Novel C-C and C-Heteroatom Bond Forming Synthetic Strategies for the Construction of Potential Scaffolds by NHC-Catalysis and Difunctionalization of Arynes

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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Dedicated to Indian Soldiers

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled "**Novel C-C and C-Heteroatom Bond Forming Synthetic Strategies for the Construction of Potential Scaffolds by NHC-Catalysis and Difunctionalization of Arynes**" submitted by Mr. Milind M. Ahire 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.

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DECLARATION BY THE CANDIDATE

I hereby declare that the original research work embodied in this thesis entitled, ***"Novel C-C and C-Heteroatom Bond Forming Synthetic Strategies for the Construction of Potential Scaffolds by NHC-Catalysis and Difunctionalization of Arynes"*** 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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Milind M. Ahire

Contents

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

NHC	N-Heterocyclic Carbene
KHMDS	Potassium bis(trimethylsilyl)amide
MeCN	Acetonitrile
CCl_4	Carbon Tetrachloride
$CHCl_3$	Chloroform
APS	$(NH_4)_2S_2O_8$/ Ammonium Persulfate
DMSO	Dimethyl Sulfoxide

THF	Tetrahydrofuran
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
LDA	Lithium Diisopropylamide
NMP	*N*-Methyl Piperazine
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. Milind Mukund Ahire
Degree Enrolment no. and Date	Ph. D. in Chemical Sciences (10CC11A26004), August 2011
Title of the Thesis	Novel C-C and C-heteroatom bond forming synthetic strategies for the construction of potential scaffolds by NHC-catalysis and difunctionalization of arynes
Research Supervisor	Dr. Santosh B. Mhaske (AcSIR, CSIR-NCL, Pune)

Abstract: This thesis demonstrates our accomplishments in the field of N-heterocyclic carbene catalysis and aryne chemistry to construct novel organic scaffolds. Chapter 1 is divided into three sections. Section 1 provides information on NHC catalyzed reactions, in particular, the Stetter reaction with selected examples from literature, whereas section 2 and 3 deals with our work on N-heterocyclic carbene catalyzed Stetter reactions of aromatic aldehydes with maleimides and *N*-substituted itaconimides, respectively. The developed Stetter reactions worked well under operationally simple reaction conditions to afford value added succinimide derivatives. Chapter 2 describes our novel work on the application of NHC catalysis in the total synthesis of cruciferane natural product. Herein, we have developed an intramolecular 3+2 cyloaddtion of homoenolate with imine as a key step to construct the cruciferane scaffold. Chapter 3 is divided into three sections. Section 1 provides information on various modes of aryne reactions and illustrates the reactivity and selectivity of aryne insertion reaction in elemental-elemental bond with the help of representative examples from the literature. Section 2 and 3 describes our studies on aryne insertion reaction in C-C and C-S bond, respectively. Section 2 shows the preparation of valuable *ortho*-methyl trifluoromethyl sulfide substituted benzophenones through aryne insertion in C-C bond. Due to fluorine's intrinsic property of modifying the pharmacological properties of drug molecules, its installation in the organic molecule through aryne chemistry was our prime motive, which was achieved successfully. Section 3 involves utilization of sulfur ylide for difunctionalization of aryne via C-S bond insertion. This section demonstrates novel reactivity for sulfur ylides.

Chapter 1. A Facile Access to Novel 1,4-Dicarbonyl Scaffolds via Stetter Reaction

Chapter 1 is divided into three sections. Section 1 narrates brief introduction of N-heterocyclic carbene

catalyzed reactions, in particular, the Stetter reaction. N-Heterocyclic carbenes (NHCs) are class of catalysts, which have attracted immense attention due to their potential applications in the field of synthetic organic chemistry. Consequently, recent research substantiates an increasing utilization of NHC towards the synthesis of natural products and useful bioactive molecules from simple feedstocks. During the Stetter reaction, the nucleophilic carbene transforms the aldehyde functionality into acyl anion equivalent via polarity reversal (Umpolung reaction), which enables aldehydes to react with Michael acceptors. This offers an elegant approach to construct new carbon-carbon bond. Section 1 elaborates on intermolecular as well as intramolecular Stetter reactions (Figure 1) with various Michael acceptors to produce 1,4-difunctionalized complex scaffold from simple starting materials. Section 2 and 3 deals with our work on the construction of novel organic scaffold by using N-heterocyclic carbene catalysis. Organocatalysis by N–heterocyclic carbene (NHC) has always stimulated synthetic chemists to understand their properties and reactivity for better applications. In section 2 we have presented our studies on intermolecular Stetter reaction of aromatic aldehydes with maleimides by employing thiazolylidene salt derived Isa–NHC as an efficient organocatalyst (Scheme 1). The synthesized Stetter products 3–aroylsuccinimides and their congeners are important building blocks for the synthesis of natural products and bioactive compounds (Figure 2). The traditional methods used for their preparation are harsh and in general low yielding. The reaction condition employed in this protocol is mild, and various substituents on aromatic aldehyde and maleimide nitrogen were tolerated. In the similar vein, in section 3, we have presented our studies on the NHC-catalyzed conjugate addition of acyl anion to *N*-substituted itaconimides representing an important

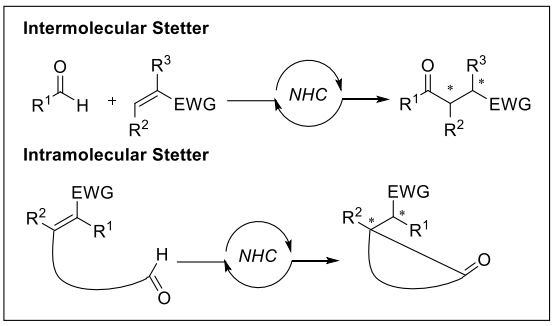
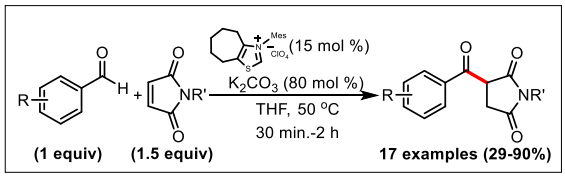


Figure 1. NHC-catalyzed Stetter reaction



Scheme 1. Stetter reaction with maleimide

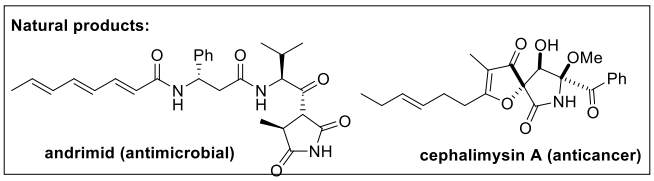
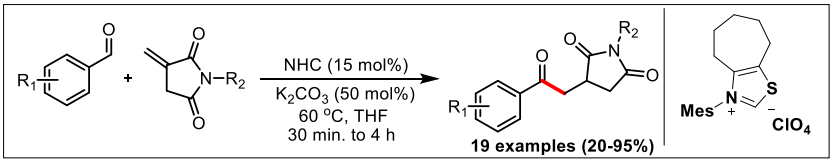


Figure 2. Natural products containing succinimide scaffold

and efficient synthetic method to construct valuable succinimide derivatives (Scheme 3). A delicate balance between the Stetter reaction and the competing base induced isomerization of the itaconimide double bond to maleimide has been achieved in this operationally simple reaction condition, which affords valuable new succinimide derivatives containing 1,4 and 1,5-dicarbonyl scaffold in good to excellent yields. Different substituents on both; aldehydes and *N*-substituted itaconimides have been examined.



Scheme 3. NHC-catalyzed Stetter reaction with N-aryl itaconimide

Chapter 2. Studies Towards the Total Synthesis of Cruciferane Using N-Heterocyclic Carbene Catalysis

Chapter 2 is divided into two sections. Section 1 gives information on the application of NHC catalysis in the total synthesis of natural products. Section 2 describes our studies on the total synthesis of (±)-cruciferane natural product. The fused quinazoline alkaloid (±)-cruciferane has potential antiviral and anticancer activity. The Figure 3 illustrates retrosynthetic analysis. We envisioned convergent construction

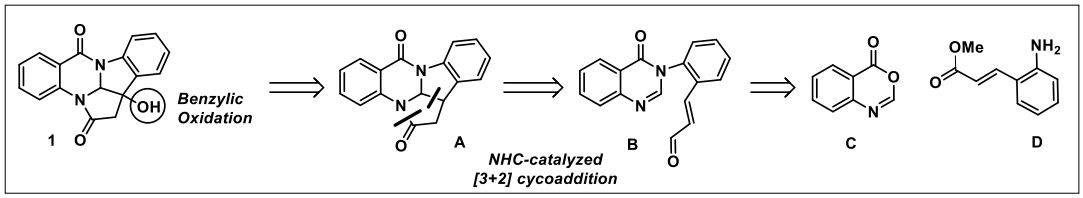
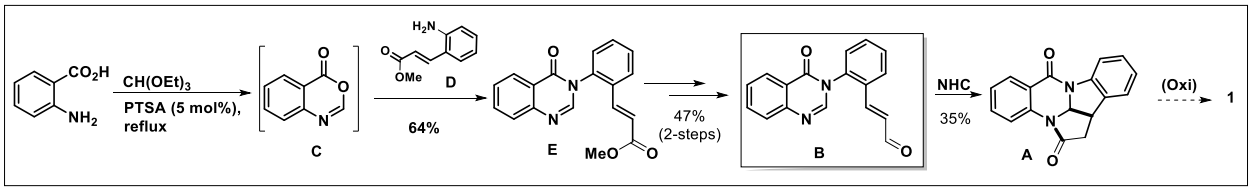


Figure 3. Retrosynthetic analysis of cruciferane

of **1** through benzylic oxidation of **A**. Compound **A** could be synthesized from aldehyde **B** via N-heterocyclic carbene catalyzed intramolecular [3+2] cycloaddition of imine and homoenolate of unsaturated aldehyde. Unsaturated aldehyde **B** was expected to be constructed from compound **C** and **D**.



Scheme 4. Synthesis of cruciferane

We began the synthesis of **1** with the formation of intermediate **C** from anthranilic acid and later its condensation with aniline **D** to form compound **E** in 64% yield over two steps (Scheme 4). To prepare

unsaturated aldehyde **B**, which is the key intermediate, compound **E** was employed to reductive and oxidative conditions. Further conversion of aldehyde **B** to compound **A** by employing NHC-catalyst is achived in 35% yield. Optimization of the protocol followed by oxidation should provide access to cruciferane.

Chapter 3. Novel 1,2-Difunctionalized Arenes Using Aryne Insertion Reaction

Chapter 3 is divided into three sections. Section 1 provides an overview of different reactions of electrophilic aryne species. Aryne has emerged as a prolific building block in organic synthesis. Due to their remarkable electrophilicity, it addresses a variety of organic transformations such as trapping of a wide variety of heteroatom and carbon nucleophiles, cycloaddition, multicomponent reaction (MCR), and elemental-elemental bond insertion reaction. This section is focused on the aryne insertion reaction, mainly into C–C, C–heteroatom or heteroatom–heteroatom bond, which is a useful transformation and provides a key strategy for the construction of important 1,2-difunctionalized arene derivatives (Figure 4). The above mentioned intriguing reactions prompted us to develop novel synthetic strategies in aryne chemistry.

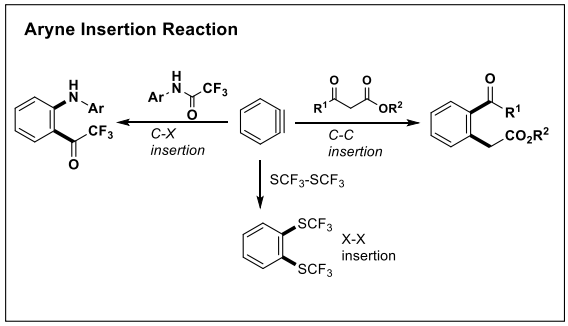
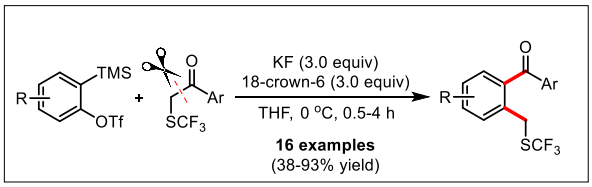


Figure 4. Elemental-elemental bond insertion reactions of aryne

Both of section 2 and 3 involve the study of highly reactive aryne intermediate towards elemental-elemental bond insertion reaction. Section 2 deals with an efficient process for the preparation of valuable *ortho*-methyl trifluoromethyl sulfide substituted benzophenones (Scheme 5). Fluorinated compounds constitute a vital structural class, which is commonly found in many bioactive molecules (Figure 5).



Scheme 5. Aryne insertion in C-C bond

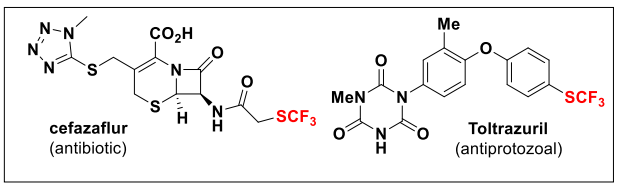


Figure 5. Bioactive compounds containing –SCF_3

Hence, in the past few years, methods involving efficient incorporation of fluorine and fluorine containing moieties into organic compounds have gained tremendous attention from the scientific community. The

developed transition-metal-free method features insertion of aryne in C-C σ-bond under a mild reaction condition for the first time to achieve *ortho*-difunctionalized arenes. A wide substrate scope has been demonstrated from the developed protocol with moderate to good yields. Section 3 reports a novel reactivity of sulfur ylide. Ylides are synthetically valuable reagents, and they are regarded as one of the powerful synthetic tools in organic chemistry. Commonly, sulfur ylides are utilized as one or two (C1 or C2) carbon synthon for the construction of valuable organic compounds (Figure 6). This section shows successful application of sulfur ylide as C1 and –SMe source with aryne, which contributes to the rare example of C-S bond insertion in aryne. A novel reactivity of sulfur ylides has been addressed in a transition-metal-free protocol to access *ortho*-substituted thioanisole derivatives by insertion of arynes into C–S σ-bond in moderate to good yields (Scheme 6). The reaction involves the formation of C–C and C–S bonds and consecutive breaking of two C–S bonds in an operationally mild reaction condition.

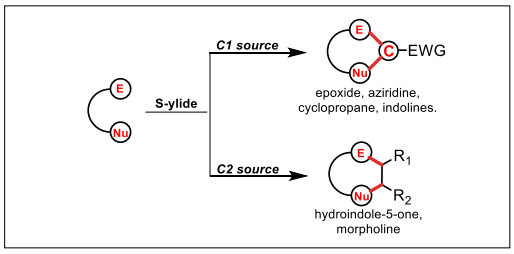
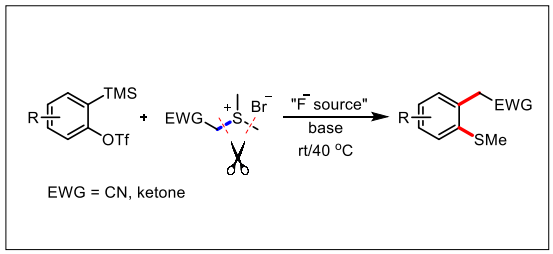


Figure 6. Application of sulfur ylides



Scheme 6. Aryne insertion in the C-S bond of ylide

In summary, we have successfully developed novel synthetic methodologies involving N-heterocyclic carbene catalysis for the construction of novel scaffolds and natural product cruciferane. We have also demonstrated efficient methodologies using aryne chemistry to access 1,2-difunctionalized arenes. The developed methods provide facile access to various scaffolds of pharmaceutical interest.

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Chapter 1

A Facile Access to Novel 1,4-Dicarbonyl Scaffolds via Stetter Reaction

Section 1: N-Heterocyclic Carbene as an Organocatalyst in Stetter reaction

1.1.1. Introduction

This section provides information on organocatalytic transformations by N-heterocyclic carbene, particularly, the Stetter reaction with selected examples from the literature. Organocatalysis involves small organic molecules containing non-metal elements as catalysts, which catalyzes wide array of organic transformations. Within realm of organocatalyst, N-heterocyclic carbenes (NHCs) have emerged as one of the powerful catalyst in a development of novel synthetic transformations for the construction of complex molecules from simple starting materials.[1] Since the first reports of isolation of stable N-heterocyclic carbenes by Bertrand et al. and Arduengo's group,[2] it has been the most studied organocatalyst in the field of synthetic organic chemistry. NHCs has astonishing journey from entity of just laboratory curiosity to entity of important organocatalysts[1] and versatile ligands for transition metal catalysts for homogenious reactions.[3]

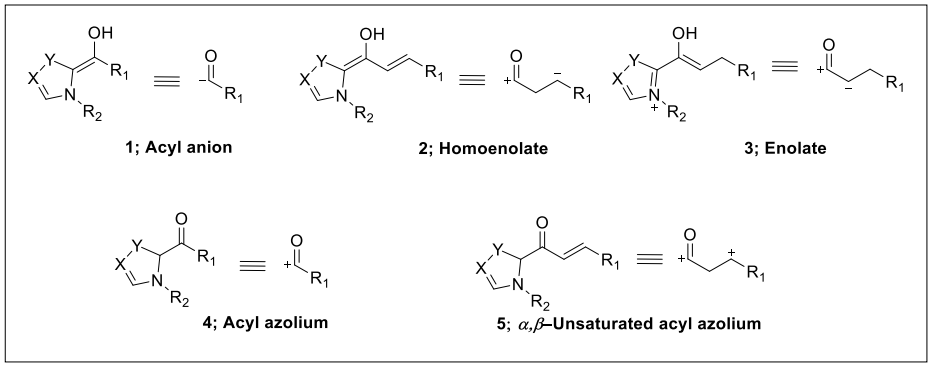


Figure 1. Key intermediates in NHC-catalyzed transformation.

N-heterocyclic carbenes intrinsic property of altering reactivity of aldehydes (Umpolung) to key reactive intermediates: nucleophilic species such as Breslow intermediate (**1**), homoenolate (**2**), enolate (**3**) and electrophilic species such as acyl azolium (**4**), *α,β*-unsaturated acyl azolium (**5**)

(Figure 1),[1] opens up new possibilities in synthetic strategies. Hence, in the past few years, methods involving efficient utilization of NHC's as an organocatalysts have gained tremendous attention from the scientific community. Organocatalysis by NHCs addresses variety of transformations such as benzoin condensation reaction, Stetter reaction, hydroacylation, redox amidation, redox esterification, halogenation, annulation, cyloaddition reaction among others.[1] Also, it involves highly enantioselective transformations by chiral NHC-precatalyst for effective construction of versatile natural products, bioactive compounds and important building blocks with distinct pharmaceutical activities.[4] Notably, for 1,4-difuctionalized molecules, Stetter reaction stood out to be the best catalytic pathway, which are difficult to construct using traditional methods.

1.1.2. Stetter Reaction

In NHC-organocatalyzed reactions, the catalysts transforms the aldehyde functionality into acyl anion equivalent via polarity reversal (Umpolung), which enables aldehyde functionality to react with various electrophiles. The nucleophilic addition of acyl anion equivalents to various Michael acceptors (Stetter reaction) has been illustrated as a powerful organocatalytic transformation (Figure 2). The Stetter reaction offers an elegant catalytic pathway to construct new carbon-carbon bond, which results in the formation of 1,4-bifunctional compounds such as γ-ketophosphonates, γ-ketosulfones, γ-nitroketones, γ-ketonitriles, γ-diketones, and γ-ketoesters etc. Further, these compounds constitute to be valuable starting material for the construction of heterocycles and natural products.[5] The cyanide catalyzed intervention of acyl anion equivalent with enone (Michael acceptor) was first developed by Stetter in 1973.[6a] Continuing this work, in 1976, Stetter demonstrated thiazolium salt derived carbene intermediate inverts the normal mode of reactivity of aldehydes and enable it to react with α,β-unsaturated ketones to form 1,4-

diketone products, where a variety of aromatic as well as aliphatic aldehydes were tested.6b Literature review revealed that the Stetter reaction can be catalyzed by wide variety of carbene catalysts such as thiazolium salts and triazolium salts.[5] Also, asymmetric variant of Stetter reaction is highly desirable transformation, which expands the scope of the reaction and it has been the object of much research in recent years.

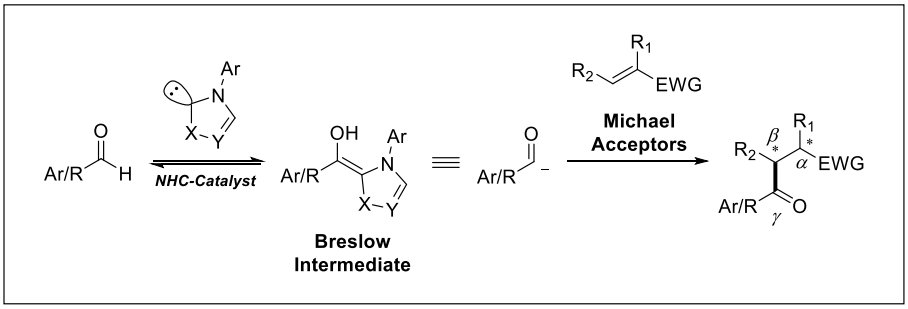


Figure 2. NHC-catalyzed Stetter reaction.

1.1.3. General Mechanism of Stetter Reaction

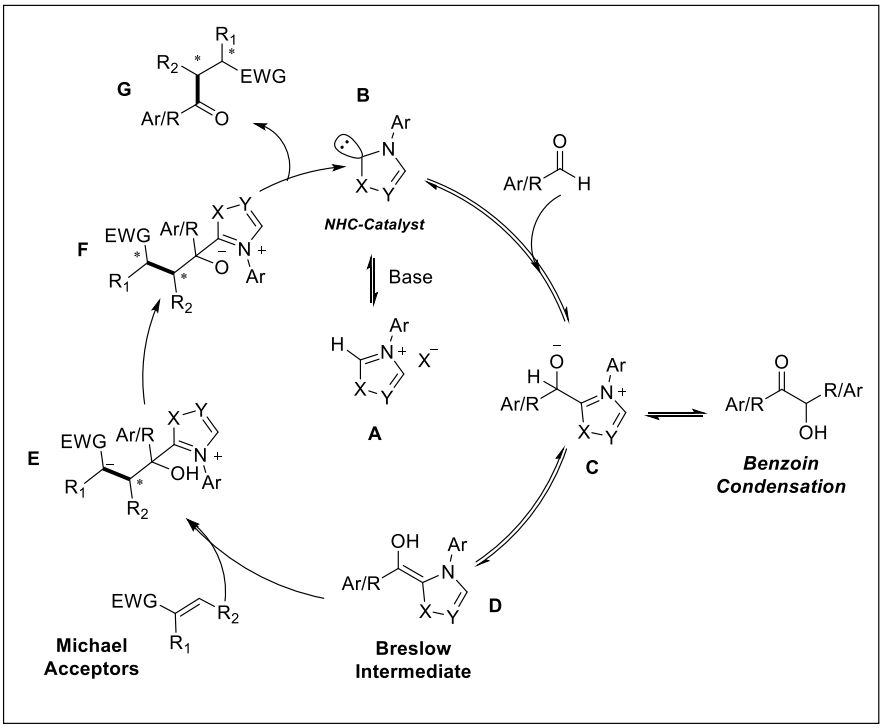


Figure 3. Postulated mechanism of Stetter reaction.

The postulated catalytic cycle of Stetter reaction is depicted in Figure 3. First, the reaction is initiated by generation of free carbene **B** from NHC-precatalyst salt **A** upon treatment with a base. Then the free carbene catalyst adds to aldehyde functionality generating the tetrahedral intermediate **C**, which undergoes proton rearrangement to form the key enaminol nucleophilic intermediate **D** (Breslow intermediate). Intermediate **D** can undergo two possible competing reactions, first one is 1-2 addition to provide the benzoin-condensation and another 1-4 addition (Stetter reaction) to form adduct **E**. Fortunately, the Benzoin-condensation is reversible, and the Stetter reaction leads irreversibly to more stable products **G** and NHC catalyst is regenerated for further catalytic cycle. Also, the chiral Breslow intermediate **D** generated by chiral NHCs has profound effect on controlling the enantioselectivity in asymmetric Stetter reactions.

There are two classes of the Stetter reaction: intermolecular and intramolecular (Figure 4, eq 1 and 2). Herein, a brief survey on variety of Michael acceptor and NHC-precatalyst for intermolecular as well as intramolecular Stetter reaction is described.

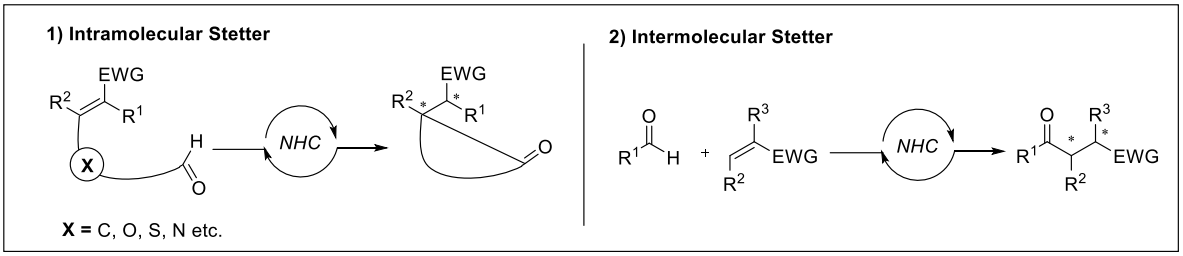


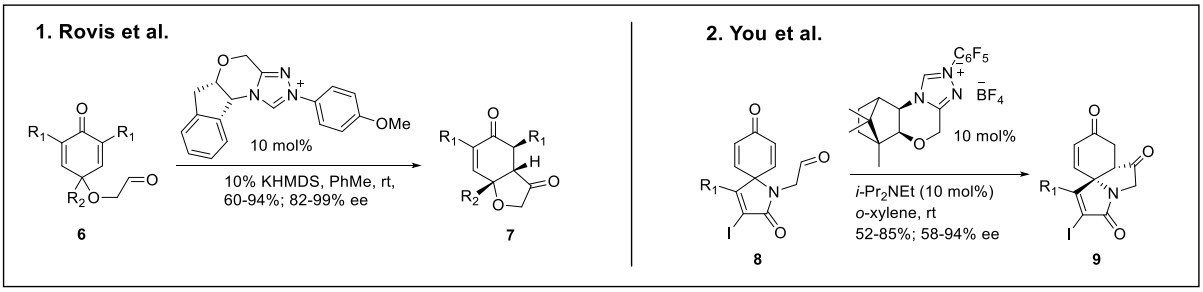
Figure 4. Types of Stetter reaction.

1.1.4. Intramolecular Stetter reaction

The intramolecular Stetter reaction consist nucleophilic addition of acyl anion equivalents of various aliphatic or aromatic aldehyde to the Michael acceptor, which are connected through a

tether atom such as carbon, oxygen, sulfur, nitrogen etc. (Figure 5, eq 1). The first intramolecular Stetter reaction was reported by Ciganek in 1995.[7a] Thereafter, in 1996, Ender reported the first asymmetric variant of intramolecular Stetter reaction using chiral NHC-precatalyst.[7b] In recent years there has been extensive research done in this area for the construction of complex scaffolds of biological interest.[5] In 2006 Rovis and colleagues demonstrated a sterioselective desymmetrization of tethered cyclohexadienes carboxaldehydes **6** through the intramolecular Stetter reaction catalyzed by chiral triazolium salts (Scheme 1, eq 1).[8] A variety of substituted cyclohexenes underwent successful cyclization leading to dicyclic system **7** with three contiguous stereocenters in excellent enantioselectivities and diastereoselectivities. Similarly, elegant work by You and group expanded the scope of Michael acceptors in enantioselective desymmetrization of cyclohexadienone **8** via a camphor-derived triazolium salt catalyst (Scheme 1, eq 2).[9] They have developed a method for construction of tricyclic system **9** possessing a quaternary stereocenter in moderate to good yields and excellent enantioselectivities. The reaction afforded various substituents on cyclohexadienones and it applies 10 mol% of NHC catalyst and base.

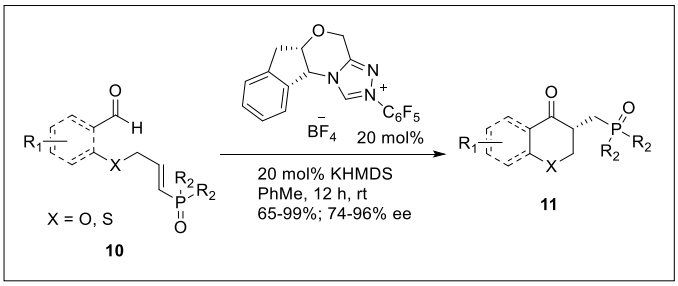
Scheme 1. Desymmetrization of Cyclohexadienes



Furthermore, Rovis group reported an intramolecular Stetter reaction with vinylphosphonates and vinylphosphine oxides **10** in operationally simple reaction conditions (Scheme 2).[10] It

involves chiral N-heterocyclic carbene catalyzed coupling of aldehyde with vinylphosphonates or vinylphosphine oxides to construct valuable organophosphorus compounds **11**. The reaction tolerates various aromatic and aliphatic substrates and provides corresponding products in good to excellent yields and enantioselectivities.

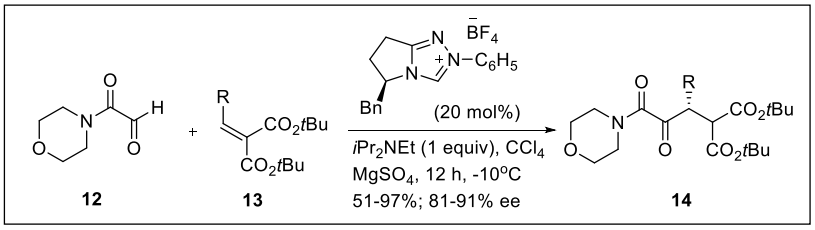
Scheme 2. Vinylphosphonates and Vinylphosphine Oxides as Reacting Partners



1.1.5. Intermolecular Stetter reaction

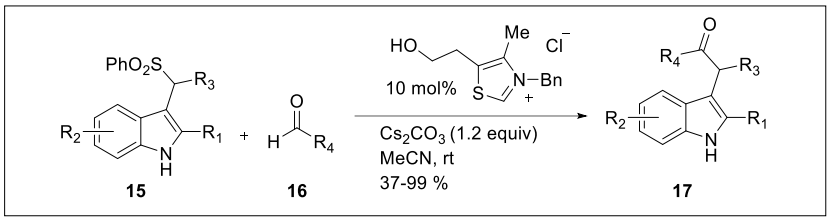
The intermolecular Stetter reaction has been illustrated as a powerful synthetic transformation to access many novel organic scaffolds, which are building blocks for the construction of variety of heterocycles, natural products, and bioactive compounds.[5] This transformation was enormously studied with chiral and achiral NHC catalysts. In 2008, Rovis and group demonstrated enantioselective intermolecular Stetter reaction of glyoxamide **12** as a nucleophilic acyl anion partner with alkylidenemalonates **13** as the Michael acceptors (Scheme 3).[11] The reaction

Scheme 3. Intermolecular Stetter Reaction of Glyoxamides with Alkylidenemalonates



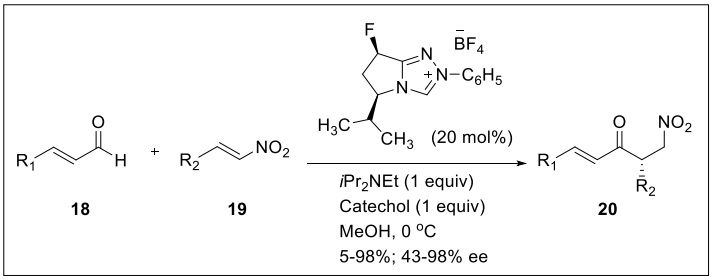
delivers expected compound **14** in high enantioselectivity in the presence of a phenylalanine-derived carbene NHC catalyst. You and co-worker demonstrated the NHC-catalyzed coupling of aldehydes **16** with electrophile generated from 3-(1-arylsulfonylalkyl) indoles **15** via elimination of tosylate (Scheme 4).[12] This reaction provides a facile access to 3-indolyl derivatives. A broad range of substitution pattern on aldehydes as well as indoles was tolerated.

Scheme 4. Scope of Arylsulfonyl Indoles



In 2011, Rovis's group reported efficient asymmetric intermolecular Stetter reaction of unsaturated aldehydes **18** with nitroalkenes **19** as the Michael acceptor (Scheme 5).[13] High asymmetric inductions has been achieved by using the fluorine containing triazolium salt as NHC-precatalysts. Furthermore, the yield and enantioselectivity has been increased by catechol

Scheme 5. Intermolecular Stetter Reaction of Enals with Nitroalkenes



additive, which acts as bifunctional Brønsted acids. The reaction has broad substrate scope, which includes aliphatic and aromatic enals. Yields of **20** are moderate to excellent (5-98%), and enantioselectivity is moderate to excellent (43-98% ee).

1.1.6. Conclusion

In last two decades, N-heterocyclic carbene has emerged as one of the important organocatalyst in chemistry. This section summarizes NHC-catalyzed reactions, in particular, the Stetter reaction with selected examples from literature. The Stetter reaction can be catalyzed by a broad range of carbene catalysts. Also, the Stetter reaction provides access to potential scaffolds of diverse biological activities. In the future, the NHC-catalyzed Stetter reaction will continue to provide new challenges by exploring new Michael acceptors and designing new efficient N-heterocyclic carbenes.

1.1.7. References

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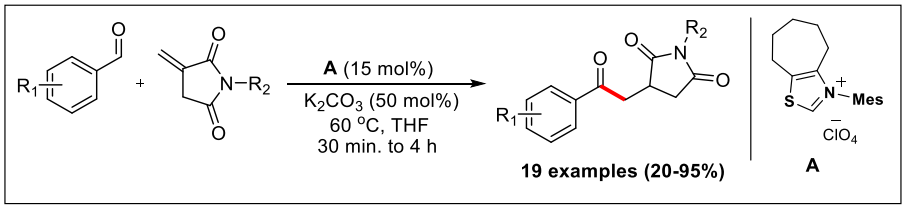
Section 2: Synthesis of Succinimide Derivatives by NHC-Catalyzed Stetter Reaction of Aromatic Aldehydes with *N*-Substituted Itaconimides

1.2.1. Abstract

An N-heterocyclic carbene catalyzed intermolecular Stetter reaction of aromatic aldehydes with *N*-substituted itaconimides has been developed. A delicate balance between the Stetter reaction and the competing isomerization of the itaconimide double bond has been achieved in this operationally simple reaction condition to afford valuable new succinimide derivatives containing 1,4 and 1,5 dicarbonyl scaffold in good to excellent yields. The reaction tolerates variable substituents on both; aldehydes and *N*-substituted itaconimides.



This work has been published in *ACS Omega* **2017**, *2*, 6598.

1.2.2. Introduction

N-Heterocyclic carbenes (NHCs), a well-documented class of catalysts have attracted immense attention due to their potential applications in the field of synthetic organic chemistry.[1] During the last few years, efforts have been devoted to the development of novel synthetic methodologies where NHC catalysts are involved as active organocatalysts or ligands for metal catalyzed reactions. Consequently, recent research substantiates an increasing utilization of NHC towards the synthesis of natural products and useful bioactive molecules from simple

feedstocks.[2] In NHC-organocatalyzed reactions, the nucleophilic carbene transforms the aldehyde functionality into acyl anion equivalent via polarity reversal (Umpolung reaction), which enables aldehydes to react with various electrophiles. The nucleophilic addition of acyl anions to various Michael acceptors (Stetter reaction) has been illustrated as a powerful organocatalytic transformation, which offers an elegant approach to construct new carbon-carbon bond.[3] The Stetter reaction with various Michael acceptors provides 1,4-difunctionalized products, which constitute highly valuable building blocks in organic synthesis.[4] NHC-catalyzed generation of active acyl anion intermediate and its intervention into new Michael acceptors is a challenging and desired synthetic transformation.[3]

1.2.3. Literature Review

This work endeavors to study the NHC-catalyzed conjugate addition of acyl anion to *N*-substituted itaconimides representing an important and efficient synthetic method to construct valuable succinimide derivatives. The succinimide derivatives are significant compounds found in various natural products, which reveal a remarkable biological and pharmaceutical activity. Also, they have several important applications in agrochemicals, functional materials, and polymer sciences.[5] Maleimides are considered to be the general synthon for the preparation of succinimide derivatives. Generally, nucleophilic additions to the active endocyclic polarized double bond or transition metal catalyzed C-H activation via olefin insertion are some of the strategies for the preparation of succinimide derivatives from maleimides.[6] Apart from these methods very less attention has been given to itaconimide derivatives, which are considered as possible synthons for succinimide derivatives. The active exocyclic double bond and an enolizable amide bond of the *N*-substituted itaconimide have been recognized as important moieties for the construction of succinimide derivatives. Despite these advantages, one challenge

that has to be addressed in the application of *N*-substituted itaconimides is a base induced isomerization to 3-alkyl *N*-substituted maleimides,[7] presumably due to its high thermodynamic stability (Figure 1).

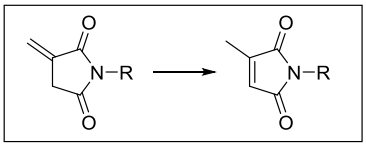


Figure 1. Isomerization of Itaconimide to Maleimide.

1.2.4. Origin of the present Work

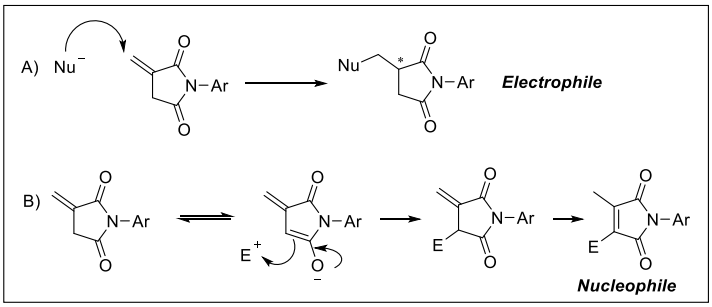


Figure 2. Modes of Reactivity of Itaconimide

There are two different reactivity modes associated with itaconimides, first one is its electrophilic nature due to exocyclic double bond (Figure 2, eq A) and another one is it's nucleophilic nature due to enolizable amide bond (Figure 2, eq B). Until now, very few reports demonstrated Michael acceptor reactivity of *N*-substituted itaconimides (Figure 3). Tan and co-workers reported enantioselective 1-4 nucleophilic addition of phospine oxides and thiols with *N*-substituted itaconimides, catalyzed by chiral bicyclic guanidine, which acts as a strong chiral Brønsted base (Figure 3, eq 1 & 2).[8] Recently, Jiang et al. demonstrated an elegant approach for the addition-protonation reaction of azlactone with *N*-substituted itaconimides (Figure 3, eq 3).[9] Further, cycloaddition reaction is an aspect of *N*-itaconimides electrophilicity and it has been studied by Jiang and co-workers. They have developed the asymmetric reaction of 5*H*-thiazol-4-

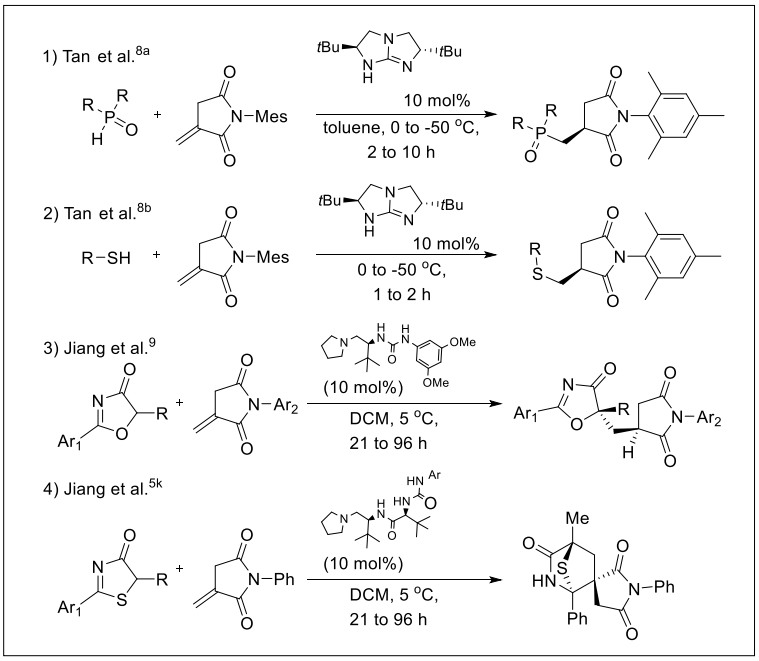


Figure 3. Prior Work on Michael Addition with *N*-Substituted Itaconimides

ones with *N*-itaconimides by employing a DP-UAA catalyst. The reaction undergoes a [4 + 2] annulation, affording chiral spirocyclic 1,4-sulfur-bridged piperidinone-based succinimides (Figure 3, eq 4).[5k]

There are very few examples highlighting nucleophilicity of *N*-substituted itaconimides. Elegant work by Tan and co-worker successfully demonstrated an allylic alkenylation of Morita-Baylis-Hillman adducts (carbonates) with *N*-itaconimides. The reactions employed Cinchona alkaloid as

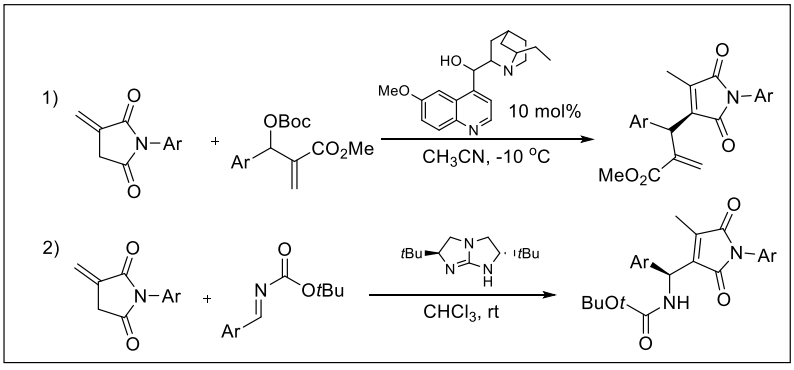


Figure 4. Nucleophilic Reactions of Itaconimide.

chiral Lewis base catalyst for this transformation (Figure 4, eq 1). Further, same group developed a direct asymmetric allylic addition reaction to imines. This reaction provides enantio-enriched maleimides and succinimides (Figure 4, eq 2).

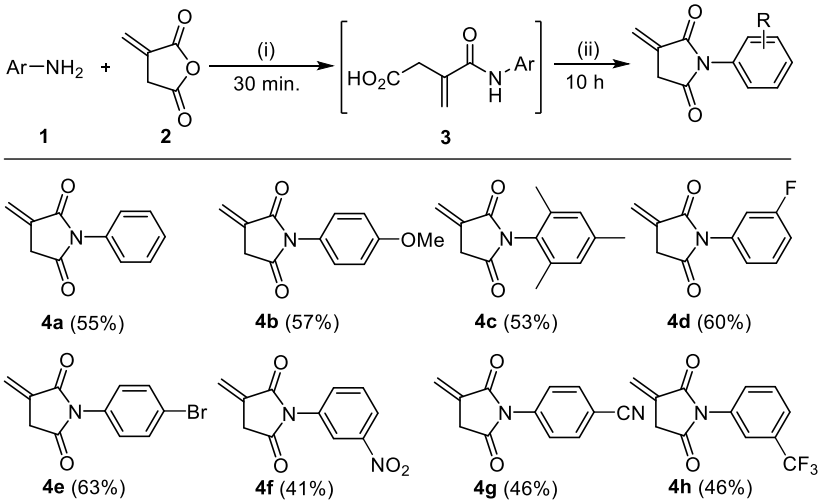
1.2.5. Objective

Inspired by this progress and our research interest we thought to investigate the reactivity of itaconimide for Stetter reaction. Though the Michael addition of hard nucleophiles such as heteroatomic anion and carbanion is known, to the best of our knowledge transformation using soft nucleophilic acyl anion is not reported. Notably, by taking advantage of the active exocyclic double bond of *N*-itaconimide, herein, we report its NHC-catalyzed Stetter reaction, avoiding the double bond isomerization.

1.2.6. Results and Discussion

We began our study by preparing *N*-substituted itaconimide using a novel method. Recently, our group has developed an expedient protocol for the synthesis of maleimide and succinimide derivatives using a new dehydrating agent $(NH_4)_2S_2O_8$–DMSO.[10] In continuation of that, herein we extended the same protocol in the synthesis of *N*-aryl itaconimide derivatives. The developed reaction condition worked very well and tolerated various electron-withdrawing and electron-donating substituents on primary aromatic amines, which gives the corresponding itaconimide in comparably good yields (41-63%). Our protocol is advantageous over the commonly used acetic anhydride-sodium acetate condition.[11] The *N*-alkyl substituted itaconimides were synthesized from maleimides using known literature procedure (Scheme 1).[12]

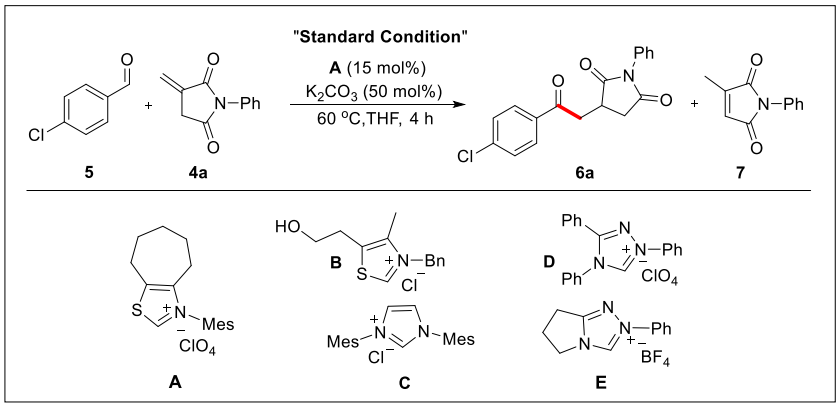
Scheme 1. *N*-Aryl Itaconimides from Aromatic Amines and Itaconic Anhydride[a,b]



[a]Reaction conditions: (i) amine (1 equiv, 1 g scale), anhydride (1.1 equiv), 1,4-dioxane (0.1 M), 25°C, 30 min; (ii) APS (2 equiv), DMSO (2 equiv), 100 °C; bisolated yields.

Our first effort for the Stetter reaction began by treating *p*-chlorobenzaldehyde (**5**) with *N*-phenyl itaconimide (**4a**) in the presence of 20 mol% thiazolydene derived pre-NHC catalyst **A** and 20 mol% of K_2CO_3 in THF at room temperature. To our delight, the reaction led to the expected product **6a** in 55% yield. However, under this reaction condition, the base facilitated isomerized product 3-methyl-*N*-phenyl maleimide was also observed along with the Stetter product. To increase the yield of the Stetter product **6a** and to suppress the formation of isomerized side product **7**, four different reaction parameters were examined, which includes pre-NHC catalysts, reaction temperature, bases, and solvents. At first, different pre-NHC catalysts **B-E** were screened, but they appeared to be less effective as compared to catalyst **A** (Table 1, entries 2-5). Further, performing the reaction at room temperature furnished **6a** in diminished yield (Table 1, entire 6). Screening of different bases for the generation of active carbene intermediate from pre-NHC catalyst concludes that various bases such as Cs_2CO_3, NEt_3, DBU furnished the expected product in low yield with increased side product 7 (Table 1, entries 7-9), but K_2CO_3 emerged as

Table 1. Optimization of Reaction Conditions[a]



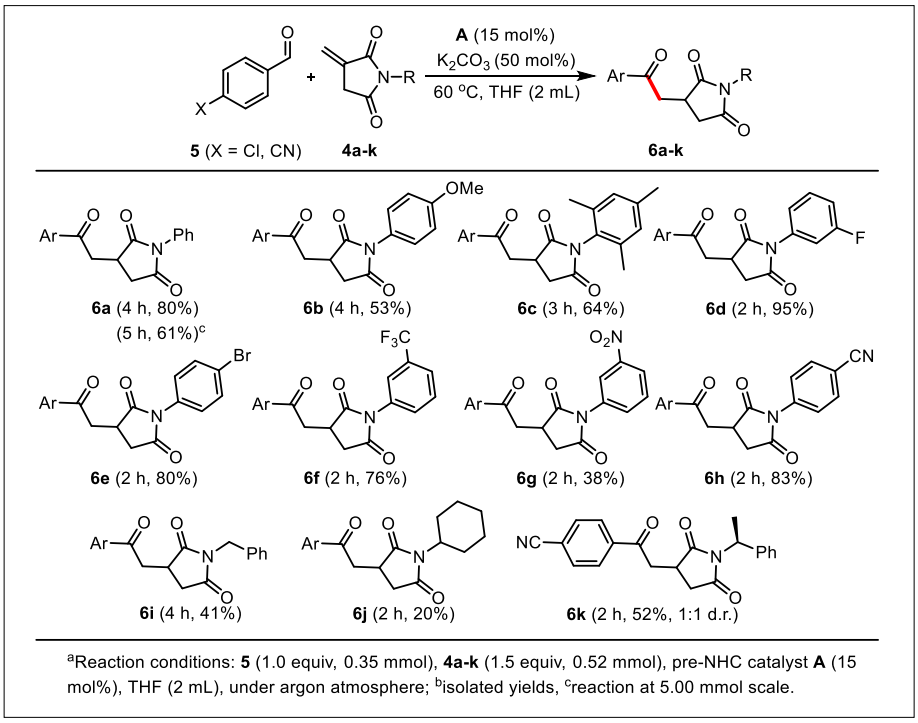
Entry	variation from the standard condition	yield of **6a**/**7** (%)[b]
1	**None**	**80/4**
2	**B** instead of **A**	25/22
3	**C** instead of **A**	<1/19
4	**D** instead of **A**	<1/27
5	**E** instead of **A**	27/34
6	reaction at room temperature	55/3
7	Cs_2CO_3 instead of K_2CO_3	60/20
8	NEt_3 instead of K_2CO_3	50/40
9	DBU instead of K_2CO_3	44/33
10	20 mol% of K_2CO_3, 10 mol% of NHC	67/5
11	1 equiv of K_2CO_3	60/17
12	CH_3CN instead of THF	10/26
13	1,4-dioxane instead of THF	53/32
14	toluene instead of THF	20/15
15	1 equiv of **4a**	65/5

[a]Reaction conditions: **5** (1.0 equiv, 0.35 mmol), **4a** (1.5 equiv, 0.52 mmol), pre-NHC catalyst **A** (15mol%), solvent (2 mL), 4 h, under argon atmosphere; [b]isolated yields.

the best base for this transformation. Also, it was observed that lowering the catalyst loading and equivalent of base substantially decreases the yield of the product (Table 1, entry 10). Furthermore, increasing the equivalents of base significantly lowers the product yield and

facilitates more side product formation (Table 1, entry 11). Solvent effect on this transformation was also studied, wherein other solvents such as acetonitrile, 1,4-dioxane, and toluene were found to be unfavorable for the current scenario (Table 1, entry 12-14). Next, the molar ratio of substrate **5** and **4a** was also examined. Conducting the reaction with reduced equivalents of *N*-phenyl itaconimide showed a reduction in the yield (Table 1, entry 15). The optimized reaction condition (Table 1, entry 1) gives expected Stetter product **6a** up to 80% yield with 4% of **7**.

Scheme 2. Variation in the Itaconimide *N*-Substituents[a,b]



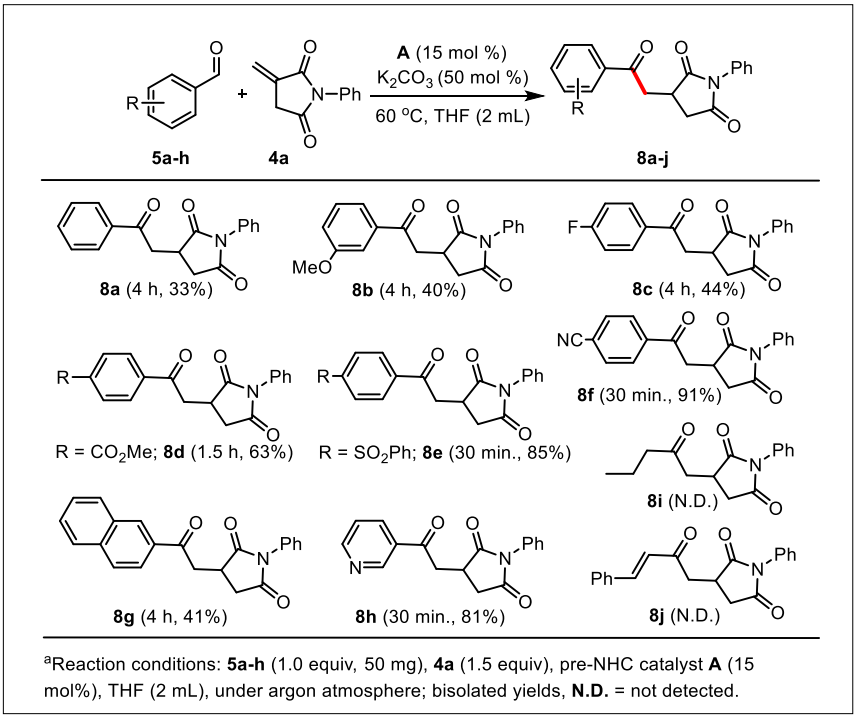
[a]Reaction conditions: **5** (1.0 equiv, 0.35 mmol), **4a-k** (1.5 equiv, 0.52 mmol), pre-NHC catalyst **A** (15 mol%), THF (2 mL), under argon atmosphere; [b]isolated yields, [c]reaction at 5.00 mmol scale.

With the optimized condition in hand, we planned to study the substrate scope of this NHC-catalyzed Stetter reaction. Initially, we screened itaconimides having various *N*-substituents by keeping *p*-chlorobenzaldehyde as the synthetic equivalent of acyl anion. The developed reaction condition worked well for both *N*-aryl, and *N*-alkyl substituted itaconimides. Gratifyingly, *N*-aryl itaconimides with a range of electron-withdrawing and electron-donating groups on the aromatic

ring were well tolerated to furnish the expected Stetter products in 38-95% yields (Scheme 2, **6a-h**). There was no drastic difference in reactivity pattern associated with electron-donating or electron-withdrawing functional groups on the aromatic ring of *N*-arylitaconimide. As mentioned above in the optimization study, the *N*-phenyl itaconimide **4a** provided the expected product in 80% yield. Also, the developed protocol gave a good yield when tested on a higher scale (5.00 mmol). Moreover, *N*-aryl substituted with -OMe, -Me, and halo functional groups (Scheme 2, **6b-e**) gave the corresponding product in good to moderate yields, while electron-withdrawing substituents $-CF_3$, $-NO_2$, -CN gave Stetter product in better yields (Scheme 2, **6f-h**). Moreover, *N*-alkyl itaconimides also worked well leading to the desired products with moderate yields under the developed reaction condition (Scheme 2, **6i-k**). The product **6k** was observed in 1:1 d.r. as the chiral center in **4k** is far away from the reaction center and hence couldn't control enantio- and diastereoselectivity. Furthermore, we observed less than 5% isomerization of itaconimide to the corresponding methyl-substituted maleimides in all above substrates, but the corresponding 3-methyl-aryl-maleimides remained unreactive under the standard reaction condition.

After exploring the reactivity pattern of *N*-substituted itaconimides, we further intended to explore the scope of the reaction using substituted aldehydes by keeping *N*-phenyl itaconimide as the Michael acceptor. Both; electron-withdrawing and electron-donating aldehydes worked well leading to the formation of the desired products (Scheme 3, entry **8a-h**) in moderate to good yields. The unsubstituted aldehyde substrate, benzaldehyde provided the expected product **8a**

Scheme 3. Variation in the Aldehyde Substrate[a,b]



[a]Reaction conditions: **5a-h** (1.0 equiv, 50 mg), **4a** (1.5 equiv), pre-NHC catalyst **A** (15 mol%), THF (2 mL), under argon atmosphere; bisolated yields, **N.D.** = not detected.

with diminished yield. The 4-fluoro and electron-donating substituent 3-OMe gave Stetter products in moderate yields (Scheme 3, **8b**,**c**). Moreover, it was observed that the aldehyde substrates with electron-donating substituents take much longer reaction time for completion as compared to the electron-withdrawing substituents. The developed reaction condition worked well with aromatic aldehydes having electron-withdrawing groups and gave corresponding products smoothly with good yields (Scheme 3, **8d**-**f**). Furthermore, *β*-naphthaldehyde gave **8g** in 41% yield. Interestingly, the protocol was also suitable for heterocyclic aldehyde and gave the desired product **8h** in good yield (Scheme 3). However, the developed condition failed to give expected products with butyraldehyde and cinnamaldehyde (Scheme 3, **8i**,**j**).

The mechanism of reaction is illustrated in Figure 4. The catalytic cycle is initiated by addition of N-heterocyclic carbene to aldehyde generating the nucleophilic Breslow intermediate. This

acyl anion equivalent attack the *N*-itaconimide eventually form 4-aroylsuccinimides and regenerate NHC for further catalytic cycle.

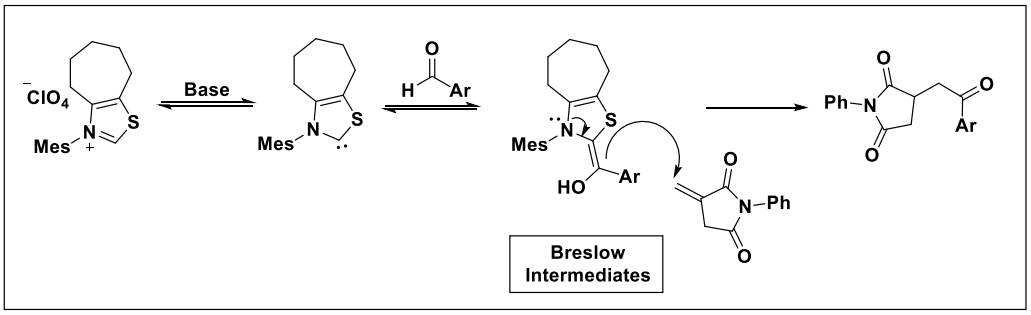


Figure 4. Mechanism of Stetter Reaction with *N*-substituted itaconimide.

1.2.7. Conclusion

In summary, we have developed a convenient and hitherto unknown NHC-organocatalyzed Stetter reaction of aromatic aldehydes with *N*-substituted itaconimides affording valuable new succinimide derivatives in good to excellent yields under an operationally simple reaction condition with broad substrate scope. Studies aimed at utilizing this Stetter reaction to construct small bioactive molecules motifs of pharmaceutical and materials significance are currently underway. Furthermore, our future investigation involves development of an asymmetric variant of this reaction by chiral Brønsted base and will be reported in the due course.

1.2.8. Experimental Procedure

[A] General Experimental Procedur for the Preparation of *N*-Aryl Itaconimide:

A solution of primary aromatic amine **1** (1 g, 1 equiv) and itaconic anhydride **2** (1.1 equiv) in 1,4-dioxane (0.1 M) was stirred at room temperature in a two-neck round bottom flask equipped with a water condenser. As soon as all the amine converts to the corresponding amic acid **3** (monitored by TLC, ~30 min.), ammonium persulfate [$(NH_4)_2S_2O_8$] (2 equiv) and DMSO (2 equiv) were added and the reaction mixture was heated to 100 °C. Heating was continued at the

same temperature for 10 h. The reaction mixture was cooled to room temperature and filtered through a cotton plug. The filtrate was evaporated under *vacuum*. The residue was dissolved in ethyl acetate and washed with dilute HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under *vacuum* to furnish the corresponding known imides **4a-h**[7-9,11,13] in good to excellent yields.

[B] Representative Experimental Procedure for the Preparation of *N*-Phenyl Itaconimides (4a):

A solution of aniline (1 g, 10.7 mmol, 1 equiv) and itaconic anhydride **2** (1.3 g, 11.8 mmol, 1.1 equiv) in 1,4-dioxane (0.1 M) was stirred at room temperature in a two-neck round bottom flask equipped with a water condenser. As soon as all the aniline converts to the corresponding amic acid **3** (monitored by TLC, ~30 min.), ammonium persulfate $[(NH_4)_2S_2O_8]$ (4.9 g, 21.4 mmol, 2 equiv) and DMSO (1.5 mL, 21.4 mmol, 2 equiv) were added and the reaction mixture was heated to 100 °C. Heating was continued at the same temperature for 10 h. The reaction mixture was cooled to room temperature and filtered through a cotton plug. The filtrate was evaporated under *vacuum*. The residue was dissolved in ethyl acetate and washed with dilute HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under *vacuum* to furnish the corresponding known imides **4a** in good to excellent yields. *Rf* : 0.5 (1:4, EtOAc:Pet. Ether), white solid (0.65 g, 55%).

[C] Procedure for The Preparation of *N*-alkyl itaconimides.

N-alkyl itaconimideswere prepared according to reported procedures.[12]

[D] General Experimental Procedure for the Preparation of 6a-k, 8a-h.

A reaction mixture containing K_2CO_3 (50 mol%), NHC-precatalyst **A** (15 mol%), *N*-itaconimide **4a-k** (1.5 equiv) and aromatic aldehyde **5**, **5a-h** (50 mg, 1.0 equiv) in THF (2 mL) under argon atmosphere was stirred at 60 ^oC for 30 min. to 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude reaction mixture was cooled to room temperature, and filtered through a bed of celite. The residue was washed with ethyl acetate (5 mL x 3) and the combined filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a solvent gradient of petroleumether:ethyl acetate to furnish the desired products **6a-k**, **8a-h** in 20-95% yield.

[E] Representative Experimental Procedure for the Preparation of 6a.

A reaction mixture containing K_2CO_3 (50 mol%), NHC-precatalyst **A** (15 mol%), *N*-phenyl itaconimide **4a** (1.5 equiv) and 4-chlorobenzalaldehyde (50 mg, 1.0 equiv) in THF (2 mL) under argon atmosphere was stirred at 60 ^oC for 30 min. to 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude reaction mixture was cooled to room temperature, and filtered through a bed of celite. The residue was washed with ethyl acetate (5 mL x 3) and the combined filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a solvent gradient of petroleum ether:ethyl acetate to furnish the desired products **6a** in 80% yield. Reaction time: 4 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 93 mg, 80%.

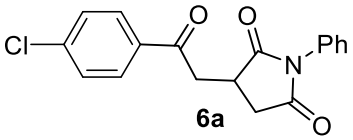
[F] Experimental procedure for large scale preparation of 6a.

A reaction mixture containing K_2CO_3 (104 mg, 50 mol%), NHC-precatalyst **A** (927 mg, 15 mol%), *N*-phenyl itaconimide **4a** (1.1 g, 1.5 equiv) and aromatic aldehyde **5** (700 mg, 1.0 equiv) in THF (25 mL) under argon atmosphere was stirred at 60 ^oC for 5 h. The progress of the

reaction was monitored by TLC. After completion of reaction, the crude reaction mixture was cooled to room temperature, and filtered through a bed of celite. The residue was washed with ethyl acetate (20 mL x 3) and the combined filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a solvent gradient of petroleum ether:ethyl acetate (7:13) to furnish the desired product **6a** in 61% yield (980 mg).

1.2.9. Characterization Data of Compounds:

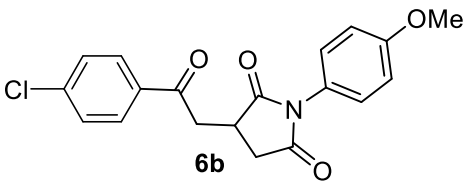
3-(2-(4-chlorophenyl)-2-oxoethyl)-1-phenylpyrrolidine-2,5-dione (6a).



6a

Reaction time: 4 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 93 mg, 80% yield; Mp = 151-153 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.47-7.37 (m, 4H), 7.36-7.32 (m, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 3.57 (dd, *J* = 18.6, 3.4 Hz, 1H), 3.52 (dd, *J* = 18.6, 6.4 Hz, 1H), 3.35-3.25 (m, 1H), 3.09 (dd, *J* = 18.1, 9.3 Hz, 1H), 2.57 (dd, *J* = 18.1, 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.65, 178.62, 175.46, 140.35, 134.17, 132.15, 129.47, 129.19, 129.14, 128.65, 126.60, 39.01, 35.72, 34.71; **ESI-HRMS**: calcd. For $C_{18}H_{14}O_3NCl$ $[M + Na]^+$: 350.0554, found: 350.0556.

3-(2-(4-chlorophenyl)-2-oxoethyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (6b).

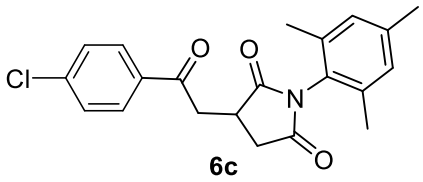


6b

Reaction time: 4 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); white solid; 67 mg, 53% yield; Mp = 170-172 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.76 (s, 3H), 3.60-3.50 (m, 2H), 3.36-3.20 (m, 1H), 3.08 (dd, *J* = 18.1, 9.5 Hz, 1H), 2.54 (dd, *J* = 18.1, 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.68, 178.86, 175.73, 159.57, 140.36, 134.25, 129.47, 129.14, 127.82,

124.81, 114.55, 55.48, 39.07, 35.71, 34.71; **ESI-HRMS** (*m/z*)**:** calcd. For $C_{19}H_{16}ClNO_4$ [M + Na]$^+$: 380.0660, found: 380.0656.

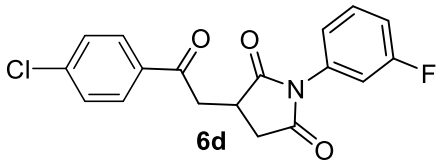
3-(2-(4-chlorophenyl)-2-oxoethyl)-1-mesitylpyrrolidine-2,5-dione (6c).



6c

Reaction time: 3 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 84 mg, 64% yield; Mp = 126-128 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.91 (s, 1H), 6.89 (s, 1H), 3.58 (dd, *J* = 18.3, 3.4 Hz, 1H), 3.49 (dd, *J* = 18.7, 6.9 Hz, 1H), 3.37-3.30 (m, 1H), 3.09 (dd, *J* = 18.0, 9.1 Hz, 1H), 2.68 (dd, *J* = 17.9, 6.1 Hz, 1H), 2.23 (s, 3H), 2.17 (s, 3H), 2.01 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.32, 178.32, 175.31, 140.29, 139.34, 136.08, 135.09, 134.26, 129.49, 129.47, 129.22, 129.11, 127.57, 38.41, 36.22, 34.76, 21.07, 17.76; **ESI HRMS** (*m/z*): calcd. For $C_{21}H_{20}ClNO_3$ [M +H]$^+$: 370.1204, found: 370.1200.

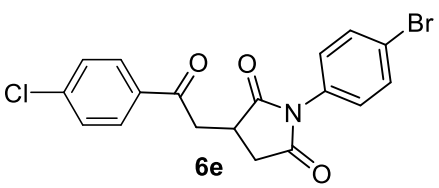
3-(2-(4-chlorophenyl)-2-oxoethyl)-1-(3-fluorophenyl)pyrrolidine-2,5-dione (6d).



6d

Reaction time: 2 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 116 mg, 95% yield; Mp = 123-125 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.45-7.33 (m, 3H), 7.15-6.98 (m, 3H), 3.55 (d, *J* = 4.4 Hz, 2H), 3.22-3.33 (m, 1H), 3.08 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.57 (dd, *J* = 18.1, 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.65, 178.24, 175.03, 162.65 (d, *J* = 247.4 Hz), 140.45, 134.09, 133.45 (d, *J* = 10.0 Hz), 130.29 (d, *J* = 8.5 Hz), 129.48, 129.16, 122.29 (d, *J* = 3.1 Hz), 115.67 (d, *J* = 20.8 Hz), 114.22 (d, *J* = 23.9 Hz), 38.91, 35.67, 34.59; **ESI HRMS** (*m/z*): calcd. for $C_{18}H_{13}ClFNO_3$ [M +Na]$^+$: 368.0460, found: 368.0454.

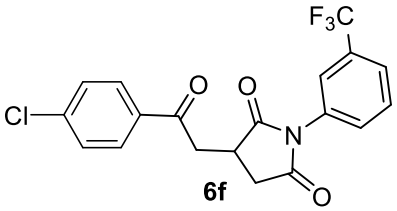
1-(4-bromophenyl)-3-(2-(4-chlorophenyl)-2-oxoethyl)pyrrolidine-2,5-dione (6e).



6e

Reaction time: 2 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 116 mg, 80% yield; Mp = 168-170 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 3.56 (d, *J* = 4.9 Hz, 2H), 3.33-3.22 (m, 1H), 3.07 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.57 (dd, *J* = 18.6, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.67, 178.29, 175.09, 140.47, 134.09, 132.36, 131.18, 129.47, 129.17, 128.15, 122.49, 38.89, 35.69, 34.60; **ESI-HRMS**: calcd. For $C_{18}H_{13}BrClNO_3$ $[M+H]^+$: 405.9840, found: 405.9833.

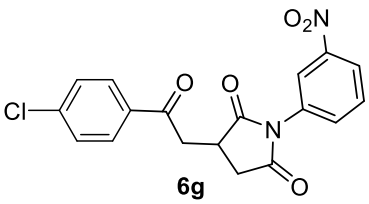
3-(2-(4-chlorophenyl)-2-oxoethyl)-1-(3-(trifluoromethyl)phenyl)pyrrolidine-2,5-dione (6f).



6f

Reaction time: 2 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 106 mg, 76% yield; Mp = 132-134 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7 Hz, 2H), 7.63-7.5 (m, 2H), 7.57-7.52 (m, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 3.57 (d, *J* = 5.0 Hz, 2H), 3.35-3.27 (m, 1H), 3.10 (dd, *J* = 18.3, 9.9 Hz, 1H), 2.60 (dd, *J* = 18.3, 5.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.68, 178.21, 174.96, 140.55, 134.11, 132.79, 131.71 (q, *J* = 32.4 Hz), 129.98, 129.75, 129.52, 129.22, 125.37 (d, *J* = 2.3 Hz), 124.56 (q, *J* = 272.7 Hz), 123.72 (d, *J* = 3.8 Hz), 38.91, 35.77, 34.63; **ESI HRMS** (*m/z*): calcd. For $C_{19}H_{13}ClF_3NO_3$ $[M+H]^+$: 396.0609, found: 396.0606.

3-(2-(4-chlorophenyl)-2-oxoethyl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (6g).

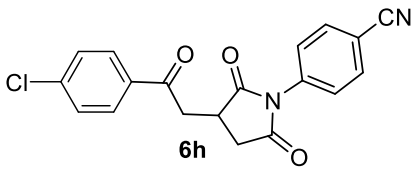


6g

Reaction time: 2 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); white solid; 50 mg, 38% yield; Mp = 152-154 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (t, *J* = 2.0 Hz, 1H), 8.23-8.18 (m, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.75-7.70 (m, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 3.64 (dd, *J* = 18.8, 6.0

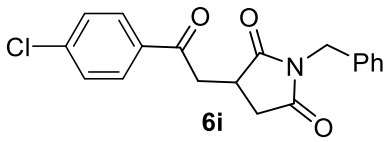
Hz, 1H), 3.57 (dd, *J* = 18.8, 3.7 Hz, 1H), 3.36-3.27 (m, 1H), 3.11 (dd, *J* = 18.3, 9.6 Hz, 1H), 2.63 (dd, *J* = 18.3, 5.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.71, 178.00, 174.73, 148.51, 140.61, 133.97, 133.28, 132.56, 129.94, 129.52, 129.21, 123.25, 121.94, 38.83, 35.72, 34.52; **ESI HRMS** (*m/z*): calcd. For $C_{18}H_{13}ClN_2O_5$ $[M+Na]^+$: 395.0405, found: 395.0399.

4-(3-(2-(4-chlorophenyl)-2-oxoethyl)-2,5-dioxopyrrolidin-1-yl)benzonitrile (6h).



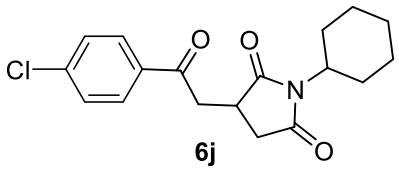
Reaction time: 2 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); white solid; 104 mg, 83% yield; Mp = 163-165 ^oC; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 3.62 (dd, *J* = 19.1, 5.9 Hz, 1H), 3.55 (dd, *J* = 18.6, 3.4 Hz, 1H), 3.35-3.23 (m, 1H), 3.08 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.60 (dd, *J* = 18.1, 5.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.71, 177.92, 174.64, 140.59, 136.21, 133.96, 132.94, 129.48, 129.20, 127.10, 118.12, 112.10, 38.79, 35.68, 34.49; **ESI-HRMS**: calcd. For $C_{19}H_{13}ClN_2O_3$ $[M+H]^+$: 353.0687, found: 353.0682.

