Transition-Metal-Free Access to Biologically Important Scaffolds via Novel C–C and C–X Bond Formations Using Aryne Chemistry

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCE

By

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Under the Guidance of

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JULY 2019

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 "**Transition-Metal-Free Access to Biologically Important Scaffolds via Novel C–C and C–X Bond Formations Using Aryne Chemistry**" submitted by **Mr. Virat Pandya** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirement 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.

It is also certified that this work done by the student under my supervision, is plagiarism free.

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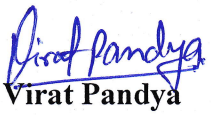
DECLARATION BY THE CANDIDATE

I hereby declare that the original research work embodied in this thesis entitled, ***"Transition-Metal-Free Access to Biologically Important Scaffolds via Novel C–C and C–X Bond Formations Using Aryne Chemistry"*** submitted to the 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.



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This journey would not have been possible without the support, encouragement and help of many people. Now, time has come to acknowledge all of them.

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Thank you.

Virat Pandya

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Abbreviations

Units

^{o}C	Degree Centigrade
mg	Milligram
h	Hour
µg	Microgram
mL	Milliliter
min	Minute
MHz	Megahertz
mmol	Milimole
mol	Mole
ppm	Parts Per Million
rt	Room Temperature
ee	Enantiomeric Excess
dr	Diastereomeric Excess
equiv	Equivalent
NR	No Reaction

Chemical Notations

KHMDS	Potassium bis(trimethylsilyl)amide
MeCN	Acetonitrile
CCl_4	Carbon Tetrachloride
$CHCl_3$	Chloroform
DMSO	Dimethyl Sulfoxide

THF	Tetrahydrofuran
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
LDA	Lithium Diisopropylamide
EtOH	Ethanol
EtOAc	Ethyl Acetate
DCE	Dichloroethane
DMF	Dimethylformamide
DCM	Dichloromethane
DME	Dimethoxyethane
18-C-6	18-crown-6
TBAF	Tetra-*n*-Butylammonium Fluoride
DIBAL-H	Diisobutylaluminium Hydride
LAH	Lithium Aluminium Hydride
TMS	Tetramethylsilane
p-TSA	*p*-Toluenesulfonic acid
MeOH	Methanol
Ph	Phenyl
Me	Methyl
Et	Ethyl
Et_2O	Diethyl ether

Other Notation

EDG	Electron Donating Group
EWG	Electron Withdrawing Group
LG	Leaving Group

MCR	Multicomponent Reactions
calcd	Calculated
J	Coupling Constant in NMR
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
δ	Chemical Shift

General Remarks

- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR analyses were performed on 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 on 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 according 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 13.

- 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. Virat Pandya
Degree Enrolment no. and Date	Ph. D. in Chemical Sciences (10CC13J26020)
Title of the Thesis	Transition-Metal-Free Access to Biologically Important Scaffolds via Novel C–C and C–X Bond Formations Using Aryne Chemistry
Research Supervisor	Dr. Santosh B. Mhaske (AcSIR, CSIR-NCL, Pune)

Abstract:

The present thesis demonstrates the importance of aryne in the construction of C–C, C–S and C–N bonds, which result into the synthesis of the biologically important scaffolds. Chapter 1 presents the introduction of aryne and its mode of reactivity especially leading to the difunctionalization of arenes. It comprises insertion, pericyclic, annulation and multicomponent reactions of aryne and their representative examples. Chapter 2 deals with difunctionalization of aryne to form sulfones and xanthones, which is further divided into two sections. Section 1 presents the transition-metal-free synthesis of sulfones using aryne chemistry. We were able to synthesize diaryl as well as alkyl aryl sulfones in excellent yields. Section 2 reveals the effort towards the total synthesis of diversonol natural product. Chapter 3 demonstrates the novel process for the synthesis of varyingly substituted oxindolylidene acetates in good yields. This method has been further extended to the one-pot synthesis of spiroxindolopyrrolidones. Chapter 4 describes the utilization of aryne in the general synthesis of octahydroquinoline scaffold in a stereoselective manner.

Chapter 1. 1,2-Difunctionalization of aromatics using aryne chemistry

Aryne chemistry has contributed unanimously to the development of efficient methodologies and also played an important role in the total synthesis of bioactive molecules and natural products. Reactive nature of aryne requires that its generation must take place *in situ*. Although many methods for aryne generation were developed, Kobayashi's protocol sustained as the most widely used method. Extreme reactivity of aryne as an electrophile make it highly desired intermediate for various significant transformations. This chapter mainly outlines the methods for the difunctionalization of aromatics using aryne chemistry (Figure 1).

The difunctionalization of aromatics applying aryne had been achieved by the cycloaddition, multicomponent reaction (MCR), and elemental-elemental bond insertion reactions (Figure 2).

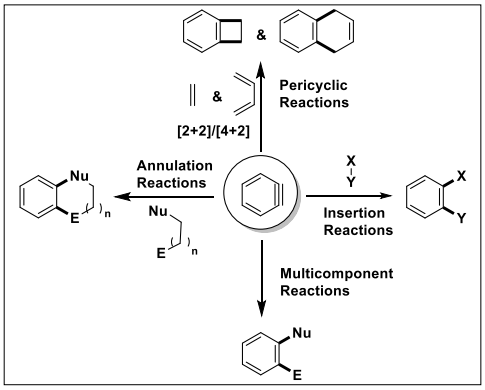


Figure 1. Modes of reactivity of aryne

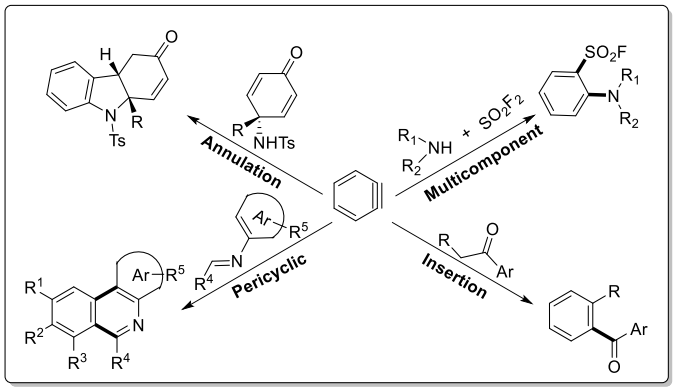


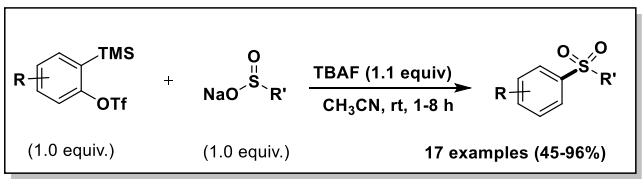
Figure 2. Examples of transition-metal-free reactions of aryne

The cycloaddition reactions of aryne are mainly accessed through either [2+2] or [4+2] pathways. Aryne has been also utilized in cycloaddition reactions with 1,3-dipolar compounds. Furthermore, aryne reactivity as the dienophile makes it highly fascinating substrate for the Diels–Alder reaction to construct diverse molecules. Another important class of aryne reactions for the difunctionalization of aromatics is the insertion reaction, where aryne is inserted between C–C bonds or C–heteroatom bonds. Furthermore, aryne has also been utilized in multicomponent reaction where a nucleophile attacks on aryne and the generated anion is further trapped by the electrophile. Above properties of aryne encouraged us to develop novel and efficient methods in aryne chemistry.

Chapter 2. Transition-metal-free double functionalization of arene via aryne to access sulfones and xanthones

The chapter 2 is divided into two sections. Section 1 reports a facile method for the synthesis of sulfones using aryne whereas section 2 explores our study towards the total synthesis of diversonol.

Section 1 highlights the significance of aryne in the development of a novel method for the synthesis of



Scheme 1: Sulfonylation of arynes

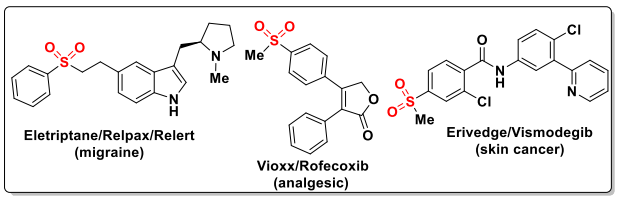


Figure 3: Bioactive compounds containing sulfone

sulfones. Sulfone is highly recognized class of compounds in organic chemistry for their immense material, biological, and synthetic applications. Sulfones are most prevailing pharmacophore in medicinal chemistry. They are ubiquitous in many marketed drugs which have profound medicinal activities (Figure 3). Hence numerous procedures for the synthesis of sulfones have been reported, which demands either transition-metal or harsh reaction conditions. In this perspective, we have demonstrated an efficient transition-metal-free process, wherein a broad range of alkyl/aryl/heteroaryl sodium sulfinates react with varyingly substituted aryne precursors (*o*-silyl aryl triflates) under mild reaction conditions to afford various sulfones in good to excellent yields (Scheme 1). This protocol is able to deliver a diverse array of sulfones such as diaryl sulfones, aryl-alkyl sulfones, and aryl-heteroaryl sulfones. It could also be extended to the double functionalization of arynes.

Section 2 reveals the study towards the total synthesis of diversonol. Diversonol is the secondary metabolite, which was isolated from *Penicillium diversum*. It exhibits potential antibacterial and antifungal activities. The synthesis of diversonol was planned using annulation reaction of aryne with the starting material **B** as the key-step (Figure 4). Compounds **B**, **C** and **D** can be derived from orcinol.

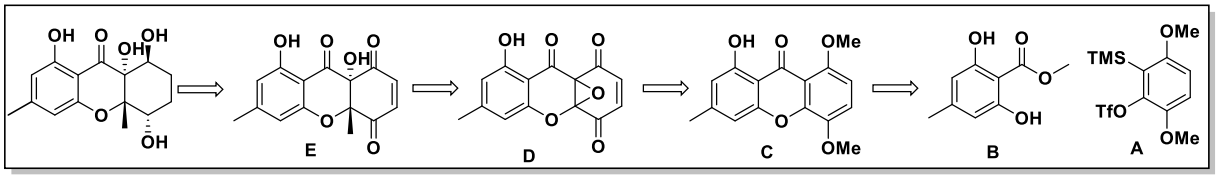
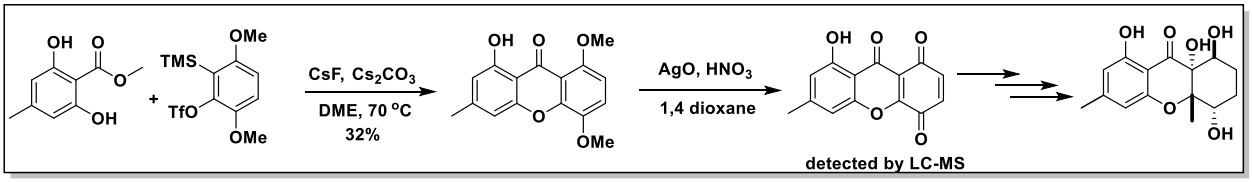


Figure 4. Retrosynthetic analysis of diversonol

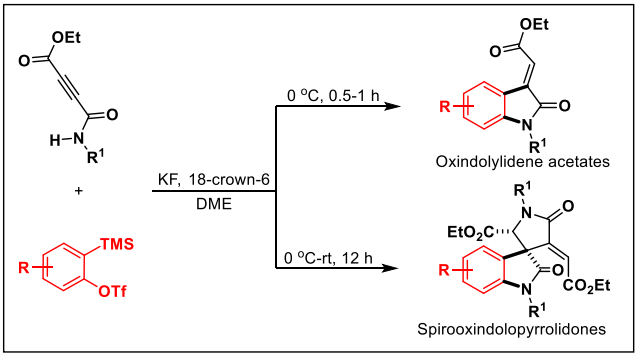
The result shows that expected product xanthone **C** was formed in low yield. Further study shows that the formation of unexpected product which on x-ray crystallography analysis identified as naphthalene derivative, is the main cause behind low yield of compound **C** (Scheme 2). Improvement in the yield of xanthones and synthesis of diversonol is underway in lab. The interesting finding that the compound **B** acts as a diene despite being aromatic ring would be worth exploring.



Scheme 2. Synthesis of diversonol

Chapter 3. General method for the synthesis of oxindolylidene acetates and spirooxindolopyrrolidones using aryne

Chapter 3 illustrates an elegant process for the synthesis of oxindolylidene acetates which was further extended to the synthesis of spirooxindolopyrrolidones. The oxindolylidene acetates and spirooxindolopyrrolidones are well-recognized scaffolds that have received much attention from



Scheme 3. Aryne in the synthesis of heterocycles

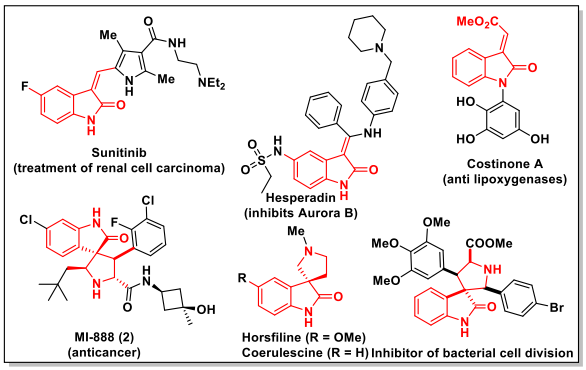


Figure 5. Bioactive compounds containing oxindole core

the scientific community due to their unique biological and pharmaceutical properties as well as challenging structural architecture. They are ubiquitous in many drug and natural products (Figure 5). Commonly, oxindolylidene acetates are prepared from isatin by Wittig homologation or by condensation with active methylene compounds, while spirooxindolopyrrolidone derivatives, are synthesized either from isatin or from 3-ylideneoxindoles. These methods encounter with serious drawbacks such as harsh reaction conditions, need of metal-catalyst and lack of diversity in the substrates. In this context, we have achieved a novel and efficient process for the divergent synthesis of oxindolylidene acetates and spirooxindolopyrrolidones by reacting aryne with carbamoylpropiolates under milder reaction conditions (Scheme 3). This process delivered varyingly substituted oxindolylidene acetates by reacting differently substituted aryne precursor with diversely substituted carbamoylpropiolates. Furthermore, this process provided the one-pot synthesis of diversely substituted novel spirooxindolopyrrolidones scaffolds.

Chapter 4. Diastereoselective synthesis of octahydroquinoline scaffold using aryne chemistry

Chapter 4 describes our studies towards the general stereoselective synthesis of octahydroquinoline scaffold using aryne. Octahydroquinoline core is known for prominent DA_2 dopaminergic effects.

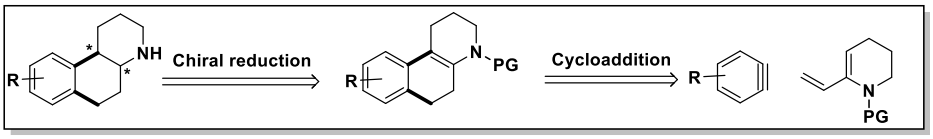
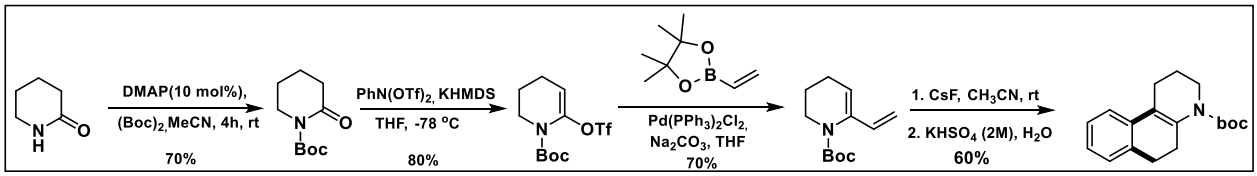


Figure 6. Retrosynthetic analysis of octahydroquinoline scaffold

We hypothesized that the reaction will proceed via [4 + 2] ([2+2] followed by [4+2]) cycloaddition between aryne and protected vinyl tetrahydropyridine, which will be subsequently followed by the isomerization of the double bond (Figure 6).



Scheme 4. Synthesis of boc-protected octahydroquinoline scaffold

After having optimized reaction condition for the cycloaddition and isomerization in hand, we prepared seven analogues of boc-protected hexahydroquinoline core (Scheme 4). The key step involves the Diels – Alder reaction of aryne with diene under milder reaction condition. Thus, the transition-metal-free, mild and novel method has been demonstrated for the synthesis of versatile benzo fused hexahydroquinoline core. Furthermore, we are able to reduce hexahydroquinoline core to achieve racemic octahydroquinoline core. The optimization study of the asymmetric reduction for the stereoselective synthesis of octahydroquinoline core is under active process.

In summary, we have successfully developed novel methodologies by employing arynes and also extended these protocols to the synthesis of biologically important scaffolds.

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(*Cited as a most read article in March 2018 by the ACS axial*)
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4) Virat Pandya, Santosh B. Mhaske "Process for the synthesis of Aryl Sulfones". **WO2015087352A**1, **US20160304447.**
5) Virat Pandya, Santosh B. Mhaske "Process for the preparation of Oxindolylidene acetates and Spirooxindolopyrrolidones" **IN 2017022130867.**

Chapter 1

1,2-Difuntionalization of arenes using aryne chemistry

Chapter 1: 1,2-Difuntionalization of arenes using aryne chemistry

1.1 Introduction: The challenge of integrating aryne into synthetic chemistry has motivated researchers since the emergence of aryne as a fascinating field of chemistry. Recent research is moving towards the synthesis of more advanced and complex targets, hence it requires continuous efforts in the evolution of synthetic methods. Therefore, there has been looking for the invention of comparatively milder and diverse protocols having significant applications. In continuation of the developments in the field of organic chemistry, aryne evolved as a paramount tool for the synthetic chemists. In contemporary research, aryne has significantly contributed to the development of many important transformations. The strained triple bond which is produced by the partial overlap of unhybridized p-orbitals provides enormous reactivity to aryne. The appearance of aryne is well-defined as an intermediate which is formed by the abstraction of two hydrogen atoms from the carbons of nearest position. Owing to extreme electrophilic nature and highly stabilized HOMO, aryne has been extensively utilized in the development of various approaches for the formation of multiple C−C and C−heteroatom bonds in a single step[1]. Employment of aryne is usually carried out with or without the transition-metal. Aryne reactivity is used commonly in the nucleophilic addition reactions, annulation reactions, cycloaddition reactions, multicomponent reactions, and pericyclic reactions.

Historically, the presence of an aryne as an intermediate was first indicated by the group of Stoermer and Kahlert in 1902. They have reported the synthesis of 2-ethoxybenzofuran from the reaction of 3-bromobenzofuran with a base in ethanol and proposed that the reaction pathway followed the formation of the 2,3-didehydrobenzofuran as a reactive intermediate[2]. Aryne was first introduced as a reactive intermediate by Bachmann and Clarke[3] in 1927. In 1942 Wittig

reported a zwitterion structure, which was formed during the transformation of fluorobenzene to biphenylene[4]. Experimental evidence was provided by John D. Roberts and co-workers in 1953 by performing classic ^{14}C labeling experiment. In this experiment, ^{14}C labeled chlorobenzene reacted with potassium amide in liquid ammonia and furnished aniline as a product in a 1:1 ratio of regioisomers[5]. Formation of this regioisomers proved the involvement of aryne intermediate in the reaction. Warmuth and co-worker trapped aryne in a hemicarcerand and stabilized it by host-guest interactions. Aryne structure was also evidenced by the infrared spectrum, solid-state ^{13}C, dipolar NMR spectrum, and ultraviolet photoelectron spectroscopy[6].

A half-century ago aryne was considered as a simple and unexplored reaction intermediate but in the light of new developments in organic chemistry, aryne chemistry underwent a renaissance. Their extreme reactivity makes them highly useful and versatile substrates. Now a day's arynes are proficiently utilized in various organic transformations, which ultimately extended to the total synthesis of complex molecules and natural products.

This chapter mainly highlights various transition-metal-free modes of aryne reactivity to achieve bi-functionalization of arenes, which are broadly classified into the following order. These are illustrated with selected examples from literature.

1. Insertion
2. Cycloaddition
3. Annulation
4. Multicomponent
5. Molecular rearrangement

1.1 Insertion of Arynes:

The insertion reaction of arynes proceeds through the insertion of strained triple bond of aryne into an elemental-elemental σ-bond, which provide direct access to bi-functionalization of arenes (Figure 1).

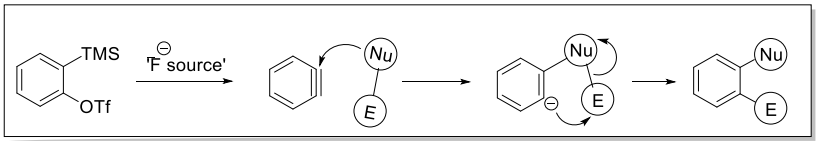
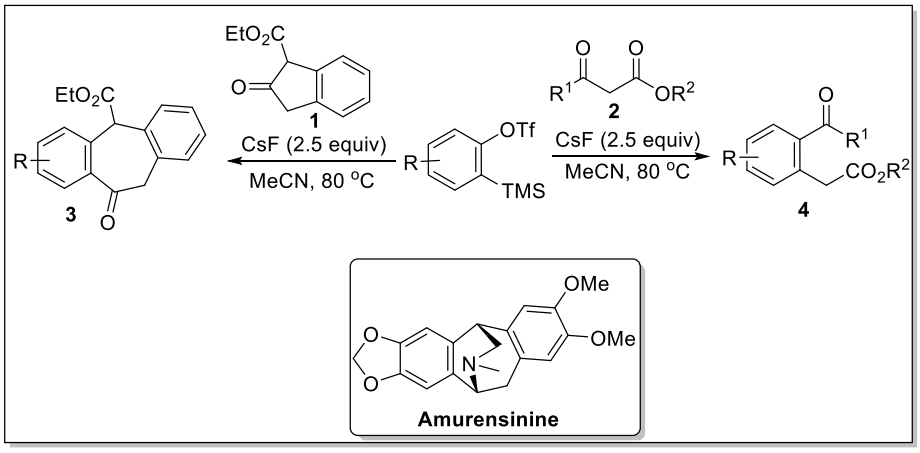


Figure 1: Mechanism of aryne insertion reaction

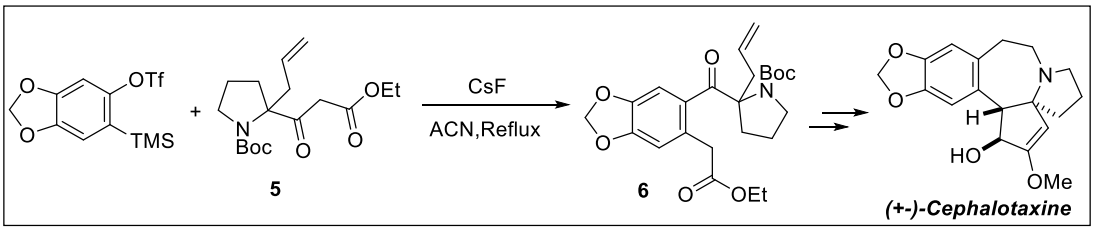
Aryne insertion reactions deliver a product with two new bonds, which can be done with or without a transition-metal catalyst. Significance of insertion reaction is further elaborated by emerging novel methodologies and their utilization in the total synthesis of various natural products and drugs. The insertion of aryne is now well-known in C−C, C−X, and X−X bonds.

A. C−C bond insertion reaction of arynes:



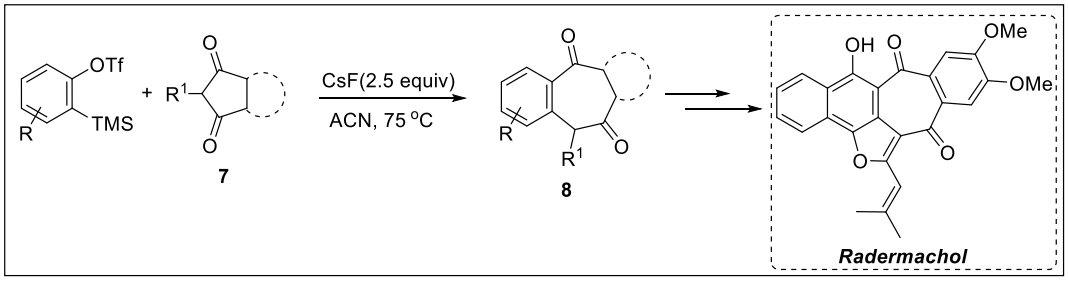
Scheme 1: Acyl-alkylation of aryne

In 2005 Stoltz and co-worker reported an efficient and facile process for the synthesis of highly important acyl-alkylated arenes. This transformation involves the insertion of arynes into the active methylene keto ester. The ultimate outcome of this approach is to afford two new C−C bonds. This method has been extended to ring expansion of cyclic β-ketoesters to attain the medium-sized carbocycles. Moreover, this methodology was utilized in the enantioselective total synthesis of the amurensinine[7a,b].



Scheme 2: Arynes insertion reaction in the synthesis of cephalotaxine and its congeners

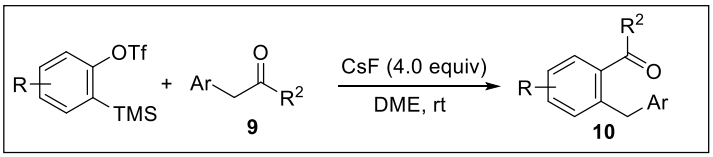
In 2016, Chandrasekhar and co-workers reported the formal total synthesis of pentacyclic core alkaloid (±)-cephalotaxine. They made use of aryne insertion reaction, where aryne get inserted into the 2- allylpyrrolidine-2-carboxaldehyde **5** to furnish bi-functionalized product **6** in good yield (Scheme 2). This total synthesis was accomplished in nine steps with an overall 10% of yield. Moreover, this method also allows to easy access to cephalotaxine congeners[8].



Scheme 3: Insertion of aryne in cyclic 1,3-diketones

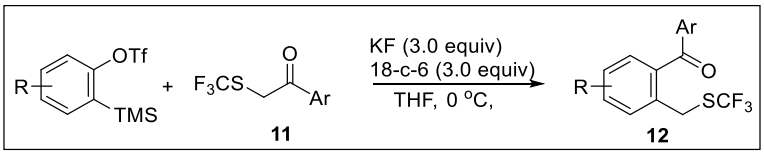
Another application of aryne insertion reaction is reported by Mehta and co-workers, where aryne has been successfully utilized in the synthesis of functionalized benzo-fused 7- and 8-

membered carbocycles **8** (Scheme 3). The reaction involves the insertion of aryne intermediate into the C−C bond of cyclic 1,3-diketones **7**. Furthermore, application of this methodology was extended to the formal synthesis of the pentacyclic natural product radermachol[9].



Scheme 4: Insertion of aryne into the benzylic C−C bond

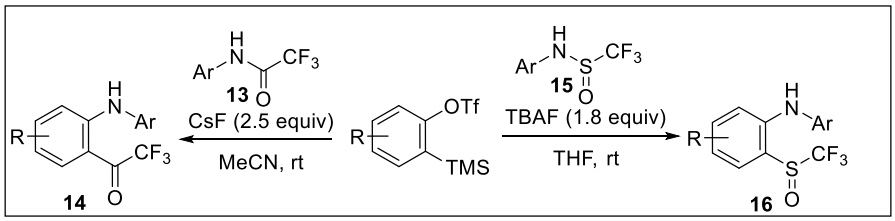
An efficient, transition-metal-free approach towards the synthesis of functionalized 2-benzyl phenyl ketones **10** has been developed by Zeng et al. This method features a direct insertion of arynes into the benzylic C−C bonds (Scheme 4). This reaction is milder operationally simple and has good functional group tolerance. This process furnished a diverse array of benzyl phenyl ketones in excellent yields[10].



Scheme 5: Insertion of aryne into the benzylic C−C bond

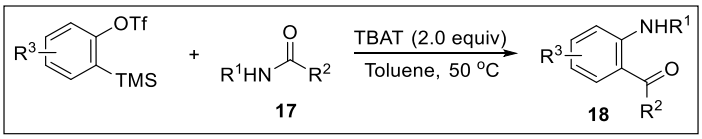
Biologically important *o*-methyl trifluoromethyl sulfide substituted benzophenones were prepared by our group (Scheme 5). This transition-metal-free method involves the insertion of aryne into a C−C σ-bond-containing compound **11** under simple reaction conditions to attain *o*-difunctionalized arenes **12**. Prepared compounds are known for various pharmaceutical applications. The importance of this protocol was established by demonstrating vast substrate scopes[11].

B. C-Heteroatom bond insertion reaction:



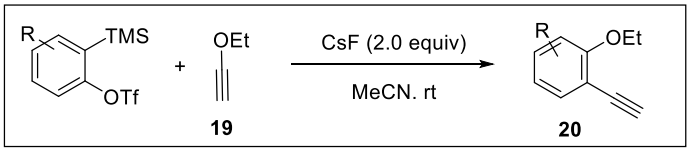
Scheme 6: C−N and C−S bond insertion of arynes

Larock and co-workers established the transition-metal-free insertion reaction of aryne with the substituted *N*-aryltrifluoroacetamides **13** and *N*-phenyltrifluoromethanesulfinamide **15** (Scheme 6). The CF_3 moiety played a key role in the feasibility of the insertion reaction. Strong electron-withdrawing groups on the nitrogen of amide and sulfinyl group, affected both acidity of amide group as well as electrophilicity of the carbonyl group of amide and sulfinyl groups of the sulfonamide compounds[12].



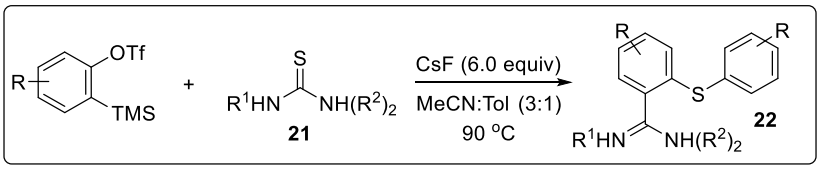
Scheme 7: Insertion of aryne into the amide bond

Greaney *et al.* reported insertion of aryne into the amide bond of aryl amide **17** to synthesize new aryl−N and aryl−C bonds. This method offers varyingly substituted amino-benzophenone compounds **18** in good to excellent yields (Scheme 7). Furthermore, the utility of this process was extended to the one-pot synthesis of acridones and acridines in good yields[13].



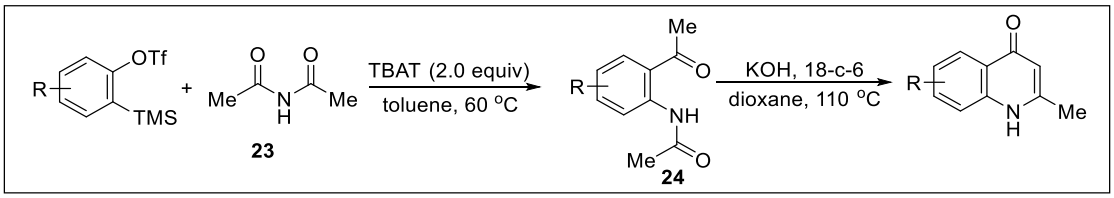
Scheme 8: Arynes insertion into a C−O σ bond

Guitian and co-workers demonstrated a facile and transition-metal-free approach towards the synthesis of 2-ethoxyethynylaryl derivatives **20** in chemo- and regioselective manner (Scheme 8). The reaction proceeds through via addition of the triple bond of the alkyne with aryne followed by formal insertion of arynes into the C(sp)−O(sp^3) σ bond of ethoxyacetylene **19** to afford *o*-bi-functionalized arenes in excellent yield. A plausible mechanism of the reaction was supported by computational studies[14].



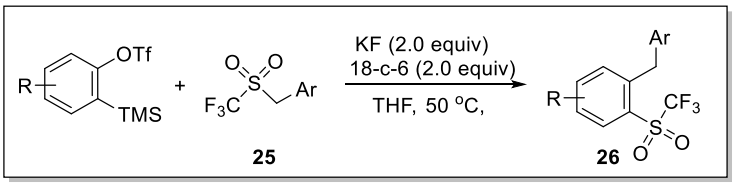
Scheme 9: Insertion of arynes into the thioureas

Application of Insertion reactions of aryne was further elaborated by Greaney group. They have successfully synthesized biologically important heterocycle amidines **22** from the insertion of arynes into the thioureas **21** (Scheme 9). The reaction diverges between arylation and insertion of aryne. Comparatively less electrophilicity of C=S bond than C=O bond of amide alters the reaction pathway from the normal insertion reaction of urea. It shows that minor changes to the nucleophile structure can provide an interesting and useful reaction pathway in aryne chemistry[15].



Scheme 10: Insertion of arynes into the acyclic imides and anhydrides

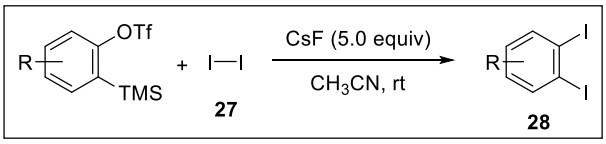
As depicted in Scheme 10, Stoltz and co-worker established a milder method for the synthesis of aryl ketoamides. Insertion of aryne into the acyclic imides and anhydrides to deliver desired compounds ketomides **24** in good yields. Formed products can be derivatized into the synthetically important scaffolds such as quinolones, indoles, and ketoanilines. The generality of the illustrated method was explored by synthetizing a diverse array of keto acyloxyarenes[16].



Scheme 11: Insertion of arynes into C–S bond

Trifone is well known for its pronounced biological activities. They are lipophilic and also have electron-withdrawing nature. Xu and coworker prepared aryl triflones **26** by insertion of arynes into the C–S bond of nucleophile **25** bearing a CF_3SO_2 group (Scheme 11). This method provides a diverse array of aryl triflones in moderate yields[17].

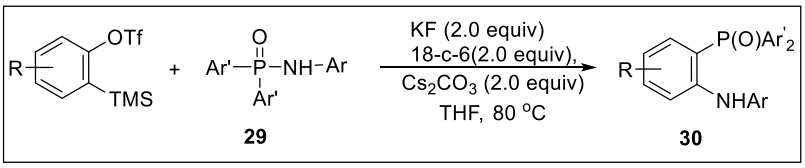
C. Heteroatom-Heteroatom bond-forming reaction:



Scheme 12: Aryne insertion into the iodine

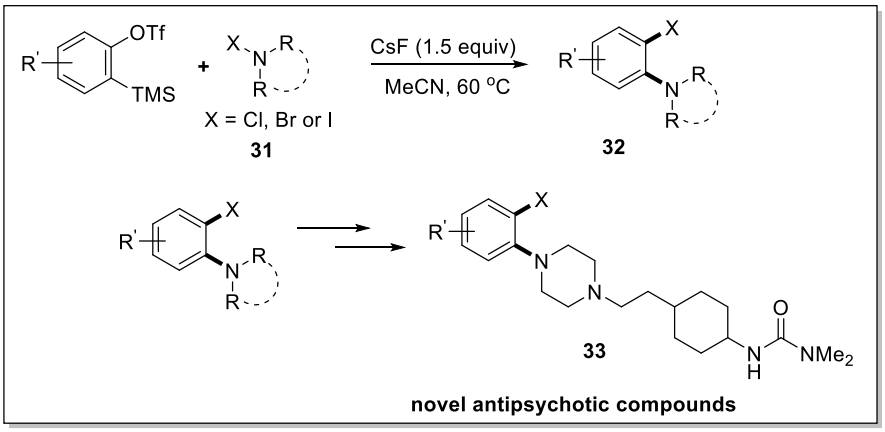
The Guitian group effectively established a process for the insertion of arynes into the σ-bond of iodine to access diverse *o*-di iodoarenes (Scheme 12). This formal insertion reaction began with the nucleophilic attack of Iodide ion on aryne to provide carbanion, which would be iodinated to

furnish *o*-diiodoarenes **28**. This method is well-suited with electron-withdrawing, neutral and electron-donating substituted aryne, polycyclic aryne, and bisarynes[18].



Scheme 13: Insertion of aryne into the aryl phosphoryl amide bond

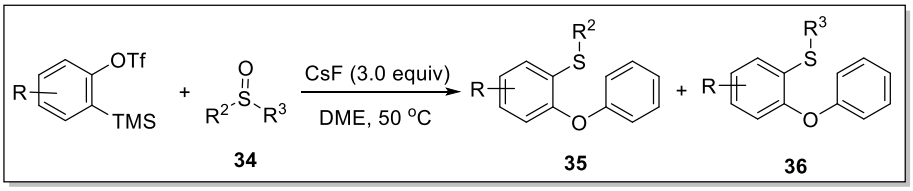
Zhang *et al.* reported the facile approach towards the synthesis of *o*-amine-substituted aryl phosphine compounds **30**. Insertion of arynes into aryl phosphoryl amide bond, resulting in the one-pot formation of C−P and C−N bonds (Scheme 13). The formed product *o*-amine-substituted aryl phosphine oxide provides a novel way for the synthesis of the number of bidentate amino-phosphines ligands[19].



Scheme 14: Aryne insertion in an N−X bond

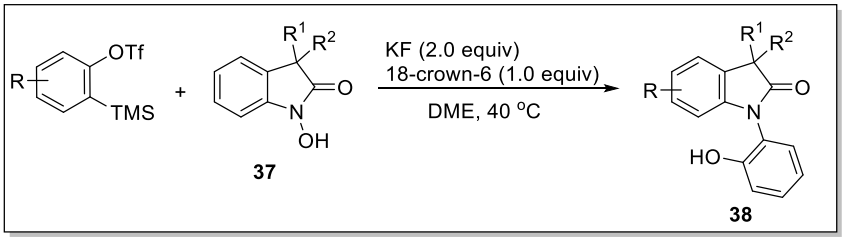
Wang and co-workers elegantly reported the milder and transition-metal-free method for the construction of *o*-haloaminoarenes **32** (Scheme 14). This protocol involves the insertion of aryne into the nitrogen-halide bond (eg. N-chloramine, N-bromoamine, and N-iodoamine). This method shows high functional group tolerance and provided the desired compounds *o*-

haloaminoarenes in an excellent yield having good regioselectivity. The utility of this protocol is demonstrated by the synthesis of analogs of the antipsychotic drug cariprazine[20] **33**.



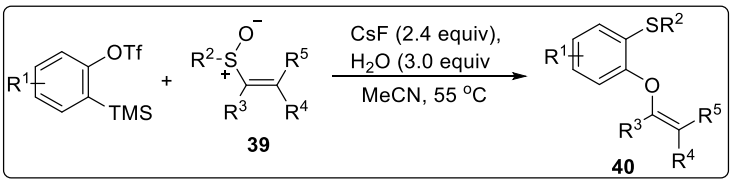
Scheme 15: Insertion of aryne into an S−O bond

Wang and co-workers effectively inserted aryne into the S−O bond. The insertion reaction of arynes with sulfoxides **34** initiated with [2+2] cycloaddition, which lead to the key intermediate sulfur ylide formation. Further reactions to form epoxide and thioether sequentially via methyl transfer in sulfur ylide intermediate (Scheme 15). This method provides a base free generation of useful sulfur ylides[21].



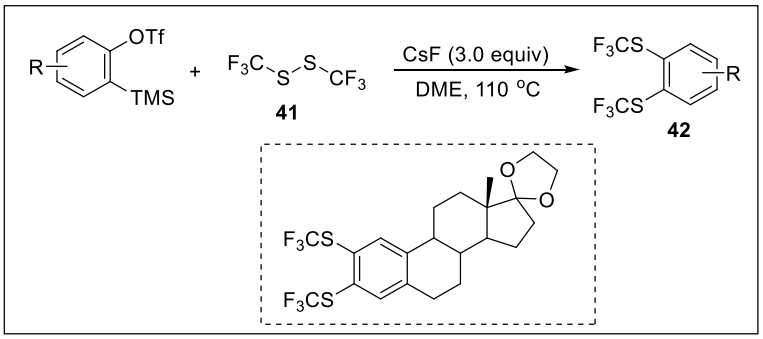
Scheme 16: Aryne insertion reaction with hydroxyl indolinones

Wang and co-workers reported the novel, mild and transition-metal-free insertion reaction of aryne, to achieve sterically hindered *o*-aminophenols **38**. Formal aryne insertion into N-O bond of hydroxyindolinones under mild reaction conditions to form bi-functionalized arenes (Scheme 16)**.** The reaction encompasses the addition of hydroxyindolinones **37** to arynes, followed by a chemo and regioselective [2,3]-Stevens rearrangement to get the desired compound in excellent yields[22].



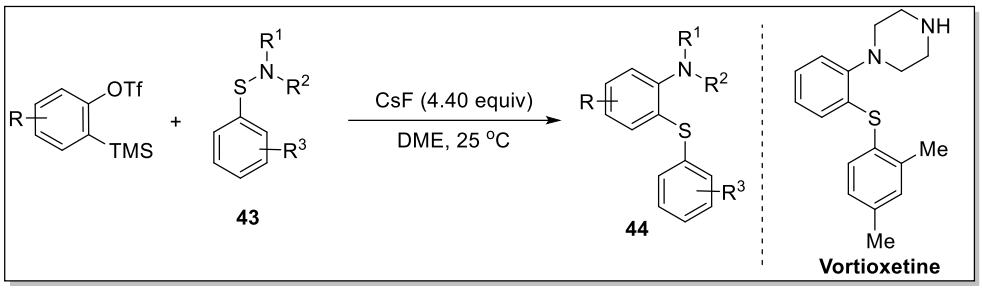
Scheme 17: Insertion of aryne to form *o*-arylsulfinylaryl vinyl ethers

Studer *et al.* developed an efficient and highly stereospecific method for the synthesis of *o*-arylsulfinylaryl vinyl ethers **40** from the aryne insertion reaction with aryl vinyl sulfoxides **39** (Scheme 17). The reaction proceeds via [2 + 2] cycloaddition reaction to form four-membered cycloadduct, which on S−O bond cleavage and subsequent ionic vinyl migration furnish desired compounds in moderate to good yields[23].



Scheme 18: Insertion of aryne into the disulfide bond

A Trifluoromethyl sulfide (SCF_3) is commonly found in many fluorinated bioactive molecules. Daugulis group reported an efficient, transition-metal-free method for the synthesis of 1,2-bis(trifluoromethylthio) arenes **42** (Scheme 18). Insertion of arynes strained triple bond into the disulfide S−S bonds of bis(trifluoromethyl)-disulfide **41** provides varyingly functionalized 1,2-bis(trifluoromethylthio) arenes in excellent yields. They have utilized this method for bis-trifluoromethylthiolation of the estrone derrivatives[24].



Scheme 19: Insertion reaction of aryne with sulfenamides

Biju and co-worker established a transition-metal-free, facile method for the this amination of arenes using aryne (Scheme 19). This method features insertion of aryne into the S−N σ-bond of sulfenamides **43** to construct new C−N and C−S bonds, which lead to the synthesis of varyingly substituted o-sulfanylaniline **44**. Additionally, the application of this milder method has been elaborated by the synthesis of the antidepressant drug vortexetine[25].

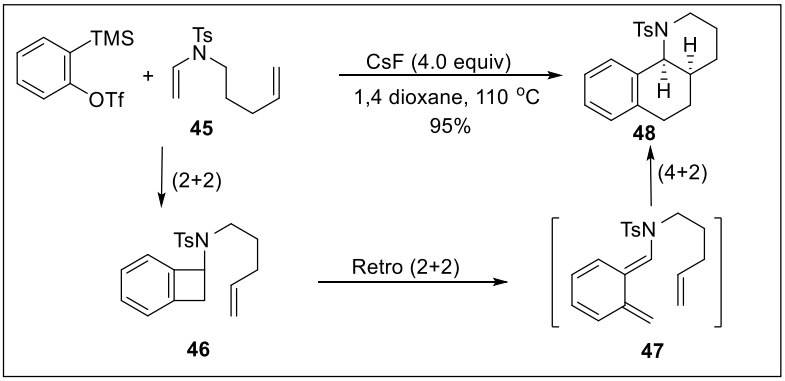
1.2 Pericyclic reactions of Arynes:

Extreme electrophilic nature of the strained triple bond and low lying LUMO makes aryne as a fascinating dienophile which performs outstanding reactivity towards the pericyclic reactions. The pericyclic reaction of aryne provides facile access towards the formation of multiple bonds in a single step. Hence pericyclic reactions of aryne are utilized in the synthesis of various drugs and natural products. The pericyclic reactions of arynes are divided into the following three categories:

1. Cycloaddition reactions
2. 1,3 dipolar reactions
3. Diels-Alder reaction

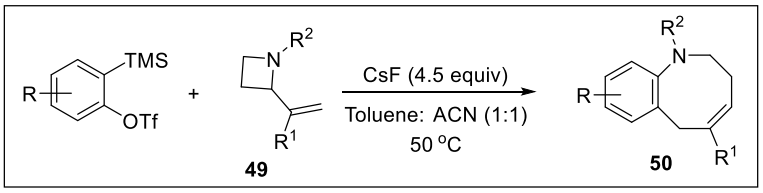
A. Cycloaddition reactions:

Arynes perform multiple types of cycloaddition reaction, with a wide range of alkenes to provide substituted benzocyclobutane adduct. Electron rich alkenes show fast reactivity towards the cycloaddition reaction with arynes.



Scheme 20: Stereoselective [2 + 2] cycloaddition of benzyne-enamide

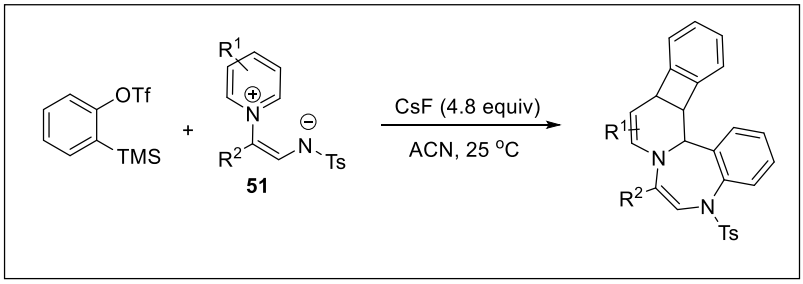
In 2009 Hsung and co-worker demonstrated a [2+2] cycloaddition reaction of arynes with enamides **45** leading to the formation of amido-benzocyclobutanes **46** (Scheme 20). Ring-opening of cycloadduct **46** provides intermediate **47** followed by intramolecular [4+2] cycloaddition, furnished the benzo fused quinoline scaffolds **48** in excellent yield [26].



Scheme 21: Cycloaddition of 2-vinylazetidines with arynes

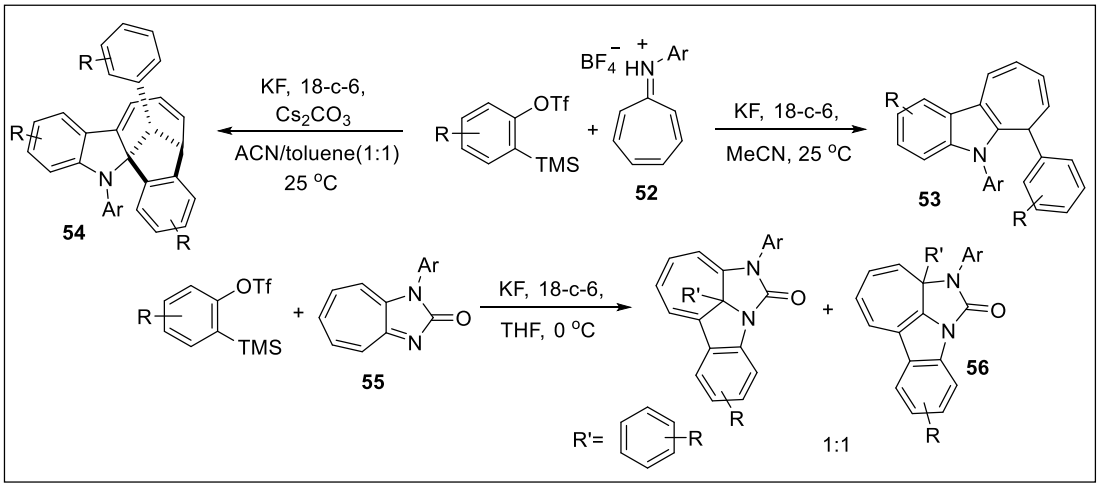
Saito *et al*. reported a catalyst-free milder method for the synthesis of biologically important 1-benzazocine derivatives **50** (Scheme 21). The cycloaddition reaction of 2-vinylazetidines **49** with benzyne, initiated with nucleophilic attack of nitrogen of 2-vinylazetidines to give an

azetidinium salt. The rearrangement in an azetidinium salt provides ring expansion products in good to moderate yields[27].



Scheme 22: [5 + 2]/[2 + 2] cycloaddition reaction of pyridine zwitterion

Midazolam, Alprazolam are well known psychotropic drugs have a tricyclic 1,4-benzodiazepine scaffold. Yoo *et al*. reported a cascade cycloaddition reaction of aryne with 1,5-dipoles containing pyridinium zwitterions **51** (Scheme 22). This metal-free synthesis of polycyclic 1,4-benzodiazepines feature [5+2] cycloaddition of aryne with pyridinium zwitterions, subsequently cyclization with another molecule of aryne in [2+2] manner, provide polycyclic 1,4-benzodiazepines in good to moderate yields[28].

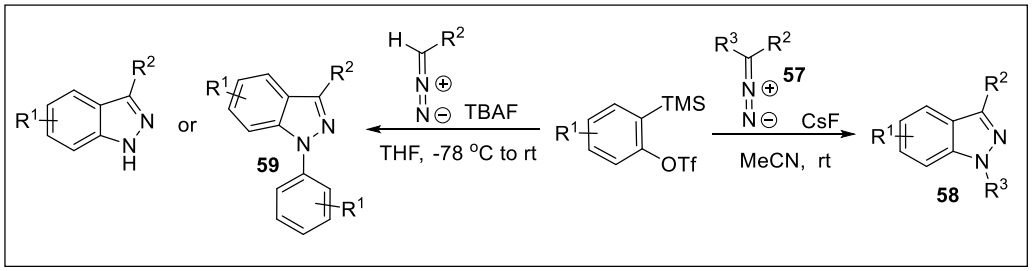


Scheme 23: Cycloaddition reaction of aza-heptafulvenes, heteroazulenes and arynes

Yun He *et al.* developed an efficient tandem [8 + 2]/aryl−ene cycloaddition reaction between aza-heptafulvenes **52** and arynes (Scheme 23), leading to the formation of cyclohepta[b]indoles **53** in a moderate yield. Moreover, the presence of excess arynes in this reaction delivers the polycyclic oxacyclohepta[b]indoles compound **54** in good yields. Additionally, they have also performed cycloaddition reaction of aryne with heteroazulenes **55** to synthesize biologically important tricyclic heterocycles **56** in good yields.[29]

B. 1,3-dipolar reactions:

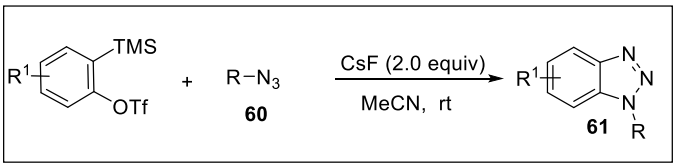
1,3-Dipolar defined as charged dipole which has at least one mesomeric form that reacts with electron-deficient dienophile aryne to give 5-membered heterocycles. This reaction has the capability to synthesize various cyclic heterocyclic cores having multiple heteroatoms in one ring.



Scheme 24: 1,3-dipolar addition reaction arynes with diazo compounds

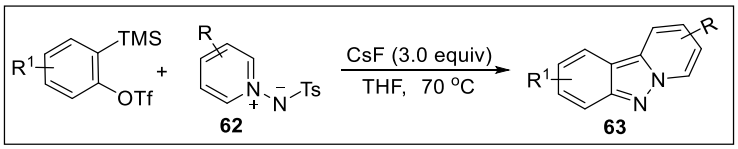
Indazole is versatile scaffolds having enormous medicinal and biological activities. In this context, Larock and co-worker demonstrated an operationally simple protocol for the synthesis of *N*-unsubstituted indazoles or 1-arylated indazoles **59** compounds from the [3+2] cycloaddition reaction of aryne with the diazo compounds **57** (Scheme 24). Substitution pattern on diazo compounds and the equivalent of the reagent alter the outcome of the reaction. Diazo compound

bearing a dicarbonyls substitution provided 1-acyl or 1-alkoxycabonyl substituted indazoles selectively[30].



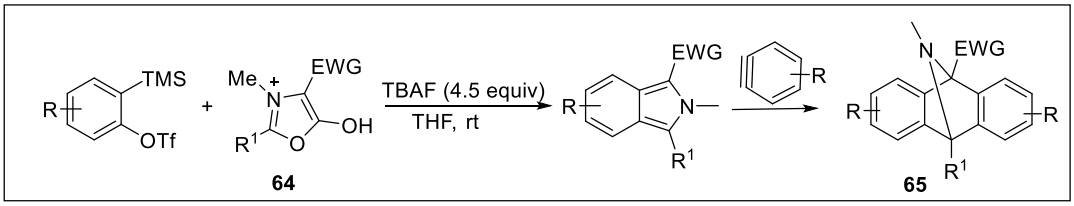
Scheme 25: Benzotriazoles from the reaction of arynes and azides

Click chemistry, which is defined as the cycloaddition reaction of alkyne with azides have several applications in organic chemistry. Yet again Larock's group developed a novel, efficient and transition-metal-free method for the synthesis of benzotriazoles using aryne. 1,3 Dipolar addition of azides on in situ generated aryne intermediate under mild reaction conditions furnish the desired benzotriazoles in excellent yields (Scheme 25). The generality of this reaction was proved by its vast substrate scope[31].



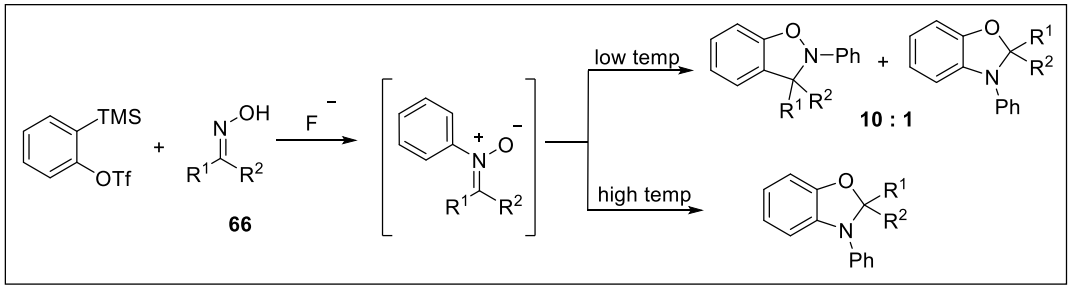
Scheme 26: Synthesis of pyrido[1,2-b]-indazoles

Shi *et al.* established another application of 1,3-dipolar reaction of aryne by synthesizing various pyrido[1,2-b]-indazoles **63** (Scheme 26). N-tosyl pyridinium **62** is well known for its dipolar character. It was reacted with aryne to from the cyclo-adduct, which on tosyl group elimination provided pyrido-indazole in good to moderate yields[32].



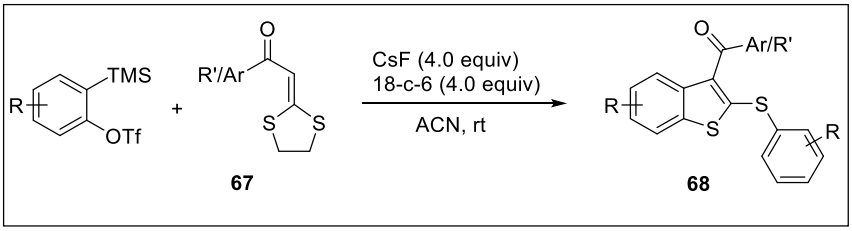
Scheme 27: 1,3-Dipolar cycloaddition reaction to access isoindoles

Larock *et al*. demonstrated a facile and efficient method for the synthesis of isoindoles and 9,10-dihydro-9,10-epiminoanthracenes. The reaction of aryne with dipolar species munchnones **64** involves [3+2] dipolar cycloaddition to access isoindoles in good yields (Scheme 27). The further [4+2] cycloaddition reaction of isoindoles with arynes furnished dihydro-9,10-epiminoanthracenes **65** in moderate yields[33].



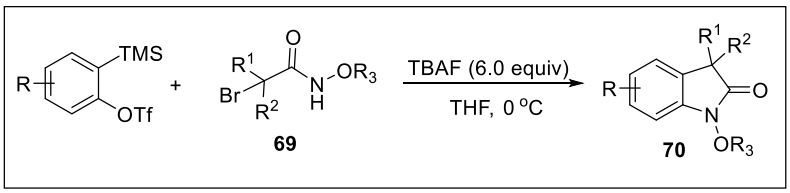
Scheme 28: 1,3-Dipolar cycloaddition reaction of oximes and arynes

Yao *et al.* developed a catalyst-free mild method for the synthesis of quaternary carbon center containing dihydrobenzo[d]isoxazoles and dihydrobenzo[d]oxazoles. The 1,3-dipolar cycloaddition reaction of ketoxime **66** and arynes proceed through the formation of ketonitrone intermediate (Scheme 28). Additionally, the cycloaddition reaction of ketonitrone with another molecule of aryne provided dihydrobenzo[d]isoxazole in good yields. Further, thermal rearrangement in dihydrobenzo[d]isoxazole leads to the formation of dihydrobenzo[d] oxazoles[34].



Scheme 29: Synthesis of benzo[b]thiophenes via [3 + 2] cycloaddition of aryne

Benzothiophene core is found in many marketed drugs and natural products. Exciting medicinal activities of benzothiophene derivatives makes their synthesis via efficient and mild method highly demanding. In this context, Singh *et al.* demonstrated the transition-metal-free synthesis of benzothiophene from the dipolar cycloaddition reaction of aryne with acyl ketene dithioacetals **67** (Scheme 29). A dipole generated form acyl ketene dithioacetals undergo [3 + 2] cycloaddition reaction with aryne to form benzo[b]thiophene-2(3H)-thione which on tautomerization and further insertion reaction with another molecule of aryne furnish desired compounds 2,3-disubstituted benzo[b]thiophenes **68** in good yields[35].

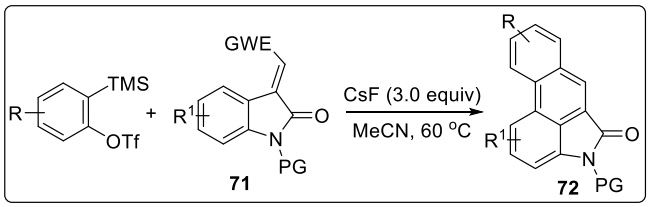


Scheme 30: [3 + 2] cycloaddition N-alkoxy oxindoles on aryne

Singh *et al.* reported the facile and efficient method for the synthesis of substituted oxindoles. The [3 + 2] cycloaddition reaction of N-alkoxy oxindoles **69** with aryne proceeds through the formation of an aza-oxyallyl carbocation intermediate (Scheme 30). The usefulness of this method was established by significant organic transformations which are performed on C3-unsubstituted oxindoles[36].

