Development of Novel Methodologies in Aryne Chemistry and their Application in the Total Synthesis of Bioactive Natural Products

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

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Under the guidance of
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May 2018

Dedicated

To

My Family

And

Teachers

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Development of Novel Methodologies in Aryne Chemistry and their Application in the Total Synthesis of Bioactive Natural Products"** submitted by **Mr. Ranjeet A. Dhokale** to Academy of Scientific and Innovative Research (**AcSIR**) in fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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DECLARATION BY THE CANDIDATE

I hereby declare that the original research work embodied in this thesis entitled, **"Development of Novel Methodologies in Aryne Chemistry and their Application in the Total Synthesis of Bioactive Natural Products''** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Santosh B. Mhaske**, Senior Scientist, Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

May 2018

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Ranjeet A. Dhokale

Contents

Abbreviations

Units

°C	Degree centigrade
mg	Milligram
hr	Hour
Hz	Hertz
µg	Microgram
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
ppm	Parts per million

Chemical Notations

Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
MeCN	Acetonitrile
n-BuLi	*n*-Butyl Lithium
DIBAL-H	Diisobutylaluminiumhydride
DMF	*N*, *N'*-Dimethylformamide
DMAP	*N*,*N'*-Dimethylaminopyridine
DIPEA	*N*, *N*-Diisopropylethylamine
Et_2O	Diethyl Ether
DCE	1,2-Dichloroethane
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl Acetate
HMDS	Bis(trimethylsilyl)amine
LiHMDS	Lithium Hexamethyl Disilazide
LAH	Lithium Aluminum Hydride
m-CPBA	*m*-Chloroperbenzoic Acid

MCR	Multicomponent Reaction
MeOH	Methanol
Me	Methyl
MeI	Methyl Iodide
Ph	Phenyl
PhMgCl	Phenyl Magnesium Chloride
PMB	*para*-Methoxy Benzyl
p-TSA	*para*-Toluenesulfonic Acid
NaH	Sodium Hydride
THF	Tetrahydrofuran
TBAI	Tetra-*n*-Butylammonium Iodide
TBAF	Tetra-*n*-Butylammonium Fluoride
TBDMS	*tert*-Butyldimethyl Silyl
TBSCl	*tert*-Butyldimethyl Silyl Chloride
TMS	Trimethylsilyl

Other Notations

calcd	Calculated
δ	Chemical shift
J	Coupling constant in NMR
equiv.	Equivalents
ESI	Electrospray ionization Mass spectrometry
HRMS	High Resolution Mass Spectrometry
IR	Infra-Red
m/*z*	Mass-to-charge ratio
MS	Molecular sieves
mp	Melting Point
NMR	Nuclear Magnetic Resonance
rt	Room temperature

General Remarks

- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz or 500 MHz spectrometers. Coupling constants were measured in Hertz. All chemical shifts are quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [(ESI^{+}, +/– 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as *m/z*. GC-HRMS (EI) was recorded in Agilent 7200 Accurate-mass-Q-TOF.
- Infrared spectra were scanned on Bruker ALPHA spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus and are uncorrected and the temperatures are in centigrade scale.
- All reactions are monitored by Thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried accordingly to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 15.1.

- Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

Synopsis of the Thesis to be Submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry

Name of the Candidate	Mr. Ranjeet Ashokrao Dhokale
Degree Enrolment no. and Date	Ph. D. in Chemical Sciences (10CC12A26021); August 2012
Title of the Thesis	Development of Novel Methodologies in Aryne Chemistry and their Application in the Total Synthesis of Bioactive Natural Products
Research Supervisor	Dr. Santosh B. Mhaske (AcSIR, CSIR-NCL, Pune)

Abstract:

The present thesis demonstrates a creative exploration of aryne as versatile building blocks to construct new C–C and C–heteroatom bonds for the synthesis of various scaffolds and complex natural products. Chapter 1 describes a brief history of aryne, different methods available for their generation and various types of aryne reactions. Representative examples of insertion, pericyclic, annulation and multicomponent reactions of aryne are described in detail. Chapter 2 deals with our studies on C–C, C–P and C–N bond forming reactions of aryne, which is divided into three sections. Section 1 covers the transition-metal-free *C*–arylation of malonamide esters. We have achieved a selective mono- or di-arylation and quaternary centre generation using arynes. Section 2 demonstrates a novel process for C–P bond construction to afford aryl phosphonates, -phosphinates and phosphine oxides for the first time using transition-metal-free protocol. Section 3 describes an unusual nucleophilic nitration protocol using aryne chemistry, and the concept has been further extended for the synthesis of ortho-difuntionalized nitro-aromatics via a multi-component reaction. Chapter 3 describes our studies on the total synthesis of bioactive natural products using aryne in two sections. Section 1 deals with the synthesis of the spiroannulated benzofuran-3-one scaffold of Leptosphaerins C and congeners via insertion reaction of aryne, whereas section 2 covers the study towards the total synthesis of Lycorane family of natural products via cycloaddition reaction of aryne.

Chapter 1. Aryne: A Versatile Building Block in Synthetic Organic Chemistry

Chapter 1 is divided into two sections. Section 1 describes a brief history of aryne and various novel methods for their generation (Figure 1). The first indication of aryne intermediate was reported by Wittig et al., and later the formation of aryne was confirmed by Robert and co-workers based on their classical aryne trapping experiment. Though there are several methods reported till date for the aryne generation, the Kobayashi's protocol remained the most extensively used method due to the easy accessibility of the aryne precursors and mild reaction conditions. Section 2 deals with the transition-metal-free reactions of aryne (Figure 2). Aryne undergoes various transformations such as insertion, pericyclic, annulation and multicomponent reactions. The insertion reaction of aryne, mostly element–element (X–Y) σ-bonds and π-

bonds is a vital operation, which introduces both elements on C–C triple bond furnishing di or polysubstituted arenes. Annulation of aryne with aromatic or aliphatic compounds bearing nucleophilic

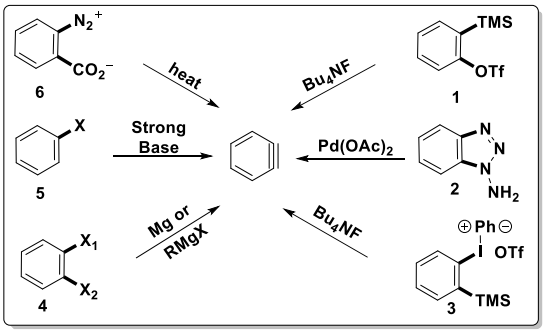


Figure 1. Selected methods of aryne generation

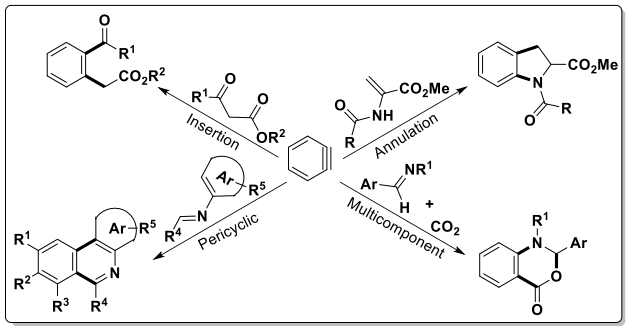
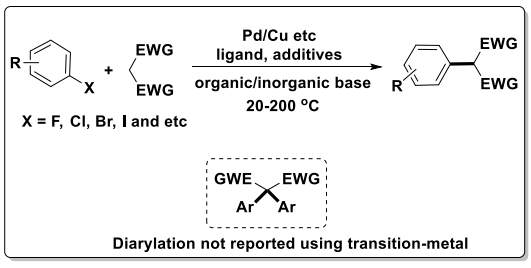


Figure 2. Various types of transition-metal-free reactions of aryne

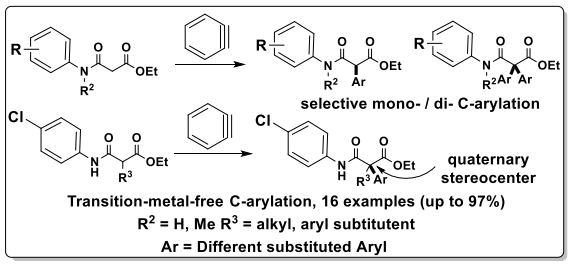
group provides varyingly substituted heterocycles. Further, arynes have been extensively used in Diels–Alder reaction due to high electrophilicity, which makes them superior dienophiles. The reactions involving an aryne, a nucleophile, and an electrophile, referred as multicomponent reaction provides diverse 1,2 bi-functional arenes. The above mentioned intriguing reactions prompted us to develop novel synthetic strategies in aryne chemistry.

Chapter 2. Novel Transition-Metal-Free Approaches for the Construction of C–C, C–N, and C–P Bonds using Aryne Chemistry

Chapter 2 is divided into three sections. Section 1 involves highly selective transition-metal-free *C*–arylation of malonamide esters at room temperature by arynes. Such α-arylation of active methylenes requires transition-metals, expensive ligands, high temperature and pressure (Scheme 1). In this context we have developed a transition-metal-free α-arylation of β-dicarbonyl compounds at room temperature by employing aryne (Scheme 2).[1] The reaction exhibits exclusive switchable mono- or di-arylation selectivity and chemoselective *C*-arylation over the *N*-arylation. The reported protocol is the unique strategy as it involves diarylation of the active methylene, which is not reported in the presence of transition-metals.



Scheme 1. Metal-catalyzed arylations



Scheme 2. Selective mono- and diarylation of malonamide esters

Further, the methodology was successfully applied for synthesizing the compounds containing benzylic quaternary stereocenters. The arylated malonamide ester compounds can serve as important precursors for

the synthesis of phenobarbital class of CNS depressant barbiturate drugs. Section 2 covers synthesis of vital aryl-phosphorus compounds via novel transition-metal-free C–P bond forming protocol using aryne chemistry.[2] Until now such aryl-phosphorous compounds are accessible by Hirao process, which requires transition-metals and harsh conditions (Figure 3). The synthesis of aryl- phosphorus compounds and their application in organic synthesis and life sciences has been a topic of contemporary interest. In this context, we have reported the first transition metal-free synthesis of aryl phosphonates, phosphinates, phosphine oxides (Scheme 3). The various alkyl phosphites, alkyl phenylphosphinite, and alkyl diphenylphosphane were

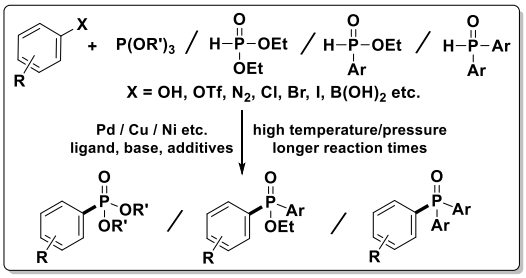
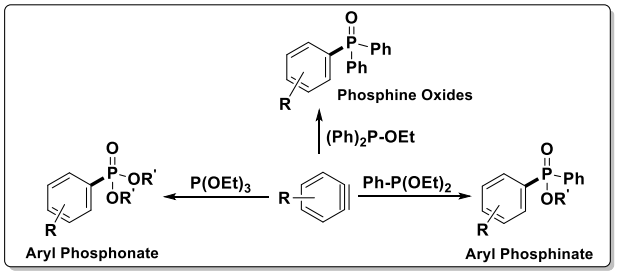


Figure 3. Metal-catalyzed phosphorylations



Scheme 3. Phosphorylation of arynes

reacted with varyingly substituted aryne precursors, which afforded respective aryl phosphonates, phosphinates, phosphine oxides in good to excellent yields. This process can provide varyingly substituted novel phosphorous ligands. This naive process has been highlighted in the organic portal and also cited in the "Name Reaction" book by Professor Jie Jack Li. Section 3 describes an unusual nucleophilic nitration

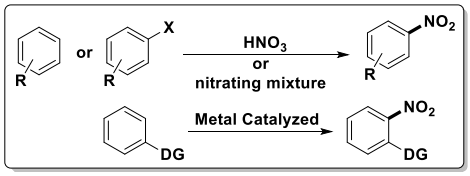
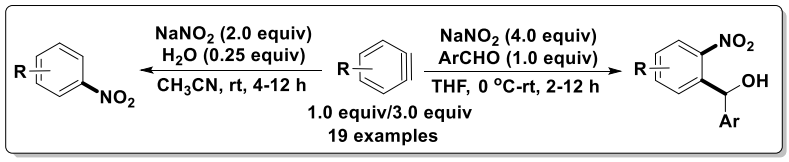


Figure 4. Reported nitration methods



Scheme 4. Nitration of varyingly substituted aryne

of arynes by $NaNO_2$ and its further application in a multicomponent reaction leading to double-functionalized nitroarenes.[3] This is first nucleophilic nitration process for the synthesis of nitroaromatic compounds. Generally, synthesis of nitroaromatic compounds involves strongly acidic conditions, transition metals, preactivated aromatic rings, expensive catalysts, etc. (Figure 4). We have developed the mild protocol in which $NaNO_2$ (2.0 equiv) was reacted with aryne precursor (1.0 equiv) in the presence of H_2O (0.25 equiv) in acetonitrile at room temperature.[3] The nitration protocol is general, regioselective and compatible with various aryne precursors. The developed nitration protocol was also extended to a multicomponent reaction by intercepting the carbanion with benzaldehydes providing ortho difunctionalized nitro-carbinols. Ortho functionalization of nitro aromatics is difficult, but we have

successfully achieved it and applied in the synthesis of pharmaceutically important carbinol derivatives by a one-pot process (Scheme 4). This was the most read article in July 2016.[3]

Chapter 3. Proficient Utilization of Aryne in the Total Synthesis of Bioactive Natural Products

Chapter 3 is divided into two sections. In Section 1, we have described the insertion reaction of aryne with variety of TIPS protected cyclohexadienone for a novel one-step approach affording a diverse range of spiroannulated benzofuran-3-one scaffold of *Leptosphaerins C*.[4] The spiro-bicyclic scaffold, in particular

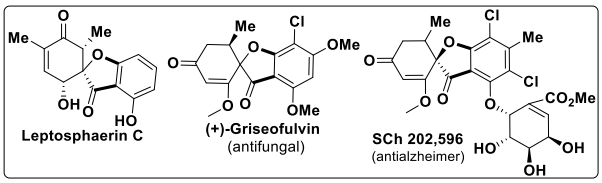
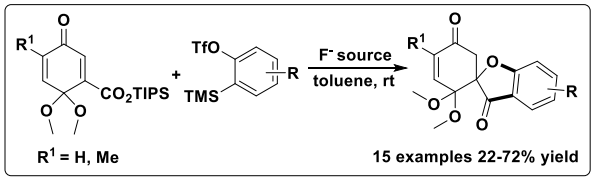


Figure 5. Spiro-benzofuran-3-one natural products



Scheme 5. Synthesis of spirobenzofuran-3-ones

the cycloalkane-fused benzofuran-3-ones are basic structural framework found in various bioactive natural products and drugs (Figure 5). We have reported a concise synthesis of functionalized cyclohexenone-fused spirobenzofuran-3-ones under milder reaction condition (Scheme 5). The reaction proceeds via insertion of aryne into C–O bond followed by a regioselective intramolecular conjugate addition. This protocol has been applied for the synthesis of *Leptosphaerin C* core and its novel analogues. Section 2 describes our studies towards the synthesis of Lycorane family of natural products (Figure 6). The lycorane family of alkaloids is well-known for their potent bioactivities. We envisioned that the pyrrolo[de]phenanthridine skeleton **13** of Lycorane and its congeners could be rapidly assembled from compound **12** via aza Diels-Alder reaction between *in situ* generated diene and imine (Scheme 6). The

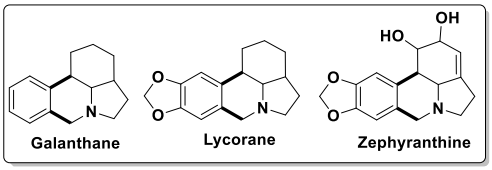
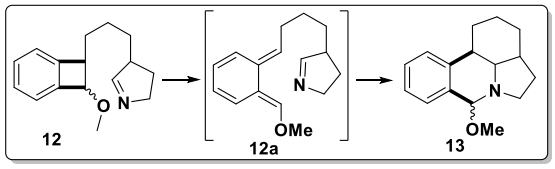
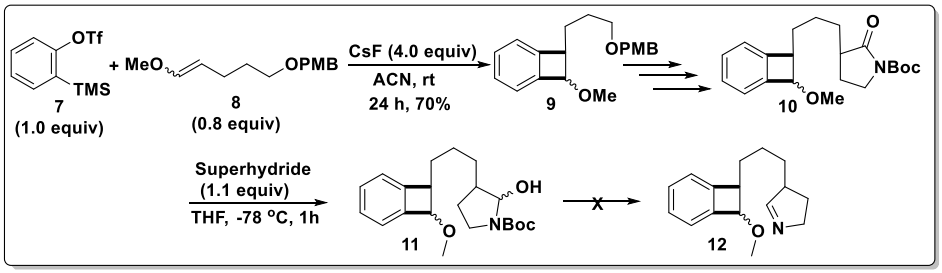


Figure 6. Lycorane family of natural products



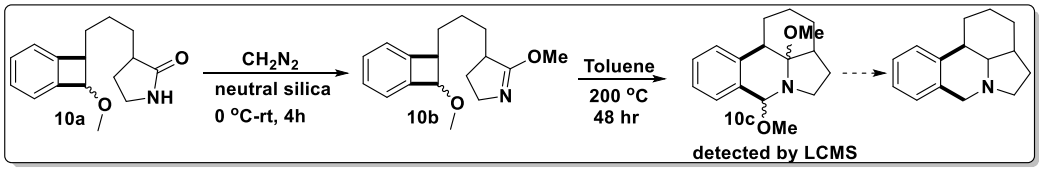
Scheme 6. Hypothesis for the key step

synthesis began with [2+2] cycloaddition of aryne precursor **7** with **8**. The [2+2] cycloadduct **9** was converted to **11** after several transformations. Unfortunately, our numerous attempts to convert the compound **11** to the key intermediate imine **12** met with failure (Scheme 7). Hence, we modified the



Scheme 7. Attempts towards the synthesis of the key intermediate

strategy and synthesized the compound **10b** from **10a**. Further, the solution of **10b** in toluene was heated in a sealed tube, which provided a trace amount of tetracyclic core **10c**. The synthesis of **10c** on a better scale and its transformation to Lycorane natural products is underway (Scheme 8).



Scheme 8. Synthesis of Lycorane natural products

In summary, we have successfully developed novel methods involving arynes and also applied in the synthesis of natural products and their congeners.

References:

1. Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *Org. Lett.* **2012**, *14*, 3994.
2. (a) Dhokale, R. A.; Mhaske, S. B. *Org. Lett.* **2013**, *15*, 2218. **(*Highlighted in Organic Portal)***
   (b) Li, J. J. *Name Reactions: A Collection of Detailed Reaction Mechanisms*; Springer-Verlag Berlin Heidelberg: Switzerland, 2014; pp 399-400.
3. Dhokale, R. A.; Mhaske, S. B. *Org. Lett.* **2016**, *18*, 3010. **(*Most read article in July 2016*)**
4. Dhokale, R. A.; Mhaske, S. B. *J. Org. Chem.* **2017**, *82*, 4875.

Chapter 1

Aryne: A Versatile Building Block in Synthetic Organic Chemistry

Introduction:

Aryne is a versatile building block in synthetic organic chemistry, which has attracted immense attention by the scientific community. A multiple carbon-carbon or carbon-heteroatom bond formation is achieved by using aryne in a single step, which provides a rapid functionalization of an aromatic ring. The chemistry for the formation of a strained triple bond of arynes from novel aryne precursors under milder conditions has undergone rapid growth in recent years. The high electrophilicity of *in situ* generated arynes has been very well explored in an inventive way for the synthesis of various biaryl motifs, fused polycyclic aromatic compounds, novel carbocycles, heterocycles, and complex natural products. The discovery of aryne species took place way back in 1902, but the aryne chemistry caught more attention of organic chemists in last few decades. The reason for this late consideration of aryne chemistry may be due to lack of facile aryne generation methods. However, Kobayashi's mild method for generation of highly reactive aryne intermediate changed the whole scenario. The Kobayashi's protocol proved very much successful and it rejuvenated the aryne chemistry. In this context various novel methods for the synthesis of aryne and their applications in diverse transition-metal-free transformations are discussed in this chapter. This chapter is divided into two sections.

Section 1: History and Generation of Arynes

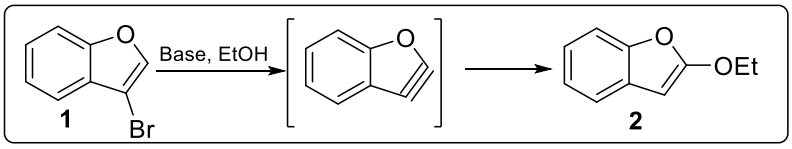
Section 2: Transition-Metal-Free Reactions of Arynes

Section 1: History and Generation of Arynes

For the last 100 years aryne have received continuing interest by the scientific community. Their use in the organic synthesis is now well-established. Investigations on novel methods for aryne generation and utility in carbon-carbon and carbon-heteroatom bond forming reactions continue to this day. Many reputed research groups have been involved in developing novel and efficient strategies for the synthesis of aryne and its application in various transformations. In the literature, the existence of aryne is reported in three different forms; ortho-benzyne, para-benzyne, and meta-benzyne. The meta and para isomers still remained unexplored in the literature. In this section, we have focused on the synthesis of ortho-benzyne by various groups. Here, in this section the existence and various methods of aryne generation have been discussed.

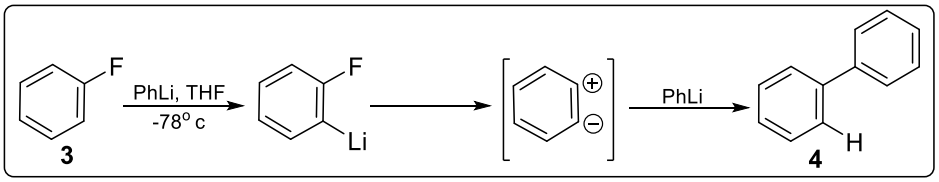
1.1.1 History of Arynes

Arynes find prime applications in organic synthesis due to the presence of a highly electrophilic strained triple bond.[1] They smoothly react with weak nucleophiles under milder reaction conditions.



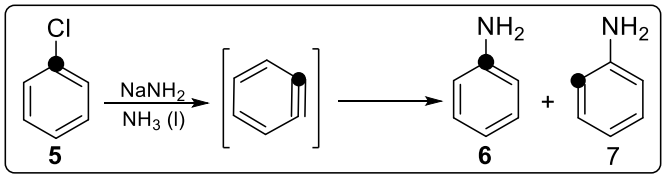
Scheme 1: Formation of 2-ethoxybenzofuran

The existence of aryne intermediate came into consideration after the experiment performed by Stoermer and Kahlert in 1902.[2] The 3-bromobenzofuran (**1)** with base in ethanol provided 2-ethoxybenzofuran **2** (Scheme 1).



Scheme 2: Formation of biphenyl

After 40 years, Wittig and co-workers reported the formation of biphenyl **4** by reacting fluorobenzene **3** and phenyllithium via zwitterionic intermediate (Scheme 2).[3]

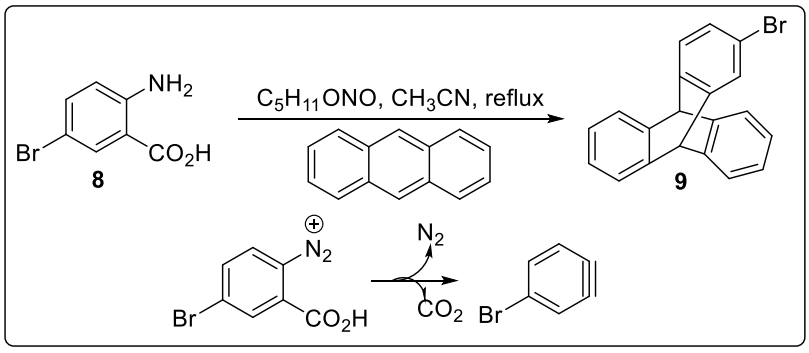


Scheme 3: Classical ^{14}C-labeling experiment

Further, Robert *et al.* confirmed the formation of aryne by classical ^{14}C-labeling experiment.[4] The ^{14}C radiolabeled chlorobenzene **5** on treatment with sodium in liquid ammonia gave the 50:50 regioisomeric mixture of radiolabeled aniline **6** and **7** (Scheme 3).

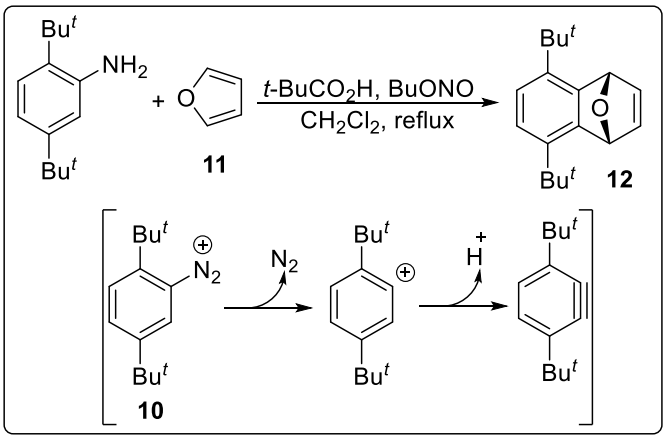
Further various groups were involved in inventing novel protocols for generation of arynes and their applications.

1.1.2 Generation of Arynes



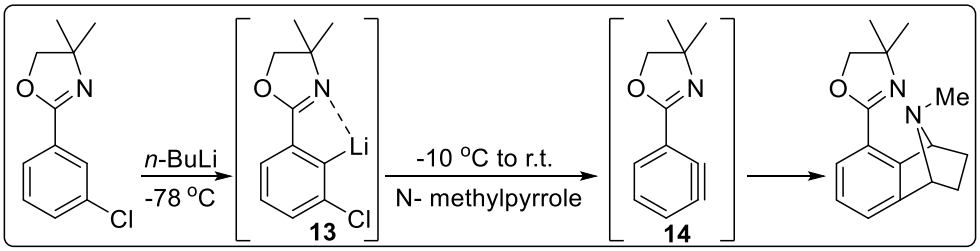
Scheme 4: Generation of aryne from anthranilic acid

The bromoanthranilic acid **8** on diazotization using alkyl nitriles provided benzenediazonium-2-carboxylate (Scheme 4) afforded aryne. The in situ generated benzenediazonium-2-carboxylate reacted with anthracene affording the Diels-Alder product **9** (Scheme 4).[5]



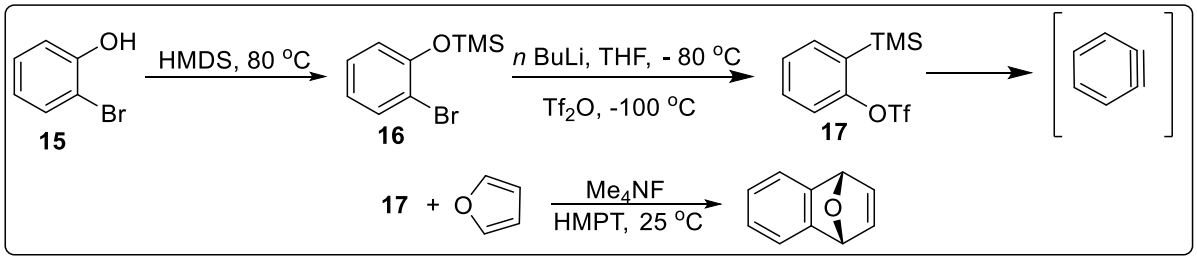
Scheme 5: Generation of aryne from 2,3-di-t-butylaniline

The diazotized 2,3-di-t-butylaniline **10** generated in situ on treatment with furan **11** yielded the Diels-Alder product **12** in low yields. The formation of the Diels-Alder product suggests the aryne formation (Scheme 5).[6]



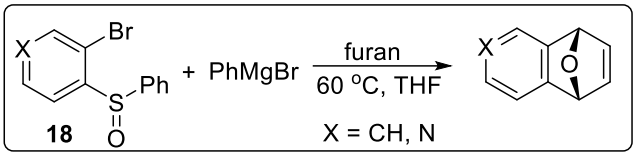
Scheme 6: Regioselective generation of aryne.

The regioselectivity in aryne generation was achieved by Riecker and co-workers by installing ortho-directing metallating groups (DMG) to meta position of halogen atom. The meta substituted DMG in **13** is responsible for the formation of an anion, which is rate-determining step. Further the elimination of halogen atom provided regioselective aryne precursor **14** (Scheme 6).[7]



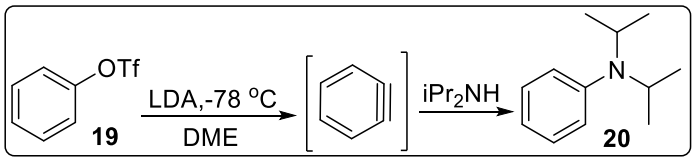
Scheme 7: Generation of aryne from 2-(trimethylsilyl)phenyltriflate

Kobayashi and co-workers in 1983 synthesized 2-(trimethylsilyl)phenyltriflate **17** as aryne precursor. Till date 2-(trimethylsilyl)phenyltriflate **17** has been the most extensively used aryne precursor by various groups. The compatibility of 2-(trimethylsilyl)phenyltriflate **17** has been observed under various reaction conditions such as in the presence of transition metals, acids, base etc. The synthesis of 2-(trimethylsilyl)phenyltriflate **17** begins with the commercially available *o*-bromophenol **15**, which on protection with HMDS provides compound **16**. The compound **16** on treatment with *n*-BuLi and Tf_2O at lower temperature provides 2-(trimethylsilyl)phenyltriflate **17** (Scheme 7).[8]



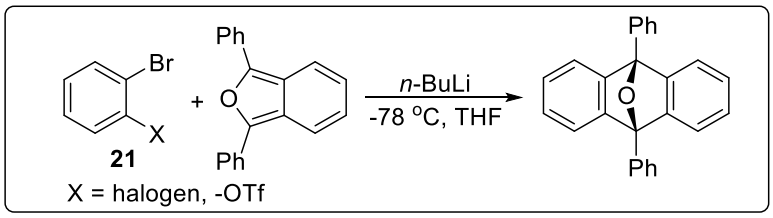
Scheme 8: Generation of aryne from *o*-bromophenyl phenyl/pyridylsulfoxides

The *o*-bromophenylphenylsulfoxides or 3-bromo-4-pyridyl phenylsulfoxides **18** on treatment with Grignard reagent in THF generates aryne. This protocol was not exploited further because of the difficulty in the starting material preparation (Scheme 8).[9]



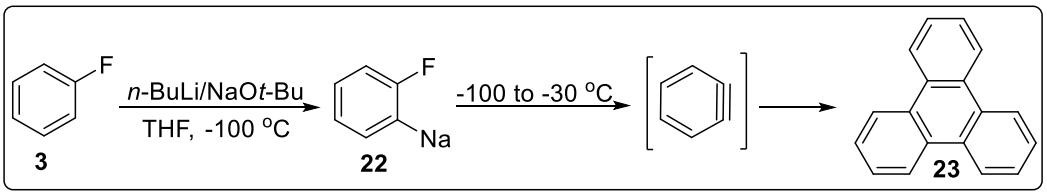
Scheme 9: Generation of aryne from phenyl trifluoromethanesulfonate

Different substituted arynes were generated from phenyl triflate **19** in the presence of strong base LDA at -78 °C, which reacts in situ with diisopropylamine furnishing **20** (Scheme 9).[10]



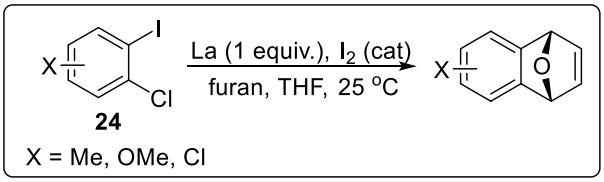
Scheme 10: Generation of aryne from *o*-dihalides and *o*-halotriflates

Arynes have also been generated using *o*-halotriflates **21**. The initial metal-bromo exchange takes place at lower temperature with *n*-BuLi, followed by elimination of a lithium salt leading to aryne generation (Scheme 10).[11]



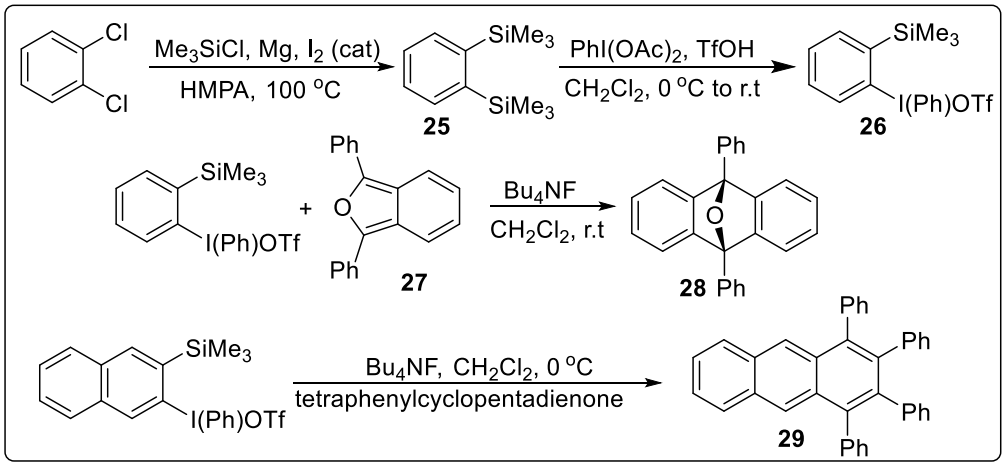
Scheme 11: Generation of aryne from fluorobenzene

Aryne formation was observed when fluorobenzene **3** was converted to **22** in the presence of equiv-molar mixtures of *n*-BuLi and NaO*t*-Bu in THF. Further at -30 °C formation of triphenylene **23** was observed (Scheme 11).[12]



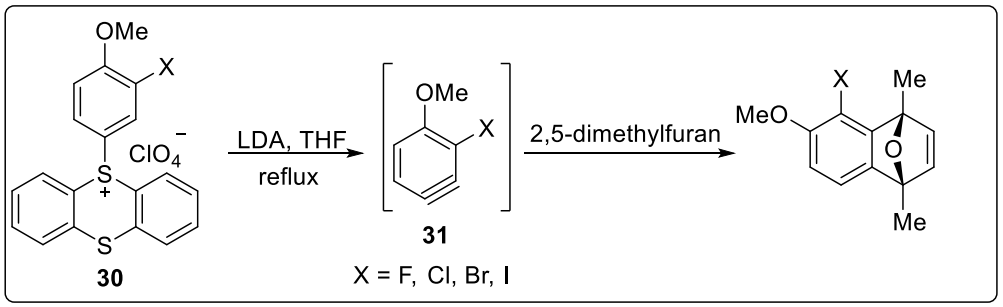
Scheme 12: Generation of aryne from *o*-dihalides using lanthum

For the very first time lanthanum metal was used for the generation of aryne by reacting with 1,2-dihalogen substituted arenes **24** in the presence of catalytic iodine (Scheme 12).[13]



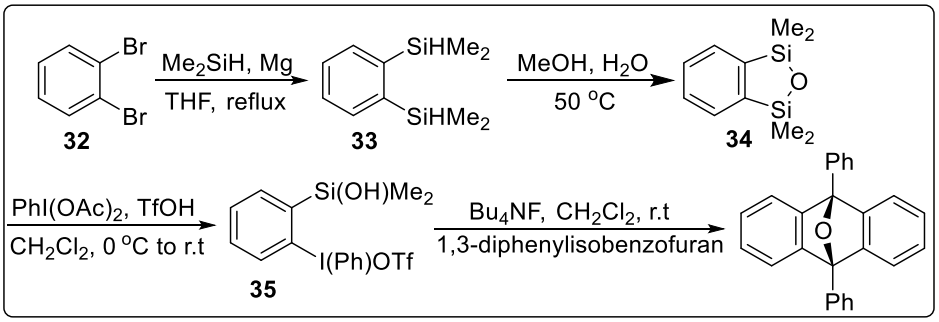
Scheme 13: Modification of Kobayashi's aryne preursor

Further Kitamura and co-workers modified the Kobayashi's aryne precursor by replacing OTf group with hypervalent iodine group. The good leaving ability of hypervalent iodine group resulted into a facile aryne formation. The reagent **26** was prepared from *o*-bis(trimethy1silyl)benzene **25** by reacting with activated iodobenzenediacetate in DCM solvent. The aryne precursor on treatment with furan **27** in the presence of Bu_4NF in CH_2Cl_2 as solvent afforded Diels-Alder products **28** and **29** quantitatively (Scheme 13).[14a-c]



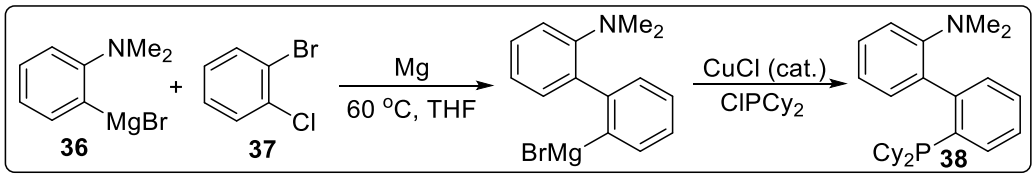
Scheme 14: Generation of aryne from thianthreniumperchlorate

The synthesis of 3-halo-4-methoxybenzyne **31** was achieved from S-(3-halo-4-methoxyphenyl)thiathrenium perchlorates **30**. The thianthrene molecule acts as a leaving group instead of a halogen atom. The aryne **31** undergoes Diels-Alder reaction with 2,5-dimethylfuran (Scheme 14).[15]



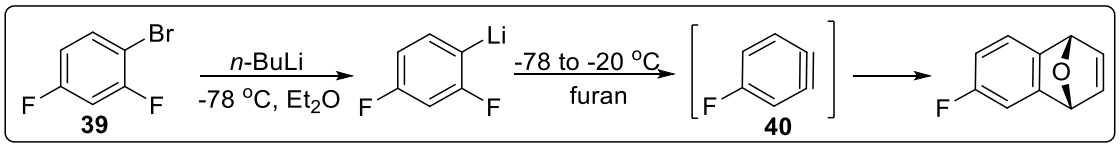
Scheme 15: Generation of aryne from 2-(hydroxydimethylsilyl)-phenyl(phenyl)iodonium

Further the same group modified the procedure for the synthesis of aryne precursor. The 1,2-Dibromobenzene **32** was converted to *o*-bis(dimethy1silyl)benzene **33**, which on treatment with methanol provided the cyclic silyl compound **34**. The cyclic silyl compound on treatment with activated iodobenzenediacetate in DCM solvent afforded [2-(hydroxydimethylsilyl)-phenyl](phenyl)iodoniumtriflate **35** (Scheme 15).[16]



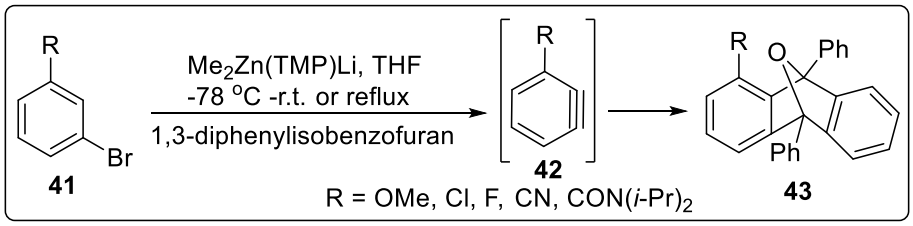
Scheme 16: Generation of aryne from *o*-dihalides

The synthesis of asymmetric biaryls was achieved from benzynes, which were generated from *o*-dihalides. The synthesis of functionalized dialkylphosphinobiphenylligands **38** were carried out by the addition of arylmagnesiumhalides **36** to benzyne prepared in situ from 1-bromo-2-chlorobenzene **37** and magnesium (Scheme 16).[17]



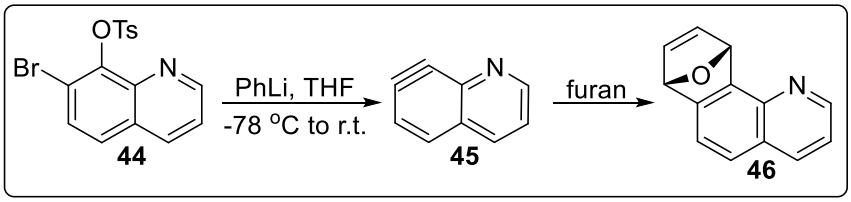
Scheme 17: Generation of aryne from *o*-dihalides

Aryne was synthesized by treating **39** with *n*-BuLi. The initial metal–bromo exchange takes place at lower temperature followed by elimination of a lithium salt furnishing aryne **40** (Scheme 17).[18]



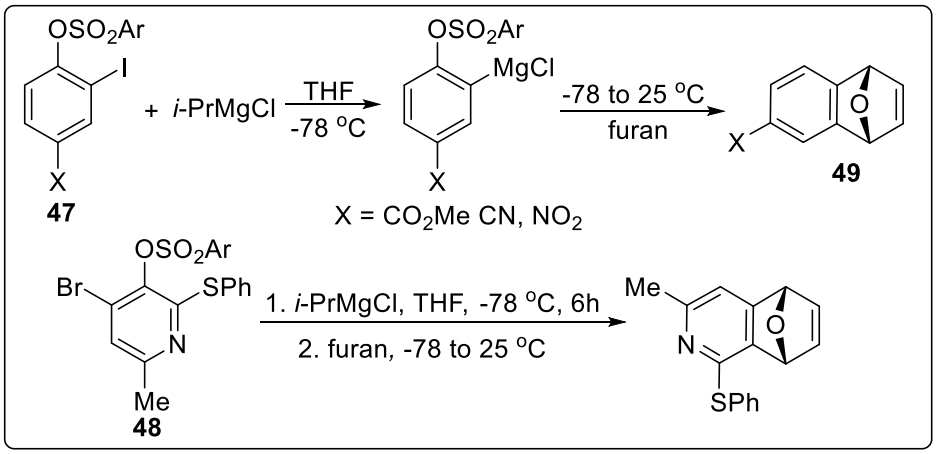
Scheme 18: Generation of aryne from meta-functionalized haloaromatics

Uchiyama and co-workers synthesized 3-substituted benzynes **42** via deprotonative zincation of meta-functionalized haloaromatics **41** using dimethyltetramethylpiperidino-zincate (Me,Zn(TMP)Li) as metallating agent. The in situ generated aryne was trapped with 1,3-diphenylisobenzofuran, which delivered Diels-Alder product **43** (Scheme 18).[19]



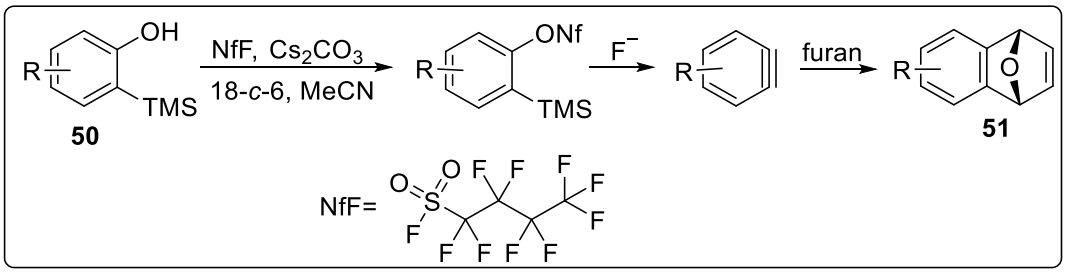
Scheme 19: Generation of aryne from *o*-halo aryltosylates

The ortho-halo aryltosylates **44** on treatment with phenyl lithium furnished aryne 7,8-quinolyne **45**, which was trapped with furan to yield desired product **46** in moderate yield (Scheme 19).[20]



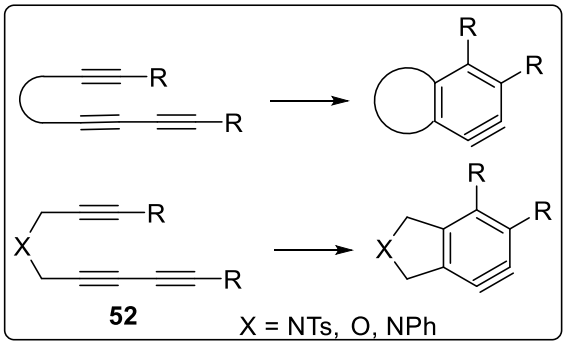
Scheme 20: Generation of aryne from *o*-halobenzenesulfonates

Knochel and co-workers developed an efficient method for generating aryne using *o*-halobenzenesulfonates **47**. Various functional groups on aromatic ring were tolerated by under this protocol. The substituted *o*-halobenzenesulfonates **47** on treatment with isopropyl magnesium chloride generates aryne which was trapped with furan to give Diels –Alder product **49**. This protocol was also compatible with pyridine moiety **48** (Scheme 20).[21]



Scheme 21: Dual activation of *o*-(trimethylsilyl)phenols by nonafluorobutanesulfonyl fluoride

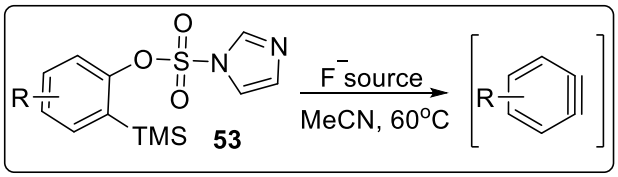
Akai and co-workers developed novel domino process for aryne synthesis. Aryne precurssors were synthesized from *o*-(trimethylsilyl)phenols **50** using nonafluorobutanesulfonyl fluoride (NfF). The in situ generated arynes were trapped with furan to afford Diels–Alder product **51** (Scheme 21).[22]



Scheme 22: Generation of aryne from 1,3-diyne

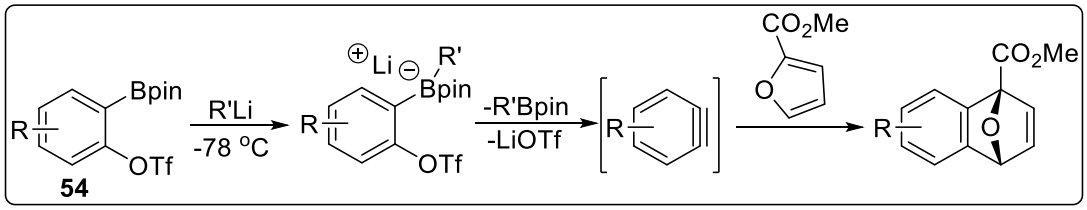
Hoye and co-workers reported the synthesis of aryne precursor from triyne **52** by implementing hexadehydro-Diels−Alder (HDDA). The 1,3-diyne is engaged in a [4+2] cycloisomerization with

a diynophile to produce the highly reactive benzyne intermediate. Interestingly this protocol is free of metals and external reagents (Scheme 22).[2]



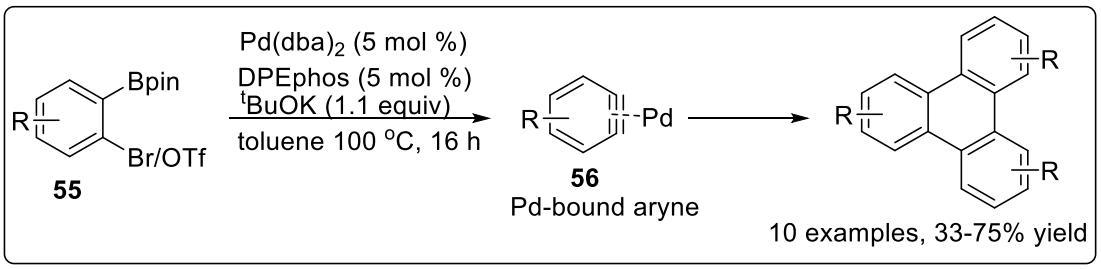
Scheme 23: Generation of aryne from *o*-(trimethylsilyl)arylimidazolylsulfonates

The different substituted *o*-(trimethylsilyl)aryl imidazolylsulfonates **53** were synthesized by using *o*-bromophenols in multiple steps without isolation of intermediates. The genotoxic trifluoromethanesulfonate side product is eliminated in this protocol. The applicability of the new aryne precursors were tested on different types of cycloaddition reactions (Scheme 23).[24]



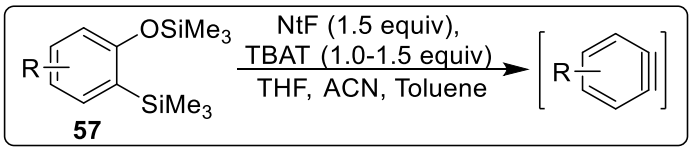
Scheme 24: Generation of aryne from *o*-triflatepinacol esters

Hosoya and co-workers in 2013 reported the aryne generation from ortho-(trifluoromethanesulfonyloxy)aryl boronic acid pinacol ester **54** on treatment with *tert*- or *sec*-butyllithium. The respective arynes generated were trapped with various nucleophiles, dienes etc (Scheme 24).[25]



Scheme 25: Generation of aryne from 2-bromo pinacol esters

Greaney *et al.* carried out the synthesis of triphenylenes by trimerization of arynes, which were derived from 2-bromo pinacol esters **55** using palladium catalyst (Scheme 25). The reaction was carried out in the presence of $Pd(dba)_2$ catalyst, DPEphos ligand, ^{t}BuOK base in toluene at 100 ^{o}C. The metal bound aryne intermediates **56** underwent trimerization (Scheme 25).[26]



Scheme 26: Generation of aryne from 2-(trimethylsilyl)phenyltrimethylsilyl ethers

Akai *et al.* reported the 2-(trimethylsilyl)phenyltrimethylsilyl ethers **57** as aryne precursors from commercially available halogenated phenols in two steps. The arynes were generated by a domino reaction of *o*-desilylation, *o*-nonaflylation, and *β*-elimination under mild conditions using nonafluorobutanesulfonyl fluoride (NfF) and tetrabutyl ammonium triphenyl difluorosilicate (TBAT) (Scheme 26).[27]

Several fluoride-free methods have been reported in the literature and recently a nice review on this interesting topic has been published by Jones *et al.*[28]

1.1.3 Conclusion:

In last several years, numerous methods have been introduced for the generation of aryne due to its high synthetic utility. The key feature for the generation of aryne is the milder reaction condition. The Kobayashi's protocol for the generation of aryne from *o*-(trimethylsily1)aryl triflates in the presence of fluoride source remains one of the best method till date as the milder condition is compatible with wide variety of nucleophiles, reagents and transition metals. Still there is a scope for the generation of aryne from readily available, cost-effective starting materials under milder condition, because expensive *o*-(trimethylsily1) aryl triflates is required to

achieve good yields. There is a wide scope to achieve vital synthetic building blocks and complex scafolds in organic synthesis utilizing aryne chemistry.

1.1.4 References:

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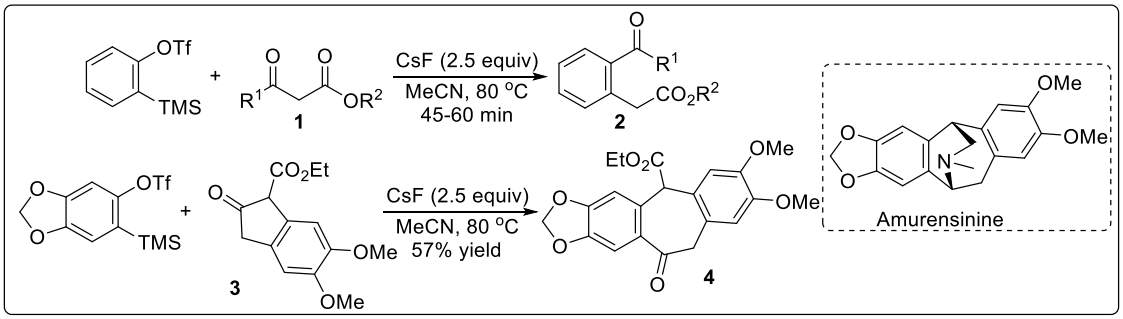
Section 2: Transition-Metal-Free Reactions of Arynes

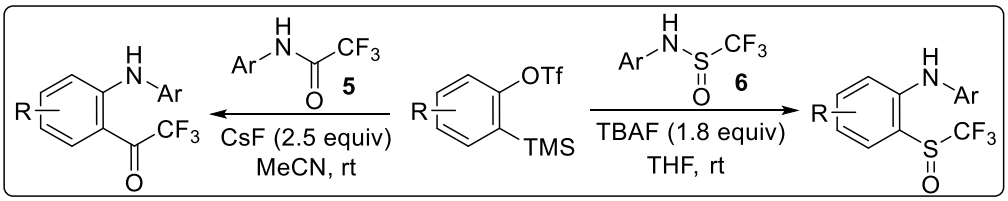
The highly strained arynes are transient reactive intermediates, which represents valuable unsaturated hydrocarbons in synthetic organic chemistry. In this section we have focused on the selective transition-metal-free reactions of arynes and their application in the total synthesis of bioactive natural products, complex heterocyclic compounds and drugs. This section is divided into four subtopics 1) Insertion of arynes 2) Annulation of arynes 3) Multicomponent reactions of arynes 4) Pericyclic reactions of arynes. The insertion reaction of arynes mostly element–element (X–Y) σ-bonds and π-bonds is a vital operation, which introduces both elements in C-C triple bond furnishing di or polysubstituted arenes. Annulation of arynes with aromatic rings or aliphatic compounds bearing nucleophic and electrophilic group provides varyingly substituted heterocycles. Further, arynes have been extensively used in Diels–Alder reactions due to its high electrophilicity, which makes them superior dienophiles. Arynes also find application in [2+2] cycloaddition reactions with electron-rich olefins and acts as excellent dipolarophiles in dipolar cycloaddition reactions. The reactions involving an aryne, a nucleophile, and an electrophile, referred as multicomponent reactions, provides diverse 1,2 bi-functional arenes. This section deals with the prime applications of arynes in various synthetic transformations.

1.2.1 Insertion of Arynes



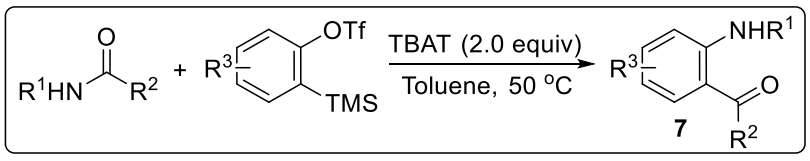
Scheme 1: Acyl-alkylation of Benzyne

In 2005 Stoltz and co-worker developed a mild and efficient process for the acyl-alkylation of arynes to synthesize interesting ortho-substituted arenes **2** (Scheme 1). The methodology developed herein affords the formation of two new C–C bonds via insertion of an arene unit into *α, β* single bond of a *β*-ketoester **1**. The ring expansion of cyclic *β*-ketoesters **3** was also achieved via aryne insertion to generate medium sized carbocycles **4**. Further, Stoltz and co-workers applied this methodology for the enantioselective synthesis of Amurensinine.[1a,b]



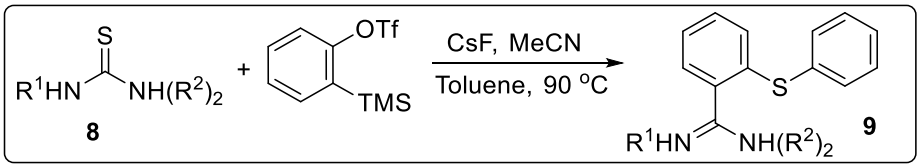
Scheme 2: Addition of amides to arynes

Larock and co-workers developed the transition-metal-free protocol for the insertion of aryne in substituted *N*-aryltrifluoroacetamides **5** and *N*-phenyltrifluoromethanesulfinamides **6** (Scheme 2). The CF_3 moiety played the crucial role in insertion chemistry; strong electron-withdrawing group increases the acidity of the amide and also increases the electrophilicity of the carbonyl carbon of the amide and sulfinyl sulfur atom of the sulfinamide.[2]



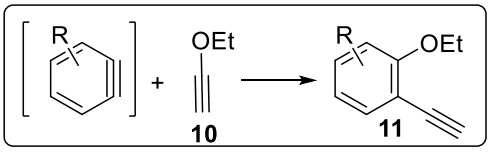
Scheme 3: Aryne insertion into the amide Bond

Greaney *et al.* reported insertion of aromatic ring into the amide bond using aryne to furnish two new aryl-N and aryl-C bonds. This process provides versatile aminobenzophenone **7** products in good to excellent yield (Scheme 3). Further this process was applied for one-pot synthesis of acridones and acridines.[3]



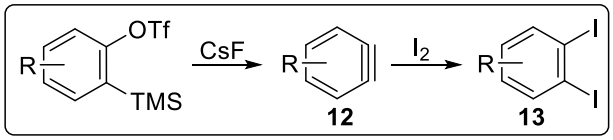
Scheme 4: Insertion of benzyne into thioureas

Further, the same group successfully carried out the synthesis of amidine **9** products via insertion of arynes into thioureas **8** (Scheme 4). This reaction differs with that of ureas, which suggests that small changes to nucleophile structure can afford divergent and synthetically useful reaction pathways in aryne chemistry.[4]



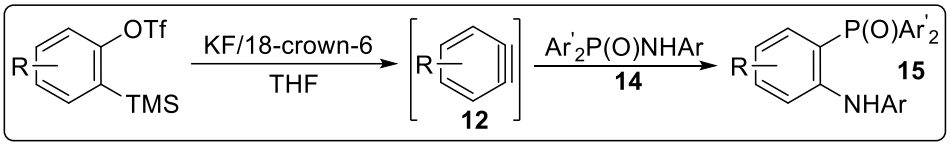
Scheme 5: Insertion of arynes into ethoxyacetylene

Guitian and co-workers reported the chemo- and regioselective formal insertion of arynes into the C(sp)–O(sp^3) bond of ethoxyacetylene **10** to afford 2-ethoxyethynylaryl derivatives **11** (Scheme 5). The computational studies suggest that the reaction proceeds by the addition of the triple bond of the alkyne to the aryne.[5]



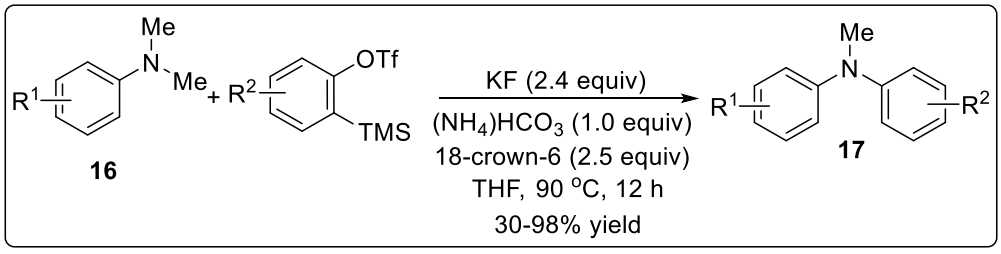
Scheme 6: Insertion of arynes into iodine

The same group successfully carried out insertion of arynes **12** in I–I σ-bond providing *o*-diiodoarene compounds **13** (Scheme 6). This method was compatible with arynes bearing electron-donating or withdrawing substituents, polycyclic arynes, and bisarynes.[6]



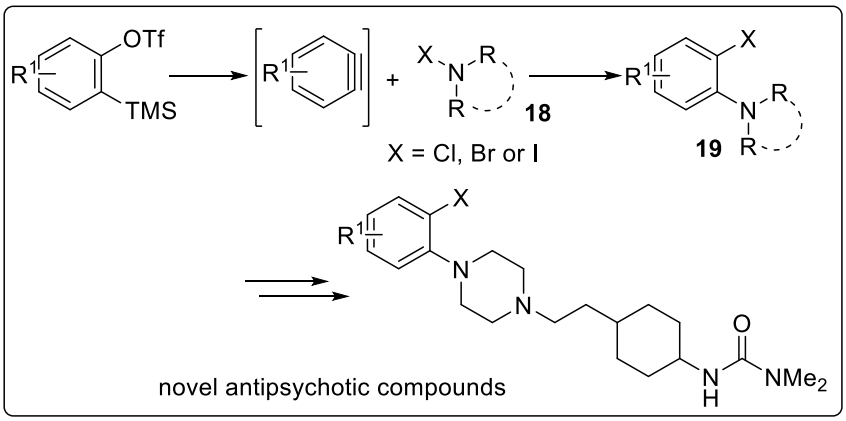
Scheme 7: Insertion of benzyne into the arylphosphoryl amide bond

Zhang *et al.* reported the insertion of arynes **12** into arylphosphoryl amides **14** to construct C–P and C–N bonds (Scheme 7). The resulting ortho-amine-substituted arylphosphine **15** oxides provide a novel method for synthesis of arylphosphines with a bulky ortho-substituted group and a number of bidentate aminophosphine ligands.[7]



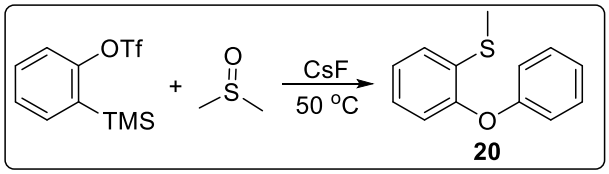
Scheme 8: Monoselective *N*-arylation of *N*,*N*-dimethylaniline

Biju and co-workers successfully carried out monoselective *N*-arylation of aromatic tertiary amines **16** by a transition-metal-free approach using arynes (Scheme 8). The reaction proceeds via the insertion of arynes into N–C bond of tertiary amines affording functionalized diaryl amines **17** in moderate to excellent yields.[8]



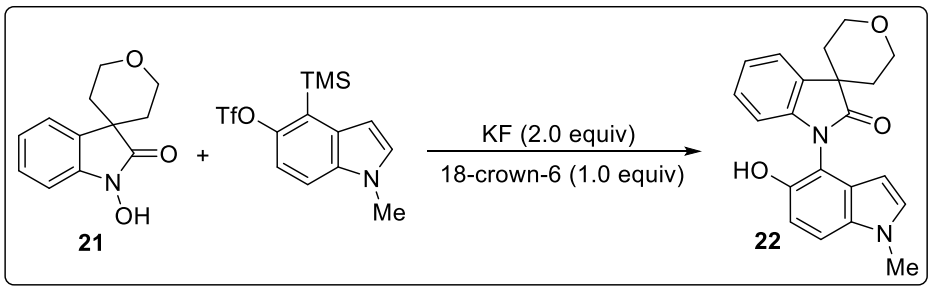
Scheme 9: Aryne insertion of N–X bonds

Wang and co-workers elegantly developed the transition metal free operation for the construction of ortho-haloaminoarenes **19** (Scheme 9). The methodology involves insertion of aryne in nitrogen-halides **18** bond (N-chloramine, N-bromoamine, and N-iodoamine) under milder reaction condition. This methodology provides an easy access to novel analogues of the antipsychotic cariprazine.[9]



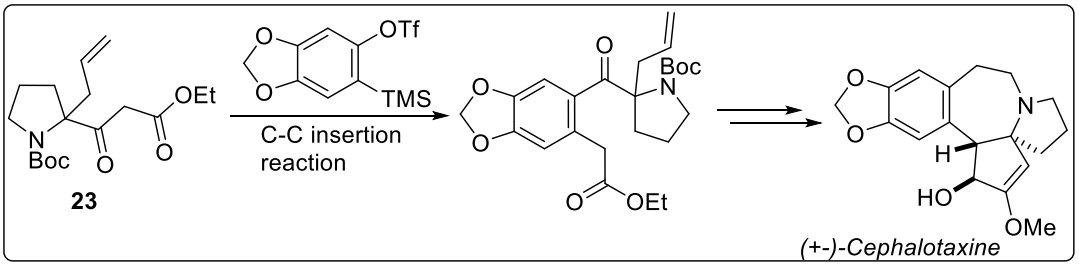
Scheme 10: Insertion of aryne into S–O bond

Wang and co-workers successfully carried out S–O bond insertion of sulfoxides with arynes (Scheme 10). The mechanism proposed suggests the formation of sulfur ylide triggered by aryne as the key intermediate, which further provides thioethers **20** through a sequential process.[10]



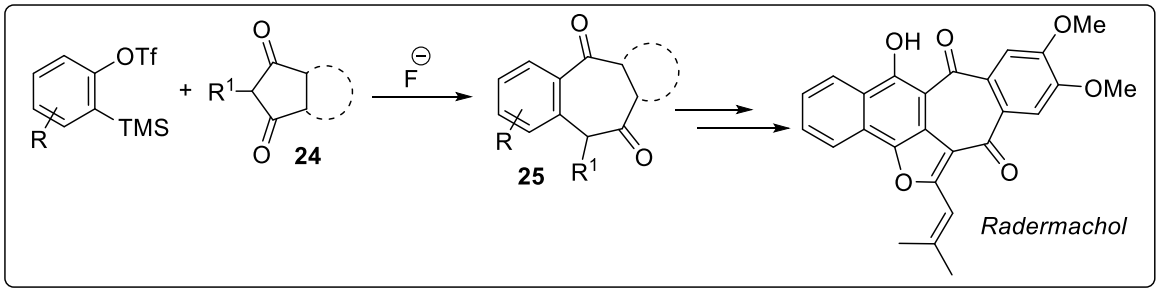
Scheme 11: Aryne insertion with hydroxyindolinones

Wang and co-workers reported the novel approach for the synthesis of sterically hindered o-aminophenols **22** by a formal aryne insertion into hydroxyindolinones **21** (Scheme 11). The reaction involves the addition of **21** to arynes followed by a chemo- and regioselective [1,3]-rearrangement.[11]



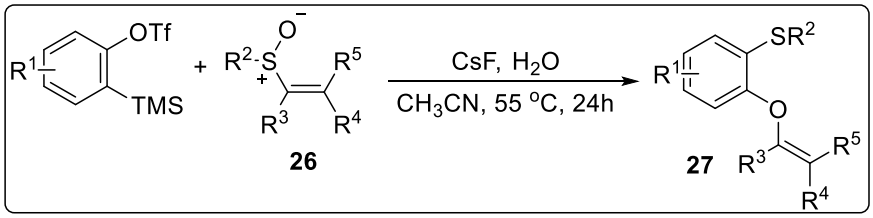
Scheme 12: Aryne insertion for synthesis of cephalotaxine and its congeners

Chandrasekhar and co-workers reported the formal total synthesis of pentacyclic core alkaloid (±)-cephalotaxine via insertion of aryne with 2- allylpyrrolidine-2-carboxaldehyde **23** as a key step (Scheme 12). The total synthesis is achieved in nine steps in 10% overall yield. The methodology developed provides an easy access to cephalotaxine congeners.[12]



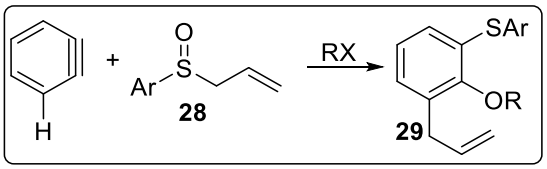
Scheme 13: Reaction of aryne with cyclic 1,3-diketones

Mehta and co-workers reported the construction of functionalized benzo-fused 7- and 8-membered carbocycles **25** (Scheme 13) via insertion of in situ generated aryne into the C−C bond of cyclic 1,3-diketones **24**. Further, application of the methodology was tested for a short synthesis of the pentacyclic natural product radermachol.[13]



Scheme 14: Insertion of aryne into S–O bond

Studer *et al.* reported the aryne insertion into aryl vinyl sulfoxides **26** (Scheme 14) via (2 + 2) cycloaddition followed by S−O bond cleavage of the four-membered benzanellated cycloadduct, and subsequent ionic vinyl migration leading to ortho-arylsulfinylaryl vinyl ethers **27**. The operation proceeds with complete stereospecificity in moderate to good yields.[14]

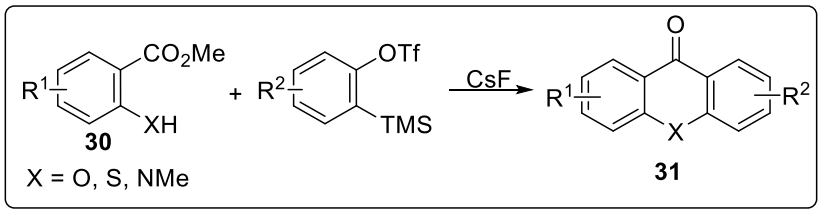


Scheme 15: Aryne 1,2,3-trifunctionalization with aryl allyl sulfoxides

The first example of 1,2,3-trisubstitution of aryne by reacting with aryl allyl sulfoxides **28** (Scheme 15) was reported by Li and co-workers. The protocol features incorporation of C−S, C−O, and C−C bonds on the consecutive positions of a benzene ring to obtain **29**. The mechanism suggests the cascade formal [2 + 2] reaction of aryne with S=O bond followed by an allyl S → O migration and finally Claisen rearrangement.[15]

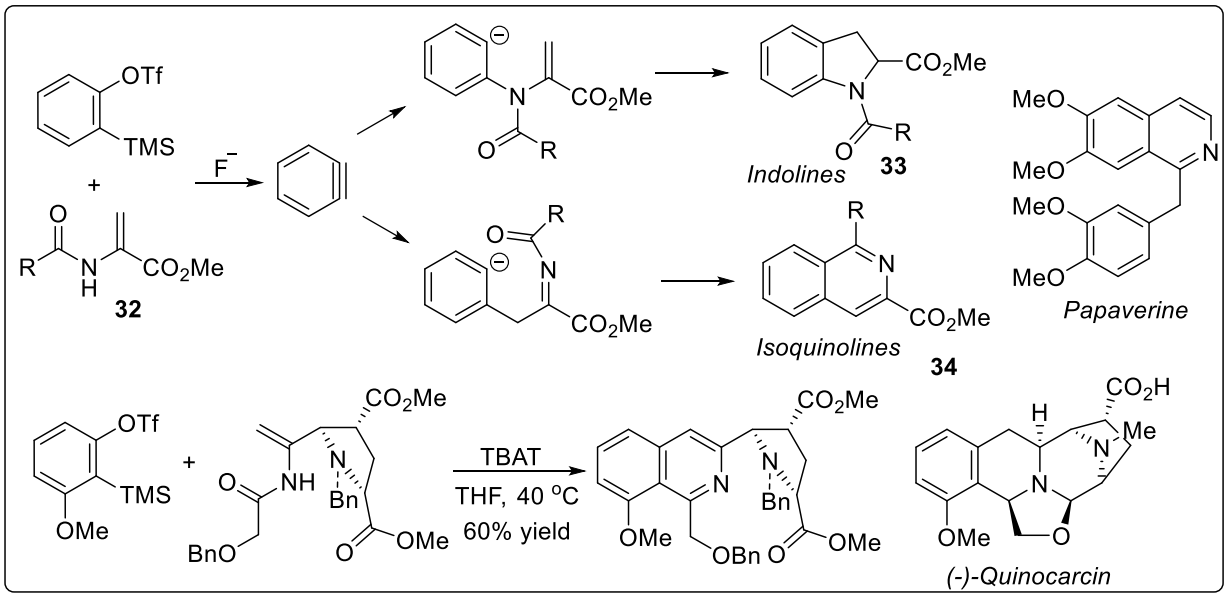
The reports on aryne insertion reactions prove its importance in organic synthesis. These reactions deliver functionalized arenes, which are the important synthetic building blocks in the total synthesis of bioactive natural products, and drugs.

1.2.2 Annulation of Arynes



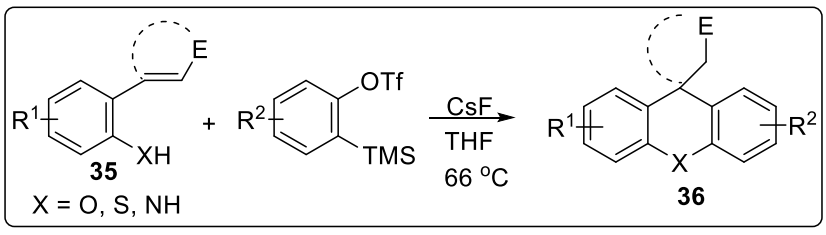
Scheme 16: Coupling of arynes and substituted benzoates

Larock and co-workers reported the synthesis of biologically interesting xanthones, thioxanthones, and acridones **31** by reacting aryne and *ortho*-heteroatom-substituted benzoates **30** (Scheme 16). The protocol follows an intermolecular nucleophilic coupling of the benzoate with an aryne followed by intramolecular electrophilic cyclization.[16]



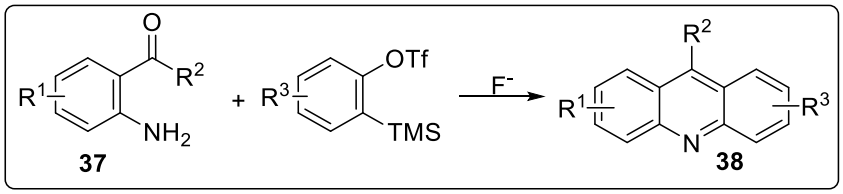
Scheme 17: Synthesis of indolines and isoquinolines via aryne annulation

Stoltz and co-workers reported the synthesis of indolines **33** and isoquinolines **34** by the coupling reaction of *N*-acyl dehydroamino esters **32** with arynes (Scheme 17). The orthogonal mode of reactivity of differentially substituted enamine derivatives has been very well described in the presence of arynes. The application of the methodology has been successfully extended for the concise total synthesis of the opiate alkaloid papavarine. Further, the same group applied this methodology in the construction of complex molecule (-)-quinocarcin.[17]



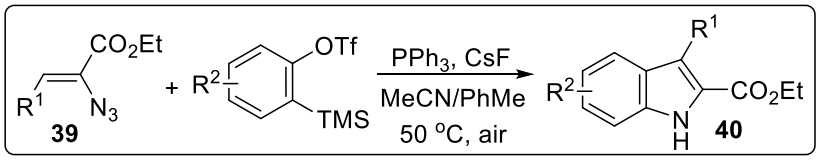
Scheme 18: Coupling of aryne with *α, β*-unsaturated groups

In 2010 Huang *et al.* successfully carried out nucleophilic addition followed by an intramolecular cyclic Michael addition on arynes by phenols or anilines bearing ortho substituted *α, β*-unsaturated groups **35** to deliver biologically important compound xanthenes and acridines **36** (Scheme 18).[18]



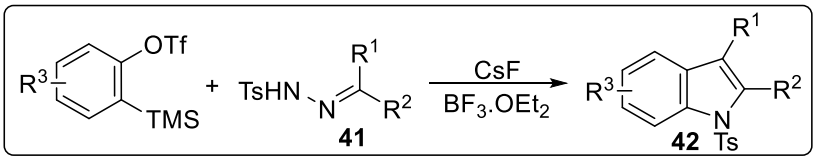
Scheme 19: Annulation of aryne and 2-aminoaryl ketones

Pioneering work by Larock group in aryne chemistry described the reaction between 2-aminoaryl ketones **37** and arynes via [4 + 2] annulation to afford medicinally important substituted acridines **38** (Scheme 19) in good yields.[19]



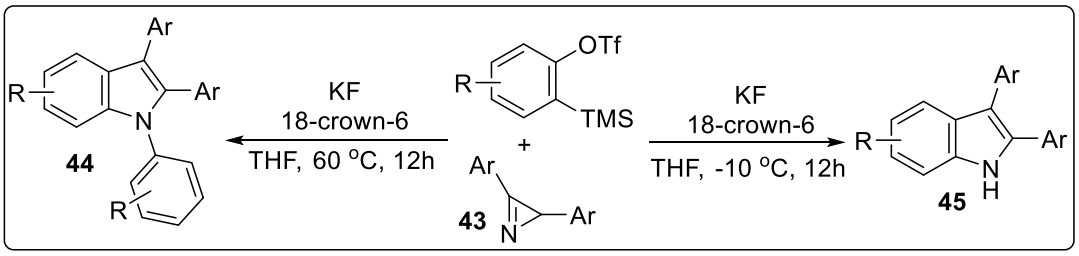
Scheme 20: Annulation of 2-azidoacrylates and aryne

The synthesis of substituted indoles **40** was achieved by reacting 2-azidoacrylates **39** with benzynes (Scheme 20). The operation involves the formation of iminophosphorane and benzyne and a subsequent double cyclization/hydrolysis/air-oxidation. The methodology was applied for the synthesis of 10H-indolo[1,2-a]indol-10-ones.[20]



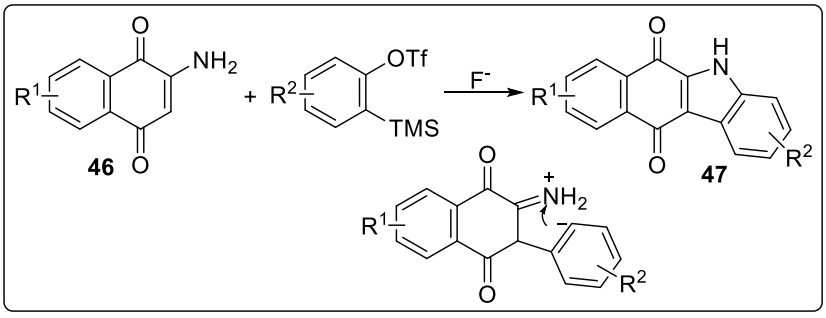
Scheme 21: Benzyne Fischer-Indole reaction

Greaney *et al.* has developed a novel Fischer-Indole synthesis method by reacting aryne and N-tosyl hydrazones **41**. The method involves *N*-arylation of *N*-tosyl hydrazones with aryne. Addition of $BF_3.OEt_2$ to the same reaction delivers *N*-tosylindole products **42** via Fischer cyclization.[21]



Scheme 22: Synthesis of *N*-unsubstituted and *N*-arylindoles via reaction of arynes with azirines

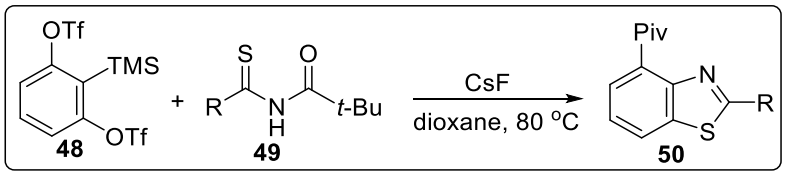
In 1975 Nair and co-workers reported the synthesis of 2,3-diphenylindole and 1,2,3-triphenylindole by reacting 2,3-diphenyl-1-azirine with aryne generated by the thermal decomposition of benzene diazonium 2-carboxylate.[22a] In this context, Biju and co-workers extended the Nair protocol by reacting 2,3-diphenyl-1-azirine with various benzyne generated from different substituted 2-(trimethylsilyl)aryl triflate precursor (Scheme 22). Arynes were reacted with 2H-azirines **43** at 60 °C which provided 2,3-diarylindoles **44** with higher selectivity and at -10 °C the formation of 1,2,3-triarylindoles **45** was observed.[22b]



Scheme 23: Reaction of arynes and 2-aminoquinones

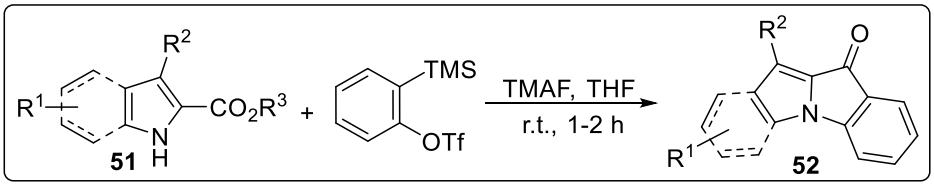
The diversity oriented synthesis of biologically and pharmaceutically important carbazolequinones **47** was reported by He and co-workers via annulation of aminoquinones **46**

(Scheme 23) with arynes. This cascade reaction proceeds through successive C−C/C−N bond formations. This novel methodology was successfully applied for the synthesis of bioactive murrayaquinone A, koeniginequinone B and their analogues.[23]



Scheme 24: Construction of 2,4-disubstituted benzothiazoles

For the very first time novel domino reaction on aryne was introduced by Li and co-workers (Scheme 24). The novel aryne precursor 2-(trimethylsilyl)-1,3-phenylene bis(trifluoromethanesulfonate) (TPBT) **48** was synthesized, which were treated with **49**. Various 2,4-disubstituted benzothiazole **49** were obtained by C–S, C–N, and C–C bonds formation by reacting aryne precursor and benzothioamide **50**.[24]

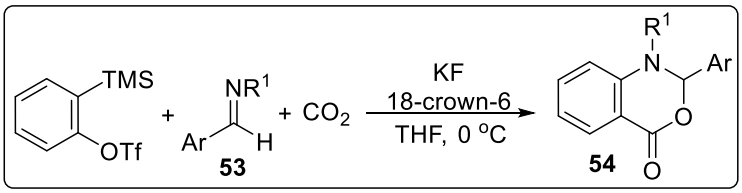


Scheme 25: Annulation of indole- and pyrrole-2-carboxylate esters with arynes

Polycyclic heterocycles containing indoles or pyrroles are a basic structural framework representing several natural products. The synthesis of such building blocks was carried out by employing aryne chemistry (Scheme 25). The method involves the annulation between indole- and pyrrole-2-carboxylate esters **51** with arynes. The attack of indole on aryne leading to *N*-arylated product followed by insertion in C–O bond provides variety of polycyclic indolone and pyrroloindolone heterocycles **52**.[25]

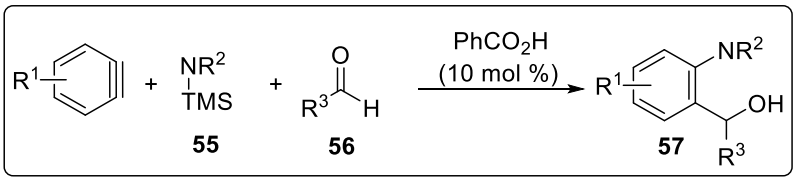
The annulation reaction of arynes with various substrates is an important asset in organic chemistry as it gives access to diverse medicinally important heterocycles and complex bioactive natural products.