1-benzyl-3-(2-(4-chlorophenyl)-2-oxoethyl)pyrrolidine-2,5-dione (6i).



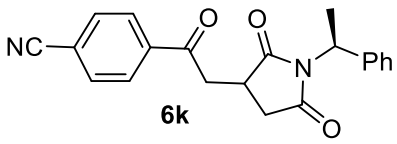
Reaction time: 4 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); white solid; 50 mg, 41% yield; Mp = 155-157 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 2H), 7.29-7.20 (m, 3H), 4.67 (d, *J* = 14.2 Hz, 1H), 4.62 (d, *J* = 14.2 Hz, 1H), 3.53 (dd, *J* = 18.1, 3.0 Hz, 1H), 3.29 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.23-3.14 (m, 1H), 2.96 (dd, *J* = 18.4, 9.4 Hz, 1H), 2.38 (dd, *J* = 18.1, 5.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.48, 179.12, 175.95, 140.29, 135.74, 134.21, 129.43, 129.12, 128.72, 128.63, 127.89, 42.59, 38.95, 35.74, 34.76; **ESI HRMS** (*m/z*): calcd. For $C_{19}H_{16}ClNO_3$ $[M+Na]^+$: 364.0711, found: 364.0711.

3-(2-(4-chlorophenyl)-2-oxoethyl)-1-cyclohexylpyrrolidine-2,5-dione (6j).



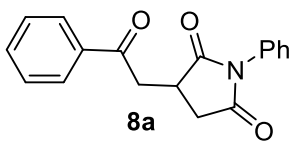
Reaction time: 2 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); white solid; 24 mg, 20% yield; Mp = 122-124 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 4.02-3.86 (m, 1H), 3.50 (dd, *J* = 18.1, 2.9 Hz, 1H), 3.32 (dd, *J* = 18.1, 7.3 Hz, 1H), 3.14-3.02 (m, 1H), 2.87 (dd, *J* = 18.1, 9.3 Hz, 1H), 3.32 (dd, *J* = 18.1, 5.4 Hz, 1H), 2.17-2.03 (m, 2H), 1.81-1.72 (m, 2H), 1.63-1.55 (m, 3H), 1.32-1.09 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.65, 179.61, 176.49, 140.21, 134.32, 129.43, 129.09, 51.91, 39.08, 35.29, 34.58, 28.76, 28.62, 25.86, 25.07; **ESI HRMS** (*m/z*): calcd. For $C_{18}H_{20}ClNO_3$ $[M+Na]^+$: 356.1024, found: 356.1019.

4-(2-(2,5-dioxo-1-((S)-1-phenylethyl)pyrrolidin-3-yl)acetyl)benzonitrile (6k).



Reaction time: 2 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); white solid; 69 mg, 52% yield; Mp = 155-157 ^{o}C.^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 7.94 (t, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 2 H), 7.30-7.24 (m, 2H), 7.21 (dd, *J* = 7.2, 1.5 Hz, 1H), 5.39 (q, *J* = 8.4 Hz, 1H), 3.52 (dd, *J* = 18.7, 3.4 Hz, 1H), 3.35 (dd, 18.7, 7.2 Hz, 0.5H), 3.31 (dd, *J* = 18.7, 7.6 Hz, 0.5H), 3.17-3.03 (m, 1H), 2.94-2.85 (m, 1H), 2.39-2.30 (m, 1H), 7.78 (d, *J* = 7.6 Hz, 1.5H), 1.77 (d, *J* = 7.2 Hz, 1.5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.54, 178.95, 178.87, 175.85, 175.78, 139.51, 139.43, 138.77, 132.62, 128.45, 128.39, 127.74, 127.50, 117.67, 116.99, 116.98, 50.50, 50.37, 39.26, 39.15, 35.35, 35.32, 34.51, 34.42, 16.48, 16.43; **ESI-HRMS** (*m/z*): calcd. For $C_{21}H_{18}N_2O_3$ $[M+H]^+$: 347.1390, found: 347.1404.

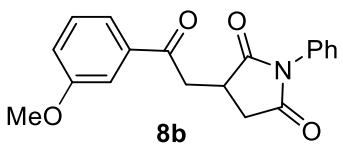
3-(2-oxo-2-phenylethyl)-1-phenylpyrrolidine-2,5-dione (8a).



Reaction time: 4 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); oil; 46 mg, 33% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.82, 2H), 7.54 (t, *J* =

7.3 Hz, 1H), 7.46-7.38 (m, 4H), 7.34 (d, *J* = 6.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 3.63 (dd, *J* = 18.6, 3.9 Hz, 1H), 3.55 (dd, *J* = 18.6, 6.4 Hz, 1H), 3.36-3.26 (m, 1H), 3.09 (dd, *J* = 18.1, 9.3 Hz, 1H), 2.57 (dd, *J* = 18.1, 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*196.82, 178.76, 175.59, 135.89, 133.81, 132.23, 129.18, 128.79, 128.60, 128.07, 126.64, 39.08, 35.81, 34.80; **ESI-HRMS**: calcd. For $C_{18}H_{15}NO_3$ $[M+H]^+$: 294.1125, found: 294.1120.

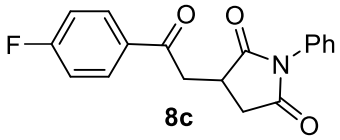
3-(2-(3-methoxyphenyl)-2-oxoethyl)-1-phenylpyrrolidine-2,5-dione (8b).



8b

Reaction time: 4 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); oil; 47 mg, 40% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.47 (d, *J* = 7.3 Hz, 1H), 7.46-7.39 (m, 3H), 7.37-7.27 (m, 4H), 7.08 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.79 (s, 3H), 3.62 (dd, *J* = 18.6, 3.4 Hz, 1H), 3.54 (dd, *J* = 18.6, 6.4 Hz, 1H), 3.35-3.26 (m, 1H), 3.09 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.57 (dd, *J* = 18.1, 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 196.70, 178.75, 175.59, 159.92, 137.22, 132.22, 129.78, 129.18, 128.61, 126.63, 120.72, 120.41, 112.13, 55.48, 39.18, 35.83, 34.77; **ESI HRMS** (*m/z*): calcd. For $C_{19}H_{17}NO_4$ $[M+H]^+$: 324.1230, found: 324.1228.

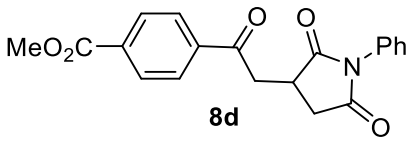
3-(2-(4-fluorophenyl)-2-oxoethyl)-1-phenylpyrrolidine-2,5-dione (8c).



8c

Reaction time: 4 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 55 mg, 44% yield; Mp = 126-128 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.93 (d, *J* = 5.4 Hz, 1H), 7.91 (d, *J* = 5.4 Hz, 1H), 7.47-7.38 (m, 2H), 7.34 (d, *J* = 6.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 8.3 Hz, 2H), 3.64-3.46 (m, 2H), 3.36-3.25 (m, 1H), 3.09 (dd, *J* = 18.1, 9.3 Hz, 1H), 2.57 (dd, *J* = 18.6, 5.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 195.22, 178.67, 175.50, 166.11 (d, *J* = 255.9 Hz), 132.36 (d, *J* = 2.3 Hz), 132.19, 130.78 (d, *J* = 9.2 Hz), 129.18, 128.63, 126.62, 115.97 (d, *J* = 21.6 Hz), 38.96, 35.78, 34.75; **ESI-HRMS** (*m/z*)**:** calcd. For $C_{18}H_{14}FNO_3$$[M+H]^+$: 312.1030, found: 312.1028.

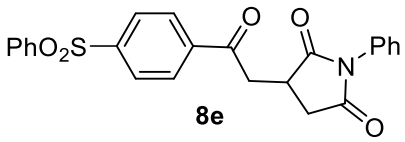
Methyl 4-(2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)acetyl)benzoate (8d).



8d

Reaction time: 1.5 h; R*f*: 0.5 (2:3 EtOAc:pet. ether); White Solid; 67 mg, 63% yield; Mp = 155-157 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.8 Hz, 2H), 7.95 (d, *J* = 7.8 Hz, 2H), 7.47-4.38 (m, 2H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 3.89 (s, 3H), 3.70-3.53 (m, 2H), 3.37-3.27 (m, 1H), 3.11 (dd, *J* = 18.1, 9.3 Hz, 1H), 2.58 (dd, *J* = 18.1, 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.43, 178.54, 175.40, 165.99, 138.93, 134.52, 132.15, 129.98, 129.20, 128.66, 128.01, 126.60, 52.54, 39.40, 35.72, 34.70; **ESI-HRMS** (*m/z*)**:** calcd. For $C_{20}H_{17}NO_5$ $[M+H]^+$: 52.1179, found: 352.1177.

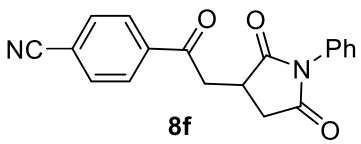
3-(2-oxo-2-(4-(phenylsulfonyl)phenyl)ethyl)-1-phenylpyrrolidine-2,5-dione (8e).



8e

Reaction time: 30 min.; R*f*: 0.5 (3:2 EtOAc:pet. ether); white solid; 75 mg, 85% yield; Mp = 179-181 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (apparent s, 4H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.58-7.51 (m, 1H), 7.50-7.37 (m, 4H), 7.37-7.30 (m, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 3.64-3.48 (m, 2H), 3.36-3.25 (m, 1H), 3.08 (dd, *J* = 18.1, 9.8 Hz, 1H), 2.54 (dd, *J* = 18.1, 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.82, 178.32, 175.24, 146.10, 140.55, 139.07, 133.76, 132.06, 129.51, 129.20, 128.89, 128.69, 128.13, 127.86, 126.56, 39.38, 35.64, 34.60; **ESI HRMS** (*m/z*): calcd. For $C_{24}H_{19}NO_5S$ $[M+H]^+$: 434.1057, found: 434.1051.

4-(2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)acetyl)benzonitrile (8f).

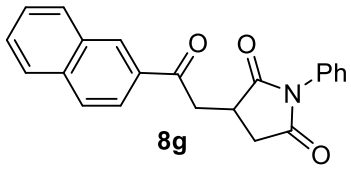


8f

Reaction time: 30 min.; R*f*: 0.5 (1:1 EtOAc:pet. ether); white solid; 110 mg, 91% yield; Mp = 187-189 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.47-7.39 (m, 2H), 7.39-7.32 (m, 1H), 7.28 (d, *J* = 7.3 Hz, 2H), 3.66-3.51 (m, 2H), 3.38-3.28 (m, 1H),

3.11 (dd, *J* = 18.6, 9.8 Hz, 1H), 2.57 (dd, *J* = 18.1, 5.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.70, 178.32, 175.22, 138.65, 132.66, 132.06, 129.21, 128.71, 128.49, 126.55, 117.65, 117.08, 39.28, 35.61, 34.59; **ESI HRMS** (*m/z*): calcd. For $C_{19}H_{14}N_2O_3$ $[M+H]^+$: 319.1077, found: 319.1076.

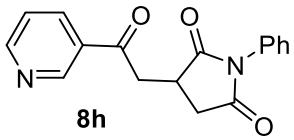
3-(2-(naphthalen-2-yl)-2-oxoethyl)-1-phenylpyrrolidine-2,5-dione (8g).



8g

Reaction time: 4 h; R*f*: 0.5 (7:13 EtOAc:pet. ether); white solid; 45 mg, 41% yield; Mp = 106-108 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.95 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.37-7.30 (m, 3H), 3.77 (dd, *J* = 18.3, 3.4 Hz, 1H), 3.68 (dd, *J* = 18.3, 6.9 Hz, 1H), 3.41-3.34 (m, 1H), 3.13 (dd, *J* = 18.3, 9.9 Hz, 1H), 2.63 (dd, *J* = 18.3, 5.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.76, 178.82, 175.60, 135.85, 133.26, 132.41, 132.26, 130.05, 129.61, 129.19, 128.87, 128.73, 128.61, 127.85, 127.04, 126.66, 123.47, 39.21, 35.94, 34.87; **ESI HRMS** (*m/z*): calcd. For $C_{22}H_{17}NO_3$ $[M+H]^+$: 344.1281, found: 344.1278.

3-(2-oxo-2-(pyridin-3-yl)ethyl)-1-phenylpyrrolidine-2,5-dione (8h).



8h

Reaction time: 30 min.; R*f*: 0.5 (EtOAc); oil; 50 mg, 81% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.74 (d, *J* = 4.3 Hz, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 7.49-7.25 (m, 6H), 3.67-3.50 (m, 2H), 3.41-3.26 (m, 1H), 3.09 (dd, *J* = 18.3, 9.8 Hz, 1H), 2.57 (dd, *J* = 18.3, 5.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.87, 178.40, 175.30, 154.11, 149.51, 135.35, 132.10, 131.22, 129.18, 128.65, 126.56, 123.78, 39.18, 35.53, 34.62; **ESI HRMS** (*m/z*): calcd. For $C_{17}H_{14}N_2O_3$ $[M+H]^+$: 295.1077, found: 295.1076.

1.2.10. References

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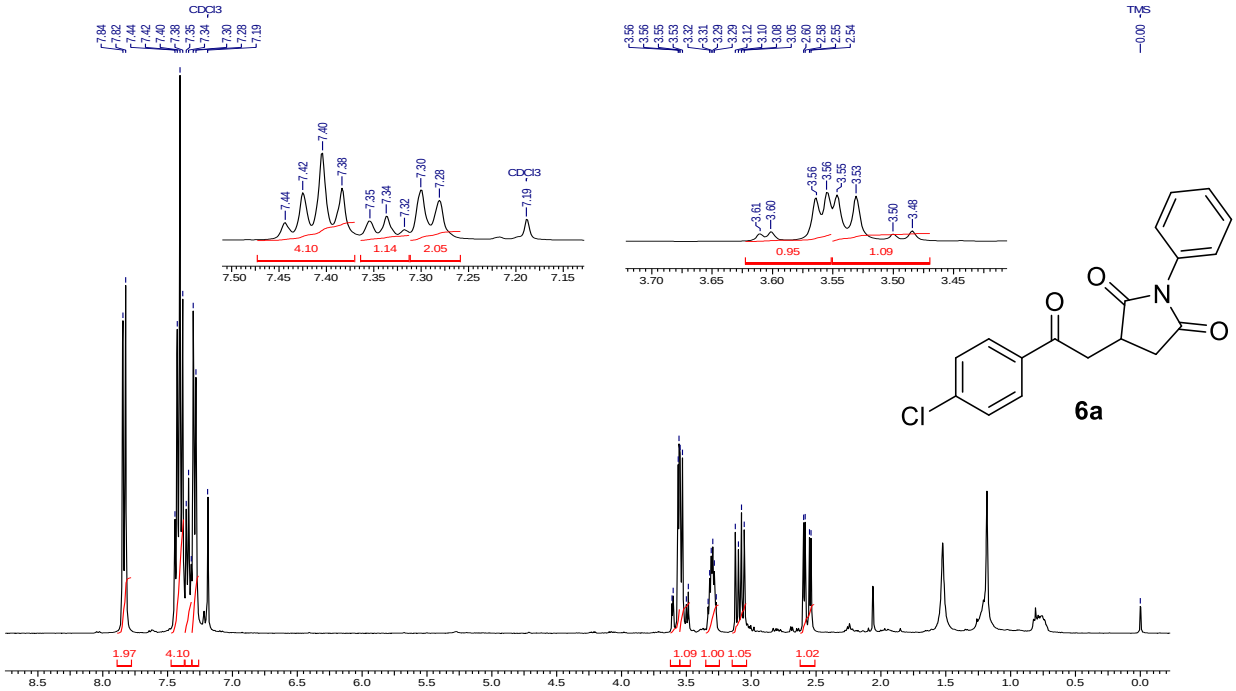
1.2.11. Spectra

^{1}H NMR Spectra



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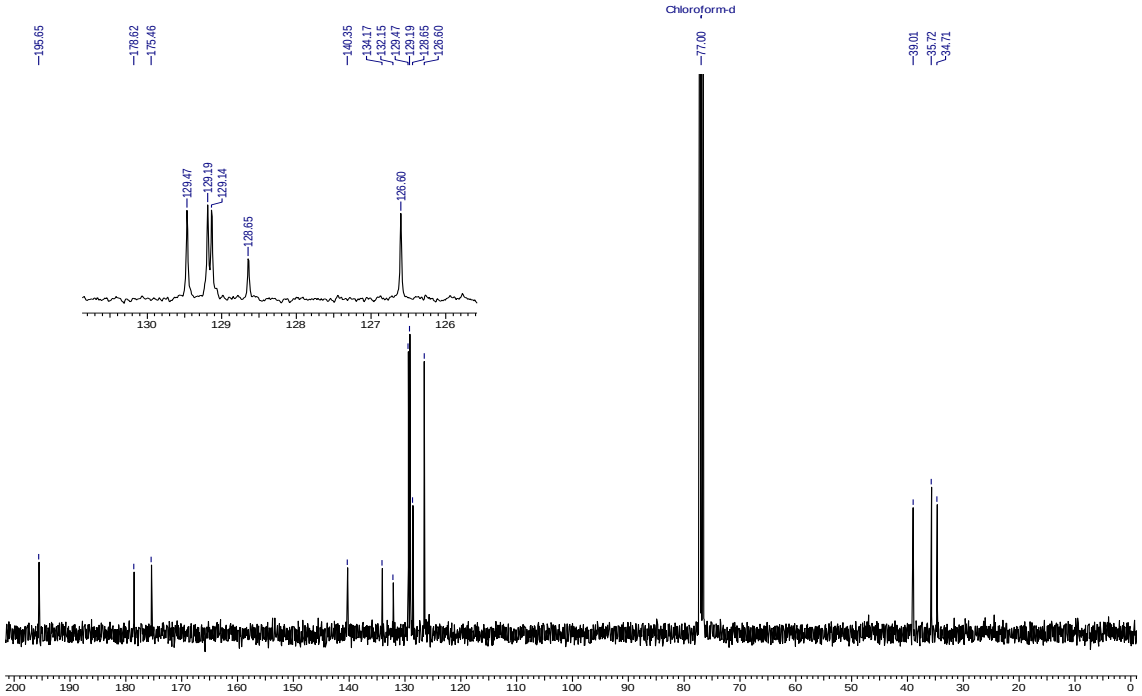

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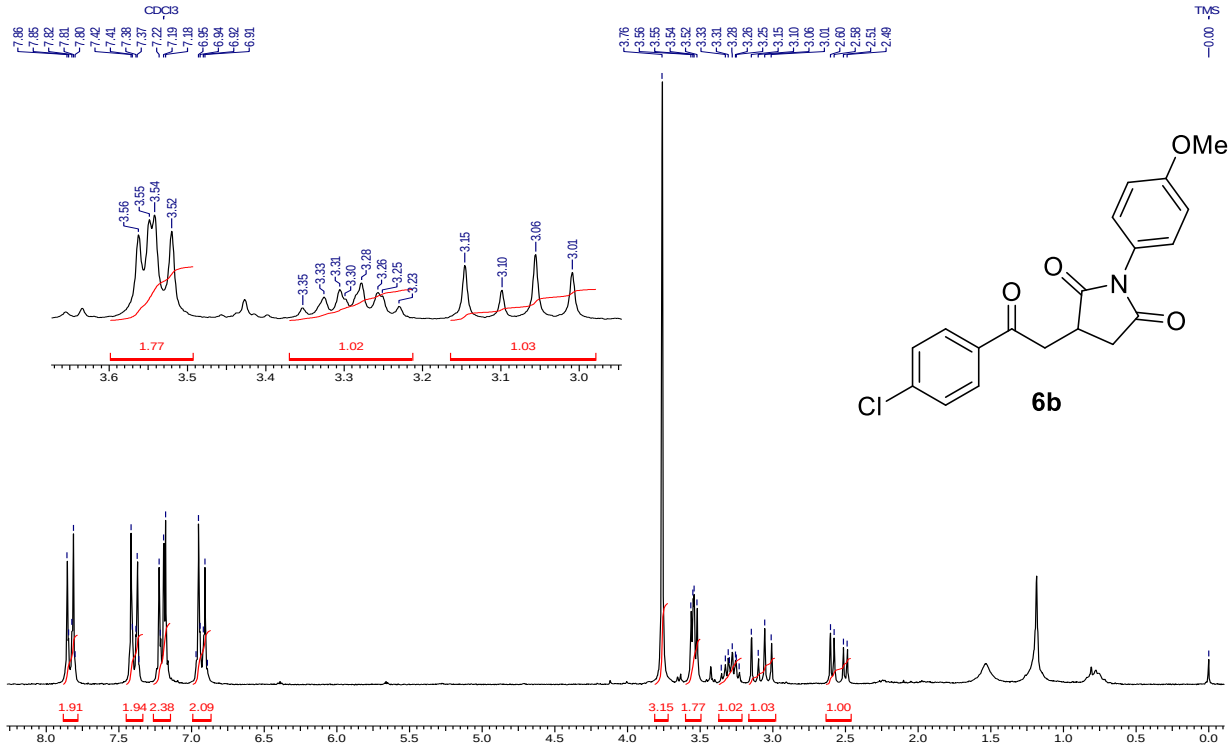

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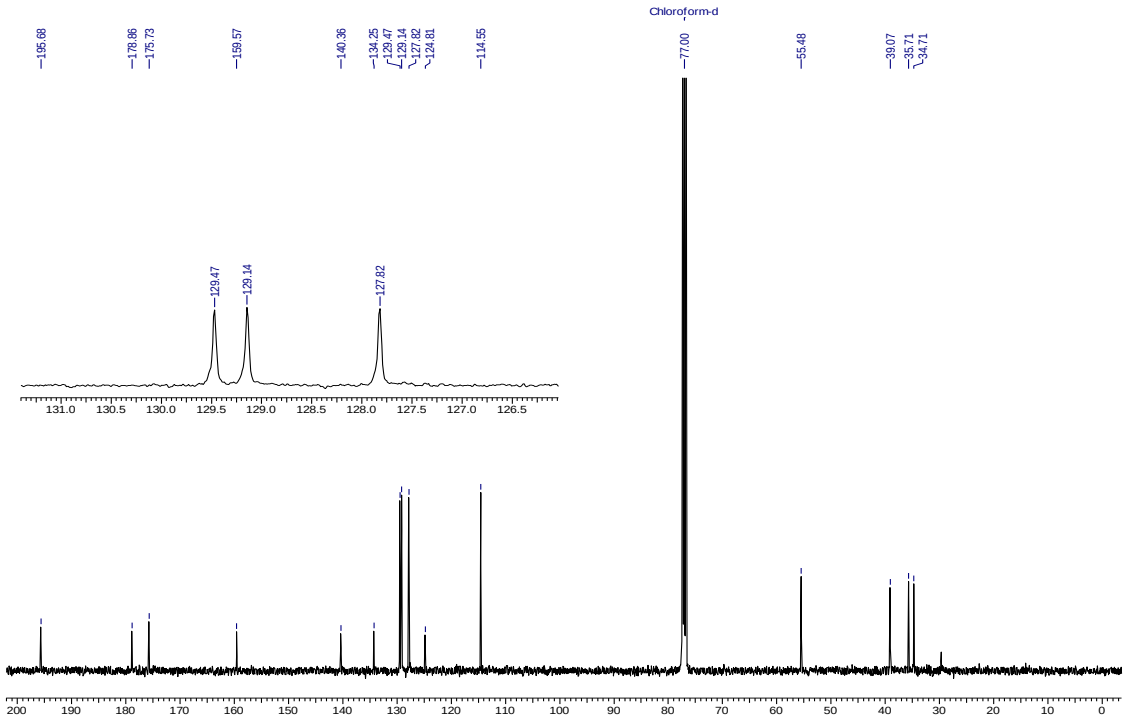

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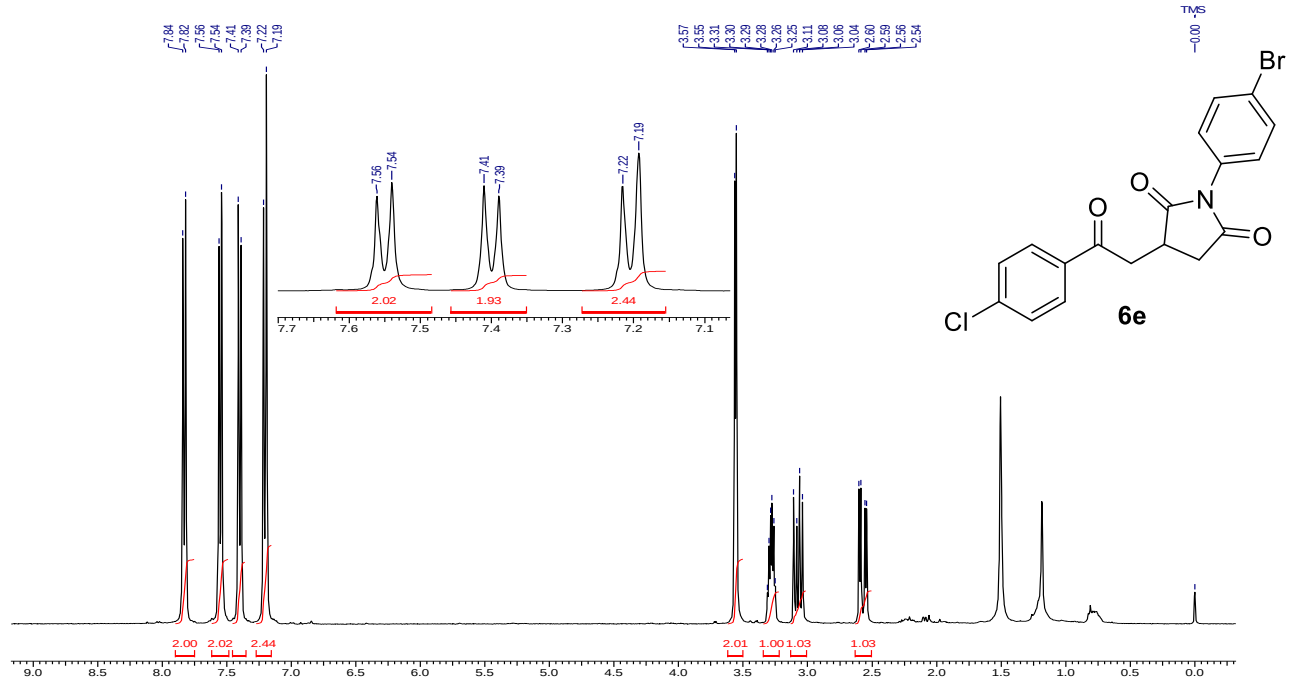

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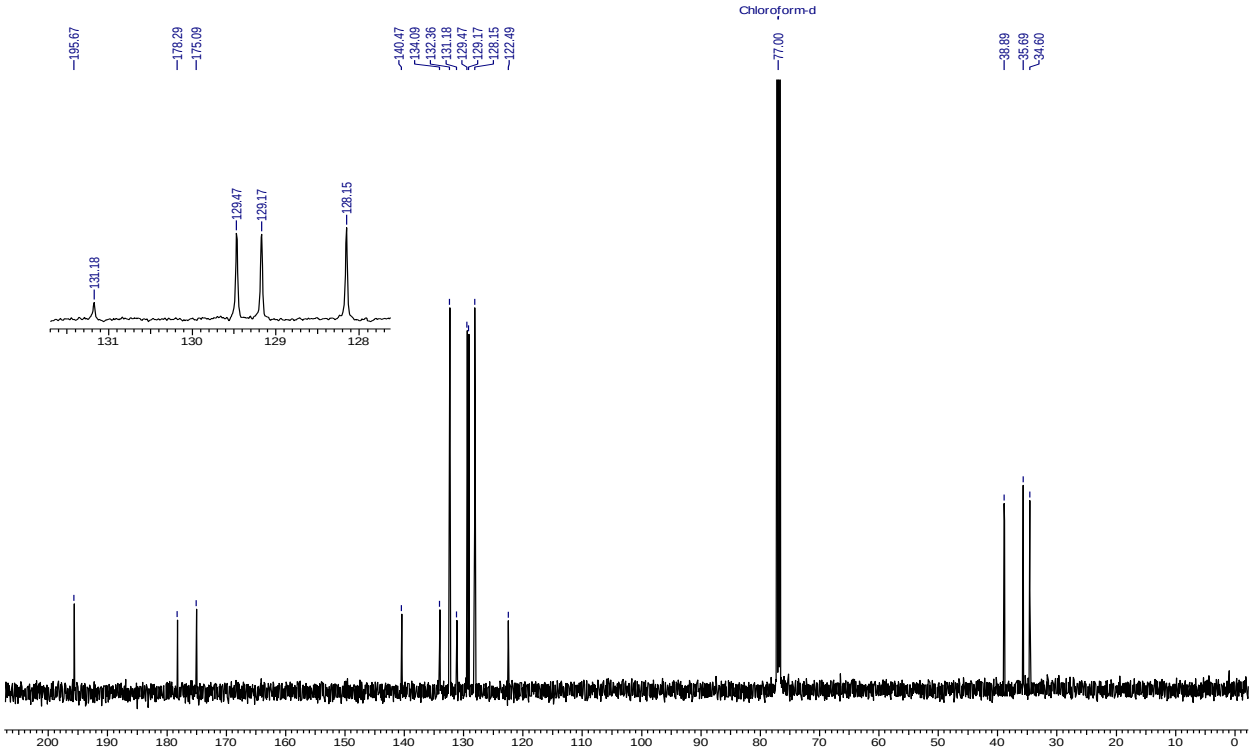

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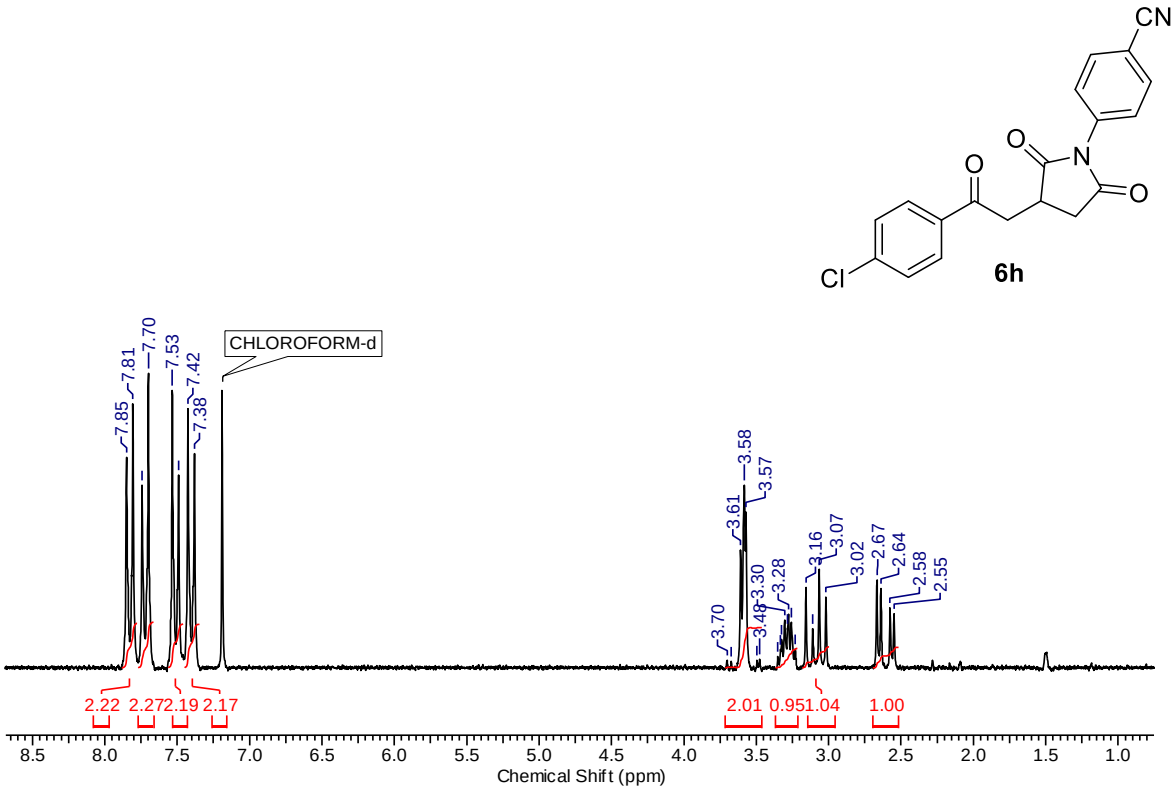

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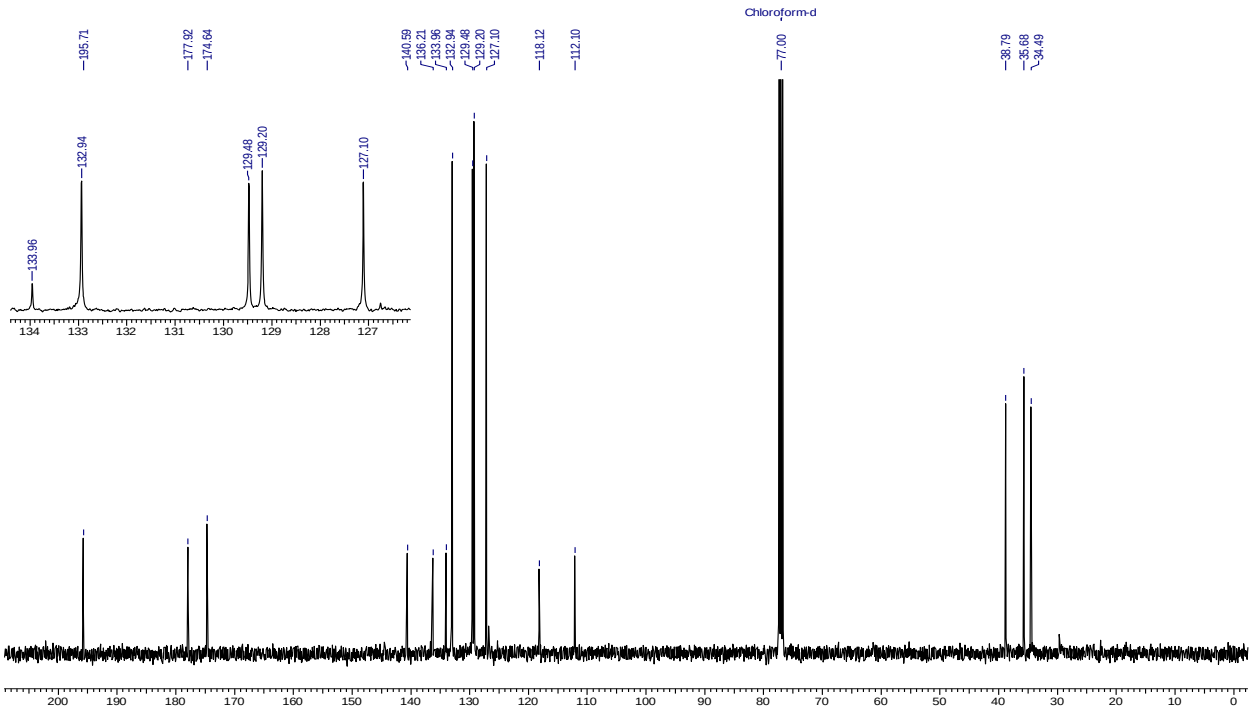

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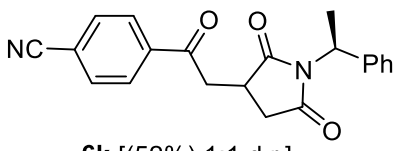
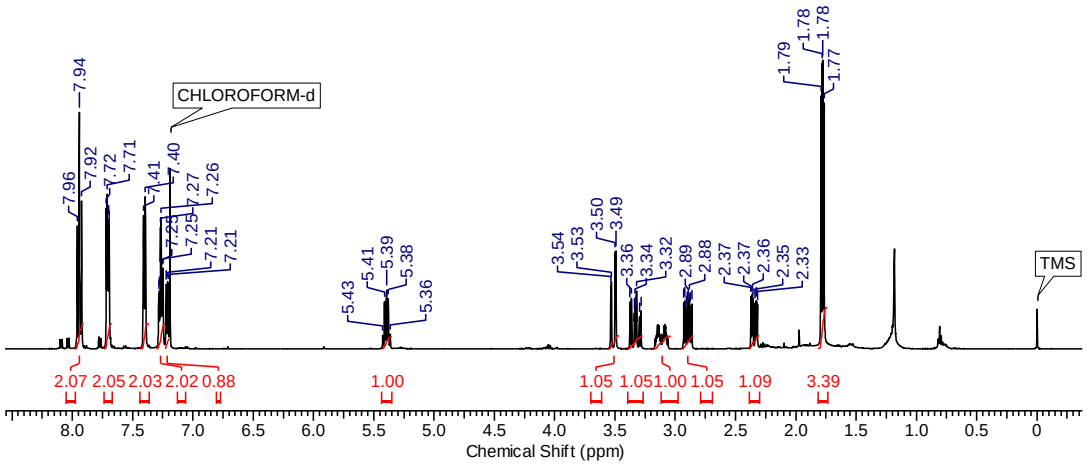


6k [(52%) 1:1 d.r.]



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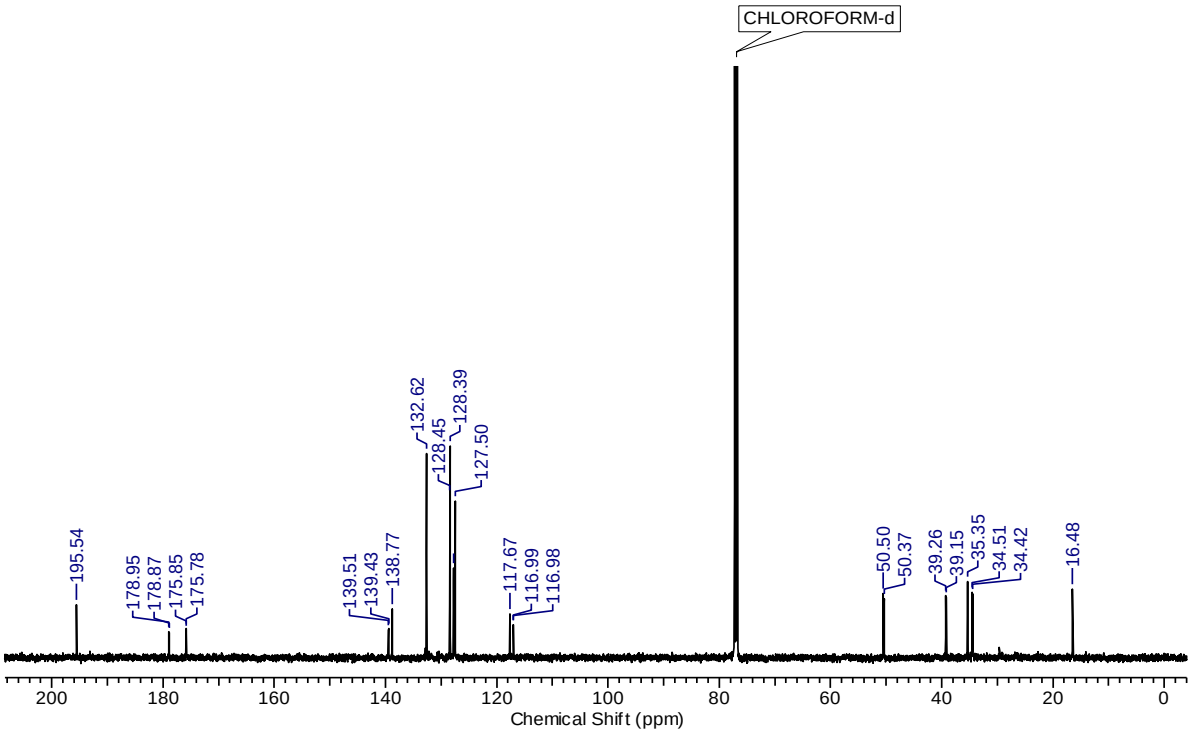

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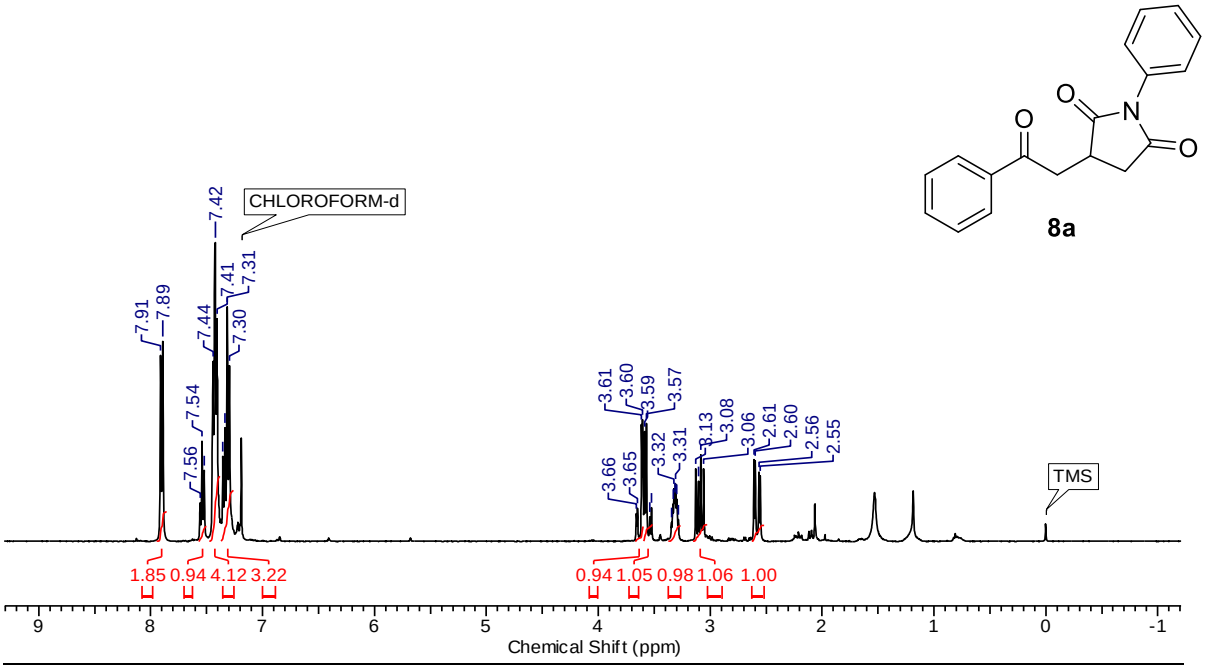

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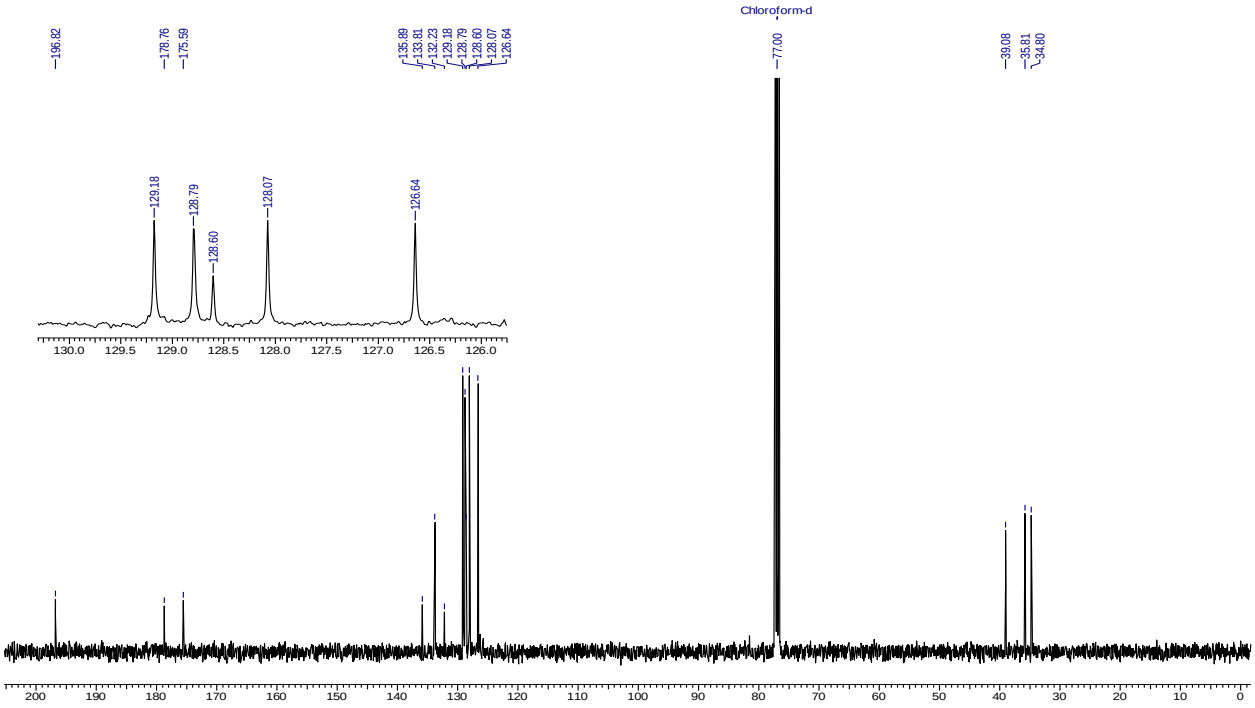

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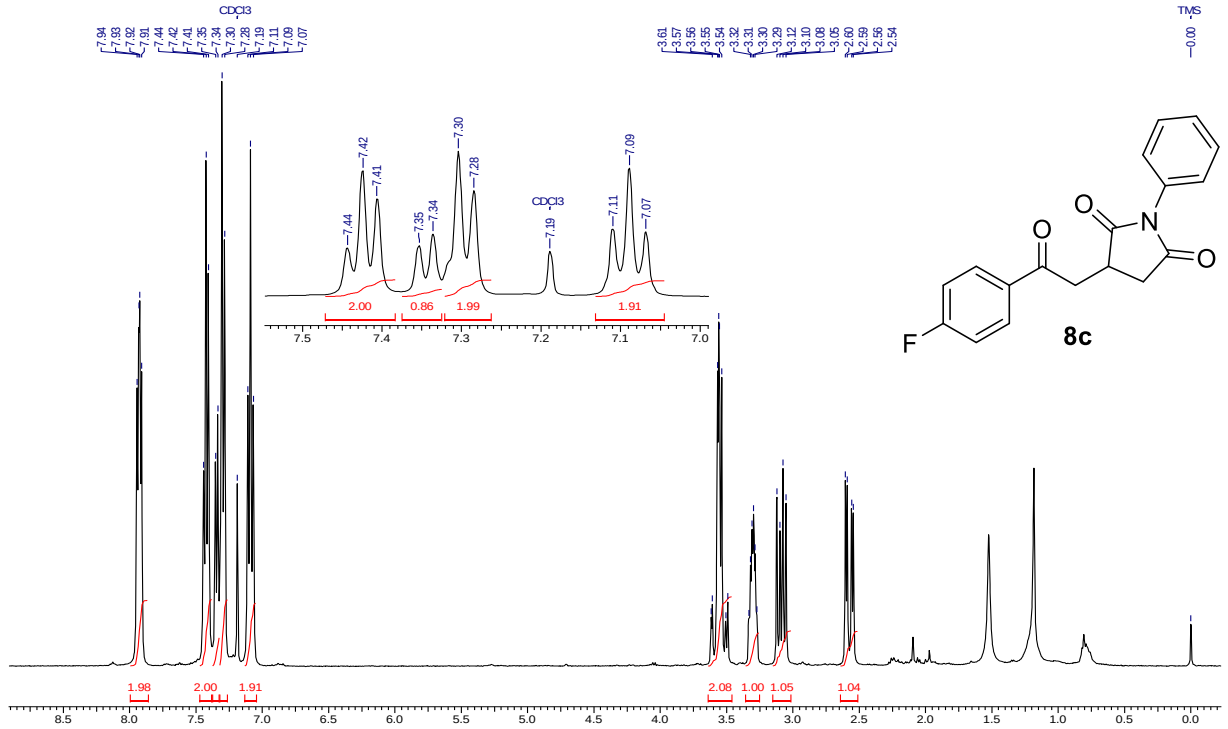

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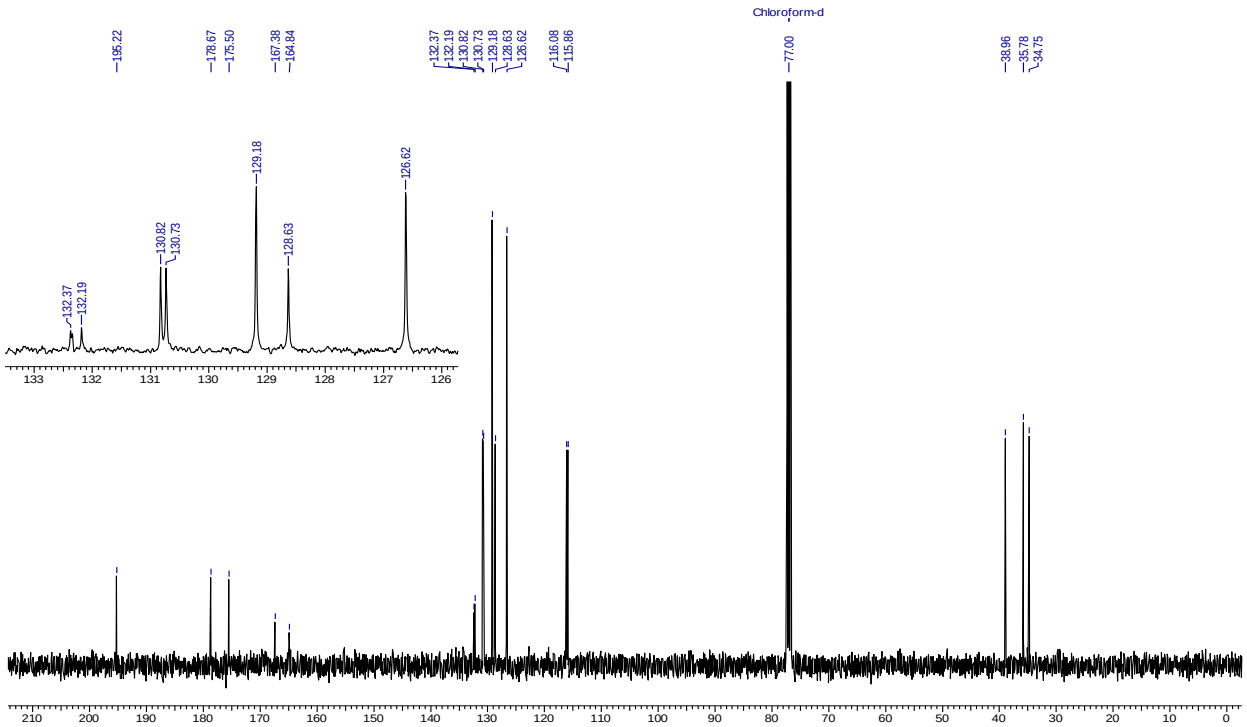

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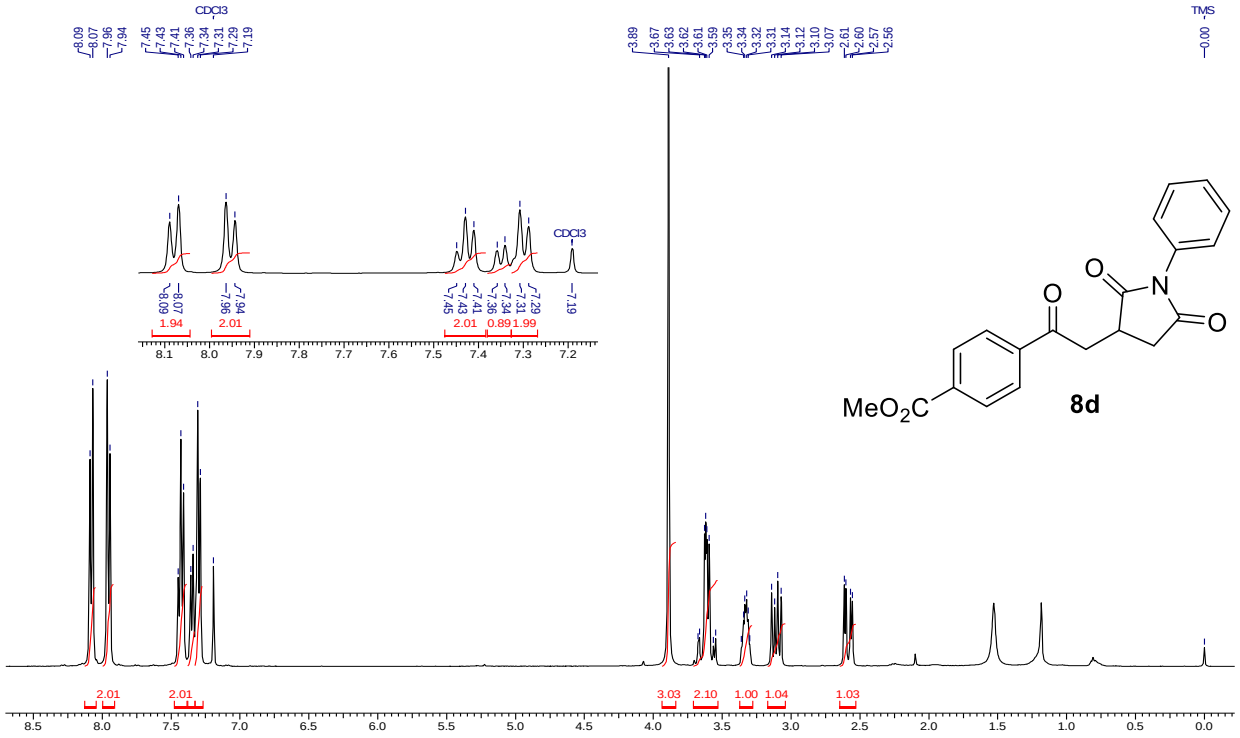
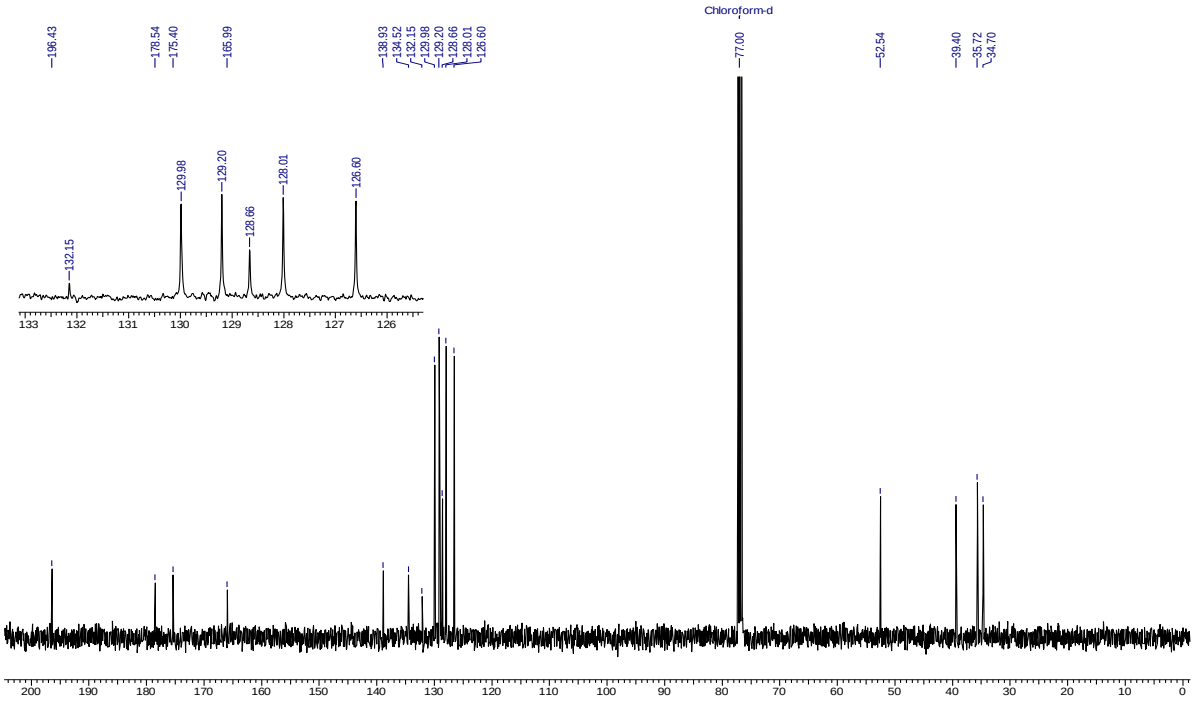
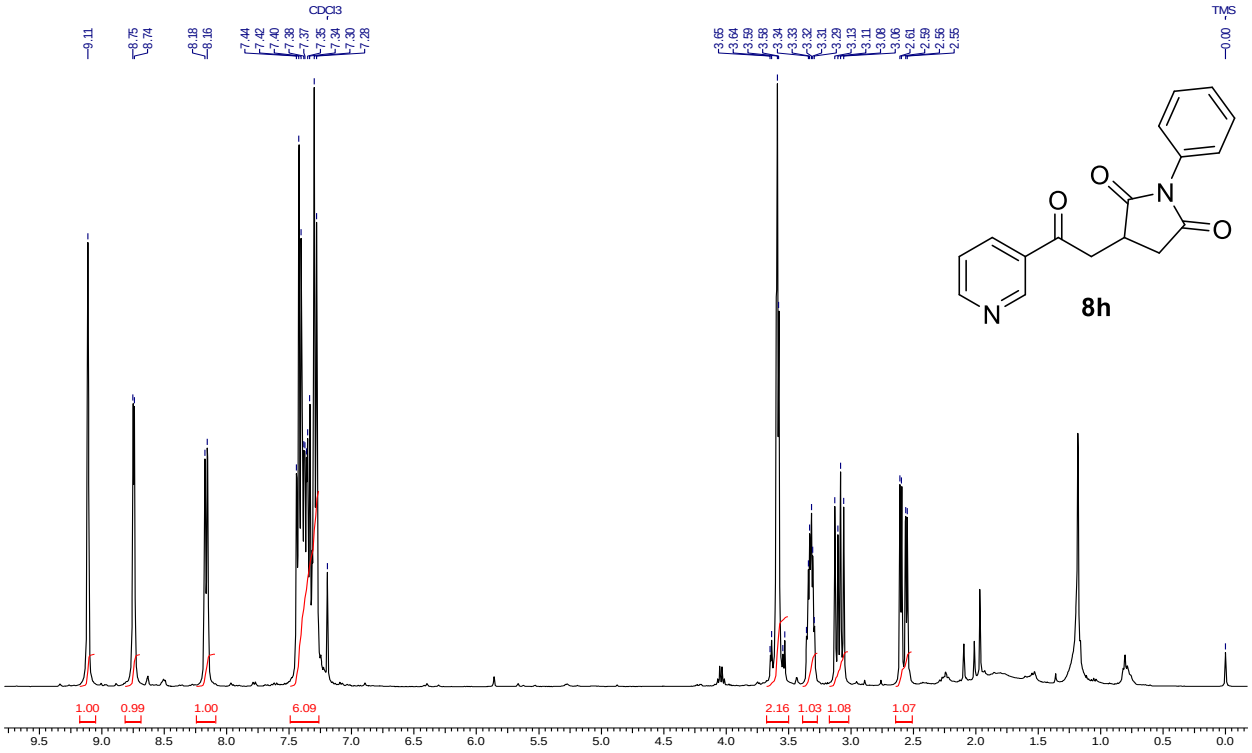


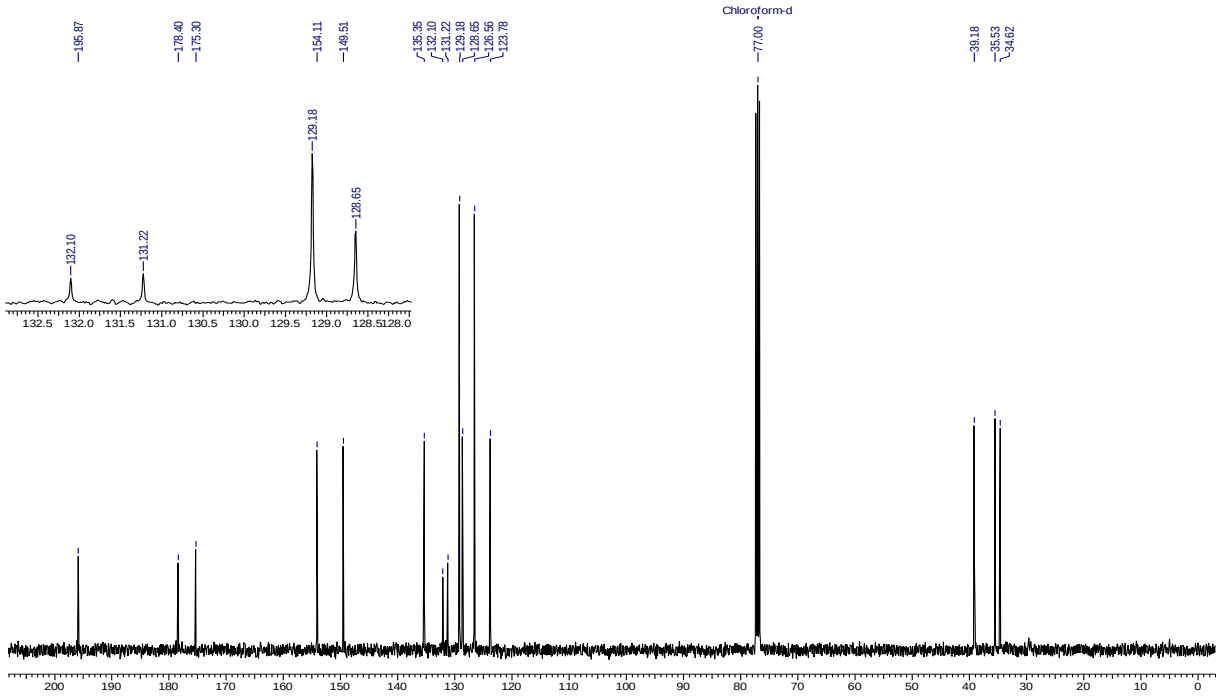
^{13}C NMR Spectra



^{1}H NMR Spectra



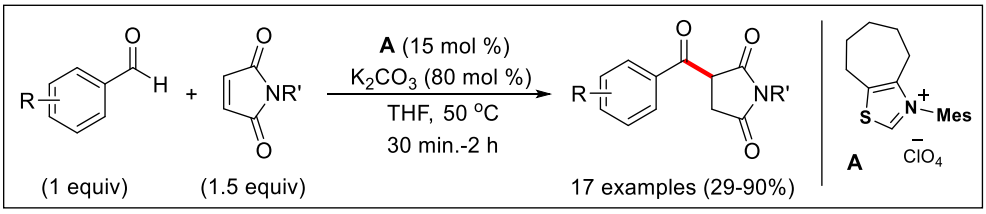
^{13}C NMR Spectra



Section 3: Isa–NHC–Catalyzed Intermolecular Stetter Reaction of Aromatic Aldehydes with Maleimides: An Efficient Access to 3–Aroylsuccinimides

1.3.1. Abstract

Section 3 involves new methodology for an intermolecular Stetter reaction of aromatic aldehydes with maleimides using thiazolylidene salt derived Isa–NHC as an efficient organocatalyst. This protocol provides an efficient and practical access to important 3–aroylsuccinimides in good to moderate yield. The synthesized Stetter products are important building blocks for the synthesis of natural products and bioactive compounds. The reaction conditions are mild, and various substituents on aromatic aldehyde and maleimide nitrogen were tolerated. One of the advantages of this developed protocol is the use of a readily available starting material.



This work has been published in *Tetrahedron* **2018**, *74*, 2079.

1.3.2. Introduction

Organocatalysis by N–heterocyclic carbene (NHC) has emerged as one of the important tools in organic synthesis over the past two decades.[1] The umpolung generated by NHC–catalysis has been reacted with several different electrophiles; specifically, the acyl anion equivalent of

aldehydes has been reacted with electrophilic alkene substrates by 1,4–conjugate addition to form new C–C bonds, thus providing scaffolds of biological interests.[1,2] This catalytic nucleophilic acylation of Michael acceptors, known as the "Stetter" reaction,[3] has been one of the highly explored reactions in the area of NHC–organocatalysis.[2,4] It provides an efficient access to unique 1,4–dicarbonyl compounds and related derivatives, such as ketophosphonates, ketosulfones, nitroketones and ketonitriles.[2] Finding new electrophilic partners for Stetter reaction and their application in the synthesis of natural products and drugs has been the focus of enduring research interest.[1,2,4,5] The current protocol demonstrates Stetter reaction of aromatic aldehydes with maleimides to access important "3–aroylsuccinimides" scaffolds.

1.3.3. Literature Review

Maleimides and their derivatives are well-known pharmacophores.[6] Previously, we have reported an efficient synthesis of succinimide derivatives by NHC–catalyzed intermolecular Stetter reaction of aromatic aldehydes with *N*–substituted itaconimides.[7] In continuation of our interest in this field, we planned to develop a intermolecular Stetter reaction of aldehydes with

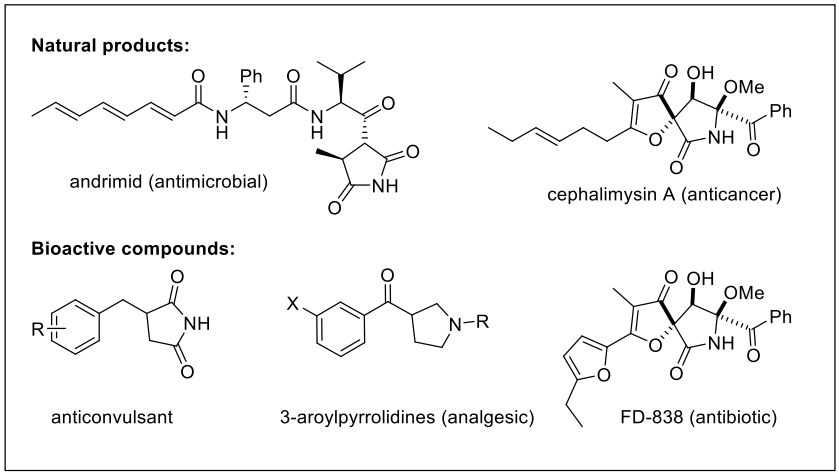


Figure 1. Representative Examples of Natural Products and Bioactive Compounds Containing Succinimide Core.

maleimide substrates to obtain corresponding ketosuccinimides **1**. Ketosuccinimides and their congeners are important building blocks for the synthesis of natural products[8-12] and bioactive compounds[13] (Figure 1). A literature survey revealed that all previous methods for the preparation of ketosuccinimides involves acylation of carbanion generated from succinimides under strong basic condition. Bryant and co-workers demonstrated synthesis of ketosuccinimides by condensation of aromatic ester with dipotassium salt of succinimide generated from potassium amide in liquid ammonia solvent (Figure 2, eq 1).[14a,b] Notably, this reaction suffers with series of drawbacks such as limited substrate scope and low yield. Yamamoto and colleagues reported the acylation of disodium salt of succinimide with benzonitrile as an acylating source. This method is limited to only benzonitrile and expected compound was obtained in very low yield (Figure 2, eq 2).[14c] In a similar method, Thomas et al. employed ester as an acylating source for acylation of succinimide under basic condition, which deliverers

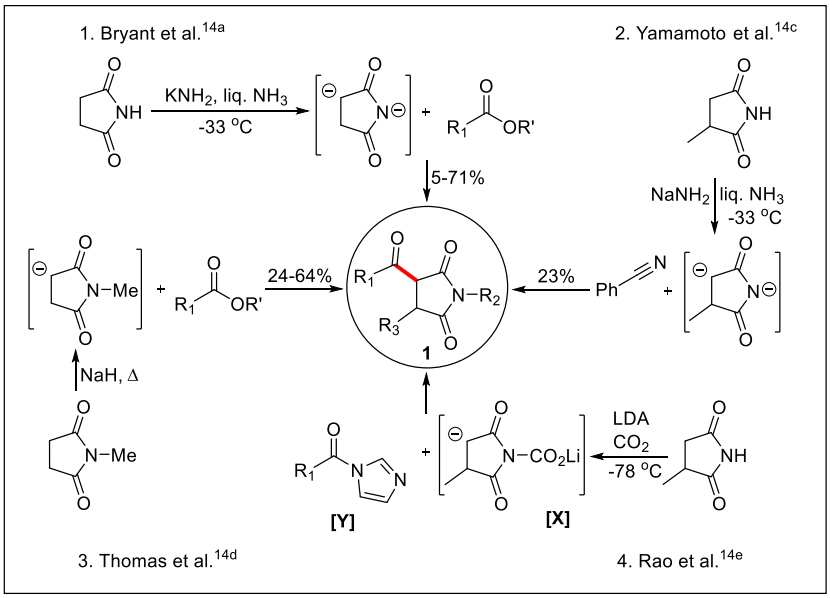


Figure 2. Traditional Methods for the Preparation of Ketosuccinimides **1**.

expected products in moderate yield (Figure 2, eq 3).[14d] Due to the lack of generality and selectivity of previous methods, Rao and co-worker developed different method for acylation of succinimides, which consist first protection of free nitrogen of succinimide by using LDA followed by treatment with CO_2 to form intermediate [**X]**. Further, the acylation of intermediate [**X]** has been accomplished by employing excess LDA and imidazole intermediate **[Y]** (Figure 2, eq 4).[14e] The main limitations of all of these traditional methods are harsh reaction condition and low yield of products. Hence, novel and general method for the preparation of these compounds is always desired.

1.3.4. Origin of the present Work

The Stetter reaction is one of the most studied reaction employing NHCs as organocatalysts. The literature survey revealed that Rovis et al. reported the NHC–catalyzed intramolecular Stetter reaction of aliphatic aldehyde with maleimide to construct the spirofuranone–lactam core of antibiotic FD–838 (Figure 1 and 3 A).[15] Recently, they have reported an elegant extension of this strategy for the total synthesis of anticancer natural product (–)-cephalimysin A (Figure 1),

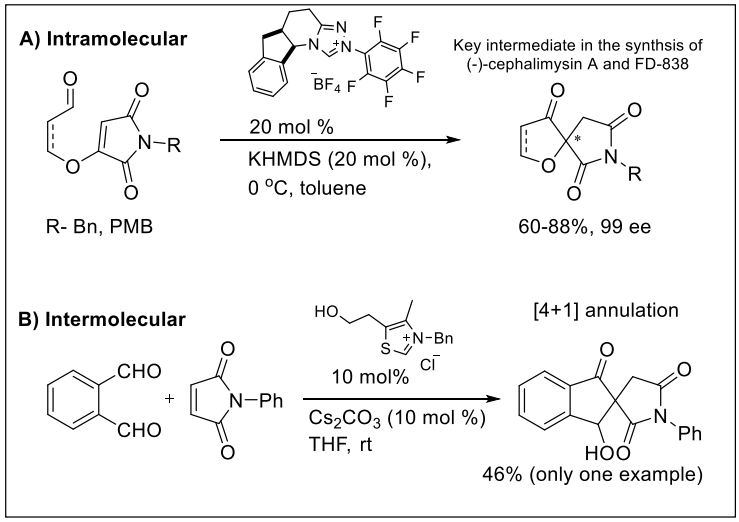


Figure 3. Prior Studies on Stetter Reaction with Maleimides.[15-17]

wherein intramolecular Stetter reaction of α–substituted unsaturated aldehyde with maleimide has been developed as key step (Figure 3 A).16 Prior to these studies, there is only one example known in the literature, wherein NHC–catalyzed [4+1] annulation of phthalaldehyde and *N*–phenylmaleimide furnished hydroxyl-indanone via a tandem process involving intermolecular Stetter reaction, proton shift and aldol reaction (Figure 3 B).[17]

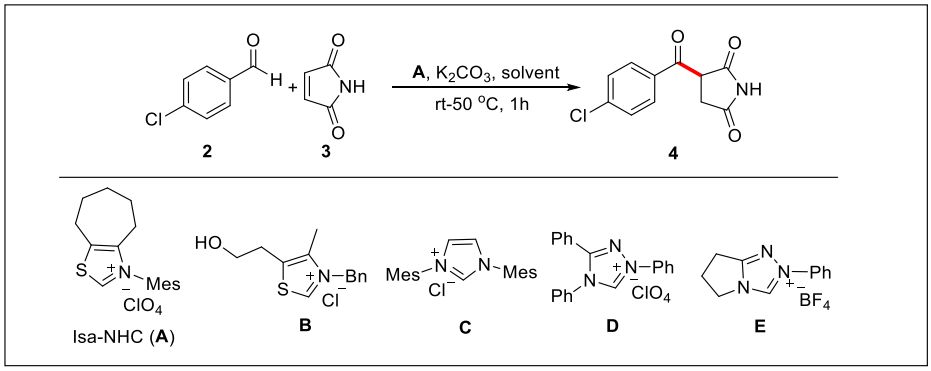
1.3.5. Objective

The succinimide derivatives are significant compounds found in various natural products, which reveal a remarkable biological and pharmaceutical activity. The work presented herein deals with an efficient protocol to access novel 3–aroylsuccinimides using intermolecular Stetter reaction. To the best of our knowledge, a general and efficient intermolecular Stetter reaction of diverse aldehydes with varyingly substituted maleimides has not been fully explored.

