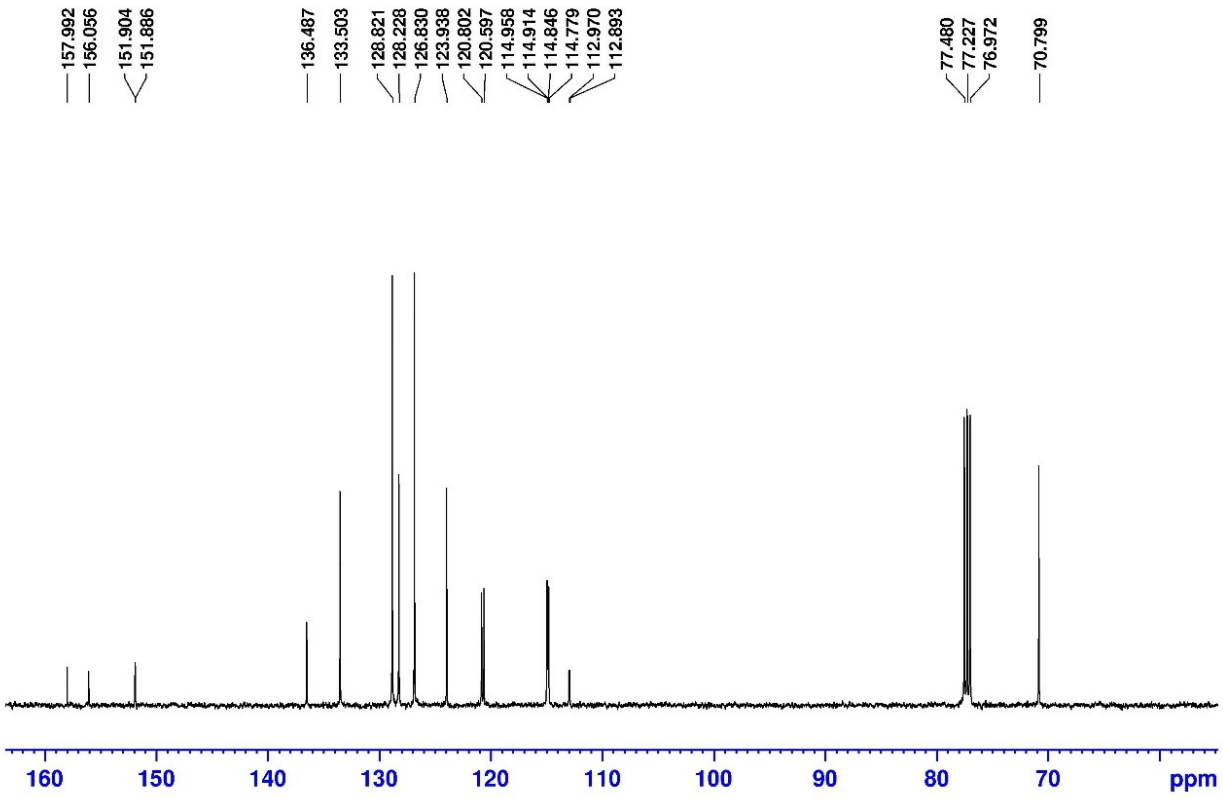

O
Ph
F
Br


7.405
7.390
7.333
7.319
7.313
7.306
7.304
7.297
7.291
7.266
7.251
7.247
7.237
7.231
6.975
6.969
6.959
6.957
6.953
6.951
6.941
6.935
6.895
6.886
6.877
6.868
6.761
6.729
6.411
6.400
6.388
6.379
6.368
6.356
4.718
4.715
4.706
4.704

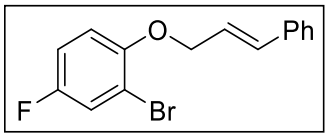

10
9
8
7
6
5
4
3
2
1
0
ppm
1.98
2.93
1.09
0.97
0.98
0.97
0.98
2.00

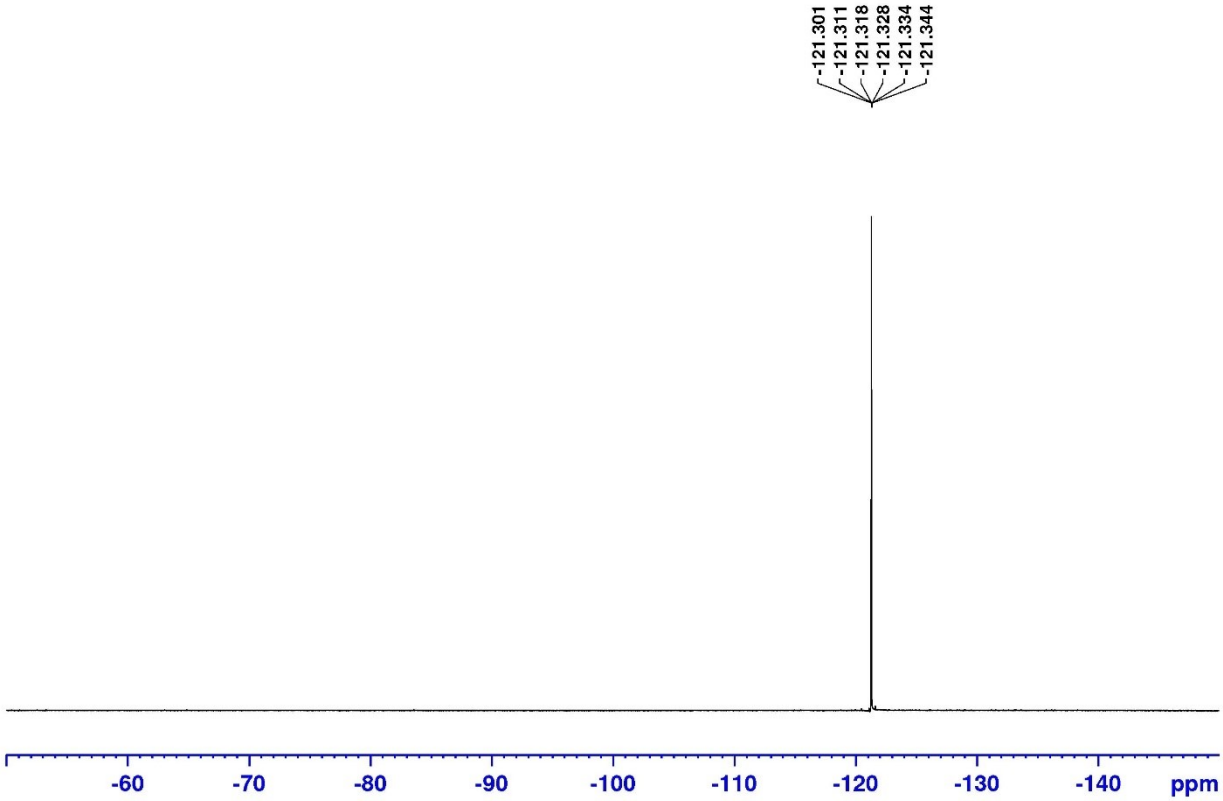
^{13}C NMR


O
Ph
F
Br


157.992
156.056
151.904
151.886
136.487
133.503
128.821
128.228
126.830
123.938
120.802
120.597
114.958
114.914
114.846
114.779
112.970
112.893
77.480
77.227
76.972
70.799
160
150
140
130
120
110
100
90
80
70
ppm

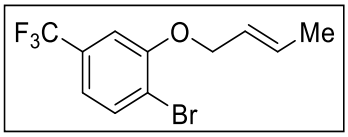
^{19}F NMR

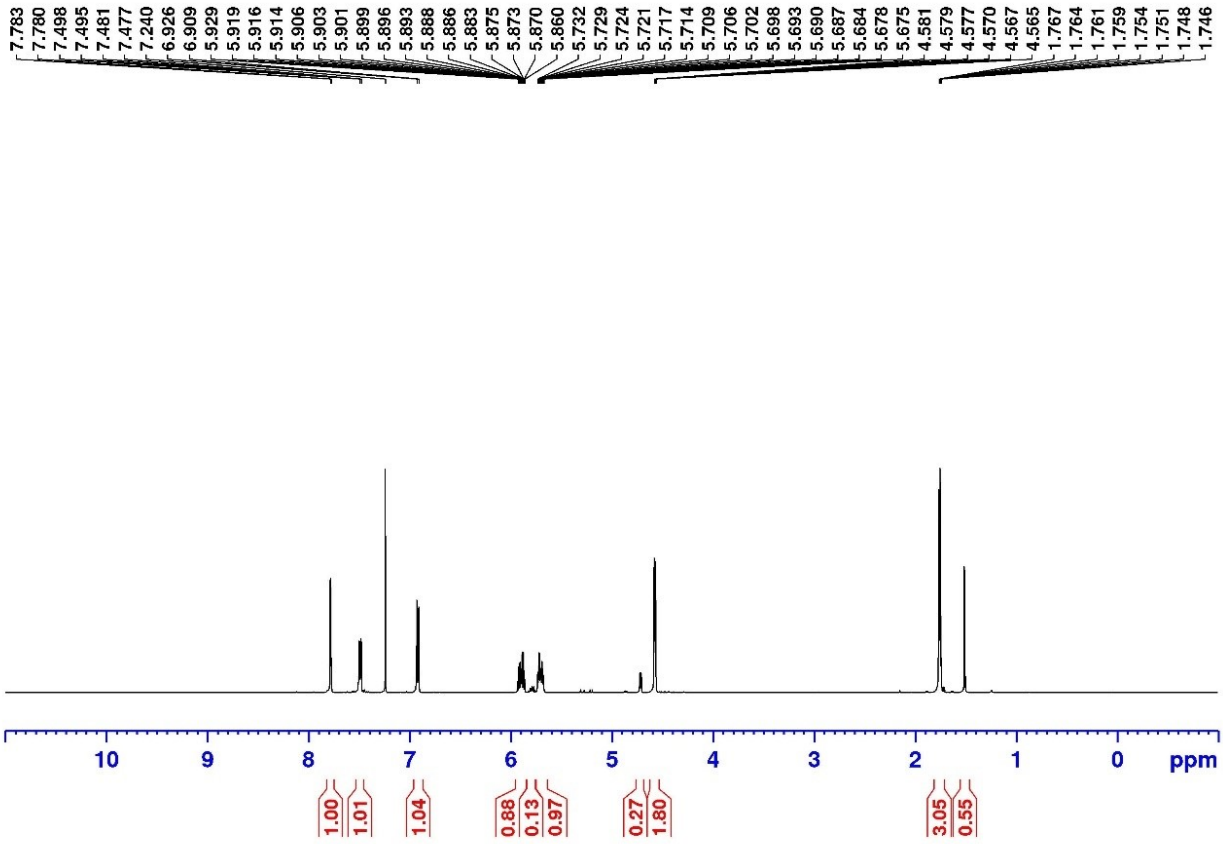

O
Ph
F
Br


-121.301
-121.311
-121.318
-121.328
-121.334
-121.344
-60
-70
-80
-90
-100
-110
-120
-130
-140
ppm

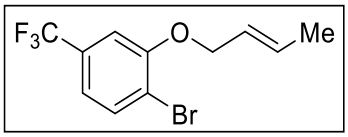
(**2.2o**)

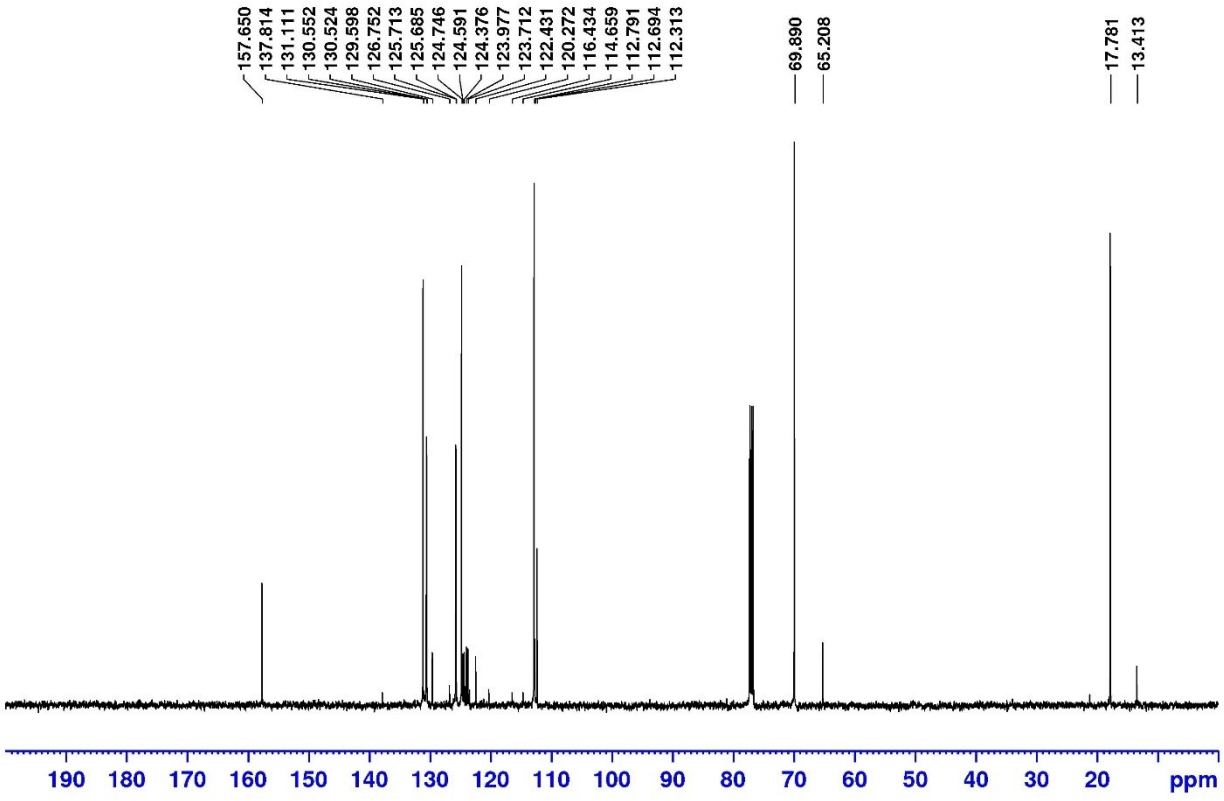
^{1}H NMR


F3C
O
Me
Br


7.783
7.780
7.498
7.495
7.481
7.477
7.240
6.926
6.909
5.929
5.919
5.916
5.914
5.906
5.903
5.901
5.899
5.896
5.893
5.888
5.886
5.883
5.875
5.873
5.870
5.860
5.732
5.729
5.724
5.721
5.717
5.714
5.709
5.706
5.702
5.698
5.693
5.690
5.687
5.684
5.678
5.675
4.581
4.579
4.577
4.570
4.567
4.565
1.767
1.764
1.761
1.759
1.754
1.751
1.748
1.746
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
1.04
0.88
0.13
0.97
0.27
1.80
3.05
0.55

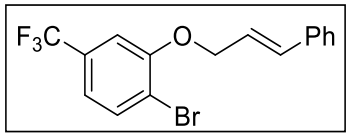
^{13}C NMR

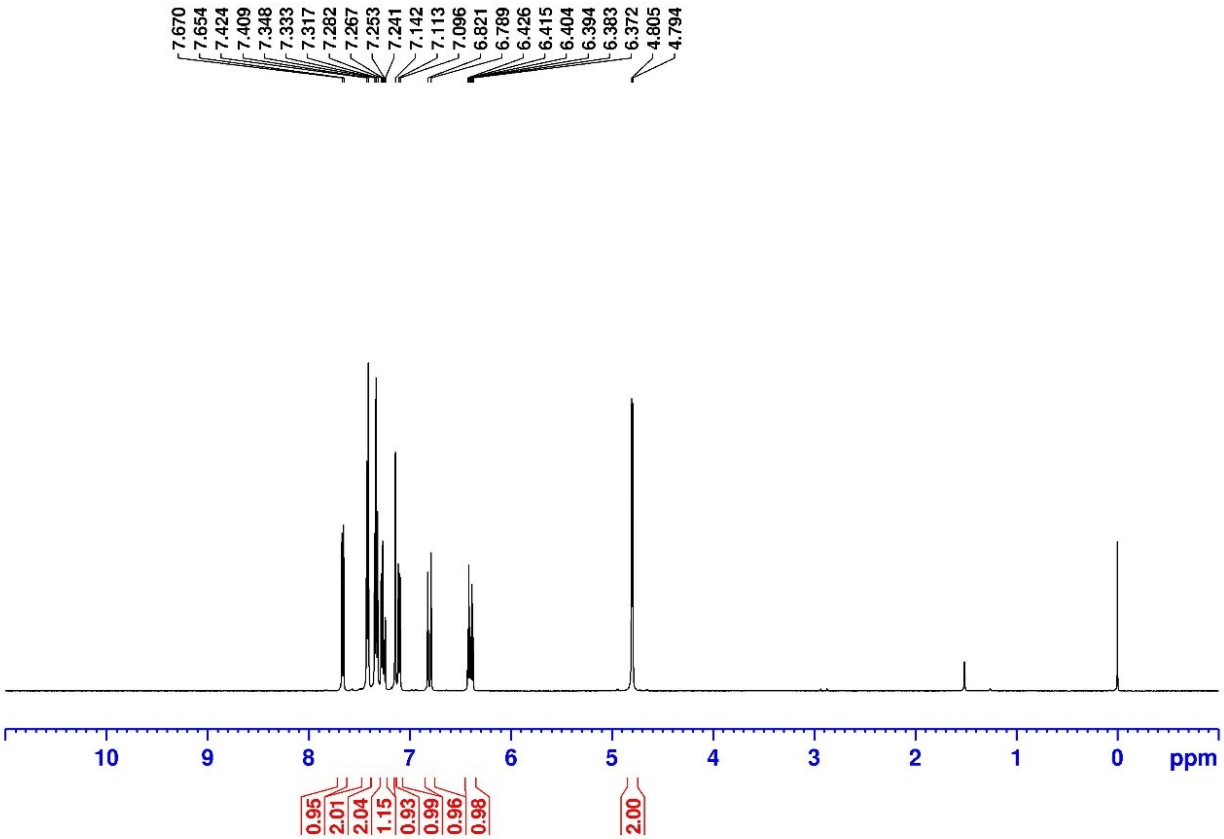

F3C
O
Me
Br


157.650
137.814
131.111
130.552
130.524
129.598
126.752
125.713
125.685
124.746
124.591
124.376
123.977
123.712
122.431
120.272
116.434
114.659
112.791
112.694
112.313
69.890
65.208
17.781
13.413
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

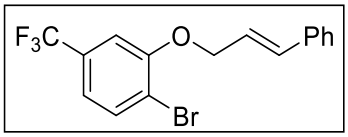
(**2.2p**)

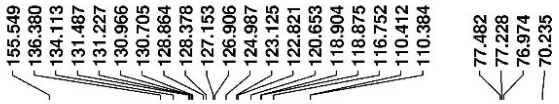
^{1}H NMR

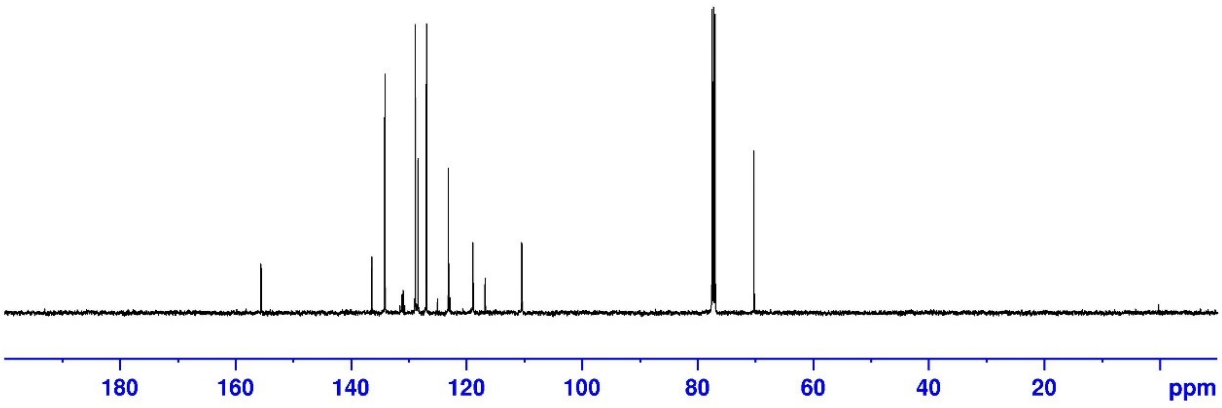

F3C
O
Ph
Br


7.670
7.654
7.424
7.409
7.348
7.333
7.317
7.282
7.267
7.253
7.241
7.142
7.113
7.096
6.821
6.789
6.426
6.415
6.404
6.394
6.383
6.372
4.805
4.794
10
9
8
7
6
5
4
3
2
1
0
ppm
0.95
2.01
2.04
1.15
0.93
0.99
0.96
0.98
2.00

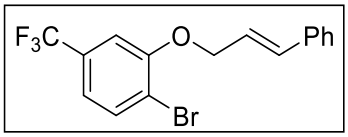
^{13}C NMR

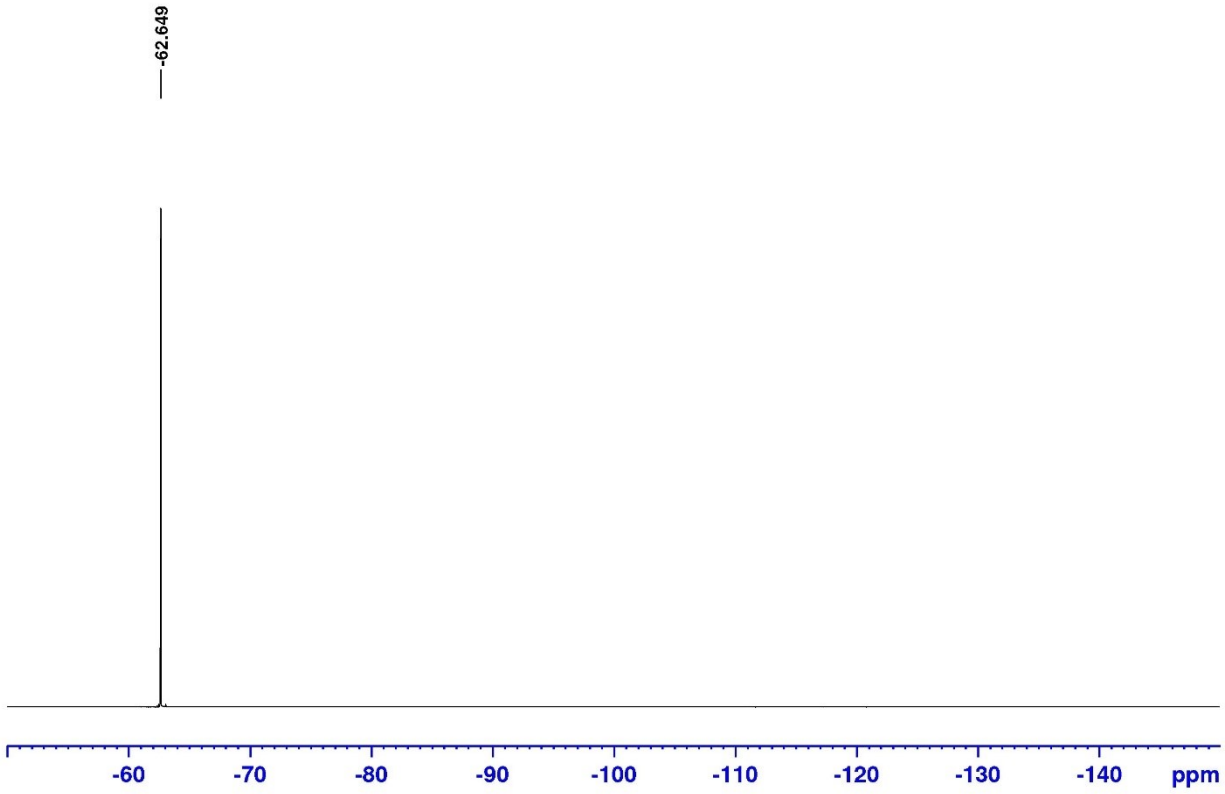

F3C
O
Ph
Br


155.549
136.380
134.113
131.487
131.227
130.966
130.705
128.864
128.378
127.153
126.906
124.987
123.125
122.821
120.653
118.904
118.875
116.752
110.412
110.384
77.482
77.228
76.974
70.235


