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By

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SCAFFOLD HOPPING WITH

SULFENYLCARBENES AND SULFENYLNITRENES

A DISSERTATION APPROVED FOR THE

DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

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Dedication

I dedicate this dissertation to my beloved wife, Ms. Krishika Kafle, and my parents, Ms. Juna Kafle and Mr. Ram Prasad Kafle. Your unwavering love, countless sacrifices, and quiet strength have been the foundation of this journey. Through every challenge and success, your belief in me never faltered, giving me the strength to persevere. You are my constant source of inspiration, and every accomplishment I have achieved reflects your support.

Abstract

Over the past decade, the cost of drug development, including failures and opportunity costs, has more than doubled. The United States now spends 17.7% of its annual income on healthcare, the highest among developed nations. Although several factors contribute to rising drug prices, a major driver is the high failure rate of new drug candidates during clinical trials and the substantial costs associated with these failures. Developing innovative medicines is inherently risky and demands significant investment in capital, skilled personnel, and advanced technology. While these challenges are widely recognized, it is less appreciated how inefficiencies in chemical research and development directly contribute to the high cost of medications available in local pharmacies. This work demonstrates a “drugs-from-drugs” approach, leveraging the effective and cost-efficient use of sulfur, often sourced from volcanic byproducts, to stabilize reactive intermediates for late-stage functionalization. This strategy enables the efficient generation of chemical libraries for rapid drug discovery.

In Chapter 2, a series of versatile sulfur-based carbene precursors (sulfenylcarbenes) were developed to enable late-stage single-carbon atom insertion into existing drug scaffolds, providing access to libraries of new, potentially bioactive molecules. In chapter 3, a series of sulfur-based nitrene precursors (sulfenylnitrenes) was developed for the chemoselective single-nitrogen-atom insertion into existing drugs at the late stage to generate a library of potential new drugs. These precursors are readily synthesized from commercially available reagents derived from volcanic waste (sulfur). These precursors can be produced on a large scale (commercialized by Lookchem), offering strong potential for industrial applications in drug discovery and contributing to efforts to reduce overall healthcare costs. Together, these studies establish a strategy for late-stage scaffold hopping via nitrogen- and carbon-atom insertion into readily accessible drug molecules. This approach enables the generation of structurally complex libraries under metal- and additive-free conditions using sulfur-based reagents.

In Chapter 4, more than two dozen sulfur-based carbene and nitrene precursors were developed to enable scaffold hopping of biowaste-derived furans into privileged N-heterocyclic scaffolds commonly found in pharmaceuticals. Furans have long been

considered structural alerts in medicinal chemistry due to their susceptibility to metabolic instability and reactivity with cellular components. This work addresses this longstanding challenge by enabling the late-stage transformation of furans, a rare scaffold in approved drugs, into *N*-heterocycles, which are present in approximately 80% of pharmaceuticals. This approach opens new avenues for drug discovery while offering potential to reduce overall drug development expense.

Overall, this dissertation establishes sulfur-based nitrene- and carbene-mediated strategies for late-stage remodeling of existing drugs to generate new therapeutics, enabling rapid and cost-effective drug discovery for affordable healthcare costs.

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I wish to express my deepest gratitude to my family, whose love and support have been the cornerstone of my journey. I am especially indebted to my parents, my mother, Ms. Juna Kafle, and my father, Mr. Ram Prasad Kafle, for their unwavering belief in me. The sacrifices and challenges you have faced to help me reach this point are beyond what I can fully comprehend. Your strength, encouragement, and constant faith have guided me every step of the way. I am profoundly thankful to my wife, Ms. Krishika Kafle, for her patience, understanding, and steadfast support throughout this journey. Your encouragement during both the highs and lows has meant more than words can express. I would also like to sincerely acknowledge my sister, Ms. Namrata Kafle, and my late brother-in-law, Keshav Subedi, whose continuous support and encouragement since my early academic years have motivated me to strive for excellence at every stage of my life.

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List of abbreviations

°C	degree centigrade/celcius
Å	angstrom
Ac	acetyl
Aq	aqueous
Bn	benzyl
Bz	benzoyl
calc.	calculated
Cbz	benzyloxy carbonyl
cm	centimeter
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
DIPA	diisopropyl amine
DMAP	4-dimethylamino pyridine
DMF	dimethylformamide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron-donating group
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
FDA	food and drug administration
g	gram
h	hour
HRMS	high-resolution mass spectrometry
Hz	Hertz
IR	infrared
J	coupling constant
L	liter
LAH	lithium aluminum hydride
LED	light-emitting diode
LRMS	low-resolution mass spectrometry
M	molar or mega
m	multiplet, mass, mili, meter, or mol
m/z	mass to charge ratio
M+Na	mass plus sodium
Me	methyl
mm	milimeter
mol	mole(s)
n.d.	not determined

n.r.	no reaction
NBS	N-bromosuccinamide
nBuLi	n-butyl lithium
nm	nanometer
NMR	nuclear magnetic resonance
p	para
p-ABSA	para acetamidobenesulfonyl azide
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
Rf	retention factor
rt	room temperature
s	singlet
SNP	sulfenylnitrene precursor
SCP	sulfenylcarbene precursor
t	triplet
TBAF	tetra-N-butyl ammonium fluoride
TBDPS	tetrabutyldiphenylsilyl
TEA	triethyl amine
THF	tetrahydrofuran
PhCl	chlorobenzene
TIPS	triisopropyl silyl
TLC	thin-layer chromatography
TMS	trimethyl silyl
Ts	tosyl
UV	ultraviolet
UV-vis	ultraviolet-visible spectroscopy

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CHAPTER 1

Drugs From Drugs: Skeletal Editing as a Toolkit in Drug Discovery

1.1. Introduction

If you asked Americans what worries them most about the current healthcare system, a common answer would be that prescription drugs are simply too expensive.[1] Over the past decade, the cost of drug development, including failures and opportunity costs, has more than doubled.[2] A study published in Drug Discovery Today estimates that developing a single new drug now costs an average of $4 billion, nearly double the figure from a widely cited 2003 study.[3] The United States allocates 17.7% of its annual income to healthcare, the highest among developed nations (**Figure 1.1.1**).[4] On an individual level, Americans spend an average of $1,105 on pharmaceuticals, $645 more than their counterparts in other developed countries.[5] This significant personal

expenditure is a key factor contributing to the stark disparity in healthcare costs between the U.S. and the rest of the world.[4] While several factors contribute to the rising cost of drugs, the primary reason is the high failure rate of new drug candidates in clinical trials and the associated costs.[6]

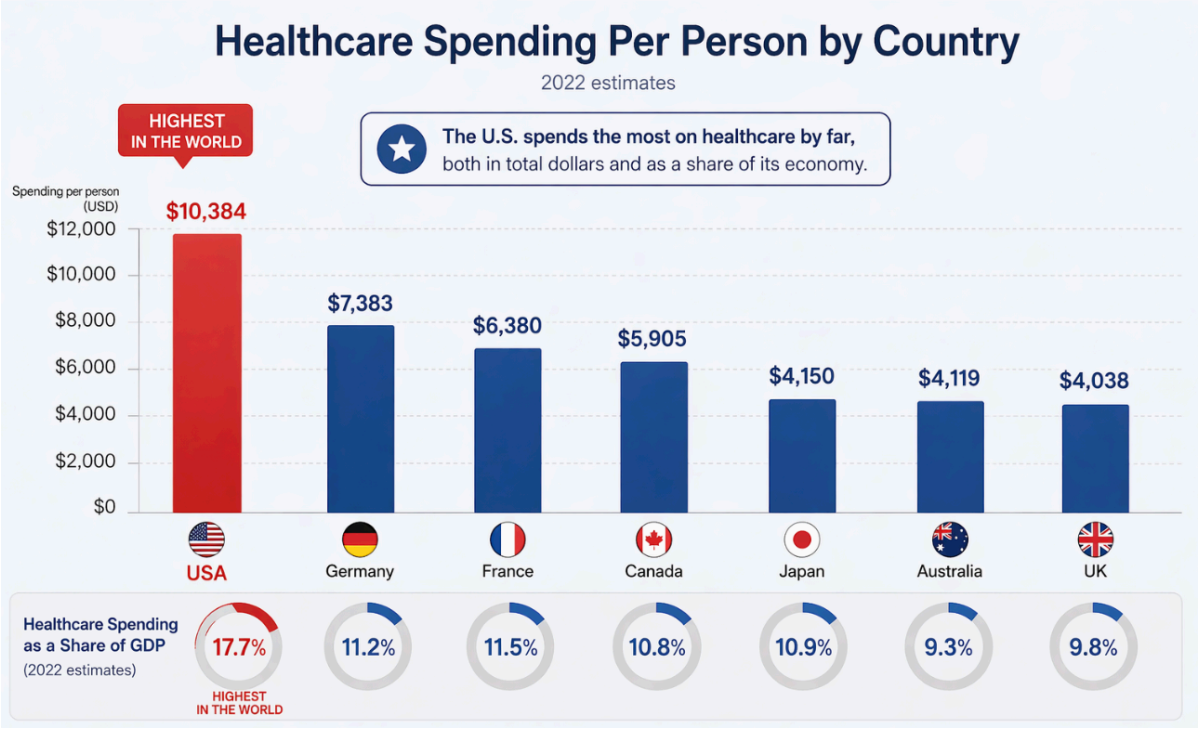


Figure 1.1.1: Healthcare spending per person by country in world.

Developing innovative drugs is inherently risky, requiring significant investment in capital, human resources, and technological expertise.[2] While this is widely acknowledged, what is less understood by the public is how ineffective research and development at the chemical level directly drives the high prices of medications sold in local pharmacies. The development of a new drug, from the initial synthesis of a compound to the approval of a New Drug Application (NDA), typically takes 10–15 years (**Figure 1.1.2**).[2] Given this extended timeline and the substantial costs involved, it is

evident why drug prices at pharmacies continue to rise. In the United States, the drug approval process is divided into three key stages: 1) Preclinical testing: research and development; 2) Clinical research and development; and 3) New drug application review. The stage where more effective research and development can have the most significant impact, without involving human safety concerns, is the "Preclinical testing: research and development" phase. During this stage, drug molecules are discovered or synthesized and undergo high-throughput screening of chemical libraries to identify potential hit compounds.

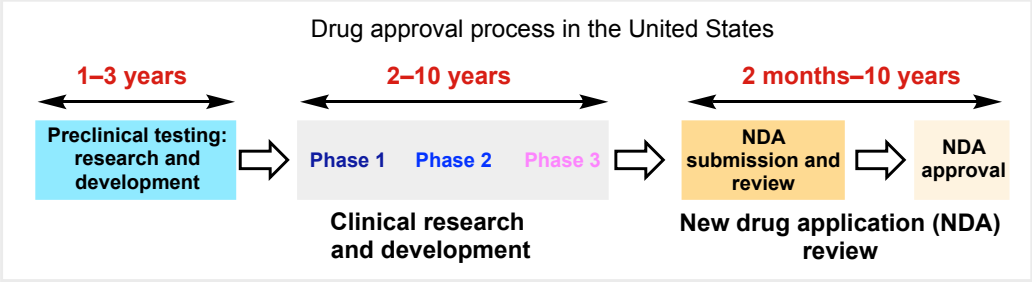


Figure 1.1.2: Flow chart for drug discovery timeline and approximate total cost.

Historically, chemical libraries have been largely built upon existing drug scaffolds or natural products, with diversity introduced primarily through their derivatization.[7] As Sir James Black a recipient of Noble prize in 1988 famously stated, "*The most fruitful basis for the discovery of a new drug is to start with an old drug.*"[8-9] Indeed, this saying is based on multiple new approvals, as simple as the discovery of ibuprofen in 1961,[10-11] after many years of relying on aspirin since 1897 as a simple painkiller (**Figure 1.1.3**).[12] However, this approach of relying on existing drugs faces significant synthetic challenges, as drug-like molecules often contain multiple reactive functionalities, making selective transformations difficult and lengthy, eventually leading to expensive route design.[9, 13-14] To save time and effort in synthesis, the computer-aided scaffold-hopping

approach was introduced by Gisbert Schneider and colleagues in 1999 to identify groups of compounds/libraries with similar biological activity.[15] This approach also suffers from computational prediction of some complex hypothetical compounds, which are sometimes almost impossible to access using known literature.[16]

As a result, current drugs fail to fully explore chemical space, leaving over 85% of the human genome classified as "undruggable."[17-18] Combined with the escalating costs of drug development, this highlights the urgent need for strategies that enable late-stage modifications of existing drugs, ultimately expanding the scope and impact of modern therapeutics.[19]

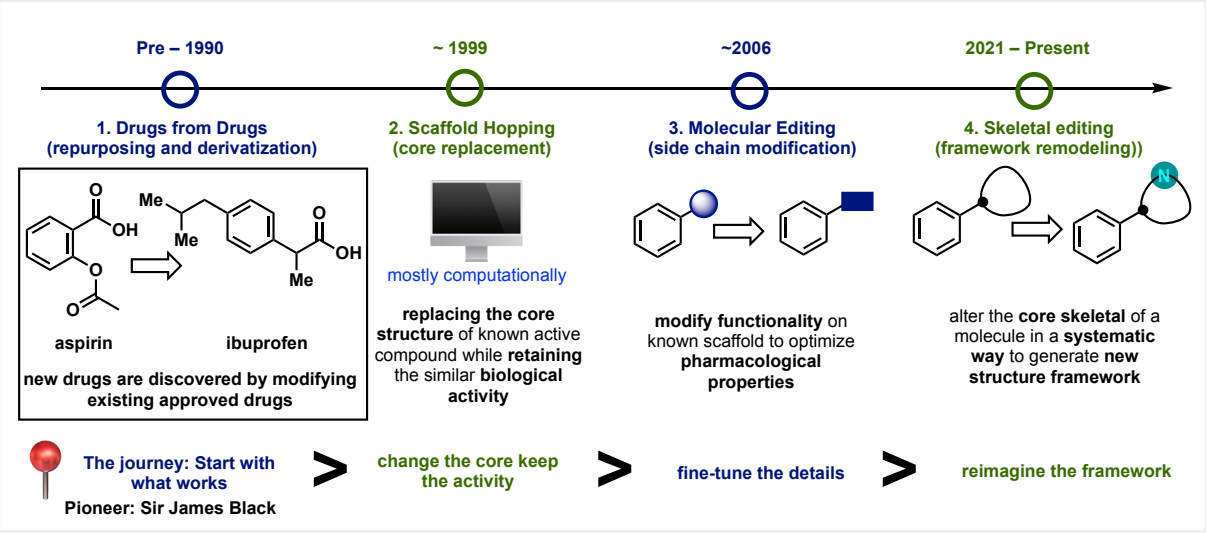


Figure 1.1.3: Conceptual evolution of skeletal editing

Keeping this limitation in mind, the concept of molecular editing was introduced by Danishefsky and colleagues in the early 2000s, allowing the selective modification of side-chain functionality to fine-tune pharmacological properties.[20-22] Inspired by this approach and the existing literature on single-atom logic, the term skeletal editing was coined by Levin and colleagues in 2021 to achieve the selective modification of a molecule's core without disrupting the substitution pattern or framework.[21-22] Even though this concept

has been on the rise recently, early reports like Ciamician-Dennstedt (1881),[23] Buchner-Curtius reaction (1885),[24] Beckmann rearrangement (1886),[25] Bayer-Villiger oxidation (1899),[26] Wolf-rearrangement (1902),[27] and Favorskii rearrangement (1913)[28] are perfect examples of single-atom skeletal editing.

1.2. Significance of Skeletal Editing

Skeletal editing of drug molecules refers to a strategy in organic and medicinal chemistry where specific atoms or bonds within the core structure (or "skeleton") of a molecule are selectively added, removed, or replaced.[22] The reasoning for this interest was inspired by the potential of skeletal editing/scaffold hopping approach to substantially change the physiochemical, pharmacological, and biological properties of molecules through what appears to be a straightforward alteration to their molecular structures.[29-30] A compelling example illustrating this impact is the conversion of fluvastatin into pitavastatin (**Figure 1.2.1**).[31-32] Here, introducing a single carbon atom resulted in a remarkable 77-fold improvement in biological activity. In a recent study by Nagib and colleagues, inserting a single carbon atom to selectively modify the indole core of LSD to access quinoline-LSD led to more than a 20-fold decrease in the hallucinogenic effect.[33] These examples highlight the significance of a single carbon change in the core of the compounds.

Similarly, replacing the CH group in an indole-based bioactive compound with an *N*-atom resulted in a 300-fold improvement in biochemical potency.[34] Also, internalizing the nitrogen atom within the arene ring improved pharmacological properties by inhibiting the formation of reactive metabolites.[30] Together, these examples highlight the

importance of inserting a single *N*-atom into the molecule's core and its potential in changing the pharmacological properties of drugs.

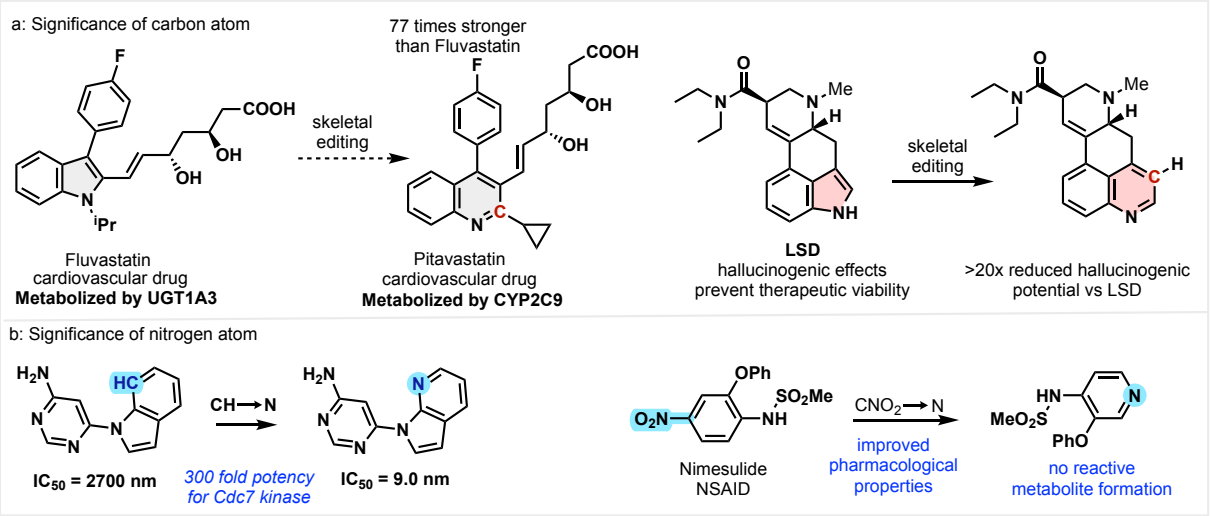


Figure 1.2.1: Significance of single atom change (a) Significance of *C*-atom change (b) Significance of *N*-atom change

Apart from manipulating the pharmacological properties of biorelevant compounds, skeletal editing allows efficient access to library synthesis in an effective and cost-efficient manner. This approach also allows for direct editing of scaffolds at the late stage of the synthesis, minimizing the steps and overall yield, and bypassing the fundamentally utilized de-novo approach (**Figure 1.2.2a**).[35] Levin and colleagues recently reported the synthesis of a potential 5α-reductase inhibitor in 3 steps with an overall yield of 10% from inexpensive, commercially available estrone ($6/g).[35] This same molecule was previously synthesized by Glaxo in 1994 in 11 steps, with an overall yield of less than 1% from the expensive nor-testosterone ($182/g).[35]

The significance of skeletal editing in the synthesis of complex analogs in a straightforward manner at the late stage is further highlighted by a report on selective

single-nitrogen insertion into tryptophan to yield quinazoline-based complex peptides (**Figure 1.2.2b**).[36-37] Two seminal reports from the Morandi group and Li group independently harnessed the skeletal approach in modifying daptomycin, an antibacterial drug, to its quinazoline core.[36-37] Several other quinazoline analogs of tryptophan-based peptides, such as semaglutide, bremelanotide, and somatostatin, were successfully synthesized using a nitrogen insertion strategy. This further highlights the need for this approach to access analogs that are almost impossible to obtain by de novo synthesis, as these substrates are mostly isolated from natural products.

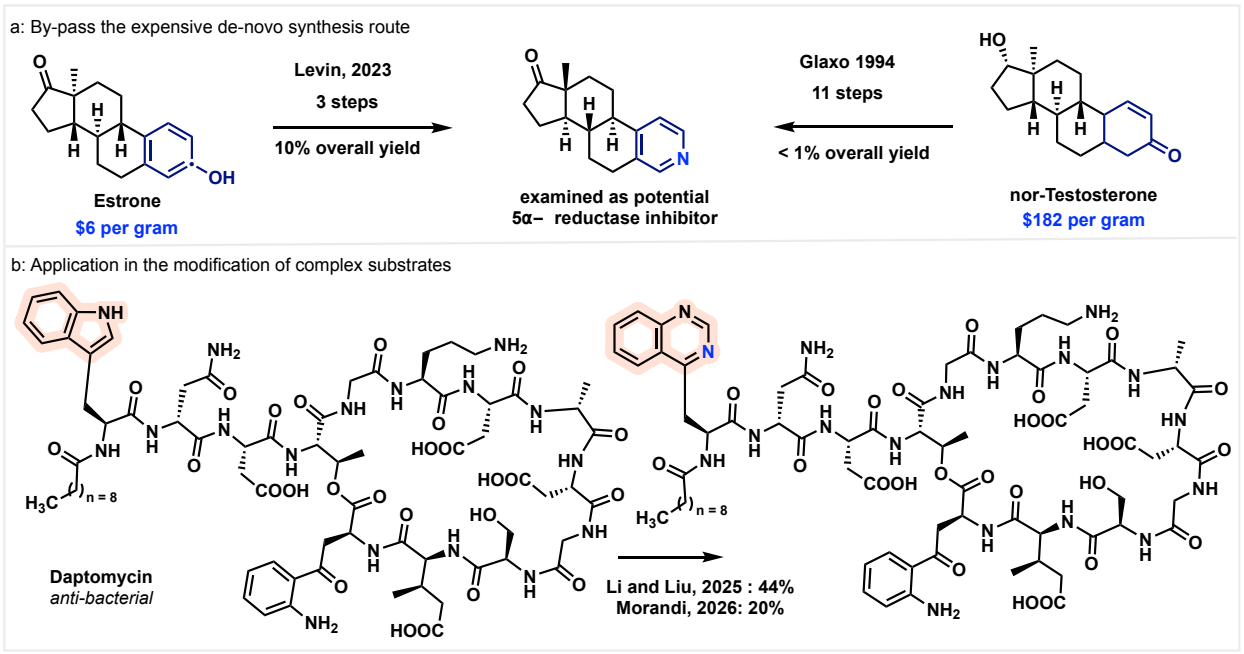


Figure 1.2.2: Skeletal editing bypassing the de-novo synthesis (a) Bypassing the expensive de-novo synthesis route (b) Application in the modification of complex substrates.

1.3. Challenges of Skeletal Editing

This approach offers significant advantages in drug discovery, medicinal chemistry, and chemical biology.[13, 19] However, key challenges remain, including the development of general, versatile methodologies or precursors that enable

chemoselective transformations while remaining compatible with a broad range of sensitive functional groups. Multicomponent reactions, while powerful, can be less effective in skeletal editing, as their inherent reactivity with multiple functional groups in complex molecules often leads to unproductive pathways and diminished selectivity.

The development of synthetic methodologies forms the backbone of advancing sustainable practices in industrial process chemistry.[38] It is also important that the rapid advancement of new methods does not come at the expense of safety, emphasizing the need to avoid potentially explosive reagents and unstable precursors.[39] Moreover, truly versatile methodologies should be capable of accommodating a wide array of similar classes of substrate, such as (pyrrole, indole, imidazole) or (pyrazole, indazole) or (furan, benzofuran), thereby expanding their utility across diverse chemical spaces.

1.4. Conclusion

In summary, skeletal editing has steadily emerged as a powerful and versatile strategy for the cost-effective generation of chemical libraries. By enabling the direct remodeling of existing molecular frameworks, it bypasses the need for de novo synthesis and significantly enhances efficiency. This approach holds promise in drug discovery, where accessing novel and diverse chemical space remains a longstanding challenge. Through precise structural modifications, skeletal editing can unlock previously inaccessible scaffolds, thereby expanding the pool of biologically relevant molecules and accelerating the identification of new therapeutic candidates.

1.5. Key gaps

While skeletal editing has emerged as a promising strategy, existing methods often rely on precious metals such as rhodium, require excess oxidizing agents, use of potential

explosive precursors, and lack site-selective reactivity. Due to the rapid growth of the skeletal editing field, the development of sustainable precursors and environmentally friendly conditions (metal-free conditions, compatibility under aqueous conditions) has not always been a primary focus. Overcoming these limitations could significantly enhance the utility of skeletal editing in chemical biology and drug discovery, particularly in the efficient synthesis of novel drug derivatives.

1.6. Objective of Dissertation

The objective of this dissertation is to develop metal-free skeletal editing conditions and applications in late-stage functionalization. We aim to design novel methodologies and reagents that utilize abundant sulfur, which is primarily recovered from volcanic sludge (**Figure 1.6**). These sulfur-based reagents generate reactive intermediates stabilized by sulfur and allow site-selective, additive-free reactions that accommodate wide functional-group tolerance and compatibility with oxidation-sensitive functionality, which is widespread in existing drug scaffolds. The main goal of this dissertation is to utilize sulfur as an alternative to rare precious metals in skeletal editing and late-stage functionalization, where sulfur assists in forming reactive intermediates, stabilizes them, and, during the reaction, acts as a leaving group, yielding a recyclable by-product.

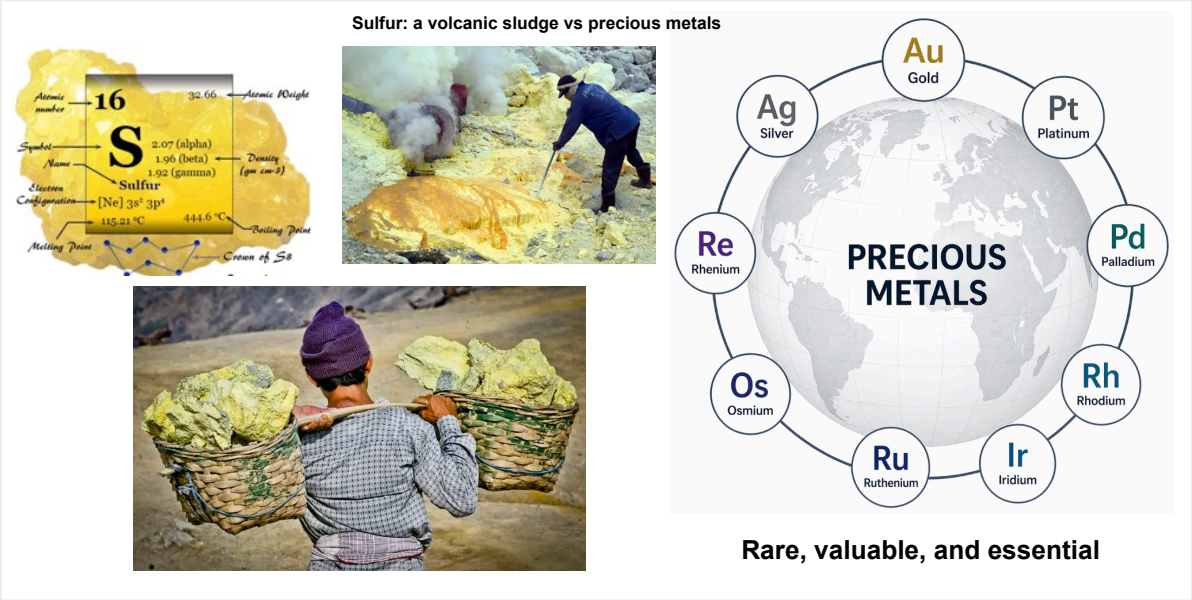


Figure 1.6: Sulfur as an alternative to previous metals.

1.7. Outline of this Dissertation

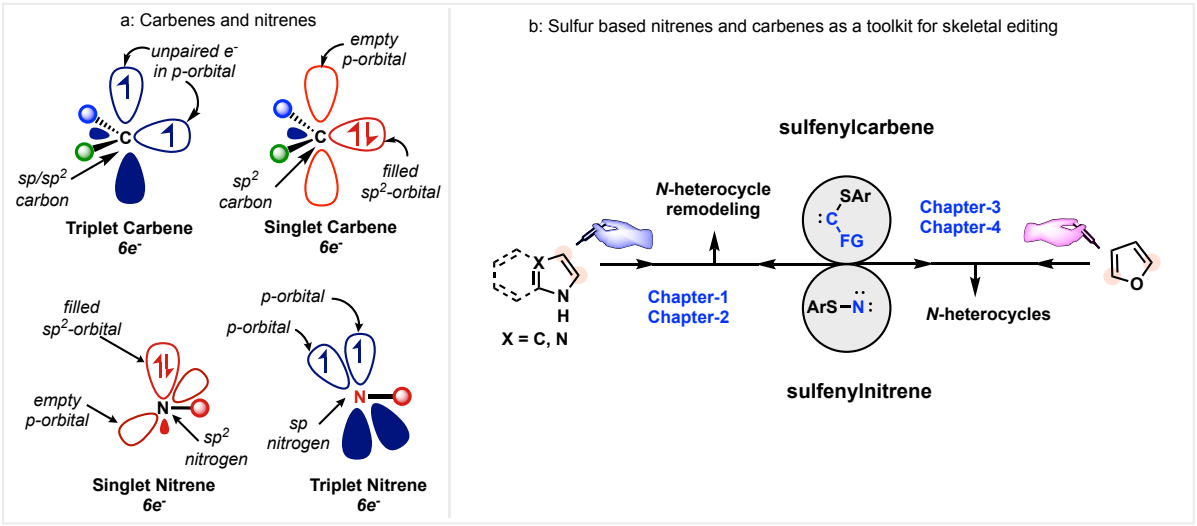


Figure 1.7: Sulfur-based nitrenes and carbenes as a toolkit for skeletal editing.

As outlined in the objective, we developed a novel methodology that utilizes sulfur-based carbenes (sulfenylcarbene) and nitrenes (sulfenylnitrene) for site-selective, additive-free skeletal editing and late-stage functionalization, addressing the key limitation in this field (**Figure 1.7**). In chapters 2 and 3, stable, versatile sulfenylcarbene and sulfenylnitrene precursors were developed and successfully applied in late-stage *N*-

heterocyclic remodeling. In these chapters, the state of the art in designing these precursors, their activation in generating carbenes and nitrenes with the assist of sulfur, and their application in skeletal editing will be discussed. In chapters 4, a new set of precursors was developed in the remodeling of readily available furans into privileged *N*-heterocycles. Chapter 5 provides a concise overview of future directions and emerging opportunities for these reactive intermediates.

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CHAPTER 2

Versatile Sulfenylcarbenes for Late-stage Functionalizations of N-Heterocycles

2.1 INTRODUCTION

Late-stage functionalization (LSF) has emerged as a powerful strategy in drug discovery, providing a means to directly modify complex molecules, including drug candidates, at a late stage.[1] This approach requires the expansion of modern synthesis to accommodate and construct highly complex molecules while maintaining functional group tolerance.[2] LSF is valuable for introducing new functional groups, enhancing biological activity, improving metabolic stability, accelerating drug candidate optimization,

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and conserving time and resources by avoiding extensive *de novo* synthesis.[3] A synthetic method must selectively react with a specific chemical motif to enable late-stage functionalization while leaving the surrounding functional groups unaffected.[2] Traditionally, this is achieved by leveraging inherent chemical reactivity or using directing groups and catalysts to modify local reactivity, ensuring site- and chemo-selectivity.[4] Despite significant progress in LSF,[1, 5] achieving the selective transformation of traditionally less reactive motifs in the presence of more reactive ones remains highly desirable yet seldom accomplished. Notably, the discoveries of olefin metathesis,[6] cross-couplings,[7] and click chemistry[8] highlight the remarkable chemoselectivity achieved with alkene and alkyne π-bonds.

Inspired by these advances and building on our work with skeletal editing,[9] we envisioned using carbenes for a chemoselective reaction with π-bonds for LSF. Carbenes are divalent, six-electron neutral species (**Figure 2.1a**). These are further classified into singlet and triplet based on their spin states; importantly, singlets are amphiphilic due to an empty *p*-orbital. Similar to sulfenylnitrene discussed in chapter 2, in a sulfenylcarbene, the neighboring sulfur provides tunable reactivity and significant stabilization to the carbene center without needing a metal catalyst.[10] These sulfenylcarbenes differ from metal carbenes, which are generally derived from the corresponding diazo compounds, known for their instability.[11] Other known carbene precursors often demand basic or oxidizing conditions.[12-13] Another class of carbene precursors, en-yn-als/-ones, are stable, but are limited to generating furyl carbene. They also require a *cis*-alkene configuration, demonstrating atom inefficiency.[14]

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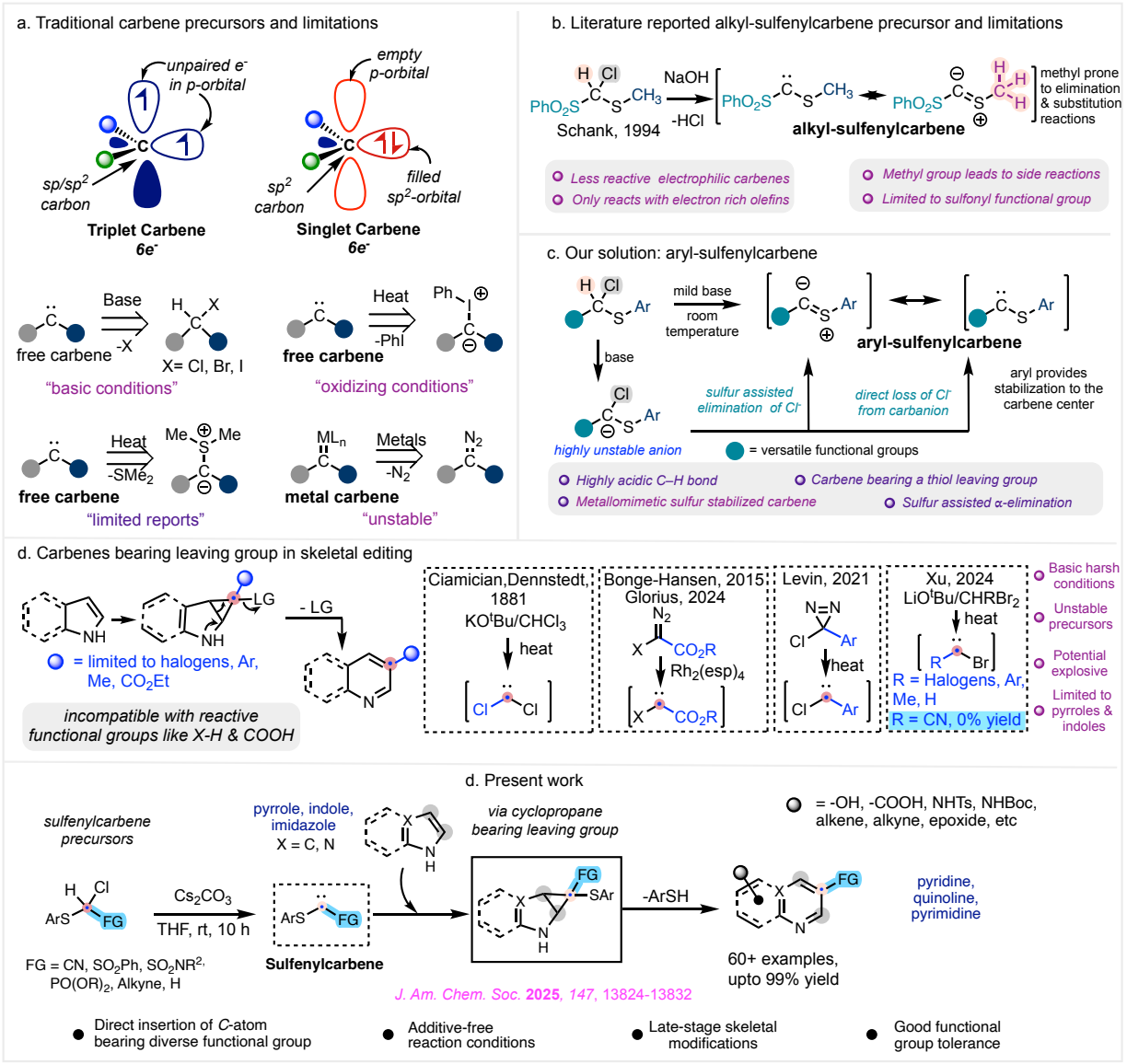


Figure 2.1: State of art for sulfenylcarbene generation. (a) Traditional carbene and their limitations. (b) Literature reported of alkylsulfenylcarbene. (c) Our solution: aryl sulfenylcarbene. (d) Present work.

To overcome the limitations of existing carbene precursors,[11-15] several mild methods for carbene generation have been published, such as the Ruppert-Prakash reagent and hydrazones.[16-18] Recently, the Nagib and MacMillan groups demonstrated the mild generation of zinc and iron carbenes, respectively, and subsequently employed

them in various conventional transformations.[19-20] However, most existing methods face challenges due to limited chemoselectivity, as carbenes often react with different functional groups. Therefore, developing a carbene bearing a leaving group with enhanced chemoselectivity towards π-bonds is essential for late-stage skeletal editing of *N*-heterocycles through a single carbon atom insertion bearing diverse functional groups.

To address this challenge, we drew inspiration from the groundbreaking work of Schank and colleagues, who generated alkyl-sulfenylcarbenes under aqueous conditions and demonstrated their reactivity with electron-rich olefins to produce cyclopropanes (**Figure 2.1b**).[21] Despite their utility, these carbenes were generated under strong basic conditions, leading to substitution and elimination reactions on the alkyl group of sulfenylcarbene, restricting their scope for broader synthetic applications. To address these limitations, we aimed to develop aryl-sulfenylcarbenes as an alternative (**Figure 2.1c**). There have been several reports on aryl-sulfenylcarbene precursors (SCPs) that accommodate functionality such as aryl, alkyne, halogen, and silyl.[22-26] However, their application has remained mostly confined to cyclopropane formation.

Several skeletal editing methods have been developed to incorporate a single carbon atom into *N*-heterocycles by utilizing carbene bearing a halogen leaving group (**Figure 2.1d**).[27-32] Despite significant advances in direct *C*-atom addition, most methods rely on carbene intermediates that require harsh basic reaction conditions,[12] health hazard haloforms,[31] unstable explosive diazo compounds,[15, 28] or expensive metals such as rhodium (Rh) (Figure 3.1c).[28] These methods are limited to the direct installation of a narrow range of functional groups, including halogens, aryl groups, esters, and methyl groups, often necessitating a linchpin for separate post-functionalization.[32]

Moreover, these transformations are sensitive to specific functional groups; for example, in one study, the presence of the cyano group led to a 0% yield of the desired product.[31] In addition, all methods known to date are limited to pyrroles and indoles, showing incompatibility with the single-carbon atom expansion of imidazoles.[29, 31-32]

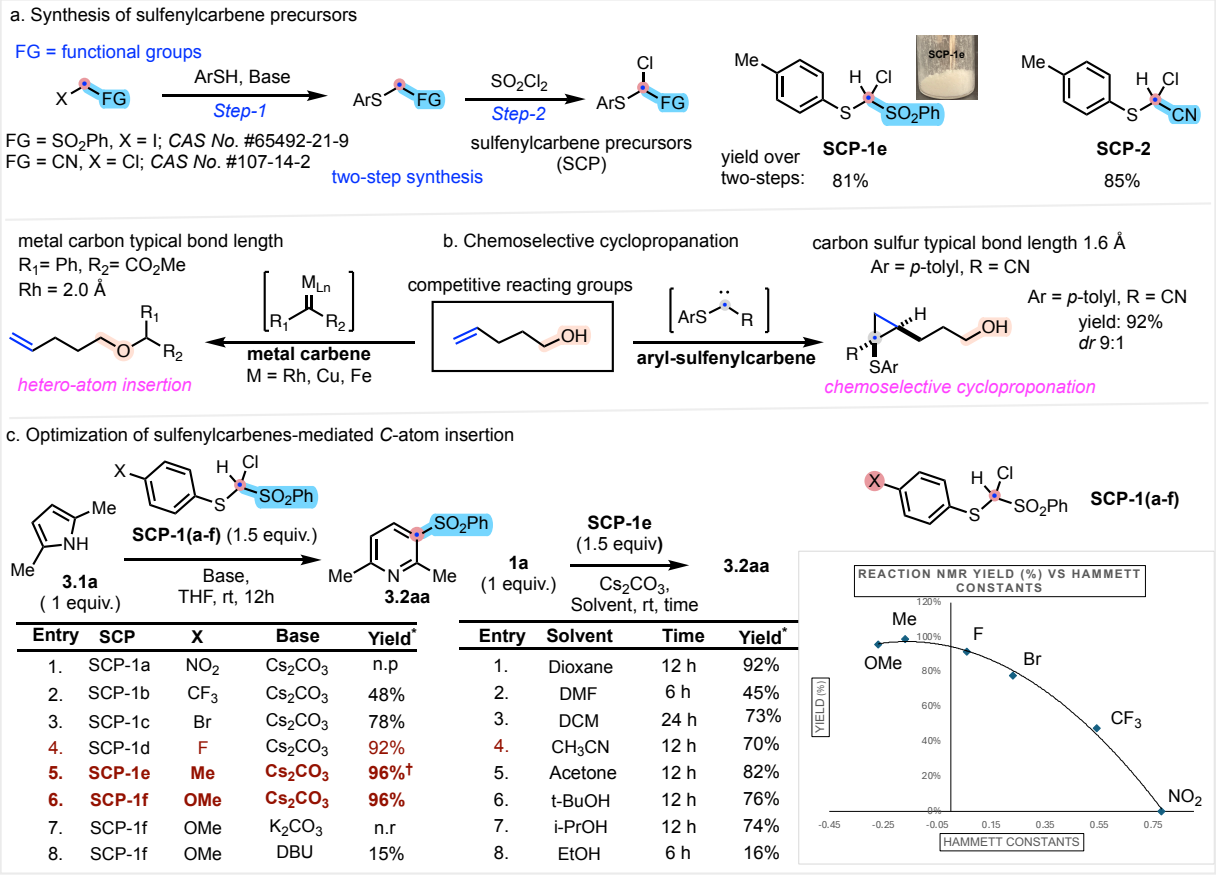
Building upon our work on sulfenylnitrenes,[9] we envisioned that sulfenylcarbenes bearing a built-in thio leaving group would enable a single carbon-atom insertion for late-stage skeletal editing of *N*-heterocycles (**Figure 2.1e**).

2.2 Results and Discussion

We initiated our work by synthesizing benchtop-stable sulfenylcarbene precursors to insert a single-carbon atom bearing diverse functional groups (**Figure 2.2.1a**). Another key design element is that several of these sulfenylcarbene precursors are easily prepared in just two steps from commercial reagents, remain stable for months at room temperature, and can be safely handled on a large scale.

To investigate the reactivity of aryl-sulfenylcarbenes, we reacted them with 4-penten-1-ol, resulting exclusively in the formation of the corresponding cyclopropane (**Figure 2.2.1b**). Notably, these carbenes exhibit reactivity similar to dihalocarbenes, in contrast to diazo-derived metal carbenes, which typically favor insertion into X–H bonds.[33] This chemoselective behavior of sulfenylcarbene can be attributed to several electronic factors, including its electrophilicity, the softness of the carbene, and orbital symmetry effects arising from resonance interactions between sulfur and the carbene center. [34] The *S*–*C* bond length in sulfenylcarbene is approximately 1.6 Å, suggesting a partial double bond character between the sulfur and the carbene carbon. Furthermore, density functional theory (DFT) calculations indicated that sulfenylcarbene exists as a

ground-state singlet, which is in accordance with the experimental results reported in the literature.[22, 25] Motivated by the observed chemoselectivity, we aim to harness sulfenylcarbenes for the late-stage functionalization of *N*-heterocycles that are commonly found in drug molecules and often feature diverse reactive functionalities, including alcohols and carboxylic acids.[35]



Entry	SCP	X	Base	Yield*
1.	SCP-1a	NO_2	Cs_2CO_3	n.p
2.	SCP-1b	CF_3	Cs_2CO_3	48%
3.	SCP-1c	Br	Cs_2CO_3	78%
4.	SCP-1d	F	Cs_2CO_3	92%
5.	**SCP-1e**	**Me**	**Cs_2CO_3**	**96%†**
6.	**SCP-1f**	**OMe**	**Cs_2CO_3**	**96%**
7.	SCP-1f	OMe	K_2CO_3	n.r
8.	SCP-1f	OMe	DBU	15%

Entry	Solvent	Time	Yield*
1.	Dioxane	12 h	92%
2.	DMF	6 h	45%
3.	DCM	24 h	73%
4.	CH_3CN	12 h	70%
5.	Acetone	12 h	82%
6.	t-BuOH	12 h	76%
7.	i-PrOH	12 h	74%
8.	EtOH	6 h	16%

Figure 2.2.1: Synthesis of sulfenylcarbene precursor and optimization. (a) Synthesis of sulfenylcarbene precursors. (b) Chemoselective cyclopropanation. (c) Optimization of sulfenylcarbene-mediated *C*-atom insertion. Reaction conditions: Reactions were carried out on a 0.5−1.0 mmol scale in a sealed vial. **2.1a** (1.0 equiv.), **SCP** (1.5 equiv.), base (3.0 equiv.), solvent (0.1 M). *Yield was determined by ^{1}H-NMR †Isolated yield. No product (n.p). No reaction (n.r).

Our optimization studies began by using commercially available symmetric 2,5-dimethylpyrrole (**2.1a**) as the model substrate (**Figure 2.2.1.c**), 1.5 equivalents of **SCP**, 3.0 equivalents of Cs_2CO_3 as a base, and tetrahydrofuran as a solvent. We selected the sulfonyl-based sulfenylcarbene **SCP-1** for initial optimization, as this precursor has been previously used in literature for cyclopropanation with electron-rich olefins. To understand the influence of thio-functionality on the carbene center, we did a Hammett study by substituting the *para*-position of aromatic thiol **SCP-1(a–f**). **SCP-1a**, bearing a nitro substitution (ρ = +0.778), failed to generate a carbene, presumably due to the high stability of the resulting carbanion. To our delight, a weaker electron-withdrawing group CF_3 (ρ = 0.540) on the aryl ring resulted in a moderate yield of pyridine **2a**. Furthermore, our study revealed that halogens such as Br (ρ = +0.232) and F (ρ = +0.062) on the aryl ring provided good yield of the product.

Finally, electron-donating groups on the aryl ring, such as **SCP-1e** (Me, ρ = –0.170) and **SCP-1f** (OMe, ρ = –0.268), proved highly efficient in facilitating carbene generation. To our delight, the corresponding pyridine **2.2a** was formed in 96% yield (entry 5,6) when the thio-functionality was para-substituted with methyl or methoxy groups. A correlation plot between Hammett constants and reaction yield has been drawn to understand the trend. This starkly contrasts with our sulfenylnitrene work, where electron-withdrawing groups were more effective.[9] Switching the base to K_2CO_3 resulted in no reaction, while using the organic base DBU led to the reaction proceeding with a lower yield.

This optimization revealed that cesium carbonate as a base is critical for the formation of the desired product. However, the role of cesium carbonate is not very clear

in this transformation. As literature suggests, this might be due to the higher solubility and easy dissociation in tetrahydrofuran, resulting in efficient carbene formation.[36-37]

Changing the reaction solvent to dioxane resulted in a slightly lower yield while using DMF led to a short reaction time and a significant yield decrease (entries 1, 2). Chlorinated solvents like dichloromethane led to longer reaction times with a slight reduction in yield (entry 3). We employed industrially preferred solvents, including acetonitrile, acetone, and primary, secondary, and tertiary alcohols.[38] The reaction worked in all solvents with good yields (entries 4–8). However, when primary alcohol (ethanol) was used as the solvent, a faster reaction was observed, but with a lower yield (entry 8).

Moving forward, we thought of demonstrating the complementary nature of our method to existing approaches [27-32], which allow the insertion of a single carbon atom into *N*-heterocycles having functional groups such as alkyl, aryl, carbonyl, and halogens. Therefore, we focused on functional groups such as cyano, alkyne, phosphate, sulfonamide, and silyl (**Figure 2.2.2a**). Several functionalized sulfenylcarbene precursors were synthesized and reacted with pyrroles. **SCP-2** bearing cyano functional group demonstrated a quantitative yield under standard conditions. Next, we utilized **SCP-3** to install an alkyne functionality that serves as a handle for library synthesis through sonogashira cross-couplings and in click chemistry for application in biology and material science.[8] **SCP-4,5** enabled the direct installation of phosphonate and sulfonamide, common functional groups in pharmaceuticals.[35] Additionally, **SCP-6** can be used for single carbon insertion bearing silyl group, a standard functionality used in Hiyama coupling.[39]

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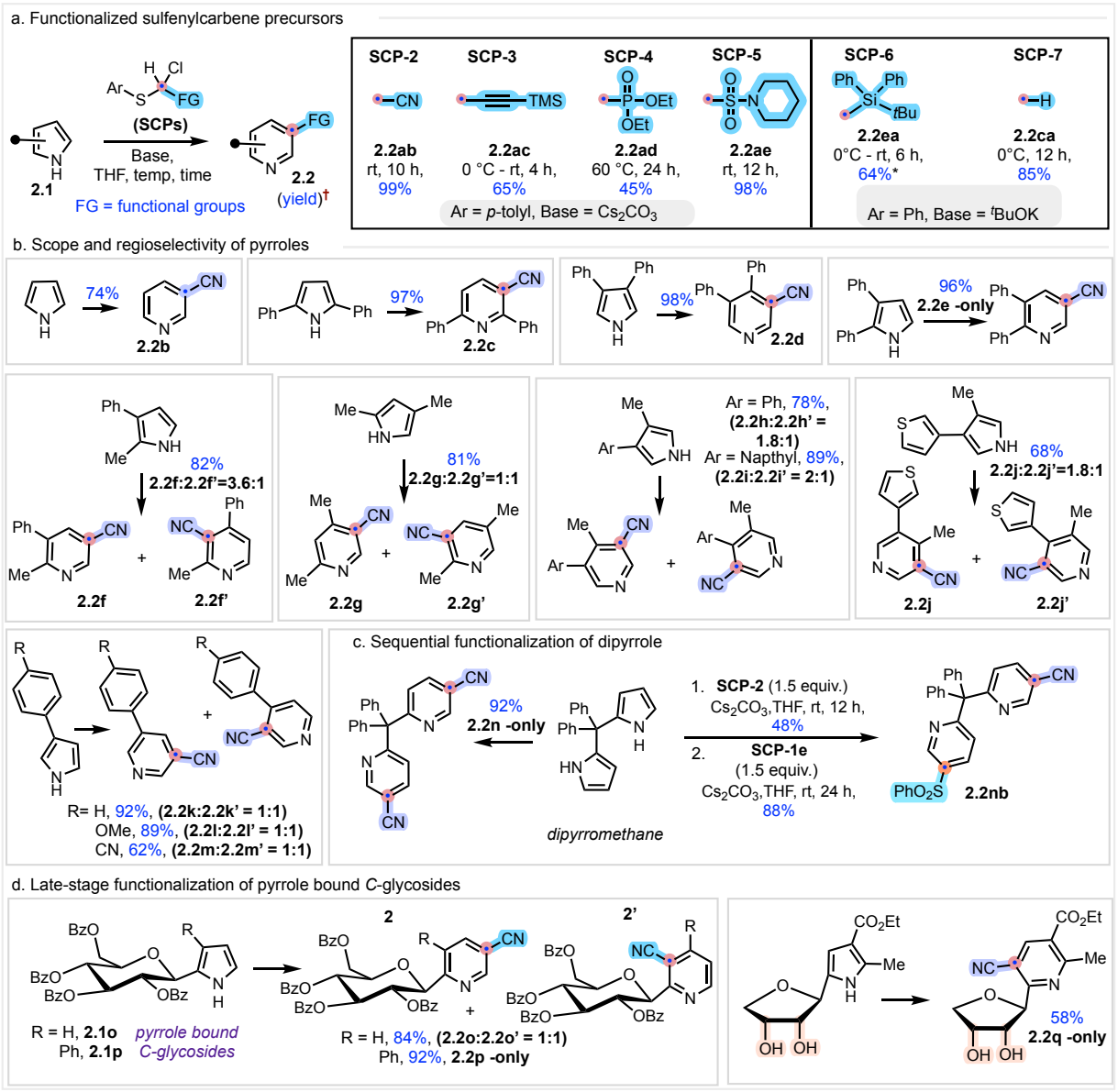


Figure 2.2.2: Scope of sulfenylcarbene and pyrroles. (a) Functionalized sulfenylcarbene precursors. (b) Scope and regioselectivity of pyrroles. (c) Sequential functionalization of di-pyrrole. (d) Late-stage functionalization of pyrrole bound *C*-glycosides. Reaction conditions: **2.1** (1.0 equiv.), **SCP** (1.5 equiv.), base (3.0 equiv.), and tetrahydrofuran (0.1 M). Reactions were carried out on 0.5−1.0 mmol scale. All the reported yields are isolated, and the regioisomeric ratio was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. *5.0 equiv. of base was used.

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We also demonstrated that commercially available **SCP-7** can be used for single carbon expansion without any functional group. This eliminates substituent-induced conformational changes essential for biological activity. For sulfenylcarbene precursors bearing less acidic *C–H*, ^{t}BuOK was used instead of Cs_2CO_3 to generate carbenes efficiently. While these are representative examples, we believe sulfenylcarbenes can be applied to many other functional groups, demonstrating their versatility and broad potential for late-stage functionalization.

SCP-2, featuring a cyano group, was selected as the optimized precursor for the substrate scope study because of the cyano group's critical importance[35] and versatility in post-modifications[40], coupled with the limitations of existing methods in introducing cyano functionality.[31-32] Cyano-containing drugs remain pivotal in recent drug approvals, with 7% of small-molecule drugs from 2013-2023 featuring a cyano group.[35] With these optimized conditions, we investigated the scope and regioselectivity of pyrroles (Scheme 3B). Notably, the *C*-atom insertion occurred preferentially on the sterically less hindered side. We first examined symmetrical pyrroles, and our method works well with free pyrrole (**2.2b**) and aryl-substituted symmetrical pyrroles (**2.2c, 2.2d**). Next, 2,3-substituted unsymmetrical pyrroles (**2.2e, 2.2f**) were subjected to the reaction conditions, and *C*-atom insertion primarily occurred on the unsubstituted side of pyrrole. We observed that 2,3-diphenyl pyrrole (**2.2e**) yielded a single regioisomer, favoring the unsubstituted position. A pyrrole with 2,4-dimethyl substitution (**2.2g**) yielded the pyridines with high yield, exhibiting no regioselectivity. Next, pyrroles featuring a methyl group at the 3-position and various aromatic substituents like phenyl, 2-naphthyl, and 3-thiophene at the 4-position consistently formed the corresponding pyridine in good yields favoring *C*-atom insertion

to the methyl side (**2.2h–2.2j**). Several 3-monosubstituted pyrroles were subjected to the reaction conditions, and *C*-atom insertion took place on both sides of pyrrole (**2.2k–2.2m**), showing no regioselectivity. We observed that phenyl rings with electron-donating or electron-withdrawing groups at the 3-position of the pyrrole did not influence regioselectivity.

Dipyrromethane, commonly used as an intermediate in porphyrin synthesis [41], proved to be compatible with the reaction, producing only a single regioisomer of dipyridylmethane (**2.2n**) (Scheme 3C). Dipyridylmethanes are effective ligands in coordination chemistry, offering bidentate binding and stabilizing metal complexes in various catalytic applications.[42] Building on the successful functionalized sulfenylcarbene precursors, we further demonstrated the effectiveness of this methodology in sequential functionalization of dipyrromethane to access functionalized dipyridylmethane (**2.2nb**) with good yield.

We next demonstrated the utility of our methodology by applying it to pyridine-bound *C*-glycosides, which are synthetically challenging to access due to the reactive pair mismatch with the glycosyl oxocarbenium ion. Our approach enables straightforward synthesis of these scaffolds from readily accessible pyrrole-bound *C*-glycosides (Scheme 3D).[43] As expected, *C*-glucopyranoside-bound pyrrole (**2.1o**) yielded a mixture of regioisomers (**2.2o**, **2.2o'**), while **2.1p** formed a single regioisomer (**2.2p**) in good yield. The compatibility of *C*-furanoside-bound pyrrole with free hydroxyl groups maintaining the stereoselectivity at the sensitive anomeric position (**2.2q**) highlights the potential of this methodology for broader applications in carbohydrate chemistry.[44]

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Furthermore, we investigated the reactivity of sulfenylcarbenes for the skeletal editing of indoles, a privileged scaffold present in many biologically active compounds (**Figure 2.2.3a**).[45] This method efficiently accommodates unsubstituted free indole (**2.4a**) and tolerates multiple substitutions, successfully transforming free indole (**2.4a**) on a gram scale into its corresponding quinoline derivative bearing a cyano group. This enabled the synthesis of various substituted quinolines, including those bearing electron-donating and electron-withdrawing groups, all obtained in good to high yields (**2.4b–2.4g**). Notably, this methodology demonstrated compatibility with the indole bearing a free hydroxyl group (**2.4h**), a functional group that previous approaches struggled with due to the need for protection.[32] A highly chemoselective single *C*-atom insertion was achieved in good yield with indoles containing terminal alkene and alkyne groups (**2.4i, 2.4j**). Our approach also allows access to quinoline compounds featuring an epoxide (**2.4k**), a valuable scaffold in drug design.[46]

To further demonstrate the potential utility of our method, late-stage skeletal editing of complex indoles was performed (**Figure 2.2.3b**)**.** Thio-ether-containing indole was well tolerated to provide corresponding quinoline (**2.4l**) in good yield, demonstrating the compatibility of sulfenylcarbene with oxidation sensitive functionality. Notably, 4-(1*H*-indol-3-yl) butane-1-ol, derived from a plant growth hormone containing linear primary alcohol, was well tolerated to form quinoline product **2.4m**. Additionally, Weinreb amide containing indole was also compatible to form product **2.4n** in good yield. We observed a smooth expansion of diazo-bound indole, furnishing the desired diazo-bound quinoline **2.4o** with a good yield. This showcases the orthogonal activation of sulfenylcarbene precursors in the presence of other carbene precursors.

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Indole-butyric acid (IBA)[47], a plant growth hormone-bearing carboxylic acid, demonstrated compatibility with the reaction, providing a yield of expansion product **2.4p** in 85%. Mono-protected tryptamine and tryptophan successfully underwent ring expansion to the corresponding quinoline products (**2.4q**, **2.4r**). This differs from sulfenylnitrenes [9], where ring cyclization was favored over ring expansion.

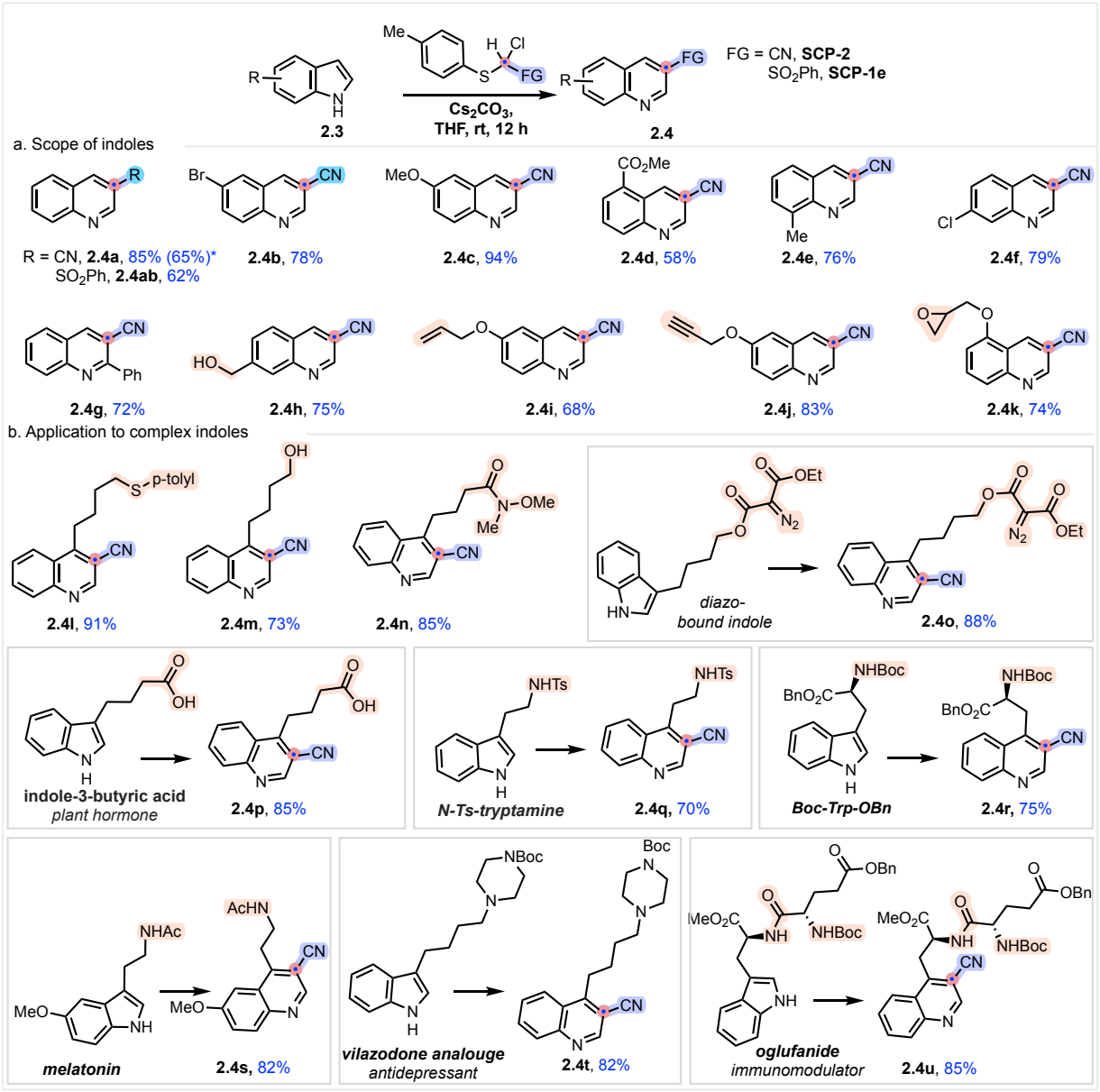


Figure 3.2.3: Scope of indoles. (a) Scope of indoles. (b) Application to complex indoles.

Furthermore, melatonin, an indoleamine used for treating sleep disorders and regulating circadian rhythms[48], demonstrated compatibility with the reaction, providing a good yield (**2.4s**). Late-stage functionalization of vilazodone, an antidepressant[49], was successfully achieved to obtain its quinoline derivative in good yield (**2.4t**). Oglufanide, an immunomodulatory peptide[50] used to enhance and regulate immune system responses in weakened immunity, was successfully transformed into its quinoline derivatives (**2.4u**) with a yield of 85%.

Building on the successful skeletal editing of indoles and pyrroles, we extended our methodology to achieve *C*-atom insertion into imidazoles, a privileged scaffold in pharmaceuticals[51], overcoming the incompatibility of previous *C*-addition methods[31-32, 52] and highlighting the significance of our approach (**Figure 2.2.3**). We started our scope with 2-phenyl substituted imidazole to access the corresponding pyrimidine in good yield (**2.6a**). It is worth noting that imidazoles offer complete regioselectivity, favoring the side with the carbon-carbon double bond. In addition to pyrimidine, minor insertion by-products were obtained, consistent with an earlier literature report.[31] Next, several 2-phenyl substituted imidazoles containing electron-donating or electron-withdrawing groups were screened to access pyrimidines, yielding moderate to good results (**2.6b–2.6d**). Furthermore, 4-alkyl and aryl-substituted imidazoles were compatible with our methodology, providing pyrimidine with complete regioselectivity (**2.6e**, **2.6f**). Additionally, 2,4-diaryl substituted imidazole was successfully expanded in good yield (**2.6g**).

Notably, the imidazole-containing amino acid L-histidine was regioselectively transformed into its unnatural pyrimidine-containing amino acid (**2.6h**). Carnosine, a dipeptide composed of beta-alanine and L-histidine known for its antioxidant properties

and potential benefits in muscle endurance, neuroprotection, and anti-aging[53], was successfully converted into its pyrimidine derivative.

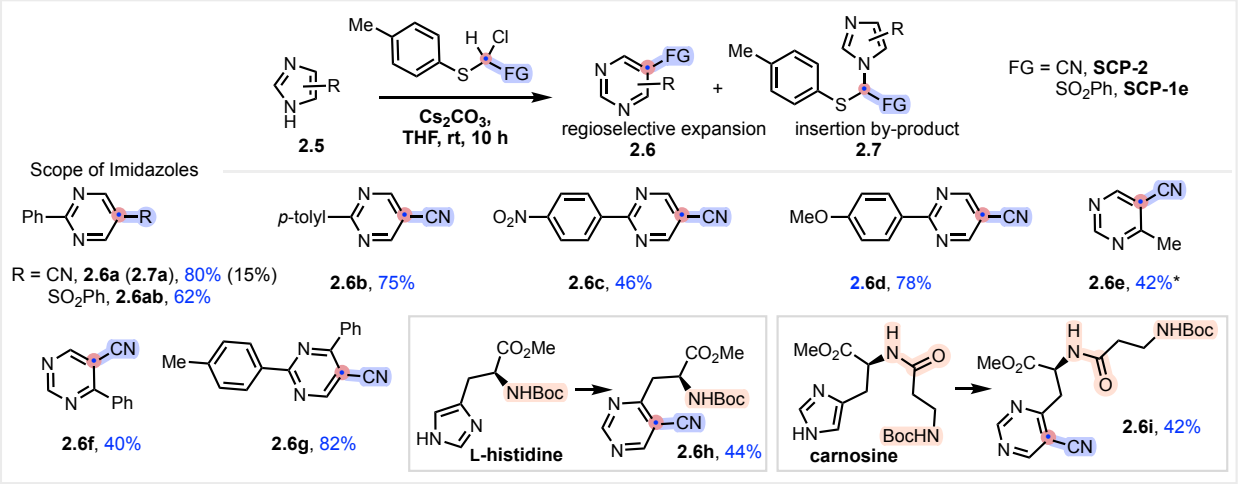


Figure 2.2.3: Scope of imidazoles. *(1:1) mixture of THF:Acetone was used as a solvent.

2.3 Conclusion

These benchtop-stable sulfenylcarbene precursors can be synthesized on a large scale, highlighting their potential for commercial use. This metal-free non-diazo approach, mild reaction conditions, simple operational protocol, high chemoselectivity, and excellent functional group tolerance make sulfenylcarbenes particularly advantageous. Their capability for late-stage functionalization to generate novel chemical entities presents promising opportunities for exploring uncharted chemical space in drug discovery.

*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

2.4 Experimental Section

Reagents: Reagents and solvents were obtained from Sigma-Aldrich (www.sigma-aldrich.com), ChemImpex (www.chemimpex.com) or Acros Organics (www.fishersci.com) and used without further purification unless otherwise indicated. Dry solvents (acetonitrile) were obtained from Acros Organics (www.fishersci.com), and dichloromethane was distilled over CaH_2 under N_2 unless otherwise indicated. THF purchased from Sigma-Aldrich was distilled over Na metal with benzophenone indicator.

Reactions: All reactions were performed in flame-dried glassware under positive N_2 pressure with magnetic stirring unless otherwise noted. Liquid reagents and solutions were transferred thru rubber septa via syringes flushed with N_2 prior to use. Cold baths were generated as follows: 0 °C with wet ice/water, –5 °C with Julabo (MeOH as a coolant), and −78 °C with dry ice/acetone.

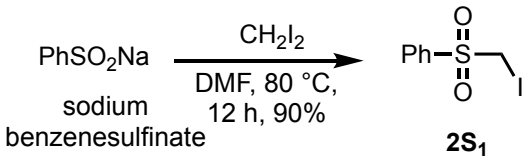
Chromatography: TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$), cerium ammonium molybdenate (CAM), phosphomolybdic acid (PMA), and ninhydrin. Silica flash chromatography was performed on Sorbtech 230–400 mesh silica gel 60.

Analytical Instrumentation: NMR spectra were recorded on a Varian VNMRS 400, 500, and 600 MHz NMR spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (^1H, 7.26 ppm, ^{13}C, 77.0 ppm); coupling constants are expressed in Hz. NMR spectra were processed using Mnova. Mass spectra were obtained at the OU Analytical Core Facility on an Agilent 6538 High-Mass-Resolution QTOF Mass Spectrometer and an Agilent 1290 UPLC.

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2.5 Synthesis of Sulfenylcarbene Precursors (SCP)

2.5.1 Synthesis of SCP-1

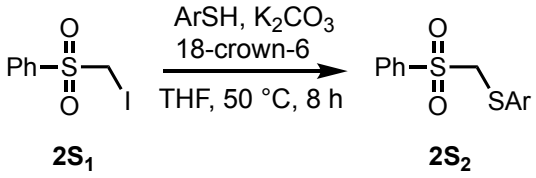


2S$_1$

To a solution of sodium benzenesulfinate (60.92 mmol, 10 g) in DMF (0.5 M), 73.1 mmol of diiodomethane was added and stirred at 80 °C next 12 h until the completion of the reaction. The reaction mixture was diluted with water, extracted with ethyl acetate, and purified by silica gel chromatography. The product was obtained as a white solid (CAS No: 65492-21-2). (15.5 g, 90% yield; **TLC**: R_f 0.25 in 30% EtOAc/Hexane).

The spectra data matched with previously reported literature.[54]

General procedure A

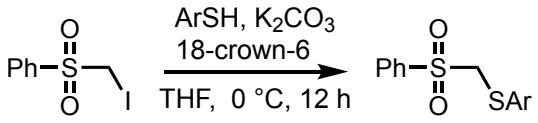


2S$_1$ **2S$_2$**

Step-1: To a solution of **2S$_1$** (1 equiv.) in THF (0.1 M) at room temperature, 2 equiv. of K_2CO_3, and 1 equiv. of 18-crown-6 was added, followed by the addition of 1.5 equiv. of thiol. The resulting mixture was heated at 50 °C for 8 h until the completion of the reaction. The resulting mixture was cooled down to room temperature, diluted with ethyl acetate, filtered through celite, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by silica gel chromatography.

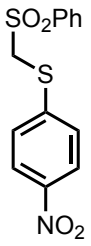
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

General procedure B



2S$_1$ **2S$_2$**

Step-1: To a solution of **2S$_1$** (1 equiv.) in THF (0.1 M) at 0 °C, 2 equiv. of K_2CO_3 and 1 equiv. of 18-crown-6 was added, followed by the addition of 1.5 equiv. of thiol. The resulting mixture was stirred at 0 °C for 12 h until the completion of the reaction. The resulting mixture was diluted with ethyl acetate, filtered through celite, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by silica gel chromatography.



2S$_3$

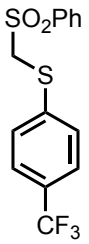
(4-Nitrophenyl)((phenylsulfonyl)methyl)sulfane (2S$_3$): Synthesized according to general procedure A using 3.5 mmol (1.0 g) of **2S$_1$**. The product was obtained as a white solid (0.93 g, 85% yield; **TLC**: R_f 0.25 in 20% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.9 Hz, 2H), 7.97 – 7.91 (m, 2H), 7.71 – 7.65 (m, 1H), 7.59 – 7.49 (m, 4H), 4.44 (s, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 146.9, 142.2, 137.3, 134.7, 129.6, 129.4, 129.1, 124.3, 57.5.

HRMS(ESI): calculated for $C_{13}H_{12}NNaO_4S_2(M+Na)^+$: 332.0022; found:332.0026.

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2S$_4$

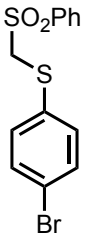
((Phenylsulfonyl)methyl)(4-(trifluoromethyl)phenyl)sulfane (2S$_4$): Synthesized according to general procedure A using 3.5 mmol (1.0 g) of **2S$_1$**. The product was obtained as a white solid (1.05 g, 85% yield; **TLC**: R_f 0.35 in 20% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.96 – 7.87 (m, 2H), 7.68 – 7.61 (m, 1H), 7.56 – 7.44 (m, 6H), 4.39 (d, *J* = 0.7 Hz, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 137.9, 137.5, 134.5, 130.5, 129.9 (q, *J* = 32.9 Hz), 129.4, 129.1, 126.2 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 271.9 Hz), 58.5.

^{19}F NMR:(376 MHz, $CDCl_3$) δ -62.7.

HRMS(ESI): calculated for $C_{14}H_{12}F3NaO_2S2(M+Na)^+$: 355.0045; found: 355.0048.



2S$_5$

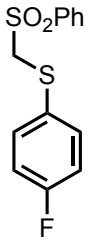
(4-Bromophenyl)((phenylsulfonyl)methyl)sulfane (3S$_5$): Synthesized according to general procedure A using 3.5 mmol (1.0 g) of **2S$_1$**. The product was obtained as a yellow solid (1.07 g, 88% yield; **TLC**: R_f 0.30 in 20% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.68 – 7.61 (m, 1H), 7.56 – 7.49 (m, 2H), 7.38 – 7.33 (m, 2H), 7.27 – 7.22 (m, 2H), 4.29 (s, 2H).

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$^{13}C\{^1H\}$ NMR:(100 MHz, $CDCl_3$) δ 137.7, 134.3, 133.5, 132.5, 132.1, 129.4, 129.1, 122.8, 59.7.

HRMS(ESI): calculated for $C_{14}H_{12}BrNaO_2S_2(M+Na)^+$: 364.9276; found: 364.9276.



$2S_6$

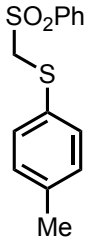
(4-Fluorophenyl)((phenylsulfonyl)methyl)sulfane ($2S_6$): Synthesized according to general procedure A using 3.5 mmol (1.0 g) of **$2S_1$**. The product was obtained as a clear oil (0.7 g, 70% yield; **TLC**: R_f 0.25 in 15% EtOAc/Hexane).

^1H NMR: (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H), 7.69 – 7.62 (m, 1H), 7.58 – 7.50 (m, 2H), 7.44 – 7.37 (m, 2H), 6.95 (t, *J* = 8.6 Hz, 2H), 4.27 (s, 2H).

$^{13}C\{^1H\}$ NMR:(100 MHz, $CDCl_3$) δ 163.1 (d, *J* = 249.5 Hz), 137.8, 135.0 (d, *J* = 8.2 Hz), 134.3, 132.6, 129.2 (d, *J* = 25.9 Hz), 128.0, 116.5 (d, *J* = 22.1 Hz), 60.6.

^{19}F NMR:(376 MHz, $CDCl_3$) δ -111.6 – -112.3 (m).

HRMS(ESI): calculated for $C_{13}H_{11}FNaO_2S_2(M+H)^+$: 305.0082; found:305.0081.



$2S_7$

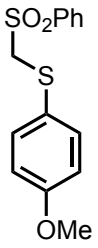
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

((Phenylsulfonyl)methyl)(*p*-tolyl)sulfane (2S$_7$): Synthesized according to general procedure A using 10.6 mmol (3.0 g) of **S$_1$**. The product was obtained as a clear oil (2.8 g, 95% yield; **TLC**: R_f 0.20 in 15% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$)δ 7.93 – 7.87 (m, 2H), 7.67 – 7.60 (m, 1H), 7.51 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.24 (d, *J* = 2.9 Hz, 2H), 7.06 – 7.01 (m, 2H), 4.28 (s, 2H), 2.29 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 138.8, 137.9, 134.1, 132.5, 130.1, 129.4, 129.2, 129.2, 60.5, 21.3.

HRMS(ESI): calculated for $C_{14}H_{15}NaO_2S_2(M+Na)^+$: 301.0333; found: 301.0329.



2S$_8$

(4-Methoxyphenyl)((phenylsulfonyl)methyl)sulfane (2S$_8$): Synthesized according to general procedure B using 17.6 mmol (5.0 g) of **S$_1$**. The product was obtained as a clear oil (4.9 g, 95% yield; **TLC**: R_f 0.20 in 20% EtOAc/Hexane).

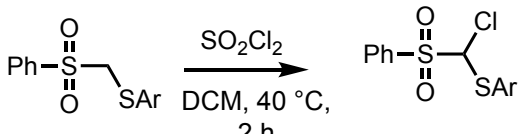
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 2H), 7.69 – 7.61 (m, 1H), 7.57 – 7.50 (m, 2H), 7.37 – 7.31 (m, 2H), 6.80 – 6.74 (m, 2H), 4.23 (s, 2H), 3.79 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 138.8, 137.9, 134.1, 132.5, 130.1, 129.4, 129.2, 129.2, 60.5, 21.3.

HRMS(ESI): calculated for $C_{14}H_{13}O_3S_2(M-H)^-$: 293.0312; found: 293.0463.

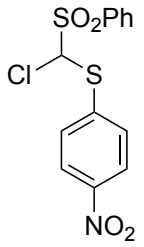
General procedure C

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$2S_{2\text{-}8}$ **SCP-1(a-f)**

Step-2: To a solution of **$2S_{3\text{-}8}$** (1 equiv.) in DCM (0.1 M) at 40 °C, 1-5 equiv. of SO_2Cl_2 in DCM was added over 1 h using a syringe pump. The mixture was heated 1 h until the completion of the reaction. The resulting mixture was cooled down to room temperature, volatiles were removed under reduced pressure, and the crude mixture was purified by silica gel chromatography.



SCP-1a

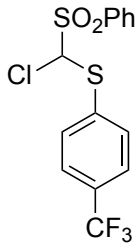
(Chloro(phenylsulfonyl)methyl)(4-nitrophenyl)sulfane (SCP-1a): Synthesized according to general procedure C using 1.62 mmol (0.5 g) of **$2S_3$** and 5.0 equiv. of SO_2Cl_2. The product was obtained as a yellow solid (365 mg, 65% yield; **TLC**: R_f 0.15 in 10% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.27 – 8.19 (m, 2H), 8.04 – 7.98 (m, 2H), 7.82 – 7.73 (m, 3H), 7.66 – 7.60 (m, 2H), 5.80 (s, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 148.4, 138.3, 135.4, 134.5, 134.2, 130.5, 129.5, 124.4, 79.4.

HRMS(ESI): calculated for $C_{13}H_{10}NaClNO_4S_2(M+Na)^+$: 365.9632; found: 365.9625.

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SCP-1b

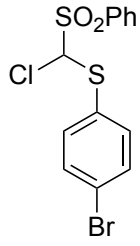
(Chloro(phenylsulfonyl)methyl)(4-(trifluoromethyl)phenyl)sulfane (SCP-1b): Synthesized according to general procedure C using 1.50 mmol (0.5 g) of **$2S_4$** and 3.0 equiv. of SO_2Cl_2. The product was obtained as a white solid (465 mg, 85% yield; **TLC**: R_f 0.20 in 10% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.74 (d, *J* = 7.8 Hz, 3H), 7.67 – 7.56 (m, 4H), 5.75 (s, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 135.2, 134.7, 134.6, 134.6, 132.0 (q, *J* = 32.8 Hz), 130.6, 129.4, 126.4 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 272.3 Hz), 80.5.

^{19}F NMR:(376 MHz, $CDCl_3$) δ -62.8 (t, *J* = 0.9 Hz)

HRMS(ESI): calculated for $C_{14}H_{10}NaClF_3O_2S_2(M+Na)^+$: 388.9655; found: 388.9655.



SCP-1c

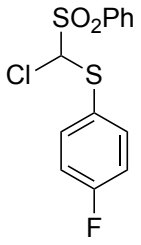
(Chloro(phenylsulfonyl)methyl)(4-bromophenyl)sulfane (SCP-1c): Synthesized according to general procedure C using 1.46 mmol (0.5 g) of **$2S_5$** and 3.0 equiv. of SO_2Cl_2. The product was obtained as a white solid (440 mg, 80% yield; **TLC**: R_f 0.20 in 10% EtOAc/Hexane).

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The dissertation author primarily performed the work reported in the Results and Discussion.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 2H), 7.78 – 7.69 (m, 1H), 7.64 – 7.57 (m, 2H), 7.56 – 7.45 (m, 4H), 5.66 (s, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) 136.8, 135.1, 134.9, 132.8, 130.5, 129.3, 128.6, 125.3, 80.9.

HRMS(ESI): calculated for $C_{13}H_{10}NaBrO_2S_2(M+Na)^+$: 398.8886; found: 398.8881.



SCP-1d

(Chloro(phenylsulfonyl)methyl)(4-fluorophenyl)sulfane (SCP-1d): Synthesized according to general procedure C using 1.77 mmol (0.5 g) of **2S$_6$** and 1.2 equiv. of SO_2Cl_2. The product was obtained as a white solid (502 mg, 90% yield; **TLC**: R_f 0.30 in 10% EtOAc/Hexane).

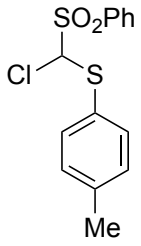
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 1.3, 0.6 Hz, 2H), 7.78 – 7.71 (m, 1H), 7.68 – 7.55 (m, 4H), 7.13 – 7.03 (m, 2H), 5.63 (s, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 164.2 (d, *J* = 252 Hz), 138.0 (d, *J* = 8.8 Hz), 135.0, 130.5, 129.3, 124.6, 124.6, 116.8 (d, *J* = 22.2 Hz), 81.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -109.3 (dd, *J* = 8.5, 5.1 Hz).

HRMS(ESI): calculated for $C_{13}H_{10}NaClFO_2S_2(M+Na)^+$: 338.9687; found: 338.9685.

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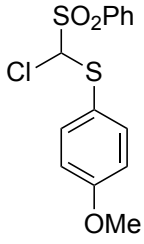
SCP-1e

(Chloro(phenylsulfonyl)methyl)(*p*-tolyl)sulfane (SCP-1e): Synthesized according to general procedure C using 7.18 mmol (2.0 g) of **2S$_7$** and 1.1 equiv. of SO_2Cl_2. The product was obtained as a white solid (2 g, 90% yield; **TLC**: R_f 0.20 in 10% EtOAc/Hexane).

^{1}H NMR: (^{1}H NMR (400 MHz, cdcl$_3$) δ 8.05 – 7.99 (m, 2H), 7.76 – 7.69 (m, 1H), 7.63 – 7.56 (m, 2H), 7.51 – 7.45 (m, 2H), 7.20 – 7.14 (m, 2H), 5.67 (s, 1H), 2.36 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 140.8, 135.3, 135.1, 134.9, 130.5, 130.4, 129.2, 126.4, 82.1, 21.5.

HRMS(ESI): calculated for $C_{14}H_{13}NaClO_2S_2(M+Na)^+$: 334.9938; found: 334.9937.



SCP-1f

(Chloro(phenylsulfonyl)methyl)(4-methoxyphenyl)sulfane (SCP-1f): Synthesized according to general procedure C using 13.5 mmol (4.0 g) of **2S$_8$** and 1.1 equiv. of SO_2Cl_2. The product was obtained as a white solid (4.25 g, 95% yield; R_f 0.15 in 10% EtOAc/Hexane).

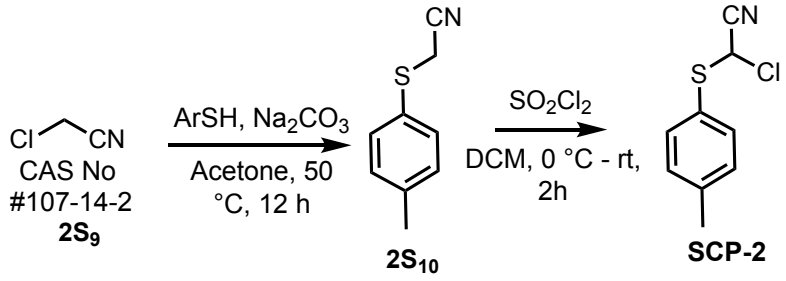
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.76 – 7.68 (m, 1H), 7.62 – 7.53 (m, 4H), 6.90 – 6.85 (m, 2H), 5.60 (s, 1H), 3.82 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 161.6, 137.7, 135.2, 134.9, 130.5, 129.2, 119.9, 115.0, 81.6, 55.6.

HRMS(ESI): calculated for $C_{14}H_{13}NaClO_3S_2(M+Na)^+$: 350.9887 found: 350.9884. **3.5.2**

2.5.2 Synthesis of SCP-2



Step-1: To a solution of **$2S_9$** (0.1 mol, 7.6 g) in acetone (1 M) at room temperature, 0.2 mol of Na_2CO_3, and 0.12 mol (15.0 g) of thiol was added. The resulting mixture was heated at 50 °C for 12 h until the completion of the reaction. The reaction mixture was cooled down to room temperature, diluted with ethyl acetate, and filtered through celite, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by silica gel chromatography. The product was obtained as a clear liquid (15.5 g, 95% yield; **TLC**: R_f 0.10 in 5% EtOAc/Hexane).

^{1}H NMR:(400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 3.51 (s, 2H), 2.37 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 139.6, 133.2, 130.4, 128.5, 116.7, 22.0, 21.3.

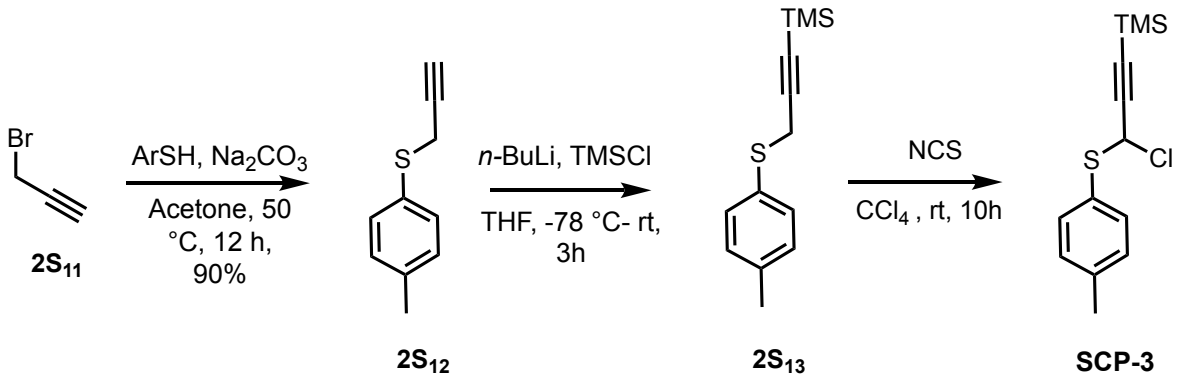
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

Step-2: To a solution of **$2S_{10}$** (0.061 mol, 10 g) in DCM (1 M) at 0 °C under N_2, 1.2 equiv. of SO_2Cl_2 in DCM was added over 2 h using a syringe pump. The reaction mixture was stirred at the same temperature for 1 h until the completion of reaction as indicated by TLC. The volatiles were removed under reduced pressure, and the crude mixture was purified by silica gel chromatography. The product was obtained as a yellowish liquid. (10.9 g, 90% yield; **TLC**: R_f 0.15 in 5% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.28 (dt, *J* = 7.8, 0.7 Hz, 2H), 5.58 (s, 1H), 2.42 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 142.0, 136.4, 130.5, 123.7, 114.1, 48.5, 21.5.

3.5.3 Synthesis of SCP-3



Step-1: To a solution of **$2S_{11}$** (8 mmol) in acetone (0.5 M) at room temperature, 16 mmol of Na_2CO_3 and 8.8 mmol of thiol was added. The resulting mixture was heated at 50 °C for 12 h until the completion of reaction. The resulting mixture was cooled down to room temperature, diluted with ethyl acetate and filtered through celite, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude mixture was purified by silica gel chromatography. The product was obtained as a

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clear liquid (1.23 g, 93% yield; **TLC**: R_f 0.30 in 5% EtOAc/Hexane). The spectral data of product **2S$_{12}$** matched with previously reported literature. [55]

Step-2: To a solution of **2S$_{12}$** (5 mmol) in THF (0.5 M) at -78 °C, 1.05 equiv. of *n*-BuLi was slowly added and stirred at this temperature for next 30 min. A solution of 7.5 mmol of TMSCl in THF was slowly added, and mixture was warmed to rt. After the completion of reaction, diluted with ethyl acetate, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude mixture was purified by silica gel chromatography. The product was obtained as a yellowish liquid. (1.15 g, 98% yield; **TLC**: R_f 0.35 in 5% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.08 (m, 2H), 3.56 (s, 2H), 2.34 (s, 3H), 0.13 (s, 9H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 137.6, 132.0, 131.3, 129.7, 101.9, 88.7, 25.0, 21.3, -0.02.

Step-3: To a solution of **2S$_{13}$** (4.2 mmol) in CCl_4 (1 M), 1.2 equiv. of NCS was added at room temperature and the resulting mixture was stirred for 10 h until the completion of the reaction. The mixture was diluted with hexanes, filtered through celite, and dried under reduced pressure (bath temperature 20 °C). The product was obtained as a yellowish oil. (1.13 g, 98% yield).

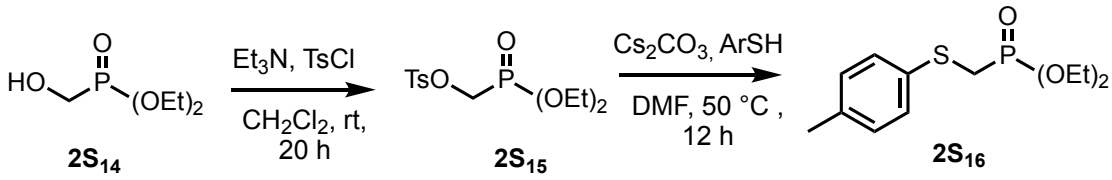
The product was obtained pure without further purification and stored at -20 °C as a molar solution in THF.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H), 7.21 – 7.18 (m, 2H), 5.73 (s, 1H), 2.38 (s, 3H), 0.16 (s, 9H).

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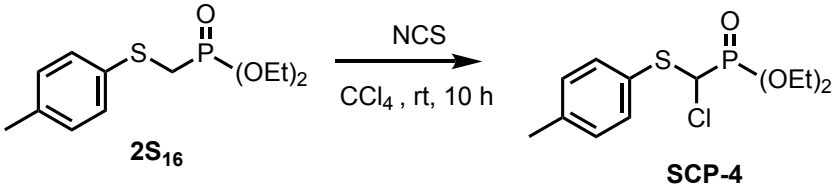
$^{13}C\{^{1}H\}$ NMR:(100 MHz, $CDCl_3$) δ 140.3, 135.5, 130.0, 127.1, 100.0, 95.5, 55.6, 21.5, -0.4.

2.5.4 Synthesis of SCP-4



Step-1: To a solution of **$2S_{14}$** (5 mmol) in CH_2Cl_2 (0.5 M) at room temperature, 2.0 equiv. of Et_3N, and 5.05 mmol of tosylchloride was added. The resulting mixture was stirred at room temperature for 12 h until the completion of the reaction. The reaction mixture was diluted with ethyl acetate, washed with aqueous $NaHCO_3$, water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the compound was used without further purification.

To a solution of **$2S_{15}$** (5 mmol) in DMF (1 M) at room temperature, 7.5 mmol of Cs_2CO_3 and 5.5 mmol of thiol was added and heated at 50 °C for next 12 h. After the completion of reaction, diluted with ethyl acetate, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude mixture was passed through short by silica pad. The product was obtained as a yellowish liquid and used without further purification.



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Step-3: To a solution of **$2S_{16}$** (5 mmol) in CCl_4 (1 M), 1.2 equiv. of NCS was added at room temperature and the resulting mixture was stirred 10 h until the completion of the reaction. The mixture was diluted with CCl_4 and filtered through celite, dried under reduced pressure. The solvent was removed under reduced pressure and crude mixture was purified by silica gel chromatography. The product was obtained as a clear liquid. (1.3 g, 95% yield; **TLC**: R_f 0.30 in 5% MeOH/CH_2Cl_2).

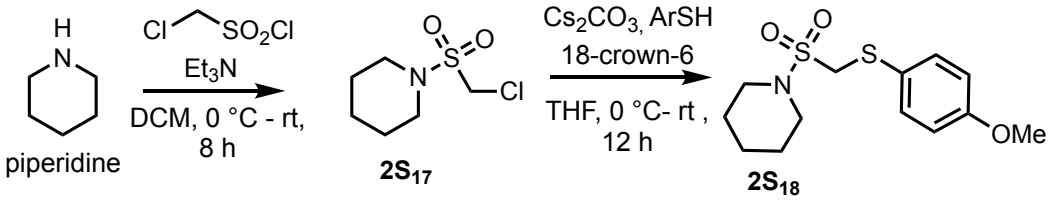
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 5.19 (d, *J* = 12.3 Hz, 1H), 4.36 – 4.23 (m, 4H), 2.37 (s, 3H), 1.39 (tdd, *J* = 7.1, 2.3, 0.7 Hz, 6H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 139.7, 133.5, 130.3, 128.6 (d, *J* = 9.9 Hz), 64.8, 64.7, 61.7 (d, *J* = 161.8 Hz), 21.38, 16.6, 16.5.

^{31}P NMR: (162 MHz, $CDCl_3$) δ 13.9.

HRMS(ESI): calculated for $C_{12}H_{18}NaClO_3PS(M+Na)^+$: 331.0300; found: 331.0294.

2.5.5 Synthesis of SCP-5



Step-1: To a solution of piperidine (6 mmol) in DCM (0.5 M) at -20 °C, 12 mmol of Et_3N was added. A solution of 9 mmol of chloro methanesulfonylchloride in 0.1 M THF was added all at once. The resulting mixture was slowly warmed to room temperature and stirred until the completion of reaction. The resulting mixture was diluted with DCM, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude mixture was purified by silica gel chromatography. The

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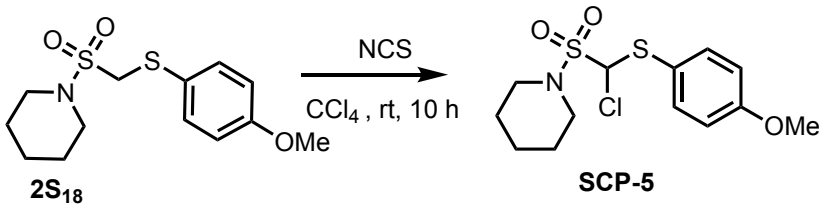
product was obtained as a yellowish solid (.81 g, 68% yield; **TLC**: R_f 0.30 in 20% EtOAc/Hexane). The spectral data of product **$2S_{17}$** matched with previously reported literature.[56]

Step-2: To a solution of **$2S_{17}$** (2.5 mmol) in THF (0.1 M) at 0 °C, 5 mmol of K_2CO_3 and 2.5 mmol of 18-crown-6 was added, followed by the addition of 1.5 equiv. of thiol. The resulting mixture was stirred at room temperature for 12 h until the completion of reaction. The resulting mixture was diluted with ethyl acetate, and filtered through celite, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude mixture was purified by silica gel chromatography. The product **$2S_{18}$** was obtained as a white solid (.6 g, 78% yield; **TLC**: R_f 0.30 in 30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 6.89 – 6.84 (m, 2H), 4.11 (s, 2H), 3.81 (s, 3H), 3.36 – 3.28 (m, 4H), 1.56 (m, 6H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 160.3, 134.9, 123.9, 114.9, 55.5, 55.4, 47.4, 26.0, 24.0.

LRMS(ESI): calculated for $C_{13}H_{20}NO_3S_2(M+H)^+$: 302.09; found: 302.30.



$2S_{18}$ **SCP-5**

Step-3: To a solution of **$2S_{18}$** (1 mmol) in CCl_4 (1 M), 1.2 equiv. of NCS was added at room temperature and the resulting mixture was stirred 10 h until the completion of the reaction. The mixture was diluted with CCl_4, filtered through celite, and dried under reduced pressure. The crude mixture was purified by silica gel chromatography. The

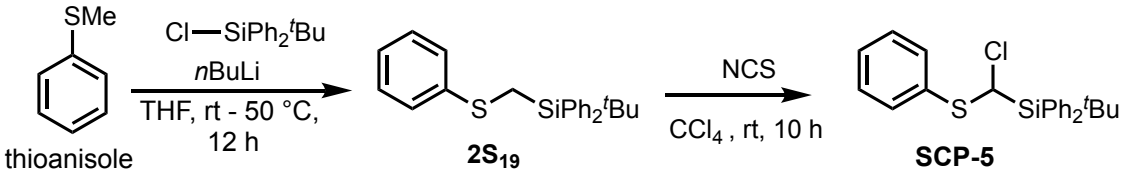
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

product was obtained as a clear liquid. (300 mg, 86% yield; **TLC**: R_f 0.30 in 15% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 2H), 6.94 – 6.88 (m, 2H), 5.65 (d, *J* = 0.5 Hz, 1H), 3.83 (s, 3H), 3.46 (t, *J* = 5.1 Hz, 4H), 1.69 – 1.61 (m, 6H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$)δ 161.5, 137.4, 120.5, 115.0, 80.3, 55.6, 48.4, 26.1, 23.9.

2.5.6 Synthesis of SCP-6



Step-1: To a solution of thioanisole (4 mmol) in THF (1 M), 1.2 equiv. of *n*-BuLi was added at room temperature and heated at 50 °C next 12 h. The mixture was cooled down to room temperature and THF (0.1 M) solution of ^{t}BuPh$_2$SiCl (1 equiv.) was added and stirred next 6 h until the completion of reaction. The resulting mixture was diluted with EtOAc, washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude mixture was purified by silica gel chromatography. The product was obtained as a clear liquid. (920 mg, 63% yield; **TLC**: R_f 0.30 in 15% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 4H), 7.46 – 7.35 (m, 6H), 7.33 – 7.27 (m, 4H), 7.11 (ddt, *J* = 7.4, 6.5, 1.6 Hz, 1H), 2.79 (s, 2H), 1.15 (s, 9H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 140.6, 136.0, 133.3, 129.8, 128.9, 127.9, 126.1, 124.9, 28.1, 18.8, 13.7.

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Step-2: To a solution of **2S$_{19}$** (1 mmol) in CCl_4 (1 M), 1.05 equiv. of NCS was added at room temperature and the resulting mixture was stirred 10 h until the completion of the reaction. The mixture was diluted with CCl_4, filtered through celite, and dried under reduced pressure. The product was used without further purification. The product was obtained as a clear liquid. (396 mg, 99% yield; **TLC**: R_f 0.60 in 5% EtOAc/Hexane).

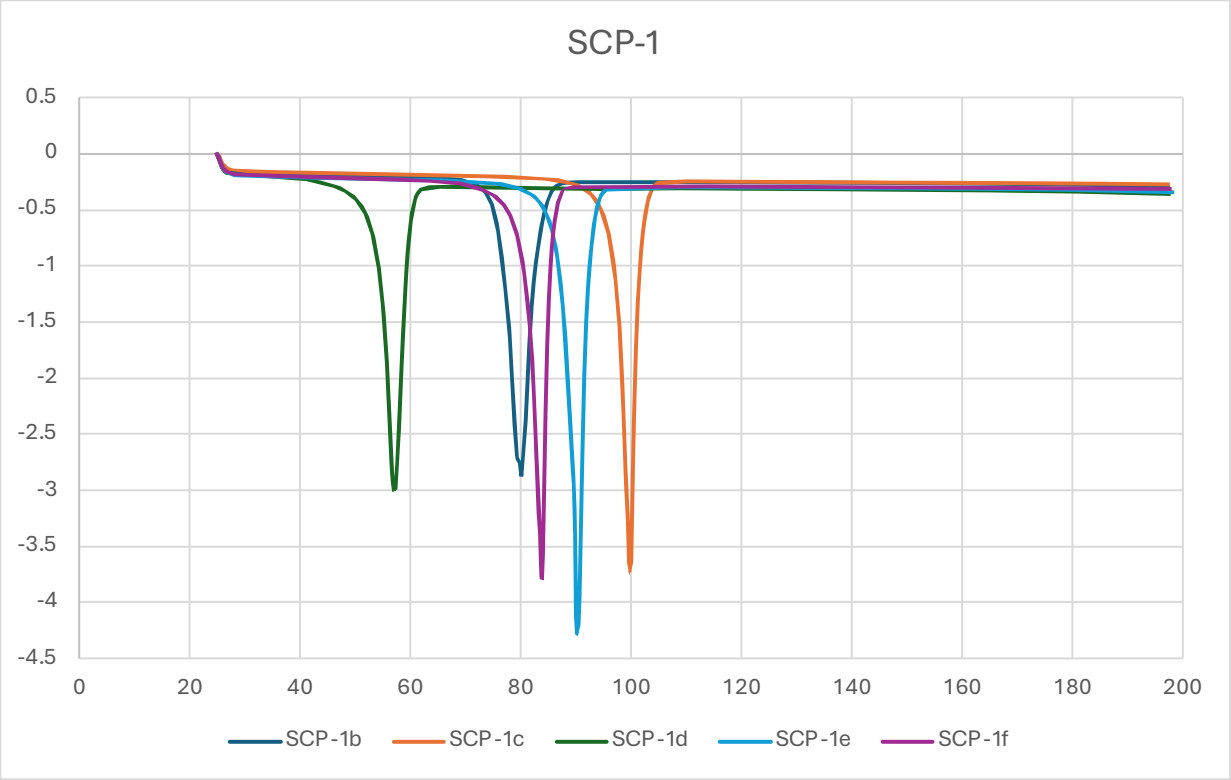
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.78 – 7.73 (m, 2H), 7.51 – 7.40 (m, 8H), 7.39 – 7.28 (m, 3H), 5.46 (s, 1H), 1.23 (s, 9H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 136.6, 136.5, 136.2, 131.6, 131.5, 130.3, 130.1, 130.0, 129.3, 127.9, 127.8, 127.7, 56.3, 28.8, 19.6.

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2.5.7 Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) of Sulfenylcarbene precursors (SCPs)

DSC analysis of SCP-1



Sulfenylcarbene precursors (SCP)	Enthalphy of melting(J/g)	Melting temperature
SCP-1b	83.564	80.18 °C
SCP-1c	78.795	100 °C
SCP-1d	75.533	57.23 °C
SCP-1e	95.588	90.32 °C
SCP-1f	79.000	83.98 °C

Figure 2.5.7.1: DSC analysis of SCP-1

As shown in **Figure S1**, **SCP-1(b-f)** was found to melt rather decomposing until high temperature. Melting temperature and and the enthalphy of melting was determined. Therefore, it can be stated that these compounds, exhibits greater stability.

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TGA analysis of SCP-1e and SCP-2

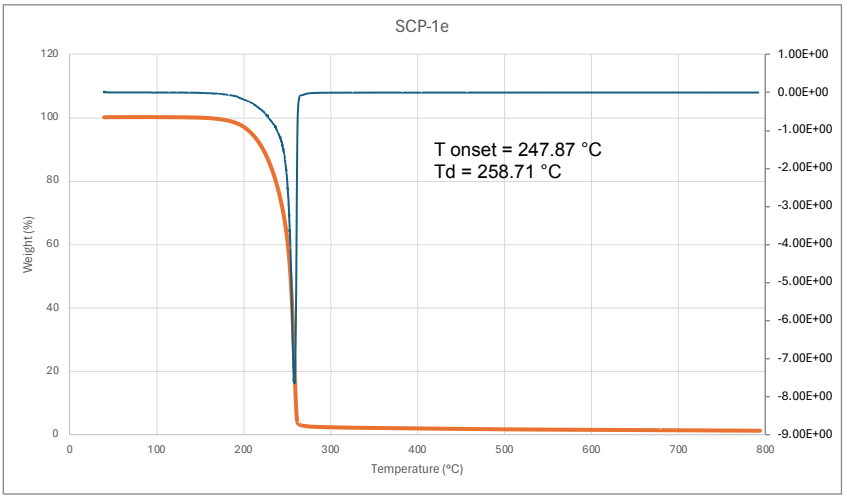


Figure 2.5.7.2: TGA analysis of SCP-1e

As shown in Figure S2, the start of decomposition temperature of compound SCP-1e is 247.87 °C, with an extrapolated onset temperature of 258.71 °C. Therefore, it can be stated that this compound exhibits greater stability.

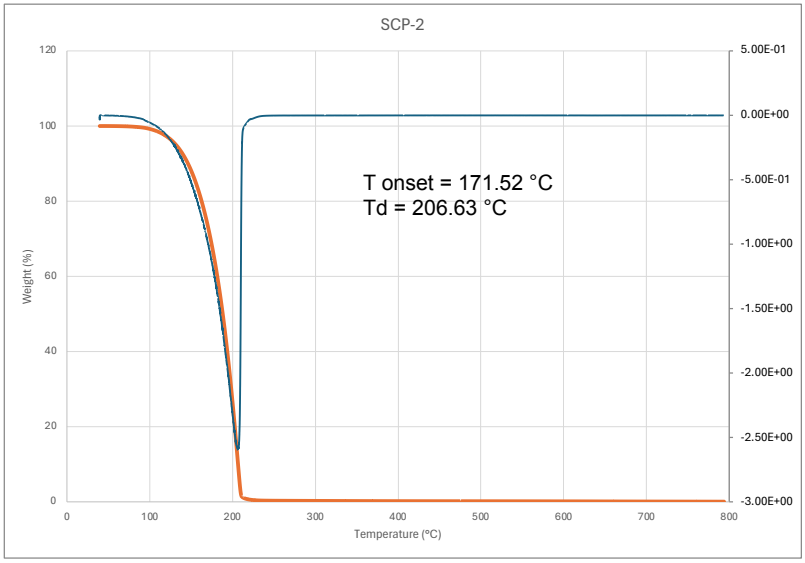
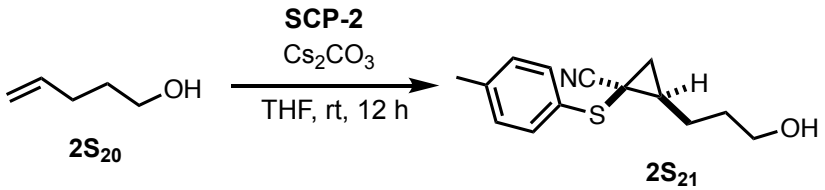


Figure 2.5.7.3: TGA analysis of SCP-2

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As shown in Figure S3, the start of decomposition temperature of compound SCP-2 is 171.52 °C, with an extrapolated onset temperature of 206.63 °C. Therefore, it can be stated that this compound exhibits greater stability.

2.5.8 Cyclopropanation of Alkenol



2S$_{20}$ **2S$_{21}$**

To a solution of alkenol **2S$_{20}$** (0.58 mmol) in THF (0.1 M), 2.5 equiv. of Cs_2CO_3 was added and stirred at room temperature for next 15 min. A solution of sulfenylcarbene precursor (1.5 equiv.) was added and stirred overnight until the completion of reaction. All the volatiles were removed under reduced pressure, and compound was purified by silica gel chromatography. The product was obtained as a clear oil. (132 mg, 92%, yield, *dr* 9:1 determined by crude ^{1}H NMR), **TLC**: R_f 0.15 in 40% EtOAc/Hexane.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 3.70 (t, *J* = 5.9 Hz, 2H), 2.36 (s, 3H), 1.85 (dd, *J* = 14.1, 7.4 Hz, 1H), 1.77 (tt, *J* = 9.5, 5.1 Hz, 2H), 1.69 (q, *J* = 8.1 Hz, 3H), 1.03 (dd, *J* = 7.4, 5.4 Hz, 1H).

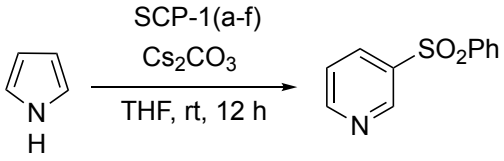
^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 138.5, 131.4, 130.3, 129.4,122.5, 62.3, 31.9, 30.6, 25.3, 24.1, 21.3, 18.6.

HRMS(ESI): calculated for $C_{14}H_{16}NOS$ $(M-H)^-$: 246.0951; found: 246.0958.

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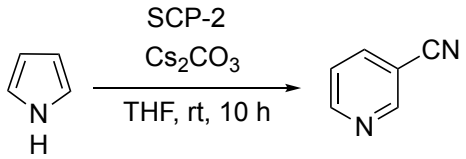
2.5.9.1 General Procedure for Carbon Atom Insertion into Pyrroles to Access Pyridines

General procedure D



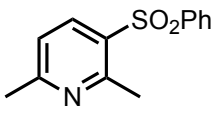
To a solution of pyrrole (1 equiv.) in 0.1 M THF, 1.5 equiv. of sulfenylcarbene precursor was added in one portion at room temperature, followed by the addition of 3.0 equiv. of Cs_2CO_3, and the resulting mixture was stirred for next 12 h. The reaction mixture was diluted with ethyl acetate, filtered through a pad of silica gel, and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography.

General procedure E



To a solution of pyrrole (1 equiv.) in 0.1 M THF, 1.5 equiv. of sulfenylcarbene precursor was added in one portion at room temperature, followed by the addition of 3.0 equiv. of Cs_2CO_3, and the resulting mixture was stirred for next 10 h. The reaction mixture was diluted with ethyl acetate, filtered through a pad of silica gel, and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography.

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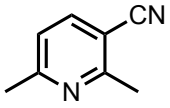
2.2aa

2,6-Dimethyl-3-(phenylsulfonyl) pyridine (2.2aa): Synthesized according to general procedure D using 0.21 mmol of corresponding pyrrole and SCP-1e. The product was obtained as a clear oil (50 mg, 96% yield; **TLC**: R_f 0.15 in 20% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.81 (m, 2H), 7.64 – 7.57 (m, 1H), 7.52 (tt, *J* = 6.6, 1.6 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 1H), 2.63 (s, 3H), 2.58 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 163.3, 157.2, 140.7, 137.8, 133.6, 133.2, 129.3, 127.9, 121.3, 24.8, 23.6.

HRMS(ESI): calculated for $C_{13}H_{14}O_2S(M+H)^+$: 248.0745; found: 248.0741.



2.2ab

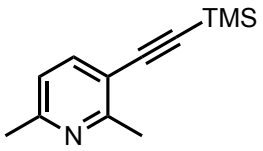
2,6-Dimethylnicotinonitrile (2.2ab): Synthesized according to general procedure D using 0.21 mmol of corresponding pyrrole. The product was obtained as a white solid (27.5 mg, 99% yield; **TLC**: R_f 0.15 in 10% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$)δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.74 (s, 3H), 2.60 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 162.5, 161.2, 140.3, 120.7, 117.4, 106.2, 25.1, 23.8.

HRMS(ESI): calculated for $C_8H_9N_2(M+H)^+$: 133.0766; found: 133.0763.

*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.



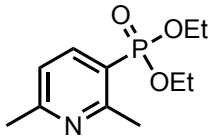
2.2ac

2,6-Dimethyl-3-((trimethylsilyl)ethynyl)pyridine (2.2ac): To a solution of pyrrole (0.21 mmol) in 0.1 M THF at 0 °C, 1.5 equiv. of sulfenylcarbene precursor was added in one portion, followed by the addition of 3.0 equiv. of Cs_2CO_3, and the resulting mixture was stirred for next 4 h. The reaction mixture was diluted with ethyl acetate, filtered through a pad of silica gel, and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography. The product was obtained as a yellowish solid (28 mg, 65% yield; **TLC**: R_f 0.15 in 5% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 2.64 (s, 3H), 2.52 (s, 3H), 0.26 (s, 9H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 160.2, 157.3, 139.8, 122.3, 120.2, 116.1, 102.4, 24.7, 23.7, 0.06.

LRMS(ESI): calculated for $C_{12}H_{18}NSi(M+H)^+$:204.1 ; found: 204.6.



2.2ad

Diethyl (2,6-dimethylpyridin-3-yl)phosphonate (2.2ad): To a solution of pyrrole (0.21 mmol) in 0.1 M THF, 1.5 equiv. of sulfenylcarbene precursor was added in one portion at room temperature, followed by the addition of 3.0 equiv. of Cs_2CO_3, and the resulting mixture was stirred for next 12 h at 60 °C. The reaction mixture was diluted with ethyl

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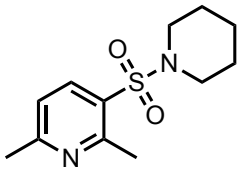
acetate, filtered through pad of silica gel, and all the volatiles were removed under reduced pressure. The product was obtained as a white solid (23 mg, 45% yield; **TLC**: R_f 0.15 in 10% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 14.1, 7.9 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 4.23 – 4.00 (m, 4H), 2.74 (s, 3H), 2.56 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 6H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 161.7, 160.9 (d, *J* = 12.4 Hz), 142.6 (d, *J* = 9.7 Hz), 120.2 (d, *J* = 11.5 Hz),119.5 (d, *J* = 189.2 Hz), 62.3 (d, *J* = 5.6 Hz), 24.8, 24.5, 16.4 (d, *J* = 6.7 Hz).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 18.90.

LRMS(ESI): calculated for $C_8H_9N_2(M+H)^+$:244.2; found: 244.5.



2.2ae

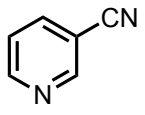
2,6-Dimethyl-3-(piperidin-1-ylsulfonyl)pyridine (2.2ae): Synthesized according to general procedure D using 0.21 mmol of corresponding pyrrole and SCP-5. The product was obtained as a yellow liquid (52.5 mg, 98% yield; **TLC**: R_f 0.15 in 30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) 8.05 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 3.18 – 3.09 (m, 4H), 2.81 (s, 3H), 2.59 (s, 3H), 1.62 (p, *J* = 5.5 Hz, 4H), 1.57 – 1.47 (m, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 162.1, 157.2, 138.7, 130.4, 120.8, 46.3, 25.5, 24.7, 23.9, 23.8.

LRMS(ESI): calculated for $C_{12}H1_9N_2O_2S(M+H)^+$:255.1; found: 255.6.

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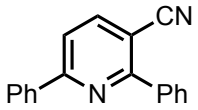


2.2b

3-Cyanopyridine (2.2b): Synthesized according to general procedure E using 0.44 mmol of pyrrole. The product was obtained as a white solid (34.5 mg, 74% yield; **TLC**: R_f 0.10 in 15% EtOAc/Hexane). Spectral data matches with the reported literature.[57]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.1 Hz, 1H), 8.85 (dd, *J* = 5.0, 1.7 Hz, 1H), 8.03 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.55 – 7.47 (m, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 152.5, 152.0, 140.0, 124.1, 116.3, 110.6.

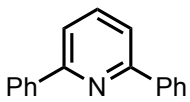


2.2c

2,6-Diphenylnicotinonitrile (2.2c): Synthesized according to general procedure E using 0.11 mmol of corresponding pyrrole. The product was obtained as a white solid (28.5 mg, 97% yield, **TLC**: R_f 0.10 in 10% EtOAc/Hexane). Spectral data matches with the reported literature.[58]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.18 – 8.14 (m, 2H), 8.12 (d, *J* = 8.3 Hz, 1H), 8.09 – 8.04 (m, 2H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.44 (m, 6H).

^{13}C NMR:(100 MHz, $CDCl_3$) δ 160.7, 159.9, 142.7, 137.6, 130.7, 130.4, 129.2, 129.1, 128.8, 127.6, 118.4, 117.9, 105.3.



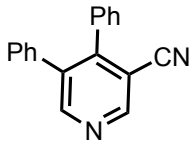
2.2ca

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2,6-Diphenylpyridine (2.2ca): To a solution of pyrrole (0.11 mmol) in 0.1 M THF, 1.5 equiv. of sulfenylcarbene precursor (**SCP-7**, *CAS #7205-91-6)* was added in one portion at 0 °C, followed by the addition of 3.0 equiv. of ^{t}BuOK, and the resulting mixture was stirred for next 12 h at 0 °C. The reaction mixture was diluted with ethyl acetate, filtered through pad of silica gel, and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography. The product was obtained as a white solid (22.5 mg, 85% yield, **TLC**: R_f 0.50 in 5% EtOAc/Hexane). Spectral data matches with the reported literature.[59]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.6 Hz, 4H), 7.86 – 7.80 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 4H), 7.43 (t, *J* = 7.2 Hz, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 156.9, 139.4, 137.8, 129.2, 128.9, 127.2, 118.9.



2.2d

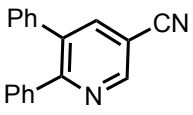
4,5-Diphenylnicotinonitrile (2.2d): Synthesized according to general procedure E using 0.13 mmol of corresponding pyrrole. The product was obtained as a white solid (34.5 mg, 98% yield; **TLC**: R_f 0.10 in 15% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.81 (s, 1H), 7.38 – 7.32 (m, 3H), 7.29 – 7.26 (m, 3H), 7.21 – 7.17 (m, 2H), 7.10 – 7.05 (m, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 153.8, 152.3, 151.1, 137.0, 135.7, 134.5, 129.8, 129.6, 129.5, 128.7, 128.6, 128.3, 116.6, 110.8.

HRMS(ESI): calculated for $C_{18}H_{13}N_2(M+H)^+$: 257.1079; found: 257.1079.

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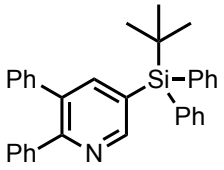
2.2e

5,6-Diphenylnicotinonitrile (2.2e): Synthesized according to general procedure E using 0.11 mmol of corresponding pyrrole. The product was obtained as a white solid (28 mg, 96% yield; **TLC**: R_f 0.10 in 10% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.36 (m, 2H), 7.33 – 7.30 (m, 3H), 7.29 – 7.25 (m, 3H), 7.18 – 7.16 (m, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 160.8, 150.7, 141.5, 138.5, 137.9, 136.5, 130.0, 129.4, 129.2, 128.9, 128.4, 128.3, 116.9, 108.2.

HRMS(ESI): calculated for $C_{18}H_{13}N_2(M+H)^+$: 257.1079; found:257.1072.



2.2ea

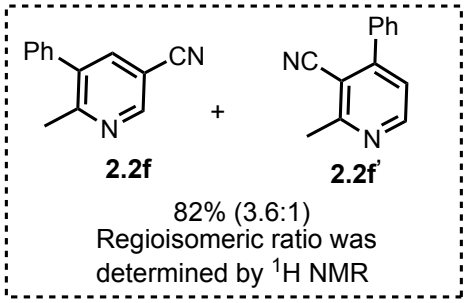
5-(*tert*-butyldiphenylsilyl)-2,3-diphenylpyridine (2.2ea): To a solution of pyrrole (0.068 mmol) in 0.1 M THF, 1.5 equiv. of sulfenylcarbene precursor (SCP-6) was added in one portion at 0 °C, followed by the addition of 5.0 equiv. of ^{t}BuOK, and the resulting mixture was stirred for next 12 h at room temperature. The reaction mixture was diluted with ethyl acetate, filtered through pad of silica gel, and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography. The product was obtained as a clear oil (20.5 mg, 64% yield, **TLC**: R_f 0.20 in 5% EtOAc/Hexane).

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^{1}H NMR: (500 MHz, $CDCl_3$ at 50 °C) δ 8.87 (d, *J* = 1.7 Hz, 1H), 7.95 – 7.88 (m, 1H), 7.64 (dt, *J* = 7.6, 1.2 Hz, 4H), 7.44 – 7.36 (m, 8H), 7.25 (dd, *J* = 6.9, 3.2 Hz, 6H), 7.16 – 7.11 (m, 2H), 1.25 (s, 9H).

^{13}C{^{1}H} NMR:(125 MHz, $CDCl_3$) δ 155.2, 146.7, 140.2, 136.6, 134.9, 133.6, 130.1, 129.7, 128.5, 128.1, 127.9, 127.4, 28.8, 19.0.

LRMS(ESI): calculated for $C_{33}H_{32}N_5(M+H)^+$: 470.2 ; found: 470.9.



6-Methyl-5-phenylnicotinonitrile (2.2f): Synthesized according to general procedure E using 0.19 mmol of corresponding pyrrole. The major product was obtained as a white solid (23 mg, **TLC**: R_f 0.15 in 10% EtOAc/Hexane). Spectral data matches with the reported literature.[60]

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.30 (dt, *J* = 7.8, 1.2 Hz, 2H), 2.58 (s, 3H).

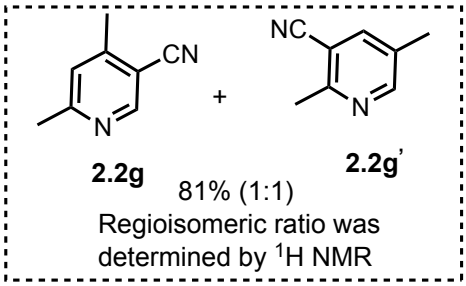
^{13}C{^{1}H} NMR:(150 MHz, $CDCl_3$) δ 161.1, 150.5, 139.9, 137.7, 137.6, 128.97, 128.91, 128.7, 116.9, 107.5, 24.1.

2-Methyl-4-phenylnicotinonitrile (2.2f'): Synthesized according to general procedure E. The minor product was obtained as a white solid (6 mg, **TLC**: R_f 0.10 in 10% EtOAc/Hexane). Spectral data matches with the reported literature.[61]

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^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.2 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.57 – 7.50 (m, 3H), 7.28 (d, *J* = 5.2 Hz, 1H), 2.88 (s, 3H).

^{13}C{^{1}H} NMR:(600 MHz, $CDCl_3$) δ 163.0, 153.6, 151.7, 136.2, 130.2, 129.2, 128.6, 121.5, 116.9, 108.1, 24.3.

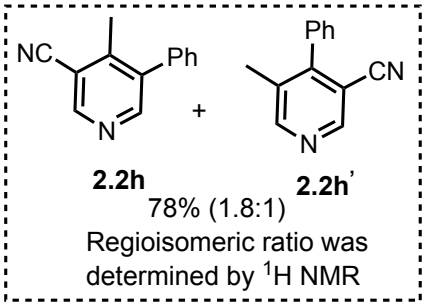


4,6-Dimethylnicotinonitrile (2.2g) and 2,5-Dimethylnicotinonitrile (2.2g') : Synthesized according to general procedure E using 0.21 mmol of corresponding pyrrole. The products were obtained as a yellowish liquid (22.5 mg, **TLC**: R_f 0.10 in 15% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.51 (s, 1H), 7.70 (s, 1H), 7.14 (s, 1H), 2.73 (s, 3H), 2.59 (s, 3H), 2.51 (d, *J* = 0.8 Hz, 3H), 2.37 – 2.35 (m, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 162.7, 158.7, 153.0, 152.3, 150.9, 140.4, 136.1, 124.7, 117.2, 116.5, 108.9, 108.1, 24.9, 23.2, 20.2, 17.9.

HRMS(ESI): calculated for $C_8H_9N_2(M+H)^+$: 133.0766; found: 133.0759.



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4-Methyl-5-phenylnicotinonitrile (2.2h): Synthesized according to general procedure E using 0.19 mmol of corresponding pyrrole. The major product was obtained as a white solid (18.5 mg, **TLC**: R_f 0.15 in 30% CH_2Cl_2/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.61 (s, 1H), 7.56 – 7.43 (m, 3H), 7.32 – 7.28 (m, 2H), 2.50 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 153.0, 151.6, 148.5, 138.3, 135.9, 129.3, 129.0, 128.8, 116.4, 111.5, 18.7.

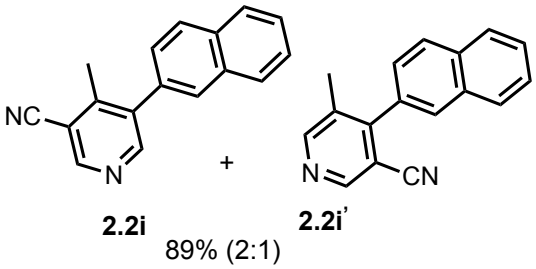
HRMS(ESI): calculated for $C_{13}H_{11}N_2(M+H)^+$: 195.0922; found:195.0916.

5-Methyl-4-phenylnicotinonitrile (2.2h'): Synthesized according to general procedure E using 0.19 mmol of corresponding pyrrole. The minor product was obtained as a white solid (10 mg, **TLC**: R_f 0.10 in 30% CH_2Cl_2/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.68 (s, 1H), 7.58 – 7.46 (m, 3H), 7.33 – 7.28 (m, 2H), 2.23 (s, 3H).

^{13}C{^{1}H} NMR:(150 MHz, $CDCl_3$) δ 154.2, 152.5, 151.0, 135.0, 132.3, 129.6, 129.1, 128.4, 116.49, 110.4, 17.4.

HRMS(ESI): calculated for $C_{13}H_{11}N_2(M+H)^+$: 195.0922; found:195.0916.



2.2i **2.2i'**

89% (2:1)

Regioisomeric ratio was determined by ^{1}H NMR

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4-Methyl-5-(naphthalen-2-yl)nicotinonitrile (2.2i): Synthesized according to general procedure E using 0.14 mmol of corresponding pyrrole . The product was obtained as a yellow solid (17 mg, **TLC**: R_f 0.15 in 20% CH_2Cl_2/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.71 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.91 (ddt, *J* = 13.3, 7.2, 3.6 Hz, 2H), 7.78 (s, 1H), 7.61 – 7.55 (m, 2H), 7.40 (dt, *J* = 8.4, 1.5 Hz, 1H), 2.54 (d, *J* = 1.0 Hz, 3H).

^{13}C{^{1}H} NMR:(150 MHz, $CDCl_3$) δ 153.2, 151.7, 148.6, 133.4, 133.3, 133.0, 128.8, 128.7, 128.3, 128.0, 127.1, 127.1, 126.7, 116.4, 18.9.

HRMS(ESI): calculated for $C_{17}H_{13}N_2(M+H)^+$: 245.1079; found: 245.1074.

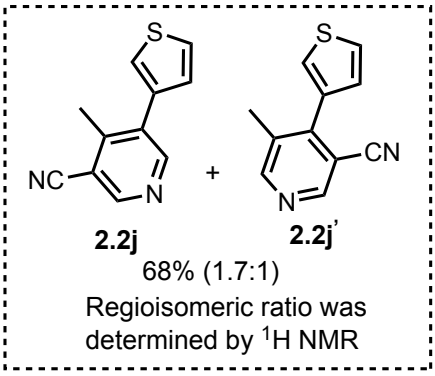
5-Methyl-4-(naphthalen-2-yl)nicotinonitrile (2.2i'): Synthesized according to general procedure E using 0.14 mmol of corresponding pyrrole. The product was obtained as a yellow solid (8.5 mg, **TLC**: R_f 0.10 in 20% CH_2Cl_2/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.72 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.96 – 7.88 (m, 2H), 7.80 (s, 1H), 7.63 – 7.55 (m, 2H), 7.38 (dd, *J* = 8.4, 1.8 Hz, 1H), 2.27 (d, *J* = 0.9 Hz, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 154.3, 152.4, 151.1, 133.5, 132.3, 129.0, 128.5, 128.3, 128.1, 127.4, 127.1, 125.5, 116.6, 110.5, 17.5.

HRMS(ESI): calculated for $C_{17}H_{13}N_2(M+H)^+$: 245.1079; found:245.1074.

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4-Methyl-5-(thiophen-3-yl)nicotinonitrile (2.2j): Synthesized according to general procedure E using 0.21 mmol of corresponding pyrrole. The products were obtained as a yellow solid (18 mg, **TLC**: R_f 0.15 in 30% CH_2Cl_2/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.67 (s, 1H), 7.49 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.34 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.14 (dd, *J* = 4.9, 1.3 Hz, 1H), 2.56 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 148.5, 136.1, 128.3, 126.9, 125.0, 116.4, 111.6, 18.9.

HRMS(ESI): calculated for $C_{11}H_9N_2S(M+H)^+$: 201.0486; found: 201.0480.

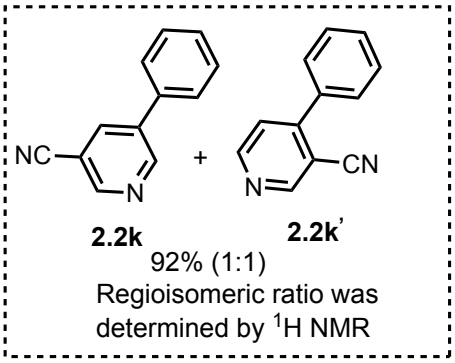
5-Methyl-4-(thiophen-3-yl)nicotinonitrile (2.2j'): Synthesized according to general procedure E using 0.21 mmol of corresponding pyrrole. The product was obtained as a yellow solid (10.5 mg, **TLC**: R_f 0.10 in 30% CH_2Cl_2/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.70 – 8.63 (m, 1H), 7.52 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.48 (dd, *J* = 3.0, 1.4 Hz, 1H), 7.17 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.31 (d, *J* = 0.8 Hz, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 154.4, 151.3, 147.4, 134.6, 132.5, 127.7, 127.0, 126.4, 116.8, 110.2, 17.7.

HRMS(ESI): calculated for $C_{11}H_9N_2S(M+H)^+$: 201.0486; found: 201.0480.

*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.



5-Phenylnicotinonitrile (2.2k): Synthesized according to general procedure E using 0.20 mmol of corresponding pyrrole. The product was obtained as a yellow solid (17.5 mg, **TLC**: R_f 0.15 in 20% CH_2Cl_2/Hexane). Spectral data matches with the reported literature.[60]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 2.3 Hz, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.13 (t, *J* = 2.1 Hz, 1H), 7.62 – 7.45 (m, 5H).

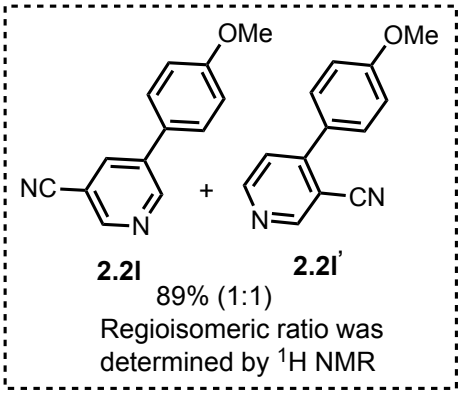
^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 151.7, 150.8, 137.4, 137.2, 135.6, 129.7, 129.4, 127.3, 116.7, 110.3.

4-Phenylnicotinonitrile (2.2k'): Synthesized according to general procedure E using 0.20 mmol of corresponding pyrrole. The product was obtained as a yellow solid. (17.5 mg, **TLC**: R_f 0.10 in 20% CH_2Cl_2/Hexane). Spectral data matches with the reported literature [60].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 0.8 Hz, 1H), 8.82 (d, *J* = 5.2 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.55 (qd, *J* = 4.0, 1.6 Hz, 3H), 7.48 (dd, *J* = 5.2, 0.8 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 154.1, 152.9, 152.6, 135.5, 130.5, 129.4, 128.5, 124.0, 116.9, 108.7.

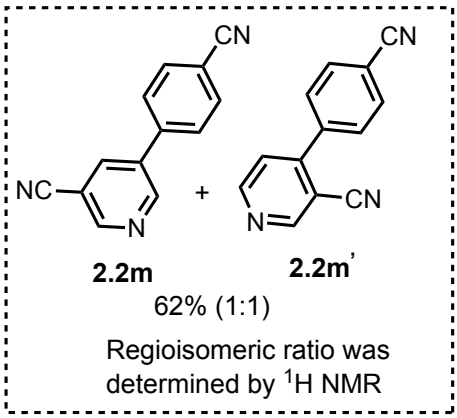
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.



5-(4-Methoxyphenyl)nicotinonitrile (2.2l) and 4-(4-Methoxyphenyl)nicotinonitrile (2.2l'): Synthesized according to general procedure E using 0.11 mmol of corresponding pyrrole. The products were obtained as a yellow solid (21.5 mg, **TLC**: R_f 0.15 in 20% CH_2Cl_2/Hexane). Spectral data matches with the reported literature.[60]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 2.3 Hz, 1H), 8.92 (d, *J* = 0.8 Hz, 1H), 8.80 (d, *J* = 2.0 Hz, 1H), 8.76 (d, *J* = 5.3 Hz, 1H), 8.08 (t, *J* = 2.1 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.55 – 7.49 (m, 2H), 7.45 (dd, *J* = 5.3, 0.8 Hz, 1H), 7.10 – 7.02 (m, 4H), 3.89 (s, 3H). 3.88 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 161.5, 160.8, 152.8, 152.1, 151.3, 150.1, 136.8, 130.0, 128.5, 127.8, 127.7, 123.5, 117.3, 116.9, 115.1, 114.8, 110.1, 108.2, 55.6, 55.6.



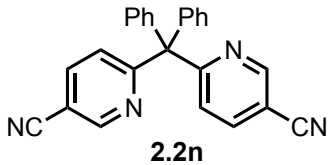
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
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5-(4-Cyanophenyl)nicotinonitrile (2.2m) and 4-(4-Cyanophenyl)nicotinonitrile (2.2m'): Synthesized according to general procedure E using 0.11 mmol of corresponding pyrrole. The products were obtained as a yellow solid (15 mg, **TLC**: R_f 0.15 in 30% CH_2Cl_2/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 2.3 Hz, 1H), 9.02 (d, *J* = 0.8 Hz, 1H), 8.94 (d, *J* = 1.9 Hz, 1H), 8.90 (d, *J* = 5.2 Hz, 1H), 8.15 (t, *J* = 2.1 Hz, 1H), 7.88 – 7.82 (m, 4H), 7.75 – 7.69 (m, 4H), 7.48 (dd, *J* = 5.2, 0.8 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 154.3, 153.5, 152.0, 151.5, 150.4, 140.0, 139.8, 137.6, 135.3, 133.4, 133.1, 129.4, 128.1, 123.7, 118.2, 118.0, 116.2, 116.1, 114.4, 113.4, 110.6, 108.6.

HRMS(ESI): calculated for $C_{13}H_6N_3(M+H)^+$: 206.0718; found:206.0710.



2.2n

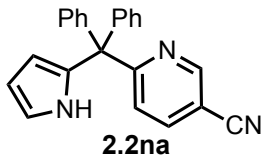
6,6'-(Diphenylmethylene)dinicotinonitrile (2.2n): Synthesized according to general procedure E using 0.067 mmol of corresponding pyrrole. The product was obtained as a yellow solid (23 mg, 92% yield; **TLC**: R_f 0.15 in 15% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 2.3, 0.9 Hz, 2H), 7.85 (dd, *J* = 8.4, 2.3 Hz, 2H), 7.47 (dd, *J* = 8.4, 0.9 Hz, 2H), 7.34 – 7.28 (m, 6H), 7.20 – 7.16 (m, 4H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 168.6, 151.2, 143.5, 139.0, 130.8, 128.4, 127.4, 126.2, 116.8, 107.5, 69.5.

HRMS(ESI): calculated for $C_{25}H_{17}N_4(M+H)^+$: 373.1453; found: 373.1451.

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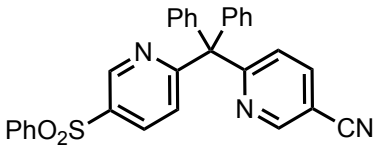
2.2na

6-(diphenyl(1*H*-pyrrol-2-yl)methyl)nicotinonitrile (2.2na): To a solution of dipyrrole (0.33 mmol) and Cs_2CO_3 (1.32 mmol) in THF (0.1 M), 0.49 mmol of sulfenylcarbene precursor in THF was added portion wise over 4 h. After the completion of reaction, the reaction mixture was diluted with ethyl acetate, passed through silica and purify by column chromatography. The product was obtained as a yellow oil (54 mg, 48% yield; **TLC**: R_f 0.12 in 30% CH_2Cl_2/Hexane).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.91 (d, *J* = 2.2 Hz, 1H), 7.87 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.28 (dd, *J* = 5.0, 1.9 Hz, 6H), 6.87 (q, *J* = 2.3 Hz, 1H), 6.80 (dd, *J* = 6.6, 3.0 Hz, 4H), 6.11 (q, *J* = 2.9 Hz, 1H), 5.66 (d, *J* = 3.5 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 170.9, 151.5, 144.9, 139.5, 134.8, 130.2, 128.2, 127.4, 124.5, 118.4, 116.7, 112.3, 107.6, 107.0, 62.0.

HRMS(ESI): calculated for $C_{23}H_{18}N_3$ $(M+H)^+$: 336.1501; found:336.1478.



2.2nb

6-(Diphenyl(5-(phenylsulfonyl)pyridin-2-yl)methyl)nicotinonitrile (2.2nb): Synthesized according to general procedure D using 0.89 mmol of **2na**. The product was obtained as a yellowish oil (38 mg, 88% yield; **TLC**: R_f 0.12, (20% EtOAc/Hexane).

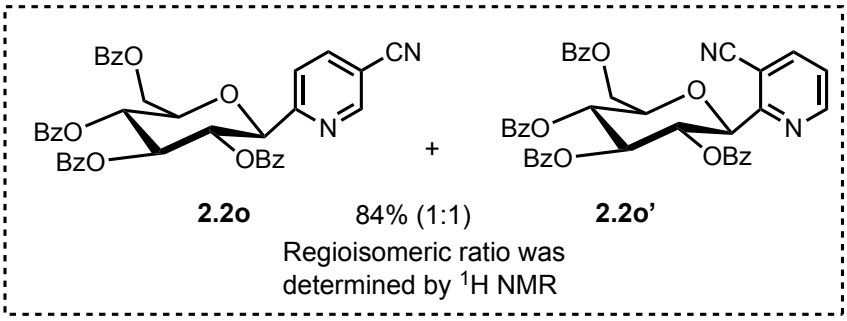
^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 2.5 Hz, 1H), 8.77 (d, *J* = 2.2 Hz, 1H), 8.07 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 2H), 7.83 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.63 (t, *J* =

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7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.45 (dd, *J* = 8.5, 2.8 Hz, 2H), 7.32 – 7.26 (m, 6H), 7.19 – 7.12 (m, 4H).

$^{13}C\{^{1}H\}$ NMR:(100 MHz, $CDCl_3$) δ 169.1, 168.7, 151.1, 147.3, 143.6, 140.7, 139.0, 135.8, 135.1, 134.0, 130.8, 129.7, 128.3, 128.1, 127.4, 126.4, 126.2, 116.9, 107.5, 69.3.

HRMS(ESI): calculated for $C_{30}H_{22}N_3O_2S$ $(M+H)^+$: 488.1354; found: 488.1416.



5-Cyano-2-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-pyridine (2.2o): Synthesized according to general procedure E using 0.031 mmol of pyrrole. The product was obtained as a yellow solid (8.5 mg; **TLC**: R_f 0.10, (30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.08 – 8.02 (m, 2H), 7.96 (ddd, *J* = 13.7, 8.3, 1.8 Hz, 3H), 7.82 (dt, *J* = 8.4, 1.4 Hz, 4H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.53 – 7.47 (m, 2H), 7.39 (dq, *J* = 22.9, 7.9 Hz, 7H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.10 (t, *J* = 9.6 Hz, 1H), 5.83 (t, *J* = 9.7 Hz, 1H), 5.64 (t, *J* = 9.7 Hz, 1H), 4.97 (d, *J* = 9.7 Hz, 1H), 4.72 (dd, *J* = 12.3, 2.9 Hz, 1H), 4.55 (dd, *J* = 12.3, 5.0 Hz, 1H), 4.38 – 4.31 (m, 1H).

$^{13}C\{^{1}H\}$ NMR:(125 MHz, $CDCl_3$) δ 166.3, 165.9, 165.4, 165.3, 160.6, 151.4, 140.4, 133.7, 133.6, 133.5, 133.4, 130.0, 129.9, 129.86, 129.85, 129.7, 128.89, 128.86, 128.8, 128.6, 128.6, 128.6, 128.5, 121.8, 116.5, 109.9, 80.4, 76.8, 73.9, 72.7, 69.6, 63.2.

LRMS(ESI): calculated for $C_{40}H_{31}N_2O_9$ $(M+H)^+$: 638.2; found: 638.8.

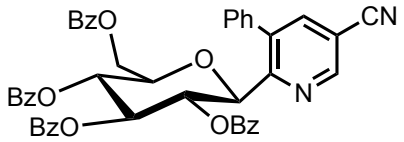
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
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3-Cyano-2-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-pyridine (2.2o'): Synthesized according to general procedure E using 0.031 mmol of pyrrole. The product was obtained as a yellow solid (9 mg; **TLC**: R_f 0.20, (30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.5 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 2H), 7.94 (t, *J* = 8.3 Hz, 3H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.79 (d, *J* = 7.7 Hz, 2H), 7.54 – 7.29 (m, 13H), 6.21 (t, *J* = 9.6 Hz, 1H), 6.10 (t, *J* = 9.5 Hz, 1H), 5.87 (t, *J* = 9.7 Hz, 1H), 5.30 (d, *J* = 9.6 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.56 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.44 (s, 1H).

^{13}C{^{1}H} NMR:(125 MHz, $CDCl_3$) δ 166.4, 166.0, 165.3, 164.7, 157.5, 152.7, 141.0, 133.6, 133.4, 133.4, 133.2, 130.1, 130.0, 129.9, 129.9, 129.7, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 128.4, 123.7, 115.8, 110.5, 79.3, 77.4, 74.6, 71.2, 69.6, 63.5.

LRMS(ESI): calculated for $C_{40}H_{31}N_2O_9$ $(M+H)^+$: 638.4; found: 638.6.



2.2p

3-Phenyl-5-cyano-2-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-pyridine (2.2p): Synthesized according to general procedure E using 0.020 mmol of pyrrole. The product was obtained as a yellow oil (15 mg; 92% yield; **TLC**: R_f 0.20, (30% EtOAc/Hexane).

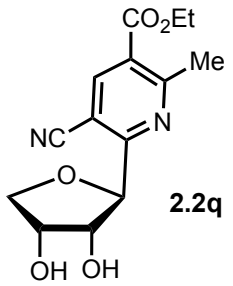
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 2H), 7.90 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 2.1 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.59 – 7.35 (m, 14H), 7.29 (d, *J* = 7.6 Hz, 3H), 6.46 (t, *J* = 9.6 Hz, 1H), 5.84 (t, *J* = 9.5 Hz,

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1H), 5.73 (t, *J* = 9.7 Hz, 1H), 4.95 (d, *J* = 9.7 Hz, 1H), 4.66 (dd, *J* = 12.3, 2.7 Hz, 1H), 4.45 (dd, *J* = 12.3, 6.6 Hz, 1H), 4.14 (t, *J* = 6.9 Hz, 1H).

$^{13}C\{^1H\}$ NMR:(125 MHz, $CDCl_3$) δ 166.3, 166.1, 165.4, 164.3, 155.0, 151.0, 141.2, 139.6, 136.0, 133.64, 133.4, 133.4, 130.0, 129.9, 129.9, 129.7, 129.4, 129.2, 129.0, 128.9, 128.6, 128.4, 116.2, 110.1, 77.4, 77.0, 74.8, 70.9, 69.9, 63.9.

LRMS(ESI): calculated for $C_{46}H_{35}N_2O_9$ $(M+H)^+$: 759.2; found: 759.1.



2.2q

Ethyl 5-cyano-6-((2*S*,3*R*,4*R*)-3,4-dihydroxytetrahydrofuran-2-yl)-2-methylnicotinate (2.2q): Synthesized according to general procedure E using 0.067 mmol of corresponding pyrrole and 5 equiv. of Cs_2CO_3. The product was obtained as a clear oil (20 mg, 58% yield; **TLC**: R_f 0.15 in 60 % EtOAc/Hexane).

^1H NMR: (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 5.07 (d, *J* = 7.4 Hz, 1H), 4.53 – 4.35 (m, 5H), 4.09 (dd, *J* = 10.1, 2.1 Hz, 1H), 2.90 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

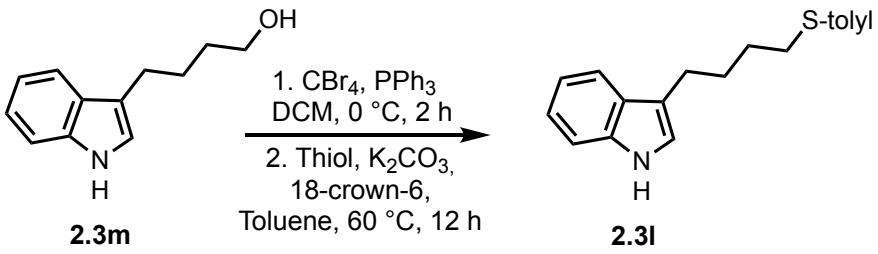
$^{13}C\{^1H\}$ NMR:(150 MHz, $CDCl_3$) δ 164.5, 164.3, 163.7, 144.2, 125.1, 115.7, 105.7, 83.0, 77.5, 74.3, 71.7, 62.2, 25.5, 14.4.

HRMS(ESI): calculated for $C_{14}H_{17}N_2O_5(M+H)^+$: 293.1137; found: 293.1130.

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2.5.9.2 Synthesis of Indoles

Synthesis of 2.3l



Step 1: To a solution of CBr_4 (4.2 mmol) and PPh_3 (4.2 mmol) in DCM (0.1 M) at ice cold condition, **2.3m** (2.1 mmol) was added and stirred at this temperature for next 2 h until the completion of reaction. All the volatiles were removed under reduced pressure and compound was purified by silica gel chromatography. The product was obtained as a yellowish liquid (510 mg, 95% yield; **TLC**: R_f 0.15 in 15% EtOAc/Hexane). Spectral data matches with the reported literature.[62]

Step 2: To a solution of bromide (1.6 mmol) in toluene (0.1 M), thiol (2 mmol), K_2CO_3 (2 mmol), and 18-crown-6 (0.2 mmol) was added and resulting mixture was heated at 60 °C next 12 h until the completion of reaction. All the volatiles were removed under reduced pressure and compound was purified by silica gel chromatography. The product was obtained as a yellowish solid (340 mg, 72% yield; **TLC**: R_f 0.20 in 15% EtOAc/Hexane).

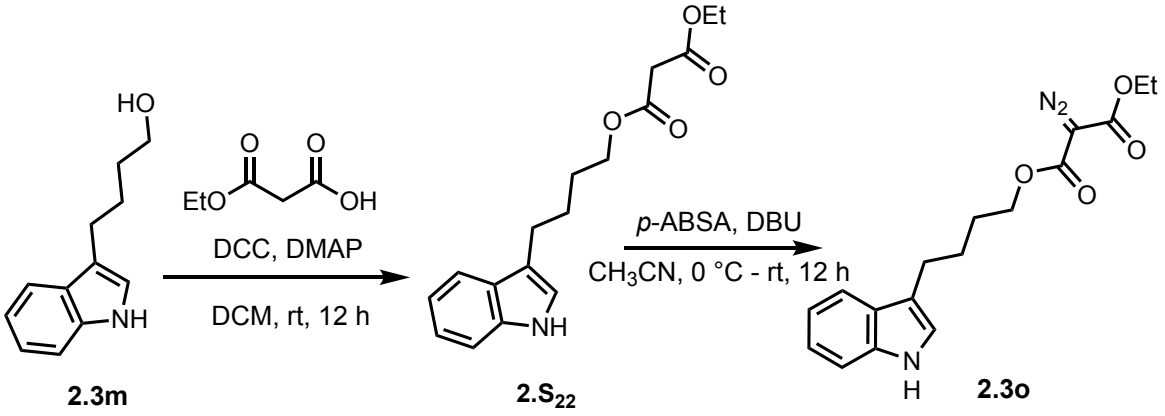
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.16 (m, 1H), 7.13 – 7.07 (m, 3H), 6.96 (dd, *J* = 2.2, 1.0 Hz, 1H), 2.92 (t, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 1.85 (p, *J* = 7.3 Hz, 2H), 1.73 (p, *J* = 7.2 Hz, 2H).

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The dissertation author primarily performed the work reported in the Results and Discussion.

$^{13}C\{^1H\}$ NMR:(100 MHz, $CDCl_3$) δ 136.5, 136.0, 133.1, 130.0, 129.8, 128.7, 122.0, 121.3, 119.3, 119.1, 116.6, 111.2, 34.4, 29.3, 29.2, 24.8, 21.2.

LRMS(ESI): calculated for $C_{12}H_{15}N(M+H)^+$:173.1; found:173.4.

Synthesis of 2.3o



Step 1: To a solution of **2.3m** (5.2 mmol) and 3-ethoxy-3-oxopropanoic acid (6 mmol) in DCM (0.1 M) , DCC (6 mmol) and DMAP (0.5 mmol) was added and stirred at this temperature for next 12 h until the completion of reaction. The reaction mixture was diluted with 30 mL DCM, filtered through celite, and all the volatiles were removed under reduced pressure. The crude compound was taken forward without further purification.

To a solution of **$2S_{22}$** (1 mmol) in CH_3CN (0.1 M), 2 mmol of DBU was added at ice cold conditions and the resulting mixture was stirred at room temperature. After the completion of the reaction, all the volatiles were removed under reduced pressure, and the crude mixture was purified by silica gel chromatography. The product was obtained as a yellowish solid (300 mg, 90% yield; **TLC**: R_f 0.20 in 20% EtOAc/Hexane).

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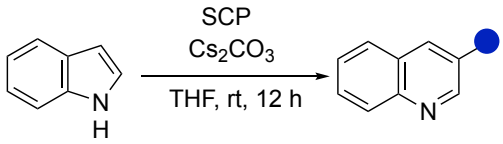
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 – 6.95 (m, 1H), 4.36 – 4.21 (m, 4H), 2.87 – 2.75 (m, 2H), 1.79 (dt, *J* = 6.4, 3.9 Hz, 4H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 161.3, 161.2, 136.5, 127.6, 122.1, 121.4, 119.3, 119.0, 116.3, 111.2, 65.6, 61.8, 28.6, 26.3, 24.8, 14.5.

LRMS(ESI): calculated for $C_{17}H_{20}3_2O_4(M+H)^+$:330.1; found:330.6.

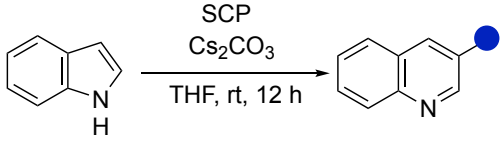
2.5.9.3 General Procedure for *C*arbon Atom Insertion into Indoles to Access Quinolines

General procedure F



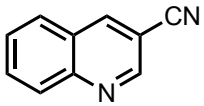
To a solution of indole (1 equiv.) in 0.1 M of THF, 2.0 equiv. of sulfenylcarbene precursor was added in one portion at room temperature, followed by the addition of 3.5 equiv. of Cs_2CO_3 and the resulting mixture was stirred for next 12 h. The reaction mixture was diluted with ethyl acetate, filtered through pad of silica gel and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography.

General procedure G



*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

To a solution of indole (1 equiv.) in 0.1 M of THF and 3.5 equiv. of Cs_2CO_3, 2.0 equiv. of sulfenylcarbene precursor was added portion wise (0.5 equiv. every 1 h) at room temperature, and the resulting mixture was stirred for next 12 h. The reaction mixture was diluted with ethyl acetate, filtered through pad of silica gel and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography.

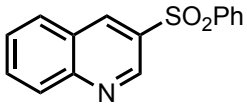


2.4a

Quinoline-3-carbonitrile (2.4a): Synthesized according to general procedure F using 0.17 mmol of corresponding indole. The product was obtained as a white solid (22.5 mg, 85% yield; **TLC**: R_f 0.15 in 20% EtOAc/Hexane). Spectral data matches with the reported literature.[63]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.1 Hz, 1H), 8.55 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.19 (dt, *J* = 9.0, 1.1 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.70 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$)δ 149.9, 148.9, 141.7, 133.0, 130.0, 128.7, 128.4, 126.4, 117.3, 106.7.



2.4ab

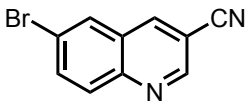
3-(Phenylsulfonyl)quinoline (2.4ab): Synthesized according to general procedure F using 0.17 mmol of corresponding indole. The product was obtained as a white solid (28.5 mg, 62% yield; **TLC**: R_f 0.10 in 20% EtOAc/Hexane).

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^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 2.3 Hz, 1H), 8.82 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.16 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.06 – 8.01 (m, 2H), 7.97 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.88 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.58 – 7.52 (m, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 149.5, 147.3, 141.1, 137.1, 134.8, 133.9, 133.0, 129.8, 129.8, 129.4, 128.6, 128.0, 126.5.

HRMS(ESI): calculated for $C_{15}H_{11}NO_2S(M+H)^+$: 270.0589; found: 270.0586.

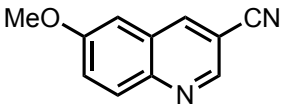


2.4b

6-Bromoquinoline-3-carbonitrile (2.4b): Synthesized according to general procedure F using 0.10 mmol of corresponding indole. The product was obtained as a white solid (18.5 mg, 78% yield; **TLC**: R_f 0.15 in 20% EtOAc/Hexane). Spectral data matches with the reported literature.[64]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.1 Hz, 1H), 8.49 – 8.40 (m, 1H), 8.07 (d, *J* = 2.7 Hz, 1H), 8.04 (s, 1H), 7.96 (dd, *J* = 9.0, 2.1 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$)δ 150.2, 147.5, 140.5, 136.4, 131.6, 130.3, 127.4, 122.9, 116.8, 107.7.



2.4c

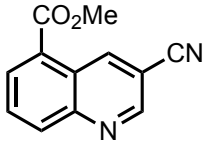
6-Methoxyquinoline-3-carbonitrile (3.4c): Synthesized according to general procedure F using 0.13 mmol of corresponding indole. The product was obtained as a white solid

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(23.5 mg, 94% yield; **TLC**: R_f 0.15 in 20% EtOAc/Hexane). Spectral data matches with the reported literature.[64]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.0 Hz, 1H), 8.44 – 8.38 (m, 1H), 8.06 (d, *J* = 9.3 Hz, 1H), 7.53 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.10 (d, *J* = 2.8 Hz, 1H), 3.97 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 159.2, 147.5, 145.2, 139.9, 131.3, 127.7, 126.0, 117.5, 106.9, 105.2, 56.0.



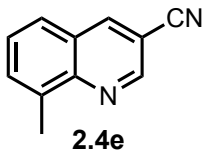
2.4d

Methyl 3-cyanoquinoline-5-carboxylate (2.4d): Synthesized according to general procedure F using 0.11 mmol of corresponding indole. The product was obtained as an off white solid (14 mg, 58% yield; **TLC**: R_f 0.10 in 20% EtOAc/Hexane).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.85 (d, *J* = 2.1 Hz, 1H), 9.09 (d, *J* = 2.1 Hz, 1H), 8.44 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H), 7.95 – 7.89 (m, 1H), 4.05 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 166.2, 150.2, 148.9, 140.6, 135.3, 132.7, 131.4, 127.0, 125.3, 117.2, 108.4, 52.9.

HRMS(ESI): calculated for $C_{12}H_9N_2O_2(M+H)^+$: 213.0664; found: 213.0659.



2.4e

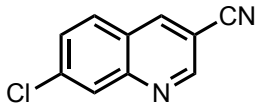
8-Methylquinoline-3-carbonitrile (2.4e): Synthesized according to general procedure F using 0.15 mmol of corresponding indole. The product was obtained as a white solid (19.5

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mg, 76% yield; **TLC**: R_f 0.20 in 20% EtOAc/Hexane). Spectral data matches with the reported literature.[64]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 2.2 Hz, 1H), 8.52 (d, *J* = 2.2 Hz, 1H), 7.80 – 7.69 (m, 2H), 7.58 (dd, *J* = 8.3, 6.9 Hz, 1H), 2.82 (d, *J* = 1.1 Hz, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 148.7, 148.0, 141.8, 138.1, 133.1, 128.4, 126.4, 126.4, 117.51, 106.4, 18.1.

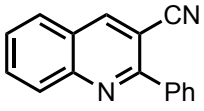


2.4f

7-Chloroquinoline-3-carbonitrile (2.4f): Synthesized according to general procedure F using 0.13 mmol of corresponding indole. The product was obtained as a white solid (17.5 mg, 79% yield; **TLC**: R_f 0.15 in 20% EtOAc/Hexane). Spectral data matches with the reported literature.[64]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.1 Hz, 1H), 8.53 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.1 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 151.0, 149.3, 141.3, 139.3, 129.9, 129.5, 129.2, 124.8, 116.9, 107.0.



2.4g

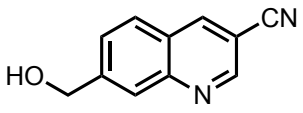
2-Phenylquinoline-3-carbonitrile (2.4g): Synthesized according to general procedure F using 0.12 mmol of corresponding indole. The product was obtained as a white solid (21.5

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mg, 72% yield; **TLC**: R_f 0.10 in 30% CH_2Cl_2/Hexane). Spectral data matches with the reported literature.[65]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.95 – 7.87 (m, 2H), 7.68 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.62 – 7.52 (m, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$)δ 158.2, 148.7, 144.5, 137.7, 133.2, 130.3, 130.0, 129.3, 128.9, 128.3, 127.9, 125.2, 118.1, 105.8.



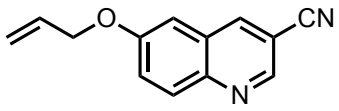
2.4h

7-(Hydroxymethyl)quinoline-3-carbonitrile (2.4h): Synthesized according to general procedure F using 0.13 mmol of corresponding indole. The product was obtained as a clear oil (19 mg, 75% yield; **TLC**: R_f 0.10 in 40% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 2.1 Hz, 1H), 8.53 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.16 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.03 – 4.92 (m, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 150.2, 149.0, 146.5, 141.4, 128.6, 127.5, 126.6, 125.7, 117.3, 106.5, 64.7.

HRMS(ESI): calculated for $C_{11}H_9N_2O(M+H)^+$: 185.07151; found: 185.0708.



2.4i

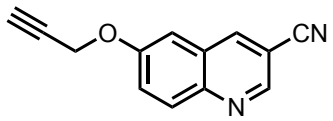
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

6-(Allyloxy)quinoline-3-carbonitrile (2.4i): Synthesized according to general procedure F using 0.15 mmol of corresponding indole. The product was obtained as a white solid (16.5 mg, 68% yield; **TLC**: R_f 0.10 in 20% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 2.1 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.56 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.11 (d, *J* = 2.7 Hz, 1H), 6.11 (ddt, *J* = 17.3, 10.6, 5.3 Hz, 1H), 5.49 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.37 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.69 (dt, *J* = 5.3, 1.6 Hz, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 158.1, 147.5, 145.2, 140.0, 132.3, 131.4, 127.6, 126.2, 118.7, 117.5, 106.9, 106.4, 69.4.

HRMS(ESI): calculated for $C_{13}H_{11}N_2O$ $(M+H)^+$: 211.0871; found: 211.0869.



2.4j

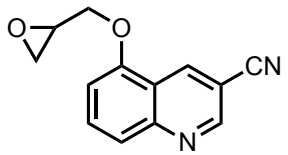
6-(Prop-2-yn-1-yloxy)quinoline-3-carbonitrile (2.4j): Synthesized according to general procedure F using 0.14 mmol of corresponding indole. The product was obtained as a white solid (25 mg, 83% yield; **TLC**: R_f 0.10 in 20% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.92 (t, *J* = 1.7 Hz, 1H), 8.45 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 7.57 (ddd, *J* = 9.3, 2.8, 1.4 Hz, 1H), 4.86 (dd, *J* = 2.4, 1.4 Hz, 2H), 2.60 (dt, *J* = 3.7, 1.7 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 157.0, 147.9, 145.4, 140.2, 131.6, 127.4, 126.0, 117.4, 107.1, 107.0, 77.6, 76.8, 56.4.

HRMS(ESI): calculated for $C_{13}H_{19}N_2O$ $(M+H)^+$: 209.0715; found:209.0702.

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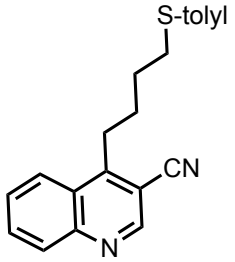
2.4k

5-(Oxiran-2-ylmethoxy)quinoline-3-carbonitrile (2.4k): Synthesized according to general procedure F using 0.10 mmol of corresponding indole. The product was obtained as a white solid (17.5 mg, 74% yield; **TLC**: R_f 0.10 in 30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.01 (dd, *J* = 15.5, 2.2 Hz, 1H), 7.82 – 7.73 (m, 1H), 7.00 (dd, *J* = 6.2, 2.5 Hz, 1H), 4.50 (dd, *J* = 11.1, 2.9 Hz, 1H), 4.14 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.50 (dq, *J* = 5.9, 2.8 Hz, 1H), 3.02 (t, *J* = 4.5 Hz, 1H), 2.84 (dd, *J* = 4.8, 2.6 Hz, 1H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 154.1, 150.5, 149.6, 137.0, 133.2, 122.4, 119.2, 117.5, 107.2, 105.8, 70.0, 50.0, 44.7.

HRMS(ESI): calculated for $C_{13}H_{11}N_2O_2$ $(M+H)^+$: 227.0821; found:228.0808.



2.4l

4-(4-(*p*-Tolylthio)butyl)quinoline-3-carbonitrile (2.4l): Synthesized according to general procedure F using 0.11 mmol of corresponding indole. The product was obtained as a yellow solid (35 mg, 91% yield; **TLC**: R_f 0.20 in 20% EtOAc/Hexane).

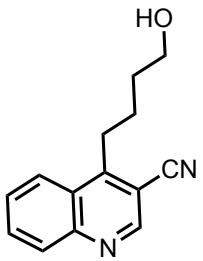
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 8.10 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.87 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.26 –

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7.20 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 3.36 – 3.30 (m, 2H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.32 (s, 3H), 1.98 – 1.87 (m, 2H), 1.80 (ddd, *J* = 13.1, 9.3, 6.4 Hz, 2H).

$^{13}C\{^1H\}$ NMR:(100 MHz, $CDCl_3$) δ 155.2, 150.0, 148.8, 136.7, 132.4, 132.1, 130.8, 130.7, 129.9, 128.4, 125.8, 124.5, 117.0, 106.9, 34.3, 31.0, 29.6, 29.0, 21.2.

LRMS(ESI): calculated for $C_{21}H_{21}N_2S$ $(M+H)^+$:333.1 found:333.9.



2.4m

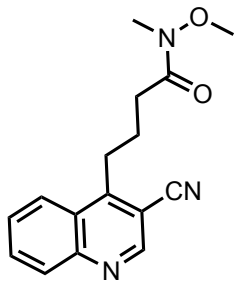
4-(4-Hydroxybutyl)quinoline-3-carbonitrile (2.4m): Synthesized according to general procedure G using 0.13 mmol of corresponding indole and 4.5 equiv of $CsCO_3$. The product was obtained as a clear oil (22 mg, 73% yield; **TLC**: R_f 0.10 in 60% EtOAc/Hexane).

^1H NMR: (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.21 – 8.09 (m, 2H), 7.86 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.70 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 3.75 (t, *J* = 6.2 Hz, 2H), 3.45 – 3.33 (m, 2H), 1.98 – 1.84 (m, 2H), 1.79 (dt, *J* = 8.3, 6.1 Hz, 2H), 1.61 (s, 1H).

$^{13}C\{^1H\}$ NMR:(100 MHz, $CDCl_3$) δ 155.4, 150.1, 148.9, 132.3, 130.8, 128.4, 125.8, 124.5, 117.1, 106.8, 62.3, 32.4, 31.1, 27.3.

HRMS(ESI): calculated for $C_{14}H_{15}N_2O$ $(M+H)^+$: 227.1184; found: 227.1169.

*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

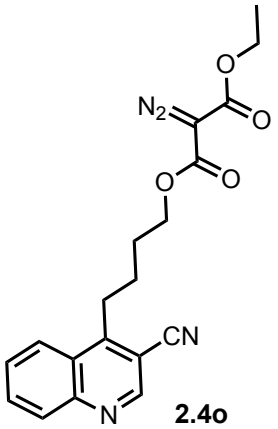


2.4n

4-(3-Cyanoquinolin-4-yl)-*N*-methoxy-*N*-methylbutanamide (2.4n): Synthesized according to general procedure F using 0.12 mmol of corresponding indole. The product was obtained as a white solid (29.5 mg, 85% yield; **TLC**: R_f 0.10 in 50% EtOAc/Hexane). **^{1}H NMR:** (400 MHz, $CDCl_3$) δ ^{1}H NMR (399 MHz, NONE) δ 8.96 (s, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.86 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.73 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 3.70 (s, 3H), 3.45 – 3.36 (m, 2H), 3.23 (s, 3H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.10 (dt, *J* = 17.1, 6.8 Hz, 2H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 173.7, 155.3, 150.0, 148.8, 132.5, 130.5, 128.6,126.0, 125.2, 117.1, 106.7, 61.4, 32.4, 31.4, 31.2, 25.3.

LRMS(ESI): calculated for $C_{16}H_{18}N_3O2$ $(M+H)^+$:284.1 found:284.7.



2.4o

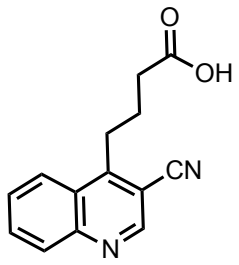
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

1-(4-(3-Cyanoquinolin-4-yl)butyl) 3-ethyl 2-diazomalonate (2.4o): Synthesized according to general procedure F using 0.075 mmol of corresponding indole. The product was obtained as a clear oil (24.5 mg, 88% yield; **TLC**: R_f 0.15 in 30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.17 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.87 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 4.38 – 4.22 (m, 4H), 3.38 (t, *J* = 7.2 Hz, 2H), 1.90 (d, *J* = 3.6 Hz, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 161.3, 161.0, 154.8, 150.1, 148.9, 132.4, 130.9, 128.5, 125.8, 124.3, 116.9, 106.9, 64.8, 61.8, 30.8, 28.8, 27.2, 14.5.

LRMS(ESI): calculated for $C_{19}H_{19}N_4O_4$ $(M+H)^+$:367.1 found:367.4.



2.4p

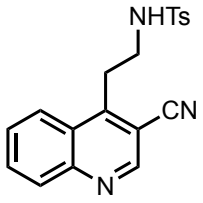
4-(3-Cyanoquinolin-4-yl)butanoic acid (2.4p): Synthesized according to general procedure G using 0.098 mmol of corresponding indole, and 5 equiv. Cs_2CO_3. After completion of the reaction, diluted with 1N HCl, extracted ethyl acetate, volatiles were removed under reduced pressure, and purified by silica gel chromatography. The product was obtained as a white solid (20 mg, 85% yield; **TLC**: R_f 0.10 in 10% MeOH/CH_2Cl_2).

^{1}H NMR: (400 MHz, CD_3OD) δ 8.98 (s, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.95 (t, *J* = 7.7 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 3.49 – 3.43 (m, 2H), 2.53 (t, *J* = 7.0 Hz, 2H), 2.06 (t, *J* = 8.0 Hz, 2H).

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The dissertation author primarily performed the work reported in the Results and Discussion.

$^{13}C\{^1H\}$ NMR:(150 MHz, CD_3OD) δ 176.6, 156.8, 151.2, 149.7, 133.8, 130.7, 129.7, 127.2, 126.2, 117.5, 108.1, 34.4, 31.6, 27.0.

HRMS(ESI): calculated for $C_{14}H_{13}N_2O_2$ $(M+H)^+$: 241.0977; found: 241.0958.



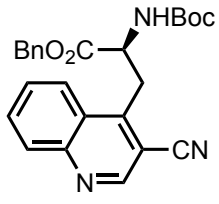
2.4q

***N*-(2-(3-Cyanoquinolin-4-yl)ethyl)-4-methylbenzenesulfonamide (2.4q):** Synthesized according to general procedure G using 0.063 mmol of corresponding indole and 4.5 equiv of $CsCO_3$. The product was obtained as a white solid (15.5 mg, 70% yield; **TLC**: R_f 0.20 in 50% EtOAc/Hexane).

^1H NMR: (600 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.17 (dd, *J* = 19.6, 8.5 Hz, 2H), 7.89 (dd, *J* = 8.5, 6.9 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.77 (t, *J* = 6.6 Hz, 1H), 3.58 (t, *J* = 7.3 Hz, 2H), 3.41 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H).

$^{13}C\{^1H\}$ NMR:(100 MHz, $CDCl_3$) δ 150.8, 149.7, 148.9, 143.9, 136.8, 132.7, 130.8, 129.9, 129.0, 127.0, 126.0, 124.5, 116.8, 107.5, 43.0, 32.3, 21.7.

HRMS(ESI): calculated for $C_{19}H_{18}N_3O_2S(M+H)^+$: 352.1114; found:352.1103.



2.4r

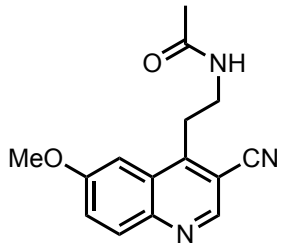
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
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Benzyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-cyanoquinolin-4-yl)propanoate (2.4r): Synthesized according to general procedure F using 0.063 mmol of corresponding indole. The product was obtained as a white solid (20.5 mg, 75% yield; **TLC**: R_f 0.15 in 50% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) 8.83 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.87 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.42 – 7.32 (m, 3H), 7.26 (s, 3H), 5.36 (d, *J* = 8.1 Hz, 1H), 5.18 (s, 2H), 4.78 (q, *J* = 7.6 Hz, 1H), 3.77 (qd, *J* = 13.7, 7.2 Hz, 2H), 1.34 (s, 9H).

^{13}C{^{1}H} NMR:(150 MHz, $CDCl_3$) δ 170.5, 155.1, 149.7, 149.5, 148.9, 134.7, 132.5, 130.8, 128.9, 128.9, 128.6, 126.2, 124.6, 117.0, 108.2, 80.6, 77.0, 68.2, 54.1, 35.2, 28.3.

HRMS(ESI): calculated for $C_{25}H_{26}N_3O_4(M+H)^+$: 432.1923; found: 432.1906.



2.4s

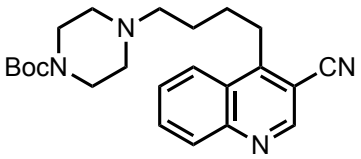
***N*-(2-(3-cyano-6-methoxyquinolin-4-yl)ethyl)acetamide (2.4s):** Synthesized according to general procedure F using 0.086 mmol of corresponding indole. The product was obtained as a white solid (19 mg, 82% yield; **TLC**: R_f 0.15, (50% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.79 (d, *J* = 2.7 Hz, 1H), 7.51 (dd, *J* = 9.2, 2.7 Hz, 1H), 5.90 (s, 1H), 4.08 (s, 3H), 3.59 – 3.54 (m, 4H), 2.03 (s, 3H).

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$^{13}C\{^{1}H\}$ NMR:(100 MHz, $CDCl_3$) δ 171.1, 159.6, 149.5, 147.3, 145.1, 131.8, 127.6, 125.7, 117.24, 107.1, 102.4, 56.3, 39.8, 31.7, 23.4.

LRMS(ESI): calculated for $C_{15}H_{16}N_3O_2(M+H)^+$: 270.1243; found:270.1227.



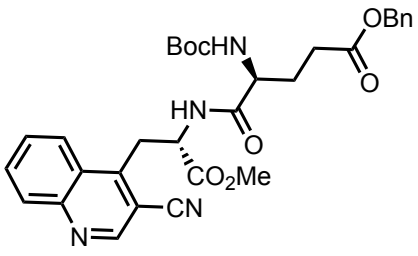
2.4t

***tert*-Butyl 4-(4-(3-cyanoquinolin-4-yl)butyl)piperazine-1-carboxylatepropanoate (2.4t):** Synthesized according to general procedure F using 0.050 mmol of corresponding indole. The product was obtained as a white solid (16 mg, 82% yield; **TLC**: R_f 0.15 in 50% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.19 – 8.14 (m, 2H), 7.86 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.72 – 7.66 (m, 1H), 3.43 (s, 4H), 3.38 – 3.34 (m, 2H), 2.40 (d, *J* = 27.3 Hz, 6H), 1.83 (p, *J* = 7.5 Hz, 2H), 1.71 (s, 2H), 1.46 (s, 9H).

$^{13}C\{^{1}H\}$ NMR:(100 MHz, $CDCl_3$) δ 155.3, 154.9, 150.2, 149.0, 132.3, 130.9, 128.3, 125.9, 124.5, 117.1, 106.9, 57.8, 53.1, 43.8, 31.2, 28.6, 28.6, 26.7.

HRMS(ESI): calculated for $C_{23}H_{31}N_4O_2(M+H)^+$: 395.2447; found: 395.2433.



2.4u

***tert*-Butyl 4-(4-(3-cyanoquinolin-4-yl)butyl)piperazine-1-carboxylatepropanoate (2.4u):** Synthesized according to general procedure G using 0.037 mmol of

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corresponding indole and 5 equiv of $CsCO_3$. The product was obtained as a clear oil (18 mg, 85% yield; **TLC**: R_f 0.15 in 50% EtOAc/Hexane).

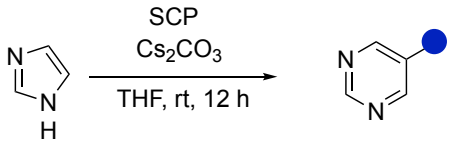
^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.89 (t, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 5.3 Hz, 6H), 7.16 (d, *J* = 23.5 Hz, 1H), 5.14 (s, 3H), 4.95 (q, *J* = 7.5 Hz, 1H), 4.19 (s, 1H), 3.85 (dd, *J* = 13.7, 6.9 Hz, 1H), 3.73 (s, 3H), 3.72 – 3.68 (m, 1H), 2.48 (dt, *J* = 15.3, 7.3 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.11 (dt, *J* = 13.2, 6.7 Hz, 1H), 1.86 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.44 (s, 9H).

^{13}C{^{1}H} NMR:(151 MHz, $CDCl_3$) δ 173.1, 171.9, 170.3, 149.5, 149.3, 148.8, 135.8, 132.7, 130.7, 129.2, 128.8, 128.5, 128.5, 126.1, 124.6, 116.9, 108.1, 66.8, 53.9, 53.3, 52.9, 34.5, 30.6, 28.4, 27.3.

HRMS(ESI): calculated for $C_{31}H_{35}N_4O_7(M+H)^+$: 575.2506; found: 575.2479.

2.5.9.4 General Procedure for *C*arbon-atom Insertion into Imidazoles to Access Pyrimidines

<u>General procedure H</u>

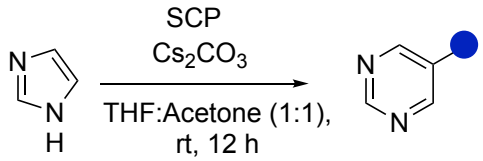


To a solution of imidazole (0.05 mmol) in 0.5 mL of THF, 0.10 mmol (2.0 equiv.) of sulfenylcarbene precursor was added in one portion at room temperature, followed by the addition of 0.17 mmol (3.5 equiv.) of Cs_2CO_3 and the resulting mixture was stirred for next 12 h. The reaction mixture was diluted with ethyl acetate, filtered through pad of silica gel

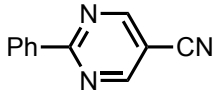
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography.

General procedure I



To a solution of imidazole (0.05 mmol) in 0.5 mL of THF:Acetone (1:1), 0.10 mmol (2.0 equiv.) of sulfenylcarbene precursor was added in one portion at room temperature, followed by the addition of 0.17 mmol (3.5 equiv.) of Cs_2CO_3 and the resulting mixture was stirred for next 12 h. The reaction mixture was diluted with ethyl acetate, filtered through pad of silica gel and all the volatiles were removed under reduced pressure. The product was purified by silica gel column chromatography.



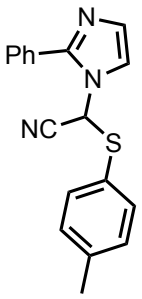
2.6a

2-Phenylpyrimidine-5-carbonitrile (2.6a): Synthesized according to general procedure H using 0.13 mmol of corresponding imidazole. The product was obtained as a white solid (20 mg, 80% yield; **TLC**: R_f 0.15 in 15% EtOAc/Hexane). Spectral data matches with the reported literature.[66]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.03 (s, 2H), 8.55 – 8.46 (m, 2H), 7.62 – 7.46 (m, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 166.4, 159.9, 135.8, 132.8, 129.4, 129.1, 115.2, 107.0.

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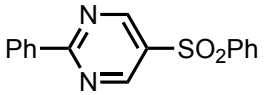
2.7a

2-(2-Phenyl-1*H*-imidazol-1-yl)-2-(*p*-tolylthio)acetonitrile (2.7a): Synthesized according to general procedure H using 0.13 mmol of corresponding imidazole. The product was obtained as a white solid (15% yield; **TLC**: R_f 0.15 in 30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 3H), 7.41 – 7.35 (m, 2H), 7.29 – 7.25 (m, 2H), 7.18 – 7.14 (m, 3H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.06 (s, 1H), 2.39 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 147.9, 142.2, 136.6, 130.7, 130.1, 129.8, 129.2, 129.1, 128.6, 123.6, 119.1, 114.0, 51.1, 21.6.

HRMS(ESI): calculated for $C_{18}H_{17}N_3S(M+H)^+$: 307.1143; found:307.1086.



2.6ab

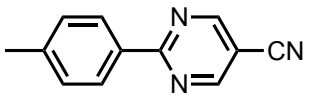
2-Phenyl-5-(phenylsulfonyl)pyrimidine (2.6ab): Synthesized according to general procedure H using 0.10 mmol of corresponding imidazole. The product was obtained as a white solid (19 mg, 62% yield; **TLC**: R_f 0.15 in 25% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.22 (s, 2H), 8.48 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 7.7 Hz, 2H), 7.56 (ddt, *J* = 32.3, 14.7, 7.3 Hz, 6H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 167.5, 156.6, 135.9, 134.3, 132.6, 130.0, 129.4, 129.0, 128.0.

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The dissertation author primarily performed the work reported in the Results and Discussion.

HRMS(ESI): calculated for $C_{16}H_{13}N_2O_2S$ $(M+H)^+$: 297.0698; found:297.0682.



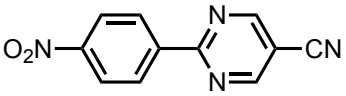
2.6b

2-(*p*-Tolyl)pyrimidine-5-carbonitrile (2.6b): Synthesized according to general procedure H using 0.12 mmol of corresponding imidazole. The product was obtained as a white solid (18 mg, 75% yield; **TLC**: R_f 0.15 in 10% EtOAc/Hexane).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.00 (d, *J* = 1.5 Hz, 2H), 8.42 – 8.35 (m, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 166.5, 159.9, 143.6, 133.2, 129.9, 129.4, 115.3, 106.6, 21.8.

HRMS(ESI): calculated for $C_{12}H_{10}N_3$ $(M+H)^+$: 196.0875; found:196.0862.



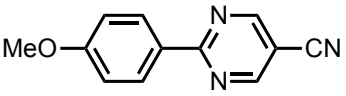
2.6c

2-(4-Nitrophenyl)pyrimidine-5-carbonitrile (2.6c): Synthesized according to general procedure H using 0.10 mmol of corresponding imidazole. The product was obtained as a white solid (11 mg, 46% yield; **TLC**: R_f 0.10 in10% EtOAc/Hexane).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.12 (s, 2H), 8.74 – 8.67 (m, 2H), 8.41 – 8.33 (m, 2H).

^{13}C{^{1}H} NMR:(150 MHz, $CDCl_3$)δ 164.3, 160.1, 150.5, 141.3, 130.3, 124.1, 114.5, 108.4.

HRMS(ESI): calculated for $C_{11}H_7N_4O_2$ $(M+H)^+$: 227.0564; found: 227.0460.



2.6d

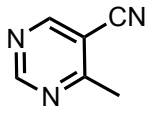
*Work discussed in this chapter was published in J. Am. Chem. Soc., **2025**, 147,102.13824-13832.*
The dissertation author primarily performed the work reported in the Results and Discussion.

2-(4-Methoxyphenyl)pyrimidine-5-carbonitrile (2.6d): Synthesized according to general procedure H using 0.11 mmol of corresponding imidazole. The product was obtained as a white solid (19 mg, 78% yield; **TLC**: R_f 0.10 in 20% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.96 (s, 2H), 8.46 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.1 Hz, 2H), 3.90 (s, 3H).

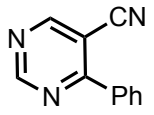
^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 166.1, 163.6, 159.8, 136.6, 131.3, 128.5, 115.5, 114.4, 105.9, 55.7.

HRMS(ESI): calculated for $C_{12}H_{10}N_3O$ $(M+H)^+$: 212.0824; found: 212.0810.



2.6e

4-Methylpyrimidine-5-carbonitrile (2.6d): Synthesized according to general procedure I using 0.18 mmol of corresponding imidazole. The product was obtained as a white solid (42% yield; **TLC**: R_f 0.30 in 10% EtOAc/Hexane). The spectra data matches with reported literature.[67]



2.6f

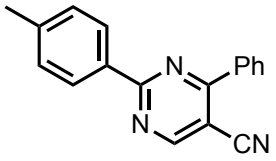
4-Phenylpyrimidine-5-carbonitrile (2.6e): Synthesized according to general procedure H using 0.13 mmol of corresponding imidazole. The product was obtained as a white solid (10 mg, 40% yield; **TLC**: R_f 0.15 in 10% EtOAc/Hexane).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 9.06 (s, 1H), 8.15 – 8.09 (m, 2H), 7.66 – 7.55 (m, 3H).

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The dissertation author primarily performed the work reported in the Results and Discussion.

$^{13}C\{^{1}H\}$ NMR:(100 MHz, $CDCl_3$) δ 167.1, 162.0, 160.3, 134.8, 132.5, 129.3, 129.2, 115.9, 106.5.

HRMS(ESI): calculated for $C_{11}H_8N_3(M+H)^+$: 182.0718; found: 182.0707.