1.3.6. Results and Discussion

We initiated the work to achieve the desired Stetter reaction on maleimide substrate by performing the reaction of *p*–chlorobenzaldehyde in the presence of thiazolidene based Isa–NHC[18] catalyst **A**. Initially, performing the reaction at room temperature did not show any product formation, but after heating the reaction at 50 ^{o}C the expected product **4** was observed though in low yield, up to 35% (Table 1, entries 1–3). Further optimization studies (Table 1, entries 4–12) executed by variation in solvents, bases, temperature and mole ratios, on the same substrate using NHC–precatalyst **A** provided the best reaction condition (Table 1, entry 11) to obtain Stetter product **4** in 90% yield. We observed that heating the reaction mixture at a higher temperature than 50 ^{o}C or keeping it for more than two hours drastically reduced the yield of the desired product. Next, the effect of catalyst loading on reaction was examined. Conducting the reaction with reduced equivalents of NHC-precatalyst **A** showed a reduction in the yield

Table 1. Optimization Studies.



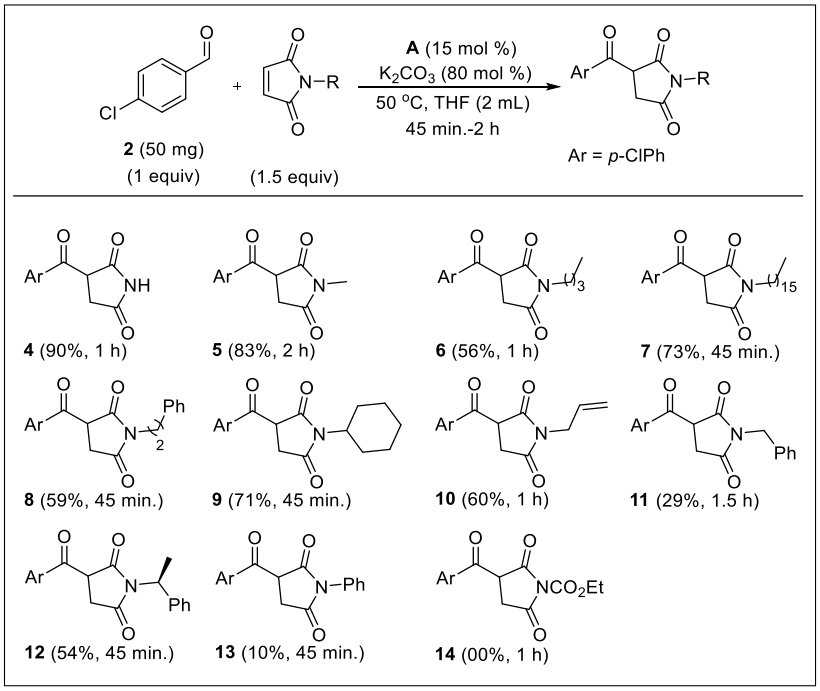
Sr. no.	2:3 (equiv)	NHC (equiv)	Base (equiv)	Solvent (2 mL)	Temp (°C)	Yield (%)[a]
1	1:1.0	A (0.20)	K_2CO_3 (0.5)	THF	rt	trace
2	1:1.0	A (0.20)	K_2CO_3 (1.0)	THF	rt	trace
3	1:1.0	A (0.20)	K_2CO_3 (0.5)	THF	50	39
4	1:1.0	A (0.20)	NMP (0.3)	THF	rt-50	NR
5	1:1.0	A (0.20)	K_2CO_3 (0.5)	toluene	rt-50	NR
6	1:1.0	A (0.20)	K_2CO_3 (0.5)	ACN	rt-50	NR
7	1:1.0	A (0.20)	NaOAc (0.3)	THF	rt-50	NR
8	1:1.5	A (0.20)	K_2CO_3 (0.3)	THF	50	71
9	1:1.5	A (0.20)	K_2CO_3 (0.3)	ACN	50	trace
10	1:1.5	A (0.20)	K_2CO_3 (0.3)	1,4-dioxane	50	50
11	**1:1.5**	**A (0.15)**	**K_2CO_3 (0.8)**	**THF**	**50**	**90**
12	1:1.5	A (0.10)	K_2CO_3 (0.8)	THF	50	60
13	1:1.5	B (0.15)	K_2CO_3 (0.8)	THF	rt-50	21
14	1:1.5	C (0.15)	K_2CO_3 (0.8)	THF	rt-50	NR
15	1:1.5	D (0.15)	K_2CO_3 (0.8)	THF	rt-50	NR
16	1:1.5	E (0.15)	K_2CO_3 (0.8)	THF	rt-50	12

[a]Isolated yield. NMP = *N*–methyl piperazine. NR = no reaction.

(Table 1, entry 12). To check the probability of further optimization and to lower the catalyst loading, four other NHC–precatalysts **B-E** were screened at room temperature as well as at 50 °C (Table 1, entries 13–16). None of them worked at room temperature. Under the optimized condition, catalyst **B** provided the compound **4** in low yield (Table 1, entry 13). However, the catalyst **C** and **D** did not show the formation of the product **4** (Table 1, entries 14 and 15). The

NHC–precatalyst **E** showed some catalytic activity, and the expected product was obtained in low yield (Table 1, entry 16). With the optimized reaction condition (Table 1, entry 11) in hand; we began to explore the scope and generality of the protocol.

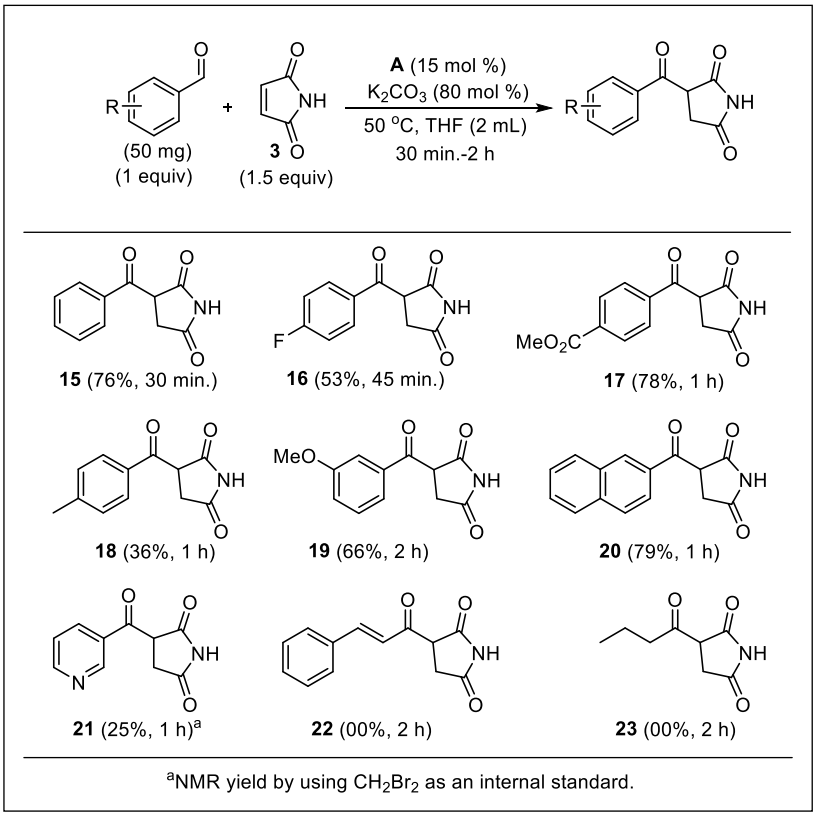
Scheme 1. Variation in the Maleimide *N*–Substituents



The substrate scope of maleimide *N*–substituents was studied by keeping the *p*–chlorobenaldehyde as a constant reacting partner (Scheme 1). We have mentioned in optimization studies that the maleimide (**3**) having free–NH furnished the product **4** in excellent yield. The maleimides with various *N*–alkyl substituents also reacted well under the developed protocol and the corresponding Stetter products (Scheme 1, **5**–**12**) were obtained in good to excellent yields. Thus, substrates with short to very long chain *N*–alkyl substituents (**5**–**7**), alkyl chain with terminal substituent (**8**) and secondary *N*–alkyl substituent (**9**) did not have much effect on the yield of the reaction and delivered the corresponding product in good to moderate yield. *N*–Allyl maleimide smoothly provided the product **10** in good yield. *N*–Benzyl maleimide

gave a low yield of the product **11**, but the corresponding benzylic carbon substituted maleimide gave better yield to obtain the product **12**. It has been observed that *N*–Phenyl maleimide was completely consumed under the optimized reaction condition, but the corresponding Stetter product **13** was obtained in very less yield along with many other unidentified side products. Similarly, we observed that *N*–ethoxycarbonylmaleimide used to get consumed, but the Stetter product **14** formation was not observed. In both the cases (**13** and **14**), it is unclear whether the

Scheme 2. Variation in the Aldehyde Substrate



consumption of starting maleimides is due to high reactivity or decomposition. In all the above-mentioned reactions, the formation of the corresponding benzoin product was also observed, however, that did not affect the yields due to its reversibility. We then turned our attention to explore the aldehyde substrate scope on maleimide (**3**) (Scheme 2). Benzaldehyde furnished the product **15** in good yield; however, *p*–flurobenzaldehyde gave compound **16** in moderate yield.

Other substituents such as methyl carboxylate-, methyl-, at *para*-position were tolerated to obtain the corresponding 3-aroylsuccinimides in good to moderate yields (**17** and **18**). Moreover, *meta*-methoxy- substituted benzaldehyde gave corresponding Stetter product in moderate yield. *β*–napthaldehyde also reacted smoothly to provide a very good yield of the corresponding product **20**. In the case of 3–pyridinecarboxaldehyde we observed the expected product **21** on TLC and confirmed its formation by ^{1}H-NMR analysis of a crude reaction mixture, but isolation of the product from the reaction mixture was not possible even after several attempts using neutral, acidic or basic column conditions. Cinnamaldehyde did not react under the developed condition; hence neither the product **22** nor the product by homoenolate addition was observed. Aliphatic aldehyde also remained unreactive and the product **23** was not formed. Overall, the developed protocol worked very well with the aromatic aldehydes.

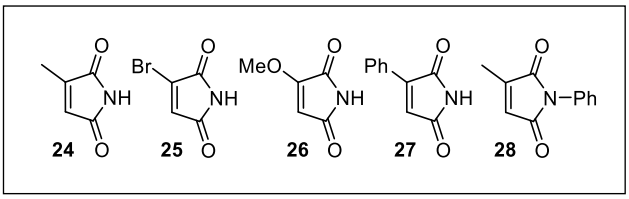


Figure 4. The Protocol did not Work with these Substituted Maleimides.

We generalized the protocol by variation in maleimide *N*–substituent and aldehyde, but generalization of the protocol with substituted maleimides (Figure 4, **24**–**27**) was not possible under the developed condition. We anticipated that the *N*–protected maleimide might prove to be a better substrate, hence *N*–phenyl 3–methylmaleimide (**28**) was used under developed condition. However, that also did not react under the developed protocol. Variation in NHC and use of some additives might facilitate the reaction.

The 3-aroylsuccinimides products obtained by our protocol (Scheme 1 and 2, **4**–**13** and **15**–**21**) themselves are important building blocks, but their utility also can be enhanced further by

converting them to the corresponding maleimides, diacids or anhydrides using well-documented literature methods (Figure 5).[6a,19]

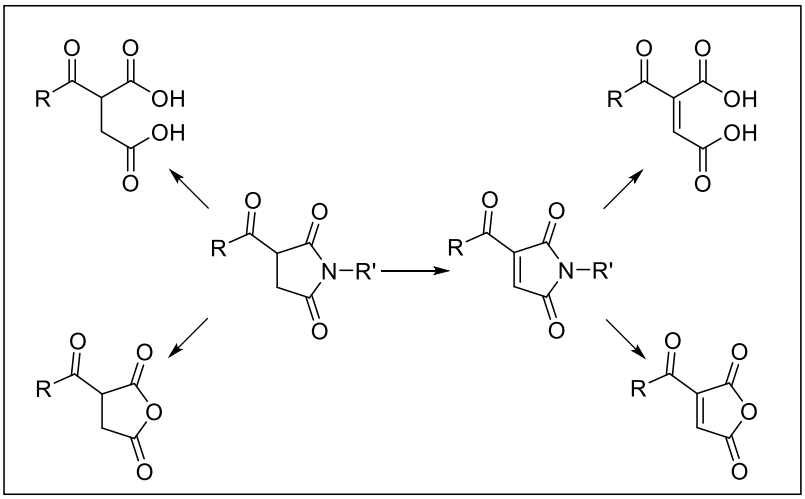


Figure 5. Well-known Transformations of 3-Aroylsuccinimide to Important Building Blocks.

The mechanism of reaction is illustrated in Figure 6. The catalytic cycle is initiated by generation of free carbene **A1** from NHC-precatalyst **A**. Then the free carbene catalyst **A1** is added to aromatic aldehydes, generating the nucleophilic Breslow intermediate **A2**. This acyl anion equivalent attacks the maleimide eventually form 3-aroylsuccinimides and regenerate NHC for further catalytic cycle.

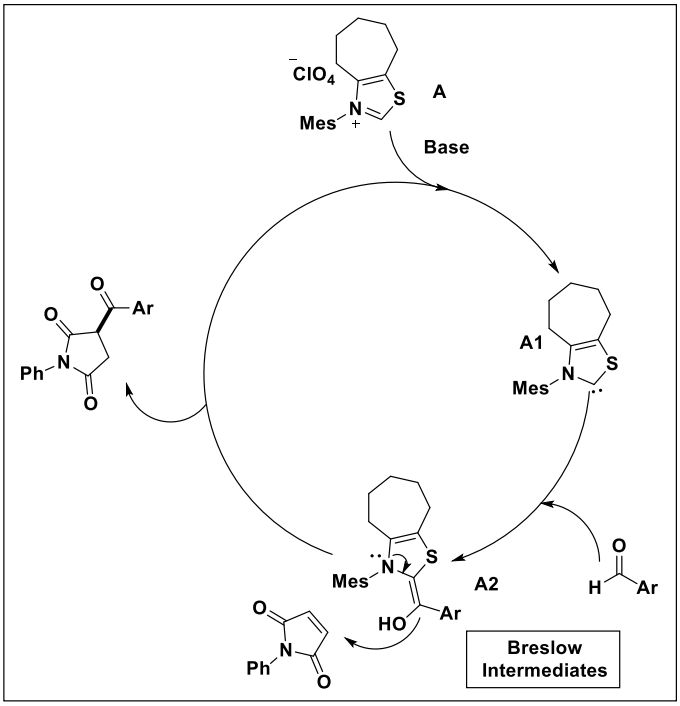


Figure 6. Mechanism of Stetter Reaction with Maleimide.

1.3.7. Conclusion

In conclusion, we have developed an efficient process for the synthesis of 3–aroylsuccinimides by an intermolecular Stetter reaction of aromatic aldehydes with maleimides. Thiazolylidene salt derived Isa–NHC was found to be the most efficient catalyst for this transformation. The protocol is operationally simple and general. The Stetter products were obtained in good to excellent yields. Future work in our laboratory is focused on the development of a suitable chiral NHC–catalyst for an intermolecular asymmetric Stetter reaction on substituted maleimides. Also the application of current methodology in total synthesis of natural products and bioactive molecules is underway in our laboratory.

1.3.8. Experimental Procedure

(All the reactions were performed on 50 mg scale of aldehyde.)

[A] General method for the preparation of 3–Aroylsuccinimides:

[All the reactions were performed on 50 mg scale of aldehyde.]

A reaction mixture containing K_2CO_3 (80 mol%), NHC-precatalyst **A** (15 mol%), maleimide **2** (1.5 equiv) and aldehyde **1** (1.0 equiv) in THF (2 mL) under argon atmosphere was stirred at 50 ^oC for 30 min. to 2 h. When the reaction was complete, the crude reaction mixture was allowed to attain room temperature, followed by filtration of the reaction mixture through a bed of celite. The residue was washed with ethyl acetate (5 mL x 3) and the combined filtrate was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel using solvent gradient of petroleum ether:ethyl acetate to furnish the desired products **4-13**, **15-21** in 10-90% yield.

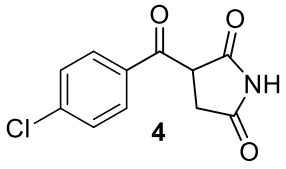
[B] Representative Experimental Procedure for the Stetter Reaction of Aromatic Aldehydes with Maleimides:

A reaction mixture containing K_2CO_3 (40 mg, 0.29 mmol, 0.80 equiv), NHC precatalyst **A** (20 mg, 0.054 mmol, 0.15 equiv), maleimide **3** (52 mg, 0.54 mmol, 1.5 equiv) and 4-chlorobenzaldehyde (50 mg, 0.36 mmol, 1.0 equiv) in THF (2 mL) under argon atmosphere was stirred at 50 ^oC for 1h. After completion of reaction, the crude reaction mixture was allowed to attain room temperature, followed by filtration of the reaction mixture through a bed of celite. The residue was washed with ethyl acetate (5 mL x 3) and the combined filtrate was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel using solvent gradient of petroleum ether:ethyl acetate (3:2) to furnish the desired

products **4** in 90% yield. Reaction time: 1 h; *Rf*: 0.5 (2:3 EtOAc: pet. ether); white solid; 76 mg, 90% yield.

1.3.9. Characterization Data of Compounds

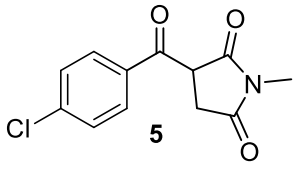
3-(4-Chlorobenzoyl)pyrrolidine-2,5-dione (4).[22]



4

Reaction time: 1 h; R*f*: 0.5 (2:3 EtOAc: pet. ether); white solid; 76 mg, 90% yield; Mp 165–167 ^{o}C; [keto : enol = 1 : 0.1]; **^{1}H NMR** (500 MHz, Acetone–d_6) δ 12.49 (s, 0.07 x 1H), 10.38 (s, 0.18 x 1H), 10.27 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 0.21 x 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 0.25 x 2H), 5.22 (dd, *J* = 8.9 and 4.3 Hz, 1H), 3.64 (s, 0.22 x 2H), 3.20 (dd, *J* = 18.0 and 4.0 Hz, 1H), 2.98 (dd, *J* = 18.0 and 8.8 Hz, 1H); **^{13}C NMR** (125 MHz, Acetone–d_6) δ 193.5, 177.2, 174.5, 140.5, 135.5, 132.3, 130.1, 129.7, 51.1, 34.8, 33.5; **HRMS-ESI** (*m/z*): calcd. for $C_{11}H_8ClNO_3$ $[M + Na]^+$: 260.0085, found: 260.0076.

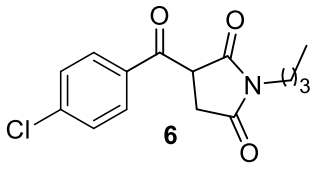
3-(4-Chlorobenzoyl)-1-methylpyrrolidine-2,5-dione (5).



5

Reaction time: 2 h; R*f*: 0.5 (3:7 EtOAc: pet. ether); white solid; 74 mg, 83% yield; Mp 111–113 ^{o}C; [keto : enol = 1 : 0.2]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.11 (s, 0.21 x 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 0.44 x 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 0.44 x 2H), 4.72 (dd, *J* = 8.7 and 4.1 Hz, 1H), 3.44 (s, 0.44 x 2H), 3.35 (dd, *J* = 18.3 and 4.1 Hz, 1H), 3.02 (s, 0.66 x 3H), 2.93 (s, 3H), 2.78 (dd, *J* = 18.3 and 9.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.0, 175.6, 173.9, 172.5, 141.0, 137.4, 133.7, 131.6, 131.2, 129.1, 129.0, 128.9, 48.6, 33.5, 31.4, 25.4, 24.5; **HRMS-ESI** (*m/z*): calcd. for $C_{12}H_{10}ClNO_3$ $[M + H]^+$: 252.0422, found: 252.0418.

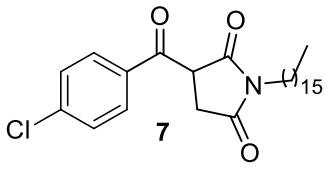
1-Butyl-3-(4-chlorobenzoyl)pyrrolidine-2,5-dione (6).



6

Reaction time: 1 h; R*f*: 0.5 (3:17 EtOAc: pet. ether); viscous oil; 59 mg, 56% yield; [keto : enol = 1 : 0.19]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.18 (s, 0.18 x 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.6 Hz, 0.40 x 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.8 Hz, 0.5 x 2H), 4.70 (dd, J = 8.8 and 3.9 Hz, 1H), 3.53 (t, J = 7.3 Hz, 0.44 x 2H), 3.47–3.40 (m, 2H), 3.32 (dd, J = 18.1 and 3.9 Hz, 1H), 2.77 (dd, J = 18.1 and 8.8 Hz, 1H), 1.60–1.52 (m, 0.55 x 2H), 1.51–1.42 (m, 2H), 1.31–1.26 (m, 0.58 x 2H), 1.24–1.18 (m, 2H), 0.88 (t, J = 7.3 Hz, 0.57 x 3H), 0.83 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.2, 175.6, 172.5, 141.0, 133.8, 131.2, 129.1, 129.0, 128.8, 48.5, 39.2, 33.5, 31.4, 29.7, 29.5, 20.1, 19.9, 13.6, 13.5; **ESI HRMS**: calcd. for $C_{15}H_{16}ClNO_3$ $[M + H]^+$: 294.0891, found: 294.0879.

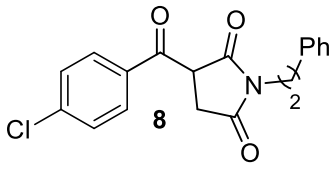
3-(4-Chlorobenzoyl)-1-dodecylpyrrolidine-2,5-dione (7).



7

Reaction time: 45 min.; R*f*: 0.5 (3:17 EtOAc: pet. ether); white solid; 120 mg, 73% yield; Mp 65–67 ^{o}C; [keto : enol = 1 : 0.22]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.19 (s, 0.19 x 1H), 8.01 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.8 Hz, 0.47 x 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.8 Hz, 0.5 x 2H), 4.70 (dd, J = 8.8 and 3.9 Hz, 1H), 3.52 (t, J = 7.5 Hz, 0.46 x 2H), 3.43 (t, J = 7.3, 2H), 3.40 (s, 0.55 x 2H), 3.33 (dd, J = 18.1 and 3.9 Hz, 1H), 2.77 (dd, J = 18.1 and 9.1 Hz, 1H), 1.23–1.14 (m, 28H), 0.81 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.2, 175.6, 172.5, 141.0, 133.8, 131.2, 129.1, 129.0, 128.9, 48.5, 39.5, 31.9, 31.4, 29.68, 29.65, 29.5, 29.4, 29.4, 29.13, 29.05, 27.5, 26.7, 22.7, 14.1; **ESI HRMS**: calcd. for $C_{27}H_{40}ClNO_3$ $[M + H]^+$: 462.2769, found: 462.2752.

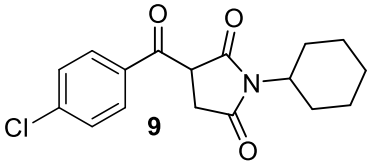
3-(4-Chlorobenzoyl)-1-phenethylpyrrolidine-2,5-dione (8).



8

Reaction time: 45 min.; R*f*: 0.5 (1:3 EtOAc: pet. ether); white solid; 72 mg, 59% yield; Mp 82–84 ^{o}C; [keto : enol = 1 : 0.16]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.13 (s, 0.15 x 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.6 Hz, 0.33 x 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.6 Hz, 0.33 x 2H), 7.28–7.09 (m, 4H), 7.09 (d, J = 7.8 Hz, 2H), 4.65 (dd, J = 8.8 and 3.9 Hz, 1H), 3.76 (t, J = 7.3 Hz, 0.40 x 2H), 3.66 (t, J = 7.3 Hz, 2H), 3.39 (s, 0.32 x 2H), 3.32 (dd, J = 18.1 and 3.9 Hz, 1H), 2.87 (t, J = 8.3 Hz, 0.38 x 2H), 2.79 (t, J = 8.3 Hz, 2H), 2.71 (dd, J = 18.1 and 9.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.8, 175.2, 172.2, 141.0, 137.4, 133.7, 131.2, 129.1, 129.0, 128.9, 128.8, 128.6, 126.7, 48.5, 40.6, 33.4, 31.2; **ESI HRMS**: calcd. for $C_{19}H_{16}ClNO_3$ $[M + H]^+$: 342.0891, found: 342.0881.

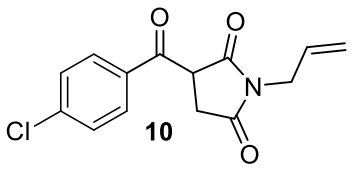
3-(4-Chlorobenzoyl)-1-cyclohexylpyrrolidine-2,5-dione (9).



9

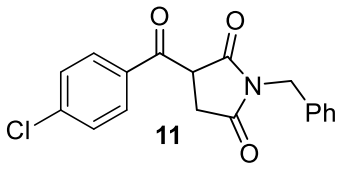
Reaction time: 45 min.; R*f*: 0.5 (3:17 EtOAc: pet. ether); white solid; 81 mg, 71% yield; Mp 99–101 ^{o}C; [keto : enol = 1 : 0.20]; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 12.32 (s, 0.21 x 1H), 8.00 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.8 Hz, 0.48 x 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.8 Hz, 0.6 x 2H), 4.65 (dd, J = 9.0 and 4.2 Hz, 1H), 4.01–3.76 (m, 1H), 3.39 (s, 0.41 x 2H), 3.28 (dd, J = 18.1 and 4.2 Hz, 1H), 2.72 (dd, J = 18.1 and 9.0 Hz, 1H), 2.14–1.91 (m, 2H), 1.85–1.55 (m, 5H), 1.31–1.04 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.4, 175.6, 172.6, 140.9, 133.8, 131.8, 131.2, 129.8, 129.1, 129.0, 128.8, 52.4, 51.6, 48.3, 33.5 31.2, 29.0, 28.7, 28.6, 25.9, 25.8, 25.7, 25.0, 24.9; **HRMS-ESI** (*m/z*): calcd. for $C_{17}H_{18}ClNO_3$ $[M + H]^+$: 320.1048, found: 320.1049.

1-Allyl-3-(4-chlorobenzoyl)pyrrolidine-2,5-dione (10).



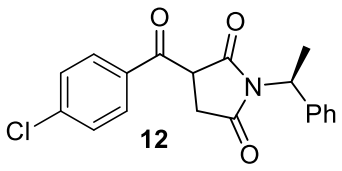
Reaction time: 1 h; R*f*: 0.5 (1:4 EtOAc: pet. ether); viscous oil; 59 mg, 60% yield; [keto : enol = 1 : 0.18]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.12 (s, 0.17 x 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.6 Hz, 0.42 x 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 0.46 x 2H), 5.84–5.75 (m, 0.17 x 1H), 5.75–5.63 (m, 1H), 5.24–5.17 (m, 0.40 x 2H), 5.17–5.08 (m, 2H), 4.75 (dd, J = 8.8 and 3.4 Hz, 1H), 4.15 (d, J = 5.9 Hz, 0.41 x 2H), 4.04 (d, J = 5.9 Hz, 2H), 3.46 (s, 0.39 x 2H), 3.37 (dd, J = 18.1 and 3.9 Hz, 1H), 2.80 (dd, J = 18.1, 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.1, 175.0, 172.0, 141.1, 133.7, 131.2, 130.1, 129.2, 129.1, 128.9, 118.6, 48.6, 41.4, 40.6, 33.5, 31.4; **HRMS-ESI** (*m/z*): calcd. for $C_{14}H_{12}ClNO_3$ $[M + H]^+$: 278.0578, found: 278.0572.

1-Benzyl-3-(4-chlorobenzoyl)pyrrolidine-2,5-dione (11).



Reaction time: 1.5 h; R*f*: 0.5 (7:13 EtOAc: pet. ether); viscous oil; 34 mg, 29% yield; [keto : enol = 1 : 0.17]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.11 (s, 0.20 x 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.8 Hz, 0.46 x 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.40–7.33 (m, 0.98 x 4H), 7.31–7.19 (m, 6H), 4.70 (dd, J = 8.8 and 3.9 Hz, 1H), 4.68 (s, 0.41 x 2H), 4.61 (d, J = 14.2 Hz, 1H), 4.53 (d, J = 14.2 Hz, 1H), 3.44 (s, 0.46 x 2H), 3.37 (dd, J = 18.1 and 3.4 Hz, 1H), 2.77 (dd, J = 18.1 and 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.9, 175.2, 172.2, 141.0, 135.2, 133.7, 131.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.11, 128.05, 48.6, 43.0, 33.6, 31.3; **ESI HRMS**: calcd. for $C_{18}H_{14}ClNO_3$ $[M + H]^+$: 328.0735, found: 328.0732.

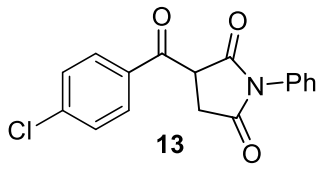
3-(4-Chlorobenzoyl)-1-((S)-1-phenylethyl)pyrrolidine-2,5-ione (12).



12

Reaction time: 45 min.; R*f*: 0.5 (1:4 EtOAc: pet. ether); white solid; 66 mg, 54% yield; Mp 111–113 ^{o}C; [keto : enol = 1 : 0.25]; d.r. (1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.20 (s, 0.23 x 1H), 7.97 (d, *J* = 3.7 Hz, 1H), 7.95 (d, *J* = 3.4 Hz, 2H), 7.55 (d, *J* = 3.4 Hz, 0.5 x 2H), 7.46–7.38 (m, 2H), 7.38–7.29 (m, 3H), 7.29–7.16 (m, 4H), 5.43 (q, *J* = 7.3 Hz, 0.25 x 1H), 5.39–5.26 (m, 1H), 4.70–4.58 (m, 1H), 3.39 (d, *J* = 2.0 Hz, 0.44 x 2H), 3.35–3.26 (m, 1H), 2.79–2.64 (m, 1H), 1.81 (d, *J* = 7.3 Hz, 0.74 x 3H), 1.74 (d, *J* = 7.3 Hz, 1.5 x 3H), 1.68 (d, *J* = 7.3 Hz, 1.5 x 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.3, 191.1, 175.3, 175.2, 173.5, 172.2, 162.5, 141.0, 140.9, 139.0, 138.9, 137.3, 133.74, 133.71, 131.24, 131.19, 129.1, 129.0, 128.8, 128.5, 128.0, 127.9, 127.5, 127.3, 95.3, 51.0, 50.7, 50.1, 48.3, 33.5, 31.3, 16.7, 16.6, 16.2. **HRMS-ESI** (*m/z*): calcd. for $C_{19}H_{16}ClNO_3$ $[M + H]^+$: 342.0891, found: 342.0880.

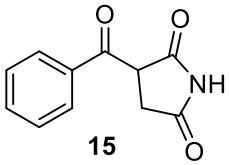
3-(4-Chlorobenzoyl)-1-phenylpyrrolidine-2,5-dione (13).



13

Reaction time: 45 min.; R*f*: 0.5 (1:4 EtOAc: pet. ether); oil; 10% yield; [keto : enol = 1 : 0.37]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.27 (s, 0.33 x 1H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.49–7.30 (m, 9H), 7.22–7.20 (m, 1H), 4.88 (dd, *J* = 9.0 and 4.1 Hz, 1H), 3.63 (s, 0.74 x 2H), 3.53 (dd, *J* = 18.3 and 4.1 Hz, 1H), 2.97 (dd, *J* = 18.3 and 9.0 Hz, 1H); **ESI HRMS**: calcd. for $C_{17}H_{12}ClNO_3$ $[M + H]^+$: 314.0578, found: 314.0575.

3-Benzoylpyrrolidine-2,5-dione (15).[14a]

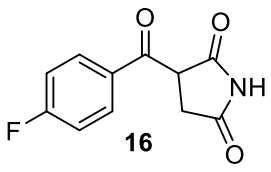


15

Reaction time: 30 min.; R*f*: 0.5 (2:3 EtOAc: pet. ether); white solid; 73 mg, 76% yield; Mp 135–137 ^{o}C; [keto : enol = 1 : 0.24]; **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 12.04 (s, 0.21 x 1H), 8.15 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 0.47 x 2H), 7.59 (t, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 2H), 7.45–7.39 (m, 0.67 x 3H), 4.83 (dd, *J* = 9.1 and 3.4 Hz, 1H), 3.52 (s, 0.48 x 2H), 3.38 (dd, *J* = 18.3 and 3.4 Hz, 1H), 2.84 (dd, *J* = 18.3 and 9.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.9, 175.9, 172.8, 135.2, 134.4, 131.4, 129.8, 128.8, 128.7, 127.6, 49.8, 34.6, 32.7. **HRMS-ESI** (*m/z*): calcd. for $C_{11}H_9NO_3$ $[M + H]^+$: 204.0655, found: 204.0654.

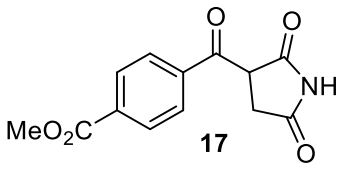
3-(4-Fluorobenzoyl)pyrrolidine-2,5-dione (16).



16

Reaction time: 45 min.; R*f*: 0.5 (2:3 EtOAc: pet. ether); white solid; 79 mg, 53% yield; Mp 143–145 ^oC; [keto : enol = 1 : 0.04]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.09 (s, 0.04 x 1H), 8.11–8.06 (m, 2H), 8.03 (s, 1H), 7.19–7.11 (m, 2H), 4.77 (dd, *J* = 8.8 and 4.2 Hz, 1H), 3.50 (s, 0.08 x 2H), 3.42 (dd, *J* = 18.3 and 4.2 Hz, 1H), 2.83 (dd, *J* = 18.3 and 8.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.0, 175.2, 172.2, 173.7 (d, *J* = 257.4 Hz), 132.7 (d, *J* = 9.2 Hz), 131.7, 116.1 (d, *J* = 22.3 Hz), 49.8, 32.5; **HRMS-ESI** (*m/z*): calcd. for $C_{11}H_8FNO_3$ $[M + H]^+$: 222. 0561, found: 222.0559.

Methyl 4-(2,5-dioxopyrrolidine-3-carbonyl)benzoate (17).

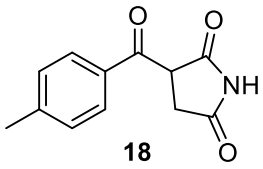


17

Reaction time: 1 h; R*f*: 0.5 (1:1 EtOAc: pet. ether); white solid; 62 mg, 78% yield; Mp 174–176 ^oC; [keto : enol = 1 : 0.16]; **^{1}H NMR** (500 MHz, Acetone–d_6) δ 12.48 (s, 0.1 x 1H), 10.44 (s, 0.16 x 1H), 10.29 (s, 1H), 8.26 (d, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 8.2 Hz, 2H), 8.13 (d, *J* = 8.2 Hz, 0.47 x 2H), 7.95 (d, *J* = 8.2 Hz, 0.32 x 2H), 5.29 (dd, *J* = 8.8 and 4.3 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 0.52 x 3H), 3.67 (s, 0.32 x 2H), 3.22 (dd, *J* = 18.0 and 4.3 Hz, 1H), 3.01 (dd, *J* = 18.0 and 8.8 Hz, 1H); **^{13}C NMR** (125 MHz, Acetone–d_6) δ 194.4, 177.2, 174.4, 166.4, 140.1, 135.3, 130.6, 130.3,

128.6, 52.8, 52.6, 51.4, 34.8, 33.6; **HRMS-ESI** (*m/z*): calcd. For $C_{13}H_{11}NO_5$ $[M + H]^+$: 262.0710, found: 262.0710.

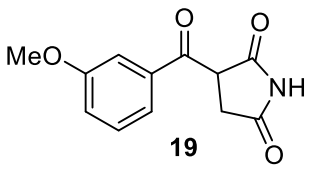
3-(4-Methylbenzoyl)pyrrolidine-2,5-dione (18).



18

Reaction time: 1 h; R*f*: 0.5 (1:1 EtOAc: pet. ether); white solid; 33 mg, 36% yield; Mp 159–161 ^oC; [keto : enol = 1 : 0.17]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.05 (s, 0.16 x 1H), 8.27 (s, 0.48 x 1H), 8.17 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 0.35 x 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 0.35 x 2H), 4.80 (dd, *J* = 9.3 and 4.4 Hz, 1H), 3.50 (s, 0.35 x 2H), 3.37 (dd, *J* = 18.1 and 3.9 Hz, 1H), 2.82 (dd, *J* = 18.6 and 9.3 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 0.89 x 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.3, 175.6, 172.7, 145.6, 132.7, 130.2, 129.9, 129.6, 129.5, 129.2, 127.6, 49.6, 34.7, 32.7, 21.7; **ESI HRMS**: calcd. for $C_{12}H_{11}NO_3$ $[M + H]^+$: 218.0812, found: 218.0810.

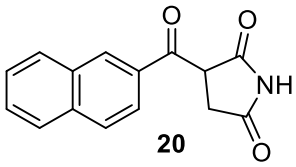
(3-(3-Methoxybenzoyl)pyrrolidine-2,5-dione (19).



19

Reaction time: 2 h; *Rf*: 0.5 (1:1 EtOAc: pet. ether); white solid; 57 mg, 66% yield; Mp 158–160 ^oC; [keto : enol = 1 : 0.07]; **^{1}H NMR** (400 MHz, DMSO–d_6) δ 12.38 (s, 0.04 x 1H), 11.55 (s, 0.08 x 1H), 11.46 (s, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.57–7.54 (m, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.2 and 2.8 Hz, 1H), 5.17 (dd, *J* = 8.2 and 5.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 0.2 x 3H), 3.00–2.86 (m, 2H); **^{13}C NMR** (100 MHz, DMSO–d_6) δ 194.6, 177.8, 175.1, 159.6, 137.1, 130.1, 122.3, 120.2, 114.2, 55.6, 50.2, 33.5; **ESI HRMS**: calcd. for $C_{12}H_{11}NO_4$ $[M + H]^+$: 234.0761, found: 234.0758.

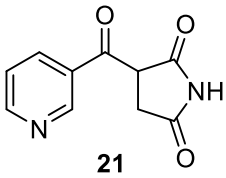
3-(2-Naphthoyl)pyrrolidine-2,5-dione (20).



20

Reaction time: 1 h; *Rf*: 0.5 (1:1 EtOAc: pet. ether); white solid; 64 g, 79% yield; Mp 176–178 ^{o}C; [keto : enol = 1 : 0.0]; **^{1}H NMR** (400 MHz, DMSO–d_6) δ 11.45 (s, 1H), 8.76 (s, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.04–7.93 (m, 3H), 7.67 (t, J = 7.1 Hz, 1H), 7.61 (t, J = 7.1 Hz, 1H), 5.30 (dd, J = 8.3 and 4.4 Hz, 1H), 3.05–2.85 (m, 2H); **^{13}C NMR** (100 MHz, DMSO–d_6) δ 194.6, 178.0, 175.3, 135.6, 133.1, 132.6, 132.2, 130.1, 129.5, 128.6, 127.9, 127.4, 124.3, 50.1, 33.5; **HRMS-ESI** (*m/z*): calcd. for $C_{15}H_{11}NO_3$ $[M + H]^+$: 254.0812, found: 254.0810.

3-Nicotinoylpyrrolidine-2,5-dione (21).



21

Reaction time: 1 h; *Rf*: 0.5 (EtOAc); 25% yield by NMR using CH_2Br_2 as an internal standard; Keto form; **^{1}H NMR** (500 MHz, Acetone–d_6) δ 10.04 (s, 1H), 9.00–8.94 (m, 1H), 8.68–8.63 (m, 1H), 8.28–8.22 (m, 1H), 8.15–8.08 (m, 1H), 4.25–4.18 (m, 1H), 3.34 (dd, J = 18.7 and 8.8 Hz, 1H), 2.75 (dd, J = 8.78 and 4.2 Hz, 1H).

1.3.10. References

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1.3.11. Spectra

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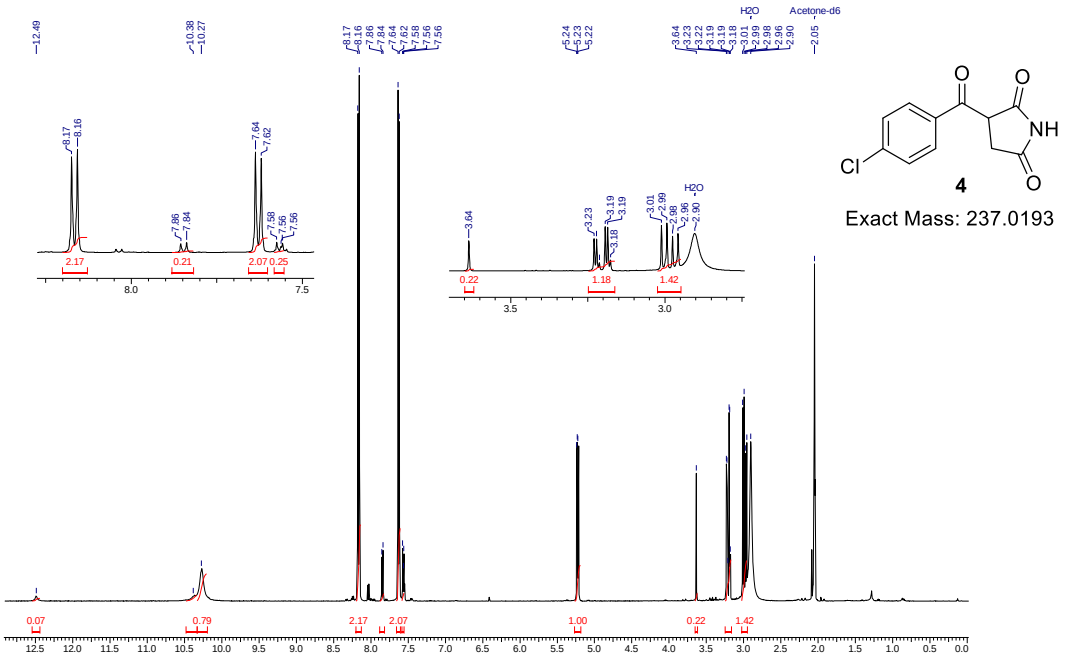

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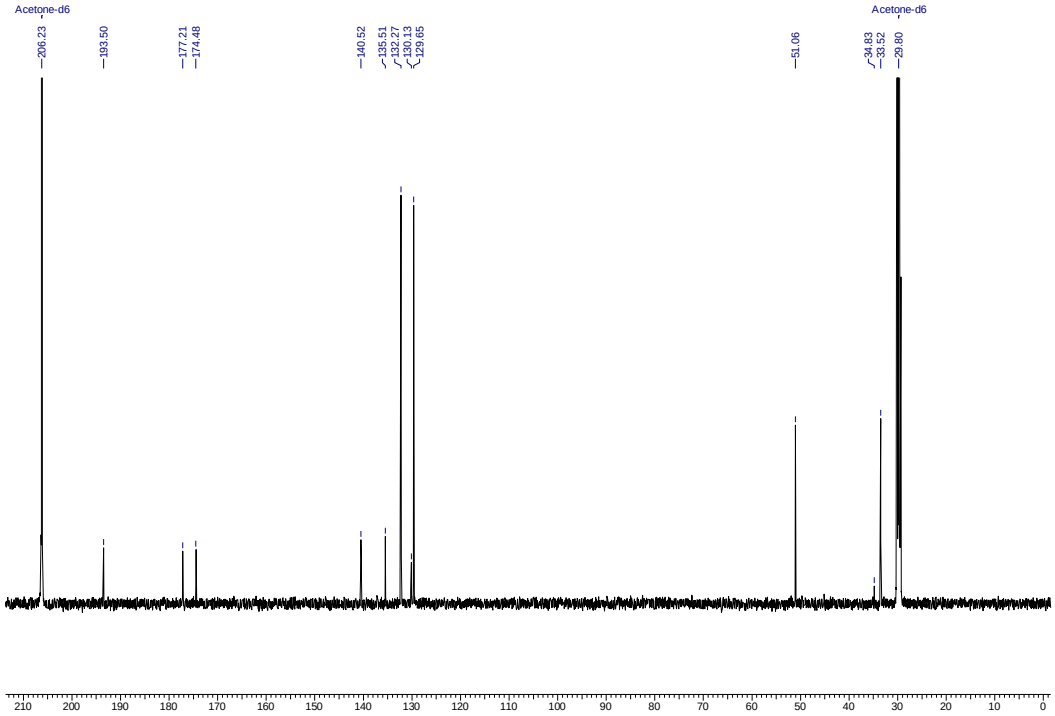

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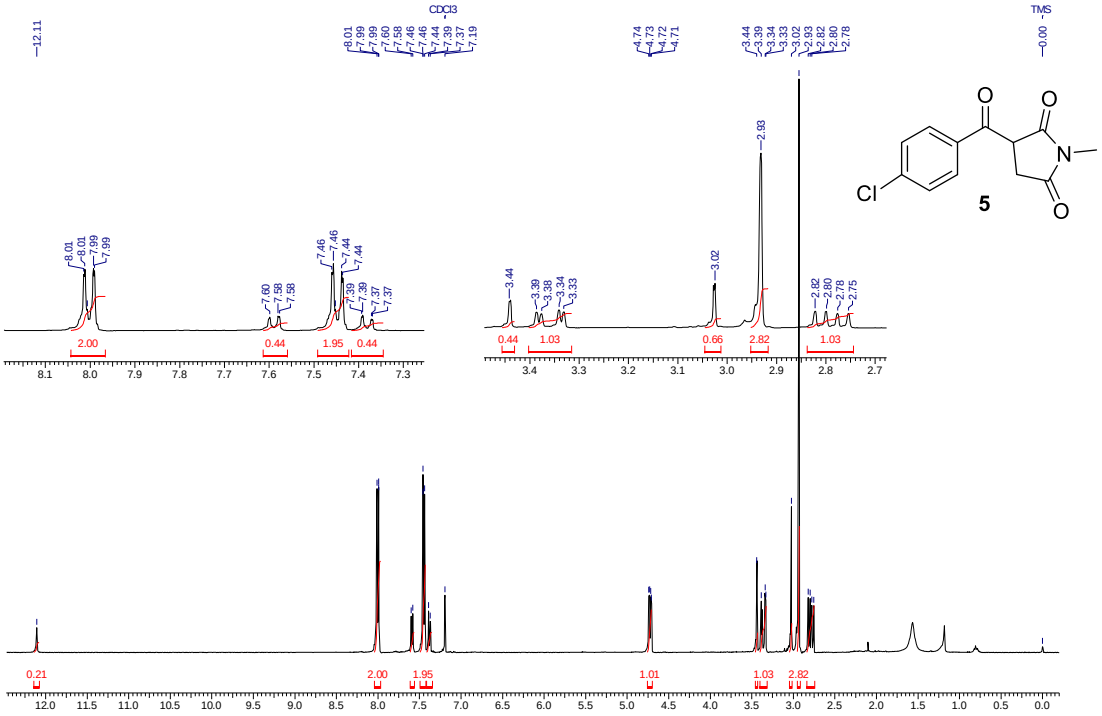

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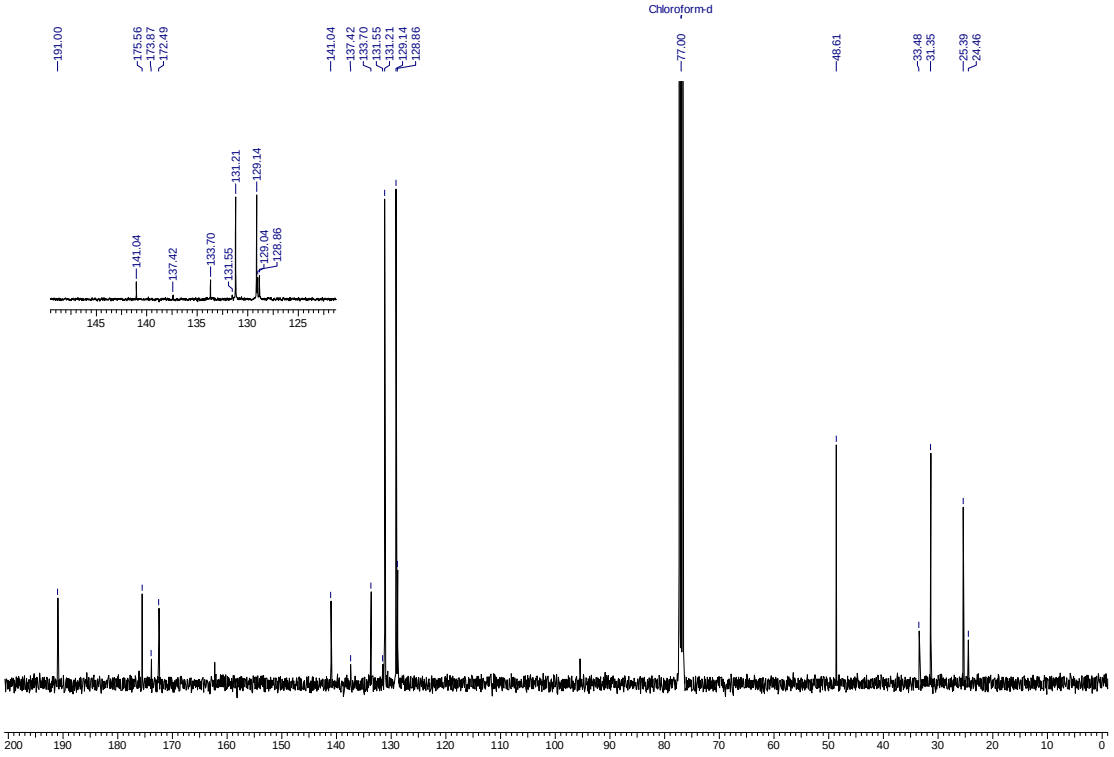

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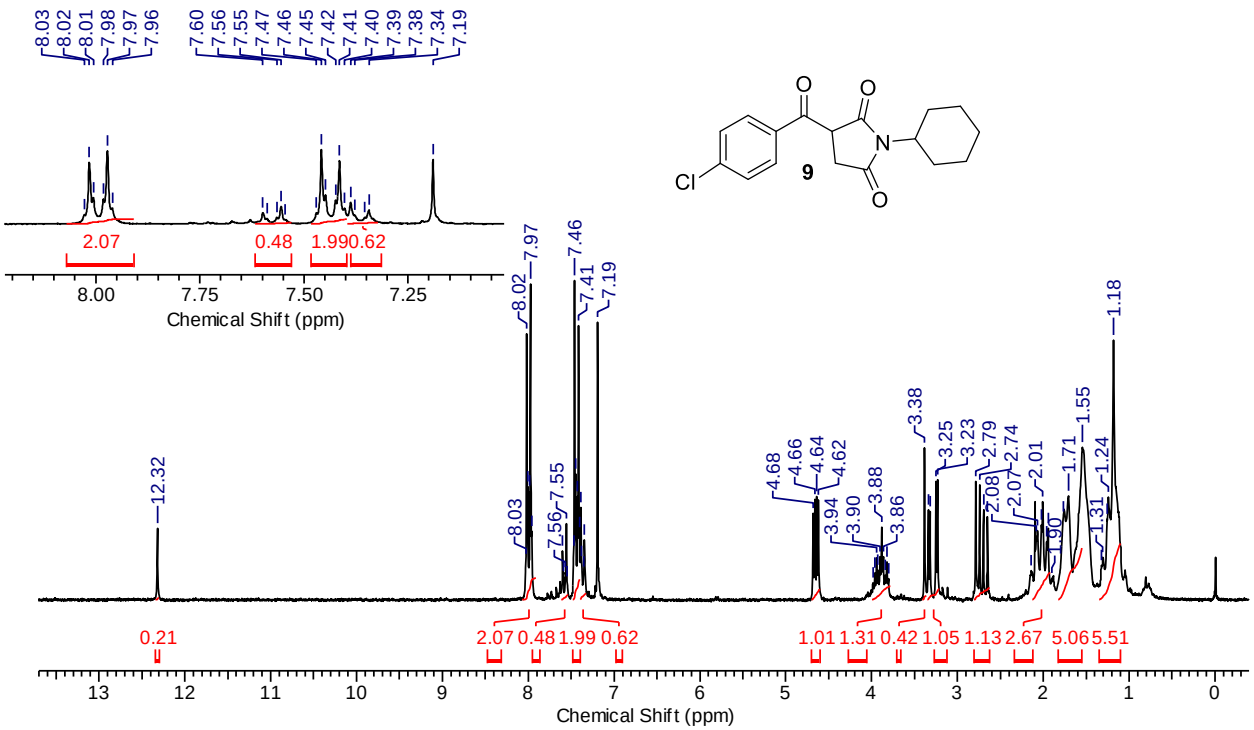

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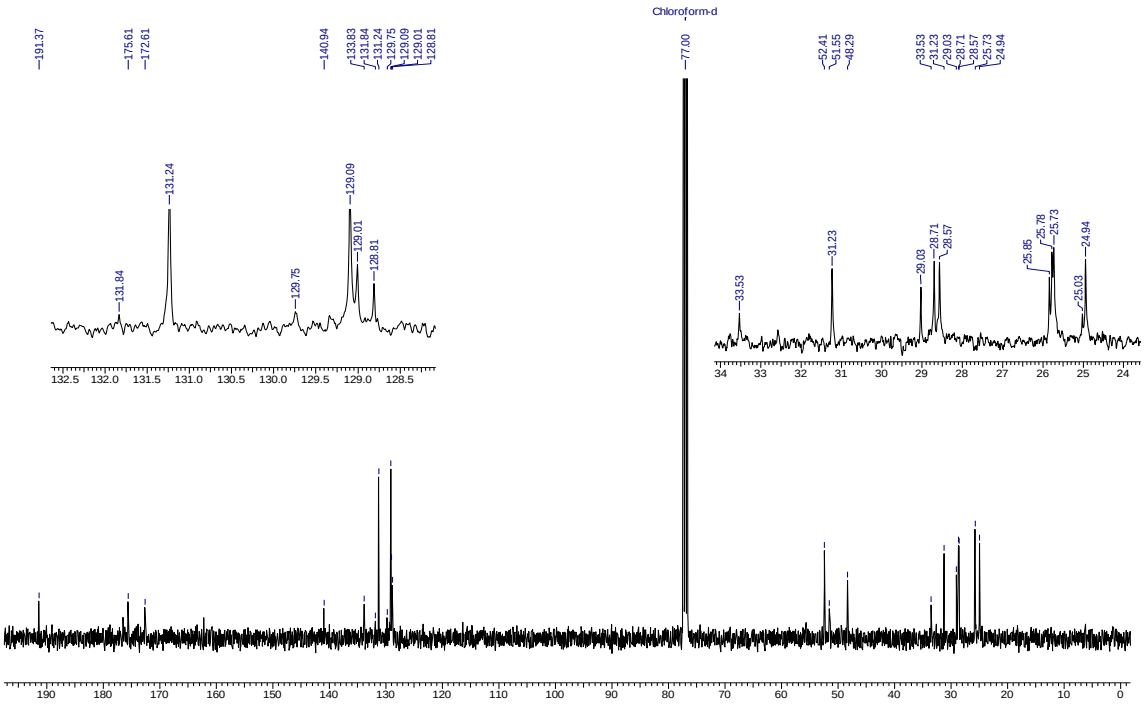

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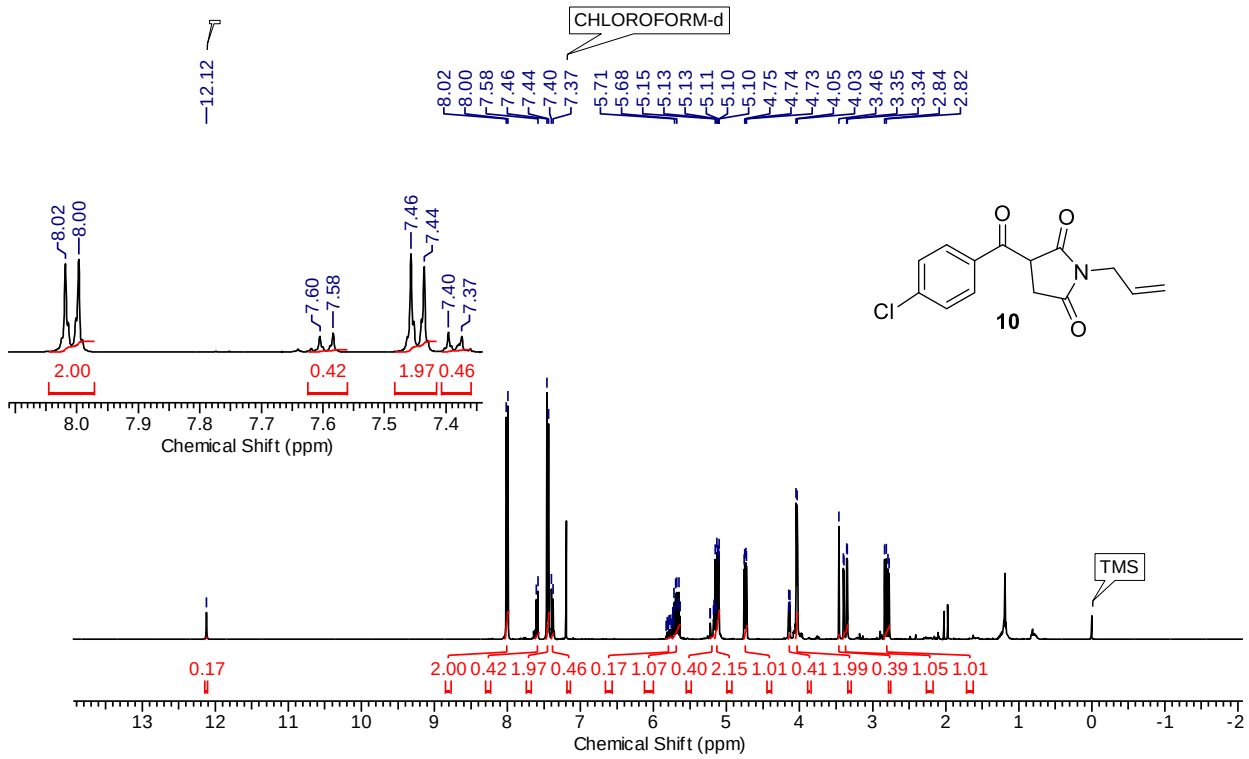

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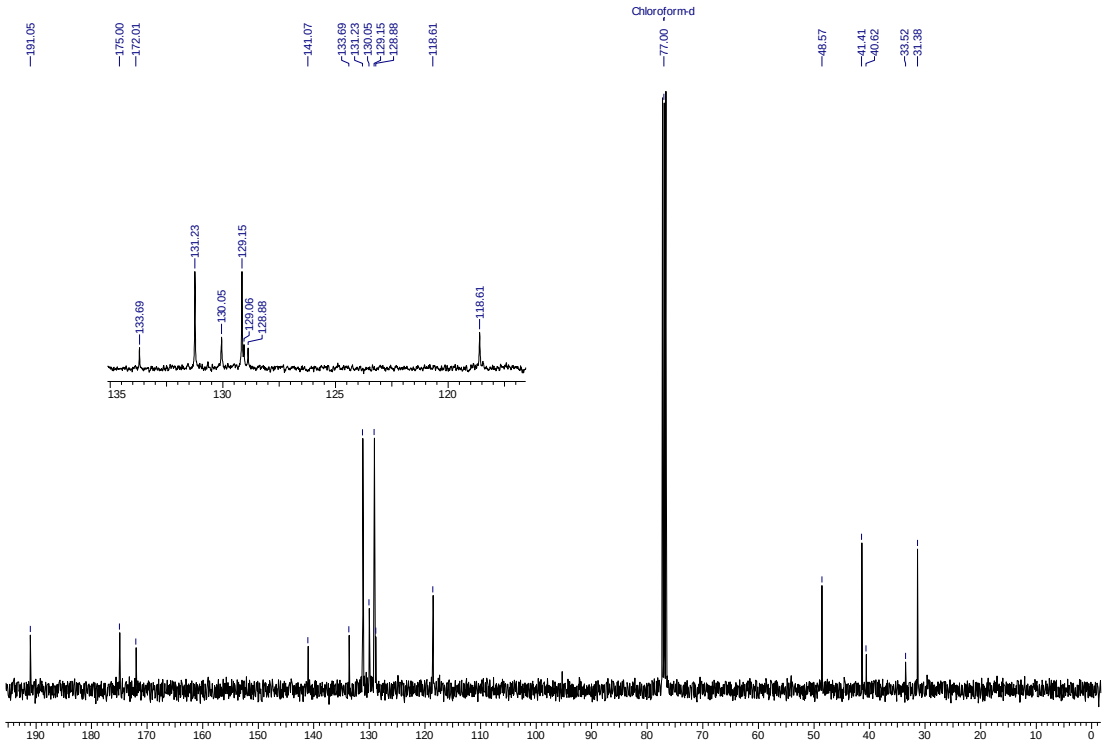

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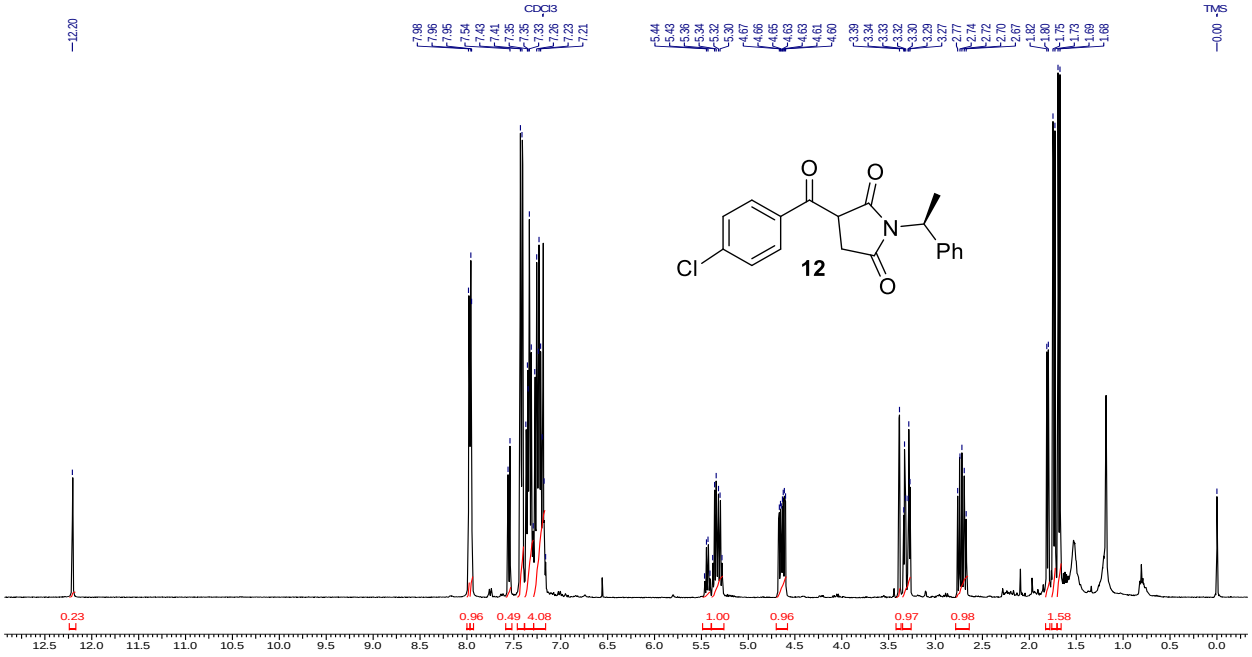

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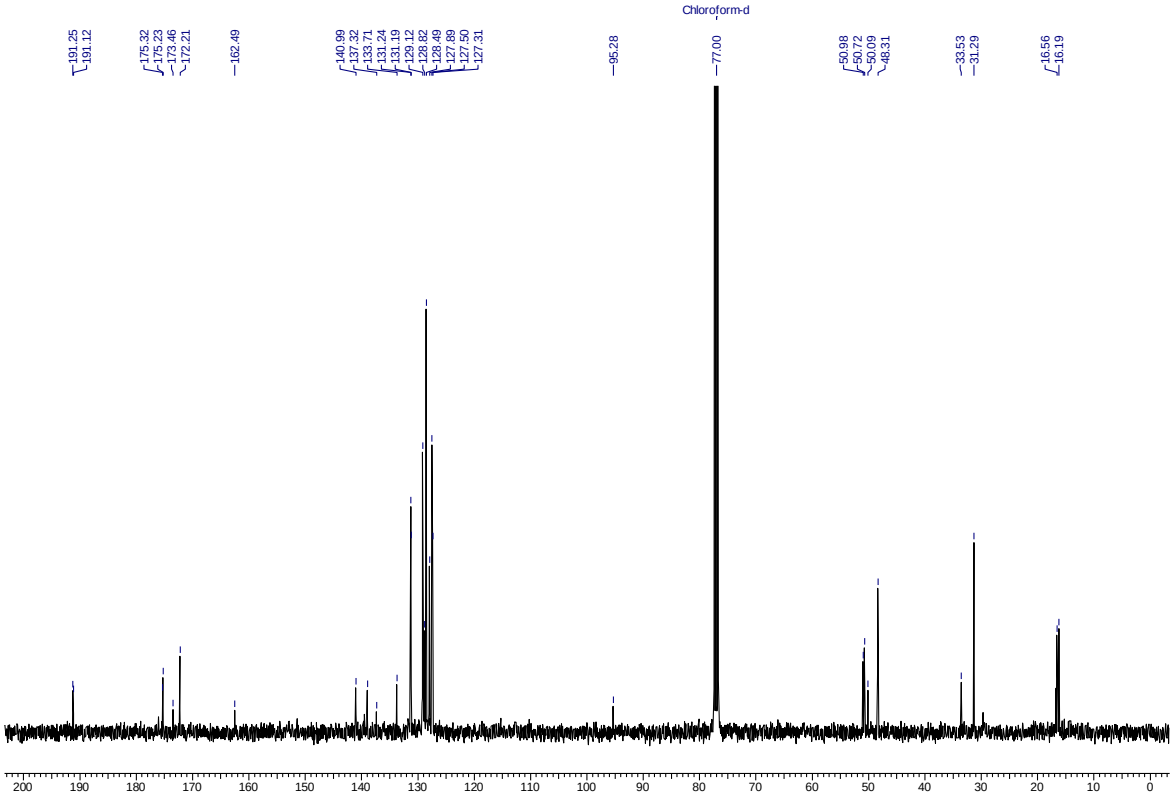

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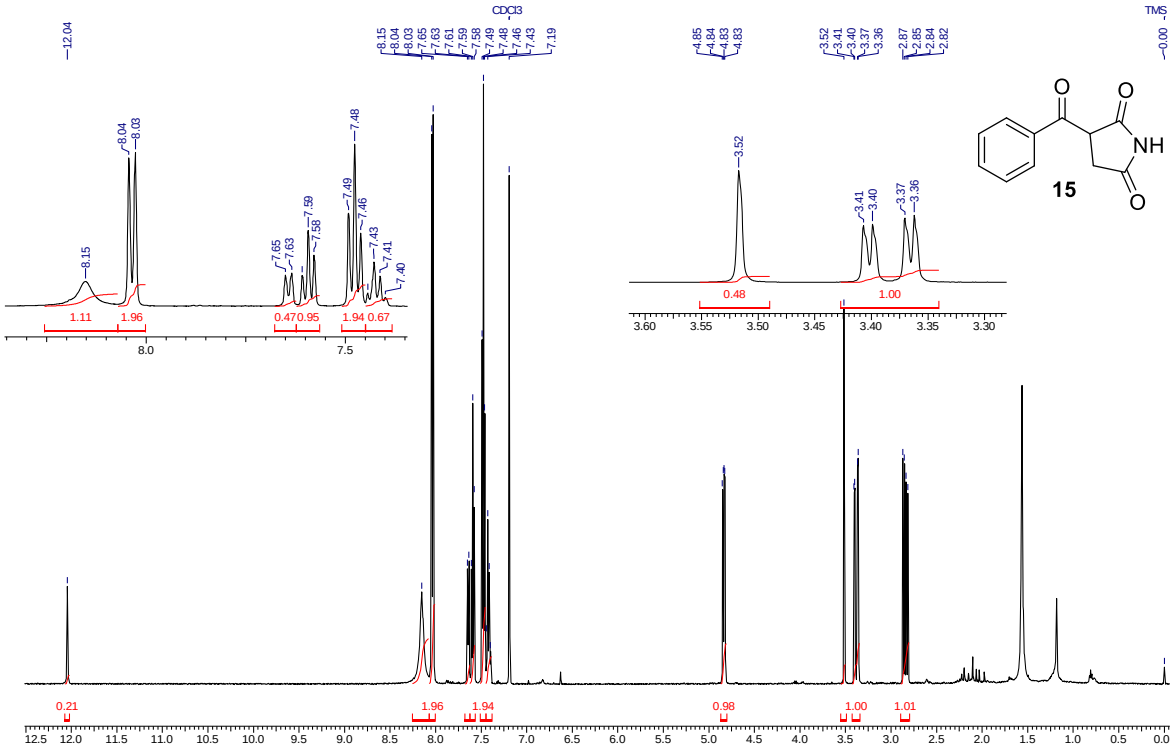

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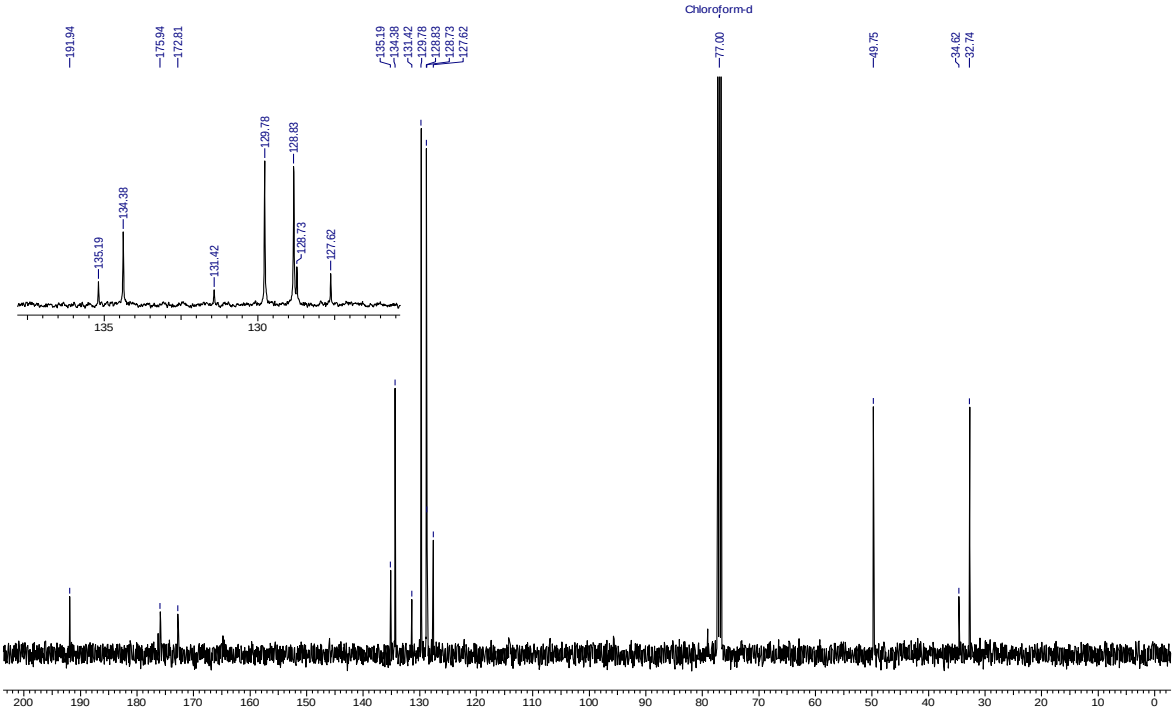

