Exploiting the Reactivity of Dienes via Electrophilic Addition with Anionic and Radical Intermediates

BY
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THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy of Chemistry
in the Graduate College of the
University of Illinois at Chicago, 2018

Chicago, Illinois

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This thesis is dedicated to the Martinez Ladies, I love you both.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my utmost gratitude toward my advisor and mentor, Professor Justin T. Mohr. Early on, Professor Mohr insisted on being called JT. This simple gesture spoke to his character. JT is the most approachable laid-back professor I know. At the same time, JT also set high standards that only motivated me to push myself every day I spent in lab. He has been supportive and enthusiastic about the projects I worked on. He has provided valuable feedback on countless synthetic challenges. I have the honor of being a member of his first class, oftentimes joking "JT, we're the same year" when asked at conferences. All jokes aside, however, I grew to admire him for all the hardships I witnessed him face as a new Assistant Professor. Even though he was first described to me as the "new hot-shot Professor from Caltech", I only ever knew his humility and quiet dignity. Lastly, he taught me how to be a dedicated educator as I led by his superb example.

I would like to give thanks to Professors Duncan J. Wardrop, Vladimir Gevorgyan, Stephanie Cologna, and Laura M. Sanchez for serving as members of my thesis committee. I am grateful for the time and energy they spent reading and editing my thesis. I thank Professor Cologna for the collaboration on my final project.

In particular, I wish to extend a special thank you to Professor Duncan J. Wardrop. I met Professor Wardrop nearly 10 years ago and he has been nothing but encouraging and helpful. His advisement and guidance during my time spent in his laboratory as an undergraduate research assistant, inspired me to pursue my Ph.D. in organic chemistry. I

can honestly say that I wouldn't be where I am today without his unwavering support. I will forever be grateful to him as staying at UIC for my graduate studies turned out to be the best decision I've ever made.

I would like to thank Professor Gevorgyan for allowing me to be an honorary member of his group several times over the last six years. I am especially grateful for the opportunity I had to work on creating potential cover letters for the publication reporting a general, auxiliary-enabled photoinduced Pd-catalyzed remote desaturation of aliphatic alcohols, discovered by Dr. Marvin Parasram.

I could never fully express my gratitude for Dr. Marvin Parasram. He served as a true inspiration to me as I held him in high regard for the work ethic that honed his synthetic and leadership skills. Marvin never turned me away, whether it was to borrow a chemical or just to talk at the end of a long day in lab on the rooftop of our building. I consider myself very fortunate to have someone in my life that offered me the constant encouragement and support Marvin always provided. He has always believed in me. In his eyes, I'm *perfect*, even at my worst, which may account for why I found it so difficult to turn away from him all these years. Marvin, you are the reason I can honestly say that my journey in the program was *unforgettable*.

I would like to thank all current and former member of Professor Mohr's research group. I was extremely fortunate to have had Dr. Xiaohong Chen as my first co-worker. Together, we were able to complete the seminal work that resulted in the lab's first

publication, a true privilige. I thank her for giving me the opportunity to work along her side, and I really do mean along her side as we shared a hood for quite some time where some of my most interesting memories were made.

The daily interactions with my long-term labmate, Dr. Nabeelah I. Kauser, were vital to my sanity during the toughest times. Along with our lab space, we also shared the same ambition, work ethic, and opinions on many matters. I look forward to the days we may sit back and (finally!) relax as we reminisce about all the times we had in JT's lab. Long live Jabeelah Kartinez, and with my thesis now complete, officially, Dr. Jabeelah Kartinez.

I have developed several friendships throughout my years in and out of the Mohr lab that have enhanced my graduate career experience. Dr. Marissa R. Cabay, from Professor Scott Shippy's group, has been my best friend at UIC from Day 1. We clicked immediately during orientation and before we knew it, we became and remained roommates for the majority of my graduate career. Missy is the most down-to-earth person I know. Her carefree attitude soothed many of my worries. I shared so many so good times outside of the lab with her and I look forward to our lifelong friendship and even better times to come.

I would also like to thank the entire chemistry department staff, in particular Ms. Rhonda Staudohar and Ms. Silivia Solis. I have known them my entire undergraduate and graduate career and they have always been more than happy to help with anything I

needed. Randy Puchalski was also always quick to respond whenever problems arose in our lab. I thank Yonilo Lim for all the paperwork he filed on my behalf. I would have never been able to complete projects without the behind-the-scenes magic of the machine shop, Don Rippon, Dan McElheny and the talented Brian Schwandt, our resident glassblower.

I also owe enormous thanks to Daniel M. Lenar. Daniel is the kindest and gentlest person I know. His companionship and emotional support over the years is something I will never forget. I have learned to be a nicer and more patient person because of you, Daniel. I have also learned to appreciate the little things and to never take things for granted. Thank you for helping me realize just how important these are in life.

I am thankful for my stepfather, Jaime Ramirez Sanchez, who has always treated me as his own. To my beautiful baby sister, Kelly S. Martinez, I love you so much. Thank you for always being there for me and for at times, switching roles and playing the part of the protective older sister. You are the reason I've worked so hard, as I aimed to be a good role model for you.

And last, but certainly not least, I would like to thank my mother, Patricia Martinez Solano. I would be nothing without her. I have a great deal of respect for her enormous sacrifice to ensure a better life for me. She left her entire family behind when she brought my sister and me to the United States from Mexico. She insisted on success through higher education and did everything to secure a sound future for us. Now, it is finally

time for me to pay her back for all she has ever selflessly done for me. Mom, this thesis is for you, I love you.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
DTBP	2,6-di-*tert*-butylpyridine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
n-Bu	butyl
t-Bu	*tert*-butyl
Calcd	calculated
cat.	catalytic amount
COD	1,5-cyclooctadiene
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
2D	two-dimensional (NMR)
d	doublet
dba	dibenzylidene acetone
DCM	dichloromethane
DCE	1,2-dichloroethane
DCE	1,2-dichloroethane

LIST OF ABBREVIATIONS (continued)

DEPT	distortionless enhancement by polarization transfer
DFT	Density Functional Theory
DMA	dimethylacetamide
DMB	2,4-dimethoxybenzyl
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDG	electron-donating group
EE	ethoxyethyl
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
eq, equiv.	molar equivalent
EWG	electron-withdrawing group
ΔG	group, Gibbs free energy
g	gram
GC	gas chromatography
h, hrs	hour(s)
HAT	hydrogen atom transfer
HMBC	heteronuclear multiple-bond correlation spectroscopy (NMR)
HMQC	heteronuclear multiple-quantum coherence spectroscopy (NMR)
HR	high resolution (mass spectrometry)
Hz	Hertz
IPr	1,3-bis(2,6-diisopropylphenyl) imidazole-2-ylidene

LIST OF ABBREVIATIONS (continued)

J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithiumdiisopropyl amide
LiHMDS	lithium hexamethyldisilazide
m	multiplet (NMR)
mp	melting point
□	micro
[M]	metal
M	molar
MS	mass spectrometry
MS	molecular sieves
Me	methyl
Mes	mesityl
MIDA	*N*-methyliminodiacetic acid
mg	milligram
min	minute
mL, ml	milliliter
mm	millimeter
mmol	millimole
mol	mole
MHz	megahertz
m/z	mass to charge ratio

LIST OF ABBREVIATIONS (continued)

NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
PA	proton affinity
Ph	phenyl
PIDA	Pinen-derived iminodiacetic acid
Piv	pivaloyl, trimethylacetyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl
q	quartet (NMR)
quint	quintet (NMR)
rt	room temperature
s	singlet (NMR)
sept	septet (NMR)
t	triplet (NMR)
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal

TMS	trimethylsilyl
Tol, tol	tolyl
Ts	*p*-toluenesulfonyl

SUMMARY

This thesis describes the development of methods to achieve γ–functionalization of cycloalkanones with the use of stabilized dienolate intermediates in both anionic and radical conditions, as well as the synthesis sterically demanding pyridines.

In Part 1, Chapter 1 describes the inherent difficulties of γ–functionalization of carbonyl compounds including a review on classical and modern strategies previously reported. Chapter 2 represents the anionic conditions developed to access γ–functionalized products. The efficient method discovered for the direct, selective conversion of readily available vinylogous esters to haloresorcinol derivatives is discussed in detail. Synthetic applications are also included. Chapter 3 represents an extension of this work, the γ–hydroxylation of cyclic enones, in which the protocol is similar. Chapter 4 represents the development of the radical conditions utilized to functionalize at the γ–position. Specifically, the Cu-catalyzed regio- and stereoselective γ-alkylation protocol to synthesize 1,6-dicarbonyl compounds is discussed at length. The experimental details the Part 1 are represented in Chapter 5.

In Part 2, Chapter 6 provides background as to the challenges of heterocylic synthesis, specifically, the synthesis of sterically encumbered pyridines. Chapter 7 is a discussion on how the Ciamician–Dennstedt rearrangement allowed us to access bulky polysubstituted halopyridines starting from customizable pyrroles. From this, the vision and ultimately, development of an economical and efficient synthesis of 2,6-di-*t*-butylpyridine analogues was discovered and is highlighted in Chapter 8. Moreover, synthetic applications and gas-phase

studies of these pyridines are also discussed in this chapter. Lastly, Chapter 9 represents the experimental details for Part 2.

CONTRIBUTION OF AUTHORS

Several parts of this thesis are reproduced from previously published articles co-authored with collaborators, who contributed significantly to the presented work.

The first part of this thesis is written based on the previously published articles ("Regiodivergent Halogenation of Vinylogous Esters: One-Pot, Transition Metal-Free Access to Differentiated Haloresorcinols" Chen, X.; Martinez, J. S.; Mohr, J. T. *Org. Lett.* **2015**, *17*, 378–381; "Practical Regioselective Halogenation of Vinylogous Esters: Synthesis of Differentiated mono-Haloresorcinols and Polyhalogenated Resorcinols" Chen, X.; Liu, X.; Martinez, J. S.; Mohr, J. T. *Tetrahedron* **2016**, *72*, 3653–3665). Specifically, Chapter 2 encompasses these papers exclusively. As first author, Dr. Xiaohong Chen was the major contributor of this work as she found the initial results and drove it to completion. I developed the scope of the project and assisted with the optimization of reaction conditions by offering ideas and contributing to the overall discussion of results. Dr. Xiaoguang Liu aided in the collection of characterization data. Professor Justin T. Mohr guided the research, provided insightful feedback and was the corresponding author of the manuscript.

PART ONE

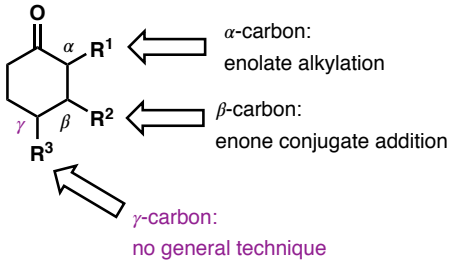
γ-FUNCTIONALIZATION OF CARBONYL COMPOUNDS VIA DIENOLATES

1. Introduction

1.1. γ-Functionalization of Carbonyl Compounds

Although there are dozens of methods reported with the focus of functionalizing the α- and β-positions of cyclic ketones,[1] the direct functionalization at the γ-position of cycloalkanones has yet to be explored by organic chemists. In fact, the existing protocols for α, α'- and β-functionalization heavily rely on the reactivity of the carbonyl group.[2] Even with these known protocols, a reliable high yielding method and control over the regio- and stereoselectivity remain the primary focus of research. Specifically, the most well established methods for α- and β-functionalization occur via reaction of electrophiles with enolates[1] or conjugate addition of nucleophiles to enones (Scheme 1).[3]

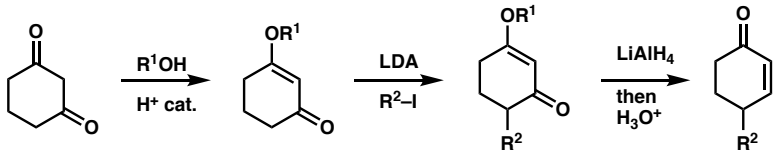
Scheme 1: Potential sites for functionalization of carbonyl compounds



As for the functionalization of the γ-position, the Stork–Danheiser sequence developed in 1973 stands as the most viable option to date (Scheme 2).[4] Although highly innovative, this method suffers from low functional group tolerance, requires multiple substrate

interconversions, and is restricted to employment of 1,3-diketone starting materials. There has, however, been some advancement in γ-functionalization of acyclic systems.[5]

Scheme 2: Stork–Danheiser Alkylation Sequence

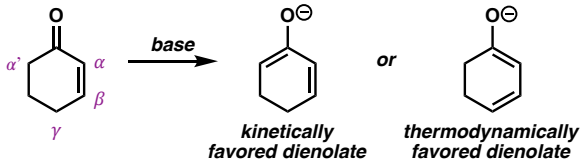


1.2. γ-Functionalization via Exploitation of Anionic Intermediates

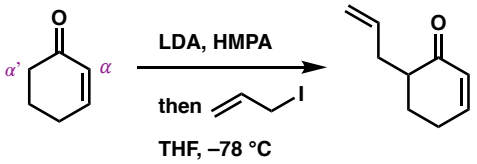
As mentioned, α- and β-functionalization is usually achieved via the formation of enolates, often times involving the use of a strong base.[6] It is well known that deprotonation of unsymmetrical ketones may result in either the kinetic or thermodynamic enolate (Scheme 3). The kinetic enolate is the result of the deprotonation of the most accessible α-H, while the thermodynamic enolate is formed via deprotonation of the γ-H to furnish the highly substituted moiety (*vide infra*). In order to favor the kinetic product, low reaction temperatures and sterically demanding bases are often utilized. For cyclic enones, deprotonation can occur at either the α'- or γ-position. A plethora of methods have been developed for α'-functionalization due to the relative ease of controlling the formation of the kinetic dienolate. For instance, the allylation of cyclohexen-2-one occurs almost exclusively at the α'-position resulting in the cross-conjugated dienolate as the major isomer (Scheme 4).[7] Conversely, selective deprotonation and functionalization at the γ-position is notoriously difficult. In the case of cyclohex-2-en-1-one, it turns out that γ-deprotonation is favored by 6.5 kcal/mol over α'- deprotonation, thus, forming the extended dienolate systems under thermodynamic conditions can be achieved.[8] Though these methods exist, reaction at the γ-position of enones often requires use of specialized reagents to achieve

high selectivity in order to out compete kinetically preferred α-functionalization.[8] Therefore, a general protocol to induce reactivity at the γ-carbon of such systems remains an outstanding synthetic challenge.

Scheme 3: Extended dienolate systems



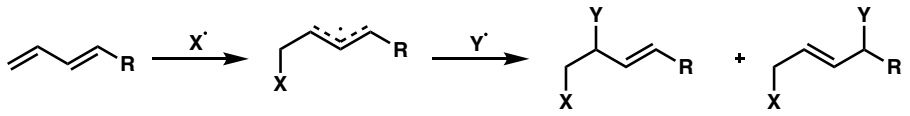
Scheme 4: Allylation of cyclohexen-2-one



1.3. γ-Functionalization via Exploitation of Radical Intermediates

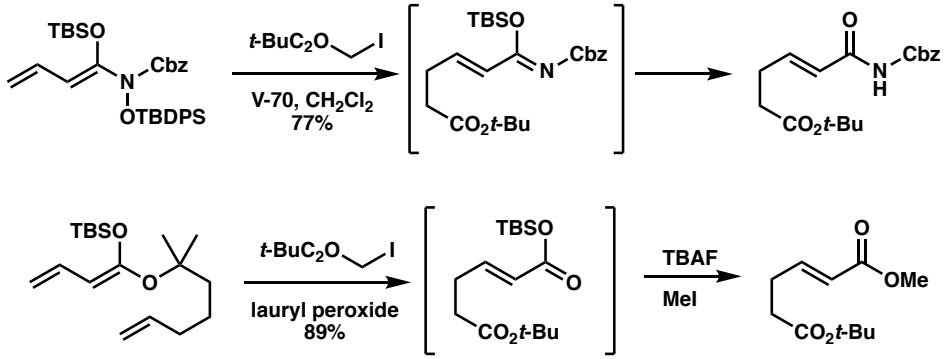
The possibility of γ-functionalization via enolate intermediates has been discussed, however, these intermediates are essentially dienes, and therefore, they may also serve as potential reactive counter partners in radical addition reactions. Though a new bond is generated, the regioselectivity of these reactions with dienes is difficult to control often resulting in a mixture of products (Scheme 5).[9]

Scheme 5: Radical addition reactions to dienolate systems



In an effort to control regioselectivity, a heteroatom may be incorporated to provide the necessary electronic stabilization of the radical intermediates produced. Kim and co-workers have used related diene systems derived from specialized amides or silyl ketene acetals to functionalize at the γ-position via radical intermediates (Scheme 6).[5] However, a radical stabilizing leaving group was required to drive the reaction forward, which highlights the low atom-economy of Kim's method. Moreover, the low substrate scope is a significant limitation of the transformation. Nonetheless, their attempt to control the regioselectivity in acyclic systems proved successful. Yet, this methodology was not extended to include cyclic systems and there has been no other report to utilize this technique for this chemical transformation to date.

Scheme 6: Radical-mediated γ-functionalizations of α,β-unsaturated carboxylic amides



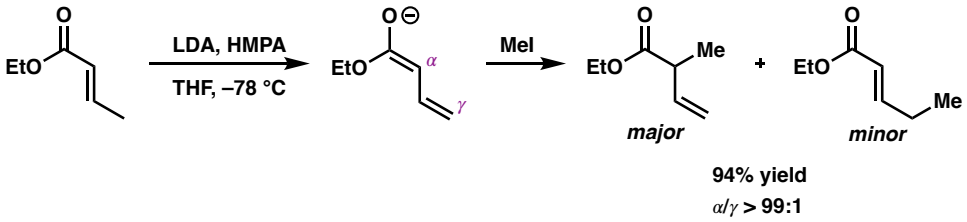
The difficulties that surround the γ-functionalization of enones have not deterred continued efforts from the synthetic community. In addition to radical addition protocols, methods for γ-

functionalization have been achieved via specialized dienolates, Lewis acid-catalyzed electrophilic γ-functionalization of α,β-unsaturated carbonyls, and transition metal stabilization of dienolates.

1.4. Previous methods for γ-Functionalization

In 1973, Schelssinger and co-workers studied the dienolate system resulting from ethyl crotonate when using a 1:1 mixture of LDA and HMPA (Scheme 7).[10] Exposure of the enolized ethyl crotonate to MeI resulted in the α-methylated product over the γ-product with high levels of selectivity. Evidently, the high nucelophilicty of the α-position of the enolate dictated the observed regioselectivity. Hence, increasing the nucelophilicity at γ-position of the enolate may result in a regioselectivity reversal, thus resulting in selective functionalization at the γ-position.[11]

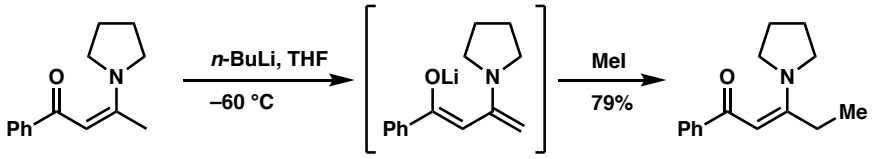
Scheme 7: Alkylation of ethyl crotonate



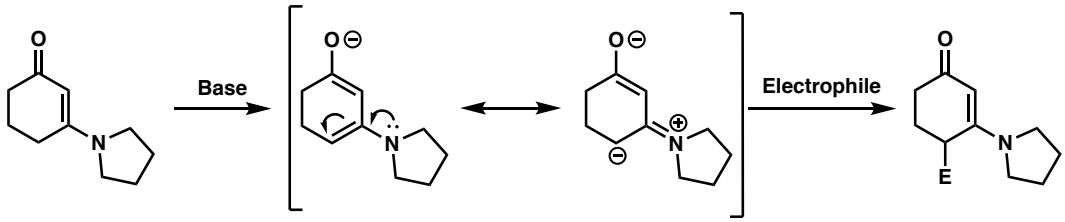
To this end, increasing the nucleophilicity of the γ-position in comparison to the α-position has inspired a new class of dienolate systems to achieve selective γ-functionalization. A primary example of this was first reported by Hiraoka and co-workers using β-enaminoketones (Scheme 8).[12] Starting from 1,3-dicarbonyl compounds, they were able to form the fully conjugated dienolate intermediate of a series of β-enamiketones under low temperatures upon exposure to *n*BuLi. Once formed, the lone-pair of electrons on the nitrogen delocalize to the γ-carbon thus,

increasing its nucleophilicity (Scheme 9). γ-Alkylation was henceforth achieved when a series of electrophiles such as alkyl halides, aryl halides, and other carbonyl containing compounds were used. Moreover, this approach was amenable to cyclic enone systems.