180
160
140
120
100
80
60
40
20
ppm

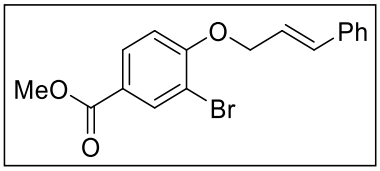
^{19}F NMR

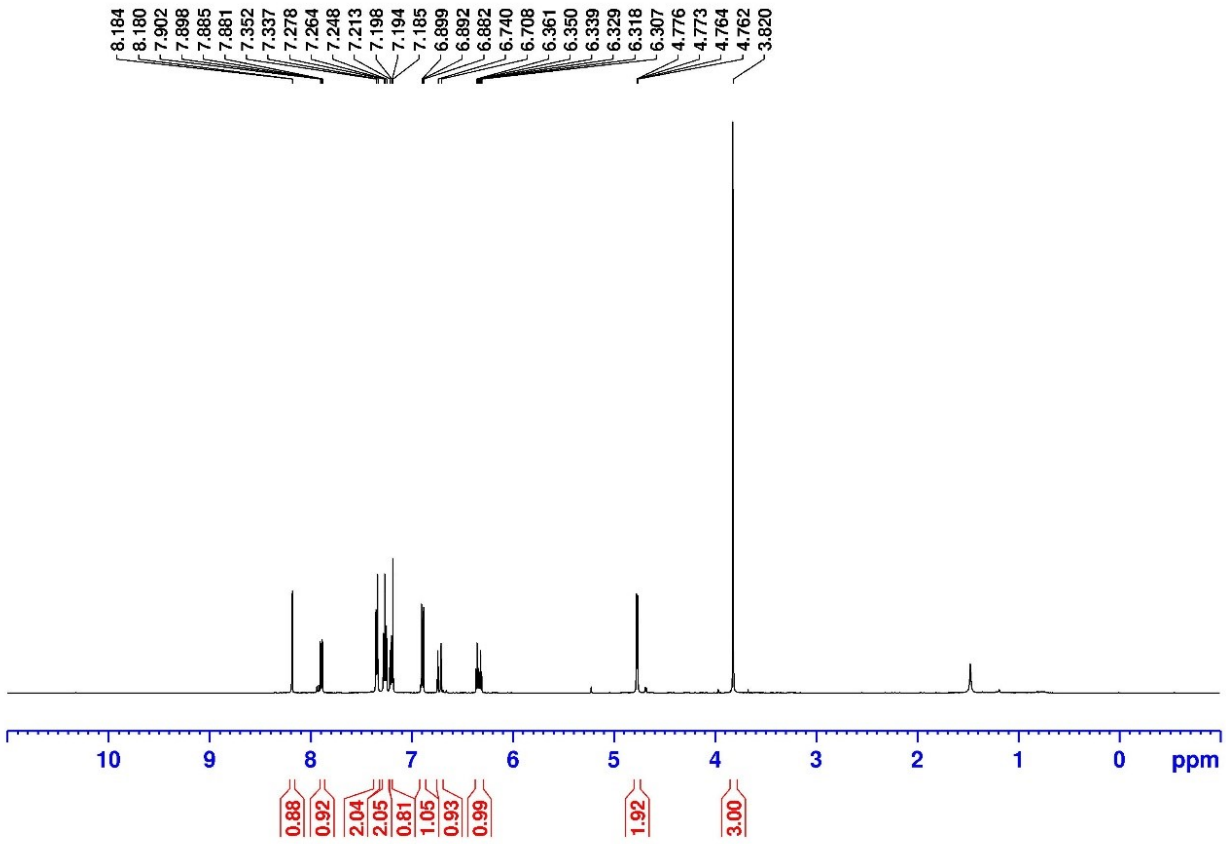




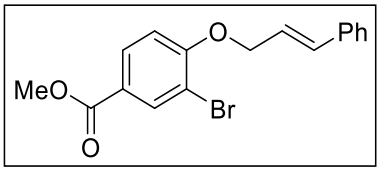
(**2.2q**)

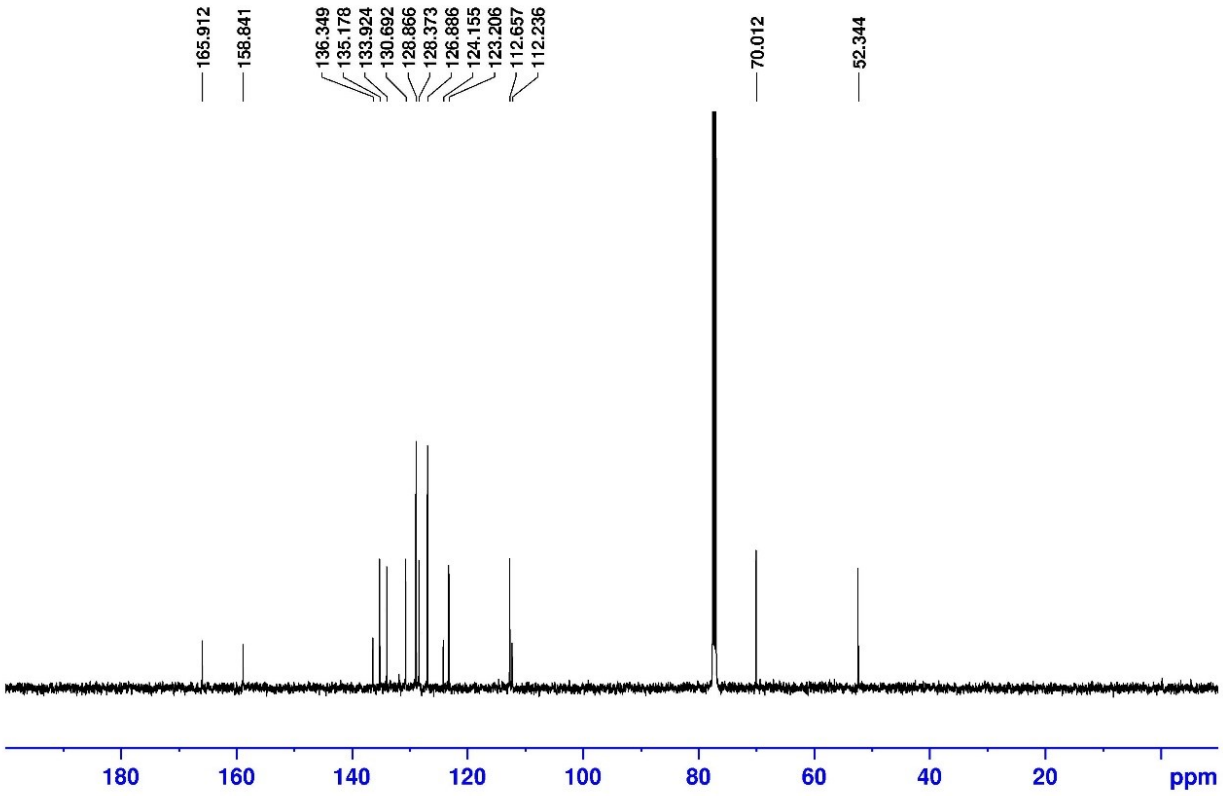
^{1}H NMR


O
Ph
MeO
Br
O


8.184
8.180
7.902
7.898
7.885
7.881
7.352
7.337
7.278
7.264
7.248
7.213
7.198
7.194
7.185
6.899
6.892
6.882
6.740
6.708
6.361
6.350
6.339
6.329
6.318
6.307
4.776
4.773
4.764
4.762
3.820
10
9
8
7
6
5
4
3
2
1
0
ppm
0.88
0.92
2.04
2.05
0.81
1.05
0.93
0.99
1.92
3.00

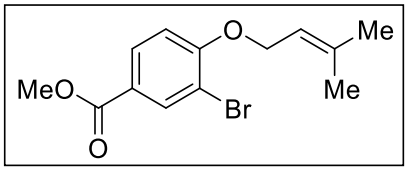
^{13}C NMR

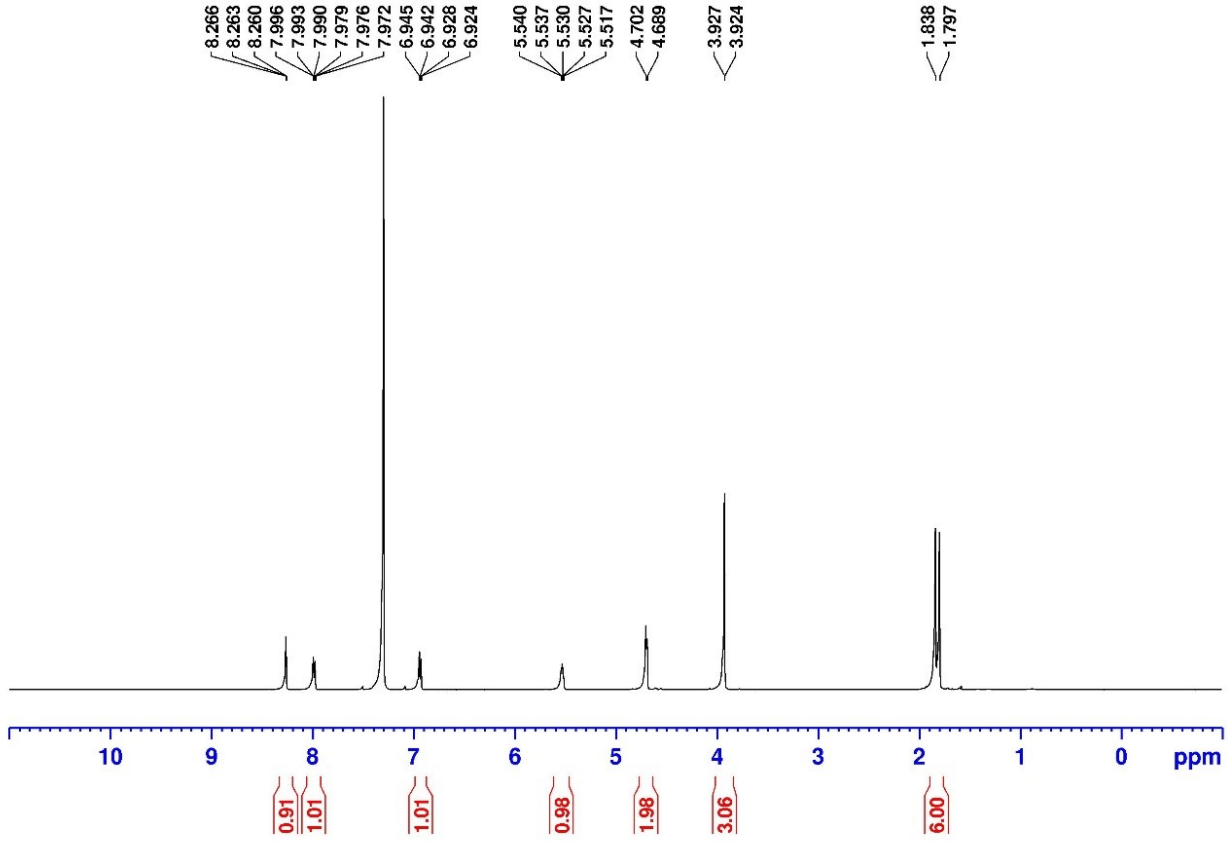

O
Ph
MeO
Br
O


165.912
158.841
136.349
135.178
133.924
130.692
128.866
128.373
126.886
124.155
123.206
112.657
112.236
70.012
52.344
180
160
140
120
100
80
60
40
20
ppm

(**2.2r**)

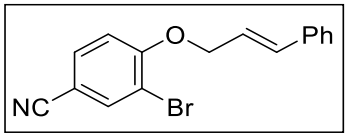
^{1}H NMR

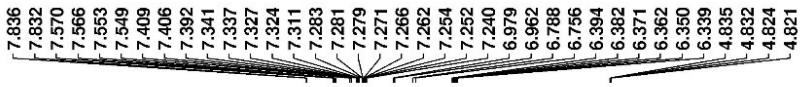

O
Me
MeO
Br
Me
O

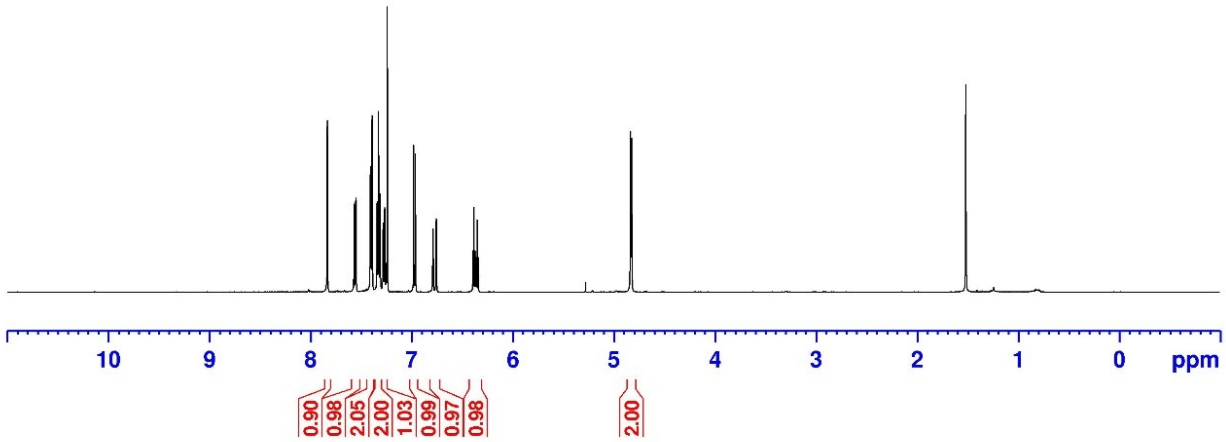

8.266
8.263
8.260
7.996
7.993
7.990
7.979
7.976
7.972
6.945
6.942
6.928
6.924
5.540
5.537
5.530
5.527
5.517
4.702
4.689
3.927
3.924
1.838
1.797
10
9
8
7
6
5
4
3
2
1
0
ppm
0.91
1.01
1.01
0.98
1.98
3.06
6.00

(**2.2s**)

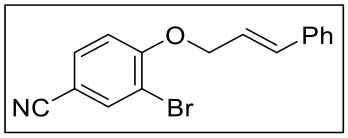
^{1}H NMR

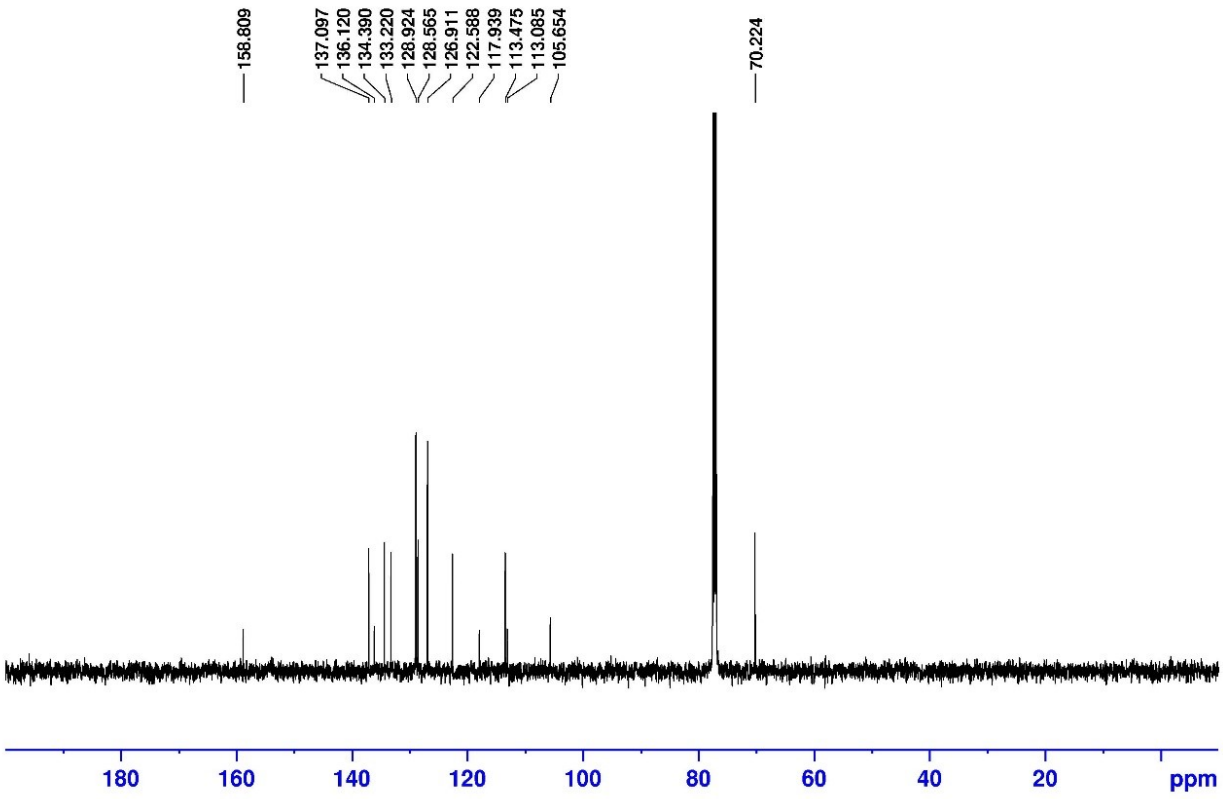

O
Ph
NC
Br


7.836
7.832
7.570
7.566
7.553
7.549
7.409
7.406
7.392
7.341
7.337
7.327
7.324
7.311
7.283
7.281
7.279
7.271
7.266
7.262
7.254
7.252
7.240
6.979
6.962
6.788
6.756
6.394
6.382
6.371
6.362
6.350
6.339
4.835
4.832
4.824
4.821


10
9
8
7
6
5
4
3
2
1
0
ppm
0.90
0.98
2.05
2.00
1.03
0.99
0.97
0.98
2.00

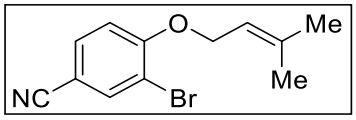
^{13}C NMR

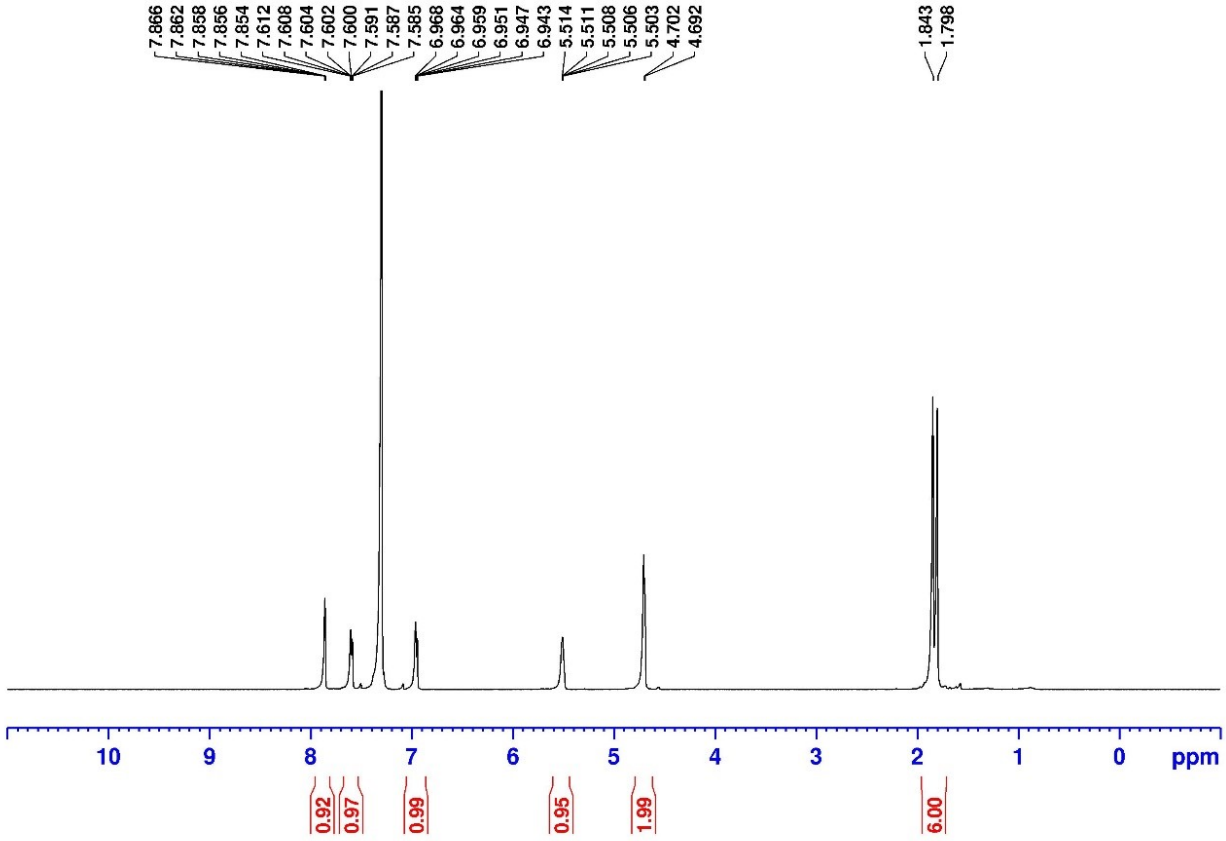

O
Ph
NC
Br


158.809
137.097
136.120
134.390
133.220
128.924
128.565
126.911
122.588
117.939
113.475
113.085
105.654
70.224
180
160
140
120
100
80
60
40
20
ppm

(**2.2t**)