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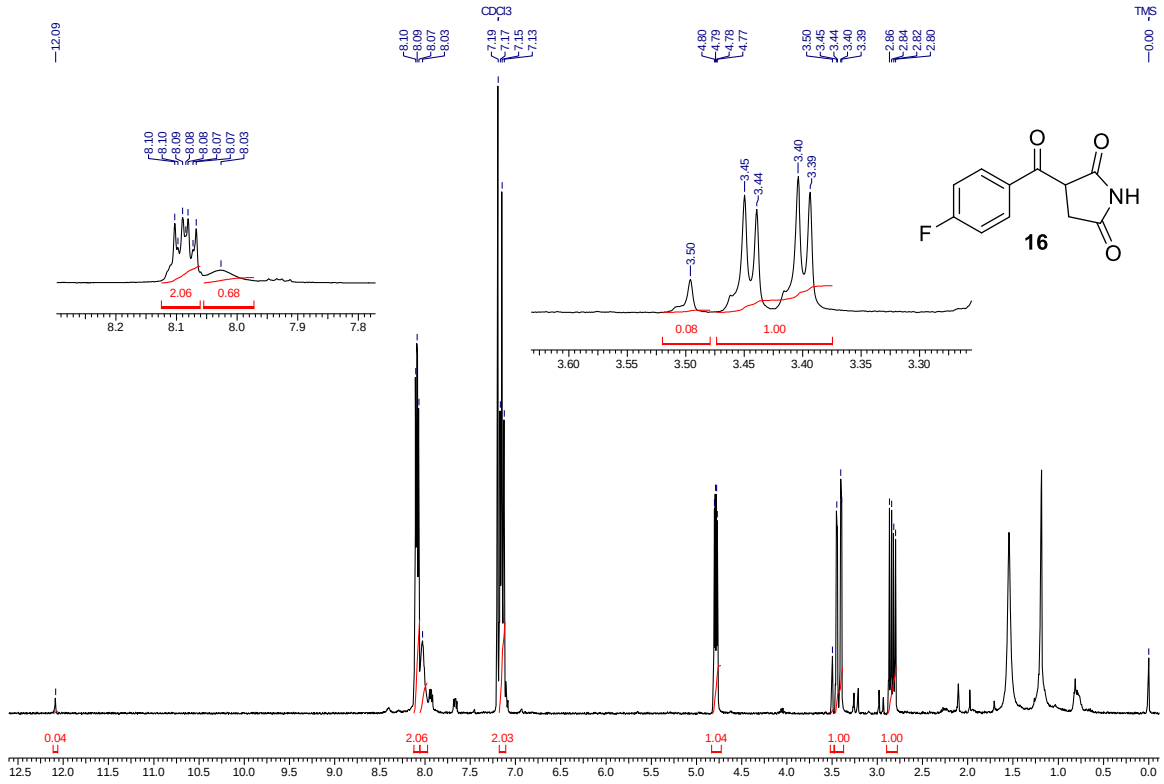

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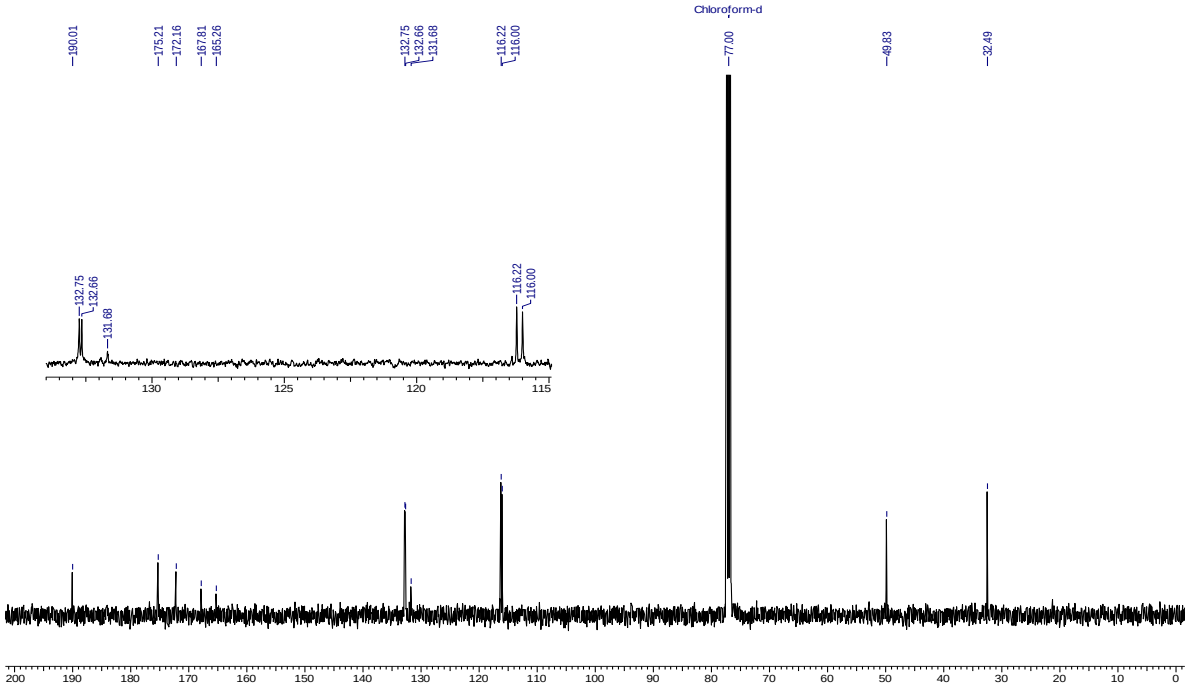

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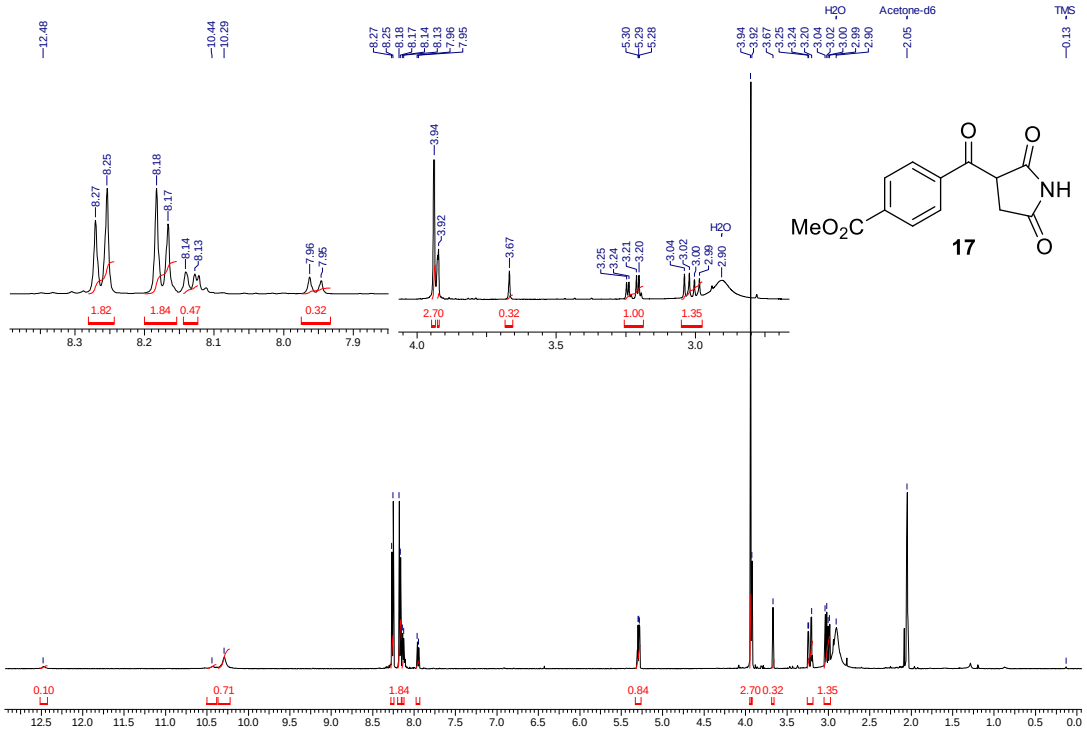

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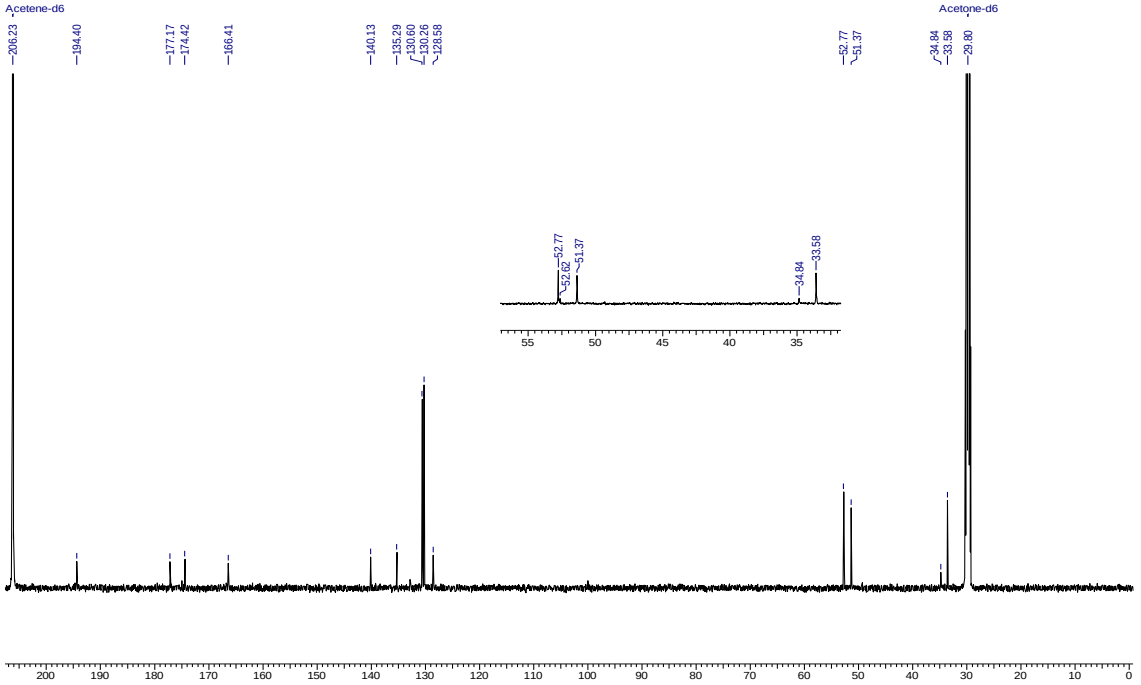

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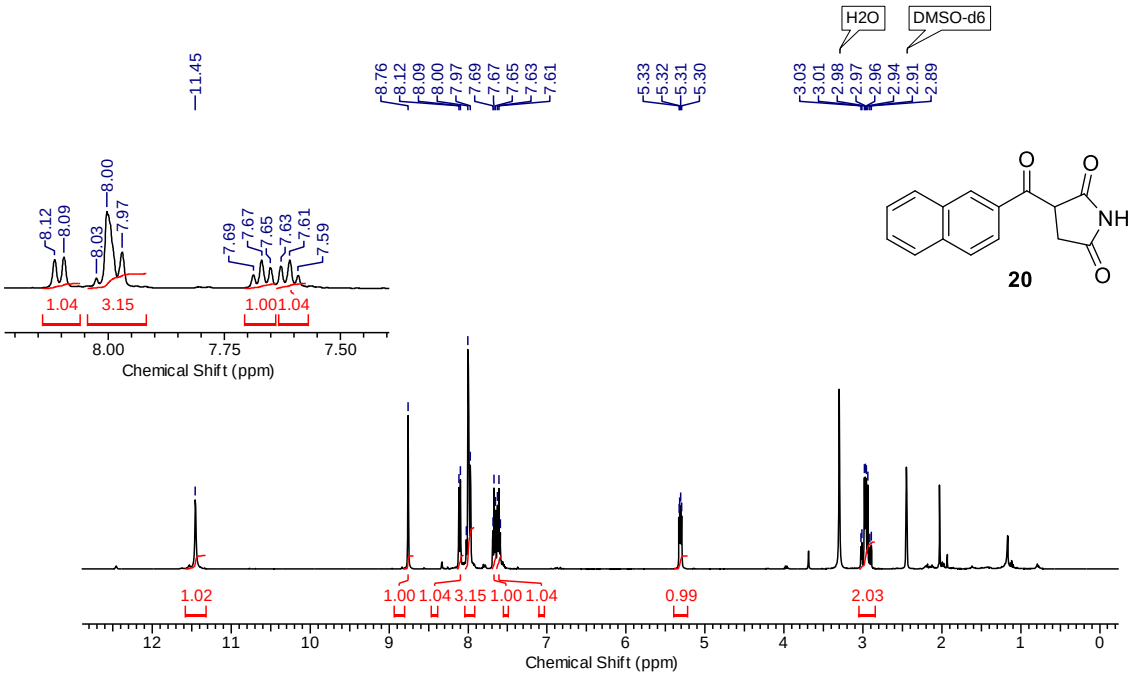

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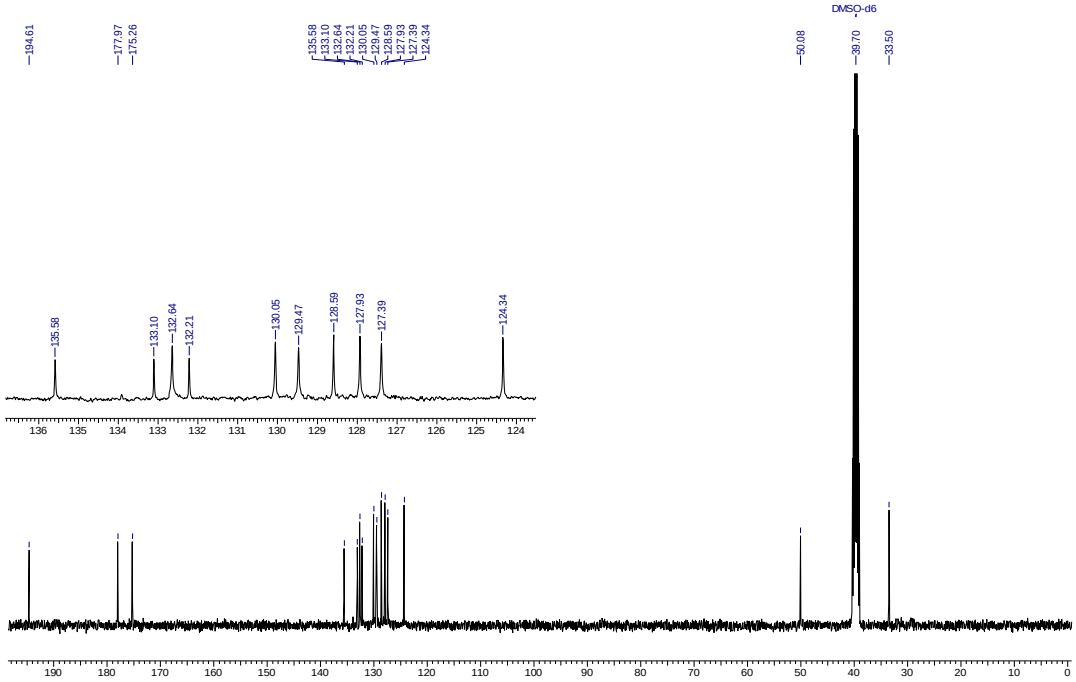


Chapter 2

Studies Towards the Total Synthesis of Cruciferane Using N-Heterocyclic Carbene Catalysis

Section 1: Application of NHC Catalysis in the Synthesis of Natural Products

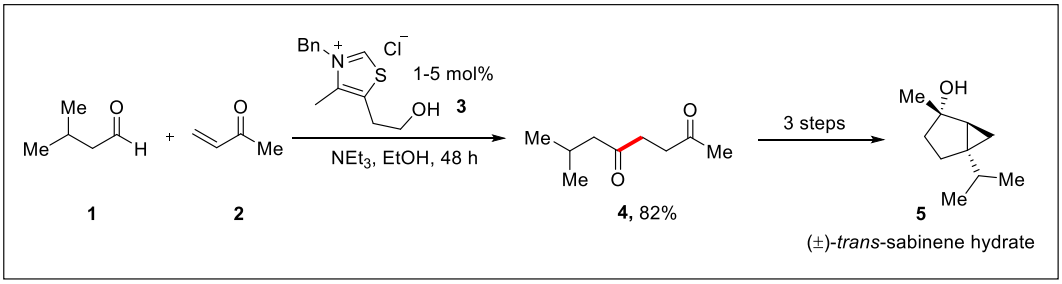
2.1.1. Introduction

The development of novel synthetic methodologies and their successful application in the total synthesis of natural products or bioactive compounds from simple precursors is always a challenging and an interesting task for synthetic organic chemist. N-heterocyclic carbenes are among the most valuable organocatalyst in organic chemistry and ligand in organometallic chemistry.[1] Organocatalysis by N-heterocyclic carbenes displays different types of reaction such as benzoin condensations, homoenolate reactions, Stetter reactions, and nucleophilic catalyst reactions etc. and that can be utilized in the preparation of complex natural products.[2] This section provides an overview of different reactions catalyzed N-heterocyclic carbene for the construction of complex targets.

2.1.2. Synthesis of (±)-*trans*-Sabinene hydrate

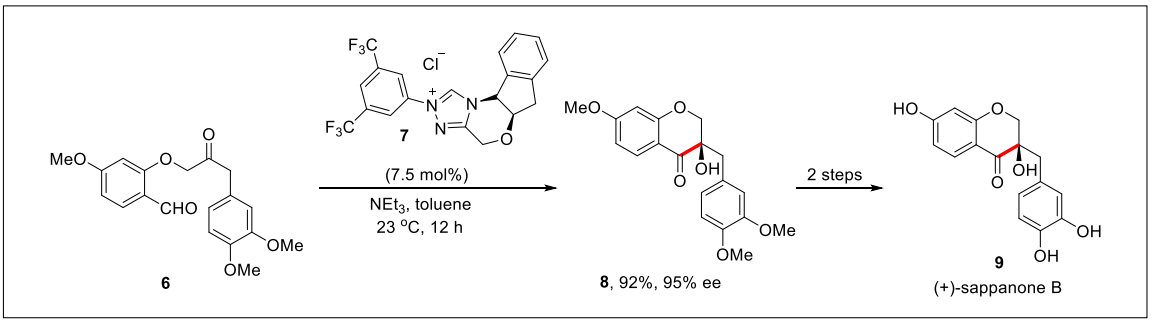
trans-Sabinene (**5**) is a natural product, which is commonly used as flavoring ingredient in a variety of essential oils.[3] In 2001, Galopin reported short and efficient total synthesis of (±)-*trans*-Sabinene hydrate (**5**) using NHC catalyzed intermolecular Stetter reaction.[4] The synthesis of *trans*-Sabinene was initiated with the synthesis of 1,4-dicarbonyl compound **4** using thiazolium salt **3** catalyzed intermolecular Stetter reaction of isovaleraldehyde **2** and methylvinylketone **1**. A sequential three step sequence from 1,4-diketone **4** furnished *trans*-sabinene (**5**) in 28% yield over four steps.

Scheme 1. Synthesis of (±)-*trans*-Sabinene hydrate



2.1.3. Synthesis of (+)-Sappanone B

Scheme 2. Synthesis of (+)-Sappanone B



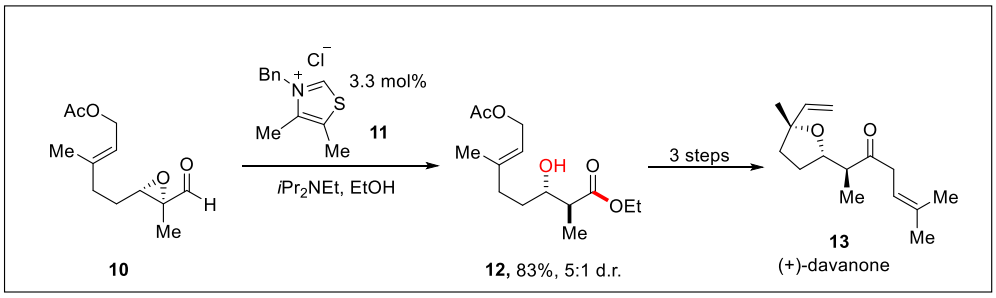
In 2007, Suzuki and group reported asymmetric total synthesis of (+)-sappanone B (**9**).[5] It belongs to homoisoflavonoid family with excellent inhibitory activity towards xanthine oxidase.[6] It was isolated from the heartwood of *Caesalpinia sappan* Leguminosae.[7] The natural product possesses 3-hydroxy cromanone core and this was constructed using chiral N-heterocyclic carbene catalyzed asymmetric intramolecular benzoin condensation as the key step. The substrate keto-aldehyde **6** was synthesized from 3-methoxysalicylic acid in five steps. In the presence of modified Rovis NHC-precatalyst **7** (7.5 mol%) and NEt_3 (7.5 mol%) at room temperature the keto-aldehyde **6** underwent a smooth intramolecular benzoin condensation to form tri-*O*-methyl sappanone B **8** with high yield (92%) and enantioselectivity (95% ee). The

3,5-trifluoromethyl substituted triazolium NHC-precatalyst **7** has important role in enhancing enantioselectivity as well as suppressing background reactions. Further, demethylation of **8** achieved in two steps leads to (+)-sappanone B (**9**) in 59% overall yield.

2.1.4. Synthesis of (+)-Davanone

In 1968, Sipma and Van der Wal isolated (+)-davanone (**13**) from *Artemisia pallens*.[8] Davanone is the major ingredient of davana oil. Davanone is a sesquiterpene which possesses both antifungal and antispasmodic activity.[8] Vosburg and group reported an asymmetric total synthesis of (+)-davanone (**13**) in only seven steps, which involves NHC-catalyzed epoxide ring opening as a key step.[9] The substrate epoxy-aldehyde **10** was synthesized from geranyl acetate in two steps. In the presence of Bode's thiazolium salt **11** (3.3 mol%) and Hunig's base epoxy-aldehyde **10** undergoes epoxide ring opening followed by esterification to form *anti*-hydroxyester **12** in 83% yield and 5:1 diastereomeric ratio. A sequential three steps sequence from *β*-hydroxy ester **12** furnished (+)-davanone (**13**).

Scheme 3. Synthesis of (+)-Davanone

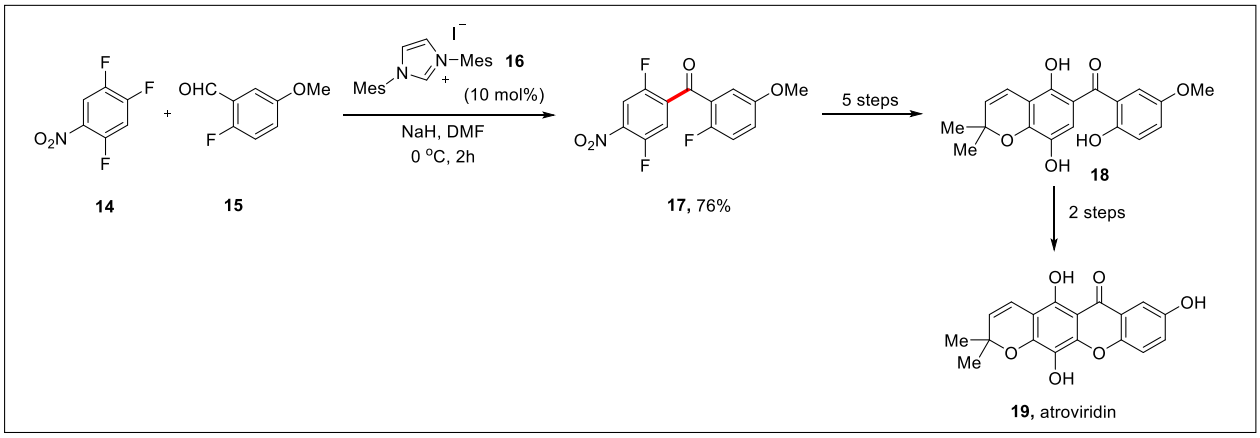


2.1.5. Synthesis of Atroviridin

The first total synthesis of atroviridin (**19**) was reported by Theodorakis and group in 14 steps.[10] In 2011, Suzuki and co-worker demonstrated total synthesis of atroviridin (**19**) natural product in

nine steps with a 14% overall yield using NHC catalyst.[11] Atroviridin is a polyphenolic xanthone isolated from *Garcinia atroviridus* Griff.[12] The synthesis of atroviridin was initiated with the synthesis of ketone **17** from aldehyde **15** and trifluoro nitrobenzene **14** in the presence of NHC-precatalyst **16** (10 mol%) and NaH (1.5 equiv) at room temperature. It involves NHC catalyzed nucleophilic aroylation of fluorobenzene as a key step. A sequential seven steps sequence from ketone **17** furnished atroviridin (**19**).

Scheme 4. Synthesis of Atroviridin

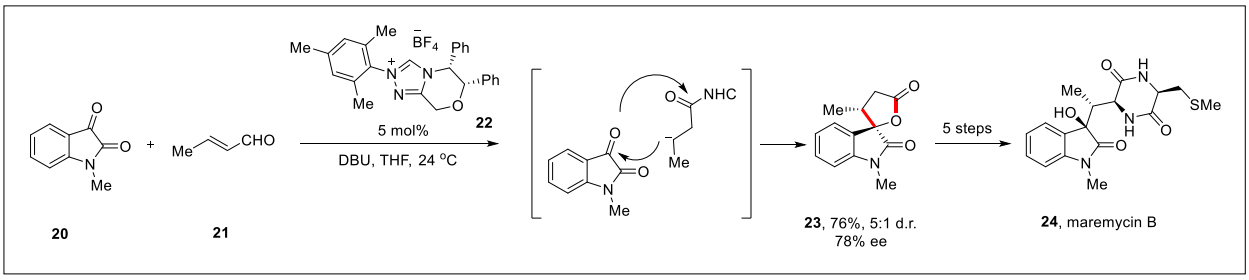


2.1.6. Synthesis of Maremycin B

Maremycin B is a diketopiperazine alkaloid and it has 3-hydroxy-2-oxindole main frame structure. In 1995, Laatsch and group isolated maremycin B (**24**) from the culture broth of Streptomyces species B90173.[14] It has anticancer activity. In 2012, Scheidt and colleague demonstrated protecting group free enantioselective total synthesis of maremycin B (**24**).[13]. The synthesis of maremycin B was initiated with the synthesis of spyro *γ*-butyrolactones **23** via enantioselective formal [3+2] cycloaddition of crotonaldehyde (**21**) to *N*-methylisatin (**20**) catalyzed by chiral NHC-precatalyst **22**. The spyro *γ*-butyrolactones **23** was obtained in 76%

yield with good diastereoselectivity (5:1) and enantioselectivity (78 % ee). The linear 5 step sequence from compound **23** furnished maremycin B (**24**). Maremycin B (**24**) was synthesized in 17% overall yield over six steps.

Scheme 5. Synthesis of Maremycin B



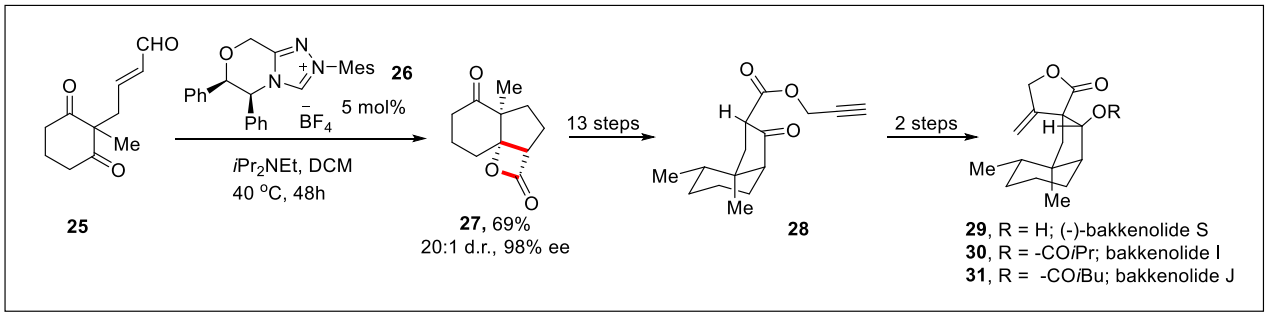
2.1.7. Synthesis of (-)-Bakkenolides I, J, and S

In 2010, Scheidt and co-worker reported NHC catalyzed strategy for the asymmetric synthesis of the bakkenolides (**29-31**) in twenty steps.[15] The bakkenolides (**29-31**) belongs to a large class of sesquiterpenes and has characteristic *cis*-fused 6,5-bicyclic backbone and the spiro γ-butyrolactone.[16] Also, they have five contiguous stereocenters out of which two are quaternary. Bakkenolide have wide variety of activity such as anticancer activity against a tumor cells, antifeedant effects, and inhibit platelet aggregation.[17]

Aldehyde **25** was prepared from cyclohexa 1,3-dione in two step sequence, which involves palladium-catalyzed allylation with vinyl oxirane followed by oxidation. The *cis*-fused 6,5-bicyclic core **27** of bakkenolides was constructed using chiral NHC-catalyzed **26** (5 mol%) via desymmetrization of 1,3-diketones, which generates key quaternary stereocenter of a natural product. Sequential 14-steps sequences from β-lactone **27** furnished (−)-bakkenolide S (**29**).

Further, acylation of **29** with the corresponding acyl chlorides led to the synthesis of bakkenolide I and J in 2% overall yield.

Scheme 6. Synthesis of (-)-Bakkenolides S



2.1.8. Conclusion

In the growing field of organocatalysis N-Heterocyclic carbenes (NHCs) stood out to be the most studied class of catalysts, which attracted immense attention due to their potential applications. This section presented the examples from literature, which consist NHC catalyzed Stetter reactions, benzoin condensations, homoenolate cycloaddition reactions and nucleophilic esterification reactions that can be utilized to deliver complex natural products with step economy. In the future, the NHC-catalyzed reaction will continue to provide new avenues and challenges by exploring new strategies for the synthesis of natural products and privileged bioactive compounds.

2.1.9. Reference

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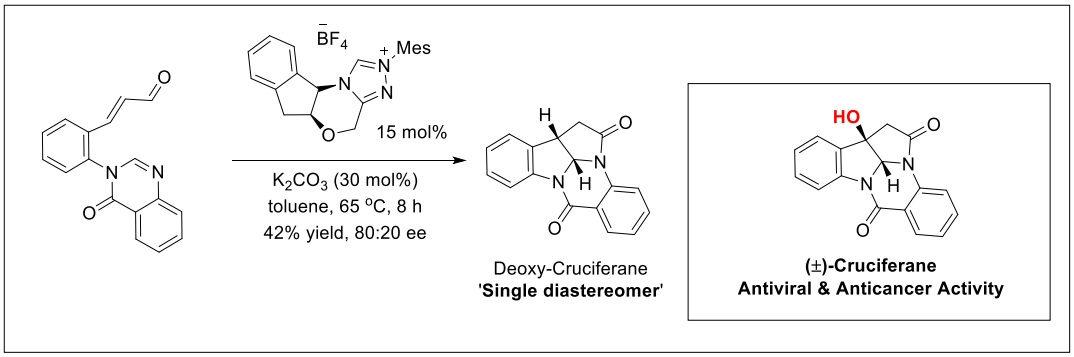
Section 2: N-Heterocyclic Carbene-Catalyzed Intramolecular Stereoselective [3+2] Annulation: Protecting Group-Free Synthesis of Deoxy-Cruciferane

2.2.1. Abstract

Intramolecular asymmetric N-heterocyclic carbene-catalyzed annulation of enals with imine was found out to be the excellent method for the protecting group-free synthesis of deoxy-cruciferane. The synthesis started from simple, commercially available starting material and was accomplished in five steps.



2.2.2 Introduction

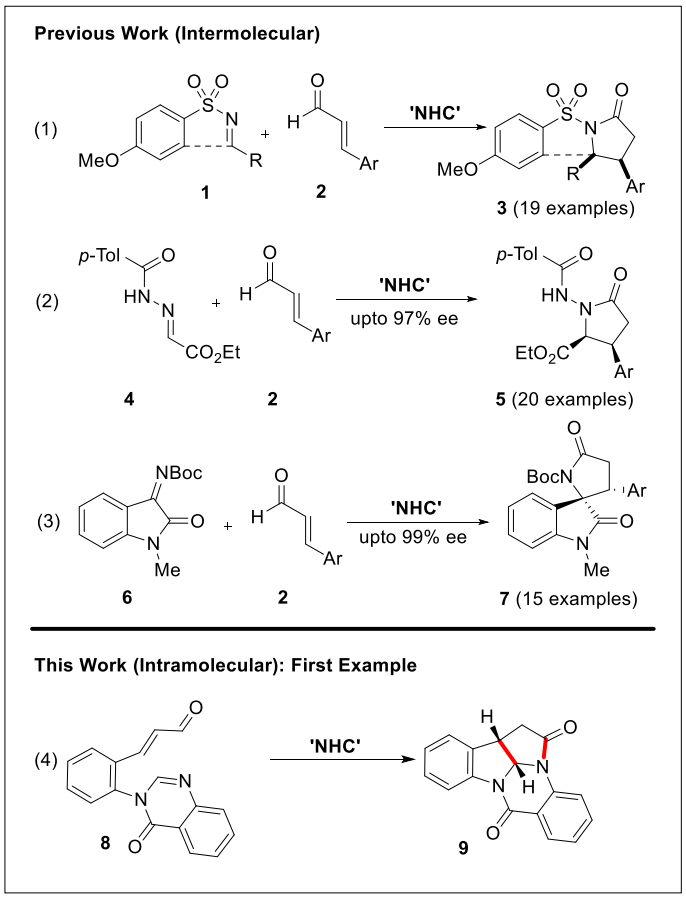
Over the past decade, astonishing development in the area of N-heterocyclic carbene (NHC)-catalyzed transformations showed its important synthetic utility in organic chemistry.[1] NHCs are being employed as organocatalysts, and ligands for p-block elements and transition-metal catalysts.[1,2] Furthermore, organocatalysis by N-heterocyclic carbene provides a platform for the synthesis of pharmaceutically important compounds and natural products.[3] NHCs have the

ability to alter the polarity of aldehyde or enal functionality to access numerous valuable synthetic methodologies via NHC-linked intermediates, such as Breslow intermediates, homoenolates, enolates, acylazoliums, and *α,β*-unsaturated acylazoliums.[1] Particularly, NHC-catalyzed reactions of homoenolate anion intermediates and its intervention with different electrophiles (imines, ketones, aldehydes etc.) through cycloaddition reaction provide access to series of novel cyclic compounds via carbon-carbon or carbon-heteroatom bond formation.[1] NHC−homoenolate pathway for the synthesis of heterocycles is always a challenging but, much desired synthetic transformation.

2.2.3. Literature Review

N-heterocyclic carbene-catalyzed annulation of enals with imines via homoenolate equivalent is a unique strategy for the synthesis of substituted *γ*-lactams. Bode group reported NHC-catalyzed addition of enals to *N*-4-methoxybenzenesulfonyl imines as well as saccharin-derived ketimines (Scheme 1, eq 1).[4a,b] The reaction tolerates various substituents on aromatic enal and imines and provides corresponding products in good to excellent yields. In 2010, Scheidt and co-worker developed highly diastereo- and enantioselective [3+2] cycloaddition reaction of *α,β*-unsaturated aldehydes with hydrazones using co-operative catalysis of NHC and Lewis acid (Scheme 1, eq 2).[4c] Furthermore, Chi group demonstrated the enantioselective construction of spirocyclic oxindole-*γ*-lactams via NHC-catalyzed annulation of isatin *N*-Boc ketimines and unsaturated aldehydes (Scheme 1, eq 3).[4d] All the above-mentioned annulation methods of enals with imines are intermolecular in nature. Interestingly, until now NHC-catalyzed intramolecular annulation is unknown probably because of a difficulty in a preparation of substrates, which consists imine

Scheme 1. N-Heterocyclic Carbene-Catalyzed Cycloaddition of Enal with Imine



and aldehyde functionality in the same molecule. Herein, we report intramolecular NHC-catalyzed [3+2] annulation of enal with the internal imine of quinazolinone (Scheme 1, eq 4), which furnish core structure of cruciferane (**12/13**) natural product stereoselectively.

2.2.4. Origin of the Present Work

Pyrroloindolines are an important class of compounds and a common structural unit for a large number of natural products and pharmacologically important compounds.[5] This family of natural products is an attractive synthetic target for the scientific community due to excellent bioactivities, such as antifungal, antibacterial, antiviral, and analgesic.[6] Figure 1 shows selected examples of pyrroloindoline alkaloids. One among them is (±)-cruciferane alkaloid, which is

pyrroloindoloquinazoline alkaloid and has been isolated from *Phaius mishmensis* and *Isatis tinctoria*.[7] It exhibits potential antiviral and anticancer activity.

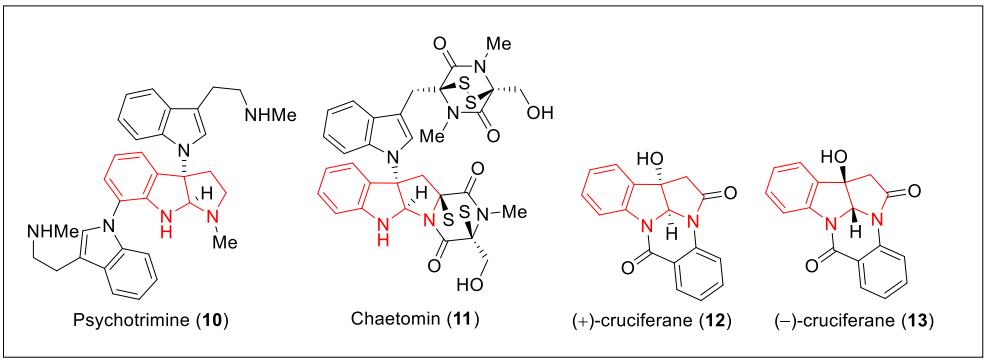
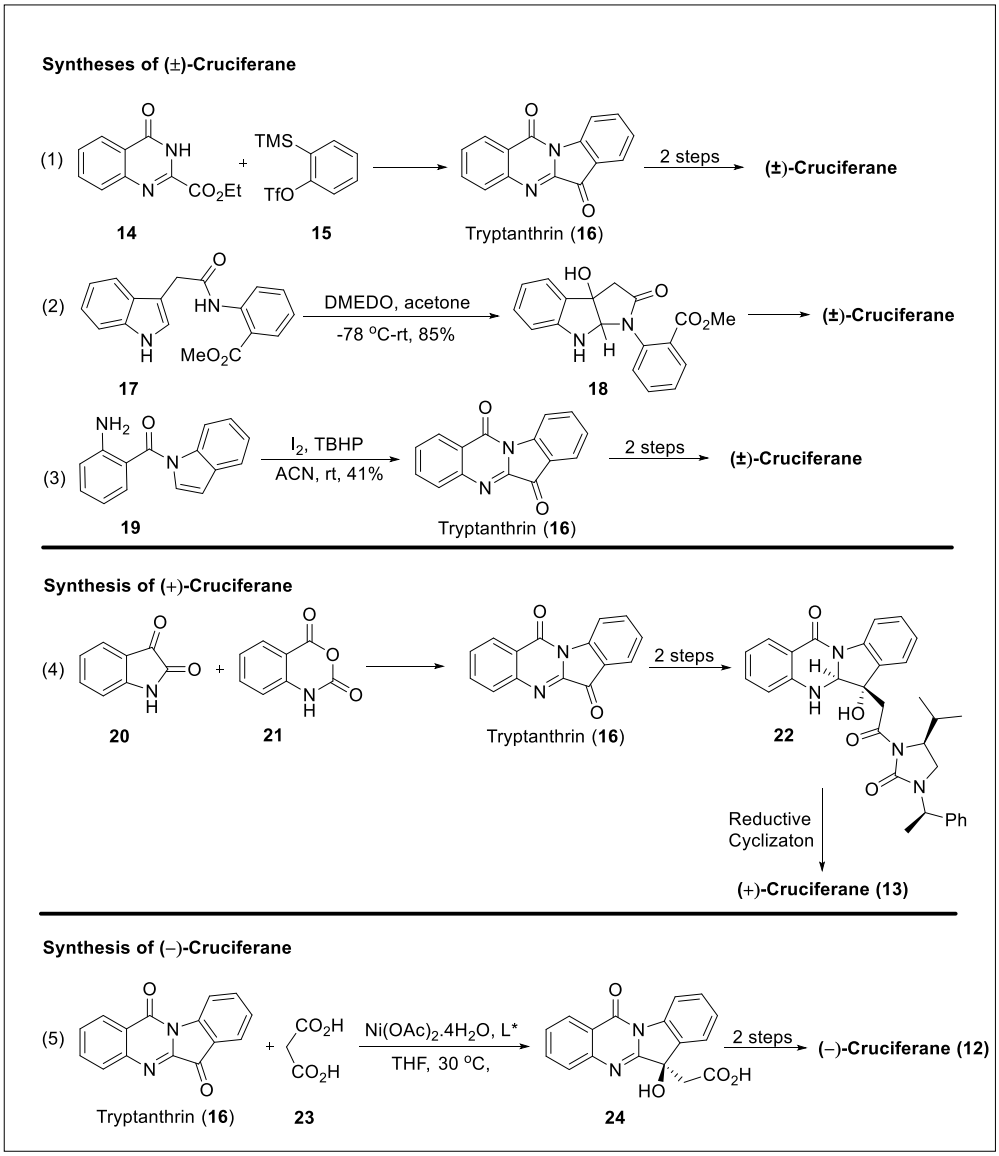


Figure 1. Selected Natural Products Containing Pyrroloindoline Skeleton.

Until now, there have been five reported total syntheses of cruciferane. Notably, most of the synthetic routes for cruciferane involves synthesis of tryptanthrin (**16**). The first total synthesis of (±)-cruciferane was reported by Argade and co-worker in 2013 (Scheme 2, eq 1),[8a] wherein, they have demonstrated an efficient utilization of aryne chemistry to construct tryptanthrin (**16**). A sequential two-step sequence from tryptanthrin (**16**) furnished (±)-cruciferane in 66% yield over four steps. In 2014, Nagarajan et al. demonstrated racemic synthesis of cruciferane, which involves in situ epoxidation of indole **17** followed by cylization with amide to give compound **18** in 85% yield. Further one-step sequence furnished (±)-cruciferane in 60% overall yield (Scheme 2, eq 2).[8b] The formal synthesis of (±)-cruciferane was reported by Ji and co-worker (Scheme 2, eq 3).[8c] They synthesized tryptanthrin (**16**) via intramolecular oxidative amination of indole with anilines in 41% yield. The first asymmetric total synthesis of (+)-cruciferane (**12**) was reported by Nair group, which consist of a chiral auxiliary mediated aldol reaction on tryptanthrin as a key step (Scheme 2, eq 4).[8d] Later, the synthesis of (−)-cruciferane (**13**) was demonstrated by

Jiang and co-worker, which involve a nickel(II) catalyzed enantioselective synthesis of *β*-hydroxy acids from malonic acid and tryptanthrin (**16**) as a key strategy (Scheme 2, eq 5).[8e]

Scheme 2. Previous Syntheses of Cruciferane

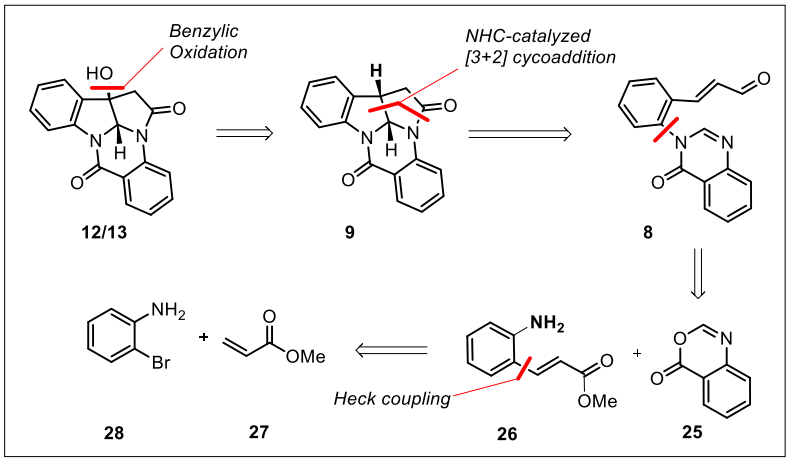


2.2.5. Objective

The scheme 3 illustrates a retrosynthetic analysis of cruciferane alkaloid **13**, wherein, we envisioned convergent construction of **13** through benzylic oxidation of **9**. The chirality in

compound **9** was envisioned via chiral N-heterocyclic carbene-catalyzed intramolecular [3+2] cycloaddition of imine and homoenolate equivalent of unsaturated aldehyde. The unsaturated aldehyde **8** was expected to be constructed from compound **25** and **26**. The unsaturated *o*-amino methyl cinnamate (**26**) could be accessible from the commercially available *o*-bromoaniline (**28**) and methyl acrylate (**27**) by Heck coupling reaction.

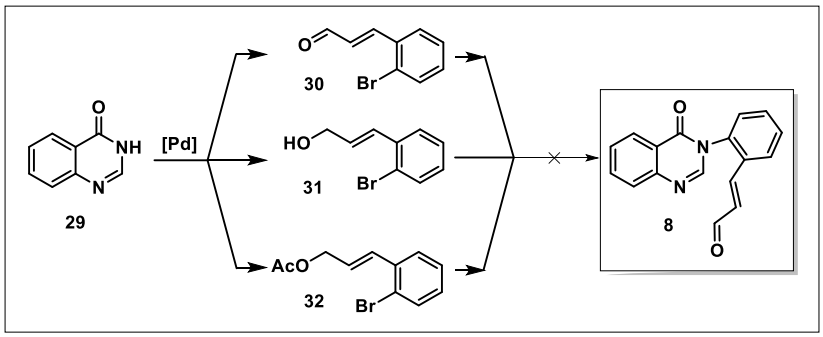
Scheme 3. Retrosynthetic Analysis of Cruciferane



2.2.6. Results and Discussion

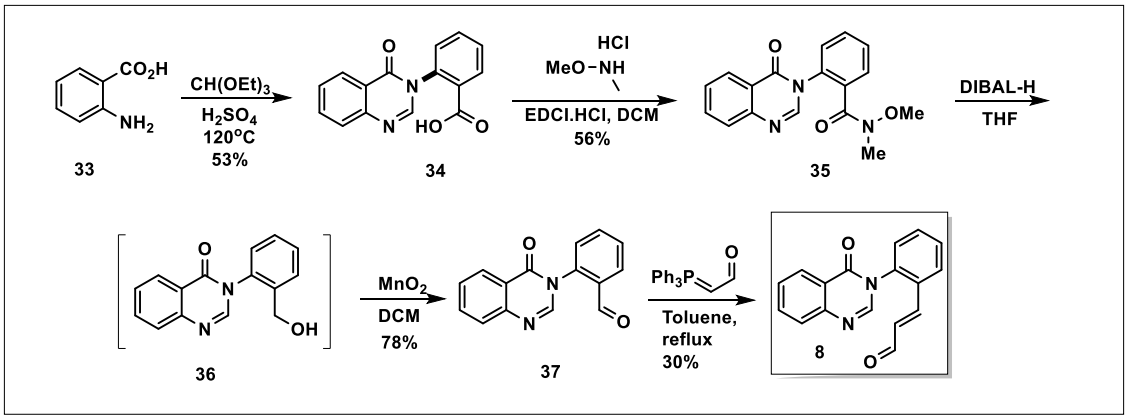
Our investigation began with the synthesis of key intermediate **8**. Initial efforts for the synthesis of compound **8** involved the palladium-catalyzed coupling of quinazolinone (**29**) with unsaturated bromoarenes, such as *o*-bromocinnamaldehyde (**30**), *o*-bromocinnamylalcohol (**31**), and protected bromocinnamylalcohol (**32**) (Scheme 4). Despite of many attempts, the desired coupled product **8** could not be observed and we always ended up in decomposition or recovery of starting materials.

Scheme 4. Synthesis of Compound 8 via Palladiu-Catalyzed Coupling



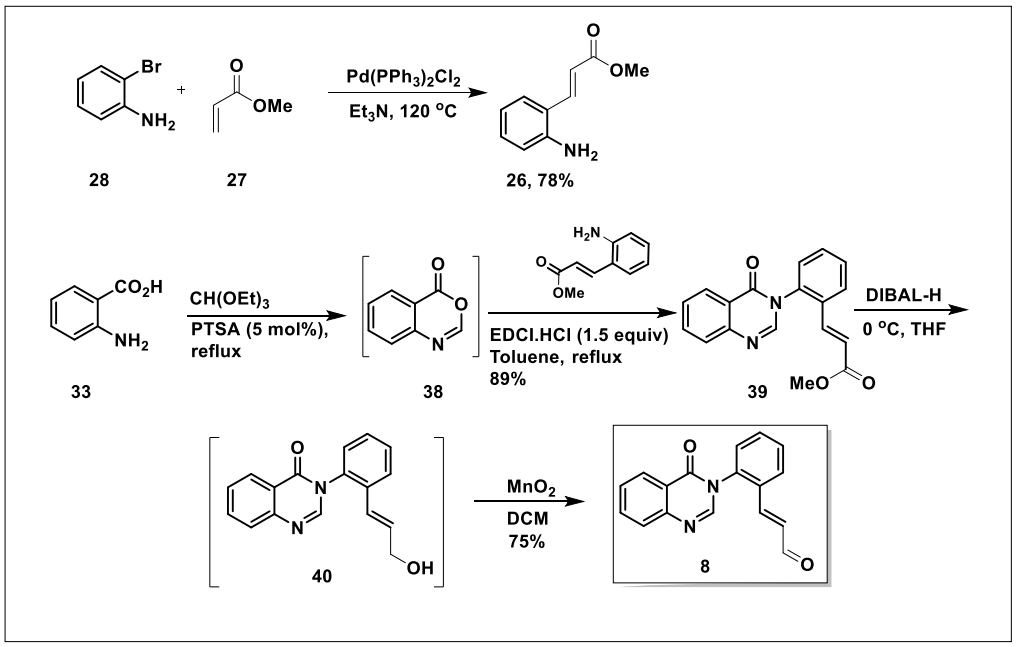
The initial failure led us to reconsider our strategy for the synthesis of **8**. The revised synthesis of compound **8** is shown in Scheme 5. Treatment of anthranilic acid (**33**) with triethyl orthoformate

Scheme 5. Synthesis of Compound 8



in the presence of catalytic amount of H_2SO_4 gave **34** in 53% yield.[9] The acid **34** was converted to the Weinreb amide **35** using EDCI and *N*-methoxymethanamine at room temperature in 56% yield. Reduction of **35** with DIBAL-H in THF at −78 °C gave compound **36** along with unknown compounds. The crude product was combinedly subjected to the oxidative condition in the presence of activated MnO_2 to provide compound **37** in 78% yield. Since the corresponding aldehyde **37** was unstable, it was used for the Wittig reaction without further purification

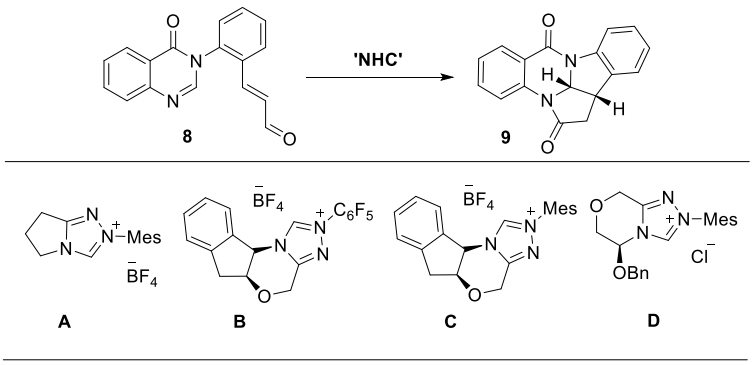
Scheme 6. Modified Synthesis of Compound 8



, which gave the desired compound **8** in 30% yield. Due to the instability of aldehyde **37**, we faced the problem with the reproducibility of Wittig reaction. Therefore, we reconsidered our synthetic strategy for compound **8**.

Another synthetic route for compound **8** is depicted in Scheme 6. Treatment of anthranilic acid **33** with triethyl orthoformate in the presence of catalytic amount of PTSA gave benzoxazine (**38**).[10] Without further purification of benzoxazine (**38**), it was reacted with *o*-amino methylcinnamate (**26**) in the presence of EDCI in toluene to give quinazolinone ester **39** in 89% yield. The *o*-amino methylcinnamate (**26)** was synthesized using the Heck coupling reaction of *o*-bromoaniline (**28**) and methyl acrylate (**27**).[11] Quinazolinone ester **39** was reduced using DIBAL-H in DCM at 0 °C to furnish compound **40** along with unknown compounds. Further, the crude product was combinedly subjected to the oxidative condition in the presence of activated MnO_2 to give aldehyde **8** in 75% yield.

Table 1. Optimization Studies



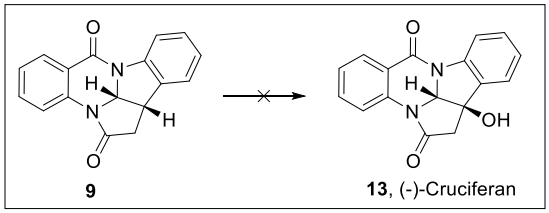
Entry	NHC	Base	Solvent	Temp (^{o}C)	Yield (%)	er
1	C	K_2CO_3	DCE	rt	10	70:30
2	C	K_2CO_3	DCM	rt	<2	ND
3	C	K_2CO_3	DMSO	rt/60	NR	ND
4	C	K_2CO_3	DMF	rt/60	NR	ND
5	C	K_2CO_3	toluene	rt	NR	ND
6	**C**	**K_2CO_3**	**toluene**	**60 ^{o}C**	**42**	**80:20**
7	C	K_2CO_3	benzene	60 ^{o}C	35	75:25
8	A	K_2CO_3	toluene	60 ^{o}C	<2	ND
9	B	K_2CO_3	toluene	60 ^{o}C	NR	ND
10	D	K_2CO_3	toluene	60 ^{o}C	13	71:29

NR = No reaction, ND = Not determined.

With the key intermediate **8** in hand, we initiated optimization of cyclization protocol. Our first effort for the [3+2] annulation reaction began by treating aldehyde **8** in the presence of 20 mol% chiral triazolium-derived pre-NHC catalyst **C** and 30 mol% of K_2CO_3 in 1,2-dichloroethane (DCE) at room temperature. The reaction led to the expected cyclized product **9** though in 10% yield (Table 1, entry 1). To obtain optimized cyclization condition we screened different pre-NHC catalyst, temperature, and solvents. First, we studied the effect of solvents on cyclization reaction. Accordingly, we screened different solvents such as DCE, DCM, DMSO, DMF, toluene, benzene, wherein toluene was found to be the best solvent for this transformation (Table

1, entry 2 to 7). Screening of different NHC-precatalyst **A**, **B**, and **D** concluded that the NHC catalyst **C** is the best catalyst for this transformation (Table 1, entry 8 to 10), with 80:20 enantioselectivity (HPLC). Herein, we observed a single diastereoisomer formation as confirmed by ^{1}H-NMR analysis.

Scheme 7. Oxidation of 9 to (−)-Cruciferane



With the compound **9** in hand, we also tried oxidation to achieve the total synthesis of (−)-cruciferane (Scheme 7). However, when the compound **9** was employed to various oxidative conditions using organic and inorganic oxidizing reagents, it always led to decomposition or recovery of starting material. The absolute configuration of **9** was unambiguously assigned on the basis of X-ray crystallographic analysis (Figure 2).

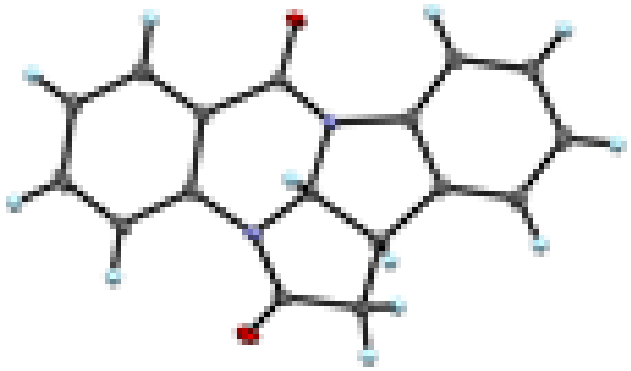


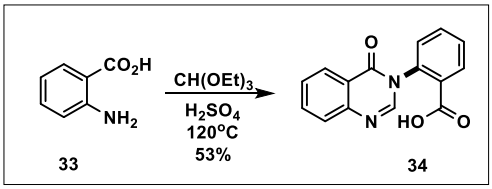
Figure 2. X-Ray Crystal Structure of **9**

2.2.7. Conclusion

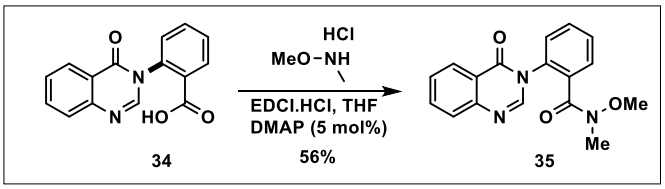
In summary, protecting group-free synthesis of deoxy-cruciferane has been achieved. The key-step was an intramolecular N-heterocyclic carbene-catalyzed [3+2] cycloaddition of enal with imine and enantioselectivity was achieved through chiral NHC. The developed protocol provides single diastereomer of cyclized product. Also, the utility of the protocol can be demonstrated by accessing libraries of a deoxy-cruciferane by fine-tuning N-heterocyclic carbene-catalyst.

2.2.8. Experimental Procedures and Characterization Data of Compounds

2-(4-oxoquinazolin-3(4H)-yl)benzoic acid (34): Compound **34** was prepared according to literature procedure.[9]



N-methoxy-N-methyl-2-(4-oxoquinazolin-3(4H)-yl)benzamide (35).



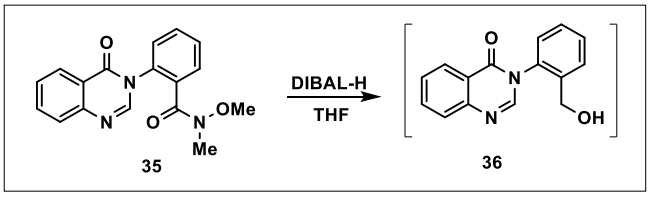
To a stirred solution of the *N*-methoxymethanamine (150 mg, 1.5 mmol, 1 equiv) and DMAP (9 mg, 0.075 mmol, 5 mol%) in THF (2.5 mL) was added the acid (**34**) (400 mg, 1.5 mmol, 1 equiv) in one portion, followed by the addition of EDCI.HCl (217 g, 1.133 mol) in one portion at room temperature. The resulting mixture was stirred at room temperature overnight, after

completion of reaction it was washed successively with 10% aq citric acid, H_2O, saturated aqueous Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4 and concentrated in *vacuo*, followed by purification by column chromatography (petrolium ether:ethyl acetate = 3:2) to provide the product **35** in 56% yield.

Reaction Time: 12 h; R*f*: 0.7 (3:2, Pet. Ether:EtOAc); thick oil; 260 mg, 56% yield. **IR** (Nujol)

ν max = 2923, 2857, 1668, 1458 cm^{-1} ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.9 Hz, 1H), 8.02 (s, 1H), 7.78-7.64 (m, 2H), 7.63-7.40 (m, 4H), 7.33 (d, J = 7.9 Hz, 1H), 3.44 (s, 3H), 3.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 147.9, 146.4, 135.3,134.5, 131.0, 128.9, 128.5, 127.7, 127.4, 126.9, 122.2, 61.3, 32.6; **ESI HRMS**: calcd for $C_{17}H_{15}O_3N_3$ $[M + H]^+$: 310.1186, found: 310.1186.

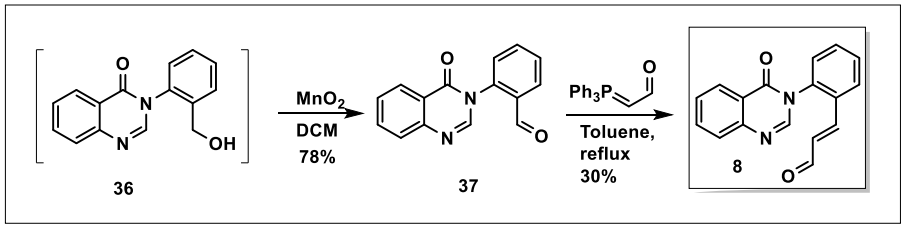
3-(2-(hydroxymethyl)phenyl)quinazolin-4(3H)-one (36).



To a solution of quinazolinone ester **35** (1.3 mmol, 400 mg, 1.0 equiv) in anhydrous THF (10 mL) in a flame-dried two neck round bottom flask was added DIBAL-H (1.0 M in THF, 3.9 mmol, 3.0 equiv) at -78 ºC under argon atmosphere. The resultant mixture was stirred at -78 ºC for 12 h under argon atmosphere before quenched with saturated Rochelle salt aqueous solution (2 mL). The aqueous phase was extracted with DCM (10 mL × 5). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered through a thin plug of celite, and

concentrated under reduced pressure. The crude product was used for next step without further purification.

(E)-3-(2-(4-oxoquinazolin-3(4H)-yl)phenyl)acrylaldehyde (8).

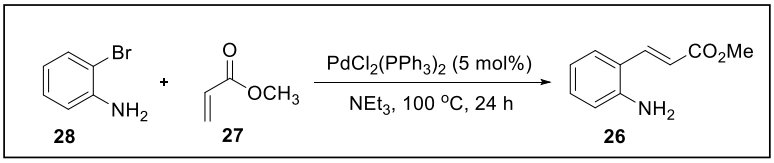


The alcohol **36** (252 mg, 1.0 mmol, 1 equiv) was dissolved in DCM (7 mL). MnO_2 (869 mg, 10 mmol, 10.0 equiv.) was added. The mixture was stirred at room temperature overnight. After completion of reaction MnO_2 was removed by filtration. The combined organic layer was concentrated. Due to instability of the aldehyde **37**, the crude product was used without further purification in next step. The (triphenylphosphoranylidene)acetaldehyde (456 mg, 1.5 mmol, 1.5 equiv) was added to an aldehyde (**37**) solution in toluene and refluxed it for 8 h. After completion, the mixture was cooled to room temperature, then H_2O (2 mL) was added and the mixture was extracted with EtOAc, dried by anhydrous Na_2SO_4. Evaporation of the solvent under *vacuo* to dryness followed by purification by column chromatography (petrolium ether:ethyl acetate = 1:1) gave the quinazoline aldehyde (**8)** in 83 mg (30% yield).

Reaction Time: 12 h; R*f*: 0.5 (3:2, Pet. Ether:EtOAc); White solid; 206 mg, 75% yield. **IR** (Nujol) ν_{max} = 2923, 1677, 1601, 1568, +1459 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.48 (d, *J* = 7.3 Hz, 1H), 8.32 (d, 7.9 Hz, 1H), 7.95 (s, 1H), 7.87-7.72 (m, 3H), 7.63-7.49 (m, 3H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.1, 160.7, 148.0,

142.7, 145.4, 136.7, 135.1, 132.3, 132.1, 131.4, 130.3, 129.0, 128.1, 127.9, 127.9, 127.3, 122.0 ; **ESI HRMS**: calcd for $C_{17}H_{12}O_2N_2$ [M + H]+: 277.0972, found: 277.0971.

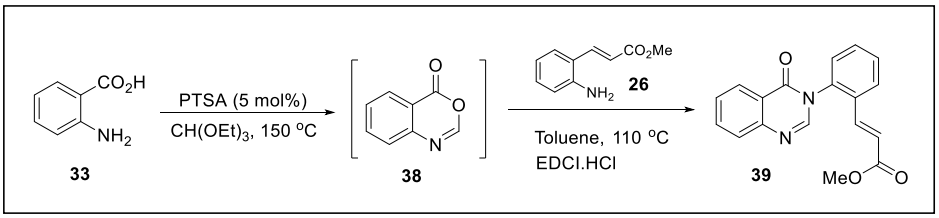
Methyl (E)-3-(2-aminophenyl)acrylate (26).[11]



A sealed tube was charged with *ortho*-bromo aniline (**28**) (2 g, 11.6 mmol, 1 equiv) and $PdCl_2(PPh_3)_2$ (410 mg, 5 mol %). Then methyl acrylate (**27**) (1.3 mL, 13.9 mmol, 1.2 equiv) and Et_3N (20 mL) were added, and flushed twice with argon gas. The tube was sealed with a screw cap and placed in a preheated oil bath at 100 ^oC for 24 h. After completion, the mixture was cooled to room temperature, then H_2O (60 mL) was added and the mixture was extracted with EtOAc, dried by anhydrous Na_2SO_4. Evaporation of the solvent under *vacuo* to dryness followed by purification by column chromatography (petrolium ether:ethyl acetate = 4:1) gave the *o*-amino methylcinnamate (**26)** in 1.6 g (78% yield).

Reaction Time: 24 h; R*f*: 0.5 (4:1, Pet. Ether:EtOAc); yellow solid; Mp = 58-60 ^oC; 1.6 g, 78% yield. **IR** (Nujol) ν_{max} = 3414, 3343, 3005, 2856, 1701, 1615, 1455 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 15.8 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 3.91 (s, 2H), 3.72 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ ; 167.7, 145.5, 140.3, 131.3, 128.0, 119.8, 118.9, 117.6, 113.7, 51.6.

Methyl (E)-3-(2-(4-oxoquinazolin-3(4H)-yl)phenyl)acrylate (39).[10] [modified procedure]

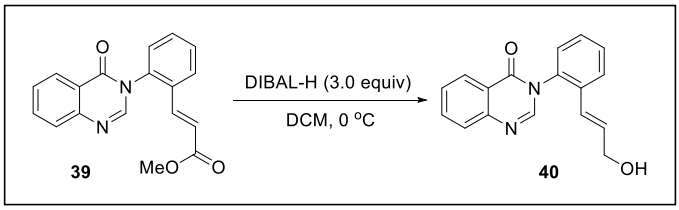


Triethyl orthoformate (8.1 g, 9 mL, 54 mmol, 15 equiv) was added to a mixture of anthranilic acid (**33**) (500 mg, 3.6 mmol, 1 equiv) and *p*-toluenesulfonic acid (30 mg, 0.18 mmol, 0.05 equiv) at room temperature. The reaction mixture was refluxed at 150 ^{o}C for 3 hours. After completion of the reaction triethyl orthoformate was evaporated under *vacuo*. The obtained pale yellow solid (**38**) in the presence of EDCI (690 mg, 3.6 mmol, 1 equiv) and *o*-amino methylcinnamate (**26**) (397 mg, 2.7 mmol, 0.75 equiv) was dissolved in 5 mL of toluene and the resulted solution was refluxed for 8 hours. After completion, the mixture was cooled to room temperature; the solution was poured into 15 mL of distilled water and extracted with EtOAc (3 x 15 mL). The organic phase was washed successively with water, brine solution and then dried over Na_2SO_4. The combined organic layer was concentrated. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (3:2) to afford quinazolinone ester **39** (610 mg, 89%) as a white solid

Reaction Time: 11 h; R*f*: 0.4 (3:2, Pet. Ether:EtOAc); white solid; Mp = 122-123 ^{o}C; 610 mg, 89% yield. **IR** (Nujol) ν_{max} = 3032, 1715, 1633, 1599, 1459 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.30 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.91 (s, 1H), 7.80-7.71 (m, 3H), 7.54-7.46 (m, 3H), 7.38 (d, *J* = 16.0 Hz, 1H), 7.31-7.24 (m, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 3.63 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.4, 160.7, 148.0, 145.8, 138.2, 136.6, 134.9, 132.6, 131.3, 130.1, 128.9, 127.9,

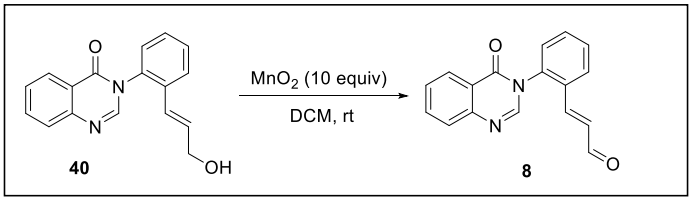
127.8, 127.7, 127.3, 122.2, 121.7, 51.6; **ESI HRMS**: calcd for $C_{18}H_{14}N_2O_3$ [M + H]+: 307.1077, found: 307.1079.

(E)-3-(2-(3-hydroxyprop-1-en-1-yl)phenyl)quinazolin-4(3H)-one (40).



To a solution of quinazolinone ester **39** (1.6 mmol, 500 mg, 1.0 equiv) in anhydrous DCM (10 mL) in a flame-dried two neck round bottom flask was added DIBAL-H (1.0 M in THF, 4.8 mmol, 3.0 equiv) at 0 ºC under argon atmosphere. The resultant mixture was stirred at 0 ºC for 6 h under argon atmosphere before quenched with saturated Rochelle salt aqueous solution (2 mL). The aqueous phase was extracted with DCM (10 mL × 5). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered through a thin plug of celite, and concentrated under reduced pressure. The crude product was used for next step without further purification.

(E)-3-(2-(4-oxoquinazolin-3(4H)-yl)phenyl)acrylaldehyde (8).

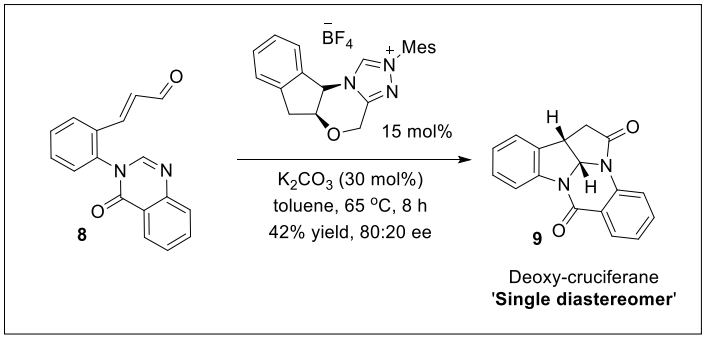


The alcohol **40** (278 mg, 1.0 mmol, 1 equiv) was dissolved in DCM (7 mL). MnO_2 (869 mg, 10 mmol, 10.0 equiv.) was added. The mixture was stirred at room temperature overnight. After completion of reaction MnO_2 was removed by filtration. The combined organic layer was

concentrated. The crude product was purified by flash column chromatography using petroleum ether:ethyl acetate (1:1) to afford quinazolinone-aldehyde **8** (206 mg, 75%) as a white solid.

Reaction Time: 12 h; R*f*: 0.5 (3:2, Pet. Ether:EtOAc); White solid; 206 mg, 75% yield. **IR** (Nujol) ν_{max} = 2923, 1677, 1601, 1568, 1459 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.48 (d, *J* = 7.3 Hz, 1H), 8.32 (d, 7.9 Hz, 1H), 7.95 (s, 1H), 7.87-7.72 (m, 3H), 7.63-7.49 (m, 3H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.1, 160.7, 148.0, 142.7, 145.4, 136.7, 135.1, 132.3, 132.1, 131.4, 130.3, 129.0, 128.1, 127.9, 127.9, 127.3, 122.0 ; **ESI HRMS**: calcd for $C_{17}H_{12}O_2N_2$ [M + H]+: 277.0972, found: 277.0971.

2a[1], 11b-dihydro-7H-2a,7a-diazabenzo[b]cyclopenta[lm]fluorene-2,7(1H)-dione (9).



A reaction mixture containing K_2CO_3 (30 mol%), NHC-precatalyst **C** (15 mol %), and aldehyde **8** (50 mg, 1.0 equiv) in toluene (2 mL) under argon atmosphere was stirred by a magnetic stirring bar at 65 °C for 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude reaction mixture was cooled to room temperature and filtered through a bed of celite. The residue as washed with ethyl acetate (5 mL × 3) and the combined filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a solvent gradient of petroleum ether:ethyl acetate (3:2) to furnish the desired product **9** in 42% yield.