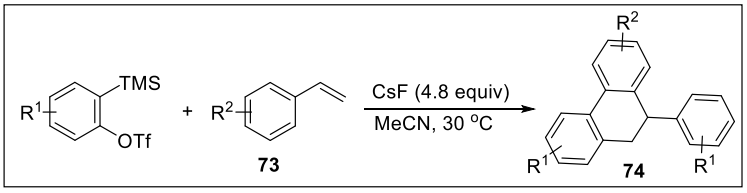
C. Diels-Alder reaction

Diels-Alder reaction is a well-recognized and powerful tool in organic chemistry which provided an efficient way to synthesize various carbocycles, heterocycles and polycyclic hydrocarbons in good yields. Aryne takes part in Diels-Alder reactions as dienophile and generated a great number of synthetically important scaffolds using comparatively milder reaction conditions.



Scheme 31: Diels-Alder reaction of aryne with methyleneindolinones

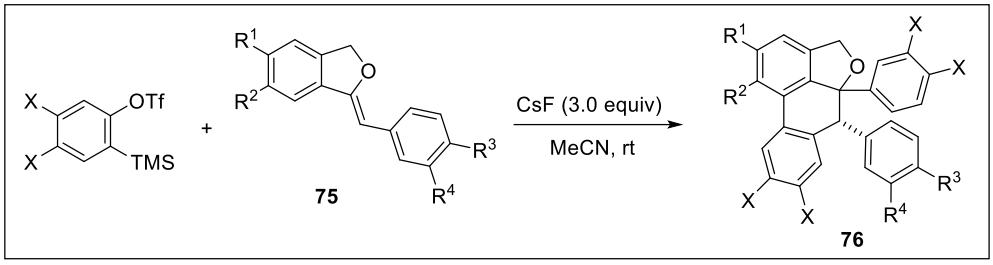
Formation of biologically significant naphtho-fused oxindoles via Diels-Alder reaction of methyleneindolinones**71** with aryne was described by Jia and co-workers (Scheme 31). Possible mechanism of this reaction demonstrated that the reaction proceeds through the [4+2] cycloaddition reaction followed by isomerization and dehydrogenation to attain desired compounds in good yields. The generality of this method was extended by synthesizing various naphtha used oxindoles[37].



Scheme 32: Aryne Diels-Alder reaction with substituted styrenes

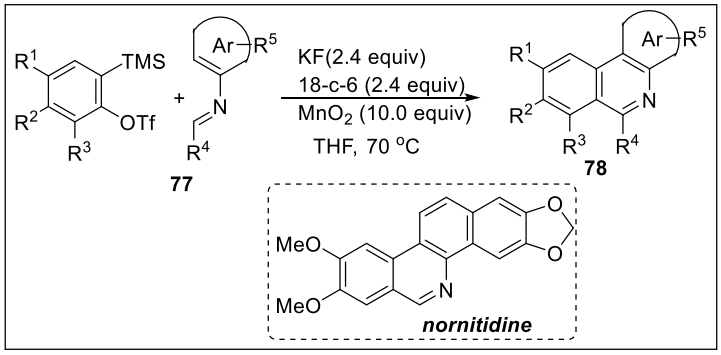
Biju and co-worker elegantly developed mild and facile Diels-Alder of styrene with arynes (Scheme 32). This method overcomes the drawback like limited substrate scope and low yields

of products which observed in the previously reported reaction of styrene **73** with arynes derived from 2-bromofluorobenzene and tetrahalogenated arynes. This protocol provides a wide substrate scope for the synthesis of 9-aryl-9,10-dihydrophenanthrene derivatives **74** in moderate to good yields[38].



Scheme 33: Diels-Alder reaction of benzylidenephthalans with aryne

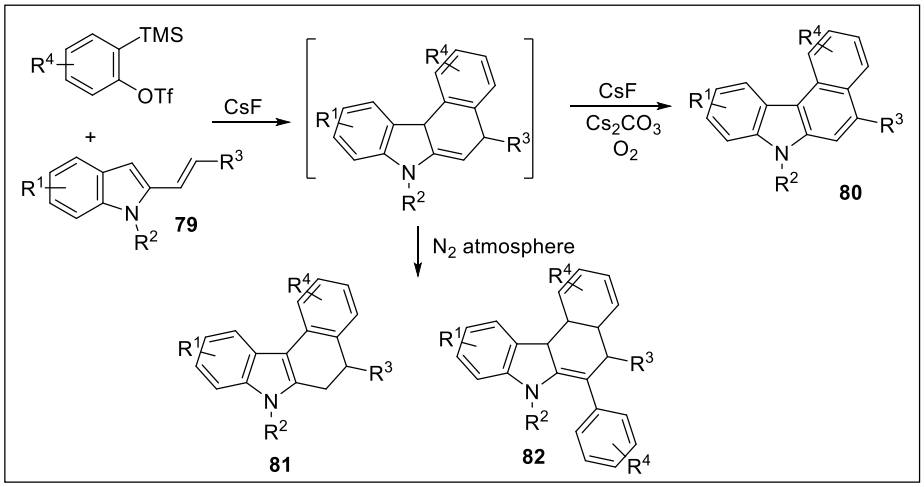
Liu and co-workers reported the Diels-Alder reaction between benzyne and functionalized benzylidenephthalans **75** to synthesize multifaceted structure called phenanthro[10,1-bc]furans **76** (Scheme 33). The formed product phenanthro[10,1-bc]furans is ubiquitous in many natural products and bio-active compounds.[39]



Scheme 34: Aza-Diels−Alder reaction of aryne

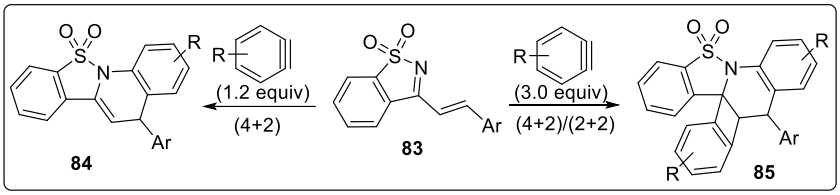
Physiochemical, medicinal and pharmaceutical properties of isoquinolines and its derivative amplified their importance in synthetic chemistry. Coquerel and co-workers established the novel protocol for the aza-Diels-Alder reaction of electron-rich aryl imines with aryne under the metal-

free, mild reaction conditions to synthesize isoquinolines in moderate yields (Scheme 34). The importance of this methodology was very well explored by the synthesis of nornitidine alkaloid in good yield.[40]



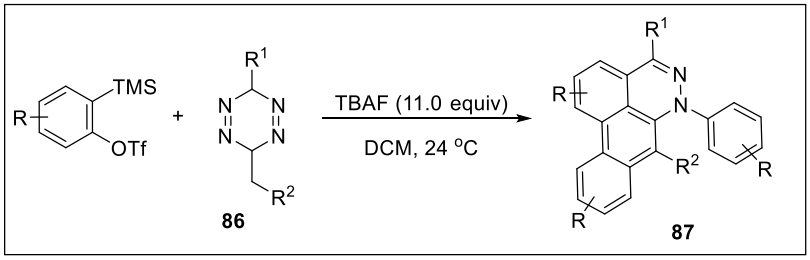
Scheme 35: Diels−Alder reaction of 2-alkenylindoles with arynes

Wu *et al.* effectively utilized Diels−Alder reaction of 2-alkenylindoles **79** with arynes for the synthesis of benzo-[c]carbazoles (Scheme 35). Formation of benzo[c]carbazole derivatives via Diels-Alder reaction of arynes with 2-alkenylidoles is attuned in such a way that the oxidized or aromatized benzo-[c]carbazoles **80** products formed under the oxygenated atmosphere, while the 7,11b-dihydrobenzo[c]carbazoles **81** and 6,7-dihydrobenzo[c]carbazoles **82** product obtained under the nitrogen atmosphere by keeping other reaction parameters constant. The synthesized compound 7,11b-dihydrobenzo [c] carbazoles derivatives showed antitumor activities. Moreover, this method was applied for the synthesis of benzo[c]carbazole amide derivative which shows inhibitory effect against both A549 and HCT-116 cell lines.[41]



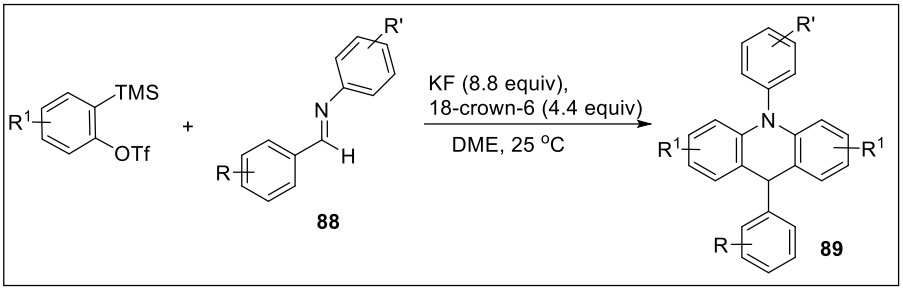
Scheme 36: [4+2]/[2+2] Aza Diels−Alder of arynes and *N*-sulfonyl ketimines

He's group demonstrated the preparation of isothiazole dioxide-fused dihydroquinoline **84** or dihydrocyclobutaquinoline **85** derivatives using the aza Diels−Alder of arynes and *N*-sulfonyl ketimines **83** under the mild reaction condition (Scheme 36). This cascade cycloaddition reaction involves [4+2] cycloaddition of arynes and *N*-sulfonyl ketimines, followed by [2+2] cycloaddition addition reaction to provide facile and one-pot generation of one C–N and three C–C bonds. This method was also extended to the synthesis of 2,4-diarylquinolines.[42]



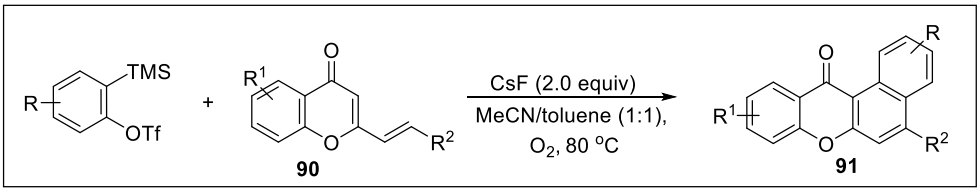
Scheme 37: Diels–Alder reactions of tetrazine and arynes

Chenoweth *et al.* established a transition-metal-free method for the synthesis of dibenzo[de,g]cinnoline **87**, a polyaromatic heterocycles which shows activity as cellular imaging agents or bioactive molecules (Scheme 37). The [4+2] Diels-Alder reaction of tetrazine **86** with aryne is quite simple and required very less time for the completion. Mechanism studies of this reaction show that controlled reactivity of aryne and small changes in the substitution on tetrazine affect the outcome of the reaction.[43]



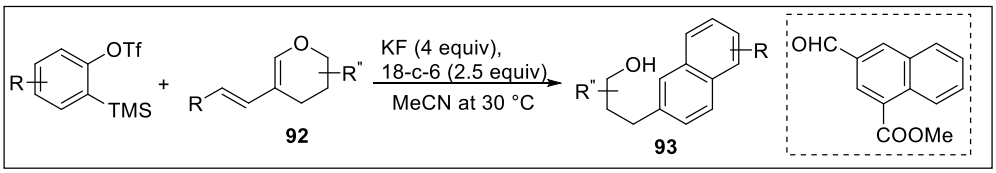
Scheme 38: [4+2] Cycloaddition between aza-o-quinone methides and arynes

Yoshida et al. reported the facile method for the synthesis of varyingly substituted acridane using aryne chemistry (Scheme 38). The cycloaddition reaction of aryne with imine was initiated in [2+2] fashion to form aza-ortho-quinone methides intermediate. This intermediate subsequently underwent [4+2] cycloaddition reaction with another molecule of aryne to furnish polysubstituted acridanes **89** in good yields.[44]



Scheme 39: Diels–Alder reactions of 2-styrylchromones and arynes

Yun He et al. developed a novel transition-metal-free Diels–Alder reaction for the synthesis of biologically important Xanthones (Scheme 39). This Diels–Alder reaction of 2-styrylchromones **90** with arynes features tandem oxidation–aromatization reactions under the oxygen environment. This method provided various substituted benzo [c] Xanthones **91** in moderate to good yields.[45]

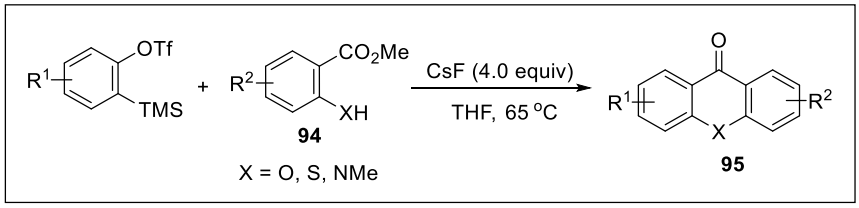


Scheme 40: [4+2] Diels−Alder addition of arynes

Mukherjee *et al.* established [4+2] cycloaddition reaction of aryne with glycal-derived dienes **92** to generate benzannulated aromatic skeleton having a chiral side chain (Scheme 40). The reaction involves annulative π-extension and translocation of the double bonds through anticipation of pyran ring. Aroamticity in the product is achieved by stereoselective pyran ring --opening having retention in stereochemical centers. The utility of this method was demonstrated by the synthesis of meta-disubstituted naphthalene aldehydes and aldolases substrates.[46]

1.3 Annulation of arynes:

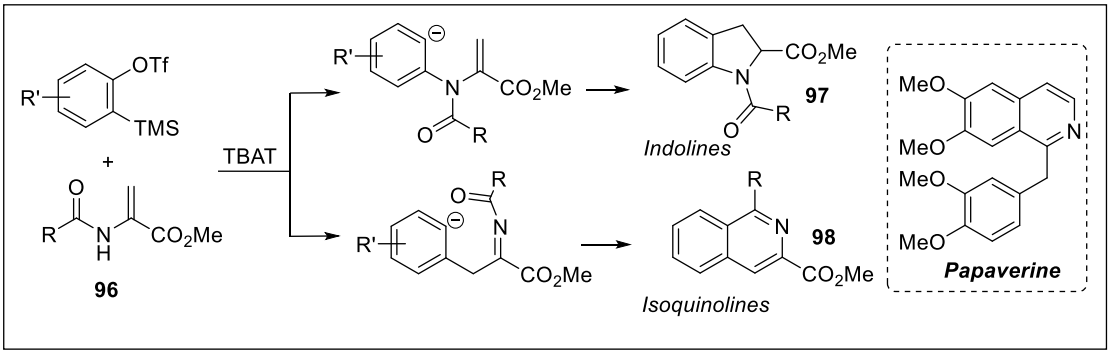
Annulation reaction of aryne surges the potential to deliver *ortho*-bi-funtionalized aromatic systems. They are well known for their significant contribution in heterocyclic chemistry. Annulation reaction provides access to form various biologically significant cyclic compounds via multiple C−C or C−X atom bond formation in a single step.



Scheme 41: [4+2] Annulation of arynes with substituted benzoates

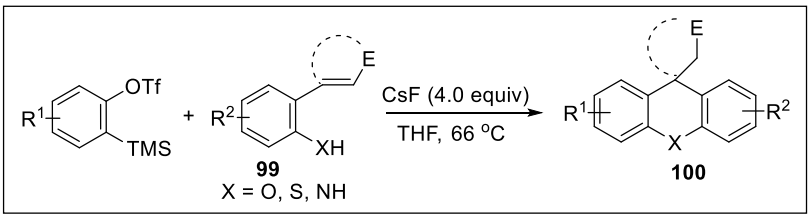
Larock and co-workers demonstrated the transition-metal-free annulation reaction of *ortho*-heteroatom-substituted benzoates **94** with arynes (Scheme 41). This method provides a novel path for the synthesis of biologically interesting compounds such as xanthones, thioxanthones,

and acridones in excellent yields. The reaction is initiated with the nucleophilic addition of the benzoate on insitu generated aryne which subsequently underwent intramolecular electrophilic cyclization to provide differently substituted Xanthones **95** in moderate yields.[47]



Scheme 42: Aryne annulation lead to the synthesis of indolines and isoquinolines

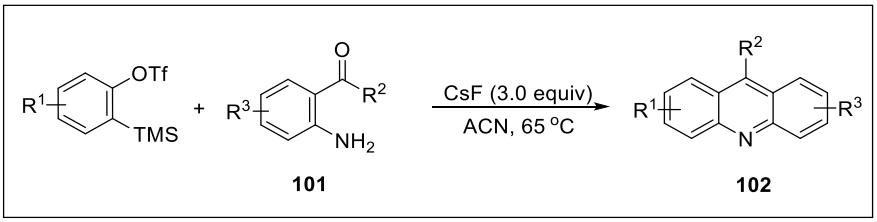
Stoltz and co-workers reported the facile process for the synthesis of indolines **97** and isoquinolines **98** using annulation reaction of aryne with the *N*-acyl dehydroamino esters **96** (Scheme 42). The orthogonal mode of reactivity of varyingly substituted enamine with aryne was explored. The utility of the methodology has been shown by successful total synthesis of the opiate alkaloid papaverine.[48]



Scheme 43: Synthesis of functionalized xanthenes or acridines from arynes

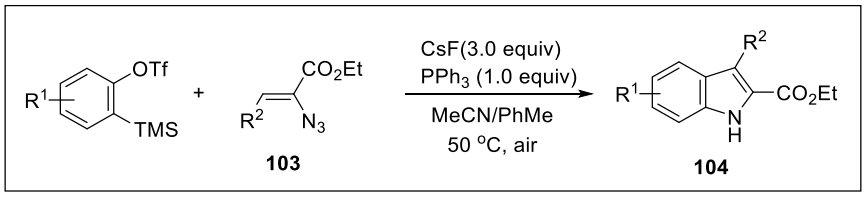
In 2010 Huang and co-workers effectively synthesized biologically significant xanthenes and acridines compounds using annulation reaction of aryne. The reaction began with nucleophilic addition of α, β-unsaturated groups substituted at *ortho* to phenol or anilines on aryne **99**,

followed by intramolecular Michael addition to access important compound 9-functionalized xanthenes and acridines **100** in good yields[49] (Scheme 43).



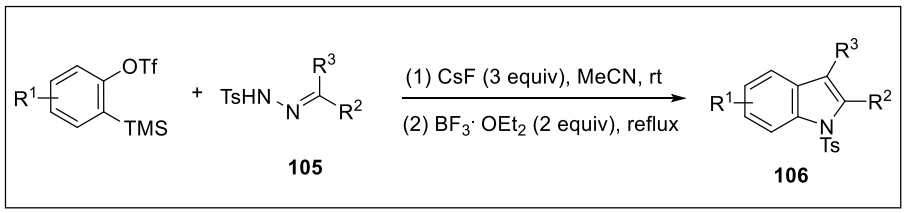
Scheme 44: [4+2] Annulation of arynes with 2-aminoaryl ketones

Pioneering work by Larock group in the field of aryne chemistry developed the [4 + 2] annulation reaction of 2-aminoaryl ketones **101** with the arynes under milder reaction conditions to furnish a vast array of medicinally useful acridines **102** in good yields (Scheme 44). [50]



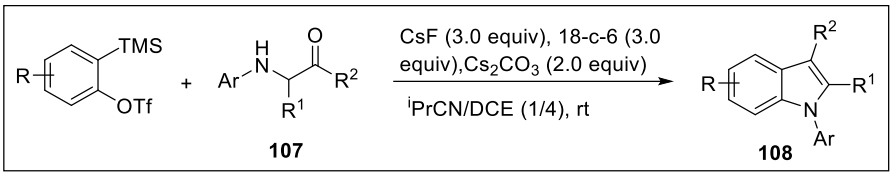
Scheme 45: Annulation of 2-azidoacrylates with aryne to get indoles

Wang *et al*. reported an efficient method for the synthesis of varyingly substituted indoles (Scheme 45). This transformation features annulation reaction of aryne with azido-acrylates **103** under the milder reaction conditions. This process is initiated via the formation of nucleophilic iminophosphorane intermediate from the reaction of azide and PPh_3. Further, nucleophilic addition reaction of iminophosphorane with aryne intermediate and sequentially cyclization followed by air oxidation provided desired compound indoles **104** in excellent yields. Application of this method was accomplished by synthesizing 10H-indolo[1,2-a]indol-10-ones.[51]



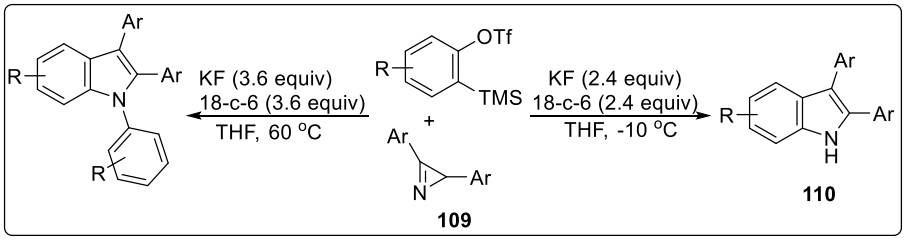
Scheme 46: Fischer-Indole reaction of aryne

Fischer-indole reaction of aryne is first time reported by Greaney *et al.* The novel synthesis of indole initiated by the reaction of aryne with the *N*-tosyl hydrazones **105** which leads to the formation of *N*-arylation of aryne (Scheme 46). Delightfully, the addition of Lewis acid to the reaction mixture leads to the Fisher cyclization of *N*-arylated compounds. This method is quite milder and provides substituted indoles **106** in excellent yield.[52]



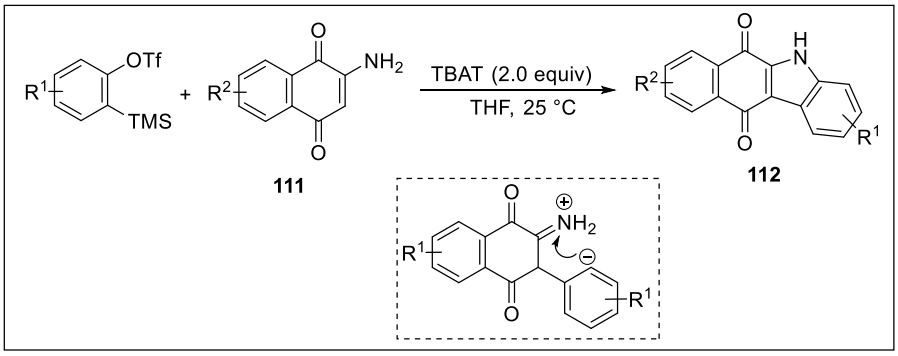
Scheme 47: Hetero-annulation of arynes with *N*-aryl aminoketones

Zhu group demonstrated a one-step protocol for the synthesis of unsymmetrical 2,3-dialkyl substituted indoles **108** using annulation reaction of aryne with N-aryl aminoketones **107** (Scheme 47). This reaction proceeds through nucleophilic addition of an amine to aryne intermediate, subsequent cyclization and dehydration provided expected compounds indoles in good yields. The generality of this method was shown by preparing differently functionalized indoles.[53]



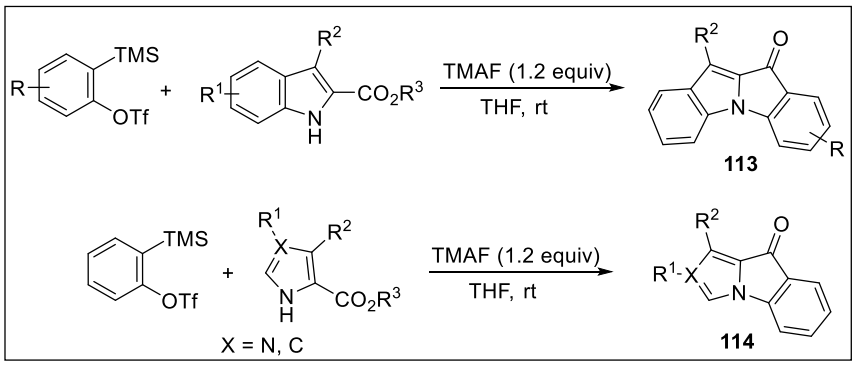
Scheme 48: Annulation reaction of arynes with azirines

Biju *et al*. developed the temperature selective annulation reaction of aryne with aziridine **109**. The annulation reaction of aryne with aziridine at high temperature 60 ^{o}C, furnished exclusively *N*-arylated indoles. Moreover, the same reaction performed at -10 °C instead of 60 ^{o}C, provided *N*-unsubstituted indoles in good yields (Scheme 48).[54]



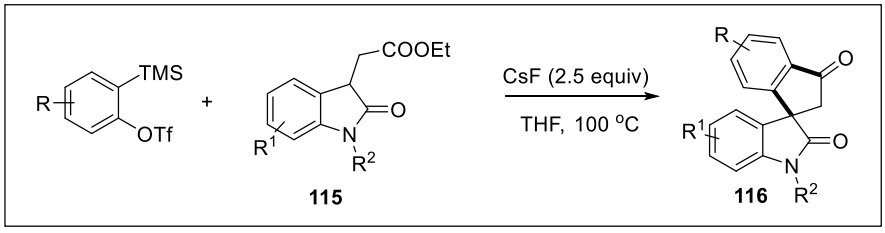
Scheme 49: [3 + 2] annulation of arynes and 2-aminoquinones

He and co-workers reported the catalyst-free [3 + 2] annulation reaction of arynes with 2-aminoquinones. This versatile synthesis of biologically and pharmaceutically important carbazolequinones **112** from aryne and 2-aminoquinones **111** proceeds through the sequential C−C and C−N bonds formation via cascade reactions (Scheme 49). This novel methodology was fruitfully utilized for the synthesis of bioactive murrayaquinone A and koeniginequinone B and their analogs .[55]



Scheme 50: Arynes annulation with indole and pyrrole-2-carboxylate esters

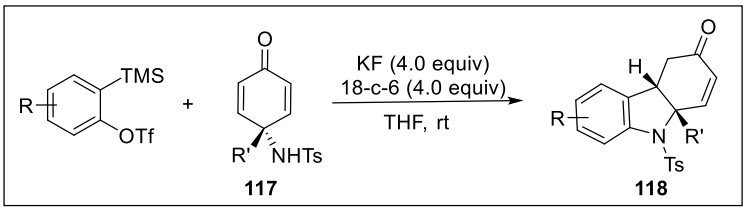
Ramtohul *et al*. developed an efficient method for the synthesis of polycyclic heterocycles containing indoles or pyrroles. The synthesis of such scaffolds was carried out by using aryne annulation chemistry (Scheme 50). The method comprises the aryne mediated annulation reaction of indoles and pyrrole-2-carboxylate esters, which proceed through the nucleophilic attack of indole on aryne leading to N-arylated product followed by electrophilic cyclization. This cyclization furnished diverse polycyclic indolone **113** and pyrroloindolone **114** heterocycles in good yields.[56]



Scheme 51: Spiroannulation of oxindoles via Aryne

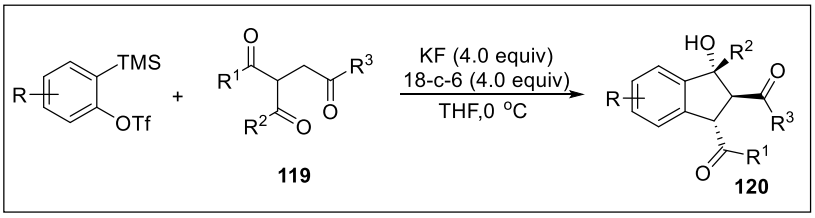
Pharmaceutically well-recognized cyclopentannulated spirooxindole was prepared by spiro-annulation reaction of arynes with oxindoles **115** bearing acetic side chain at 3-position. This transition-metal method features nucleophilic addition of carbanion generated on 3-position of oxindole core followed by intramolecular cyclization, furnish cyclopentannulated spirooxindole

116 in excellent yields (Scheme 51). Diversity of this protocol was proved by synthesizing various cyclopentannulated spirooxindoles.[57]



Scheme 52: (3 + 2)-Annulation of *p*-quinamine and aryne

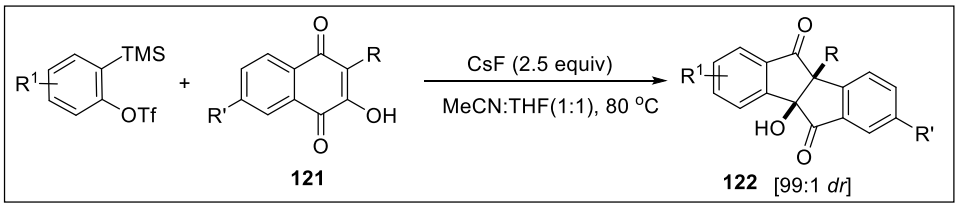
Hydrocarbazoles is a ubiquitous motif found in numerous biologically important alkaloids. She *et al*. demonstrated the transition-metal-free method for the synthesis of hydrocarbazoles using (3 + 2)-annulation reaction of p-quinamines **117** and arynes (Scheme 52). This synthetic method provides varyingly substituted indole-fused hydrocarbazoles **118** in excellent yields. Moreover, this method can be easily scaled-up and simple modification in the formed product provides useful skeletons.[58]



Scheme 53: Annulation reaction of arynes and α,γ-diketo esters

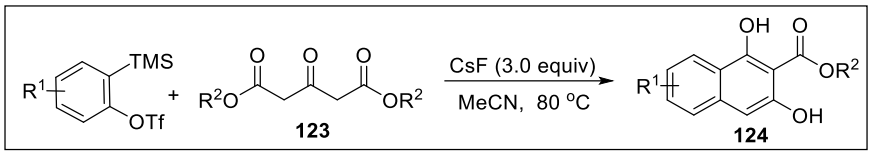
Highly substituted indanes are prepared from the annulation reaction between aryne and α,γ-diketo esters **119**. Indanes are well-recognized scaffolds having promising medicinal activities. An unprecedented process for the synthesis of indanes **120** has been demonstrated by Huang and co-workers, where indanes are prepared from the mild, catalyst-free and pH-neutral reaction conditions (Scheme 53). A plausible mechanism of this reaction showed that reaction proceeds

through a formation of benzocyclobutane intermediate, followed by ring opening and intramolecular cyclization provided substituted indanes in excellent yields.[59]



Scheme 54: Stereoselective annulation of arynes into lawsones

Ramachary and coworker demonstrated a stereoselective process for the synthesis of biologically significant and versatile benzannulated Bicyclo [3.3.0] octanes **122**. The reaction is proceeding via insertion of aryne with Lawson **121**, followed by [2+2] cycloaddition and subsequent rearrangement furnished desired compounds in excellent yields (Scheme 54).[60]



Scheme 55: Benzannulation of 1,3-oxopentanedioate with arynes

Muthukrishnan *et al.* demonstrated a transition-metal-free, one-pot annulation reaction of aryne and 1,3-oxopentanedioate **123** for the synthesis of naphthalene derivatives (Scheme 55). Possible Reaction pathway concludes that nucleophilic addition of 1,3-oxopentanedioate compound on aryne intermediate generate carbanion which undergoes intramolecular cyclization followed by Claisen rearrangement provides 1,3-dihydroxy-2-naphthoate **124** scaffolds in good yields. Moreover, this method is applied for the synthesis of asymmetric rhodamine dyes.[61]

1.4 Multicomponent reactions of arynes

Multicomponent reactions of aryne involve as the nucleophile addition on aryne to generate aryl carbanion which is subsequently quenched by electrophiles to form bi-functionalize arenes(Figure 2). Aryne is prone to undergo multicomponent reaction because it acts as neutral

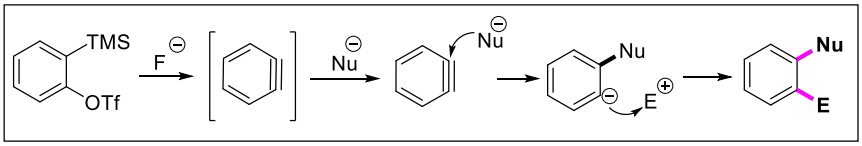
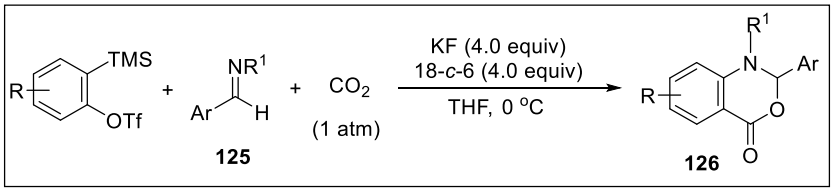


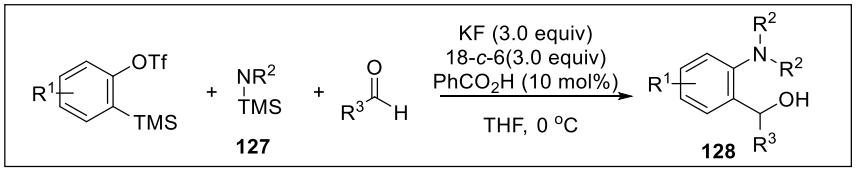
Figure 2: Mechanism of aryne multicomponent reaction

mediator to transfer charge between nucleophiles to electrophiles in its all common transformations. The multicomponent reaction of aryne has tremendous potential to construct multiple bonds in a single step and one-pot fashion, which ultimately lead to a synthesis of complex architectures. Herein some representative examples of the multicomponent reaction of aryne are described which prove its utility in organic chemistry.



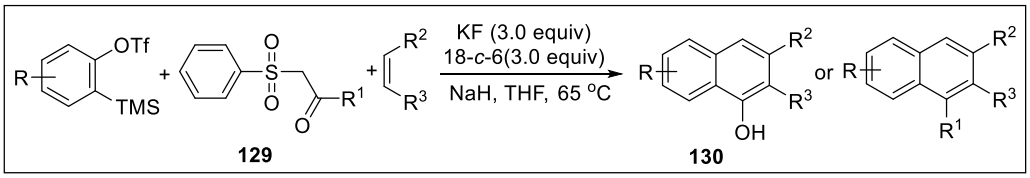
Scheme 56: Synthesis of benzoxazinone

The idea of multicomponent reactions in aryne chemistry was well studied by Yoshida group. They have synthesized benzoxazinone derivatives **126** via multicomponent reaction of aryne, imine **125** and CO_2 at 0 ^{o}C (Scheme 56). Benzoxazinone derivatives have vast applications in pharmaceutical industries. The reaction is takings place through nucleophilic addition of imines on arynes to form zwitterion, which is quenched with CO_2 to provide benzoxazinone derivatives in good yields.[62]



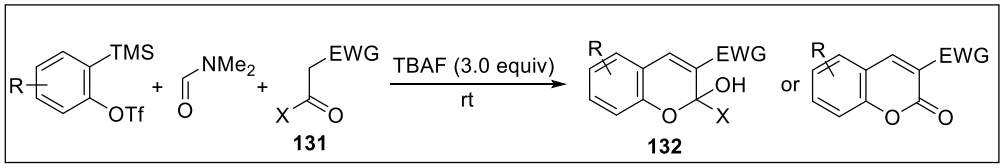
Scheme 57: Three-component coupling of aryne, imines, and CO_2

Another interesting application of multicomponent reaction was demonstrated by Yoshida and co-worker. This multicomponent reaction of arynes, aminosilanes **127**, and aldehydes give access to the pharmacologically important 2-aminobenzhydrol scaffolds **128** (Scheme 57). Acid-catalyzed the formation of bi-functionalized arenes having two substituents amino and hydroxymethyl on neighboring positions shows the importance of this method in the synthesis of various organic skeletons.[63]



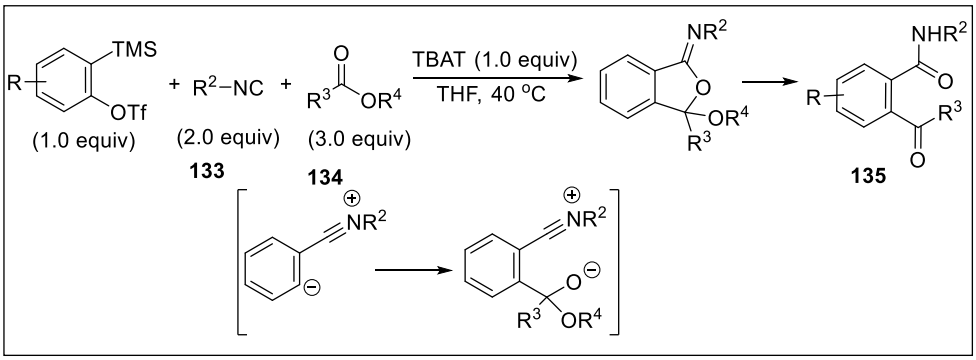
Scheme 58: Multicomponent reaction of arynes, *β*-keto sulfones, and Michael acceptors

Huang and co-workers reported a transition-metal-free, novel multicomponent reaction of arynes, *β*-keto sulfones **129** and Michael acceptors (Scheme 58). The outcome of this novel multicomponent reaction is polysubstituted naphthols **130** and naphthalenes which have a huge significance in medicinal chemistry. The reaction proceeds via a successive nucleophilic addition of *β*-keto sulfones on arynes followed by a Michael addition. Furthermore, ring closure-elimination provides desired compounds in moderate yields.[64]



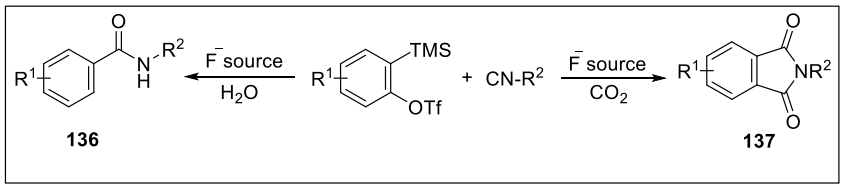
Scheme 59: MCR of arynes, formamide, and active methylene compounds

Miyabe *et al*. described the competent process for the synthesis of the coumarin derivative via multicomponent reaction of arynes, DMF and β-keto esters **131** (Scheme 59). The reaction proceeds through the insertion of aryne into C=O bond of formamide and leads to reactive intermediate which is further trapped by active methylene containing keto ester furnishing coumarin **132** derivatives in good yields. The methodology was effectively utilized in the synthesis of a neuropeptide YY5 receptor antagonist.[65]



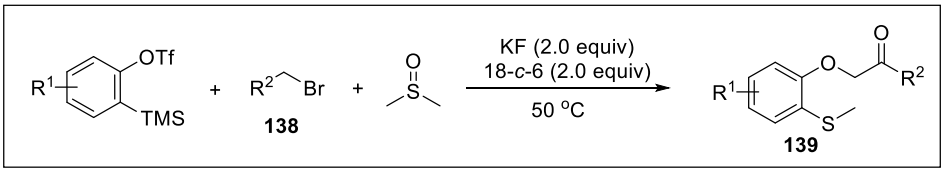
Scheme 60: Synthesis of iminoisobenzofurans and *o*-ketobenzamides

Aryne mediated Passerini multicomponent reaction and its synthetic utility was demonstrated by the Stoltz and coworkers. Phenoxy iminoisobenzofurans are achieved by the coupling reaction of aryne, tert-butyl isocyanide **133**, and phenyl acetate **134** under milder reaction condition (Scheme 60). They have extended this protocol to synthesize various *o*-ketobenzamide **135** and iminoindenones in excellent yields.[66]



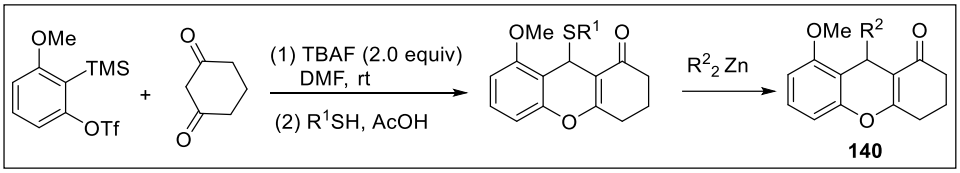
Scheme 61: MCR Involving arynes, isocyanides, and CO_2

Biju *et al.* synthesized pharmaceutically important compounds phthalimides and benzamides selectively using multicomponent reactions of arynes, isocyanides with either water or carbon dioxide (Scheme 61). Selectivity in products formation was controlled by the third component of the reaction**.** When the MCR has CO_2 as the third component, N-substituted phthalimides **137** formed in good yields while MCR having water as third component instead of CO_2, furnished benzamides **136**. [67]



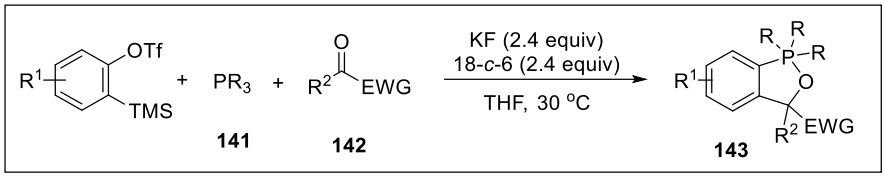
Scheme 62: Synthesis of aryl methyl thioethers via MCR of aryne

Xiao et al. described the first report on the utilization of DMSO in the multicomponent reaction of aryne. The multicomponent reaction of aryne, DMSO and α-bromo carbonyl compounds **138** was stimulated by the insertion reaction of aryne with DMSO to synthesize biologically important multisubstituted aryl methyl thioethers **139**. In this reaction, DMSO works as a source of oxygen and methylthiol. Remarkably, this reaction provides a one-pot and milder path for the formation of two new C−O bonds and C−S bond.[68]



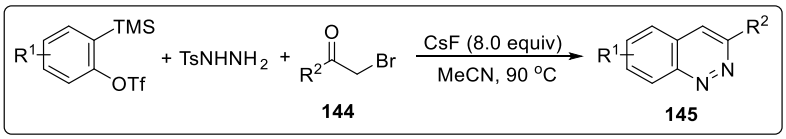
Scheme 63: Synthesis of xanthene derivatives using MCR

Miyabe *et al.* developed a cascade multicomponent reaction of arynes with DMF and active methylenes compounds to construct xanthene analogs **140** (Scheme 63). This multicomponent reaction involves the formation of benzoxetene from the insertion reaction of aryne and DMF, which further reacted with di-keto compound to form tricyclic structure. Moreover, nucleophilic attack of thiophenol on tricyclic structure and alkylation with dialkyl zinc reagent furnish desired compound in good yields.[69]



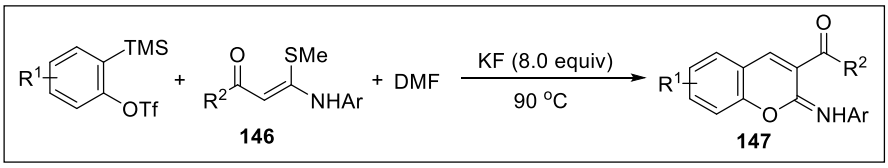
Scheme 64: Preparation of benzoxaphospholes by MCR of aryne

Organophosphorus compounds have vital application in agrochemical industries. Herein, Biju and co-workers established a transition-metal-free synthesis of phosphorus heterocycles **143** via multicomponent reaction of phosphines **141**, activated carbonyl compounds **142** and aryne. The reaction proceeds through 1,3-dipolar addition fashion, where nucleophilic addition of phosphine on aryne generates carbanion on aryl ring which further undergoes nucleophilic addition with carbonyl compound to form enolate, which on intramolecular cyclization, furnished the expected compound in good yields.[70]



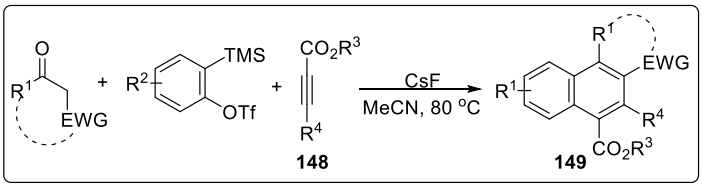
Scheme 65: Access to cinnolines via MCR

Wu and co-workers illustrated the unique protocol for the synthesis of bioactive cinnoline derivatives (Scheme 65). Cinnolines **145** are known for their inhibitory activity against CSF-1R, ulceration, and inflammation. The metal-free multicomponent reaction of arynes, tosyl hydrazine, and α-bromo ketones **144** leads to the formation of two C−N bonds and one C−C bond in a single step and one-pot fashion.[71]



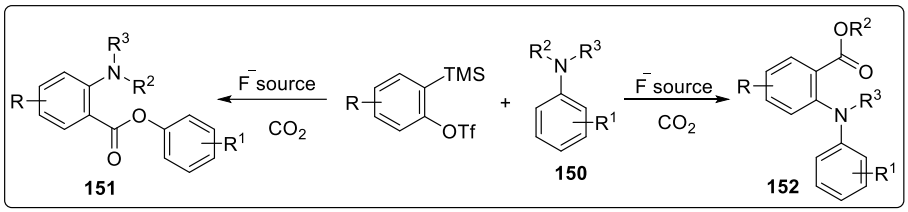
Scheme 66: MCR involving arynes, N,S-Ketene acetals, and DMF

The 2-aryliminochromene skeleton is found in many of drugs and natural products which is useful for the treatment of cancer and Alzheimer's disease. Li and co-workers developed a transition-metal-free, three-component coupling reaction of arynes, *N*, *S*-keteneacetals **146**, and DMF (Scheme 66). The process ensues smoothly via [2+2] cycloaddition between aryne and DMF followed by [4+2] cycloaddition reaction with *N*, *S*-keteneacetals giving arylimino-2H chromene-3-carboxamides **147** in excellent yields.[72]



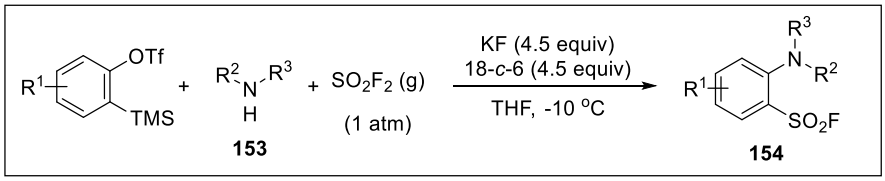
Scheme 67: MCR of arynes with ketones and alkynoates to form naphthalenes

Shu *et al.* demonstrated the multicomponent reaction of arynes, ketones, and alkynoates **148** to provide naphthalene derivatives **149** in good to moderate yields (Scheme 67). The process involved [2 + 2 + 2] cycloaddition reaction to build-up multiple C−C bonds in a single step which leads to the synthesis of varyingly substituted naphthalene derivatives. This method has been utilized for the synthesis of 1-phenanthrenol derivatives.[73]



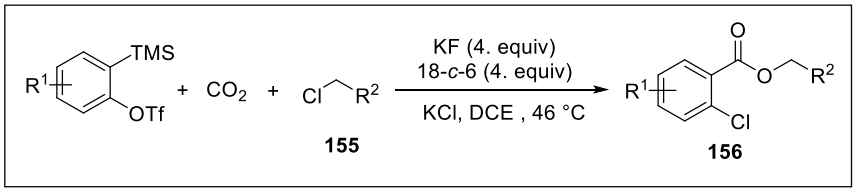
Scheme 68: MCR Involving arynes, aromatic tertiary amines, and CO_2

Once again Biju and co-workers elaborated their interest in aryne chemistry via synthesis of 2-aminoaryl benzoates using aryne. The multicomponent reaction of arynes, aromatic tertiary amines **150**, and CO_2 (Scheme 68) under the simple reaction condition, provided bi-functionalized arenes in good yields. Electronic natures of the aromatic amines are responsible for the selectivity in products. The amines having electron-donating or neutral groups undergo nitrogen to oxygen alkyl group migration to afford 2-arylamino benzoates **152**. While the electron-deficient amines furnished 2-aminoaryl benzoates **151** via the aryl to aryl amino group migration similar to the Smiles rearrangement.[74]



Scheme 69: Synthesis of 2-aminoarenesulfonyl fluoride from aryne

Pronounced chemo selectivity and comparatively good stability make aryl sulfonyl fluorides as a unique reagent in the drugs and natural products discovery. Kim's group developed a facile and catalyst-free method for the synthesis of aryl sulfonyl fluorides from the multicomponent reaction of aryne, amine **153** and sulfuryl fluoride. Nucleophilic addition of secondary amine on aryne intermediate leads to the generation of carbanaion, which subsequently quench by electrophile sulfonyl fluorides to give bi-functionalized arenes in good yield. The generality of this protocol was demonstrated by constructing varyingly substituted 2-aminoarenesulfonyl fluoride derivatives **154** in good to excellent yields.[75]



Scheme 70: Synthesis of *o*-chloro benzoates via MCR reaction of aryne

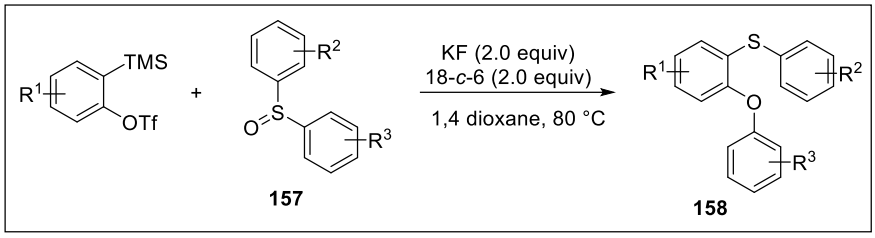
o-Chloro benzoates are privileged structure found in many pharmaceuticals and agrochemicals. Jiang et al. developed an efficient and transition-metal free multicomponent process for the synthesis of *o*-chloro benzoates **156**. This three-phase four-component (3P-4CR) coupling reaction comprises KCl, arynes, chloroalkanes **155** and CO_2 components. The outcome of reaction provides three diverse bonds in a one-pot manner, which lead to the synthesis of various *o*-chloro benzoates in good yields.[76]

1.5 Molecular rearrangement to access bi-functionalized arenes:

There are many reports on the aryne mediated molecular rearrangement which elaborate significance of aryne in the field of synthetic chemistry. The rearrangements which are anticipated by arynes provide the various bi-functionalized arenes in good yields, which lead to

the synthesis of biologically important molecules. Representative aryne mediated molecular rearrangements are listed below.

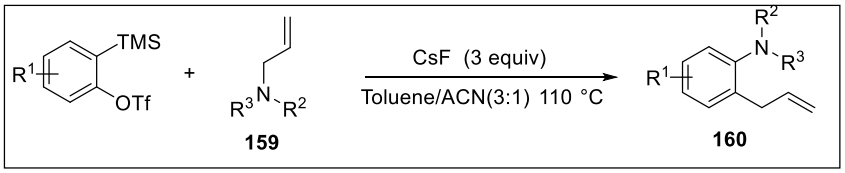
1. Aryne facilitated oxythiolation:



Scheme 71: Synthesis of *o*-arylthio-functionalized diaryl Ethers

Hosoya and co-workers developed a proficient method for the synthesis of *o*-aryl thio-substituted diaryl ethers. The reaction between arynes and diaryl sulfoxides **157** at high temperature features oxythiolation of aryne followed by migratory O-arylation which results in a rearranged product having two new carbon–oxygen and carbon–sulfur bonds. This reaction has broad functional group tolerance and provides vastly substituted 1,2-bi-substituted arenes **158** in good yields.[77]

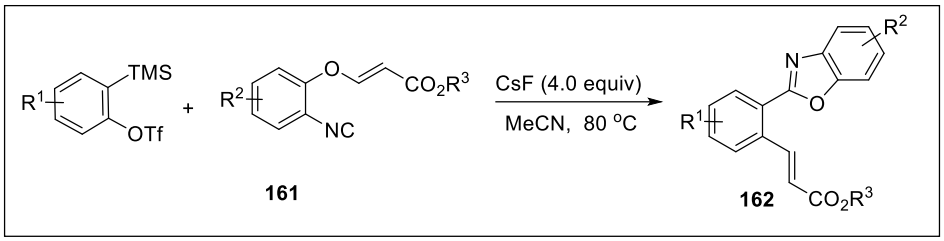
2. Claisen rearrangement:



Scheme 72: Aza-Claisen rearrangement

Commonly Claisen rearrangements need high reaction temperature or Lewis acids for the completion. Greaney *et al.* established a novel and comparatively milder method for the synthesis of the various 2-allyl anilines. The reaction of aryne with allyl aniline originate by the nucleophilic addition of tertiary allylic amine **159** on aryne to generate 1,3 zwitterionic

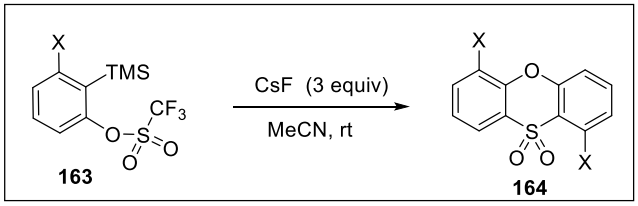
intermediate, which further get protonated and underwent aza-Claisen rearrangement to furnish varyingly substituted 2-allyl anilines **160** in good yields.[78]



Scheme 73: Claisen reaction of 2-isocyanophenyloxyacrylate and aryne

The present method is reported by Li *et al*. where the vicinal difunctionalization of arenes is achieved by the reaction of 2-isocyanophenyloxyacrylate **161** and aryne under the transition-metal-free, milder protocol. This process involved nucleophilic addition of on aryne followed by intramolecular Michael addition to providing enolate which on further rearrangement furnish arene having benzoxazole and an olefin substitution at vicinal position **162**.[79]

3. Aryne thia-Fries rearrangement:

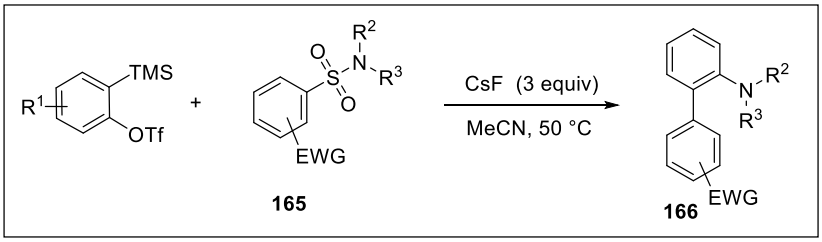


Scheme 74: Synthesis of phenoxathiin-dioxides

Greaney and co-workers established the facile method for the synthesis of phenoxathiin-dioxides via thia-Fries rearrangement of arynes, which is generated from the Kobayashi precursor 2-(trimethylsilyl) aryl trifluoromethanesulfonate **163**. Electron withdrawing group on the 3-position of aryne precursors has considerable influence on the reaction outcomes. This anionic thia-Fries rearrangement began with cleavage of C–Si bond followed by thia-Fries reaction of

the phenolate ion which on cyclization via elimination of –CF3 group of trifluoromethanesulfonate provides respective phenoxathiin-dioxide derivatives **164** in moderate to good yields.[80]

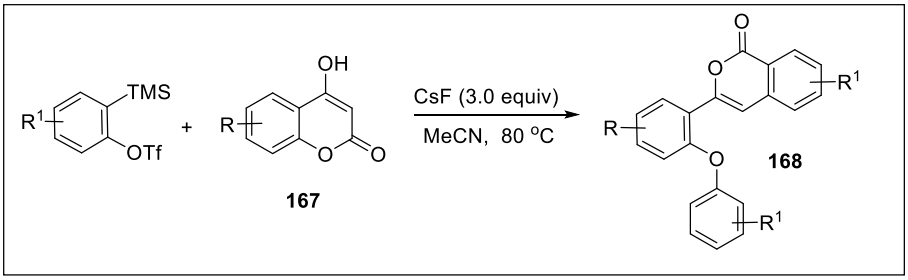
4. Aryne Truce-Smiles rearrangement



Scheme 75: Synthesis of 2-amino-biaryls

The importance of biaryl motif in materials, medicinal, and agrochemicals chemistry is well explored. Greaney group disclosed a transition-metal-free facile procedure for the synthesis of functionalized 2-amino-biaryls using arynes. Particularly, the reaction of aryl sulfonamides **165** with arynes initiates with nucleophilic addition of sulfonamides on aryne intermediate, followed by Truce–Smiles rearrangement provides Meisenheimer complex. Extrusion of sulfur dioxide from the Meisenheimer complex, furnished the sterically hindered, varyingly substituted biaryls **166** in good yields.[81]

5. Aryne prompted rearrangement of hydroxyl coumarin to Isocoumarin:



Scheme 76: Rearrangement of hydroxyl coumarin to isocoumarin via aryne

The extensive utilization of 3-substituted isocoumarin in the field of pharmaceuticals and agrochemicals make their synthesis via milder and efficient protocols is of enduring interest. In this context, Gogai and co-workers demonstrated an operationally simple method to form bi-functionalized arenes isocoumarin through multiple cleavages of C−O and C−C bond cleavage as well as the formation of new C−O and C−C bond. This one-pot, single-step rearrangement provided various 3-substituted isocoumarin **168** in excellent yields.[82]

1.6 Conclusion:

Recent extraordinary achievement in the field of aryne chemistry established aryne as the designated part of the realm of organic chemistry. The enormous reactivity of aryne intermediate has been utilized for the synthesis of highly complex organic structures. The strength of aryne to construct carbon–carbon, and carbon–heteroatom bonds using transition-metal-free and comparatively milder reaction conditions makes arynes as a precious asset in the field of synthetic organic chemistry. The leading transformation of arynes in the form of insertion reaction, annulation reactions, multicomponent reactions, pericyclic reactions have led to the formation of various functionalized heterocycles, 1,2-bi-functionalized arenes, and biologically active natural products, which have vast application in various fields of chemistry. Owing to the usefulness and enormous applications of aryne chemistry, arynes have emerged as a fascinating tool in organic chemistry. Presently, prominence of aryne in organic chemistry is successfully increasing and guiding to astonishing developments. However, there is a great opportunity to elaborate aryne reactivity in the enantioselective transformation. Additionally, challenges assisted with aryne are the high cost and low atom economy of aryne precursor as well as lack of regioselectivity in many transformations where unsymmetrical aryne precursor was used. The above exciting conversions using arynes have increased our interest in aryne chemistry, which

led us to think of novel methods for the synthesis of complex architectures. In this perspective, we deliberate to develop efficient and novel methodologies using aryne chemistry, which would be further utilized in the total synthesis of drugs and natural products.

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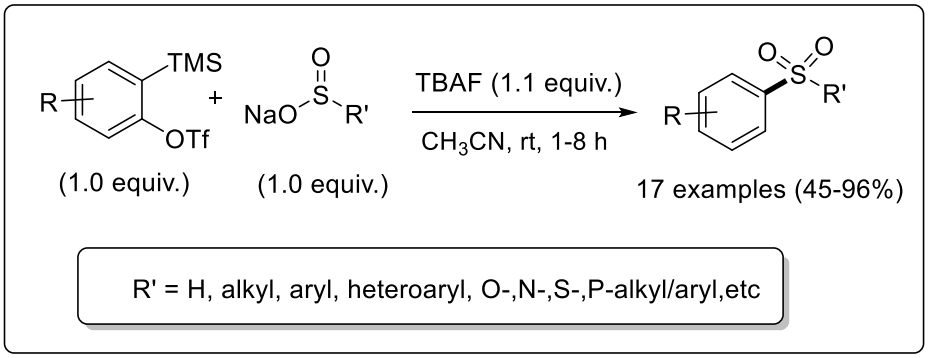
Chapter 2

Transition-metal-free double functionalization of arene via aryne to access sulfones and xanthones

Section 1: Transition-Metal-Free Sulfonylation of Arenes via Aryne

2.1.1. Abstract:

This section includes the development of novel transition-metal-free C–S bond-forming method using aryne chemistry. This section demonstrates an efficient transition-metal-free process, wherein a broad range of alkyl/aryl/heteroaryl sodium sulfinates react with varyingly substituted aryne precursors (*o*-silyl aryl triflates) under mild reaction conditions to afford diverse sulfones in good to excellent yields.