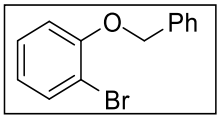
^{1}H NMR

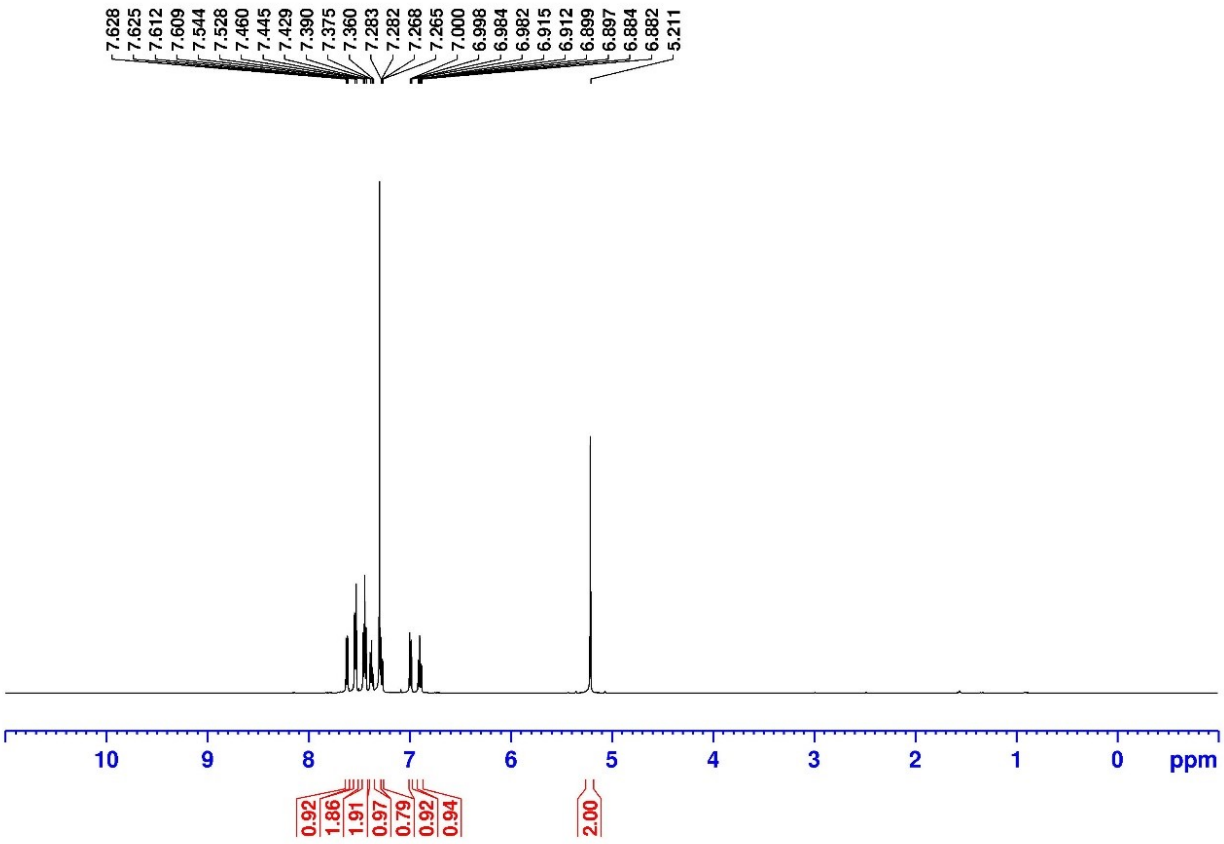

O
Me
Me
NC
Br


7.866
7.862
7.858
7.856
7.854
7.612
7.608
7.604
7.602
7.600
7.591
7.587
7.585
6.968
6.964
6.959
6.951
6.947
6.943
5.514
5.511
5.508
5.506
5.503
4.702
4.692
1.843
1.798
10
9
8
7
6
5
4
3
2
1
0
ppm
0.92
0.97
0.99
0.95
1.99
6.00

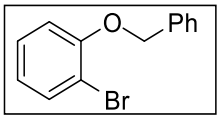
(**2.2u**)

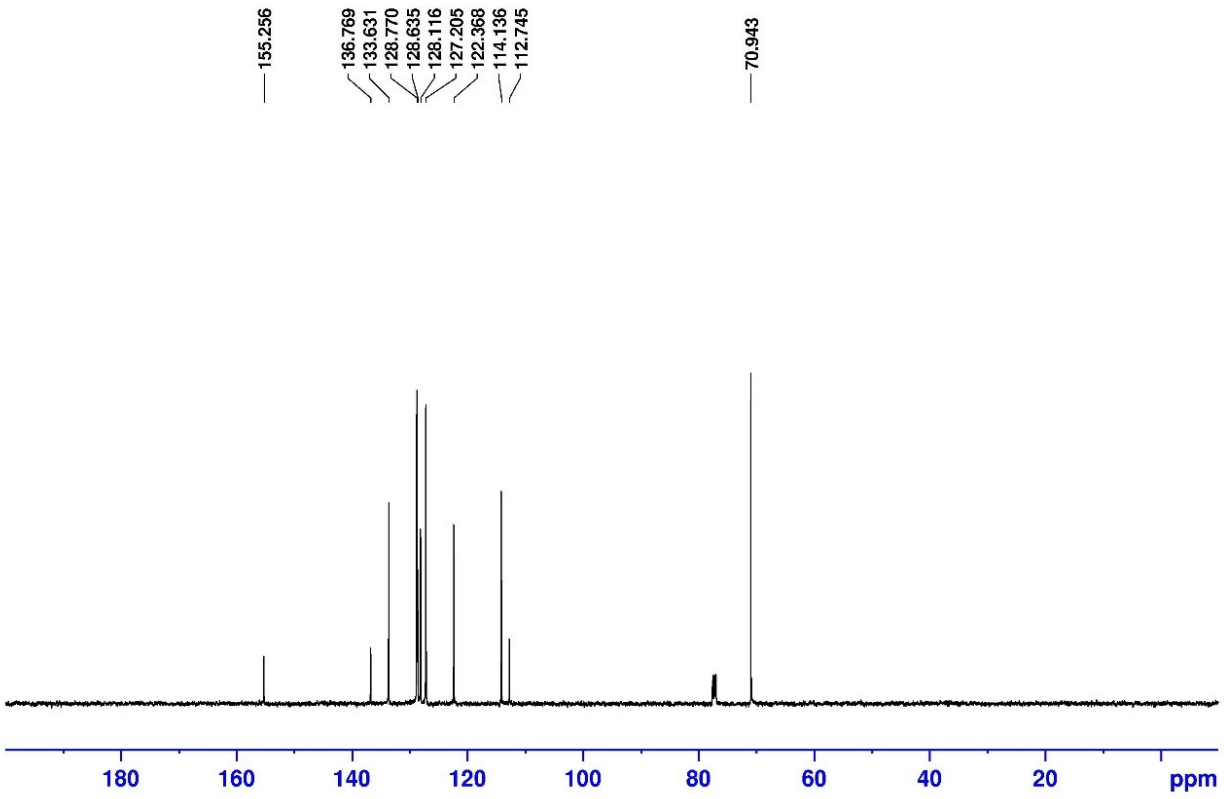
^{1}H NMR


O
Ph
Br


7.628
7.625
7.612
7.609
7.544
7.528
7.460
7.445
7.429
7.390
7.375
7.360
7.283
7.282
7.268
7.265
7.000
6.998
6.984
6.982
6.915
6.912
6.899
6.897
6.884
6.882
5.211
10
9
8
7
6
5
4
3
2
1
0
ppm
0.92
1.86
1.91
0.97
0.79
0.92
0.94
2.00

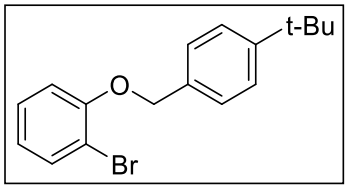
^{13}C NMR

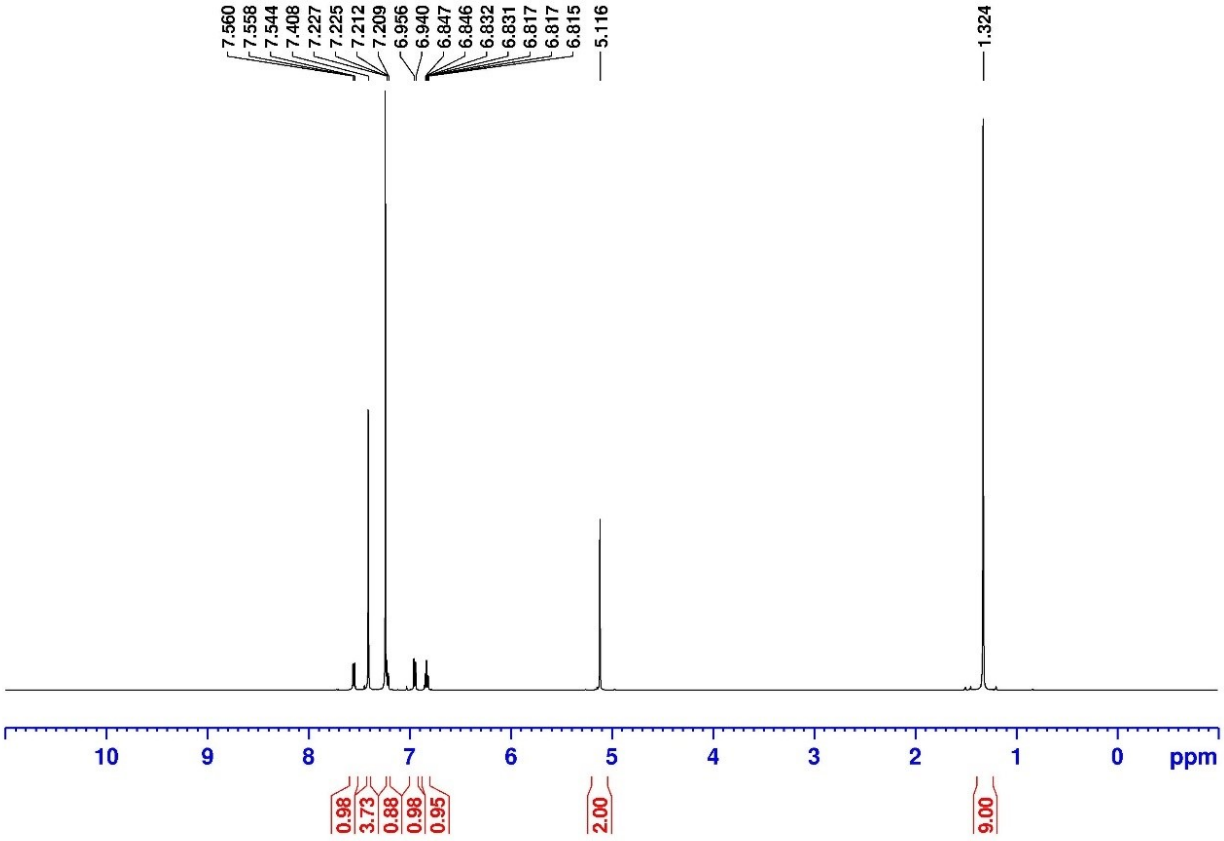

O
Ph
Br


155.256
136.769
133.631
128.770
128.635
128.116
127.205
122.368
114.136
112.745
70.943
180
160
140
120
100
80
60
40
20
ppm

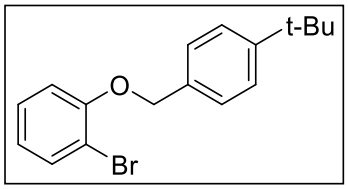
(**2.2v**)

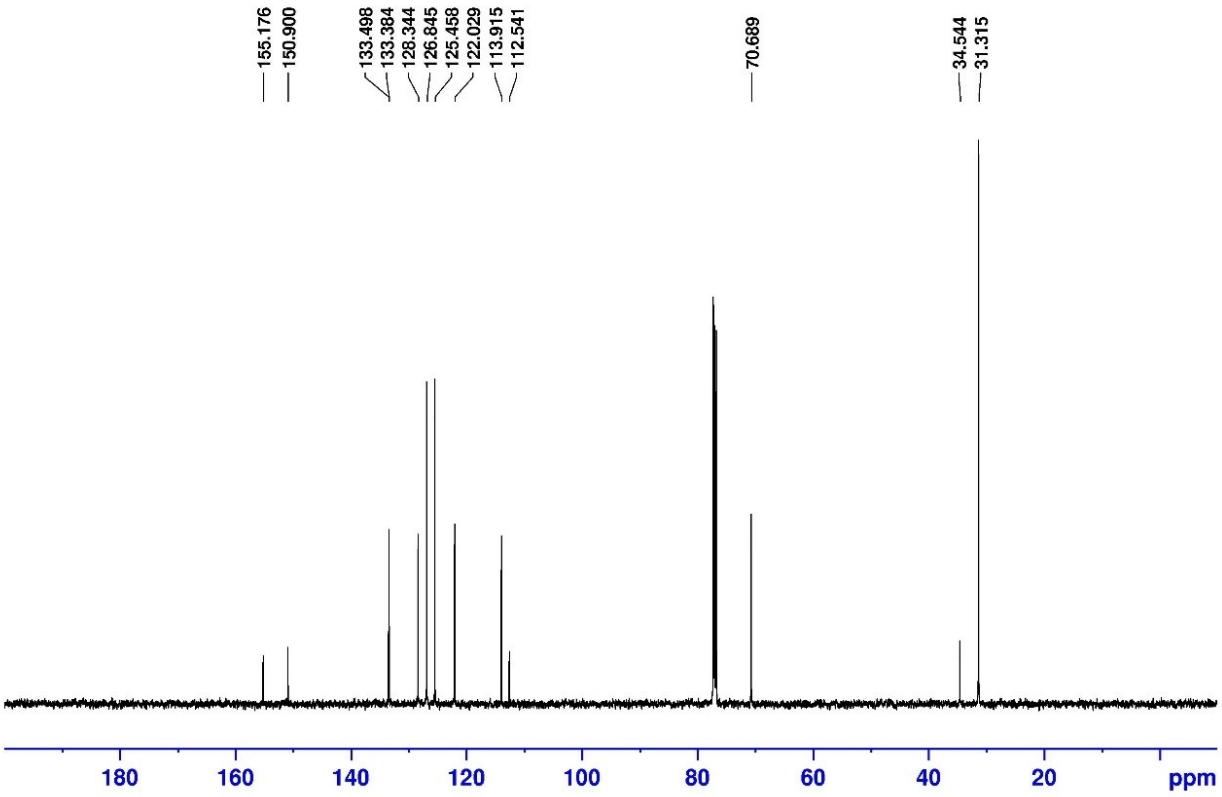
^{1}H NMR


t-Bu
O
Br


7.560
7.558
7.544
7.408
7.227
7.225
7.212
7.209
6.956
6.940
6.847
6.846
6.832
6.831
6.817
6.817
6.815
5.116
1.324
10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
3.73
0.88
0.98
0.95
2.00
9.00

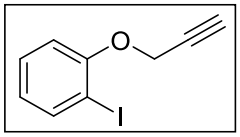
^{13}C NMR

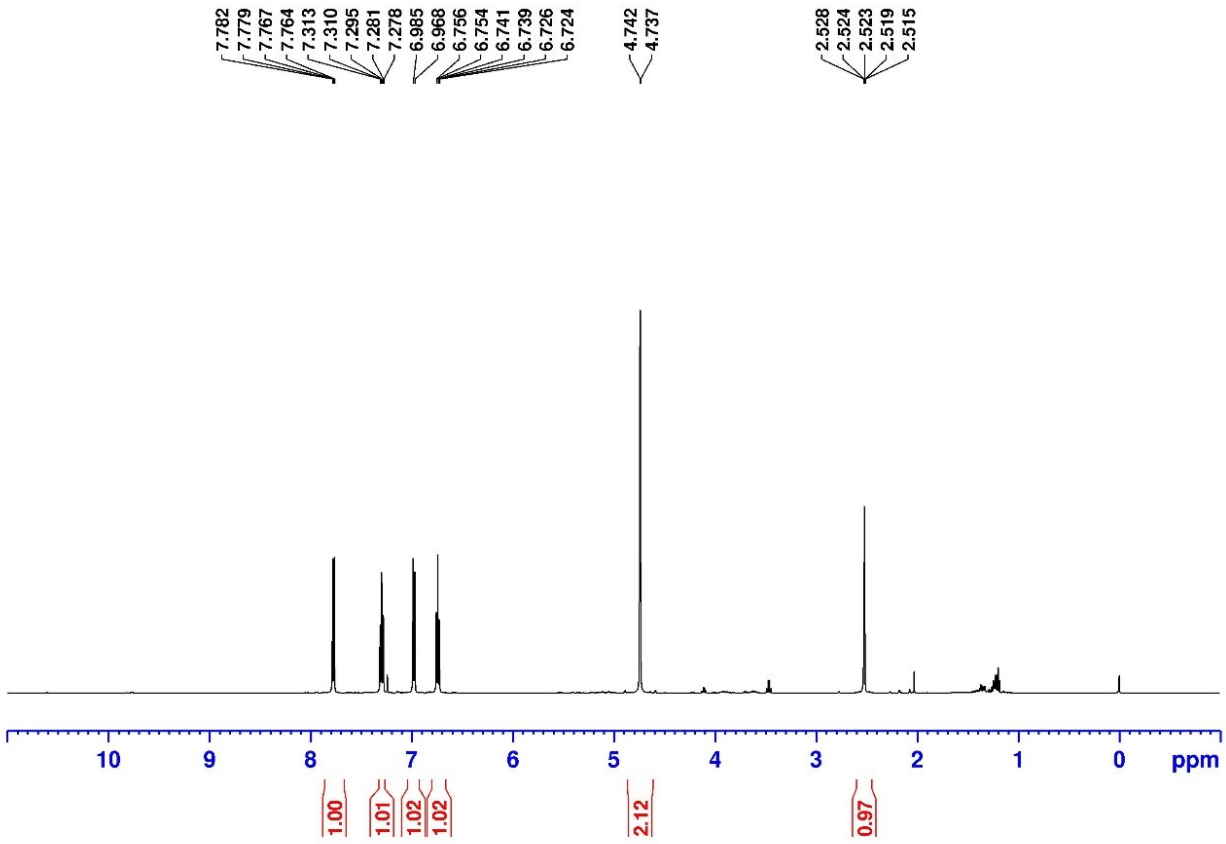

t-Bu
O
Br


155.176
150.900
133.498
133.384
128.344
126.845
125.458
122.029
113.915
112.541
70.689
34.544
31.315
180
160
140
120
100
80
60
40
20
ppm

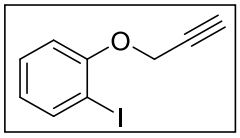
(**2.2w**)

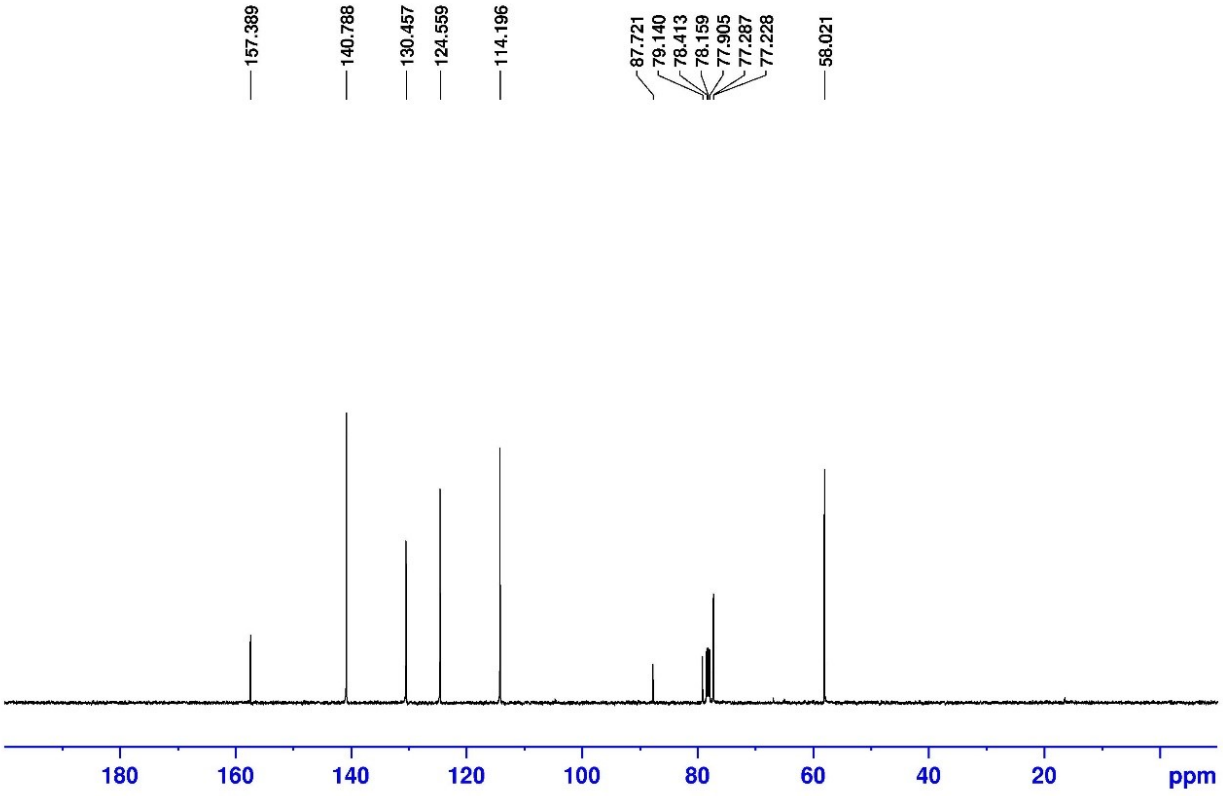
^{1}H NMR


O
I


7.782
7.779
7.767
7.764
7.313
7.310
7.295
7.281
7.278
6.985
6.968
6.756
6.754
6.741
6.739
6.726
6.724
4.742
4.737
2.528
2.524
2.523
2.519
2.515
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
1.02
1.02
2.12
0.97

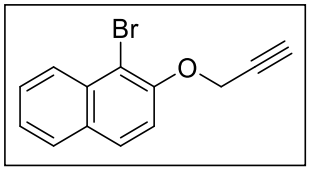
^{13}C NMR

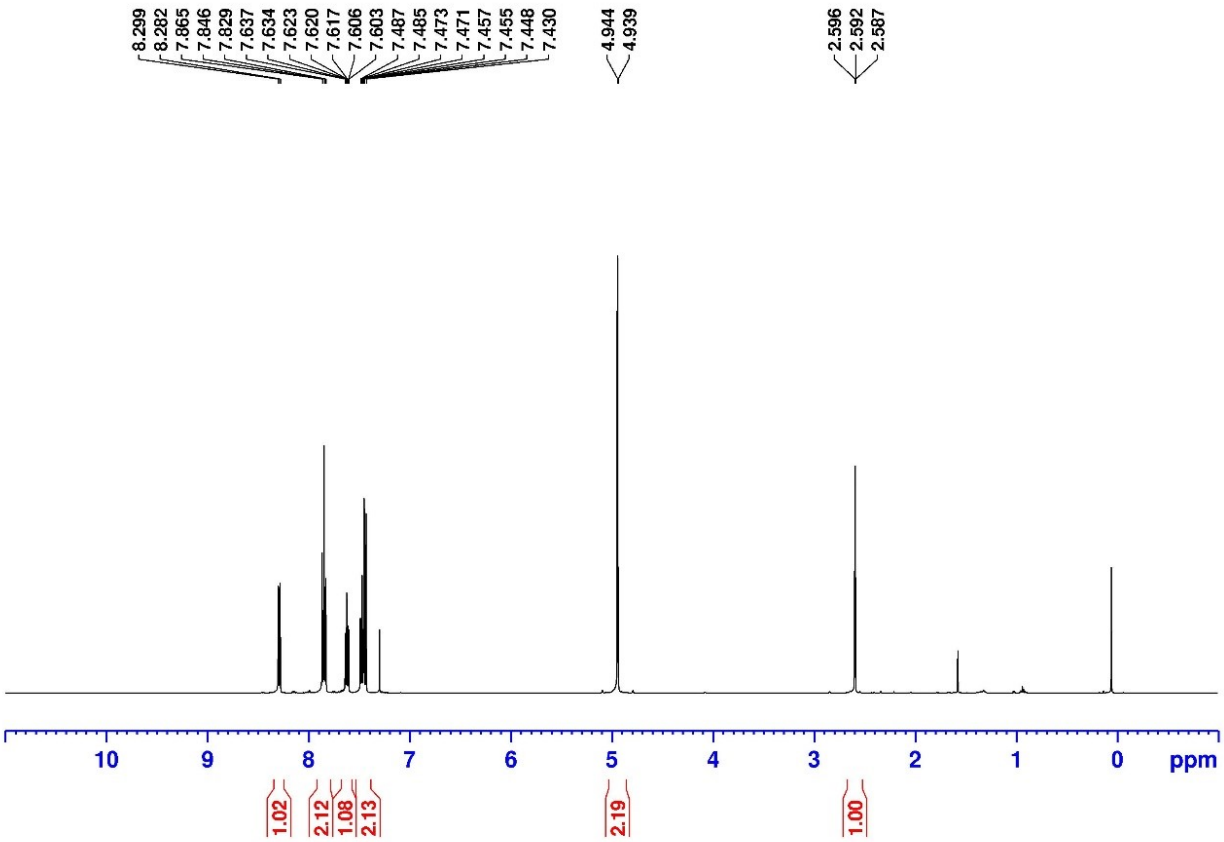

O
I


157.389
140.788
130.457
124.559
114.196
87.721
79.140
78.413
78.159
77.905
77.287
77.228
58.021
180
160
140
120
100
80
60
40
20
ppm