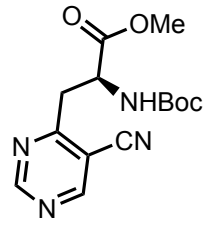
2.6g

4-Phenyl-2-(*p*-tolyl)pyrimidine-5-carbonitrile (2.6g): Synthesized according to general procedure H using 0.085 mmol of corresponding imidazole. The product was obtained as a white solid (19 mg, 82% yield; **TLC**: R_f 0.20, (10% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.52 – 8.45 (m, 2H), 8.25 – 8.18 (m, 2H), 7.65 – 7.57 (m, 3H), 7.37 – 7.31 (m, 2H), 2.46 (s, 3H).

$^{13}C\{^{1}H\}$ NMR:(125 MHz, $CDCl_3$) δ 166.9, 166.0, 162.3, 143.3, 135.6, 133.5, 132.1, 129.8, 129.4, 129.2, 129.1, 116.9, 103.0, 21.8.

HRMS(ESI): calculated for $C_{18}H_{14}N_3(M+H)^+$: 272.1188; found: 272.1187.



2.6h

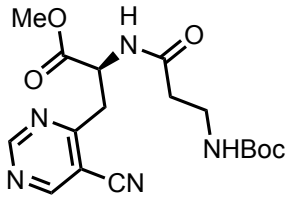
Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(5-cyanopyrimidin-4-yl)propanoate (2.6h): Synthesized according to general procedure H using 0.11 mmol of corresponding imidazole. The product was obtained as a white solid (15 mg, 44% yield; **TLC**: R_f 0.15 in 60% EtOAc/Hexane).

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^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.91 (s, 1H), 5.54 (s, 1H), 4.89 (s, 1H), 3.76 (s, 3H), 3.56 (d, *J* = 5.4 Hz, 2H), 1.42 (s, 9H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 171.4, 169.5, 160.0, 159.8, 155.3, 114.0, 110.2, 80.6, 53.0, 51.6, 38.6, 28.4.

HRMS(ESI): calculated for $C_{14}H_{18}NaN_4O_4$ $(M+Na)^+$: 329.1220; found: 329.1216.



2.6i

Methyl (*S*)-2-(3-((*tert*-butoxycarbonyl)amino)propanamido)-3-(5-cyanopyrimidin-4-yl)propanoate (2.6i): Synthesized according to general procedure H using 0.058 mmol of corresponding imidazole. The product was obtained as a white solid (9.5 mg, 42% yield; **TLC**: R_f 0.15 in 15% MeOH/CH_2Cl_2).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.93 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.25 – 5.00 (m, 2H), 3.76 (s, 3H), 3.66 – 3.53 (m, 2H), 3.40 (q, *J* = 6.1 Hz, 2H), 2.44 (q, *J* = 5.7 Hz, 2H), 1.43 (s, 9H).

^{13}C{^{1}H} NMR:(100 MHz, $CDCl_3$) δ 171.5, 171.0, 169.2, 160.2, 159.8, 156.2, 113.9, 110.1, 76.8, 53.2, 50.1, 37.8, 36.3, 29.9, 28.5.

HRMS(ESI): calculated for $C_{17}H_{24}KN_5O_5$ $(M+K)^+$: 416.1337; found: 416.1350.

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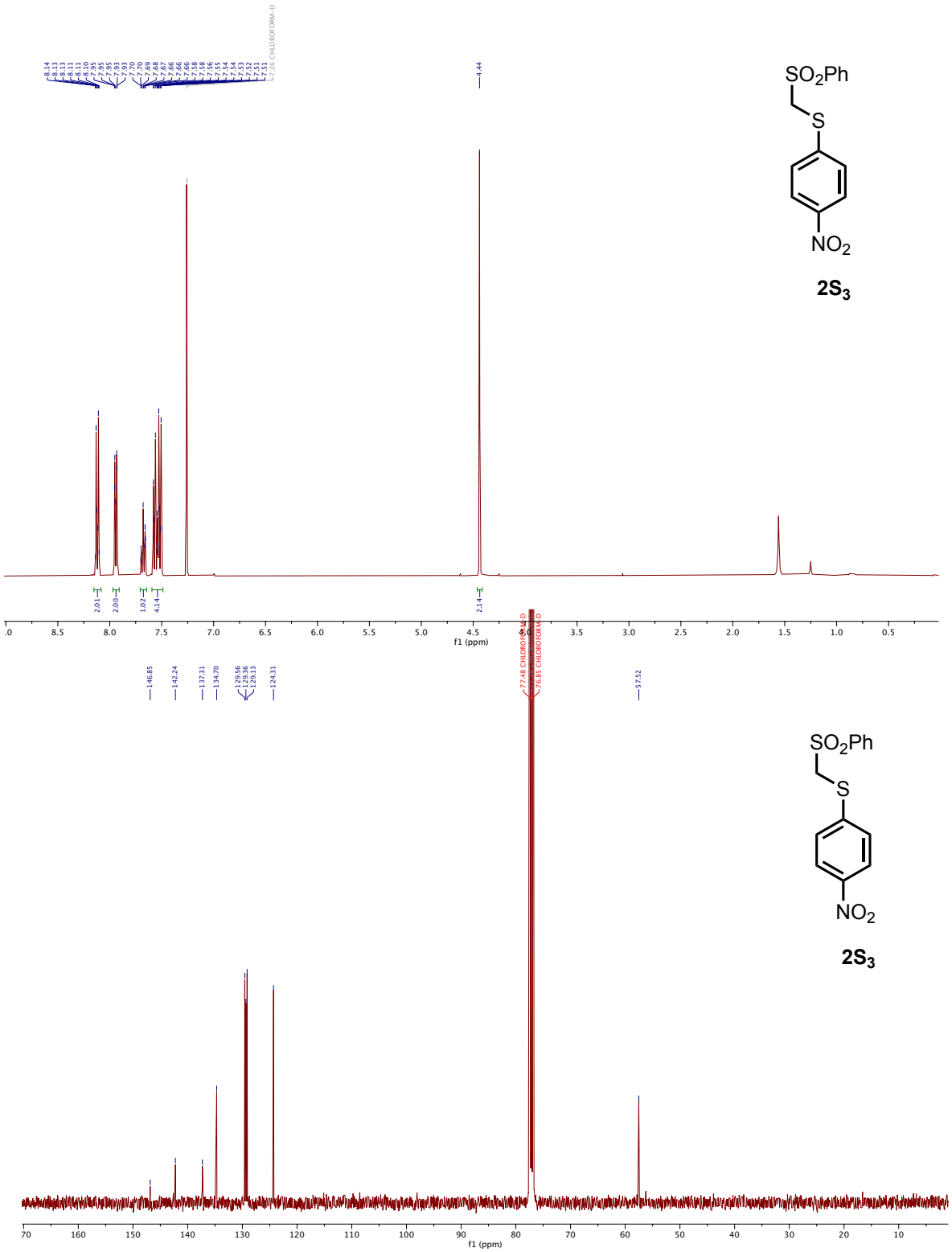
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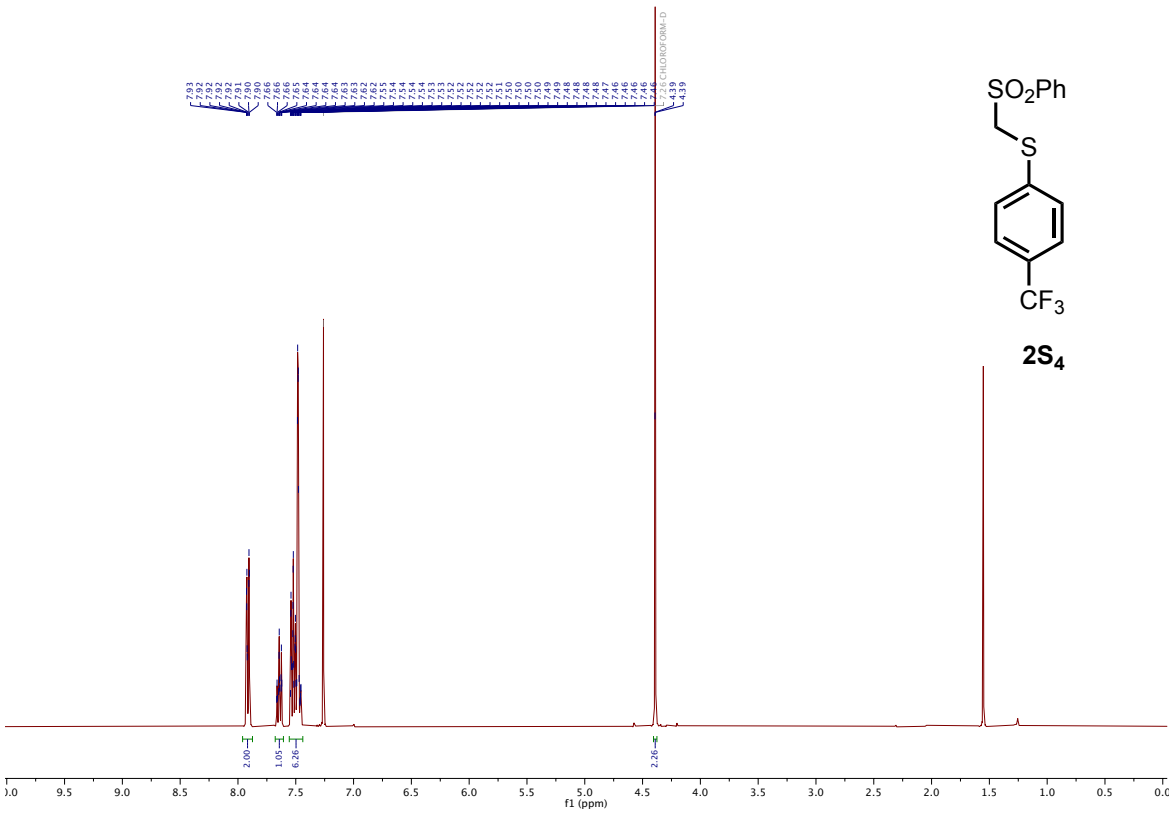
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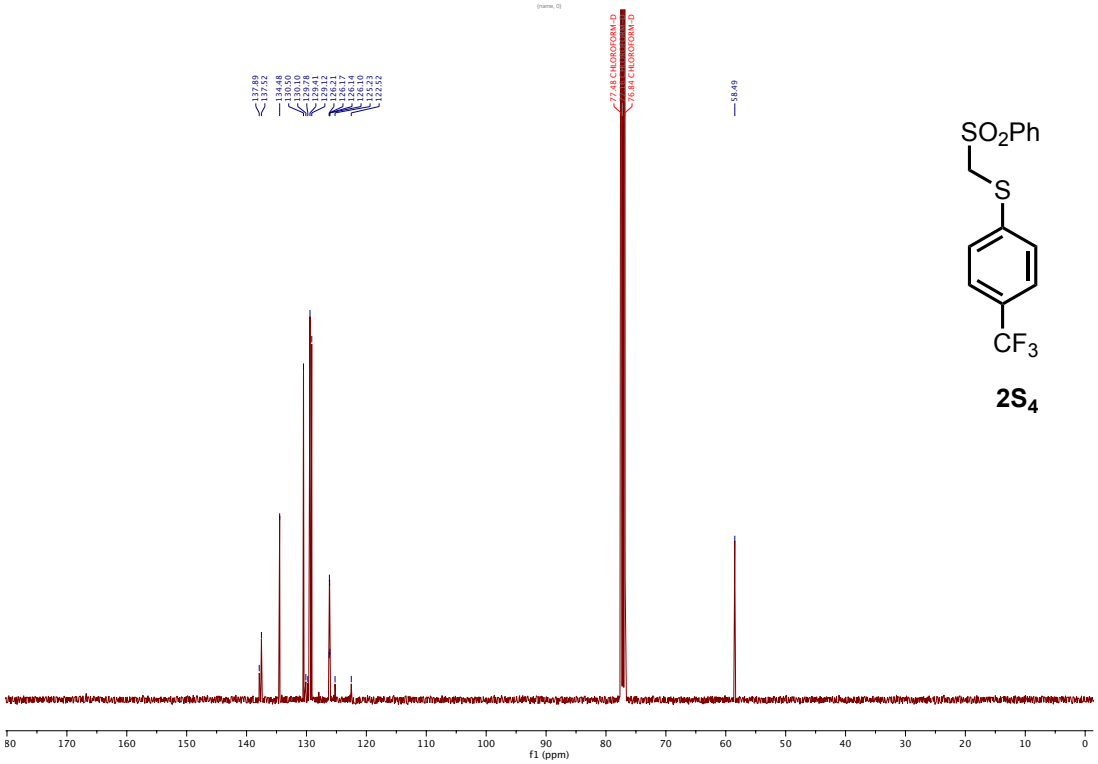
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2.7 NMR spectra

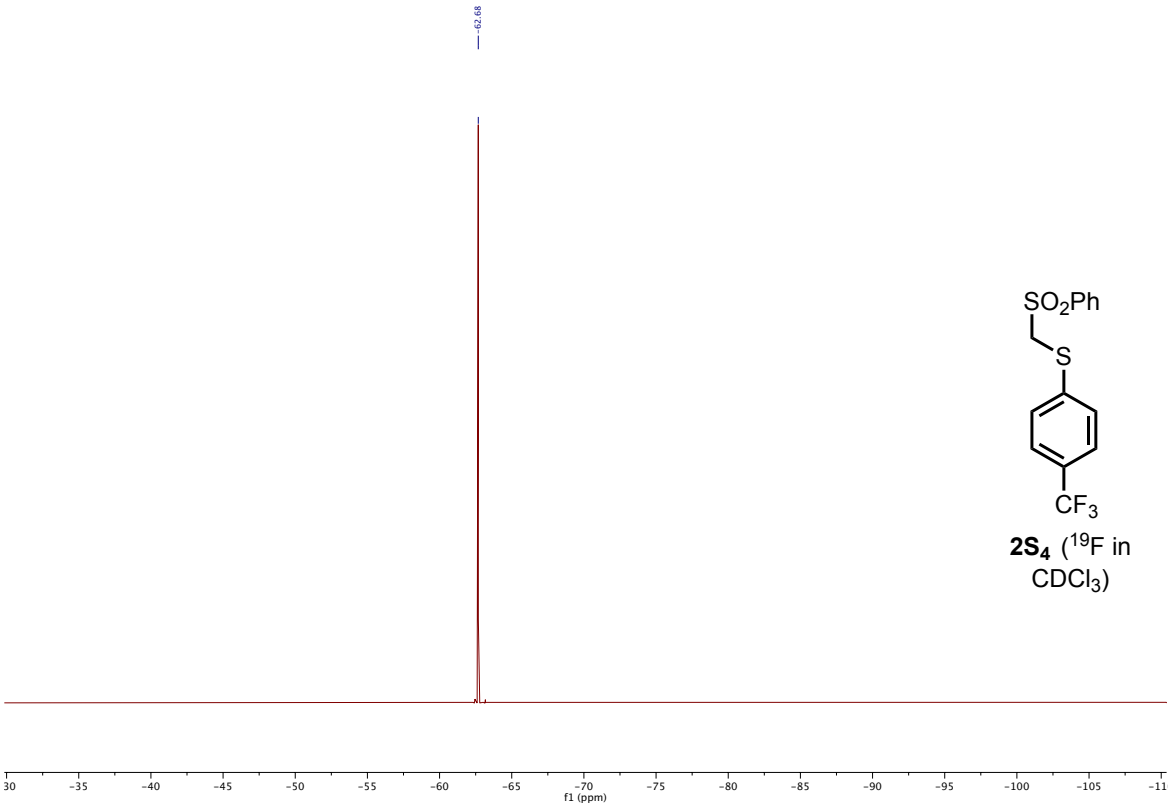


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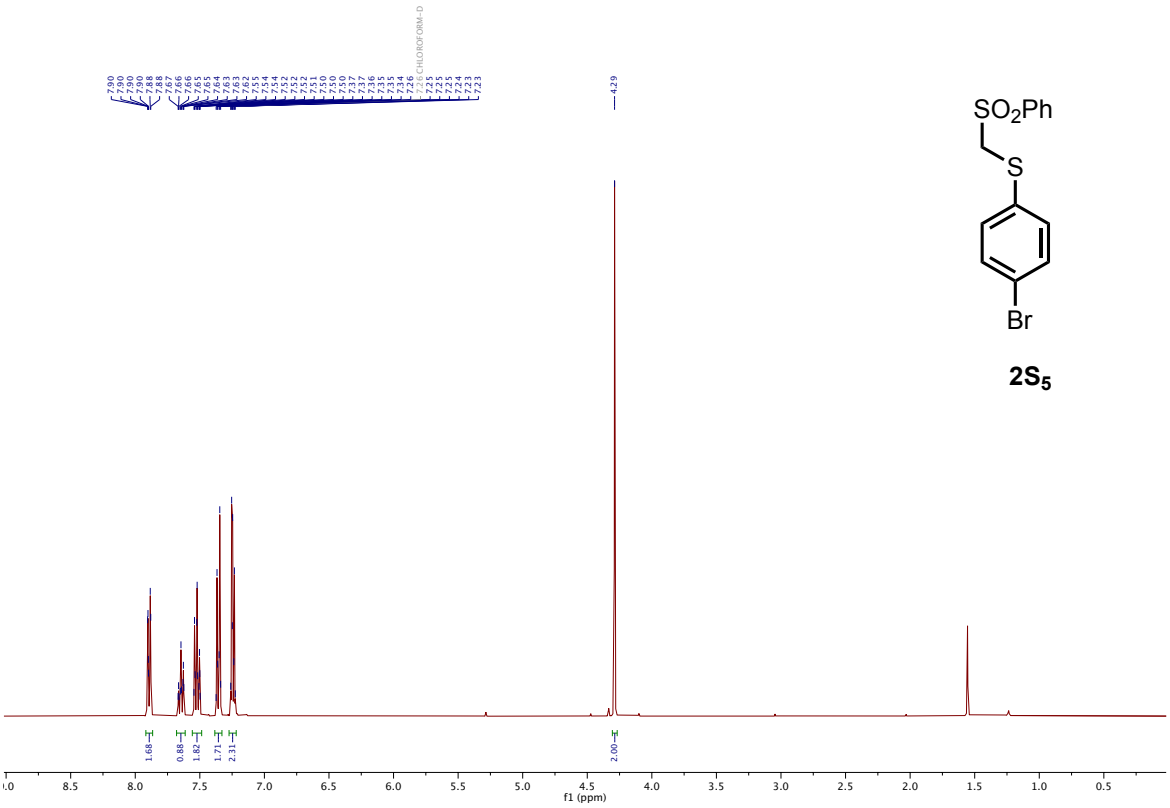


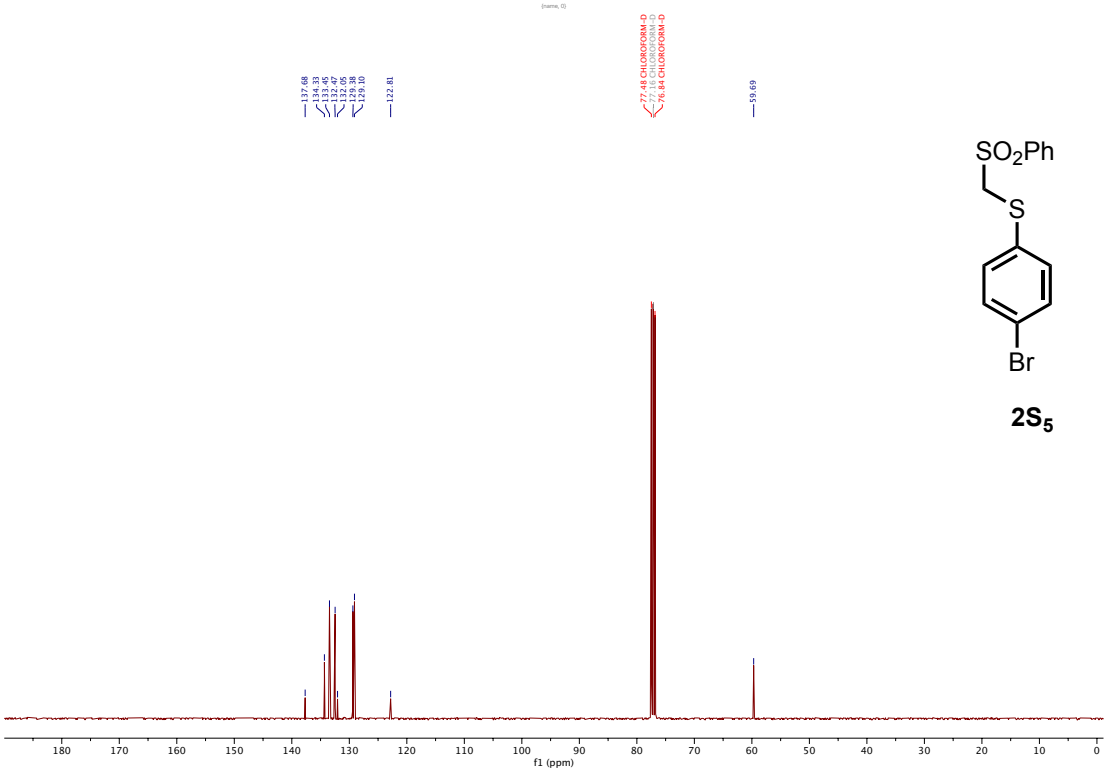
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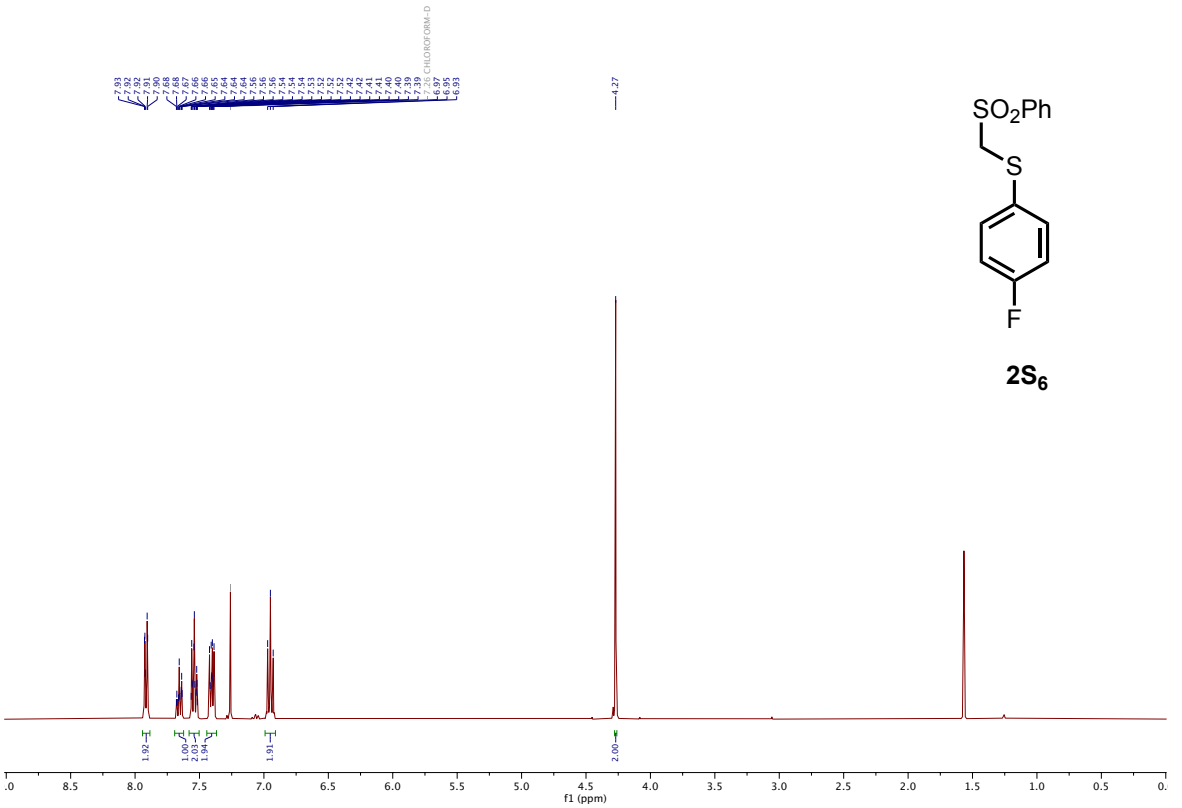
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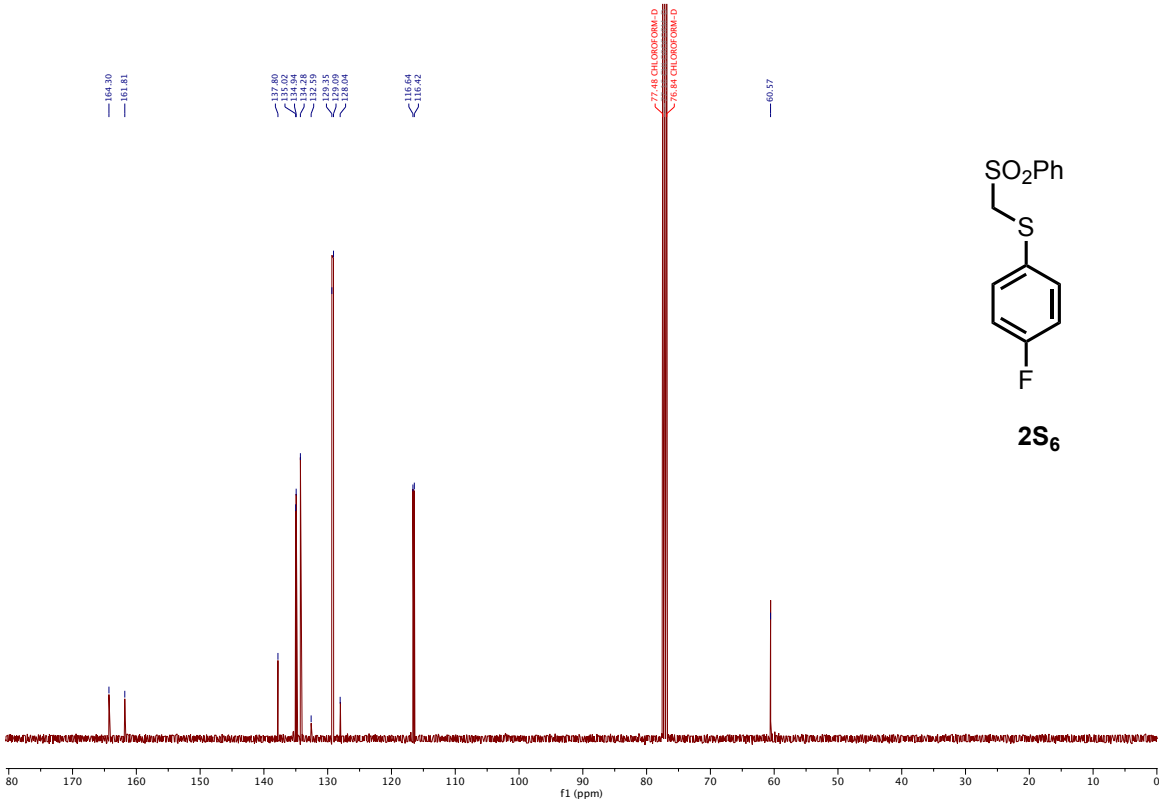
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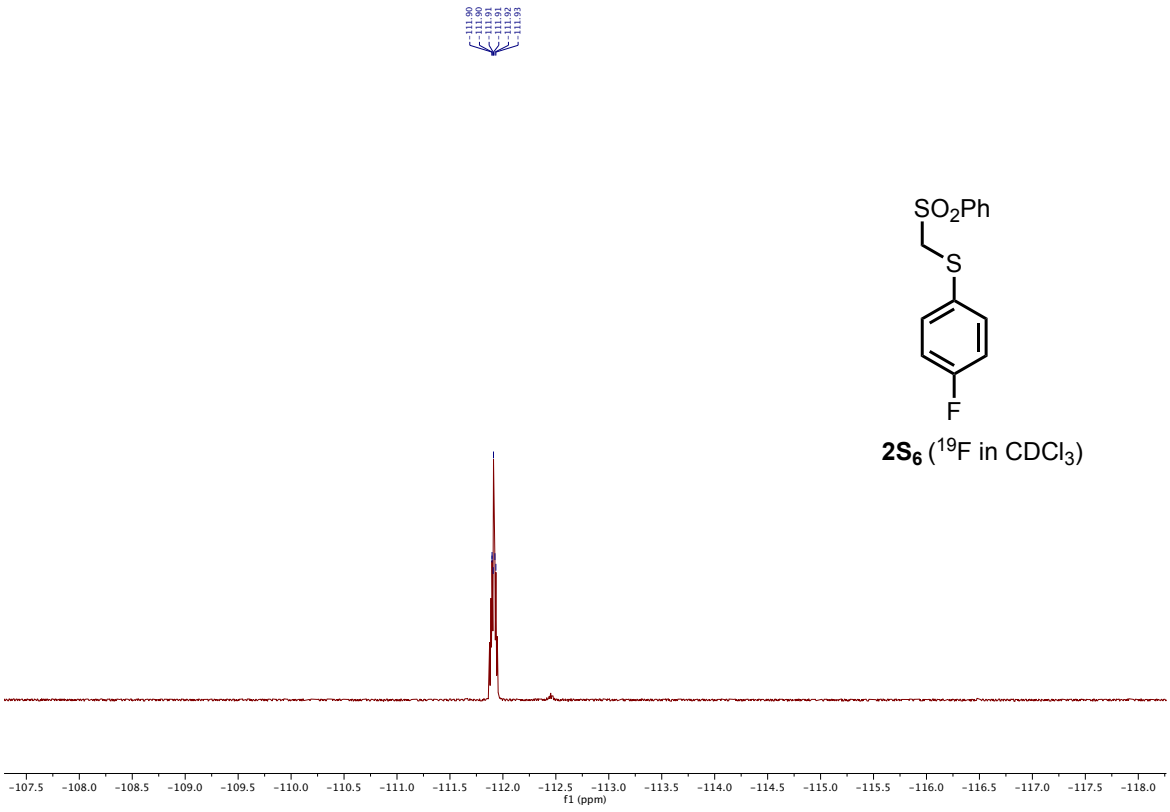


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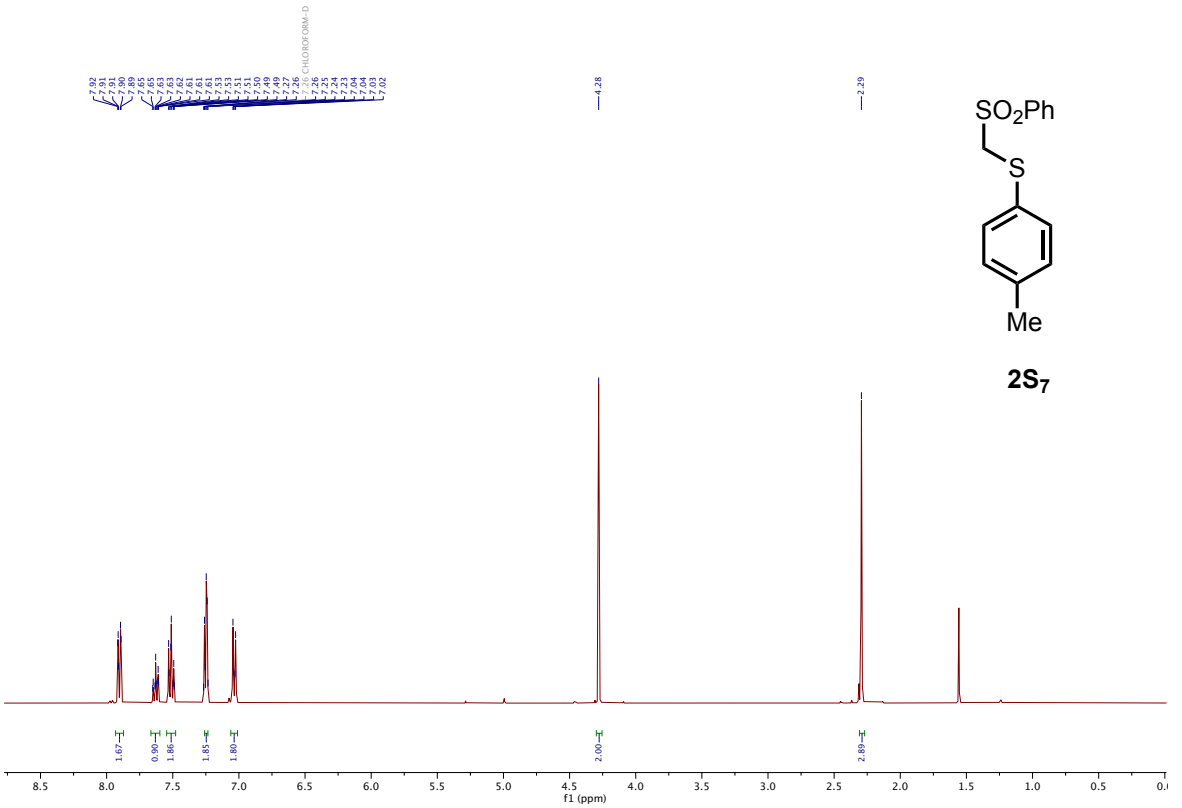


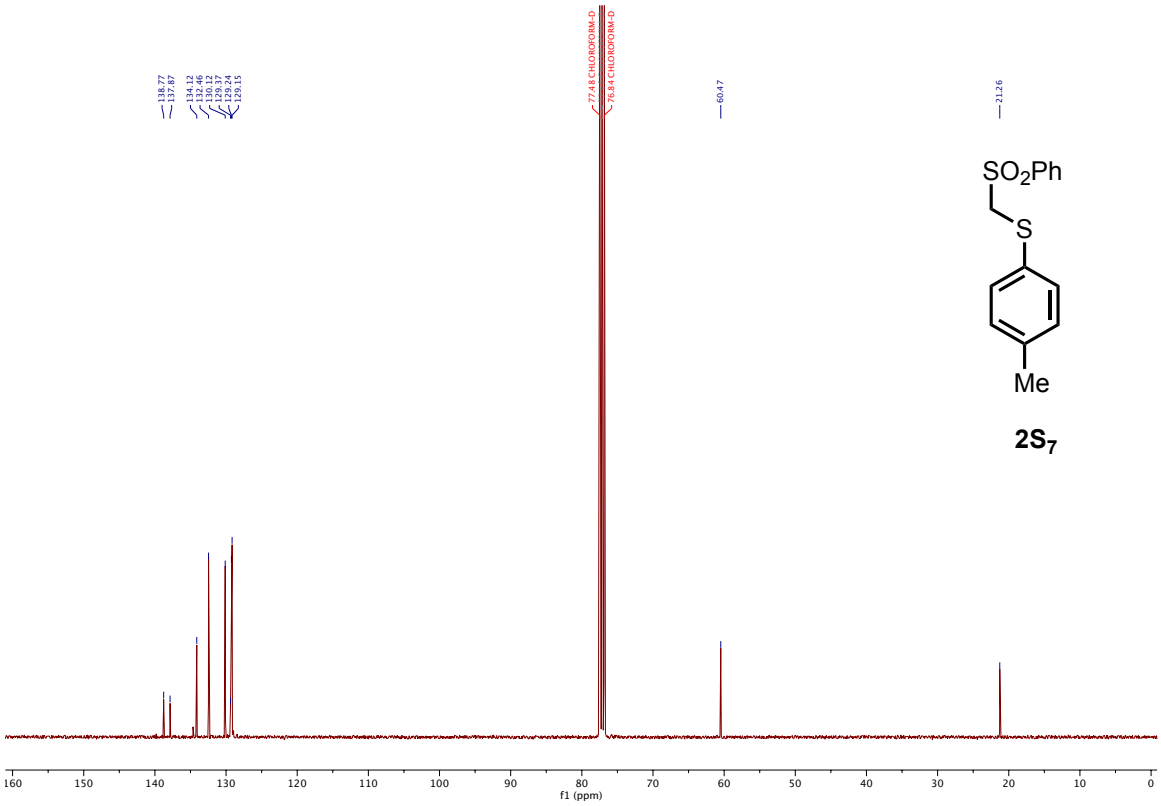


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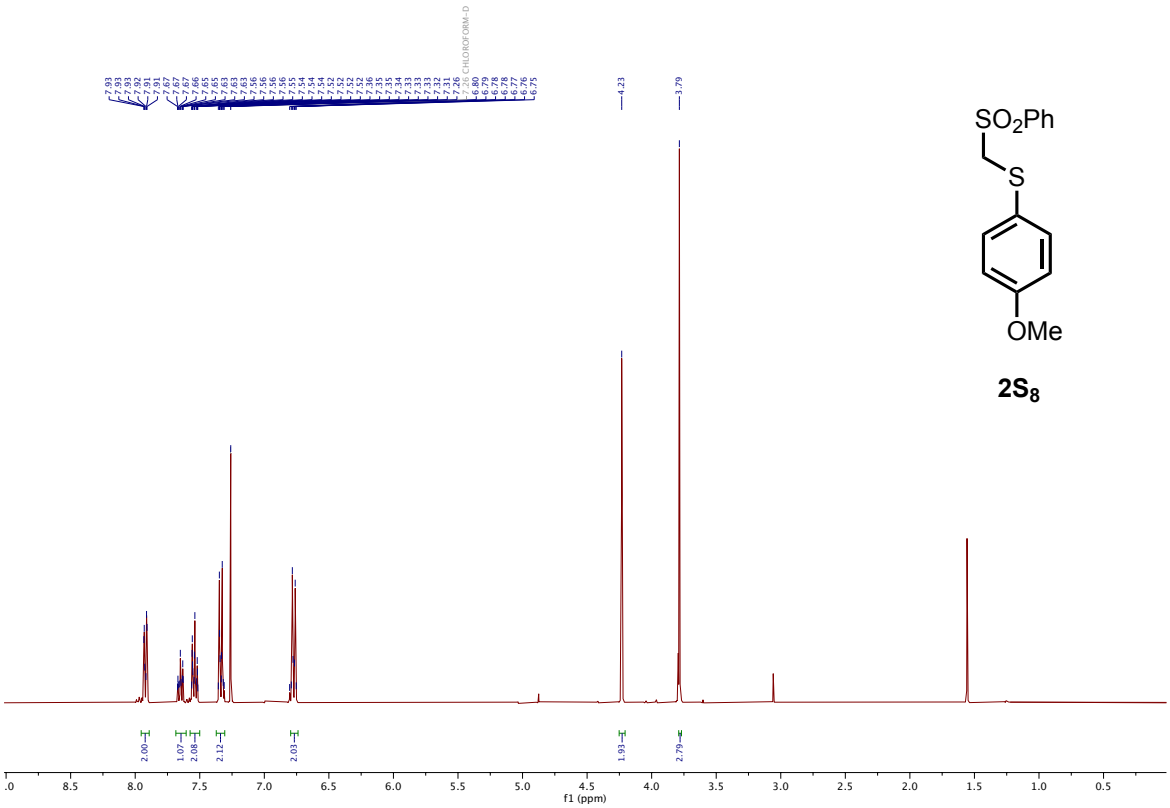


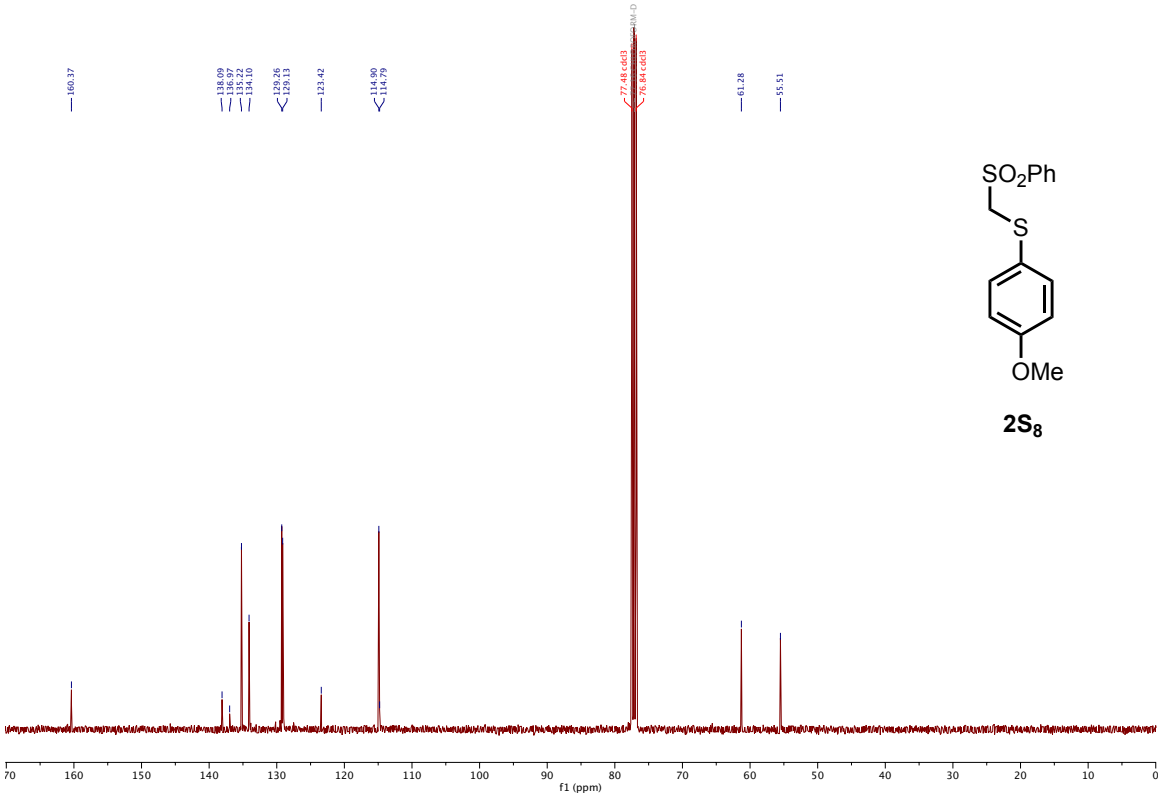
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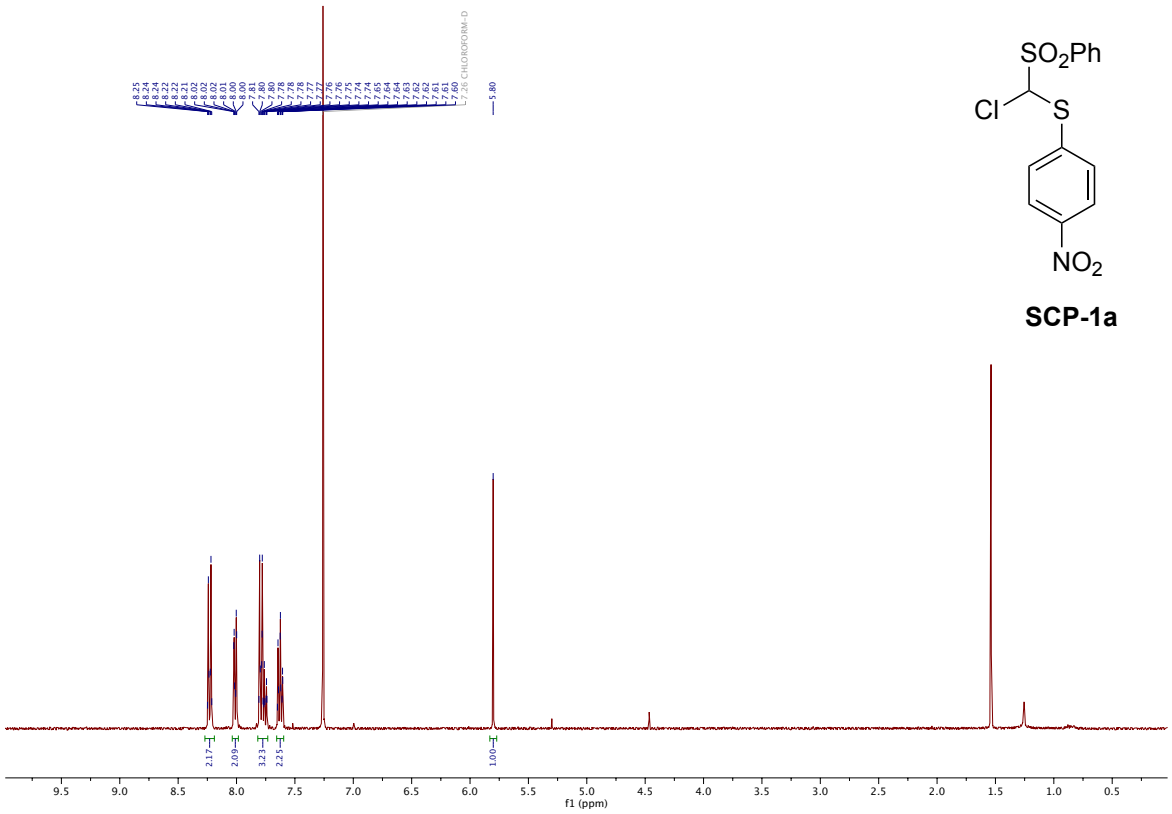


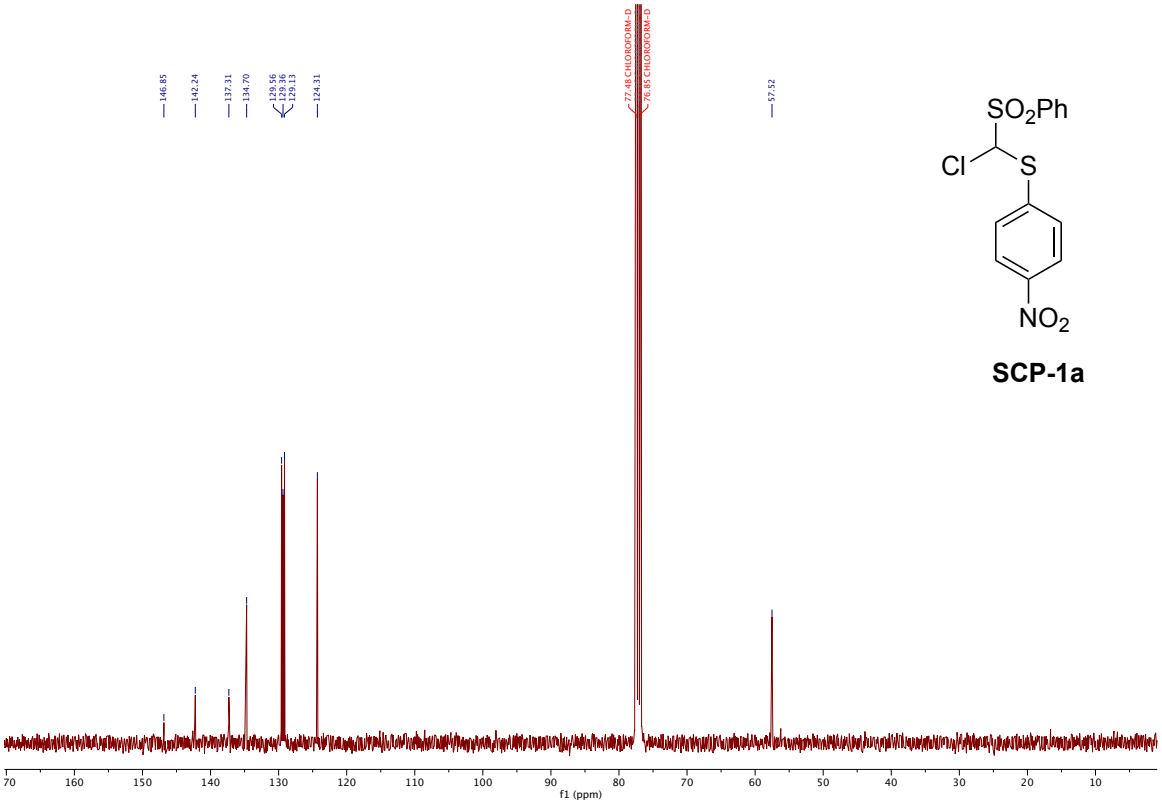
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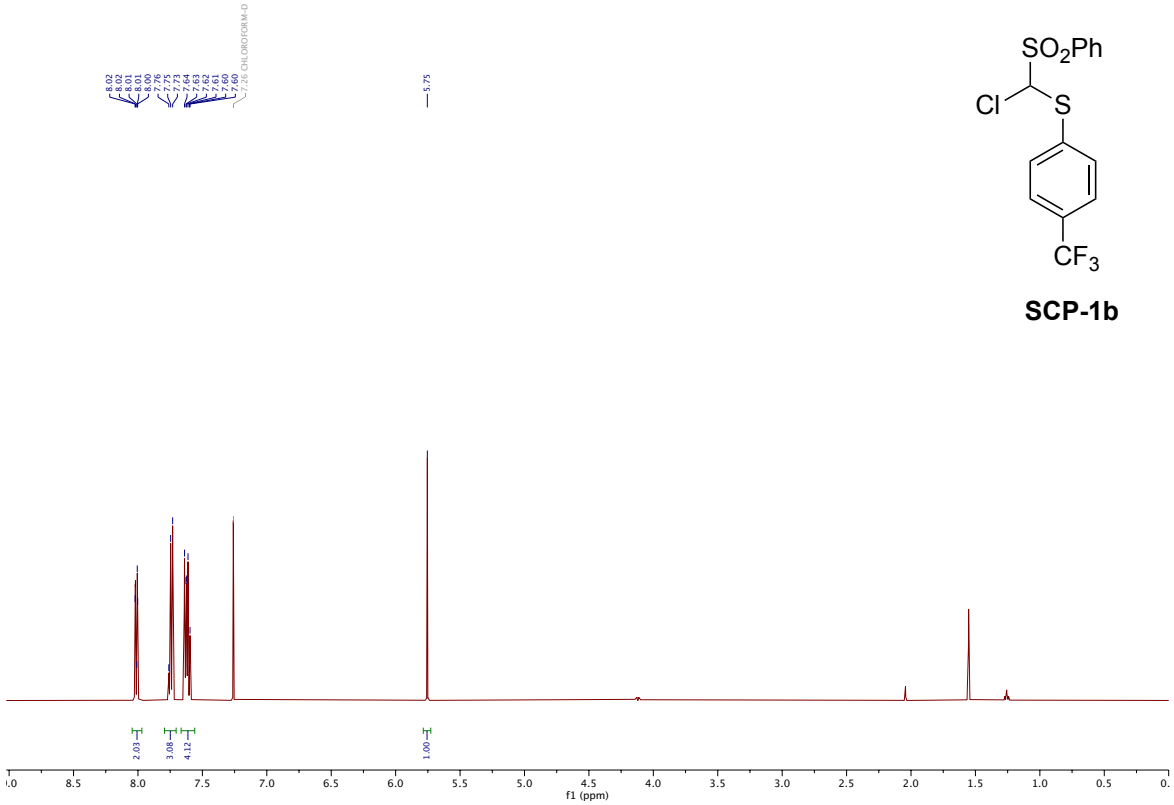


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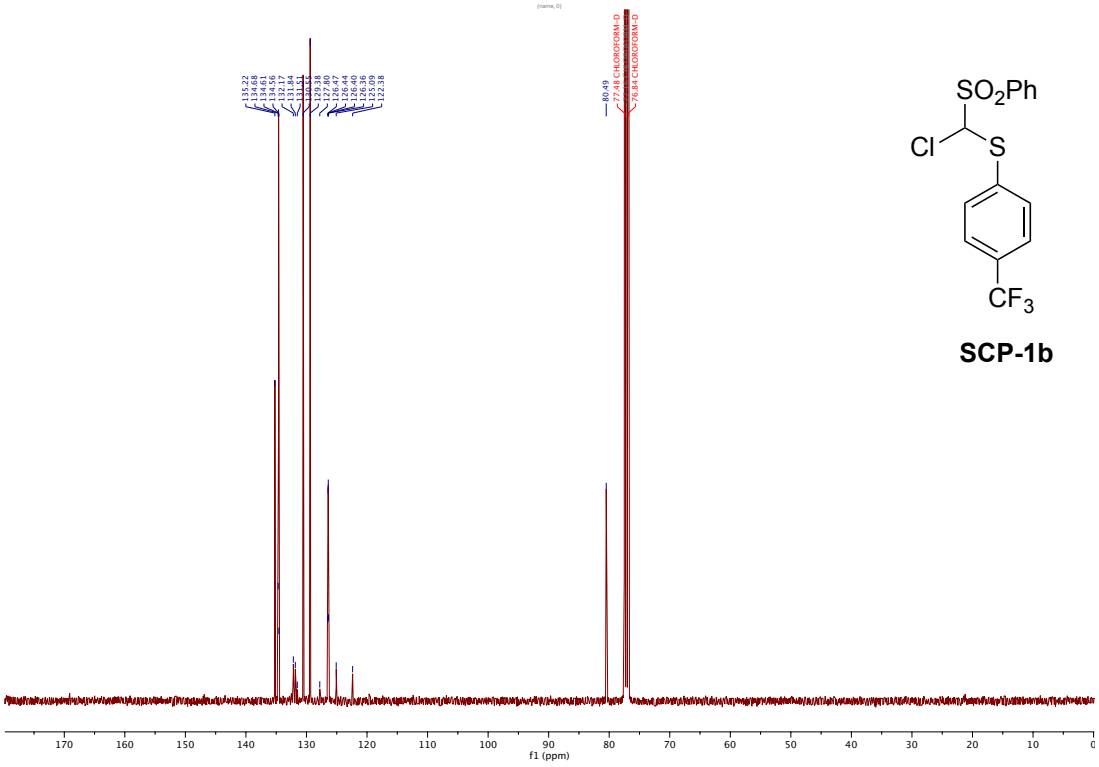




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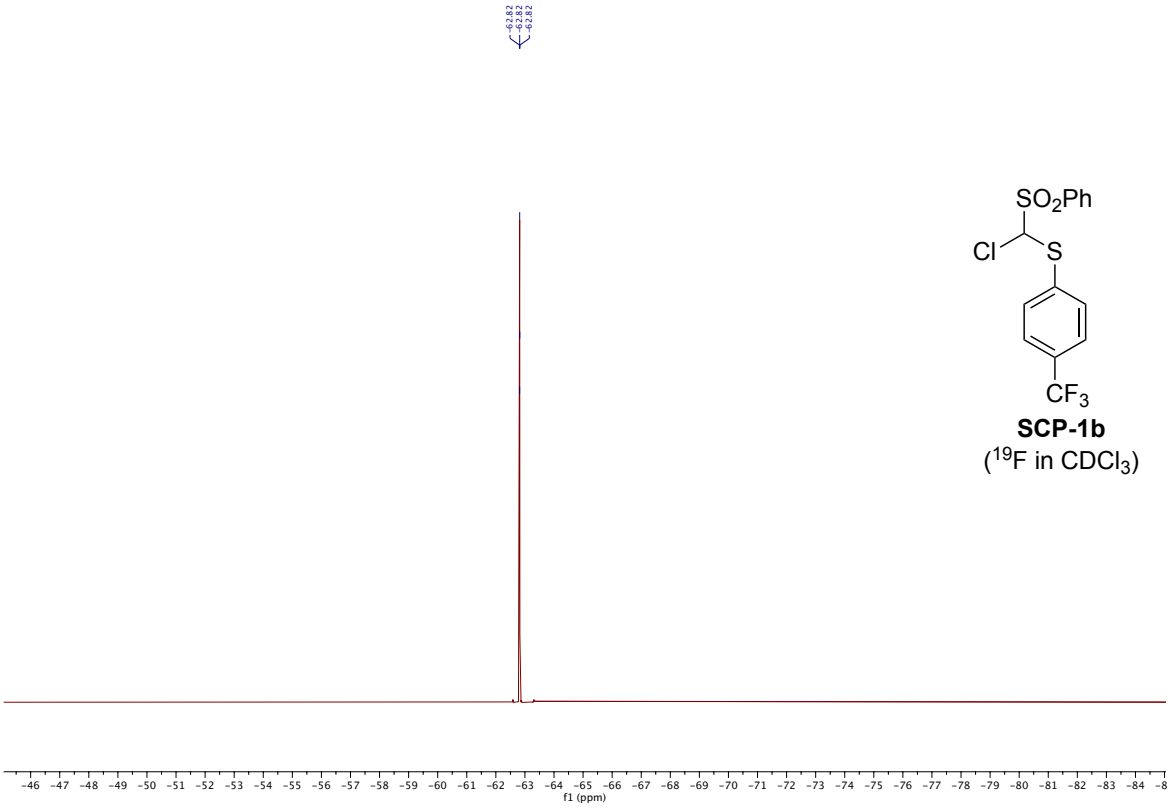


SCP-1b

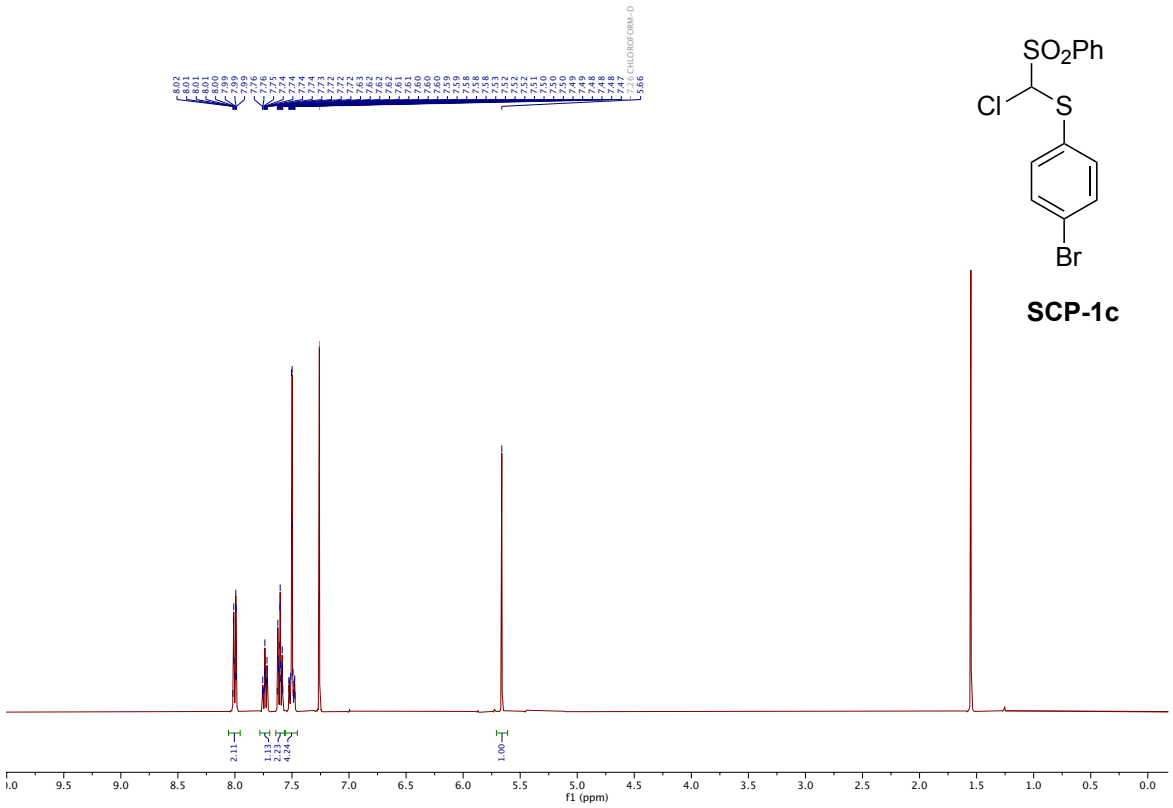


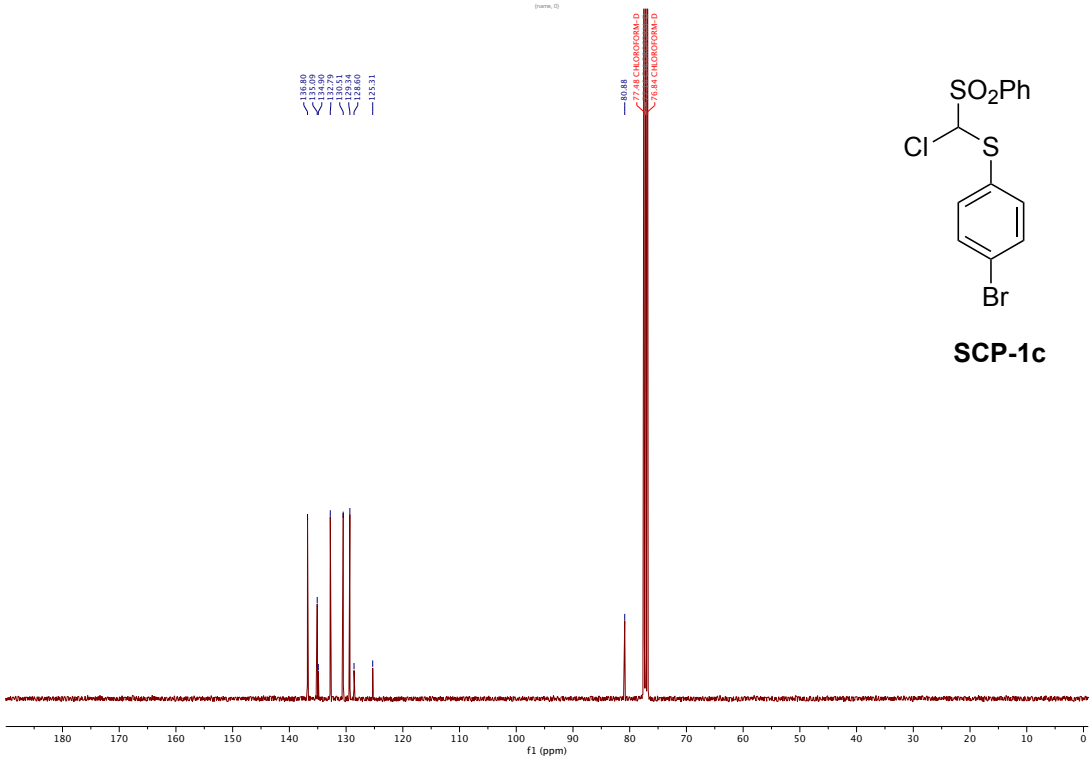
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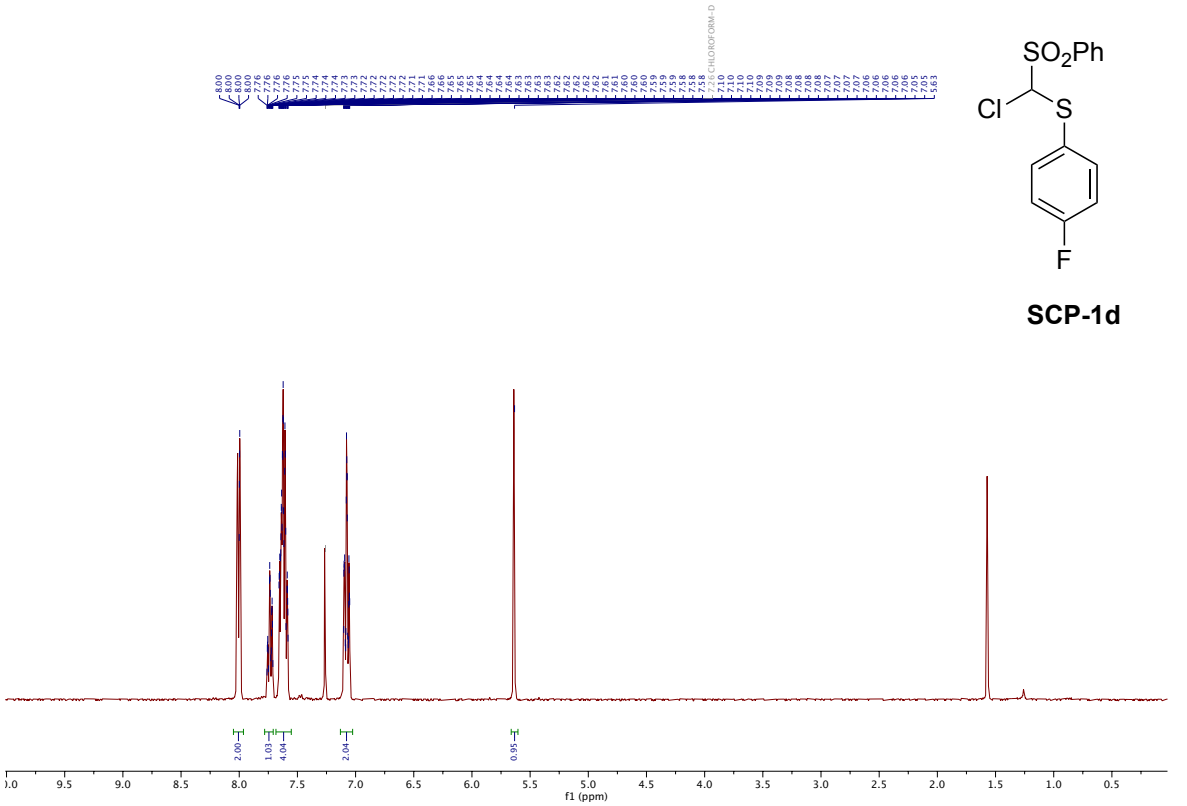


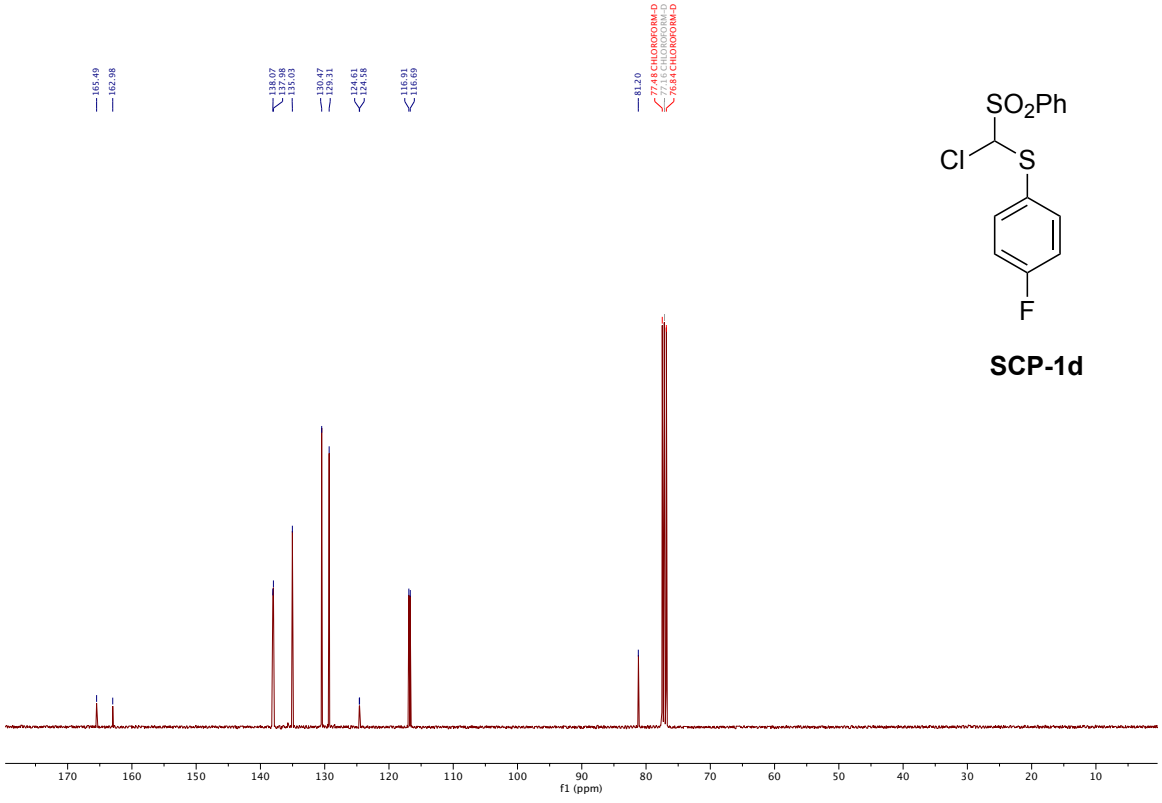
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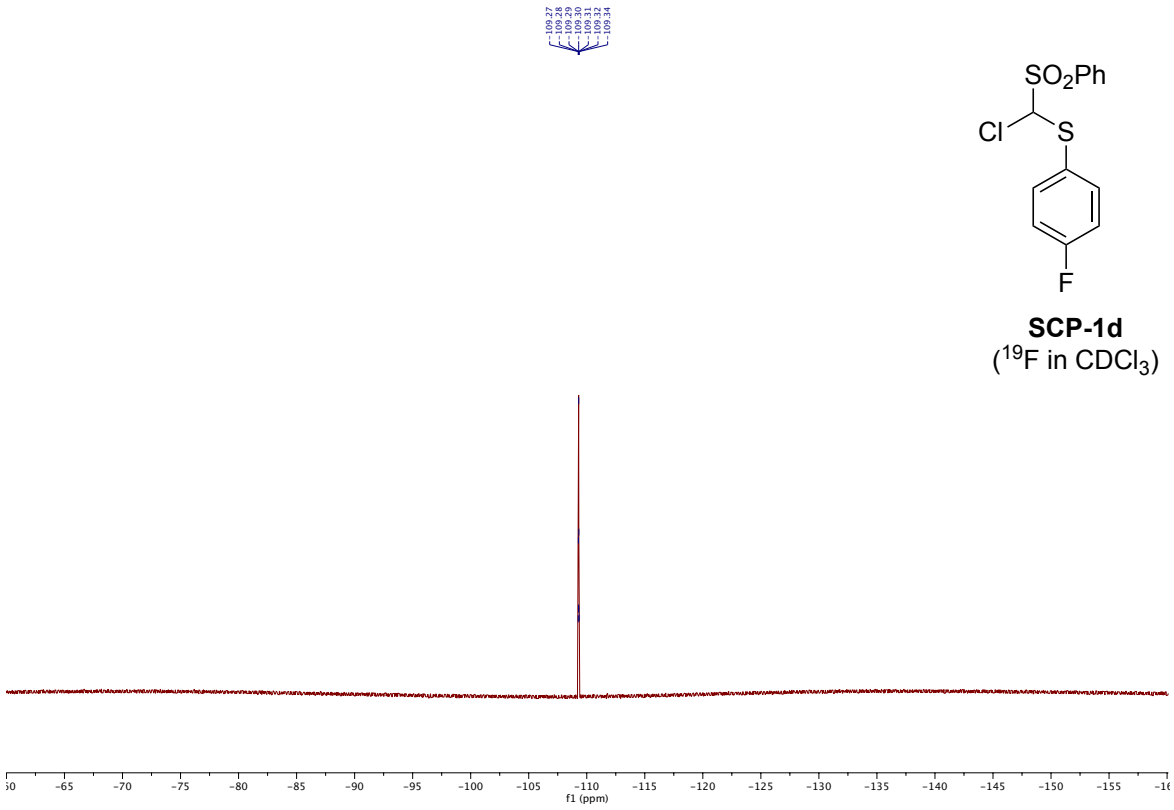


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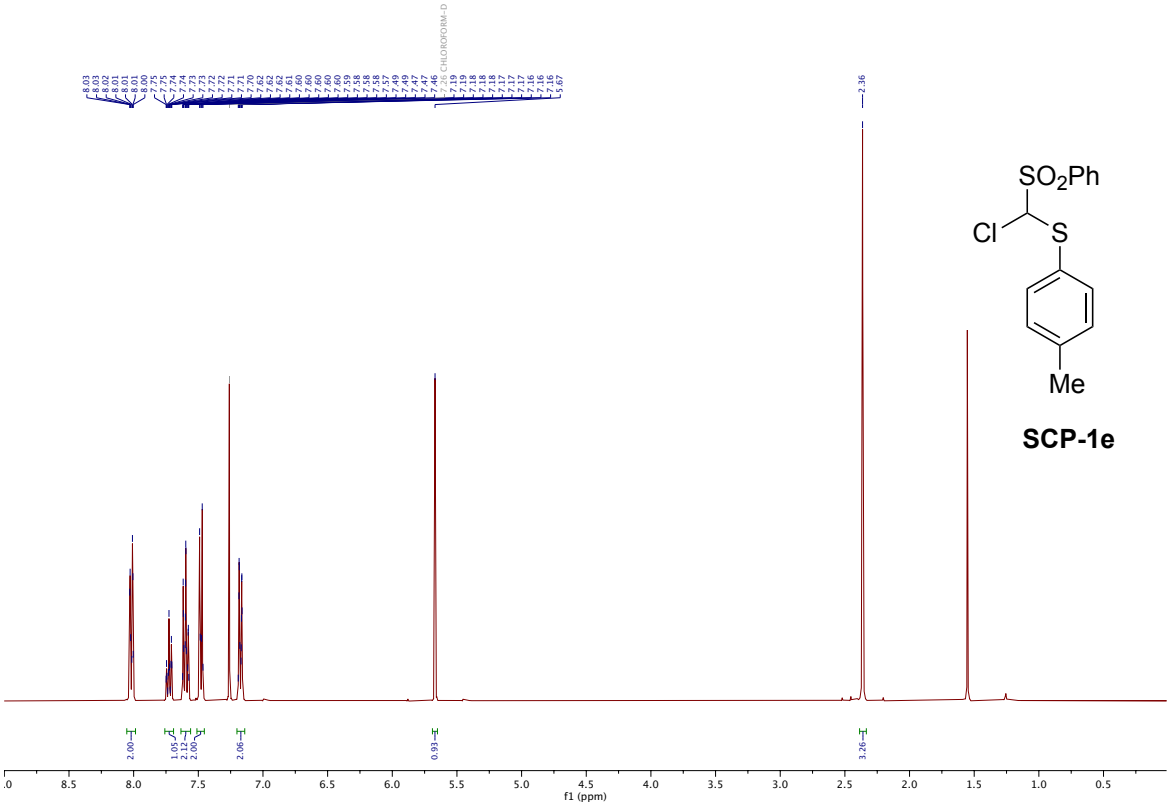


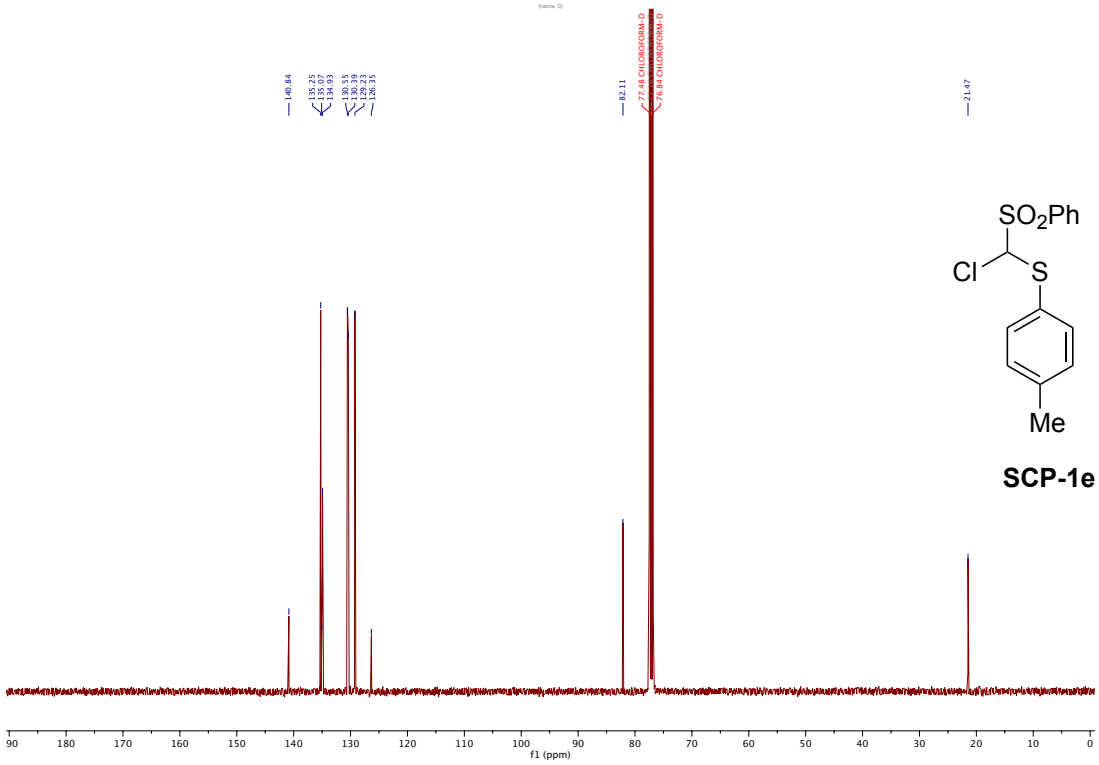


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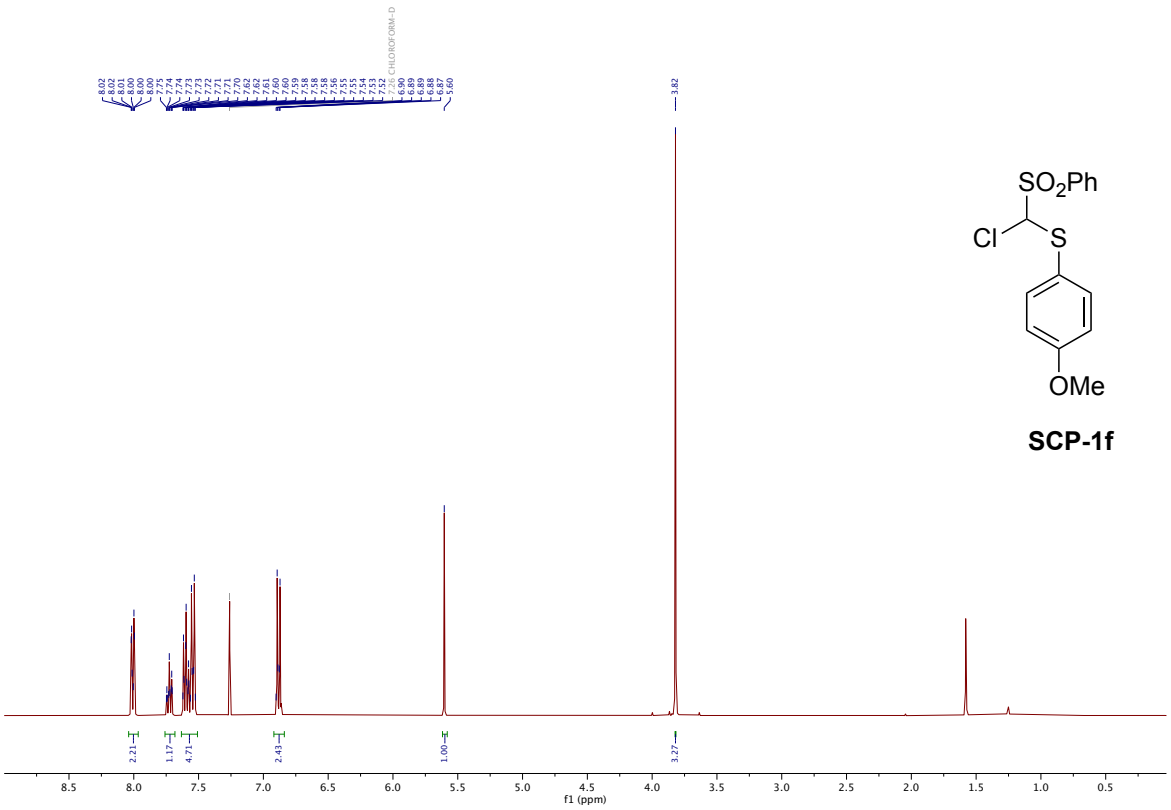


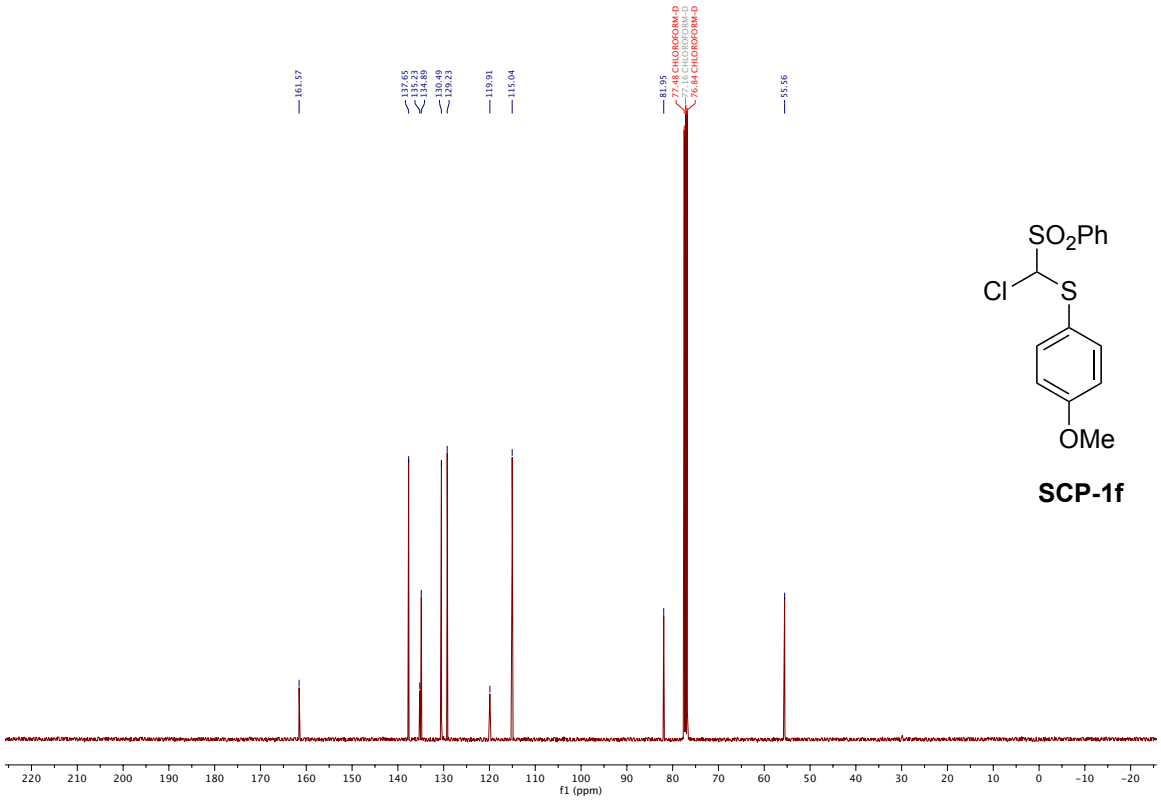
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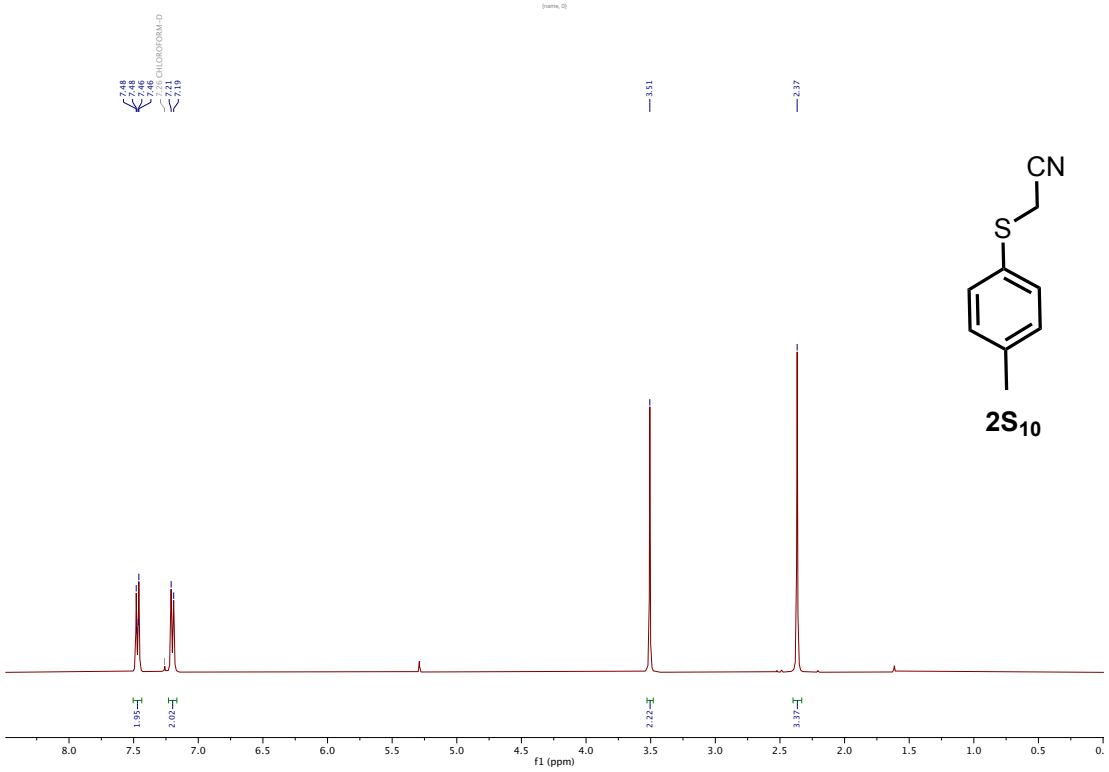


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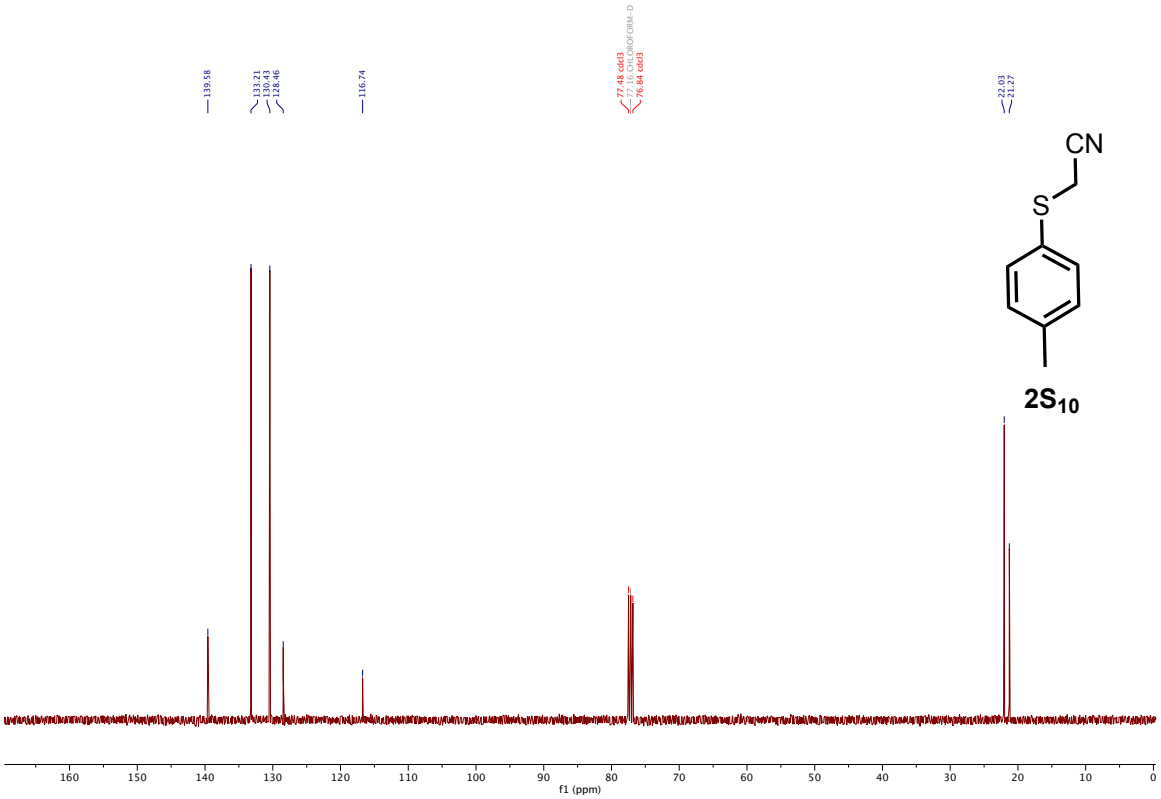




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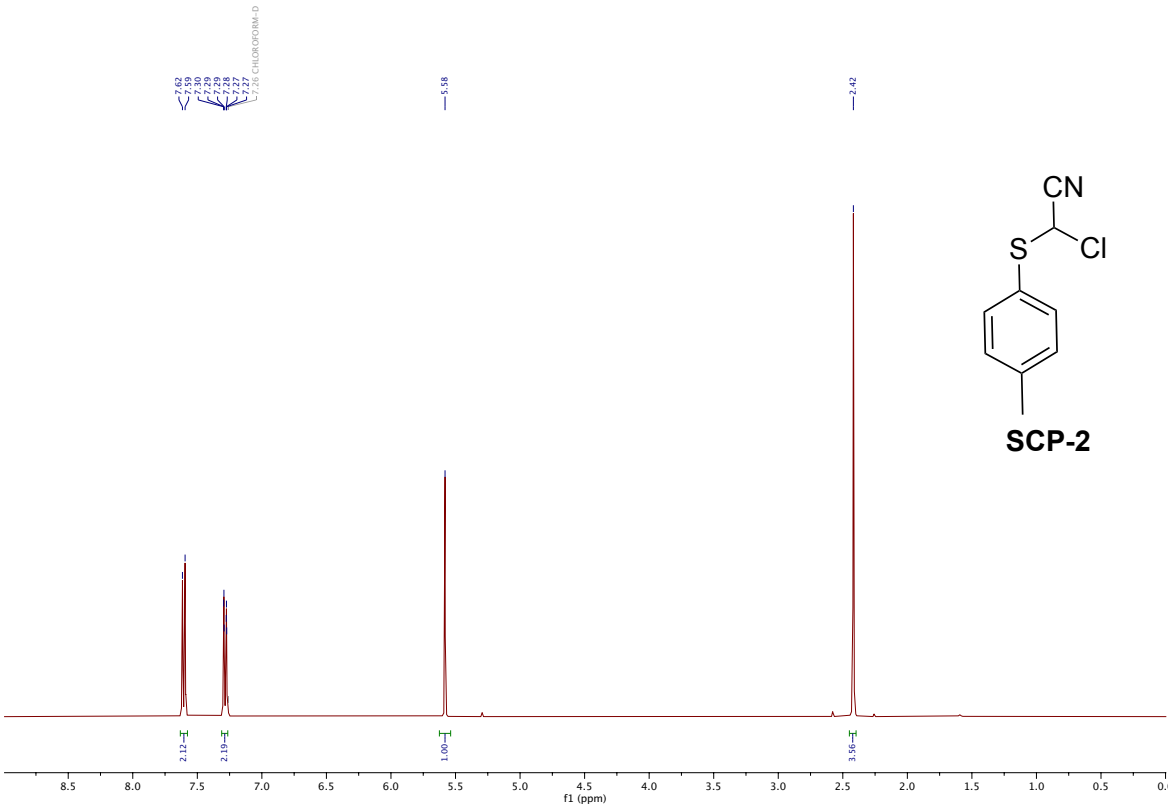


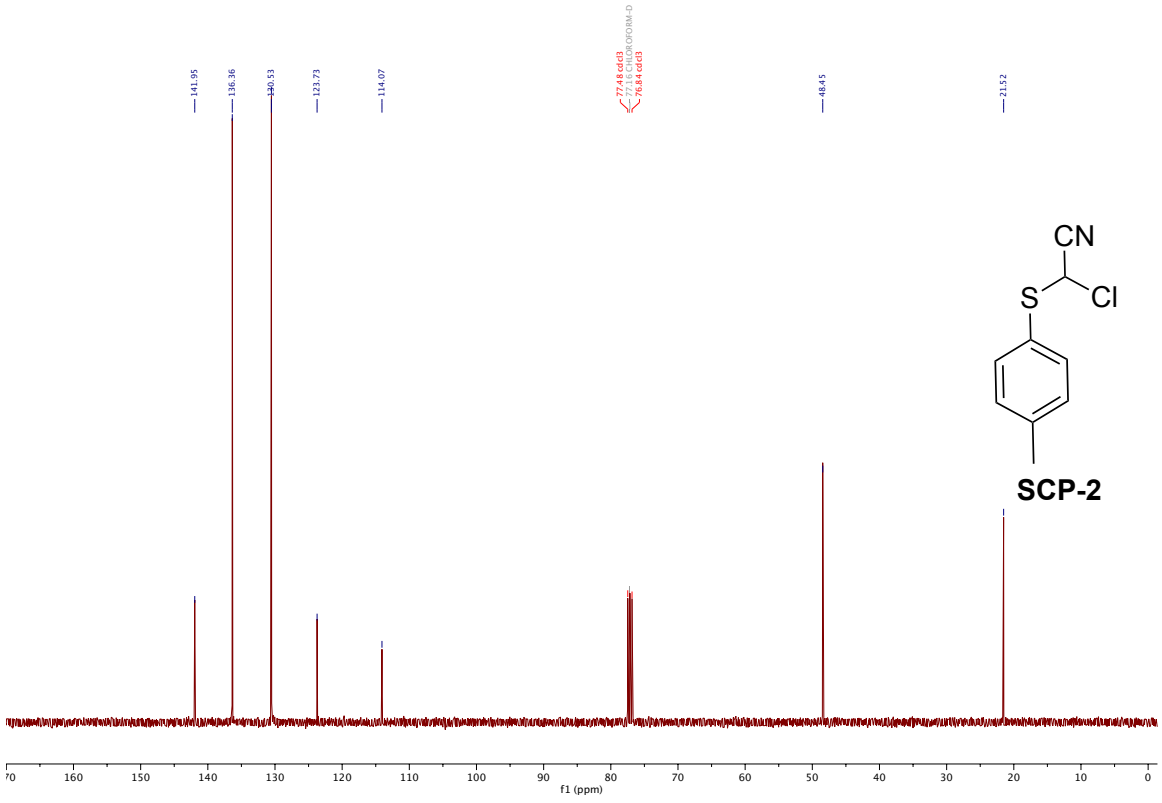
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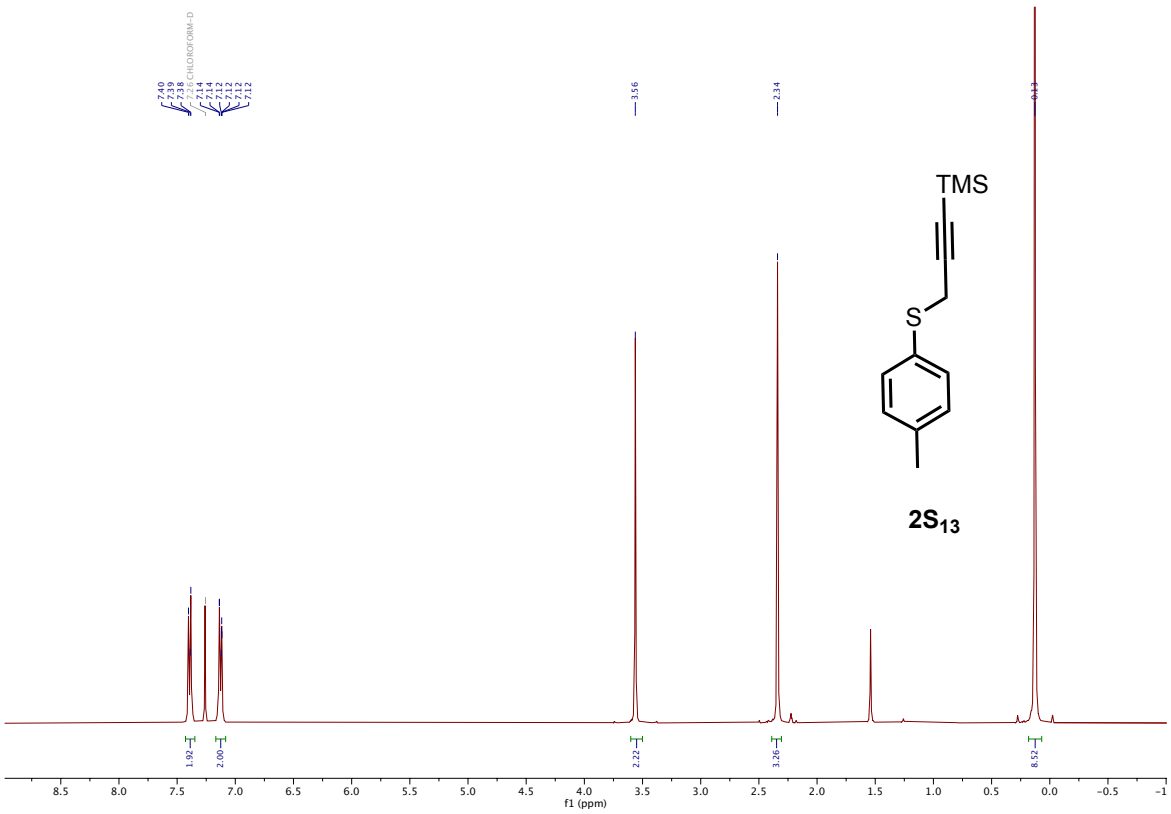
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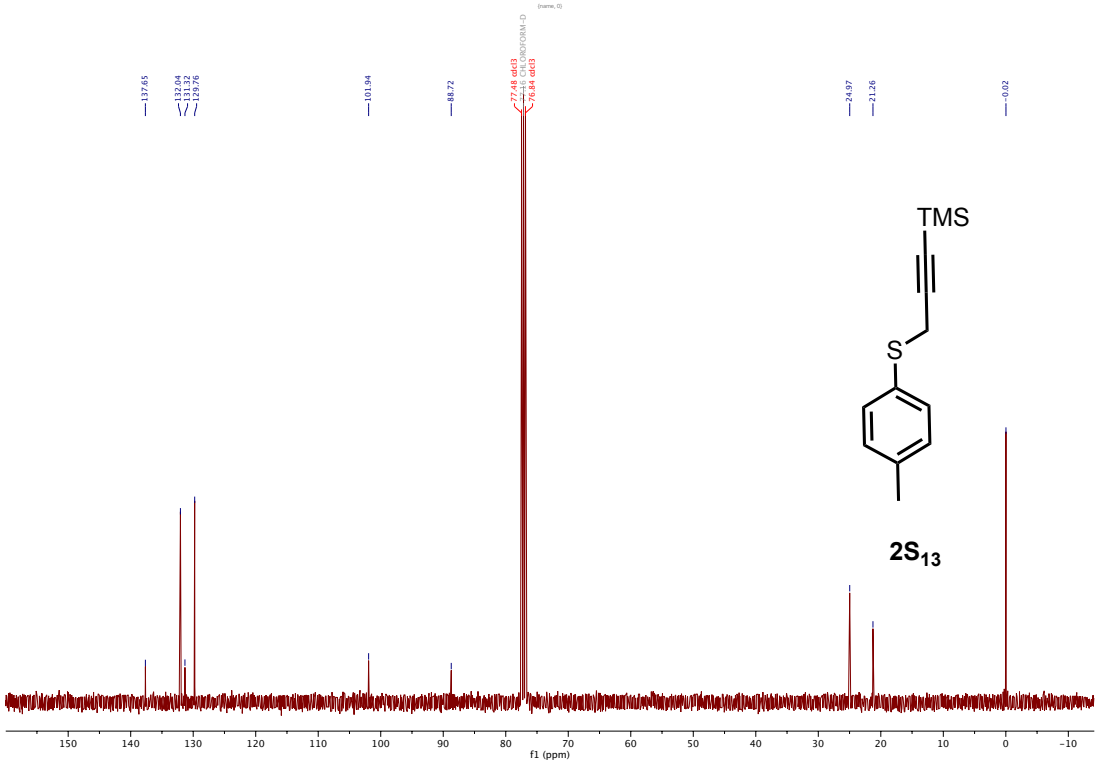
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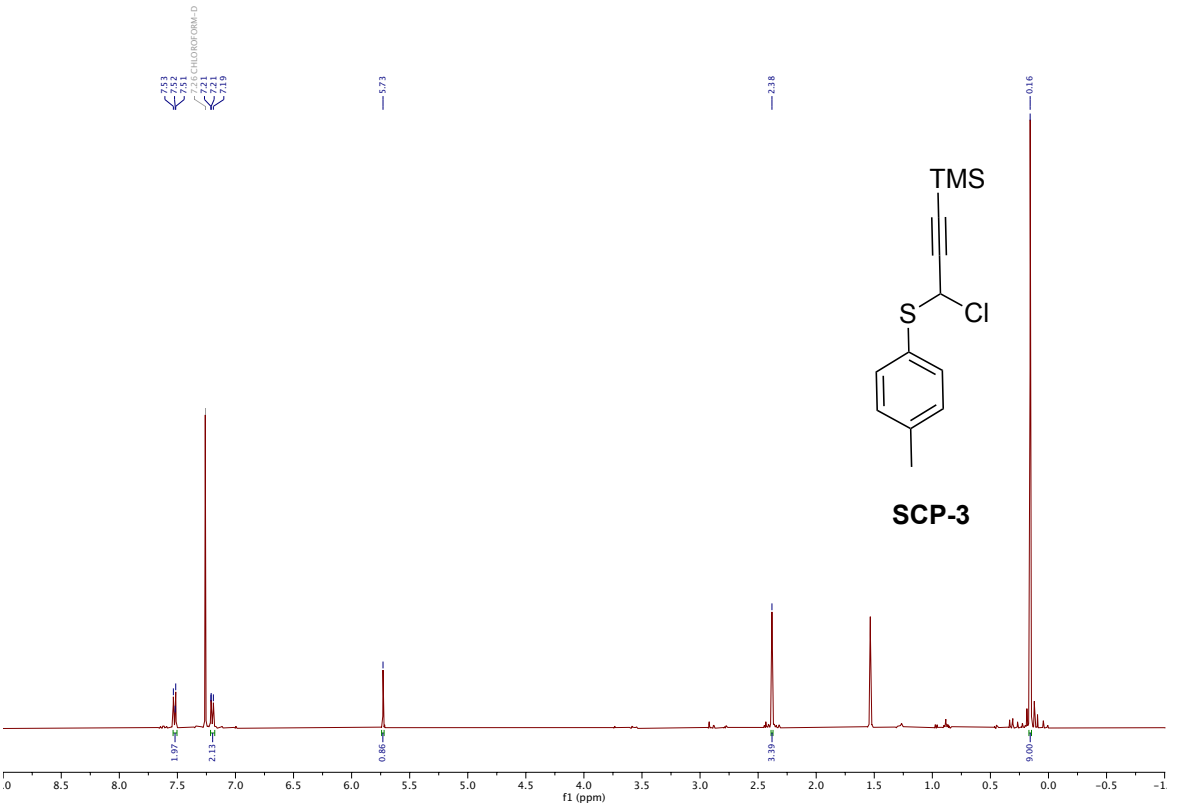


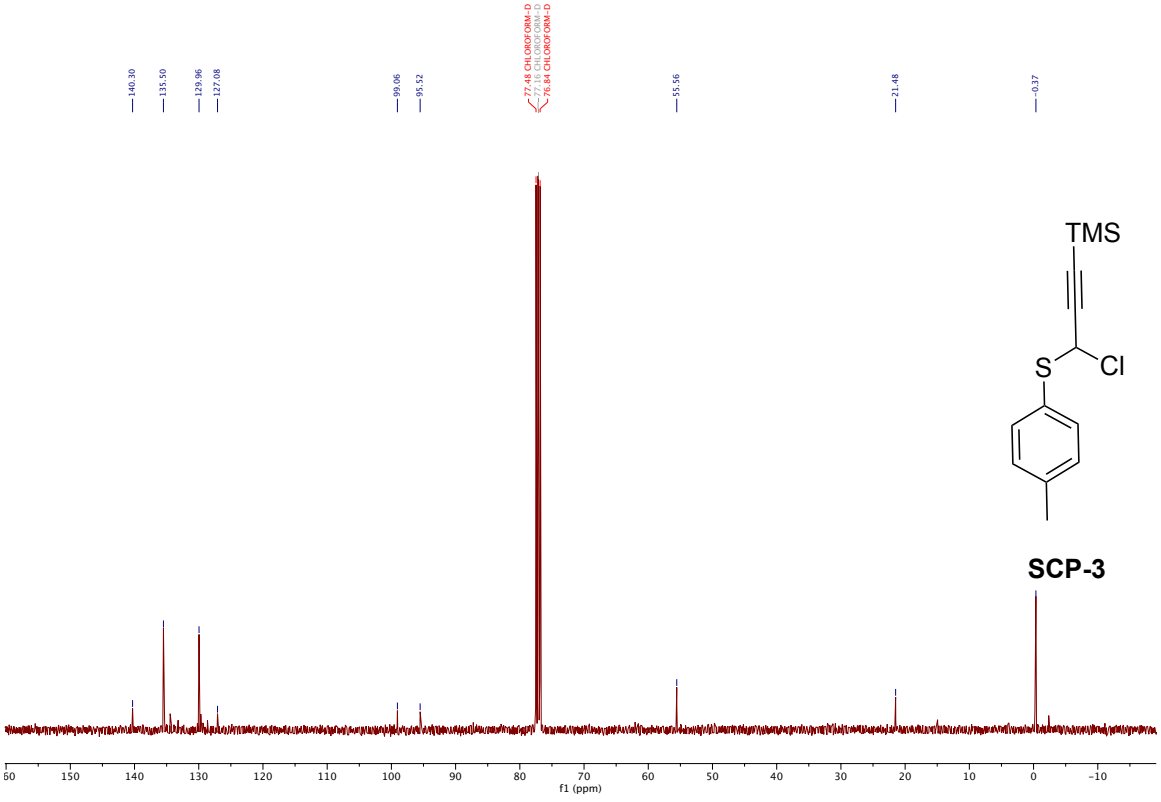
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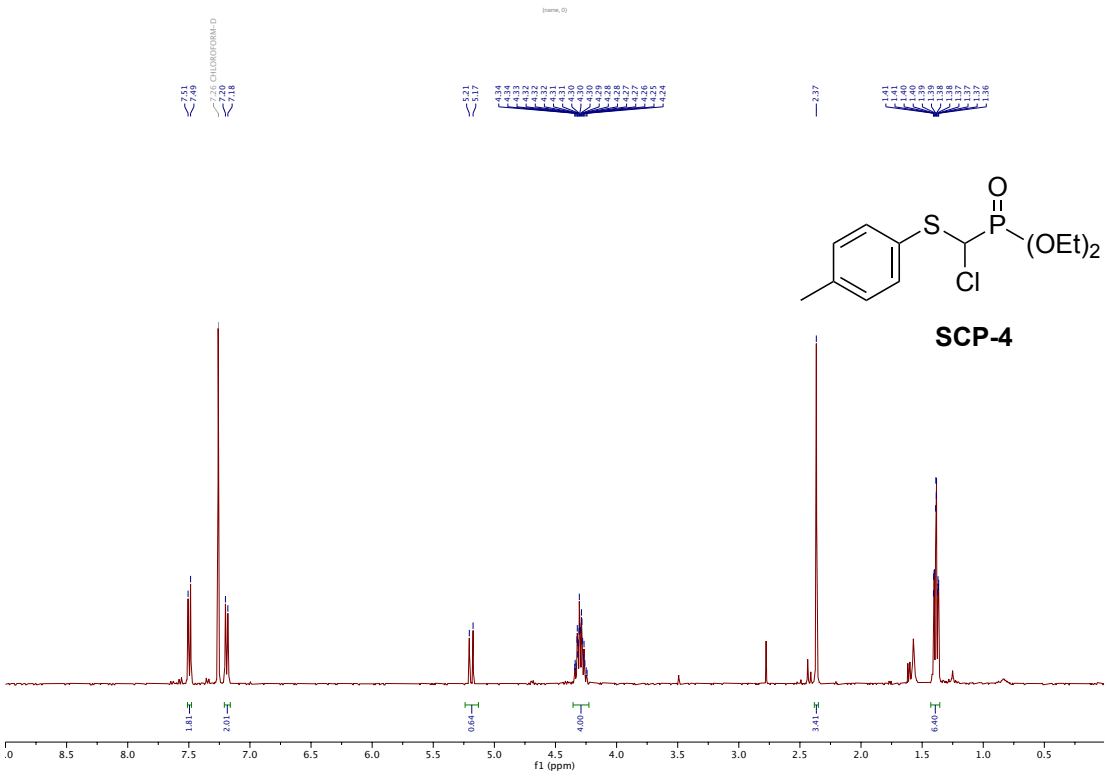


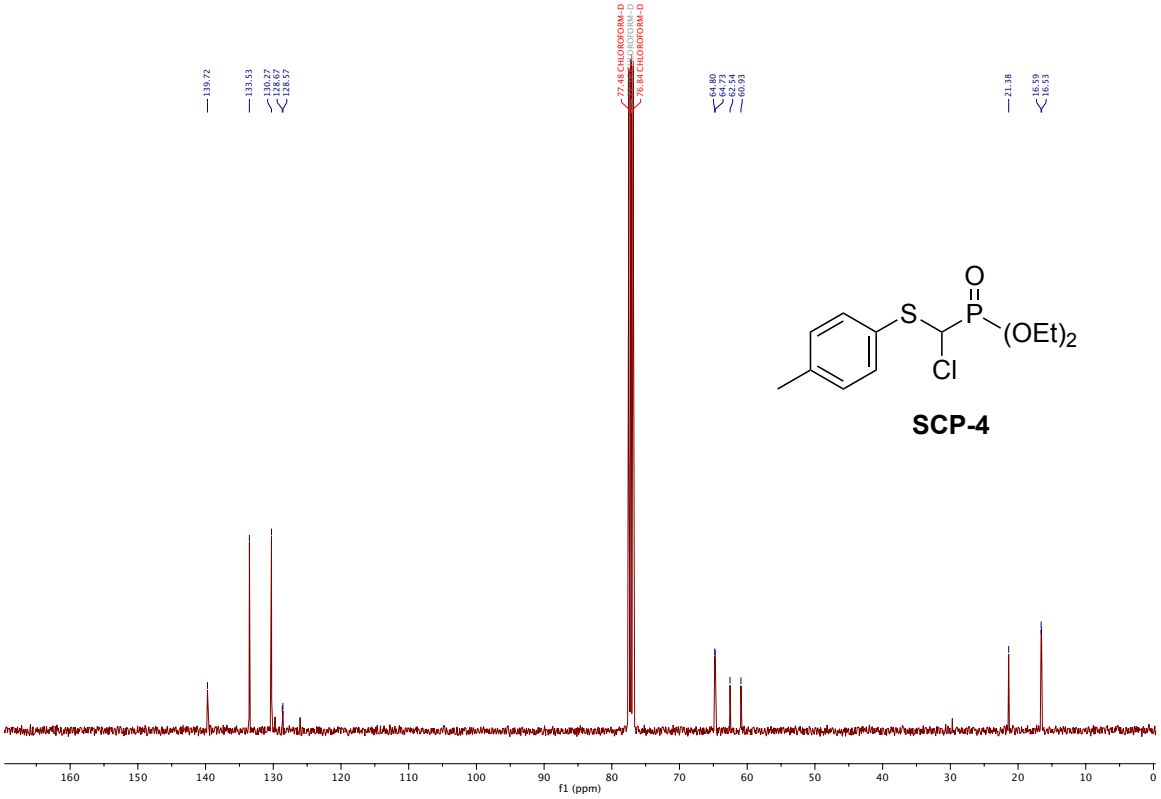
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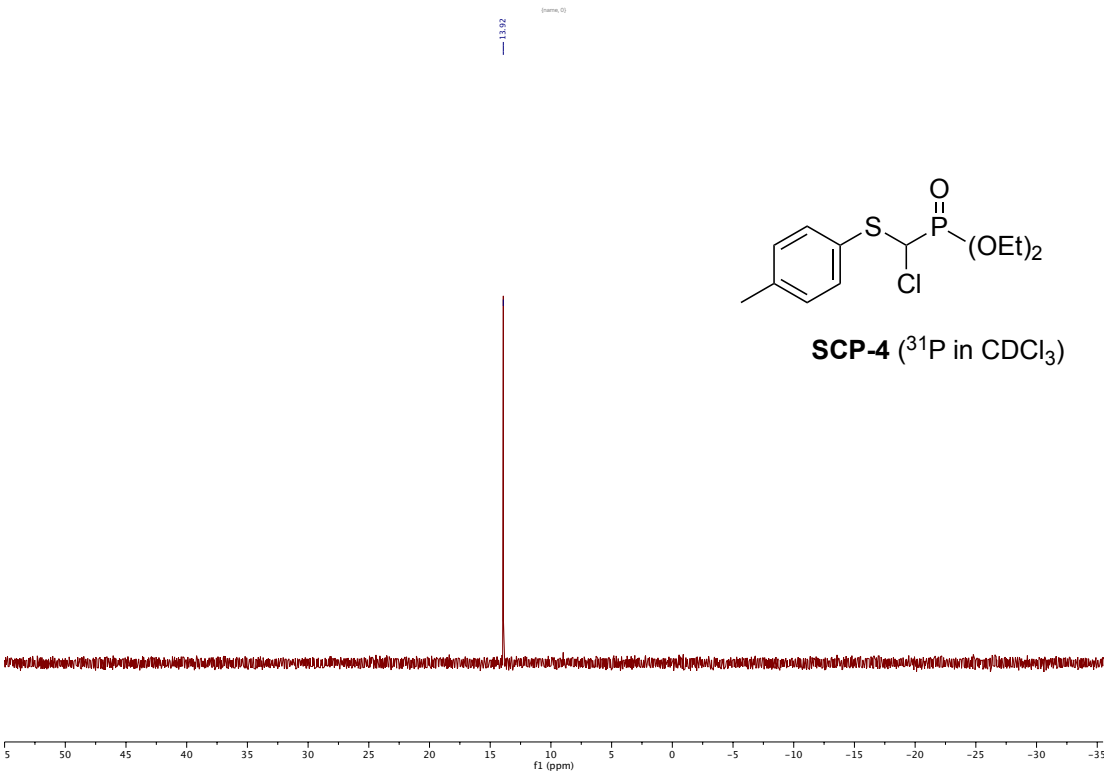


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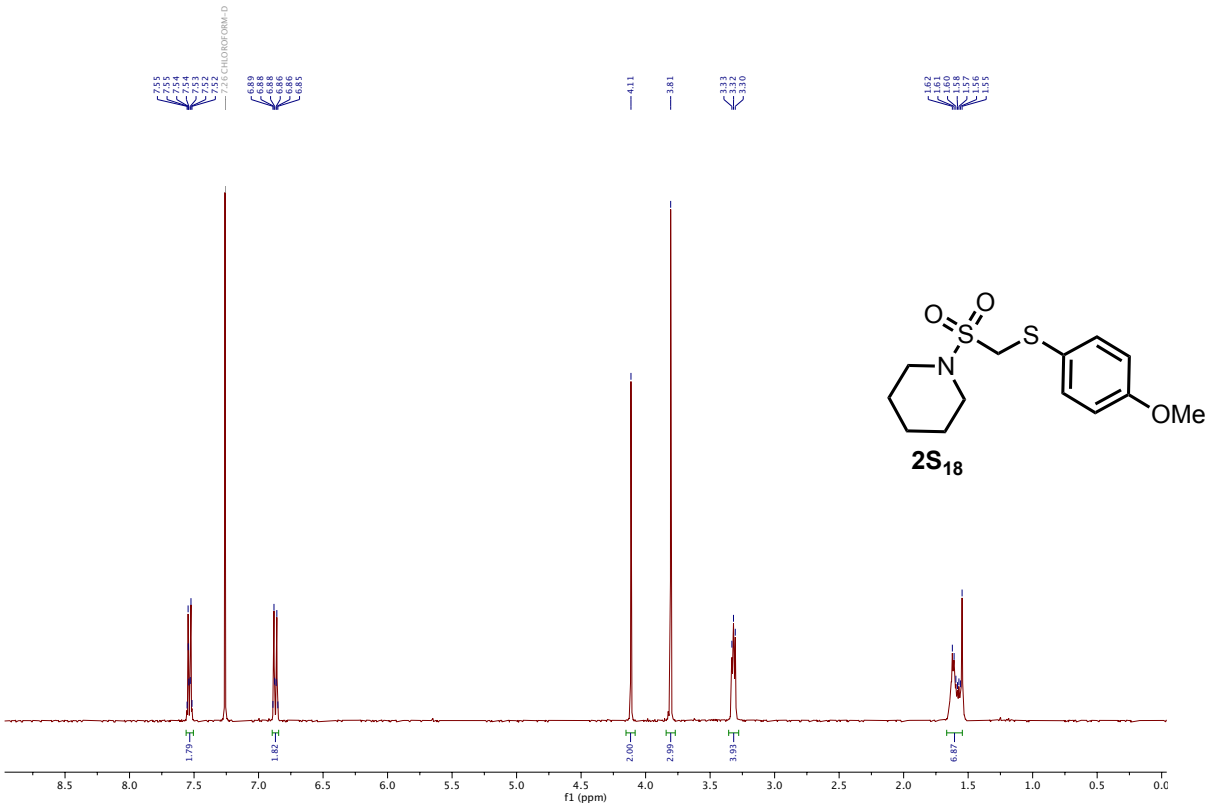


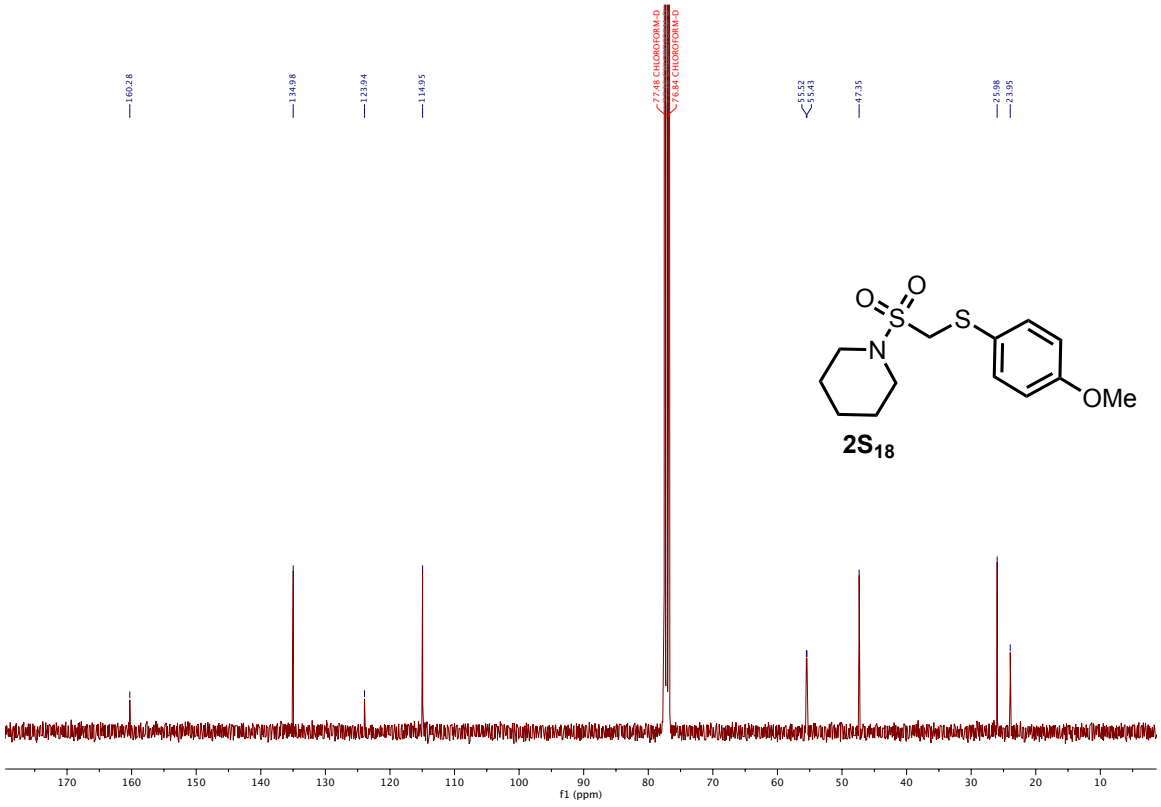
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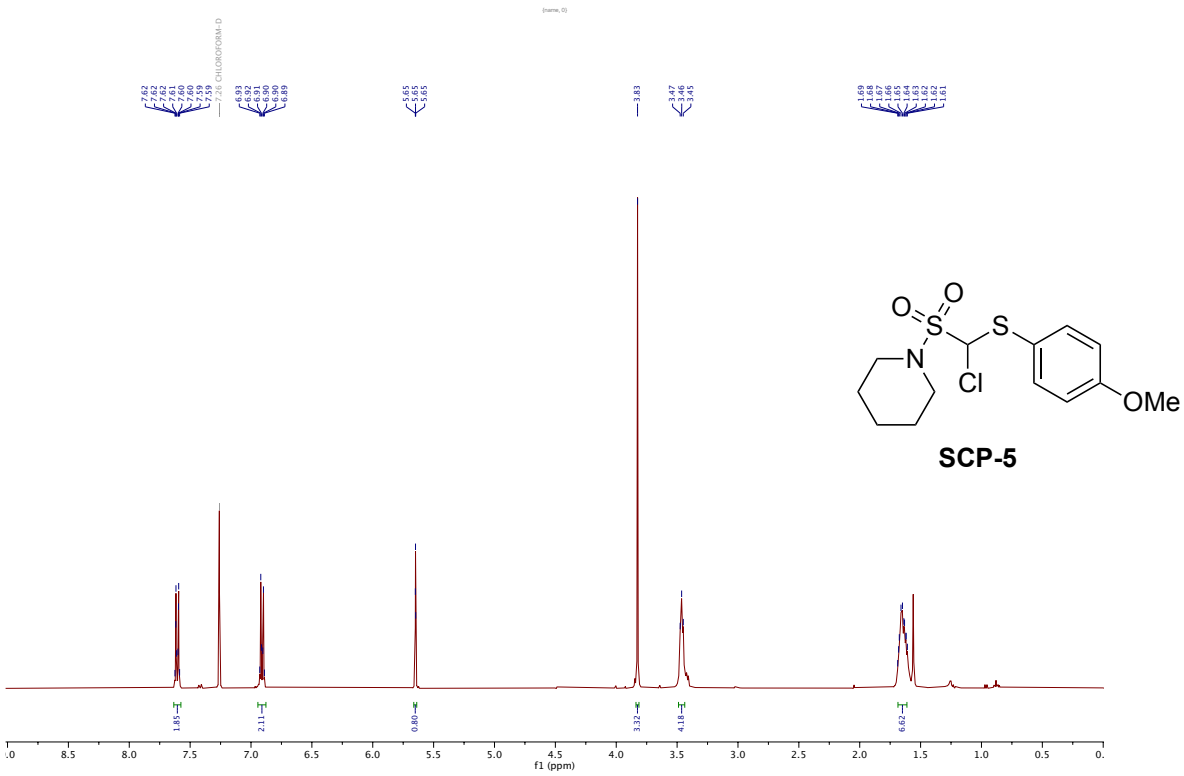
SCP-4 (^{31}P in $CDCl_3$)

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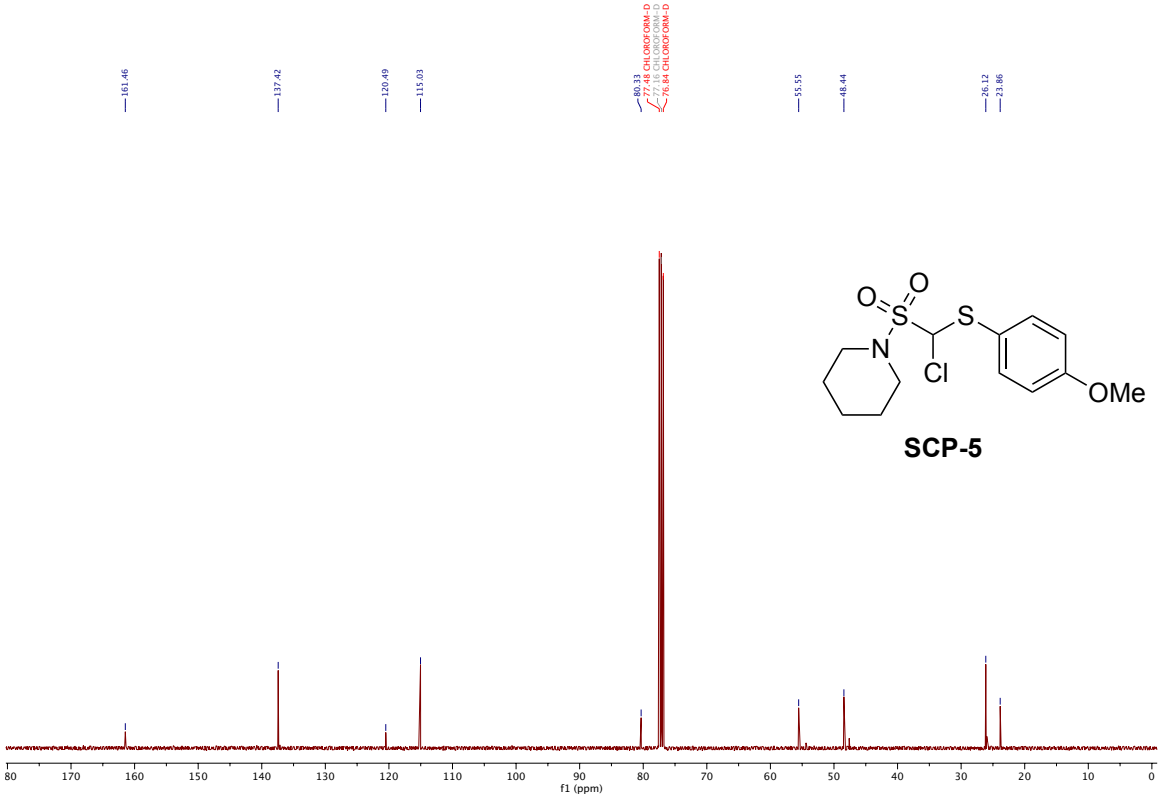




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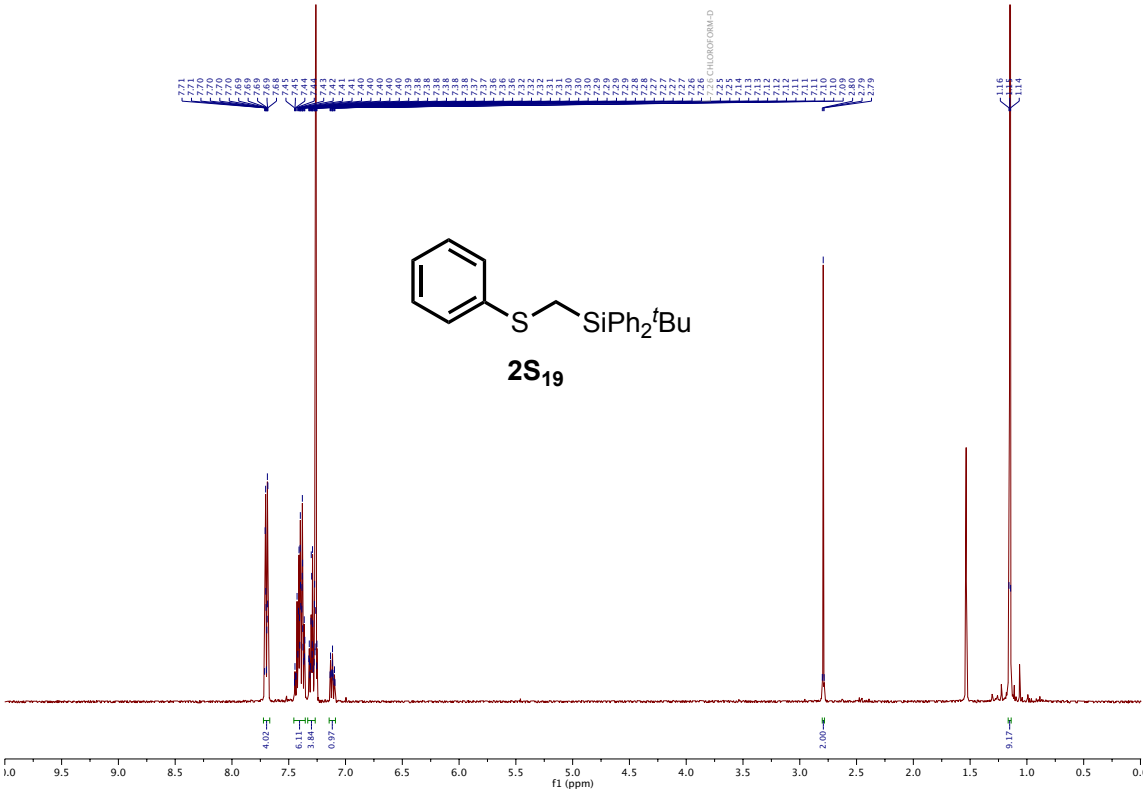


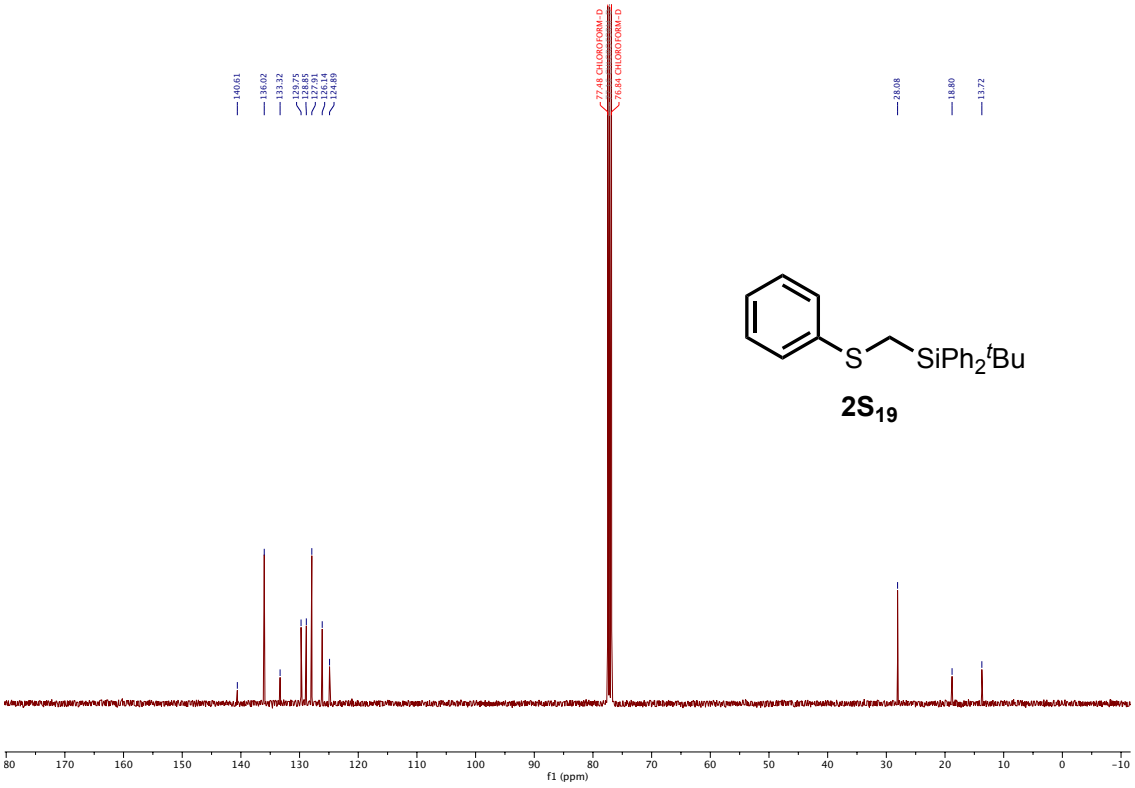
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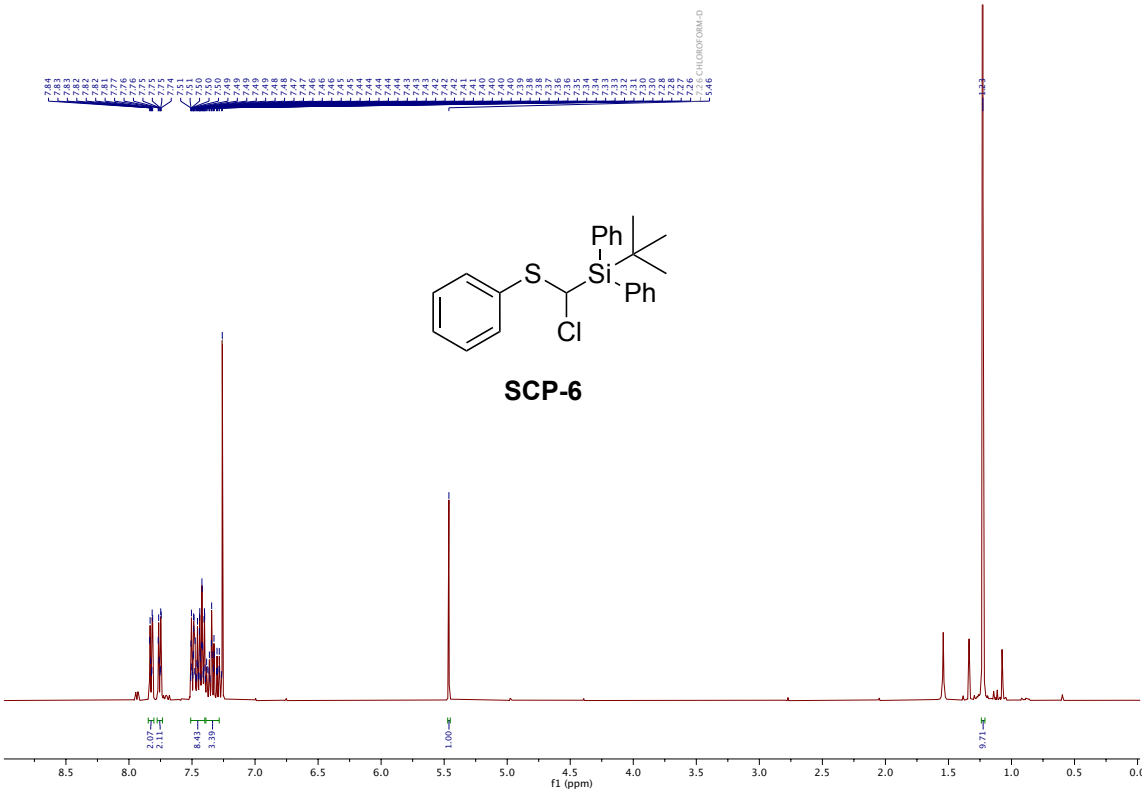
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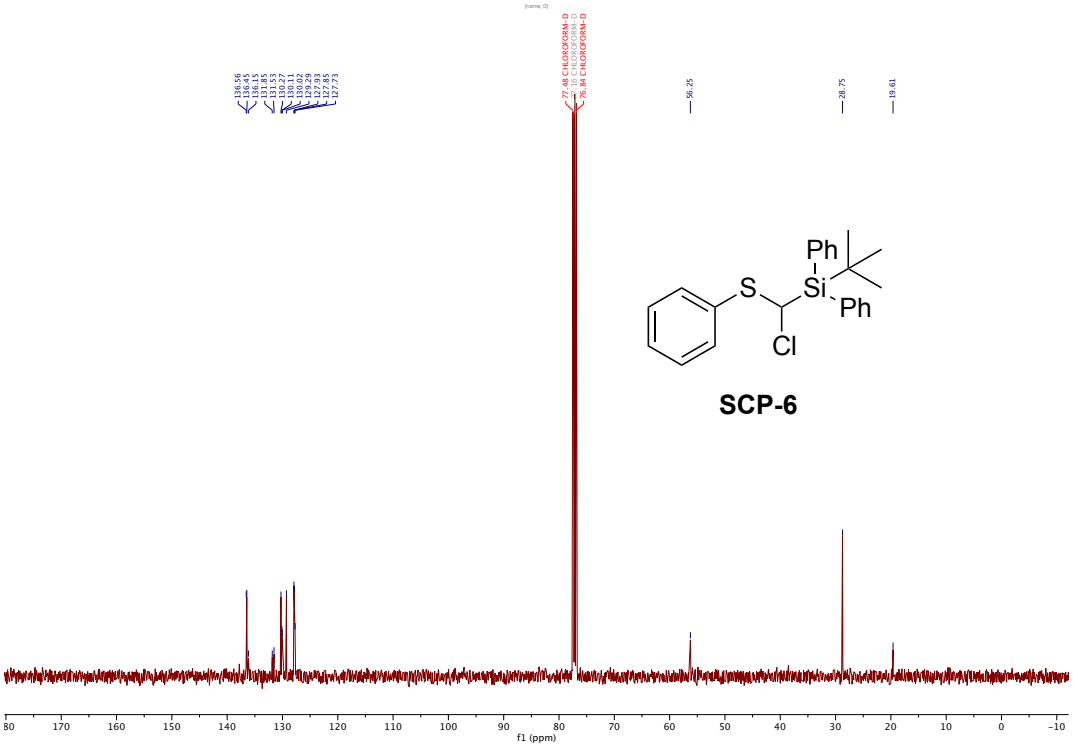
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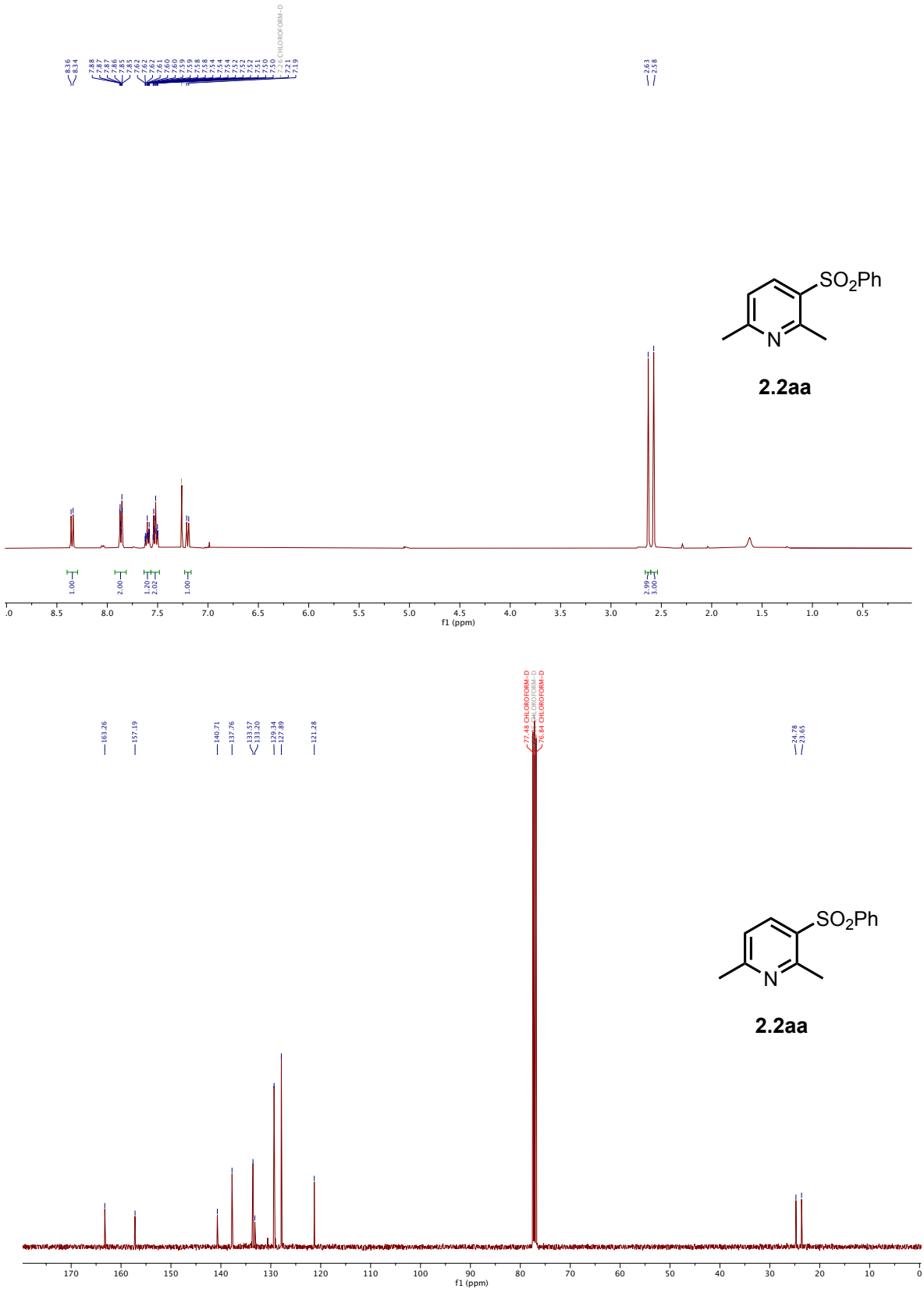


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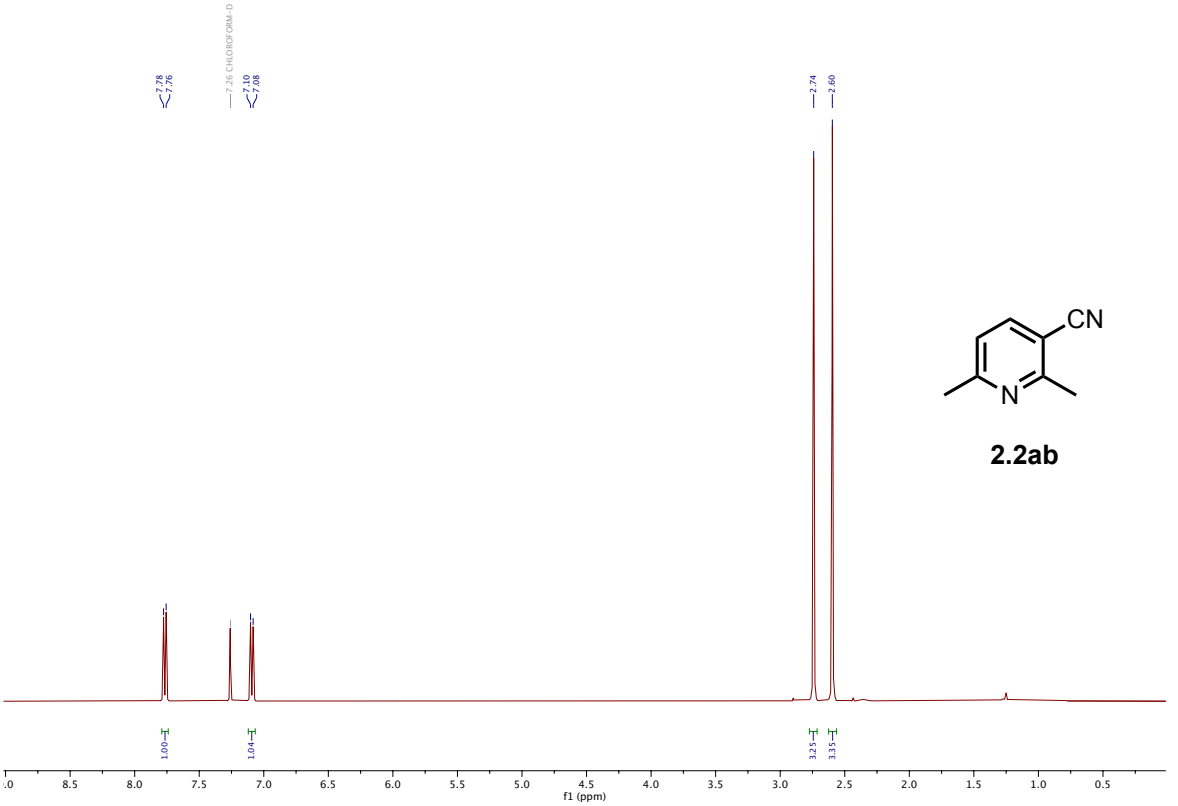




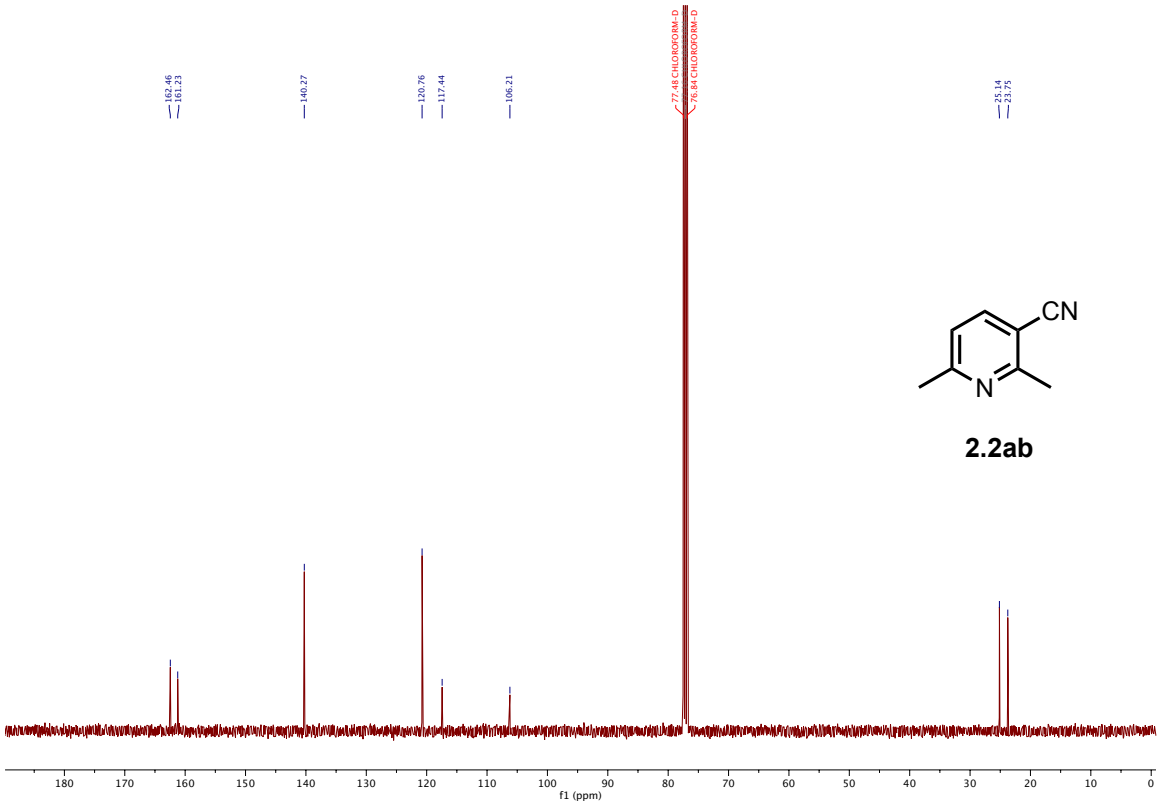
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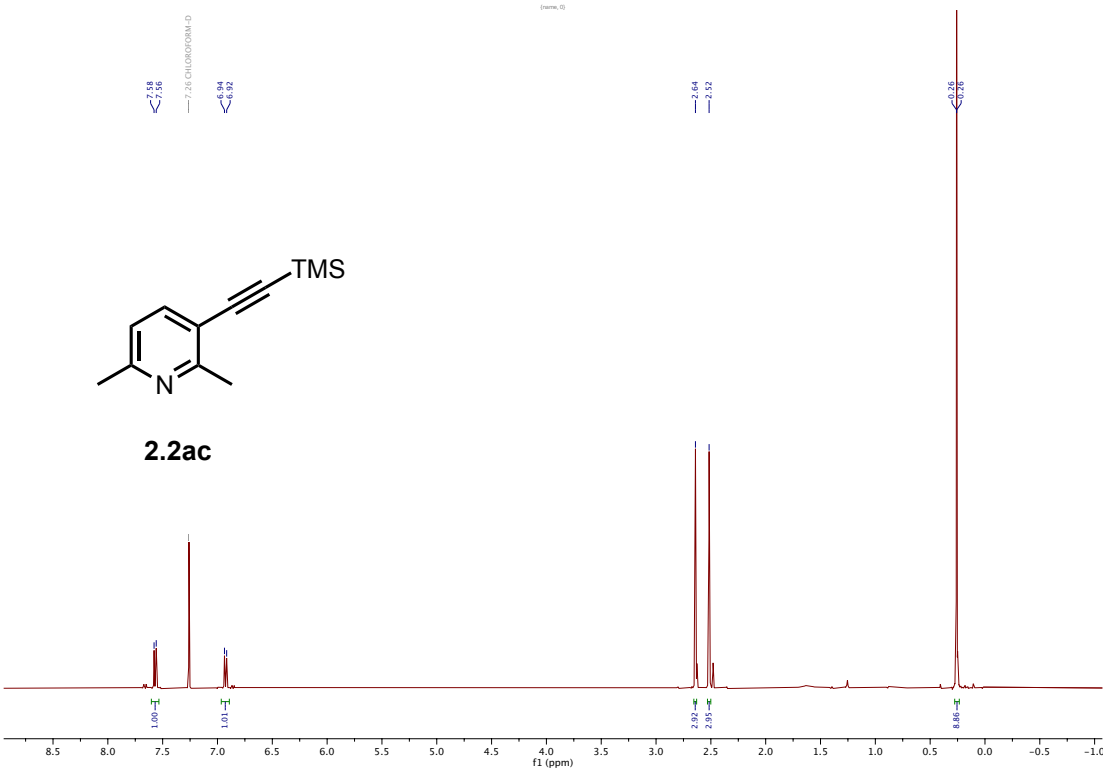


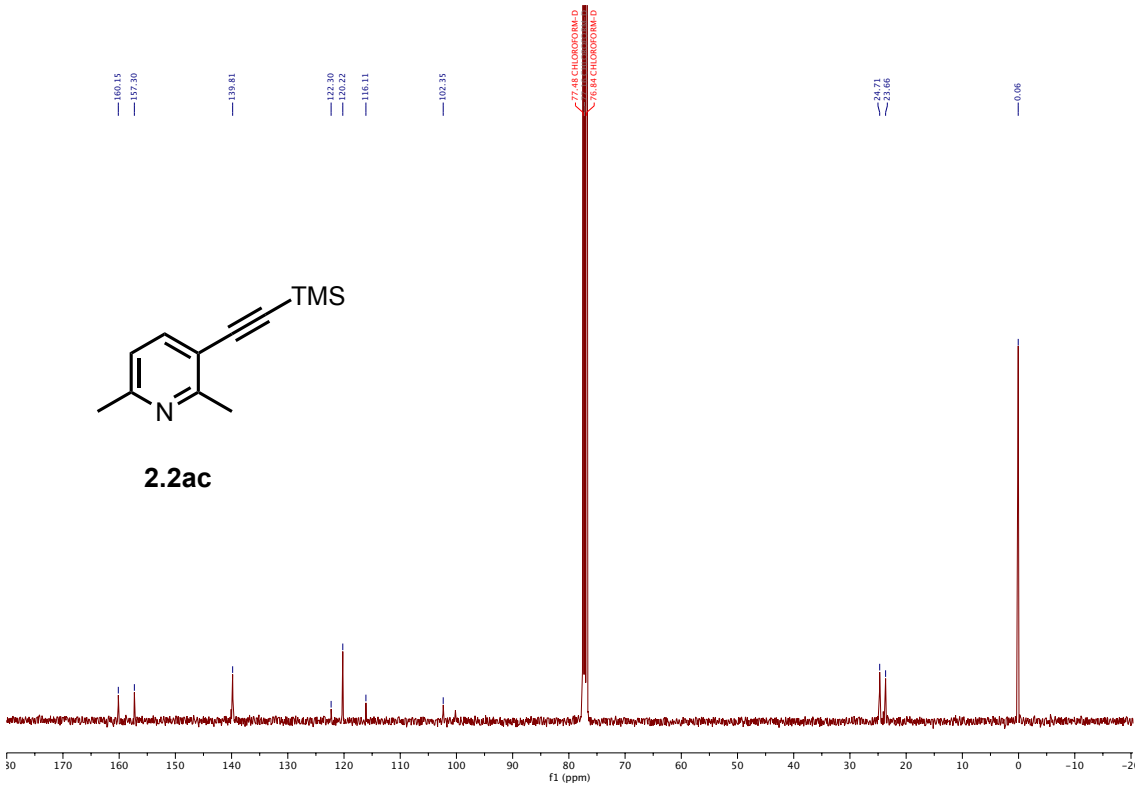
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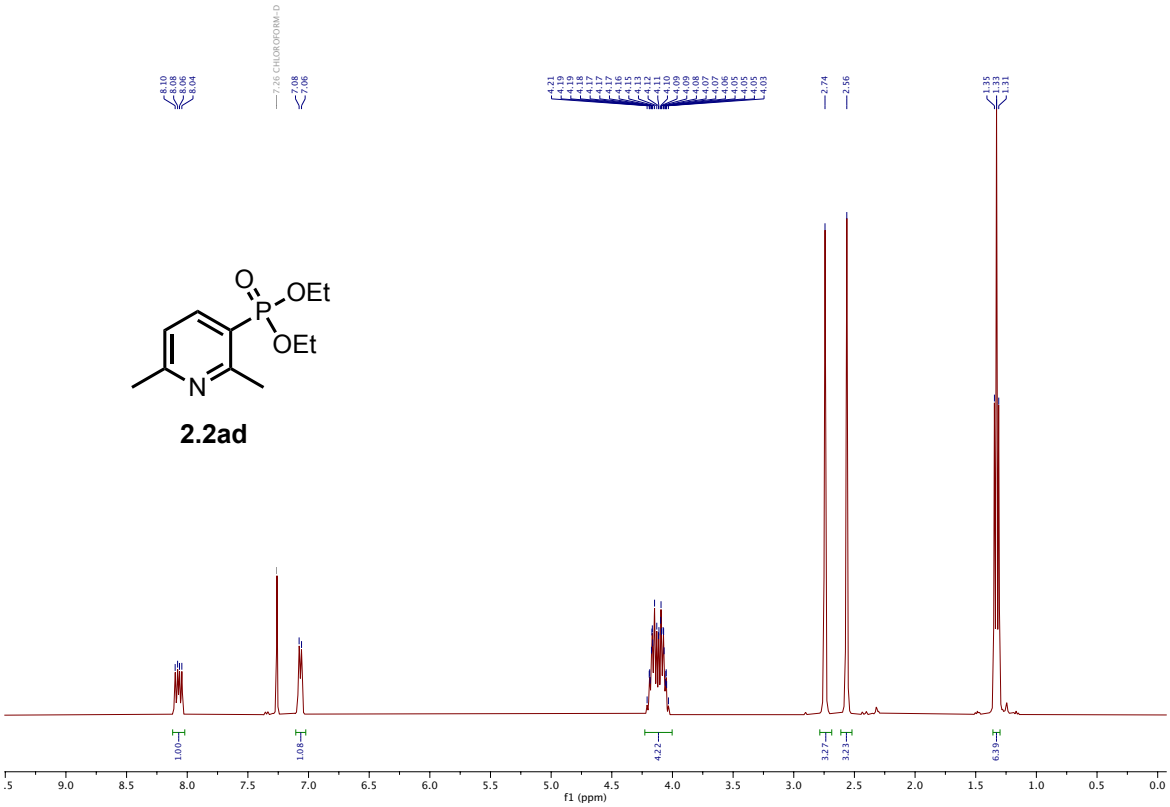
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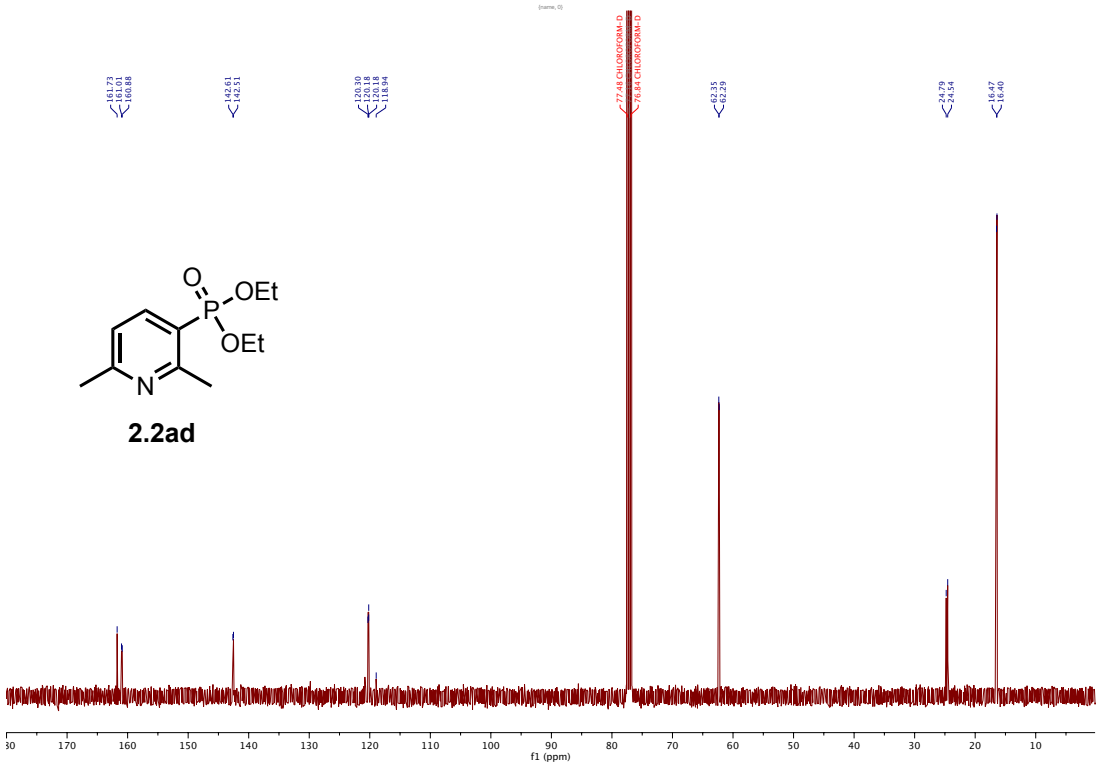
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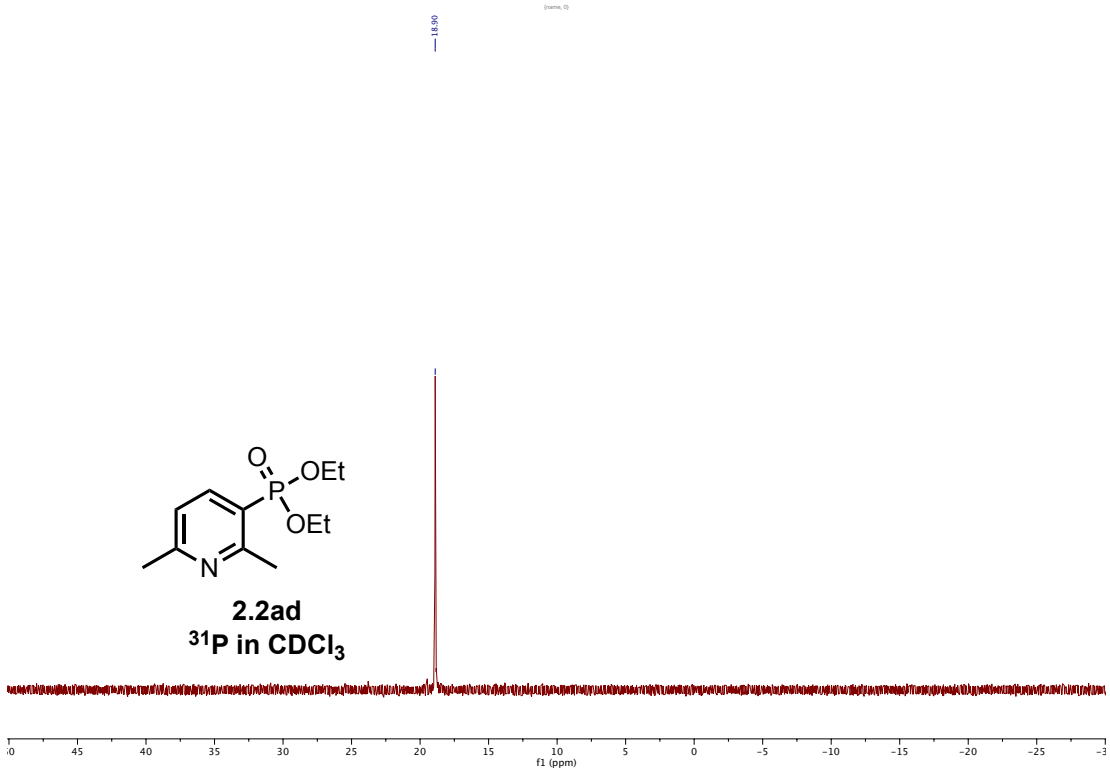


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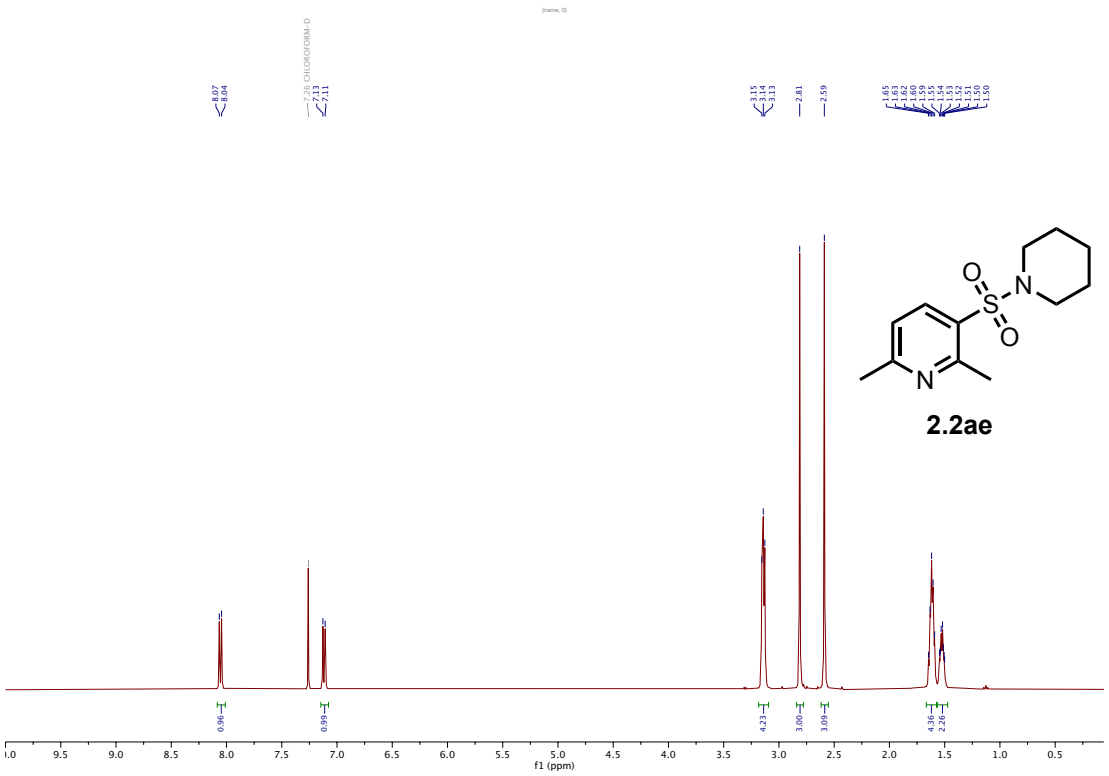


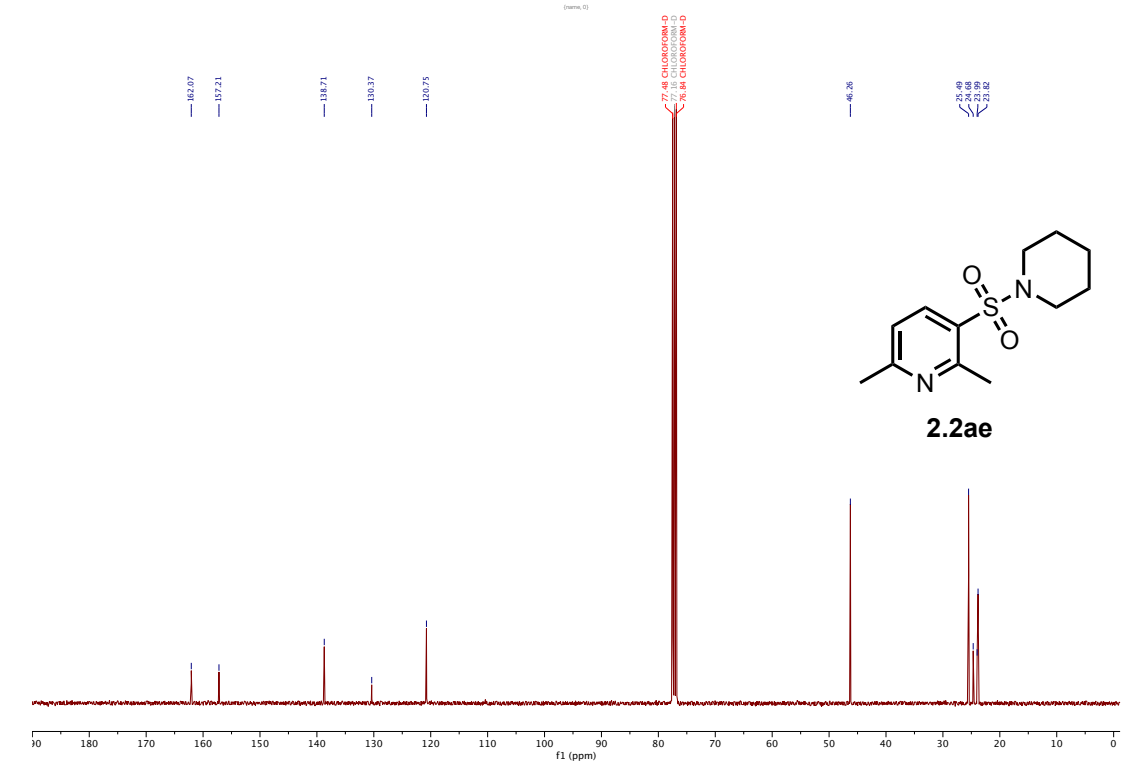


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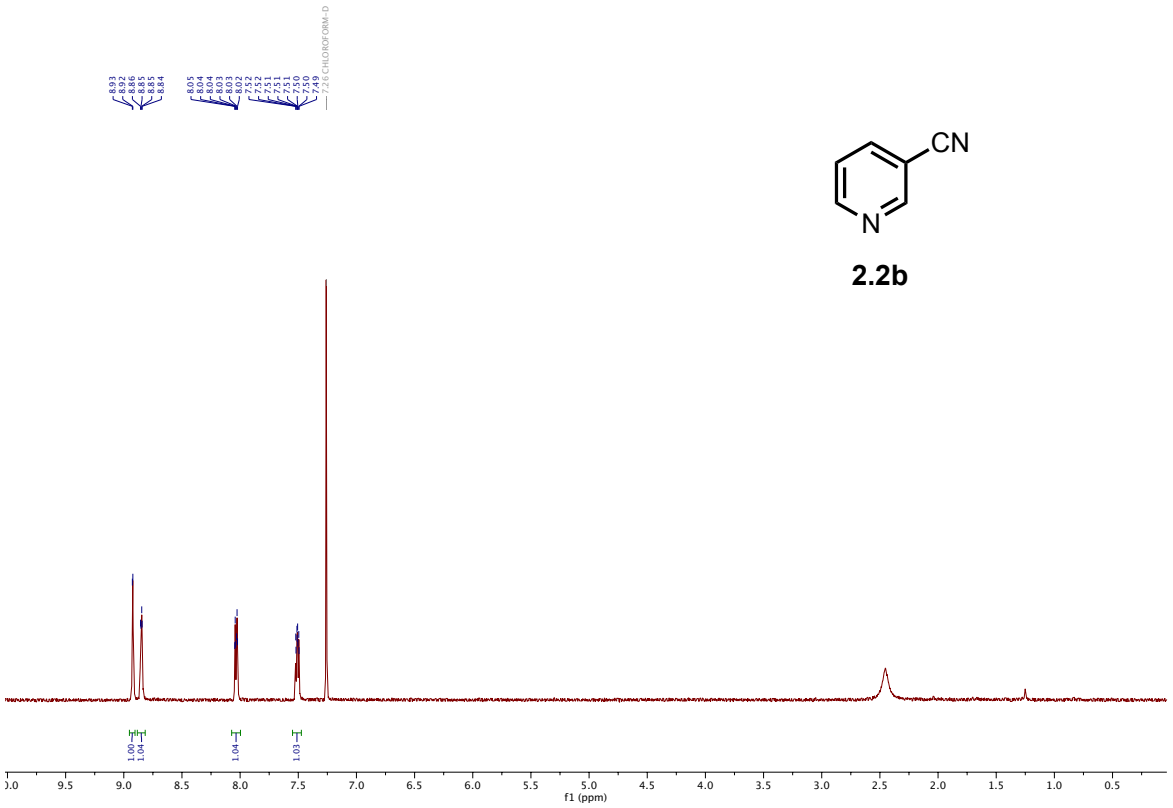


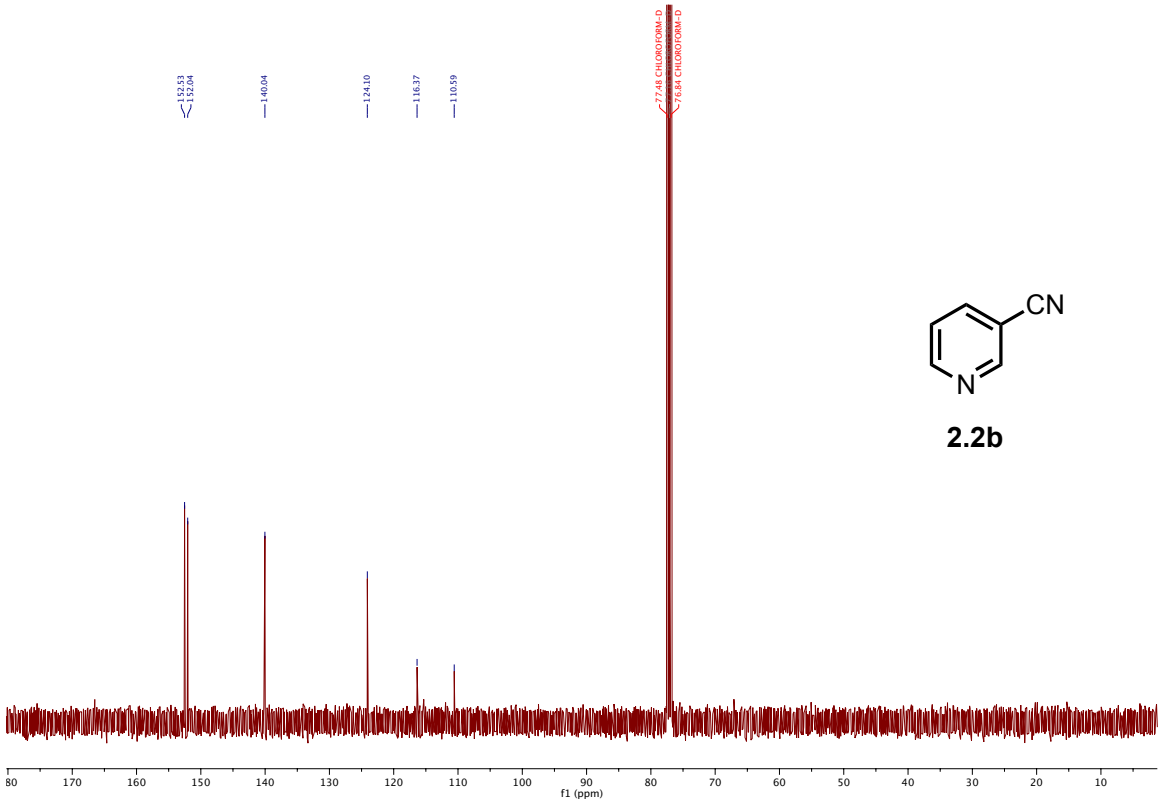
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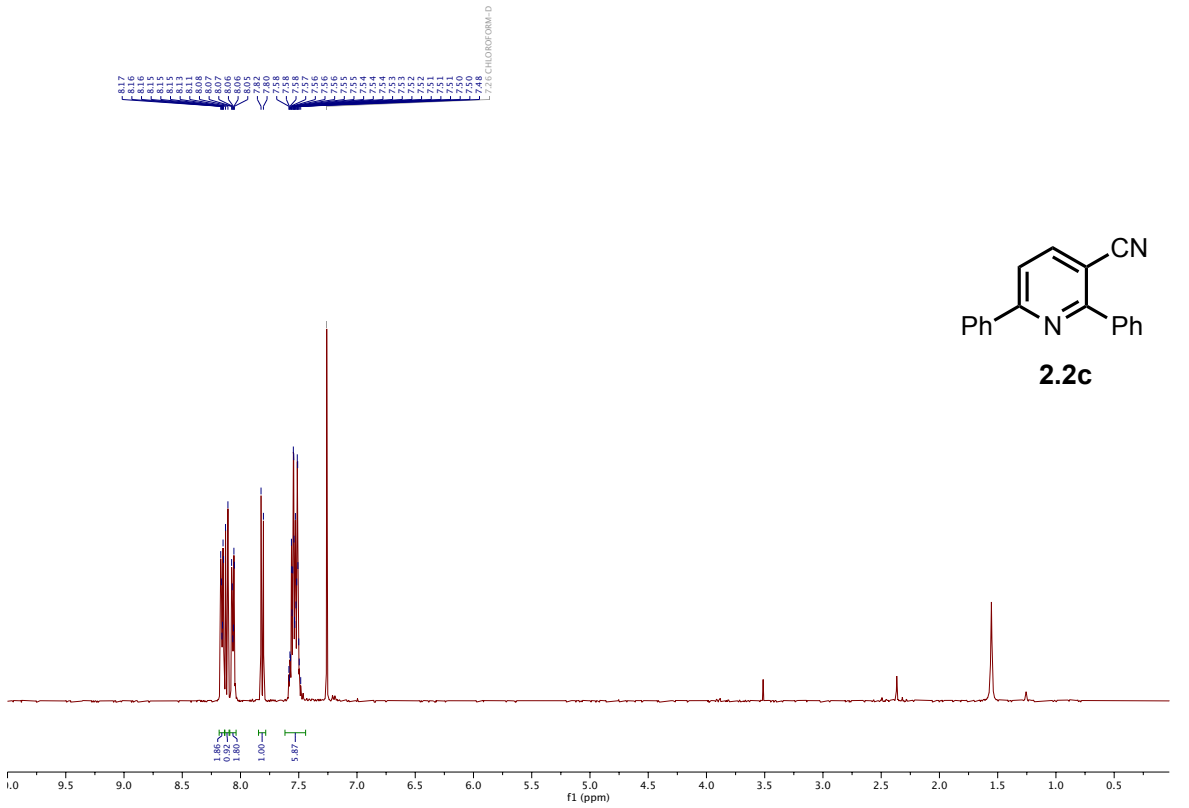


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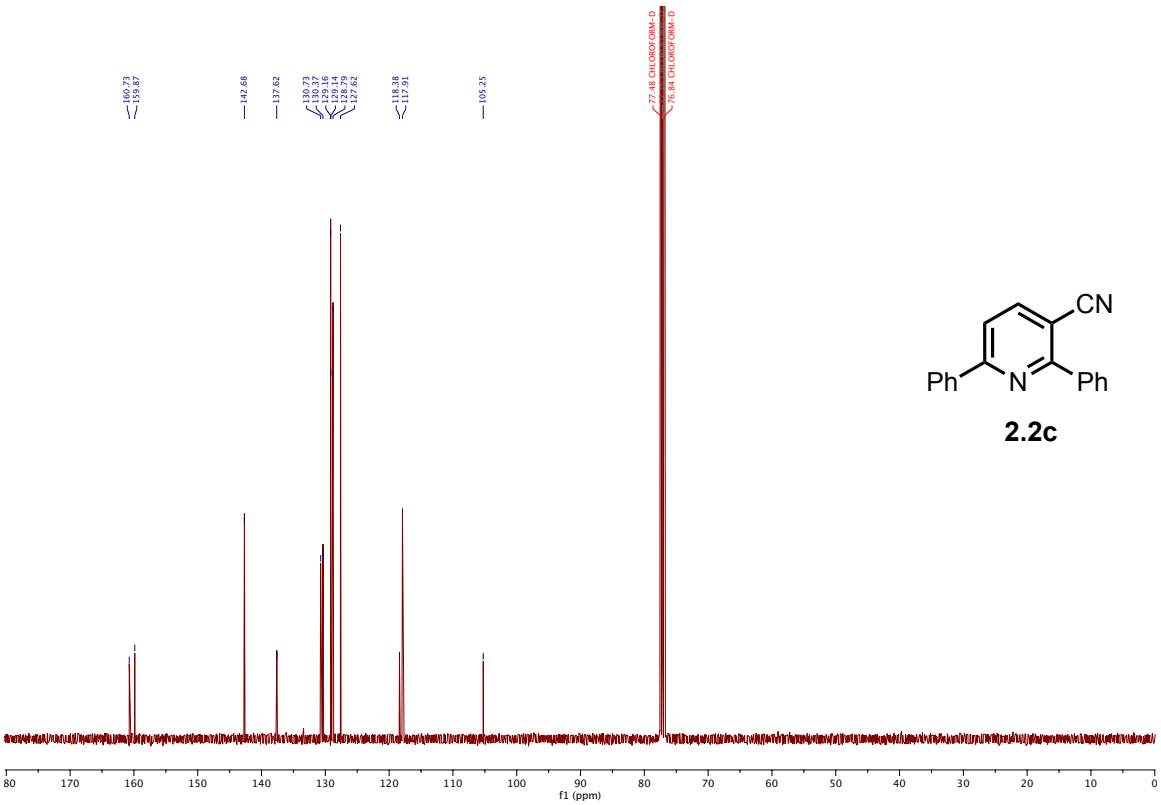




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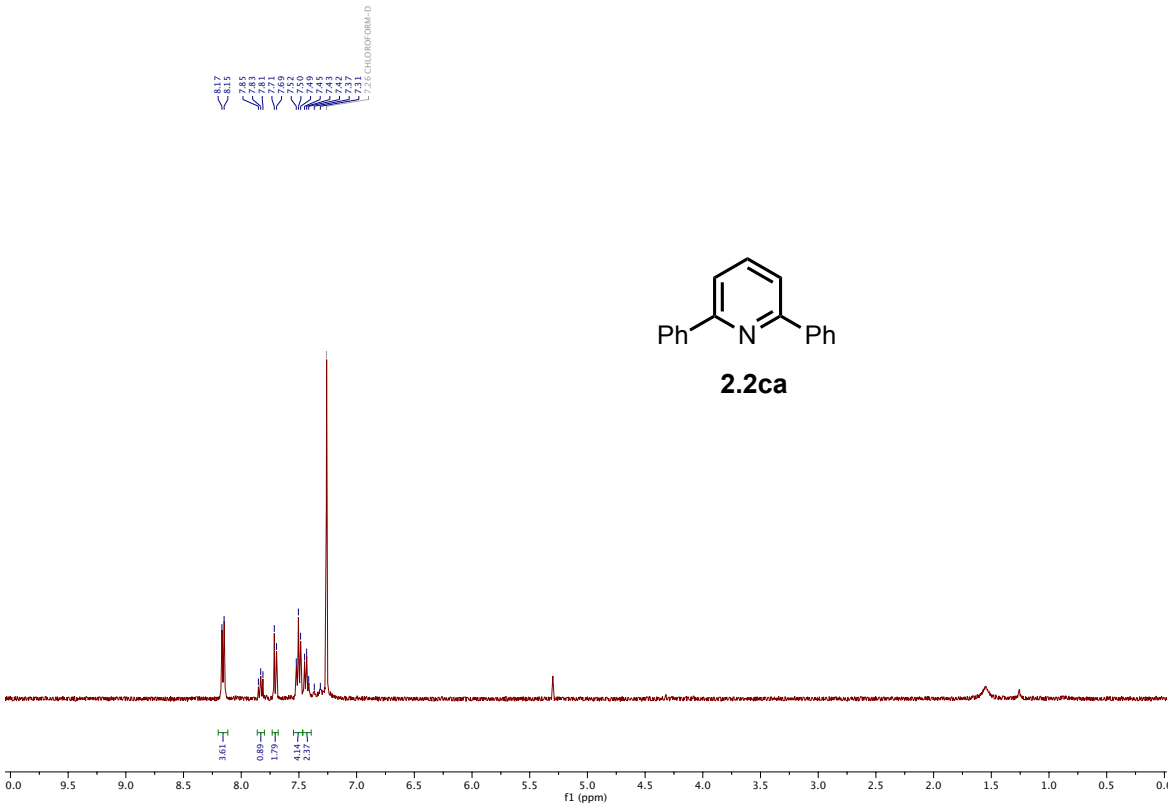