This novel work has been published in the journal *Org. Lett*. **2014**, *16*, 3836. It was the most read article in July 2014. It is also highlighted in the organic chemistry portal.

2.1.2. Introduction:

Sulfones are highly recognized the class of organic synthetic chemistry for their immense biological, material[1] and synthetic applications. Sulfones are most prevailing pharmacophore in medicinal chemistry[2]. They are ubiquitous in many marketed drugs which have profound medicinal activities. As shown in Figure 1, eletriptan (used for migraine), Casodex (used for prostate cancer), dapsone (for leprosy), vismodegib (for skin cancer) and many more drugs have sulfones as active pharmacophore. Furthermore, they are also found in the agrochemicals[3]. Mesotrione, pyroxasulfone, and cafenstrole are the well-known agrochemicals having sulfone unit. Moreover, they are also utilized as multifaceted building blocks for various transformations, which include Ramberg–Bäcklund reaction[4] and Julia

olefination[5]. Additionally, sulfones have used an intermediate for the synthesis of various important compounds such as oxazoles, imidazoles, and quinolines. [6]

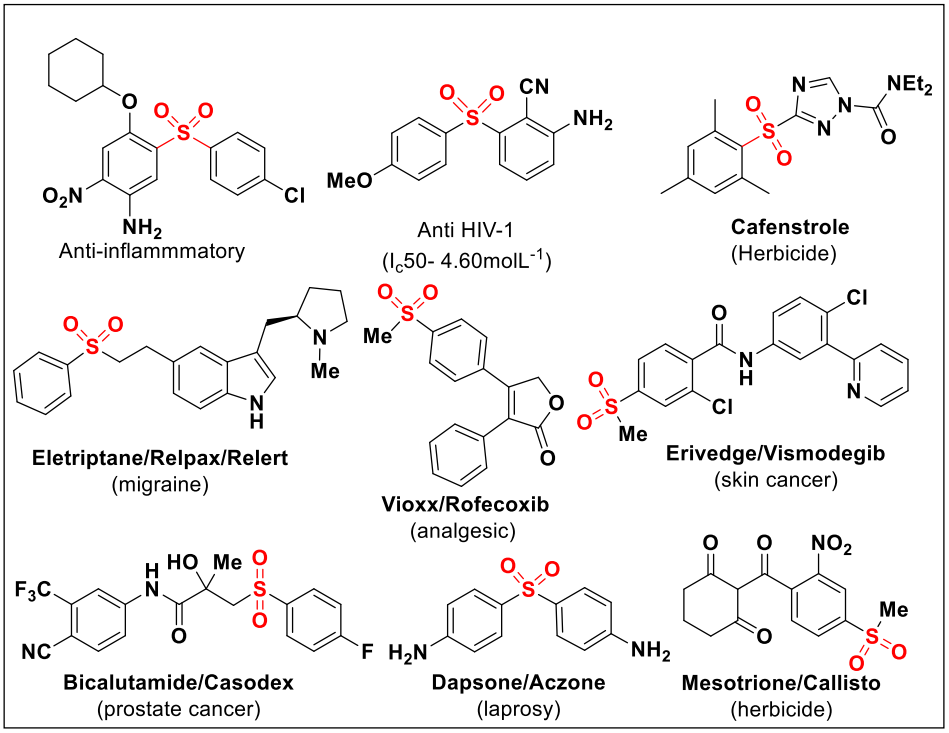


Figure 1. Sulfone containing drugs and natural products

In this perspective, the development of efficient processes for the synthesis of sulfone has been a subject of enduring interest due to their compelling synthetic utility and substantial biological as well as material applications

2.1.3. Review Literature:

Due to enormous capability and versatility in the field of organic chemistry, sulfones evolved as a fascinating target for the synthetic chemist. Numerous procedures for the synthesis of sulfones have been reported, which comprise the oxidation of sulfides and sulfoxides, sulfonylation of arenes, reaction between organomagnesium and organolithium compounds with sulfonate esters, oxidative coupling of aryl boronic acids with aryl sulfonyl chlorides or other Pd- and Cu-catalyzed coupling reactions.[7-12] Recent advancement shows that many research groups are involved in the synthesis of sulfones. The methods by Jiang,[7] Mascitti and Toste[8a] as well as Willis[9a] require transition-metal-catalyst, whereas, the methods by

Manolikakes,[10a,b] Kumar[10c,] and Willis[9c] are transition-metal free. Though these methods are quite competent, they are associated with the considerable limitation like harsh reaction conditions, low substrate scope and multistep synthesis of starting materials.

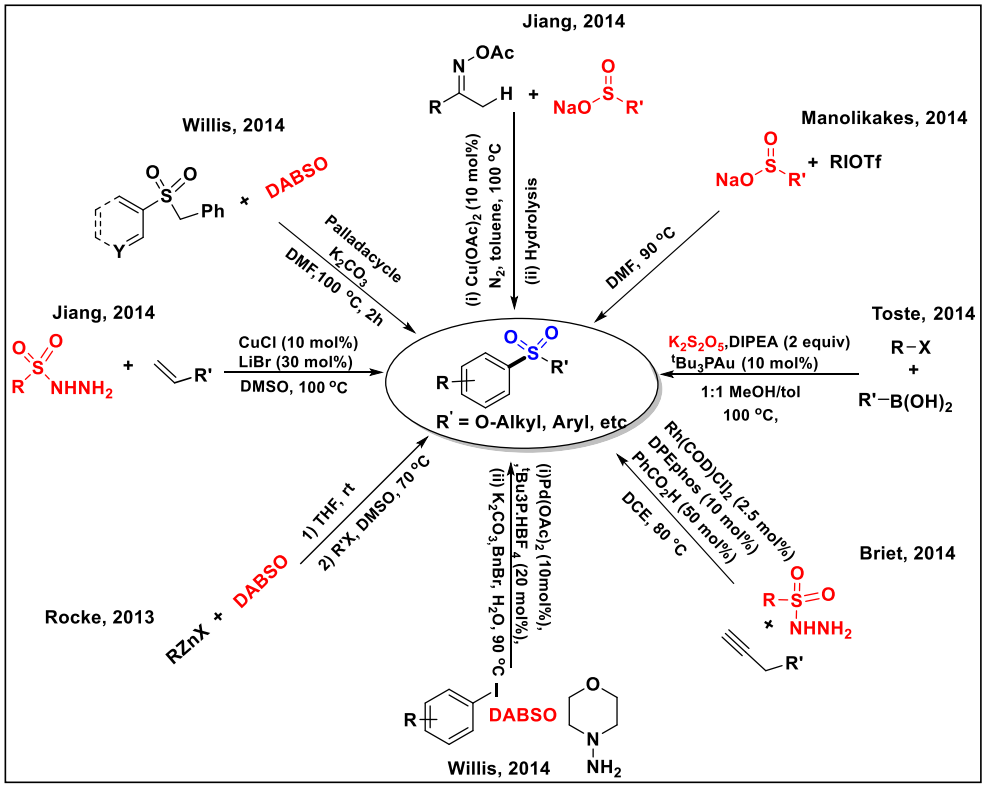


Figure 2: Previous reports on the preparation of sulfones

2.1.4. Origin of Present Work:

The literature reports concluded that the previously developed protocols for the synthesis of sulfones are struggled to get high regioselectivity as well as high versatility in the synthesis of sulfones. Furthermore, most of the reported methods for the synthesis of sulfones demands transition- metals and expensive reagents.

2.1.5. Objective:

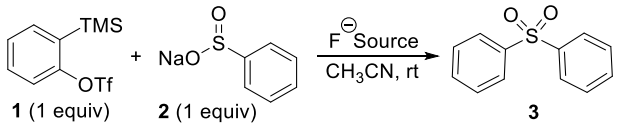
Arynes have been successfully used for the development of several useful synthetic methodologies[12] and total synthesis of natural products.[13] There are several methods available for aryne generation, but the Kobayashi's protocol[14] using *o*-silyl aryl triflate and fluoride source provides an excellent opportunity to demonstrate the application of arynes in various

useful synthetic methodologies. New efficient methods for the synthesis of sulfones are always sought after. In continuation of our interest in the development and application of aryne methodologies[15], we envisaged that the high reactivity of arynes could be explored to access synthetically useful and biologically important sulfone derivatives. In this context, we report herein facile access to various aryl sulfones via arynes.

2.1.6. Results and Discussion:

The protocol was first optimized using *o*-silyl aryltriflate **1** and sodium benzenesulfonate **2** (Table 1). Three different commonly used fluoride sources were screened under various conditions. Though CsF alone provided diaryl sulfone **3** in good yield (entry 1), it was required in large excess. Use of phase transfer catalyst 18-crown-6-ether reduced the required amount of CsF to 2 equivalents keeping almost the same yield. Further decrease in the amount of CsF reduced the yield drastically. The combination of KF (2.0 equiv) and 18-crown-6-ether provided sulfone **3** in lower yield than obtained under similar conditions using CsF. Use of TBAF as a fluoride source, however, proved to be fruitful and the final conditions were optimized, wherein the treatment of *o*-silyl aryltriflate **1** (1 equiv) and sodium sulfinate **2** (1 equiv) with TBAF (1.1 equiv) at room temperature furnished the desired sulfone **3** in excellent yield (entry 8). We believe that the high yields and faster reaction could be due to the effect of TBAF acting as phase transfer catalyst in addition to being an efficient fluoride source. The generality and scope of the developed protocol to obtain diaryl sulfones were demonstrated by varying *o*-silyl aryl triflates (Scheme 1).

Table 1: Optimization studies[a]

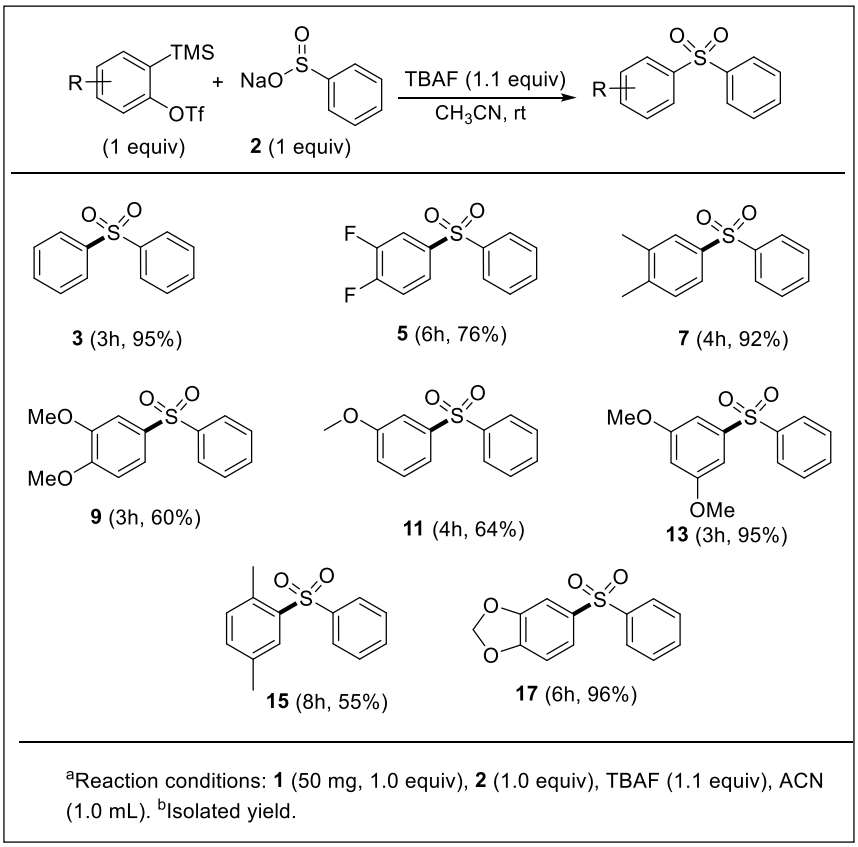


entry	F⁻ source (equiv)	additive[b]	time	yield
1	CsF (5.5)	-	6.0 h	86%
2	CsF (2.5)	A	6.0 h	88%
3	CsF (2.0)	A	7.0 h	82%
4	CsF (1.5)	A	7.0 h	56%
5	KF (2.0)	A	6.0 h	67%
6	TBAF (2.5)	-	1.5 h	95%
7	TBAF (1.5)	-	2.5 h	94%
8	**TBAF (1.1)**	**-**	**3.0 h**	**94%**
9	TBAF (1.0)	-	5.0 h	72%

[a]Reactions were performed on a 25 mg scale of **1** in a solvent (1.0 mL). [b] (5 mol%)18-crown-6 was used with KF.

The synthesis of diaryl sulfone **3** worked equally well on a large scale (entry 1). Triflate **4** containing two fluorine atoms also provided the corresponding sulfone **5** in good yield (entry 2). The substrates with two alkyl substituents *meta* (triflate **6**) and *ortho* (triflate **8**) to the reaction center furnished corresponding sulfones **7** and **9** respectively, but it is interesting to note that the presence of both methyl substituents away from the reaction center (entry 3) enables easy attack of nucleophile thus providing excellent yield in shorter reaction time. However, in the case of triflate **8,** the steric hindrance probably increases the reaction time and reduces the yield.

Scheme 1: Preparation of sulfones from various silyl triflates[a,b]

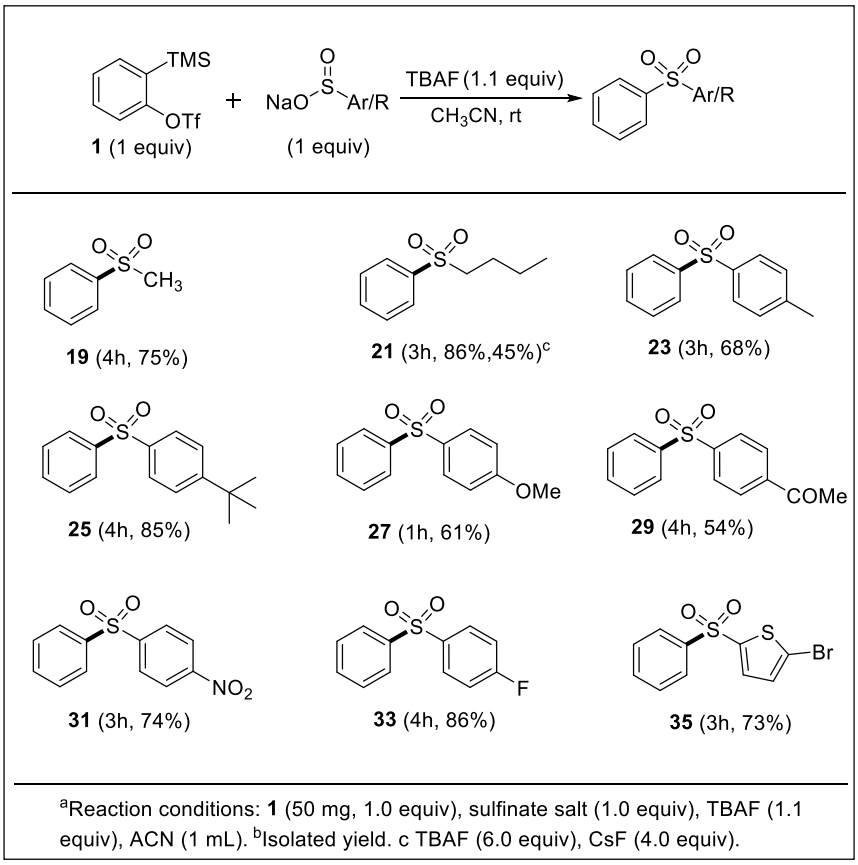


[a]Reaction conditions: **1** (50 mg, 1.0 equiv), **2** (1.0 equiv), TBAF (1.1 equiv), ACN (1.0 mL). [b]Isolated yield.

In the case of unsymmetrically substituted silyl triflate **10,** excellent regioselectivity was observed to obtain only the *meta* substituted diaryl sulfone **11**. Highly electron-rich silyl triflates **12**, **14** and **16** furnished the desired sulfones **13**, **15** and **17** respectively in good to excellent yields.

The scope of the protocol was also established by varying sodium sulfinates (Scheme 2). All the sodium sulfinates were prepared easily by using literature procedures.[12a] Methyl sodium sulfinate **18** furnished the alkyl-aryl sulfone **19** in good yield. We could obtain sulfone **21** in only 45% yield from butyl sodium sulfinate **20** using TBAF but the very good yield was observed with CsF.

Scheme 2: Preparation of sulfones from various sulfinates[a,b]



[a]Reaction conditions: **1** (50 mg, 1.0 equiv), sulfinate salt (1.0 equiv), TBAF (1.1 equiv), ACN (1 mL). [b]Isolated yield. c TBAF (6.0 equiv), CsF (4.0 equiv).

The reason for this observation is obscure. The alkyl-substituted aryl sodium sulfinates **22** and **24** reacted smoothly to furnish diaryl sulfones **23** and **25** respectively in good yields. The sodium sulfinate **26** having an electron-donating group requires much less reaction time as compared to the sodium sulfinate **28** and **30** having electron-withdrawing groups to give corresponding sulfones **27**, **29** and **31** respectively. Fluorine substituted sodium sulfinate provides diaryl sulfone **33** in very good yield. Similar to the alkyl/aryl sodium sulfinates the heteroaryl sodium sulfinate **34** also worked well to furnish aryl-heteroaryl sulfone **35** having a labile bromine substituent, thus indicating the mildness of the developed protocol.

A plausible mechanism for this transformation has been depicted in figure 3. In the presence of fluoride source, generation of aryne intermediate is taking place. This reactive aryne intermediate is trapped by the nucleophile sodium sulfinate salt, which results in the

formation of carbon-sulfur bond and carbanion on aryl ring of aryne. This carbanion is quenched by water or proton of acetonitrile to furnish sulfones.

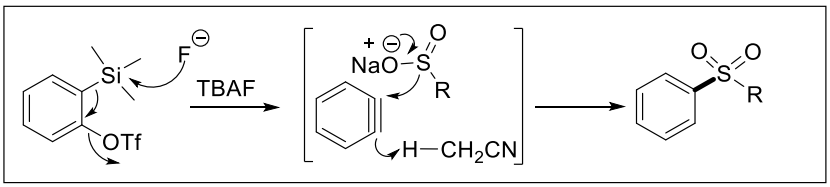
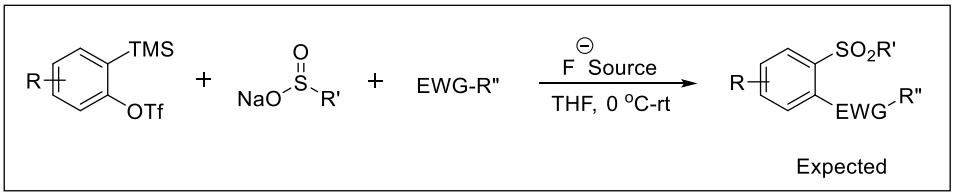


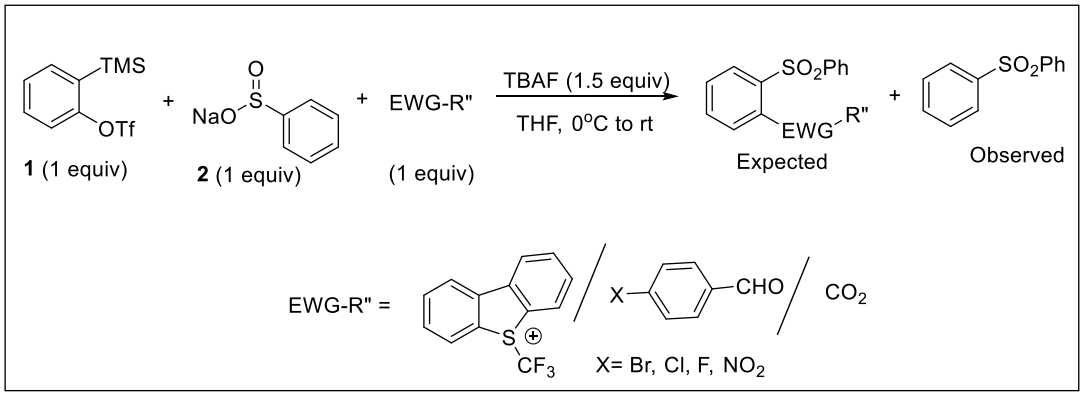
Figure 3. Plausible reaction mechanism

Attempted Multicomponent Reactions Leading to Difunctionalization of Arenes:



Scheme 3: MCR using aryne, sodium sulfinate salt and EWG containing substrates.

To increase the significance of our sulfonylation protocol, we have attempted to utilize this protocol into the synthesis of difuctionalized arenes. We performed a multicomponent reaction of aryne with sodium sulfinic acid salts and substrates containing electron-withdrawing groups by applying optimized sulfonylation condition. Unfortunately, our protocol failed to furnish bi-functionalized arenes containing sulfones. We reasoned that the moisture in sulfinic acid salt, as well as hydrated TBAF, might be quenching the carbanion formed on aryl, which make the reaction to stop at mono-functionalized arenes. Hence further reaction with substrate containing electron withdrawing groups with sulfonylated aryl didn't work. We have obtained the same result with other fluoride sources such as KF and CsF.



2.2.7 Conclusion:

In conclusion, we have demonstrated an efficient, transition-metal-free approach for the synthesis of aryl sulfones starting from easily accessible alkyl/aryl sodium sulfinates and *o*-silyl aryl triflates. The developed protocol is mild, robust and avoids the use of excess reagents or additives. It is capable of delivering a diverse array of sulfones such as diaryl sulfones, aryl-alkyl sulfones as well as aryl-heteroaryl sulfones. It could also be extended to the double functionalization of arynes. Application of this C-S bond-forming methodology for the synthesis of complex bioactive sulfone heterocycles and existing drugs is underway in our laboratory.

Our work presented in this chapter and publication has been cited 62 times in the literature.

2.2.8 Experimental Procedure:

[A] Typical Experimental Procedure for the Preparation of Sodium Sulfinates

4-Methoxybenzenesulfinic acid sodium salt (26) was prepared by heating of sodium sulfite (2.5 g, 20 mmol), 4-methoxybenzenesulfonyl chloride (2.06 g, 10 mmol) and sodium bicarbonate (1.68 g, 20 mmol) in water (9.6 mL) at 70-80 ^{o} C for 4 h. After cooling to room temperature, water was removed under vacuum and the residue was extracted in ethanol. Recrystallization from ethanol furnished sodium sulfinate 26 (1.34 g, 67%) as a white solid.[10a, 11d]

[B] General Experimental Procedure for the Sulfonylation

To a round-bottom flask containing TBAF (1.10 equiv) and sodium sulfinate (1.0 equiv) was added *o*-silylaryl triflate (1.00 equiv) in acetonitrile (1 mL) at room temperature, 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 purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether to afford the corresponding diaryl/aryl-alkyl/aryl-heteroaryl sulfones in good to excellent yields.

[C] Typical Experimental Procedure for the preparation of compound 3:

To a round-bottom flask containing TBAF (581 mg, 1.84 mol, 1.10 equiv) and aryl sulfinic acid sodium salt (275 mg, 1.67 mol, 1.0 equiv) was added o-silyl aryl triflate (500 mg, 1.67 mol, 1.0 equiv) in acetonitrile (10 mL) at room temperature, under Argon atmosphere. The reaction mixture was stirred at room temperature and the progress was monitored by TLC. After completion of the reaction (3 h), acetonitrile was removed on rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (3:17) to afford the sulfone 3 (260 mg, 95%) as a white solid.

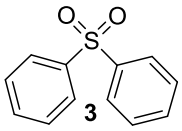
[D] Typical Experimental Procedure Using CsF: (Butylsulfonyl)benzene (21)

To a round-bottom flask containing CsF (101 mg, 670 mmol) butyl sulfinic acid sodium salt (36.2 mg, 251 mmol) and 18-Crown-6-ether (4.4 mg, 16.7 mmol) was added o-silyl aryl triflate (50 mg, 167.5 mmol) in acetonitrile (2 mL) at room temperature, under Argon atmosphere. The reaction mixture was stirred at room temperature and the progress was monitored by TLC. After completion of the reaction (3 h), acetonitrile was removed on rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (1:4) to afford the sulfone 21 (29 mg, 86%) as a yellow thick oil.

Characterization Data of Compounds:

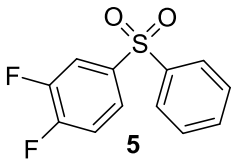
All reactions were performed on 50 mg scale of o-silyl aryl triflates

1-Phenyl (sulfonyl) benzene (**3**)[10a]



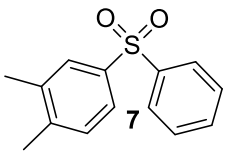
Reaction Time: 3 h; R*f*: 0.3 (1:4 EtOAc: Pet Ether); White solid; 34 mg, 94%; mp 120 ^{o}C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.88 (d, *J* = 8.0 Hz, 4H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 4H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 141.6, 133.2, 129.3, 127.7; **HRMS-ESI** (*m/z*) calcd $[C_{12}H_{10}O_2S+ H]^+$: 219.0474, found : 219.0474.

1,2-Difluoro-4-(phenylsulfonyl)benzene (**5**)[16e]



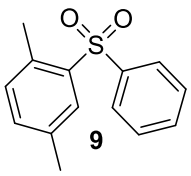
Reaction Time: 6 h; R*f*: 0.3 (1:4 EtOAc:Pet Ether); White solid; 28.9 mg, 76%; mp 179-181 ^{o}C **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.75-7.65 (m, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.18-7.28 (m, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 153.6 (dd, *J* = 257.8, 12.4 Hz), 150.3 (dd, *J* = 255.9, 17.2 Hz) , 140.8, 138.5 (t, *J* = 7.6 Hz), 133.7, 129.5, 127.7, 124.8 (q, *J* = 3.84 Hz), 118.4 (d, *J* = 18.2 Hz), 111.7 (d, *J* = 18.2 Hz); **HRMS-ESI** (*m/z*) calcd $[C_{12}H_8O_2SF_2Na]^+$: 277.0105 found: 277.0100.

1,2-Dimethyl-4-(phenylsulfonyl)benzene (**7**)[16c]



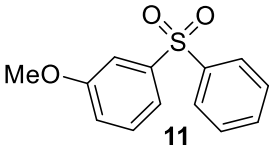
Reaction Time: 4 h; R*f*: 0.3 (1:4 EtOAc:Pet Ether); White solid; 34.7 mg, 92%; mp 114-116 ^{o}C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.86 (d, *J* = 7.3 Hz, 2H), 7.63-7.58 (m, 2H), 7.50-7.38 (m, 3H), 7.17 (s, 1H), 2.23 (s, 3H), 2.22 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 142.9, 142.1, 138.7, 138.1, 132.9, 130.4, 129.2, 128.4, 127.5, 125.2, 20.0, 19.8; **HRMS-ESI** (*m/z*) calcd $[C_{14}H_{14}O_2S+ H]^+$: 247.0787, found : 247.0786.

1,4-Dimethyl-2-(phenylsulfonyl)benzene (**9**)[10a]



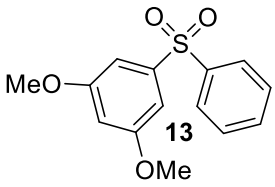
Reaction Time: 8 h; R*f*: 0.3 (1:4 EtOAc:Pet Ether); White solid; 20.7 mg, 55%; mp 111-113 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.98 (s, 1H), 7.79 (d, *J* = 7.6 Hz,2H), 7.52-7.38 (m, 3H), 7.21 (d, *J* = 7.6 Hz, 1H),7.04 (d, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 141.5, 138.4, 136.5, 134.8, 134.3, 132.9, 132.6, 129.7, 128.9, 127.6, 20.9, 19.7; **HRMS-ESI** (*m/z*) calcd $[C_{14}H_{14}O_2S+ H]^+$: 247.0787, found: 247.0786.

1-Methoxy-3-(phenylsulfonyl)benzene (**11**) [2b]



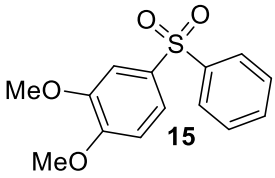
Reaction Time: 4 h; R*f*: 0.3 (1:4 EtOAc:Pet Ether); White solid; 24.2 mg, 64%; mp 82 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.88 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.46-7.40 (m,3H), 7.38 (t, J = 2.2 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.01 (dd, J = 2.2, 2.2 Hz, 1H), 3.77 (s, 3H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 160.0, 142.7, 141.5, 133.2, 130.4, 129.5, 127.6, 119.9, 119.5, 112.2, 55.7; **HRMS-ESI** (m/z) calcd $[C_{13}H_{12}O_3S + H]^+$: 249.0580, found: 249.0579.

1,3-Dimethoxy-5-(phenylsulfonyl)benzene (**13**)



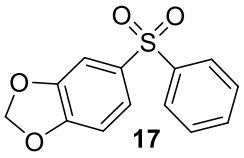
Reaction Time: 4 h; R*f*: 0.2 (1:4 EtOAc:Pet Ether); Yellow solid; 33.4 mg, 86%; mp 92-94 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.87 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.9 Hz, 2H), 6.99 (d, J = 2.8 Hz, 2H), 6.52 (t, J = 2.5 Hz, 1H), 3.74 (s, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 161.2, 143.3, 141.5, 133.2, 129.2, 127.6, 105.5, 105.4, 55.80; **HRMS-ESI** (*m/z*) calcd $[C_{14}H_{14}O_4S+ H]^+$: 279.0686, found : 279.0682.

1,2-Dimethoxy-4-(phenylsulfonyl)benzene (**15**)[16g]



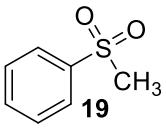
Reaction Time: 3 h; R*f*: 0.4 (3:7 EtOAc:Pet Ether); Red solid; 23.3 mg, 60%; mp 118-119 ^{o}C; ^{1}H **NMR (400 MHz, CDCl$_3$)** δ 7.85 (d, J = 7.3 Hz, 2H), 7.54-7.40 (m, 4H), 7.32 (s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 153.0, 149.3, 142.2, 133.0, 132.9, 129.2, 127.3, 121.9, 110.8, 109.9, 56.3, 56.2; ESI-Mass (M + Na) 301. **HRMS-ESI** (*m/z*) calcd $[C_{14}H_{14}O_4S+ H]^+$: 279.0686, found : 279.0678.

5-(Phenylsulfonyl)benzo[d][1,3]dioxole (**17**)[16f]



Reaction Time: 6 h; R*f*: 0.2 (1:4 EtOAc:Pet Ether); White solid; 37 mg, 96%; mp102-104 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.84 (d, J = 7.3 Hz, 2H), 7.51-7.40 (m, 4H), 7.24 (d, J = 1.8 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.97 (s, 2H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 151.9, 148.4, 142.0, 134.9, 133.0, 129.2, 127.4, 123.6, 108.5, 107.8, 102.4; **HRMS-ESI** (m/z) calcd $[C_{13}H_{10}O_4S +H]^+$: 263.0373, found: 263.0371.

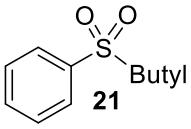
(Methylsulfonyl)benzene (**19**)[16b]



19

Reaction Time: 4 h; R*f*: 0.2 (1:4 EtOAc:Pet Ether); Yellow solid; 19.6 mg, 75%; mp 256-258 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.89 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 2.99 (s, 3H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 140.6, 133.7, 129.4, 127.3, 44.5; **HRMS-ESI** (m/z) calcd $[C_7H_8O_2S + H]^+$: 157.0318 found: 157.0319.

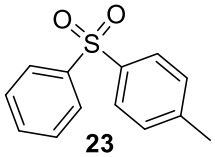
(Butylsulfonyl)benzene (**21**)[16a]



21

Reaction Time: 3 h; R*f*: 0.5 (1:4 EtOAc:Pet Ether); thick oil; 28.9 mg, 86%; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.84 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 1.67-1.58 (m, 2H), 1.38-1.27 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 139.2, 133.6, 129.2, 128.1, 56.1, 24.6, 21.5, 13.5; **HRMS-ESI** (m/z) calcd $[C_{10}H_{14}O_2S + H]^+$: 199.0787 found: 199.0788.

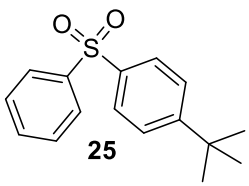
1-Methyl-4-(phenylsulfonyl)benzene (**23**)[10a]



23

Reaction Time: 3 h; R*f*: 0.5 (1:4EtOAc:Pet Ether); White solid; 26.5 mg, 68%; mp 198-200 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.86 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 2.32 (s, 3H); δ 144.1, 141.9, 138.6, 133.0, 129.9, 129.2, 127.7, 127.5, 21.5; **HRMS-ESI** (m/z) calcd $[C_{13}H_{12}O_2S + H]^+$: 233.0631 found: 233.0630. (

1-(Tert-butyl)-4-(phenylsulfonyl)benzene (**25**)[10a]

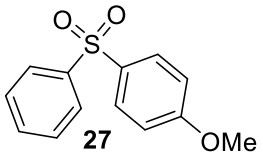


25

Reaction Time: 4 h; R*f*: 0.5 (1:4 EtOAc:Pet Ether); White solid; 38.7 mg, 85%; mp 129-130 ^{o}C; ^{1}H **NMR (400 MHz, CDCl$_3$)** δ 7.88 (d, J =

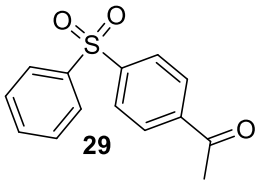
7.0 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.52-7.40 (m, 5H), 1.24 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.1, 141.9, 138.5, 133.0, 129.2, 127.6, 127.5, 126.3, 35.2, 31.0; **HRMS-ESI** (m/z) calcd $[C_{16}H_{18}O_2S + H]^+$: 275.1100 found: 275.1099.

1-Methoxy-4-(phenylsulfonyl)benzene (**27**)[10a]



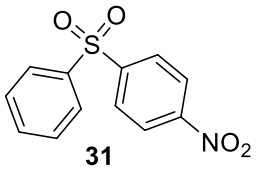
Reaction Time: 1 h; R*f*: 0.2 (1:4 EtOAc:Pet Ether); White solid; 25.4 mg, 61%; mp 90-91 ^oC; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87-7.78 (m, 4H), 7.50-7.38 (m, 3H), 6.92-6.87 (m, 2H), 3.77 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 163.3, 142.3, 133.1, 132.8, 129.9, 129.2, 127.3, 114.5, 55.6; **HRMS-ESI** (m/z) calcd $[C_{13}H_{12}O_3S + H]^+$: 249.0580 found: 249.0579.

1-(4-(phenylsulfonyl)phenyl)ethan-1-one (**29**)[16d]



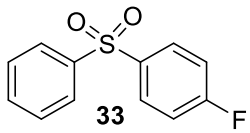
Reaction Time: 4 h; R*f*: 0.2 (1:4 EtOAc:Pet Ether); Yellow solid; 22.5 mg, 54%; mp 132-134 ^oC; ^{1}H **NMR (400 MHz, $CDCl_3$)** δ 7.98 (s, 4H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 8.5 Hz, 2H), 2.55 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.7, 145.4, 140.7, 140.3, 133.6, 129.5, 129.0, 128.0, 127.8, 26.9; ESI-Mass (M + 1) 261. **HRMS-ESI** (*m/z*) calcd $[C_{14}H_{12}O_3S + H]^+$: 261.0580, found : 261.0573.

1-Nitro-4-(phenylsulfonyl)benzene (**31**)[10a]



Reaction Time: 3 h; R*f*: 0.5 (1:4 EtOAc:Pet Ether); White solid; 32.6 mg, 74%; mp 144-145 ^oC **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.28 (d, *J* = 9 Hz, 2H), 8.07 (d, *J* = 9 Hz, 2H), 7.90 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.3, 147.3, 140.0, 134.1, 129.7, 129.0, 128.0, 124.5; ESI-Mass (M + Na) 209;

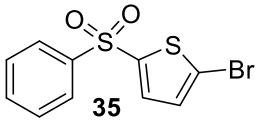
1-Fluoro-4-(phenylsulfonyl)benzene (**33**)[10a]



33

Reaction Time: 3 h; R*f*: 0.5 (1:4 EtOAc:Pet Ether); White solid; 34 mg, 86%; mp 113-115 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.93-7.83, (m, 4H), 7.55-7.41 (m, 3H), 7.22-7.08 (m, 2H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.4 (d, J = 255.8 Hz), 141.5, 137.7, 133.3, 130.5 (d, J = 9.2 Hz), 129.4, 127.6, 116.6 (d, J = 32.1 Hz); **HRMS-ESI** (m/z) calcd $[C_{12}H_9O_2SF + H]^+$: 237.0380 found: 237.0379.

2-bromo-5-(phenylsulfonyl)thiophene (**35**)



35

Reaction Time: 3 h; R*f*: 0.5 (1:4 EtOAc:Pet Ether); White solid; 37.09 mg, 73%; mp 105-107 ^{o}C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.90 (d, J = 6.8 Hz, 2H), 7.54 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 4.1 Hz, 1H), 6.99 (d, J = 4.1 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 143.8, 141.5, 133.6, 133.4, 130.8, 129.5, 127.3, 122.1; **HRMS-ESI** (m/z) calcd $C_{10}H_7O_2S_2{}^{81}Br+Na]^+$: 326.8943, found: 326.8936.

2.2.9. References:

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2.1.10 Selected Spectra

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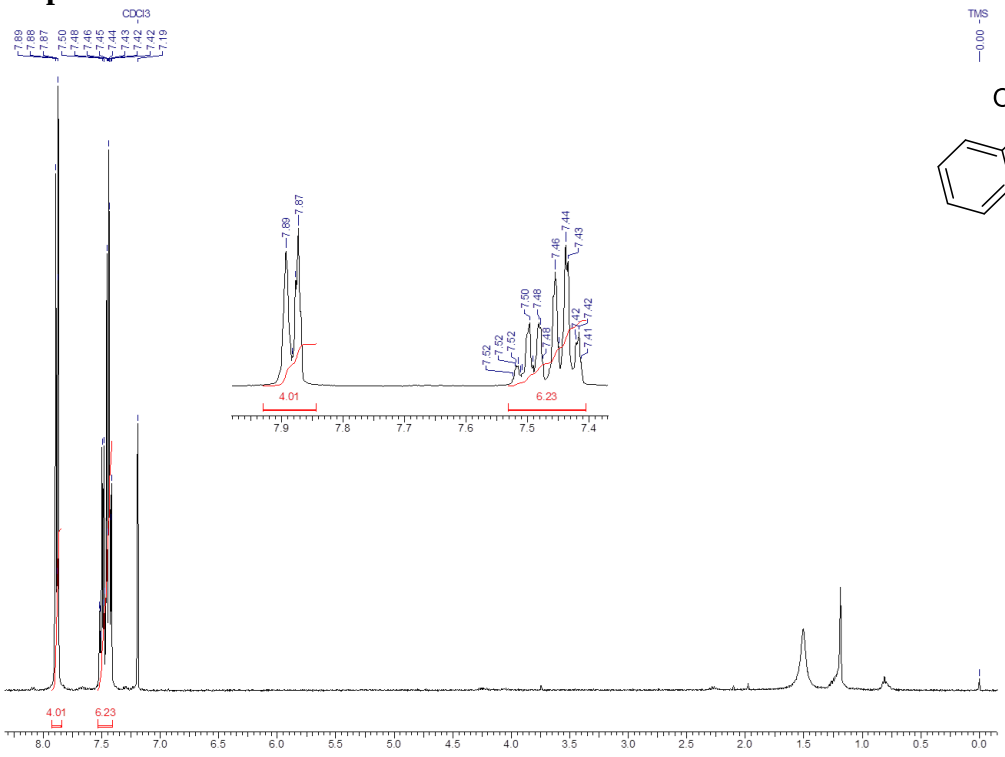

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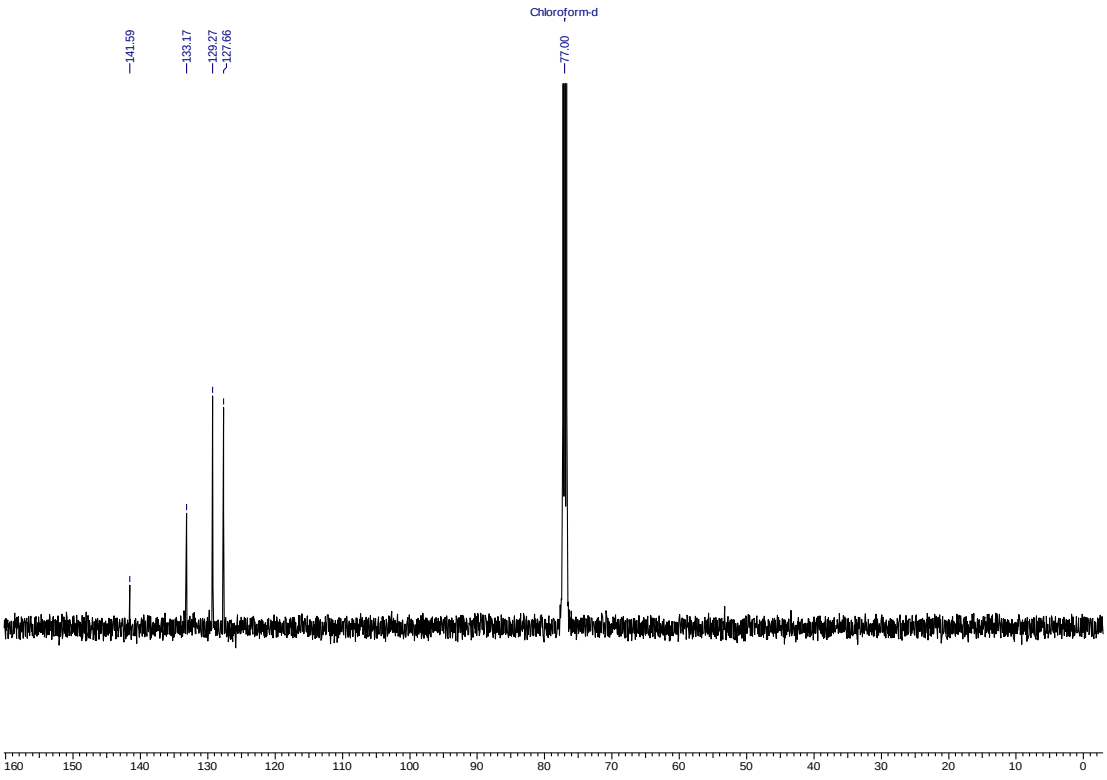

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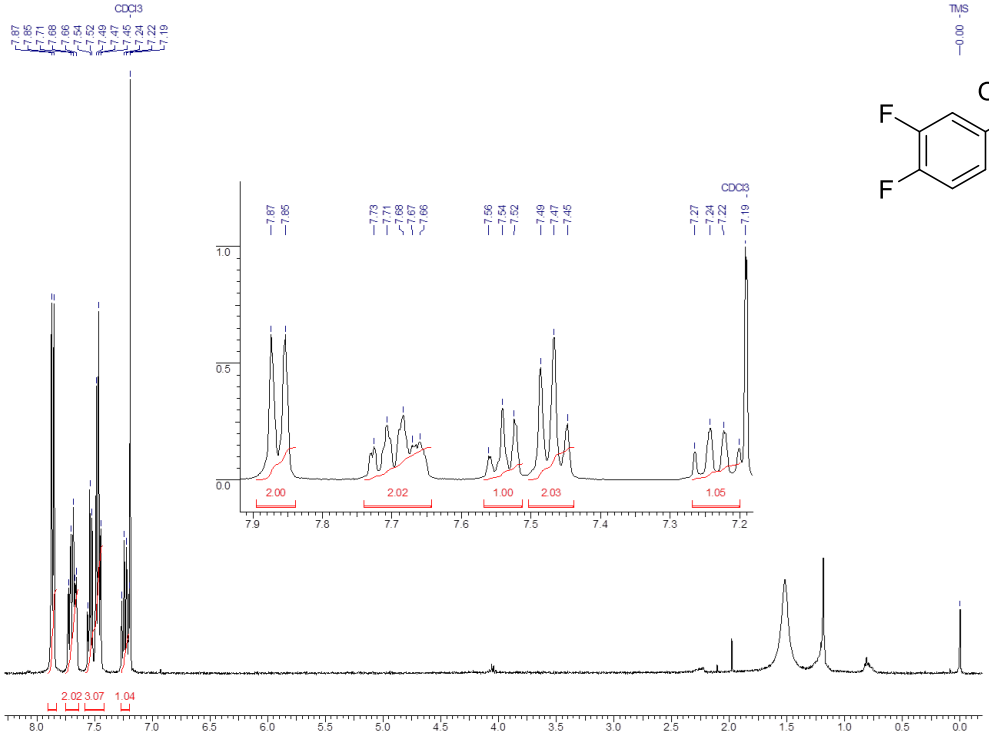

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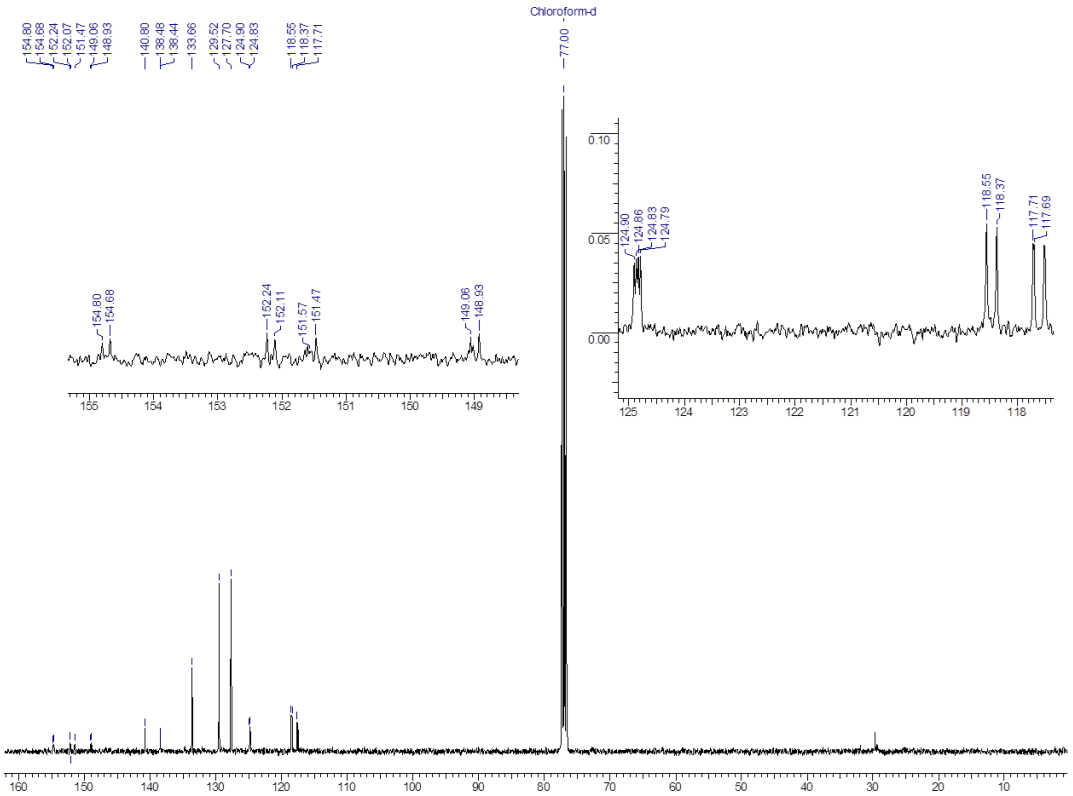

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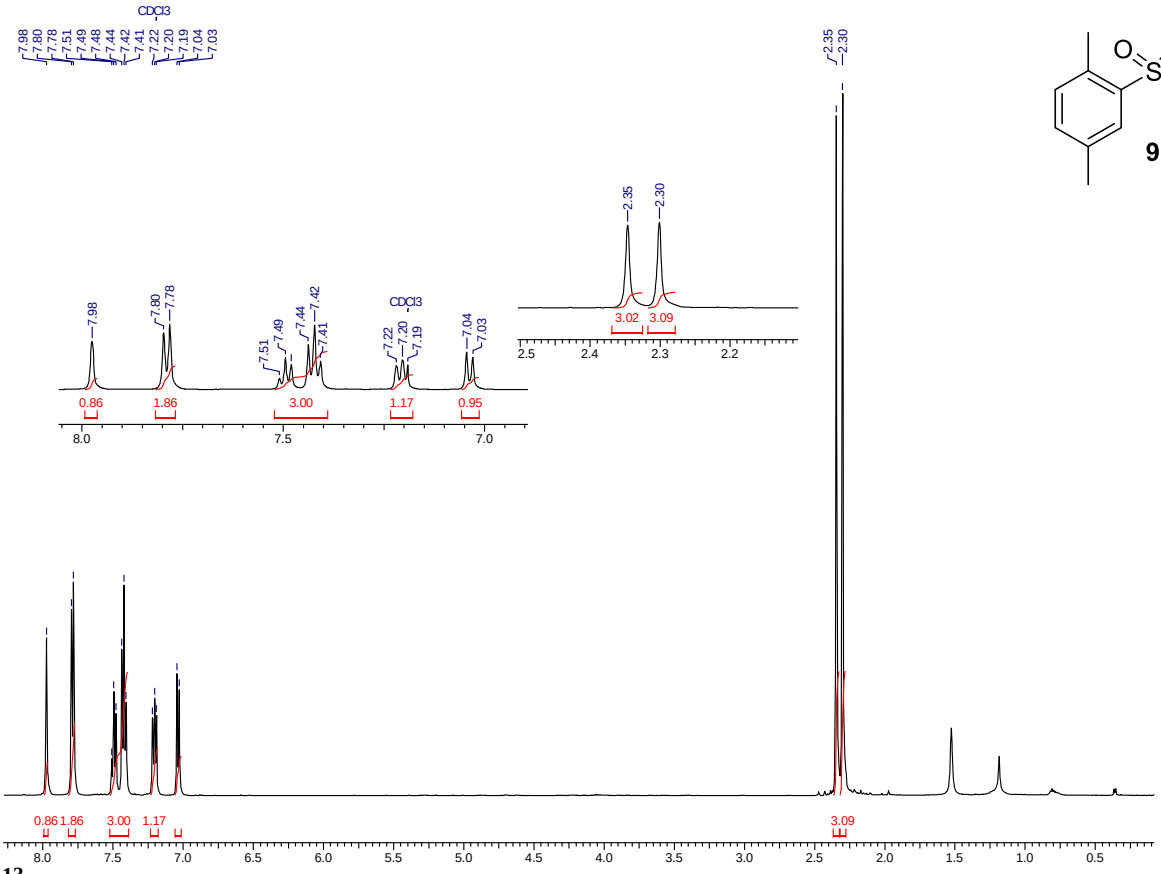

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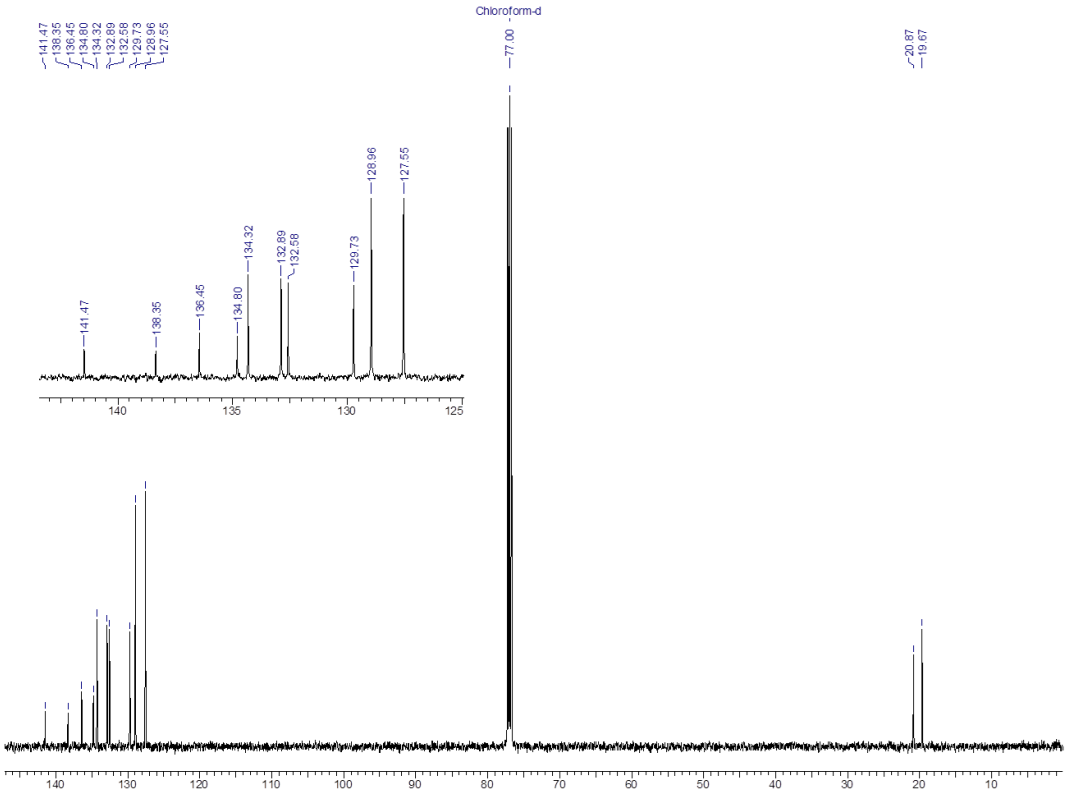

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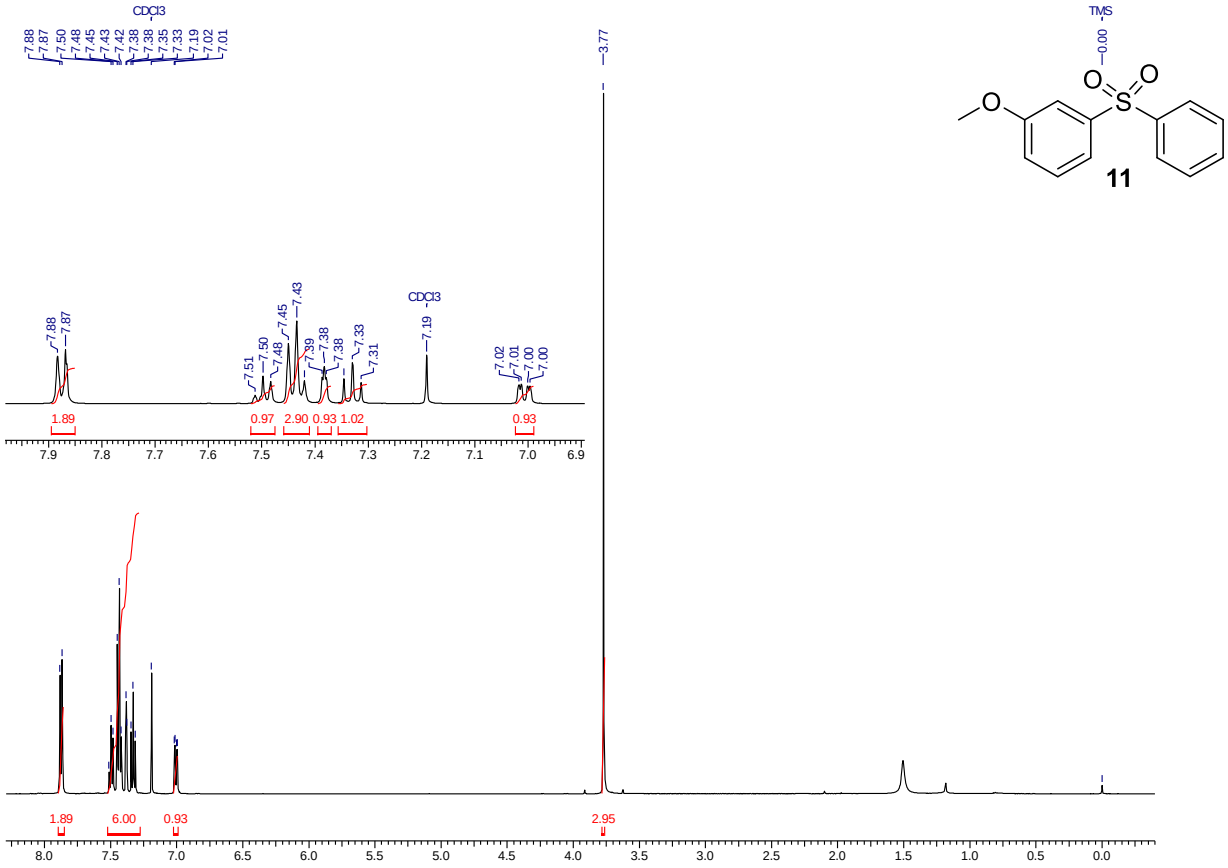

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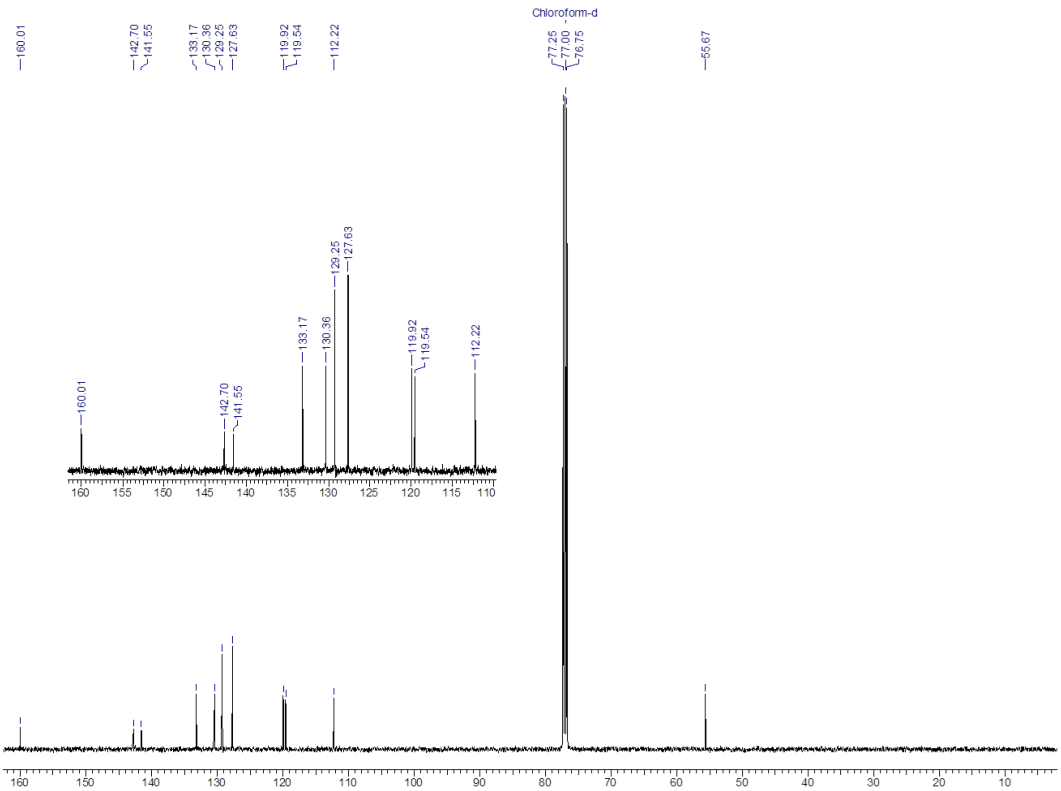