Scheme 8: γ-Functionalization of β-enamiketones

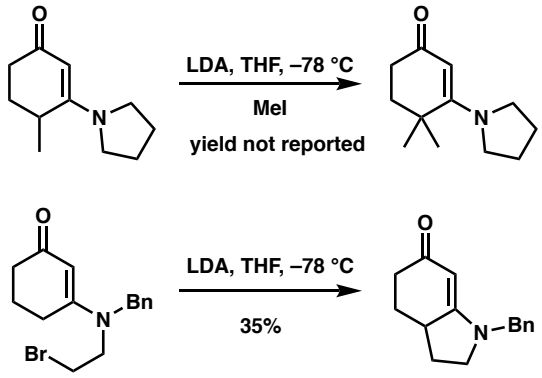


Scheme 9: Mechanism for γ-Functionalization of β-enamiketones



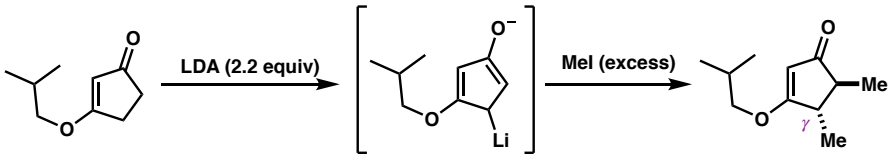
Gammill and co-workers also chose to show the versatility of the γ-alkylation of β-enaminoketones (Scheme 10).[13] They were able to show that the preparation of quaternary centers could be achieved through this methodology. They also reported intramolecular γ-alkylation of these species resulted in a heterocyclic ring system that may be further utilized in alkaloid synthesis. It should be mentioned, however, that the amine functionality of the formed vinylogous amides products cannot be further manipulated, which highlights a significant limitation in terms of building molecular complexity.

Scheme 10: γ-Alkylation of β-enamiketone resulting in quaternary centers and intramolecular alkylation



In 1979, Koreeda and co-workers reported the α- and γ-functionalization of vinylogous cyclopentyl esters (Scheme 11).[14] It was found that incorporation of an oxygen heteroatom at the *β*-position plays a curical role in stabilizing the dianionic intermediate upon deprotonation of the γ-C–H bond. Trapping the dianionic intermediate with MeI resulted in the α- and γ-alkylated product in high overall yield.

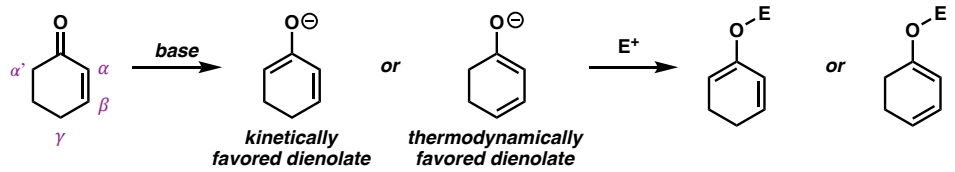
Scheme 11: Koreeda's γ-alkylation of vinylogous esters



The employment of Lewis acids for C–C bond formation via dienolates and a reacting electrophile is a well-studied area in organic synthesis. This approach can be simplified into two distinct categories: 1) the Lewis acid activates the electrophile towards nucleophilic addition with a dienolate present in the reaction mixture; and/or 2) a regioselective deprotonation of the

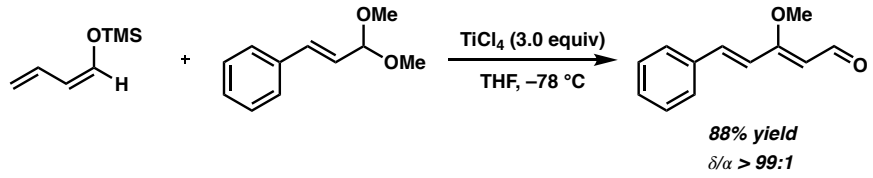
α,β-unsaturated carbonyl moiety and trapping with a given Lewis acid and/or electrophile (Scheme 12).

Scheme 12: Electrophilic trapping of dienolate intermediates



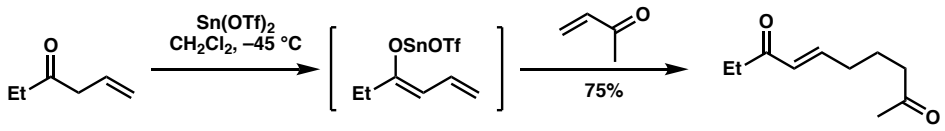
In pursuit of γ-selective carbon–carbon bond forming reactions involving Lewis acids, Mukaiyama was the first to report the vinylogous alkylation of a silyl dienol ether utilizing crotonaldehyde and a dimethyl acetal (Scheme 13).[15] Since then, acetoacetates and lactones have also been used to generate reactive dienol ethers in catalytic, enantioselective aldol additions.

Scheme 13: Mukaiyama's vinylogous alkylation of a silyl dienol ether



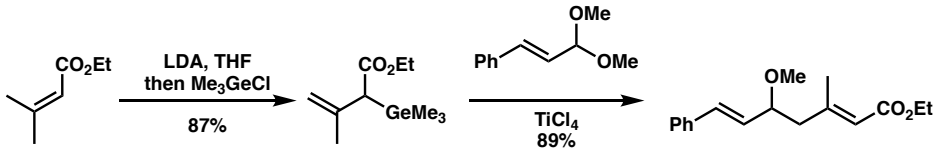
In 1985, Mukaiyama studied the chemistry of tin(II) dienolates.[16] It was found that these tin(II) dienolate intermediates underwent γ-selective 1,4-conjugate addition to α,β-unsaturated ketones (Scheme 14). Although their substrate scope was limited, it should be noted that this method solely delivered trans-olefinic 1,7-diketones.

Scheme 14: The Mukaiyama's Michael addition of tin dienolates



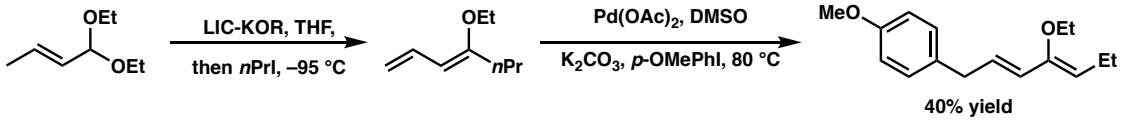
Yamamoto and co-workers were also able to trap metallodienolates with tin and germanium halides (Scheme 15).[17] The α-germylated ester was a product of 3-methyl-2-butenoate reacting with Me_3GeCl. Exposure of the α-germanium masked dienolate to a variety of carbon electrophiles such as acetals, aldehydes, and reactive halides resulted in the γ-alkylated products exclusively. Although this was an exciting result at the time, there were only two examples of dienolates reported by Yamamoto for carbon–carbon bond formation at the γ-position.

Scheme 15: Germanium masked dienolate aldol reaction



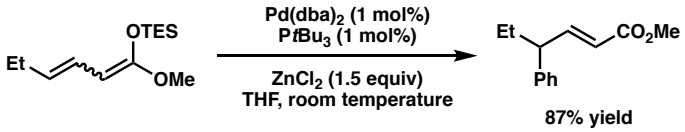
γ-Functionalization of α,β-unsaturated carbonyl compounds is also possible via transition metal catalysis. Venturello and co-workers reported the palladium-catalyzed γ-arylation of acyclic enone and enals via alkyl dienolates (Scheme 16).[18] With the use of Schlosser's LIC-KOR superbase, they were able to promote an elimination reaction that generates 1-alkoxy-1,3-butadienes from the corresponding α,β-unsaturated acetals. They discovered that these dienol ethers could be used for the palladium-catalyzed γ-arylation Heck reaction. The high regioselectivity can be rationalized by the formation of the more stabilized terminal palladium π-allyl complex.

Scheme 16: Palladium catalyzed γ-functionalization of α,β-unsaturated carbonyl compounds



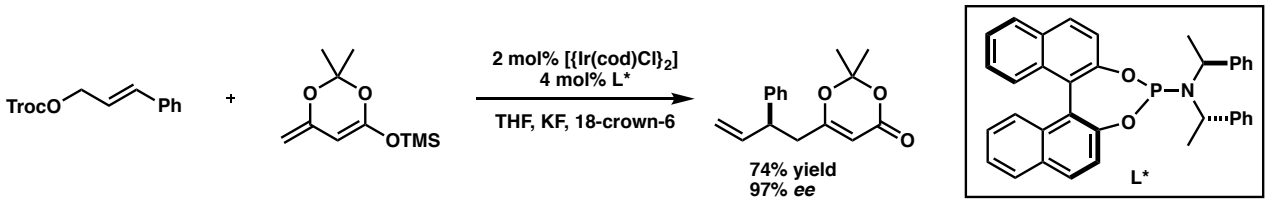
In 2010, Hartwig and co-workers improved Venturello's method by developing milder reaction conditions (Scheme 17).[19] They utilized silyl ketene acetals derived from α,β-unsaturated esters to catalyze γ-arylation and γ-vinylation with palladium. They were able to expand the scope of the reaction with ambient reaction temperature, a weak Lewis acid, and low catalyst and ligand loading.

Scheme 17: Palladium-catalyzed γ-functionalization of silyl dienol ethers



γ-Allylated products are also readily accessed with the use of iridium phosphoramidite complexes and nucleophilic dienolate or dienolate equivalents. Hartwig and co-workers reported the iridium catalyzed regio- and enantioselective γ-allylation of dioxinones with silyl dienolates (Scheme 18).[20] The scope of the reaction was further explored with the numerous substituted cinnamyl and allyl carbonates rather than their dienolate counter partner. Nevertheless, their methodology resulted in high regio- and stereoselectivity in moderate yields.

Scheme 18: Iridium-catalyzed γ-allylation of dioxinones



1.5. Conclusions

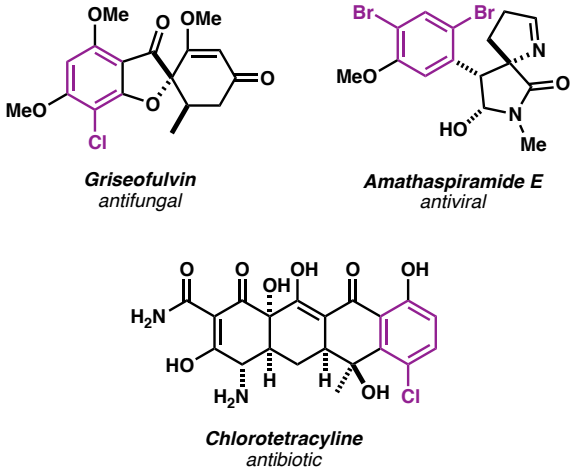
As it can be concluded, γ-functionalization of α,β-unsaturated carbonyl compounds remains a synthetic challenge. Although several advances have been made, many of these methods suffer from a limited substrate scope due to the difficulty in making the starting materials. The methods described often employ stoichiometric amounts of Lewis acids and/or rely on the use of costly transition metal catalysts. An important observation from the surveyed protocols is how the dienolate system is affected by its electronic environment. Electronic perturbation of the dienolate may aid the necessary switch in nucleophilic reactivity of the α and γ-positions. Addressing these issues may lead to the development of a direct, reliable, and regioselective method for γ-functionalization of enones.

2. Regiodivergent Halogenation of Vinylogous Esters: Step Economical Access to Haloresorcinols*

2.1. Reaction Development

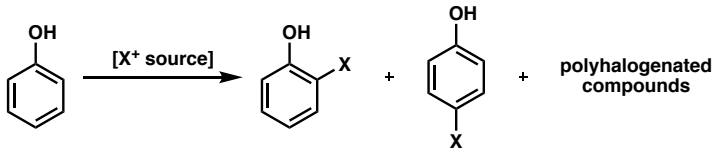
Haloresorcinols are a principle component of a variety of valuable pharmaceutical drugs, bioactive compounds, and agrochemicals (Scheme 19).[21] However, methods to synthesize these important fragments often rely on the use of classical electrophilic aromatic substitution (EAS) reactions, which involve electron rich arenes with highly electrophilic elemental halogen reagents typically in the presence of stoichiometric amounts of Lewis acids (Scheme 20).[22]

Scheme 19: Naturally occurring bioactive aryl halides



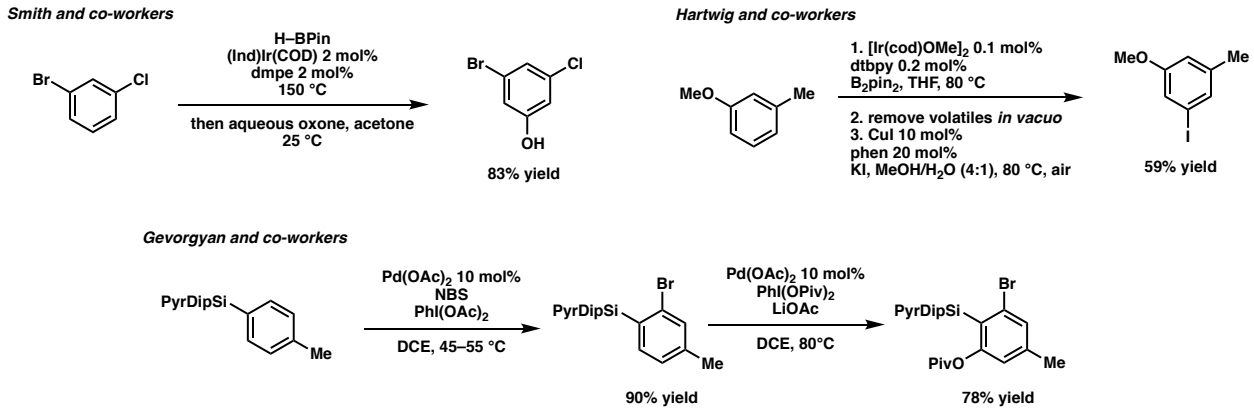
*Previously published as Chen, X.; Liu, X.; Martinez, J. S.; Mohr, J. T. "Practical Regioselective Halogenation of Vinylogous Esters: Synthesis of Differentiated mono-Haloresorcinols and Polyhalogenated Resorcinols," *Tetrahedron* **2016**, *72*, 3653–3665.; Chen, X.; Martinez, J. S.; Mohr, J. T. "Regiodivergent Halogenation of Vinylogous Esters: One-Step, Transition Metal-Free Access to Differentiated Haloresorcinols," *Org. Lett.* **2015**, *17*, 378–381.

Scheme 20: Classical halogenation via electrophilic aromatic substitution

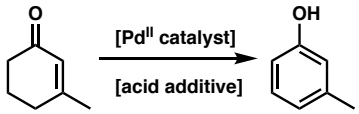


Although well studied, these approaches are plagued by low regioselectivity and overhalogenation, which has deterred widespread use.[23] In order to circumvent the vexatious attributes of classical EAS reactions, transition-metal catalyzed methods were developed (Scheme 21).[24] In most cases, haloresorcinols were formed in high degrees of regioselectivity, however, pre-functionalized arenes and/or arenes containing a directing group (DG) is a requisite for these methods. Consequently, significant substrate limitations exist in terms of atom and step economy.[25] Recently, Stahl and co-workers reported a novel Pd-catalyzed oxidation of cyclohexanone derivatives into substituted phenols (Scheme 22).[26] The employment of inexpensive and abundant cyclohexanone feedstock is particularly noteworthy, however, the requirement of an expensive transition metal and the added acid leaves room for improvement.

Scheme 21: Previous methods for synthesis of haloresorcinol derivatives

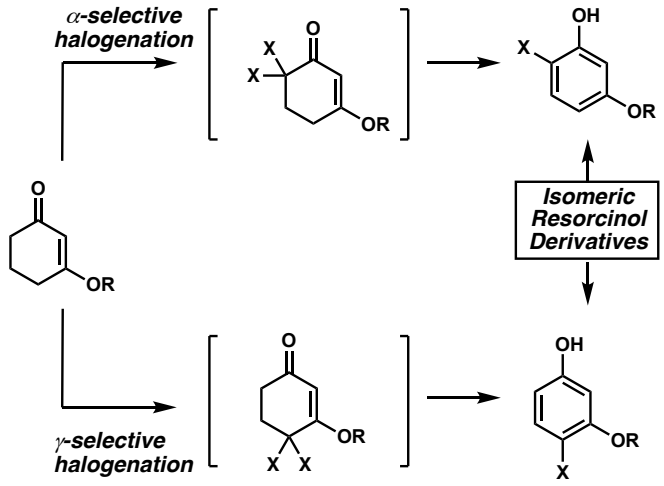


Scheme 22: Transition metal-catalyzed oxidative aromatization



Hence, we envisaged that a regiodivergent anionic halogenation of vinylogous esters and subsequent elimination/aromatization would furnish synthetically valuable haloresorcinols building blocks without the employment of exogenous oxidants or expensive transition metals (Scheme 23).

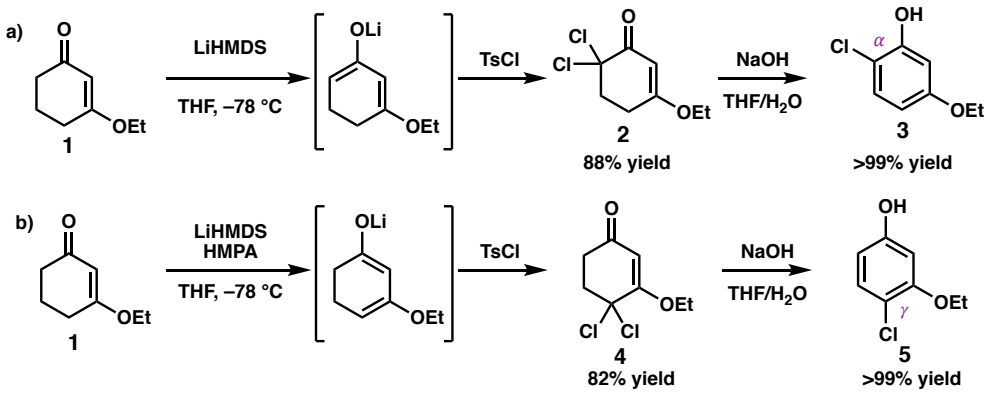
Scheme 23: Strategy for regioselective halogenation/aromatization cascade



As stated previously, our goal was to access halogenated enones from unsaturated cyclic ketones that would then easily aromatize and lead to isomeric resorcinol derivatives. A benefit of our proposed strategy is also the fact that it differentiates the two similarly reactive resorcinol oxygen atoms. As of now, there are only a limited number of direct halogenations of monoalkylresorcinols. These methods, however, require the two oxygen atoms to be

differentiated prior to halogenation and product mixtures are often times obtained. In order to test our hypothesis, we used the base (LiHMDS) established by Koreeda in order to form the kinetic enolate under non-equilibrating conditions (Scheme 11).[14] In terms of the electrophile employed, we aimed to use tosyl chloride since it has been proven to be the optimal Cl^+ source in the chlorination of ketones previously reported by Brummond.[27] Thus, we believed it could serve the same purpose in our chemistry as a chlorination agent. Indeed, exposure of vinylogous ester **1** to lithium diisopropylamide in the presence of tosyl chloride resulted in the kinetic α,α-functionalized product (**2**) in moderate yield (Scheme 24a).