1.2.3 Multicomponent Reactions of Arynes



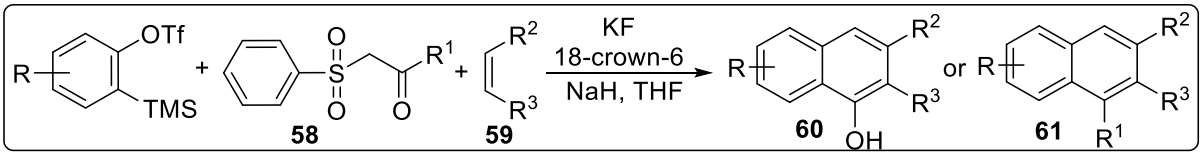
Scheme 26: Synthesis of benzoxazinone

The concept of multicomponent reactions in aryne chemistry is well explored by Yoshida group (Scheme 26). Various pharmacologically active benzoxazinone **54** derivatives were synthesized by reacting aryne, immine **53** and CO_2 at 0 ^oC. The reaction proceeds through a zwitterion, arising from nucleophilic addition of imines to arynes, which further gets intercepted by CO_2 providing benzoxazinone derivatives **54**.[26]



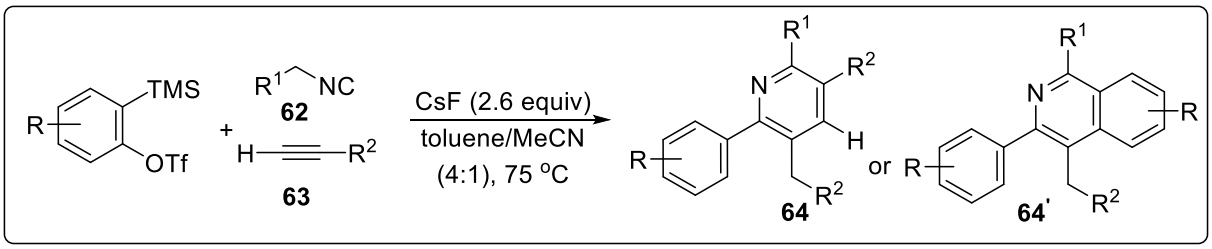
Scheme 27: Three-component coupling of benzyne, imines, and CO_2

Further, the same group reported the multicomponent reaction of arynes, aminosilanes **55**, and aldehydes **56** (Scheme 27) to access pharmacologically active compounds 2-aminobenzhydrol derivatives **57**.[27]



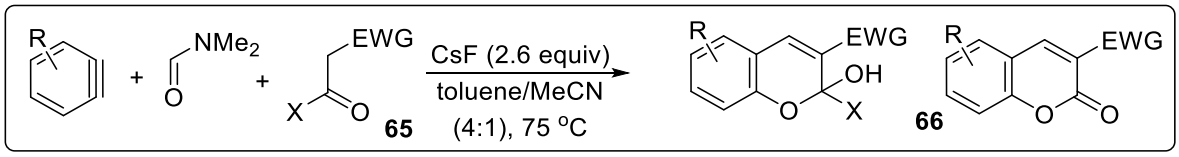
Scheme 28: Multicomponent reaction of arynes, β-keto sulfones, and Michael-type acceptors

The novel multicomponent reaction of arynes, β-keto sulfones **58**, and Michael acceptors **59** (Scheme 28) was established by Huang and co-workers providing pharmaceutically important polysubstituted napthols **60** and naphthalenes **61**. The reaction proceeds via a sequential nucleophilic attack of β-keto sulfones **58** on arynes followed by a Michael addition, and a ring closure-elimination process.[28]



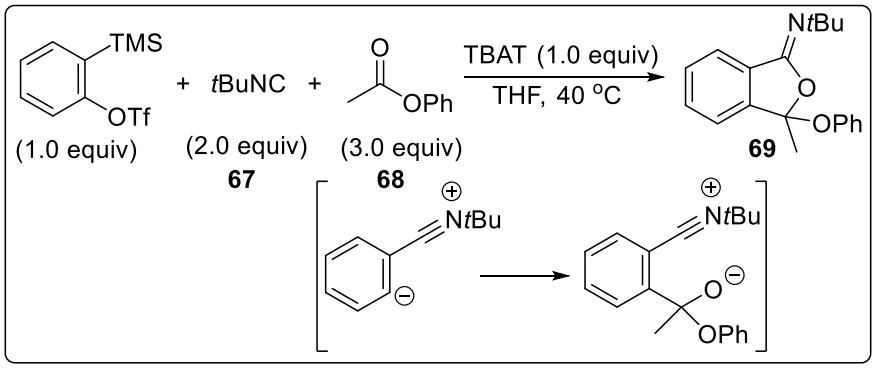
Scheme 29: Multicomponent reaction of arynes, isocyanides, and terminal alkynes

The high reactivity of arynes was successfully explored in three component coupling reaction involving arynes, isocyanides **62**, and terminal alkynes **63** (Scheme 29) producing chemo and regioselective polysubstituted pyridines **64**. Interestingly when 2.5 equivalents of aryne precursors were employed different substituted isoquinolines were the resulting product. The striking feature of this methodology is that three molecules have been assembled into the desired azacyclic compounds in a highly efficient and atom-economic manner.[29]



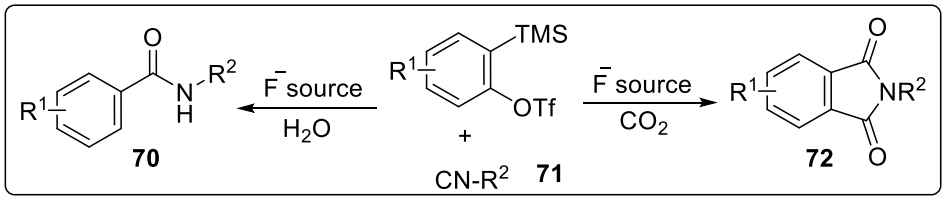
Scheme 30: Multicomponent coupling between arynes, formamide and active methylene

The insertion of aryne into C=O bond of formamide (Scheme 30) leads to reactive intermediate, which was further trapped with active methylene compounds **65** providing the coumarin **66** derivatives. The methodology was successfully applied in the synthesis of a neuropeptide Y Y5 receptor antagonist.[30]



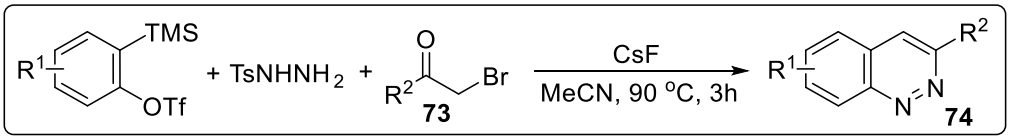
Scheme 31: Benzannulated bicycles via three-component aryne reactions

Stoltz and coworkers reported the benzannulated bicycles **69** (Scheme 31) via aryne-intercepted version of the Passerini reaction. In Passerini reaction the aldehyde plays dual role, an electrophile and a latent nucleophile. The protocol was modified in which aryne played the role of aldehyde and the third component was ester **68**. [31]



Scheme 32: MCR involving arynes, isocyanides, and CO_2

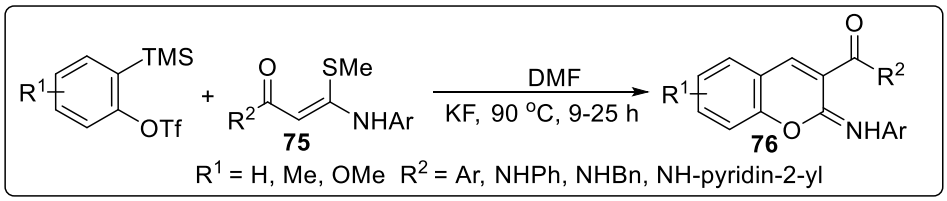
The pharmaceutically important phthalimides and benzamides were synthesized by Biju and co-workers (Scheme 32). The multicomponent reaction between arynes, isocyanides **71** and CO_2 furnished the *N*-substituted phthalimides **72** via construction of two new C−C bonds and a new C−N bond. In the presence of H_2O benzamide derivatives **70** were obtained.[32]



Scheme 33: Access to cinnolines from diazene with arynes, and α-bromo ketones

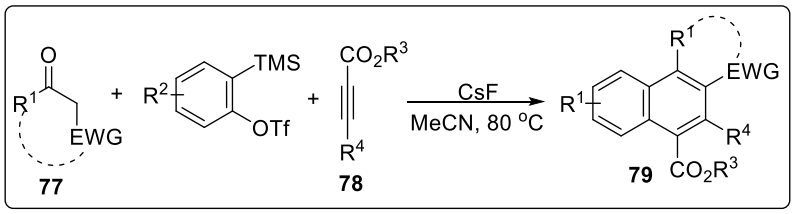
Wu and co-workers developed the novel protocol for the synthesis bioactive cinnoline derivatives **74** (Scheme 33). The reaction involves transition-metal-free multicomponent

coupling cyclization of arynes, tosylhydrazine, and α-bromo ketones **73**. Three new bonds were constructed which, includes two C−N bonds and one C−C bond in a single step.[33]



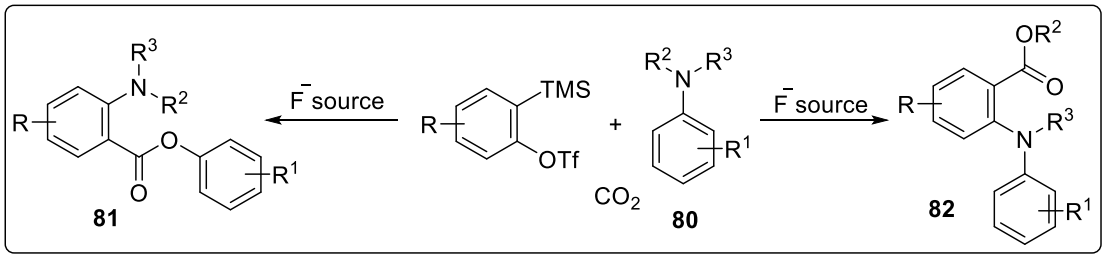
Scheme 34: Construction of 2-aryliminochromenes from arynes, N,S-keteneacetals, and DMF

The construction of biologically important 2-aryliminochromene skeleton was established by Li and co-workers using three-component coupling reaction of arynes, N, S-keteneacetals **75**, and DMF (Scheme 34). The operation proceeds smoothly via a route involving the trapping reaction of *o*-quinone methide intermediates generated in situ from aryne and DMF with N, S-keteneacetals affording arylimino-2Hchromene-3-carboxamides **76**.[34]



Scheme 35: Transition-metal-free MCR of arynes with ketones and alkynoates

The annulation reaction of arynes, ketones **77**, and alkynoates **78** provided 1-phenanthrenol derivatives **79** (Scheme 35). The process of [2 + 2 + 2] cycloaddition was compatible with different functional groups delivering naphthalene derivatives with high chemoselectivity.[35]

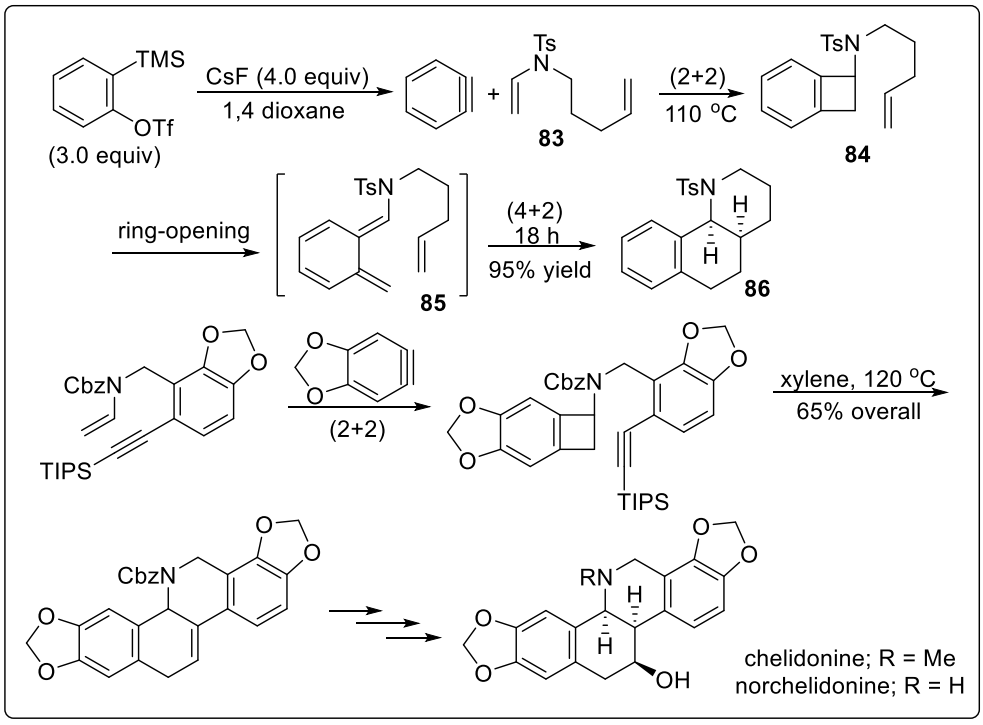


Scheme 36: MCR Involving arynes, aromatic tertiary amines, and CO_2

Biju and co-workers reported the three component coupling reaction involving arynes, aromatic tertiary amines **80**, and CO_2 (Scheme 36). The switchable selectivity of reaction was very much dependent on the electronic nature of the aromatic amines used. The amines bearing electron donating or neutral groups afforded 2-arylamino benzoates **81** via a nitrogen to oxygen alkyl group migration. The electron deficient amines furnished 2-aminoaryl benzoates **82** via the aryl to aryl amino group migration resembling a Smiles rearrangement.[36]

Multicomponent reactions of arynes thus provides an efficient and elegant access to novel disubstituted arenes, which otherwise would require multi-step transformations.

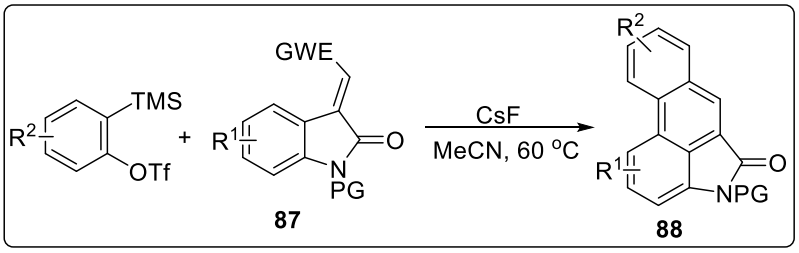
1.2.4 Pericyclic Reactions of Arynes



Scheme 37: Tandem benzyne-enamide-[2 + 2]-[4 + 2]

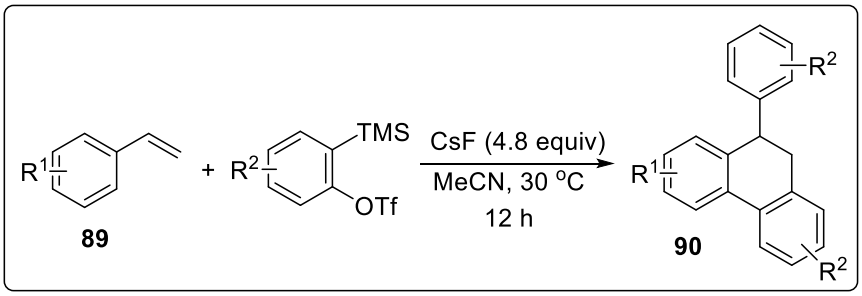
In 2009 Hsung *et al.* reported [2+2] cycloaddition of arynes with enamides **83** leading to amido-benzocyclobutanes **84** (Scheme 37). The amido- benzocyclobutanes **84** upon ring opening

provided *o*-quinonedimethide **85** which underwent intramolecular [4 + 2] cycloaddition with alkene providing nitrogen heterocycles **86**. Further the same group successfully applied the methodology for the total synthesis of bioactive natural products chelidonine and norchelidonine.[37a, b]



Scheme 38: Aryne Diels-Alder reaction with methyleneindolinones

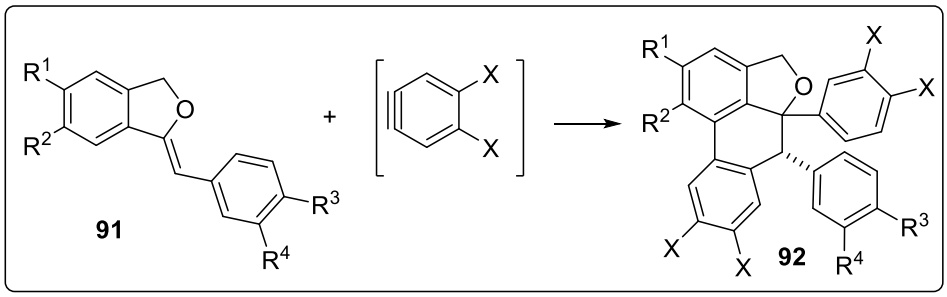
Jia and co-workers reported the construction of biologically important naphtho-fused oxindoles **88** via Diels-Alder reactions between methyleneindolinones **87** as dienes and substituted arynes (Scheme 38). The compatability of protocol was tested on various methyleneindolinones **87** and different substituted aryne precursors, which afforded oxindoles **88** in good yields.[38]



Scheme 39: Aryne Diels-Alder reaction with substituted styrenes

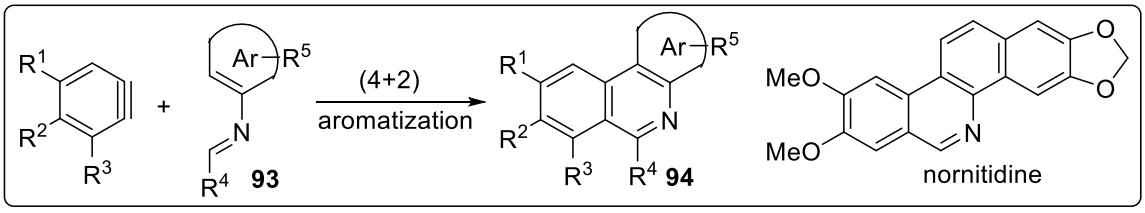
The reaction of styrene with arynes derived from 2-bromofluorobenzene and tetrahalogenated arynes was reported in literature.[39a-c] However the limited substrate scope and low yields of the product were the major drawbacks of these reported protocols. In this context Biju and co-

workers elegantly developed the mild and wide substrate protocol for the synthesis of 9-aryl-9,10-dihydrophenanthrene **90** derivatives in moderate to good yields (Scheme 39).[39d]



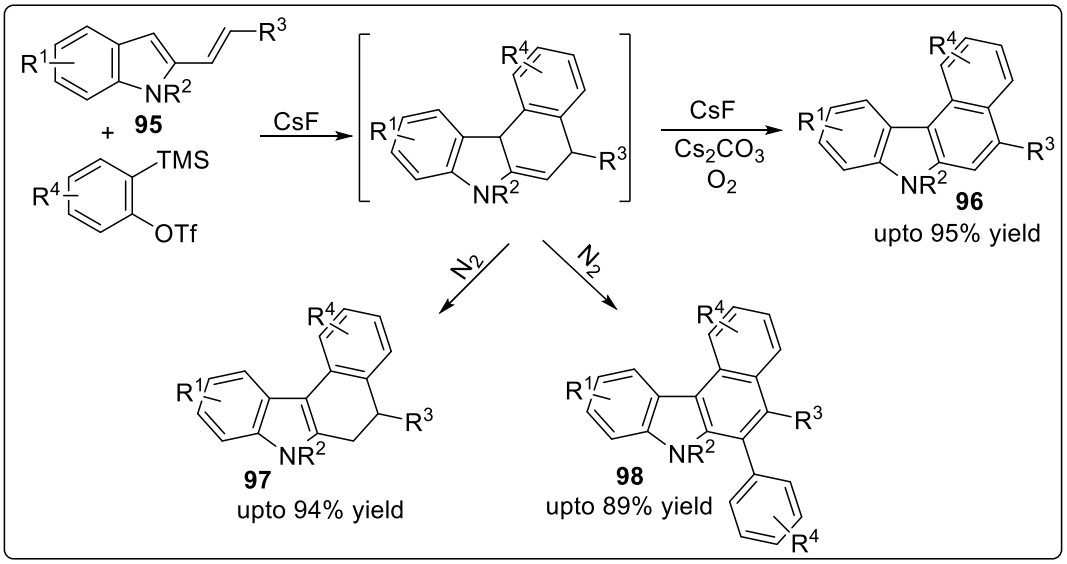
Scheme 40: Reactions of benzylidenephthalans and benzyne

Liu and co-workers reported the synthesis of complex structure phenanthro[10,1-bc]furans **92** via Diels-Alder reaction between benzyne with functionalized benzylidenephthalan **91** (Scheme 40). The resulting product phenanthro[10,1-bc]furans **92** is a valuable structural motif in different natural products and biologically active compounds.[40]



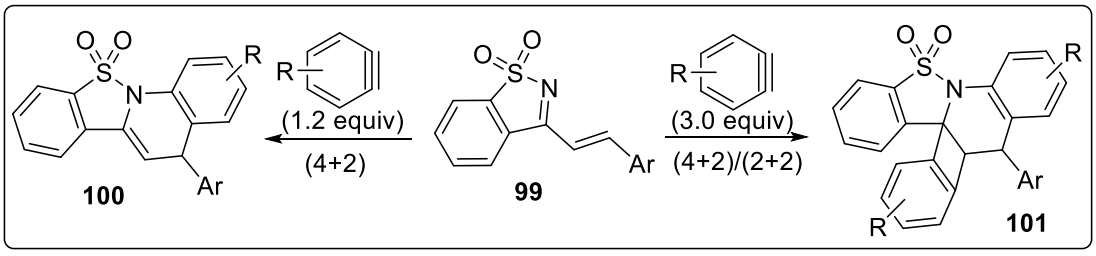
Scheme 41: Aryne aza-Diels–Alder reaction

Coquerel and co-workers developed the aza-Diels-Alder reaction of electron rich aryl imines **93** followed by aromatization leading to biologically important isoquinoline core **94** (Scheme 41). This methodology was very well extended for the synthesis of benzo[c]phenanthridine alkaloid nornitidine. [41]



Scheme 42: Diels−Alder reaction of 2-alkenylindoles and arynes

Wu *et al.* successfully developed an elegant method for constructing benzo[c]carbazole **96** derivatives via Diels-Alder reaction of arynes and readily available 2-alkenylidoles **95** (Scheme 42). The product selectivity was adjusted in such a way that in the presence of oxygen atmosphere the formation of oxidated/aromatized products benzo-[c]carbazoles **96** were observed. Whereas under nitrogen atmosphere the protocol afforded the 6,7-dihydrobenzo[c]carbazoles **97** and further increasing the equivalent of aryne precursor under same protocol furnished 7,11b-dihydrobenzo[c]carbazoles **98**. The 7,11b-dihydrobenzo [c] carbazoles derivatives showed decent antitumor activities.[42]



Scheme 43: Aza Diels−Alder and domino [4+2]/[2+2] cycloaddition reactions of arynes with *N*-sulfonyl ketimines

The synthesis of isothiazole dioxide-fused dihydroquinoline **100** or dihydrocyclobutaquinoline **101** derivatives was demonstrated by He and coworkers (Scheme 43). The electron-demanding aza Diels−Alder and domino [4+2]/[2+2] cycloaddition reaction of arynes and N-sulfonyl ketimines **99** produces one C–N and three C–C bonds leading to the synthesis of attractive cyclic sulfonamides **101**.[43]

The above examples of arynes in pericyclic reactions demonstrate its significance as a powerful tool for constructing bioactive natural products, carbocycles and heterocycles of synthetic importance.

1.2.5 Conclusion:

There has been substantial progress recently in expanding the utility of arynes in organic chemistry. The extremely reactive aryne species have been very well employed for the synthesis of highly complex organic molecules. The transition-metal-free reactions of arynes enabling carbon–carbon and carbon–heteroatom bond formation are a valuable asset in synthetic organic chemistry. The prime application of arynes in the insertion reaction, annulation reactions, multicomponent reactions, and pericyclic reactions have led to various complex medicinally important heterocycles, 1,2-difunctionalized arenes and biologically active natural products. Due to the versatility and immense progress in the aryne chemistry, arynes have emerged as a powerful synthetic tool in organic chemistry. The importance of aryne in organic chemistry is flourishing and leading to surprising developments. There is still a wide scope in understanding exact reactivity pattern of arynes and other characteristics. The above fascinating transformations using arynes increased our curiosity in aryne chemistry, which led us to think of novel protocols for the synthesis of complex scaffolds and valuable building blocks. In this context we planned

to develop novel methodologies in aryne chemistry for the synthesis of vital synthetic building blocks, which would be further applied in total synthesis of bioactive natural products.

1.2.6 References

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Chapter 2

Novel Transition-Metal-Free Approaches for the Construction of C–C, C–N and C–P Bonds using Aryne Chemistry

Introduction:

The C–C, C–P, and C–N bonds are the backbone of the organic chemistry because they constitute majority of natural products, well known drugs, biologically important compounds, dyes, valuable polymer composites, functional materials etc. Various novel synthetic methodologies have been reported in the literature for the construction of C–C, C–P, and C–N bonds. The known methods use transition-metal-catalyzed reactions, amide coupling reactions, reactions involving acidic and basic conditions etc. In recent years, aryne has emerged as an efficient prime synthetic tool in C–C, C–P, and C–N bond forming methodologies. The aryne chemistry has grabbed the attention of scientific community and has been an imperative subject in organic chemistry. Various groups have explored novel synthetic utility of arynes towards C–C, C–P, and C–N bond forming reactions. Further, such novel methodologies are articulately explored for the total synthesis of complex bioactive natural products and drugs containing disubstituted arenes. The high reactivity of aryne and its utilization in constructing complex organic molecules motivated our research group to initiate work in this area. In this context we have reported several novel transformations by employing aryne. This chapter deomonstrates a creative exploration of aryne as versatile building blocks to construct new C–C and C–heteroatom bonds for the synthesis of various useful scaffolds. The chapter is divided into three sections.

Section 1: Transition-Metal-Free C-Arylation at Room Temperature by Arynes.

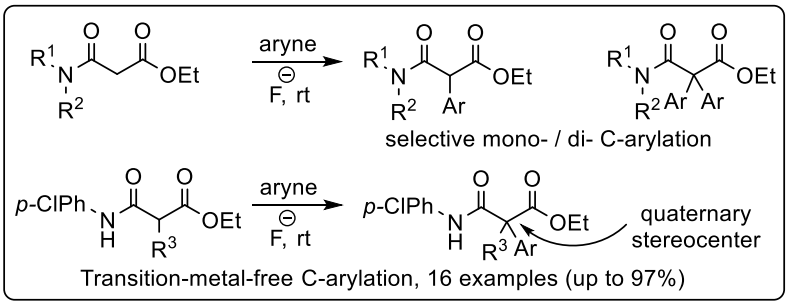
Section 2: P-Arylation: Arynes to Aryl-Phosphonates, -Phosphinates, and -Phosphine Oxides.

Section 3: Nucleophilic Nitration of Arynes by Sodium Nitrite and its Multicomponent Reaction Leading to Double-Functionalized Arenes.

Section 1: Transition-Metal-Free C-Arylation at Room Temperature by Arynes

2.1.1 Abstract:

The section 1 involves highly selective transition-metal-free *C*–arylation of malonamide esters at room temperature by arynes. Such *α*-arylation of active methylenes requires transition-metals, expensive ligands, high temperature and pressure. In this context we have developed a transition-metal-free *α*-arylation of *β*-dicarbonyl compounds at room temperature by employing aryne. The reaction exhibits exclusive switchable mono- or di-arylation selectivity and chemoselective *C*-arylation over the *N*-arylation. The reported protocol is the unique strategy as it involves diarylation of active methylene group, which is not reported in the presence of transition-metals. Further, the methodology was successfully applied for synthesiszing the compounds containing benzylic quaternary stereocenters. The arylated malonamide ester comounds can serve as important precursors for the synthesis of phenobarbital class of CNS depressant barbiturate drugs.



This work has been published in *Org. Lett*. **2012**, *14*, 3994.

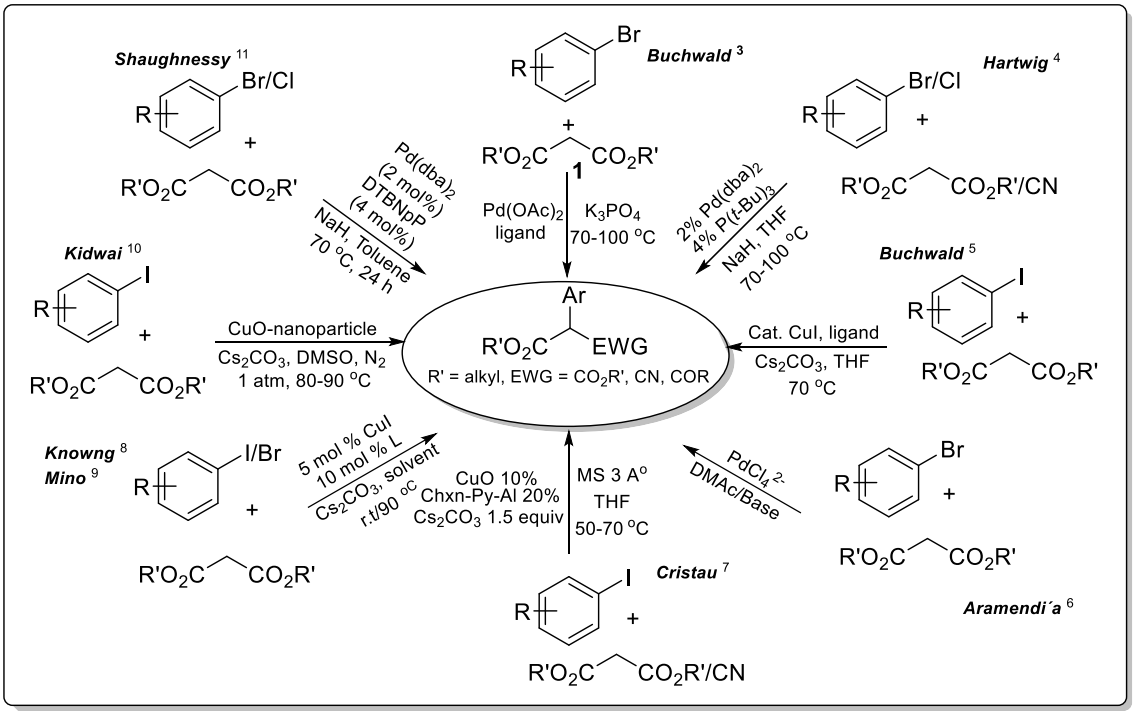
2.1.2 Introduction:

α-Aryl malonate compounds are an important class of organic compounds and vital building blocks in biologically active natural/synthetic products. They have been reported as effective

modulators in mammalian membranes.[1] The α-aryl acid derivatives accessed from α-aryl malonates represent number of natural products architecture and finds prime applications in pharmaceutical chemistry.[2] Due to high applicability, the scientific community has been constantly engaged in developing novel protocol for the synthesis of α-aryl malonates.

2.1.3 Review Literature:

In literature usually the arylation of active methylene has been carried out by using transition-metals. Herein we have documented some reports on arylation of active methylene groups using different transition-metals.



Scheme 1: Known methods for arylation of active methylenes

Buchwald and coworkers reported the $Pd(OAc)_2$ catalyzed arylation of diethyl malonate, cyclic 1,3-diketones, and nitroalkanes in the presence of ligand 2-methyl-2¢-dicyclohexylphosphinobiphenyl (Scheme 1).[3] Further, similar type of transformation was acheived by Hartwig *et al* by coupling of aryl bromides and chlorides with dialkyl malonates and

alkyl cyanoesters in the presence of catalyst $Pd(dba)_2$ and ligand $P(t\text{-}Bu)_3$ at 70 ^oC (Scheme 1). This reaction was proved to be highly efficent, as electron-poor/electron-rich, sterically hindered/unhindered aryl bromides and chlorides were shown to react with diethyl malonate, di-tertbutyl malonate, diethyl fluoromalonate, ethyl cyanoacetate, and ethyl phenylcyanoacetate.[4]

Again, Buchwald and co-workers reported arylation of diethyl malonate (Scheme 1). The methodology was successfully carried out at 70 ^oC in the presence of Cs_2CO_3 and catalytic amounts of copper (I) iodide and 2-phenylphenol affording α-aryl malonates in excellent yields.[5]

Aramendı´a reported workup free methdodlogy for arylation of diethyl malonate with aryl bromides in the presence of heterogeneous base $Ba(OH)_2$ and catalyst $PdCl_4$ (Scheme 1). The base removal through filtration makes this process very simple and easy.[6] There was another highly efficient report on coupling of aryl iodide/bromide with diethyl malonate/ethyl cyanoacetate/malononitrile in the presence of CuO and ligand Chxn-Py-Al (Scheme 1).[7]

The highly important synthesis of α-aryl malonates was reported by Kwong and co-workers via room-temperature coupling of aryl iodides with malonates (Scheme 1). This protocol involves catalytic amount of 2-picolinic acid and CuI.[8] Mino and co-workers successfully carried out the C–C coupling of aryl iodides and diethyl malonate using CuI catalyst and hydrazones as ligand in toluene at 70 ^oC (Scheme 1). The advantage of this methodology is it was carried under aerobic atmosphere.[9]

The application of CuO-nanoparticles was successfully tested for the arylation on active methylene compounds using various aryl halides by Kidwai group (Scheme 1). The catalyst was recycled four times with almost constant efficiency.[10]

Shaughnessy and his group reported the combination of $Pd(dba)_2$ and di-tert-butylneopentylphosphine (DTBNpP) ligand as an effective catalyst for coupling of aryl bromides

and chlorides with diethyl malonate or ethyl cyanoacetates (Scheme 1). The combination was also effective for the coupling of electron-rich and electron-neutral aryl bromides and with ethyl cyanoacetates.[11]

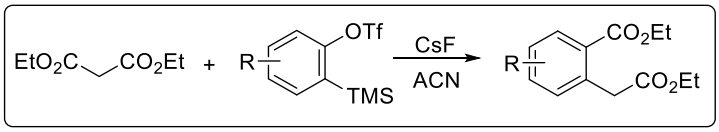
2.1.4 Origin of the present Work:

It has been observed from the literature that the transformation of active methylene groups to α-arylated compounds always requires transition metals, expensive ligands, high temperature and pressure. To overcome these hurdles there is a wide scope for metal-free approaches under milder reaction conditions.

2.1.5 Objective:

To tackle this issue we have developed an efficient protocol, transition-metal-free chemo-selective α-arylation of β-dicarbonyl compounds (malonamide esters) at room temperature using aryne. The methodology was applied for selective mono-/di-arylation and generation of quaternary benzylic stereocenter of malonamide esters.

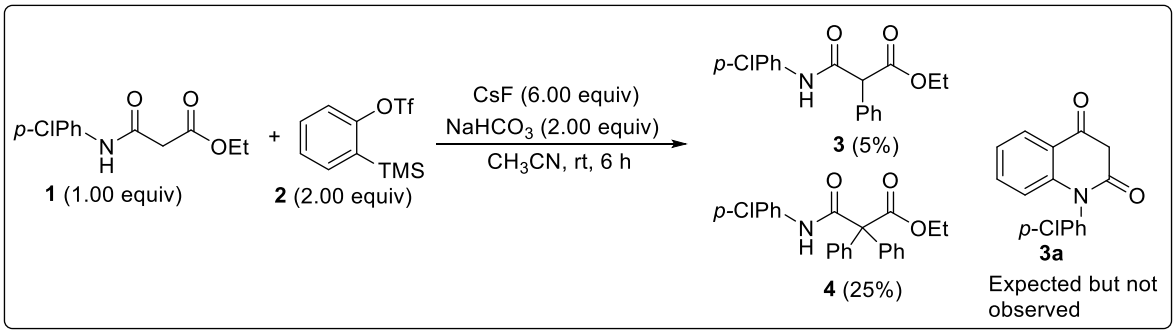
There are several reports in lietratur of insertion of aryne in element-element σ-bond and π-bond have been reported,[12,13] however examples of aryne insertion into the C–H σ-bond to directly provide C-arylated products are rare and found on anilines,[14] aldehydes[15] and β-enamino esters/ketones.[16] The exclusive insertion of benzyne into C–C σ-bond as the only product was reported by Stoltz and co-workers (Scheme 2).[13g] However, Wang and coworkers reported the C-arylation of 1,3-diones using anthranilic acid and isoamylnitrite at 60 ^{o}C in presence of transition metal catalyst CuBr and trichloroacetic acid.[17]



Scheme 2. Insertion of aryne

Leake *et al.* reported phenylation of dialkyl malonates using bromobenzene and sodium amide in poor yields.[18] In this context we have developed a mild, chemoselective α-arylation of malonamide esters.

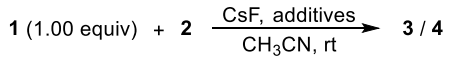
2.1.6 Results and Discussion:



Scheme 3. Initial studies on arylation using arynes

Our methodology began with the hypothesis of formation of **3a** by reacting malonamide ester **1** with benzyne precursor **2** (Scheme 3). We were able to isolate two compounds and it was confirmed that product **3** and **4** were formed instead of **3a**. Interestingly such one pot diarylation of α-aryl malonates is very much difficult and rare in literature. Due to high impotance of α-aryl malonates and challenges in their synthesis as reported in the literature, we shifted our plan from annulation of malonamide esters with aryne to arylation of maloanimde estres. For this purpose initially we focussed on achieving exclusive diarylated compound **4**.

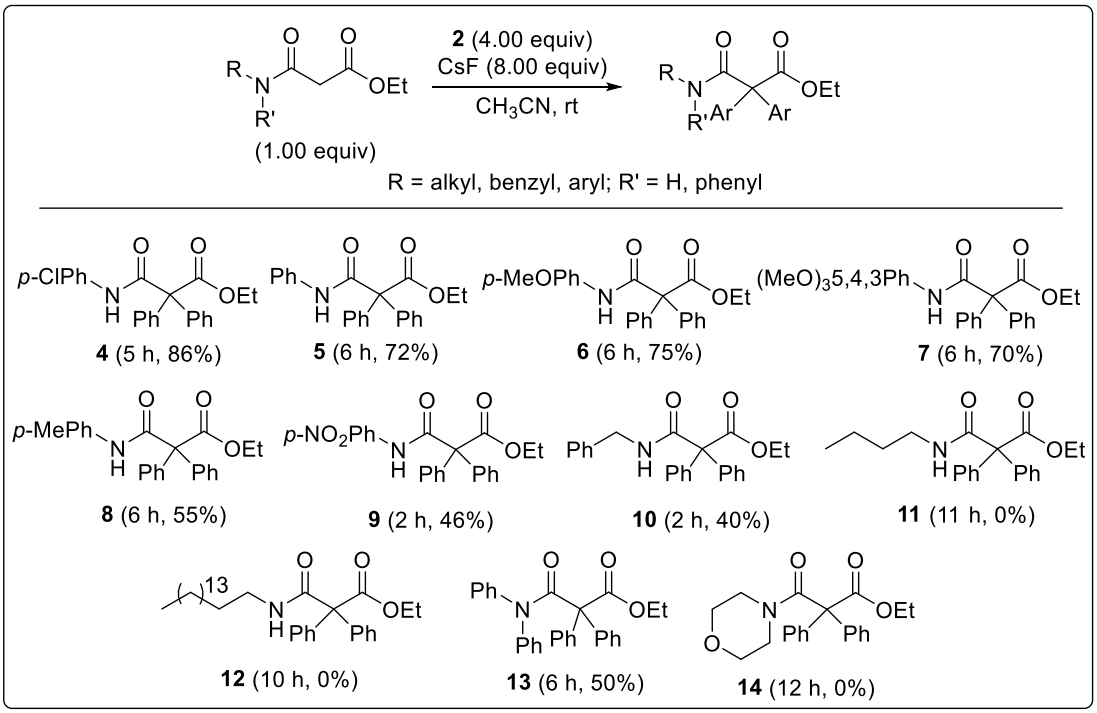
Table 1. Optimization of the arylation protocol



entry	**2** (equiv)	CsF (equiv)	additives (equiv)	time (h)	**3**/**4** yield (%)
1	2.00	6.00	$NaHCO_3$ (1.0)	06	5/25
2	2.00	8.00	$NaHCO_3$ (1.0)	20	7/26
3	2.00	4.00	$NaHCO_3$ (1.0)	24	10/20
4	2.00	12.00	TEA (1.0)	12	5/55
5	4.00	5.00	TEA (1.0)	13	30/5
6	4.00	6.00	TEA (1.0)	12	35/5
7	4.00	6.00	TEA (1.0)	48	35/5
8	2.50	15.00	–	04	0/70
9	3.30	16.50	–	04	0/75
10	4.00	8.00	–	05	0/86
11	4.00	8.00	18-crown-6 (2.0)	06	5/63

We began our optimization studies by reacting **2** (2.00 equiv) with **1** (1.00 equiv) in the presence of base $NaHCO_3$, but the condition provided 5/25 % yield of **3** and **4** respectively (Table 1, entry 1) and unreacted ester **1**. Further, by increasing the amount of CsF (Table 1, entry 2) no significant changes in the yield was observed. The conversion of **3** to **4** decreased when 4.00 equiv of CsF was employed (Table 1, entry 3). The use of organic base TEA and increasing the equivalent of CsF increased the exclusive diarylated compound **4** formation. To our delight we obsereved the maximum yield of expected product **4** (55%) alongwith 5 % monoaryled compound **3** (Table 1, entry 4). After decreasing the stoichiometric amount of CsF (Table 1, entries 4-7) the conversion of **3** to **4** decreased drastically. Finally involvement of base was avoided, however 15 equivalent of CsF was employed (Table 1, entry 7) and gratifyingly **1** and **2** were completely consumed within four hours providing 70% yield of product **4**. It was observed that by increasing equivalent of aryne precursor **2** high yield of the expected product **4** was observed. Further optimizations provided the best reaction condition (Table1, entry 10), which

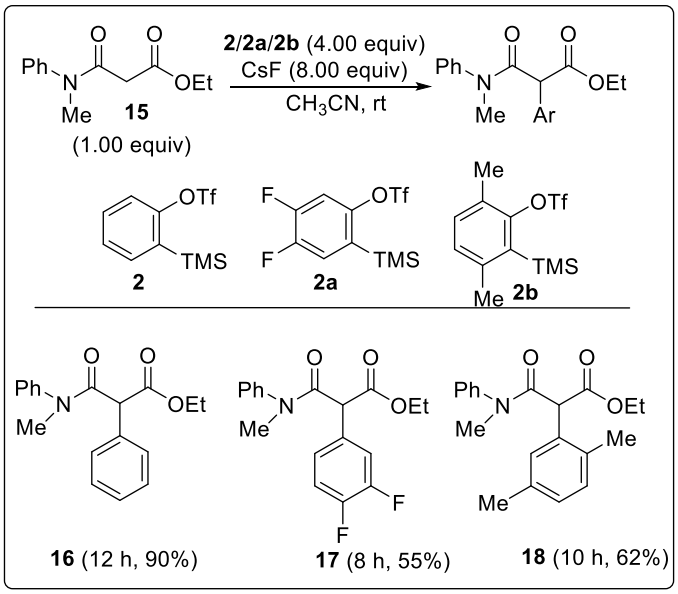
gave exclusively product **4** in high yields (86%). The use of 18-crown-6 ether (Table 1, entry 11) led to deterioration of yield of the product **4** giving only 63% yield alongwith 5% of monoaryled product **3**.



Scheme 4. Screening of malonamide esters

Having optimized condition in our hand our next target was to check the compatibility of the optimized protocol on various malonamide esters. The malonamide esters containing primary aromatic amines (Scheme 4) were tested. For unsubstituted phenylmalonamide ester the corresponding diarylated product **5** was obtained in 72% yield. The electron rich *p*-methoxyphenylmalonamide ester and 3,4,5-trimethoxyphenylmalonamide ester provided the expected diarylated products **6** and **7** in 75% and 70% yield. *p*-Toludinemalonamide ester afforded only 55% yield of the di-arylated product **8**. There was no strong support for low yield of *p*-toludinemalonamide ester. The reaction rate for *p*-nitrophenylmalonamide ester was fast compared to other substituted phenylmalonamide, but yield of diarylated compound **9** was only

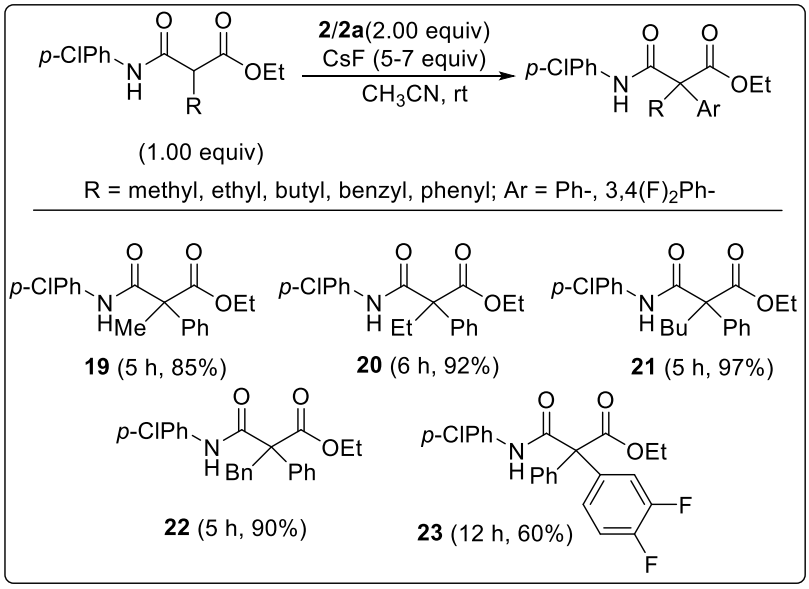
46% yield. The same observation was found for malonamide ester containing benzylamine which was quite reactive but provided the expected diarylated product **10** in only 40% yield. We tested the optimized protocol on primary and secondary alkylmalonamide esters but they were unreactive and failed to furnish the expected diarylated compounds **11, 12** and **14**. The diphenylmalonamide ester was also employed which was less reactive and provided only 50% yield of the diaryl product **13**.



Scheme 5. Substrate scope for selective monoarylation

After successful diarylation on substituted phenylmalonamide ester, we tested the optimized protocol on *N*-Methylphenylmalonamide ester and interestingly we observed exclusive formation of monoarylated product **16** (Scheme 5) in 90% yield. The sequential diarylation was observed for secondary phenylmalonamide ester probably, becasue the basicity of seconday amine group plays crucial role in abstracting the acidic proton of active methylene after first arylation. Accordingly, the acidity of methylene protons in the malonamide ester **15** is finely balanced in between mono/dialkyl malonamides and aryl malonomides, which probably results into selective mono arylation. Further difluoroaryne precursor **2a** was reacted with **15** under the same

condition and to our delight, we could isolate mono-arylated product **17** in 55% yield. The dimethyl aryne **2b** precursor smoothly reacted producing **18** in 62% yield.



Scheme 6. Generation of quaternary sterocenters

Our next objective was the generation of racemic quaternary stereocenters, via arylation protocol, which are found in several important molecules in medicinal applications and in many natural products.[19] The synthesis of quaternary stereocentres is a challenging job in organic chemistry.[20] The α-substituted malonamide esters[21] containing *p*-chloroaniline was selected for arylation (Scheme 6). The α-methyl substituted malonamide esters when treated with **2**, excellent yield was observed for the corresponding arylated compound **19** in 85% yield. Further quantitative yields were obatined for the corresponding α-ethyl, butyl substituted substrate providing **20** and **21** in 92% and 97%. The arylation of α-benzyl substituted malonamide ester provided expected product **22** in excellent yield. The optimized protocol was also tested on 3,4-difluorinated aryne precursor **2a** and α-phenyl substituted substrate, which provided **23** in 60% yield.

All the compounds synthesized by this methodology are new and novel analogues of these compounds are very well known sedative-tranquillizers.[22] The compounds synthesized in scheme 5 are important precursors to CNS depressant drugs barbiturates. Similarly a library of such compounds can be prepared for SAR studies.

2.1.7 Conclusion:

In conclusion, we have disclosed the application of aryne chemistry for the α-arylation of α-substituted/ unsubstituted malonamide esters. The preferential chemo-selective C-arylation over the N-arylation/aryne insertion into C–N σ-bond, formation of selective mono- or di- arylated products and an easy access to compounds containing benzylic quaternary stereocenters is noteworthy. Application of the present methodology to the total synthesis of drugs and bioactive natural products is in progress in our laboratory.

Interestingly, our work presented in this chapter and publication has been cited 25 times in the literature. A similar type of work has been reported by Rodriguez and Mohanan group. [23]

2.1.8 Experimental Procedures:

[A] General Experimental Procedure for the preparation of diarylated/monoarylated compounds:

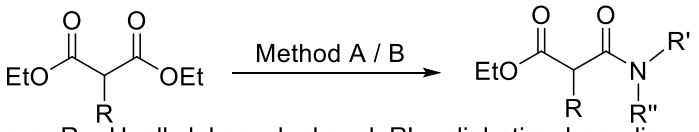
To a dried CsF (8.00/5.00-7.00equiv) in a two necked flame dried round bottom flask was added *o*-silyl triflate (4.00/2.00 equiv) in acetonitrile (0.5 mL) then malonamide ester (1.00 equiv) in acetonitrile (0.5 mL) was added under Argon atmosphere. The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, acetonitrile was removed on rotary evaporator and the crude reaction mixture was purified on flash silica gel column using a gradient of Ethyl Acetate-Pet. ether to afford the desired product diarylated/monoarylated compounds.

[B] Typical Experimental Procedure for the preparation of 4:

To a dried CsF (99 mg, 0.65 mmol, 8.00 equiv) in a two necked flame dried round bottom flask was added *o*-silyl triflate **2** (98 mg, 0.33 mmol, 4.00 equiv) in acetonitrile (0.5 mL) then malonamide ester **1** (20 mg, 0.082 mmol, 1.00 equiv) in acetonitrile (0.5 mL) was added under Argon atmosphere. The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, acetonitrile was removed on rotary evaporator and the crude reaction mixture was purified on flash silica gel column using a gradient of Ethyl Acetate-Pet. ether to afford the desired product **4**. Reaction time: 6 hrs, R*f* : 0.76 (1:4, EtOAc:Pet. Ether), white solid (32 mg, 86%).

[C] Malonamide esters synthesis (methods A/B):

Most of the known malonamide esters were either purchased or prepared by using one of the following methods.[24a-d]



Where, R = H, alkyl, benzyl, phenyl; R' = aliphatics, benzylic, aromatics; R'' = H, aliphatics, phenyl

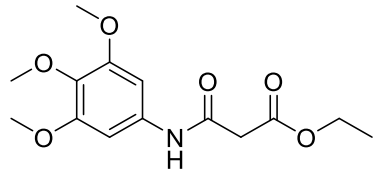
Method A: amine, 100-130 ^{o}C. Method B: a) i) THF/aq. KOH (1.00 equiv), 0 ^{o}C, ii) H_3O^+; b) $SOCl_2$; c) amine, $(Et)_3N$

The crude products obtained after performing both the methods were directly loaded on silica gel column and purified by using mixture of ethyl acetate and petroleum ether as eluents.

2.1.9 Characterization Data:

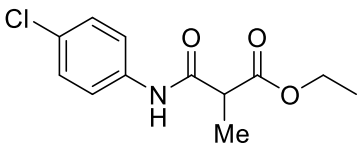
Selected entries data has been represented. The data of all the compounds is available in published paper.

Ethyl 3-oxo-3-(3,4,5-trimethoxyphenylamino)propanoate (Starting material used in **Scheme 4**):



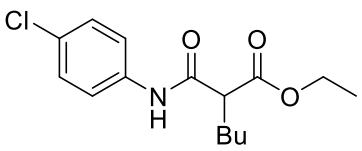
Reaction time: 24 hrs, R*f* : (1:1, EtOAc:Pet. Ether). Off white solid, 70%. m.p. 104-106°C; IR ($CHCl_3$) ν_{max} = 3339, 3019, 1719, 1682, 1607, 1551, 1415, 1216, 756 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 9.19 (bs, 1H), 6.85 (s, 2H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 6H), 3.79 (s, 3H), 3.45 (s, 2H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 169.7, 162.9, 153.1, 134.5, 133.6, 97.5, 61.8, 60.8, 55.9, 41.6, 13.9. HRMS-ESI (*m/z*) calcd [$C_{14}H_{19}O_6N+H]^+$: 298.1285; found: 298.1276.

Ethyl 3-(4-chlorophenylamino)-2-methyl-3-oxopropanoate (Starting material used in **Scheme 6**):



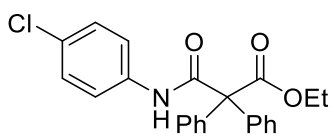
Reaction time: 24 hrs, R*f* : (1:1, EtOAc:Pet. Ether). Off white solid, 80%. m.p. 87-89°C; IR ($CHCl_3$) ν_{max} = 3422, 3020, 1719, 1597, 1538, 1400, 1216, 758 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ 8.83 (bs, 1H), 7.49 (d, *J* = 8.9 Hz, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.44 (q, *J* = 7.3 Hz, 1H), 1.53 (d, *J* = 7.3 Hz, 3H) 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 172.6, 167.2, 136.2, 129.3, 128.9, 121.2, 61.9, 47.3, 15.3, 13.9. HRMS-ESI (*m/z*) calcd [$C_{12}H_{14}O_3NCl+H]^+$: 256.0735; found: 256.0732.

Ethyl 2-(4-chlorophenylcarbamoyl)hexanoate (Starting material used in **Scheme 6**):



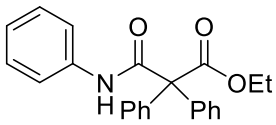
Reaction time: 30 hrs, R*f* : (1:1, EtOAc:Pet. Ether). White solid, 75%. m.p. 94-96°C; IR ($CHCl_3$) ν_{max} = 3333, 3019, 1714, 1688, 1596, 1537, 1400, 1215, 1026 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 8.87 (bs, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 4.32-4.19 (m, 2H), 3.35 (t, *J* = 7.3 Hz, 1H), 2.00 (q, *J* = 7.0 Hz, 2H) 1.43-1.27 (m, 7H), 0.91 (t, *J* = 6.0 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 172.9, 166.7, 136.2, 129.3, 128.9, 121.2, 61.8, 53.5, 31.5, 29.3, 22.2, 14.0, 13.7 . HRMS-ESI (*m/z*) calcd [$C_{15}H_{20}O_3NCl+H]^+$: 298.1204; found: 298.1201.

Ethyl 3-(4-chlorophenylamino)-3-oxo-2,2-diphenylpropanoate (**4**):



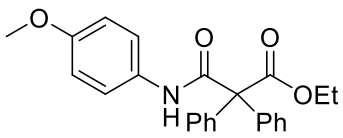
Reaction time: 5 hrs, R*f* : 0.76 (1:4, EtOAc:Pet. Ether). White solid, 86%. m.p. 108-110 ^{o}C; IR ($CHCl_3$) ν_{max} = 3325, 3019, 1714, 1679, 1594, 1215, 757 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ 10.07 (bs, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.31-7.25 (m, 6H), 7.22-7.17 (m, 6H), 4.24 (q, *J* = 7.3 Hz, 2H), 1.14 (t, *J* = 7.3 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 173.9, 167.7, 139.1, 136.4, 129.3, 128.9, 128.2, 127.9, 121.2, 69.6, 62.8, 13.8. HRMS-ESI (*m/z*) calcd for $[C_{23}H_{20}ClNO_3+Na]^+$: 416.1030; found: 416.1018.

Ethyl 3-oxo-2,2-diphenyl-3-(phenylamino)propanoate (**5**):



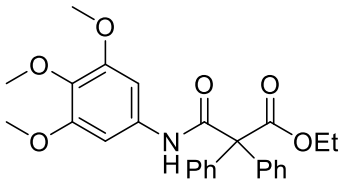
Reaction Time: 6 hrs, R*f* : 0.75 (1:4, EtOAc:Pet. Ether). Yellow thick oil, 72%; IR ($CHCl_3$) ν_{max} = 3404, 3297, 3062, 1714, 1680, 1598, 1238, 755, 694 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 10 (bs, 1H), 7.61 (d, *J* = 7.7 Hz, 2H), 7.41-7.28 (m, 12H), 7.12 (t, *J* = 7.7 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 2H), 1.24 (t, *J* = 7.0, 3H), ^{13}CMR (100 MHz, $CDCl_3$, TMS) δ: 173.7, 167.6, 139.2, 137.8, 129.4, 128.9, 128.2, 127.8, 124.4, 119.9, 69.7, 62.7, 13.8. HRMS-ESI (*m/z*) calcd for $[C_{23}H_{21}NO_3+Na]^+$: 382.1419; found: 382.1407.

Ethyl 3-(4-methoxyphenylamino)-3-oxo-2,2-diphenylpropanoate (**6**):



Reaction Time: 6 hrs, R*f* : 0.64 (1:4, EtOAc:Pet. Ether). White Solid, 75%. m.p. 89-91 ^{o}C; IR ($CHCl_3$) ν_{max} = 3327, 3020, 1713, 1674, 1599, 1216, 1036, 755cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 9.85 (bs, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.40-7.28 (m, 10H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 173.7, 167.3, 156.4, 139.3, 131.1, 129.4, 128.1, 127.7, 121.5, 114.0, 69.5, 62.6, 55.5, 13.8. HRMS-ESI (*m/z*) calcd for $[C_{24}H_{23}NO_4+Na]^+$: 412.1525; found: 412.1509.

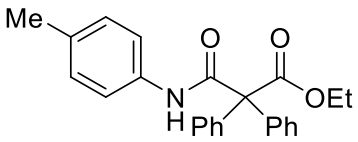
Ethyl 3-oxo-2,2-diphenyl-3-(3,4,5-trimethoxyphenylamino)propanoate (**7**):



Reaction Time: 6 hrs, R*f* : 0.73 (1:4, EtOAc:Pet. Ether). Off White Solid, 70%. m.p. 109-111 ^{o}C; IR ($CHCl_3$) ν_{max} = 3298, 3018, 1713, 1675, 1604, 1216, 756 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 10.18 (bs, 1H), 7.41-7.34 (m, 6H), 7.31-7.26 (m, 4H), 6.96 (s, 2H), 4.34 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (100 MHz,

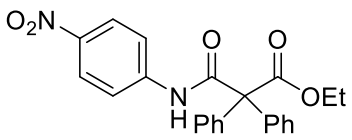
$CDCl_3$, TMS): δ 174.2, 167.5, 153.3, 139.1, 134.6, 134.1, 129.3, 128.2, 127.8, 97.2, 69.6, 62.8, 60.9, 56.1, 13.7. HRMS-ESI (*m/z*) calcd for $[C_{26}H_{27}NO_6+Na]^+$: 472.1736; found: 472.1723.

Ethyl 3-oxo-2,2-diphenyl-3-(p-tolylamino)propanoate (**8**):



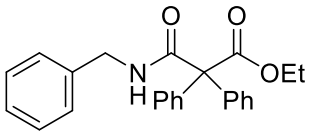
Reaction Time: 6 hrs, R*f* : 0.71 (1:4, EtOAc:Pet. Ether). White Solid, 55%. m.p. 88-90 ^oC; IR ($CHCl_3$) ν_{max} = 3325, 3017, 1713, 1679, 1596, 1216, 815, 755 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 9.89 (bs, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.40-7.28 (m, 10H), 7.13 (d, *J* = 8.2 Hz, 2H), 4.33 (q, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 1.24 (t, *J* = 7.3 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 173.7, 167.4, 139.3, 135.3, 134.0, 129.4, 129.3, 128.1, 127.7, 119.9, 69.6, 62.6, 20.8, 13.8. HRMS-ESI (*m/z*) calcd for $[C_{24}H_{23}NO_3+Na]^+$: 396.1576; found: 396.1572.

Ethyl 3-(4-nitrophenylamino)-3-oxo-2,2-diphenylpropanoate (**9**):



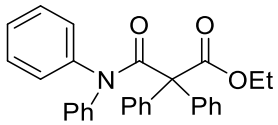
Reaction Time: 2 hrs, R*f* : 0.65 (1:4, EtOAc:Pet. Ether). Thick oil, 46%; IR ($CHCl_3$) ν_{max} = 3291, 3019, 1717, 1612, 1597, 1545, 1216, 853, 757 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 10.72 (bs, 1H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.42-7.36 (m, 6H), 7.31-7.25 (m, 4H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS) : δ 174.1, 168.5, 143.7, 143.6, 138.6, 129.2, 128.3, 128.1, 124.9, 119.6, 69.7, 63.1, 13.7. HRMS-ESI (*m/z*) calcd for $[C_{23}H_{20}N_2O_5+Na]^+$: 427.1270; found: 427.1260.

Ethyl 3-(benzylamino)-3-oxo-2,2-diphenylpropanoate (**10**):



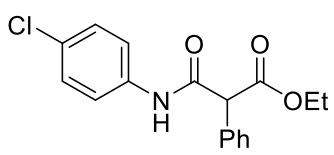
Reaction Time: 2 hrs, R*f* : 0.33 (1:9, EtOAc:Pet. Ether). Thick oil, 40%; IR ($CHCl_3$) ν_{max} = 3428, 3018, 1714, 1668, 1600, 1523, 1216, 756, 698, 668 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$, TMS): δ 8.00 (bs, 1H), 7.40-7.16 (m, 15H), 4.53 (d, *J* = 5.6 Hz, 2H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 172.9, 169.6, 139.5, 138.1, 129.5, 128.6, 128.0, 127.57, 127.55, 127.3, 69.2, 62.3, 43.9, 13.7. HRMS-ESI (*m/z*) calcd for $[C_{24}H_{23}NO_3+Na]^+$: 396.1576; found: 396.1572.

Ethyl 3-(diphenylamino)-3-oxo-2,2-diphenylpropanoate (13):



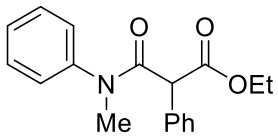
Reaction Time: 6 hrs, R*f* : 0.55 (1:4, EtOAc:Pet. Ether). Thick oil, 50%; IR ($CHCl_3$) ν_{max} = 3019, 1737, 1666, 1597, 1492, 1217, 754, 667 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ 7.47-7.41 (m, 4H), 7.28-7.22 (m, 7H), 7.20-6.65 (m, 9H), 4.13 (q, *J* = 7.0 Hz, 2H), 1.31(t, *J* = 7.0 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 169.8, 169.1, 139.6, 129.9, 128.8, 127.7, 127.3, 67.1, 61.6, 13.6. HRMS-ESI (*m/z*) calcd for $[C_{29}H_{25}NO_3+Na]^+$: 458.1732; found: 458.1731.

Ethyl 3-(4-chlorophenylamino)-3-oxo-2-phenylpropanoate (3):



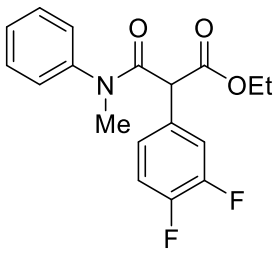
Reaction Time: 6 hrs, R*f* : 0.35(1:4, EtOAc:Pet. Ether). Thick oil, 5%; IR ($CHCl_3$) ν_{max} = 3419, 2925, 1715, 1680, 1596, 908, 732, 650 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ 9.19 (bs, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.40-7.32 (m, 3H), 7.25 (d, *J* = 8.8 Hz, 2H), 4.62 (s, 1H), 4.32-4.18 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 171.3, 165.2, 135.9, 133.8, 129.5, 129.2, 128.9, 128.5, 127.9, 121.2, 62.3, 58.7, 13.9. HRMS-ESI (*m/z*) calcd for $[C_{17}H_{16}ClNO_3+Na]^+$: 340.0717; found: 340.0701.

Ethyl 3-(methyl(phenyl)amino)-3-oxo-2-phenylpropanoate (16):



Reaction Time: 12 hrs, R*f* : 0.46 (1:4, EtOAc:Pet. Ether). Thick oil, 90%; IR ($CHCl_3$) ν_{max} = 3019, 1746, 1658, 1596, 1496, 1215, 756, 668 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$, TMS): δ 7.42-7.32 (m, 3H), 7.30-7.21 (m, 3H), 7.20-7.02 (m, 4H), 4.59 (s,1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.28 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 168.8, 167.8, 143.2, 133.5, 129.8, 129.4, 128.3, 128.2, 127.8, 127.7, 61.5, 55.7, 37.7, 14.0; HRMS-ESI (*m/z*) calcd for $[C_{18}H_{19}NO_3+Na]^+$: 320.1263; found: 320.1259.

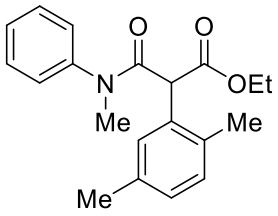
Ethyl 2-(3,4-difluorophenyl)-3-(methyl(phenyl)amino)-3-oxopropanoate (17):



Reaction Time: 8 hrs, R*f* : 0.25 (1:4, EtOAc:Pet. Ether). Thick oil, 55%; IR ($CHCl_3$) ν_{max} = 2933, 1748, 1661, 1596, 1279, 773, 701 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ 7.47-7.38 (m, 3H), 7.19-6.99 (m, 4H), 6.81-6.76 (m, 1H), 4.54 (s, 1H), 4.21-4.13 (m, 2H), 3.28 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 168.2, 167.3, 151.1, 149.1,

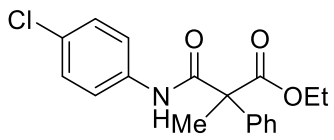
143.1, 130.4, 130.0, 128.6, 127.8, 125.6, (118.8, 118.7), (116.9, 116.8), 61.9, 54.6, 37.8, 14.0. HRMS-ESI (*m/z*) calcd for $[C_{18}H_{17}F_2NO_3+Na]^+$: 356.1074; found: 356.1056.

Ethyl 2-(2,5-dimethylphenyl)-3-(methyl(phenyl)amino)-3-oxopropanoate (18)



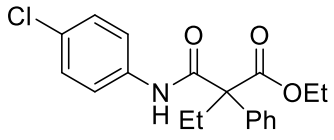
Reaction Time: 10 hrs, R*f* : 0.40 (1:4, EtOAc:Pet. Ether). Thick oil, 62%; IR ($CHCl_3$) ν_{max} = 3020, 1745, 1655, 1596, 1230, 760, 668 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ 7.34-7.29 (m, 4H), 7.02-6.93 (m, 3H), 6.87 (d, *J* = 7.3 Hz, 1H), 4.71 (s, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.29 (s, 3H), 2.32 (s, 3H), 1.58 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 169.0, 168.3, 143.2, 135.6, 132.8, 132.2, 129.9, 129.7, 129.5, 128.5, 128.1 127.8, 61.5, 52.8, 37.8, 21.1, 18.5, 14.1. HRMS-ESI (*m/z*) calcd for $[C_{20}H_{23}NO_3+Na]^+$: 348.1576; found: 348.1561.

Ethyl 3-(4-chlorophenylamino)-2-methyl-3-oxo-2-phenylpropanoate (19):



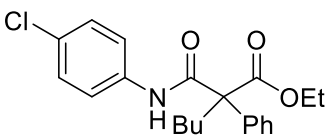
Reaction Time: 5 hrs, R*f* : 0.60 (1:4, EtOAc:Pet. Ether). White Solid, 85%. M.p. 104-106 ^oC; IR ($CHCl_3$) ν_{max} = 3410, 3019, 1709, 1681, 1595, 1215, 773, 669 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 8.87 (bs,1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.40-7.30 (m, 5H), 7.26 (d, *J* = 8.7 Hz, 2H), 4.32 (q, *J* = 7.32 Hz, 2H), 1.88 (s, 3H), 1.32 (t, *J* = 7.3, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 173.8, 168.6, 140.6, 136.3, 129.4, 129.02, 128.9, 127.9, 126.4, 121.1, 62.4, 59.9, 22.9, 13.9. HRMS-ESI (*m/z*) calcd for $[C_{18}H_{18}ClNO_3+Na]^+$: 354.0873; found: 354.0854.

Ethyl 2-(4-chlorophenylcarbamoyl)-2-phenylbutanoate (20):



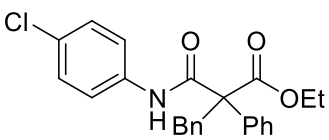
Reaction Time: 6 hrs, R*f* : 0.60 (1:4, EtOAc:Pet. Ether). Yellow thick oil, 92%; IR ($CHCl_3$) ν_{max} = 3286, 3019, 1712, 1676, 1594, 1492, 1216, 756, 668 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ 10.28 (bs, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.38-7.32 (m, 4H), 7.31-7.25 (m, 3H), 4.35-4.19 (m, 2H), 2.72 (ddd, *J* = 7.3 Hz, 1H), 2.34 (ddd, *J* = 7.3 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.0 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 174.7, 168.2, 139.5, 136.5, 129.3, 128.9, 128.8, 127.8, 126.5, 121.3, 63.3, 62.2, 28.7, 13.9, 10.2. HRMS-ESI (*m/z*) calcd for $[C_{19}H_{20}ClNO_3+Na]^+$: 368.1030; found: 368.1010.

Ethyl 2-(4-chlorophenylcarbamoyl)-2-phenylhexanoate (**21**):



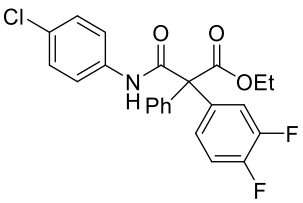
Reaction Time: 5 hrs, R*f* : 0.73 (1:4, EtOAc:Pet. Ether). Yellow thick oil, 97%; IR ($CHCl_3$) ν_{max} = 3320, 3286, 3019, 2962, 1711, 1594, 1215, 757, 668 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$, TMS): δ 10.40 (bs, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.40-7.20 (m, 7H), 4.40-4.10 (m, 2H), 2.67 (ddd, *J* = 4.0 Hz, 1H), 2.29 (ddd, *J* = 4.0 Hz, 1H), 1.50-1.30 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.6 Hz, 3H); ^{13}CMR (125 MHz, $CDCl_3$, TMS): δ 174.9, 168.3, 139.6, 136.4, 129.2, 128.9, 128.8, 127.8, 126.5, 121.3, 62.4, 62.1, 35.3, 27.9, 23.0, 13.87, 13.85. HRMS-ESI (*m/z*) calcd for $[C_{21}H_{24}ClNO_3+Na]^+$: 396.1343; found: 396.1323.

Ethyl 2-benzyl-3-(4-chlorophenylamino)-3-oxo-2-phenylpropanoate (**22**):



Reaction Time: 5 hrs, R*f* : 0.70 (1:4, EtOAc:Pet. Ether). White Solid, 90%. m.p. 83-85 ^oC; IR ($CHCl_3$) ν_{max} = 3289, 3019, 1715, 1671, 1594, 1215, 756, 669 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 10.33 (bs, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.42-7.10 (m, 12H), 4.25-4.13 (m, 3H), 3.57 (d, *J* = 13.0 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 174.2, 168.1, 139.5, 136.5, 136.3, 129.7, 129.4, 128.9, 128.8, 128.3, 127.9, 127.0, 126.5, 121.6, 63.4, 62.2, 40.9, 13.7. HRMS-ESI (*m/z*) calcd for $[C_{24}H_{22}ClNO_3+Na]^+$: 430.1186; found: 430.1167.

Ethyl 3-((4-chlorophenyl)amino)-2-(3,4-difluorophenyl)-3-oxo-2-phenylpropanoate (**23**):



Reaction Time: 5 hrs, R*f* : 0.70 (1:4, EtOAc:Pet. Ether). Thick oil, 60%; IR ($CHCl_3$) ν_{max} = 3292, 3019, 1716, 1595, 1216, 757, 668 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ 10.07 (bs, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.44-7.36 (m, 3H), 7.32-7.24 (m, 4H), 7.15-6.99 (m, 2H), 6.96-6.87 (m, 1H), 4.32 (q, *J* = 7.3 Hz, 2H), 1.23 (t, *J* = 7.3 Hz, 3H); ^{13}CMR (100 MHz, $CDCl_3$, TMS): δ 173.3, 167.0, (151.1, 150.96, 150.92, 150.8), (148.6, 148.5, 148.44, 148.38), 138.3, (136.23, 136.16), 129.7, 129.0, 128.8, 128.5, (125.96, 125.93, 125.91), 121.3, 119.4, 119.2, 116.6, 116.5, 68.8, 63.2, 13.8. HRMS-ESI (*m/z*) calcd for $[C_{23}H_{18}ClF_2NO_3+Na]^+$: 452.0841; found: 452.0820.

2.1.10 References:

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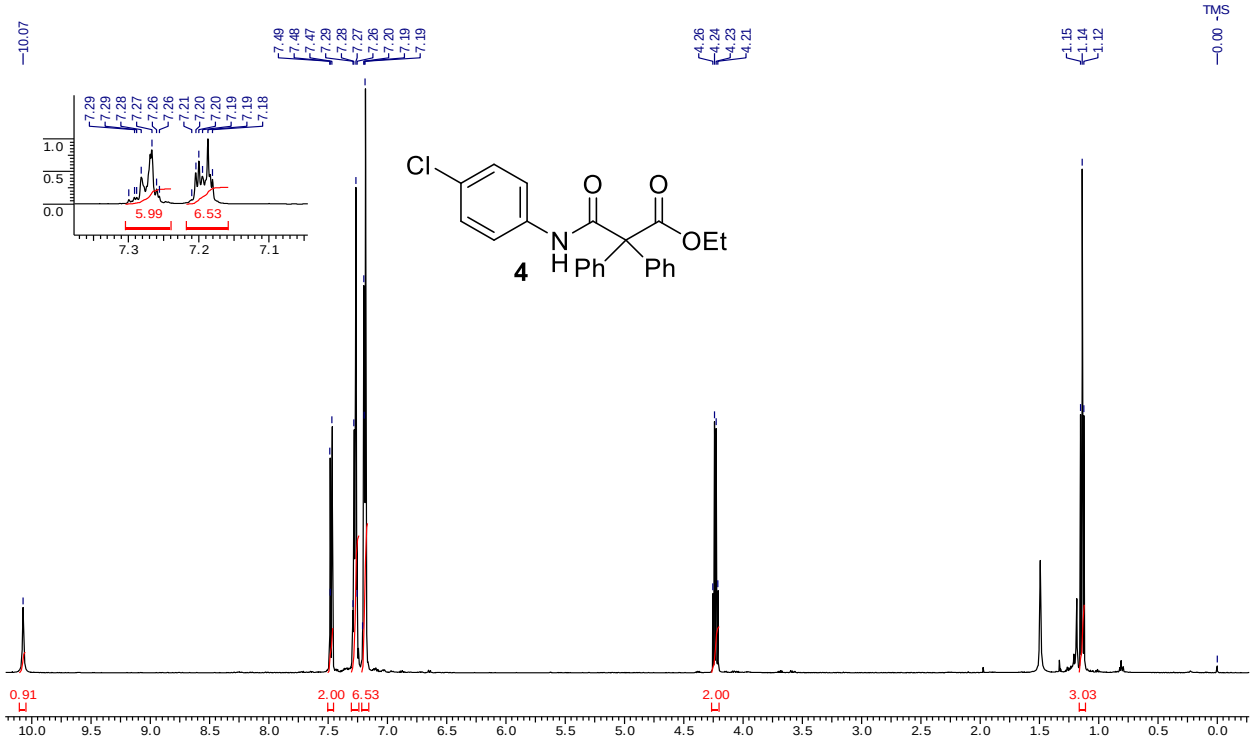
2.1.11 Selected Spectra

^{1}H NMR Spectra



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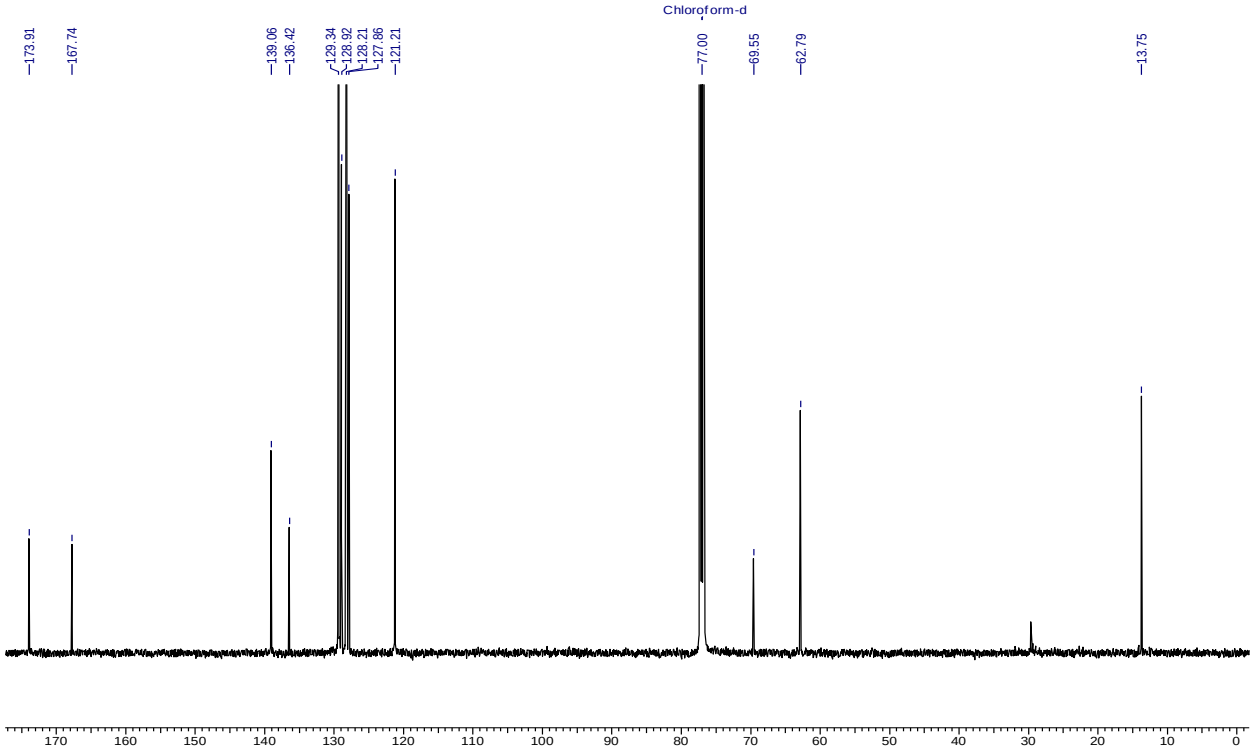

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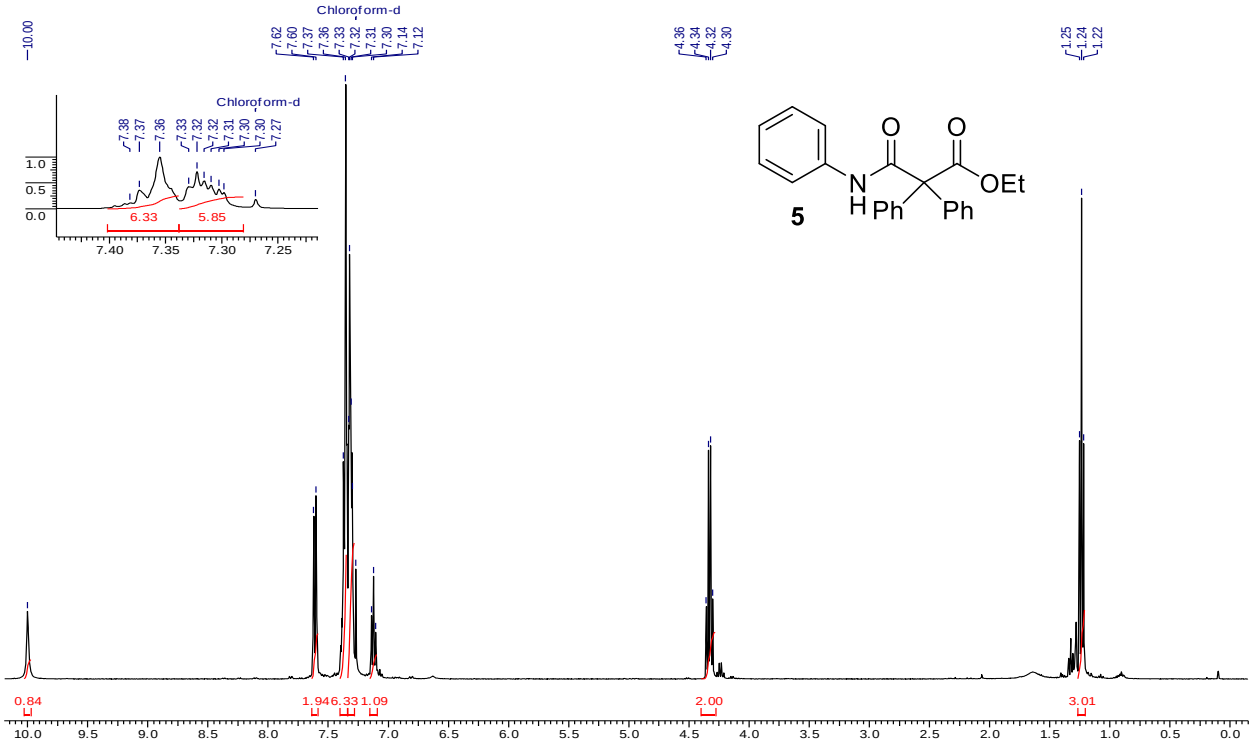

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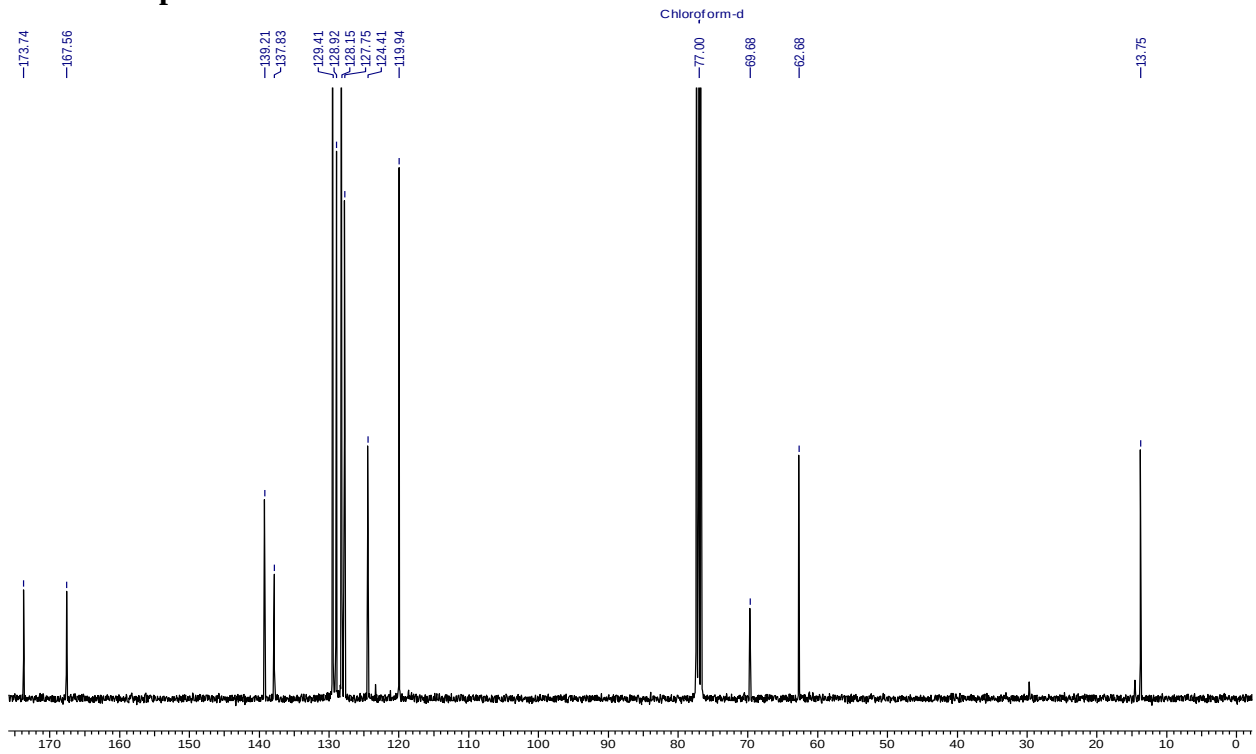

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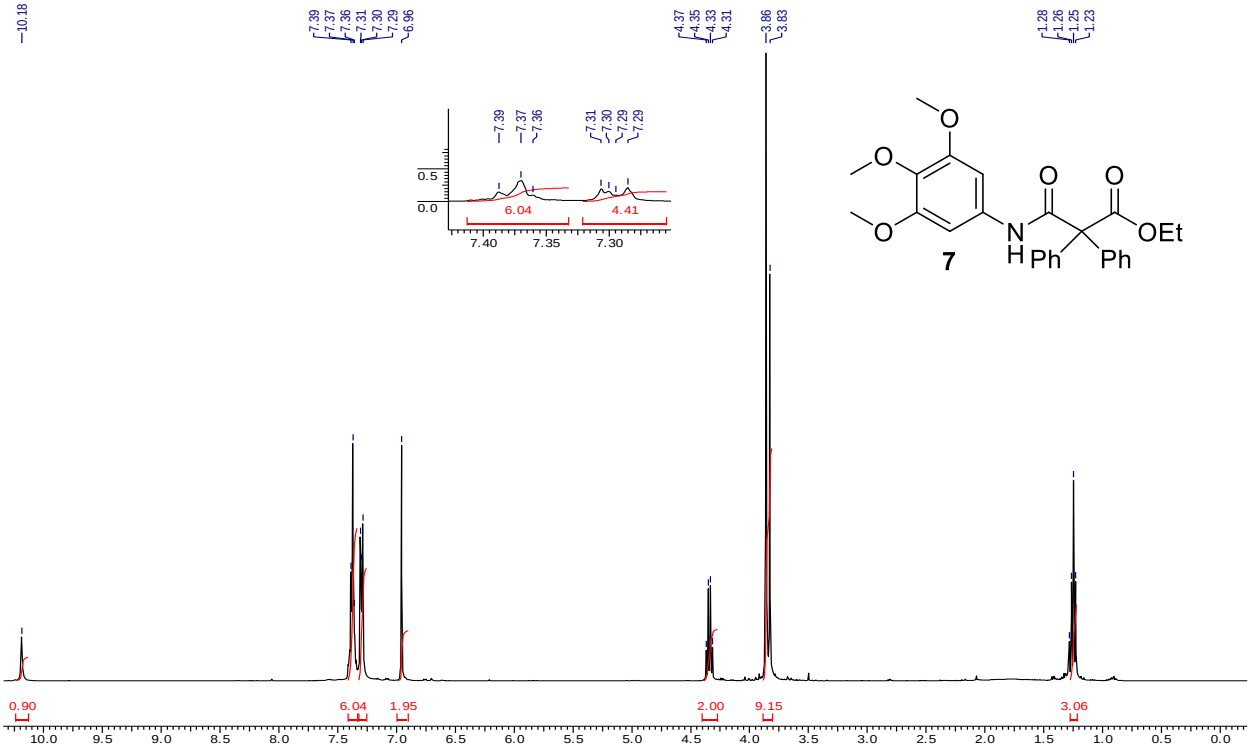