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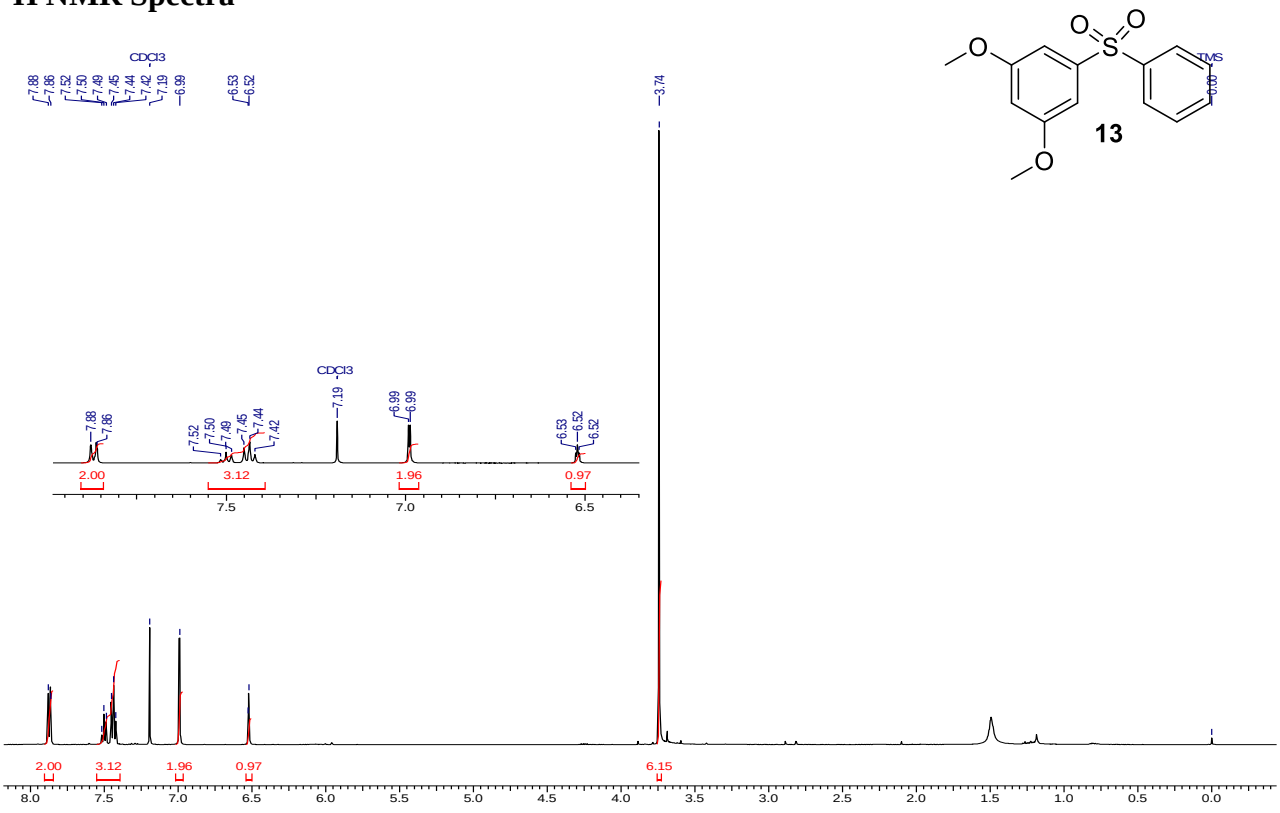

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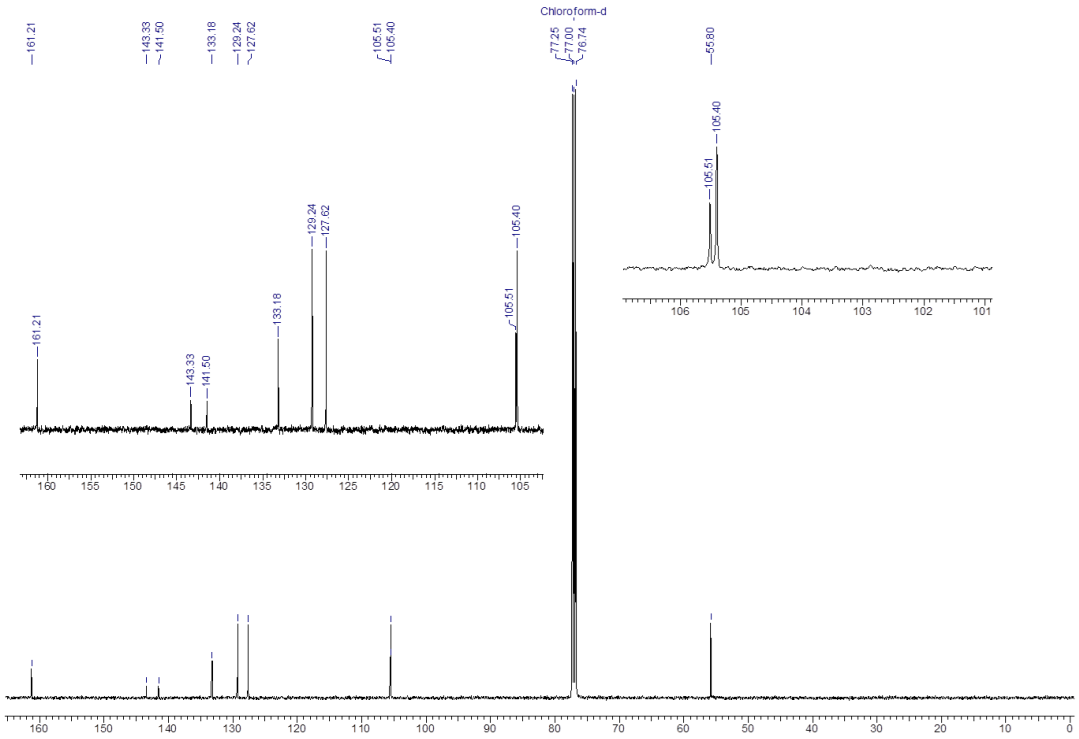

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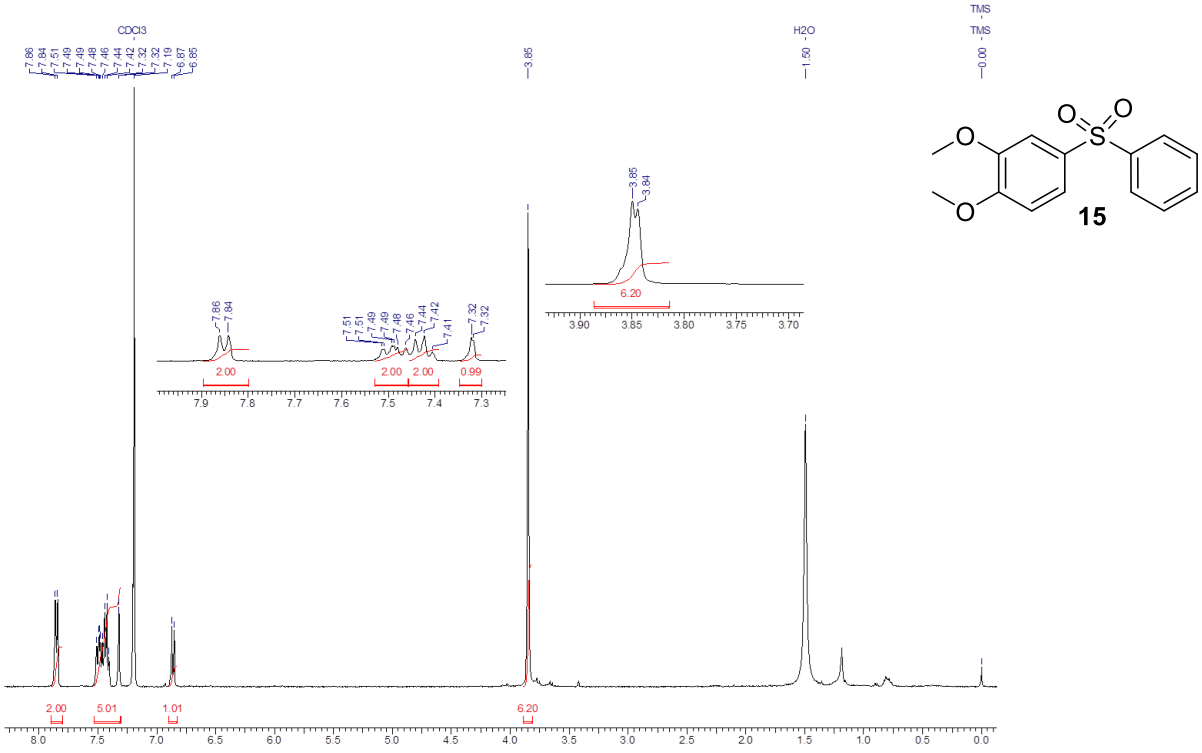

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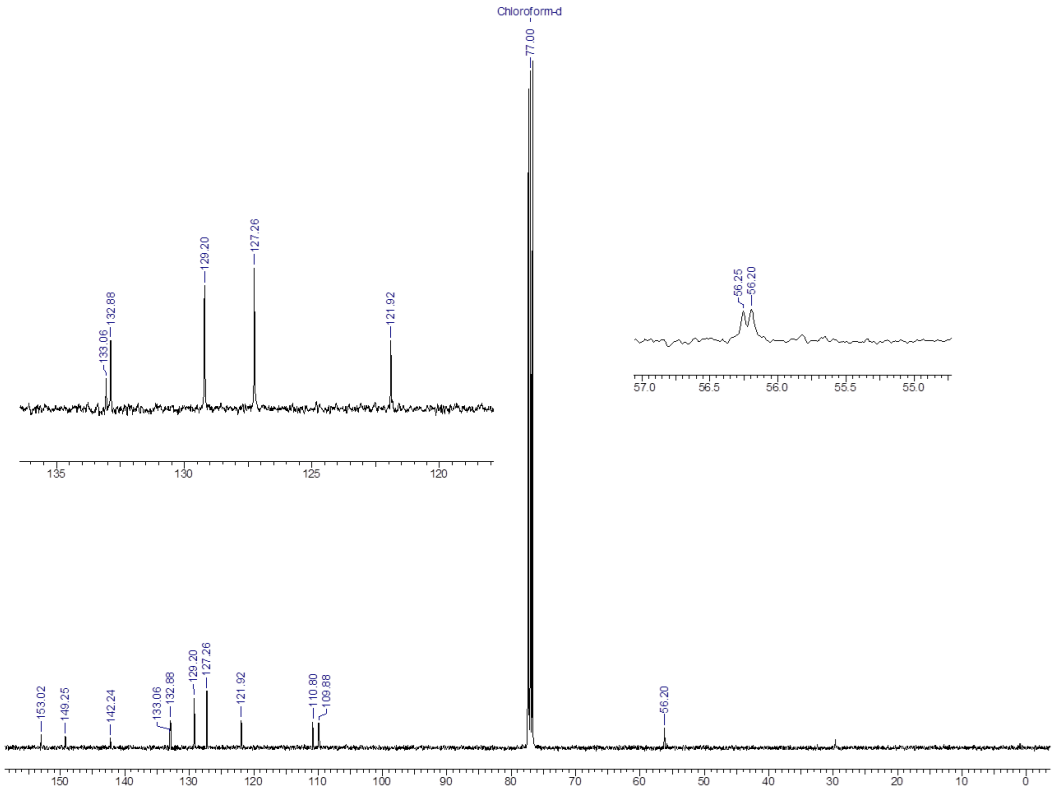

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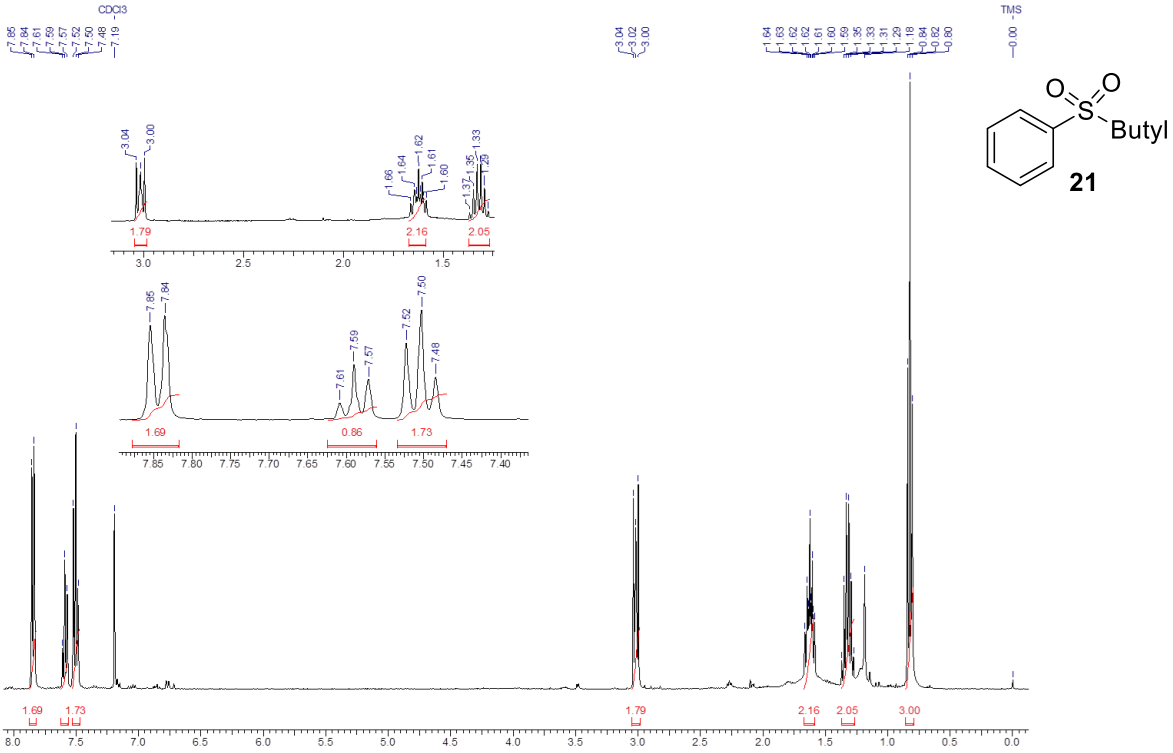

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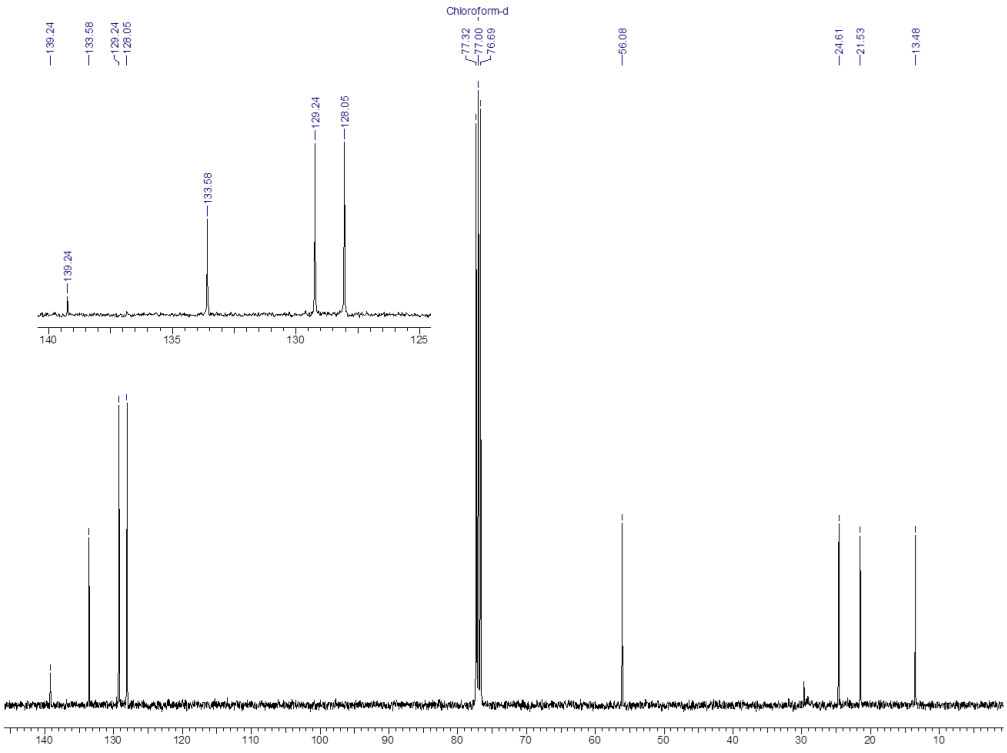

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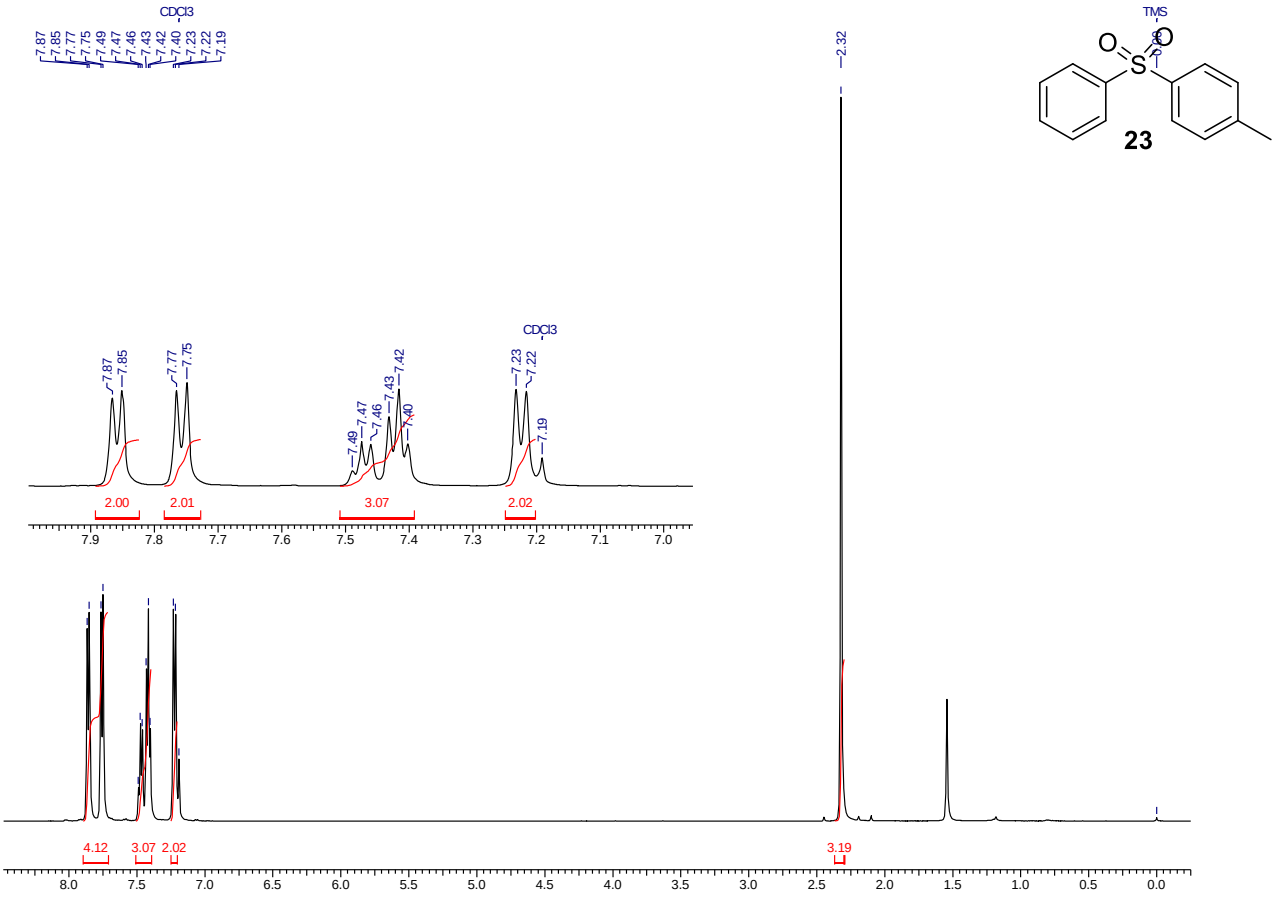

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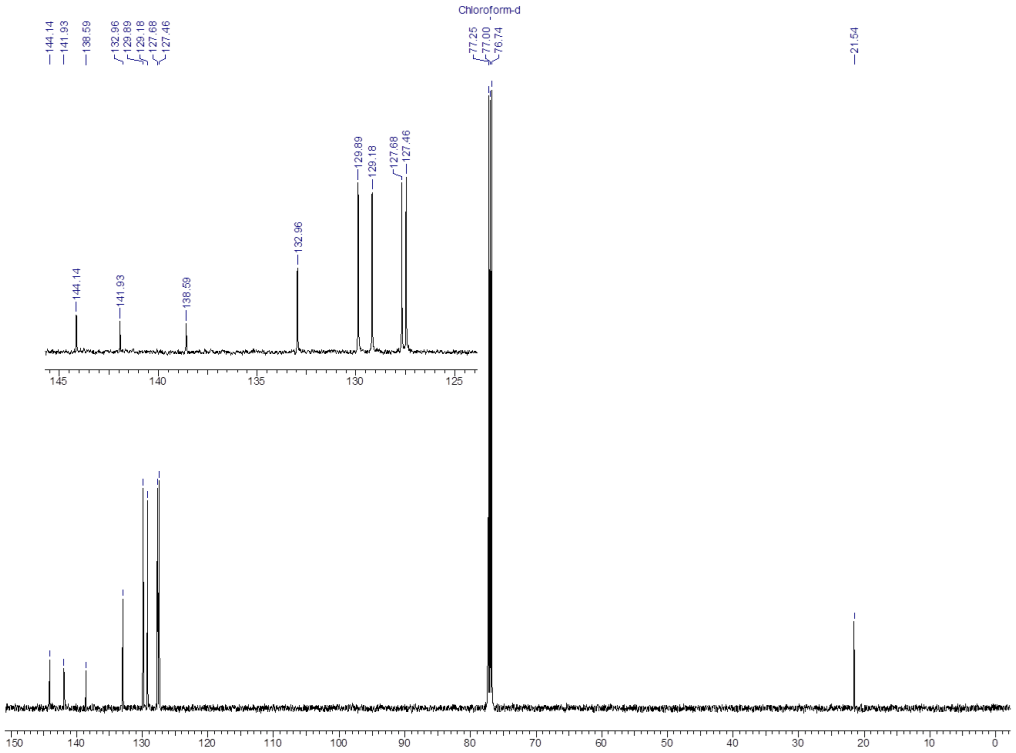

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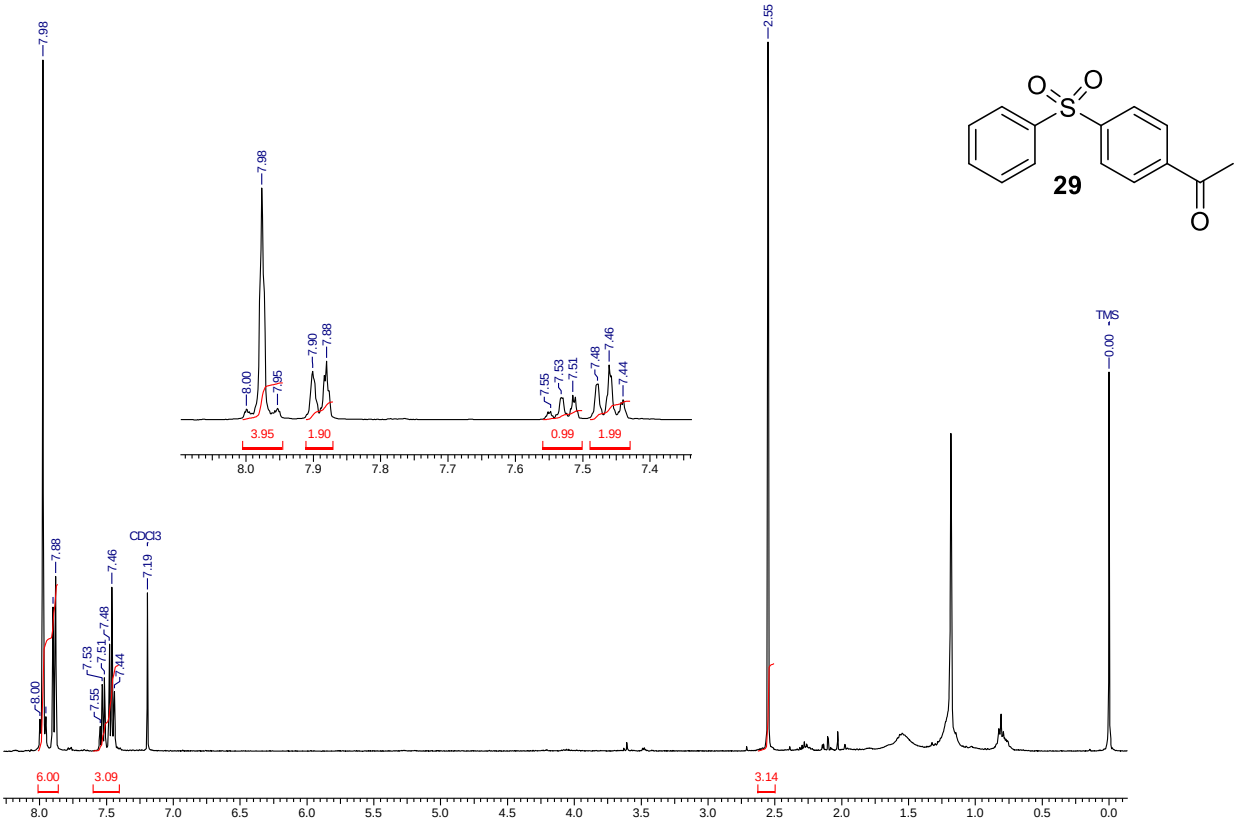

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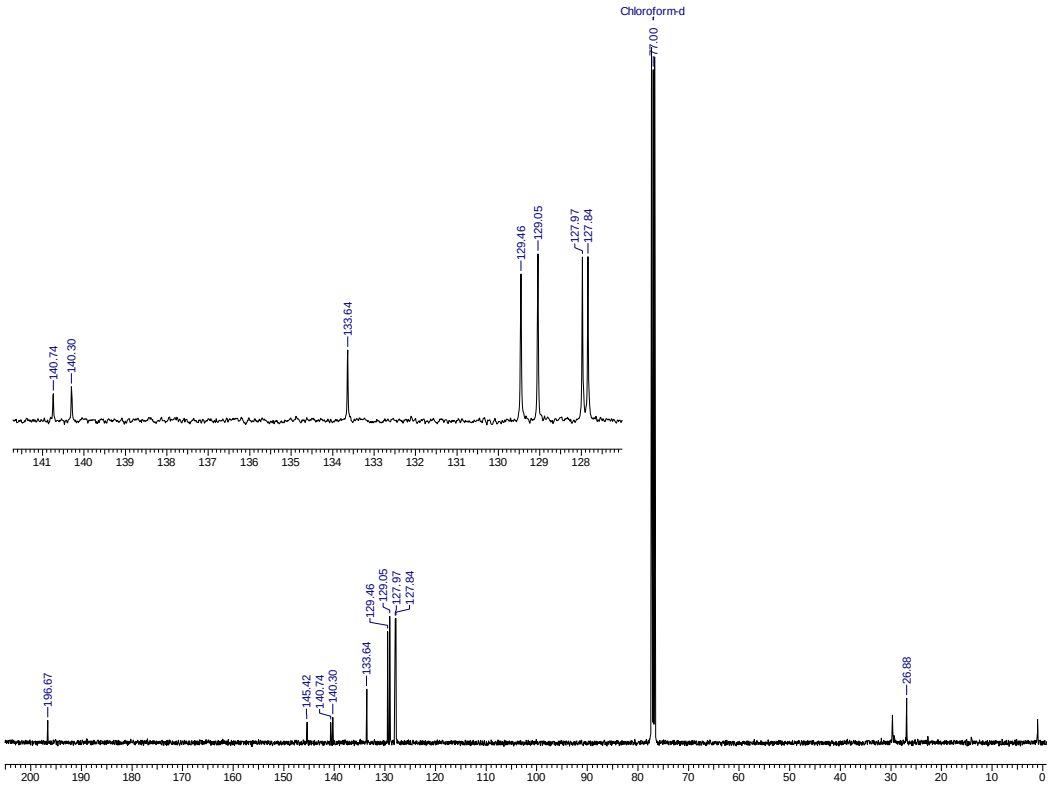

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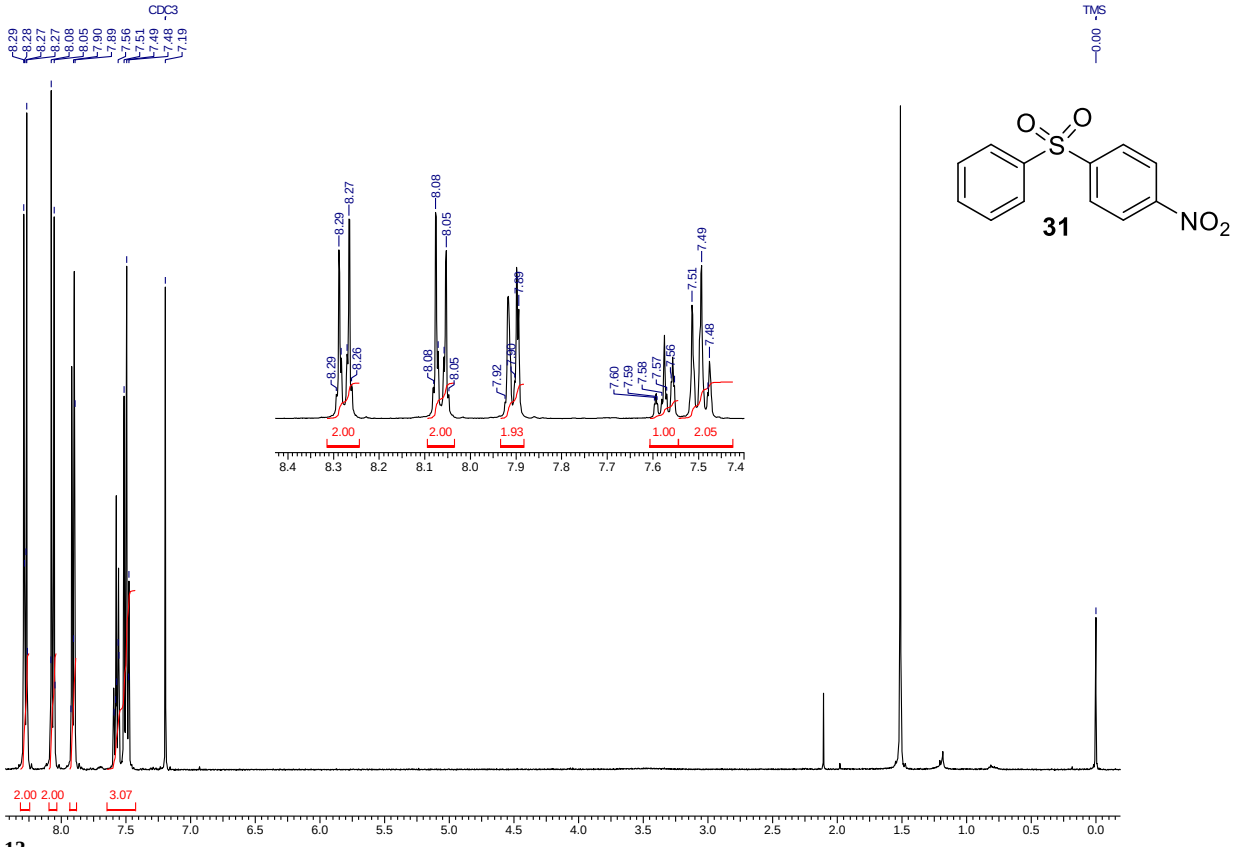

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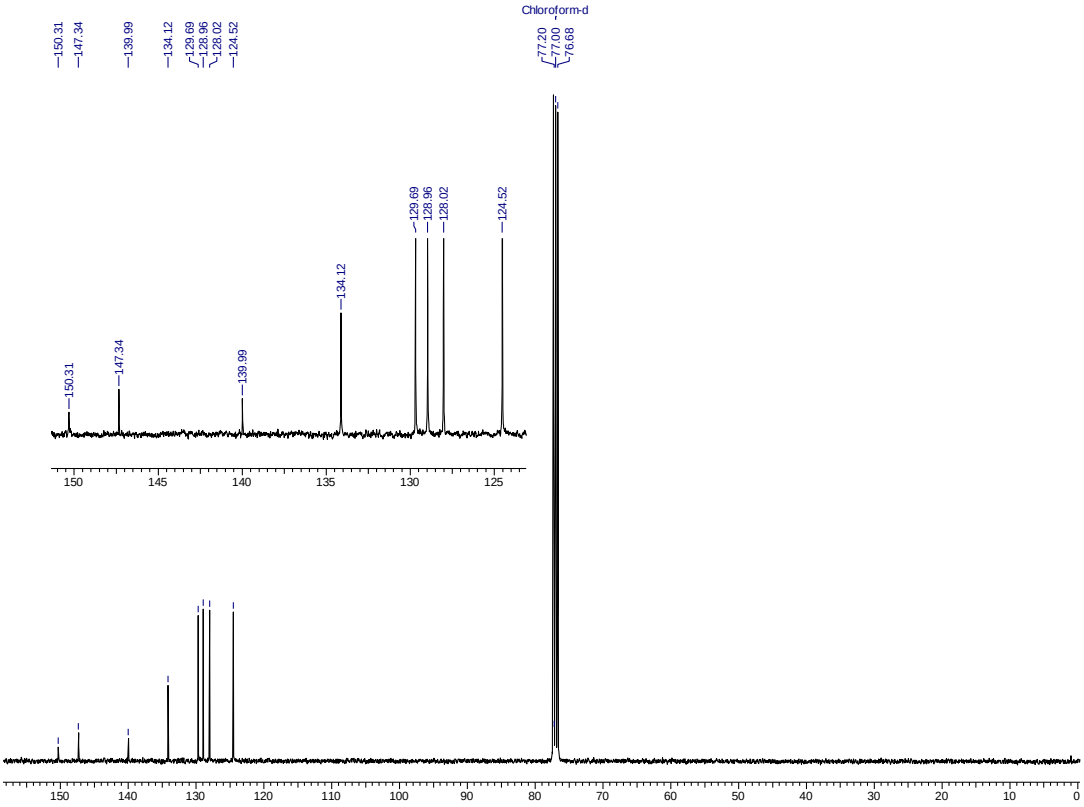

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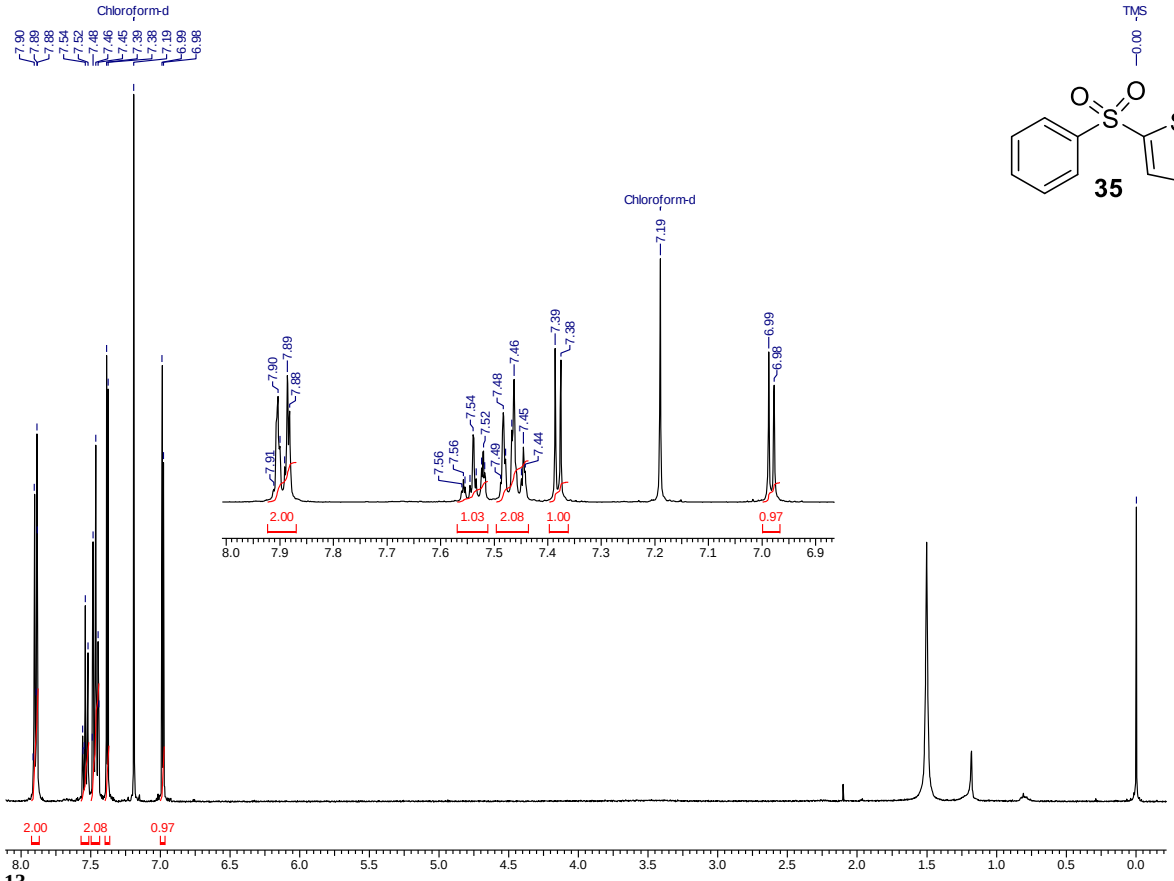

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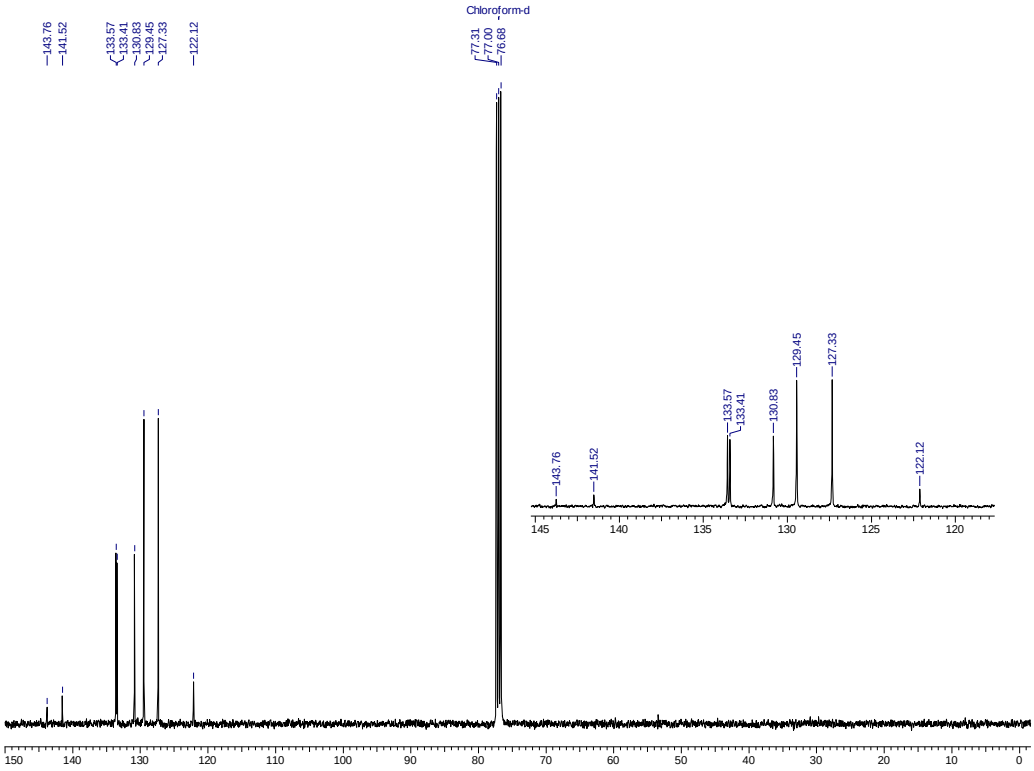
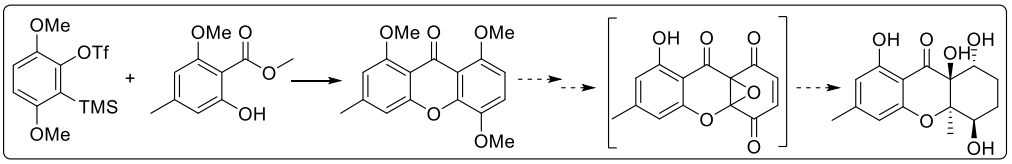


Section 2: Double Functionalization of Arene via Aryne to access Xanthone derived Diversonol

2.2.1. Abstract:

The section 2 involves our efforts towards the total synthesis of xanthone derived diversonol. The synthesis of bi-functionalized arene is accomplished by annulation reaction of aryne with orcinol derivative. Further attempts were made for the oxidation of xanthone which on further various transformations to furnish diversonol.



2.2.2. Introduction:

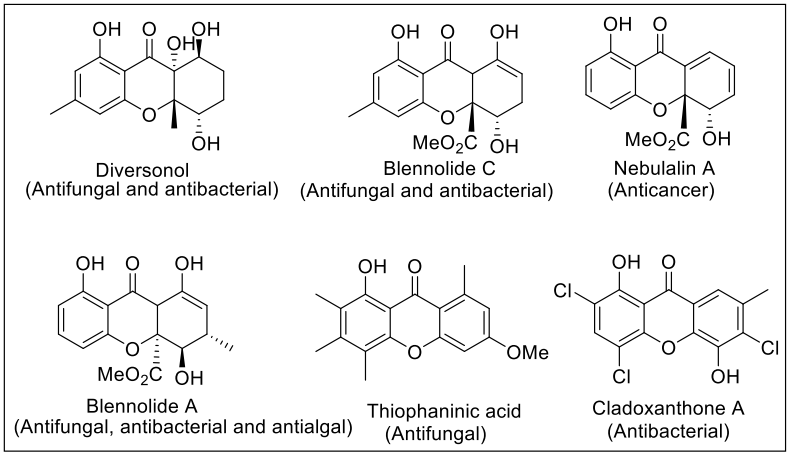


Figure 1: Natural products having xanthone core

Xanthones are secondary metabolites usually found in fungi and lichen[1]. Their privileged scaffolds and unique medicinal activity make them a highly demanding target for the synthetic chemists. Near about 515 diverse molecules having xanthone core are known which are isolated form 20 families of plants.[2] The occurrence of polysubstituted xanthones in compounds is categorized as tetrahydroxanthones, dihyroxanthones, and aromatic xanthones. Tetrahydroxanthone core containing molecules shows a vast range of biological

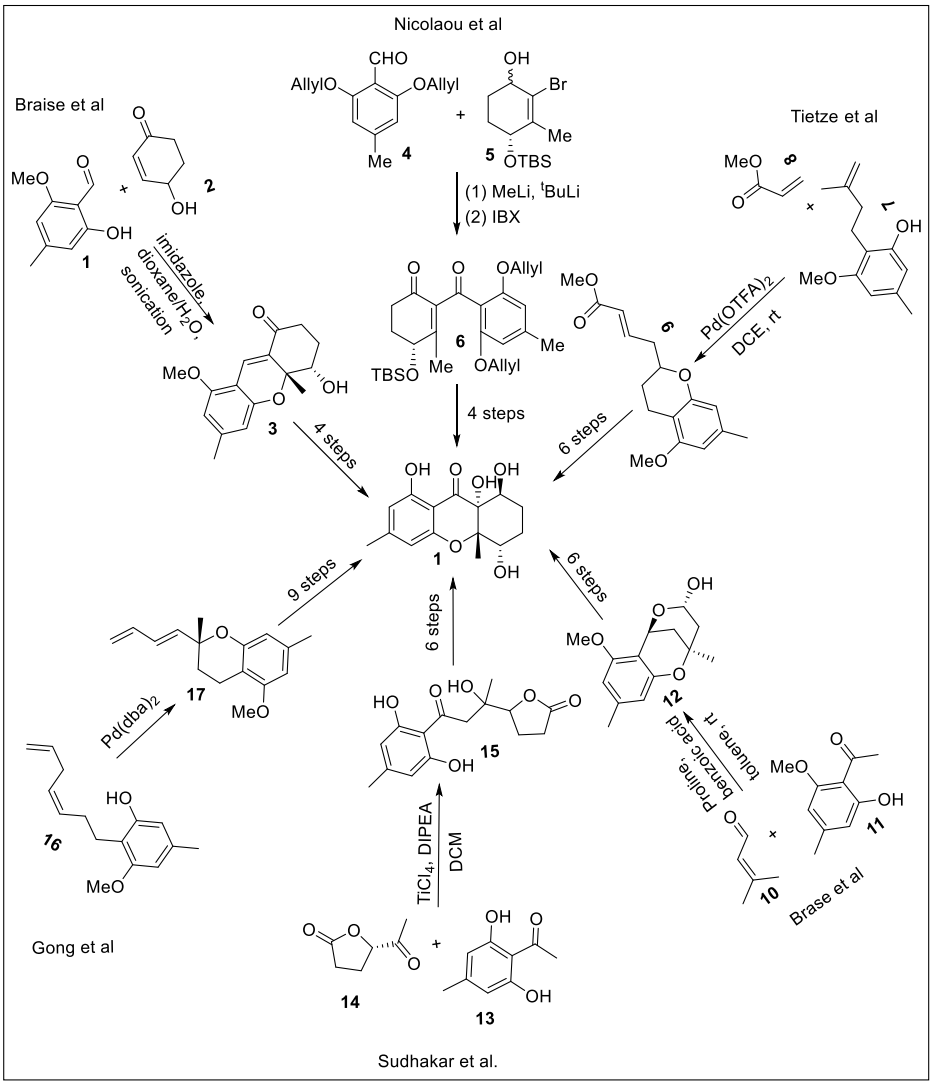
activities[3]. Their biological activity ranges from antibiotic to antibacterial activities. The last decade witnessed many reports on both synthetic and pharmacological research on this novel class of xanthones. The 8-hydroxy-1,4,4a,9a-tetrahydro-9H-xanthen-9-one represent a common framework for blennolides, dihydroglobosuxanthone, diversonol, diversonolic esters, globosuxanthone B, Nidulalin A and their congeneric natural compounds which exhibit many significant biological activities[4] (Figure 1).

Diversonol, representing the tetrahydroxanthones skeleton was isolated form the cultured Penicillium diversum and Microdiplodia sp. by Turner group[5] in 1978. Due to the unique structure and prominent antibacterial and antifungal activities of diversonol, many research groups have actively involved in the total synthesis of diversonol and its congeners[6].

2.2.3. Review Literature:

Till date, there have been six reports on the total syntheses of diversonol. Notably, most of the synthetic paths for diversonol involved oxa-Michael–aldol or Wacker reaction as key steps. The first successful racemic synthesis of diversonol was reported by Brase and co-worker in 2006. This synthesis was commenced by the reaction of substituted salicylic aldehyde **1** with hydroxycyclohexenone **2** which provided intermediate tetrahydroxanthone **3** This method utilized domino oxa-Michael–aldol reaction as a key step. Further transformations of intermediate **3** provided racemic diversonol in overall 10 steps.

In 2008, Nicolaou et al. demonstrated the synthesis of diversonol. The synthesis proceeds via the reaction of bromo hydroxy ester **5** with acyl cyanide **4** under the strong basic condition to furnish intermediate diketo **6**. This process involved deprotonation followed by oxidation. Further transformation on pivotal intermediate **6** provided diversonol in overall 10 steps.



Scheme 1: Schematic representation of Diversonol synthesis

In the following year, Tietze and co-workers successfully achieved an enantioselective total synthesis of diversonol. This process involved Pd-catalyzed domino Wacker/carbonylation/methoxylation reactions as key steps. The Wacker reaction of compound **7** with methyl acrylate **8** under the presence of $Pd(OTf)_2$ and (S,S)-Bn-BOXAX ligand furnished the chromane **9** which on sequential transformation provided diversonol.

In 2011 Brase et al. developed an efficient method for the enantioselective synthesis of diversonol. Organocatalyst mediated domino-oxa- Michael−aldol reaction of compound **10** and **11** provided chiral tricyclic lactol **12** with 83% ee. Sequential reaction on lactol **12**, accomplished the enantioselective synthesis of diversonol.

Sudhakar and co-worker demonstrated the formal synthesis of diversonol using Lewis acid-catalyzed aldol reaction of compound **13** with compound **14.** Formed aldol adduct **15** underwent various transformations to access diversonol.

In 2015 Gong et al. reported a palladium-catalyzed enantioselective intramolecular allylic C−H oxidation reaction for the synthesis of chromans. They have utilized this methodology for the synthesis of diversonol. Chromans **17** which was prepared by Pd-catalyzed allylic C−H activation of compound **16**, provided diversonol via various chemical transformation.

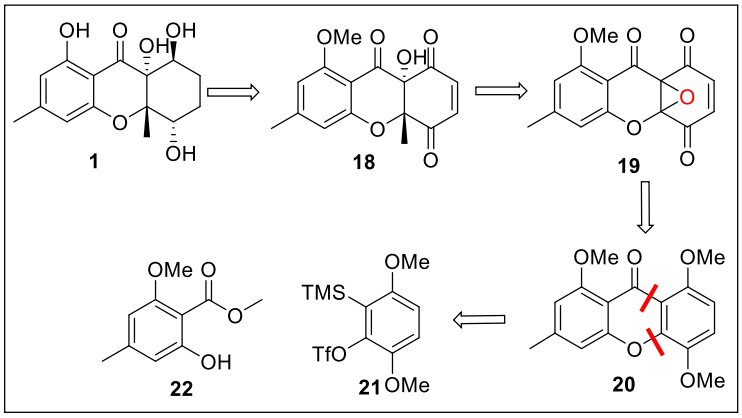
2.2.4. Origin of the work:

The literature study revealed that the total synthesis of diversonol is accomplished by using transition metals, organocatalysts, and harsh reaction conditions. The synthesis of diversonol always involves multistep procedures on pre-activated species. To overcome this limitation many researchers have shown consistent efforts to develop a short and efficient protocol for the total synthesis of diversonol.

2.2.5 Objective of the work:

The construction of xanthones has always been a fascinating task in synthetic chemistry.

Scheme 2. The retrosynthetic strategy of diversonol



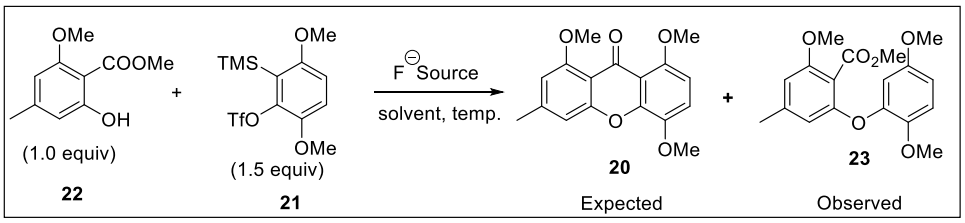
The scheme 3 demonstrates our retrosynthetic strategy for the diversonol metabolite, wherein, we have proposed convergent construction of diversonol **1** form the reduction of enone **18**. The enone **18** can be accessible from the intermediate **19** via the opening of

epoxide ring by MeLi**.** The epoxide **19** was expected to be constructed from compound **20** through the oxidation followed by epoxidation. Xanthone **20** could be accessible by the nucleophilic addition of compound **22** on aryne **21**.

2.2.6. Result and Discussion:

Our study towards the total synthesis of diversonol began with the synthesis of key intermediate xanthone **20**. Initial efforts for the synthesis of compound **20** involved the nucleophilic addition reaction of orcinol derivative **22** with aryne precursor **21**, (Scheme 4). Despite of many attempts (Table 1), the desired xanthone product **20** could not be observed and we always ended up with O-arylated product **23**.

Table 1: Optimization studies to obtain xanthone product **20** [a,b]



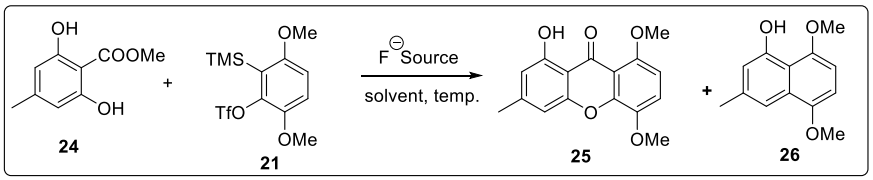
Sr. No.	fluoride source (equiv)	solvent	base (equiv)	temperature	**20**/**23** (yield)
1	CsF (2.0)	ACN	-	rt to 50°C	-
2	KF /18-c-6 (2.0)	THF	-	rt to 50°C	-/30
3	CsF	THF	-	rt to 70°C	-/30
4	KF + 18-c-6	THF :Toluene		80 to 90°C	-
5	KF + 18-c-6	DME	K_2CO_3 (1.0 equiv)	90 °C	-/50
6	CsF	DME	Cs_2CO_3 (1.0 equiv)	90 °C	-/60
7	CsF	DME	Cs_2CO_3 (2.0 equiv)	90 °C	-/60
8.	TBAT (2.0)	1,4 dioxane	Cs_2CO_3 (1.0 equiv)	rt to reflux	-

a) all reactions were performed on 20 mg of **22**, 0.5 mL of solvent, b) isolated yields

Formation of O-arylated product **23** led us to re-examine our approach for the synthesis of **20.** We envisaged that the methoxy group which is ortho to ester moiety on compound **22** is

affecting the reactivity of carbonyl group of ester. Hence the carbanion generated on aryne ring form the nucleophilic addition of compound **22** could not furnish the cyclized product **20** via nucleophilic addition reaction on the carbonyl group of ester and the reaction stopped at O-arylated product **23**.

Table 2: Optimization studies to obtain xanthone product **25**[a,b]



entry	equiv **1a/2a**	F^- source (equiv)	base	temp (°C)	solvent	**25/26** yield (%)
1	1:1	CsF (2.0)	-	rt to 50°C	ACN	-
2	1:1	KF /18-c-6 (2.0)	-	rt to 50°C	THF	-
3	1:1	CsF (3.0)	-	rt to 70°C	THF	-
4	1:1	KF/18-c-6 (3.0)	-	80 to 90°C	ACN :Toluene	Trace
5	1:1.5	KF/18-c-6 (3.0)	K_2CO_3 (1.0 equiv)	90 °C	DME	20/-
6	1:1.5	CsF (2.0)	Cs_2CO_3 (1.0 equiv)	90 °C	DME	30/35
7	**1:1.5**	**CsF (2.0)**	**Cs_2CO_3 (2.0 equiv)**	**70 °C**	**DME**	**32/48**
8.	1:1.5	TBAT (2.0)	$KHCO_3$(1.0 equiv)	rt to reflux	1,4 dioxane	30/35
9.	1:1.5	CsF (3.0)	$NaHCO_3$ (1.0 equiv)	70 °C	DME	35/40

a) all reactions were performed on 20 mg of **24**, 0.5 mL of solvent, b) isolated yields.

We changed our starting material from **22** to **24** and performed an optimization study for the synthesis of compound **25**. The outcome of optimization reactions which are summarized in table 2, demonstrated that expected compound **25** was formed in comparatively lower yield along with naphthalene derivative compound **26.** Formation of the unexpected product which on x-ray crystallography analysis identified as naphthalene derivative **26**, is the main cause

behind low yield of compound **25**. Preliminary study shows that the formation of interesting compound **9** is only possible when compound **24** can react as diene with dienophile **21**. Presently, we are working on the improvement of the yield of expected product **25** as well as also trying to optimize further steps for the synthesis of diversonol **1**.

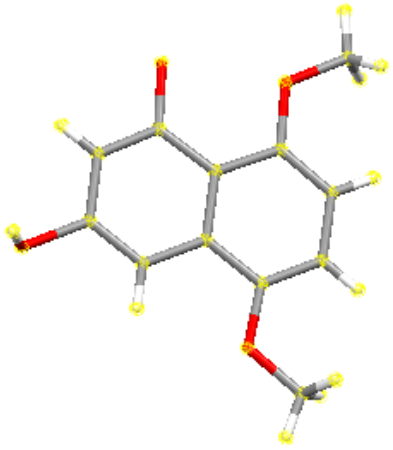


Figure 2: X-Ray Crystal Structure of **26**

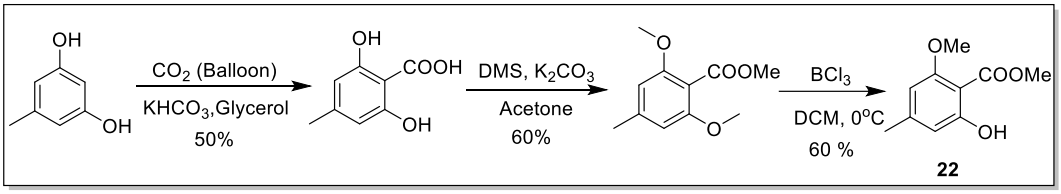
2.2.7. Conclusion:

In conclusion, we have made the efforts towards the total synthesis of diversonol. The nucleophilic reaction has been established on aryne with orcinol derivative. We are trying to optimize the key transformation for better yields. Formation of naphthyl derivative **26**, shows that the orcinol derivative **24** can act as a diene. This interesting result may be worth exploring. This method has the potential to provide general access to the diversonol as well as it also can be utilized in the total synthesis of 2-methoxy-stypandrone.

2.2.8. Experimental procedure and characterization data:

Compound **22** and **24** were prepared according to a literature procedure.

Methyl 2,6-dimethoxy-4-methyl benzoate (22):[7]



A mixture of orcinol (5.00 g, 40 mmol) and potassium bicarbonate (10.0 g, 100 mmol) in glycerol (8.00 mL) was heated for 8 h at 120 ^{o}C in a carbon dioxide atmosphere. The cooled reaction mixture was diluted with water (150 mL) and added with 2 N HCl to acidify the reaction mixture. The aqueous phase was extracted with ethyl acetate (3 x 30 mL), the combined organic phases were washed with brine solution, dried over Na_2SO_4, filtered and concentrated under vacuum. The 2,6-dihydroxy-4-methyl-benzoic acid compound was obtained as a white solid (4.4 g, 65%). This 2,6-dihydroxy-4-methyl-benzoic acid compound (2 g, 11.9 mmol) was treated with, potassium carbonate (6.5 g, 47.6 mmol) and dimethyl sulfate (6.0 g, 4.5 mL, 47.6 mmol) in dry acetone (40 mL) was heated for 10 h under reflux. The cooled reaction mixture was diluted with water (20 mL) and Et_2O (20 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under vacuum. Purify by column chromatography on silica gel to get methyl 2,6-dimethoxy-4-methyl benzoate as white solid (2.0 g, 80 %).

Reaction Time: 10 h; R*f*: 0.6 (9:1, Pet. Ether: EtOAc); white solid; 1.9 g, 81 % yield.