Reaction Time: 4 h; R*f*: 0.5 (3:2, Pet. Ether:EtOAc); White solid; 21 mg, 40% yield. **IR** (Nujol) ν_{max} = 2922, 1671, 1568, 1474 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.25 (d, *J* =8.3 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 5.94 (d, *J* = 8.3 Hz, 1H), 4.18-4.05 (m, 1H), 3.23 (dd, *J* = 18.8, 11.2 Hz, 1H), 2.62 (dd, *J* = 18.8, 5.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.8, 159.7, 141.3, 136.2, 133.6, 132.23, 129.3, 129.0, 126.3, 124.9, 124.9, 123.6, 121.7, 115.8, 76.7, 37.9, 36.1; **ESI HRMS**: calcd for $C_{17}H_{12}O_2N_2$ [M + H]+: 277.0972, found: 277.0970. **HPLC**: Chiralpak IC, n-hexane/IPA = 70:30, 1.0 mL/min, λ = 220 nm, t_R (major) = 25.257 min, t_R (minor) = 28.610 min (80:20 er)

2.2.9. Reference

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2.2.10. Spectra

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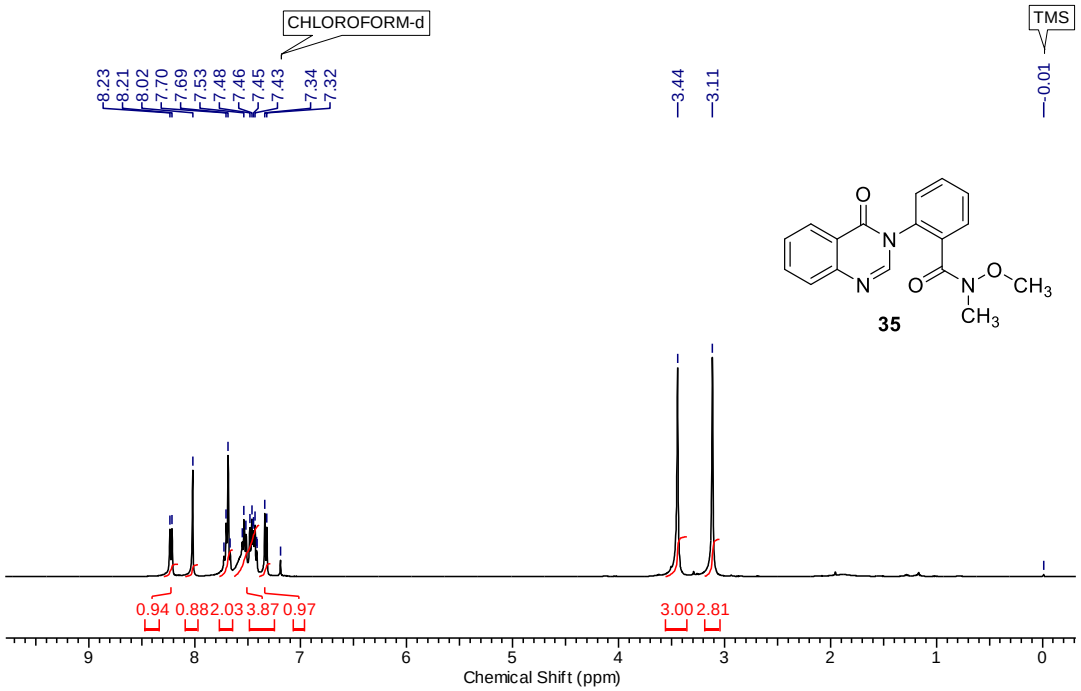

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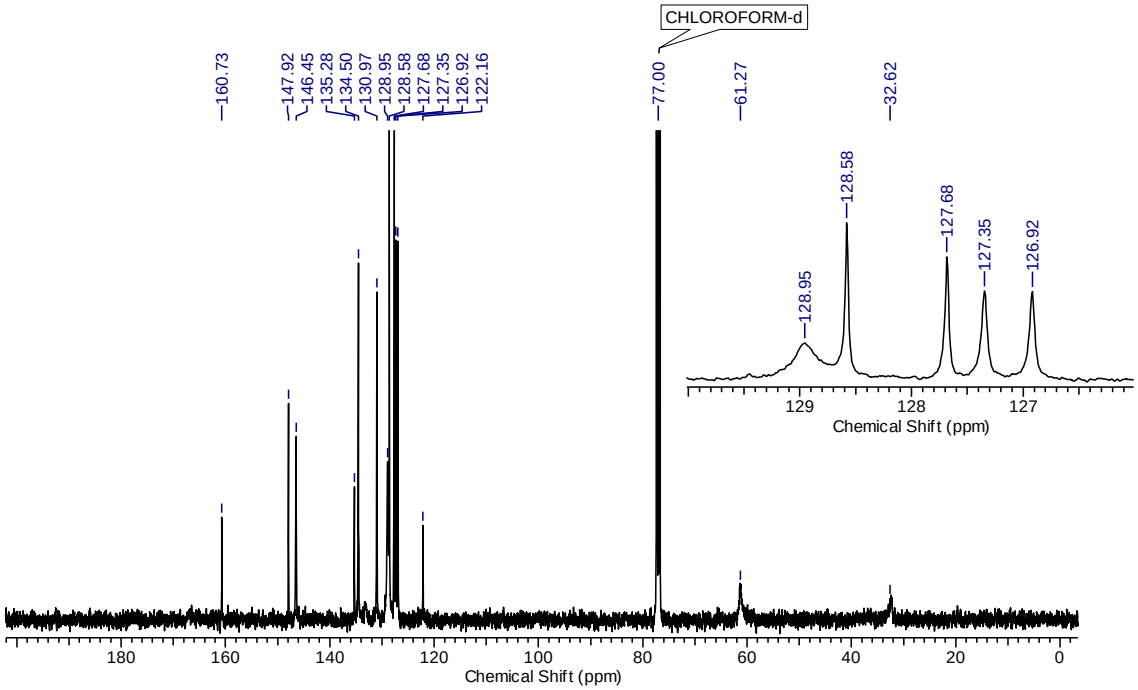

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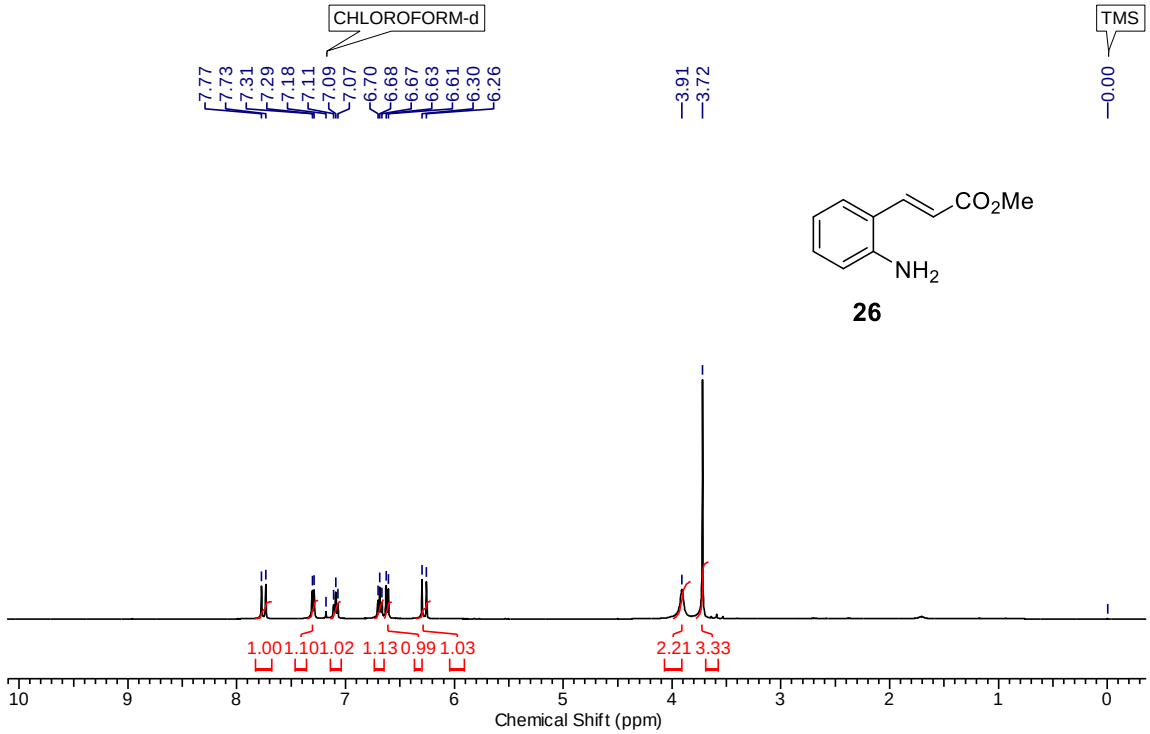

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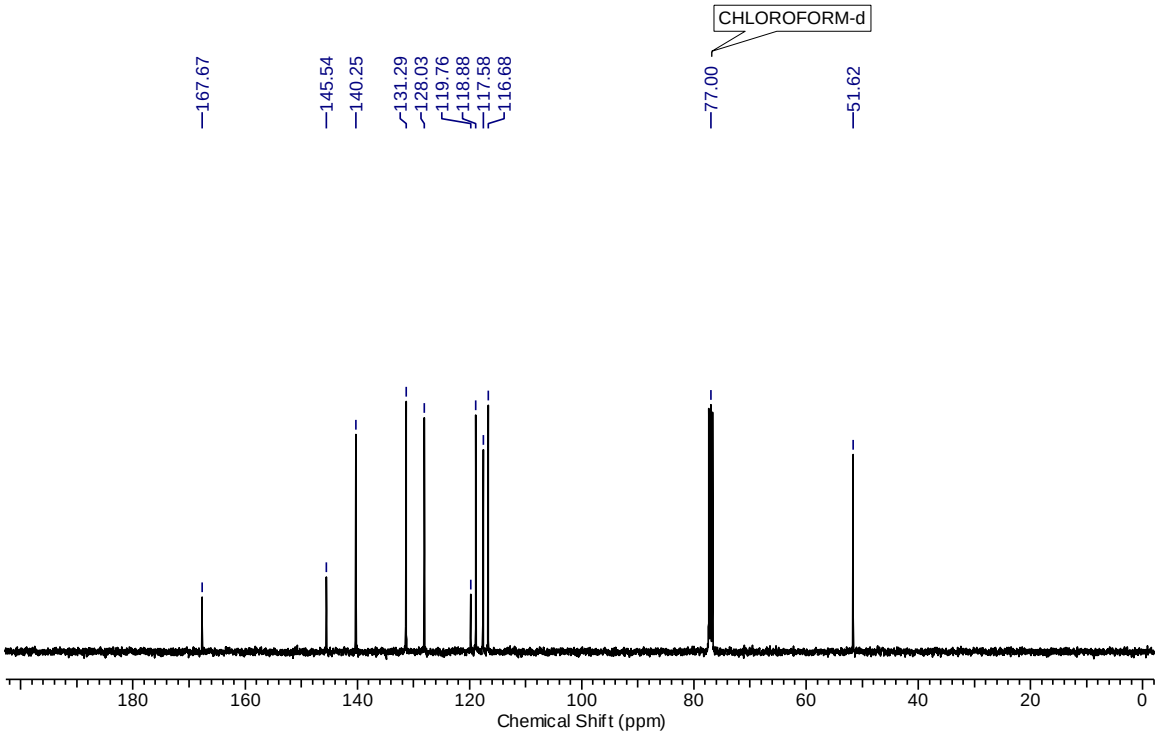

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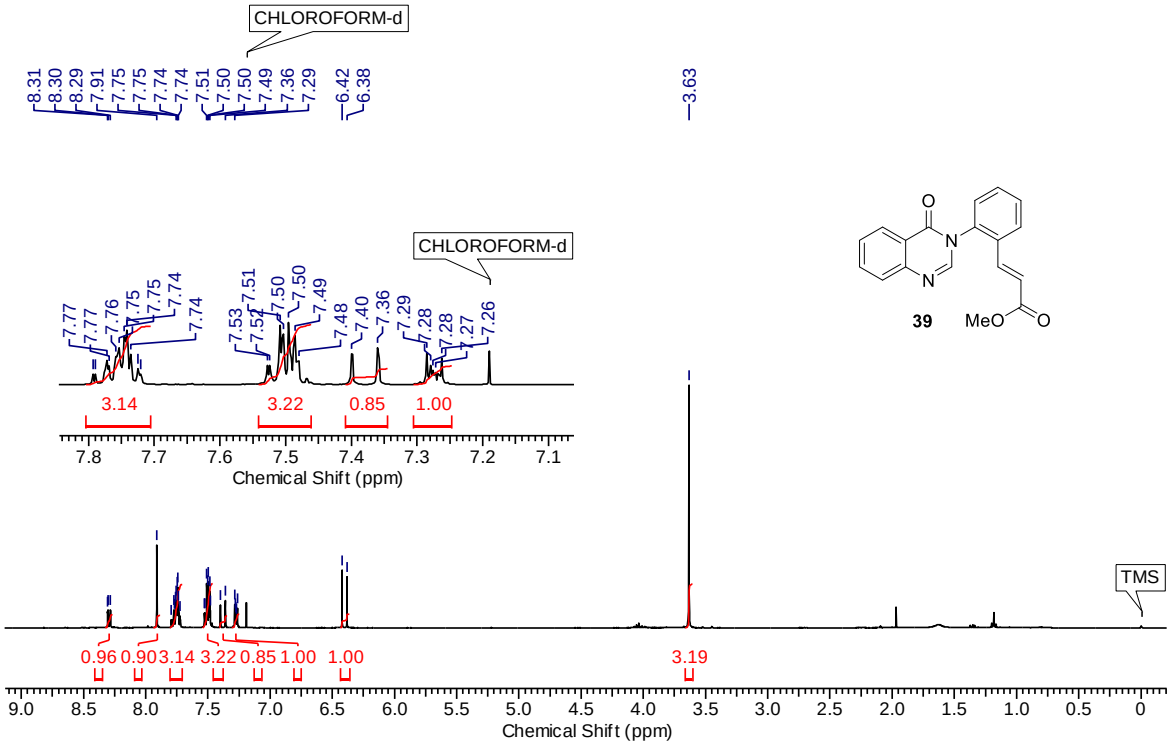

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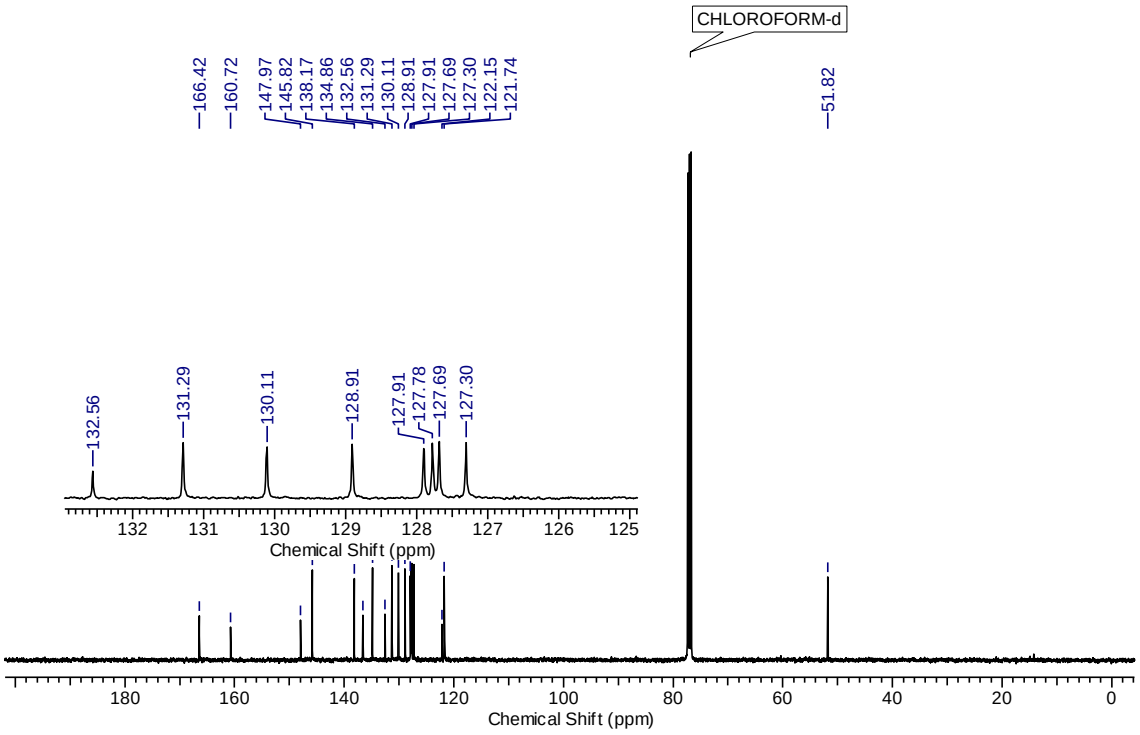

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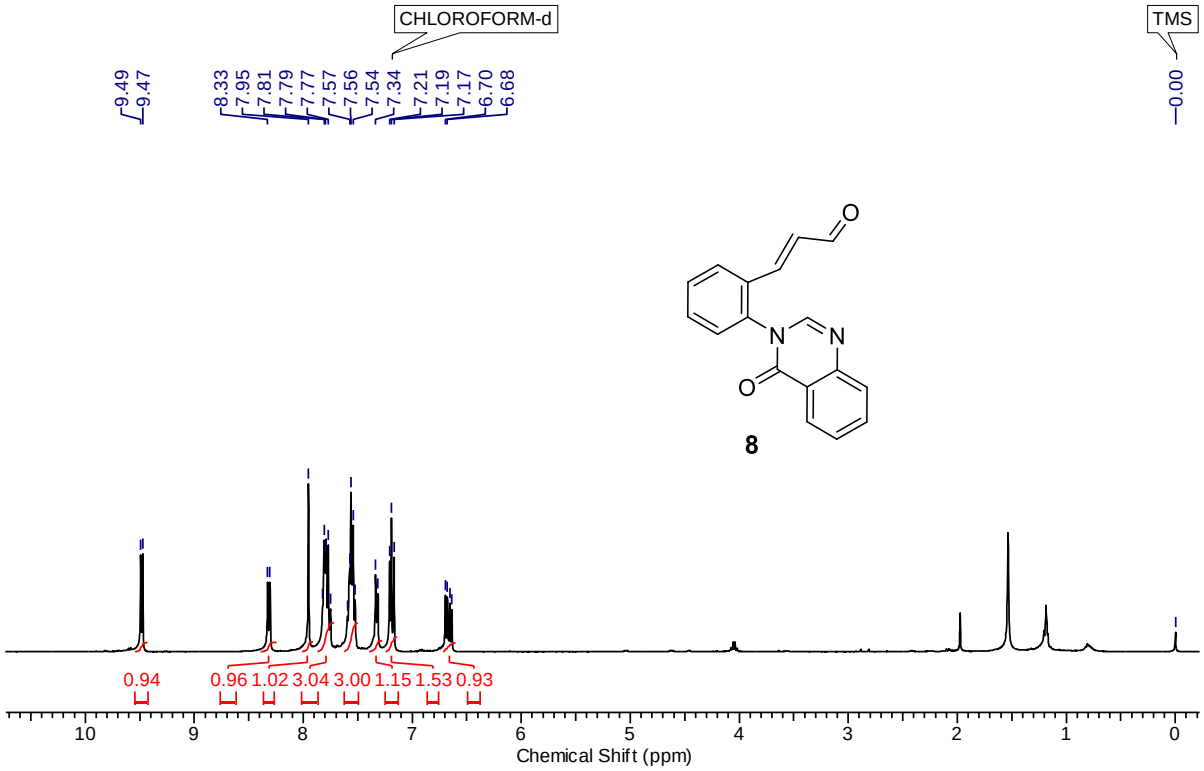

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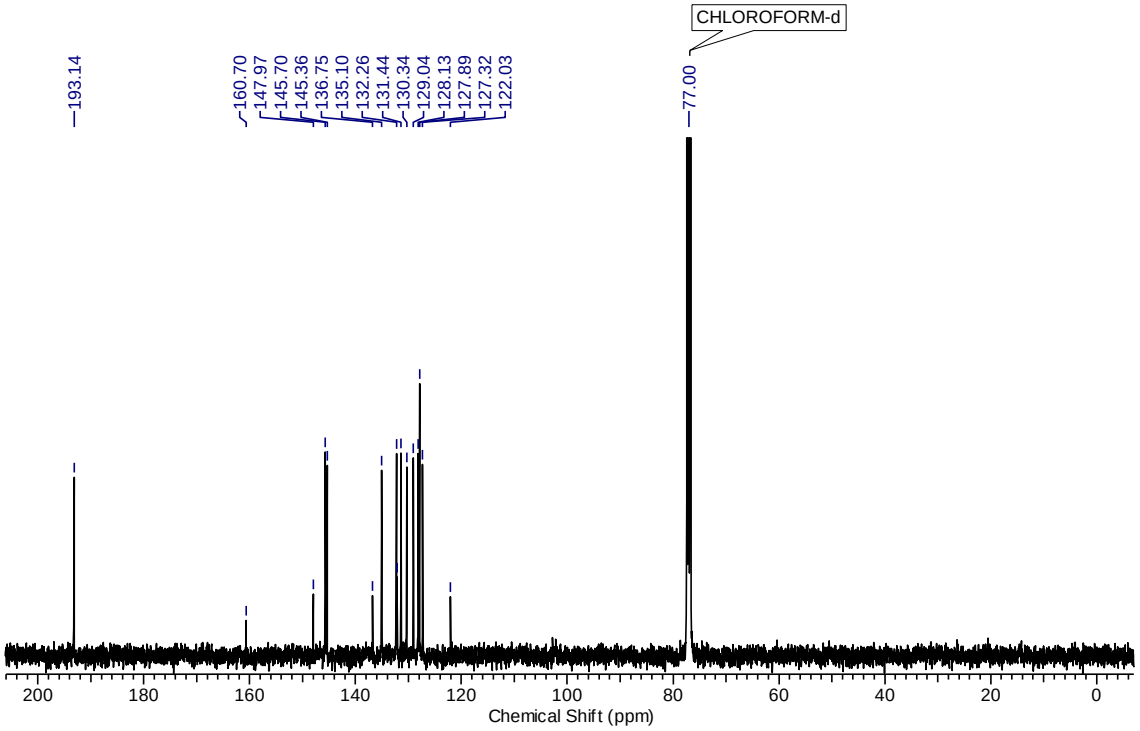

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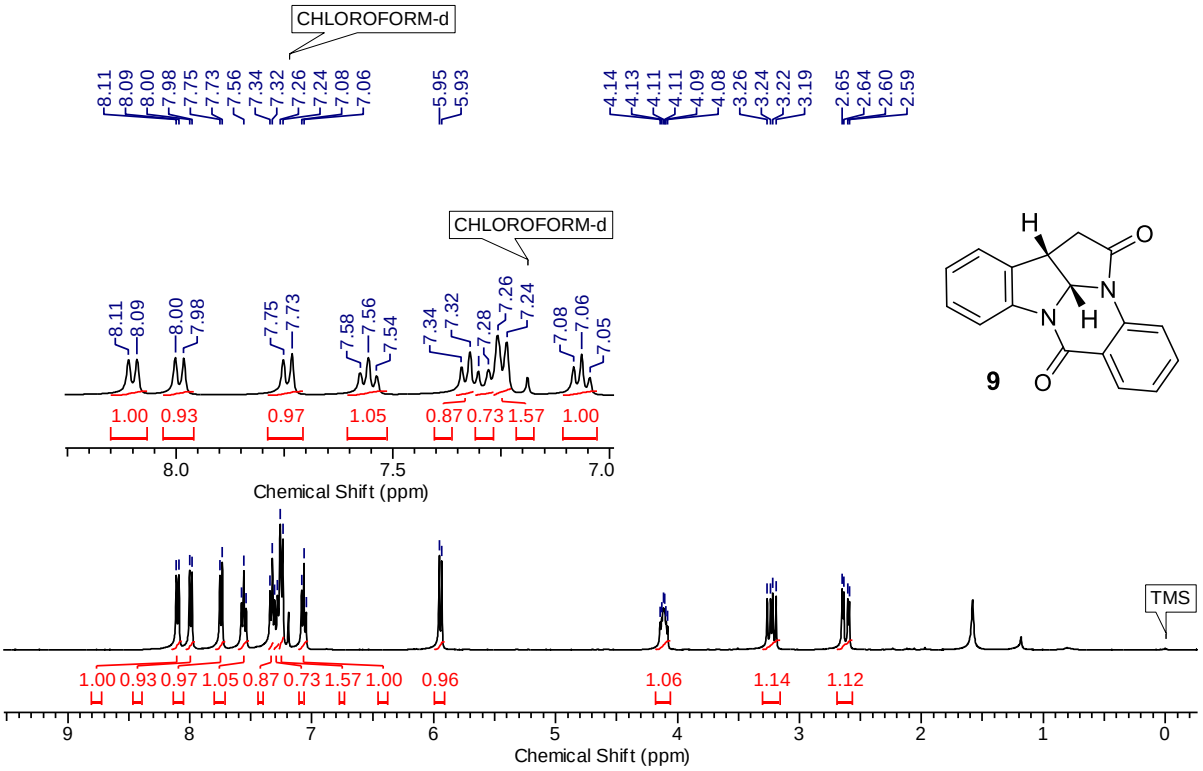

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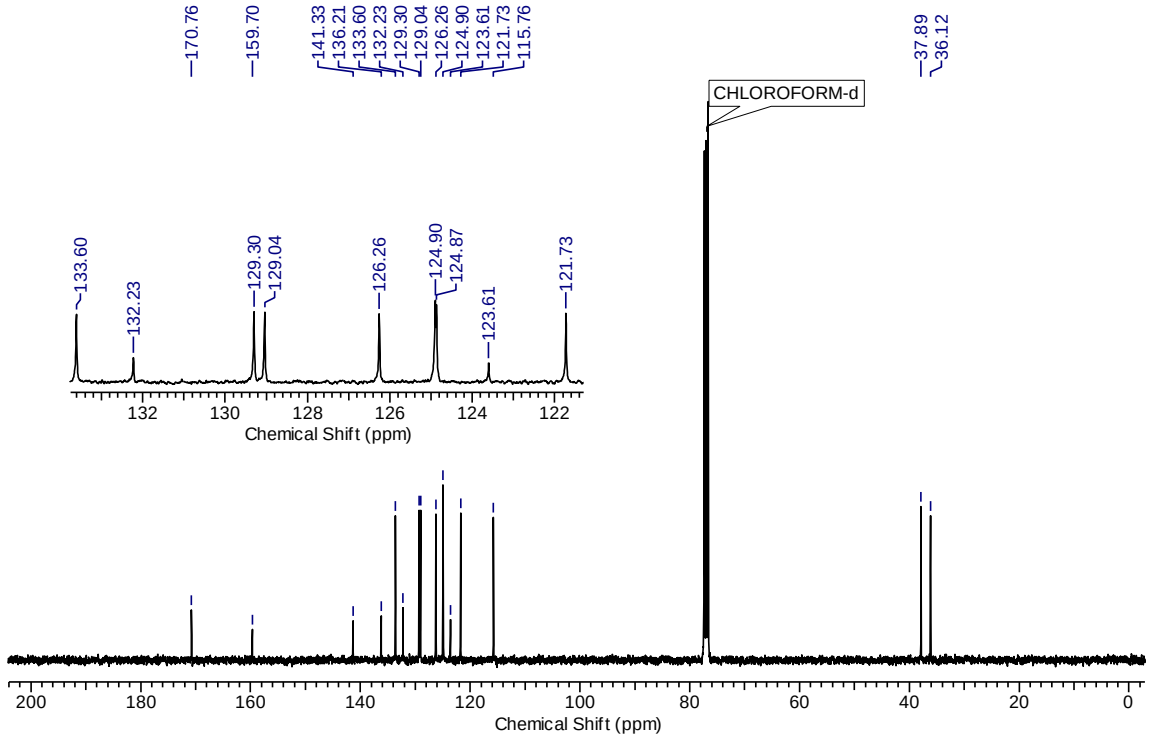
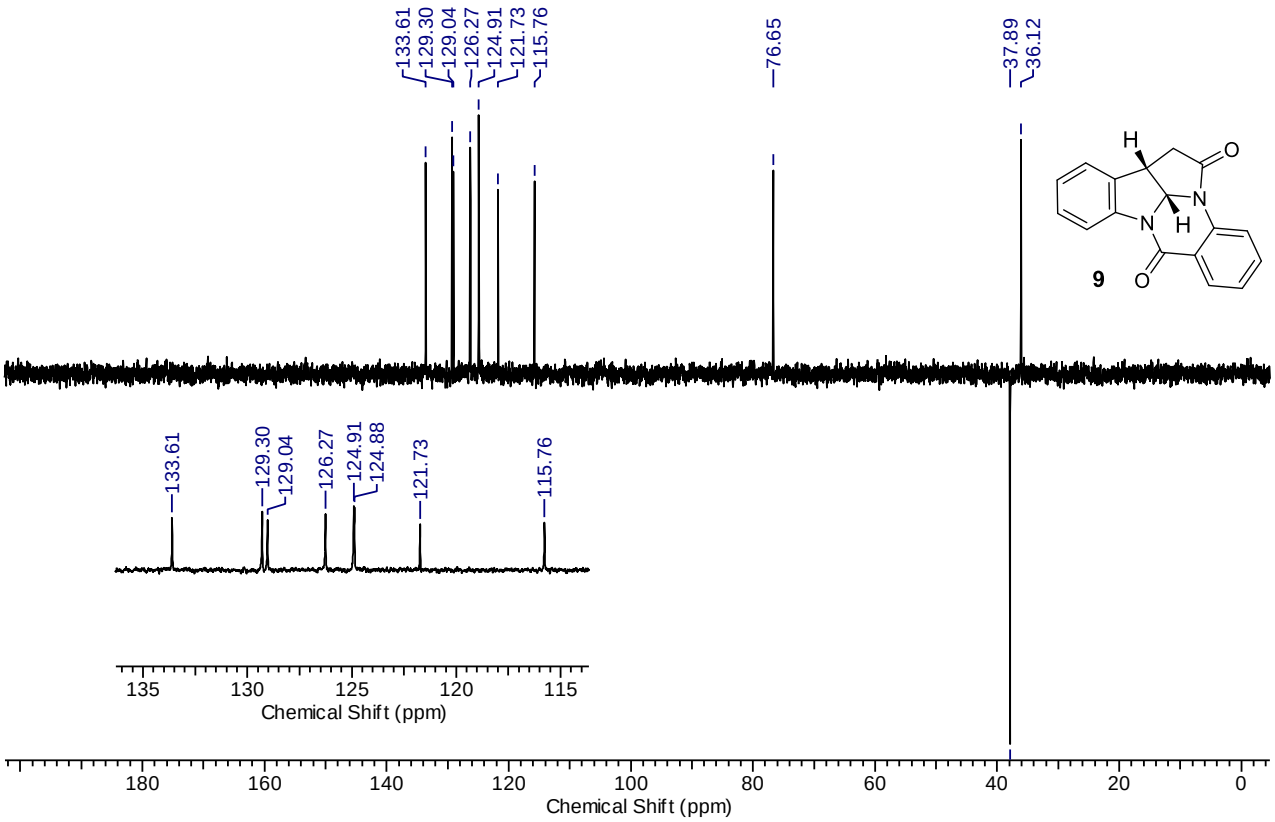


DEPT-Spectra



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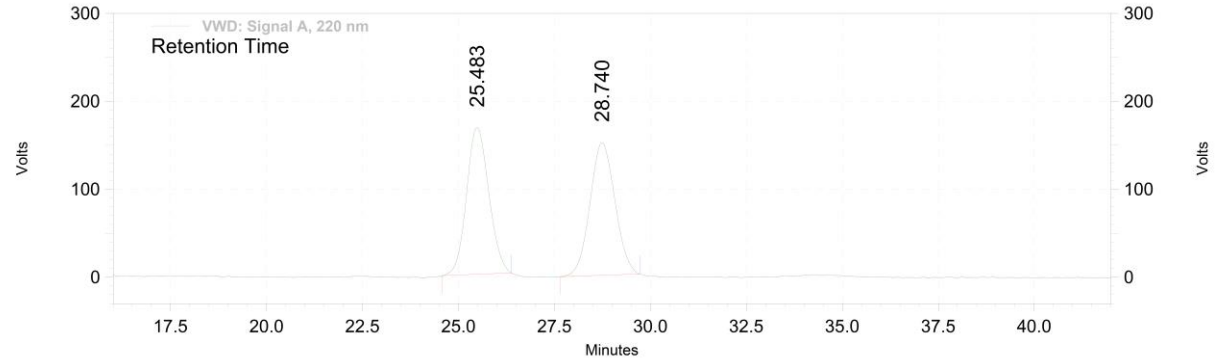
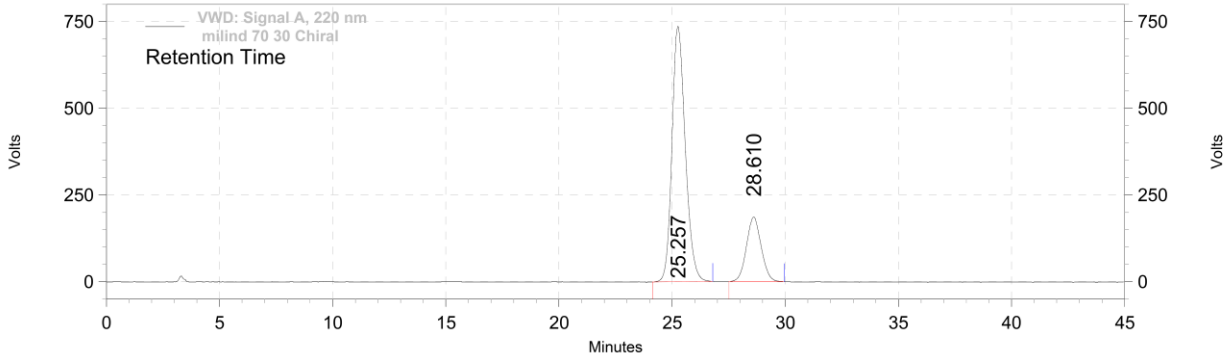


VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
25.483	113108711	49.68	2797384	52.49
28.740	114575458	50.32	2532288	47.51
Totals	227684169	100.00	5329672	100.00

Chiral



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
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28.610	142209070	21.82	3124585	20.17
Totals	651731633	100.00	15487575	100.00

Chapter 3

Novel 1,2-Difunctionalized Arenes Using Aryne Insertion Reaction

Section 1: Transition-Metal-Free Insertion Reactions of Aryne

3.1.1. Introduction

This section illustrates the reactivity and selectivity of aryne insertion reaction in elemental-elemental bond with the help of representative examples from the literature. Arynes are very reactive neutral and structurally strained intermediates, which provide rapid functionalization of aromatic ring via multiple carbon-carbon or carbon-heteroatom bond formation strategies. In 1927, Bachmann and Clarke reported the first evidence of *ortho*-benzyne reactive intermediate.[1] Initial methods for aryne generation and their applications were restricted due to the harsh reaction conditions for the preparation of aryne species.[2] However, the advent of milder and efficient methods for aryne generation from simple starting materials propelled synthetic organic chemistry towards the synthesis of complex molecules. Currently, the efficient method for aryne generation involves the use of *ortho*-silyl aryl triflates as aryne precursor in the presence of fluoride sources to trigger the reaction under neutral and milder reaction conditions.[3] Recent research highlights an increasing utilization of aryne chemistry towards the synthesis of natural products and useful bioactive molecules. Till date, nearly 80 natural products have been synthesized using aryne chemistry.[4]

Arynes are resulted by the expulsion of adjacent two leaving groups of an aromatic ring to form weakly bonding low-lying LUMO, which exhibits high electrophilicity.[5] The literature review revealed that the aryne chemistry has been associated in the development of many novel synthetic methodologies.[4,5] Generally, aryne has been reacted with various carbon and heteroatom nucleophiles in assembling new carbon−carbon and carbon−heteroatom bonds respectively. Also, it involves cycloaddition, multicomponent reaction (MCR), and elemental-elemetal bond insertion reaction (Figure 1).[5]

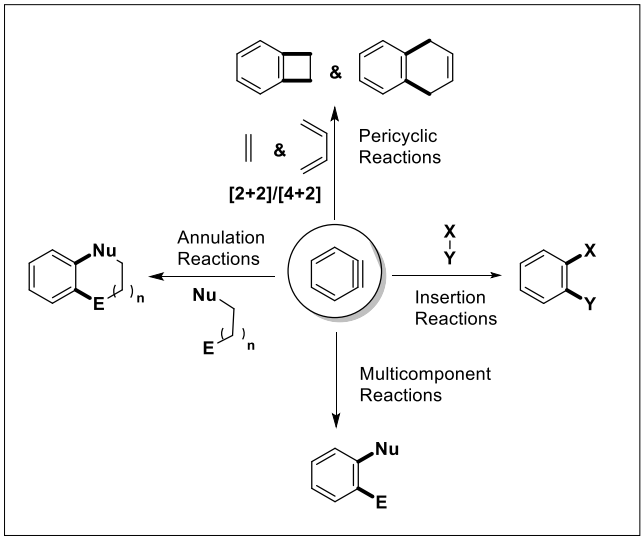


Figure 1. Different Modes of Reactivity of Aryne Intermediate.

3.1.2. Transition-metal-free Aryne Insertion Reaction in Elemental-Elemental Bond

Extensively used methods for aromatic ring functionalization are transition-metal-catalyzed reactions such as C−H activation reactions[6a,b] and various coupling reactions.[6c-e] Also, the electrophilic[7a,b] and nucleophilic[7c] aromatic substitution reactions are traditional methods for aromatic functionalization. However, these methods can generally functionalize only one carbon atom of aromatic ring at a time, whereas the bifunctionalization of aromatics could be possible by using aryne chemistry via insertion and multicomponent reactions.[5b,g] For example, 1,2-difunctionalization of arenes by aryne insertion reaction into a σ-bond is a considerable transformation with or without transition metal catalyst.[8] The addition of arynes strained carbon-carbon triple bond to elemental-elemental σ-bond allow two fold bond forming strategies, which forms complex molecular scaffolds containing *ortho*-difunctionalized aromatic ring in a smooth manner. The synthetic utility of insertion reaction is further enhanced by developing strategies

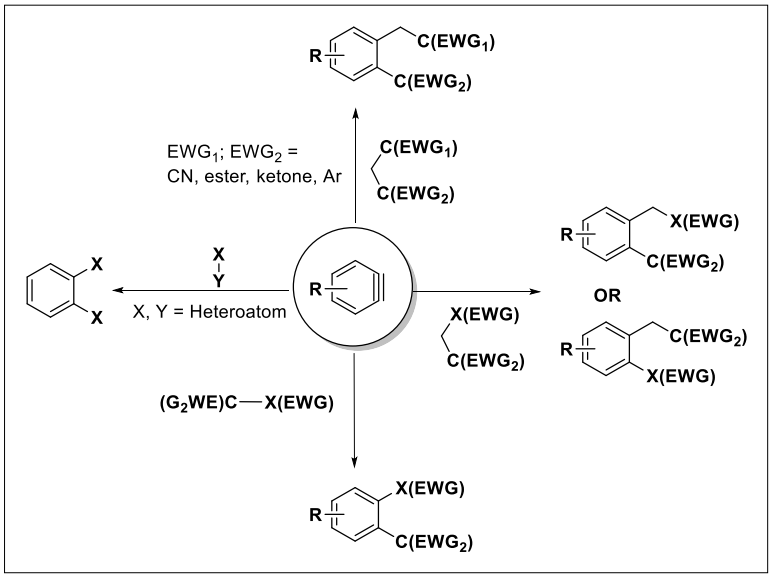


Figure 2. Different Types of Insertion Reaction.

along with rearrangement reaction, which provides trifunctionalization of arenes without transition-metal catalysts.[9] There are three different types of elemental-elemental bond insertion reactions with arynes: carbon-carbon, carbon-heteroatom, heteroatom-heteroatom bond insertion reaction (Figure 2).

3.1.3. General Reaction Mechanism of Transition-metal-Free Aryne Insertion Reaction

The general reaction mechanism of aryne insertion reaction into an elemental-elemental bond is depicted in Figure 3. The reaction is initiated by the formation of aryne intermediate **1a** from *ortho*-(trimethylsilyl)aryl triflates **1** (Kobayashi aryne precursor) by employing a fluoride source. The electrophilic aryne intermediate **1a** is reacted with potentially nucleophilic center of an elemental-elemental bond to form intermediate **1a'**, which further reacted intramolecularly with potential electrophilic center with simultaneous breaking of an elemental-elemental bond leading to 1,2-difunctionalization arene derivatives **3**.

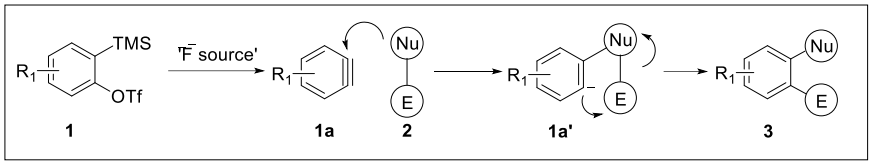
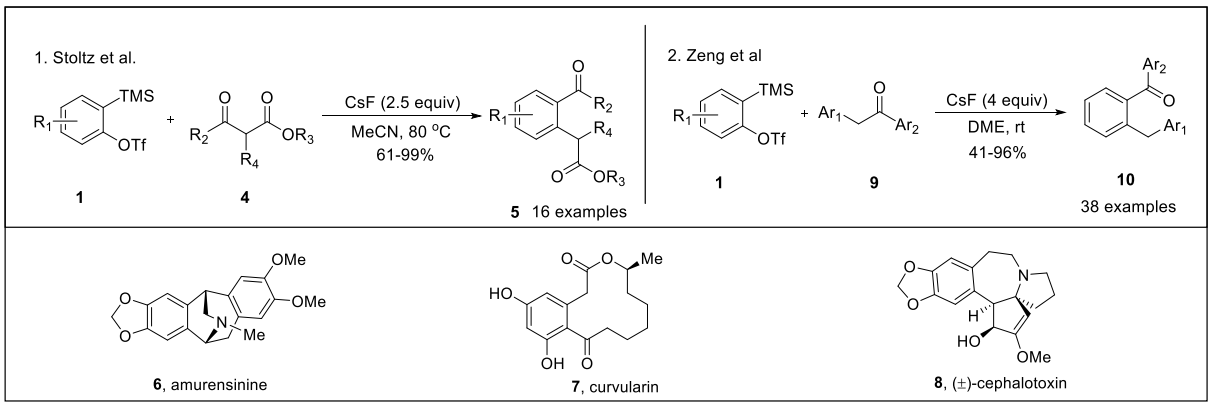


Figure 3. General Reaction Mechanism of Aryne Insertion.

3.1.4. Aryne Insertion in Carbon-Carbon Bond

Scheme 1. Aryne Insertion in Carbon−Carbon bond



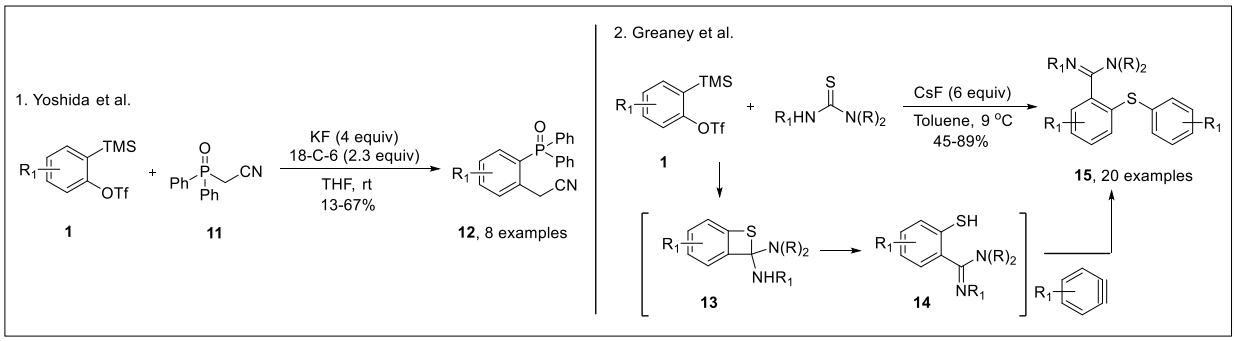
In 2005, Stoltz group developed an efficient method for aryne insertion in C−C bond of 2-substituted 1,3-dicarbonyl system **4**, which resulted into acyl-alkylation product **5** formation under mild reaction condition (Scheme 1, eq 1).[10a] Later on the same group has reported the asymmetric total synthesis of amurensinine (**6**)[10b] and curvularin (**7**)[10c] natural products by employing similar strategy. Also, Chandrasekhar and colleagues demonstrated effective utilization of the same strategy for the total synthesis of complex alkaloid natural product (±)-cephalotoxin (**8**).[10d] In 2016, Zeng and co-worker demonstrated transition-metal-free method for the synthesis of 2-benzylphenyl ketones **10** via aryne insertion in an unactivatived C−C bond of substituted 2-phenylacetophenones **9** (Scheme 1, eq 2).[11] A diverse range of aryne precursors and

ketones underwent successful insertion reaction. Overall, the aryne insertion reaction in C−C bond involves the formation of two new C−C bonds with breaking of one C−C bond.

3.1.5. Aryne Insertion in Carbon-Heteroatom Bond

Based on the extreme importance of the arylphosphines moiety in biologically important compounds as well as ligand in organometallic chemistry, Yoshida and co-worker disclosed the aryne addition to carbon-phosphorus *σ*-bond of cyanomethyldiphenylphosphine oxide **11** for the efficient synthesis of *ortho*-cyanomethyl phosphonates **12** (Scheme 2, eq 1).[12] This method of carbophosphinylation of arynes suffers with a series of drawbacks: the expected compound obtained in low to moderate yields with limited substrate scopes.

Scheme 2. Aryne Insertion in Carbon-Heteroatom bond

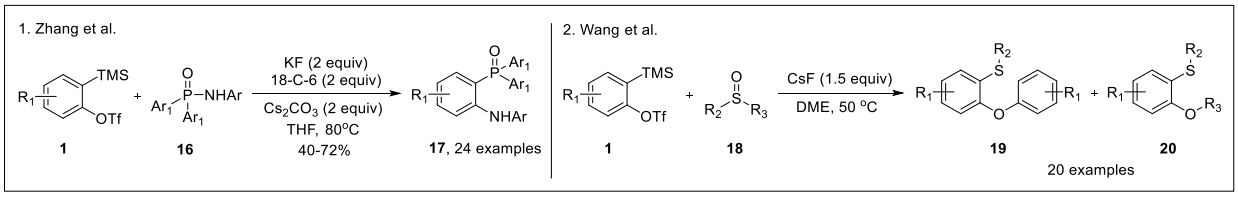


In 2011, Greaney and group demonstrated aryne reaction with thiourea for the synthesis of functionalized amidine derivatives **15** (Scheme 2, eq 2).[13] The reaction involves aryne insertion into C−S *π*-bond to form four membered intermediate **13**, which upon rearrangement generates thiphenol derivatives **14**. Furthermore, thiols **14** underwent arylation with other molecule of aryne resulted into amidine derivatives **15**. A diverse range of aryne precursors and thiourea underwent successful insertion reaction.

3.1.6. Aryne Insertion in Heteroatom-Heteroatom Bond

The addition of arynes into *σ*-bonds is an important method for the construction of 1,2-disubstituted arenes. By applying this strategy, Zhang and colleagues reported one step synthesis of *o*-amine-substituted arylphosphine oxides **17** via aryne insertion into P − N *σ*-bond of arylphosphoryl amide **16** (Scheme 3, eq 1).[14] A variety of substituted aryne precursors underwent successful insertion reaction. In 2015, Wang and co-worker demonstrated transition-metal-free aryne addition to S−O bond of sulfoxide **18** for the synthesis of sulfane **19** in moderate to good yields along with side product **20** in trace amount (Scheme 3, eq 2).[15] The reaction tolerates various substituted aryne precursors and sulfoxides substrates and provides corresponding products in good to excellent yields.

Scheme 3. Aryne Insertion in Heteroatom-Heteroatom Bond



3.1.7. Conclusion

This section provides information on the reactivity and selectivity of aryne insertion reaction in elemental-elemental bond with the help of representative examples from the literature. The success gained in the aryne chemistry since the past two decades is mainly due to the Kobayashi's aryne precursor. Many novel methods have been reported until now in the aryne-based methodologies. Arynes possesses different types of reactivity, however, aryne insertion reaction in an elemental-elemental bond to access novel *ortho*-substituted arenes under mild and

transition-metal-free conditions, which are otherwise difficult to synthesize by using traditional methods is promising. The concept of aryne insertion reaction could be further explored for other elemental-elemental bonds to access novel compounds, and will largely add to the arsenal of aryne insertion reactions application in the synthesis of complex targets.

3.1.8. References

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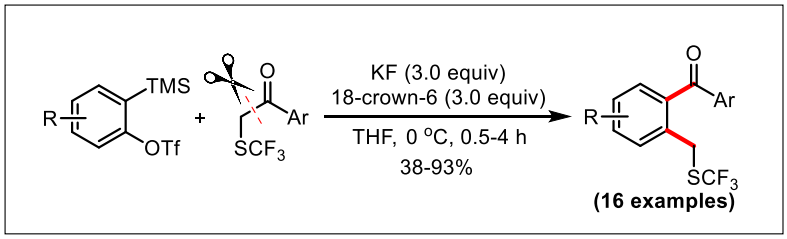
Section 2: Synthesis of *ortho*-Methyl Trifluoromethyl Sulfide Substituted Benzophenones via 1,2-Difunctionalization of Aryne by Insertion into C-C Bond

3.2.1. Abstract

An efficient process for the preparation of valuable *ortho*-methyl trifluoromethyl sulfide substituted benzophenones has been developed. The transition-metal free method features insertion of aryne in C-C σ-bond under a mild reaction condition for the first time to achieve *ortho*-difunctionalized arenes containing pharmaceutically important trifluoromethylthio functional group. A wide substrate scope has been demonstrated for the developed protocol.



This work has been published in *Org. Lett.* **2017**, *19*, 2134.

3.2.2. Introduction

Fluorinated compounds constitute a vital structural class, which is commonly found in bioactive molecules, agrochemicals, polymers, and functional materials.[1] Until now, more than 20% of modern pharmaceutical ingredients are known to contain fluorine atom, which highlights its importance in new drug design and development.[1a] Due to fluorine's intrinsic property of modifying the pharmacological and physicochemical properties of drug molecules, its installation has become an important objective. Hence, in the past few years, methods involving

efficient incorporation of fluorine and fluorine containing moieties into organic compounds have gained tremendous attention from the scientific community.[2] Among the fluorinated moieties, trifluoromethylthio (-SCF_3) has experienced long standing attention for its unique biological properties such as extremely high Hansch lipophilicity parameter, protein binding affinity, metabolic stability and strong electron withdrawing effect, which allows high permeability of drug candidate through lipid membrane to exert their effects.[3] Hence, novel strategies for the preparation of -SCF_3 containing compounds are always sought-after for designing new drugs.[2a-b,4] As shown in Figure 1, some biologically active molecules possesses fluorine containing moities as an important pharmacophore.[5]

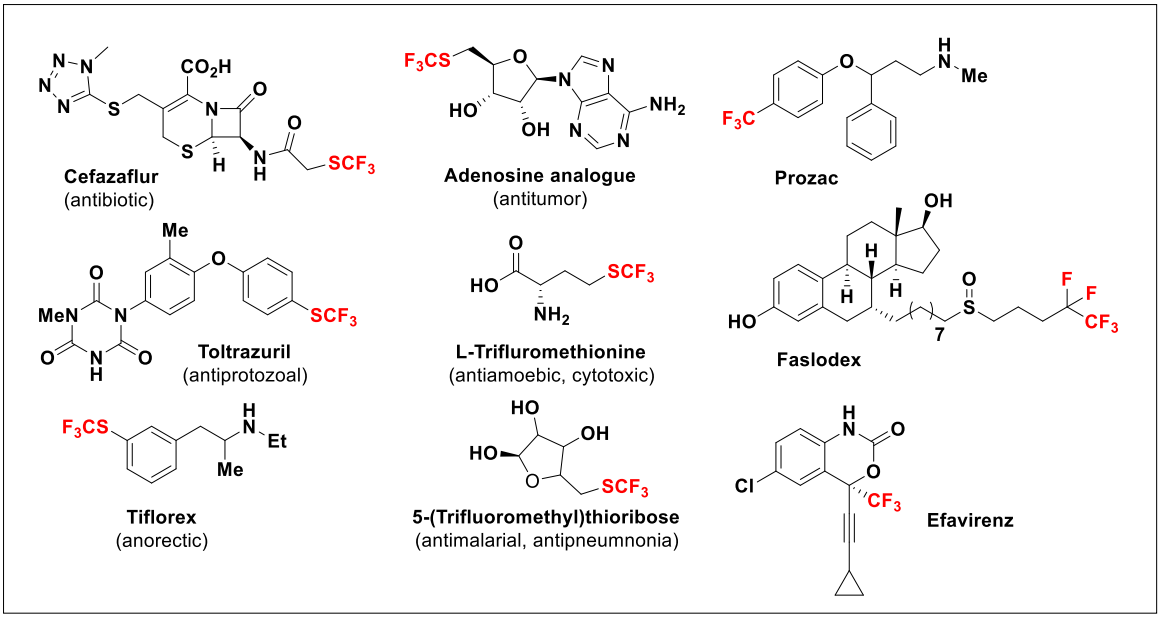


Figure 1. Bioactive Active Compounds Containing Fluorine Atom.[5]

3.2.3. Literature Review

The literature review revealed that vast number of synthetic methods for the introduction of trifluoromethylthio (-SCF_3) group on the aromatic ring has been well developed.[2a-b,4] Transition metal-catalyzed C-H activation, cross-coupling reactions of aryl halides or aryl boronic acids

with -SCF_3 containing reagents, electrophilic and nucleophilic substitution reactions are some of the important methods.[2a-b,4] However, very less consideration has been given on the aliphatic -SCF_3 bond formation reactions.[4b] The known synthetic methods largely deals with the preparation of trifluoromethylthiolation by means of prefunctionalized starting materials.[4,6] These methods consist of nucleophilic displacement of good leaving groups by -SCF_3.

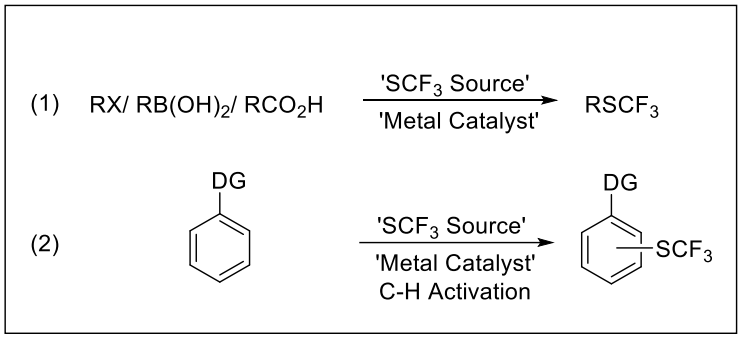


Figure 2. Transition-metal-catalyzed Trifluoromethylthiolation.

3.2.4. Origin of the Present Work

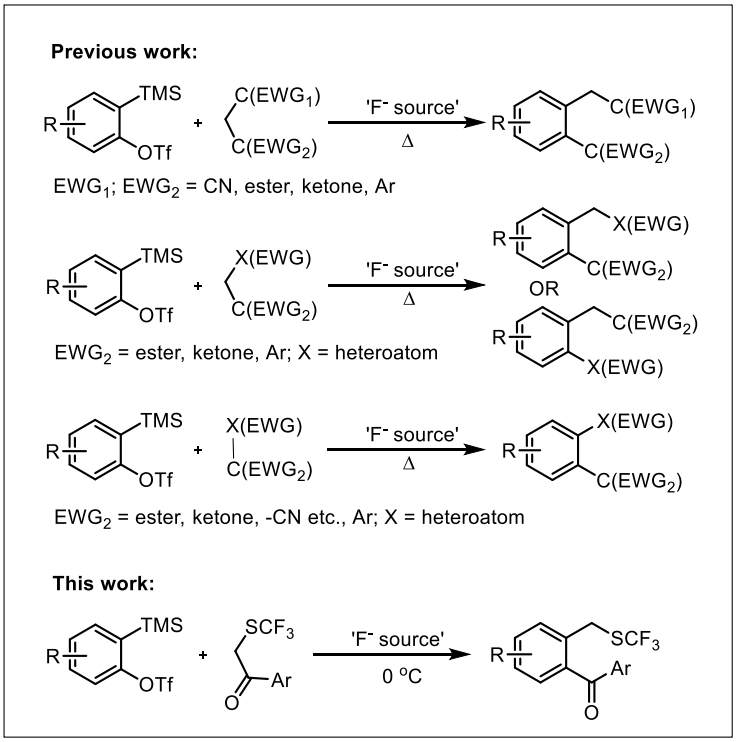


Figure 2. Previous Aryne Insertion Reactions into C-C and C-X Bond and this Work.[12]

Arynes are very reactive intermediates and have fascinated synthetic chemists for quite a long time.[7,8] Due to its high electrophilicity, it has been involved in the development of many new synthetic methodologies. Generally, aryne has been trapped by various nucleophiles in assembling new carbon-carbon and carbon-heteroatom bonds for efficient construction of diverse array of useful synthetic building blocks.[8] Also, aryne has been successfully applied for

designing valuable *ortho*-disubstituted arenes by dipolar cylcoaddition and multicomponent reactions (MCR).[8g,9] Notably, for 1,2-disubstituted arenes, aryne insertion into element-element σ-bond is a considerable transformation and varietiy of substrates have been studied with or without transition metal catalysts.[10] Our group has been involved in developing novel synthetic methodologies involving arynes.[11] Inspired by the importance and the recent progress in the area of aryne insertion reactions, we have developed a new synthetic methodology for the expedient synthesis of *o*-CH_2SCF_3 substituted benzophenones. In contrast to most of the previous reports, this newly developed aryne insertion reaction takes place on heteroatom substituted methylene ketone under a much milder condition (Figure 2).[12]

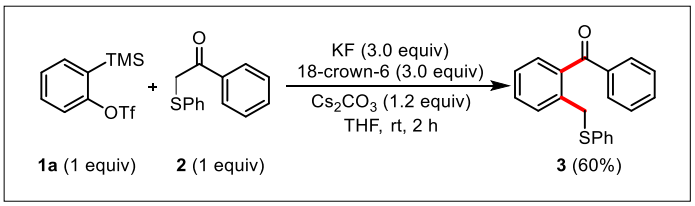
3.2.5. Objective

The method implying the addition of α-SCF_3 ketones on aryne to form novel compounds with additional functionality on organic molecule has not been reported till date. Herein, we planned to develop a mild synthetic strategy for ketone derivatives (particularly benzophenones) with additional *ortho*-benzylic trifluoromethylthio functionality, using stable and easy to handle α-SCF_3 ketones and arynes generated by Kobayashi's method.[7]

3.2.6. Results and Discussion

Our investigation of insertion reaction started with the treatment of benzyne generated from 2-(trimethylsilyl)phenyltriflate (**1a**) with α-SPh ketone **2**[13] in the presence of KF, 18-crown-6 ether, and Cs_2CO_3 in THF under argon atmosphere at room temperature. Gratifyingly, we observed the formation of the expected insertion product **3** in 60% yield. Encouraged, by this result and taking into consideration the importance of fluorine containing organic compounds, we envisaged that this process will be more useful to insert aryne into the C-C σ-bond of the α-SCF_3 ketones to

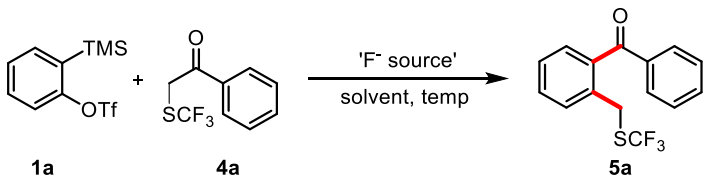
Scheme 1. The First Reaction Attempted



obtain more value added products. Hence, we prepared α-SCF_3 ketone **4a** by the reported procedure[14] and applied the above mentioned aryne insertion reaction condition. Interestingly, 63% yield of the expected product **5a** was observed within 30 minutes (Table 1, entry 1).

Initially, for attaining optimized reaction condition, we screened effective fluoride sources along with corresponding solvents. The outcome of the entries 1-3 (Table 1) led us to conclude that KF and 18-crown-6 ether stood out to be the best fluorinating source in THF at room temperature. Our initial hypothesis behind using a base for generating active carbanion species was ruled out after performing the reaction in the absence of Cs_2CO_3. Comparable yield (Table 1, entry 4)

Table 1. Optimization of Reaction Conditions[a,b]



1a **4a** **5a**

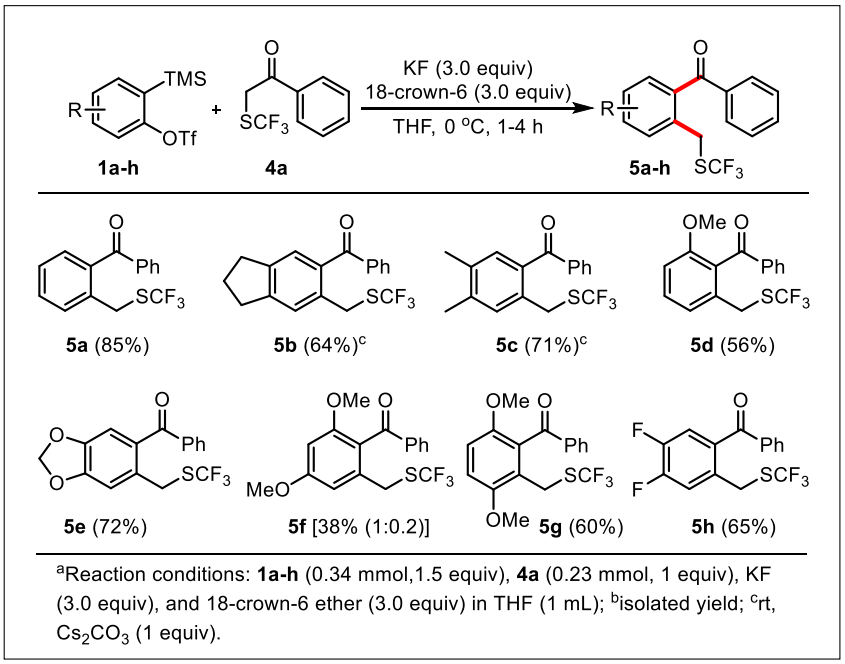
entry	solvent	F⁻ source	temp (°C)	additive	time (h)	5a (%)[c]
1	THF	KF, 18-*c*-6	rt	Cs_2CO_3	0.5	63
2	toluene	KF, 18-*c*-6	rt	Cs_2CO_3	12	60
3	CH_3CN	CsF	rt	Cs_2CO_3	2	45
4	THF	KF, 18-*c*-6	rt	--	1	60
5	THF	KF, 18-*c*-6	0	--	1	85
6[d]	THF	KF, 18-*c*-6	0	--	2	67
7	toluene	KF, 18-*c*-6	0	--	12	70
8	CH_3CN	CsF	0	--	3	51

[a]Selected entries, [b]reaction conditions: **1a** (0.34 mmol, 1.5 equiv), **4a** (0.23 mmol, 1 equiv), Cs_2CO_3 (1.2 equiv), CsF (3.0 equiv) / KF (3.0 equiv) and 18-crown-6 (3.0 equiv) in solvent (1 mL); [c]isolated yield; [d]**1a** (1 equiv), **4a** (1 equiv).

obtained for the product **5a** without any base, determines the role of excess KF as a base for this transformation. The shorter time required for the completion of the reaction illustrates the faster reaction rate, hence the same reaction was executed at 0 °C, which provided **5a** with increased yield up to 85% (Table 1, entry 5). Furthermore, the variation in the molar ratio of the substrates **1a** and **4a** was also examined. Reduction in the yield was noticed with reduced aryne precursor equivalents (Table 1, entry 6). Similarly, performing the reaction in toluene and acetonitrile at 0 °C (Table 1, entry 7 and 8) furnished **5a** in 70% and 51% yield respectively with mixture of side products, thus THF was found to be the best solvent for this transformation. The reproducibility of the optimized reaction protocol (Table 1, entry 5) at higher scale was confirmed by

performing the reaction on the substrate **4a** at 1 mmol scale, which furnished the product **5a** in 70% yield.

Scheme 2. Reaction With Various Silyl-triflates[a,b]

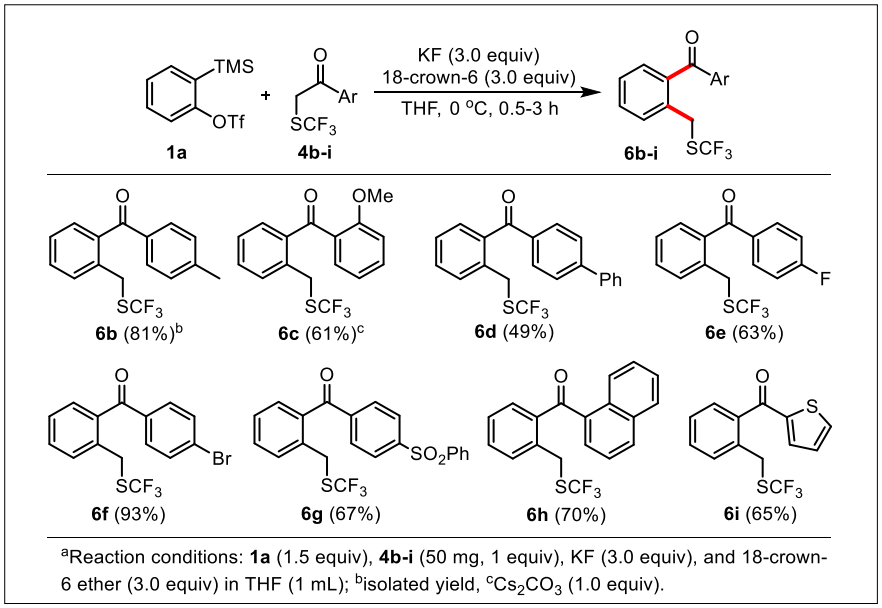


[a]Reaction conditions: **1a-h** (0.34 mmol,1.5 equiv), **4a** (0.23 mmol, 1 equiv), KF (3.0 equiv), and 18-crown-6 ether (3.0 equiv) in THF (1 mL); [b]isolated yield; [c]rt, Cs_2CO_3 (1 equiv).

With the optimized reaction conditions in hand, we investigated the substrate scope of this newly developed protocol by varying the silyl-triflates (**1a-h**). A variety of electron-donating and electron-withdrawing groups on silyl-triflates were tested and the corresponding products were obtained in good to moderate yields (Scheme 2, entry **5a-h**). As mentioned above in the optimization study, the unsubstituted silyl-triflate **1a** provided expected product in 85% yield. However, surprisingly simple alkyl substituted aryne precursors **1b** and **1c** did not react at 0 ^{o}C and less product formation was observed even at room temperature. Improved yield was observed only when additional base Cs_2CO_3 was added at 0 ^{o}C, followed by stirring the reaction mixture at room temperature. The reason behind this observation is obscure. Remarkably, for the unsymmetrical aryne precursor **1d**, we were pleased to observe the expected product formation

of only one regioisomer **5d**. The observed regioselectivity might be due to the low reaction temperature and electronic effects of the methoxy group. It is noteworthy that electron rich substrates **1e** and **1g** furnished the expected products **5e** and **5g** respectively in good chemical yields. However, aryne precursor **1f** was unreactive at 0 ^{o}C and formed complex mixture of products at room temperature. The desired product **5f** was observed, though in low yield, when the reaction was performed at 15 ^{o}C for 1h. Further stirring the reaction mixture for longer time again showed formation of complex reaction mixture. The difluoro substituted aryne precursor **1h** provided a good yield of the desired product **5h** under the optimized condition.

Scheme 3. Reaction With Various α-SCF_3 Ketones[a,b]



[a]Reaction conditions: **1a** (1.5 equiv), **4b-i** (50 mg, 1 equiv), KF (3.0 equiv), and 18-crown-6 ether (3.0 equiv) in THF (1 mL); [b]isolated yield, [c]Cs_2CO_3 (1.0 equiv).

After understanding the reactivity pattern on different aryne precursors, we further turned our attention to study the substrate scope by varying the α-SCF_3 ketones (**4b-i**) and keeping constant the aryne precursor **1a**. Various electron-donating and electron-withdrawing substituents on the phenyl ring of α-SCF_3 ketones were examined. The corresponding inserted products were

obtained with good to moderate yields (Scheme 3, **6b**-**i**). The substrate **4b** reacted smoothly to provide the aryne inserted product **6b** in very good yield. However, the ketone **4c** remained unreactive at 0 ^{o}C as well as at room temperature. Hence, we used a base Cs_2CO_3, which can abstract the methylene protons easily and to our delight, the product **6c** was obtained in good yield. The *p*-phenyl substituted ketone **4d** furnished the corresponding product **6d** without difficulty. The substrates **4e** and **4f** having halo-groups (F and Br respectively), provided the products **6e** and **6f** in good to excellent yields respectively. These products can also be further derivatized by coupling reactions. Furthermore, the substrate **4g** having electron-withdrawing group (*p*-SO_2Ph) furnished the relevant product **6g** smoothly with decent yield. We were pleased to find that the developed condition worked very well on naphthyl substrate **4h** to provide the corresponding product **6h** in 70% yield. The developed process was also successfully employed on heterocyclic ketone **4i** containing thiophene moiety to obtain **6i** with good yield.

A plausible reaction mechanism of the reaction is depicted in Figure 3. The reaction was initiated by generation of aryne intermediate **A** by fluoride source from precursor **1**. Next, the α-SCF_3 ketone **4** under basic condition generates carbanion species **B**. Subsequently, the addition of carbanion to aryne intermediate produces intermediate **C**. Intramolecular attack of the carbanion on carbonyl carbon eventualy breakes of C-C bond to form intermediate **D**, which upon further protonation forms expected compound *ortho*-methyl trifluoromethyl sulfide substituted benzophenones **5**.

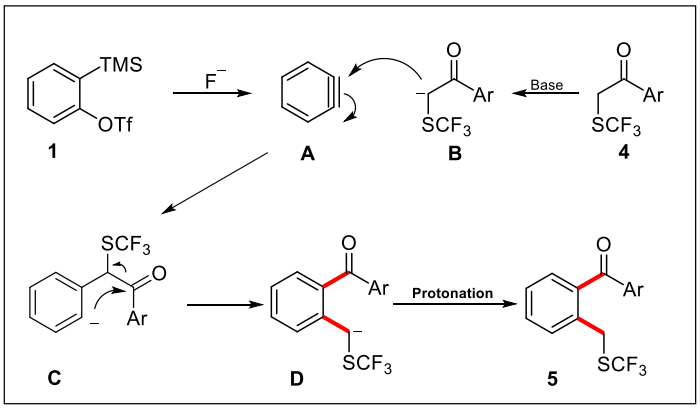


Figure 3. Paussible Reaction Mechanizm of Aryne Insertion in C-C bond of α-SCF_3 Ketones.

3.2.7. Conclusion

In conclusion, we have developed a convenient and a novel method for the preparation of *ortho*-difunctionalized arenes having trifluoromethylthio functional group by aryne insertion in to α-SCF_3 ketones. The reaction tolerates a variety of substituents on arynes as well as ketones. This methodology allows metal free access to a range of value added aromatic ketones bearing *o*-CH_2SCF_3 group. Furthermore, we are in the process of screening the final compounds for potential biological activities and currently focusing on the development of novel methodologies for aryne insertion into elemental-elemental bond and their application in the synthesis of bioactive molecules and natural products.

3.2.8. Experimental Procedures

[A] Experimental procedure for the preparation of benzophenone 3 (Scheme 1):

To a Schlenk tube containing KF (38 mg, 3.0 equiv), 18-crown-6 ether (174 mg, 3.0 equiv) and Cs_2CO_3 (86 mg, 1.2 equiv) was added **2** (50 mg, 1.0 equiv) in THF (0.5 mL) and stirred for 5 minute at room temperature, followed by the addition of **1a** (65 mg, 1.0 equiv) solution in THF (0.5 mL) at the same temperature. The progress of the reaction was monitored by TLC. After

completion of the reaction (2 h), THF was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column chromatography using a gradient of ethyl acetate:petroleum ether (1:19) to afford the corresponding product **3** in 60% yield.

[B] General Experimental Procedure for the preparation of compounds 5a-h (Scheme 2) and 6b-i (Scheme 3): All the reactions were performed on 50 mg of α-SCF_3 ketone.

To a Schlenk tube containing KF (3.0 equiv) and 18-crown-6 ether (3.0 equiv) was added *o*-silyl aryl triflate (1.5 equiv) in THF (0.5 mL) and stirred for 5 minute at 0 ^oC, followed by the addition of α-SCF_3 ketone (50 mg, 1.0 equiv) solution in THF (0.5 mL) at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, THF was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column chromatography using a gradient of ethyl acetate:petroleum ether to afford the corresponding product in 38-93% yields.

[C] Typical experimental procedure for the preparation of compound 5a:

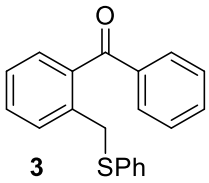
To a Schlenk tube containing KF (40 mg, 0.69 mmol) and 18-crown-6 ether (182 mg, 0.69 mmol) was added *o*-silyl aryl triflate (102 mg, 0.34 mmol) in THF (0.5 mL) and stirred for 5 minute at 0 ^oC, followed by the addition of α-SCF_3 ketone (50 mg, 0.23 mmol) solution in THF (0.5 mL) at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (1 h), THF was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column chromatography using a gradient of ethyl acetate:petroleum ether (1:19) to afford **5a** in 85% (57 mg) yield.

[D] Representative experimental procedure at 1 mmol scale for the synthesis of compound 5a:

To a Schlenk tube containing KF (175 mg, 3.0 mmol) and 18-crown-6 ether (792 mg, 3.0 mmol) was added *o*-silyl aryl triflate (447 mg, 1.5 mmol) in THF (2 mL) and stirred for 5 minute at 0 ^{o}C, followed by the addition of α-SCF_3 ketone (220 mg, 1.0 mmol) solution in THF (2 mL) at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (2 h), THF was evaporated on rotary evaporator. The crude product obtained was dried under high vacuum and purified by flash silica gel column chromatography using a gradient of ethyl acetate:petroleum ether (1:19) to furnish **5a** in 70% (207 mg) yield.

3.2.9. Characterization Data of Compounds

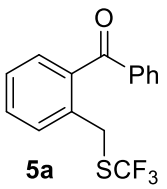
Phenyl(2-((phenylthio)methyl)phenyl)methanone (3).