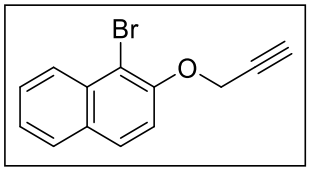
(**2.2x**)

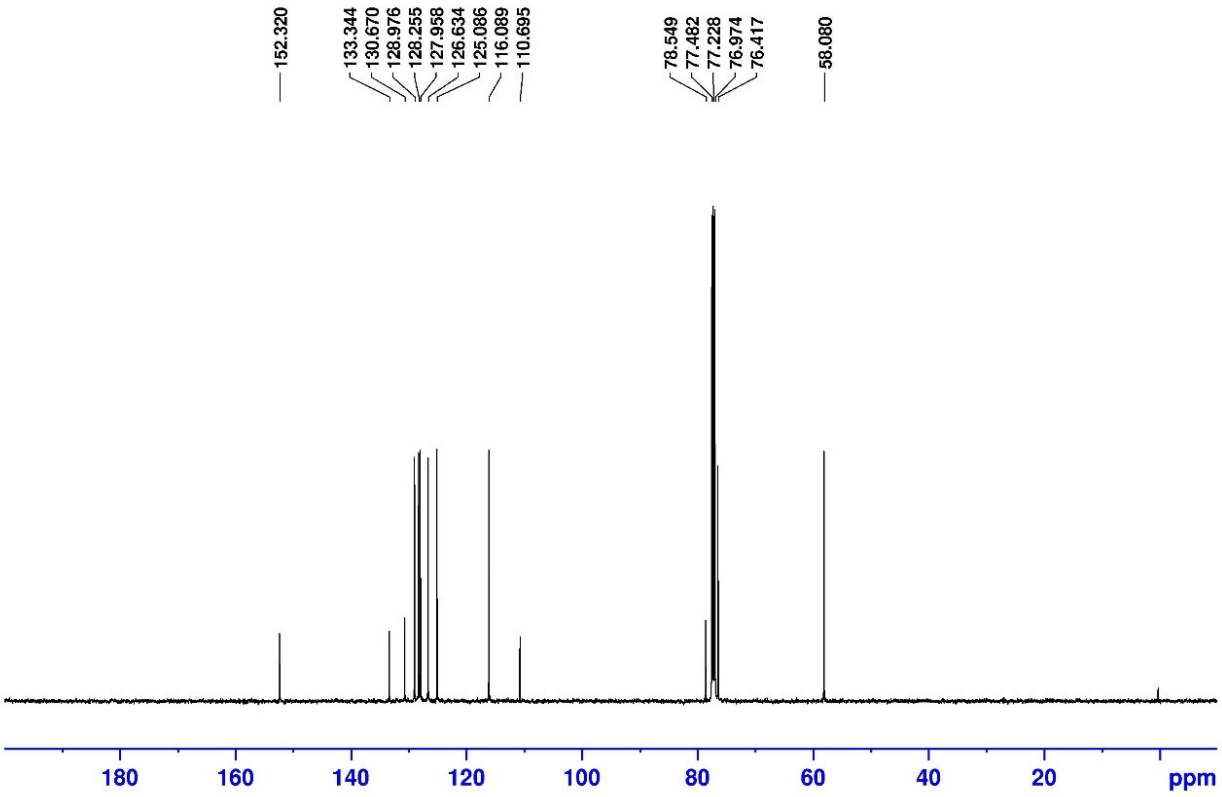
^{1}H NMR


Br
O


8.299
8.282
7.865
7.846
7.829
7.637
7.634
7.623
7.620
7.617
7.606
7.603
7.487
7.485
7.473
7.471
7.457
7.455
7.448
7.430
4.944
4.939
2.596
2.592
2.587
10
9
8
7
6
5
4
3
2
1
0
ppm
1.02
2.12
1.08
2.13
2.19
1.00

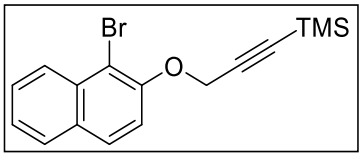
^{13}C NMR

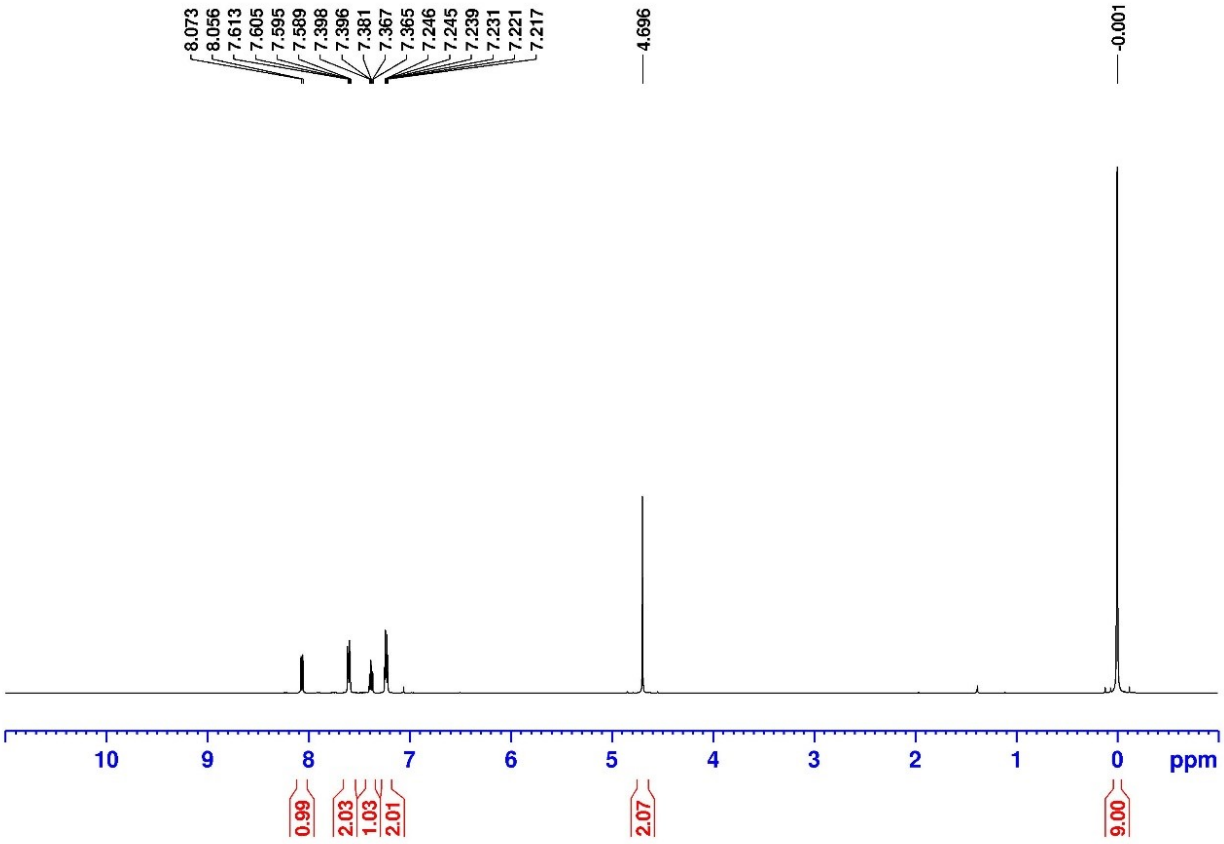

Br
O


152.320
133.344
130.670
128.976
128.255
127.958
126.634
125.086
116.089
110.695
78.549
77.482
77.228
76.974
76.417
58.080
180
160
140
120
100
80
60
40
20
ppm

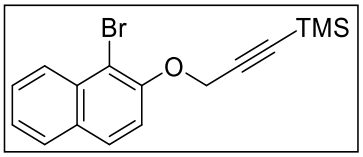
(**2.2y**)

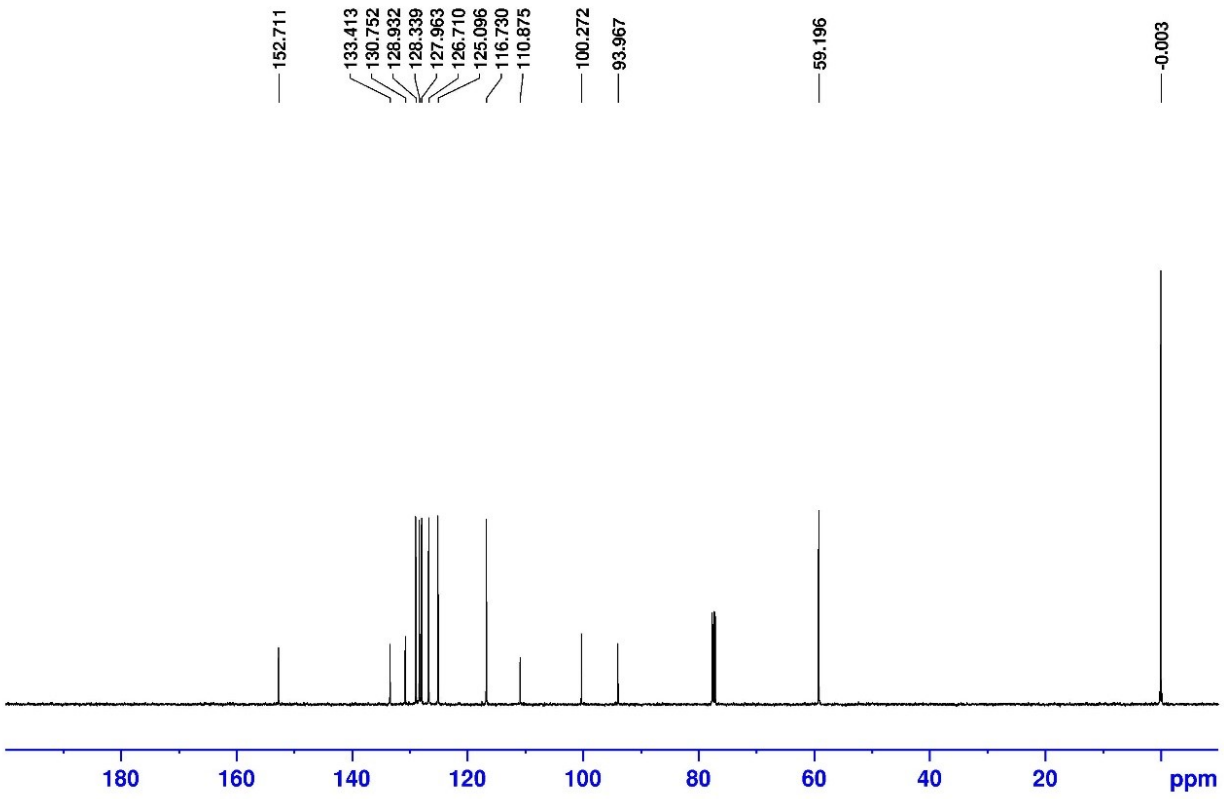
^{1}H NMR


Br
TMS
O


8.073
8.056
7.613
7.605
7.595
7.589
7.398
7.396
7.381
7.367
7.365
7.246
7.245
7.239
7.231
7.221
7.217
4.696
-0.001
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
2.03
1.03
2.01
2.07
9.00

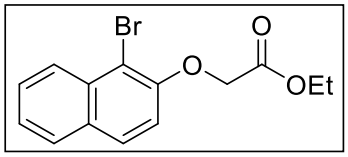
^{13}C NMR

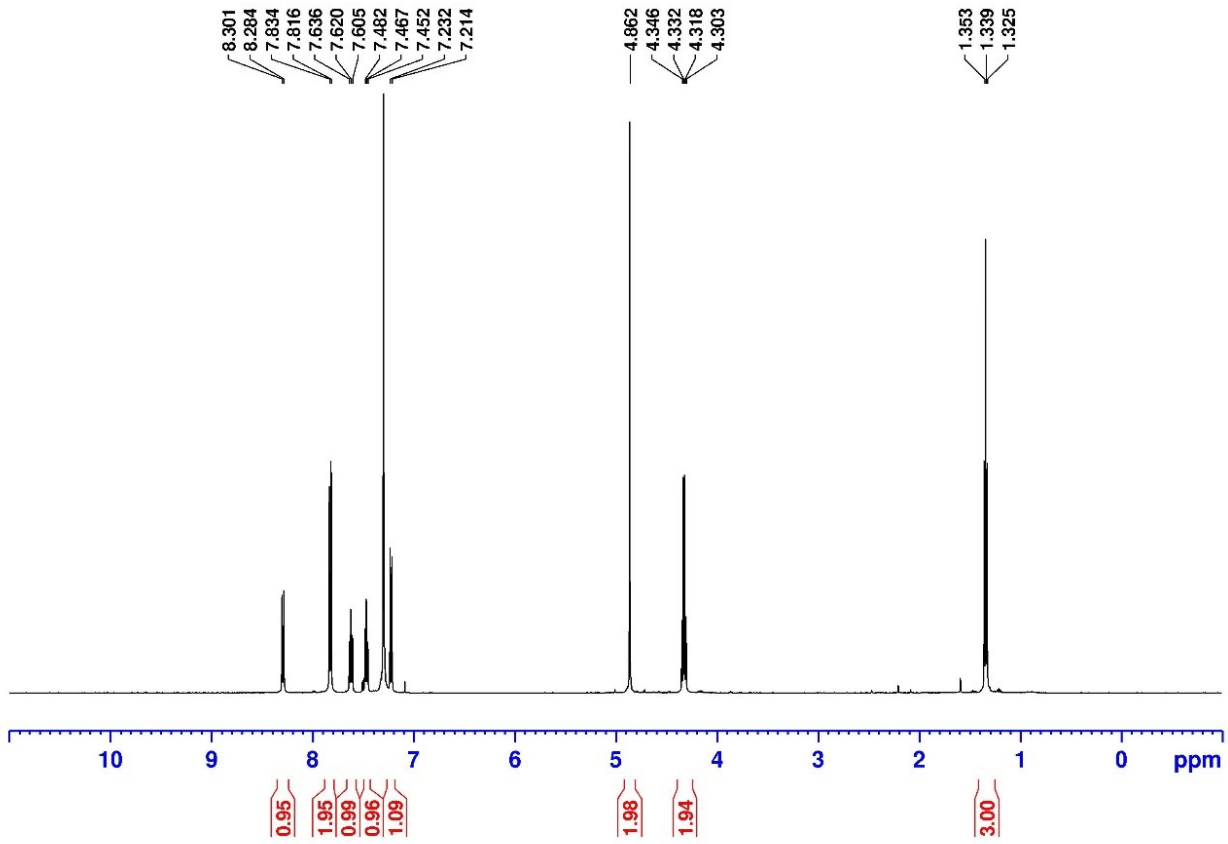

Br
TMS
O


152.711
133.413
130.752
128.932
128.339
127.963
126.710
125.096
116.730
110.875
100.272
93.967
59.196
-0.003
180
160
140
120
100
80
60
40
20
ppm

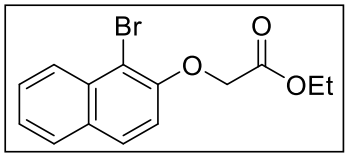
(**2.2z**)

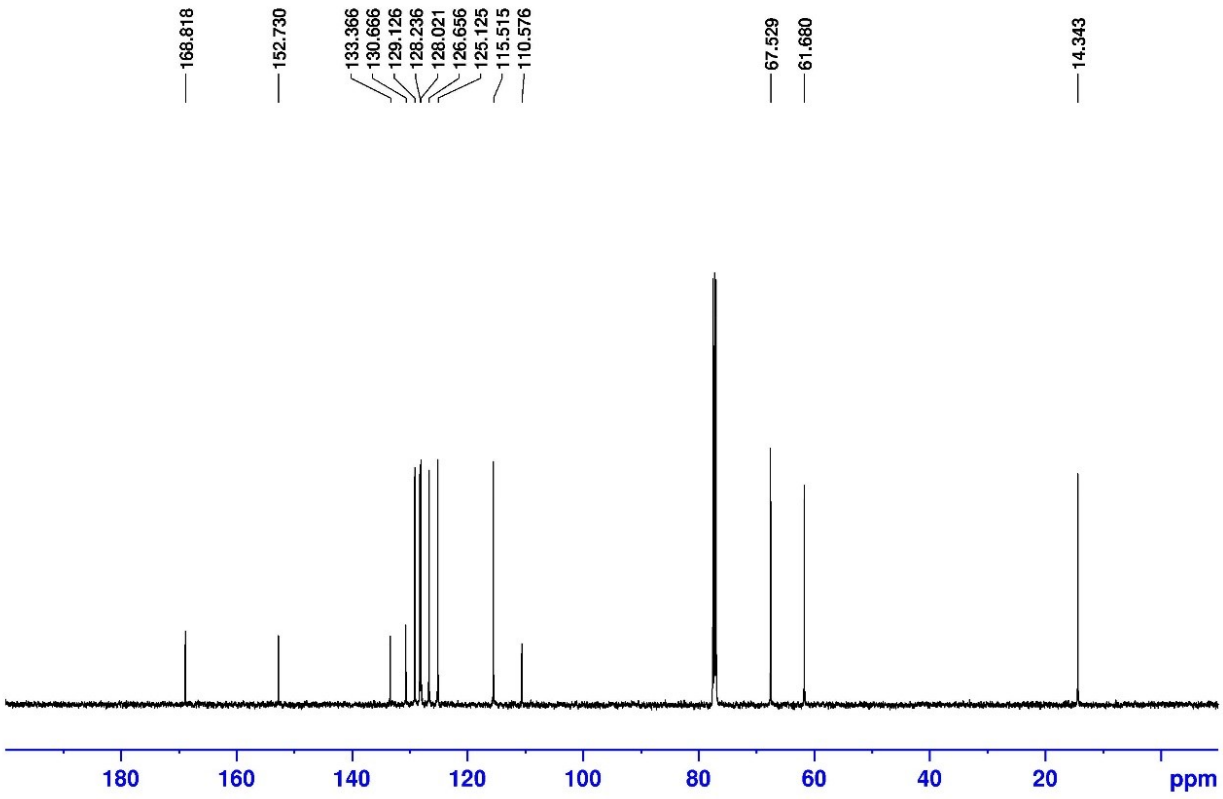
^{1}H NMR


Br
O
O
OEt


8.301
8.284
7.834
7.816
7.636
7.620
7.605
7.482
7.467
7.452
7.232
7.214
4.862
4.346
4.332
4.318
4.303
1.353
1.339
1.325
10
9
8
7
6
5
4
3
2
1
0
ppm
0.95
1.95
0.99
0.96
1.09
1.98
1.94
3.00

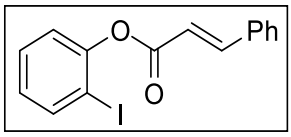
^{13}C NMR

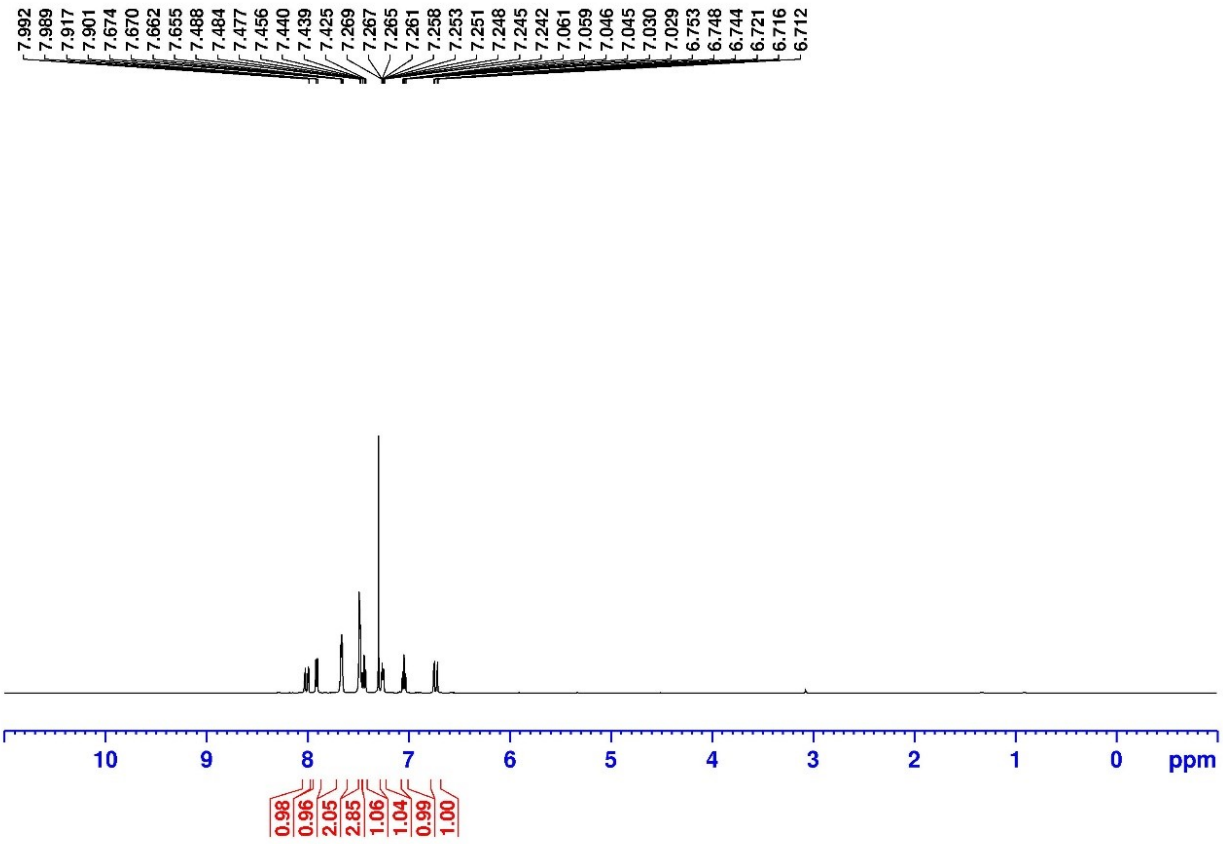

Br
O
O
OEt


168.818
152.730
133.366
130.666
129.126
128.236
128.021
126.656
125.125
115.515
110.576
67.529
61.680
14.343
180
160
140
120
100
80
60
40
20
ppm