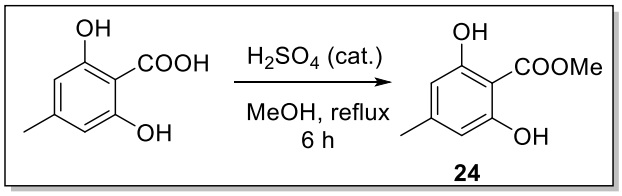
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.30 (s, 2 H), 3.82 (s, 3 H), 3.73 (s, 6 H), 2.27 (s, 3 H).

Methyl 2,6-dimethoxy-4-methyl benzoate in DCM cooled to 0 ^{o}C was added BCl_3 (3.0 equiv) in DCM. Stirring the reaction mixture for 2 h at the same temperature is furnished desire compound **22** in 60 % of yield.

Reaction Time: 10 h; R*f*: 0.6 (9:1, Pet. Ether: EtOAc); white solid; 1.9 g, 81 % yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 11.49 (s, 1 H), 6.36 (s, 1 H), 6.16 (s, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 2.23 (s, 3 H).

Methyl 2,6-dihydroxy-4-methylbenzoate (24):[8]

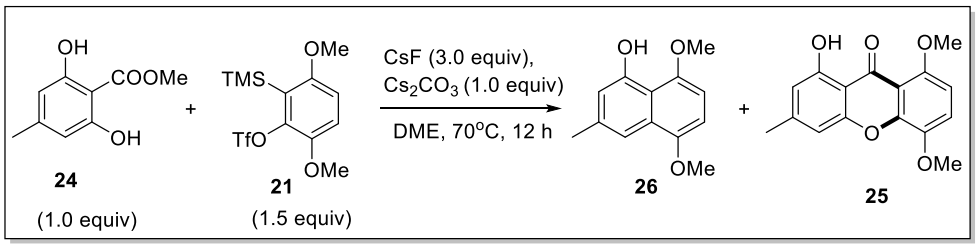


This 2,6-dihydroxy-4-methyl-benzoic acid (1.0 g) compound dry methanol (10 mL) was added the catalytic amount of sulphuric acid (0.2 mL), the mixture was heated to 80 ^oC for 6 h. The reaction mixture was cooled concentrated under vacuum. The residue was dissolved in ethyl acetate washed with sodium bicarbonate. Organic layer concentrated and purified by column chromatography to get compound **24** as a white solid in (0.7 g, 65%) yield

Reaction Time: 6 h; R*f*: 0.3 (9:1, Pet. Ether: EtOAc); white solid; 0.7 g, 65 % yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.54 (br. s., 2 H), 6.24 (d, J = 0.4 Hz, 2 H), 3.98 (s, 3 H), 2.18 (s, 3 H).

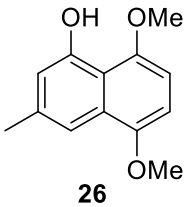
General procedure for the synthesis of xanthone and naphthalene derivative:



To a reaction mixture of CsF (0.5 g, 3.3 mmol), Cs_2CO_3 (0.35 g, 1.1 mmol) and **24** (0.2 g, 1.1 mmol) in dry DME (2 mL) under N_2 atmosphere, solution of aryne precursor **21** (0.59 g, 1.65 mmol) in dry DME (2 mL) was added. The resultant mixture was stirred at 70 ^oC for 12 h under argon atmosphere before quenched with water (2 mL). The aqueous phase was extracted with EtOAc (10 mL × 2). The combined organic layer dry on Na_2SO_4 and

evaporated under reduced pressure. The crude product was purified by flash column chromatography using petroleum ether and ethyl acetate gradient.

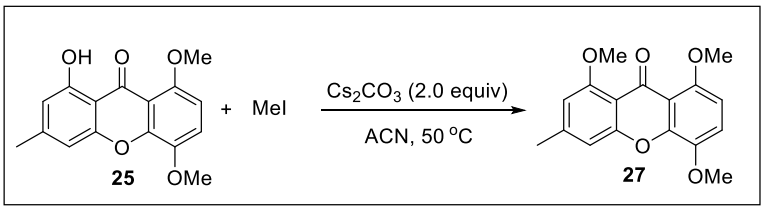
5,8-dimethoxy-3-methylnaphthalen-1-ol (26):



26

Reaction Time: 6 h; R*f*: 0.6 (3:2, Pet. Ether: EtOAc); white solid; 0.11 g, 48 % yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.30 (s, 1 H), 7.43 (s, 1 H), 6.70 (d, J = 0.8 Hz, 1 H), 6.63 (d, J = 8.39 Hz, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 2.37 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.1, 150.1, 149.8, 137.5, 128.4, 113.7, 113.0, 112.3, 103.0, 102.2, 56.2, 55.7, 21.8; **ESI HRMS**: calcd for $C_{13}H_{14}O_3$ $[M + H]^+$: 219.1016, found: 219.1017.

1,5,8-trimethoxy-3-methyl-9H-xanthen-9-one (27):



To a stirred solution of the compound **25** (100 mg, 0.35 mmol) in acetonitrile (0.5 mL) was added to Cs_2CO_3 (227 mg, 0.70 mmol) and Methyl iodide (33 µL, 0.52 mmol) in acetonitrile (1.0 mL) The resulting mixture was stirred at 50 ^{o}C for 8h, after completion of reaction it was quenched with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated in *vacuo*, followed by purification by column chromatography (petroleum ether:ethyl acetate = 2:3) to provide the product **27**.

Reaction Time: 12 h; R*f*: 0.6 (2:3, Pet. Ether:EtOAc); yellow solid; 68 mg, 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 8.8 Hz, 1 H), 6.85 (s, 1 H), 6.59 (d, J = 9.2 Hz, 1 H), 6.50 (s, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.35 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 160.2, 156.8, 153.7, 145.5, 141.9, 118.4, 116.0, 115.7, 111.6, 109.7, 107.1, 105.0, 56.9, 56.7, 56.2, 22.3;

2.2.9. References:

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2.2.10. Selected Spectra

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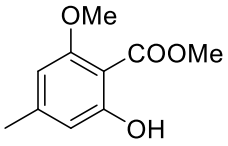

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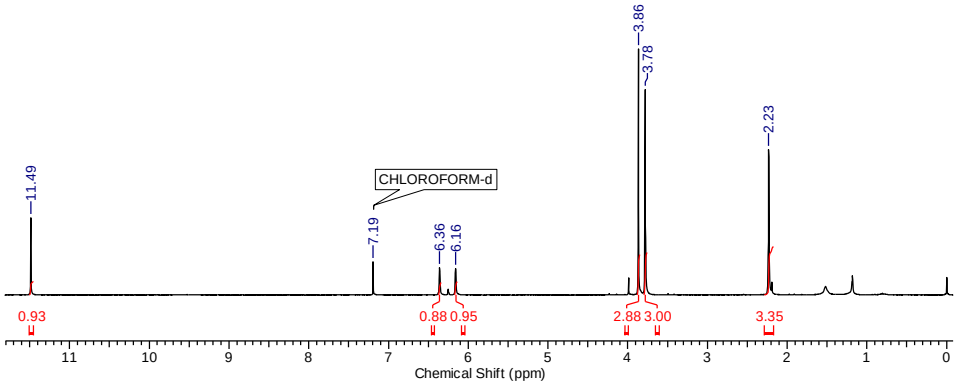

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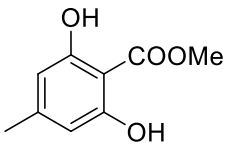

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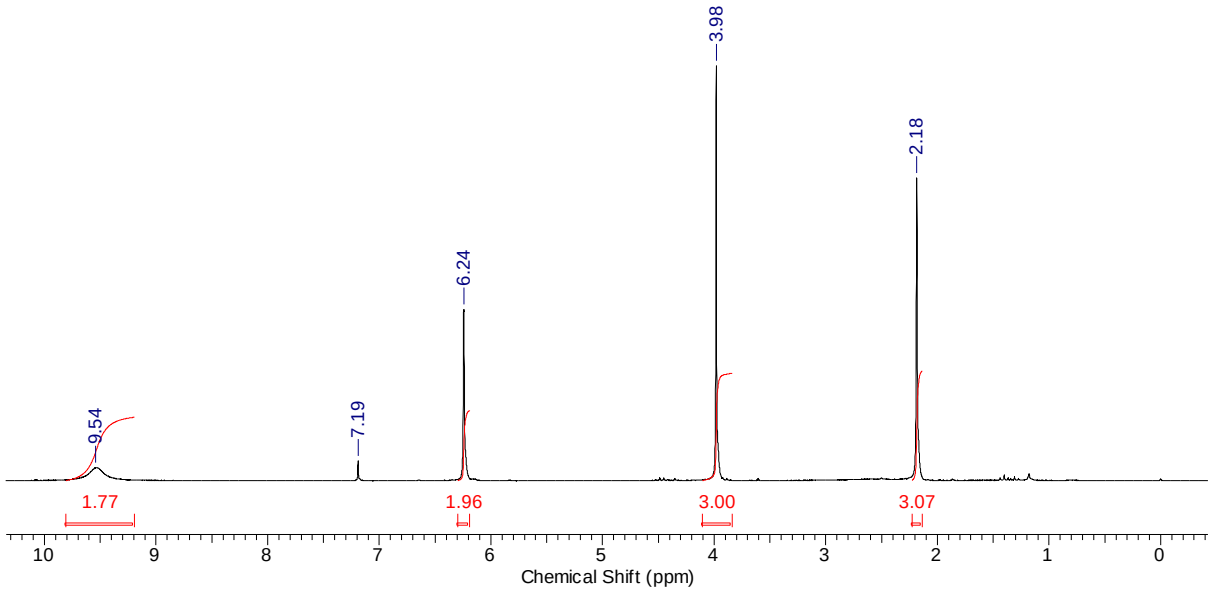
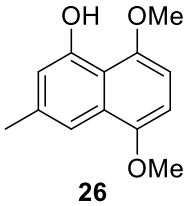
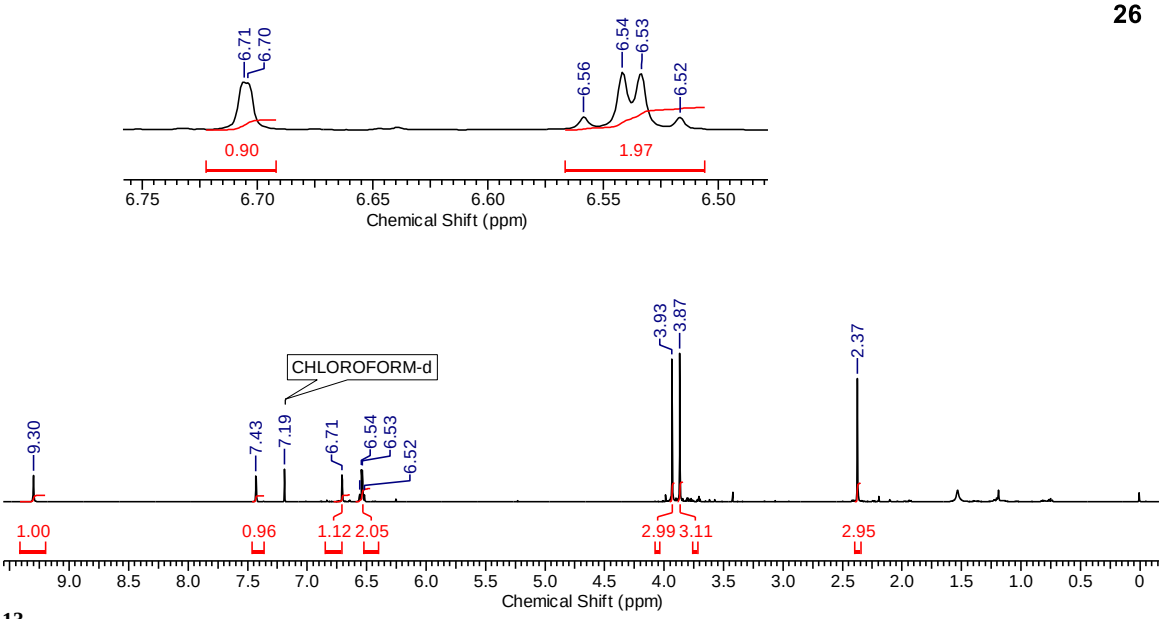


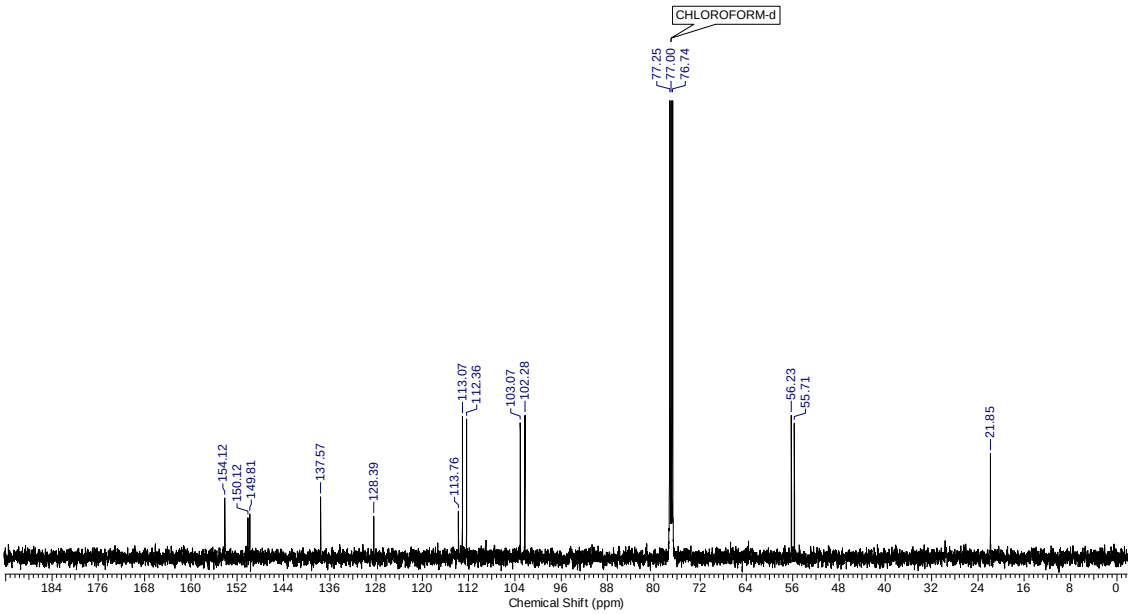
^{1}H NMR Spectra



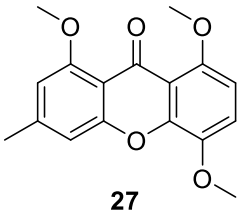
26



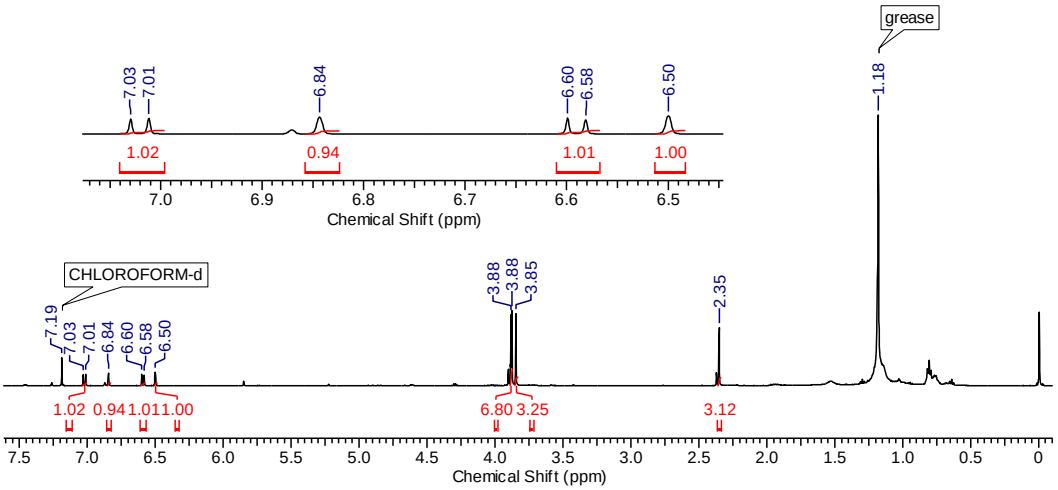
^{13}C NMR Spectra



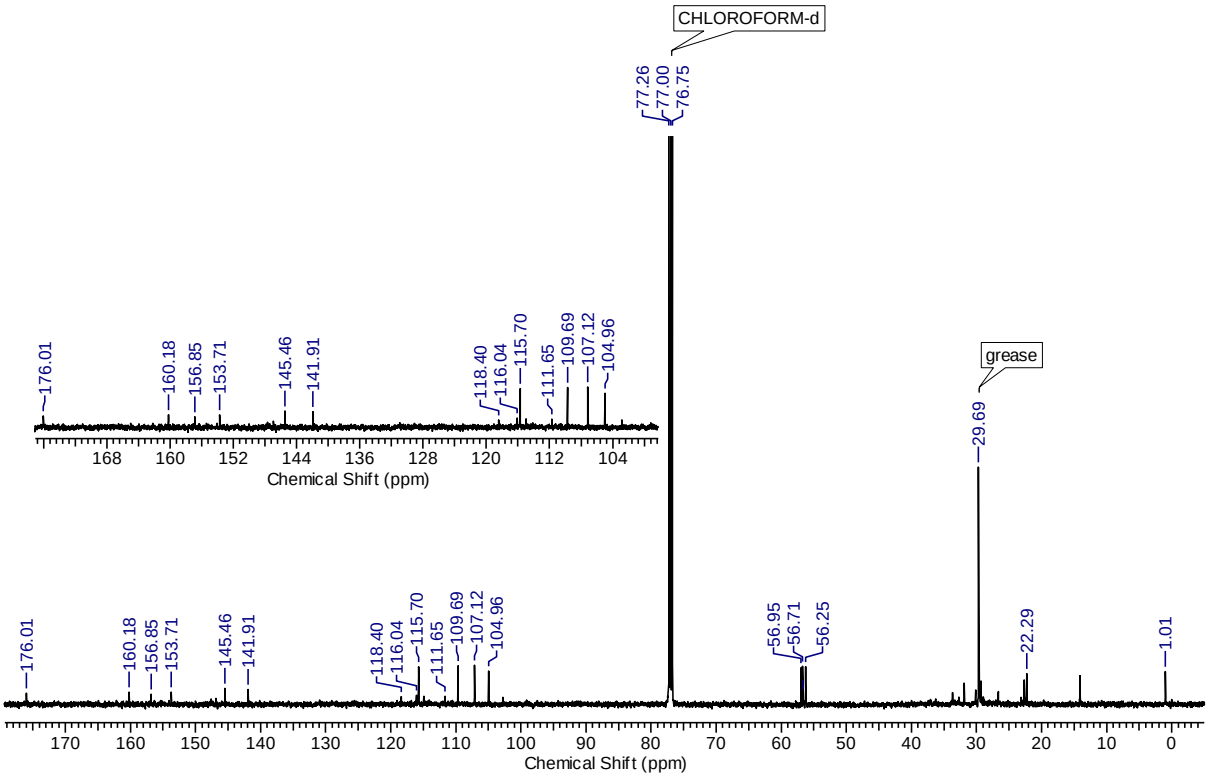
^{1}H NMR Spectra



27



^{13}C NMR Spectra



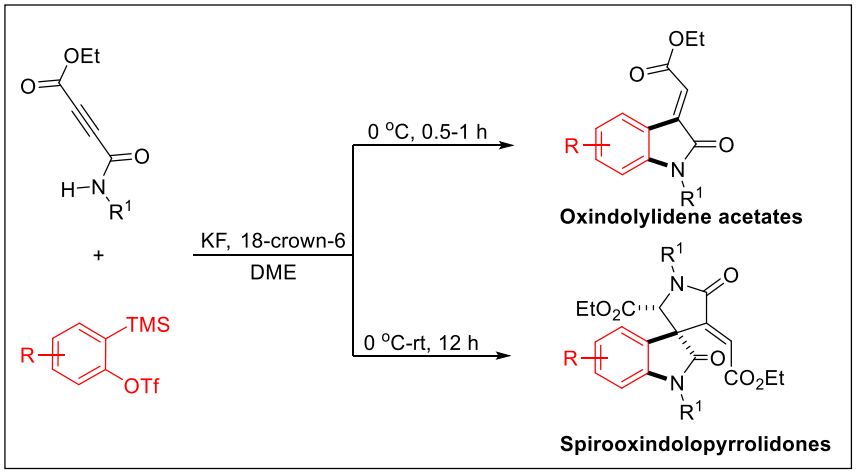
Chapter 3

General method for the synthesis of oxindolylidene acetates and spirooxindolopyrrolidones using aryne

Chapter 3: General method for the synthesis of oxindolylidene acetates and spirooxindolopyrrolidones using aryne

3.1. Abstract:

A novel process for the preparation of various (*E*)-oxindolylidene acetates using arynes and carbamoylpropiolates has been developed. The utility of this protocol is also further extended to the one-pot synthesis of complex spirooxindolopyrrolidones. This method provides milder and transition-metal-free access to the construction of multiple new bonds, which results in the synthesis of both the target scaffolds in moderate to good yields.



This work has been published in *Org. Lett*. **2018**, *20*, 1483.

3.2. Introduction:

Diverse functional groups, intriguing structure and a broad range of biological activities make oxindole scaffold containing compounds a fascinating target for chemists.[1]Among oxindoles, oxindolylidene acetates, and their derivatives are versatile substrates. They have been used in the synthesis of drugs, bioactive molecules, and natural products. Oxindolylidene acetates commonly show multiple biological activities. It's antifungal, anticancer, and antiviral activities

makes it the most fascinating target for the synthetic chemists. 3-Ylideneoxindole is the core found in marketed drugs such as sunitinib and hesperadin. Sunitinib acts as tyrosine kinase binding receptor hence it use for the treatment of renal cell carcinoma while the hesperadin is use for the treatment of aurora B. (Figure 1). 3-Ylideneoxindole is also ubiquitous in a number of natural molecules such as costinoneA, costinine B, which work as anti lipoxygenases[2].

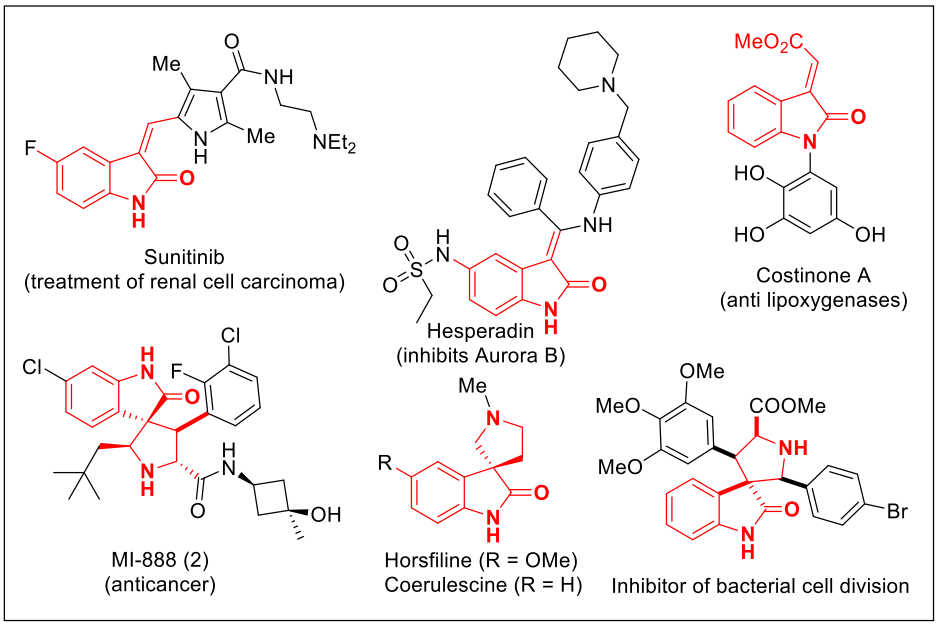


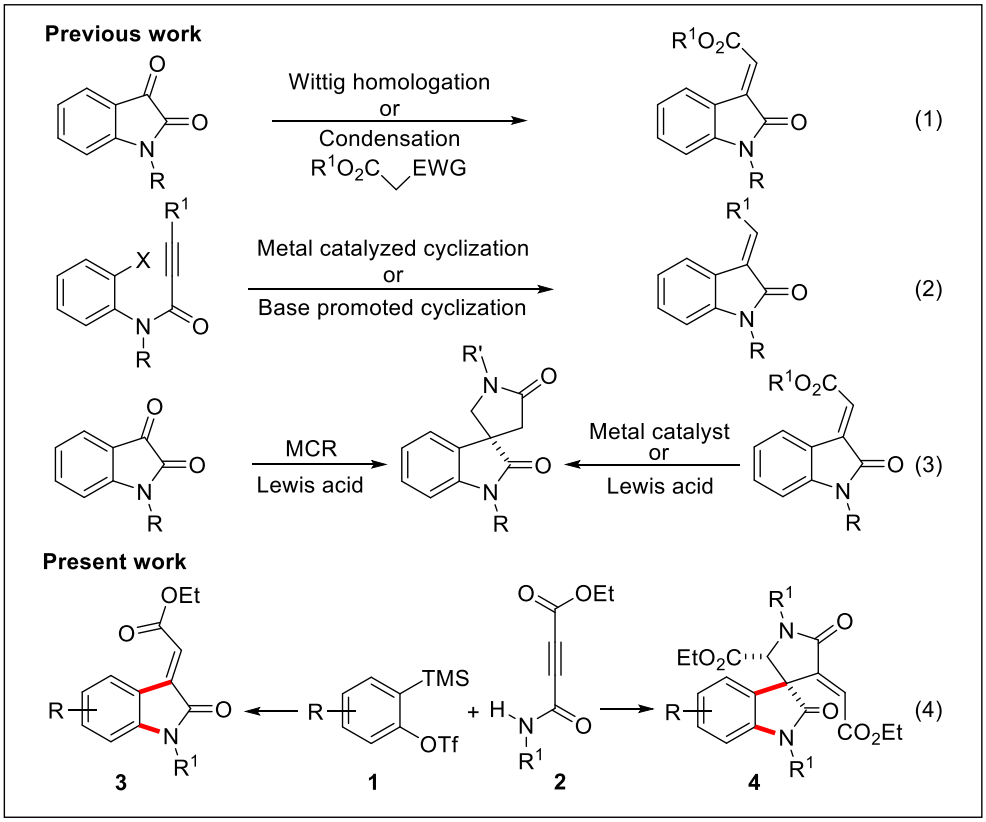
Figure 1. Representative drugs and natural products

Spirooxindoles are also well-recognized scaffolds, which have received much attention from the scientific community due to their unique biological and pharmaceutical properties, as well as challenging structure architecture (Figure1).[4]Among spirooxindoles, spirooxindolopyrrolidone has a distinct structural type having various biological activities. They have been widely considered for their prominent anticancer activity. They act as potent inhibitors of p53–MDM2 interaction eg, MI-888. Additionally, they are also found in natural products like horsfiline and coerulescine (Figure 1).

3.3. Literature Review

A literature survey disclosed that various methods for the synthesis of 3-ylideneoxindole core have been developed, but they have their virtue and shortcomings.[3] Conventionally, they are synthesized from isatin by Wittig homologation[3l,q] or by condensation[3i] with active methylene compounds (Scheme 1, eq 1). Few reports demonstrated the synthesis of 3-ylideneoxindoles by transition-metal-catalyzed[3c,m] or base- promoted[3b] cyclization methods starting from the corresponding substituted propiolamides (Scheme 1, eq 2).

Scheme 1. Previous and present work



Several methods are known for the construction of spirooxindolopyrrolidone derivatives,[5] but often they are synthesized either from isatin or from 3-ylideneoxindoles, which demands transition-metal or organocatalysts, and in some cases, harsh reaction conditions (Scheme 1, eq 3).In view of the importance of oxindole scaffolds, their synthesis using a general and mild

protocol is of enduring interest to industry and academia. Recently, Mehta et al. reported spiroannulation of oxindoles with arynes to obtain cyclopentanone fused spirooxindoles.[6] However, to date, the synthesis of oxindolylidene acetates and spirooxindolo-pyrrolidones using aryne chemistry has not been explored.

3.4. Origin of Work:

The literature reports concluded that the previously developed protocols for the synthesis of this heterocycles are struggled to get high regioselectivity as well as high versatility in the synthesis of 3-ylideneoxindole acetates and spirooxindolo-pyrrolidones. Furthermore, most of the reported methods for the synthesis of these compounds demands transition-metals and expensive reagents.

3.5. Objectives

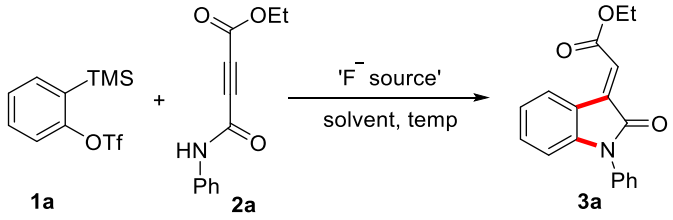
Over the last decade, the aryne chemistry has evolved as a versatile synthetic tool for organic chemists.[7] Owing to their high reactivity as an electrophile and easy accessibility, they have been used in the development of several methodologies[7] and total synthesis of natural products.[8] Our group has been involved in the development of expedient methodologies using arynes.[9] Intrigued by the recent advances in the construction of nitrogen-containing heterocyclic cores,[10] such as isatins, indoles, quinazolinones and carbazoles from aryne, we endeavored to develop a milder and metal-free process for the synthesis of 3-ylideneoxindole acetates and spirooxindolo-pyrrolidones using aryne chemistry.

3.6. Results and Discussion:

To develop an efficient protocol for the synthesis of oxindolylidene acetates, we examined the possibility of double functionalization of arynes via the formation of carbon–nitrogen and carbon–carbon bonds. The reaction of aryne precursor **1a** with phenyl carbamoylpropiolate**2a**[11] in the presence of CsF in acetonitrile was performed at 0 ^{o}C to room temperature (Table 1, entry

1). Further screening of solvents with CsF didn't provide desired compounds (entry 2-4). Delightfully, we observed a trace amount of product formation when CsF is replaced by KF in acetonitrile (entry 5). Moreover, increment in the yield of expected product was observed when equivalents of reagents were tuned ((entry 6-9).

Table 1. Optimization to Obtain Oxindolylidene Acetates[a-d]



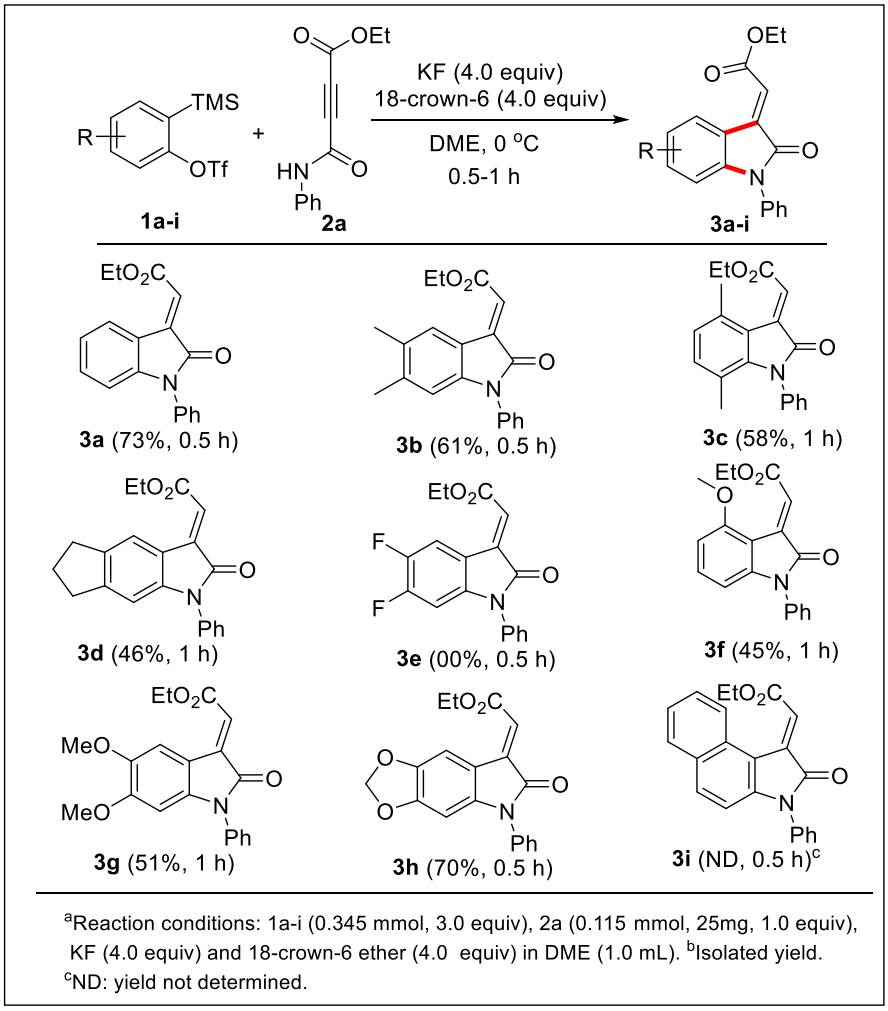
entry	equiv**1a/2a**	F⁻ source (equiv)	solvent/ temp (°C)	time (h)	yield (%)
1	1:1	CsF (1.5)	ACN/0-rt	2	–
2	1:1	CsF (1.5)	DME/0-rt	2	–
3	1:1	CsF (1.5)	THF/0-rt	2	–
4	1:1	CsF (1.5)	DME/0-rt	2	–
5	1:1	KF (1.5)	ACN/0-rt	0.5-2	trace/–
6	1:1	KF (1.5)	toluene/0	0.5	20
7	2:1	KF (3.0)	DME/0	0.5	51
8	2:1	KF (3.0)	THF/0	0.5	50
9	2:1	KF (3.0)	DME/–5	0.5	50
10	2:1	TBAF (2.0)	THF/0-rt	0.5-3	–
11	2:1	TBAT (2.0)	THF/0-rt	0.5-3	–
12	3:1	KF (4.0)	THF/0	0.5	70
13	**3:1**	**KF (4.0)**	**DME/0**	**0.5**	**73**
14	3:1	KF (4.0)	DME/–5	0.5	73
15	3:1	KF (4.0)	DME/rt	0.5	<10

[a]Selected entries.[b]Reactions were performed on a 50 mg scale of **2a** in a solvent (2.0 mL). [c]Isolated yield. [d]Equivalent quantity of 18-crown-6 was used with KF.

We did not observe any product formation when TBAF or TBAT were used (entry 10-11). After several permutations and combinations (Table 1, entries 12-15) the best yield for the desired compound **3a** was obtained when the reaction was performed using 3.0 equivalents of aryne

precursor, KF, and 18-crown-6 ether in DME solvent at 0 °C (Table 1, entry 13). The *E*-configuration of **3a** was confirmed by literature comparision.[3q]

Scheme 2. Oxindolylidene Acetates from Various Arynes[a,b]

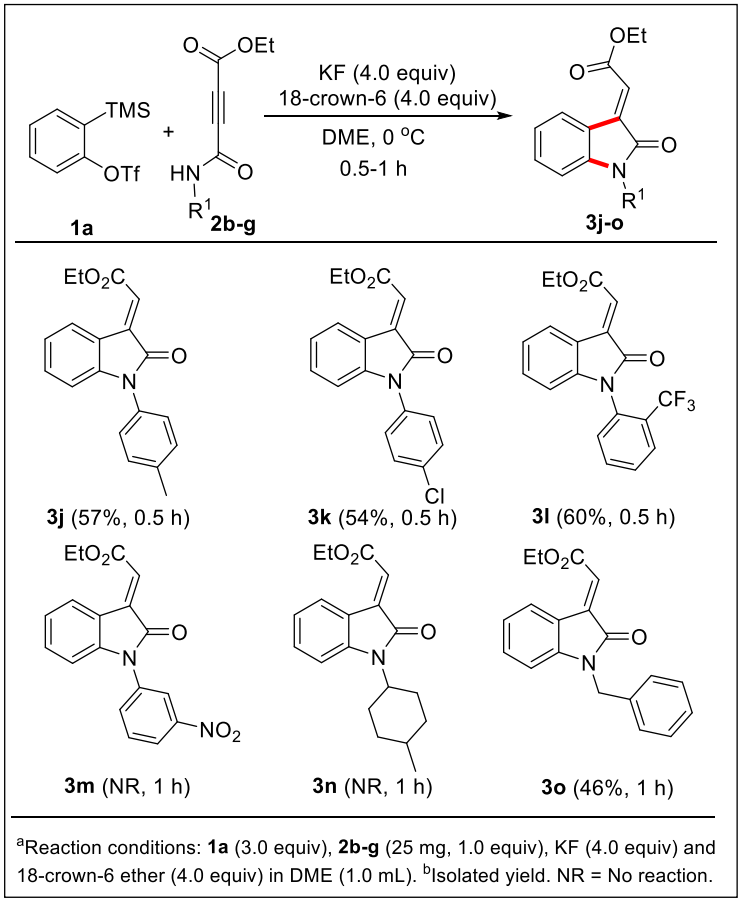


[a]Reaction conditions: 1a-i (0.345 mmol, 3.0 equiv), 2a (0.115 mmol, 25mg, 1.0 equiv), KF (4.0 equiv) and 18-crown-6 ether (4.0 equiv) in DME (1.0 mL). [b]Isolated yield. [c]ND: yield not determined.

To establish the generality and scope of the reaction a variety of aryne precursors **1a-i** was reacted with phenyl carbamoylpropiolate**2a** under the optimized conditions. As outlined in Scheme 2, the reaction worked smoothly with aryne precursors **1b-d** having alkyl substitution to furnish the corresponding oxindolylidene acetates **3b-d** in good to moderate yields. Notably, the aryne precursor 1c having the alkyl substitution near the reaction center also provided the desired compound **3c** in 58% yield, which suggests that the steric hindrance has no effect on the reaction.

The difluoro- substituted aryne precursor **1e**, however, failed to give the corresponding compound **3e**. The aryne precursors **1f-h** having electron releasing groups at different positions delivered the expected products **3f-h** in moderate to good yields. Remarkably, the unsymmetrically substituted aryne precursor **1f** endowed the respective compound **3f** as a single regioisomer because of the strong electronic and steric effects of the methoxy group. The naphthyl aryne precursor **1i** also furnished the corresponding oxindolylidene acetate **3i**, but due to its labile nature, it could not be purified. ^{1}H NMR and HRMS of the crude product clearly indicates the formation of **3i**.

Scheme 3. Substrate Scope of Carbamoylpropiolates[a,b]



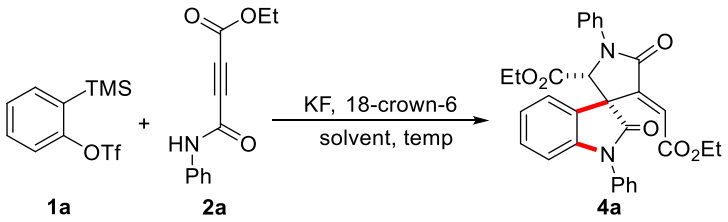
[a]Reaction conditions: **1a** (3.0 equiv), **2b-g** (25 mg, 1.0 equiv), KF (4.0 equiv) and 18-crown-6 ether (4.0 equiv) in DME (1.0 mL). [b]Isolated yield. NR = No reaction.

We also studied the scope of the protocol with various carbamoylpropiolates. Carbamoylpropiolates **2a-g** were synthesized from the corresponding isocyanates.[11] They reacted

smoothly with aryne precursor **1a** and delivered the corresponding oxindolylidene acetates in moderate to good yields (Scheme 3). Carbamoylpropiolates **2b** and **2c** bearing alkyl and halo group respectively at the C4-position of the aryl moiety provided products **3j** and **3k**, respectively in moderate yields. Gratifyingly, carbamoylpropiolate **2d** having $–CF_3$ group at the C2-position of the aryl moiety was well tolerated leading to the desired product **3l** in good yield. We did not observe products **3m** and **3n** from the corresponding carbamoylpropiolates **2e** and **2f**. However, *N*–benzyl substituted carbamoylpropiolate**2g** afforded the corresponding oxindolylidene acetate **3o** in moderate yield.

Further experimentation and detailed analysis of the optimized reaction conditions (Table 1, entry 13) indicated that this protocol can generate spirooxindolo-pyrrolidone**4a** (Table 2).

Table 2: Optimization to Obtain Spiro Products[a-d]



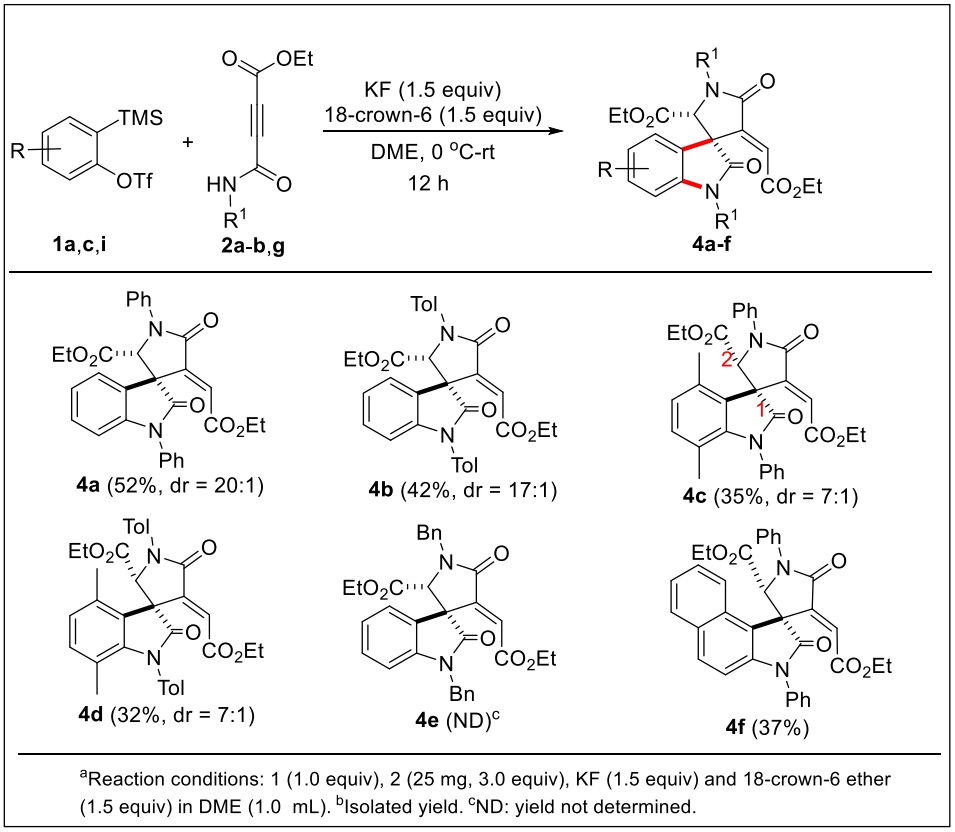
entry	equiv 1a/2a	KF equiv	temp (°C)	Yield (%)
1	3.0:1.0	2.5	0-rt	21
2	1.8:1.0	2.5	0-rt	37
3	1.5:1.0	2.5	0-rt	35
4	1.8:1.0	2.5	rt	13
5	1.0: 1.0	2.5	0-rt	19
6	1.0: 2.0	2.5	0-rt	21
7	**1.0: 3.0**	**1.5**	**0-rt**	**52**
8	1.0: 5.0	1.5	0-rt	41
9	1.0: 5.0	2.5	0-rt	46

[a]Selected entries.[b]Reactions were performed on a 25 mg scale of 2a in DME solvent (1.0 mL), 12 h. [c]Isolated yield.[d]Equivalent quantity of 18-crown-6 ether was added.

In this context, we performed the reaction of **1a**with **2a** at 0 ^{o}C using our optimized reaction conditions and the reaction mixture was then allowed to attain room temperature gradually (Table 2, entry 1). When the reaction was continued for a comparatively longer time, we observed the formation of a new product spirooxindolopyrrolidone **4a**. To improve the yield of **4a**, we screened various parameters and the selected results (Table 2, entries 2-9) indicate that the best yield of the product **4a** was obtained when the reaction was performed using **2a** (3.0 equiv) and **1a** (1.0 equiv) in the presence of KF and 18-crown-6 ether in DME at 0 ^{o}C to room temperature (Table 2, entry 7). The structure of **4a** was confirmed by spectroscopic analysis and by comparison of the NMR data with structurally similar compounds reported in the literature.[5c,l]

After finding the optimal condition for spirooxindolopyrrolidones, we examined the substrate scope (Scheme 4). Aryne precursor **1a** reacted smoothly with both carbamoylpropiolates **2a** and **2b** to furnish the corresponding spiro products **4a** and **4b** in moderate yields. Notably, aryne precursor **1c** bearing alkyl substitution near the reaction center was well tolerated to provide the spirooxindolopyrrolidones**4c** and **4d** in moderate yields. The single-crystal X-ray diffraction data obtained for the spiro-product **4c** confirmed the structure and 1,2-*cis* relative configuration between the ester and amide group, as well as the presence of *E*-olefin. A complex mixture was observed, along with the expected compound **4e**, when *N*–benzyl substituted carbamoylpropiolate **2g** was reacted with the aryne precursor **1a**. ^{1}H NMR and HRMS indicate the formation of **4e**. Naphthyl aryne precursor **1i** on treatment with carbamoylpropiolate**2a** furnished the expected product **4f** in moderate yield.

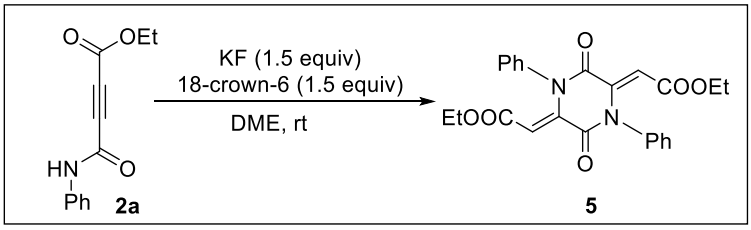
Scheme 4. Spirooxindolo-Pyrrolidones Substrate Scope[a,b]



[a]Reaction conditions: 1 (1.0 equiv), 2 (25 mg, 3.0 equiv), KF (1.5 equiv) and 18-crown-6 ether (1.5 equiv) in DME (1.0 mL). [b]Isolated yield. [c]ND: yield not determined.

It is a mixture of regio- and diastereomers. The isolation of stable product **4f** indirectly confirms the formation of product **3i** (Scheme 2) in the reaction mixture.

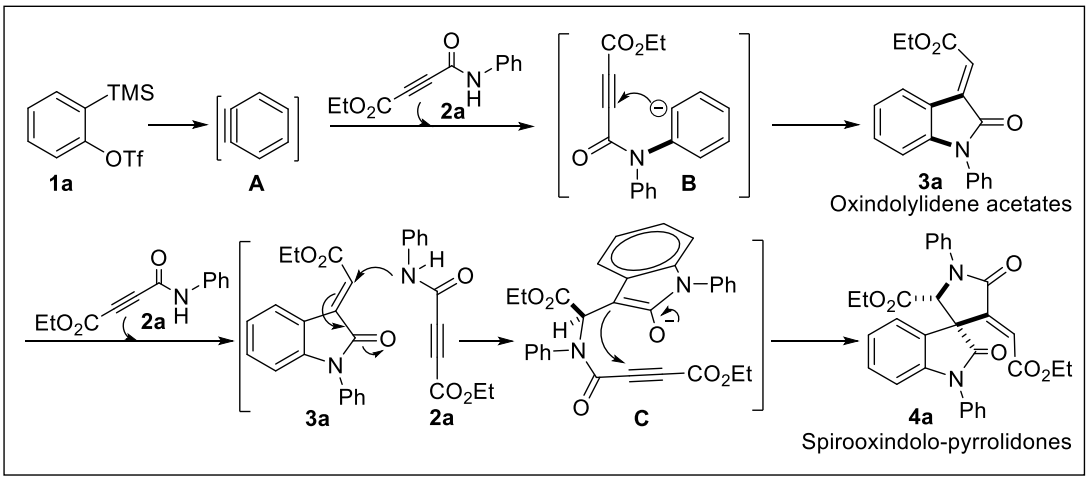
Scheme 5: Dimerization of carbamoylpropiolate



Potassium fluoride mediated dimerization or oligomerization of carbamoylpropiolate and high tenacity of products **4** to react with nucleophiles could be the reason behind the moderate yields (Scheme 5).

On the basis of the literature precedence and our experience in the field of aryne chemistry, a plausible mechanism for the developed protocol is depicted in Scheme 6. The aryne species A was trapped by a nucleophile carbamoylpropiolate **2a** and formed the intermediate B.

Scheme 6. Plausible Mechanism



Subsequently, intramolecular Michael addition provides the cyclized product oxindolylidene acetate **3a**. Furthermore, nucleophilic attack of another molecule of carbamoylpropiolate**2a** on the product **3a** at the most electrophilic carbon[51] generates intermediate C, which upon cyclization provides spirooxindolo-pyrrolidone**4a.**

3.7. Conclusion

In summary, we have demonstrated an efficient and facile route to access pharmacologically important and versatile building blocks, 'oxindolylidene acetates'. The process is also optimized to obtain spirooxindolo-pyrrolidones, which is a common scaffold found in drugs, natural products, and bioactive molecules. This transition-metal-free one-pot approach provides varyingly substituted oxindole scaffolds from the easily available carbamoylpropiolates and aryne precursors. The diversity-oriented protocol developed herein has a good functional group tolerance, which will be useful in generating a focused library of oxindolylidene or

spirooxindolecongeners for SAR studies. Presently, we are working on the application of this protocol in the total syntheses of related drugs and natural products.

3.8. Experimental Procedures:

[A] General procedure for the preparation of carbamoylpropiolates:

Ethyl propiolate (1.0 equiv) was dissolved in THF and the solution was cooled to –78 ^{o}C, followed by the slow addition of *n*-BuLi (1.2 equiv, 1.5 M in hexane). The mixture was stirred for 30 min and a solution of the corresponding isocyanate (300 mg, 1.0 equiv) in THF was added drop-wise. The reaction mixture was then stirred for 2 h at –78 ^{o}C and acetic acid was added to quench the reaction. The reaction mixture was allowed to warm to room temperature, water was added and the aqueous layer was extracted three times with ethyl acetate. The combined organic extract was dried over anhydrous Na_2SO_4 and removal of solvent gave a residue that was subjected to flash column chromatography on silica gel using ethyl acetate:petroleum ether (1:5) as eluent to afford the corresponding compounds.

[B] General experimental procedure for the preparation of compounds 3a-i and 3j-o:

All the reactions were performed on 25 mg of carbamoylpropiolates.

To a flame dried two-neck round-bottom flask containing KF (4.0 equiv) and 18-crown-6 ether (4.0 equiv),*o*-silyl aryl triflate**1**(3.0equiv) in DME was added at room temperature. The solution was cooled to 0 ^{o}C and carbamoylpropiolate**2** (25 mg, 1.0 equiv) in DME was added drop-wise under argon atmosphere. The reaction mixture was stirred at 0 ^{o}Cand the progress was monitored by TLC. After completion of the reaction, water was added. The aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over anhydrous Na_2SO_4 and removal of solvent gave a residue that was subjected to flash column chromatography on silica-gel using ethyl acetate:petroleum ether to afford corresponding compounds.

[C] General experimental procedure for the synthesis of spirooxindolo-pyrrolidones 4a-f:

To a flame dried two-neck round-bottom flask containing KF (1.5equiv) and 18-crown-6 ether (1.5 equiv), *o*-silyl aryl triflate**1**(1.0equiv) in DME (0.5 mL) was added at room temperature. The solution was cooled to 0 ^{o}C and carbamoylpropiolate**2** (25 mg, 3.0 equiv) in DME (0.5mL) was added drop-wise under argon atmosphere. The reaction mixture was allowed to attainroom temperature and stirred until 12 h.The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed on rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate:petroleumto afford corresponding products **4a-f** in good yields.

[D] Representative experimental procedure at 1 mmol scale for the synthesis of the compound 4c:

To a flame dried two-neck round-bottom flask containing KF (87 mg, 1.5 mmol, 1.5equiv) and 18-crown-6 ether (396 mg, 1.5 mmol, 1.5equiv), *o*-silyl aryl triflate**1c** (326 mg, 1 mmol, 1.0 equiv) in DME (10 mL) was added at room temperature. The solution was cooled to 0 ^{o}C and carbamoylpropiolate**2a** (651 mg, 3.0 mmol, 3.0 equiv) in DME (10mL) was added drop-wise under argon atmosphere. The reaction mixture was allowed to attain room temperature and stirred until 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed on a rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate:petroleum (1:10) to afford the corresponding product **4c** in 37% (200 mg) yield.

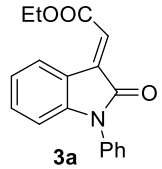
[E] Procedure for the synthesis of dimerization product 5 from carbamoylpropiolate 2a:

To a flame dried two-neck round-bottom flask containing KF (10.0 mg, 1.5 equiv) and 18-crown-6 ether (45 mg, 1.5 equiv), carbamoylpropiolate**2a** (25 mg, 1.0 equiv) in DME was added

drop-wise under argon atmosphere at room temperature. The reaction mixture was allowed to stir at room temperature for 30 minutes. After complete consumption of **2a**, the solvent was removed on a rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate:petroleum to afford compound **5** in 25% yield.

Characterization Data of compounds:

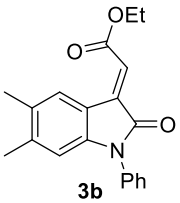
Ethyl (E)-2-(2-oxo-1-phenylindolin-3-ylidene) acetate (3a)



3a

Reaction time: 0.5 h; R*f*: 0.5 (1:10, EtOAc:Pet. Ether); orange solid; mp 106–108 ^{o}C; 24.6 mg, 73% yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.58 (d, *J* = 7.7 Hz, 1H), 7.51–7.43 (m, 2H), 7.38–7.32 (m, 3H), 7.27–7.24 (m, 1H), 7.07–7.00 (m, 1H), 6.94 (s, 1H), 6.72 (d, *J* = 7.96 Hz, 1H), 4.29 (q, *J* = 7 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 167, 165.6, 145.9, 137.6, 133.9, 132.3, 129.7, 128.9, 128.3, 126.6, 123.3, 123.1, 119.9, 109.5, 61.2, 14.2. **LC-MS (M+H)**: 294.

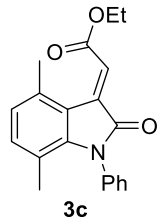
Ethyl (E)-2-(5,6-dimethyl-2-oxo-1-phenylindolin-3-ylidene)acetate (3b)



3b

Reaction time: 0.5 h; R*f*: 0.4 (1:10, EtOAc:Pet. Ether); yellow solid; mp 118–119 ^{o}C; 22.5 mg, 61% yield.**^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.35 (s, 1H), 7.48–7.44 (m, 2H), 7.36–7.32 (m, 3H), 6.84 (s, 1H), 6.51 (s, 1H), 4.28 (q, *J* = 7.32 Hz, 2H), 2.21 (s, 3H), 2.16 (s, 3H), 1.32 (t, *J* = 7 Hz, 3 H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 167.3, 165.9, 144.3, 142, 138, 134.2, 131.3, 129.8, 129.6, 128.1, 126.6, 121.3, 117.6, 110.8, 61.1, 20.8, 19.5, 14.2. **ESI HRMS:** calcd for $C_{20}H_{19}NO_3$ $[M+H]^+$: 322.1438, found: 322.1440.

Ethyl (E)-2-(4,7-dimethyl-2-oxo-1-phenylindolin-3-ylidene)acetate (3c)

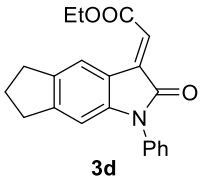


3c

Reaction time: 1 h; R*f*: 0.5 (1:10, EtOAc:Pet. Ether); yellow solid; mp 130–131 ^{o}C; 21.4 mg, 58% yield.**^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.41–7.34 (m, 3H), 7.24 (d, *J* = 7.3 Hz, 2H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.76 (s, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 4.29

(q, *J* = 7.3 Hz, 2H), 2.40 (s, 3H), 1.57 (s, 3H), 1.28 (t, *J* = 7 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 167, 166.2, 141.9, 136.4, 134.3, 133.3, 132.3, 129.2, 128.7, 128.6, 125.8, 125.3, 119.2, 118.5, 61.8, 20.5, 18.6, 14. **ESI HRMS:** calcd for $C_{20}H_{19}NO_3$ $[M+H]^+$: 322.1438, found: 322.1441.

Ethyl (E)-2-(2-oxo-1-phenyl-1,5,6,7-tetrahydrocyclopenta[f]indol-3(2H)-ylidene) acetate (3d)

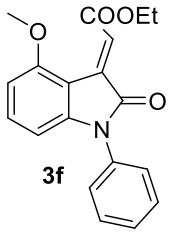


3d

Reaction time: 1 h; R*f*: 0.5 (1:10, EtOAc:Pet. Ether); yellow solid; mp 188–190 ^{o}C; 17.6 mg, 46% yield.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.44 (s, 1H), 7.48–7.44 (m, 2H), 7.36–7.32 (m, 3H), 6.85 (s, 1H), 6.58 (s, 1H), 4.27 (q, *J* = 6.9 Hz, 2H), 2.86–2.75 (m, 4H), 2.01 (quint, *J* = 7.3 Hz, 2H), 1.31 (t, *J* = 7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ167.5, 166, 149.7, 145.1, 139, 138.2, 134.2, 129.7, 128.1, 126.7, 124.8, 121.2, 118.3, 106, 61, 33.7, 32.3, 25.4, 14.2.**ESI HRMS:** calcd for $C_{21}H_{19}NO_3$ $[M+H]^+$: 334.1438, found: 334.1441.

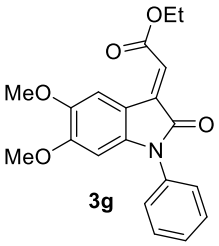
Ethyl (E)-2-(4-methoxy-2-oxo-1-phenylindolin-3-ylidene) acetate (3f)



3f

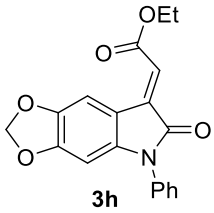
Reaction time: 1 h; R*f*: 0.4 (1:10, EtOAc:Pet. Ether); thick oil; 16.7 mg, 45% yield.**^{1}H NMR (400 MHz, $CDCl_3$)**δ 7.46–7.42 (m, 2H), 7.35–7.31 (m, 3H), 7.15 (t, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 6.35 (d, *J* = 7.9 Hz, 1H), 4.30 (q, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.3, 167.1, 156.6, 145.9, 134.2, 132.5, 129.6, 128.9, 128.2, 126.7, 123.9, 107.9, 106.1, 102.8, 61, 55.6, 14.2. **ESI HRMS**: calcd for $C_{19}H_{17}NO_4$ $[M+H]^+$: 324.1230, found: 324.1231.