Scheme 24: Initial results to access haloresorcinols

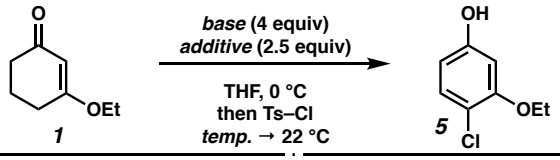


Gratifyingly, addition of hexamethylphosphoramide (HMPA) to Koreeda's conditions generated the γ,γ-dihalide product selectively (Scheme 24b). Notably, this example represents the first selective γ-functionalization of vinylogous esters. Next, we proceeded to expose the *gem*-dihalide (**2** and **4**) products to another equivalent of base to drive the aromatization forward. Both the 6-chlororesorcinol (**2**→**3**) and 4-chlororesorcinols (**4**→**5**) were obtained in quantitative yield. We then set out to establish a one-pot procedure to access both haloresorcinol isomers in order to increase effiency to rapidly access these building blocks.

2.3. Optimization of the Reaction Conditions

Our extensive investigation started with the examination of various bases and polar additives that we hypothesized would favor formation of the desired dienolate (Scheme 25). Simultaneously, we found that tosyl chloride could be the primary Cl^+ source (*vide infra*). We failed to obtain the desired 4-chlororesorcinol (**5**) when we used DBU, NaH, $LiN(Cy)_2$, or LDA (entries 1–4). To our delight, however, hexamethyldisilazide-derived bases yielded the desired product (entry 5). In particular, the Li amide provided the best results in comparison to the Na or K amides (entries 6–7). Prior investigations led us to believe that we could control the Li enolate with the addition of polar additives. We discovered the use of HMPA to be vital to obtain the product **5**. We envisioned the HMPA aided the formation of the thermodynamic dienolate as it helped to solvate the lithium cation by weakening the Li^+-carbonyl oxygen interaction.[28] Temperature was also a crucial factor in the formation of either isomer (entries 13–17). It was imperative to only warm the reaction above –78 ºC once all the reagents were added. We suspect that the mixtures of α- and γ-halogenated arenes are the result of rapid equilibration of the two isomeric enolates or a kinetic resolution of a mixture of the two enolates as previously seen with similar reactions involving α-enolates.[28]

Scheme 25: Base optimization of reaction conditions for 4-haloresorcinols

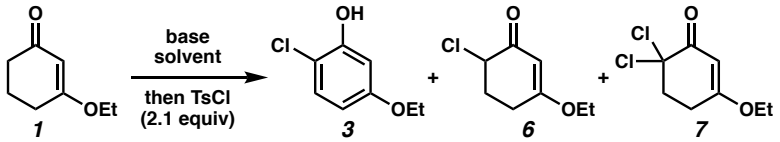


entry	base	additive	temp. (°C)	yield (%)
1	DBU	HMPA	–78	0
2	NaH	HMPA	–78	0
3	$LiN(Cy)_2$	HMPA	–78	0
4	$LiN(i\text{-}Pr)_2$	HMPA	–78	0
5	LiHMDS	HMPA	–78	88
6	NaHMDS	HMPA	–78	69
7	KHMDS	HMPA	–78	60
8	LiHMDS	Ph_3PO	–78	56
9	LiHMDS	TMEDA	–78	0
10	LiHMDS	DMPU	–78	33
11	LiHMDS	DMPU (5 equiv)	–78	54
12	LiHMDS	DMPU (10 equiv)	–78	60
13	LiHMDS	HMPA	–45	78
14	LiHMDS	HMPA	–30	69
15	LiHMDS	HMPA	–20	61
16	LiHMDS	HMPA	–10	59
17	LiHMDS	HMPA	0	66

Next, we turned our attention to establishing conditions for the synthesis of 6-haloresorcinols (Scheme 26). Our previous model led us to believe that an amide base would be less likely to participate in the dienolate equilibration required for γ-halogenation. For similar reasons, we also chose to exclude HMPA. To confirm our assumptions, however, we screened a variety of bases to α-halogenate. Our attempts with LDA under cryogenic conditions resulted in the *mono*-α-chloroketone **6** as the major product along with a small amount of the *gem*-dihalide **7** (entry 1). We then proceeded to warm the reaction to room temperature after reagent addition and increased the quantity of LDA (entry 2). Unfortunately, our efforts only increased the yield for the *gem*-dihalide. It was only after increased reaction time at room temperature that we were able to obtain the desired haloarene **3**, though the major product remained as the *mono*-α-chloroketone **6** (entry 3). We speculated that LDA was too bulky and the E2-type elimination step to aromatize the intermediate was too slow. Continued failure to obtain the 6-halo isomer with LDA encouraged us to introduce catalytic quantities of hexamethyldisilazane as we had found success with its use previously (entry 8–10). Interestingly, we discovered that with 50 mol% HMDS the *mono*-α-chloroketone was not obtained at all (entry 10). To test our hypothesis

on how hindered amide bases favor the α-dienolate, we also tested a 1:1 and 1:2 mixture of LDA and LiHMDS additive (entries 11–12). Excitingly, we found that under these conditions the desired 6-haloarene **3** was found to be the predominant isomer. At this stage, we decided to continue our optimization with LiHMDS exclusively (entries 13–17). We were, at last, able to isolate the chlororesorcinol as the sole product in 85% yield (entry 13). We also performed a solvent screen that ultimately proved the need for a nonpolar solvent to deliver nearly quantitative yields of the desired 6-halo isomers (entries 14–17). We screened a number of aprotic solvents that would favorably promote the formation of the kinetic dienolate. In particular, bromo- and iodoarenes were accessed with toluene. In the case of chlorination, a 2:1 pentane/THF ratio yielded the product. Mechanistically speaking, the 6-halo isomer is presumed to form by the α-enolization/halogenation sequence described by Brummond.[27]

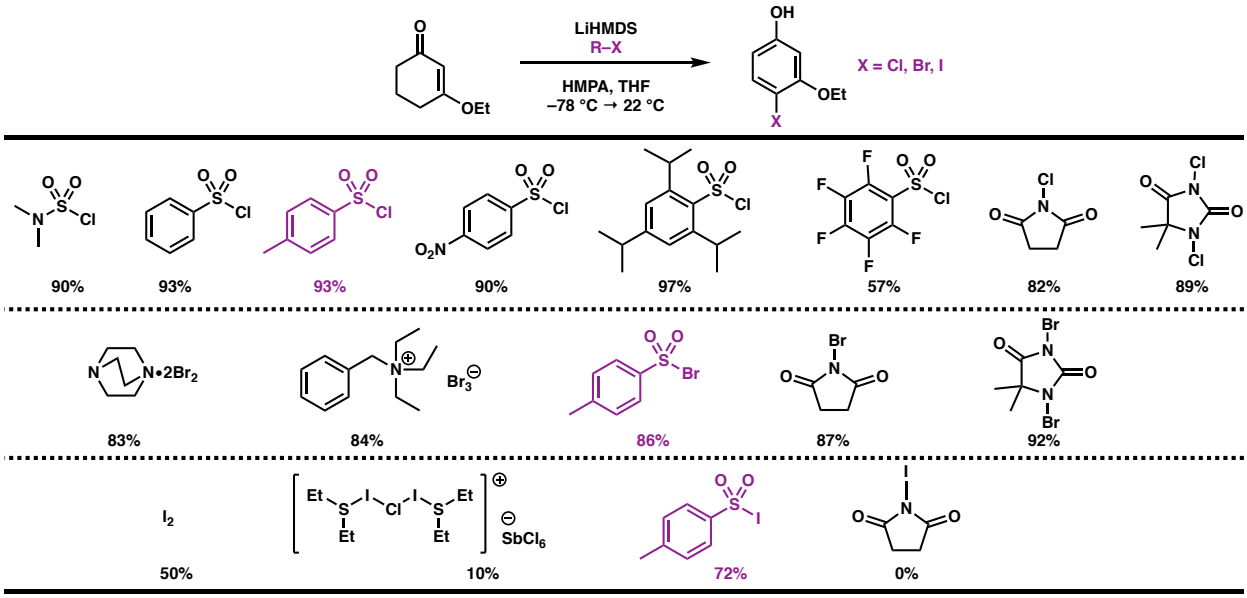
Scheme 26: Base optimization of reaction conditions for 6-haloresorcinols



entry	base	equiv	solvent	temp (°C)	time (h)	yield (%)		
						3	*6*	*7*
1	LDA	1.1	THF	–78	0.5	0	68	6
2	LDA	2.5	THF	–78 → 22	0.5	0	40	31
3	LDA	2.5	THF	–78 → 22	4.5	26	43	4
4	LDA	3.0	THF	–78 → 22	0.5	0	44	47
5	LDA	3.0	THF	–78 → 22	4.5	32	52	9
6	LDA	4.0	THF	–78 → 22	0.5	10	42	36
7	LDA	4.0	THF	–78 → 22	4.5	44	32	10
8	LDA + 10% HMDS	4.0	THF	–78 →22	0.5	trace	57	22
9	LDA + 20% HMDS	4.0	THF	–78 → 22	0.5	trace	62	18
10	LDA + 50% HMDS	4.0	THF	–78 → 22	0.5	12	0	68
11	LDA/LiHMDS (1/1)	4.0	THF	–78 → 22	0.5	86	0	0
12	LDA/LiHMDS (1/2)	4.0	THF	–78 → 22	0.5	91	0	0
13	LiHMDS	4.0	THF	–78 → 22	0.5	85	0	0
14	LiHMDS	4.0	Et_2O	–78 → 22	0.5	66	14	0
15	LiHMDS	4.0	1,4-dioxane	–78 → 22	0.5	54	0	18
16	LiHMDS	4.0	THF/toluene (1/2)	–78 → 22	0.5	82	0	0
17	LiHMDS	4.0	THF/pentane (1/2)	–78 → 22	0.5	95	0	0

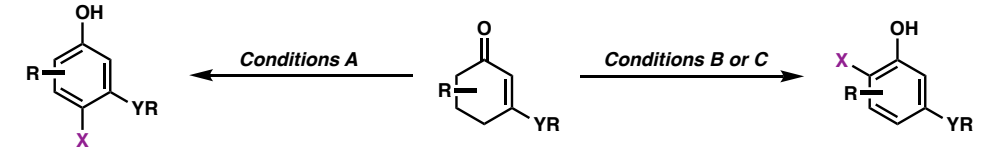
In our screening of halogen donors, aromatic sulfonyl halides proved to be the most effective (Scheme 27). Trisyl chloride was the optimal donor for chlorination. The use of these donors led to sulfur-containing byproducts most easily removed when trisyl chloride is used. Despite these byproducts, we opted to continue our studies with TsX reagents for practical purposes given that they are the more economical choice. Non-halogenated arenes were only obtained in trace amounts with the use of these tosyl halide reagents. TsBr and TsI were readily accessed through known methods and were employed to synthesize bromo- and iodoresorcinols.[29] We also attempted to fluorinate with TsF, however, we only observed products of sulfonyl transfer.[30] With alkyl sulfonyl halides, only trace amounts of product were obtained. It should be noted that *N,N*-dimethylsulfamoyl chloride also performed well. Succinimide-based halogen donors, however, failed to succeed over the range of halides.

Scheme 27: Halogen source optimization



In conclusion, we were able to establish three different protocols to access 4- and 6-haloresorcinols (Scheme 28). A general and efficient synthesis of 4-haloresorcinols was achieved (Scheme 28, conditions A). In the case of 6-haloresorcinols we found a difference in the synthesis of 4-chlororesorcinols (Scheme 28, conditions B) in comparison to bromo- and iodoresorcinols (Scheme 28, conditions C).

Scheme 28: Synthesis of 4- and 6-haloresorcinols

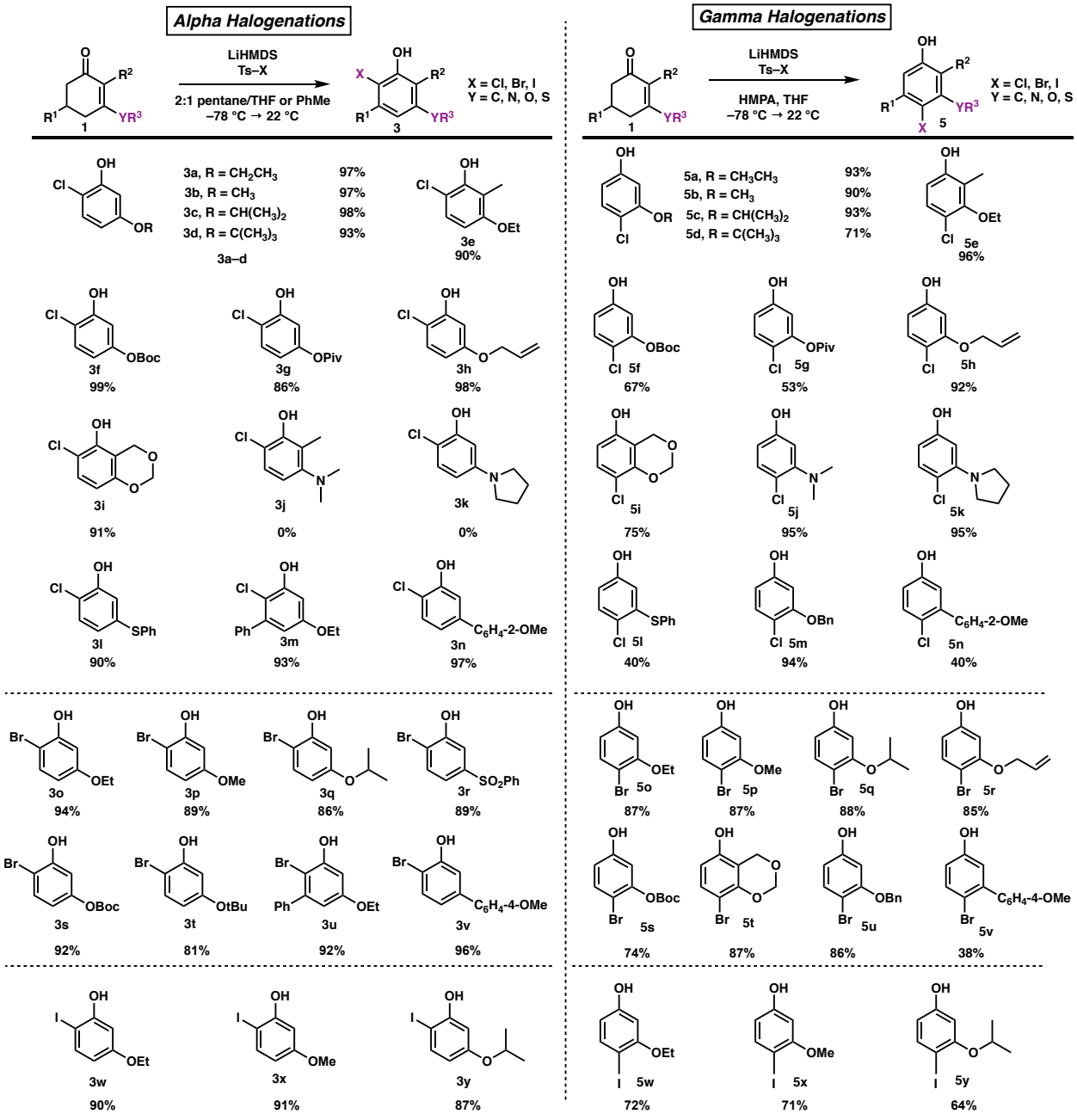


Conditions A:	*Conditions B:*	*Conditions C:*
3 equiv LiHMDS HMPA, THF 0 °C, 1h then 2.1 equiv Ts–X –78 °C, 0.5 h then 1 equiv LiHMDS –78 °C→ 22 °C, 0.5 h	3 equiv LiHMDS 2:1 pentane/THF, –78 °C, 0.5 h then 2.1 equiv Ts–Cl –78 °C, 0.5 h then 1 equiv LiHMDS –78 °C→ 22 °C, 1 h	3 equiv LiHMDS PhMe, –78 °C, 0.5 h then 2.1 equiv Ts–X –78 °C, 0.5 h then 1 equiv LiHMDS –78 °C→ 22 °C, 1 h

2.4. Scope and Limitations

We were delighted to find that both 4- and 6-chlororesorcinol derivatives were isolated in good to high yield (Scheme 29). The highest yielding vinylogous ester substrates were those bearing a carbon-based substituent, such as, alkyl (**3a**–**d**; **5a**–**d**) and allyl groups (**3h**; **5h**). Notably, we were also pleased to observe that both Boc (**3f**; **5f**) and Piv (**3g**; **5g**) protecting groups were tolerated under the reaction conditions. Vinylogous amides worked well for γ-halogenation (**5j–k**). In contrast, under α-halogenation conditions, the desired α-halogenation product was not formed (**3j–k**); instead the γ-halogenation product (**5k**) was obtained selectively. This result indicates that when an amino group is present at the β-carbon of the enone, the formed enolate intermediate undergoes rapid equilibration to form an extended enolate (kinetic enolate), which is in agreement with prior reports on γ-halogenation of vinylogous amides.[12,13] Thioesters were also tolerated and did not suffer from oxidative decomposition under the reaction conditions (**3l–5l**). Carbon substituents on the ring were also not problematic and allowed us to access highly substituted arenes (**3n**; **5n**). To our delight, 4- and 6-bromoresorcinols bearing different substituent patterns were all synthesized in excellent yields (**3o–v**; **5o–v**). Lastly, 4- and 6-iodoresorcinol derivatives were also achieved with different alkyl groups such as methyl, ethyl, and isopropyl, all of which were isolated in good yield (**3w**–**y**; **5w**–**y**).

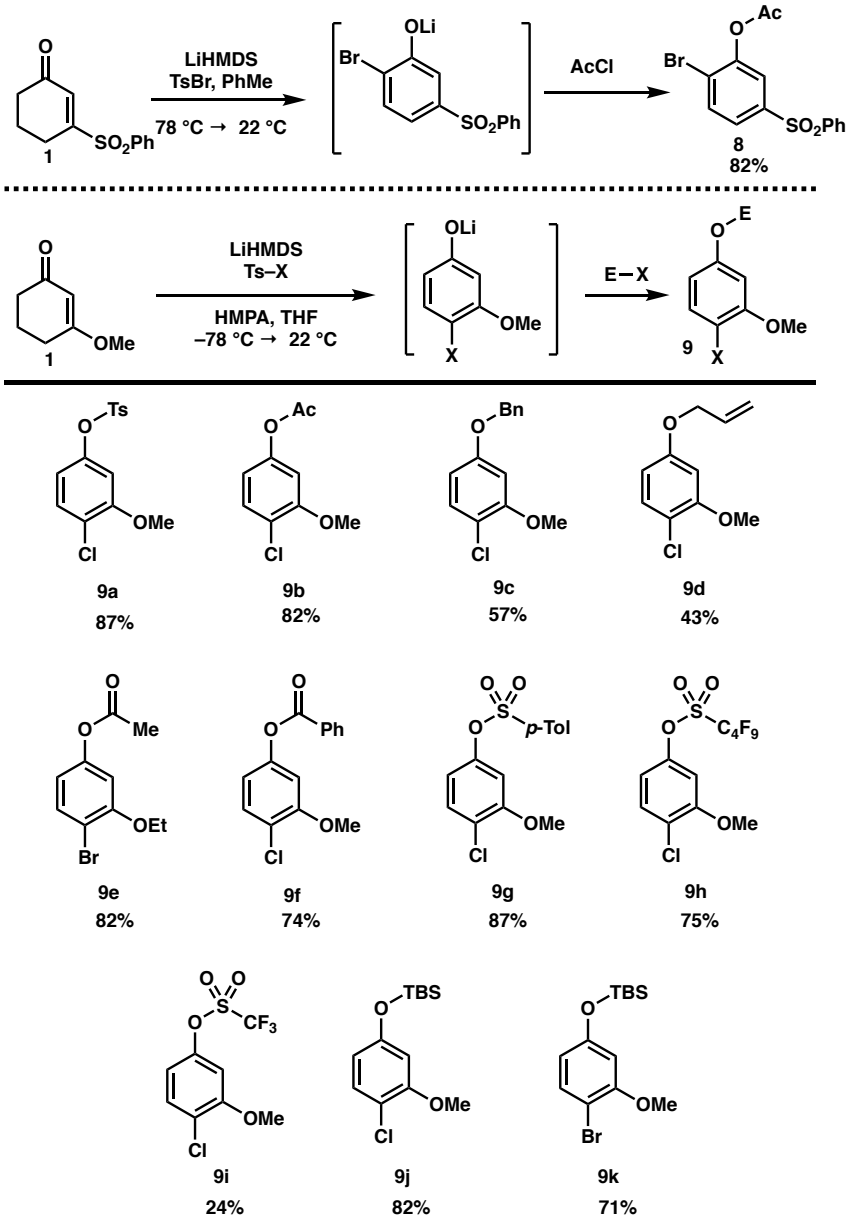
Scheme 29: Synthesis of 4- and 6-haloresorcinols



2.4. Synthetic Applications

We postulated that the reaction proceeded through a phenoxide intermediate and pursued trapping this nucleophile in order to synthesize a variety of protected resorcinol derivatives (Scheme 30). By adding electrophiles such as, *tert*-butyldimethylsilyl chloride (TBSCl) or acetyl chloride, directly after aromatization was complete, we were able to access arenes **9j**–**k** and **8**, respectively. We found this protocol to be superior to a previously established report involving the costly 4-bromoresorcinol in a multi-step sequence.[31] Further investigation of electrophiles also provided esters **9b** and **9e**–**f** in high yields. Additional TsCl added to the reaction mixture resulted in sulfonate **9g** in excellent yield. It should be mentioned that **9g** is not an intermediate under our standard reaction conditions based on TLC analysis. The use of $PhNTf_2$ resulted in the synthetically valuable aryl triflate **9i**, albeit at a low yield. Interestingly enough, we discovered nonafluorobutanesulfonyl fluoride (Nf–F) reacted with the phenoxide intermediate more readily and resulted in good yield of **9h**. The successful trapping of a diverse array of protecting groups is encouraging for future synthetic applications.