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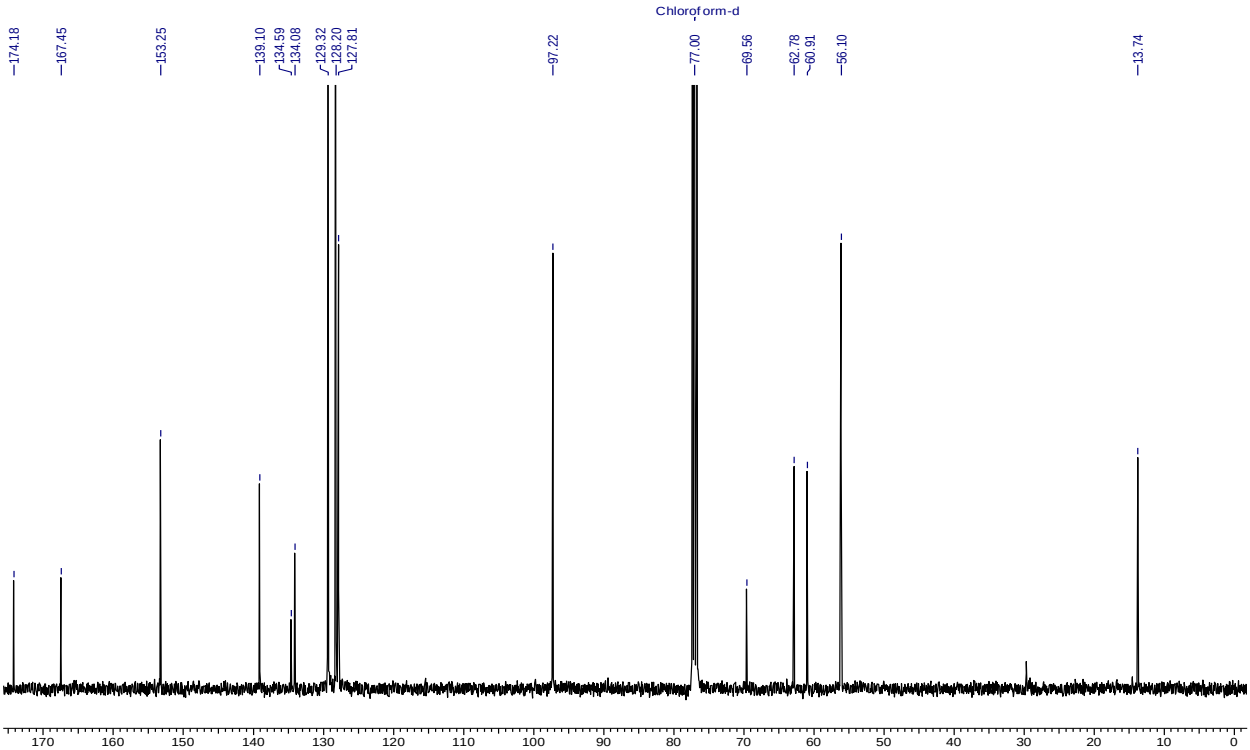

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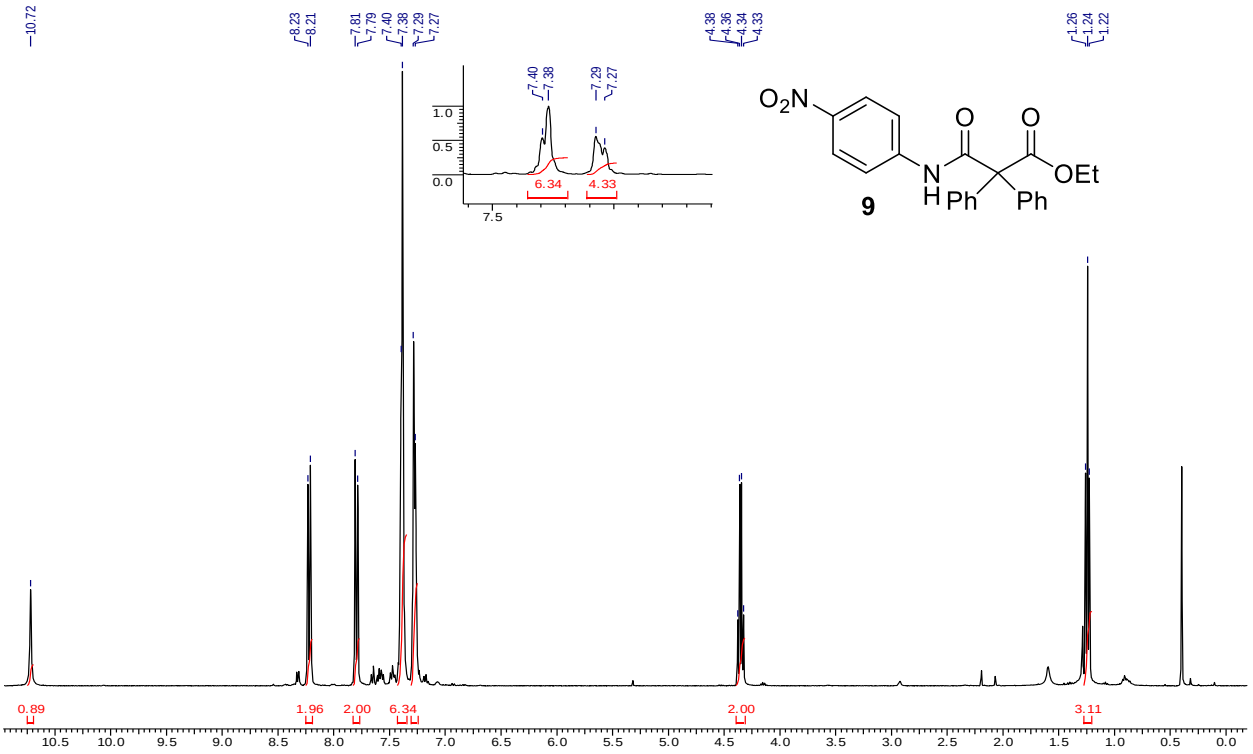

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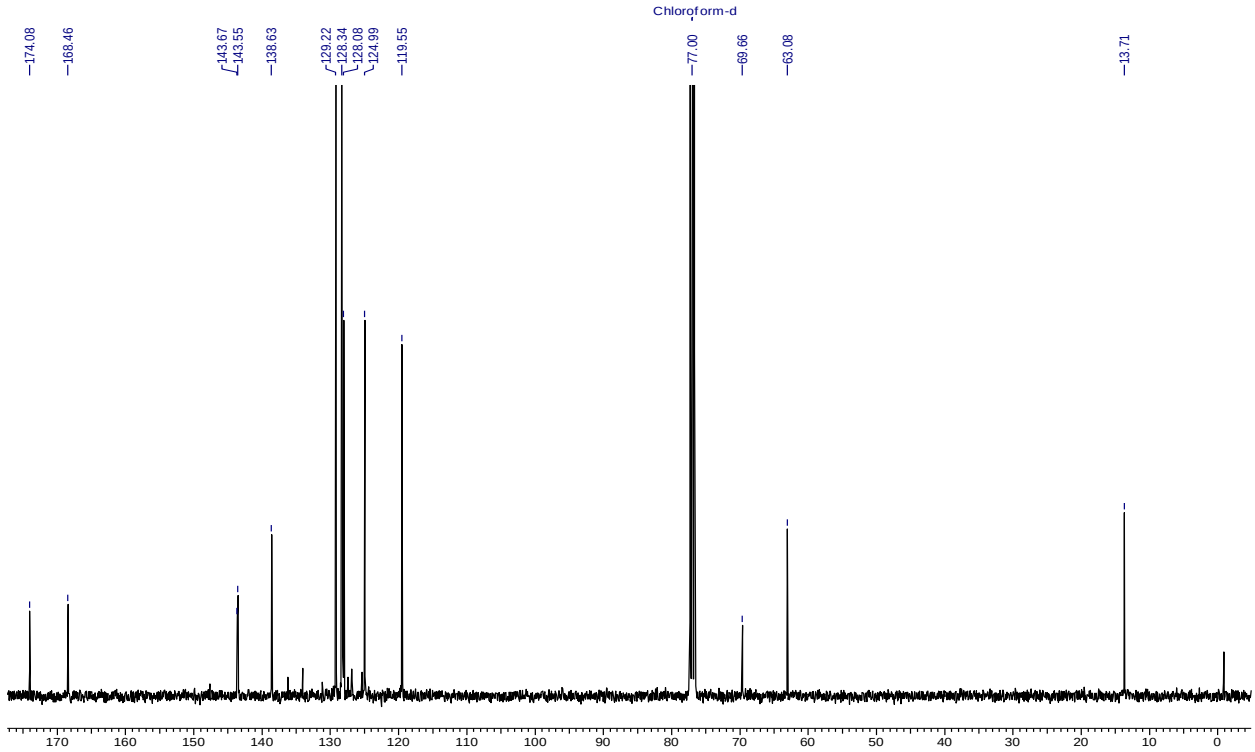

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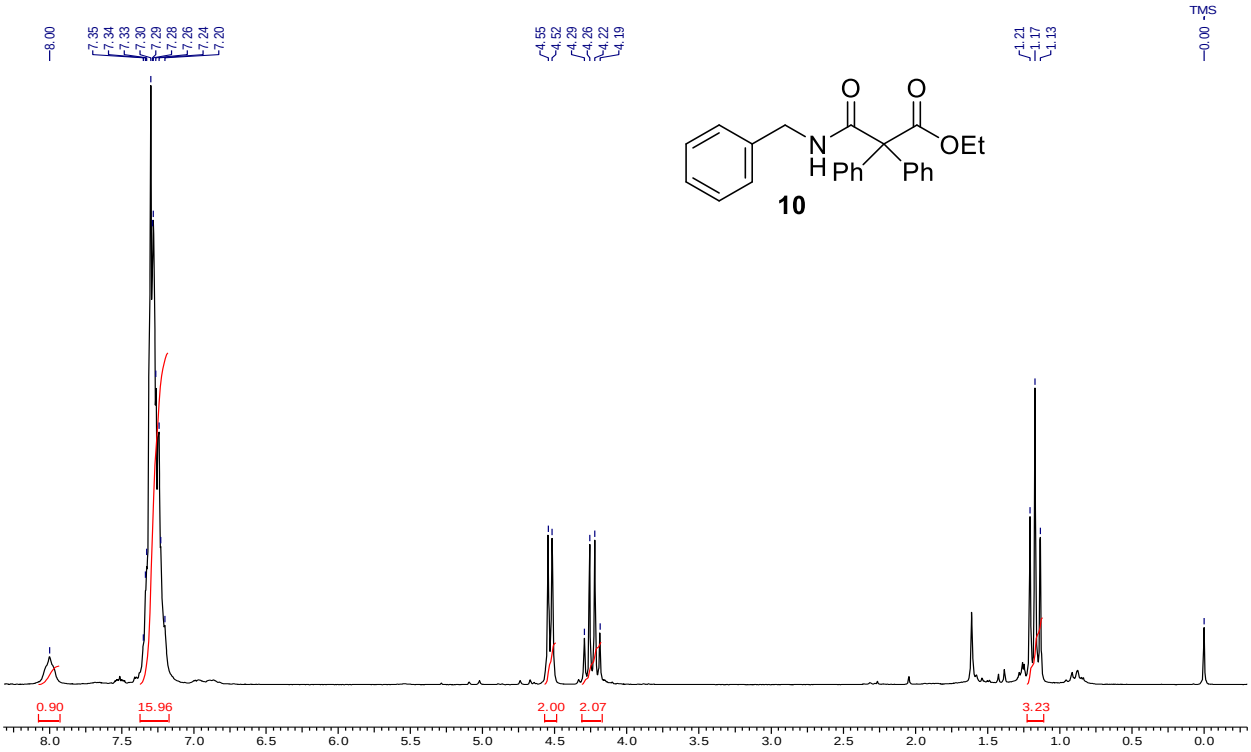

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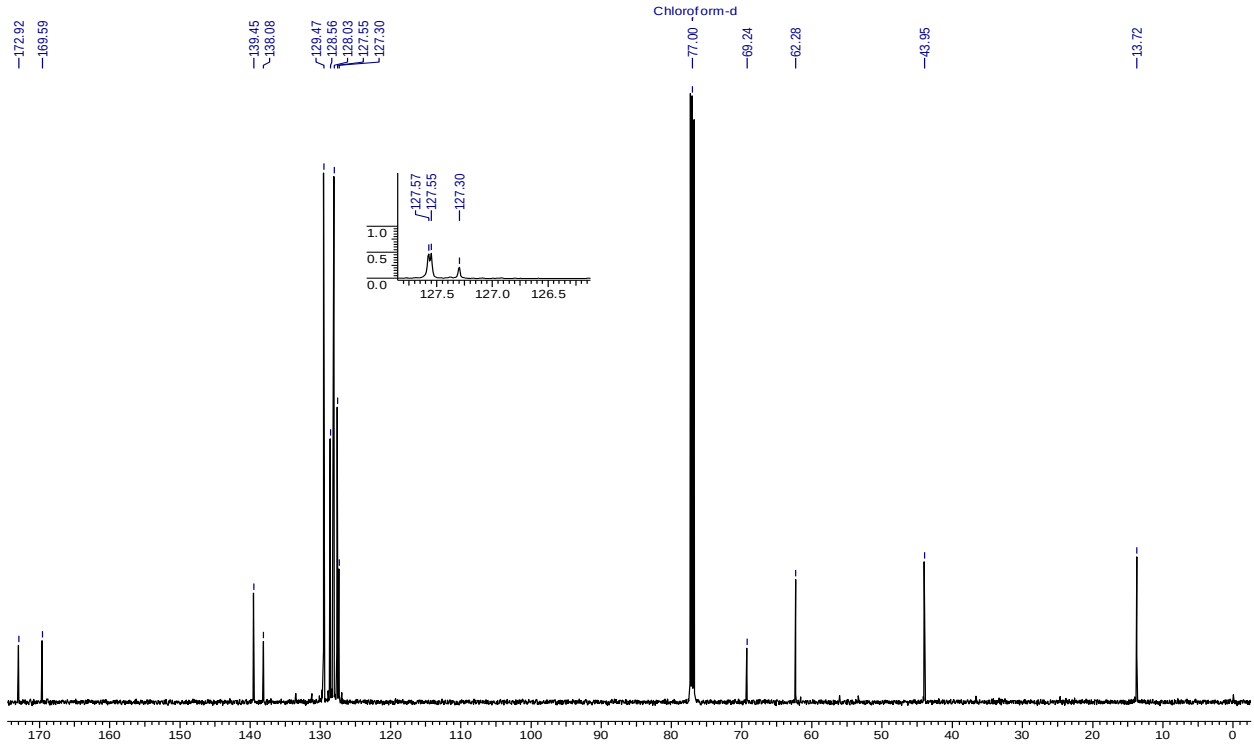

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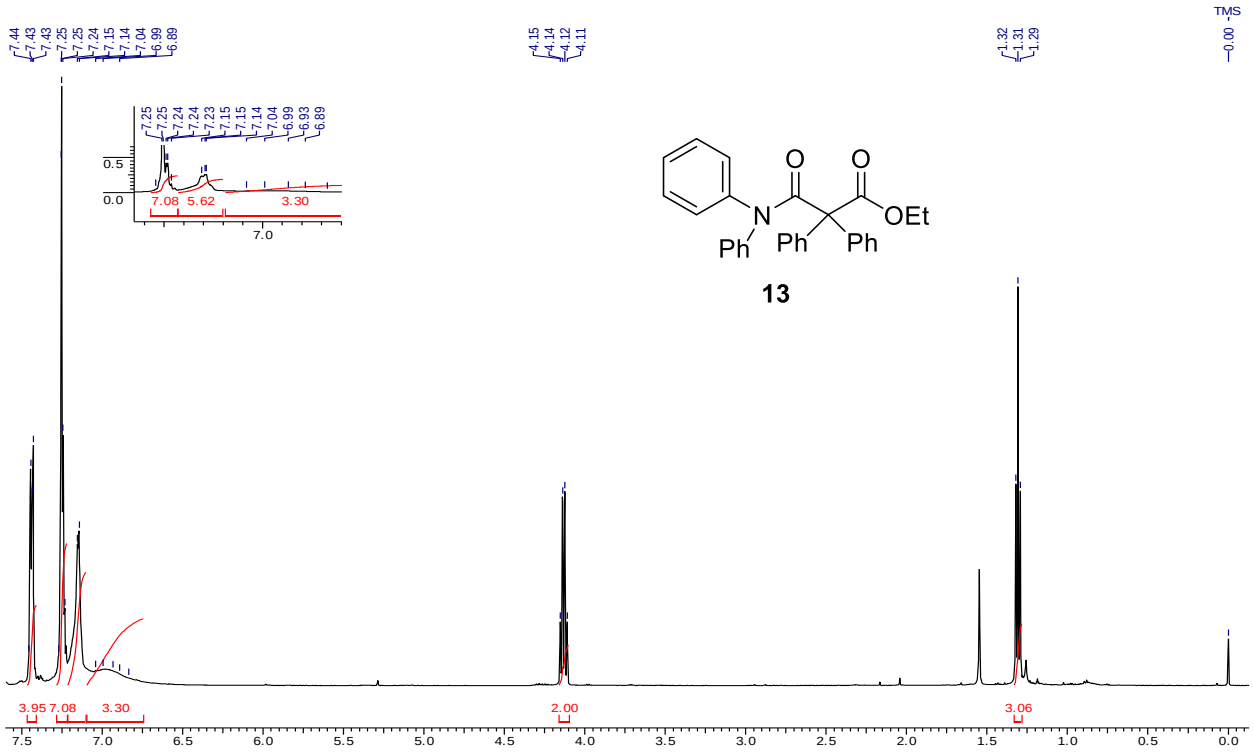

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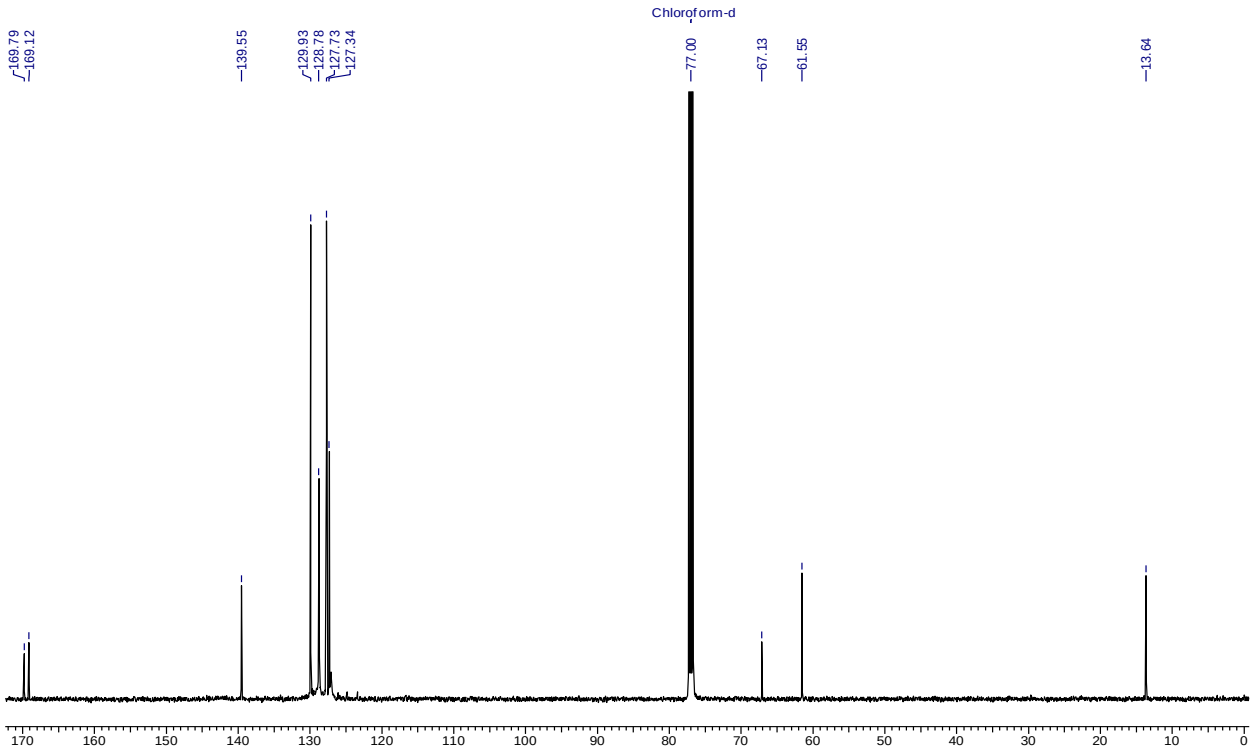
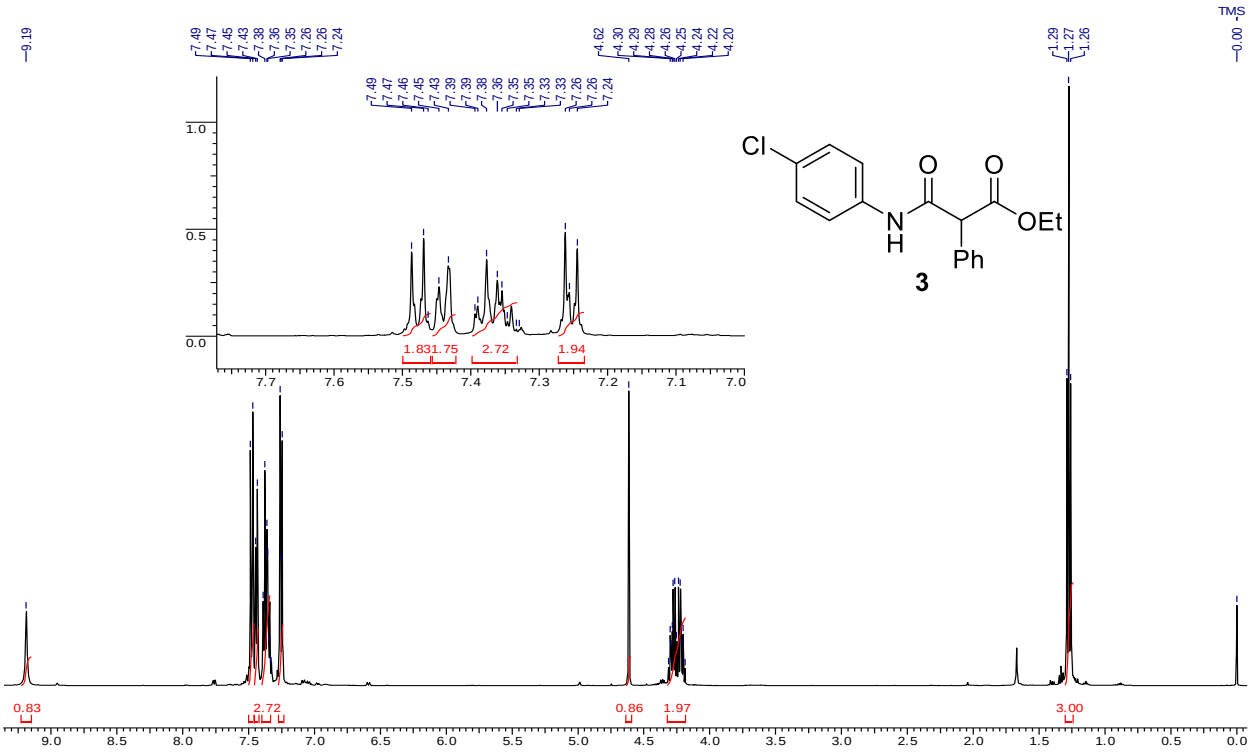
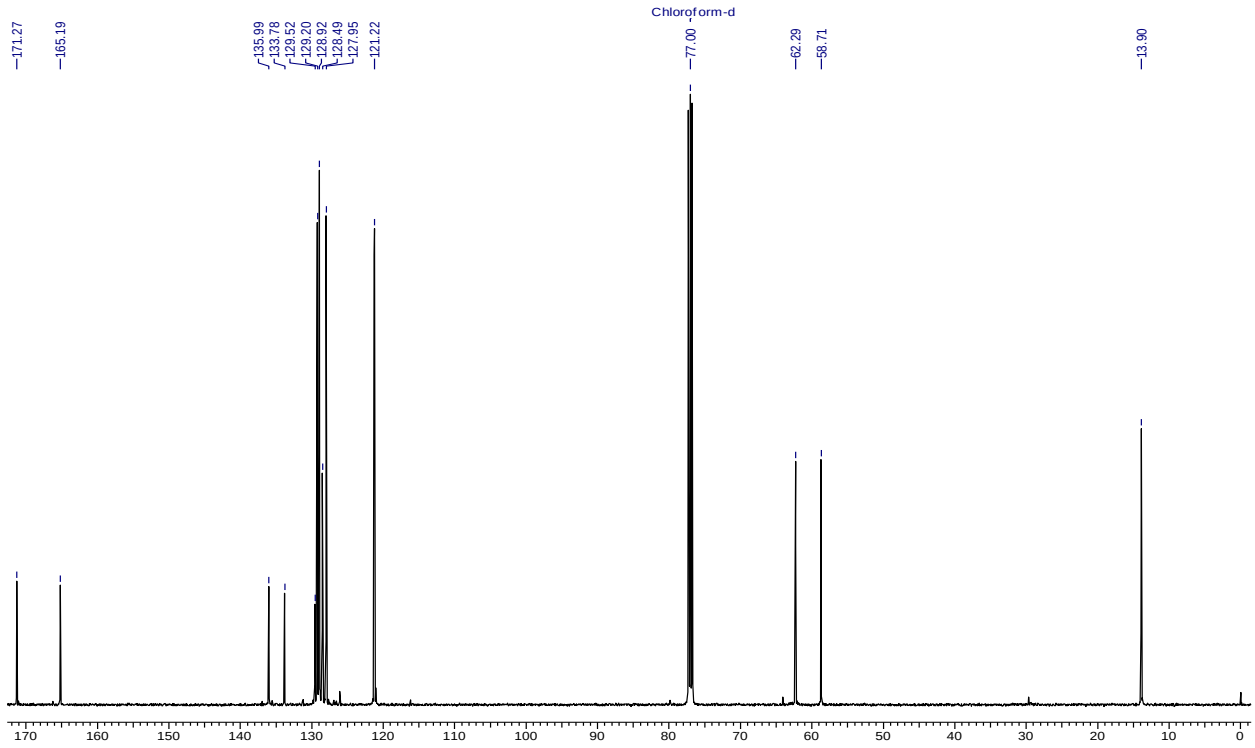


^{1}H NMR Spectra



^{13}C NMR Spectra



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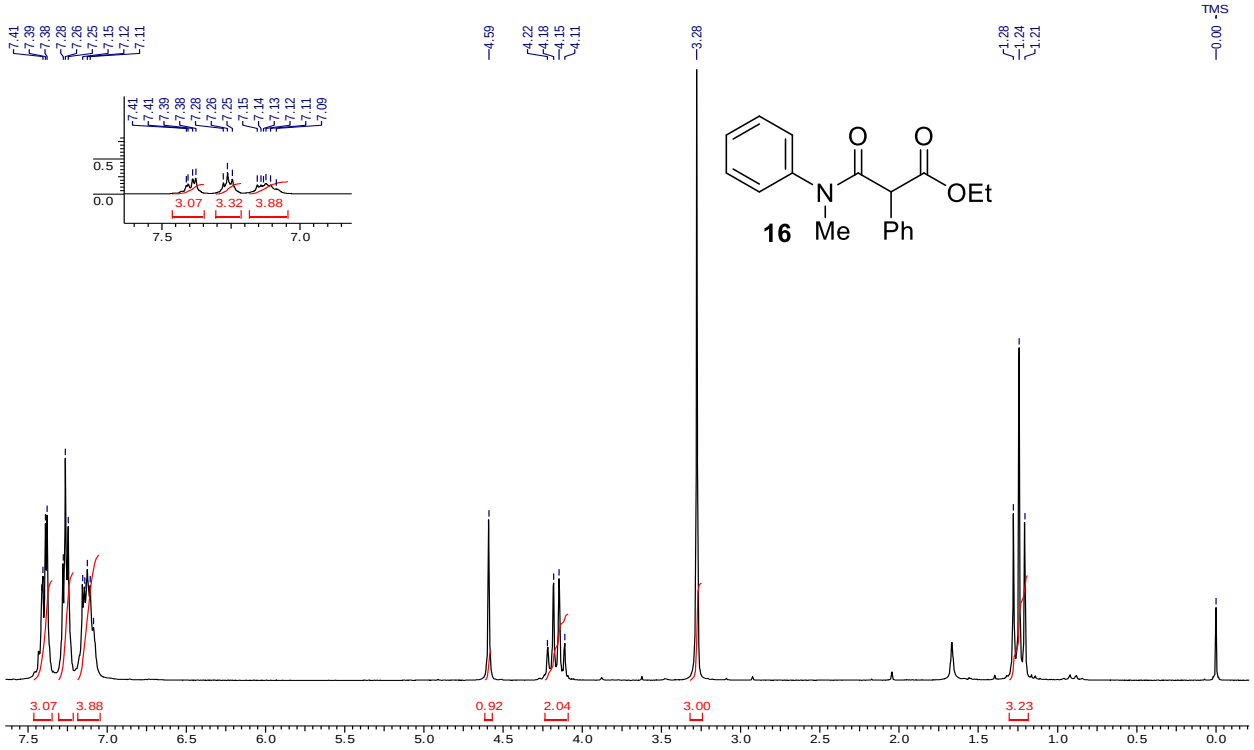

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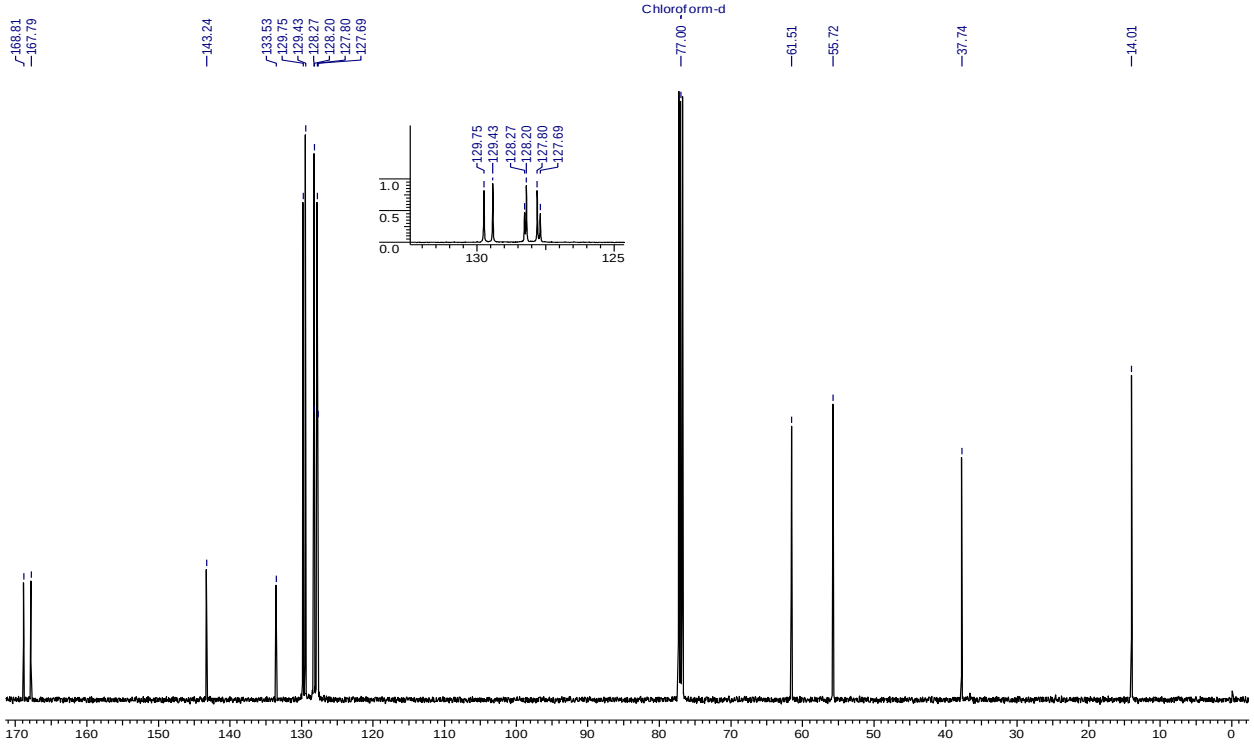

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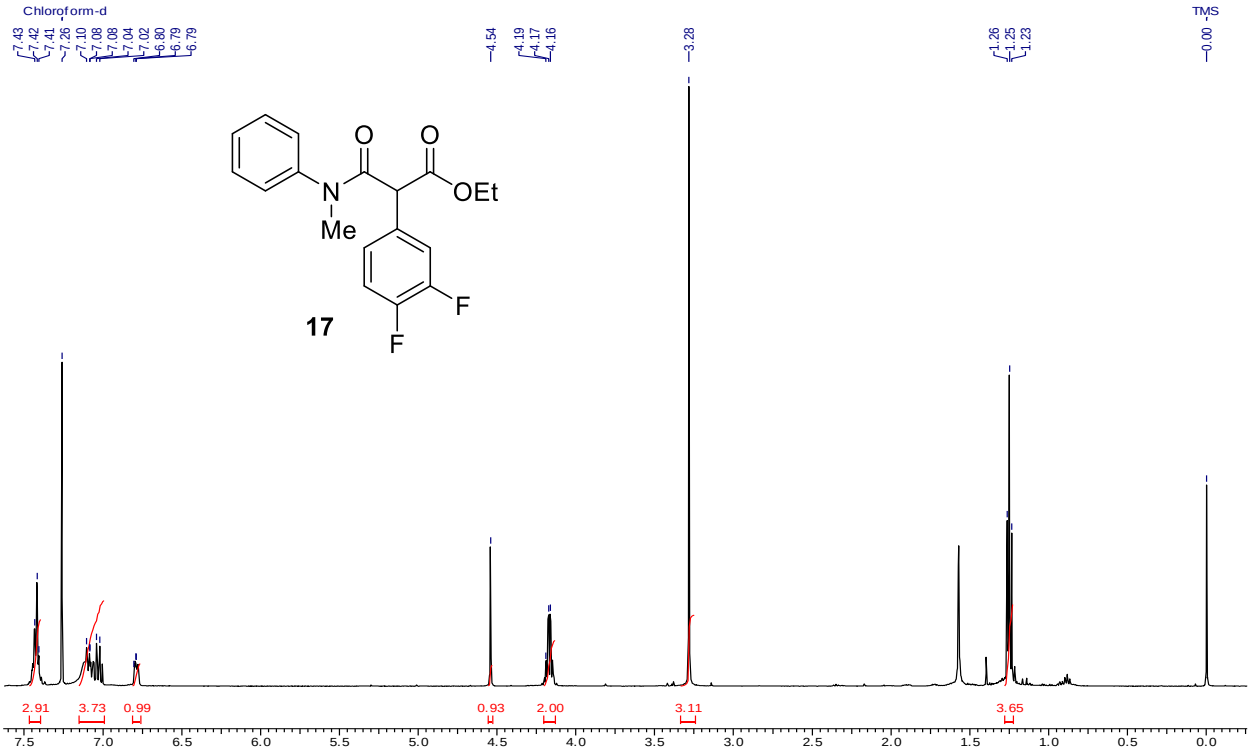

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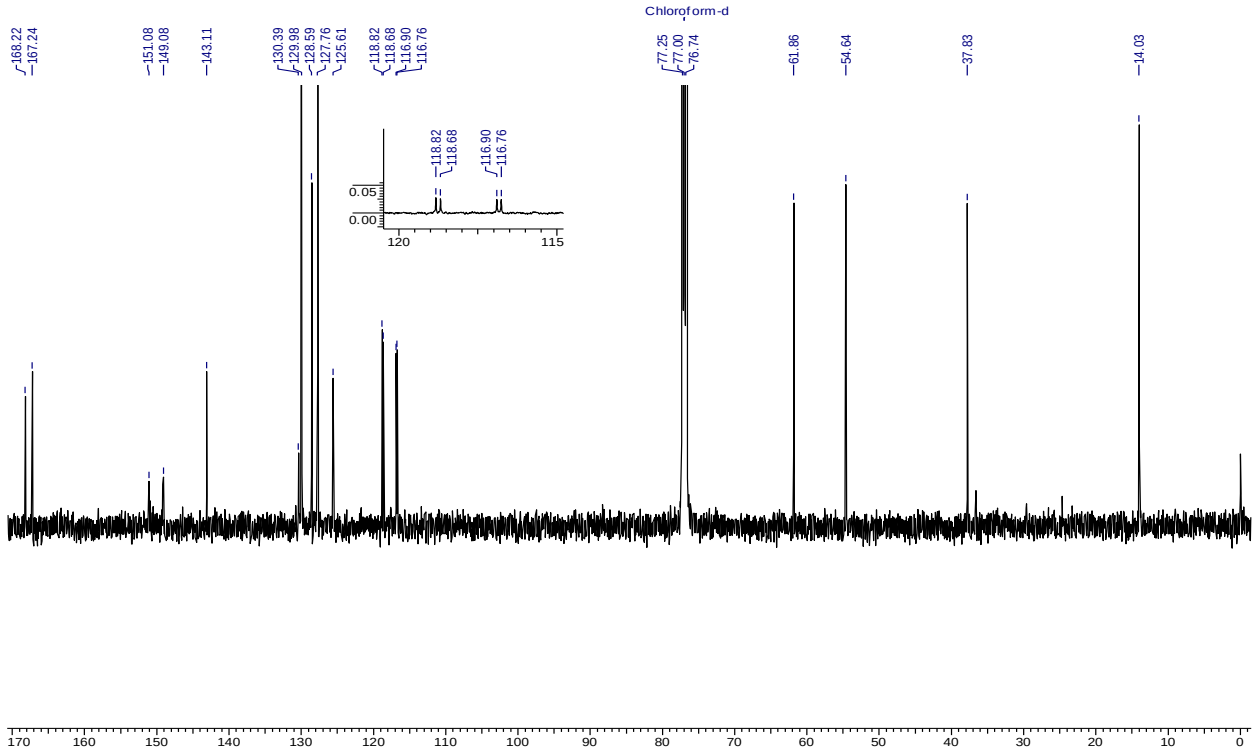

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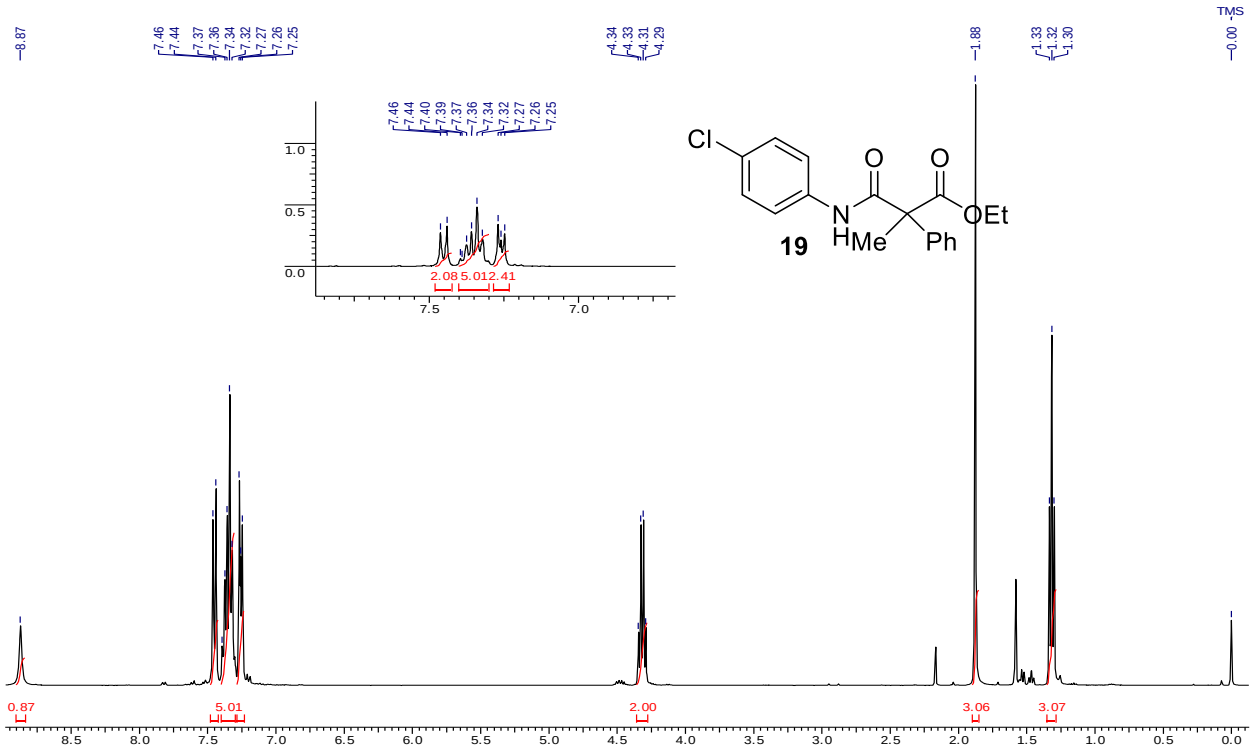
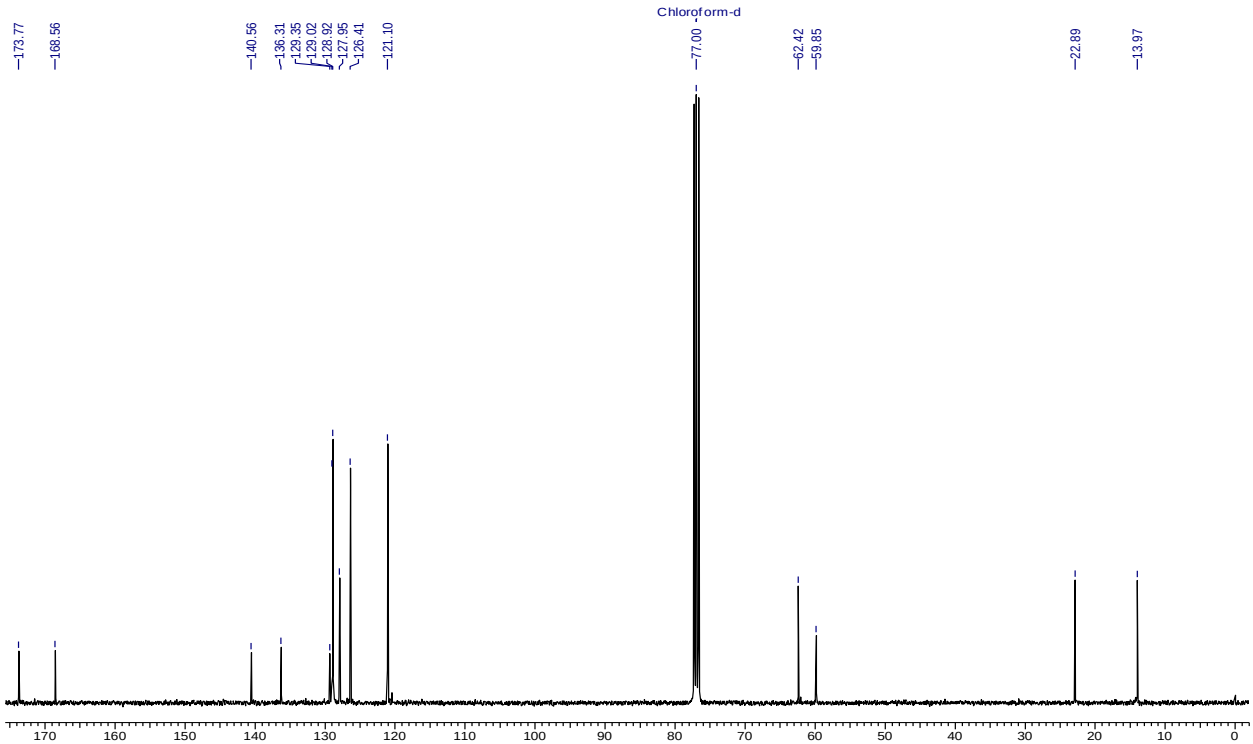


^{13}C NMR Spectra



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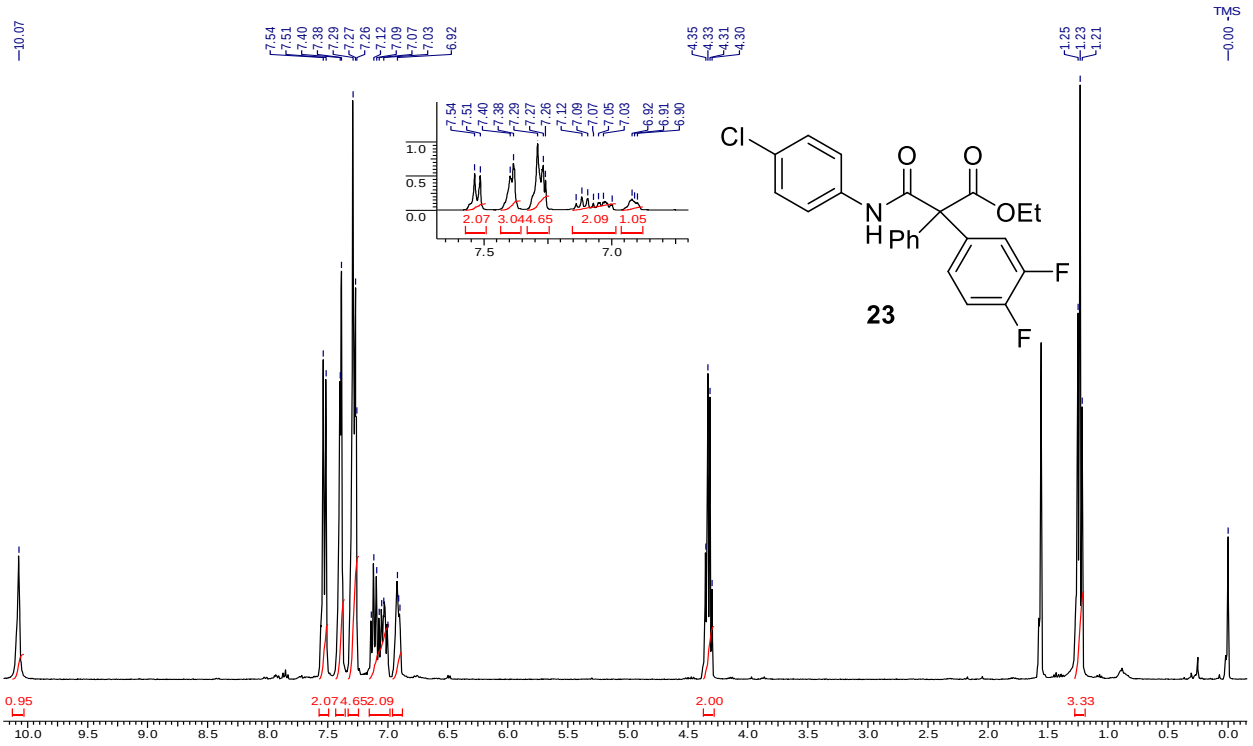
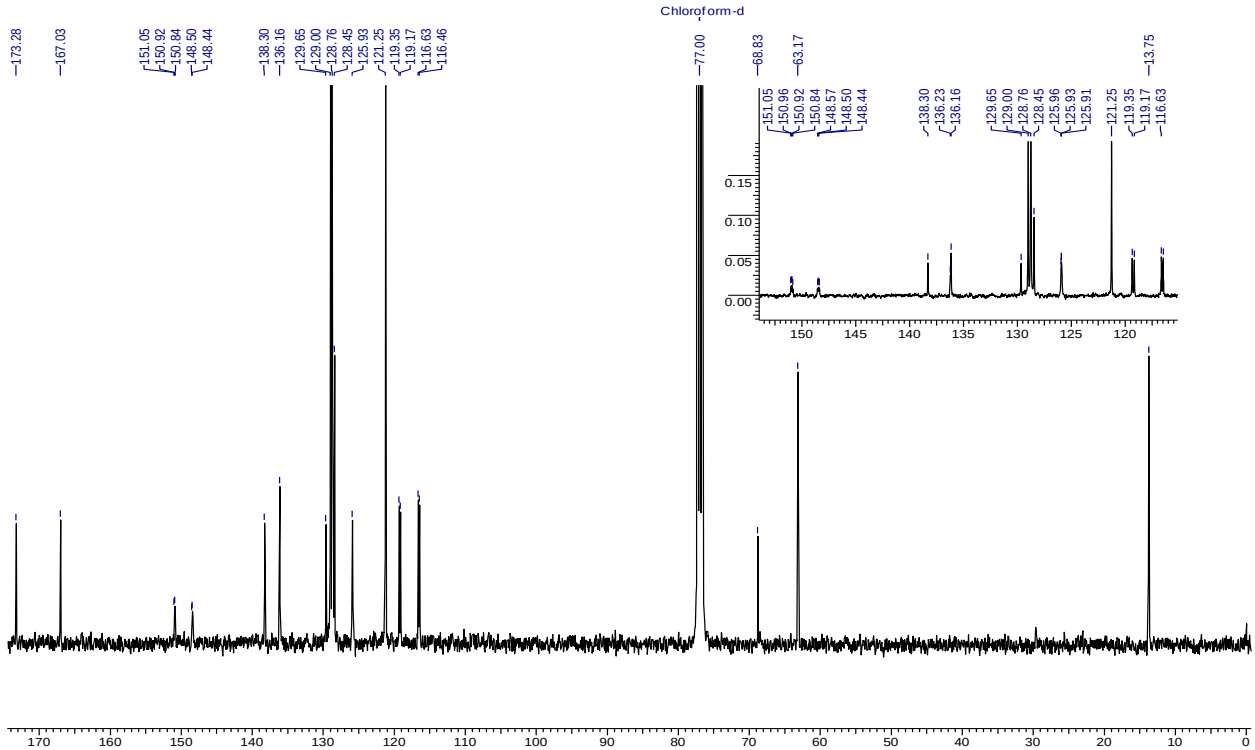


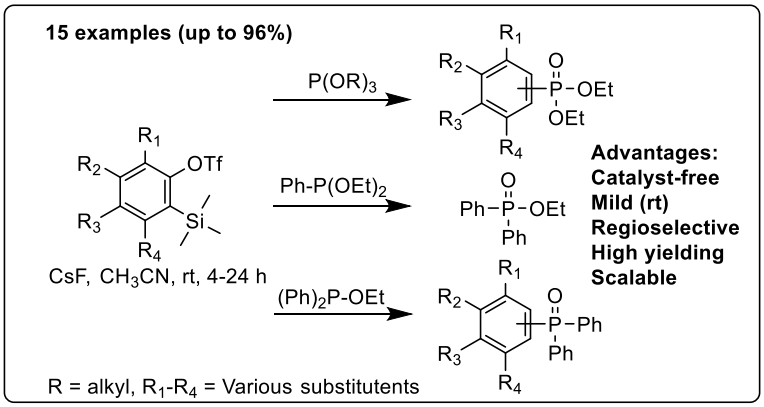
^{13}C NMR Spectra



Section 2: P-Arylation: Arynes to Aryl-Phosphonates, Phosphinates, and -Phosphine Oxides

2.2.1 Abstract:

This section covers the novel transition-metal-free C–P bond forming protocol using aryne chemistry, which provides organo-phosphorus compounds. The synthesis of such organo-phosphorus compounds and their application in organic synthesis and life sciences has been a topic of contemporary interest. Traditionally Michaelis-Arbuzov reaction is commonly used method for their preparation, but it is applicable for aliphatic halides. Whereas, the aryl phosphorous compounds are accessible via Arbuzov/Hirao reaction, which requires relatively harsh reaction conditions and transition-metal. We have successfully reported the synthesis of aryl phosphorous compounds by reacting alkyl phosphites, alkyl phenylphosphinite and alkyl diphenylphosphane with varyingly substituted aryne precursors, which afforded respective aryl phosphonates, phosphinates, phosphine oxides in good to excellent yields. This process has the ability to provide varyingly substituted novel phosphorous ligands. This naive process has been highlighted in the organic chemistry portal and also cited in the "Name Reaction" book by Professor Jie Jack Li.



This work has been published in *Org. Lett*. **2013**, *15*, 2218.

2.2.2 Introduction:

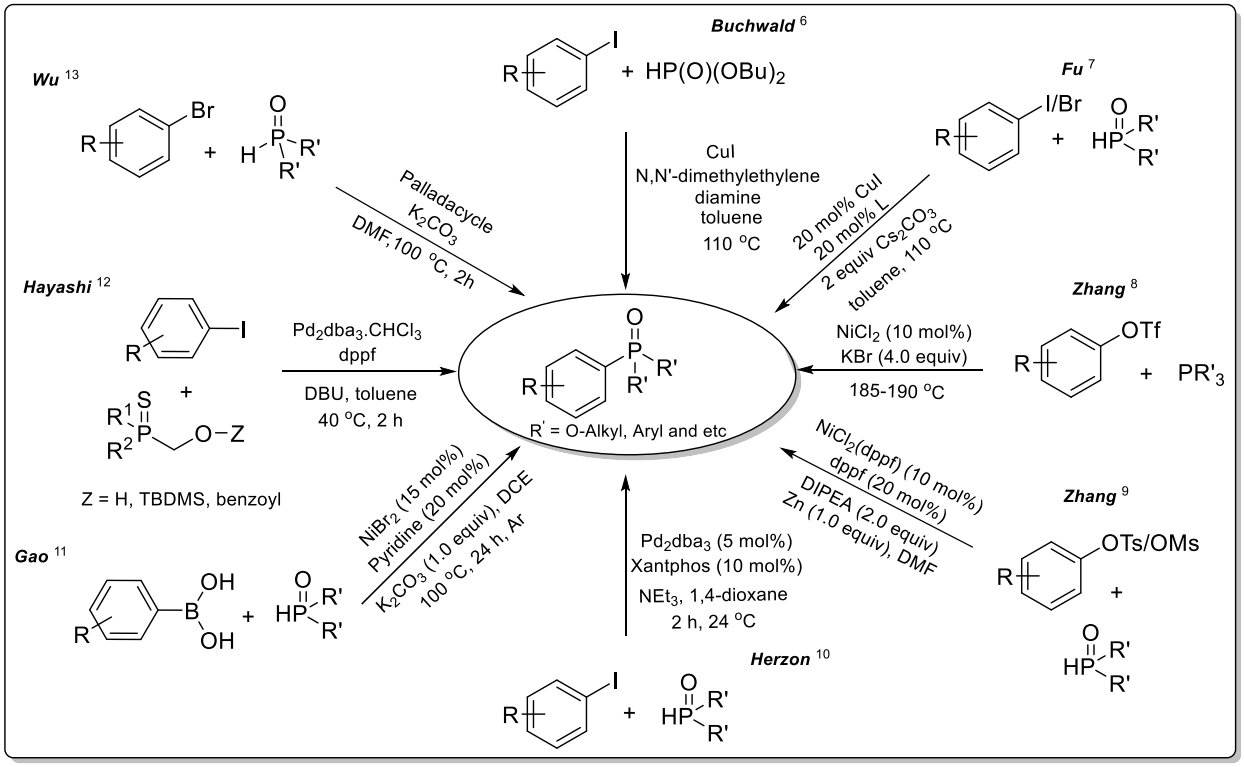
Number of organo-phosphorus compounds constitutes significant class of chemicals. Several phosphonic groups are present in diverse molecules, which are responsible for various biological functions. They are present in therapeutic agents possessing anticancer, antibacterial, and anti-HIV activity.[1] In nature the phosphorous compounds such as protein tyrosine phosphatases (PTPs) belongs to the family of enzymes that dephosphorylate phosphotyrosine residues in their protein substrates.[2] The phosphate and phosphonate represent an important class of prodrugs known as HepDirect prodrugs.[3] In addition to its pharmaceutical importance the organo-phosphorus compounds also plays key role in organic chemistry for vital organic transformations. The striking feature of organo-phosphorus compounds is its significant application as a ligand in metal catalysed reaction. They always have major contribution in C–C and C–heteroatoms bond forming reactions.[4] Due to such high importance of organo-phosphorus compounds, the scientific community has always been keen in developing novel process for their synthesis.

2.2.3 Review Literature:

Many reputed research groups have shown useful contribution in introducing novel strategies for the synthesis of oragno-phosphorus compounds. The Michaelis-Arbuzov reaction is a classical method for the synthesis of alkyl-phosphorus compounds.[5] The synthesis of aryl-phosphorus compounds always remains a challenging task. Generally synthesis of such aryl-phosphorus compounds is achieved via transition-metal-catalyzed Arbuzov or Hirao C–P bond construction reaction.

In 2003, Buchwald and co-workers developed a novel protocol for coupling various aryl iodides with dibutyl phosphite in the presence of CuI catalyst and *N*,*N*'-dimethylethylenediamine as a

ligand (Scheme 1). The desired aryl-phosphonates were synthesized in good to excellent yields.[6] A novel, versatile and efficient ligand pyrrolidine-2-phosphonic acid phenyl monoester (PPAPM) was synthesized for the construction of C–P bond by Fu and co-workers (Scheme 1).[7]



Scheme 1: Known literature for the synthesis of aryl phosphonates/phosphinates/phosphine oxide [5-13]

Further, aryl-phosphonates were synthesized by Zhang and co-workers via nickel-catalyzed reaction involving aryl triflates and triethyl phosphite in the presence of KBr additive, which played an important role (Scheme 1).[8] For the very first time Nickel catalyst $NiCl_2$(dppf) was introduced for C–P coupling, where aryl mesylates/tosylates were reacted with alkyl-aryl phosphates (Scheme 1).[9] The combination of ligand Xantphos and $Pd_2(dba)_3$ catalyst worked very for the coupling of aryl iodides with secondary phosphine oxides (Scheme 1). The protocol was highly applicable for the generation of P-chiral phosphines and PCP ligands.[10]

The aryl boronic acids were coupled with H–phosphites, H–phosphinate esters, and H–phosphine oxides in the presence of nickel catalyst which delivered wide range of aryl-phosphorous compounds (Scheme 1). This was the first Nickel catalyzed C–P cross coupling report in the presence of arylboronic acids and P(O)H compounds.[11]

Hayashi and co-workers established the novel deformylative P–C cross-coupling protocol by employing Pd catalyst (Scheme 1). The monohydroxymethylphosphine sulfide was coupled with iodo toluene in presence of $Pd_2(dba)_3 CHCl_3$, DBU and dppf ligand.[12]

Further the palladacycle complex with ligand X-phos as a unit was involved in cross coupling C–P reaction, where aryl halides were coupled with diisopropyl H-phosphonate (Scheme 1).[13]

2.2.4 Origin of Present Work:

The literature reports mentioned above shows that there is always a crucial role of transition metal in the synthesis of aryl-phosphonates, phosphinates, and phosphine oxides. In addition, expensive ligands are also required for the transformation. The high temperature and pressure is also must for many C–P cross coupling reactions.

2.2.5 Objective:

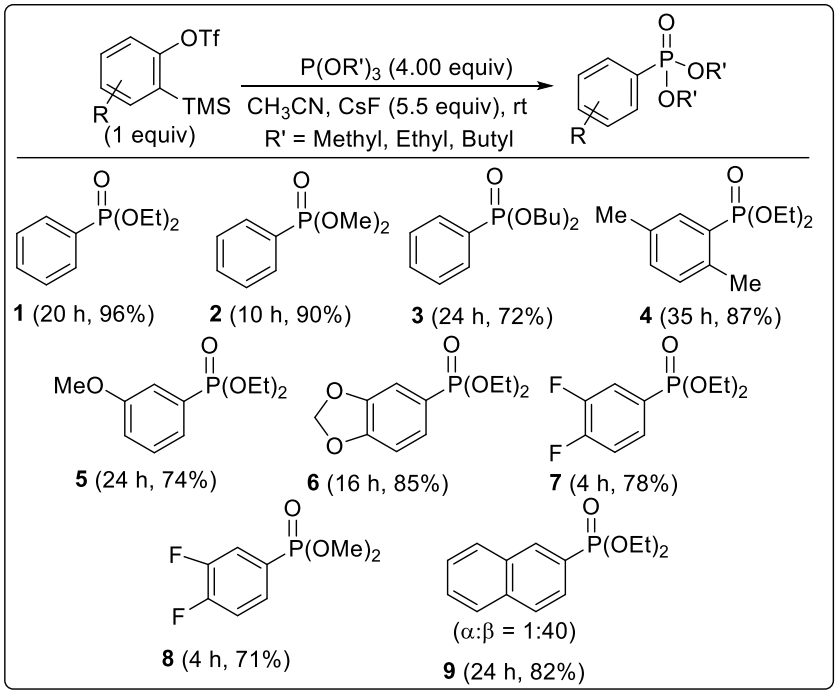
To avoid the use of expensive metals, ligands and extreme conditions, there is a need of intensive investigation for the development of mild protocol for the synthesis of aryl-phosphorous compounds.

Due to wide applications of organo-phosphorous compounds and our interest in benzyne chemistry, we were curious to develop an efficient method for the synthesis of organo-phosphorous compounds. The utilization of high reactivity of arynes for constructing C–P bond would be an asset in synthetic organic chemistry. Prior to our report Juge *et al* reported synthesis of quaternary and P-stereogenic phosphonium triflates via reaction between phosphines and

arynes.[14] Herein, in this section, we report the first metal free synthesis of aryl-phosphonates, phosphinates, and phosphine oxides by employing aryne.

2.2.6 Results and Discussion:

We started our first experiment by treating silyl triflate **1** (1.0 equiv) with triethyl phosphite (**1** equiv) and cesium fluoride (1.2 equiv) in acetonitrile at room temperature for 24 h. To our delight the formation of the expected product diethyl phenylphosphonate (**1**) in 47% yield was observed.



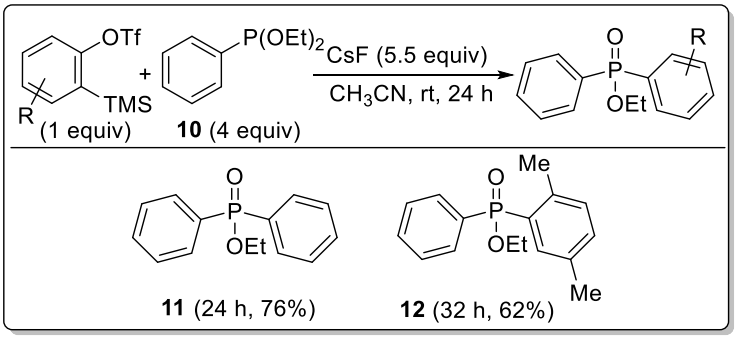
Scheme 2: Synthesis of various phosphonates

During the optimization of this methodology, increasing the equivalent of triethyl phosphite (4.0 equiv) and silyl triflate (1.0 equiv, 0.084 mmol) and cesium fluoride (5.5 equiv) in acetonitrile at room temperature for 20 h delivered phosphonate **1** in 92% yield. The yield was increased to 96% when the same reaction was performed at higher scale of silyl triflate (1.68 mmol) (Scheme 2).

This exciting result prompted us to synthesize various phosphonates. Trimethyl phosphite was treated with simple unsubstituted aryne precursor and excellent yield was achieved for phosphonate **2**. Surprisingly yield for the corresponding phosphonate **3** decreased to 72% when tributyl phosphite was employed. Further, various substituted aryne precursors were tested. Very good yield was achieved for aryl-phosphonate **4** (87%), when symmetrical dimethyl aryne precursor was reacted with triethyl phosphite, however the steric effect due to dimethyl substitutent on aryne precursor might be the reason for long reaction time. The excellent regioselectivity was observed for unsymmetrically substituted electron rich aryne bearing methoxy substituent when treated with triethyl phosphite delivering phosphonate **5** in 74% yield. The formation of phosphonate **6** (85%) was observed in high yield when triethyl phosphite was reacted with electron rich aryne precursor.

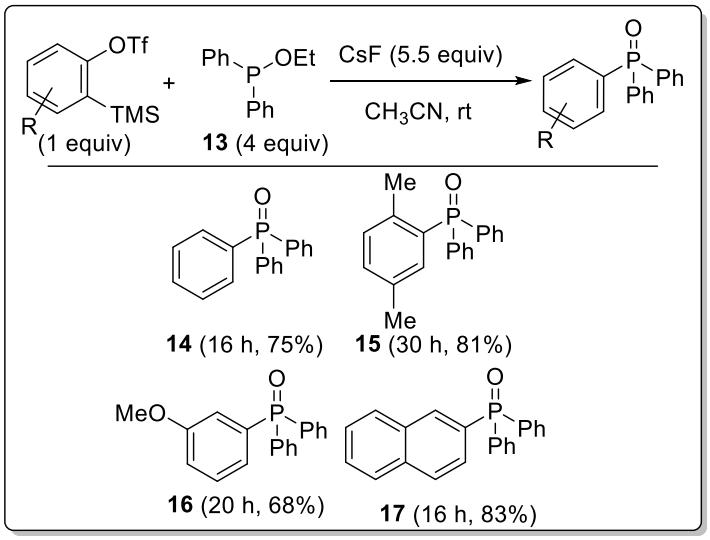
The halo-aryne precursor bearing di-fluoro group was reacted with both triethyl phosphite and trimethyl phosphite delivering phosphonate **7** and **8** in 78% and 71% respectively in very short time (4h). The presence of fluorine atom on aryne precursor increases the electrophilicity, which reduces reaction time. The reaction between asymmetrically substituted napthyl aryne precursor and triethyl phosphite worked very well providing respective phosphonate **9** in 82% yield, but inseparable mixtures of regioisomers **9** (α:β = 1:40) was observed by the ^{1}H NMR spectra (Scheme 2). The synthesis of corresponding aryl-phosphonates was successfully carried using developed protocol.

Our next plan was synthesis of different substituted aryl-phosphinates. The simple unsubstituted aryne precursor was reacted with diethyl phenylphosphonite (**10**) under the optimized protocol resulting into the formation of diethyl phenylphosphonite (**11)** in 76% yield (Scheme 3).



Scheme 3: Synthesis of various phosphinates

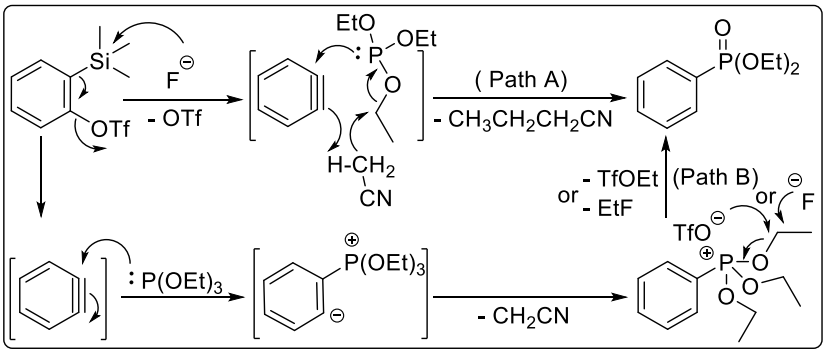
Further diethyl phenylphosphonite (**10**) was treated with dimethyl substiuted symmetrically substituted aryne precursor providing phosphinate **12** in 62% yield (Scheme 3).



Scheme 4: Synthesis of various phosphine oxides

After successful synthesis of aryl-phosphinates, our next objective was to synthesize the important class of phosphorous compounds, phosphine oxides. They are vital precursors in the preparation of various ligands, which are highly useful in organic synthesis. The synthesis of triphenyl phosphine oxide (**14)** (scheme **4**) was carried out in good yield (75%) by reacting ethyl diphenylphosphinite (**13)** and simple aryne precursor under same optimized condition. Ethyl diphenylphosphinite (**13)** on reaction with dimethyl substituted symmetric aryne precursor afforded phosphine oxide **15** in 81% yield, but the reaction completion time was 30 h. The

exclusive regioisomer phosphine oxide **16** was achieved in 68% yield, when unsymmetrically substituted methoxy aryne precursor was treated with ethyl diphenylphosphinite. The unsymmetrically substituted naphthyl aryne precursor was treated with bulky nucleophile ethyl diphenylphosphinite (**13**) and exclusive single regioisomer, naphthalen-2-yldiphenylphosphine oxide (**17**), was observed in this case. This novel protocol would be very useful for the synthesis of interesting phosphine oxides with three different substituents attached to phosphorus. This methodology would provide access for the synthesis of phosphine oxides under mild conditions. These products will serve as precursors to obtain novel phosphine ligands.



Scheme 5. Proposed mechanism

The developed interesting reaction might be following either 'Path A' or 'Path B' (scheme **5)**. In 'Path A' after the attack of triethyl phosphite the proton abstraction from solvent acetonitrile generates a carbanion, which attacks on the ethyl group leading to respective aryl phosphoante. In 'Path B' the OTf or fluoride ion source might be responsible for de-ethylation providing corresponding arylphosphonate, which follows a Michaelis-Arbuzov type of mechanism. Therefore the 'Path B' involving fluoride ion seems to be more appropriate pathway.

2.2.7 Conclusion:

We have successfully established the mild and expedient aryl-C–P bond forming reaction protocol. This metal-free protocol features synthesis of variety of organo-phosphorous

compounds aryl-phosphonates, -phosphinates, and -phosphine oxides. The advantage of this protocol includes highly regioselective, convenient reaction conditions, and generality. This protocol provides a straightforward access to various aryl-phosphorus compounds and vital phosphorous ligands.

Our work presented in this chapter and publication has been cited 40 times in the literature. Further the idea for the synthesis of aryl phosphonates, phosphinates, and phosphine oxides using aryne chemistry was further reported in literature by different groups.[15]

2.2.8 Experimental Procedure:

[A] General Experimental Procedure for the Phosphorylation:

To a flame dried two-neck round-bottom flask containing CsF (5.5 equiv.) was added *o*-silyl aryl triflate (1.00 equiv.) in acetonitrile, followed by addition of alkyl phosphite/phosphonite/phosphinite (4.00 equiv.) in acetonitrile under Argon atmosphere. The reaction mixture was stirred at room temperature and the progress was monitored by TLC. After completion of the reaction, acetonitrile was removed on rotary evaporator and the crude product was dried under high vacuum and purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether to afford corresponding aryl-phosphonates, phosphinates, and phosphine oxides in good to excellent yields.

[B] Typical Experimental Procedure for the preparation of compound 1:

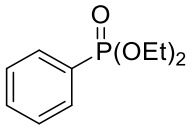
To a flame dried two-neck round-bottom flask containing CsF (69 mg, 0.46 mmol, 5.5 equiv.) was added *o*-silyl aryl triflate (25 mg, 0.08 mmol, 1.00 equiv.) in acetonitrile, followed by addition of triethyl phosphite (55 mg, 0.33 mmol, 4.00 equiv.) in acetonitrile under Argon atmosphere. The reaction mixture was stirred at room temperature and the progress was monitored by TLC. After completion of the reaction in 20 h, acetonitrile was removed on rotary

evaporator and the crude product was dried under high vacuum and purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether affording **1** (16.5 mg, 92 %) as a oil.

2.2.9 Characterization Data:

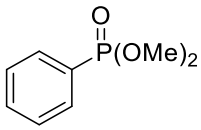
Selected entries data has been represented. The data of all the compounds is available in published paper.

Diethyl phenylphosphonate (1):[16a]



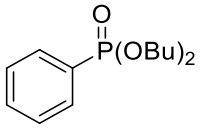
Reaction Time: 20 h, R*f*: 0.4 (1:1 EtOAc:Pet. Ether); Thick oil; 16.5 mg, 92 % (345 mg, 96 %, from 500 mg of *o*-silyl phenyl triflate); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.88-7.77 (m, 2H), 7.60-7.52 (m, 1H), 7.51-7.43 (m, 2H), 4.22-4.02 (m, 4H), 1.33 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 132.3 (d, J = 2.3 Hz), 131.7 (d, J = 10.0 Hz), 128.4 (d, J = 14.6 Hz), 128.3 (d, J = 188.0 Hz), 62.0 (d, J = 5.4 Hz), 16.3 (d, J = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.8; Mass $(M+Na)^+$ 237.

Dimethyl phenylphosphonate (2):[16a]



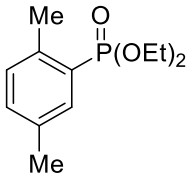
Reaction Time: 16 h; R*f*: 0.4 (1:1 EtOAc:Pet. Ether); Thick oil; 14.0 mg, 90 %; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.80 (dd, J = 8.2, 13.4 Hz, 2H), 7.60-7.55 (m, 1H), 7.51-7.46 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 132.6 (d, J = 2.9 Hz), 131.8 (d, J = 9.5 Hz), 128.5 (d, J = 15.3 Hz), 126.9 (d, J = 188.8), 52.6 (d, J = 5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.7; Mass $(M + Na)^+$ 209.

Dibutyl phenylphosphonate (3):[16b]



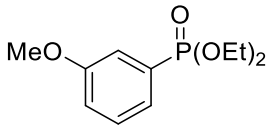
Reaction Time: 24 h; R*f*: 0.4 (1:3 EtOAc:Pet. Ether); Thick oil; 16.3 mg, 72 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.80 (dd, J = 6.8, 13.3 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.50-7.42 (m, 2H), 4.12-3.95 (m, 4H), 1.65 (quint, J = 7.3 Hz, 4H), 1.39 (sext, J = 7.3 Hz, 4H), 0.9 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 132.3 (d, J = 3.1 Hz), 131.7 (d, J = 9.3 Hz), 128.4 (d, J = 15.4 Hz), 128.3 (d, J = 187.3 Hz), 65.8 (d, J = 5.4 Hz), 32.4 (d, J = 6.9 Hz), 18.7, 13.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.8; Mass $(M + Na)^+$ 293.

Diethyl 2,5-dimethylphenylphosphonate (4):[16c]



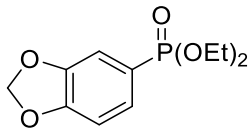
Reaction Time: 35 h; R*f*: 0.3 (1:4 EtOAc:Pet Ether); Thick oil; 16.1 mg, 87 % ; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.75 (d, J = 14.8, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 7.17-7.10 (m, 1H), 4.21-4.00 (m, 4H), 2.52 (s, 3H), 2.34 (s, 3H), 1.33 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.5 (d, J = 10.0 Hz), 134.9 (d, J = 14.6 Hz), 134.5 (d, J = 10.8 Hz), 133.2, 131.1 (d, J = 15.4 Hz), 126.3 (d, J = 182.7 Hz), 61.8 (d, J = 5.4 Hz), 20.7, 20.6, 16.3 (d, J = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.0; Mass $(M + Na)^+$ 265.

Diethyl 3-methoxyphenylphosphonate (5):[8]



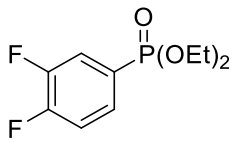
Reaction Time: 24 h; R*f*. 0.3 (2:3 EtOAc:Pet Ether); Thick oil; 13.7 mg, 74 %; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.45-7.28 (m, 3H), 7.15-7.01 (m, 1H), 4.25-3.96 (m, 4H), 3.85 (s, 3H), 1.33 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 159.4 (d, J = 18.5 Hz), 129.7 (d, J = 17.7 Hz), 129.6 (d, J = 187.3 Hz), 124.0 (d, J = 9.3 Hz), 118.8 (d, J = 3.1 Hz), 116.4 (d, J = 11.6 Hz), 62.2 (d, J = 5.4 Hz), 55.41, 16.3 (d, J = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.7; Mass $(M + Na)^+$ 267.

Diethyl benzo[d][1,3]dioxol-5-ylphosphonate (6):[8]



Reaction Time: 16 h; R*f*. 0.3 (2:3 EtOAc:Pet Ether); Thick oil; 16.0 mg, 85 %; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.38 (dd, J = 7.9, 14.0 Hz, 1H), 7.20 (d, J = 12.8 Hz, 1H), 6.88 (dd, J = 3.4, 7.6 Hz, 1H), 6.03 (s, 2H), 4.17-4.01 (m, 4H), 1.32 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 151.2 (d, J = 2.9 Hz), 147.8 (d, J = 22.9 Hz), 127.4 (d, J = 11.4 Hz), 121.3 (d, J = 193.6 Hz), 111.2 (d, J = 12.4 Hz), 108.6 (d, J = 18.1 Hz), 101.5, 62.0 (d, J = 5.7 Hz), 16.3 (d, J = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.0 ; Mass $(M + Na)^+$ 281.

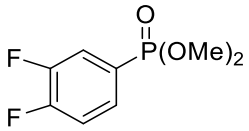
Diethyl 3,4-difluorophenylphosphonate (7):



Reaction Time 4 h; R*f*: 0.5 (2:3 EtOAc:Pet Ether); Thick oil; 14.6 mg, 78 %; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.67-7.55 (m, 2H), 7.31-7.23 (m, 1H), 4.21-4.05 (m, 4H), 1.34 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 153.1 (ddd, J = 3.8, 12.4, 255.6 Hz), 150.2 (ddd, J = 13.4, 22.9, 252.7 Hz), 128.8 (ddd, J

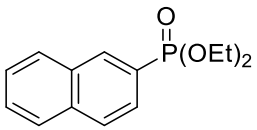
= 3.8, 6.7, 10.5 Hz), 125.9 (dt, *J* = 3.8, 192.7 Hz), 121.1 (dd, *J* = 11.4, 18.1 Hz), 117.9 (t, *J* = 18.1 Hz), 62.4 (d, *J* = 4.8 Hz), 16.2 (d, *J* = 5.7 Hz) ^{31}P NMR (162 MHz, $CDCl_3$) δ 15.8 (apparent t, J_{PF} = 6.1 Hz); HRMS-ESI (*m/z*) calcd $(C_{10}H_{13}F_2O_3P + H)^+$: 251.0643 found: 251.0643.

Dimethyl 3,4-difluorophenylphosphonate (8):



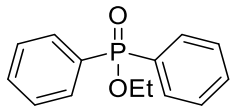
Reaction Time: 4 h; R*f*. 0.4 (1:3 EtOAc:Pet Ether); Thick oil; 11.8 mg, 71 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 7.67-7.53 (m, 2H), 7.34-7.24 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 153.3 (ddd, *J* = 3.9, 12.3, 256.6 Hz), 150.3 (ddd, *J* = 12.3, 22.4, 252.0 Hz), 129.0 (ddd, *J* = 3.9, 6.9, 10.8 Hz), 124.2 (dt, *J* = 3.9, 193.4 Hz), 121.3 (dd, *J* = 11.6, *J* = 18.5 Hz), 118.0 (t, *J* = 17.7 Hz), 52.9 (d, *J* = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.6 (d, J_{PF} = 7.5 Hz); HRMS-ESI (*m/z*) calcd $(C_8H_9F_2O_3P + H)^+$: 223.0330 found: 223.0335.

Diethyl naphthalen-2-ylphosphonate (9):[16a]



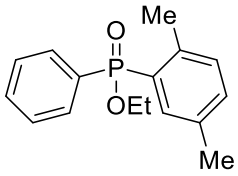
Reaction Time 24 h; R*f*: 0.3 (1:3 EtOAc:Pet. Ether); Thick oil; 15.5 mg, 82 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.44 (d, *J* = 15.6 Hz, 1H), 7.97-7.85 (m, 3H), 7.81-7.72 (m, 1H), 7.64-7.52 (m, 2H), 4.26-4.05 (m, 4H), 1.34 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 135.0 (d, *J* = 2.3 Hz), 134.0 (d, *J* = 10.0 Hz), 132.3 (d, *J* = 16.2 Hz), 128.9, 128.3 (d, *J* = 14.7 Hz), 128.2, 127.8, 126.8, 126.4 (d, *J* = 9.2 Hz), 125.3 (d, *J* = 188.1 Hz), 62.1 (d, *J* = 5.4 Hz), 16.3 (d, *J* = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.1; Mass $(M + Na)^+$ 287.

Ethyl diphenylphosphinate (11):[16d]



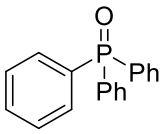
Reaction Time: 24 h; R*f*. 0.3 (1:1 EtOAc:Pet Ether); Thick oil; 15.7 mg, 76 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 7.87-7.77 (m, 4H), 7.55-7.48 (m, 2H), 7.47-7.39 (m, 4H), 4.11 (apparent quint, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 132.0 (d, *J* = 2.1 Hz), 131.6 (d, *J* = 136.4 Hz), 131.5 (d, *J* = 10.1 Hz), 128.4 (d, *J* = 13.1 Hz), 61.1 (d, *J* = 5.4 Hz), 16.4 (d, *J* = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.3; HRMS-ESI (*m/z*) calcd $(C_{14}H_{15}O_2P + H)^+$: 247.0882 found: 247.0886.

Ethyl (2,5-dimethylphenyl)(phenyl)phosphinate (12):



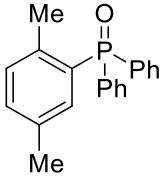
Reaction Time: 32 h; R*f*. 0.4 (1:1 EtOAc:Pet Ether); Thick oil; 13.0 mg, 62 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.81-7.70 (m, 3H), 7.52-7.40 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.12-7.05 (m, 1H), 4.11 (apparent quint, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 2.33 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.6 (d, *J* = 10.8 Hz), 135.0 (d, *J* = 12.3 Hz), 133.9 (d, *J* = 9.3 Hz), 132.5 (d, *J* = 124.1 Hz), 128.4 (d, *J* = 13.4 Hz), 131.7, 131.5 (d, *J* = 7.7 Hz), 131.4, 131.3, 129.0 (d, *J* = 133.3 Hz), 128.4 (d, *J* = 13.1Hz), 60.7 (d, *J* = 5.4 Hz), 20.9, 20.7 (d, *J* = 3.9 Hz), 16.4 (d, *J* = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$,) δ 32.2; HRMS-ESI (*m/z*) calcd $(C_{16}H_{19}O_2P + H)^+$: 275.1195 found: 275.1193.

Triphenylphosphine oxide (14):[16e]



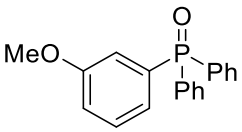
Reaction Time: 16 h; R*f*. 0.3 (1:3 EtOAc:Pet Ether); White Solid; 17.5 mg, 75 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.74-7.63 (m, 6H), 7.59-7.51 (m, 3H), 7.50-7.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 132.5 (d, *J* = 104.0 Hz), 132.1 (d, *J* = 10.0 Hz), 131.9 (d, *J* = 2.3 Hz); 128.5 (d, *J* = 12.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.2; Mass $(M + Na)^+$ 301.

(2, 5-Dimethylphenyl)diphenylphosphine oxide (15):



Reaction Time: 30 h; R*f*. 0.3 (1:1 EtOAc:Pet Ether); White Solid; mp 157-159^{o}c; 19.0 mg, 81 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.75-7.60 (m, 4H), 7.59-7.52 (m, 2H), 7.51-7.43 (m, 4H), 7.26-7.20 (m, 1H), 7.19-7.13 (m, 1H), 6.88 (d, *J* = 14.4 Hz, 1H), 2.37 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 140.0 (d, *J* = 7.7 Hz), 134.7 (d, *J* = 13.1 Hz), 133.9 (d, *J* = 12.3 Hz), 132.9 (d, *J* = 103.3 Hz), 132.8 (d, *J* = 2.3 Hz), 131.9 (d, *J* = 10.0 Hz), 131.8, 131.7 (d, *J* = 3.1 Hz), 130.4(d, *J*= 103.3 Hz), 128.5 (d, *J* = 11.6 Hz), 21.2 (d, *J* = 4.6 Hz), 21.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.7; HRMS-ESI (*m/z*) calcd $(C_{20}H_{19}OP + H)^+$: 307.1246 found: 307.1244.

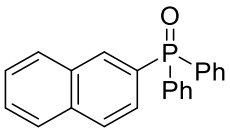
(3-Methoxy)diphenylphosphine oxide (16):[16f]



Reaction Time: 20 h; R*f*. 0.3 (1:1 EtOAc:Pet Ether); Thick oil; 16.0 mg, 68 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.71-7.63 (m, 4H), 7.59-7.52 (m,

2H), 7.50-7.43 (m, 4H), 7.40-7.29 (m, 2H), 7.18-7.05 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 159.6 (d, *J* = 15.4 Hz), 133.8 (d, *J* = 103.3 Hz), 132.4 (d, *J* = 104.0 Hz), 132.1 (d, *J* = 10.0 Hz), 131.9 (d, *J* = 3.1 Hz), 129.6 (d, *J* = 14.6 Hz), 128.5 (d, *J* = 12.3 Hz), 124.4 (d, *J* = 10.0 Hz), 118.2 (d, *J* = 3.1 Hz), 116.7 (d, *J* = 10.8 Hz), 55.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.5; HRMS-ESI (*m/z*) calcd $(C_{19}H_{17}O_2P + H)^+$: 309.1039 found: 309.1034.

Naphthalen-2-yldiphenylphosphine oxide (17):[16g]



Reaction Time: 16 h; R*f*. 0.4 (1:3 EtOAc:Pet Ether); Thick oil; 19.5 mg, 83 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.28 (d, *J* = 13.8 Hz, 1H), 7.95-7.84 (m, 3H), 7.79-7.40 (m, 13 H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 134.7 (d, *J* = 2.3 Hz), 134.0 (d, *J* = 9.3 Hz), 133.0, 132.3, 132.1 (d, *J* =10.0 Hz), 132.0 (d, *J* = 1.5 Hz), 131.3 (d, *J* = 243.5 Hz), 128.9, 128.5 (d, *J* = 12.3 Hz), 128.4, 128.2, 127.4 (d, *J* = 87.9 Hz), 126.8 (d, *J* = 10.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.3; HRMS-ESI (*m/z*) calcd $(C_{22}H_{17}OP + H)^+$: 329.1090 found: 329.1086.