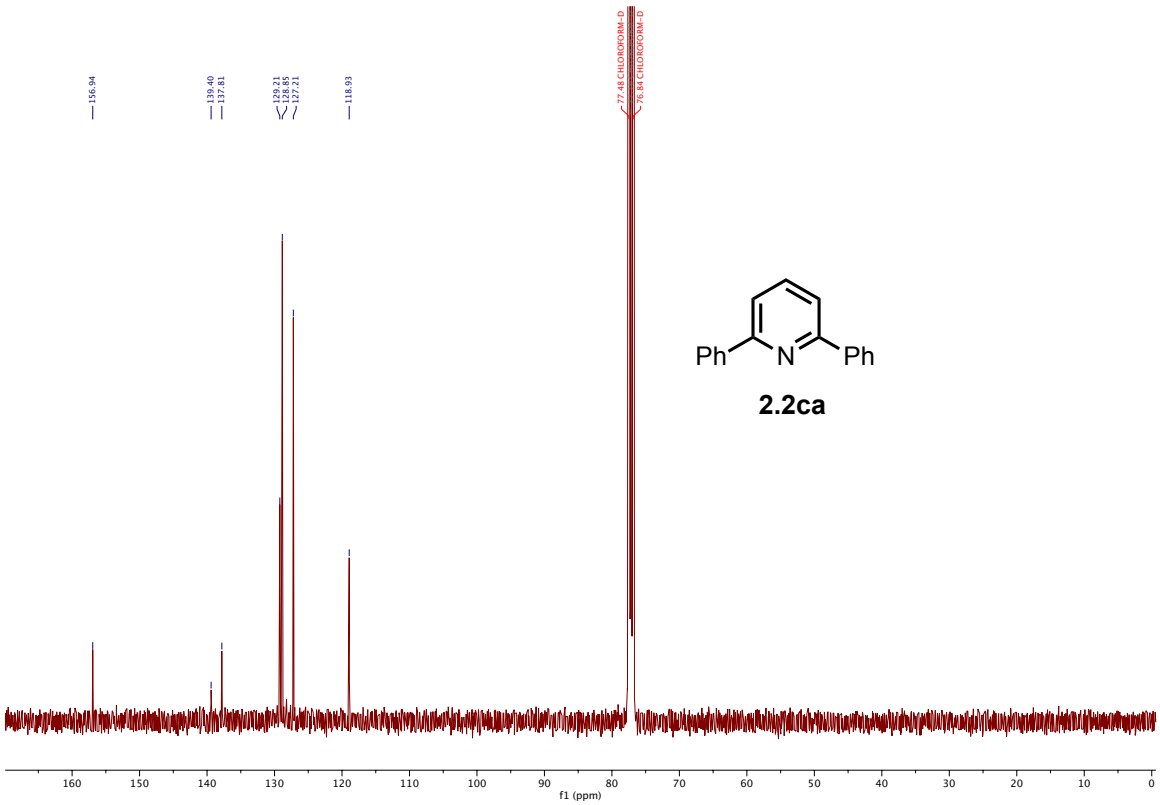
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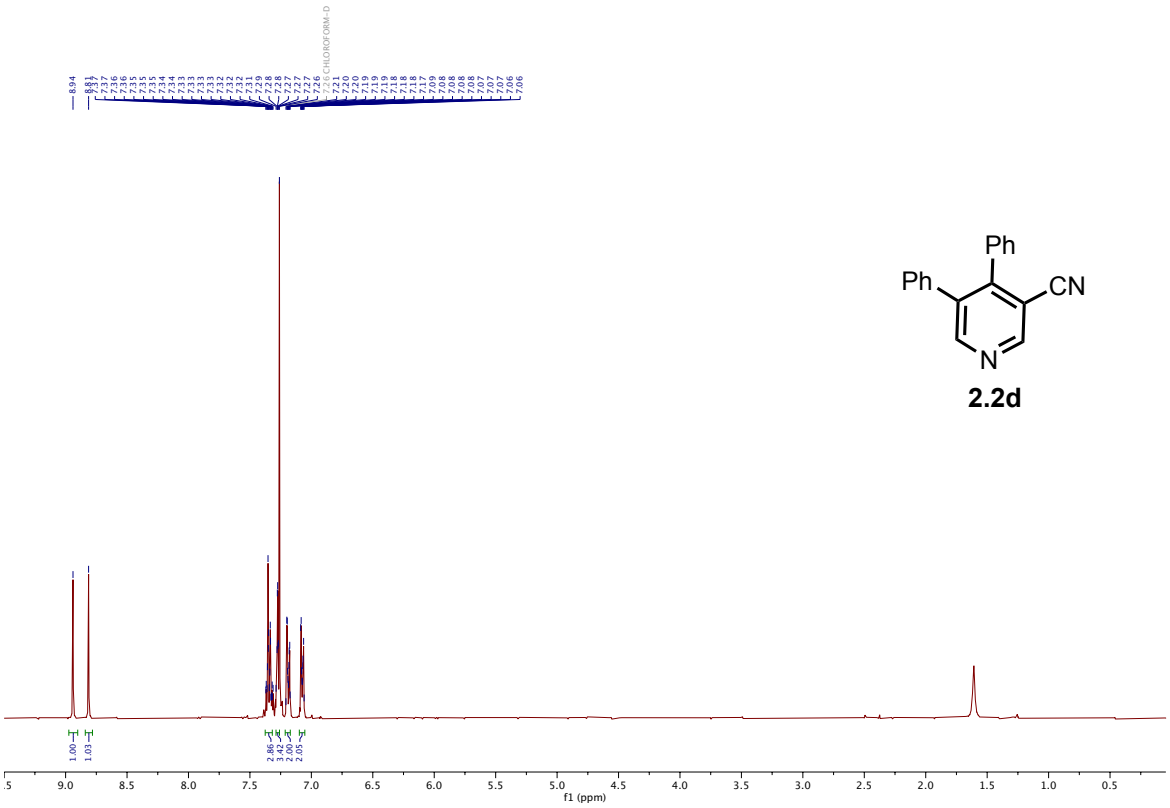
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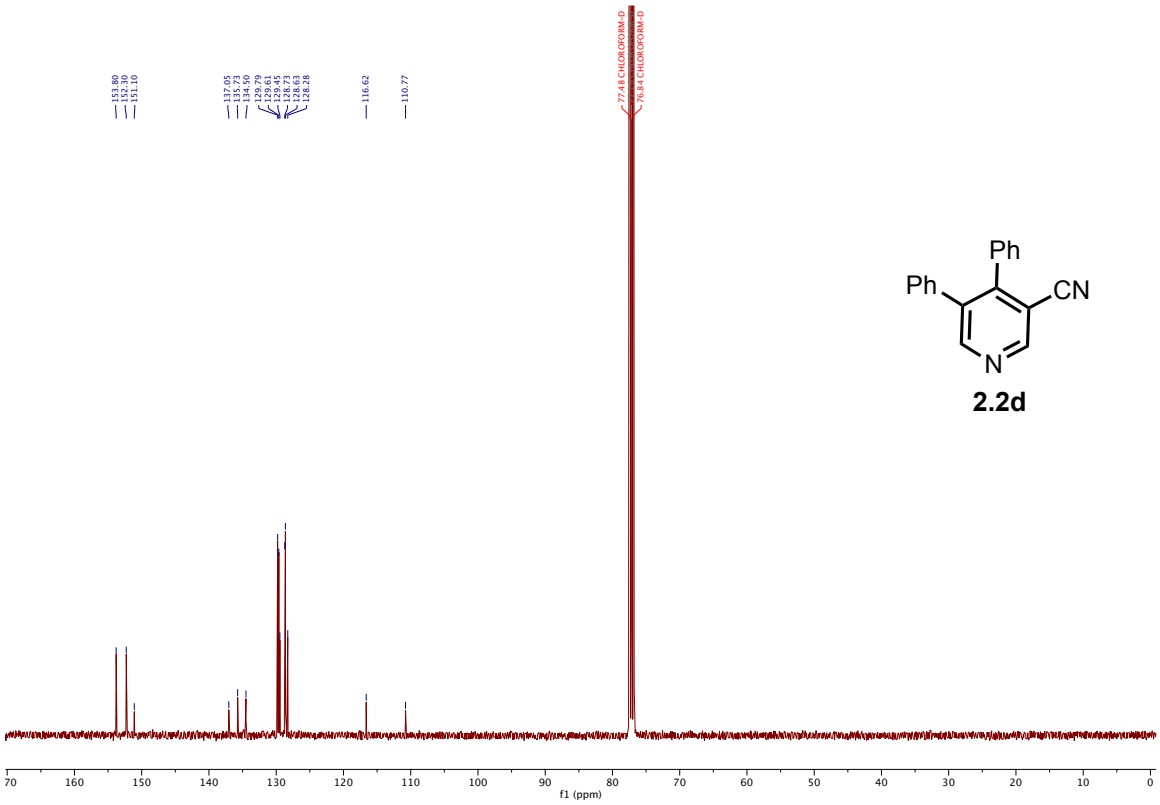




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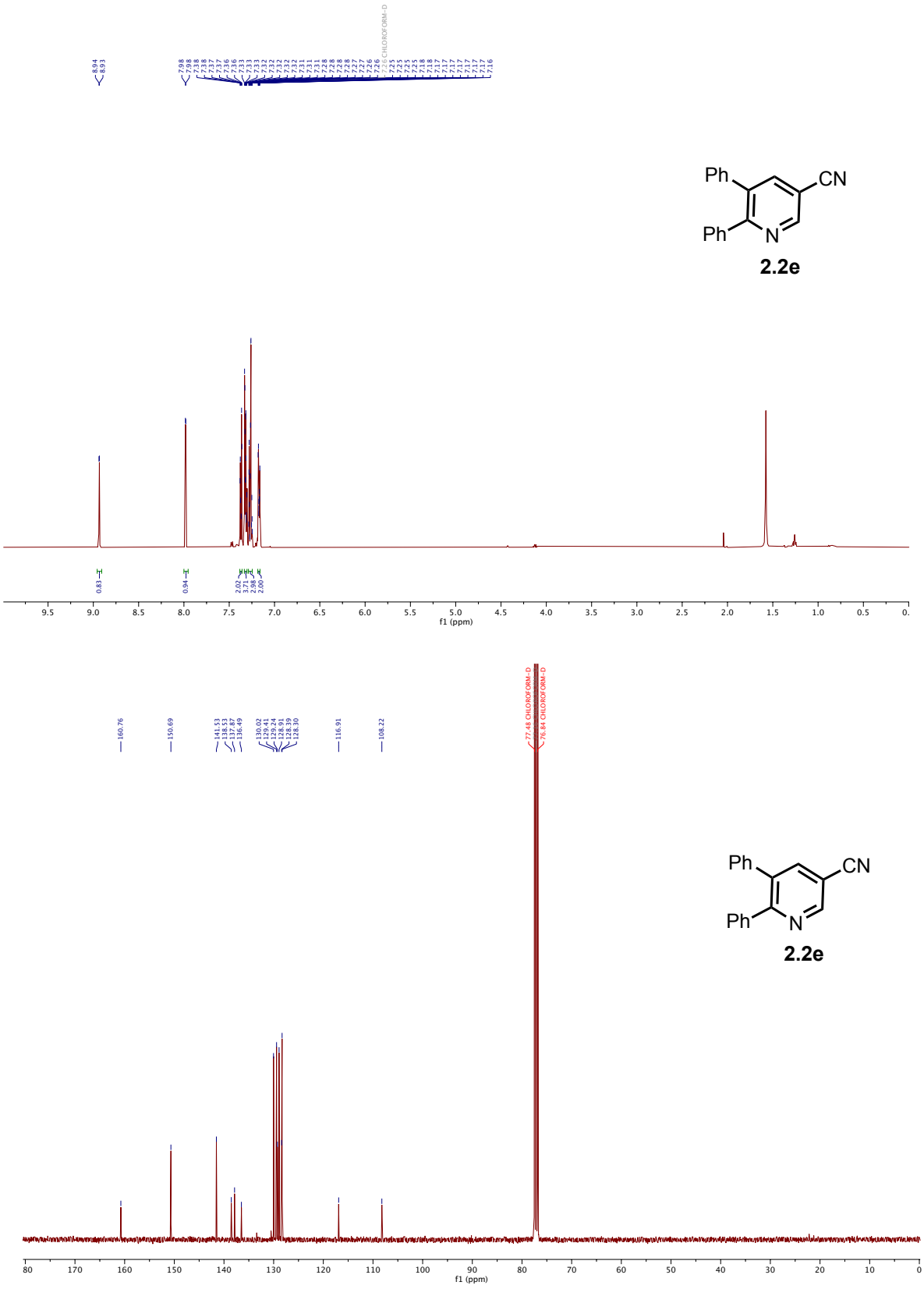


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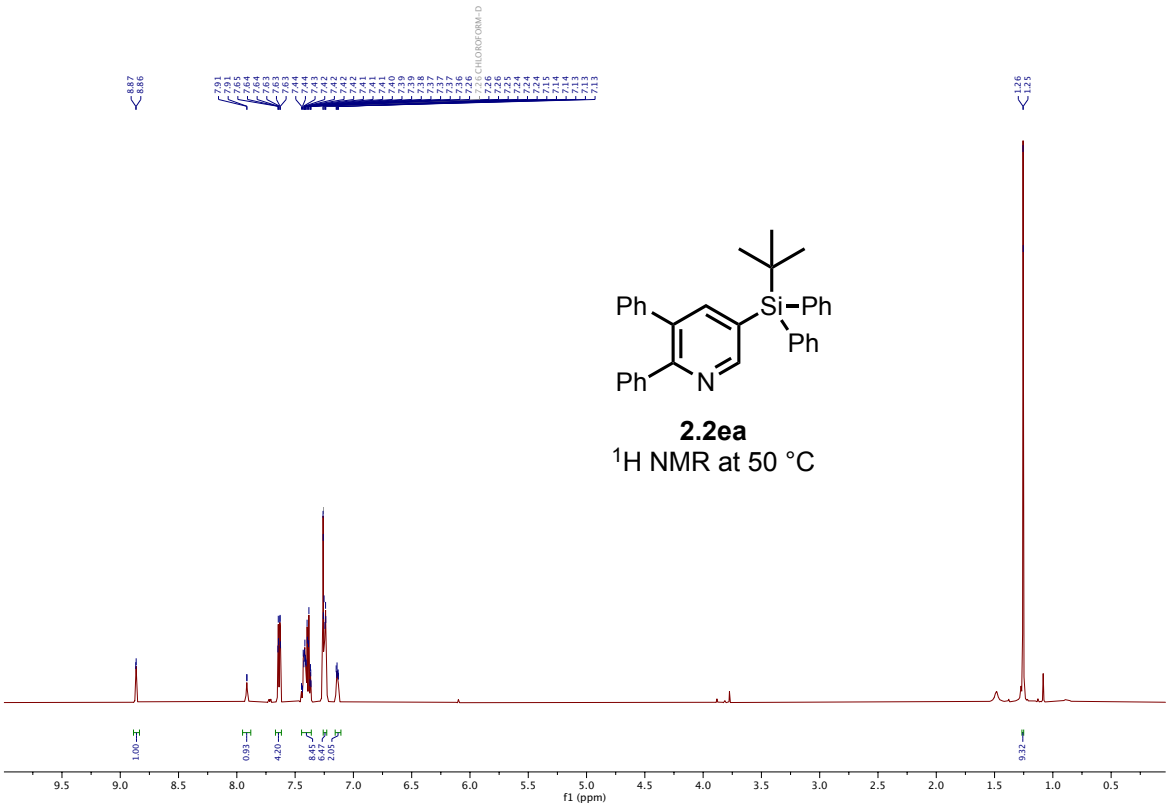


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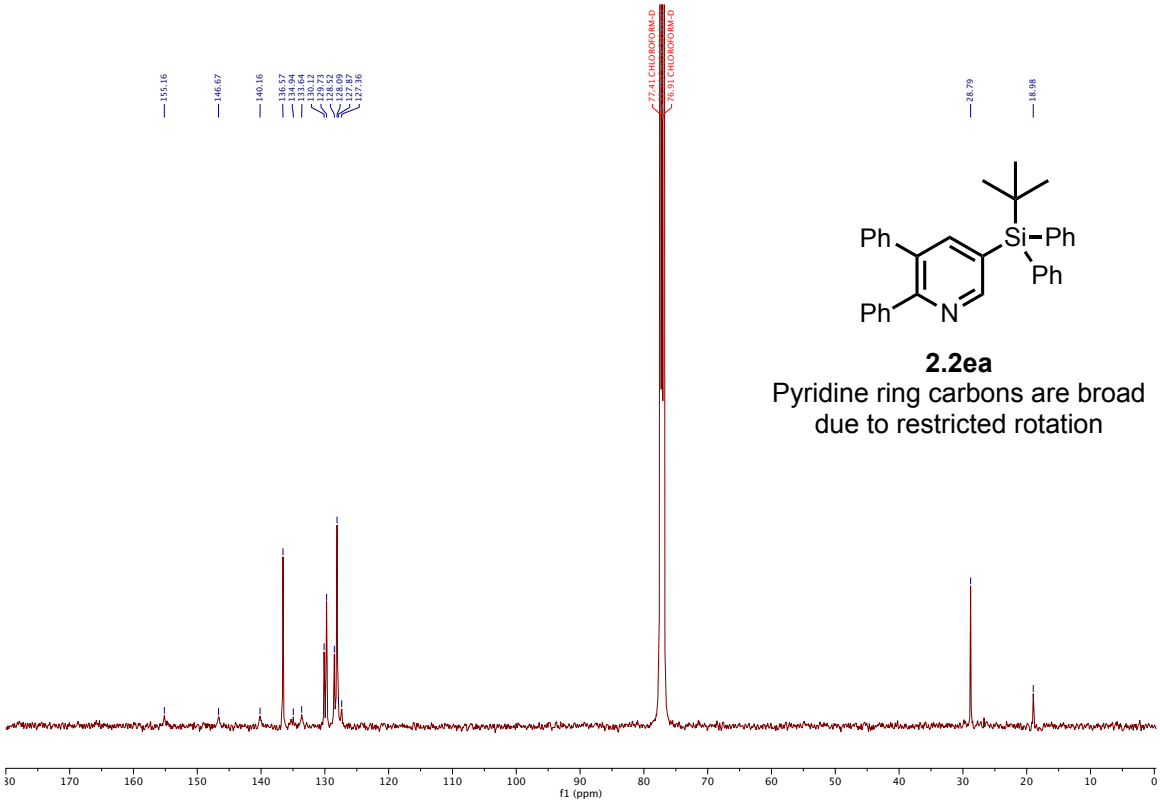
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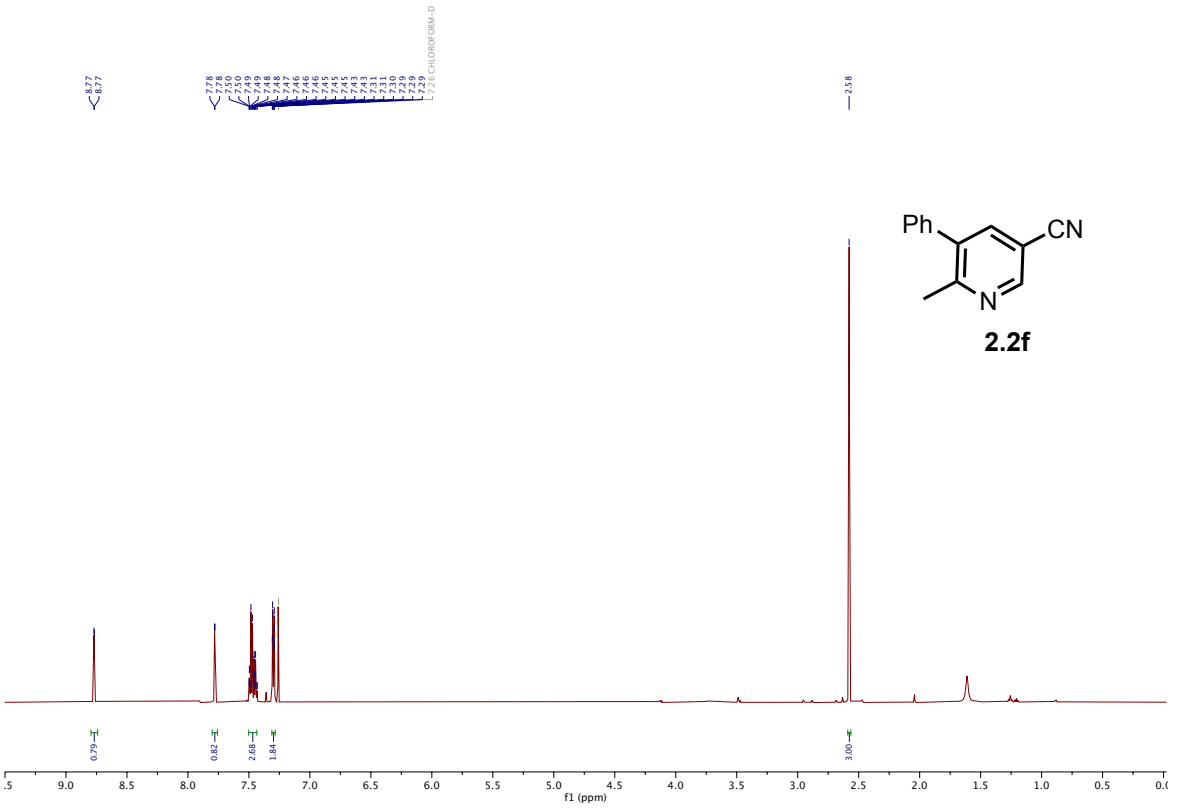


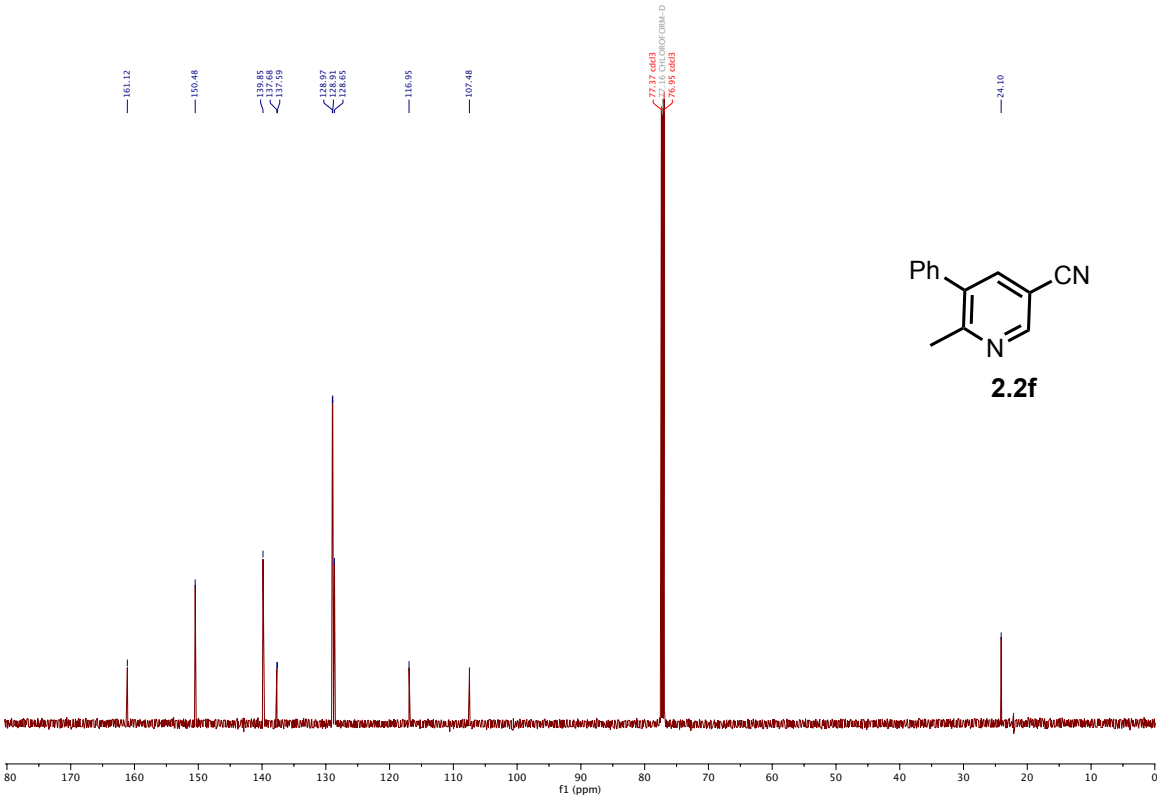
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^{1}H NMR at 50 °C



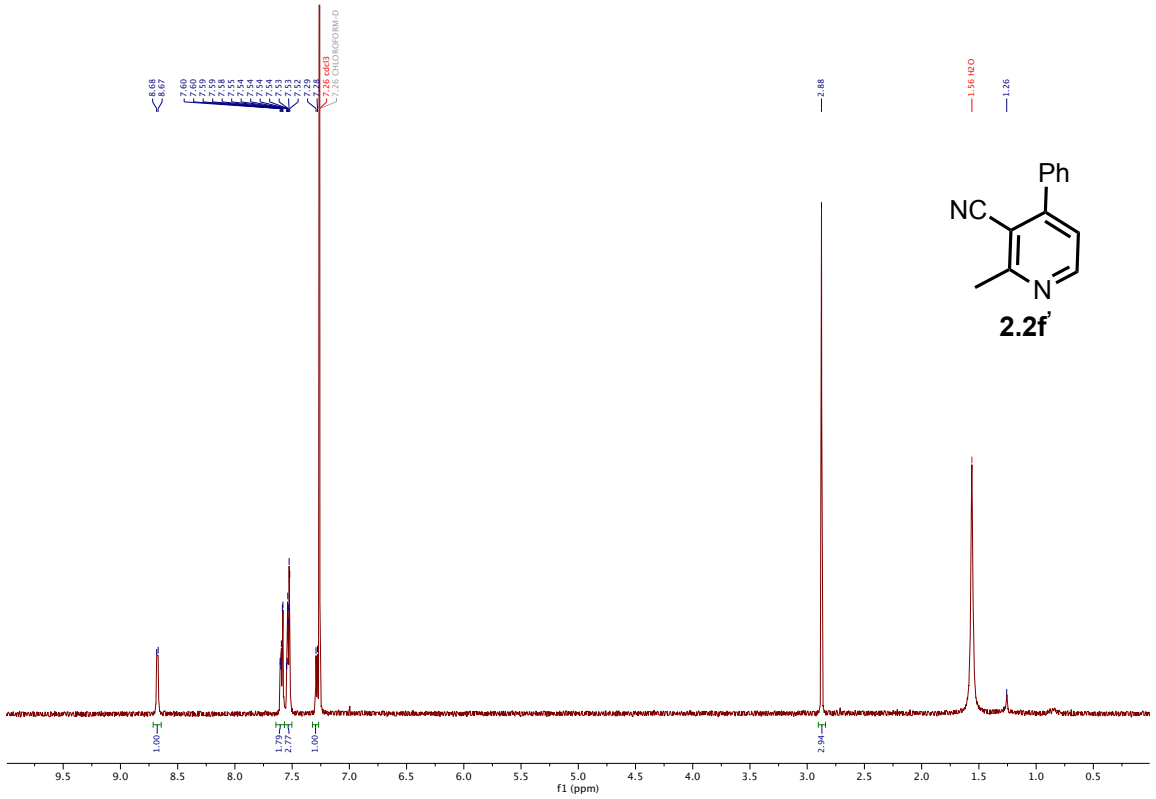
2.2ea
Pyridine ring carbons are broad due to restricted rotation

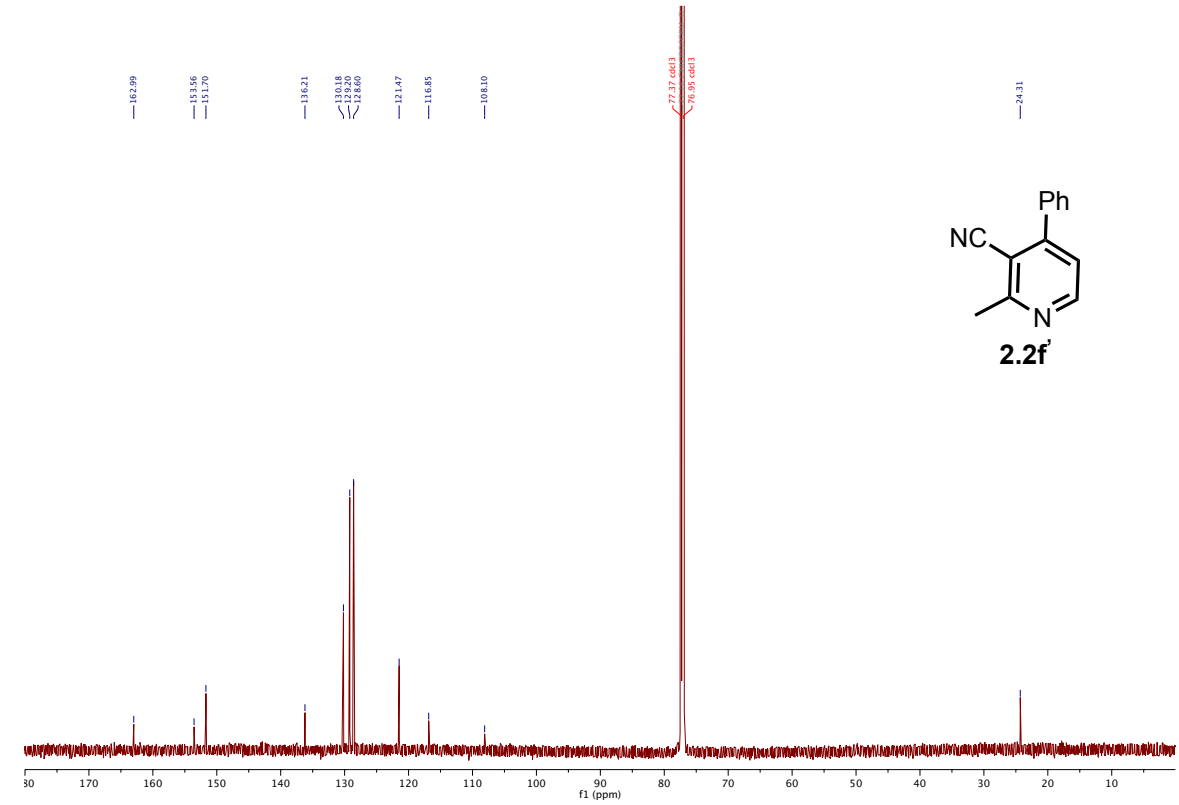
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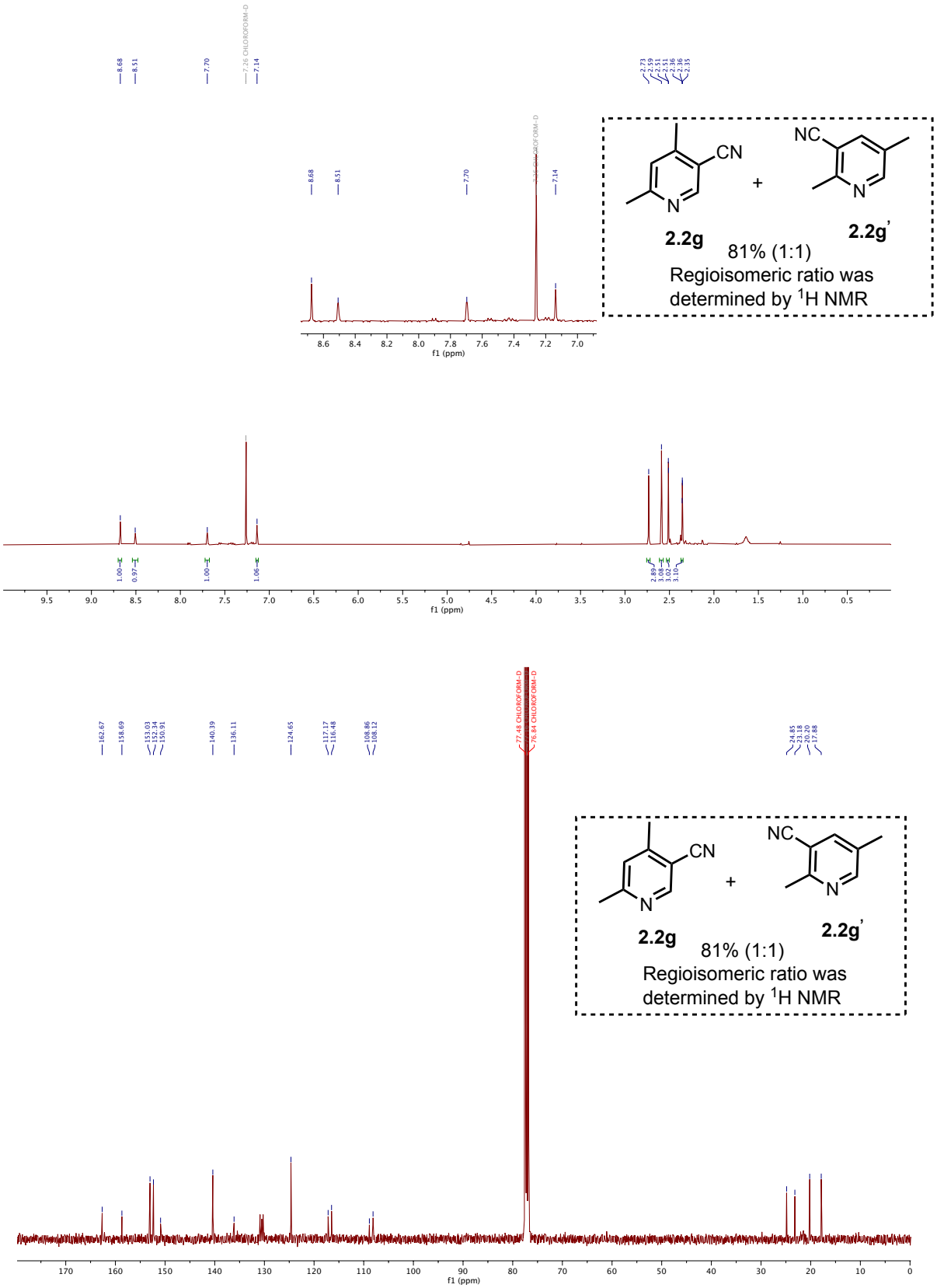


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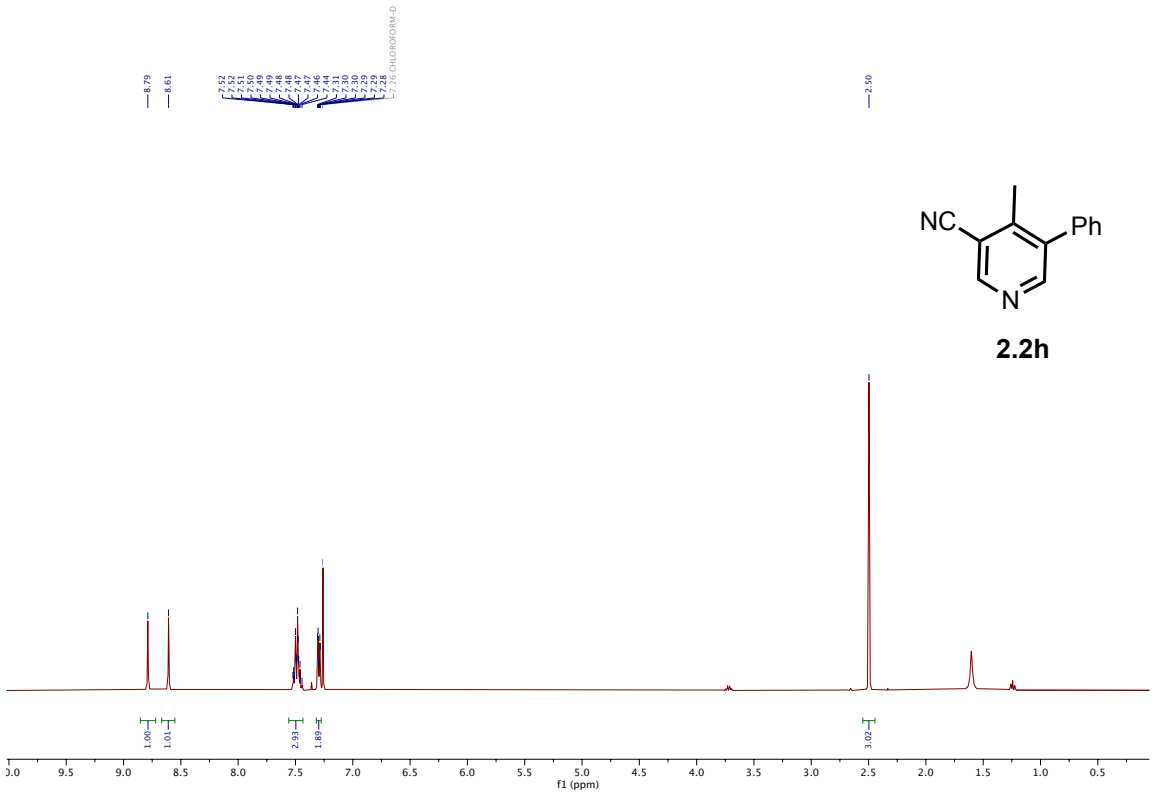


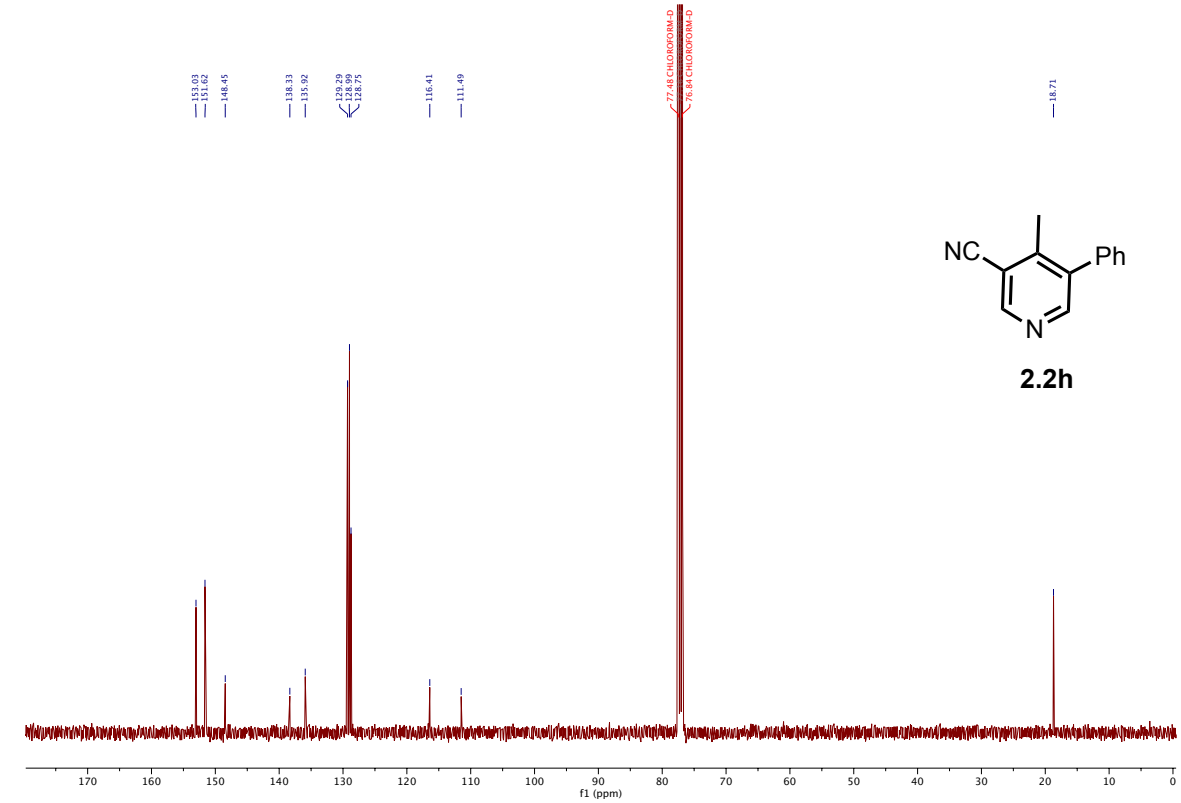


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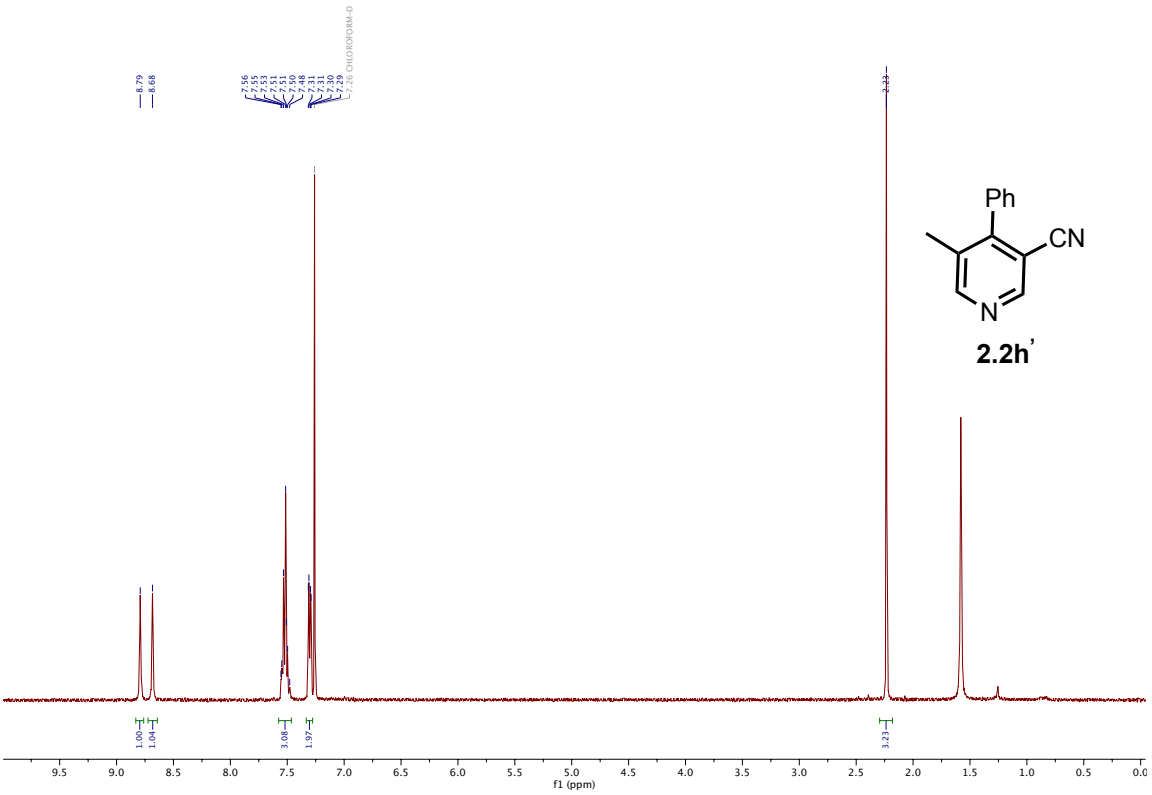


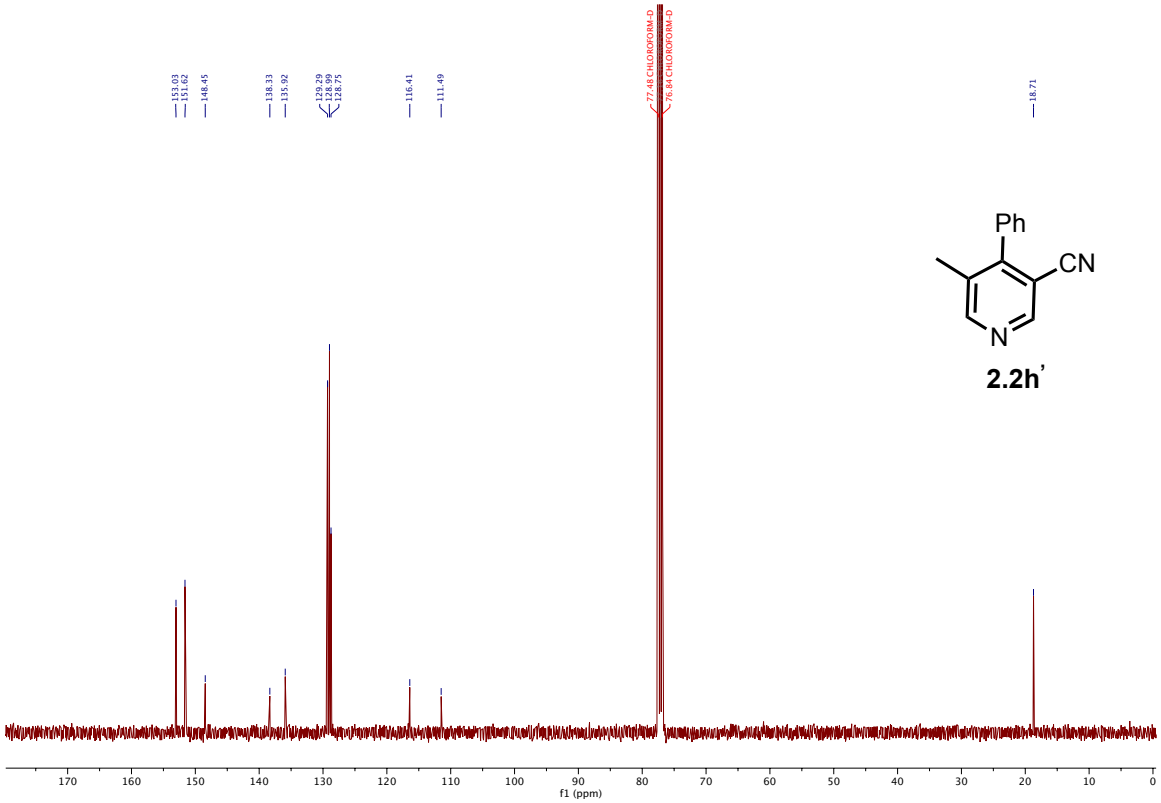
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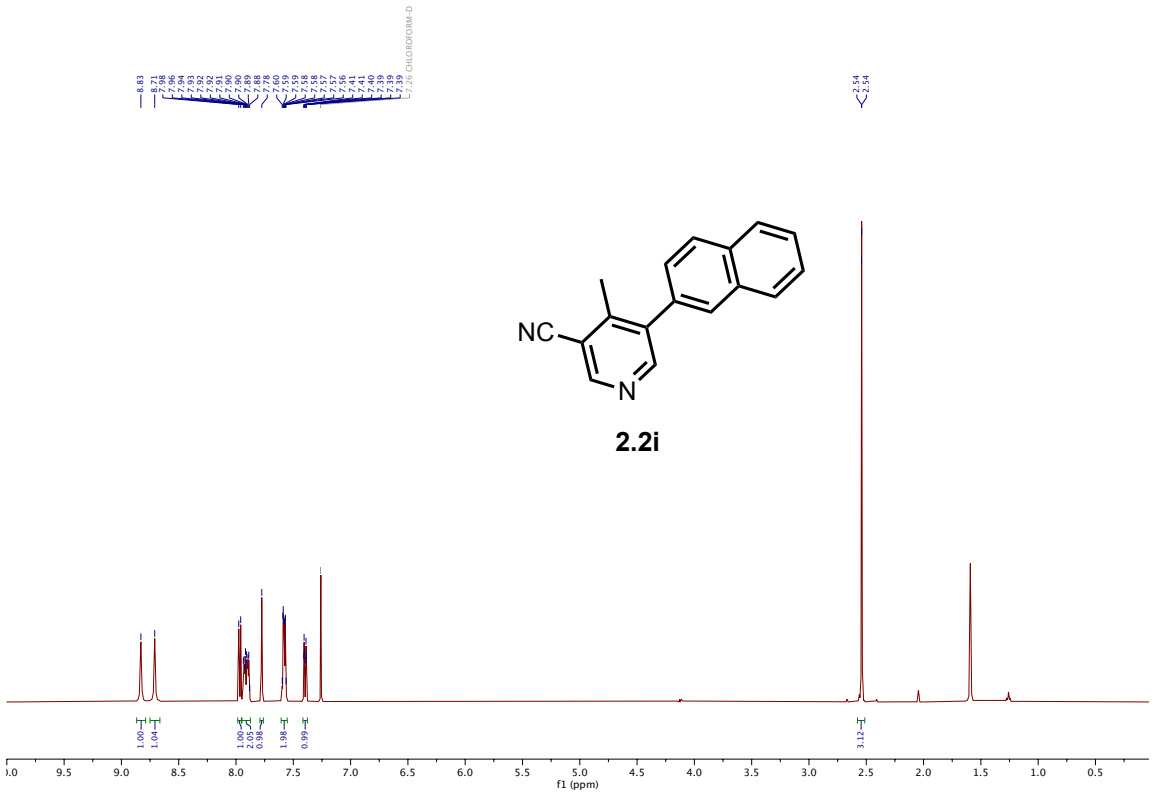


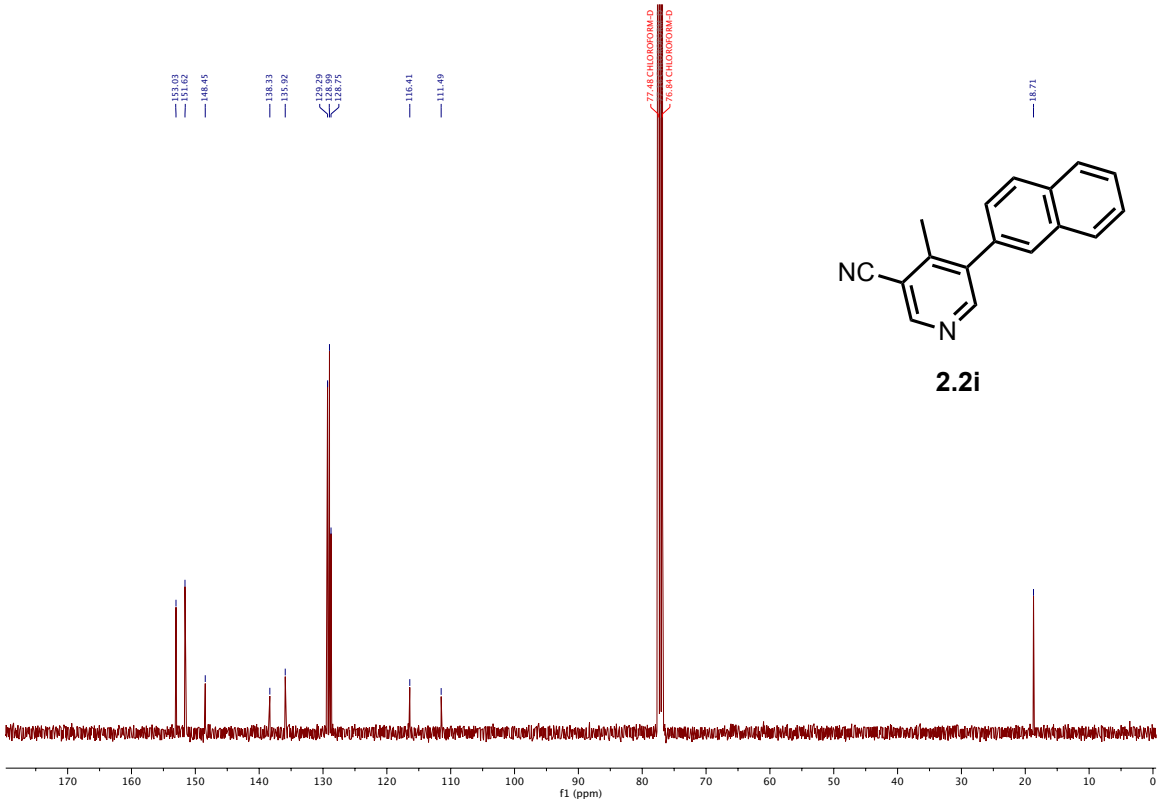
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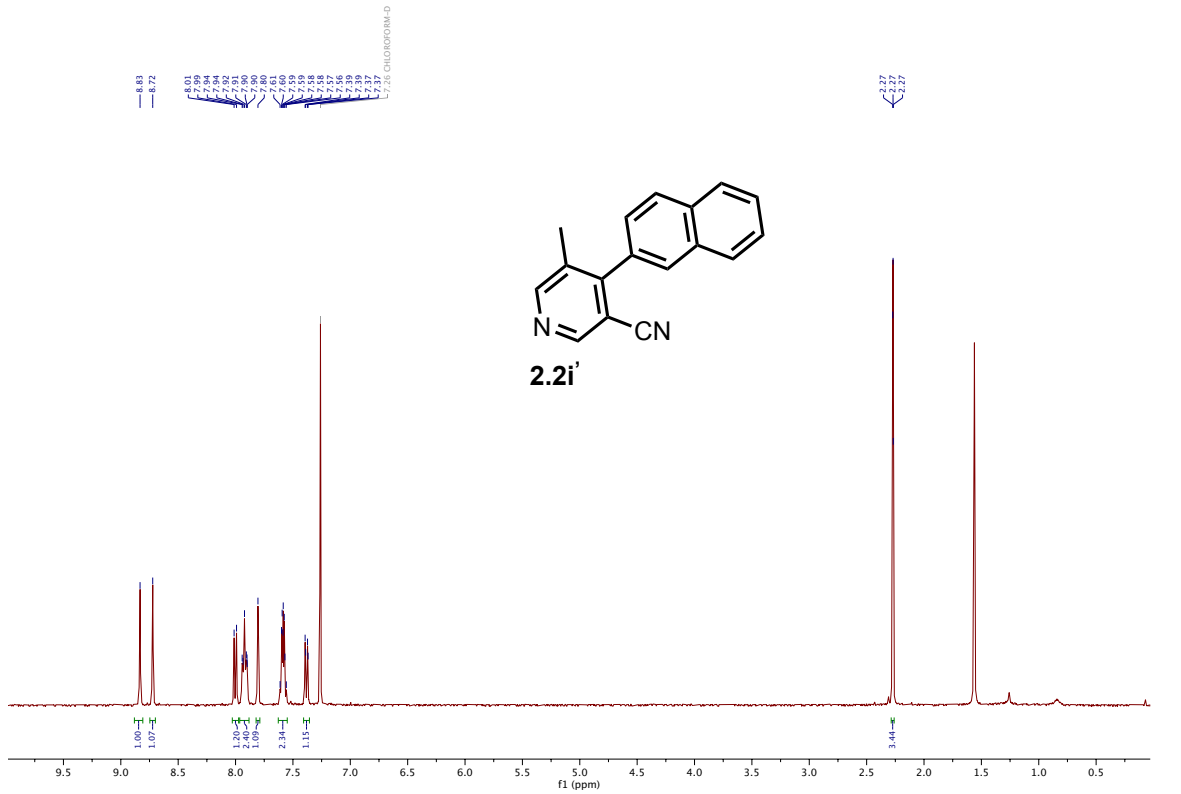


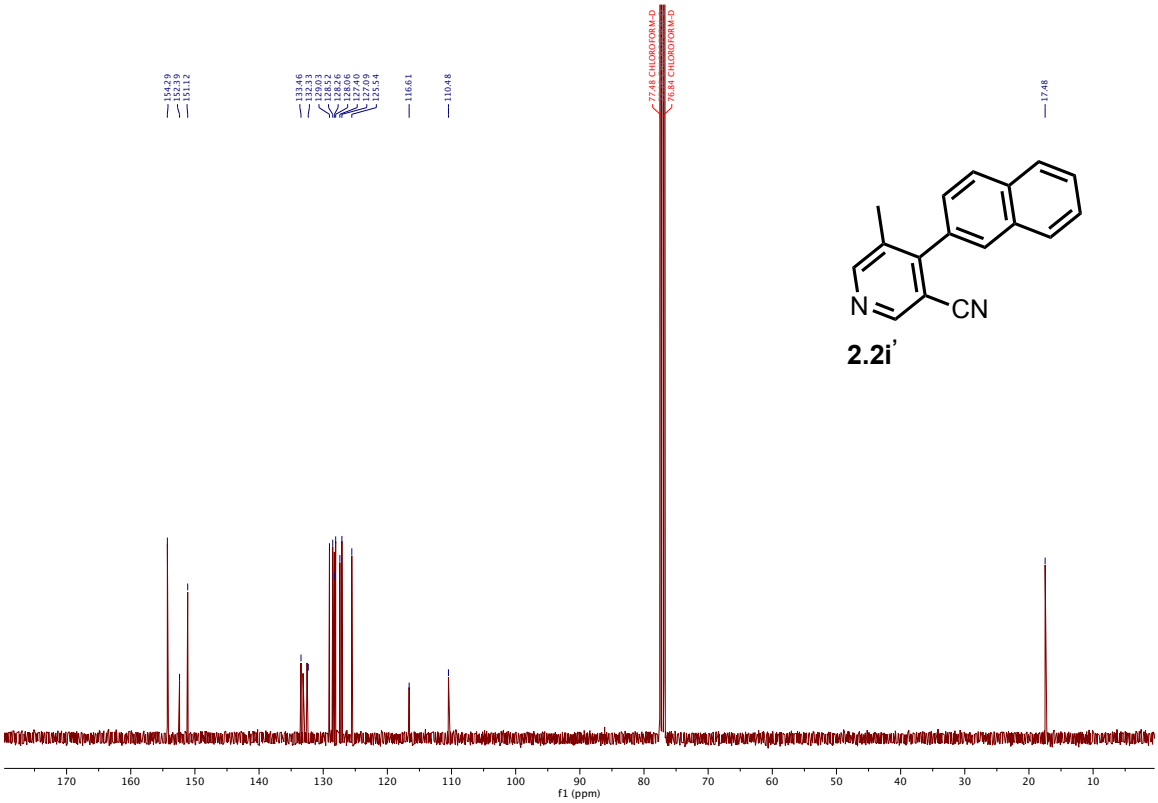
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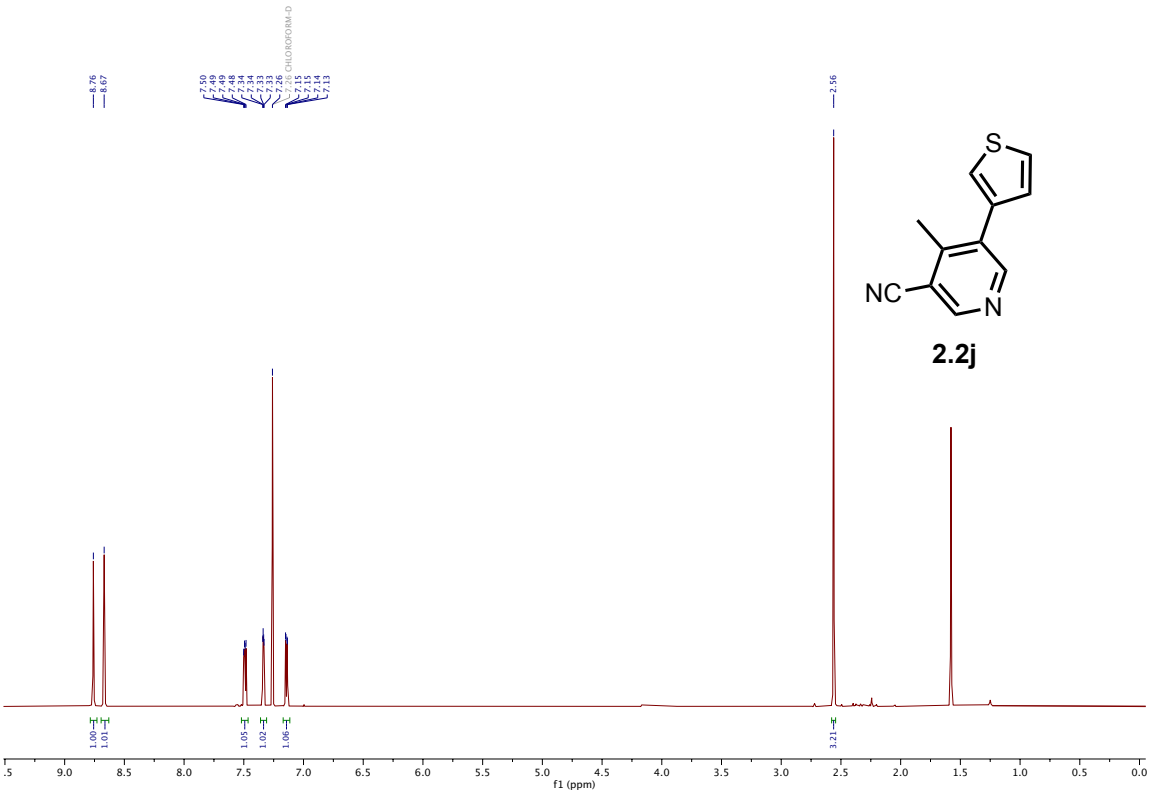


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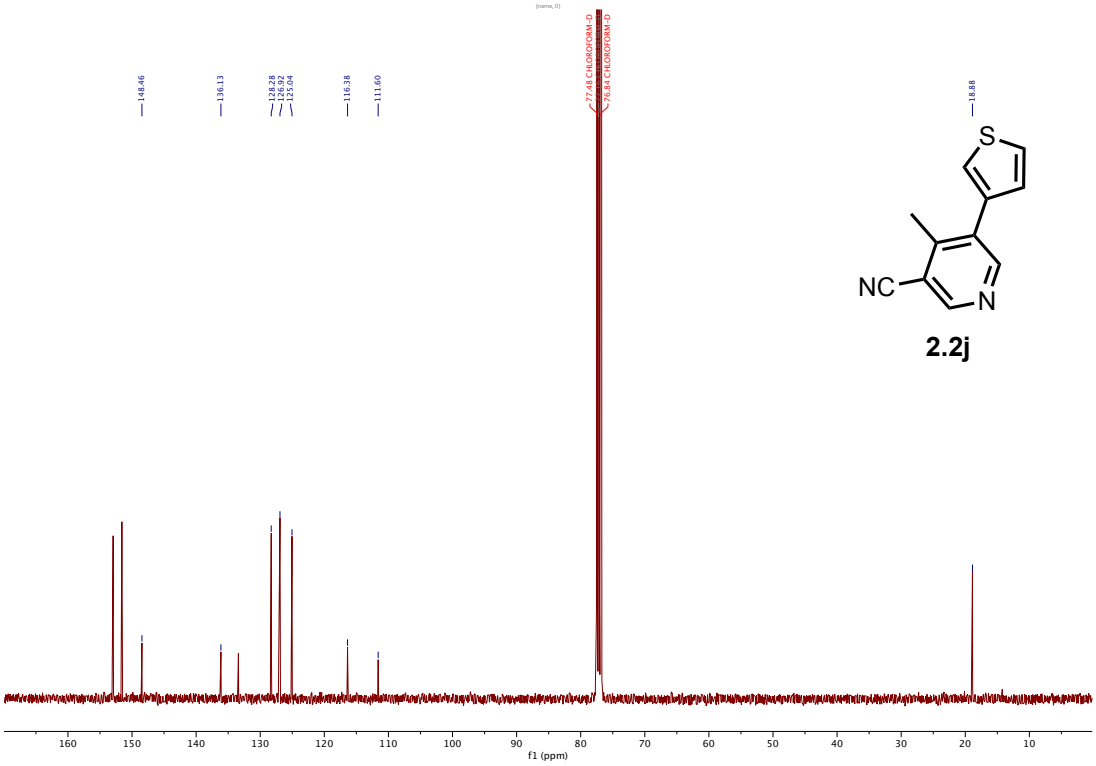




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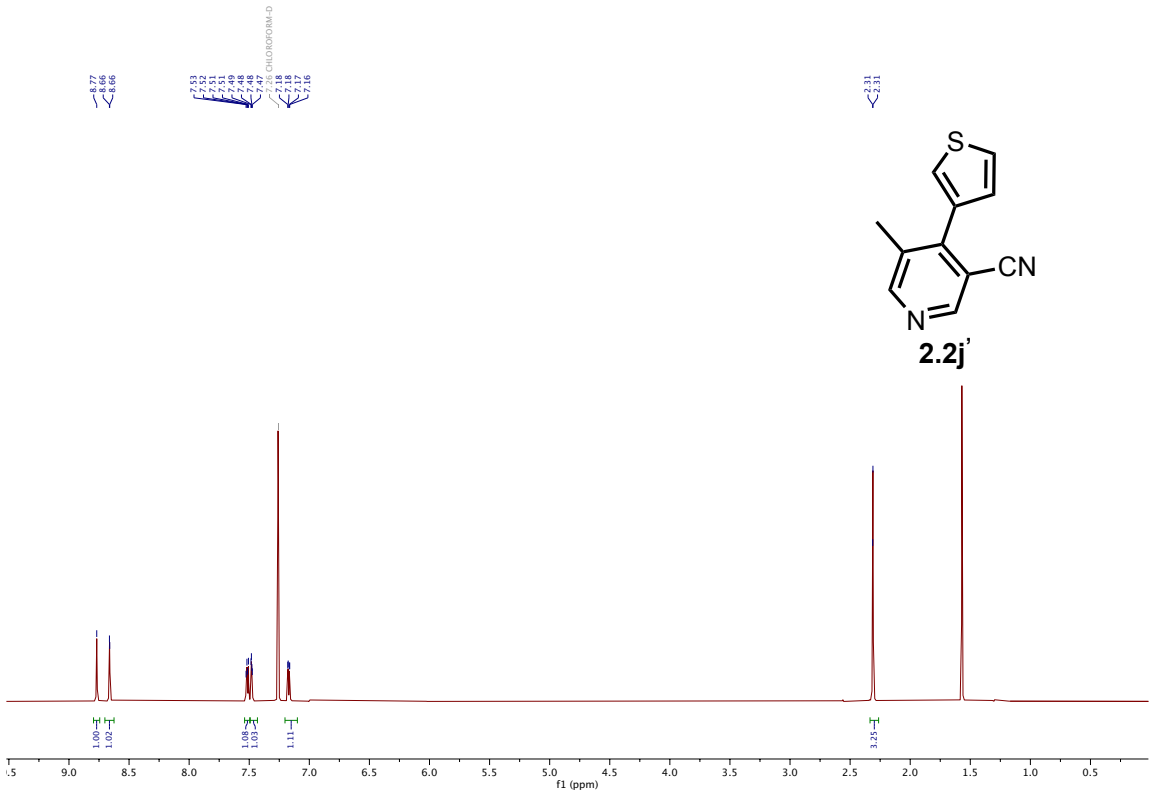


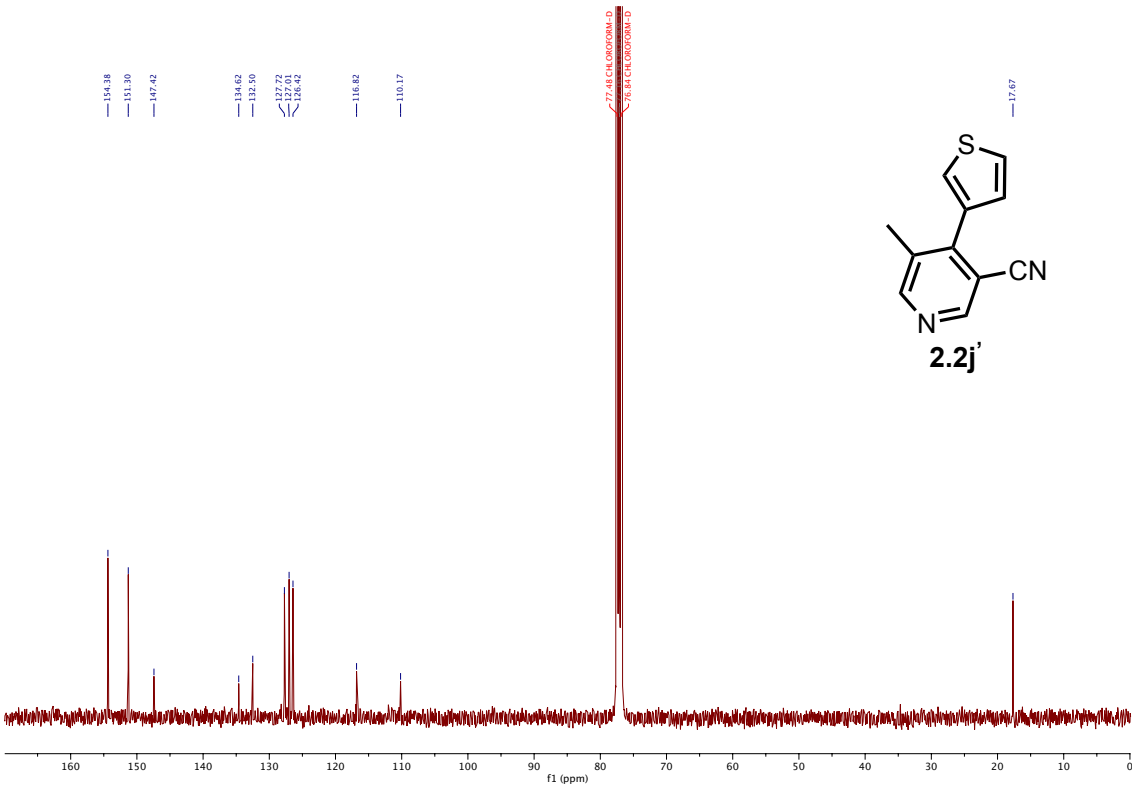
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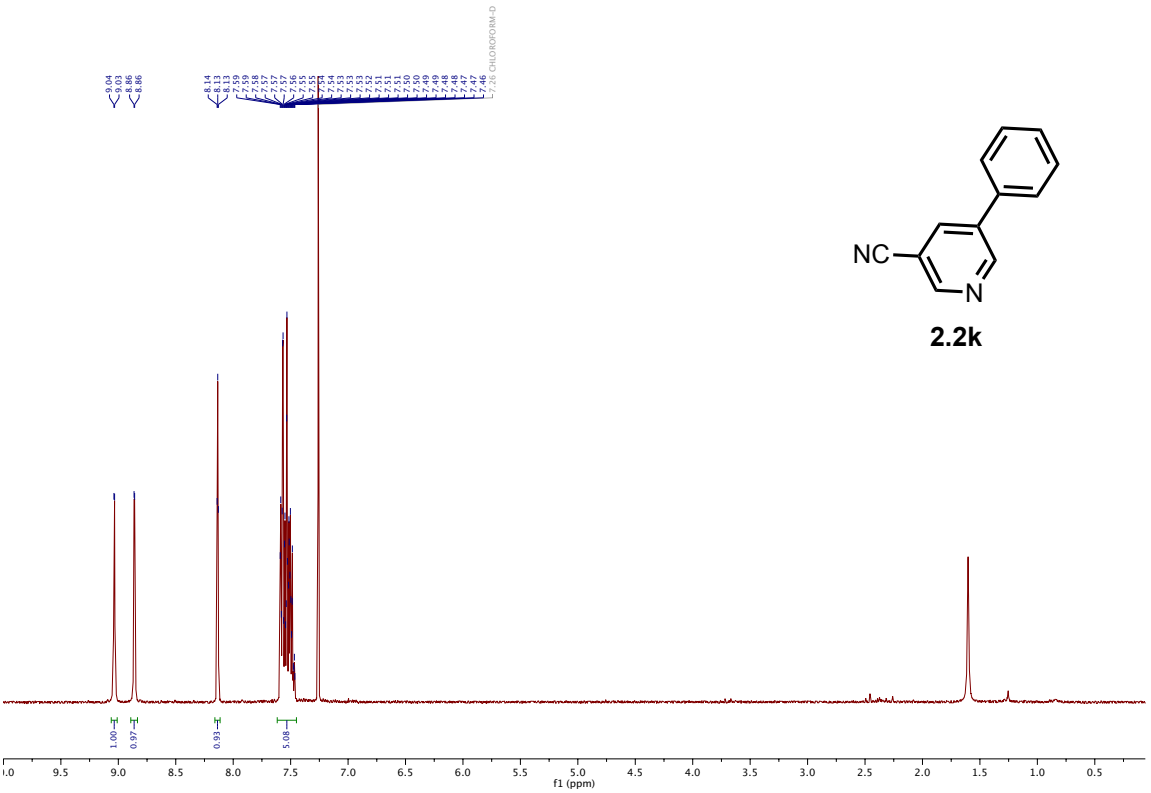
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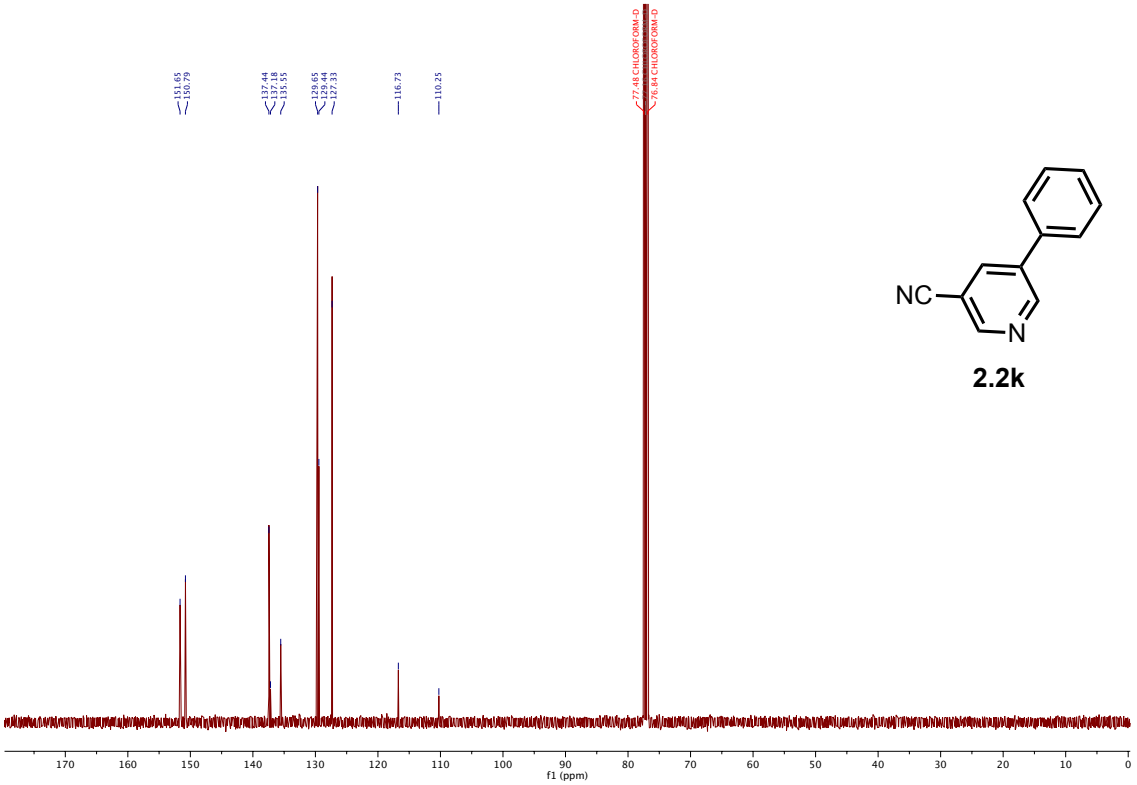
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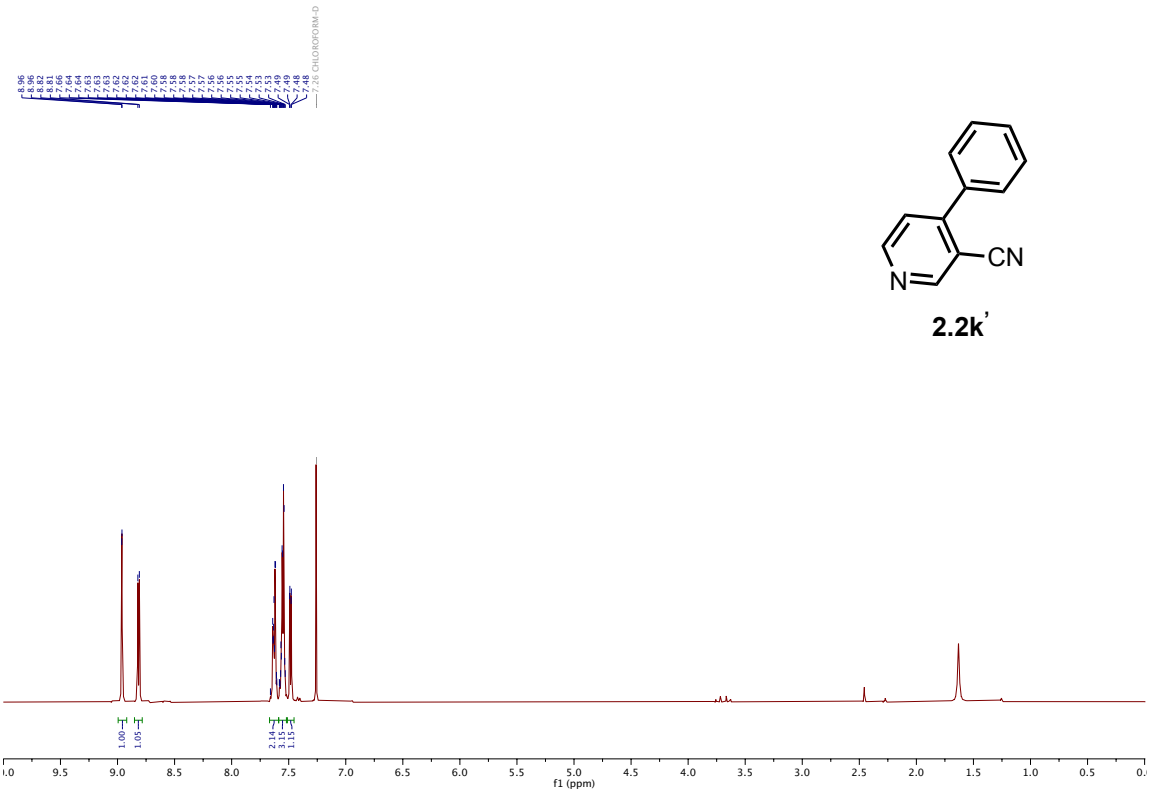


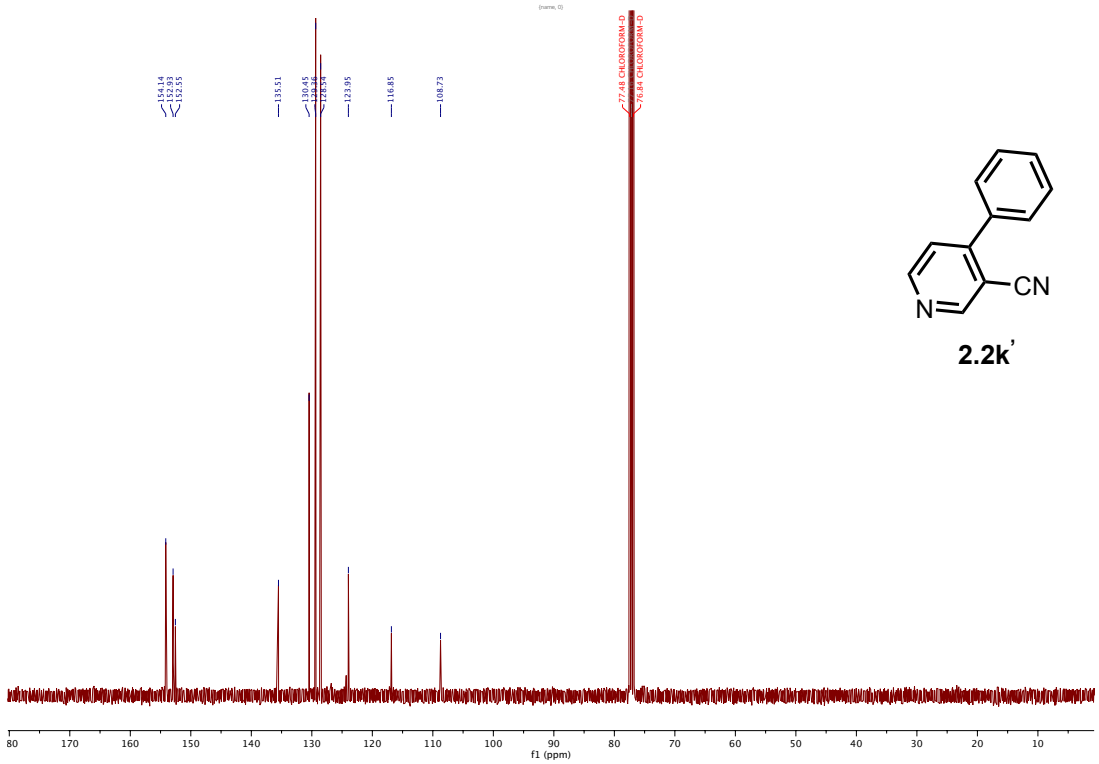
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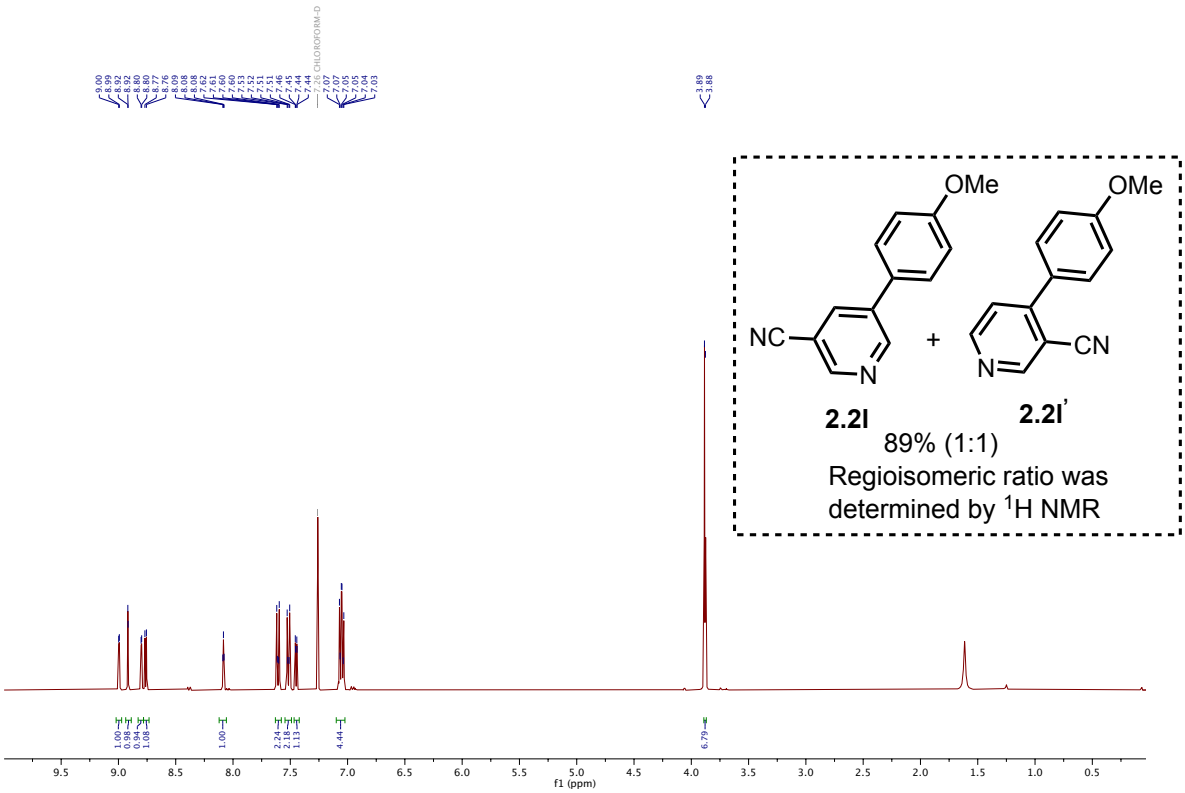


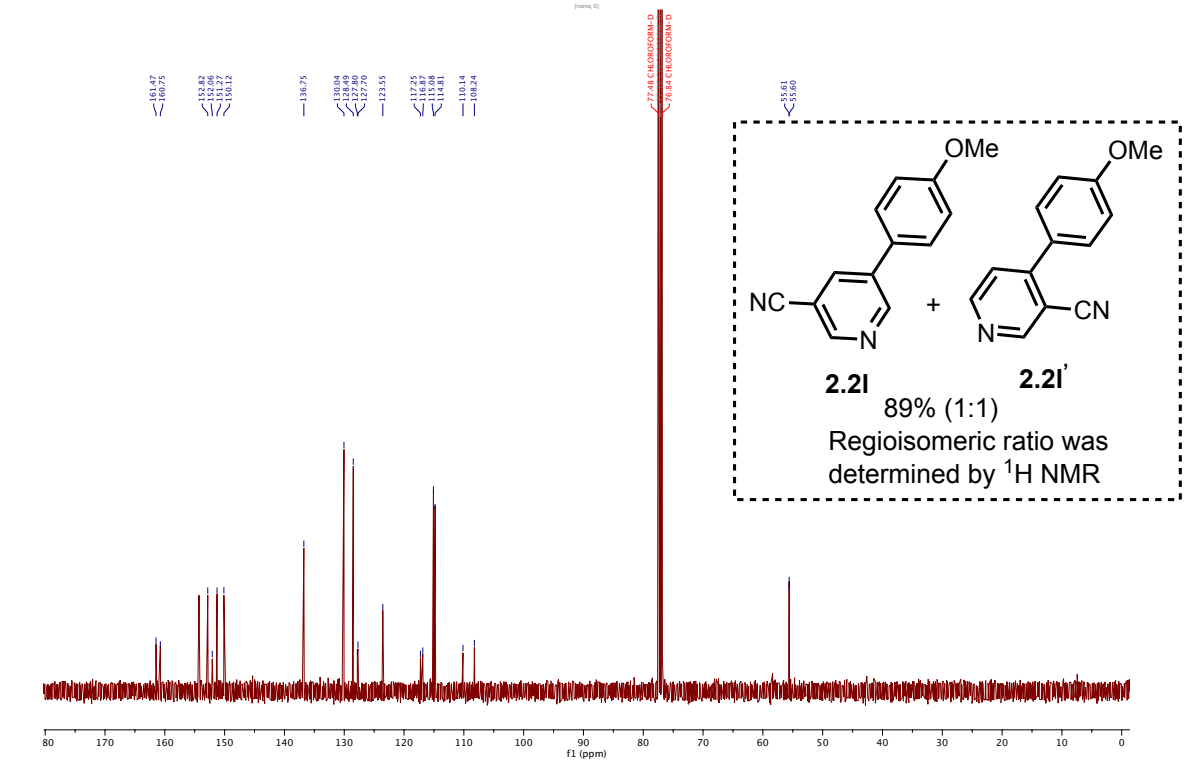
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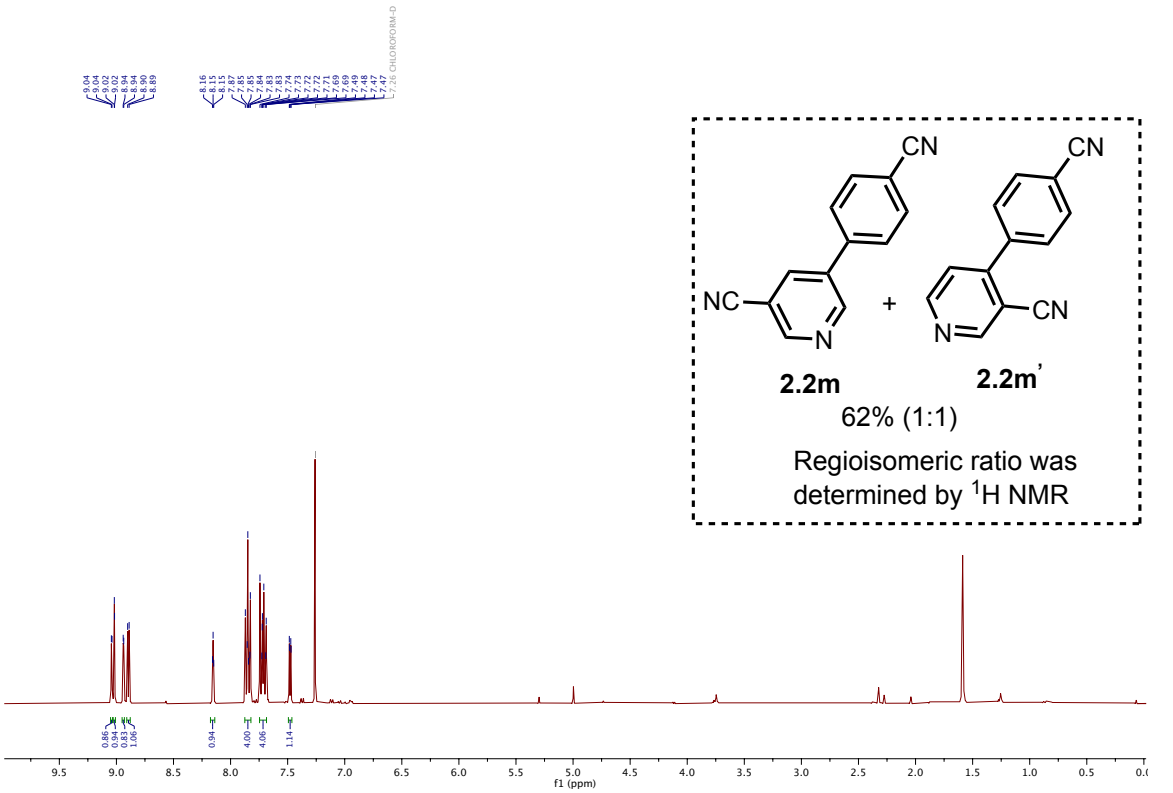


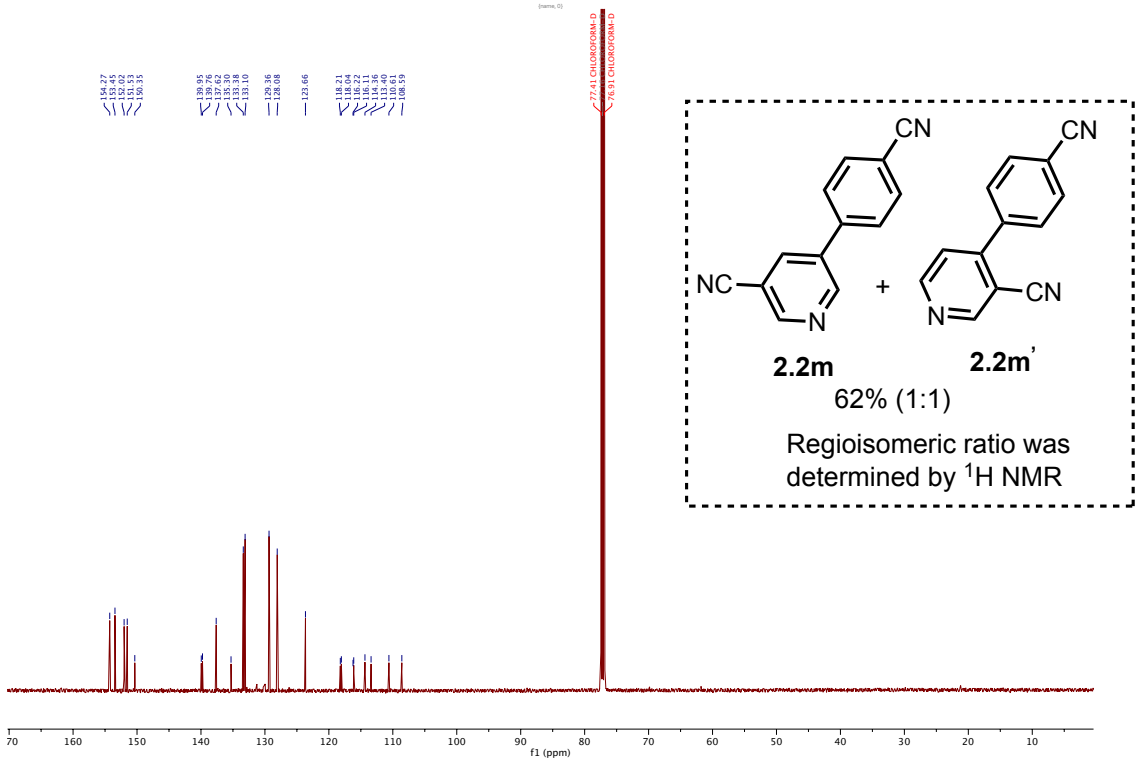
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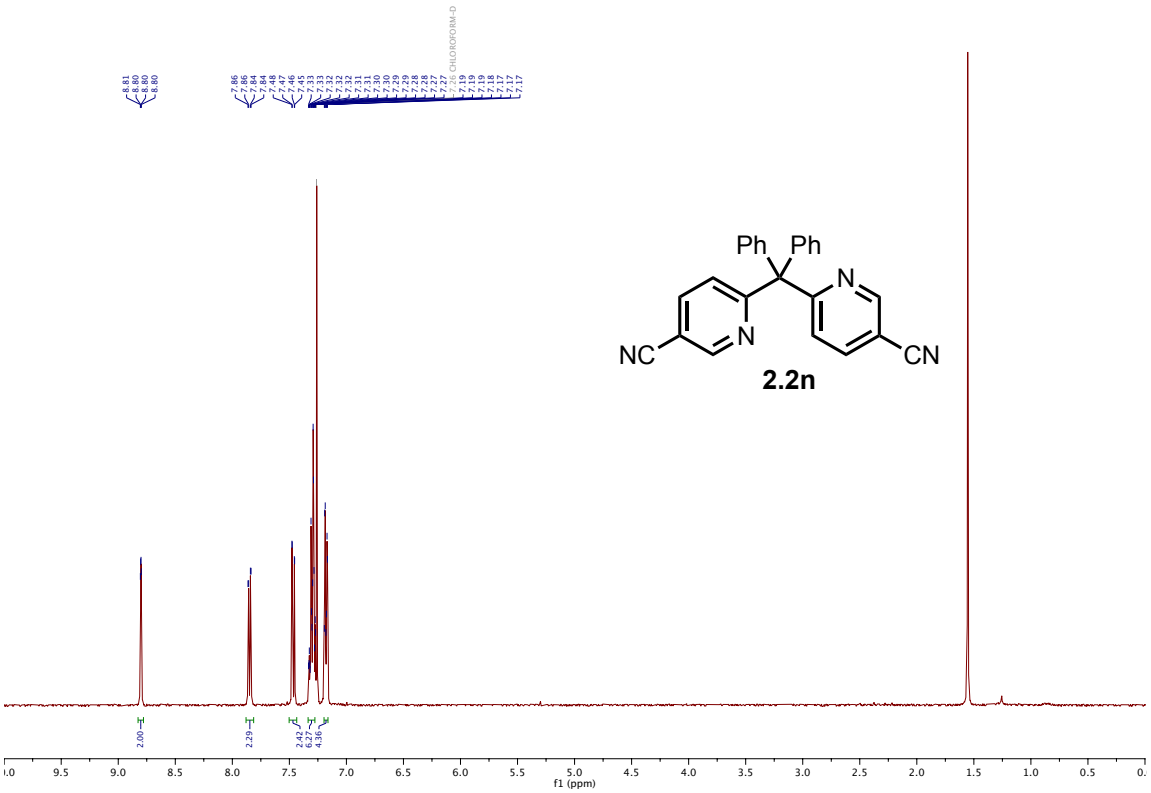


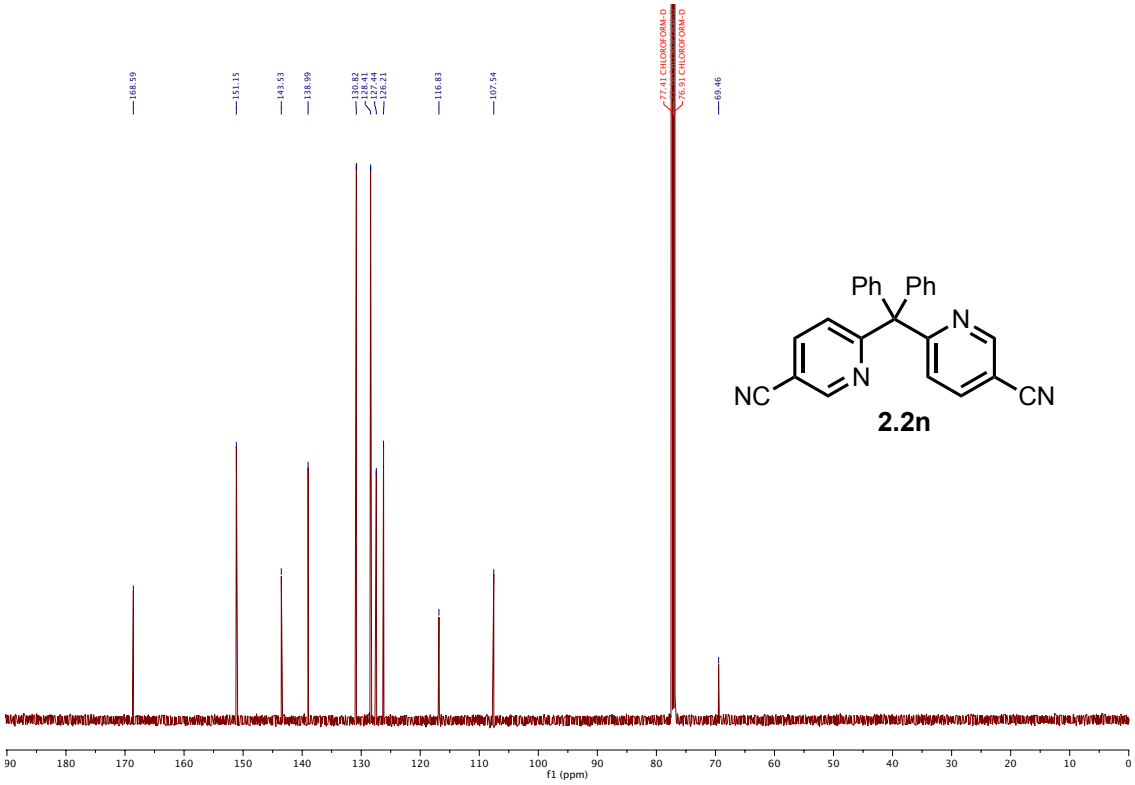
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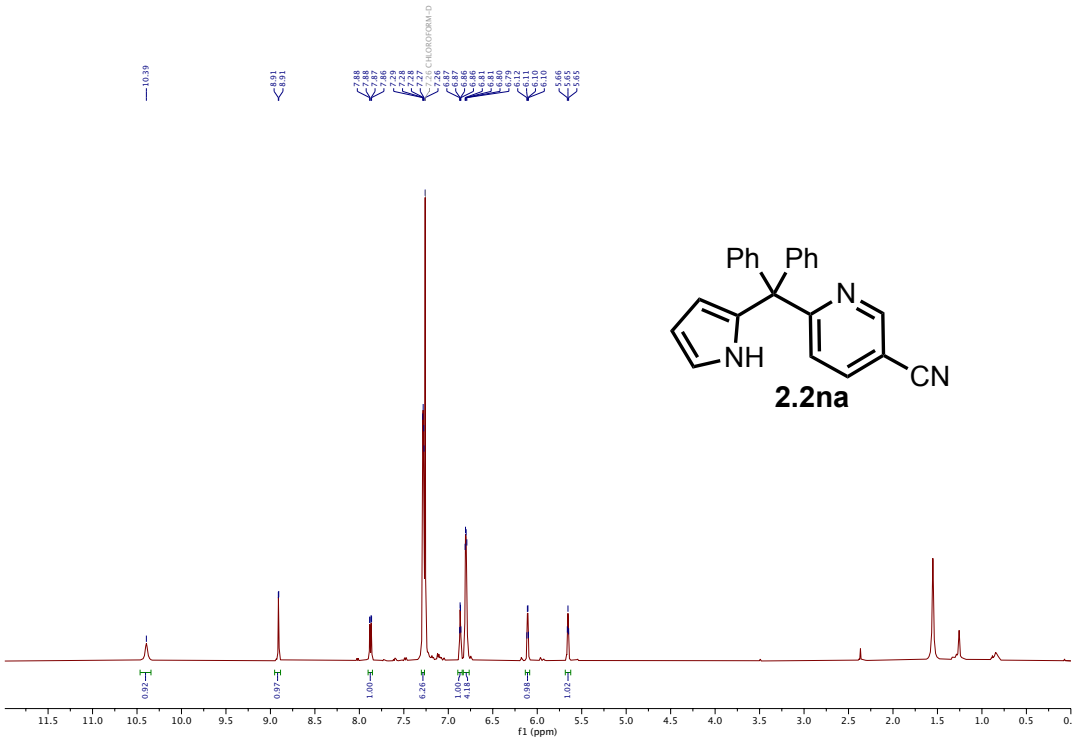


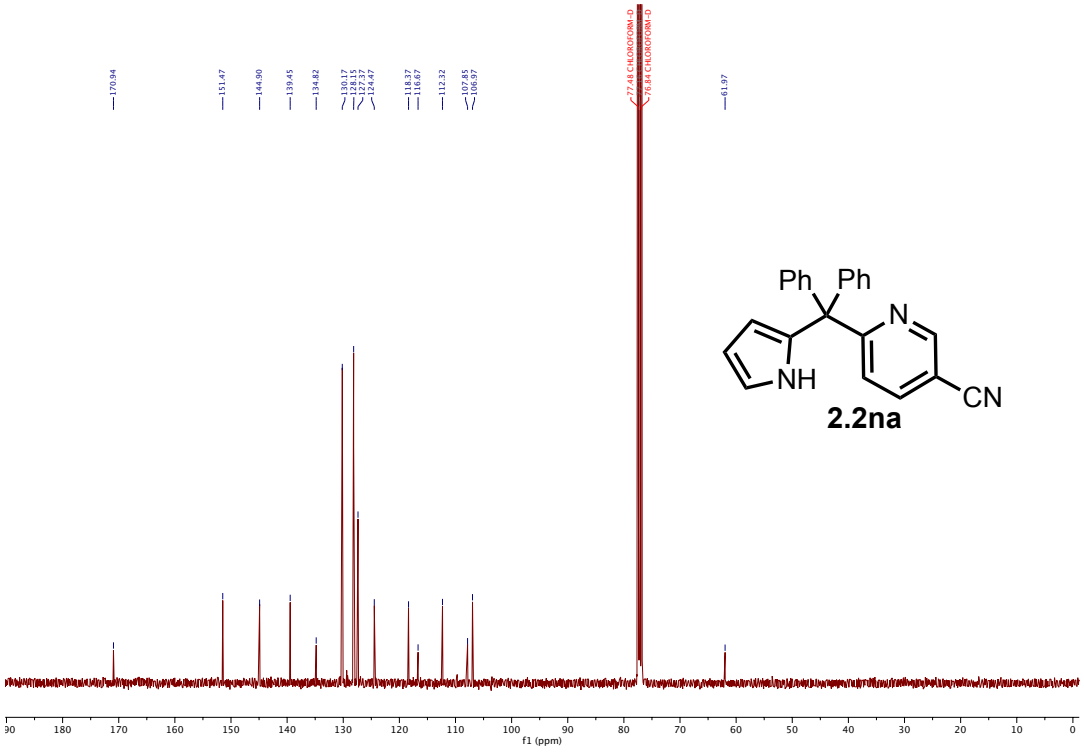
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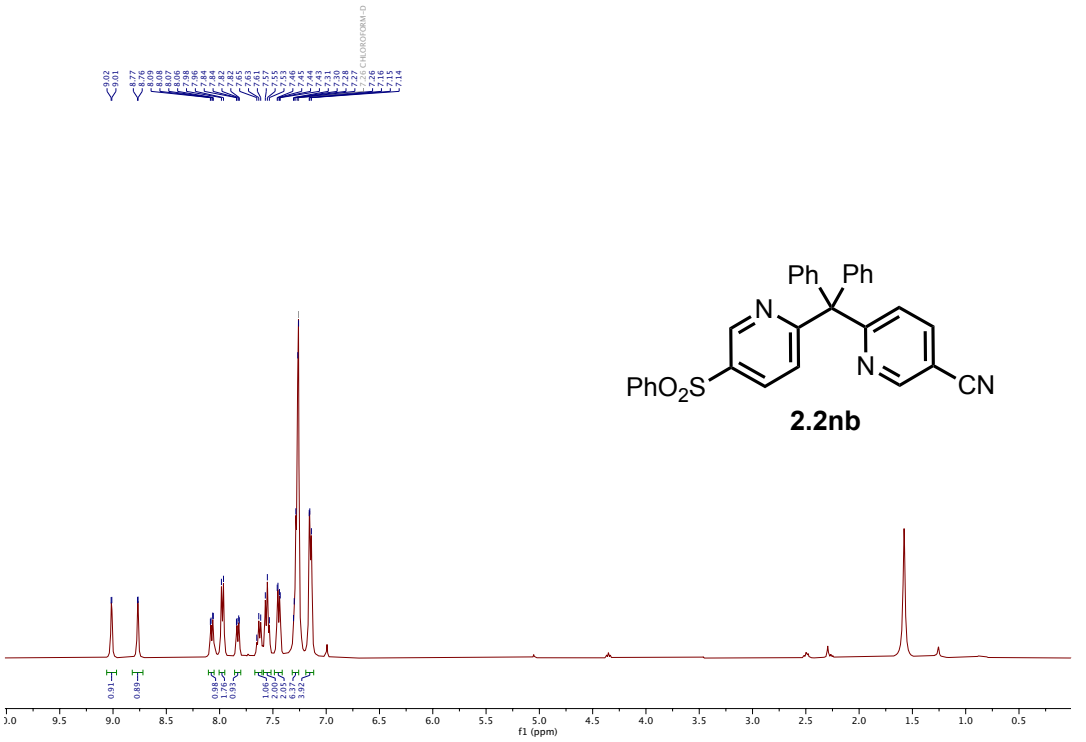


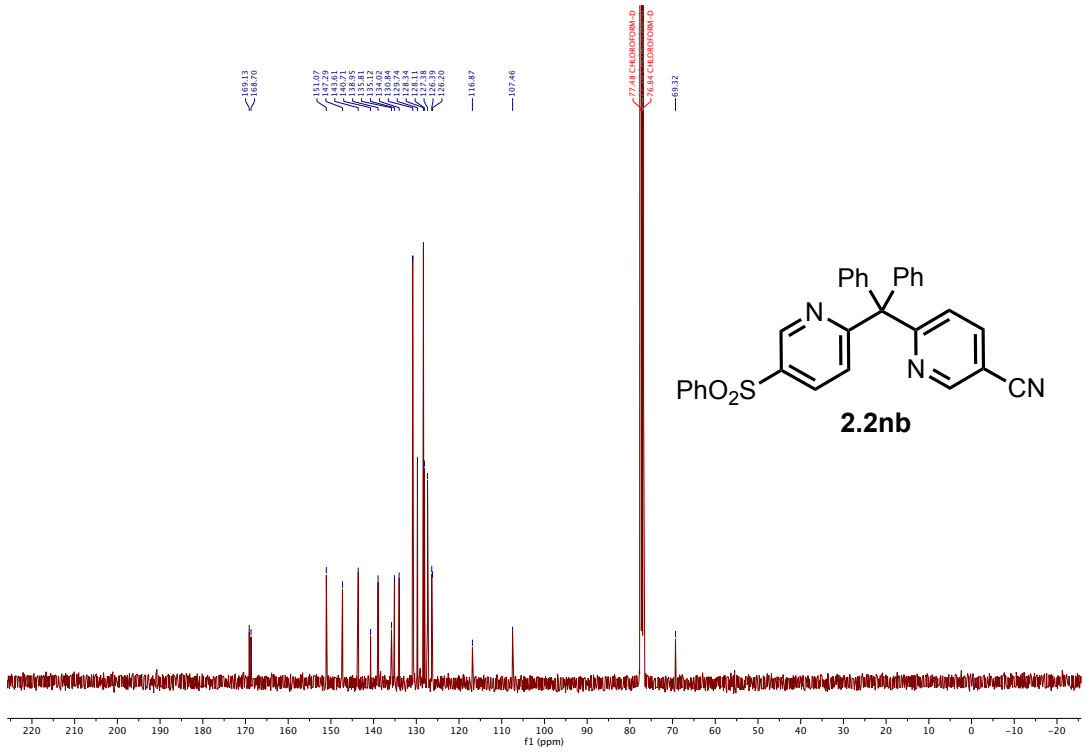
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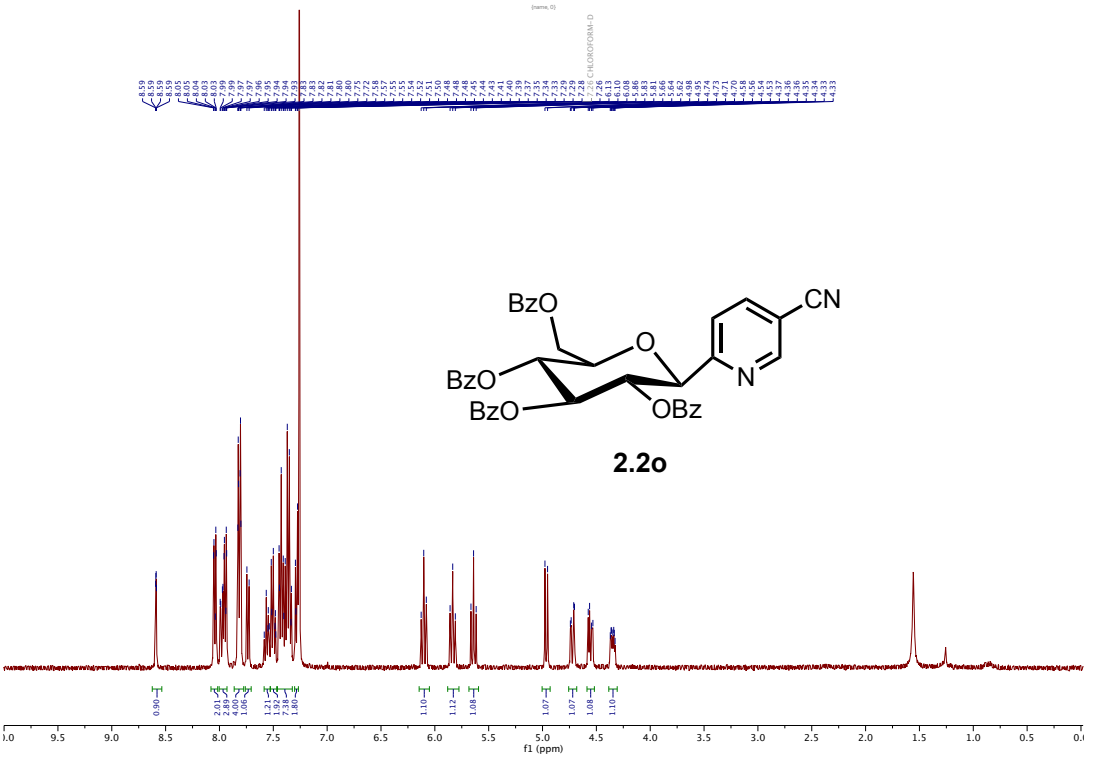


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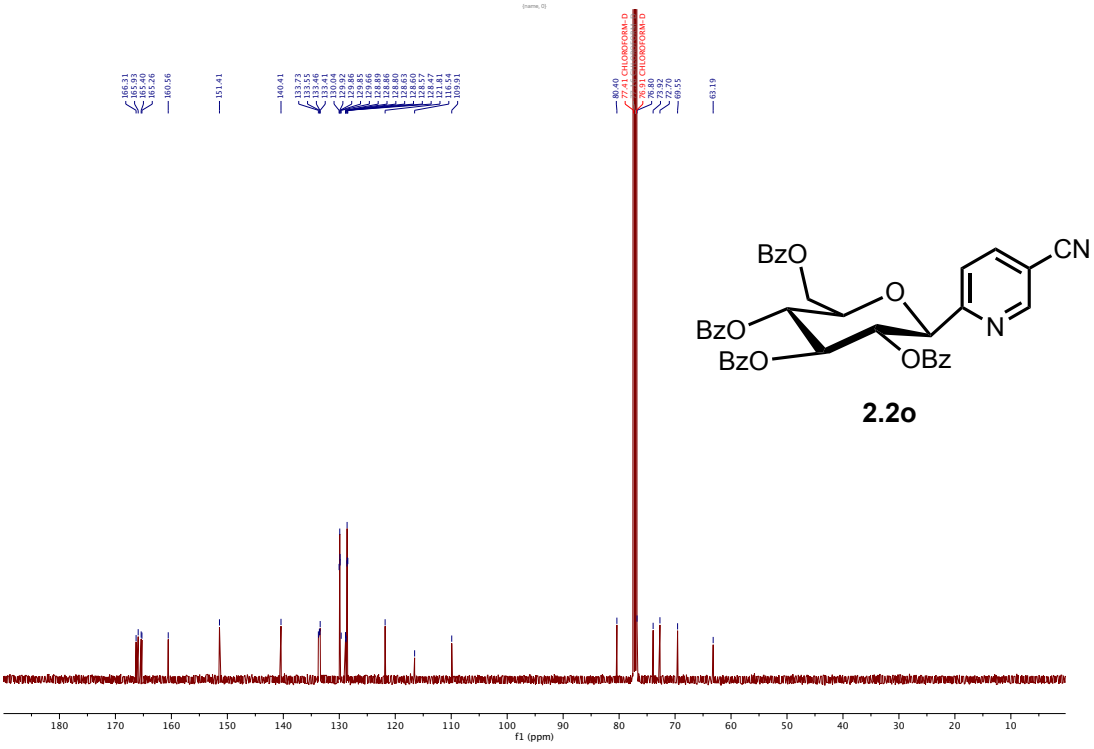




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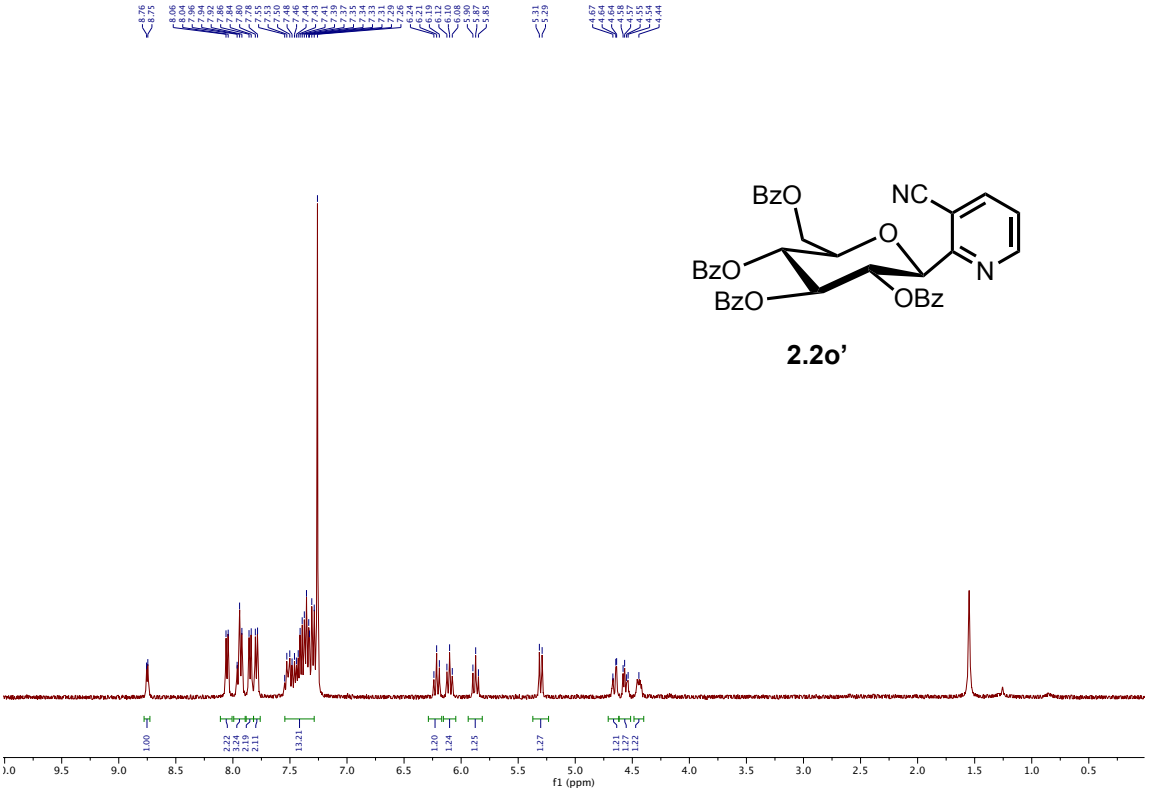


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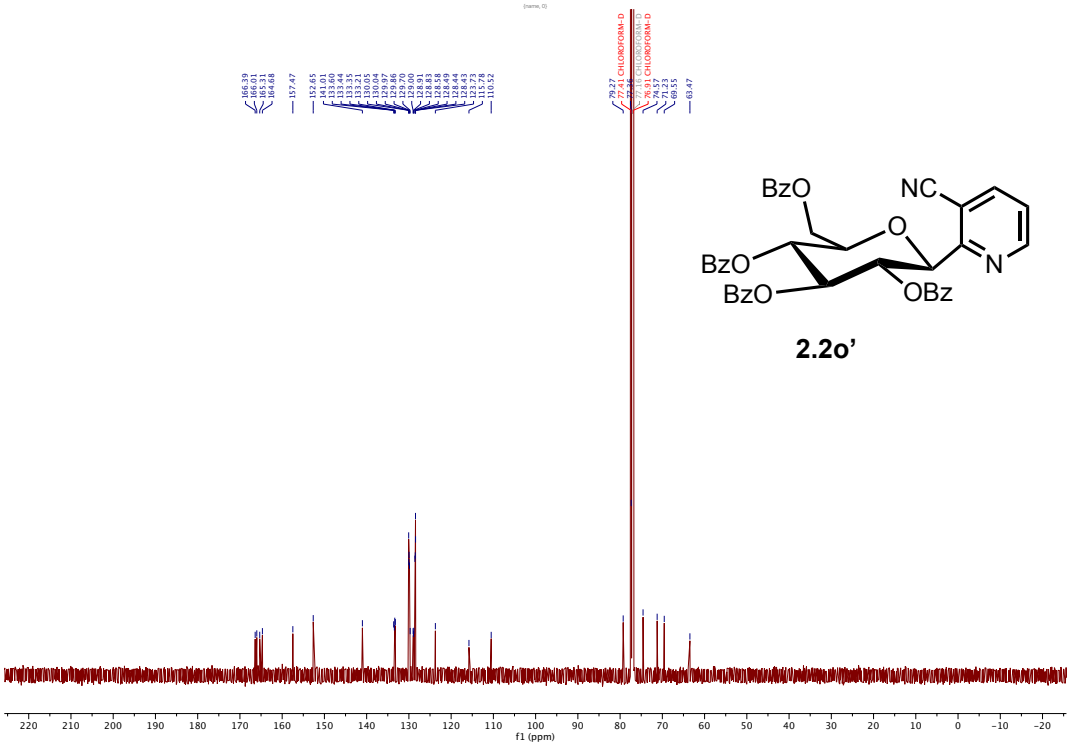


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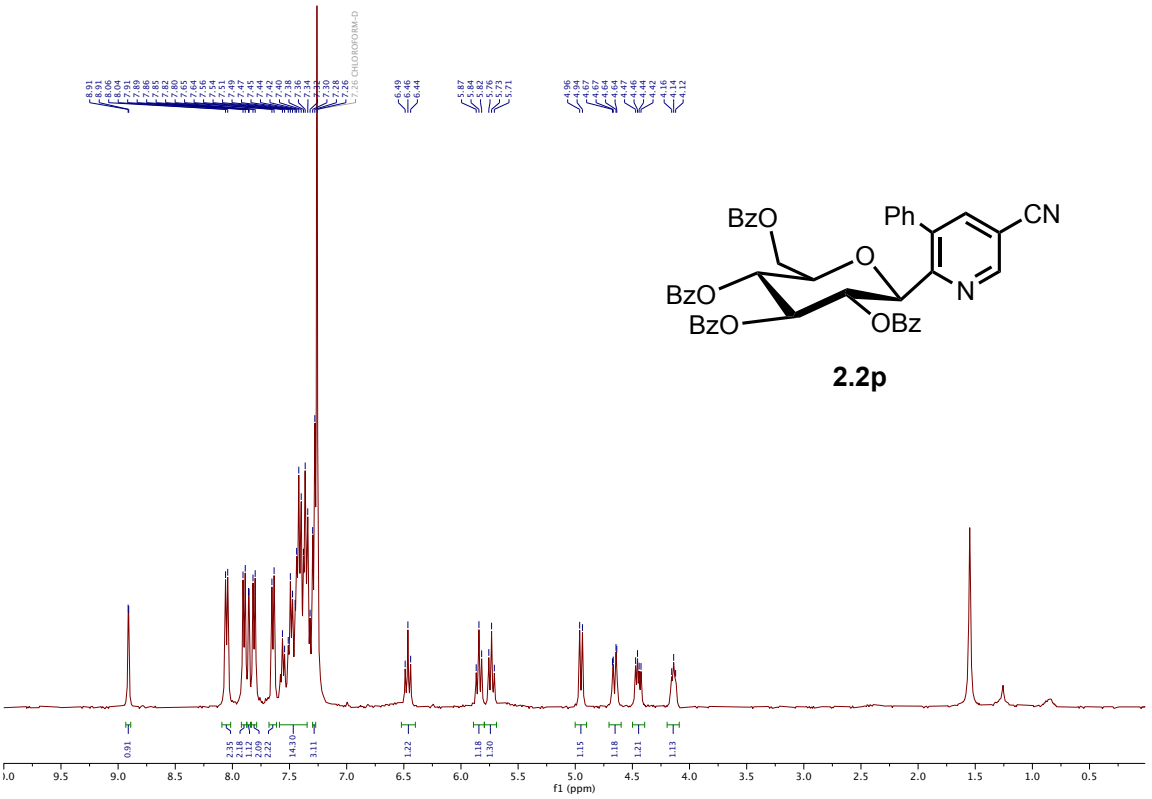


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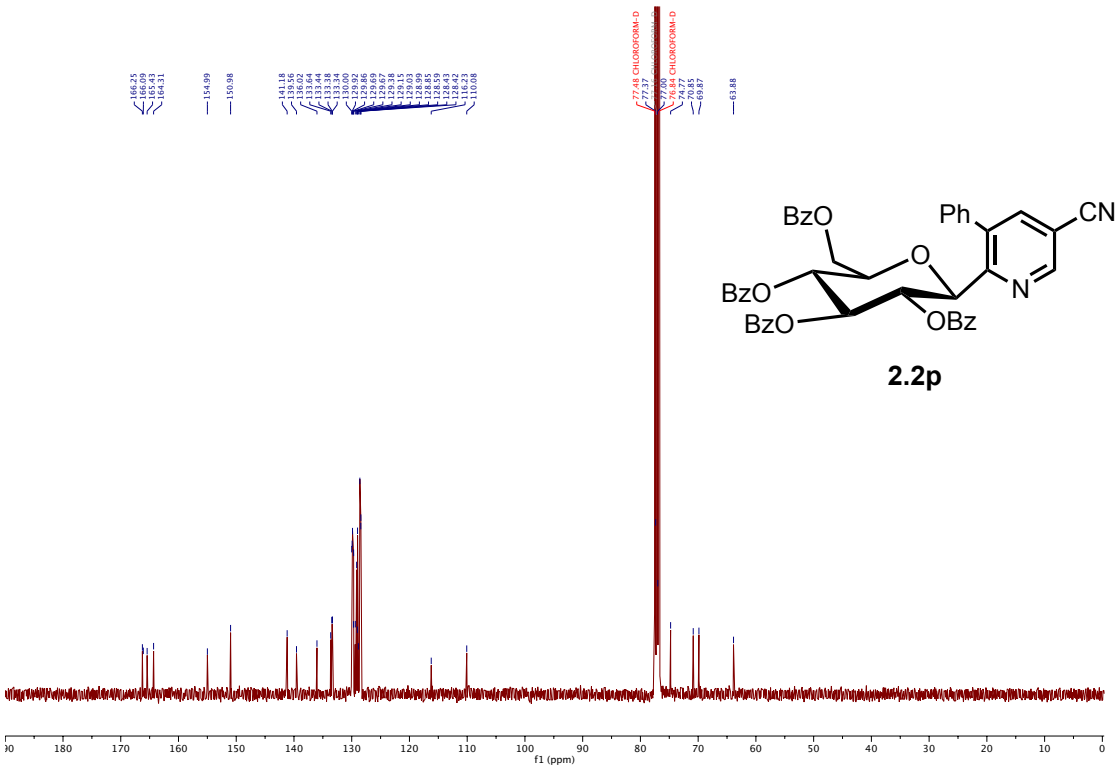


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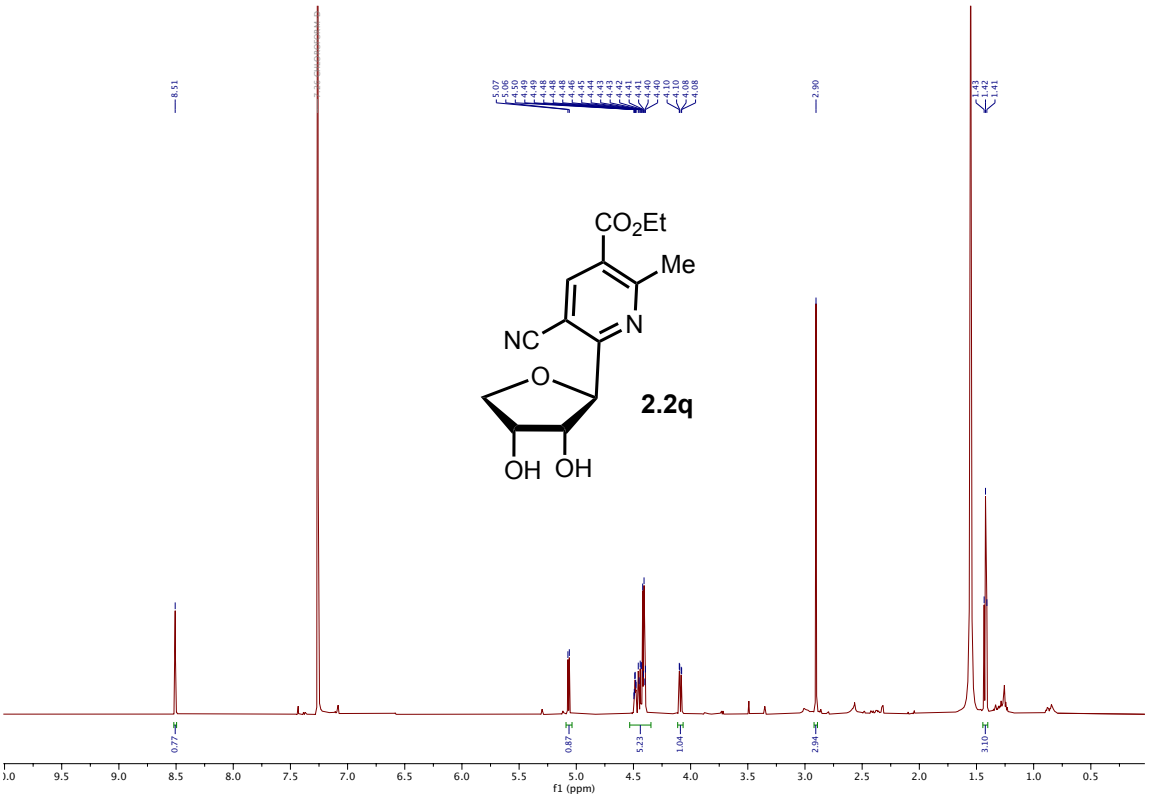


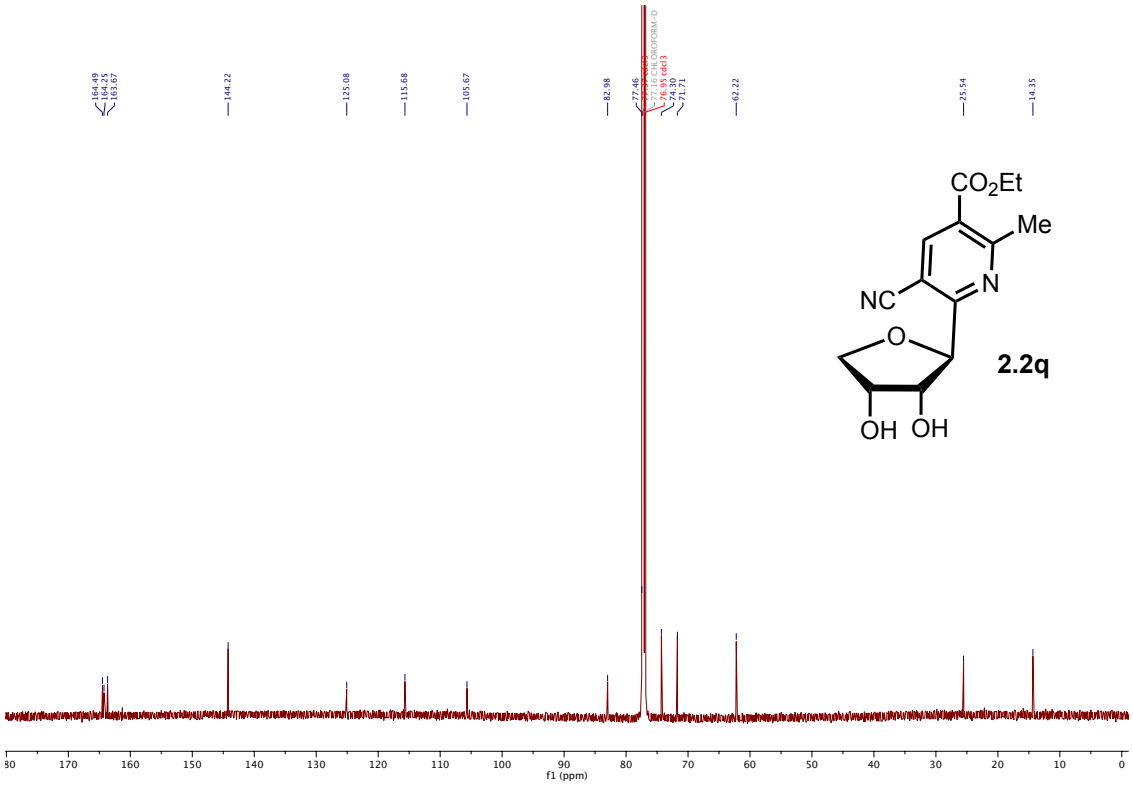
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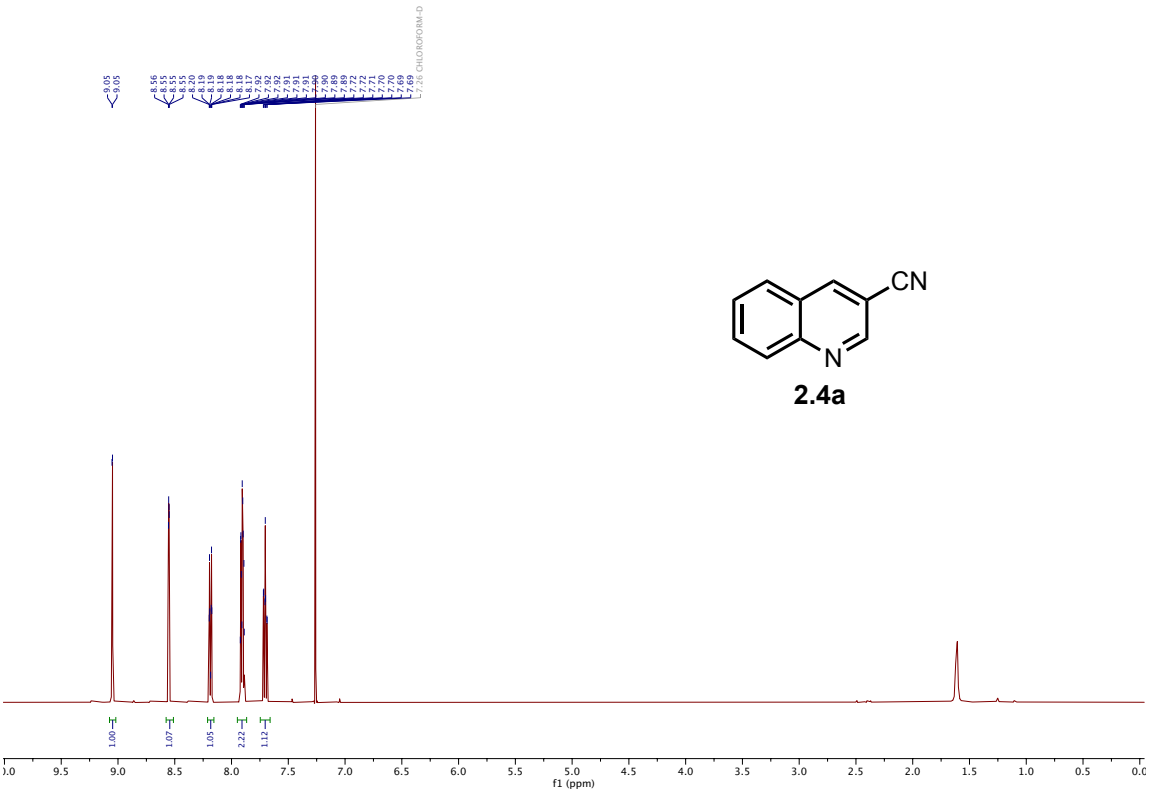
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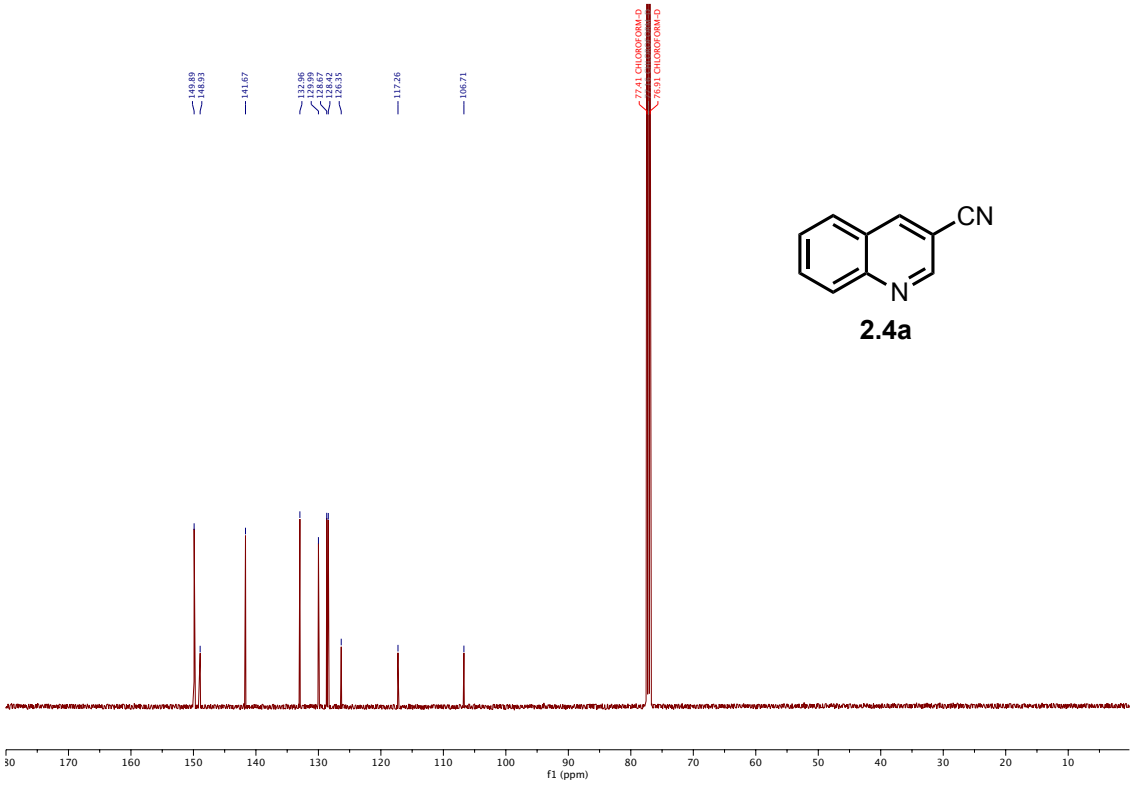
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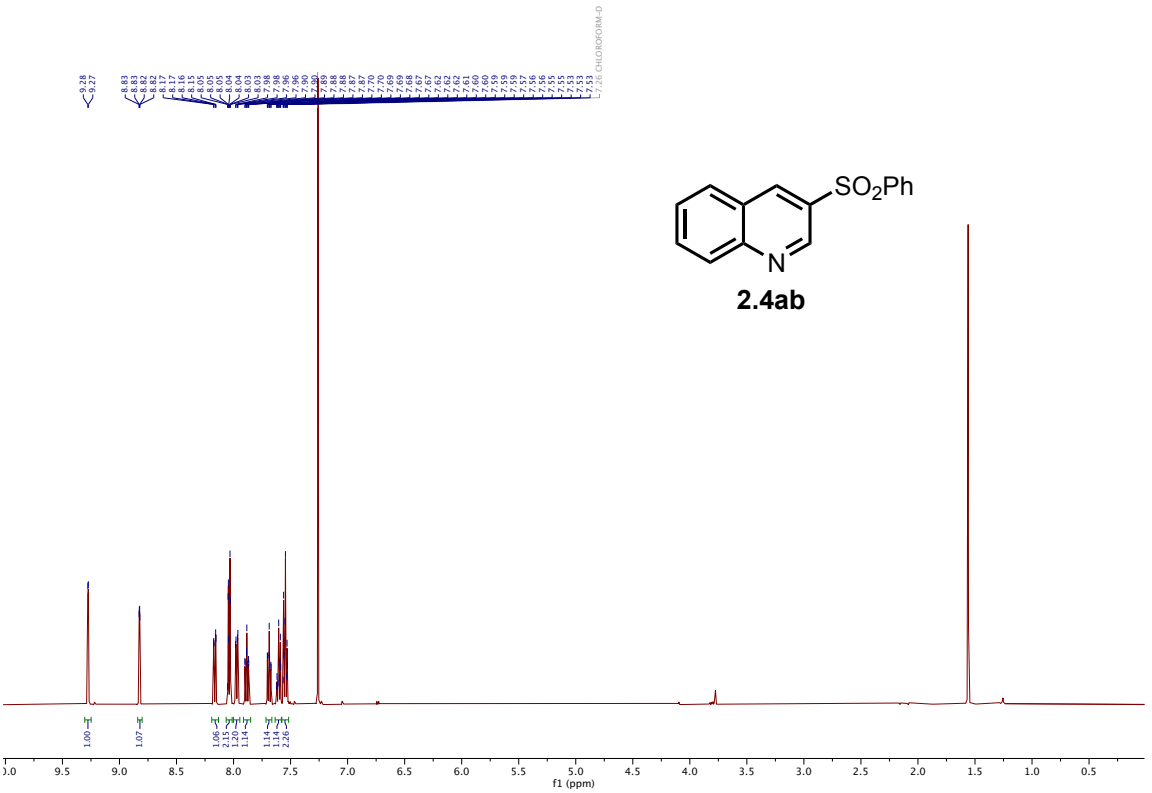


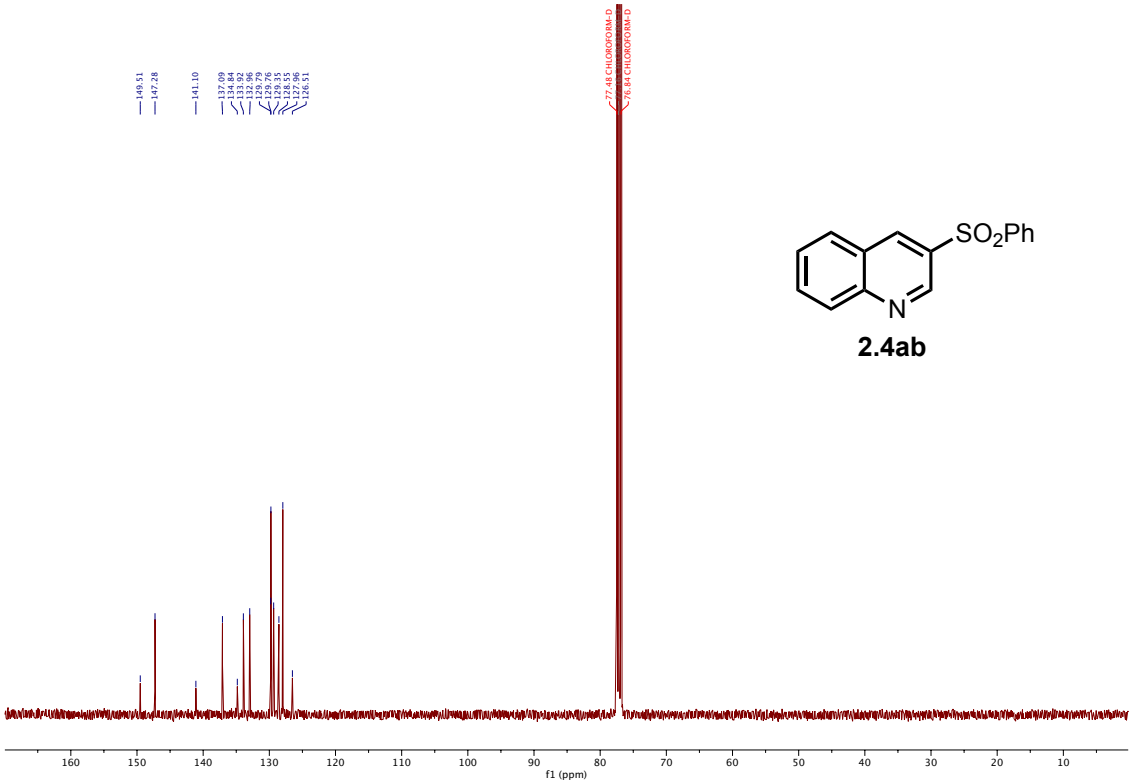
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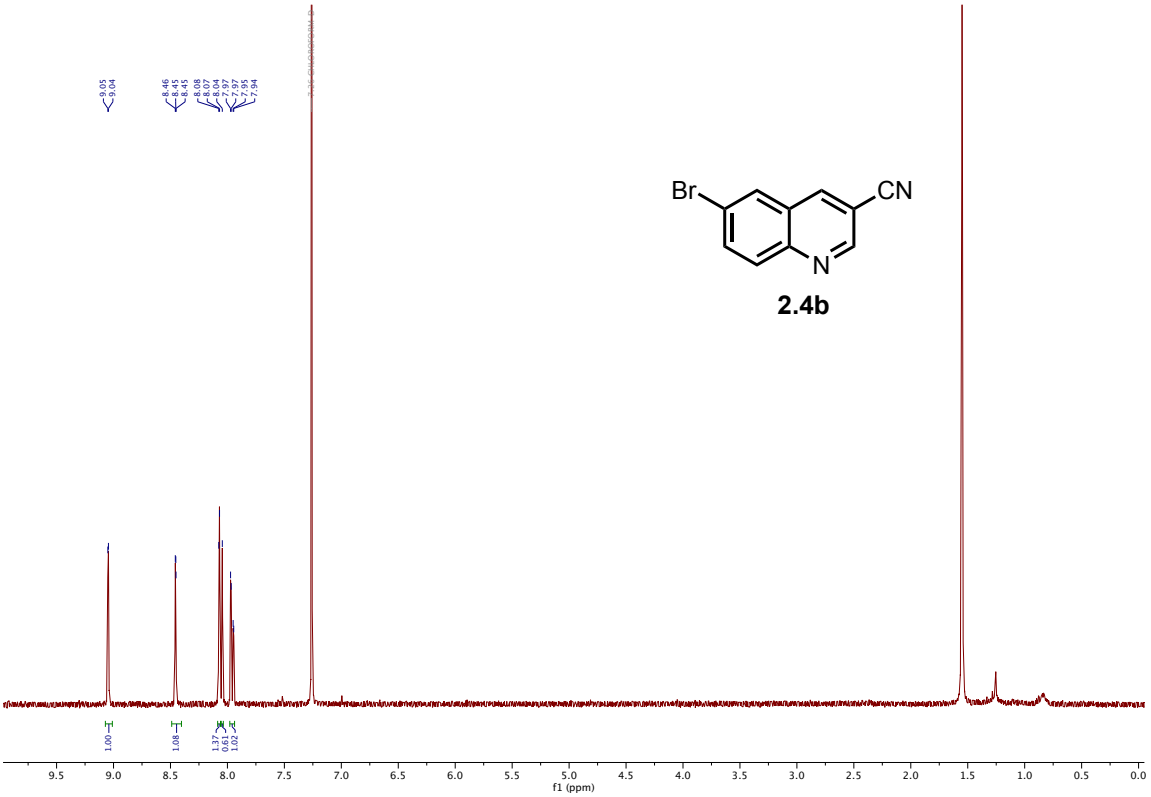


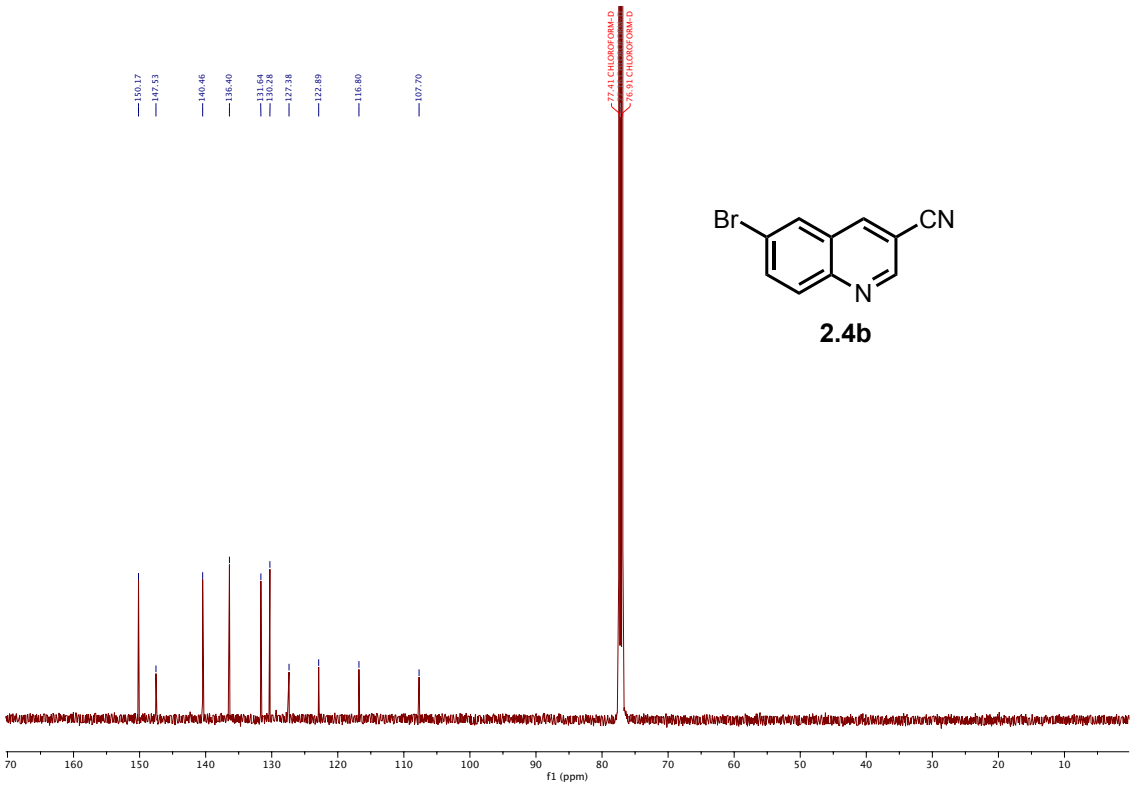
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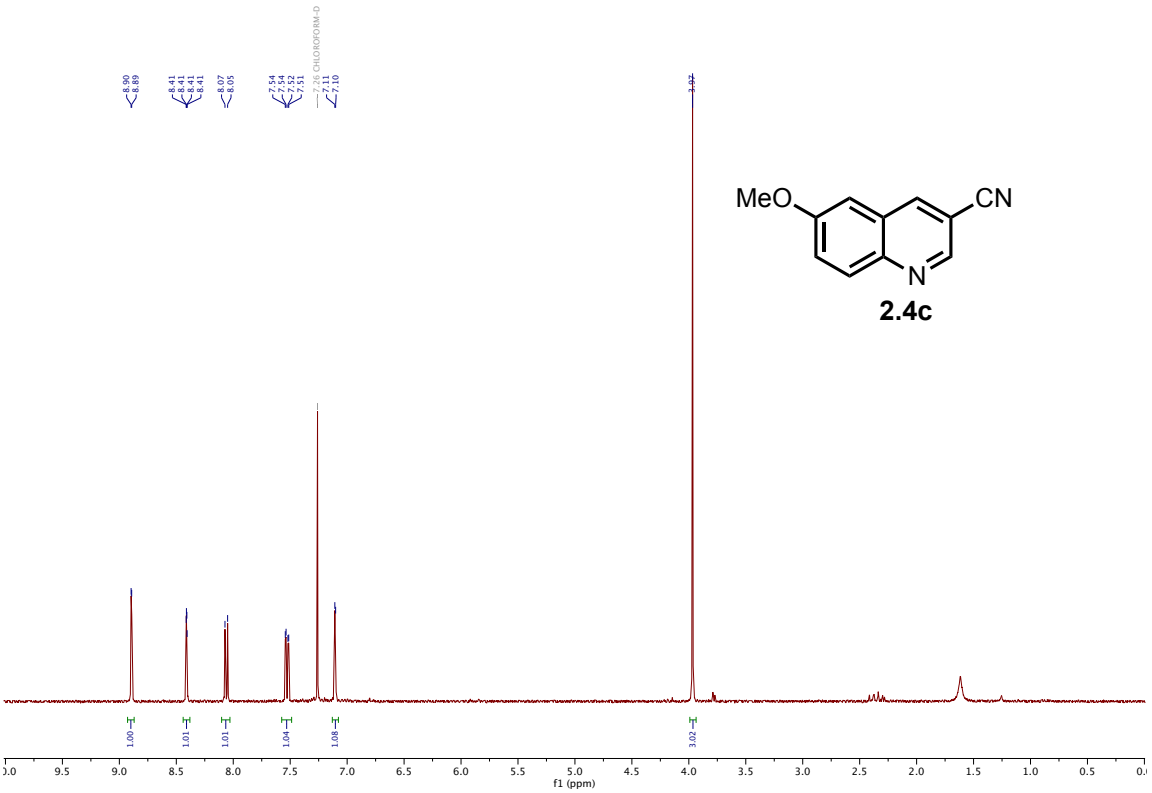


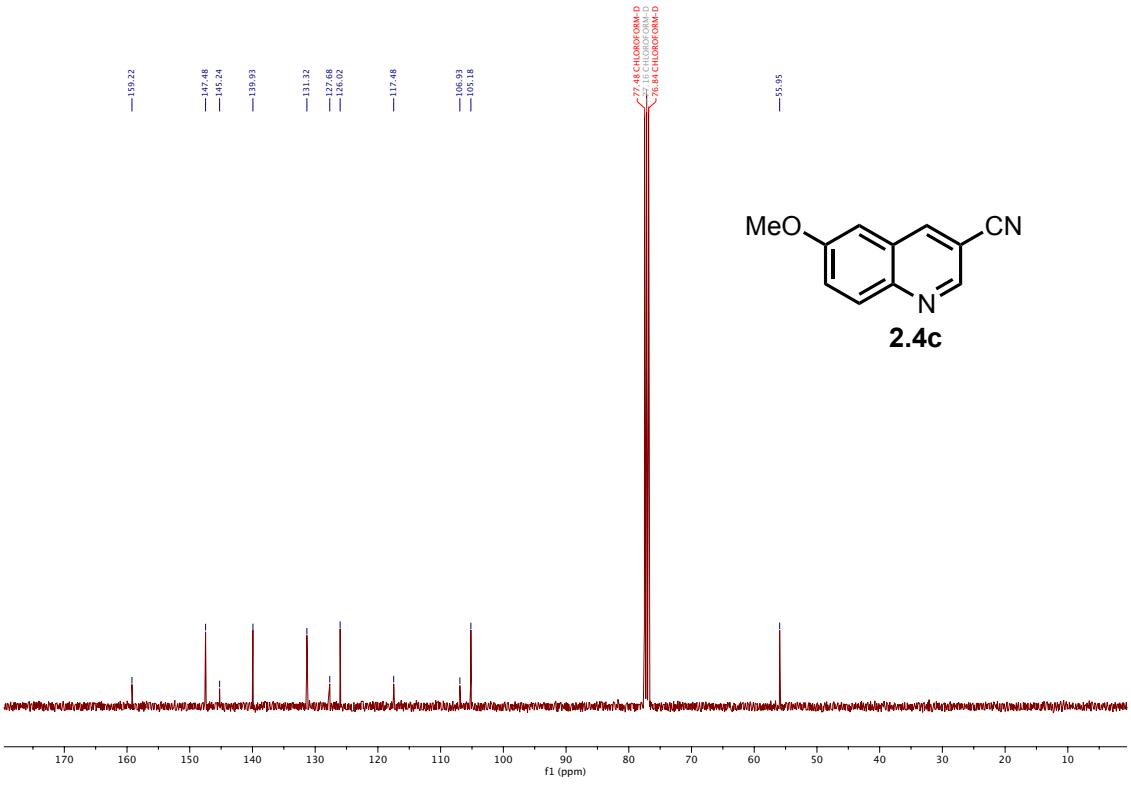
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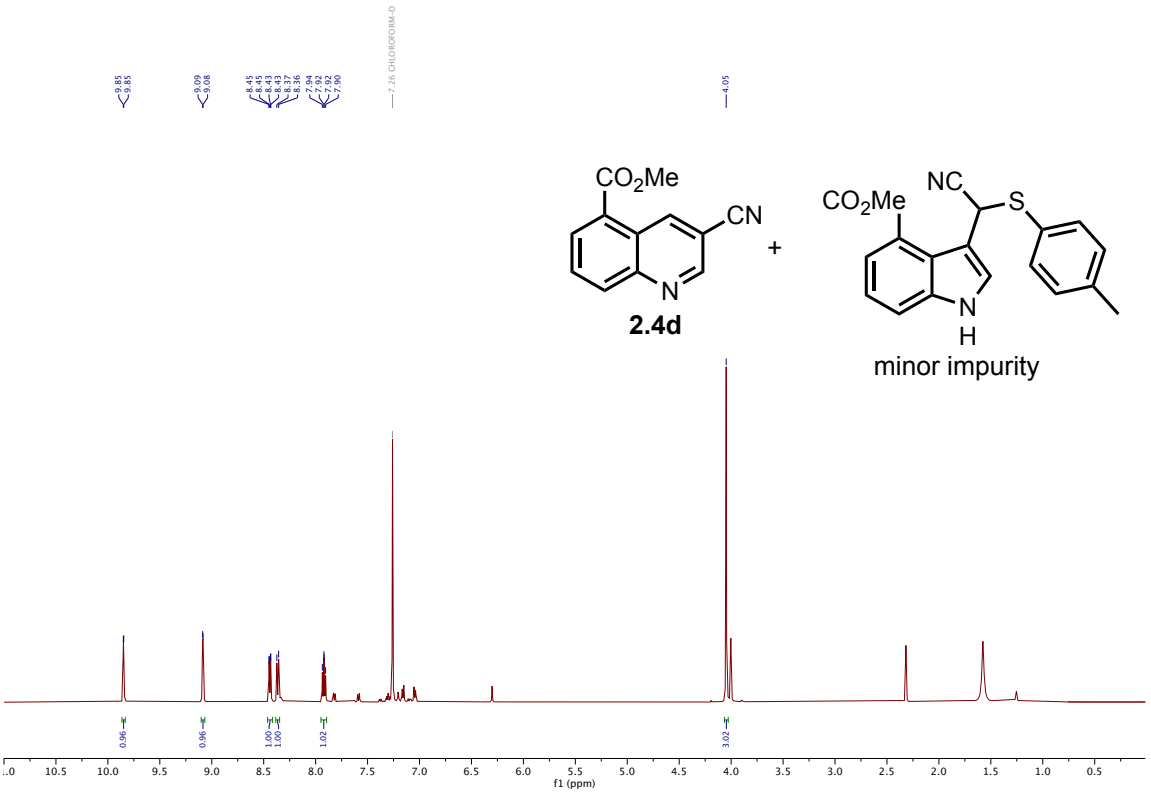


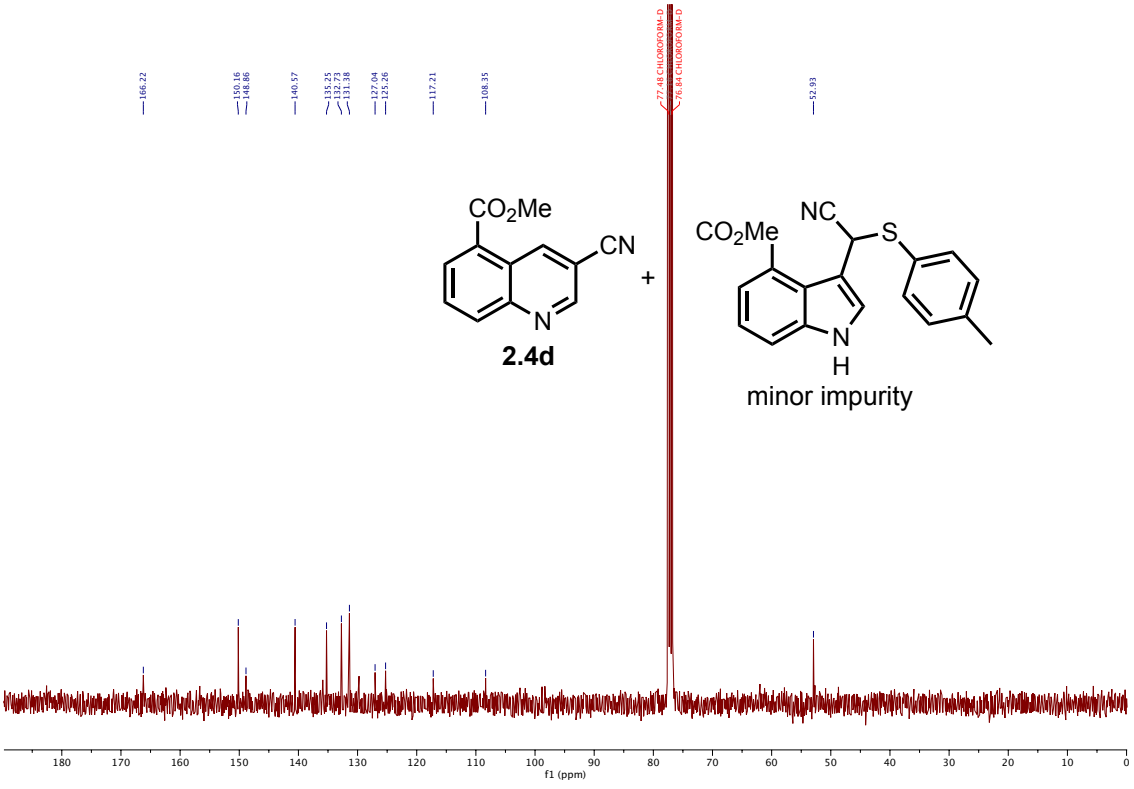
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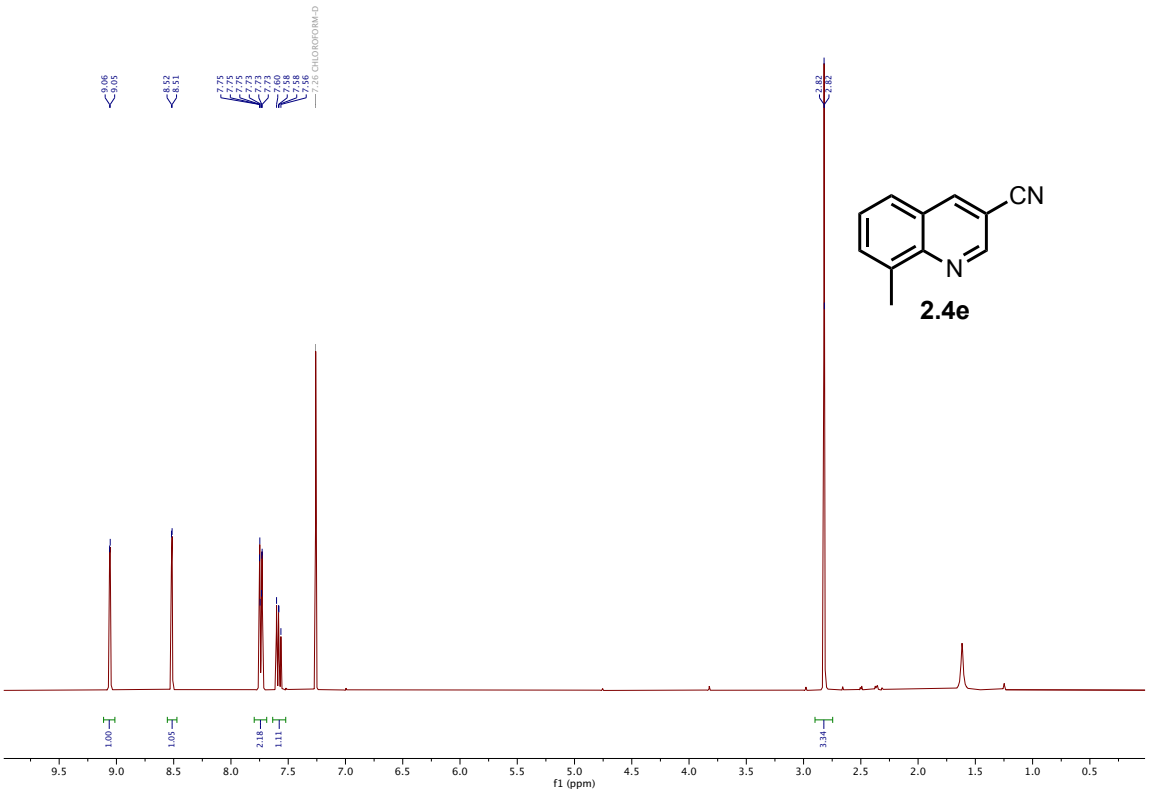


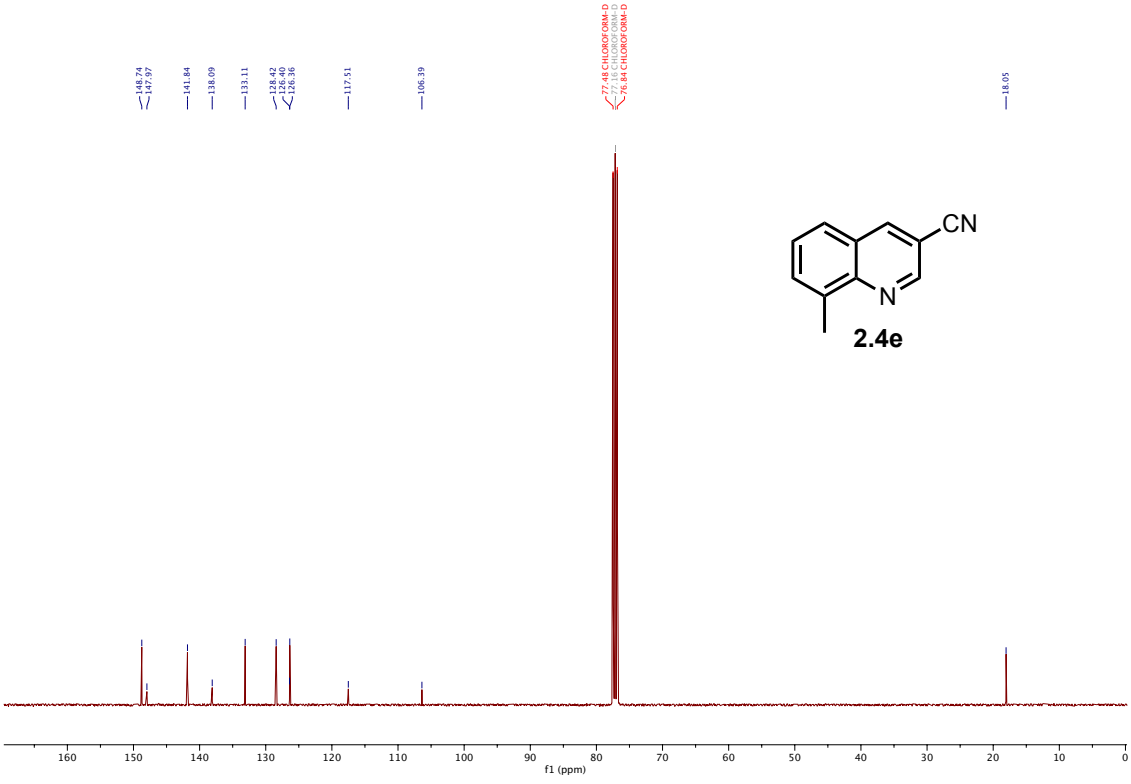
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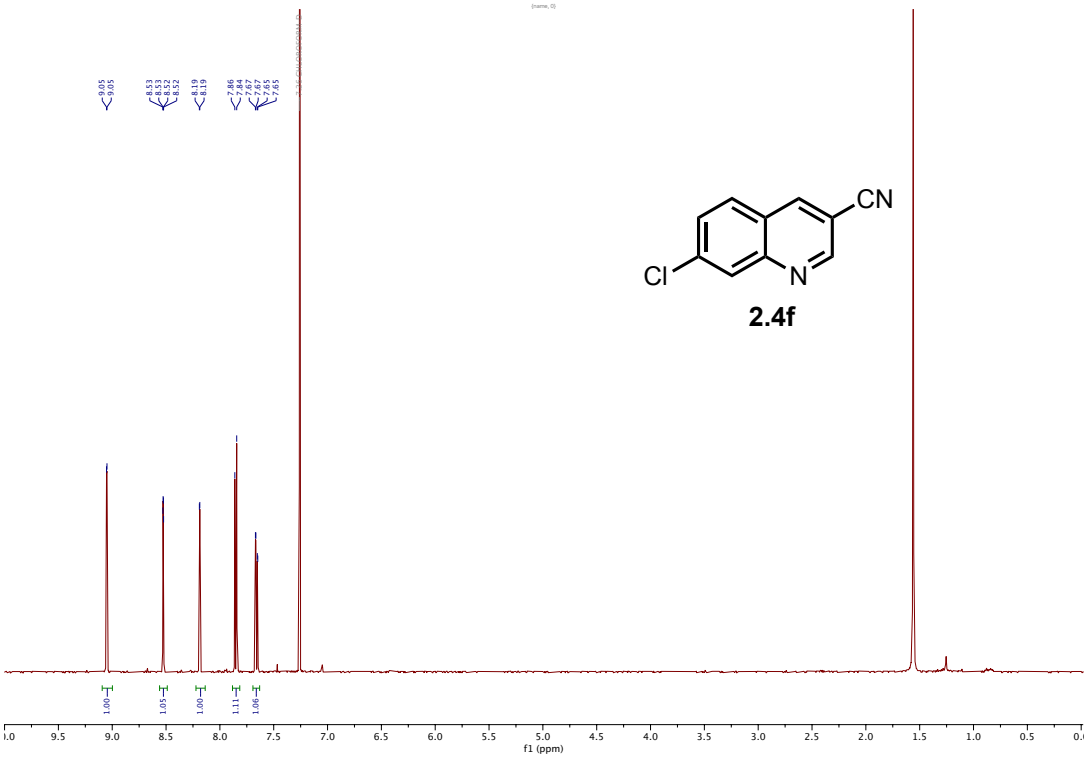


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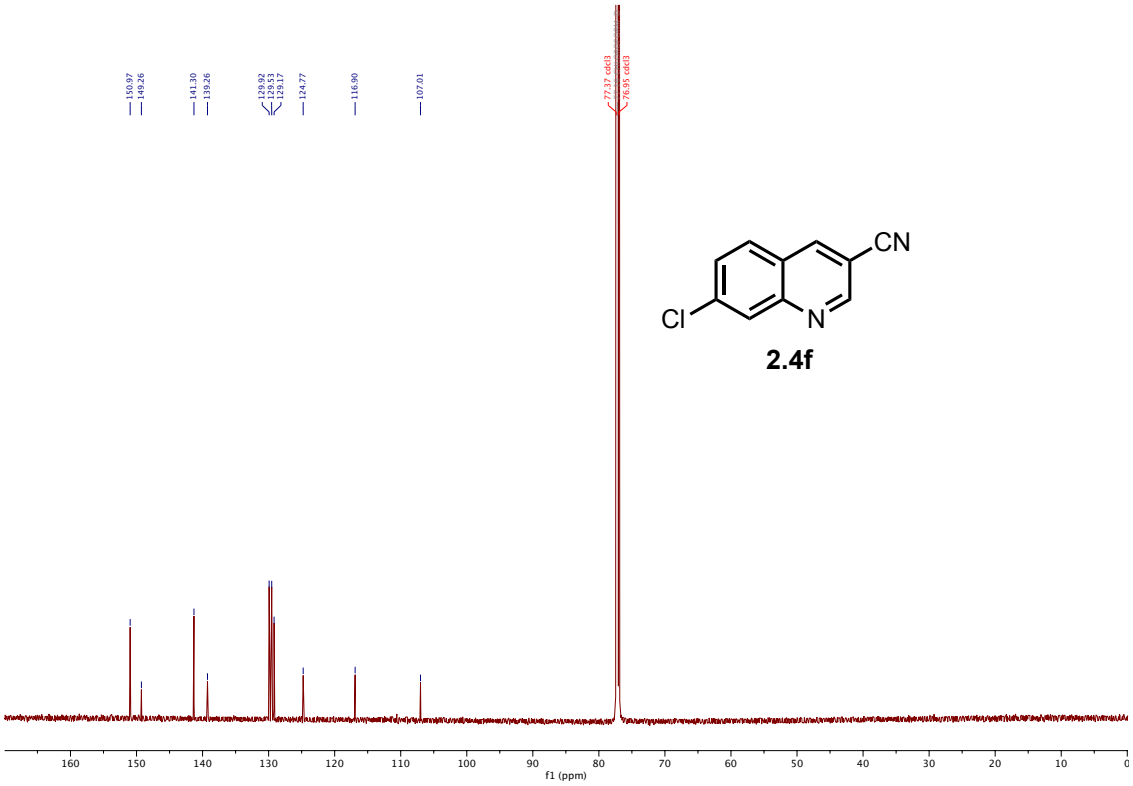




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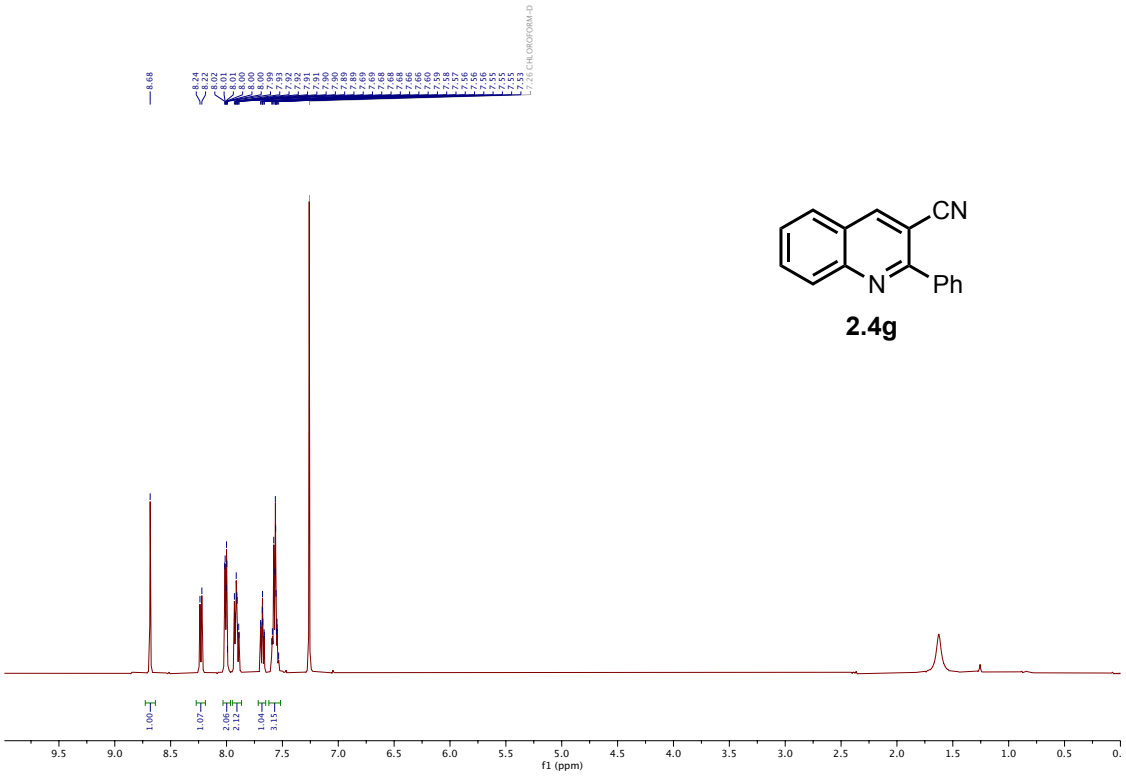


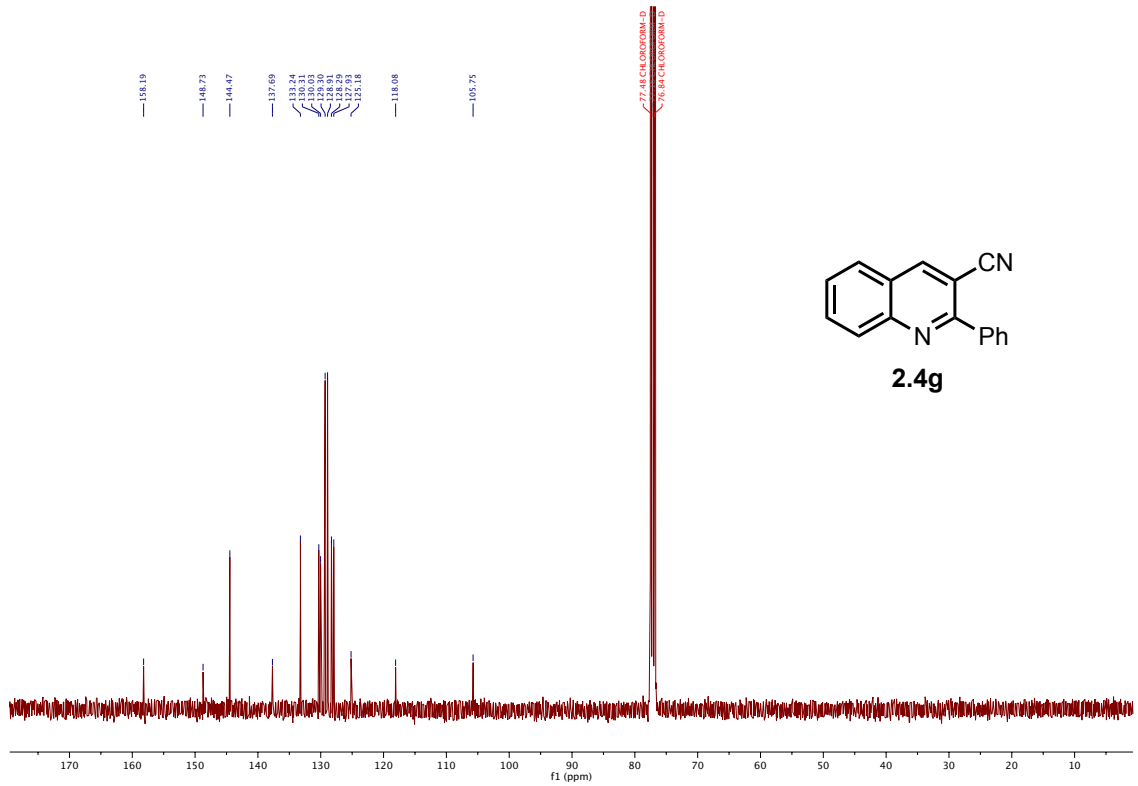
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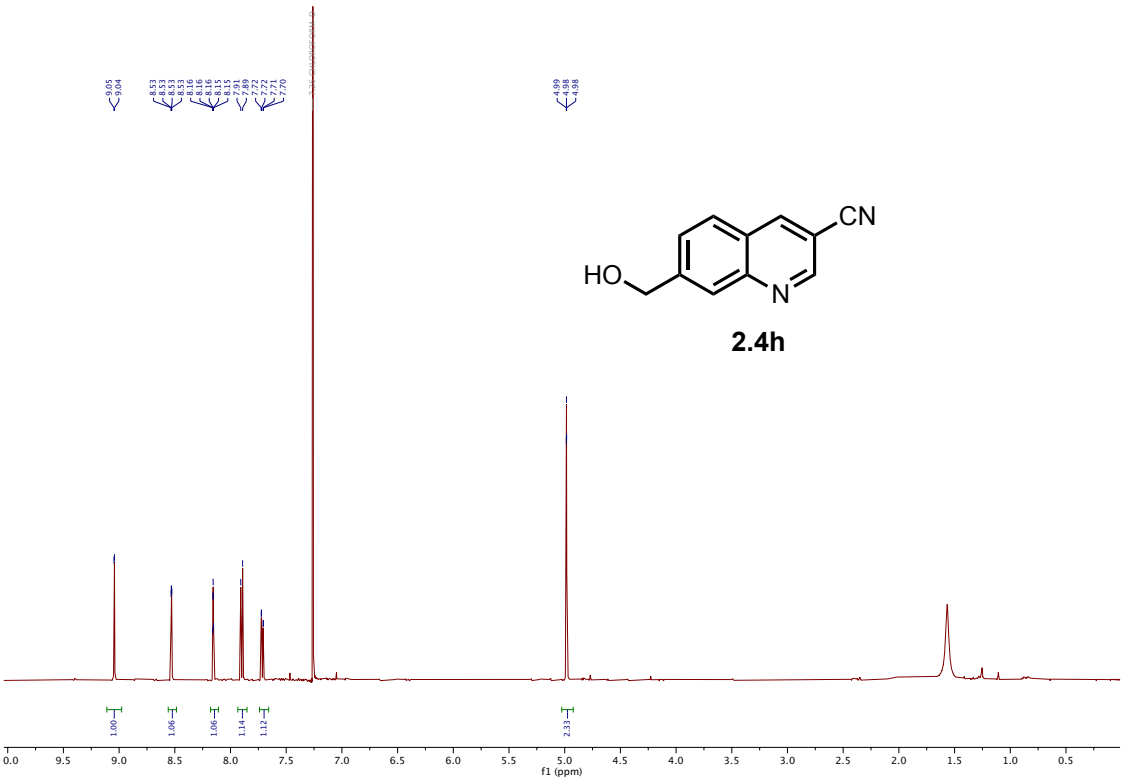
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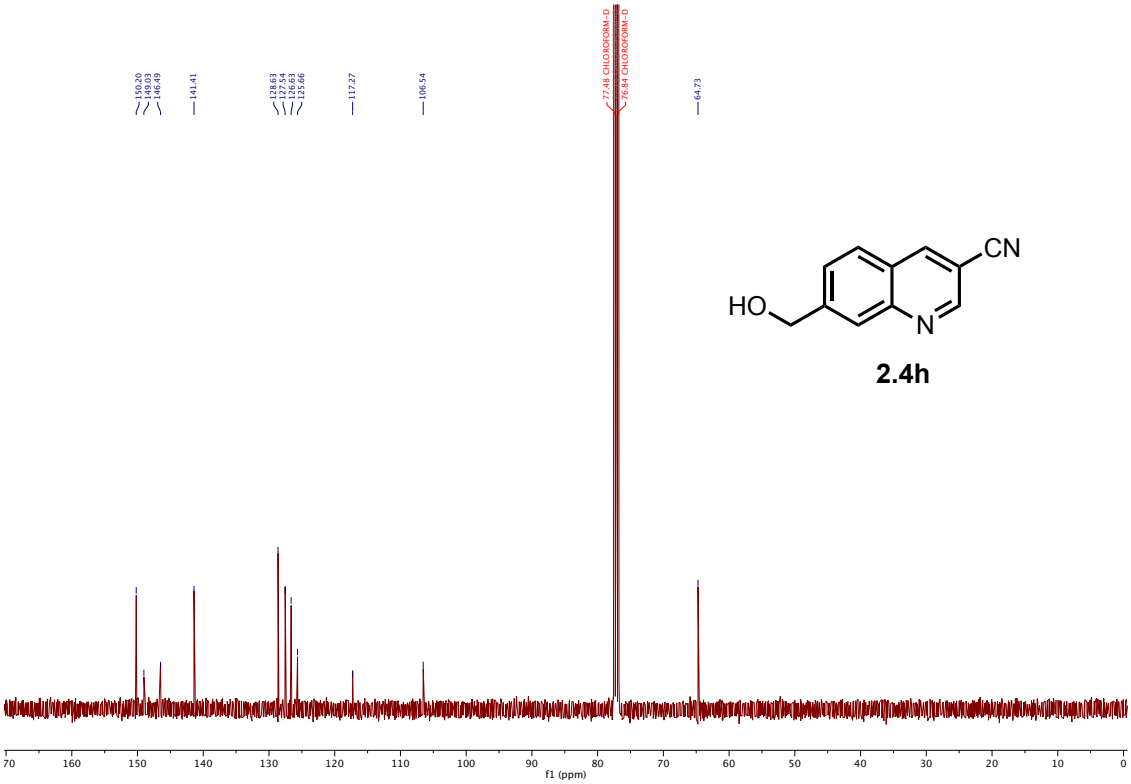
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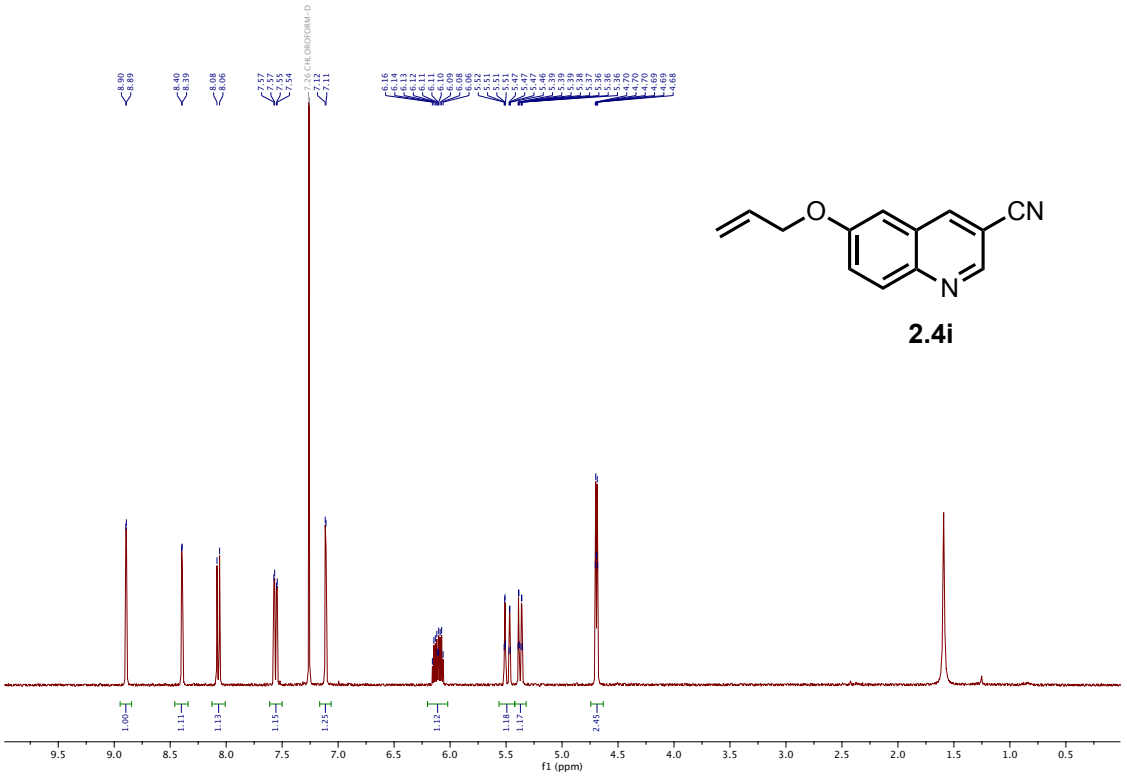