Scheme 30: One-pot aromatization/phenoxide trapping

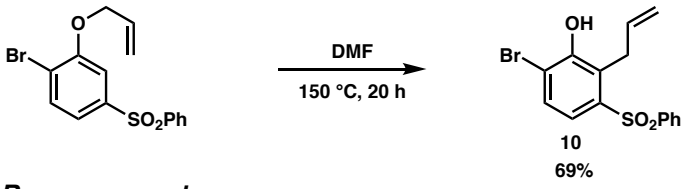


Trapping the phenoxide intermediate with an electrophile those possess a reacting group, such as an alkene, broadens the range of synthetic transformations our haloresorcinol derivatives can achieve (Scheme 31). For example, the allyl and acyl group appended onto our haloaromatic compounds provided the optimal substrates for both a Claisen[32] rearrangement and a Fries[33]

rearrangement/cyclization cascade, resulting in **10** and **11**, respectively. Moreover, our haloresorcinols were also well suited for a series of transition metal-catalyzed transformations including Mizoroki–Heck cyclization (**12**),[34] Sonogashira coupling (**13**),[35] Suzuki–Miyaura coupling (**14**),[36] and a Buchwald–Hartwig amination (**16**),[37] leading to a wide array of functionalized arenes.

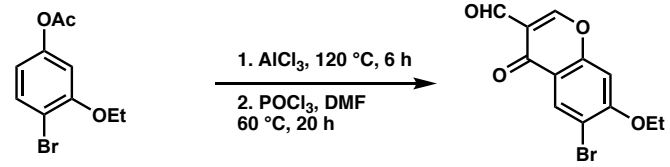
Scheme 31: Synthetic Applications of Haloresorcinols

Claisen Rearrangement



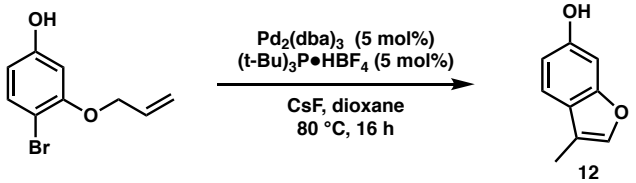
10
69%

Fries Rearrangement



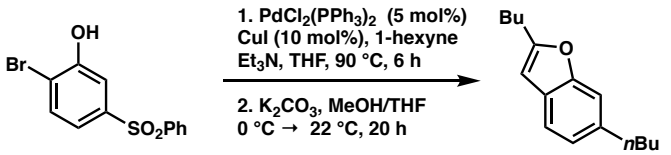
11
61%
(2 steps)

Mizoroki–Heck Cross-Coupling



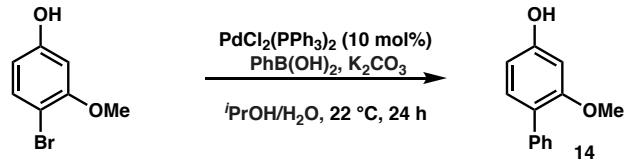
12
90%

Sonogoshira Cross-Coupling



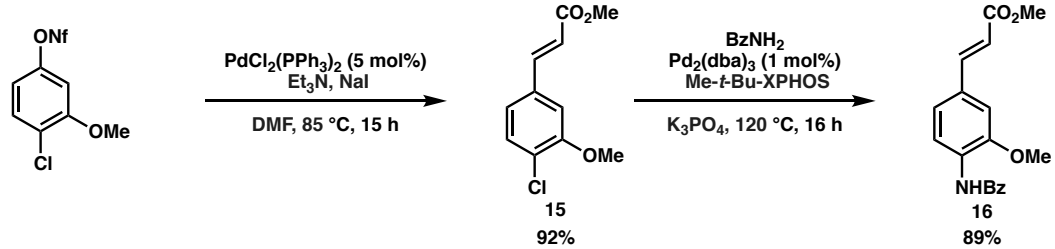
83%
(2 steps) 13

Suzuki–Miyaura Cross-Coupling



14
86%

Sequential Cross-Coupling Reactions



15
92%

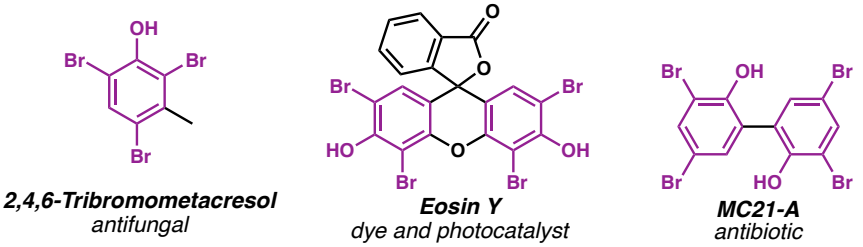
16
89%

Furthermore, our group has also been able to demonstrate the usefulness of our halogenation protocol in the pursuit of natural product synthesis. The outcomes of our research have resulted in the synthesis of grifolin, grifolic Acid, LL-Z1272α, LL-Z1272β, ilicicolinic acid A[38] and aeroplysinin.[39] These selected natural products have exhibited anti-inflammatory, antifungal, antibacterial, cytotoxicic, antiviral, and antioxidant effects. Thus, we have proven our synthetic methods have the potential to provide a pathway towards natural products, pharmaceuticals, and agricultural products.

2.5. Synthesis of Polyhalogenated Resorcinols

With our understanding of the α- and γ-halogenation protocols, we sought to develop useful methodology to access poly-haloresorcinols. We speculated we could isolate tri- and dibromoresorcinol derivatives with additional equivalents of Br^+. Notably, our strategy to access these arene building blocks could serve as precursors to access oxygenated arene natural products (Scheme 32).[21]

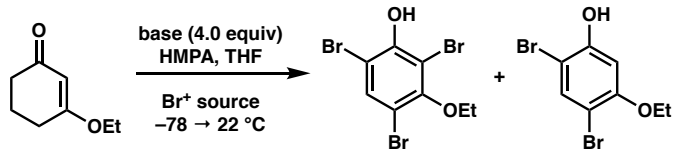
Scheme 32: Selected Arenes



Our screening for a Br^+ source began with TsBr (Scheme 33). Not surprisingly, the only product isolated was the mono-bromoresorcinol (**5n**, Scheme 29). With NBS, however, the desired tribromoresorcinol **17** was the major product (entry 2). Utilizing the hydantoin analog, the yield of this product increased (entry 4). Ultimately, the DABCO•2Br_2 complex proved to be the

optimal reagent for this transformation (entry 6). Interestingly, using a 1:1 mixture of LiHMDS and LDA in the presence of DABCO•2Br_2 complex resulted in dibromoresorcinol **18** selectively in moderate yield (entry 7).

Scheme 33: Optimization of polybromoresorcinol synthesis

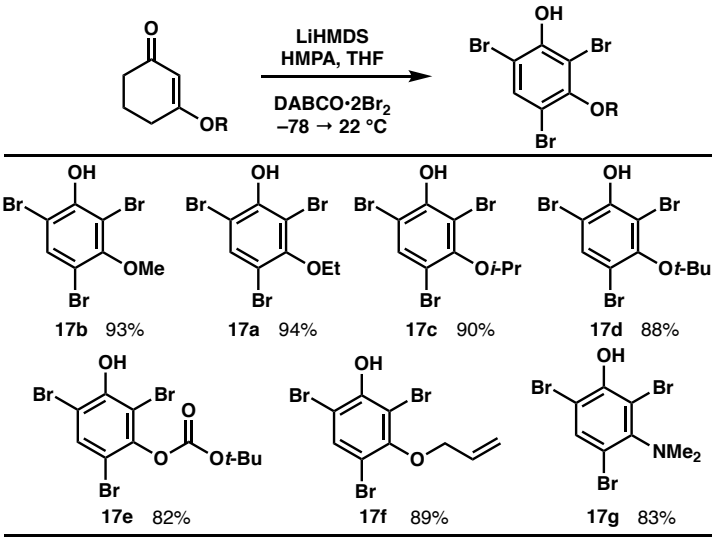


1 *17a* *18*

entry	base	Br^+ source	equiv	yield (%)	
				17a	*18*
1	LiHMDS	Ts–Br	4.2	0	0
2	LiHMDS	*N*-bromosuccinimide	3.2	33	14
3	LiHMDS	*N*-bromosuccinimide	4.2	67	8
4	LiHMDS	1,3-Dibromo-5,5-dimethylhydantoin	2.2	88	0
5	LiHMDS	DABCO•2Br_2	1.6	50	22
6	LiHMDS	DABCO•2Br_2	2.2	94	0
7	LDA/LiHMDS (1:1)	DABCO•2Br_2	2.2	0	50

With these optimal reaction conditions, we chose to explore the scope of 2,4,6-tribromoresorcinols (Scheme 34). Once more, we were pleased to see potentially acid sensitive groups such as *t*-Bu (**17d**), Boc, (**17e**), oxidizable allyl (**17f**), and dimethylamino groups (entry **17g**) were all well tolerated. Also, we were delighted to not witness any over halogenation, as this was also a possibility and is often a byproduct in conventional methods for polyhalogenation.[40]

Scheme 34: Scope of 2,4,6-tribromoresorcinols



2.6. Summary

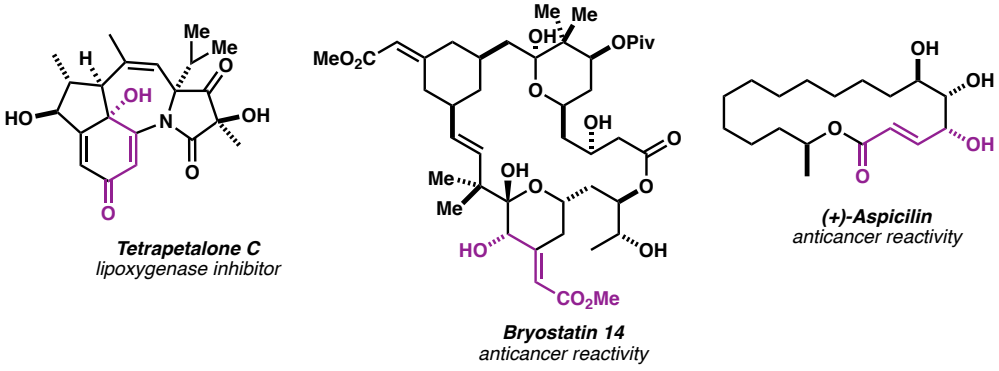
In conclusion, we have shown a step economical and regiodivergent approach towards synthetically valuable haloresorcinols and derivatives via selective halogenation/elimination sequence of readily available enones. The method developed is highly advantageous compared to the state-of-the-art methods as precious transition metals and/or strong exogenous oxidants are not employed. The synthetic utility of our transformation was examined and diverse haloarene scaffolds were obtained via Claisen and Fries rearrangement and cross-couplings methods, all of which highlights the synthetic usefulness of our method. Importantly, our full investigation on the reaction conditions leading to the regioselective C–halogen bond formation discussed in this chapter allowed us to gain valuable insight as to the overall reactivity of the dienolate intermediates. Moreover, our studies also provided us with a platform to address the synthetic challenge of γ-functionalization of ketone moieties. We foresee that this regioselective protocol will become a general approach toward haloresorcinols building blocks and will be widely implemented in natural product synthesis, medicinal chemistry, and material synthesis.

3. γ-Hydroxylation of Vinylogous Esters

3.1. Reaction Development

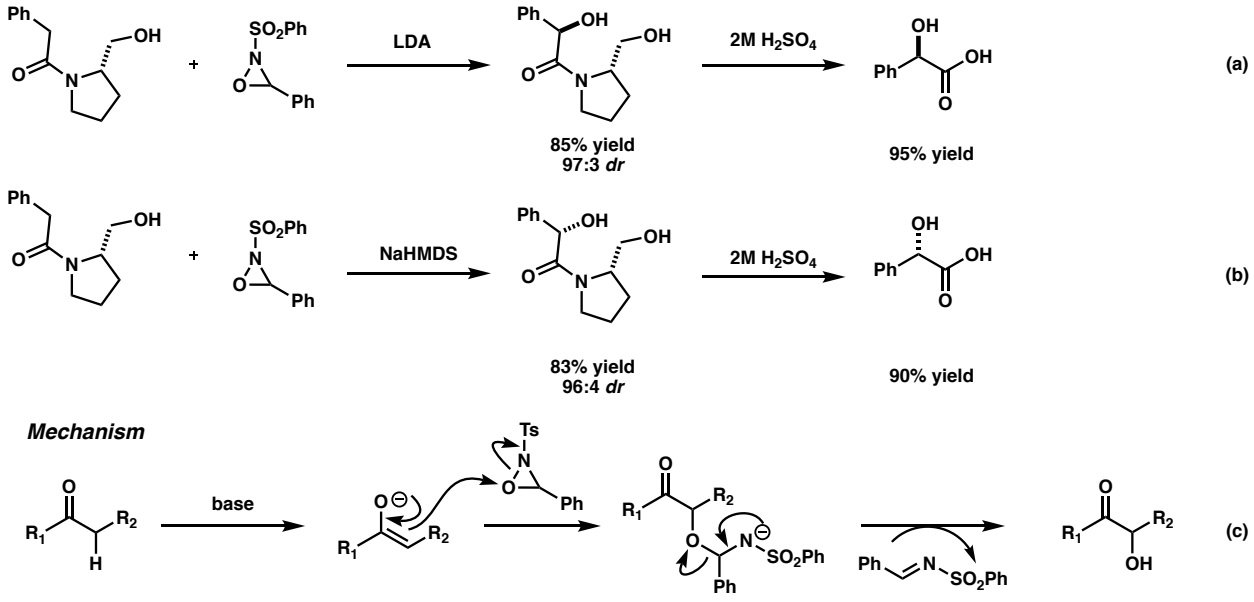
There are countless reports dedicated to the synthesis of naturally occurring γ-oxygenated compounds (Scheme 35). These species are valuable natural products that are known to exhibit highly beneficial medicinal properties such as their roles as lipoxygenase inhibitors and anticancer reactivity.[41] Many research groups have focused their efforts towards the development of γ-oxygenated of enones and related systems, however, these approaches are plagued with low reaction efficiency and regioselectivity.

Scheme 35: Naturally occurring γ-oxygenated compounds



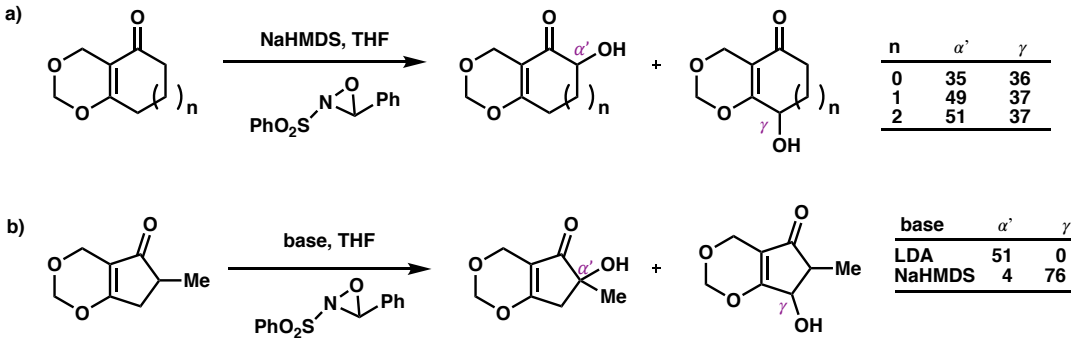
Since the late 1970s, the Davis oxaziridine has been utilized as an oxidant to yield hydroxylated products. In 1985, they found it to be the optimal reagent for achieving high diastereoselectivities in direct oxidation of chiral enolates (Scheme 36).[42] Oxaziridines have many unusual physical properties that contribute to their distinctive reactivity. The most well characterized reactivity of oxaziridines is their ability to serve as electrophilic oxygen atom transfer reagents.[43]

Scheme 36: Oxidation of chiral amide enolates



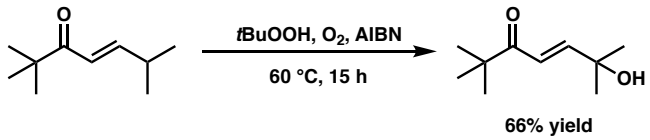
In 1988, Smith and co-workers employed the Davis oxaziridine for hydroxylation of cyclic vinylogous esters (Scheme 36).[44] As expected, the use of lithium diisopropylamide led to kinetic deprotonation and thus, the α'-hydroxylated product was obtained as the major product (Scheme 36a). Conversely, with sodium bis(trimethylsilyl)amide, the γ-hydroxylated product was formed as the major constitutional isomer (Scheme 37b). Unfortunately, the highest yield was observed when the α-position was substituted, thus, limiting the utility of the overall method.

Scheme 37: Smith's γ-hydroxylation of vinylogous esters



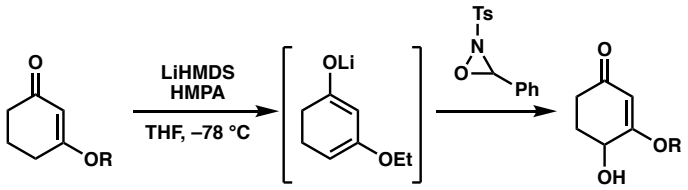
In the same year, the Watt group also aimed to oxidize a series of enones at the γ-position (Scheme 38).[45] Although they were able to provide a fair number of substrates, their reaction yields ranged from low to moderate. Additionally, their scope was also limited to α'-substituted acyclic enones and their use of elemental oxygen poses a safety hazard when considering scalability.

Scheme 38: γ-Hydroxylation of enones



Based on our work discussed in previous chapters, we have shown that the thermodynamic enolate of cyclic vinylogous ester can be formed selectively in the presence of LiHMDS and HMPA. Thus, we hypothesized that this intermediate could effectively react with the Davis oxaziridine to furnish the γ-hydroxylated product in a highly regioselective manner (Scheme 39). Notably, our proposed protocol will not only solve the aforementioned limitations of the state-of-the-art methods in terms of regioselectivity, but will also provide a new avenue for γ-hydroxylation of enone derivatives.