2.2.10 References:

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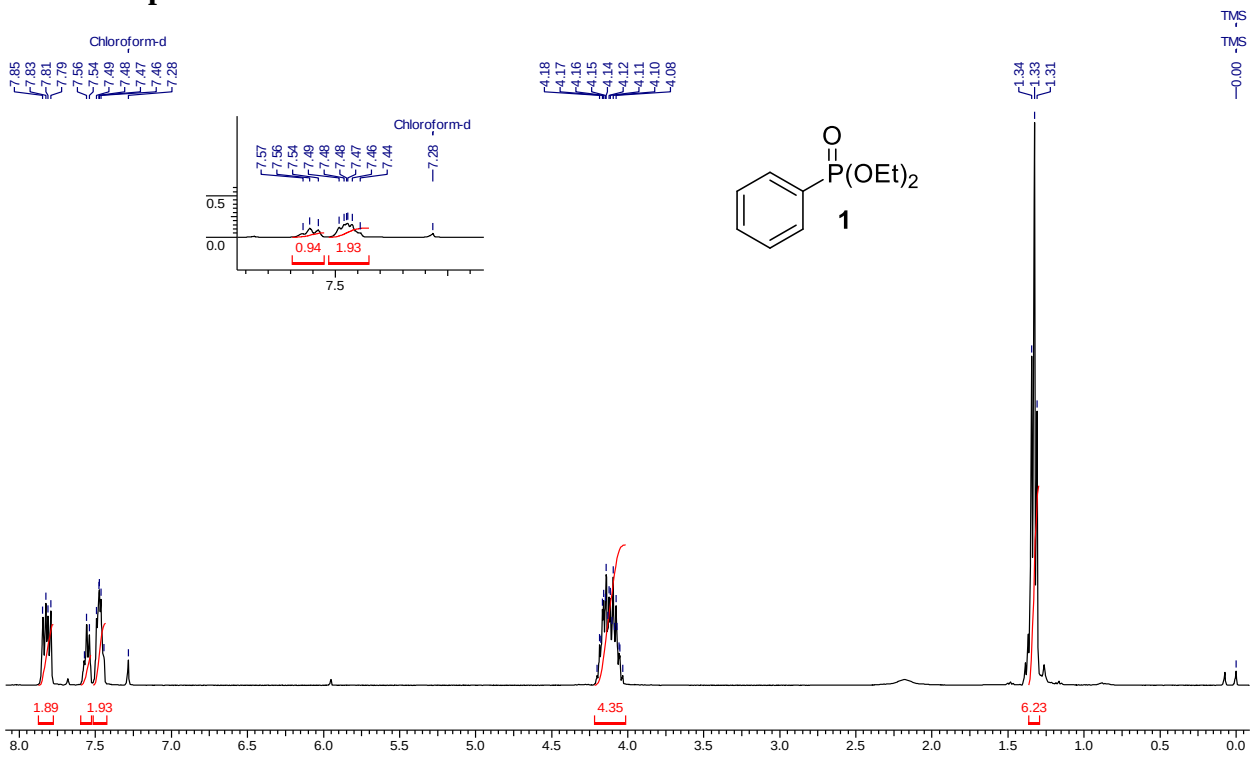
2.1.11 Selected Spectra

^{1}H NMR Spectra



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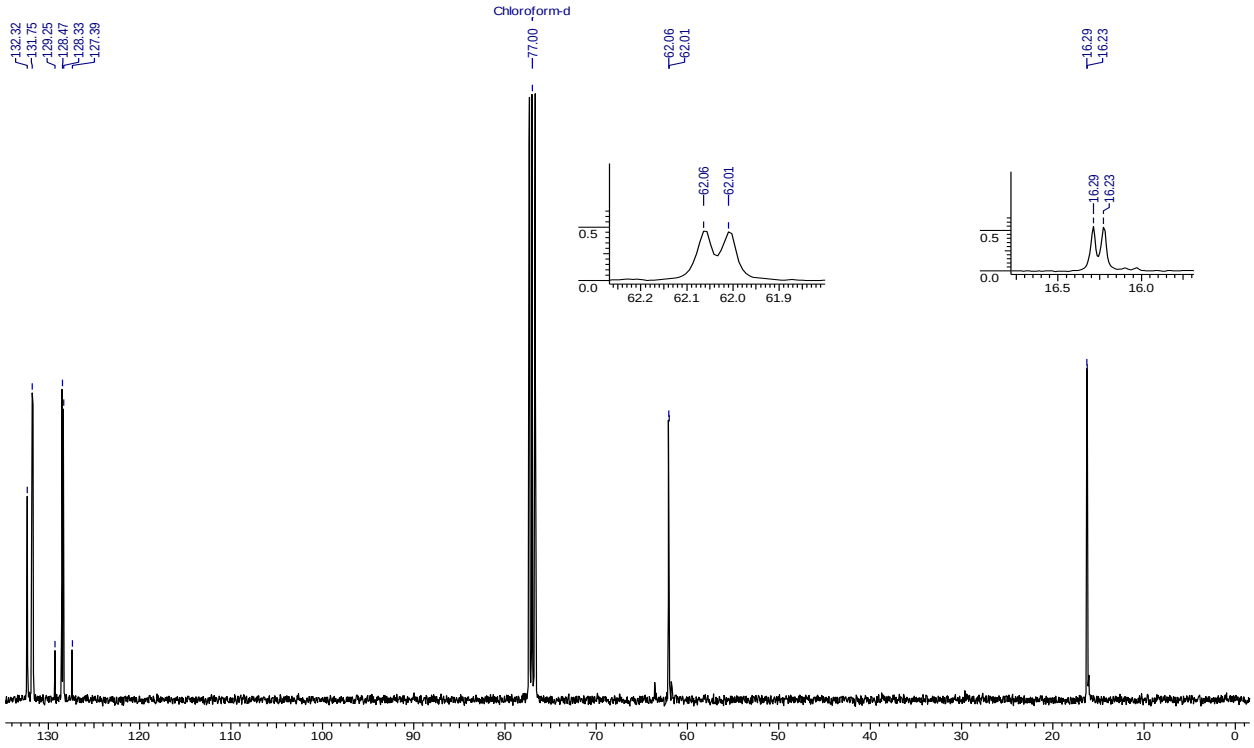

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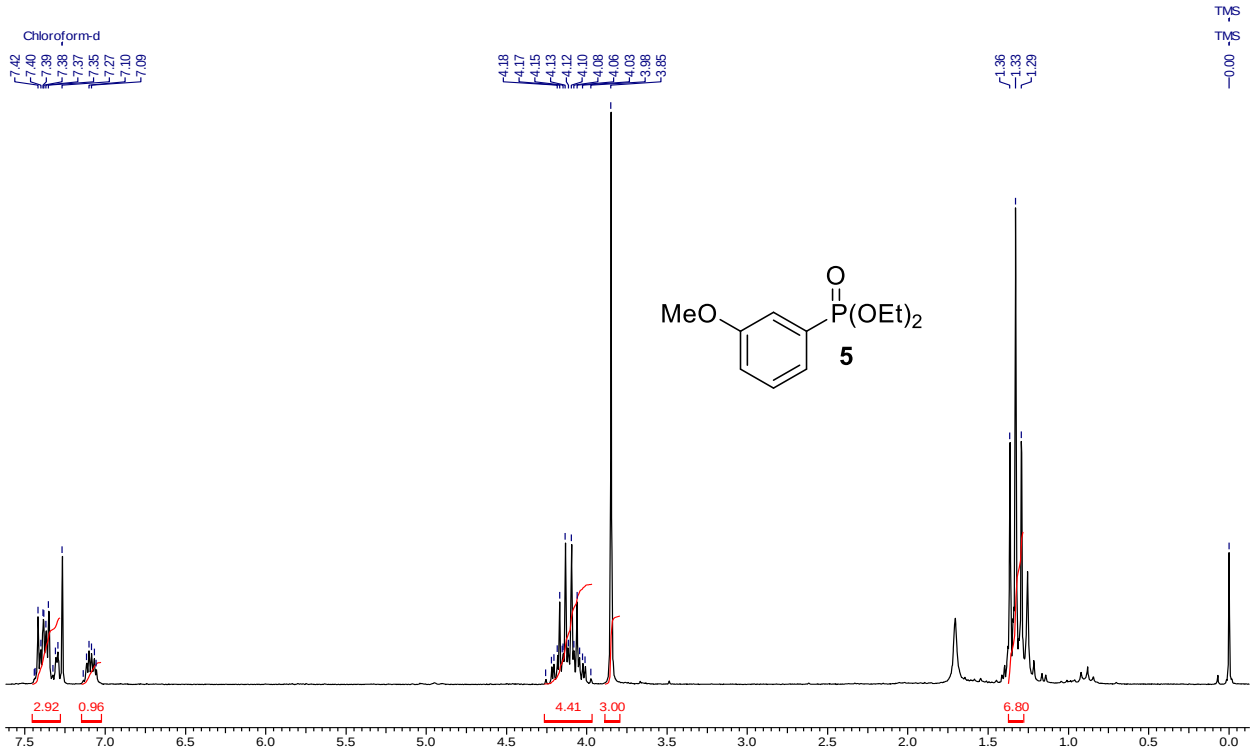

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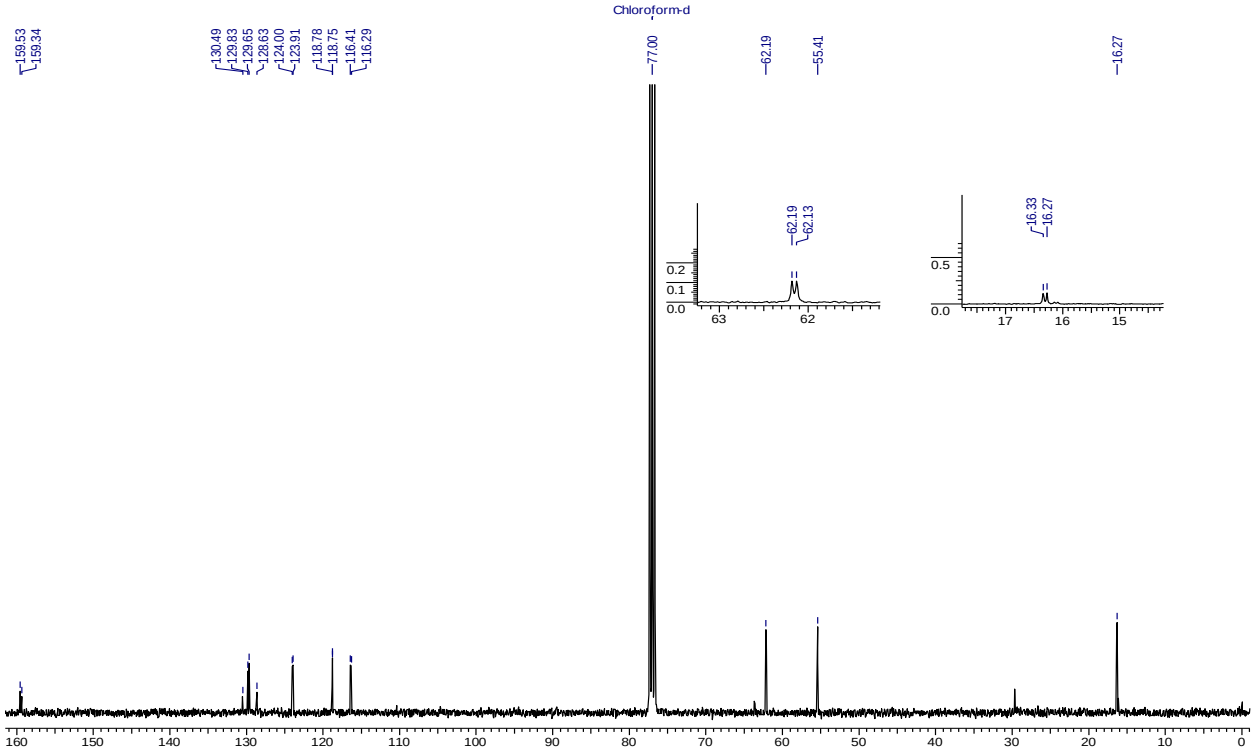

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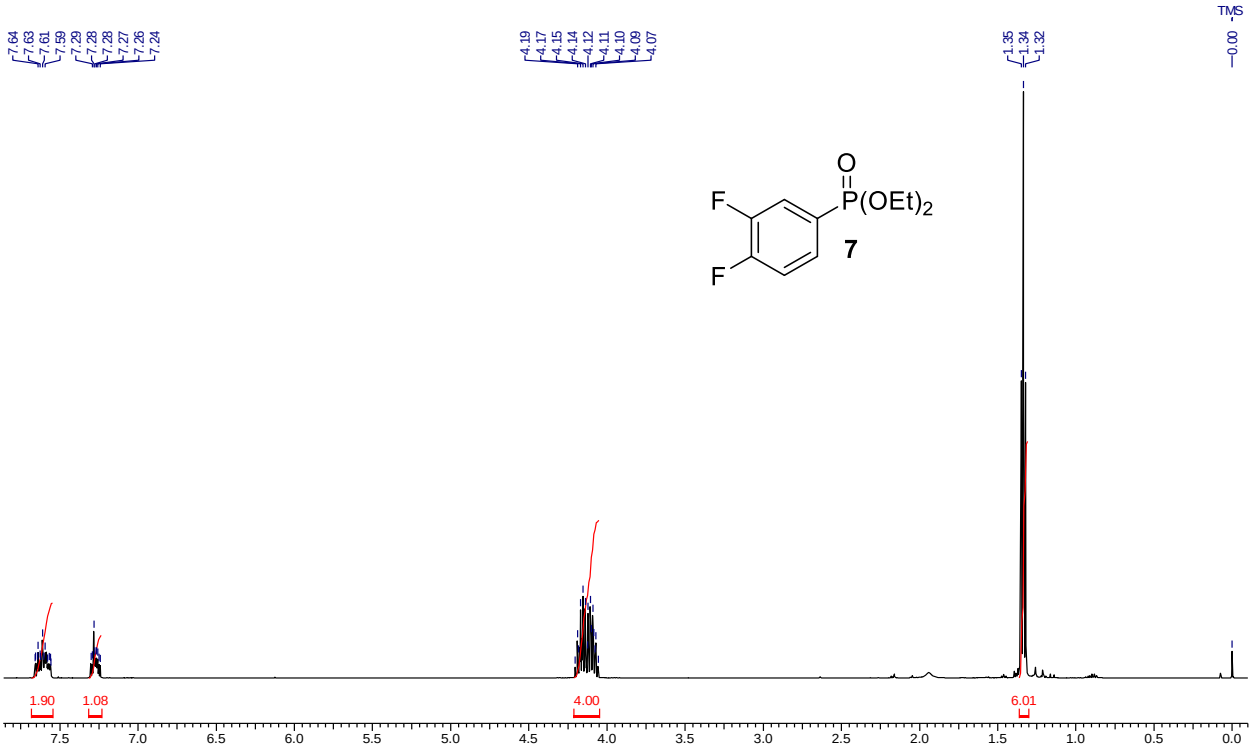

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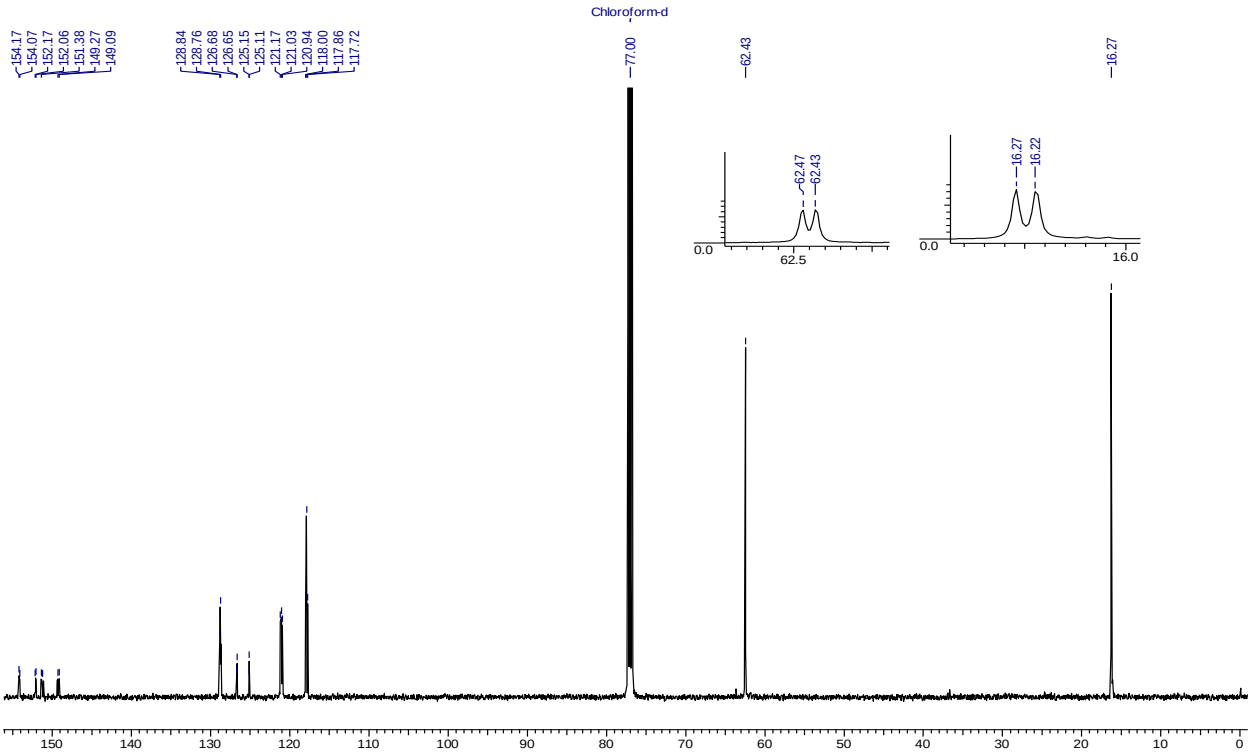

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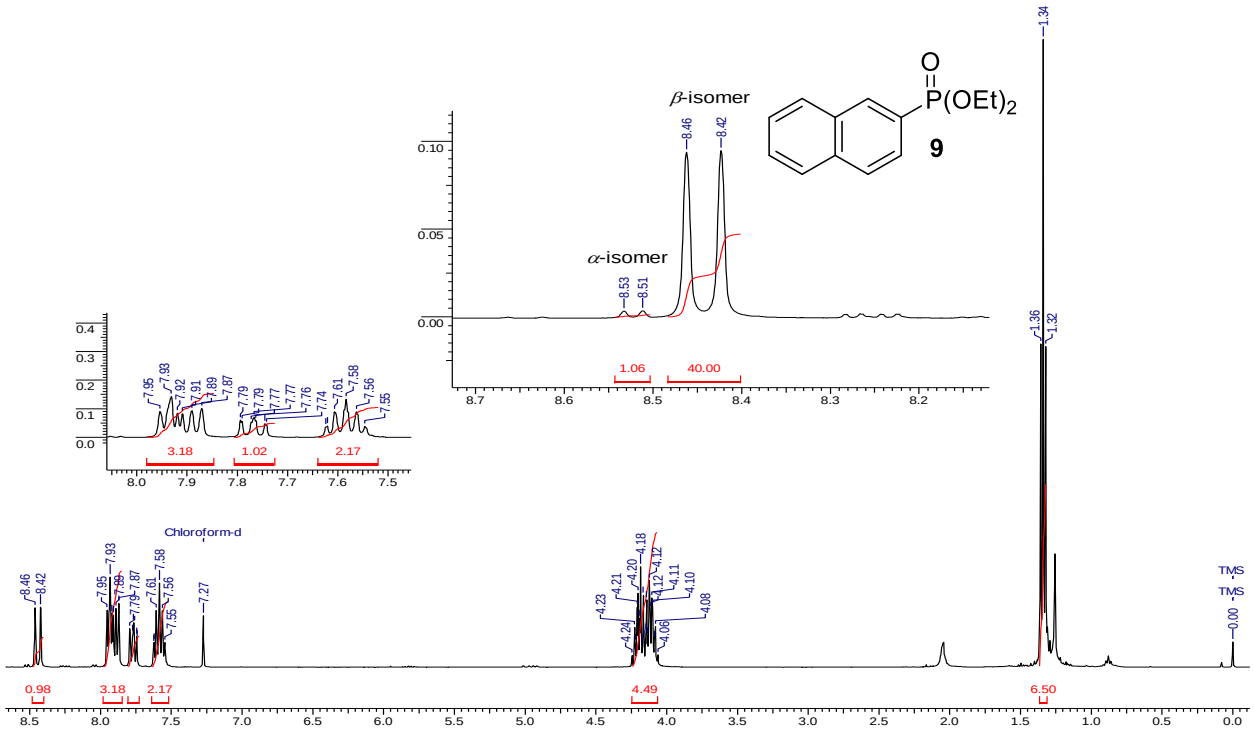

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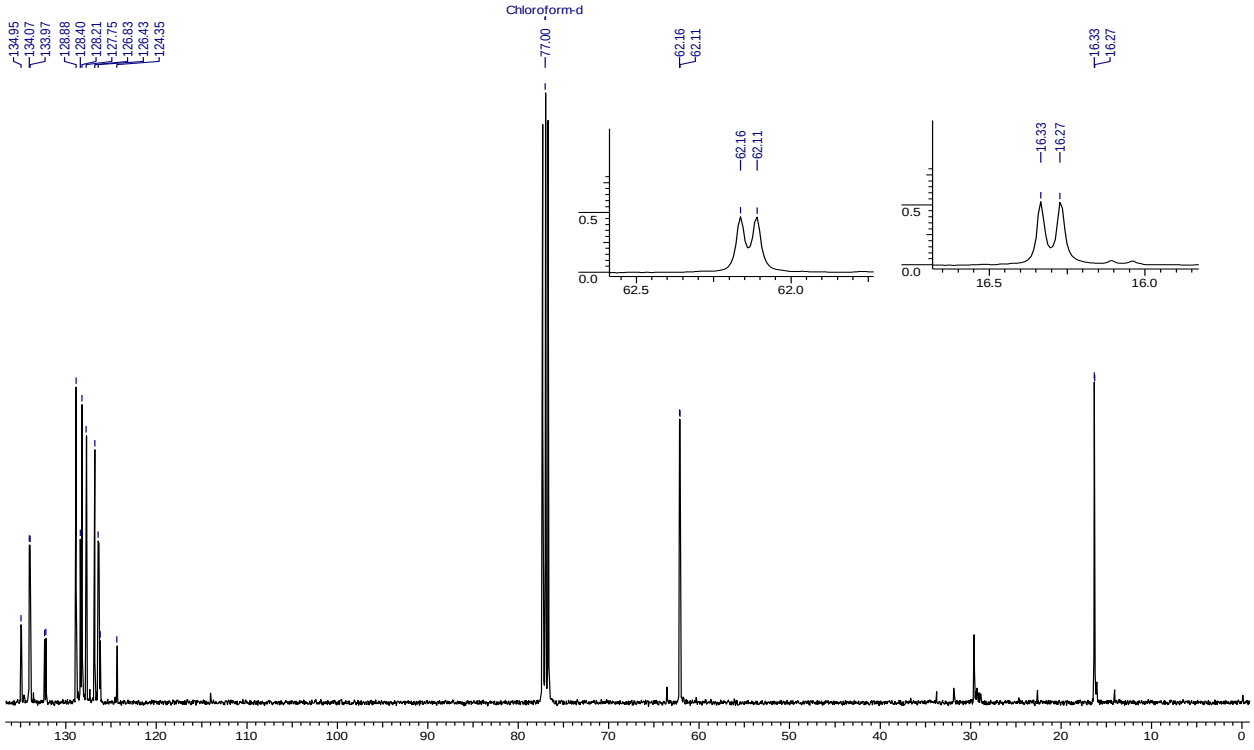

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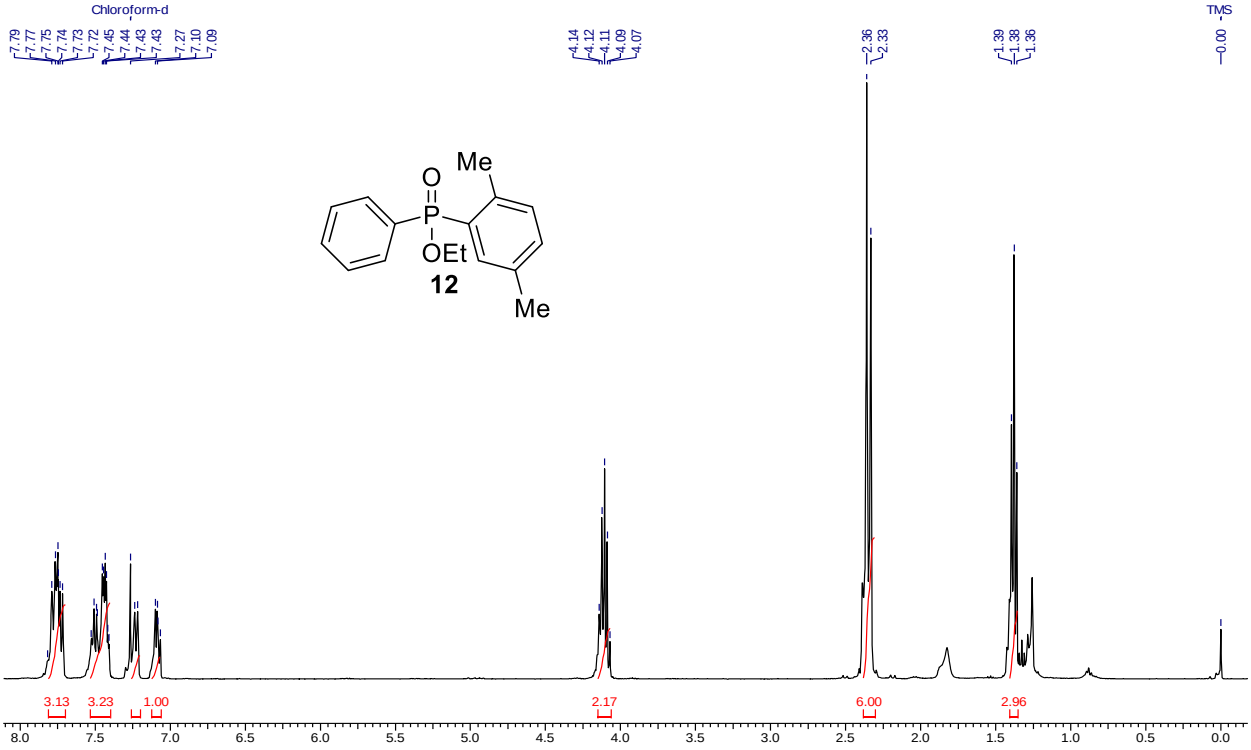

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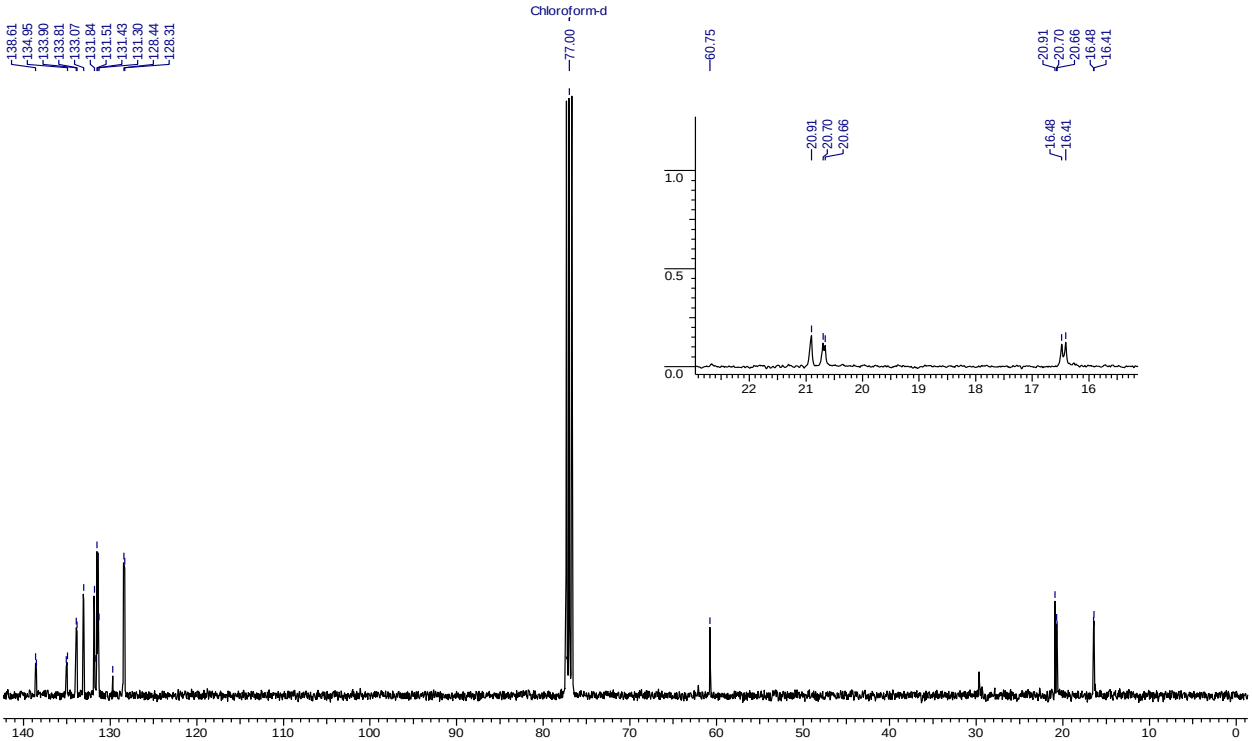

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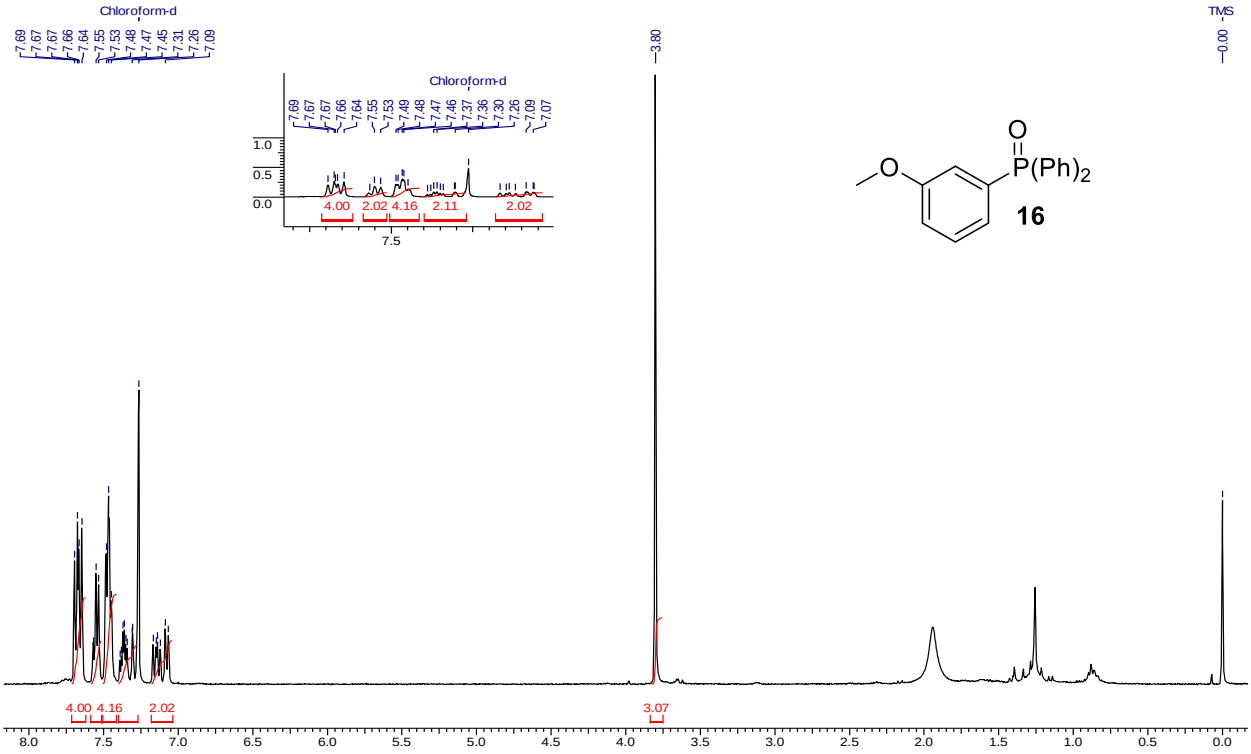

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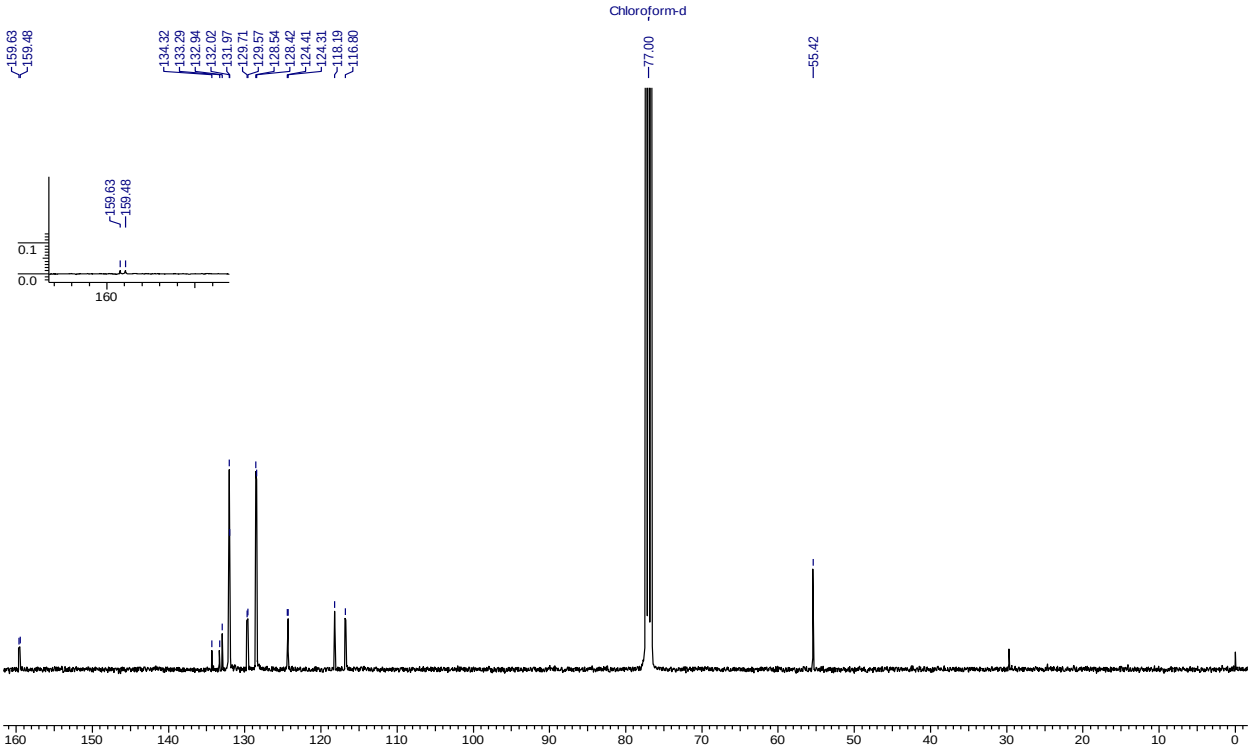

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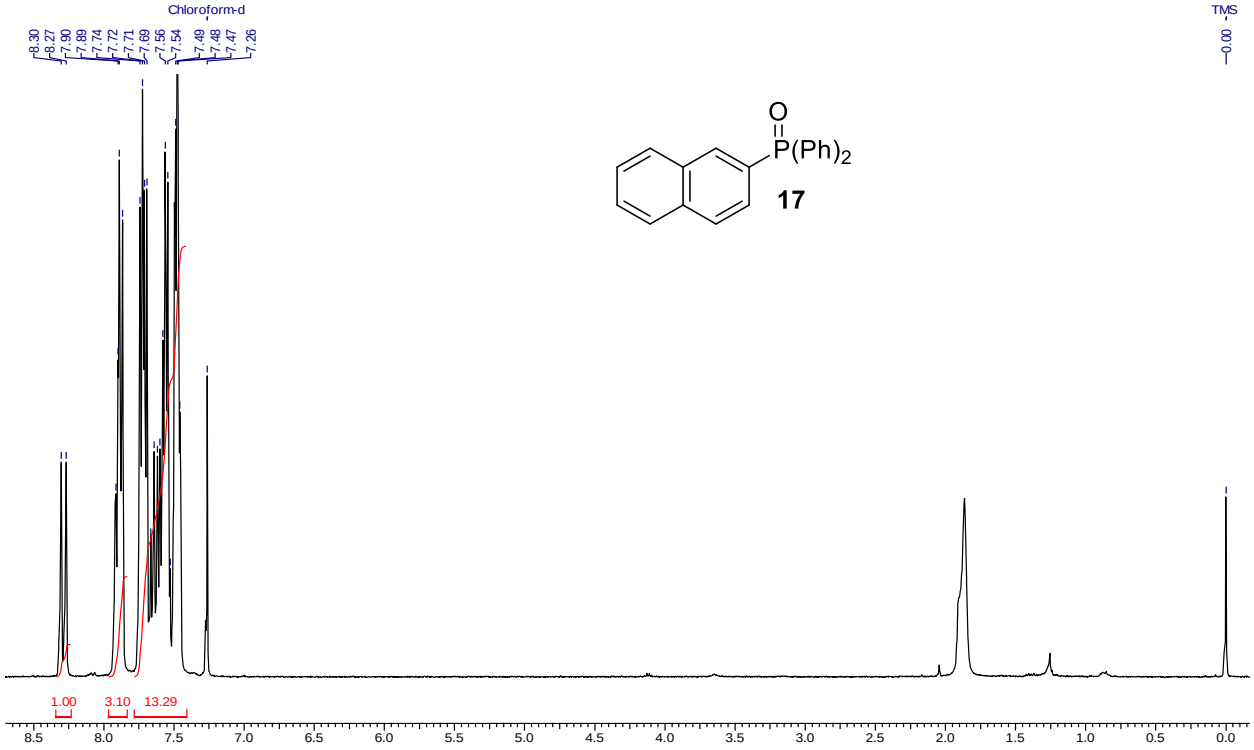
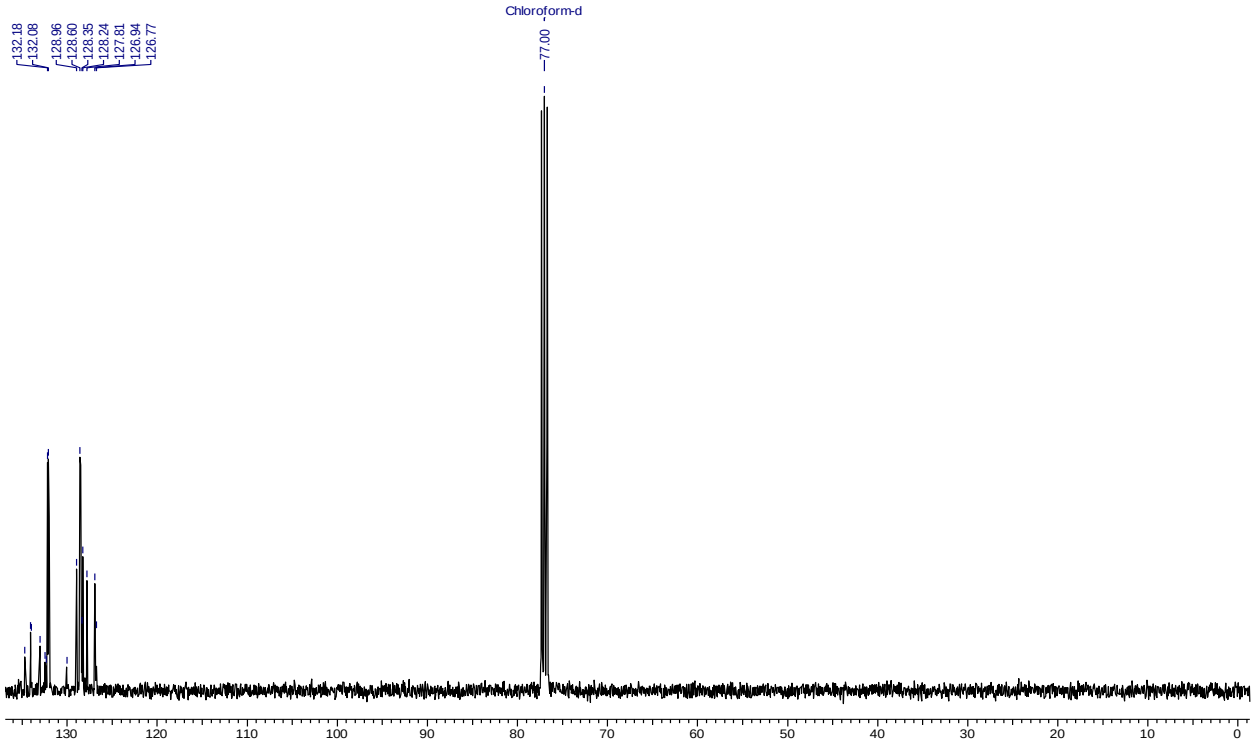


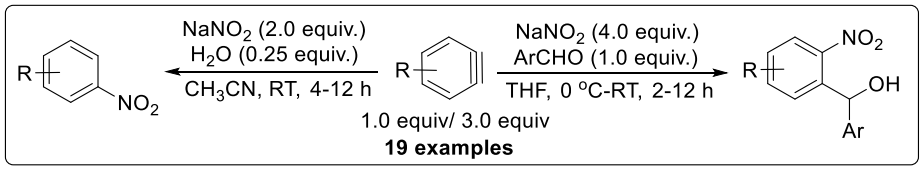
^{13}C NMR Spectra



Section 3: Nucleophilic Nitration of Arynes by Sodium Nitrite and its Multicomponent Reaction Leading to Double-Functionalized Arenes

2.3.1 Abstract:

This section deals with C–N bond construction via unusual nucleophilic nitration of arynes using $NaNO_2$ in the presence of water. Traditionally nitration processes are carried out using strong-acids such as HNO_3 and many other nitrating agents. Herein we have developed acid free and much milder nitration process, which has also been further extended for difunctionalization of arynes furnishing pharmaceutically important (2-nitrophenyl)methanol derivatives. The introduction of ortho-substituent to $–NO_2$ is difficult and requires multiple steps, but we have achieved this challenging transformation in single-step. The reaction conditions are mild and avoid the use of strong acids, expensive transition metal catalysts, and additives. Various substituted nitro-aromatics and diverse 2- nitrophenylmethanol were synthesized under this mild novel protocol.



This work has been published in *Org. Lett*. **2016**, *18*, 3010.

2.3.2 Introduction:

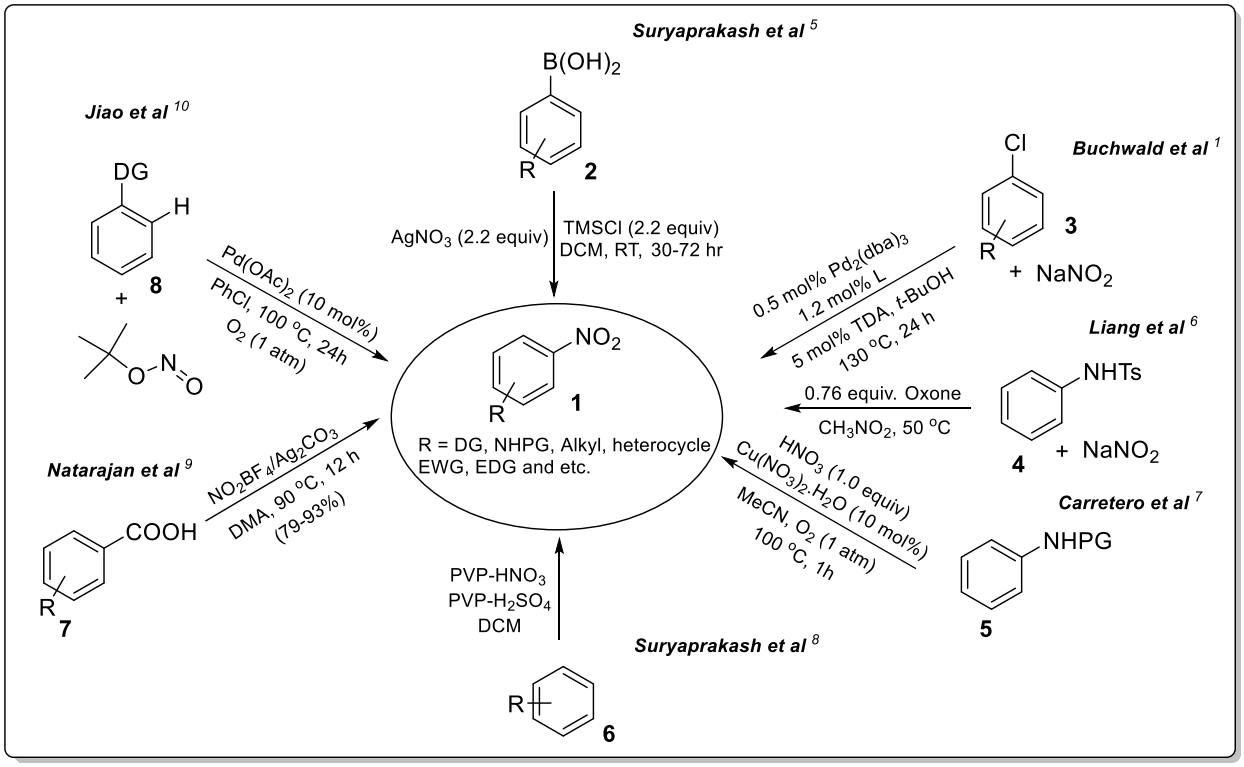
Aromatic nitro compounds have gained tremendous importance in the chemical field. Especially they are found in wide range of scientifically applicative compounds such as pharmaceuticals, dyes, advanced materials, pigments, agro-chemicals, rubber, pesticides, and explosives.[1] They are key intermediates in the synthesis of vital synthetic motifs.[2] The introduction of nitro group on aromatic ring is one of the oldest and industrially significant process.[3] In APIs synthesis,

nitration is one of the most common step observed. One of the nitro-bearing compounds referred as carbinol are important chemical entities from pharmaceutical perspective. The carbinol and its derivatives are promising inhibitors of PqsD enzyme. They displayed anti-biofilm activity, which are responsible for development of anti-infectives.[4] Due to such high importance of nitro aryl moieties; the nitration process remains an intensive investigation topic in scientific community.

2.3.3 Review Literature:

Several groups have established nitration processes successfully in many ways. Interestingly the synthesis of pharmaceutically important nitro-aryl compounds referred as nitro-carbinols remains the challenging subject in scientific community.

A) Nitration on Aromatic ring



Scheme1: Known nitration protocols

Suryaprakash and co-workers have developed general and efficient method for the synthesis of substituted nitro benzene **1** (Scheme 1). The *ipso* nitration was carried out on various arylbronic acid **2** when treated with the mixture of nitrate salt and chlorotrimethylsilane in the presence of silver nitrate. The mild condition, easy workup, and wide substrate scope are the advantages of this methodology.[5]

The pioneering work in transition metal cross coupling reaction by Buchwald group, established yet another protocol for C–N bond configuration (Scheme 1). The catalytic $Pd_2(dba)_3$ was employed for coupling of aromatic halides **3** with $NaNO_2$.[1] Further Liang and co-workers established the transition-metal-free nitration protocol (Scheme 1). The oxidative nitration of substituted sulfonamides **4** was achieved in presence of oxone and $NaNO_2$ on gram scale.[6]

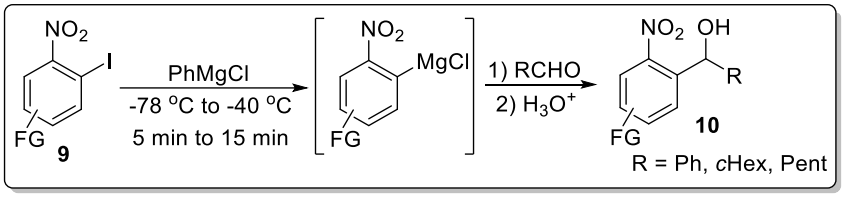
Carretero group successfully developed an efficient Cu-catalyzed nitration protocol for various substituted protected anilines **5** (Scheme 1). Nitric acid was employed as a nitrating agent in the presence of $Cu(NO_3)_2$ catalyst. Oxygen atmosphere was essential for the above transformation.[7]

Bench-stable solid complexes of poly(4-vinylpyridine) with nitric (PVP-HNO_3) and sulfuric acids (PVP-H_2SO_4) were synthesized and used for the efficient green nitration process of activated and deactivated aromatic rings **6** (Scheme 1). The recyclability of the catalyst, high *para*-selectivity, and mono-nitration are the striking features of this methodology.[8] The *ipso* nitration of aromatic and aliphatic acids **7** was successfully carried out using mixture of nitronium tetrafluoroborate and silver carbonate as a novel reagent system in dimethylacetamide (Scheme 1). The reaction proceeds via the alkyl-silver or aryl-silver intermediate, followed by the attack on nitronium ion to form nitro compounds.[9]

The transition-metal catalyzed C–H activation through directing group is another alternative method employed for the synthesis of wide range of nitro compounds **1** (Scheme 1). The

regioselective C–H nitration via Pd-catalysis under oxygen atmosphere involves cheap starting material *tert*-butyl nitrite and substrates **8** with various directing groups such as pyridine, pyrimidine, pyrazole, pyridol, pyridylketone, oxime, and azo group.[10]

B) Carbinol Synthesis



Scheme 2: Reported synthesis of nitro-substituted carbinol

In the literature there are no reports involving the synthesis of *ortho*-nitro carbinols in one pot. However, Knochel and co-workers reported the synthesis of *ortho*-nitro carbinols by employing preactivated nitro arenes. The nitro-substituted carbinols **10** (Scheme 2) were synthesized from aryl-iodide **9** via iodine-magnesium exchange when reacted with Grignard reagent PhMgCl, followed by the attack on different substituted aldehydes.[11]

2.3.4 Origin of Present Work:

In the literature the synthesis of aromatic nitro compounds involves the preactivated aromatic rings such as organoboron, *ortho* directing substituted arenes, electron rich anilines, etc. In addition expensive catalysts, acidic conditions and expensive ligands are also the crucial needs for the C–N bond formation. The construction of C–N bond for building various nitro compounds under milder conditions remains a topic contemporary interest in scientific community and a challenging task.

2.3.5 Objective:

The high significance of substituted aromatic nitro compounds in wide range of chemical industries, pharmaceutical chemistry, and their use as a vital building block in several

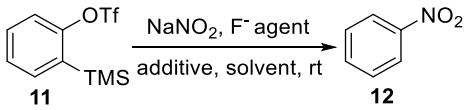
transformations makes them attractive targets. Generally synthesis of nitrobenzene is performed in the presence of transition metal, acidic conditions, oxidizing agents etc. Our continuous interest in aryne chemistry prompted us to develop a novel protocol for the synthesis of nitroaromatics under much milder reaction conditions using simple reagents.

2.3.6 Results and Discussion:

In our initial experiment, trace amount of nitrobenzene formation was observed (Table 1, entry 1) when *o*-silylaryltriflate 11 was treated with $NaNO_2$ in the presence of CsF. The same protocol was performed in THF solvent, but the aryne precursor remained unconsumed (Table 1, entry 2). The addition of TBAF (0.1 equiv), CsF (3.0 equiv) in acetonitrile increased the yield of nitrobenzene 12 to 15% (Table 1, entry 3). We thought that stoichiometric amount of TBAF might improve the yield, so in our next attempt 2 equivalent of TBAF was used(Table 1, entry 4). We expected that TBAF would play the dual role of fluoride source as an additive. But our idea met with failure, and only trace amount of nitrobenzene 12 was formed. We tried different combinations of solvents, fluoride sources, additives etc. (Table 1, entries 5 - 11) and we were able to achieve maximum 40 % yield of nitrobenzene 12 (Table 1, entry 9). Several efforts (Table 1, entry 12 -15) proved unsuccessful in increasing the yield of nitroaromatics. At this stage we speculated that the water present in TBAF might be facilitating the reaction and probably TBAF as such has no role as an additive.

Our hypothesis was found to be correct when we performed the reaction using water as an additive. Finally, by the addition of a controlled amount of water as an additive, we could obtain nitrobenzene in maximum 54% yield (Table 1, entry 18).

Table 1. Optimization of protocol for Nitration of aryne

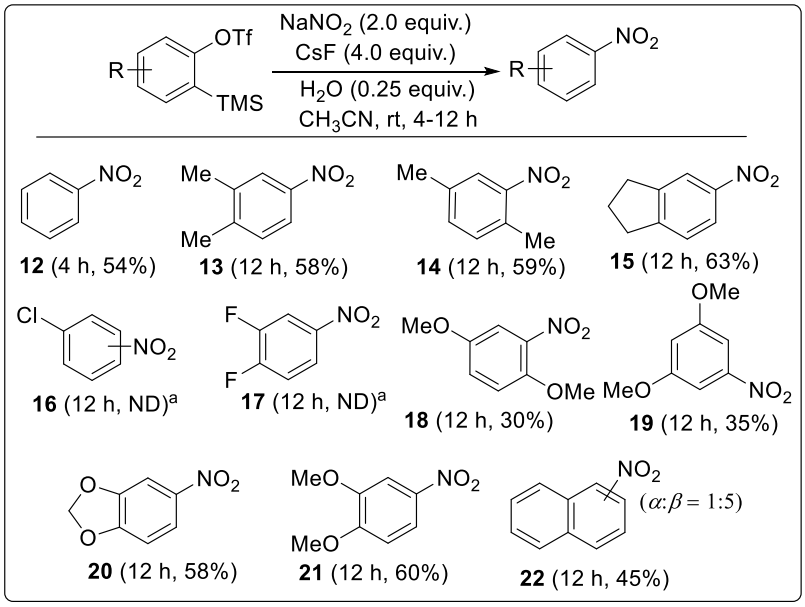


11 12

Entry	Solvent	$NaNO_2$ (equiv.)	F^- (equiv.)	Additive (equiv)	Time (h)	Yield (%)
1	CH_3CN	1.2	CsF (3.0)	--	24	trace
2	THF	1.2	CsF (3.0)	--	24	--[a]
3	CH_3CN	1.2	CsF (3.0)	TBAF (0.1)	05	15
4	CH_3CN	1.2	TBAF (2.0)	--	24	trace
5	CH_3CN	3.0	KF (2.0)	18 CE (2.0) + TBAF (0.1)	01	29
6	Toluene	3.0	KF (2.0)	18 CE (2.0) + TBAF (0.1)	24	27
7	THF	2.0	KF (3.0)	18 CE (3.0)	05	38
8	CH_3CN	1.5	CsF (2.0)	TBAF (0.1)	12	30
9	CH_3CN	1.5	CsF (4.0)	TBAF (0.1)	07	40
10	CH_3CN	4.0	CsF (4.0)	TBAF (0.2)	07	35
11	CH_3CN	4.0	CsF (4.0)	TBAF (0.2)	24	27
12	CH_3CN	1.5	CsF (4.0)	H_2O (0.2)	24	trace[a]
13[b]	CH_3CN	2.5	CsF (4.0)	--	24	40
14[b]	CH_3CN+H_20 (1:1)	2.5	CsF (4.0)	--	24	--[a]
15[b]	CH_3CN+H_20 (2:1)	2.5	CsF (4.0)	--	24	--[a]
16	CH_3CN	2.0	CsF (4.0)	H_2O (1.0)	24	27
17	CH_3CN	2.0	CsF (4.0)	H_2O (1.0) premixed in ACN	24	40
18	CH_3CN	2.0	CsF (4.0)	H_2O (0.25) in ACN	04	54

a = aryne precursor remained unconsumed
b = bottle grade acetonitrile

The compatibility of the protocol was tested on different substituted aryne precursors (Scheme 3). The alkyl substituted aryne precursors smoothly reacted with sodium nitrate providing respective nitrobenzenes. The disubstituted dimethyl aryne precursors furnished the nitrobenzene **13** and **14** in 58% and 59% yield respectively. The cyclo-alkyl aryne precursor also reacted with sodium nitrate providing nitrobenzene **15** in 63% yield (Scheme 3). The halo aryne precursors also reacted with sodium nitrate furnishing expected nitrobenzenes **16** and **17**, but its purification failed even after several attempts. Electron-donating substituents also provided the corresponding nitro compounds **18-21** (Scheme 3) in moderate to good yields. The symmetrical dimethoxy-substituted aryne precursor afforded nitrobenzene **18** in 30% yield (Scheme 3). However slight increase in the yield was observed for unsymmetrical dimethoxy-substituted aryne precursor producing 35% yield of expected nitrobenzene **19**. The symmetrical cyclic dimethoxy aryne precursor smoothly reacted with sodium nitrate furnishing nitrobenzene **20** in

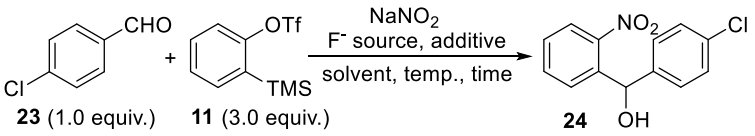


Scheme 3. Nitration of varyingly substituted arynes

58% yield (Scheme 3). The symmetrical 3,4-dimethoxy aryne precursor also provided good yield for respective nitrobenzene **21**. The nitration protocol furnished *β*-nitronaphthalene **22** as the major product in moderate yield with regioselectivity *α*:*β* =1:5, when unsymmetrically substituted naphthalene based aryne precursor was employed.

The exciting result of nucleophilic nitration of arynes encouraged us to develop the three-component reaction. The ortho-funtionalized nitroaromatics would be easily accessible by using this novel protocol. To achieve this goal the carbanion generated *in situ* by nucleophilic addition of nitrate ion on aryne needed to be intercepted with electrophile. For this purpose different electrophiles were tried such as ketones, aldehydes, alkynes, alkenes, arynes, alkyl halides etc. The positive outcome was observed only for aromatic aldehydes. We started the optimization of MCR by applying the standard nitration protocol in the presence of aldehyde **23**. Unfortunately we did not observe the formation of MCR product. The reason might be the quenching of carbanion intermediate by acetonitrile or water. We carried out the next reaction in THF solvent

Table 2. Optimization of MCR

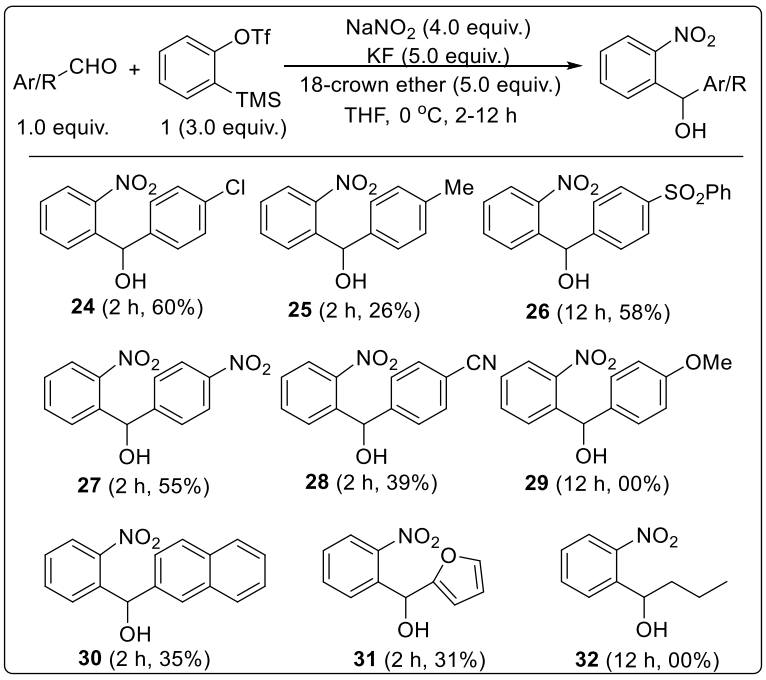


23 (1.0 equiv.) **11** (3.0 equiv.) **24**

Entry	Solvent	$NaNO_2$ (equiv.)	F^-source (equiv.)	Additive (equiv)	Temp	Time (h)	Yield (%)[a]
1	CH_3CN	2.0	CsF (4.0)	H_2O (0.25)	0 °C-rt	12	--
2	THF	3.0	KF (5.0)	18 CE (5.0)	0 °C-rt	24	44
3	THF	3.0	KF (5.0)	18 CE (5.0)	0 °C-rt	2	60
4	THF	2.0	KF (5.0)	18 CE (5.0)	0 °C-rt	2	36
5	THF	3.0	KF (5.0)	18 CE (6.0) + $Mg(O_tBu)_2$ (0.2)	0 °C-rt	24	--
6	THF	3.0	KF (5.0)	18 CE (6.0) + $Cu(OTf)_2$ (0.2)	0 °C-rt	24	--

by reacting benzaldehyde **23** (1.0 equiv), aryne precursor (3.0 equiv) and $NaNO_2$ (3.0 equiv) and to our delight the expected MCR product **24** was formed in 44% yield (Table 2, entry 2). Further reduction in the reaction time to 2 h helped in increasing the yield of the expected MCR product **24** to 60% (Table 2, entry 3). After decreasing the equivalent of $NaNO_2$, yield decreased to 36% (Table 4, entry 4). There was no product **24** formation when lewis acid $Mg(O_tBu)_2$ and $Cu(OTf)_2$ were employed (Table 2, entry **5-6**).

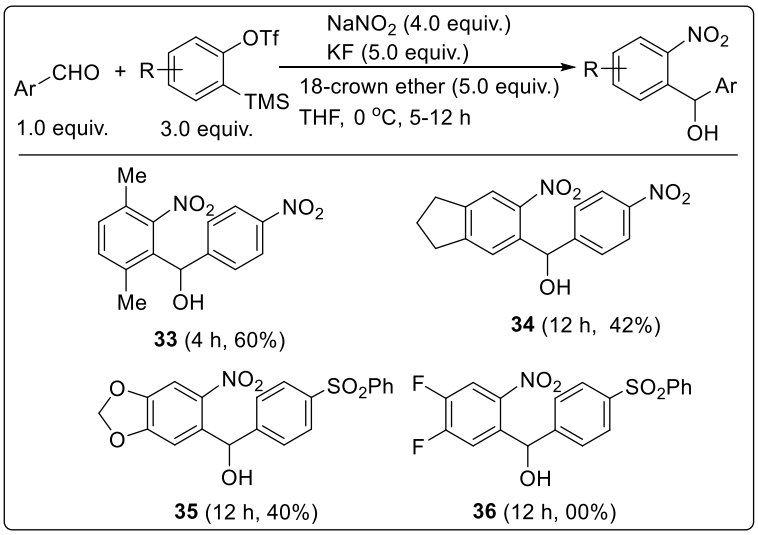
After having optimized condition, our next job was the screening of different para-substituted aldehydes. When the *p*-substituent was switched from chloro to methyl group, the formation of carbinol **25** (Scheme 4) was obtained in only 26%. The decrease in the electrophilicity declines the yield of the expected MCR product. However, when *p*-tosyl substituted benzaldehyde was employed; moderate yield was obtained for carbinol **26** in 12 hours. Similarly for *p*-nitrobenzaldehyde the corresponding carbinol **27** was obtained in 55% yield albeit in 2 hours. The yield of carbinol **28** was low (39%) for *p*-cyanobenzaldehyde. The MCR reaction involving *p*-methoxybenzaldehyde failed to produce carbinol **29** (Scheme 4). The above obtained results



Scheme 4. MCR demonstrating aldehyde substrate scope

gave the strong impression that the *p*-substitutent present on benzaldehyde plays the crucial role in MCR. The *p*-substituted electron-donating group decreases the electrophilicty of carbonyl groups to undergo further MCR. *β*-Napthaldehyde and furfuraldehyde in MCR provided carbinols **30** and **31** in 35% and 31% yield respectively (Scheme 4). Butyraldehyde was unsuccessful in MCR (Scheme 4). After substantial study in MCR, we were interested in testing the protocol on different substituted aryne precursors. The symmetrically substituted di-methyl aryne precursor was reacted with $NaNO_2$ and *p*-nitrobenzaldehyde, which provided the respective carbinol **33** (Scheme 5) in good yield.

The alkyl-ring substituted aryne precursor was tested for MCR delivering carbinol 34 in 42% yield (Scheme 5). The similar observation was experienced when electron donating cyclic methoxy aryne precursor was treated with *p*-tosyl substituted benzaldehyde furnishing carbinol 35 in 40% yield (Scheme 5). However, symmetrically di-fluoro substituted aryne precursor was found to be unsuitable for MCR protocol.



Scheme 5. MCR with selected aryne precursors

2.3.7 Conclusion:

In conclusion, we have developed a novel transformation on arynes to obtain nitroaromatics using $NaNO_2$ under a mild reaction condition in the presence of water and also demonstrated an application of the concept in a multicomponent reaction involving aromatic aldehyde to synthesize pharmaceutical important carbinol derivatives. We believe that both the protocols developed herein will be useful in late stage functional group transformation. Currently, we are working towards developing multicomponent reaction involving other electrophiles and also exploring the possibility of applying the developed protocol in the total synthesis of natural products.

Our work presented in this chapter and publication has been cited 16 times in the literature. This paper was the most read article in the month July 2016.

2.3.8 Experimental Procedure:

A] General Experimental Procedure for Nitration of arynes: All the reactions were performed on 50 mg of aryne precursor.

To around-bottom flask containing CsF (4.00 equiv.) was added *o*-silyl aryl triflate (1.00 equiv.) in acetonitrile (1 ml) and H_2O (0.25 equiv.), followed by addition of $NaNO_2$ (2.00 equiv.) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether to afford corresponding substituted nitrobenzene.

B] General Experimental Procedure for MCR reaction involving aryne precurssor, sodium nitrite and aromatic aldehyde:

A round-bottom flask containing KF (5.00 equiv.) and 18-crown-6 (5.00 equiv.) was kept under high vaccum for 30 mins. *o*-Silyl aryl triflate (3.00 equiv.) in anhydrous THF (0.5 ml) was added to the reaction mixture, followed by the addition of aromatic aldehyde (1.00 equiv.) and $NaNO_2$ (4.00 equiv.) at 0 ^oC. The reaction mixture was stirred further and the progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate three times. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to furnish crude product. It was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether to afford corresponding MCR product.

C] Typical Experimental Procedure for the preparation of compound 12:

To around-bottom flask containing CsF (97 mg, 0.64 mmol) was added *o*-silyl aryl triflate (**1**, 48 mg, 0.16 mmol) in acetonitrile (1 ml) and H_2O (0.7 µL, 0.04 mmol), followed by addition of $NaNO_2$ (22.2 mg, 0.32 mmol) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (4 h), acetonitrile was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column

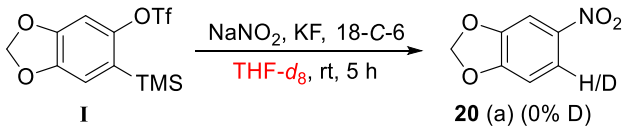
using a gradient of ethyl acetate-petroleum ether (0.1:10) to afford nitrobenzene (**12**) 10.8 mg (54%).

D] Typical Experimental Procedure for the preparation of compound 24:

A round-bottom flask containing KF (16.3 mg, 0.28 mmol) and 18-crown-6 (74.3 mg, 0.28 mmol) was kept under high vaccum for 30 mins. *o*-Silyl aryl triflate (**11**, 50 mg, 0.16 mmol) in anhydrous THF (1 ml) was added to the reaction mixture, immediately followed by the addition of *p*-chlorobenzaldehyde (**23**, 7.9 mg, 0.0.56 mmol) and $NaNO_2$ (11.5mg, 0.16 mmol) at room temperature. The reaction mixture was stirred further and the progress was monitored by TLC. After completion of the reaction (24 h), the reaction mixture was diluted with water and extracted with ethyl acetate three times. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to furnish a crude product. It was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (1:4) to afford 8.9 mg (60%) of MCR product **24**.

Deuterium incorporation experiments:

A] THF-d_8 as a solvent:



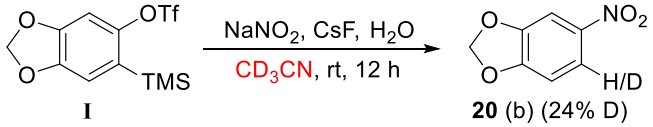
I **20** (a) (0% D)

A round-bottom flask containing KF (25 mg, 0.43 mmol) and 18-crown-6 (115 mg, 0.43 mmol) was kept under high vaccum for 30 mins. *o*-Silyl aryl triflate (**I,** 50 mg, 0.14 mmol) in THF-d_8 (1 ml) was added to the reaction mixture, followed by the addition of $NaNO_2$ (20 mg, 0.29 mmol) at room temperature. The reaction mixture was stirred further and the progress was monitored by TLC. After completion of the reaction (5 h), the reaction mixture was diluted with water and extracted with ethyl acetate three times. The organic layer was dried over sodium sulphate and

concentrated under reduced pressure to furnish a crude product. It was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (1:9) to afford 10 mg (40%) of **20** (a) product. There was 0% deuterium incorporation.

The ^{1}H NMR data and HRMS of the product **20** (a) was in exact agreement with the synthesized compound **20**.

B] CD_3CN as a solvent and H_2O as an additive:

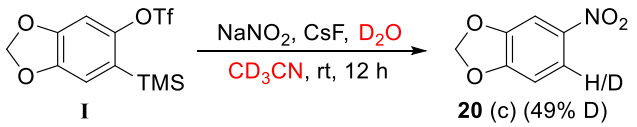


I **20** (b) (24% D)

To around-bottom flask containing CsF (88 mg, 0.58 mmol) was added *o*-silyl aryl triflate (**I**, 50 mg, 0.14 mmol) in CD_3CN (1 ml) and H_2O (0.6 µL, 0.036 mmol), followed by addition of $NaNO_2$ (20 mg, 0.29 mmol) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (12 h), acetonitrile was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (1:9) to afford nitrobenzene **20** (b)14.3 mg (58%). There was 24% deuterium incorporation.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (dd, J = 2.2, 8.6 Hz, 0.76 H), 7.61 (d, J = 2.2 Hz, 0.93 H), 6.76-6.84 (m,1H), 6.08 (s, 2H); HRMS-ESI (m/z) calcd $(C_7H_4{}^2HO_4N+ H)^+$: 169.0354 found: 169.0351.

C] CD_3CN as a solvent and D_2O as an additive:



I **20** (c) (49% D)

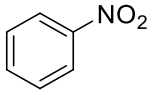
To around-bottom flask containing CsF (88 mg, 0.58 mmol) was added *o*-silyl aryl triflate (**I**, 50 mg, 0.14 mmol) in CD_3CN (1 ml) and D_2O (0.6 µL, 0.036mmol), followed by addition of $NaNO_2$ (20 mg, 0.29 mmol) at room temperature. The progress of the reaction was monitored by

TLC. After completion of the reaction (12 h), acetonitrile was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (1:9) to afford nitrobenzene **20** (c) 14 mg (57%). There was 49% deuterium incorporation.

1H NMR (200 MHz, CDCl3) δ 7.83 (dd, J = 2.2, 8.6 Hz, 0.51 H), 7.60 (d, J = 2.2 Hz, 0.89 H), 6.76-6.84 (m, 1H), 6.08 (s, 2H); HRMS-ESI (m/z) calcd ($C_7H_4{}^2HO_4N$+ H)+ : 169.0354 found: 169.0351.

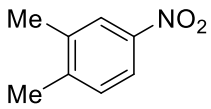
2.3.9 Characterization Data:

Nitrobenzene (12):[12a]



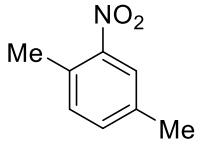
Reaction Time: 4 h, R*f*: 0.3 (Pet. Ether); oil; 10.8 mg, 54%; ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 0.9, 8.6 Hz, 2H), 7.63 (dt, J = 0.9, 8.6 Hz, 1H), 7.51-7.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 134.6, 129.3, 123.5; GC-MS (M^+) 123.

1,2-Dimethyl-4-nitrobenzene (13):[12b]



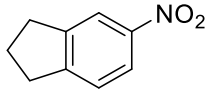
Reaction Time: 12 h; R*f*: 0.3 (Pet. Ether); oil; 13.0 mg, 58%; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.98-7.86 (m, 2H), 7.23-7.19 (m, 1H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 144.6, 138.1, 130.2, 124.3, 121.0, 20.0, 19.9; GC-MS (M^+) 151.1.

1,4-Dimethyl-2-nitrobenzene (14):[1]



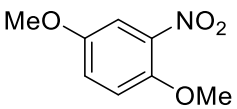
Reaction Time: 12 h; R*f*: 0.3 (Pet. Ether); oil; 13.2 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 2.48 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 137.1, 133.8, 132.5, 130.5, 124.9, 20.7, 20.0; GC-MS (M^+) 151.1.

5-Nitro-2,3-dihydro-1H-indene (15):[12c]



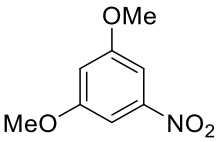
Reaction Time: 48 h; R*f*: 0.2 (Pet. Ether); oil; 15.2 mg, 63%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.96 (dd, J = 2.1, 8.2 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 2.96-2.89 (m, 4H) 2.15-2.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 145.9, 124.6, 122.0, 119.5, 32.9, 32.6, 25.5; GC-MS (M^+) 163.1.

1,4-Dimethoxy-2-nitrobenzene (18):[12d]



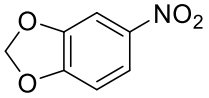
Reaction Time: 12 h; R*f*: 0.3 (1:4 Ethyl Acetate:Pet. Ether); oil; 7.7 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 2.9 Hz, 1H), 7.05 (dd, J = 2.9, 9.3 Hz, 1H), 6.97 (d, J = 9.3 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 147.4, 121.0, 115.1, 110.0, 57.1, 56.10; HRMS-ESI (m/z) calcd ($C_8H_9O_4N$+ Na)$^+$: 206.0424 found: 206.0423.

1,3-Dimethoxy-5-nitrobenzene (19):[1]



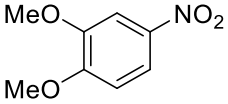
Reaction Time: 12 h; R*f*: 0.2 (1:9 Ethyl Acetate:Pet. Ether); oil; 9.0 mg, 35%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 2.4 Hz, 2H), 6.68 (t, J = 2.4 Hz, 1H), 3.80 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 107.2, 101.5, 55.9; GC-MS (M^+) 183.1.

5-Nitrobenzo[d][1,3]dioxole (20):[1]



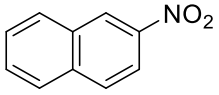
Reaction Time: 4 h; R*f*: 0.3 (1:9 Ethyl Acetate:Pet. Ether); oil; 14.2 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 2.2, 8.6 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.08(s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 148.2, 119.9, 107.6, 104.5, 103.0; GC-MS (M^+) 167.0.

1,2-Dimethoxy-4-nitrobenzene (21):[12a]



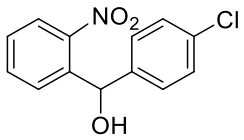
Reaction Time: 12 h; R*f*: 0.3 (1:9 Ethyl Acetate:Pet. Ether); oil; 15.4 mg, 60%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (dd, J = 2.7, 9.0 Hz, 1H), 7.69 (d, J = 2.7 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 148.8, 141.5, 117.8, 109.8, 106.4, 56.4, 56.3; GC-MS (M^+) 183.1.

2-Nitronaphthalene (22):[12a]



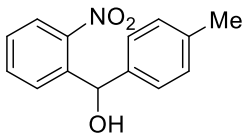
Reaction Time: 12 h; R*f*: 0.3 (1:8 Ethyl Acetate:Pet. Ether); oil; 11.2 mg, 45%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, J = 1.5 Hz, 1H),8.18 (dd,J = 2.1, 9.2 Hz, 1H),7.98 (d, J = 8.2 Hz, 1H), 7.96-7.86 (m, 2H) 7.66-7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 135.8, 131.9, 130.0, 129.7, 129.6, 128.0, 127.9, 124.7, 119.3;GC-MS (M^+) 173.0.

(4-Chlorophenyl)(2-nitrophenyl)methanol (24):



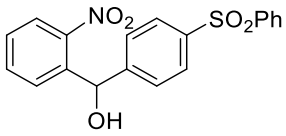
Reaction Time: 2 h; R*f*: 0.2 (1:5 Ethyl Acetate:Pet. Ether); oil; 8.9 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 1H), 7.65-7.54 (m, 2H), 7.44-7.36 (m, 1H), 7.27- 7.19 (m, 4H), 6.33 (s, 1H), 2.80 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 138.1, 133.8, 133.6, 129.4, 128.8, 128.7, 124.9, 70.9; HRMS-ESI (m/z) calcd $(C_{13}H_{10}O_3N^{35}Cl+Na)^+$: 286.0241 found: 286.0244.

(2-Nitrophenyl)(p-tolyl)methanol (25):[12e]



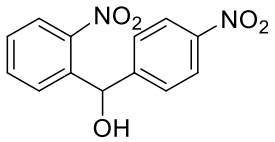
Reaction Time: 2 h; R*f*: 0.3 (1:5 Ethyl Acetate:Pet. Ether); oil; 3.5 mg, 26%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H) 7.38 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.34 (s, 1H), 2.62 (bs, 1H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 138.6, 137.9, 133.4, 129.3, 128.4, 126.9, 124.7, 71.4, 21.1.

(2-Nitrophenyl)(4-(phenylsulfonyl)phenyl)methanol (26):



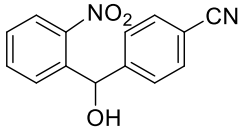
Reaction Time: 12 h; R*f*: 0.4 (2:3 Ethyl Acetate:Pet. Ether); oil; 11.9 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.75 (m, 5H), 7.56-7.28 (m, 8H), 6.37 (s, 1H), 2.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.0, 141.4, 141.0, 137.5, 133.9, 133.3, 129.7, 129.3, 129.1, 127.9, 127.75, 127.70, 124.9, 70.7; HRMS-ESI (m/z) calcd $(C_{19}H_{15}O_5NS+Na)^+$: 392.0563 found: 392.0567.

(2-Nitrophenyl)(4-nitrophenyl)methanol (27):



Reaction Time: 2 h; R*f*: 0.3 (2:3 Ethyl Acetate:Pet. Ether); oil; 8.3 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.65-7.55 (m, 2H), 7.55-7.40 (m, 3H), 6.43 (d, *J* = 4.9 Hz, 1H), 3.04 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.5, 137.4, 134.0, 129.8, 129.3, 127.7, 125.1, 123.7, 70.7; HRMS-ESI (m/z) calcd $(C_{13}H_{10}O_5N_2+Na)^+$: 297.0482 found: 297.0482.

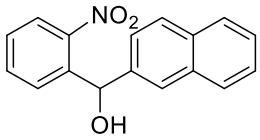
4-(Hydroxy(2-nitrophenyl)methyl)benzonitrile (28):



Reaction Time: 2 h; R*f*: 0.3 (2:3 Ethyl Acetate:Pet. Ether); oil; 5.5 mg, 39%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 1H), 7.63-7.55 (m, 4H), 7.44-7.38 (m, 3H), 6.38 (d, *J* = 4.4 Hz, 1H), 3.01 (d, *J* = 4.9 Hz, 1H); ^{13}C

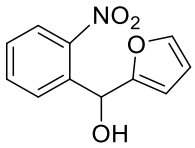
NMR (100 MHz, $CDCl_3$) δ 146.6, 137.4, 133.9, 132.4, 129.7, 129.2, 127.5, 125.0, 118.6, 111.8, 70.9; HRMS-ESI (m/z) calcd $(C_{14}H_{10}O_3N_2+Na)^+$: 277.0584 found: 277.0586.

Naphthalen-2-yl(2-nitrophenyl)methanol (30):[4b]



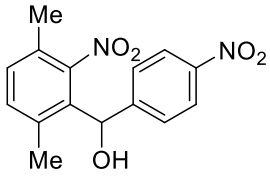
Reaction Time: 2 h; R*f*: 0.2 (1:5 Ethyl Acetate:Pet. Ether); oil; 5.4 mg, 35%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.89 (d, *J* = 7.9 Hz, 1H), 7.79 (s, 1H), 7.78-7.74 (m, 3H), 7.66 (d, *J* = 7.9, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.44-7.34 (m, 3H), 7.33 (dd, *J* = 1.4, 8.5 Hz, 1H), 6.54 (s, 1H), 2.88 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 133.5, 133.2, 133.0, 129.7, 128.6, 128.4, 128.2, 127.7, 126.4, 125.7, 124.82, 124.78, 71.5.

Furan-2-yl(2-nitrophenyl)methanol (31):



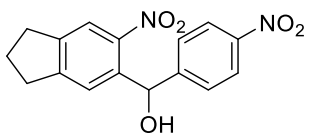
Reaction Time: 2 h; R*f*: 0.3 (1:5 Ethyl Acetate:Pet. Ether); oil; 3.8 mg, 31%; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.93 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.25 (d, *J* = 2.0 Hz, 1H), 6.10 (d, *J* = 2.9 Hz, 1H), 2.77 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 148.0, 142.7, 136.0, 133.6, 129.1, 129.0, 124.8, 110.4, 107.9, 65.9; HRMS-ESI (m/z) calcd $(C_{11}H_9O_4N+Na)^+$: 242.0424 found: 242.0426.

(3,6-Dimethyl-2-nitrophenyl)(4-nitrophenyl)methanol (33):



Reaction Time: 4 h; R*f*: 0.4 (1:4 Ethyl Acetate:Pet. Ether); oil; 9.2 mg, 60%; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.11 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.15 (s, 2H), 5.93 (s, 1H), 2.80 (bs, 1H), 2.23 (s, 1H), 2.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 148.2, 147.1, 136.9, 133.5, 131.3, 131.2, 127.4, 126.8, 123.5, 70.1, 19.8, 17.2; HRMS-ESI (m/z) calcd $(C_{15}H_{14}O_5N_2+Na)^+$: 325.0795 found: 325.0793.

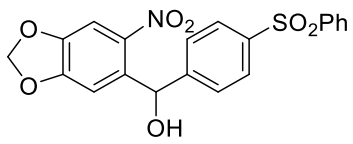
(6-Nitro-2,3-dihydro-1H-inden-5-yl)(4-nitrophenyl)methanol (34):



Reaction Time: 12 h; R*f*: 0.4 (2:3 Ethyl Acetate:Pet. Ether); oil; 6.4 mg, 42%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.13 (d, *J* = 8.8 Hz, 2H), 7.78 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.27 (s, 1H), 6.35 (s, 1H), 3.12 (bs,

1H), 2.96-2.84 (m, 4H), 2.15-2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 146.1, 137.9, 135.8, 127.5, 125.3, 123.6, 121.0, 70.9, 33.0, 32.5, 25.4; HRMS-ESI (m/z) calcd ($C_{16}H_{14}O_5N_2$+Na): 337.0795 found: 337.0794.

(6-Nitrobenzo[d][1,3]dioxol-5-yl)(4-(phenylsulfonyl)phenyl)methanol (35):



Reaction Time: 12 h; R*f*: 0.4 (2:3 Ethyl Acetate:Pet. Ether); oil; 8.0 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.90-7.80 (m, 4H), 7.52-7.40 (m, 6H), 6.94 (s, 1H), 6.39 (d, *J* = 0.8 Hz, 1H), 6.05 (d, *J* = 3.4 Hz, 2H), 2.88 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 147.7, 147.0, 142.2, 141.4, 141.0, 135.1, 133.3, 129.3, 127.9, 127.7, 127.6, 108.3, 105.6, 103.3, 70.6; HRMS-ESI (m/z) calcd $(C_{20}H_{15}O_7NS+Na)^+$: 436.0461 found: 436.0468.