3

Reaction Time: 2 h; R*f*: 0.4 (1:19 EtOAc:Pet. Ether); oil; 40 mg, 60% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 7.9 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.35-7.27 (m, 2H), 7.26-7.17 (m, 3H), 7.15-7.05 (m, 4H), 4.23 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.99, 138.28, 137.67, 137.59, 135.83, 133.13, 130.79, 130.34 (3C), 129.47, 128.76, 128.34, 126.51 (2C), 36.44; **HRMS-ESI** (*m/z*) calcd For $[(C_{20}H_{16}OS) + H]^+$: 305.0995, found: 305.0992.

Phenyl(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (5a).

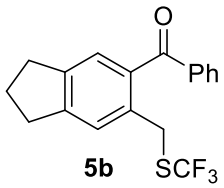


5a

Reaction Time: 1 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 57 mg, 85% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 7.9 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.58-7.51 (m, 4H), 7.37-7.26 (m, 2H), 4.23 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.78, 137.57, 137.35, 136.69, 133.26, 131.25, 131.04, 130.79 (q, *J* = 307 Hz, CF_3), 130.55,

130.30, 128.43, 127.30, 31.83 (apparent d, J = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{15}H_{11}OF_3S)+H]^+$: 297.0555, found: 297. 0547.

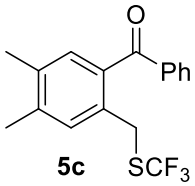
Phenyl(6-(((trifluoromethyl)thio)methyl)-2,3-dihydro-1H-inden-5-yl)methanone (5b).



5b

Reaction Time: 1 h; R*f*: 0.6 (1:19 EtOAc:Pet. Ether); oil; 49 mg, 64% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (d, J = 7.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.26 (s, 1H), 7.18 (s, 1H), 4.19 (s, 2H), 2.90 (t, J = 7.3 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 2.06 (quint, J = 7.3 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.14, 148.29, 143.57, 138.12, 135.40, 134.86, 132.91, 130.95 (q, J = 307 Hz, CF_3), 130.23, 128.33, 127.04, 126.76, 32.87, 32.45, 32.11 (apparent d, J = 2 Hz, CH_2), 25.28; **HRMS-ESI** (*m/z*) calcd For $[(C_{18}H_{15}OF_3S) + H]^+$: 337.0868, found: 337.0869.

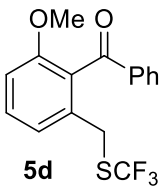
(4,5-Dimethyl-2-(((trifluoromethyl)thio)methyl)phenyl)(phenyl)methanone (5c).



5c

Reaction Time: 4 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 52 mg, 71% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75-7.67 (m, 2H), 7.53 (s, 1H), 7.40 (s, 2H), 7.17 (s, 1H), 7.11 (s, 1H), 4.18 (s, 2H), 2.26 (s, 3H), 2.18 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.80, 140.62, 138.07, 135.83, 134.74, 134.18, 132.91, 132.36, 132.14, 131.08 (q, J = 305 Hz, CF_3), 130.22, 128.34, 31.64 (apparent s, CH_2), 19.78, 19.38; **HRMS-ESI** (*m/z*) calcd $[(C_{17}H_{15}OF_3S)+H]^+$: 325.0868, found: 325.0869.

(2-Methoxy-6-(((trifluoromethyl)thio)methyl)phenyl)(phenyl)methanone (5d).

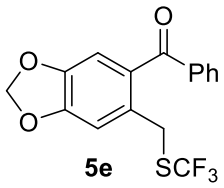


5d

Reaction Time: 2 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); Thick oil; 41 mg, 56% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73 (d, J = 7.3 Hz, 2H), 7.51 (t, J = 7.0 Hz, 1H), 7.41-7.30 (m, 3H), 7.01 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 3.94 (s, 2H),

3.59 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.88, 157.18, 137.62, 134.74, 133.52, 130.86, 130.43 (q, J = 307 Hz, CF_3), 129.40, 128.81, 128.46, 122.49, 110.86, 55.76, 31.15 (apparent d, J = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{16}H_{13}O_2F_3S) + H]^+$: 327.0661, found: 327.0664.

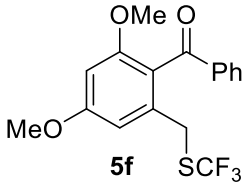
Phenyl(6-(((trifluoromethyl)thio)methyl)benzo[d][1,3]dioxol-5-yl)methanone (5e).



5e

Reaction Time: 1 h; R*f*: 0.5 (1:9 EtOAc:Pet. Ether); Thick oil; 56 mg, 72% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.69 (d, J = 7.3 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H), 6.88 (s, 1H), 6.81 (s, 1H), 5.99 (s, 2H), 4.15 (s, 2H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.58, 149.96, 146.58, 137.94, 132.99, 132.71, 131.00, 130.97 (q, J = 307 Hz, CF_3), 130.12, 128.42, 111.17, 111.10, 102.09, 32.15 (apparent d, J = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{16}H_{11}O_3F_3S) + H]^+$: 341.0454, found: 341.0456.

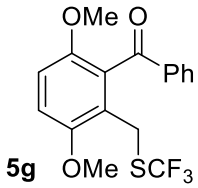
(2,4-Dimethoxy-6-(((trifluoromethyl)thio)methyl)phenyl)(phenyl)methanone (5f).



5f

Reaction Time: 4 h; R*f*: 0.3 (1:9 EtOAc:Pet. Ether); Thick oil; 31 mg, 38% yield;isomer's ratio (1:0.2); **^{1}H NMR (400 MHz, $CDCl_3$)**δ 7.70 (d, J = 7.9 Hz, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 6.52 (s, 1H), 6.39 (s, 1H), 3.94 (s, 2H), 3.80 (s, 3H), 3.54 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.70, 161.79, 158.95, 138.41, 136.63, 133.14, 129.51 (q, J = 306 Hz, CF_3), 129.31, 128.33, 121.52, 106.86, 98.22, 55.68, 55.54, 31.57 (apparent d, J = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{17}H_{15}O_3F_3S) + H]^+$: 357.0767, found: 357.0769.

(3,6-Dimethoxy-2-(((trifluoromethyl)thio)methyl)phenyl)(phenyl)methanone (5g).

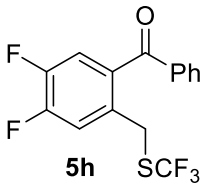


5g

Reaction Time: 4 h; R*f*: 0.5 (1:9 EtOAc:Pet. Ether); White Solid; 49 mg, 60% yield; Mp= 84-86 ^{o}C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 (d, J = 7.9 Hz, 2H),

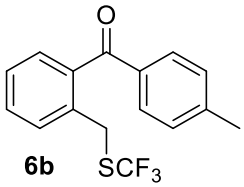
7.50 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 3.96 (s, 2H), 3.81 (s, 3H), 3.55 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.20, 151.97, 150.65, 137.36, 133.59, 130.67 (q, *J* = 306 Hz, CF_3), 130.39, 129.53, 128.43, 122.69, 112.32, 111.74, 56.20 (2C), 25.24 (apparent d, *J* = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{17}H_{15}O_3F_3S)+H]^+$: 357.0767, found: 357.0769.

(4,5-Difluoro-2-(((trifluoromethyl)thio)methyl)phenyl)(phenyl)methanone (5h).



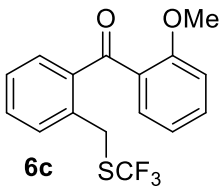
Reaction Time: 1 h; R*f*: 0.6 (1:19 EtOAc:Pet. Ether); oil; 49 mg, 65% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 7.9 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.30-7.24 (m, 1H), 7.24-7.14 (m, 1H), 4.17 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.40, 151.47 (dd, *J* = 264, 13 Hz) , 151.26 (dd, *J* = 264, 13 Hz), 147.31 (t, *J* = 13 Hz), 136.84, 134.80 (t,*J* = 5.4 Hz), 133.73, 130.60 (q, *J* = 307 Hz, CF_3), 130.16, 128.69, 120.20 (apparent d, *J* = 12.3 Hz, 1C), 120.2 (apparent d, *J* = 11.6 Hz, 1C), 31.06; **HRMS-ESI** (*m/z*) calcd For $[(C_{15}H_9OF_5S) + H]^+$: 333.0367, found: 333.0366.

***p*-Tolyl(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6b).**



Reaction Time: 2 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 54 mg, 81% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.9 Hz, 2H), 7.45-7.37 (m, 2H), 7.34-7.25 (m, 2H), 7.20 (d, *J* = 9.1 Hz, 2H), 4.20 (s, 2H), 2.37 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.42, 144.29, 137.75, 136.38, 134.94, 131.00, 130.94, 130.78 (q, *J* = 306 Hz, CF_3), 130.50, 130.26, 129.16, 127.25, 31.81 (apparent d, *J* = 2 Hz, CH_2), 21.73; **HRMS-ESI** (*m/z*) calcd For $[(C_{16}H_{13}OF_3S) + H]^+$: 311.0712, found: 311.0715.

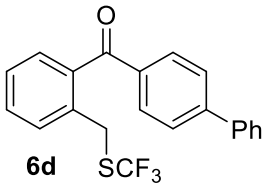
(2-Methoxyphenyl)(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6c).



6c

Reaction Time: 1h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 40 mg, 61% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (t, *J* = 8.0 Hz, 1H), 7.40-7.35 (m, 3H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.0 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.39 Hz, 1H), 4.33 (s, 2H), 3.60 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.93, 158.16, 137.88, 136.88, 133.03, 131.64, 131.53, 131.22 (q, *J* = 307.08 Hz, CF_3), 130.96, 130.65, 128.83, 127.51, 120.49, 111.68, 55.50, 32.43 (apparent s, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{16}H_{13}O_2F_3S) + H]^+$: 327.0661, found: 327.0660.

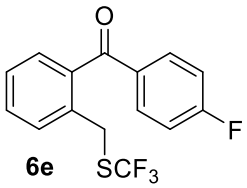
[1,1'-Biphenyl]-4-yl(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6d).



6d

Reaction Time: 1 h; R*f*: 0.4 (1:19 EtOAc:Pet. Ether); oil; 31 mg, 49% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.9 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.46-7.37 (m, 5H), 7.37-7.28 (m, 2H), 4.24 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.32, 146.04, 139.80, 137.49, 136.61, 136.20, 131.21, 131.05, 130.93, 130.8 (q, *J* = 306, CF_3), 130.43, 128.98, 128.33, 127.32, 127.12, 31.85 (apparent d, *J* = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{21}H_{15}OF_3S) + H]^+$: 373.0868, found: 373.0873.

(4-Fluorophenyl)(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6e)

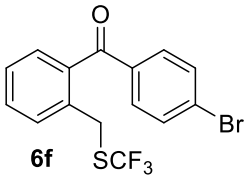


6e

Reaction Time: 1 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 42 mg, 63% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.46-7.38 (m, 2H), 7.34-7.26 (m, 2H), 7.08 (t, *J* = 8.5 Hz, 2H), 4.22 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.18, 165.88 (d, *J* = 255.85 Hz, 1C), 137.20, 136.58, 133.84 (d, *J* = 3.0 Hz, 1C), 132.96 (d, *J* = 10.0 Hz, 2C), 131.20 (d, *J* = 17.0 Hz, 2C),

130.71 (q, *J* = 307 Hz, CF_3), 130.18, 127.36, 115.77, 115.56, 31.74 (apparent d, *J* = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{15}H_{10}OF_4S) + H]^+$: 315.0461, found: 315.0478.

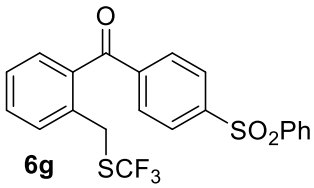
(4-Bromophenyl)(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6f)



6f

Reaction Time: 1 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 58 mg, 93% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.47-7.39 (m, 2H), 7.31 (m, 2H), 4.23 (s, 2H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.66, 136.86, 136.83, 136.31, 131.81, 131.74, 131.47, 131.18, 130.72 (q, *J* = 307 Hz, CF_3), 130.33, 128.58, 127.39, 31.79 (apparent d, *J* = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{15}H_{10}OBrF_3S)+H]^+$: 374.9661, found: 374.9661.

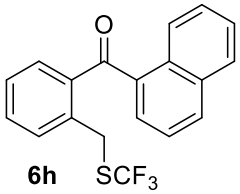
(4-(Phenylsulfonyl)phenyl)(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6g).



6g

Reaction Time: 30 min.; R*f*: 0.5 (1:5 EtOAc:Pet. Ether); oil; 41 mg, 67% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.79 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.33-7.23 (m, 2H), 4.24 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.35, 145.42, 141.47, 140.67, 137.51, 135.88, 133.71, 132.09, 131.41, 130.93, 130.82, 130.68 (q, *J*= 307 Hz, CF_3), 129.50, 127.95, 127.72, 127.54, 31.82 (apparent d, *J* = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{21}H_{15}O_3F_3S_2) + Na]^+$: 459.0307, found: 459.0331.

Naphthalen-1-yl(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6h).

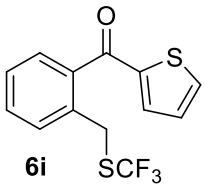


6h

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 45 mg, 70% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.42-8.33 (m, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.97-7.90 (m, 1H), 7.60-7.53 (m, 3H), 7.53-7.44 (m, 3H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.34-7.27 (m, 1H), 4.46 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.55, 137.95,

137.91, 136.11, 133.79, 132.55, 132.47, 132.09, 131.21, 131.09 (q, J = 306 Hz, CF_3), 131.07, 129.96, 128.49, 127.81, 127.69, 126.61, 125.64, 124.26, 32.49 (apparent d, J = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{19}H_{13}OF_3S) + Na]^+$: 369.0531, found: 369.0547.

Thiophen-2-yl(2-(((trifluoromethyl)thio)methyl)phenyl)methanone (6i).



6i

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); yellow oil; 43 mg, 65% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, J = 4.3 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.48-7.38 (m, 3H), 7.33 (t, J = 7.0 Hz, 1H), 7.08 (t, J = 3.4 Hz, 1H), 4.21 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.32, 144.41, 137.44, 136.03, 135.77, 135.33, 131.28, 131.06, 130.77 (q, J = 307.4 Hz, CF_3), 129.73, 128.19, 127.43, 31.63 (apparent d, J = 2 Hz, CH_2); **HRMS-ESI** (*m/z*) calcd For $[(C_{13}H_9OF_3S_2) + H]^+$: 303.0120, found: 303.0134.

3.2.10. References

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3.2.11. Spectra

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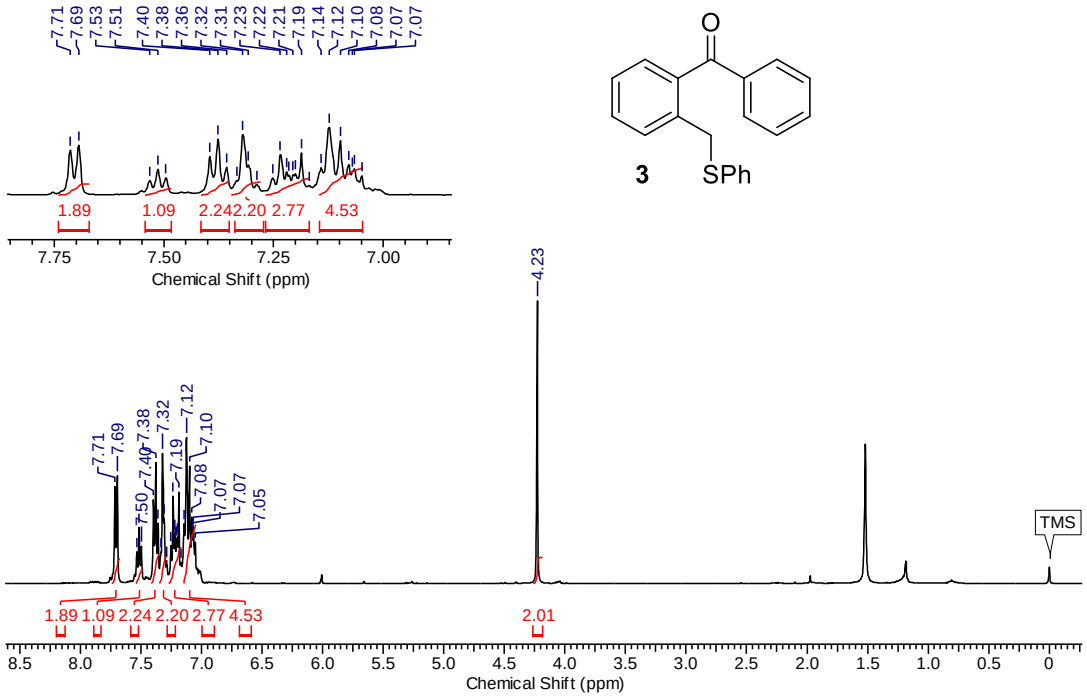

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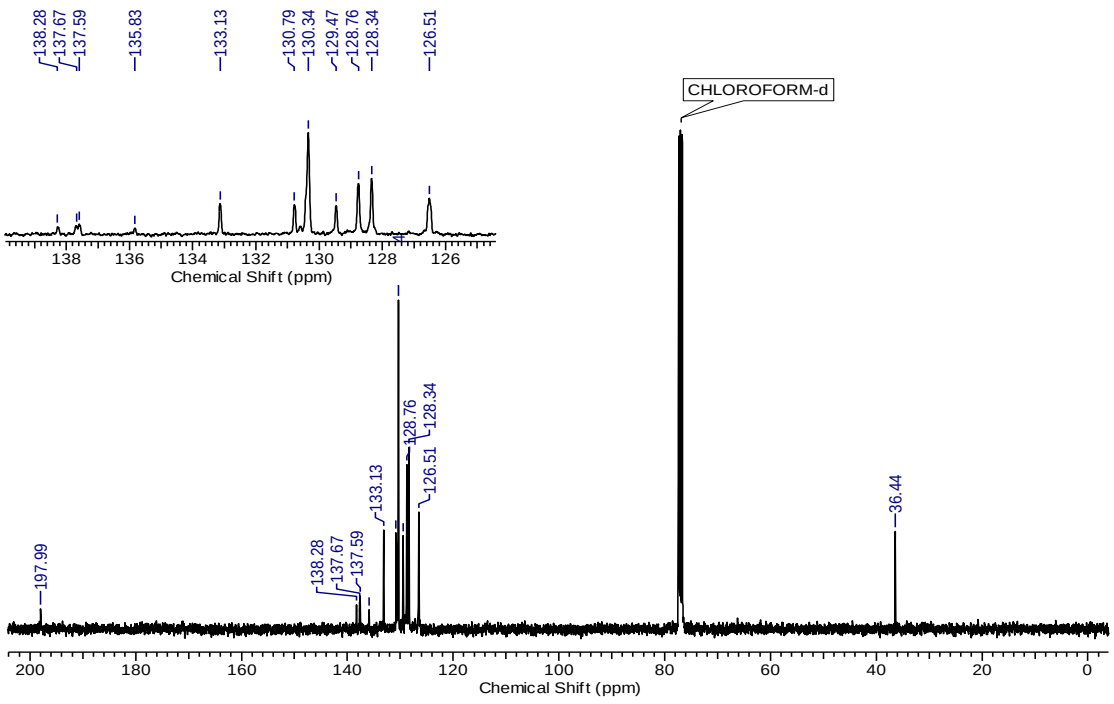

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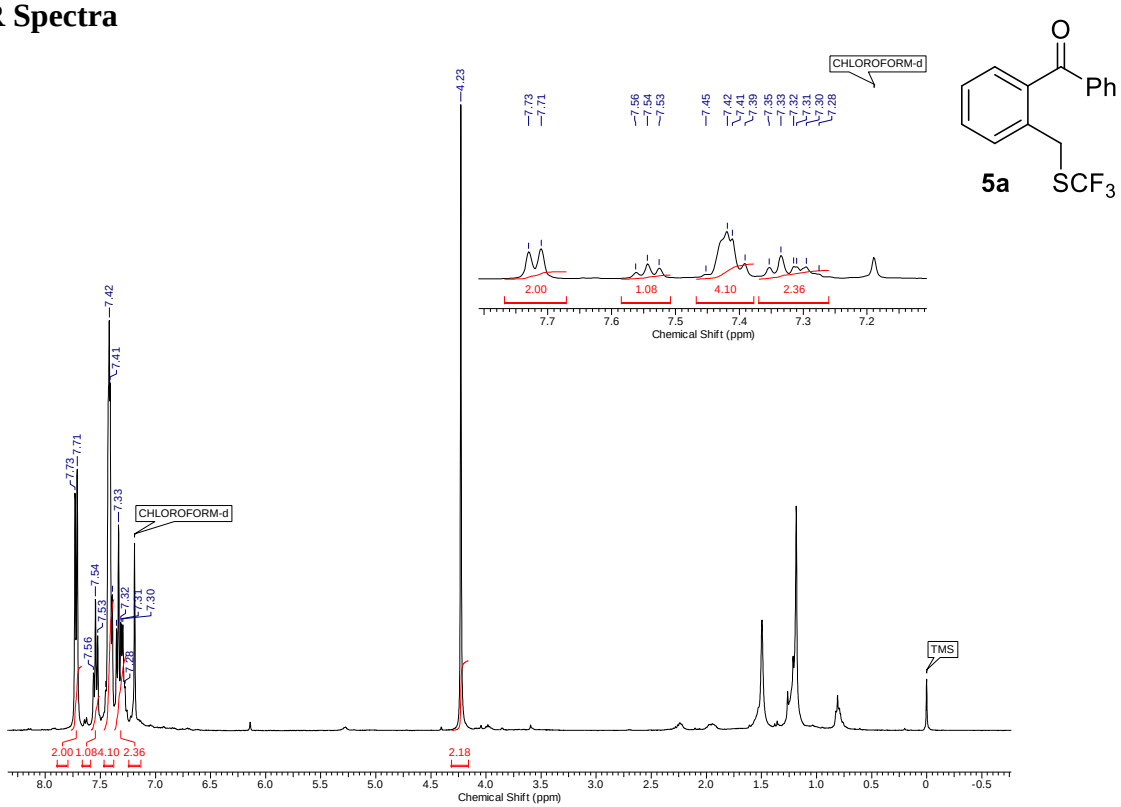

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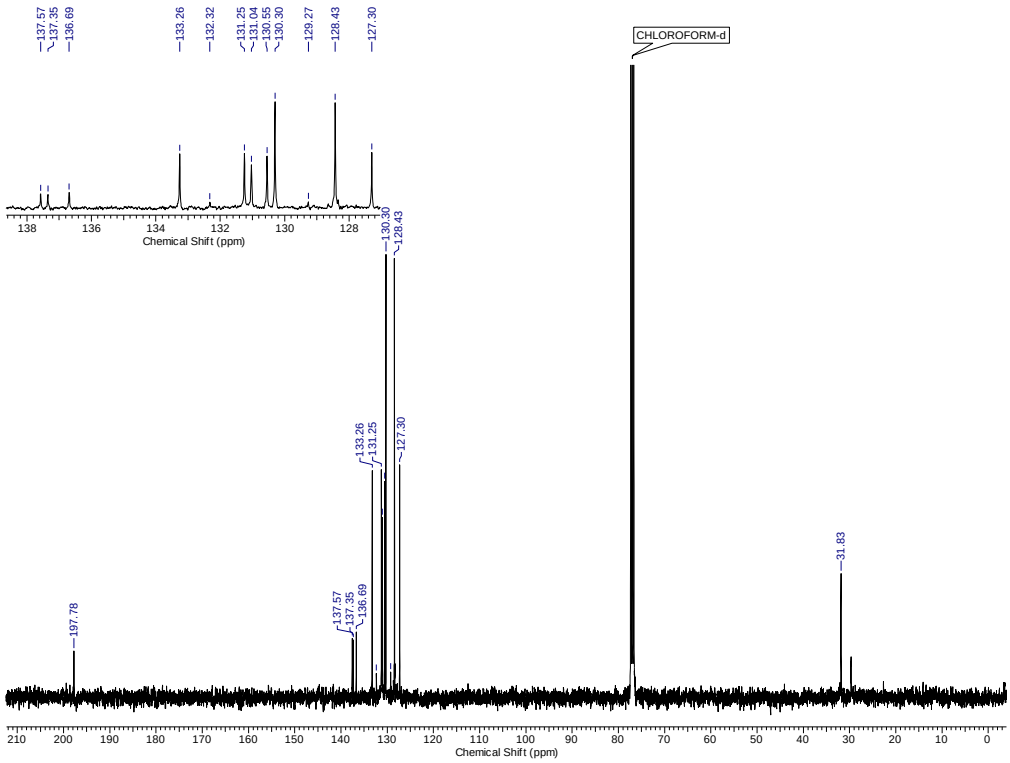

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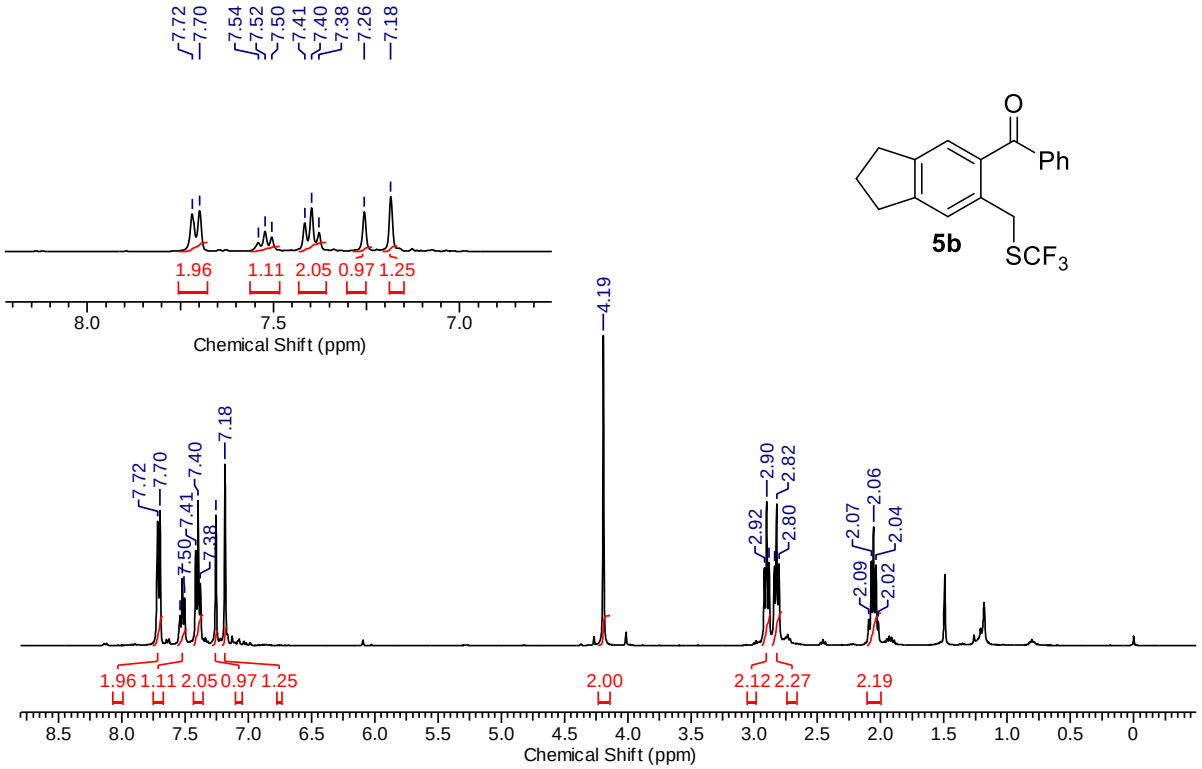

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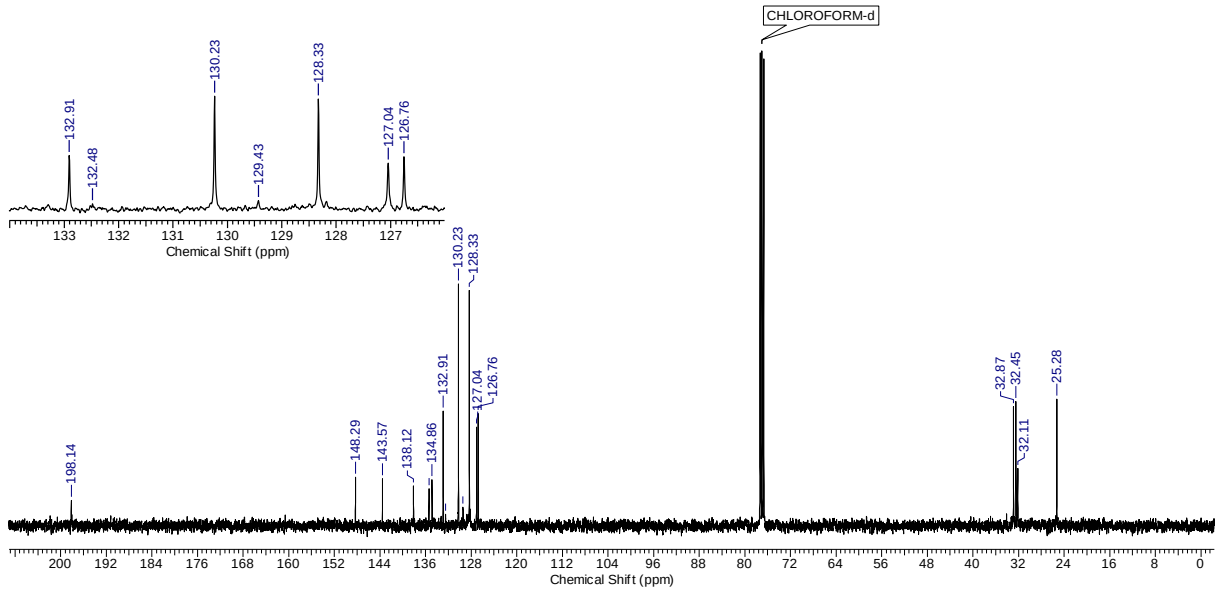

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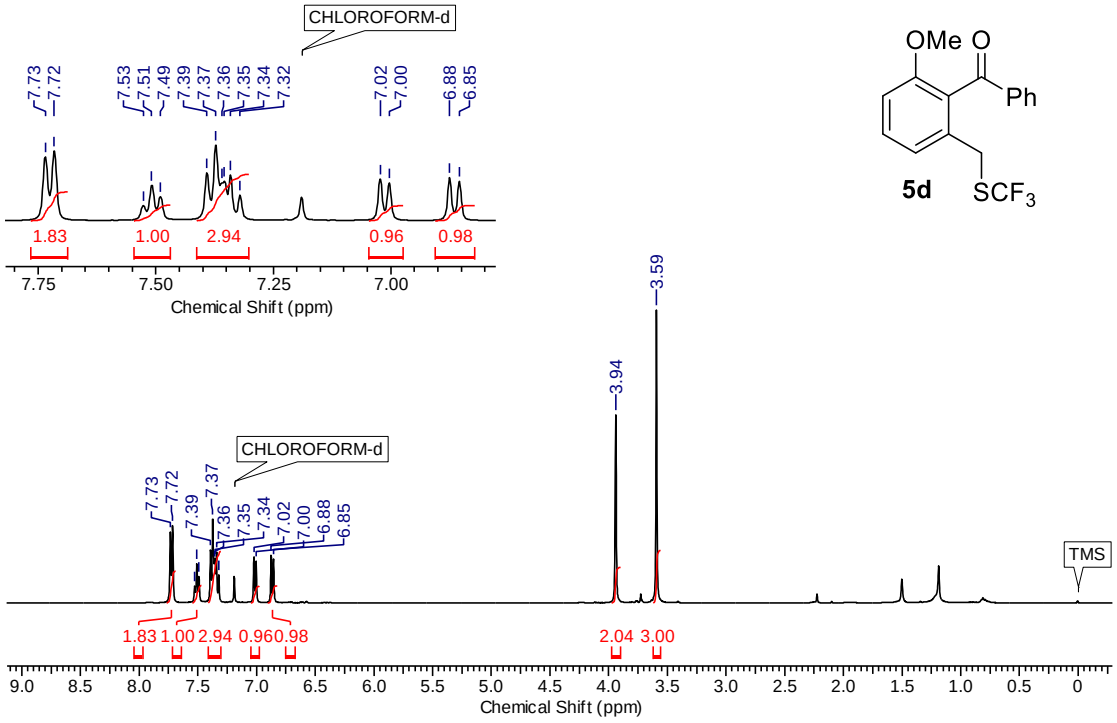

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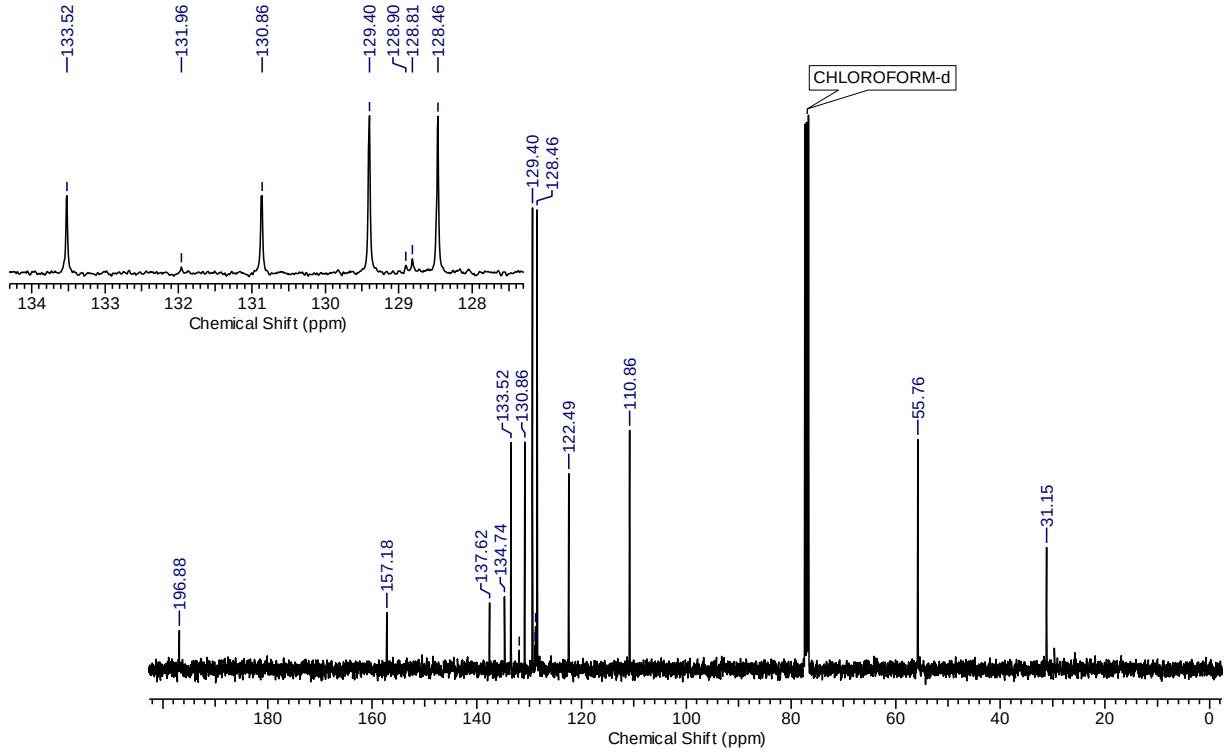

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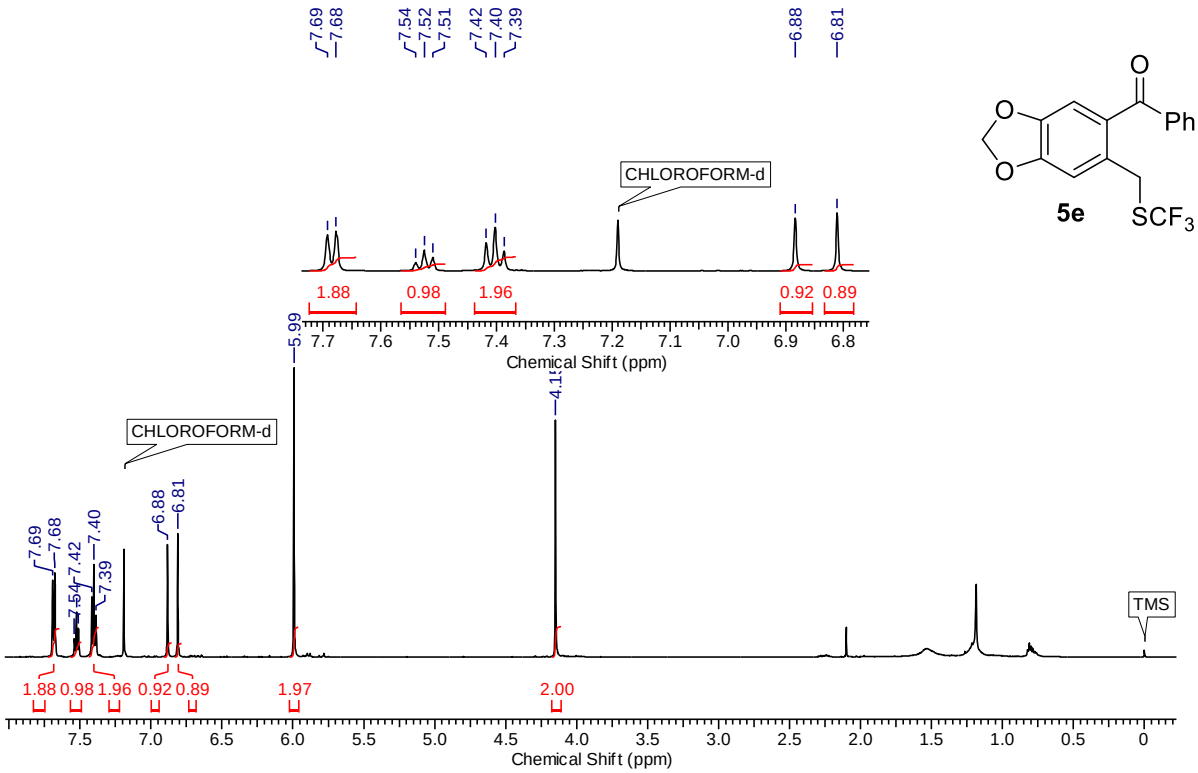

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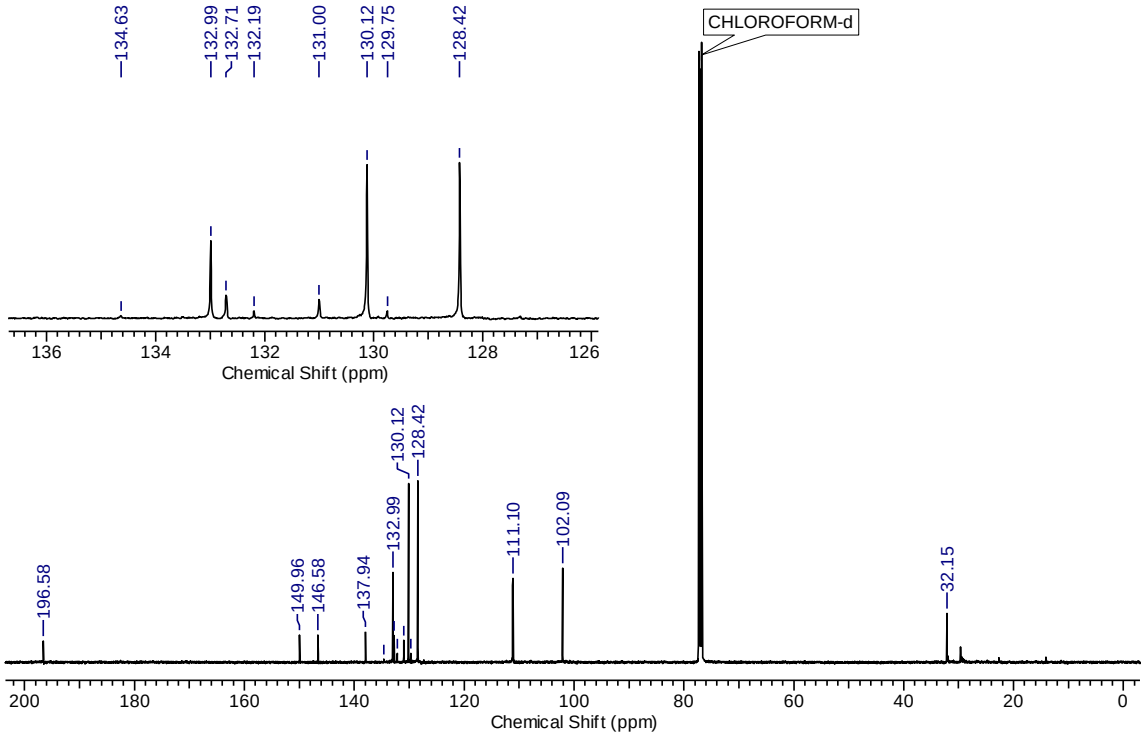

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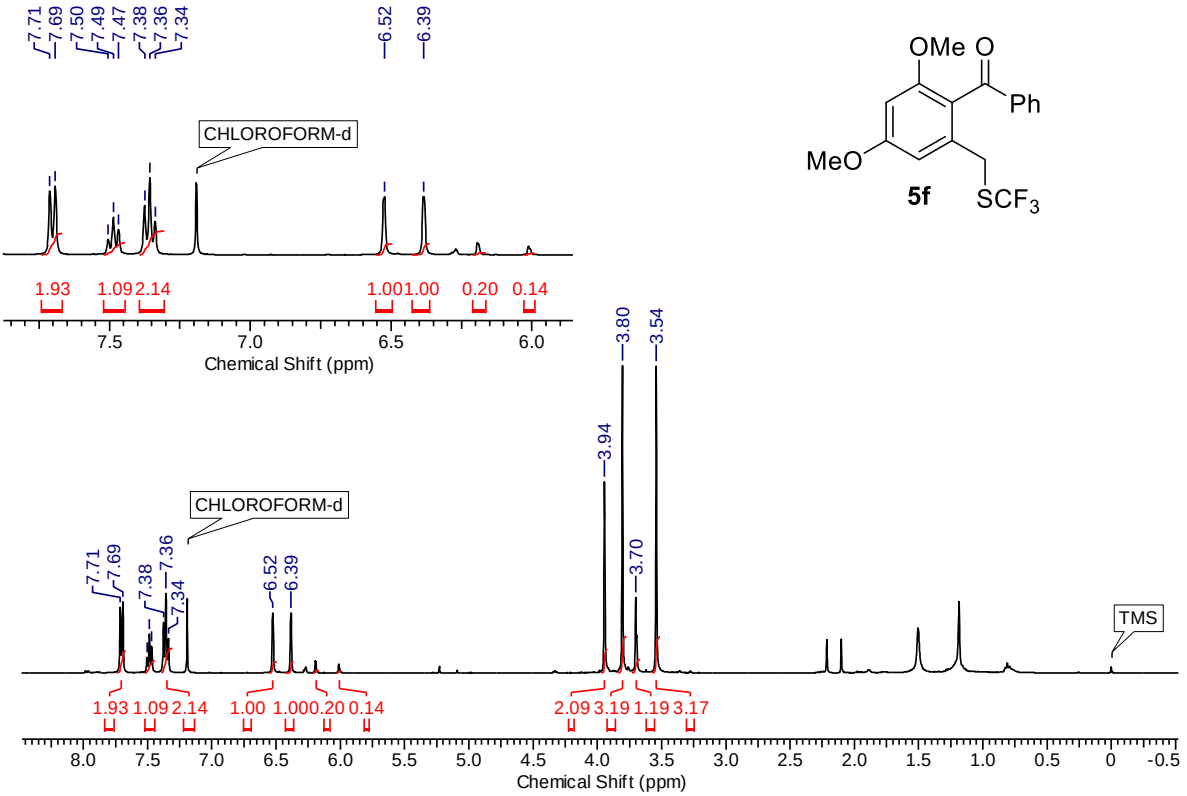

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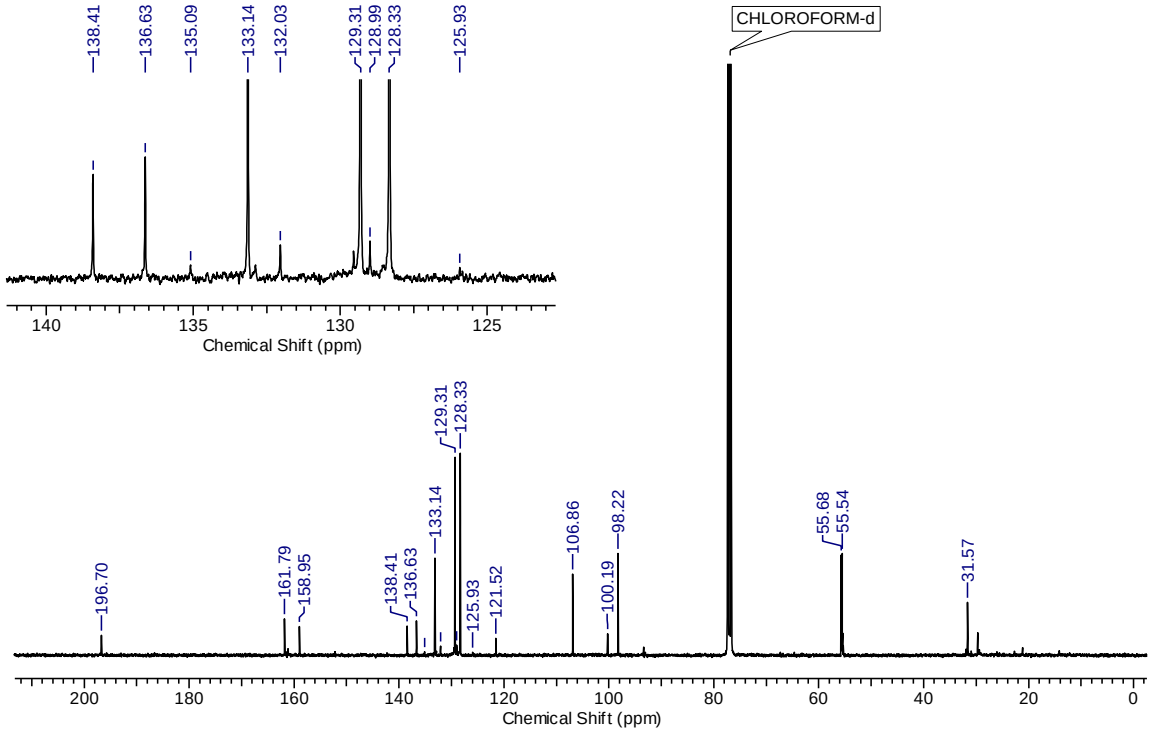

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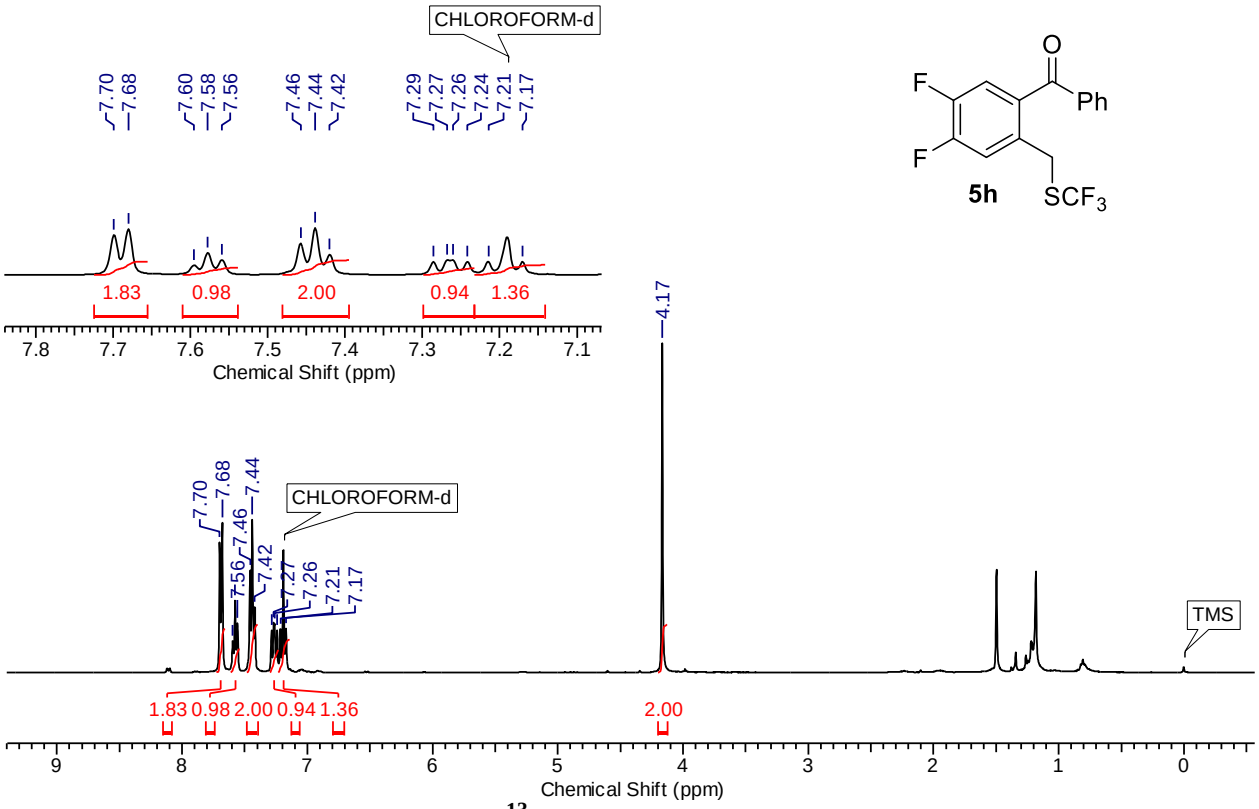

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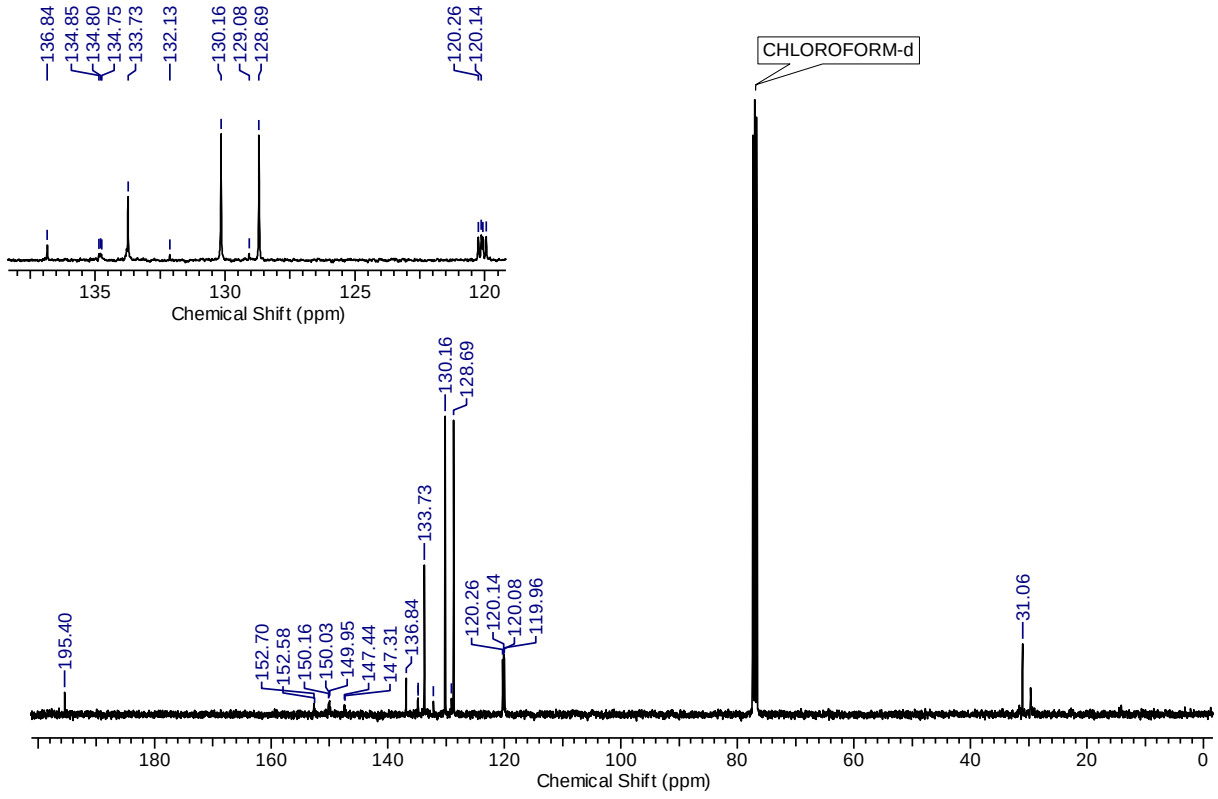

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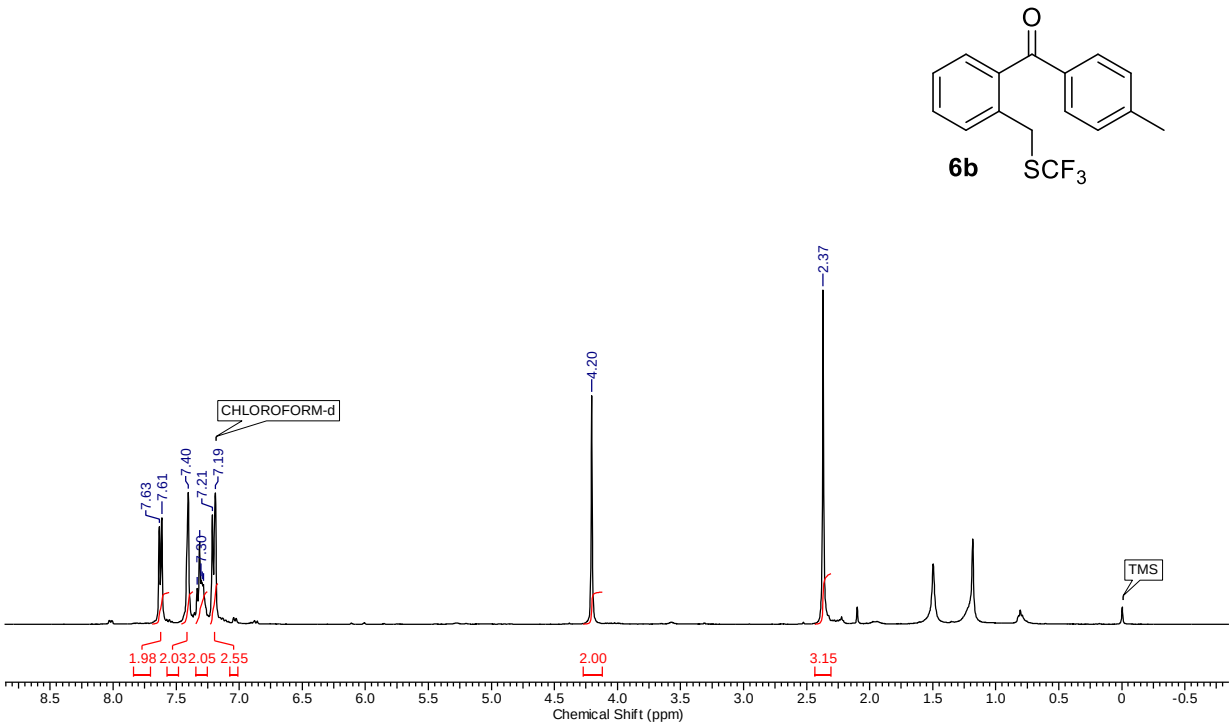

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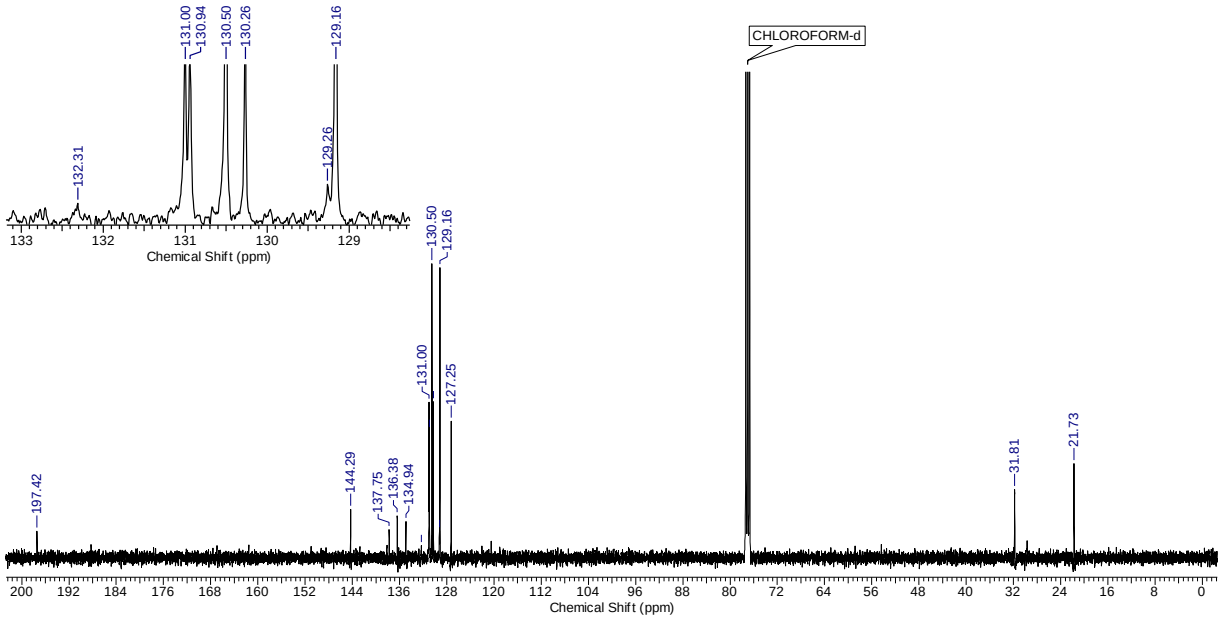

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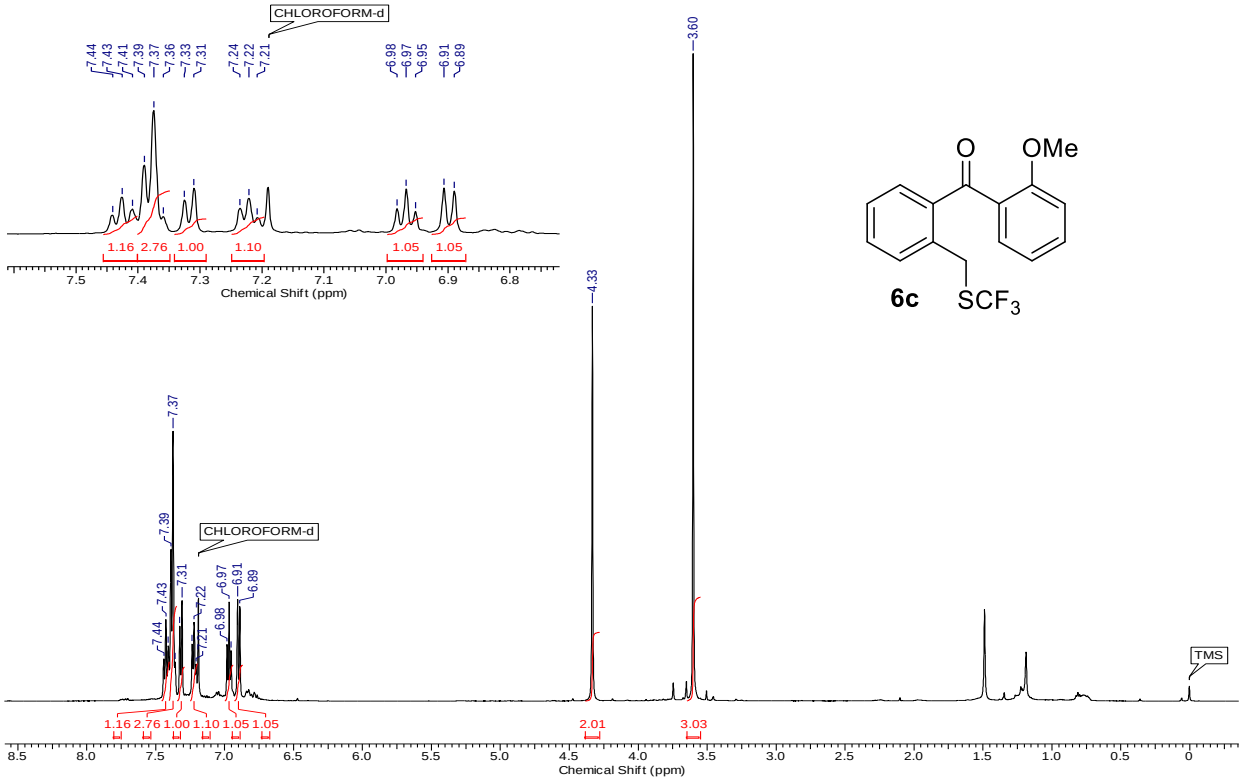

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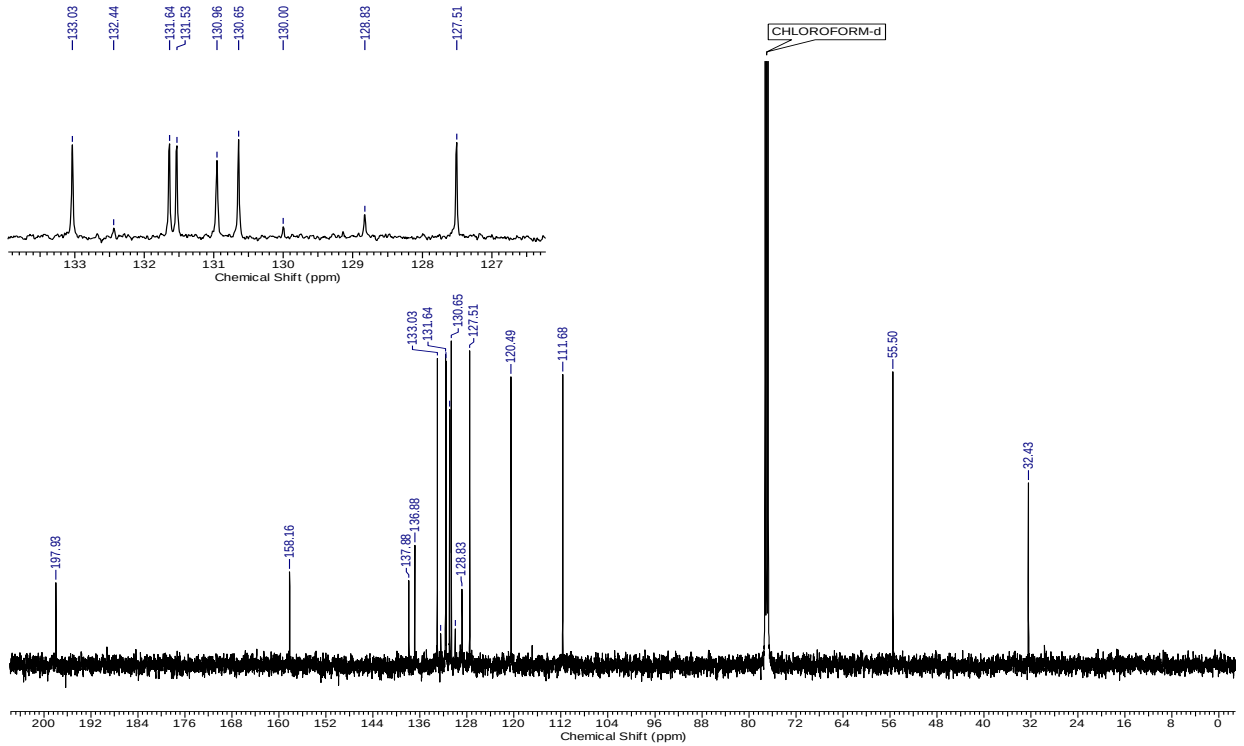

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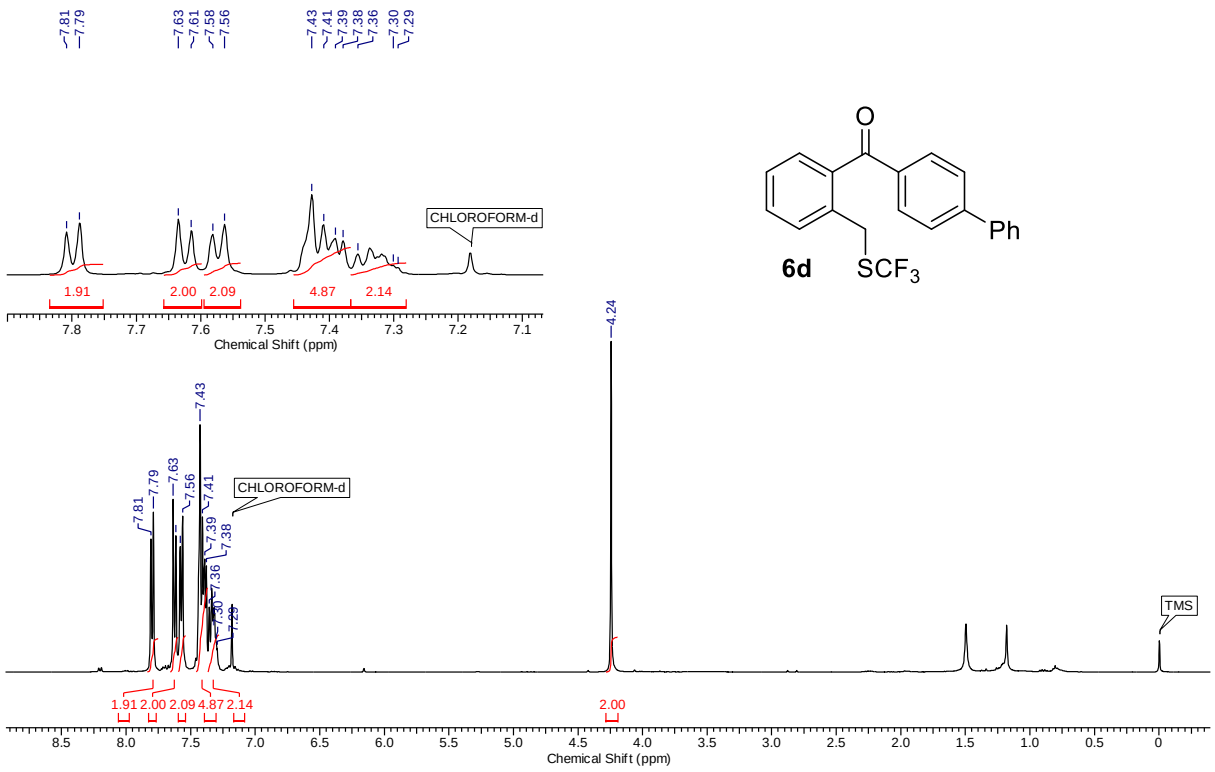

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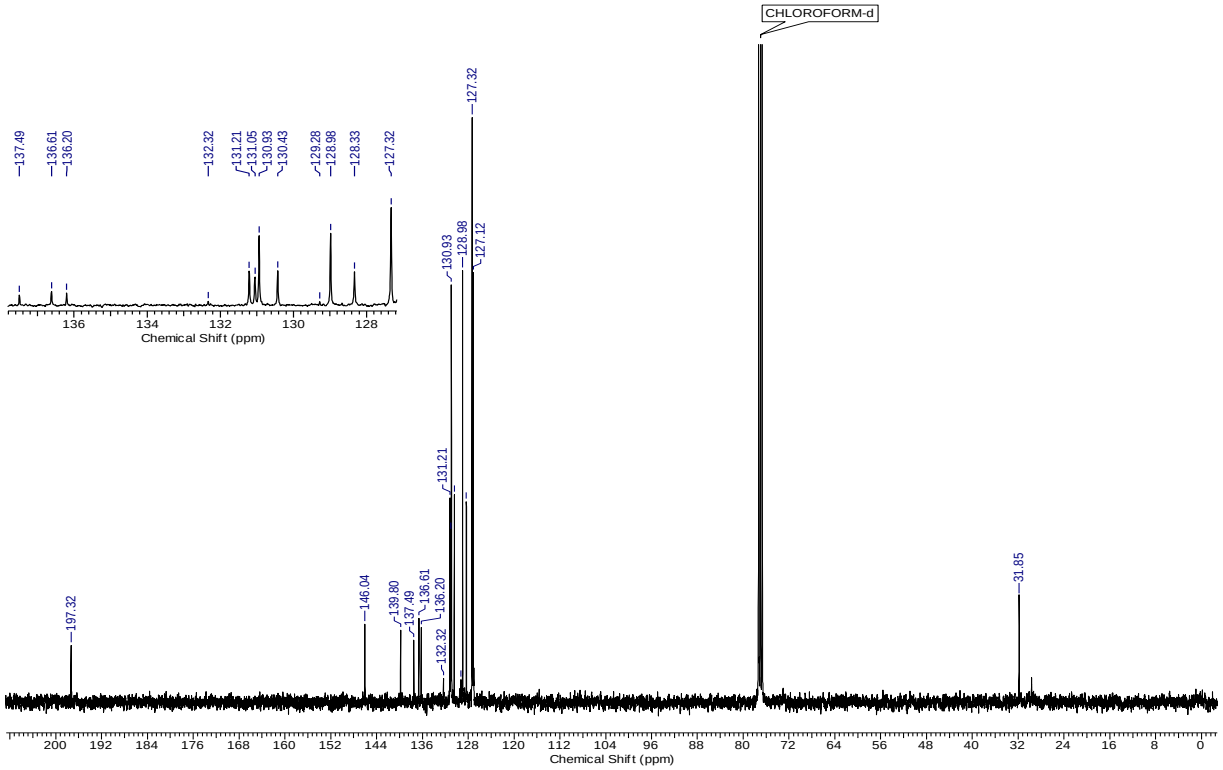

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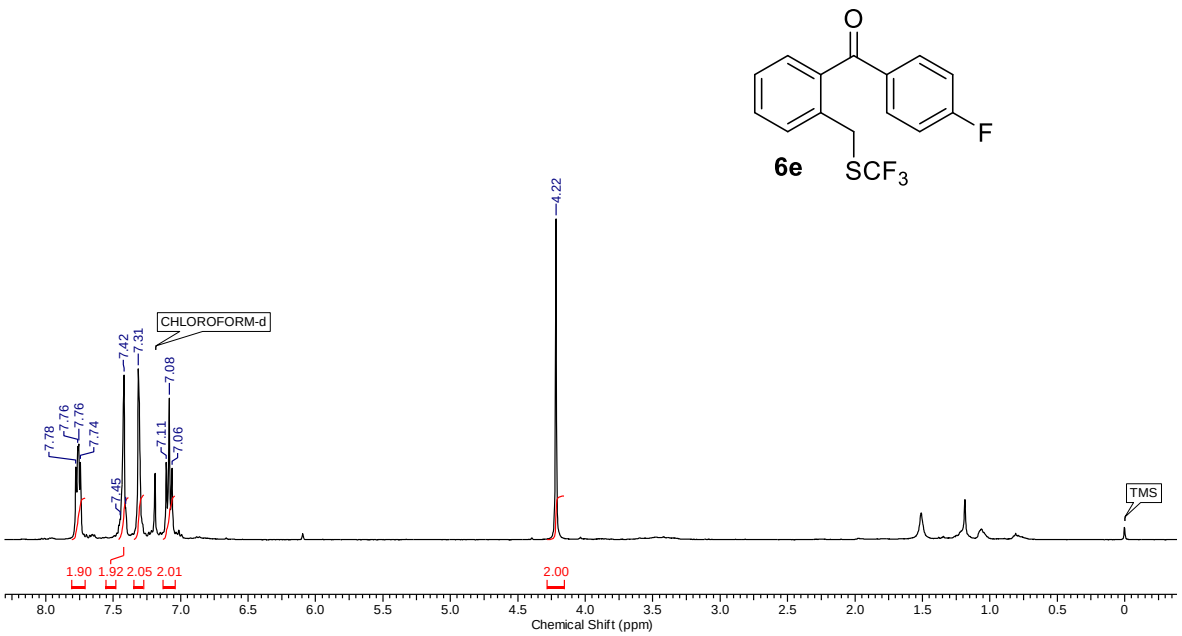