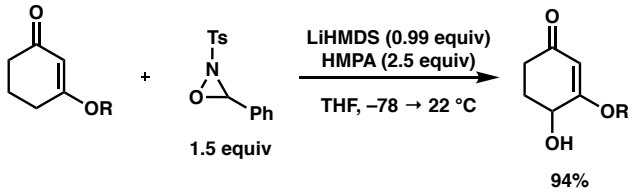
Scheme 39: Strategy for γ-hydroxylation of vinylogous esters



3.2. Optimization of the Reaction Conditions

With the optimal anionic method for halogenation at the γ-position (*vide supra*), we proceeded to apply our developed conditions to achieve the desired hydroxylated transformation. Fortunately, it was found that our prior anionic conditions worked well, and the desired γ-hydroxylation was obtained in high yield in the presence of Davis oxaziridine as the hydroxylation agent (Scheme 40). During our slight optimization of the reaction conditions we uncovered, however, that fewer equivalents of base generated the best results. Also, we learned that it was crucial to carry out these reactions under cryogenic conditions to ensure the generation of the reactive thermodynamic dienolate. Similar to our previous work, the reaction was completed after warming it to room temperature.

Scheme 40: Optimized reaction condition for γ-hydroxylation of vinylogous esters

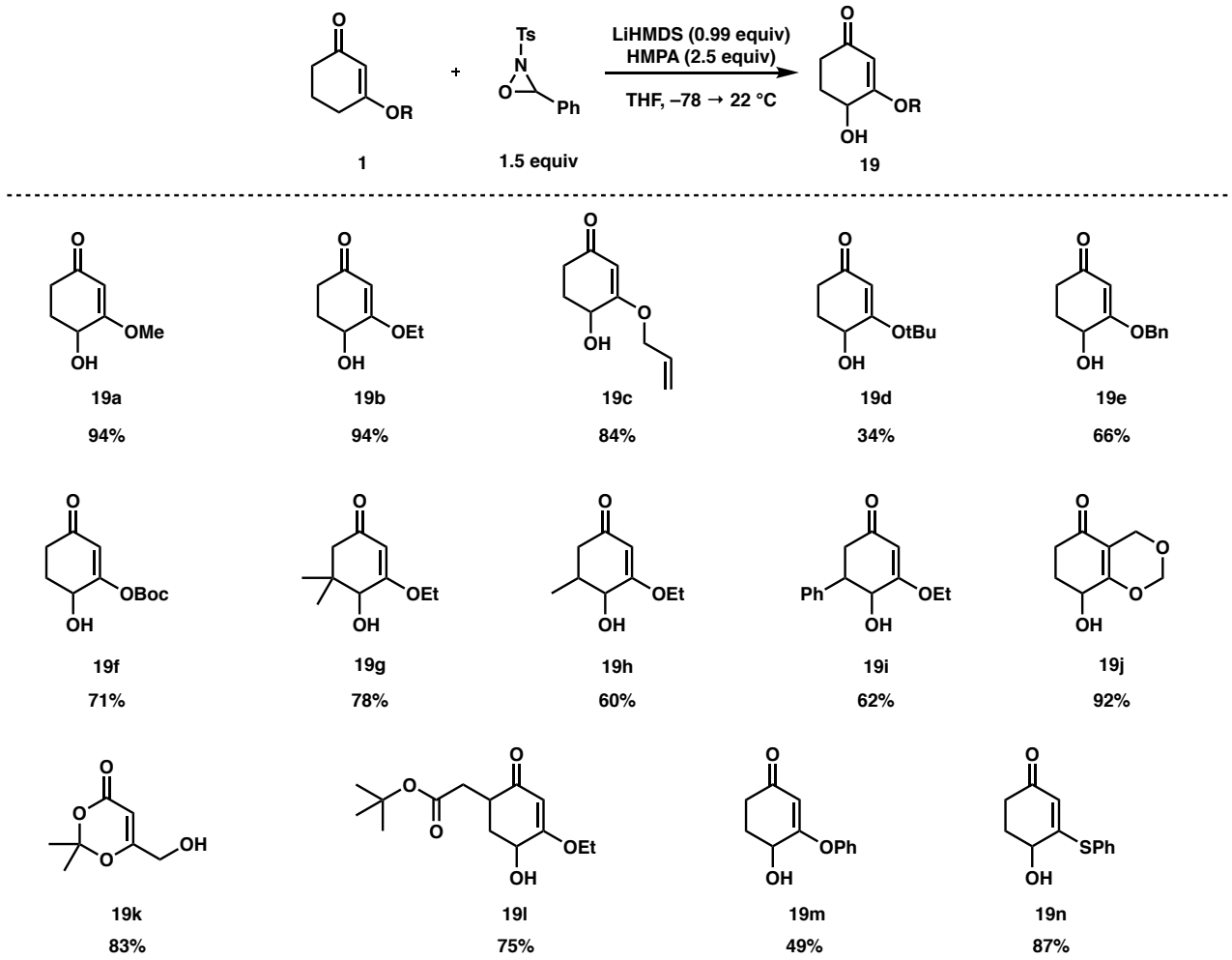


3.3. Scope and Limitations

The substrate scope for γ-hydroxylation resembled that of our γ-halogenation method because we utilized the same staring vinylogous ester substrates. Not surprisingly, we found the majority of the same functional groups were tolerated and resulted in efficient formation of the desired γ-hydroxylation products (Scheme 41). Once again, we asserted the viability of acid-sensitive

groups such as alkyl ethers, allyl ether, and carbonyl-containing substrates (entries **19a**–**f**). Carbon substituents on the cyclic ester worked well, resulting the corresponding γ-hydroxylation products (entries **19g**–**h**) in good yield. Delightfully, formal allylic C–H hydroxylation of pseudo trans enolate leading to **19k** occurred efficiently. Phenyl thiol and benzoate vinylogous esters performed fairly well, resulting in high yields of **19m** and **19n**, respectively. Overall, the reaction scope was found to quite general as a variety of functional groups were tolerated and resulted in good to excellent yields.

Scheme 41: Scope of γ-hydroxylation



3.4. Summary

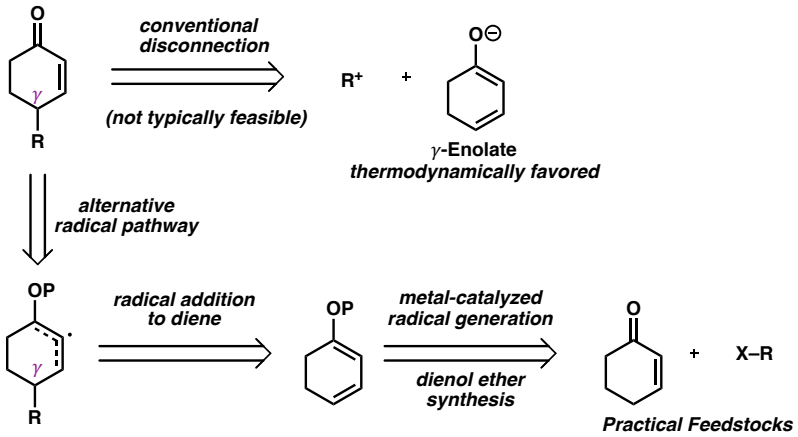
To conclude, we have demonstrated a general and highly regioselective protocol for γ-hydroxylation of enones. Our transformation is amenable to a wide array of cyclic vinylogous esters possessing sensitive functional groups and reactive groups, which highlight the robustness and modularity, respectively, of our method. Given the inaccessibility of regioselective methods for γ-hydroxylation, we are enthusiastic about the prospects of our protocol and we anticipate that it will find broad use in areas of natural product synthesis and drug discovery. Lastly, with the success of employing Davis oxaziridine as a hydroxylation agent, we aim to utilize chiral oxaziridines in future studies into furnish important chiral γ-hydroxy-enones.

4. Cu-Catalyzed γ-Alkylation of Enones

4.1. Reaction Development

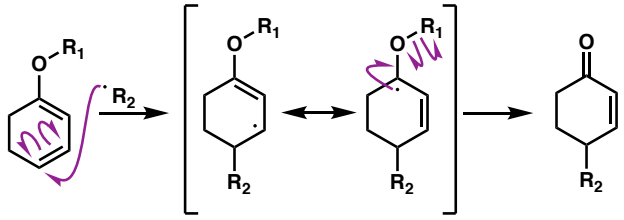
As mentioned in Chapter 1, methods for anionic γ-alkylation of enones have been reported, however, regioselectivity still remains an issue. In order to advance our laboratory's program on γ-selective functionalization, we aimed to solve the inherent regioselectivity problem of γ-alkylation. To this end, we reasoned that changing the nature of the reaction from an anionic pathway to a radical pathway could result in selective alkylation at the γ-position of enones based on the electronic properties of the reacting diene and the alkyl radical (Scheme 42).

Scheme 42: γ-Selective alkylation via anionic and radical pathways



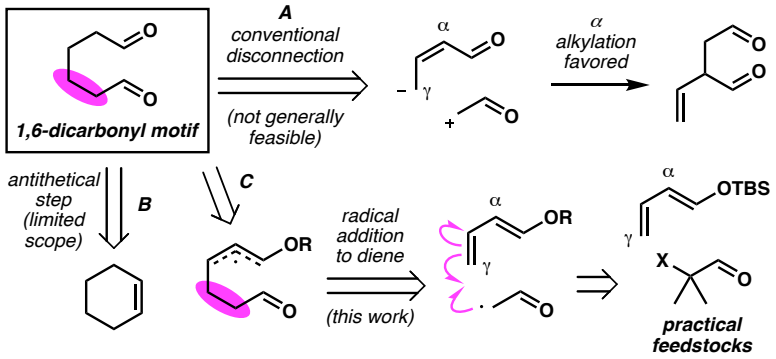
As stated, we believe this new bond forming process to occur via radical intermediates. Our strategy involved the addition of radical intermediates to dienol ethers. We hypothesized site selectivity would be controlled due to the preferred stabilized oxylallyl radical that is the result of the γ-addition pathway (Scheme 43).

Scheme 43: Potential mechanism for radical γ-functionalization



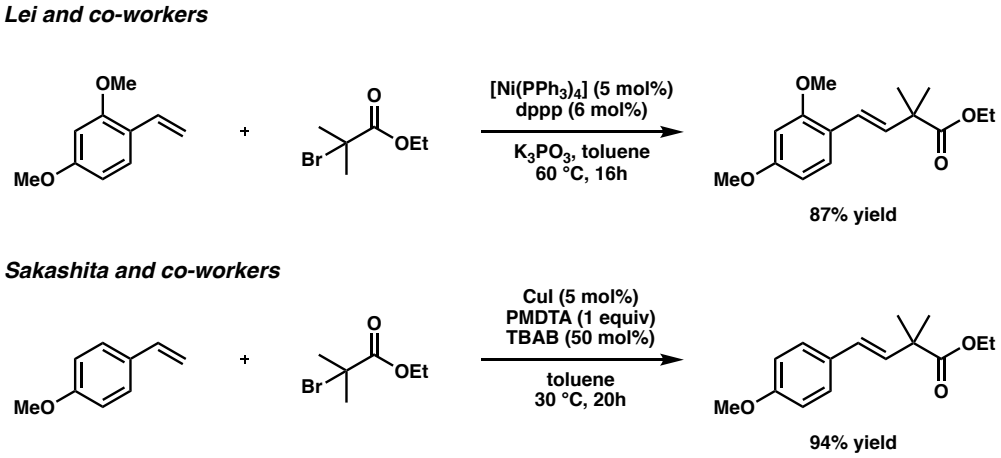
Our vision led us to believe we could use this strategy to access 1,6-dicarbonyl compounds. To date, the synthesis of dicarbonyl compounds has been accomplished through various methods. Claisen condensation, enolate alkylation with α-halocarbonyl electrophiles, and Michael addition protocols are robust classical platforms for generating 1,3-, 1,4-, and 1,5-dicarbonyl compounds. In comparison, the 1,6-dicarbonyl motif has proven to be more challenging. Outlined below are three general disconnection approaches to consider for the synthesis of 1,6-dicarbonyl compounds (Scheme 44). From our previous work, discussed in Chapter 2, we gained valuable insight when utilizing dienolate derivatives as synthons for this purpose[46] (Scheme 44, path A). Most electrophiles are found to react preferentially at the more nucleophilic α-C. [47] In addition, the decreased electron density at the γ-site complicates this hypothetical reaction for γ-selective functionalization. As a result, we also considered antithetical disconnections such as oxidative cleavage of cyclohexenes, though these methods suffer from substantial scope limitations (Scheme 44, path B). Therefore, we believed our strategy involving the addition of radical intermediates to dienol ethers could prove promising to fulfill the need for a direct γ-C–C bond formation technique (Scheme 44, path C).

Scheme 44: Strategies for 1,6-dicarbonyl synthesis



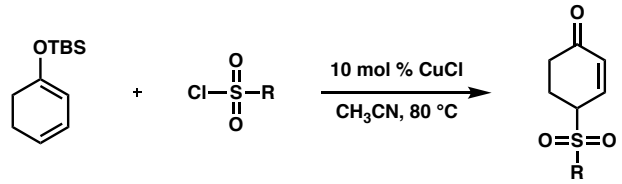
We were encouraged by recent reports utilizing α-haloesters as radical precursors to create new C–C bonds.[48] Lei and co-workers featured the first nickel-catalyzed Heck-type reaction of secondary and tertiary α-carbonyl alkyl bromides with olefins. Similarly, the Sakashita group also investigated this transformation (Scheme 45). They developed a copper–triamine catalyzed protocol to produce new olefin products via a radical pathway. We postulated that these α-haloesters may also participate in radical reactions with our ambident nucleophilic intermediates. Thus, we may expose our reactive dienolates to α-haloesters to generate 1,6-dicarbonyl compounds directly.

Scheme 45: α-Haloesters used for alkenylation reactions



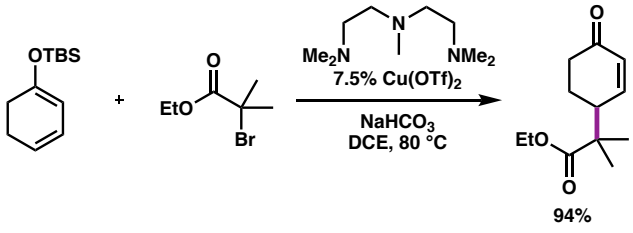
Former group members of the laboratory, Dr. Xiaohong Chen and Dr. Xiaoguang Liu laid the foundation for γ-functionalization with the use of silyl dienol ethers.[49] They achieved a copper-catalyzed regioselective method to introduce sulfonyl groups at the γ-carbon (Scheme 46). The discovery of these results paved the way for our group to explore the use of silyl dienol ethers for other regioselective bond forming reactions.

Scheme 46: γ-Sulfonylation of silyl dienol ethers



The seminal results for our γ-sulfonylation protocol encouraged us to apply Cu-catalysis to promote γ-alkylation of dienol ethers. Consequently, Dr. Chen and Dr. Liu developed such a method utilizing α-halocarbonyl compounds to form the 1,6-dicarbonyl moiety selectively (Scheme 47).[50]

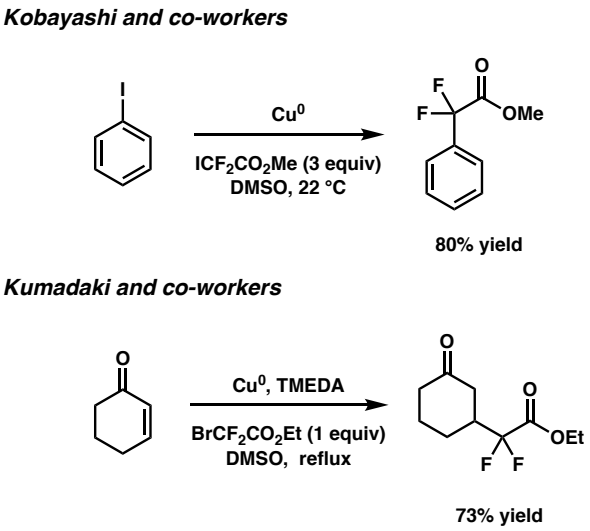
Scheme 47: Cu-catalyzed stereoselective γ-alkylation of enones



Early reports from the Kobayashi and Kumadaki group also led us to believe we could eventually use α-dihaloesters to generate dihalo carbonyl compounds (Scheme 48).[51] In 1986, Kobayashi developed the alkoxycarbonyldifluoromethylation of aryl and alkenyl halides with

iododifluoroacetate. Although the reaction was complete in under an hour, the scope was mainly limited to vinyl halide starting materials. Kumadaki reinvestigated this transformation with bromodifluoroacetates. They provided a new set of reacting counterpartners, α,β-unsaturated carbonyl compounds that are efficient for radical conjugate addition. These reports only served to further encourage us to use these α-dihaloesters as coupling partners in a regioselective γ-C−C bond formation event.

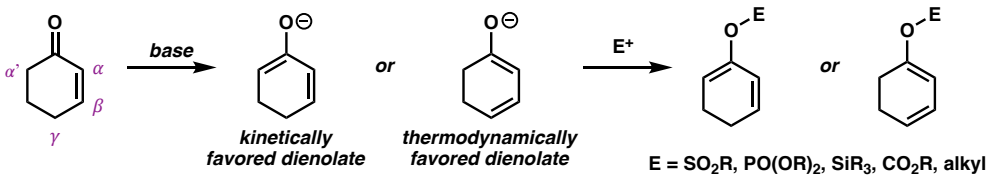
Scheme 48: Previous methods for synthesis of 2,2-difluoroesters



4.2. Synthesis of Silyl Dienol Ethers

Having already reviewed the inherent and potential problems with radical reactions of dienes in Chapter 1, we recognized the need for a stabilized dienol equivalent to control the regioselectivity of reactions.

Scheme 49: Generation of stable dienol equivalents

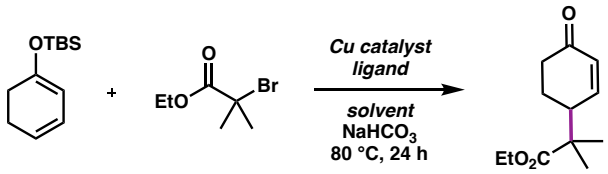


To find a suitable radical acceptor system for the proposed transformation, we synthesized a number of isolable dienol derivatives with a series of hard oxophilic electrophiles (e.g., $SO_2CF_3^+$, TMS^+, $PO(OR)_2^+$) (Scheme 49). Sulfonates were particularly attractive to us since many of them could be accessed from economical commercial sulfonyl halides. Another advantage of utilizing sulfonates is the potential to reduce the group to the corresponding sulfininate in the termination step of the radical process. We saw the potential for altering the electronics of phosphates by changing the alkoxy groups. Silyl and tin groups were also potential substrates since they are known to continue radical chain reactions without reagents such as tin hydrides. Finally, we considered carbonates as well because we could change the functionality to favor the desired ketone formation. Ideally, the oxygen prevents undesired β-addition to the dienol intermediate while also being susceptible to undergo cleavage faster than other reactions of the allylic radical. Ultimately, we chose to pursue our studies with silyl dienol ethers due to their accessibility and potential to promote radical chain reactions.

4.3. Optimization of the Reaction Conditions

As stated, our laboratory previously reported the development of the copper-catalyzed γ-alkylation protocol.[50] During optimization of this transformation (Scheme 50), the role of the supporting ligand became clear (entries 2–5). Unligated Cu(II) and the bpy complex failed to catalyzed the coupling (entries 2–3). Delightfully, employment of tertiary amine Cu complexes worked well, in particular when pentamethyldiethylenetriamine (PMDTA) was used as a ligand (entry 5). Among the Cu salts tested, none were superior to $Cu(OTf)_2$ (entries 6-10). Interestingly, decreasing this catalyst loading from 10 to 7.5 mol% and employing DCE as solvent resulted in a higher reaction (entry 15).