2.3.10 References:

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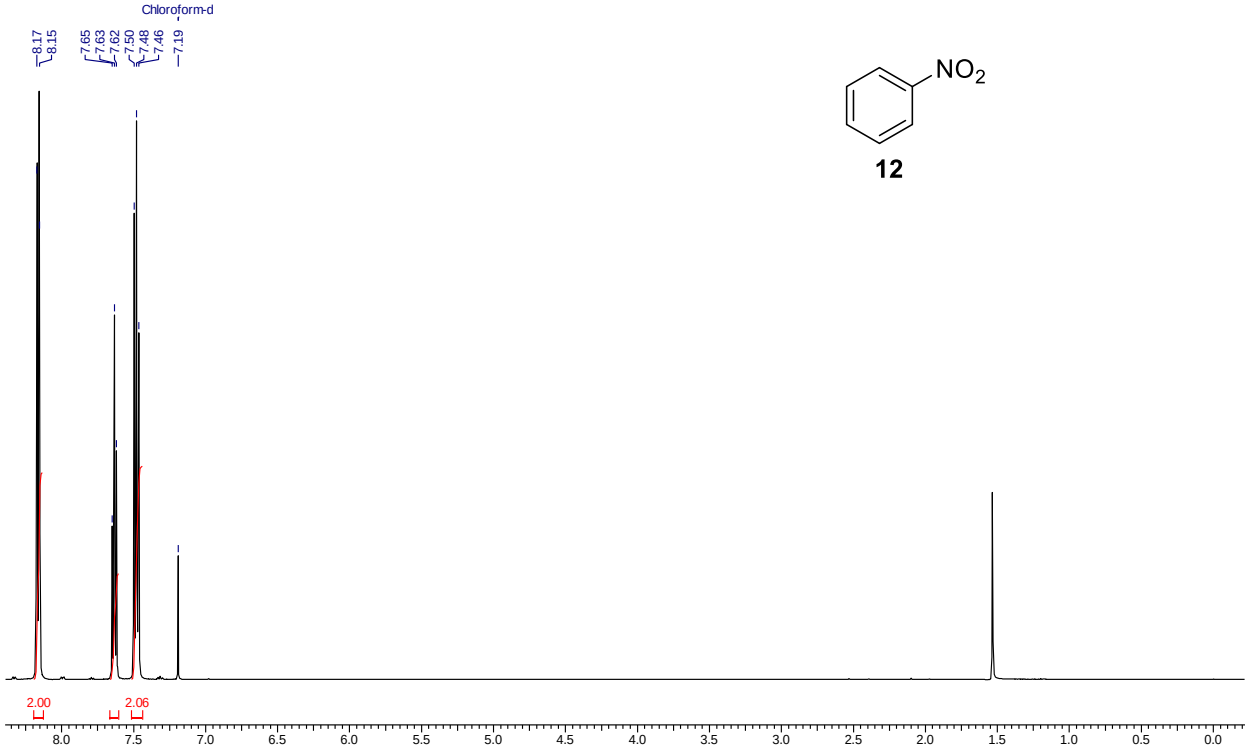
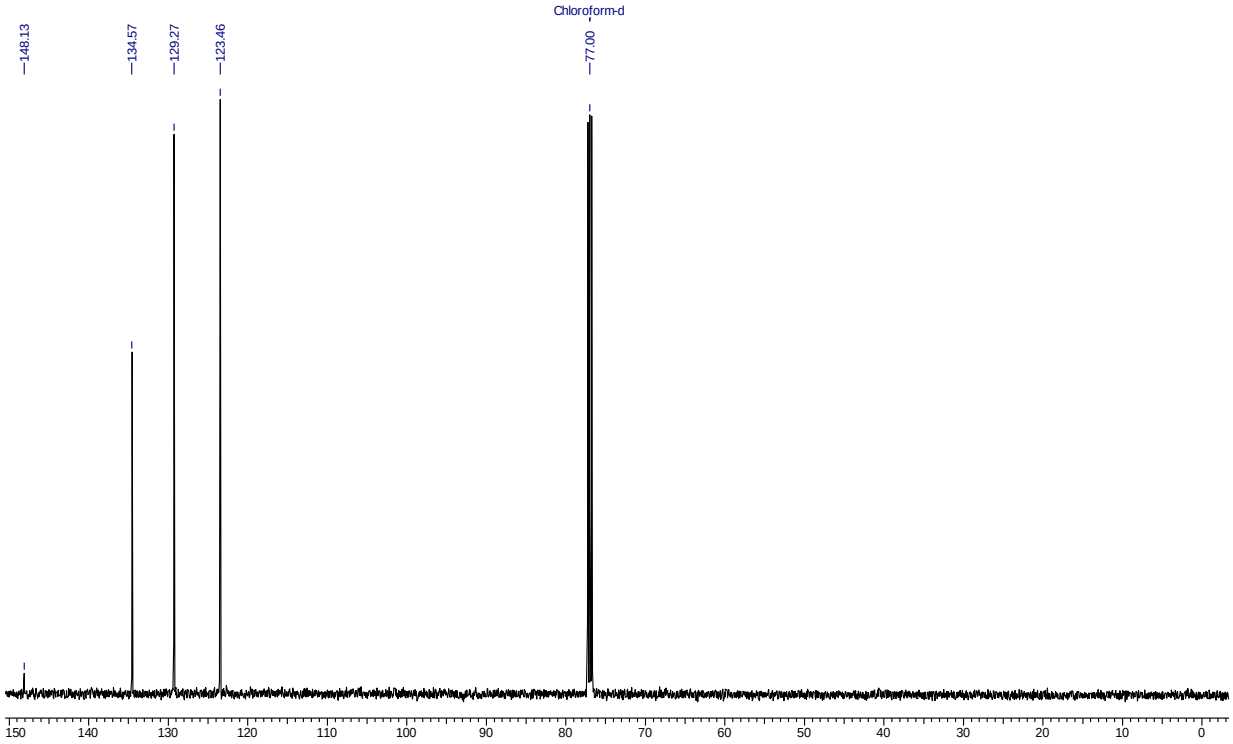
2.3.11 Selected Spectra

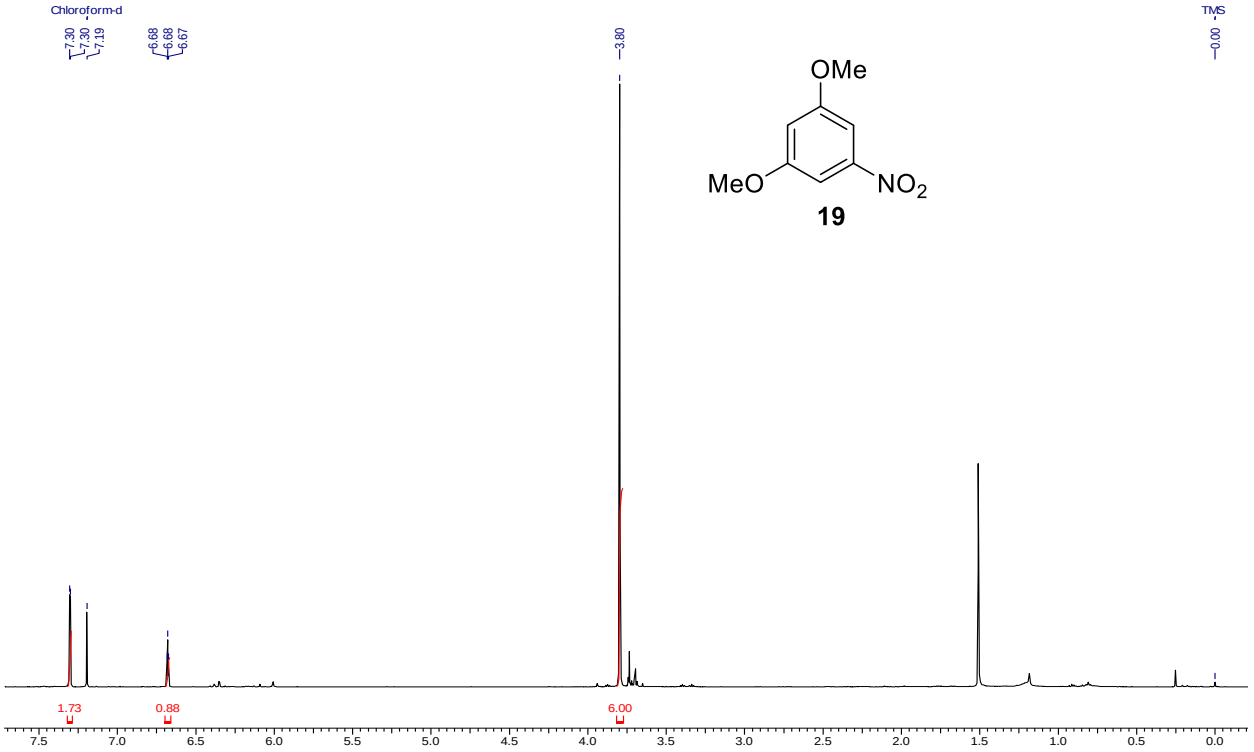
^{1}H NMR Spectra



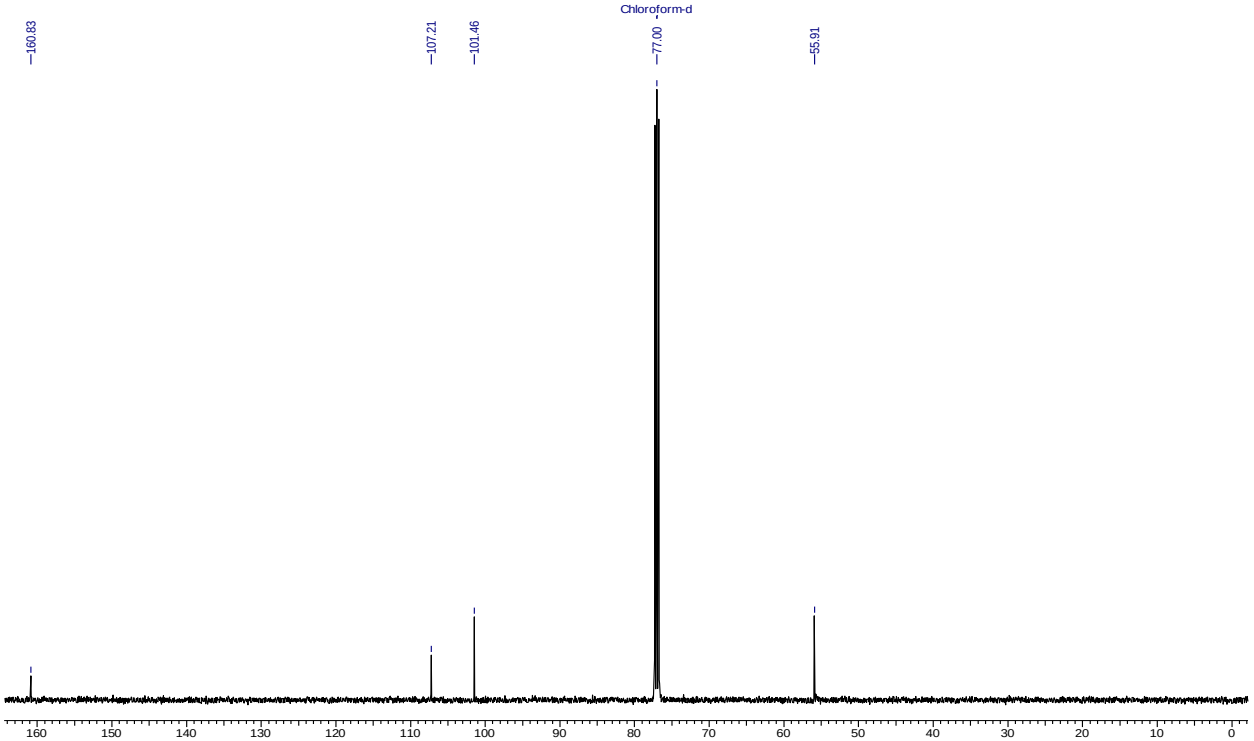
^{13}C NMR Spectra



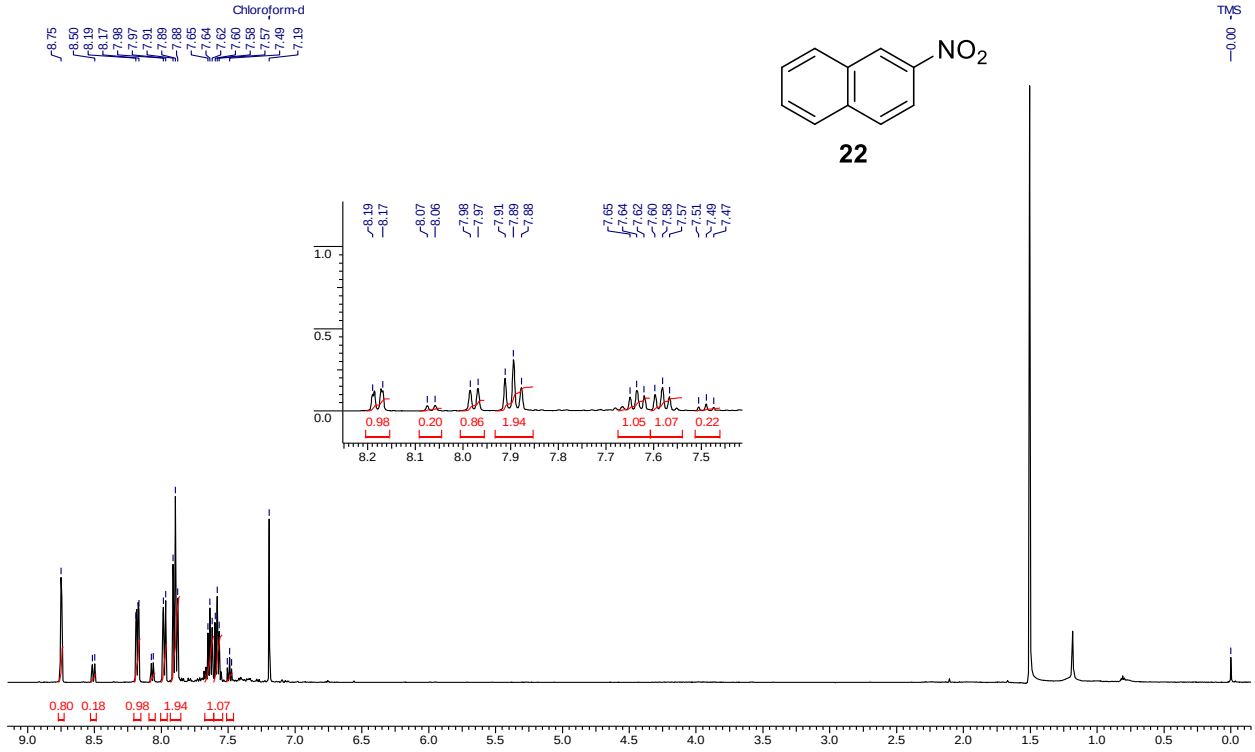
^{1}H NMR Spectra



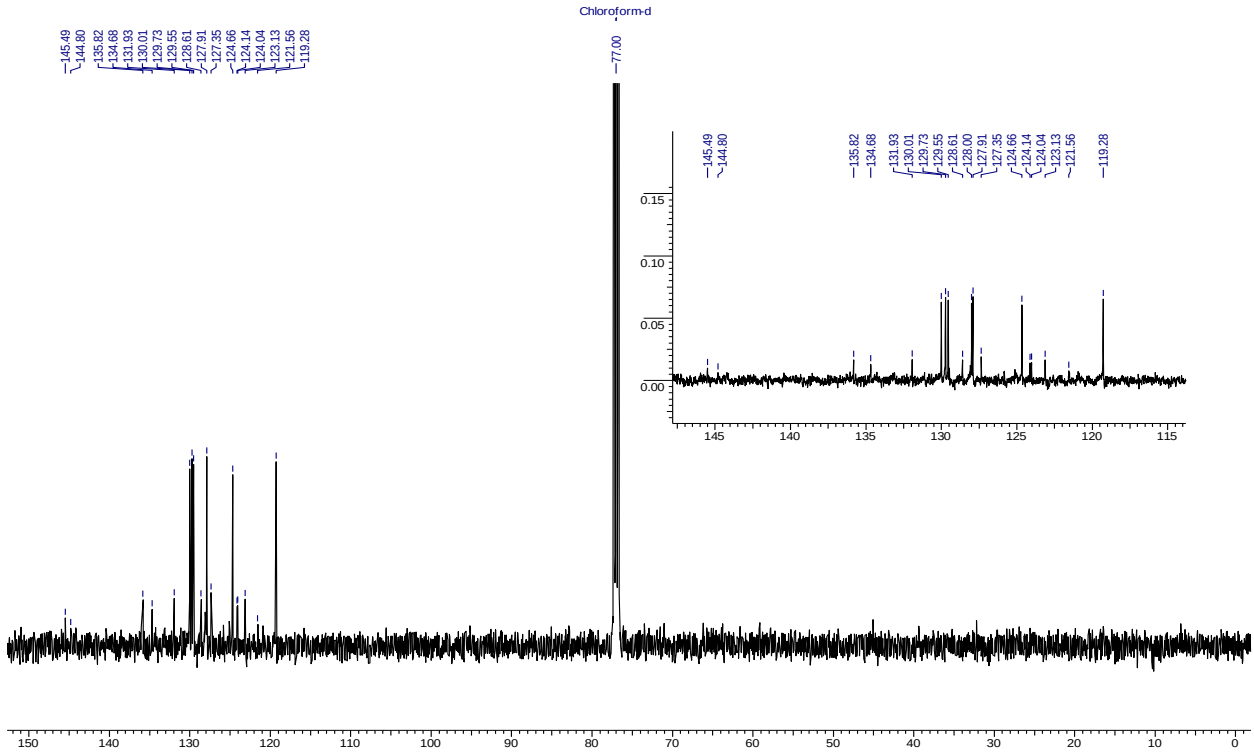
^{13}C NMR Spectra



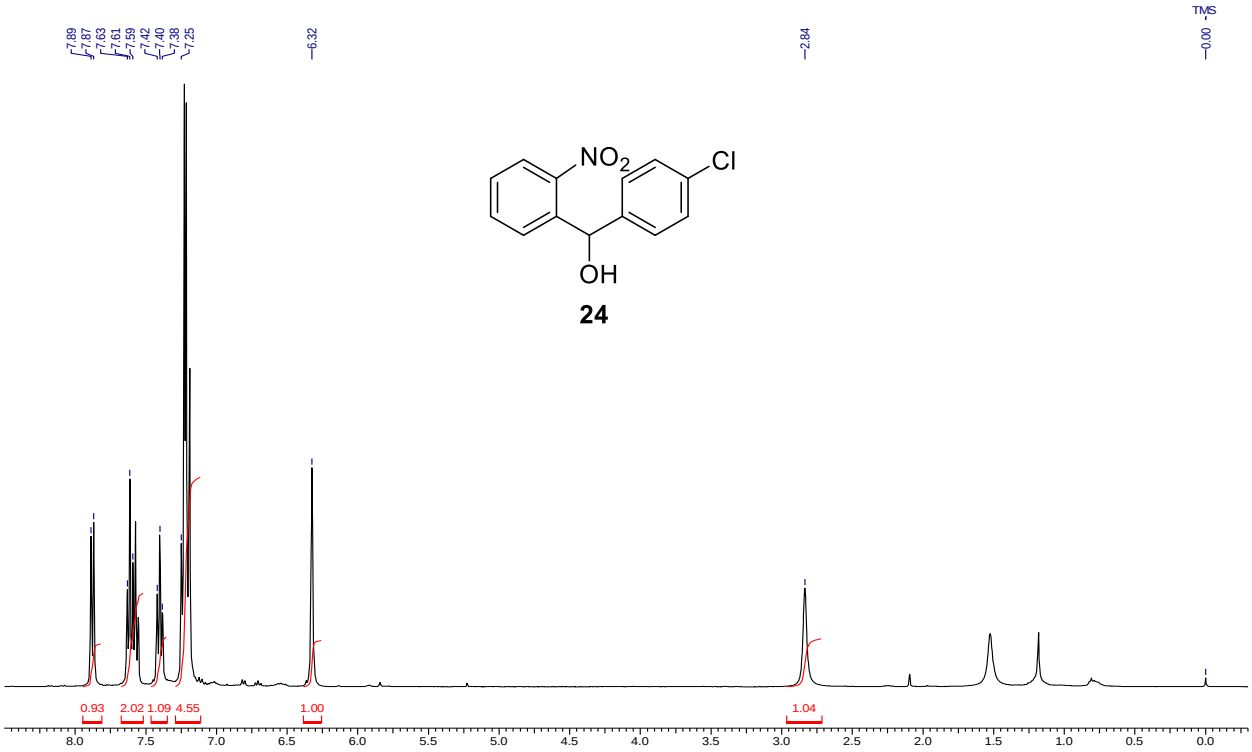
^{1}H NMR Spectra



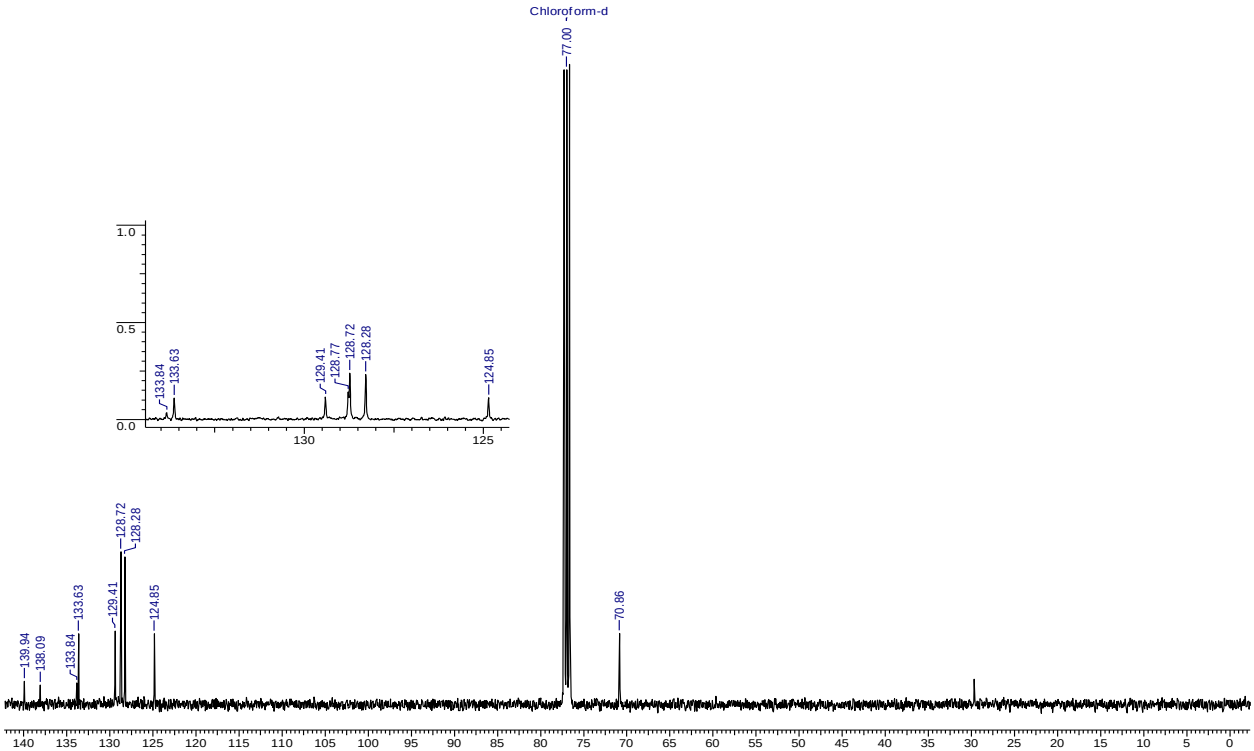
^{13}C NMR Spectra



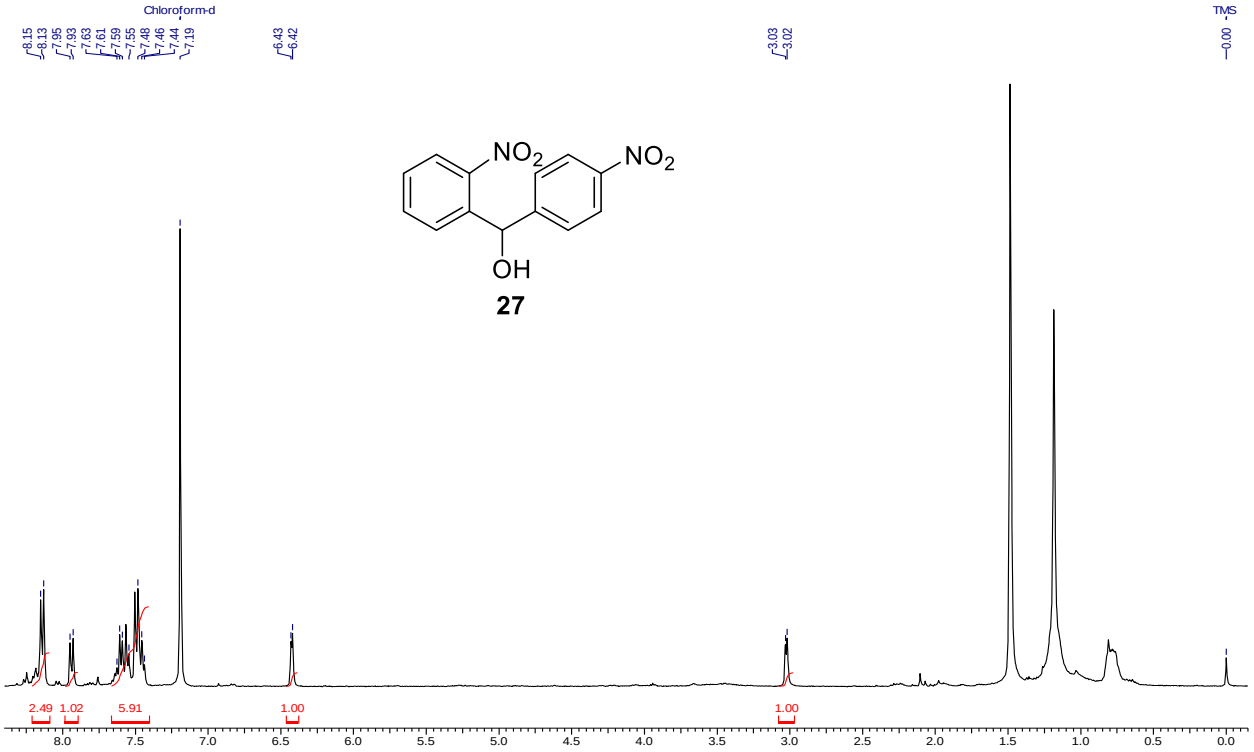
^{1}H NMR Spectra



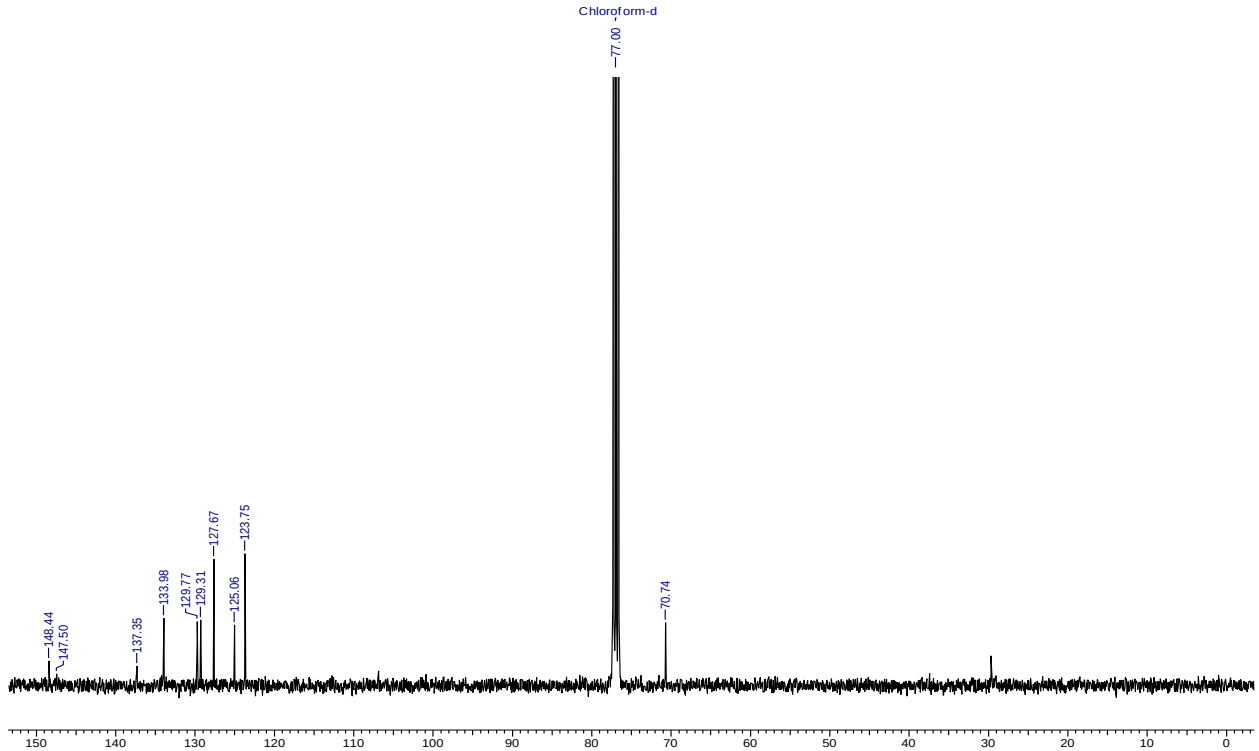
^{13}C NMR Spectra



^{1}H NMR Spectra



^{13}C NMR Spectra



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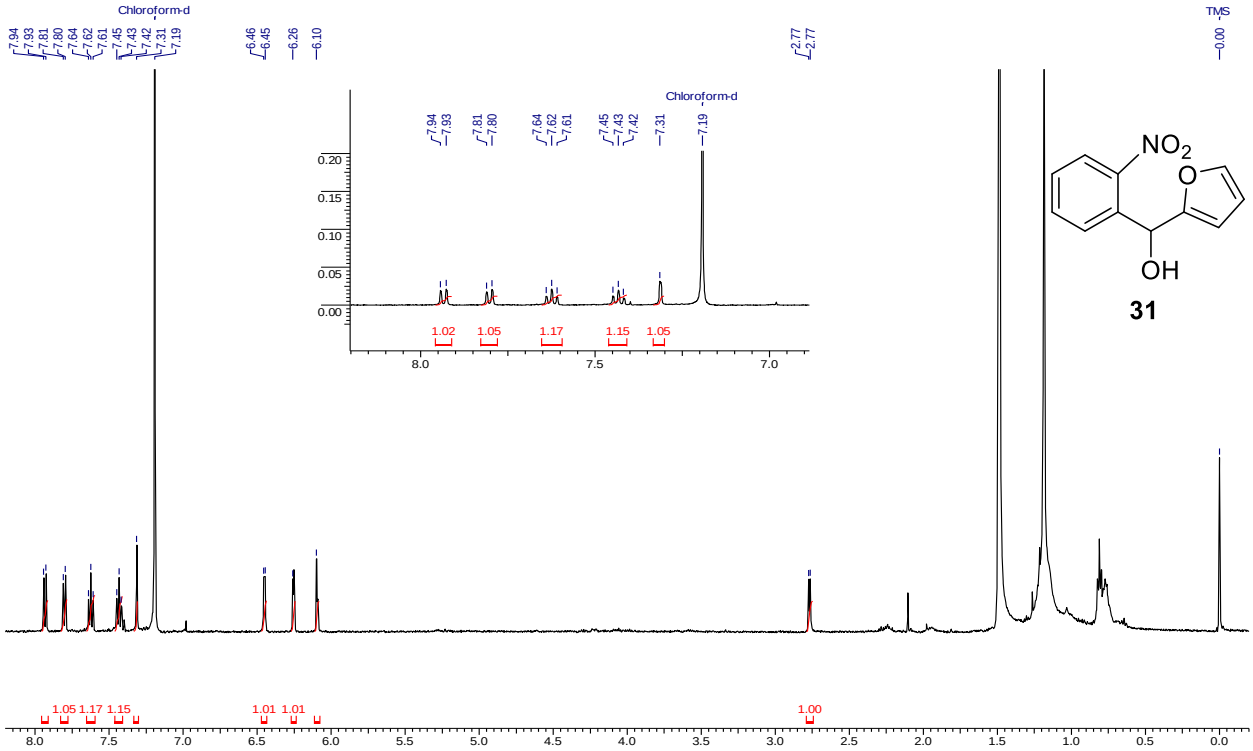

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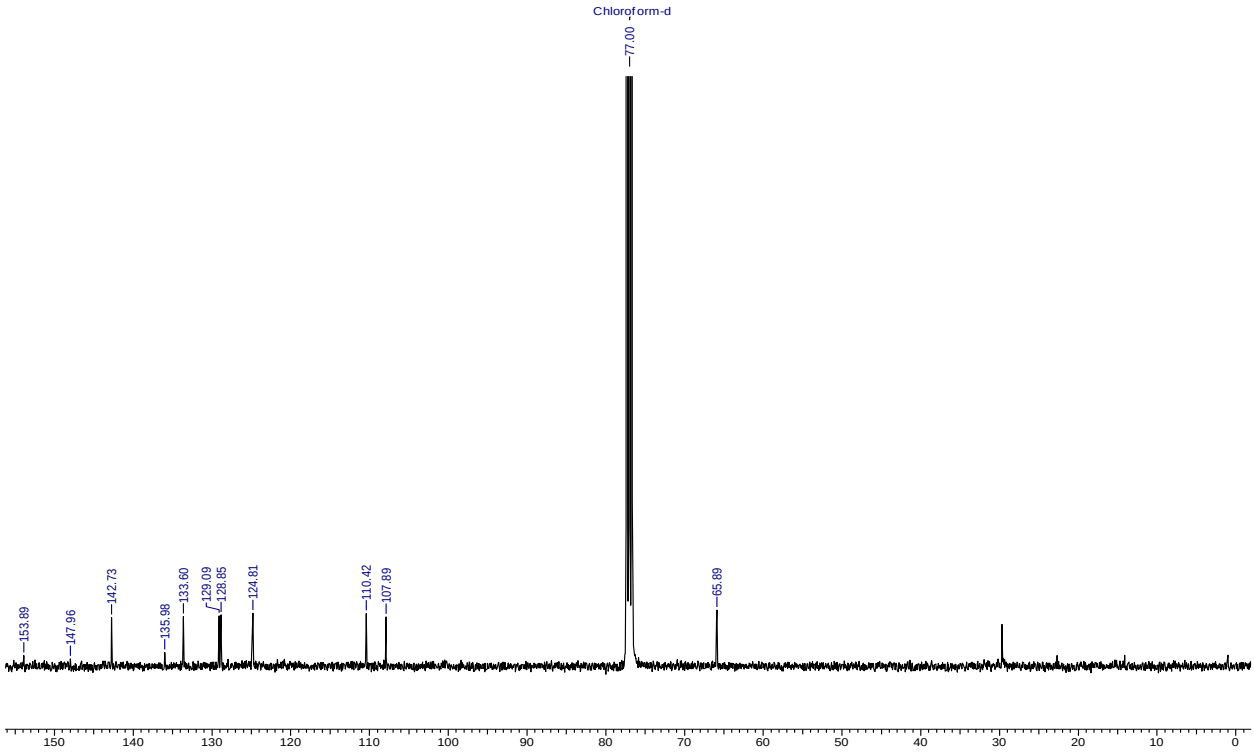

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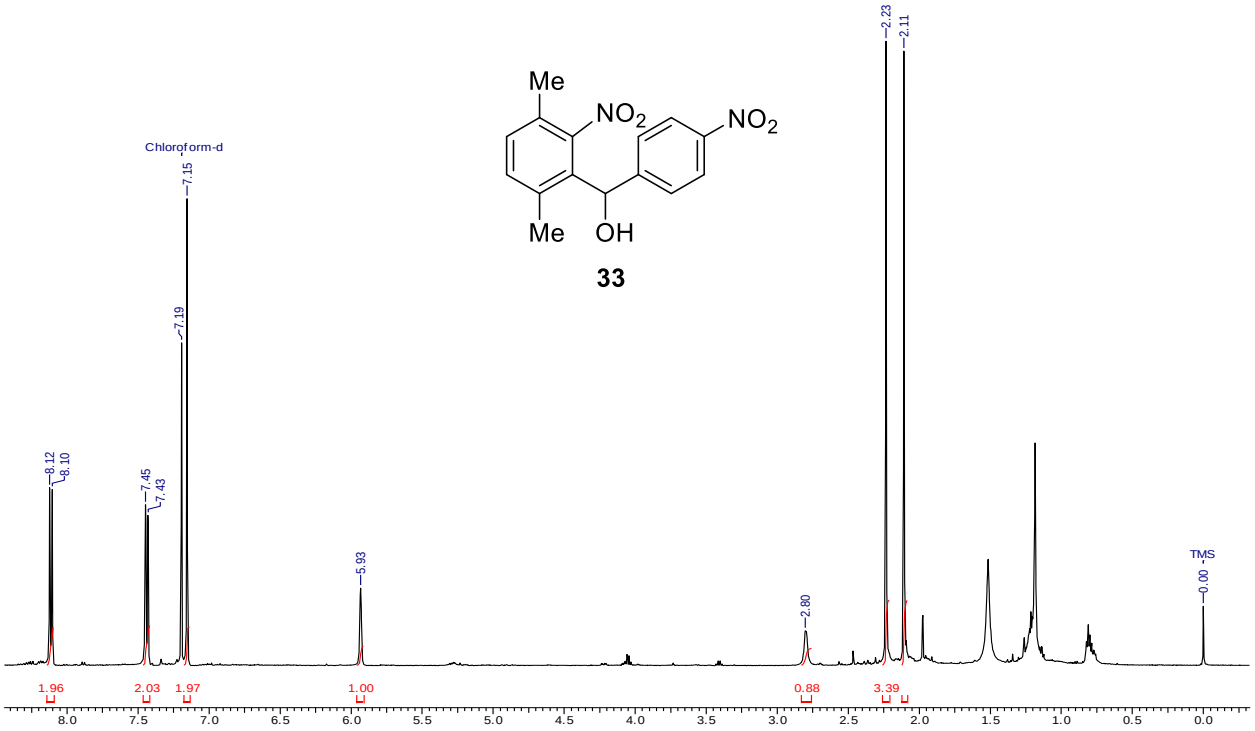

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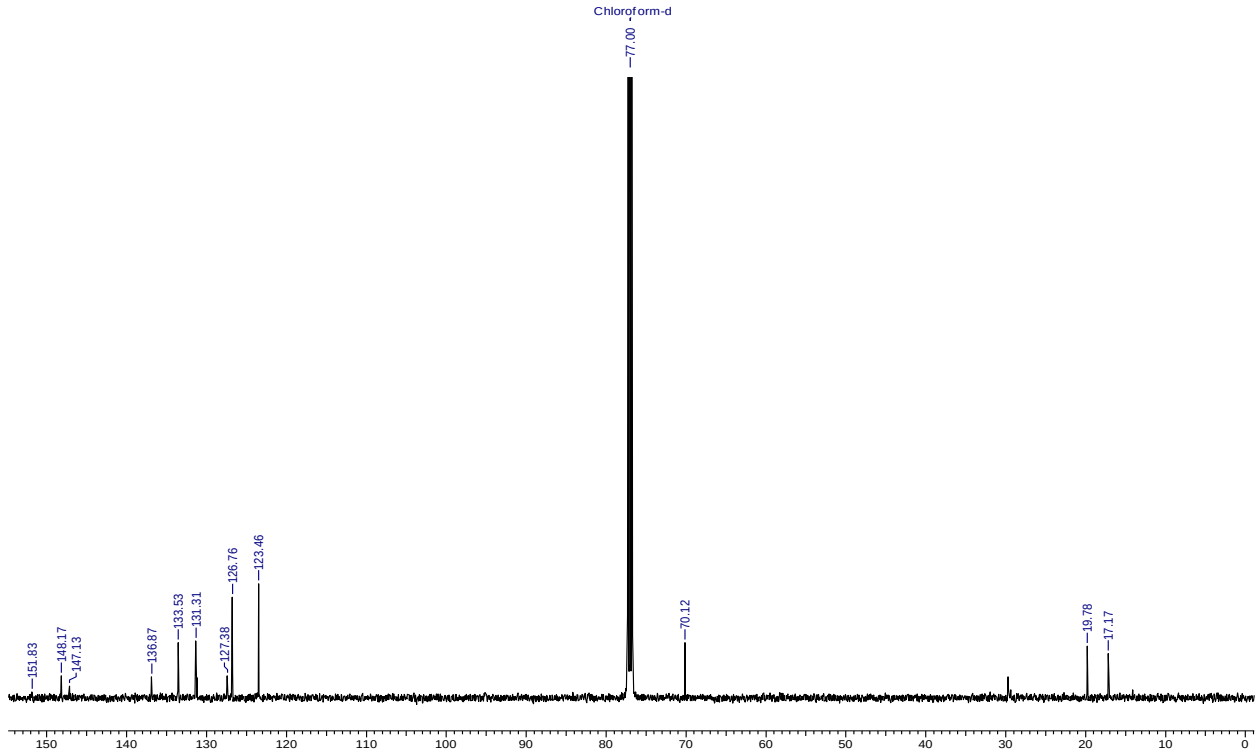

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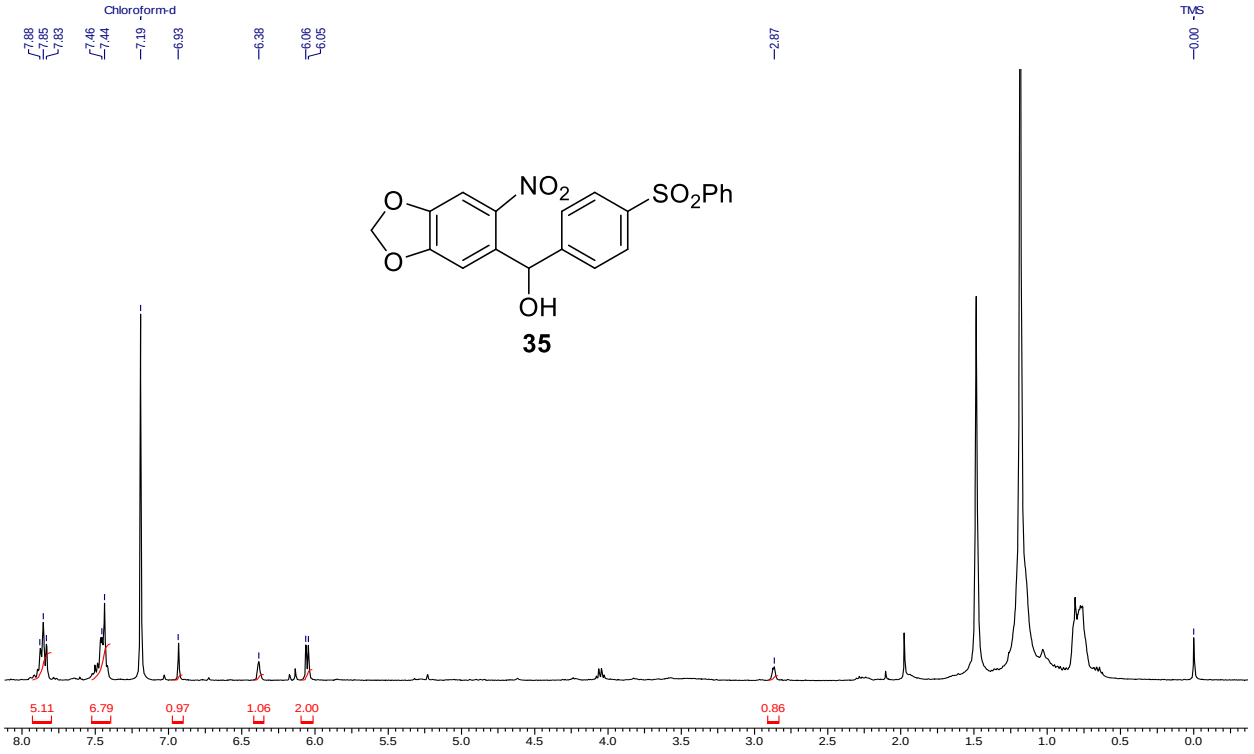

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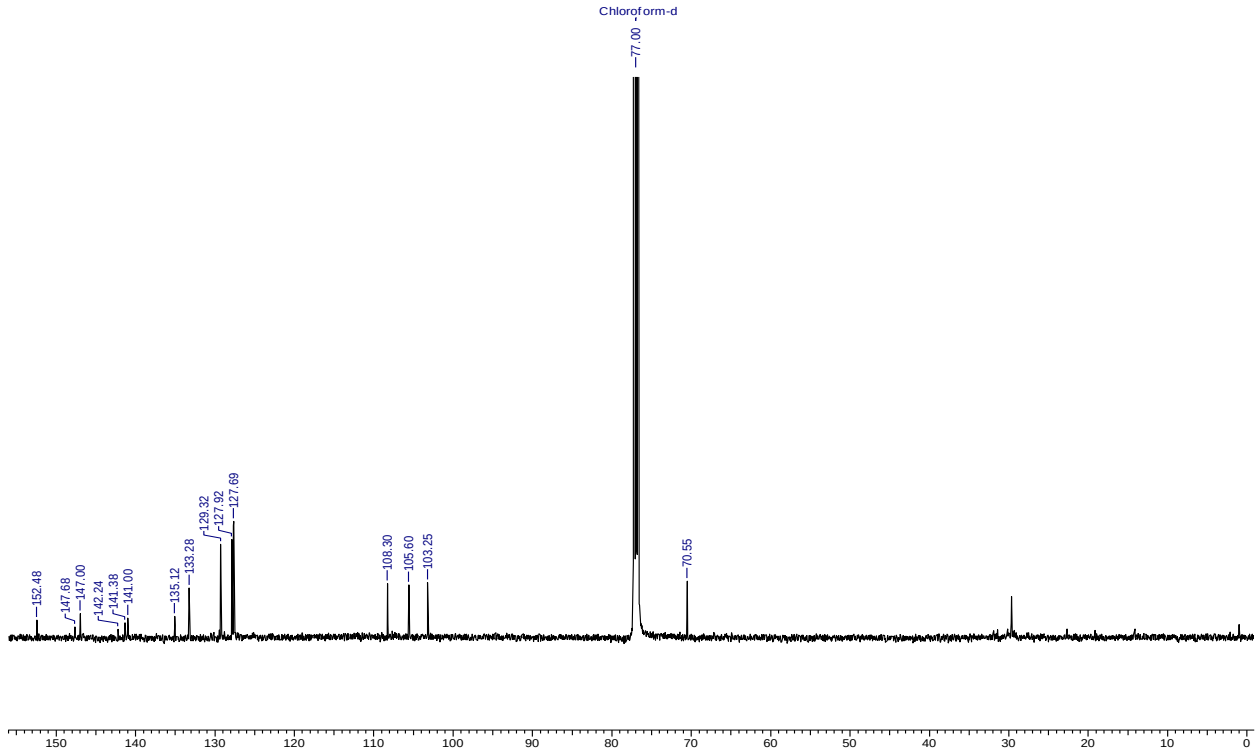

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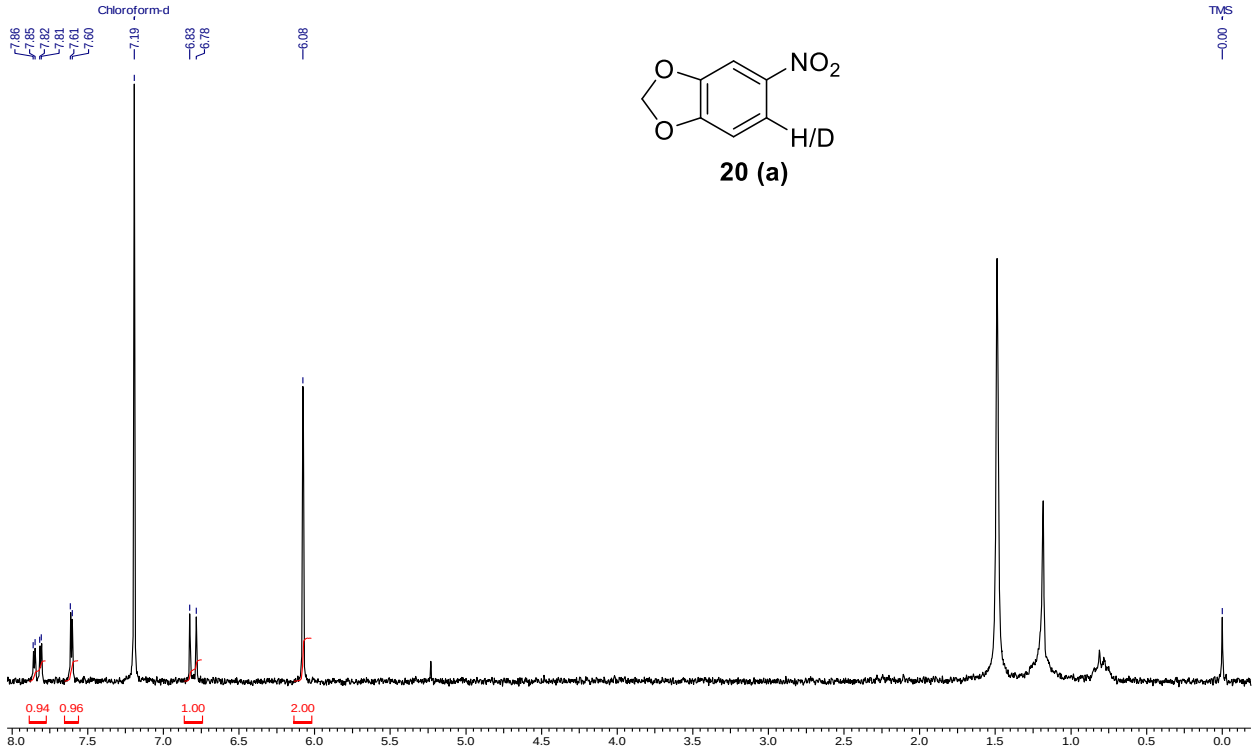
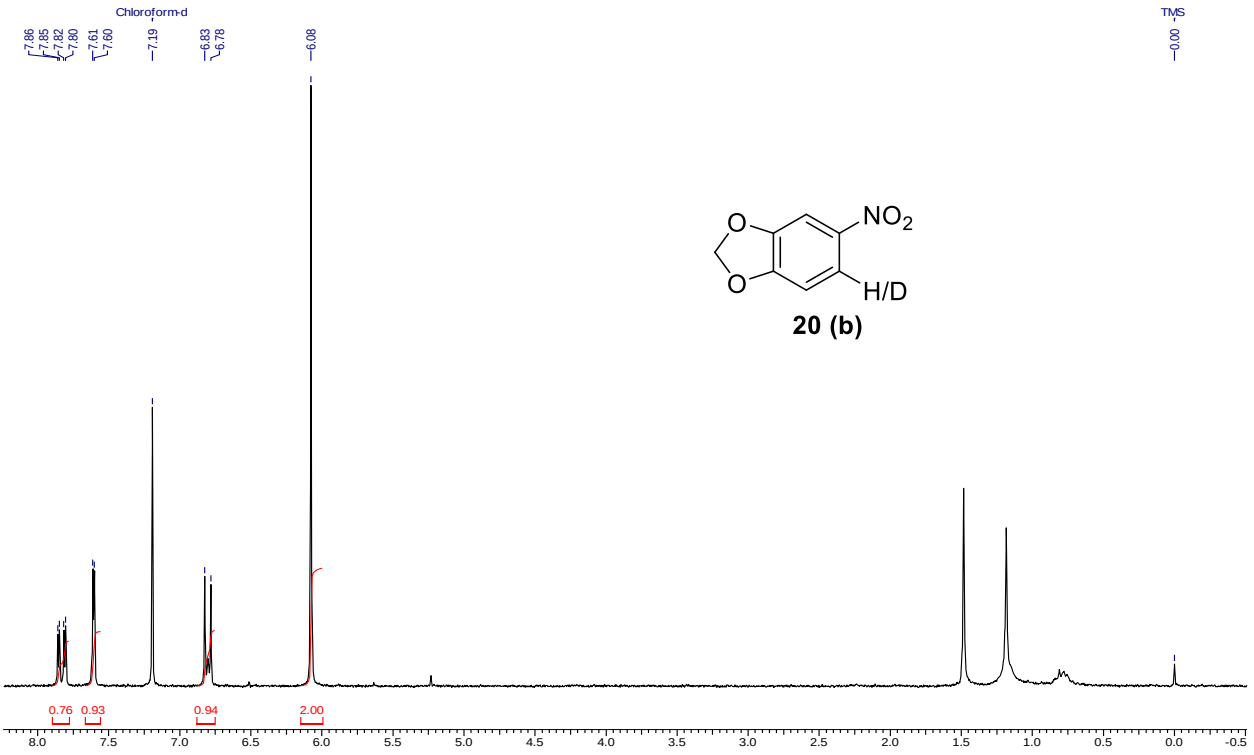


20 (a)



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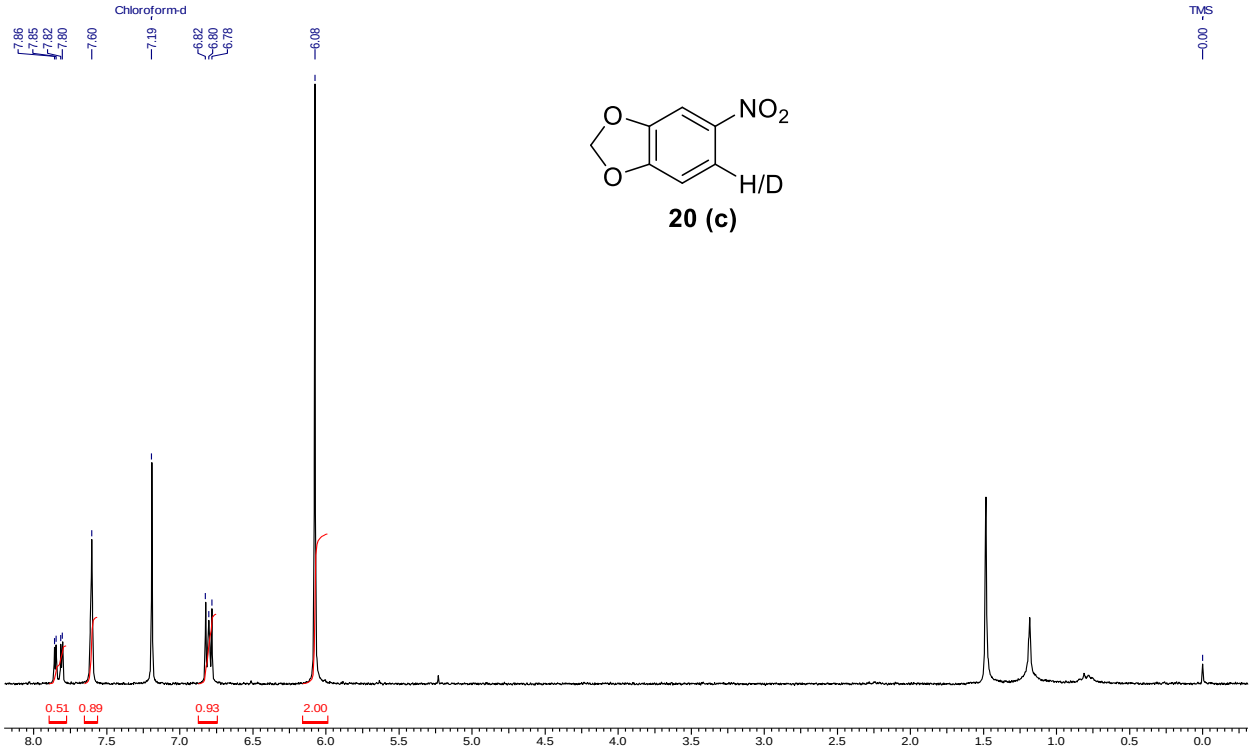
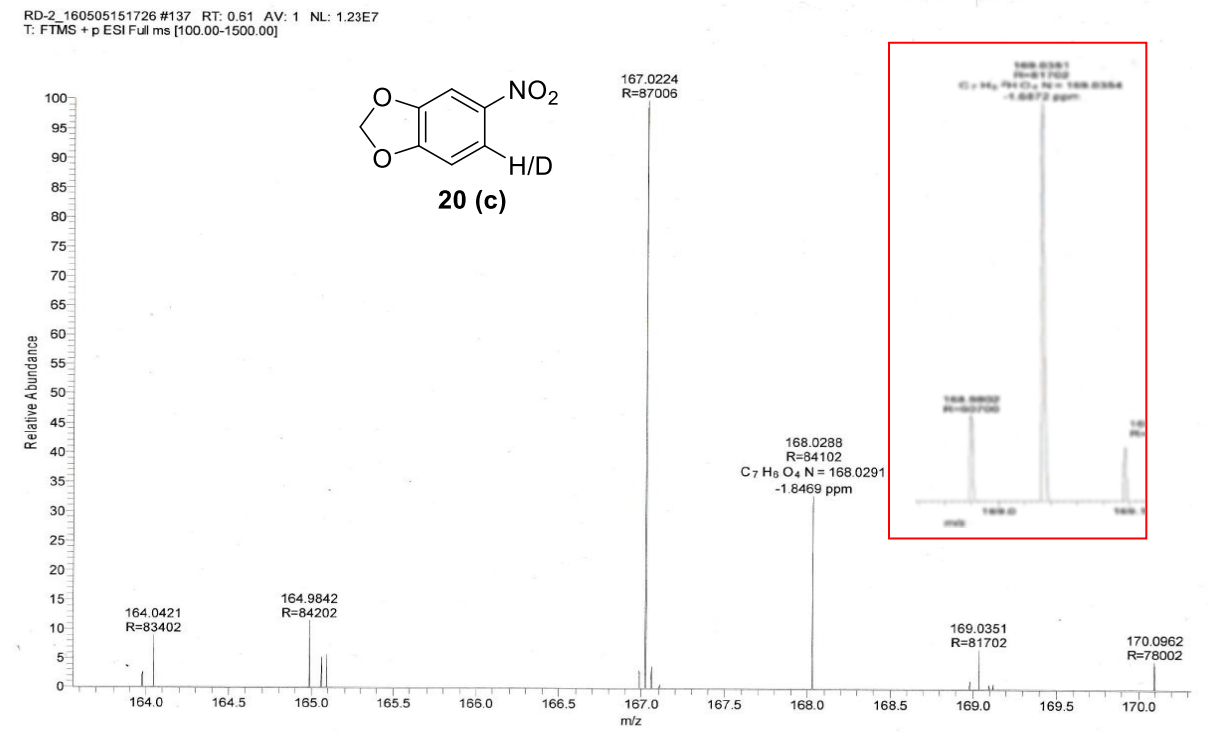
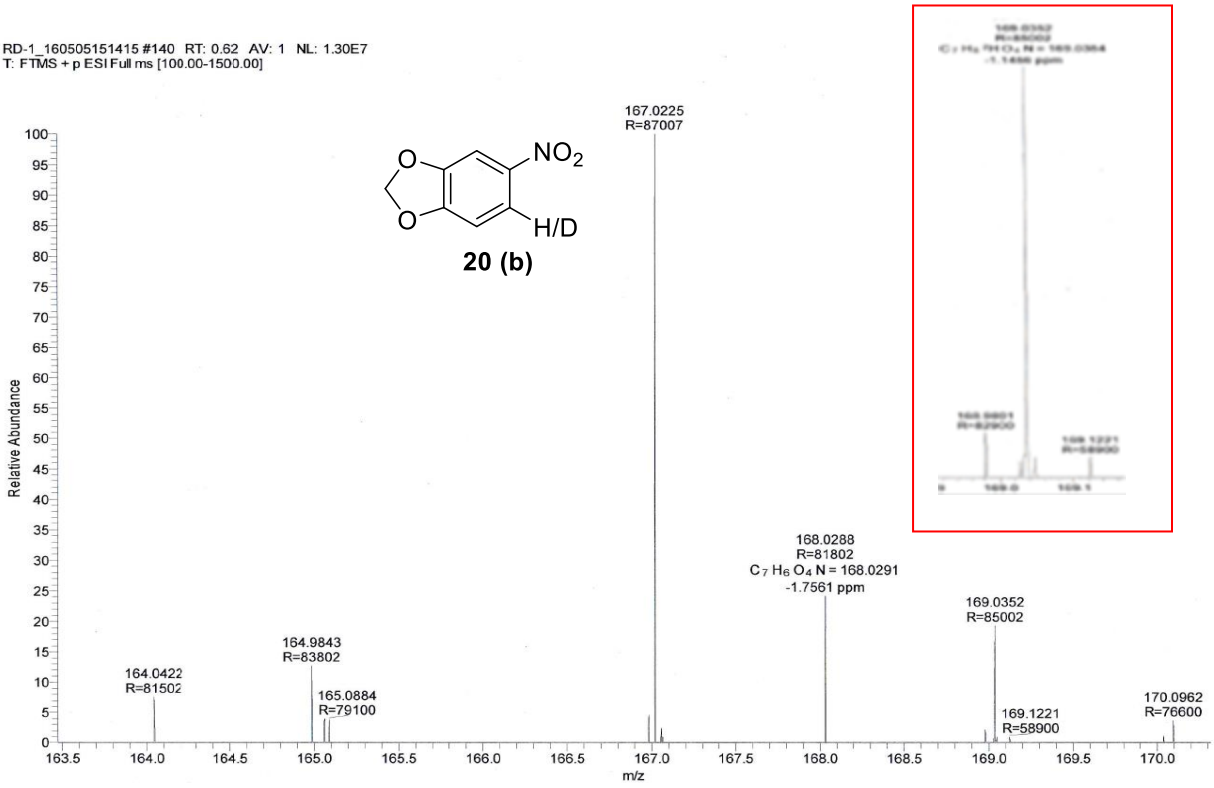


20 (c)

HRMS Spectra of Deuterated compounds





Chapter 3

Proficient Utilization of Aryne in the Total Synthesis of Bioactive Natural Products

Introduction:

The aryne chemistry has paved a new direction in the area of total synthesis of bioactive natural products and pharmaceutically important heterocyclic compounds. Aryne have been wisely implemented in generating key synthetic intermediates in total synthesis of natural products. However in early days of aryne chemistry its utilization in the total synthesis of bioactive natural products was limited due to the harsh reaction conditions required to synthesize aryne species. Nevertheless, Kobayashi's mild method for generation of highly reactive aryne intermediate widely increased its application in total synthesis. Many groups have been involved in using aryne chemistry in total synthesis of natural products (examples covered in Chapter 1, Section II). Our continuous interest in the construction of C–C and C–heteroatom bond by utilizing aryne chemistry prompted us to develop novel synthetic strategies in total synthesis of bioactive natural products by using aryne. In this context we have developed novel synthetic route for the total synthesis of bioactive natural products by means of aryne chemistry. This chapter deals with novel transformations using aryne chemistry for the synthesis of vital synthetic building block, which has been implemented in total synthesis of bioactive natural products. The chapter is divided into two sections.

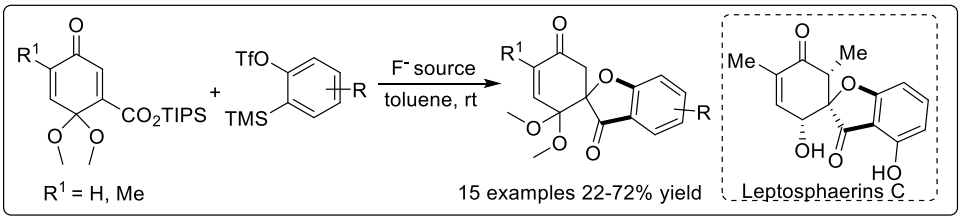
Section 1: Diversity-Oriented Synthesis of Spiroannulated Benzofuran-3-one Scaffold of Leptosphaerin C and Congeners via Aryne Insertion.

Section 2: Study towards Total Synthesis of Lycorane and its Alkaloids.

Section 1: Diversity-Oriented Synthesis of Spiroannulated Benzofuran-3-one Scaffold of Leptosphaerin C and Congeners via Aryne Insertion

3.1.1 Abstract:

The section 1 involves the concise synthesis of functionalized cyclohexenone-fused spirobenzofuran-3-ones under mild reaction conditions. The reaction proceeds in the presence of fluoride source via attack of oxyanion on *in situ* generated aryne leading to insertion of aryne into the C−O bond followed by a regioselective intramolecular conjugate addition. The use of silyl-protected acid was crucial for the transformation. Further, this protocol was successfully demonstrated for the synthesis of Leptosphaerin C core and its novel analogues. In an attempt towards total synthesis of Leptosphaerin C, the vital products were isolated which resemble the natural products cores isolated along with Leptosphaerin C.



This work has been published in *J. Org. Chem*. **2017**, *82*, 4875.

3.1.2 Introduction:

Various bioactive natural products and drugs encompass vital spiro-bicyclic scaffold, in particular the cycloalkane-fused benzofuran-3-ones structural framework is very common.[1]

In literature, the synthetic routes for complex architecture spirobenzofuran-3-ones possessing biological importance have always been a topic of intensive investigation in the scientific community.[1e,2] The building of spirocyclic skeleton has always been a challenging task, which requires synthetic design based on specific strategies. The spiro carbon atoms having steric strain

are responsible for facile rearrangements/ring opening that can lead to different compounds.[3] Generally, the construction of spirocyclo-benzofuranones requires prefunctionalized benzofuran ring, multiple steps, organo-/metal-catalyst and in some cases harsh reaction conditions.[1e,2] In this context we postulated the construction of spirocyclo-benzofuranones via aryne chemistry.

The polyketide Leptosphaerins C isolated from solid cultures of the ascomycete fungus *Leptosphaeria*[1b] featuring spirocyclohexane benzofuran-3-one core caught our attention because the compounds of this class exhibits antifungal properties and the synthesis of this intriguing structural motif has not been reported.

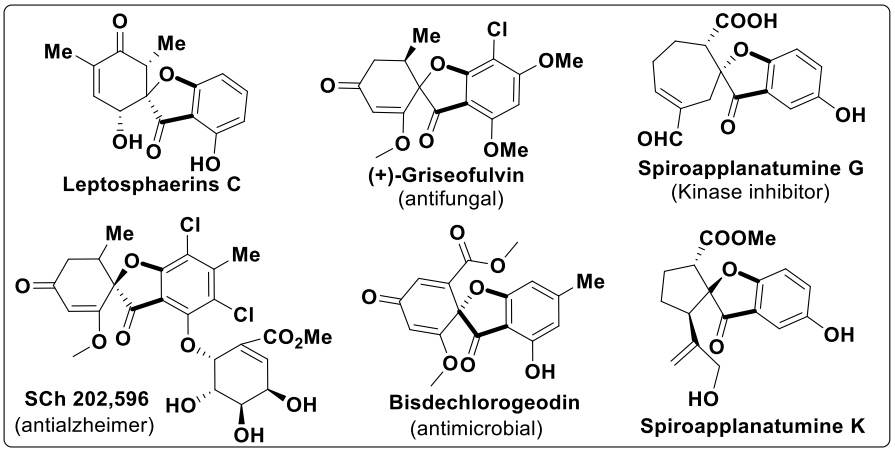
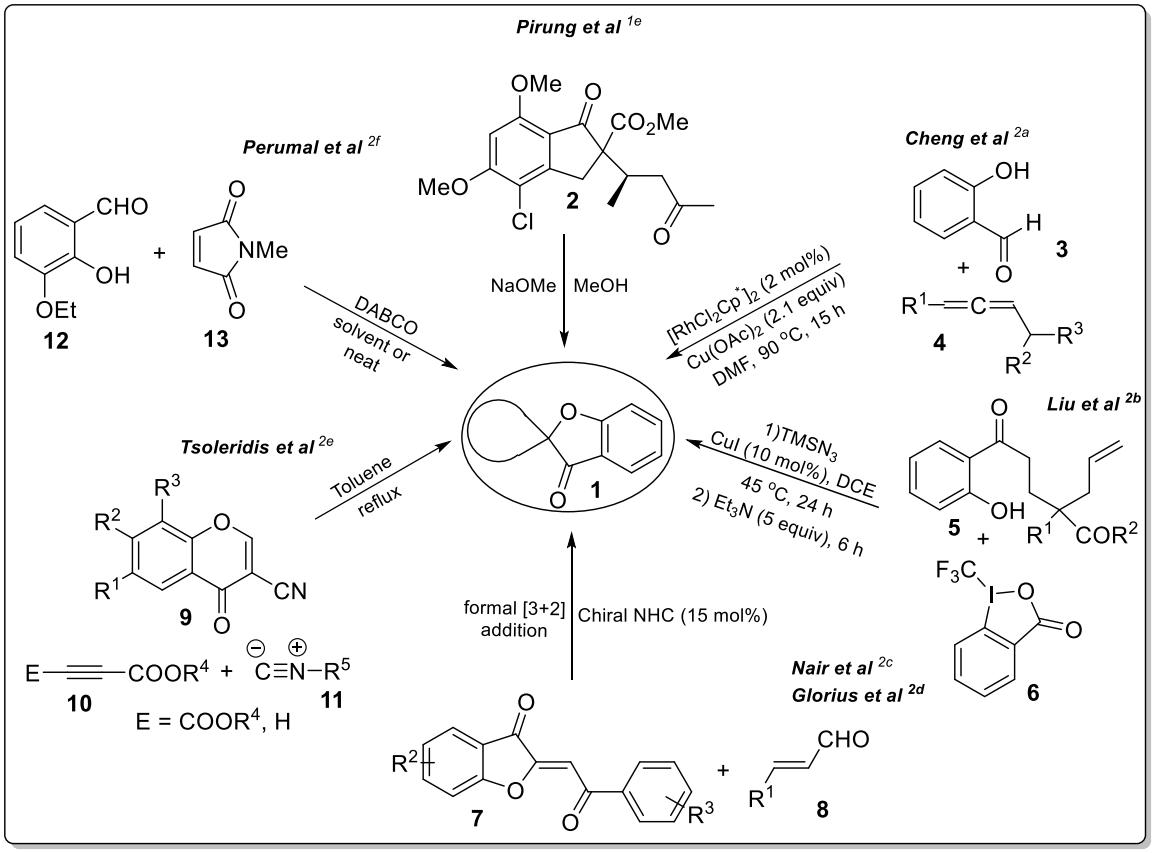


Figure 1: Natural products and drugs having cycloalkyl-fused spirobenzofuran-3-one core[1]

3.1.3 Review Literature:

In literature there have been many interesting methodologies reported for the construction of spiro-core. Herein, few of them we are documented. Pirrung and co-workers reported the first enantiomeric synthesis of griseofulvin. However the construction of spiro motif was carried in two steps (Scheme 1). The compound **2** was synthesized in six steps, which underwent further transformation under basic condition to yield spiro-core **1**.[1e] Cheng *et al* demonstrated the synthesis of spiro core **1** by reacting salicylaldehyde **3** and allenes **4** in the presence of $[RhCl_2Cp^*]_2$ at 90 ^oC (Scheme 1).[2a] Liu *et al* reported the one-pot domino operation for the



Scheme 1: Schematic representation of reported spiro-core structures

synthesis of various CF_3-bearing spirobenzofuranone-lactam units by reacting **5** and **6**. The attractive feature of this process is the incorporation of pharmacophore CF_3 group on spirolactam moiety (Scheme 1).[2b] Further, Nair and co-workers carried out successful synthesis of homoenolate annulation of enal **7** and aurone **8** providing diverse range of cyclopentene-fused spirobenzofuran-3-ones by implementing nucleophilic heterocyclic carbene (Scheme 1).[2c] Glorius group reported the enantioselective synthesis of various substituted spiro-heterocycles via [3+2] cycloaddition annulation of α,β,-unsaturated aldehydes **7** with aurones **8** using chiral N-heterocyclic carbene (Scheme 1).[2d] The successful utilization of 3-cyanochromones **9** was achieved for the synthesis of functionalized spirobenzofuranones in multicomponent reaction involving isocyanides **10** and acetylenecarboxylates **11** (Scheme 1).[2e] Perumal and co-workers

elegantly reported the application of Baylis–Hillman reaction for the synthesis of spirobenzofuranol derivatives. The unexpected cyclization was observed in Baylis-Hillman reaction involving salicylaldehyde **12** with *N*-aryl/ alkyl maleimides **13** under neat conditions (Scheme 1). [2f]

3.1.4 Origin of the work:

The literature reports mainly deals in the construction of spirobenzofuranone involving prefunctionalized benzofuran-3-one core or chromones. In most of the cases it has been observed that the operation involves expensive transition metals, costly organocatalysts and reagents, high reaction temperature etc.

3.1.5 Objective:

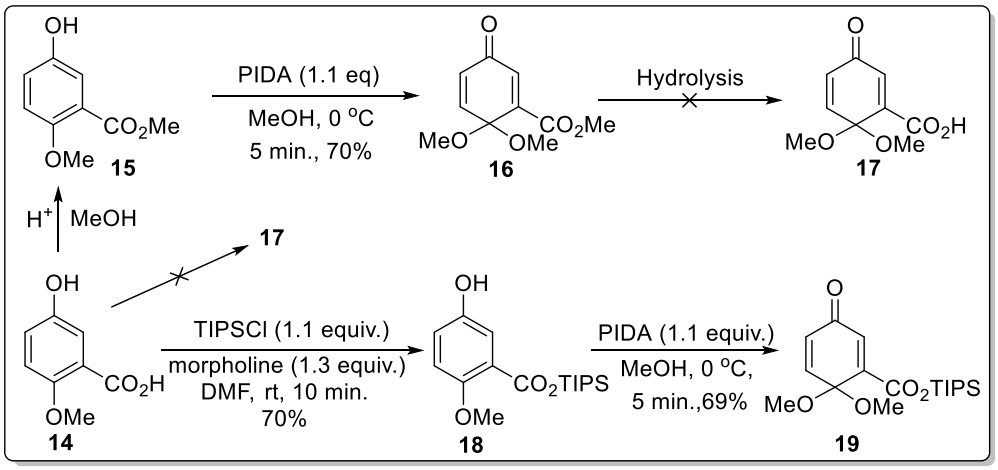
The high importance of spirobenzofuranone bearing natural products and bioactive drugs encouraged us to develop its synthesis under much milder reaction conditions. At this stage, our research in developing novel methodologies by employing aryne chemistry, prompted us to utilize it for the construction of such complex spiro motif. In this context we planned to develop a milder and concise protocol using arynes, which would install the spiro and the benzofuranone core in a single step.

For the construction of 2-spirocyclohexane benzofuran-3-one skeleton we thought, insertion of aryne into C–O bond followed by intramolecular Michael addition would be a promising method. Prior to our methodology Larock *et al* reported the synthesis of *o*-hydroxyaryl ketones, xanthones, 4-chromanones, and flavones[4] via intermolecular C–O addition of carboxylic acids to arynes at 120 ^{o}C. Ma and coworkers reported the synthesis of chromone motifs from 2,3-allenoic acids[5] by extending Larock's protocol. Further, Guo and co-workers implemented the same concept in the construction of *o*-hydroxy-substituted arylphosphine oxides, -phosphinates, and -

phosphonates using organophosphorous acid substrates.[6] To further explore the aryne insertion methodology we planned the construction of spirobenzofuranone core which would be further applied for the synthesis of Leptosphaerin C and its congeners.

In this section, we describe the aryne insertion into C–O bond followed by Michael addition leading to interesting spiro-bicyclic compounds at room temperature.

3.1.6 Result and Discussion:



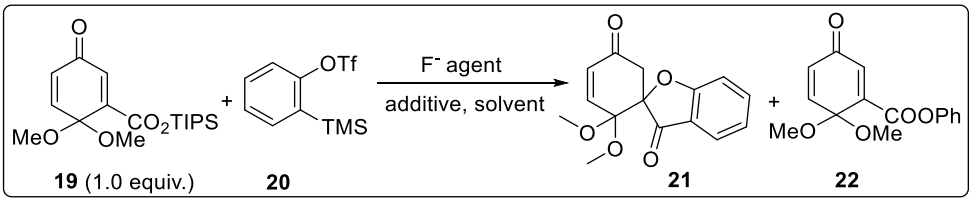
Scheme 2: Synthesis of the key substrate 19

The methodology commenced with the synthesis of the substrate **19** (Scheme 2). The synthesis of vital compound **17** from acid **14**[7] and from dearomatized compound **16**[8] met with failure.

The unsuccessful attempt for synthesis of acid **17** led to its modification. The protection of acid **14** using 1.1 equiv of TIPS chloride and morpholine (1.3 equiv) as a base in DMF at room temperature furnished **18**.[9] Further, **18** on treatment with 1.1 equiv of PIDA in methanol furnished the silyl-protected dearomatized compound **19** in good yield (Scheme 1).

We started our optimization studies by reacting **19** and **20** (Table 1, selected entries). The reaction failed in THF solvent when CsF was employed (Table 1, entries 1 & 2). The solvent switch from THF to acetonitrile and THF-acetonitrile (Table 1, entries 3 & 4) resulted in

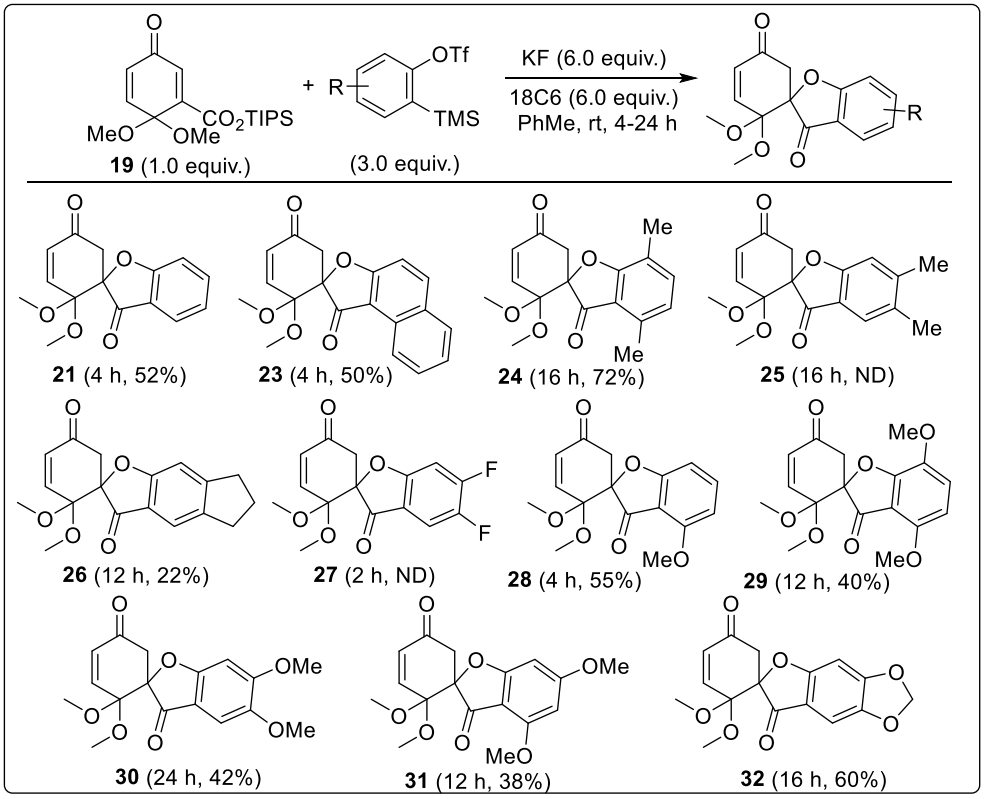
Table 1: Optimization studies to obtain spiro-bicyclic benzofuran-3-one[a,b]



entry no	Solvent[b]	20 (equiv.)	F⁻ (equiv.)	additive (equiv.)	temp	time (h)	21/22 (yield%)[c]
1	THF	2.0	CsF (3.0)	-	rt	12	-
2	THF	4.0	CsF (6.0)	-	80-120 °C	4-12	-
3	ACN	4.0	CsF (6.0)	-	rt	4	-/60
4	THF-ACN(1:1)	4.0	CsF (6.0)	-	rt	4	-/45
5	DCE/toluene	4.0	CsF (6.0)	-	rt-80°C	4-12	-
6	THF	2.0	TBAF (4.0)	-	rt-80°C	4-12	-
7	THF	2.0	KF (3.0)	18C6 (3.0)	rt	4	20/10
8	1,4-dioxane	2.0	KF (4.0)	18C6 (4.0)	rt	12	20/5
9	toluene	2.0	KF (4.0)	18C6 (4.0)	rt	4	32/7
10	toluene	2.0	KF (4.0)	18C6 (4.0)	rt	12	24/5
11	toluene	2.5	KF (5.0)	18C6 (5.0)	rt	4	42/8
12	**toluene**	**3.0**	**KF (6.0)**	**18C6 (6.0)**	**rt**	**4**	**52/6**

a) all reactions were performed on 29 mg of **19**, b) 0.5 mL of solvent, c) isolated yields

exclusive O-arylated **22** product formation. The combination of DCE-toluene also failed to give the expected product **21** (Table 1, entry 5). TBAF as a fluoride was also unsuccessful (Table 1, entry 6). Finally formation of expected product **21** took place in 20% along with 10% of **22** (Table 1, entry 7) when, KF and 18-crown-6 (18C6) in THF was employed. The same protocol was repeated in 1,4–dioxane for 12 h taking 4.00 equiv of KF, but there was no improvement in the yield of compound **21** (Table 1, entry 8). The change in solvent to toluene and decrease in the reaction time to 4 h (Table 1, entry 9) improved the yield of spiro motif **21** to 32%. Further, reaction time was extended (Table 1, entry 10) and it was observed that yield of **21** got deteriorated. The decent yield of product **21** (42%) was achieved in 4 h when, 2.5 equiv of aryne precursor, 5.00 equiv of KF and 18-crown-6 (18C6) was utilized (Table 1, entry 11). Finally we were successful in achieving the maximum possible yield of the spiro product **21** in 52% (Table 1, entry 12) by increasing the equivalent of aryne precursor to 3.0.

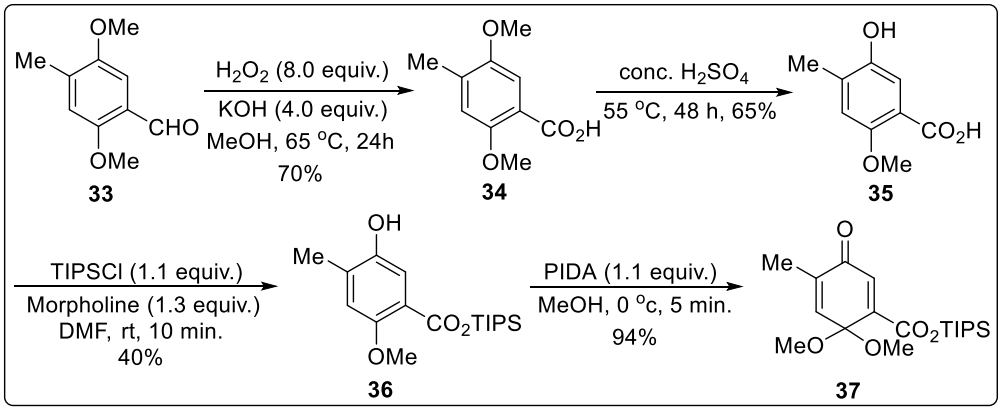


a) all reactions were performed on 25 mg of **19**, b) 0.5 mL of toluene, c) isolated yields, ND = not determined

Scheme 3: Scope of the developed protocol on various aryne substrates [a-c]

The optimized condition in our hand prompted us to test the reactivity of different substituted aryne precursors (Scheme 3) with compound **19**. The unsymmetrically substituted naphthalene based aryne precursor worked similar to simple aryne precursor providing the single regioisomer spiro-product **23** in 50% yield. The spiro-product **24** was formed in excellent yield when 2,5-dimethyl substituted aryne precursor was reacted with **19**. In the case of 3,4-dimethyl aryne precursor, complex product formation was observed and the spiro-product **25** was not detected. Indane based aryne precursor also provided less yield of the spiro-product **26**. The difluoro-aryne precursor on reaction with **19** provided the expected product **27** in low yield and its purification could not meet the analytical requirements. Overall; electron donating group substituted aryne precursors delivered the corresponding spiro-products **28-32** in moderate to good yields.

Interestingly, excellent regioselectivities were observed for unsymmetrically substituted aryne precursors furnishing **28** and **31** as the only regioisomers (Scheme 3).

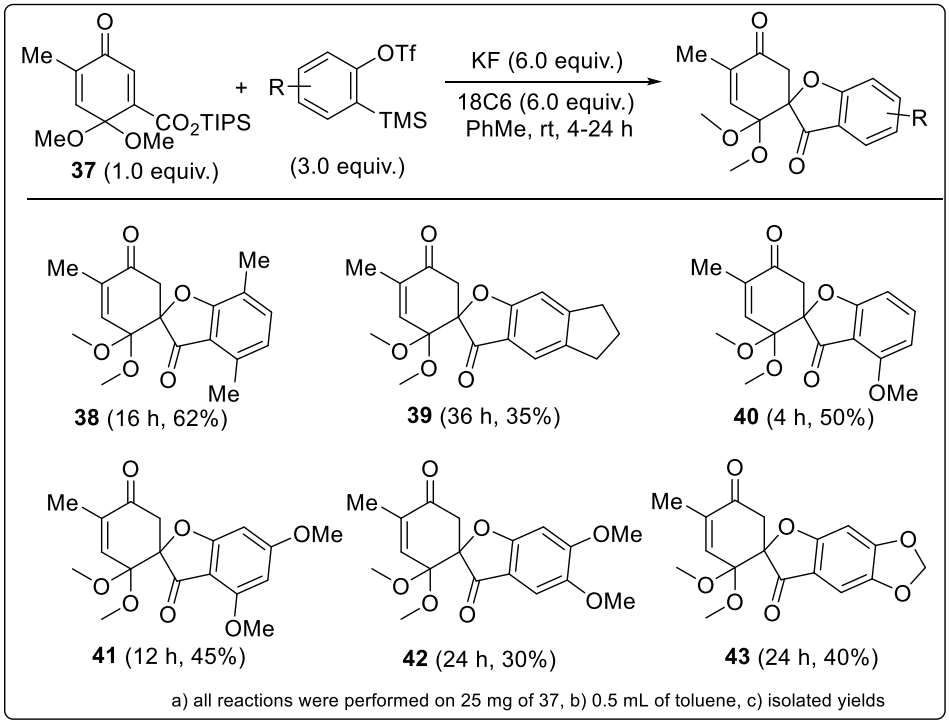


Scheme 4: Synthesis of the substrate **37**

The optimized protocol worked very well in the case of symmetrically substituted dienone substrate **19.** We were also curious to check the reactivity of unsymmetrically substituted dienone with different substituted aryne precursors. The unsymmetrically substituted dienone substrate **37** (Scheme 4) was tested under optimized protocol with different aryne precursors. For this purpose the synthesis of **37** was achieved from starting material aldehyde **33**.[10] The aldehyde **33** was converted to acid **34** in the presence of H_2O_2 (8.0 equiv), KOH (4.0 equiv) in methanol at 65 ^oC. Further, selective demethylation of acid **34** was achieved by using concentrated H_2SO_4 furnishing **35** in 65% yield. The protection of acid **35** and dearomatization of **36** followed same procedure as for compound **19**.