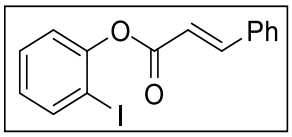
(**2.2aa**)

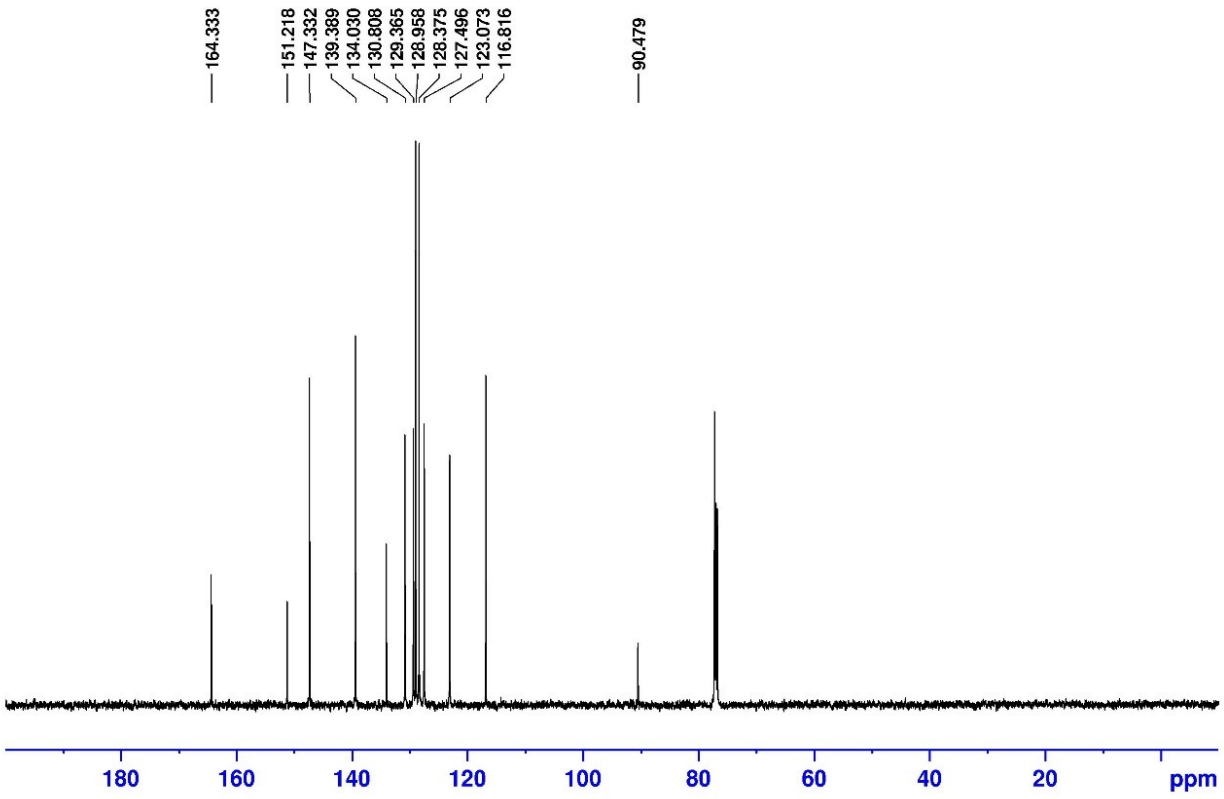
^{1}H NMR


O
Ph
O
I


7.992
7.989
7.917
7.901
7.674
7.670
7.662
7.655
7.488
7.484
7.477
7.456
7.440
7.439
7.425
7.269
7.267
7.265
7.261
7.258
7.253
7.251
7.248
7.245
7.242
7.061
7.059
7.046
7.045
7.030
7.029
6.753
6.748
6.744
6.721
6.716
6.712
10
9
8
7
6
5
4
3
2
1
0
ppm
0.98
0.96
2.05
2.85
1.06
1.04
0.99
1.00

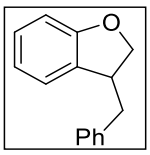
^{13}C NMR

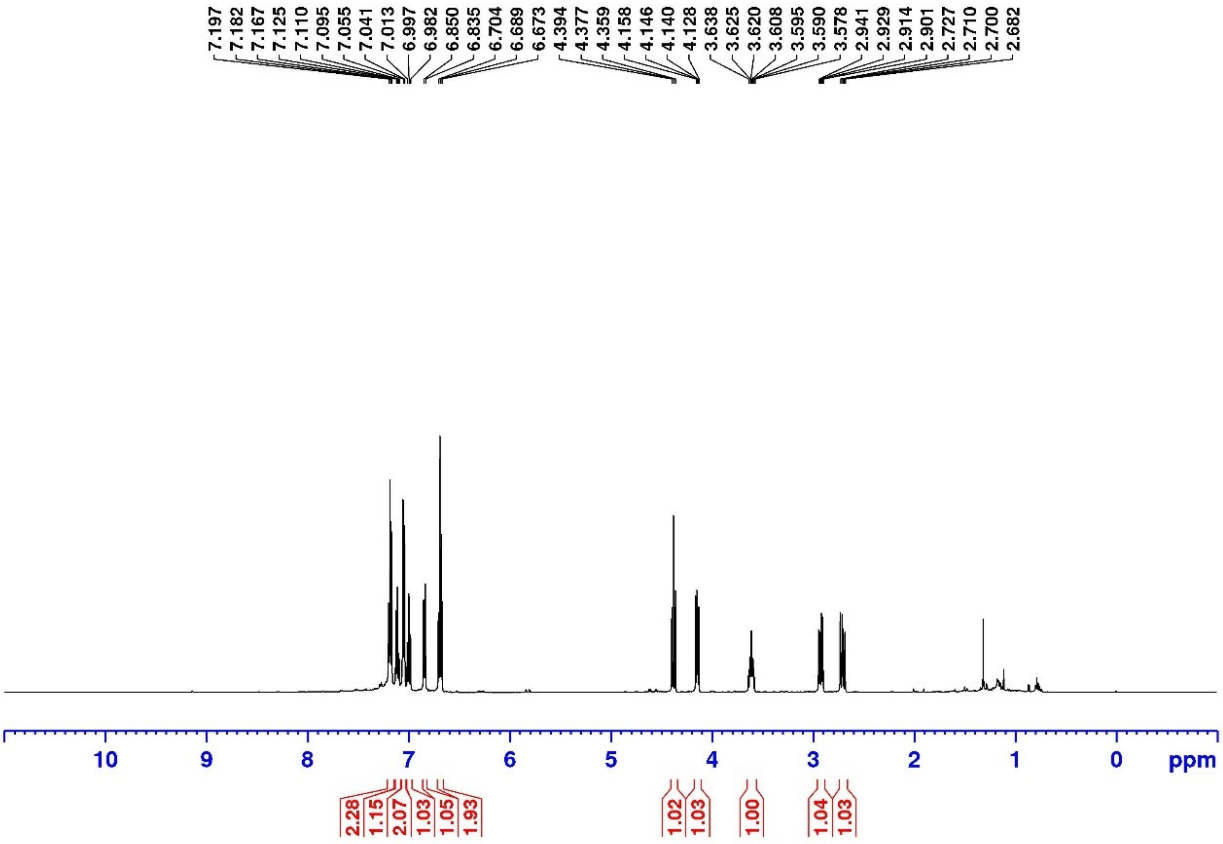

O
Ph
O
I


164.333
151.218
147.332
139.389
134.030
130.808
129.365
128.958
128.375
127.496
123.073
116.816
90.479
180
160
140
120
100
80
60
40
20
ppm

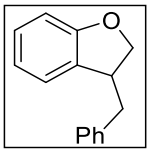
(**2.2A**)

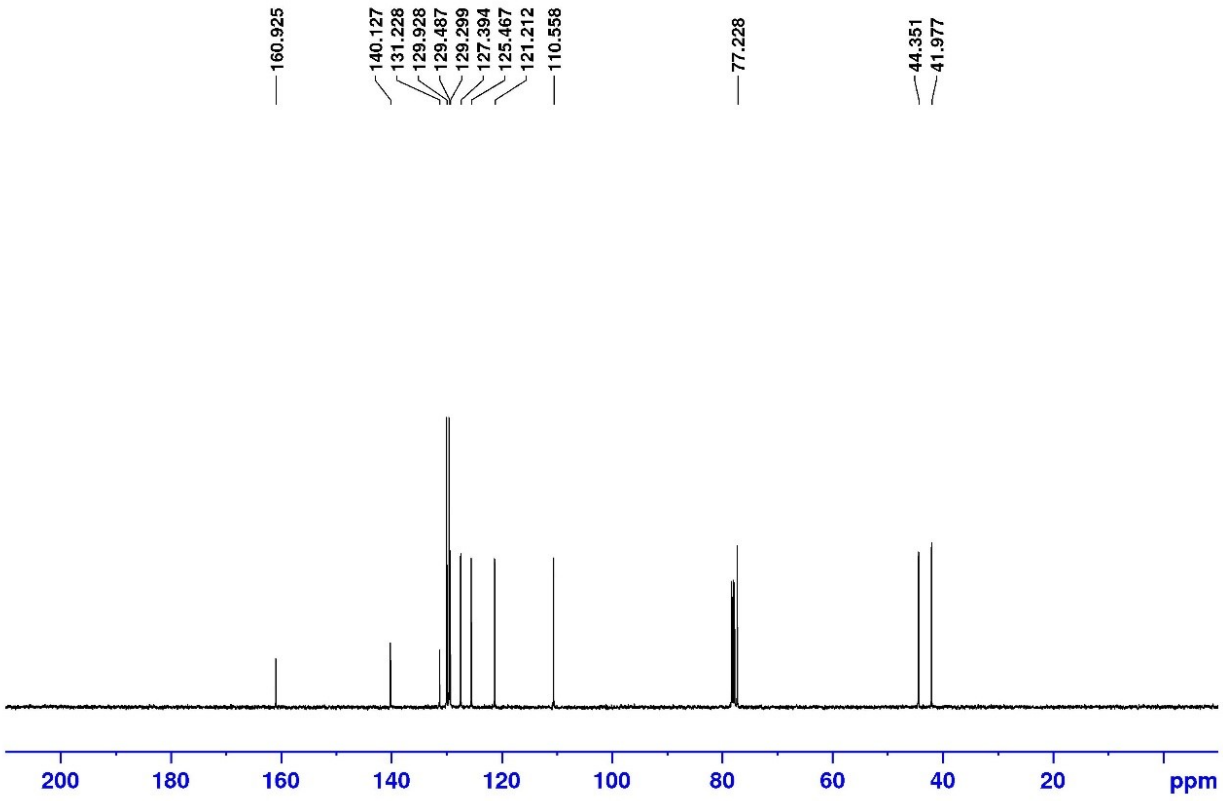
^{1}H NMR


O
Ph


7.197
7.182
7.167
7.125
7.110
7.095
7.055
7.041
7.013
6.997
6.982
6.850
6.835
6.704
6.689
6.673
4.394
4.377
4.359
4.158
4.146
4.140
4.128
3.638
3.625
3.620
3.608
3.595
3.590
3.578
2.941
2.929
2.914
2.901
2.727
2.710
2.700
2.682
10
9
8
7
6
5
4
3
2
1
0
ppm
2.28
1.15
2.07
1.03
1.05
1.93
1.02
1.03
1.00
1.04
1.03

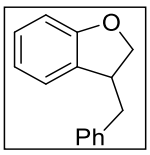
^{13}CNMR

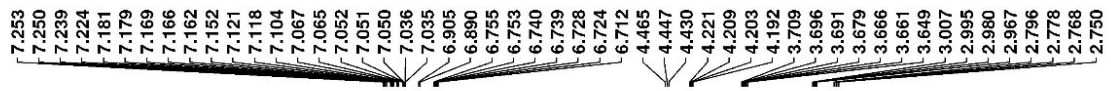

O
Ph

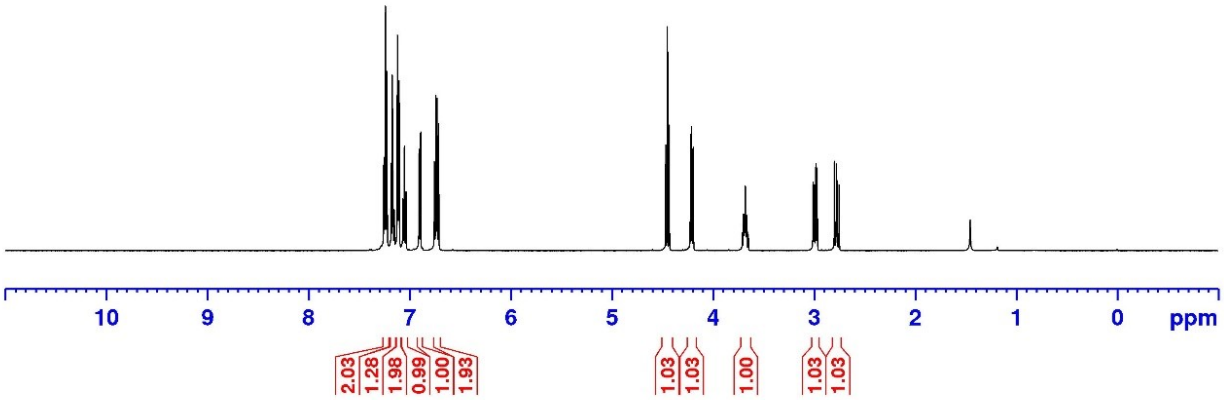

160.925
140.127
131.228
129.928
129.487
129.299
127.394
125.467
121.212
110.558
77.228
44.351
41.977
200
180
160
140
120
100
80
60
40
20
ppm

(**2.2B**)

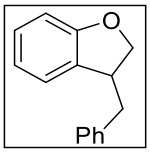
^{1}H NMR

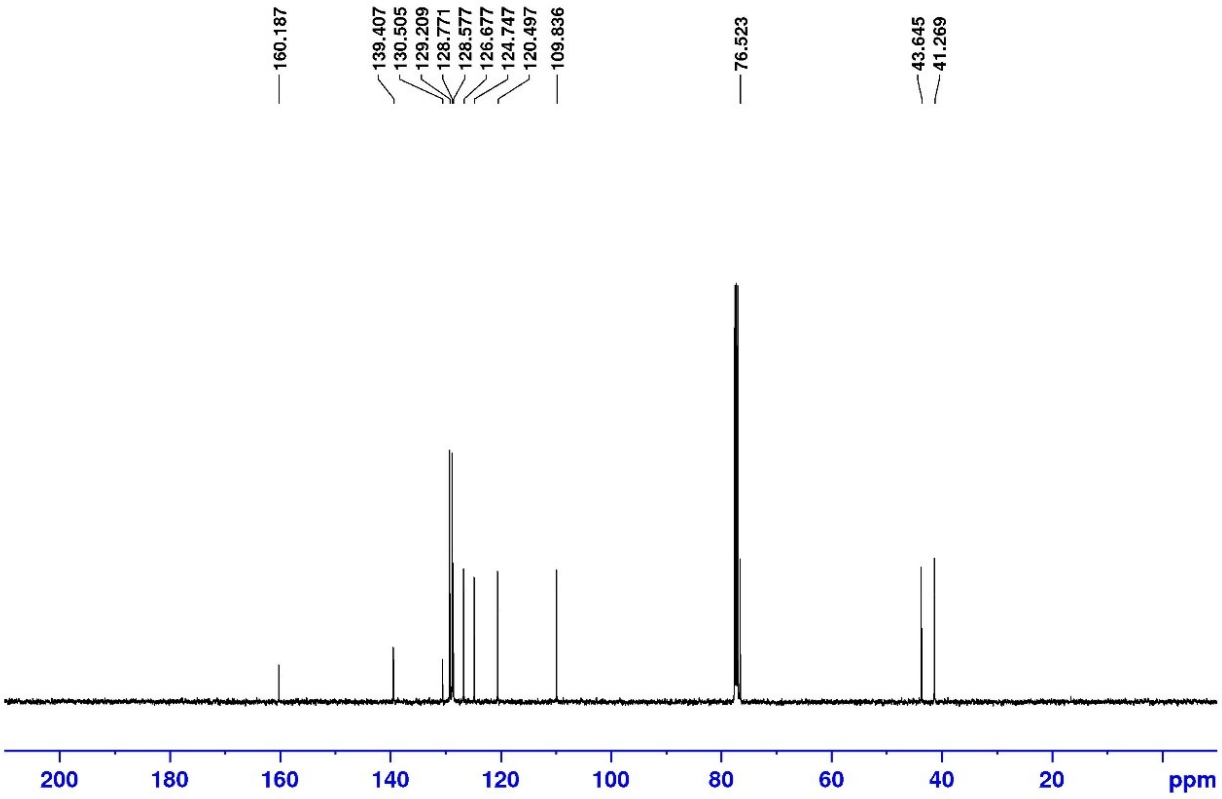

O
Ph


7.253
7.250
7.239
7.224
7.181
7.179
7.169
7.166
7.162
7.152
7.121
7.118
7.104
7.067
7.065
7.052
7.051
7.050
7.036
7.035
6.905
6.890
6.755
6.753
6.740
6.739
6.728
6.724
6.712
4.465
4.447
4.430
4.221
4.209
4.203
4.192
3.709
3.696
3.691
3.679
3.666
3.661
3.649
3.007
2.995
2.980
2.967
2.796
2.778
2.768
2.750


10
9
8
7
6
5
4
3
2
1
0
ppm
2.03
1.28
1.98
0.99
1.00
1.93
1.03
1.03
1.00
1.03
1.03

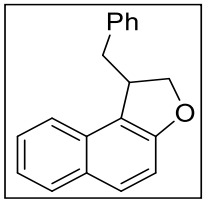
^{13}C NMR

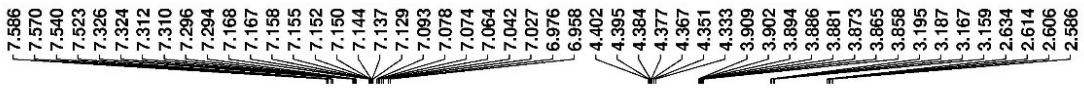

O
Ph

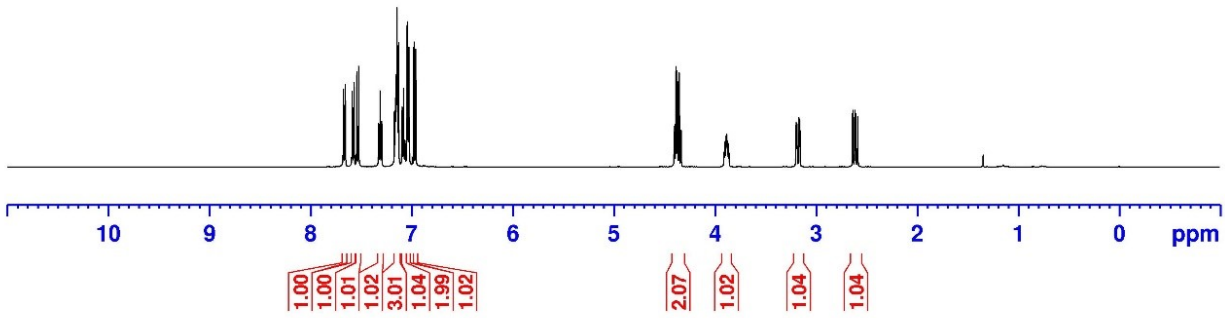

160.187
139.407
130.505
129.209
128.771
128.577
126.677
124.747
120.497
109.836
76.523
43.645
41.269
200
180
160
140
120
100
80
60
40
20
ppm

(**2.2D**)

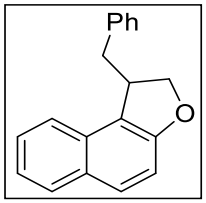
^{1}H NMR

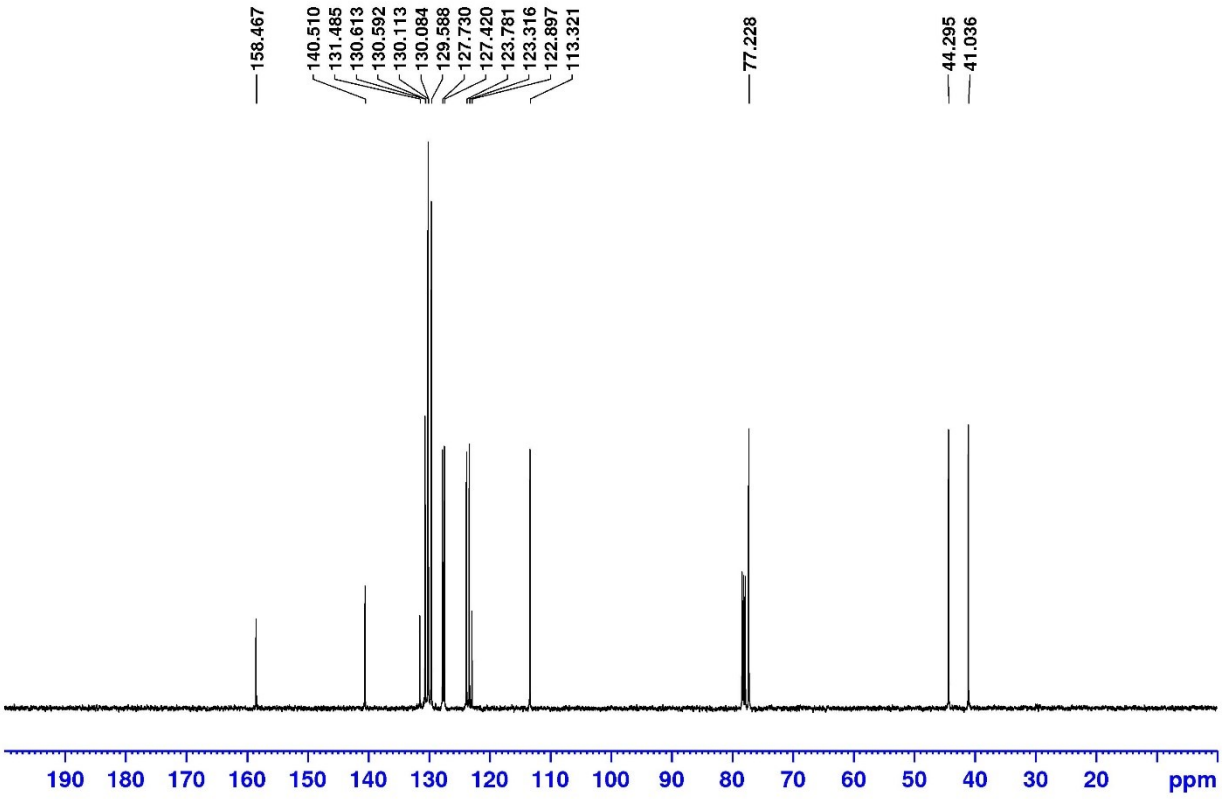

Ph
O


7.586
7.570
7.540
7.523
7.326
7.324
7.312
7.310
7.296
7.294
7.168
7.167
7.158
7.155
7.152
7.150
7.144
7.137
7.129
7.093
7.078
7.074
7.064
7.042
7.027
6.976
6.958
4.402
4.395
4.384
4.377
4.367
4.351
4.333
3.909
3.902
3.894
3.886
3.881
3.873
3.865
3.858
3.195
3.187
3.167
3.159
2.634
2.614
2.606
2.586


10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.01
1.02
3.01
1.04
1.99
1.02
2.07
1.02
1.04
1.04