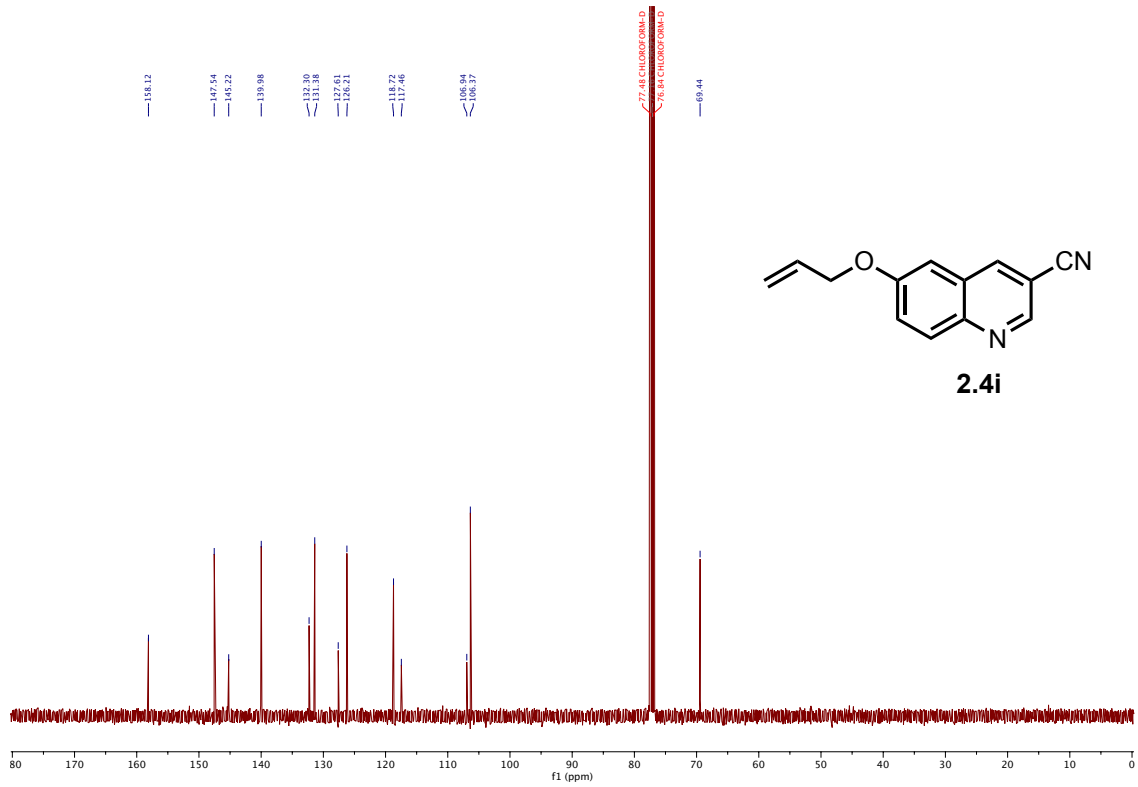
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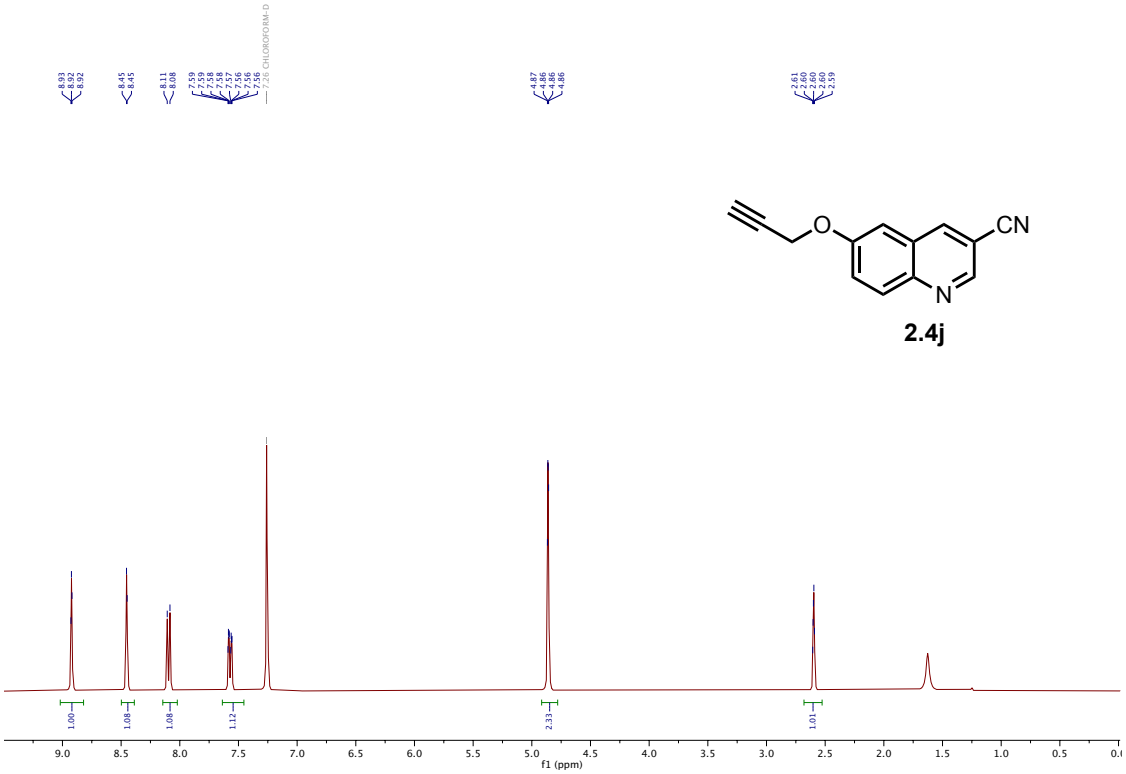


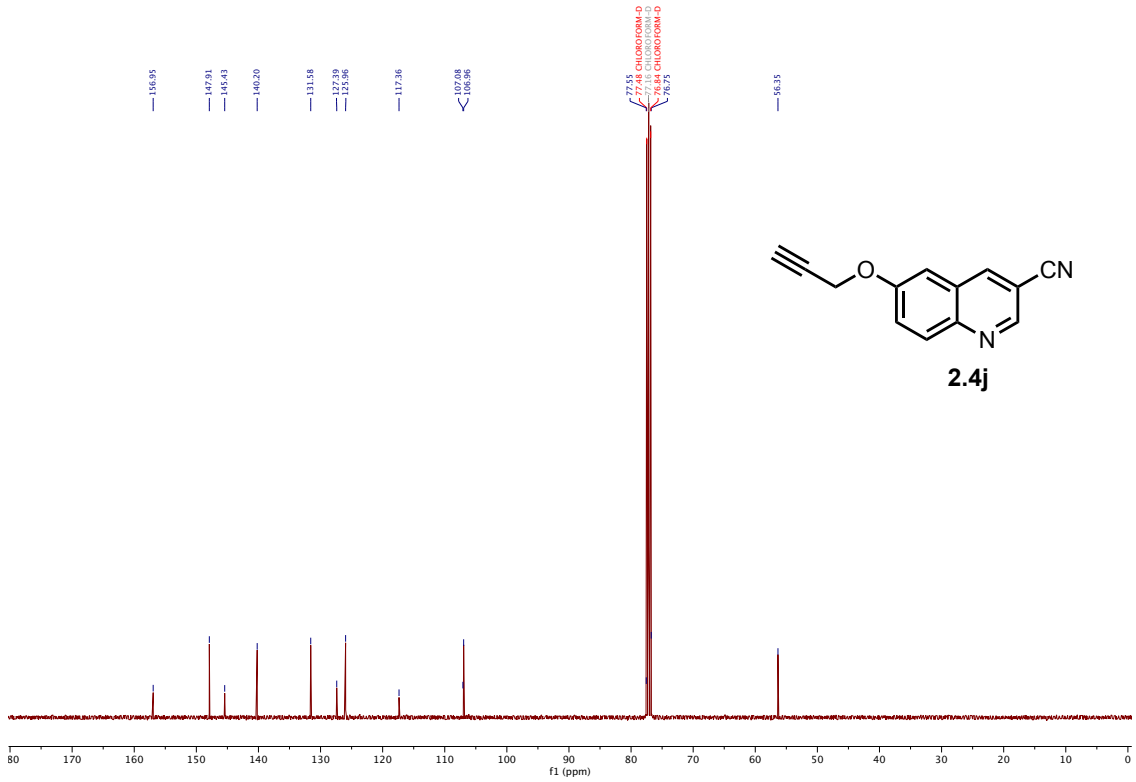
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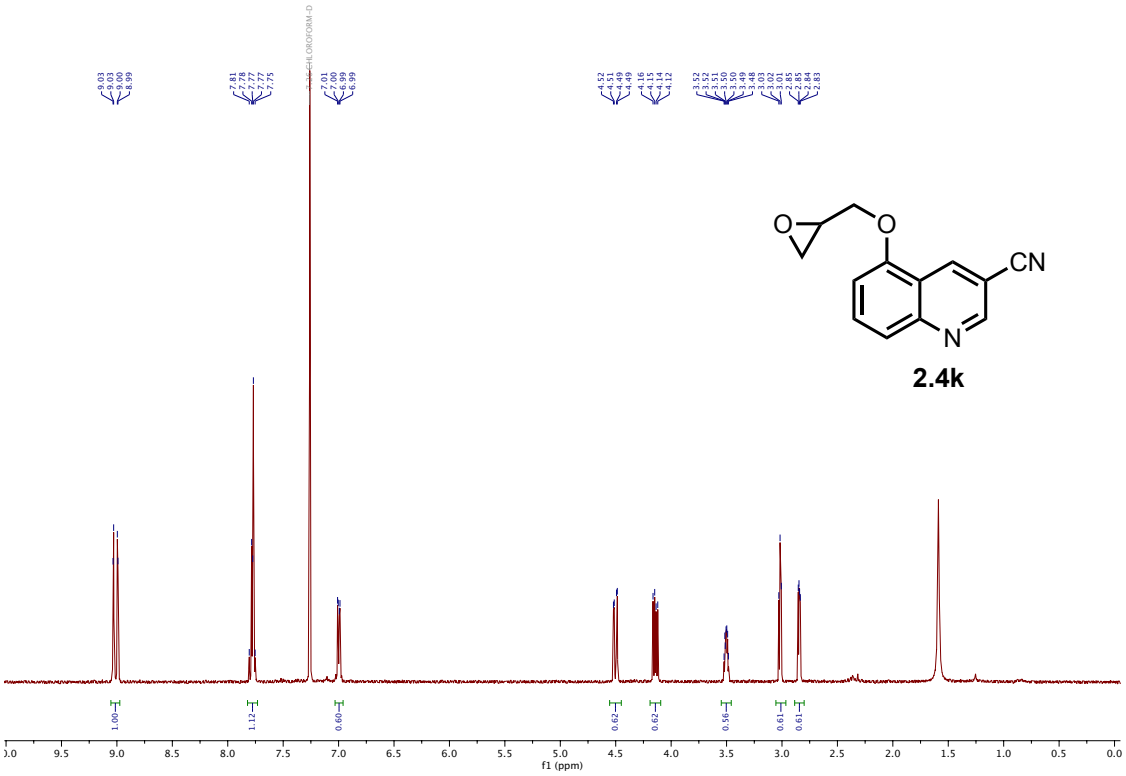


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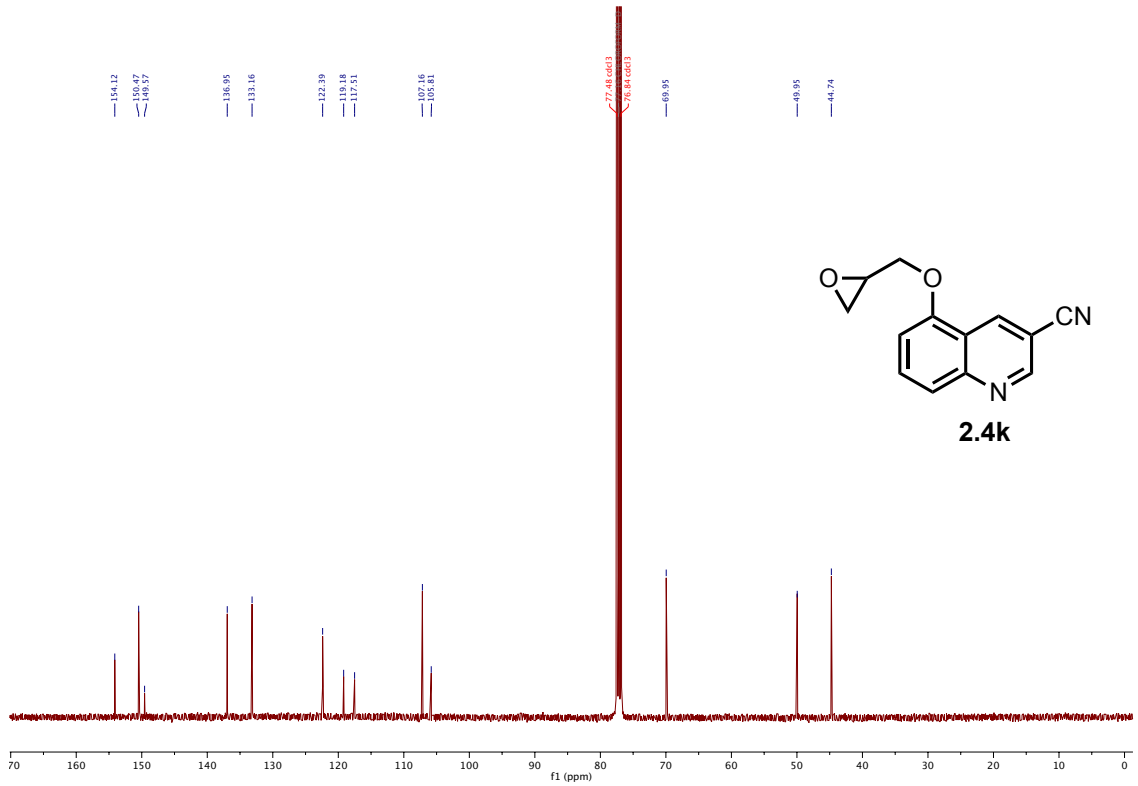




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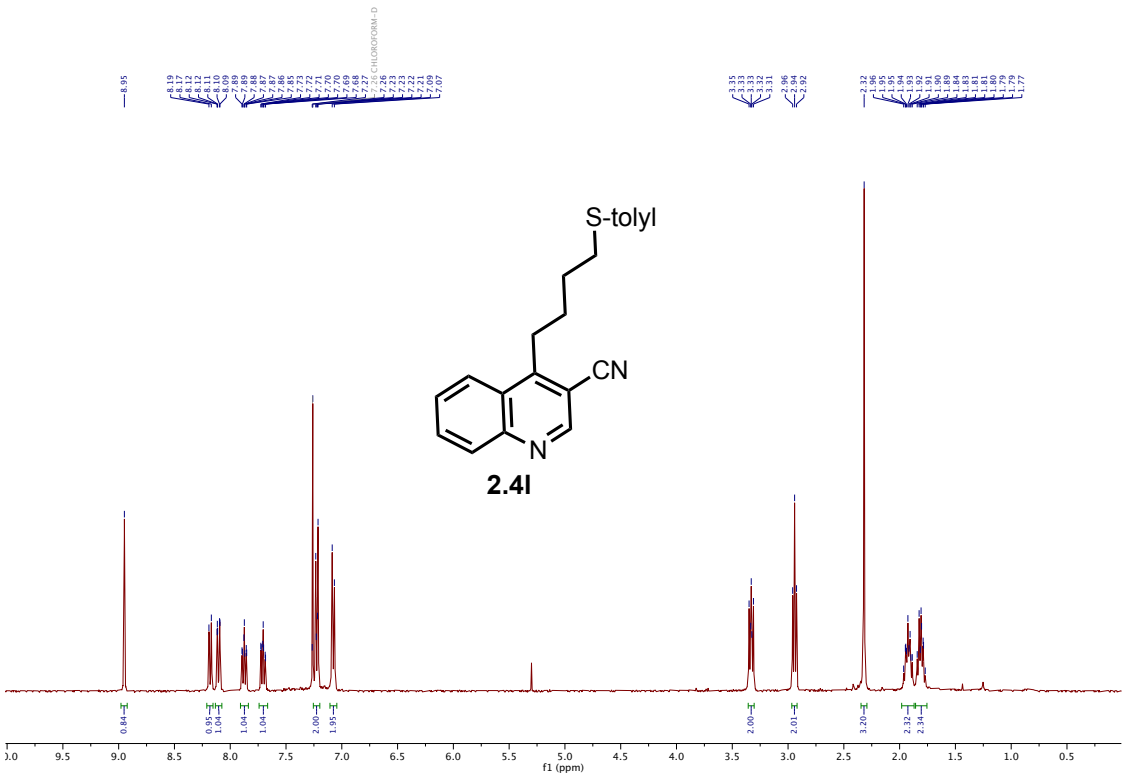


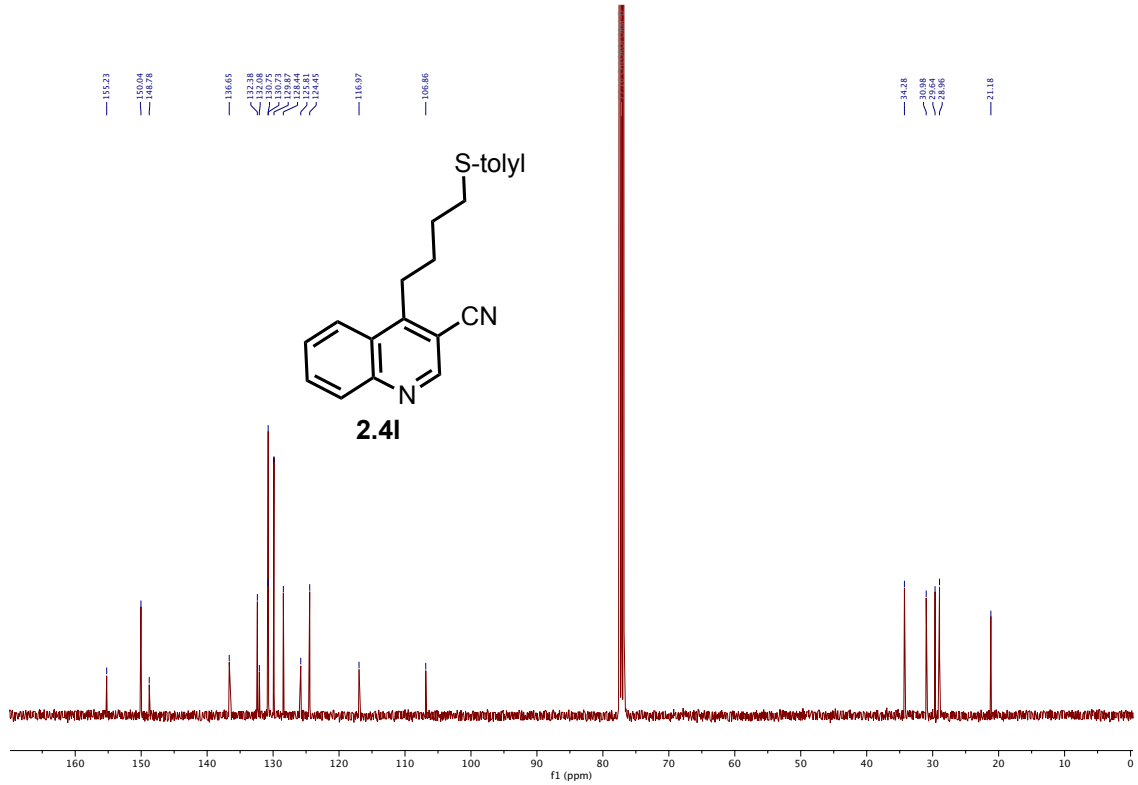
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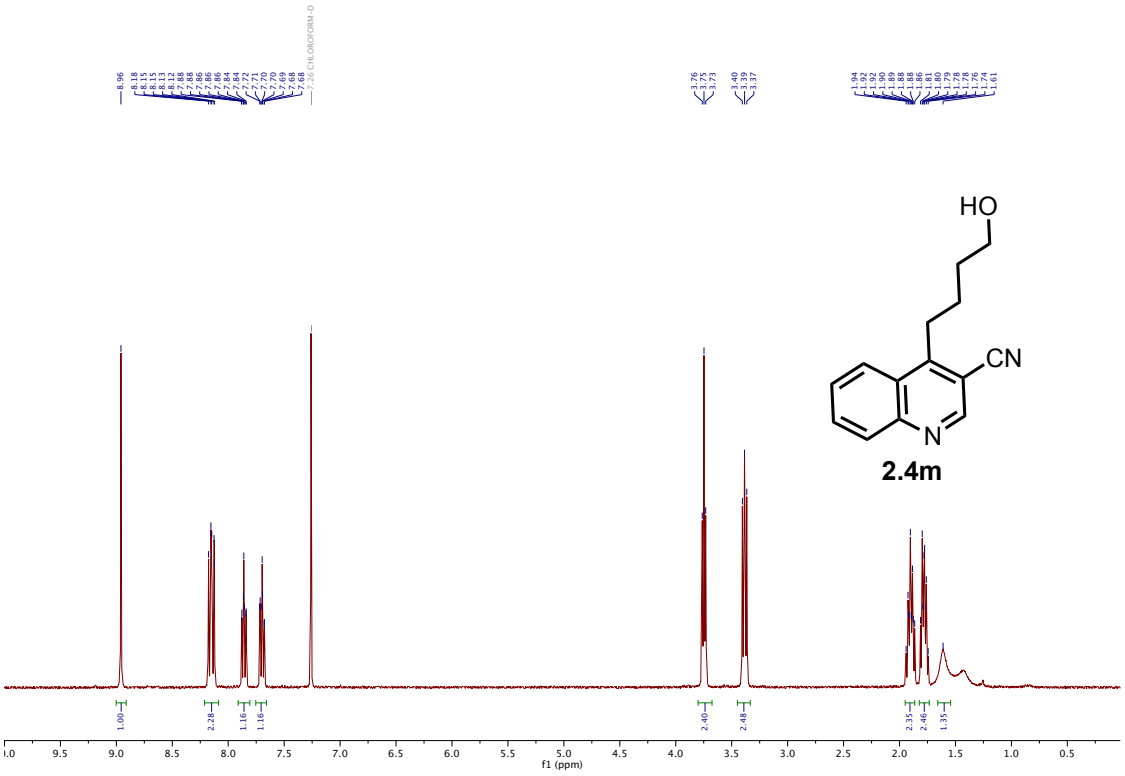
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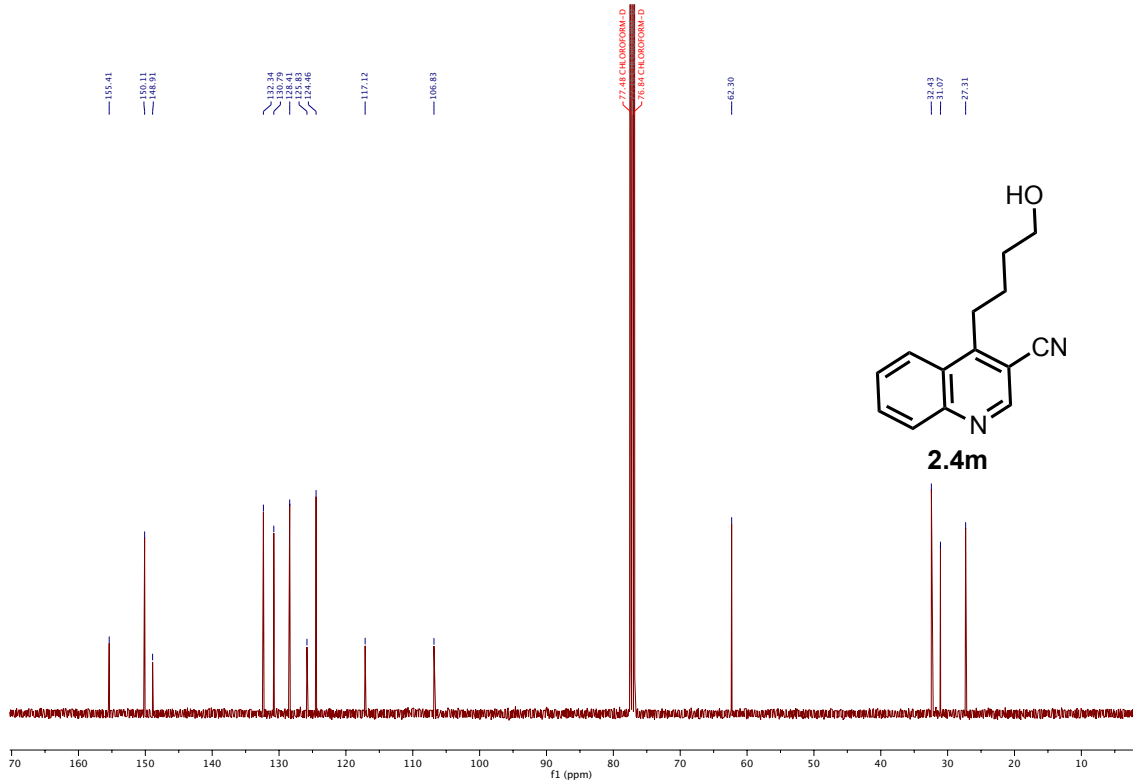
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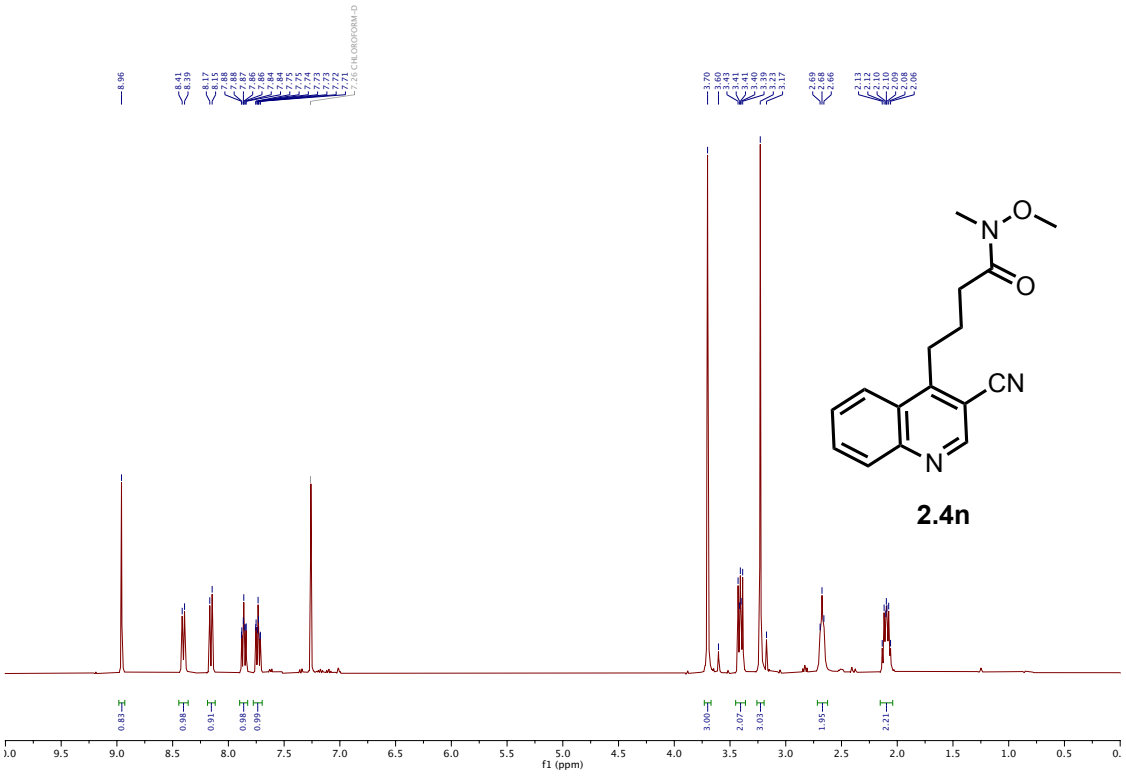


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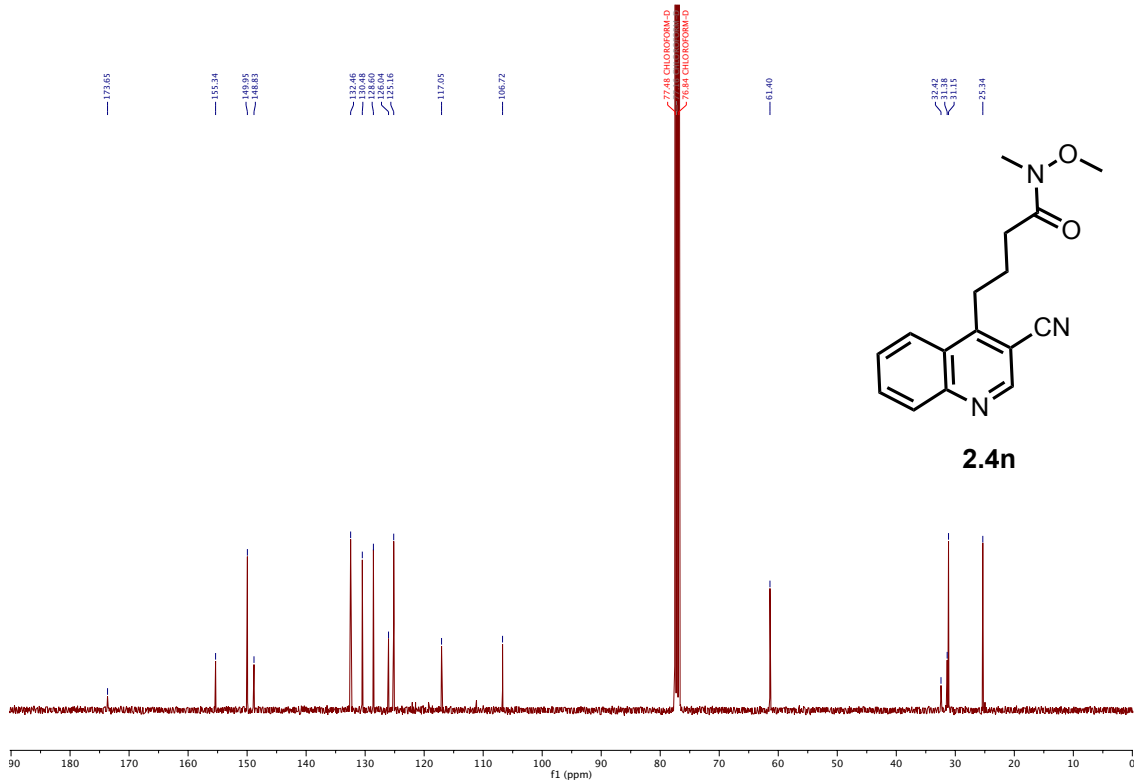




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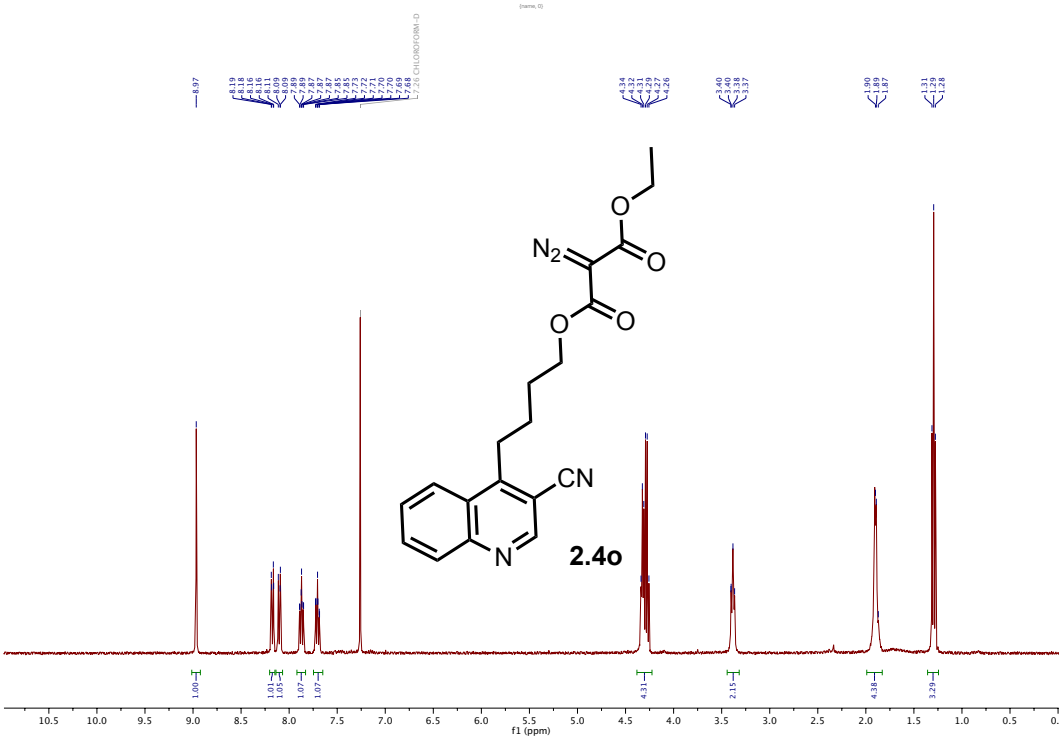


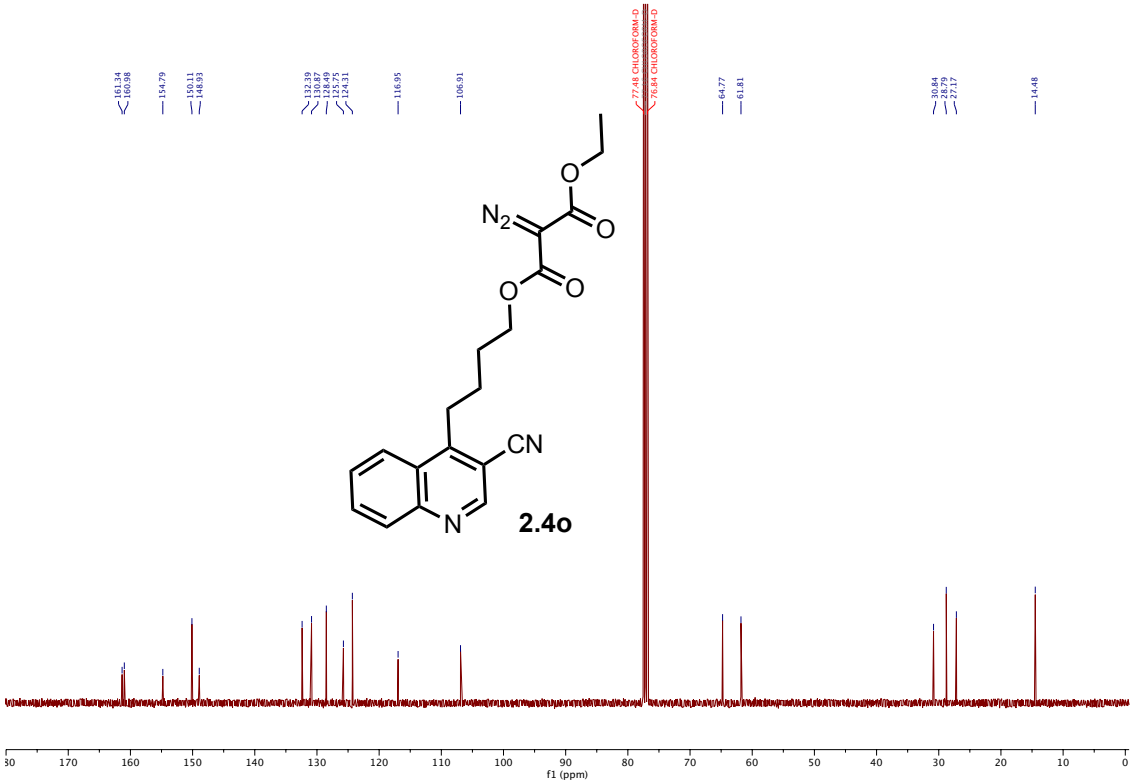
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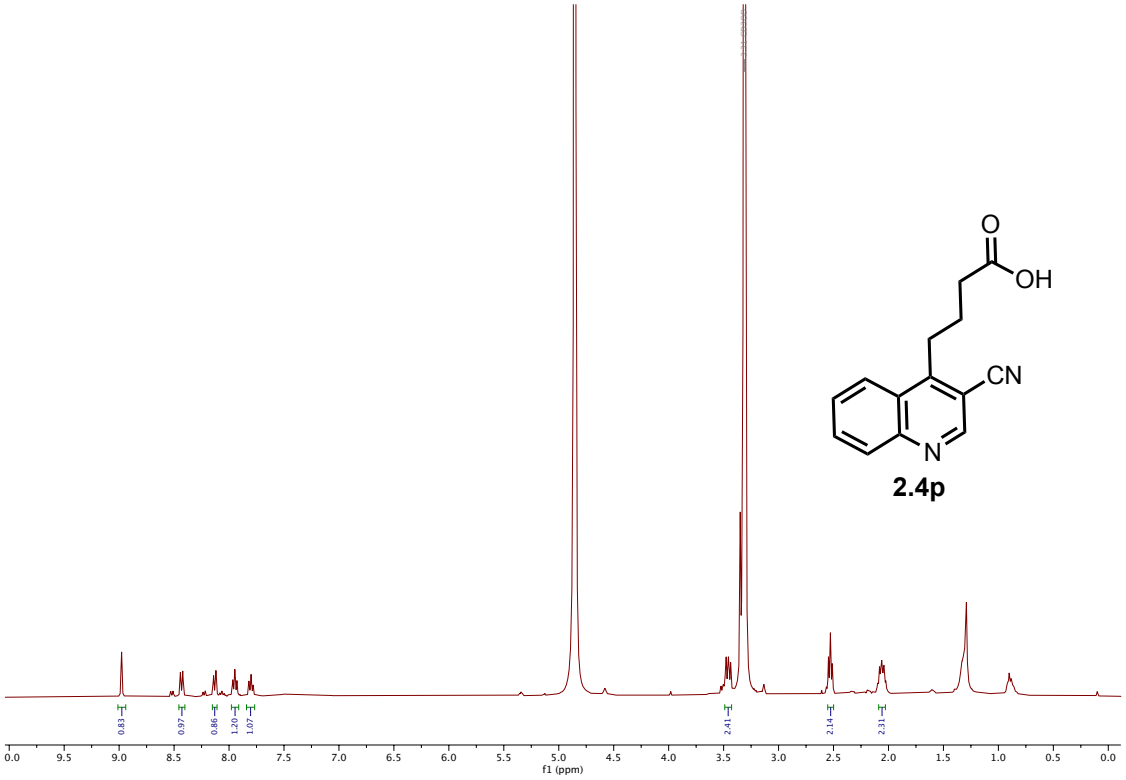
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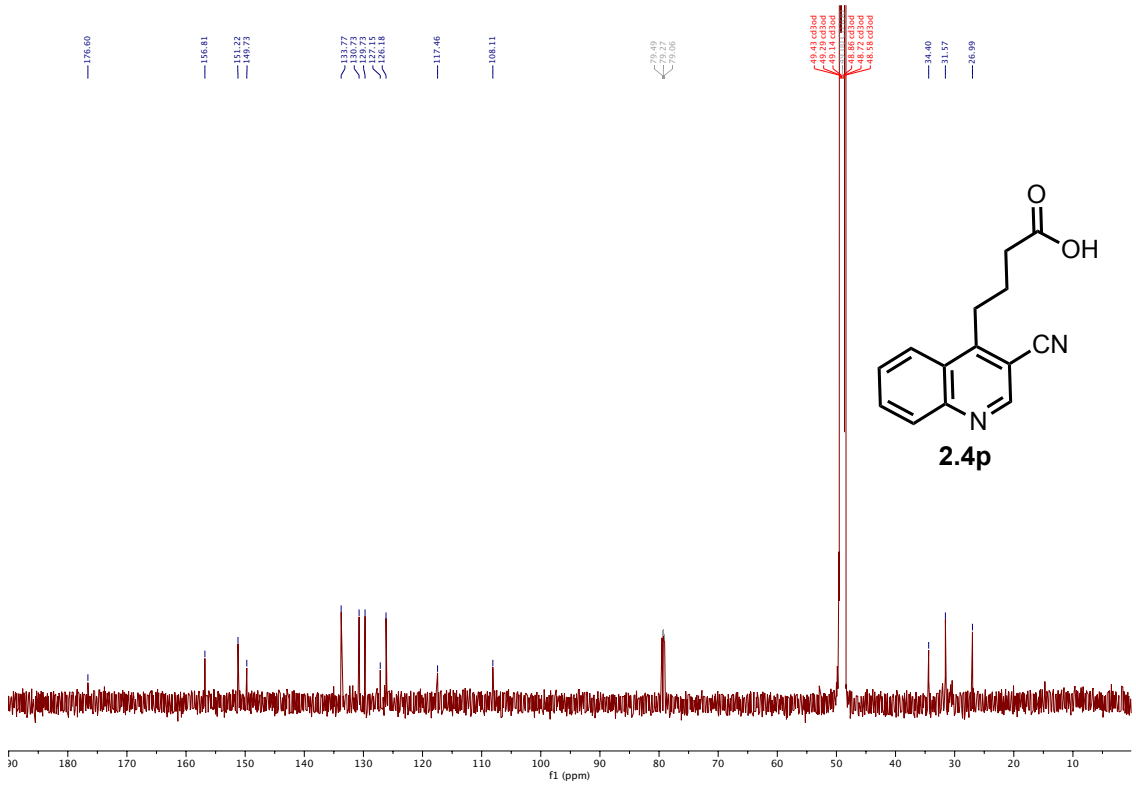
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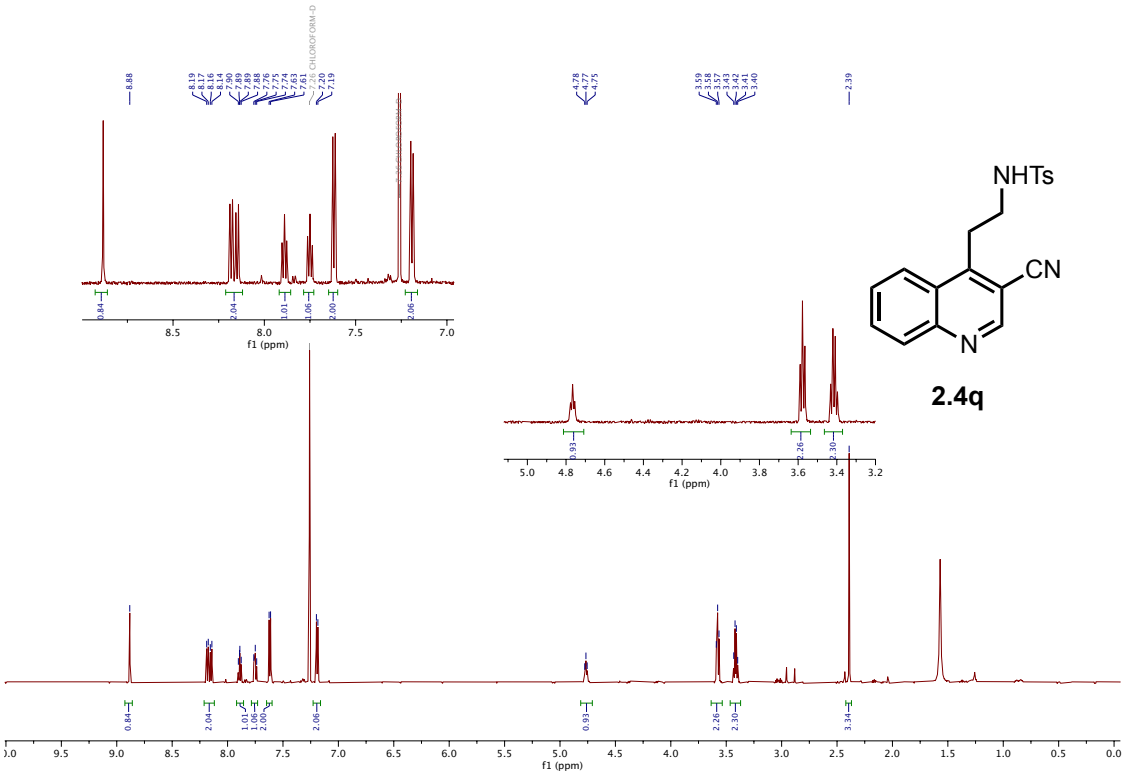


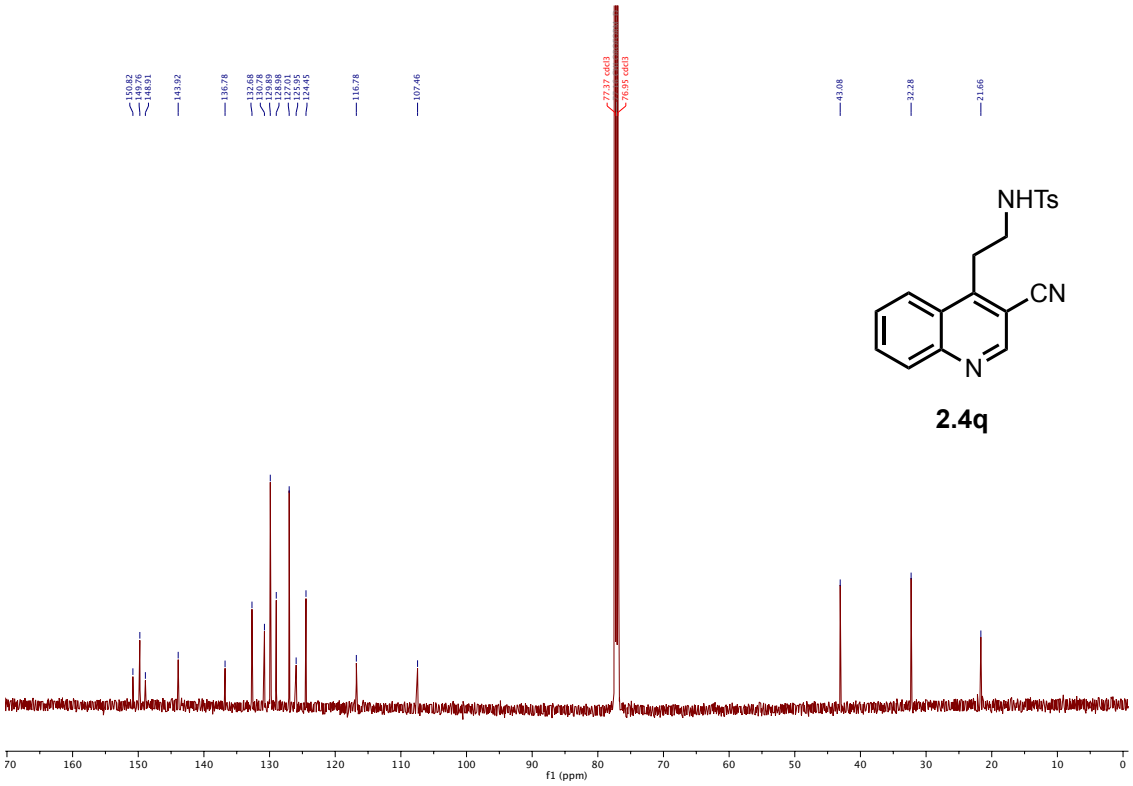
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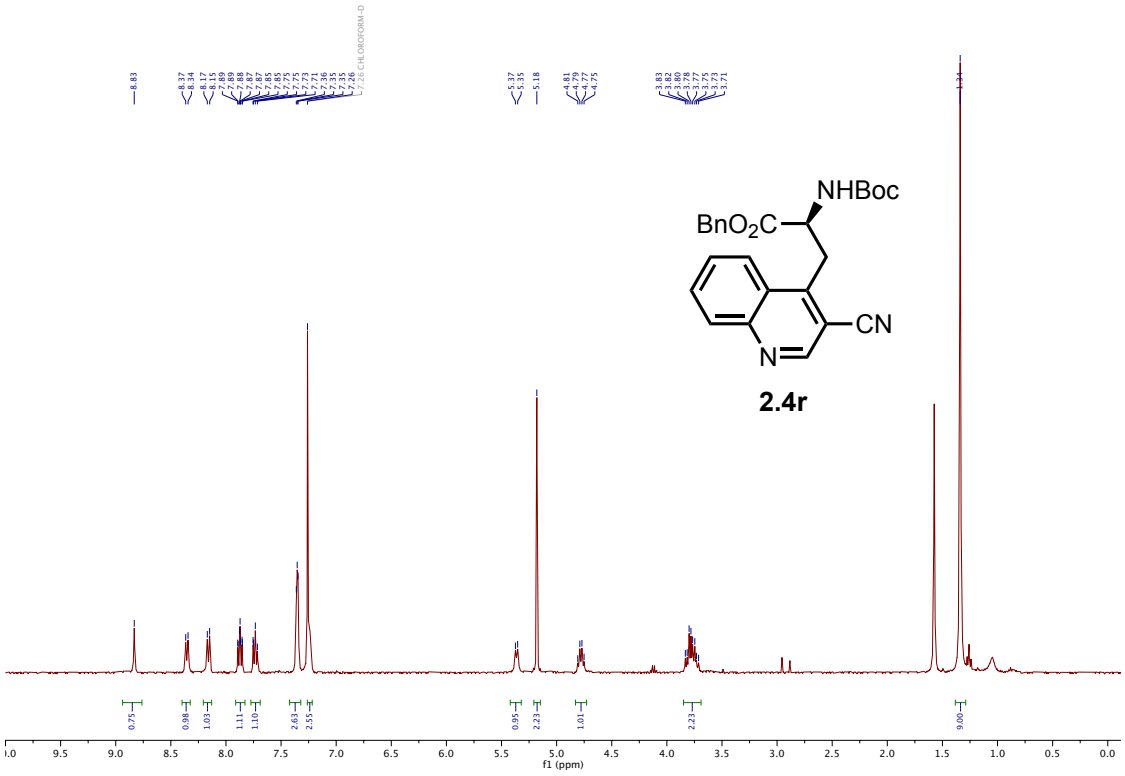


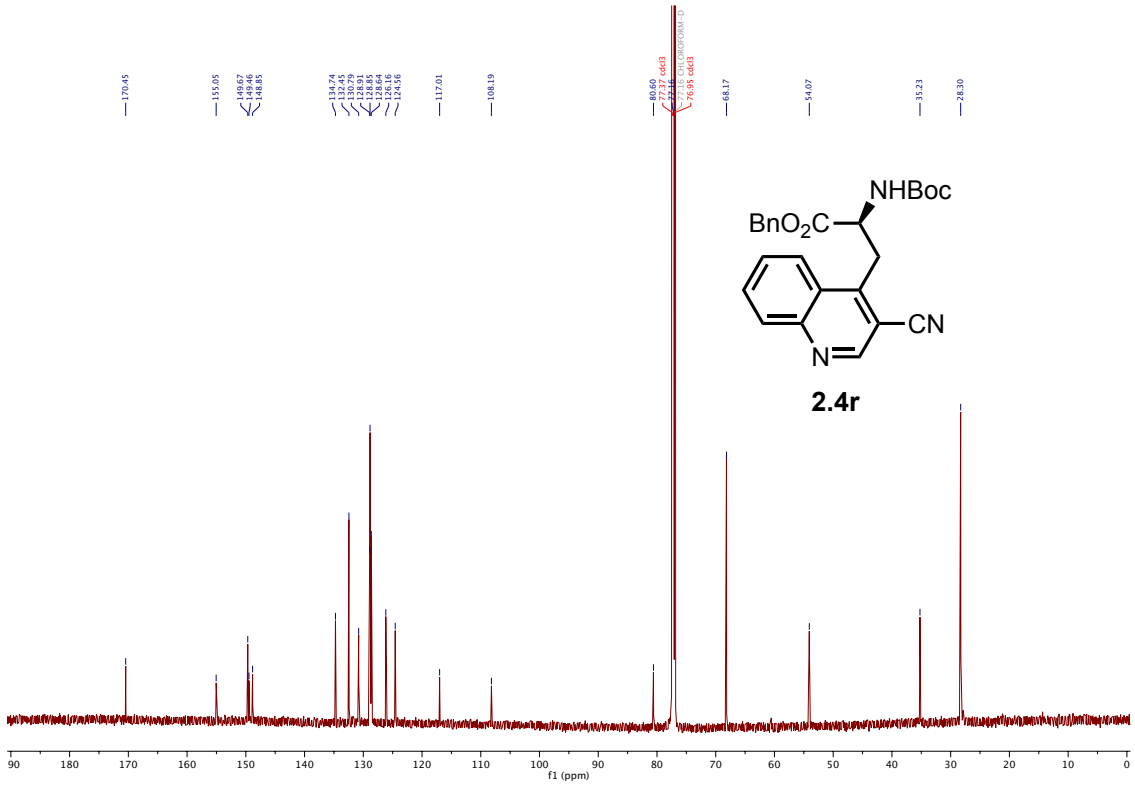
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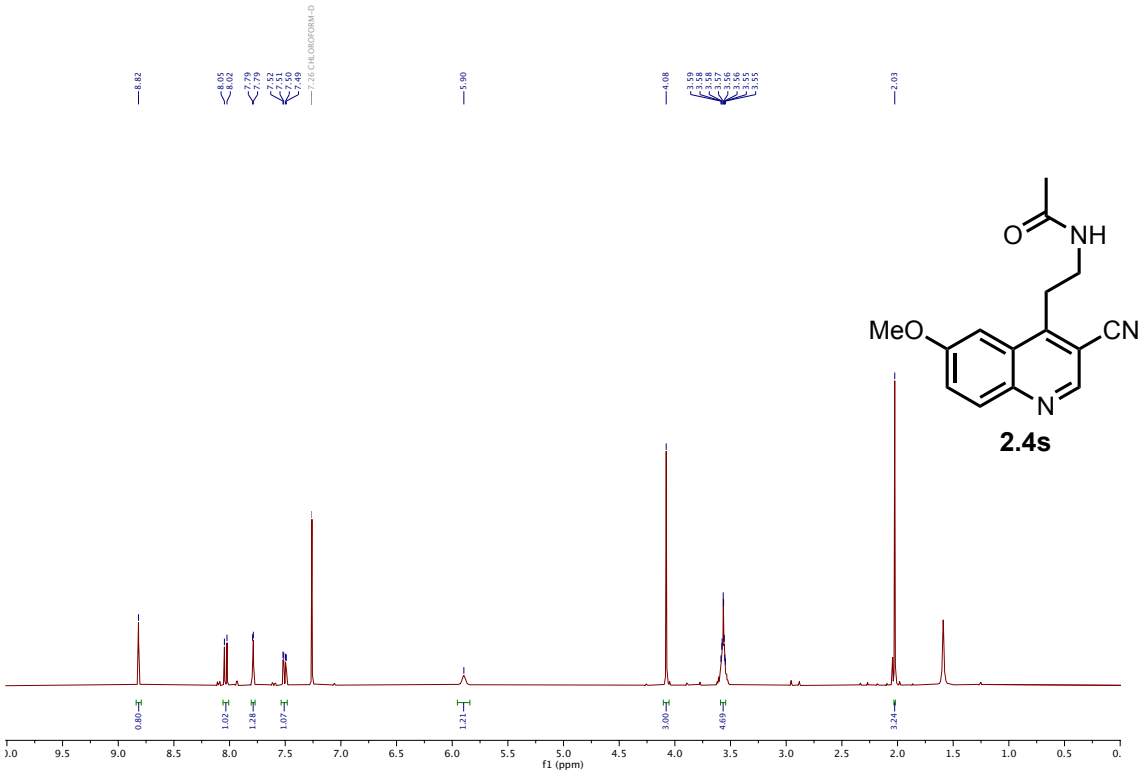


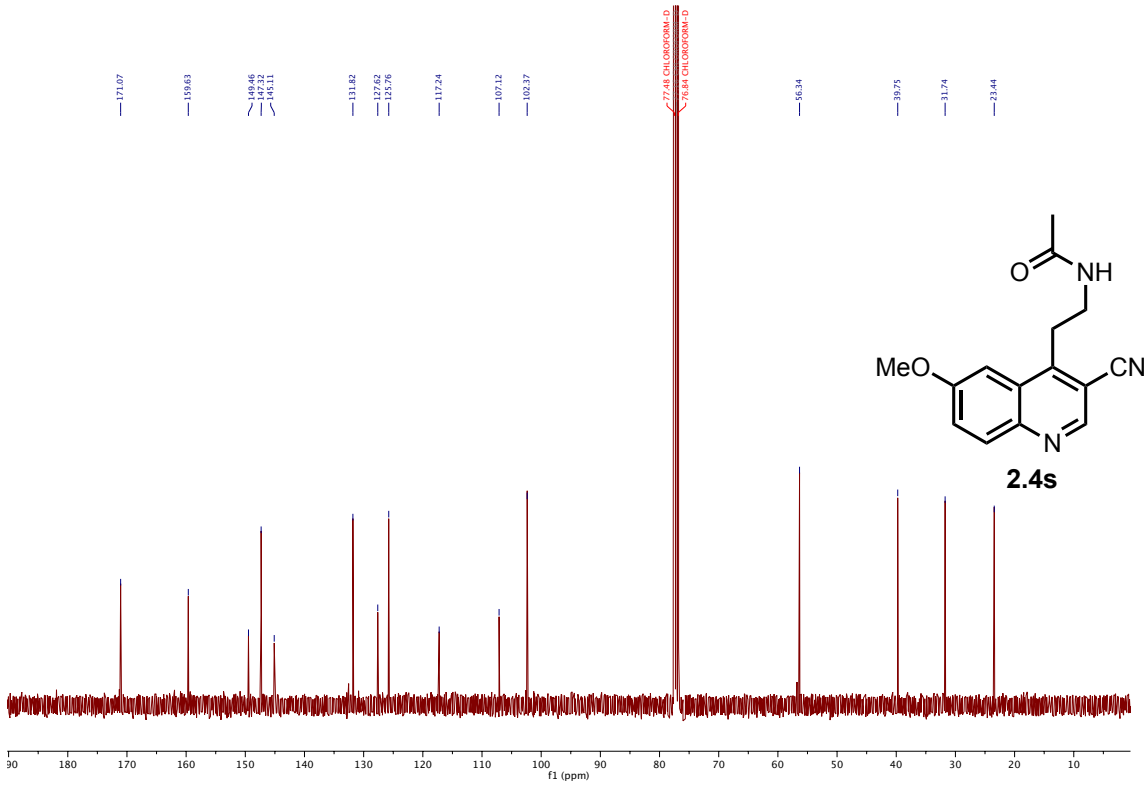
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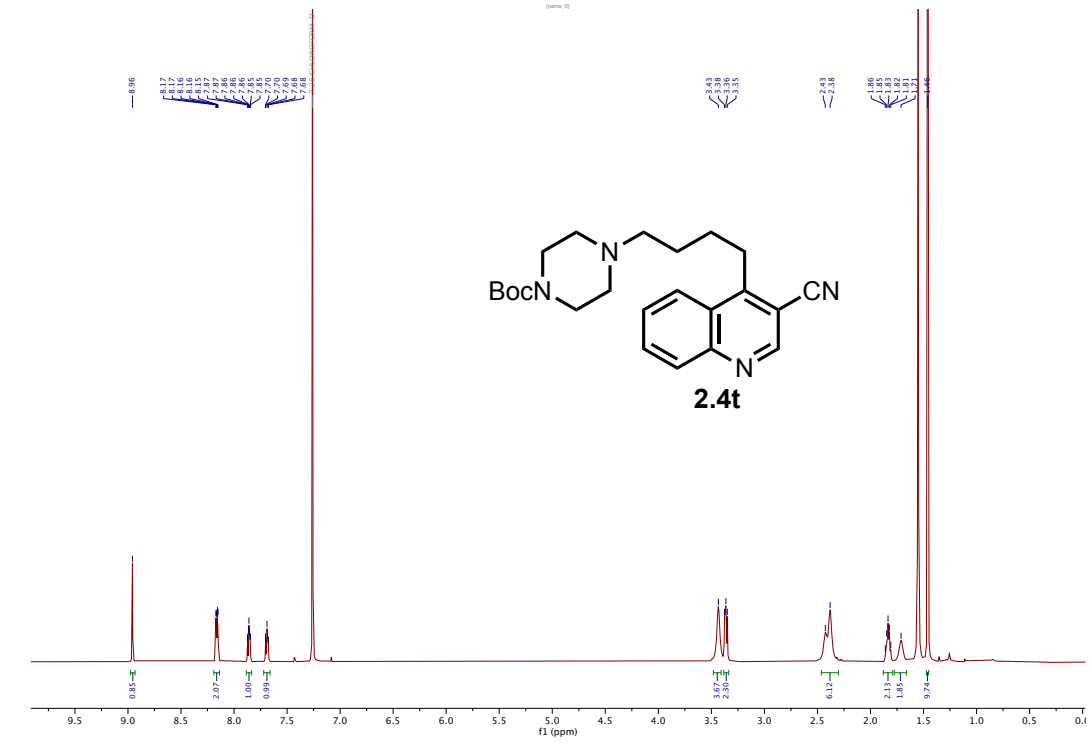


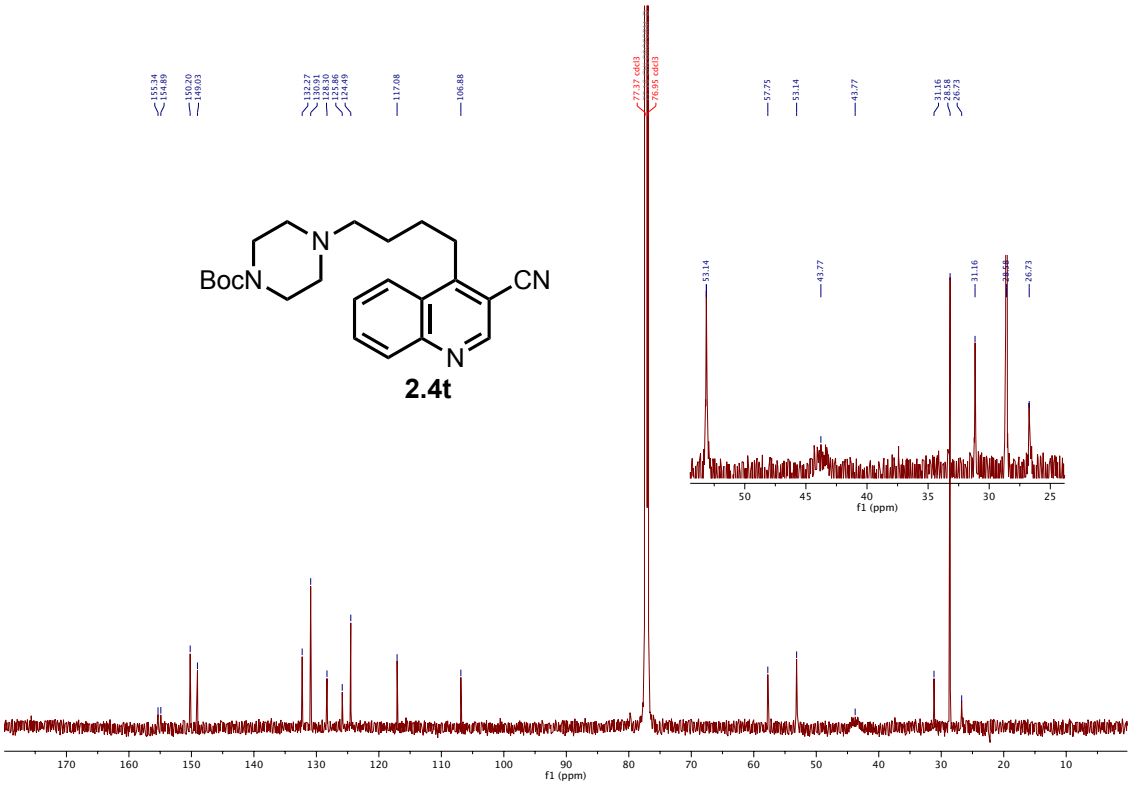
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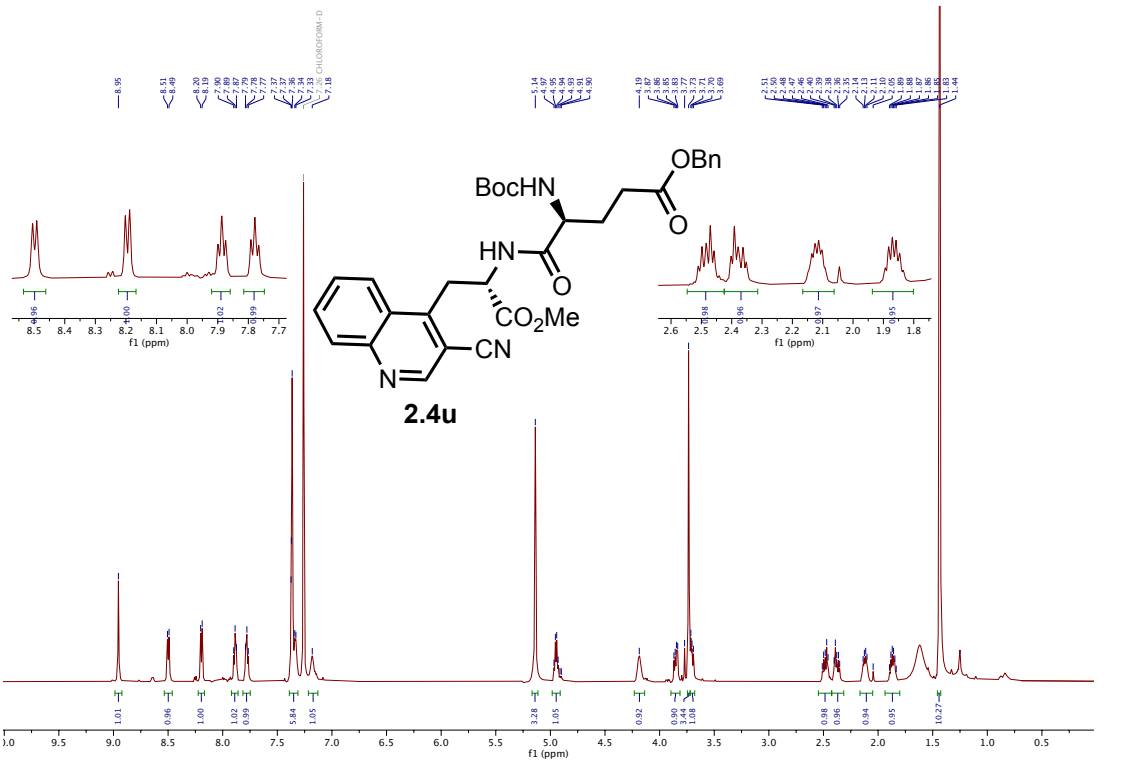


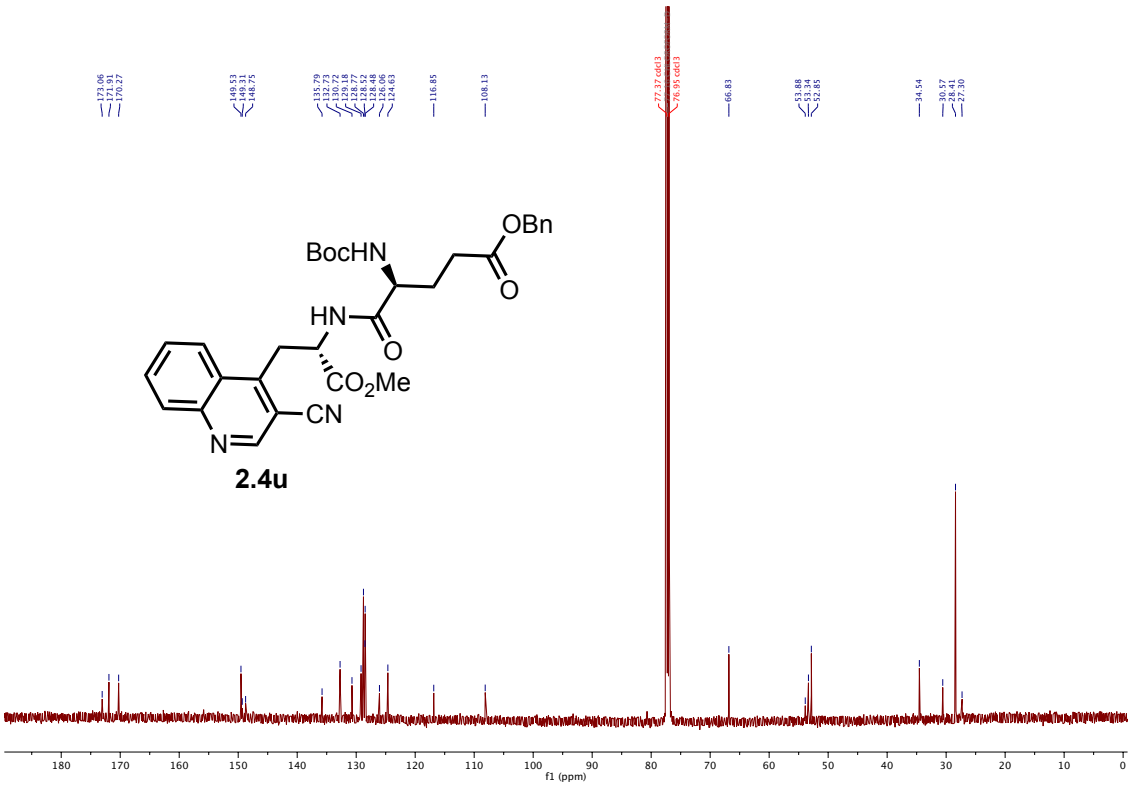
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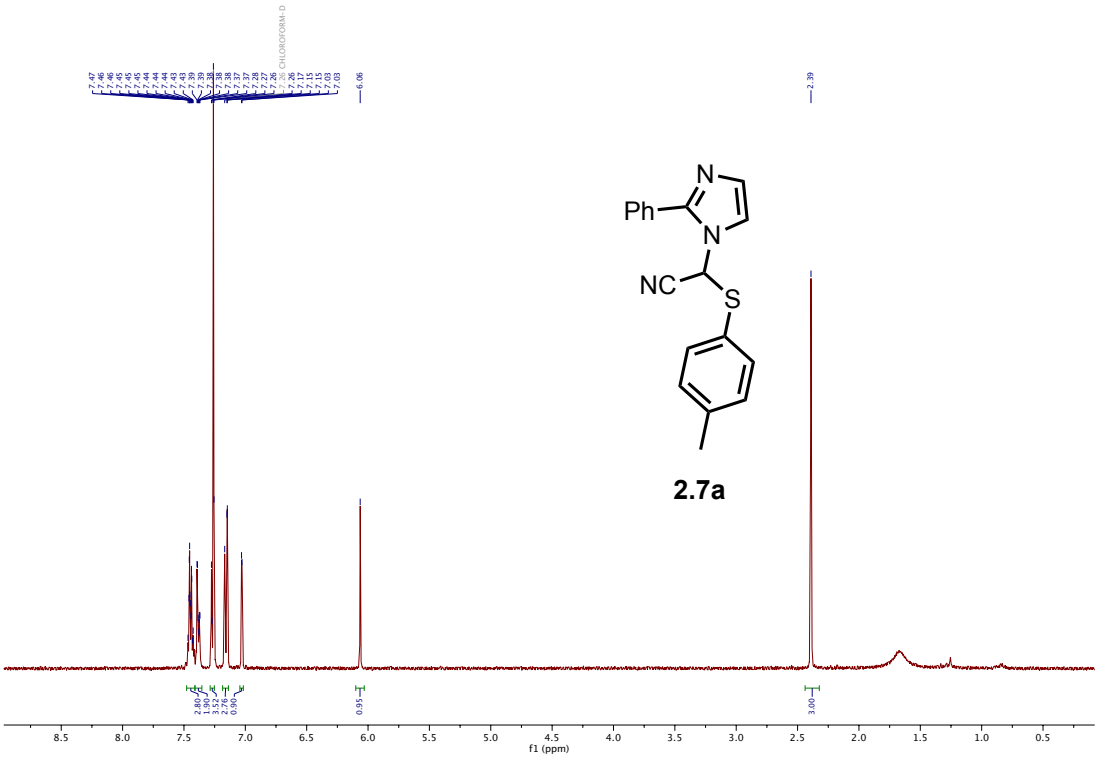


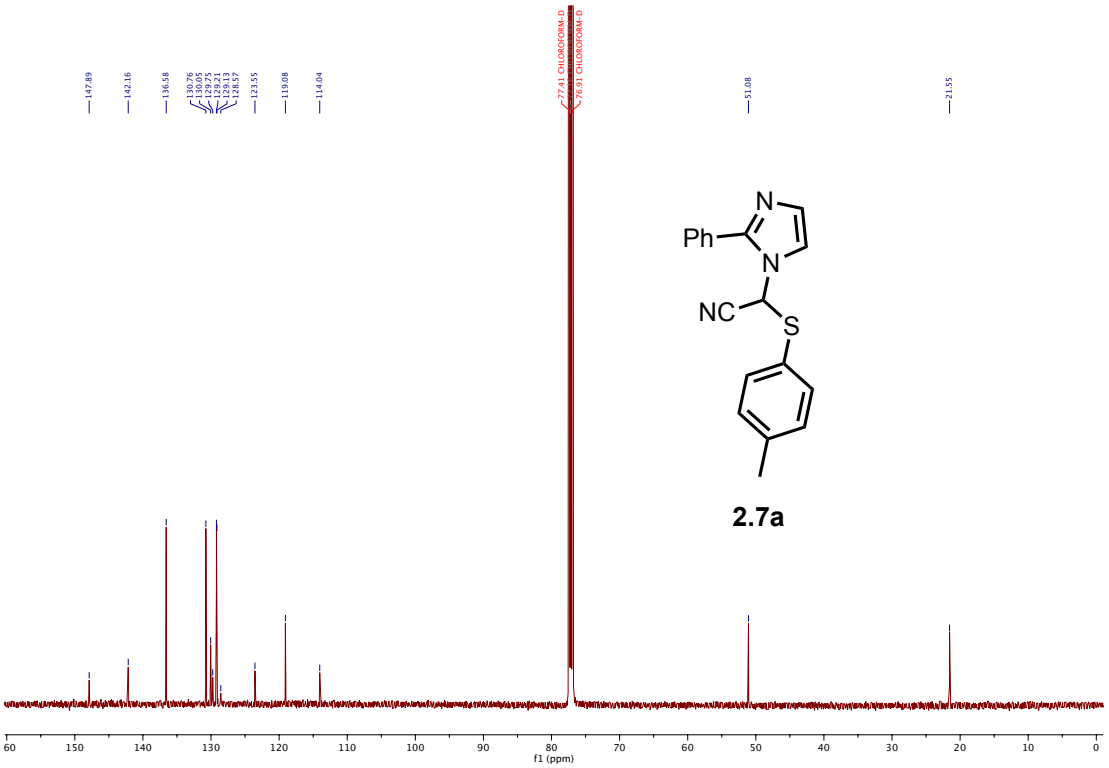
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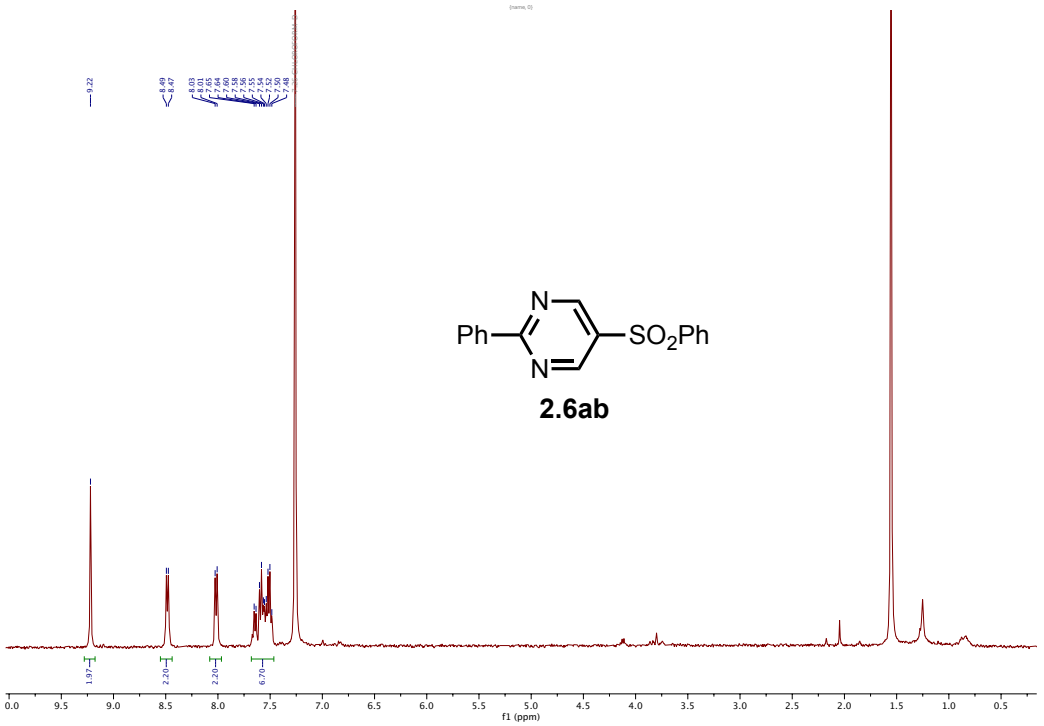


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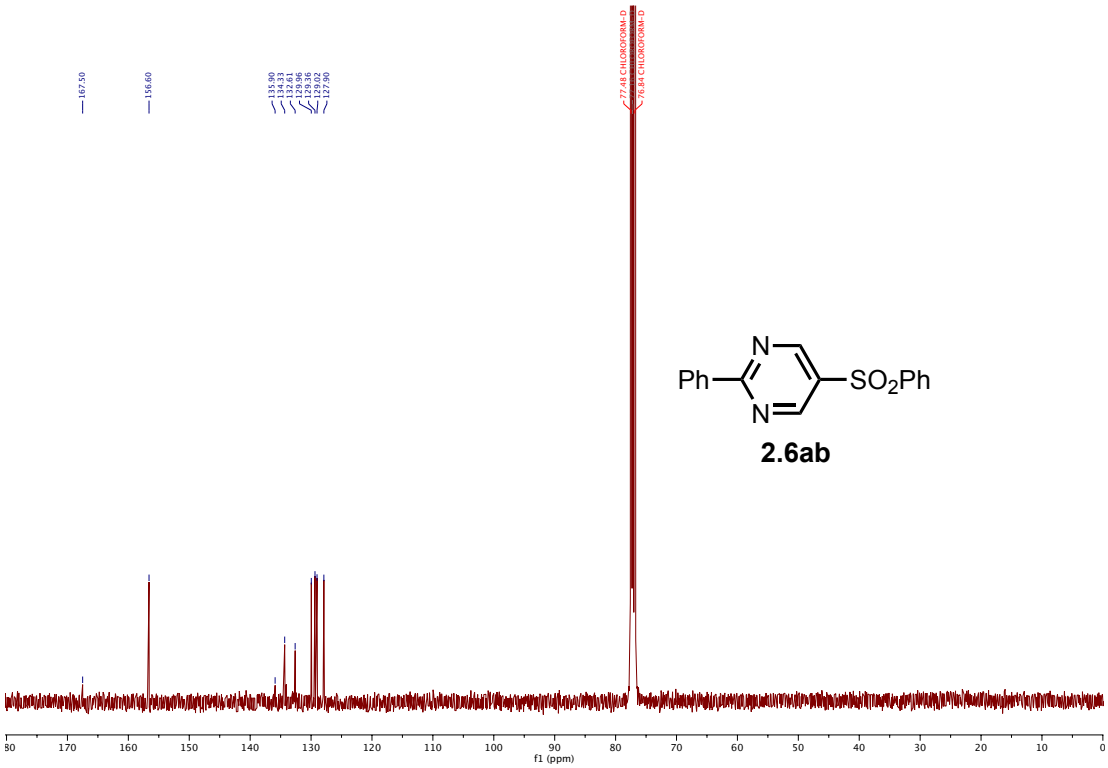




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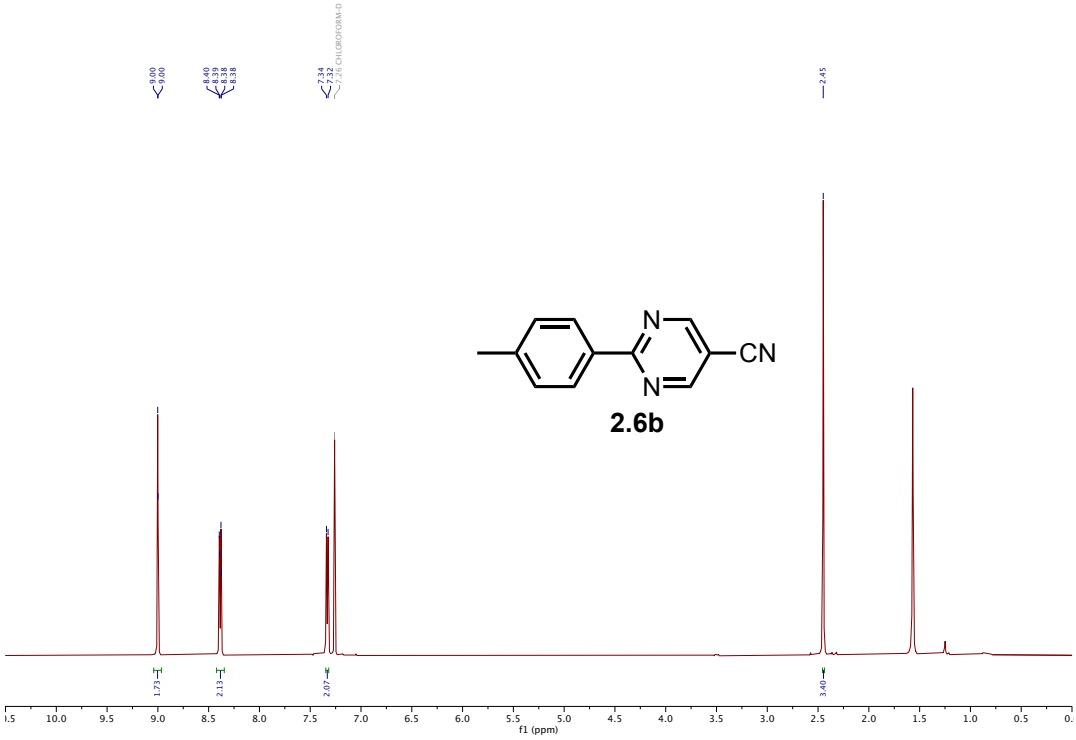


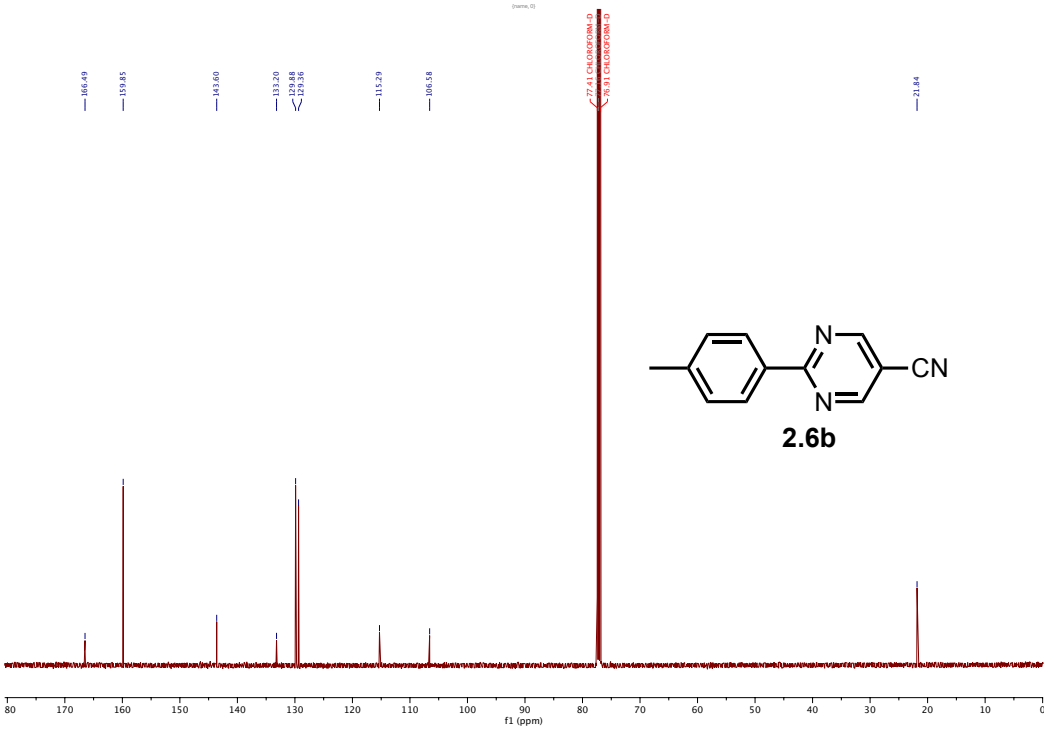
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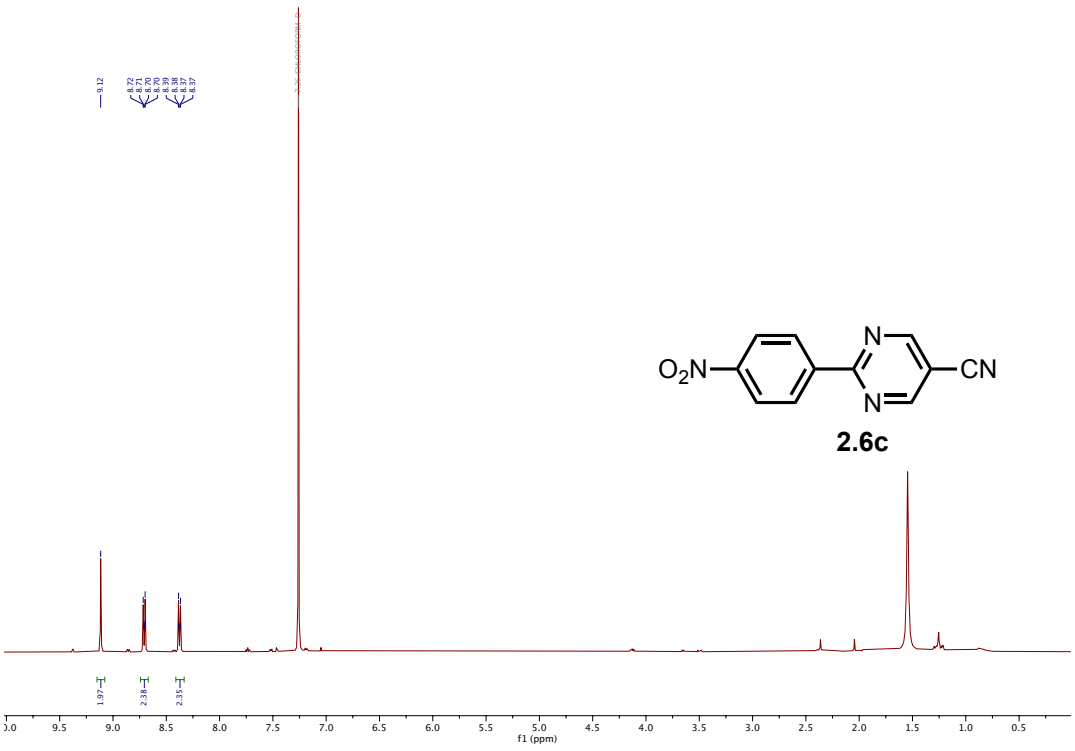
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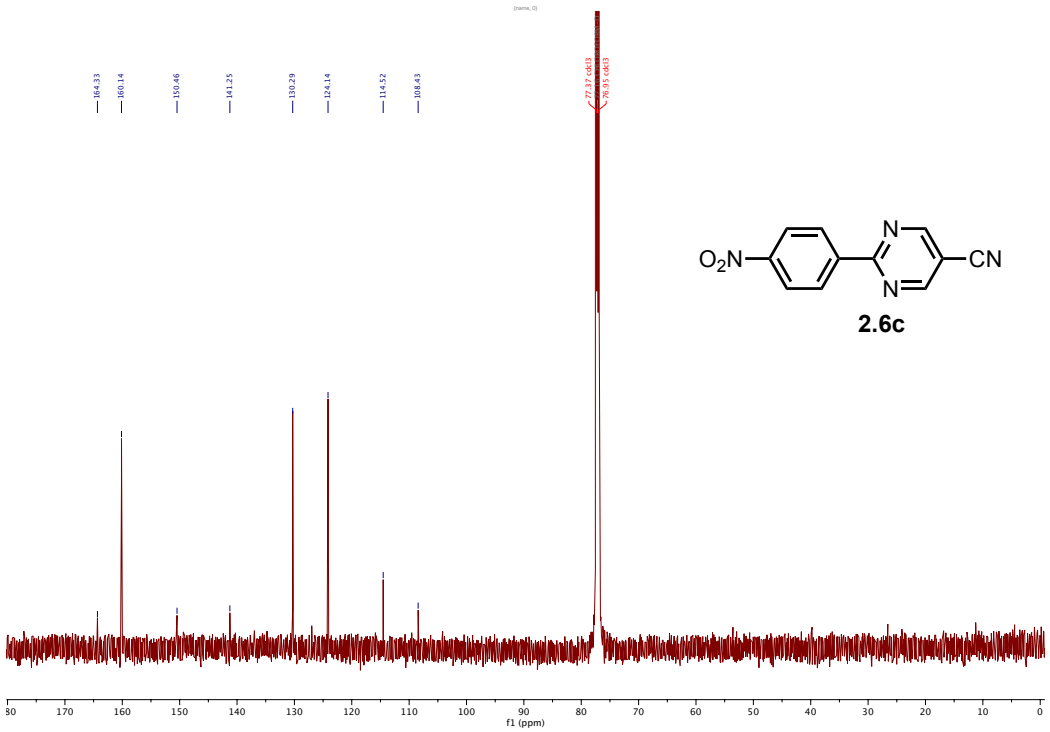




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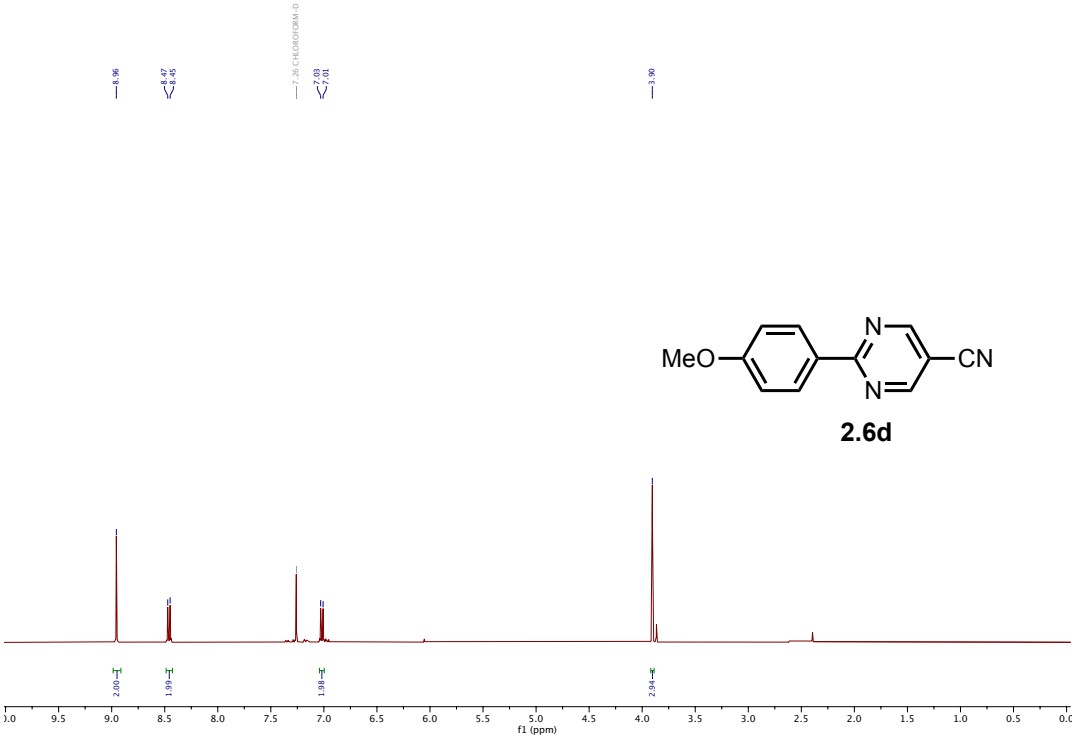


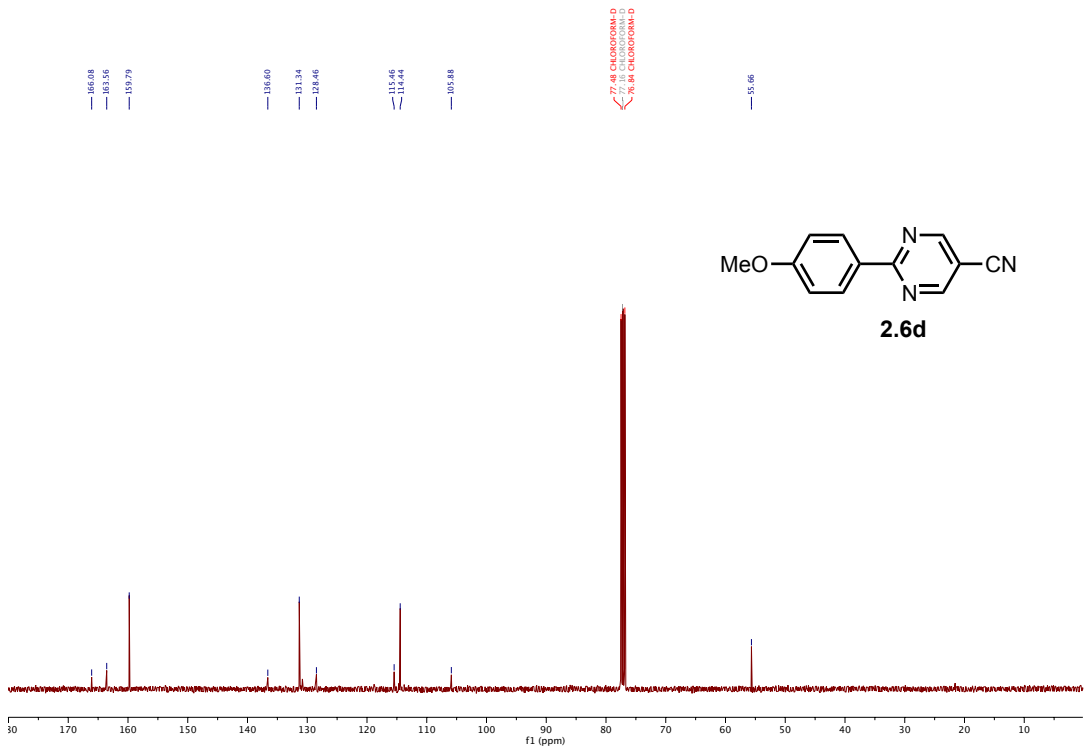
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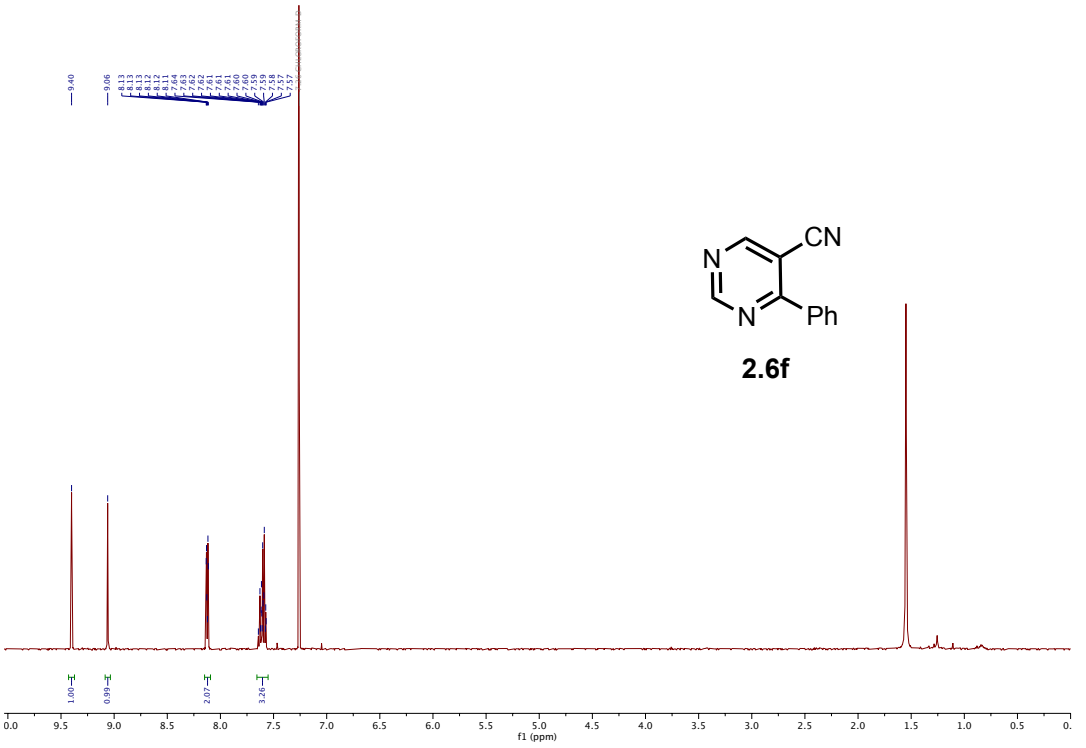
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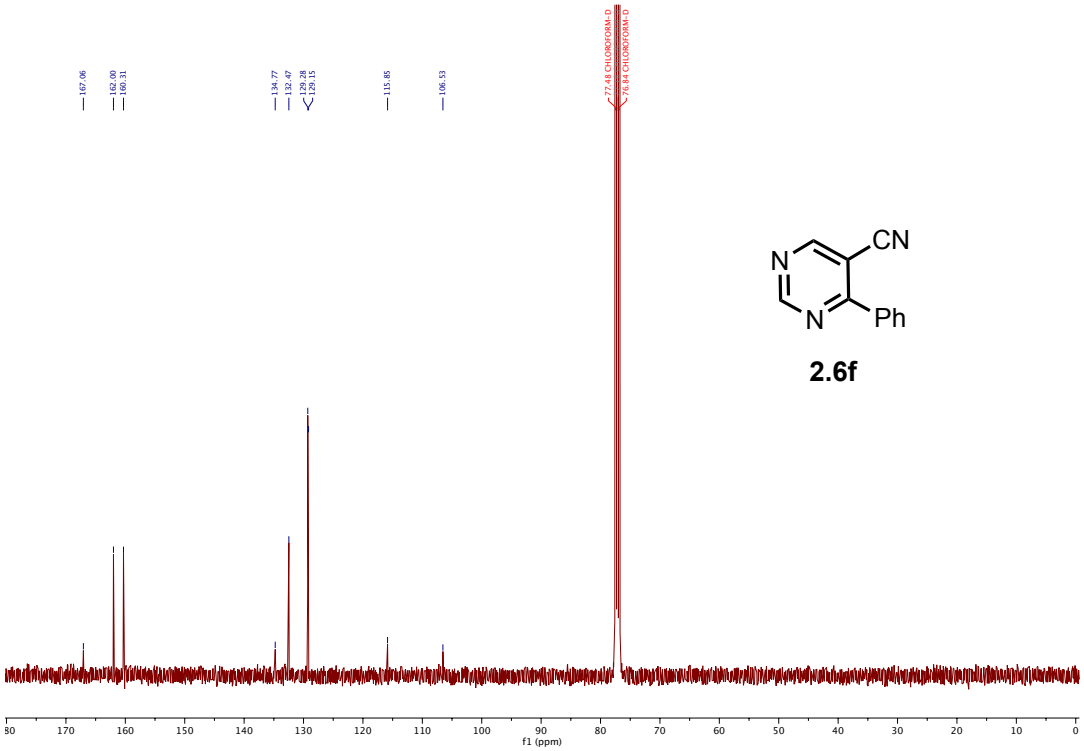




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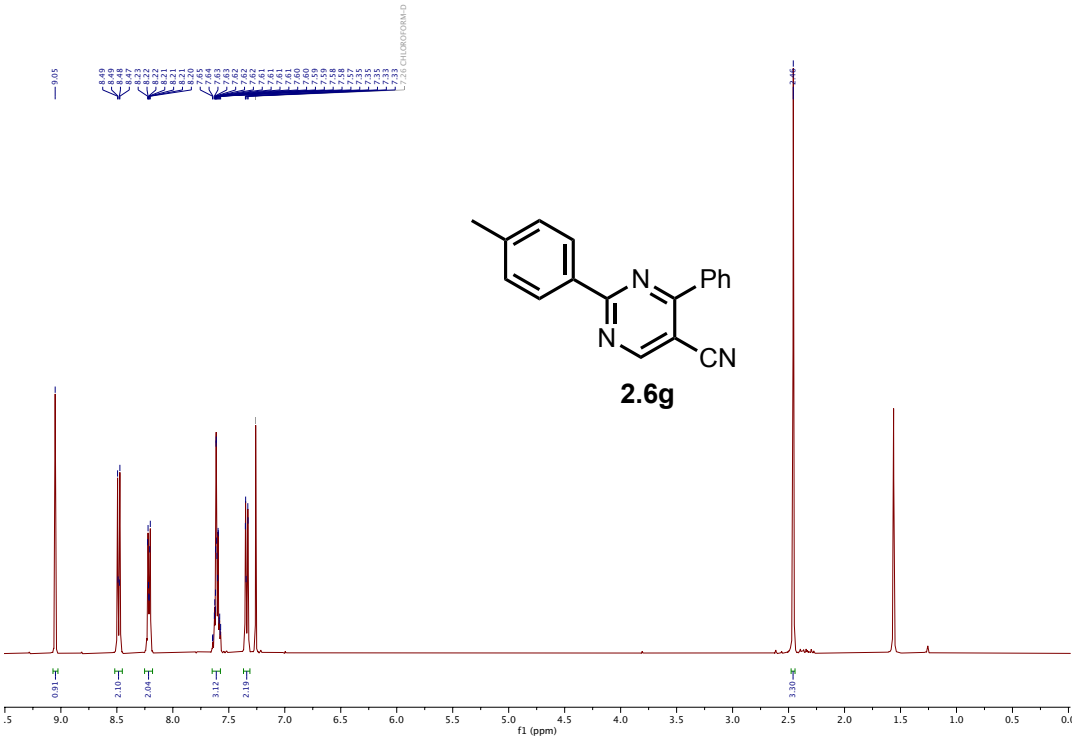


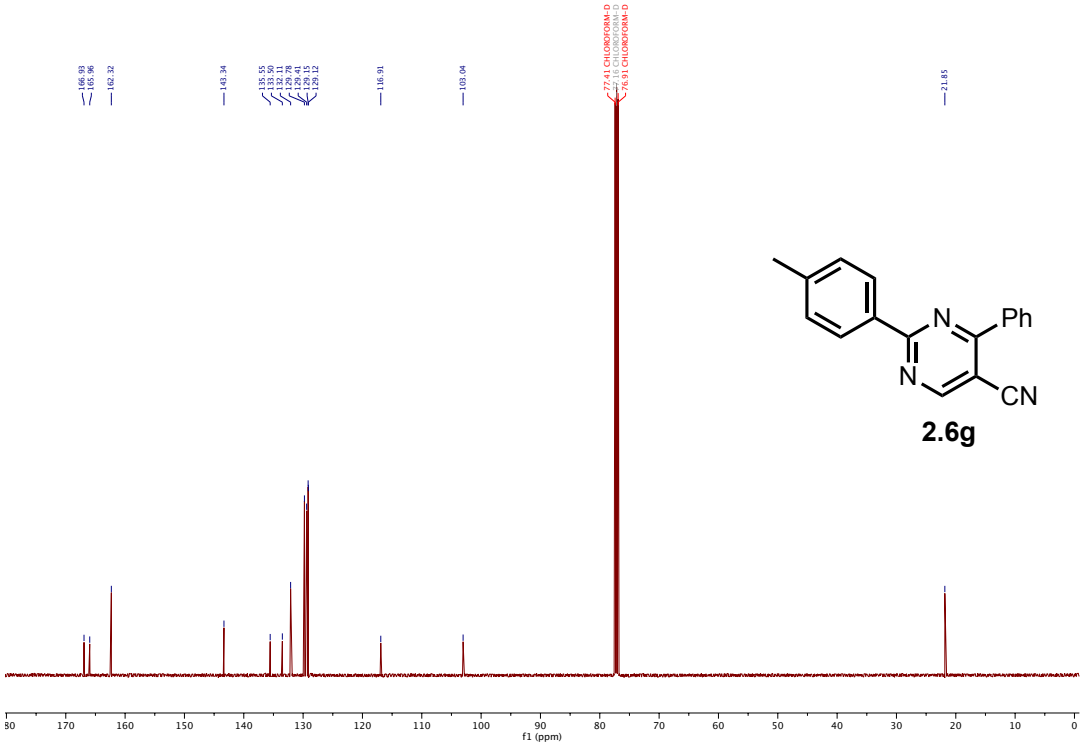
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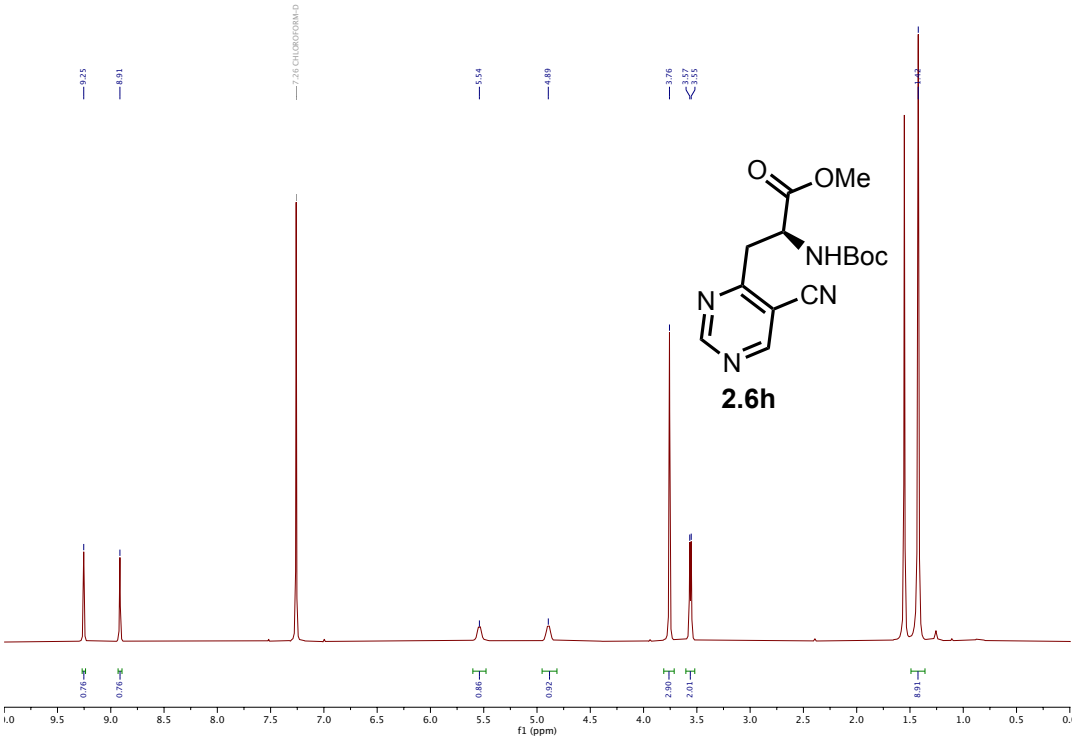
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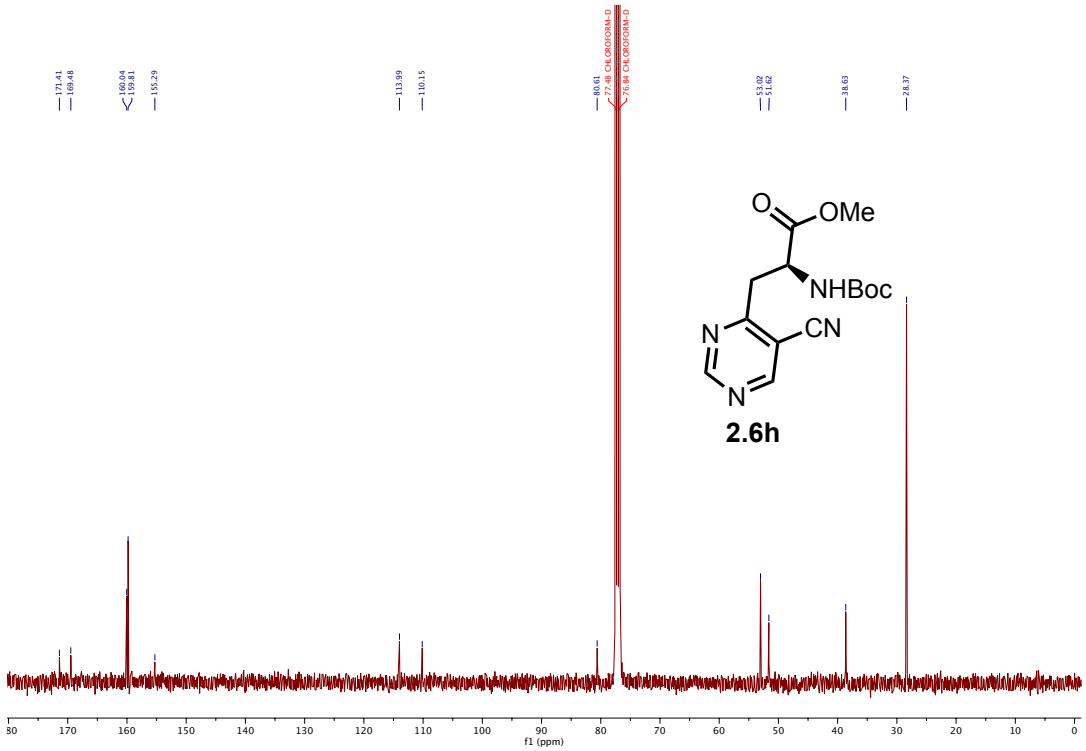
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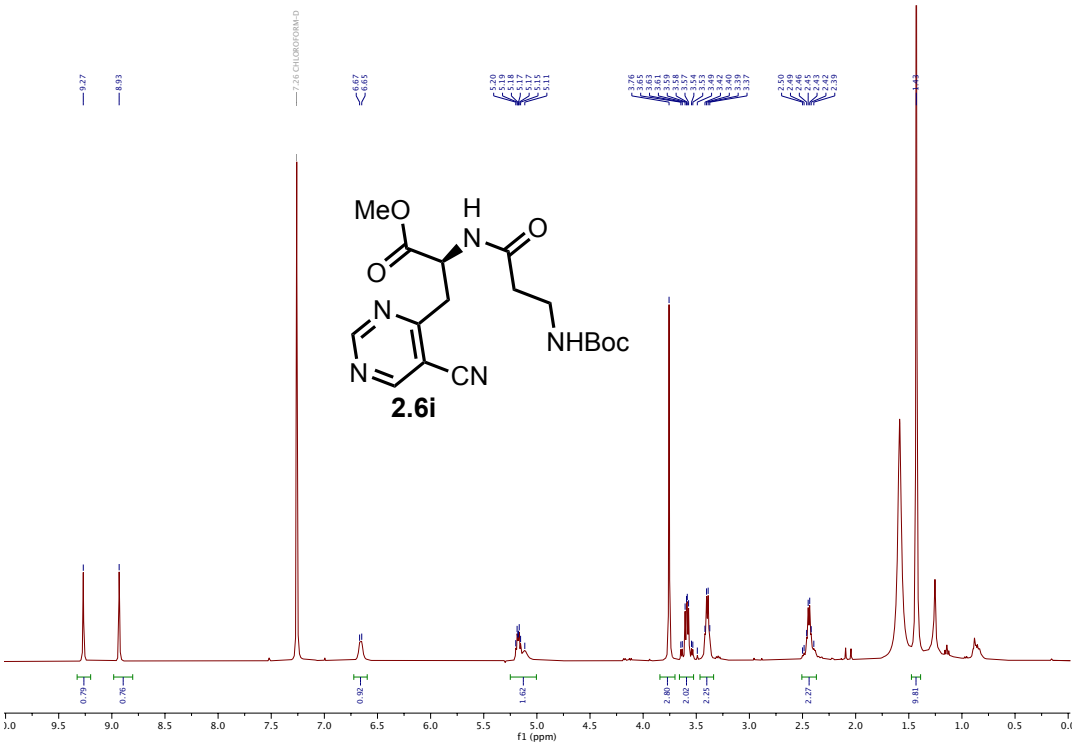


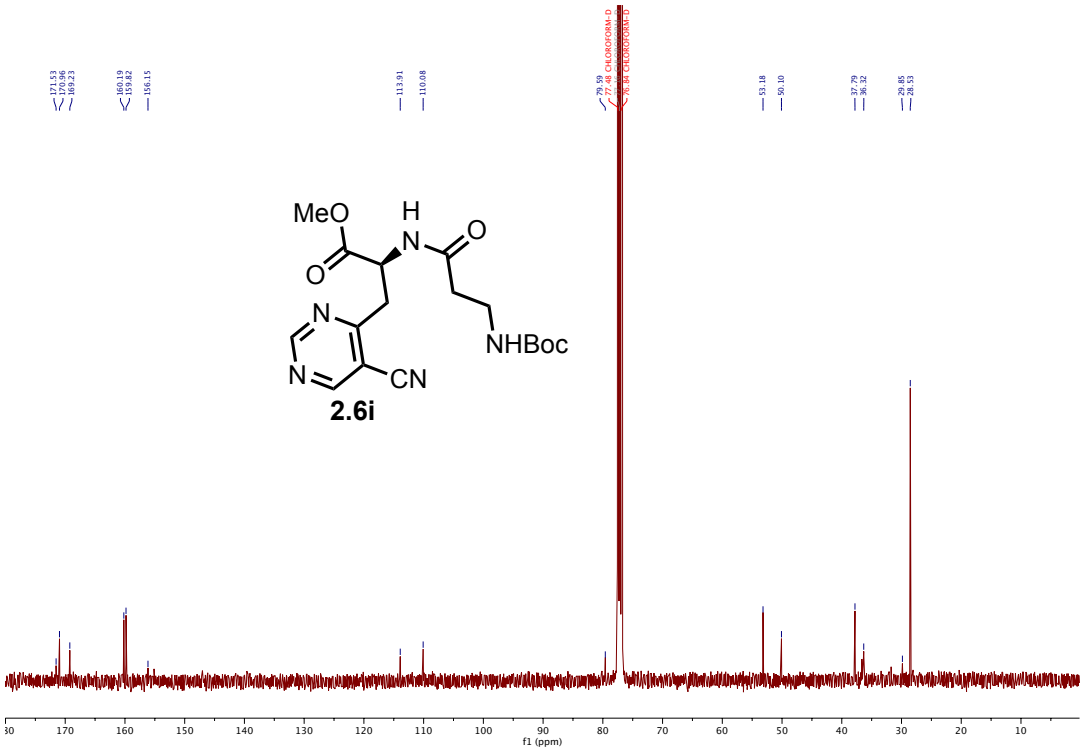
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CHAPTER 3

Application of SulfenylNitrenes for Late-Stage Nitrogen Atom Incorporation

3.1 Introduction

Nitrogen atoms play a central role in medicinal chemistry and drug development due to their profound impact on molecular recognition, solubility, and biological activity.[1-3] The widespread presence of nitrogen-containing heterocycles in bioactive molecules, particularly pharmaceuticals and chemical probes, has fueled growing interest in strategies for selective nitrogen-atom editing. Notably, over 80% of FDA-approved drugs between 2013 and 2023 feature at least one nitrogen heterocycle, with pyridines, pyrimidines, indoles, and imidazoles ranking among the most frequently encountered scaffolds (**Figure 3.1.1a**).[3] Consequently, late-stage single nitrogen-atom insertion offers

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a compelling opportunity to diversify drug discovery libraries by introducing pharmacophore-rich, structurally complex frameworks.

Nitrenes, as highly reactive intermediates, are valuable nitrogen sources for skeletal editing transformations (**Figure 3.1.1b**). These are analouges to carbenes discussed in chapter 2. They are formally monovalent, neutral nitrogen species with six valence electrons and can exist in different spin states, most commonly singlet and triplet. In the singlet state, the electrons are paired with opposite spins, leading to ambiphilic reactivity that allows interaction with both nucleophilic and electrophilic partners. In contrast, triplet nitrenes contain two unpaired electrons with parallel spins in separate orbitals and typically display diradical-type reactivity. The fundamental reactivity of nitrenes with alkenes results in the formation of versatile aziridine intermediates, especially for skeletal editing (**Figure 3.1.1c**).

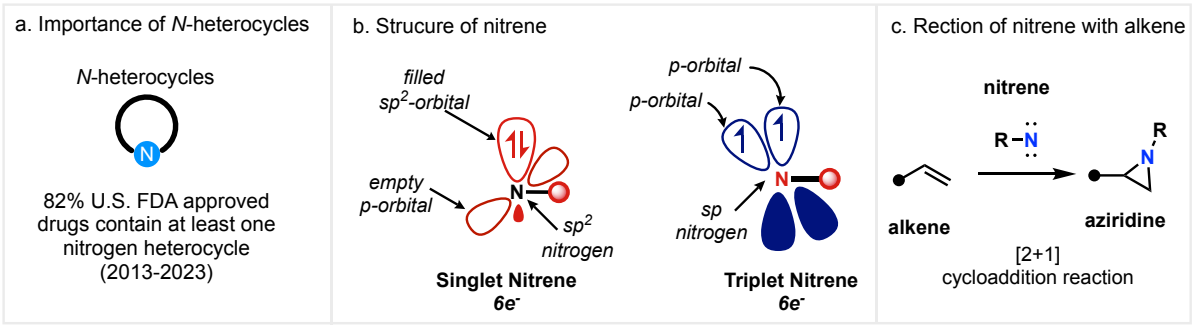


Figure 3.1.1: *N*-Heterocycles and nitrenes (a) Importance of *N*-heterocycles (b) Structure of nitrene (c) Reaction of nitrene with alkene.

The concept of nitrogen insertion into arenes involves the reaction of a nitrene with the arene to form an in-situ aziridine intermediate bearing a leaving group, which subsequently undergoes ring expansion upon loss of the leaving group (**Figure 3.1.2**). The concept of inserting a single nitrogen atom into aromatic systems dates back to 1964 when Fields and co-workers employed ammonium chloride as a nitrogen source in the

presence of strong oxidants to achieve this transformation.[4] Given the high prevalence of nitrogen-containing heterocycles in pharmaceuticals, single-atom skeletal editing via carbon or nitrogen insertion has garnered increasing attention in recent years.[5-9]

Most existing skeletal editing methods for nitrogen-atom incorporation into *N*-heterocycles or to access *N*-heterocycles from aromatic hydrocarbons rely on nitrene intermediates bearing a leaving group, which require specific and often demanding conditions for generation.[5, 9-20] These include heavy metals,[17] excessive use of potent oxidizing agents,[16] multi-step reaction conditions,[21] and elevated temperatures,[6] thus limiting their operational simplicity and broad synthetic applicability (**Figure 3.1.2**). Additionally, some methods require the protection of free nitrogen in substrates like indoles, necessitating a separate pre-functionalization step.

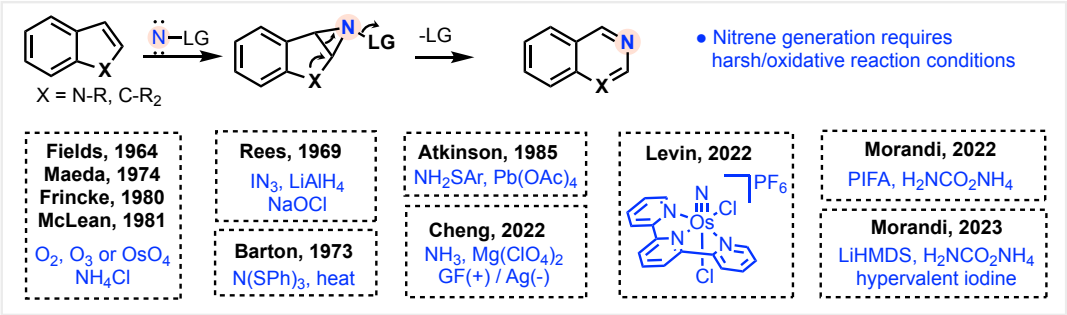


Figure 3.1.2: Concept of nitrogen-atom insertion into arenes.

Keeping all these limitations in mind, we sought to develop a nitrene-bearing leaving group under additive-free conditions (**Figure 3.1.3**). Guided by literature precedent and retrosynthetic analysis, we identified sulfenylnitrene, which is nitrene next to sulfur. These nitrenes are stabilized by adjacent sulfur and later act as a leaving group, enabling the skeletal editing. Despite their discovery in 1967,[22] these nitrenes have not been extensively explored [15, 23-27]. We identified sulfenylnitrene precursors capable of

generating sulfenylnitrenes over a broad temperature range. These thermal precursors have only been used in a few prior reports of aziridination [24-25, 28-29]. Here we have developed two different methodologies using sulfenylnitrene for late-stage nitrogen atom insertion: (1) *Thermal generation of sulfenylnitrene and its application in nitrogen atom insertion*, (2) *Photolysis as a mode of sulfenylnitrene generation and its applications in late-stage nitrogen atom insertion*.

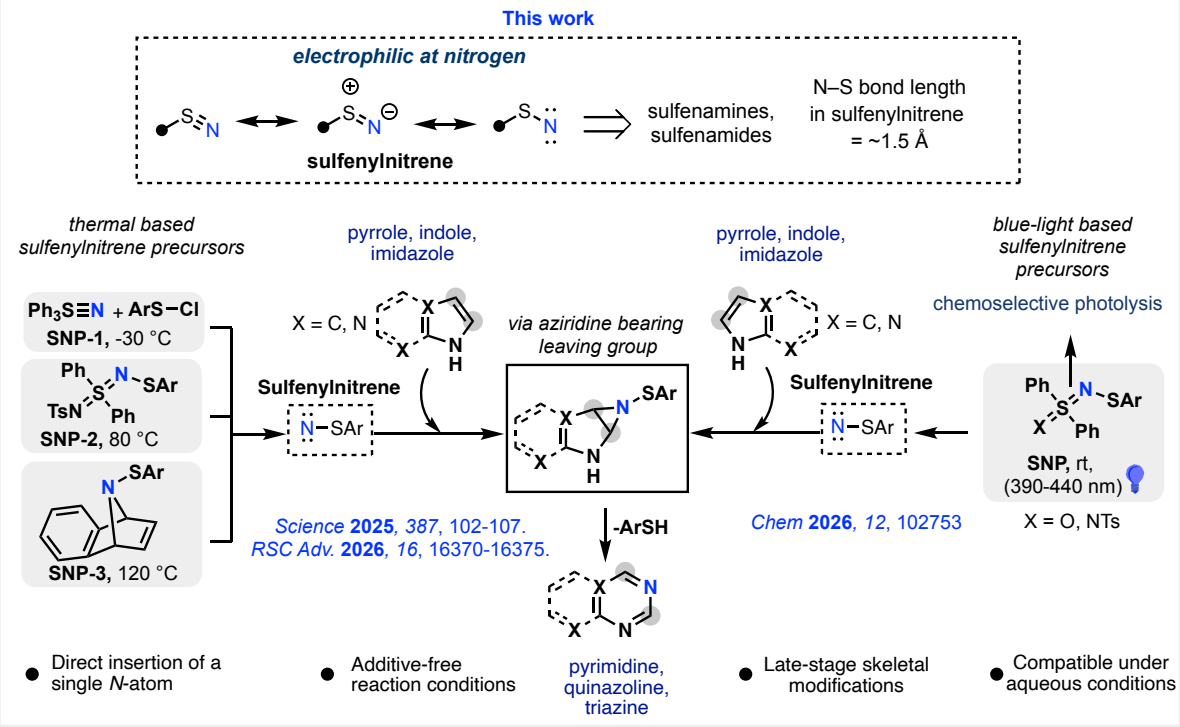


Figure 3.1.3: Present work.

In this chapter, we report the development of multiple sulfenylnitrene precursors that can be activated either thermally or by photolysis. First, we utilize a thermally generated sulfenylnitrene (-30 °C to 120 °C) for single-nitrogen-atom insertion into a diverse class of *N*-heterocycles under additive-free conditions. Later, we developed sulfenylnitrene precursors that generate sulfenylnitrenes under mild blue-light conditions, metal-free, allowing a broad substrate scope, including DNA-encoded libraries.

3.2 Results and Discussion

3.2.1 Development of Sulfenylnitrene Precursors (SNPs)

3.2.1.1 Development of Thermal Sulfenylnitrene Precursors

3.2.1.1.1 Design and Synthesis of Thiazyne Precursor

We initiated our work by synthesizing a thiazyne-based precursor from commercially available diphenylsulfide. We developed a straightforward two-step route for the synthesis of sulfinimine (**3.1**). This sulfinimine was converted to fluorothiazyne (**3.2**) in two steps, which can be purified by recrystallization. This fluorothiazyne (**3.2**) was reacted with phenyllithium at low temperature to synthesize triphenyl thiazyne (**SNP-1**). This precursor was found to be solid and stable at room temperature with no decomposition for more than a year.

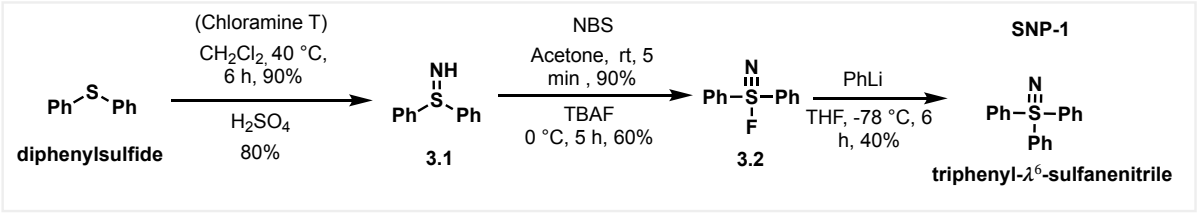


Figure 3.2.1.1.1: Synthesis of thiazine-based sulfenylnitrene precursor (**SNP-1**).

3.2.1.1.2 Design and Synthesis of Sulfodiimide-based Precursors

We also synthesized a sulfodiimide-based precursor using a similar route as we used for the synthesis of **SNP-1**. Here, we reacted the sulfinimine (**3.1**) with chloramine-T to obtain intermediate **3.3**. By reacting this intermediate **3.3** with sulfenylchloride in the presence of sodium hydride (NaH) as a base, sulfodiimide-based precursors (**SNP-2a**) were obtained. These precursors were found to be stable at room temperature and don't require extensive purification after saturated bicarbonate workup.

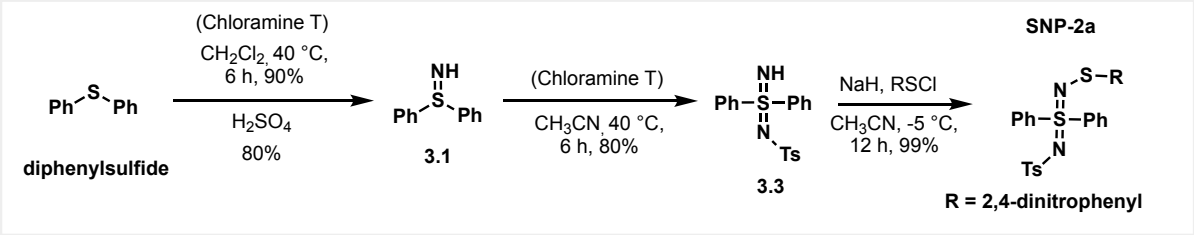


Figure 3.2.1.1.2: Synthesis of a sulfodiimide-based sulfenylnitrene precursor (**SNP-2**).

3.2.1.1.3 Design and Synthesis of Naphthalene-based Precursors

Naphtalene precursors were also synthesized using well-established benzyne chemistry, in which Boc-protected pyrrole was trapped by benzyne to isolate cycloadduct **3.4** as a stable white solid. The obtained solid was treated with anhydrous hydrochloric acid conditions to isolate the deprotonated amine, which was subsequently utilized to react with sulfenylchloride to form naphthalene-based precursor **SNP-3** as a stable solid. This precursor was scaled up to 20 g in our academic setup.

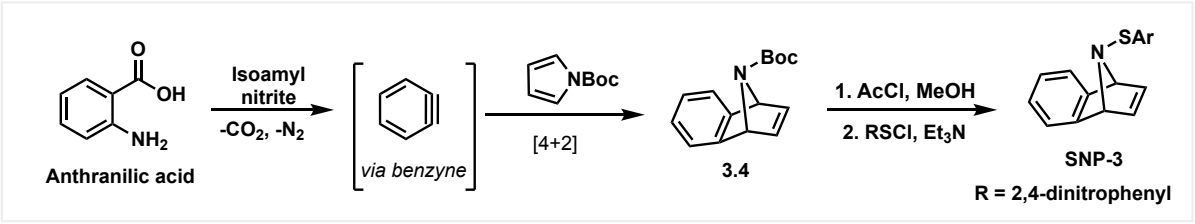


Figure 3.2.1.1.3: Synthesis of naphthalene-based precursor (**SNP-3a**).

3.2.1.2 Development of Blue-light Sulfenylnitrene Precursors

3.2.1.2.1 Design and Synthesis of Sulfoximine-based Precursor

Similarly, like the synthesis of thermal precursors, we initiated the synthesis of blue light precursors from commercially available diphenylsulfide. These sulfides were reacted with NH_4OAc and PIDA to isolate sulfoximine (**3.5**) as a stable white solid. These sulfoximines (**3.5**) were reacted with sulfenylchloride under basic conditions to isolate sulfoximine-based sulfenylnitrene precursors **SNP-4a** and **SNP-4b.** These precursors

were purified and used in subsequent reactions without further purification and were found to be stable at room temperature.

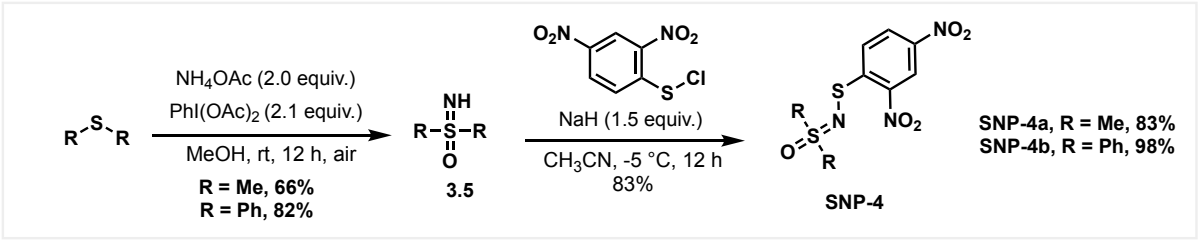


Figure 3.2.1.2.1: Synthesis of sulfoximine-based precursors (**SNP-4a and SNP-4b).**

3.2.1.2.2 Design and Synthesis of Sulfodiimide-based Precursors

Using the protocol developed for the synthesis of **SNP-2a**, we also synthesized a sulfodiimide-based precursor, **SNP-2b,** via a similar route. Both precursors were found to be stable solids at room temperature.

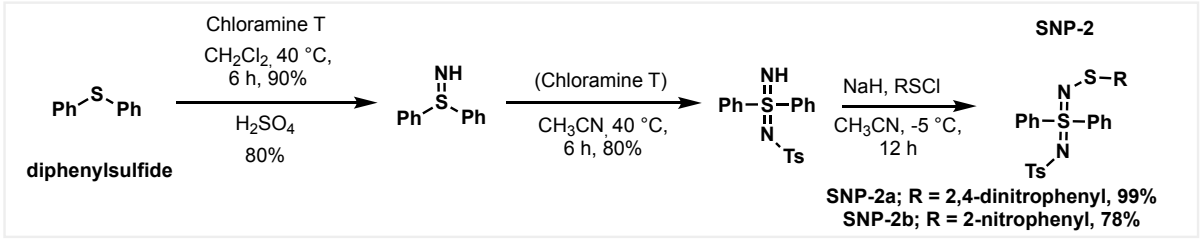


Figure 3.2.1.2.2: Synthesis of sulfodimide-based precursors (**SNP-2a and SNP-2b).**

3.2.2 Reaction Optimization for Single Nitrogen-Atom Insertion

3.2.2.1 Reaction Optimization of SNP-1 Under Thermal Conditions

We began our optimization with thiazyne-based **SNP-1** as the precursor. In literature, this thiazyne is known to react with sulfenylchloride to form adduct at low temperature which can decompose to generate sulfenylnitrene (**Figure 3.2.2.1a**).[29] We use the symmetric 2,5-diphenylpyrrole **3.4a** as the model substrate to overcome the regioselectivity challenge. We employed two equivalents of **SNP-1**, which was generated in situ by the reaction of triphenyl sulfanenitrile with commercially available 2,4-dinitrobenzenesulfenyl chloride at low temperature using dichloromethane as a solvent

(**Figure 3.2.2.1b**), following literature precedent for the aziridination.[29] To our delight, the reaction produced the corresponding pyrimidine **2.5a** at –30 ºC, albeit in a modest yield (15%, entry 1). To enhance the yield, we switched to chlorobenzene as the solvent, inspired by its successful application in aziridination by Atkinson and coworkers [27], and the yield improved to 30%. Further raising the reaction temperature to 0 ºC resulted in an increased yield of 50%; however, temperatures above this led to increased byproduct formation.

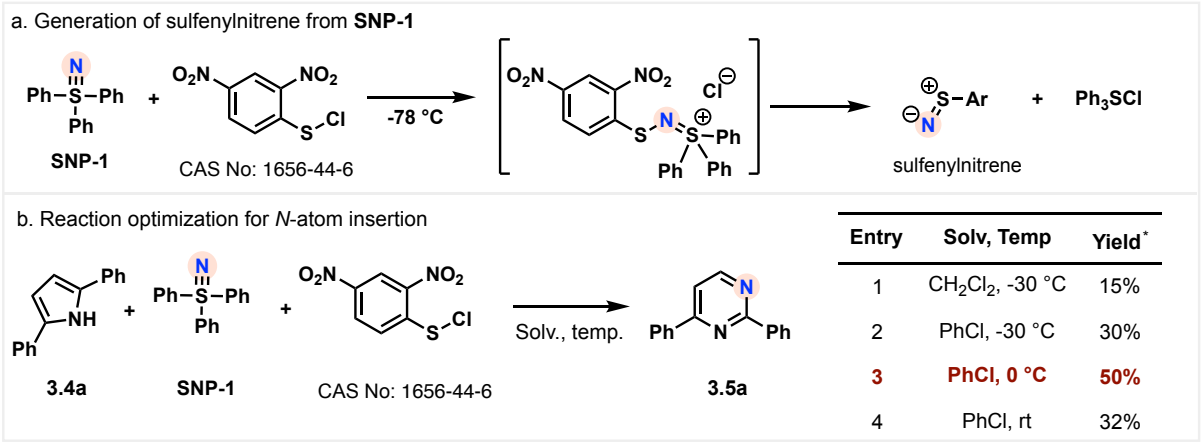
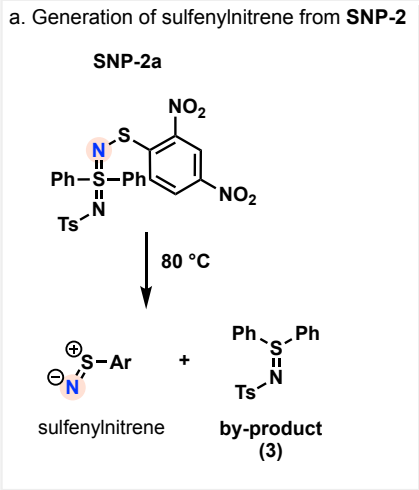


Figure 3.2.2.1: Generation of sulfenylnitrene from **SNP-1** and reaction optimization for *N*-atom insertion.

3.2.2.2 Reaction Optimization of SNP-2 Under Thermal Conditions

We next examined the reaction with **SNP-2**. This nitrene precursor undergoes chemoselective thermolysis upon heating to release sulfenylnitrene. In this case, acetonitrile was initially chosen as the solvent, following precedent in the literature for aziridination.[24] Gratifyingly, the reaction resulted in the formation of the corresponding pyrimidine **3.5a** with 77% yield (Fig. 2B, entry 1). Changing the solvent to dichloroethane or toluene did not significantly improve the yield (entries 2, 3). However, using chlorobenzene as the solvent led to a nearly quantitative yield of pyrimidine **3.5a** (99%)

(entry 4). We also tested industrially preferred solvents, including esters and alcohols, and were pleased to find that the reaction proceeded in both with moderate yields (entries 5–8). Finally, we screened 1 and 1.5 equivalents of **SNP-2** precursors, but this resulted in slightly lower yields and left some pyrrole unreacted (entries 9, 10).



b. Reaction optimization for *N*-atom insertion



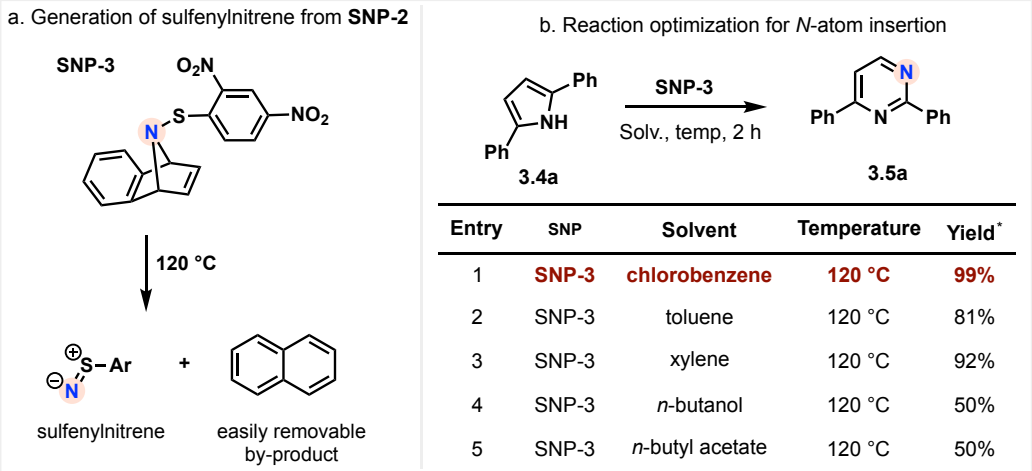
Entry	Solvent	Yield*
1	acetonitrile	77%
2	dichloroethane	75%
3	toluene	80%
4	**chlorobenzene**	**99%**
5	ethyl acetate	73%
6	*t*-butanol	48%
7	isopropanol	40%
8	ethanol	45%
9.†	chlorobenzene	68%
10.‡	chlorobenzene	82%

Figure 3.2.2.2: Generation of sulfenylnitrene from **SNP-2** and reaction optimization for *N*-atom insertion. †1 equiv. of SNP-2 was used. ‡1.5 equiv. of SNP-2 was used.

3.2.2.3 Reaction Optimization of SNP-3 Under Thermal Conditions

Moving forward, we investigated the reactivity of the **SNP-3** precursor. This sulfenylnitrene precursor generates sulfenylnitrene via rearomatization under thermal conditions (**Figure 3.2.2.3a**). Next, we optimized this precursor for the *N*-insertion reaction with pyrrole **2.4a** (**Figure 3.2.2.3b**). **SNP-3** exhibited better reactivity toward pyrrole **3.4a**, affording the desired pyrimidine **3.5a** in nearly quantitative yield using chlorobenzene as the solvent (entries 1). Other aromatic solvents, such as toluene and xylene, provided slightly lower yields (entries 2, 3). However, the industrially preferred solvents (esters and alcohols) provided moderate yields of the desired pyrimidine **3.5a** (entries 4, 5).

We selected **SNP-3** as the optimal nitrene precursor due to the generation of sublimable naphthalene as a byproduct, easing the purification process at scale. Additionally, **SNP-3** can be easily synthesized at a large scale (~10–20 g) in three simple steps.



Entry	SNP	Solvent	Temperature	Yield*
1	**SNP-3**	**chlorobenzene**	**120 °C**	**99%**
2	SNP-3	toluene	120 °C	81%
3	SNP-3	xylene	120 °C	92%
4	SNP-3	*n*-butanol	120 °C	50%
5	SNP-3	*n*-butyl acetate	120 °C	50%

Figure 3.2.2.3: Generation of sulfenylnitrene from **SNP-3** and reaction optimization for *N*-atom insertion.

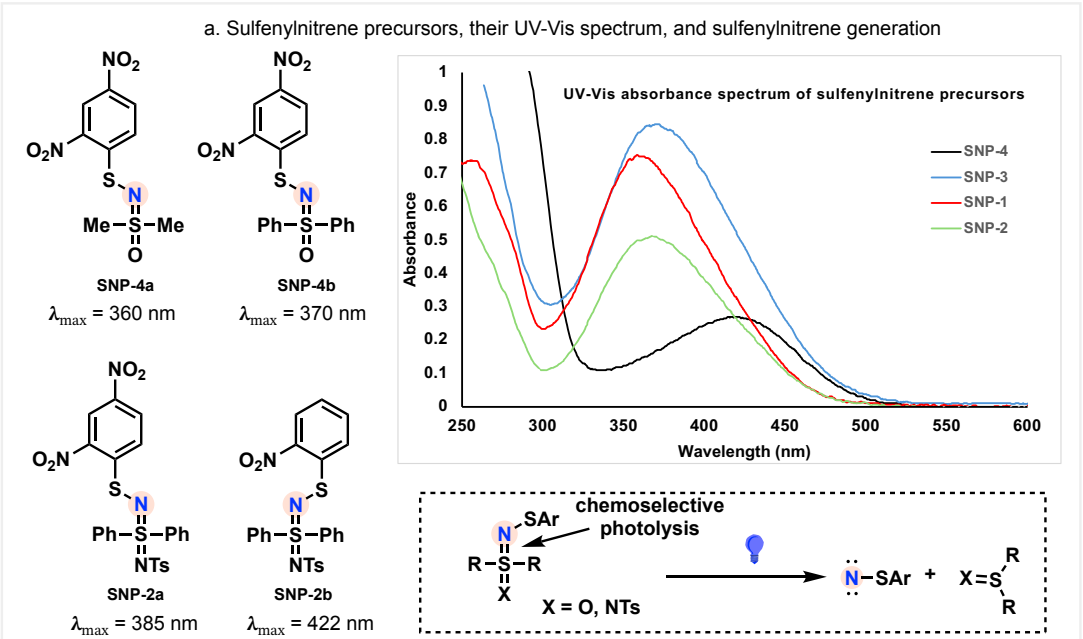
3.2.2.4 Reaction Optimization of SNP-2 Under Photolysis Conditions

We initiated our optimization by UV-Vis study. Our study revealed that sulfenylnitrene precursors **SNP-4a**, **SNP-4b**, **SNP-2a**, and **SNP-2b** exhibit visible light absorption with Lambda wavelength (λ_{max}) of 375 nm, 382 nm, 385 nm, and 422 nm, respectively (**Figure 3.2.2.4**). We initiated our optimization by irradiating a solution of **SNP-4a** (1.5 equiv.) and 2,5-diphenylpyrrole (**3.4a**) in dichloromethane (CH_2Cl_2) with blue LEDs (390 nm, 100% intensity). Under these conditions, **SNP-4a** decomposed entirely; however, no formation of the corresponding pyrimidine product was observed (entry 1). We next evaluated **SNP-4b** under identical conditions, but no product formation was detected (entry 2).

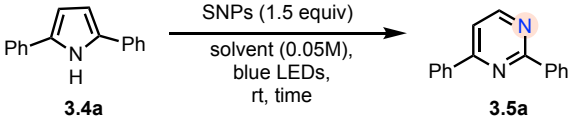
Encouraged to explore further, we subjected **SNP-2a** to the reaction conditions. To our delight, a simple substitution of the oxygen atom in **SNP-2a** with an *N*-tosyl group

in **SNP-2a** resulted in the formation of the desired pyrimidine **3.5a** with 78% yield (entry 3). Changing the reaction solvent to 1,2-dichloroethane (DCE) or chloroform ($CHCl_3$) led to a slight decrease in reaction yields (entries 4, 5). To further increase the reaction yield, we screened ether-based solvents, tetrahydrofuran (THF), and dioxane, which did not significantly improve the reaction yields (entries 6, 7). Employing acetone as a reaction solvent led to a decrease in yield (entry 8).

We screened the blue LED's lower intensity to enhance the reaction yield, resulting in longer reaction times (entries 9, 10). When 390 nm with 75% intensity was applied to 1.8 equiv. of **SNP-2a**, the reaction yield increased to 83% (entry 11). Next, we investigated the sulfenylnitrene precursor **SNP-2b** to understand the effect of electronic changes in the thioaryl moiety on the reaction yield. Notably, the reaction proceeded with a yield of 92% in a shorter time when 1.5 equiv. of **SNP-2b** and dichloromethane was employed as solvent (entry 12). We also screened the blue LED with a wavelength of 440 nm and found that the reaction achieved quantitative yield (entry 13). To further explore the compatibility of this methodology for broader applications, we conducted the reaction under aqueous conditions. The reaction worked well in THF/H_2O conditions (entry 14). Finally, a control experiment confirmed that no reaction occurred without light, leaving all starting materials unreacted (entry 15).



b. Visible-light mediated *N*-atom insertion



3.4a → **3.5a**

Entry	SNP	Solvent	Time (h)	Conversion (%)	Yield of 2.5a (%)[a]
1	SNP-1	CH_2Cl_2	12 h	10%	—
2	SNP-2	CH_2Cl_2	12 h	12%	—
3	SNP-3	CH_2Cl_2	7 h	100%	78%
4	SNP-3	DCE	7 h	95%	62%
5	SNP-3	$CHCl_3$	7 h	80%	65%
6	SNP-3	THF	7 h	88%	73%
7	SNP-3	Dioxane	7 h	85%	60%
8	SNP-3	Acetone	7 h	50%	33%
9[b]	SNP-3	CH_2Cl_2	12 h	60%	50%
10[c]	SNP-3	CH_2Cl_2	12 h	88%	76%
11[d]	SNP-3	CH_2Cl_2	12h	100%	83%
12	SCP-4	CH_2Cl_2	6 h	100%	92%
13[e]	**SCP-4**	**CH_2Cl_2**	**6 h**	**100%**	**99%(97%)[g]**
14[e]	**SCP-4**	**THF/H_2O(9:1)**	**6 h**	**100%**	**97%**
15[f]	SCP-4	CH_2Cl_2	6 h	0%	n.d.

Figure 3.2.2.4: Generation of sulfenylnitrene from **SNPs** under photolysis conditions and optimization for *N*-atom insertion. [a]Yields were determined by ^{1}H-NMR. [b]Irradiation with blue LEDs (390nm, 50% intensity). [c] Irradiation with blue LEDs (390 nm, 75% intensity.) [d] Irradiation with blue LEDs (390 nm, 75% intensity) and 1.8 equiv. of SNP-3. [e] Irradiation with blue LEDs (440m, 100% intensity). [f] No irradiation. [g] Isolated yield.

3.2.2.5 Substrate Scope Study for Thermal Precursors

With these optimized conditions, we next investigated the scope and regioselectivity of pyrroles (**Figure 3.2.2.5.1**). The *N*-insertion preferentially occurs adjacent to electron-donating over electron-withdrawing substituents. For instance, a pyrrole featuring an aryl group at the 3-position and electron-withdrawing substituents at the 4-position consistently produced the corresponding pyrimidine in good to excellent yields favoring *N*-insertion next to the aryl side (**3.5b**–**3.5c**). Furthermore, pyrrole with a Boc-protected aromatic amine underwent the ring expansion reaction with a nearly quantitative yield (**3.5d**), highlighting the robustness of this method. As anticipated, 3-naphthyl-pyrrole produced the corresponding pyrimidine in high yield (90%) with 1:5 regioselectivity (**3.5e'**). A pyrrole derivative featuring an 8-membered carbocycle furnished the corresponding pyrimidine in a high yield (**3.5f**).

To further expand the utility of this methodology, we applied it to complex bioactive pyrroles. Elopiprazole, an antipsychotic drug,[30] demonstrated compatibility with the reaction, providing a yield of 72%, with only one regioisomer obtained (**3.5g'**). The reaction also proved effective with fenpiclonil, an agricultural phenylpyrrole fungicide, [31] yielding the expansion product in a good yield (**3.5h**). Furthermore, fludioxonil, a fungicide used for seed treatment,[32] was successfully transformed to the corresponding pyrimidine (**3.5i**). Finally, a trimethoxy-phenyl substituted pyrrole, recognized as an antitumor agent,[33] successfully expanded into the corresponding pyrimidine (**3.5j**) with a high yield of 88%.

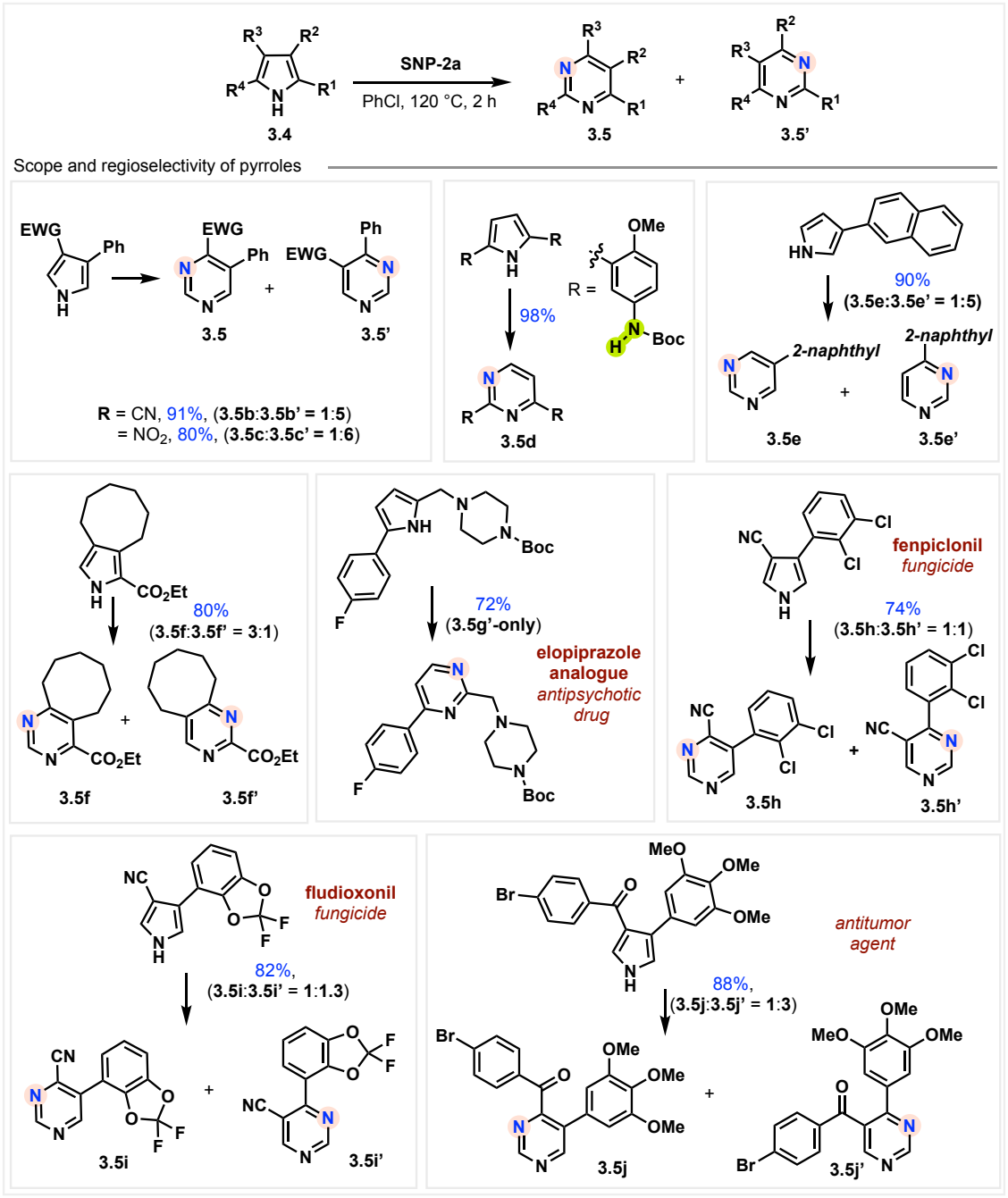


Figure 3.2.2.5.1: Substrate scope of pyrroles under thermal conditions.

Next, we harnessed the potential of sulfenylnitrenes to add a single *N*-atom to indoles, an important motif in numerous bioactive molecules[34] (**Figure 3.2.2.5.2**). Contrary to reports in the literature, in which indole *N*-protection was necessary for *N*-insertion, our methodology did not require any protection.[5] This methodology

accommodated various indoles, bearing electron-donating and -withdrawing groups, and provided the corresponding quinazolines in good to high yields (**3.7a-3.7d**). The method also exhibited compatibility with the oxidation-sensitive functionality phenol (**3.7c**), which was incompatible with the existing methods as they require potent oxidizing agents. An indole containing a Boc-protected amine was compatible (**3.7d**). We also attempted the reaction with 2-deuterated indole to understand the mechanism further and as expected, no loss of deuterium was observed in the product (**3.7e**).

We used phthalimide-protected tryptophan and transformed it to the respective quinazoline products (**3.7f**), thereby providing access to previously underexplored unnatural amino acids and their derivatives.[35] We further demonstrated the potential of this method for synthesizing readily accessible starting materials for medicinally relevant compounds, such as the anti-cancer agents erlotinib and gefitinib [36], which could aid in developing a robust library of drugs leads. To access their analogues, a substituted indole bearing a thioether functionality was transformed into quinazoline **3.7h**, which could be readily converted into erlotinib or gefitinib analogs as outlined in the literature.[37]

Additionally, 23% of newly FDA-approved small-molecule drugs from 2013-2023 feature sulfur moieties [3]. To demonstrate the compatibility with oxidation-sensitive sulfur-containing complex substrates, methionine-derivatized indole was expanded to corresponding quinazoline **3.7i**. Furthermore, azaindoles are crucial core structures in pharmaceuticals and natural products, widely used in various areas of medicinal chemistry.[38] However, existing *N*-insertion methods have proven inadequate for expanding azaindoles. Our methodology successfully expanded azaindoles to the corresponding 1,3,8-triazanaphthalenes (**3.7j**, **3.7k**) with high efficiency. We were

particularly pleased to observe that a phenol-containing azaindole, a DYRK1A inhibitor [39], underwent a smooth *N*-insertion reaction, furnishing the desired product in high yield.

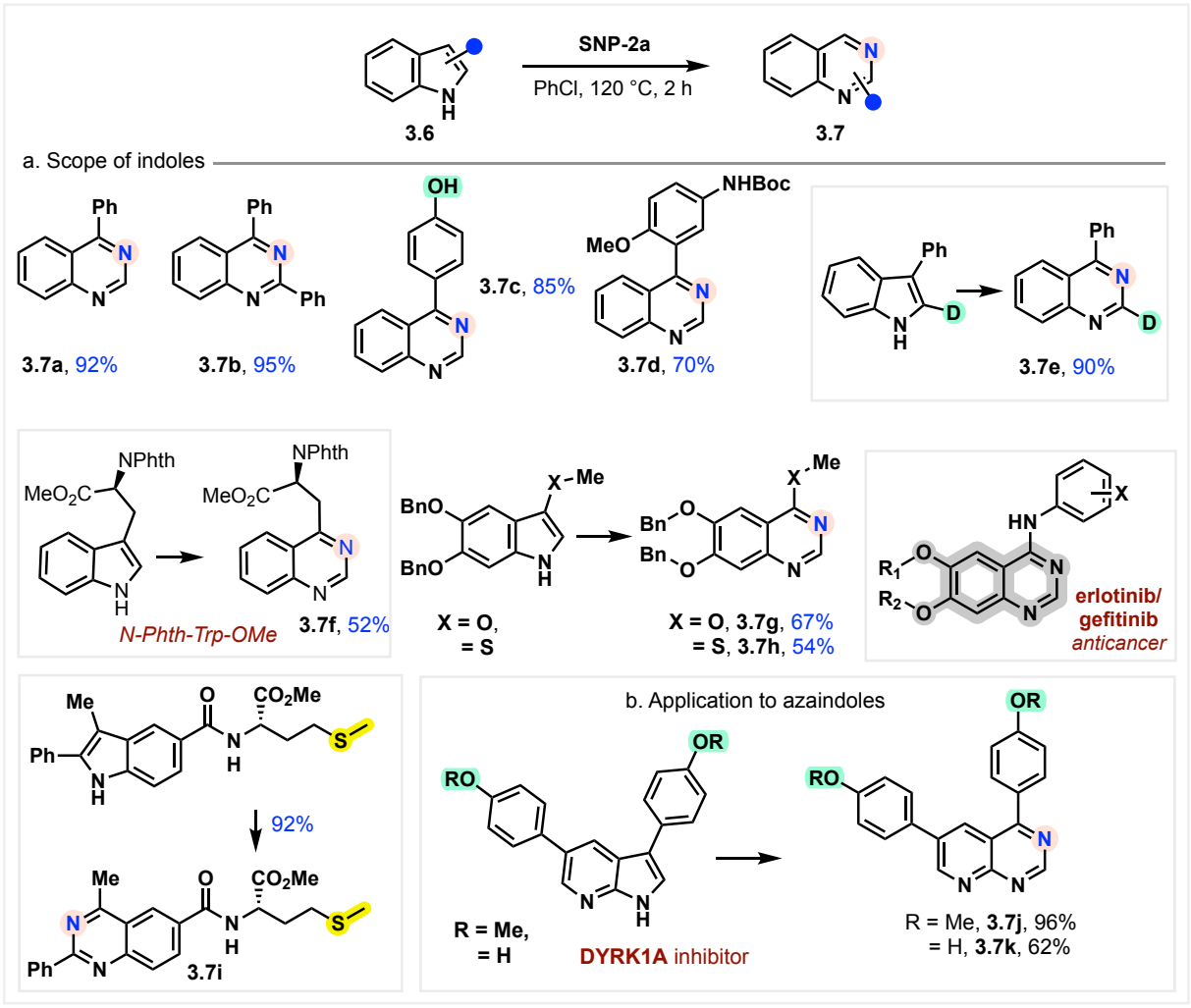


Figure 3.2.2.5.2: Scope of indoles under thermal conditions.

Following the successful implementation of *N*-insertion into pyrroles and indoles, we also extended its application to imidazole's **(Figure 3.2.2.5.3)**. We were pleased to observe that various aryl-substituted imidazoles smoothly converted into the corresponding 1,3,5-triazenes, a privileged motif in drug discovery **(3.9a–3.9d)**.. Additionally, the phthalimide-protected L-histidine methyl ester was successfully transformed into the corresponding unnatural triazine amino acid (**3.9e**) at a gram scale.

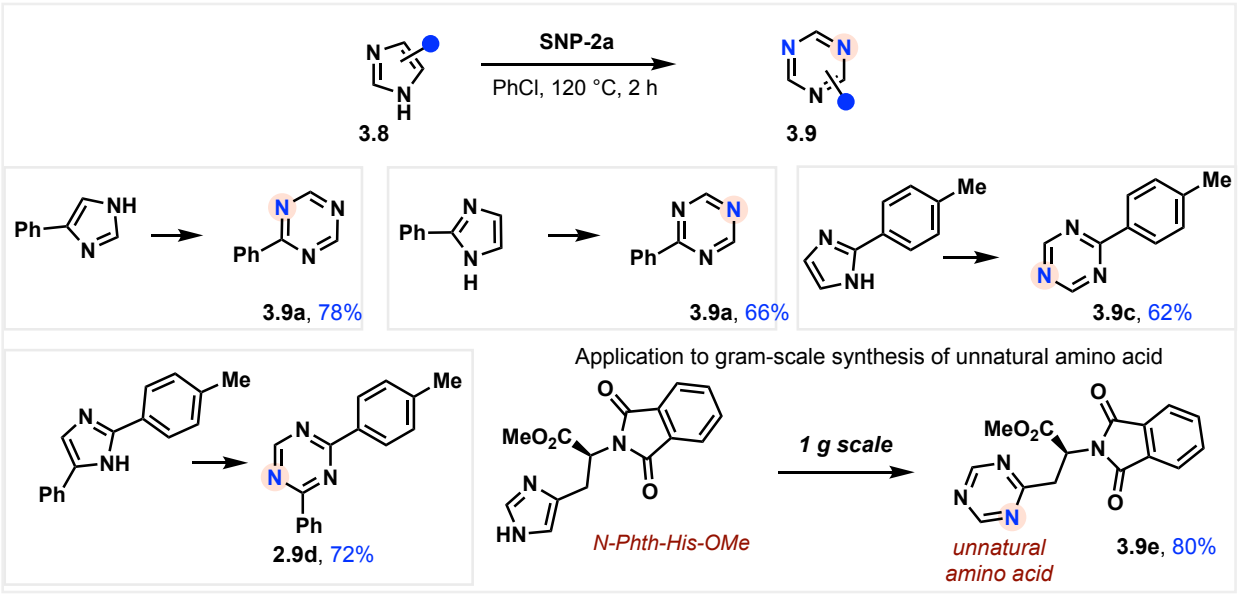


Figure 3.2.2.5.3: Scope of imidazoles under thermal conditions.

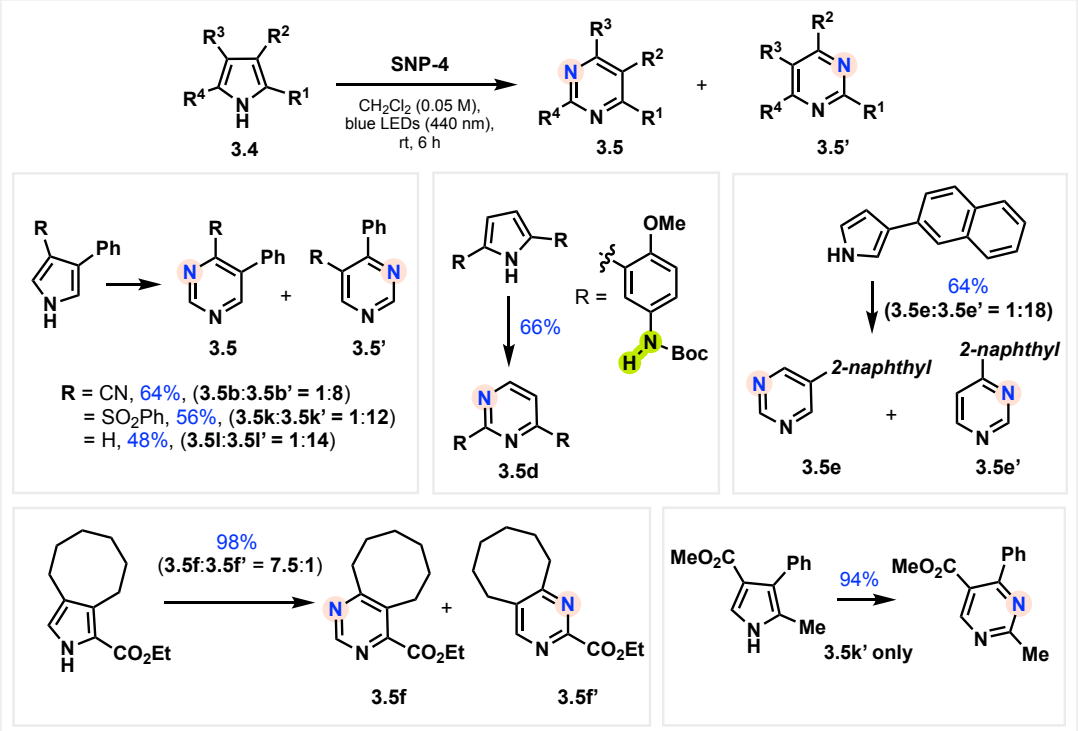
3.2.2.6 Substrate Scope Study for Photolysis Precursors

With these optimized conditions in hand for photolysis, we investigated the scope and regioselectivity of pyrroles (**Figure 3.2.2.6.1**). Consistent with our findings under thermal conditions,[6] the nitrogen atom insertion preferentially occurred at the more electron-rich position, exhibiting improved regioselectivity. Next, pyrroles featuring an electron-withdrawing group at the 4-position and phenyl substitution at the 3-position consistently form the corresponding pyrimidine with moderate yields and good regioselectivity, favoring *N*-atom insertion to the phenyl side (**3.5b', 3.5k',** and **3.5l'**). This methodology is also compatible with sensitive functionalities, such as mono-protected amines (**3.5d**).

Pyrrole featuring phenyl 2-naphthyl at the 3-position shows regioselectivity 1:14 and 1:18, respectively (**3.5l, 3.5e**). These results exhibit improved regioselectivity compared to our previous work, having 1:5 regioselectivity with the same substrates.[6] Cyclooctane ring-bound tri-substituted pyrrole also provided the corresponding pyrimidine

with quantitative yield and better regioselectivity (**3.5f**). Trisubstituted pyrrole yields a single regioisomer, favoring the more substituted side (**3.5k'**).

Figure 3.2.2.6.1: Scope of pyrroles under photolytic conditions.



Next, we expand the synthetic utility of this methodology for the skeletal editing of indoles, a privileged scaffold present in many biologically active compounds (**Figure 3.2.2.6.2a**).[34] This method efficiently accommodates substituted indoles (**3.7a-3.7e**) and successfully transforms indoles into their corresponding quinazolines. This methodology also shows compatibility with various functionalities like mono-protected amines, phenol, and thioether (**3.7c, 3.7d, 3.7l**). We also observed a smooth *N*-atom insertion of diazo-bound indole, furnishing the desired diazo-bound quinazoline (**3.7m**) with a good yield. This result showcases the selective photolysis of sulfenylnitrene precursors under blue light in the presence of diazos, a well-known carbene precursor.[40] Additionally, an essential amino acid, tryptophan, demonstrated compatibility with the reaction, providing

a yield of insertion product **3.7f** of 86%. Our methodology successfully expanded azaindole, a typical core structure in pharmaceuticals and natural products. We observed that an azaindole, a DYRK1A inhibitor, underwent a smooth *N*-insertion reaction, furnishing the desired product with a good yield.[39]

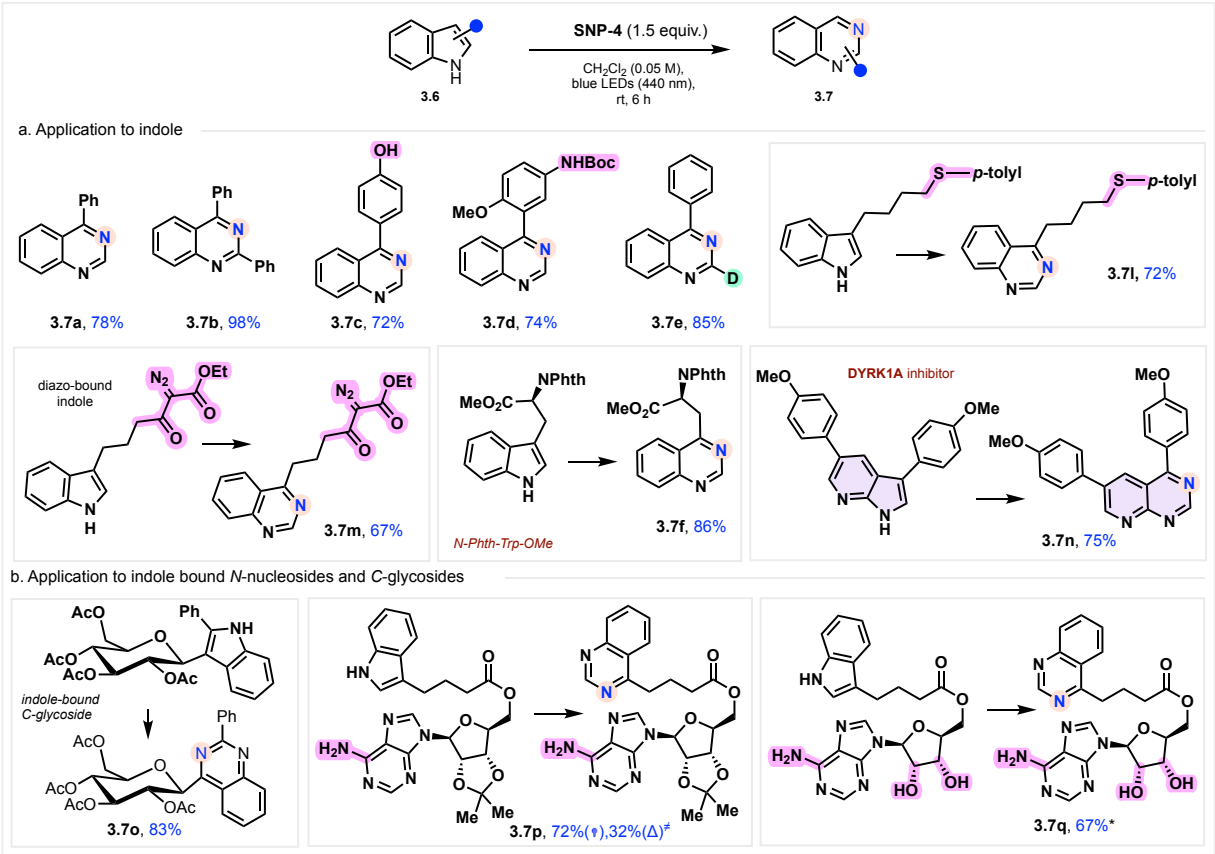
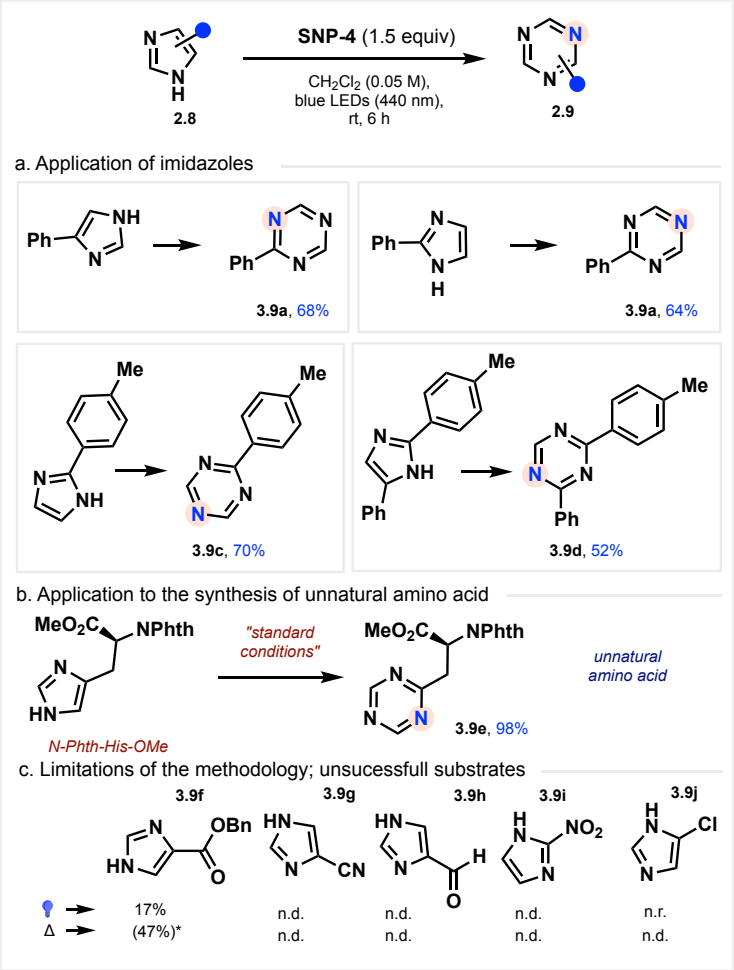


Figure 3.2.2.6.2: Scope of pyrroles under photolytic conditions.

Our methodology enables efficient single-nitrogen-atom insertion to access quinazoline-linked, structurally challenging *C*-glycosides (**3.7o**) (**Figure 3.2.2.6.2b)**. This methodology was applied to indole-tethered *N*-nucleosides, which are essential scaffolds in medicinal chemistry due to their prevalence in antiviral and anticancer agents.[41-43] Notably, an indole linked to acetonide-protected adenosine underwent a smooth transformation to afford the desired product **3.7p** with good yield. However, the substrate

3.7p under thermal conditions leads to a lower yield of the product. Moreover, this method demonstrated compatibility with indole tethered to free adenosine (**3.7q**), underscoring its broad functional group tolerance and potential utility in complex molecule synthesis.

Figure 3.2.2.6.3: Scope of imidazole under photolytic conditions.



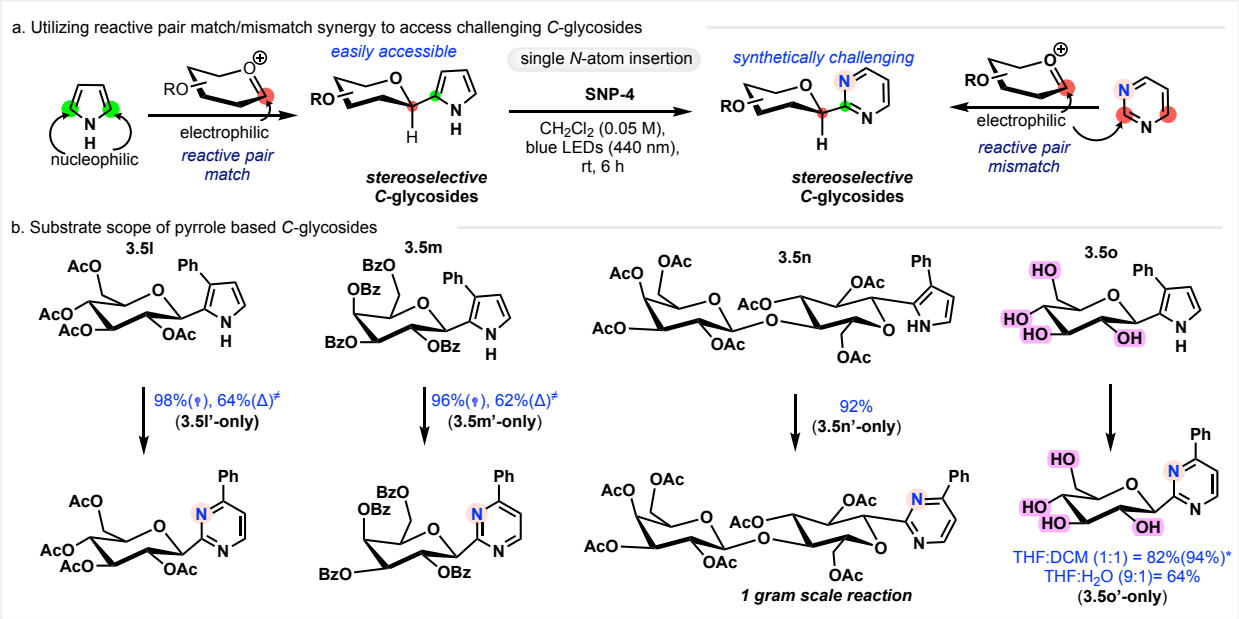
We began a substrate-scope study with 4-phenyl-substituted imidazole, which smoothly transformed into the corresponding triazine (**3.9a**) with good yield (**Figure 3.2.2.6.3a)**. Consistent with our prior studies involving sulfenylcarbenes and sulfenylnitrenes,[6, 8] imidazoles demonstrated complete regioselectivity, with insertion occurring selectively at the carbon-carbon double bond. Next, 2-phenyl-substituted

imidazoles (**3.9b-3.9c**) were screened to access triazines with good yield. Our method also shows compatibility with diaryl-substituted imidazole (**3.9d**) to access the corresponding triazine. Notably, the imidazole-containing amino acid L-histidine was regioselectively transformed into its unnatural triazine-containing amino acid (**3.9e**), providing a quantitative yield (**Figure 3.2.2.6.3b)**. However, a different electron-withdrawing group directly attached to the imidazole (**3.9f-3.9j**) did not lead to the corresponding triazine product with satisfying yield under optimized photolysis conditions, highlighting the limitation of this methodology (**Figure 3.2.2.6.3c)**. However, **3.9f** led to a corresponding triazine product with moderate yield under thermal conditions.

Next, we demonstrated the utility of our methodology by applying it to pyrimidine-bound *C*-glycosides, which are synthetically challenging to access due to the reactive pair mismatch with the glycosyl oxocarbenium ion (**Figure 3.2.2.6.4a**).[44] Our approach enables straightforward synthesis of these scaffolds from readily accessible pyrrole-bound *C*-glycosides (**Figure 3.2.2.6.4b**).[45] As expected, *C*-glucopyranoside- and *C*-galactopyranoside-bound pyrrole (**3.5l-3.5o**) led to single regioisomers of the corresponding pyrimidines (**3.5l'-3.5o'**) with good yields under photolysis conditions. However, when these substrates were screened under thermal conditions, a significant decrease in yield was observed. Our methodology is compatible with disaccharide-bound pyrrole to yield a single regioisomer of the corresponding pyrimidine (**3.5n'**) product in good yield. Notably, this transformation was successfully performed on a gram scale, demonstrating its practicality. The compatibility of unprotected *C*-glucopyranoside-bound pyrrole with free hydroxyl groups, maintaining the stereoselectivity at the sensitive anomeric position (**3.5o'**), highlights the potential of this methodology for broader

applications in carbohydrate chemistry.[46] The scope of this methodology under aqueous conditions (THF:H_2O = 9:1) was further demonstrated by its compatibility with an unprotected *C*-glucopyranoside-bound pyrrole.

Figure 3.2.2.6.4: Scope of *C*-glycosides bearing pyrrole.



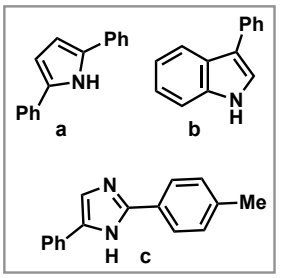
3.2.2.7 Relative Reactivity Study and Rate of Reaction in Photolytic Conditions

We also investigated the relative reactivity of pyrrole, indole, and imidazole with sulfenylnitrene precursor **SNP-2a (Figure 3.2.2.7a)**. Combinations of equimolar amounts of pyrrole (**a**), indole (**b**), and imidazole (**c**) were subjected to the standard reaction conditions with 1.0, 2.0, and 3.0 equiv. of **SNP-2a** (Fig. 5C). Rate of *N*-insertion with 1.0 and 2.0 equiv. **SNP-2a** followed the order: imidazole > pyrrole > indole. Notably, 3 equiv. of **SNP-2a** fully converted all combinations to the desired products.