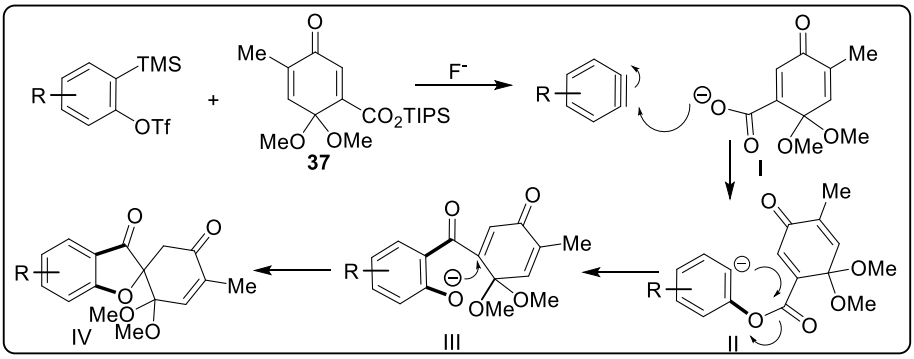
We began our next plan by treating 2,5-dimethyl substituted aryne precursor with unsymmetrically substituted dienone **37**, which provided good yield of spiro-product **38** (Scheme 5). The spiro-product **39** was formed in 35% yield for indane based aryne precursor. The similar reactivity pattern for aryne precursors bearing electron-donating methoxy group was observed (Scheme 3 and 5). The electron-rich aryne precursor provided moderate to good yields of

respective spiro-products **40-43** (Scheme 5). In the case of unsymmetrically substituted methoxy aryne precursors excellent regioselectivity was observed to furnish exclusive single regio-product **40** and **41**.



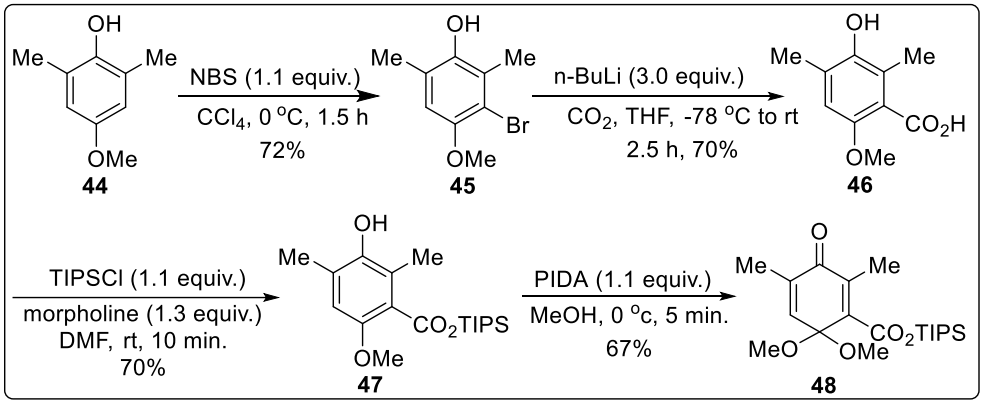
Scheme 5: The scope of the protocol on unsymmetrically substituted dienone **37**[a-c]

A tentative mechanism for the formation of spiro-benzofuranones has been depicted in scheme 6. The reaction proceeded in the presence of fluoride source generating aryne *in situ* and oxyanion **I** (Scheme 6). The attack of oxyanion on *in situ* generated aryne leads to intermediate **II** which



Scheme 6: Plausible Mechanism

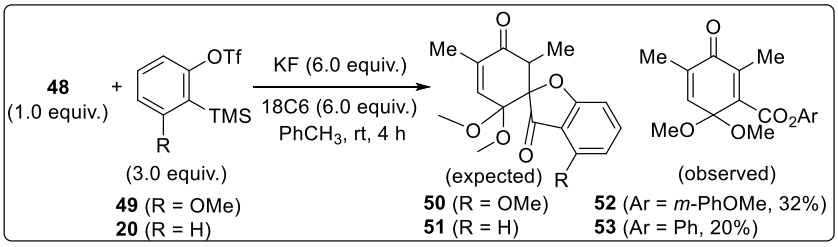
undergoes insertion into the C−O bond followed by a regioselective intramolecular conjugate addition furnishing spiro motif **IV** (Scheme 6).



Scheme 7: Synthesis of dimethyl substituted dienone 48

This result prompted us to apply our developed methodology for the synthesis of Leptosphaerins C. So we carried out the synthesis of dimethyl substituted dienone **48** in four steps from starting material **44**. The compound **44** was brominated by using NBS (1.1 equiv) in CCl_4 at 0 °C. Further, carboxylation of **45** was successfully carried out using *n*-BuLi and CO_2 gas. The protection of acid **46** and dearomatization of **47** followed same procedure as for compound **19** (Scheme 7).

The compatibility of the developed methodology was tested on dienone **48** with methoxy substituted and unsubstituted aryne precursors **49** and **20** respectively. But, unfortunately the



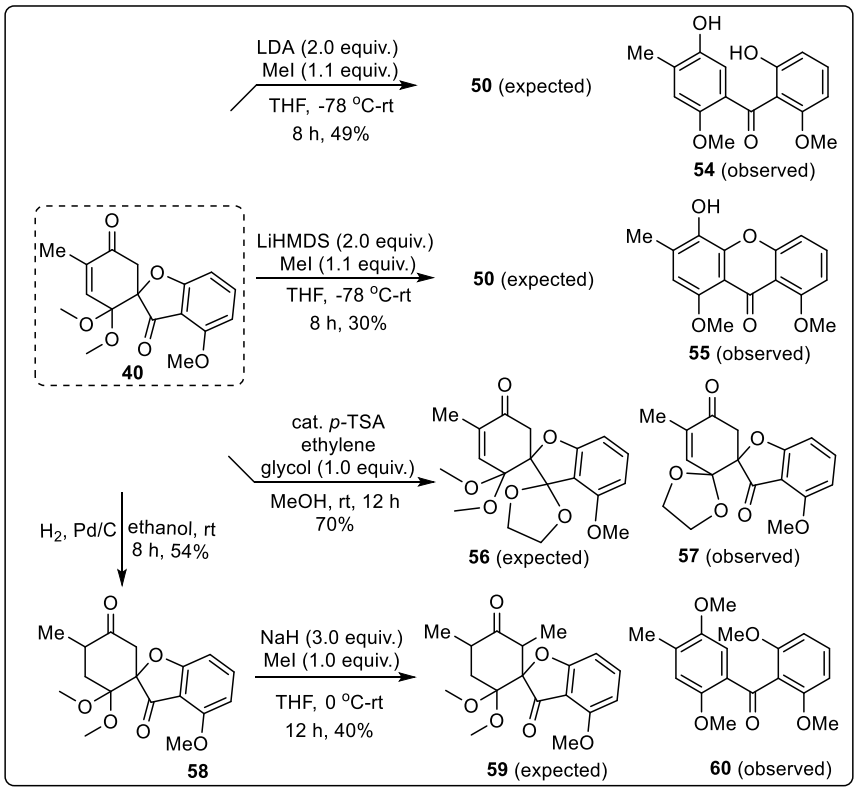
Scheme 8: Attempts towards the synthesis of Leptosphaerins C

optimized protocol failed to deliver the expected spiro-product **50** and **51**. Instead of expected spiro-products we could only isolate corresponding esters **52** and **53**. This result suggests the

steric effect induced due to methyl group at the beta-position to silyl ester might be affecting the C–O insertion, hence resulting into exclusive formation of O-arylated product (Scheme 8).

After unsuccessful attempt in synthesis of **50** (Scheme 8), we utilized spirobenzofuranone **40** for further transformation for the total synthesis of Leptosphaerins C.

Our next target was α-methylation of Leptosphaerins C core compound **40** (Scheme 9). The compound **40** on treatment with LDA and MeI furnished spiro ring opened product **54** (Scheme 9), whereas in case of LiHMDS the rearrangement product **55** was obtained via spiro ring opening followed by rearrangement. The efforts were made for protection of carbonyl group next



Scheme 9: Attempts towards the conversion of **40** to Leptosphaerins C

to the aromatic ring by treating **40** with ethylene glycol in the presence of *p*-TSA, but product **57** was formed instead of **56**. Further, double bond was reduced to minimize the chances of ring opening of the spiro-compound **40**, but again we observed the ring opened product **60** when

treated with NaH (Scheme 8). The efforts for the synthesis of Leptosphaerins C met with failure, but products **54**, **55** and **60** obtained during the synthesis of natural product represents the basic core of the natural products isolated along with Leptosphaerins C.[1b] This suggest that these products might be the building blocks in the biosynthesis of Leptosphaerins C or its metabolites.

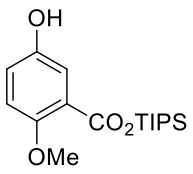
3.1.7 Conclusion:

In summary, a diversity-oriented synthesis of spiroannulated benzofuran-3-ones for the concise synthesis of Leptosphaerins C core and its library has been demonstrated. The two new bonds C−C and C−O have been formed by aryne insertion into C−O bond followed by intramolecular Michael addition at room temperature. Efforts were made for the first total synthesis of Leptosphaerins C, which also furnished novel compounds of biological interest. Screening of all the synthesized spirobenzofuran-3-ones for antifungal properties and application of the developed protocol for the synthesis of related natural products of this class is currently underway in our laboratory.

Our work presented in this chapter and publication has been cited 5 times in the literature.

3.1.8 Experimental Procedure and Characterization Data:

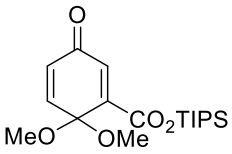
Triisopropylsilyl 5-hydroxy-2-methoxybenzoate (18):



To the solution of compound **14**[7] (1.0 g, 5.95 mmol) in anhydrous DMF (5 ml) was added morpholine (667 μl, 7.73 mmol) followed by TIPSCl[9] (1402 μl, 6.54 mmol). Reaction mixture was stirred for 10 min. and diluted with deionised water. Further, it was extracted by 1,2 dichloromethane and dried over sodium sulphate. After evaporation of solvent, the crude product was purified by using column chromatography on silica gel (1:4 EtOAc:PE) to yield **18** as a white solid (1.35 g, 70%).

Reaction Time: 10 min, R*f*: 0.3 (1:4 EtOAc:Pet. Ether); solid; m.p. 76-78 ^{o}C; 1.35 g, 70%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.35 (d, *J* = 3.2 Hz, 1H), 6.92 (dd, *J* = 3.2, 9.1 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 1H), 5.66 (bs, 1H), 3.74 (s, 3H), 1.37-1.26 (m, 3H), 1.05 (d, *J* = 7.3 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 165.7, 154.2, 149.0, 121.3, 120.7, 118.8, 113.7, 56.3, 17.8, 12.1; HRMS-ESI (m/z) calcd $(C_{17}H_{28}O_4Si + H)^+$: 325.1830 found: 325.1830.

Triisopropylsilyl 6,6-dimethoxy-3-oxocyclohexa-1,4-diene-1-carboxylate (19):



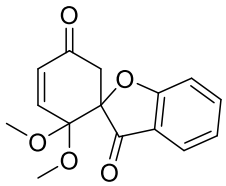
To the precooled 0 ^{o}C solution of compound **18** (500 mg, 1.54 mmol) in anhydrous methanol (7.5 ml), PIDA (496 mg, 1.54 mmol) dissolved in methanol was added dropwise at 0 ^{o}C. After complete addition, reaction mixture was diluted by 1, 2-dichloromethane and further quenched with aqueous $NaHCO_3$.Further reaction mixture was extracted by 1, 2-dichloromethane and dried over sodium sulfate. After evaporation of solvent, crude product was purified by column chromatography on silica gel (1:9 EtOAc:PE) to yield **19** as a yellow liquid (380 mg, 69%).

Reaction Time: 5 min, R*f*: 0.3 (1:9 EtOAc:Pet. Ether); oil; 380 mg, 69%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 6.92 (d, *J* = 2.1 Hz, 1H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.44 (dd, *J* = 2.1, 10.1 Hz, 1H), 3.33 (s, 6H), 1.44-1.33 (m, 3H), 1.12 (d, *J* = 7.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 185.5,163.2, 145.9, 145.0, 134.9, 130.8, 95.1, 51.4, 17.7, 11.9; HRMS-ESI (m/z) calcd $(C_{18}H_{30}O_5Si + Na)^+$: 377.1755 found: 377.1757.

General Procedure for preparation of Spiro compounds:

To a round bottom flask containing KF (6.00 equiv.) and 18-crown-6-ether (6.00 eqiuv.) was added *o*-silyl aryl triflate (3.00 equiv.) in toluene (0.25 ml) and stirred for 1 h. To the above reaction mixture, TIPS-protected dearomatized compound (1.00 equiv) in toluene (0.25 ml) was added and the reaction mixture was stirred. Further, reaction mixture was concentrated under reduce pressure and crude product was purified by column chromatography on silica gel EtOAc:Pet. Ether to yield spiro compounds.

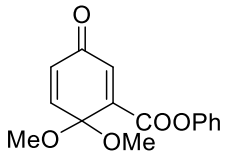
Typical Procedure for the preparation of the compound 2',2'-dimethoxy-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (21):



To a round bottom flask containing KF (28 mg, 0.49 mmol) and 18-crown-6-ether (129 mg, 0.49 mmol) was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **20** (73 mg, 0.24 mmol) in toluene (0.25 ml) and stirred for 1 h. To the above reaction mixture, compound **19** (29 mg, 0.082 mmol) in toluene (0.25 ml) was added and the reaction mixture was stirred for 4 h. Further, reaction mixture was concentrated under reduce pressure and crude product was purified by column chromatography on silica gel (1:4 EtOAc:Pet. Ether) to yield spiro compound **21** as a white solid (11.7 mg, 52% yield) and compound **22** in 6%.

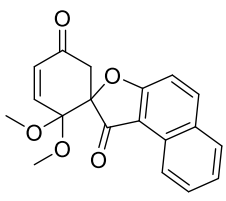
Reaction Time: 4 h, R*f*: 0.3 (1:4 EtOAc:Pet. Ether); White solid; m.p. 144-146 ^{o}C; 11.7 mg, 52%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.66-7.52 (m, 2H), 7.14-7.02 (m, 2H), 6.76 (d, J = 10.3 Hz, 1H), 6.25 (d, J = 10.3 Hz, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 2.85 (d, J = 17.1 Hz, 1H), 2.76 (d, J = 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 197.1, 194.3, 170.5, 144.9, 138.4, 131.6, 124.9, 122.6, 120.6, 113.5, 98.0, 90.4, 51.2, 50.5, 42.6; HRMS-ESI (m/z) calcd $(C_{15}H_{14}O_5 + Na)^+$: 297.0733 found: 297.0731.

Phenyl 6,6-dimethoxy-3-oxocyclohexa-1,4-diene-1-carboxylate (22):



Reaction Time: 4 h, R*f*: 0.35 (1:4 EtOAc:Pet. Ether); oil; 1.2 mg, 6%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.34 (t, J = 7.8 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 10.3 Hz, 1H), 6.43 (dd, J = 2.0, 10.3 Hz, 1H), 3.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 184.8, 162.1, 150.3, 144.7, 144.1, 135.4, 130.7, 129.5, 126.3, 121.3, 94.9, 51.6; HRMS-ESI (m/z) calcd $(C_{15}H_{14}O_5 + Na)^+$: 297.0733 found: 297.0736.

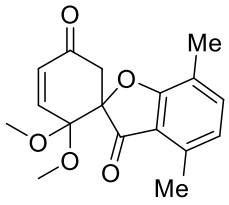
2,2-Dimethoxy-1'H-spiro[cyclohexane-1,2'-naphtho[2,1-b]furan]-3-ene-1',5-dione (23):



Reaction Time: 2 h, R*f*: 0.3 (1:4 EtOAc:Pet. Ether); oil; 11.44 mg, 50%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.66 (d, J = 7.9 Hz, 1H), 8.05 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.61 (t, J = 7.0 Hz, 1H), 7.43 (t, J = 7.0 Hz,

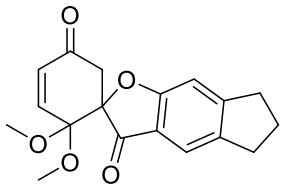
1H), 7.23 (d, *J* = 9.2 Hz, 1H), 6.79 (d, *J* = 10.4 Hz, 1H), 6.28 (d, *J* = 10.4 Hz, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 2.96 (d, *J* = 17.1 Hz, 1H), 2.83 (d, *J* = 17.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 196.7, 194.5, 173.3, 145.1, 140.4, 131.6, 130.2, 129.5, 129.3, 128.6, 125.8, 123.2, 113.7, 112.7, 98.1, 91.1, 51.3, 50.6, 42.8; HRMS-ESI (m/z) calcd $(C_{19}H_{16}O_5 + Na)^+$: 347.0890 found: 347.0892.

2',2'-Dimethoxy-4,7-dimethyl-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (24):



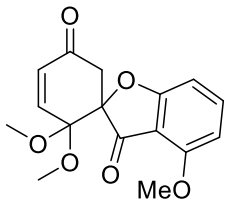
Reaction Time: 16 h, R*f*: 0.3 (1:4 EtOAc:Pet. Ether); Off White solid; m.p. 72-74 ^{o}C; 15.4 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.21 (d, *J* = 7.6 Hz, 1H), 6.75, (d, *J* = 10.5 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.23 (d, *J* = 10.5 Hz, 1H), 3.27 (s, 3H), 3.23 (s, 3H), 2.84 (d, *J* = 16.9 Hz, 1H), 2.75 (d, *J* = 16.9 Hz, 1H), 2.45 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 198.6, 194.9, 169.6, 144.4, 138.3, 137.3, 131.6, 123.6, 120.2, 118.0, 98.0, 90.0, 51.2, 50.3, 42.9, 17.4, 14.0; HRMS-ESI (m/z) calcd $(C_{17}H_{18}O_5 + Na)^+$: 325.1046 found: 325.1047.

2',2'-Dimethoxy-4,7-dimethyl-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (26):



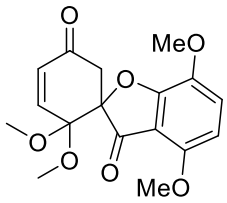
Reaction Time: 12 h, R*f*: 0.4 (1:4 EtOAc:Pet. Ether); Yellow solid; m.p. 102-104 ^{o}C; 5 mg, 22%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.38 (s, 1H), 6.90 (s, 1H), 6.75 (d, *J* = 10.4 Hz, 1H), 6.23 (d, *J* = 10.4 Hz, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 2.90-2.70 (m, 6H), 2.20-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 196.7, 194.7, 170.5, 157.8, 145.2, 139.4, 131.6, 119.4, 119.1, 109.1, 98.0, 90.9, 51.1, 50.5, 42.9, 33.8, 31.5, 25.9; HRMS-ESI (m/z) calcd $(C_{18}H_{18}O_5 + H)^+$: 315.1227 found: 315.1217.

2',2',4-Trimethoxy-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (28):



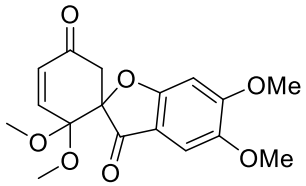
Reaction Time: 4 h, R*f*: 0.4 (2:3 EtOAc:Pet. Ether); White solid; m.p. 128-130 ^{o}C; 11.9 mg, 55%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.49 (t, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 10.4 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 6.43 (d, *J* = 8.2 Hz, 1H), 6.22 (d, *J* = 10.4 Hz, 1H), 3.87 (s, 3H), 3.27 (s, 3H), 3.25 (s, 3H), 2.83 (d, *J* = 17.1 Hz, 1H), 2.77 (d, *J* = 17.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 194.45, 194.44, 171.5, 158.7, 144.7, 139.9, 131.6, 109.8, 105.2, 103.9, 97.9, 90.4, 56.1, 51.2, 50.5, 42.8; HRMS-ESI (m/z) calcd $(C_{16}H_{16}O_6 + Na)^+$: 327.0839 found: 327.0842.

2',2',4,7-Tetramethoxy-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (29):



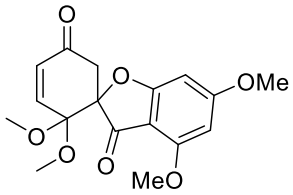
Reaction Time: 12 h, R*f*: 0.2 (2:3 EtOAc:Pet. Ether); oil; 9.5 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.03 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 10.4 Hz, 1H), 6.32 (d, J = 8.8 Hz, 1H), 6.22 (d, J = 10.4 Hz, 1H), 3.81 (s, 6H), 3.28 (s, 3H), 3.25 (s, 3H), 2.86 (d, J = 16.8 Hz, 1H), 2.79 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 194.8, 194.4, 160.9, 151.8, 144.5, 140.0, 131.6, 121.6, 111.1, 102.9, 97.9, 91.0, 56.9, 56.1, 51.2, 50.4, 42.7; $(C_{17}H_{18}O_7 + Na)^+$: 357.0945 found: 357.0934.

2',2',5,6-Tetramethoxy-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (30):



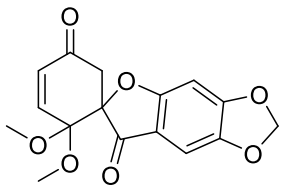
Reaction Time: 24 h, R*f*: 04 (2:3 EtOAc:Pet. Ether); off-white solid; m.p. 223-225 ^{o}C; 9.9 mg, 42%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 6.95 (s, 1H), 6.75 (d, J = 10.7 Hz, 1H), 6.56 (s, 1H), 6.23 (d, J = 10.7 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.28 (s, 3H), 3.21 (s, 3H), 2.91 (d, J = 16.8 Hz, 1H), 2.70 (d, J = 16.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 195.3, 194.6, 168.0, 159.0, 146.2, 145.5, 131.5, 111.7, 103.5, 98.0, 95.7, 91.0, 56.6, 56.3, 51.1, 50.6, 42.9; HRMS-ESI (m/z) calcd $(C_{17}H_{18}O_7 + Na)^+$: 357.0945 found: 357.0943.

2',2',4,6-Tetramethoxy-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (31):



Reaction Time: 12 h, R*f*: 0.2 (2:3 EtOAc:Pet. Ether); White solid; m.p. 195-197 ^{o}C; 9.0 mg, 38%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.80 (d, J = 10.4 Hz, 1H), 6.28 (d, J = 10.4 Hz, 1H), 6.20 (apparent s, 1H), 6.04 (apparent s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.34 (s, 6H), 2.90 (d, J = 17.1 Hz, 1H), 2.79 (d, J = 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 194.6, 192.2, 173.5, 170.1, 159.5, 145.0, 131.5, 104.1, 97.9, 93.5, 91.2, 89.1, 56.1, 56.0, 51.1, 50.5, 43.0; $(C_{17}H_{18}O_7 + H)^+$: 335.1125 found: 335.1124.

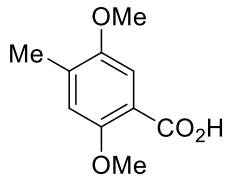
2,2-Dimethoxy-7'H-spiro[cyclohexane-1,6'-[1,3]dioxolo[4,5-f]benzofuran]-3-ene-5,7'-dione (32):



Reaction Time: 16 h, R*f*: 0.4 (2:3 EtOAc:Pet. Ether); off -white solid; m.p. 150-152 ^{o}C; 13.5 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.89 (s, 1H), 6.73 (d, J = 10.5 Hz, 1H), 6.51 (s, 1H), 6.22 (d, J = 10.5 Hz, 1H), 6.01 (apparent d, 2H), 3.27 (s, 3H), 3.23(s, 3H), 2.85 (d, J = 16.9

Hz, 1H), 2.73 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 195.0, 194.4, 169.4, 157.3, 145.1, 144.7, 131.5, 113.4, 102.8, 101.3, 97.9, 94.5, 91.7, 51.1, 50.5, 42.8; HRMS-ESI (m/z) calcd $(C_{16}H_{14}O_7 + Na)^+$: 341.0632 found: 341.0634.

2,5-Dimethoxy-4-methylbenzoic acid (34):

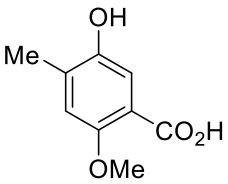


The compound **34** as a white solid was prepared from compound **33**[10] according to the literature procedure.[10]

Aqueous hydrogen peroxide (30%, 6.5 mL, 57.7 mmol) was added dropwise to a stirred solution of 50% aq. KOH (3.2 mL, 28.8 mmol) and **33** (1.3 g, 7.2 mmol) in methanol (20 mL) at 65^{o}C for 20 min. The mixture was then stirred at the same temperature for 24 h, cooled, acidified with concentrated hydrochloride to afford **34** (1.0 g, 70%) as a white solid.

Reaction Time: 12 h, R*f*: 0.3 (3:2 EtOAc:Pet. Ether); white solid; 124-126 ^{o}C 1.0 g, 70% yield; ^{1}H NMR (500 MHz, DMSO-d_6, TMS) δ 12.43 (bs, 1H), 7.19 (s, 1H), 6.98 (s, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, TMS) δ 167.1, 152.7, 150.9, 131.9, 118.4, 116.0, 112.4, 56.6, 55.8, 16.5; HRMS-ESI (m/z) calcd $(C_{10}H_{12}O_4 + H)^+$: 197.0809 found: 197.0809.

5-Hydroxy-2-methoxy-4-methylbenzoic acid (35):

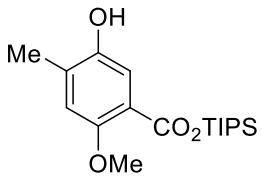


The compound **35** (1.0 g, 65%) grey solid was prepared from compound **34** according to the literature procedure[7] as used in synthesis of compound **14**.

A solution of **34** (1.65 g, 8.4 mmol) in 6 ml concentrated sulfuric acid was heated to 55 ^{o}C for 48 h. The reaction was then poured to. A precipitate formed and the reaction mixture was allowed to stand overnight. The resulting crystals were dried in vacuo to afford **35** as grey solid (1.0 g, 65%).

Reaction Time: 48 h, R*f*: 0.2 (EtOAc); grey solid; 156-158 ^{o}C; 1.0 g, 65%; ^{1}H NMR (500 MHz, DMSO-d_6, TMS) δ 12.31 (bs, 1H), 9.12 (bs, 1H), 7.13 (s, 1H), 6.86 (s, 1H), 3.72 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, TMS) δ 167.0, 151.7, 148.8, 130.2, 118.4, 116.6, 115.9, 56.7, 16.6; HRMS-ESI (m/z) calcd $(C_9H_{10}O_4 + H)^+$: 183.0652 found: 183.0651.

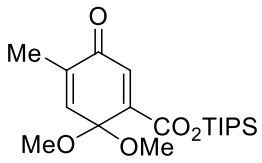
Triisopropylsilyl 5-hydroxy-2-methoxy-4-methylbenzoate (36):



The compound **36** (740 mg, 40%) white solid was prepared from compound **35** (1 g, 5.4 mmol) following the same procedure[9] as used in synthesis of compound **18**.

Reaction Time: 10 min, R*f*: 0.4 (1:9 EtOAc:Pet. Ether); White solid; 75-77 ^{o}C; 740 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.36 (s, 1H), 6.76 (s, 1H), 4.94 (bs, 1H), 3.84 (s, 3H), 2.29 (s, 3H), 1.50-1.10 (m, 3H), 1.13 (d, J = 7.6 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 165.2, 154.4, 146.9, 130.9, 118.5, 118.4, 115.3, 56.4, 17.9, 16.5, 12.1; HRMS-ESI (m/z) calcd $(C_{18}H_{30}O_4Si + Na)^+$: 361.1806 found: 361.1806.

Triisopropylsilyl 6,6-dimethoxy-4-methyl-3-oxocyclohexa-1,4-diene-1-carboxylate (37):

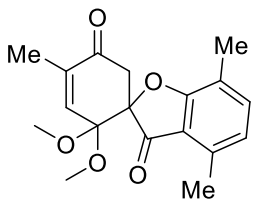


The compound **37** (1.04 g, 94%) yellow oil was prepared from compound **36** (1.02 g, 3.0 mmol) following the same procedure as used in synthesis of compound **19**.

Reaction Time: 5 min, R*f*: 0.5 (1:9 EtOAc:Pet. Ether); oil; 1.04 g, 94%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.90 (s, 1H), 6.56 (unresolved q, 1H), 3.30 (s, 6H), 1.97 (unresolved d, 3H), 1.45-1.30 (m, 3H), 1.12 (d, J = 7.3 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 186.3, 163.2, 145.8, 140.4, 138.2, 135.0, 95.5, 51.3, 17.7, 15.2, 11.9; HRMS-ESI (m/z) calcd $(C_{19}H_{32}O_5Si + Na)^+$: 391.1911 found: 391.1912.

Note: Same procedure was followed for preparation of Spiro compounds (**38-43**) as described for **21**.

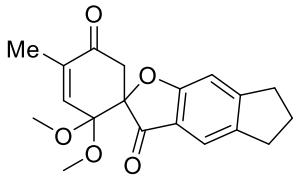
2',2'-Dimethoxy-4,4',7-trimethyl-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (38):



Reaction Time: 16 h, R*f*: 0.4 (1:4 EtOAc:Pet. Ether); oil; 13.4 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.22 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 6.51 (q, J = 1.2 Hz, 1H), 3.30 (s, 1H), 3.20 (s, 1H), 2.92 (d, J = 16.5 Hz, 1H), 2.69 (d, J = 16.5 Hz, 1H), 2.44 (s, 3H), 2.20 (s, 3H), 1.90 (d,

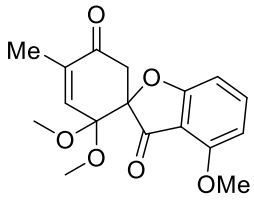
J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 199.0, 195.0, 170.0, 138.9, 138.8, 138.2, 137.3, 123.5, 120.2, 118.1, 98.3, 90.4, 51.1, 50.1, 42.8, 17.4, 15.5, 14.0; HRMS-ESI (m/z) calcd $(C_{18}H_{20}O_5 + Na)^+$: 339.1203 found: 339.1205.

2,2-Dimethoxy-4-methyl-6',7'-dihydrospiro[cyclohexane-1,2'-indeno[5,6-b]furan]-3-ene-3',5(5'H)-dione (39):



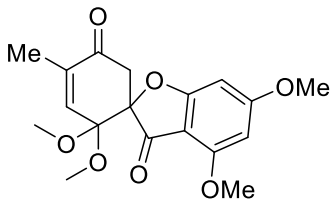
Reaction Time: 36 h, R*f*: 0.4 (1:4 EtOAc:Pet. Ether); Yellow solid; 91-93 ^{o}C; 7.9 mg, 35%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.36 (s, 1H), 6.90 (s, 1H), 6.50 (q, *J* = 1.5 Hz, 1H), 3.23 (s, 6H), 2.90-2.75 (m, 6H), 2.10-2.00 (m, 2H), 1.89 (q, *J* = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 196.8, 194.8, 170.5, 157.7, 139.9, 139.3, 138.7, 119.3, 119.2, 109.0, 98.4, 91.2, 51.0, 50.4, 42.9, 33.8, 31.5, 25.9, 15.5; HRMS-ESI (m/z) calcd $(C_{19}H_{20}O_5 + Na)^+$: 351.1203 found: 351.1204.

2', 2', 4-Trimethoxy-4'-methyl-3H-spiro [benzofuran-2, 1'-cyclohexan]-3'-ene-3, 5'-dione (40):



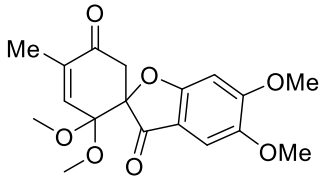
Reaction Time: 4 h, R*f*: 0.5 (2:3 EtOAc:Pet. Ether); Off-white solid; 139-141 ^{o}C; 10.9 mg, 50%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.48 (t, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.48 (q, *J* = 1.22 Hz, 1H), 6.42 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 3.27 (s, 3H), 3.23 (s, 3H), 2.84 (d, *J* = 16.8 Hz, 1H), 2.77 (d, *J* = 16.8 Hz, 1H), 1.88 (d, *J* = 1.22 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 194.7, 194.6, 171.5, 158.7, 139.8, 139.2, 138.9, 109.9, 105.2, 103.8, 98.3, 90.7, 56.1, 51.1, 50.4, 42.7, 15.4; HRMS-ESI (m/z) calcd $(C_{17}H_{18}O_6 + Na)^+$: 341.0996 found: 341.0995.

2',2',4,6-Tetramethoxy-4'-methyl-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (41):



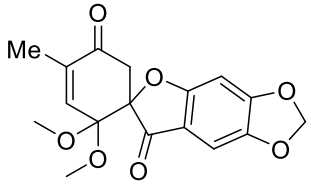
Reaction Time: 12 h, R*f*: 0.2 (2:3 EtOAc:Pet. Ether); oil; 10.7 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.47 (s, 1H), 6.13 (d, *J* = 1.2 Hz, 1H), 5.96 (d, *J* = 1.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.26 (s, 3H), 3.24 (s, 3H), 2.81 (s, 2H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 194.7, 192.4, 173.5, 170.1, 159.4, 139.5, 138.8, 104.1, 98.3, 93.4, 91.5, 89.0, 56.02, 56.0, 51.0, 50.4, 43.0, 15.4; HRMS-ESI (m/z) calcd $(C_{18}H_{20}O_7 + Na)^+$: 371.1101 found: 371.1096.

2', 2', 5, 6-Tetramethoxy-4'-methyl-3H-spiro[benzofuran-2,1'-cyclohexan]-3'-ene-3,5'-dione (42):



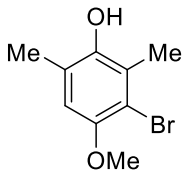
Reaction Time: 24 h, R*f*: 0.4 (1:3 EtOAc:Pet. Ether); oil; 7.1 mg, 30%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 6.94 (s, 1H), 6.55 (s, 1H), 6.51 (q, *J* = 1.5 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.25 (s, 3H), 3.20 (s, 3H), 2.90 (d, *J* = 17.0 Hz, 1H), 2.73 (d, *J* = 17.0 Hz, 1H), 1.89 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 195.4, 194.8, 168.0, 158.9, 146.2, 140.2, 138.7, 111.8, 103.5, 98.5, 95.7, 91.4, 56.6, 56.3, 51.0, 50.4, 42.9, 15.5; HRMS-ESI (m/z) calcd $(C_{18}H_{20}O_7 + Na)^+$: 371.1101 found: 371.1103.

2,2-Dimethoxy-4-methyl-7'H-spiro[cyclohexane-1,6'-[1,3]dioxolo[4,5-f]benzofuran]-3-ene-5,7'-dione (43):



Reaction Time: 24 h, R*f*: 0.4 (2:3 EtOAc:Pet. Ether); off-white solid; 186-188 ^{o}C; 9.1 mg, 40%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 6.87 (s, 1H), 6.51 (s, 1H), 6.49 (q, *J* = 1.5 Hz, 1H), 6.00 (m, 2H), 3.24 (s, 3H), 3.22 (s, 3H), 2.83 (d, *J* = 16.8 Hz, 1H), 2.76 (d, *J* = 16.8 Hz, 1H), 1.88 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 195.1, 194.6, 169.4, 157.2, 144.6, 139.8, 138.8, 113.5, 102.8, 101.3, 98.3, 94.5, 92.1, 51.0, 50.4, 42.9, 15.5; HRMS-ESI (m/z) calcd $(C_{17}H_{16}O_7 + Na)^+$: 355.0788 found: 355.0791.

3-Bromo-4-methoxy-2,6-dimethylphenol (45):

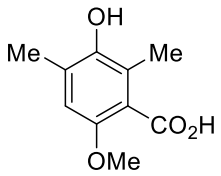


To the precooled 0 ^{o}C solution of 4-methoxy-2,6-dimethylphenol[11] **44** (1.00 g, 6.4 mmol) in carbon tetrachloride (30 ml) was added *N*- bromosuccinimde (1.28 g, 7.2 mmol) portionwise over 15-30 mins. The reaction mixture was stirred for 60 min. Then reaction mixture was diluted with carbon tetrachloride and quenched by saturated sodium thiosulphate solution. The organic layer was separated and dried over sodium sulphate. After evaporation of solvent, the crude product was purified by using column chromatography on silica gel (1:9 EtOAc:PE) to yield **45** as a light brown solid (1.08 g, 72%).

Reaction Time: 1.5 h, R*f*: 0.5 (1:9 EtOAc:Pet. Ether); brown solid; m.p. 102-104 ^{o}C; 1.08 g, 72%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.60 (s, 1H), 4.42 (s, 1H), 3.84 (s, 3H), 2.38 (s, 3H),

2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 149.9, 146.3, 125.3, 122.4, 112.3, 111.8, 56.8, 16.4, 16.2.

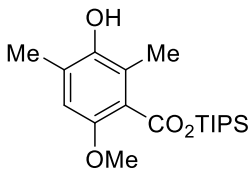
3-Hydroxy-6-methoxy-2,4-dimethylbenzoic acid (46):



To the solution of **45** (850 mg, 3.67 mmol) in anhydrous THF (20 ml) was added *n*-BuLi (11 mmol, 1M THF solution) at -78 ^{o}C under argon atmosphere. Then carbon dioxide gas was purged into the above reaction mixture for 30 min at -78 ^{o}C. The reaction mixture was stirred at room temperature for 2 h. Excess of *n*-BuLi was quenched by saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried over sodium sulphate. After evaporation of solvent, the crude product was purified by using column chromatography on silica gel (3:2 EtOAc:PE) to yield **46** as a white solid (510 mg, 70%).

Reaction Time: 2.0 h, R*f*: 0.2 (3:2 EtOAc:Pet. Ether); White solid; m.p. 166-168 ^{o}C; 510 mg, 70%; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 12.75 (bs, 1H), 7.96 (s, 1H), 6.65 (s, 1H), 3.66 (s, 3H), 2.17 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6, TMS) δ 169.2, 148.4, 146.8, 126.3, 124.1, 122.4, 111.6, 56.2, 17.3, 13.7; HRMS-ESI (m/z) calcd $(C_{10}H_{12}O_4 + H)^+$: 197.0809 found: 197.0808.

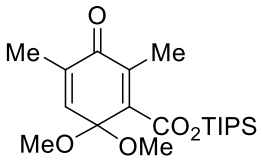
Triisopropylsilyl 3-hydroxy-6-methoxy-2,4-dimethylbenzoate (47):



The compound **47** was prepared from compound **46** (800 mg, 4.0 mmol) following the same procedure[9] as used in synthesis of compound **18** to afford the title compound **47** as a white solid (1.00 g, 70%).

Reaction Time: 10.0 min, R*f*: 0.3 (1:4 EtOAc:Pet. Ether); White solid; 87-89 ^{o}C; 1.00 g, 70%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.47 (s, 1H), 3.66 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 1.40-1.26 (m, 3H), 1.07 (d, J = 7.3 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 168.0, 149.8, 145.8, 124.9, 124.7, 121.8, 111.5, 56.1, 17.8, 16.6, 13.1, 12.1; HRMS-ESI (m/z) calcd $(C_{19}H_{32}O_4Si + H)^+$: 353.2143 found: 353.2146.

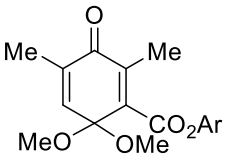
Triisopropylsilyl 6,6-dimethoxy-2,4-dimethyl-3-oxocyclohexa-1,4-diene-1-carboxylate (48):



The compound **48** (292 mg, 67%) was prepared from compound **48** (400 mg, 1.1 mmol) following the same procedure as used in synthesis of compound **19**.

Reaction Time: 5 min, R*f*: 0.3 (1:9 EtOAc:Pet. Ether); solid; 292 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.37 (d, J = 1.5 Hz, 1H), 3.23 (s, 6 H), 1.92 (s, 3H), 1.90 (d, J = 1.5 Hz, 3H), 1.36-1.26 (m, 3H), 1.07 (d, J = 1.07, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 186.2, 165.0, 144.2, 138.6, 138.4, 135.6, 95.3, 51.3, 17.7, 15.8, 13.0, 12.1; HRMS-ESI (m/z) calcd $(C_{20}H_{34}O_5Si + Na)^+$: 405.2068 found: 405.2063.

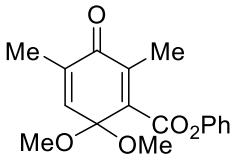
3-Methoxyphenyl 6,6-dimethoxy-2,4-dimethyl-3-oxocyclohexa-1,4-diene-1-carboxylate (52):



To a round bottom flask containing KF (22 mg, 0.39 mmol), 18-crown-6-ether (103 mg, 0.39 mmol), was added aryne precursor **49** (64 mg, 0.19 mmol) in toluene (0.25 ml) and stirred for 1 h. To the above reaction mixture, compound **48** (25 mg, 0.065 mmol) in toluene (0.25 ml) was added and the reaction mixture was stirred for 4 h. Further reaction mixture was concentrated under reduce pressure and crude product was purified by column chromatography on silica gel (1:4 EtOAc:Pet. Ether) to yield compound **52** as an oil (7.0 mg, 32% yield).

Reaction Time: 4 h, R*f*: 0.4 (1:4 EtOAc:Pet. Ether); oil; 7.0 mg, 32 %; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.24 (t, J = 8.2 Hz, 2H), 6.70-6.78 (m, 2H), 6.67 (unresolved q, 1H), 6.47 (s, 1H), 3.75 (s, 3H), 3.32 (s, 6H), 2.02 (s, 3H), 1.94 (unresolved d, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 185.6, 163.6, 160.6, 151.1, 142.1, 138.6, 138.5, 137.2, 129.9, 113.7, 112.1, 107.6, 95.2, 55.5, 51.5, 15.9, 13.1; HRMS-ESI (m/z) calcd $(C_{18}H_{20}O_6 + H)^+$: 333.1333 found: 333.1337.

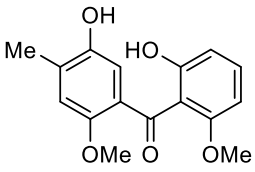
Phenyl 6,6-dimethoxy-2,4-dimethyl-3-oxocyclohexa-1,4-diene-1-carboxylate (53):



Same procedure was repeated as for compound **52** to obtain **53** (4.0 mg) from **48** (25.0 mg, 0.065 mmol) and **20** (58 mg, 0.19 mmol).

Reaction Time: 4 h, R*f*: 0.4 (1:4 EtOAc:Pet. Ether); oil; 4.0 mg, 20.0 %; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.35 (t, J = 7.8 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 6.48 (unresolved q, 1H), 3.32 (s, 6H), 2.03 (s, 3H), 1.94 (unresolved d, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 185.6, 163.7, 150.2, 142.1, 138.6, 138.5, 137.2, 129.6, 126.3, 121.5, 95.2, 51.5, 15.8, 13.2; HRMS-ESI (m/z) calcd $(C_{17}H_{18}O_5 + Na)^+$: 325.1046 found: 325.1044.

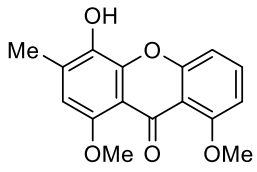
(5-Hydroxy-2-methoxy-4-methylphenyl)(2-hydroxy-6-methoxyphenyl)methanone (54):



To the compound **40** (20 mg, 0.062 mmol) in anhydrous THF (0.5 ml) was added 1M LDA in THF (125 μl, 0.125 mmol) at -78 ^{o}C and stirred for 10 min. To the above reaction mixture methyl iodide (9.8 μl, 0.069 mmol) was added at -78 ^{o}C. The reaction mixture was allowed to attain room temperature and stirred for 8 h. After completion of starting material, reaction was quenched by aqueous ammonium choride and extracted by ethyl acetate. Further, organic layer was concentrated under reduce pressure and crude product was purified by column chromatography on silica gel (3:2 EtOAc:Pet. Ether) to yield compound **54** as a yellow solid (8.8 mg, 49%).

Reaction Time: 8 h, R*f*: 0.4 (3:2 EtOAc:Pet. Ether); Yellow solid; 167-169 ^{o}C; 8.8 mg, 49%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 12.04 (s, 1H), 7.27 (t, J = 8.2 Hz, 1H), 6.68 (s, 1H), 6.59 (s, 1H), 6.54 (d, J = 8.6 Hz, 1H), 6.23 (d, J = 8.6 Hz, 1H), 4.62 (bs, 1H), 3.57 (s, 3H), 3.41 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 198.8, 163.3, 161.4, 150.7, 147.3, 136.2, 130.9, 127.5, 114.6, 113.8, 112.7, 110.3, 101.5, 56.3, 55.5, 16.4; $(C_{16}H_{16}O_5 + H)^+$: 289.1071 found: 289.1070.

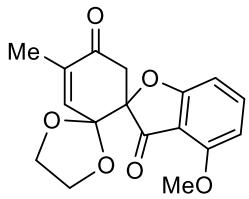
4-Hydroxy-1,8-dimethoxy-3-methyl-9H-xanthen-9-one (55):



To the compound **40** (20 mg, 0.062 mmol) in anhydrous THF (0.5 ml) was added 1M LiHMDS in THF (125 μl, 0.125 mmol) at -78 ^{o}C and stirred for 10 min. To the above reaction mixture methyl iodide (9.8 μl, 0.069 mmol) was added at -78 ^{o}C. The reaction mixture was allowed to attain room temperature and stirred for 8 h. After completion of starting material, reaction was quenched by aqueous ammonium chloride and extracted by ethyl acetate. Further organic layer was concentrated under vacuuo and crude product was purified by column chromatography on silica gel (3:2 EtOAc:Pet. Ether) to yield compound **55** as a major compound (yellow solid, 5.5 mg, 30%).

Reaction Time: 12 h, R*f*: 0.2 (3:2 EtOAc:Pet. Ether); Yellow solid; 209-211 ^{o}C; 5.5 mg, 30%; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.45 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.49 (s, 1H), 5.42 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 175.9, 160.7, 156.4, 152.5, 144.0, 135.5, 133.9, 129.9, 113.6, 112.1, 108.9, 108.2, 106.2, 56.7, 56.4, 16.4; $(C_{16}H_{14}O_5 + H)^+$: 287.0914 found: 287.0915.

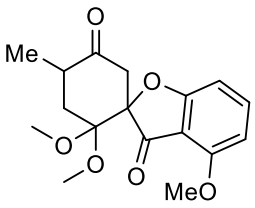
4-Methoxy-4'-methyl-3H-dispiro[benzofuran-2,1'-cyclohexane-2',2''-[1,3]dioxolan]-3'-ene-3,5'-dione (57):



To the compound **40** (20 mg, 0.062 mmol) in methanol (0.5 ml) was added ethylene glycol (3.5 μl, 0.062 mmol), and catalytic *p*-TSA (1 mg, 0.0062 mmol) at rt. The reaction mixture was stirred for 12 h. After complete consumption of starting material, reaction was quenched by aqueous sodium bicarbonate and extracted with ethyl acetate. Further, organic layer was concentrated under vacuuo and crude product was purified by column chromatography on silica gel (1:4 EtOAc:Pet. Ether) to yield compound **57** as a Yellow solid (13.5 mg, 70 %).

Reaction Time: 12 h, R*f*: 0.4 (2:3 EtOAc:Pet. Ether); Yellow solid; 185-187 ^{o}C; 13.5 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47 (t, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 6.25 (apparent q, 1H), 4.05-4.00 (m, 2H), 4.00- 3.90 (m, 2H), 3.86 (s, 3H), 2.90 (d, *J* = 16.5 Hz, 1H), 2.85 (d, *J* = 16.5 Hz, 1H), 1.84 (apparent d, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 194.9, 194.4, 172.3, 158.5, 139.7, 139.1, 138.8, 110.1, 105.6, 104.7, 103.8, 89.8, 66.8, 66.5, 56.1, 42.2, 15.4; $(C_{17}H_{16}O_6 + H)^+$: 317.1020 found: 317.1021.

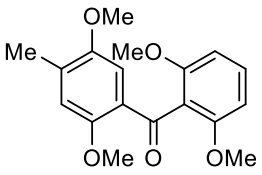
2',2',4-Trimethoxy-4'-methyl-3H-spiro[benzofuran-2,1'-cyclohexane]-3,5'-dione (58):



To the compound **40** (100 mg, 0.31 mmol) in ethanol (1 ml) was added Pd 10% (10 mg). Reaction mixture as kept for stirring under H_2 gas for 8 h. After complete consumption of starting material, reaction was filtered through celite. The reaction mixture was concentrated under vacuum. The crude product was further purified by silica gel column chromatography (2:3 EtOAc: Pet. Ether) to yield **58** (54.5 mg, 54%) as off-white solid.

Reaction Time: 8 h, R*f*: 0.6 (2:3 EtOAc:Pet. Ether); Off-white solid; 155-157 ^{o}C; 54.5 mg, 54%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47 (t, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.49 (s, 3H), 3.11 (s, 3H), 3.01 (d, *J* = 14.2 Hz, 1H), 2.49-2.58 (m, 1H), 2.30-2.18 (m, 2H), 2.14-2.10 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 205.9, 197.4, 172.2, 158.5, 139.7, 109.4, 104.9, 103.5, 99.7, 91.9, 56.0, 50.7, 49.7, 44.9, 40.7, 34.2, 13.7; $(C_{17}H_{20}O_6 + Na)^+$: 343.1152 found: 343.1155.

(2,5-Dimethoxy-4-methylphenyl)(2,6-dimethoxyphenyl)methanone (60):



To the precooled 0 ^{o}C solution of compound **58** (10 mg, 0.031 mmol) in THF (0.25 ml) was added NaH (2.25 mg, 0.093 mmol). The reaction mixture was allowed to attain room temperature and further stirred for 12 h. After consumption of starting material reaction mixture was diluted with water and ethyl acetate. Further, aqueous layer was extracted with ethyl acetate 3 times and dried over sodium sulphate. After evaporation of solvent, the crude product was purified by using column

chromatography on silica gel (1:4 EtOAc:PE) to yield compound **60** as a yellow solid (4.4 mg, 44%).

Reaction Time: 16 h, R*f*: 0.4 (1:4 EtOAc:Pet. Ether); Yellow solid; 124-126 ^{o}C; 4.4 mg, 44%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.29 (s, 1H), 7.19 (t, J = 8.5 Hz, 1H), 6.66 (s, 1H), 6.51 (d, J = 8.5 Hz), 3.73 (s, 3H), 3.64 (s, 6H), 3.47 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 193.1, 157.1, 154.6, 151.8, 134.4, 129.7, 125.8, 122.3, 116.4, 112.0, 104.1, 57.0, 56.0, 55.8, 16.8; $(C_{18}H_{20}O_5 + H)^+$: 317.1384 found: 317.1373.

3.1.9 References:

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3.1.10 Selected Spectra

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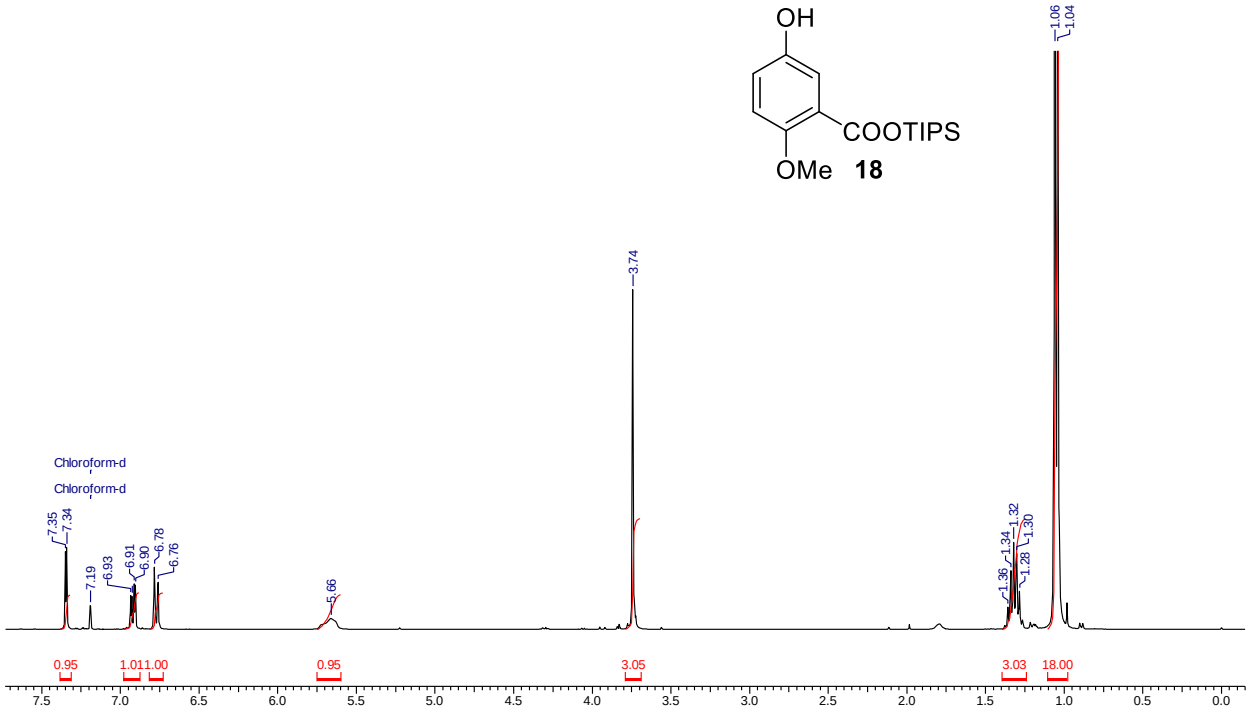

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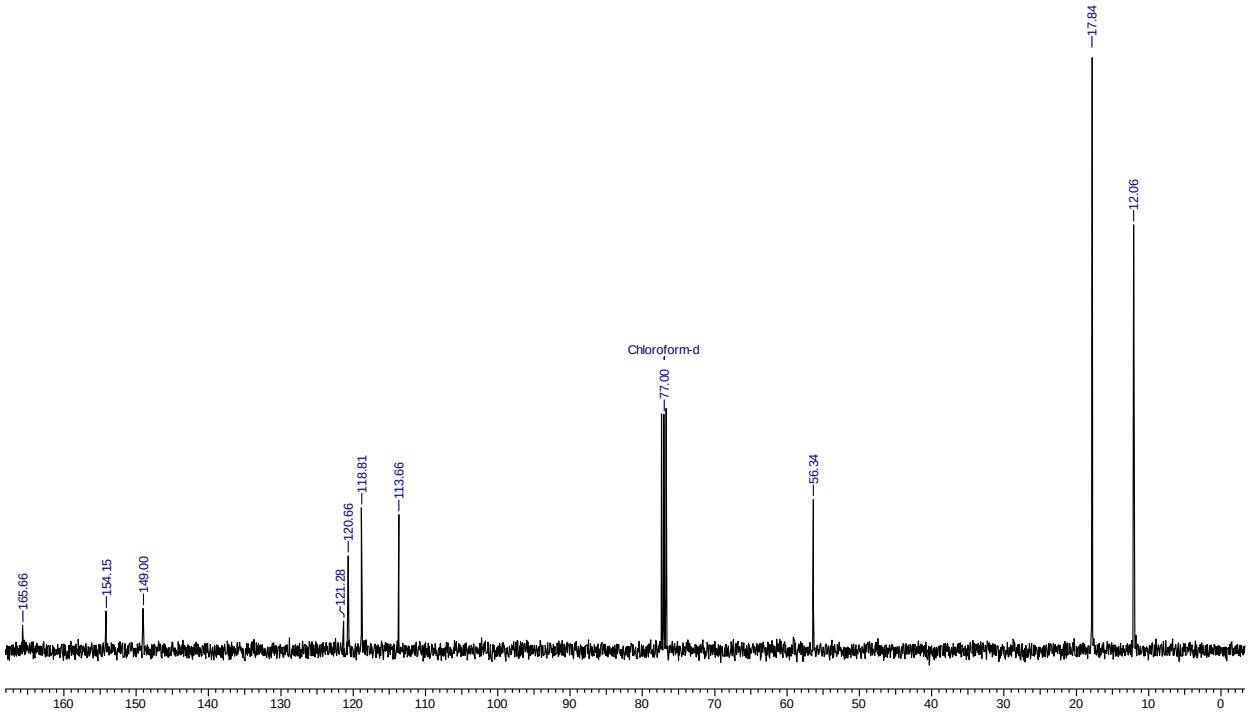

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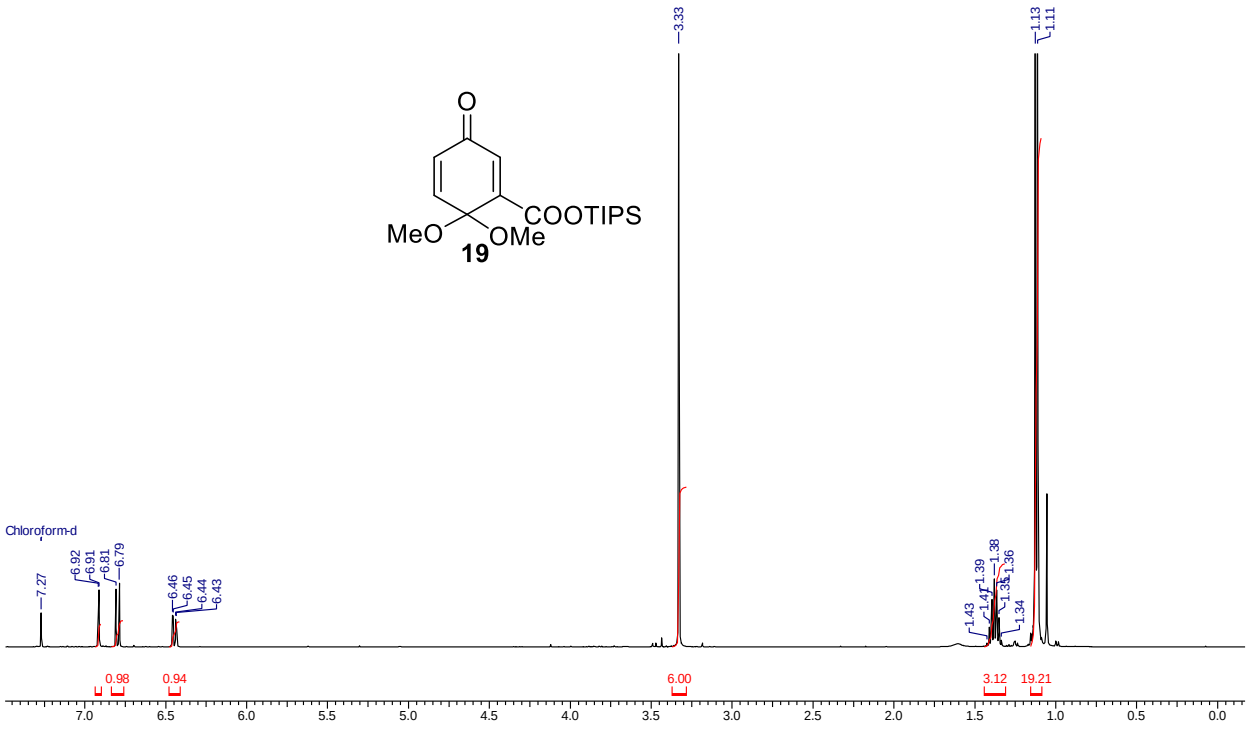

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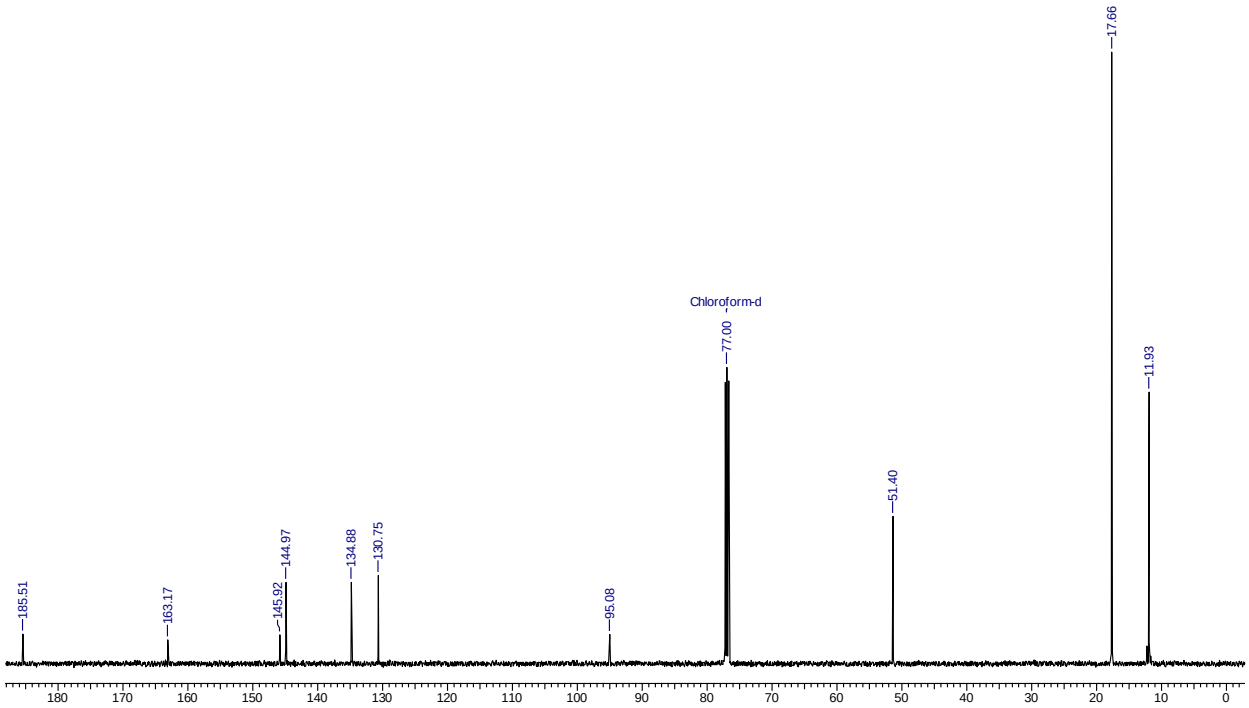

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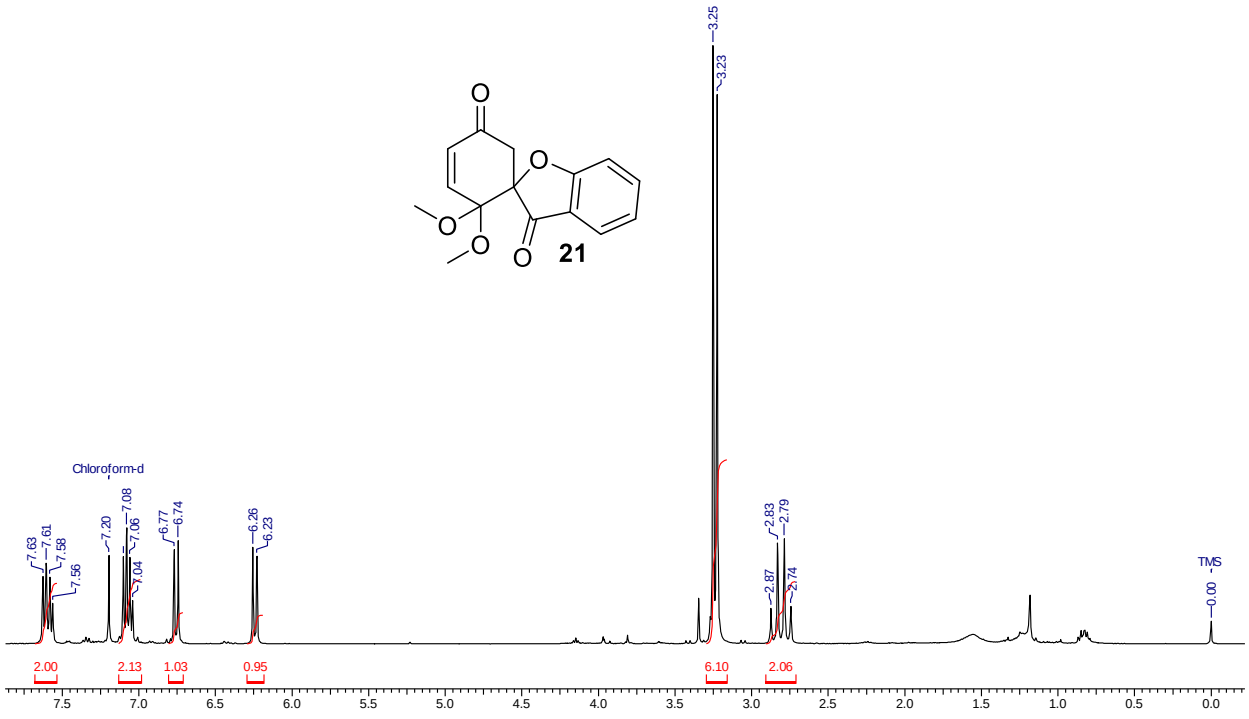

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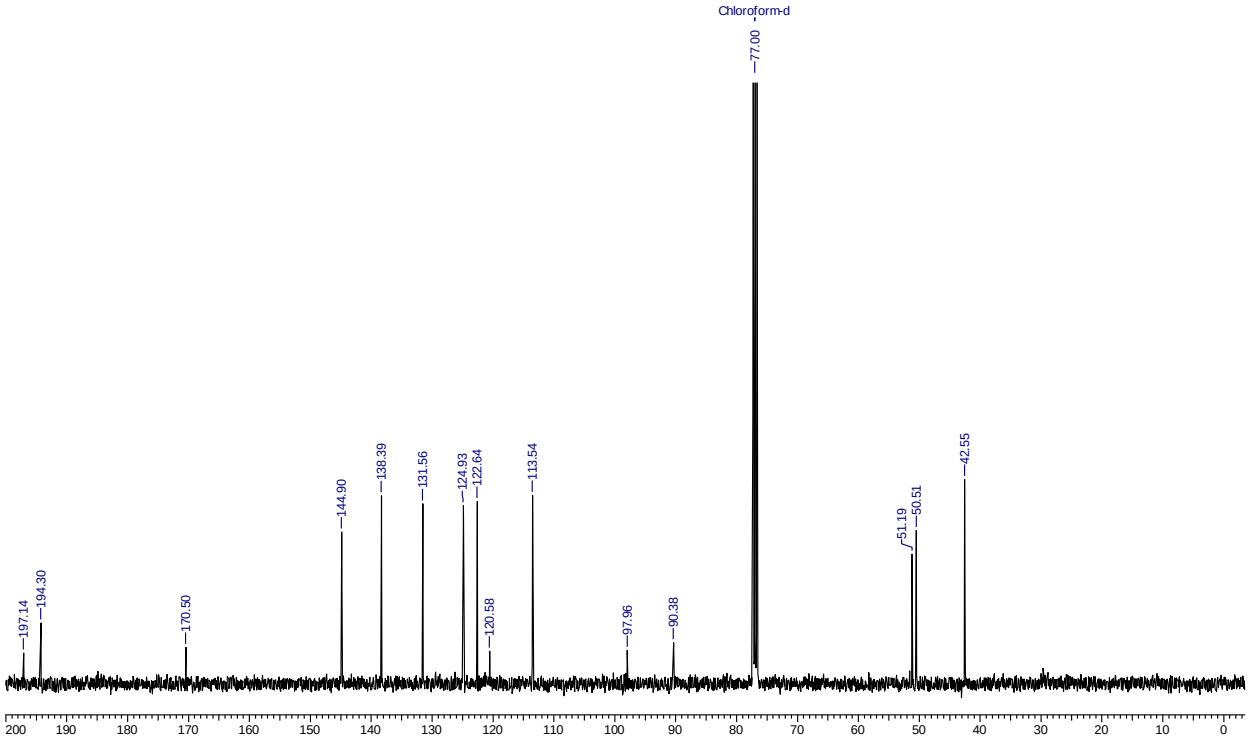

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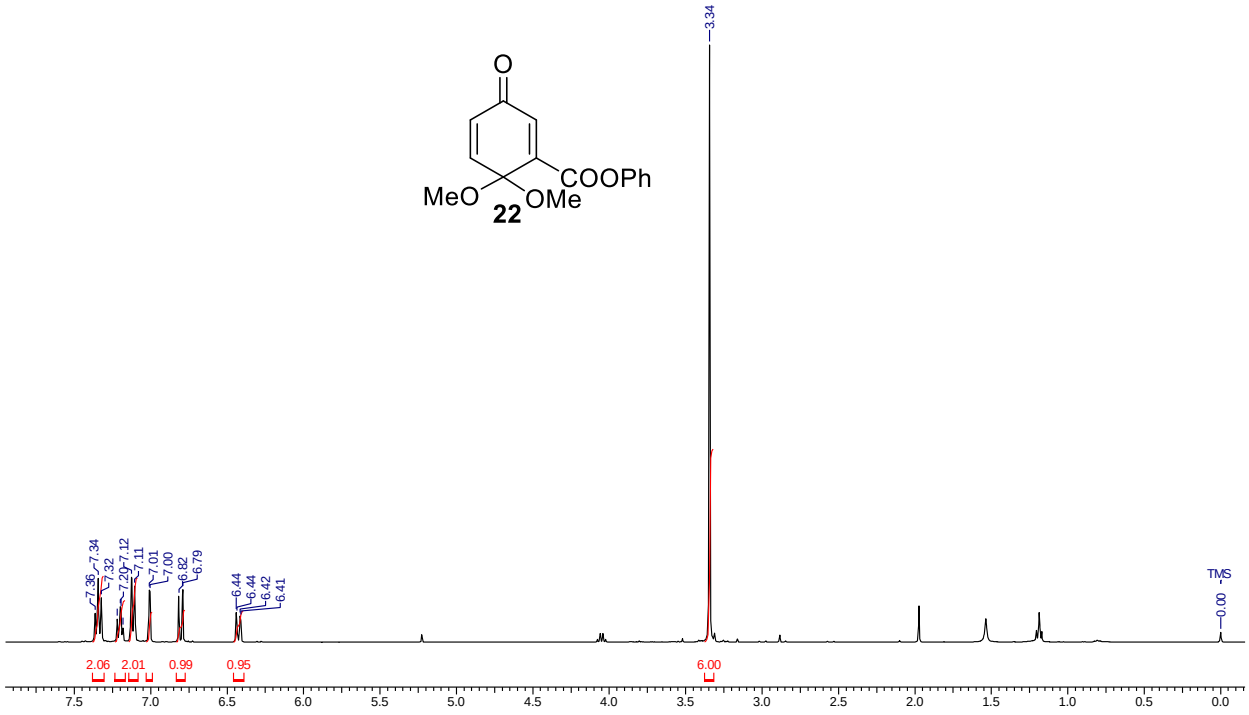

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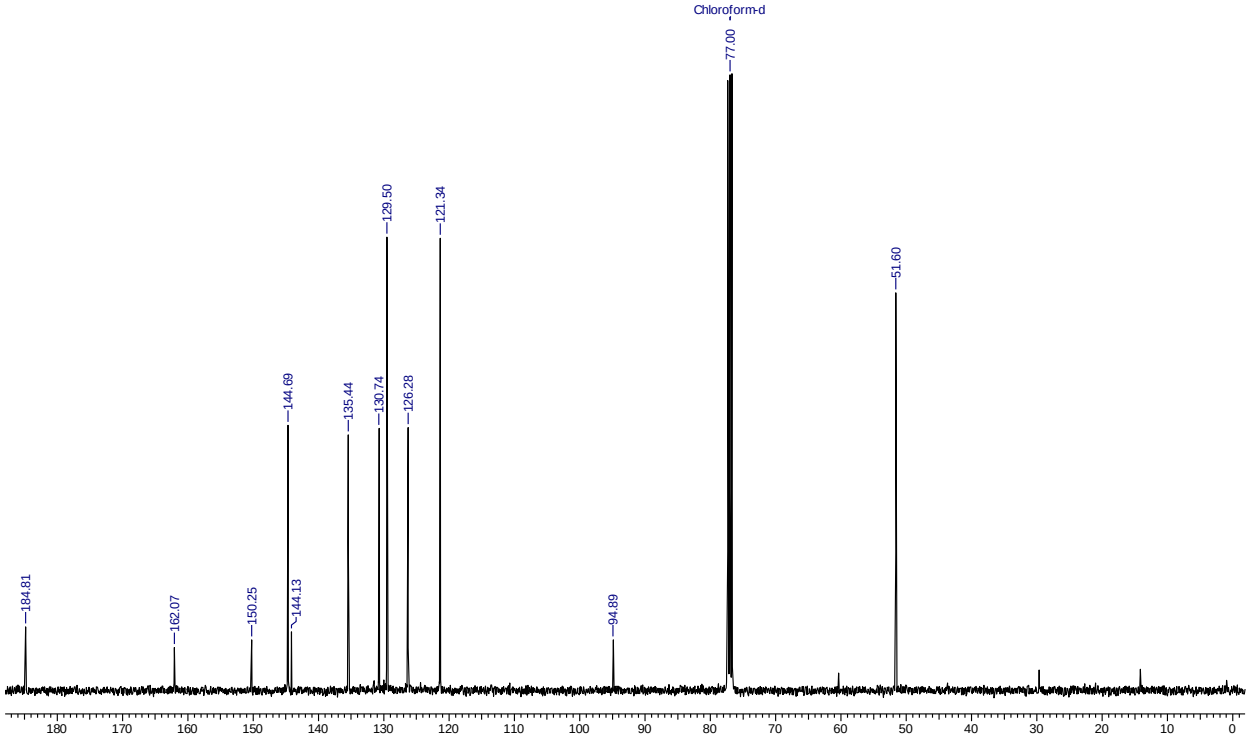

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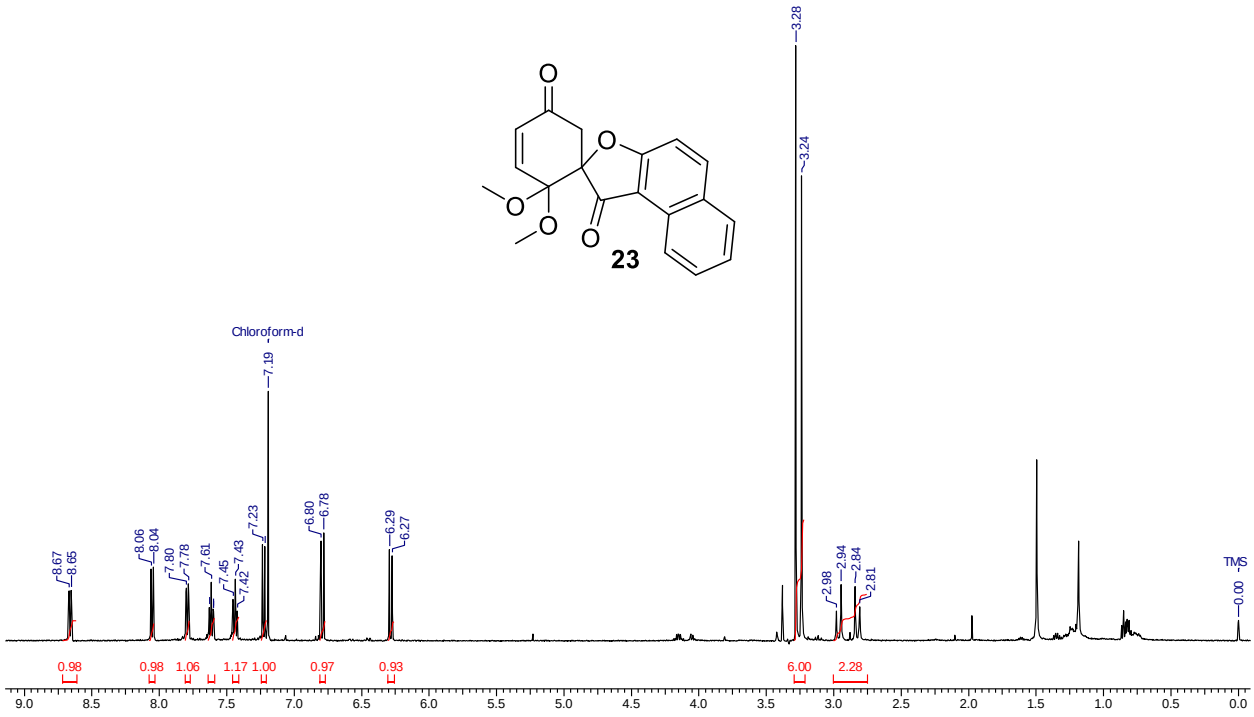

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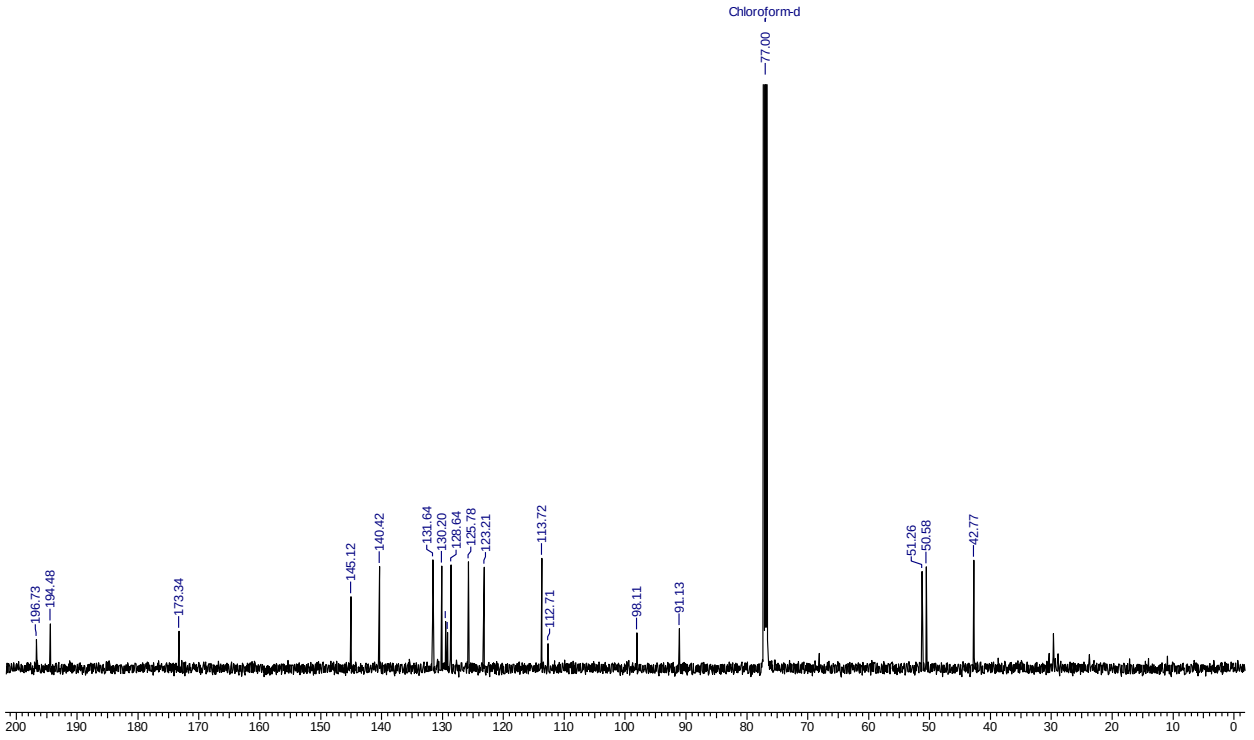

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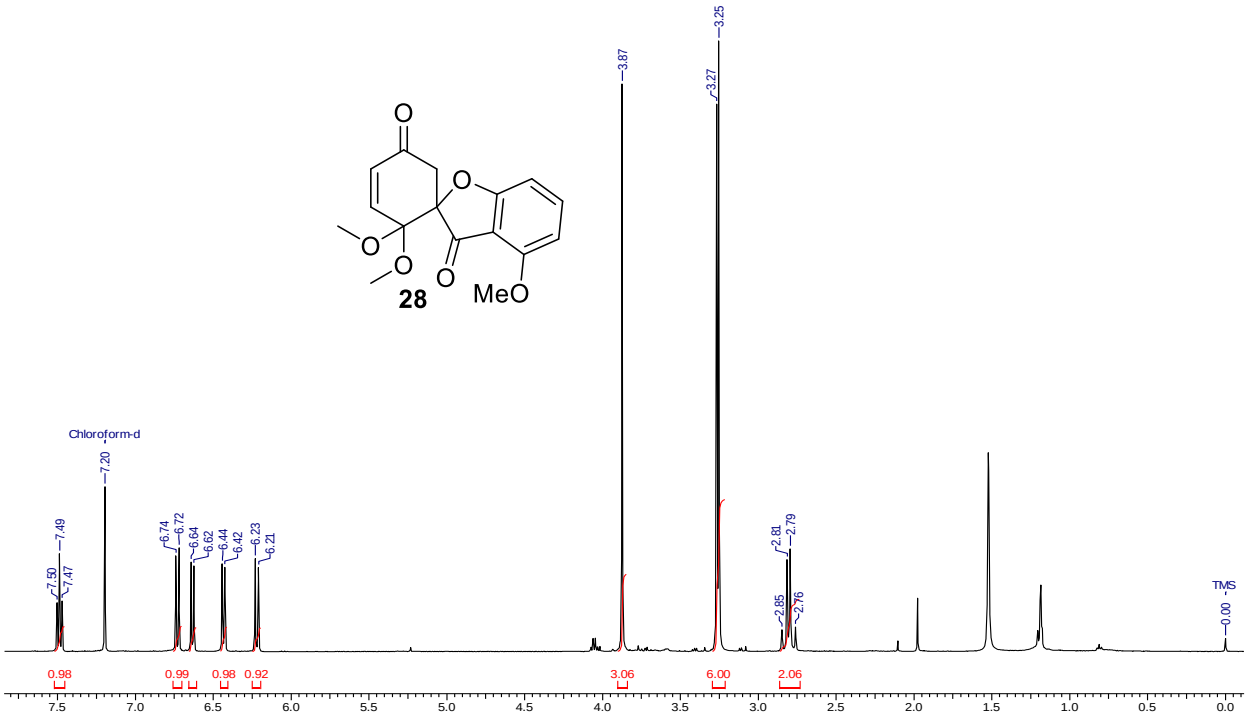

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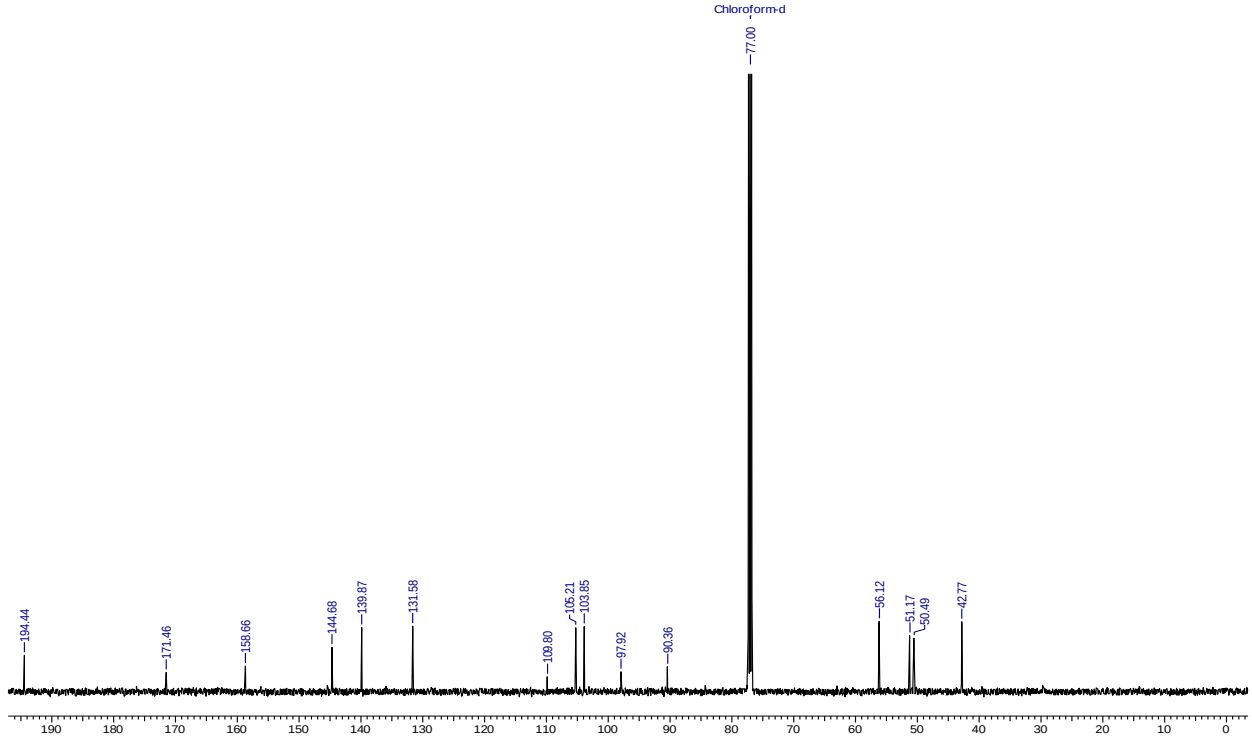