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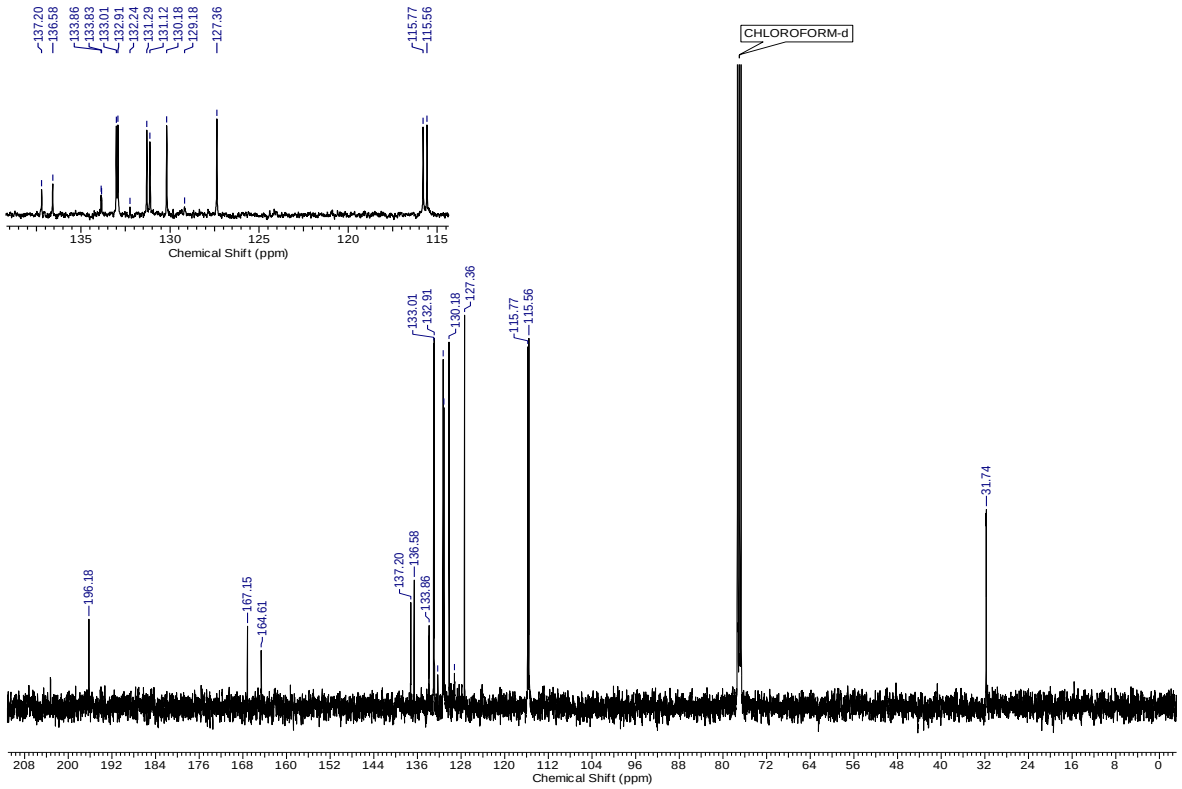

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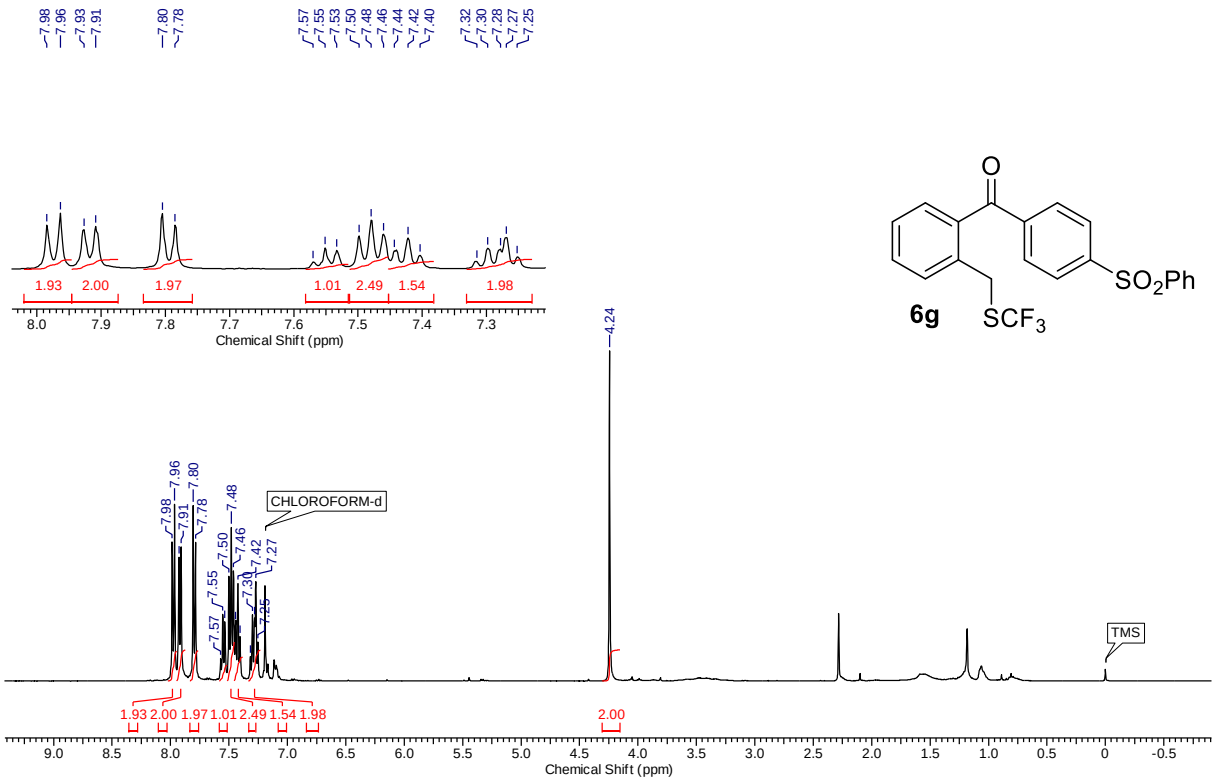

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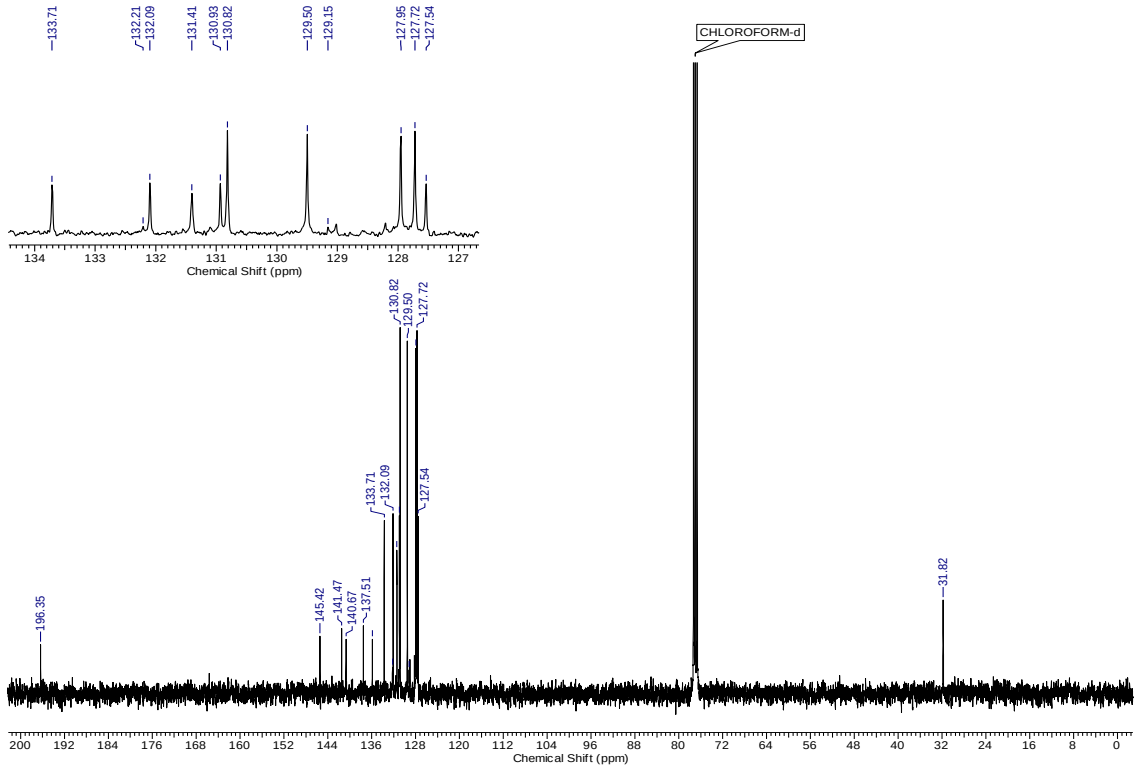

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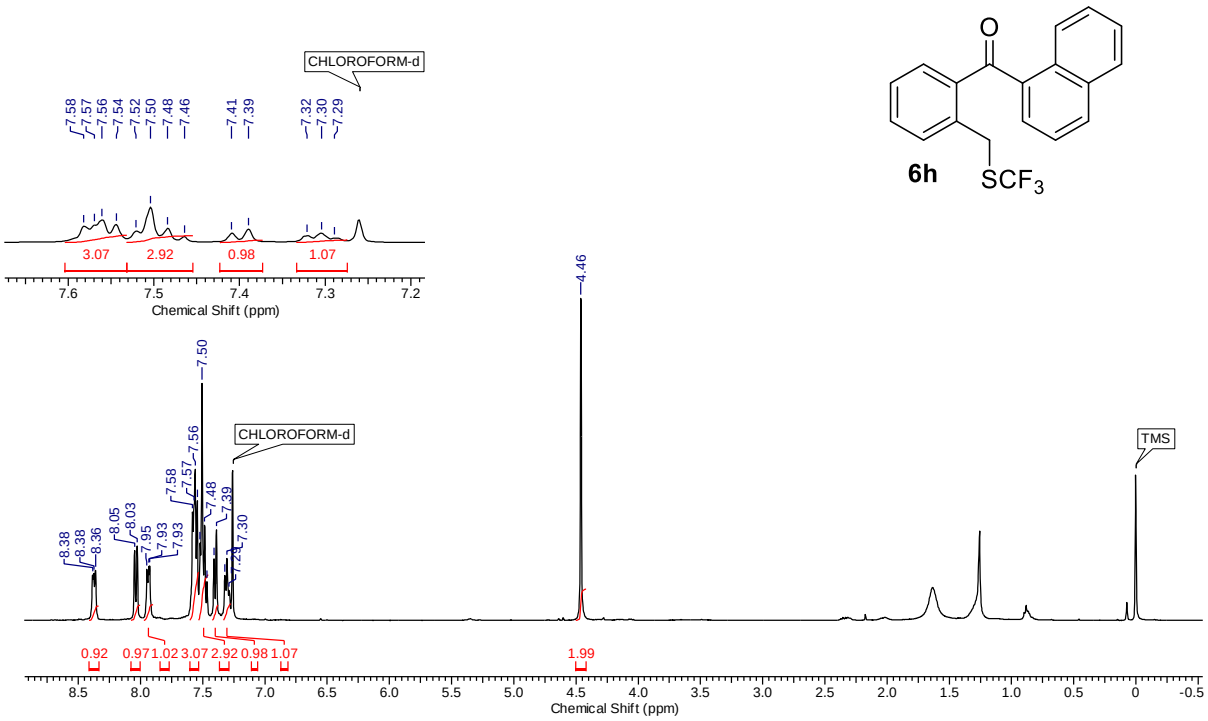

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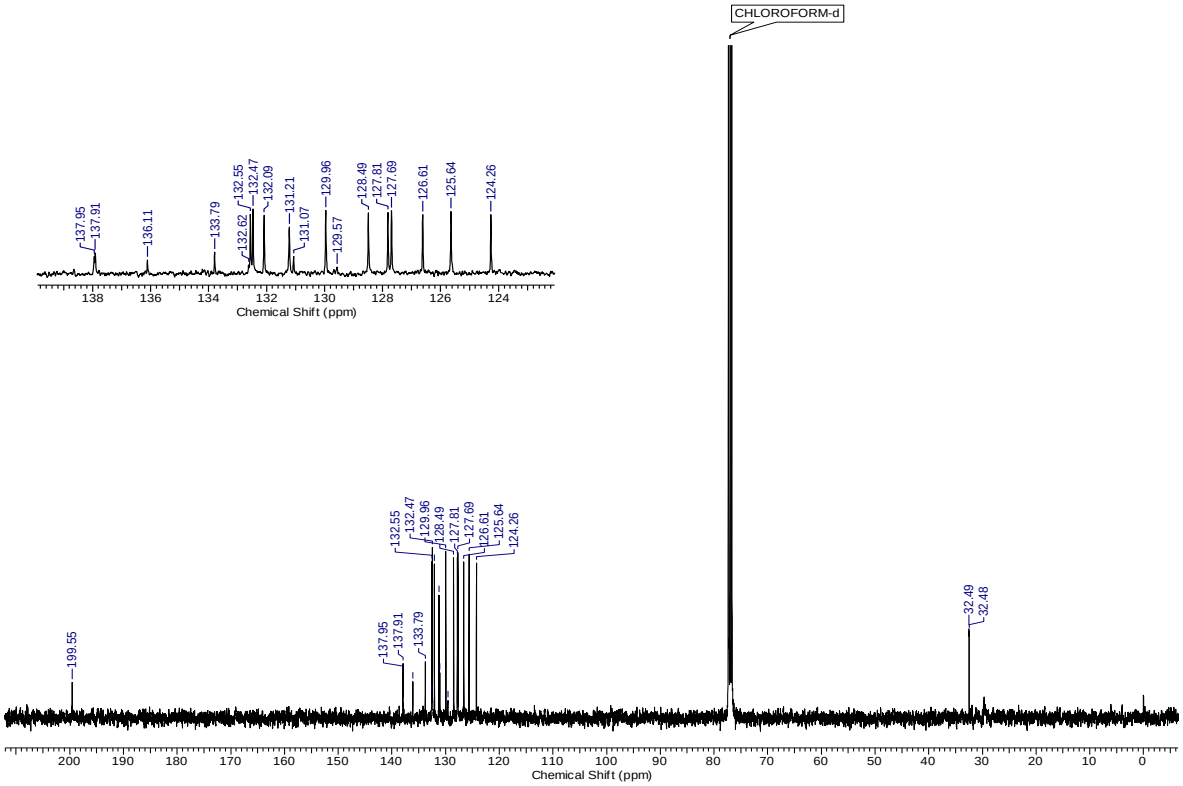

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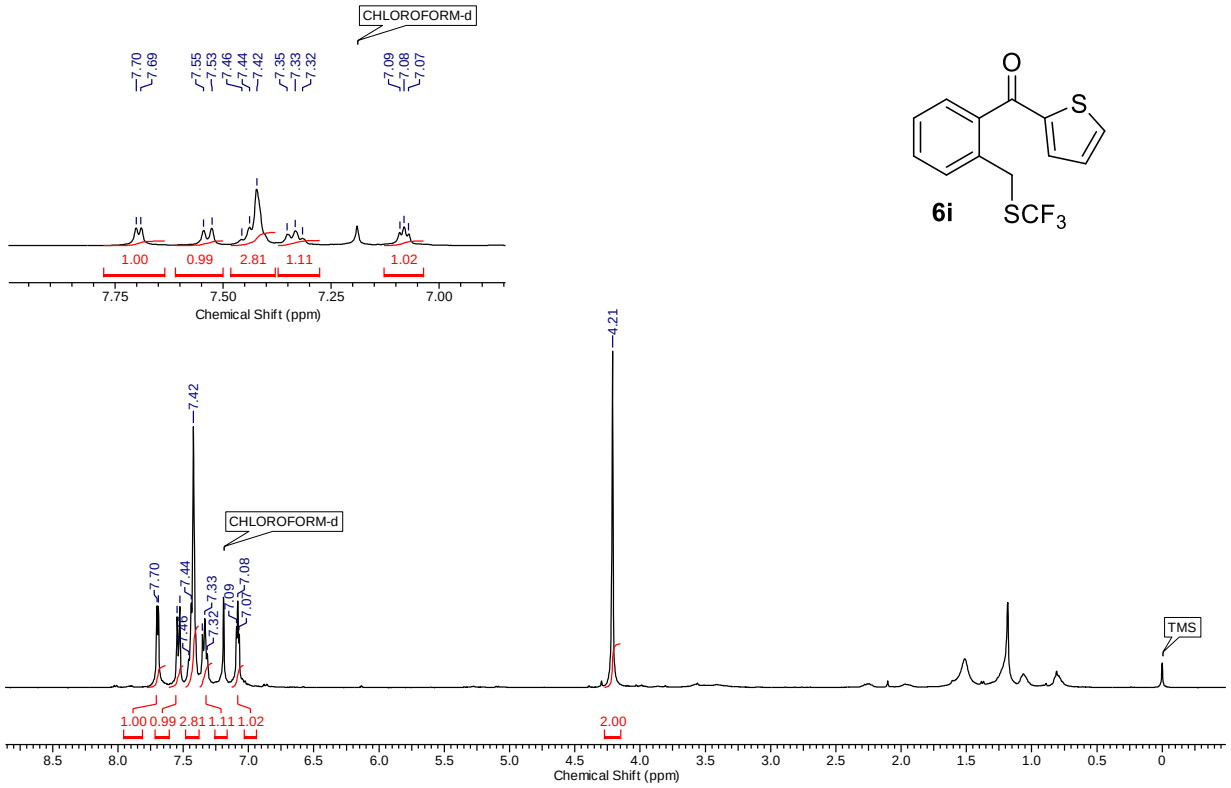

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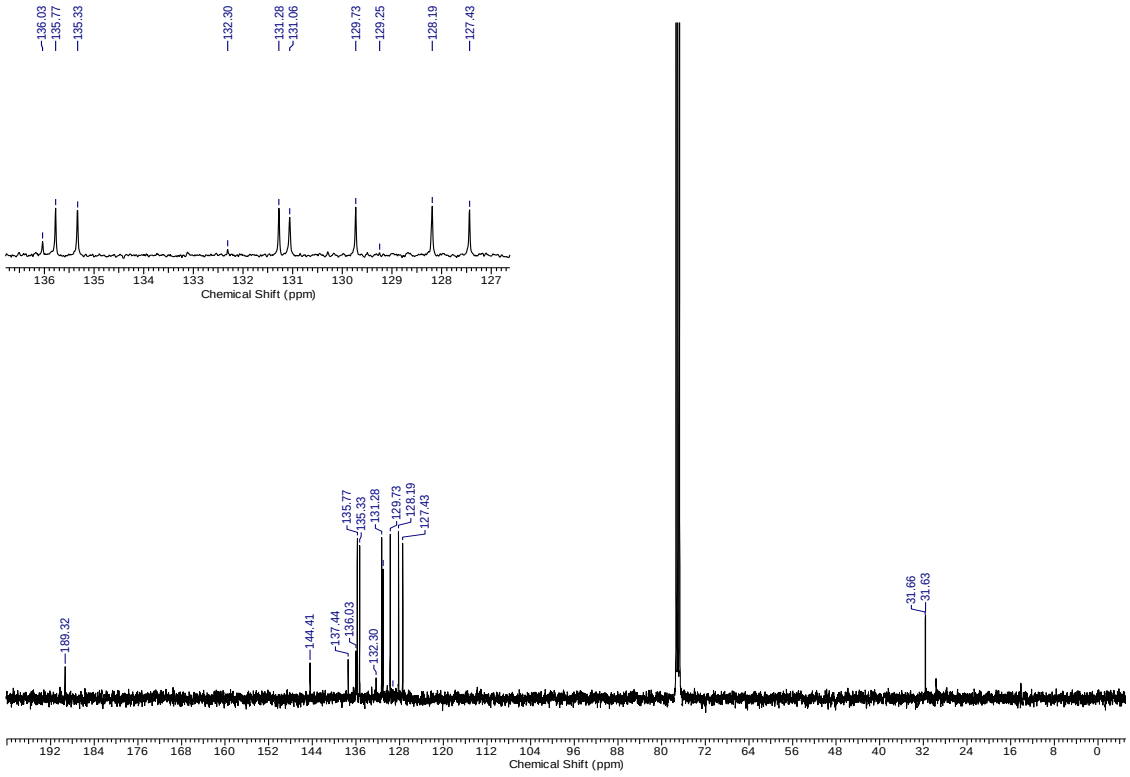
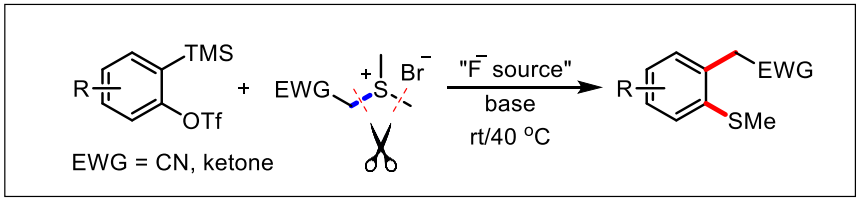


Section 3: Application of Sulfur Ylides in 1,2-Difunctionalization of Arynes via Insertion into a C−S σ-Bond

3.3.1. Abstract

Herein, we have demonstrated a novel reactivity of sulfur ylides using a transition-metal-free protocol to access *ortho*-substituted thioanisole derivatives by insertion of arynes into a C−S σ-bond in moderate to good yields. A sulfur ylide works as an effective reagent for difunctionalization of aryne. The reaction involves the formation of C−C and C−S bonds and consecutive breaking of two C−S bonds under operationally mild reaction conditions.



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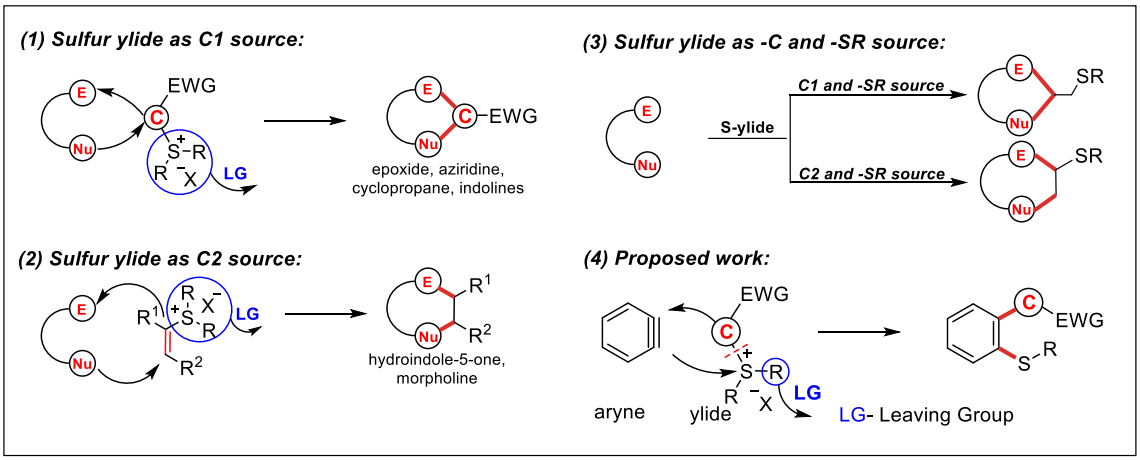
3.3.2. Introduction

Ylides are synthetically valuable reagents, and they are regarded as one of the powerful synthetic tools in organic chemistry.[1] A ylide is a neutral 1,2-dipolar species consisting of electron-rich carbon atom and an adjacent electro-positive heteroatom such as phosphorus, sulfur, nitrogen, etc. Among them, sulfur ylides are commonly used as one[2] or two[3] (C1 or C2) carbon synthons for the construction of cyclopropanes,[2a] indolines,[2b] epoxides,[2c] pyrrolines,[2d] oxazolidin-2-ones,[2e] aziridines,[2c,3a] hydroindol-5-ones,[3b] morpholines,[3c] etc. (Scheme 1, eq 1 and 2). Few examples of sulfur ylide as a C1/C2 and −SR source are known (Scheme 1, eq 3).[3d,e] Recently, sulfur ylides have been introduced as an active catalyst for organic synthesis,[4] and pioneering works by

Aggarwal et al. and other groups demonstrated asymmetric transformations using sulfur ylides, which provide an implicit route to many complex useful compounds.[2c–e,5] Such development of novel strategies for the construction of new scaffolds using sulfur ylides is an area of contemporary interest.[2–6] However, the proposed application of sulfur ylide as a C1 and −SMe source with aryne is unknown (Scheme 1, eq 4).

Scheme 1. Applications of Sulfur Ylides

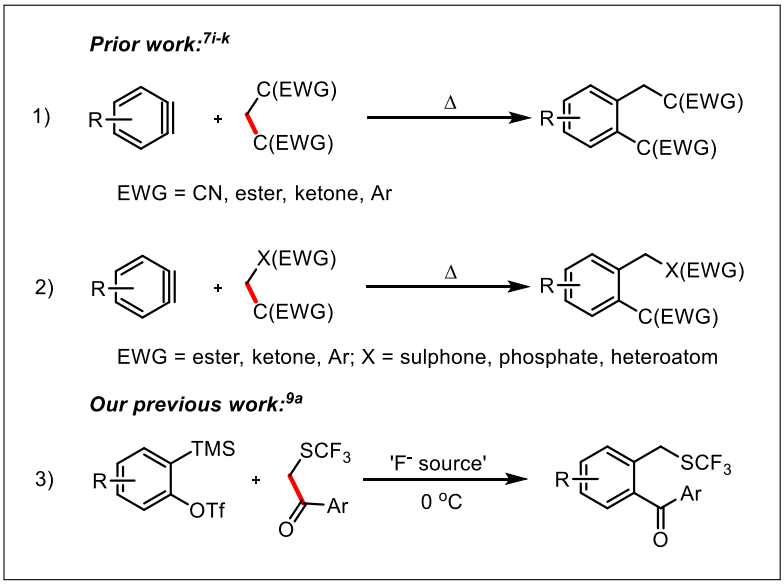


3.3.3. Literature Review

On the other hand, a highly reactive electrophilic aryne species has emerged as a prolific building block in organic synthesis.[7] The advent of Kobayashi's simple aryne precursor and a mild fluoride-mediated method of aryne generation revolutionized aryne chemistry.[8] Because of the low-lying LUMO, their remarkable electrophilicity addresses a variety of organic transformations such as trapping of a wide variety of heteroatom and carbon nucleophiles, cycloaddition, multicomponent reaction (MCR), and elemental-elemental bond insertion reaction.[7] Aryne insertion into C−C, C−heteroatom, or heteroatom−heteroatom bonds is a useful transformation that provides a key strategy for the construction of important 1,2-difunctionalized arene derivatives. It has been studied extensively with or without metal catalysts (Scheme 2, eq 1

and 2).[7i–k] Our laboratory has been associated with a development of novel synthetic methodologies involving aryne as a reacting partner,[9] and recently, we have reported a process for aryne insertion into C−C bond for the synthesis of *o*-methyl trifluoromethyl sulfide substituted benzophenones (Scheme 2, eq 3).[9a]

Scheme 2. Aryne Insertions into Active Methylenes



3.3.4. Origin of the present Work

Very recently, Studer and co-worker demonstrated the generation of ylide from the in situ generated arynes and vinyl sulfides through [3+2] cycloaddition, which upon further rearrangement generated the corresponding di-, tri-, tetrasubstituted alkene with high sterioselectivity (Figure 1, eq 1).[13a] However, to the best of our knowledge, application of sulfur ylide reagent with aryne to form 1,2-disubstituted arene derivatives has not been known until now. Further, Wang and co-worker demonstrated an elegant method for the epoxidation of carbonyl compounds by using sulfoxide and aryne. The reaction involves formation of sulfur ylide intermediate from sulfoxide and aryne through S-O bond insertion and deprotonation (Figure 2, eq 2).[13b] After our publication Chandrasekhar et al. demonstrated the efficient route

for the construction of 2-aroyl benzofurans at room temperature via the cascade [2+2] followed by a [4+1] annulation on arynes. The reaction proceeds through the formation of *ortho*-quinone methide by the insertion of transient aryne into N,N-dimethylformamide and successive trapping with sulfur ylide (Figure 2, eq 3).[13c]

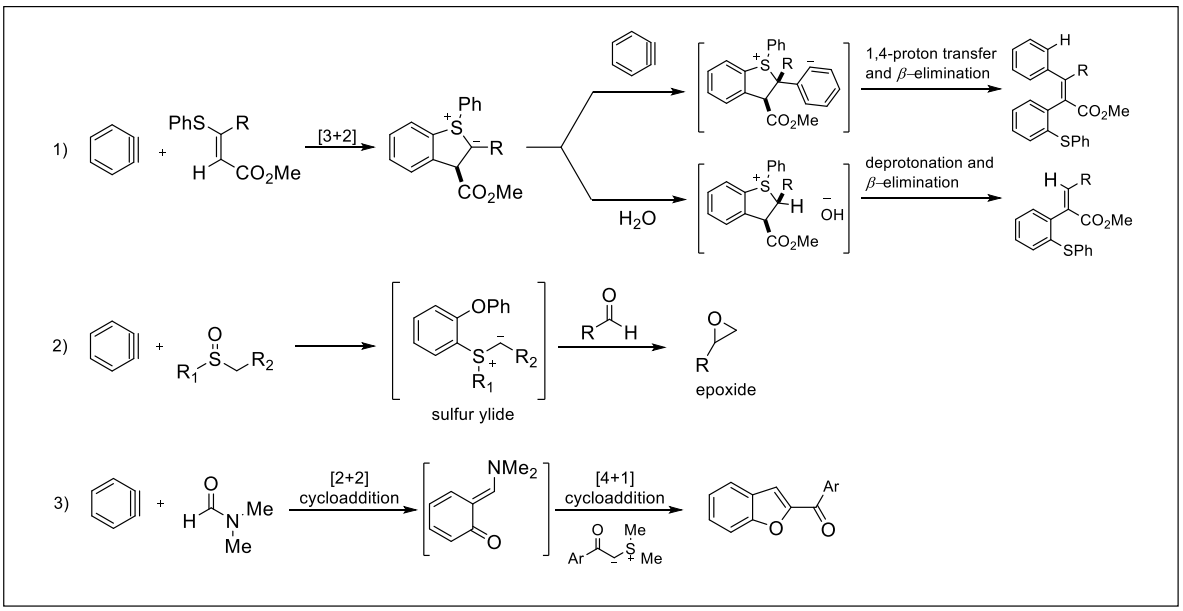


Figure 2. Application of Sulfur ylide with Aryne.

3.3.5. Objective

In continuation of our interest in the aryne chemistry, we herein aim to report aryne insertion into the C−S bond of sulfur ylide to form *ortho*-substituted thioanisole derivatives (Scheme 3). Sulfur-containing compounds display a wide range of biological activities and serve as an important motif in the pharmaceutical and agrochemical related activities.[10] Hence, new strategies for the incorporation of sulfur in organic compounds are always sought after.[11] Interestingly, there are very few reports in the literature dealing with aryne insertion into a C−S bond.[12]

3.3.6. Results and Discussion

We began our investigation by reacting unsubstituted aryne precursor **1a** with the sulfonium salt **2a** in the presence of Cs_2CO_3, KF, and 18-crown-6 in THF under an argon atmosphere at room temperature (Figure 3). Initially, based on the literature reports,[7i–k] we hypothesized the aryne insertion in between active methylene and carbonyl carbon of ylide to form **3a′** (Figure 3). However, surprisingly, we observed an unexpected aryne insertion in the C−S bond of ylide to form the product **3a** in 37% yield within 4 h (Table 1, entry 1).

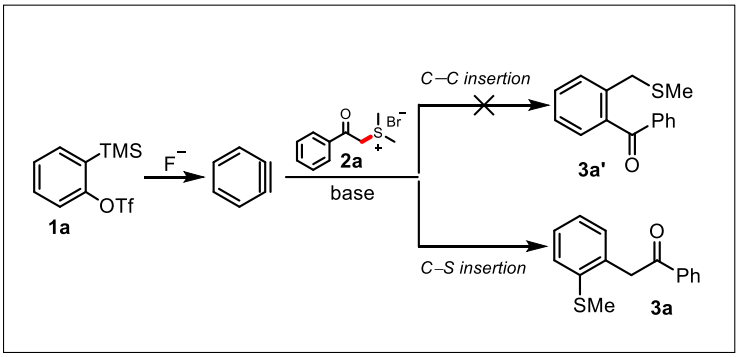
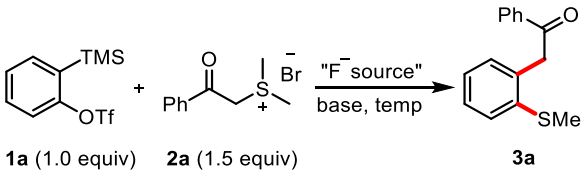


Figure 3. Aryne Insertion into the C−S Bond of Sulfur Ylide.

Encouraged by our preliminary observation, we further intended to find the optimized condition for this transformation. Selected observations are described in Table 1. Initially, we screened different fluoride sources such as TBAF and cesium fluoride along with the corresponding solvent combination, but we could not improve the product formation (Table 1, entries 2, 3). Additionally, the equivalent ratio of **1a/2a** was examined, and improvement in the yield was observed after the number of equivalents of the salt **2a** was increased to 1.5 equiv (Table 1, entry 4). Moreover, screening of other solvents such as toluene and 1,4-dioxane gave unsatisfactory results (Table 1, entries 5, 6), but DME offered better yield (Table 1, entry 7). After the reaction mixture was heated to 40 °C, a slight improvement in the yield was observed (Table 1, entry 8),

Table 1. Optimization of Reaction Condition.[a,b]



1a (1.0 equiv) **2a** (1.5 equiv) **3a**

entry	solvent	F^- source	temp (^oC)	base	time (h)	3a (%)[c]
1[d]	THF	KF, 18-*c*-6	Rt	Cs_2CO_3	4	37
2[d]	THF	TBAF	Rt	Cs_2CO_3	12	NR
3[d]	CAN	CsF	Rt	Cs_2CO_3	12	trace
4	THF	KF, 18-*c*-6	Rt	Cs_2CO_3	4	49
5	toluene	KF, 18-*c*-6	Rt	Cs_2CO_3	4	14
6	1,4-dioxane	KF, 18-*c*-6	Rt	Cs_2CO_3	4	19
7	DME	KF, 18-*c*-6	Rt	Cs_2CO_3	4	53
8	**DME**	**KF, 18-*c*-6**	**40**	**Cs_2CO_3**	**4**	**57**
9	DME	KF, 18-*c*-6	60	Cs_2CO_3	4	30
10	DME	KF, 18-*c*-6	0	Cs_2CO_3	4	NR
11	DME	KF, 18-*c*-6	40	--	4	NR
12	DME	KF, 18-*c*-6	40	K_2CO_3	4	46
13	DME	KF, 18-*c*-6	40	KO*t*Bu	4	trace
14	DME	KF, 18-*c*-6	40	$NaHCO_3$	4	45
15	DME	KF, 18-*c*-6	40	NPh_3	4	32

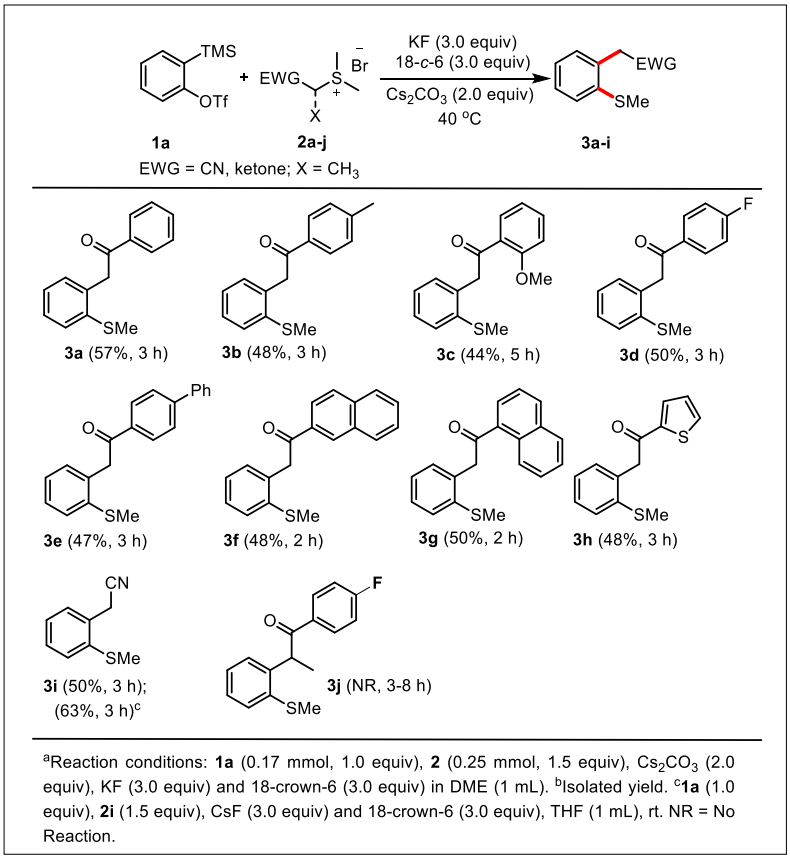
[a]Selected entries. [b]Reaction conditions: **1a** (0.17 mmol, 1.0 equiv), **2a** (0.25 mmol, 1.5 equiv), base (2.0 equiv), TBAF (2.0 equiv)/CsF (3.0 equiv)/KF (3.0 equiv) and 18-crown-6 (3.0 equiv) in solvent (1 mL). [c]Isolated yield. [d]**1a** (1.0 equiv), **2a** (1.0 equiv).

but further running the reaction at higher or lower temperature resulted in diminished yields or no reaction (Table 1, entries 9, 10). At higher temperature, the active methylene functionality of product **3a** might be further undergoing some side reactions. The reaction did not work in the absence of the base (Table 1, entry 11). Screening of different inorganic and organic bases such

as K_2CO_3, KO*t*Bu, $NaHCO_3$, and NPh_3 did not give better results (Table 1, entries 12−15). Our further efforts for the optimization of the reaction did not improve the reaction yield to a great deal. With these optimized conditions (Table 1, entry 8) in hand, we planned to explore this protocol on different sulfonium salts and aryne precursors.

First, we explored the substrate scope of this newly developed protocol by reacting various sulfonium salts (**2a−j**) (Scheme 3) with 2-(trimethylsilyl) phenyl triflate (**1a**). The developed conditions worked well for all sulfonium salts, affording the corresponding products (**3a−i**) (Scheme 3) in good to moderate yields. As mentioned in the optimization studies, the unsubstituted benzene ring containing sulfonium salt **2a** provided the expected product **3a** in 57% yield. In addition, the developed protocol worked well on sulfonium salts having electron-donating substituents such as −Me and −OMe on the phenyl ring (**3b** and **c**) (Scheme 3). Next, the tolerance of *p*-halo and *p*-Ph functionality was investigated, and we observed the formation of the corresponding aryne-inserted products (**3d** and **e**) (Scheme 3) in moderate yields. The naphthyl substituted sulfonium salt **2f** and **2g** participated well in the reaction to give the desired product **3f** and **3g** respectively. Interestingly, the developed protocol was also suitable for heterocyclic sulfonium salt **2h**, which smoothly furnished the desired product **3h** (Scheme 3). Notably, with cyanosubstituted sulfonium salt **2i**, we observed 50% yield of the inserted product **3i**, but with little modification in the reaction conditions an improved yield was observed. The reaction worked well with CsF and 18-crown-6 in THF. Surprisingly, for the sulfonium salt **2i** external base was not required. Perhaps the fluoride source acts as a base and the reaction takes place at room temperature. The α-substituted sulfonium salt **2j** failed to give the inserted product **3j**, which might be due to steric crowding at the reacting center.

Scheme 3. Reaction with Various Sulfonium Salts[a,b]

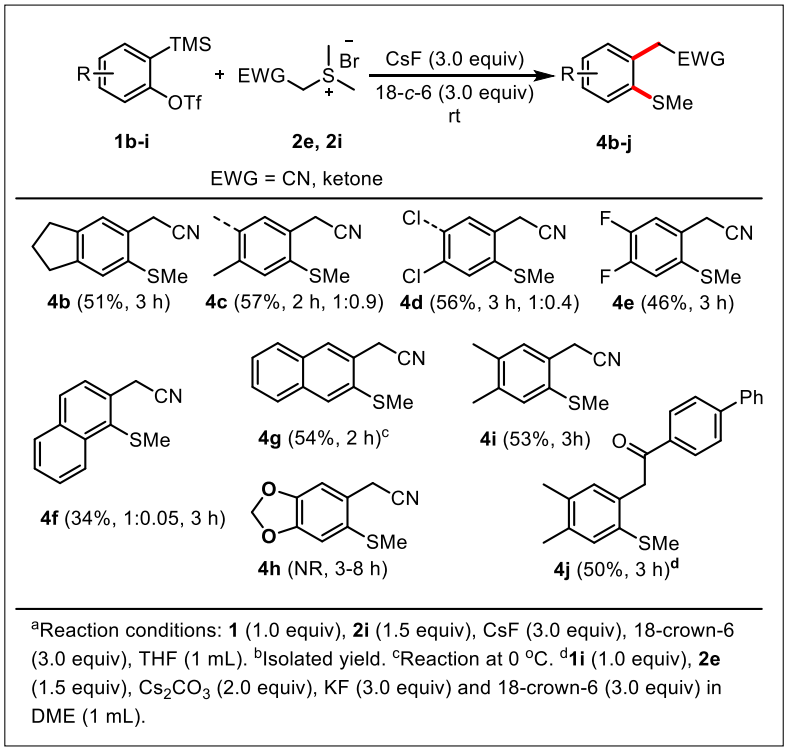


[a]Reaction conditions: **1a** (0.17 mmol, 1.0 equiv), **2** (0.25 mmol, 1.5 equiv), Cs_2CO_3 (2.0 equiv), KF (3.0 equiv) and 18-crown-6 (3.0 equiv) in DME (1 mL). [b]Isolated yield. [c]**1a** (1.0 equiv), **2i** (1.5 equiv), CsF (3.0 equiv) and 18-crown-6 (3.0 equiv), THF (1 mL), rt. NR = No Reaction.

We then turned our attention to the screening of various silyl triflates **1b−i**. A variety of electron−donating and electron−withdrawing substituents on silyl triflates were examined with sulfonium salt **2i** because we observed a good yield of product **3i** (Scheme 3) even in the absence of a base. Aryne precursors having an alkyl substituent gave the respective products in good yields (**4b** and **c**) (Scheme 4). The aryne precursors consisting of halo substituents (**1d** and **e**) (Scheme 4) were found to be suitable substrates for this reaction, and the corresponding products **4d** and **4e** were isolated in optimum yields. In addition, the naphthyl aryne precursors (**1f** and **g**) performed well, furnishing the expected products **4f** and **g** (Scheme 4), respectively, in moderate yields. The silyl triflate **1h**, having an electron-donating substituent, failed to give the inserted product **4h**. However, the alkyl-substituted aryne precursor **1i** gave the desired product **4i** in

moderate yield. The ketosulfonium salt **2e** afforded the desired product **4j** in good yield by reacting with the aryne precursor **1i** using KF and 18-crown-6.

Scheme 4. Reaction with Various Silyl-Triflates[a,b]

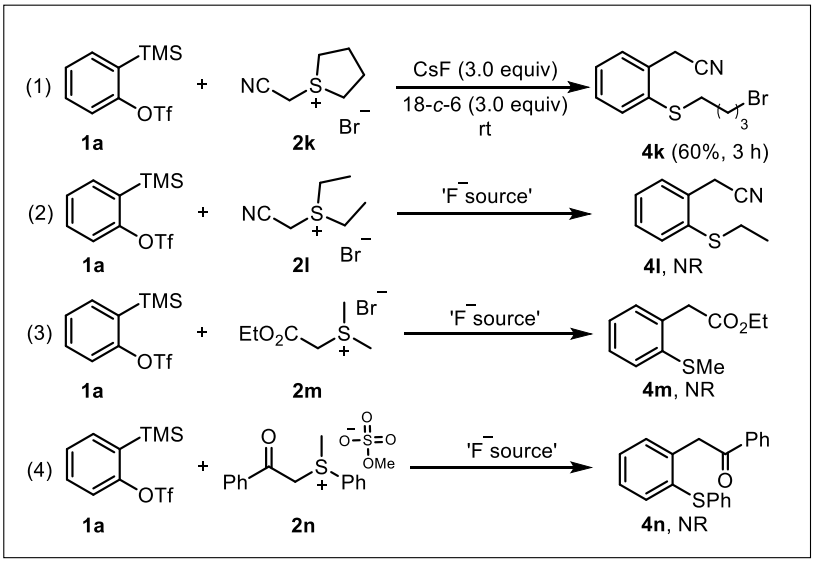


[a]Reaction conditions: **1** (1.0 equiv), **2i** (1.5 equiv), CsF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (1 mL). [b]Isolated yield. [c]Reaction at 0 °C. [d]**1i** (1.0 equiv), **2e** (1.5 equiv), Cs_2CO_3 (2.0 equiv), KF (3.0 equiv) and 18-crown-6 (3.0 equiv) in DME (1 mL).

During the substrate scope study (Scheme 3), we utilized various sulfonium salts **2a−j**. We noticed that there is a profound effect of sulfonium salt substituents on the reaction. Hence, we were further interested in investigating the role of substituents. The first sulfonium salt selected was tetrahydrothiophene-derived **2k**, and our purpose behind this selection was also to observe the trapping of the bromide anion. The salt **2k** reacted smoothly with the aryne precursor **1a** to obtain the expected product **4k** in good yield with the intervention of bromine atom (Scheme 5, eq 1). Interestingly, the diethyl substituted sulfonium salt **2l** failed to give the product **4l** (Scheme 5, eq 2). The sulfonium salt **2k** showed better reactivity than **2l** probably because of its strained cyclic structure, which facilitated the attack of bromide anion leading to the product formation.

The steric crowding in the sulfonium salt **2l** as compared to **2i** might be the reason behind its low reactivity. The ethyl ester substituted sulfonium salt **2m** failed to provide the product **4m** (Scheme 5, eq 3). Further, the sulfonium salt **2n** consisting of methyl and phenyl substituents on sulfur atom along with non-nucleophilic methyl sulfate anion failed to react with **1a** presumably due to the absence of nucleophilic bromide counteranion (Scheme 5, eq 4). The reaction of the sulfonium salts **2l**−**n** did not work, although we attempted using different fluoride sources at various temperatures.

Scheme 5. The Effect of the Sulfonium Salt Substituents



A plausible mechanism of the reaction is depicted in Figure 4. First, the sulfonium salt **2** under basic conditions generates ylide species **A**. Subsequently, the addition of ylide to aryne produces zwitterionic intermediate **B**, which upon cyclization generates four-membered cyclic adduct **C**. The attack of bromide ion on one of the methyl gives methyl bromide, which was followed by a ring opening of the strained four-membered cyclic adduct. Similar intermediates have been previously proposed in the literature.[11a,f,i] Further protonation of the intermediate **D** gives the

final *ortho*-substituted thioanisole derivatives **3/4**. The formation of alkyl bromide in the reactions of sulfur ylides is well documented in the literature.[3d,e] Additionally, the trapping of bromide anion to furnish the alkyl bromide **4k** (Scheme 5, eq 1) also supports our hypothesis.

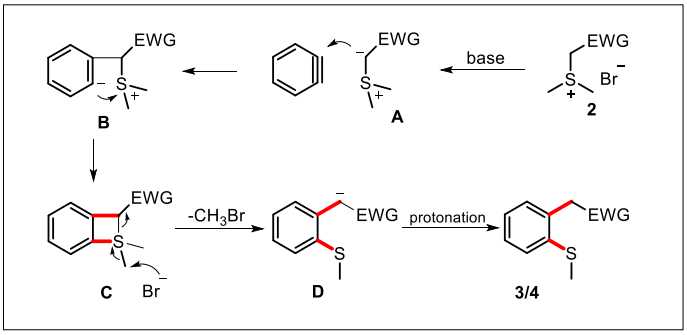


Figure 4. Plausible Reaction Mechanism.

3.3.7. Conclusion

In summary, we have developed a transition-metal-free protocol for aryne insertion into a C−S bond, which uncovers a new reactivity pathway for sulfur ylides. A good range of functionality on arynes as well as sulfonium salts was tolerated under operationally mild reaction conditions to form orthosubstituted thioanisole derivatives. Currently, we are exploring the application of the new reactivity of sulfur ylides for the synthesis of sulfur-containing heterocycles from arynes and alkynes. We will also investigate a similar reactivity of other ylides with arynes and their potential applications.

3.3.8. Experimental Procedures

All sulfonium salts **2** were easily prepared according to the known literature procedures.[14]

[A] General Experimental Procedure for the Preparation of 3a-j and 4j.

To a Schlenk tube containing KF (3.0 equiv), 18-crown-6 ether (3.0 equiv), Cs_2CO_3 (2.0 equiv) and finely powdered sulfonium salt **2** (1.5 equiv) was added DME (0.5 mL) and the reaction mixture was stirred for 5 minutes at room temperature, followed by the addition of **1a/i** (50 mg, 1.0 equiv) in DME (0.5 mL) at the same temperature. The Schlenk tube was then placed in a preheated (40 ^oC) oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, DME was evaporated on a rotary evaporator. The crude products obtained were purified by flash silica gel column chromatography using a gradient of ethyl acetate:petroleum ether to afford the corresponding products **3a-j** and **4j**.

[B] Detail Experimental Procedure for the preparation of 3a.

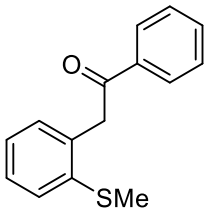
To a Schlenk tube containing KF (174 mg, 3 mmol, 3.0 equiv), 18-crown-6 ether (792 mg, 3 mmol, 3.0 equiv), Cs_2CO_3 (652 mg, 2 mmol, 2.0 equiv) and finely powdered sulfonium salt **2a** (392 mg, 1.5 mmol, 1.5 equiv) was added DME (3 mL) and the reaction mixture was stirred for 5 minutes at room temperature, followed by the addition of **1a** (298 mg, 1 mmol, 1.0 equiv) in DME (3 mL) at the same temperature. The Schlenk tube was then placed in a preheated (40 ^oC) oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, DME was evaporated on a rotary evaporator. The crude products obtained were purified by flash silica gel column chromatography using a gradient of ethyl acetate:petroleum ether (1:19) to afford the corresponding product **3a** in 52% yield (131 mg).

[C] General Experimental Procedure for the Preparation of 3i and 4b-i.

To a Schlenk tube containing CsF (3.0 equiv), 18-crown-6 ether (3.0 equiv), and a finely powdered sulfonium salt **2i** (1.5 equiv) was added THF (0.5 mL) and the reaction mixture was stirred for 5 minutes at room temperature, followed by the addition of **1** (50 mg, 1.0 equiv) in THF (0.5 mL) at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, THF was evaporated on a rotary evaporator. The crude product obtained was purified by flash silica gel column chromatography using a gradient of ethyl acetate:petroleum ether to furnish the corresponding products **3i** and **4b-i**.

3.3.9. Characterization Data of Compounds

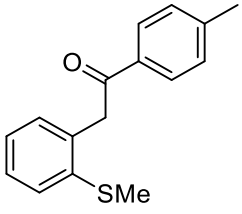
2-(2-(Methylthio)phenyl)-1-phenylethan-1-one (3a).[15]



3a

Reaction Time: 3 h; R*f*: 0.4 (1:19 EtOAc:Pet. Ether); oil; 23 mg, 57% yield; **IR** ($CHCl_3$) ν_{max} = 3018, 2921, 1684, 1591, 1439, 768, 676 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.22-7.13 (m, 1H), 7.12-7.03 (m, 2H), 4.36 (s, 2H), 2.34 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.22, 137.72, 136.77, 134.03, 133.09, 130.51, 128.58, 128.35, 127.82, 127.38, 125.60, 43.48, 16.69; **ESI HRMS:** calcd for $C_{15}H_{14}OS$ $[M + H]^+$: 243.0838, found: 243.0833.

2-(2-(Methylthio)phenyl)-1-(p-tolyl)ethan-1-one (3b).

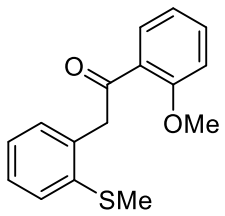


3b

Reaction Time: 3 h; R*f*: 0.5 (1:24 EtOAc:Pet. Ether); oil; 20 mg, 48% yield; **IR** ($CHCl_3$) ν_{max} = 3015, 2923, 1680, 1604, 1435, 762 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.23-

7.14 (m, 3H), 7.12-7.04 (m, 2H), 4.34 (s, 2H), 2.36 (s, 3H), 2.35 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.92, 143.91, 137.71, 134.32, 134.25, 130.50, 129.29, 128.53, 127.76, 127.36, 125. 60, 43.37, 21.64, 16.70; **ESI HRMS:** calcd for $C_{16}H_{16}OS$ $[M + H]^+$: 257.0995, found: 257.0988.

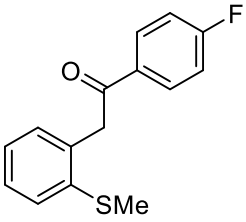
1-(2-Methoxyphenyl)-2-(2-(methylthio)phenyl)ethan-1-one (3c).



3c

Reaction Time: 5 h; R*f*: 0.2 (1:19 EtOAc:Pet. Ether); oil; 20 mg, 44% yield; **IR** ($CHCl_3$) ν_{max} = 3014, 2928, 1674, 1594, 1473, 1215, 755, 663 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.18-7.11(m, 1H), 7.09-7.02 (m, 2H), 6.94 (d, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.37 (s, 2H), 3.86 (s, 3H), 2.34 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.22, 158.52, 137.97, 134.84, 133.43, 130.72, 130.64, 128.30, 127.56, 127.12, 125.38, 120.66, 111.47, 55.53, 48.77, 16.64; **ESI HRMS:** calcd for $C_{16}H_{16}O_2S$ $[M + H]^+$: 273.0944, found: 273.0936.

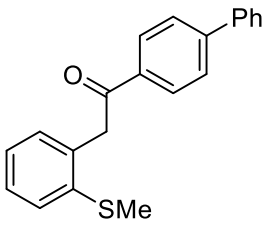
1-(4-Fluorophenyl)-2-(2-(methylthio)phenyl)ethan-1-one (3d).[15]



3d

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 22 mg, 50% yield; **IR** ($CHCl_3$) ν_{max} = 3018, 2923, 1685, 1507, 1423, 767, 664 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 4.3 Hz, 1H), 7.09 (apparent s, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 4.32 (s, 2H), 2.36 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.71, 165.75 (d, *J* = 254.3 Hz), 137.66, 133.78, 133.17 (d, *J* = 3.1 Hz), 131.03 (d, *J* = 9.25 Hz), 130.46, 127.94, 127.37, 125.65, 115.70 (d, *J* = 21.6 Hz), 43.41, 16.67; **ESI HRMS:** calcd for $C_{15}H_{13}FOS$ $[M + H]^+$: 261.0744, found: 261.0749.

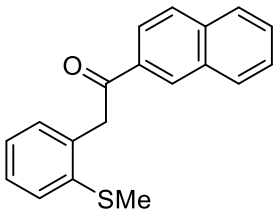
1-([1,1'-Biphenyl]-4-yl)-2-(2-(methylthio)phenyl)ethan-1-one (3e).



3e

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); white solid; mp = 87-89 ^{o}C; 25 mg, 47% yield; **IR** ($CHCl_3$) ν_{max} = 3020, 2925, 1681, 1476, 1435, 764, 669 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (d, *J* = 7.9 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.44-7.39 (m, 2H), 7.37-7.28 (m, 2H), 7.25-7.20 (m, 1H), 7.14-7.06 (m, 2H), 4.41 (s, 2H), 2.39 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.87, 145.79, 139.88, 137.72, 135.47, 134.08, 130.52, 128.99, 128.92, 128.92, 1288.19, 127.85, 127.40, 127.25, 125.65, 43.54, 16.72; **ESI HRMS:** calcd for $C_{21}H_{18}OS$ $[M + H]^+$: 319.1151, found: 319.1144.

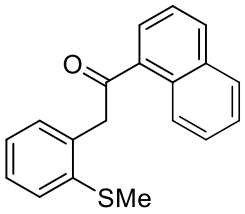
2-(2-(Methylthio)phenyl)-1-(naphthalen-2-yl)ethan-1-one (3f).



3f

Reaction Time: 2 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); off white; mp = 82-84 ^{o}C; 24 mg, 48% yield; **IR** ($CHCl_3$) ν_{max} = 3056, 1681, 1590, 1461, 758, 671 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.57 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.48-7.44 (m, 3H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.23-7.20 (m, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 4.47 (s, 2H), 2.37 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 201.05, 137.95, 135.72, 134.25, 133.96, 132.67, 130.81, 130.33, 128.33, 127.95, 127.87, 127.73, 127.59, 126.41, 125.95, 125.70, 124.32, 47.14, 16.86; **ESI HRMS:** calcd for $C_{19}H_{16}OS$ $[M + H]^+$: 293.0995, found: 293.0987.

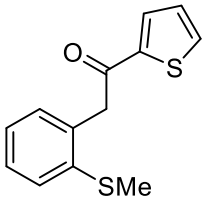
2-(2-(Methylthio)phenyl)-1-(naphthalen-2-yl)ethan-1-one (3g).



3g

Reaction Time: 2 h; R*f*: 0.5 (1:19, EtOAc:Pet. Ether); off white solid; mp 82–84 ^{o}C; 25 mg, 50% yield; **IR** ($CHCl_3$) ν_{max} = 3017, 2925, 1681, 1433, 1314, 759, 666 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.57 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 7.3 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.48–7.42 (m, 3H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.24–7.19 (m, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 4.46 (s, 2H), 2.36 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 201.1, 137.9, 135.7, 134.2, 134.0, 132.7, 130.8, 130.3 128.3, 128.0, 127.9, 127.7, 127.6, 126.4, 125.9, 125.7, 124.3, 47.1, 16.9; **ESI HRMS:** calcd for $C_{19}H_{16}OS$ $[M + H]^+$: 293.0995, found: 293.0987.

2-(2-(Methylthio)phenyl)-1-(thiophen-2-yl)ethan-1-one (3h).



3h

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); white solid; mp = 86-88 ^{o}C; 20 mg, 48% yield; **IR** ($CHCl_3$) ν_{max} = 3019, 2925, 1660, 1416, 760, 668 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 3.6 Hz, 1H), 7.57 (d, *J* = 4.8 Hz, 1H), 7.27-7.22 (m, 1H), 7.20-7.13 (m, 2H), 7.12-7.04 (m, 2H), 4.30 (s, 2H), 2.37 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 190.09, 143.97, 137.79, 133.77, 133.60, 132.37, 130.52, 128.10 127.97, 127.38, 125.65, 44.07, 16.74; **ESI HRMS:** calcd for $C_{13}H_{12}OS_2$ $[M + H]^+$: 249.0402, found: 249.0395.

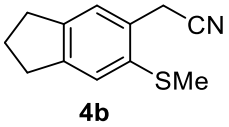
2-(2-(Methylthio)phenyl)acetonitrile (3i).

3i

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 17 mg, 63% yield; **IR** ($CHCl_3$) ν_{max} = 2924, 2856, 2249, 1590, 1460, 745, 615 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 7.93 Hz, 1H), 7.37-7.28 (m, 2H), 7.23 (t, *J* = 7.32 Hz, 1H), 3.83 (s, 2H), 2.52 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 137.24, 128.90, 128.65, 127.08,

125.92, 117.39, 21.95, 16.33; **ESI HRMS:** calcd for C_9H_9NS $[M + H]^+$: 164.0528, found: 164.0527

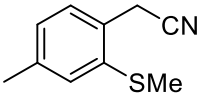
2-(6-(Methylthio)-2,3-dihydro-1H-inden-5-yl)acetonitrile (4b).



4b

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); white solid; mp = 64-66 ^oC; 15 mg, 51% yield; **IR** ($CHCl_3$) ν_{max} = 3019, 2399, 1684, 1601, 1477, 771, 669 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33 (s, 1H), 7.25 (s, 1H), 3.85 (s, 2H), 2.92 (t, *J* = 6.7 Hz, 4H), 2.49 (s, 3H), 2.15-2.06 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.40, 143.14, 134.06, 127.16, 124.76, 124.70, 117.97, 32.67, 32.45, 25.44, 22.01, 17.37; **ESI HRMS:** calcd for $C_{12}H_{13}NS$ $[M + H]^+$: 204.0841, found: 204.0843.

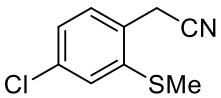
2-(4-Methyl-2-(methylthio)phenyl)acetonitrile (4c).



4c

Reaction Time: 2 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); oil; 16 mg, 57% yield; ratio of regioisomers 1:0.9]; **IR** ($CHCl_3$) ν_{max} = 3021, 2860, 2355, 2253, 1600, 1478, 772, 624 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26-7.19 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.09-6.92 (m, 2H), 3.75 (s, 1H), 3.71 (s, 1H), 2.42 (s, 1.5H), 2.39 (s, 1.5H), 2.29 (s, 1.5H), 2.27 (s, 1.5H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.03, 138.84, 136.78, 136.50, 133.45, 129.67, 129.48, 129.34, 129.20, 128.56, 128.47, 127.94, 126.80, 125.76, 117.66, 117.63, 29.69, 21.58, 21.15, 20.84, 17.12, 16.45; **ESI HRMS:** calcd for $C_{10}H_{11}NS$ $[M + H]^+$: 178.0685, found: 178.0686

2-(4-Chloro-2-(methylthio)phenyl)acetonitrile (4d).

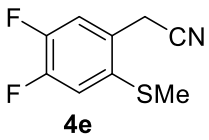


4d

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); white solid; mp = 51-53 ^oC; 17 mg, 56% yield. [ratio of regioisomers 1:0.4]; **IR** ($CHCl_3$) ν_{max} = 3020,

2856, 2403, 2254, 1581, 1468, 1439, 765 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32-7.20 (m, 1H), 7.15 (d, 9.2 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 3.69 (s, 2H), 2.43 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.39, 134.89, 129.65, 129.01, 128.67, 128.41, 126.40, 125.84, 125.59, 116.87, 21.83, 21.42, 16.53, 15.92; **ESI HRMS:**

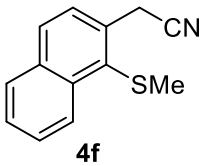
2-(4,5-Difluoro-2-(methylthio)phenyl)acetonitrile (4e).



4e

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); white solid; mp = 62-64 ^oC; 14 mg, 46% yield; **IR** ($CHCl_3$) ν_{max} = 3021, 2858, 2254, 1601, 1496, 767 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.24 (dd, *J* = 10.3, 8.0 Hz, 1H), 7.05 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.70 (s, 2H), 2.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 150.29 (dd, *J* = 242.5, 12.7 Hz), 148.35 (dd, *J* = 239.8, 12.7 Hz), 133.7 (dd, *J* = 6.4, 3.6 Hz), 125.30 (dd, *J* = 5.4, 3.6 Hz), 117.95 (d, *J* = 19.1 Hz), 116.70 (d, *J* = 19.1 Hz), 116.69, 21.42, 16.95; **ESI HRMS:** calcd for $C_9H_7NF_2S$ $[M + H]^+$: 200.0340, found: 200.0340.

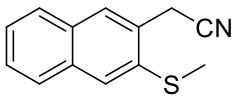
2-(1-(Methylthio)naphthalen-2-yl)acetonitrile (4f).



4f

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); white solid; mp = 89-91 ^oC; 11 mg, 34% yield. [ratio of regioisomers 1:0.05]; **IR** ($CHCl_3$) ν_{max} = 3019, 2926, 2249, 1590, 1425, 766, 671 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.78 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.64-7.51 (m, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 4.46 (s, 0.11x2H), 4.34 (s, 2H), 2.52 (s, 3H), 2.30 (s, 0.17x3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 136.07, 132.23, 131.64, 129.56, 128.94, 127.88, 126.50, 126.05, 125.32, 122.85, 117.45, 18.07, 17.91.7h; **ESI HRMS:** calcd for $C_{13}H_{11}NS$ $[M + H]^+$: 214.0685, found: 214.0688.

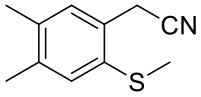
2-(3-(Methylthio)naphthalen-2-yl)acetonitrile (4g).



4g

Reaction Time: 2 h; R*f*: 0.5 (1:19, EtOAc:Pet. Ether); white solid; mp 85–87 ^{o}C; 16 mg, 54% yield; **IR** ($CHCl_3$) ν_{max} = 2920, 2254, 1626, 1590, 1458, 756, 646 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.56 (s, 1H), 7.46−7.33 (m, 2H), 3.86 (s, 2H), 2.53 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 134.9, 133.3, 131.1, 127.6, 127.0, 126.5, 126.4, 126.0, 124.7, 117.4, 22.0, 16.2; **ESI HRMS:** calcd for $C_{13}H_{11}NS$ $[M + H]^+$: 214.0685, found: 214.0679.

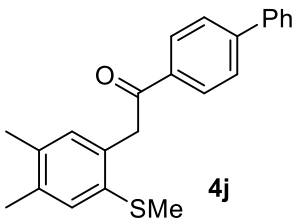
2-(4,5-Dimethyl-2-(methylthio)phenyl)acetonitrile (4i).



4i

Reaction Time: 3 h; R*f*: 0.5 (1:19, EtOAc:Pet. Ether); thick oil; 15 mg, 53% yield; **IR** ($CHCl_3$) ν_{max} = 2924, 2857, 2246, 1602, 771, 722 cm^{-1}, **H NMR (400 MHz, $CDCl_3$)** δ 7.22 (s, 1H), 7.15 (s, 1H), 3.82 (s, 2H), 2.48 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 137.5, 135.4, 133.4, 130.2, 130.0, 126.9, 117.9, 21.5, 19.4, 19.2, 17.4. **ESI HRMS:** calcd for $C_{11}H_{13}NS$ $[M + Na]^+$: 214.0661, found: 214.0661.

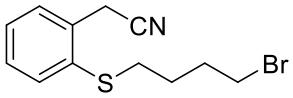
1-([1,1'-Biphenyl]-4-yl)-2-(4,5-dimethyl-2-(methylthio)phenyl)ethan-1-one (4j).



4j

Reaction Time: 3 h; R*f*: 0.5 (1:19 EtOAc:Pet. Ether); white solid; mp = 89-91 ^{o}C; 26 mg, 50% yield; **IR** ($CHCl_3$) ν_{max} = 3021, 2927, 1680, 1522, 1485, 770, 671 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 7.9 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 7.3 Hz, 2H), 7.53-7.47 (m, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.19 (s, 1H), 7.01 (s, 1H), 4.46 (s, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.34, 145.70, 139.95, 136.35, 135.56, 134.80, 133.94, 132.19, 131.82, 130.33, 129.02, 128.93, 128.17, 127.26, 127.25, 43.22, 19.46, 19.25, 17.75; **ESI HRMS:** calcd for $C_{23}H_{22}OS$ $[M + H]^+$: 347.1464, found: 347.1456.

2-(2-((4-Bromobutyl)thio)phenyl)acetonitrile (4k).



4k

Reaction Time: 3 h; R*f*: 0.5 (1:19, EtOAc:Pet. Ether); thick oil; 27 mg, 60% yield; **IR** ($CHCl_3$) ν_{max} = 3061, 3015, 2249, 1588, 1466, 753, 662 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (d, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 3.81 (s, 2H), 3.35 (t, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 1.94 (quint., *J* = 6.7 Hz, 2H), 1.74 (quint., *J* = 7.3 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 135.2, 130.6, 130.4, 129.1, 128.9, 127.1, 117.6, 33.5, 32.8, 31.5, 27.5, 22.3; **ESI HRMS:** calcd for $C_{12}H_{14}NBrS$ $[M + Na]^+$: 305.9923, found: 305.9921.