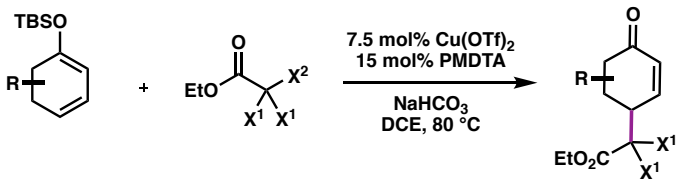
Scheme 50: Optimization for the γ-Alkylation of dienol ethers



entry	Cu catalyst (mol %)	ligand (mol %)	solvent	% yield
1	none	none	toluene	0
2	$Cu(OTf)_2$ (10)	none	toluene	0
3	$Cu(OTf)_2$ (10)	bipy (20)	toluene	0
4	$Cu(OTf)_2$ (10)	TMEDA (20)	toluene	16
5	$Cu(OTf)_2$ (10)	PMDTA (20)	toluene	58
6	CuI (10)	PMDTA (20)	toluene	16
7	$CuCl_2$ (10)	PMDTA (20)	toluene	12
8	$CuBr{\cdot}SMe_2$ (10)	PMDTA (20)	toluene	49
9	$CuCO_3$ (10)	PMDTA (20)	toluene	42
10	none	PMDTA (20)	toluene	0
11	$Cu(OTf)_2$ (10)	PMDTA (20)	CH_3CN	73
12	$Cu(OTf)_2$ (10)	PMDTA (20)	THF	77
13	$Cu(OTf)_2$ (10)	PMDTA (20)	1,4-dioxane	86
14	$Cu(OTf)_2$ (10)	PMDTA (20)	DCE	92
15	***$Cu(OTf)_2$ (7.5)***	***PMDTA (15)***	***DCE***	***94***

In this work, we also began to explore dihalogenated esters as electrophiles. Specifically, we utilized ethyl trichloroacetate and ethyl bromodifluoroacetate as α-polyhalo coupling partners (Scheme 51). However, the scope of these desirable dihaloacetate derivatives has to be expanded.

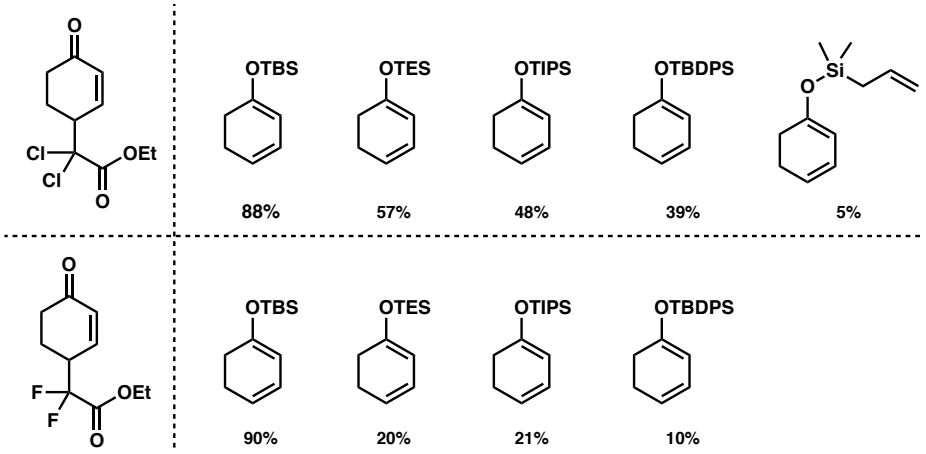
Scheme 51: α-Polyhalo coupling partners



4.4. Scope and Limitations

In order to ensure that we were utilizing the optimal silyl dienol ether for our transformation, we set out to test a variety of substrates possessing different silane protecting groups (Scheme 52). We found little success in both cases under our standard conditions. Among the dienols analyzed in the case of 2,2-dichloroesters, we were unable to find an improvement in yield in comparison to the TBS dienol ether. Similarly, we found the same with the use of bromodifluoroacetate.

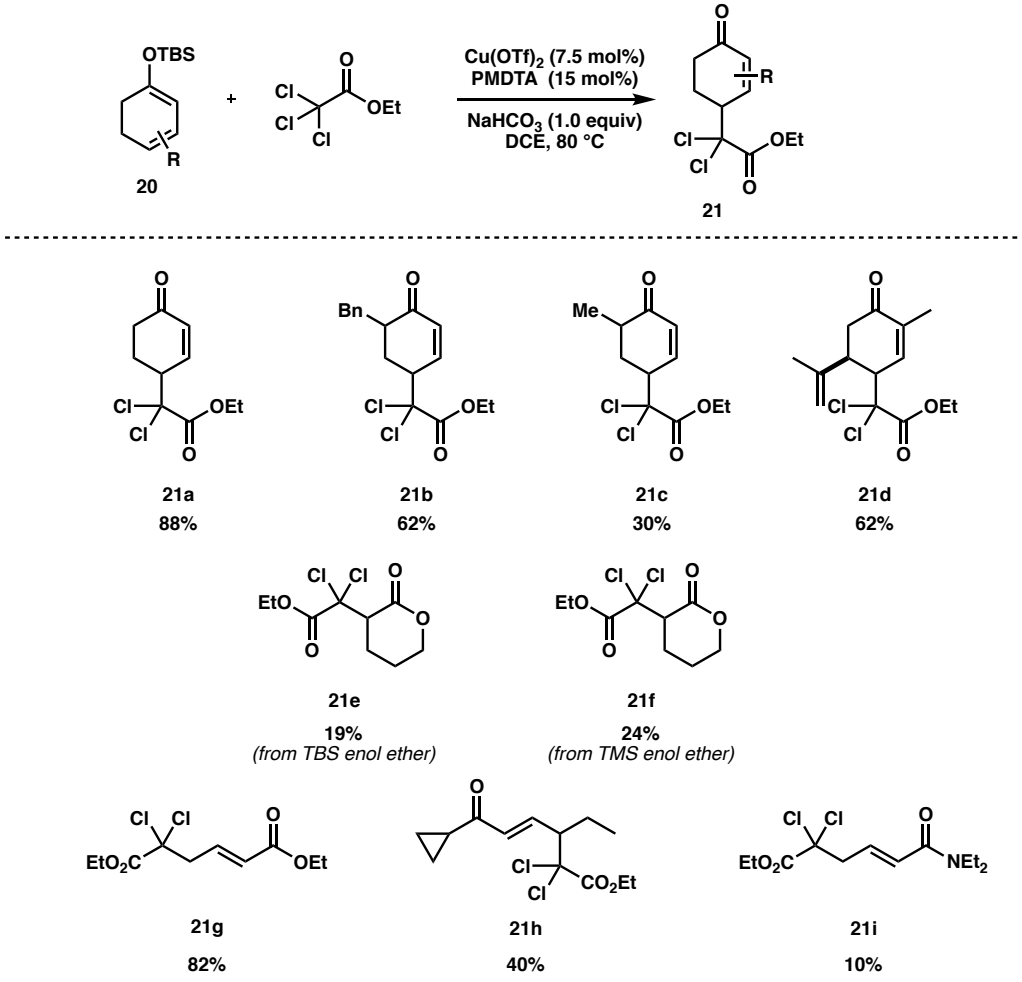
Scheme 52: Scope of varied silyl dienol ethers



We began exploring the scope of α-dihalo esters (**21**) by exposing a number of silyl dienol ethers (**20**) to ethyl trichloroacetate (Scheme 53). We found that the reaction conditions did not have to be altered from the original γ-alkylation protocol. Substituting at the α'-position of the silyl

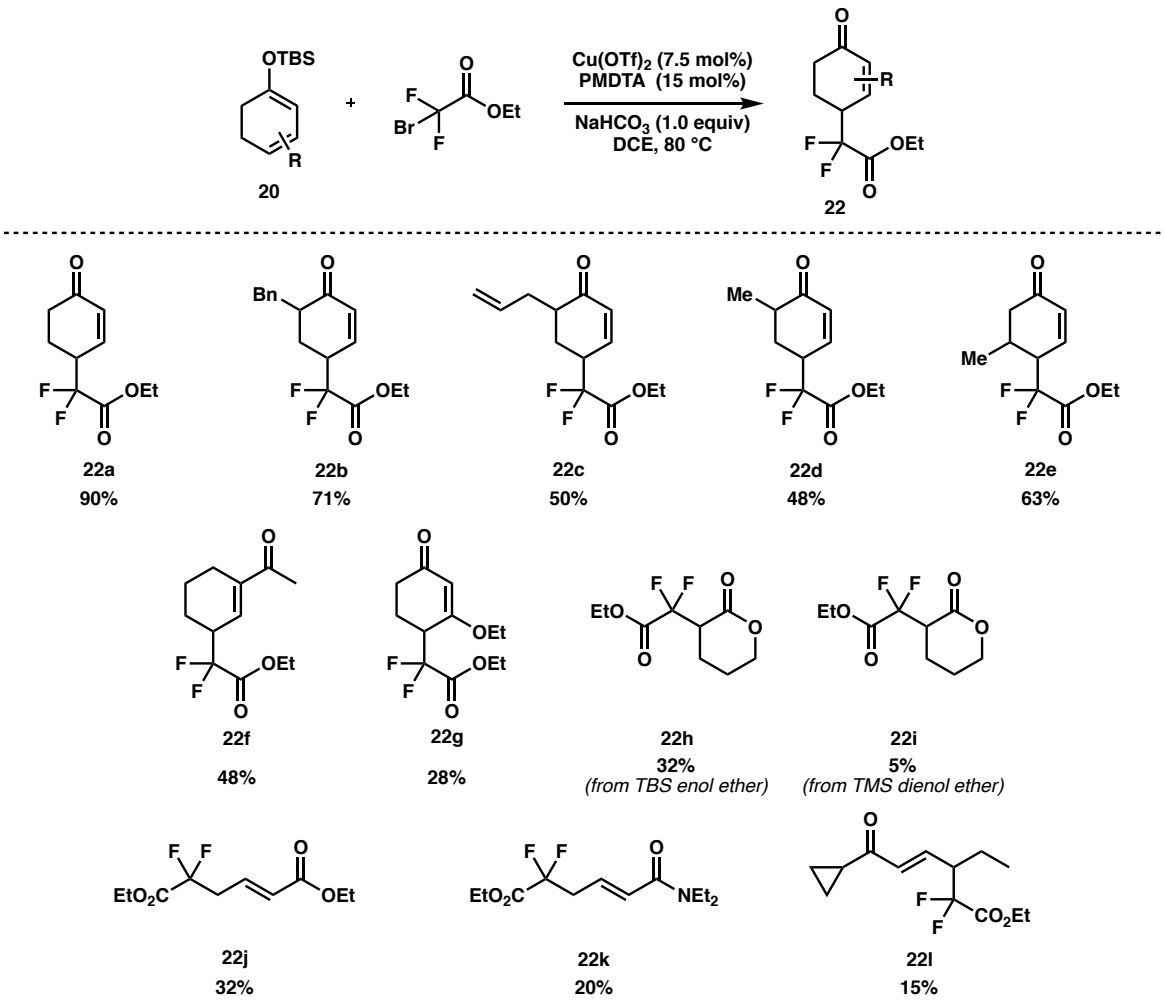
dienol with a benzyl group did not result in a significant decrease of yield (**21b**). However, employment of α'-methyl silyl dienol resulted in low reaction yield of the corresponding product (**21c**). Pleasantly, carvone-derived silyl dienol ether performed well (**21d**), even with a competitive reacting site (i.e., alkene) present in the molecule. TBS- and TMS-δ-valerolactone derived dienols were found to be compatible substrates under the reaction conditions, however, the α'-alkylation products were formed predominately owing to the high electron density at that position (**21e-f**). Finally, γ-alkylation of acyclic dienols worked well, resulting in respective products **21g–i** in moderate to very good yield.

Scheme 53: Scheme of dichloroacetate esters



We were eager to test our γ-alkylation strategy towards the synthesis of medicinally and industrially important difluoroacetate esters.[52] Delightfully, exposure of commercially available bromodifluoroester to our standard reaction conditions resulted in the desired γ-difluoroacetate esters (**22**) in good reactions yields (Scheme 54). Overall, the generation of 2,2-difluoroesters proceeded with more ease and in higher yield than that of its dichloro-halogen analog (*vide supra*). Exposure of α'-allyl silyl dienol to our optimized conditions resulted in the desire γ-alkylation product in good yield (**22c**). Remarkably, pseudo trans silyl dienol reacted well, as the γ-difluoro acetate product **22f** was obtained in a highly efficient manner. Similar to the aforementioned dichloroalkylation protocol, γ-difuloroalkylation of TBS- and TMS-δ-valerolactone derived dienols resulted in low yields of **22h** and **22i**, respectively. Lastly, γ-alkylation of acyclic systems resulted in their corresponding fluorinated products in respectable yields (**22j-i**).

Scheme 54: Scope of difluoroacetate esters



4.5. Summary

To summarize, we have been able to expand on the Cu-catalyzed protocol for the γ-dihaloalkylation of dienol ether derivatives. Our method was found to be highly robust, regioselective, and diastereoselective. We successfully expanded upon the results of our previous work by incorporating dihalogenated esters as coupling partners to generate valuable *gem*-dichloro- and difluoroacetate esters, which are largely present in many classes of compounds, such as therapeutics and agricultural chemicals.

5. Experimental Section[†]

5.1. General Information

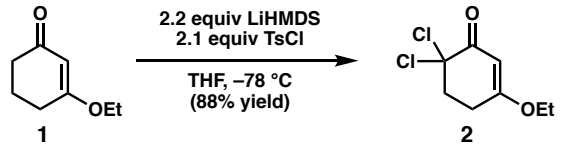
Unless otherwise stated, reactions were performed in oven-dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous dichloromethane, pentane, toluene, and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[53] on a Pure Process Technology system. Potassium bis(trimethylsilyl)amide (KHMDS) and sodium bis(trimethylsilyl)amide (NaHMDS) were purchased from Aldrich and used as received. Molecular sieves (MS) were purchased from Aldrich and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted. Hexamethylphosphoramide (HMPA) was purchased from Chem-Impex International, Inc., distilled over CaH_2 prior to use, and stored over 4 Å MS under argon atmosphere. Bis(trimethylsilyl)amine (HMDS) was purchased from Alfa Aesar, distilled over NaH, and stored over 4 Å MS under N_2 atmosphere. Tris(dibenzylideneacetone)dipalladium(0) and bis(triphenylphosphine)palladium(II) dichloride were purchased from Strem and used as received. Sodium hydride (NaH) was purchased as 60% dispersion in mineral oil from Acros and used as received. Starting materials, including 1,3-diketones, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. Vinylogous ester substrates were prepared according to literature procedures.[54] Tosyl bromide[55] and tosyl iodide[56] were prepared

[†] Previously published as Chen, X.; Liu, X.; Martinez, J. S.; Mohr, J. T. "Practical Regioselective Halogenation of Vinylogous Esters: Synthesis of Differentiated mono-Haloresorcinols and Polyhalogenated Resorcinols," *Tetrahedron* **2016**, *72*, 3653–3665.; Chen, X.; Martinez, J. S.; Mohr, J. T. "Regiodivergent Halogenation of Vinylogous Esters: One-Step, Transition Metal-Free Access to Differentiated Haloresorcinols," *Org. Lett.* **2015**, *17*, 378–381.

according to literature procedures and recrystallized from 1:5 benzene/hexane prior to use. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[57] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Bruker Avance DRX-400 at 376 MHz and are reported relative to the external standard F_3CCO_2H (δ –76.53 ppm). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model 6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). High-resolution mass spectra (HRMS) were obtained from the University of Illinois at Urbana–Champaign Mass Spectral Facility.

5.2. γ-Functionalization of Carbonyl Compounds

5.2.1. Procedures and Experimental Data for Dihalogenated Intermediates



6,6-Dichloro-3-ethoxycyclohex-2-enone (2). An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with a solution of LiHMDS (1.00 M in THF, 2.20 mL, 2.20 equiv), dry THF (3 mL), and dry pentane (6 mL) and then cooled to –78 °C. The mixture was stirred for 10 min, and then a solution of 3-ethoxycyclohex-2-enone (**1**, 140.2 mg, 1.00 mmol, 1.00 equiv) in dry THF (2 mL) was added dropwise over 3 min. Stirring at –78 °C was continued for 30 min. A solution of tosyl chloride (400. mg, 2.10 mmol, 2.10 equiv) in THF (3.0 mL, then the vial was rinsed with 1.0 mL and added to the reaction) was then added dropwise over 10 min. After 20 min at –78 °C, the reaction was quenched with a saturated aq NH_4Cl solution (10 mL) and then EtOAc (20 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 20:1 hexanes/EtOAc) to afford the product as a white solid (183 mg, 88% yield). (*Note:* The product slowly decomposed during workup and chromatography.)

TLC (SiO_2) R_f = 0.48 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 64–66 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.95 (q, *J* = 7.0 Hz, 2H), 2.78 (t, *J* = 5.9 Hz, 2H), 2.65 (t, *J* = 5.9 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H)

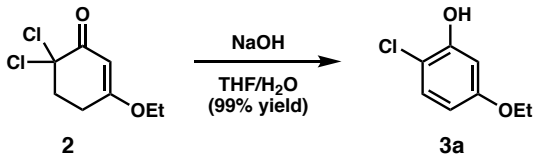
^{13}C NMR (126 MHz, $CDCl_3$) δ 185.0, 176.5, 98.0, 84.9, 65.2, 41.3, 28.0, 14.0

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 98.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 98.6, 65.5 (–), 41.7 (–), 28.4 (–), 14.3

IR (neat) 3073, 2991, 1671, 1596, 1465, 1440, 1310, 1270, 1252, 1194, 1119, 1023, 872, 854, 805, 758, 697, 653, 588 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_{10}Cl_2O_2$ $[M]^+$: 209.0136, found 209.0135



2 3a

6-Chloro-3-ethoxyphenol (3a). To a solution of 6,6-dichloro-3-ethoxycyclohex-2-enone (**SI18**, 20.9 mg, 0.100 mmol, 1.00 equiv) in THF (1 mL) was added a 2 M NaOH solution (aq, 0.2 mL, 0.4 mmol, 4 equiv) and the mixture was stirred at room temperature for 2 h. When TLC indicated complete consumption of the substrate, the mixture was cooled to 0 °C and a 1 M HCl solution was added dropwise until a pH ~2 was achieved. Ethyl acetate (5 mL) was added, and then phases were separated and the aqueous phase was then extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (1 x 5 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (SiO_2, 8:1 hexanes/EtOAc) to give product in quantity yield as white solid (17.2 mg, >99% yield).

TLC (SiO_2) R_f = 0.40 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 36–38 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.9 Hz, 1H), 6.58 (d, J = 2.8 Hz, 1H), 6.44 (dd, J = 8.9, 2.8 Hz 1H), 5.52 (s, 1H), 3.98 (q, J = 7.0 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H)

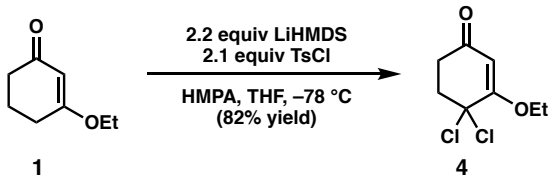
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 151.9, 129.0, 111.2, 108.2, 102.2, 63.8, 14.7

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 128.8, 108.4, 102.2

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 128.8, 108.4, 102.2, 63.9 (–), 14.7

IR (neat) 3527, 3203, 2982, 2938, 1588, 1508, 1473, 1434, 1313, 1219, 1179, 1138, 1058, 980, 850, 781, 658, 620 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_9ClO_2$ $[M]^+$: 172.0291, found 172.0294



1 4

4,4-Dichloro-3-ethoxycyclohex-2-enone (4). An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with 3-ethoxycyclohex-2-enone (**1**, 140.2 mg, 1.00 mmol, 1.00 equiv), hexamethylphosphoramide (HMPA, 435 μL, 448 mg, 2.50 mmol, 2.50 equiv), and dry THF (5 mL) and then cooled to 0 °C in an ice/water bath. A solution of LiHMDS (1.00 M in THF, 2.20 mL, 2.20 equiv) was added dropwise over 3 min. After stirring the mixture for 1 h, the reaction system was cooled to –78 °C. A solution of tosyl chloride (400. mg, 2.10 mmol, 2.10 equiv) in THF (3.0 mL, then the vial was rinsed with 1.0 mL

and added to the reaction) was added dropwise over 10 min. After 20 min at –78 °C, the reaction was quenched with a saturated aq NH_4Cl solution (20 mL) and then EtOAc (20 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 8:1 hexanes/EtOAc) to afford the product as a white solid (172 mg, 82% yield). (*Note:* The product slowly decomposed during workup and chromatography.)