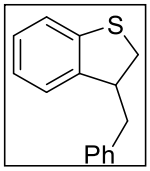
^{13}C NMR

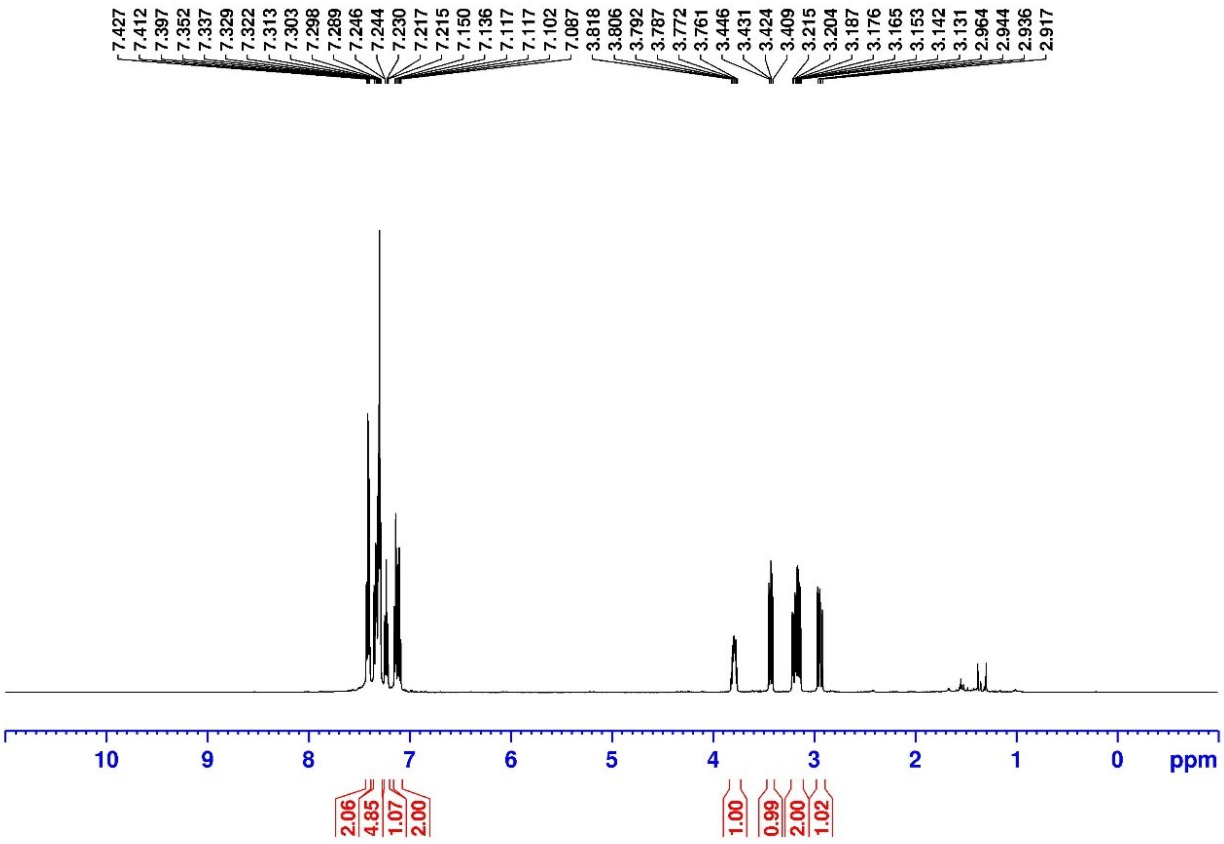

Ph
O


158.467
140.510
131.485
130.613
130.592
130.113
130.084
129.588
127.730
127.420
123.781
123.316
122.897
113.321
77.228
44.295
41.036
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

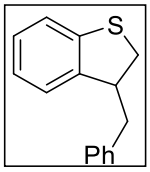
(**2.2E**)

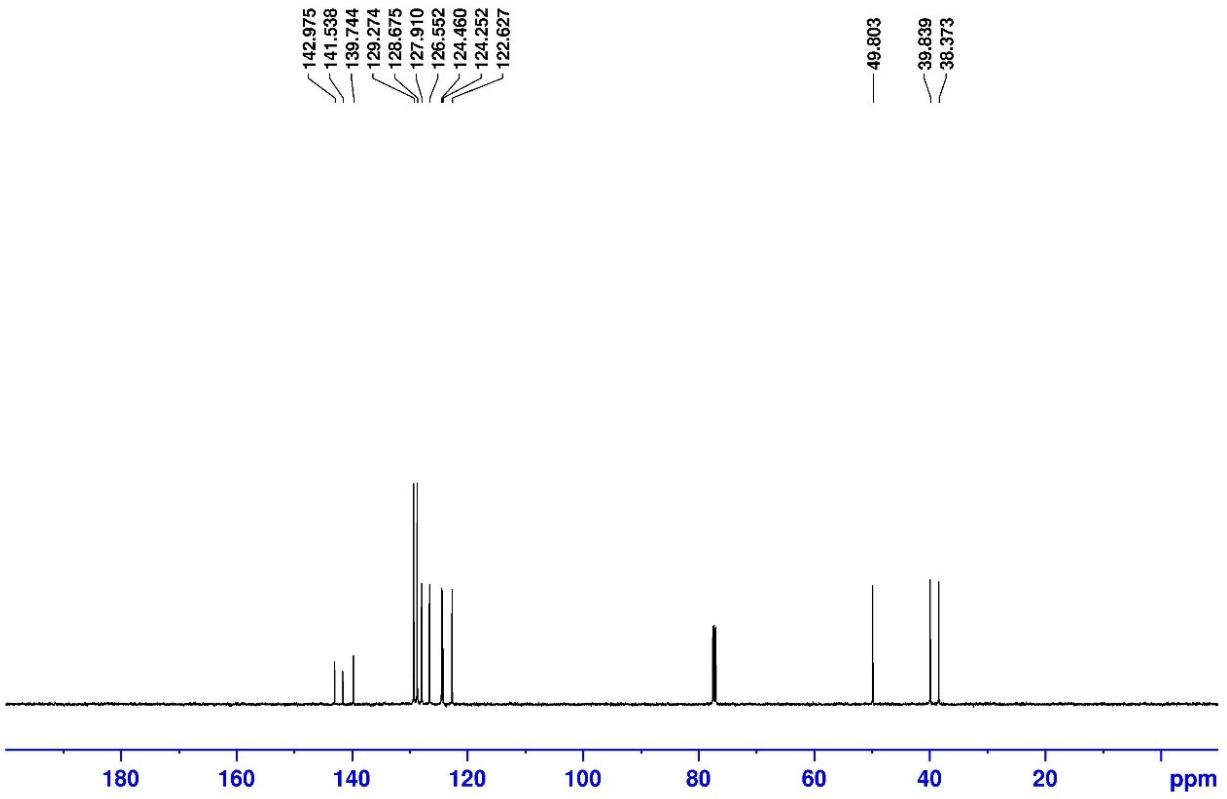
^{1}H NMR


S
Ph


7.427
7.412
7.397
7.352
7.337
7.329
7.322
7.313
7.303
7.298
7.289
7.246
7.244
7.230
7.217
7.215
7.150
7.136
7.117
7.117
7.102
7.087
3.818
3.806
3.792
3.787
3.772
3.761
3.446
3.431
3.424
3.409
3.215
3.204
3.187
3.176
3.165
3.153
3.142
3.131
2.964
2.944
2.936
2.917
10
9
8
7
6
5
4
3
2
1
0
ppm
2.06
4.85
1.07
2.00
1.00
0.99
2.00
1.02

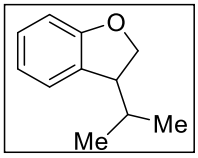
^{13}C NMR

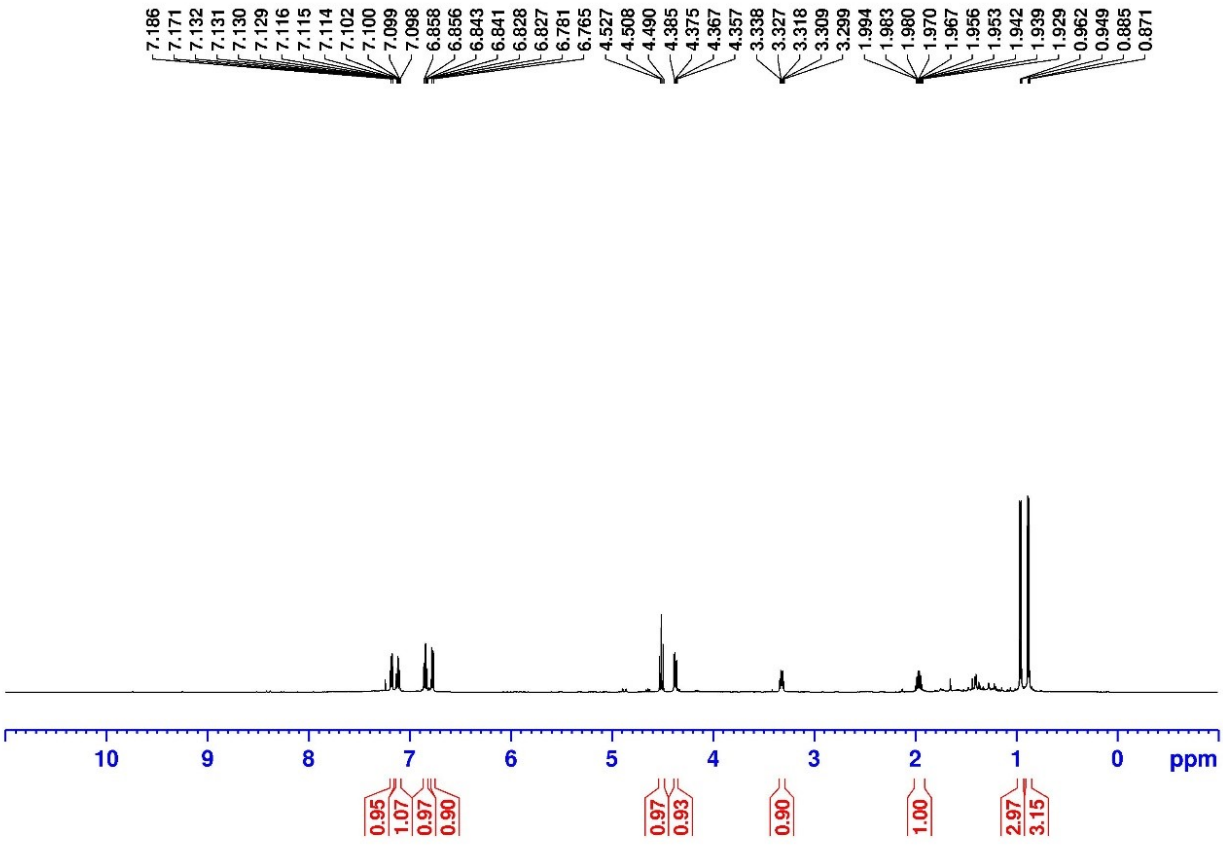

S
Ph


142.975
141.538
139.744
129.274
128.675
127.910
126.552
124.460
124.252
122.627
49.803
39.839
38.373
180
160
140
120
100
80
60
40
20
ppm

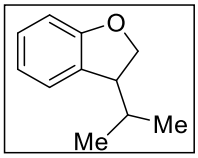
(**2.2F**)

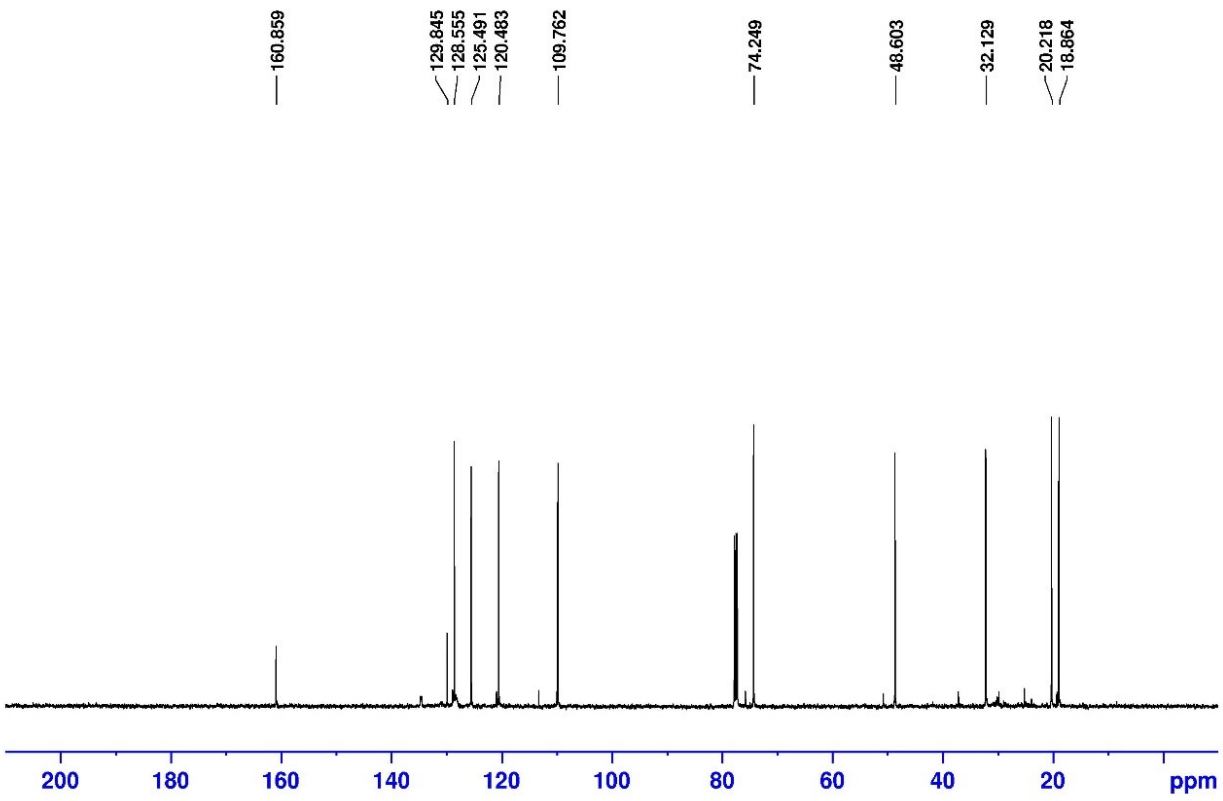
^{1}H NMR


O
Me
Me


7.186
7.171
7.132
7.131
7.130
7.129
7.116
7.115
7.114
7.102
7.100
7.099
7.098
6.858
6.856
6.843
6.841
6.828
6.827
6.781
6.765
4.527
4.508
4.490
4.385
4.375
4.367
4.357
3.338
3.327
3.318
3.309
3.299
1.994
1.983
1.980
1.970
1.967
1.956
1.953
1.942
1.939
1.929
0.962
0.949
0.885
0.871
10
9
8
7
6
5
4
3
2
1
0
ppm
0.95
1.07
0.97
0.90
0.97
0.93
0.90
1.00
2.97
3.15

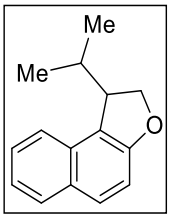
^{13}C NMR

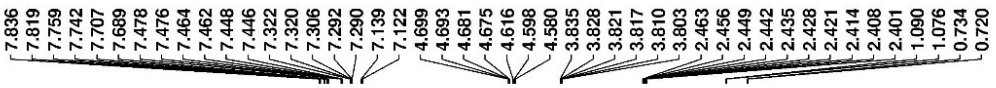

O
Me
Me

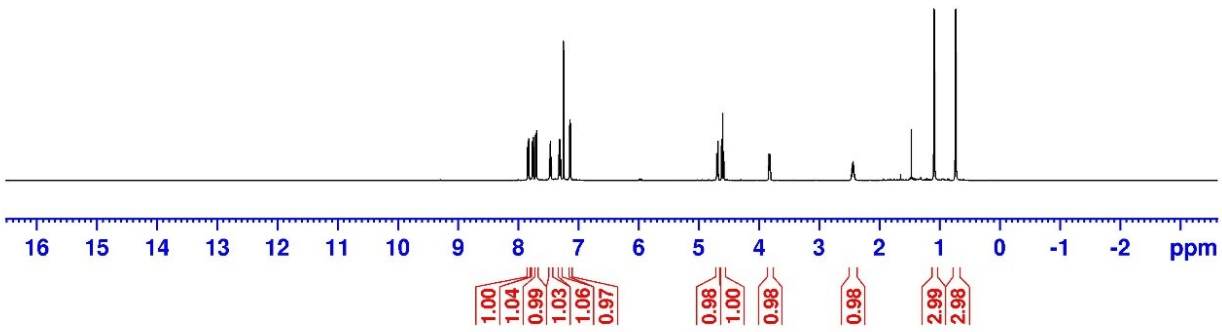

160.859
129.845
128.555
125.491
120.483
109.762
74.249
48.603
32.129
20.218
18.864
200
180
160
140
120
100
80
60
40
20
ppm

(**2.2G**)

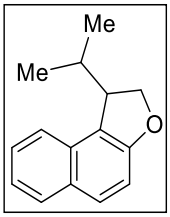
^{1}H NMR

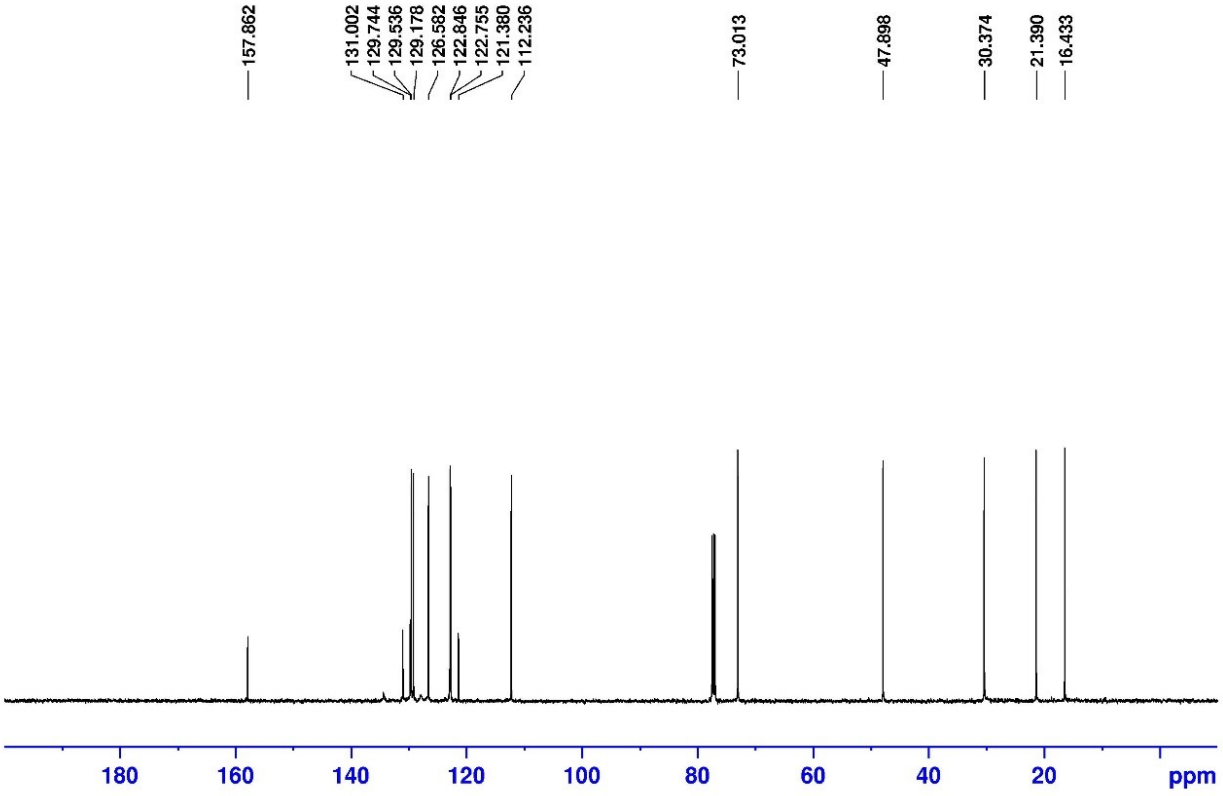

Me
Me
O


7.836
7.819
7.759
7.742
7.707
7.689
7.478
7.476
7.464
7.462
7.448
7.446
7.322
7.320
7.306
7.292
7.290
7.139
7.122
4.699
4.693
4.681
4.675
4.616
4.598
4.580
3.835
3.828
3.821
3.817
3.810
3.803
2.463
2.456
2.449
2.442
2.435
2.428
2.421
2.414
2.408
2.401
1.090
1.076
0.734
0.720


16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm
1.00
1.04
0.99
1.03
1.06
0.97
0.98
1.00
0.98
0.98
2.99
2.98

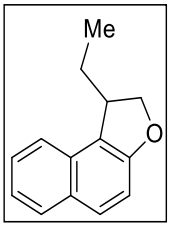
^{13}C NMR

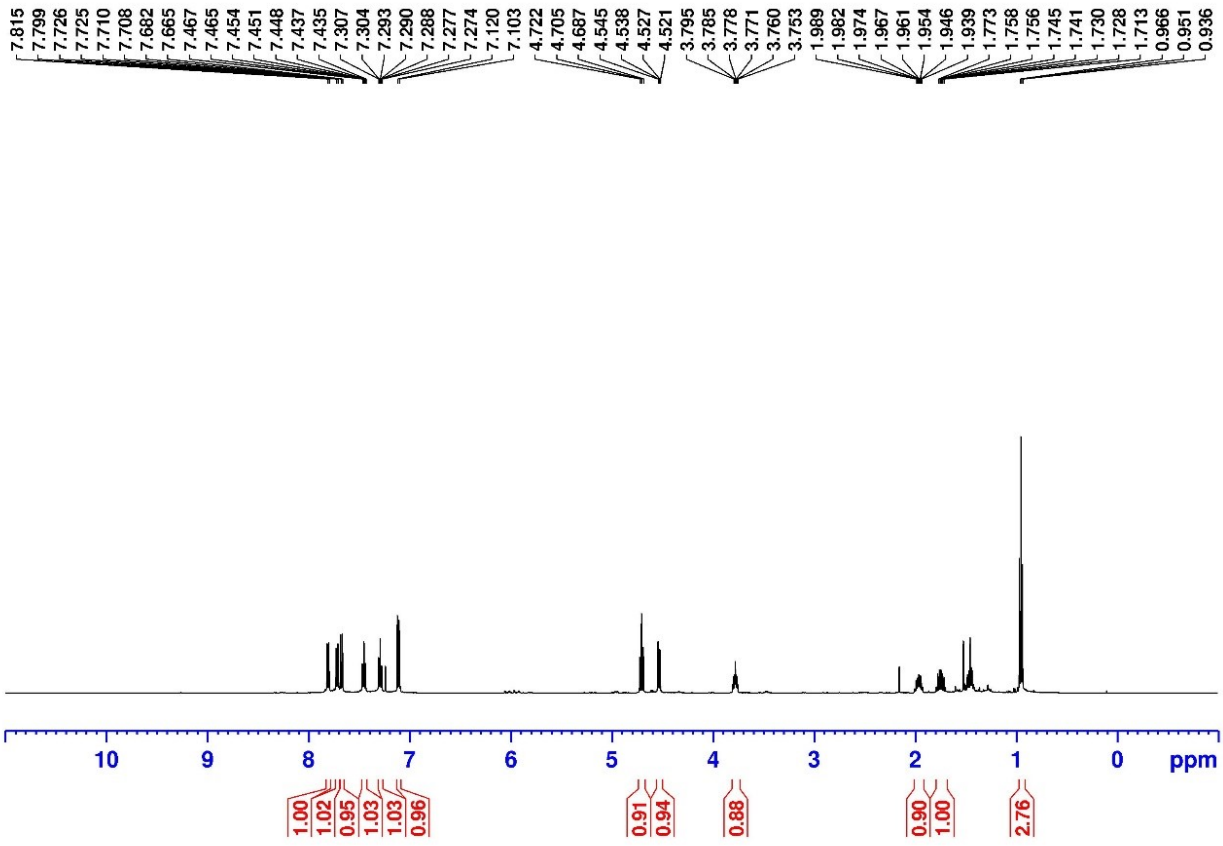

Me
Me
O


157.862
131.002
129.744
129.536
129.178
126.582
122.846
122.755
121.380
112.236
73.013
47.898
30.374
21.390
16.433
180
160
140
120
100
80
60
40
20
ppm