3.3.10. References

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3.3.11. Spectra

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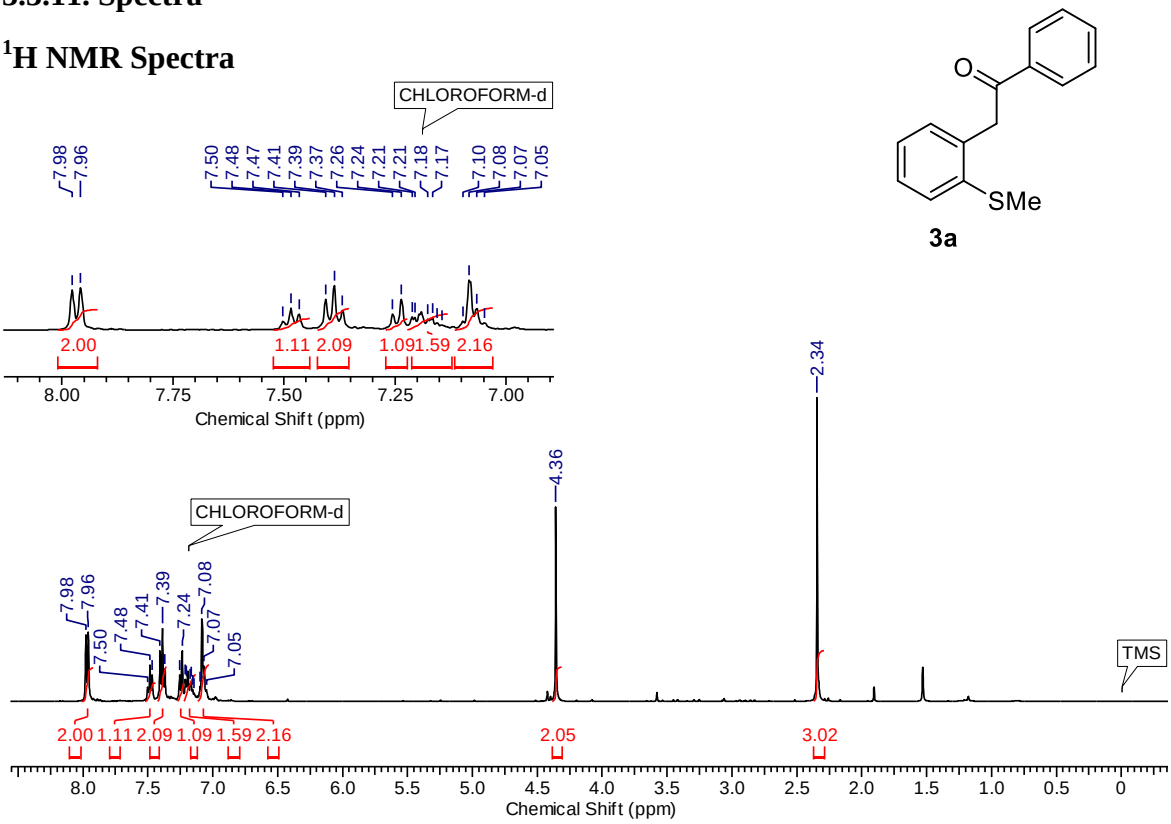

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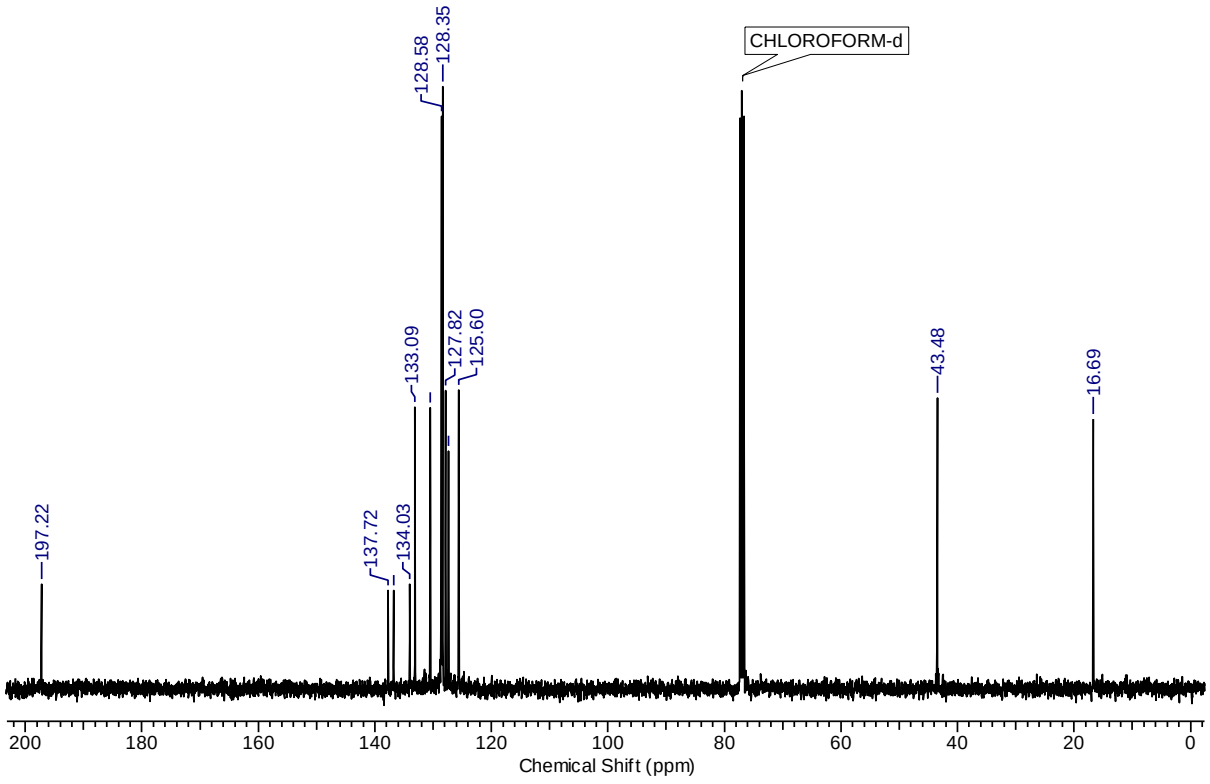

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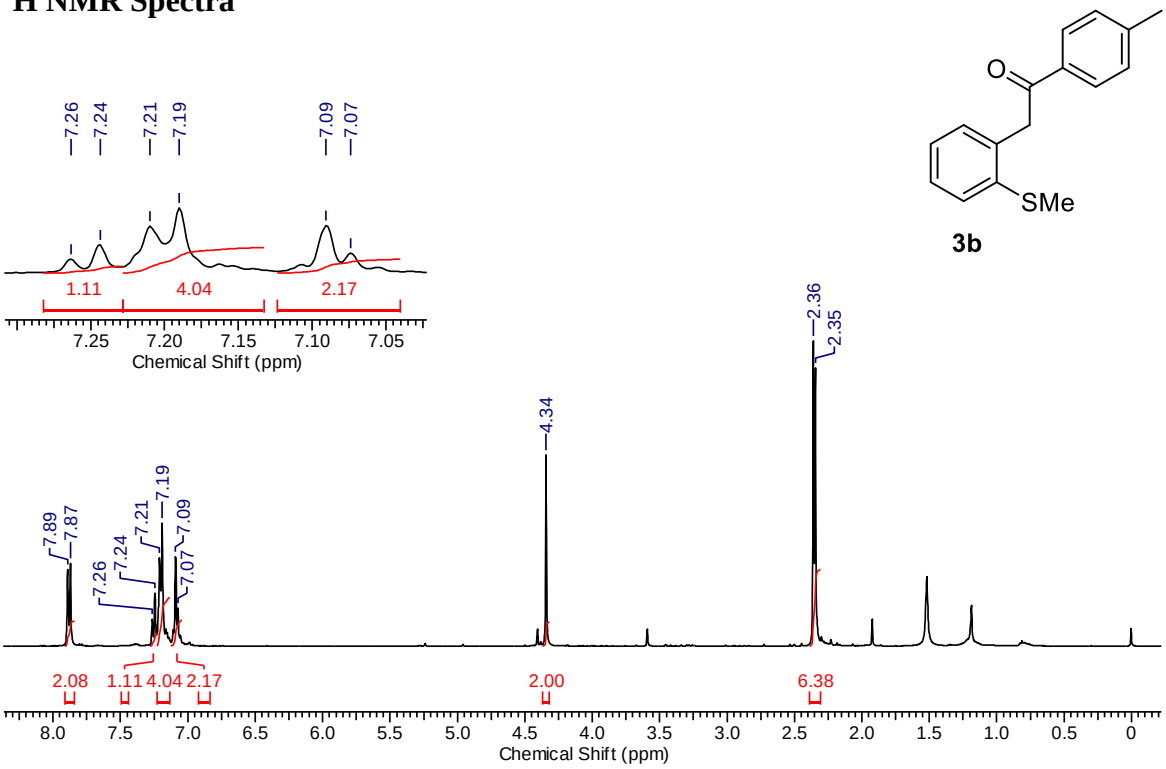

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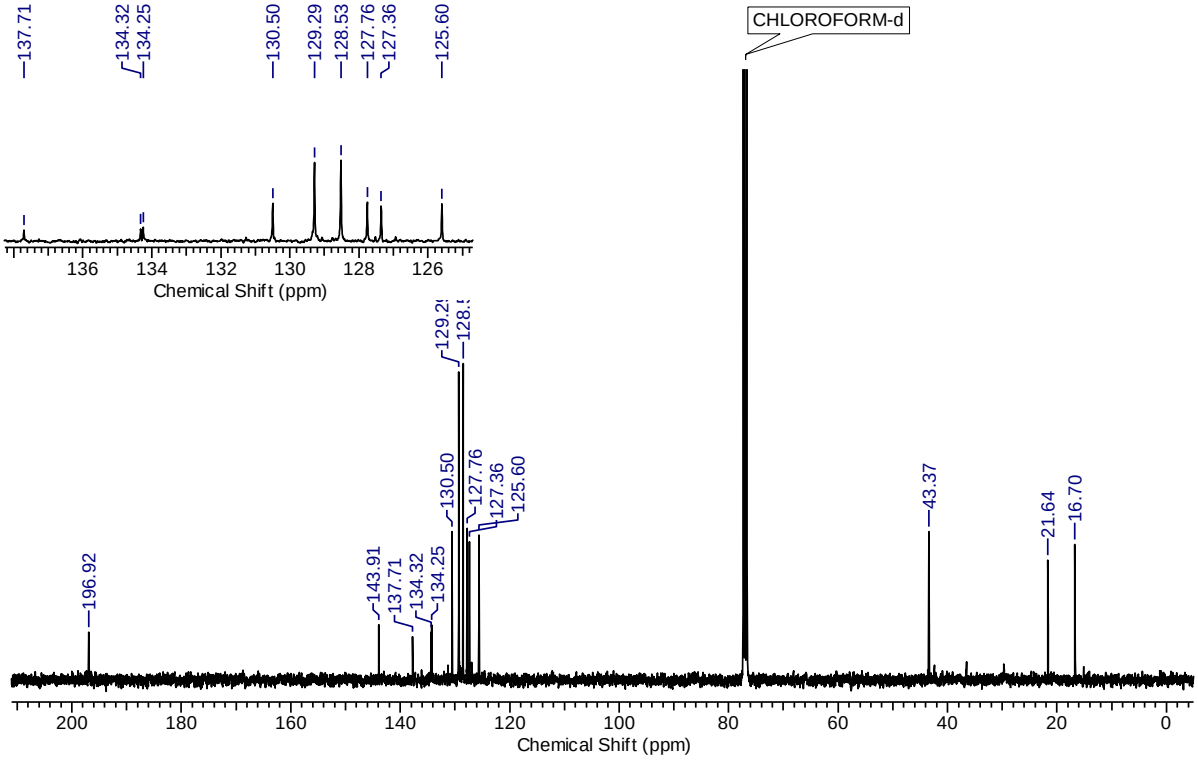

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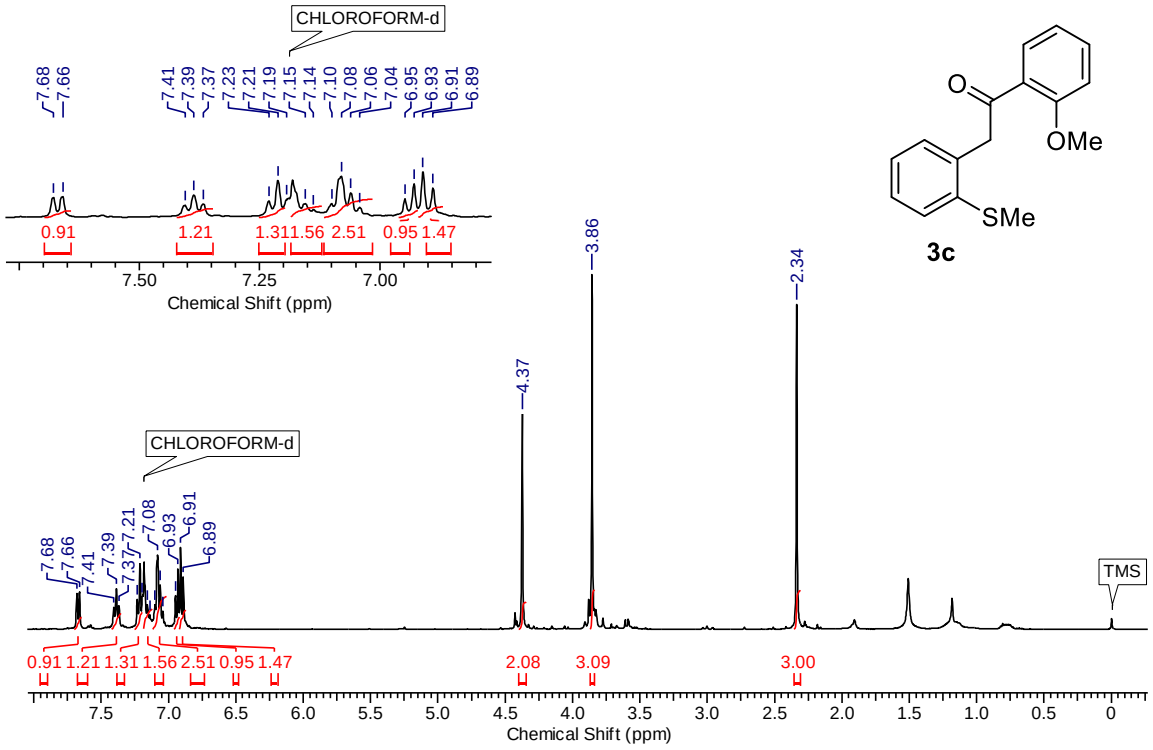

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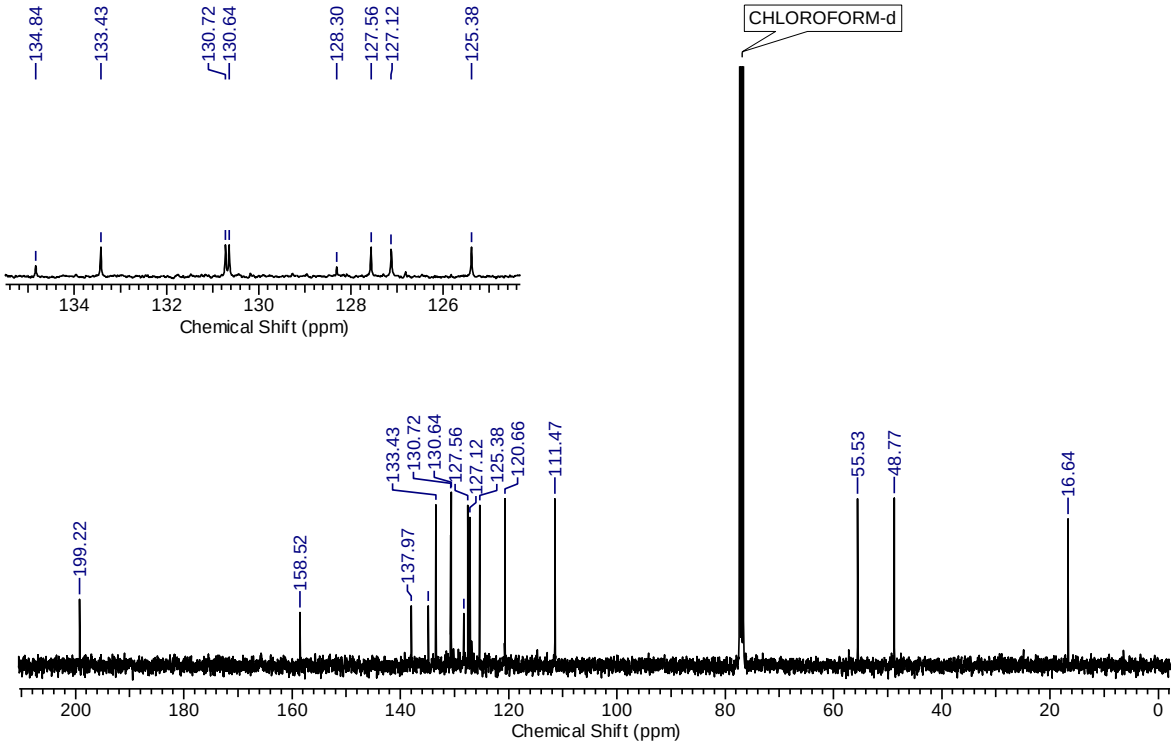

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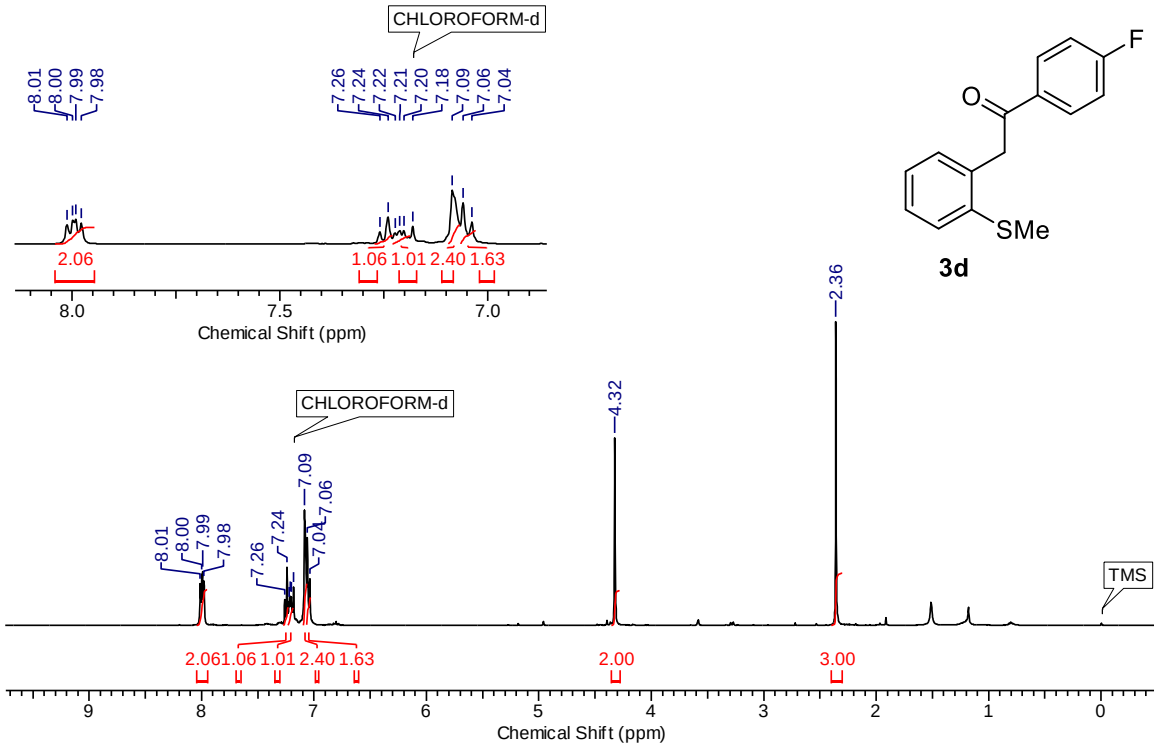

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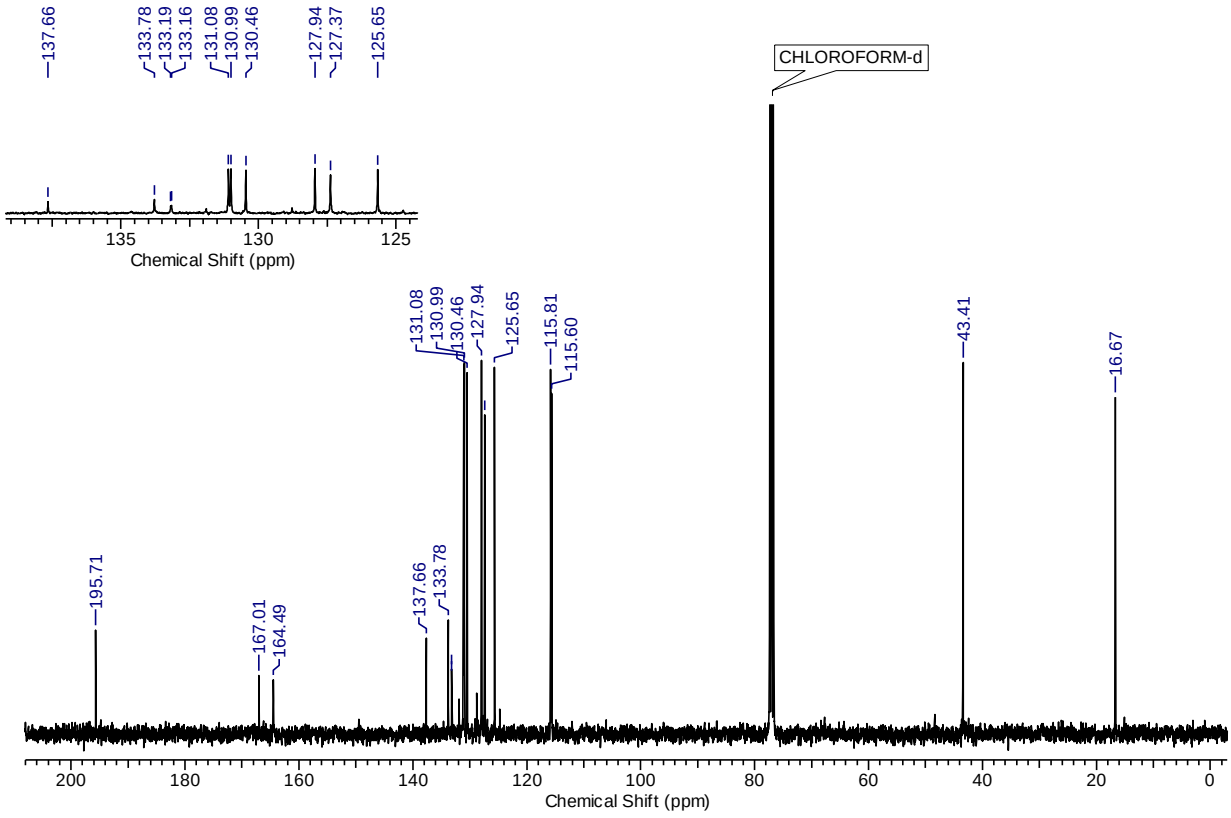

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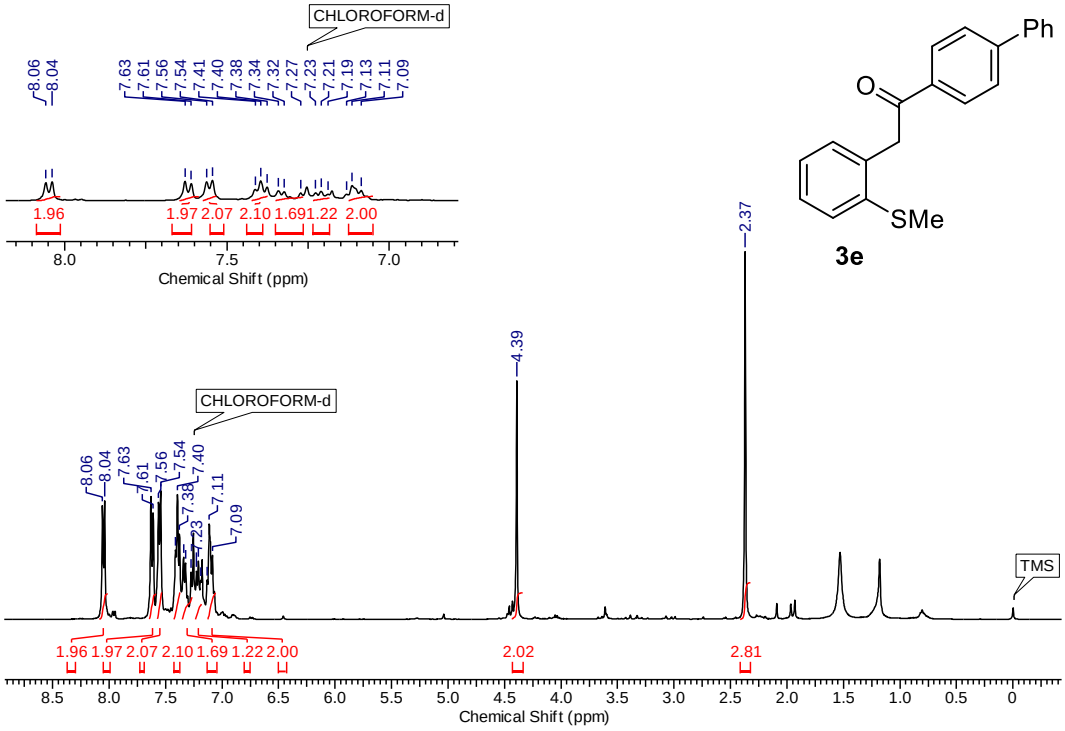

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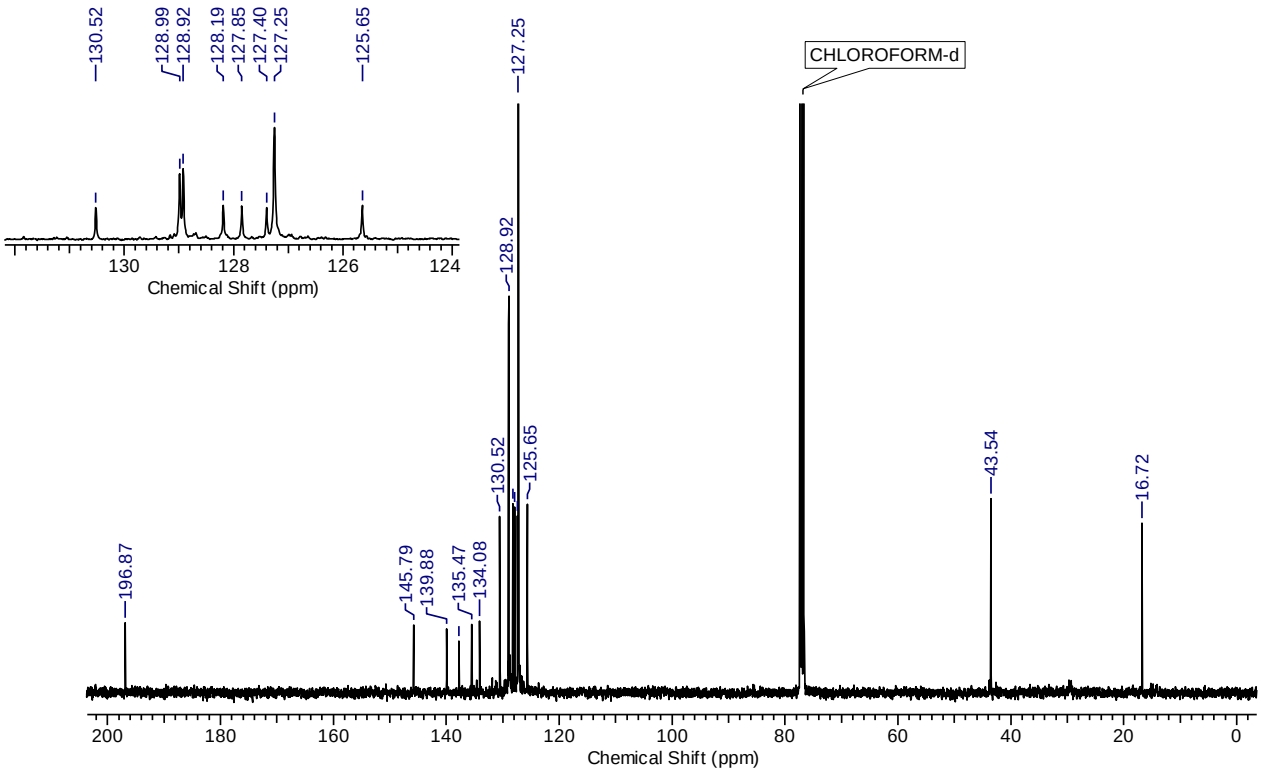

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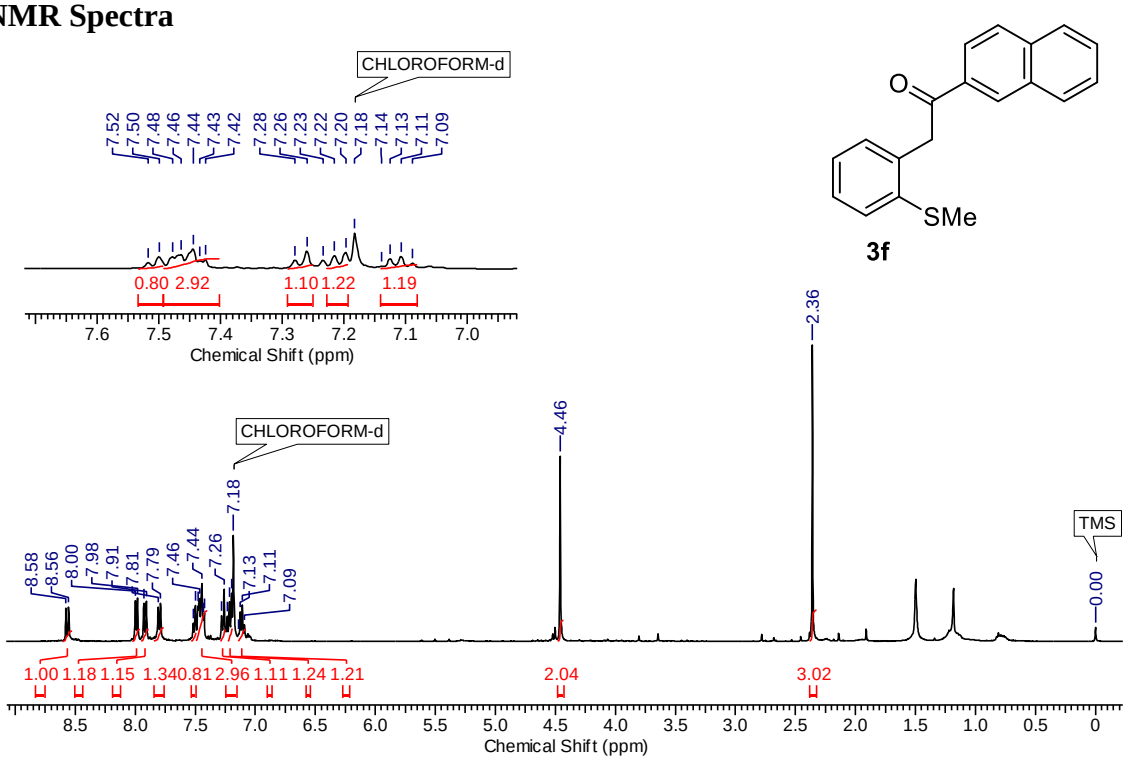

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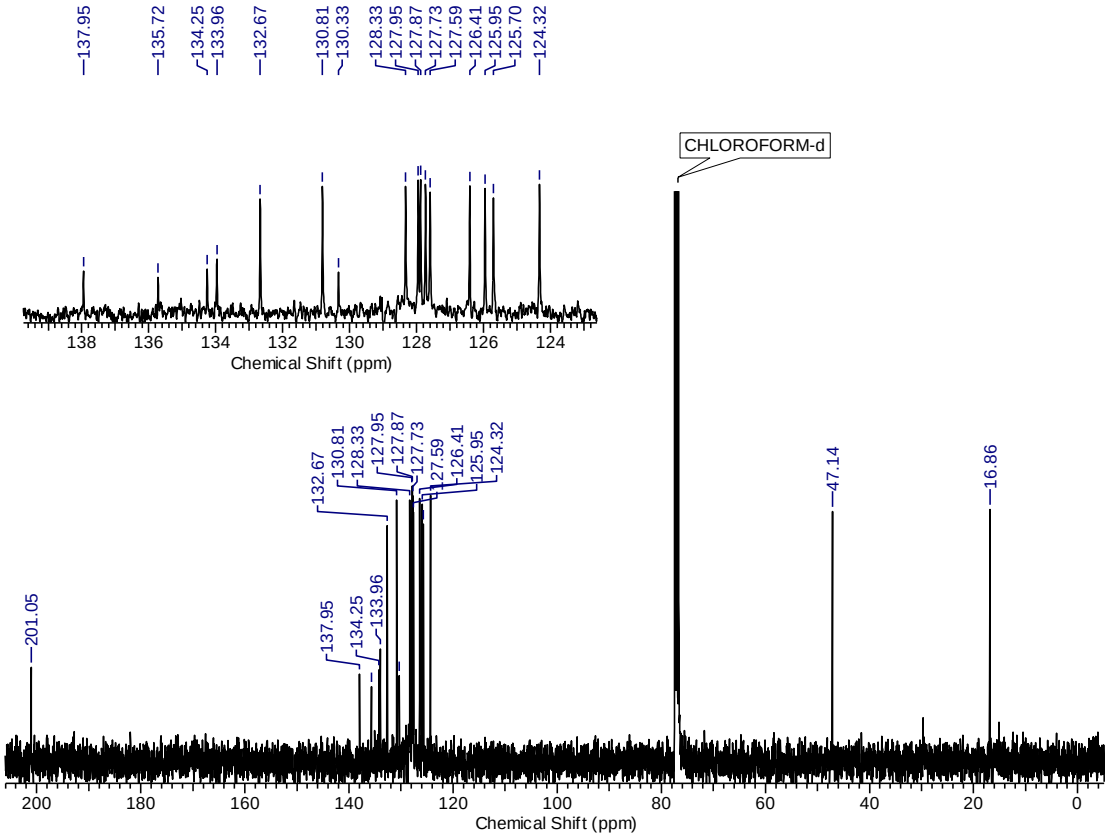

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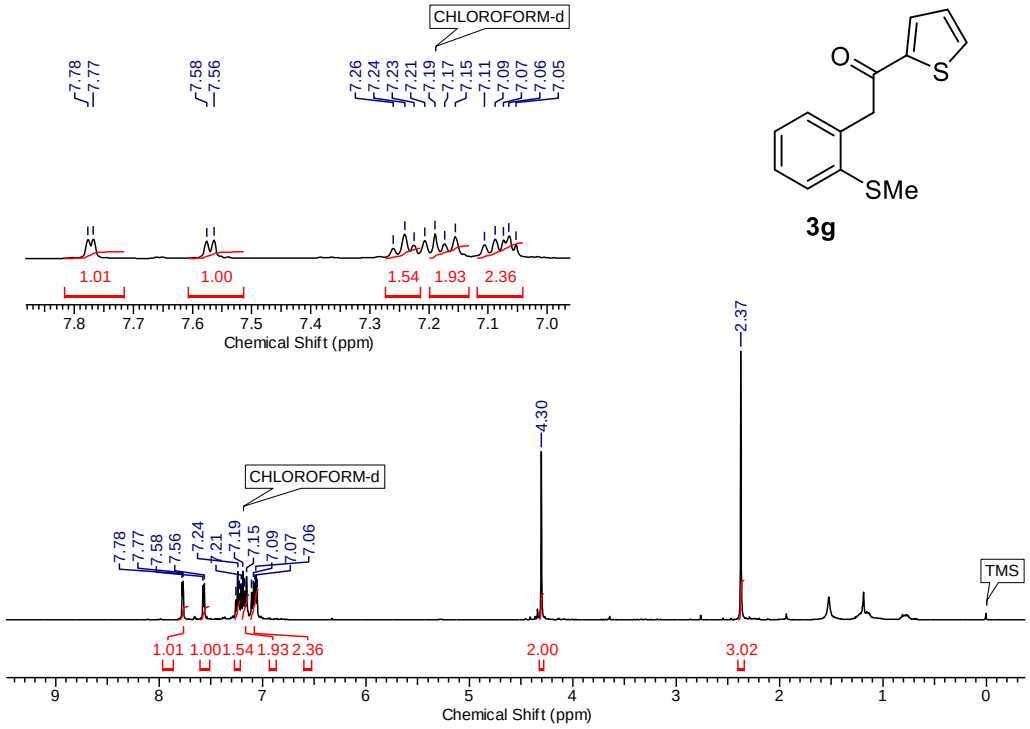

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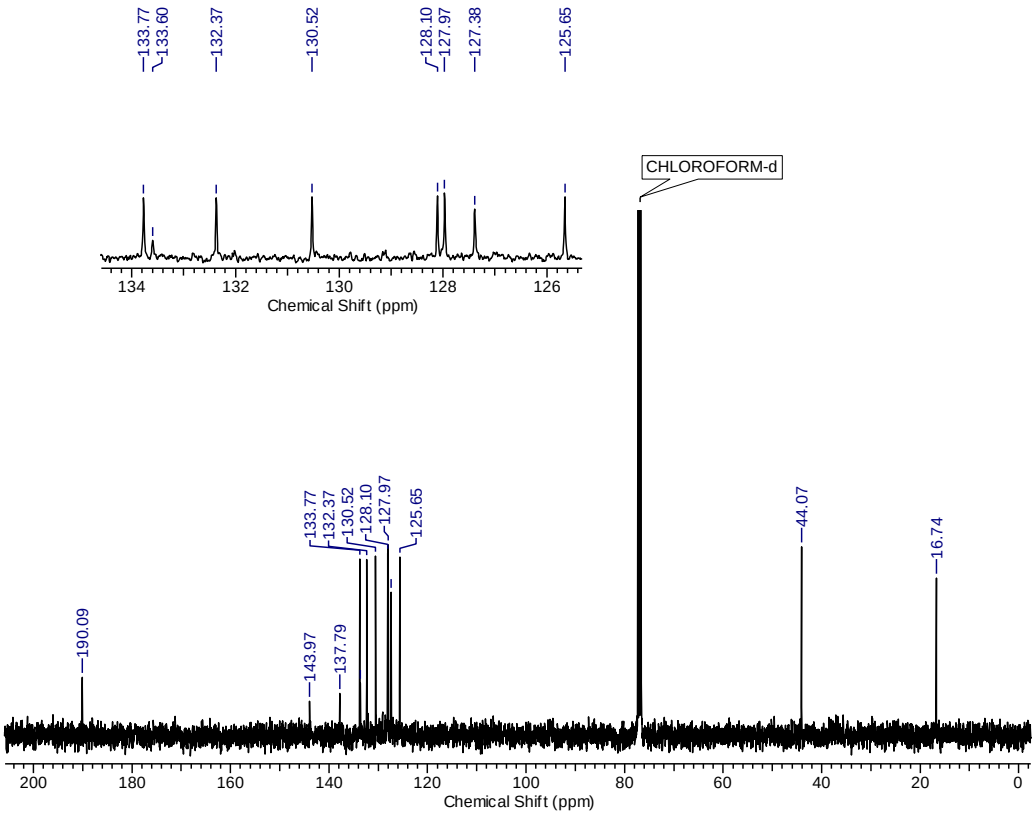

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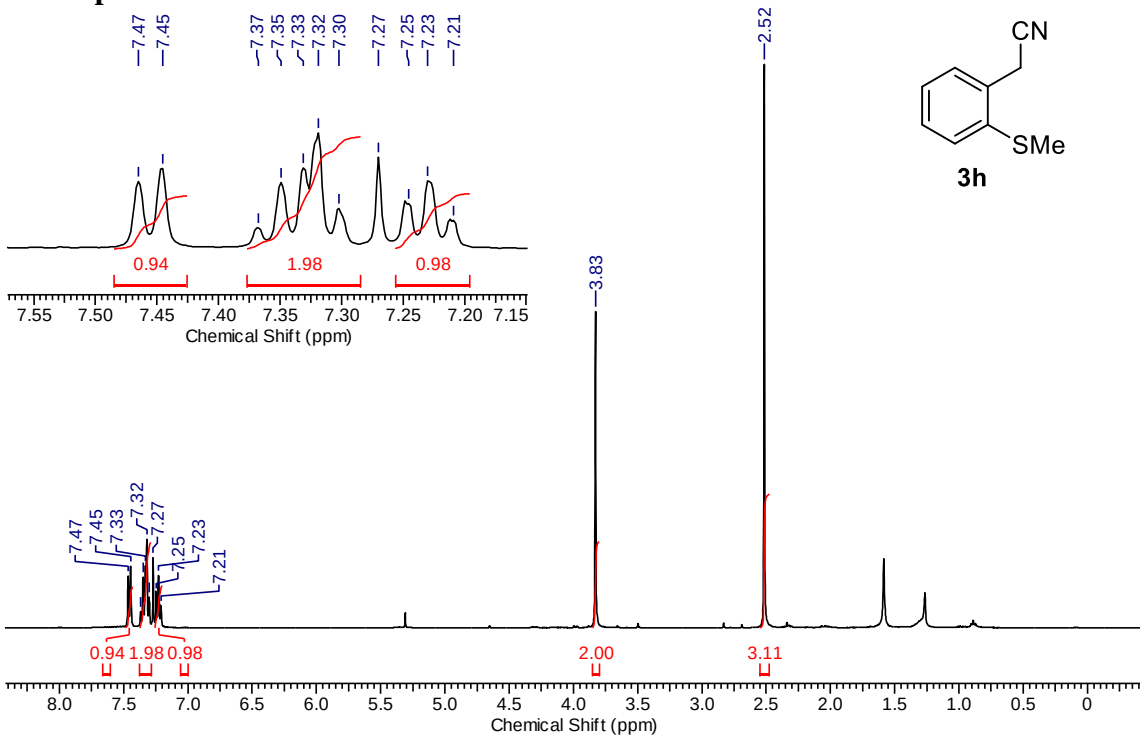

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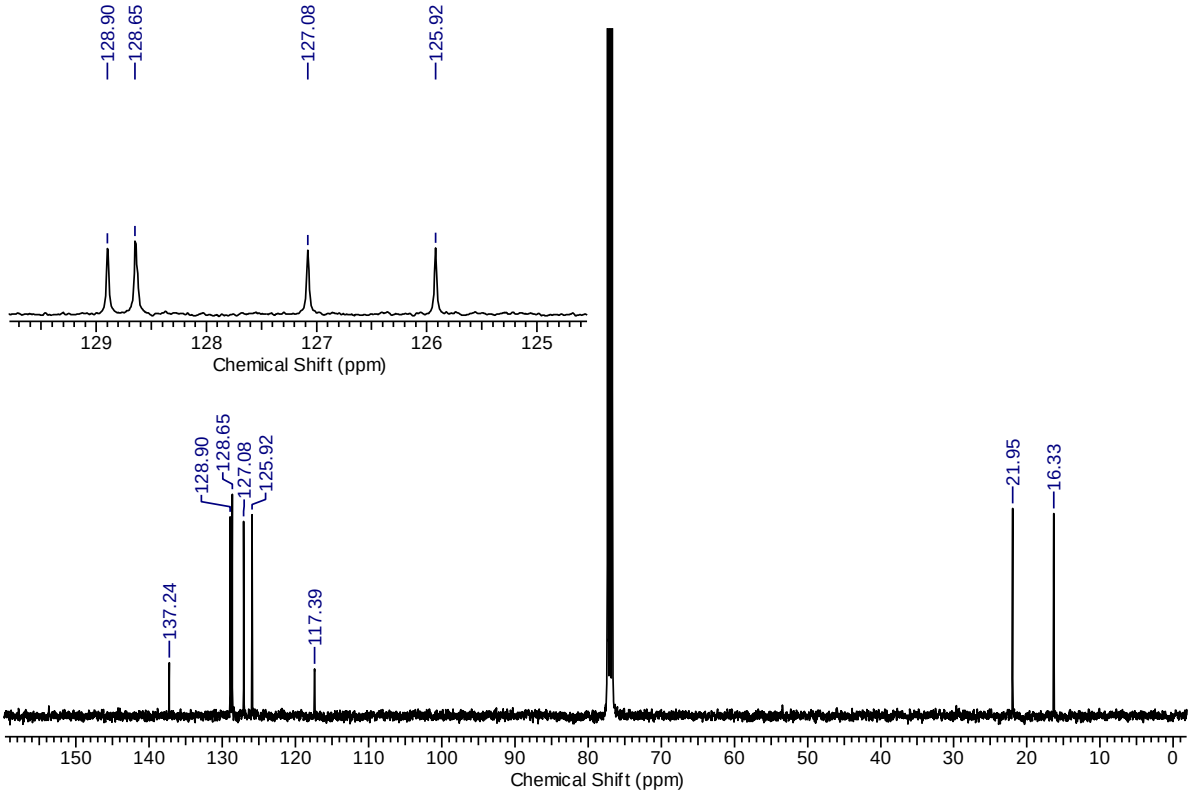

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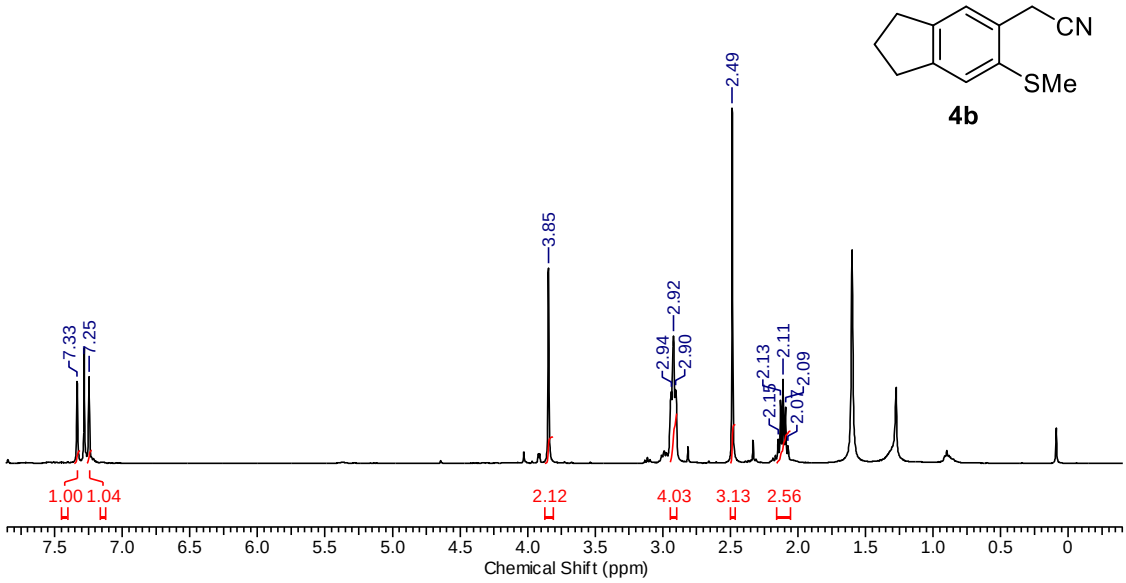

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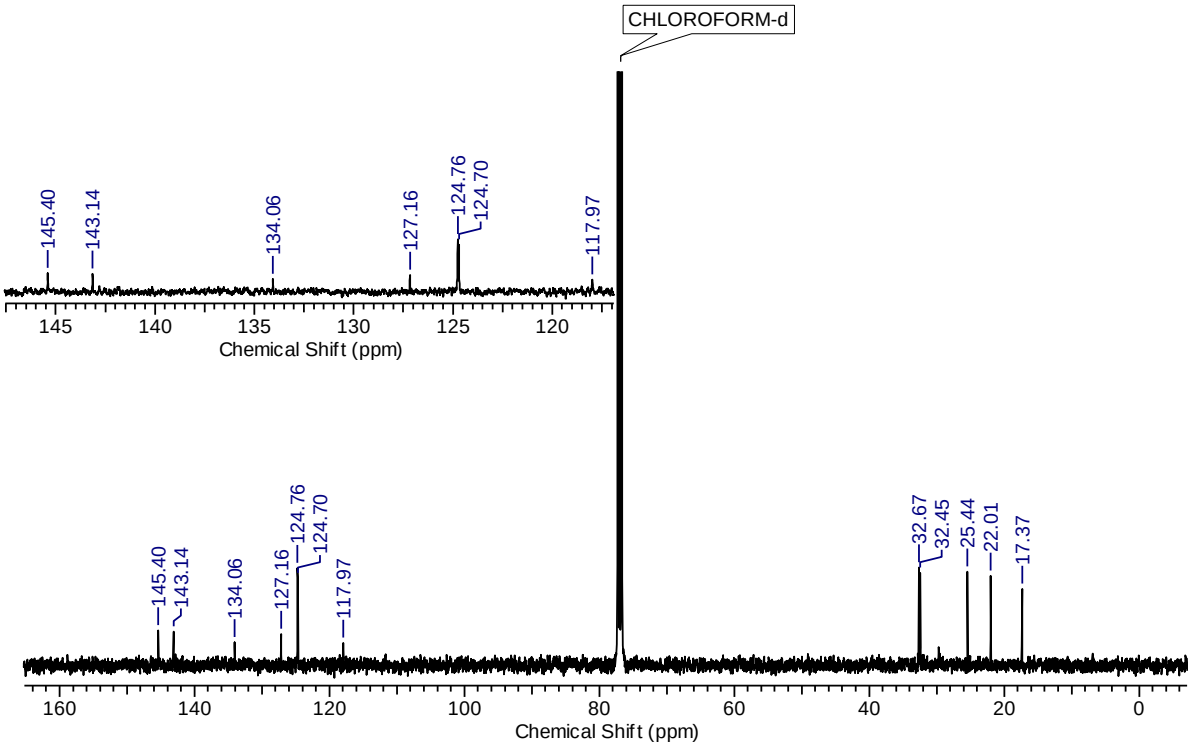

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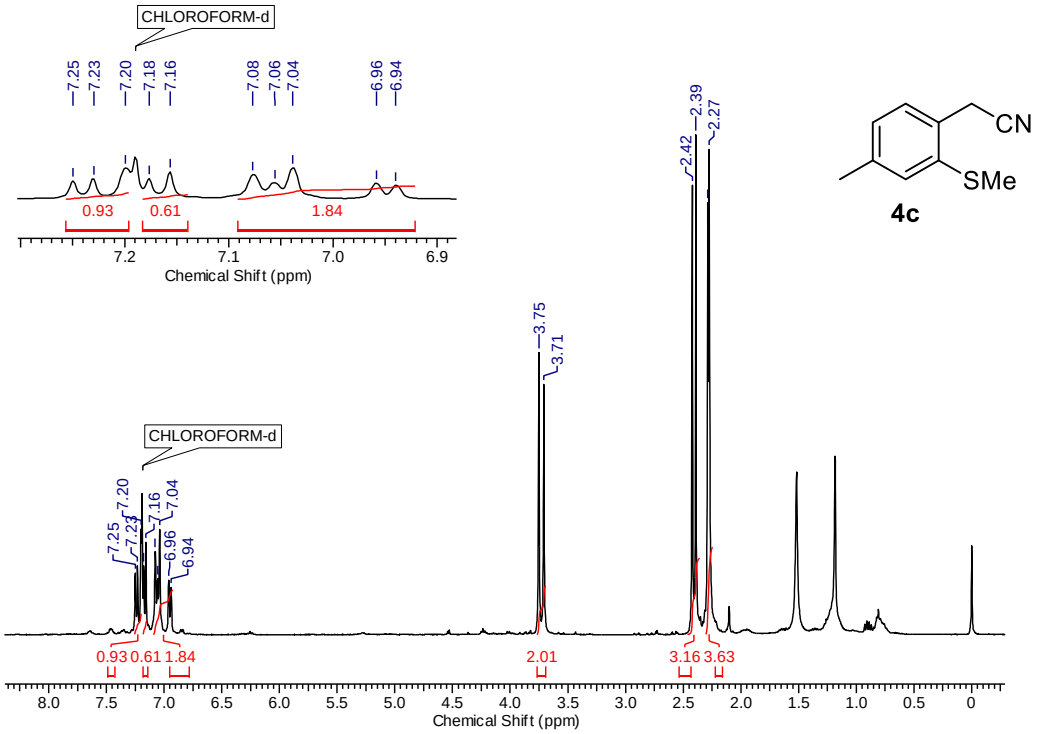

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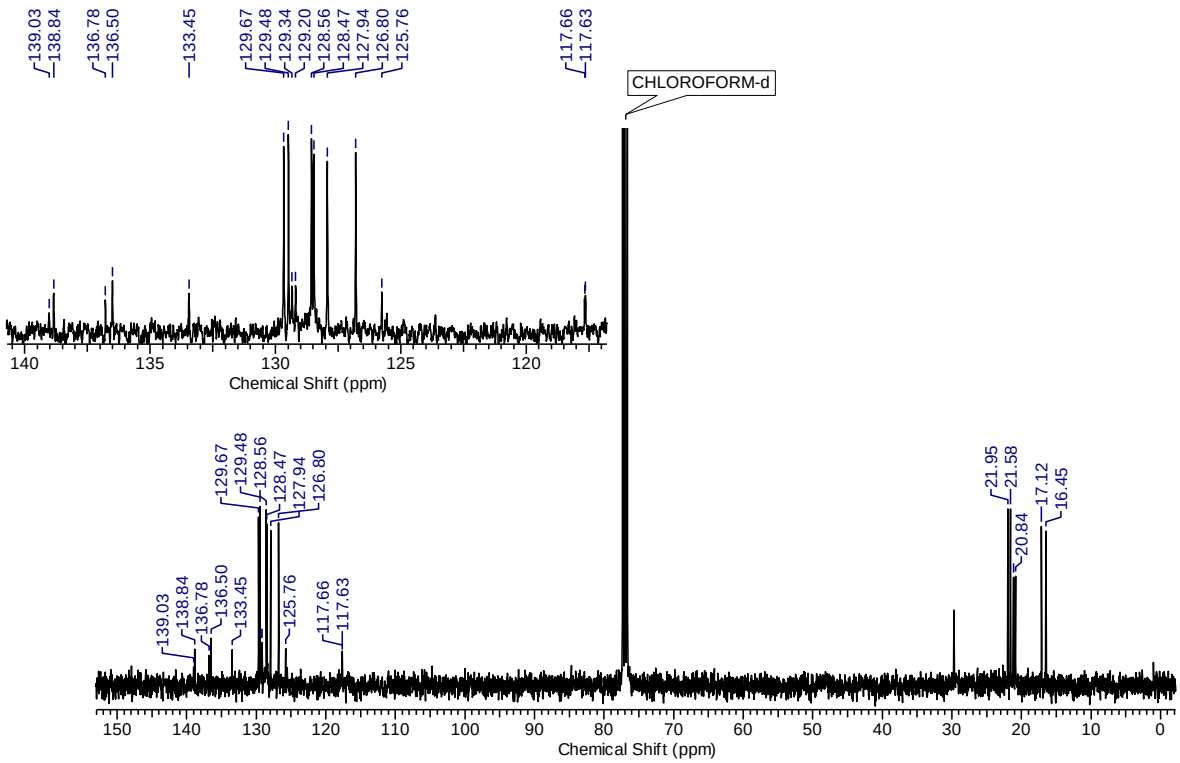

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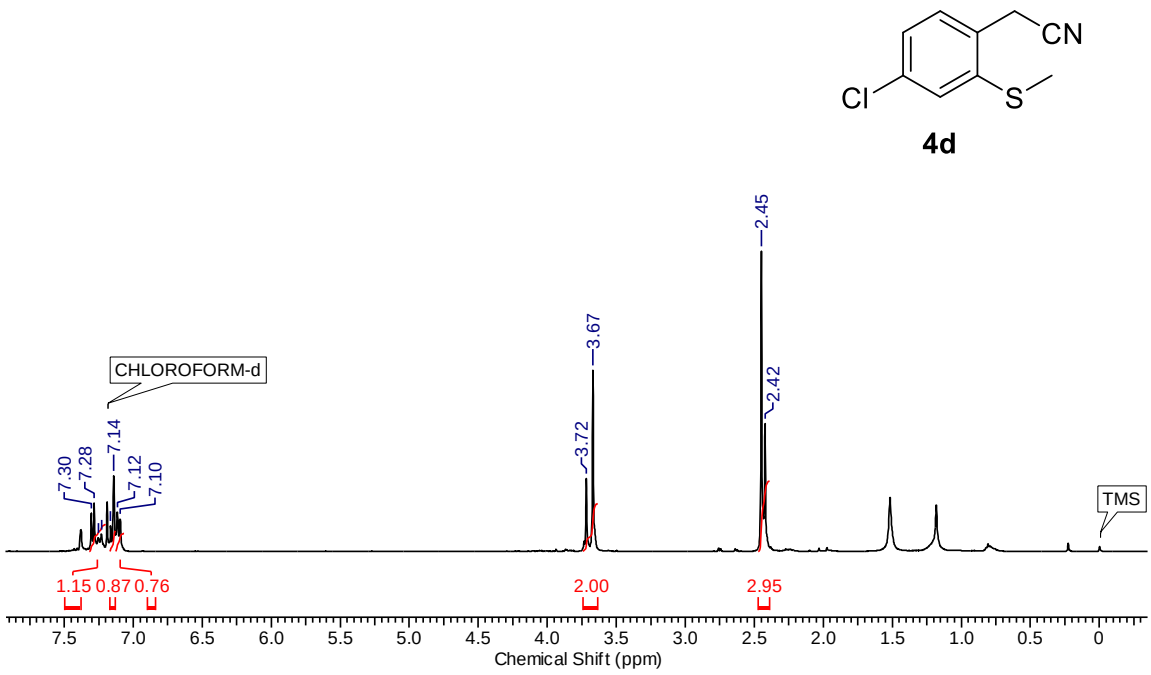

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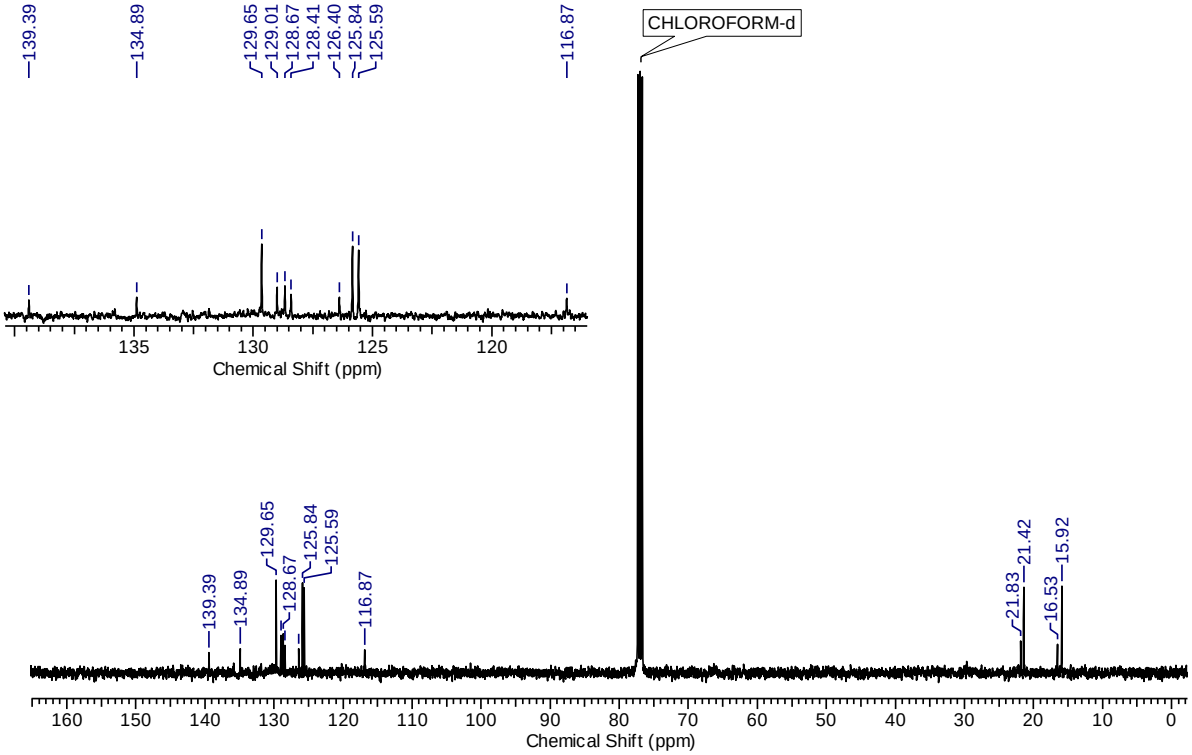

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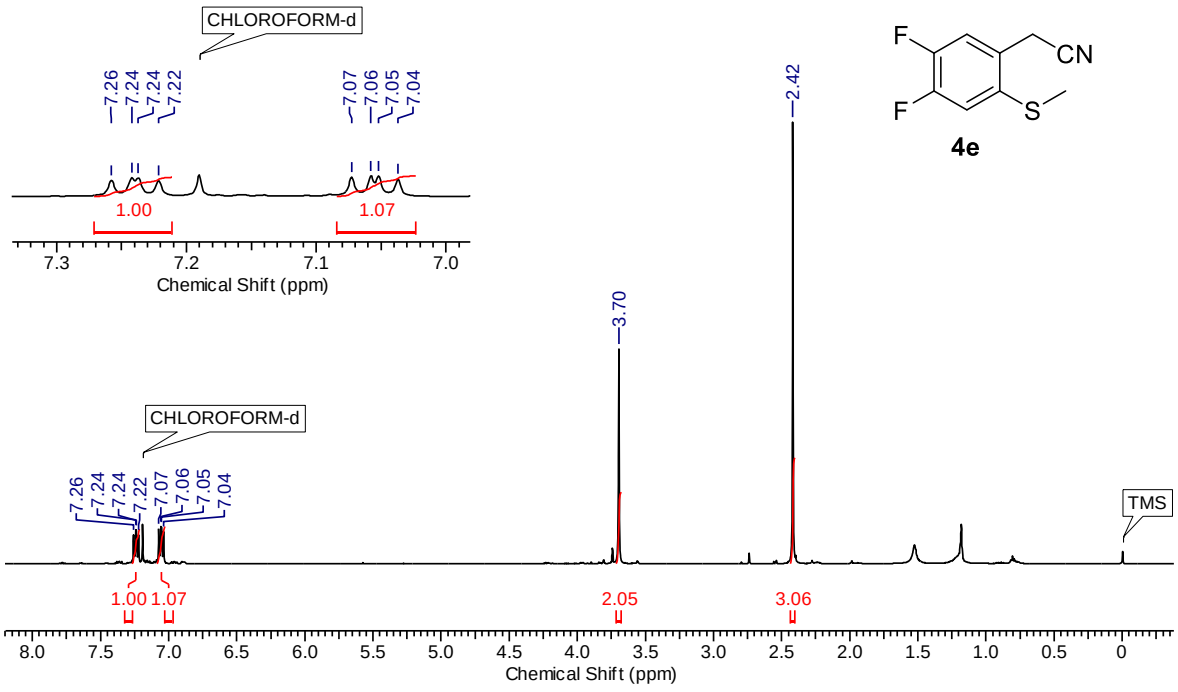

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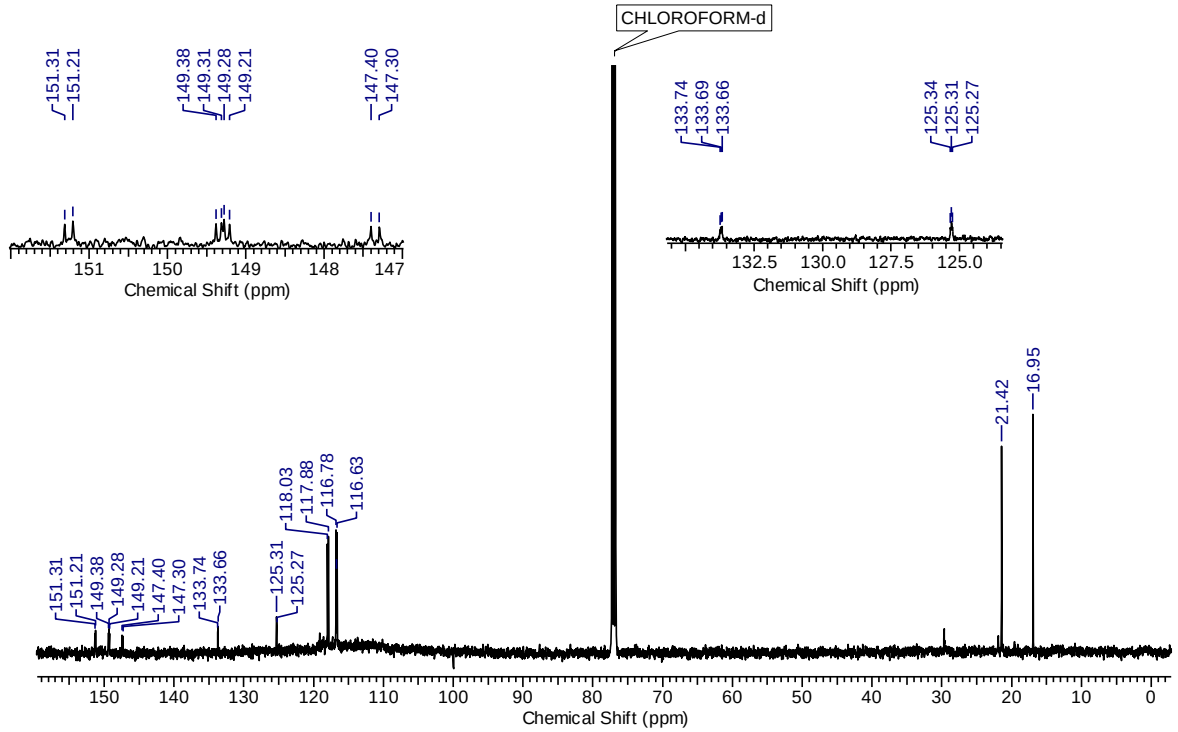

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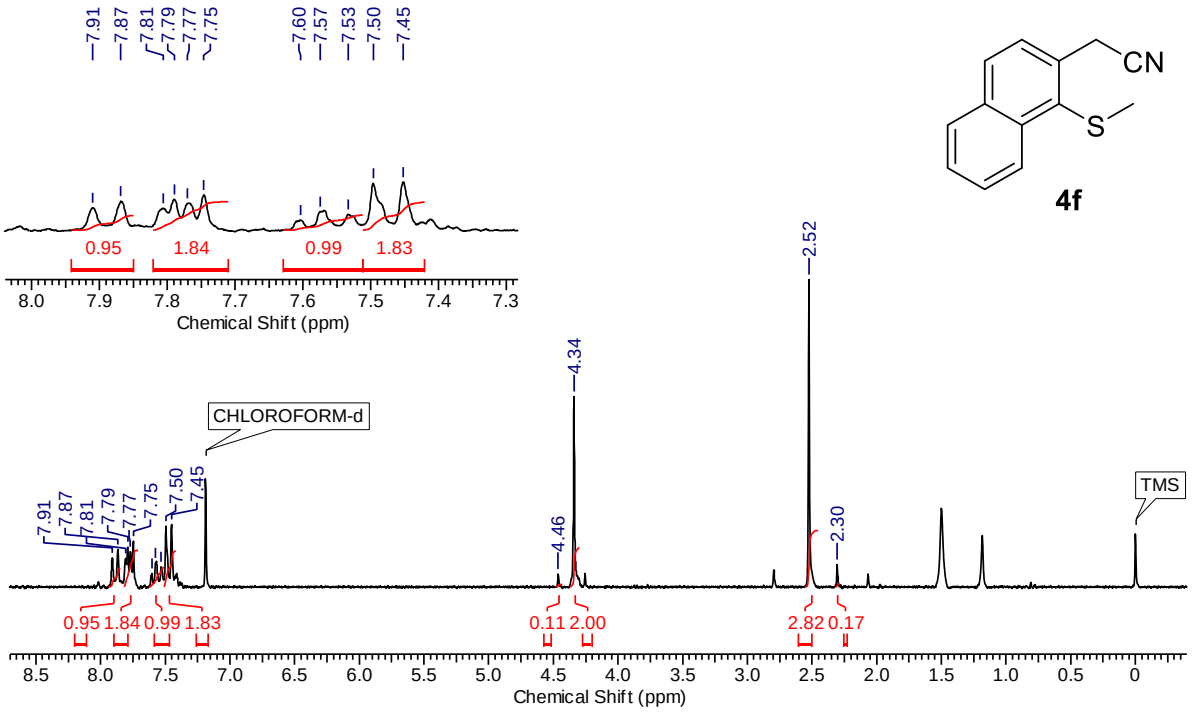

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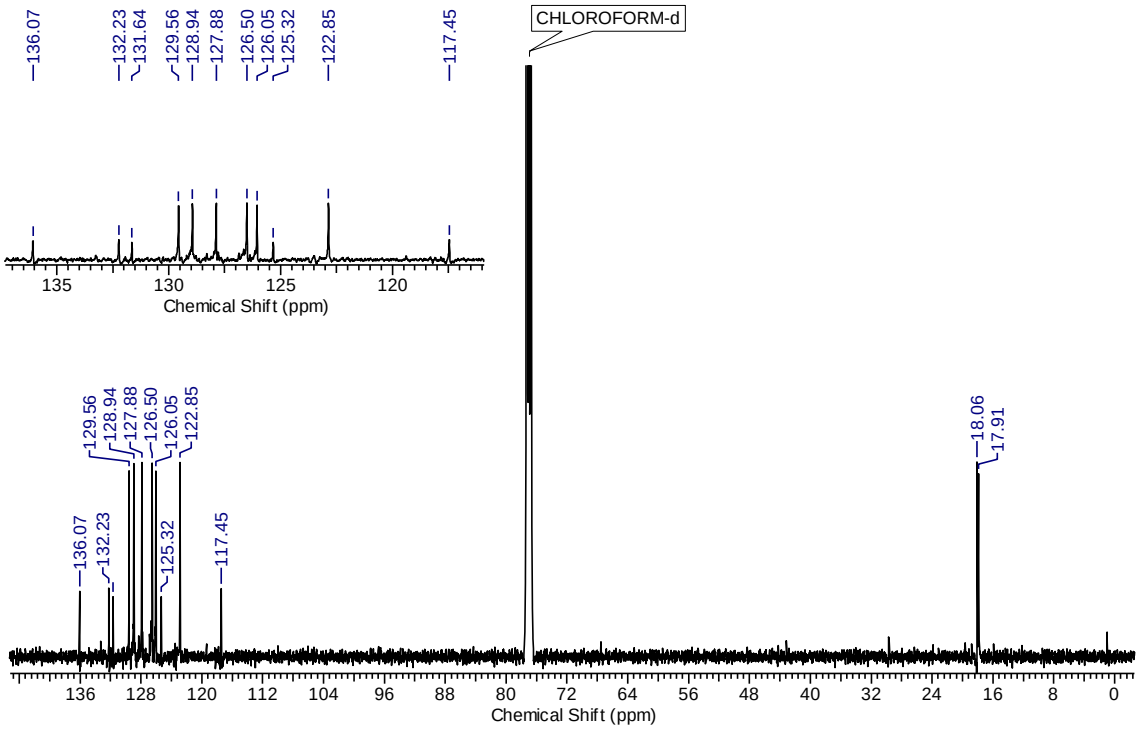

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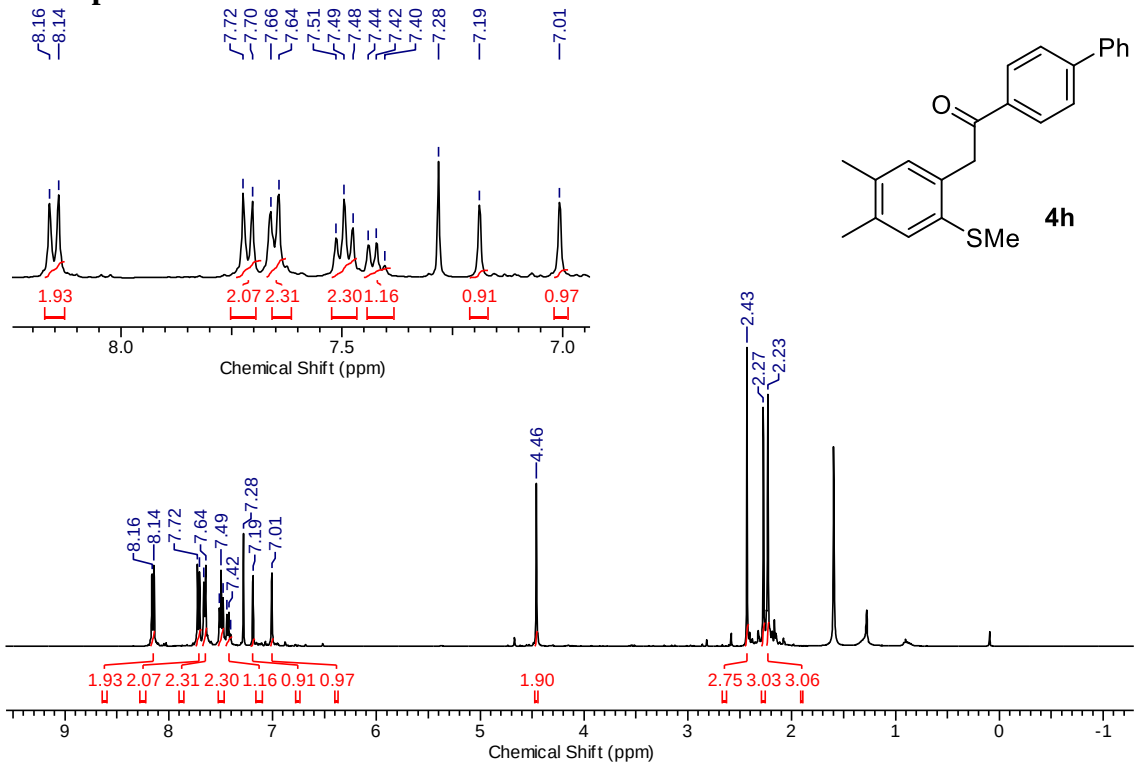

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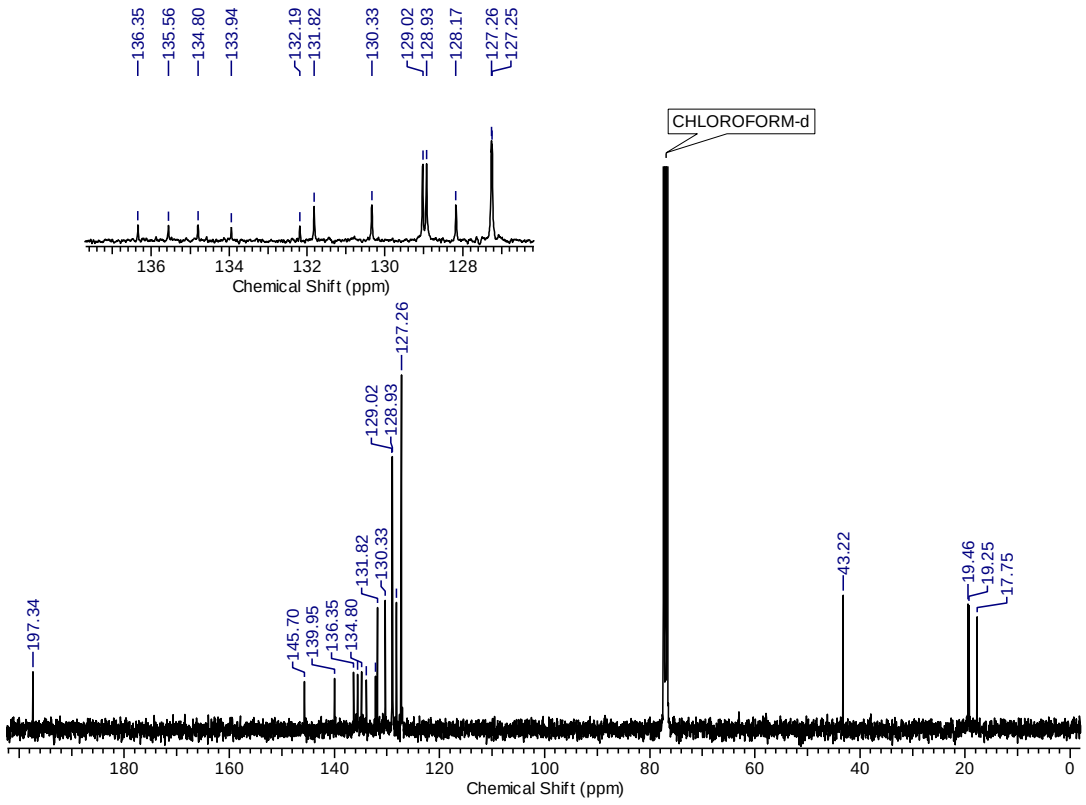

Publications and Patents

- "Application of Sulfur Ylides in 1,2-Difunctionalization of Arynes via Insertion into a C– S σ-Bond" *Org. Lett.* **2018**, *20*, 848.

  Milind M. Ahire, Mahesh B. Thoke, and Santosh B. Mhaske

- "Synthesis of *o*-Methyl Trifluoromethyl Sulfide Substituted Benzophenones via 1,2-Difunctionalization of Aryne by Insertion into the C–C Bond" *Org. Lett.* **2017**, *19*, 2134.

  Milind M. Ahire, Ruhima Khan, and Santosh B. Mhaske

- "Isa–NHC–catalyzed Intermolecular Stetter Reaction of Aromatic Aldehydes with Maleimides: An Efficient Access to 3–Aroylsuccinimides" *Tetrahedron*, **2018**, *74*, 2079.

  Milind M. Ahire and Santosh B. Mhaske

- "Synthesis of Succinimide Derivatives by NHC-Catalyzed Stetter Reaction of Aromatic Aldehydes with *N*-Substituted Itaconimides" *ACS Omega*, **2017**, *2*, 6598.

  Milind M. Ahire and Santosh B. Mhaske

- "Asymmetric NHC-Catalyzed Intramolecular [3+2] Annulation of Enals with Imine: Total Synthesis of Cruciferane and its Analogues" (Manuscript under preparation)

  Milind M. Ahire, Mahesh D. Pol and Santosh B. Mhaske

- "Catalytic Allylic Alkylation of α-SCF_3 ketones leading to synthesis of α-SCF_3 containing lactone" (Manuscript under preparation)

  Milind M. Ahire and Santosh B. Mhaske

- "*Ortho*-methyl trifluoromethyl sulfide substituted benzophenones, process for preparation and use thereof" 2017-NCL-0019 2017-NF-0055 IN 201711017655

  Milind M. Ahire and Santosh B. Mhaske

Erratum

Erratum