Ethyl (E)-2-(5,6-dimethoxy-2-oxo-1-phenylindolin-3-ylidene)acetate (3g)



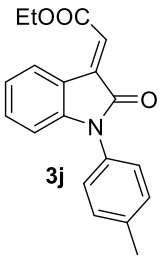
Reaction time: 1 h; R*f*: 0.4 (1: 9, EtOAc:Pet.Ether); yellow solid; mp 118–119 ^{o}C; 20.7 mg, 51% yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.36 (s, 1H), 7.49–7.45 (m, 2H), 7.37–7.33 (m, 3H), 6.76 (s, 1H), 6.28 (s, 1H), 4.26 (q, *J* = 6.7 Hz, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ167.6, 166.2, 153, 144.9, 141.8, 138, 134.1, 129.8, 128.2, 126.5, 119.6, 112.6, 111.4, 94.2, 61, 56.5, 56.2, 14.2. **ESI HRMS:** calcd for $C_{20}H_{19}NO_5$ $[M+H]^+$: 354.1336, found: 354.1338.

Ethyl(E)-2-(6-oxo-5-phenyl-5,6-dihydro-7H-[1,3]dioxolo[4,5-f]indol-7-ylidene)acetate (3h)



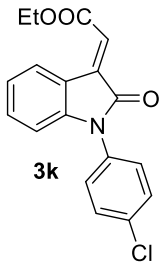
Reaction time: 0.5 h; R*f*: 0.2 (1:9, EtOAc:Pet. Ether); Red solid; mp 166–168 ^{o}C; 27.2 mg, 70% yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.20 (s, 1H), 7.47–7.43 (m, 2H), 7.36 –7.29 (m, 3H), 6.76 (s, 1H), 6.27 (s, 1H), 5.90 (s, 2H), 4.25 (q, *J* = 7.3 Hz, 2H), 1.30 (t, *J* = 7 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ167.5, 166, 151.1, 143.6, 143.1, 137.7, 133.9, 129.7, 128.3, 126.6, 120, 112.4, 109.3, 101.7, 92.8, 61.1, 14.2.**ESI HRMS:** calcd for $C_{19}H_{15}NO_5$ $[M+H]^+$: 338.1023, found: 338.1026.

Ethyl (E)-2-(2-oxo-1-(p-tolyl)indolin-3-ylidene)acetate (3j)



Reaction time: 0.5 h; R*f*: 0.5 (1:9, EtOAc:Pet. Ether); yellow solid; mp 100–102 ^{o}C; 20.1 mg, 57% yield.**^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.56 (d, *J* = 7.9 Hz, 1H), 7.26–7.23 (m, 2H), 7.21–7.18 (m, 3H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 4.28 (q, *J* = 6.9 Hz, 2H), 2.35 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 167, 165.7, 146.2, 138.3, 137.7, 132.3, 131.2, 130.3, 128.9, 126.4, 123.1, 122.9, 119.8, 109.4, 61.2, 21.2, 14.2. **ESI HRMS:** Calcd for $C_{19}H_{17}NO_3$ $[M+H]^+$: 308.1281, found: 308.1275.

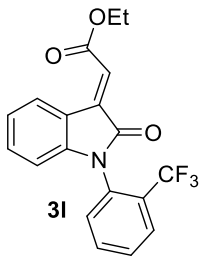
Ethyl (E)-2-(1-(4-chlorophenyl)-2-oxoindolin-3-ylidene) acetate (3k)



3k

Reaction time: 0.5 h; R*f*: 0.4 (1:9, EtOAc:Pet. Ether); yellow solid; mp 139–140 ^{o}C; 20.3 mg, 54% yield.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.58 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 4.29 (q, *J* = 6.8 Hz, 2H), 1.32 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.9, 165.5, 145.4, 137.3, 134, 132.5, 132.4, 129.9, 129.1, 127.9, 123.5, 123.4, 119.9, 109.3, 61.3, 14.2.**ESI HRMS:** calcd for $C_{18}H_{14}NClO_3$ [M+ Na]$^{+}$: 350.0554, found: 350.0554.

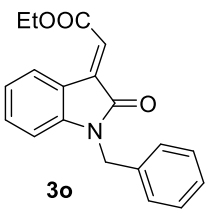
Ethyl (E)-2-(2-oxo-1-(2-(trifluoromethyl)phenyl)indolin-3-ylidene)acetate (3l)



3l

Reaction time: 0.5 h; R*f*: 0.5 (1:9, EtOAc:Pet. Ether); yellow solid; mp 116–118 ^{o}C; 24.9 mg, 60% yield.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.57 (d, *J* = 7.3 Hz, 1H),7.81 (d, *J* = 7.9 Hz, 1H),7.70– 7.66 (m, 1H), 7.60–7.56 (m, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.22–7.19 (m, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.92 (s, 1H)), 6.27 (d, *J* = 7.9 Hz, 1H), 4.29 (q, *J* = 7 Hz, 2H), 1.32 (t, *J* = 7 Hz, 3H). **^{13}C NMR (400 MHz, $CDCl_3$)** δ 167.5, 165.6, 146.7, 137.2, 133.8, 132.4, 131.3, 130 (q, J^{2}= 31.4 Hz), 129.9, 129.4, 128.8, 128 (q, J^{3}= 4.7 Hz), 123.4, 123.3, 122.8 (q, J^{1}= 273.4 Hz), 119.8, 109.6, 61.3, 14.2.**ESI HRMS** m/z: calcd for $C_{19}H_{14}NO_3F_3$ [M+H]$^{+}$: 362.0999, found: 362.0991.

Ethyl (E)-2-(1-benzyl-2-oxoindolin-3-ylidene) acetate (3o)

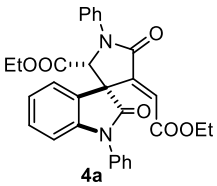


3o

Reaction time: 1 h; R*f*: 0.4 (1:9, EtOAc: Pet. Ether); thick oil; 16.2 mg, 46% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.49 (d, *J* = 7.9 Hz, 1H), 7.26–7.17 (m, 6H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 4.87 (s, 2H), 4.27 (q, *J* = 7.5 Hz, 2H), 1.31 (t, *J* =7.5 Hz, 3H). **^{13}C NMR (100 MHz,**

$CDCl_3$) δ 167.7, 165.7, 145.1, 137.7, 135.4, 132.3, 128.8, 127.7, 127.2, 122.9, 122.8, 122.2, 120, 109.1, 61.2, 43.9, 14.2. **ESI HRMS:** calcd for $C_{19}H_{17}NO_3$ [M+ H]$^+$: 308.1281, found: 308.1275.

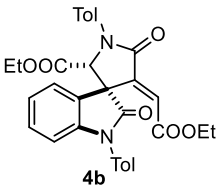
Ethyl (E)-4'-(2-ethoxy-2-oxoethylidene)-2,5'-dioxo-1,1'-diphenylspiro[indoline-3,3'-pyrrolidine]-2'-carboxylate (4a)



4a

Reaction time: 12 h; R*f*: 0.5 (1:4, EtOAc: Pet. Ether); yellow thick oil; 10.2 mg, 52%; dr 20:1.**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53–7.48 (m, 6H), 7.41–7.40 (m, 1H), 7.36 (t, *J* = 8 Hz, 2H), 7.22–7.19 (m, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 6.92 (t, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 5.30 (s, 1H), 4.0–3.89 (m, 2H), 3.68–3.61 (m, 1H), 3.52–3.47 (m, 1H), 1.07 (t, *J* = 7. 1 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.1, 166.5, 164.8, 163.8, 145.9, 145.8, 137.5, 134.5, 129.7, 129.4, 129.1, 128.5, 127.1, 126.7, 126.4, 124.5, 124.3, 122.9, 122.5, 109, 68, 61.7, 61.1, 53.9, 13.9, 13.5. **ESI HRMS:** calcd for $C_{30}H_{26}N_2O_6$ [M+ H]$^+$: 511.1864, found: 511.1857.

Ethyl (E)-4'-(2-ethoxy-2-oxoethylidene)-2,5'-dioxo-1,1'-di-p-tolylspiro[indoline-3,3'-pyrrolidine]-2'-carboxylate (4b)

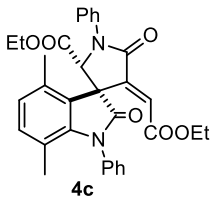


4b

Reaction time: 12 h; R*f*: 0.5 (1:4, EtOAc:Pet. Ether); thick oil; 8.1 mg, 42%; dr 17:1.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41–7.35 (m, 4H), 7.30 (d, *J* = 8 Hz, 2H), 7.16–7.11 (m, 4H), 7.0 (d, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.68 (d, *J* = 8 Hz, 1H) 5.26 (s, 1H), 4.0–3.86 (m, 2H), 3.67–3.60 (m, 1H), 3.52–3.44 (m, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 1.06 (t, *J* = 7 Hz, 3H), 0.74 (t, *J* = 7 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)**δ 174.2, 166.6, 164.8, 163.8, 146.1, 145.9, 138.5, 136.7, 134.9, 131.8, 130.3, 129.7, 129.5, 129.3, 127.6, 126.9, 126.4, 124.3, 122.7, 122.6, 113, 109, 68, 61.6, 61, 53.9, 21.3, 21, 13.8, 13.5.

ESI HRMS: calcd for $C_{32}H_{30}N_2O_6$ [M+ H]$^+$: 539.2177, found: 539.2179.

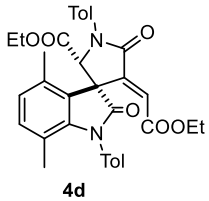
Ethyl (E)-4'-(2-ethoxy-2-oxoethylidene)-4,7-dimethyl-2,5'-dioxo 1,1'diphenylspiro [indoline-3,3'-pyrrolidine]-2'-carboxylate (4c)



4c

Reaction time: 12 h; R*f*: 0.5 (1:4, EtOAc: Pet. Ether); mp 91–93 ^{o}C; 7.2 mg, 35%; dr 7:1.**^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.62 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* =7.6 Hz, 1H), 7.43–7.39 (m, 3H), 7.38–7.33 (m, 2H), 7.32 –7.28 (m, 1H), 7.21–7.18 (m, 2H), 7.01 (s, 1H), 6.84 (d, *J* = 8 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 4.94 (s, 1H), 4.07–3.93 (m, 4H), 2.06 (s, 3H), 1.62 (s, 3H), 1.12 (t, *J* = 7 Hz, 3H), 1.0 (t, *J* = 7 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 172.8, 168.1, 165.1, 163.9, 145.7, 142.2, 137.4, 137.1, 132.7, 130.3, 129.5, 129.2, 129.1, 128.9, 128.8, 126.5, 125.5, 125.2, 121.5, 118.2, 68.6, 62.5, 61, 54.7, 18.7, 18.4, 13.9, 13.7. **ESI HRMS:** calcd for $C_{32}H_{30}N_2O_6$ [M+ H]$^+$: 539.2177, found: 539.2177.

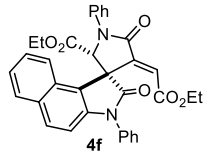
Ethyl (E)-4'-(2-ethoxy-2-oxoethylidene)-4,7-dimethyl-2,5'-dioxo-1,1'-di-p-tolylspiro [indoline-3,3'-pyrrolidine]-2'-carboxylate (4d)



4d

Reaction time: 12 h; R*f*: 0.5 (1:4 EtOAc: Pet. Ether); thick oil; 6.6 mg, 32%; dr 7:1. **^{1}H NMR (400 MHz, CDCl$_3$)**δ 7.50–7.48 (m, 1H), 7.42 (d, *J* = 8.5 Hz,2H), 7.26–7.20 (m, 1H), 7.18–7.13 (m, 4H), 6.99 (s, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 4.89 (s, 1H), 4.06–3.94 (m, 4H), 2.35 (s, 3H), 2.28 (s, 3H), 2.05 (s, 3H), 1.64 (s, 3H), 1.11 (t, *J* = 7 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 172.8, 168.2, 165.1, 163.9, 145.9, 142.3, 138.7, 136.4, 134.8, 134.4, 132.6, 130.3, 130.3, 129.9, 129.8, 129.7, 129.5, 129.2, 128.8, 125.3, 124.9, 121.5, 118.1, 68.7, 62.4, 60.9, 54.7, 21.3, 21, 18.7, 18.3, 13.9, 13.8. **ESI HRMS:** calcd for $C_{34}H_{34}N_2O_6$ [M+ H]$^+$: 567.2490, found: 567.2491.

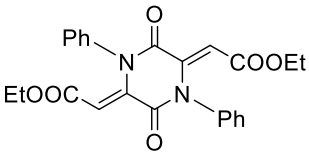
Ethyl (1R,E)-4'-(2-ethoxy-2-oxoethylidene)-2,5'-dioxo-1',3-diphenyl-2,3-dihydrospiro [benzo[e]indole-1,3'-pyrrolidine]-2'-carboxylate (4f)



4f

Reaction time: 12 h; R*f*: 0.5 (1:4, EtOAc:Pet. Ether); thick oil; 7.9 mg, 37%. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.83–7.75 (m, 2 H), 7.72–7.67 (m, 1H), 7.58–7.49 (m, 10H), 7.40–7.33 (m, 7H), 7.31–7.26 (m, 2H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.08 (s, 1H), 7.07–7.04 (m, 1H), 7.01 (d, *J* = 6.1 Hz, 1H), 5.14 (s, 1H), 4.04–3.91 (m, 4H), 3.87–3.76 (m, 1H), 3.55–3.47 (m, 1H), 3.23–3.17 (m, 1H), 1.04–0.94 (m, 6H), 0.50 (t, *J* = 7.0 Hz, 1H), 0.39 (t, *J* = 7.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.9, 167.8, 165.2, 163.7, 146.2, 143.3, 137.4, 134.5, 131.1, 130.7, 130.4, 130.1, 129.8, 129.7, 129.2, 129.1.128.6, 128.4, 127.5, 127.2, 126.9, 127.3, 127.2, 126.9, 125.7, 123.9, 122.9, 122.5, 121.1, 110.8, 68.7, 68.4, 62.4, 60.9, 55.3, 13.8, 13.7.**ESI HRMS:** calcd for $C_{34}H_{28}N_2O_6$ $[M+ H]^+$: 561.2020, found: 561.2014.

Diethyl2,2'-(3,6-dioxo-1,4-diphenylpiperazine-2,5-diylidene)(2Z,2'Z)-diacetate (5)



5

R*f*: 0.2 (1:4, EtOAc:Pet. Ether); thick oil; 12.5 mg, 25%. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 –7.49 (m, 2H), 7.46–7.42 (m, 1H), 7.40–7.35 (m, 2H), 7.32–7.26 (m, 3H), 7.25–7.22 (m, 2H), 6.52 (s, 1H), 5.30 (s, 1H), 4.14 (q, *J* = 7 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.6, 164, 157.1, 155.3, 136.7, 136, 135.7, 135, 130.5, 129.7, 128.9, 128.7, 128.2, 128, 114.6, 112.4, 61.6, 61.1, 13.8, 13.7.**ESI HRMS:** calcd for $C_{24}H_{22}N_2O_6$ $[M+ Na]^+$: 457.1370, found: 457.1367.

3.9. References

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3.10. Selected Spectra

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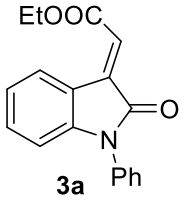

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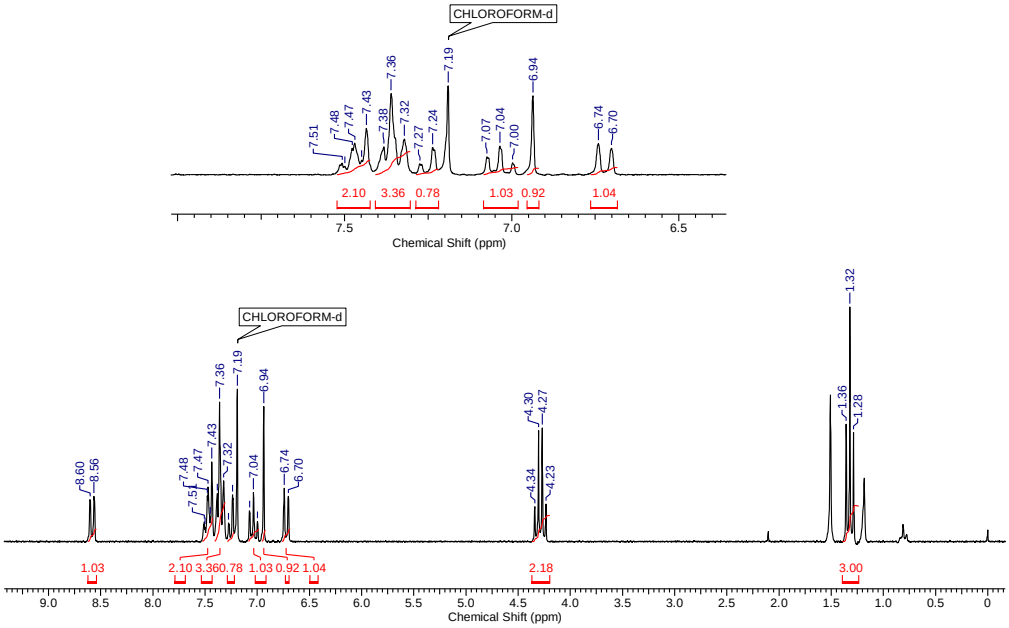

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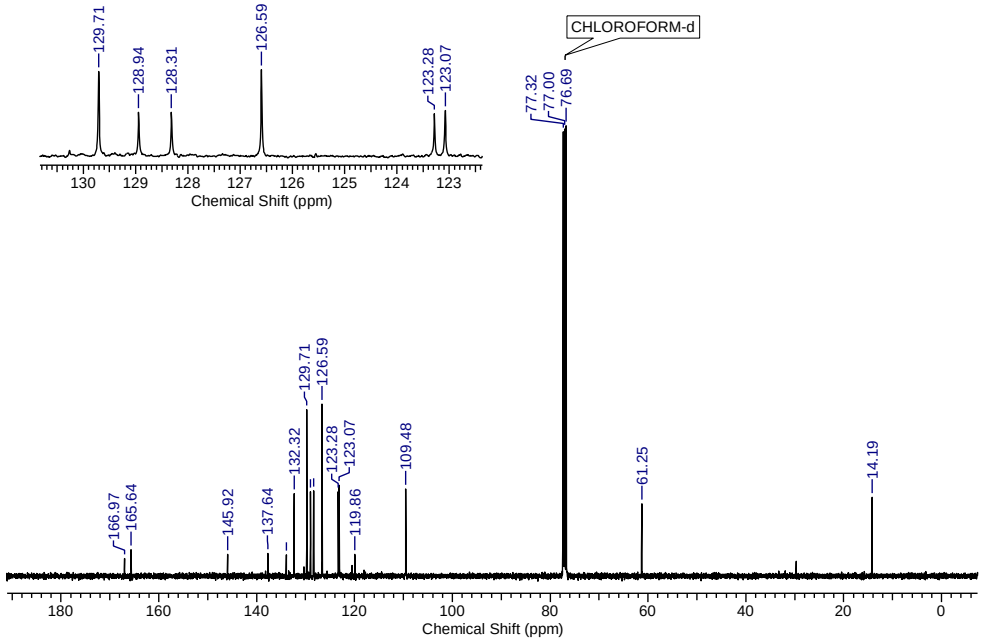

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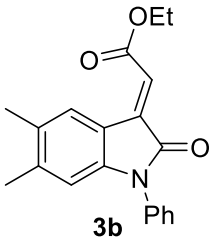

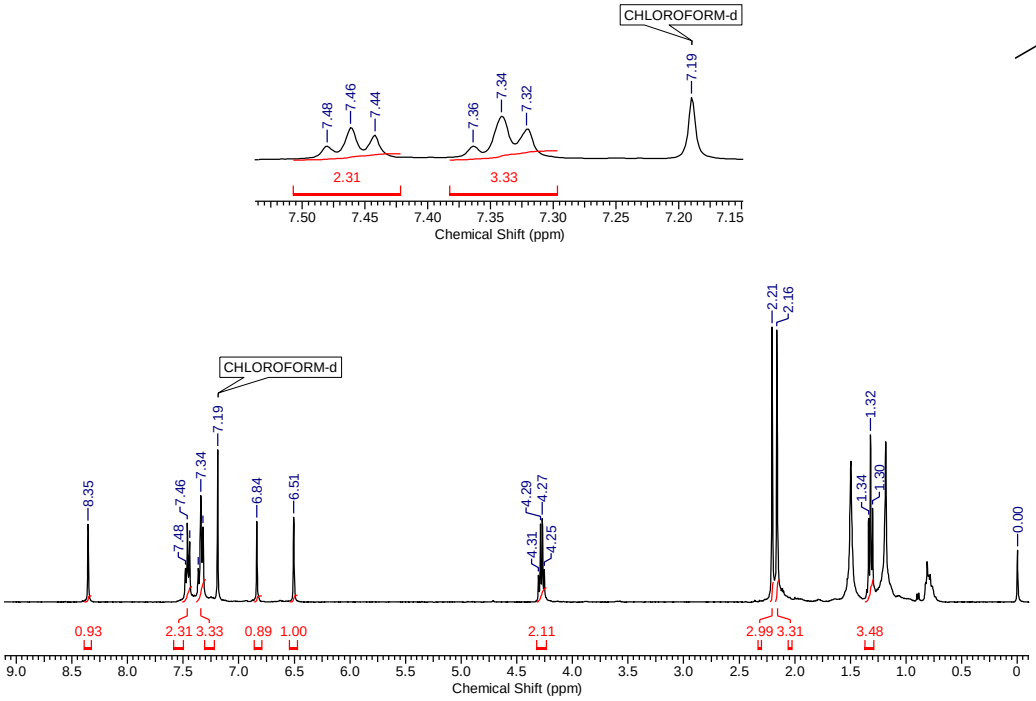

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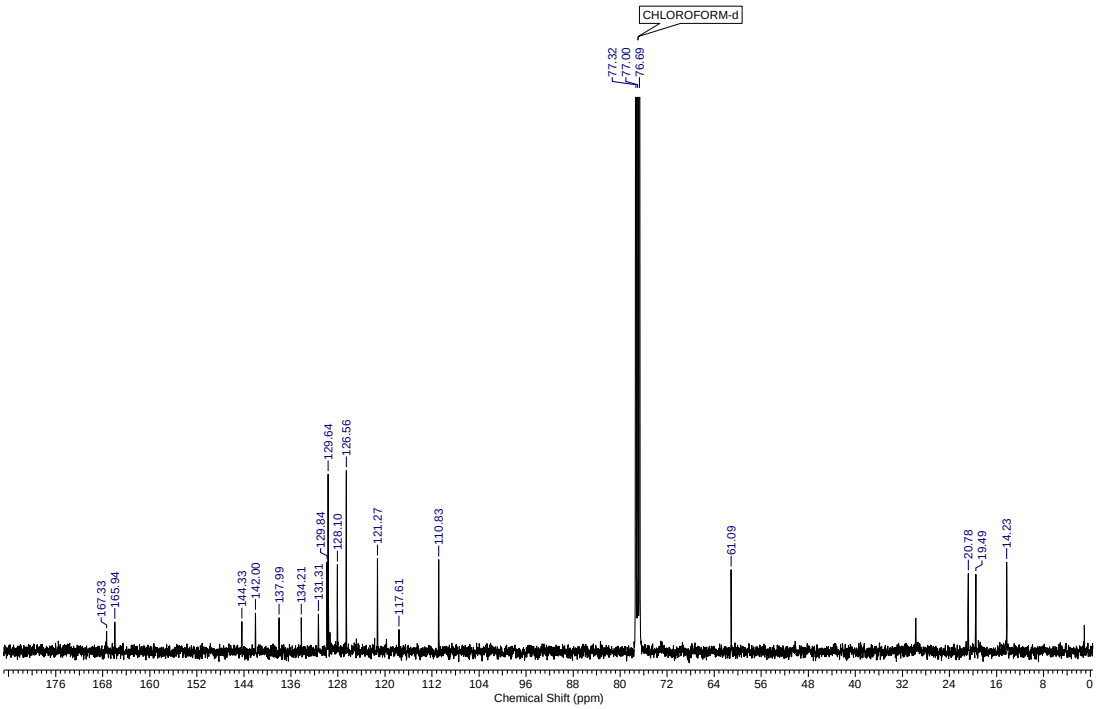

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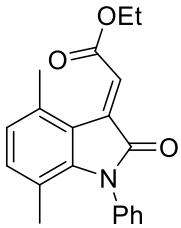

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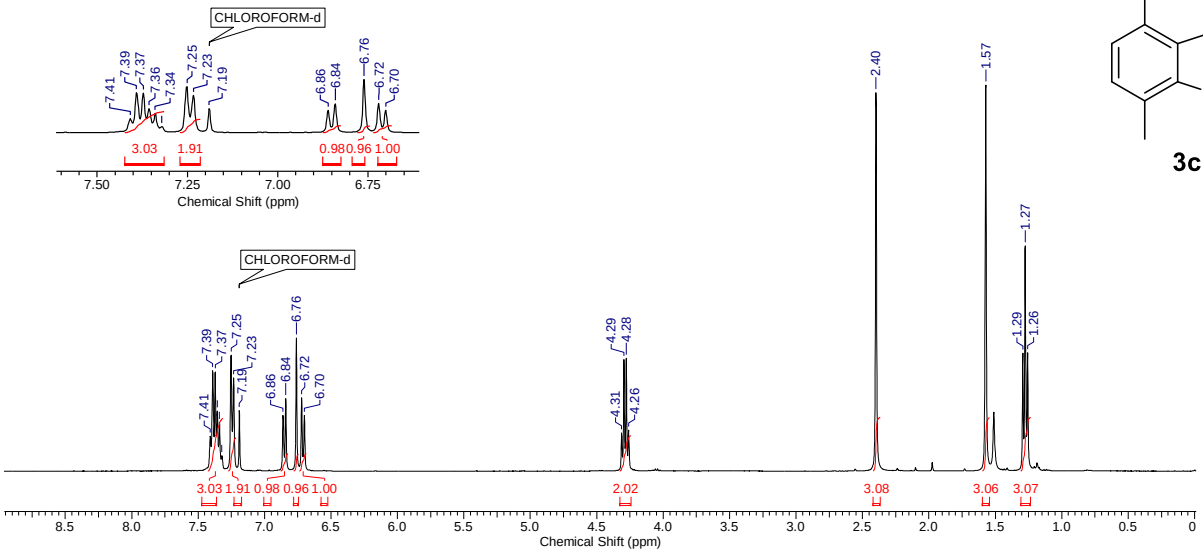

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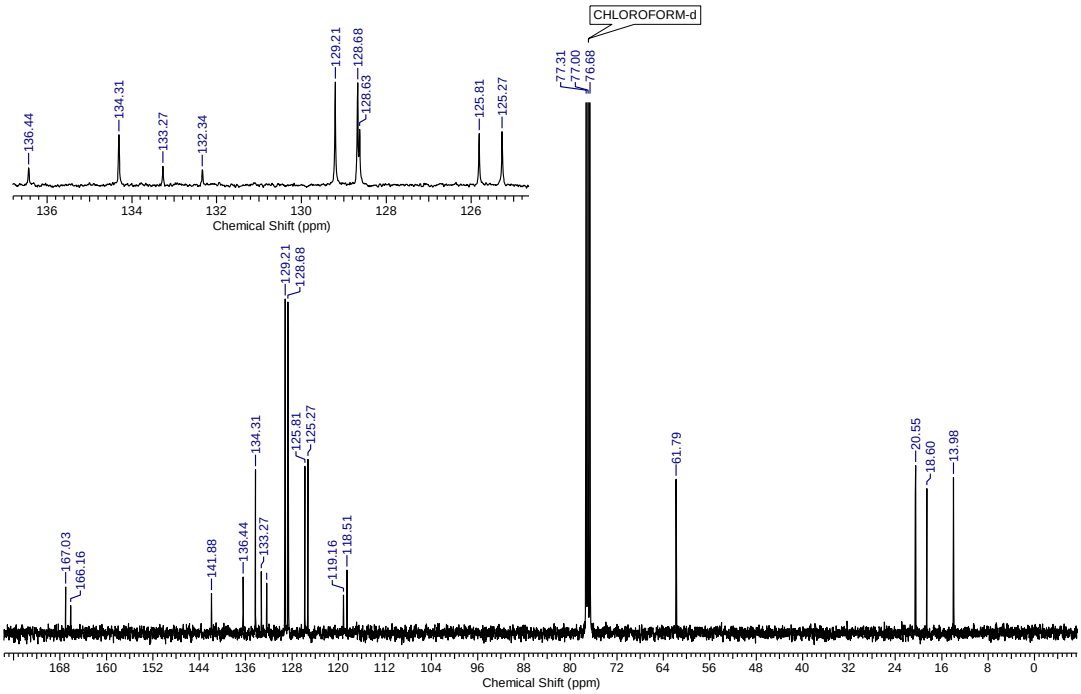

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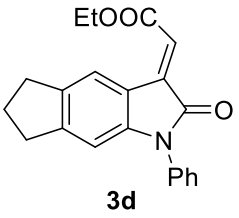

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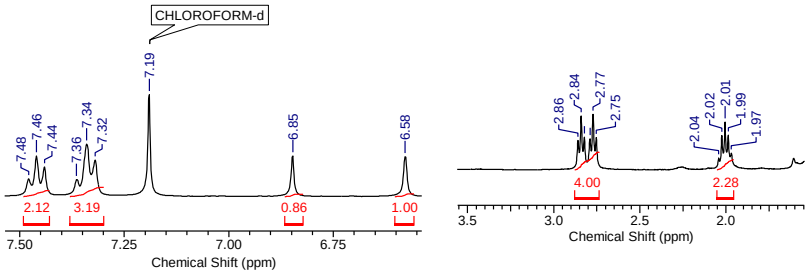

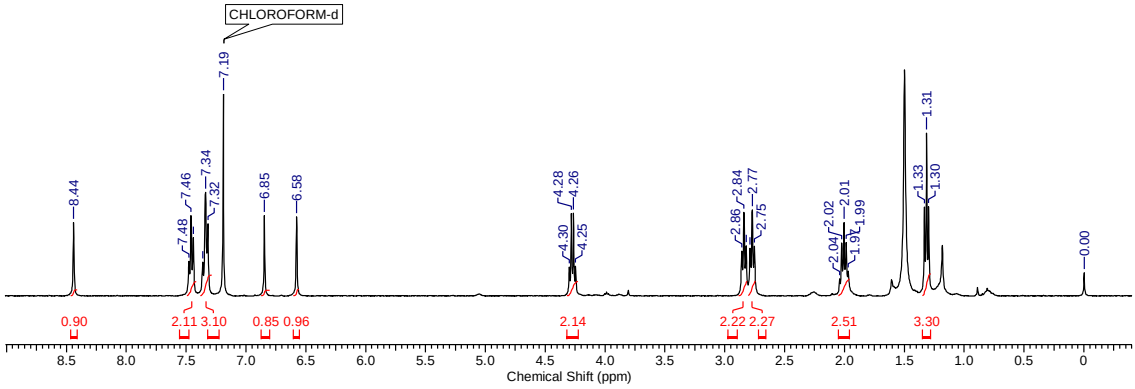

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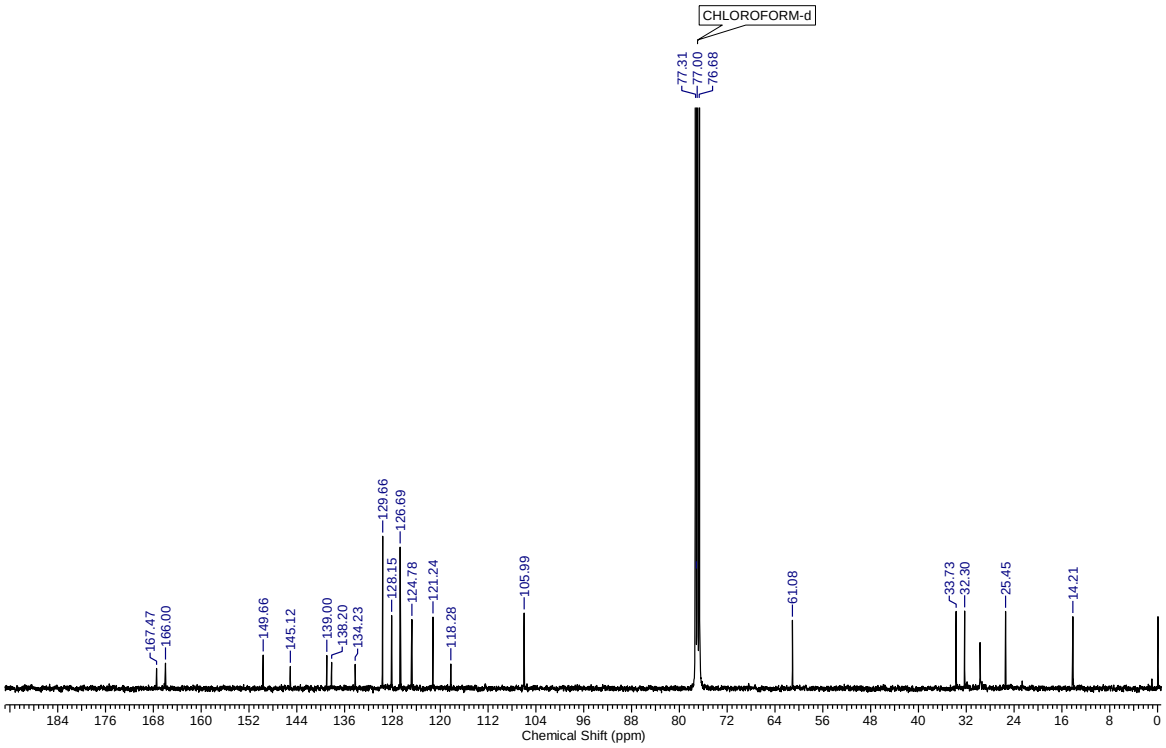

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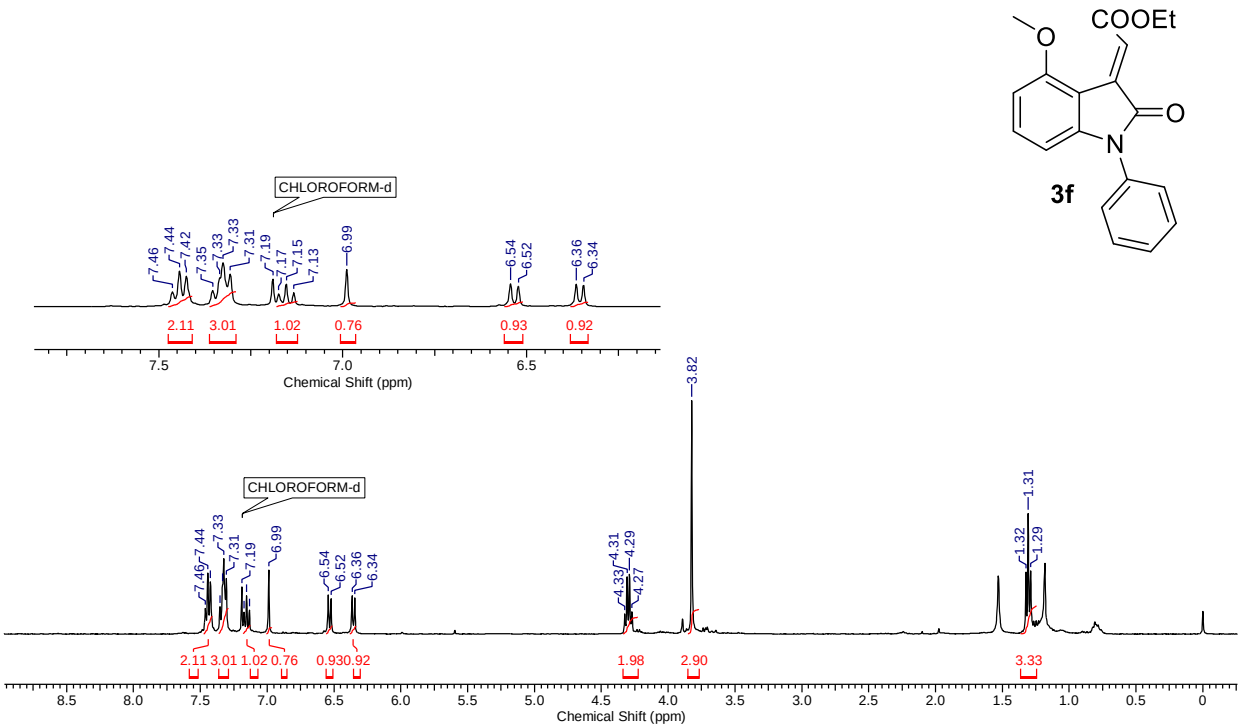

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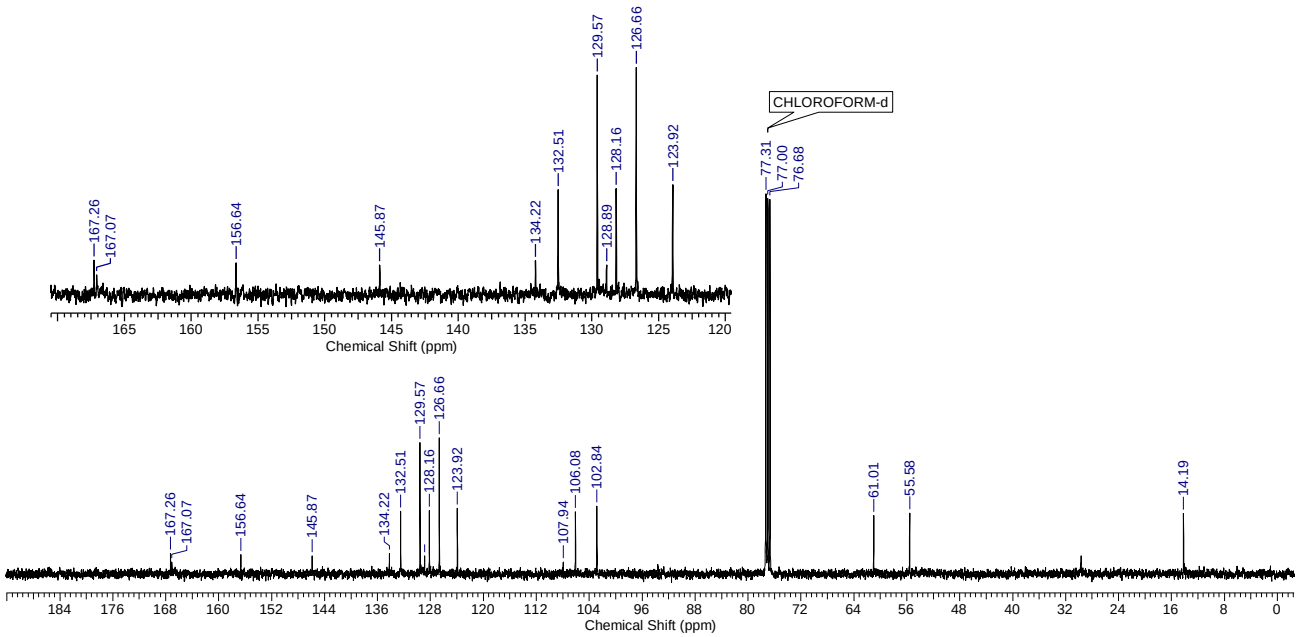

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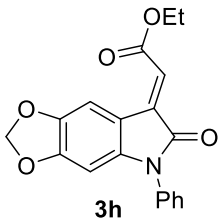

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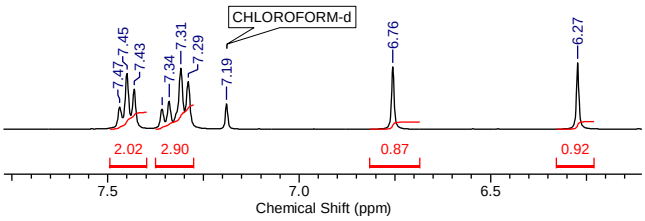

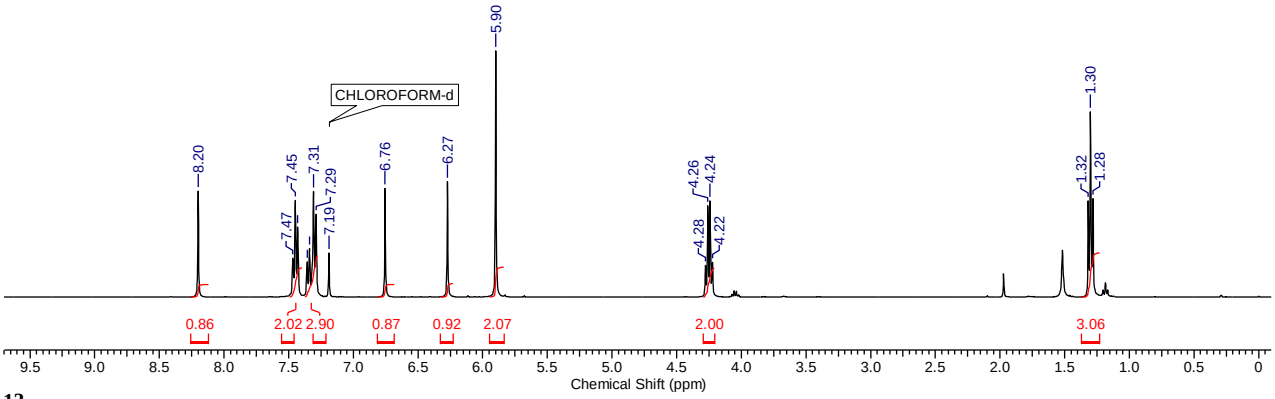

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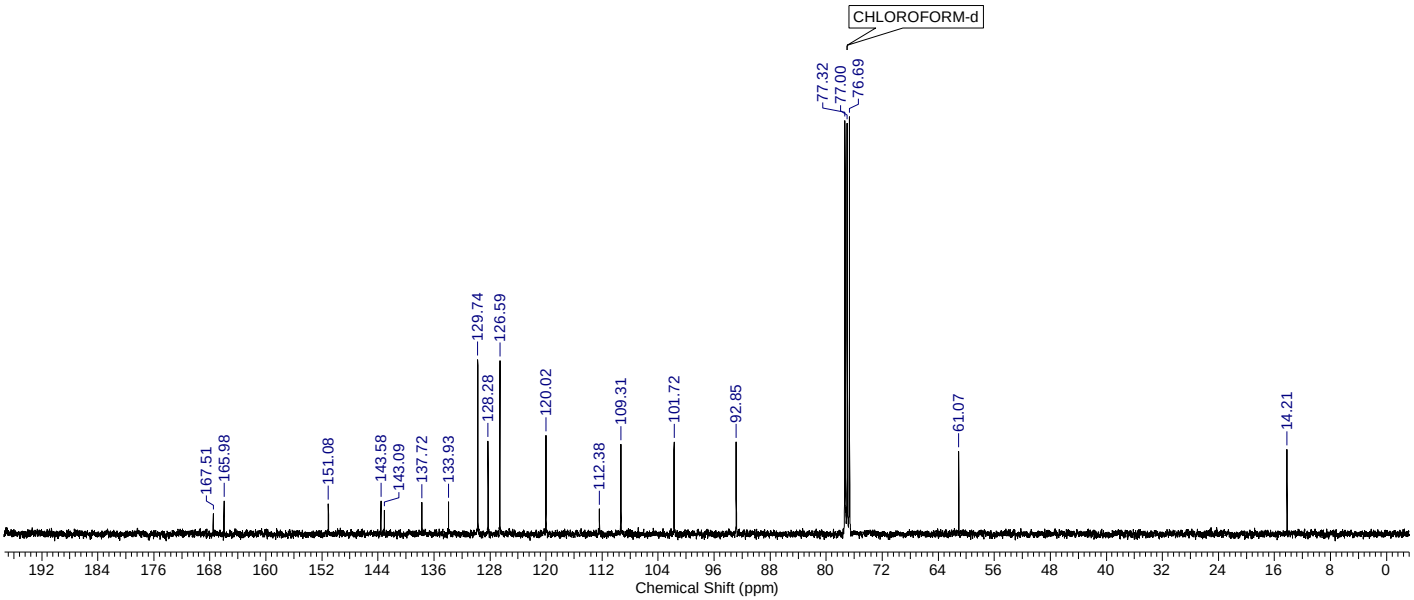

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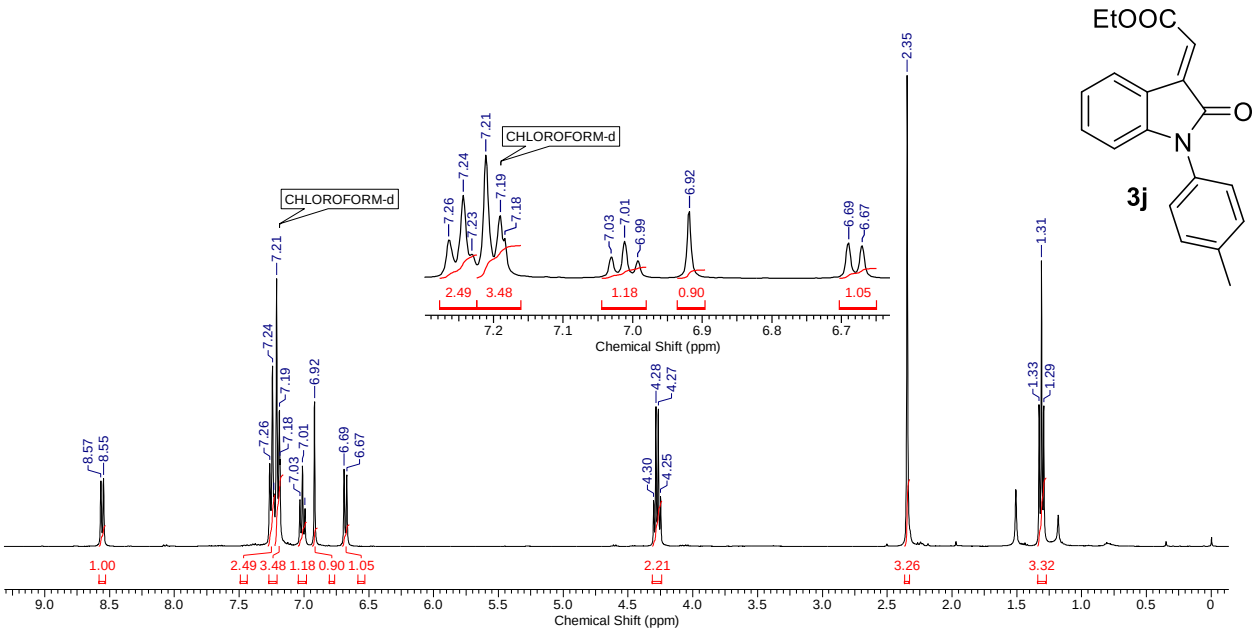

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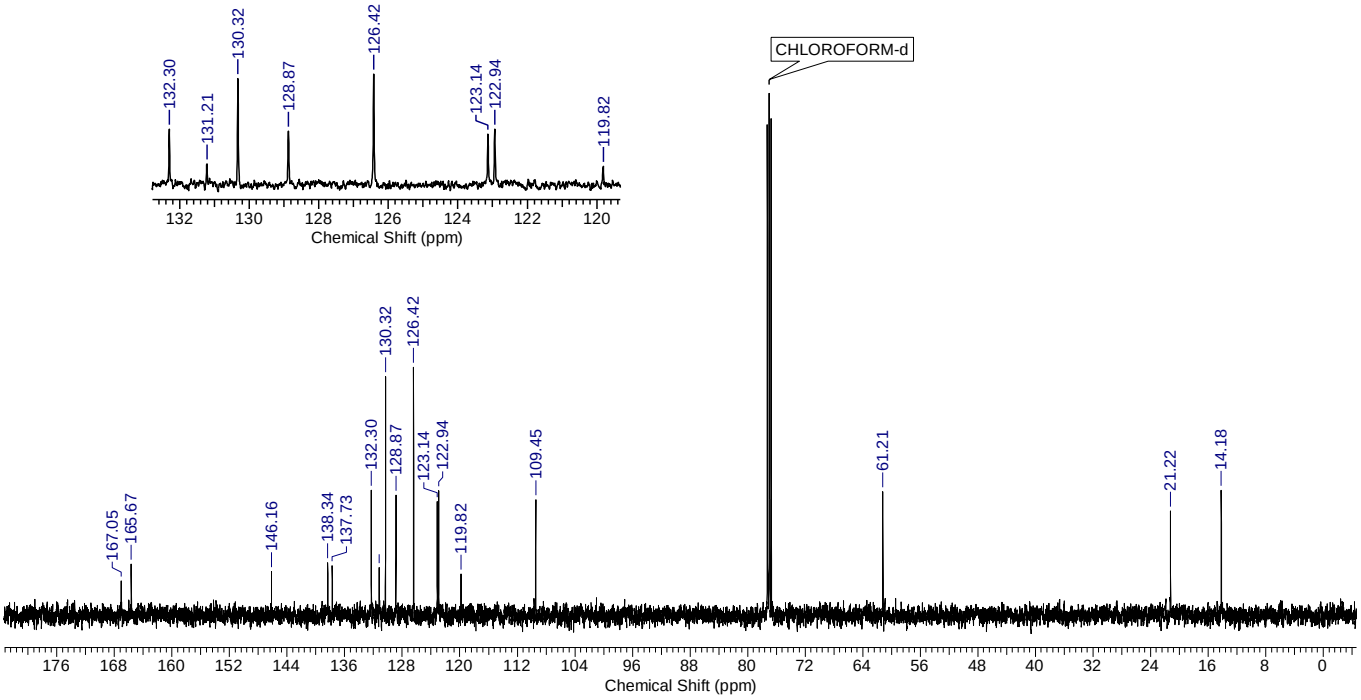

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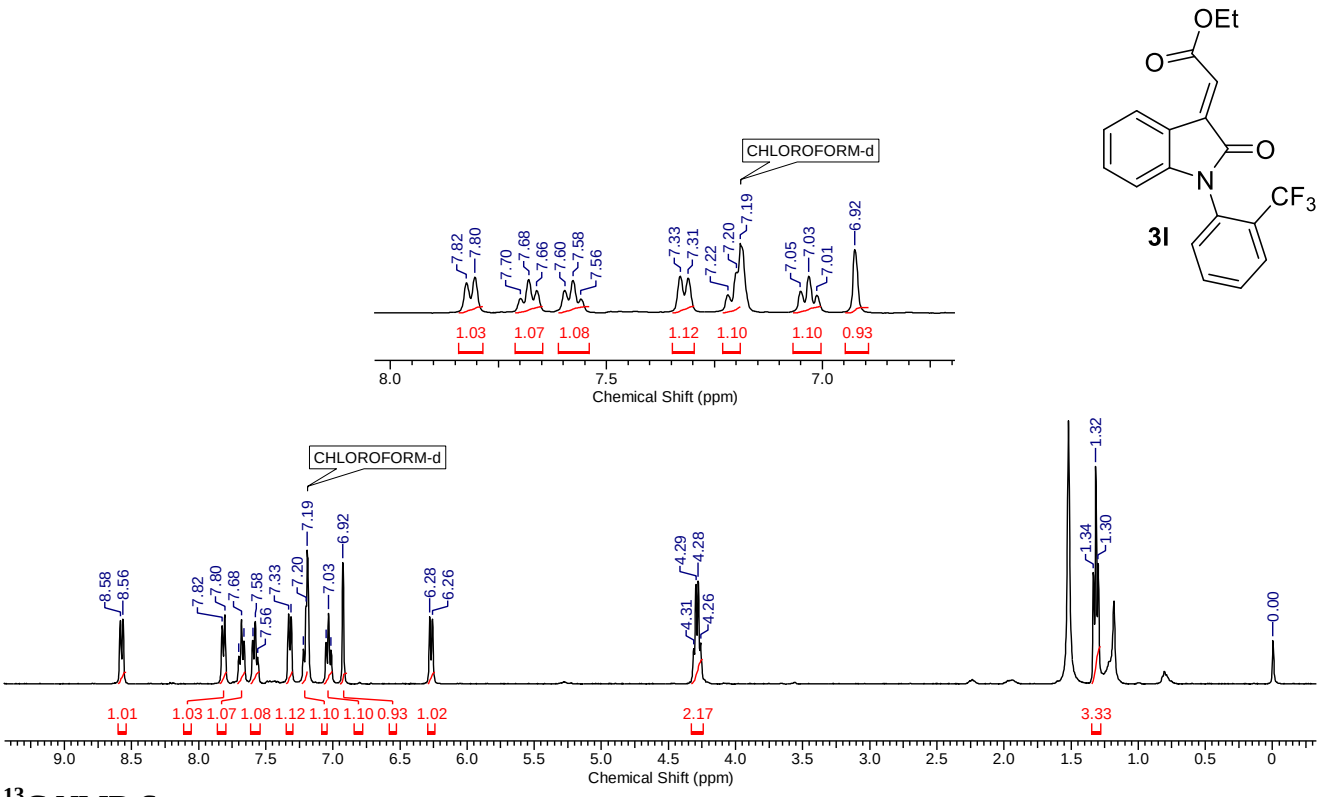

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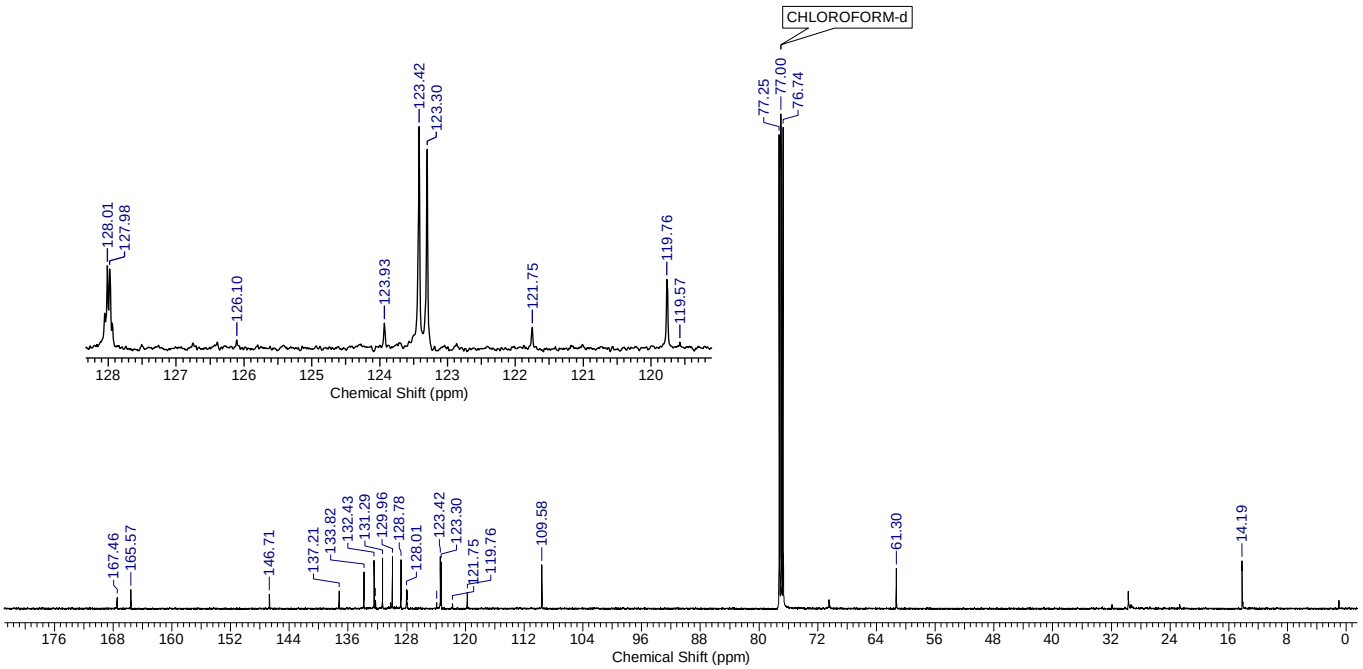

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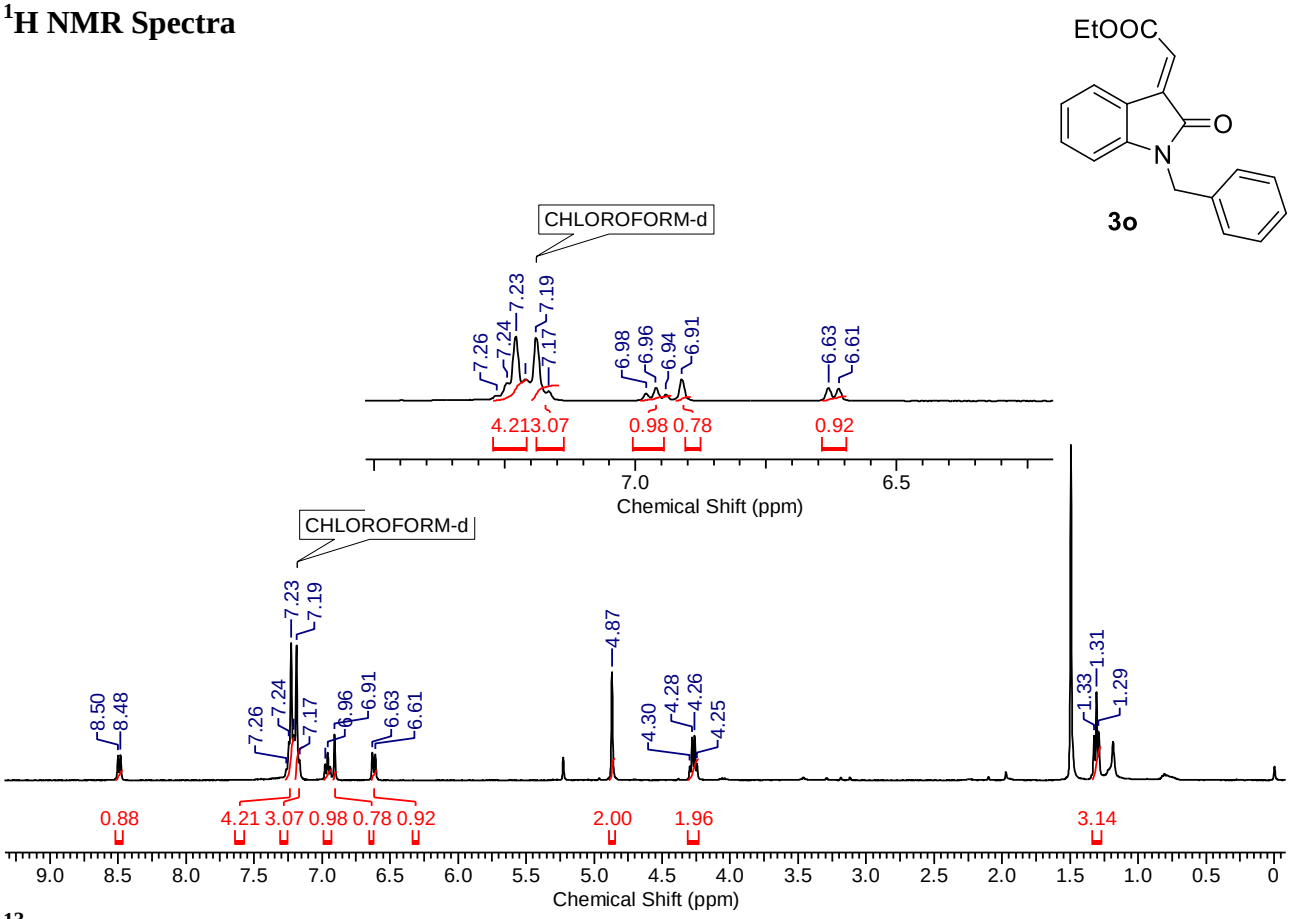