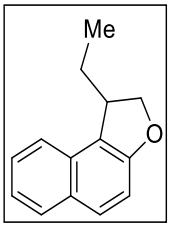
(**2.2H**)

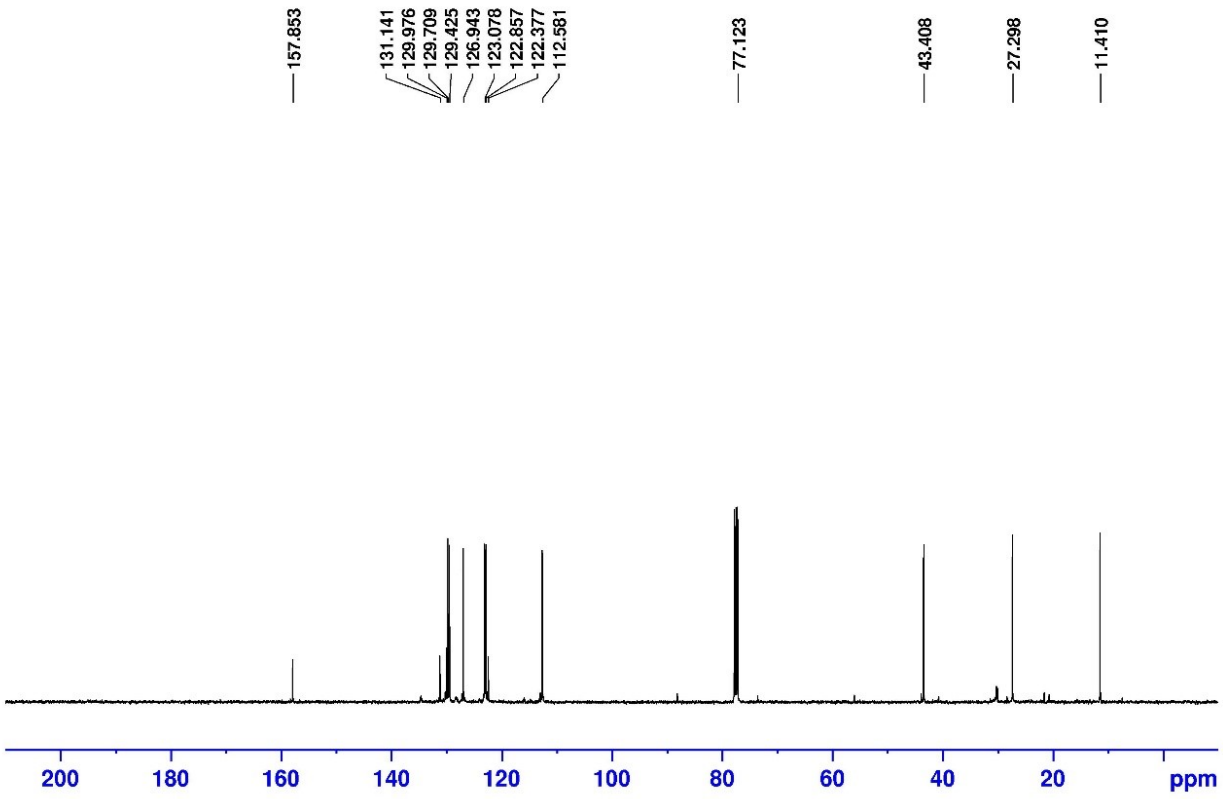
^{1}H NMR


Me
O


7.815
7.799
7.726
7.725
7.710
7.708
7.682
7.665
7.467
7.465
7.454
7.451
7.448
7.437
7.435
7.307
7.304
7.293
7.290
7.288
7.277
7.274
7.120
7.103
4.722
4.705
4.687
4.545
4.538
4.527
4.521
3.795
3.785
3.778
3.771
3.760
3.753
1.989
1.982
1.974
1.967
1.961
1.954
1.946
1.939
1.773
1.758
1.756
1.745
1.741
1.730
1.728
1.713
0.966
0.951
0.936
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.02
0.95
1.03
1.03
0.96
0.91
0.94
0.88
0.90
1.00
2.76

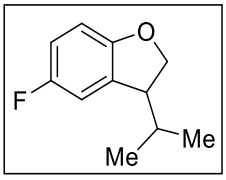
^{13}C NMR

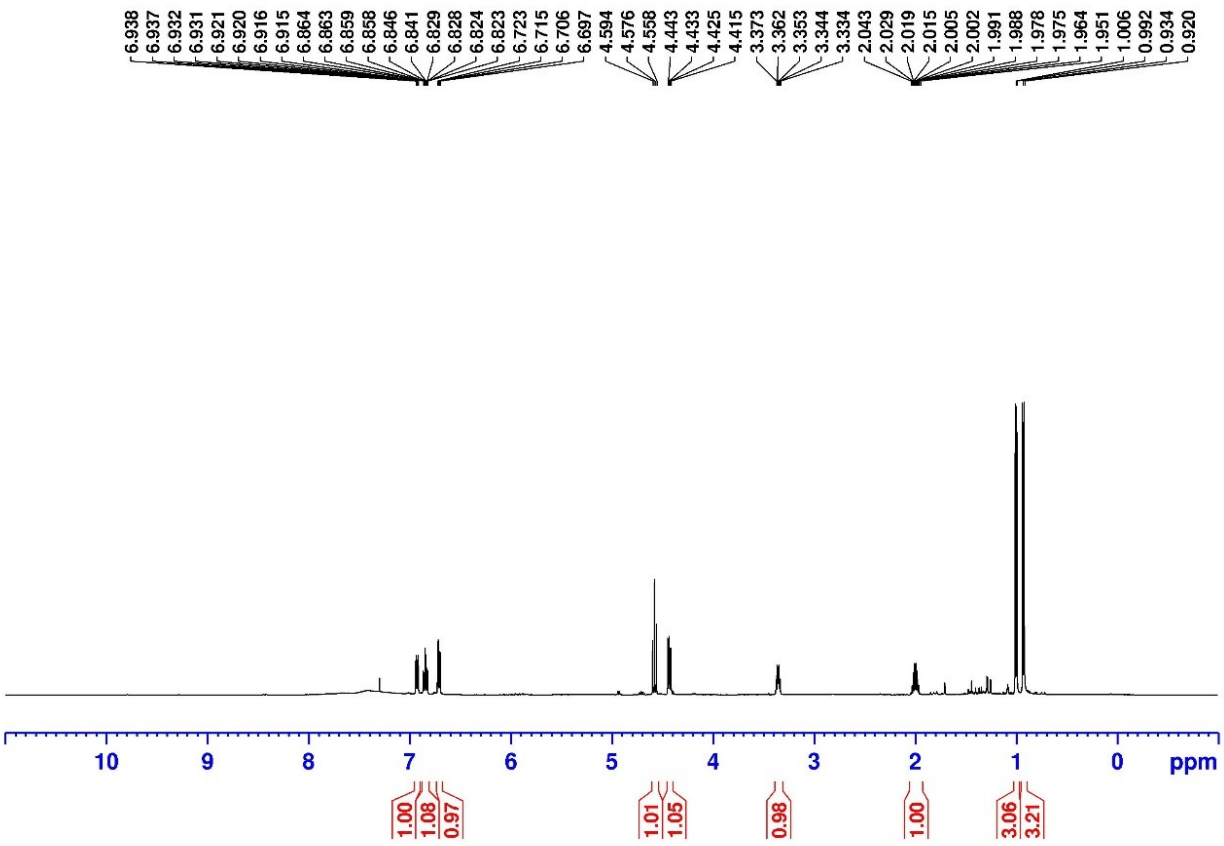

Me
O


157.853
131.141
129.976
129.709
129.425
126.943
123.078
122.857
122.377
112.581
77.123
43.408
27.298
11.410
200
180
160
140
120
100
80
60
40
20
ppm

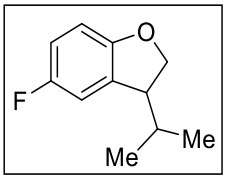
(**2.2M**)

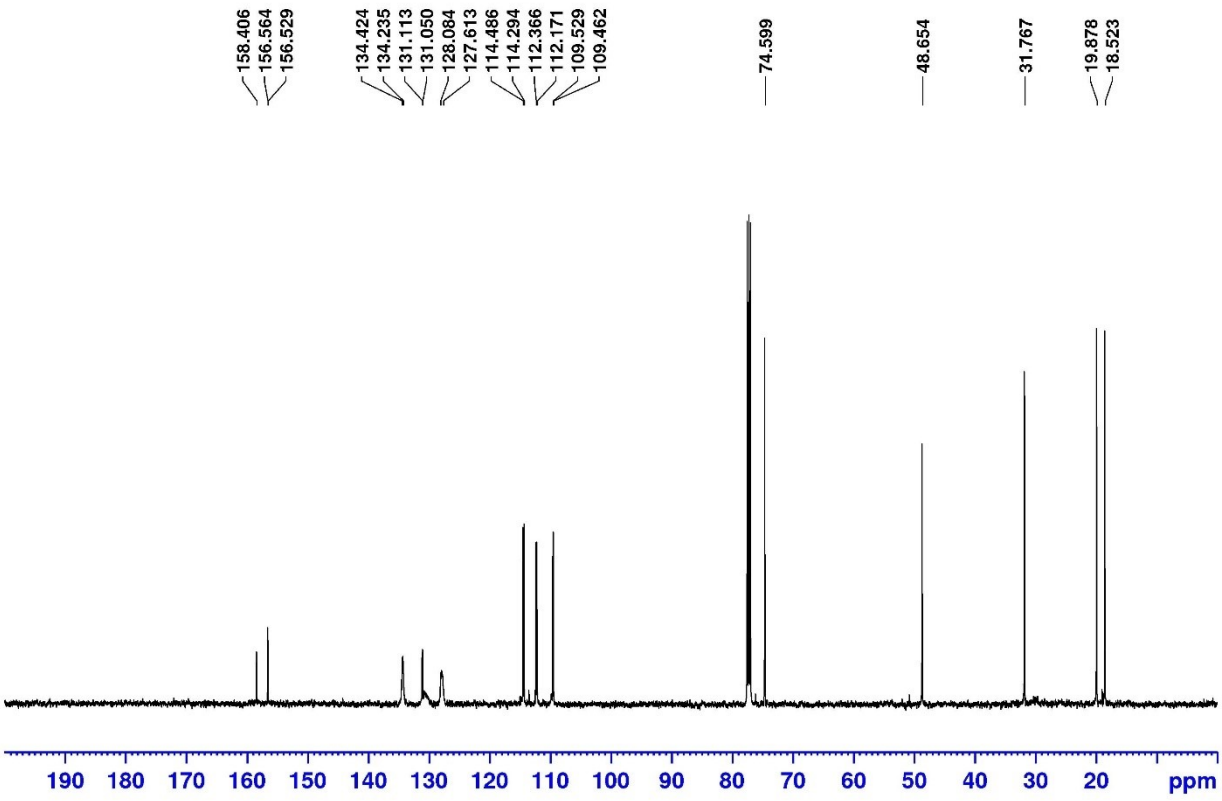
^{1}H NMR


O
F
Me
Me


6.938
6.937
6.932
6.931
6.921
6.920
6.916
6.915
6.864
6.863
6.859
6.858
6.846
6.841
6.829
6.828
6.824
6.823
6.723
6.715
6.706
6.697
4.594
4.576
4.558
4.443
4.433
4.425
4.415
3.373
3.362
3.353
3.344
3.334
2.043
2.029
2.019
2.015
2.005
2.002
1.991
1.988
1.978
1.975
1.964
1.951
1.006
0.992
0.934
0.920
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.08
0.97
1.01
1.05
0.98
1.00
3.06
3.21

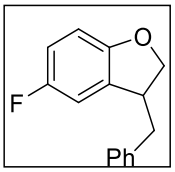
^{13}C NMR

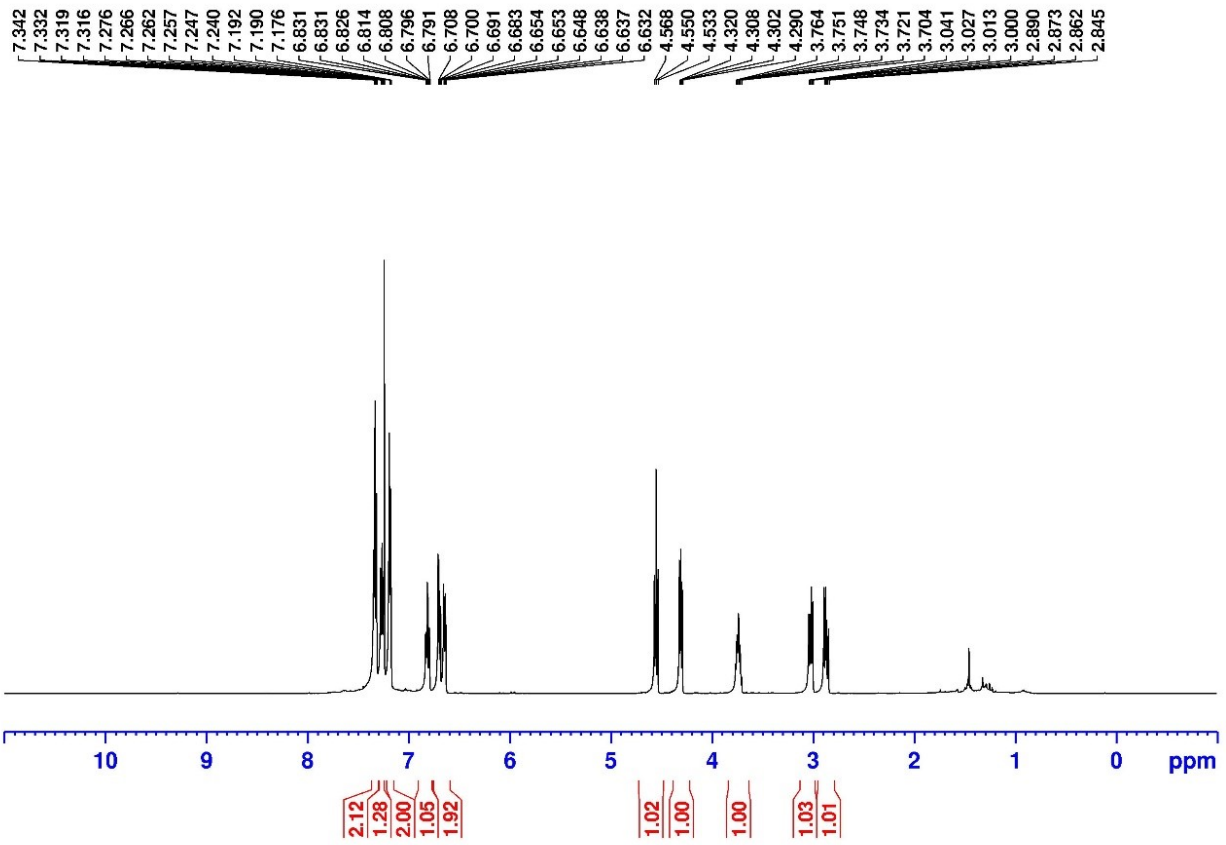

O
F
Me
Me


158.406
156.564
156.529
134.424
134.235
131.113
131.050
128.084
127.613
114.486
114.294
112.366
112.171
109.529
109.462
74.599
48.654
31.767
19.878
18.523
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

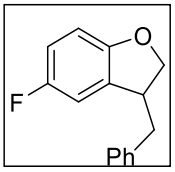
(**2.2N**)

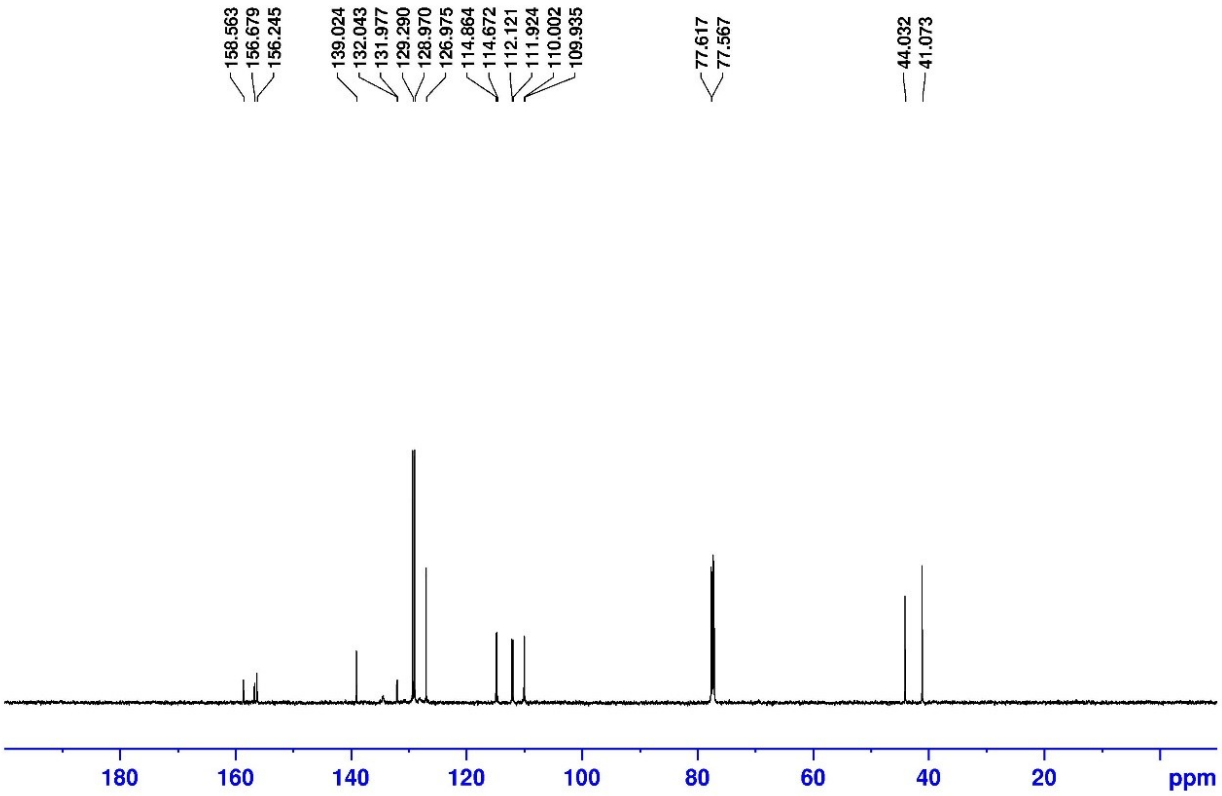
^{1}H NMR


O
F
Ph

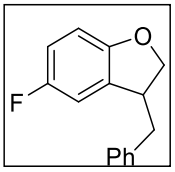

7.342
7.332
7.319
7.316
7.276
7.266
7.262
7.257
7.247
7.240
7.192
7.190
7.176
6.831
6.826
6.814
6.808
6.796
6.791
6.708
6.700
6.691
6.683
6.654
6.653
6.648
6.638
6.637
6.632
4.568
4.550
4.533
4.320
4.308
4.302
4.290
3.764
3.751
3.748
3.734
3.721
3.704
3.041
3.027
3.013
3.000
2.890
2.873
2.862
2.845
10
9
8
7
6
5
4
3
2
1
0
ppm
2.12
1.28
2.00
1.05
1.92
1.02
1.00
1.00
1.03
1.01

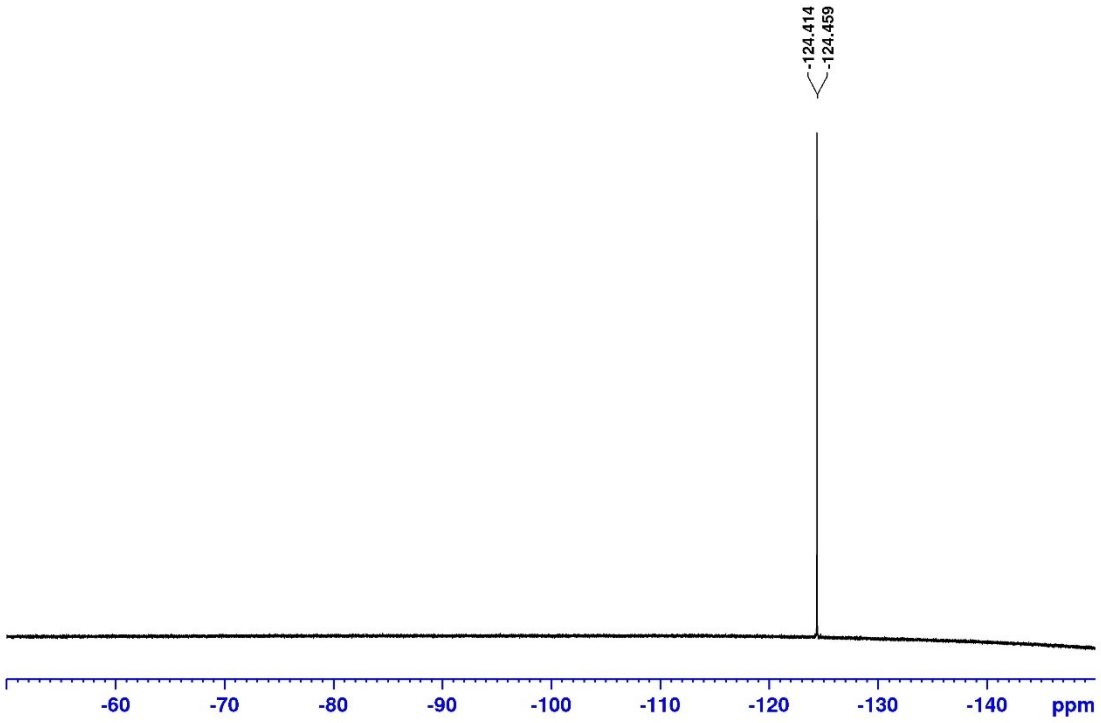
^{13}C NMR


O
F
Ph


158.563
156.679
156.245
139.024
132.043
131.977
129.290
128.970
126.975
114.864
114.672
112.121
111.924
110.002
109.935
77.617
77.567
44.032
41.073
180
160
140
120
100
80
60
40
20
ppm