Next, we also looked into the rate of reaction under photolytic conditions. To a solution of diphenylpyrrole **(**5 mg, 1.0 equiv) in 0.05 M CD_2Cl_2, 1.5 equiv. of solid sulfenylnitrene precursor was added in one portion. The resulting solution was irradiated

with blue LED (Kessil lamp (10V), PR160L-440 nm, 100% intensity) at room temperature for the next 0.5 h and ^{1}H NMR was performed to calculate the percent conversion with product. The solution was stored in the dark for another 0.5 hour and repeated until the complete conversion.

a. Relative reactivity study of pyrrole, indole, and imidazole under thermal conditions

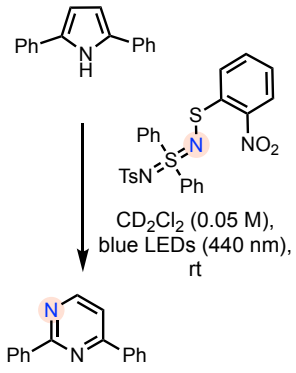


reaction mixture under "standard conditions"

% of product conversion *(calculated by ^{1}H NMR)*

SNP-3b *(equiv.)*	**a + b**	**a + c**	**b + c**
1 equiv.	**a'** (46%); **b'** (15%)	**a'** (25%); **c'** (45%)	**b'** (14%); **c'** (70%)
2 equiv.	**a'** (90%); **b'** (50%)	**a'** (72%); **c'** (100%)	**b'** (60%); **c'** (100%)
3 equiv.	**a'** (100%); **b'** (100%)	**a'** (100%); **c'** (100%)	**b'** (100%); **c'**(100%)

b. Study on rate of reaction: Light on/off experiment



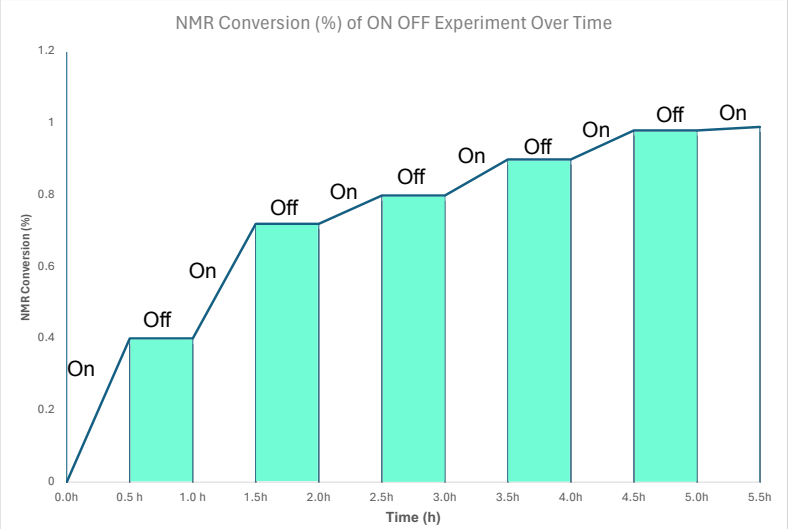


Figure 3.2.2.7: Relative reactivity and rate of reaction in photolytic conditions.

3.2.2.8 Conclusion

These unique sulfenylnitrene precursors can be synthesized at a large scale, highlighting their potential for commercial availability. Additive-free nitrene generation under thermal or photolytic conditions, an operationally simple protocol, and good

functional-group compatibility highlight the advantages of sulfenylnitrenes for creating unique chemical entities to explore the uncharted chemical space in drug discovery.

3.3 Experimental Section

Reagents: Reagents and solvents were obtained from Sigma-Aldrich (www.sigma-aldrich.com), ChemImpex (www.chemimpex.com) or Acros Organics (www.fishersci.com) and used without further purification unless otherwise indicated. Dry solvents (acetonitrile) were obtained from Acros Organics (www.fishersci.com), and dichloromethane was distilled over CaH_2 under N_2 unless otherwise indicated. THF purchased from Sigma-Aldrich was distilled over Na metal with benzophenone indicator.

Reactions: All reactions were performed in flame-dried glassware under positive N_2 pressure with magnetic stirring unless otherwise noted. Liquid reagents and solutions were transferred thru rubber septa via syringes flushed with N_2 prior to use. Cold baths were generated as follows: 0 °C with wet ice/water, –5 °C with Julabo (MeOH as a coolant), and −78 °C with dry ice/acetone.

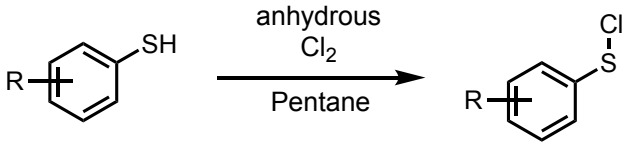
Chromatography: TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$), cerium ammonium molybdenate (CAM), phosphomolybdic acid (PMA), and ninhydrin. Silica flash chromatography was performed on Sorbtech 230–400 mesh silica gel 60.

Analytical Instrumentation: NMR spectra were recorded on a Varian VNMRS 400, 500, and 600 MHz NMR spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (^1H, 7.26 ppm, ^{13}C, 77.0 ppm); coupling constants are expressed in Hz. NMR spectra were processed using Mnova.

Mass spectra were obtained at the OU Analytical Core Facility on an Agilent 6538 High-Mass-Resolution QTOF Mass Spectrometer and an Agilent 1290 UPLC.

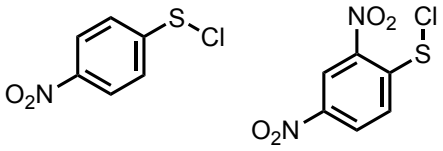
3.3.1 Synthesis of Sulfenylnitrene Precursors

3.3.1.1 General procedure A for the synthesis of sulfenyl chloride



To a solution of thiol (10 mmol) in 20 mL of pentane, anhydrous chlorine gas was continuously bubbled for 20 minutes at room temperature, and the resulting yellowish solution was further stirred for an extra 10 minutes. After completion, N_2 gas was bubbled for 15 min to remove all the dissolved chlorine. Next, all the volatiles were removed under reduced pressure at room temperature to obtain the product.

Generation of anhydrous chlorine gas: To solid $KMnO_4$ in two-neck round bottom flask was added concentrated hydrochloric acid dropwise (1 drop/5 sec). The formed chlorine gas was passed through drierite and purged into the reaction solution.

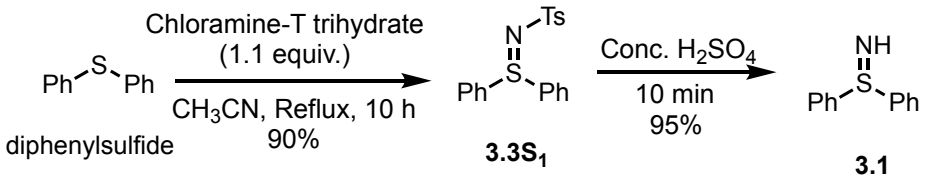


SC1 **SC2**

SC1 is synthesized using general procedure A and the ^1H NMR data matches with the reported literature.[47]

SC2 is commercially available from TCI Chemicals. (CAS No: 528-76-7).

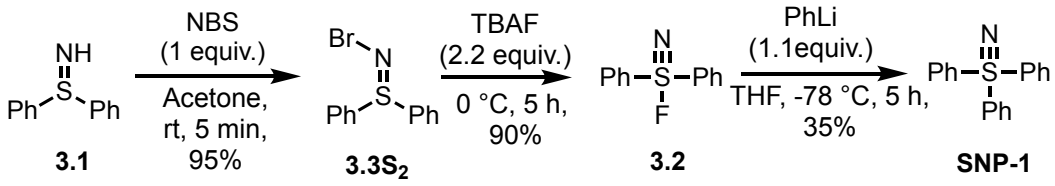
3.3.1.2 Synthesis of SNP-1



Step-1: To a solution of diphenylsulfide (53 mmol) in 100 mL of CH_3CN was added chloramine T trihydrate (59 mmol), and the resulting solution was refluxed for 10 h. After the completion of reaction, CH_3CN was dried under reduced pressure, and the resulting solid was dissolved in dichloromethane. The resulting solution was filtered, and the filtrate was concentrated under reduced pressure. The crude solid was recrystallized from ethyl acetate/hexane to obtain compound **3.3S$_1$** as a white needle solid (17g, 90% yield). The spectral data for product *N*-tosyldiphenylsulfinimine matched those reported in the literature.[48]

Step-2: To a 100 mL round bottom flask charged with compound **3.3S$_1$** (30 mmol) at 0 °C, was added 10 mL concentrated H_2SO_4 dropwise. It was then stirred at room temperature for ~10 min until all the solid compound dissolves to form pink solution. The reaction mixture was warmed to room temperature and stirred for next 45 minutes. The pink acid solution was then added dropwise to an ice-cold water solution over 5 minutes and the resulting aqueous solution was washed with dichloromethane. The organic layer was back extracted with water and combined with rest of the aqueous layer. The resulting aqueous solution was basified to pH 10 using 3N NaOH in ice cold condition and extracted with dichloromethane (3 times). The organic portion was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to obtain compound **3.1** as a white

crystalline solid (5.9 g, 95% yield). The spectral data of product **3.1** matched with previously reported literature. [48]

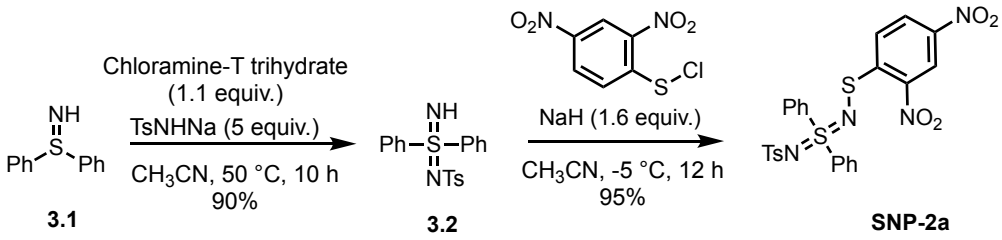


Step-3: To a solution of **3.1** (10 mmol) in 20 mL of acetone at ambient temperature was added NBS (1 equiv.), and stirred for 5 minutes. The resulting solution was poured into 100 mL ice cold water and stirred for another 15 min until all the solid precipitate was formed. The yellow solid was collected by filtration, washed with water multiple times, and air dried to obtain the yellow solid. The crude solid was recrystallized from dichloromethane/hexane to obtain compound *N*-bromodiphenylsulfinimine as a yellow solid (2.6 g, 95% yield). The spectral data of product matched with previously reported literature. [49]

Step-4: To a solution of TBAF (16 mL, 1.0 M in THF) at 0 °C was added solid compound **2.3S$_2$** (7 mmol), and stirred for 5 h at 0 °C. The reaction mixture was diluted with 400 mL of $CHCl_3$, and the resulting organic layer was washed with 100 mL water (10 times), brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude product as yellowish oil. The crude oil was dissolved in benzene, gently sonicated, cooled at 8-10 °C for 15 min, and the precipitated impurity was discarded by filtration. The filtrate was dried under reduced pressure at 25 °C followed by overnight high vacuum to obtain **3.2** as off-white solid (1.4g, 90% yield). The spectral data of product **3.2** matched with previously reported literature. [50]

Step-5: To a stirred solution of **3.2** (5.5 mmol) in anhydrous 50 mL THF at –78 °C was slowly added a solution of PhLi (1.1 equiv.) over 1 h. After stirring for next 4 h at same temperature, it was quenched with water, extracted with diethyl ether and then CH_2Cl_2. The organic portions were dried over Na_2SO_4, and solvent was removed under reduced pressure to obtain the crude product as a red oil. The crude oil was purified by silica gel column chromatography (4-8% MeOH/$CHCl_3$), followed by recrystallization from CH_2Cl_2/Hexane to obtain **SNP-1** as a white solid (0.55 g , 35% yield). The spectral data of product **SNP-1** matched with previously reported literature.[51]

3.3.1.3 Synthesis of SNP-2



Step-1: To a solution of compound **3.1** (15 mmol) in CH_3CN (0.2 M) was added chloramine T trihydrate (16.5 mmol), TsNHNa (75 mmol), and heated to 50 °C for 10 h. After completion, the resulting mixture was diluted with dichloromethane. The mixture was then filtered, and the filtrate was washed with saturated aq. $NaHCO_3$, brine, and dried over Na_2SO_4. It was then concentrated under reduced pressure and purified by silica gel column chromatography to obtain compound **3.2** as a white solid (4.95 g, 90% yield). The spectral images for this compound are published in our research article.[52]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17 – 7.89 (m, 4H), 7.87 – 7.67 (m, 2H), 7.55 – 7.49 (m, 2H), 7.48 – 7.39 (m, 4H), 7.20 – 7.00 (m, 2H), 3.01 (s, 1H), 2.33 (s, 3H).

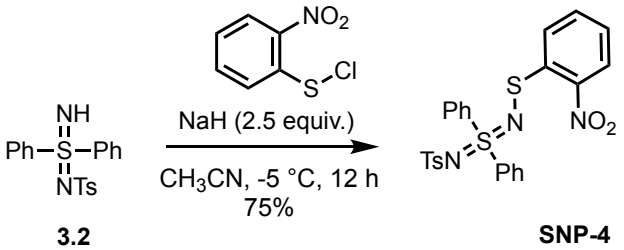
^{13}C NMR:(100 MHz, $CDCl_3$) δ 142.21, 141.52, 141.28, 133.08, 129.33, 129.07, 127.46, 126.63, 21.42.

HRMS(ESI): calculated for $C_{19}H_{19}N_2O_2S_2(M+H)^+$: 371.0886; found: 371.0893.

Step-2: To a solution of **3.2** (5.4 mmol) in CH_3CN (0.1M), NaH (1.6 equivalent) was added at -5 °C followed by the addition of sulfenyl chloride (6.4 mmol). The resulting solution was stirred at -5 °C for 12 h until the complete consumption of compound. The reaction mixture was diluted with dichloromethane and washed with aq. saturated $NaHCO_3$ (3 times), water (2 times), brine, and dried over Na_2SO_4. It was then concentrated under reduced pressure to obtain pure compound **SNP-1** as an orange solid (melting point = 127 °C – 130°C), (2.9 g, 95% yield). No further purification was needed. The spectral data of product **SNP-2a** matched with previously reported literature (Reference 32 in main manuscript)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 2.4 Hz, 1H), 8.51 (d, *J* = 9.1 Hz, 1H), 8.30 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.16 – 8.09 (m, 4H), 7.73 – 7.66 (m, 2H), 7.60 (dd, *J* = 8.5, 6.9 Hz, 4H), 7.54 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 2.26 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 152.43, 143.95, 142.84, 140.78, 140.45, 138.22, 134.20, 132.26, 130.00, 129.85, 129.12, 128.74, 128.25, 127.33, 127.24, 126.99, 126.28, 126.02, 120.54, 21.30.



3.2 **SNP-4**

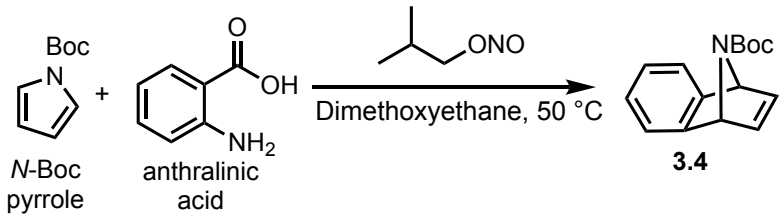
To a solution of **3.2** (1.5 g, 4.0 mmol) in CH_3CN (0.1M), NaH (2.5 equivalent) was added at -5 °C followed by the addition of sulfenyl chloride (6.4 mmol). The resulting solution was stirred at -5 °C for 12 h until the complete consumption of compound. The reaction mixture was diluted with dichloromethane and washed with aq. saturated $NaHCO_3$ (3 times), water (2 times), brine, and dried over Na_2SO_4. It was then concentrated under reduced pressure (water bath temperature 30°C) and purified by silica gel column chromatography (solvent system; 100% CH_2Cl_2 to 1% EtOAc/CH_2Cl_2) to obtain compound **SNP-4** as an orange solid. (melting point =101 °C-103 °C), (1.6 g, 75% yield, R_f = 0.2 in 50% CH_2Cl_2/Hexane). The spectral data of product **SNP-4** matched with previously reported literature.[53]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.18 – 8.10 (m, 5H), 7.63 – 7.54 (m, 9H), 7.21 – 7.16 (m, 1H), 6.90 (d, *J* = 7.7 Hz, 2H), 2.24 (s, 3H).

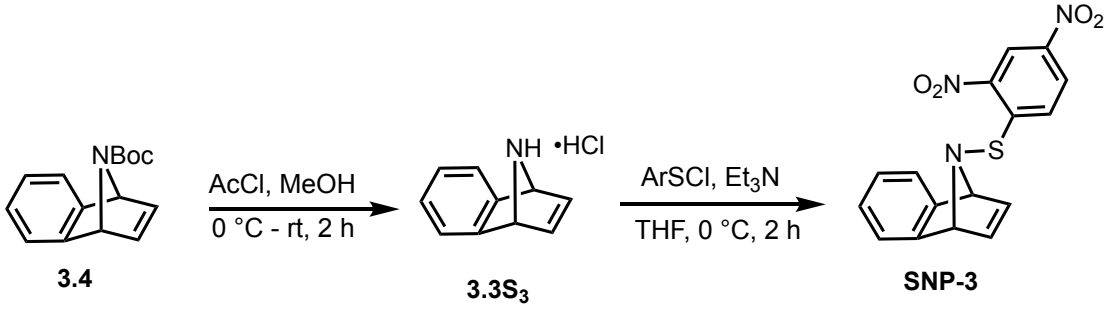
^{13}C NMR: (100 MHz, $CDCl_3$) δ 144.2, 142.5, 141.5, 140.7, 138.9, 134.0, 133.9, 129.9, 128.7, 128.4, 126.3, 125.9, 125.1, 124.3, 21.4.

LRMS(ESI):inactive.

3.3.1.4 General procedure for the synthesis of SNP-3a/b



Step-1: To a 500 mL two-neck round bottom flask charged with compound protected pyrrole (40 mmol), 20 mL dimethoxyethane was added and heated to 50 °C. Compound anthralinic acid (60 mmol in 60 mL of dimethoxyethane) and isoamyl nitrite (60 mmol in 60 mL of dimethoxyethane) were simultaneously added (1mL/1 min) to the mixture through syringe pump, and the resulting solution was stirred at the same temperature for next 1 h. After completion of the reaction, the resulting mixture was cooled down to room temperature and diluted with 200 mL of ethyl acetate. The resulting organic layer was washed with 100 mL of aq. saturated K_2CO_3 (twice), brine, and dried over Na_2SO_4 to obtain the crude product. The crude was purified using silica-gel column chromatography to obtain a yellowish solid. This yellowish solid was further washed with cold pentane to obtain a white solid of pure **3.4** (6.8 g, 70 % yield). The spectral data of product **3.4** matched with previously reported literature. [54]



3.4 **3.3S$_3$** **SNP-3**

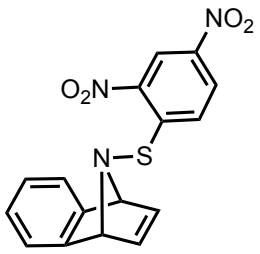
Step-2: **1,4-Dihydro-1,4-epiminonaphthalene hydrochloride salt**: Acetyl chloride (150 mmol) was slowly added to anhydrous methanol (1 mL/1mmol of salt) at ice cold condition and the resulting mixture was stirred at room temperature for 15 minutes. Next, compound **3.4** (25 mmol) was quickly added to the mixture at ice cold condition, and the resulting white sluggish mixture was vigorously stirred at room temperature until the completion of reaction indicated by TLC. After completion, cold hexane was added and stirred for next

5 min to get white precipitation. The precipitated white solid was collected by filtration and further washed with cold hexane to get a white solid of compound as hydrochloride salt (4.2 g, 95% yield). The spectral images for this compound are published in our research article.[52]

^{1}H NMR: (400 MHz, D_2O) δ 7.61 – 7.54 (m, 2H), 7.27 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.15 (t, *J* = 1.5 Hz, 2H), 5.70 (d, *J* = 1.6 Hz, 2H).

^{13}C NMR:(100 MHz, D_2O) δ 141.50, 139.68, 127.44, 123.11, 64.90.

Step-3: The compound salt (1.2) equiv.) was dissolved in THF (0.1 M) and 2.5 equiv. Triethylamine was slowly added at ice cold conditions. The resulting mixture was stirred for 30 min at room temperature. It was then cooled down to 0 °C and another 2.5 equiv. of triethylamine was added followed by the slow addition of sulfenyl chloride (1 equiv.) in THF (0.2 M) over 15 minutes. The reaction mixture was slowly warmed to room temperature over 30 minutes and further stirred for 30 minutes. After the completion of the reaction, the mixture was diluted with ethyl acetate, filtered through the sintered funnel, and washed with aq. saturated $NaHCO_3$ (x2), brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography.



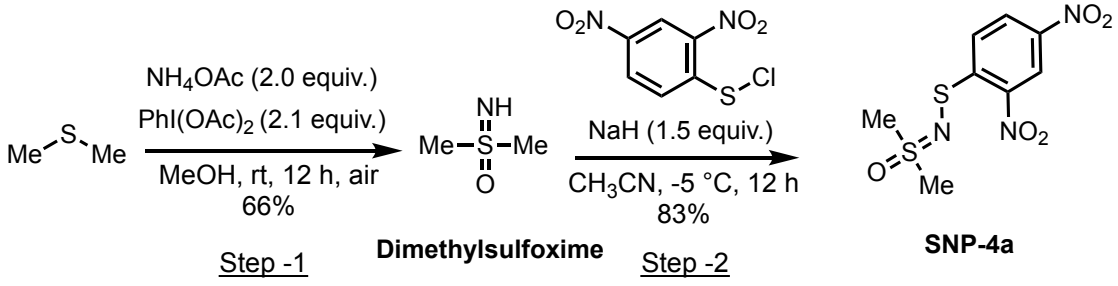
SNP-3

SNP-3 was synthesized from amine (50 mmol) according to general procedure using sulfenyl chloride **SC2** (42 mmol) and was purified using silica gel column chromatography (3→7% EtOAc/Hexane). The product was obtained as orange solid (m.p. = 138 °C – 140 °C; 11.4 g, 80% yield, R_f = 0.25 in 10% EtOAc/Hexane). The spectral images for this compound are published in our research article.[52]

^{1}H NMR: (600 MHz, $CDCl_3$ at 60 °C) δ 9.00 (d, *J* = 2.4 Hz, 1H), 8.44 (d, *J* = 9.1 Hz, 1H), 8.28 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.32 (dd, *J* = 5.1, 3.0 Hz, 2H), 7.12 (t, *J* = 1.5 Hz, 2H), 7.05 (dd, *J* = 5.1, 3.0 Hz, 2H), 5.01 (s, 2H).

^{13}C NMR: (150 MHz, $CDCl_3$ at 60 °C) δ 151.31, 148.11, 144.44, 143.51, 142.01, 127.97, 127.16, 125.66, 121.58, 121.16, 121.13, 74.41.

3.3.1.5 General procedure B for the synthesis of SNP-4a/4b



Step-1: To a solution of dimethyl sulfide 300 mg (4.8 mmol, 1.0 equiv) and NH_4OAc (9.6 mmol) in MeOH (2 mL/mmol with reference to the sulfide) at rt under air, solid $PhI(OAc)_2$ (10 mmol) was added portion-wise. The resulting mixture was stirred at rt for 6 h open to the air. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude mixture was diluted with CH_2Cl_2, solid $NaHCO_3$ was added, and the mixture was stirred 15 min followed by the addition of Na_2SO_4 and stirred another 15 min. The solid was removed by filtration and the filtrate was concentrated under

reduced pressure. Purification by silica-gel chromatography afforded sulfoximine as a pale-yellow oil (298 mg, 66% yield, R_f = 0.1 in 40% Acetone/EtOAc). The spectral data of product matched with previously reported literature.[55]

^{1}H NMR: (500 MHz, $CDCl_3$) δ 3.06 (s, 6H), 2.76 (s, 1H).

^{13}C NMR:(125 MHz, $CDCl_3$) δ 45.4.

LRMS(ESI): calculated for $C_2H_8NOS(M+H)^+$: 94.0; found:94.1.

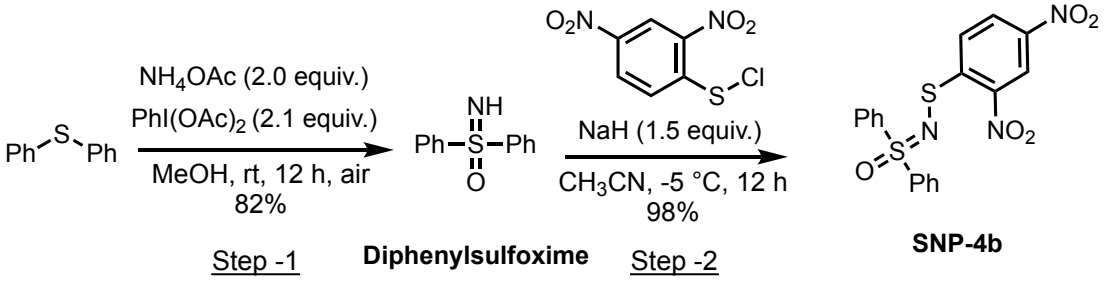
Step-2: To a solution of sulfoximine (200 mg, 2.1 mmol) in CH_3CN (0.1 M), NaH (1.5 equiv.) was added at -5 °C followed by the addition of sulfenyl chloride (503 mg, 2.1 mmol). The resulting solution was stirred at -5 °C for 12 h until the complete consumption of compound. The reaction mixture was diluted with dichloromethane and washed with aq. saturated $NaHCO_3$ (3 times), water (2 times), brine, and dried over Na_2SO_4. It was then concentrated under reduced pressure to obtain pure compound **SNP-4a** as an orange solid (melting point = 208 °C – 210 °C), (520 mg, 83% yield, R_f = 0.2 in 50% EtOAc/Hexane). No further purification was needed.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.12 (d, *J* = 2.6 Hz, 1H), 8.38 (dd, *J* = 9.1, 2.4 Hz, 1H), 8.29 (d, *J* = 9.3 Hz, 1H), 3.33 (s, 6H).

^{13}C NMR:(125 MHz, $CDCl_3$) δ 154.9, 144.3, 127.1, 126.6, 121.3, 42.1.

LRMS(ESI):inactive.

Synthesis of SNP-4b



Step-1: To a solution of diphenyl sulfide 500 mg (2.6 mmol, 1.0 equiv) and NH_4OAc (5.3 mmol) in MeOH (2 mL/mmol with reference to sulfide) at rt under air, solid $PhI(OAc)_2$ (5.6 mmol) was added portion-wise. The resulting mixture was stirred at rt for 12 h under air. After the completion of reaction, the reaction mixture was concentrated under reduced pressure. The crude mixture was diluted with CH_2Cl_2, solid $NaHCO_3$ was added stirred 15 min followed by the addition of Na_2SO_4 and stirred another 15 min. The solid was removed by filtration and the filtrate was concentrated under reduced pressure. Purification by silica-gel chromatography afforded sulfoximine as a white solid (480 mg, 82% yield, R_f = 0.2 in 40% EtOAc/Hexane). The spectral data of product matched with previously reported literature.[56]

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.08 – 8.00 (m, 4H), 7.56 – 7.43 (m, 6H), 2.82 (s, 1H).

^{13}C NMR:(125 MHz, $CDCl_3$) δ 143.4, 132.7, 129.3, 128.1.

LRMS(ESI): calculated for $C_{12}H_{12}NOS(M+H)^+$: 218.1; found:218.5.

Step-2: To a solution of sulfoximine (300 mg, 1.3 mmol) in CH_3CN (0.1 M), NaH (1.5 equiv.) was added at -5 °C followed by the addition of sulfenyl chloride (388 mg, 1.6 mmol). The resulting solution was stirred at -5 °C for 12 h until the complete consumption of compound **S_4**. The reaction mixture was diluted with dichloromethane and washed with

aq. saturated $NaHCO_3$ (3 times), water (2 times), brine, and dried over Na_2SO_4. It was then concentrated under reduced pressure to obtain pure compound **SNP-4b** as an orange solid (melting point = 191 °C – 192 °C), (560 mg, 98% yield, R_f = 0.2 in 40% EtOAc/Hexane). No further purification was needed.

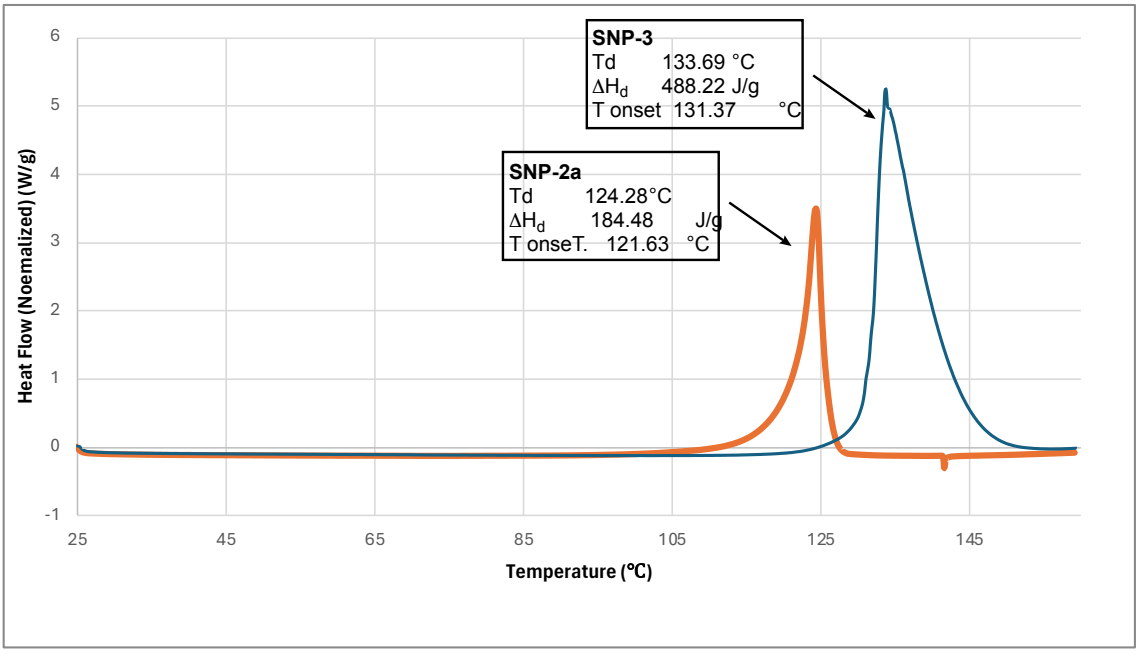
^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.09 (d, *J* = 2.4 Hz, 1H), 8.48 (d, *J* = 9.1 Hz, 1H), 8.37 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.08 – 8.02 (m, 4H), 7.68 – 7.64 (m, 2H), 7.62 – 7.57 (m, 4H).

^{13}C NMR:(125 MHz, $CDCl_3$) δ 155.4, 144.1, 141.4, 139.5, 134.1, 130.0, 128.4, 127.1, 127.0, 121.2.

LRMS(ESI):inactive.

3.3.1.6 DSC Analysis

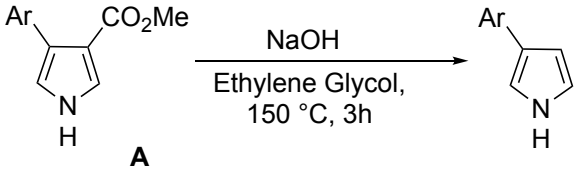
DSC Method: Approximately 3 mg of compound **SNP-2a** or **SNP-3** was weighed into a high-pressure stainless-steel crucible. The crucible was fitted with a disposable gold-



coated copper seal, then sealed under air. After equilibrating the sample at 25 °C, the sample was heated at a rate of 5 °C/minute. Measurements were made to 150 °C. Exothermic events are positive in the y-axis.

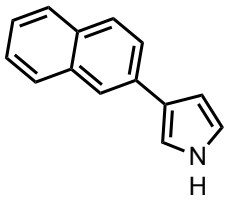
3.3.1 Synthesis of Pyrroles, Indoles, and Imidazoles

Synthesis of Pyrroles:



A

To a solution of pyrrole **A** in ethylene glycol (1 M), 1.5 equiv. of NaOH was added and the reaction mixture was heated to 150 °C for 3 h. After completion, it was diluted with ethyl acetate, washed with water, brine, and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the crude was purified by silica gel column chromatography.



3.5e

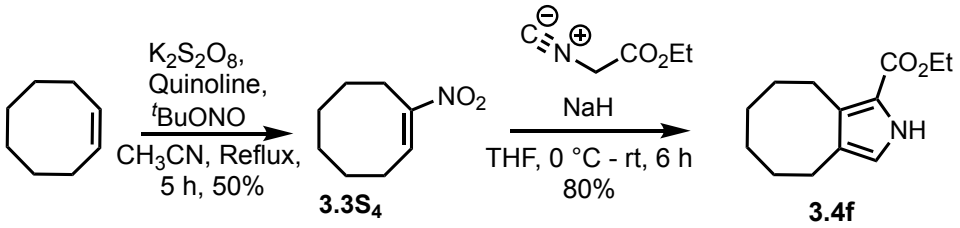
3-(Naphthalen-2-yl)-1*H*-pyrrole (3.5e): Compound **3.5e** was synthesized from corresponding pyrrole (1 mmol). The product was obtained as yellowish solid. (98 mg, 50% yield, R_f = 0.30 in 5% EtOAc/Hexane). The spectral images for this compound are published in our research article.[52]

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.96 (s, 1H), 7.84 – 7.78 (m, 3H), 7.73 – 7.68 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.23 (s, 1H), 6.89 (d, *J* = 2.6 Hz, 1H), 6.69 (s, 1H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 134.16, 133.37, 132.10, 128.24, 127.79, 127.77, 126.14, 125.10, 124.99, 124.83, 122.80, 119.25, 115.15, 106.87.

HRMS(ESI): calculated for $C_{14}H_{10}N$ $(M-H)^-$: 192.0813; found: 192.0819.

Synthesis of 3.4f:



(*E*)-1-Nitrocyclooct-1-ene (3.3S$_4$): To a solution of 1-cyclooctene (5 mmol) in 5 mL of $K_2S_2O_8$ (5 mmol) and quinoline (5 mmol), was added slowly a solution of ^{t}BuONO (6 mmol) at room temperature over 15 minutes and the resulting mixture was refluxed for 5 hours. After completion of the reaction, all the volatiles were removed under reduced pressure, and the crude was purified by silica gel column chromatography. The product was obtained as yellowish liquid. (390 mg, 50% yield, R_f = 0.50 in 1% EtOAc/Hexane).

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 8.8 Hz, 1H), 2.78 – 2.70 (m, 2H), 2.35 – 2.28 (m, 2H), 1.75 – 1.65 (m, 4H), 1.50 (qt, *J* = 4.1, 2.2 Hz, 4H).

^{13}C NMR: (150 MHz, $CDCl_3$ δ 152.43, 136.38, 29.15, 28.41, 26.77, 26.53, 25.78, 24.94.

HRMS(ESI): calculated for $C_8H_{12}NO_2$ $(M-H)^-$: 154.0946; found: 154.0869.

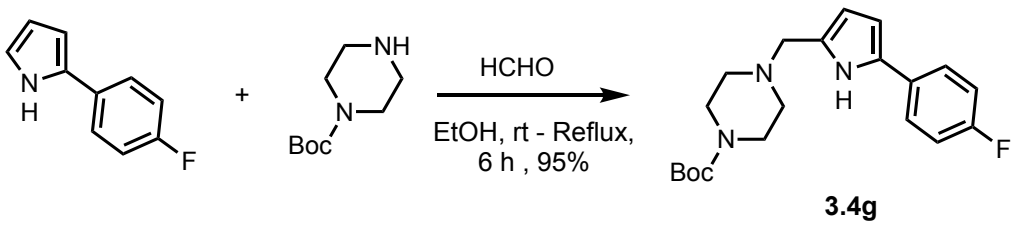
Ethyl 4,5,6,7,8,9-hexahydro-2*H*-cycloocta[*c*]pyrrole-1-carboxylate (3.4f): To a solution of ethyl 2-isocyanoacetate (1.5 mmol) in 5 mL THF, NaH (1.7 mmol) was added at ice cold condition and the mixture was stirred for 10 minutes at the same temperature. Next, a solution of (*E*)-1-nitrocyclooct-1-ene (1 mmol) in 5 mL THF was added to the reaction and the resulting mixture was slowly warmed to room temperature. The reaction was monitored by TLC. After completion, it was diluted with ethyl acetate, washed with aq. sat. NH_4Cl, brine, and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the crude product was purified by silica gel column chromatography. The product was obtained as yellow solid. (180 mg, 80% yield, R_f = 0.30 in 20% EtOAc/Hexane).

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.77 (s, 1H), 6.63 (d, *J* = 2.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.90 (dd, *J* = 7.3, 5.4 Hz, 2H), 2.65 – 2.50 (m, 2H), 1.66 (dt, *J* = 10.5, 5.0 Hz, 2H), 1.62 – 1.53 (m, 2H), 1.54 – 1.44 (m, 2H), 1.43 – 1.31 (m, 5H).

^{13}C NMR: (150 MHz, $CDCl_3$) δ 161.87, 131.34, 126.78, 119.34, 118.55, 59.87, 32.78, 30.08, 26.07, 25.91, 24.67, 22.77, 14.64.

HRMS(ESI): calculated for $C_{13}H_{18}NO$ $(M-H)^-$: 220.1338; found: 220.1342.

Synthesis of 3.4g



3.4g

***tert*-Butyl 4-((5-(4-fluorophenyl)-1*H*-pyrrol-2-yl)methyl)piperazine-1-carboxylate (3.4g):** To a solution of Boc-piperazine (1 mmol) in absolute ethanol (5 mL), 1.5 mmol of

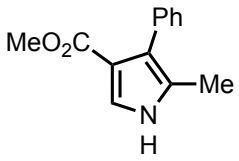
formaldehyde (37% in H_2O) was added and the mixture was stirred at room temperature for 30 minutes. A solution of 2-(4-fluorophenyl)-1*H*-pyrrole (1 mmol) in ethanol (1 M) was added to the mixture and it was heated to reflux for 6 h until the consumption of all starting materials. After completion, all the volatiles were removed under reduced pressure, and the crude product was purified by silica gel column chromatography. The product was obtained as pink solid (340 mg, 95% yield, R_f = 0.10 in 10% MeOH/DCM).

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.47 – 7.38 (m, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.33 (t, *J* = 3.1 Hz, 1H), 6.07 (t, *J* = 3.0 Hz, 1H), 3.53 (s, 2H), 3.44 (s, 4H), 2.41 (s, 4H), 1.46 (s, 9H).

^{13}C NMR: (150 MHz, $CDCl_3$) δ 162.36, 160.74, 154.90, 131.38, 129.30, 125.43, 125.38, 115.98, 115.84, 109.84, 105.67, 79.87, 55.71, 53.02, 28.57.

^{19}F NMR:(564 MHz, $CDCl_3$) δ -116.54.

HRMS(ESI): calculated for $C_{20}H_{25}FN_3O_2$ $(M-H)^-$: 358.1931; found: 358.1931.



3.4k

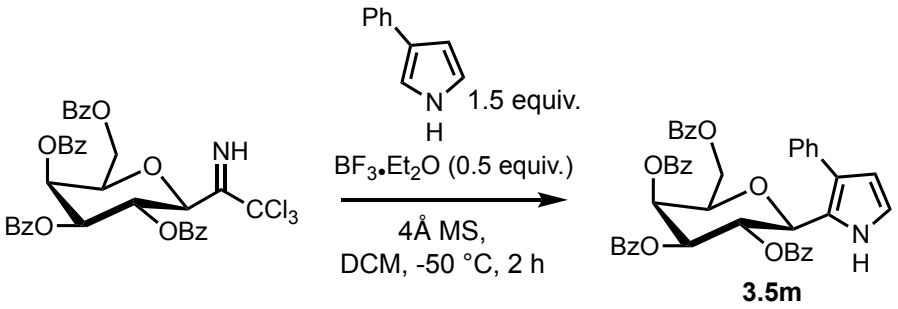
Methyl 5-methyl-4-phenyl-1*H*-pyrrole-3-carboxylate (3.4k): Compound **3.4k** was synthesized from corresponding α,β -unsaturated compound (1 mmol) and 1-((1-isocyanoethyl)sulfonyl)-4-methylbenzene (CAS No. 58379-80-9). The compound was collected as a light yellow solid (130 mg, 60% yield, R_f = 0.35 in 20% EtOAc/Hexane). The spectral images for this compound are published in our research article.[57]

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.32 – 7.28 (m, 2H), 7.27 – 7.23 (m, 3H), 7.22 – 7.18 (m, 1H), 3.62 (s, 3H), 2.08 (s, 3H).

^{13}C NMR:(125 MHz, $CDCl_3$) δ 165.49, 135.04, 130.43, 127.55, 126.69, 126.22, 123.03, 122.16, 114.00, 50.76, 11.48.

HRMS(ESI): calculated for $C_{13}H_{13}NaNO_2(M+Na)^+$: 238.0844; found: 238.0847.

Synthesis of 3.5m:



3.5m

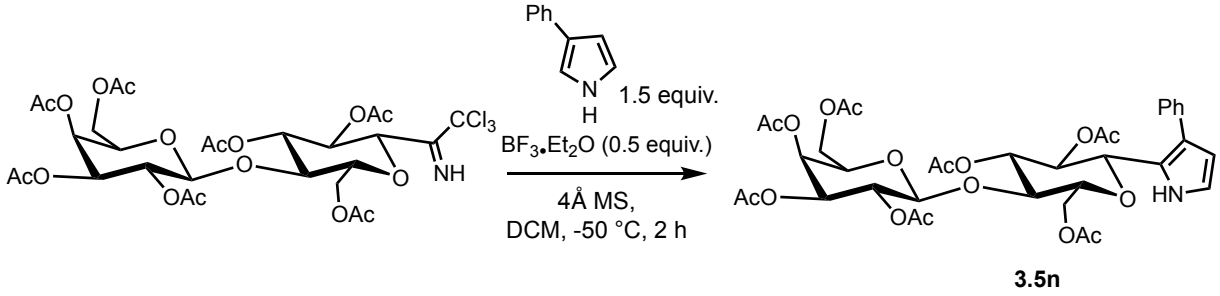
To a solution of doner (200 mg, 0.27 mmol, 1.0 equiv.), 1.5 equiv. of 3-phenylpyrrole and 4Å molecular sieves (2 mg/1 mg of doner) in dichloromethane (0.1 M) at -50 °C, a solution of BF_3Et_2O in CH_2Cl_2 (0.1 M) was added dropwise over the period of 5 minutes. The resulting solution was stirred next 2 h at same temperature. After the completion of reaction, the crude mixture was filtered through a pad of celite and purified by silica gel column chromatography to obtain **3.5m** as an off-white solid (176 mg mg, 88% yield, R_f = 0.3 in 30% EtOAc/Hexane).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.14 – 8.09 (m, 2H), 8.08 – 8.05 (m, 2H), 7.76 – 7.63 (m, 5H), 7.58 – 7.50 (m, 4H), 7.45 – 7.39 (m, 7H), 7.29 – 7.18 (m, 5H), 6.86 (t, *J* = 2.8 Hz, 1H), 6.28 (t, *J* = 2.7 Hz, 1H), 6.18 (t, *J* = 10.1 Hz, 1H), 6.10 (d, *J* = 3.5 Hz, 1H), 5.74 (dd, *J* = 10.0, 3.4 Hz, 1H), 4.99 (d, *J* = 10.2 Hz, 1H), 4.64 – 4.58 (m, 1H), 4.57 – 4.50 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 166.3, 166.1, 165.7, 165.6, 136.0, 133.8, 133.6, 133.5, 133.4, 130.1, 129.97, 129.88, 129.81, 129.54, 129.30, 128.87, 128.63, 128.41, 128.40, 126.99, 126.28, 121.4, 119.1, 109.8, 75.2, 73.3, 73.0, 69.3, 68.7, 63.1.

LRMS(ESI): calculated for $C_{44}H_{36}NO_9(M+H)^+$: 722.2; found:722.8.

Synthesis of 2.5n:



To a solution of doner (150 mg, 0.19 mmol, 1.0 equiv.), 1.5 equiv. of 3-phenylpyrrole and 4Å molecular sieves (2 mg/1 mg of doner) in dichloromethane (0.1 M) at -50 °C, a solution of BF_3Et_2O in CH_2Cl_2 (0.1 M) was dropwise over the period of 5 minutes. The resulting solution was further stirred 2 h at same temperature. After the completion of reaction, the crude mixture was filtered through a pad of celite and purified by silica gel column chromatography to obtain **3.5n** as a brown solid (120 mg, 80% yield, R_f = 0.2 in 50% EtOAc/Hexane).

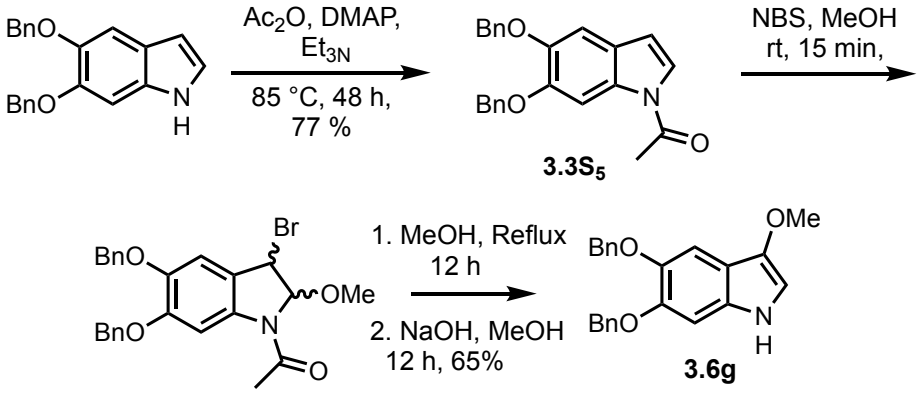
^{1}H NMR: (500 MHz, $CDCl_3$) δ ^{1}H NMR δ 8.47 (s, 1H), 7.45 – 7.37 (m, 4H), 7.28 (d, *J* = 7.4 Hz, 1H), 6.79 (t, *J* = 2.9 Hz, 1H), 6.30 (d, *J* = 2.9 Hz, 1H), 5.36 (d, *J* = 3.4 Hz, 1H), 5.33 – 5.28 (m, 2H), 5.16 – 5.10 (m, 1H), 4.96 (dd, *J* = 10.4, 3.5 Hz, 1H), 4.68 – 4.63 (m, 1H), 4.50 (d, *J* = 7.7 Hz, 1H), 4.48 – 4.41 (m, 1H), 4.16 – 4.09 (m, 3H), 3.87 (dt, *J* = 18.7, 7.9 Hz, 3H), 2.16 (s, 3H), 2.12 (s, 3H), 2.06 (s, 9H), 1.97 (s, 3H), 1.79 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 170.63, 170.53, 170.33, 170.24, 169.79, 169.24, 136.0, 128.7, 128.2, 126.4, 121.3, 119.0, 109.5, 101.3, 76.98, 76.76, 74.1, 72.3, 71.1, 70.9, 70.8, 69.2, 66.7, 62.9, 61.0, 21.0, 20.96, 20.81, 20.79, 20.77, 20.66, 20.61.

LRMS(ESI): calculated for $C_{36}H_{44}NO_{17}(M+H)^+$: 762.2; found:762.5.

Synthesis of Indoles:

Synthesis of 2.6g



To a solution of indole (1 mmol) in 10 mmol of acetic anhydride, 20 mol % of DMAP, and 1.5 mmol of Et_3N were added. The mixture was heated to 85 °C for 24 h until complete conversion (indicated by TLC). After completion, the reaction mixture was diluted with dichloromethane, and washed with saturated $NaHCO_3$ (x3), brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography. The product **3.3S$_5$** was obtained as yellow solid (290 mg, 77% yield, R_f = 0.20 in 40% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.52 (ddt, *J* = 7.5, 1.4, 0.7 Hz, 2H), 7.49 – 7.45 (m, 2H), 7.37 (dddt, *J* = 6.5, 5.5, 4.8, 1.0 Hz, 4H), 7.33 – 7.25 (m, 4H), 7.08 (s, 1H), 6.49 (dd, *J* = 3.7, 0.6 Hz, 1H), 5.21 (d, *J* = 18.2 Hz, 4H), 2.59 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.61, 148.16, 146.67, 137.46, 137.27, 130.47, 128.46, 127.79, 127.75, 127.56, 127.37, 124.05, 123.73, 108.99, 106.58, 103.47, 71.87, 71.48, 23.72.

HRMS(ESI): calculated for $C_{24}H_{22}NO_3$ $(M+H)^+$: 372.1600; found: 372.1603.

To a solution **3.3S$_5$** of (0.7 mmol) in anhydrous methanol (1 M), 1.1 mmol of *N*-bromo succinimide was added at room temperature and the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used for the next step without further purification.

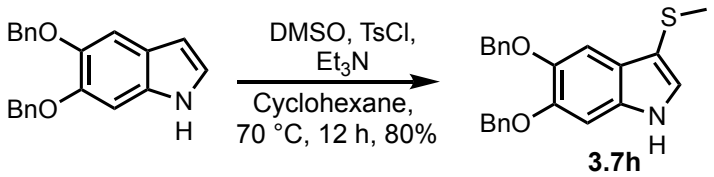
The crude mixture was re-dissolved in anhydrous methanol (0.1 M) and refluxed overnight. Afterwards, 4.0 mmol of powdered NaOH was added and refluxed for overnight. After completion, the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography. The product **3.6g** was obtained as a reddish solid (180 mg, 65% yield, R_f = 0.20 in 30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.47 (ddd, *J* = 14.5, 7.1, 1.5 Hz, 4H), 7.35 (ddd, *J* = 7.8, 6.3, 1.8 Hz, 4H), 7.33 – 7.27 (m, 2H), 7.24 (s, 1H), 7.18 (s, 1H), 6.83 (s, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 5.16 (d, *J* = 4.0 Hz, 4H), 3.85 (s, 3H).

^{13}C NMR:(100 MHz, $CDCl_3$) δ 147.47, 144.49, 142.23, 137.73, 137.51, 129.47, 128.44, 128.39, 127.69, 127.63, 127.51, 127.33, 113.12, 103.37, 102.86, 98.39, 72.11, 71.84, 58.05.

HRMS(ESI): calculated for $C_{23}H_{22}NO_3$ $(M+H)^+$: 360.1600; found: 360.1607.

Synthesis of 2.6h



3.7h

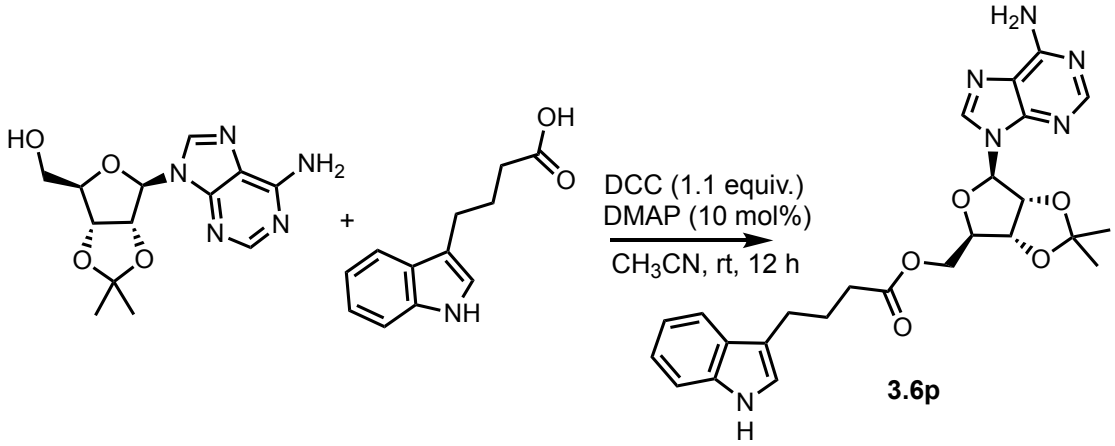
To a solution of DMSO (1.5 mmol) and TsCl (1.5 mmol) in cyclohexane (1 M) at room temperature, 1.5 mmol of Et_3N and 1 mmol of indole were added, and the resulting mixture was heated to 70 °C for 12 h. After completion, the reaction mixture was quenched with water. The aqueous layer was extracted three times with diethylether. The organic extracts were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The compound was purified by silica gel column chromatography. The product **3.7h** was obtained as a yellowish solid (305 mg, 80% yield, R_f = 0.20 in 30% EtOAc/Hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.39 – 7.32 (m, 5H), 7.29 (d, *J* = 6.4 Hz, 2H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.94 (s, 1H), 5.20 (d, *J* = 16.1 Hz, 4H), 2.30 (s, 3H).

^{13}C NMR:(100 MHz, $CDCl_3$) δ 147.37, 145.49, 137.64, 137.45, 130.95, 128.45, 128.42, 128.39, 127.73, 127.69, 127.63, 127.34, 126.83, 122.72, 110.39, 107.78, 104.97, 98.85, 72.25, 72.07, 20.23.

LRMS(ESI): calculated for $C_{23}H_{22}NO_2S$ $(M+H)^+$: 376.1; found: 376.1.

Synthesis of 3.6p:



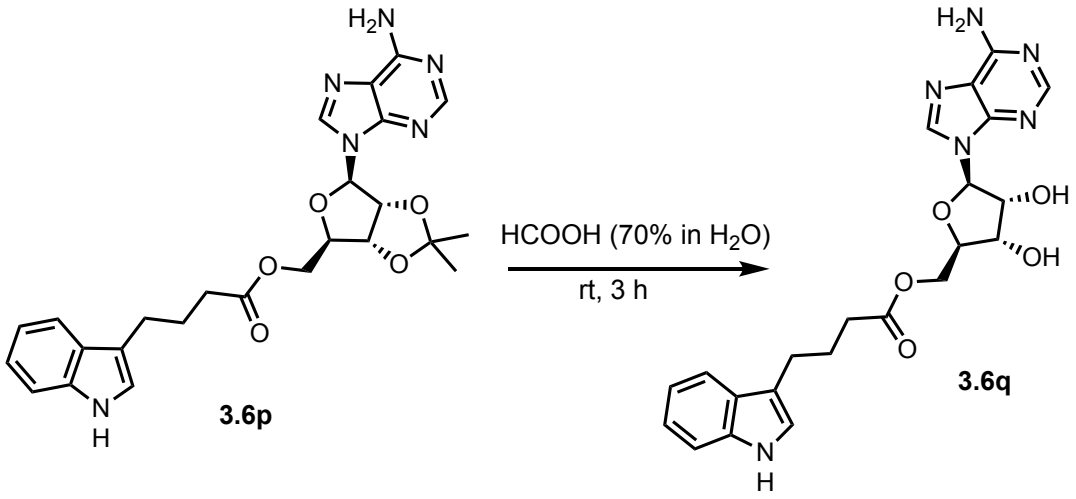
To a solution of adenosine (150 mg, 0.51 mmol, 1.0 equiv.), 1.1 equiv. of acid, and DCC (1.1 equiv.) in CH_3CN (0.1 M) at rt, solid DMAP (10 mol%) was added and the resulting solution was stirred at same temperature overnight. After the completion of reaction, as indicated by TLC, the reaction mixture was diluted with dichloromethane, filtered through a pad of celite, and purified by silica gel column chromatography to obtain **3.6p** as a white solid (180 mg, 70% yield, R_f = 0.2 in 10% MeOH/CH_2Cl_2).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.17 (s, 1H), 7.86 (s, 1H), 7.57 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.09 (d, *J* = 2.1 Hz, 1H), 5.88 (s, 2H), 5.43 (dd, *J* = 6.3, 2.1 Hz, 1H), 5.00 (dd, *J* = 6.3, 3.3 Hz, 1H), 4.48 (dt, *J* = 5.9, 3.9 Hz, 1H), 4.32 (dd, *J* = 11.9, 4.3 Hz, 1H), 4.21 (dd, *J* = 11.9, 5.9 Hz, 1H), 2.75 (tdd, *J* = 7.3, 3.1, 0.9 Hz, 2H), 2.27 (td, *J* = 7.4, 2.8 Hz, 2H), 2.03 – 1.94 (m, 3H), 1.61 (s, 3H), 1.39 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 173.3, 155.4, 152.9, 149.4, 139.9, 136.5, 127.5, 122.1, 121.7, 120.4, 119.3, 119.0, 115.4, 114.7, 111.3, 91.3, 85.1, 84.4, 81.7, 64.0, 33.6, 27.3, 25.5, 25.2, 24.5.

LRMS(ESI): calculated for $C_{25}H_{29}N_6O_5(M+H)^+$: 493.2; found:493.1.

Synthesis of 3.6q:



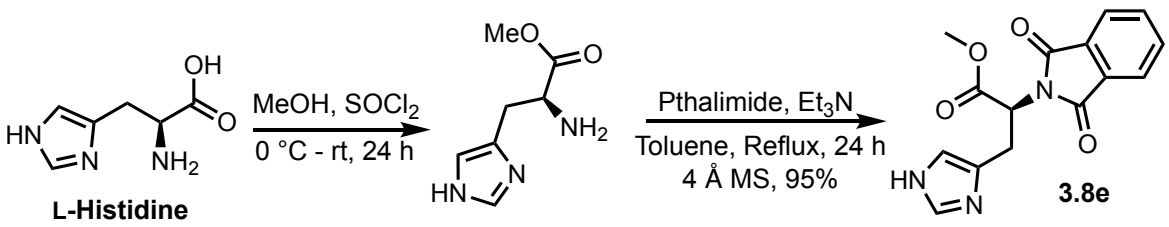
To solid **3.6p** (100 mg, 0.20 mmol, 1.0 equiv.), 2 mL of HCOOH (70% in H_2O) was added and the resulting solution was stirred at same temperature next 3 h. After the completion of reaction as indicated by TLC, all the volatiles were removed under reduced pressure. The compound was purified by silica gel column chromatography to obtain **3.6q** as a brown solid (82 mg, 89% yield, R_f = 0.2 in 20% MeOH/CH_2Cl_2).

^{1}H NMR: (500 MHz, CD_3OD) δ 8.22 (s, 2H), 8.18 (d, *J* = 5.2 Hz, 1H), 7.89 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.07 – 6.99 (m, 1H), 6.94 (dd, *J* = 15.1, 7.6 Hz, 2H), 6.00 (d, *J* = 4.4 Hz, 1H), 4.73 (q, *J* = 4.6 Hz, 1H), 4.37 (dt, *J* = 9.2, 3.3 Hz, 3H), 4.25 (q, *J* = 4.7 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.42 – 2.35 (m, 2H), 2.02 – 1.96 (m, 2H).

^{13}C NMR: (125 MHz, CD_3OD) δ 175.1, 164.6, 157.1, 153.5, 150.5, 141.3, 138.2, 128.7, 123.1, 122.2, 119.4, 119.3, 115.4, 112.1, 90.5, 83.5, 75.2, 71.8, 64.6, 34.4, 26.8, 25.4.

LRMS(ESI): calculated for $C_{22}H_{25}N_6O_5(M+H)^+$: 453.1; found:453.6.

Synthesis of imidazoles:



To a solution of L-histidine (1 equivalent) in MeOH (1 M), 2.0 equivalent of thionyl chloride was added dropwise over a period of 15 minutes at ice cold condition. The resulting solution was slowly warmed to room temperature, and the mixture was stirred for 24 hours. After completion, all the volatiles were removed under reduced pressure to obtain the methyl L-histidine hydrochloride salt as a white powder. The crude salt was dissolved in THF and 3.0 equiv. of Et_3N was added and stirred for 30 minutes. The resulting mixture was filtered through celite, and all the volatiles were removed under reduced pressure and used for the next step without further purification.

To the methyl L-histidine (1 mmol) in toluene (0.5 M), 1 mmol of Et_3N was added followed by the addition of 1.2 mmol of phthalimide, and molecular sieves. The resulting sluggish mixture was heated to reflux for 24 hours. All the volatiles were removed under reduced pressure and the crude mixture was purified by silica gel column chromatography. The product was obtained as yellowish solid (285 mg, 90% yield, R_f = 0.20 in 10% MeOH/DCM).

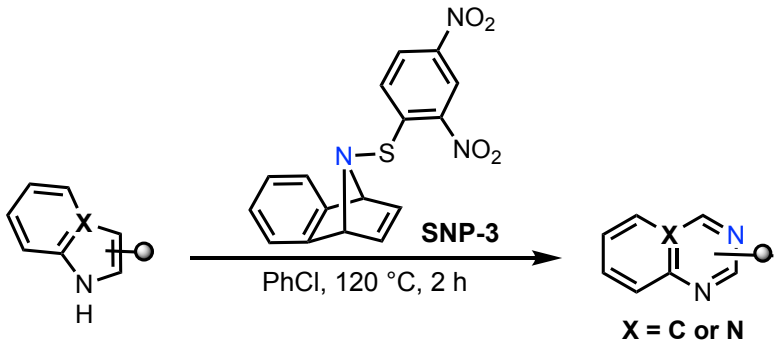
^{1}H NMR:(400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.74 – 7.69 (m, 2H), 7.53 (d, *J* = 1.1 Hz, 1H), 6.79 (d, *J* = 1.1 Hz, 1H), 5.20 (t, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 3.54 (d, *J* = 7.6 Hz, 2H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 169.61, 167.41, 135.13, 134.12, 131.68, 123.50, 52.90, 52.03, 26.77.

HRMS(ESI): calculated for $C_{15}H_{14}N_3O_4$ $(M+H)^+$: 300.0984; found: 300.0984.

3.3.3 General Procedure for *N*-atom Insertion

3.3.3.1 General Procedure A for the *N*-atom Insertion Under Thermal Conditions

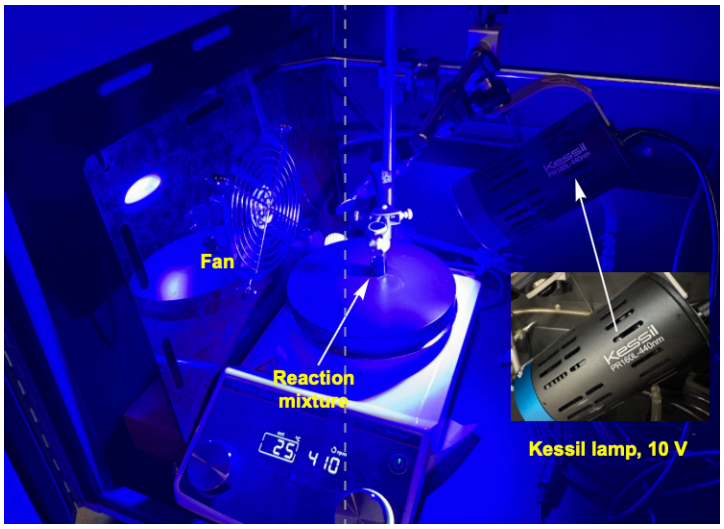


To a solution of pyrrole/indole/imidazole (1 equiv.) in chlorobenzene (0.1 M), (2 equiv.) of solid sulfenylnitrene precursor was added in one portion. The resulting solution was placed in a 120 °C pre-heated stirred plate and stirred for 2 h. Next, all the volatiles were removed at 50 °C under reduced pressure and the product was purified by silica gel column chromatography. Yields reported are isolated yields, except for the products having regioisomeric ratios, which were determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

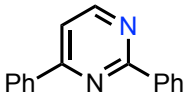
3.3.3.2 General Procedure B for the *N*-atom Insertion Under Photolytic Conditions

To a solution of pyrrole or indole or imidazole (1.0 equiv.) in 0.05 M dichloromethane (DCM), 1.5 equiv. of solid sulfenylnitrene precursor was added in one portion. The resulting solution was stirred and irradiated with blue LED (Kessil lamp (10V), PR160L-440 nm, 100% intensity) at room temperature for next 6 h. Next, all the volatiles were removed under reduced pressure and the product was purified by silica gel column chromatography.

Reaction set-up



Pyrimidines



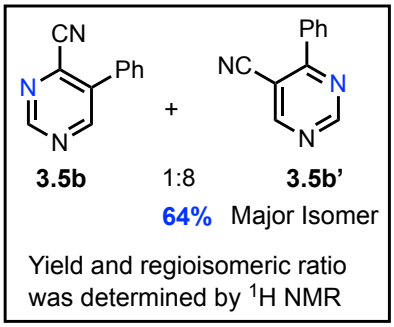
3.5a

2,4-Diphenylpyrimidine (3.5a): Synthesized according to general procedure **A** using 20 mg (0.091 mmol) of pyrrole and 2.0 equiv. of **SNP-2a**. The product was obtained as off-white solid (20.5 mg, 97% yield), R_f = 0.15 in 10% ethyl acetate/hexane. The spectral data of product matched with previously reported literature.[5]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 5.3 Hz, 1H), 8.62 – 8.56 (m, 2H), 8.26 – 8.22 (m, 2H), 7.61 (d, *J* = 5.2 Hz, 1H), 7.57 – 7.51 (m, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.7, 164.0, 158.0, 138.0, 137.1, 131.1, 130.9, 129.1, 128.7, 128.4, 127.4, 114.7.

LRMS(ESI) calculated $C_{16}H_{13}N_2$ $(M+H)^+$: 233.1; found:233.4.

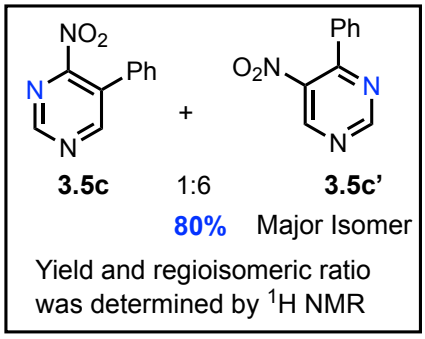


4-Phenylpyrimidine-5-carbonitrile (3b', major isomer): Synthesized according to general procedure **B** using 15 mg (0.089 mmol) of pyrrole and 1.5 equiv. of **SNP-2b**. The major isomer was obtained as yellowish solid (8.5 mg, R_f = 0.30 in 10% ethyl acetate/hexane). The spectral data of product matched with previously reported literature.[58]

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 9.06 (s, 1H), 8.15 – 8.09 (m, 2H), 7.66 – 7.55 (m, 3H).

^{13}C NMR:(100 MHz, $CDCl_3$) δ 167.1, 162.0, 160.3, 134.8, 132.5, 129.3, 129.2, 115.9, 106.5.

LRMS(ESI) calculated $C_{11}H_8N_2$ $(M+H)^+$: 182.1; found:182.5.

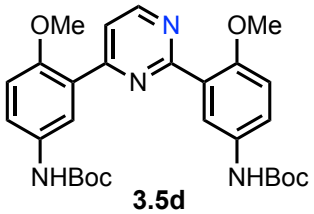


5-Nitro-4-phenylpyrimidine (3.5c', major isomer): Synthesized according to general procedure **E** using 20 mg (0.10 mmol) of pyrrole and 2 equiv. of **SNP-3**. The major isomer was obtained as yellowish solid (14 mg, R_f = 0.20 in 10% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 9.14 (s, 1H), 7.76 – 7.64 (m, 2H), 7.62 – 7.55 (m, 1H), 7.55 – 7.45 (m, 2H).

^{13}C NMR: (150 MHz, $CDCl_3$) δ 159.91, 152.63, 133.44, 131.69, 129.46, 129.05, 128.49, 128.06.

HRMS(ESI): calculated for $C_{10}H_7N_2O(M\text{-}NO)^-$: 171.0558; found: 171.0558.



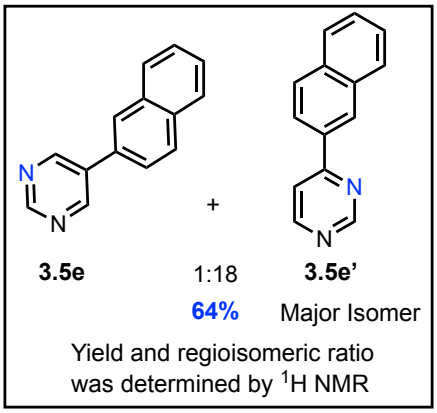
3.5d

Di-*tert*-butyl(pyrimidine-2,4-diylbis(4-methoxy-3,1-phenylene))dicarbamate (3.5d): Synthesized according to general procedure **E** using 30 mg (0.058 mmol) of pyrrole and 2 equiv. of **SNP-3**. The compound was obtained as a yellow solid (30 mg, 98% yield), R_f = 0.20 in 50% ethyl acetate/hexane.

^{1}H NMR 600 MHz, $CDCl_3$, at 60 °C) δ 8.79 (d, *J* = 5.2 Hz, 1H), 7.98 (d, *J* = 2.8 Hz, 1H), 7.87 (dd, *J* = 5.3, 0.8 Hz, 1H), 7.69 (d, *J* = 2.8 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 6.98 (dd, *J* = 10.8, 8.9 Hz, 2H), 6.40 (d, *J* = 23.5 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 1.52 (d, *J* = 2.8 Hz, 18H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 164.99, 162.11, 156.49, 154.15, 153.94, 153.09, 132.02, 131.45, 129.03, 126.40, 122.60, 122.00, 121.53, 119.21, 112.88, 112.24, 80.27, 56.55, 55.97, 28.36, 28.34.

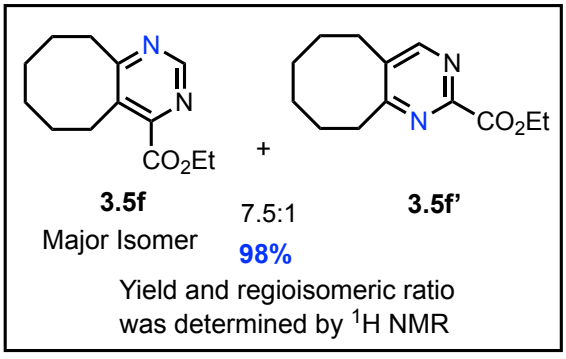
LRMS(ESI) calculated $C_{28}H_{36}N_4O_6$ $(M+2H)^+$: 524.2; found:524.2.



4-(Naphthalen-2-yl)pyrimidine (3.5e', major isomer): Synthesized according to general procedure **B** using 20 mg (0.10 mmol) of pyrrole and 2 equiv. of **SNP-2b**. The major isomer was obtained as white solid (15 mg, R_f = 0.30 in 5% ethyl acetate/hexane). **^{1}H NMR:** (600 MHz, $CDCl_3$) δ 9.33 (d, *J* = 1.4 Hz, 1H), 8.82 (d, *J* = 5.4 Hz, 1H), 8.64 (d, *J* = 1.8 Hz, 1H), 8.18 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.94 – 7.85 (m, 2H), 7.62 – 7.52 (m, 2H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 164.02, 159.35, 157.69, 134.85, 133.92, 133.43, 129.22, 129.06, 127.94, 127.75, 127.73, 126.91, 123.92, 117.40.

HRMS(ESI): calculated for $C_{14}H_{11}N_2(M+H)^+$: 207.0922; found: 207.0927.



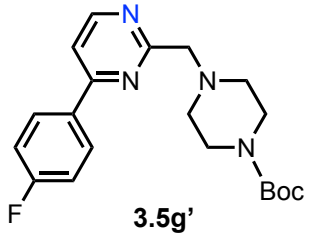
Ethyl 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyrimidine-4-carboxylate (3.5f, major isomer): Synthesized according to general procedure **B** using 20 mg (0.09 mmol) of

pyrrole and 2 equiv. of **SNP-2b**. The major isomer was obtained as yellowish solid (12 mg, R_f = 0.20 in 5% ethyl acetate/hexane).

^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.03 (s, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 3.03 – 2.99 (m, 2H), 2.98 – 2.94 (m, 2H), 1.83 (ddt, *J* = 10.0, 6.4, 3.6 Hz, 4H), 1.43 (t, *J* = 7.1 Hz, 5H), 1.38 (ddt, *J* = 12.2, 6.1, 2.8 Hz, 2H).

^{13}C NMR: (150 MHz, $CDCl_3$) δ 172.78, 165.63, 156.05, 154.82, 132.08, 62.22, 34.81, 30.66, 30.33, 26.47, 26.12, 25.75, 14.15.

HRMS(ESI): calculated for $C_{13}H_{19}N_2O_2$ $(M+H)^+$: 235.1447; found: 235.1453.



3.5g'
Exclusive product

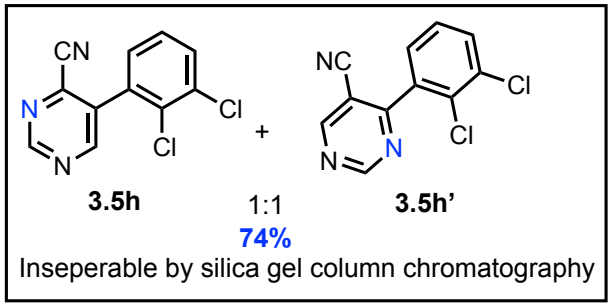
***tert*-Butyl 4-((4-(4-fluorophenyl)pyrimidin-2-yl)methyl)piperazine-1-carboxylate (3.5g', exclusive product):** Synthesized according to general procedure **A** using 20 mg (0.055 mmol) of pyrrole and 2 equiv. of **SNP-3**. The product was obtained as yellow solid (14 mg, 72% yield), R_f = 0.20 in 5% MeOH/DCM.

^{1}H NMR:(600 MHz, $CDCl_3$) δ 8.77 (d, *J* = 5.3 Hz, 1H), 8.11 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.54 (d, *J* = 5.3 Hz, 1H), 7.19 (t, *J* = 8.6 Hz, 2H), 3.91 (s, 2H), 3.53 (s, 4H), 2.62 (s, 4H), 1.46 (s, 9H).

^{13}C NMR: (150 MHz, $CDCl_3$) δ 165.70, 164.03, 163.05, 158.13, 158.10, 154.92, 132.88, 129.47, 129.42, 128.40, 116.30, 116.15, 114.65, 79.76, 65.21, 53.31,43.96, 42.95 28.57.

^{19}F NMR: (564 MHz, $CDCl_3$) δ -109.3

HRMS(ESI): calculated for $C_{20}H_{26}FN_4O_2$ $(M+H)^+$: 373.2040; found: 373.2044.

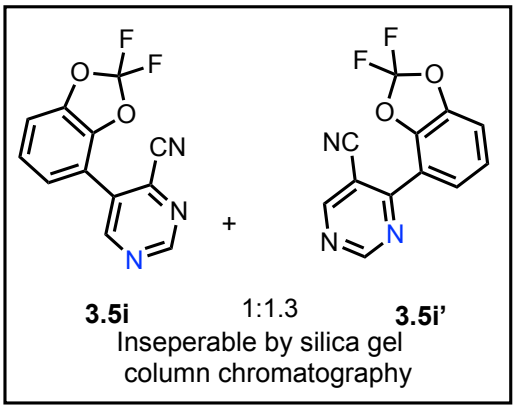


5-(2,3-Dichlorophenyl)pyrimidine-4-carbonitrile (3.5h) and **4-(2,3-Dichlorophenyl)pyrimidine-5-carbonitrile (3.5h'):** Synthesized according to general procedure **A** using 25 mg (0.10 mmol) of pyrrole and 2 equiv. of **SNP-3**. The mixture of isomers was obtained as yellowish solid (19.5 mg, 74% yield), R_f = 0.20 in 20% ethyl acetate/hexane.

^{1}H NMR:(600 MHz, $CDCl_3$) δ 9.47 (s, 1H), 9.36 (s, 1H), 9.12 (s, 1H), 8.97 (s, 1H), 7.68 (dd *J* = 8.1, 2.2, 1.5 Hz, 2H), 7.41 (t, *J* = 7.9, 4.4 Hz, 2H), 7.36 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.6 Hz, 1H).

^{13}C NMR:(600 MHz, $CDCl_3$) δ 167.01, 160.51, 160.15, 159.22, 158.57, 140.45, 136.20, 135.76, 134.68, 134.51, 132.79, 132.70, 132.57, 131.85, 130.94, 129.27, 128.55, 128.07, 127.90, 114.16, 113.83, 110.07, 77.32, 77.00, 76.69.

HRMS(ESI): calculated for $C_{11}H_6N_3OCl_2$ $(M+H)^+$: 249.9939; found: 249.9941.



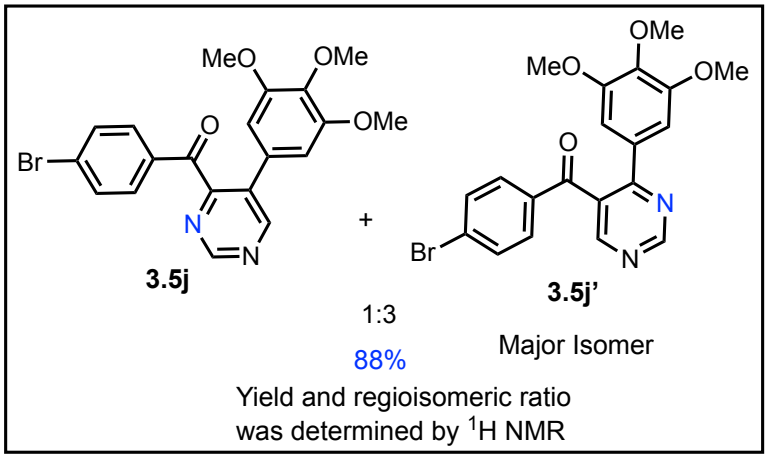
5-(2,2-difluorobenzo[*d*][1,3]dioxol-4-yl)pyrimidine-4-carbonitrile (3.5i) and **4-(2,2difluoro benzo[*d*][1,3]dioxol-4-yl)pyrimidine-5-carbonitrile (3.i') :** Synthesized according to general procedure **B** using 25 mg (0.10 mmol) of pyrrole and 2 equiv. of **SNP-3**. The mixture of isomers was obtained as yellowish waxy solid (21.5 mg, 82% yield), R_f = 0.15 in 20% ethyl acetate/hexane.

^{1}H NMR:(600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 9.38 (s, 1H), 9.13 (s, 1H), 9.12 (s, 1H), 7.55 (m, 1H), 7.33 – 7.29 (m, 4H), 7.29 – 7.27 (m, 1H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 162.71, 161.55, 160.41, 159.07, 158.74, 144.63, 144.44, 139.74, 134.33, 131.76, 131.58, 131.30, 124.91, 124.40, 124.37, 124.23, 118.48, 114.58, 114.49, 114.32, 112.84, 111.89, 108.69.

^{19}F NMR:(564 MHz, $CDCl_3$) δ -49.36 (s, 2F), -49.27 (s, 2F)

HRMS(ESI): calculated for $C_{12}H_6F_2N_3O_2$ $(M+H)^+$: 262.0428; found: 262.0427.

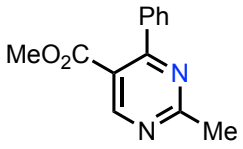


(4-Bromophenyl)(4-(3,4,5-trimethoxyphenyl)pyrimidin-5-yl)methanone (3.5j', major isomer): Synthesized according to general procedure **A** using 20 mg (0.048 mmol) of pyrrole and 2 equiv. of **SNP-3**. The major isomer was obtained as a yellow solid (12 mg, R_f = 0.25 in 20% ethyl acetate/hexane). Only the major isomer was characterized.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.80 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 6.85 (s, 2H), 3.79 (s, 3H), 3.74 (s, 6H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 194.33, 163.08, 159.28, 156.99, 153.38, 140.44, 134.73, 132.14, 131.49, 130.98, 130.71, 129.53, 106.76, 60.89, 56.09.

LRMS(ESI): calculated $C_{20}H_{18}BrN_2O_4$ $(M+H)^+$: 429.04; found= 429.10.



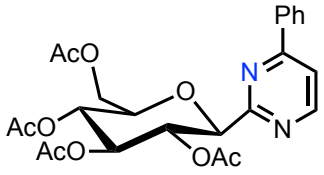
3.5k'
Exclusive product

Methyl 2-methyl-4-phenylpyrimidine-5-carboxylate (3.5k', exclusive product): Synthesized according to general procedure **B** using 20 mg (0.087 mmol) of pyrrole and 2 equiv. of **SNP-2b**. The compound was collected as a white solid (19.5 mg, 92% yield), R_f = 0.30 in 25% ethyl acetate/hexane.

^{1}H NMR 600 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 6.9 Hz, 3H), 3.76 (s, 3H), 2.84 (s, 3H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 169.95, 166.74, 165.94, 158.56, 137.60, 130.10, 128.66, 128.31, 121.30, 52.45, 26.33.

HRMS(ESI) calculated $C_{13}H_{13}N_2O_2$ $(M+H)^+$: 229.0977; found: 229.0987.



3.5l'
exclusive product

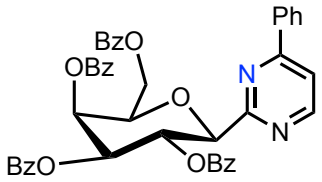
(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(4-phenylpyrimidin-2-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3.5l', exclusive product): Synthesized according to general

procedure **B** using 20 mg (0.042 mmol) of pyrrole and 1.5 equiv. of **SNP-2b**. The product was obtained as a yellowish solid (20.2 mg, 98% yield), R_f = 0.20 in 50% ethyl acetate/hexane.

^{1}H NMR: (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $cdcl_3$) δ 8.82 (d, *J* = 5.3 Hz, 1H), 8.17 – 8.08 (m, 2H), 7.68 (d, *J* = 5.3 Hz, 1H), 7.57 – 7.48 (m, 3H), 5.83 (t, *J* = 9.7 Hz, 1H), 5.43 (t, *J* = 9.4 Hz, 1H), 5.31 (t, *J* = 9.7 Hz, 1H), 4.79 (d, *J* = 9.9 Hz, 1H), 4.33 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.19 (dd, *J* = 12.5, 2.2 Hz, 1H), 3.96 (ddd, *J* = 10.0, 5.0, 2.2 Hz, 1H), 2.08 – 2.03 (m, 9H), 1.77 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 170.96, 170.70, 169.64, 169.33, 164.60, 164.03, 158.3, 136.0, 131.6, 129.2, 127.5, 116.3, 81.3, 76.7, 74.6, 70.9, 68.5, 62.4, 20.96, 20.89, 20.81, 20.66.

LRMS(ESI): calculated for $C_{24}H_{27}N_2O_9$ $(M+H)^+$: 487.1; found: 487.5.



3.5m'
exclusive product

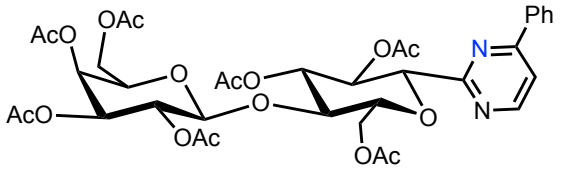
(2*S*,3*R*,4*S*,5*R*,6*R*)-2-((Benzoyloxy)methyl)-6-(4-phenylpyrimidin-2-yl)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (3.5m', exclusive product): Synthesized according to general procedure **B** using 30 mg (0.041 mmol) of pyrrole and 1.5 equiv. of **SNP-2b**. The product was obtained as white solid (29.5 mg, 96% yield), R_f = 0.20 in 40% ethyl acetate/hexane.

^{1}H NMR: (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $cdcl_3$) δ 8.83 (d, *J* = 5.4 Hz, 1H), 8.23 – 8.17 (m, 2H), 8.09 – 8.00 (m, 4H), 7.87 – 7.82 (m, 2H), 7.78 – 7.72 (m, 2H), 7.63 (dd, *J*

= 6.4, 4.7 Hz, 2H), 7.56 – 7.36 (m, 10H), 7.26 – 7.19 (m, 4H), 6.57 (t, *J* = 10.0 Hz, 1H), 6.20 – 6.14 (m, 1H), 5.84 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.15 (d, *J* = 9.8 Hz, 1H), 4.71 (dd, *J* = 11.1, 6.2 Hz, 1H), 4.64 – 4.55 (m, 1H), 4.48 (dd, *J* = 11.1, 6.6 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 166.22, 165.89, 165.74, 165.03, 164.58, 164.55, 136.3, 133.6, 133.33, 133.13, 131.28, 130.31, 129.99, 129.72, 129.61, 129.42, 129.35, 129.13, 129.05, 128.76, 128.55, 128.42, 128.32, 127.5, 116.4, 82.2, 75.6, 73.4, 69.4, 68.8, 62.5.

LRMS(ESI): calculated for $C_{44}H_{45}N_2O_9$ $(M+H)^+$: 735.2; found: 735.8.



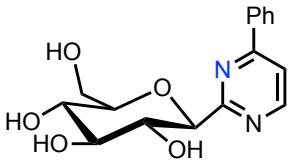
3.5n'
exclusive product

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(Acetoxymethyl)-6-(((2*S*,3*S*,4*R*,5*R*,6*R*)-4,5-diacetoxy-2-(acetoxymethyl)-6-(4-phenylpyrimidin-2-yl)tetrahydro-2*H*-pyran-3-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3.5n', exclusive product): Synthesized according to general procedure **B** using 1.0g (1.31 mmol) of pyrrole and 1.5 equiv. of **SNP-2b**. The product was obtained as brown solid (940 mg, 92% yield), R_f = 0.20 in 70% ethyl acetate/hexane.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 5.3 Hz, 1H), 8.12 (dd, *J* = 6.9, 2.8 Hz, 2H), 7.66 (d, *J* = 5.3 Hz, 1H), 7.51 (dd, *J* = 5.1, 1.8 Hz, 3H), 5.73 (t, *J* = 9.7 Hz, 1H), 5.43 (t, *J* = 9.2 Hz, 1H), 5.39 – 5.35 (m, 1H), 5.19 – 5.09 (m, 2H), 4.97 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 4.57 – 4.47 (m, 2H), 4.20 – 4.08 (m, 4H), 4.03 – 3.95 (m, 1H), 3.89 (q, *J* = 7.4 Hz, 2H), 2.17 (d, *J* = 0.7 Hz, 3H), 2.10 – 2.06 (m, 12H), 1.97 (d, *J* = 0.7 Hz, 3H), 1.77 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 170.67, 170.58, 170.37, 170.26, 170.21, 169.64, 169.36, 164.6, 164.2, 158.2, 136.1, 131.6, 129.2, 127.5, 116.3, 101.3, 81.1, 76.6, 74.4, 71.29, 71.22, 70.9, 69.2, 66.8, 62.8, 61.0, 21.1, 20.84, 20.80, 20.69.

LRMS(ESI): calculated for $C_{36}H_{43}N_2O_{17}$ $(M+H)^+$: 775.3; found: 775.1.



3.5o'
exclusive product

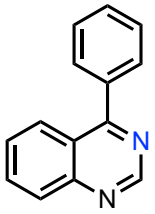
(2*S*,3*R*,4*S*,5*S*,6*R*)-2-(hydroxymethyl)-6-(4-phenylpyrimidin-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol (3.5o', exclusive product): Synthesized according to modified general procedure **B** using 20 mg (0.065 mmol) of pyrrole and 1.5 equiv. of **SNP-2b** in THF:DCM (1:1) as a reaction solvent. The product was obtained as sticky oil (15 mg, 84% yield), R_f = 0.10 in 50% MeOH/CH_2Cl_2.

^{1}H NMR: (400 MHz, CD_3OD) δ 8.84 (d, *J* = 5.4 Hz, 1H), 8.55 (s, 1H), 8.24 – 8.16 (m, 2H), 7.93 (d, *J* = 5.4 Hz, 1H), 7.55 (dd, *J* = 5.2, 2.0 Hz, 3H), 4.51 (d, *J* = 9.6 Hz, 1H), 3.96 – 3.84 (m, 2H), 3.74 (dd, *J* = 12.1, 4.7 Hz, 1H), 3.62 – 3.46 (m, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 168.0, 166.0, 159.1, 137.6, 132.5, 130.1, 129.3, 117.6, 84.2, 82.5, 79.5, 74.7, 71.4, 62.8.

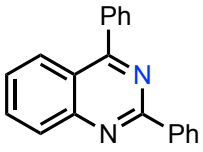
LRMS(ESI): calculated for $C_{16}H_{18}N_2NaO_5$ $(M+Na)^+$: 341.1; found: 341.6.

Quinazolines



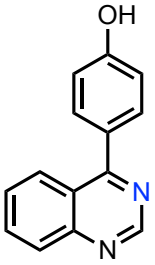
3.7a

4-Phenylquinazoline (3.7a): Synthesized according to general procedure **A** using 20 mg (0.10 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (19.5 mg, 92% yield, R_f = 0.20 in 20% ethyl acetate/hexane). The ^{1}H NMR data matches with the reported literature [59].



3.7b

2,4-Diphenylquinazoline (3.7b): Synthesized according to general procedure **A** using 15 mg (0.055 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (15 mg, 95% yield, R_f = 0.20 in 10% ethyl acetate/hexane). The ^{1}H NMR data matches with the reported literature [60].



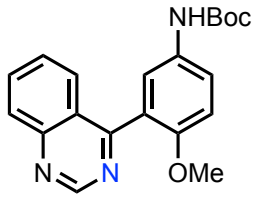
3.7c

4-(Quinazolin-4-yl)phenol (3.7c): Synthesized according to general procedure **A** using 20 mg (0.095 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as orange solid (18 mg, 85% yield), R_f = 0.20 in 40% ethyl acetate/hexane.

^{1}H NMR:(400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.95 (dd, *J* = 8.5, 6.9 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 167.95, 158.44, 153.67, 150.89, 134.18, 132.02, 128.64, 127.99, 127.48, 122.99, 115.98.

HRMS(ESI): calculated for $C_{14}H_{11}N_2(M+H)^+$: 223.0871; found: 223.0870.



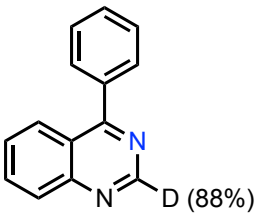
3.7d

***tert*-Butyl (4-methoxy-3-(quinazolin-4-yl)phenyl)carbamate (3.7d):** Synthesized according to general procedure **A** using 25 mg (0.073 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as yellow solid (18 mg, 70% yield), R_f = 0.20 in 40% ethyl acetate/hexane.

^{1}H NMR:(400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.08 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.88 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.54 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 2H), 7.40 (d, *J* = 2.7 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.51 (s, 1H), 3.68 (s, 3H), 1.49 (s, 9H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 167.19, 154.83, 153.15, 153.00, 150.34, 133.83, 131.91, 128.58, 127.77, 127.52, 126.62, 124.39, 121.95, 112.00, 80.65, 55.99, 28.42.

LRMS(ESI): calculated for $C_{20}H_{22}N_3O_3(M+H)^+$: 352.1661; found:352.8.

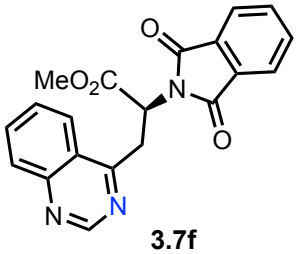


3.7e

4-Phenylquinazoline-2-*d* (3.7e): Synthesized according to general procedure **A** using 20 mg (0.10 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (19.5 mg, 90% yield), R_f = 0.20 in 20% ethyl acetate/hexane.

^{1}H NMR:(400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.47 – 7.42 (m, 3H), 7.31 – 7.27 (m, 1H), 7.24 (d, *J* = 1.2 Hz, 1H), 7.20 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 136.73, 135.67, 128.90, 127.61, 126.11, 125.86, 122.53, 121.91, 120.45, 119.94, 111.54.



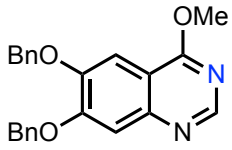
3.7f

Methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(quinazolin-4-yl)propanoate (3.7f): Synthesized according to general procedure **A** using 30 mg (0.086 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (16 mg, 52% yield), R_f = 0.20 in 40% ethyl acetate/hexane).

^{1}H NMR: (600 MHz, $CDCl_3$) δ) δ 9.16 (s, 1H), 8.19 – 8.13 (m, 1H), 8.04 – 7.99 (m, 1H), 7.87 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 – 7.69 (m, 2H), 7.64 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 5.98 (dd, *J* = 9.2, 5.3 Hz, 1H), 4.32 (dd, *J* = 16.4, 5.3 Hz, 1H), 4.22 (dd, *J* = 16.4, 9.2 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR:(150 MHz, $CDCl_3$): δ 169.50, 167.45, 166.41, 154.21, 149.76, 134.17, 133.79, 131.72, 129.13, 127.92, 124.08, 124.00, 123.56, 53.09, 49.94, 32.64.

HRMS(ESI): calculated for $C_{20}H_{16}N_3O_4$ $(M+H)^+$: 362.1141; found: 362.1143



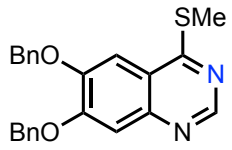
3.7g

6,7-Bis(benzyloxy)-4-methoxyquinazoline (3.7g): Synthesized according to general procedure **A** using 50 mg (0.13 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (35 mg, 67% yield), R_f = 0.20 in 30% ethyl acetate/hexane.

^{1}H NMR:(400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 7.54 – 7.47 (m, 5H), 7.39 (q, *J* = 7.6 Hz, 4H), 7.36 – 7.29 (m, 3H), 5.30 (d, *J* = 22.0 Hz, 4H), 4.14 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 165.65, 154.84, 153.08, 149.15, 148.25, 136.37, 136.02, 128.63, 128.58, 128.07, 128.02, 127.23, 127.13, 110.87, 108.65, 103.72, 70.92, 70.65, 54.03.

HRMS(ESI): calculated for $C_{23}H_{21}N_2O_3$ $(M+H)^+$: 373.1551; found: 373.1553.



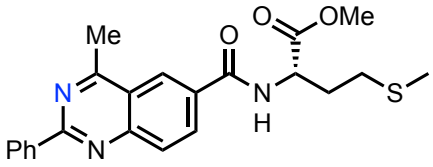
3.7h

6,7-bis(Benzyloxy)-4-(methylthio)quinazoline (3.7h): Synthesized according to general procedure **A** using 50 mg (0.13 mmol) of indole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (28 mg, 54% yield, R_f = 0.20 in 30% ethyl acetate/hexane).

^{1}H NMR:(400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.51 (dd, *J* = 11.2, 7.5 Hz, 4H), 7.44 – 7.30 (m, 8H), 5.31 (d, *J* = 9.3 Hz, 4H), 2.70 (s, 3H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 136.00, 135.75, 128.69, 128.67, 128.20, 128.16, 127.37, 127.21, 125.21, 121.69, 119.09, 104.15,71.09, 70.81, 12.59.

LRMS(ESI): calculated for $C_{23}H_{21}N_2O_2S$ $(M+H)^+$:389.1324 ; found:389.1.



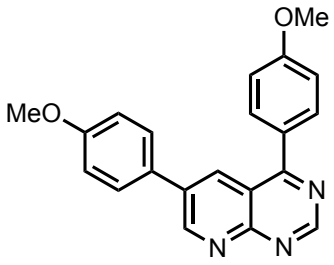
3.7i

Methyl (4-methyl-2-phenylquinazoline-6-carbonyl)-*L*-methioninate (3.7i): Synthesized according to general procedure **A** using 20 mg (0.05 mmol) of indole and 2 equiv. of **SNP-3.** The product was obtained as a yellow solid (19 mg, 92% yield), R_f 0.20 in 60% EtOAc/Hexane.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.64 (dt, *J* = 5.0, 2.5 Hz, 3H), 8.21 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.54 (dtd, *J* = 6.5, 4.6, 2.8 Hz, 3H), 7.22 (s, 1H), 5.01 (td, *J* = 7.2, 5.0 Hz, 1H), 3.84 (s, 3H), 3.07 (s, 3H), 2.66 (t, *J* = 7.1 Hz, 2H), 2.36 (dtd, *J* = 14.6, 7.3, 5.0 Hz, 1H), 2.22 (dt, *J* = 14.3, 7.0 Hz, 1H), 2.16 (s, 3H).

^{13}C NMR:(100 MHz, $CDCl_3$) δ 172.64, 169.85, 166.15, 161.66, 152.02, 137.81, 131.68, 131.12, 130.96, 129.95, 128.93, 128.79, 128.29, 125.68, 122.56, 52.98, 52.60, 31.36, 30.34, 22.34, 15.75.

LRMS(ESI): calculated for $C_{22}H_{24}N_3O_3S(M+H)^+$: 410.5120; found: 410.8.



3.7j

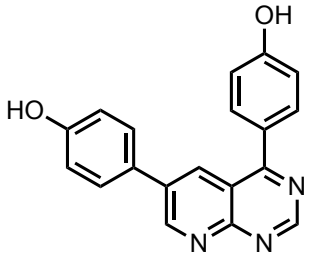
4,6-Bis(4-methoxyphenyl)pyrido[2,3-*d*]pyrimidine (3.7j): Synthesized according to general procedure **A** using 20 mg (0.06 mmol) of indole and 2 equiv. of **SNP-3.** The

product was obtained as yellowish solid (20 mg, 96% yield, R_f = 0.15 in 60% ethyl acetate/hexane).

^{1}H NMR:(400 MHz, $CDCl_3$) δ 9.55 – 9.47 (m, 2H), 8.58 (d, *J* = 2.6 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.64 – 7.56 (m, 2H), 7.18 – 7.10 (m, 2H), 7.08 – 7.01 (m, 2H), 3.93 (s, 3H), 3.88 (s, 3H).

^{13}C NMR:(100 MHz, $CDCl_3$) δ 169.67, 161.97, 160.54, 158.14, 157.39, 156.95, 135.85, 132.33, 132.00, 128.87, 128.85, 128.78, 117.83, 115.08, 114.65, 55.68, 55.61.

LRMS(ESI): calculated for $C_{21}H_{18}N_3O_2(M+H)^+$: 344.1; found: 344.4.



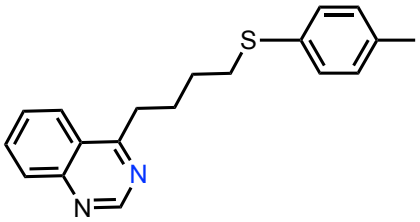
3.7k

4,4'-(Pyrido[2,3-*d*]pyrimidine-4,6-diyl)diphenolpyrimidine (3.7k): Synthesized according to general procedure **A** using 30 mg (0.066 mmol) of indole and 2 equiv. of **SNP-3** using n-Butanol/PhCl (1:2) as a solvent. The product was obtained as yellowish solid (19.5 mg, 62% yield), R_f = 0.20 in 20% MeOH/CH_2Cl_2.

^{1}H NMR:(400 MHz, CD_3OD) δ 9.45 (d, *J* = 2.6 Hz, 1H), 9.24 (s, 1H), 8.69 (d, *J* = 2.6 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.62 – 7.56 (m, 2H), 6.93 (ddd, *J* = 9.0, 5.5, 2.7 Hz, 4H).

^{13}C NMR:(100 MHz, CD_3OD) δ 171.94, 161.20, 158.49, 157.56, 157.39, 137.76, 133.81, 133.60, 129.69, 127.75, 125.79, 125.41, 119.06, 118.71, 117.87.

LRMS(ESI): calculated for $C_{19}H_{14}N_3O_2(M+H)^+$: 316.1; found: 316.2.



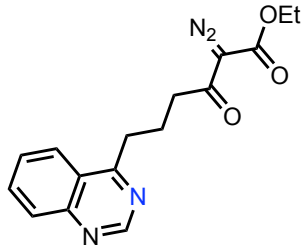
3.7l

4-(4-(*p*-Tolylthio)butyl)quinazoline (3.7l): Synthesized according to general procedure **B** using 20 mg (0.071 mmol) of indole and 1.5 equiv. of **SNP-2b**. The product was obtained as yellowish solid (15 mg, 72% yield), R_f = 0.30 in 40% ethyl acetate/hexane.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 3.33 – 3.27 (m, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 2.05 (p, *J* = 7.6 Hz, 2H), 1.79 (p, *J* = 7.4 Hz, 2H).

^{13}C NMR:(150 MHz, $CDCl_3$): δ 154.2, 136.4, 134.0, 132.9, 130.5, 129.8, 129.3, 128.0, 124.8, 124.1, 34.5, 34.0, 29.3, 27.8, 21.1.

LRMS(ESI): calculated for $C_{19}H_{21}N_2S$ $(M+H)^+$:309.1; found:309.8.



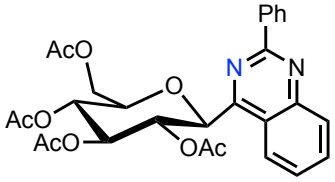
3.7m

Ethyl 2-diazo-3-oxo-6-(quinazolin-4-yl)hexanoate (3.7m): Synthesized according to general procedure **B** using 20 mg (0.066 mmol) of indole and 1.5 equiv. of **SNP-2b**. The product was obtained as yellowish solid (16 mg, 76% yield), R_f = 0.20 in 50% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 4.33 (d, *J* = 6.5 Hz, 2H), 3.36 (t, *J* = 7.6 Hz, 2H), 2.03 (p, *J* = 7.5 Hz, 2H), 1.88 (dt, *J* = 13.9, 6.6 Hz, 2H), 1.29 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR:(125 MHz, $CDCl_3$) δ 161.4, 161.1, 154.6, 134.2, 132.4, 130.0, 129.3, 127.4, 126.5, 124.8, 61.8, 33.8, 28.7, 24.9, 14.5.

LRMS(ESI): calculated for $C_{16}H_{17}N_4O_3$ $(M+H)^+$: 313.1; found: 313.2.



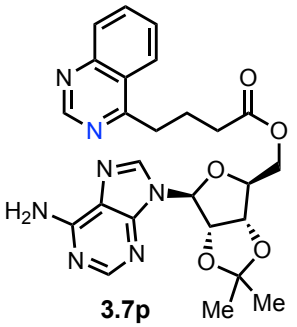
3.7o

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(Acetoxymethyl)-6-(2-phenylquinazolin-4-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3.7o): Synthesized according to general procedure **B** using 15 mg (0.028 mmol) of indole and 1.5 equiv. of **SNP-2b**. The product was obtained as yellowish solid (12.8 mg, 83% yield, R_f = 0.30 in in 50% ethyl acetate/hexane).

^{1}H NMR:(400 MHz, $CDCl_3$) δ 8.71 – 8.63 (m, 2H), 8.20 (t, *J* = 8.4 Hz, 2H), 7.92 (t, *J* = 7.7 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.52 (t, *J* = 7.6 Hz, 3H), 6.16 (t, *J* = 9.6 Hz, 1H), 5.53 (t, *J* = 9.4 Hz, 1H), 5.34 (t, *J* = 9.9 Hz, 2H), 4.30 (dd, *J* = 12.4, 5.5 Hz, 1H), 4.24 – 4.17 (m, 1H), 4.15 – 4.07 (m, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.73 (s, 3H).

^{13}C NMR:(125 MHz, $CDCl_3$) δ 170.8, 170.7, 169.6, 169.4, 134.2, 131.1, 129.6, 129.2, 128.9, 128.8, 127.6, 124.6, 123.4, 123.1, 122.4, 120.7, 77.8, 74.9, 69.7, 68.4, 62.5, 20.9, 20.8, 20.7.

LRMS(ESI): calculated for $C_{28}H_{29}N_2O_9(M+H)^+$:537.2; found:537.4.



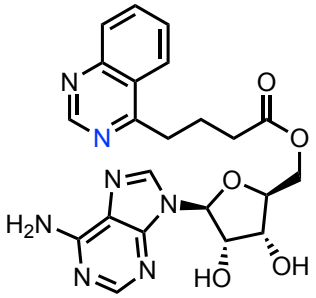
3.7p

((3a*S*,4*S*,6*S*,6a*S*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl 4-(quinazolin-4-yl)butanoate (3.7p): Synthesized according to general procedure **A** using 25 mg (0.050 mmol) of indole and 1.5 equiv. of **SNP-2b**. The product was obtained as yellowish solid (18.5 mg, 72% yield, R_f = 0.15 in 5% MeOH/DCM).

^{1}H NMR:(600 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.34 (s, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.63 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 6.10 (d, *J* = 2.0 Hz, 1H), 5.84 (s, 2H), 5.48 (dd, *J* = 6.3, 2.0 Hz, 1H), 5.07 (dd, *J* = 6.3, 3.5 Hz, 1H), 4.49 (dt, *J* = 6.1, 4.0 Hz, 1H), 4.39 (dd, *J* = 11.9, 4.4 Hz, 1H), 4.26 (dd, *J* = 11.9, 6.2 Hz, 1H), 3.30 (td, *J* = 7.2, 1.3 Hz, 2H), 2.51 – 2.37 (m, 2H), 2.19 (p, *J* = 7.3 Hz, 2H), 1.61 (s, 3H), 1.39 (s, 3H).

^{13}C NMR:(100 MHz, $CDCl_3$) δ 172.8, 170.4, 155.4, 154.7, 152.8, 150.1, 149.4, 140.0, 133.8, 129.4, 127.8, 124.7, 124.1, 120.5, 114.8, 91.2, 85.2, 84.4, 81.8, 64.2, 33.5, 33.4, 27.3, 25.5, 23.4.

LRMS(ESI): calculated for $C_{25}H_{28}N_7O_5(M+H)^+$:506.2 ; found: 506.9.



3.7q

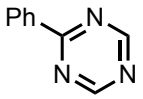
((2*S*,3*R*,4*S*,5*S*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl 4-(quinazolin-4-yl)butanoate (3.7q): Synthesized according to general procedure **A** using 25 mg (0.055 mmol) of indole and 1.5 equiv. of **SNP-2b**. The product was obtained as yellowish solid (16.8 mg, 67% yield, R_f = 0.15 in 15% MeOH/DCM).

^{1}H NMR:(500 MHz, CD_3OD) δ 9.09 (s, 1H), 8.32 – 8.22 (m, 3H), 8.17 (s, 1H), 7.96 (dd, *J* = 6.9, 1.7 Hz, 2H), 7.69 (ddd, *J* = 8.3, 6.1, 2.0 Hz, 1H), 6.01 (d, *J* = 4.4 Hz, 1H), 4.75 (t, *J* = 4.8 Hz, 1H), 4.46 – 4.37 (m, 3H), 4.27 (q, *J* = 4.6 Hz, 1H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.17 (p, *J* = 7.2 Hz, 2H).

^{13}C NMR:(125 MHz, CD_3OD) δ 174.5, 173.0, 157.3, 155.0, 153.9, 150.6, 150.5, 141.2, 135.6, 129.4, 129.1, 126.3, 125.1, 124.4, 120.5, 90.4, 83.4, 75.1, 71.8, 64.8, 34.2, 24.7.

LRMS(ESI): calculated for $C_{22}H_{24}N_7O_5(M+H)^+$:466.2; found: 466.5.

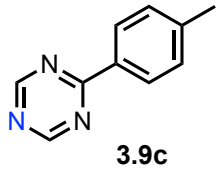
Triazines



3.9a

2-Phenyl-1,3,5-triazine (3.9a): Synthesized according to general procedure **A** using 20 mg (0.12 mmol) of imidazole and 2 equiv. of **SNP-3**. The product was obtained as

yellowish solid (17 mg, 78% yield, R_f = 0.20 in 5% ethyl acetate/hexane). The ^{1}H NMR data matches with the reported literature. [61]



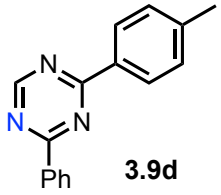
3.9c

2-(*p*-Tolyl)-1,3,5-triazine (3.9c): Synthesized according to general procedure **A** using 20 mg (0.12 mmol) of imidazole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (13.5 mg, 62% yield, R_f = 0.20 in 5% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.18 (s, 2H), 8.45 – 8.37 (m, 2H), 7.37 – 7.30 (m, 2H), 2.45 (s, 3H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 171.18, 166.20, 143.95, 132.21, 129.64, 128.91,21.69.

HRMS(ESI): calculated for $C_{10}H_{10}N_3$ $(M+H)^+$: 172.0875; found: 172.0870.



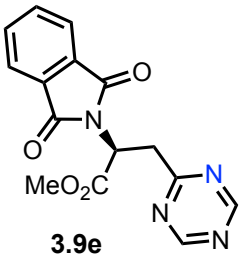
3.9d

2-Phenyl-4-(*p*-tolyl)-1,3,5-triazine(3.9d): Synthesized according to general procedure **A** using 20 mg (0.085 mmol) of imidazole and 2 equiv. of **SNP-3**. The product was obtained as yellowish solid (15 mg, 72% yield, R_f = 0.25 in 5% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.68 – 8.59 (m, 2H), 8.57 – 8.49 (m, 2H), 7.64 – 7.48 (m, 3H), 7.38 – 7.31 (m, 2H), 2.47 (s, 3H).

^{13}C NMR:(150 MHz, $CDCl_3$) δ 171.48, 171.38, 166.80, 143.69, 135.84, 132.86, 129.69, 129.06, 129.02, 128.87, 21.88.

HRMS(ESI): calculated for $C_{16}H_{14}N_3$ $(M+H)^+$: 248.1188; found: 248.1184.



3.9e

Methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(1,3,5-triazin-2-yl)propanoate (3.9e): To a sealed capped vial were added a solution of imidazole (1.0 g) in chlorobenzene (5.0 mL) and a solution of sulfenylnitrene precursor (2.0 equivalent in 10 mL of PhCl) portion-wise (1mL/15mins) at 120 °C. The reaction progress was monitored by TLC. After completion, all the volatiles were removed, and the crude was purified using silica gel column chromatography. The product was obtained as reddish solid (0.845 g, 80% yield), R_f = 0.25 in 40% ethyl acetate/hexane.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 1.1 Hz, 2H), 7.88 – 7.82 (m, 2H), 7.78 – 7.71 (m, 2H), 5.71 (dd, *J* = 8.9, 5.9 Hz, 1H), 3.97 (ddd, *J* = 16.1, 5.9, 1.1 Hz, 1H), 3.75 (d, *J* = 1.1 Hz, 3H), 3.72 (ddd, *J* = 16.1, 9.0, 1.1 Hz, 1H).

^{13}C NMR: (150 MHz, $CDCl_3$) δ 175.59, 168.89, 167.26, 165.92, 134.30, 131.70, 123.68, 53.14, 49.54, 37.91.

HRMS(ESI): calculated for $C_{15}H_{12}N_2NaO_4(M+Na)^+$: 335.0750; found: 335.0756.

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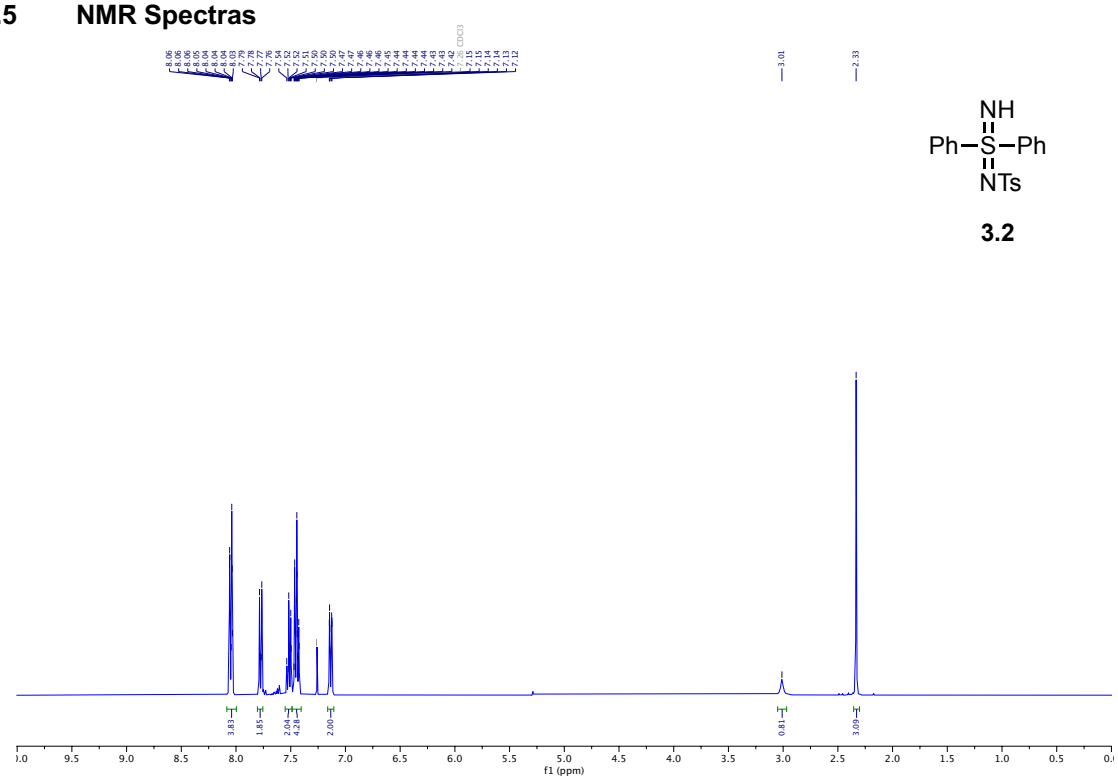
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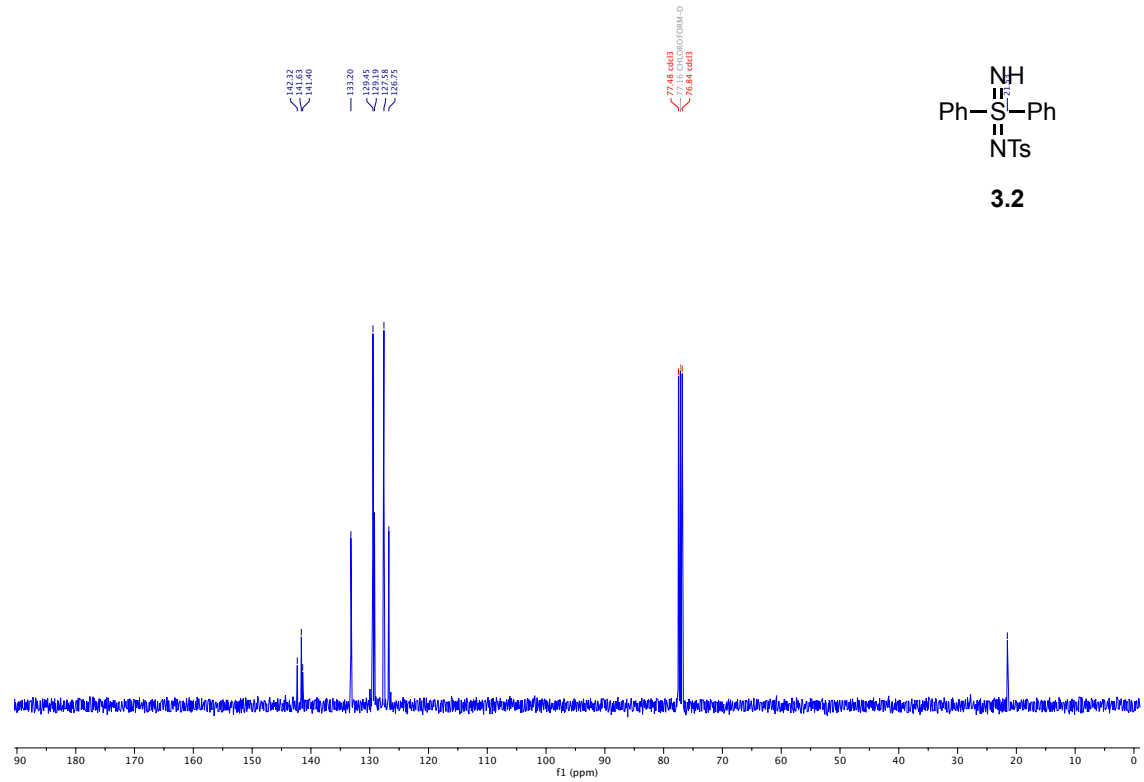
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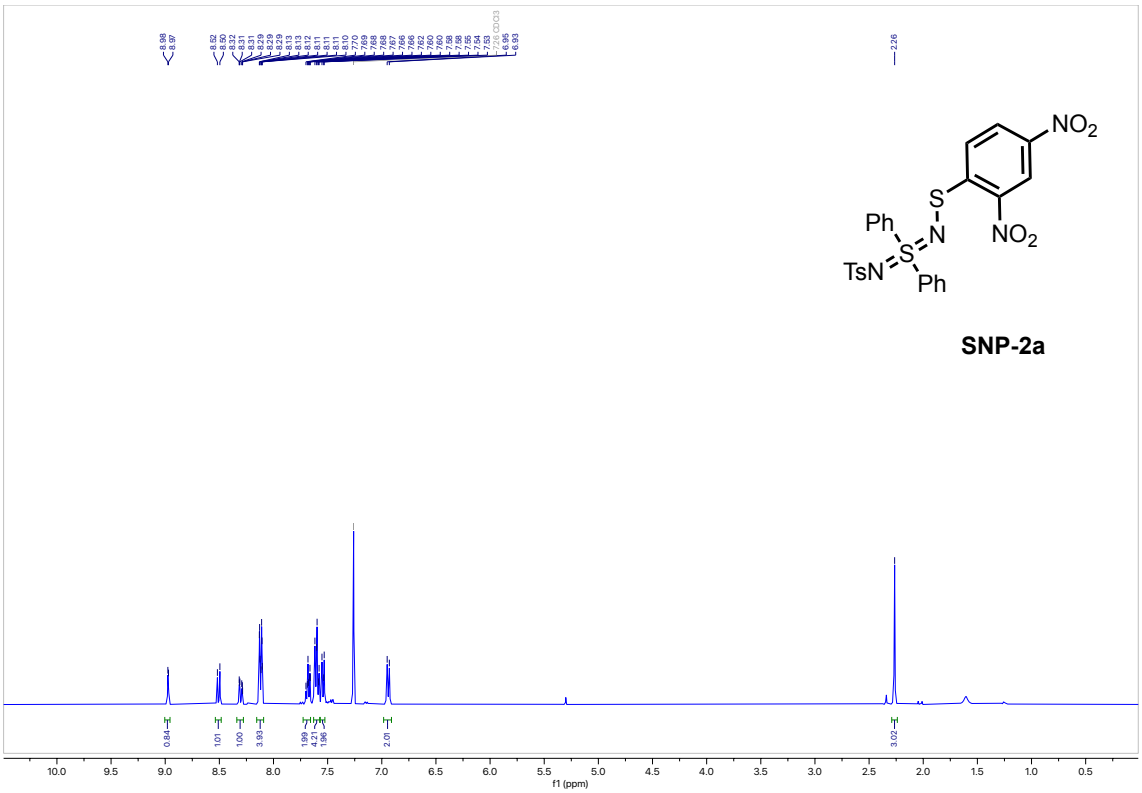
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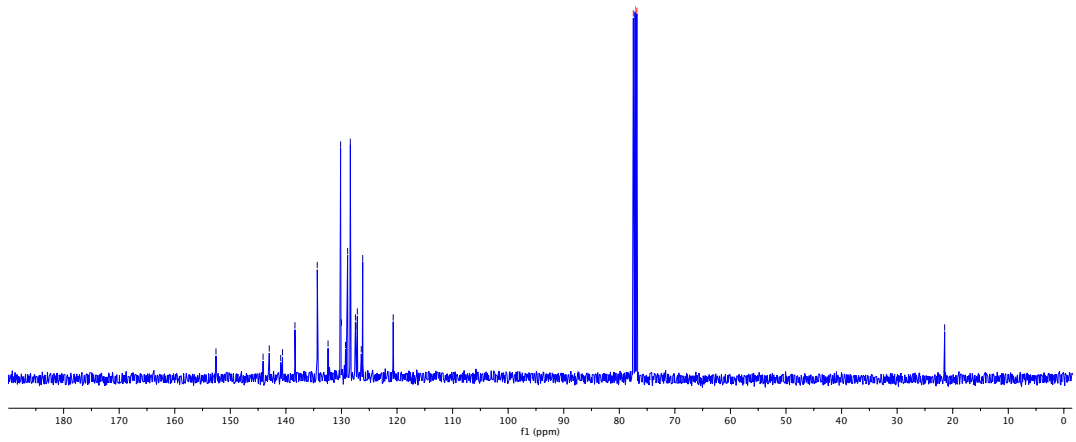
3.5 NMR Spectras

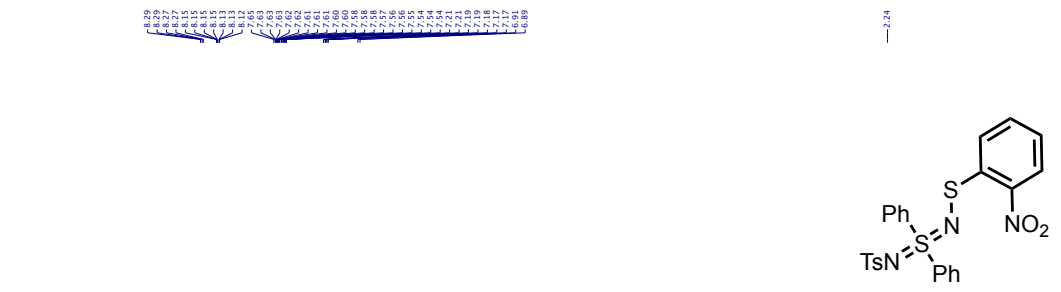





NO2
S
N
NO2
Ph
S
TsN
Ph
SNP-2a
f1 (ppm)

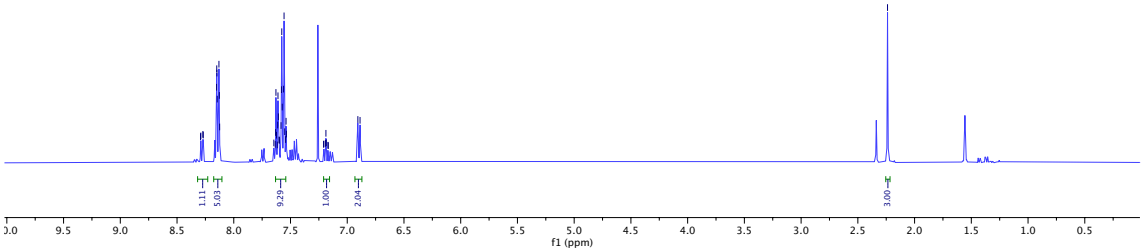

NO2
S
N
NO2
Ph
S
TsN
Ph
SNP-2a


f1 (ppm)

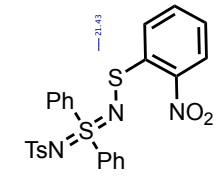


S
N
Ph
S
NO2
TsN
Ph

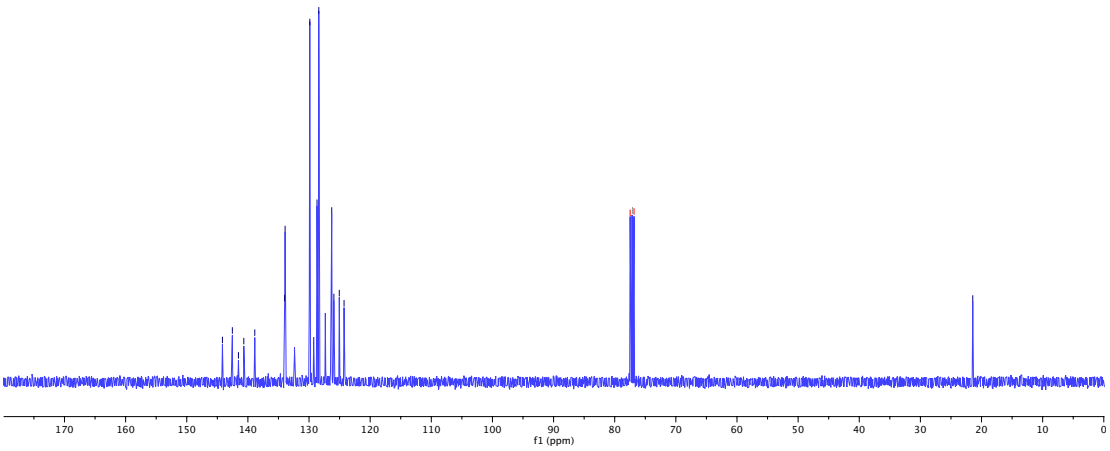
SNP-2b

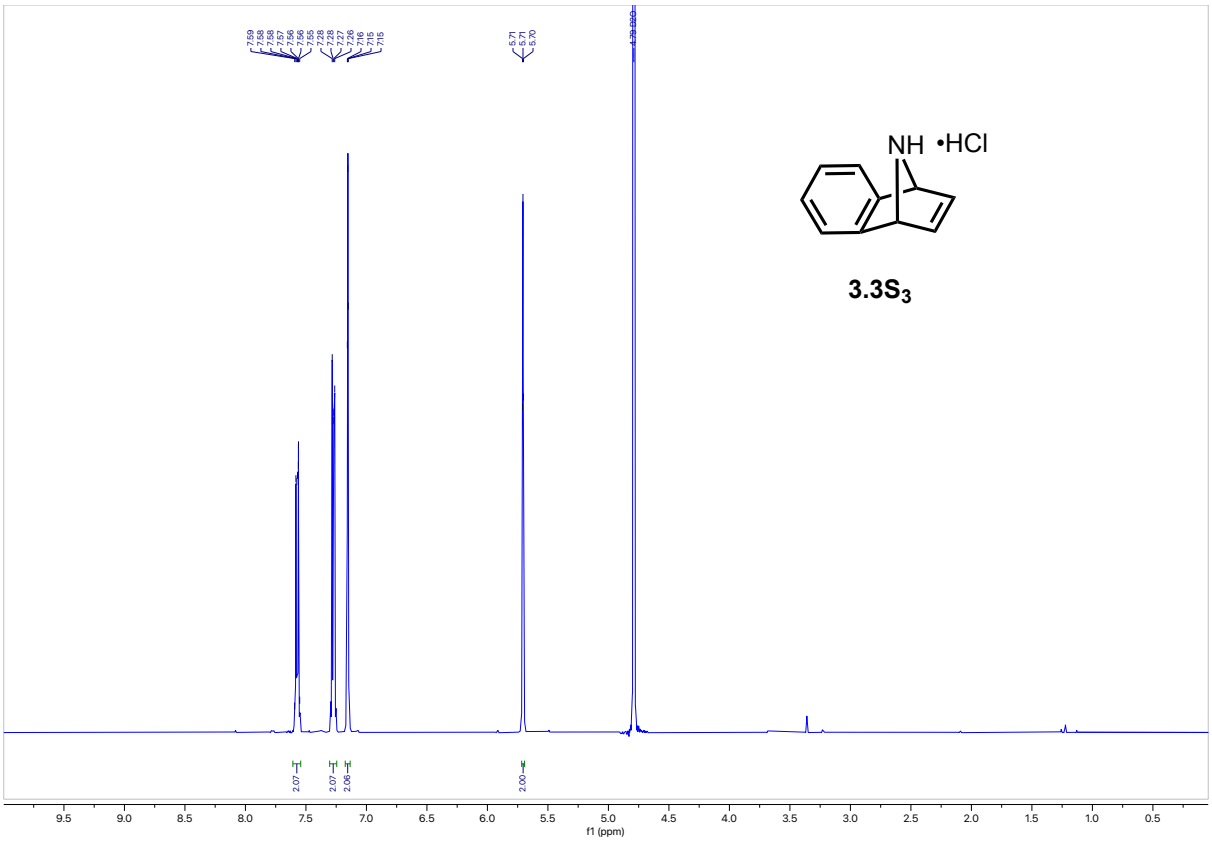

1.11
5.03
9.29
1.00
2.04
3.00
f1 (ppm)

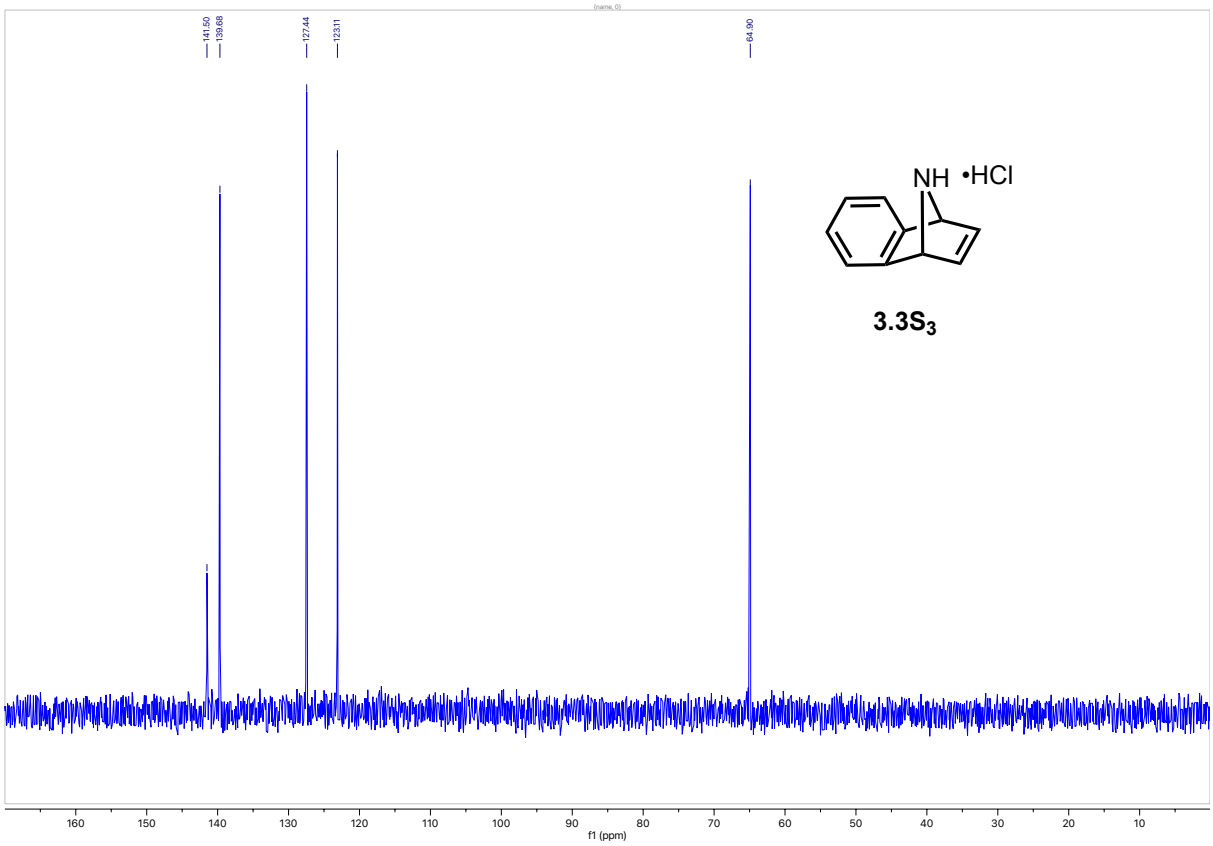

144.16
143.54
141.55
140.67
138.87
133.99
133.91
130.37
128.69
128.40
126.39
125.93
125.05
124.27
77.48 cdcl3
77.16 CHLOROFORM-D
76.84 cdcl3
21.43

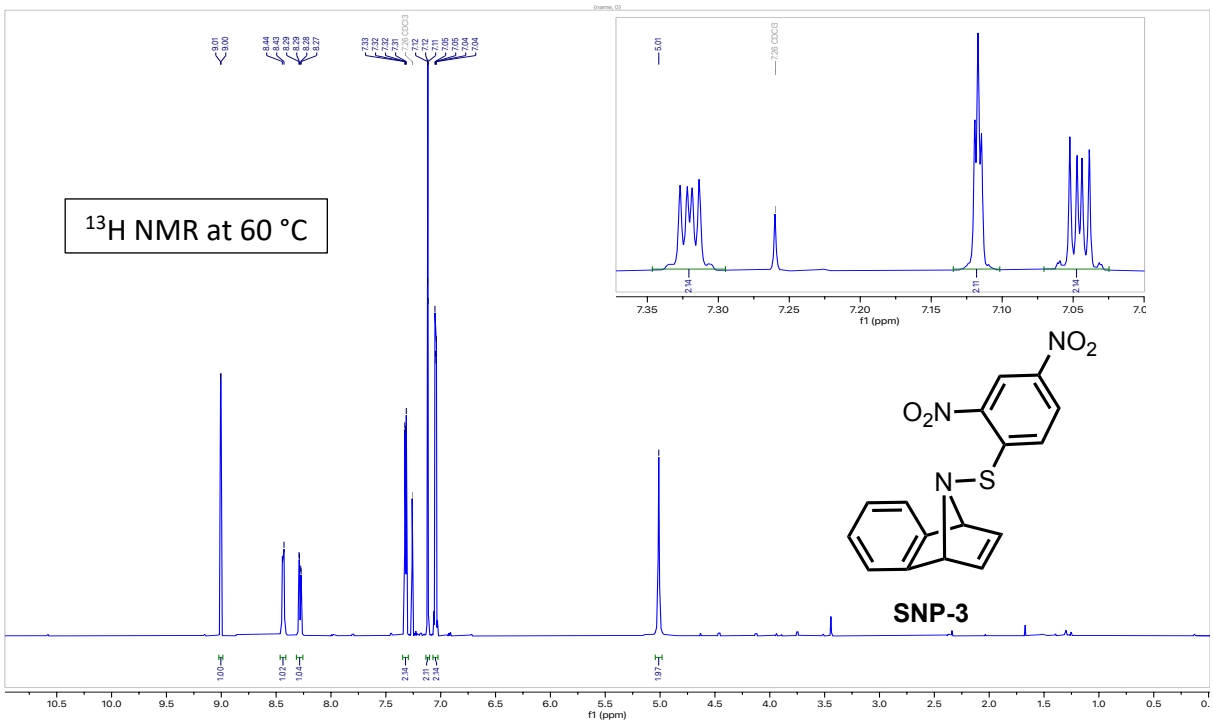

S
N
Ph
S
NO2
TsN
Ph

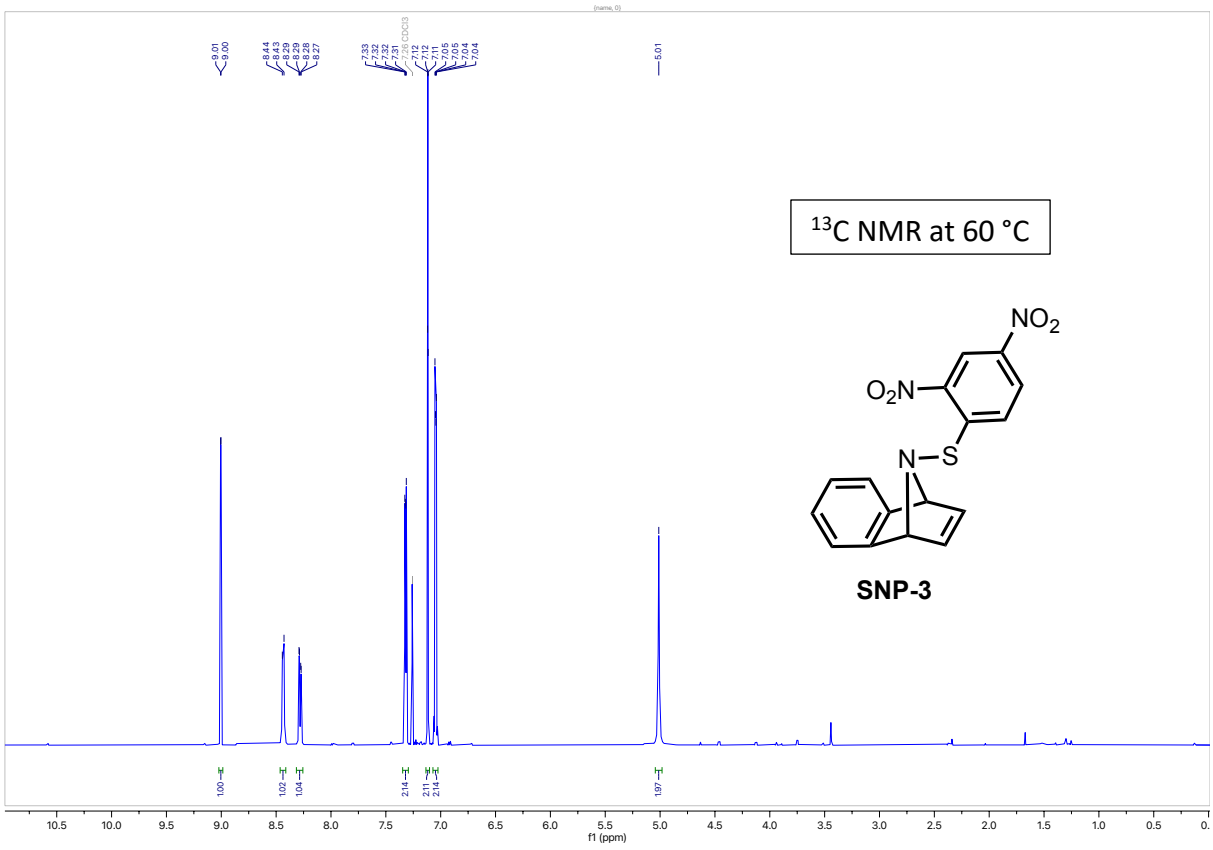
SNP-2b

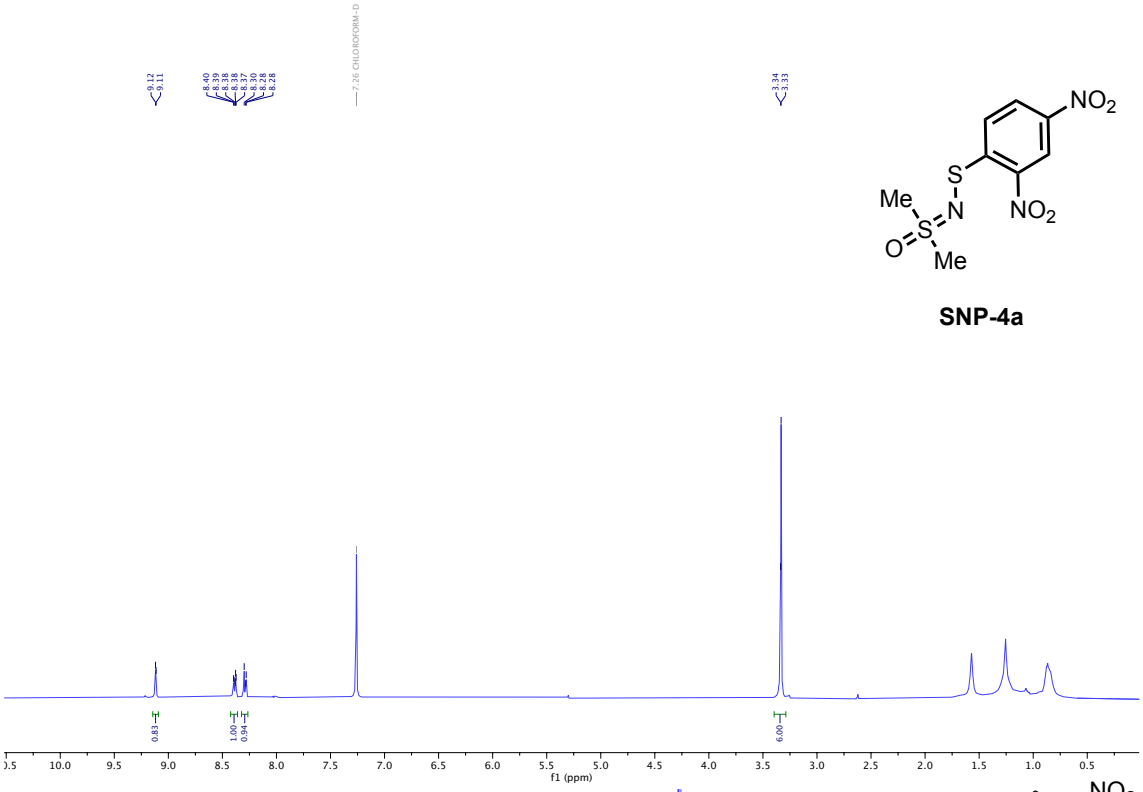

f1 (ppm)


NH •HCl
3.3S3
f1 (ppm)


NH •HCl
3.3S3
f1 (ppm)

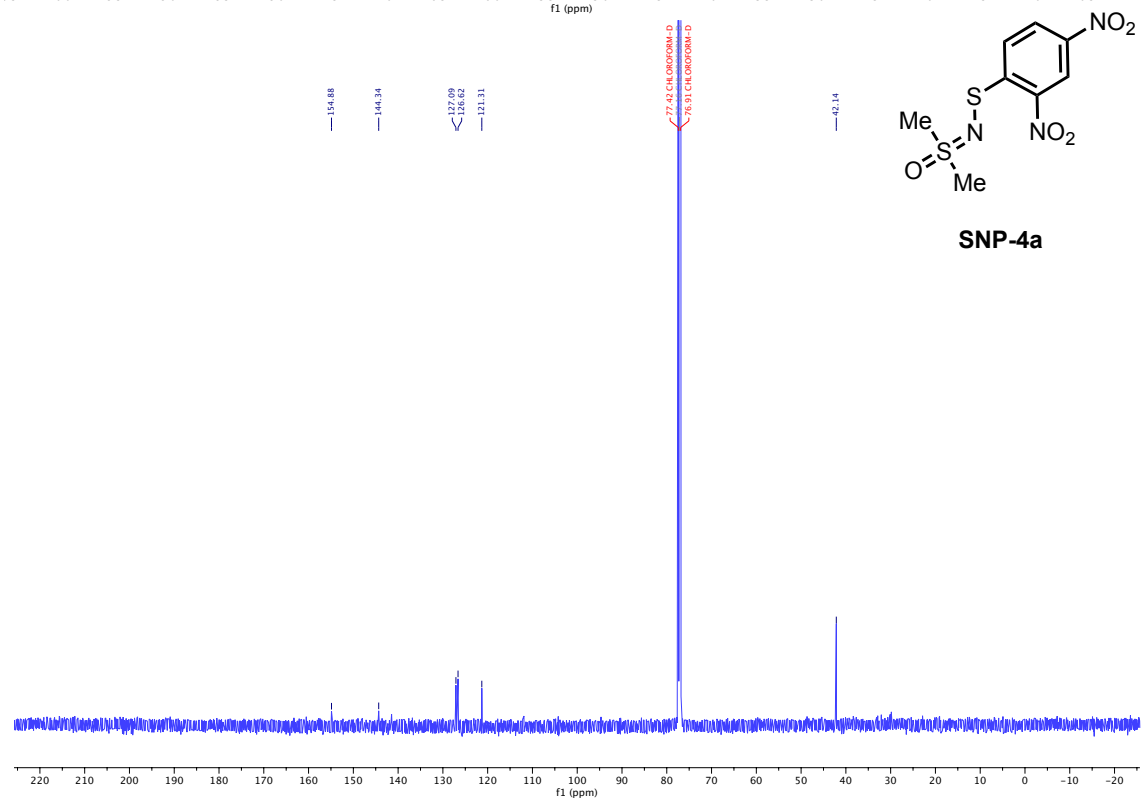

^{13}H NMR at 60 °C
NO_2
O_2N
N–S
SNP-3
f1 (ppm)


^{13}C NMR at 60 °C
NO_2
O_2N
N–S
SNP-3
f1 (ppm)


9.12
9.11
8.40
8.39
8.38
8.38
8.37
8.30
8.29
8.28
7.26 CHLOROFORM-D
3.34
3.33
0.83
1.00
0.94
6.00
f1 (ppm)

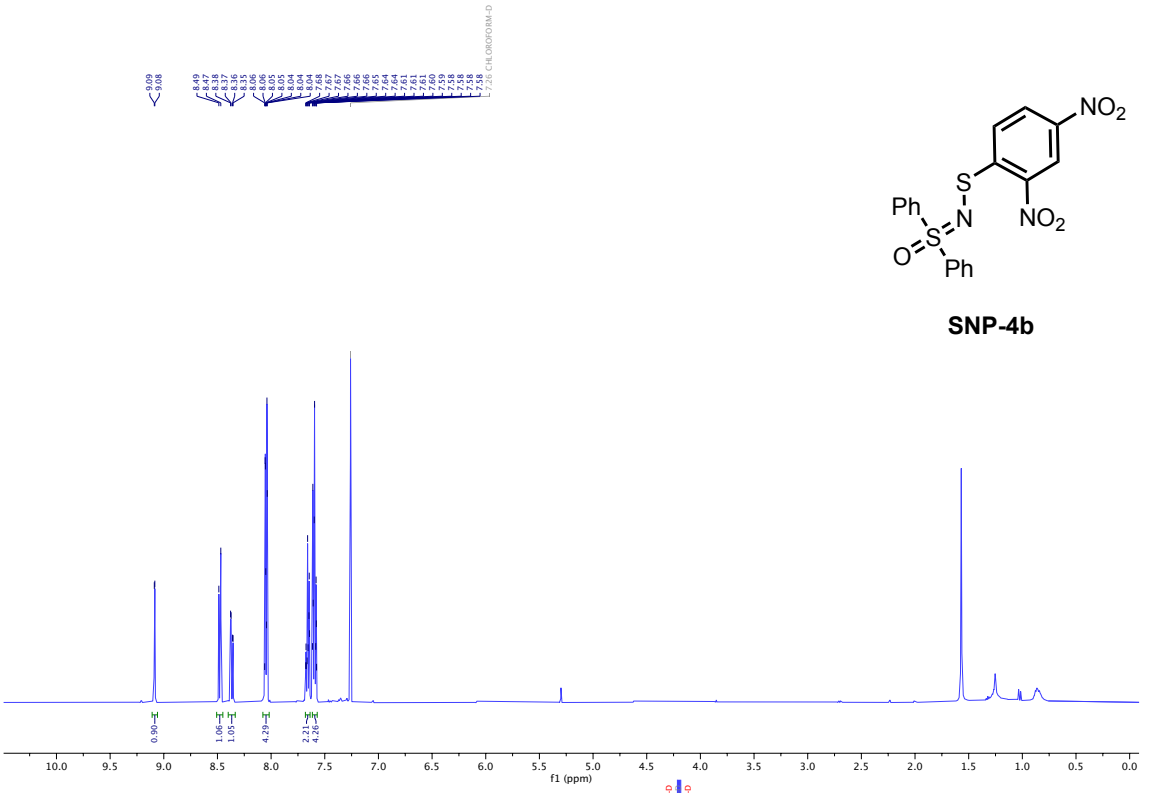
NO2
S
N
Me
O
S
Me
NO2

SNP-4a

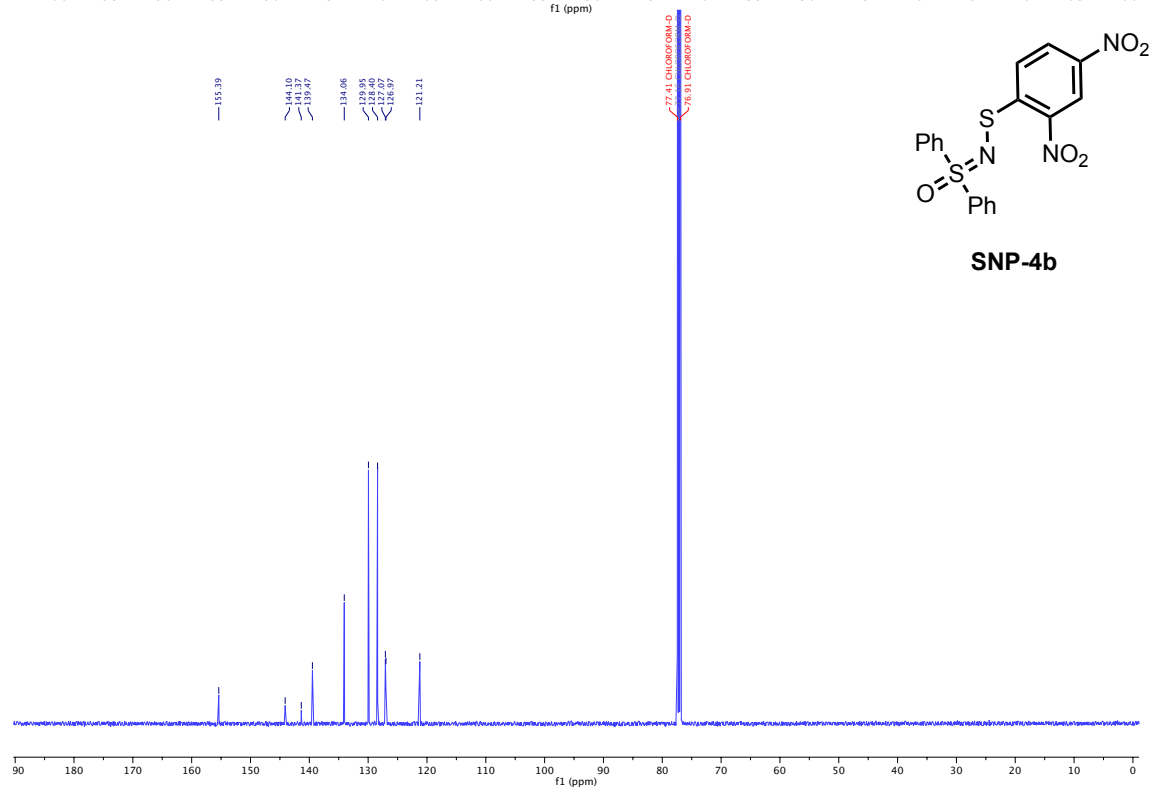

154.88
144.34
127.09
126.62
121.31
77.42 CHLOROFORM-D
77.16 CHLOROFORM-D
76.91 CHLOROFORM-D
42.14
f1 (ppm)

NO2
S
N
Me
O
S
Me
NO2

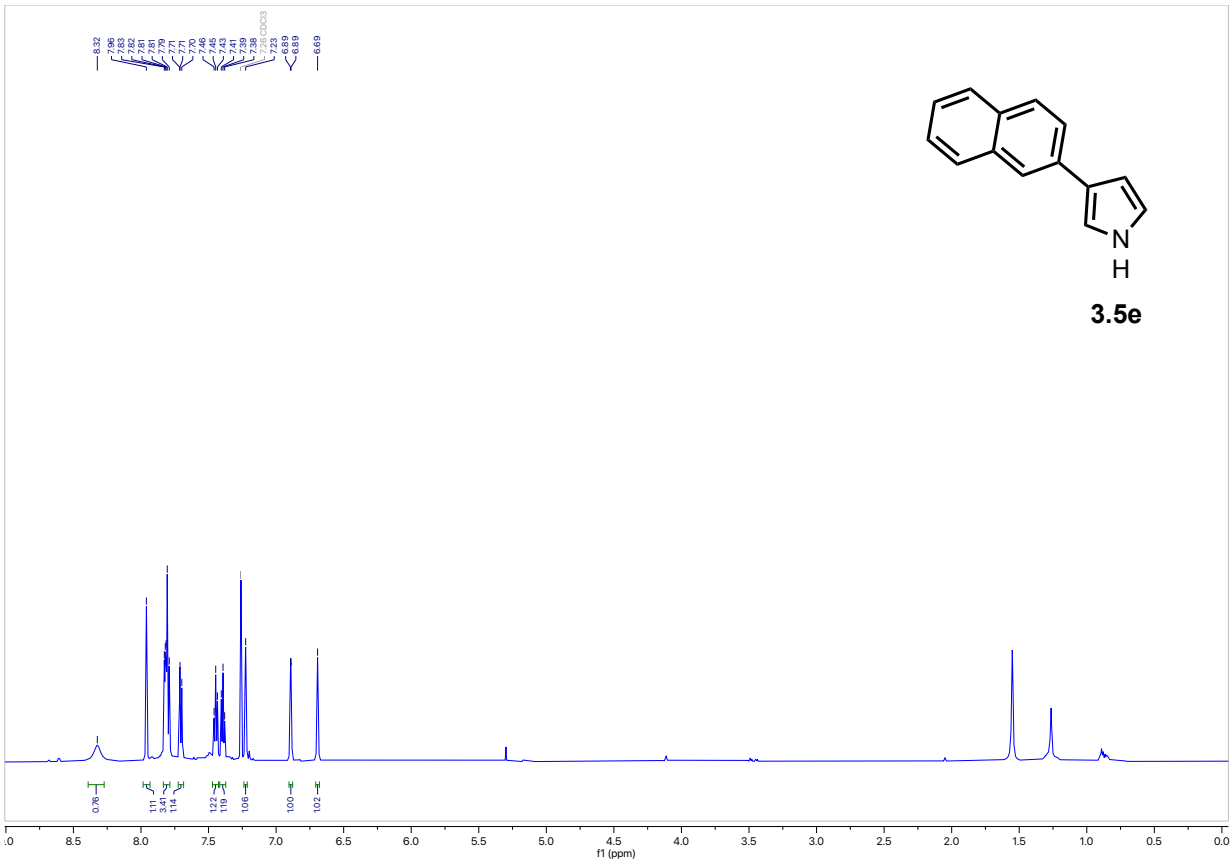
SNP-4a

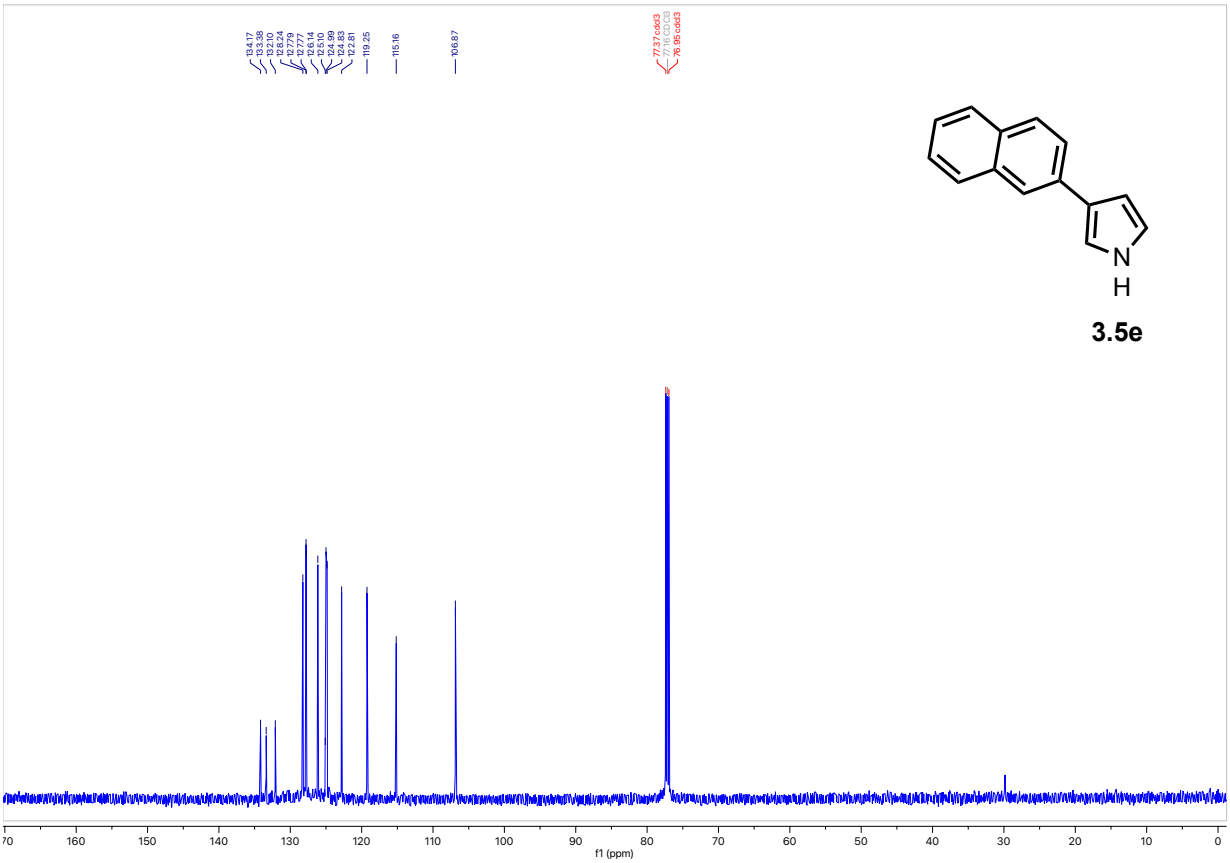


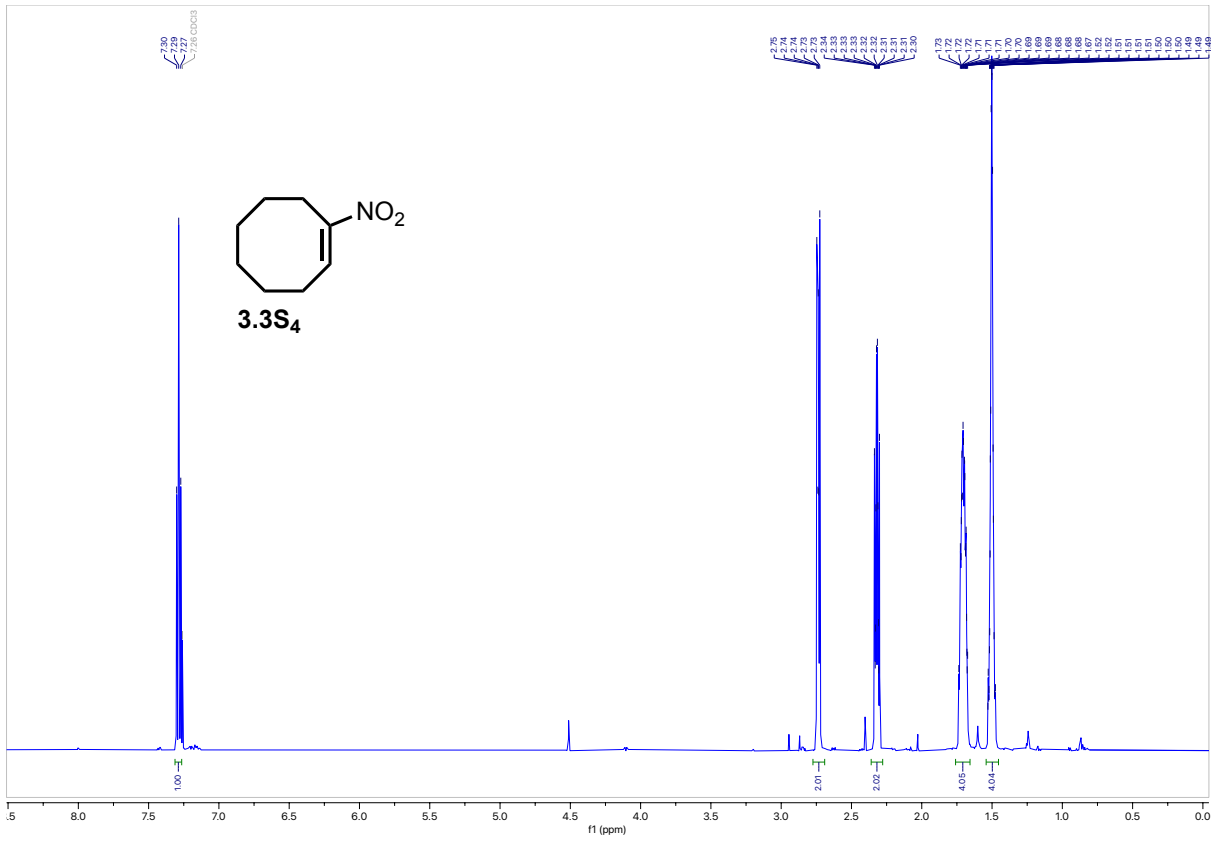
SNP-4b

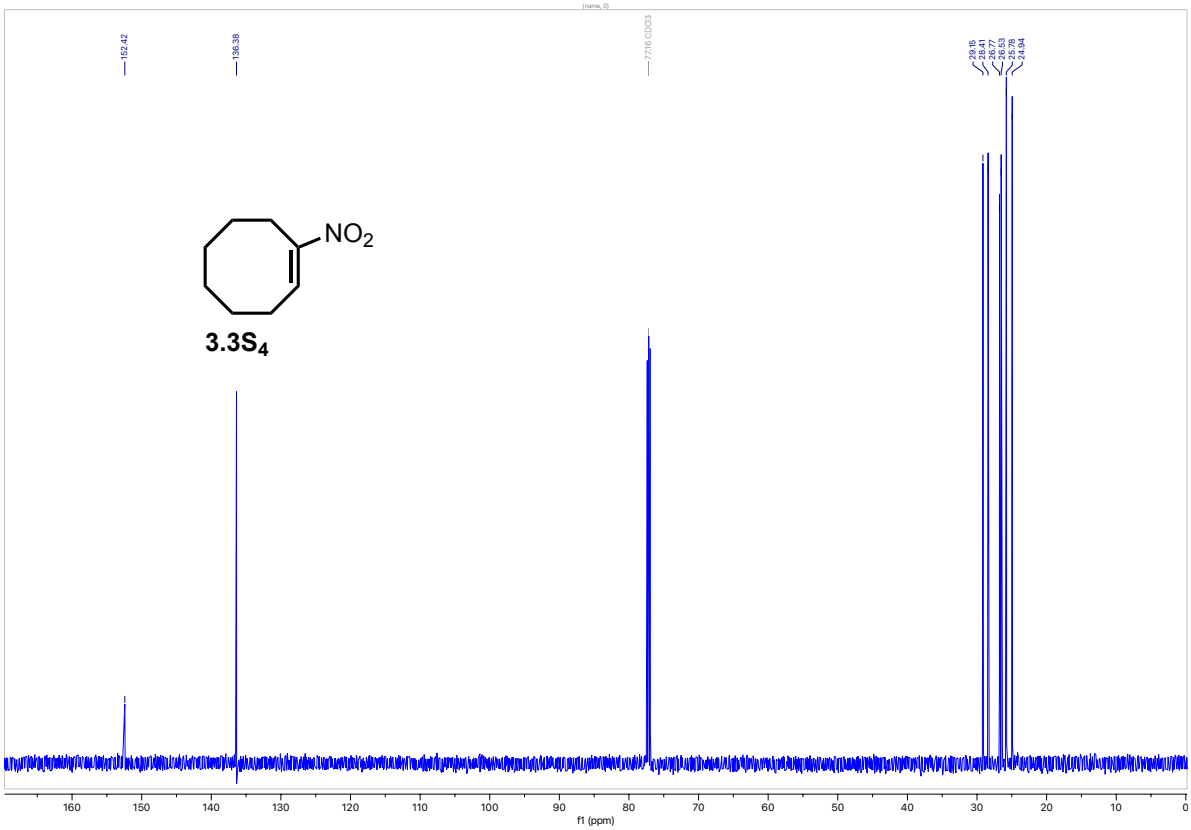


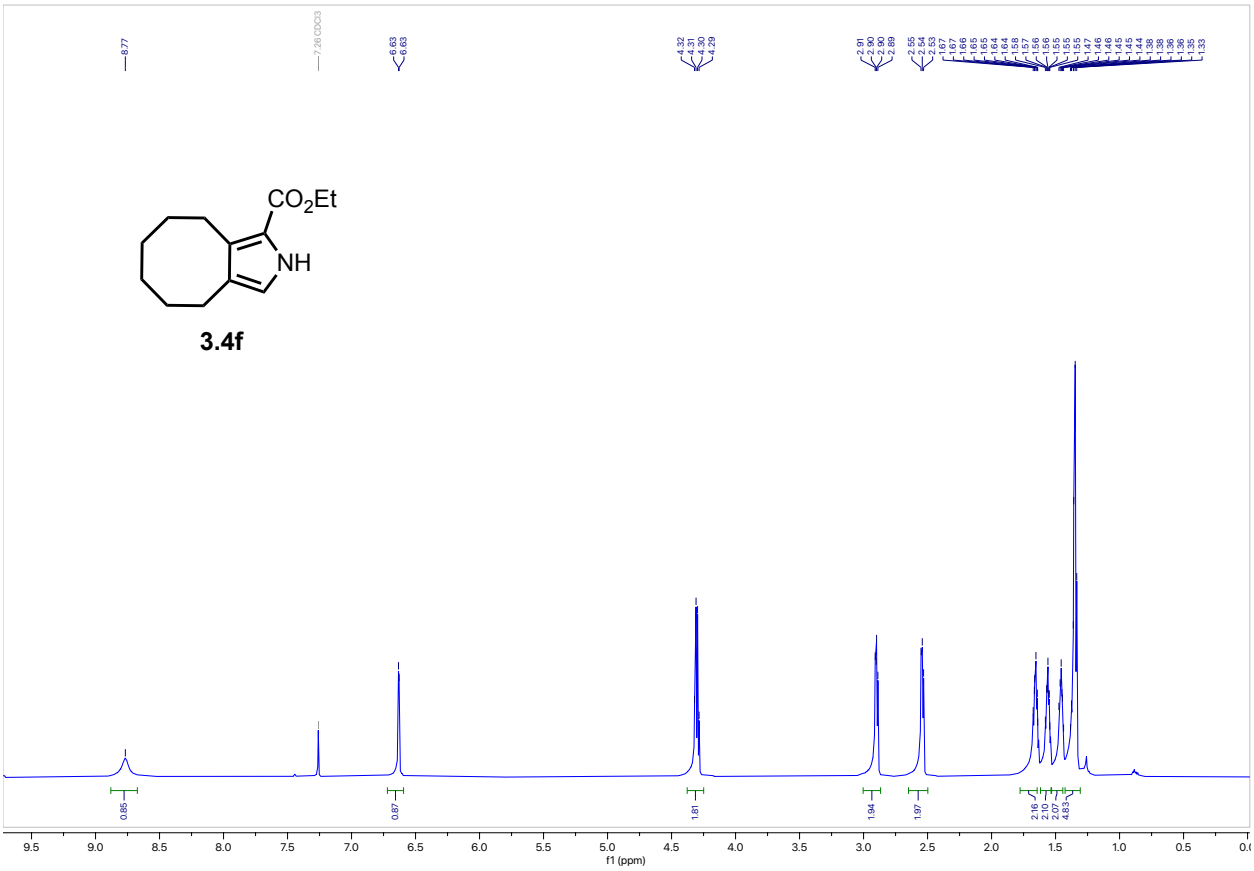
SNP-4b

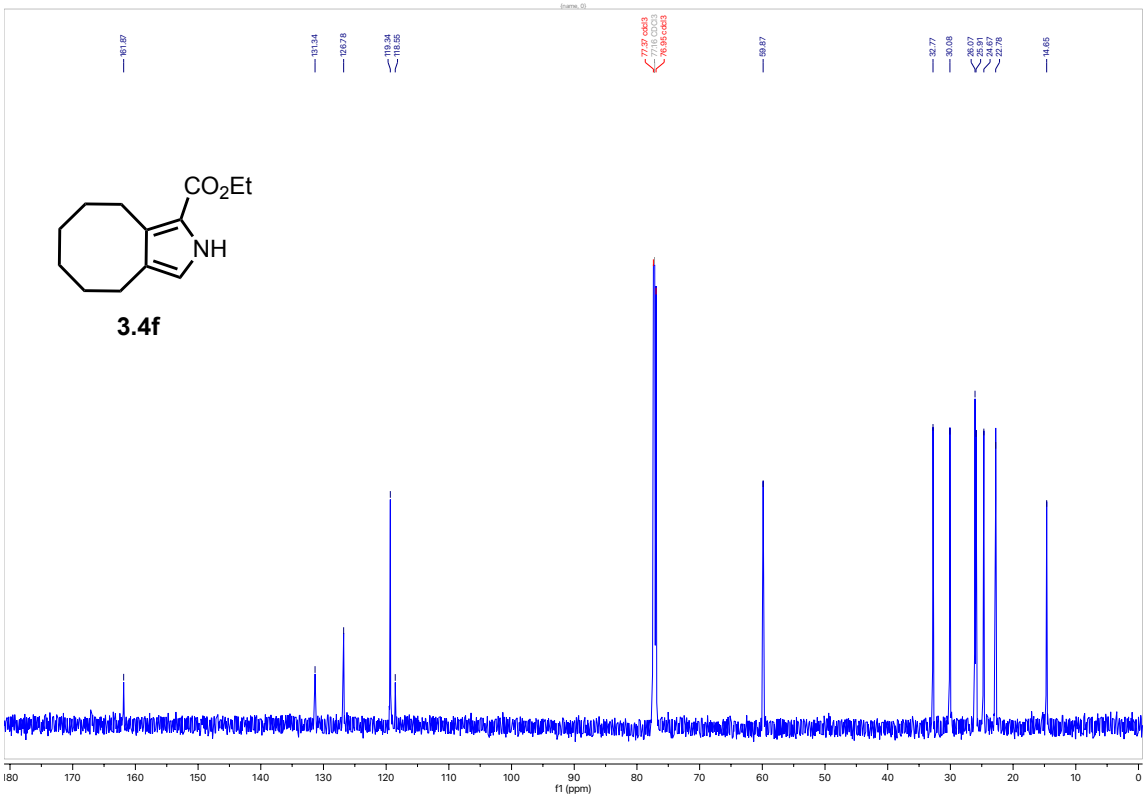

8.32
7.96
7.83
7.82
7.81
7.81
7.79
7.77
7.71
7.70
7.46
7.45
7.43
7.41
7.39
7.38
7.26 CDCl3
7.23
6.89
6.89
6.69
0.76
1.11
3.41
1.14
1.22
1.19
1.06
1.00
1.02
f1 (ppm)
N
H
3.5e

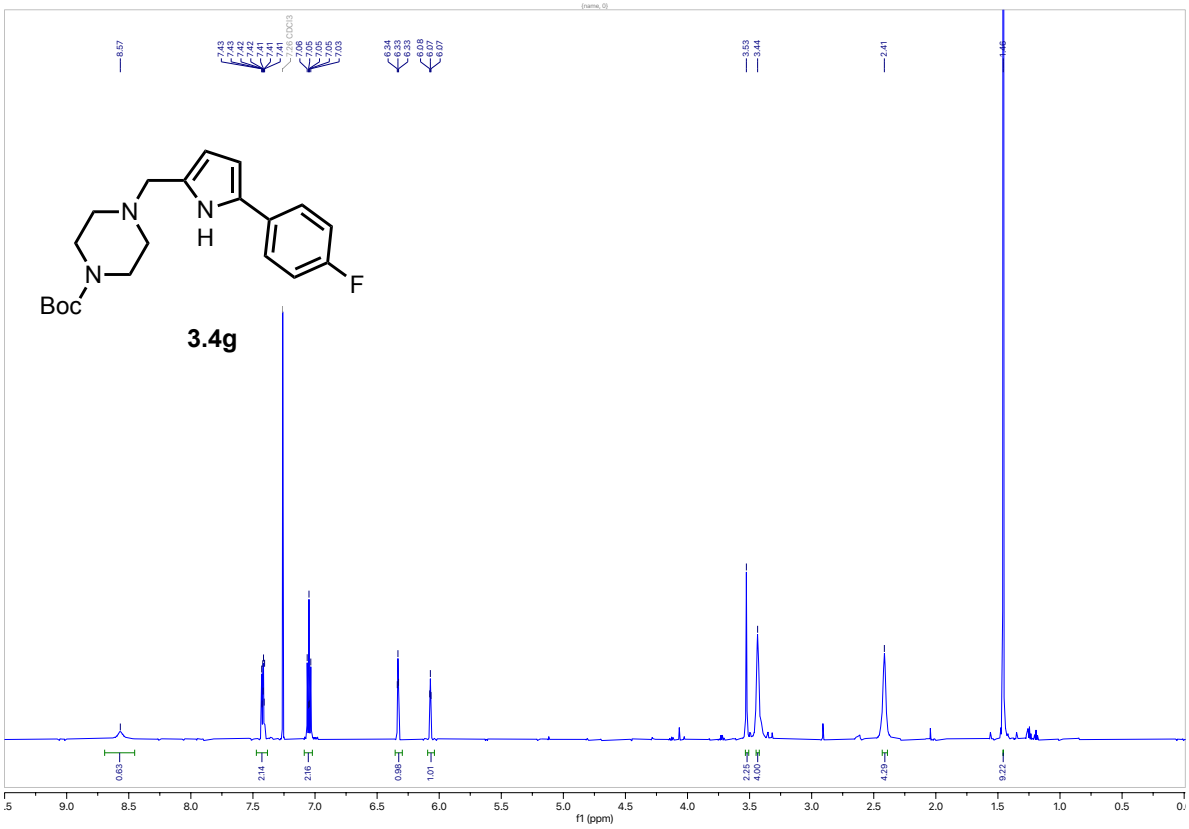

134.17
133.98
133.10
128.24
127.79
127.77
126.14
125.10
124.99
124.65
122.81
119.25
115.16
106.87
77.37 cdcl3
77.16 CDCl3
76.95 cdcl3
f1 (ppm)
N
H
3.5e

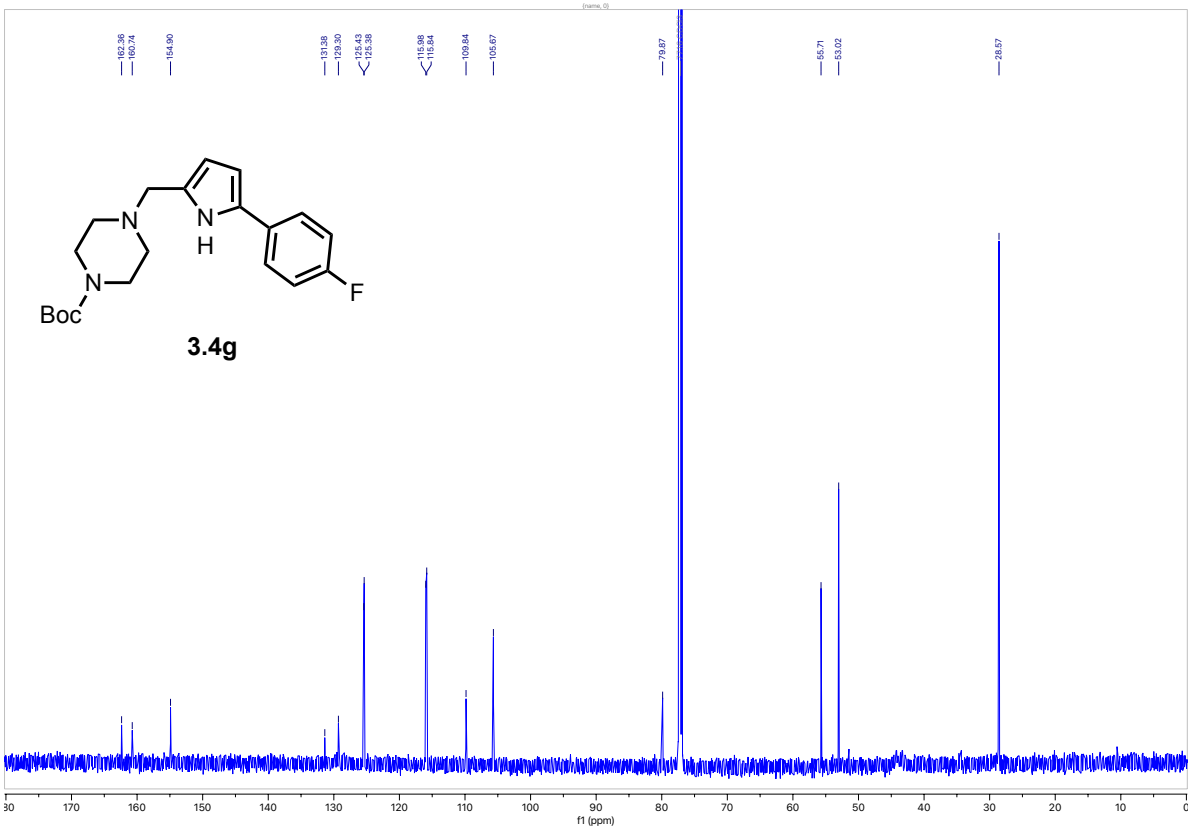

NO2
3.3S4
f1 (ppm)

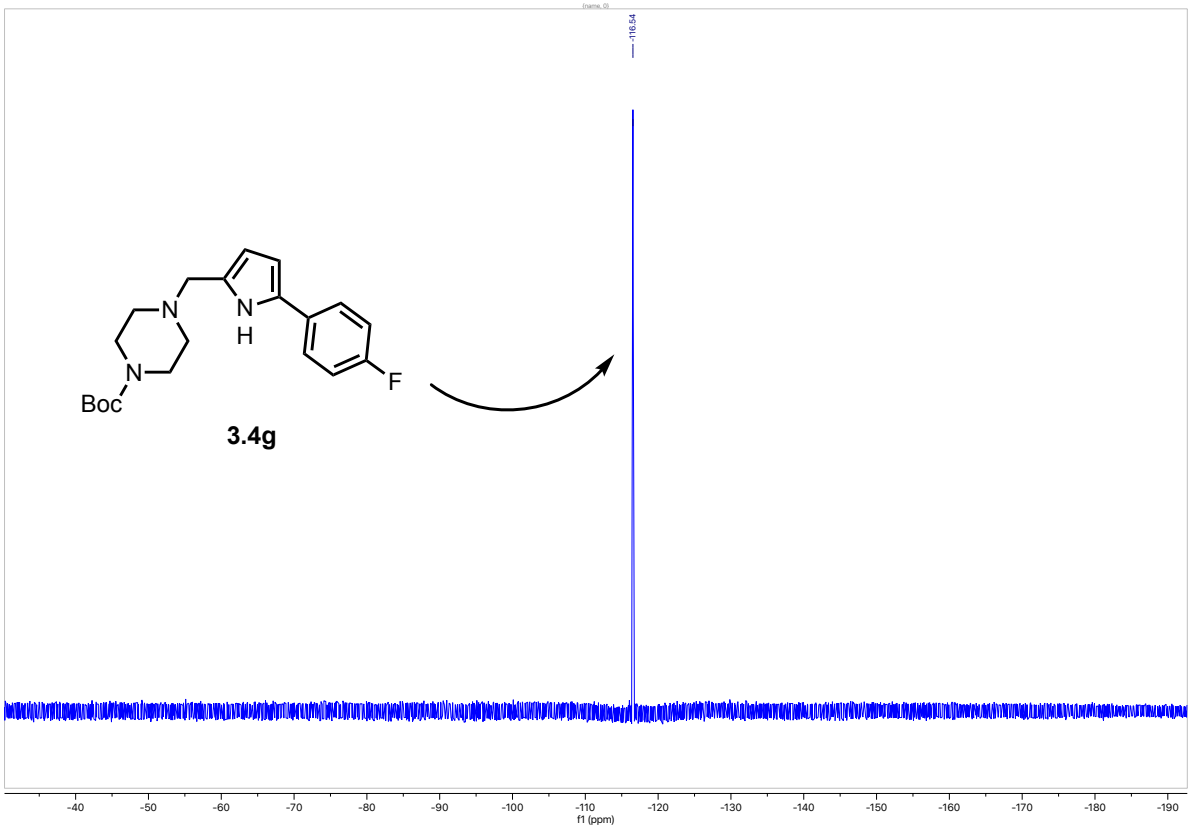

NO2
3.3S4
f1 (ppm)

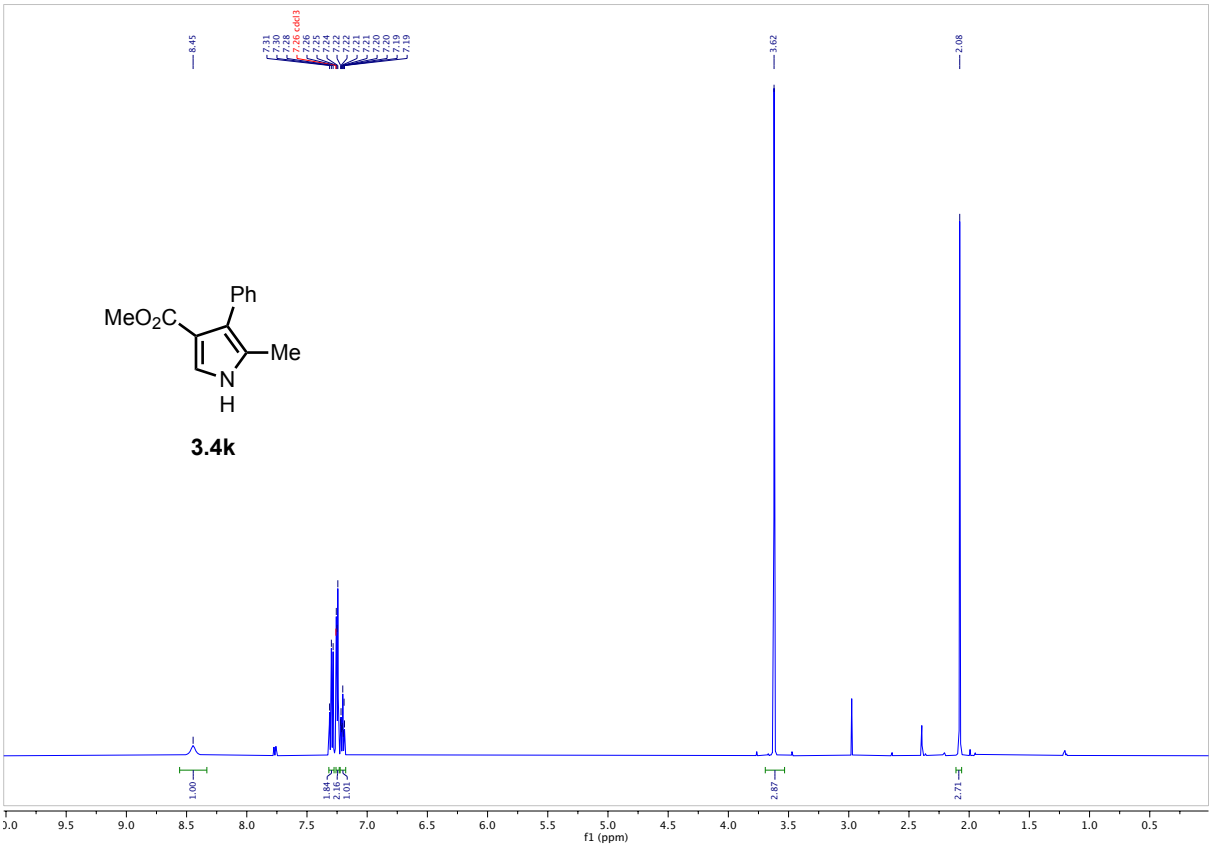

CO2Et
NH
3.4f
f1 (ppm)