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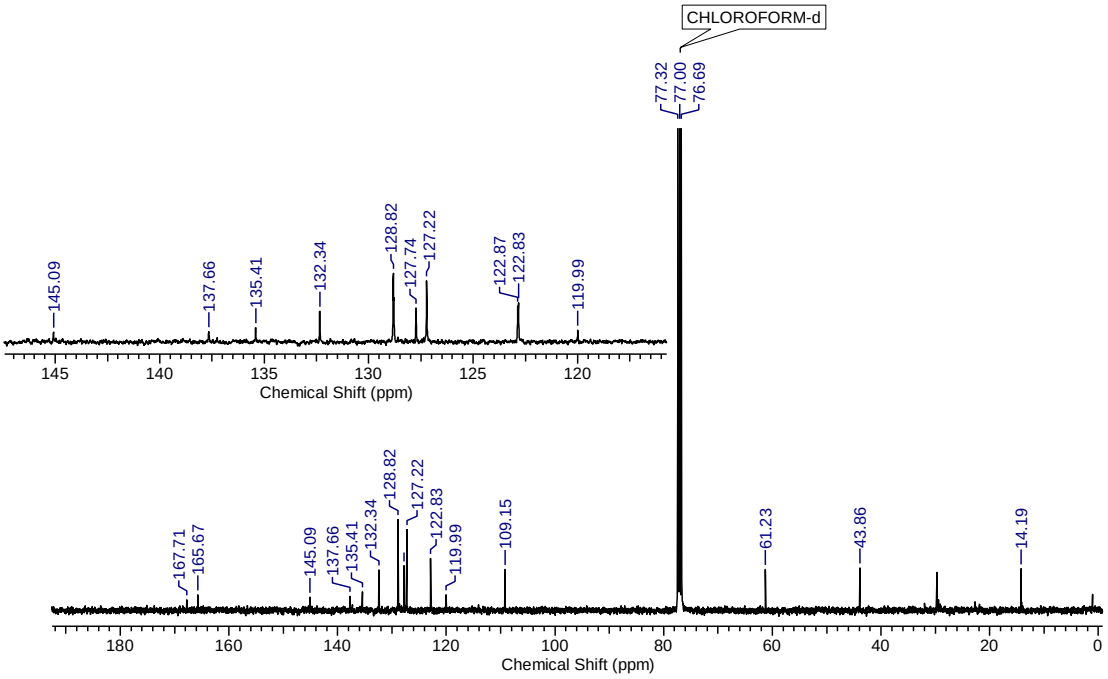

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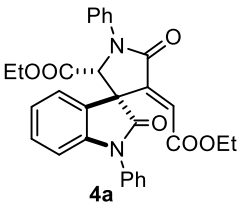

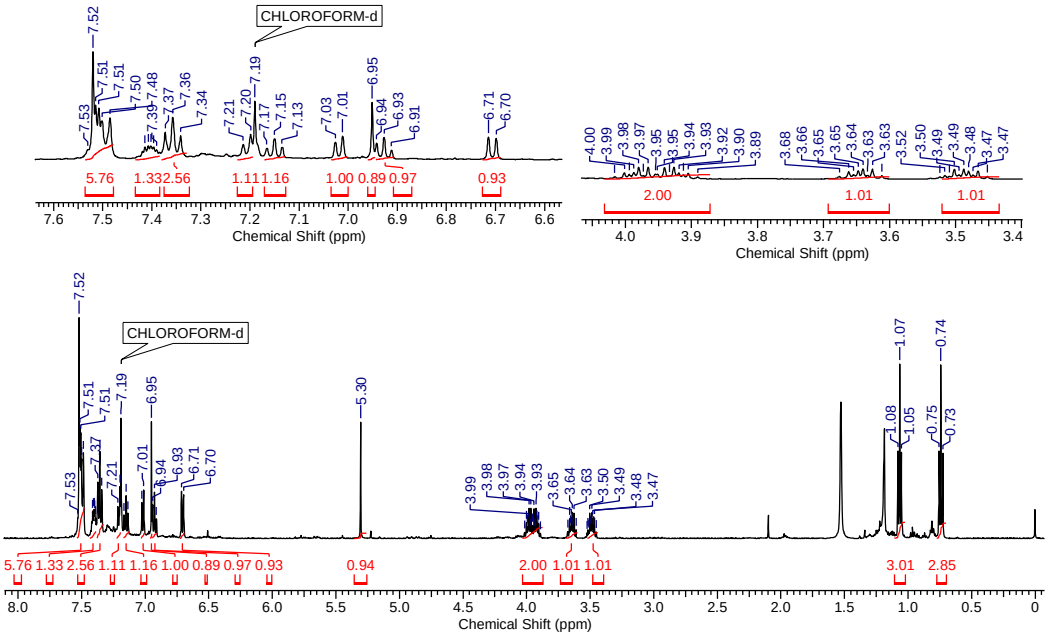

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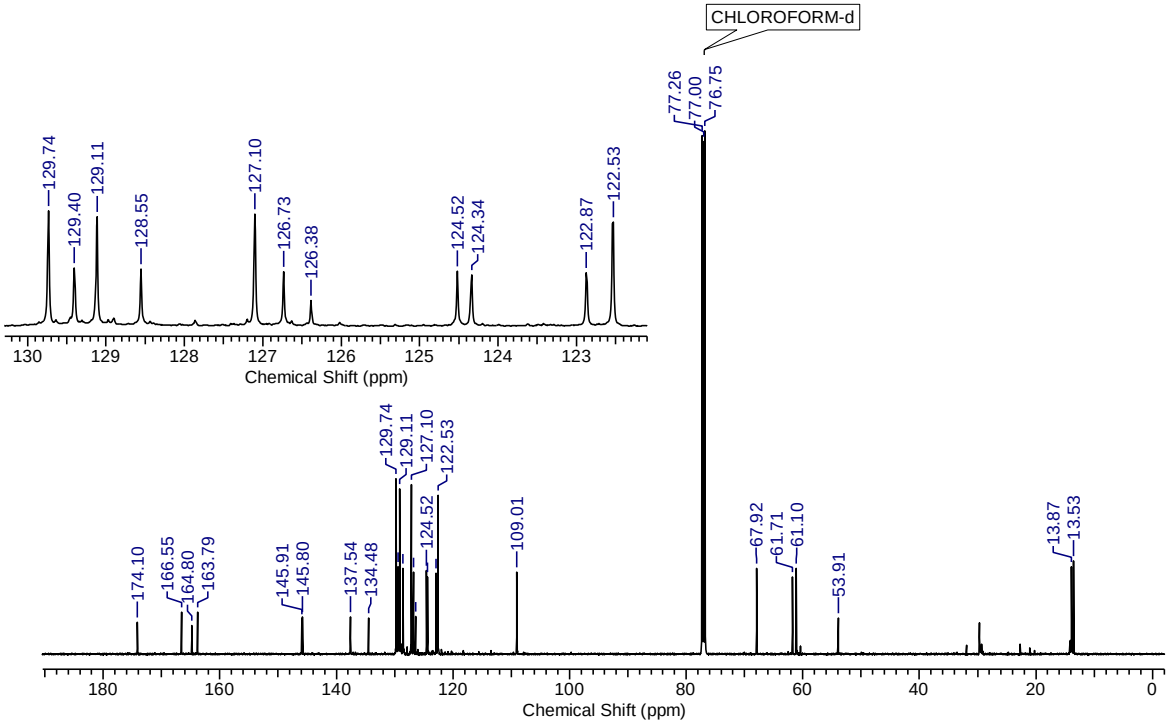

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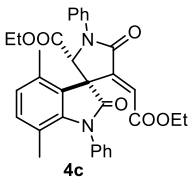

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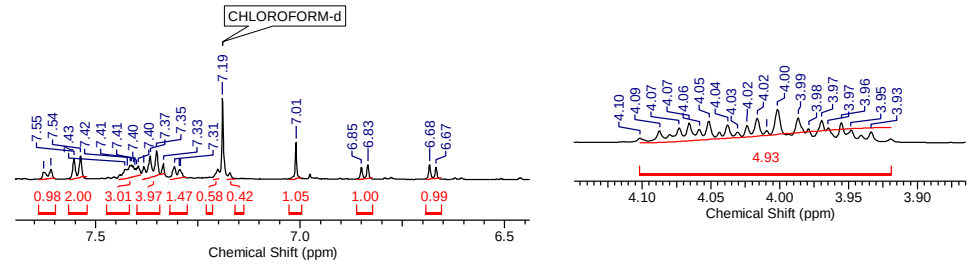

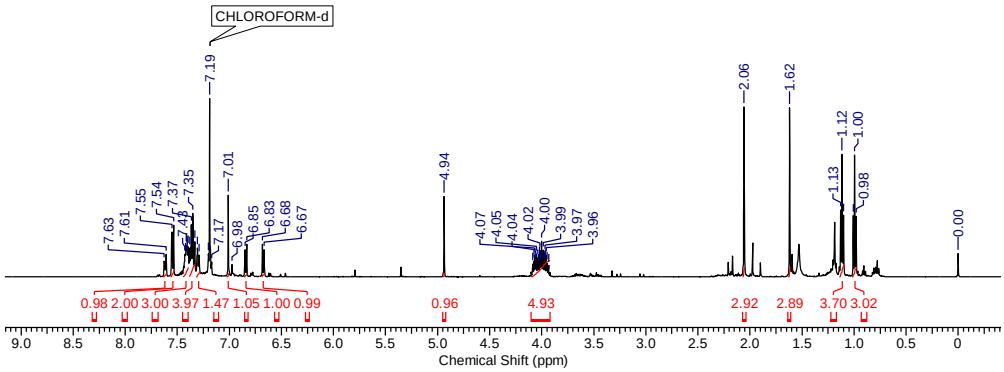

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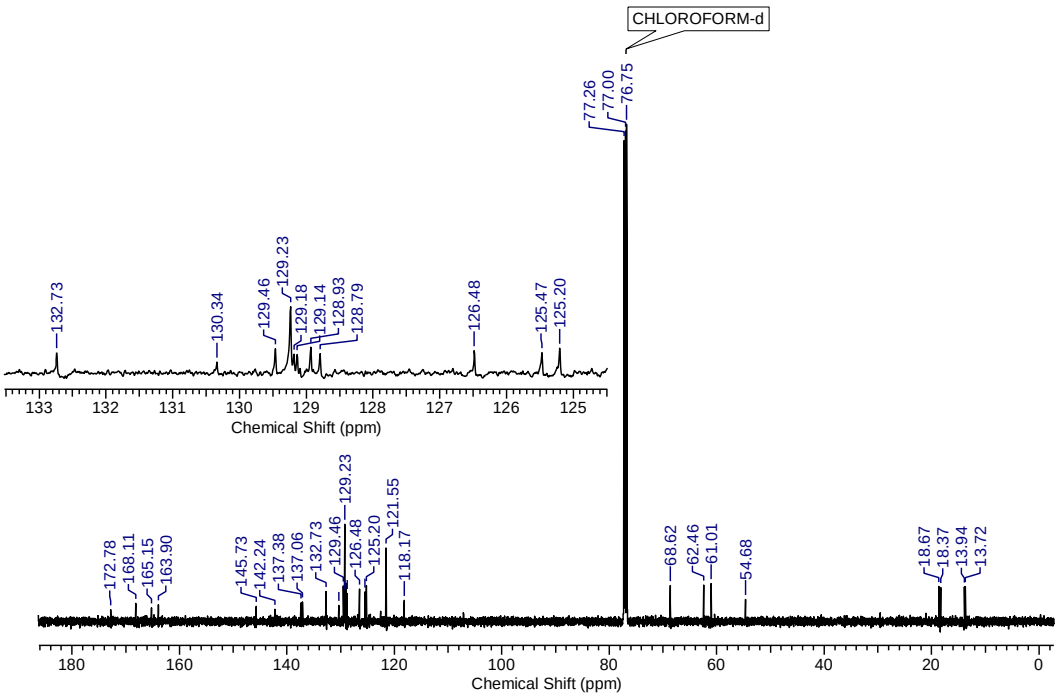

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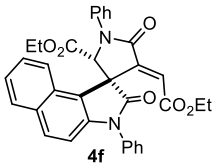

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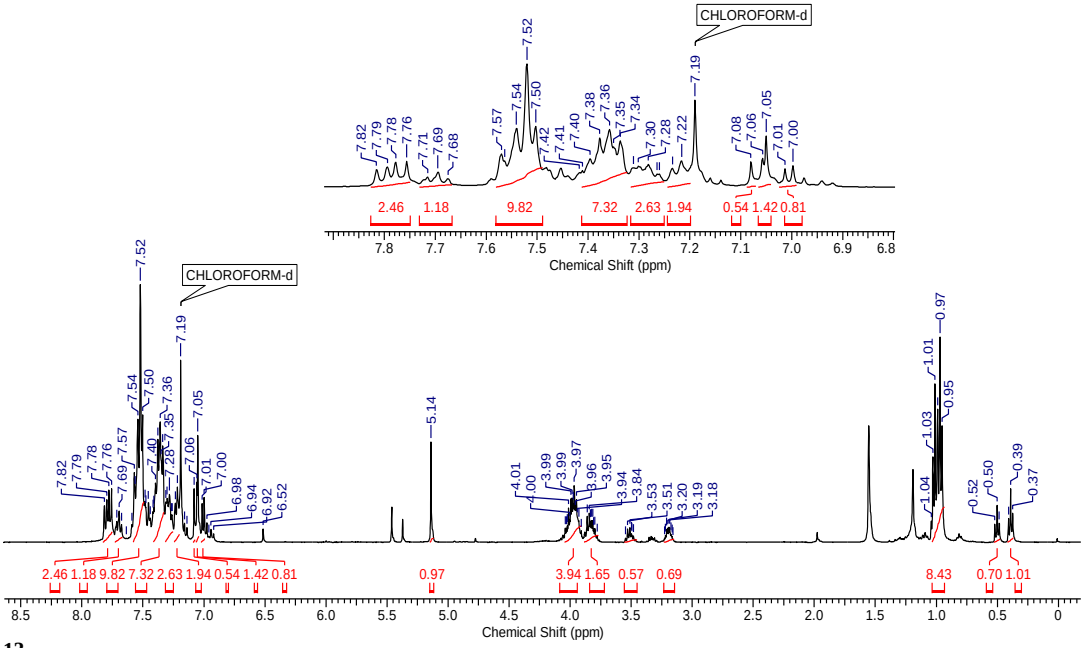

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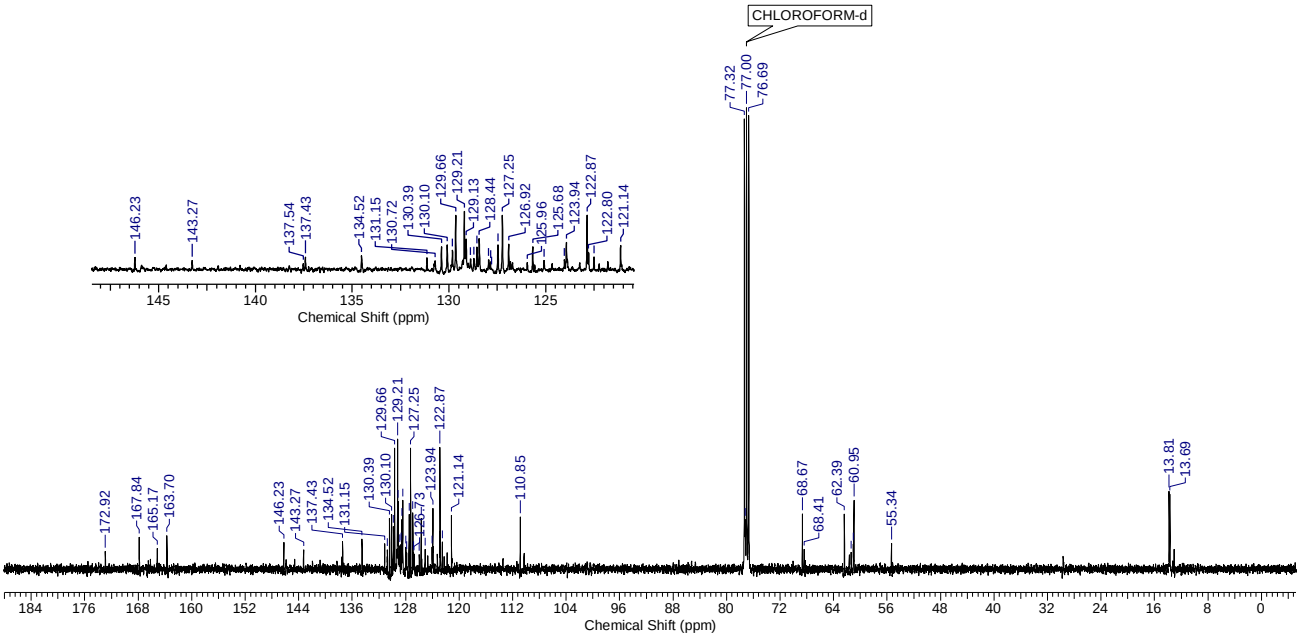

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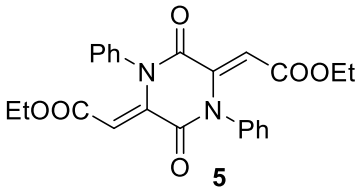

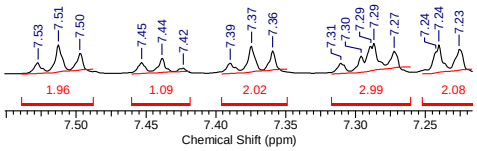

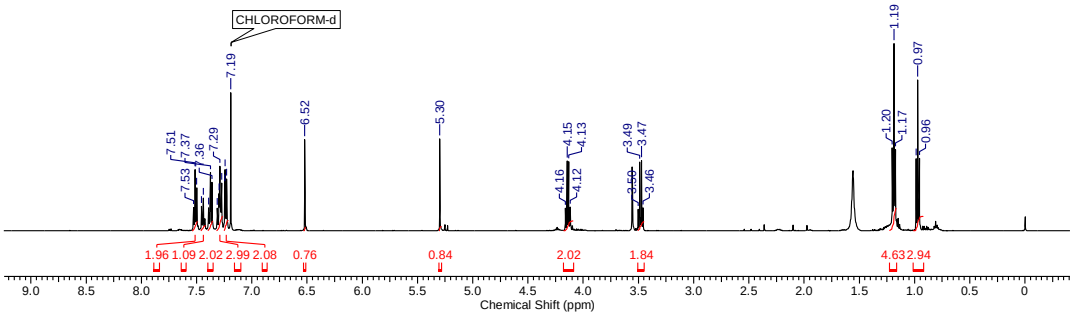

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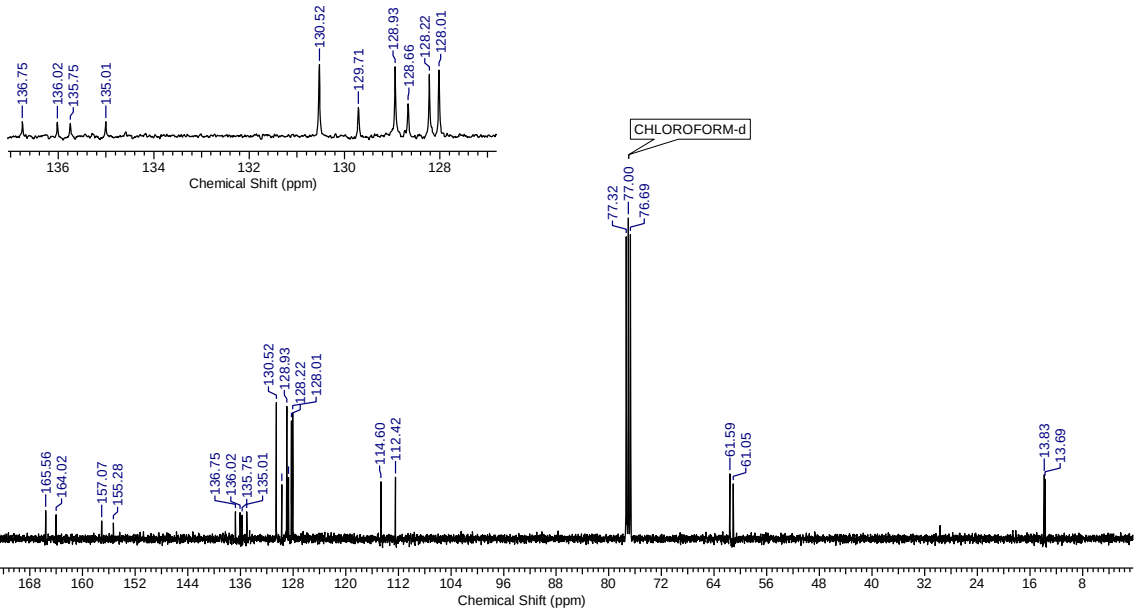


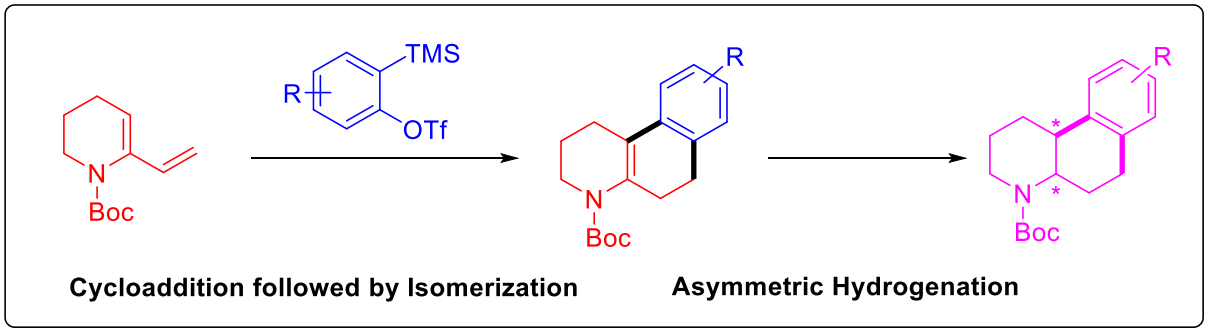
Chapter 4

Diastereoselective synthesis of octahydroquinoline scaffold using aryne chemistry

Chapter 4: Diastereoselective synthesis of octahydroquinoline scaffold using aryne chemistry

4.1. Abstract:

An efficient, milder and novel route for the synthesis of hexahydroquinoline scaffolds using Diels-Alder reaction of aryne with diene has been developed. Furthermore, we have attempted an asymmetric hydrogenation of hexahydroquinoline core to achieve octahydroquinoline core in a stereo selective manner.



4.2. Introduction:

Nitrogen-containing heterocyclic scaffolds are ubiquitous in various drugs, natural products, and synthetic materials[1]. Their tremendous biological activities fascinate both synthetic as well as a medicinal chemist in the field of drug discovery. Among them, hexahydroquinoline and octahydroquinoline cores are found in many of medicinally important compounds (Figure 1).[2] Representative molecules are shown in the figure 1. Lysergic acid diethylamide (LSD) and ololiuqui are ergot alkaloids, which are known for their potent hallucinogenic activity.[2a] Ergoline is used for the treatment of migraines and Parkinson's disease[2b]. Ergometrine is used for the treatment for vaginal bleeding after childbirth[2c].

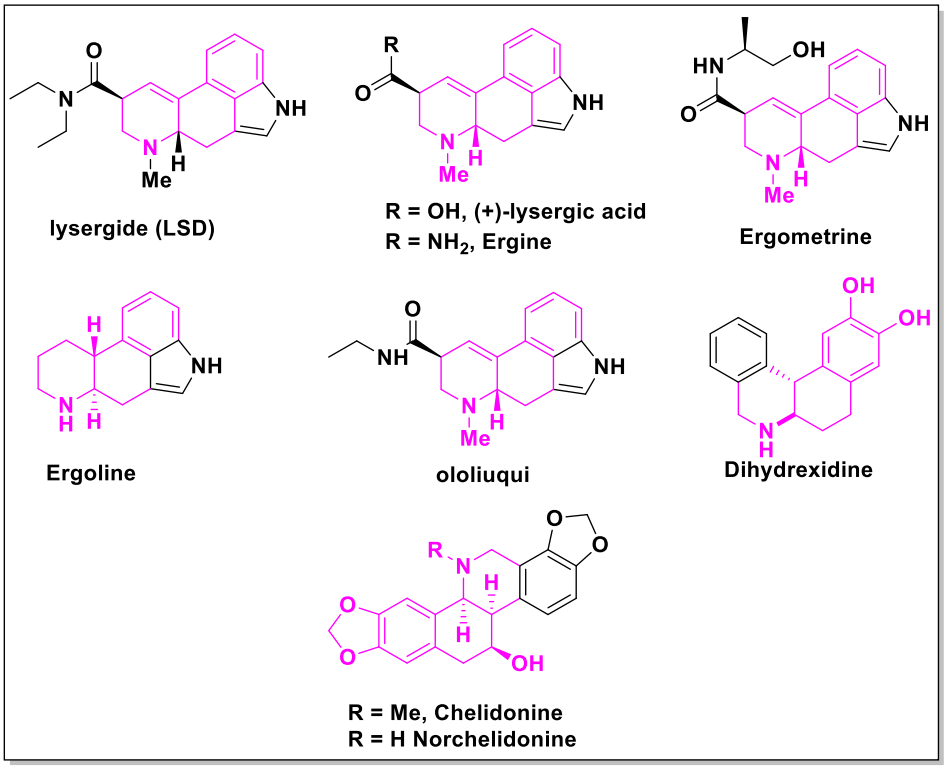


Figure 1: Representative examples having hexahydroquinoline & octahydroquinoline core

Dihydrexidine which is a benzo fused octahydroquinoline, which exhibit prominent α-adrenoceptor agonist effects as well as dopaminergic effects.[2j] Octahydrobenzo[f]quinoline containing compounds also shows hypotensive and bradycardia effects. [2k]

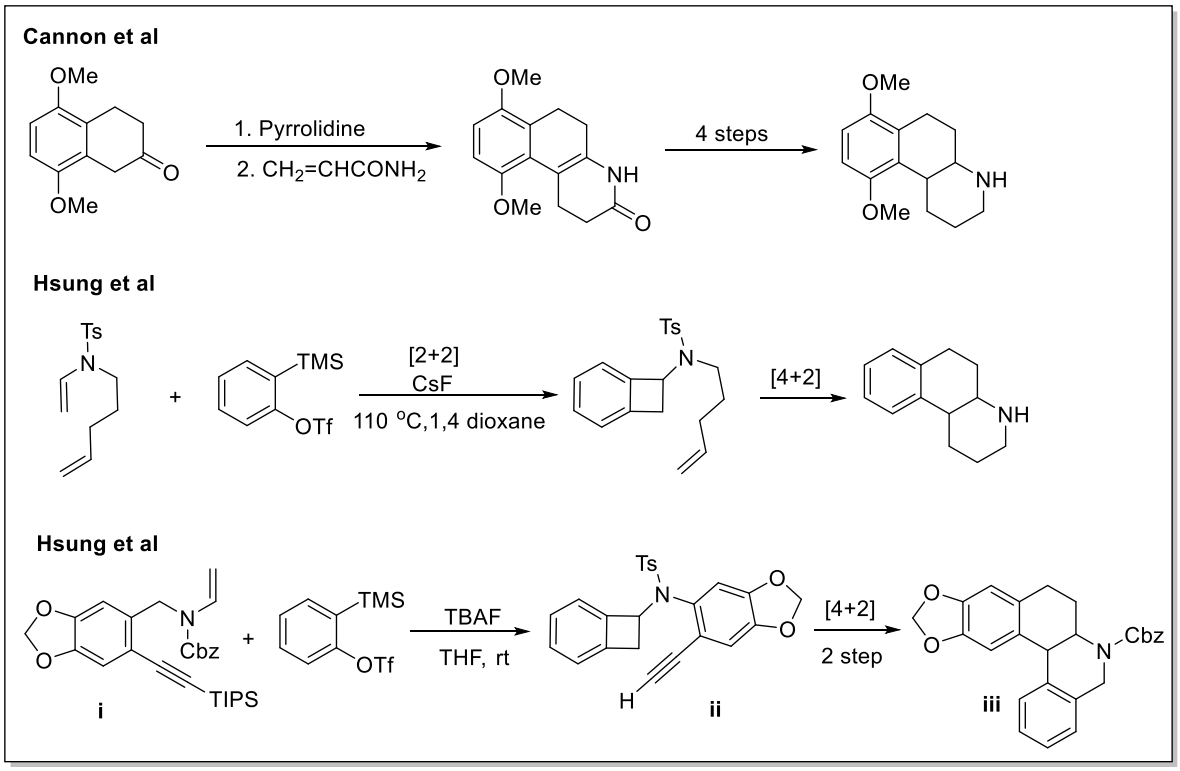
4.3. Literature Review

Although octahydrobenzo[f] quinolines have diverse biological applications, unfortunately, till date it did not gain proper exposure in the area of synthetic and medicinal chemistry. Few methods were reported where this core was achieved by multistep synthesis and harsh reaction conditions[3]. Nevertheless, till date, there is no report for synthesizing such cores in an asymmetric manner.

In 1986 Cannon and co-workers demonstrated the synthesis the octahydrobenzo[f]quinolone. This synthesis was started from the 5,8-dimethoxy-2-tetralone reacted with pyrrolidones to form

intermediate enamine. Further transformation on this enamine provided racemic quinolone core in good yield[3c].

Scheme 1. Previous work



In 2009 Hsung et al. have reported the construction of tricyclic quinolone core via cascade enamide-benzyne [2+2] cycloaddition. Cycloadduct amidobenzocyclobutanes underwent pericyclic ring-opening reaction followed by subsequent intramolecular Diels-Alder reaction to provide octahydrobenzo[f]quinolone in good yield[3b].

In 2012 Hsung and group demonstrated the utilization of Diels –Alder reaction of aryne into the total synthesis of chelidonine and norchelidonine. They achieved octahydrobenzo[f]quinolone containing molecules chelidonine and norchelidonine starting from the enamide **i**. Enamide **i** was reacted with aryne to form cyclobutane adduct **ii**, which on further transformation furnished the desired compounds **iii** in good yields[3a].

4.4. Origin of the work:

The literature study revealed that the synthesis of octahydrobenzo[f]quinolone is accomplished by using transition metals, and harsh reaction conditions. The synthesis of octahydrobenzo[f]quinoline always involves multistep procedures on pre-activated species. Hsung and co-worker developed a comparatively effective procedure for the synthesis octahydrobenzo[f]quinoline core. It is noteworthy that till date an efficient method for the stereoselective synthesis of such scaffolds is sought after. To overcome this limitation we have attempted to develop a short and efficient protocol for the stereoselective synthesis of octahydrobenzo[f]quinoline and its analogs.

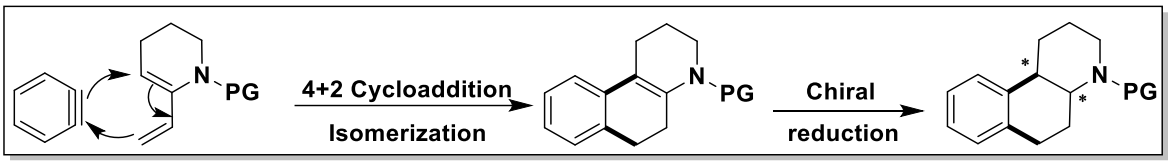
4.5. Objective of the work:

In continuation of our curiosity and interest in the aryne chemistry, we planned to utilize aryne chemistry for the synthesis of medicinally important benzo-fused octahydroquinoline core. Diels-Alder reaction is a well-recognized and powerful tool in organic chemistry which provided an efficient ways to synthesize various complex carbocycals, heterocycles and polycyclic hydrocarbons in a one-pot manner with good yields[4]. Extreme electrophilic nature of the strained triple bond and low lying LUMO makes aryne as a fascinating dienophile, which shows outstanding reactivity towards the Diels-Alder reaction. Utilization of aryne in Diels-Alder reactions as dienophile has generated a great number of synthetically important scaffolds using comparatively milder reaction conditions. Diels-Alder reaction of aryne provides facile access towards the formation of multiple bonds in a single step[5]. Hence Diels-Alder reaction of aryne is being utilized in the synthesis of various drugs and natural products.

Key step and hypothesis:

On the basis of literature precedence and our understanding of aryne chemistry, we have hypothesized (Scheme 2) that the reaction will proceed via [4 + 2] ([2+2] followed by [4+2]) cycloaddition between aryne and protected vinyl tetrahydropyridine, which will be subsequently followed by the isomerization of the double bond.

Scheme 2: Our hypothesis

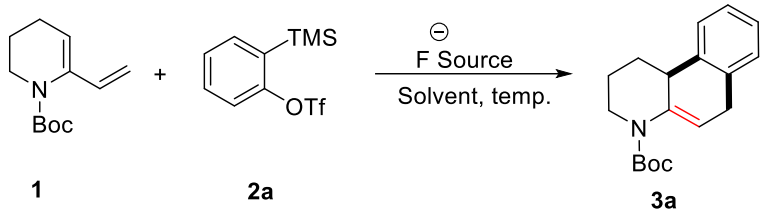


Asymmetric hydrogenation of isomerized product benzo-fused hexahydroquinoline will furnish the expected compound benzo-fused octahydroquinoline core in diastereoselective manner.

4.6. Results and Discussion:

To test our hypothesis, we began our investigation by reacting unsubstituted aryne precursor **2a** with the Boc-protected vinyl tetrahydropyridine **1** in the presence of CsF in acetonitrile under an argon atmosphere at room temperature. Delightfully, we observed our expected product **3a** in 40 % of isolated yield. Motivated by our initial observation, we further planned to find the optimized condition for this transformation. Changing the solvent from acetonitrile to DME, could not provide a satisfactory result (entry 2). Moreover, we observed 37 % of product formation when CsF is replaced by KF in THF (entry 3). Additionally, we performed screening of various solvents with KF, wherein ACN provided a slight increment in yield of product **3a** (entry 4), while KF in toluene deteriorated yield of compound **3a** (entry 5). Delightfully, increment in the yield was observed when equivalents of reagents were altered (entries 6, 7). Moreover, screening of other fluoride source TBAF and TBAT with THF solvent showed diminished yield of the desired product (entries 8, 9).

Table 1. Optimization of the Reaction Conditions [a–d]



1 **2a** **3a**

entry	equiv 1a/2a	F^- source (equiv)	solvent/ temp (°C)	time (h)	yield (%)
1	1:1	CsF (1.5)	ACN/rt	6	40
2	1:1	CsF (1.5)	DME/rt	6	23
3	1:1	KF (1.5)	THF/rt	6	37
4	1:1	KF (1.5)	ACN/rt	6	40
5	1:1	KF (1.5)	Toluene/rt	12	20
6	1:1.5	KF (3.0)	ACN	6	53
7	1:1.5	KF (3.0)	THF	6	50
8	1:1.5	TBAF (2.0)	THF/rt	12	20
9	1:1.5	TBAT (2.0)	THF/rt	12	30
10	**1:1.5**	**CsF (2.5)**	**ACN/rt**	**3**	**63**
11	1:1.5	CsF (2.5)	ACN / 70	3	54
12	1: 2	CsF (3.0)	ACN	3	54

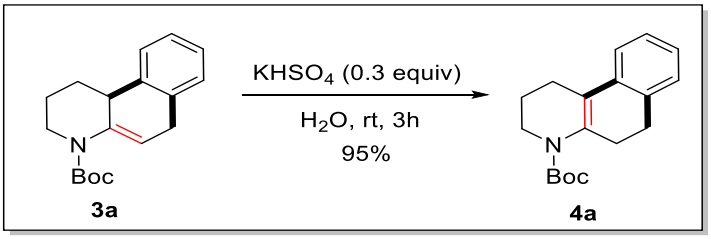
[a]Selected entries. [b]Reactions were performed on a 10 mg scale of **1** in a solvent (1.0 mL).
[c]Isolated yield. [d]Equivalent quantity of 18-crown-6 was used with KF.

Pleasingly, an increasing amount of CsF in acetonitrile solvent provided an increment in the yield of compound **3a** up to 63% (entry 10). Our further efforts for the optimization of the reaction did not improve the reaction yield to a great extent (entries 11, 12).

Our initial aim was to get compound **4a** in a single step, hence we have tried various modifications in the optimized reaction condition to get compound **4a** directly to avoid purification as well as the use of additives for isomerization. Unfortunately, our all attempts are vein, hence we started screening of bases and acids to provide isomerized compound **4a** from **3a**. $KHSO_4$ was found to be the best additive to provide isomerized compound **4a** in comparatively less time with good yield. The purified compound **3a** was treated with 2M aqueous solution of

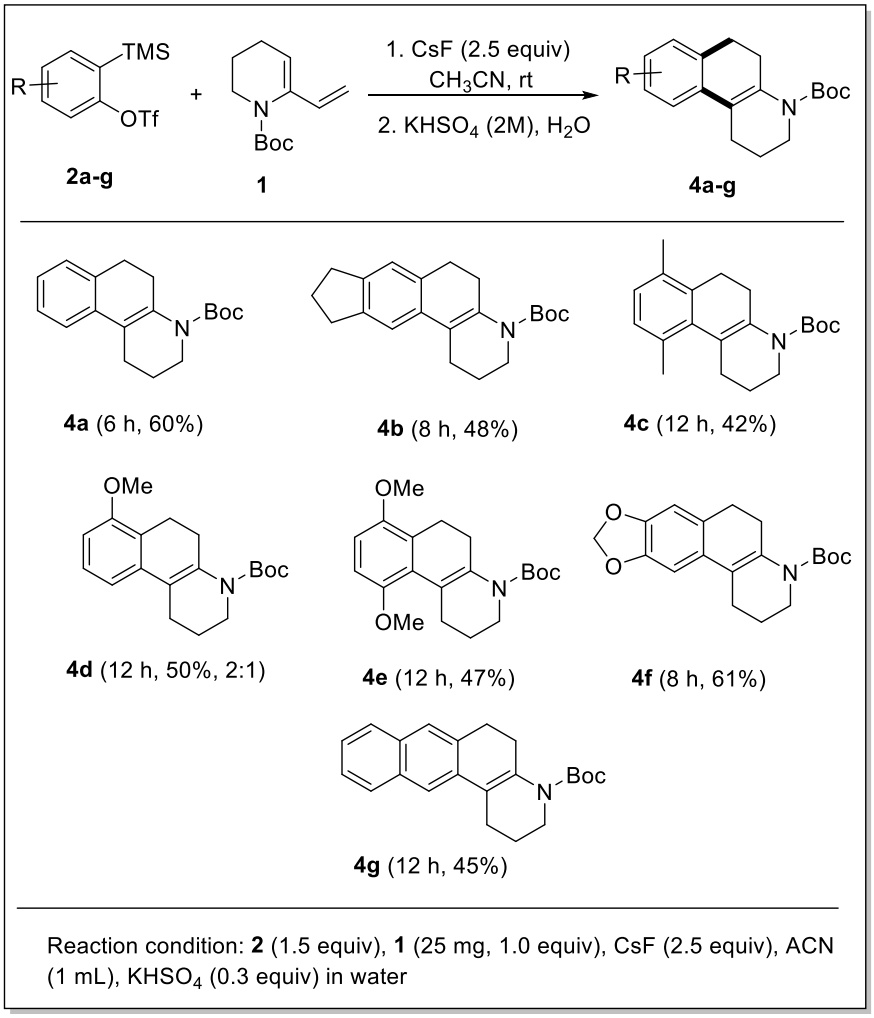
$KHSO_4$ acid in acetonitrile and kept stirring for 3 h at room temperature to afford isomerized compound **4a** in quantitative yield (Scheme 3).

Scheme 3: Isomerization of 3a to 4a



However, we wanted to avoid the isolation of **3a**, hence $KHSO_4$ was added to the reaction mixture containing **1** and **2a** after stipulated time. We observed 60% yield of **4a**.

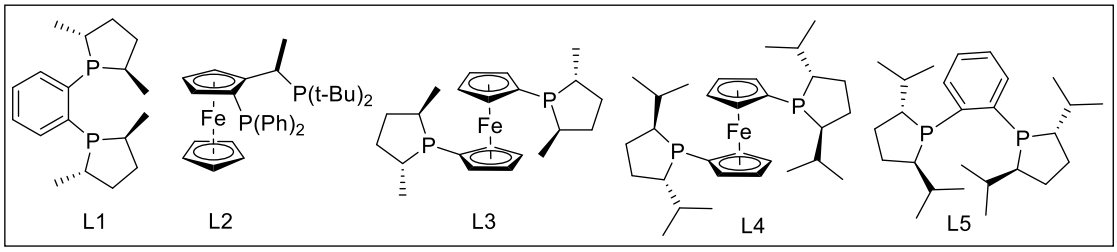
Scheme 4. Hexahydrobenzoquinoline from Various Arynes[a,b]



After the establishment of one-pot optimization condition for this method, we have screened varyingly substituted aryne precursors **2a-g**. These were treated with diene **1** under the optimized reaction condition. As summarized in scheme 4, the reaction worked well with aryne precursors **2b-c** substituted with electronically unbiased alkyl groups. It is noteworthy that the aryne precursor **2c** having the alkyl substitution near the reaction centre also provided the desired compound **4c** in good yield, which shows that the steric hindrance does not affect the protocol. The aryne precursors **2d** and **2e** having electron-donating groups at diverse places endowed the expected products **4d** and **4e** in moderate to good yields. Unsymmetrically substituted aryne precursor **2d** furnished the respective product **4d** as an inseparable mixture of regioisomer having 2:1 ratio. Notably, aryne precursor **2e** substituted with electron-donating group near the reaction centre, provided respective compound **4e** in good yield. Remarkably, the symmetrical dioxyl and naphthyl aryne precursors **2f** and **2g** also furnished the corresponding hexahydroquinoline **4f** and **4g** in good yield.

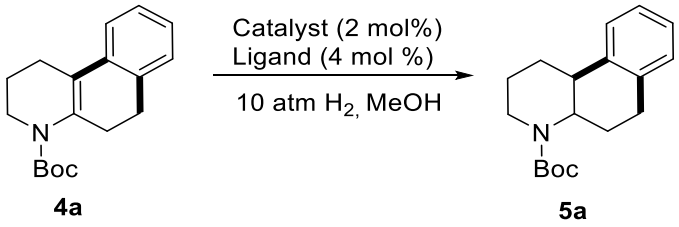
Attempts towards the asymmetric hydrogenation:

Medicinal activities and unique architect of octahydroquinoline core containing molecules such as ergoline prompted us to perform asymmetric hydrogenation on benzo fused hexahydroquinoline scaffolds, which were successfully prepared by Diels-Alder reaction of arynes with diene followed by isomerization (scheme 4). Initially, the reduction of the compound **4a** was performed using Pd/C (10%) in methanol to obtain product **5a**. Similarly, we prepared compounds **5b-5g**, for HPLC comparison purpose. After having the racemic compounds **5a-5g** in hand we began the study of diastereoselective reduction of compound **4a.** The results are summarized in Table 2. We commenced our asymmetric reduction by employing $Rh(COD)_2OTf$ catalyst with different ligands (L1-L5) in methanol solvent at 10 atm pressure of hydrogen.



Unfortunately, we ended with racemic compound **5a** with ligands L1 and L2 (Table 2, entries 1-2). Screening of different ligands by keeping other reaction condition unchanged couldn't provide desired compound (entries 3-5). Moreover, replacing $Rh(COD)_2OTf$ catalyst with ruthenium metal complexes such as A, B, and C, didn't make any positive change in reaction (entries 6-8).

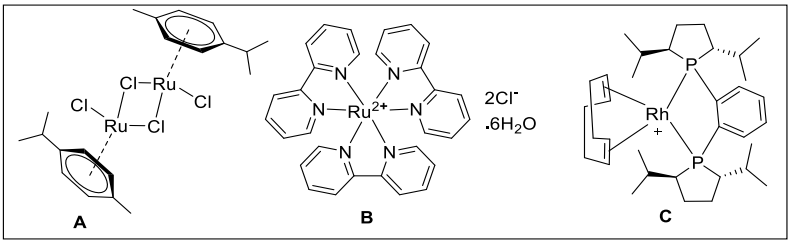
Table 2. Optimization for the asymmetric hydrogenation of compound 4a[a-c]



4a **5a**

entry	Ligand	metal	temp (°C)	time (h)	yield (%)	dr
1	L1	$Rh(COD)_2OTf$	rt	6	40	1:1
2	L2	$Rh(COD)_2OTf$	rt	6	50	1:1
3	L3	$Rh(COD)_2OTf$	rt	6	NR	NR
4	L4	$Rh(COD)_2OTf$	rt	6	40	1:1
5	L5	$Rh(COD)_2OTf$	rt	6	20	1:1
6	-	A (5 mol%)	50	12	NR	1:1
7	-	B (5 mol%)	rt-50	12	NR	NR
8	-	C (5 mol%)	rt-50	12	20	1:1

[a]Selected entries. [b]Reactions were performed on a 10 mg scale of **1** in a solvent (1.0 mL). [c]Isolated yield.



Further screening of solvents, temperature, and catalyst to achieve diastereoselectivity and enantioselectivity to a great extent is under way.

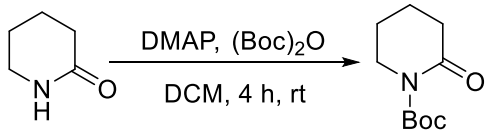
4.7. Conclusion:

In summary, transition-metal-free, mild and novel method has been demonstrated for the synthesis of versatile benzo fused hexahydroquinoline core. The key step involves the Diels – Alder reaction of aryne with diene under milder reaction condition. The developed protocol provides varyingly substituted analogs of hexahydroquinoline core. Furthermore, we are able to reduce hexahydroquinoline core to achieve racemic octahydroquinoline core. The optimization study of the asymmetric reduction for the stereoselective synthesis of octahydroquinoline core is under active process.

4.8. Experimental Procedure and characterization of data

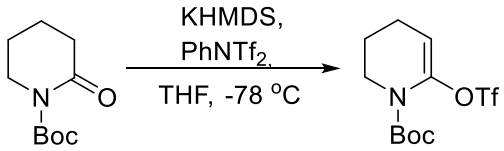
(A) Procedure for preparation of diene 1:

***t*-Butyl 2-oxopiperidine-1-carboxylate**



To a stirring solution of δ-valerolactam (1.0 g, 10.08 mmol) and DMAP (0.122 g, 0.100 mmol) in dichloromethane (20 mL) was added triethylamine (1.40 mL, 10.08 mmol). After 10 minutes at same temperature, Boc_2O (3.30 g, 15.12 mmol) was added to the solution. The reaction mixture was allowed to stir at rt for 4 h. After the completion of reaction, the reaction mixture was washed with saturated solution of sodium bicarbonate, brine and water. The organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/ PE 1:5) to furnish the desired product in (1.41 g, 70%) yield.[6a] **^{1}H NMR (200 MHz, $CDCl_3$)** δ 3.57 (t, J = 6.2 Hz, 2 H), 2.43 (t, J = 6.9 Hz, 2 H), 1.81-1.70 (m, 4H), 1.45 (s, 9H).

***t*-Butyl 6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydropyridine-1(2H)-carboxylate**

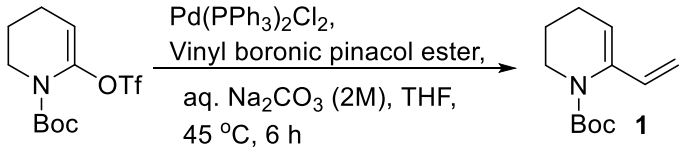


To a solution of KHMDS (0.5 M toluene solution, 10.0 mL, 5 mmol) in THF (20 mL) was added a solution of boc-protected 2-piperidone (0.5 g, 2.5 mmol) in THF (5 mL) drop wise at −78 °C. The solution was stirred for 2 h at the same temperature. A solution of $PhNTf_2$ (1.07 g, 3 mmol) in THF (3 mL) was then added drop wise and the resultant reaction mixture was warmed to room temperature. After stirring for 2 h at room temperature, the solution was diluted with diethyl ether, and water was added for quenching the reaction. The organic layer was washed with 10 % solution of NaOH, brine and dried over anhydrous sodium sulfate. The solution was concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford triflate compound as a yellow oil[6b] (0.662 g, 80%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.22 (t, J = 3.6 Hz, 1 H), 3.53 (t, J = 5.4 Hz, 2 H), 2.27 - 2.10 (m, 2 H), 1.80 - 1.58 (m, 2 H), 1.42 (s, 9 H).

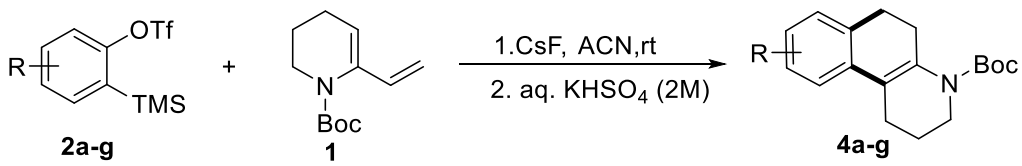
***t*-Butyl 6-vinyl-3,4-dihydropyridine-1(2H)-carboxylate (1)**



Under the nitrogen atmosphere, to a solution of trifluoromethanesulfonate compound (500 mg, 1.51 mmol) and vinylboronic pinacol ester (348.9 mg, 2.26 mmol) in THF (20 ml) was added $(Ph_3P)_2PdCl_2$ (53 mg, 0.075 mmol) and 2 M Na_2CO_3 (aq) (1.10 g, 10.57 mmol). The mixture was heated to 45 °C, left under stirring for 6 h, and, after cooling, diluted with water and extracted with Et_2O. The organic phase was concentrated under reduced pressure. The crude oil was purified by silica gel chromatography to furnish the compound **1.**

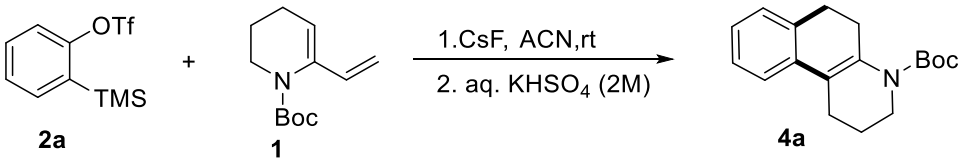
Reaction Time: 6.0 h; Rf: 0.5 (1: 19 EtOAc : Pet. Ether); yellow liquid; 222 mg, 70 %; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.16 (dd, J = 11.0, 17.1 Hz, 1 H), 5.28 (t, J = 4.0 Hz, 1 H), 5.18 (d, J = 17.1 Hz, 1 H), 4.86 (d, J = 11.0 Hz, 1 H), 3.51- 3.43 (m, 2 H), 2.16 - 2.05 (m, 2 H), 1.79 - 1.63 (m, 2 H), 1.38 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.0, 138.9, 135.8, 114.7, 110.9, 80.7, 44.3, 28.3, 23.4, 23.3; **HRMS (ESI-TOF)** m/z: Calcd for $[(C_{12}H_{19}NO_2) + H]+$: 210.01489, found: 210.01487.

(B) General Experimental Procedure for the preparation of compounds 4a-g



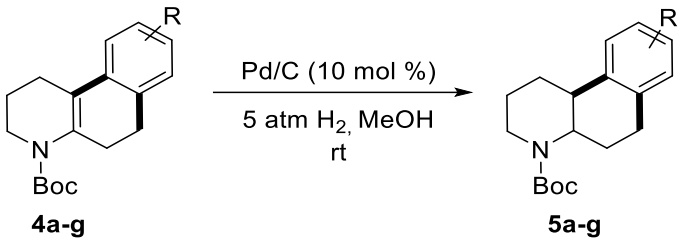
To a flame dried two-neck round-bottom flask containing CsF (2.50 equiv) was added o-silyl aryl triflate (1.50 equiv) in ACN, stirred for 5 minute at room temperature followed by addition of diene (1.0 equiv) in ACN under argon atmosphere at the same temperature. The reaction mixture was stirred at rt and the progress was monitored by TLC. After completion of the first reaction, 2M aqueous solution of $KHSO_4$ (0.3 equiv) was added and stirring was continued until completion of the isomerization. The reaction progress was monitored by ^1H NMR. The aqueous layer was extracted with ethyl acetate. The combined organic extract was dried and removal of solvent gave a residue that was subjected to flash column chromatography on silica-gel using Pet. Ether/ethyl acetate to afford corresponding compounds in afford 42-61% yields.

(C) Typical experimental procedure for the preparation of compound 4a:



To a flame dried two-neck round-bottom flask containing CsF (54 mg, 0.355 mmol) was added *o*-silyl aryl triflate **2a** (64 mg, 0.213 mmol) in ACN (0.5 mL), stirred for 5 minute at room temperature, followed by addition of diene **1** (30 mg, 0.142 mmol) in ACN (0.5 mL) under argon atmosphere at rt. The reaction mixture was stirred at rt and the progress was monitored by TLC. After completion of the reaction, 2M aqueous solution of $KHSO_4$ (20 µl) was added. The stirring was continued for 3 h at rt. The aqueous layer was extracted with ethyl acetate. The combined organic extract was dried and removal of solvent gave a residue that was subjected to flash column chromatography on silica-gel using Pet. Ether/ethyl acetate to afford corresponding compound in afford 60 % yield.

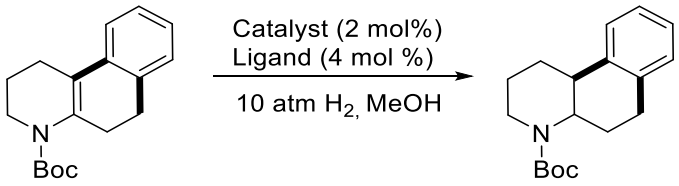
(D) General Experimental Procedure for the Preparation of Racemic Compounds 5a-g:



4a-g **5a-g**

Pd/C (10%) (1:0.2 weight by weight) was added to a solution of compounds **4a-4g** in methanol. The reaction mixture was placed under 10 atmosphere of H_2 pressure and allowed the reaction to stir at rt for 4h. The suspension was filtered on celite, washed with EtOAc and dried over Na_2SO4. The organic layer was evaporated on reduced pressure. No further purification was needed.

(E) General Experimental Procedure for the Asymmetric reduction of compounds 4a-g:



4a **5a**

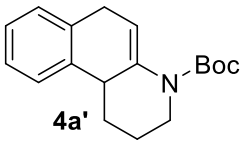
Catalyst (2 mol%), ligand (4 mol%) and compound **4a** (1.0 equiv) were weighed and transferred to a vial under argon in a glove box. After four vacuum/ hydrogen cycles, methanol was added, and the reaction mixture was stirred at rt or 50 ^oC under 10 atmospheric H_2 pressure. The conversion was determined by LC-MS. After completion of reaction, the resulting mixture was filtered through a short silica gel column and concentrated under reduced pressure to give hydrogenation product in a good yield.

Characterization Data of Compounds:

All reactions were performed on 30 mg scale of diene.

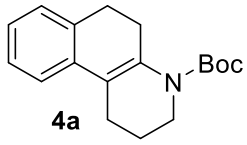
The NMR of products **4a**, **4c**, **4d** and **4g** shows 1-2% of partially aromatized compound.

***t*-Butyl 2,3,6,10b-tetrahydrobenzo[f]quinoline-4(1H)-carboxylate (4a')**



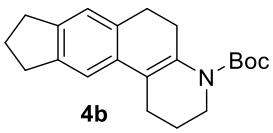
Reaction Time: 3.0 h; R*f*: 0.4 (1: 19 EtOAc : Pet. Ether); thick oil; 26 mg, 63%; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.17 - 7.02 (m, 4H), 5.65 (t, *J* = 2.9 Hz, 1H), 4.21 (d, *J* = 12.6 Hz, 1H), 3.50 (t, *J* = 4.4 Hz, 2H), 3.24 - 3.12 (m, 1H), 2.73 (dt, *J* = 4.0, 12.3 Hz, 1H), 2.34 - 2.22 (m, 1H), 1.77 - 1.67 (m, 2H), 1.50 - 1.41 (m, 1 H), 1.38 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 154.2, 137.4, 136.7, 132.1, 128.3, 127.5, 126.2, 117.8, 79.6, 38.9, 35.4, 29.8, 28.4, 25.9,; **ESI-HRMS** m/z: Calcd for $[(C_{18}H_{23}O_2N) + Na]^+$: 308.1621 , found: 308.1617.

***t*-Butyl 2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxylate (4a)**



Reaction Time: 6.0 h; R*f*: 0.4 (1: 19 EtOAc : Pet. Ether); thick oil; 25 mg, 60 %; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.12 - 7.02 (m, 4 H), 3.55 (t, *J* = 5.4 Hz, 2 H), 2.77 - 2.68 (m, 2 H), 2.61 - 2.49 (m, 2 H), 2.38 (t, *J* = 6.7 Hz, 2 H), 1.95 - 1.82 (m, 2 H), 1.43 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 151.7, 138.6, 135.8, 134.6, 128.8, 126.3, 125.6, 121.9, 117.5, 80.8, 44.4, 29.1, 28.3 , 28.0, 23.7, 23.2; **ESI-HRMS** m/z: Calcd for $[(C_{18}H_{23}O_2N) + H]^+$: 286.1802 , found: 286.1797.

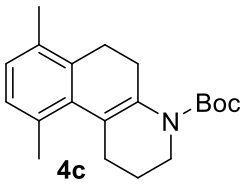
***t*-Butyl 1,2,3,5,6,8,9,10-octahydro-4H-indeno[5,6-f]quinoline-4-carboxylate (4b)**



Reaction Time: 8 h; R*f*: 0.4 (1:19 EtOAc:Pet Ether); thick oil; 23 mg, 48 %; **^{1}H NMR (400 MHz, $CDCl_3$)** $\boldsymbol{\delta}$ 6.99 (s, 1H), 6.93 (s, 1H), 3.54 (t, *J* = 5.49 Hz, 2 H), 2.85 - 2.75 (m, 4H), 2.72 - 2.62 (m, 2 H), 2.46 - 2.57 (m, 2

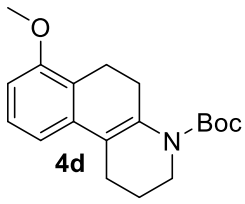
H), 2.37 (t, *J* = 6.71 Hz, 2 H), 1.98 (quint, *J* = 7.32 Hz, 2 H), 1.81 - 1.91 (m, 2 H), 1.42 (s, 9H)); **^{13}C NMR (100 MHz, $CDCl_3$)** ***δ*** 153.8, 142.1, 141.6, 135.7, 134.0, 132.8, 123.0, 118.0, 117.9, 80.6, 44.4, 32.8, 32.6, 29.4, 28.4, 25.5, 23.8, 23.4.

***t*-Butyl 7,10-dimethyl-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxylate (4c)**



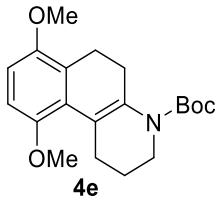
Reaction Time: 12 h; R*f*: 0.4 (1:19 EtOAc:Pet Ether); thick oil; 20 mg, 42 %; **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 6.85 (d, *J* = 7.78 Hz, 1 H), 6.80 (d, *J* = 7.79 Hz, 1 H), 3.47 (t, *J* = 6.64 Hz, 2 H), 2.59 - 2.48 (m, 2 H), 2.42 -2.28 (m, 4H), 2.27 (s, 3H), 2.18 (s, 3 H), 1.77 - 1.66 (m, 2H), 1.43 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 153.7, 136.7, 136.3, 134.6, 131.2, 130.8, 129.2, 127.4, 121.4, 80.5, 45.5, 29.7, 27.7, 26.5, 24.3, 22.7, 22.1, 19.7.