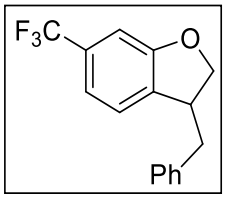
^{19}F NMR

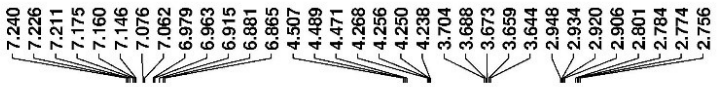


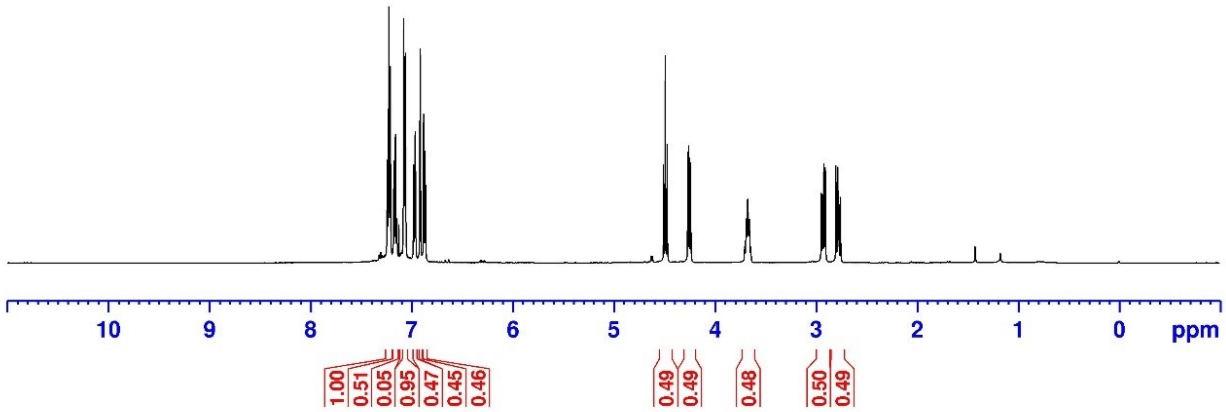


(**2.2P**)

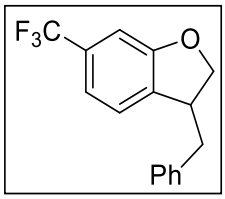
^{1}H NMR

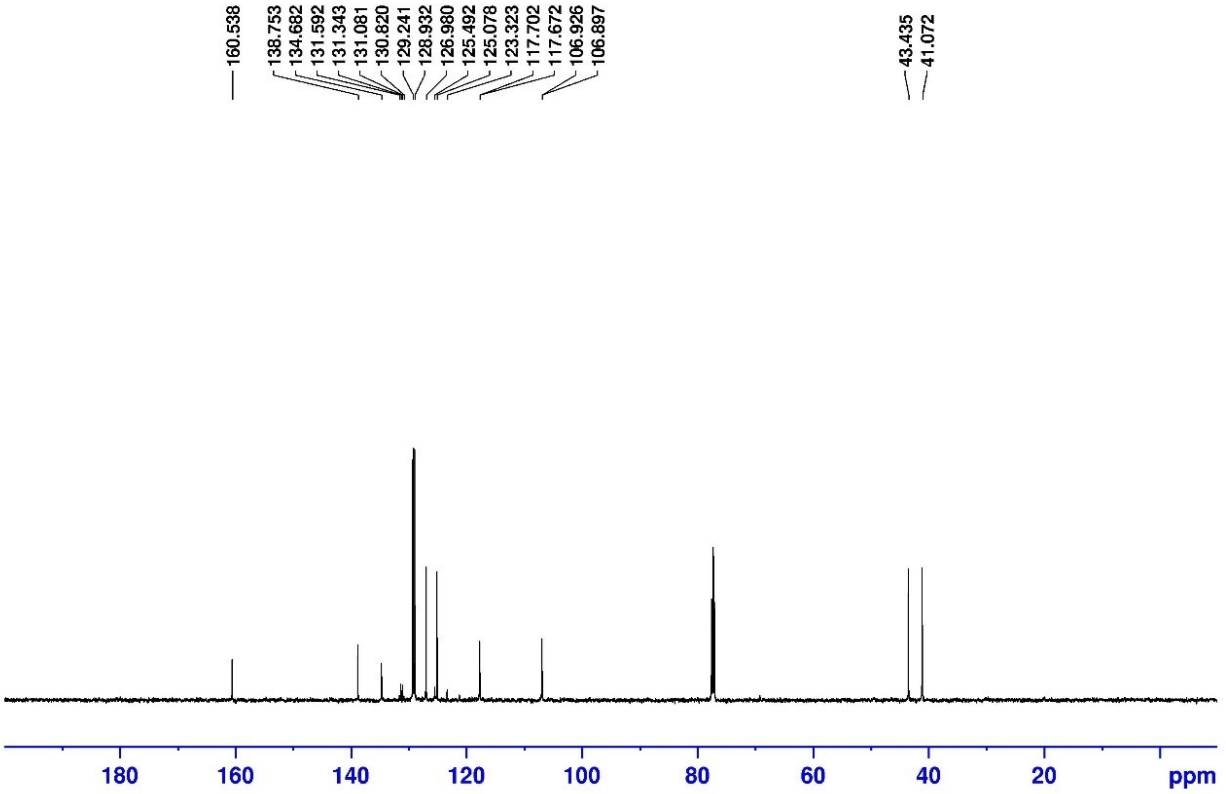

F3C
O
Ph


7.240
7.226
7.211
7.175
7.160
7.146
7.076
7.062
6.979
6.963
6.915
6.881
6.865
4.507
4.489
4.471
4.268
4.256
4.250
4.238
3.704
3.688
3.673
3.659
3.644
2.948
2.934
2.920
2.906
2.801
2.784
2.774
2.756

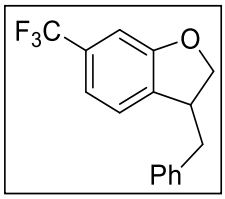

10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.51
0.05
0.95
0.47
0.45
0.46
0.49
0.49
0.48
0.50
0.49

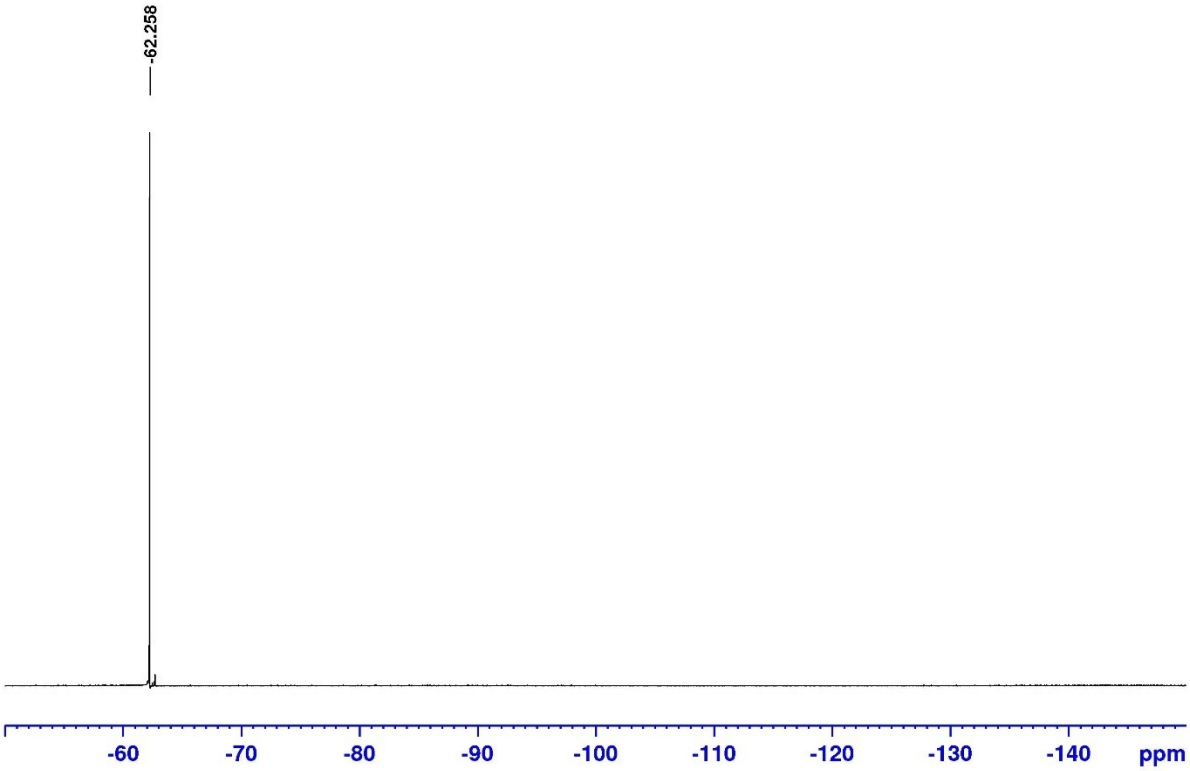
^{13}C NMR


F3C
O
Ph


160.538
138.753
134.682
131.592
131.343
131.081
130.820
129.241
128.932
126.980
125.492
125.078
123.323
117.702
117.672
106.926
106.897
43.435
41.072
180
160
140
120
100
80
60
40
20
ppm

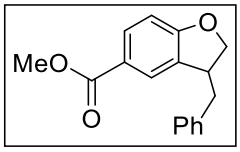
^{19}F NMR

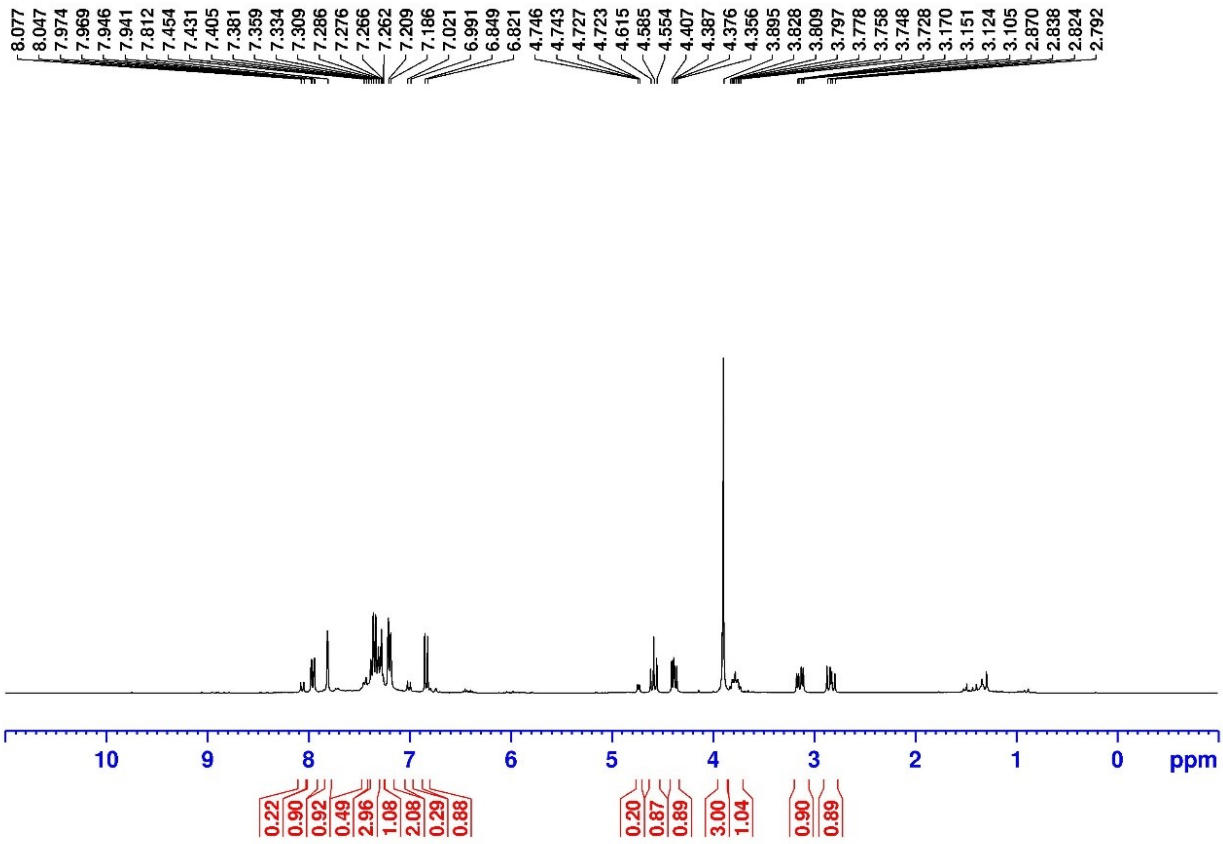




(**2.2Q**)

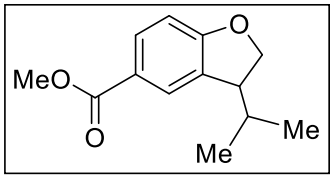
^{1}H NMR

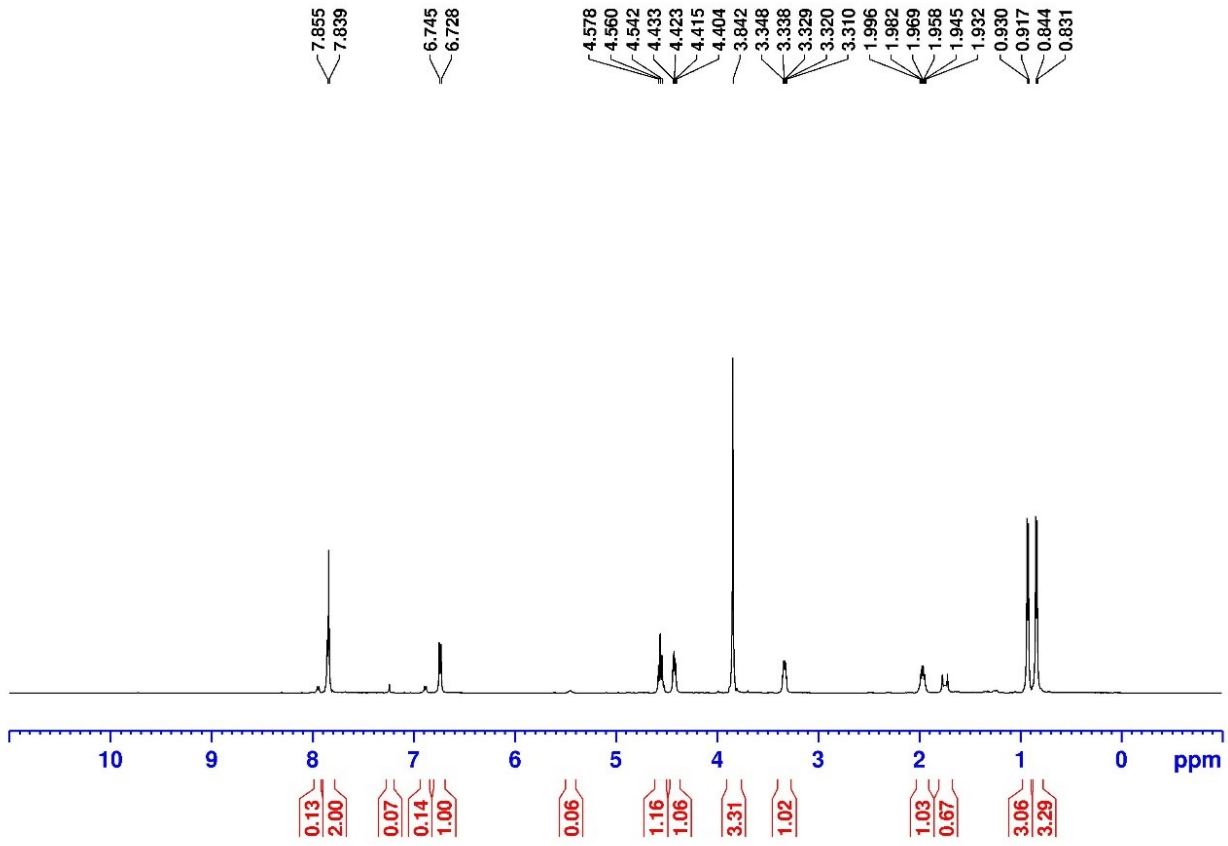

MeO
O
O
Ph


8.077
8.047
7.974
7.969
7.946
7.941
7.812
7.454
7.431
7.405
7.381
7.359
7.334
7.309
7.286
7.276
7.266
7.262
7.209
7.186
7.021
6.991
6.849
6.821
4.746
4.743
4.727
4.723
4.615
4.585
4.554
4.407
4.387
4.376
4.356
3.895
3.828
3.809
3.797
3.778
3.758
3.748
3.728
3.170
3.151
3.124
3.105
2.870
2.838
2.824
2.792
10
9
8
7
6
5
4
3
2
1
0
ppm
0.22
0.90
0.92
0.49
2.96
1.08
2.08
0.29
0.88
0.20
0.87
0.89
3.00
1.04
0.90
0.89

(**2.2R**)

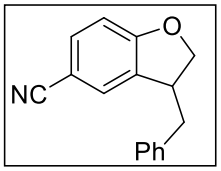
^{1}H NMR

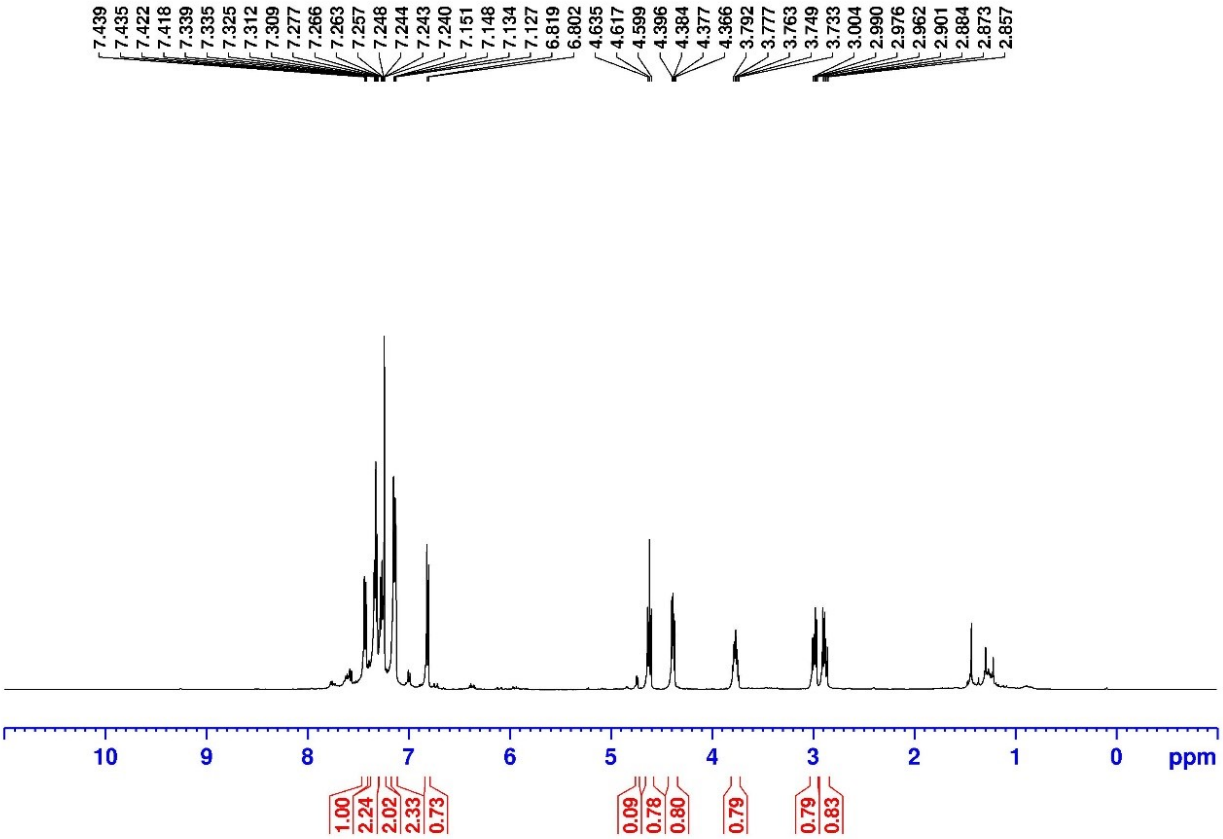

MeO
O
O
Me
Me


7.855
7.839
6.745
6.728
4.578
4.560
4.542
4.433
4.423
4.415
4.404
3.842
3.348
3.338
3.329
3.320
3.310
1.996
1.982
1.969
1.958
1.945
1.932
0.930
0.917
0.844
0.831
10
9
8
7
6
5
4
3
2
1
0
ppm
0.13
2.00
0.07
0.14
1.00
0.06
1.16
1.06
3.31
1.02
1.03
0.67
3.06
3.29

(**2.2S**)

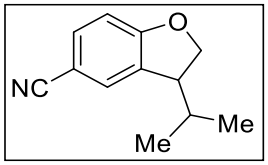
^{1}H NMR

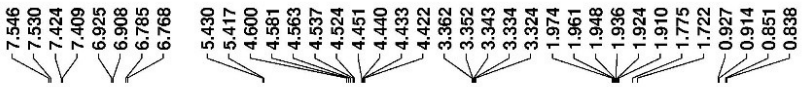

O
NC
Ph

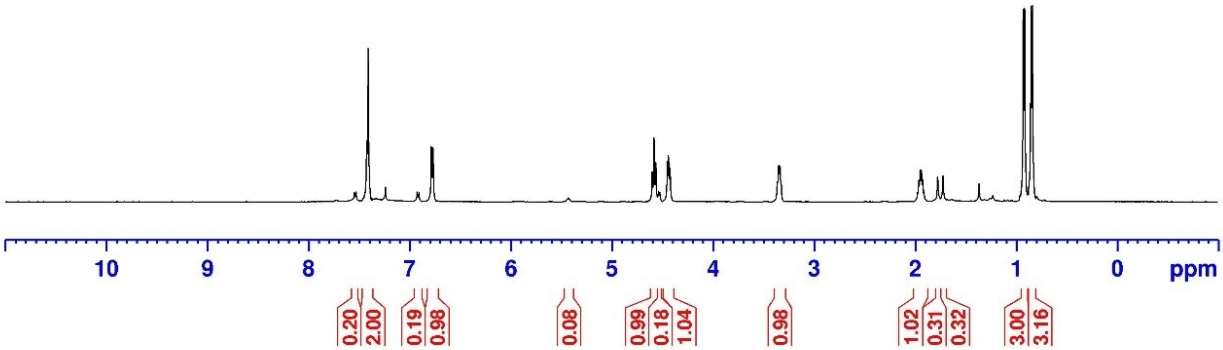

7.439
7.435
7.422
7.418
7.339
7.335
7.325
7.312
7.309
7.277
7.266
7.263
7.257
7.248
7.244
7.243
7.240
7.151
7.148
7.134
7.127
6.819
6.802
4.635
4.617
4.599
4.396
4.384
4.377
4.366
3.792
3.777
3.763
3.749
3.733
3.004
2.990
2.976
2.962
2.901
2.884
2.873
2.857
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.24
2.02
2.33
0.73
0.09
0.78
0.80
0.79
0.79
0.83

(**2.2T**)

^{1}H NMR


O
NC
Me
Me


7.546
7.530
7.424
7.409
6.925
6.908
6.785
6.768
5.430
5.417
4.600
4.581
4.563
4.537
4.524
4.451
4.440
4.433
4.422
3.362
3.352
3.343
3.334
3.324
1.974
1.961
1.948
1.936
1.924
1.910
1.775
1.722
0.927
0.914
0.851
0.838


10
9
8
7
6
5
4
3
2
1
0
ppm
0.20
2.00
0.19
0.98
0.08
0.99
0.18
1.04
0.98
1.02
0.31
0.32
3.00
3.16

Appendix B: NMR Spectra for Chapter 3

(**3.3**)

^{1}H NMR