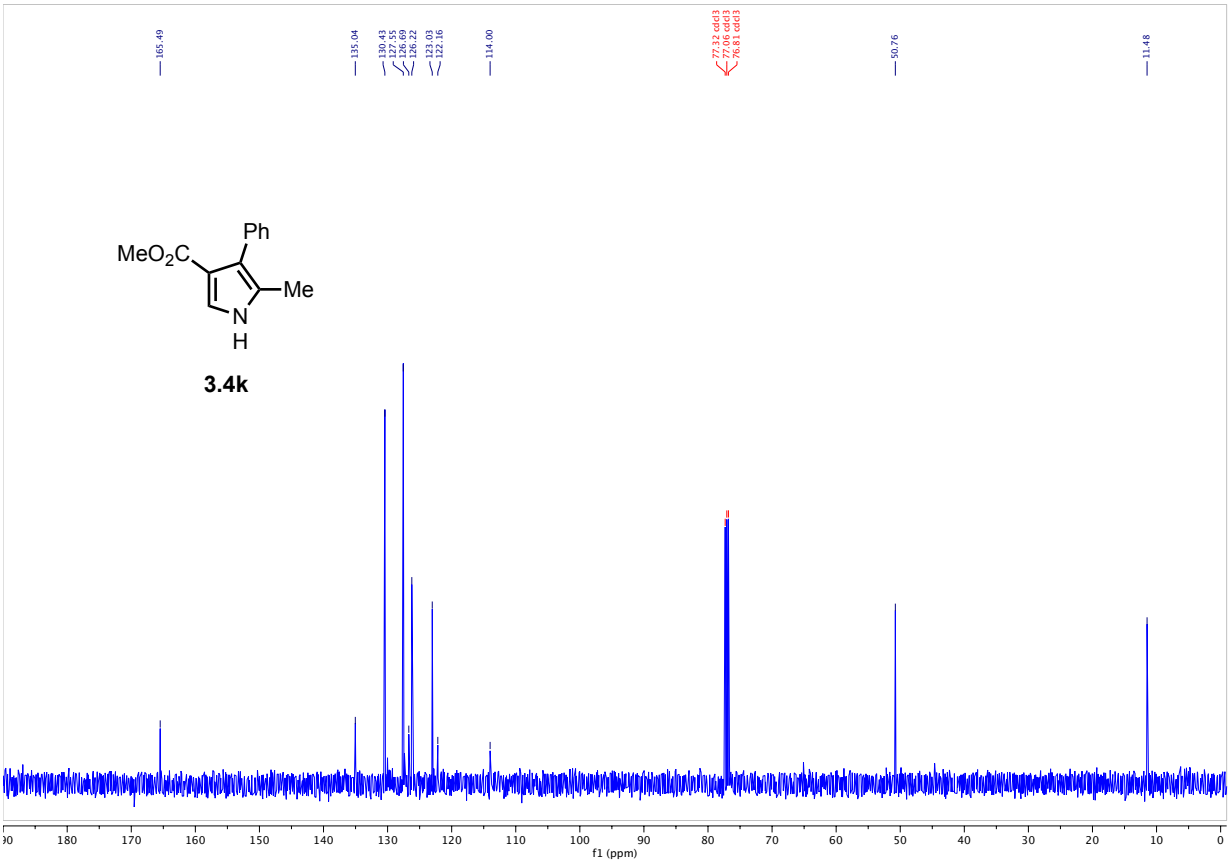

CO2Et
NH
3.4f
f1 (ppm)

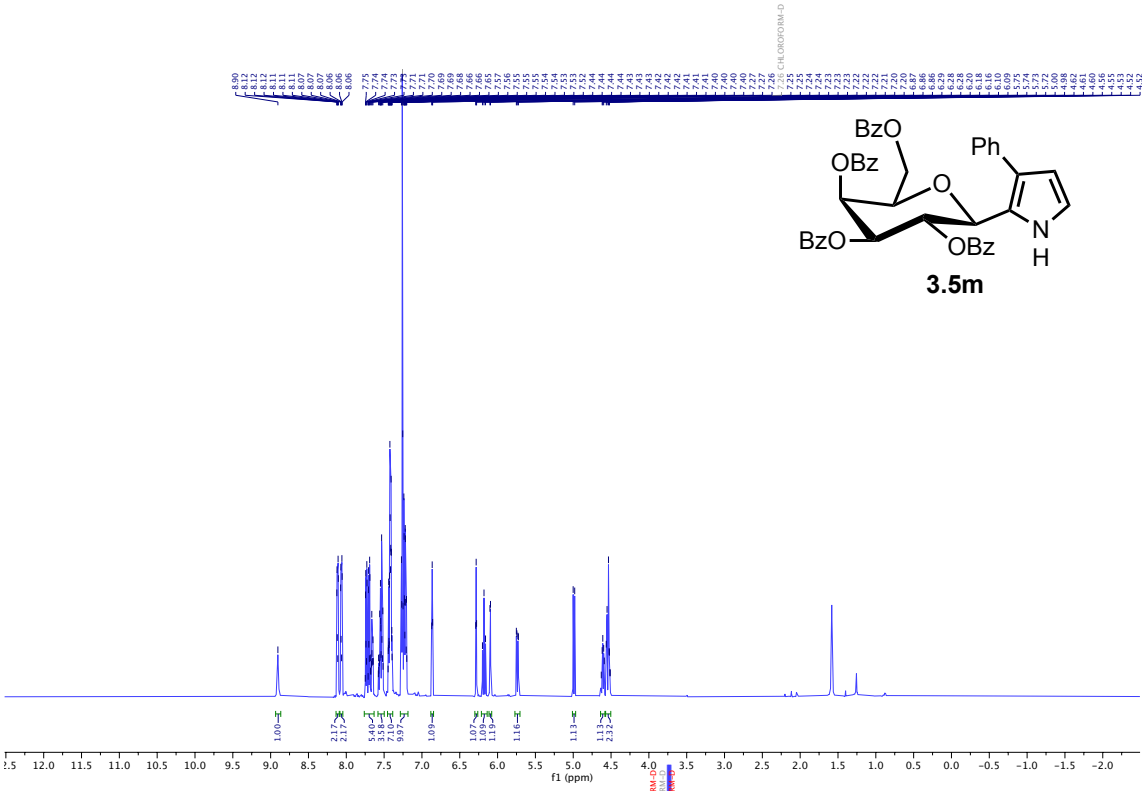

8.57
7.43
7.43
7.42
7.42
7.41
7.41
7.41
7.26 CDCl3
7.06
7.06
7.05
7.05
7.03
6.34
6.33
6.33
6.08
6.07
6.07
3.53
3.44
2.41
1.46
N
N
H
N
Boc
F
3.4g
0.63
2.14
2.16
0.98
1.01
2.25
4.00
4.29
9.22
f1 (ppm)


162.36
160.74
154.90
131.38
129.30
125.43
125.38
115.98
115.84
109.84
105.67
79.87
55.71
53.02
28.57
N
N
H
N
Boc
F
3.4g
f1 (ppm)

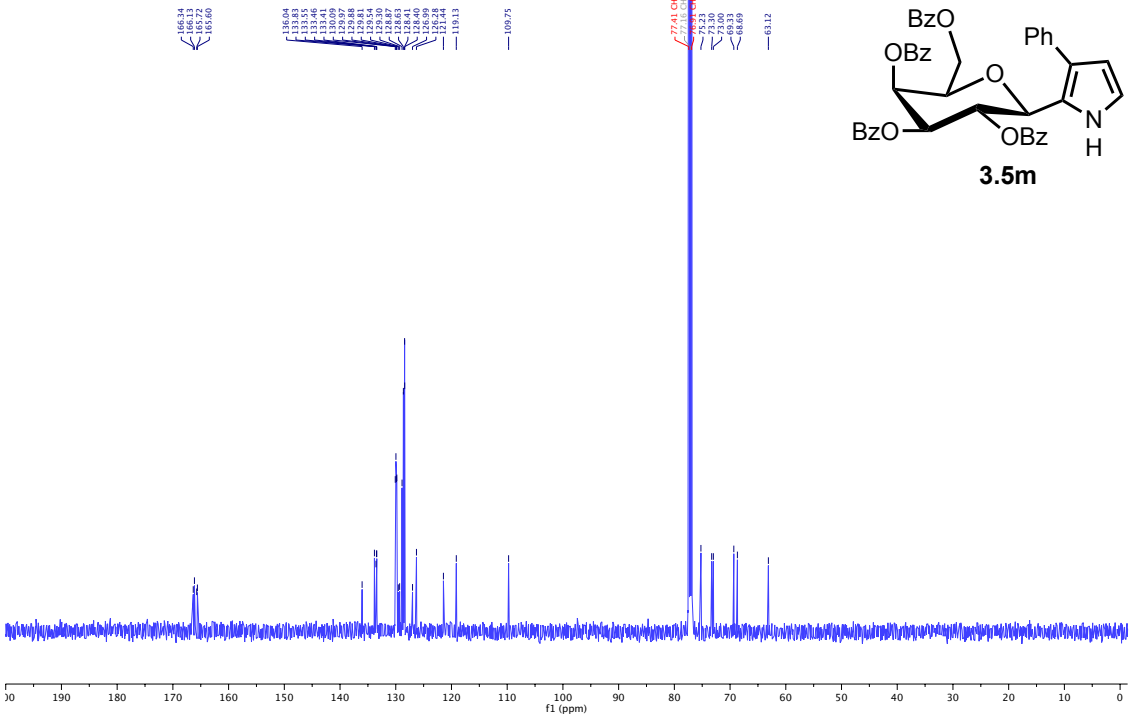

-116.54
N
N
H
N
Boc
F
3.4g
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


8.45
7.31
7.30
7.28
7.26 cdd3
7.26
7.25
7.24
7.22
7.21
7.20
7.19
3.62
2.08
Ph
MeO2C
Me
N
H
3.4k
1.00
1.84
2.16
1.01
2.87
2.71
f1 (ppm)

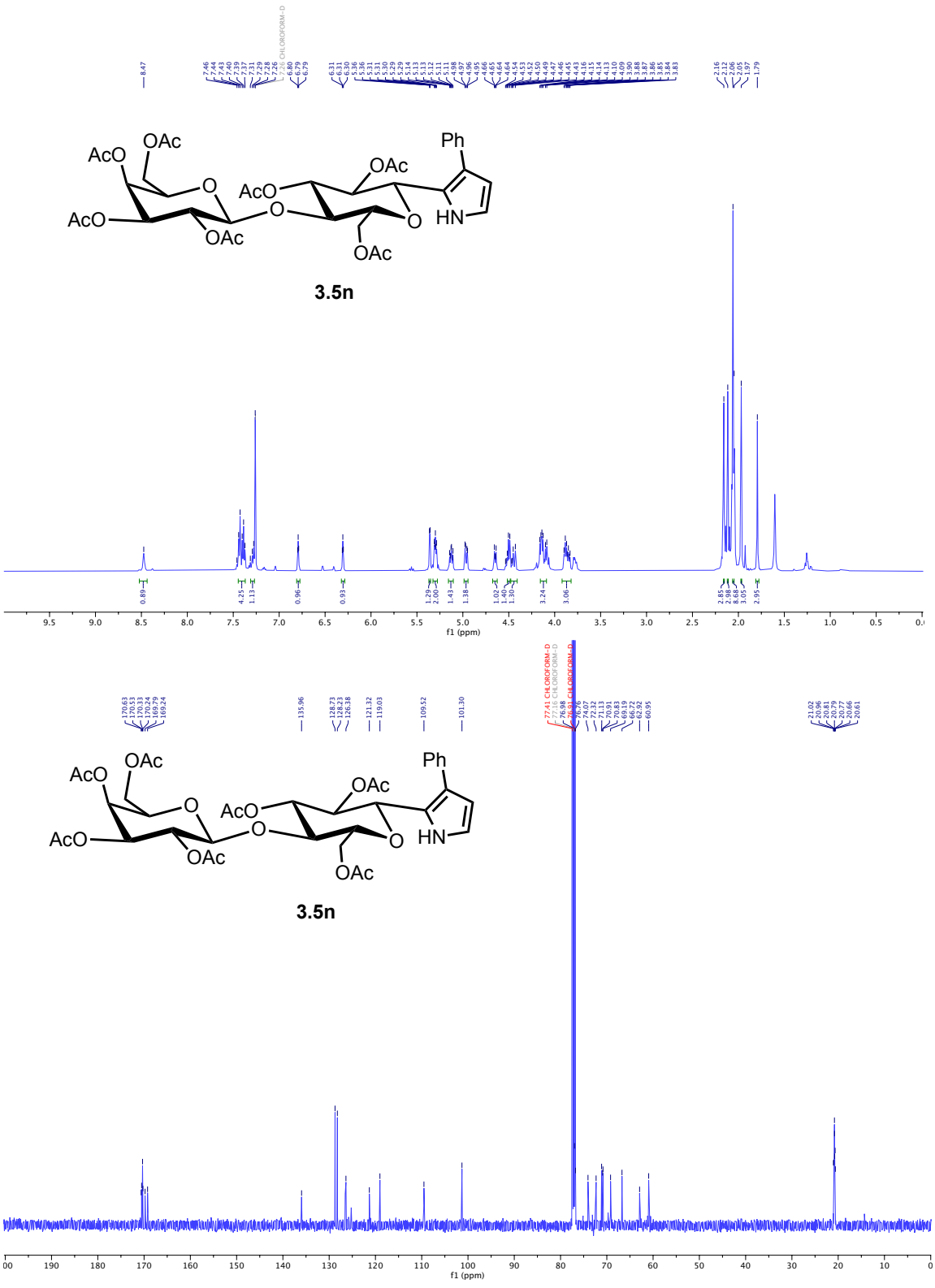

165.49
135.04
130.43
127.55
126.69
126.22
123.03
122.16
114.00
77.32 cdd3
77.06 cdd3
76.81 cdd3
50.76
11.48
Ph
MeO2C
Me
N
H
3.4k
f1 (ppm)

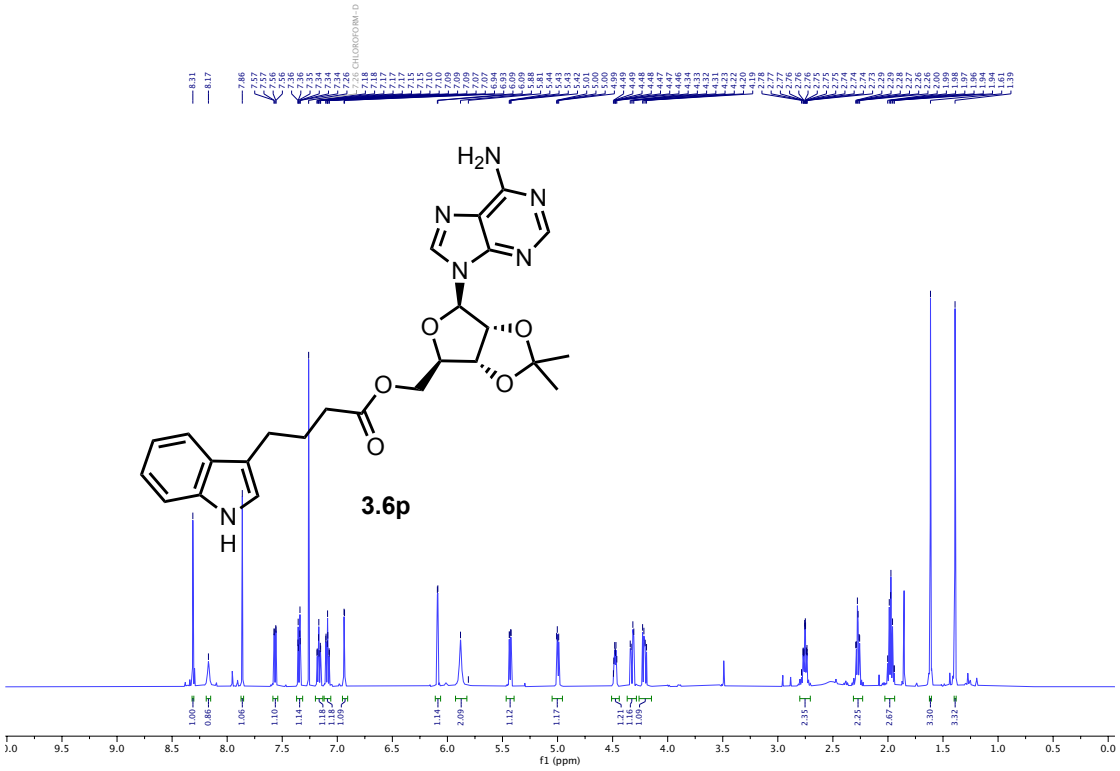


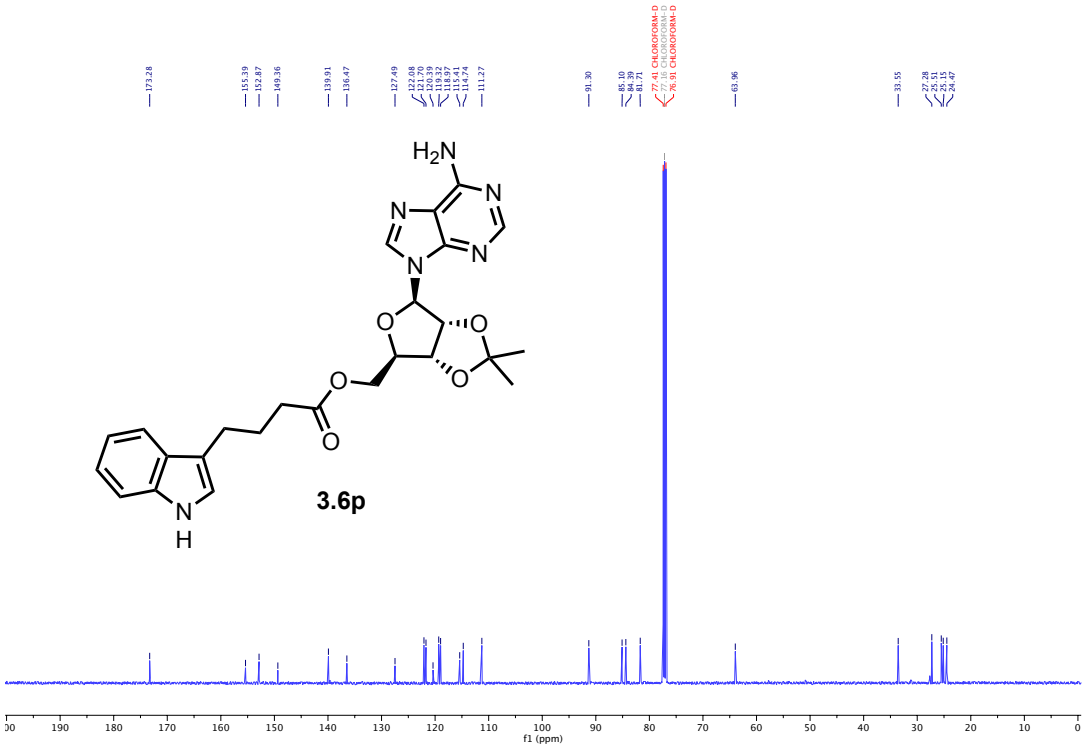
3.5m

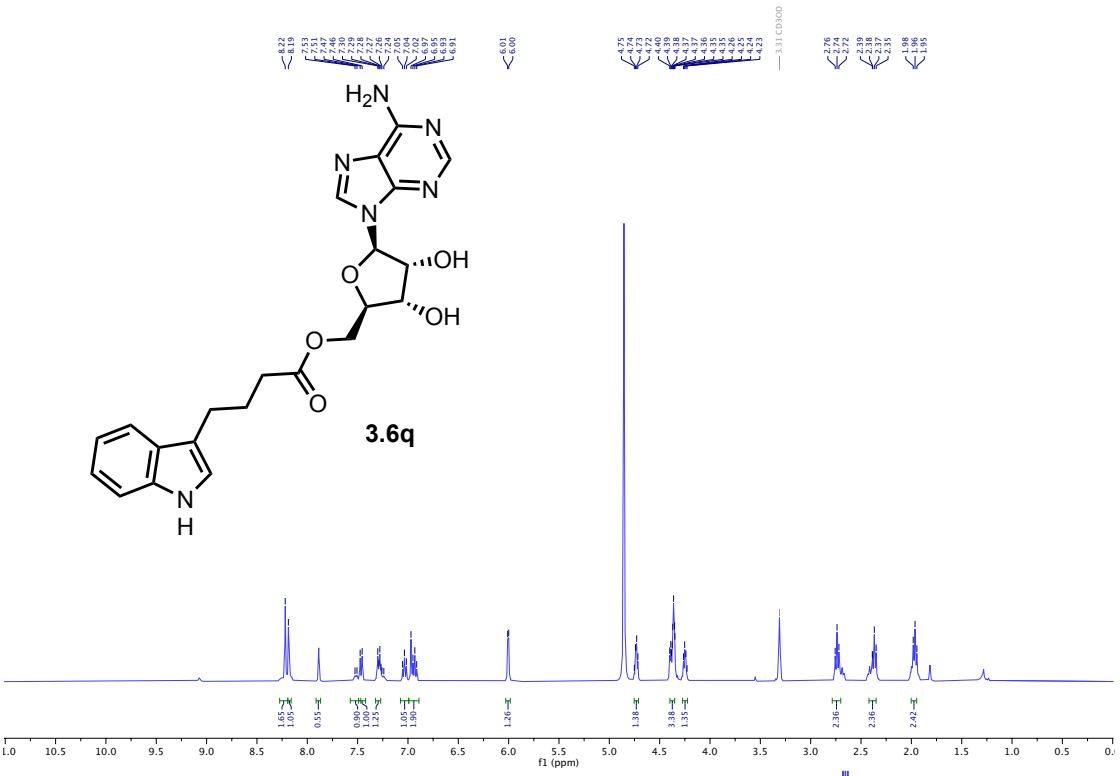


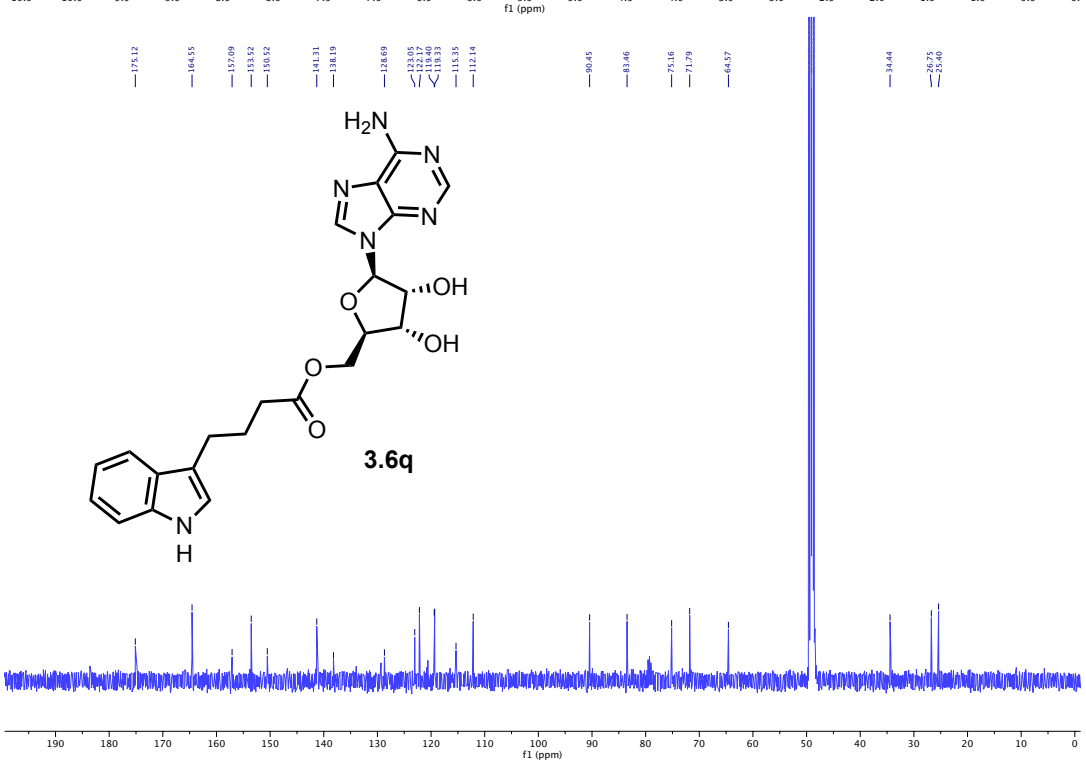
3.5m

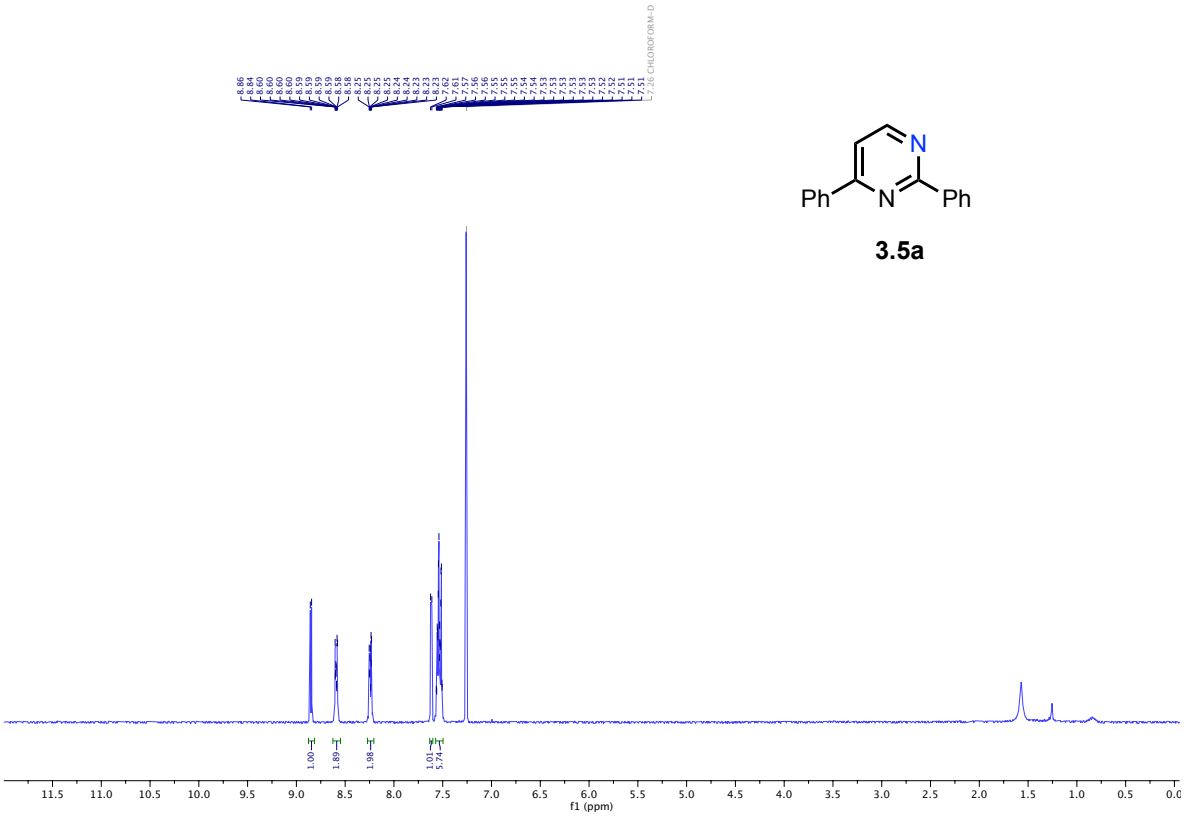

AcO
OAc
AcO
AcO
O
OAc
AcO
O
OAc
O
Ph
HN
OAc
3.5n
f1 (ppm)
3.5n
f1 (ppm)


3.6p
f1 (ppm)


3.6p
f1 (ppm)

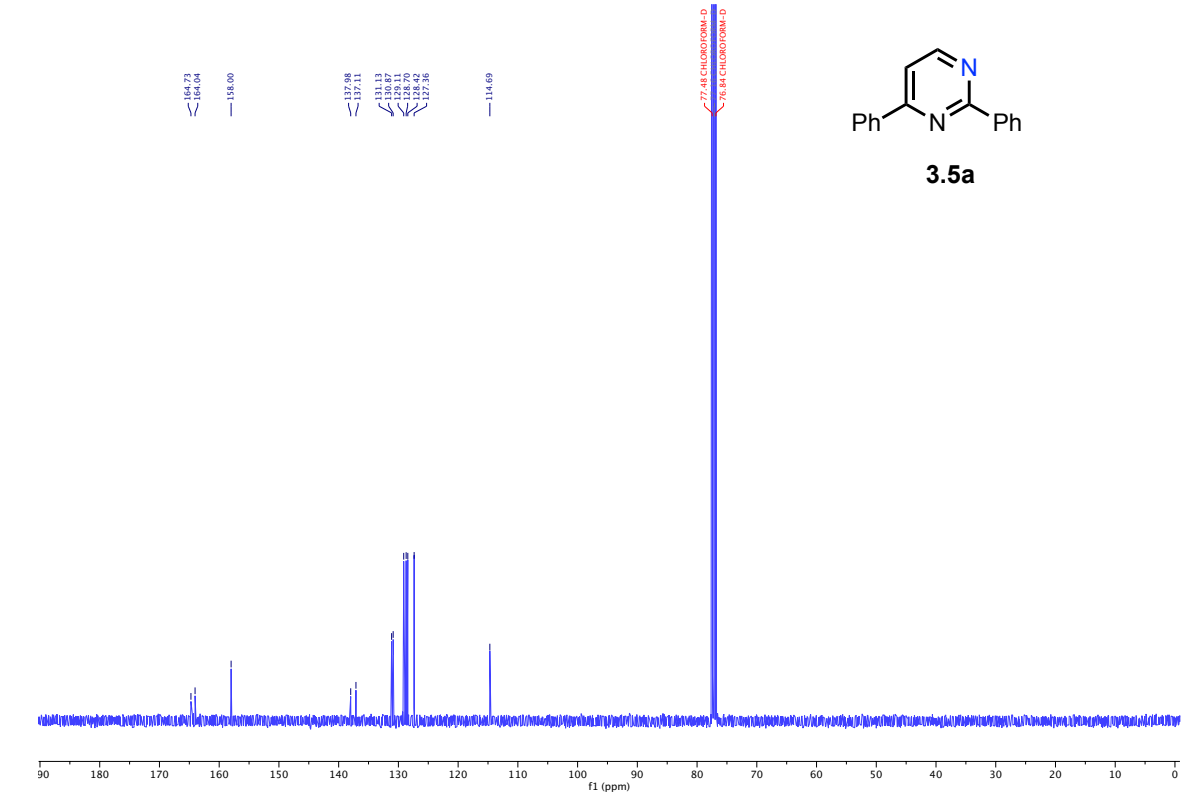

3.6q
f1 (ppm)


3.6q
f1 (ppm)


7.26 CHLOROFORM-D
1.00
1.89
1.98
1.01
5.74
f1 (ppm)

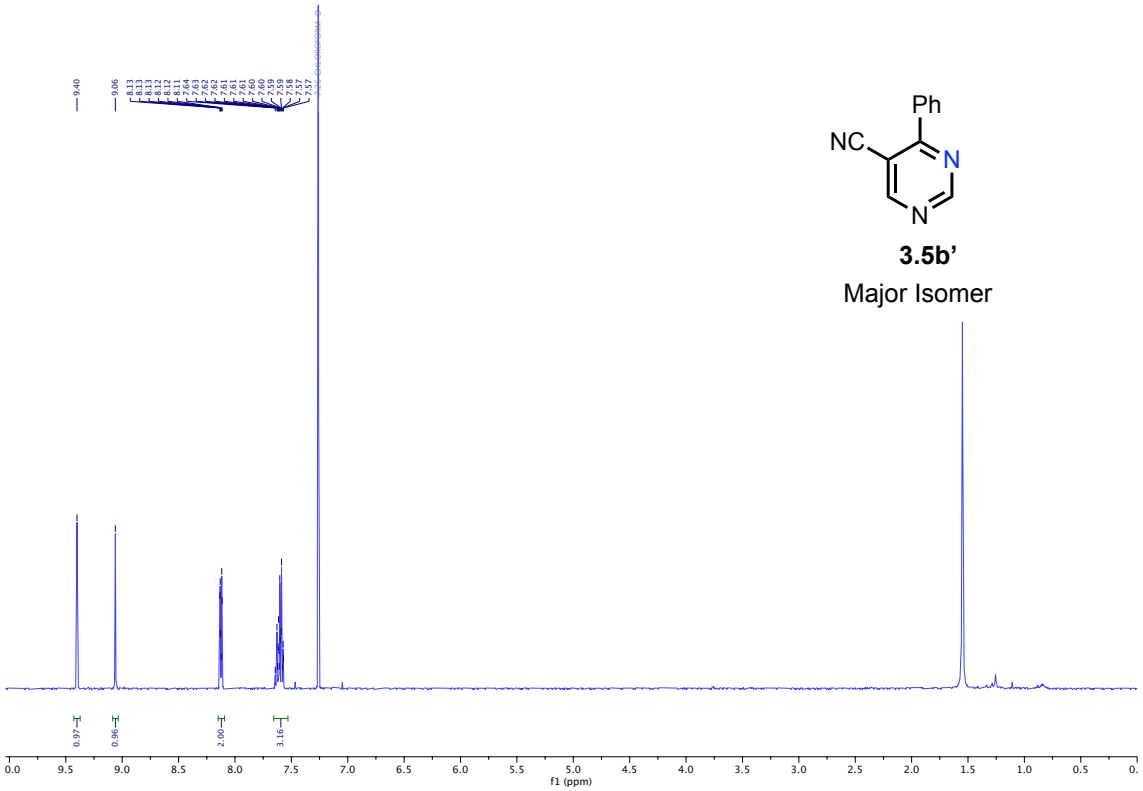
N
Ph
N
Ph

3.5a


164.73
164.04
158.00
137.98
137.11
131.13
130.87
129.11
128.70
128.42
127.36
114.69
77.48 CHLOROFORM-D
76.84 CHLOROFORM-D
f1 (ppm)

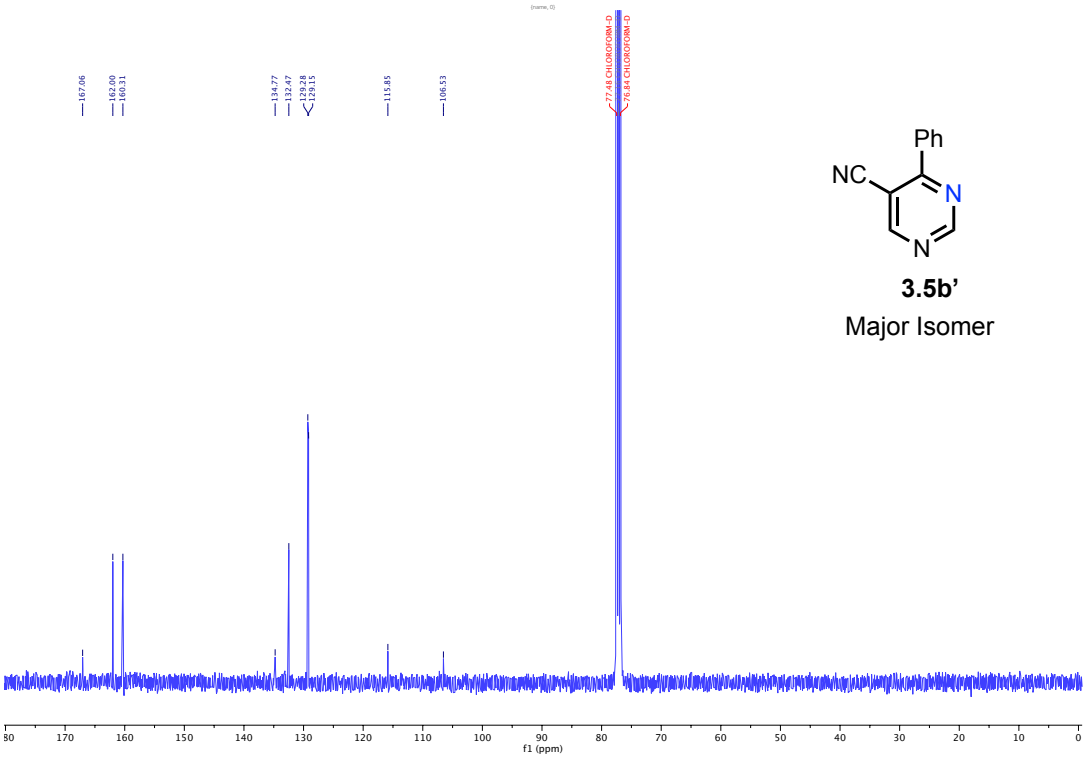
N
Ph
N
Ph

3.5a



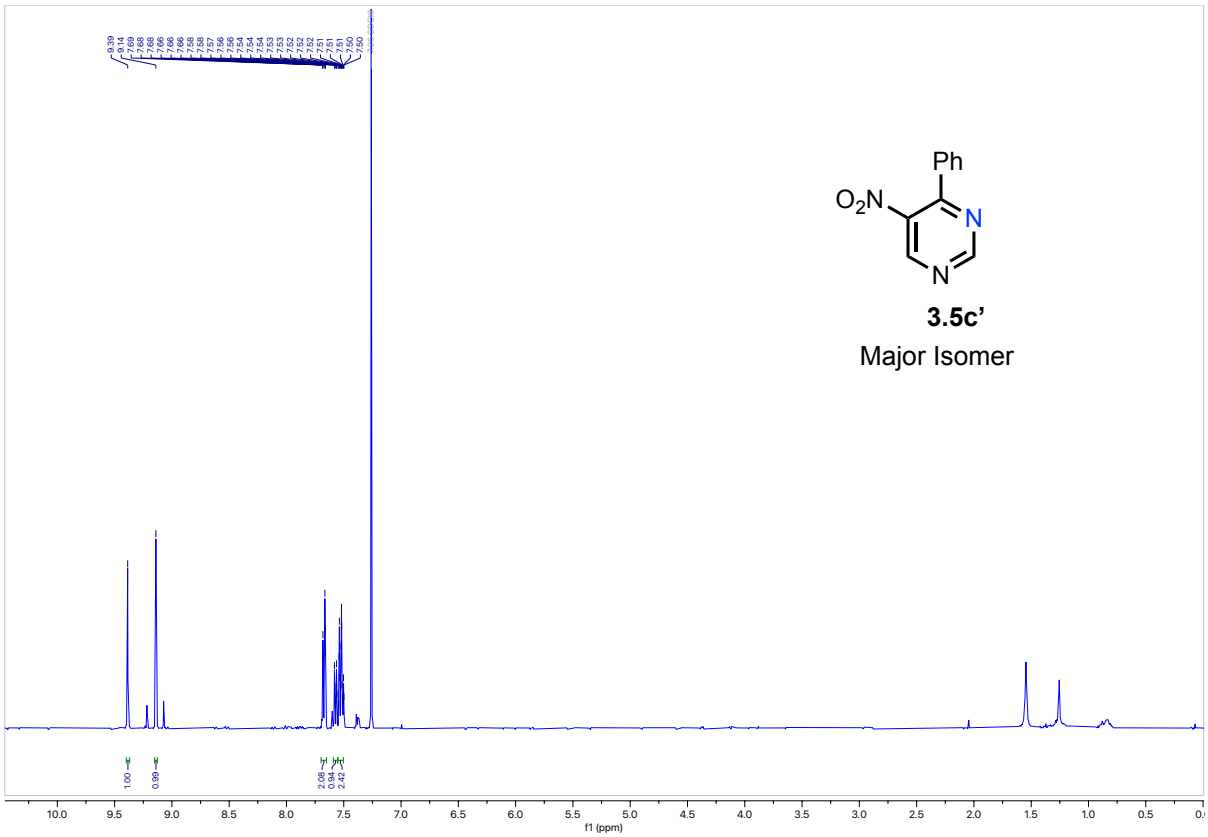
3.5b'

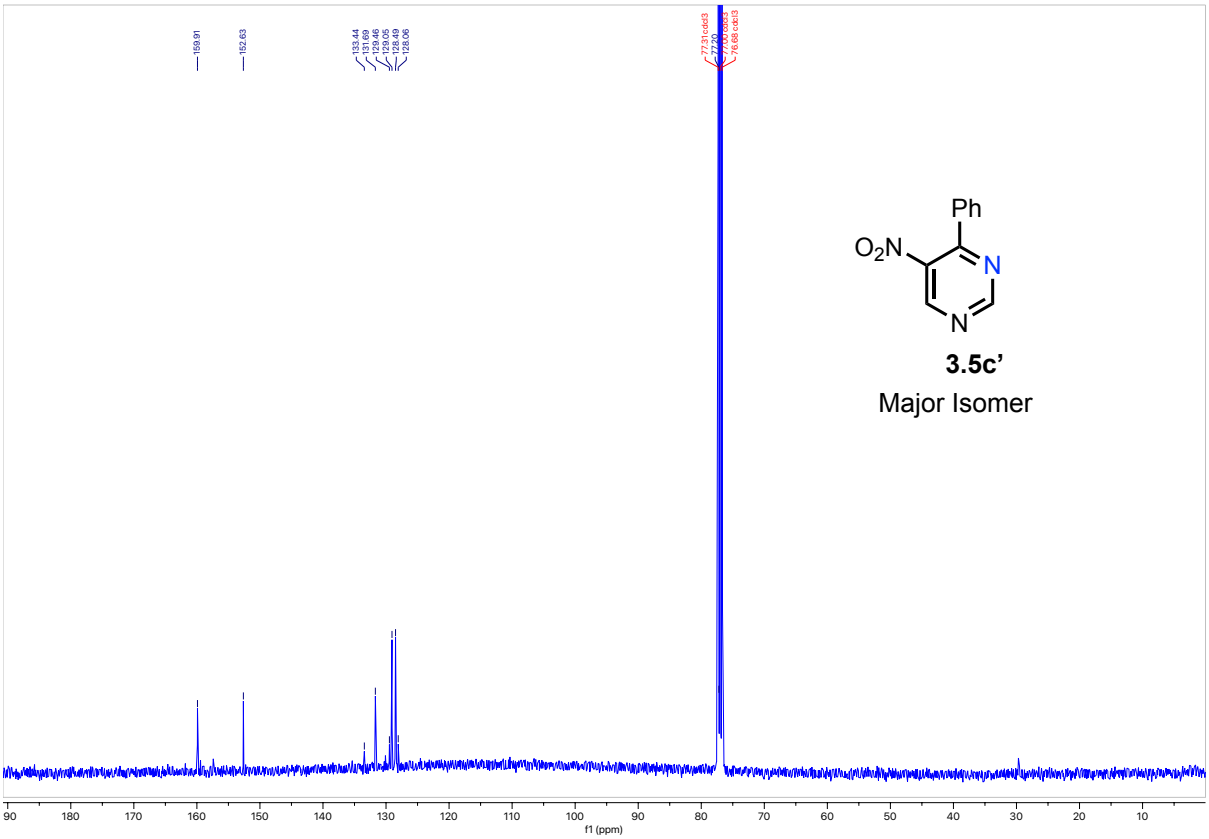
Major Isomer

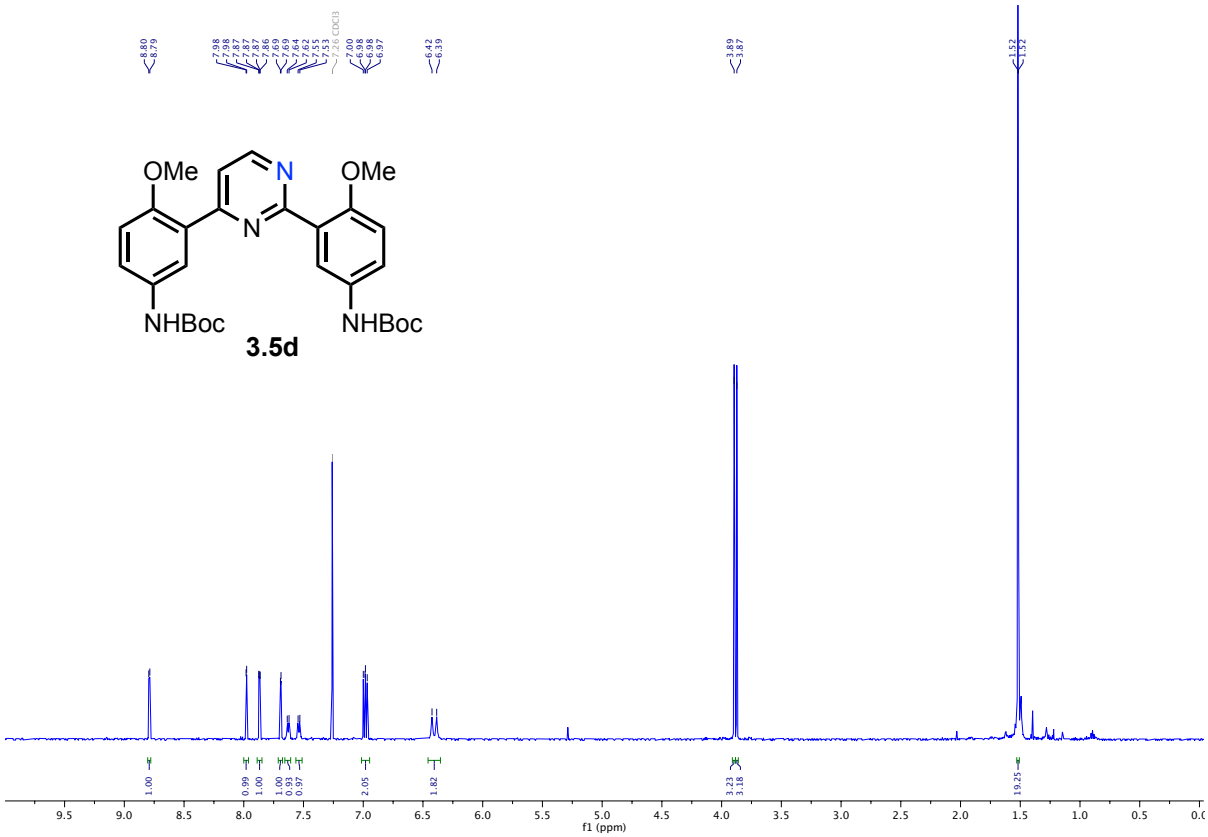


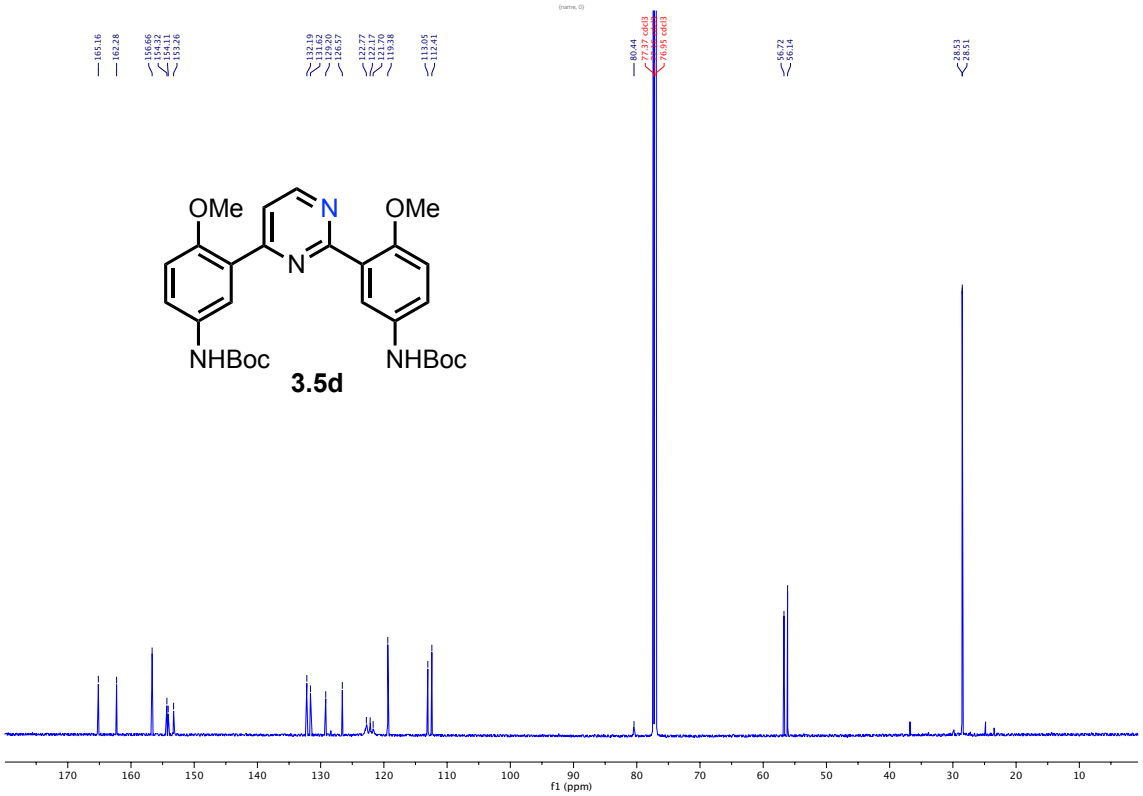
3.5b'

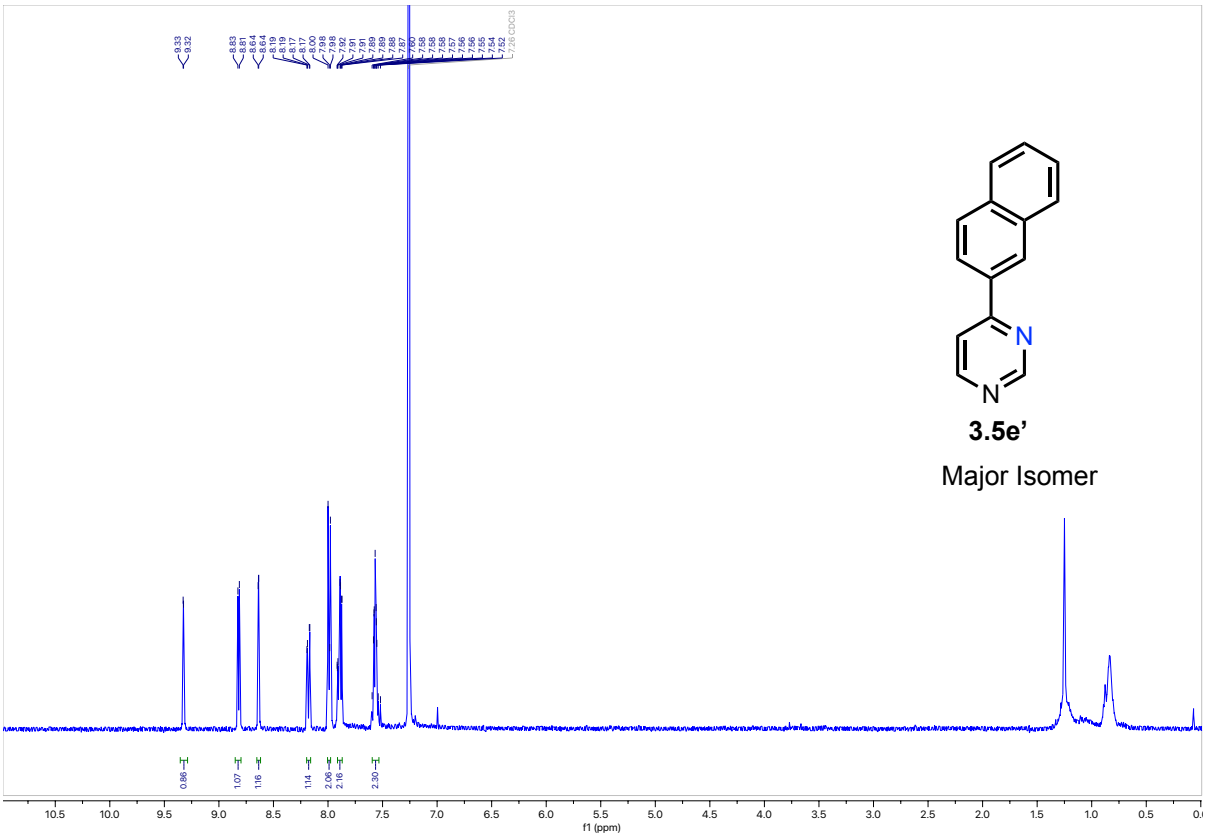
Major Isomer

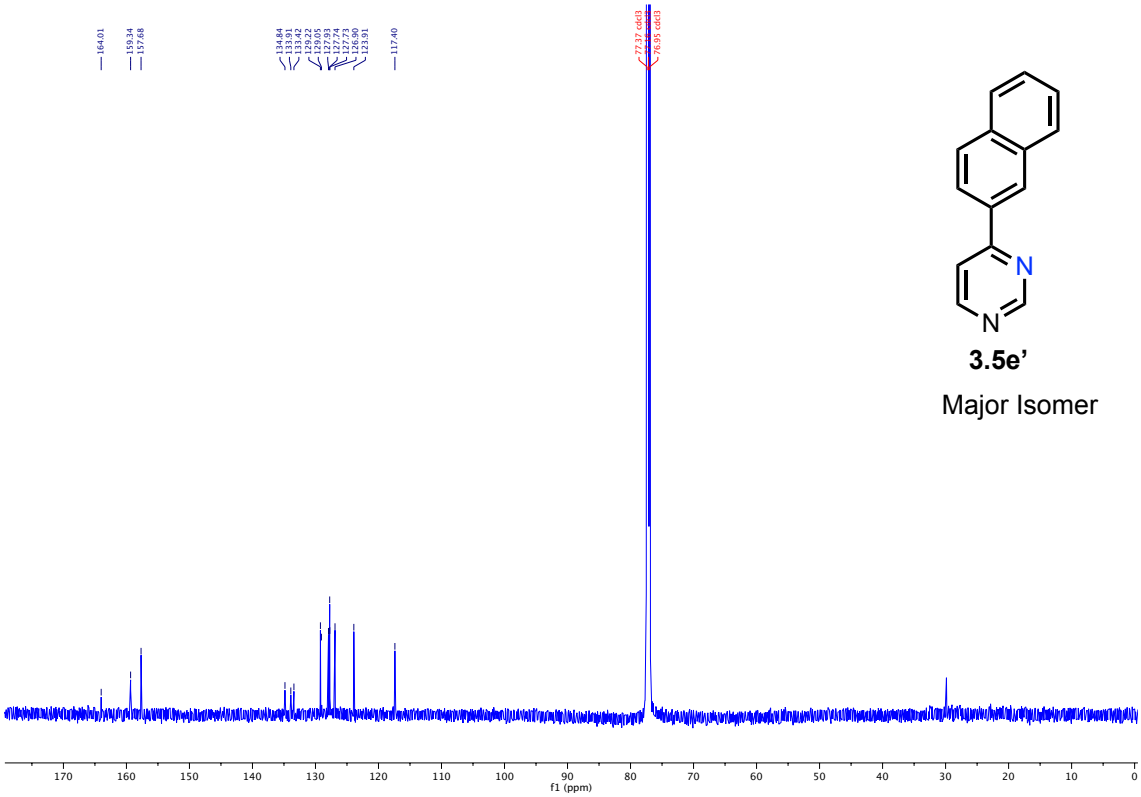

Ph
O_2N
N
N
3.5c'
Major Isomer
f1 (ppm)

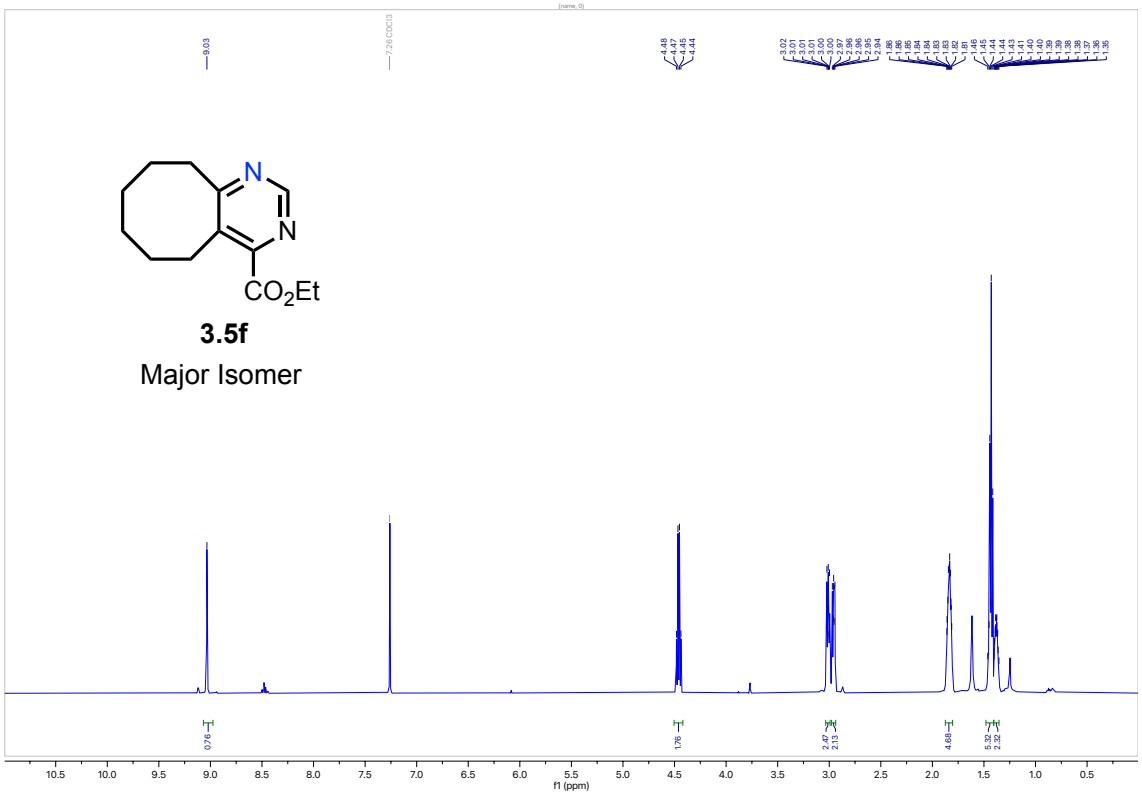

Ph
O_2N
N
N
3.5c'
Major Isomer
f1 (ppm)

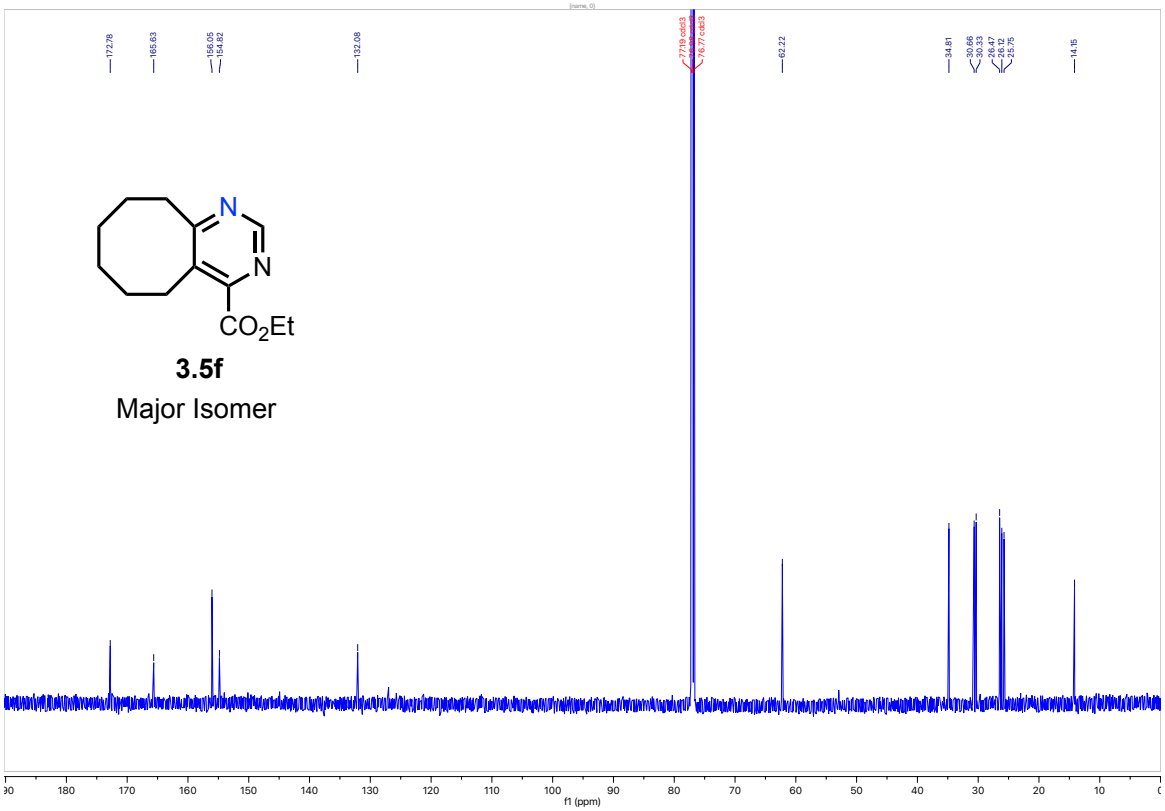

OMe
N
OMe
N
NHBoc
NHBoc
3.5d
f1 (ppm)

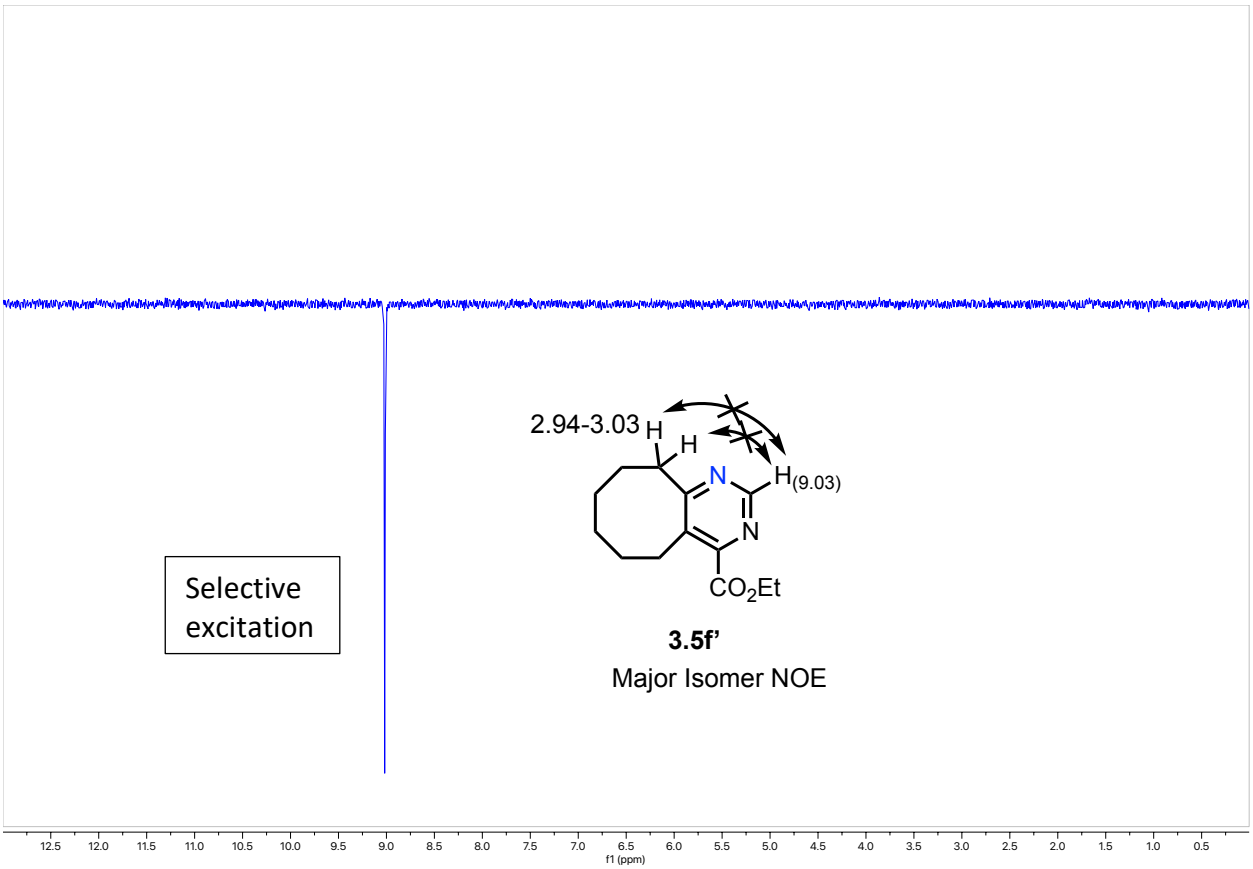

OMe
N
OMe
N
NHBoc
NHBoc
3.5d
f1 (ppm)

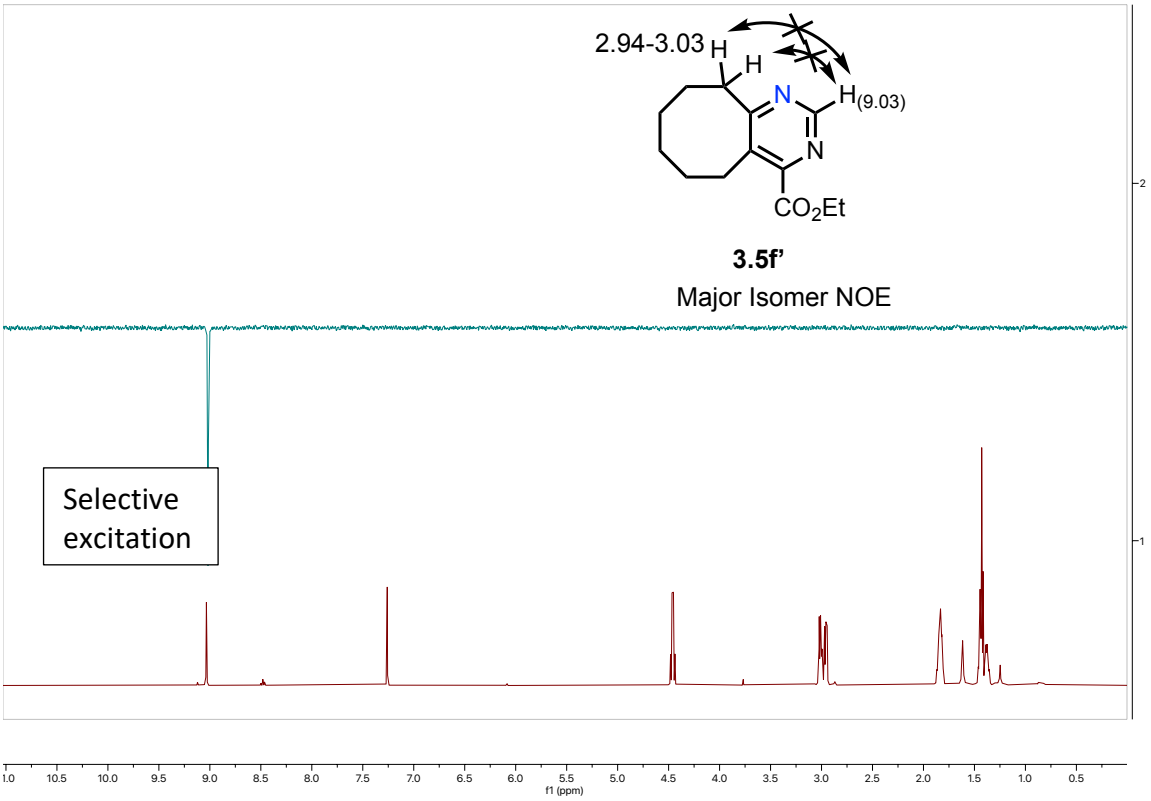

9.33
9.32
8.88
8.86
8.64
8.62
8.19
8.17
8.07
8.05
7.98
7.96
7.92
7.91
7.89
7.88
7.87
7.58
7.58
7.58
7.57
7.56
7.56
7.55
7.54
7.52
7.26 CDCl3
0.86
1.07
1.16
1.14
2.06
2.16
2.30
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
N
N
3.5e'
Major Isomer

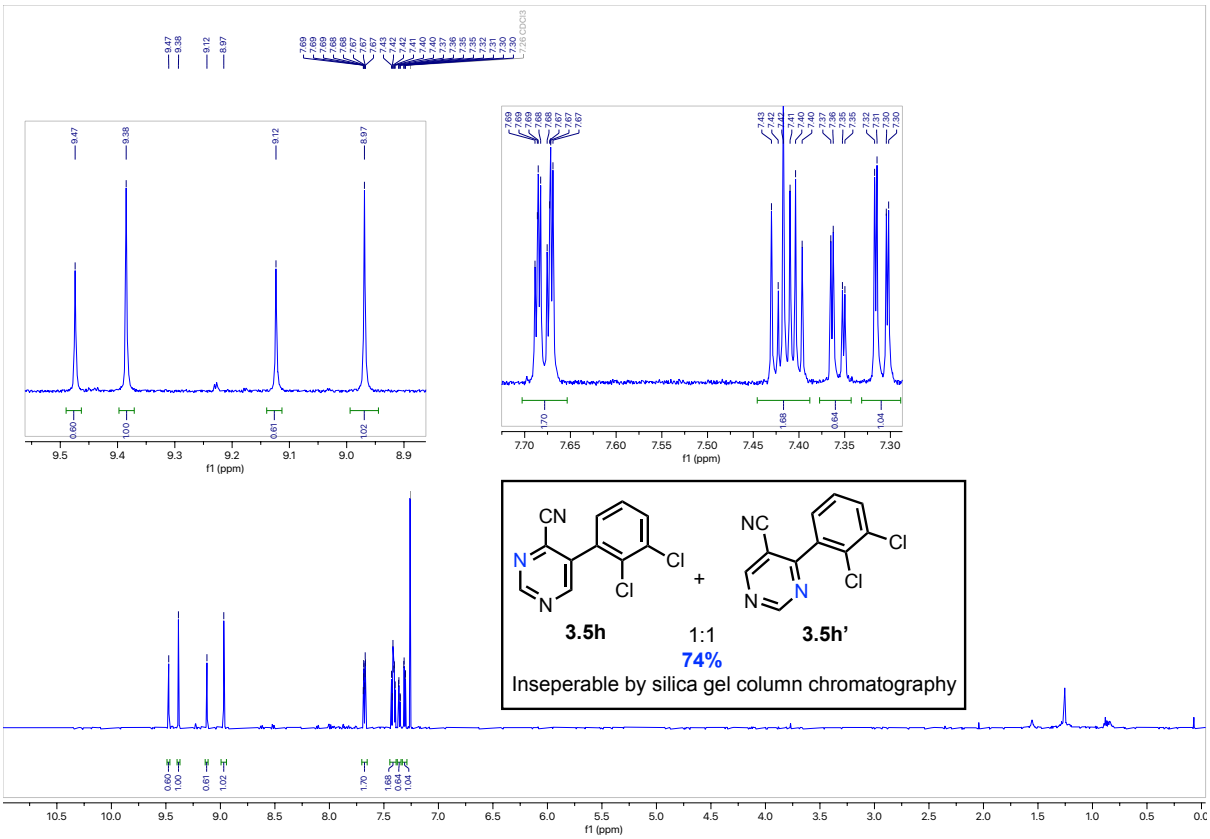

164.01
159.34
157.68
134.84
133.91
133.23
129.22
129.05
127.74
127.54
127.23
126.90
123.91
117.40
77.37 cdcl3
77.05 cdcl3
76.95 cdcl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
N
N
3.5e'
Major Isomer

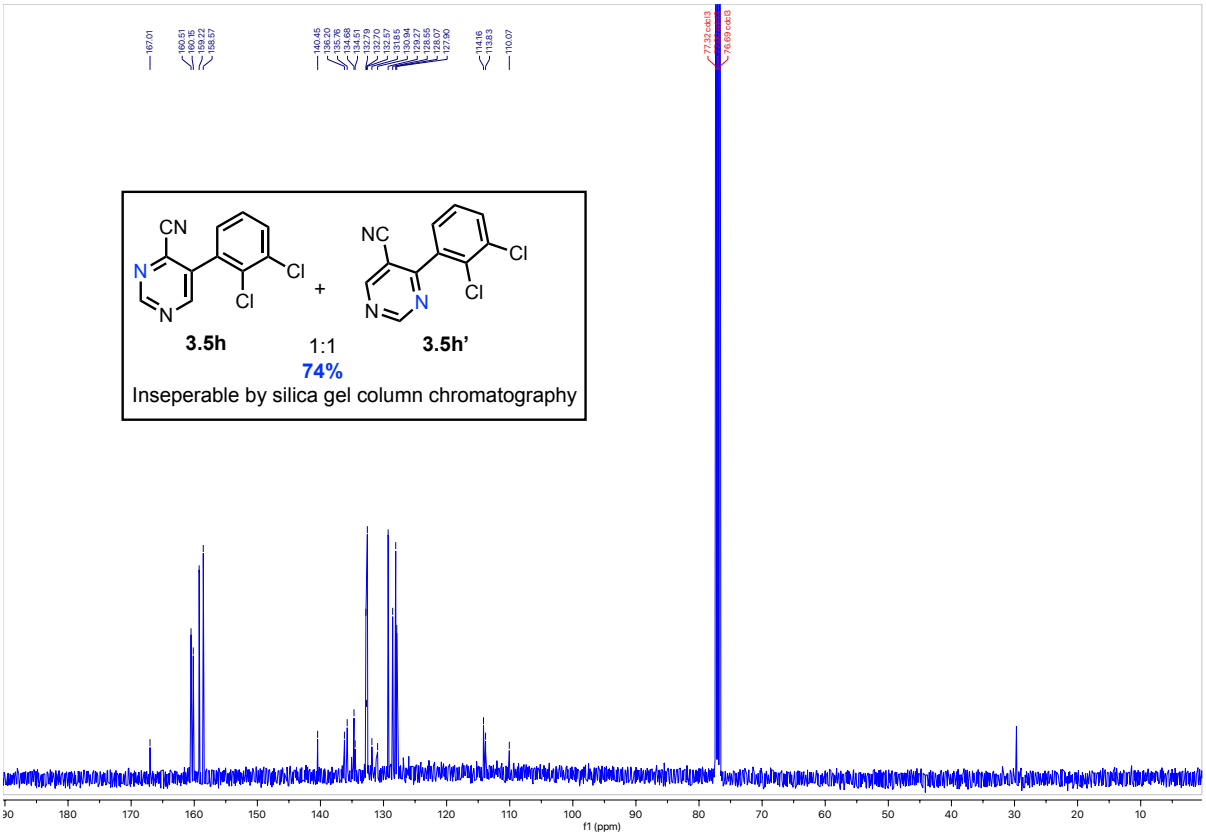

N
N
CO_2Et
3.5f
Major Isomer
f1 (ppm)

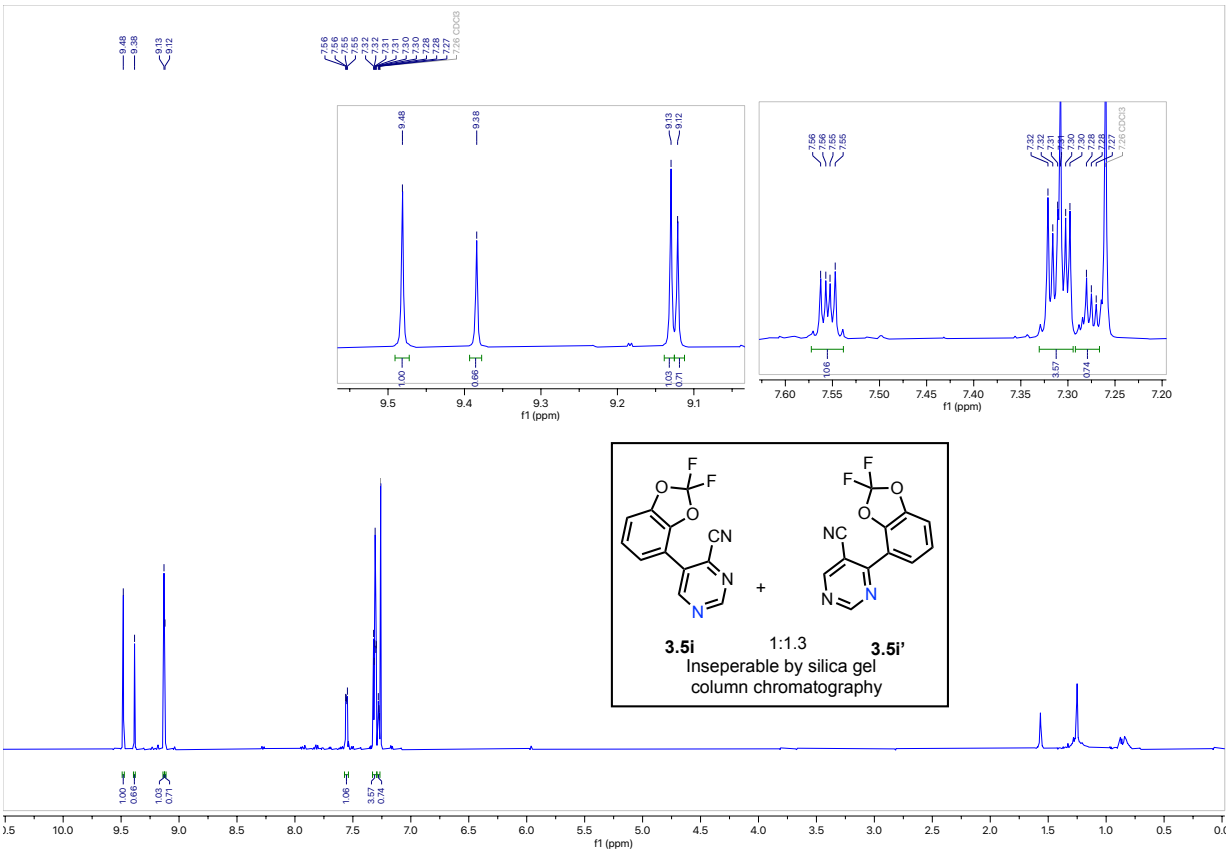

N
N
CO_2Et
3.5f
Major Isomer
f1 (ppm)

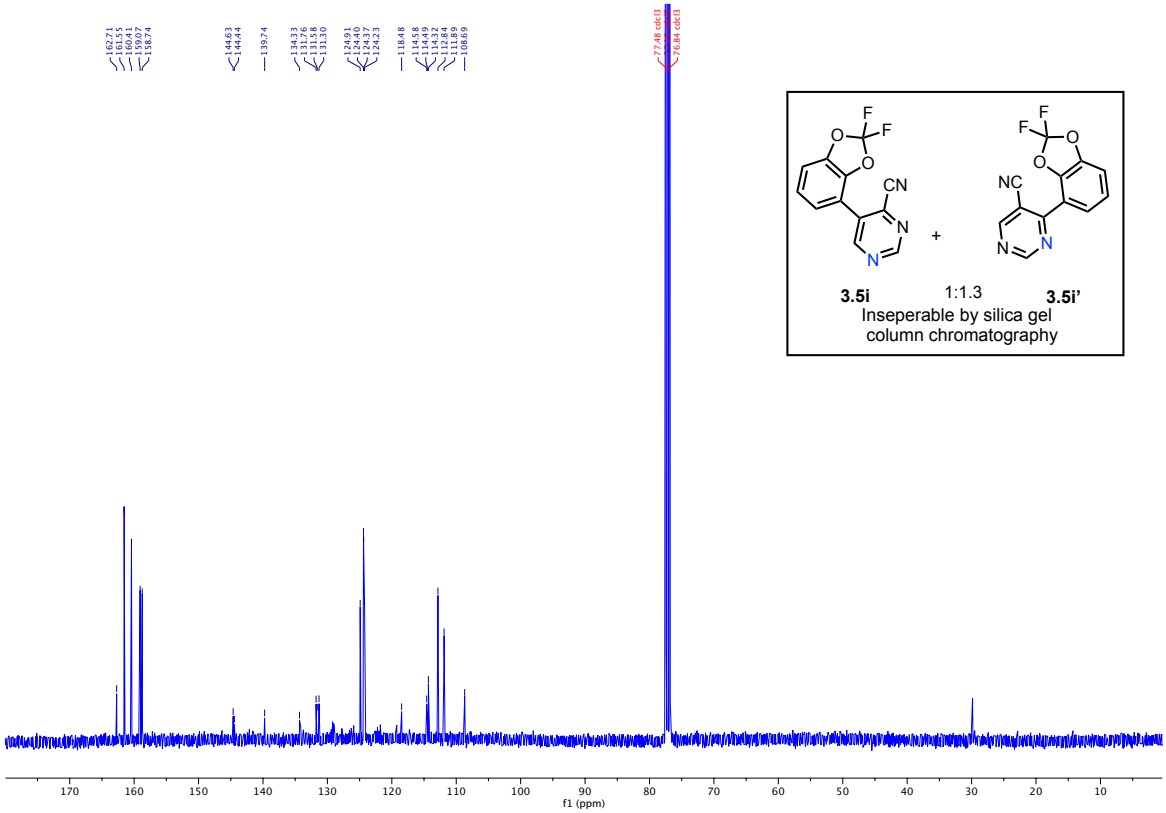

2.94-3.03
H
H
N
H(9.03)
N
CO2Et
Selective excitation
3.5f'
Major Isomer NOE
f1 (ppm)

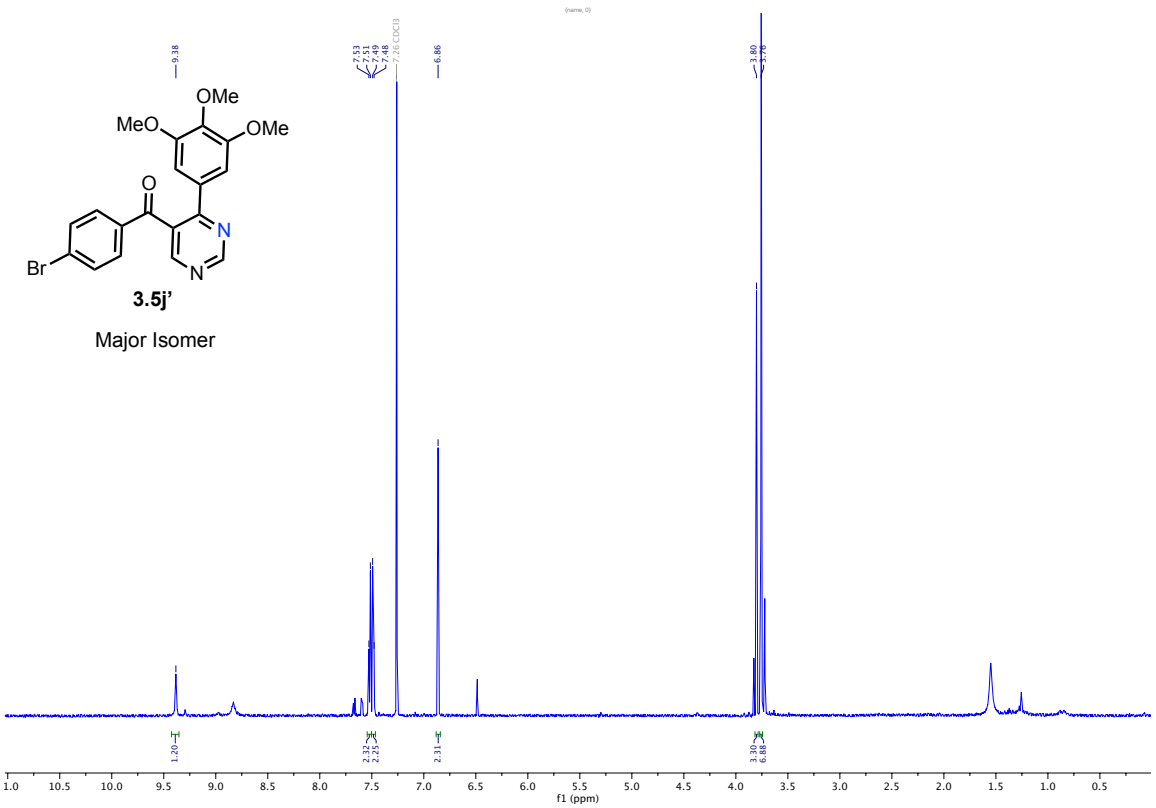

2.94-3.03
H
H
N
H(9.03)
N
CO2Et
3.5f'
Major Isomer NOE
Selective excitation
f1 (ppm)

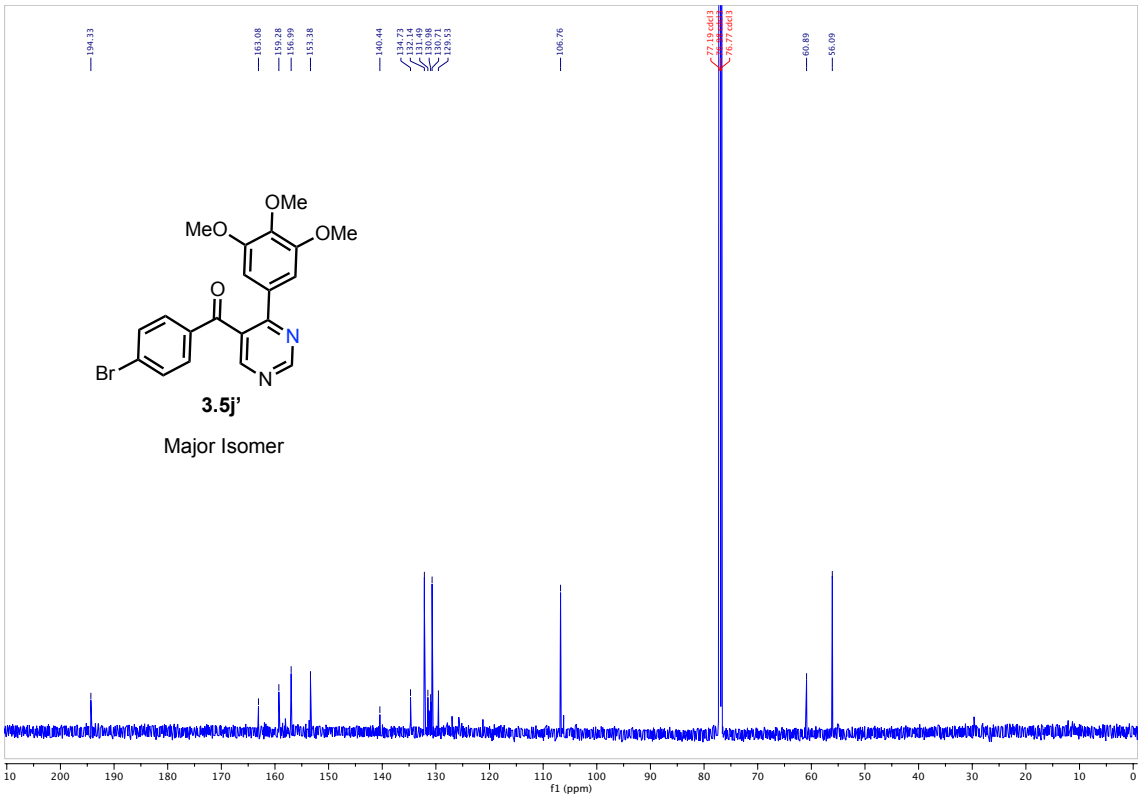

3.5h
1:1
3.5h'
74%
Inseperable by silica gel column chromatography
f1 (ppm)

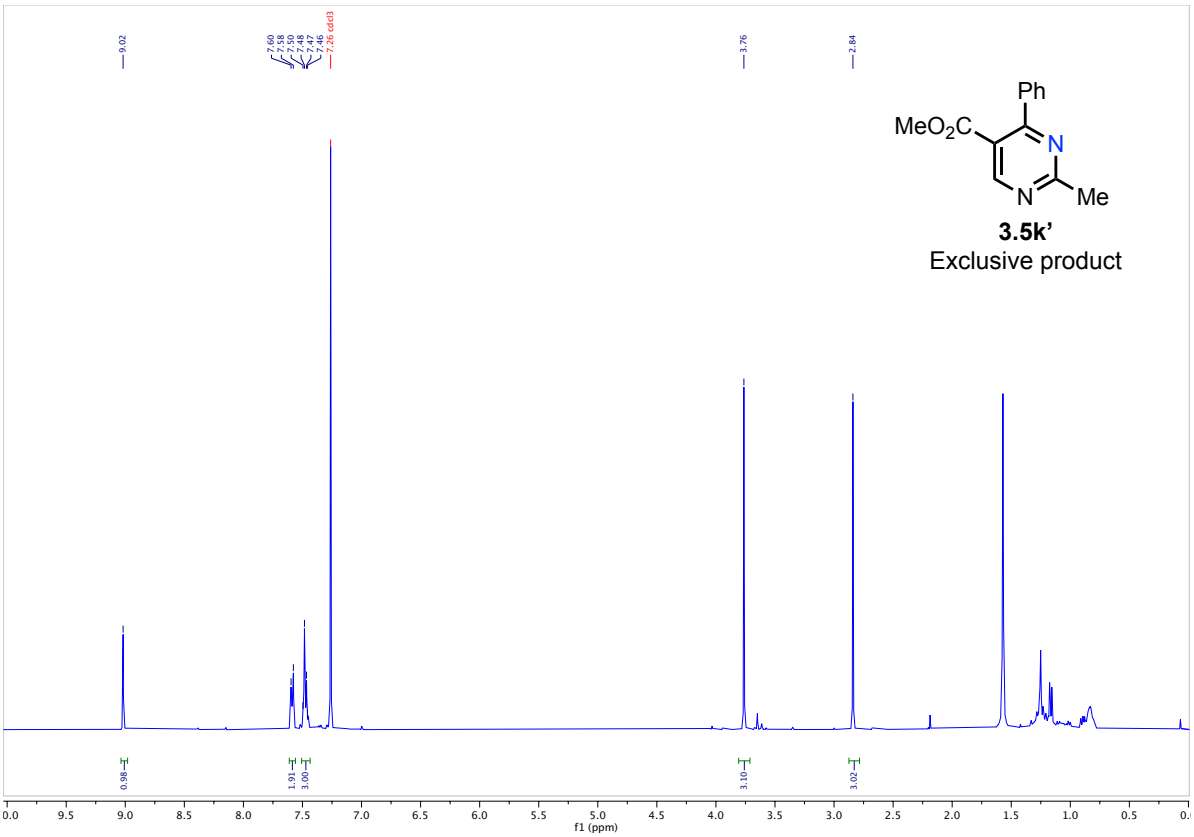

3.5h
1:1
3.5h'
74%
Inseperable by silica gel column chromatography
f1 (ppm)

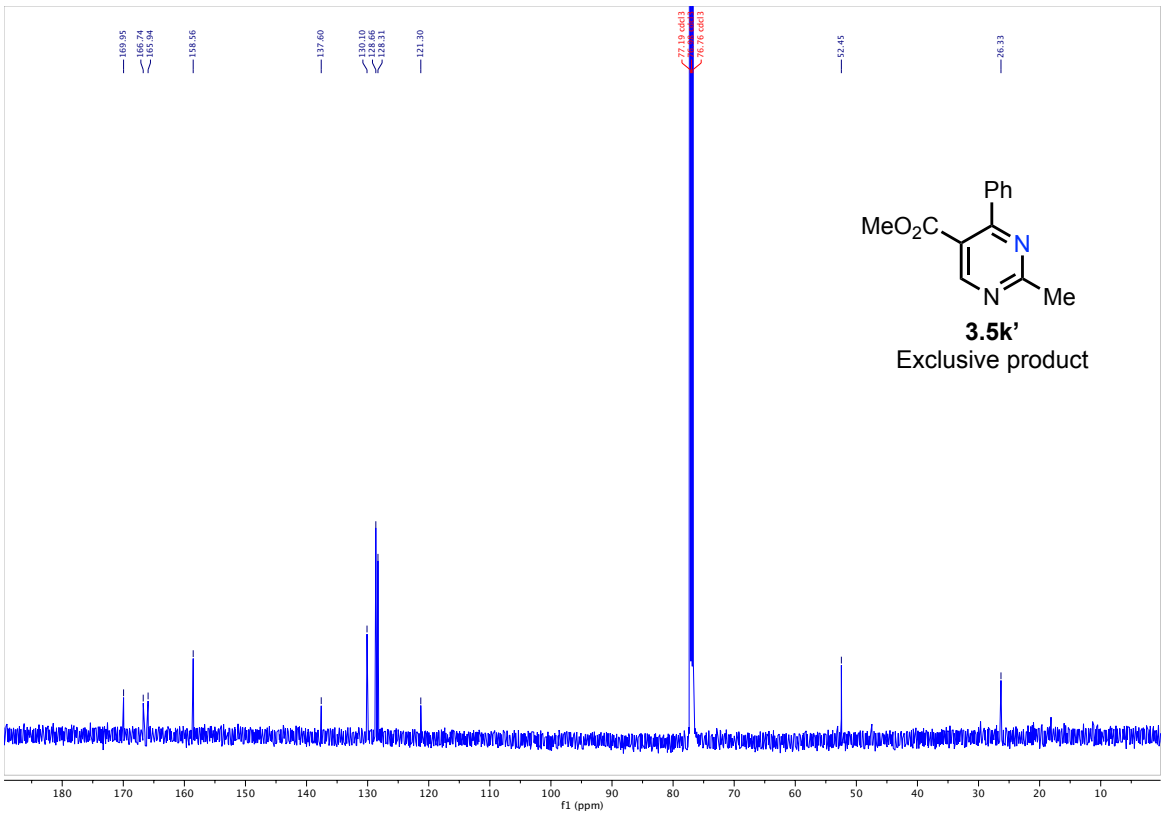

9.48
9.38
9.13
9.12
7.56
7.55
7.32
7.31
7.30
7.28
7.27
7.26 CDCl3
f1 (ppm)
F
O
O
F
CN
N
N
+
NC
3.5i
1:1.3
3.5i'
Inseperable by silica gel
column chromatography

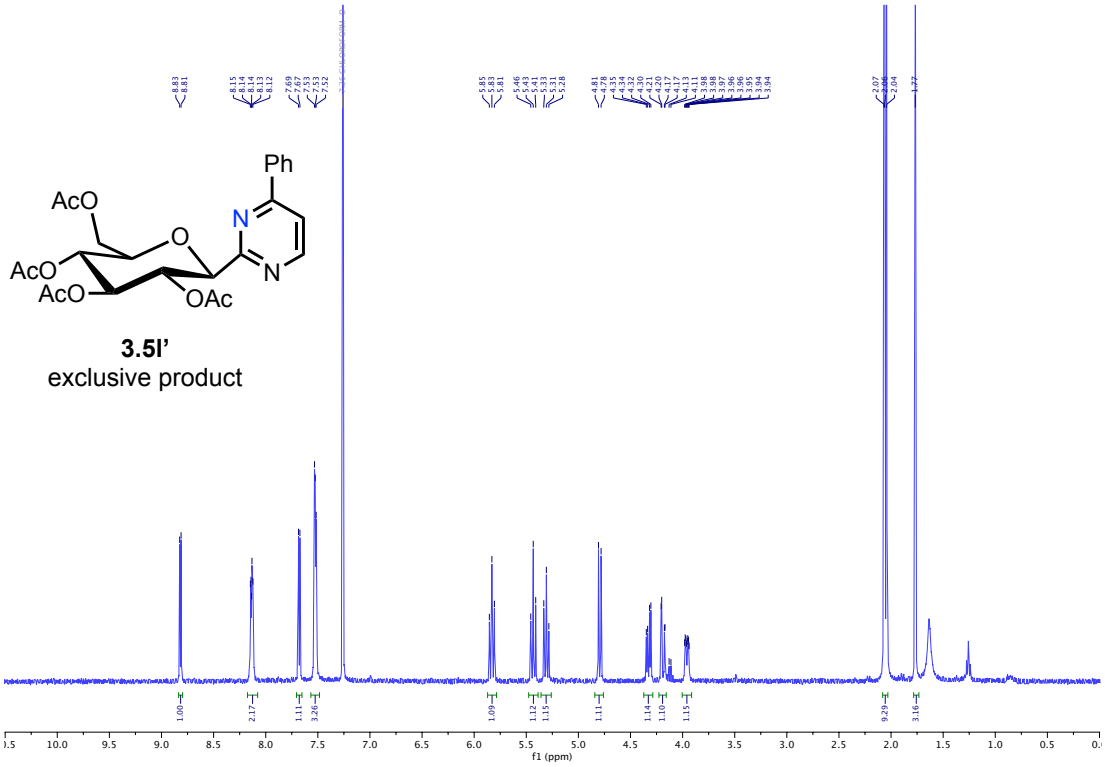

162.71
161.55
160.41
159.07
158.74
144.63
144.44
139.74
134.33
131.76
131.58
131.30
124.91
124.40
124.27
124.23
118.48
114.58
114.49
114.32
112.84
111.89
108.69
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
f1 (ppm)
F
O
O
F
CN
N
N
+
NC
3.5i
1:1.3
3.5i'
Inseperable by silica gel
column chromatography


OMe
MeO
OMe
O
N
Br
N
3.5j'
Major Isomer
f1 (ppm)

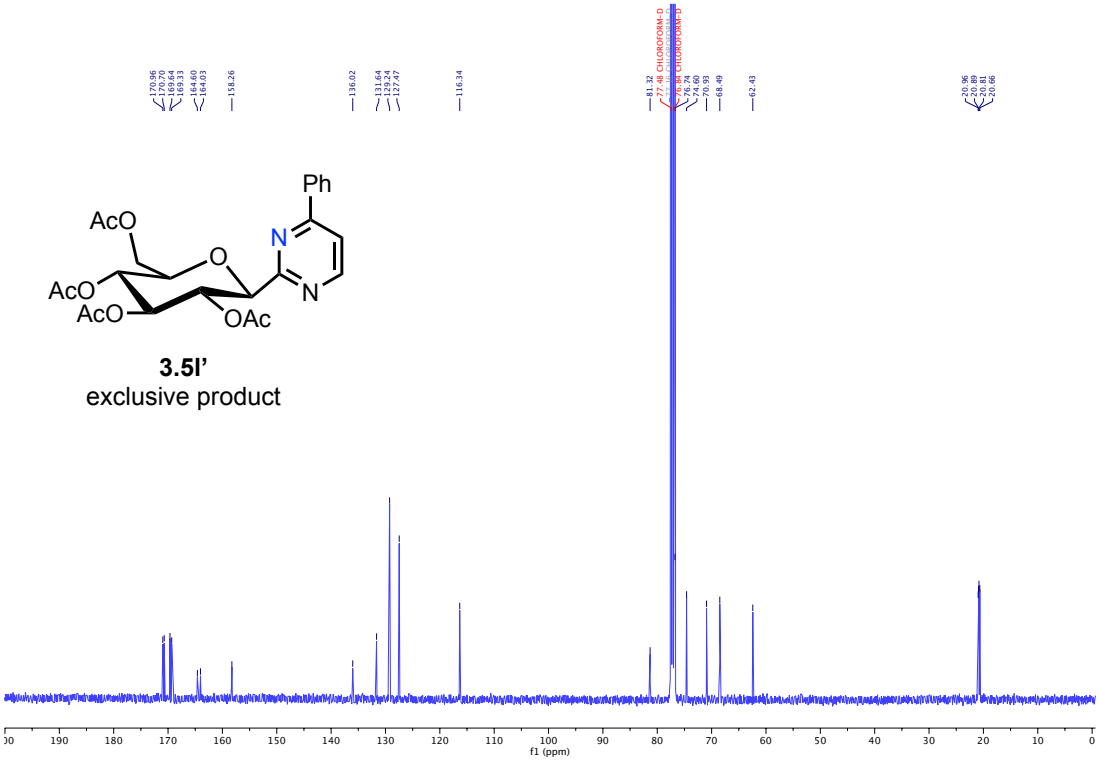

OMe
MeO
OMe
O
N
Br
N
3.5j'
Major Isomer
f1 (ppm)


9.02
7.60
7.58
7.55
7.48
7.47
7.46
7.26 cdcl3
3.76
2.84
0.98
1.91
3.00
3.10
3.02
f1 (ppm)
Ph
MeO2C
N
N
Me
3.5k'
Exclusive product

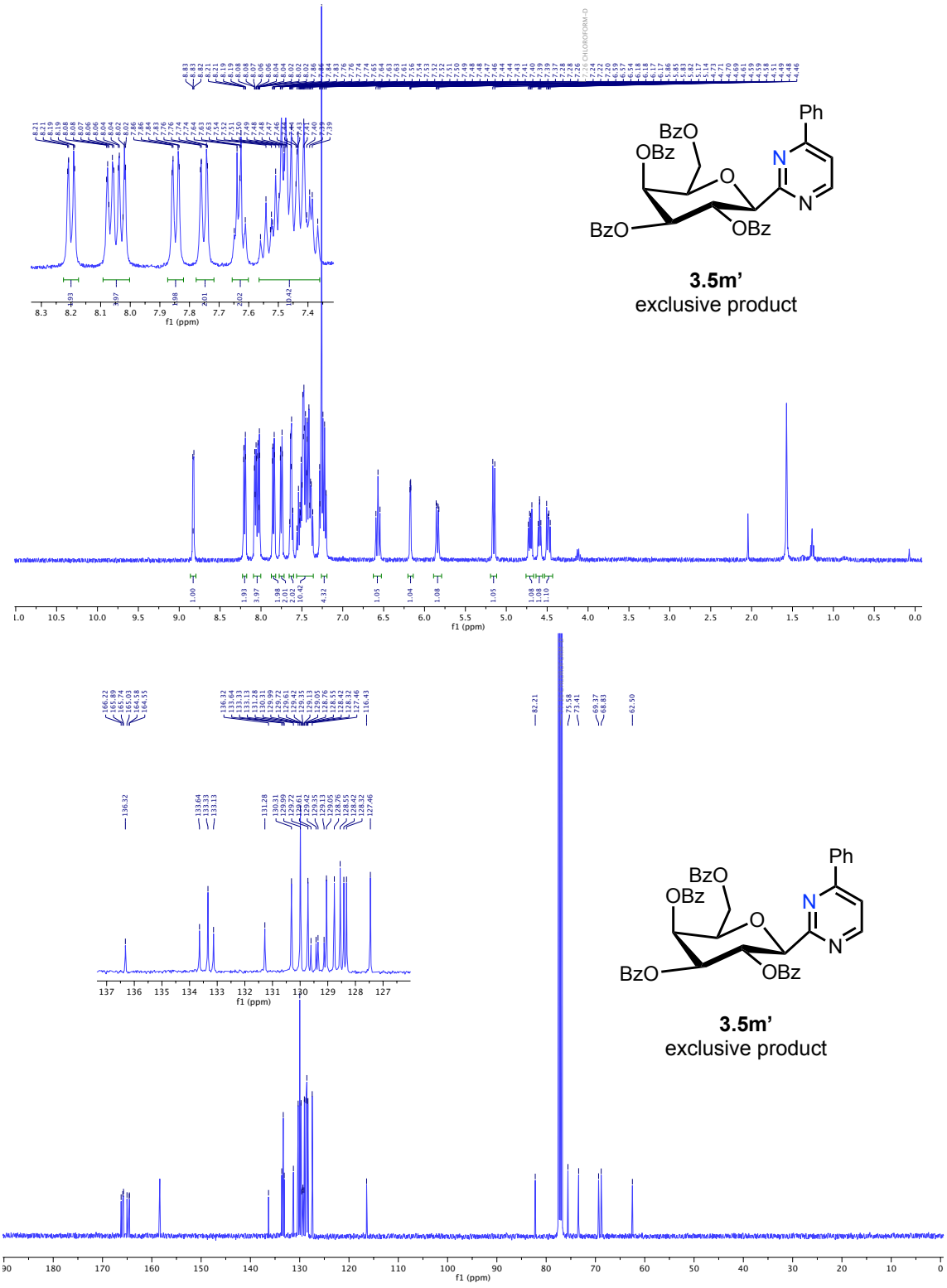

169.95
166.74
165.94
158.56
137.60
130.10
128.66
128.31
121.30
77.19 cdcl3
76.76 cdcl3
52.45
26.33
f1 (ppm)
Ph
MeO2C
N
N
Me
3.5k'
Exclusive product

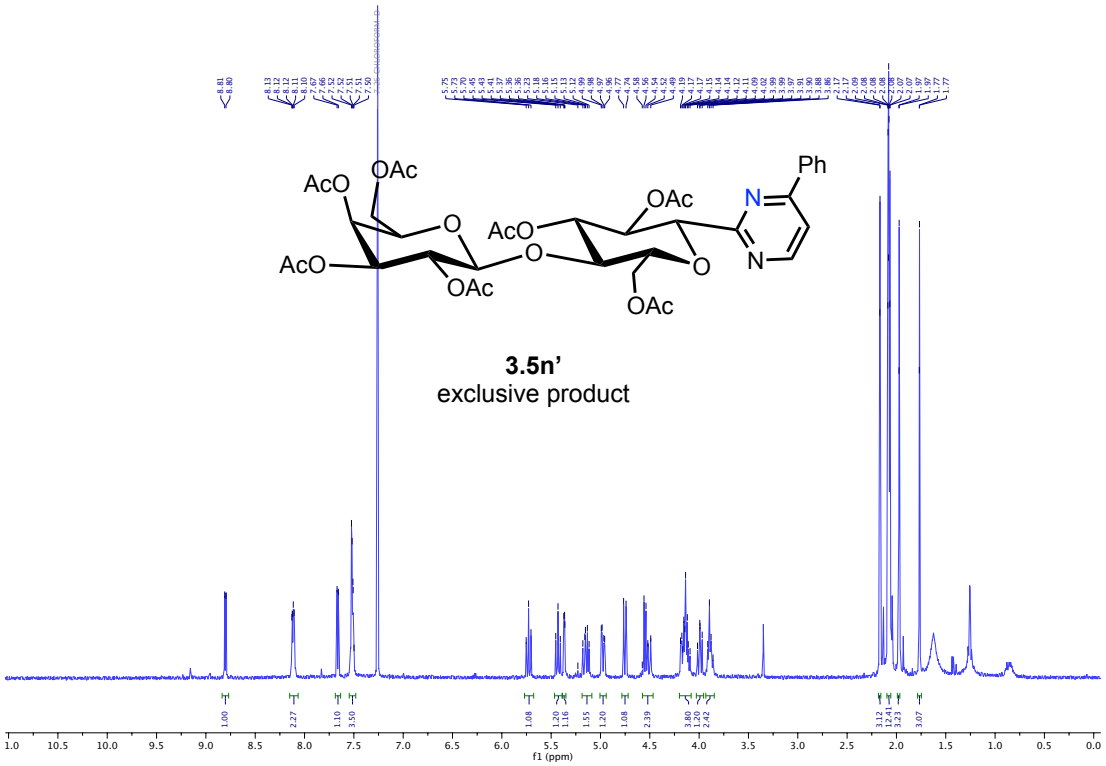


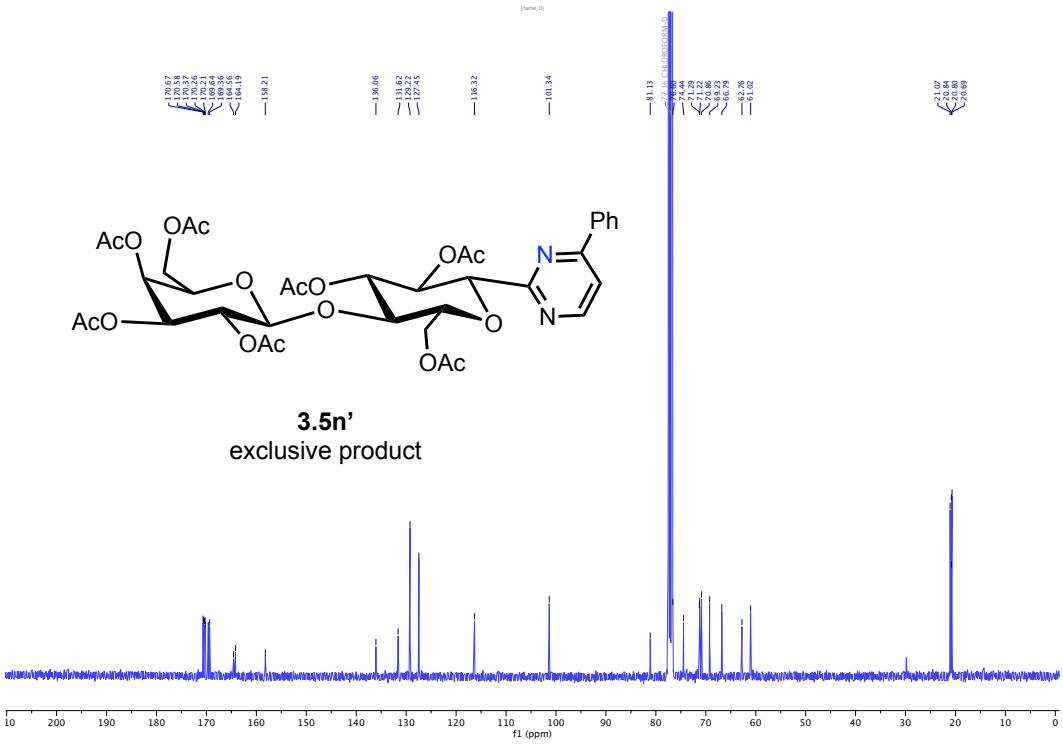
3.5l'
exclusive product

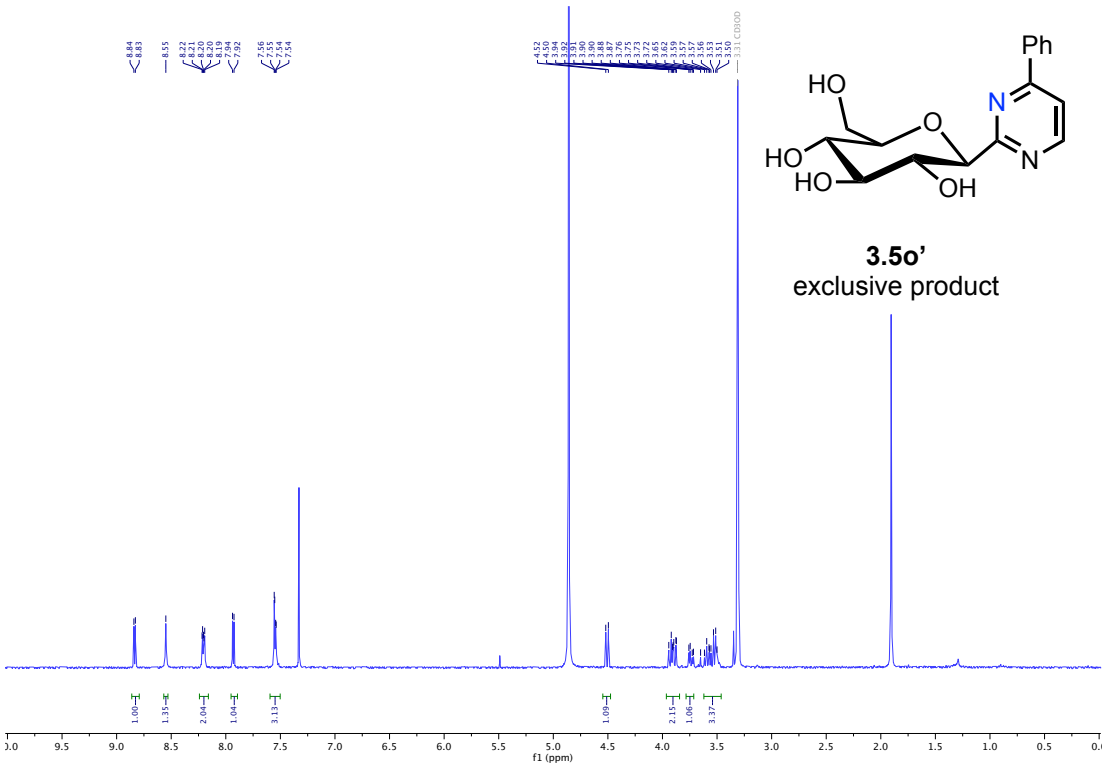


3.5l'
exclusive product

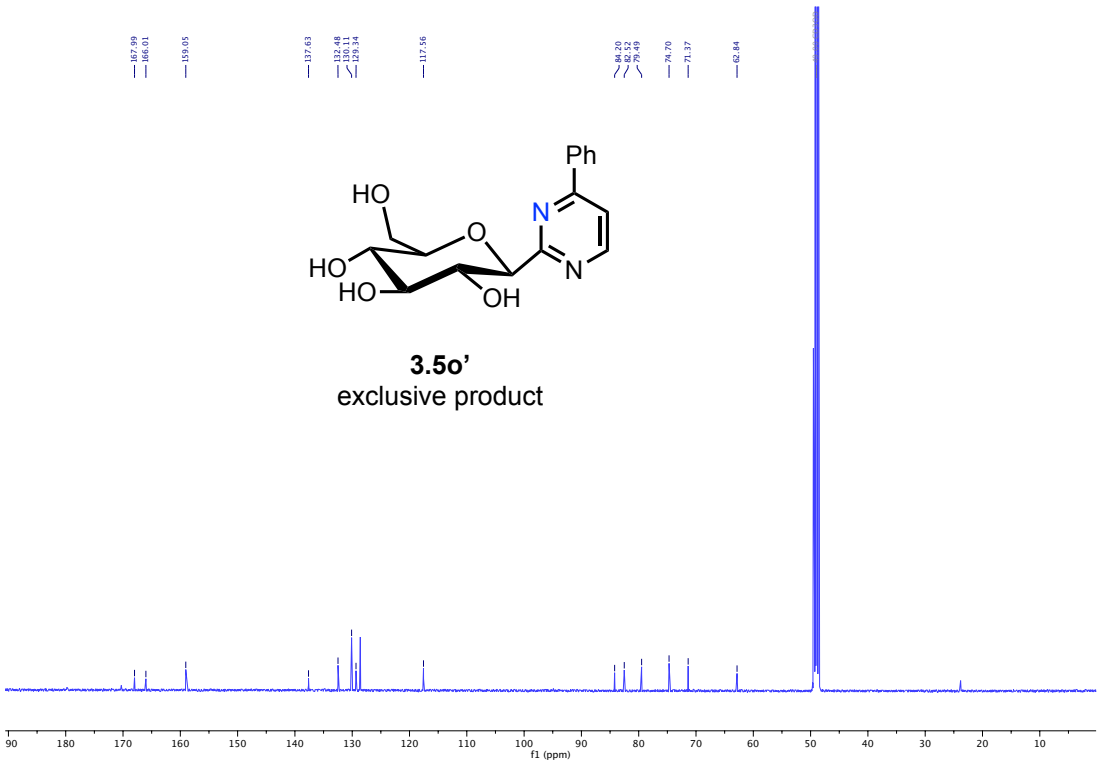

Ph
BzO
OBz
N
O
N
BzO
OBz
3.5m'
exclusive product
f1 (ppm)
Ph
BzO
OBz
N
O
N
BzO
OBz
3.5m'
exclusive product
f1 (ppm)


AcO
OAc
AcO
O
AcO
OAc
O
OAc
N
Ph
N
OAc
3.5n'
exclusive product
f1 (ppm)

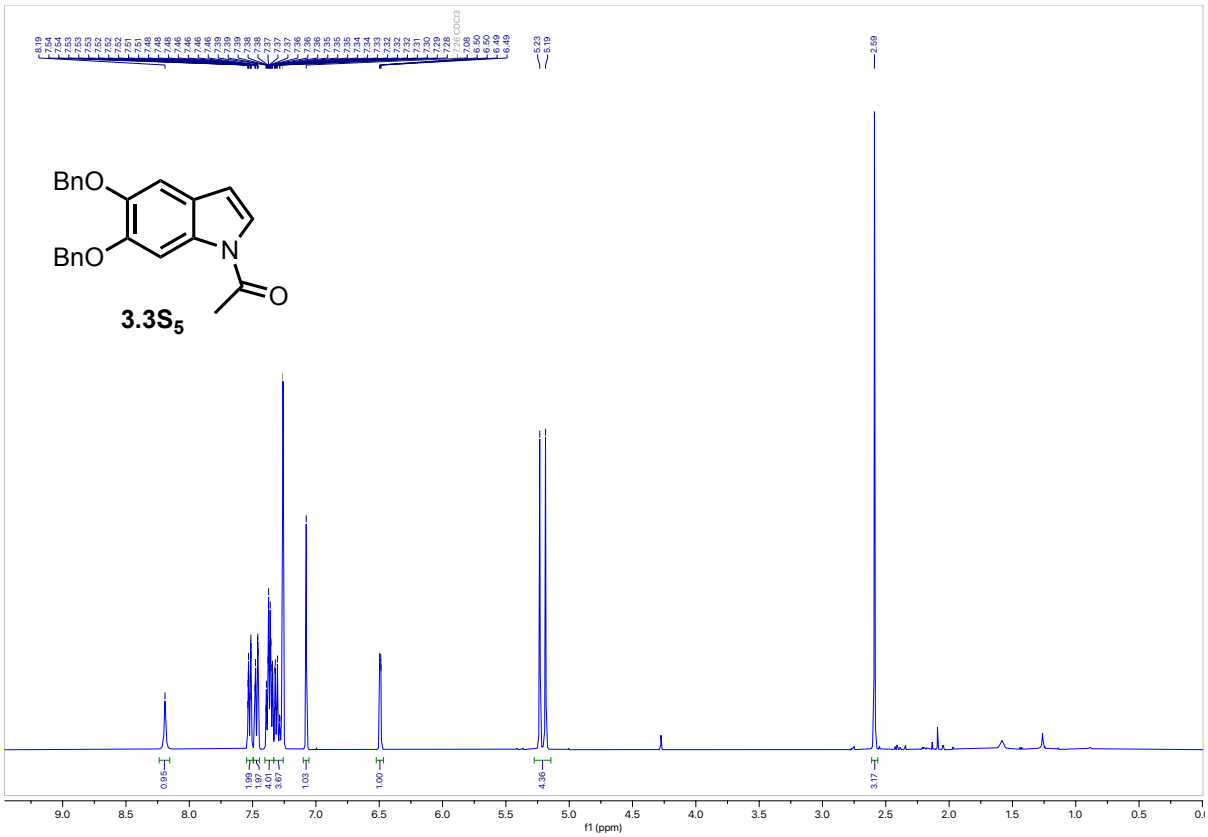

AcO
OAc
AcO
O
AcO
OAc
O
OAc
N
Ph
N
OAc
3.5n'
exclusive product
f1 (ppm)

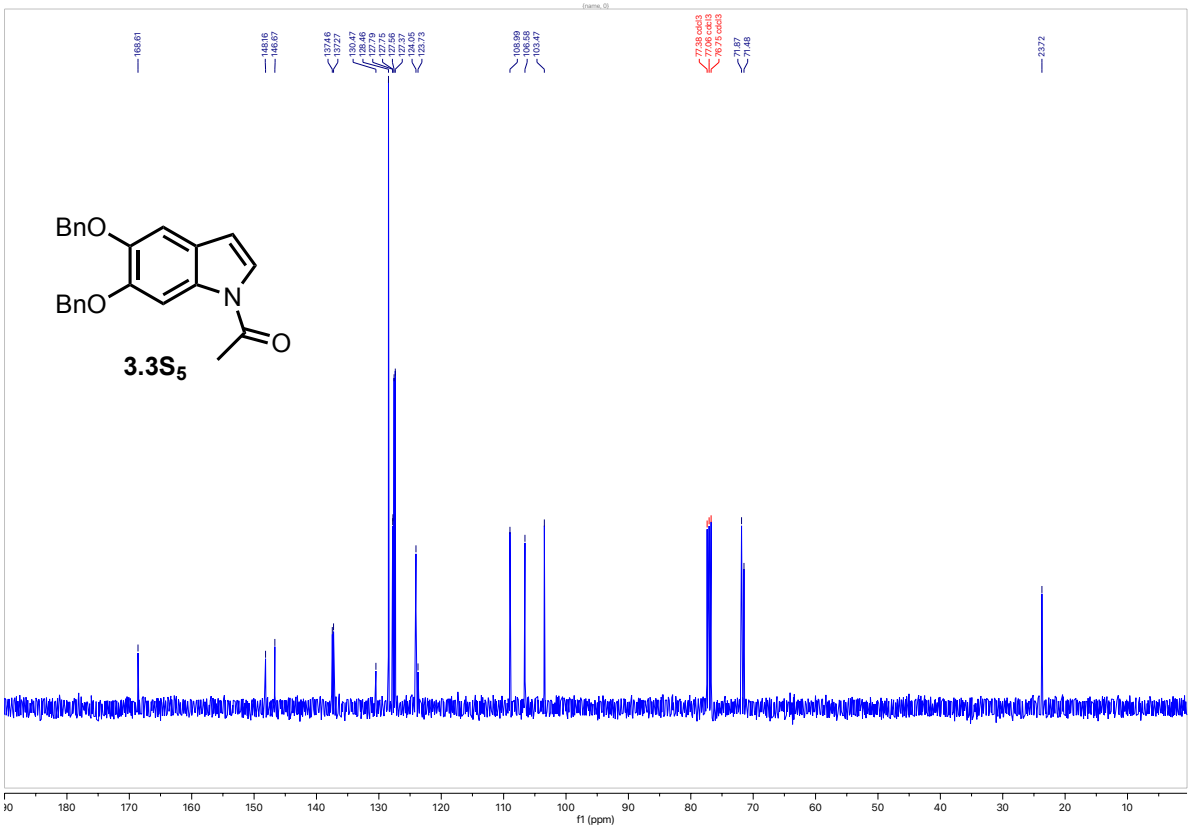


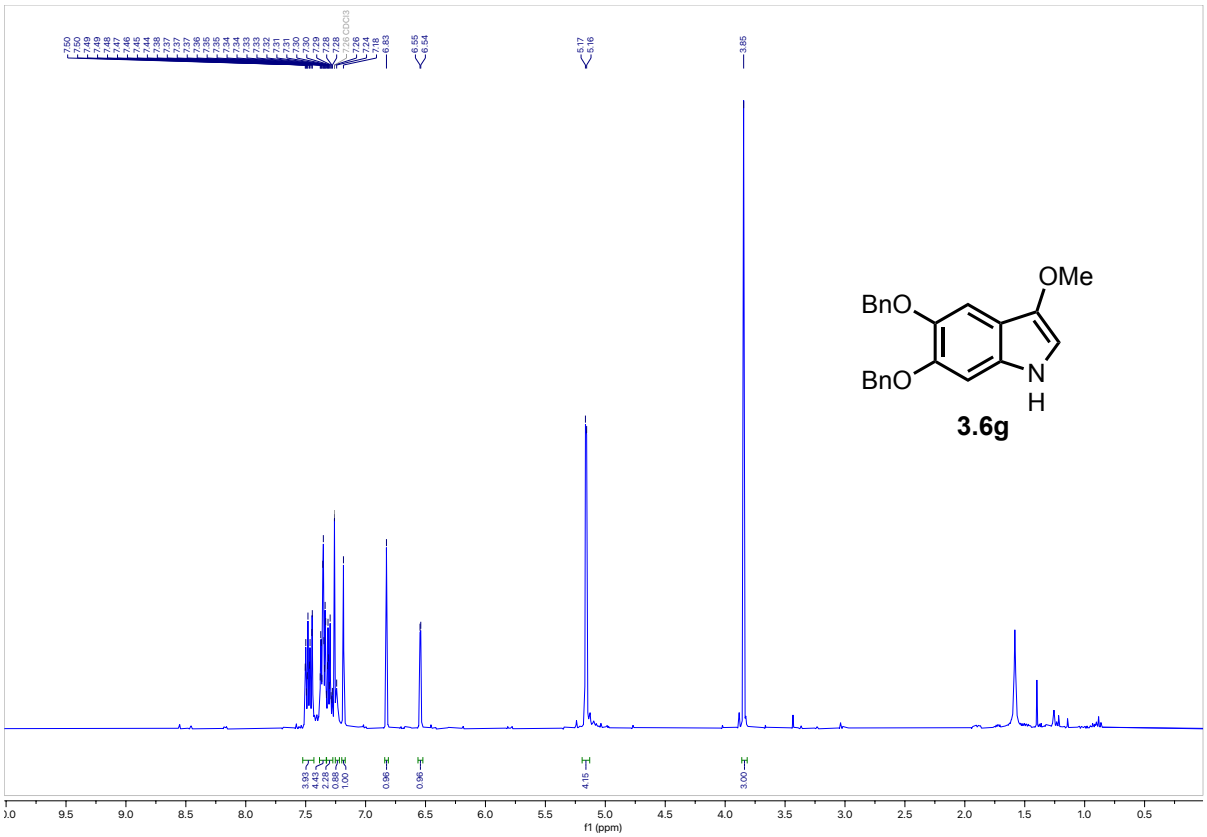
3.5o'
exclusive product

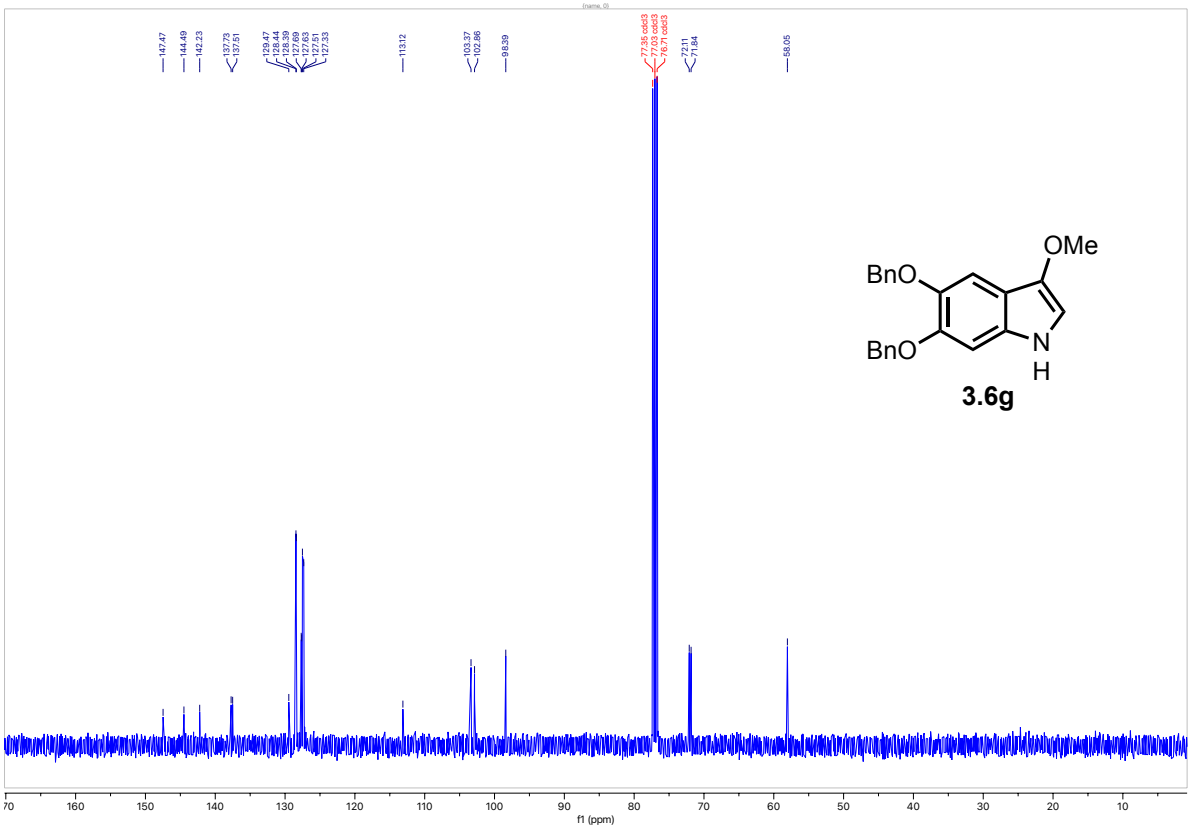


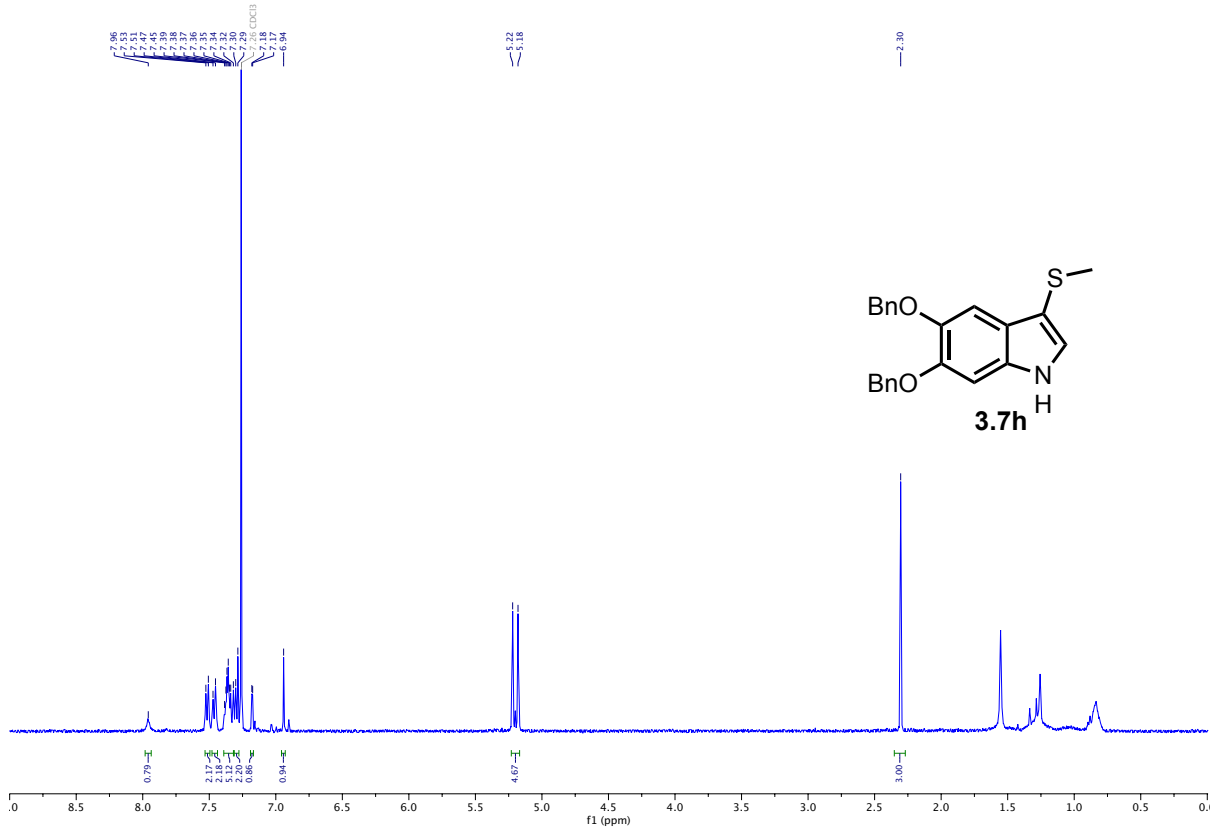
3.5o'
exclusive product

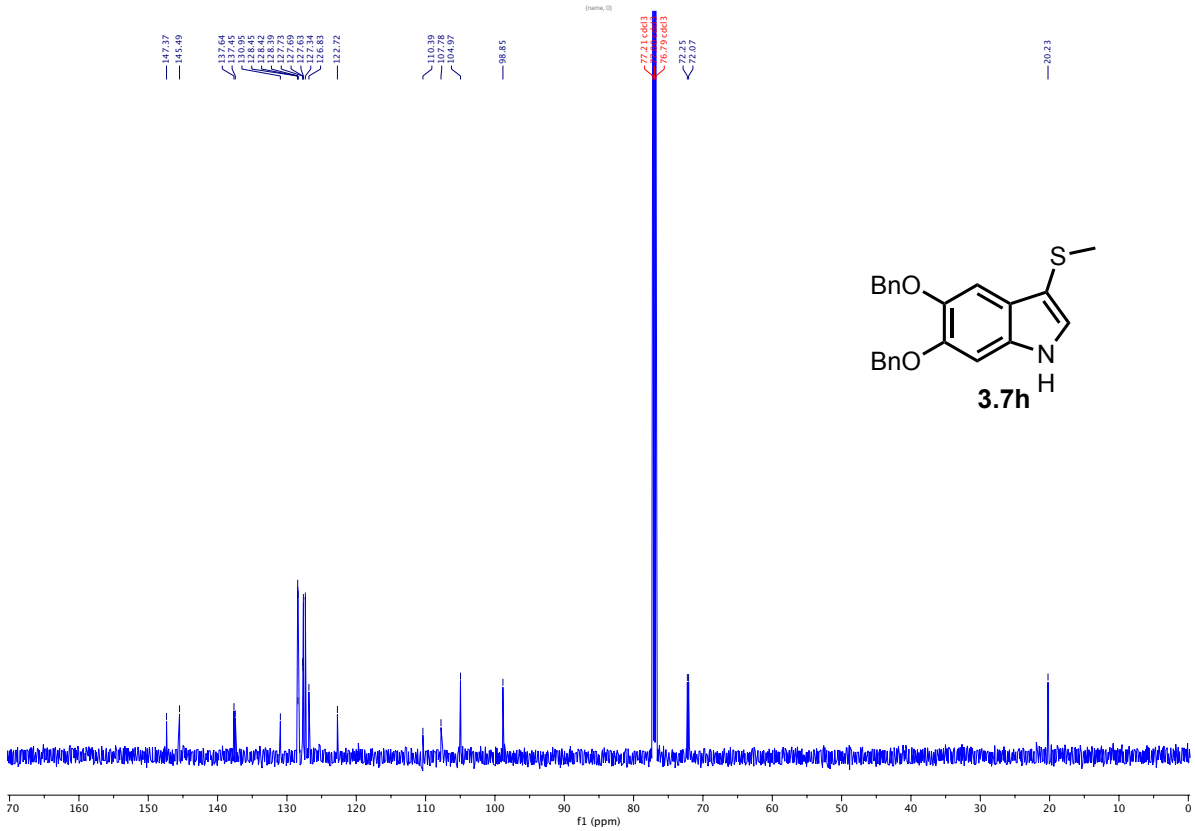

BnO
BnO
N
O
3.3S5
f1 (ppm)

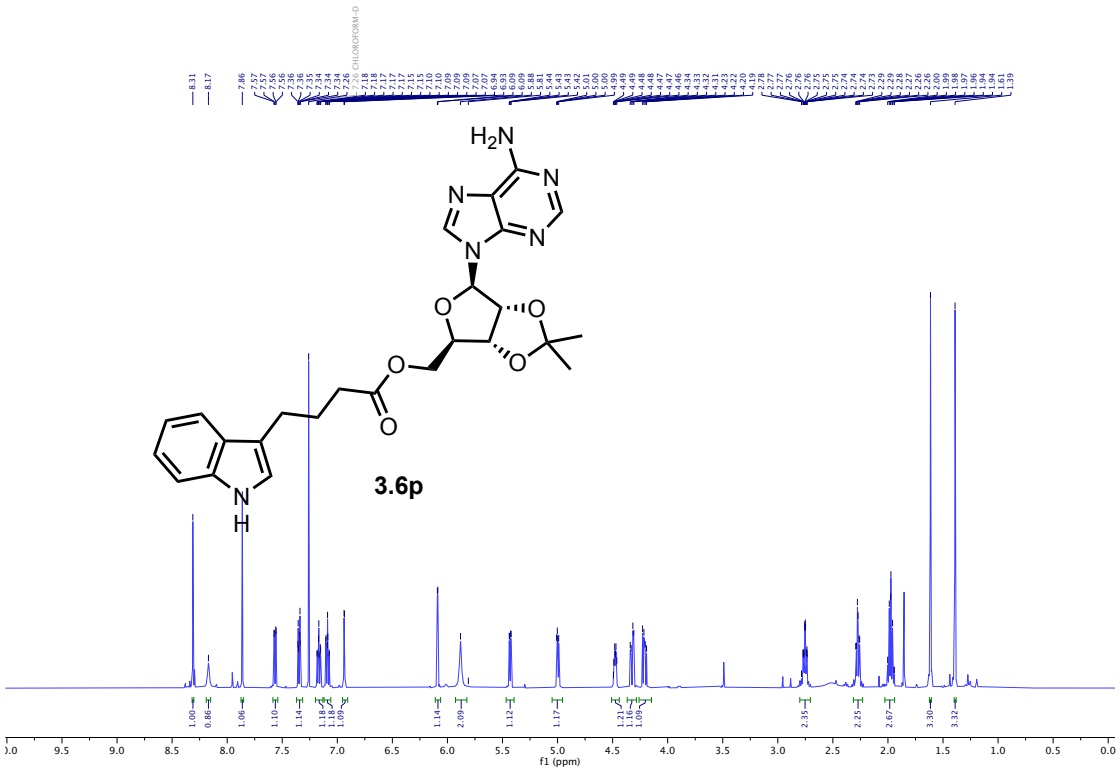

BnO
BnO
N
O
3.3S5
f1 (ppm)

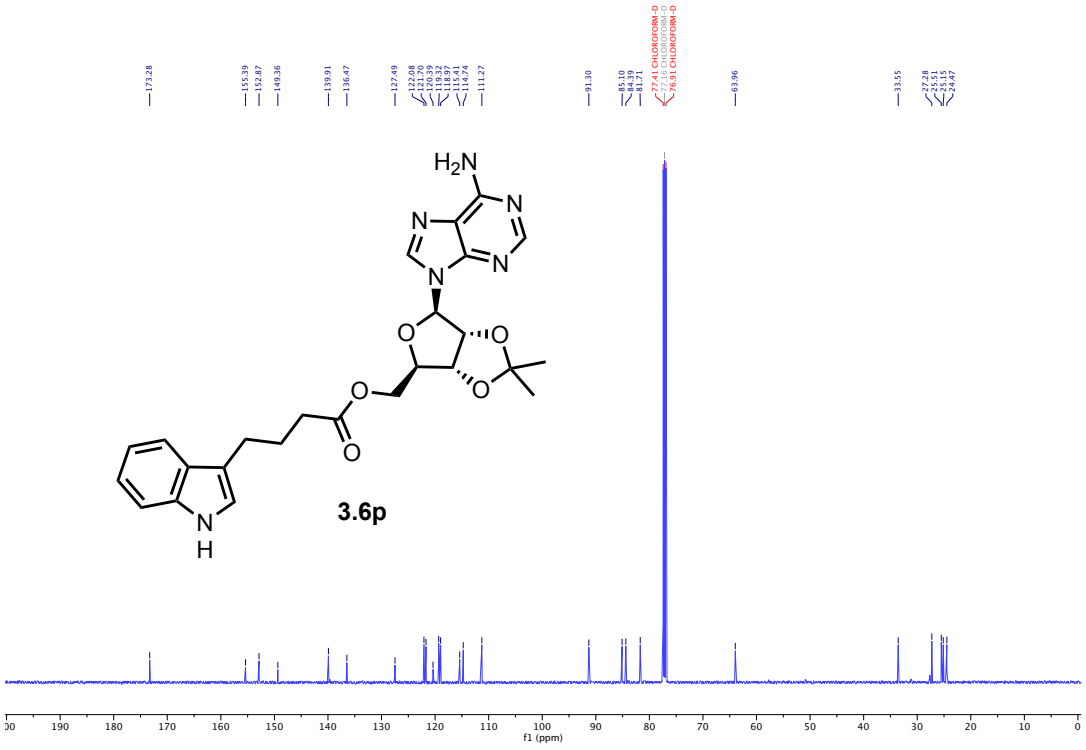

OMe
BnO
BnO
N
H
3.6g
f1 (ppm)

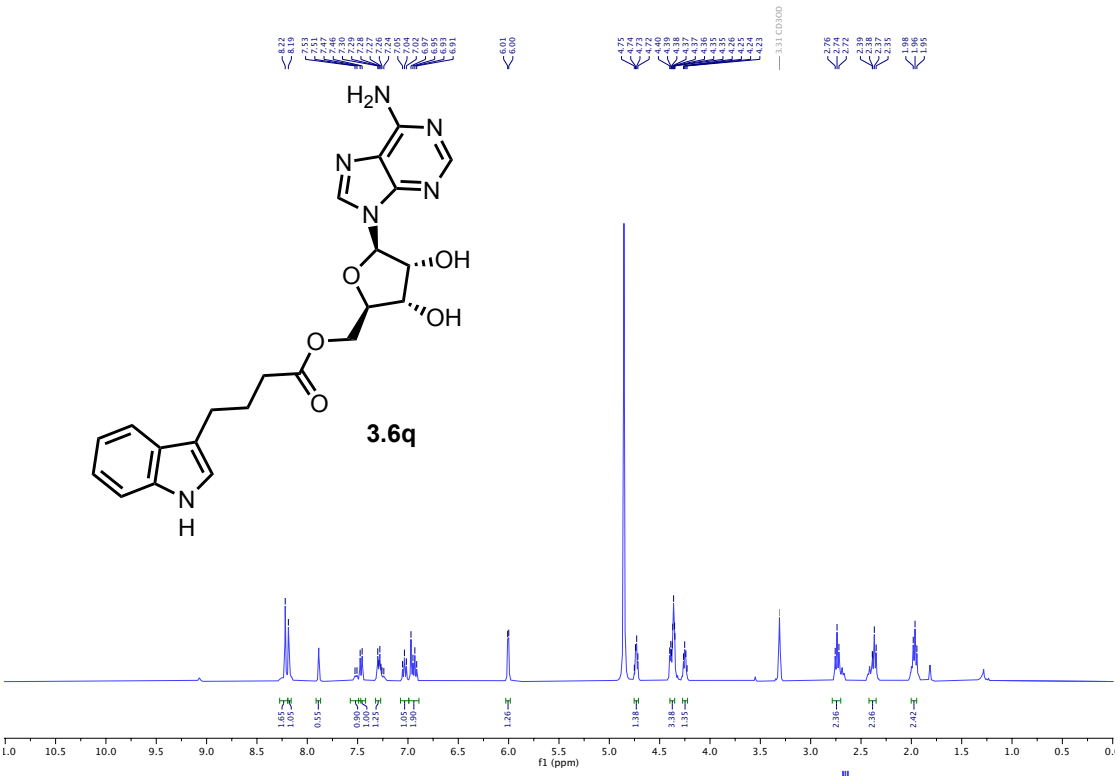

OMe
BnO
BnO
N
H
3.6g
f1 (ppm)

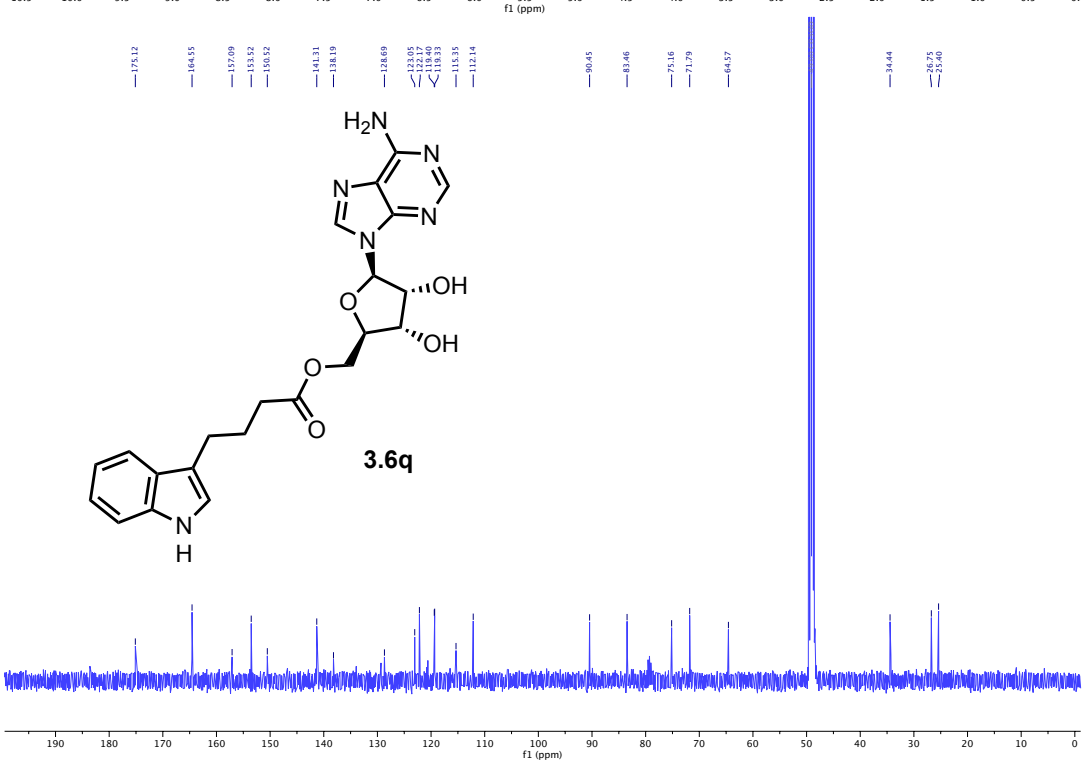

BnO
BnO
S
N
H
3.7h
f1 (ppm)

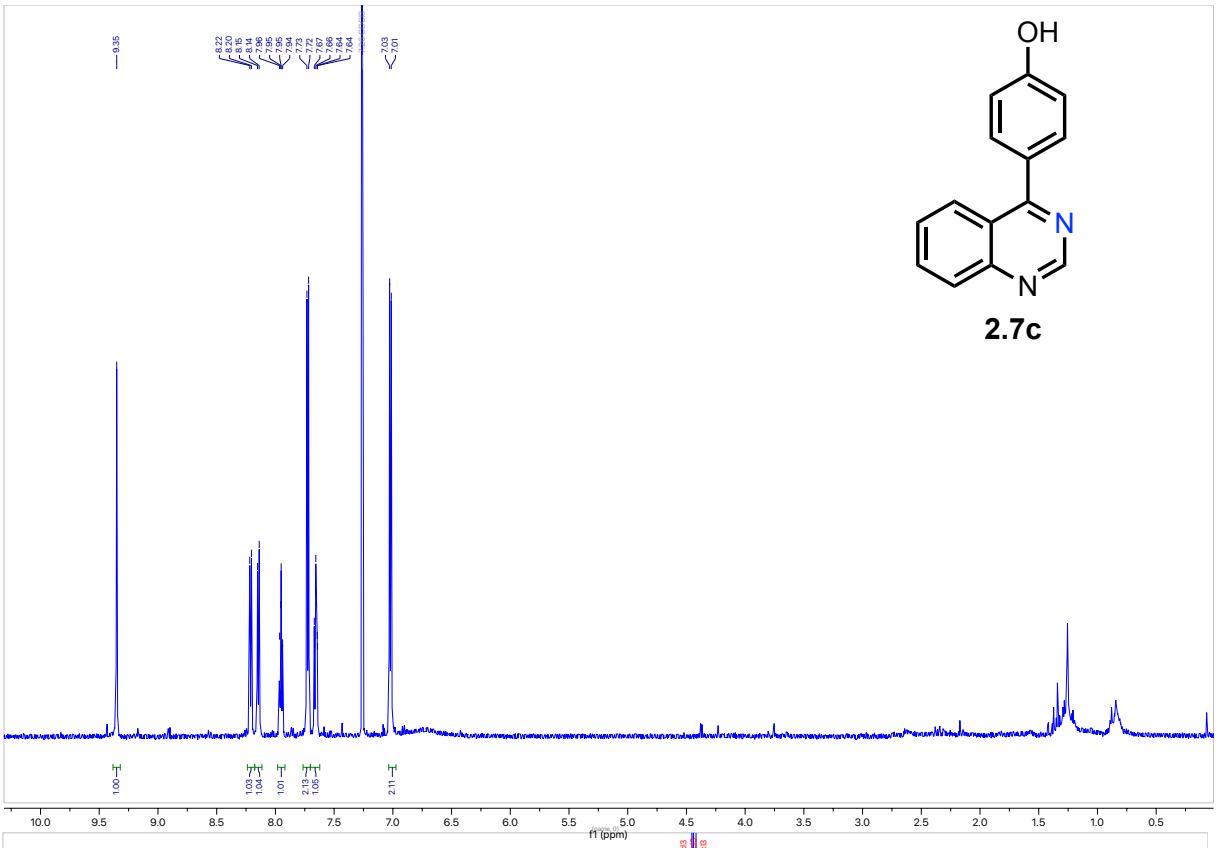

BnO
BnO
S
N
H
3.7h
f1 (ppm)

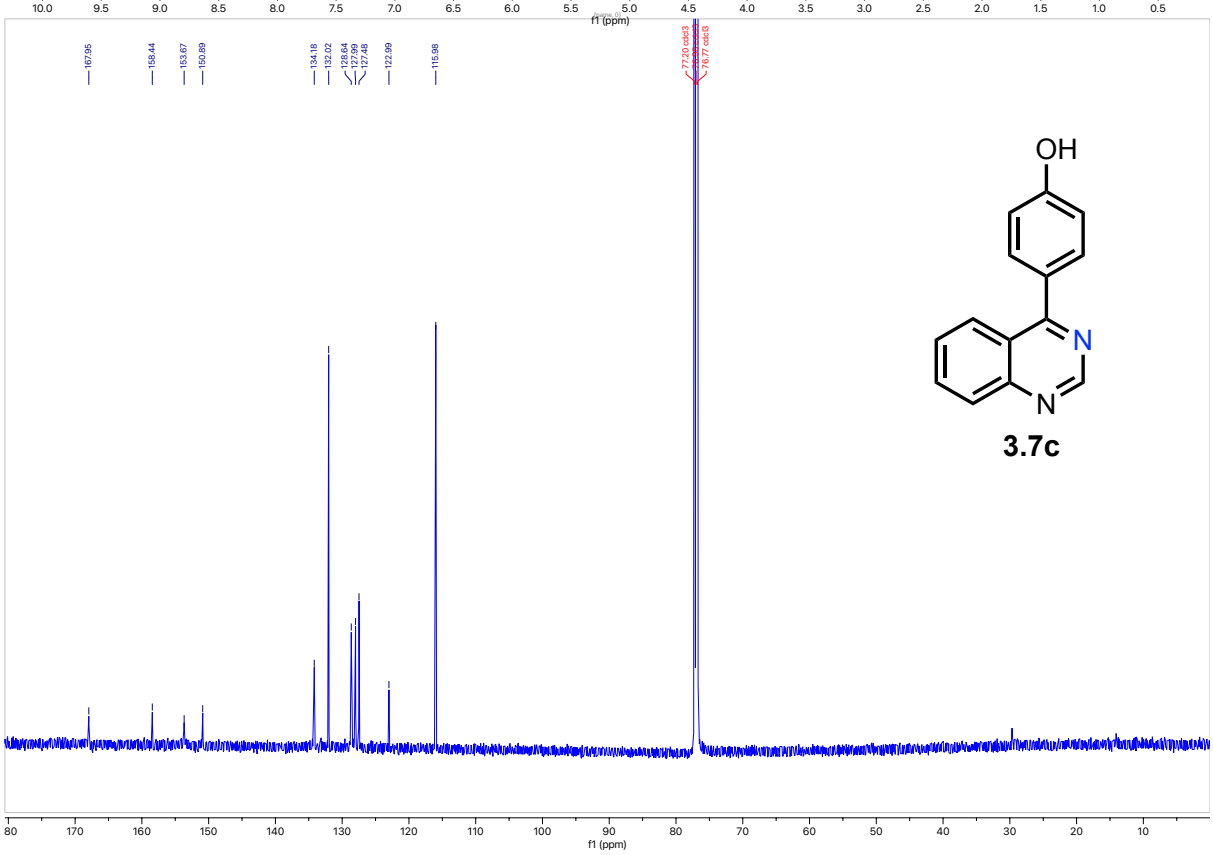

3.6p
f1 (ppm)

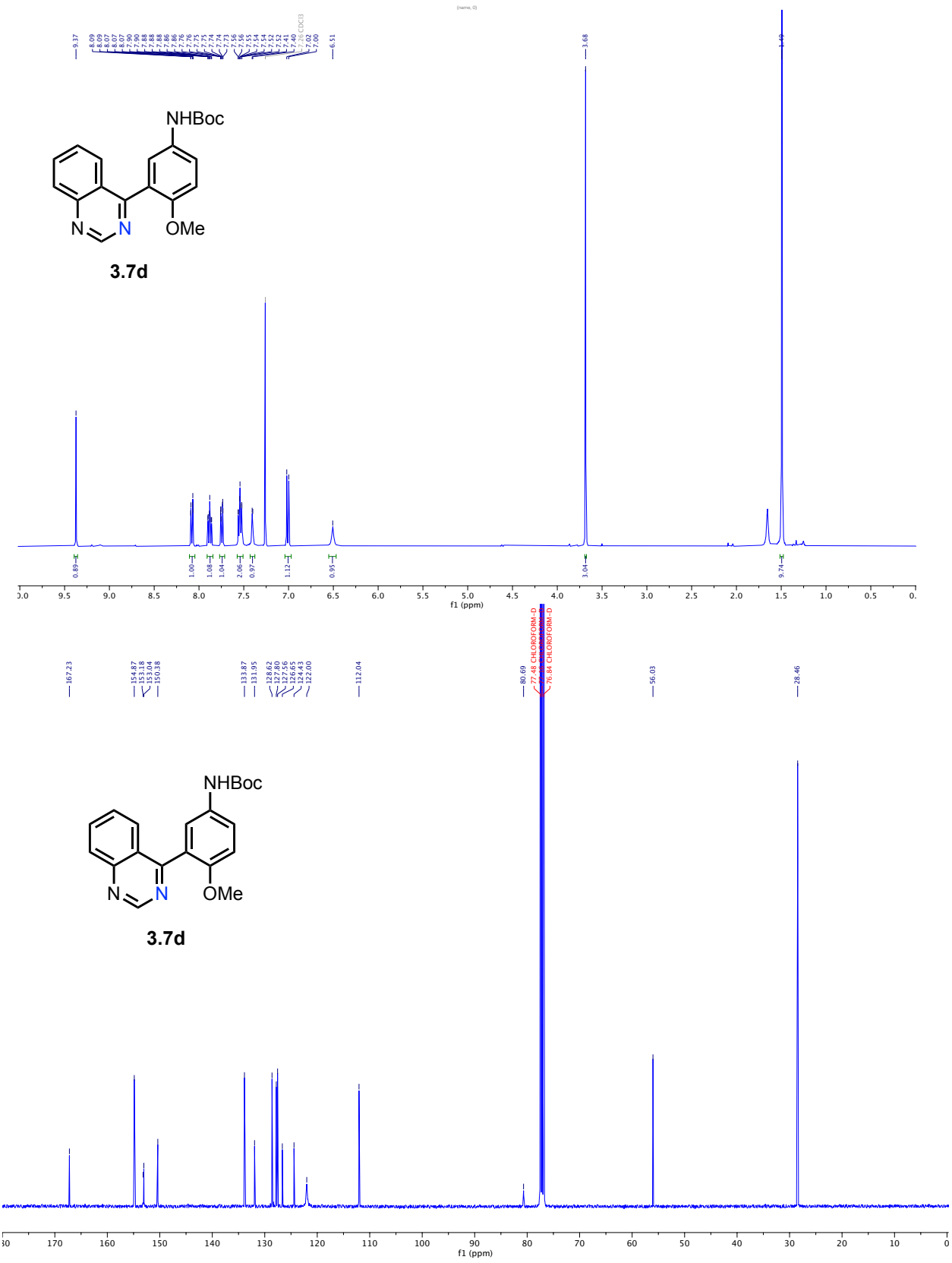

3.6p
f1 (ppm)

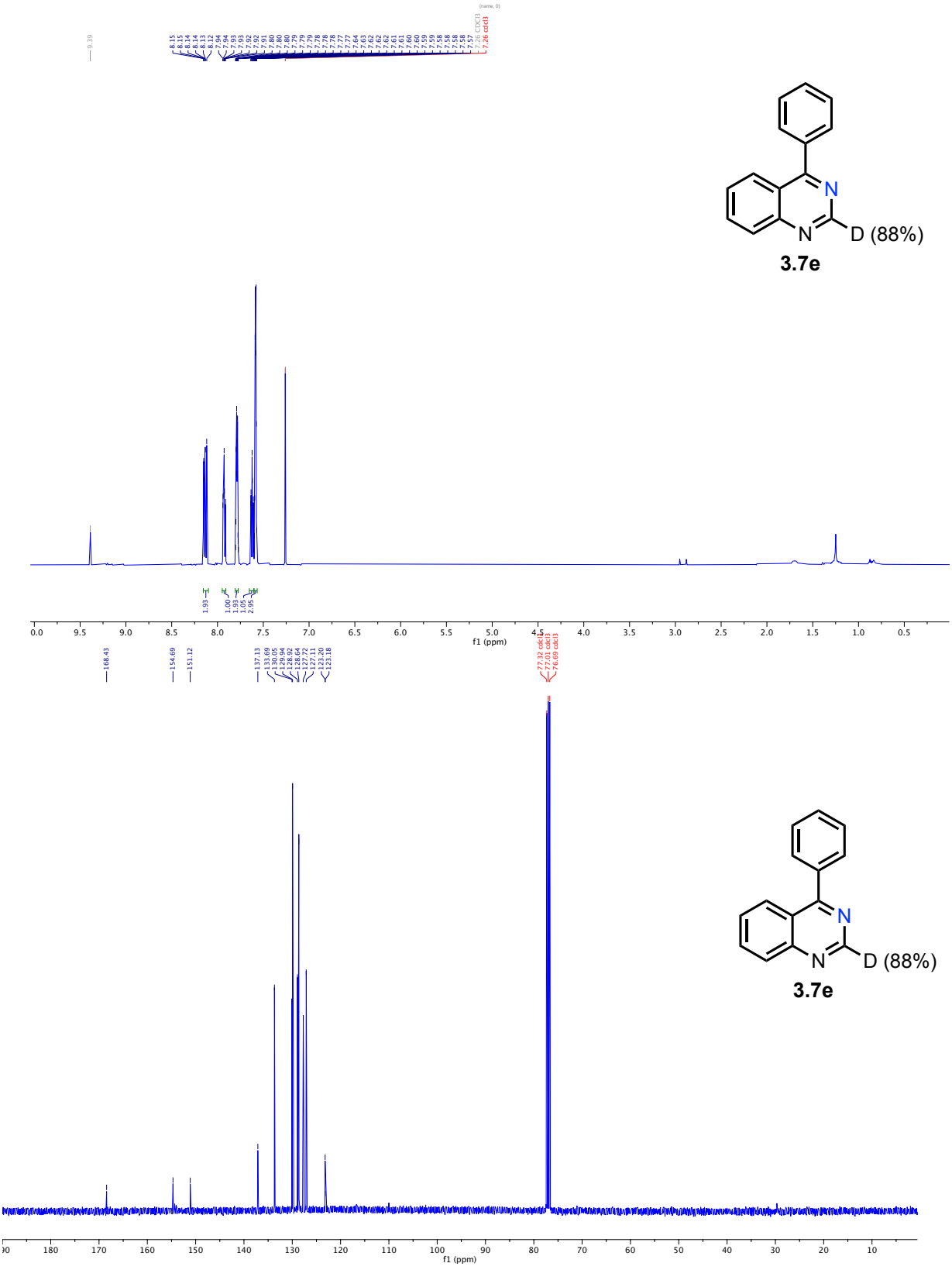

3.6q
f1 (ppm)

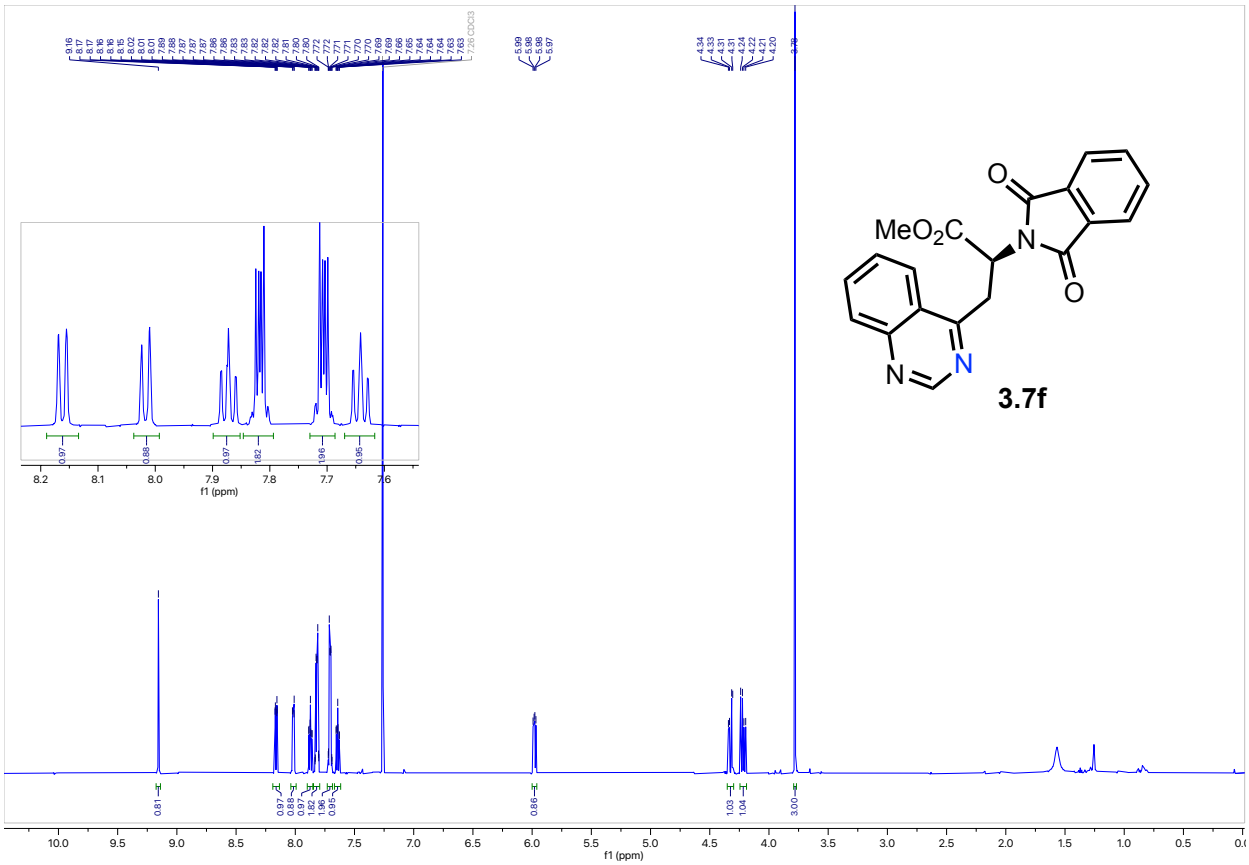

3.6q
f1 (ppm)

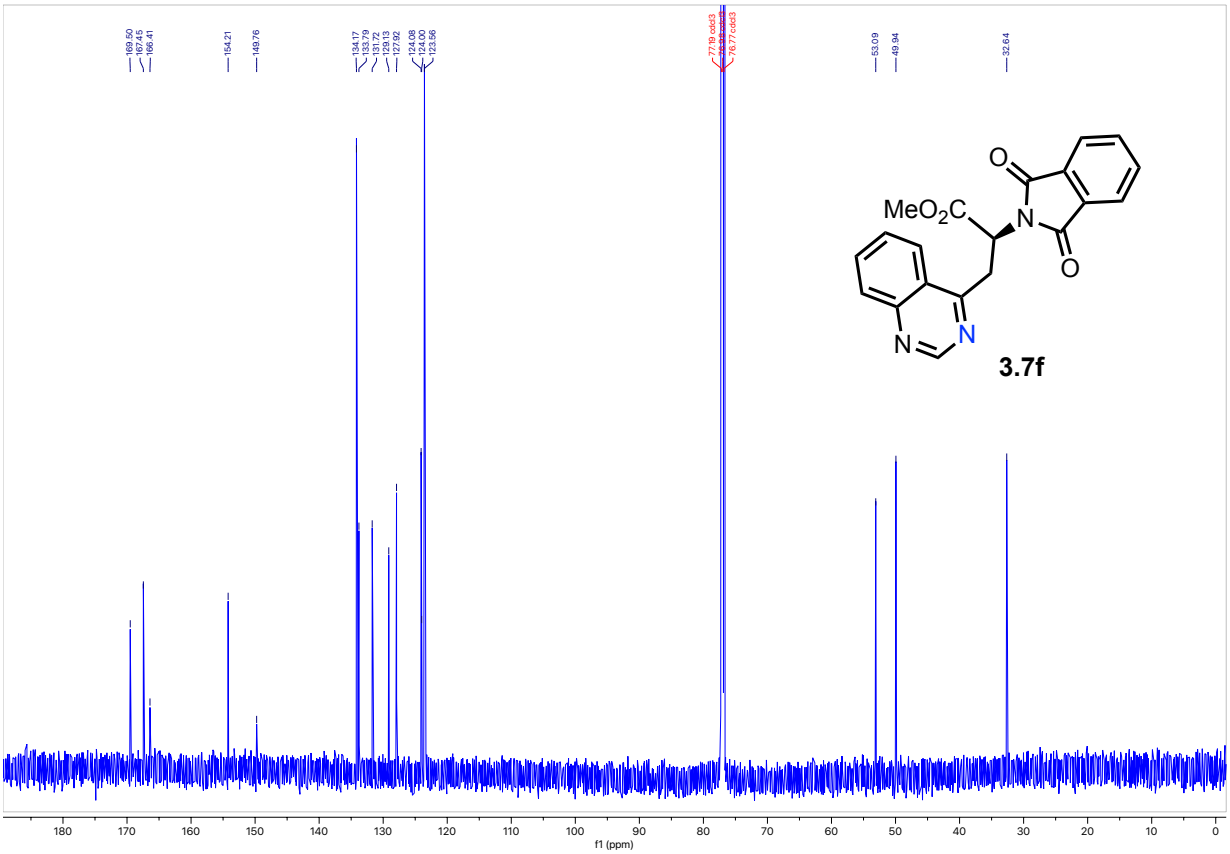

OH
N
N
2.7c
f1 (ppm)

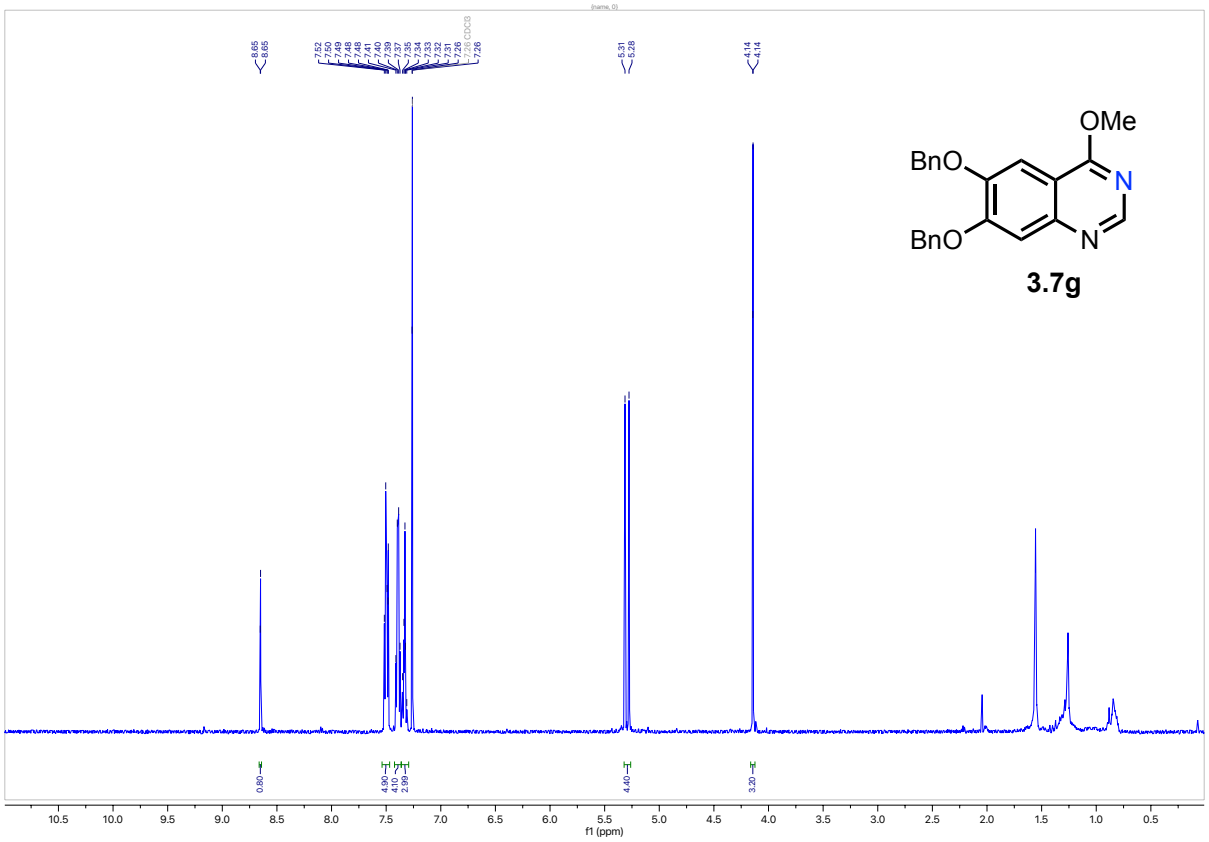

OH
N
N
3.7c
f1 (ppm)

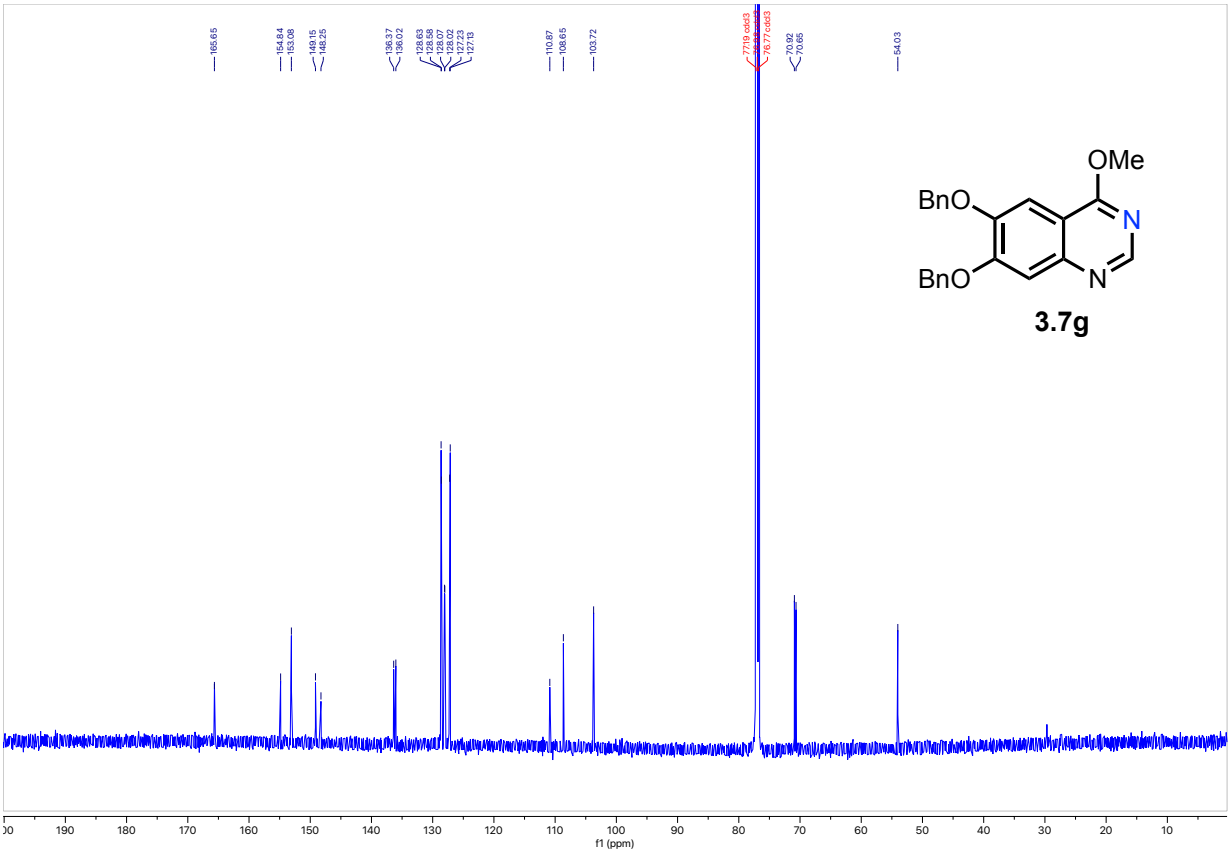

NHBoc
N
N
OMe
3.7d
f1 (ppm)
NHBoc
N
N
OMe
3.7d
f1 (ppm)

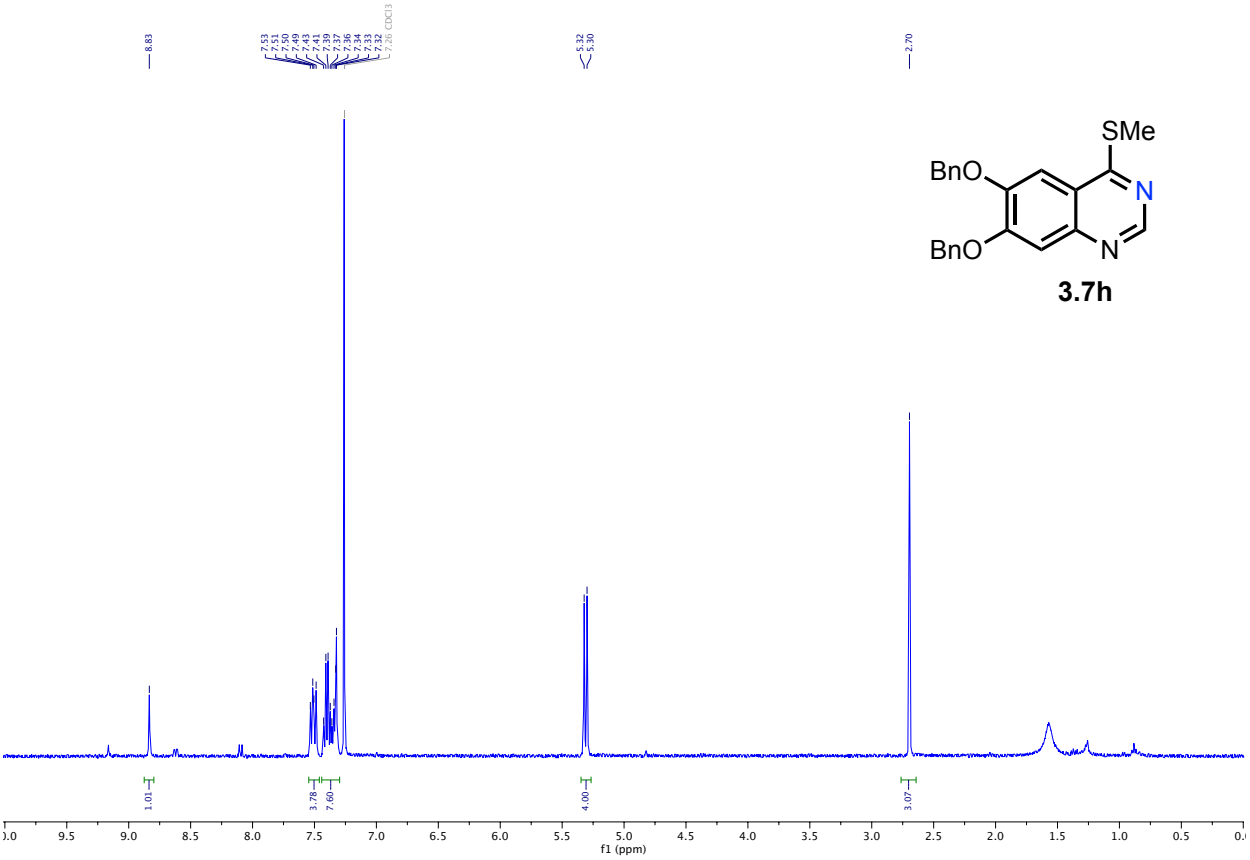

N
N
D (88%)
3.7e
f1 (ppm)
N
N
D (88%)
3.7e
f1 (ppm)

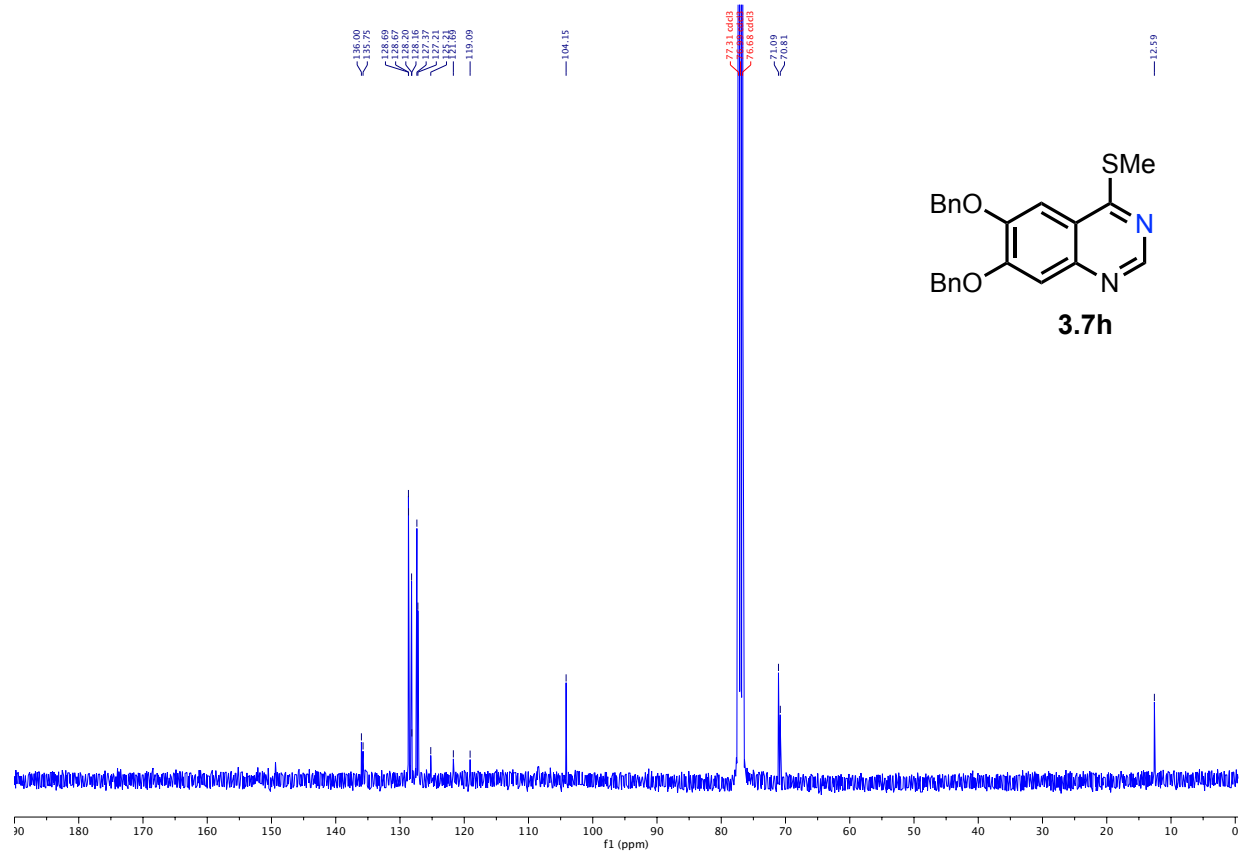

MeO2C
O
N
O
N
N
3.7f
f1 (ppm)

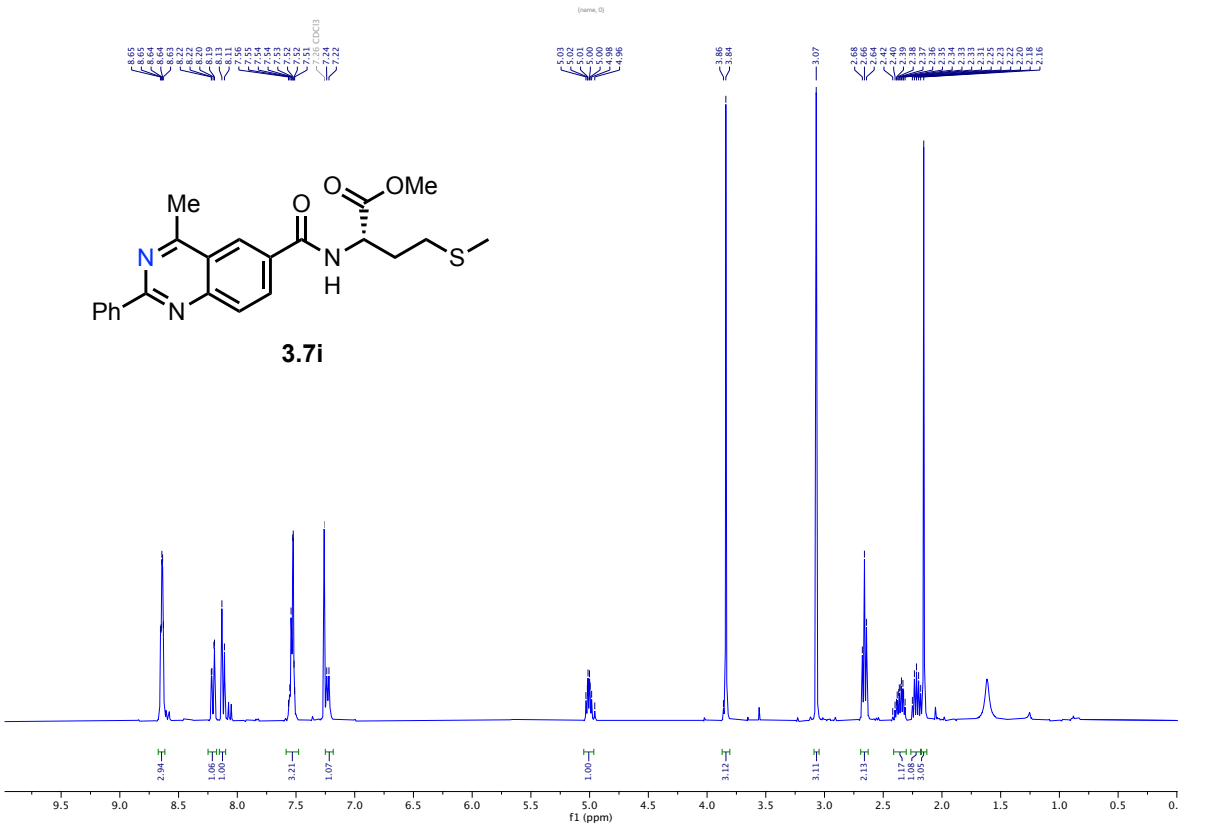

MeO2C
O
N
O
N
N
3.7f
f1 (ppm)