***t*-Butyl 7-methoxy-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxylate (4d)**



Reaction Time: 12 h; R*f*: 0.2 (1:19 EtOAc:Pet Ether); thick oil; 23 mg, 50 %; ratio of regioisomers [2:1]; **^{1}H NMR (400 MHz, $CDCl_3$)** ***δ*** 7.07 (t, *J* = 7.93 Hz, 1H), 6.77 (d, *J* = 7.93 Hz, 1H), 6.73 - 6.65 (m, 1 H), 3.76 (s, 3 H), 3.54 (t, *J* = 5.49 Hz, 2 H), 2.73 (t, *J* = 7.9 Hz, 2 H), 2.64 - 2.54 (m, 2H), 2.63 - 2.46 (m, 2H), 2.43 - 2.31 (m, 2 H), 1.93 - 1.71 (m, 2 H), 1.42 (s, 9H)); **^{13}C NMR (100 MHz, $CDCl_3$)** ***δ*** 156.2, 155.7, 153.8, 137.9, 137.2, 136.7, 126.5, 126.2, 122.4, 119.6, 117.3, 115.0, 110.3, 108.6, 80.8, 80.4, 55.5, 55.4, 45.3, 44.3, 30.5, 29.7, 28.4, 27.5, 26.1, 24.0, 23.8, 23.6, 21.1.

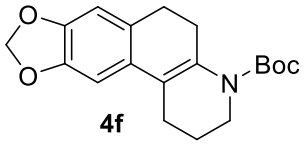
t-Butyl 7,10-dimethoxy-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxylate (4e)



4e

Reaction Time: 12 h; R*f*: 0.2 (1:19 EtOAc:Pet Ether); thick oil; 24 mg, 47%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.62 (d, *J* =7.3 Hz, 2 H), 3.72 (s, 3H), 3.68 (s, 3H), 3.49 (t, *J* = 6.2 Hz, 2 H), 2.65 – 2.51 (m, 4 H), 2.35 (t, *J* = 7.0 Hz, 2 H), 1.81 - 1.69 (m, 2 H), 1.41 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.7, 150.9, 150.0, 136.3, 127.0, 125.8, 119.0, 110.2, 109.0, 80.5, 56.0, 45.3, 28.4, 28.0, 26.1, 24.0, 22.4; **ESI-HRMS** m/z: Calcd for $(C_{20}H_{27}O_4N)$+ Na]$^+$: 388.1832, found: 388.1832.

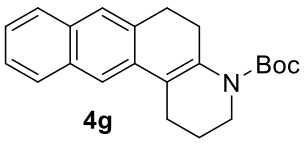
t-Butyl 2,3,5,6-tetrahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-f]quinoline-4(1H)-carboxylate (4f)



4f

Reaction Time: 8 h; R*f*: 0.2 (1:19 EtOAc:Pet Ether); thick oil; 29 mg, 61%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.64 (s, 1 H), 6.57 (s, 1 H), 5.83 (s, 2 H), 3.46 - 3.59 (m, 2 H), 2.62 (d, *J* = 8.5 Hz, 2 H), 2.50 (d, *J*=7.3 Hz, 2 H), 2.30 (t, *J* = 6.1 Hz, 2 H), 1.78 - 1.91 (m, 2 H), 1.42 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.7, 146.1, 145.1, 135.1, 129.9, 128.4, 117.4, 107.9, 103.3, 100.6, 80.7, 44.4, 29.3, 28.4, 28.2, 23.7, 23.6; **ESI-HRMS** m/z: Calcd for $(C_{19}H_{23}O_4N)$+ H]$^+$: 330.1700, found: 330.1671.

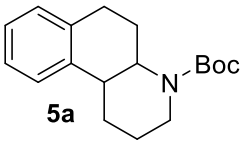
t-Butyl 2,3,5,6-tetrahydronaphtho[2,3-f]quinoline-4(1H)-carboxylate (4g)



4g

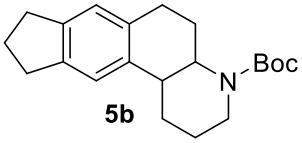
Reaction Time: 12 h; R*f*: 0.5 (1:19 EtOAc:Pet Ether); thick oil; 22 mg, 45%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 - 7.70 (m, 1H), 7.64 (m, , 1 H), 7.49 (s, 1 H), 7.45 (s, 1H), 7.32 - 7.27 (m, 2 H), 3.62 - 3.56 (m, 2 H), 2.90 (t, *J* = 7.25 Hz, 2 H), 2.62 (t, *J* = 7.25 Hz, 2 H), 2.53 (t, *J* = 6.87 Hz, 2 H), 1.98 - 1.89 (m, 2 H), 1.44 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.7, 138.0, 136.4, 134.0, 132.8, 132.0, 127.6, 126.6, 125.1, 125.2, 124.6, 120.1, 117.7, 80.7, 45.5, 29.7, 28.4, 23.7, 23.3

LC-MS of racemic compounds:

1. 

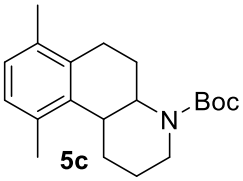
5a

M - Boc + 1: 188.0

2. 

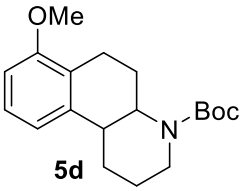
5b

M - Boc + 1: 228.0

3. 

5c

M - Boc + 1: 216.1

4. 

5d

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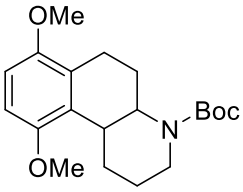
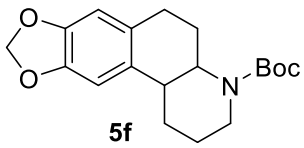
5. 

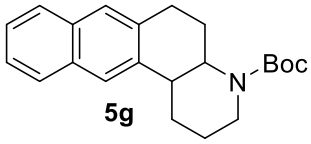
5e

M - Boc + 1: 248.1

6. 

5f

M - Boc + 1: 232.0

7. 

5g

M - Boc + 1: 238.0

4.9. References:

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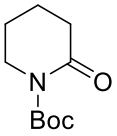
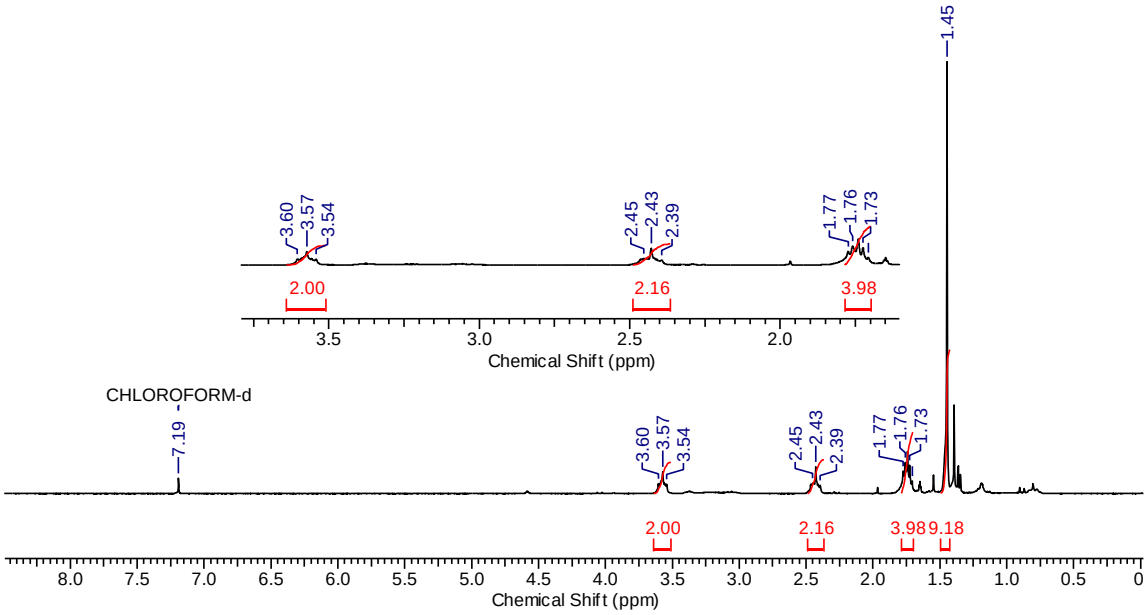
4.10. Selected Spectra

^{1}H NMR Spectra





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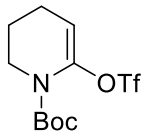

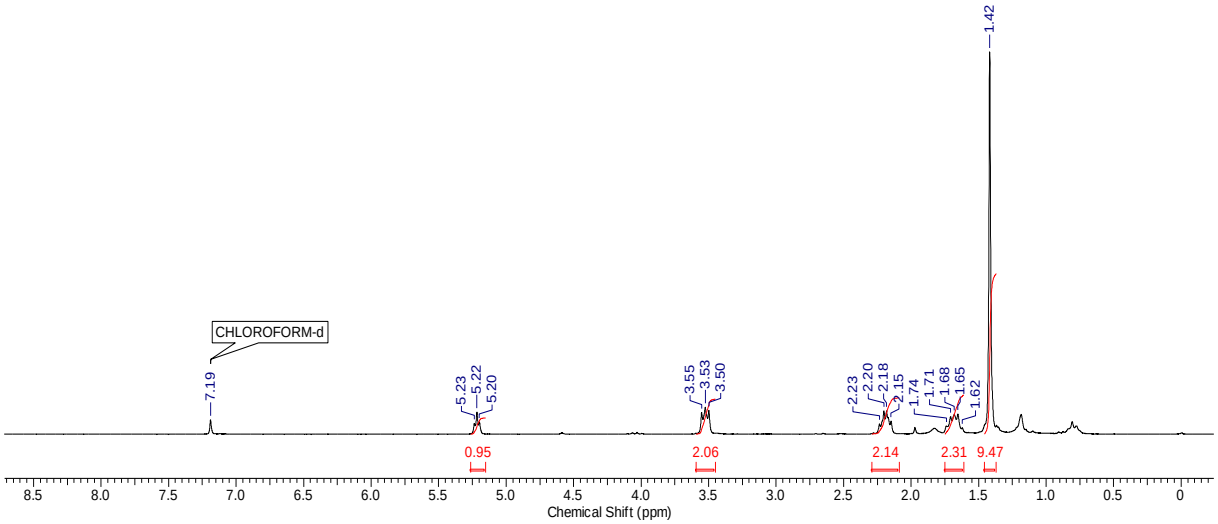

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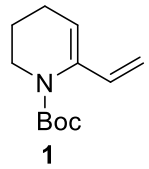
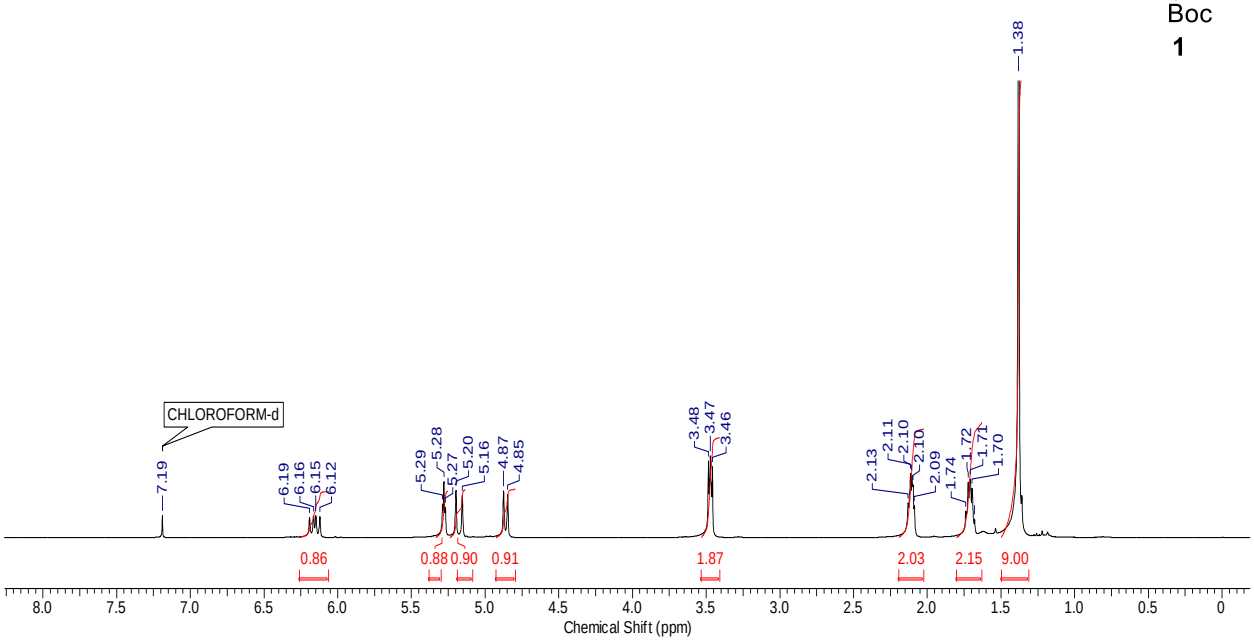


1



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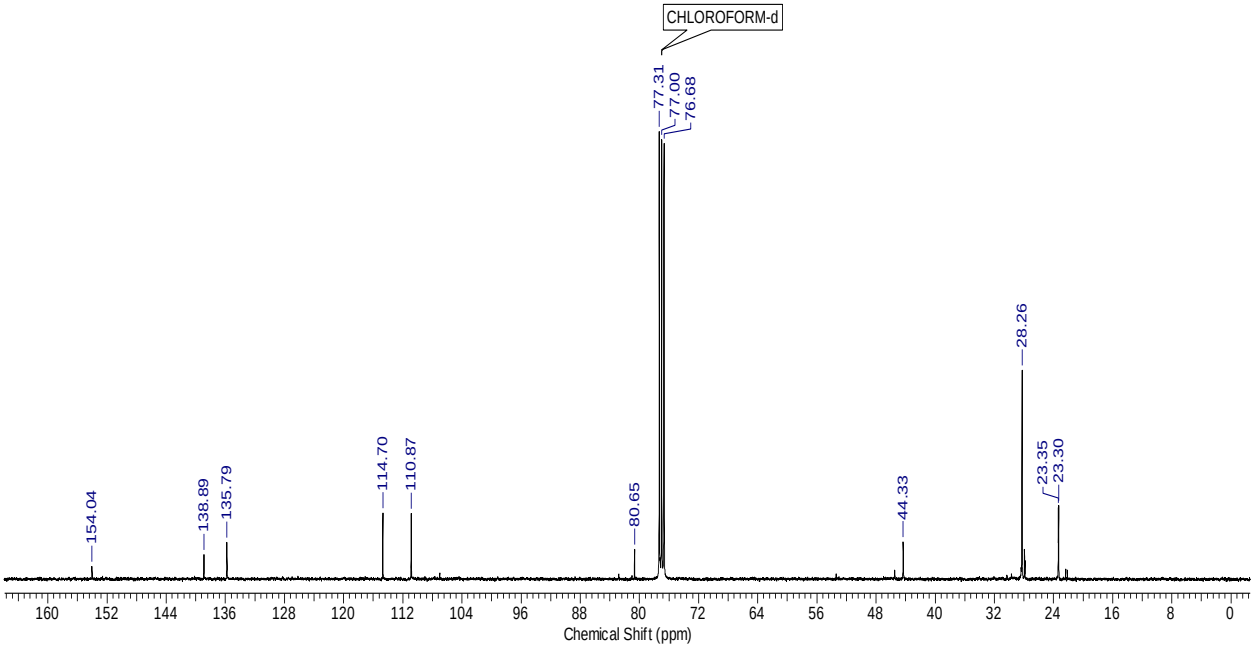

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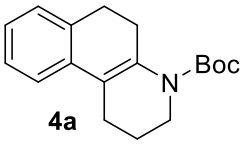

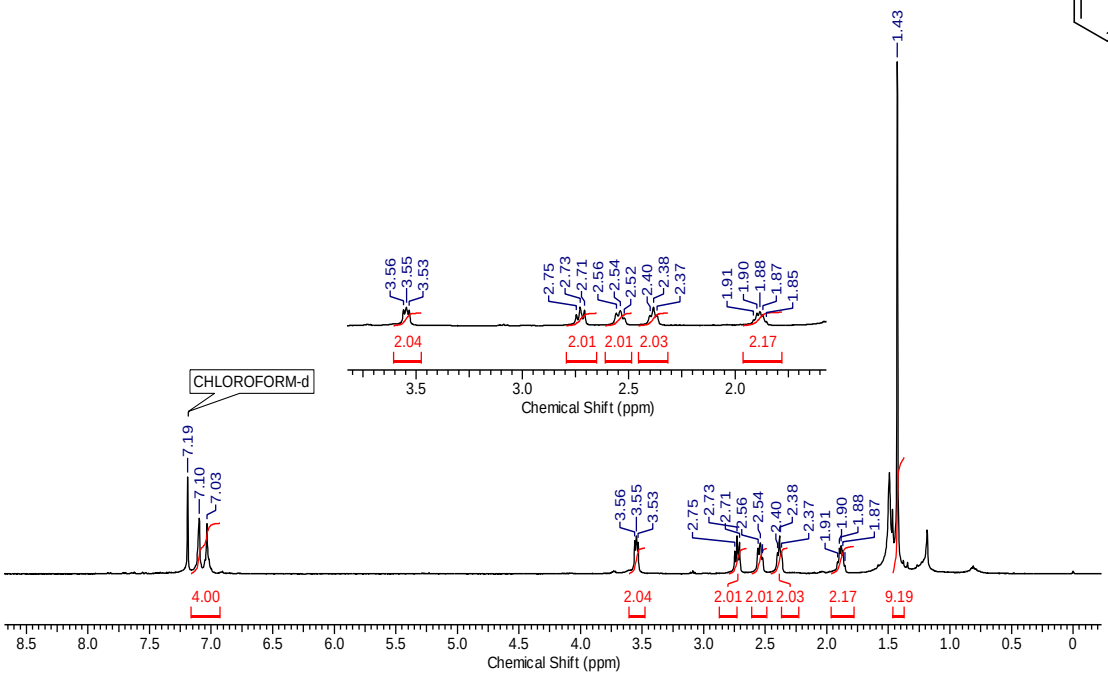

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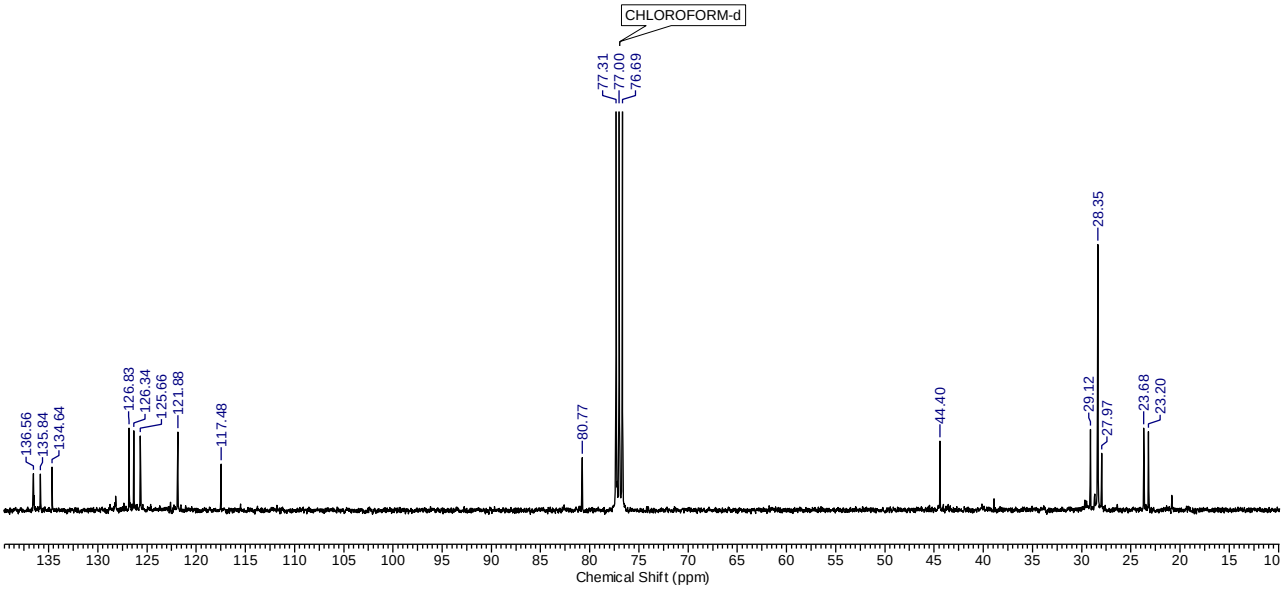

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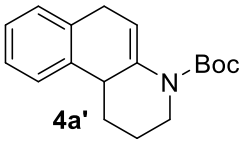

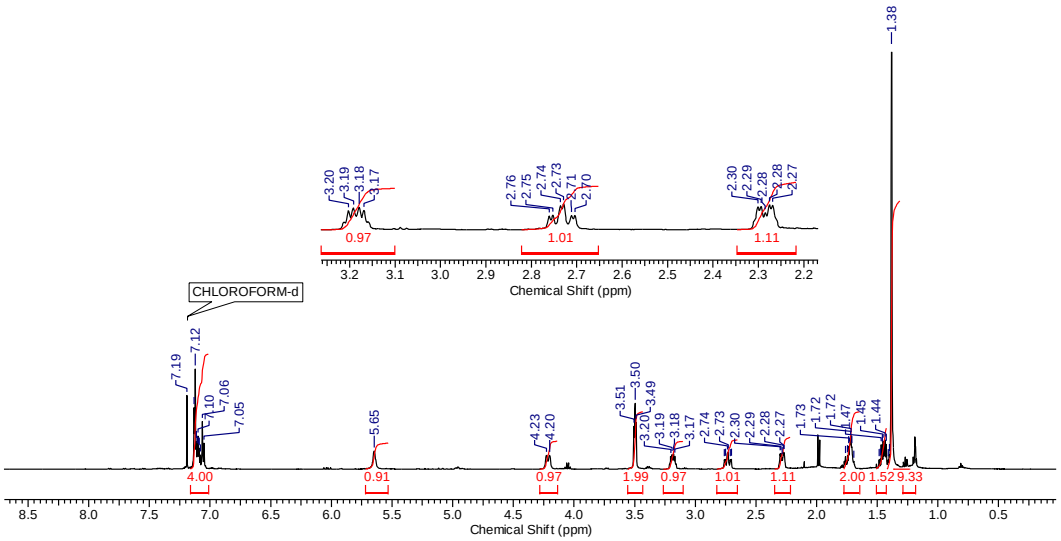

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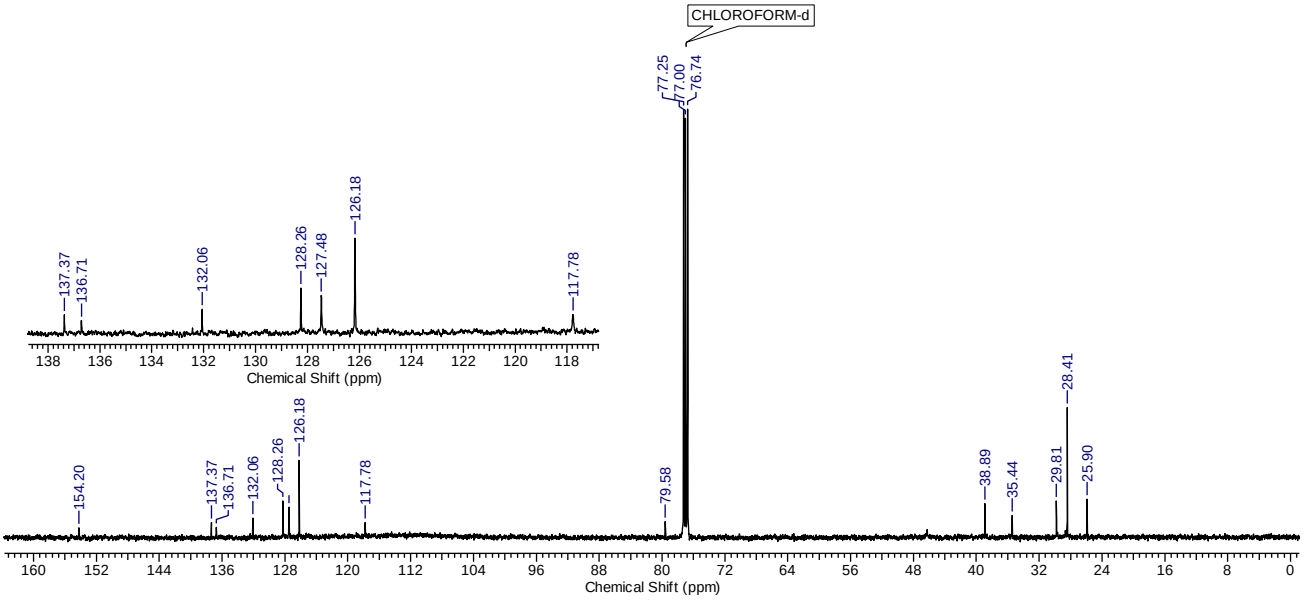

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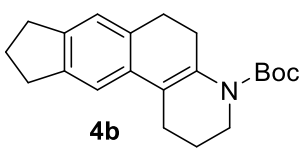

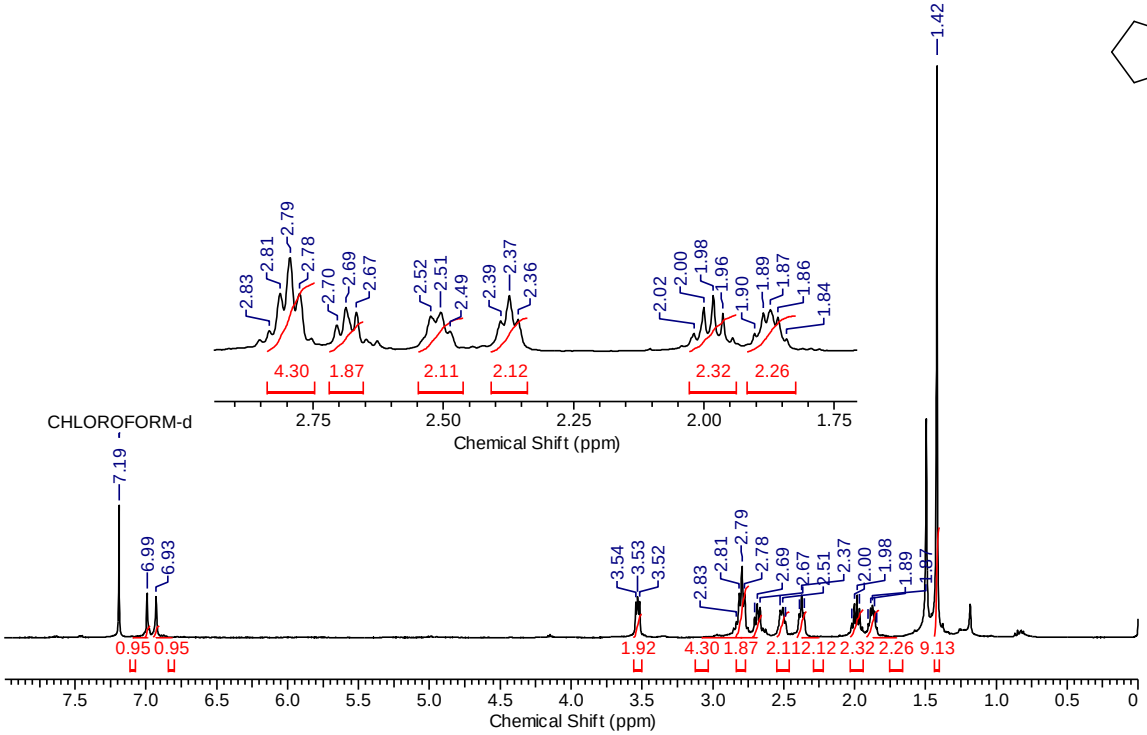

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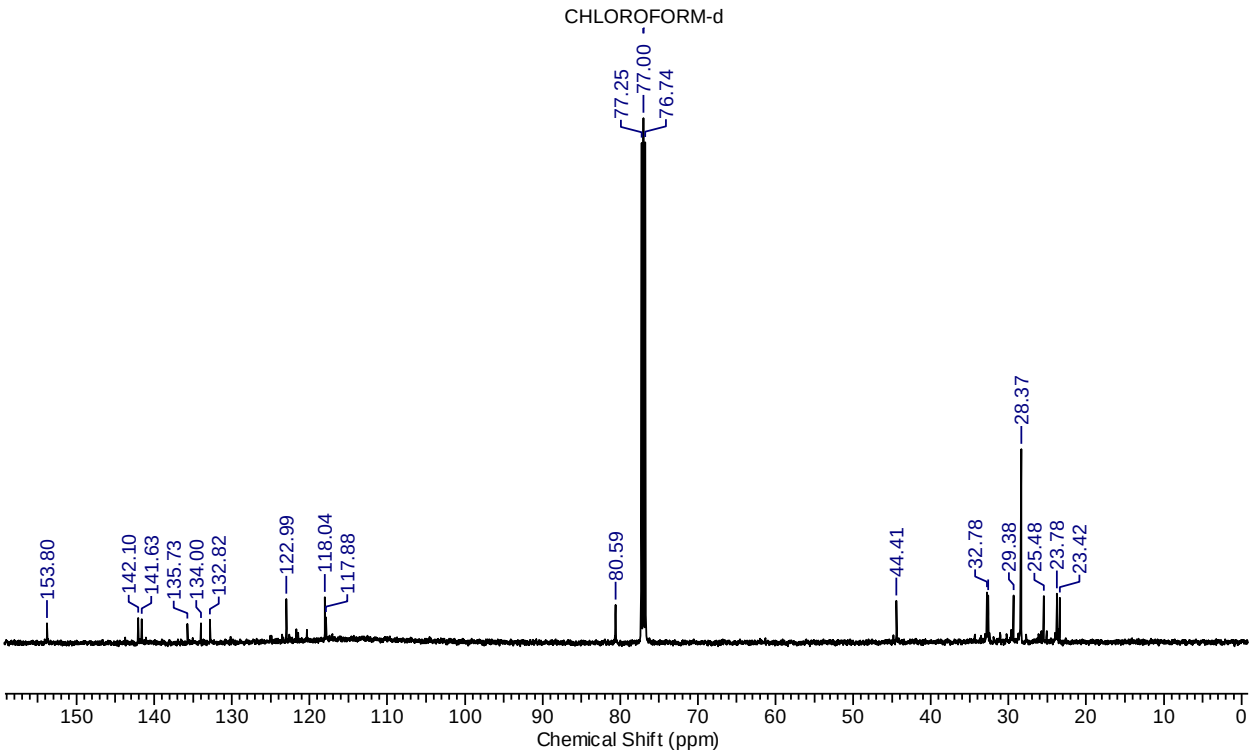

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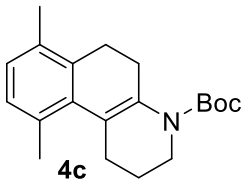

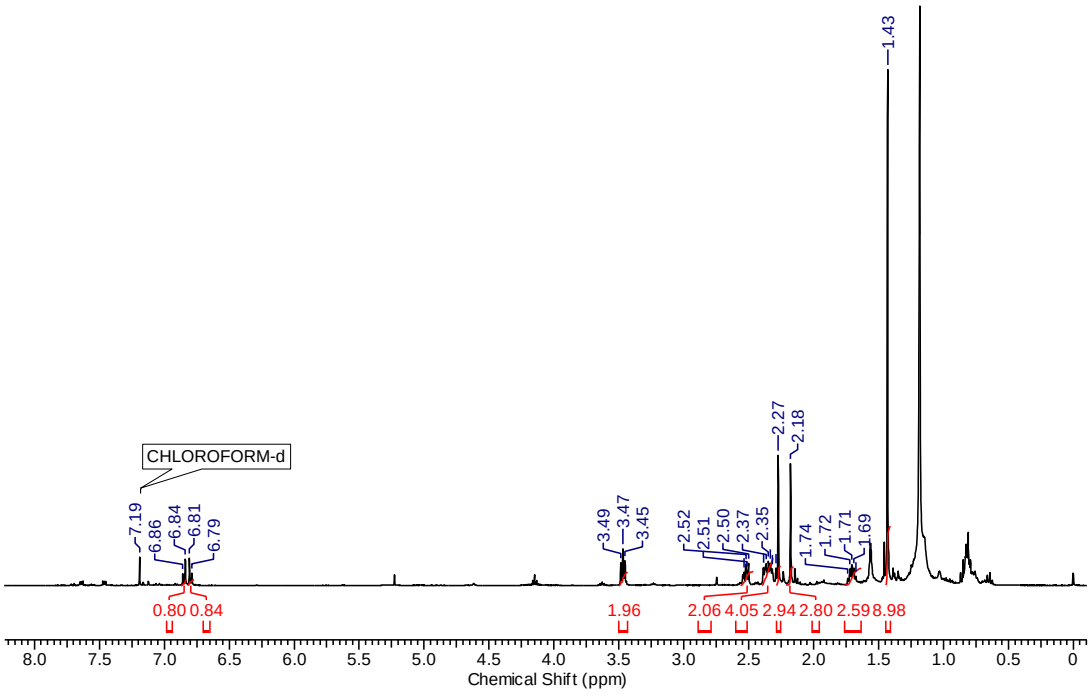

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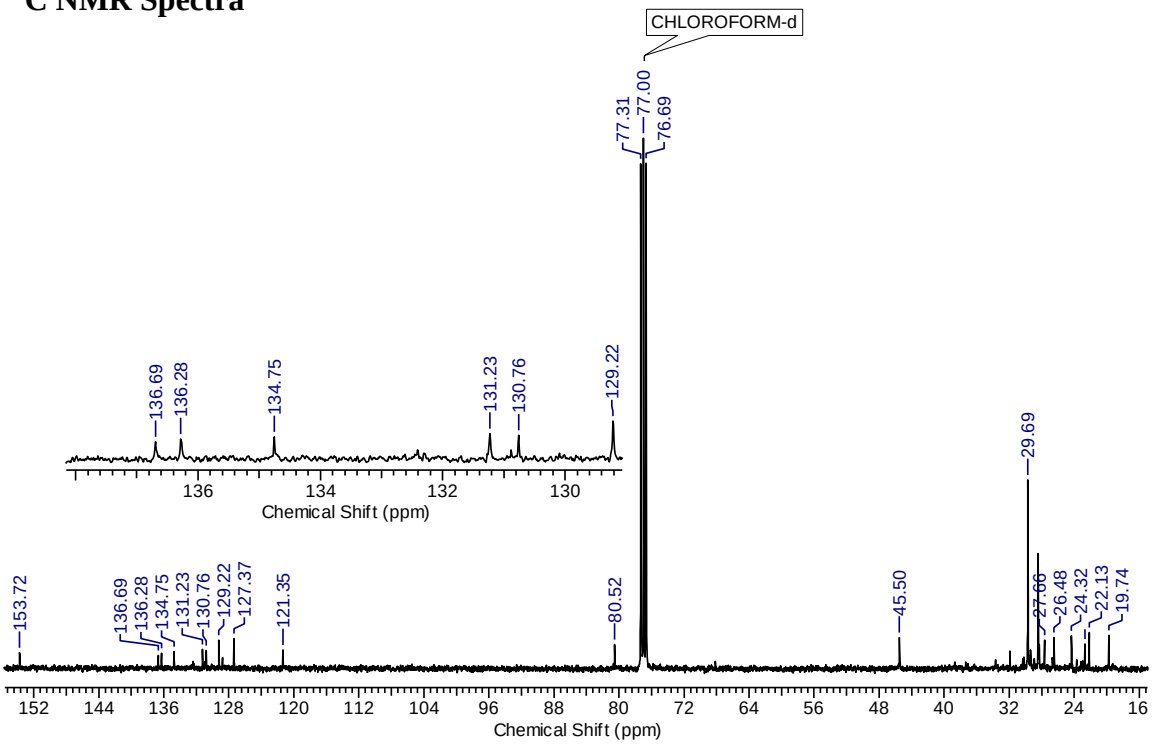

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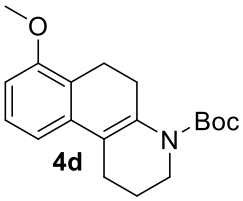

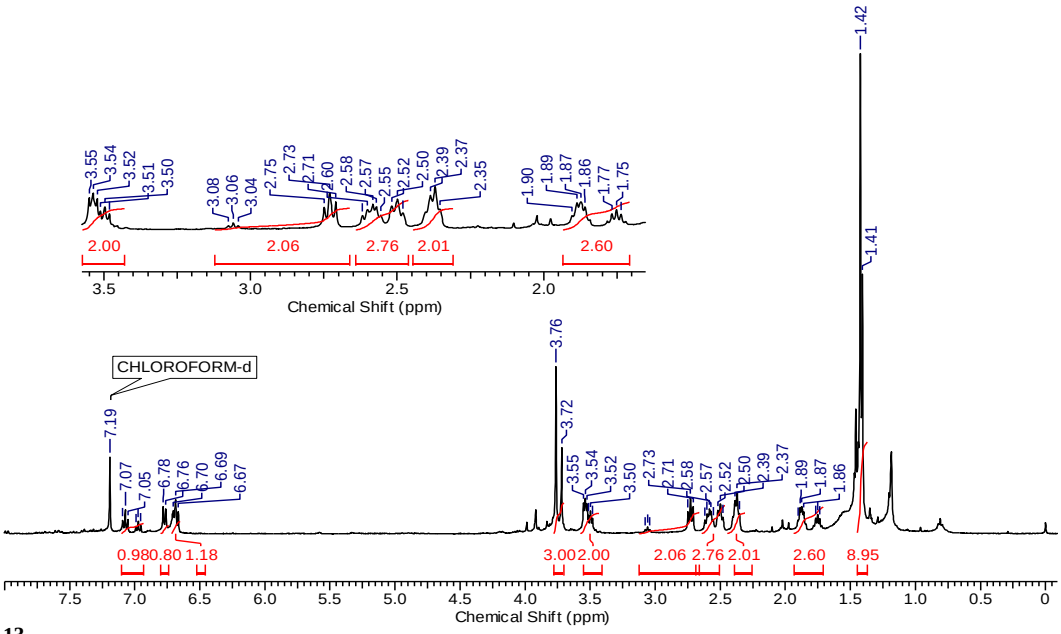

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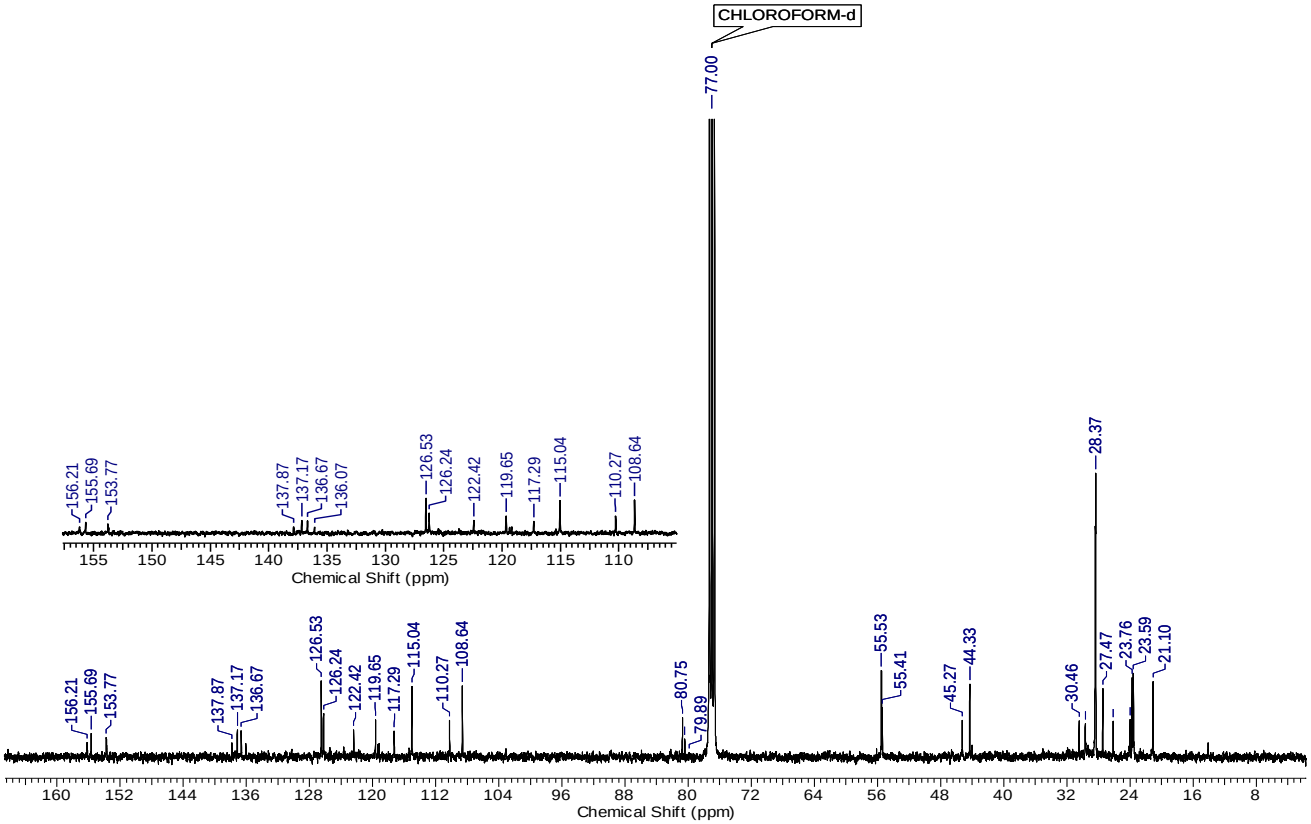
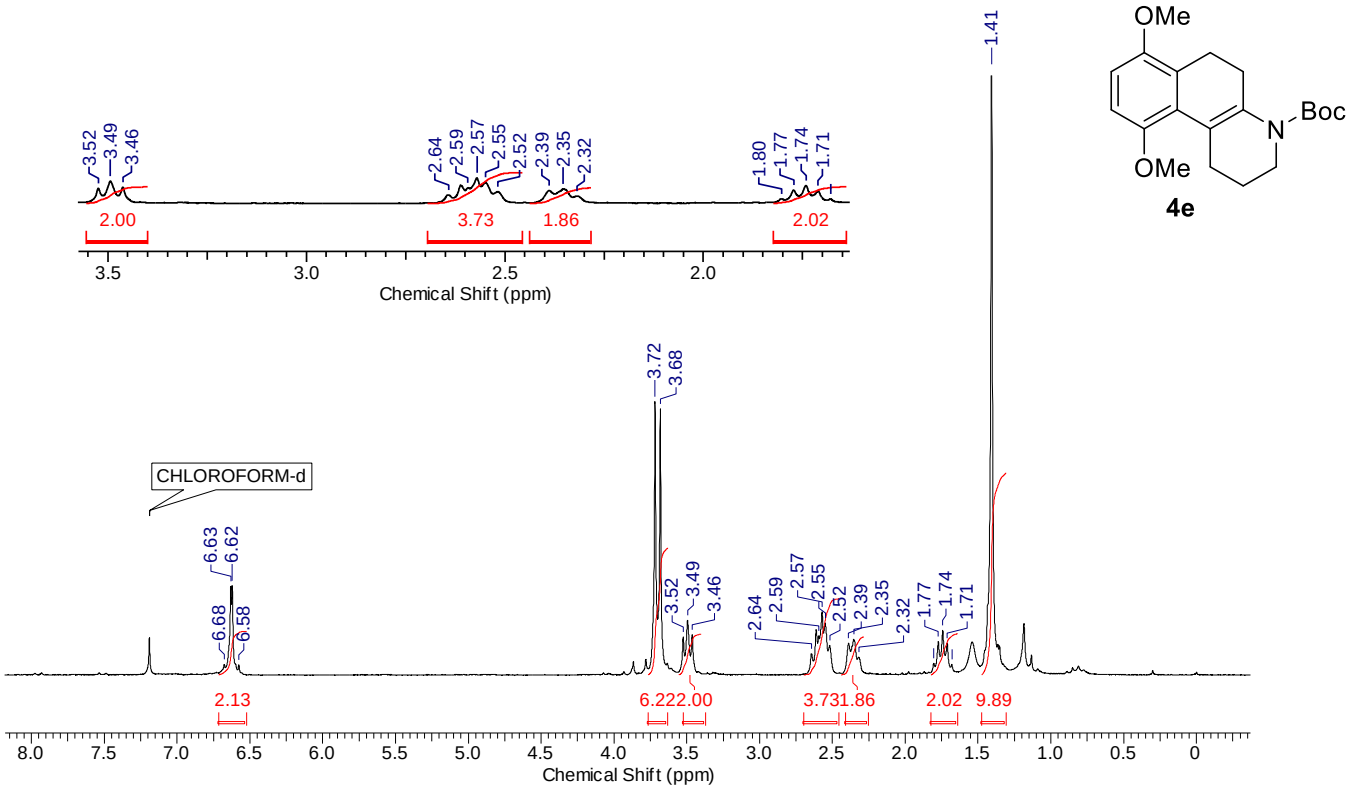
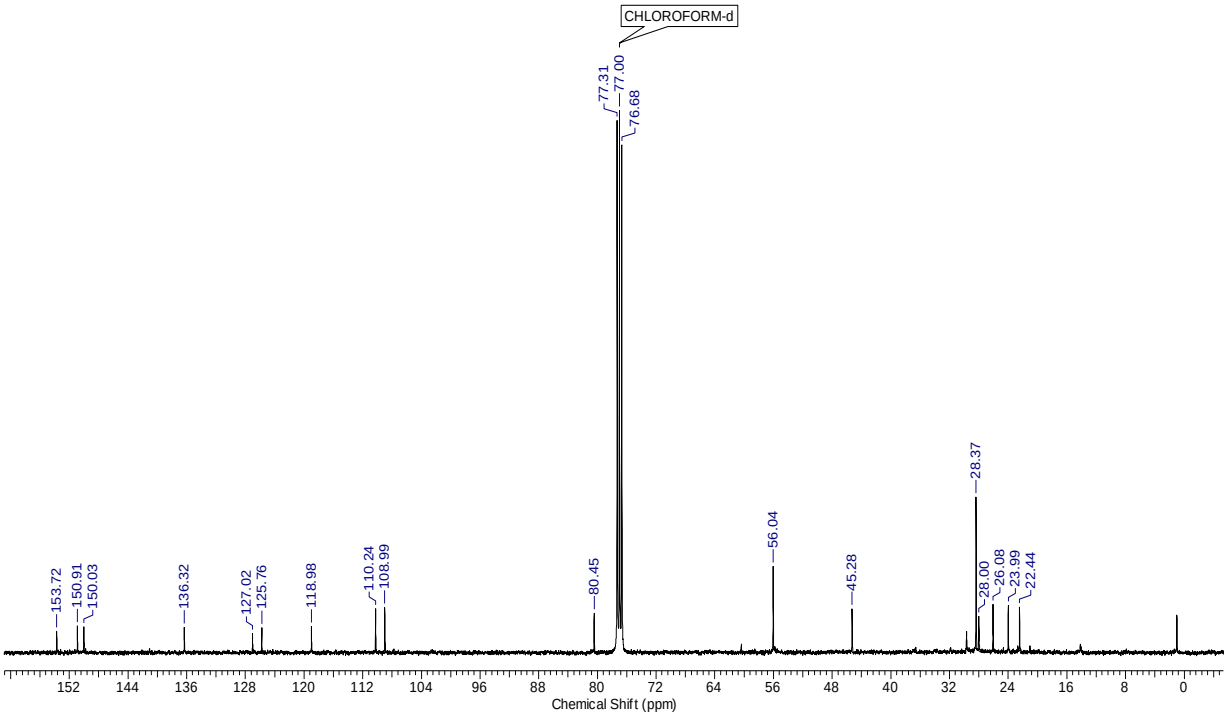


^{1}H NMR Spectra



^{13}C NMR Spectra



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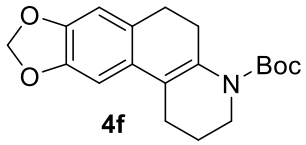

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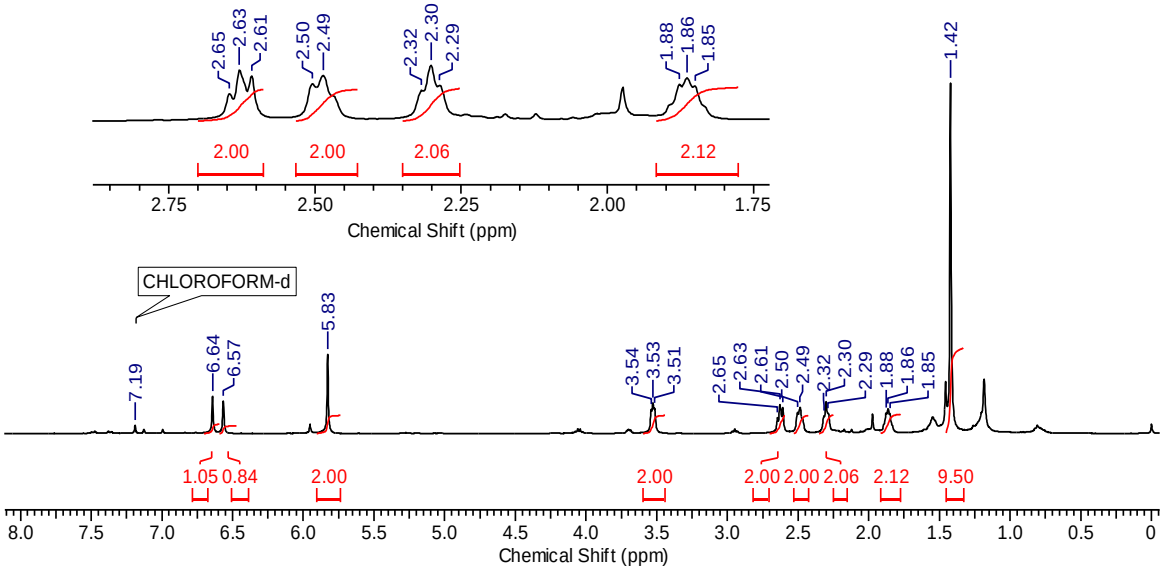

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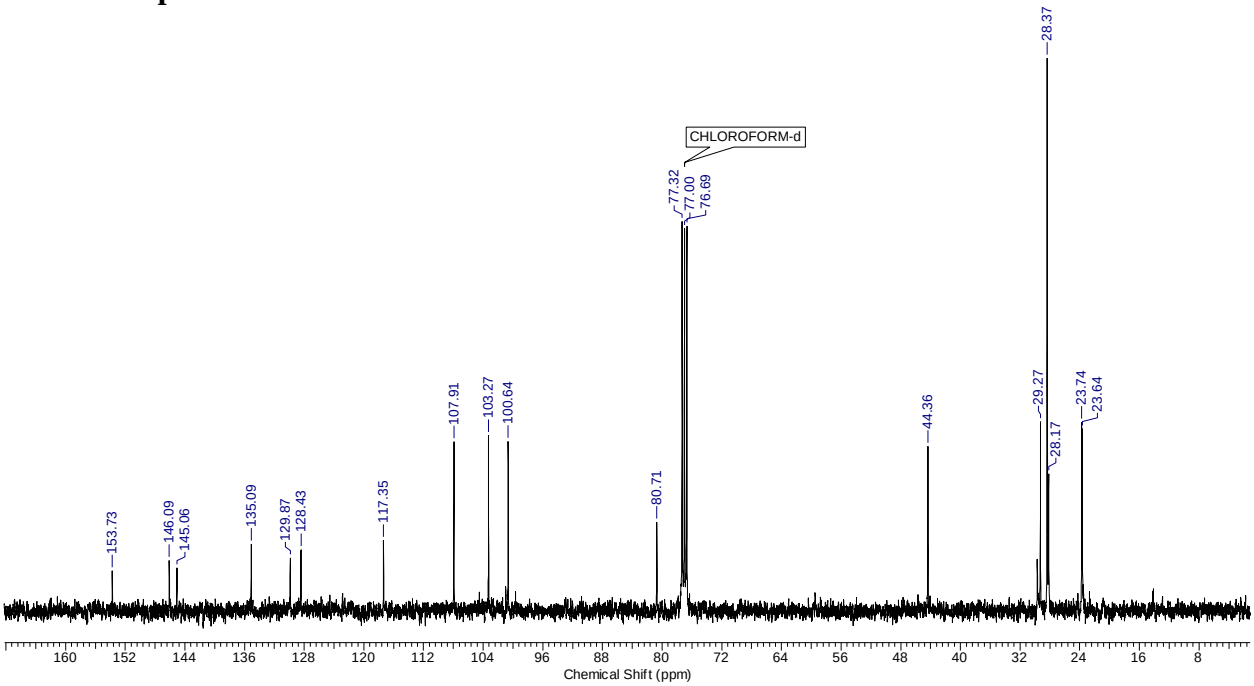

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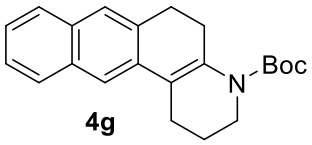

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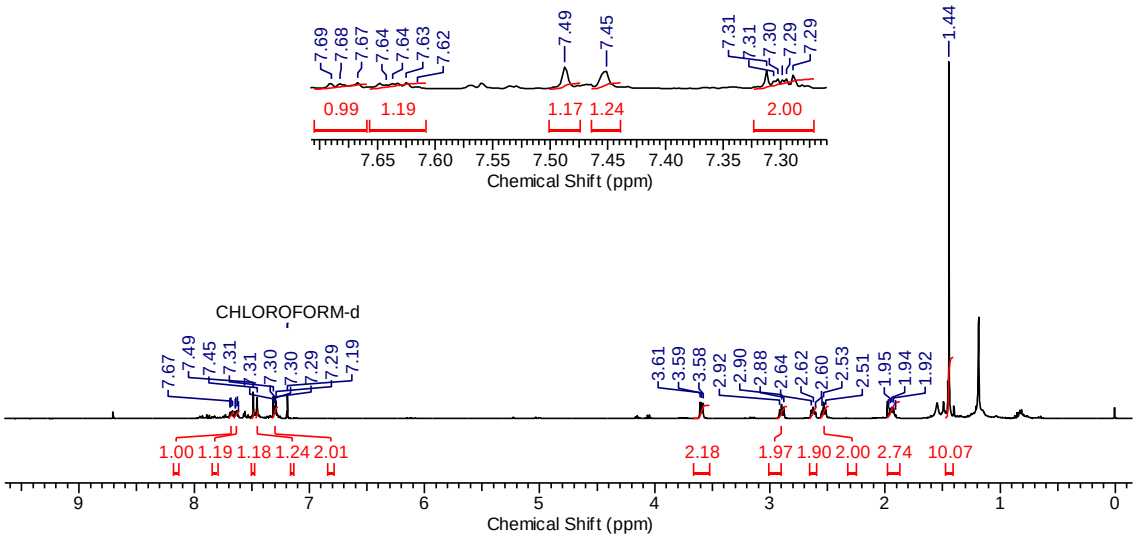

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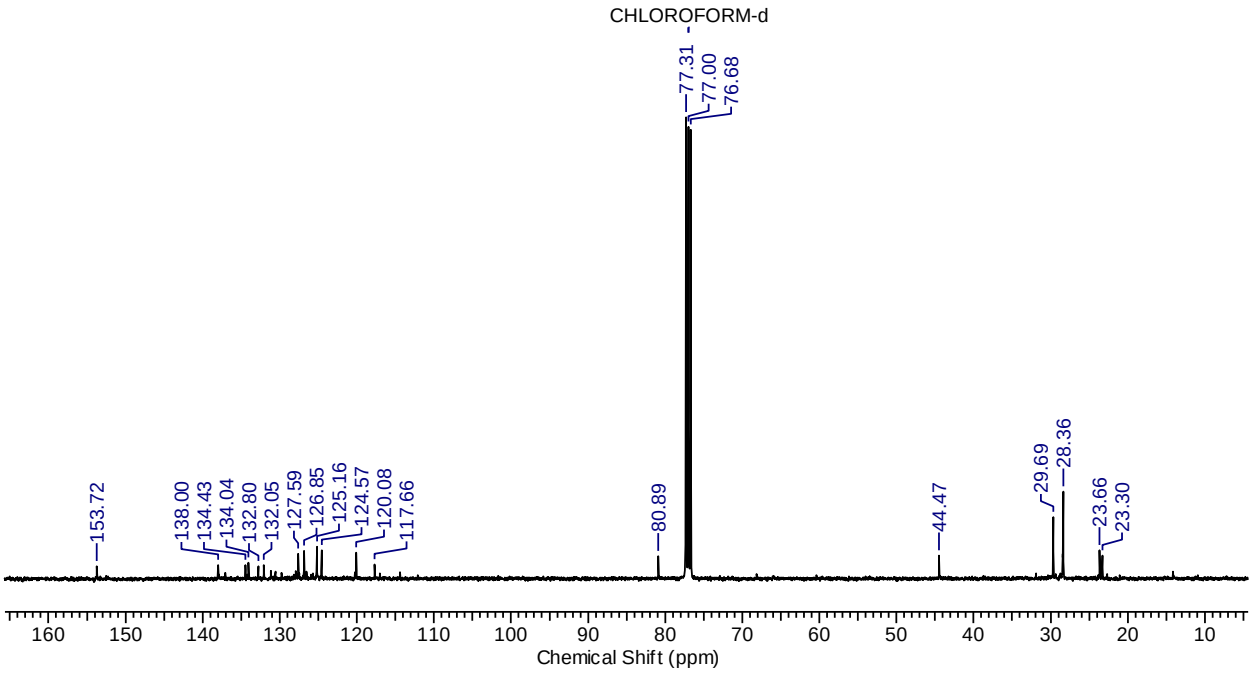

Publications and Patents

- "Transition-Metal-Free C–S Bond Formation: A Facile Access to Aryl Sulfones from Sodium Sulfinates via Arynes". *Org. Lett.* **2014,** *16***,** 3836**.**

  Virat G. Pandya and Santosh B. Mhaske

  (*Most read an article in July 2014* and highlighted in organic chemistry portal)

- "Divergent Synthesis of Oxindolylidene Acetates and Spirooxindolopyrrolidones from Arynes". *Org. Lett.* **2018**, *20*, 1483**.**

  Virat G. Pandya and Santosh B. Mhaske

  (Cited as a most read article in March 2018 by the ACS axial)

- "Process for the synthesis of Aryl Sulfones". WO2015087352A1, **US20160304447**.

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- "Process for the preparation of Oxindolylidene acetates and Spirooxindolopyrrolidones". **IN 2017022130867.**

  Virat G. Pandya and Santosh B. Mhaske

- "Diastereoselective synthesis of octahydroquinoline scaffolds using aryne chemistry" (Work under process)

  Virat G. Pandya and Santosh B. Mhaske

Erratum

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