TLC (SiO_2) R_f = 0.40 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

mp 72–74 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 2.88 (t, *J* = 6.3 Hz, 2H), 2.63 (m, 2H), 1.46 (t, *J* = 7.0 Hz, 3H)

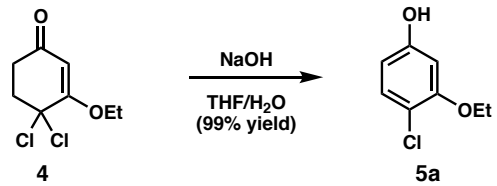
^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7, 169.1, 102.0, 81.8, 66.0, 43.2, 35.0, 13.7

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 98.0

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 98.1, 65.4 (–), 41.3 (–), 28.0 (–), 14.0

IR (neat) 3058, 2987, 2939, 1660, 1598, 1467, 1409, 1444, 1374, 1342, 1287, 1224, 1186, 1125, 1034, 1017, 990, 951, 926, 822, 797, 742, 639, 602, 566 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_{10}Cl_2O_2$ $[M]^+$: 208.0058, found 208.0055



4-Chloro-3-ethoxyphenol (5a). To a solution of 4,4-dichloro-3-ethoxycyclohex-2-enone (**SI17**, 20.9 mg, 0.100 mmol, 1.00 equiv) in THF (1 mL) was added a 2 M NaOH solution (aq, 0.2 mL,

0.4 mmol, 4 equiv) and the mixture was stirred at room temperature for 2 h. When TLC indicated complete consumption of the substrate, the mixture was cooled to 0 °C and a 1 M HCl solution was added dropwise until a pH ~2 was achieved. Ethyl acetate (5 mL) was added, and then the phases were separated and the aqueous phase was then extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (SiO_2, 4:1 hexanes/EtOAc) to give the product (**2a**) in quantitative yield as white solid (18 mg, >99% yield).

Characterization data for the chlororesorcinols appear below.

5.2.2. General Procedures

General Procedure for preparation of 1 M LiHMDS in THF or toluene:[58]

An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with dry solvent (THF or toluene, 9.5 mL) and 1,1,1,3,3,3-hexamethyldisilazane (distilled over NaH, 5.50 mL, 26.3 mmol, 1.05 equiv) and then cooled in an ice/water bath. A solution of *n*-butyllithium (2.50 M in hexane, 10.0 mL, 25.0 mmol, 1.00 equiv) was added dropwise via syringe over 5–10 min and the resulting mixture was stirred at 0 °C for 20 min. Portions of this solution are then transferred to separate reaction flasks via syringe.

NOTE: Commercially available solutions of LiHMDS in THF (Aldrich) may also be used with no decrease in reaction yield.

General Procedure A (Procedure for 4-haloresorcinols, Conditions A, Scheme 28):

An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with substrate ketone (1.00 mmol, 1.00 equiv), hexamethylphosphoramide (HMPA, 435 μL, 448 mg, 2.50 mmol, 2.50 equiv), and dry THF (5 mL) and then cooled to 0 °C in an ice/water bath. A solution of LiHMDS (1.00 M in THF, 3.00 mL, 3.00 equiv) was added dropwise over 3 min. After stirring the mixture for 1 h, the reaction system was cooled to –78 °C. A solution of tosyl halide (2.10 mmol, 2.10 equiv) in THF (3.0 mL, then the vial was rinsed with 1.0 mL and added to the reaction) was added dropwise over 10 min. After 30 min at –78 °C, a solution of LiHMDS (1.00 M in THF, 1.00 mL) was added dropwise over 1 min. When the addition was complete, the mixture was warmed to room temperature over 20 min at which time TLC indicated complete consumption of the dihalogenated intermediate (R_f ~0.3 in 4:1 hexanes/EtOAc, visualized with *p*-anisaldehyde stain). The reaction was quenched with a saturated aq NH_4Cl solution (10 mL) and then EtOAc (20 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

General Procedure B (Procedure for 6-chlororesorcinols, Conditions B, Scheme 28):

An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with a solution of LiHMDS (1.00 M in THF, 3.00 mL, 3.00 equiv), dry THF (3.0 mL), and dry pentane (6.0 mL) and then cooled to –78 °C. After stirring the mixture for 10 min, a solution of substrate ketone (1.00 mmol, 1.00 equiv) in THF (2.0 mL) was added dropwise over 3 min. Stirring was continued for 30 min at –78 °C. A solution of tosyl chloride (400 mg, 2.10 mmol, 2.10 equiv) in THF (3.0 mL, then the vial was rinsed with 1.0 mL and added to the reaction) was added dropwise over 10 min. Stirring was continued for 30 min at –78 °C and then a solution of LiHMDS (1.00 M in THF, 1.00 mL, 1.00 equiv) was added dropwise over 1 min. When the addition was complete, the mixture was warmed to room temperature over 20 min. The mixture was stirred at room temperature for an addition 30 min at which time TLC indicated complete consumption of the dihalogenated intermediate (R_f ~0.4 in 8:1 hexanes/EtOAc, visualized with *p*-anisaldehyde stain). The reaction was quenched by addition of 1.0 M aq HCl solution (10 mL) and then EtOAc (20 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

General Procedure C (Procedure for 6-bromo- or 6-iodoresorcinols, Conditions C, Scheme 28):

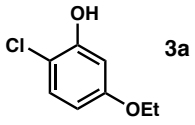
An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with a solution of LiHMDS (1.00 M in toluene, 3.00 mL, 3.00 equiv) and dry toluene (10 mL) and then cooled to –78 °C. After stirring the mixture for 10 min, a solution of substrate ketone (1.00 mmol, 1.00 equiv) in toluene (2.0 mL) was added dropwise over 3 min. Stirring was continued for 30 min at –78 °C. A solution of tosyl halide (2.10 mmol, 2.10 equiv) in toluene (3.0 mL, then the vial was rinsed with 1.0 mL and added to the reaction) was added dropwise over 10 min. Stirring was continued for 30 min at –78 °C, and then a solution of LiHMDS (1.00 M in toluene, 1.00 mL, 1.00 equiv) was added dropwise over 1 min. The mixture was warmed to room temperature over 20 min. THF (5.0 mL) was added, and then the reaction was maintained at room temperature for 30 min at which time TLC indicated complete consumption of the dihalogenated intermediate (R_f ~0.4 in 8:1 hexanes/EtOAc, visualized with *p*-anisaldehyde stain). The reaction was quenched by addition of 1 M aq HCl solution (10 mL) and then EtOAc (20 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

NOTE: Elimination is sluggish if THF is not added after warming the reaction mixture.

General Procedure D (one-pot aromatization/phenoxide trapping, Scheme 4):

An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with substrate ketone (1.00 mmol, 1.00 equiv) and HMPA (435 μL, 448 mg, 2.50 mmol, 2.50 equiv) and dry THF (5.0 mL) and then cooled to 0 °C in an ice/water bath. A solution of LiHMDS (1.00 M in THF, 3.00 mL, 3.00 equiv) was added dropwise over 3 min. After stirring for 1 h, the reaction mixture was cooled to –78 °C. A solution of tosyl halide (2.10 mmol, 2.10 equiv) in THF (3.0 mL, then the vial was rinsed with 1.0 mL and added to the reaction) was added dropwise over 10 min. Stirring was continued for 30 min at –78 °C, and then a solution of LiHMDS (1.00 M in THF, 1.00 mL, 1.00 equiv) was added dropwise. When the addition was complete, the mixture was warmed to room temperature over 20 min. The mixture was maintained at room temperature for 30 min at which point TLC indicated the dihalogenated vinylogous ester intermediate was consumed (for γ,γ-dihalogenated intermediate: R_f ~0.3 in 4:1 hexanes/EtOAc; for α,α-dihalogenated intermediate: R_f ~0.4 in 8:1 hexanes/EtOAc). The trapping electrophile (2.10 mmol, 2.10 equiv) was added in one portion. The reaction was stirred at room temperature for another 2 h when TLC indicated complete consumption of the phenol intermediate (visualized with $KMnO_4$ stain), the reaction was quenched with a saturated aq NH_4Cl solution (10 mL) and then EtOAc (20 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

5.2.3. Experimental Data for 4-Haloresorcinols



3a

2-Chloro-5-ethoxyphenol (3a): The title compound was prepared according to General Procedure B, using 3-ethoxycyclohex-2-enone (140.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 167 mg (97% yield)

2nd run: 166 mg (97% yield)

TLC (SiO_2) R_f = 0.40 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 36–38 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.9 Hz, 1H), 6.58 (d, J = 2.8 Hz, 1H), 6.44 (dd, J = 8.9, 2.8 Hz 1H), 5.52 (s, 1H), 3.98 (q, J = 7.0 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H)

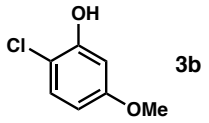
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 151.9, 129.0, 111.2, 108.2, 102.2, 63.8, 14.7

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 128.8, 108.4, 102.2

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 128.8, 108.4, 102.2, 63.9 (–), 14.7

IR (neat) 3527, 3203, 2982, 2938, 1588, 1508, 1473, 1434, 1313, 1219, 1179, 1138, 1058, 980, 850, 781, 658, 620 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_9ClO_2$ $[M]^+$: 172.0291, found 172.0294



3b

2-Chloro-5-methoxyphenol (**3b):** The title compound was prepared according to General Procedure B, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 153 mg (95% yield)

2nd run: 156 mg (99% yield)

TLC (SiO_2) R_f = 0.36 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.9 Hz, 1H), 6.59 (d, J = 2.9 Hz, 1H), 6.45 (dd, J = 8.9, 2.8 Hz, 1H), 5.56 (s, 1H), 3.77 (s, 3H)

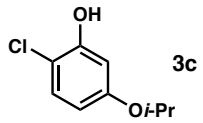
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 152.0, 129.0, 111.4, 107.7, 101.7, 55.5

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 128.8, 108.2, 102.2

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 128.8, 108.2, 102.2, 63.7 (–), 14.8

IR (neat) 3441, 2941, 2837, 1587, 1488, 1465, 1297, 1253, 1205, 1191, 1148, 1065, 1021, 953, 834, 787, 735, 695, 632 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_7H_7ClO_2$ $[M]^+$: 158.0135, found 158.0137



2-Chloro-5-isopropoxyphenol (3c). The title compound was prepared according to General Procedure B, using 3-isopropoxycyclohex-2-en-1-one (154.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 183 mg (98% yield)

2nd run: 182 mg (98% yield)

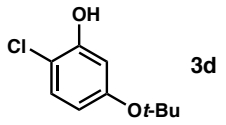
TLC (SiO_2) R_f = 0.37 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.8 Hz, 1H), 6.58 (d, J = 2.8 Hz, 1H), 6.43 (dd, J = 8.8, 2.8 Hz, 1H), 5.51 (s, 1H), 4.47 (septet, J = 6.0 Hz, 1H), 1.32 (d, J = 6.1 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 151.9, 129.0, 111.1, 109.5, 103.5, 70.3, 21.9

IR (neat) 3443, 2977, 2933, 1585, 1487, 1384, 1373, 1295, 1148, 1132, 1109, 984, 923, 833, 791, 665, 623 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_{11}ClO_2$ $[M]^+$: 186.0448, found 186.0449.



3d

5-(*tert*-Butoxy)-2-chlorophenol (3d). The title compound was prepared according to General Procedure C, using 3-(*tert*-butoxy)cyclohex-2-enone (168.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 186 mg (93% yield)

2nd run: 187 mg (94% yield)

TLC (SiO_2) R_f = 0.45 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 68–70 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.53 (dd, J = 8.7, 2.6 Hz, 1H), 5.53 (s, 1H), 1.34 (s, 9H)

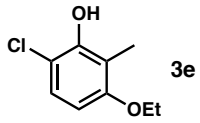
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 151.4, 128.4, 117.3, 114.4, 111.9, 109.5, 79.1, 28.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 128.8, 117.7, 112.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 128.8, 117.7, 112.3, 29.2

IR (neat) 3301, 2982, 2935, 1587, 1500, 1454, 1414, 1396, 1367, 1295, 1262, 1245, 1206, 1177, 1141, 1125, 1057, 974, 874, 840, 817, 776, 704, 682, 585 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{10}H_{13}ClO_2$ $[M]^+$: 200.0604, found 200.0605



3e

6-Chloro-3-ethoxy-2-methylphenol (3e). The title compound was prepared according to General Procedure B, using 3-ethoxy-2-methylcyclohex-2-enone (154.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 165 mg (89% yield)

2nd run: 171 mg (92% yield)

TLC (SiO_2) R_f = 0.54 in 11% EtOAc in hexanes, $KMnO_4$ stain

mp 50–52 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.7 Hz, 1H), 6.51 (d, J = 8.7 Hz, 1H), 5.21 (s, 1H), 3.98 (q, J = 7.0 Hz, 2H), 2.19 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H)

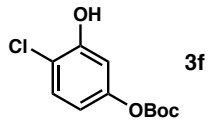
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 127.0, 119.8, 119.5, 111.4, 69.1, 15.5, 9.5

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 127.0, 111.4

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 127.0, 111.4, 69.3 (–), 15.5, 9.5

IR (neat) 3391, 3257, 2981, 2924, 1596, 1505, 1465, 1395, 1364, 1333, 1292, 1272, 1237, 1187, 1174, 1112, 1077, 1024, 946, 868, 850, 804, 764, 719, 707, 602, 572 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_{11}ClO_2$ $[M]^+$: 186.0448, found 186.0448



3f

***tert*-Butyl (4-chloro-3-hydroxyphenyl) carbonate (3f).** The title compound was prepared according to General Procedure B, using *tert*-butyl (3-oxocyclohex-1-en-1-yl) carbonate (212.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 3% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 242 mg (99% yield)

2nd run: 240 mg (98% yield)

TLC (SiO_2) R_f = 0.60 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 70–72 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 2.7 Hz, 1H), 6.72 (dd, J = 8.8, 2.7 Hz, 1H), 5.69 (s, 1H), 1.55 (s, 9H)

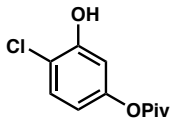
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 151.4, 150.7, 129.1, 116.9, 114.3, 109.7, 84.0, 27.6

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 129.0, 114.4, 109.7

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 129.0, 114.4, 109.7, 27.9

IR (neat) 3397, 2982, 1732, 1605, 1588, 1481, 1455, 1394, 1368, 1300, 1278, 1254, 1203, 1141, 1121, 1060, 1046, 1022, 957, 881, 854, 815, 795, 781, 699, 656, 608 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{11}H_{13}ClO_4$ $[M]^+$: 244.0502, found 244.0503



3g

4-Chloro-3-hydroxyphenyl pivalate (3g). The title compound was prepared according to General Procedure B, using 3-oxocyclohex-1-en-1-yl pivalate (196.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 193 mg (85% yield)

2nd run: 198 mg (87% yield)

TLC (SiO_2) R_f = 0.52 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 63–65 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 2.6 Hz, 1H), 6.60 (dd, J = 8.7, 2.6 Hz, 1H), 5.75 (s, 1H), 1.34 (s, 9H)

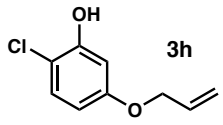
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 151.9, 150.8, 116.8, 114.6, 109.9, 39.1, 27.0

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 128.8, 114.7, 109.9

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 128.8, 114.7, 109.9, 27.1

IR (neat) 3399, 2979, 2935, 2872, 1726, 1606, 1588, 1500, 1471, 1456, 1423, 1394, 1370, 1341, 1286, 1199, 1151, 1130, 1118, 1053, 1025, 968, 903, 858, 792, 765, 670, 595, 574 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{11}H_{13}ClO_3$ $[M]^+$: 228.0553, found 228.0555



5-(Allyloxy)-2-chlorophenol (3h). The title compound was prepared according to General Procedure B, using 3-(allyloxy)cyclohex-2-enone (152.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 9% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 182 mg (99% yield)

2nd run: 179 mg (97% yield)

TLC (SiO_2) R_f = 0.40 in 14% EtOAc in hexanes, *p*-anisaldehyde stain

mp 29–31 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 2.6 Hz, 1H), 6.47 (dd, J = 8.8, 2.4 Hz, 1H), 6.03 (ddd, J = 16.0, 10.3, 5.3 Hz, 1H), 5.55 (s, 1H), 5.41 (d, J = 17.3 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 4.49 (d, J = 5.1 Hz, 2H)

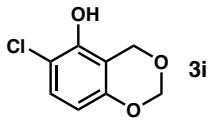
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 151.9, 132.8, 129.0, 117.9, 111.5, 108.4, 102.6, 69.1

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 132.9, 129.2, 108.4, 102.6

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 132.9, 129.2, 118.0 (–), 108.4, 102.6, 69.0 (–)

IR (neat) 3513, 3085, 2920, 1589, 1487, 1460, 1423, 1299, 1251, 1142, 1060, 996, 926, 833, 786, 677, 624 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_9ClO_2$ $[M]^+$: 184.0291, found 184.0292



3i

6-Chloro-4H-benzo[d][1,3]dioxin-5-ol (3i). The title compound was prepared according to General Procedure B, using 7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one[60] (154.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 171 mg (92% yield)

2nd run: 167 mg (90% yield)

TLC (SiO_2) R_f = 0.30 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 94–96 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 5.62 (s, 1H), 5.21 (s, 2H), 4.88 (s, 2H)

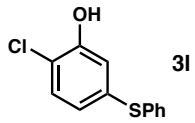
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 147.3, 127.1, 111.4, 109.8, 109.7, 90.9, 63.1

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 127.6, 110.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 127.6, 110.0, 91.4 (–), 63.6 (–)

IR (neat) 3450, 2953, 2872, 1614, 1603, 1458, 1371, 1322,1296, 1272, 1230, 1081, 1032, 948, 851, 787, 743, 720, 696, 621 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_7ClO_3$ $[M]^+$: 186.0084, found 186.0085



3l

2-Chloro-5-(phenylthio)phenol (3l). The title compound was prepared according to General Procedure B, using 3-(phenylthio)cyclohex-2-enone (204.3 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 216 mg (91% yield)

2nd run: 208 mg (88% yield)

TLC (SiO_2) R_f = 0.55 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.33 (m, 3H), 7.22 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 6.82 (dd, J = 8.4, 2.2 Hz, 1H), 5.56 (s, 1H)

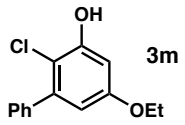
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 137.3, 134.2, 132.2, 129.4, 129.3, 127.8, 122.8, 118.3, 117.4

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 132.2, 129.4, 129.3, 127.8, 122.8, 117.4

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 132.2, 129.4, 129.3, 127.8, 122.8, 117.4

IR (neat) 3511, 3058, 1702, 1567, 1472, 1439, 1402, 1295, 1187, 1081, 1042, 1023, 902, 858, 799, 739, 701, 688, 606, 578 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{14}H_{13}ClO_2$ $[M]^+$: 236.0063, found 236.0066



2-chloro-5-ethoxy-[1,1'-biphenyl]-3-ol (3m). The title compound was prepared according to General Procedure B, using 5-ethoxy-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (216.3 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 234 mg (94% yield)

2nd run: 229 mg (92% yield)

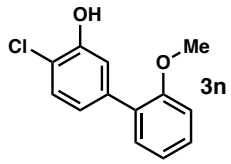
TLC (SiO_2) R_f = 0.42 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 5H), 6.64 (d, J = 2.9 Hz, 1H), 6.54 (d, J = 2.9 Hz, 1H), 5.82 (s, 1H), 4.04 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 152.4, 141.4, 139.1, 129.2, 128.1, 127.8, 110.3, 109.9, 101.2, 63.8, 14.7

IR (neat) 3507, 2979, 2930, 1598, 1584, 1574, 1464, 1417, 1395, 1371, 1298, 1202, 1172, 1151, 111, 1089, 1032, 1007, 844, 818, 765, 698, 678, 646, 615cm^{-1}

HRMS (EI$^+$) *m/z* calc'd for $C_{14}H_{13}ClO_2$ $[M+H]^+$: 249.0682, found 249.0675.