OMe
BnO
BnO
N
N
3.7g
f1 (ppm)

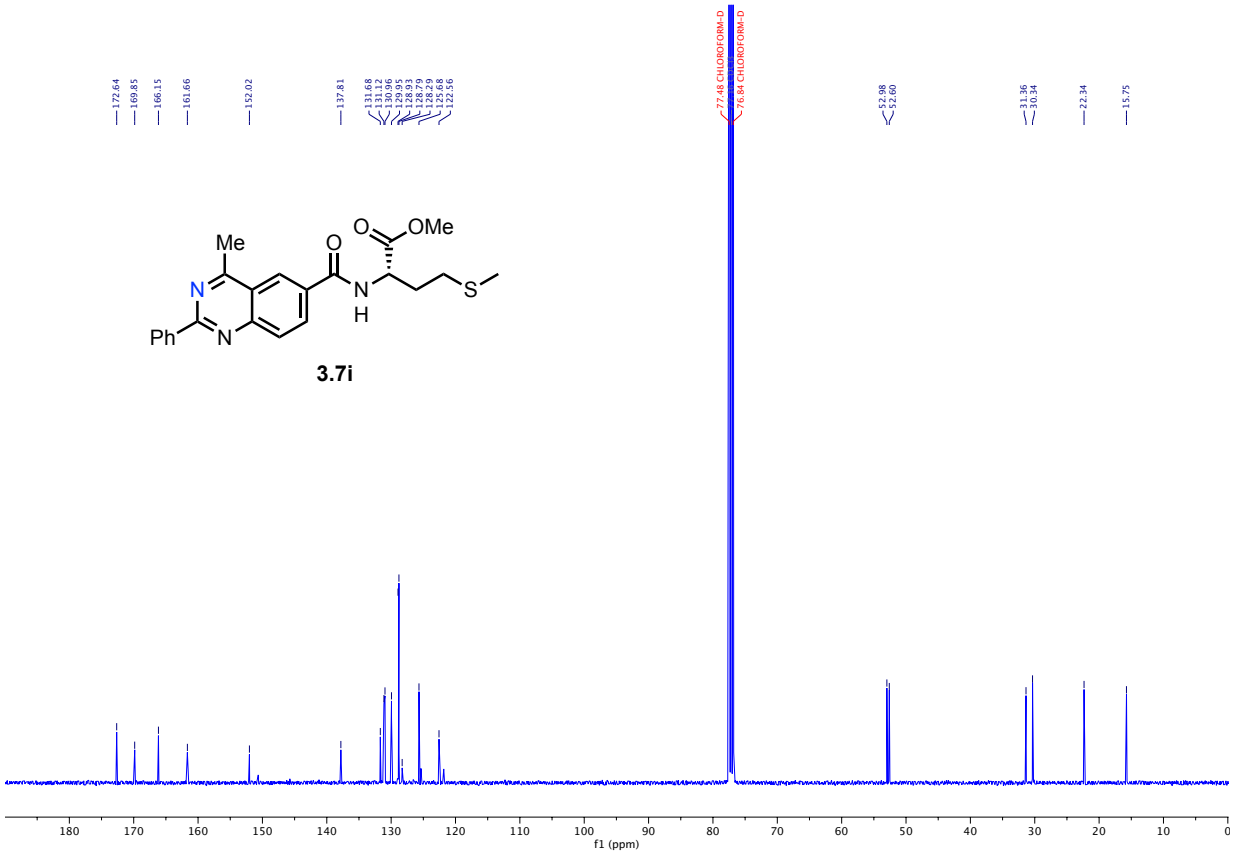

OMe
BnO
BnO
N
N
3.7g
f1 (ppm)


8.83
7.53
7.51
7.50
7.49
7.43
7.41
7.39
7.37
7.36
7.34
7.33
7.32
7.26 CDCl3
5.32
5.30
2.70
SMe
BnO
BnO
N
N
3.7h
1.01
3.78
7.60
4.00
3.07
f1 (ppm)

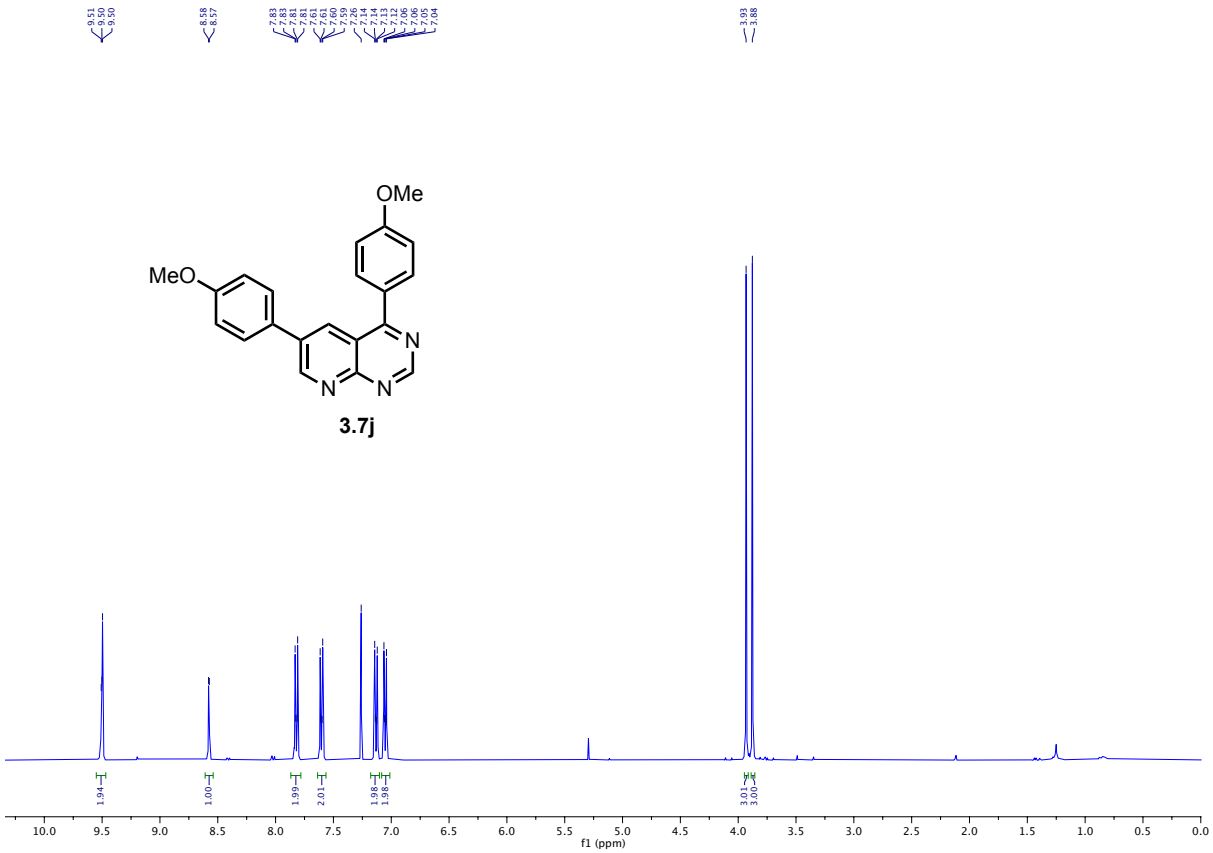

136.00
135.75
128.69
128.67
128.20
128.16
127.77
127.21
121.41
120.68
119.09
104.15
77.31 cdcl3
77.00
76.68 cdcl3
71.09
70.81
12.59
SMe
BnO
BnO
N
N
3.7h
f1 (ppm)

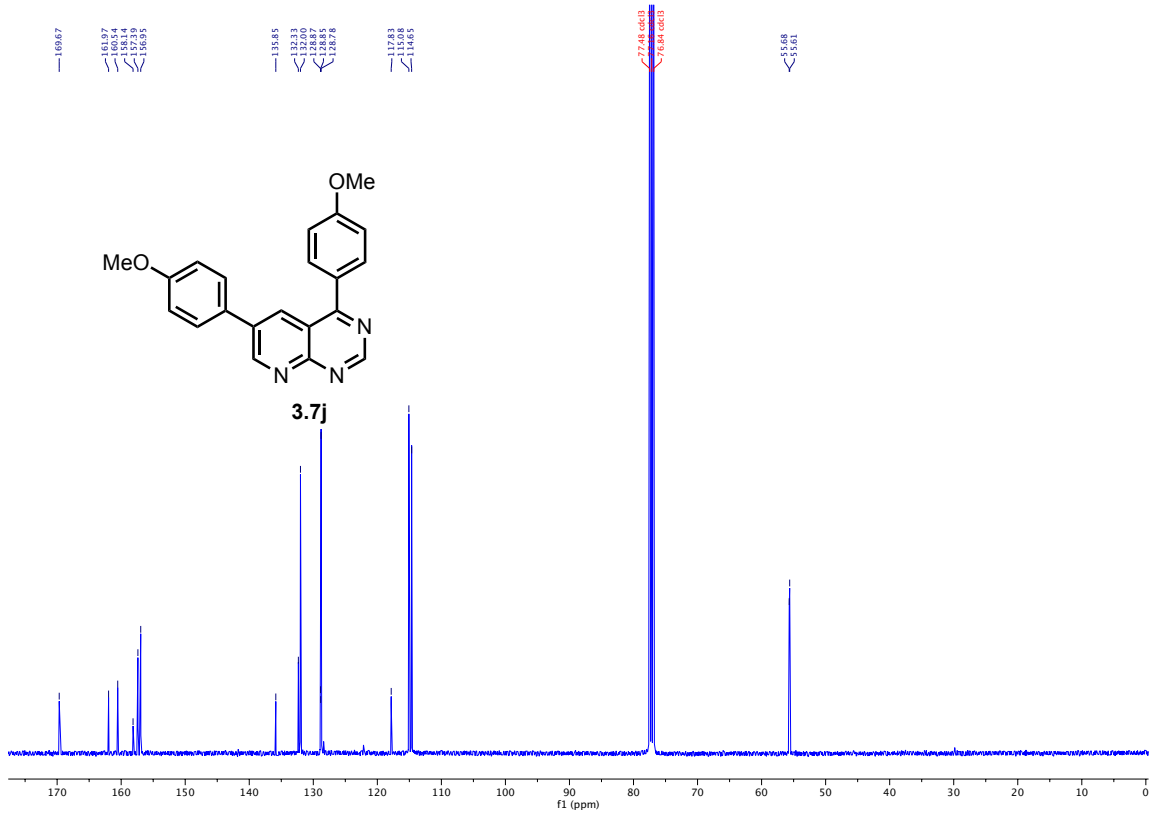


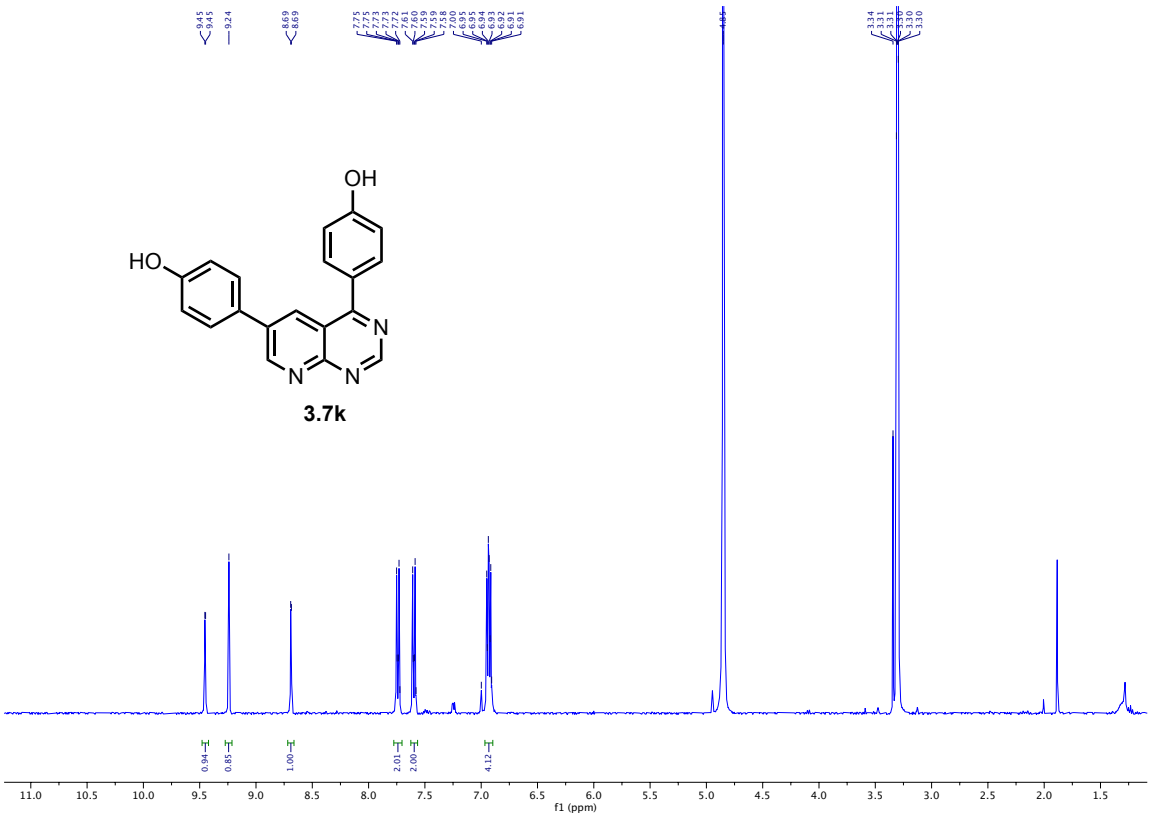
3.7i

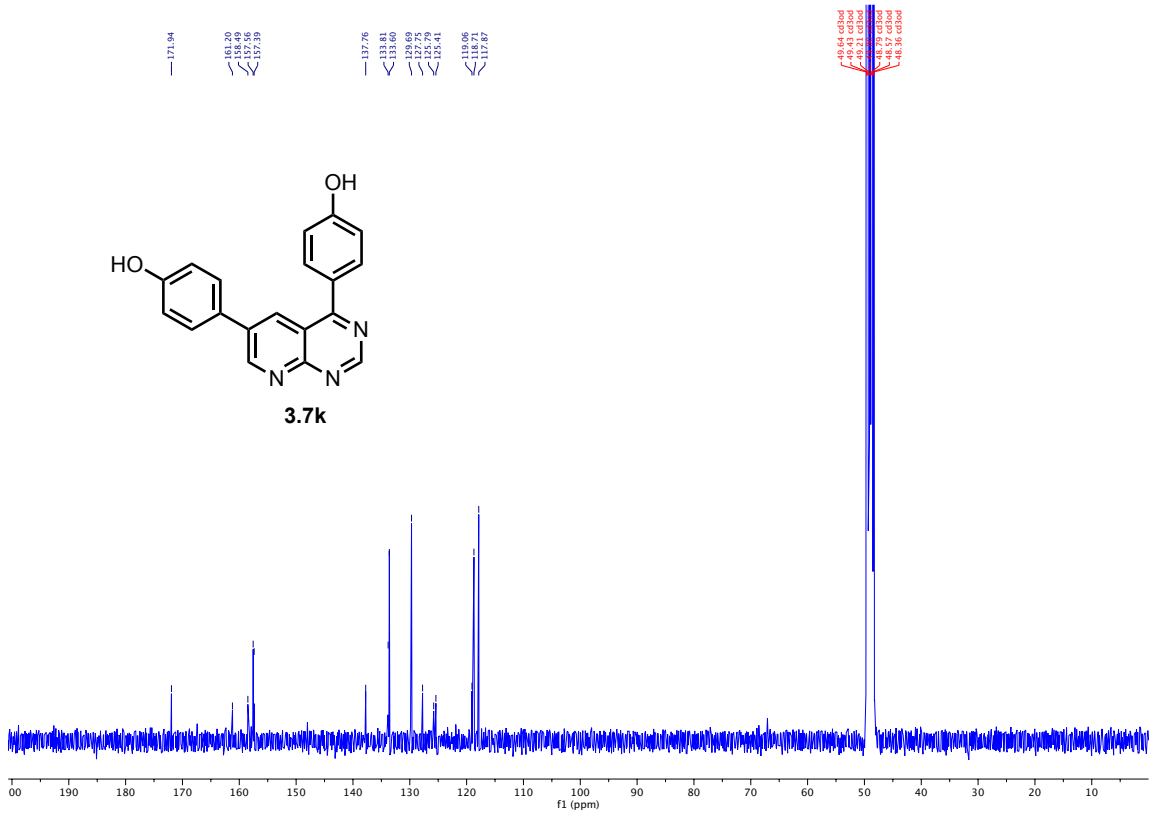


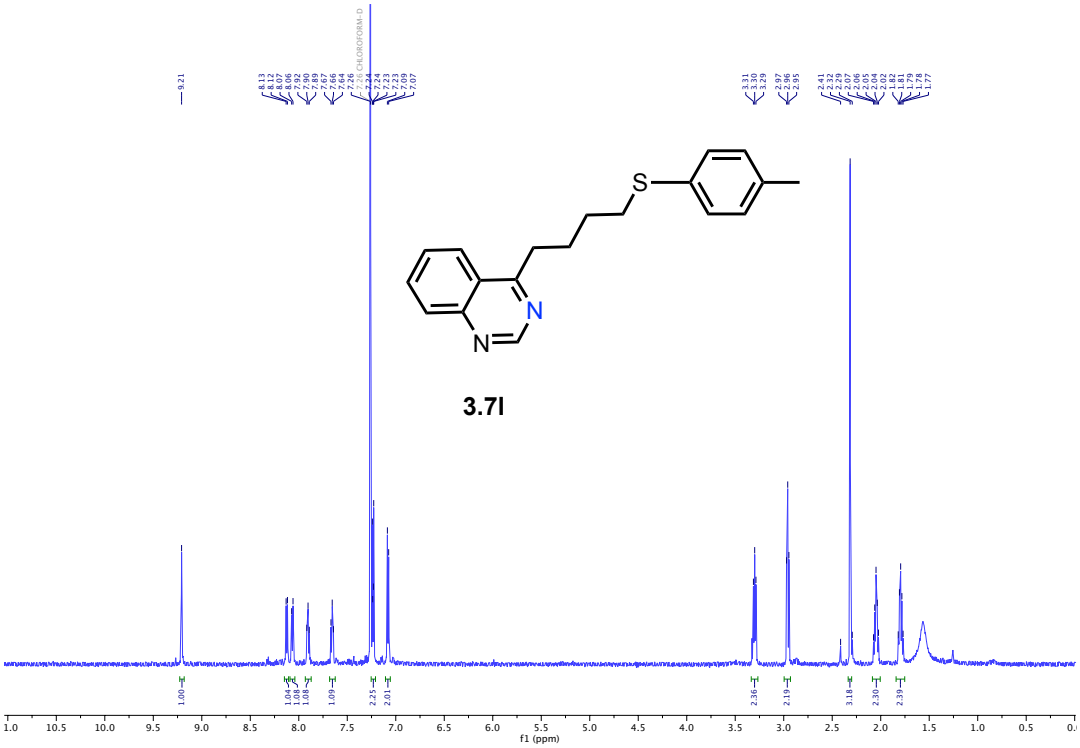
3.7i

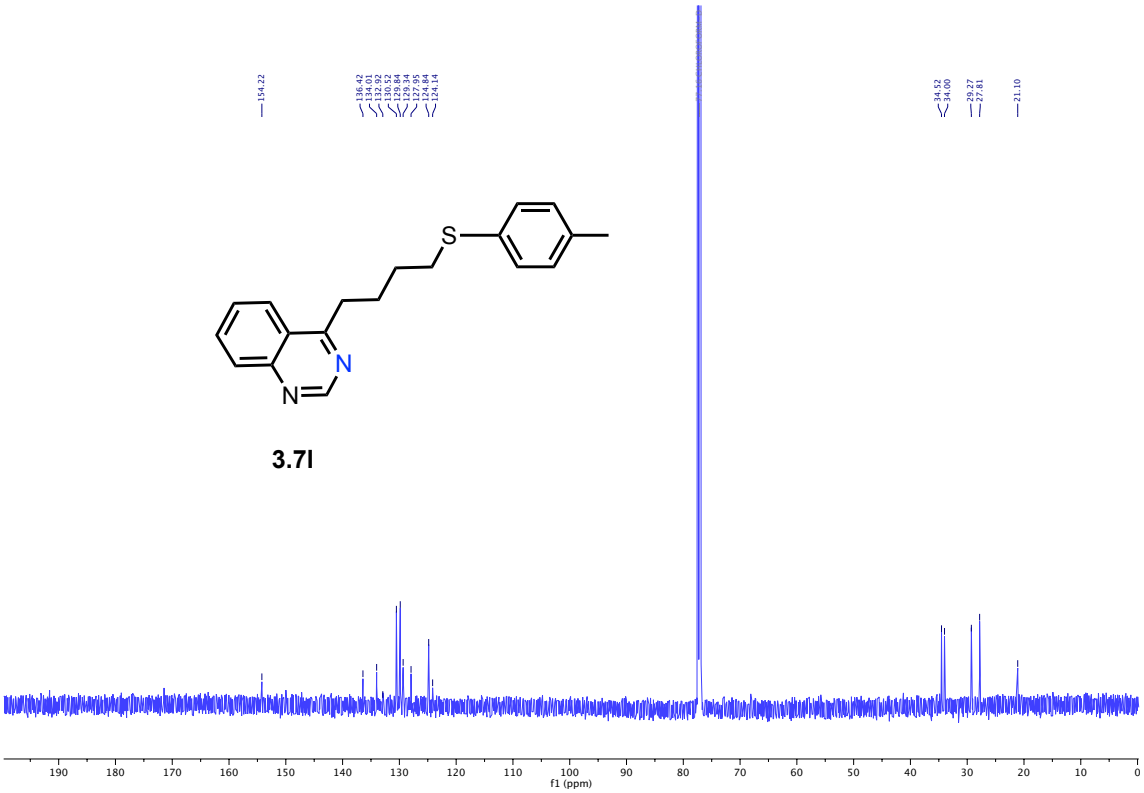

OMe
MeO
N
N
N
3.7j
f1 (ppm)

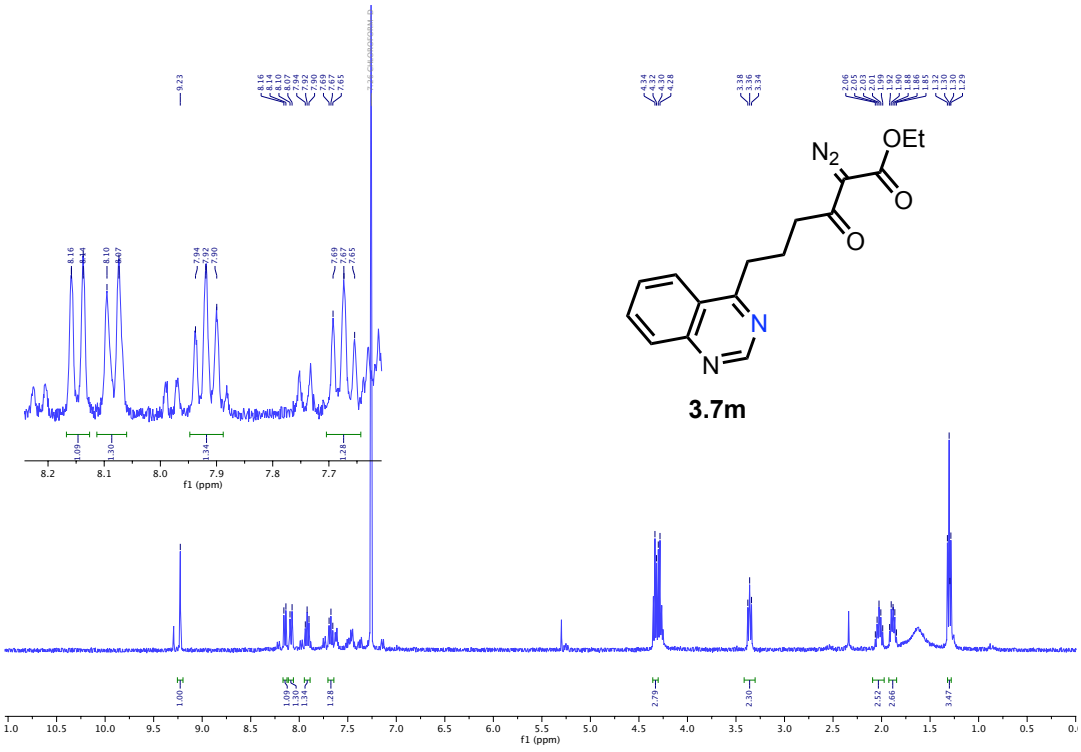

OMe
MeO
N
N
N
3.7j
f1 (ppm)

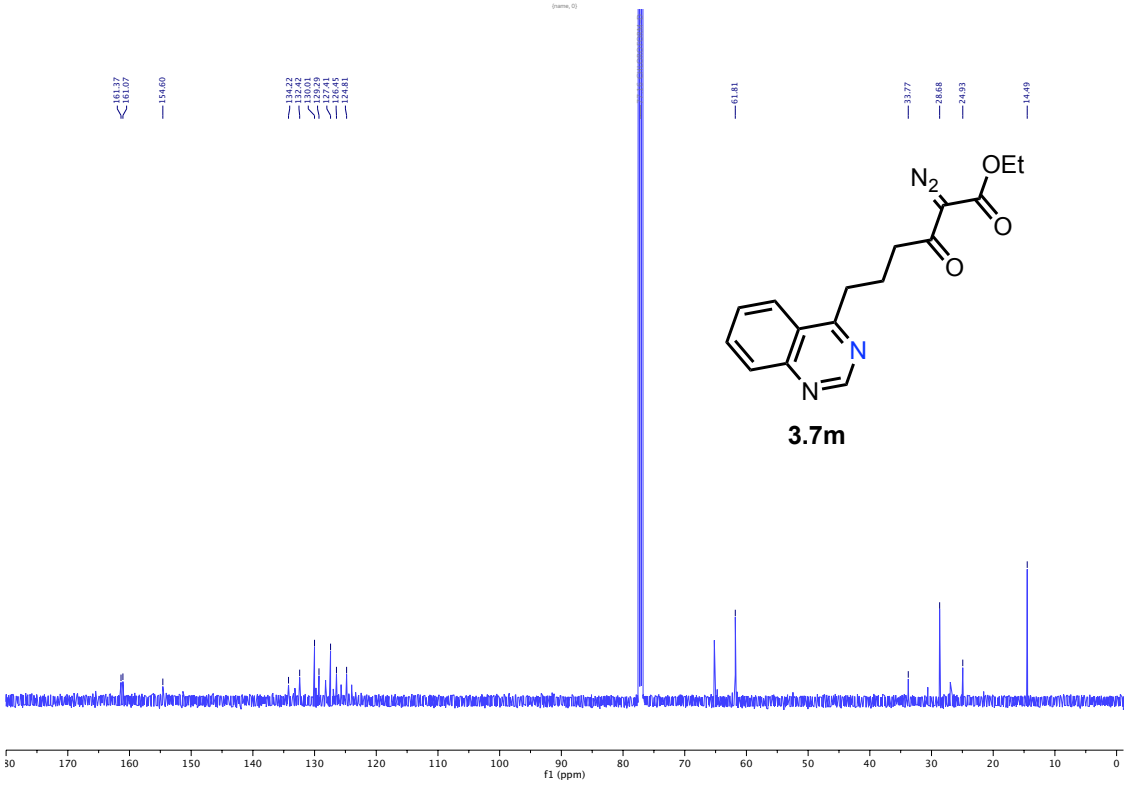

OH
HO
N
N
N
3.7k
f1 (ppm)

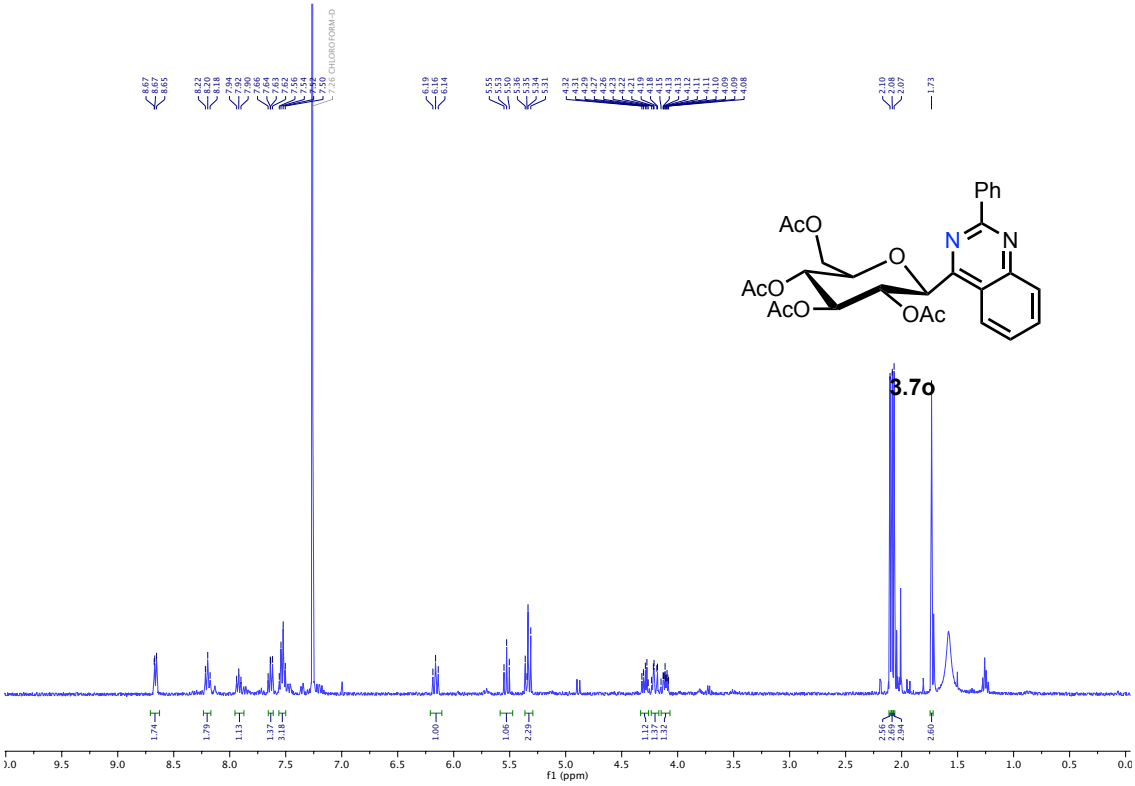

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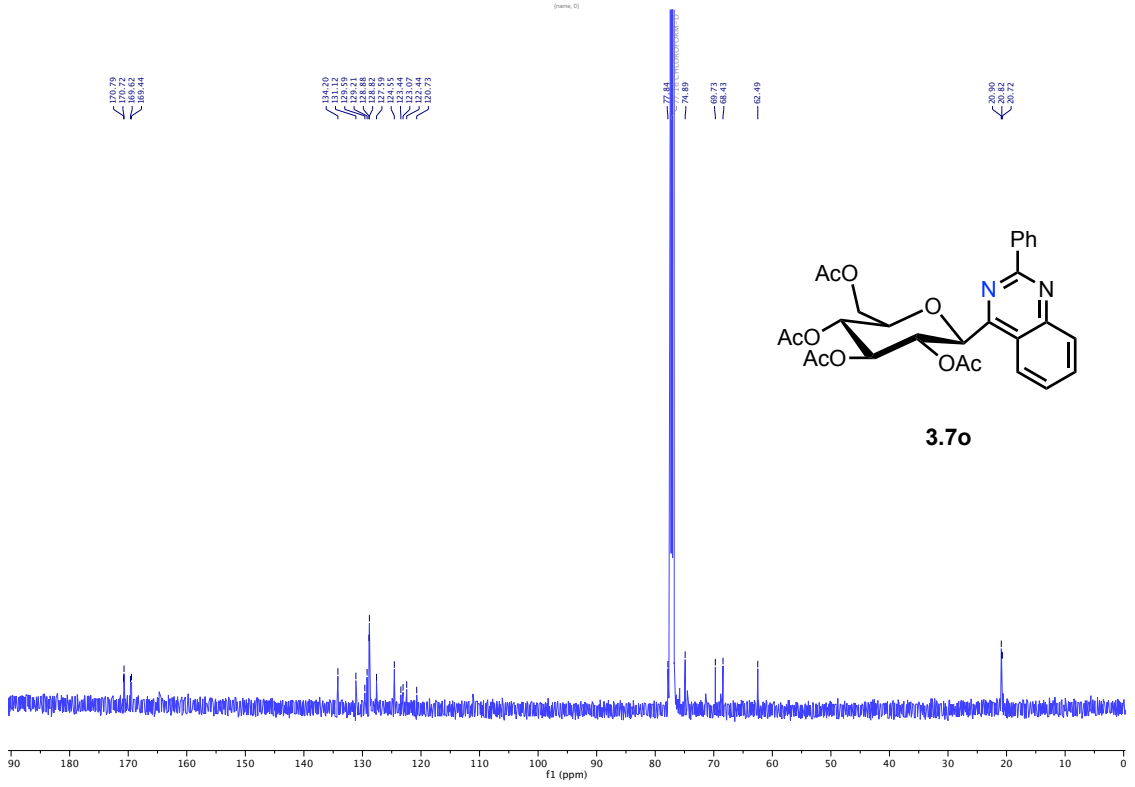

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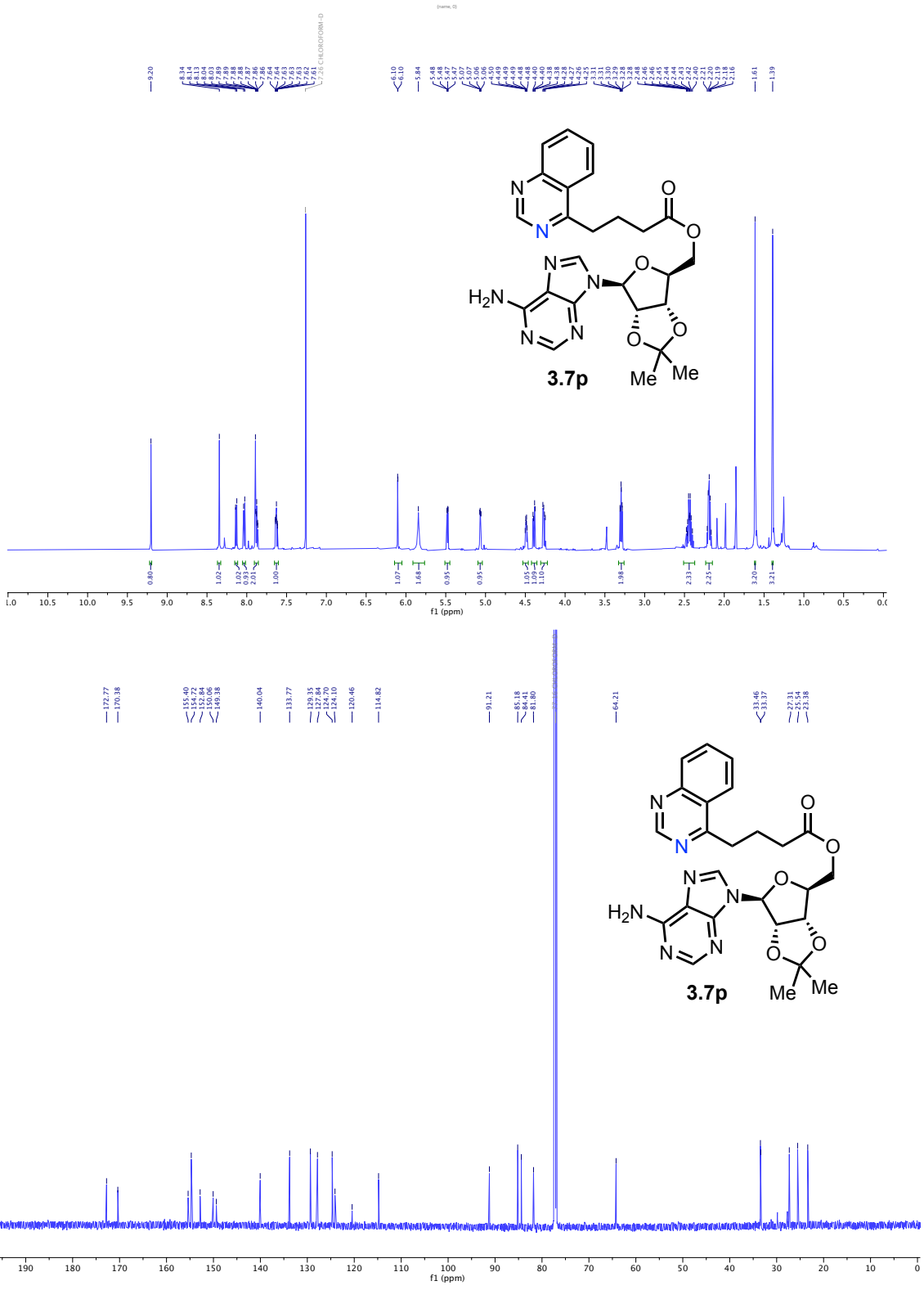

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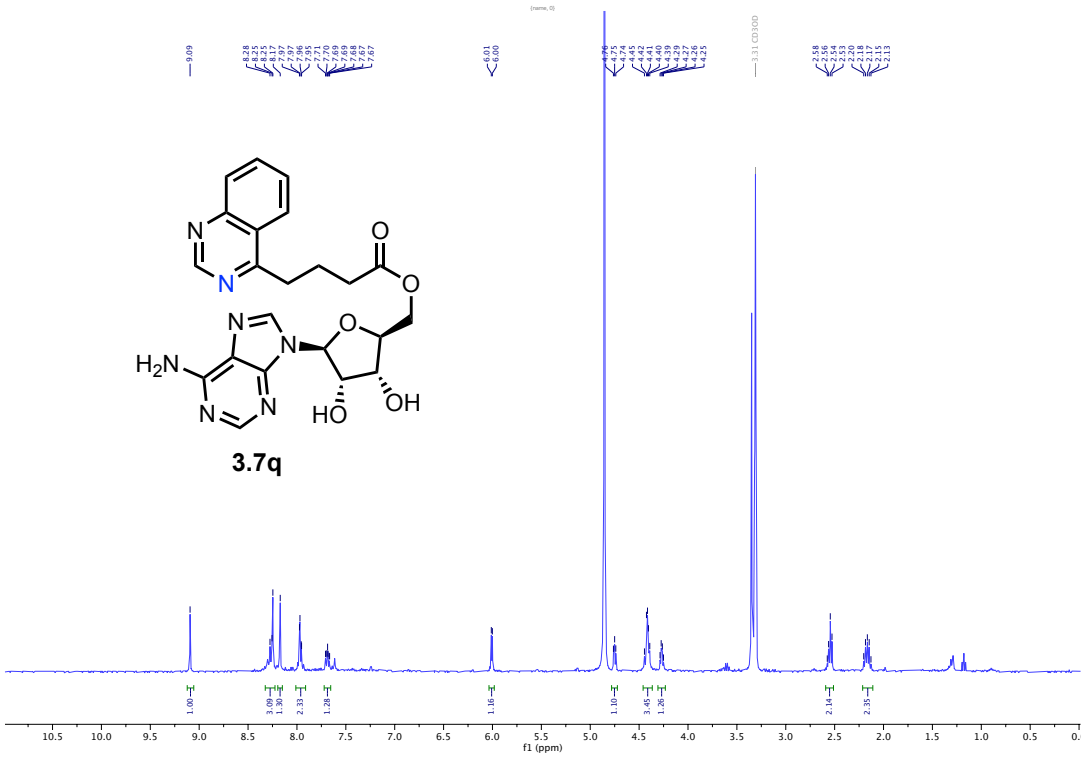


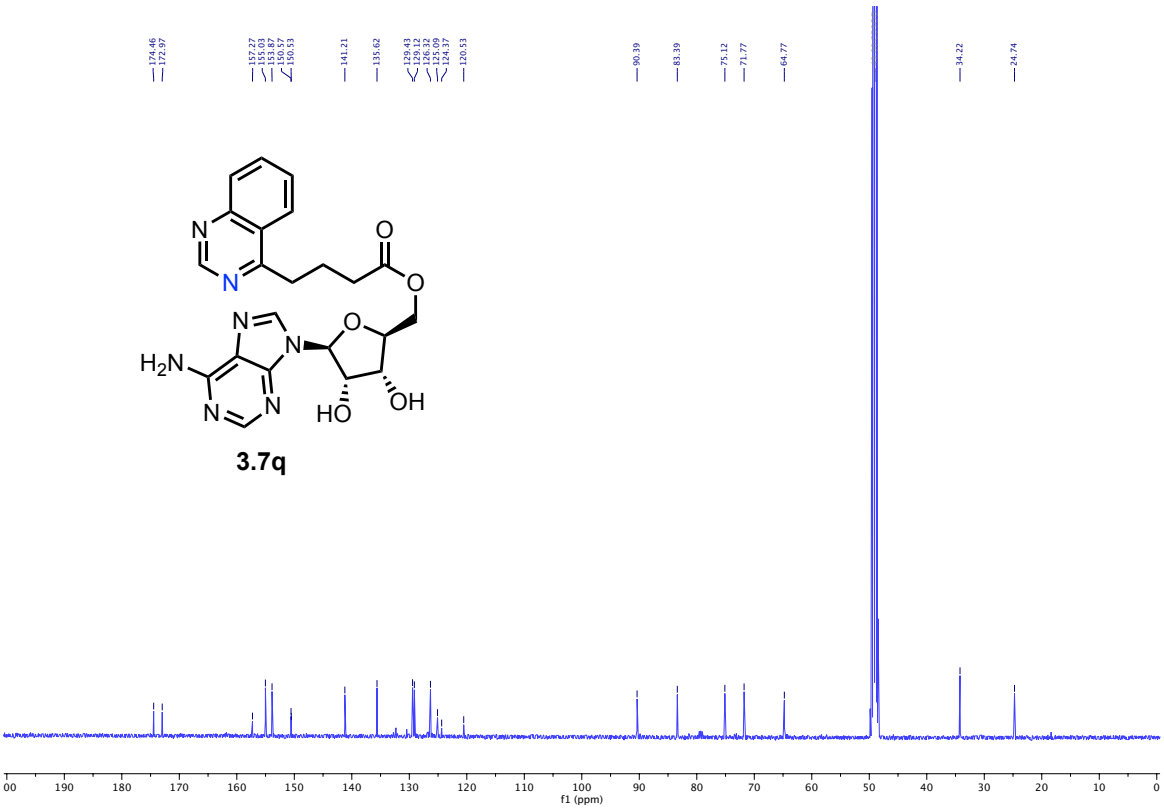
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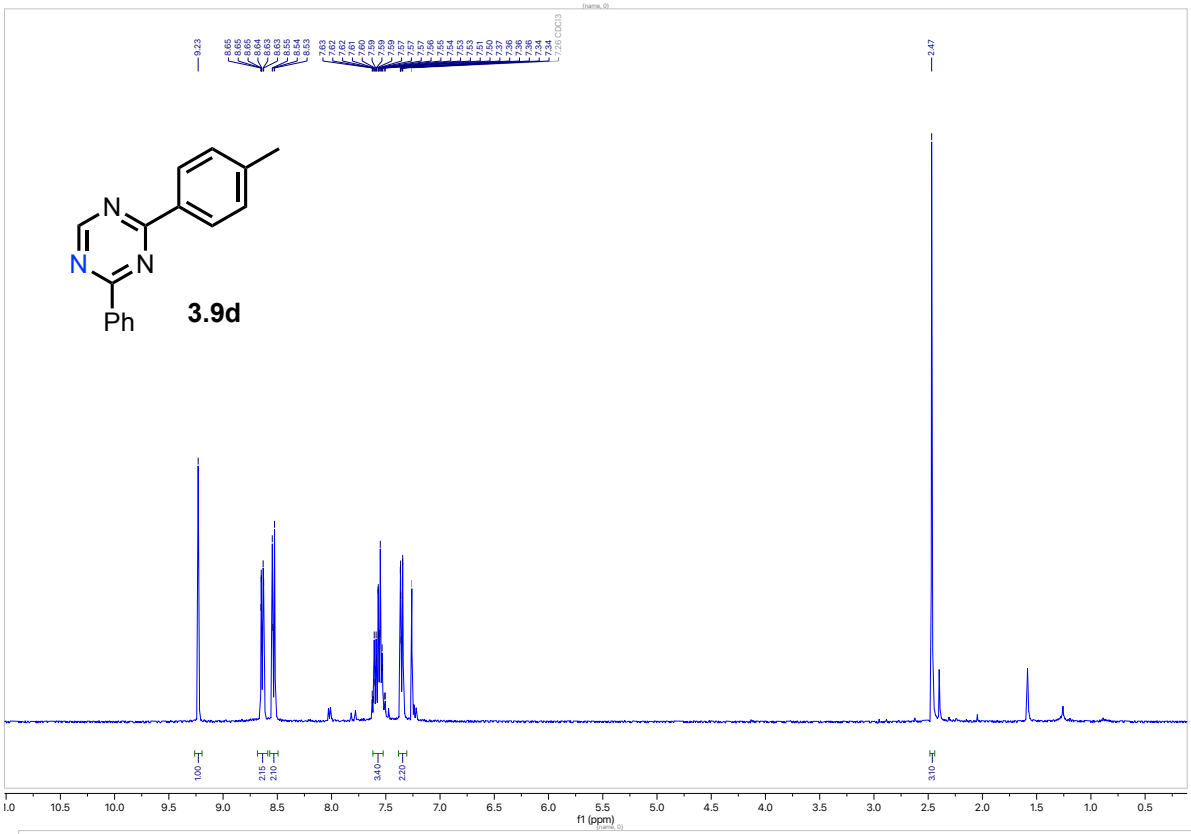
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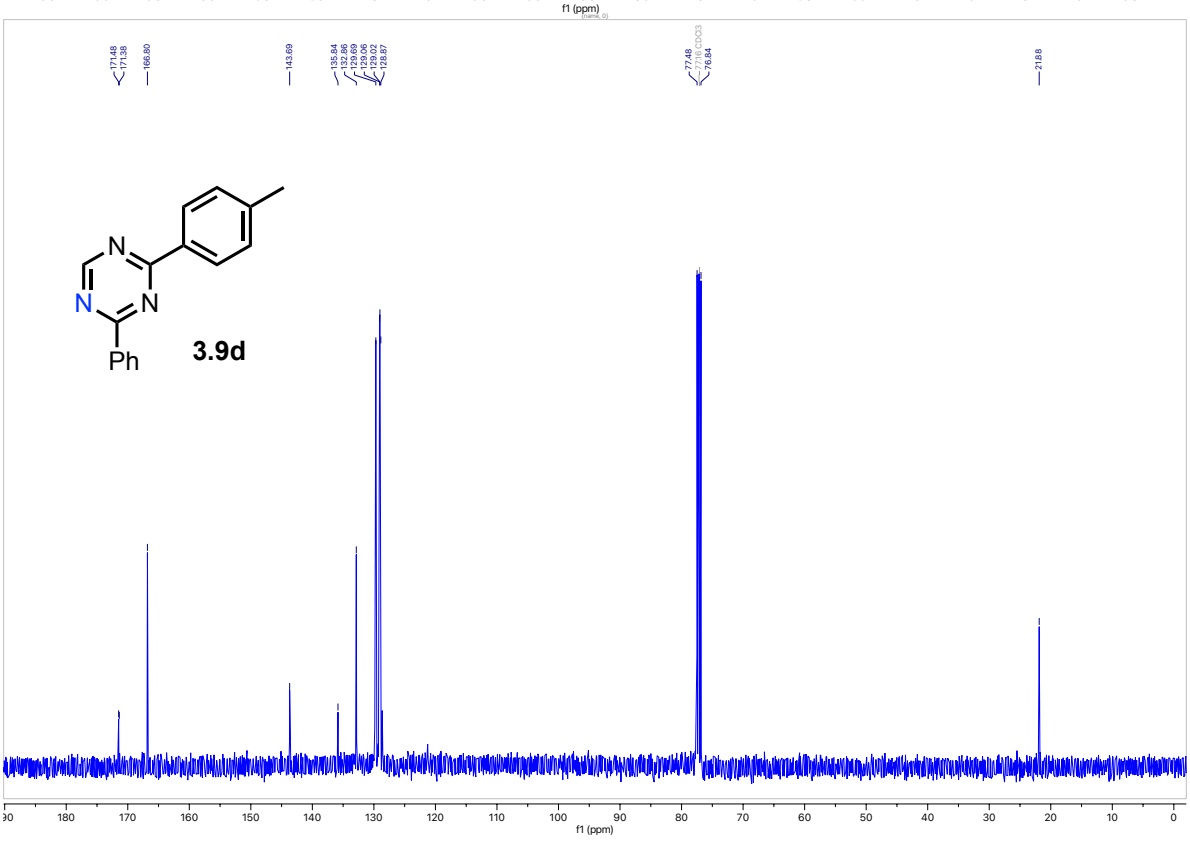

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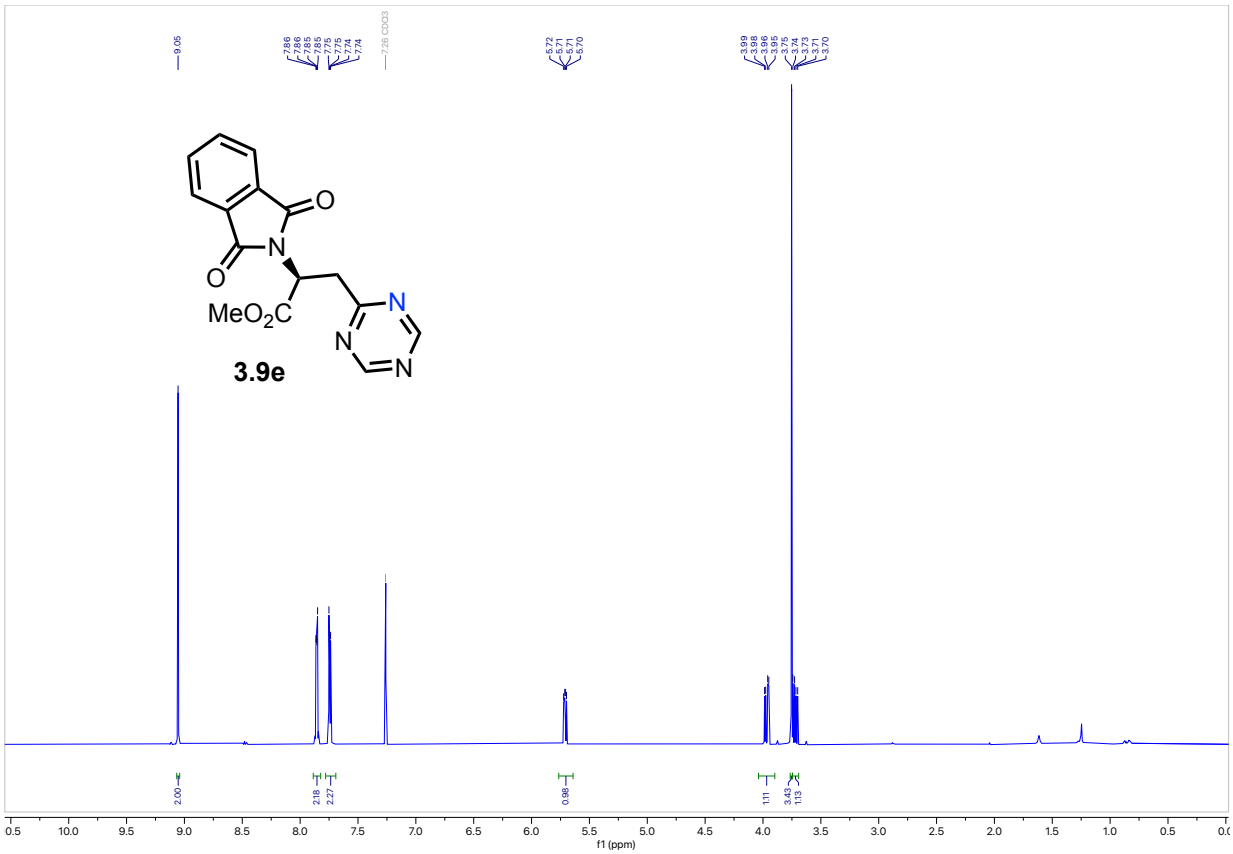


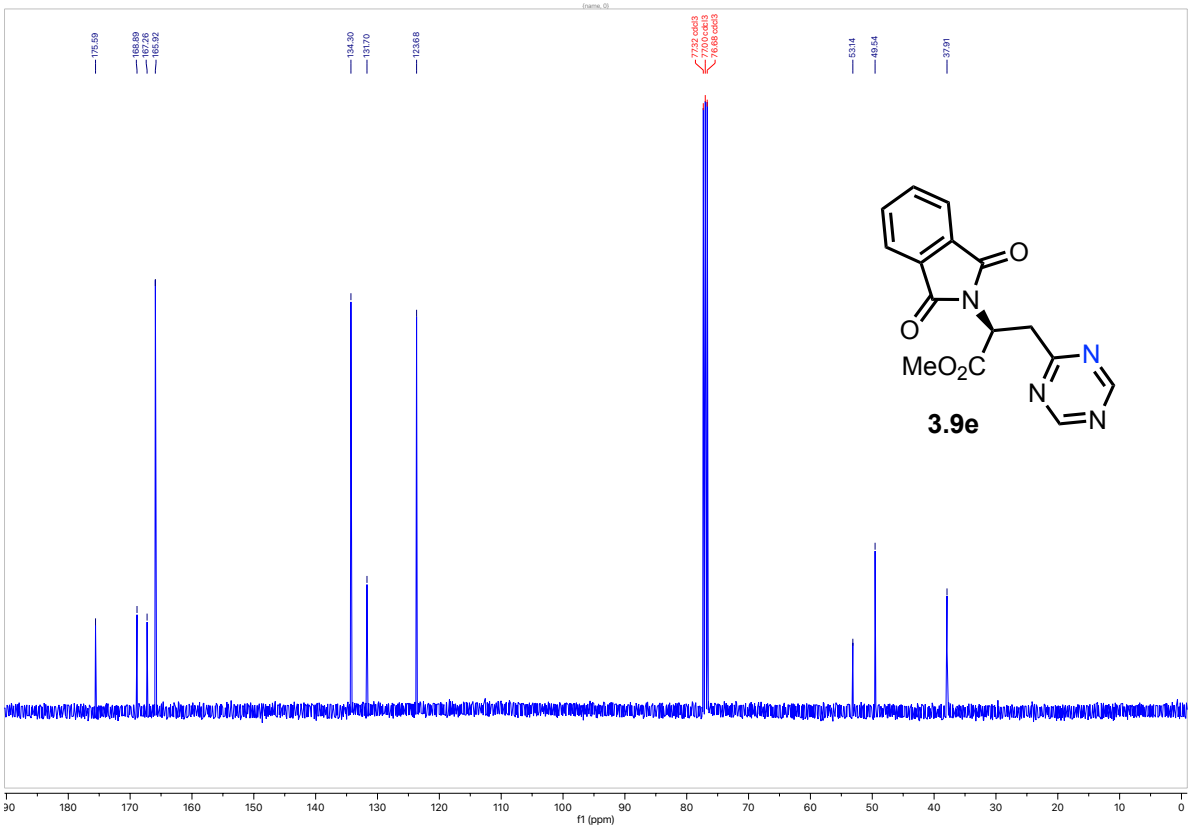


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3.9d
f1 (ppm)


3.9d
f1 (ppm)


9.05
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3.73
3.71
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2.27
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CHAPTER 4

Scaffold Hopping of Furans into N-Heterocycles

4.1 INTRODUCTION

Furans are valuable and cost-effective bulk chemicals primarily produced from renewable feedstocks, such as lignocellulosic biomass, the most abundant organic material on Earth.[1-3] This biomass, which includes agricultural residues, forestry waste, and other plant-based materials, serves as a sustainable feedstock for the generation of furfural, a key intermediate in the production of furans.[4-5] The conversion of lignocellulose to furfural, and subsequently to furans, represents a pivotal route in the biorefinery landscape, offering an environmentally friendly alternative to fossil fuel–based chemical synthesis and contributing to the development of greener chemical manufacturing processes.[3, 5]

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Furan is a crucial core in many natural products, yet it is rare in FDA-approved drugs.[6-7] The primary reason for this disconnect is furan's ability to undergo oxidative ring opening in the presence of cytochrome P450 (CYP2E1) (**Figure 4.1a**).[8] This results in an electrophilic toxic en-dial/-one intermediate that can deplete essential cellular nucleophiles like amino acids, proteins, DNA, etc, responsible for various biological functions.[8-12] This reactivity helps explain why furans are relatively uncommon in approved pharmaceuticals compared to other heterocyclic scaffolds.[13-14]

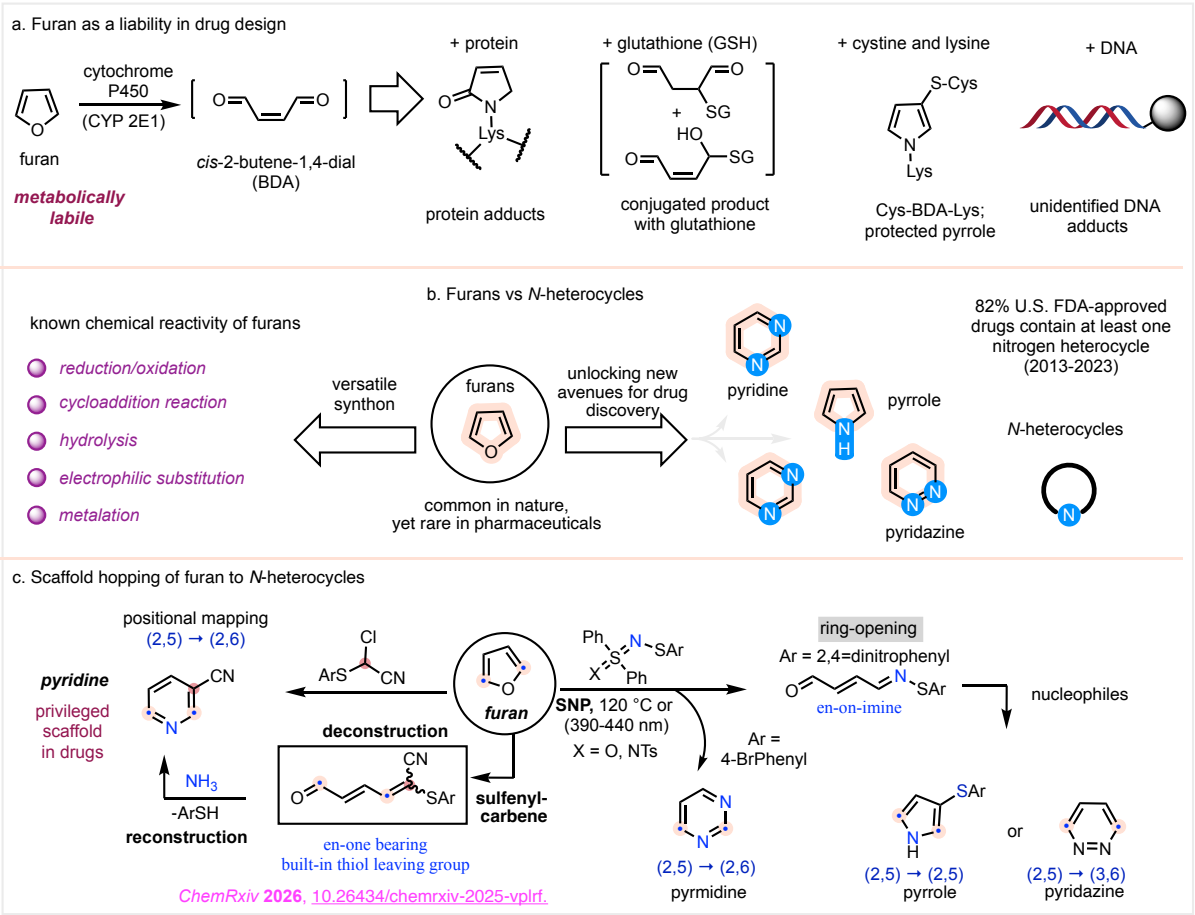


Figure 4.1: Scaffold hopping of furans into *N*-heterocycles by sulfenylcarbene or sulfenylnitrene.

Nitrogen-containing heterocycles are central to pharmaceuticals, playing a critical role in drug efficacy and safety.[13, 15-16] They are constructed using a combination of

classical synthetic methods and modern catalytic strategies, enabling precise control over substitution patterns and functional group incorporation.[17-19] Recent advances in synthetic organic chemistry, particularly in late-stage functionalization and scaffold hopping, have further expanded access to diverse *N*-heterocyclic frameworks, facilitating the rapid generation of molecules with improved properties.[20-25] However, analogous furan scaffolds, while abundant in nature, remain underrepresented in pharmaceuticals.[26-27] Although relatively few diaryl furans exhibit significant bioactivity, their conversion into diverse heterocycles offers a powerful strategy to expand molecular diversity and access scaffolds with enhanced biological relevance.[28] While furans are readily available and easily functionalized,[2-3, 29-30] they can exhibit metabolic instability and limited hydrogen-bonding capacity in biological systems.[8, 31] In contrast, *N*-heterocycles such as pyrimidines, pyrroles, pyridazines, and related nitrogen-containing frameworks often exhibit improved chemical robustness, richer coordination and hydrogen-bonding profiles, and superior pharmacokinetic properties.[13-14] Transforming furans into *N*-heterocycles enables rapid scaffold hopping while preserving key structural features,[28] addressing the need to convert abundant oxygen heterocycles into higher-performing nitrogen analogues.

Due to their low cost and ready availability, furans and their derivatives such as furfuryl alcohol, furfuryl amine, and methylfuran are attractive starting materials for the synthesis of diverse C5 compounds.[32-33] Therefore, the rearrangement of furfural and related furan derivatives into functionalized pyrans, piperidines, and pyridines represents a synthetically sustainable strategy. The Achmatowicz and Aza-Achmatowicz rearrangement elegantly accomplishes this transformation.[34-37]

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Among scaffold-hopping strategies,[38-40] skeletal editing has emerged as a transformative approach in drug discovery, enabling the direct reconfiguration of molecular frameworks within complex bioactive compounds.[41-47] This strategy allows chemists to convert one core scaffold into another without de novo synthesis, effectively creating new chemical space from existing lead structures.[46, 48-49] By facilitating the precise modification of molecular skeletons, skeletal editing enhances biological activity, improves pharmacokinetic profiles, and accelerates the optimization of lead compounds in a time- and resource-efficient manner.[45-46, 49] Notably, substantial advances have been made in the skeletal editing of five-membered heterocycles such as pyrroles, pyrazoles, imidazoles, and thiazoles, which are prevalent motifs in pharmaceuticals.[21, 50-56] In contrast, analogous skeletal editing transformations of furans remain largely unexplored, although a few reports have described related transformations in benzofurans.[57-58] In a recent study, the Park group reported a photocatalytic approach for late-stage skeletal editing of furans, enabling their conversion into pyrroles.[28] These limited precedents highlight the significant challenges and opportunities in establishing general and selective skeletal editing strategies for furan-containing molecules.[59-60]

Furans exhibit versatile reactivity, functioning both as arene analogues and as masked alkenes or dienes.[61-63] One attractive approach to harnessing their synthetic utility involves reactions with carbenes/nitrenes, which generate valuable intermediates for subsequent functionalization.[63-64]

The reaction between furans and carbenes was first reported in 1958 and was found to yield unstable cyclopropane intermediates that gradually decompose into a mixture of diene products.[65] Multiple literature reports describes the formation of diene–carbonyl

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mixtures; however, these compounds have limited synthetic utility due to the absence of a suitable leaving group.[66-69] In addition, furans are known to undergo intra- and inter-molecular reactions with various metal carbenes to produce products such as pyrroles, cyclopentenes, and dihydropyridines with an alternate rearranged backbone.[68, 70-74]

Similarly, the reaction of furans with nitrene (pthalidoimidonitrene) was first reported in 1972 and was shown to proceed through ring-opening to form stable hydrazone intermediates (Fig. 1c).[75] Although multiple subsequent studies have documented the formation of such ring-opened products under oxidizing/metal-catalyzed conditions, these intermediates were generally not leveraged for downstream transformations or synthetic diversification (**Figure 4.1b**).[76-79] In addition, Barton and co-workers demonstrated that furans can participate in ring-expansion reactions with tribenzenesulfenamide under thermal conditions, affording pyrimidines through a unique double-nitrogen insertion pathway.[80] Additionally, substantial efforts have focused on reactions of furans with highly reactive electrophilic species to convert furan cores into value-added carbocyclic and heterocyclic scaffolds.[34-35, 37, 65-71, 73-74, 81-82] These transformations proceed via diverse pathways, including oxidative rearrangements, cycloadditions, ring-opening reactions, and electrophile-induced ring expansion, thereby providing efficient access to structurally distinct and functionally enriched frameworks. Together, these studies highlight the latent potential of furan and carbene/nitrene chemistry while underscoring the need for more general and synthetically useful strategies to convert furans into value-added *N*-heterocyclic frameworks. Building upon our findings and known reactivity of furans, we achieved the skeletal editing of furans to cyanopyridine with sulfenylcarbenes in a deconstruction/reconstruction manner (**Figure 4.1c**). Inspired by Barton's work from

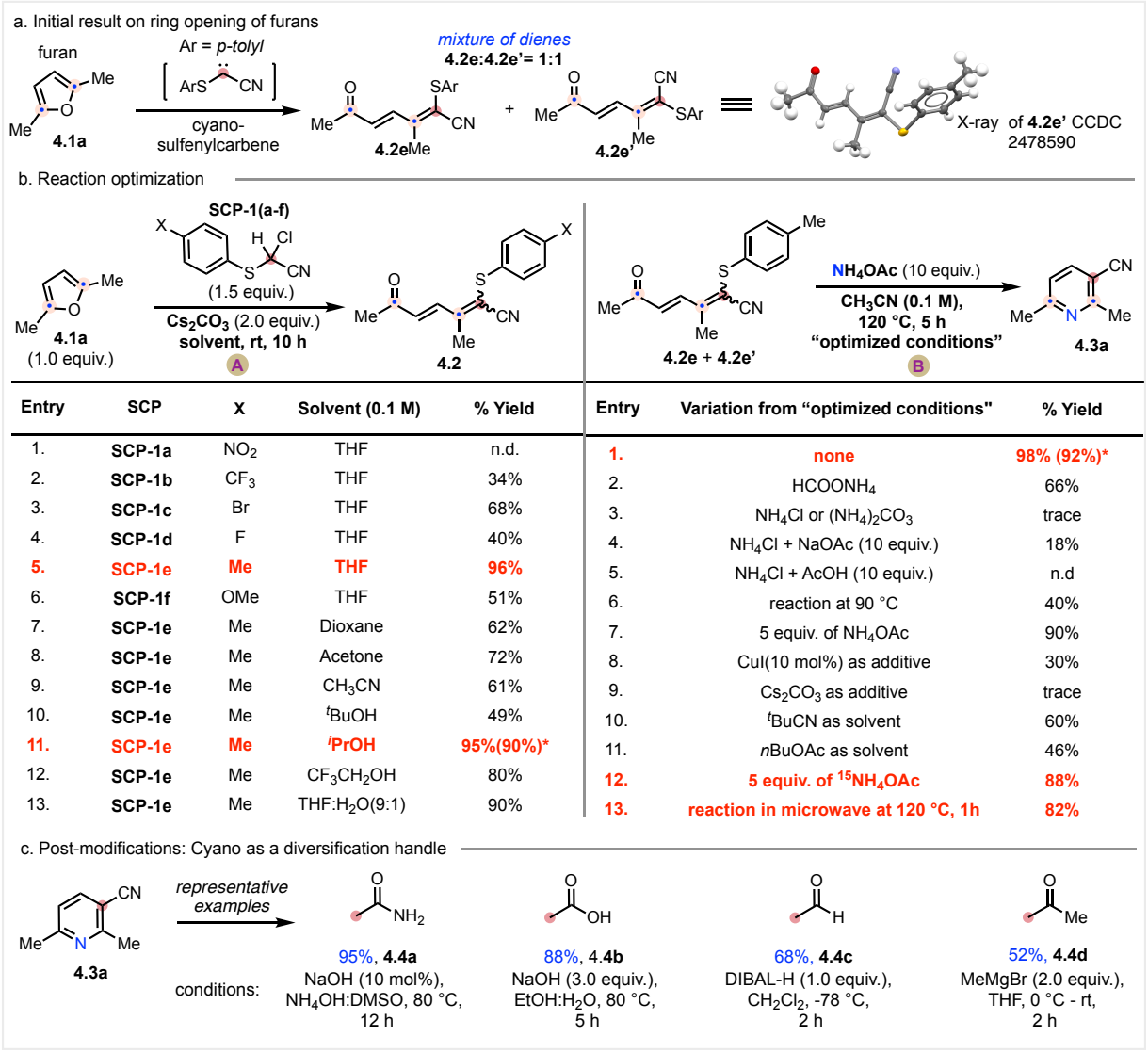
1970's to form trace pyrimidine from furans, we achieved nitrogen atom/s insertion into furans to access pyrimidines, pyridazines, and pyrroles, privileged heterocycles in drug discovery (**Figure 4.1c**). This expanded methodology deepens our understanding of reactivity across different molecular frameworks and enhances the versatility of our approaches to access the uncharted chemical space.

4.2 Results and Discussion

4.2.1 Reaction Optimization for Furans to 3-Cyanopyridines

We initiated our study by using commercially available symmetric 2,5-dimethylfuran (**4.1a**) as the model substrate (**Figure 4.2.1.1a**), with cyano sulfenylcarbene developed by our group for the skeletal editing of *N*-heterocycles.[83] Remarkably, 2,5-dimethylfuran (**4.1a**) resulted in efficient formation of the desired dienone intermediates (**4.2e** and **4.2e'**), featuring a thioaryl moiety as a built-in leaving group. These intermediates were confirmed by detailed NMR and X-ray crystallography analyses. After the initial success with cyano sulfenylcarbene, we synthesized a series of cyano sulfenylcarbene precursors (SCPs) to understand the influence of thio-functionality on the carbene center (**Figure 4.2.1.1b**). We performed a Hammett study by substituting the *para*-position of aromatic thiol in the cyano sulfenylcarbene precursors. SCP-1a bearing a nitro substitution (ρ = +0.778), failed to yield a dienone intermediate (entry 1), however, a weaker electron-withdrawing group, CF_3 (ρ = 0.540) on the aryl ring, resulted in intermediates with a low yield (entry 2). Furthermore, our study revealed that halogens such as Br (ρ = +0.232) and F (ρ = +0.062) on the aryl ring provided a moderate yield of the intermediate (entries 3,4). Finally, electron-donating groups on the aryl ring, such as SCP-1e (Me, ρ = –0.170) and SCP-1f (OMe, ρ = –0.268), also provided the intermediate

2 (entry 5,6). To our delight, the corresponding intermediate 2e and 2e' was formed in 96% yield (entry 5) when the thio-functionality was para-substituted with a methyl group.



Entry	SCP	X	Solvent (0.1 M)	% Yield
1.	**SCP-1a**	NO_2	THF	n.d.
2.	**SCP-1b**	CF_3	THF	34%
3.	**SCP-1c**	Br	THF	68%
4.	**SCP-1d**	F	THF	40%
5.	**SCP-1e**	**Me**	**THF**	**96%**
6.	**SCP-1f**	OMe	THF	51%
7.	**SCP-1e**	Me	Dioxane	62%
8.	**SCP-1e**	Me	Acetone	72%
9.	**SCP-1e**	Me	CH_3CN	61%
10.	**SCP-1e**	Me	^{t}BuOH	49%
11.	**SCP-1e**	**Me**	**^{i}PrOH**	**95%(90%)***
12.	**SCP-1e**	Me	CF_3CH_2OH	80%
13.	**SCP-1e**	Me	THF:H_2O(9:1)	90%

Entry	Variation from "optimized conditions"	% Yield
1.	**none**	**98% (92%)***
2.	$HCOONH_4$	66%
3.	NH_4Cl or $(NH_4)_2CO_3$	trace
4.	NH_4Cl + NaOAc (10 equiv.)	18%
5.	NH_4Cl + AcOH (10 equiv.)	n.d
6.	reaction at 90 °C	40%
7.	5 equiv. of NH_4OAc	90%
8.	CuI(10 mol%) as additive	30%
9.	Cs_2CO_3 as additive	trace
10.	^{t}BuCN as solvent	60%
11.	*n*BuOAc as solvent	46%
12.	**5 equiv. of $^{15}NH_4OAc$**	**88%**
13.	**reaction in microwave at 120 °C, 1h**	**82%**

Figure 4.2.1.1: Reaction optimization of furans to 3-cyanopyridines. Conditions A. Reactions were carried out on a 0.5−1.0 mmol scale in a sealed vial. 1a (1.0 equiv.), SCP (1.5 equiv.), base (2.0 equiv.), solvent (0.1 M); Conditions B. Reactions were carried out on a 0.5−1.0 mmol scale in a sealed tube 2 (1.0 equiv.), source of ammonia (10 equiv.), solvent (0.1 M). Yields were determined by ^{1}H-NMR. Not detected (n.d). *Isolated yield of reaction in 1 mmol scale.

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Changing the reaction solvent to dioxane resulted in a slightly lower yield (entry 7). We also employed industrially preferred solvents, including acetone, acetonitrile, and tertiary, secondary, and primary alcohols (entries 8-12).[84] The reaction yielded moderate to good results in all solvents. When secondary alcohol (isopropyl alcohol) was used as the solvent, the reaction worked similarly to tetrahydrofuran (THF) (entry 11). To evaluate the broader applicability of this methodology, the reaction was performed under aqueous conditions and proceeded efficiently in THF/H_2O (entry 13).

To optimize the cyclization–rearomatization step, we treated the dienone intermediates **4.2e** and **4.2e'** with 10 equivalents of ammonium acetate in acetonitrile (0.1 M) at 120 °C. Under these conditions, the reaction proceeded cleanly to afford the 3-cyanopyridine **4.3a** with quantitative yield. We then evaluated various sources of ammonia ($HCOONH_4$, NH_4Cl, and $(NH_4)_2CO_3$); however, none outperformed ammonium acetate under the optimized conditions (entries 2 and 3). These results indicate that ammonium salts (NH_4OAc and $HCOONH_4$) of weaker organic acids (pKa ~4) are more effective than salts (NH_4Cl) derived from strong acids (e.g., HCl) in facilitating the initial step of reconstruction, which is imine formation. However, $(NH_4)_2CO_3$ is a salt of a weak acid that may be too weak (pKa ~6) to enable easy formation of imine. When sodium acetate was used as an additive in the presence of NH_4Cl, it produced the desired product, albeit in low yield (entry 4), likely due to in situ formation of NH_4OAc, whereas excess organic acid (AcOH, 10 equiv.) in the presence of ammonium chloride led to substrate decomposition (entry 5).

Lowering the reaction temperature resulted in a significant decrease in yield, indicating that an elevated temperature is crucial for efficient cyclization (entry 6). To

determine the optimal amount of ammonia source required, we tested 5 equivalents of ammonium acetate. While the reaction still proceeded, the yield was slightly reduced, suggesting that a higher concentration of ammonia facilitates complete conversion (entry 7). We also examined the effect of additives. The addition of a mild Lewis acid, such as copper(I) iodide, resulted in a diminished yield, whereas the use of cesium carbonate as a base additive led to decomposition of the intermediate, with only trace amounts of the desired product observed (entries 8, 9). When higher-boiling solvents *tert*-butylnitrile or *n*-butyl acetate was used, the reaction proceeded with moderate yield, further confirming acetonitrile as the optimal solvent for the reconstruction pathway (entries 10, 11).

We tested a ^{15}N-labeled ammonia source to demonstrate the applicability of this methodology for isotopic labeling of pyridines, and the reaction proceeded with good yield (entry 12) (See SI for additional details). To shorten the reaction time, we carried out the reaction using a microwave reactor, which significantly reduced the reaction time with a slight decrease in yield (entry 13) (See SI for additional details on microwave reaction conditions). Collectively, these studies established a robust and reproducible skeletal editing protocol for the efficient conversion of furan-derived dienones into 3-cyanopyridines. Furthermore, the cyano group is a versatile diversification handle that can be readily transformed into a broad range of functional groups (>10).[85] As a post-modification, we have diversified the cyano group into representative functional groups like amide, carboxylic acid, aldehyde, and ketone (**Figure 4.2.1.1c**).

Next, we also examined a broad range of literature-reported carbene precursors bearing leaving groups, including those previously employed by our group for the skeletal editing of pyrroles to introduce diverse substituents at the C-3 position of the resulting

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pyridines (Scheme 3). When sulfonyl- and sulfonamide-derived sulfenylcarbene precursors were tested, they failed to produce the desired ring-opening products, emphasizing the specific role of the cyano group in the ring opening of furans **(Figure 4.2.1.2a)**.

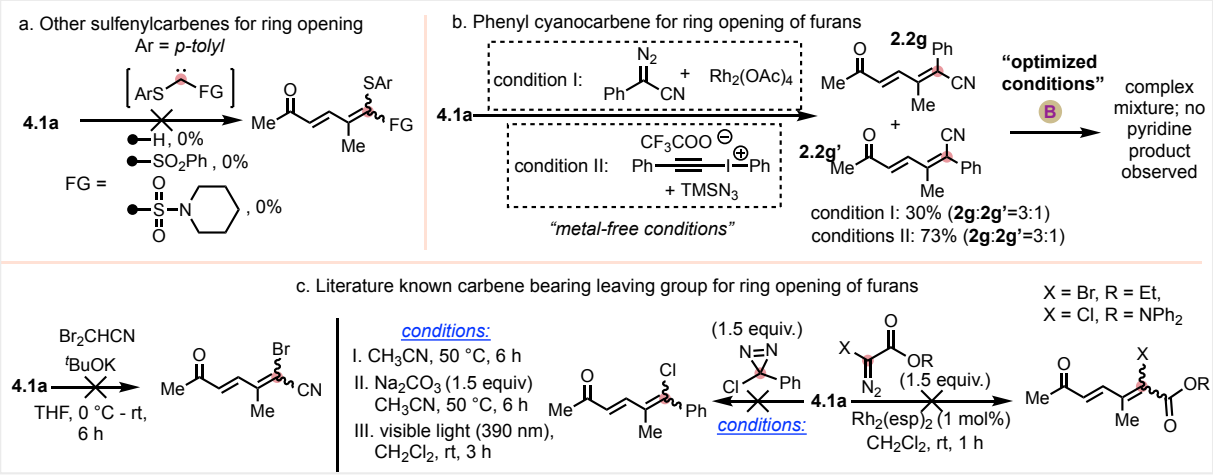


Figure 4.2.1.2: Ring of furans with other carbene-bearing leaving group.

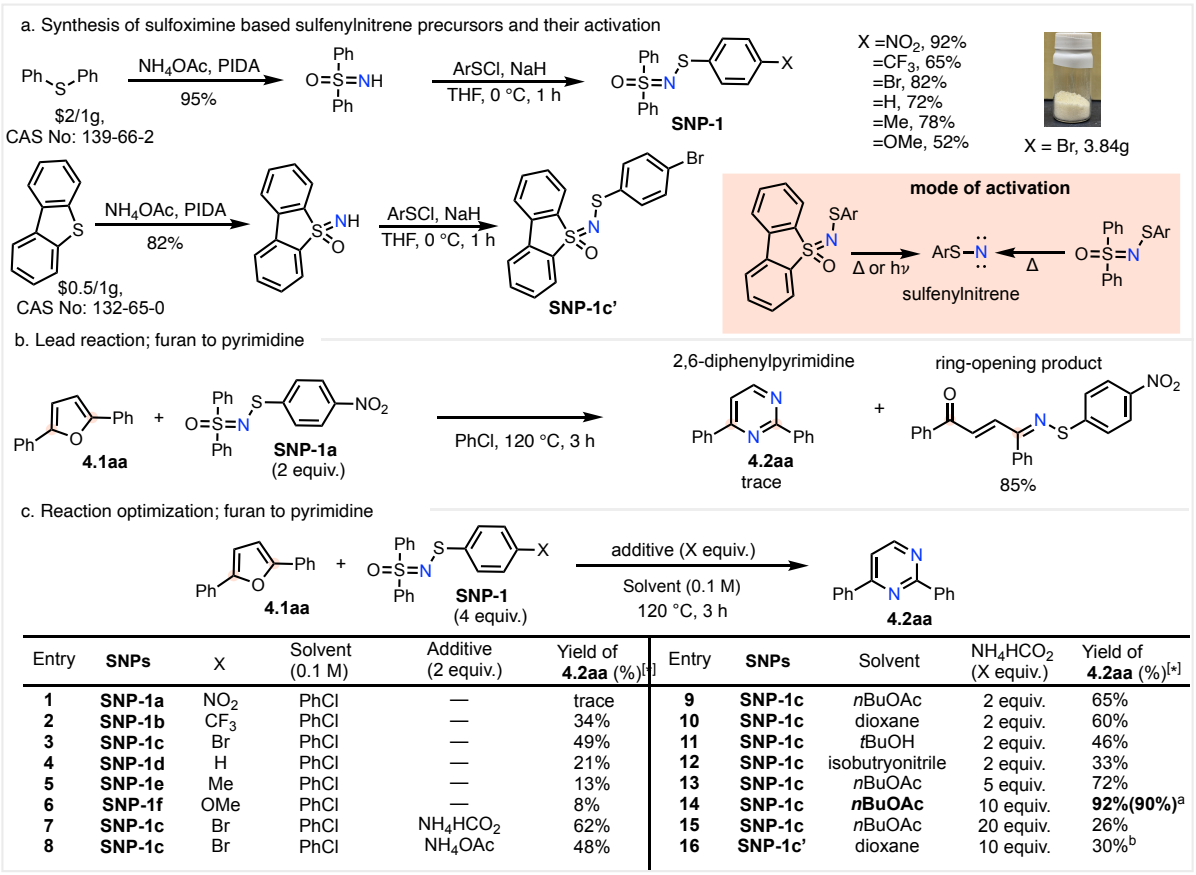
To elucidate the role of the cyano-substituted carbene in promoting furan ring opening, we next investigated both metal-mediated and metal-free strategies for generating phenyl cyanocarbene to achieve the desired ring-opening products **(Figure 4.2.1.2b)**. Both approaches produced the corresponding ring-opened intermediate, with the metal-free conditions providing superior yields. As the ring-opened intermediates **4.2g** and **4.2g'** did not have a leaving group, our optimized conditions (NH_4OAc in acetonitrile) for the reconstruction pathway did not furnish the targeted pyridine. Building upon these results, we next performed a reaction with cyanocarbene bearing a bromo leaving group using the dibromoacetonitrile precursor. However, this precursor was unable to open the furan ring.[86] Next, we investigated other carbene precursors, such as diazirine [50, 87] and diazo-based[88-90] precursors commonly used in skeletal editing of *N*-heterocycles, but none yielded the desired product under literature-reported conditions **(Figure 4.2.1.2c)**.

All these results further highlight the optimal electronic match of the cyano sulfenylcarbene as a donor/acceptor carbene for the successful scaffold-hopping of furans into 3-cyanopyridines.

4.2.2 Reaction Optimization for Furans to Pyrimidines

Motivated by prior studies on furan reactivity with nitrenes and our work on sulfur-based carbenes and nitrenes (discussed in chapter 2 and 3),[21, 51, 56, 91] we envisioned a strategy leveraging tunable sulfenylnitrenes equipped with a built-in thioaryl leaving group to enable scaffold hopping of furans into *N*-heterocycles. We demonstrate that these sulfenylnitrenes can engage the electron-rich furan ring to directly form pharmaceutically relevant pyrimidines or versatile en-on-imine intermediates, which can subsequently be converted, through nucleophile treatment, into functionalized pyrroles or pyridazines.

We initiated our study by synthesizing *N*-sulfenyl sulfoximine-based sulfenylnitrene precursors (**SNPs**) in two steps from a commercially available sulfide **(Figure 4.2.2a)**. These stable precursors generate tunable sulfenylnitrenes upon thermolysis or photolysis. When sulfenylnitrene was generated from **SNP-1a** in the presence of furan **4.1aa** as a model reaction using chlorobenzene as a solvent, the ring-opened product was obtained as the major outcome, along with trace amounts of the corresponding pyrimidine (entry 1) **(Figure 4.2.2b)**. This reactivity is consistent with previous reports describing the reaction of furans with other nitrene species.[77, 80]



Entry	SNPs	X	Solvent (0.1 M)	Additive (2 equiv.)	Yield of **4.2aa** (%)[a]
1	**SNP-1a**	NO_2	PhCl	—	trace
2	**SNP-1b**	CF_3	PhCl	—	34%
3	**SNP-1c**	Br	PhCl	—	49%
4	**SNP-1d**	H	PhCl	—	21%
5	**SNP-1e**	Me	PhCl	—	13%
6	**SNP-1f**	OMe	PhCl	—	8%
7	**SNP-1c**	Br	PhCl	NH_4HCO_2	62%
8	**SNP-1c**	Br	PhCl	NH_4OAc	48%

Entry	SNPs	Solvent	NH_4HCO_2 (X equiv.)	Yield of **4.2aa** (%)[a]
9	**SNP-1c**	*n*BuOAc	2 equiv.	65%
10	**SNP-1c**	dioxane	2 equiv.	60%
11	**SNP-1c**	*t*BuOH	2 equiv.	46%
12	**SNP-1c**	isobutryonitrile	2 equiv.	33%
13	**SNP-1c**	*n*BuOAc	5 equiv.	72%
14	**SNP-1c**	***n*BuOAc**	10 equiv.	**92%(90%)**[a]
15	**SNP-1c**	*n*BuOAc	20 equiv.	26%
16	**SNP-1c'**	dioxane	10 equiv.	30%[b]

Figure 4.2.2: Reaction optimization of furans to pyrimidine. Conditions: Reactions were carried out on a 0.5−1.0 mmol scale in a sealed vial. **4.1aa** (1.0 equiv.), **SNP** (4.0 equiv.), additive (10.0 equiv.), solvent (0.1 M). *Yields were determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [a]Isolated yield. [b] Reaction was done in UV-irradiation (300 nm) at rt for 12 h.

To further understand the reactivity trends, a series of sulfenylnitrene precursors (**SNP-1b** to **SNP-1f**) was synthesized and reacted with furan (entries 2-6). Overall, no clear or systematic trend in reactivity was observed across the series; however, sulfenylnitrene **SNP-1c** bearing a *para*-bromo thioaryl group uniquely favored ring expansion, delivering the pyrimidine product **2a** as the dominant outcome (entry 3). To enhance the reaction yield, we investigated the use of an external ammonia source

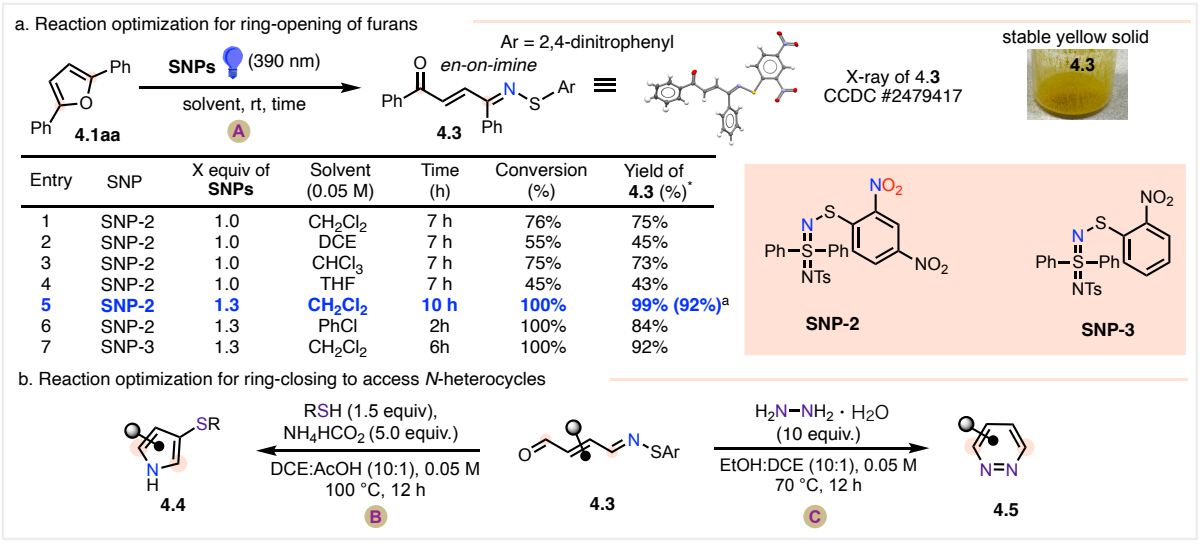
(entries 7-8). Among the conditions examined, ammonium formate was optimal, as addition of 2.0 equivalents increased the yield to 62% (entry 7). Importantly, this adjustment also resulted in a cleaner reaction and improved overall reaction efficiency. We also screened a range of solvents and found that the industrially preferred solvent *n*-butyl acetate performed comparable to chlorobenzene with moderate yield (entries 8-12).[84] To further improve the reaction yield, we examined higher loadings of the ammonia source, identifying 10 equivalents as optimal (entry 14). In contrast, the use of excess ammonia resulted in decreased yields (entries 15). Alternatively, we developed **SNP-1c′**, which generates the sulfenylnitrene under UV irradiation (300 nm) at mild temperatures compared to the thermal conditions (entries 16). However, this approach resulted in lower reaction yields. Consequently, the thermal conditions were selected as the optimal method in substrate scope study.

4.2.3 Reaction optimization for furans to pyrroles and pyridazines.

Next, we investigated the selective ring opening of furans using sulfenylnitrenes generated under photolytic conditions upon irradiation with visible light **(Figure 4.2.3a)**. Using furan **4.1aa** as a model substrate, irradiation of **SNP-2** (1.0 equivalent) in dichloromethane led to formation of the ring-opened product (en-one-imine) **4.3**, along with a significant amount of unreacted furan (**Figure 4.3.3a**, entry 1). This intermediate was confirmed by detailed NMR and X-ray crystallography analyses (CCDC 2479417; see SI for additional details). Changing the solvent to other chlorinated solvents (DCE or $CHCl_3$) or to tetrahydrofuran did not improve the reaction yield (entries 2-4). Increasing the loading of **SNP-2** to 1.3 equivalents resulted in quantitative conversion, with complete consumption of the furan substrate (entry 5). Thermal activation of **SNP-2** resulted in a

shorter reaction time with reduced yield (entry 6). When using **SNP-3** as the sulfenylnitrene precursor, the reaction proceeded smoothly, giving the ring-opened product in slightly lower yield (entry 7).

The resulting ring-opening product, an en-one–imine, serves as a versatile intermediate that incorporates a thioaryl moiety as a built-in leaving group (**Figure 4.3.3b**). Upon activation with a thiol nucleophile, either in the presence or absence of an external ammonia source, this intermediate undergoes cyclization to afford C-3-functionalized pyrroles. When hydrazine hydrate is employed as the nucleophile in presence of en-on-imine (**4.3**), the reaction follows an alternative ring-closing pathway to form pyridazines a heterocyclic motif of significant importance in pharmaceutical chemistry.



Entry	SNP	X equiv of **SNPs**	Solvent (0.05 M)	Time (h)	Conversion (%)	Yield of **4.3** (%)*
1	SNP-2	1.0	CH_2Cl_2	7 h	76%	75%
2	SNP-2	1.0	DCE	7 h	55%	45%
3	SNP-2	1.0	$CHCl_3$	7 h	75%	73%
4	SNP-2	1.0	THF	7 h	45%	43%
5	**SNP-2**	**1.3**	**CH_2Cl_2**	**10 h**	**100%**	**99% (92%)[a]**
6	SNP-2	1.3	PhCl	2h	100%	84%
7	SNP-3	1.3	CH_2Cl_2	6h	100%	92%

Figure 4.2.3: Reaction optimization of furans to pyrroles and pyridazine. Condition A. Reactions were carried out on a 0.1−1.0 mmol scale in a sealed vial. **4.1aa** (1.0 equiv.), **SNP-2** (1.3 equiv.), dichloromethane (CH_2Cl_2) (0.1 M) and irradiated at 390 nm. *Yields were determined by ^{1}H-NMR. [a]Isolated yield and reaction was done in 1 mmol scale.

4.2.4 Substrate Scope of Furans to 3-Cyanopyridines

With optimized conditions for transforming furan to pyridines, we investigated the scope and regioselectivity of furans (**Figure 4.2.4.1**). We began by investigating an unsymmetrical furan substrates. The reaction proceeded efficiently with the functionalized or non-functionalized 2,5-dialkyl-substituted furans, affording a mixture of regioisomeric pyridines (**b** to **e**) due to the ring opening from the C2 and C5 positions of the furan. In contrast, a trisubstituted furan with a carbonyl group directly attached at the C3-position influenced the site of carbene insertion, slightly favoring the more substituted side, forming the corresponding tetrasubstituted pyridines (**4.3f** and **4.3f'**) with moderate regioselectivity.

The furan ring bound in *N*-protected indole-3-acetic acid, was selectively converted to the corresponding pyridines (**4.3g** and **4.3g'**), while the *N*-methylindole moiety remained untouched. The furan moiety bound to ciprofibrate, was also successfully converted, demonstrating the compatibility of our methodology with cyclopropane functionality (**4.3h** and **4.3h'**). When our standard reaction conditions were applied to the ketoprofen-bound furan, the furan moiety was efficiently converted into the corresponding pyridines with good yield, demonstrating the compatibility of the methodology with ketone functionality (**4.3i** and **4.3i'**). Together, these results suggest that the regioselectivity of the pyridine products is established at the initial carbene-induced ring-opening step. Multiple factors, including electronic effects, steric constraints, and conformational preferences, dictate the ring-opening step and determine which C–O bond is cleaved, thereby dictating the substitution pattern in the final pyridine products.

Work discussed in this chapter was published as a preprint in Chemrxiv 2026, 10.26434/chemrxiv-2025-vplrf/v2.
The dissertation author primarily performed the work reported in the Results and Discussion.

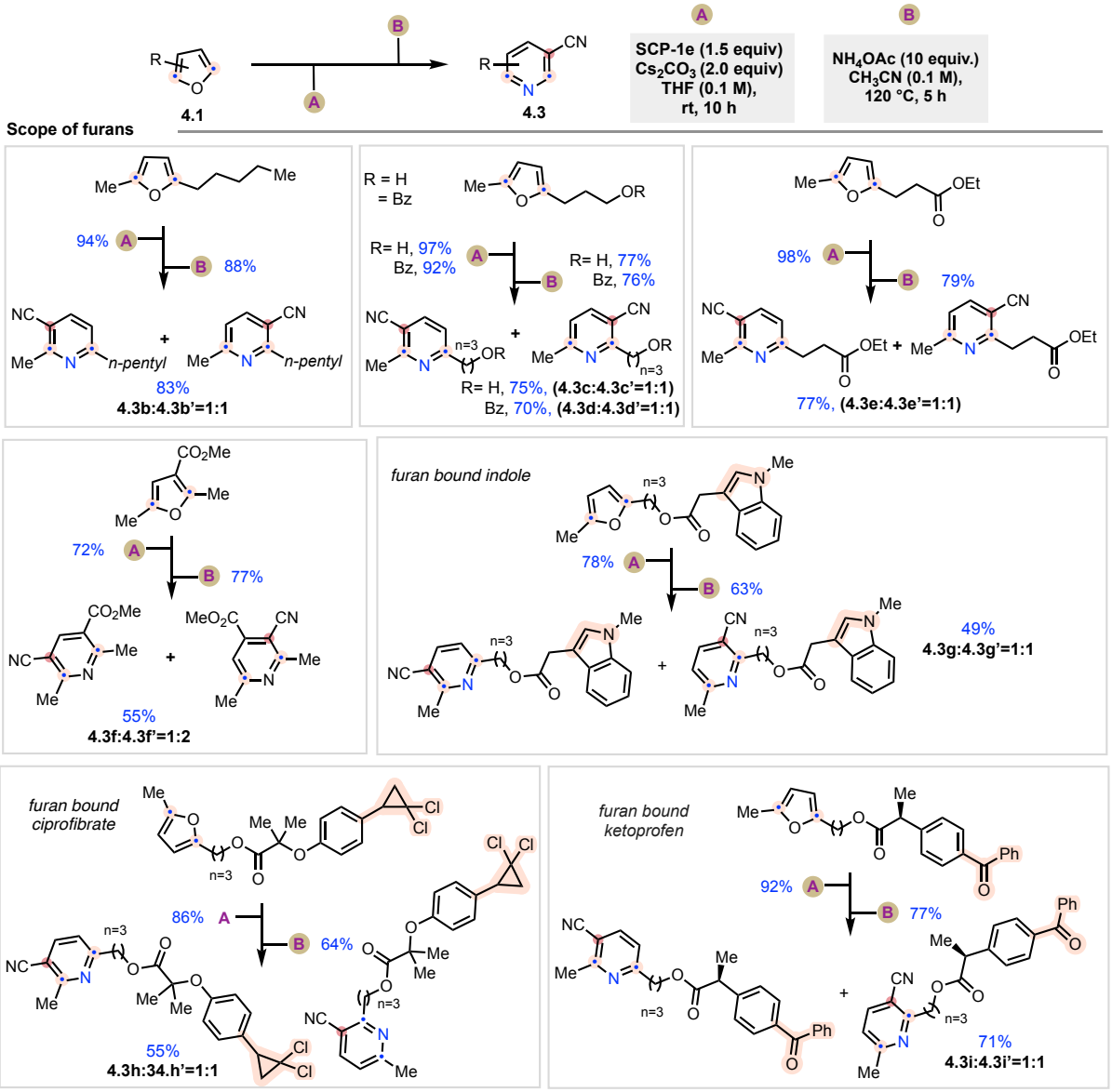


Figure 4.2.4.1: Scope and regioselectivity of furans.

Next, we investigated 2-methyl-5-aryl-substituted furan, which furnish the corresponding pyridine derivative (**4.3j**) as a single regioisomer (**Figure 4.2.4.2**). In these cases, ring opening occurs preferentially on the sterically less-hindered and electron-rich methyl-substituted side, in line with the established behavior of unsymmetrical substituted furans.[92-93]

Motivated by this precedent, we next examined unsymmetrical furans with systematically varied electronic properties with similar steric constrains.

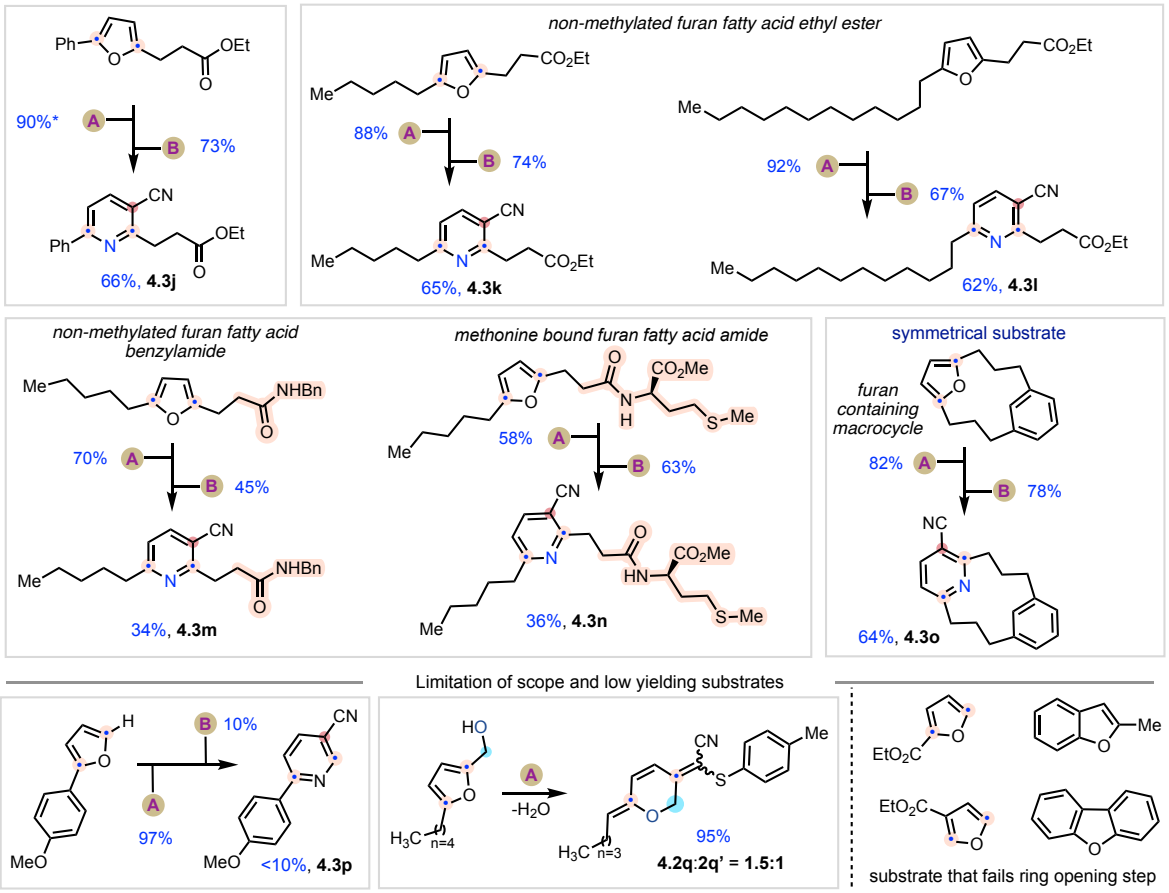


Figure 4.2.4.2: Application to biorelevant furans and limitations of the methodology.

Furan fatty acids (F-acids) and their derivatives (esters, amides) are a rare type of minor fatty acids present in sources such as fish, milk fat, soybeans, and various green plants.[94] They are recognized for their potent antioxidant properties and play a crucial role in protecting polyunsaturated fatty acids from oxidative damage **(Figure 4.2.4.2)**.[95] Our scaffold-hopping methodology enables the regioselective conversion of rare non-methylated furan fatty acid ethyl esters and benzylamide into their corresponding pyridine derivatives. Using our optimized conditions, the amino acid L-methionine bound to furan

was successfully transformed into the corresponding pyridine, demonstrating its compatibility with both amide and thioether linkages.

Furan-containing macrocycles are important scaffolds, valued for their electronic properties, flexibility, and molecular recognition capacity in host–guest systems and in material design.[96] We expanded the scope of our methodology to selectively edit the furan-containing macrocycle**,** thereby accessing the synthetically challenging pyridine-containing macrocycle **4.3o**, which also exhibits anisotropic effects during NMR analyses. We evaluated a C-2 monosubstituted furan to achieve regioselective ring opening from the sterically less hindered unsubstituted C-5 position; however, the subsequent reconstruction step proceeded with poor yield. This outcome highlights a limitation of the methodology, which appears to require 2,5-disubstituted furans for efficient product formation.

The deconstruction of substituted furfuryl alcohol afforded the corresponding substituted dihydropyrans (**4.2qand 4.2q'**), which are presumably produced in a manner similar to an Achmatowicz-type rearrangement via an intramolecular condensation of the ring-opened intermediates generated by regioselective ring opening of the furan from its electron-rich side. This methodology is ineffective for the ring-opening of C-2- and C-3 -substituted furans bearing electron-withdrawing groups. Additionally, furan derivatives such as benzofurans and dibenzofurans did not undergo the desired transformation.

4.2.5 Substrate Scope of Furans to Pyrimidines, Pyrroles, and Pyrimidines

With these optimized conditions for single-step scaffold hopping of furans to pyrimidine, we investigated the scope and regioselectivity of furans (**Figure 4.2.5a**). We began by investigating symmetrical furan substrates. The reaction proceeded efficiently

with 2,5-diaryl-substituted symmetrical furan, yielding a corresponding pyrimidine (**4.2ab**, **4.2ac**). 2,5-aryl-substituted unsymmetrical furans undergo double-nitrogen insertion to afford the corresponding pyrimidine derivatives as a mixture of regioisomers, with no selectivity in second nitrogen insertion (**4.2ad**, **4.2ae**).

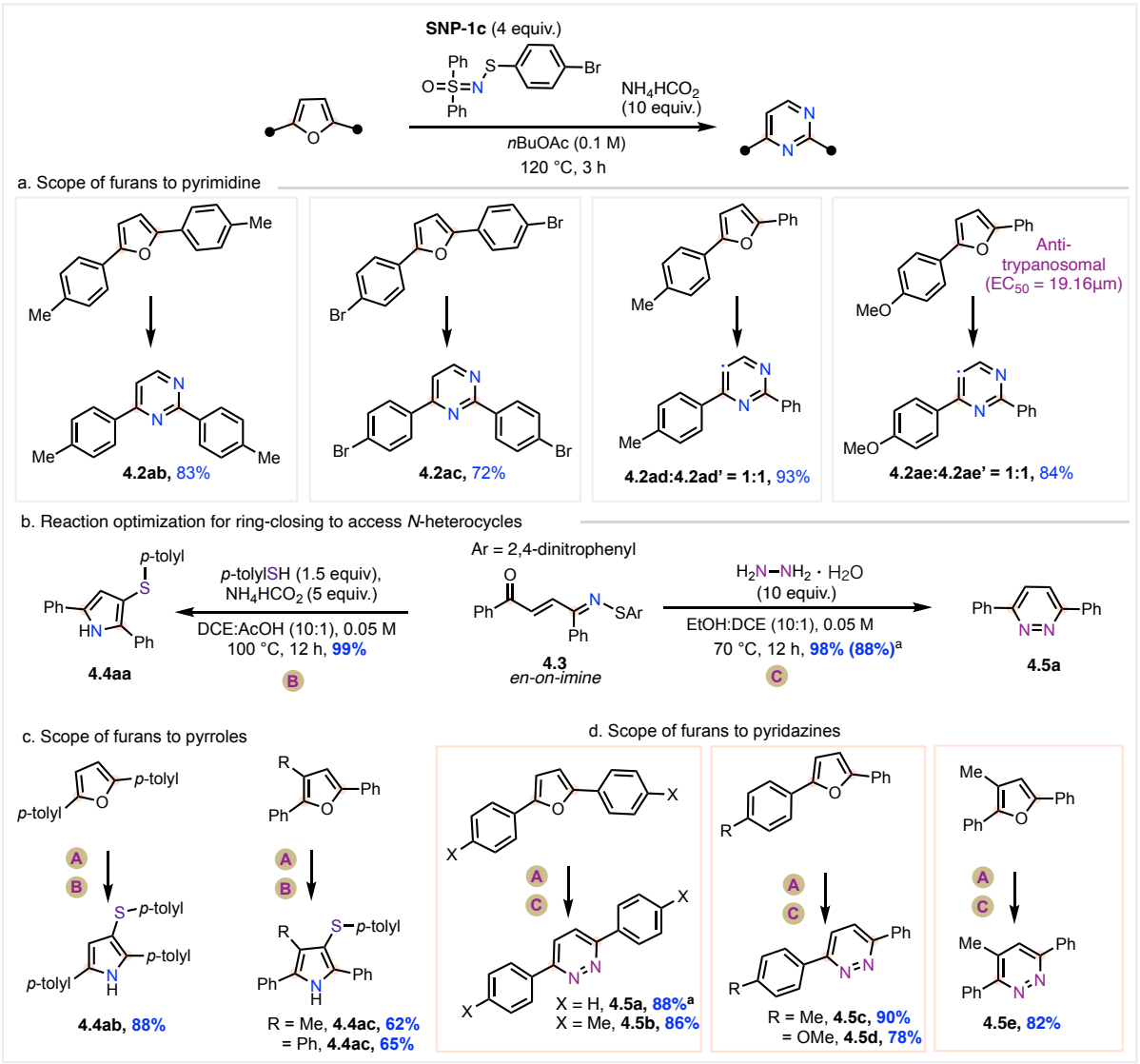


Figure 4.2.5: Scope and regioselectivity of furans to pyrimidines, pyrroles, and pyridazine.

Next, we explored the scope and regioselectivity of furans in their conversion to functionalized pyrroles (**Figure 4.2.5b**). We began with the symmetrical furan substrate,

which was smoothly converted to the corresponding pyrrole **4.4ab** with good yield. Trisubstituted furans (**4.4ac** and **4.4ac**) were also efficiently transformed, providing the corresponding tetrasubstituted pyrroles with good yields. We also explored the scope of furan substrates in their scaffold hopping to pyridazines. Both 2,5-disubstituted symmetrical (**4.5a** and **4.5b**) and unsymmetrical furans (**4.5c** and **4.5d**) were efficiently converted to the corresponding pyridazines. Trisubstituted furan also underwent smooth transformation, affording the desired pyridazine (**4.5e**) with good to moderate yield. This result demonstrates that the methodology is broadly applicable across a range of substitution patterns on the furan core.

4.2.6 Control Experiments, Isotopic Labeling, and Mechanistic Understanding.

To gain insight into the underlying mechanism of the double-nitrogen insertion, we performed a series of control experiments. The ring-opening product was independently synthesized and then subjected to the optimized conditions for scaffold hopping of furans to pyrimidines (**Figure 4.2.6a)**. Under these conditions, the en-on–imine intermediate underwent significant decomposition; however, no pyrimidine formation was observed. Similarly, treatment of the ring-opening product with a sulfoximine-based sulfenylnitrene precursor in the absence of an external ammonia source led to the same outcome, with no desired product detected. In contrast, when the ring-opening product was exposed solely to the ammonia source, it remained largely unreactive and was recovered in significant amounts after the reaction. Overall, these experiments indicate that the double-nitrogen insertion does not proceed via a ring-opening/ring-closing mechanism.

Work discussed in this chapter was published as a preprint in Chemrxiv 2026, 10.26434/chemrxiv-2025-vplrf/v2.
The dissertation author primarily performed the work reported in the Results and Discussion.

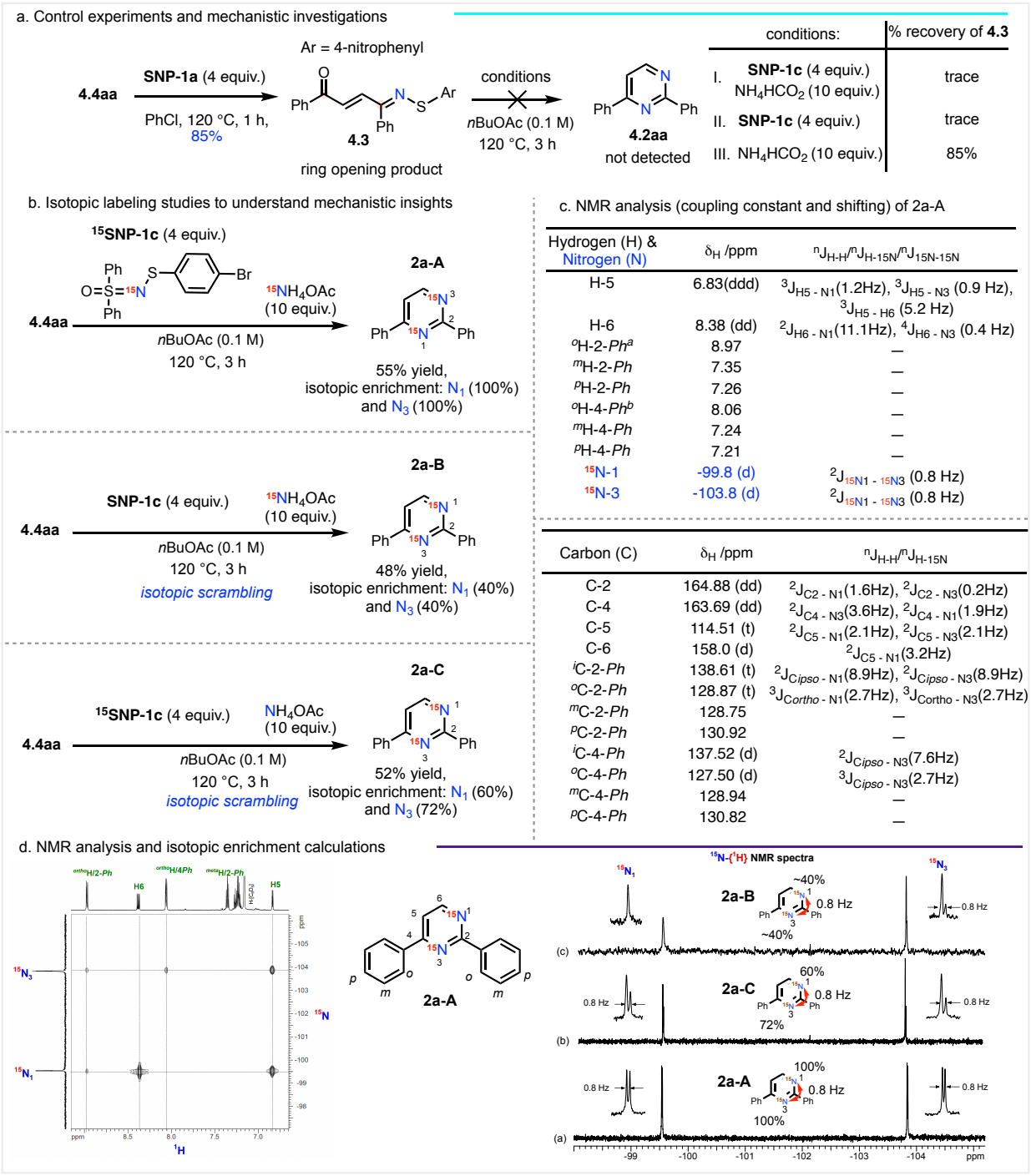


Figure 4.2.6: Control experiment, isotopic labeling, and mechanistic insight.

Next, we performed *¹⁵N* isotopic labeling experiments to elucidate the origin of the nitrogen atoms in the pyrimidine product (**Figure 4.2.6b)**. When a ¹⁵N-labeled ammonia source was employed, isotopic scrambling was observed at the N_1 and N_3 positions of

the pyrimidine (**Figure 4.2.6c** and **d)**. We then synthesized a ^{15}N-labeled sulfenylnitrene precursor and subjected it to the standard reaction conditions. In this case as well, the resulting pyrimidine showed isotopic scrambling at the N_1 and N_3 positions. Finally, when both the sulfenylnitrene precursor and the ammonia source were ^{15}N-labeled, complete labeling at both the N_1 and N_3 positions of the pyrimidine was observed.

4.3 Conclusion

In summary, we have developed a selective, scaffold hopping strategy for furans using cyano sulfenylcarbenes and sulfenylnitrene, enabling the formation of reactive intermediates equipped with an intrinsic thioaryl leaving group. Building on this transformation, we established a streamlined approach for converting these furans into pharmaceutically relevant pyridines, pyrimidines, pyrroles, and pyridazines. Notable features of this methodology include the use of metal-free, bench-stable sulfenylcarbene and sulfenylnitrene precursors, broad substrate scope, excellent functional-group tolerance, and comprehensive mechanistic elucidation through both experimental and computational studies. Overall, this work provides an efficient platform for conceptually innovative strategies for skeletal editing of furans to *N*-heterocycles.

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The dissertation author primarily performed the work reported in the Results and Discussion.

4.4 Experimental Section

Reagents: Reagents and solvents were obtained from Sigma-Aldrich (www.sigma-aldrich.com), ChemImpex (www.chemimpex.com) or Acros Organics (www.fishersci.com) and used without further purification unless otherwise indicated. Dry solvents (acetonitrile) were obtained from Acros Organics (www.fishersci.com), and dichloromethane was distilled over CaH_2 under N_2 unless otherwise indicated. THF purchased from Sigma-Aldrich was distilled over Na metal with benzophenone indicator.

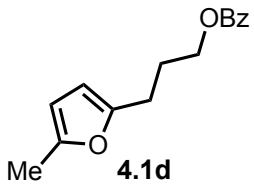
Reactions: All reactions were performed in flame-dried glassware under positive N_2 pressure with magnetic stirring unless otherwise noted. Liquid reagents and solutions were transferred thru rubber septa via syringes flushed with N_2 prior to use. Cold baths were generated as follows: 0 °C with wet ice/water, –5 °C with Julabo (MeOH as a coolant), and −78 °C with dry ice/acetone.

Chromatography: TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$), cerium ammonium molybdenate (CAM), phosphomolybdic acid (PMA), and ninhydrin. Silica flash chromatography was performed on Sorbtech 230–400 mesh silica gel 60.

Analytical Instrumentation: NMR spectra were recorded on a Varian VNMRS 400, 500, and 600 MHz NMR spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (^1H, 7.26 ppm, ^{13}C, 77.0 ppm); coupling constants are expressed in Hz. NMR spectra were processed using Mnova. Mass spectra were obtained at the OU Analytical Core Facility on an Agilent 6538 High-Mass-Resolution QTOF Mass Spectrometer and an Agilent 1290 UPLC.

4.5 Preparation and Characterization of Furans

3-(5-Methylfuran-2-yl)propyl benzoate (4.1d):



4.1d

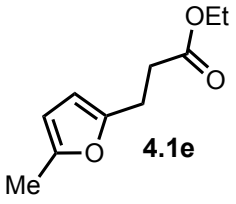
To a solution of alcohol (1.0 equiv., 100 mg, 0.713 mmol) in 5 mL dry CH_2Cl_2 at ice cold conditions, triethylamine (3.0 equiv., 216 mg, 0.30 mL, 2.13 mmol) was added followed by a dropwise addition of benzoyl chloride (1.1 equiv., 110 mg, 0.782 mmol). The reaction mixture was stirred at 25°C for 2 hours. After completion of the reaction, resulting mixture was diluted in H_2O (10 mL) and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by silica gel flash column chromatography to yield title compound as clear oil. (150 mg, 86% yield; **TLC**: R_f 0.30 in 5% EtOAc/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.10 – 8.03 (m, 2H), 7.59 – 7.52 (m, 1H), 7.48 – 7.40 (m, 2H), 5.92 (t, *J* = 2.0 Hz, 1H), 5.86 (dt, *J* = 3.0, 1.1 Hz, 1H), 4.38 (t, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.25 (s, 3H), 2.11 (tt, *J* = 7.3, 6.4 Hz, 2H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 166.6, 153.0, 150.6, 132.9, 130.4, 129.7, 129.6, 128.4, 106.0, 77.5, 76.8, 64.3, 27.4, 24.8, 13.5, 13.52.

HRMS(ESI): calculated for $C_{15}H_{17}O_3(M+H)^+$: 245.1172; found: 245.1168.

Ethyl 3-(5-methylfuran-2-yl)propanoate (4.1e):



4.1e

A solution of 5-methylfurfural (1.0 equiv. 500 mg, 4.54 mmol) in dry THF (0.5 M) at 0°C was treated with triethyl phosphonoacetate (2.0 equiv., 1.81 mL, 9.08 mmol) and sodium hydride (60% NaH, 2.5 equiv., 454 mg, 11.4 mmol). The mixture was allowed to warm to 25°C and stirred at the same temperature for 12 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel flash column chromatography to yield acrylate. (700 mg, 85% yield; **TLC**: R_f 0.20 in 5% EtOAc/hexane) The spectral data of product matched with previously reported literature.[78]

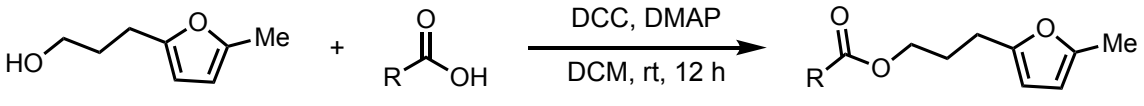
Further, this acrylate (1.0 equiv., 700 mg) was dissolved in 1:1 mixtures of EtOH/THF (10 mL), and 5% palladium on carbon (3 wt%, 21 mg) was added. The resulting solution was stirred vigorously under H_2 gas (open air) at 25 °C for 5 minutes. After the completion of reaction, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated and dried in vacuo to afford the title compound (700 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (d, *J* = 3.0 Hz, 1H), 5.85 – 5.79 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.90 (t, *J* = 7.7 Hz, 2H), 2.61 (dd, *J* = 8.5, 6.8 Hz, 2H), 2.23 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 172.8, 152.5, 150.8, 106.00, 105.95, 60.6, 33.1, 23.7, 14.3, 13.6.

HRMS(ESI): calculated for $C_{10}H_{15}O_3(M+H)^+$: 183.1016; found: 183.1006.

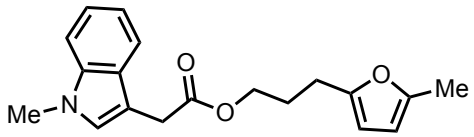
General procedure C



4.1c carboxylic acid **4.g, 4.1h,** and **4.1i**

To a solution of **4.1i** (1.0 equiv.) in dry CH_2Cl_2 (0.1 M) was added corresponding carboxylic acid (1.1 equiv.), *N,N'*-dicyclohexylcarbodiimide (DCC, 1.5 equiv.), and 4-(dimethylamino)pyridine (DMAP, 20 mol%) at room temperature. The resulting reaction mixture was stirred at 25 °C for 12 hours. Upon completion, the resulting mixture was directly loaded onto silica gel and purified by flash column chromatography.

3-(5-Methylfuran-2-yl)propyl 2-(1-methyl-1H-indol-3-yl)acetate (4.1k):



4.1g

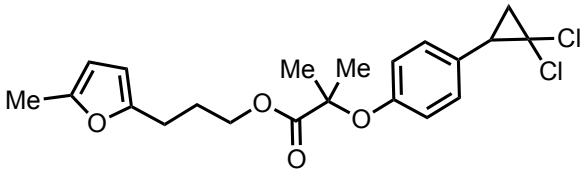
Synthesized according to general procedure C using **4.1c** (1.0 equiv., 50 mg, 0.357 mmol), 2-(1-methyl-1*H*-indol-3-yl)acetic acid (1.2 equiv. 80.9 mg, 0.428 mmol), DCC (1.5 equiv., 110.4 mg, 0.535 mmol), and DMAP (20 mol%, 8.7 mg, 0.071 mmol). Silica gel flash column chromatography gave the title compound as a waxy colorless oil. (90 mg, 81% yield; **TLC**: R_f 0.30 in 10% EtOAc/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.32 – 7.20 (m, 2H), 7.12 (tq, *J* = 6.9, 0.9 Hz, 1H), 7.05 (s, 1H), 5.86 – 5.77 (m, 2H), 4.13 (td, *J* = 6.5, 1.3 Hz, 2H), 3.76 (s, 5H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.24 (s, 3H), 2.00 – 1.90 (m, 2H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 172.4, 153.1, 150.6, 137.0, 127.8, 127.8, 121.9, 119.3, 109.4, 107.0, 106.0, 64.2, 32.9, 31.4, 27.4, 24.7, 13.7.

HRMS(ESI): calculated for $C_{19}H_{22}NO_3(M+H)^+$: 312.1594; found: 312.1592.

3-(5-Methylfuran-2-yl)propyl-2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methylpropa-noate (4.1h):



4.1h

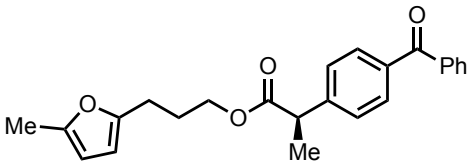
Synthesized according to general procedure C using **4.1c** (1.0 equiv., 60 mg, 0.428 mmol), 2-(4-(2,2-dichlorocyclopropyl)-phenoxy)-2-methylpropanoic acid (1.1 equiv. 136.1 mg, 0.471 mmol), DCC (1.5 equiv., 132.5 mg, 0.642 mmol), and DMAP (1.0 equiv., 52.3 mg, 0.428 mmol). Silica gel flash column chromatography gave the title compound as a colorless oil. (120 mg, 68% yield); **TLC**: R_f 0.20 in 5% EtOAc/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.83 – 5.81 (m, 1H), 5.80 – 5.78 (m, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 2.82 (dd, *J* = 10.7, 8.3 Hz, 1H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.23 (s, 3H), 1.97 – 1.86 (m, 3H), 1.80 – 1.72 (m, 1H), 1.61 (s, 6H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 174.4, 155.1, 152.8, 150.7, 129.8, 128.2, 118.5, 106.0, 105.9, 79.2, 64.8, 60.9, 34.9, 27.1, 25.9, 25.5, 24.4, 13.6.

HRMS(ESI): calculated for $C_{21}H_{25}Cl_2O_4(M+H)^+$: 411.1105; found: 411.1097.

3-(5-Methylfuran-2-yl)propyl (*S*)-2-(4-benzoylphenyl)propanoate (4.1i):



4.1i

Synthesized according to general procedure C using **4.1c** (1.0 equiv., 50 mg, 0.357 mmol), (*S*)-2-(4-benzoylphenyl)propanoic acid (1.1 equiv., 99.8 mg, 0.392 mmol),

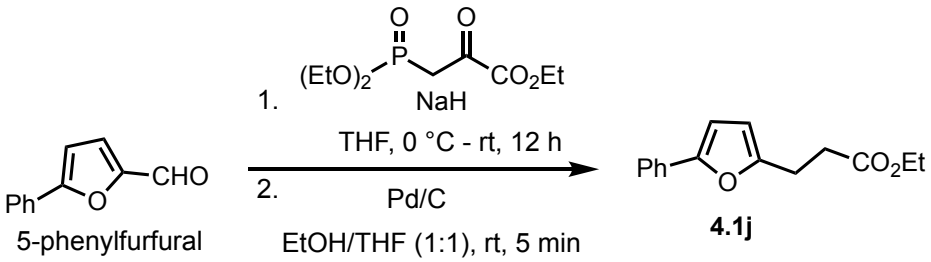
N,N'-dicyclohexylcarbodiimide (DCC, 1.5 equiv. 110.4 mg, 0.535 mmol), and 4-(dimethylamino)pyridine (DMAP, 20 mol%, 8.7 mg, 0.071 mmol); the reaction mixture was stirred at 25 °C for 12 hours. Silica gel flash column chromatography gave the title compound as a colorless oil. (120 mg, 81% yield; **TLC**: R_f 0.20 in 5% EtOAc/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 3H), 7.68 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.50 – 7.42 (m, 3H), 5.83 – 5.76 (m, 2H), 4.11 (td, *J* = 6.5, 1.1 Hz, 2H), 3.80 (q, *J* = 7.1 Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.22 (d, *J* = 1.0 Hz, 3H), 1.96 – 1.85 (m, 2H), 1.54 (d, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 196.7, 174.2, 152.9, 150.7, 141.0, 138.0, 137.6, 132.6, 131.7, 130.2, 129.4, 129.2, 128.7, 128.5, 106.0, 64.3, 45.6, 27.3, 24.5, 18.5, 13.6.

HRMS(ESI): calculated for $C_{24}H_{25}O_4(M+H)^+$: 377.1747; found: 377.1742.

Ethyl 3-(5-phenylfuran-2-yl)propanoate (1r):



A solution of 5-phenylfurfural (1.0 equiv. 200 mg, 1.16 mmol) in dry THF (0.5 M) at 0°C was treated with triethyl phosphonoacetate (1.5 equiv., 391 mg, 1.74 mmol) and sodium hydride (60% NaH, 2.0 equiv., 93 mg, 2.32 mmol). The mixture was allowed to warm to 25 °C and stirred at the same temperature for 12 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered,

concentrated, and passed through short silica pad and used without further purification.

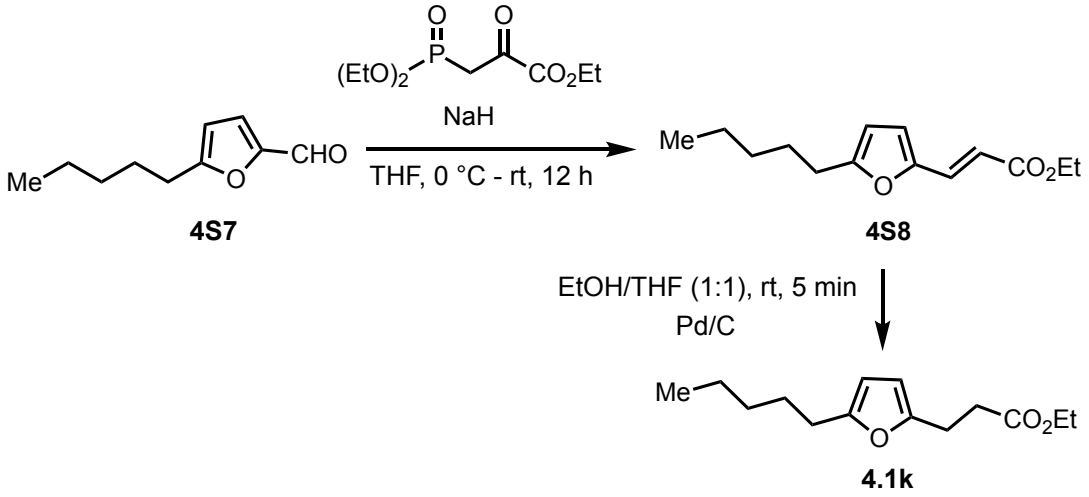
Further, this acrylate (1.0 equiv., 280 mg) was dissolved in 1:1 mixture of EtOH/THF (10 mL), and 5% palladium on carbon (3 wt%, 8 mg) was added. The resulting solution was stirred vigorously under H_2 gas (open air) at 25 °C for 5 minutes. After the completion of reaction, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated and dried in vacuo to afford the title compound (280 mg, 80% yield over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.59 (m, 2H), 7.39 – 7.33 (m, 2H), 7.25 – 7.20 (m, 1H), 6.54 (d, *J* = 3.2 Hz, 1H), 6.11 (dt, *J* = 3.2, 0.9 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.08 – 3.00 (m, 2H), 2.71 (dd, *J* = 8.2, 7.0 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 172.67, 154.07, 152.78, 131.13, 128.75, 127.09, 123.54, 107.66, 105.82, 60.74, 32.96, 23.84, 14.37.

HRMS(ESI): calculated for $C_{15}H_{17}O_3(M+H)^+$: 245.1178; found: 245.1176.

Synthesis of 4.1k:



Ethyl (*E*)-3-(5-pentylfuran-2-yl)acrylate (4S8): A solution of 5-pentylfurfural (1.0 equiv. 500 mg, 4.54 mmol) in dry THF (0.5 M) at 0°C was treated with triethyl phosphonoacetate (2.0 equiv.) and sodium hydride (60% NaH, 2.5 equiv.). The mixture was allowed to warm to 25 °C and stirred at the same temperature for 12 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel flash column chromatography to obtain the product. (600 mg, 85% yield; **TLC**: R_f 0.40 in 5% EtOAc/hexane).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 15.7 Hz, 1H), 6.50 (d, *J* = 3.3 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 6.07 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.66 (p, *J* = 7.4 Hz, 2H), 1.37 – 1.30 (m, 7H), 0.93 – 0.88 (m, 3H).

^{13}C{^{1}H} NMR: (125 MHz, $CDCl_3$) δ 167.6, 160.1, 149.5, 131.4, 116.4, 114.1, 108.1, 60.5, 31.5, 28.4, 27.6, 22.5, 14.6, 14.1.

HRMS(ESI): calculated for $C_{14}H_{21}O_3(M+H)^+$: 237.1485; found: 237.1486.

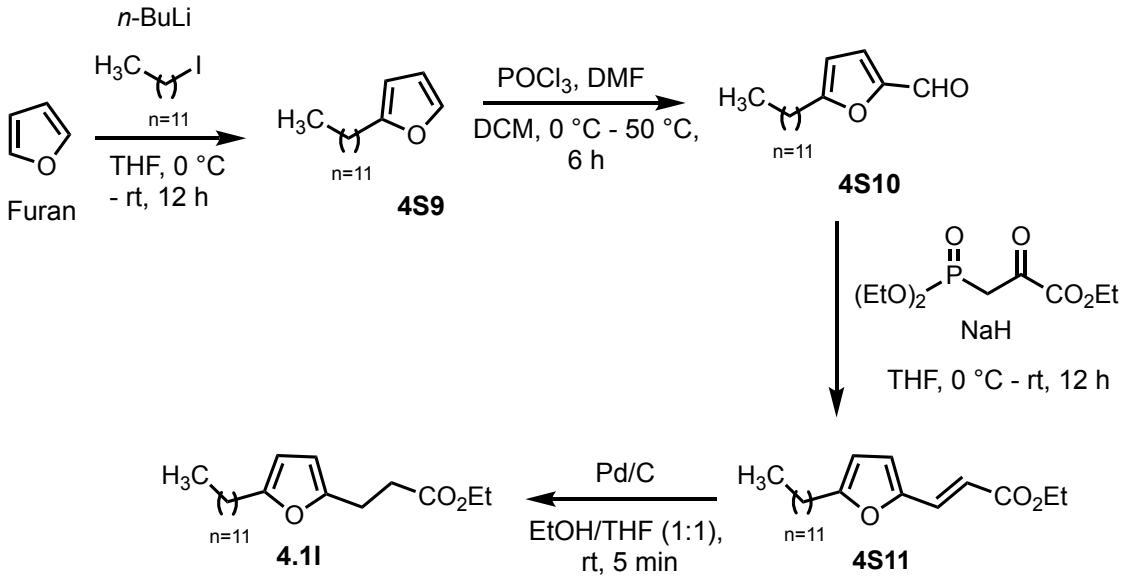
Ethyl 3-(5-pentylfuran-2-yl)propanoate (4.1k): To the acrylate **4S8** (1.0 equiv., 600 mg) dissolved in 1:1 mixtures of EtOH/THF (20 mL), and 5% palladium on carbon (3 wt%, 27 mg) was added. The resulting solution was stirred vigorously under H_2 gas (open air) at 25 °C for 5 minutes. After the completion of reaction, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated and dried in vacuo to afford the title compound. (600 mg, 99% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.88 (d, *J* = 3.0 Hz, 1H), 5.83 (d, *J* = 2.9 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.91 (dd, *J* = 8.7, 6.7 Hz, 2H), 2.62 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.60 (t, *J* = 7.5 Hz, 2H), 1.33 – 1.29 (m, 4H), 1.25 (s, 3H), 0.90 (q, *J* = 4.0 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) δ 172.8, 155.4, 152.3, 105.7, 105.1, 60.6, 33.1, 31.5, 28.1, 27.9, 23.7, 22.6, 14.4, 14.1.

HRMS(ESI): calculated for $C_{14}H_{23}O_3(M+H)^+$: 239.1642; found: 239.1645.

Synthesis of 4.1l:



2-Dodecylfuran(S9): Under N_2 atmosphere at 0°C, *n*-butyllithium (*n*-BuLi, 1.6 M in hexane, 1.5 equiv.) was added slowly to a solution of furan (1.0 equiv., 200 mg, 1.45 mmol) in dry THF (0.5 M). The mixture was allowed to warm to room temperature and stirred at this temperature for 3 hours. The resulting mixture was cooled to 0 °C before the addition of alkyl iodide (1.2 equiv.) and the reaction mixture was stirred at 25 °C for another 12 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl, diluted in H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel flash column chromatography (hexane as an eluent) to afford title compound as a yellow liquid. (280 mg, 41% yield; **TLC**: R_f 0.60 in 1% EtOAc/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 1.8 Hz, 1H), 6.30 – 6.24 (m, 1H), 5.96 (d, *J* = 3.1 Hz, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.61 (d, *J* = 7.5 Hz, 2H), 1.25 (s, 18H), 0.87 (d, *J* = 7.0 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) δ 156.8, 140.8, 110.2, 104.6, 32.1, 29.8, 29.8, 29.7, 29.51, 29.50, 29.4, 29.3, 28.2, 28.1, 22.8, 14.3.

HRMS(ESI): calculated for $C_{16}H_{29}O(M+H)^+$: 237.2123; found: 237.2129.

5-Dodecylfuran-2-carbaldehyde (4S10): Under N_2 atmosphere at 0°C, $POCl_3$ (1.4 equiv.) was dissolved in CH_2Cl_2, followed by the addition of DMF (5 equiv.). After 30 min at room temperature, **4S9** (1 equiv., 280 mg, 1.18 mmol) in dry CH_2Cl_2 was added and the resulting mixture was refluxed at 50 °C for next 6 hours. After completion of reaction, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 . The organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel flash column chromatography to afford title compound as a yellow liquid. (250 mg, 79% yield; **TLC**: R_f 0.60 in 5% EtOAc/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.17 (d, *J* = 3.6 Hz, 1H), 6.23 (d, *J* = 3.5 Hz, 1H), 2.71 (t, *J* = 7.7 Hz, 2H), 1.69 (p, *J* = 7.5 Hz, 2H), 1.25 (s, 18H), 0.88 (t, *J* = 6.7 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) δ 177.1, 164.4, 151.9, 108.8, 32.1, 29.8, 29.6, 29.5, 29.4, 29.3, 28.6, 27.7, 22.8, 14.3.

HRMS(ESI): calculated for $C_{17}H_{29}O_2(M+H)^+$: 265.2168; found: 265.2172.

Ethyl (*E*)-3-(5-dodecylfuran-2-yl)acrylate (4S11): A solution of **4S10** (1.0 equiv. 250 mg, 0.94 mmol) in dry THF (0.5 M) at 0 °C was treated with triethyl phosphonoacetate (2.0 equiv.) and sodium hydride (60% NaH, 2.5 equiv.). The mixture was allowed to warm to 25 °C and stirred at the same temperature for 12 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel flash column chromatography to obtain the title

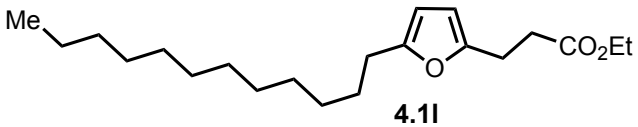
compound as a yellowish liquid. (265 mg, 84% yield; **TLC**: R_f 0.60 in 5% EtOAc/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 15.6 Hz, 1H), 6.50 (d, *J* = 3.3 Hz, 1H), 6.22 (d, *J* = 15.6 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.70 – 1.60 (m, 2H), 1.28 (d, *J* = 22.6 Hz, 21H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 167.6, 160.1, 149.5, 131.3, 116.4, 114.1, 108.1, 60.4, 32.1, 29.80, 29.77, 29.66, 29.50, 29.46, 29.30, 28.4, 27.9, 22.8, 14.5, 14.3.

HRMS(ESI): calculated for $C_{21}H_{35}O_3(M+H)^+$: 335.2586; found: 335.2581.

Ethyl 3-(5-dodecylfuran-2-yl)propanoate (4.1l):



4.1l

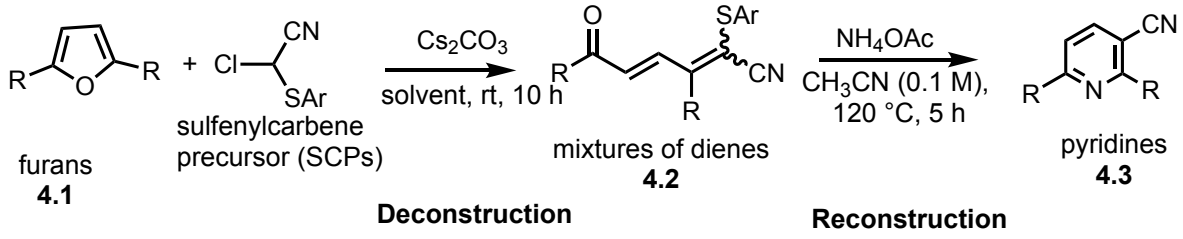
To the acrylate **4S8** (1.0 equiv., 150 mg) dissolved in 1:1 mixtures of EtOH/THF (20 mL), and 5% palladium on carbon (3 wt%, 27 mg) was added. The resulting solution was stirred vigorously under H_2 gas (open air) at 25 °C for 5 minutes. After the completion of reaction, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated and dried in vacuo to afford the title compound. (150 mg, 99% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 3.0, 1.0 Hz, 1H), 5.83 (dd, *J* = 3.0, 1.0 Hz, 1H), 4.14 (qd, *J* = 7.1, 1.0 Hz, 2H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.66 – 2.58 (m, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.60 (d, *J* = 7.1 Hz, 2H), 1.27 – 1.24 (m, 21H), 0.89 – 0.85 (m, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 172.9, 155.4, 152.3, 105.7, 105.1, 60.6, 33.0, 32.1, 29.8, 29.8, 29.7, 29.5, 29.5, 29.4, 28.19, 28.18, 23.7, 22.8, 14.4, 14.3.

HRMS(ESI): calculated for $C_{21}H_{37}O_3(M+H)^+$: 337.2737; found: 337.2735.

4.6 General Procedure for the Deconstruction/Reconstruction of Furans to Access Pyridines



General Procedure D: Deconstruction of furans: To a mixture of an appropriate furan (1 equiv.) and sulfenylcarbene precursors (SCPs) (1.5 equiv.) in THF or ^{i}PrOH (0.1 M), was added cesium carbonate (2 equiv.) and the reaction mixture was stirred at 25 °C for 10 hours. After completion of reaction as indicated by TLC, the reaction mixture was diluted with ethyl acetate, passed over a pad of silica, and concentrated under reduced pressure. Major impurities were removed by passing through a short pad of silica before conducting the next step. (*Note: complete removal of Cs_2CO_3 is required for the reproducibility of reconstruction step*)

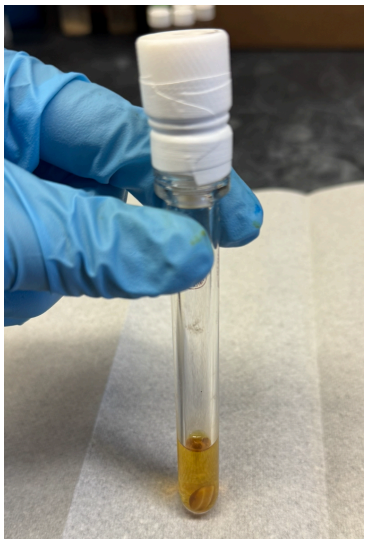
***Alternative work-up 1*:** The reaction mixture was diluted in water and extracted with ethyl acetate; the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

***Alternative work-up 2*:** The solvent was removed by blowing nitrogen across the surface of the reaction mixture at room temperature. (*Note: the deconstructed products were slightly decomposed at ca. 40 °C in the presence of Cs_2CO_3*)

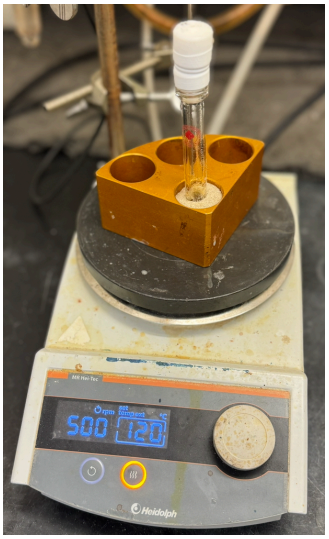
General Procedure E: Reconstruction to Pyridines: An oven-dried sealed tube was charged with a corresponding mixture of dienones (1.0 equiv.), 10 equiv. of ammonium acetate (NH_4OAc), and MeCN (0.1 M). The reaction mixture was placed into a 120 °C pre-heated sand bath and stirred at the same temperature for 5 hours. The resulting black mixture was passed over a pad of silica while eluting with EtOAc and concentrated under reduced pressure. The crude material was purified by silica gel

flash column chromatography to obtain the pyridines. (*Note-1: 0.1 M MeCN concentration is required for the reproducibility of reconstruction step, Note-2: Reactions were done in seal tube and covered with blast-shield as shown in reaction-set up below.)*

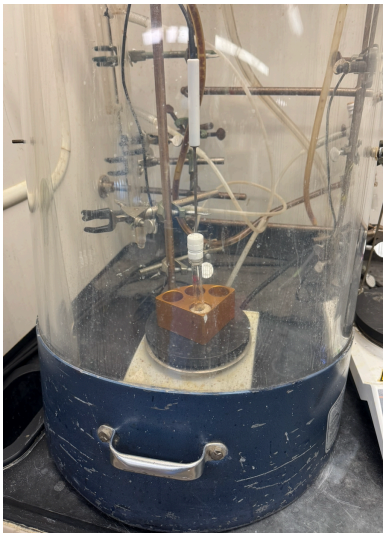
Caution: Superheated solvents can undergo rapid boiling or explosive decompression upon disturbance or vessel opening, posing a significant risk; therefore, appropriate pressure-rated equipment, temperature control, and shielding should be used at all times.



reaction mixture before heating



reaction set up

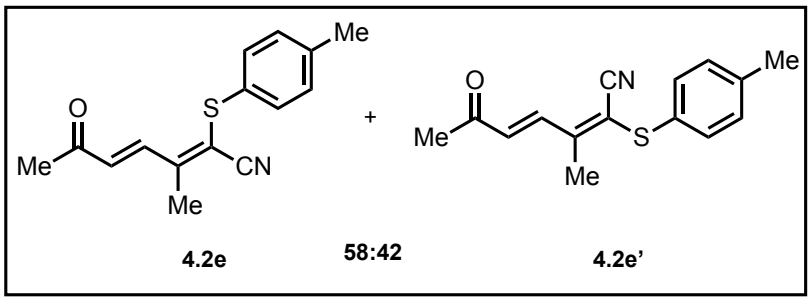


blast shield for safety

Alternative reconstruction conditions: A 5 mL microwave vial was dried in an oven and cooled to room temperature. To this vial were added dienes (1.0 equiv.), 10 equiv of ammonium acetate (NH_4OAc), and MeCN (0.1 M), after which it was closed with a silicone cap. The reaction vessel was placed in the CEM microwave reactor with an external IR and heated at 120 °C for 1 hour. The resulting black mixture was passed over a pad of silica while eluting with EtOAc and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography

to obtain the pyridines. (*Note: 0.1 M MeCN concentration is required for the reproducibility of reconstruction step*)

4.6.1 Characterization of Ring Opening Products

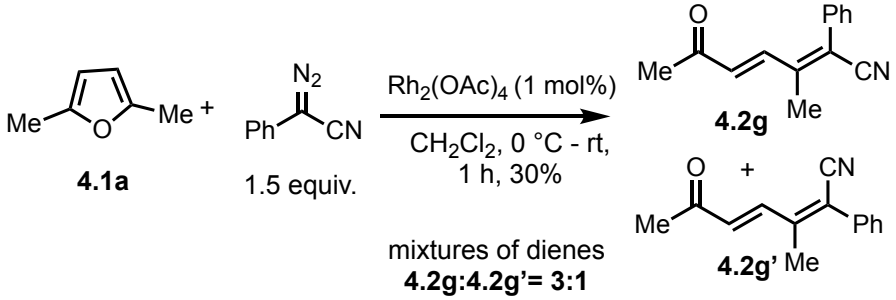


^{1}H NMR of **4.2e and 4.2e'** (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 16.1 Hz, 2H), 7.59 (d, *J* = 15.9 Hz, 1H), 7.41 – 7.39 (m, 2H), 7.39 – 7.34 (m, 3H), 7.24 – 7.20 (m, 2H), 7.19 – 7.15 (m, 3H), 6.46 (d, *J* = 15.9 Hz, 2H), 6.35 (d, *J* = 12.2 Hz, 1H), 2.39 (s, 5H), 2.38 (s, 3H), 2.37 (2, 5H), 2.37 (s, 3H) 2.30 (s, 5H), 2.20 (s, 3H).

^{13}C{^{1}H} NMR of **4.2e and 4.2e'** (150 MHz, $CDCl_3$): δ 198.3, 190.0, 149.2, 146.7. 140.5, 139.9, 137.0, 134.2, 133.1, 132.9, 131.8, 130.6, 127.3, 126.2, 117.9, 115.6, 115.0, 113.8, 28.0, 27.3, 21.4,19.3, 15.7.

4.6.2 Ring Opening of Furans with Phenylcyanocarbene

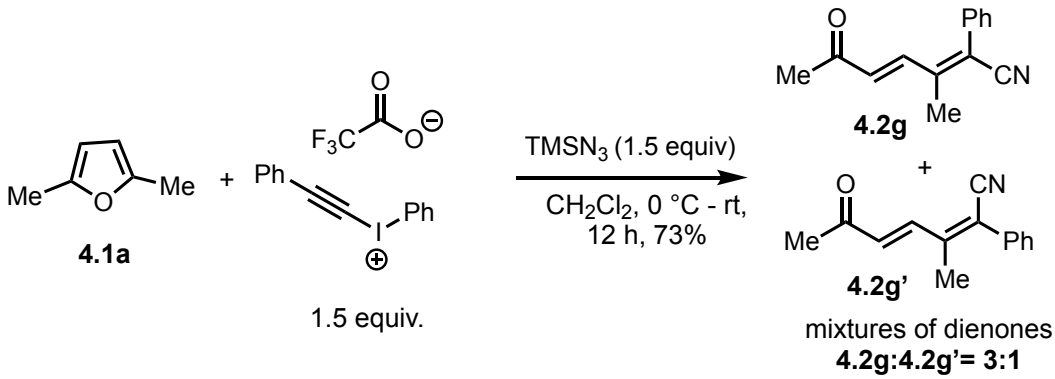
Diazo based metal catalyzed approach:



To a solution of **4.1a** (100 mg, 1.04 mmol) in CH_2Cl_2 (0.1 M) at ice cold conditions, 1 mol% of $Rh_2(OAc)_4$ was added, followed by the dropwise addition of diazo (1.5 equiv. 223 mg, 1.56 mmol) [synthesized according to reported literature][97] dissolved in 0.1 M CH_2Cl_2. The resulting solution was allowed to stir at room temperature for 1 h,

reaction mixture was filtered through short pad of celite, and compound was purified by silica-gel column chromatography.

Diazo based metal catalyzed approach:



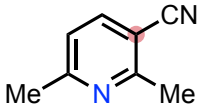
To a solution of **4.1a** (100 mg, 1.04 mmol) in CH_2Cl_2 (0.1 M) at ice cold conditions, solid phenyl(phenylethynyl)iodonium trifluoroacetate (1.5 equiv., 652 mg, 1.56 mmol) [synthesized according to literature][98] was added all at once and stirred until all solid get dissolved (~ 5 minutes). To the resulting solution $TMSN_3$ (1.5 equiv. 180 mg, 1.56 mmol) dissolved in 0.1 M CH_2Cl_2 was added dropwise over 15 minutes. The resulting solution was allowed to warm to room temperature and stirred at this temperature for overnight. The reaction mixture was filtered through short pad of celite, and compound was purified by silica-gel column chromatography.

^{1}H NMR: (400 MHz, C_6D_6) δ 7.23-7.20 (m, 3H), 6.95-6.97 (m, 4H), 6.21 (d, *J* = 12.1 Hz, 0.3 H), 5.70 (d, *J* = 12.3 Hz, 1H), 5.63 (d, *J* = 12.1 Hz, 1H), 5.35 (d, *J* = 12.3 Hz, 1H), 2.14 (s, 3H), 1.75 (s, 1H), 1.70 (s, 1H), 1.57 (s, 3H).

^{13}C{^{1}H} NMR: (100 MHz, C_6D_6) δ 197.08, 197.77, 151.88, 150.65, 138.93, 137.99, 134.23, 133.85, 131.32, 130.93, 129.58, 129.30, 128.96, 128.83, 128.73, 128.59, 118.30, 118.16, 115.63, 113.43, 30.10, 29.9 ,22.05, 18.96.

4.6.3 Characterization of Pyridines

2,6-Dimethylnicotinonitrile (4.3a):



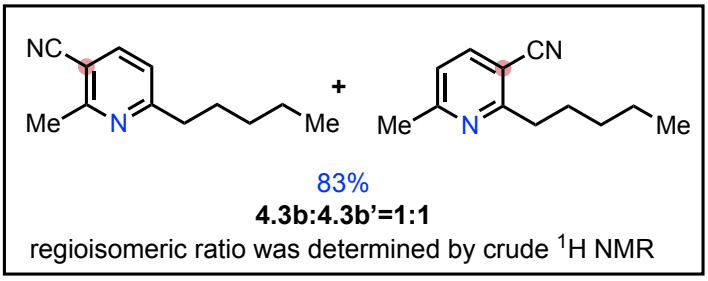
4.3a

The compound was synthesized as described in general procedures D and E, starting from furan (1.0 equiv., 150 mg, 1.56 mmol) and **SCP-1e** (1.5 equiv.) in ^{i}PrOH (.1 M). The title compound was obtained as a white solid after purification by silica gel flash column chromatography. (171 mg, 83% yield over 2 steps; **TLC**: R_f 0.10 in 20% EtOAc/hexane). The spectral data of product matched with previously reported literature.[51]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.74 (s, 3H), 2.60 (s, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 162.5,161.2, 140.3, 120.8, 117.4, 106.2, 25.1, 23.8.

2-Methyl-6-pentylnicotinonitrile (4.3b) and 6-Methyl-2-pentylnicotinonitrile (4.3b'):



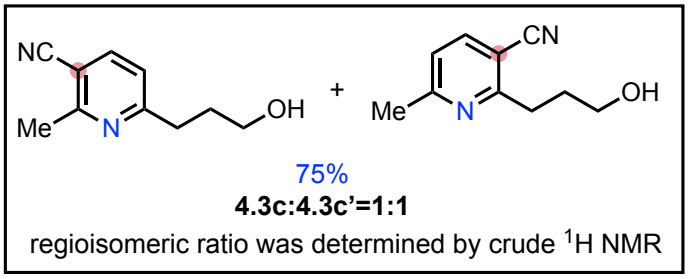
The compounds were synthesized as described in general procedures D and E, starting from furan (20 mg, 0.13 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The mixture of isomers were obtained as a white solid (20 mg, 83% yield over 2 steps, **TLC**: R_f 0.20 in 20% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.0, 5.4 Hz, 2H), 7.07 (dd, *J* = 8.0, 1.5 Hz, 2H), 3.01 – 2.94 (m, 2H), 2.80 (d, *J* = 1.5 Hz, 2H), 2.74 (s, 3H), 2.60 (s, 3H), 1.72 (ddd, *J* = 15.3, 7.8, 5.2 Hz, 4H), 1.35 (dq, *J* = 10.7, 3.5 Hz, 8H), 0.91 – 0.88 (m, 6H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 166.6, 165.4, 162.6, 161.3, 140.4, 140.2, 120.7, 120.1, 117.6, 117.5, 106.2, 105.7, 39.0, 37.4, 31.68, 31.65, 29.6, 29.5, 25.2, 23.8, 22.60, 22.57, 14.11, 14.10.

HRMS(ESI): calculated for $C_{12}H_{17}N_2(M+H)^+$: 189.1386; found: 189.1379.

6-(3-Hydroxypropyl)-2-methylnicotinonitrile (4.3c) and **2-(3-Hydroxypropyl)-6-methylnicotinonitrile (4.3c'):**



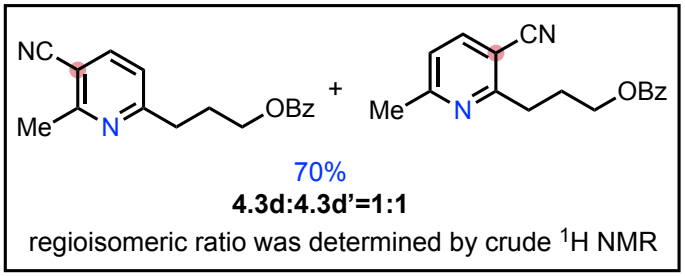
The compounds were synthesized as described in general procedures D and E, starting from furan (20 mg, mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The mixture of isomers were obtained as a white solid (18.5 mg, 77% yield over 2 steps, **TLC**: R_f 0.30 in 50% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.13 (dd, *J* = 8.1, 2.5 Hz, 2H), 3.71 (q, *J* = 5.8 Hz, 4H), 3.18 (t, *J* = 6.9 Hz, 2H), 2.98 (t, *J* = 7.1 Hz, 2H), 2.75 (s, 3H), 2.61 (s, 3H), 2.08 – 1.97 (m, 4H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 165.4, 164.2, 162.2, 161.1, 140.5, 140.4, 120.9, 120.4, 117.1, 117.0, 106.5, 106.0, 62.1, 62.1, 33.9, 33.5, 31.4, 31.0, 24.9, 23.5.

HRMS(ESI): calculated for $C_{10}H_{13}N_2O(M+H)^+$: 177.1022; found: 177.1024.

2-(5-Cyano-6-methylpyridin-2-yl)ethyl benzoate (4.3d) and 2-(3-Cyano-6-methylpyridin-2-yl)ethyl benzoate (4.3d'):



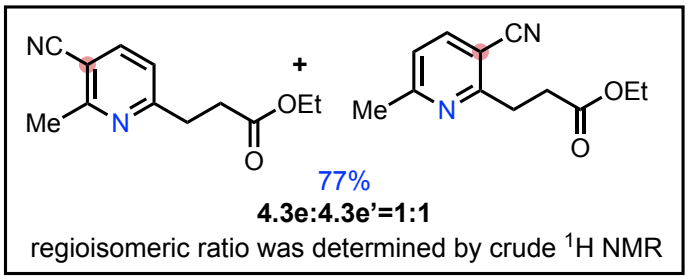
The compounds were synthesized as described in general procedures D and E, starting from furan (20 mg, 0.081mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The mixture of isomers was obtained as a colorless oil (16 mg, 70% yield over 2 steps, **TLC**: R_f 0.20 in 15% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.05 – 8.01 (m, 2H), 8.00 – 7.95 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.45 – 7.41 (m, 4H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 4.40 (dt, *J* = 10.0, 6.3 Hz, 4H), 3.23 – 3.16 (m, 2H), 3.02 – 2.96 (m, 2H), 2.73 (s, 3H), 2.58 (s, 3H), 2.34 – 2.25 (m, 4H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 166.64, 166.54, 164.9, 163.7, 162.65, 162.49, 140.44, 140.42, 133.2, 133.1, 130.24, 129.70, 129.59, 128.51, 128.41, 121.1, 120.3, 117.22, 117.16, 106.67, 106.03, 64.3, 64.3, 35.3, 33.7, 28.3, 28.1, 25.1, 23.7.

HRMS(ESI): calculated for $C_{17}H_{17}N_2O_2(M+H)^+$: 281.1284; found: 281.1286.

Ethyl 3-(5-cyano-6-methylpyridin-2-yl)propanoate (3e) and **Ethyl 3-(3-cyano-6-methylpyridin-2-yl)propanoate (3e'):**



77%

4.3e:4.3e'=1:1

regioisomeric ratio was determined by crude ^{1}H NMR

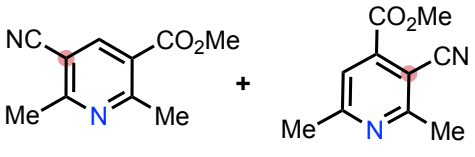
The compounds were synthesized as described in general procedures D and E, starting from furan (20 mg, 0.109 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The mixture of isomers was obtained as a white solid (18.5 mg, 77% yield over 2 steps, **TLC**: R_f 0.30 in 20% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.0, 4.3 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 4.13 (qd, *J* = 7.2, 5.6 Hz, 4H), 3.32 (t, *J* = 7.2 Hz, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.73 (s, 3H), 2.57 (s, 3H), 1.26 – 1.22 (m, 6H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 172.8, 172.6, 164.0, 162.54, 162.49, 161.4, 140.30, 140.27, 121.0, 120.5, 117.4, 117.2, 106.7, 106.2, 60.74, 60.70, 33.2, 32.8, 32.28, 31.33, 25.1, 23.8, 14.34, 14.28.

HRMS(ESI): calculated for $C_{12}H_{15}N_2O_2(M+H)^+$: 219.1128; found: 219.1124.

Methyl 3-cyano-2,6-dimethylisonicotinate (4.3f' major isomer):



55%

4.3f:4.3f'=1:2

regioisomeric ratio was determined by ^{1}H NMR

separable by silica gel chromatography

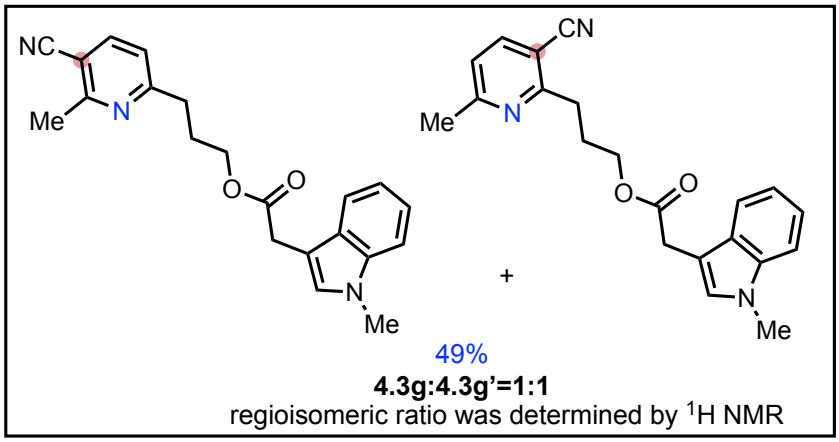
The compound was synthesized as described in general procedures D and E, starting from furan (20 mg, 0.129 mmol), Cs_2CO_3 (4.0 equiv.), and **SCP-1e** (3.0 equiv.) in THF (0.1 M). The compound was obtained as a brown solid (**TLC**: R_f 0.10 in 30% ethyl acetate/hexane). Only the major isomer was characterized.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 4.02 (s, 3H), 2.84 (s, 3H), 2.66 (s, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 164.0, 163.5, 162.9, 140.3, 121.1, 116.0, 104.8, 53.5, 25.1, 24.2.

HRMS(ESI): calculated for $C_{10}H_{11}N_2O_2$ $(M+H)^+$: 191.0815; found: 191.0812.

3-(5-Cyano-6-methylpyridin-2-yl)propyl 2-(1-methyl-1*H*-indol-3-yl)acetate (4.3g) and **3-(3-Cyano-6-methylpyridin-2-yl)propyl 2-(1-methyl-1*H*-indol-3-yl)acetate (4.3g'):**



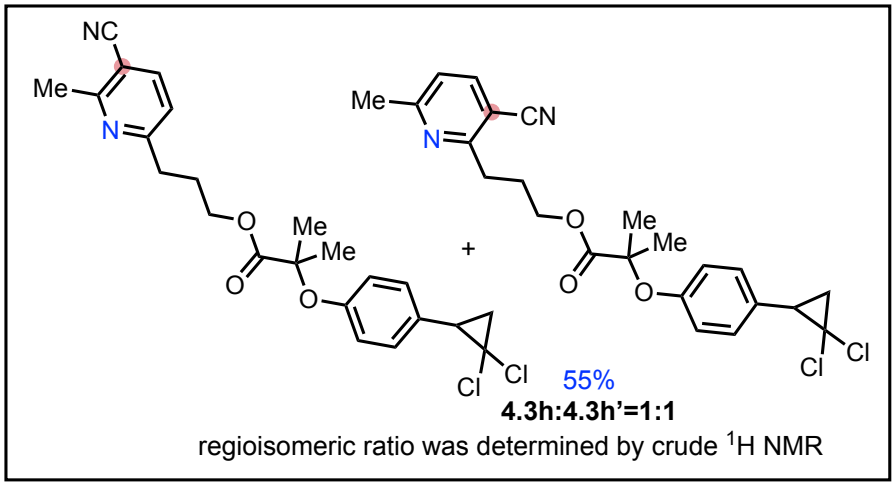
The compounds were synthesized as described in general procedures D and E, starting from furan (20 mg, 0.064 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The mixture of isomers were obtained as a yellowish solid (11 mg, 49% yield over 2 steps, **TLC**: R_f 0.30 in 30% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.61 (ddt, *J* = 7.8, 1.9, 1.0 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 7.14 – 7.10 (m, 2H), 7.07 (d, *J* = 1.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.19 – 4.12 (m, 4H), 3.78 – 3.76 (m, 10H), 3.11 – 3.06 (m, 2H), 2.81 – 2.77 (m, 2H), 2.73 (s, 3H), 2.59 (s, 3H), 2.20 – 2.12 (m, 2H), 2.11 – 2.03 (m, 2H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 172.32, 172.26, 164.8, 163.7, 162.6, 161.3, 140.5, 137.04, 136.97, 128.0, 127.9, 127.82, 127.76, 122.0, 121.8, 121.1, 120.4, 119.3, 119.23, 119.1, 109.5, 109.4, 106.94, 106.87, 106.1, 64.0, 63.90, 34.8, 33.4, 32.89, 32.86, 31.5, 31.3, 29.9, 28.2, 28.0, 25.1.

HRMS(ESI): calculated for $C_{21}H_{22}N_3O_2$ $(M+H)^+$: 348.1712; found: 348.1710.

3-(5-Cyano-6-methylpyridin-2-yl)propyl 2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methylpropanoate (4.3h) and **3-(3-Cyano-6-methylpyridin-2-yl)propyl 2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methylpropanoate (4.3h'):**



The compounds were synthesized as described in general procedures D and E, starting from furan (20 mg, 0.048 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF

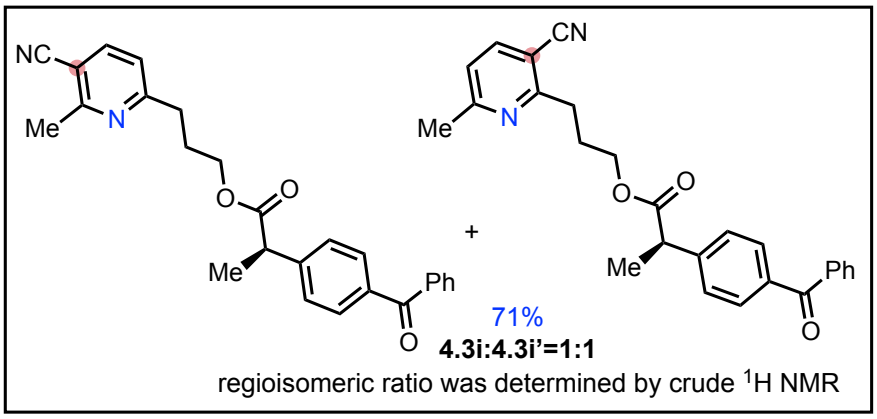
(0.1 M). The mixture of isomers were obtained as a yellowish solid (9.3 mg, 55% yield over 2 steps, **TLC**: R_f 0.30 in 15% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.10 (dd, *J* = 7.2, 5.1 Hz, 5H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.85 – 6.78 (m, 4H), 4.25 (t, *J* = 6.4 Hz, 2H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.00 – 2.76 (m, 5H), 2.71 (d, *J* = 11.5 Hz, 4H), 2.58 (s, 3H), 2.11 (dd, *J* = 14.5, 7.2 Hz, 2H), 2.09 – 2.01 (m, 2H), 1.96 – 1.89 (m, 2H), 1.76 (dd, *J* = 8.4, 7.3 Hz, 2H), 1.61 (d, *J* = 1.7 Hz, 12H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 174.37, 174.29, 164.57, 163.38, 162.61, 161.36, 155.07, 155.01, 140.37, 140.35, 129.8, 128.2, 128.10, 121.1, 120.3, 118.8, 118.3, 117.3, 117.1, 105.91, 79.28, 79.14, 64.72, 64.70, 60.96, 60.92, 34.88, 34.88, 34.84, 34.71, 33.2, 27.9, 27.71, 25.88, 25.55, 25.52, 25.45, 25.13.

HRMS(ESI): calculated for $C_{23}H_{25}ClN_2O_3$ $(M+H)^+$: 447.1242; found: 447.1245.

3-(5-Cyano-6-methylpyridin-2-yl)propyl (*S*)-2-(4-benzoylphenyl)propanoate (4.3i) and **3-(3-Cyano-6-methylpyridin-2-yl)propyl (*S*)-2-(4-benzoylphenyl)propanoate (4.3i'):**



The compounds were synthesized as described in general procedures D and E, starting from furan (20 mg, 0.053 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF

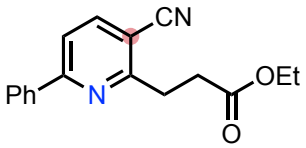
(0.1 M). The mixture of isomers were obtained as a white solid (15.5 mg, 71% yield over 2 steps, **TLC**: R_f 0.15 in 15% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.83 – 7.72 (m, 7H), 7.67 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.62 – 7.53 (m, 4H), 7.52 – 7.41 (m, 7H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.23 – 4.08 (m, 4H), 3.81 (p, *J* = 7.0 Hz, 2H), 3.02 (td, *J* = 7.3, 2.2 Hz, 2H), 2.79 – 2.73 (m, 2H), 2.71 (s, 3H), 2.57 (s, 3H), 2.12 (q, *J* = 7.0 Hz, 2H), 2.09 – 1.99 (m, 2H), 1.55 (d, *J* = 7.2 Hz, 6H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 196.7, 196.6, 174.2, 174.1, 164.7, 163.6, 162.7, 161.4, 141.1, 141.0, 138.1, 138.0, 137.7, 137.5, 132.8, 132.6, 131.8, 131.6, 129.4, 129.3, 129.24, 129.15, 128.73, 128.69, 128.5, 128.4, 121.0, 120.3, 117.4, 117.2, 107.0, 106.0, 64.1, 64.1, 45.54, 45.50, 34.8, 33.3, 28.1, 27.9, 25.2, 23.8, 18.6, 18.5.

HRMS(ESI): calculated for $C_{26}H_{25}N_2O_3$ $(M+H)^+$: 413.1859; found: 413.1856.

Ethyl 3-(3-cyano-6-phenylpyridin-2-yl)propanoate (4.3j)



66%, **4.3j**

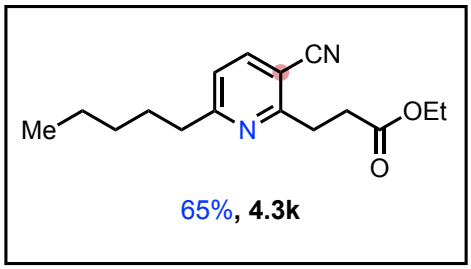
The compounds were synthesized as described in general procedures D and E, starting from furan (30 mg, 0.122 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in ^{i}PrOH (0.1 M). The mixture of isomers were obtained as a white solid (19.5 mg, 66% yield over 2 steps, **TLC**: R_f 0.40 in 20% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.09 – 8.05 (m, 2H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.52 – 7.48 (m, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 6.9 Hz, 2H), 2.98 (t, *J* = 6.9 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) δ 172.87, 162.62, 159.36, 140.94, 137.57, 130.62, 129.06, 127.49, 117.39, 117.13, 107.05, 60.73, 31.65, 31.23, 14.36.

HRMS(ESI): calculated for $C_{17}H_{17}N_2O_2(M+H)^+$: 281.1290; found: 281.1288.

Ethyl 3-(3-cyano-6-pentylpyridin-2-yl)propanoate (4.3k):



65%, **4.3k**

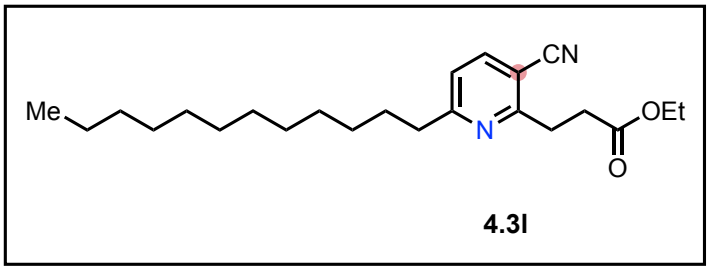
The compound was synthesized as described in general procedures D and E, starting from furan (20 mg, 0.083 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The product was obtained as a white solid (15 mg, 65% yield over 2 steps, **TLC**: R_f 0.30 in 20% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.34 (t, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.83 – 2.75 (m, 2H), 1.70 (p, *J* = 7.5 Hz, 2H), 1.32 (td, *J* = 8.0, 4.6 Hz, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) δ 172.5,166.3, 162.3, 140.0, 120.2, 117.0, 106.0, 60.5, 38.6, 32.0, 31.4, 31.1, 28.8, 22.4, 14.2, 13.9.

HRMS(ESI): calculated for $C_{16}H_{23}N_2O_2$ $(M+H)^+$: 275.1760; found: 275.1762.

Ethyl 3-(3-cyano-6-dodecylpyridin-2-yl)propanoate (4.3l):



4.3l

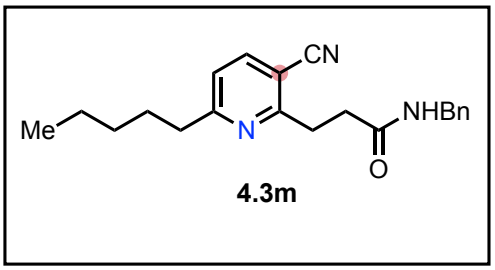
The compound was synthesized as described in general procedures D and E, starting from furan (30 mg, 0.089 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The product was obtained as a white solid (20.5 mg, 62% yield over 2 steps, **TLC**: R_f 0.30 in 15% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.33 (t, *J* = 7.1 Hz, 2H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.81 – 2.75 (m, 2H), 1.69 (t, *J* = 7.5 Hz, 2H), 1.36 – 1.20 (m, 21H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 172.7, 166.5, 162.4, 140.2, 120.4, 117.3, 106.1, 60.7, 38.8, 32.07, 32.05, 31.3, 29.80, 29.79, 29.77, 29.68, 29.57, 29.50, 29.43, 29.33, 22.8, 14.34, 14.28.

HRMS(ESI): calculated for $C_{23}H_{37}N_2O_2$ $(M+H)^+$: 373.2849; found: 373.2851.

***N*-Benzyl-3-(3-cyano-6-pentylpyridin-2-yl)propanamide (4.3m):**



4.3m

The compound was synthesized as described in general procedures D and E, starting from furan (20 mg, 0.066 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF

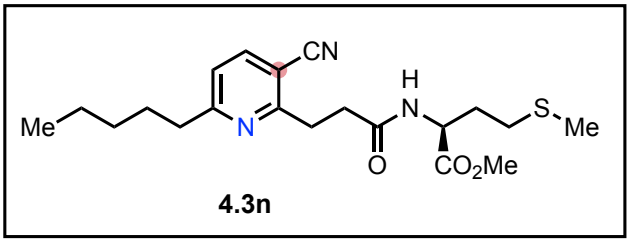
(0.1 M). The product was obtained as a white solid (11.5 mg, 34% yield over 2 steps, **TLC**: R_f 0.30 in 30% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.24 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.43 (s, 1H), 4.43 (d, *J* = 5.6 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.72 – 2.63 (m, 2H), 1.63 (s, 2H), 1.28 (ddd, *J* = 9.4, 7.5, 5.2 Hz, 4H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) δ 171.8, 166.3, 162.7, 140.7, 138.4, 128.8, 128.0, 127.6, 120.6, 117.0, 106.5, 43.8, 38.6, 34.1, 31.8, 31.5, 29.1, 22.6, 14.1.

HRMS(ESI): calculated for $C_{21}H_{26}N_3O$ $(M+H)^+$: 336.2070; found: 336.2071.

Methyl (3-(3-cyano-6-pentylpyridin-2-yl)propanoyl)methioninate (4.3n):



4.3n

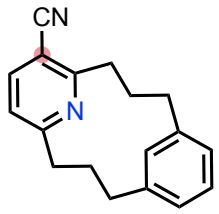
The compound was synthesized as described in general procedures D and E, starting from furan (30 mg, 0.084 mmol), Cs_2CO_3 (3.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The product was obtained as a white solid (12 mg, 36% yield over 2 steps, **TLC**: R_f 0.20 in 45% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 4.68 (q, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 3.20 (t, *J* = 7.0 Hz, 2H), 3.06 – 2.99 (m, 2H), 2.77 (t, *J* = 7.1 Hz, 2H), 2.46 – 2.39 (m, 2H), 2.14 (dt, *J* = 13.8, 7.0 Hz, 1H), 2.07 (s, 3H), 1.94 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.77 (d, *J* = 9.6 Hz, 2H), 1.38 (m, 4H), 0.92 (d, *J* = 6.8 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) δ 172.5, 171.8, 165.3, 163.9, 141.0, 140.0, 121.1, 117.1, 52.7, 51.6, 36.9, 34.7, 31.8, 31.6, 30.0, 29.4, 22.6, 15.6, 14.1.

HRMS(ESI): calculated for $C_{20}H_{30}N_3O_3S$ $(M+H)^+$: 392.2002; found: 392.2008.

1(2,6)-Pyridina-5(1,3)-benzenacyclooctaphane-13-carbonitrile (4.3o)



64%, **4.3o**

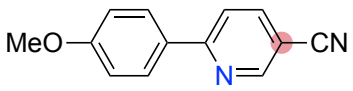
The compound was synthesized as described in general procedures D and E, starting from furan (20 mg, 0.088 mmol), Cs_2CO_3 (2.0 equiv.), and **SCP-1e** (1.5 equiv.) in THF (0.1 M). The product was obtained as a white solid (15 mg, 64% yield over 2 steps, **TLC**: R_f 0.10 in 10% ethyl acetate/hexane).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 7.3 Hz, 1H), 3.16 (s, 2H), 2.99 (s, 2H), 2.80 (dt, *J* = 15.5, 6.0 Hz, 4H), 2.41 (d, *J* = 4.2 Hz, 2H), 2.25 (s, 2H).

$^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) δ 165.8, 164.0, 139.8, 139.5, 134.1, 128.0, 126.3, 126.0, 120.2, 105.1, 39.4, 37.9, 36.7, 36.2, 29.4, 27.8.

HRMS(ESI): calculated for $C_{18}H_{19}N_2$ $(M+H)^+$: 263.1542; found: 263.1546.

6-(4-methoxyphenyl)nicotinonitrile (4.3p):

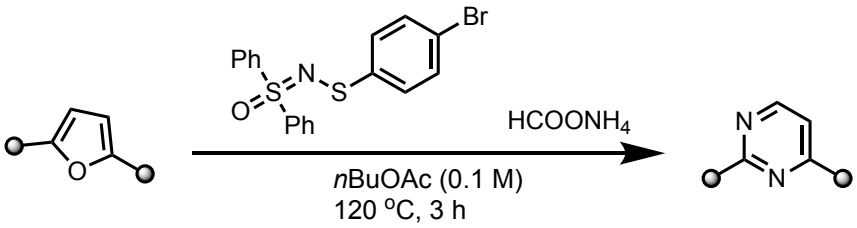


^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 2.8 Hz, 1H), 8.05 – 8.02 (m, 2H), 7.96 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.04 – 7.02 (m, 2H), 3.89 (s, 3H).

^{13}C{^{1}H} NMR: (100 MHz, $CDCl_3$) 162.0, 160.1, 152.5, 139.9, 129.8, 129.1, 119.3, 117.3, 114.6, 107.0, 55.6.

The spectral data of the **4.3p** product matched with previously reported literature.[99]

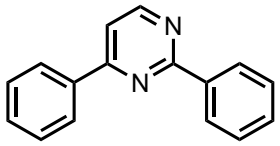
4.6.4 General Procedure F for Conversion of Furans into Pyrimidines



To a solution of furan (1.0 equiv.) in n-butylacetate (0.1 M), 4.0 equiv. of solid precursor **SNP-1c** and 10.0 equiv. of ammonium formate is added in one portion. The resulting solution was stirred for 3 hours at 120 ºC. Upon the completion of reaction, all the volatiles were removed under reduced pressure and purified by silica gel chromatography.

Pyrimidines

2,4-Diphenylpyrimidine (4.2aa):



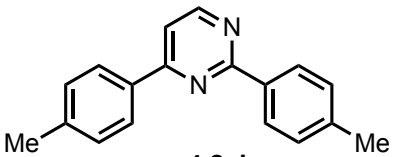
4.2aa

Synthesized according to general procedure **F** using 20 mg (0.091 mmol) of furan. The product was obtained as an off-white solid (20.5 mg, 97% yield), Rf = 0.15 in 10% ethyl acetate/hexane.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 5.3 Hz, 1H), 8.62 – 8.56 (m, 2H), 8.26 – 8.22 (m, 2H), 7.61 (d, *J* = 5.2 Hz, 1H), 7.57 – 7.51 (m, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.7, 164.0, 158.0, 138.0, 137.1, 131.1, 130.9, 129.1, 128.7, 128.4, 127.4, 114.7.

2,4-Di-*p*-tolylpyrimidine (4.2ab):



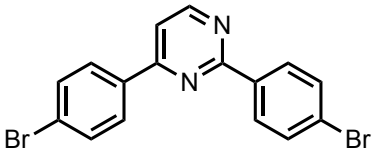
4.2ab

Synthesized according to general procedure **F** using 10.0 mg (0.040 mmol) of furan. The product was obtained as an off-white solid (8.7 mg, 83% yield), Rf = 0.15 in 10% ethyl acetate/hexane. The spectral data matched with previously reported literature.

1H NMR: (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 5.3 Hz, 1H), 8.47 (d, *J* = 8.1 Hz, 2H), 8.13 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 5.3 Hz, 1H), 7.36 – 7.29 (m, 4H), 2.45 (s, 3H), 2.44 (s, 3H).

13C NMR: (100 MHz, $CDCl_3$) δ 164.59, 164.02, 157.58, 141.54, 141.11, 134.33, 129.81, 129.45, 128.37, 127.29, 114.06, 21.68, 21.66.

2,4-Bis(4-bromophenyl)pyrimidine (4.2ac):



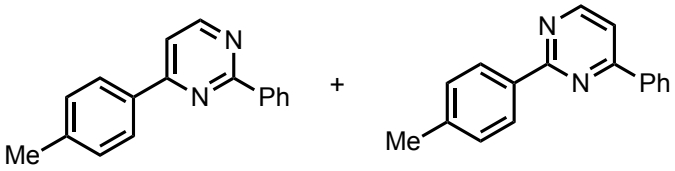
4.2ac

Synthesized according to general procedure **F** using 10 mg (0.026 mmol) of furan. The product was obtained as an off-white solid (7.5 mg, 72% yield), Rf = 0.15 in 10% ethyl acetate/hexane.