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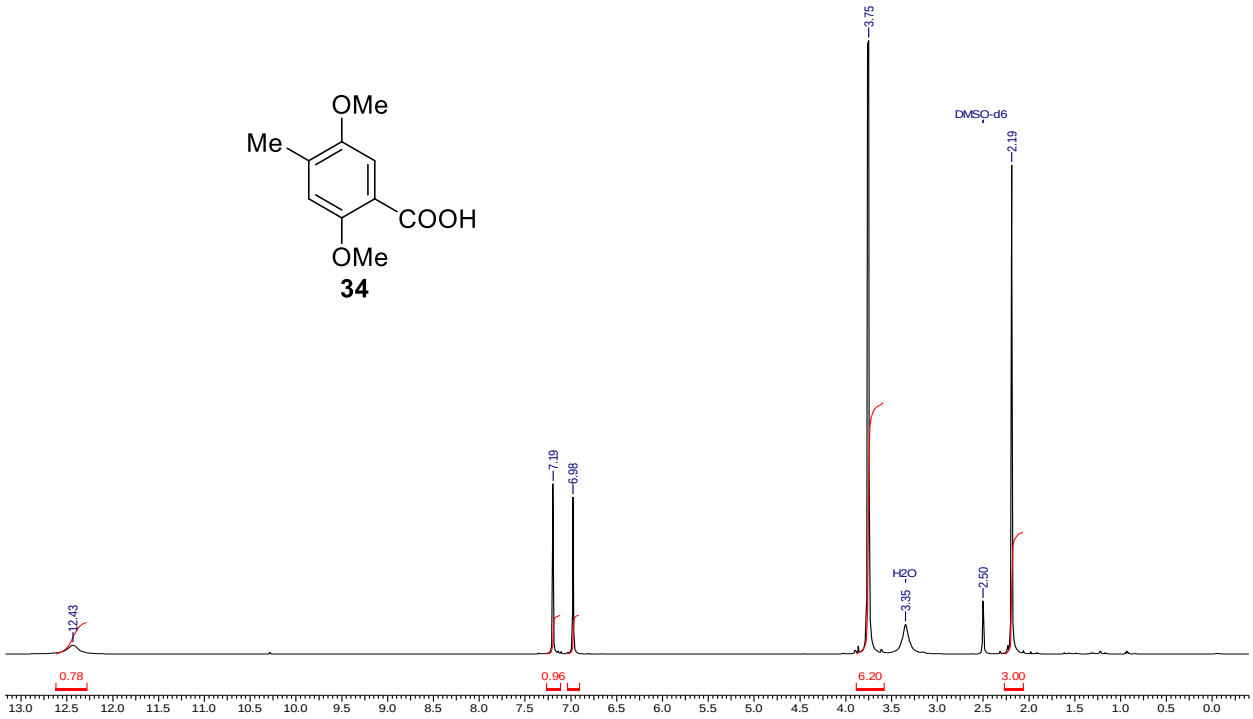

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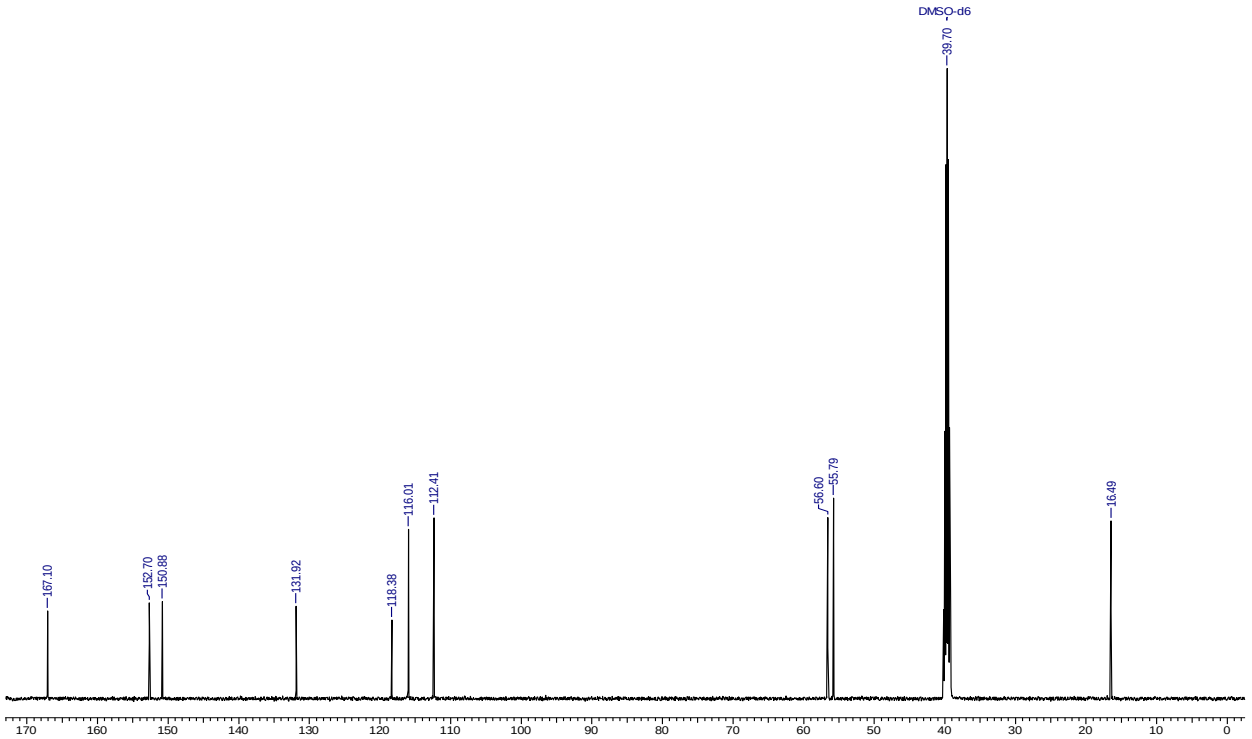

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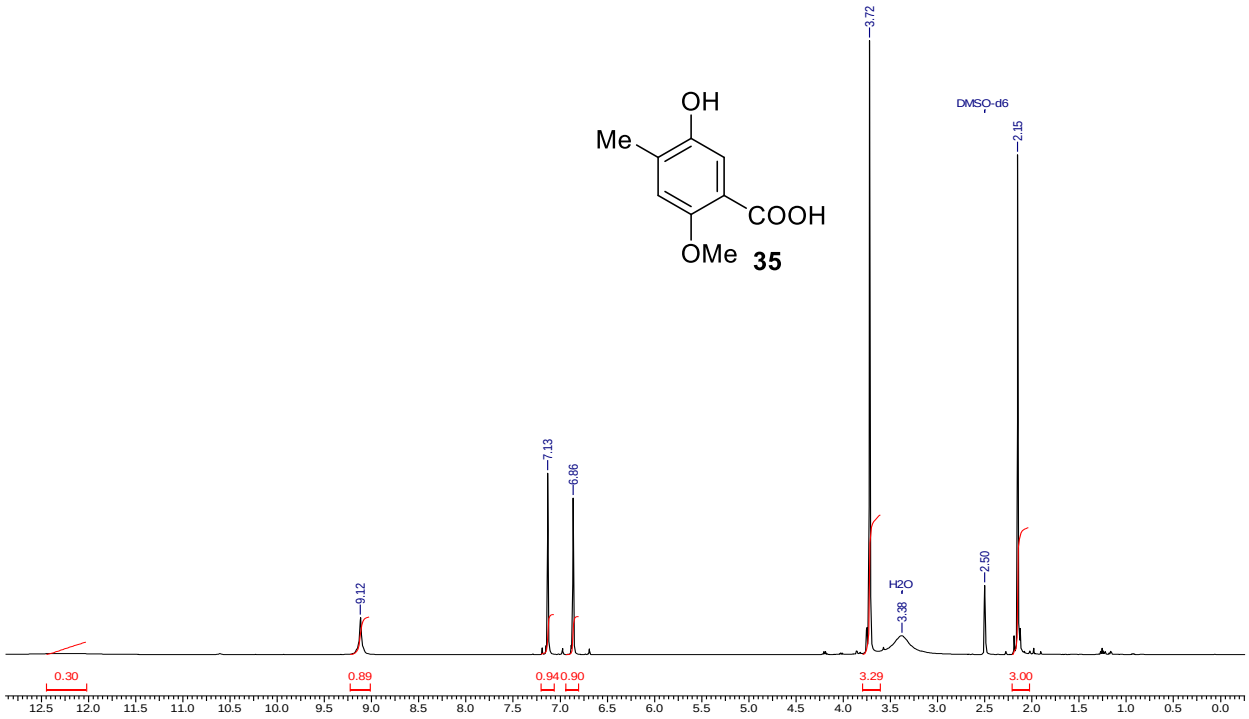

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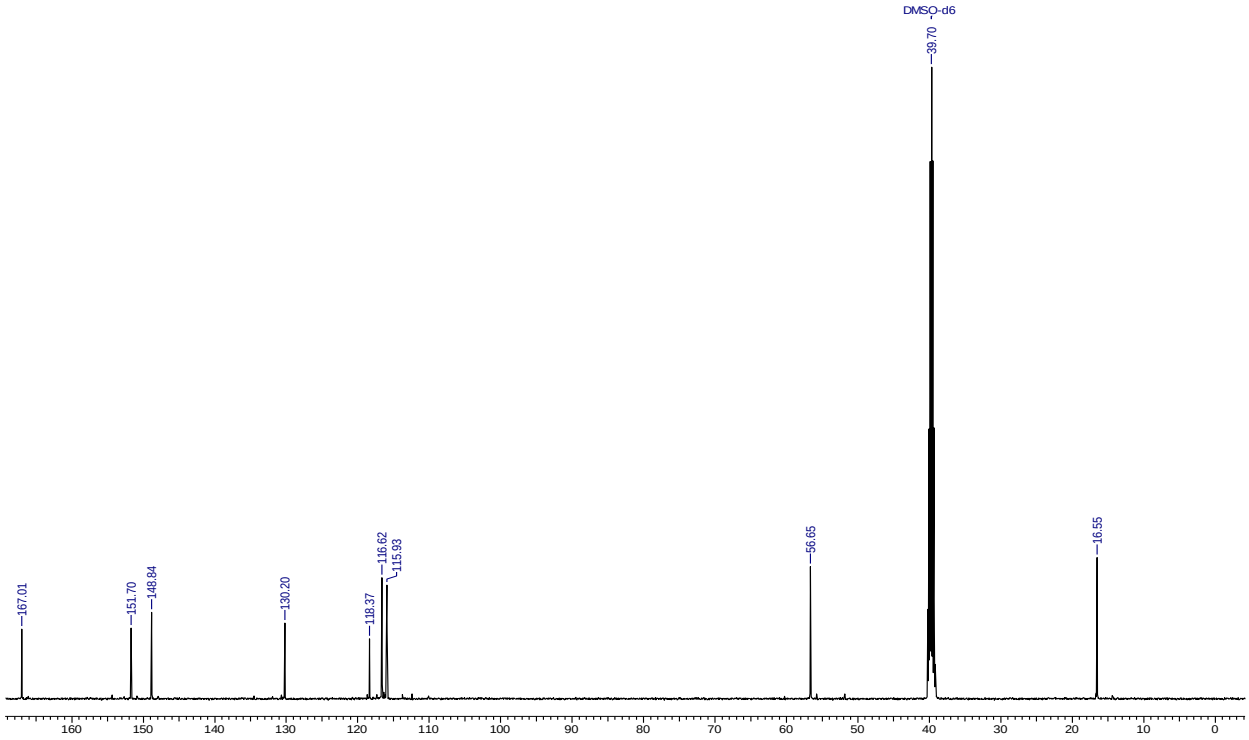

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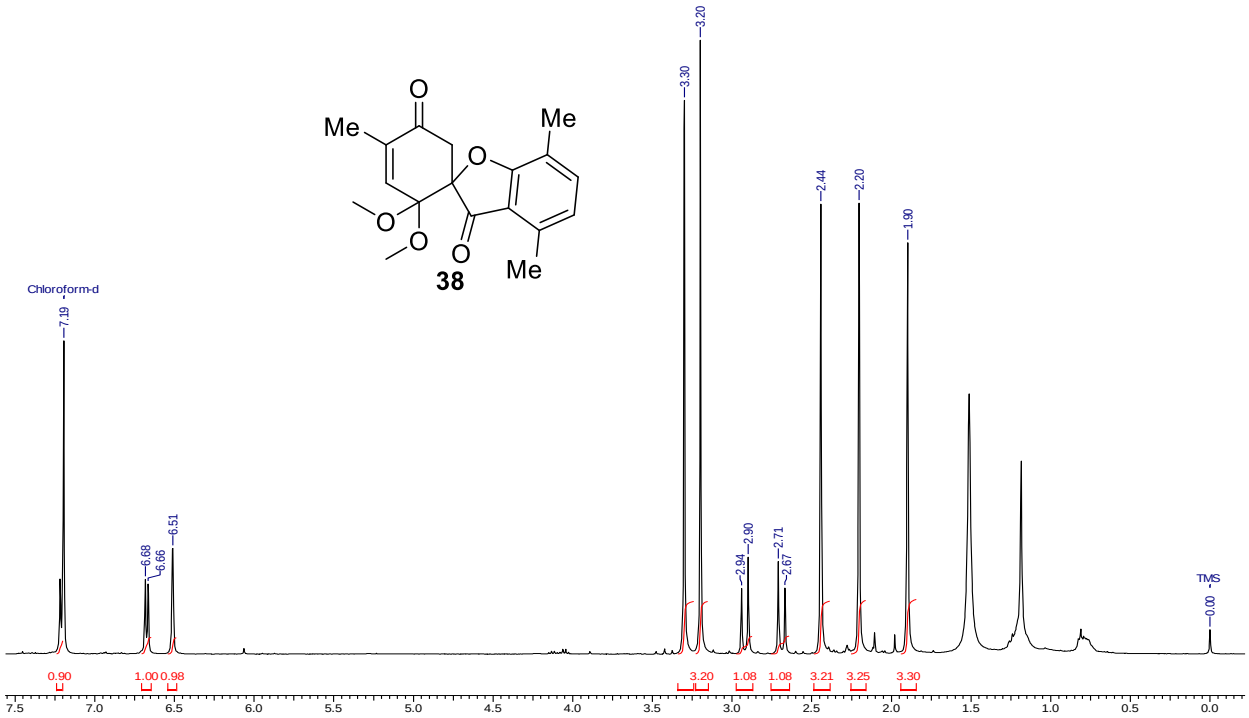

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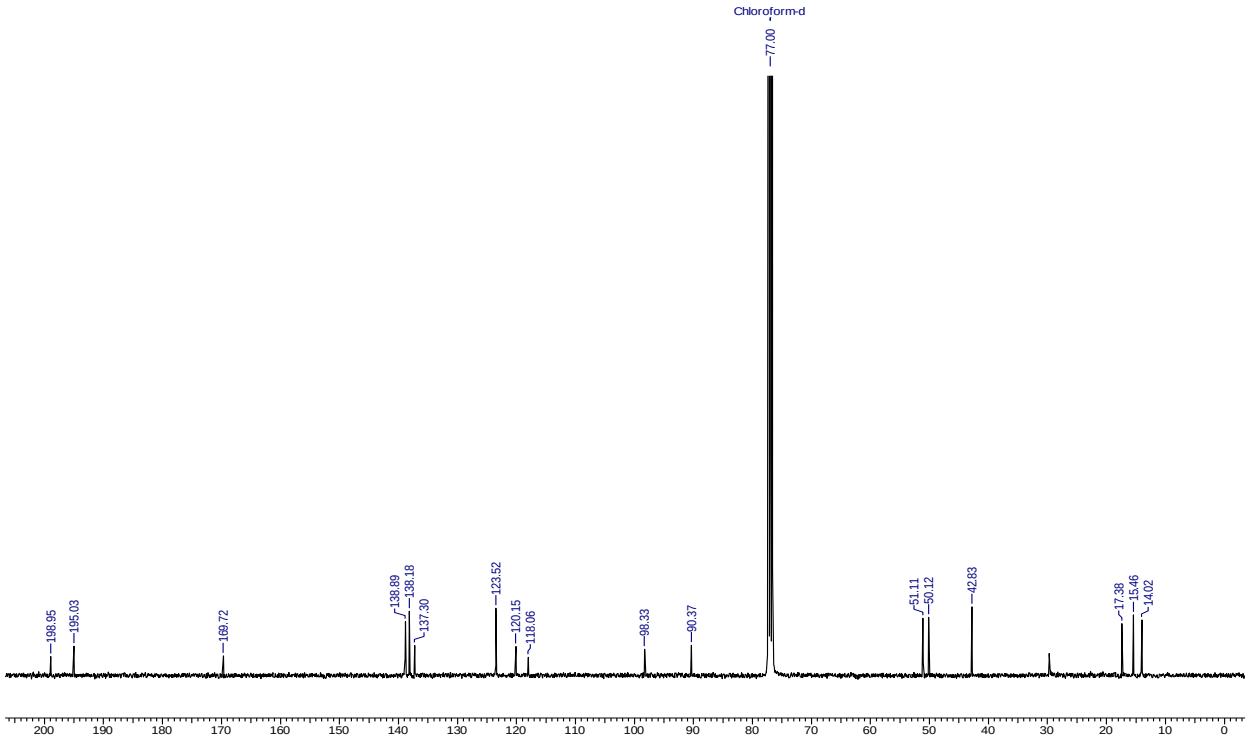

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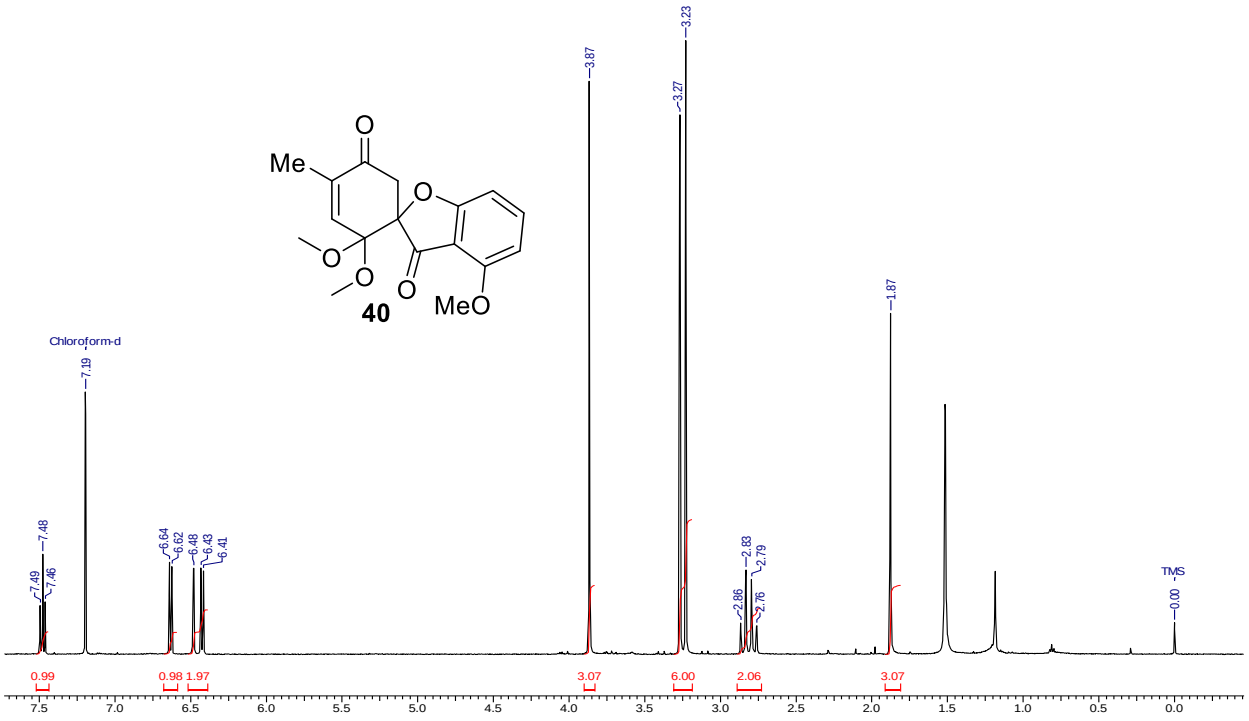

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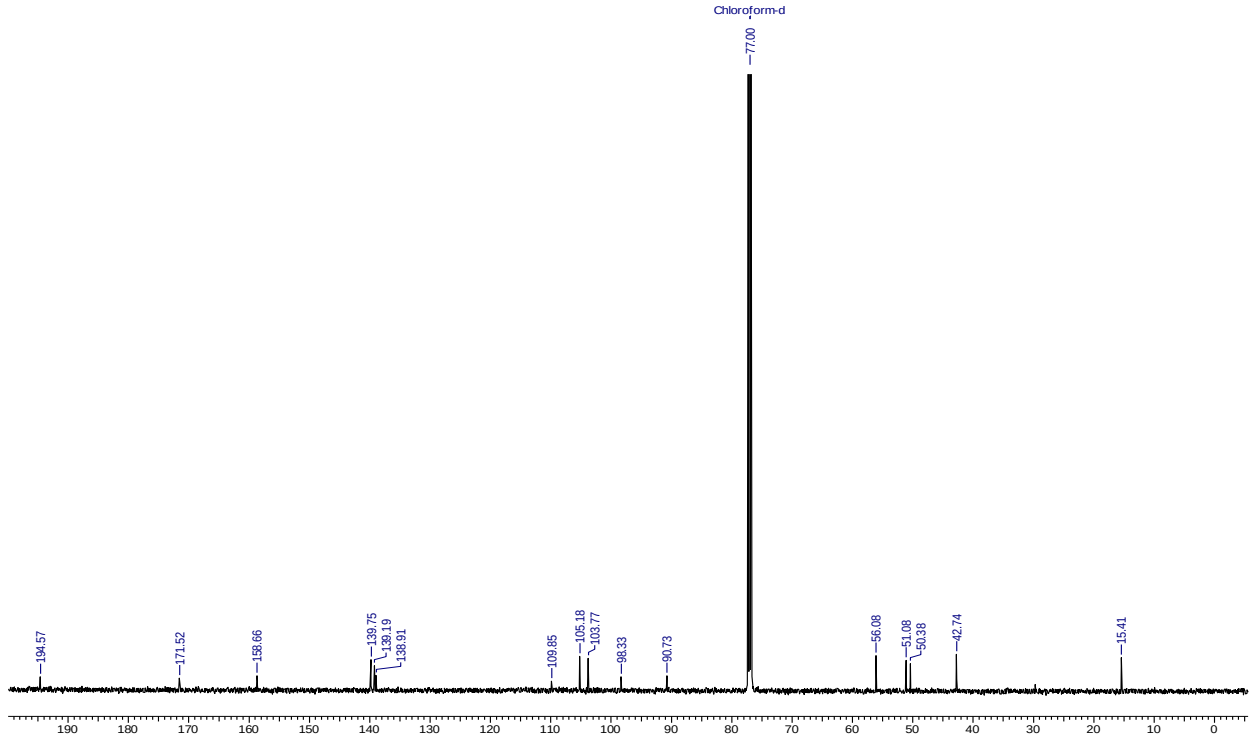

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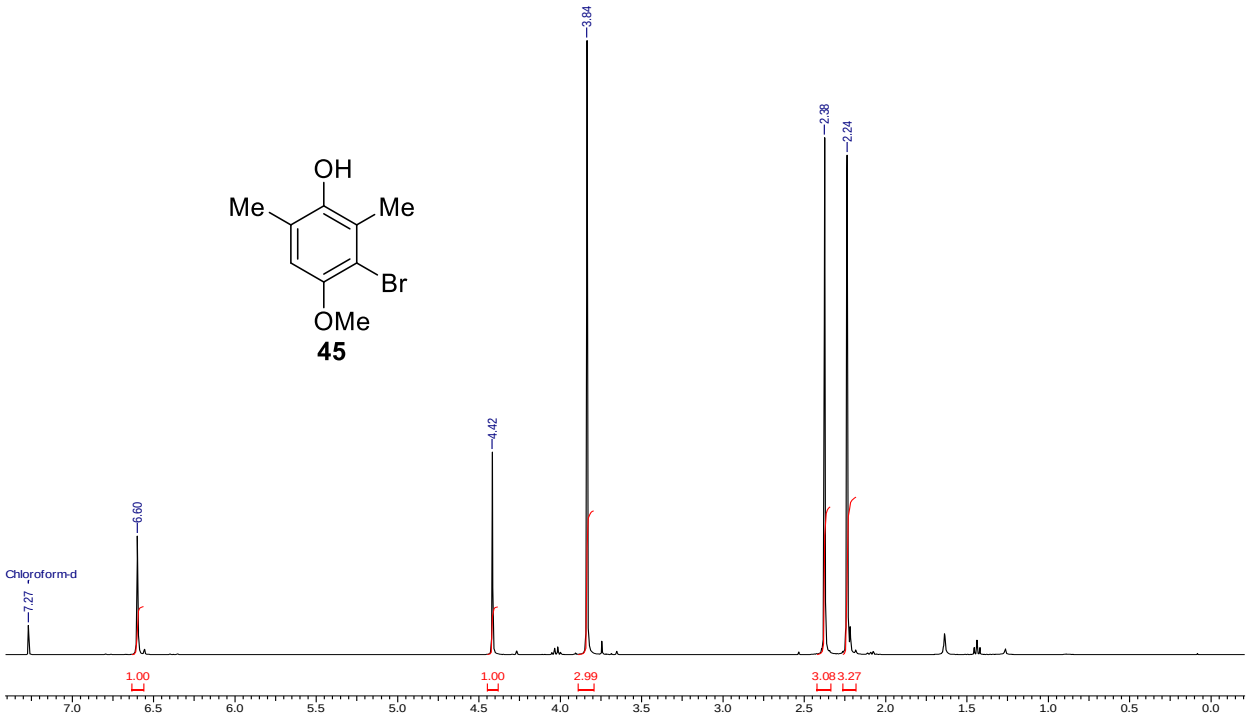

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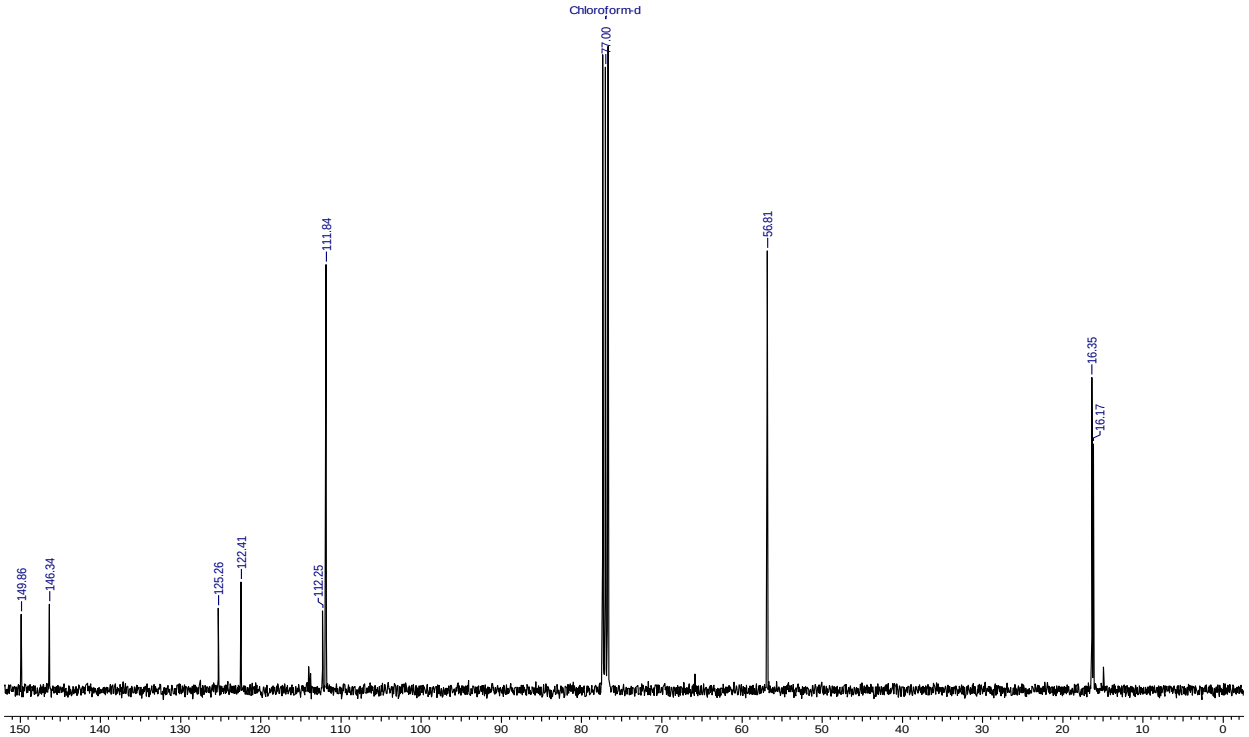

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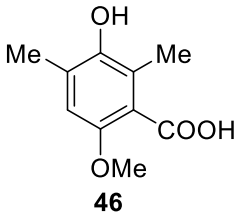

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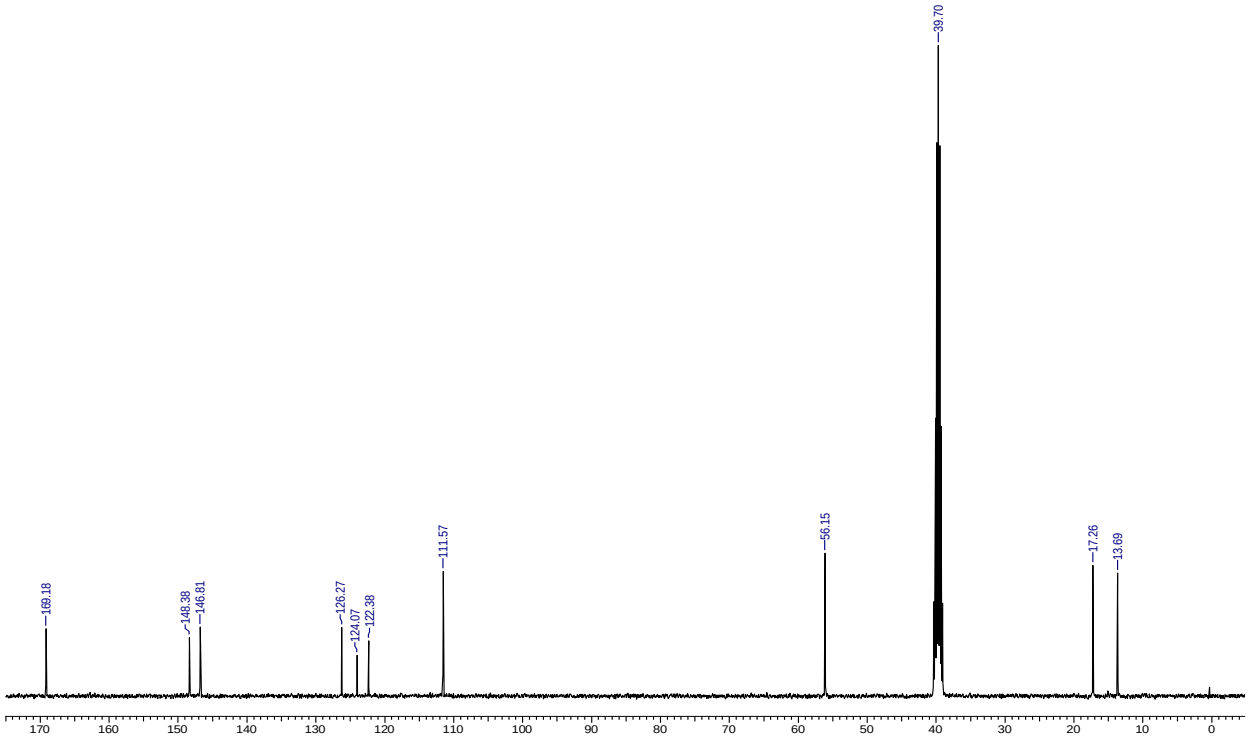

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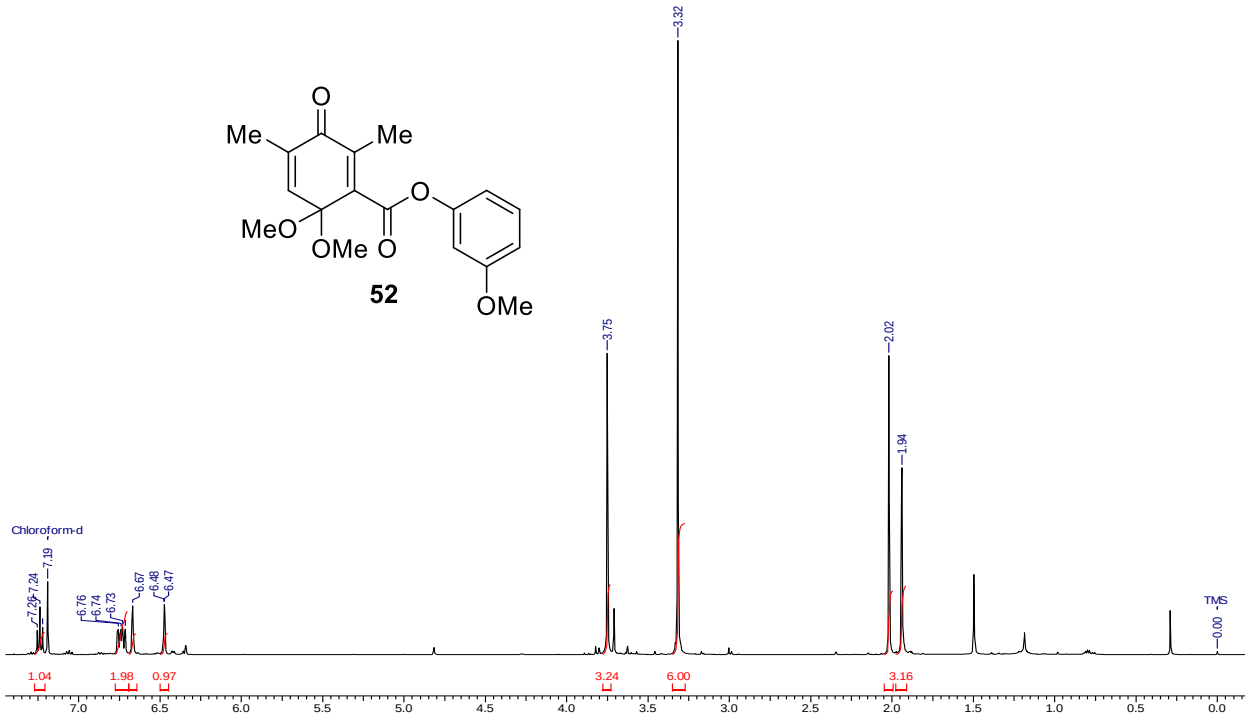

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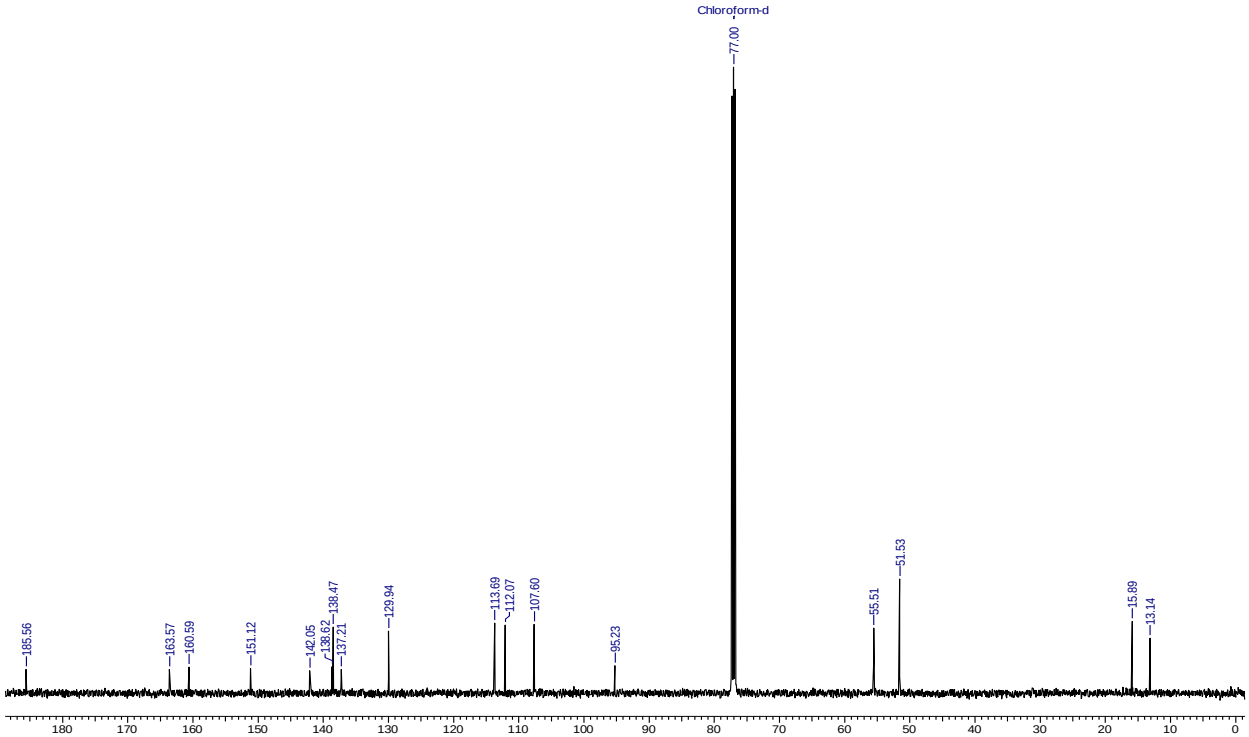

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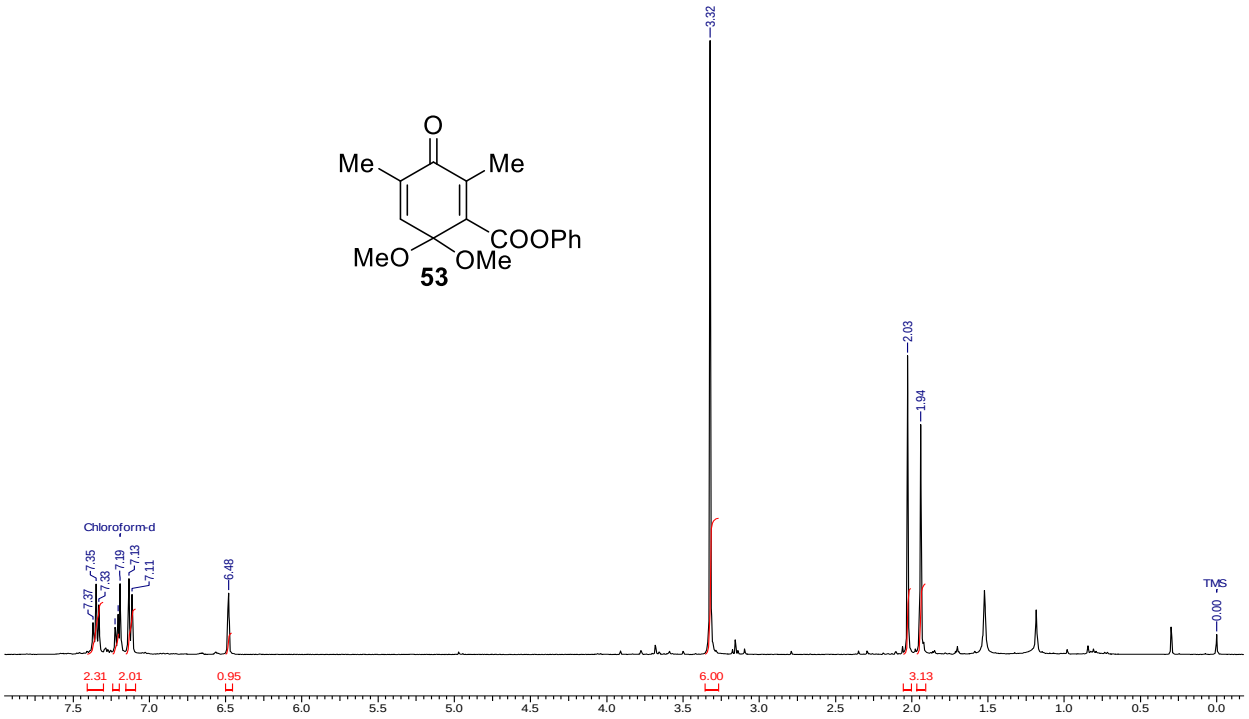

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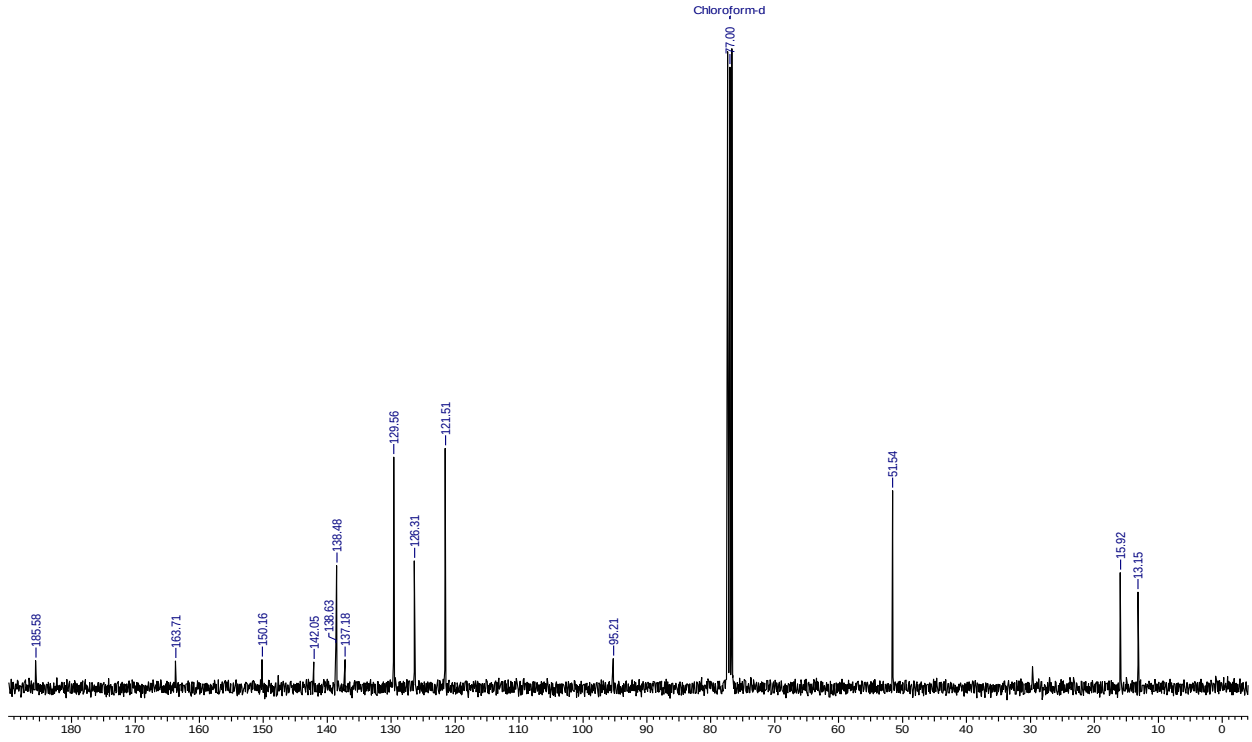

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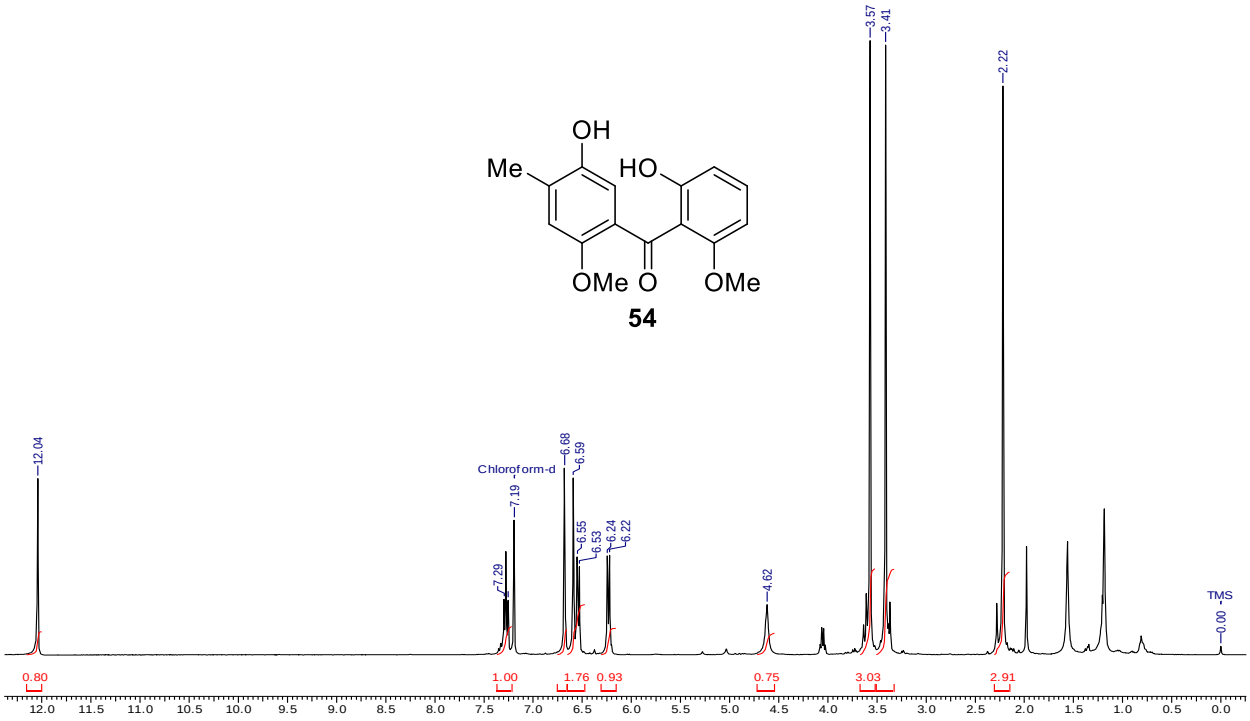

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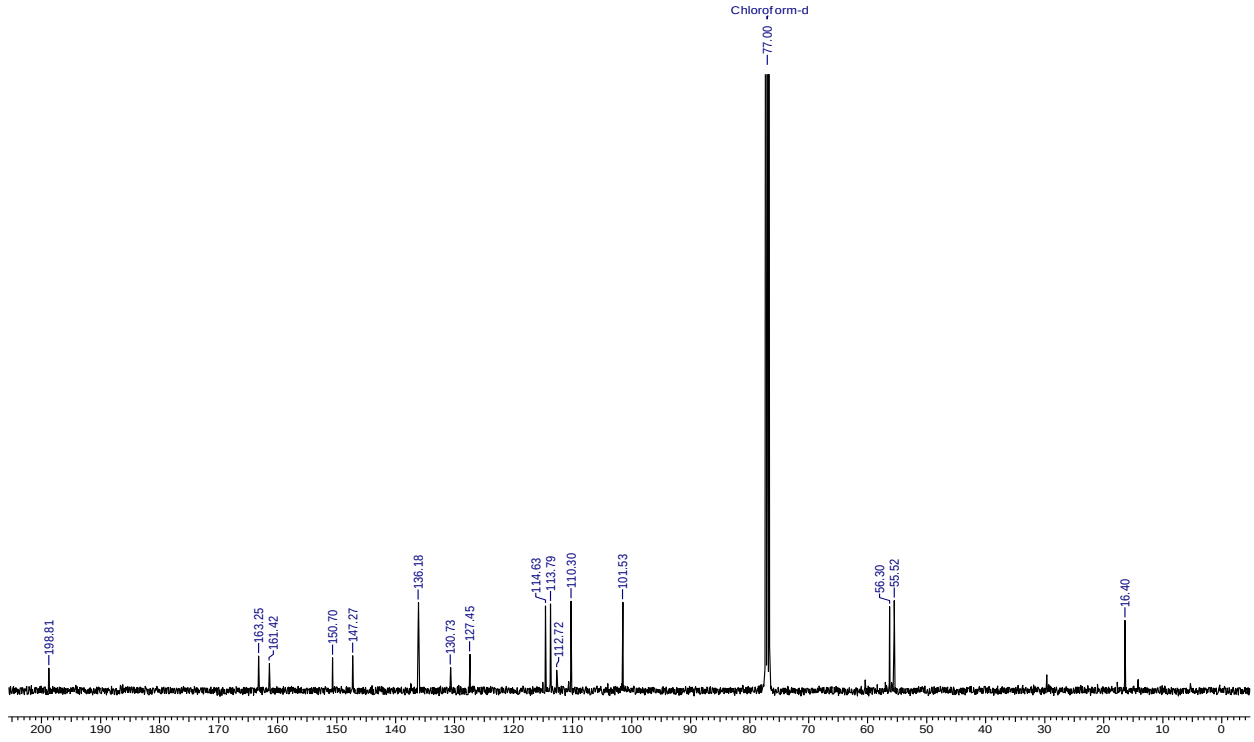

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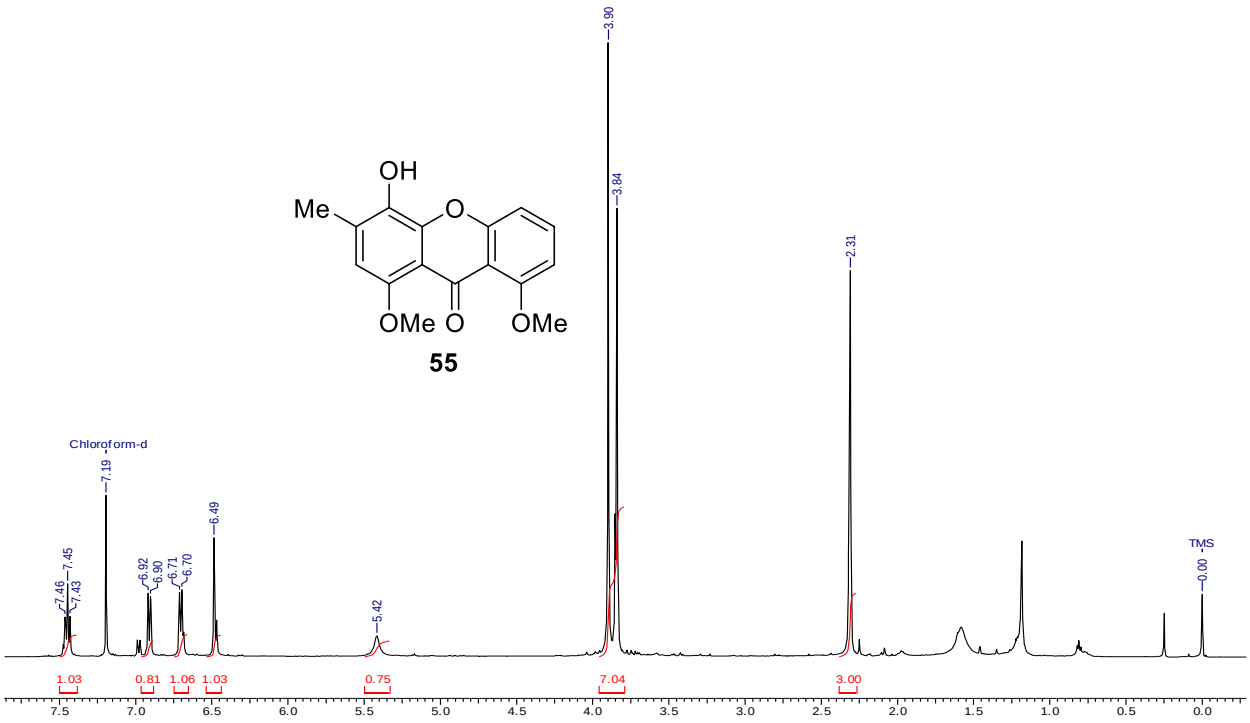

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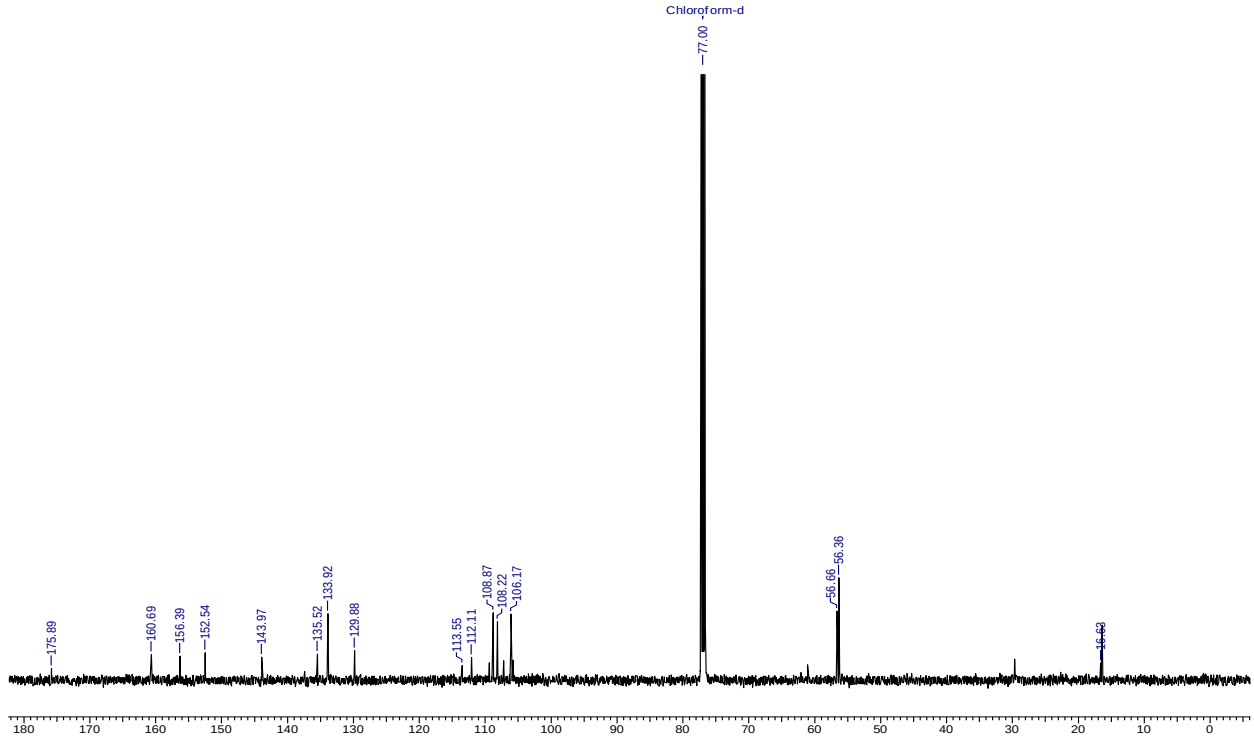

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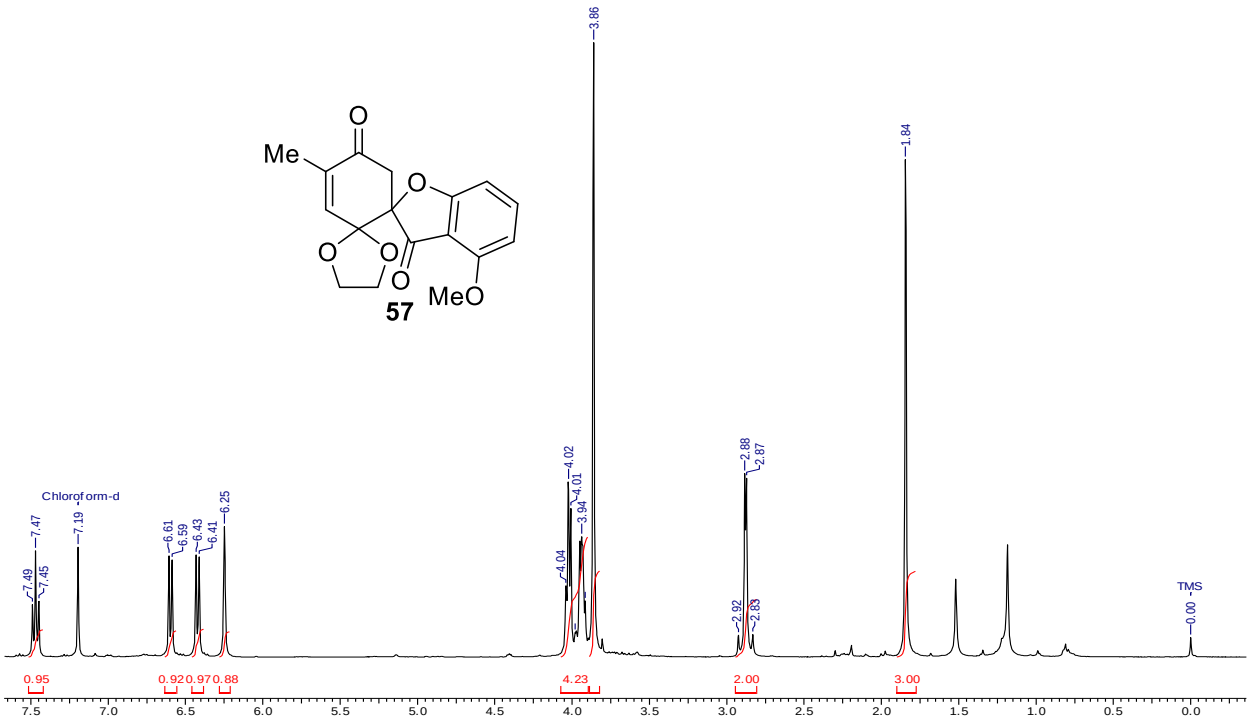

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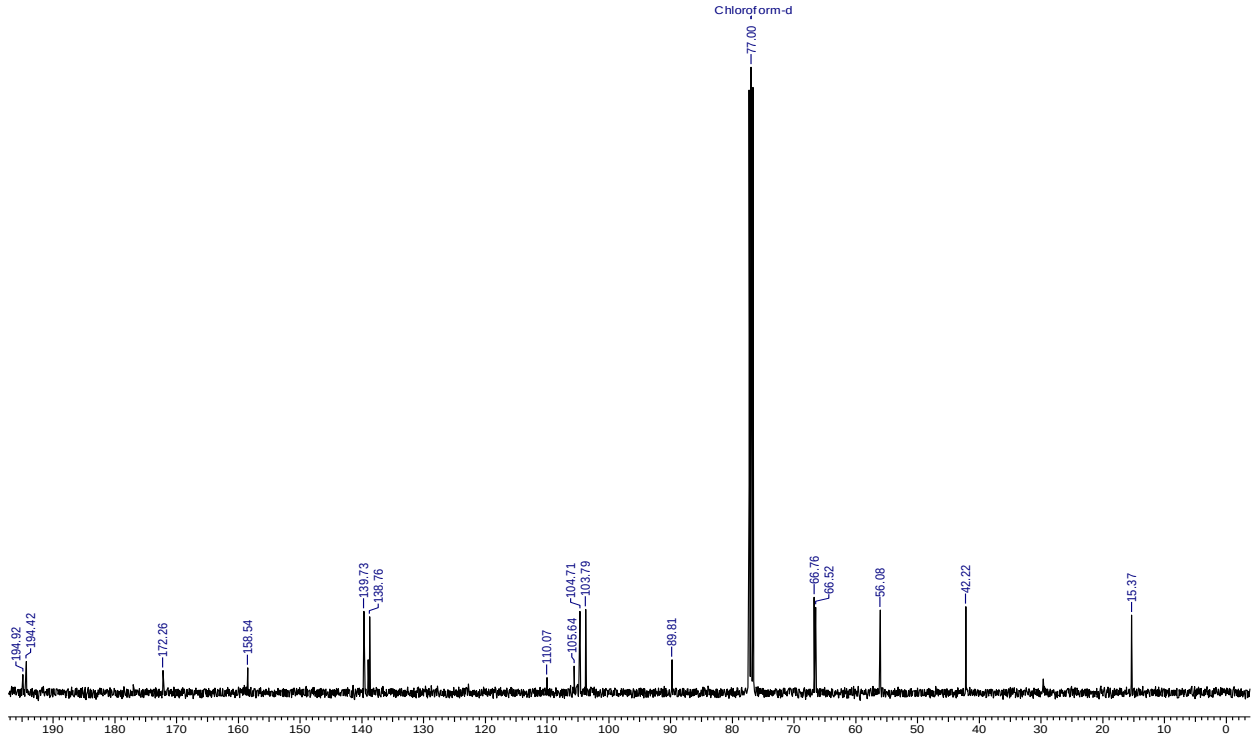

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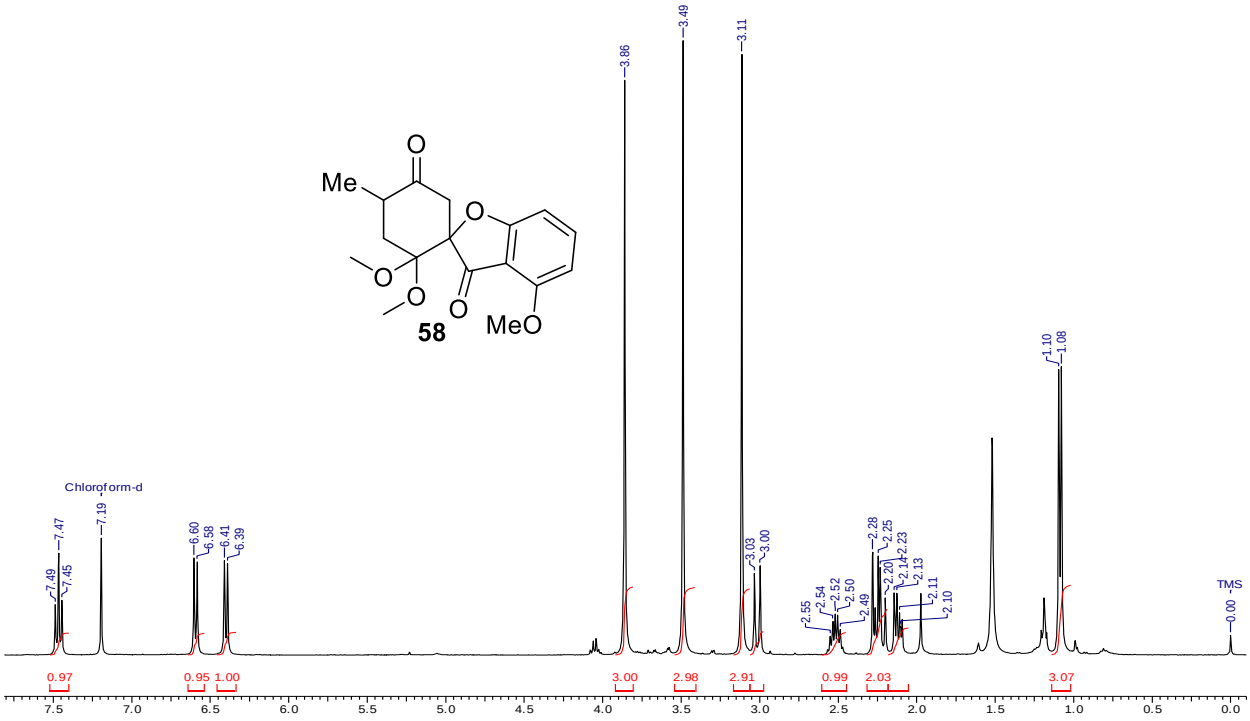

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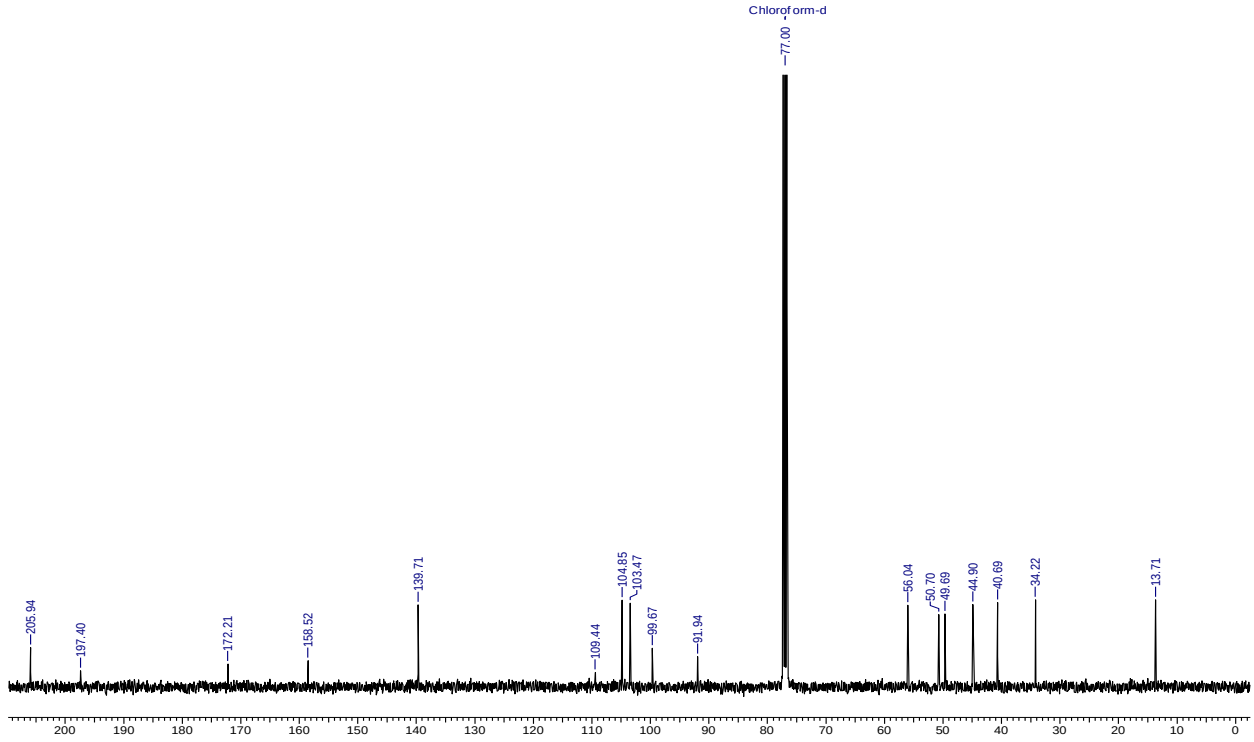

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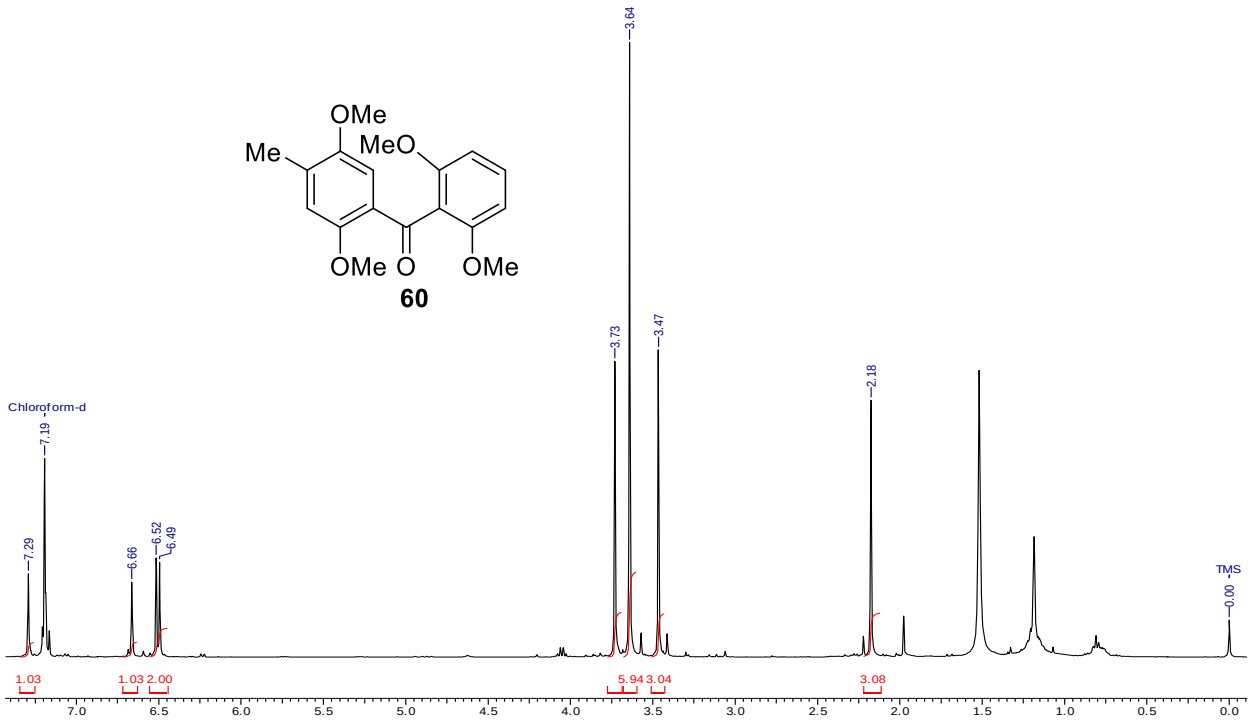
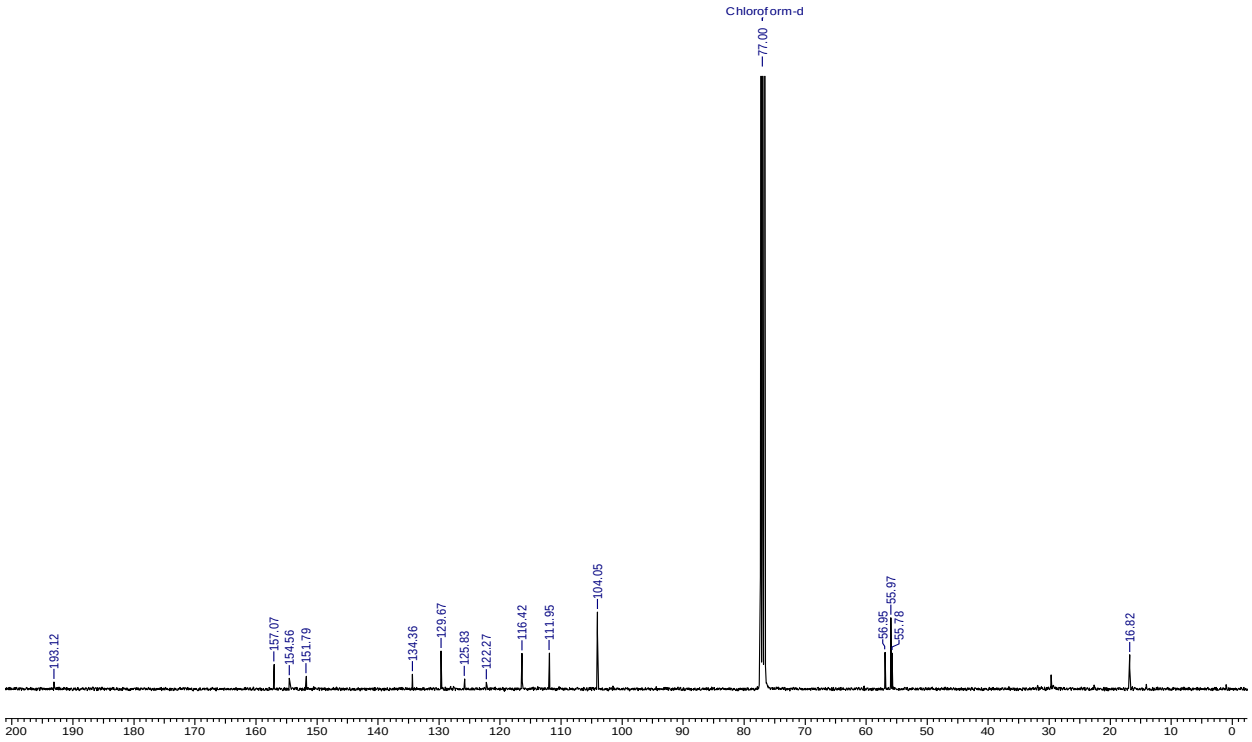


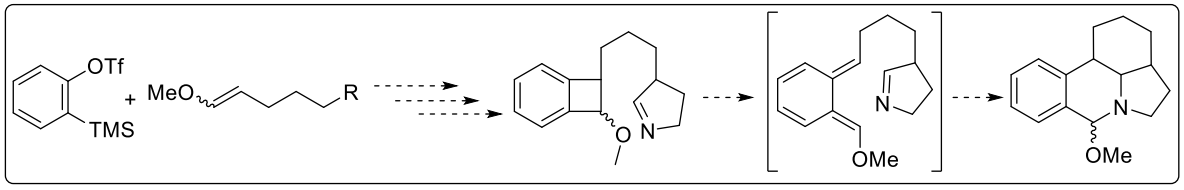
^{13}C NMR Spectra



Section 2: Study towards Total Synthesis of Lycorane and Class of Alkaloids

3.2.1 Abstract:

The section 2 involves the efforts towards the total synthesis of lycorane core. The [2+2] cycloaddition of aryne with substituted methoxy-ethene has been demonstrated for the synthesis of substituted cyclobutane ring. Further, efforts were made for the synthesis of diene via thermal ring opening of four membered cyclobutane ring followed by its intramolecular [4+2] Diels-Alder reaction with *in situ* generated imine for rapid construction of galanthane core.



3.2.2 Introduction:

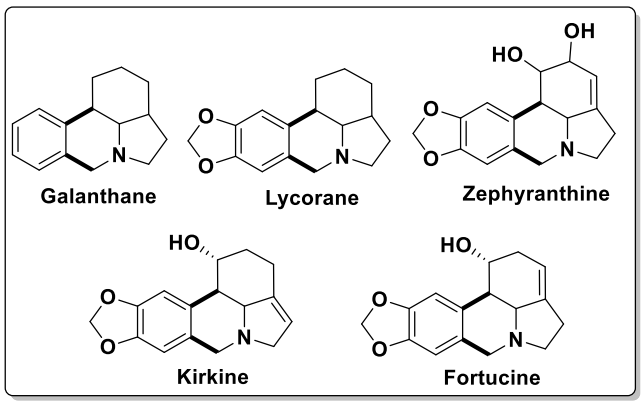


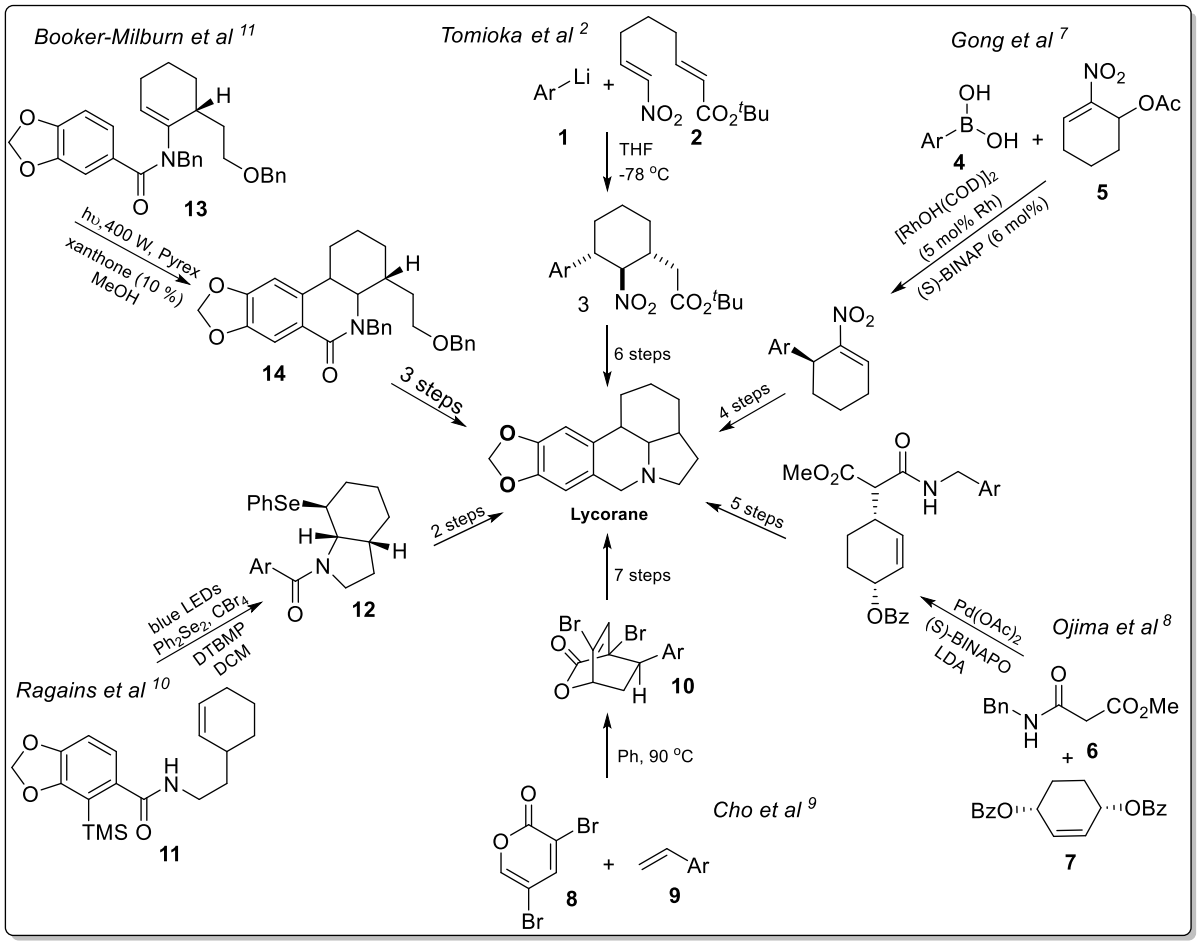
Figure 1: Natural products having galanthane core

The Amaryllidaceae family of plants has produced large number of highly potential medicinally important alkaloids.[1] These Amaryllidaceae families of plants have yielded over 300 different alkaloids including galanthamine, crinine, lycorine and highly saturated lycoranes.[2] The pyrrolo[de]phenanthridine representing common framework lycorane and its

congeneric natural compounds exhibit many important biological activities ranging from the inhibition of ascorbic acid biosynthesis to the prevention of cyanide-insensitive respiration.[3] The highly saturated lycoranes exhibits inhibition of cell growth and cell division. They have also been screened for antitumor activity in human cell lines.[4]

Lycoranes represents the deoxygenated skeletons of the class Amarylliaceae alkaloids.[5] The unique pentacyclic challenging structure and potent biological activities[6] of lycorane has attracted wide attention of synthetic chemists for its total synthesis. Due to its wide biological activities many groups have successfully accomplished the total synthesis of lycorane and its congeners.

3.2.3 Review Literature:



Scheme 1: Schematic representation of Lycorane synthesis

In this section we have focused on short and efficient total synthesis of lycorane natural products. Tomioka and co-workers acheived the total synthesis of lycorane via chemoselective conjugate addition of the aryl-lithium **1** with nitro-olefin moiety **2** furnishing unsaturated ester, followed by stereoselctive intramolecular nitro-Michael cyclization giving a functionalized cyclohexane **3**, which was further applied for total synthesis of lycorane.[2] Gong *et al* developed a novel protocol for enantioselective allylation of 2-nitrocyclohex-2-enol esters **5** with arylboronic acids **4** in the presence of rhodium complex $[RhOH(COD)]_2$. Further this methodology was implemented in total synthesis of (+)-γ-lycorane.[7]

The asymmetric allylic alkylation of methyl 3-(benzylamino)-3-oxopropanoate **6** with (1R,4S)-cyclohex-2-ene-1,4-diyl dibenzoate **7** catalyzed by $Pd(OAc)_2$ in combination with novel chiral biphenol-based monodentate phosphoramidite ligands has been demonstrated by Ojima group. Further, this methodology was applied for efficient short total synthesis of (+)-γ-lycorane.[8] The total synthesis of α-lycorane was achieved via Diels-Alder reaction of 3,5-dibromo-2-pyrone **8** with styrene-type dienophile **9** providing the pivotal intermediate **10** which on further transformation provided α-lycorane.[9] Ragains and co-workers reported short synthesis of the Amaryllidaceae alkaloid (±)-γ-lycorane by employing novel visible-light-promoted methodology for the intra- and intermolecular selenofunctionalization of alkenes **11** providing bicyclic seleno-motif **12**.[10] The total synthesis of (±)-β-lycorane alkaloid was carried out by employing a 6π-photoelectrocyclization reaction of an enamide **13**. The synthesis of (±)-β-lycorane was completed in just four steps from the ketone **14**. The brevity of this route enabled gram scale synthesis of (±)-β-lycorane.[11]

3.2.4 Origin of the work:

In literature the total synthesis of lycorane is performed in the presence of transition metals, photochemistry, organocatalysts and harsh conditions. The synthesis of lycorane always

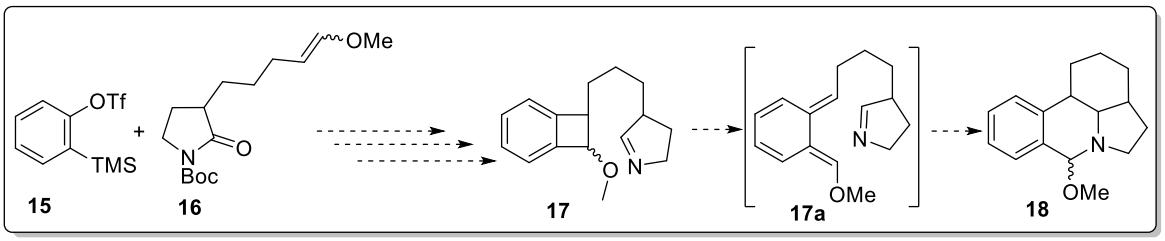
involves multistep operations on pre-activated species. To overcome this hurdles different groups have shown consistent involvement in short and efficient total synthesis of lycorane.

3.2.5 Objective of the work:

The construction of penatcyclic lycorane core has always been challenging task in synthetic chemistry. Most of the times it has been observed that the construction of pentacyclic core is carried out usually by constructing each cyclic structure at a time. In 2009 Hsung group have reported the construction of tricyclic N-heterocycles via cascade enamide-benzyne [2+2] cycloaddition followed by pericyclic ring-opening of amidobenzocyclobutanes and intramolecular Diels-Alder reaction.[12] They have successfully extended the methodology in total synthesis of Chelidonine and Norchelidonine.[13] Our continuous efforts in exploring aryne chemistry prompted us that combination of thermally driven [2+2] cycloaddition reaction of benzyne with methoxy substituted alkene and the powerful IMDA would lead to complex and medicinally important galanthane cores. In this context we have planned and made efforts towards synthesis of galanthane core.

We have successfully carried out [2+2] cycloaddition reaction and synthesised the precursor which would be involved in Diels-Alder reaction.

3.2.6 Result and Discussion:

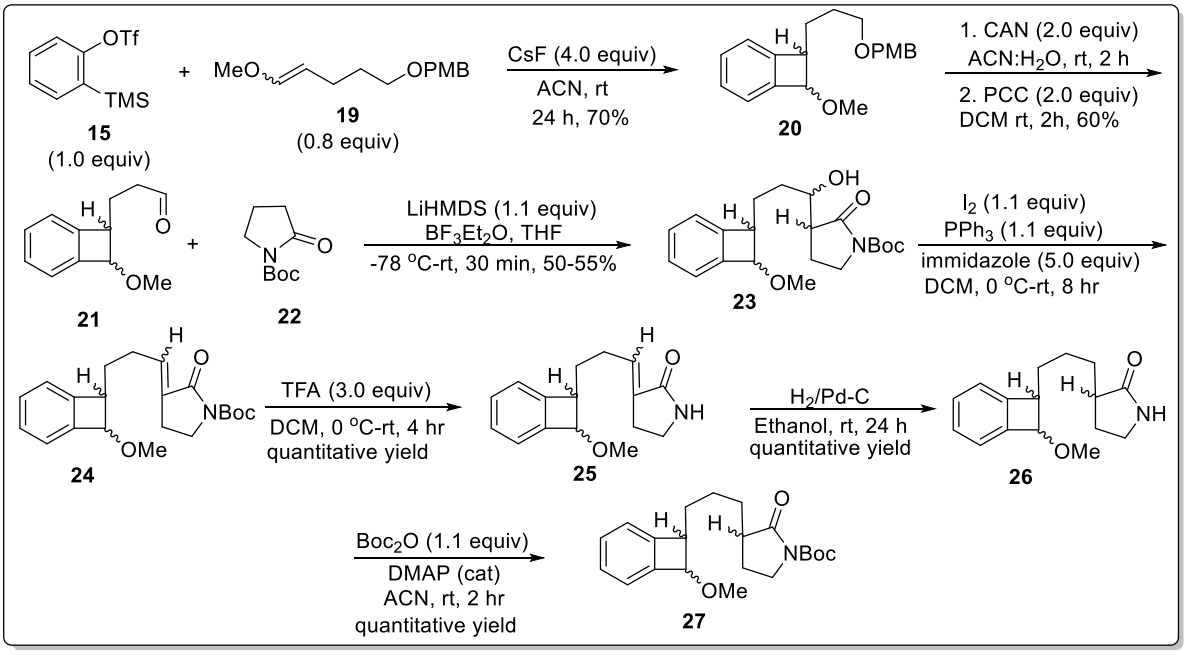


Scheme 2: Hypothesis for key step

Our hypothesis for the synthesis of galanthane core was the [2+2] cycloaddition reaction of N-Boc pyrolidinone compound **16** with aryne, which would further furnish *in situ* ring

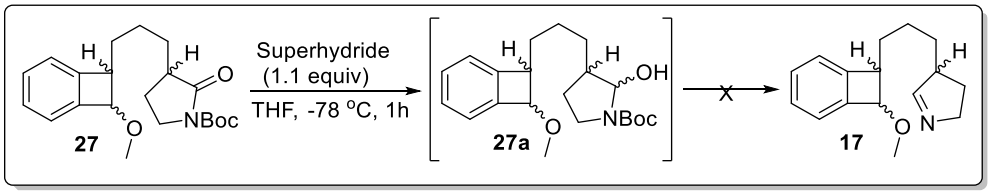
opened product imine **17a**. Diels-Alder reaction of *in situ* generated diene **17a** would lead to galanthane core **18** (Scheme 2).

Different strategies were employed for the synthesis of vital compound **16**, but unfortunately the synthesis met with failure. The unsuccessful synthesis of **17** compeled us to modify the strategy for the synthesis of galanthane core.