1H NMR: (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 5.2 Hz, 1H), 8.44 (d, *J* = 8.5 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 2H), 7.67 (dd, *J* = 15.4, 8.5 Hz, 4H), 7.59 (d, *J* = 5.3 Hz, 1H).

13C NMR: (100 MHz, $CDCl_3$) δ 163.82, 163.18, 158.06, 136.49, 135.67, 132.39, 131.95, 130.04, 128.88, 126.08, 125.93, 114.62.

2-Phenyl-4-(*p*-tolyl)pyrimidine (4.2ad) + 4-Phenyl-2-(*p*-tolyl)pyrimidine (4.2ad'):



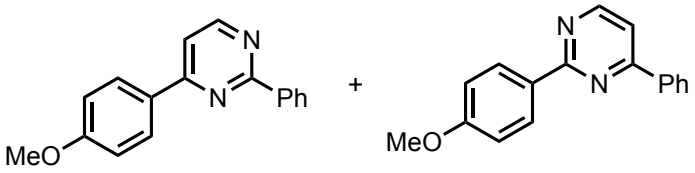
4.2ad:4.2ad' = 1:1

Synthesized according to general procedure **F** using 10 mg (0.042 mmol) of furan. The product was obtained as an off-white solid (9.8 mg, 93% yield), Rf = 0.15 in 10% ethyl acetate/hexane.

1H NMR: (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 3.7 Hz, 1H), 8.81 (d, *J* = 3.8 Hz, 1H), 8.60 – 8.56 (m, 2H), 8.48 (d, *J* = 8.2 Hz, 2H), 8.27 – 8.20 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 5.3 Hz, 2H), 7.56 – 7.50 (m, 6H), 7.37 – 7.31 (m, 4H), 2.45 (s, 3H), 2.45 (s, 3H).

13C NMR: (100 MHz, $CDCl_3$) δ 164.53, 164.06, 157.81, 157.78, 157.74, 157.70, 141.62, 141.60, 141.20, 137.14, 134.25, 131.11, 130.86, 130.85, 129.84, 129.48, 129.09, 128.69, 128.42, 128.39, 127.38, 127.29, 114.40, 114.34, 21.69, 21.66.

4-(4-Methoxyphenyl)-2-phenylpyrimidine (4.2ae) + 2-(4-Methoxyphenyl)-4-phenylpyrimidine (4.2ae'):



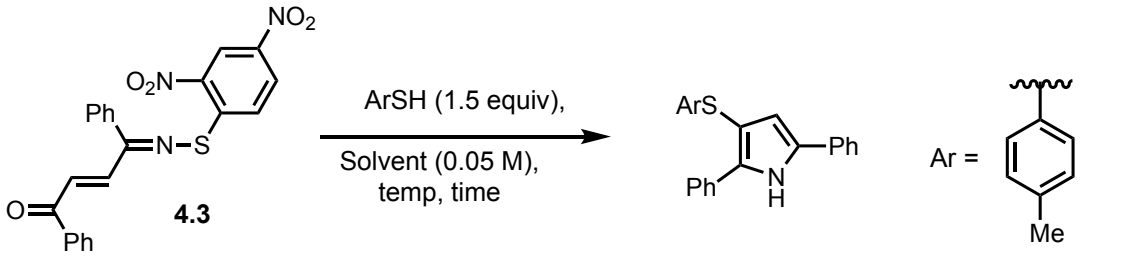
4.2ae:4.2ae' = 1:1

Synthesized according to general procedure **F** using 10 mg (0.039 mmol) of furan. The product was obtained as an off-white solid (8.8 mg, 83% yield), Rf = 0.15 in 20% ethyl acetate/hexane.

1H NMR: (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 5.1 Hz, 2H), 8.61 – 8.51 (m, 4H), 8.26 – 8.18 (m, 4H), 7.58 – 7.48 (m, 8H), 7.04 (dd, *J* = 10.1, 9.0 Hz, 4H), 3.90 (s, 3H), 3.90 (s, 3H).

13C NMR: (100 MHz, $CDCl_3$) δ 164.50, 164.42, 163.98, 163.56, 163.55, 162.23, 162.03, 157.82, 157.62, 138.07, 137.22, 131.06, 130.79, 130.07, 129.48, 129.07, 128.92, 128.67, 128.38, 127.34, 114.43, 114.00, 113.97, 113.82, 55.61, 55.54.

4.6.5 General Procedure and Optimization for Furan Ring Opening to Pyrroles

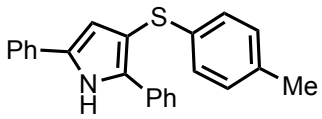


Entry	Additive	Solvent	Temp	Time (h)	Conversion (%)	Yield of **4.4aa** (%)[a]
1	$HCOONH_4$ (5 equiv)	AcOH	120 ºC	15 min	100%	54%
2	$HCOONH_4$ (5 equiv)	DCE:AcOH	80 °C	12 h	100%	77%
3	$HCOONH_4$ (5 equiv)	DCE:AcOH	100 °C	12 h	100%	**99%***
4	–	DCE:AcOH	100 °C	12 h	100%	**99%**
5	PTSA (50 mol%)	DCE	100 °C	12 h	90%	68%

*Reaction was clean in TLC and easier isolation of the final product as compared to entry 4, which was without the use of an external ammonia source.

To a solution of opening product 3 (1.0 equiv.) in 0.05 M DCE: AcOH (1:10), 1.5 equiv. of thiol was added, followed by the addition of 10.0 equiv. of ammonium formate. The resulting solution was stirred for 12 hours at 100 ºC. Upon completion, the all the volatiles were removed under reduced pressure and crude mixture was purified by silica-gel column chromatography.

3-((4-Methylphenyl)thio)-2,5-diphenyl-1*H*-pyrrole (4aa):



4.4aa

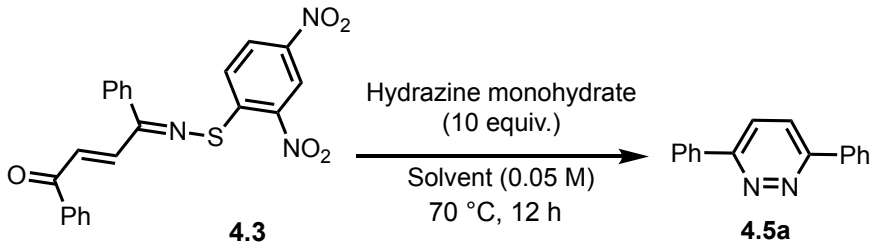
Synthesized using 10 mg (0.023 mmol) of furan ring-opening product. The product was obtained as an off-white solid (7.80 mg, 99% yield), Rf = 0.5 in 20% ethyl acetate/hexane.

1H NMR: (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.66 (d, J = 7.7 Hz, 2H), 7.52 (d, J = 7.7 Hz, 2H), 7.40 (td, J = 7.6, 4.1 Hz, 4H), 7.33 – 7.27 (m, 1H), 7.13 – 7.09 (m, 2H), 7.05 – 7.02 (m, 2H), 6.67 (d, J = 2.9 Hz, 1H), 2.28 (s, 3H).

13C NMR: (100 MHz, $CDCl_3$) δ 135.97, 134.42, 132.31, 131.46, 129.43, 128.90, 128.56, 127.35, 126.73, 126.07, 123.61, 114.10, 108.65, 20.73.

HRMS(ESI) calculated C23H19NS (M+H) +: 342.1316; found: 342.1324.

4.6.6 General procedure and optimization for furan ring opening to pyridazine



4.3 **4.5a**

Entry	Source	Solvent	Time (h)	Conversion (%)	Yield of **4.5a** (%)[a]
1	**NH_2NH_2:H_2O**	DCM:EtOH	7 h	20%	–
2	**NH_2NH_2:H_2O**	DCM:EtOH	7 h	100%	37%
2	**NH_2NH_2**	DCM	7 h	100%	trace
3	**NH_2NH_2:H_2O**	THF	12 h	100%	73%
4	**NH_2NH_2:H_2O**	MeOH	12 h	100%	84%
5	**NH_2NH_2:H_2O**	EtOH	12 h	100%	**99%**
6	**NH_2NH_2:H_2O**	EtOH:DCE (10:1)	12 h	100%	**98%**

[a] NMR yield

To a solution of opening product 4.3 (1 equiv.) in 0.05 M, DCE: EtOH (1:10), was followed by the addition of 10 equiv. of hydrazine hydrate in one portion. The resulting solution was stirred for 12 hours at 70 °C. Upon completion, the solvent was dried from the reaction mixture and purified by silica gel chromatography. The spectral data of 4.5a matched with the reported literature.[100]

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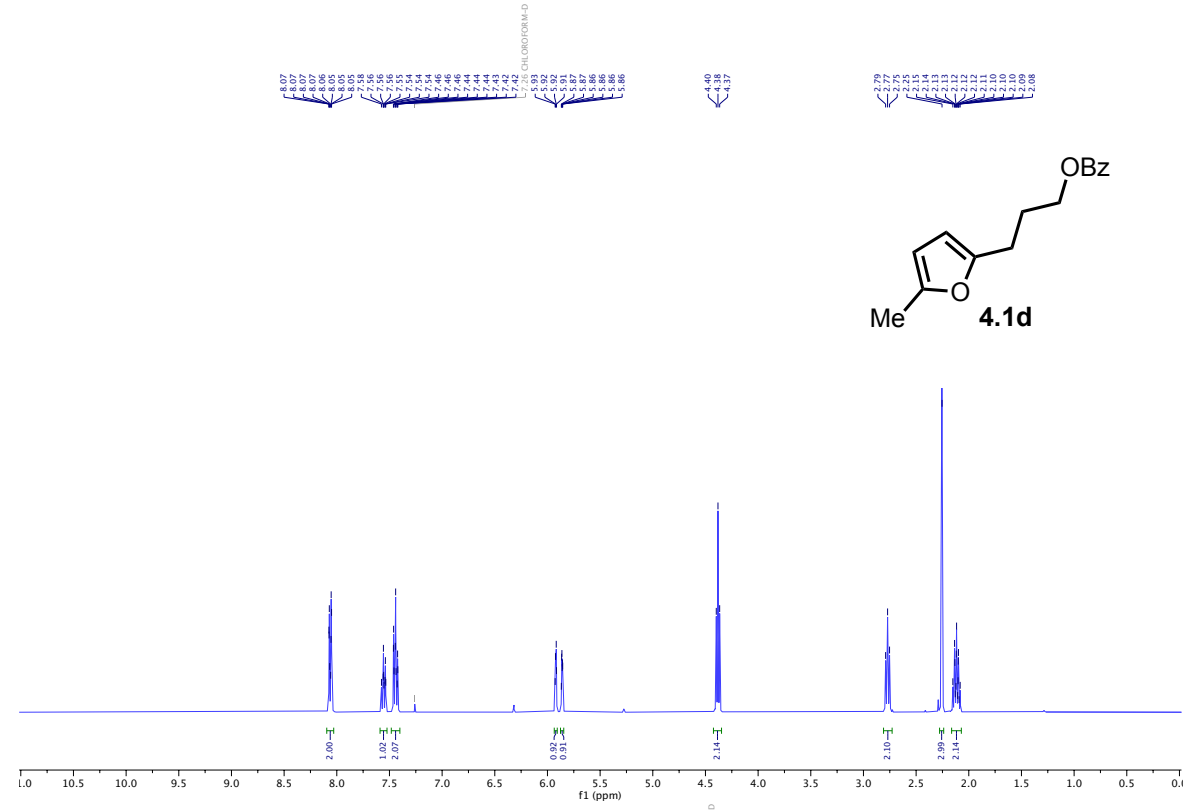
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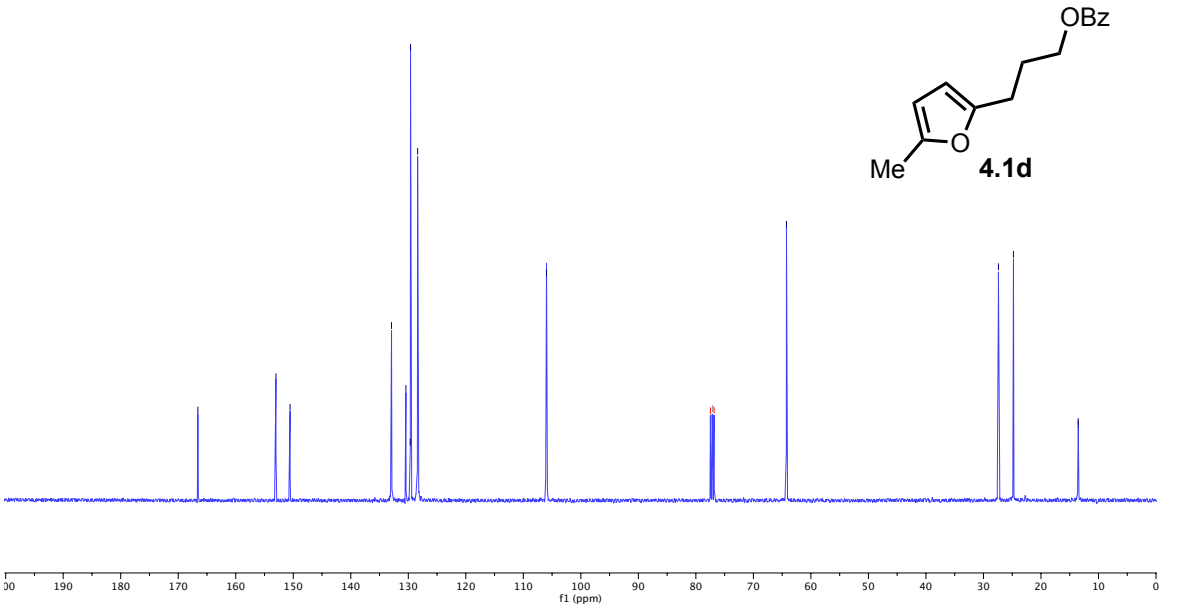
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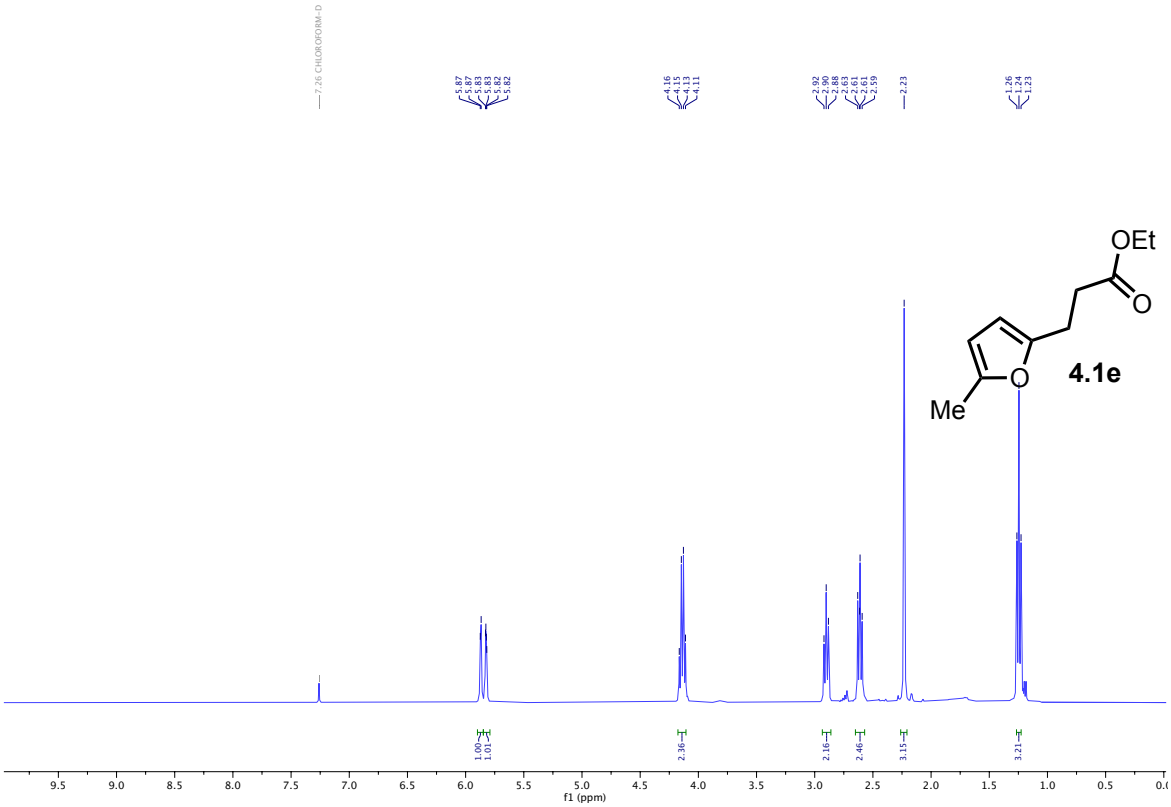
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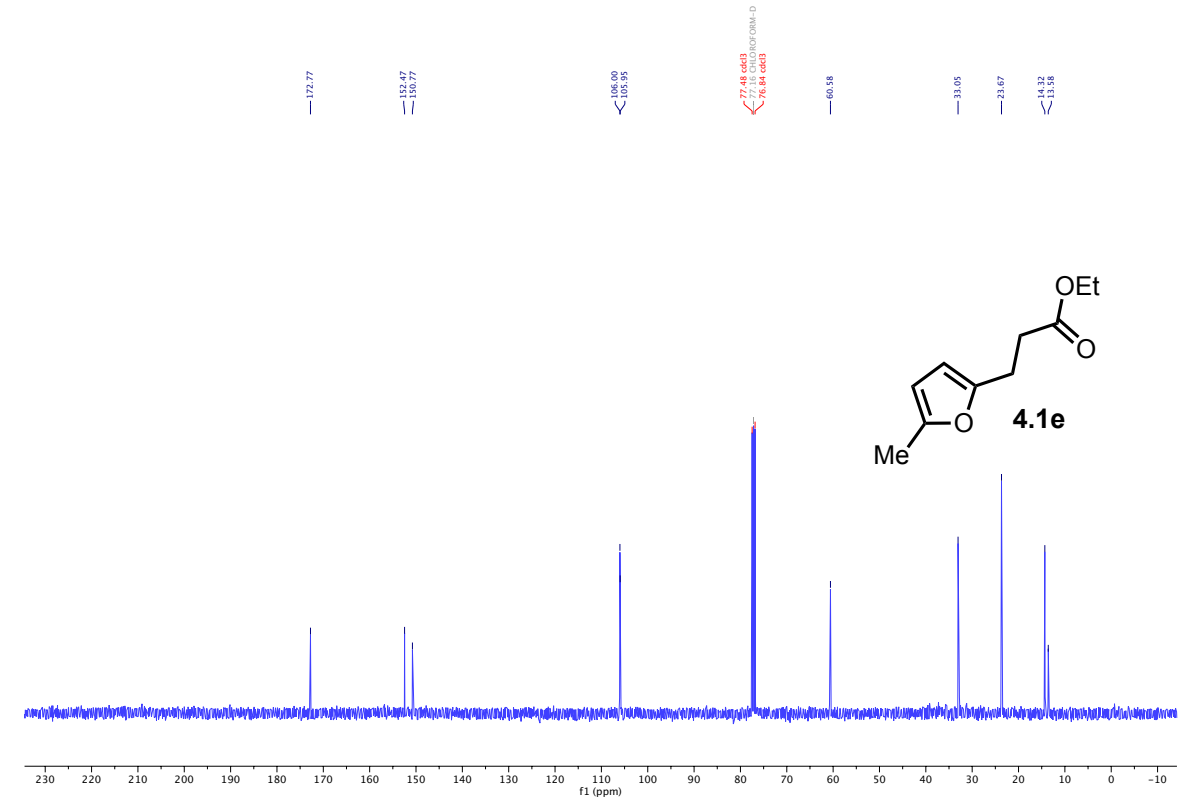
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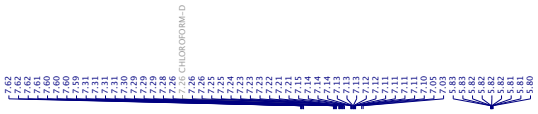
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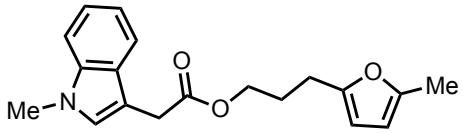




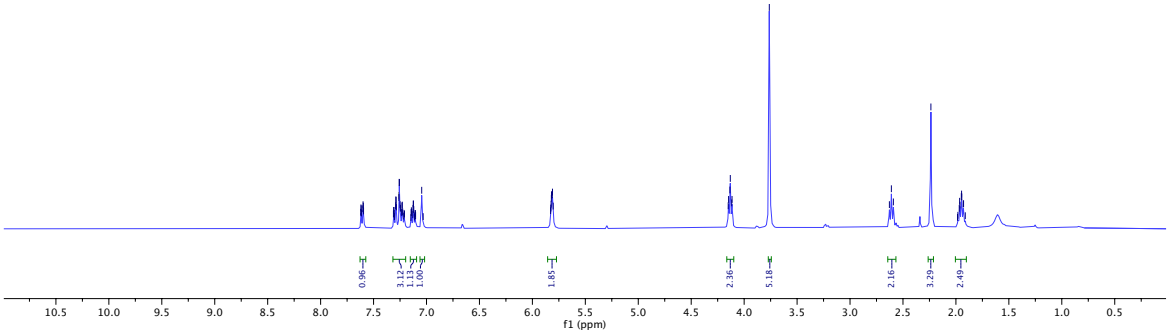

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5.87
5.87
5.83
5.83
5.82
5.82
4.16
4.15
4.13
4.11
2.92
2.90
2.88
2.63
2.61
2.61
2.59
2.23
1.26
1.24
1.23
OEt
O
O
Me
4.1e
1.00
1.01
2.36
2.16
2.46
3.15
3.21
f1 (ppm)

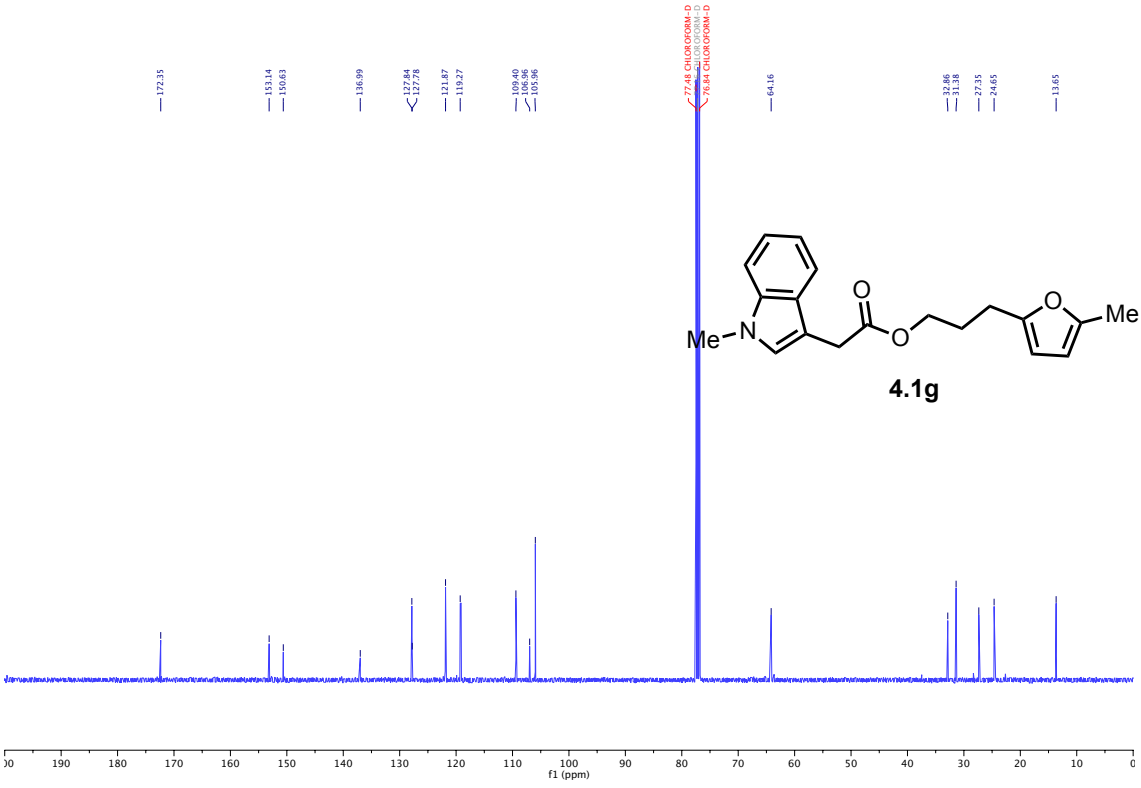

172.77
152.47
150.77
106.00
105.95
77.48 cdcl3
77.16 CHLOROFORM-D
76.84 cdcl3
60.58
33.05
23.67
14.32
13.98
OEt
O
O
Me
4.1e
f1 (ppm)



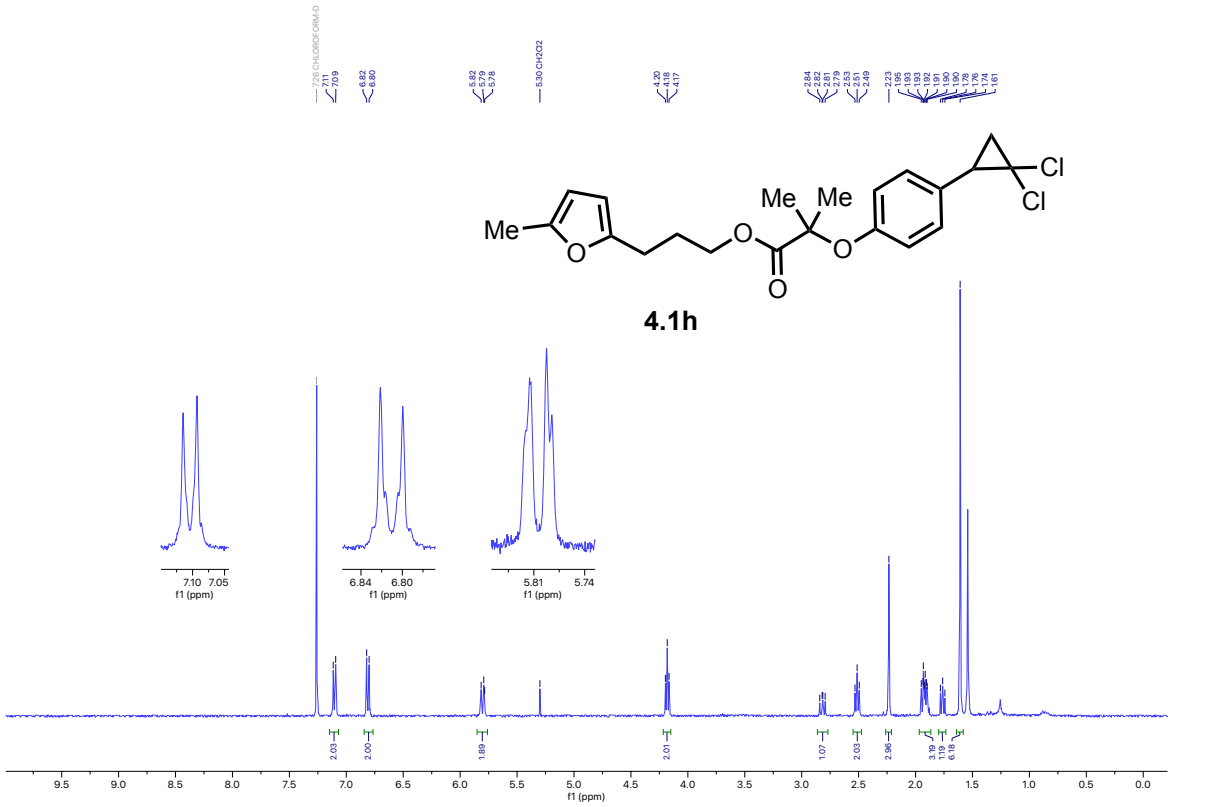


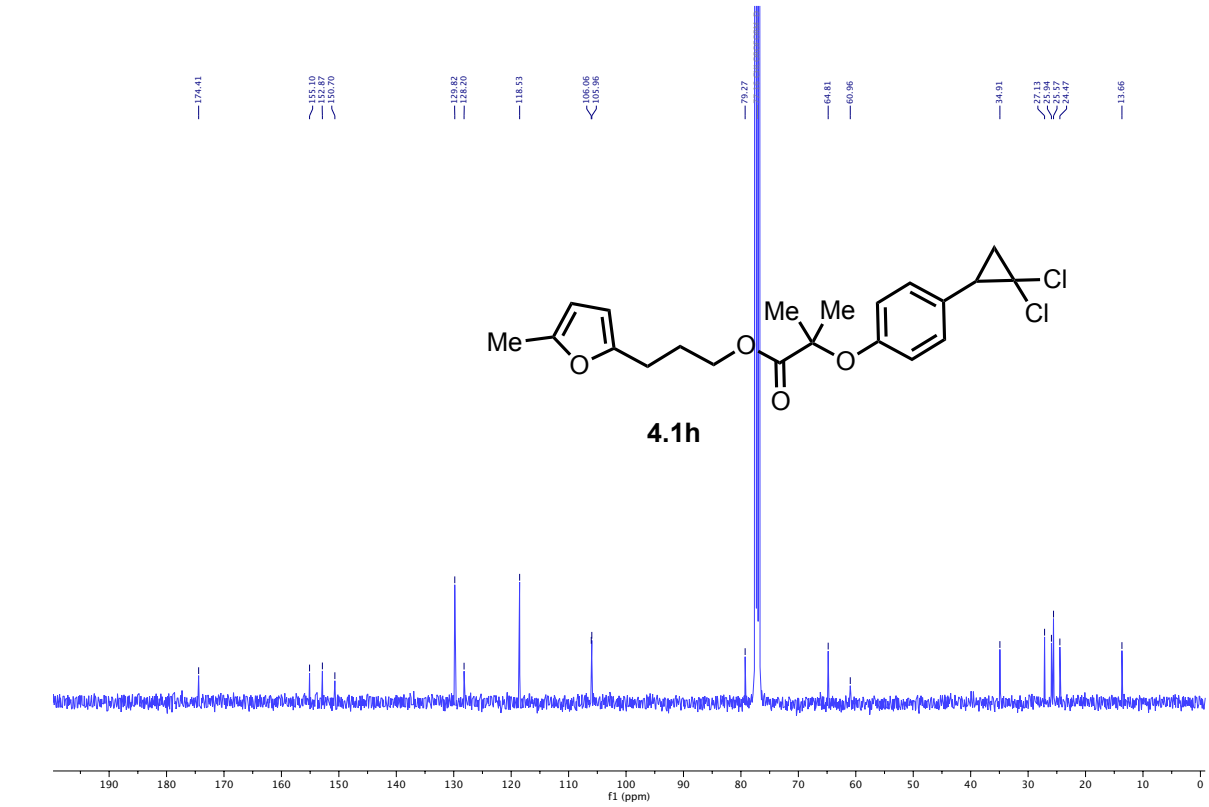
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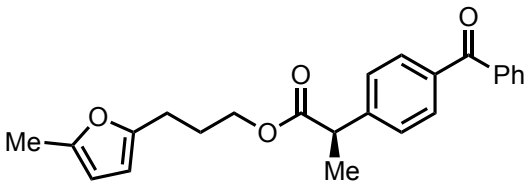


4.1g

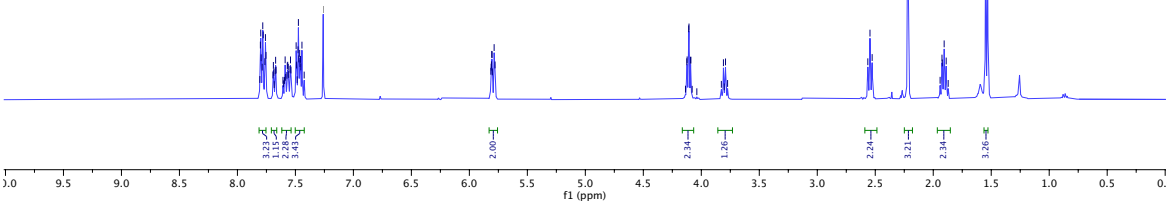

Me
O
Me
Me
O
O
O
Cl
Cl
4.1h
f1 (ppm)

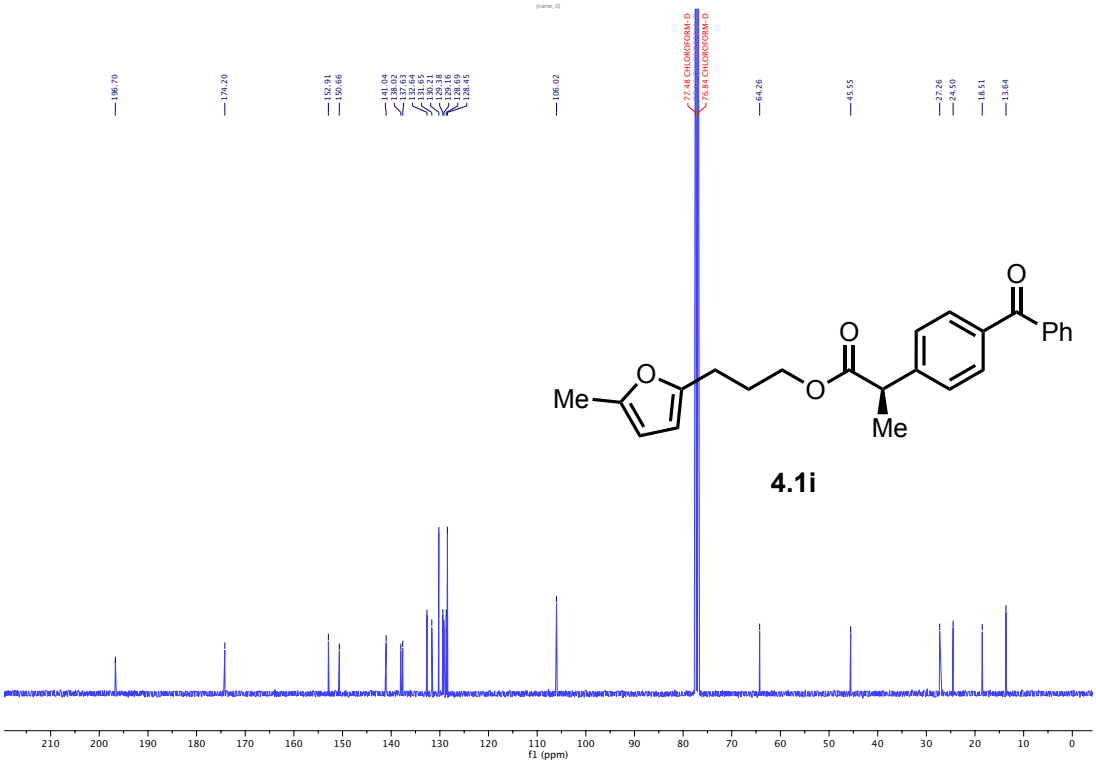

Me
O
Me
Me
O
O
O
Cl
Cl
4.1h
f1 (ppm)





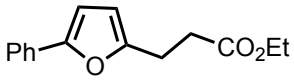
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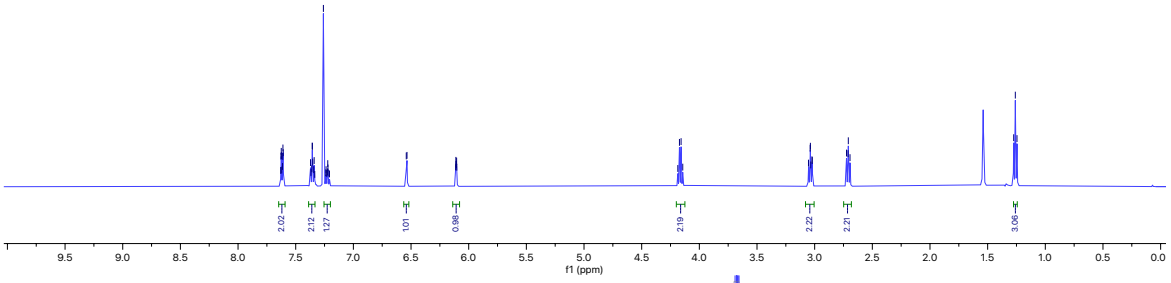


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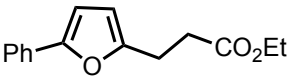




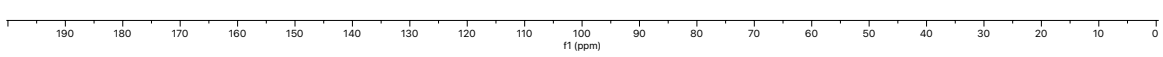
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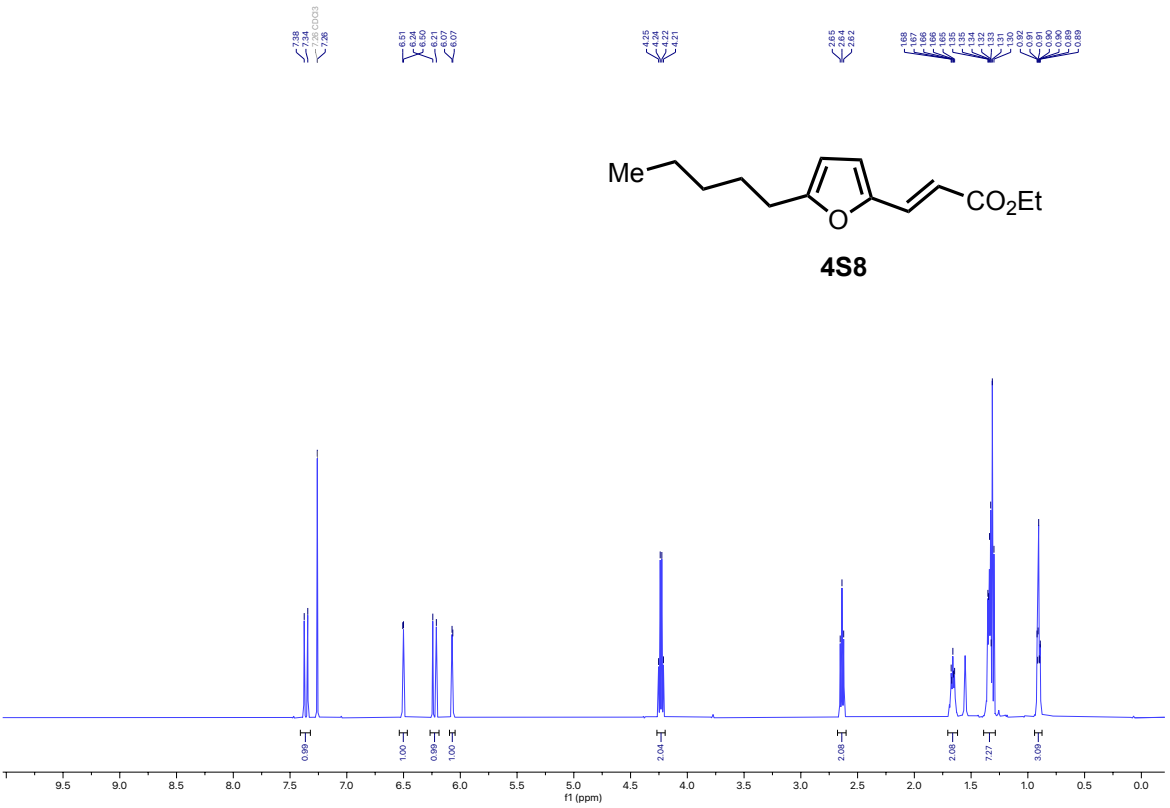


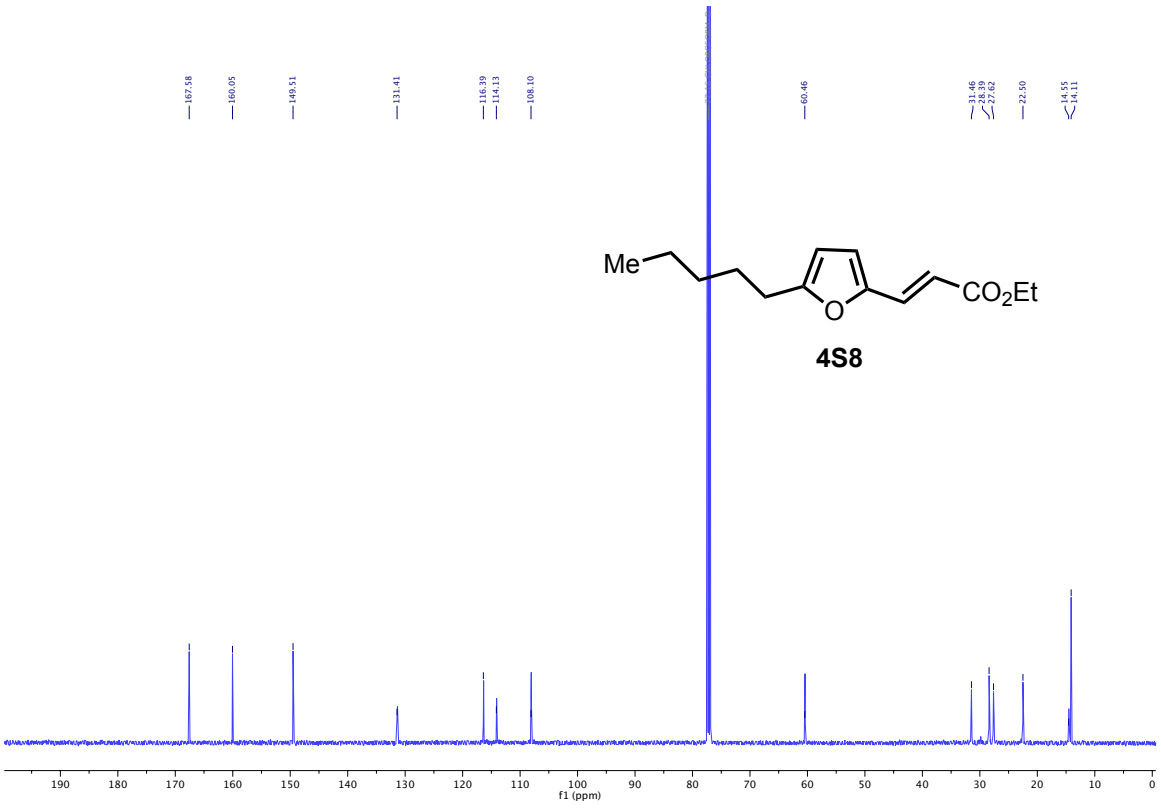




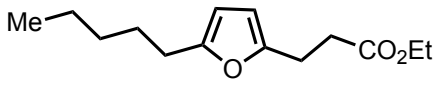
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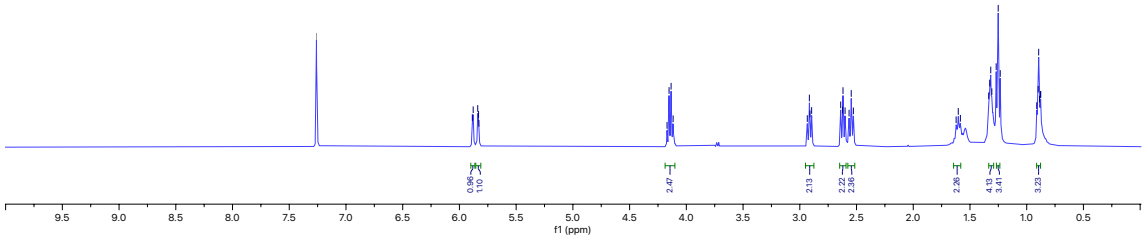

Me
CO2Et
O
4S8
f1 (ppm)


Me
CO2Et
O
4S8
f1 (ppm)

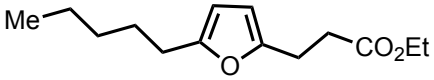




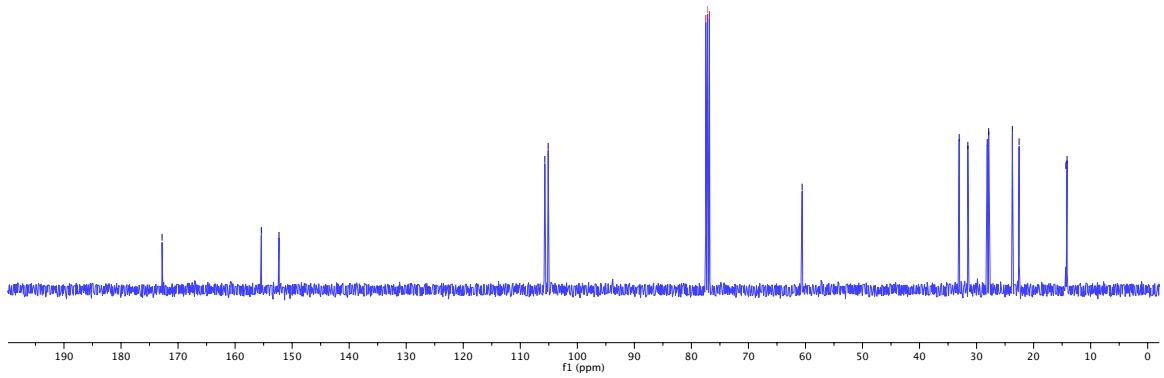
4.1k

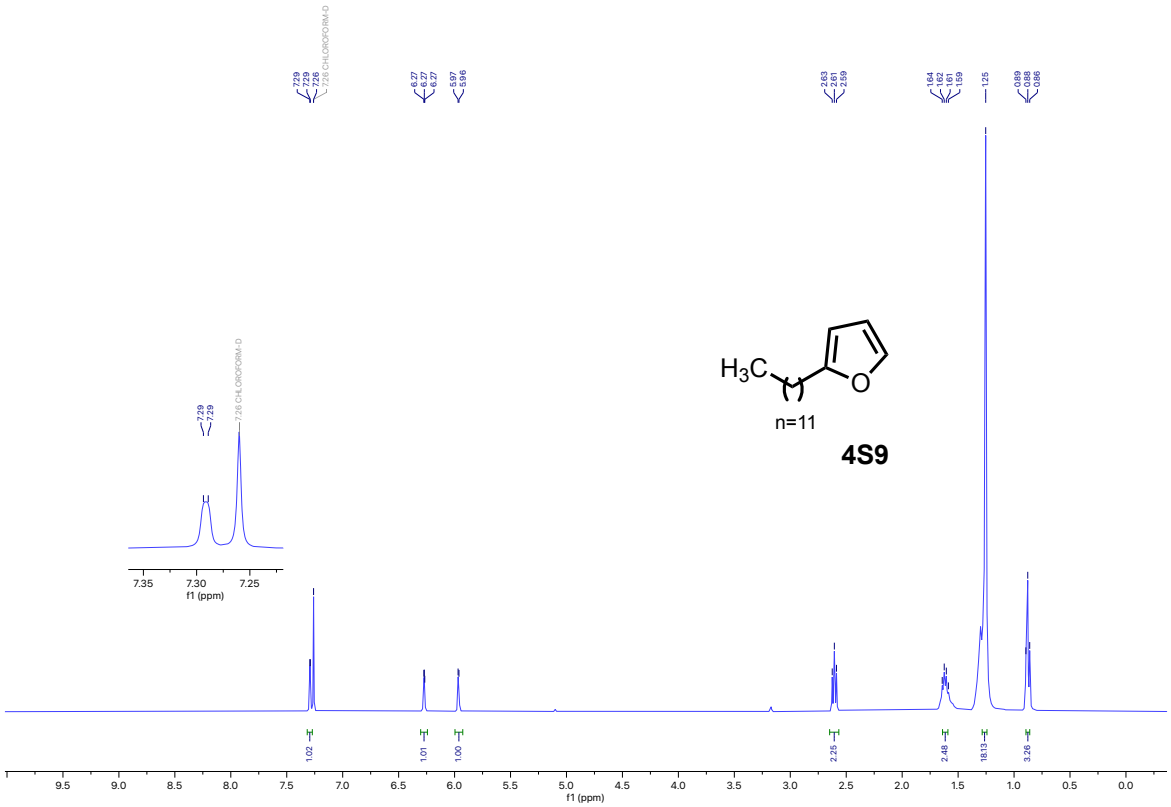


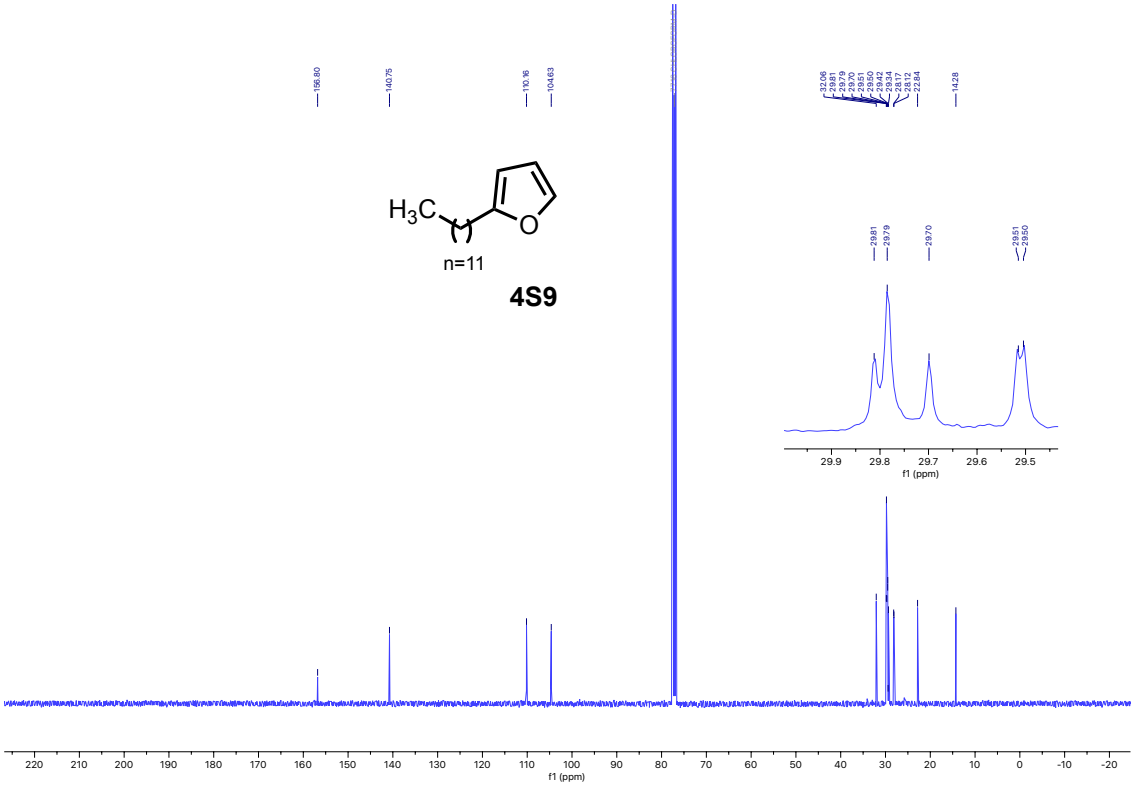


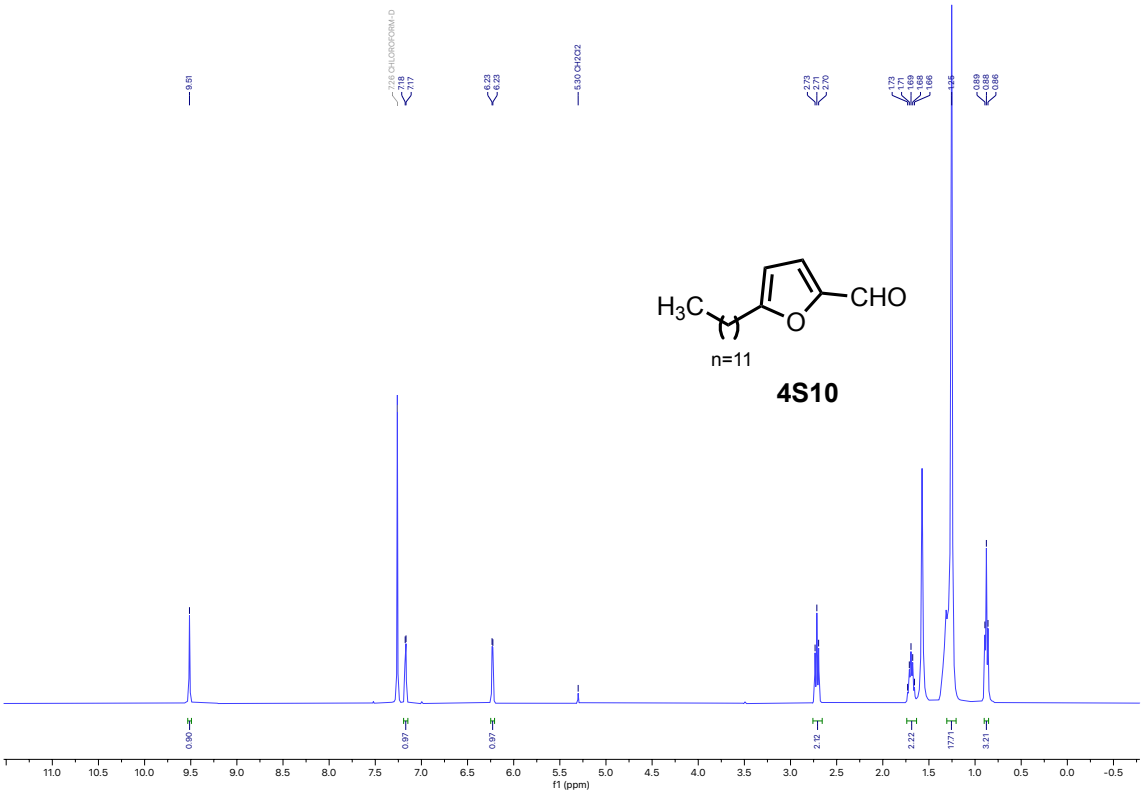


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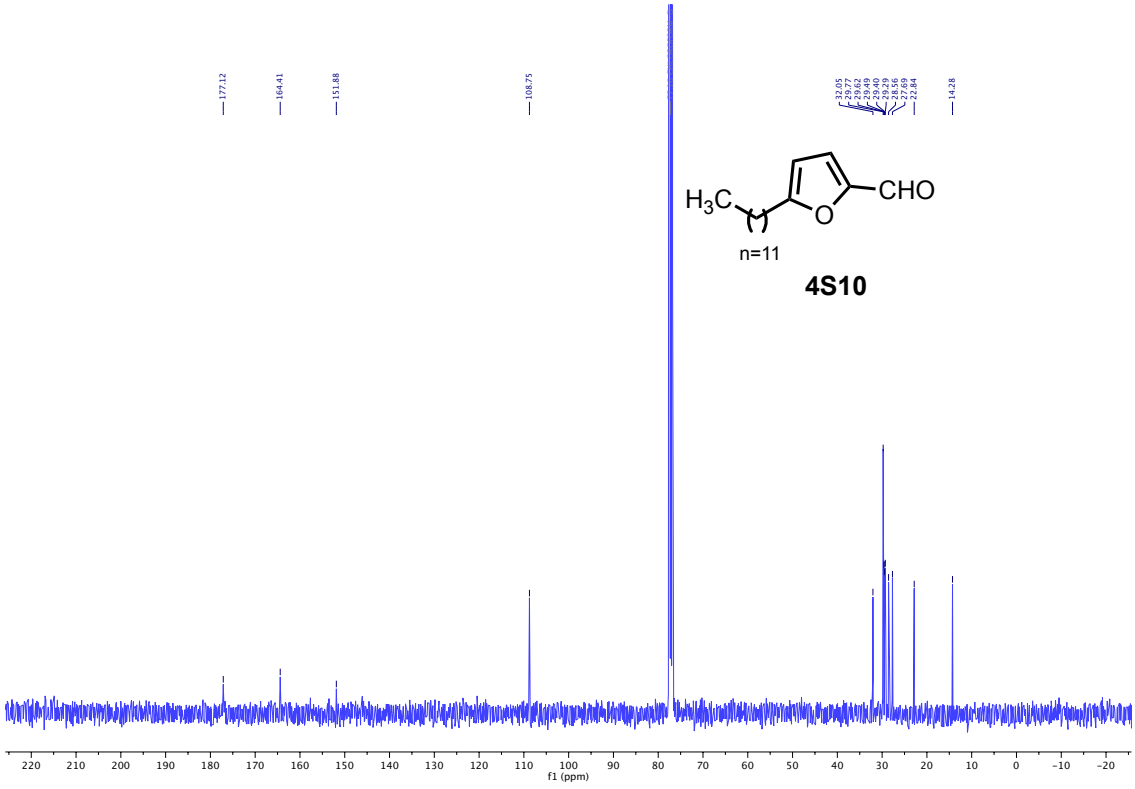

7.29
7.29
7.26 CHLOROFORM-D
6.27
6.27
6.27
5.97
5.96
2.63
2.61
2.59
1.64
1.62
1.61
1.59
1.25
0.89
0.88
0.86
H3C
O
n=11
4S9
7.35
7.30
7.25
f1 (ppm)
1.02
1.01
1.00
2.25
2.48
18.13
3.26
f1 (ppm)


156.80
140.75
110.16
104.63
77.32
77.00
76.68
32.06
29.81
29.79
29.70
29.51
29.50
29.34
28.17
23.13
22.84
14.28
H3C
O
n=11
4S9
29.81
29.79
29.70
29.51
29.50
29.9
29.8
29.7
29.6
29.5
f1 (ppm)
f1 (ppm)


9.51
7.26 CHLOROFORM-D
7.18
7.17
6.23
6.23
5.30 CH2Cl2
2.73
2.71
2.70
1.73
1.71
1.69
1.68
1.66
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0.97
0.97
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2.22
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3.21
f1 (ppm)

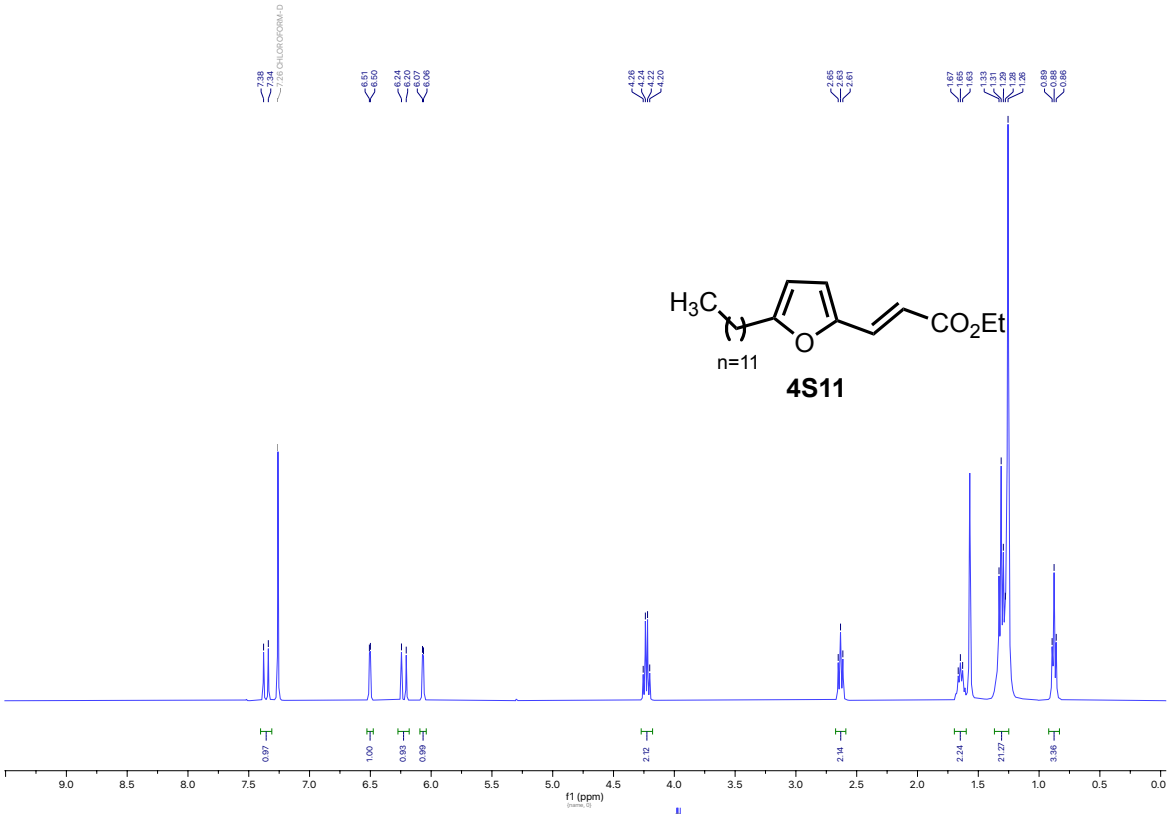
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CHO
O
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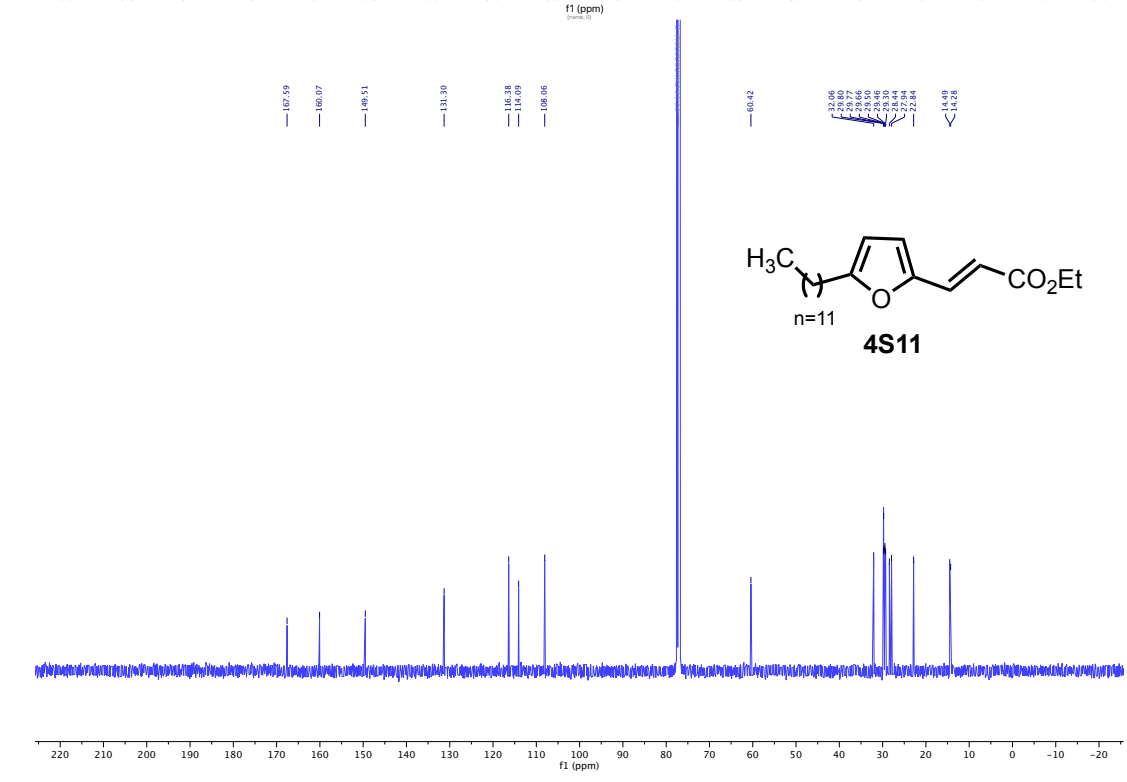
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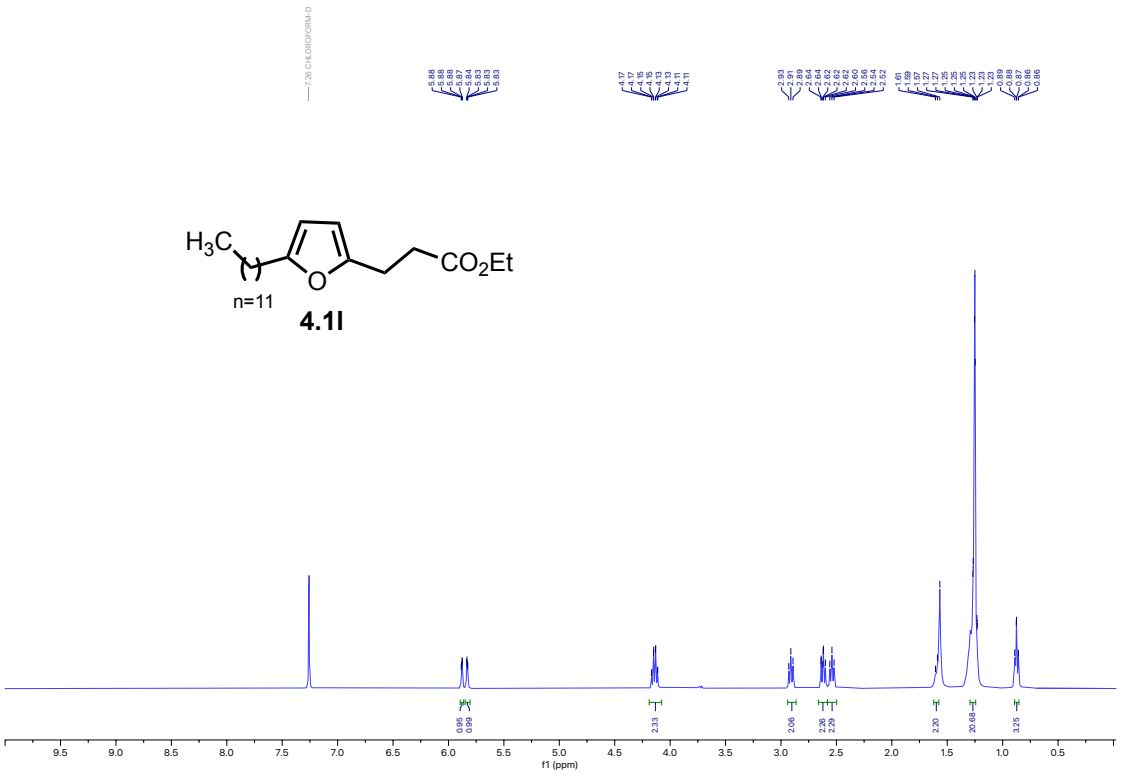

177.12
164.41
151.88
108.75
32.05
29.77
29.72
29.49
29.40
29.39
28.56
27.69
22.84
14.28
f1 (ppm)

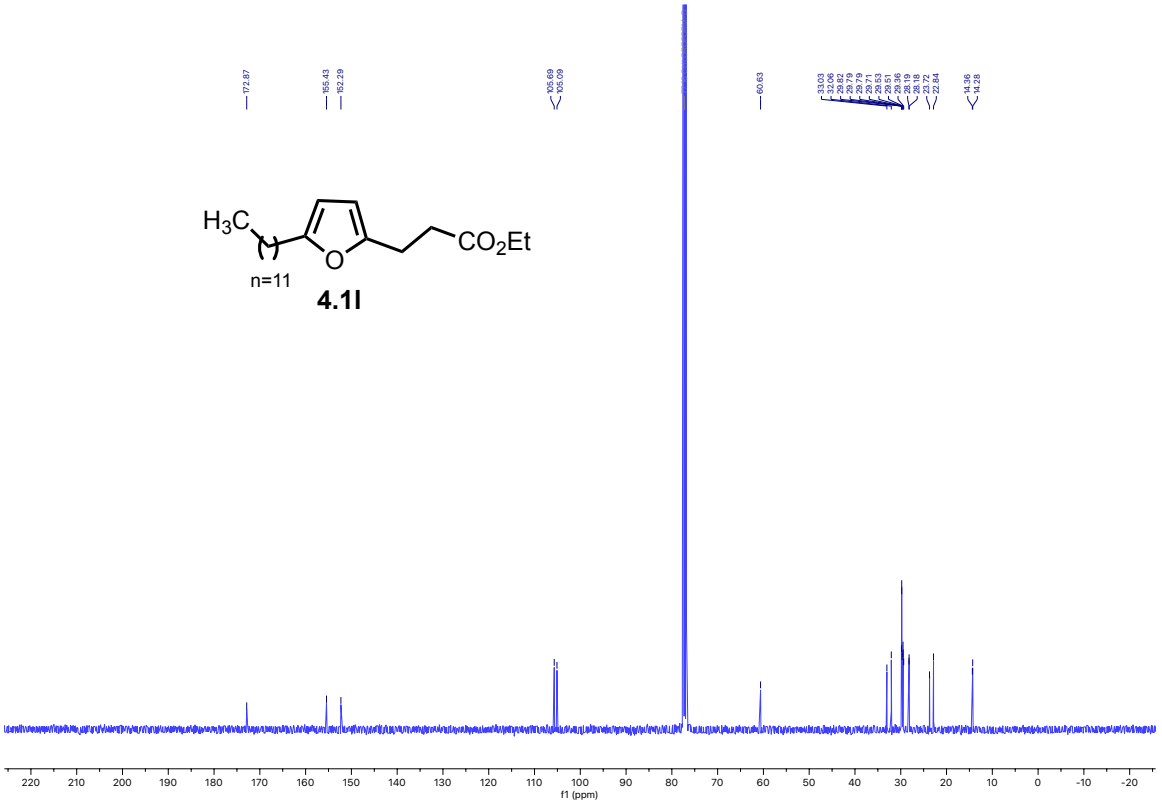
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CHO
O
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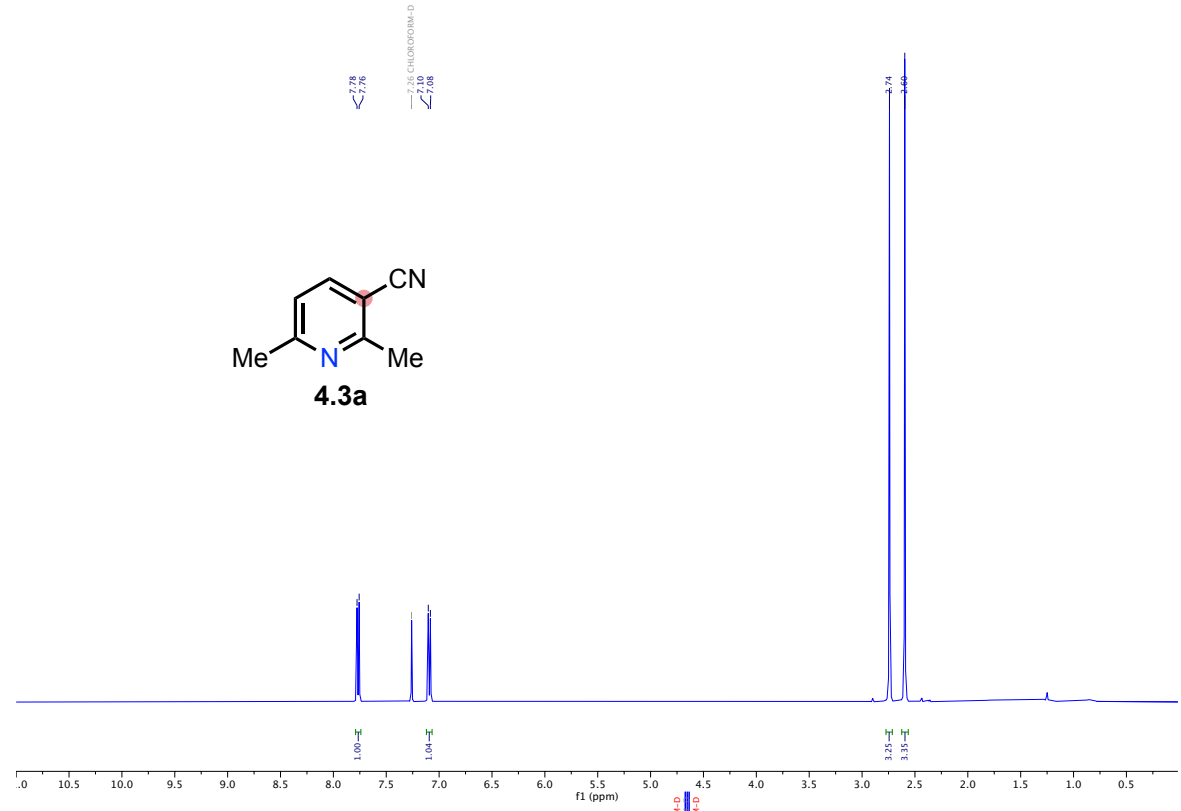
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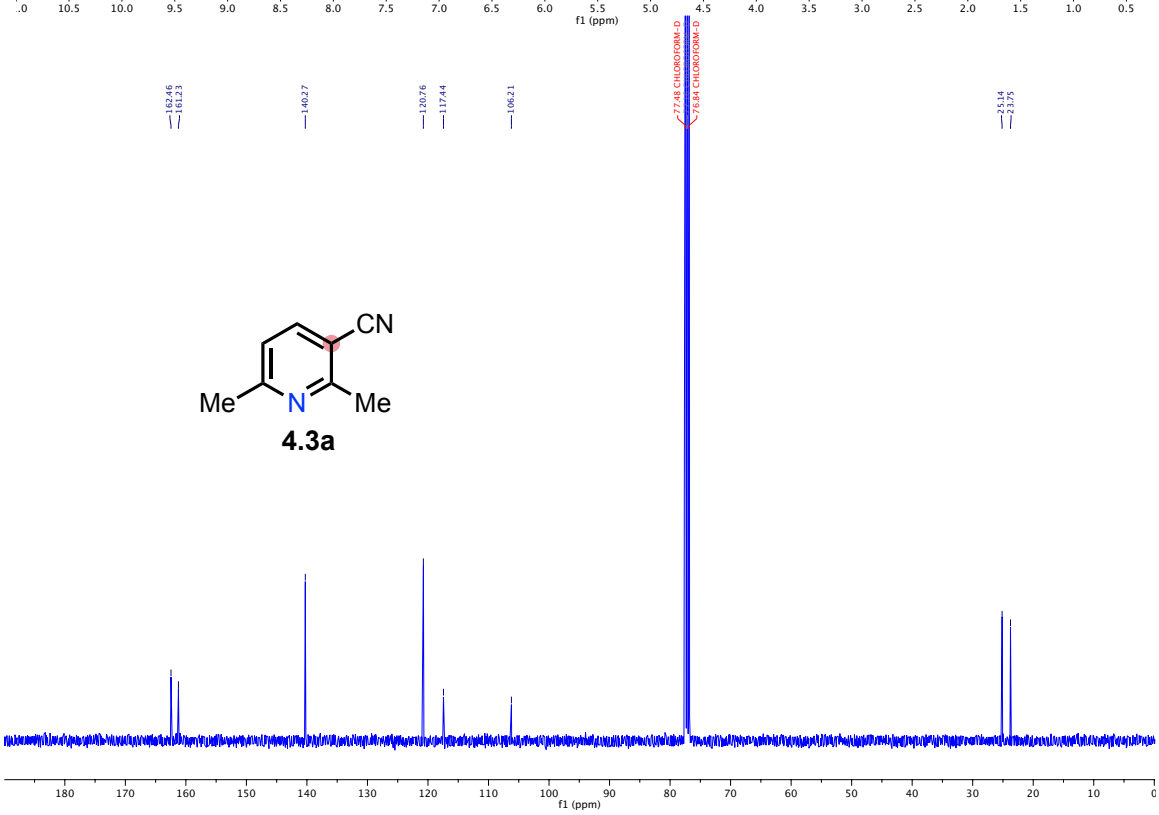

7.38
7.34
7.30 CHLOROFORM-D
6.51
6.50
6.24
6.20
6.07
6.06
4.26
4.24
4.22
4.20
2.65
2.63
2.61
1.67
1.65
1.63
1.33
1.31
1.29
1.28
1.26
0.89
0.88
0.86
H3C
n=11
O
CO2Et
4S11
0.97
1.00
0.93
0.99
2.12
2.14
2.24
21.27
3.36
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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0.0
f1 (ppm)

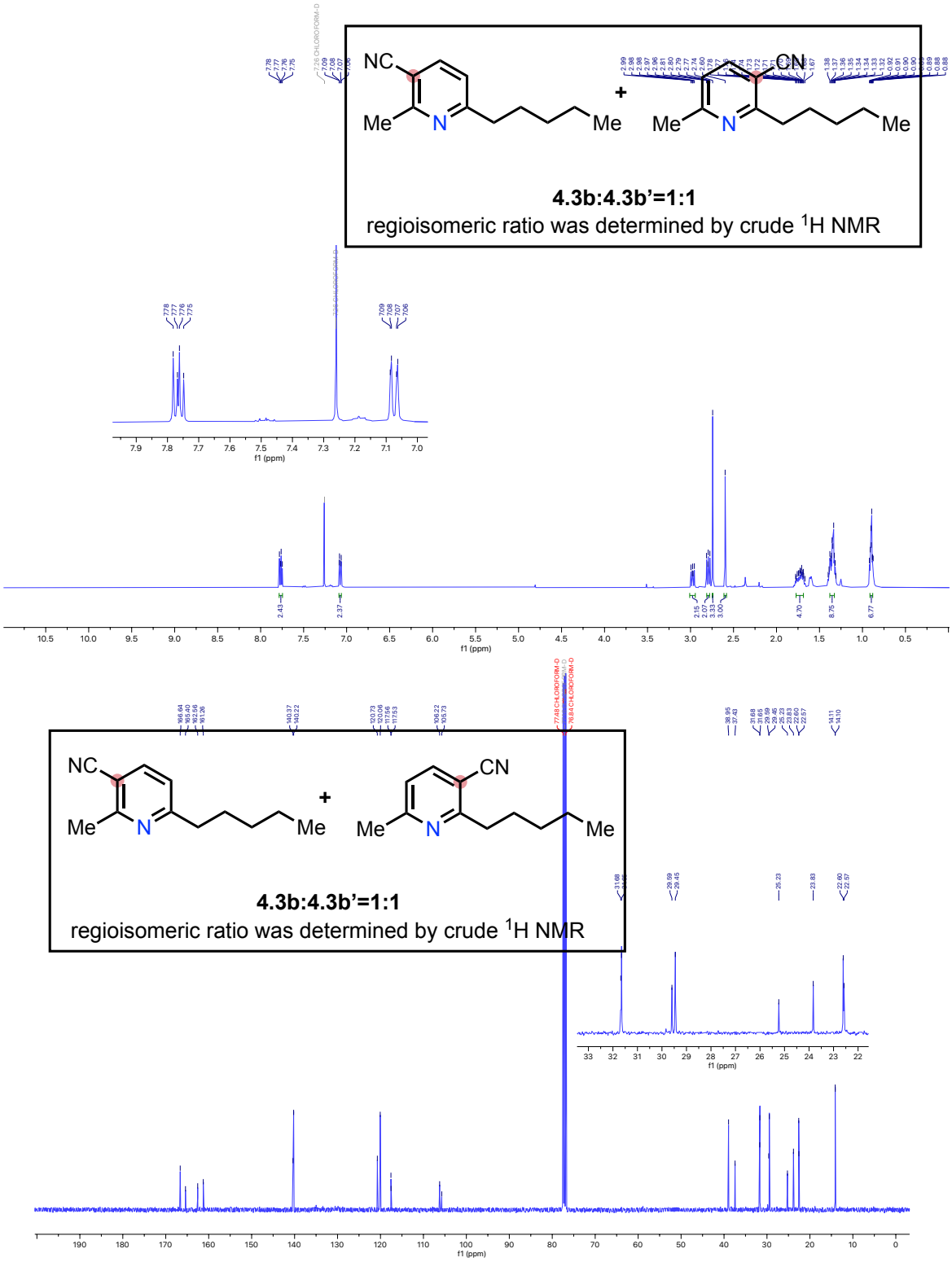

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160.07
149.51
131.30
116.38
114.09
108.06
60.42
33.06
31.80
29.77
29.66
29.56
29.46
29.30
28.44
27.94
22.64
14.49
14.28
H3C
n=11
O
CO2Et
4S11
220
210
200
190
180
170
160
150
140
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120
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100
90
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60
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20
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-10
-20
f1 (ppm)

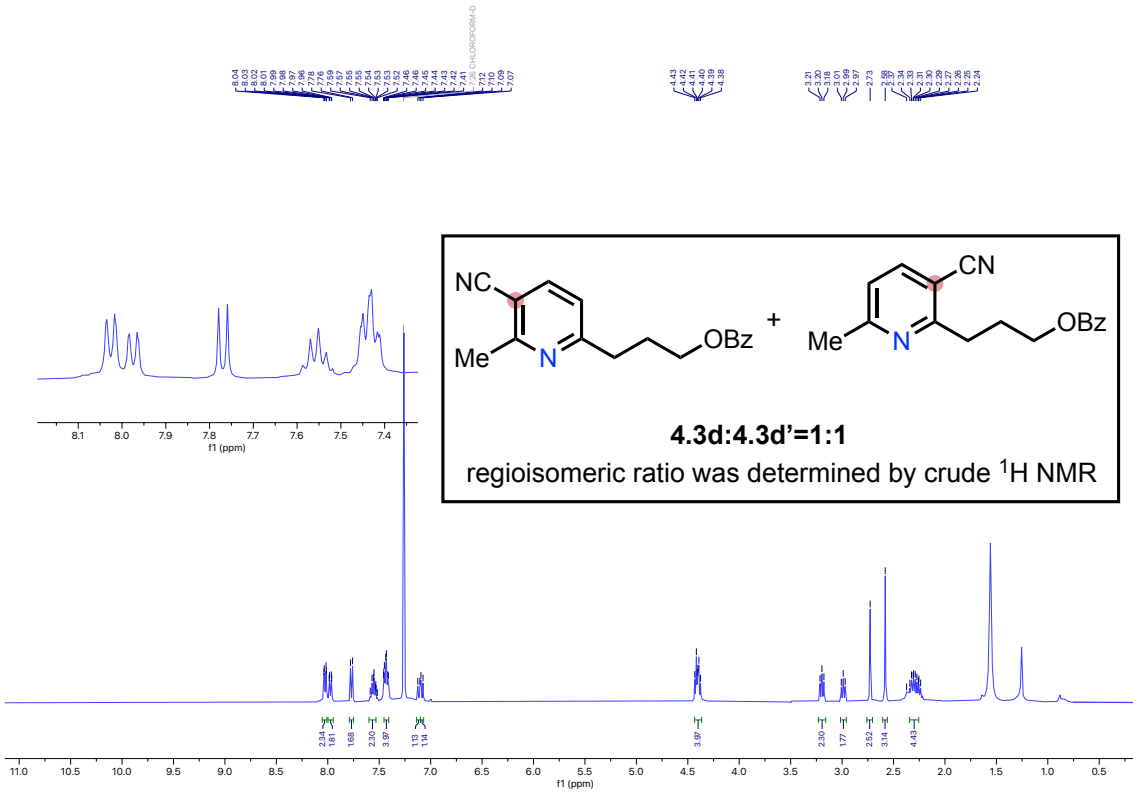

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4.1l
f1 (ppm)

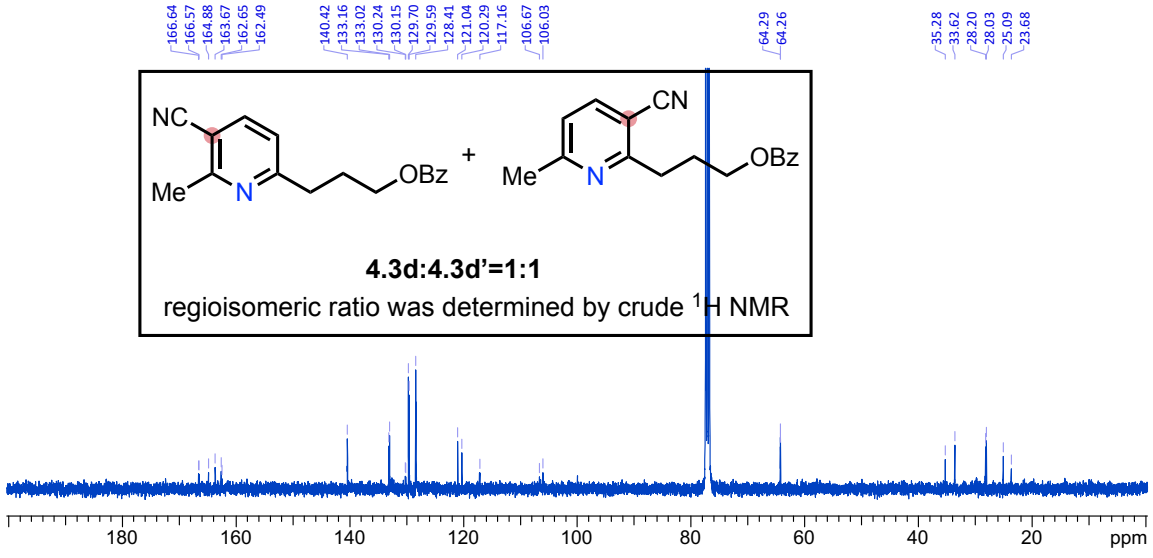

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O
CO2Et
4.1l
f1 (ppm)

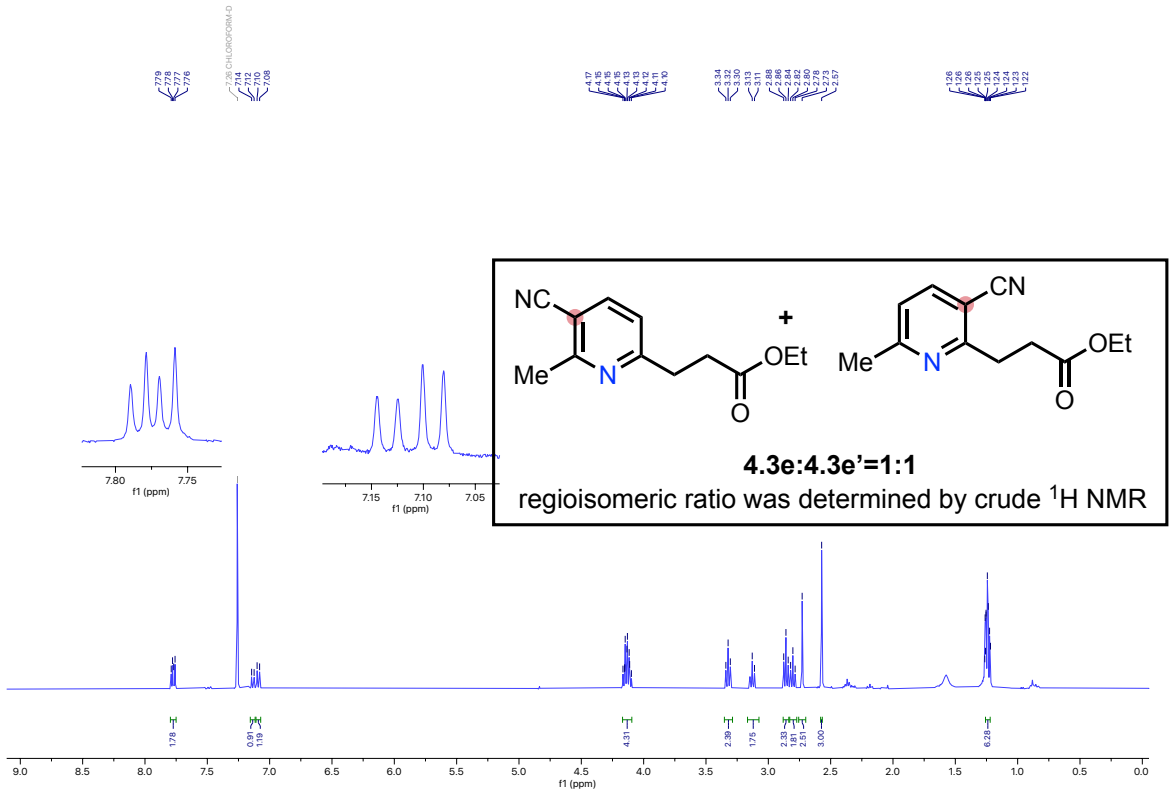

7.78
7.76
7.26 CHLOROFORM-D
7.10
7.08
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2.60
CN
Me
N
Me
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1.00
1.04
3.25
3.35
f1 (ppm)

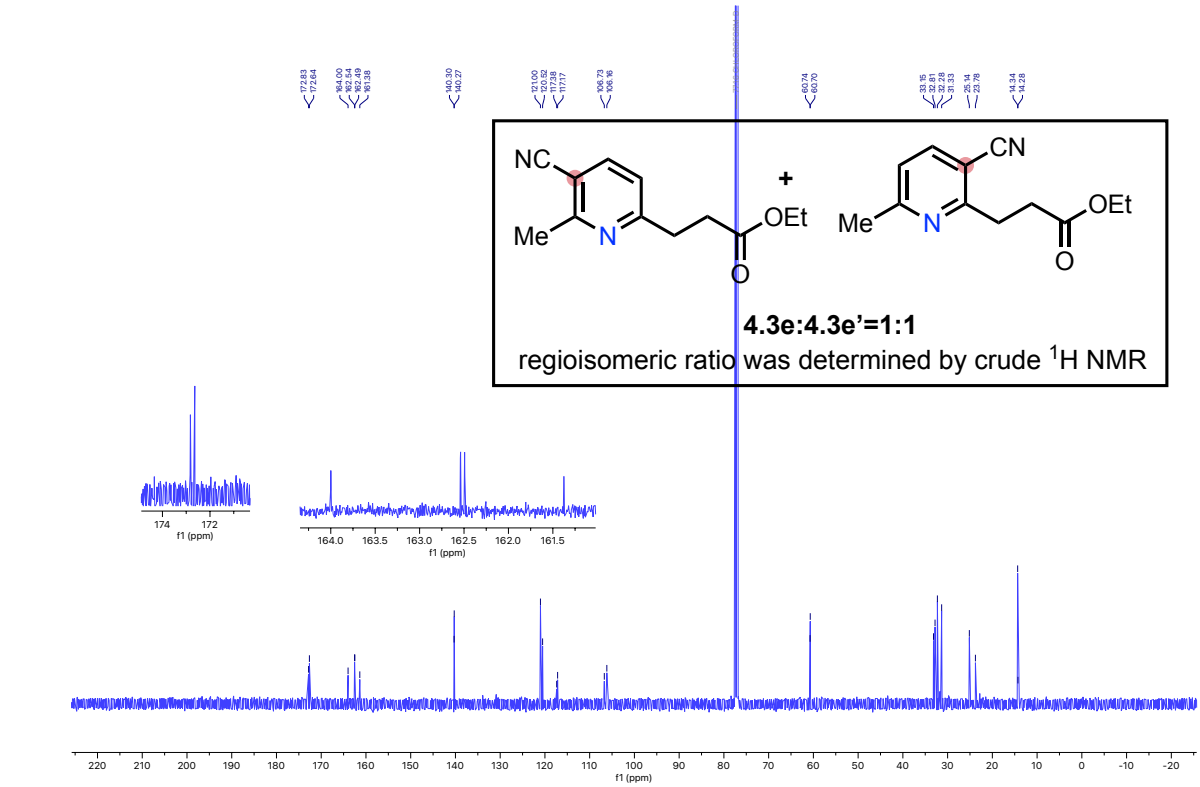

162.46
161.23
140.27
120.76
117.44
106.21
77.48 CHLOROFORM-D
76.84 CHLOROFORM-D
25.14
23.75
CN
Me
N
Me
4.3a
f1 (ppm)

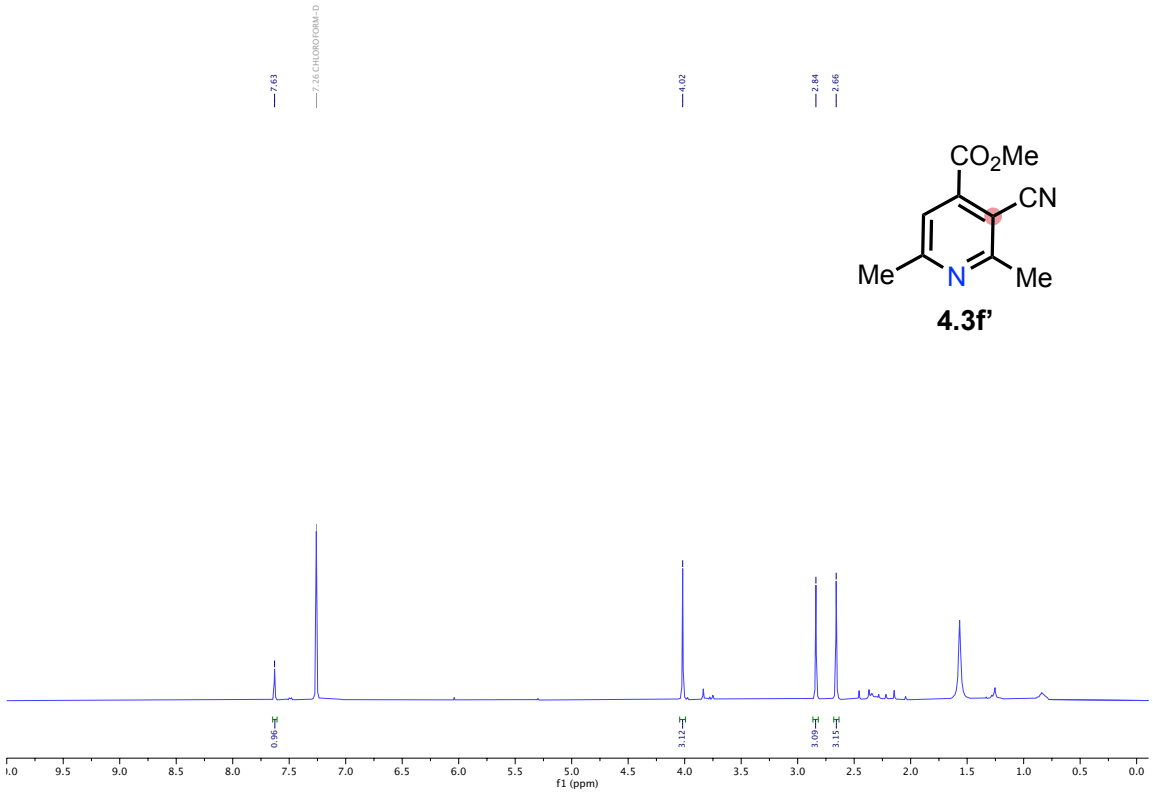

NC
Me
N
Me
+
CN
Me
N
Me
4.3b:4.3b'=1:1
regioisomeric ratio was determined by crude 1H NMR
f1 (ppm)
NC
Me
N
Me
+
CN
Me
N
Me
4.3b:4.3b'=1:1
regioisomeric ratio was determined by crude 1H NMR
f1 (ppm)
f1 (ppm)


NC
Me
N
OBz
+
CN
Me
N
OBz
4.3d:4.3d'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
f1 (ppm)


NC
Me
N
OBz
+
CN
Me
N
OBz
4.3d:4.3d'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
ppm

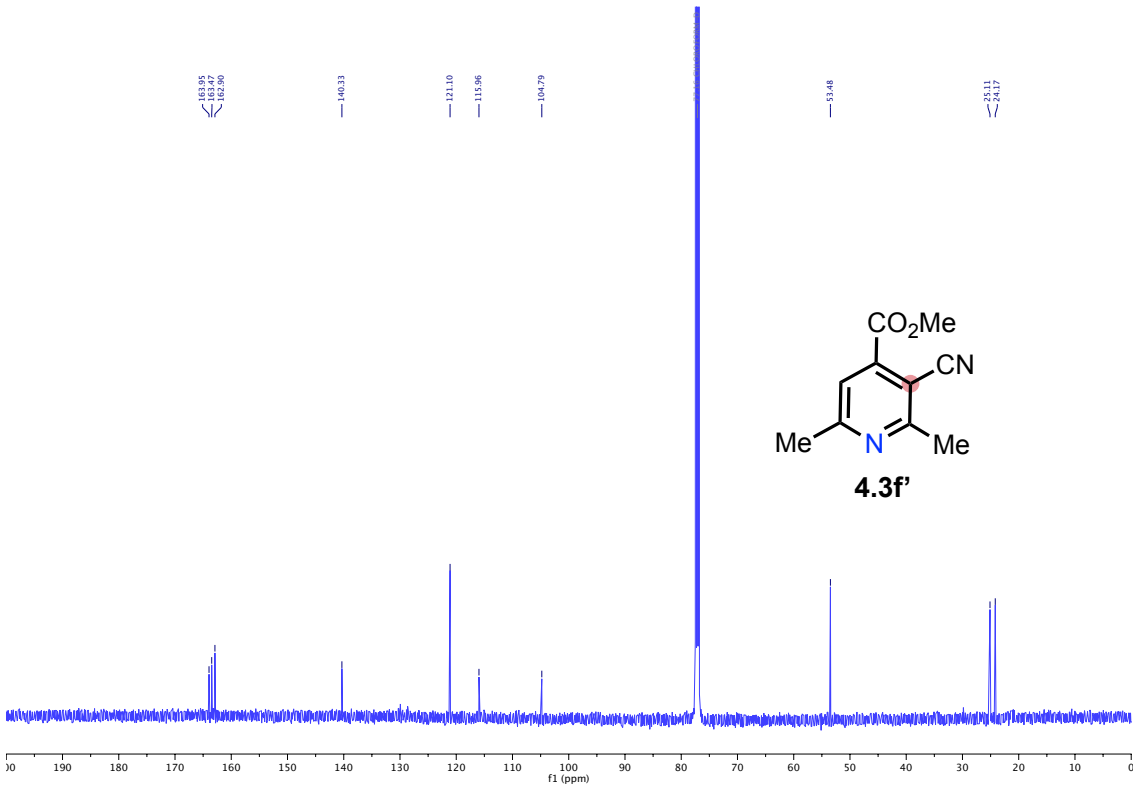

NC
Me
N
OEt
O
+
CN
Me
N
OEt
O
4.3e:4.3e'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
f1 (ppm)


NC
Me
N
OEt
O
+
CN
Me
N
OEt
O
4.3e:4.3e'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
f1 (ppm)


7.63
7.26 CHLOROFORM-D
4.02
2.84
2.66
0.96
3.12
3.09
3.15
f1 (ppm)

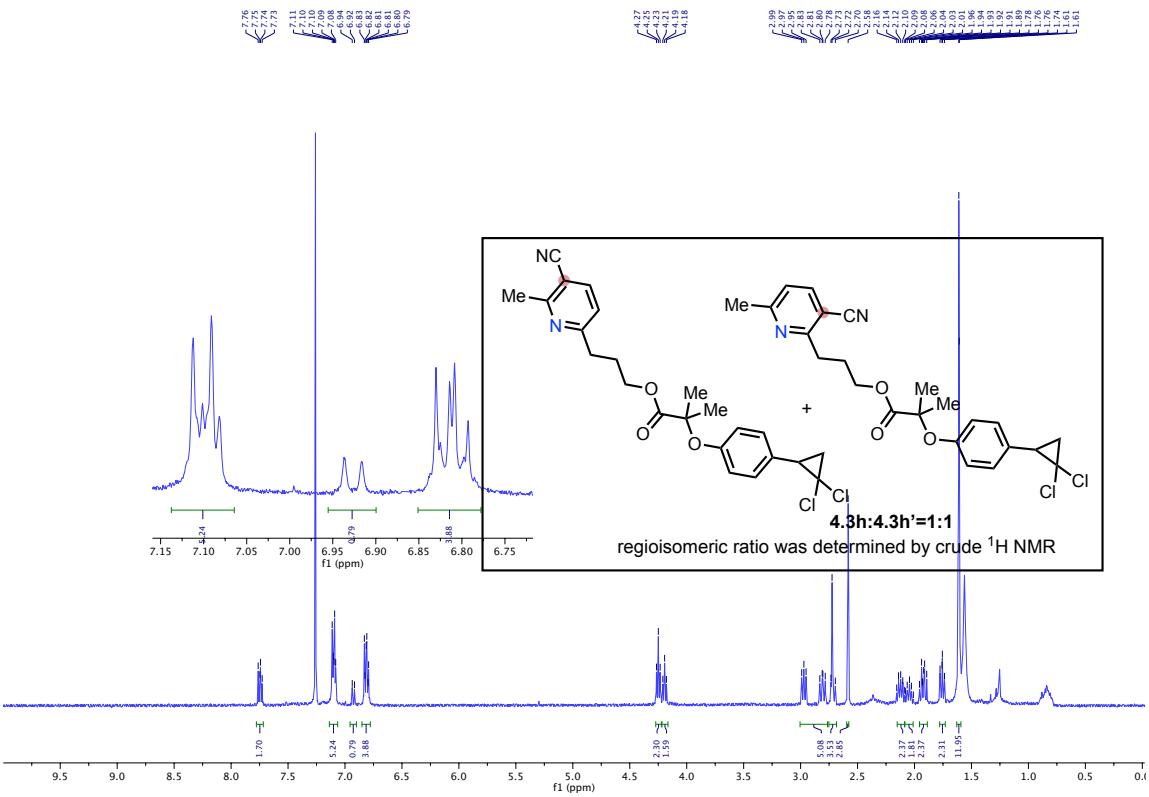
CO2Me
CN
Me
N
Me

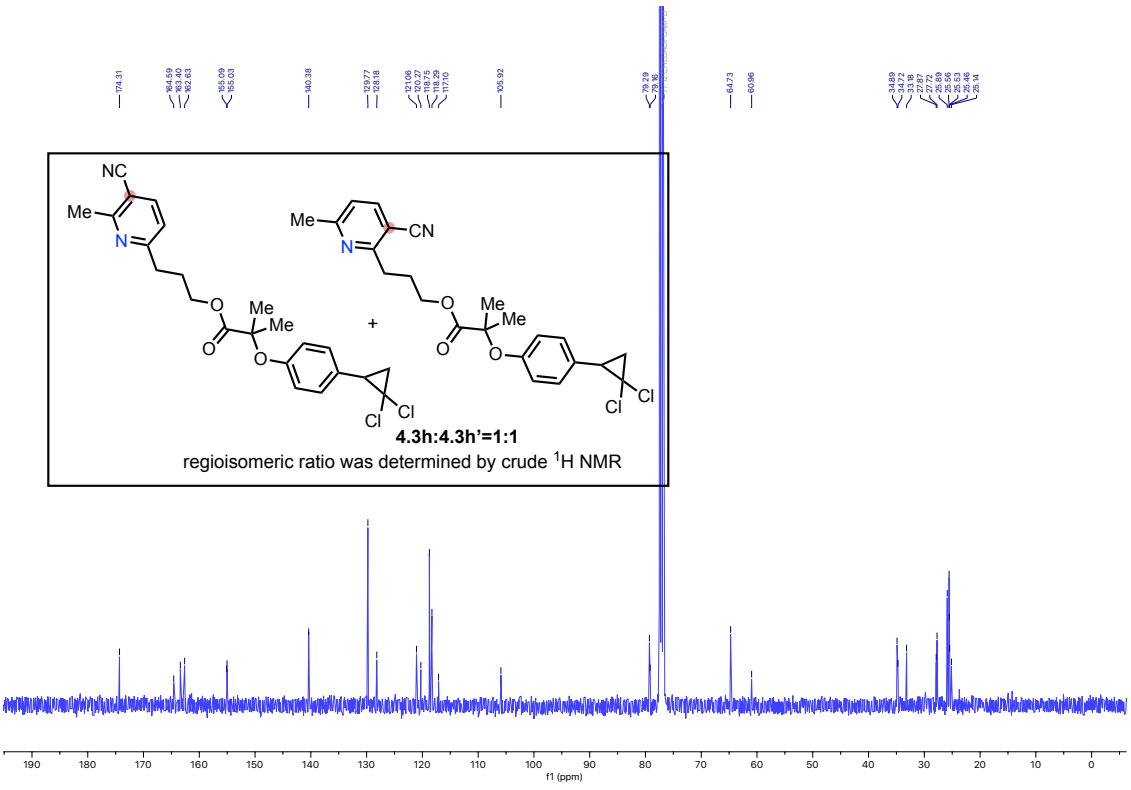
4.3f'

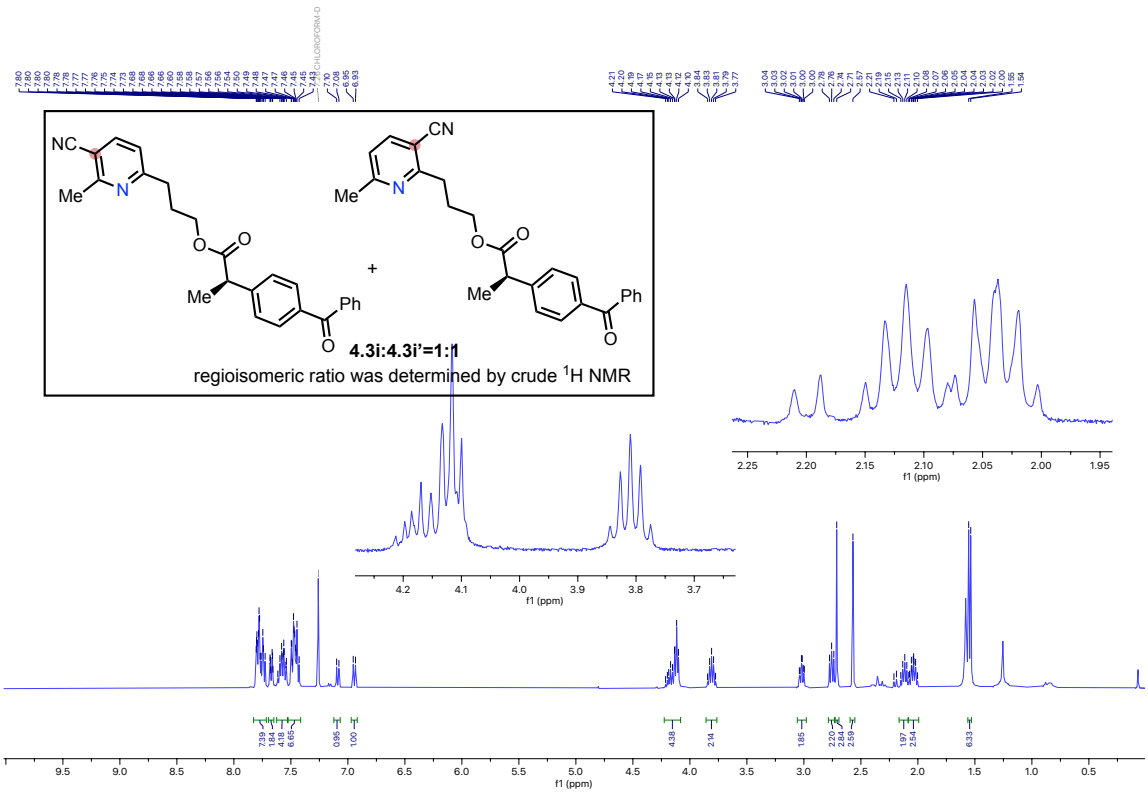

163.95
163.47
162.90
140.33
121.10
115.96
104.79
53.48
25.11
24.17
f1 (ppm)

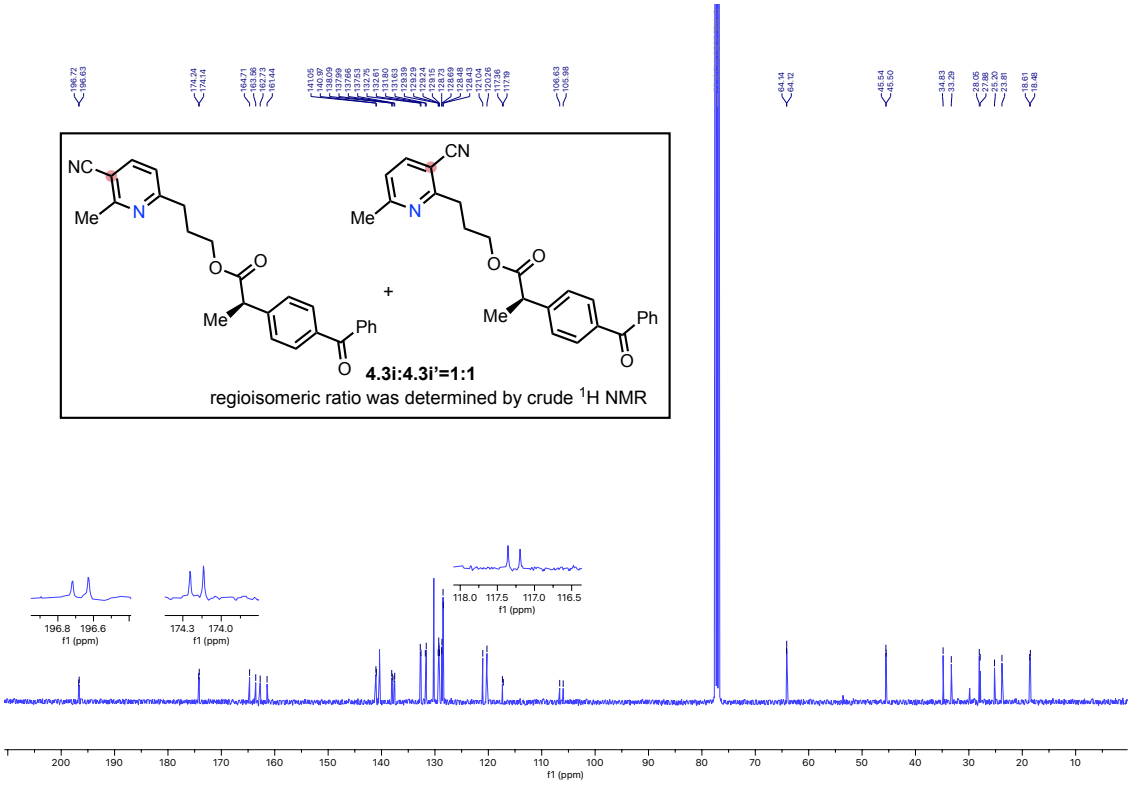
CO2Me
CN
Me
N
Me

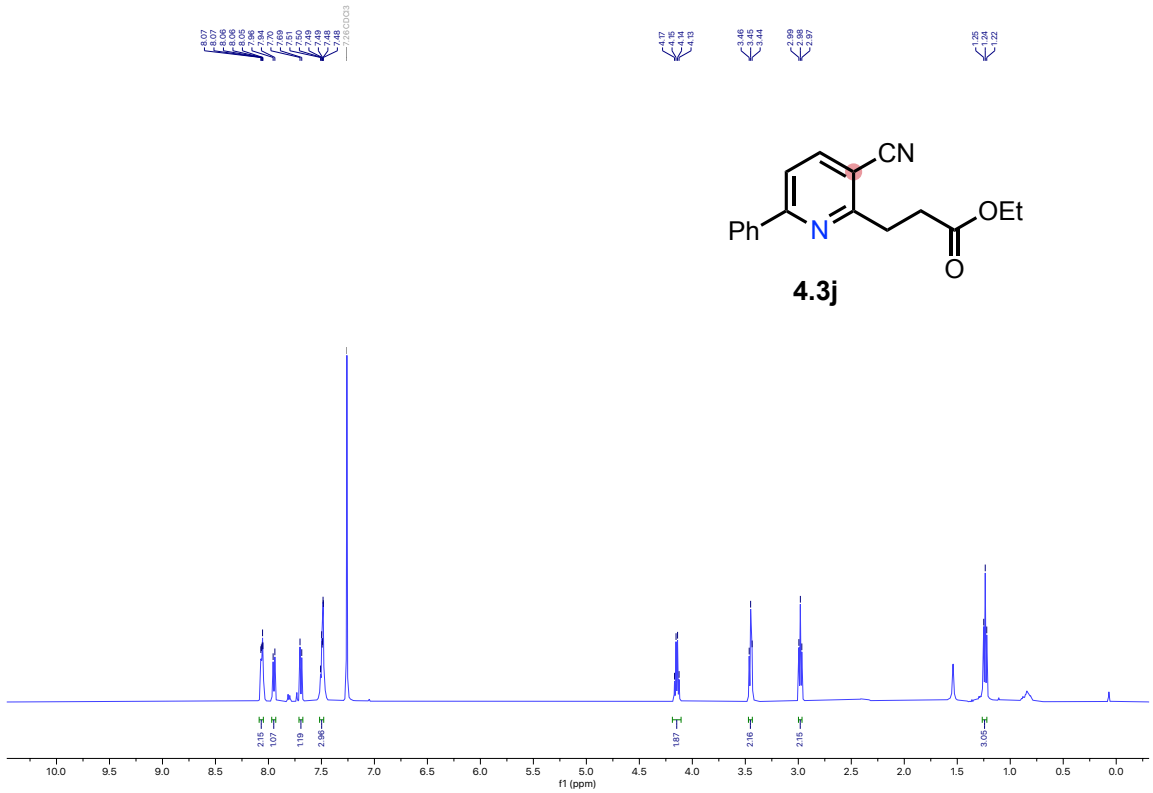
4.3f'

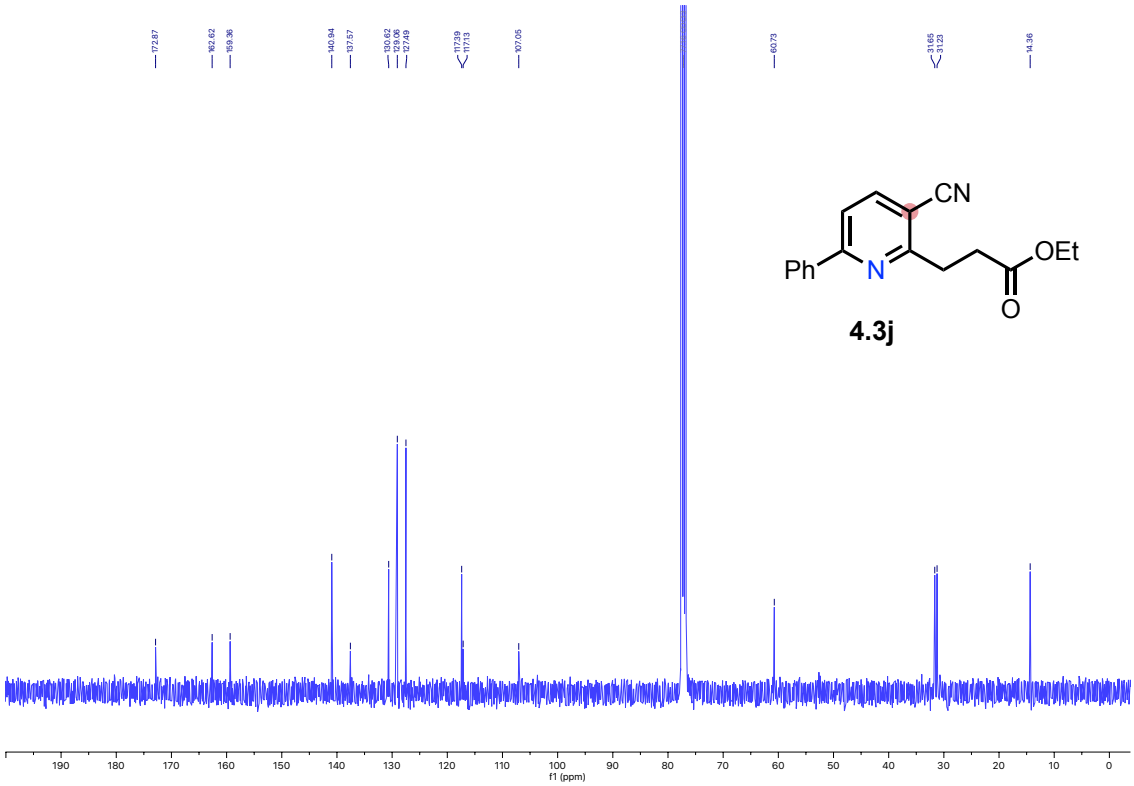

NC
Me
N
Me
CN
O
Me
Me
O
O
Cl
Cl
+
4.3h:4.3h'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
f1 (ppm)

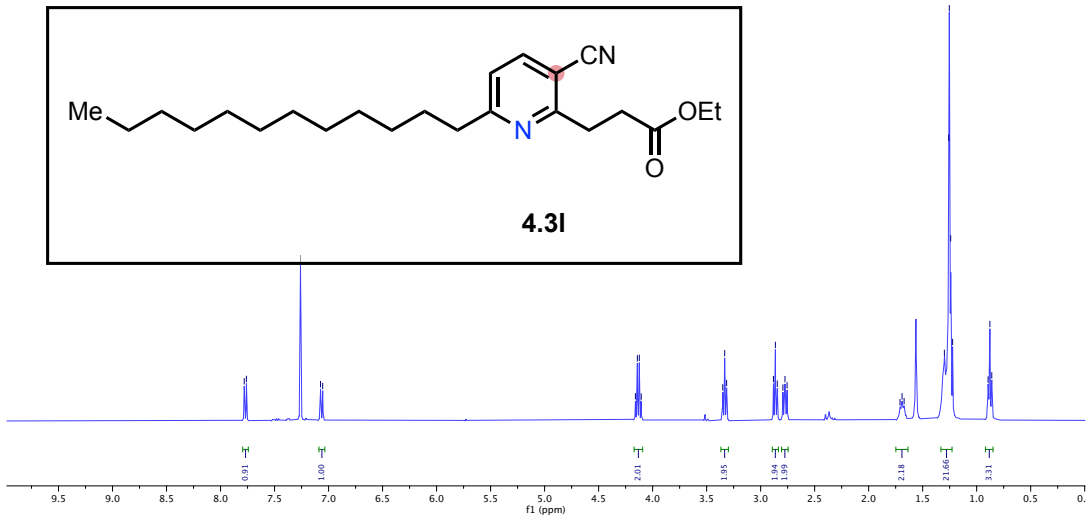

NC
Me
N
Me
CN
O
Me
Me
O
O
Cl
Cl
+
4.3h:4.3h'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
f1 (ppm)

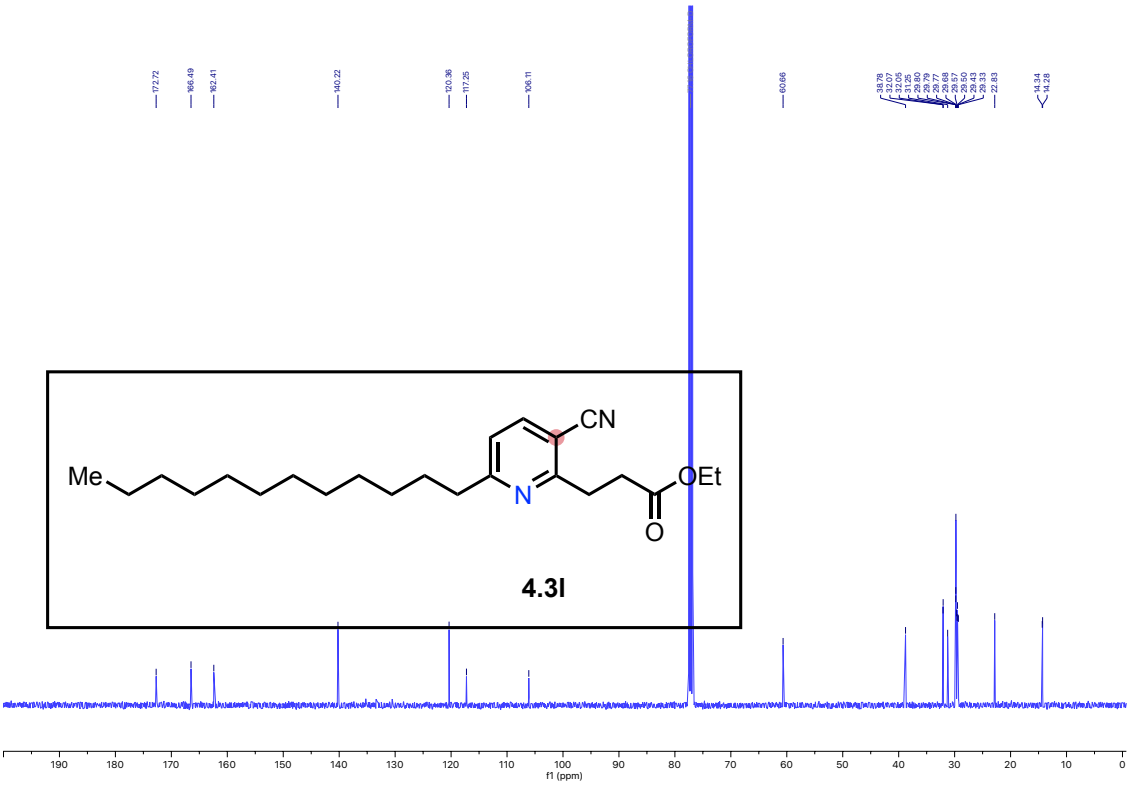

NC
Me
N
O
O
Me
Ph
O
+
CN
Me
N
O
O
Me
Ph
O
4.3i:4.3i'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
f1 (ppm)

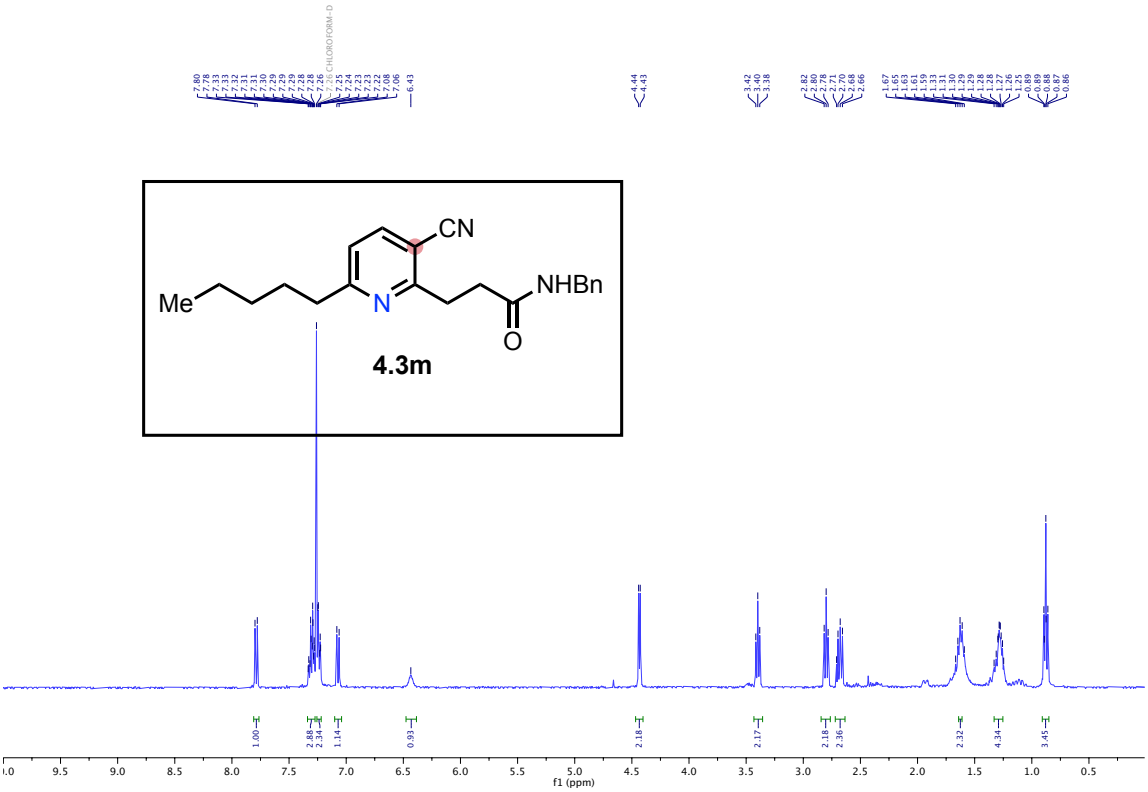

NC
Me
N
O
O
Me
Ph
O
+
CN
Me
N
O
O
Me
Ph
O
4.3i:4.3i'=1:1
regioisomeric ratio was determined by crude ^{1}H NMR
f1 (ppm)

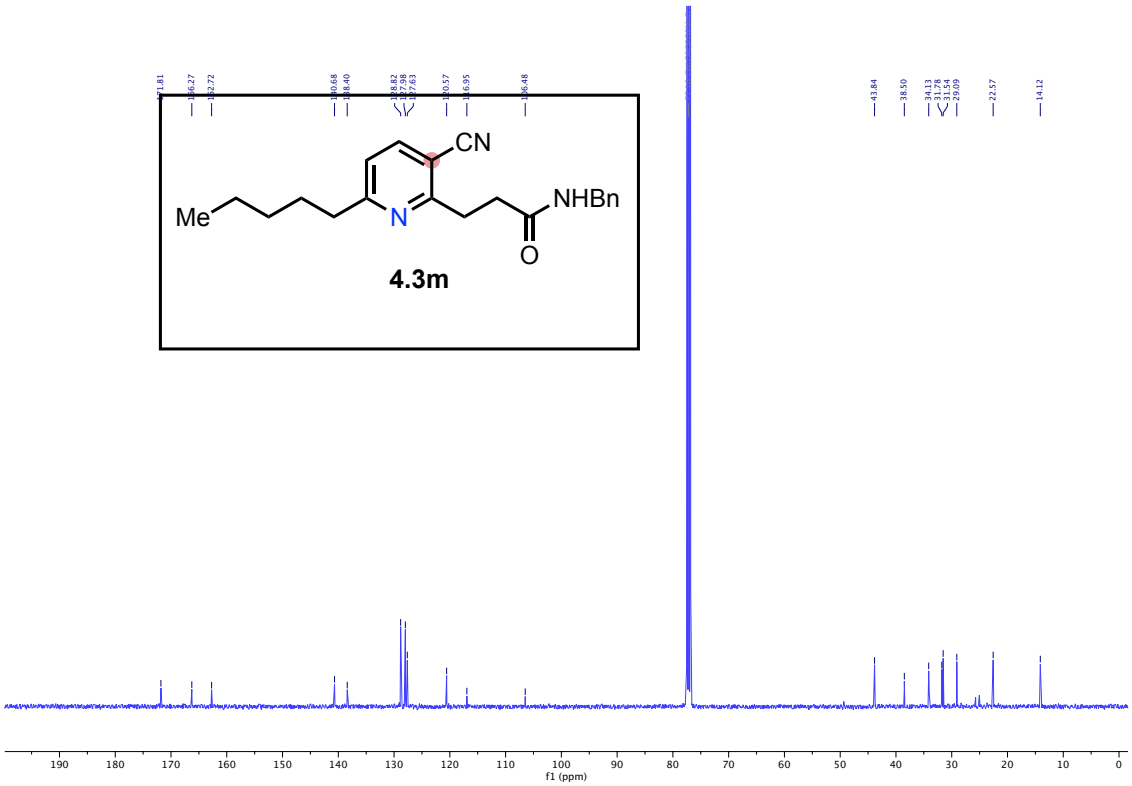

CN
Ph
N
OEt
O
4.3j
f1 (ppm)

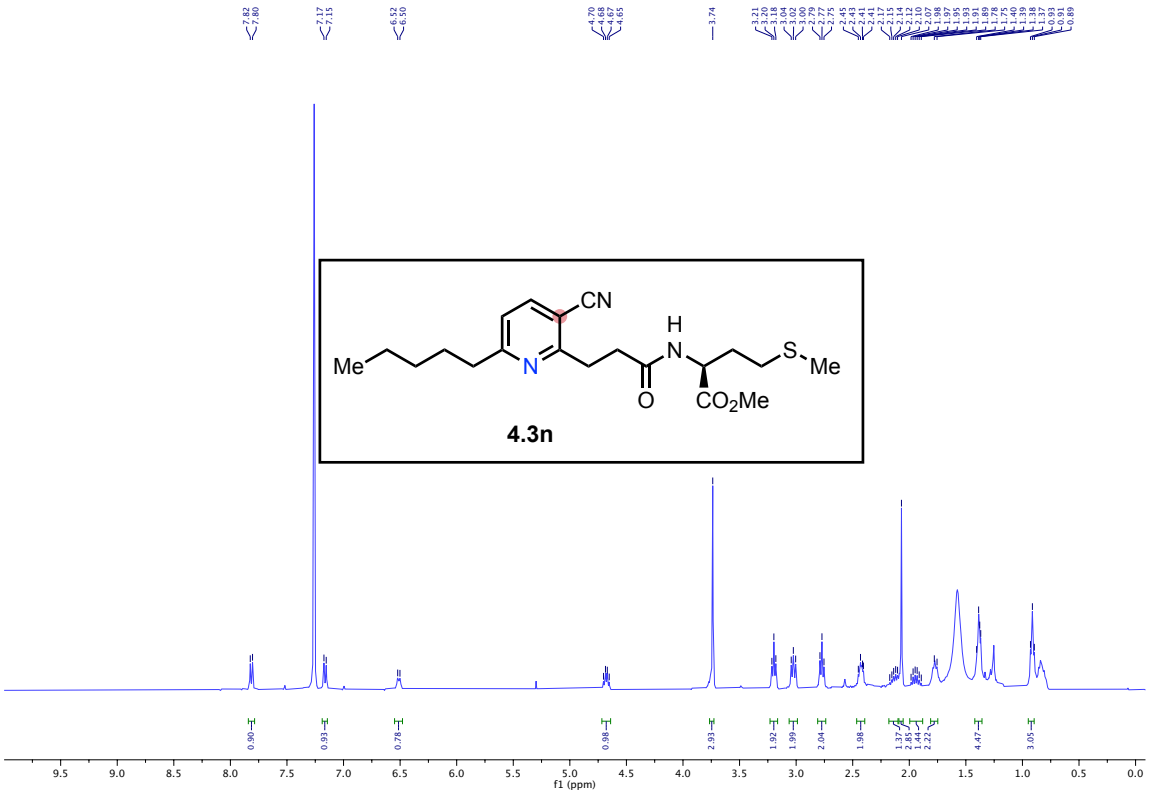

CN
Ph
N
OEt
O
4.3j
f1 (ppm)

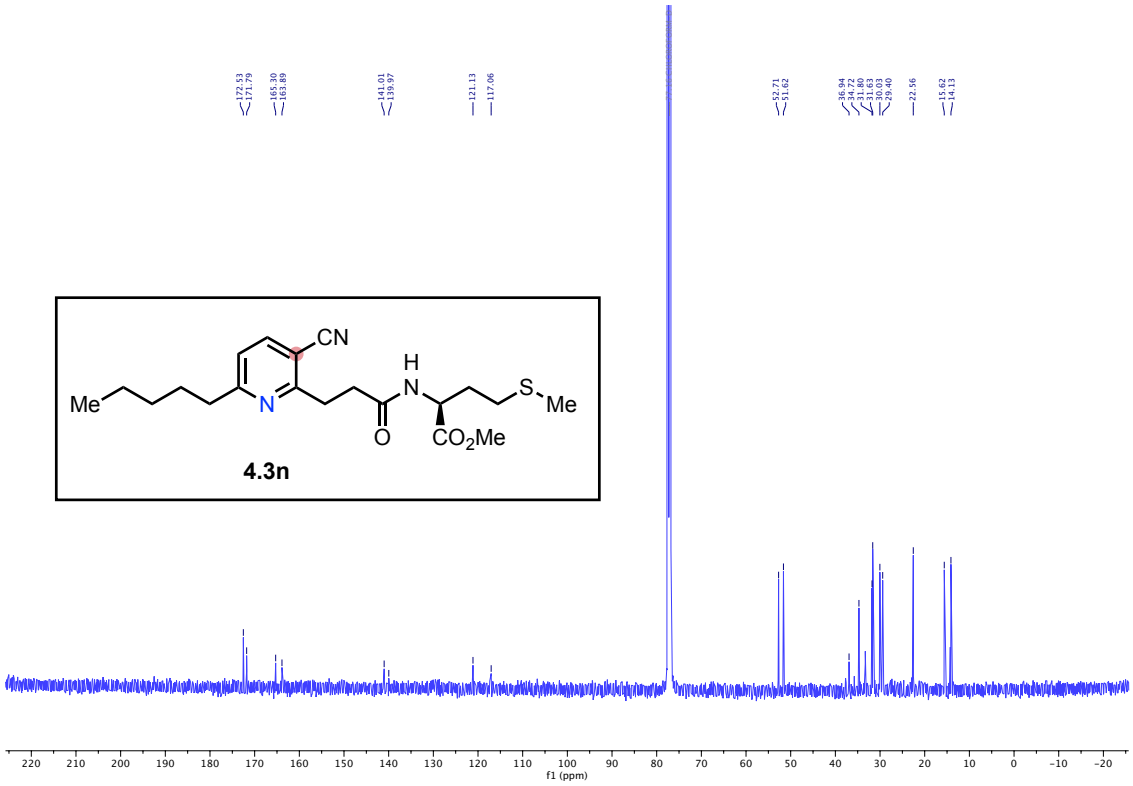

CN
Me
N
OEt
O
4.3l
f1 (ppm)

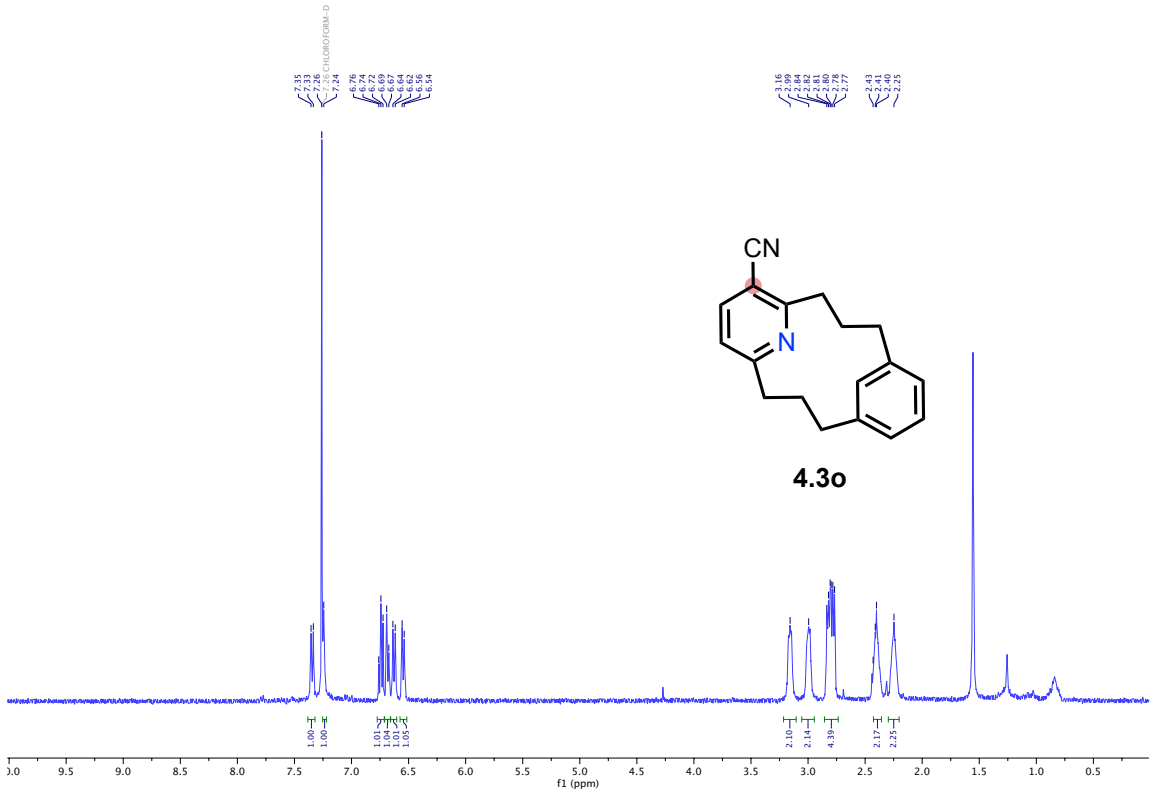

CN
Me
N
OEt
O
4.3l
f1 (ppm)

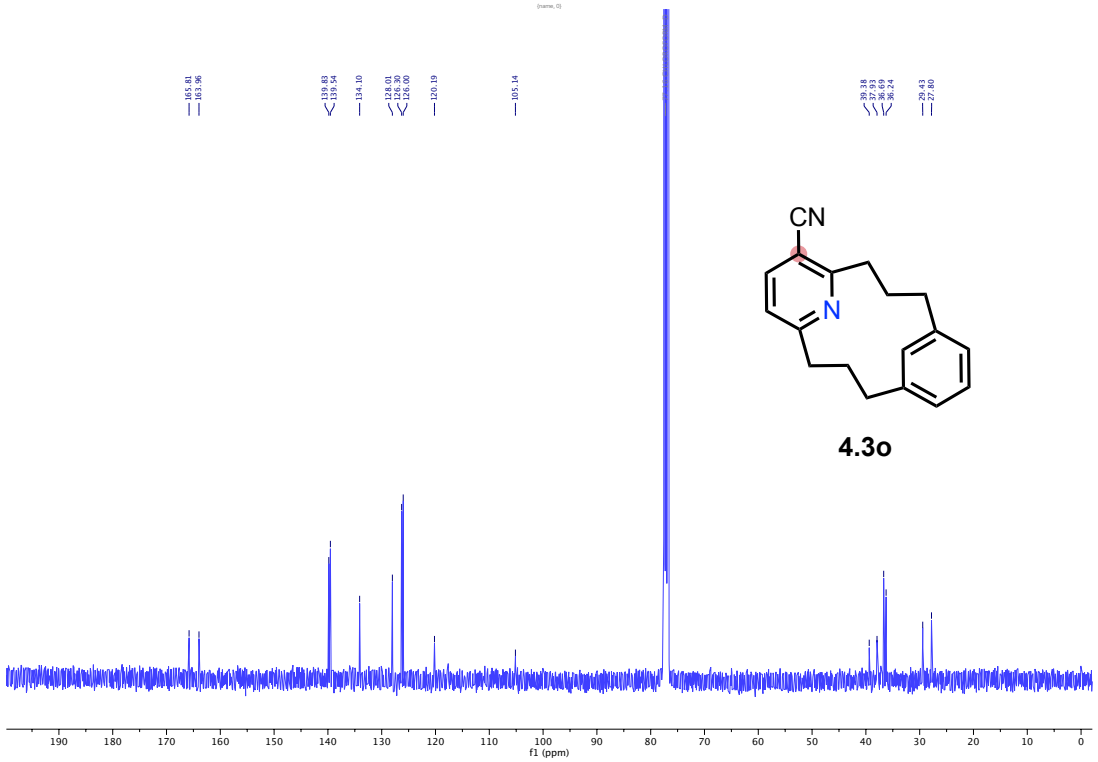

CN
Me
N
NHBn
O
4.3m
f1 (ppm)

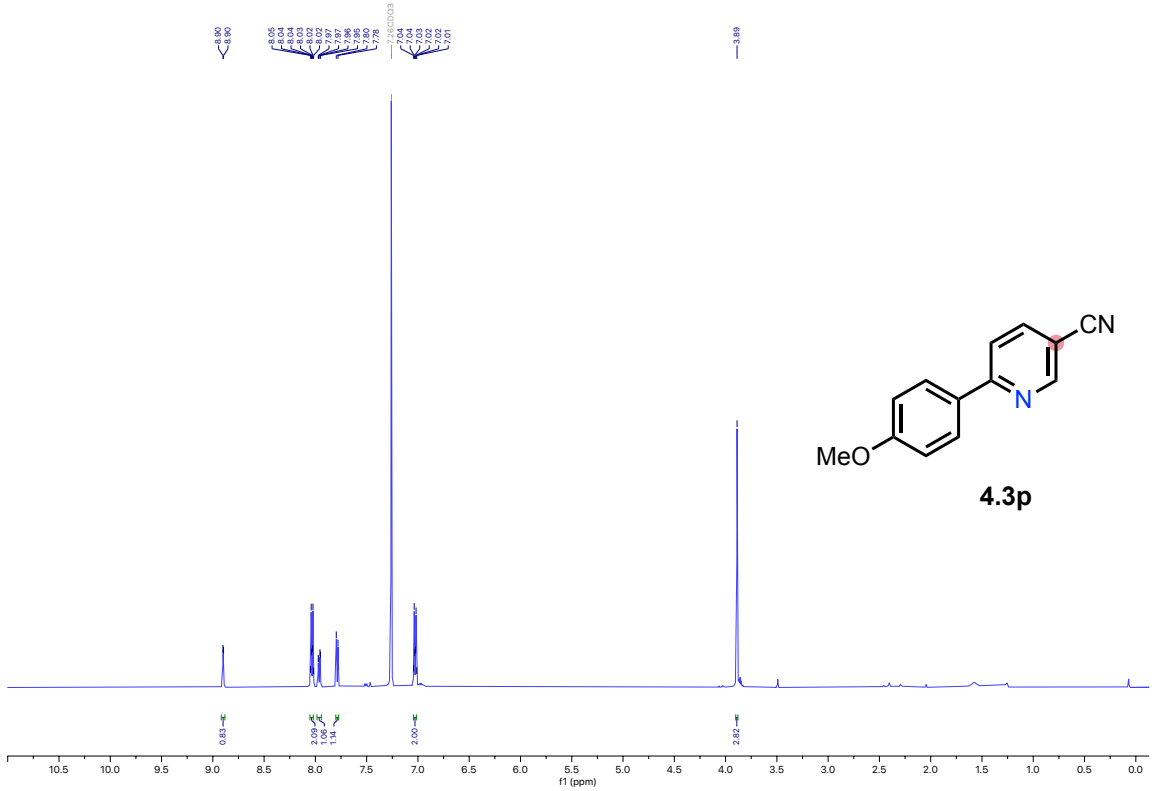

CN
Me
N
NHBn
O
4.3m
f1 (ppm)


CN
H
N
Me
N
S
Me
O
CO2Me
4.3n
f1 (ppm)


CN
H
N
Me
N
S
Me
O
CO2Me
4.3n
f1 (ppm)

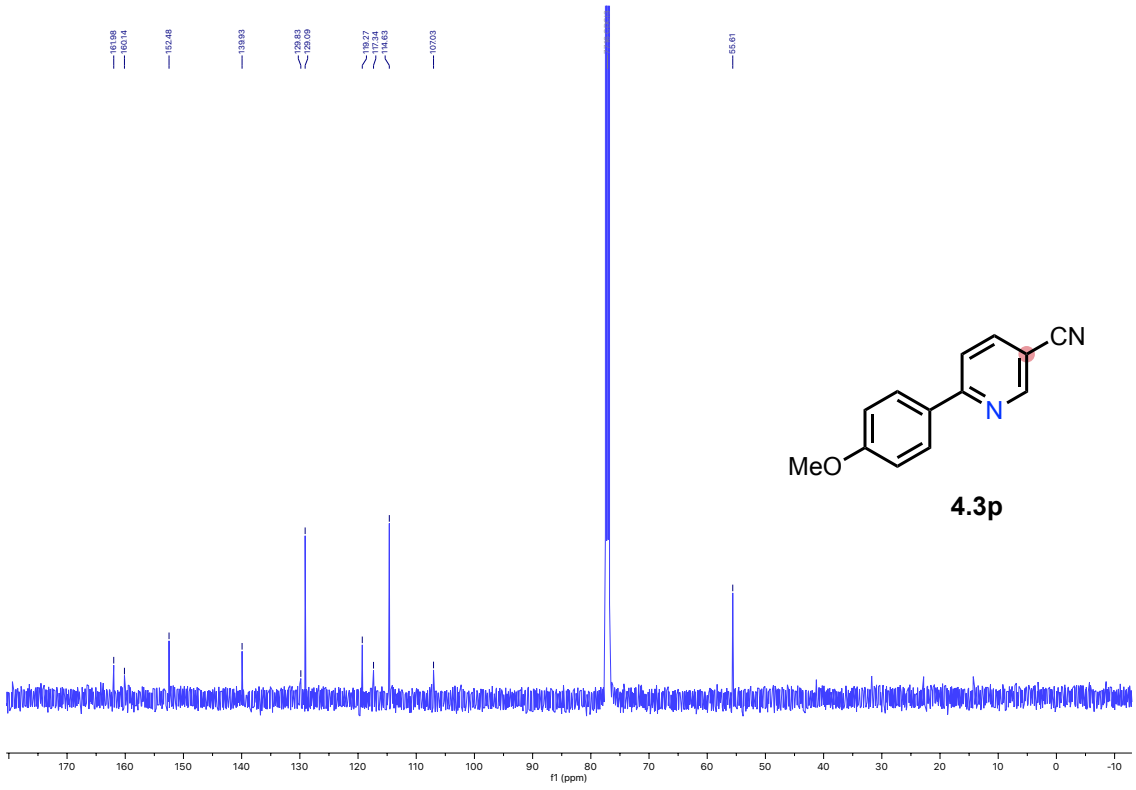

CN
N
4.3o
f1 (ppm)


CN
N
4.3o
f1 (ppm)


8.90
8.90
8.05
8.04
8.04
8.03
8.02
8.02
7.97
7.97
7.96
7.96
7.80
7.78
7.04
7.04
7.03
7.03
7.02
7.02
7.01
3.89
0.83
2.09
1.06
1.14
2.00
2.82
f1 (ppm)

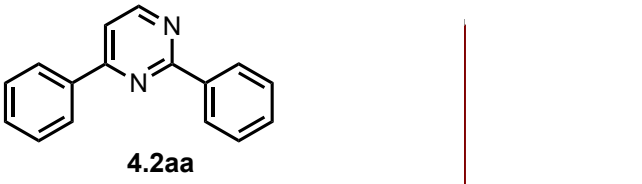
CN
N
MeO

4.3p


161.98
160.14
152.48
139.93
130.83
129.09
119.27
117.34
114.63
107.03
55.61
f1 (ppm)

CN
N
MeO

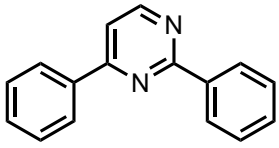
4.3p



4.2aa

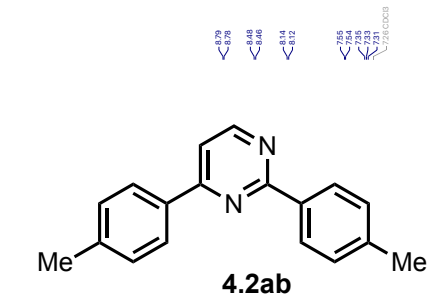
1.00
1.90
2.00
1.04
5.88
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)



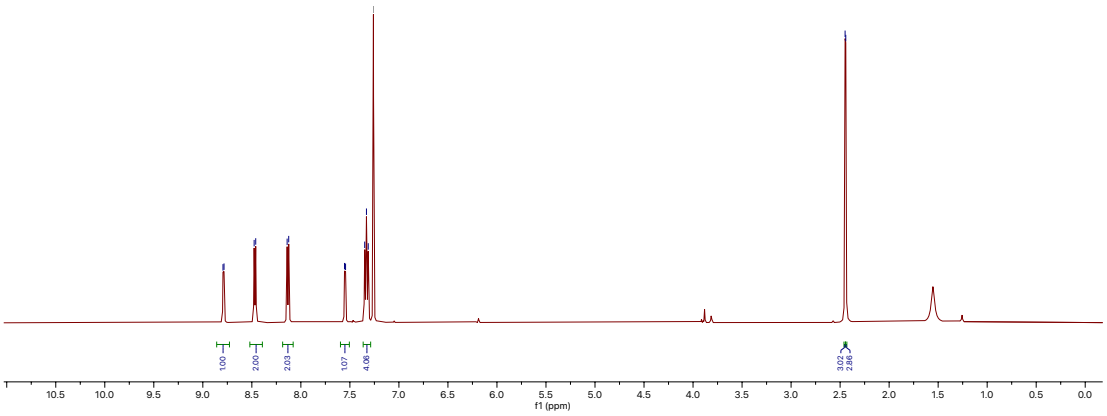


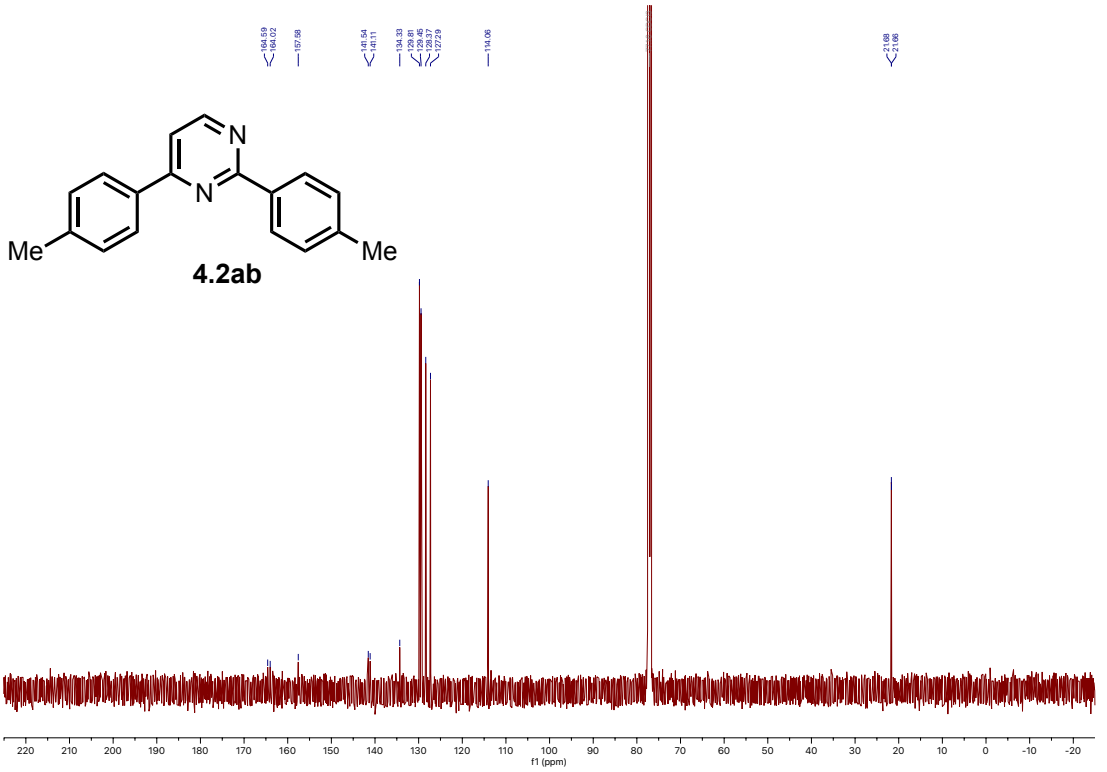
4.2aa

164.73
164.04
158.00
137.99
137.11
131.13
130.87
129.71
128.70
123.42
121.98
114.69
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

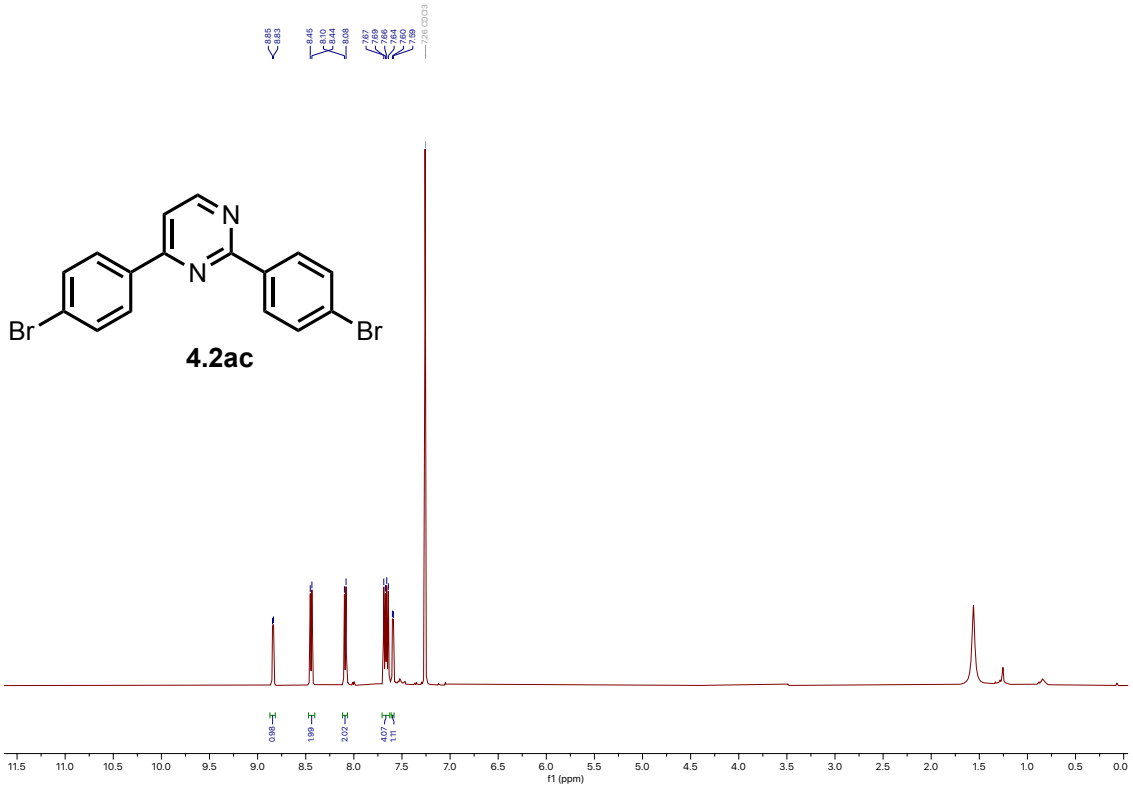


4.2ab

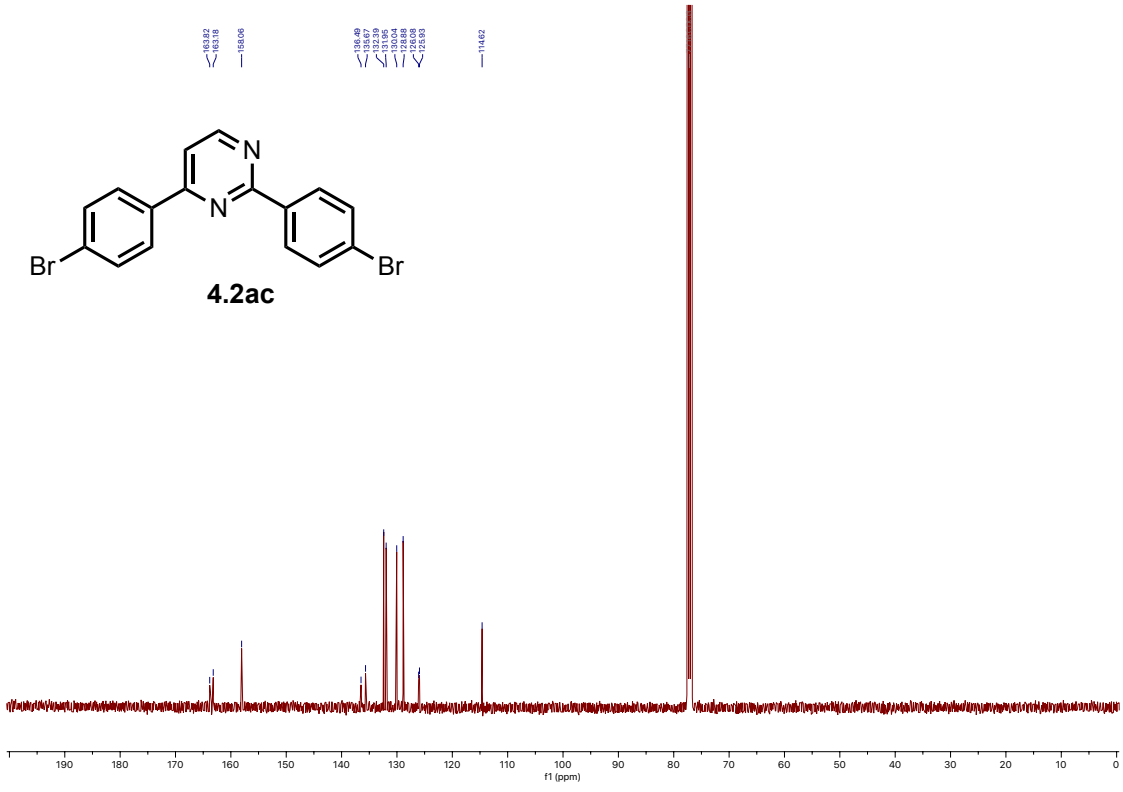




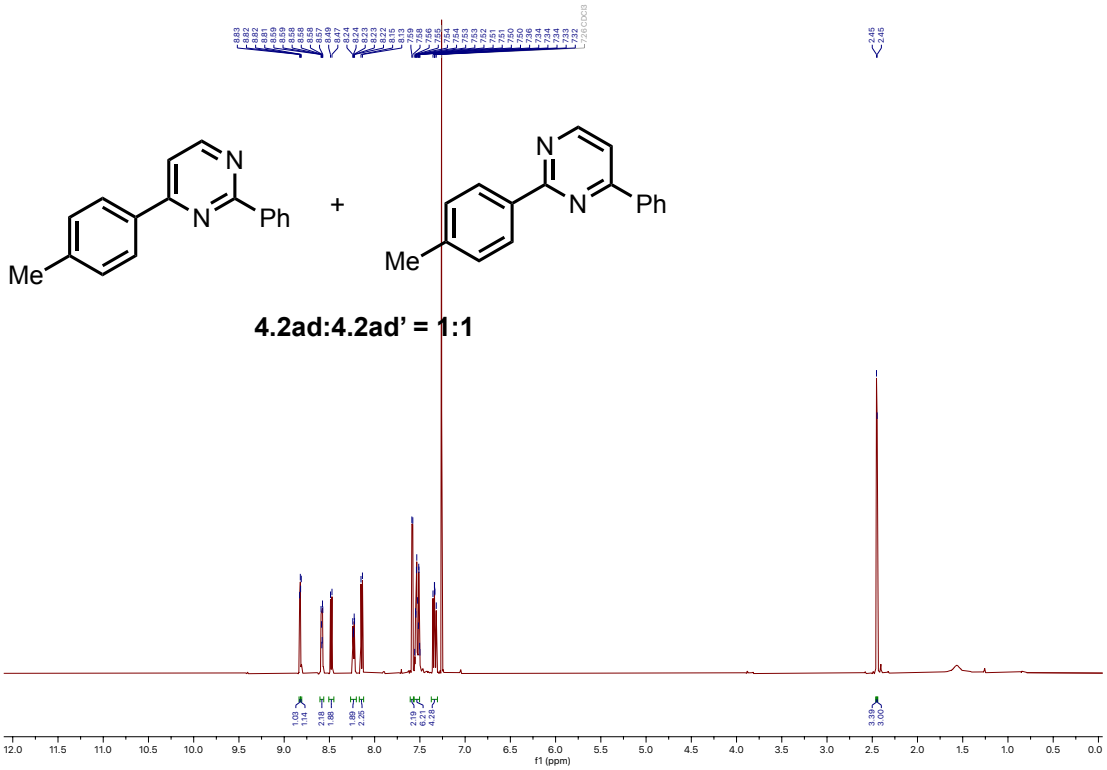
4.2ab

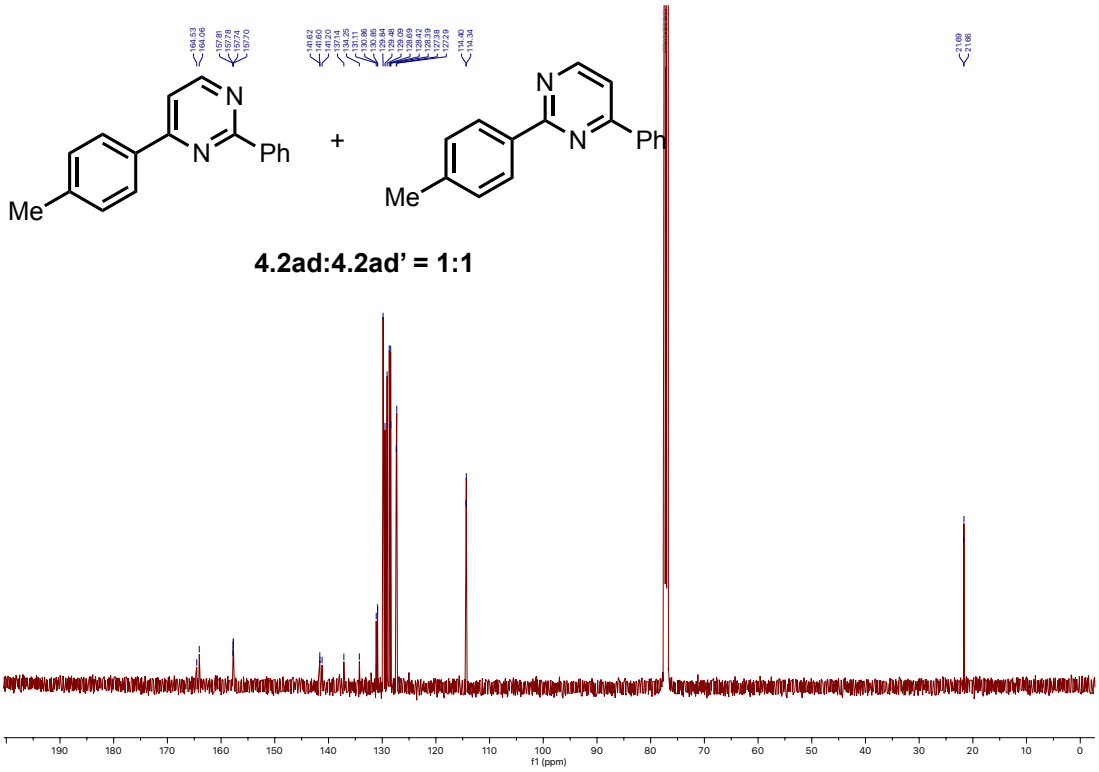

8.85
8.83
8.45
8.43
8.10
8.08
7.87
7.86
7.84
7.83
7.80
7.79
7.26 CDCl3
N
N
Br
Br
0.98
1.99
2.02
4.07
1.11
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

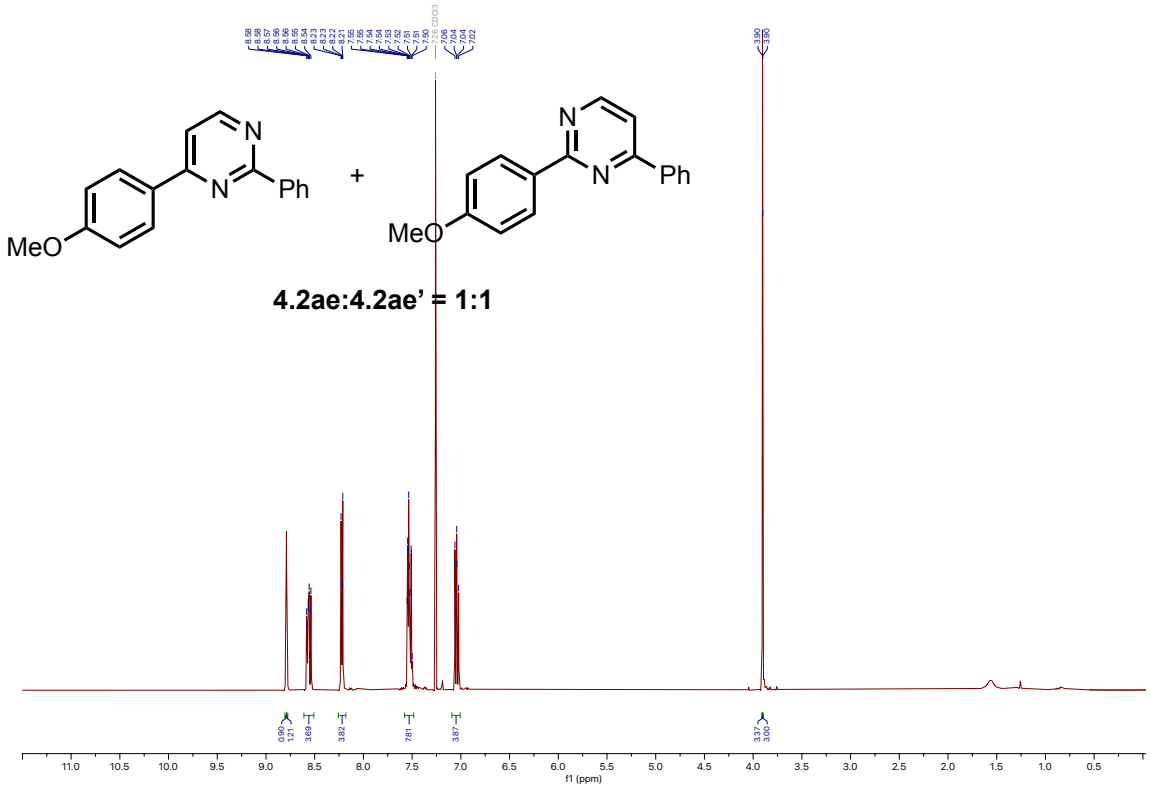
4.2ac

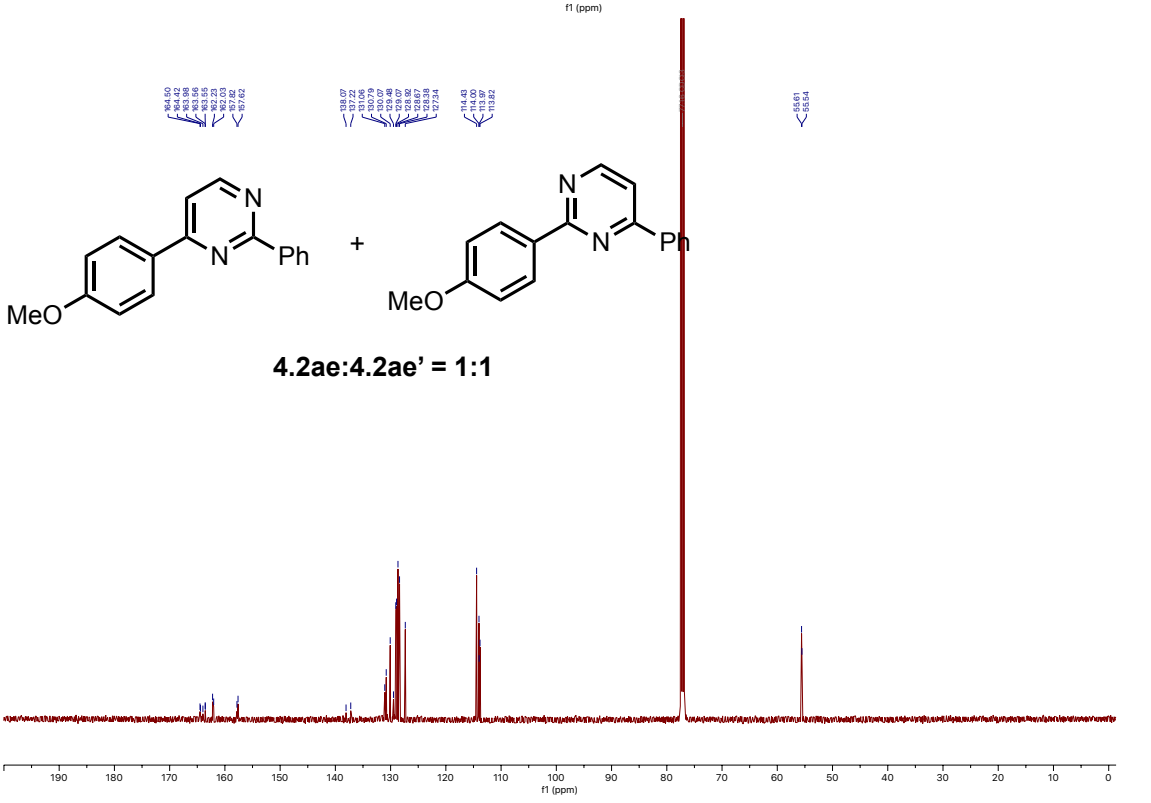

163.82
163.18
158.06
136.49
135.67
132.39
131.95
130.04
128.88
128.68
125.93
114.62
N
N
Br
Br
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

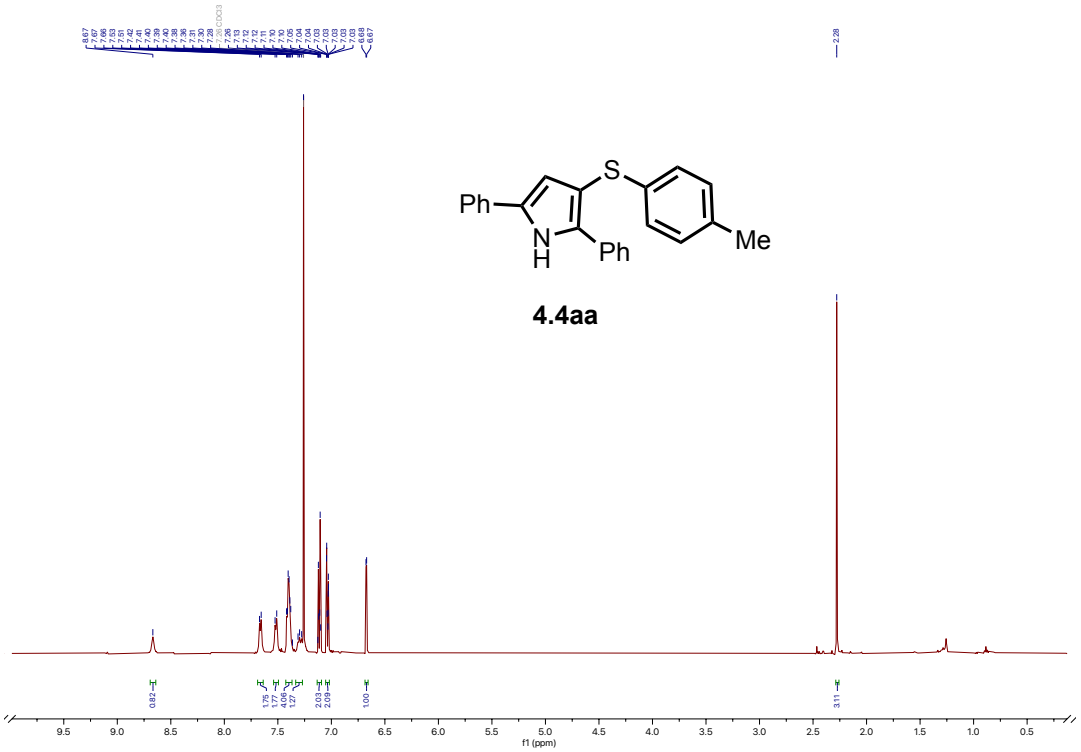
4.2ac


Me
N
N
Ph
+
Me
N
N
Ph
4.2ad:4.2ad' = 1:1
f1 (ppm)

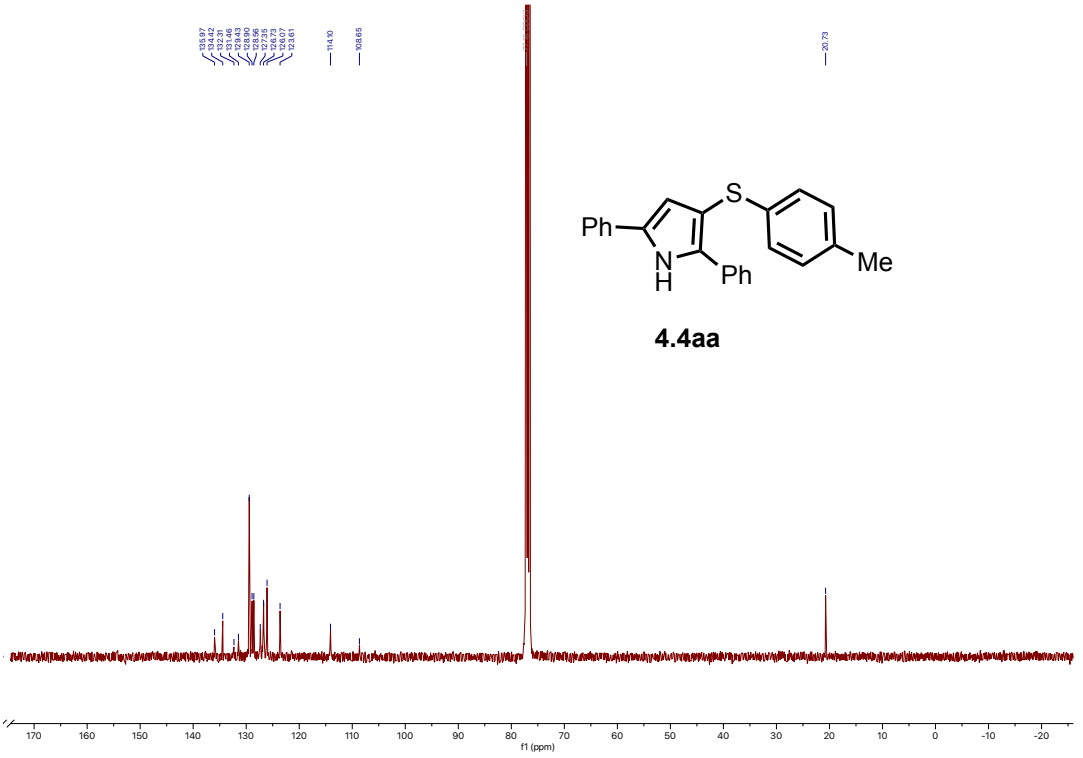

Me
N
N
Ph
+
Me
N
N
Ph
4.2ad:4.2ad' = 1:1
f1 (ppm)


MeO
Ph
+
MeO
Ph
4.2ae:4.2ae' = 1:1
f1 (ppm)


MeO
Ph
+
MeO
Ph
4.2ae:4.2ae' = 1:1
f1 (ppm)



4.4aa



4.4aa

CHAPTER 5

Conclusions and Future Directions

The primary goal of this dissertation was to develop sulfur-based intermediates for late-stage skeletal editing. This work is motivated by the need for efficient methodologies that enable the rapid generation of chemical libraries for drug discovery. Through this research, a deeper understanding of the reactivity of sulfur-stabilized carbenes and nitrenes was achieved, particularly their ambiphilic nature and utility in skeletal editing and late-stage functionalization.

Throughout this dissertation in **Chapter 2**, a series of versatile sulfur-based carbene reagents was developed and successfully applied to skeletal editing. These methodologies were further utilized for the late-stage remodeling of commercially available pharmaceuticals, enabling the rapid discovery of structural analogues. In **Chapter 3**, a range of sulfenylnitrene precursors was designed, allowing efficient nitrogen atom insertion under metal-free conditions using readily accessible sulfur-based reagents. In **Chapter 4**, this strategy was extended to the transformation of bio-waste-

derived furans into privileged N-heterocycles, including pyridines, pyrimidines, pyrroles, and pyridazines.

As a future direction, these sulfur-based precursors have been extended toward applications in DNA-encoded library (DEL) synthesis, where preliminary results demonstrate their compatibility with biomolecule-constrained environments. This opens the possibility of integrating skeletal editing strategies into high-throughput screening platforms, enabling the rapid generation of structurally diverse and complex small-molecule libraries directly on DNA.

Another promising avenue involves accessing the oxidized analogues of these reactive intermediates, particularly sulfinylnitrenes. The development of such species could provide new reactivity profiles and enhanced selectivity for installing sulfur-centered functionality. Exploring their generation and controlled reactivity may further expand the scope of late-stage functionalization, especially for complex molecules and drug-like scaffolds. Collectively, these efforts aim to broaden the utility of sulfur-based intermediates in modern synthetic chemistry and drug discovery.

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101 Stephenson Parkway, Norman, OK-73019

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Email: prakashabiral06@gmail.com
Linkedin

Education and Training

08/2021–06/2026 **Graduate Student** with Prof. Indrajeet Sharma, the University of Oklahoma (OU), Norman, Oklahoma, OK. GPA: 3.86
"*Scaffold Hopping with Sulfenylcarbenes and Sulfenylnitrenes*"

08/2019–05/2021 **Research Associate** with Sr. Scientist Michael W. Stutelberg, Agricultural Utilization Research Institute (AURI), Marshall, MN
"Cannabinoid Analysis on Agricultural Hemp Products"

08/2018–05/2021 **Undergraduate Research Assistant** with Prof. Jay Brown, Center for Electroanalytical Studies at SMSU, Marshall, MN
"*Electrochemistry of Cinnamaldehyde*"

07/2016–12/2020 **B.A in Chemistry (Minor: Biology)** with Prof. Noelle Beyer, Southwest Minnesota State University (SMSU), Marshall, MN. GPA: 3.7

Fellowships and Awards

05/2025 **Nancy L. Mergler Dissertation Completion Fellowship** from Graduate College, OU.

04/2025 **Excellence in Graduate Research Award** from Chemistry and Biochemistry, OU.

01/2025 **ACS Future Innovators Award** from American Chemical Society (ACS), among 25 students nationwide.

04/2024 **Llyod E. Swearingen Award** from Chemistry and Biochemistry, OU.

03/2024 **Dissertation Fellowship Award** from the Dodge Family College of Arts and Science, OU.

10/2022 **Kenneth and Joye Harwell Endowed Scholarship** from OU.

08/2016 - 12/2020 **Dean's List** at Southwest Minnesota State University.

05/2020 **Medicinal Chemistry Achievement** Award from Southwest Minnesota State University (SMSU).

05/2019 **Organic Chemistry Achievement** Award from SMSU.

05/2019 **Adam Johan Bergren** Chemistry Scholarship Award from SMSU.

Publications:

Published/ accepted/ under review

1. **Kafle, P.;** Ghosh, B.; Hunter, A.; Mukherjee, R.; Nicholas, K. M.; Sharma, I. Iron-carbene initiated O–H Insertion/Aldol Cascade for the stereoselective synthesis of functionalized tetrahydrofurans, *ACS Catal.* **2024**, *14*, 1292–1299.
2. Ghosh, B; **Kafle, P**; Mukherjee, R; (equal contributors BG, PK, RM); Welles, R; Herndon, D; Nicholas, K.M.; Shao, Y; Sharma, I. Sulfenylnitrene-mediated nitrogen-atom insertion for late-stage skeletal editing of *N*-heterocycles, *Science* **2025**, *387*, 102-107. (**Equal-Co first author**). *Highlighted in* C&EN News, Phys. Org, OU News.
3. **Kafle, P**.; Herndon, D; Sharma, I. Sulfenylcarbene-mediated carbon atom insertion for the late-stage functionalization of *N*-heterocycles, *J. Am. Chem. Soc.* **2025**, *147*, 13824-13832. *Highlighted in* Phys. Org, OU News.
4. **Kafle, P**; Herndon, D; Sharma, I. Sulfenylcarbenes and sulfenylnitrenes in organic synthesis, *Chem. Soc. Rev.* **2025**, *54*, 10344-10362.
5. **Kafle, P**; Kharel, P; Nelson, D; Yasuda, S; Sharma, I. Photolysis-generated sulfenylnitrenes enable site-selective nitrogen-atom insertion into *N*-heterocycles, Chem, **2026**, *12*, 102753.
6. **Kafle, P**; Sharma, I. 9-((2,4-Dinitrophenyl)thio)-1,4-Dihydro-1,4-Epiminonaphthalene, e-*EROS*, **2026**, 1-2.
7. Herndon, D; **Kafle, P**; Mukherjee,R; Sharma, I. Sulfenylnitrene-mediated aminative cyclizations for the diastereoselective synthesis of fused bicyclic indolines, *RSC Adv.* **2026**, *387*, 102-107.
8. **Kafle, P**; Mukherjee, R; Yasuda, S; Sharma, I. Sulfinylnitrenes via Chemoselective S-N bond cleavage: Design, synthesis, and applications. *Org. Lett.* **2026**, *28*, 21, 6791-6796.
9. **Kafle, P**; Yasuda, S; Nilson, D; Herndon, D; Fox, R; Sharma, I. Skeletal editing of furans into pyridines, ChemRxiv **2026**, *Preprint Available!* DOI: 10.26434/chemrxiv-2025-vplrf (manuscript under review.)
10. **Kafle, P**.; Singh, S. P.; Mukherjee, R.; Sharma, I.; Application of 9-((2,4-dinitrophenyl)thio)-1,4-dihydro-1,4-epiminonaphthalene in nitrogen atom insertion, Org. Synth. **2026**, (accepted).
11. **Kafle, P**; Kharel, P; Mukherjee, R; Yasuda, S; Sharma, I. Tunable sulfenylnitrenes for scaffold hopping of furans to *N*-heterocycles, (manuscript under review).

Under preparation

12. Chaudhary, U; **Kafle, P**; Yasuda, S; Sharma, I. Synthetic utility of sulfinylnitrenes, *Review article,* **2026** (manuscript under preparation).
13. Chatterjee, U; **Kafle, P**; Yasuda, S; Sharma, I. Mechanistic understanding on the leaving group tendency of sulfenylcarbenes in skeletal editing, (manuscript under preparation).

14. Tran, K; **Kafle, P**; Chamakuri, S; Young, D; Sharma, I Application of Sulfenyl-carbenes/-nitrenes for Skeletal-Editing of DNA-encoded Library **2026** (manuscript under preparation in collaboration with Baylor College of Medicine).

Conferences and Oral/Poster Presentations:

Pfizer Chemistry Connect, Virtual Symposium, **2025**: Oral Presentation
"*Harnessing sulfenyl-carbenes/-nitrenes for skeletal editing*"

ACS Fall Meeting; Division of Organic Chemistry, Washington, DC, **2025**: Oral Presentation
"*Drugs from drugs: Scaffold hopping with sulfenyl-carbenes*"

ACS Fall Meeting; ACS Pharma Scholars, Washington, DC, **2025**: Poster Presentation
"*Skeletal editing with sulfenyl-carbenes/nitrenes*"

Gordon Research Seminar; Heterocyclic Compounds, New Port, RI **2025**: Oral and Poster Presentation
"*Skeletal Editing with Sulfenyl-carbenes/-nitrenes*"

ACS Pentasectional Meeting, Tulsa, OK **2025**: Oral Presentation
"*Late-Stage Functionalization of N-heterocycles with Sulfenyl-carbenes/-nitrenes*"

Great Plains Catalysis Society Meeting, Norman, OK **2024**: Poster Presentation
"*Iron-carbene Cascade Reaction to Functionalized Tetrahydrofurans"*

ACS Southwest regional Meeting, Oklahoma City, OK **2023**: Poster Presentation
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