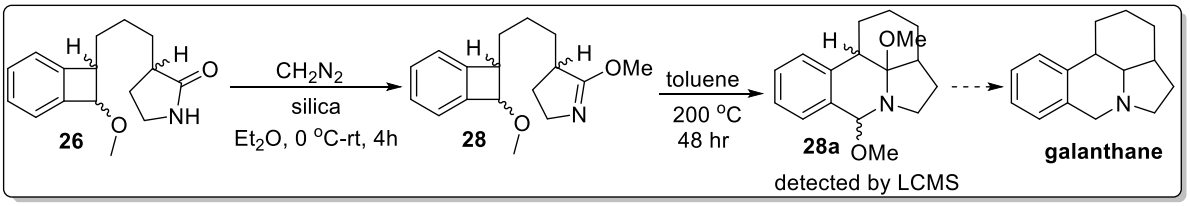
Scheme 3: Synthesis of imine precursor

The plan began with the synthesis of **20** by [2+2] cycloaddition of aryne precursor **15** and electron rich alkene **19**. The deprotection of PMB group of compound **20** was carried out by CAN in ACN:H_2O followed by oxidation of primary alcohol in PCC furnishing **21** (Scheme 3). The aldol condensation of compound **21** with N-Boc pyrolidine **22** in LiHMDS provided secondary alcohol **23**, which in the presence of Appel condition provided the eliminated product **24**. Further, compound **24** was deprotected and subjected to reduction in presence of hydrogen atmosphere furnishing **26**. The compound **26** was again subjected to Boc protection for further transformations (Scheme 3).



Scheme 4: Attempt for synthesis of **17**

The compound **27** was reduced in presence of superhydride, which was treated under different acidic conditions without purification and characterization, but unfortunately we met with failure (Scheme 4). This unsuccessful transformation resulted in altering the synthetic strategy. Further, the modification in imine **17** was carried out by synthesizing **28** from **26**



Scheme 5: Attempt for synthesis of galanthane core

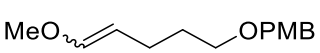
in the presence of diazomethane and neutral silica (Scheme 5). The compound **28** on heating in toluene at 200 ^{o}C for 2 days provided a trace amount of compound, which showed the exact mass of the expected compound **28a**. Further, the backup for compound **28a** and optimization for Diels-Alder reaction is in process.

3.2.7 Conclusion:

In conclusion we have made the efforts towards the total synthesis of lycorane core. The thermal [2+2] cycloaddition has been established on aryne and methoxy substituted alkene. The synthesis of precursor which is essential for pericyclic [4+2] cycloaddition has been carried out. The optimization study for pericyclic reaction is in the process. Further, its application in synthesis of lycorane and its congeners is underway.

3.2.8 Experimental Procedure and Characterization Data:

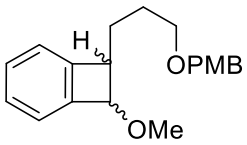
1-Methoxy-4-(((5-methoxypent-4-en-1-yl)oxy)methyl)benzene (19):



To a suspension (methoxymethyl)triphenylphosphonium chloride (3.94 g, 9.6 mmol) in THF (30 ml) under N_2 atm at -78 ^oC, was added NaHMDS (11.5 ml, 2 M in THF) drop-wise and stirred at that temperature for 1 h. A solution of aldehyde 4-((4-methoxybenzyl)oxy)butanal[14] (1.0 g, 4.8 mmol) in THF (10 mL) was then slowly added via syringe and stirred for an additional 2 h at –78 °C. The mixture was then warmed to room temperature and stirred for 30-45 min. The reaction was then quenched with a saturated aqueous $NaHCO_3$ solution, extracted with Et_2O and washed with brine. The organic layer was then dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography (5:95 EtOAc:Pet. Ether) to yield **19** as a yellow oil (678 mg, 70%).

Reaction Time: 3.5 h, R*f*: 0.3 (1:9 EtOAc:Pet. Ether); oil; 678 mg, 70%; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.20 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.22 (d, *J* = 12.8 Hz, 0.87 H), 4.70-4.58 (m, 0.94 H), 3.74 (s, 3H), 3.42 (s, 3H), 3.39 (t, *J* = 6.7 Hz, 2H), 1.95 (q, *J* = 7.3 Hz, 2H), 1.64-1.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 159.1, 147.3, 146.3, 130.7, 130.3, 129.2, 120.4, 113.7, 106.2, 102.3, 72.5, 69.8, 69.2, 55.9, 55.2, 30.7, 29.8, 24.3, 20.5. Mass $(M + H)^+$ 237.

7-Methoxy-8-(3-((4-methoxybenzyl)oxy)propyl)bicyclo[4.2.0]octa-1(6),2,4-triene (20):

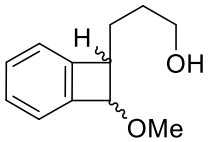


To a suspension 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (1.96 g, 6.6 mmol) and CsF (4.63 g, 30 mmol) in dry CH_3CN (15 ml) under N_2 atmosphere, was added the solution of **19** (1.2 g, 5.0 mmol, 10 ml CH_3CN) drop-wise and stirred at room temperature for 24 h. The reaction mixture was filtered and concentrated. Further, water was added in the reaction mixture and it was extracted by EtOAc and dried over Na_2SO_4. After evaporation of solvent, the crude product was purified by using column chromatography on silica gel (10:90 EtOAc:Pet. Ether) to yield **20** as oil (1.2 g,

76%). The product was isolated as a mixture of diastereomers that were used in the subsequent transformation without separation.

Reaction Time: 24 h, R*f*: 0.3 (1:9 EtOAc:Pet. Ether); oil; 1.2 g, 76%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.31-7.14 (m, 6H), 7.09 (d, *J* = 6.9 Hz, 0.6H), 6.84-6.77 (m, 2H), 5.72-5.62 (m, 0.3H), 5.61-5.52 (m, 0.5H), 4.92 (d, *J* = 4.9 Hz, 0.13H), 4.85 (d, *J* = 4.9 Hz, 0.18H), 4.51 (d, *J* = 7.3 Hz, 0.2H), 4.47 (d, *J* = 1.1 Hz, 0.3H), 4.41-4.35 (m, 3H), 3.74 (s, 3H), 3.66-3.60 (m, 0.3H), 3.5-3.39 (m, 3.65H), 3.34-3.28 (m, 0.4H), 3.24 (s, 1.2H), 2.51-2.40 (m, 0.3H), 2.35-2.25 (m, 0.5H), 1.85-1.70 (m, 2H), 1.25-1.17 (m, 0.57H), 0.85-0.77 (m, 0.44H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 159.1, 147.6, 146.3, 145.5, 143.5, 141.6, 141.4, 132.5, 132.3, 130.7, 130.6, 130.5, 130.4, 129.7, 129.2, 129.1, 128.5, 128.4, 128.3, 127.5, 127.4, 127.3, 126.7, 126.5, 123.2, 123.0, 122.9, 113.7, 84.3, 83.7, 80.2, 78.8, 72.6, 72.5, 72.4, 70.2, 69.9, 69.3, 69.2, 57.6, 56.6, 56.2, 55.2, 51.5, 49.5, 32.7, 29.1, 28.4, 28.2, 25.9, 22.6, 14.1. Mass $(M + Na)^+$ 335.

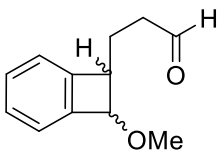
3-(8-Methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propan-1-ol (20a):



To a suspension of Cerric Ammonium Nitrate (4.21 g, 7.6 mmol) in acetonitrile: water (20:6 ml), was added the solution of **20** (1.2 g, 3.8 mmol) in CH_3CN: H_2O (10:3) dropwise at 0 ^{o}C. The reaction was allowed to attain room temperature and stirred for additional 2 h. The reaction mixture was diluted with water and extracted with DCM twice. The combined organic layers were dried on Na_2SO_4 and concentrated to afford crude product, which was purified on silica gel (40:60 EtOAc:Pet. Ether) to yield **20a** as yellow oil (450 mg, 61%).

Reaction Time: 2 h, R*f*: 0.3 (2:3 EtOAc:Pet. Ether); oil; 450 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.26-7.15 (m, 3H), 7.10 (d, *J* = 7.1 Hz, 1H), 4.89 (d, *J* = 4.9 H, 0.6H), 4.49 (apparent d, 0.4H), 3.70-3.60 (m, 3H), 3.50 (s, 1.8H), 3.48-3.40 (m, 1.5H), 3.38-3.30 (m, 0.5H), 1.90-1.60 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 147.6, 146.1, 145.2, 143.5, 129.3, 129.2, 127.5, 127.4, 123.2, 123.1, 122.9, 83.7, 80.3, 62.8, 62.5, 57.5, 56.6, 51.4, 49.4, 31.4, 31.3, 28.7, 25.1. Mass $(M + H)^+$ 193.

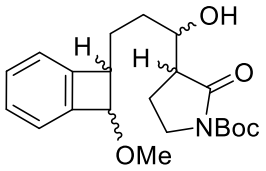
3-(8-Methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propanal (21):



To the slurry of PCC (671 mg, 3.1 mmol) in DCM (10 mL), a solution of alcohol **20a** (400 mg, 2.0 mmol) in DCM (5 mL) was added at room temperature under N_2 atmosphere with vigorous stirring. After stirring for 4 h at room temperature, anhydrous diethyl ether was added, and the reaction mixture was filtered through celite. The filtrate was concentrated *in vacuo*, and the product was purified on silica gel (20:80 EtOAc:Pet. Ether) to yield the desired aldehyde **21** as yellow oil (300 mg, 76%).

Reaction Time: 4 h, R*f*: 0.3 (1:4 EtOAc:Pet. Ether); oil; 300 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 9.77 (apparent t, 0.4H), 9.73 (apparent t, 0.4H), 7.35-7.15 (m, 3H), 7.14-7.02 (m, 1H), 4.86 (d, *J* = 4.4 Hz, 0.55H), 4.49 (apparent d, 0.45H), 3.72-3.60 (m, 0.55H), 3.47 (s, 1.6H), 3.42 (s, 1.5H), 3.38-3.28 (m, 0.65H), 2.64-2.48 (m, 2H), 2.18-1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 202.7, 201.7, 146.5, 145.5, 145.2, 143.4, 129.5, 129.3, 127.8, 127.6, 123.4, 123.2, 122.9, 122.8, 83.4, 80.0, 57.5, 56.6, 50.7, 48.6, 42.3, 42.2, 24.5, 22.0. Mass $(M + H)^+$ 191.

tert-Butyl 3-(1-hydroxy-3-(8-methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propyl)-2-oxopyrrolidine-1-carboxylate (23):

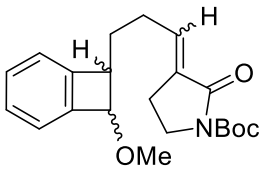


To a cooled (–78 °C) solution of LiHMDS (4.21 mL, 4.2 mmol, 1.0 M in THF) was added the solution of **21** (600 mg, 3.0 mmol) in THF (12 mL) dropwise. After 1 h, a cooled (–78 °C) solution of **22** (616 mg, 3.0 mmol) and $BF_3{\cdot}OEt_2$ (400 µl, 3.0 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 40 min at –78 °C. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was warmed to room temperature. Water (5mL) was added and the aqueous layer was extracted with Et_2O thrice. The combined organic layers were washed with 1M HCl (5 mL), brine (5 mL), saturated aqueous $NaHSO_3$ (5 mL), dried on $Na_2S_2O_4$ and concentrated *in vacuo* to afford oil. The crude oil was purified was purified on silica gel (30:70 EtOAc:Pet.

Ether) to afford the product as a thick clear oil (750 mg, 62%). The product was isolated as a mixture of diastereomers that were used in the subsequent transformation without separation.

Reaction Time: 1.4 h, R*f*: 0.4 (3:7 EtOAc:Pet. Ether); oil; 750 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.25-7.15 (m, 3H), 7.02-7.12 (m, 1H), 4.94-4.80 (m, 0.6H), 4.50-4.40 (m, 0.4H), 4.40-4.28 (m, 0.6H), 4.15-4.19 (m, 0.35H), 3.82-3.58 (m, 3.6H), 3.48-3.50 (m, 0.6H), 3.47 (s, 1.7H), 3.42 (s, 1.3H) 3.34-3.28 (m, 0.5H), 2.62-2.47 (m, 1H), 2.43 (t, *J* = 7.9 Hz, 1H), 2.10-2.00 (m, 1H), 1.95-1.85 (m, 2H), 1.80-1.70 (m, 1H), 1.46 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.4, 129.3, 129.1, 127.5, 127.42, 127.35, 127.3, 123.2, 123.1, 122.9, 122.84, 122.81, 83.6, 83.5, 83.3, 82.7, 80.1, 72.5, 71.8, 60.4, 57.5, 56.6, 51.4, 49.5, 49.4, 48.1, 46.4, 44.7, 44.6, 32.9, 32.6, 32.3, 27.99, 27.96, 21.4, 21.2, 21.0, 17.4, 14.2; boc deprotected Mass $(M + H)^+$ 276.

tert-Butyl (E)-3-(3-(8-methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propylidene)-2-oxopyrrolidine-1-carboxylate (24):

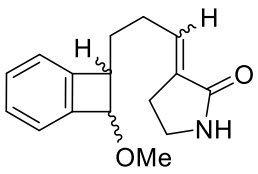


To a cooled (0 °C) solution of alcohol **23** (730 mg, 1.9 mmol) in DCM (15 mL) was added imidazole (390 mg, 5.8 mmol), Ph_3P (620 mg, 2.3 mmol), and iodine (588 mg, 2.3 mmol). The red/orange reaction mixture was slowly warmed to room temperature and stirred for 8 h, during which time a yellow precipitate (Ph_3P=O) formed. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The resultant colourless solution was diluted with H_2O (5 mL) and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4 and concentrated *in vacuo* to provide crude orange oil. The crude oil was purified was purified on silica gel (15:85 EtOAc:Pet. Ether) to afford the product as a thick oil **24** (370 mg, 53%).

Reaction Time: 8 h, R*f*: 0.4 (1.5:8.5 EtOAc:Pet. Ether); oil; 370 mg, 53%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.25-7.15 (m, 3H), 6.75-6.62 (m, 0.9H), 6.0-6.08 (m, 1H), 4.87 (d, J = 4.3 Hz, 0.6H), 4.52-4.48 (m, 0.4H), 3.70-3.60 (m, 3H), 3.47 (s, 1.8H), 3.42 (s, 1.4H), 3.35-3.28 (m, 0.5H), 2.65-2.55 (m, 2H), 2.35-2.25 (m, 2H), 1.92-1.80 (m, 1H), 1.80-1.68 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.9, 166.8, 150.93, 150.88, 147.0, 145.6, 145.5, 143.5, 137.8, 137.0, 131.6, 131.2, 127.6, 127.5, 123.3, 122.8, 83.4, 82.8, 82.7,

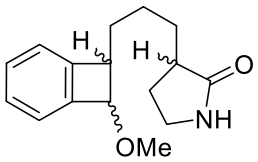
80.1, 60.4, 57.5, 56.5, 51.1, 48.9, 43.1, 30.9, 28.0, 27.7, 21.0, 20.7, 14.2; Mass $(M + Na)^+$ 380.

(E)-3-(3-(8-Methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propylidene)pyrrolidin-2-one (25):



To a cooled (0 °C) solution of alcohol **24** (370 mg, 1.0 mmol) in DCM (10 mL) was added TFA (478 µl, 6.0 mmol) dropwise and stirred at room temperature for 4h. After consumption of starting material, reaction mixture was concentrated *in vacuo* and quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc thrice. The combined organic extracts were washed with brine and dried over Na_2SO_4 and concentrated *in vacuo* to provide thick oil **25** (220 mg, 82%). The product was isolated as a crude product that was used in the subsequent transformation without purification and characterization.

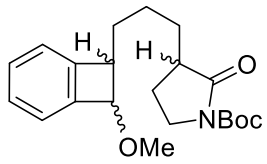
3-(3-(8-Methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propyl)pyrrolidin-2-one (26):



To the solution of **25** (230 mg, 0.9 mmol) in MeOH (5 mL), were added 10% Pd/C (23 mg) and triethylamine (2.5 µl, 0.017 mmol) and then stirred at room temperature under hydrogen atmosphere for 48h. The mixture was filtered through celite, and the filtrate was evaporated to give the crude product **26** (200 mg, 90%) as a grey liquid.

Reaction Time: 48 h, R*f*: 0.2 (4:1 EtOAc:Pet. Ether); oil; 200 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.27-7.15 (m, 3H), 7.12-7.05 (m, 1H), 6.05 (bs, 1H), 4.84 (d, *J* = 4.8 Hz, 0.6 H), 4.47 (d, *J* = 4.5 Hz, 0.4H), 3.46 (s, 1.8H), 3.42 (s, 1.3H), 3.35-3.18 (m, 3H), 2.40-2.15 (m, 3H), 1.90-1.80 (m, 2H), 1.60-1.50 (m, 2H), 1.36-1.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 180.7, 180.5, 147.70, 147.66, 146.3, 145.5, 143.5, 129.3, 129.1, 127.4, 127.3, 123.2, 123.1, 123.0, 122.88, 83.8, 80.2, 57.6, 57.5, 51.6, 49.54, 49.46, 40.85, 40.76, 40.71, 40.4, 32.4, 31.0, 30.9, 30.7, 29.2, 28.9, 27.63, 27.55, 27.50, 27.44, 25.96, 25.86, 25.80, 25.3; Mass $(M + H)^+$ 260.

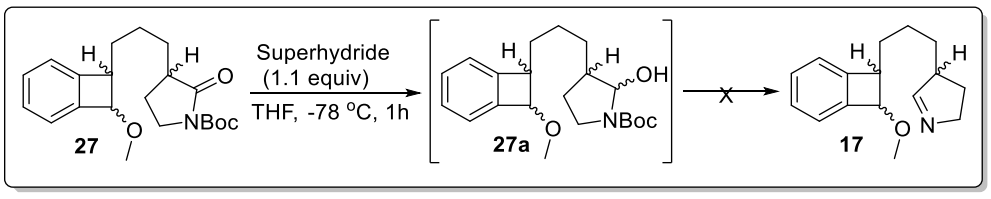
tert-Butyl 3-(3-(8-methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propyl)-2-oxopyrrolidine-1-carboxylate (27):



To a stirred solution of crude product **26** (20 mg, 0.07 mmol) in CH_3CN (1 ml) at room temperature were added di-tert-butyl dicarbonate (21 µl, 0.09 mmol) and DMAP (1 mg, 0.007 mmol) and the reaction mixture was stirred for 2 h. After removal of volatiles *in vacuo*, the residue was diluted with EtOAc and the solution was washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (30:70 EtOAc:Pet. Ether) to give product **27** (13 mg, 47%) as a yellow oil.

Reaction Time: 2 h, R*f*: 0.4 (1:4 EtOAc:Pet. Ether); oil; 13 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.30-7.15 (m, 3H), 7.12-7.05 (m, 1H), 4.85 (d, *J* = 4.6 Hz, 0.5 H), 4.48 (apparent d, 0.4H), 3.80-3.55 (m, 2.4H), 3.47 (s, 1.6H), 3.43 (s, 1.4H), 3.35-3.25 (m, 0.7H), 2.55-2.37 (m, 1H), 2.08-2.05 (m, 1H), 1.95-1.80 (m, 1H), 1.75-1.54 (m, 5H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 176.1, 175.9, 150.5, 129.3, 129.1, 127.5, 127.3, 123.3, 123.25, 123.0, 122.9, 83.7, 82.8, 82.7, 80.2, 57.6, 56.6, 51.6, 49.5, 44.5, 43.7, 43.5, 32.3, 30.7, 30.6, 30.5, 30.4, 30.3, 29.1, 28.9, 25.8, 25.7, 25.6, 25.3, 25.2, 24.43, 24.37, 24.31, 24.2; boc deprotected Mass $(M + H)^+$ 260.

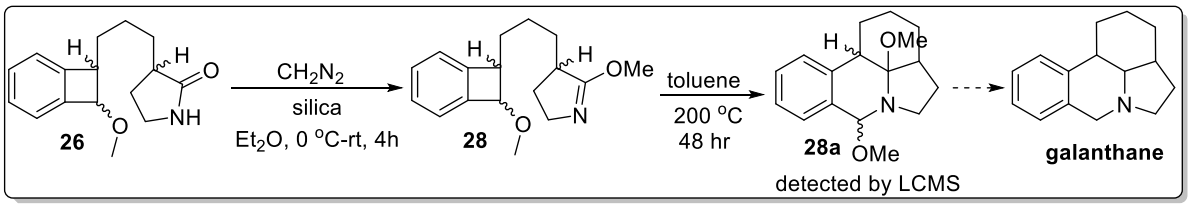
Unsuccessful attempt for synthesis of 17:



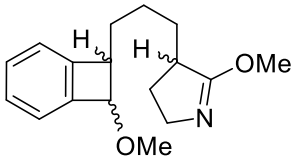
The compound **27** (30 mg, 0.08 mmol) was dissolved in THF (2 mL) and cooled to −78 °C. Super-Hydride (0.12 mL, 0.12 mmol, 1M solution in THF) was added dropwise over 5 minutes and stirring continued at −78 °C for a further 30 minutes. The excess reducing agent was quenched by the addition of saturated NH_4Cl (0.5 ml) and aqueous solution of Na_2CO_3 (0.5 ml). The mixture was extracted with dichloromethane, dried over Na_2SO_4 and

concentrated *in vacuo*. A 1:1 mixture of DCM:TFA (2 mL), that had been precooled to 0 °C, was then added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 minutes. The majority of the volatile organics were then quickly removed *in vacuo*. But unfortunately the expected product **17** formation was not observed.

Note: Several different acidic conditions were tried for synthesis of **17**, but the synthesis met with failure.



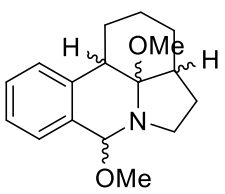
5-Methoxy-4-(3-(8-methoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)propyl)-3,4-dihydro-2H-pyrrole (28):



To the solution of **26** (20 mg, 0.07 mmol) in Et_2O (1 mL), was added silica twice the weight of compound **26**. The diazomethane in ether was added in excess amount at 0 °C to the above reaction mixture and allowed to stir at room temperature for 4h. The reaction mixture was filtered and concentrated *in vacuo*, the residue was purified by silica gel column chromatography (40:60 EtOAc:Pet. Ether) to furnish product **28** (3.5 mg, 17%) as oil.

Reaction Time: 4 h, R*f*: 0.4 (2:3 EtOAc:Pet. Ether); oil; 3.5 mg, 17%; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.26-7.15 (m, 3H), 7.12-7.05 (m, 1H), 4.83 (apparent dd, 0.35H), 4.46 (apparent d, 0.65H), 3.73 (s, 3H), 3.64-3.48 (m, 2H), 3.47 (s, 1H), 3.43 (s, 2H), 3.36-3.25 (m, 1H), 2.75-2.52 (m, 1H), 2.30-2.10 (m, 1H), 1.82-1.55 (m, 6H); Mass $(M + H)^+$ 274.

3a1,7-Dimethoxy-2,3,3a,3a1,4,5,7,11b-octahydro-1H-pyrrolo[3,2,1-de]phenanthridine (28a):



The compound **28** (3.5 mg, 0.012 mmol) was heated in toluene at 200 °C in sealed tube for 2 days. After consumption of starting material excess solvent was evaporated *in vacuo*, the residue was purified by silica gel

column chromatography (80:20 EtOAc:Pet. Ether) to furnish product the **28a** (1.2 mg, 34%) as oil.

Reaction Time: 48 h, R*f*: 0.2 (1:4 EtOAc:Pet. Ether); oil; 1.2 mg, 17%; Mass $(M + H)^+$ 274.1

Note: The preparation of compound **28** in gram quantity and optimization of [4+2] pericyclic reaction is in process.

3.2.9 References:

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(12)) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett*. **2009**, 11, 3666.

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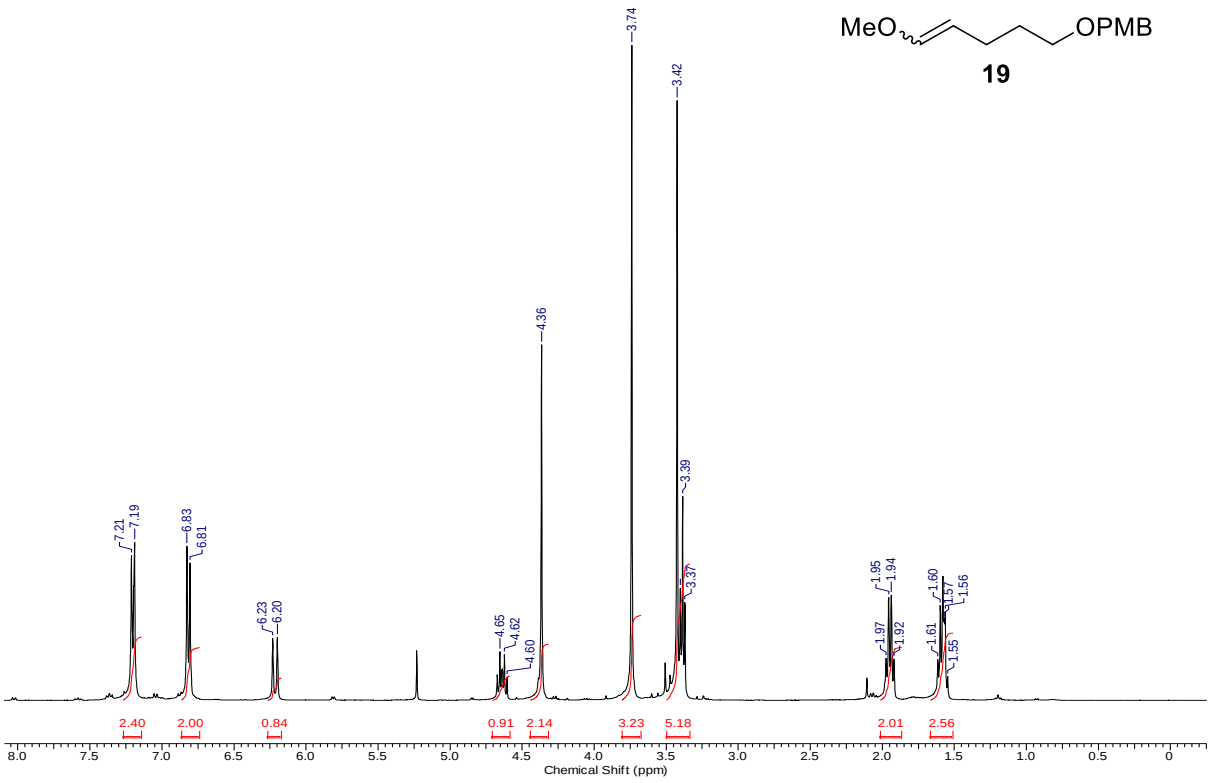
3.2.10 Spectra

^{1}H NMR Spectra



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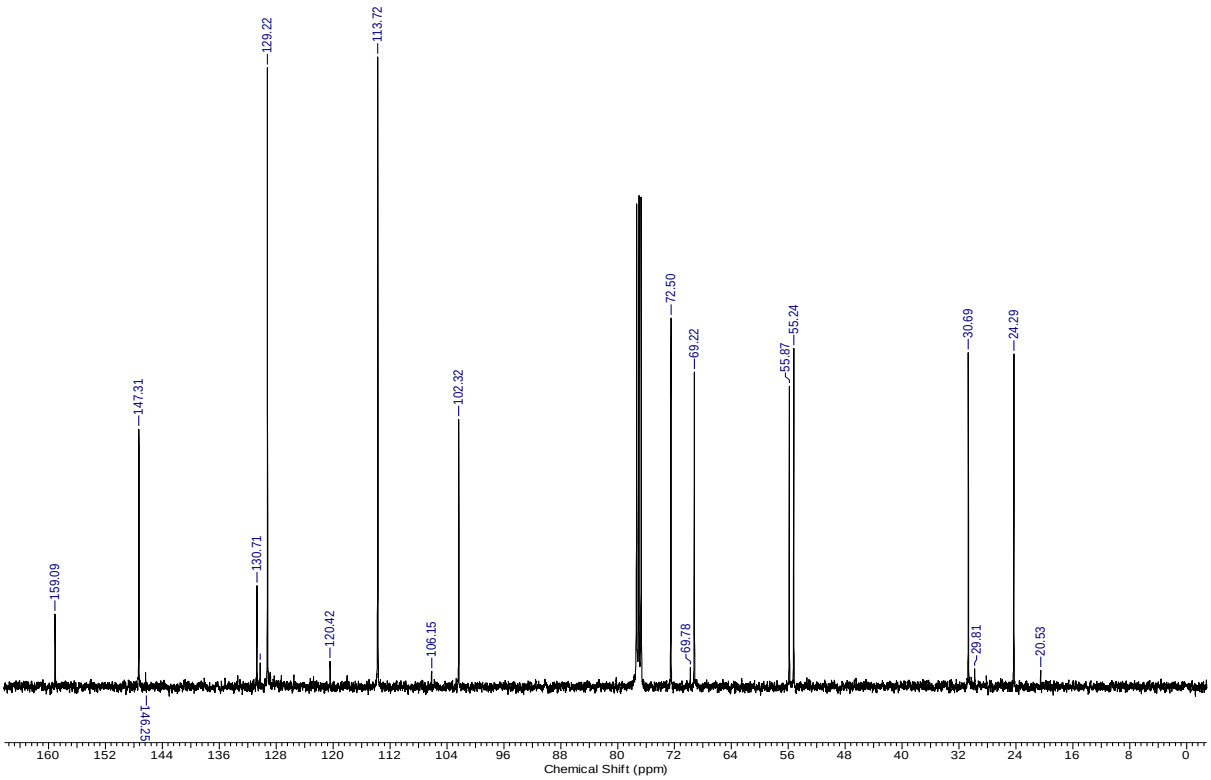

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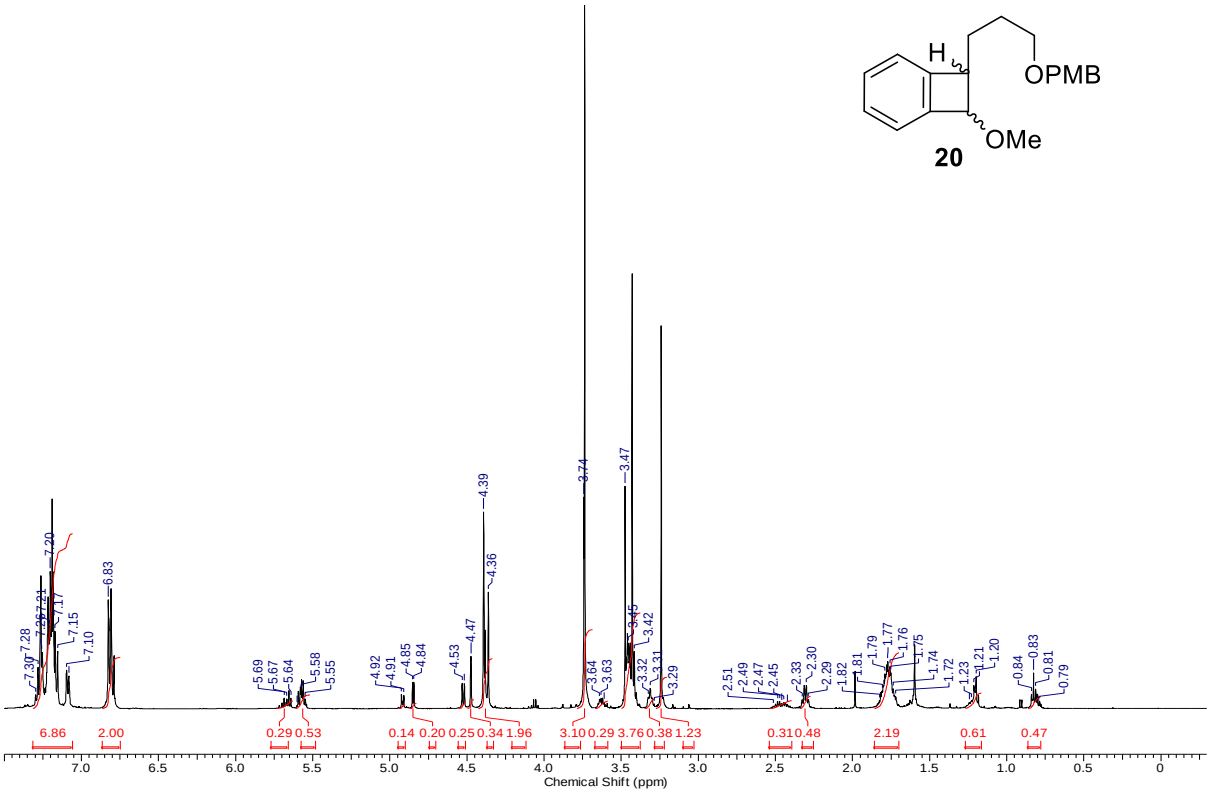

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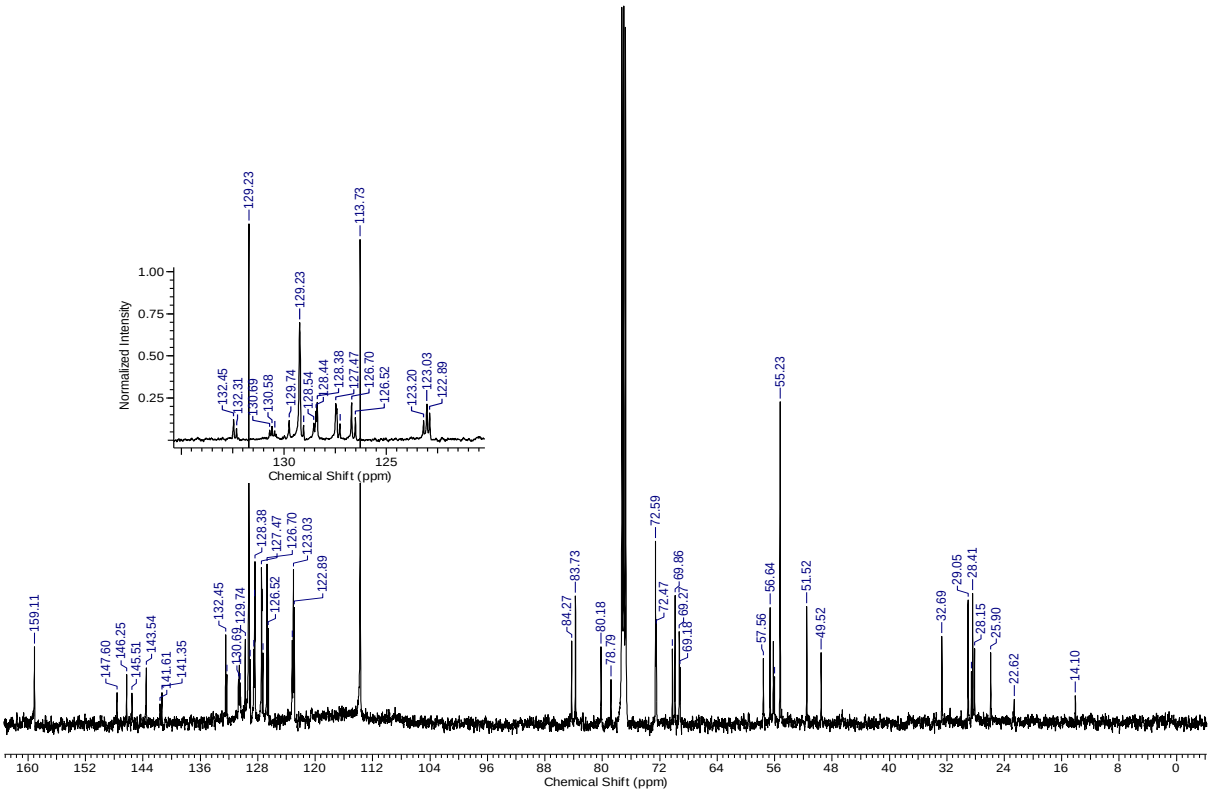

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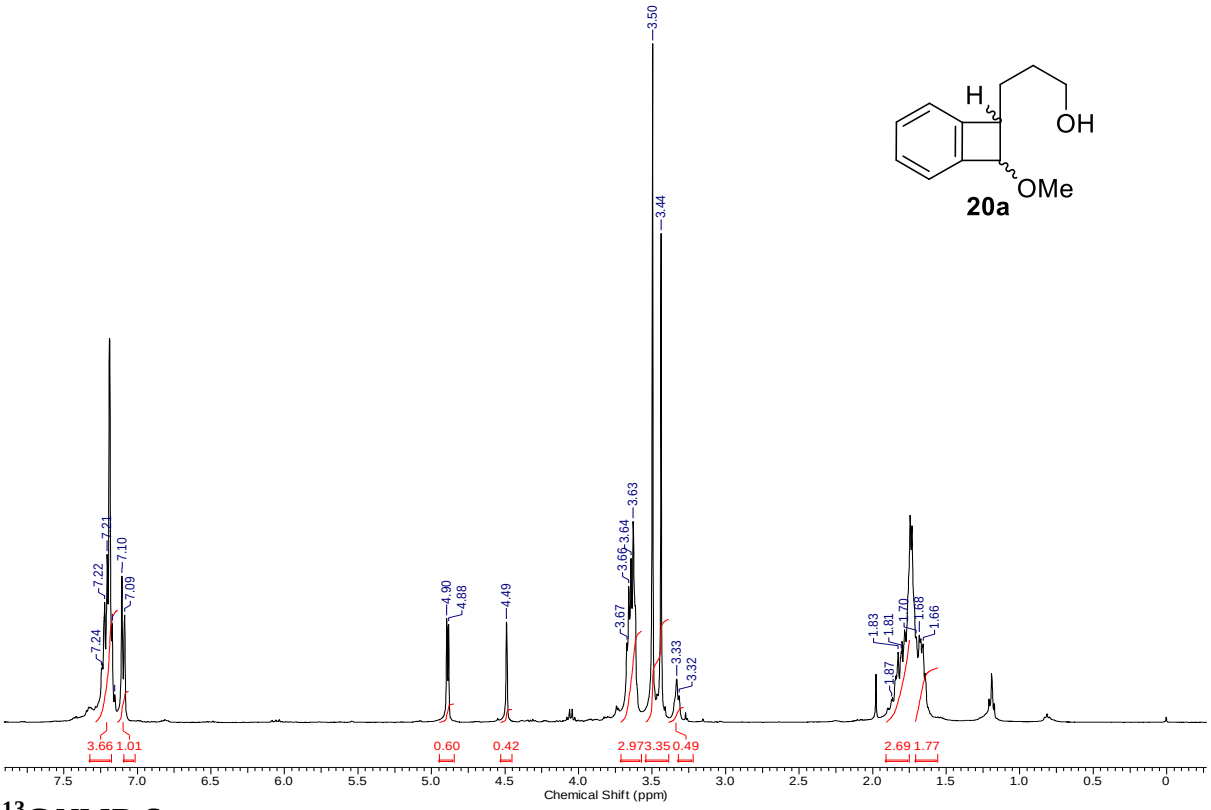

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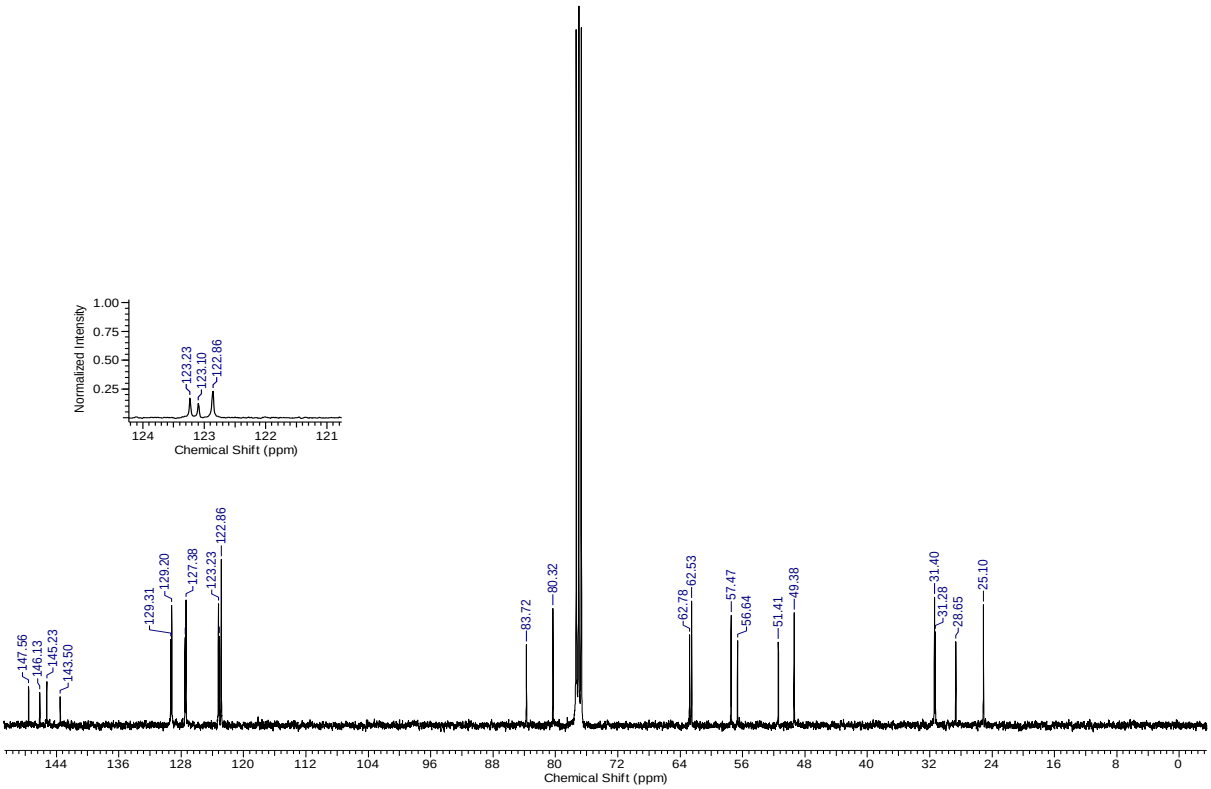

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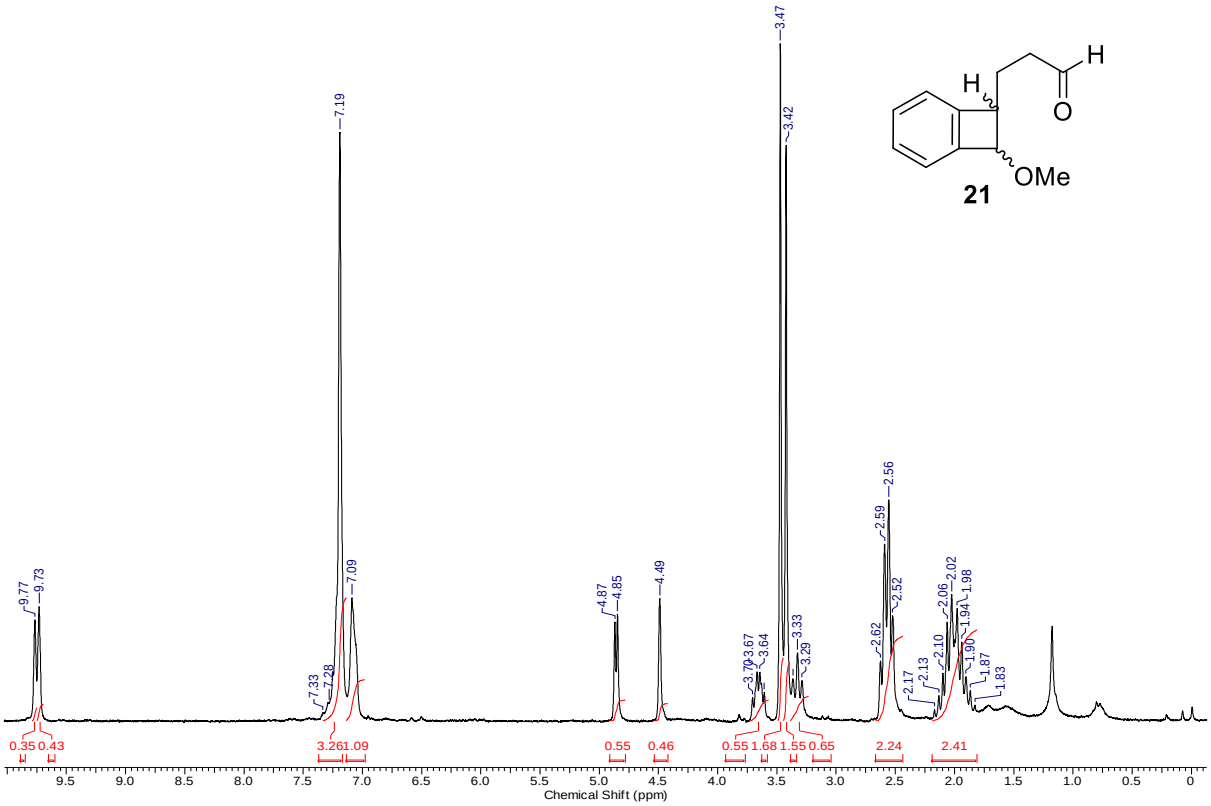

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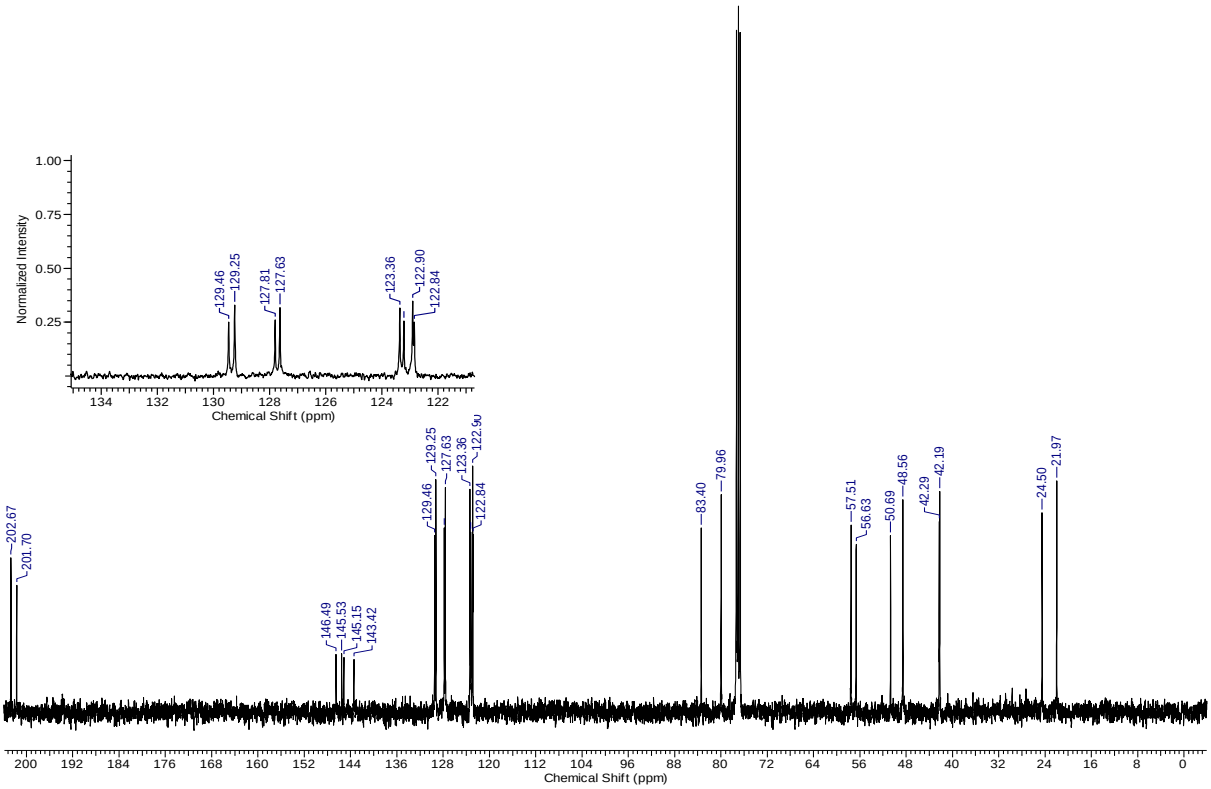

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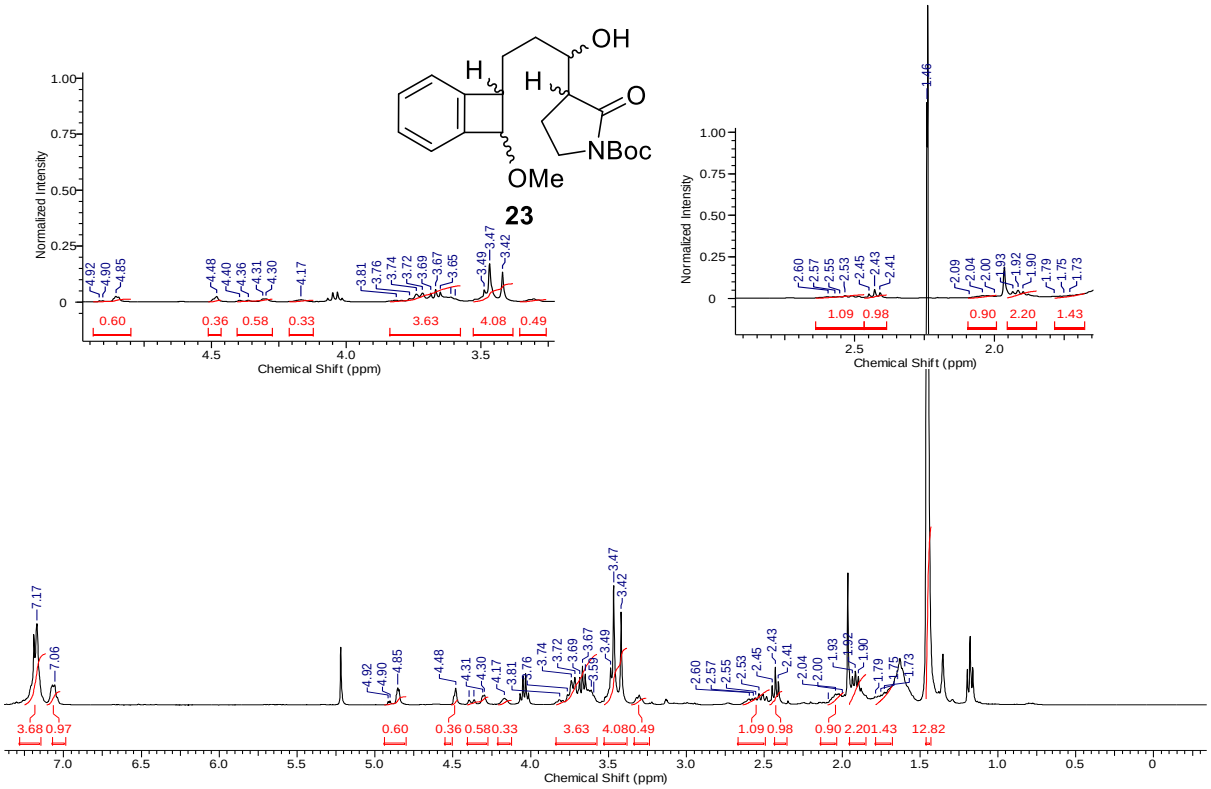

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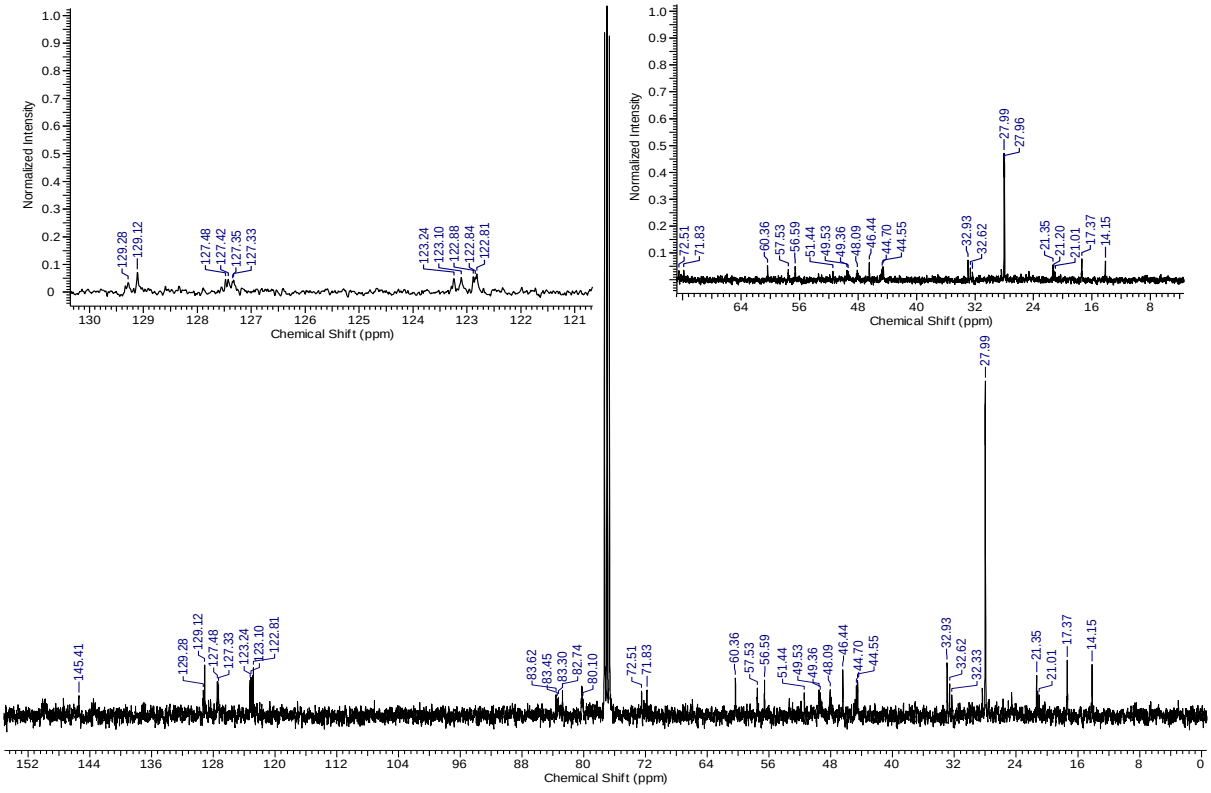

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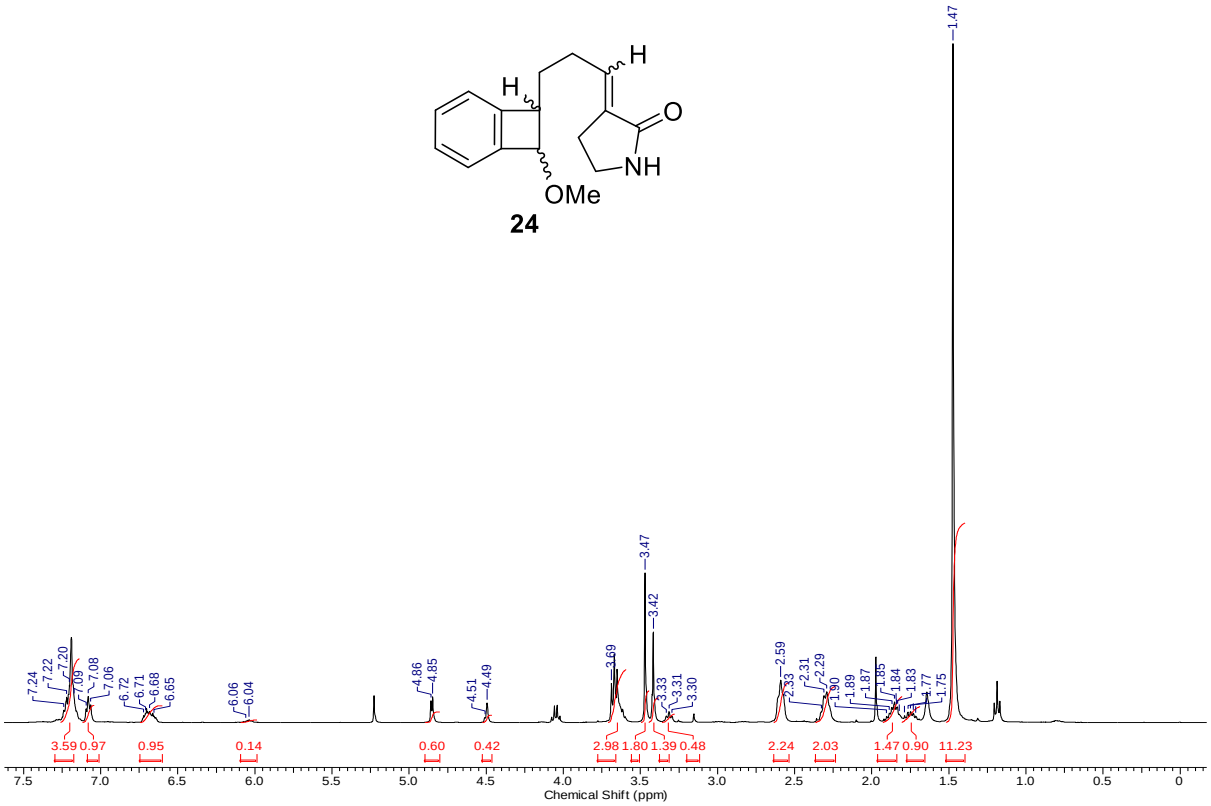

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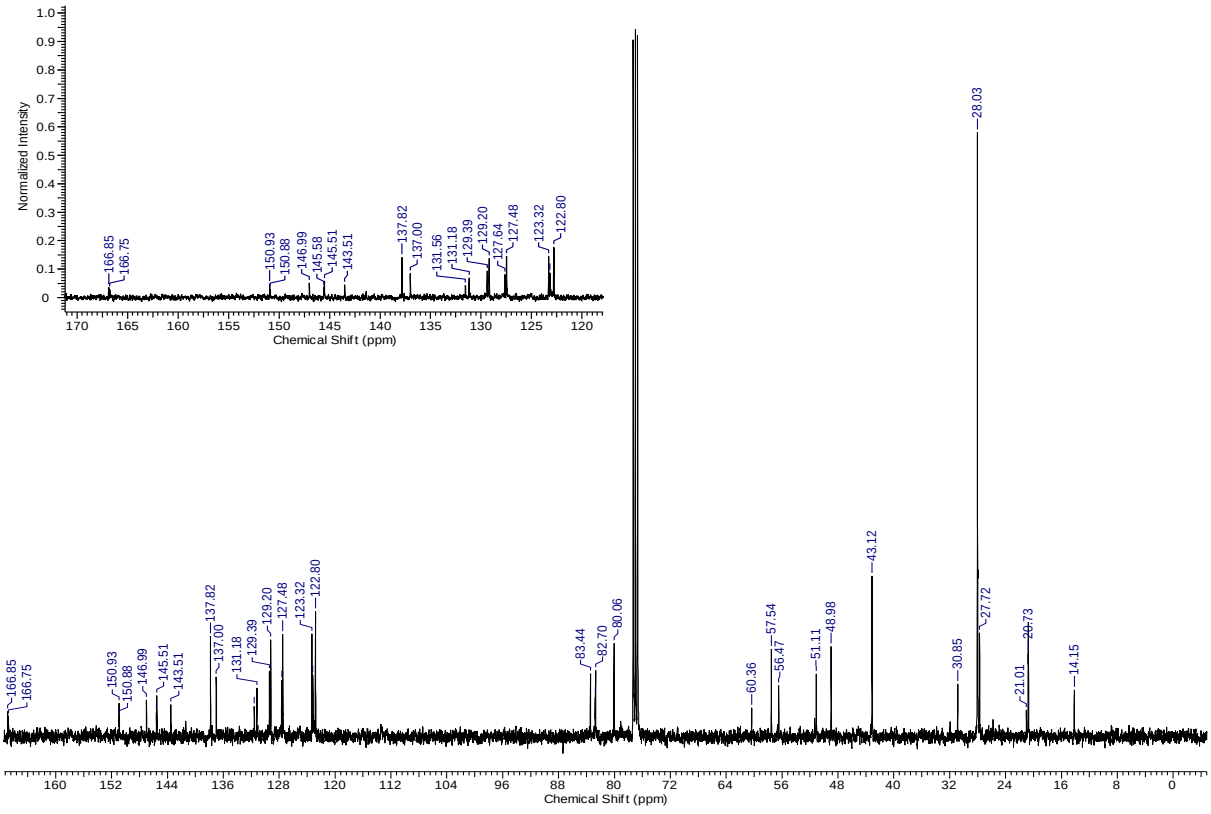

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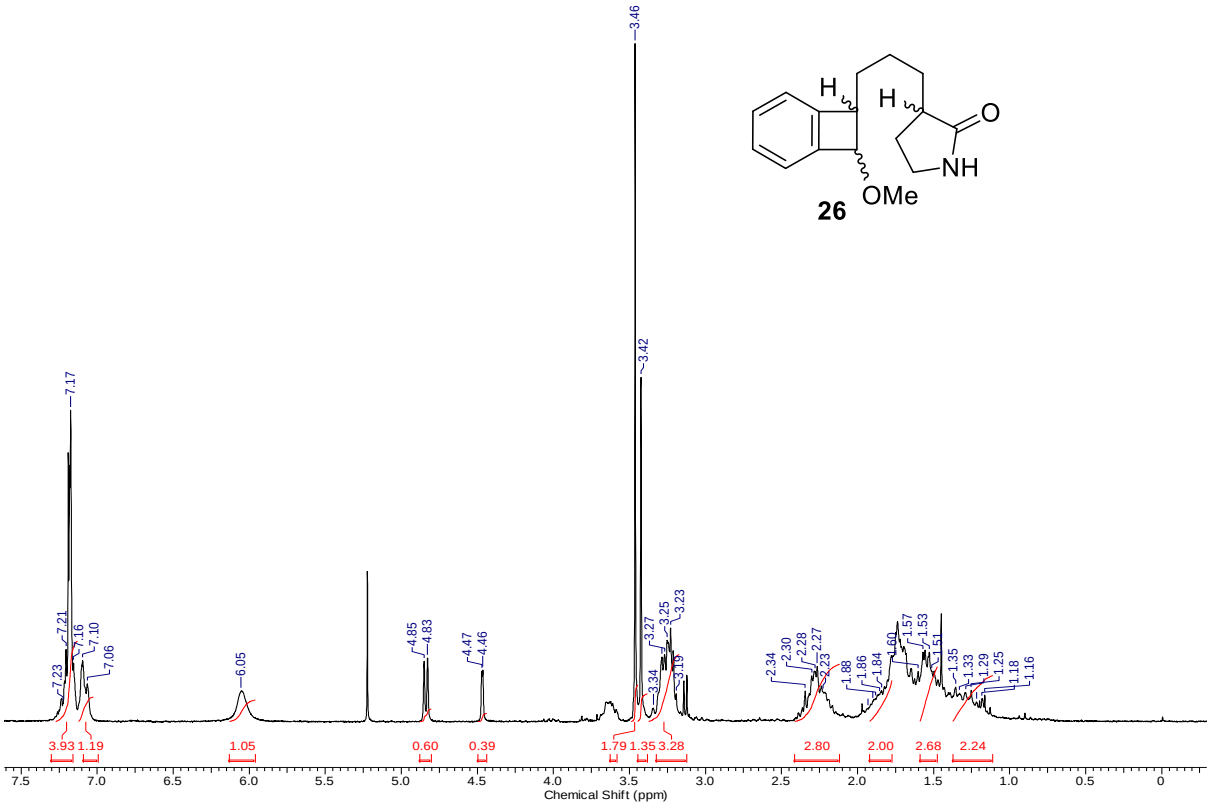

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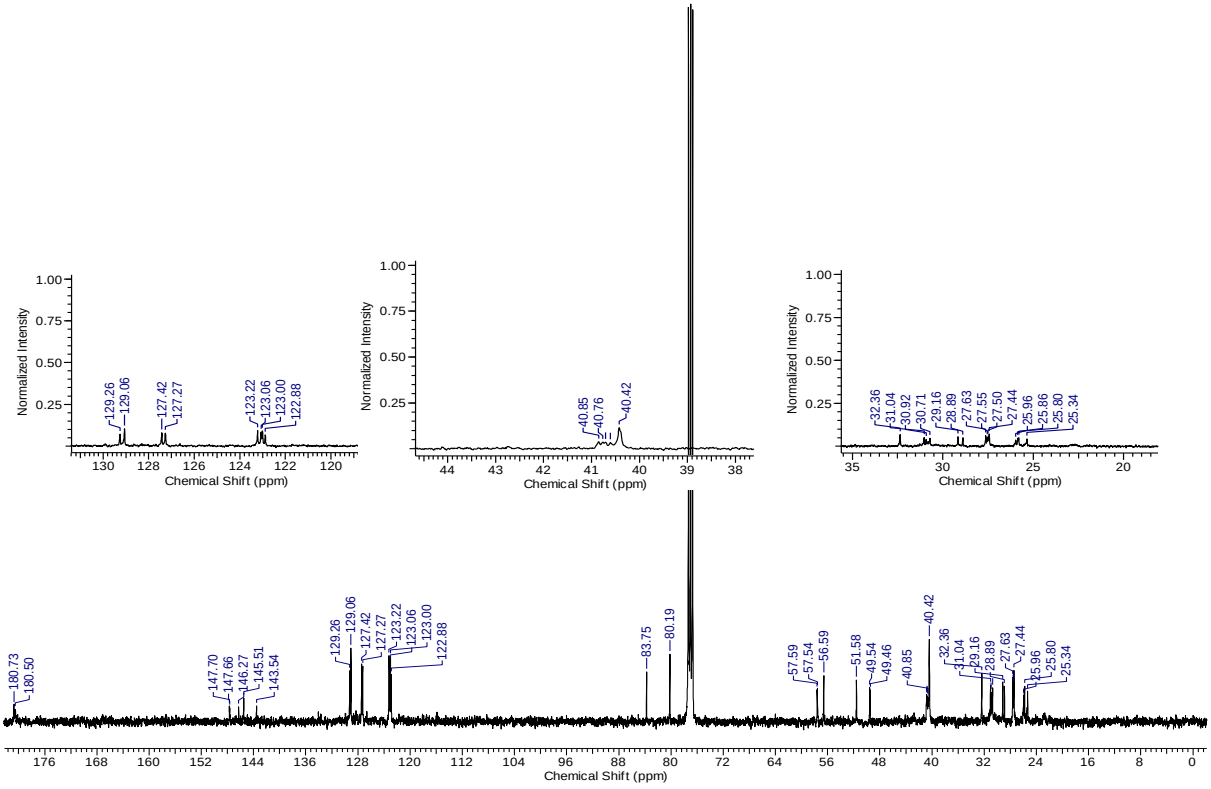

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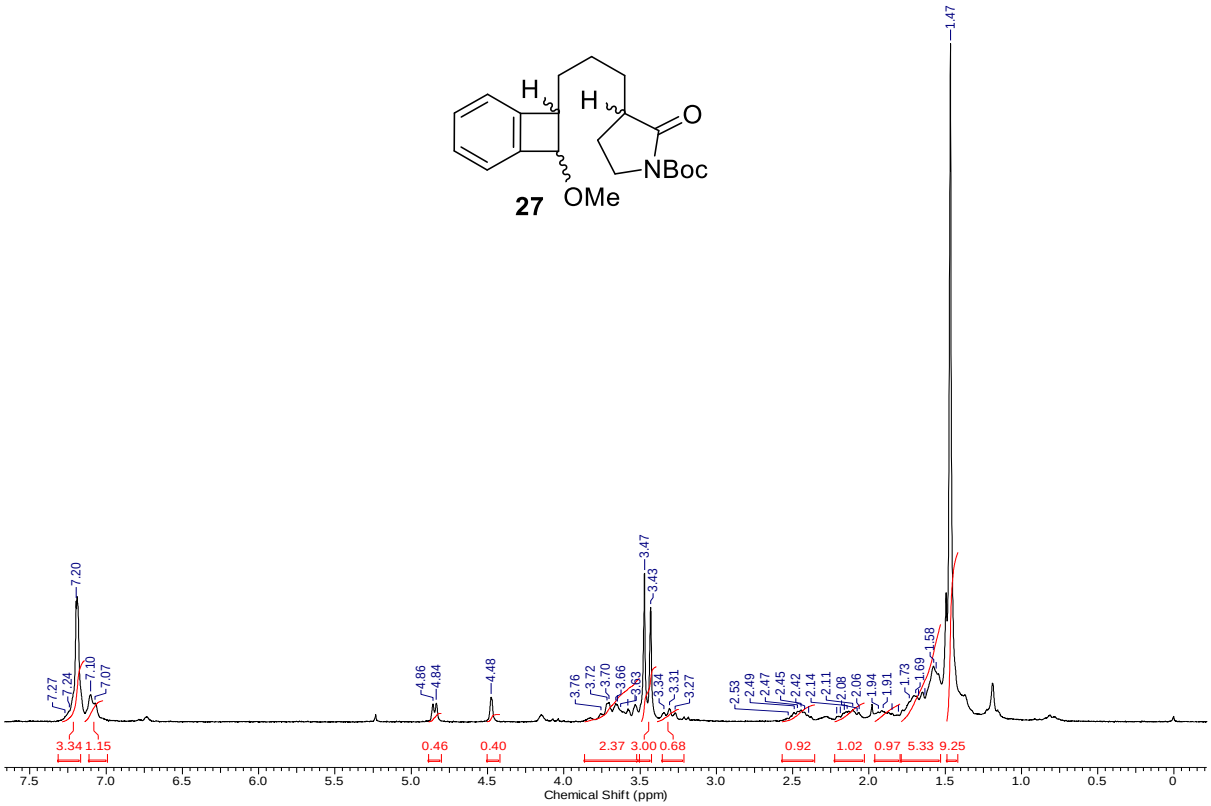
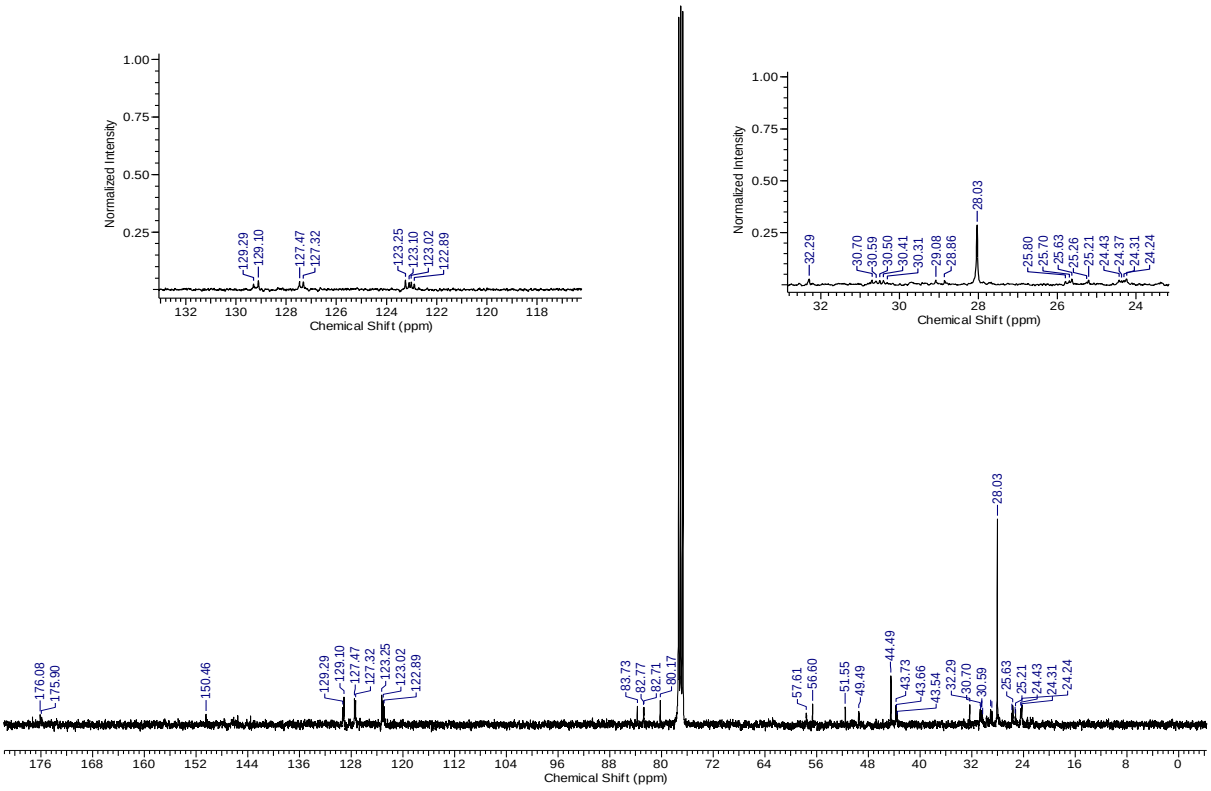


^{13}C NMR Spectra



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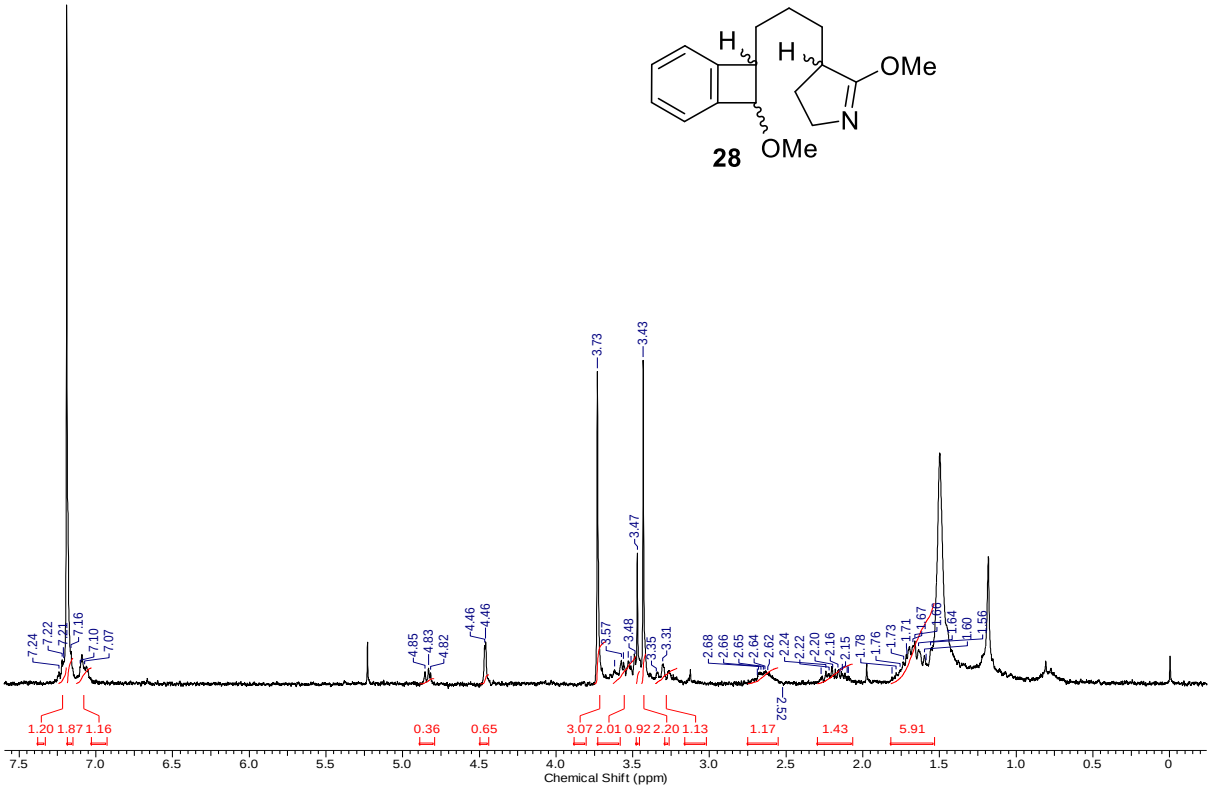
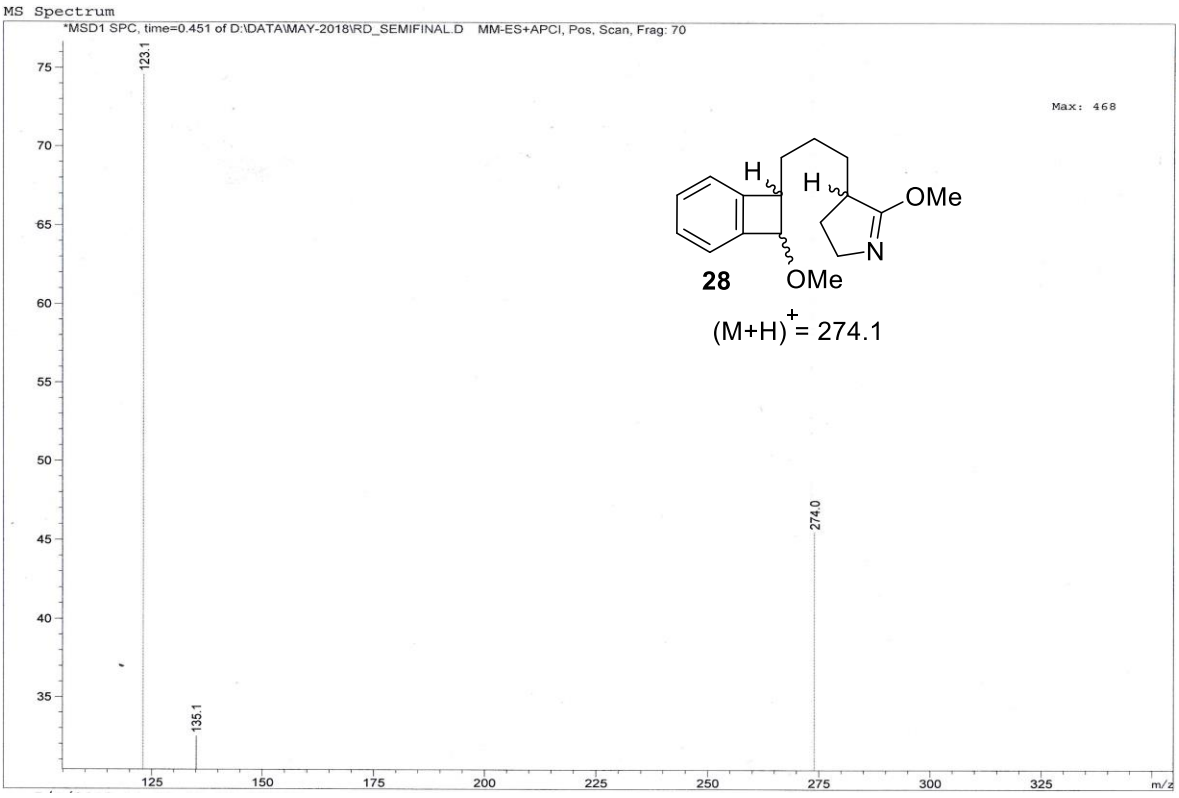


LC-MS Spectra



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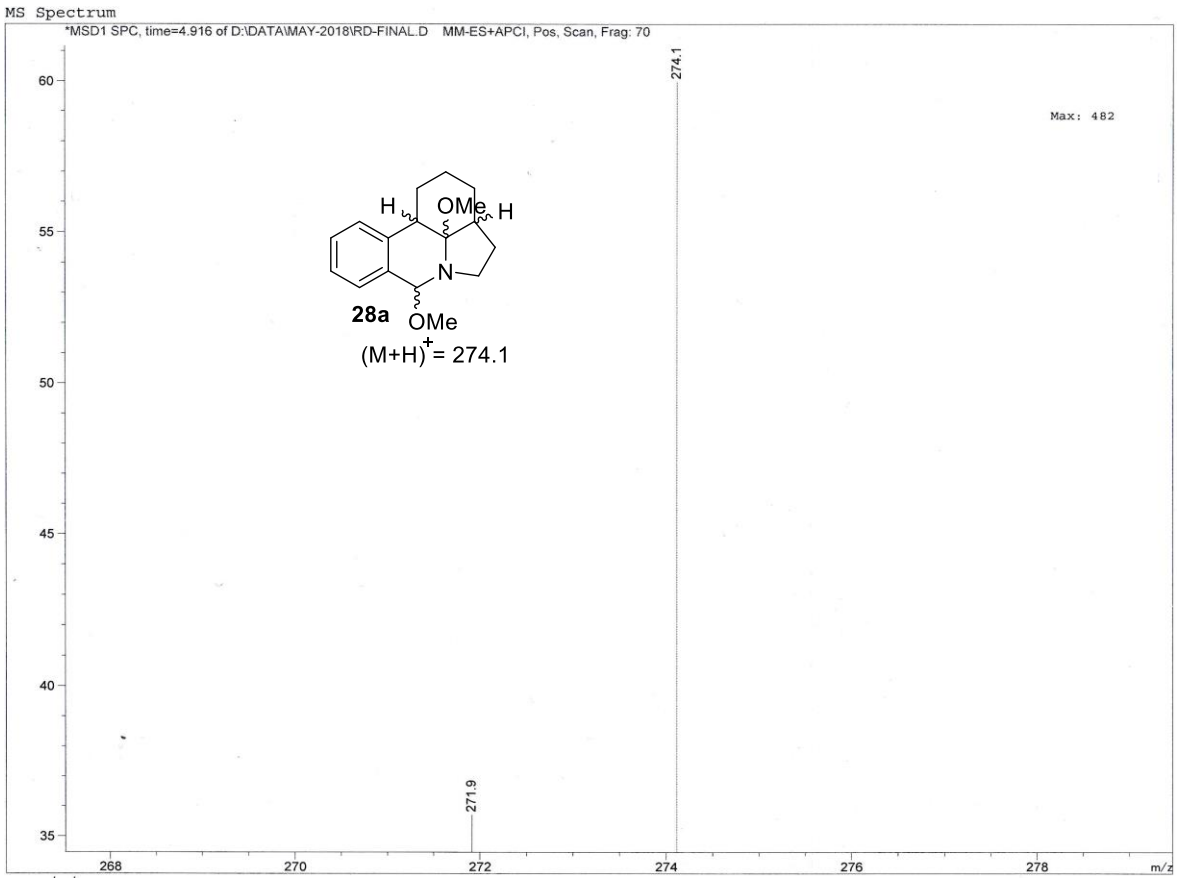

Publications and Patents

1. Transition-Metal-Catalyzed Reactions Involving Aryne (Review).

   Dhokale, R. A.; Mhaske, S. B. *Synthesis* **2018**, *50*, 1.

2. Diversity-oriented Synthesis of Spiroannulated Benofuran-3-one Scaffold of Leptosphaerin C and Congeners via Aryne insertion.

   Dhokale, R. A.; Mhaske, S. B. *J. Org. Chem*. **2017**, *82*, 4875.

3. Nucleophilic Nitration of Arynes by Sodium Nitrite and its Multicomponent Reaction Leading to Double-Functionalized Arenes.

   Dhokale, R. A.; Mhaske, S. B. *Org. Lett*. **2016**, *18*, 3010. (*Most read article in July 2016*)

4. P-Arylation: Arynes to Aryl Phosphonates, -Phosphinates, Phosphine oxides.

   Dhokale, R. A.; Mhaske, S. B. *Org. Lett*. **2013**, *15*, 2218. (*Highlighted in Organic Portal,* Cited in Li, J. J. *Name Reactions: A Collection of Detailed Reaction Mechanisms*; Springer-Verlag Berlin Heidelberg: Switzerland, 2014; pp 399-400)

5. Transition-Metal-Free C-Arylation at Room Temperature by Arynes.

   Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *Org. Lett*. **2012**, *14*, 3994.

6. α–Arylation of *β*-Dicarbonyl Compounds

   Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *US9056817*.

7. Aryl Phosphonates and process for preparation of thereof.

   Dhokale, R. A.; Mhaske, S. B. *US9200018*.

List of Conferences attended

1. Presented Poster at National Science Day celebration, National Chemical Laboratory, 25th-26th February 2016.

2. Attended 17 th CRSI National Symposium in Chemistry at National Chemical Laboratory, Pune, 6th-8th February 2015.

3. Presented Poster at National Science Day celebration, National Chemical Laboratory, 25th-26th February 2014.

4. Presented Poster at 2nd UK-India Medchem Congresss, IICT Hyderabad 22nd-23rd March, 2013.

5. Presented Poster at National Science Day celebration, National Chemical Laboratory, 26th-27th February 2013.

6. Attended the full agenda of ACS on campus events at National chemical laboratory, 10th October 2012.

7. Attended CRSI (Chemical Research Society of India) 1st Zonal Symposium at national Chemical Laboratory, Pune, 13th-14th May 2011.

Awards and Recognition

1. Awarded NCL RF-KEERTHI SANGORAM MEMORIAL ENDOWMENT AWARD, Best Research Scholar Award of the Year 2017 in Chemical Sciences.

2. Selected for presenting oral talk at National Conference on Chemistry of Chalcogens at DIAT, Pune, 12th-13th January 2015.

3. Selected for presenting oral talk at 10th NOST Conference for Research Scholars (J-NOST 2014) at IIT MADRAS, 4th-6th December 2014.

4. Selected to give Flash Presentation at 2nd UK-India MedChem Congress at IICT, Hyderabad March 2013.

Erratum

Erratum