4-chloro-2'-methoxy-[1,1'-biphenyl]-3-ol (3n). The title compound was prepared according to General Procedure B, using 2'-methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (216.3 mg, 1.00

mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 230 mg (98% yield)

2nd run: 225 mg (96% yield)

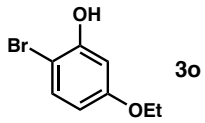
TLC (SiO_2) R_f = 0.50 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.25 (d, J = 2.0 Hz, 1H), 7.05 (m, 3H), 5.57 (s, 1H), 3.84

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 150.8, 139.1, 130.6, 129.2, 129.1, 128.4, 122.7, 120.8, 118.5, 117.4, 111.3, 55.5

IR (neat) 3409, 2930, 2833, 1590, 1580, 1568, 1500, 1487, 1477, 1409, 1354, 1311, 1293, 1258, 1231, 1213, 1116, 1060, 1044, 1015, 933, 901, 879, 863, 852, 813, 785, 752, 743, 712, 636, 589, 559 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{13}H_{11}ClO_2$ $[M]^+$: 234.0448, found 234.0450.



3o

2-Bromo-5-ethoxyphenol (3o). The title compound was prepared according to General Procedure C, using 3-ethoxycyclohex-2-enone (140.2 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a yellow oil.

1st run: 206 mg (96% yield)

2nd run: 199 mg (92% yield)

TLC (SiO_2) R_f = 0.40 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 6.40 (dd, *J* = 8.8, 2.6 Hz, 1H), 5.58 (s, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H)

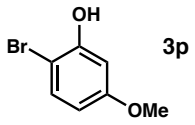
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 152.9, 131.9, 108.9, 102.2, 100.7, 63.8, 14.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 132.2, 109.4, 102.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 132.2, 109.4, 102.6, 64.2 (–), 15.2

IR (neat) 3399, 2980, 1703, 1667, 1589, 1488, 1470, 1441, 1421, 1379,1297, 1253, 1192, 1148, 1115, 1047, 1025, 979, 846, 804, 698, 636, 590 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_9BrO_2$ $[M]^+$: 215.9786, found 215.9790



3p

2-Bromo-5-methoxyphenol (3p). The title compound was prepared according to General Procedure C, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 193 mg (95% yield)

2nd run: 189 mg (93% yield)

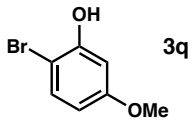
TLC (SiO_2) R_f = 0.44 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.9 Hz, 1H), 6.60 (d, *J* = 2.8 Hz, 1H), 6.42 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.49 (s, 1H), 3.77 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 152.9, 131.9, 108.4, 101.6, 100.8, 55.5

IR (neat) 3491, 2938, 2836, 1587, 1486, 1325, 1268, 1252, 1205, 1148, 1118, 1051, 1015, 952, 832, 785, 732, 691, 601 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_7H_7BrO_2$ $[M]^+$: 201.9629, found 201.9631



2-Bromo-5-isopropoxyphenol (3q). The title compound was prepared according to General Procedure C, using 3-isopropoxycyclohex-2-enone (154.2 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 203 mg (88% yield)

2nd run: 196 mg (85% yield)

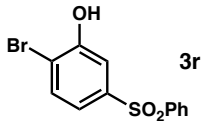
TLC (SiO_2) R_f = 0.46 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 1H), 6.59 (d, J = 2.7 Hz, 1H), 6.40 (dd, J = 8.8, 2.7 Hz, 1H), 5.49 (s, 1H), 4.48 (septet, J = 6.1 Hz, 1H), 1.32 (d, J = 6.1 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 152.9, 131.9, 110.1, 103.4, 100.5, 70.3, 21.9

IR (neat) 3499, 2976, 2932, 1581, 1482, 1419, 1384, 1373, 1293, 1252, 1182, 1147, 1128, 1108, 984, 922, 832, 788, 746, 693, 639 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_{11}BrO_2$ $[M]^+$: 229.9942, found 229.9944.



2-Bromo-5-(phenylsulfonyl)phenol (3r). The title compound was prepared according to General Procedure C, using 3-(phenylsulfonyl)cyclohex-2-en-1-one [59] (216.3 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 14% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 277 mg (88% yield)

2nd run: 286 mg (91% yield)

5 mmol scale procedure:

An oven-dried 250 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with a solution of LiHMDS (1.00 M in toluene, 15.0 mL, 3.00 equiv) and dry toluene (50 mL) and then cooled to –78 °C in an immersion bath. After 10 min, a solution of 3-ethoxycyclohex-2-enone (700.9 mg, 5.00 mmol, 1.00 equiv), in dry toluene (10 mL) was added dropwise over 10 min. After stirring the mixture for 30 min, a solution of tosyl bromide (2.47 g, 10.5 mmol, 2.1 equiv) in toluene (20 mL, then the vial was rinsed with 5 mL and added to the reaction) was added dropwise over 30 min. Stirring was continued for 30 min at –78 °C, and then a solution of LiHMDS (1.00 M in toluene, 5.00 mL, 1.00 equiv) was added dropwise over 5 min. When the addition was complete the mixture was warmed to room temperature over 20 min and then dry THF (15 mL) was added. The reaction was stirred for 30 min at which time TLC indicated completion of the reaction (visualized with *p*-anisaldehyde stain). The reaction was quenched by addition of a 1.0 M aq HCl solution (30 mL) and then EtOAc (80 mL) was

added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 14% EtOAc in hexanes) to afford the desired product as a white solid (1.404 g, 89% yield).

TLC (SiO_2) R_f = 0.34 in 30% EtOAc in hexanes, $KMnO_4$ stain

mp 142–143 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 2H), 7.59 (m, 3H), 7.51 (m, 2H), 7.37 (dd, J = 8.3, 2.2 Hz, 1H), 6.03 (s, 1H)

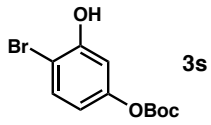
^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 142.5, 140.9, 133.5, 133.1, 129.4, 127.7, 120.5, 116.0, 115.2

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 133.6, 133.2, 130.0, 129.2, 127.6, 122.3

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 133.6, 133.2, 130.0, 129.2, 127.6, 122.3

IR (neat) 3371, 3064, 2923, 1593, 1573, 1480, 1447, 1404, 1355, 1305, 1285, 1264, 1206, 1151, 1125, 1101, 1073, 1030, 997, 913, 864, 808, 759, 726, 695, 684, 618, 589 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{12}H_9BrO_3S$ $[M]^+$: 311.9456, found 311.9454



3s

4-bromo-3-hydroxyphenyl *tert*-butyl carbonate (3s). The title compound was prepared according to General Procedure C, using *tert*-butyl (3-oxocyclohex-1-en-1-yl) carbonate (212.2 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 263 mg (91% yield)

2nd run: 267 mg (92% yield)

TLC (SiO_2) R_f = 0.5 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 58–60 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 1H, J = 8.7 Hz), 6.87 (d, J = 2.7 Hz, 1H), 6.68 (dd, J = 8.7, 2.7 Hz, 1H), 5.63 (s, 1H), 1.55 (s, 9H)

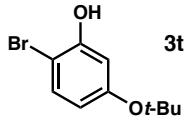
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 151.5, 151.3, 132.0, 114.9, 109.6, 106.8, 84.0, 27.6

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 132.1, 114.9, 109.5

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 132.1, 114.9, 109.5, 27.7

IR (neat) 3422, 2985, 1743, 1597, 1473, 1456, 1395, 1370, 1252, 1166, 1136, 1111, 1052, 1034, 1024, 957, 880, 846, 804, 780, 743, 726, 632, 602 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{11}H_{13}BrO_4$ $[M]^+$: 287.9997, found 288.0002



3t

2-Bromo-5-(tert-butoxy)phenol (3t). The title compound was prepared according to General Procedure C, using 3-(tert-butoxy)cyclohex-2-en-1-one (168.3 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 203 mg (88% yield)

2nd run: 196 mg (85% yield)

TLC (SiO_2) R_f = 0.50 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

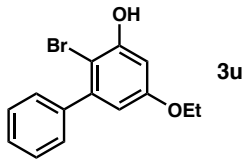
mp 68–69 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 1H), 6.70 (d, J = 2.7 Hz, 1H), 6.49 (dd, J = 8.7, 2.7 Hz, 1H), 5.44 (s, 1H), 1.35 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 152.3, 131.3, 117.8, 111.7, 104.1, 79.2, 28.8

IR (neat) 3262, 2981, 2933, 1589, 1495, 1456, 1410, 1395, 1367, 1344, 1263, 1205, 1141, 1117, 1035, 976, 872, 836, 807, 776, 701, 665, 596 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{10}H_{13}BrO_2$ $[M]^+$: 244.0099, found 244.0099.



3u

2-Bromo-5-ethoxy-[1,1'-biphenyl]-3-ol (3u). The title compound was prepared according to General Procedure C, using 5-ethoxy-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (216.3 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 6% EtOAc in hexanes), the title compound was isolated as a yellow oil.

1st run: 273 mg (93% yield)

2nd run: 268 mg (92% yield)

TLC (SiO_2) R_f = 0.58 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 5H), 6.64 (d, J = 2.9 Hz, 1H), 6.52 (d, J = 2.9 Hz, 1H), 5.79 (s, 1H), 4.03 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H)

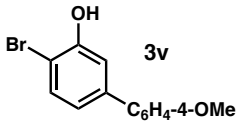
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 153.3, 143.5, 140.9, 129.1, 128.0, 127.7, 110.1, 101.9, 100.9, 63.8, 14.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 129.6, 128.3, 128.0, 110.4, 100.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 129.6, 128.3, 128.0, 110.4, 100.5, 63.5 (–), 15.0

IR (neat) 3488, 2978, 2929, 1595, 1574, 1499, 1460, 1370, 1348, 1259, 1202, 1173, 1151, 1110, 1059, 1023, 1005, 911, 843, 817, 764, 698, 671, 633, 602 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{14}H_{31}BrO_2$ $[M]^+$: 292.0099, found 292.0099



3v

4-Bromo-4'-methoxy-[1,1'-biphenyl]-3-ol (3v). The title compound was prepared according to

General Procedure C, using 4'-methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (168.3 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 268 mg (96% yield)

2nd run: 266 mg (96% yield)

TLC (SiO_2) R_f = 0.48 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

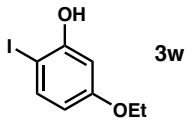
mp 126–127 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 3H), 7.22 (s, 1H), 7.01 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.98 (s, 1H), 6.96 (s, 1H), 5.54 (s, 1H), 3.85 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 152.3, 142.2, 132.2, 132.0, 128.0, 120.2, 114.2, 114.1, 108.5, 55.3

IR (neat) 3498, 3396, 2933, 2840, 1603, 1585, 1522, 1495, 1475, 1427, 1394, 1332, 1281, 1224, 1141, 1128, 1056, 1005, 896, 835, 800, 696, 595, 555 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{13}H_{11}BrO_2$ $[M]^+$: 277.9942, found 277.9942.



3w

2-Iodo-5-ethoxyphenol (3w). The title compound was prepared according to General Procedure C, using 3-ethoxycyclohex-2-enone (140.1 mg, 1.00 mmol) and tosyl iodide (592 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 240 mg (91% yield)

2nd run: 245 mg (93% yield)

TLC (SiO_2) R_f = 0.42 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

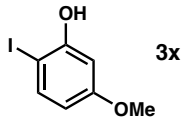
mp 70–72 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.8 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.31 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.34 (s, 1H), 4.48 (sept, *J* = 6.0 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 155.6, 137.9, 109.9, 101.4, 74.1, 63.7, 14.6

IR (neat) 3396, 2987, 2940, 1586, 1496, 1471, 1411, 1396, 1341, 1295, 1261, 1115, 1107, 1033, 1018, 986, 890, 837, 819, 802, 696, 636, 619 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_9IO_2$ $[M]^+$: 263.9647, found 263.9648.



3x

2-Iodo-5-methoxyphenol (3x). The title compound was prepared according to General Procedure C, using 3-methoxycyclohex-2-en-1-one (250.1 mg, 1.00 mmol) and tosyl iodide (592 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 230 mg (92% yield)

2nd run: 225 mg (90% yield)

TLC (SiO_2) R_f = 0.38 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

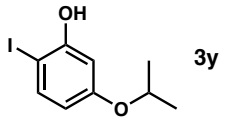
mp 63–65 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.8 Hz, 1H), 6.60 (d, *J* = 2.8 Hz, 1H), 6.34 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.27 (s, 1H), 3.77 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 155.6, 137.9, 109.4, 100.9, 74.4, 55.4

IR (neat) 3333, 3027, 2946, 2838, 1587, 1503, 1426, 1353, 1281, 1199, 1162, 1128, 1046, 1012, 938, 830, 784, 776, 733, 694, 642, 596, 555 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_7H_7IO_2$ $[M]^+$: 249.9491, found 249.9499.



3y

2-Iodo-5-isopropoxyphenol (3y). The title compound was prepared according to General Procedure C, using 3-isopropoxycyclohex-2-enone (154.2 mg, 1.00 mmol) and tosyl iodide (592 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 242 mg (87% yield)

2nd run: 240 mg (86% yield)

TLC (SiO_2) R_f = 0.30 in 11% EtOAc in hexanes, *p*-anisaldehyde stain

mp 35–37 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.8 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.31 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.34 (s, 1H), 4.48 (sept, *J* = 6.0 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 155.6, 138.0, 111.0, 102.7, 74.0, 70.2, 21.9

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.4, 111.5, 103.0, 70.7

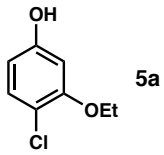
^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 138.4, 111.5, 103.0, 70.7, 22.6

IR (neat) 3551, 3469, 3043, 2976, 2938, 2720, 2594, 1583, 1498, 1413, 1383, 1372, 1309, 1253, 1228, 1189,1105, 1023, 995, 922, 831, 805, 628 cm^{-1}

HRMS (EI$^+$) *m/z* calc'd for $C_9H_{11}IO_2$ [M]$^+$: 277.9804, found 277.9808

5.2.4. Experimental Data for 4-Haloresorcinols

Substrates were synthesized by the previously reported methods,[54] unless otherwise stated.



5a

4-Chloro-3-ethoxyphenol (5a). The title compound was prepared according to General Procedure A, using 3-ethoxycyclohex-2-enone (140.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a white solid.

1st run: 158 mg (92% yield)

2nd run: 162 mg (94% yield)

3rd run: 158 mg (92% yield)

10 mmol scale procedure:

An oven-dried 250 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with 3-ethoxycyclohex-2-enone (1.40 g, 10.0 mmol, 1.00 equiv), hexamethylphosphoramide (HMPA, 4.35 mL, 4.48 g, 25.0 mmol, 2.50 equiv) and dry THF (60 mL) and then cooled to 0 °C in an ice/water bath. A solution of LiHMDS (1.00 M in THF, 30.0 mL, 3.00 equiv) was added dropwise over 25 min. After stirring the mixture for 1 h, the reaction system was cooled to –78 °C. A solution of tosyl chloride (4.00 g, 21.0 mmol, 2.10 equiv) in THF (30 mL, then the vial was rinsed with 10 mL and added to the reaction) was added dropwise over 40 min. Stirring was continued for 40 min at –78 °C, and then a solution of LiHMDS (1.00

M in THF, 10.0 mL, 1.00 equiv) was added dropwise over 10 min. When the addition was complete the mixture was warmed to room temperature over 20 min, at which time TLC indicated completion of the reaction (visualized with *p*-anisaldehyde stain). The reaction was quenched by addition of a saturated aq NH_4Cl solution (50 mL) and then EtOAc (150 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (1 x 50 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 10% EtOAc in hexanes) to afford the desired product as a white solid (1.694 g, 98% yield).

TLC (SiO_2) R_f = 0.34 in 20% EtOAc in hexane, *p*-anisaldehyde stain

mp 47–49 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.5 Hz, 1H), 6.45 (d, J = 2.7 Hz, 1H), 6.35 (dd, J = 8.5, 2.7 Hz, 1H), 5.00 (s, 1H), 4.05 (q, J = 7.0 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H)

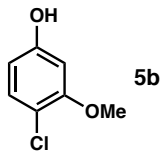
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 130.3, 114.4, 107.7, 101.5, 64.7, 14.6

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 130.2, 107.6, 101.5

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 129.9, 107.4, 101.5, 64.5 (–), 14.6

IR (neat) 3540, 3433, 3035, 2984, 2940, 2814, 1633, 1592, 1501, 1459, 1394, 1376, 1361, 1292, 1276, 1263, 1241, 1187, 1106, 1050, 1064, 1027, 987, 889, 821, 789, 658, 624 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_9ClO_2$ $[M]^+$: 172.0291, found 172.0291



5b

4-Chloro-3-methoxyphenol (**5b**). The title compound was prepared according to General Procedure A, using 3-methoxycyclohex-2-en-1-one (126.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a white solid.

1st run: 141 mg (89% yield)

2nd run: 144 mg (91% yield)

TLC (SiO_2) R_f = 0.33 in 20% EtOAc in hexane, *p*-anisaldehyde stain

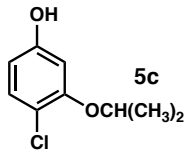
mp 90–91 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.5 Hz, 1H), 6.47 (d, J = 2.7 Hz, 1H), 6.37 (dd, J = 8.5, 2.7 Hz, 1H), 5.24 (s, 1H), 3.84 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 155.3, 130.3, 114.0, 107.9, 100.5, 56.1

IR (neat) 3477, 3015, 2936, 1611, 1590, 1487, 1470, 1457, 1424, 1317, 1298, 1270, 1228, 1196, 1166, 1157, 1136, 1062, 1021, 948, 930, 827, 798, 658, 625 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_7H_7ClO_2$ $[M]^+$ 158.0135, found 158.0136.



4-chloro-3-isopropoxyphenol (**5c**). The title compound was prepared according to General Procedure A, using 3-isopropoxycyclohex-2-en-1-one (154.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless oil.

1st run: 175 mg (94% yield)

2nd run: 171 mg (92% yield)

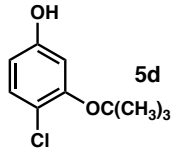
TLC (SiO_2) R_f = 0.40 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 1H), 6.47 (t, *J* = 2.7 Hz, 1H), 6.36 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.13 (s, 1H), 4.47 (septet, *J* = 6.0 Hz, 1H), 1.36 (d, *J* = 6.1 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 154.3, 130.4, 115.8, 108.3, 103.9, 72.3, 21.9

IR (neat) 3375, 2978, 2930, 1586, 1486, 1450, 1374, 1291, 1185, 1162, 1105, 1059, 996, 918, 828, 798, 701, 655 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_{11}ClO_2$ $[M]^+$: 186.0448, found 186.0452.



3-(*tert*-butoxy)-4-chlorophenol (**5d**). The title compound was prepared according to General Procedure A, using 3-(*tert*-butoxy)cyclohex-2-en-1-one (168.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexane), the title compound was isolated as a white solid.

1st run: 146 mg (73% yield)

2nd run: 138 mg (69% yield)

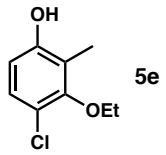
TLC (SiO_2) R_f = 0.50 in 5% EtOAc in CH_2Cl_2, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ) 7.17 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.51 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.21 (s, 1H), 1.39 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 152.0, 130.3, 120.6, 112.2, 111.8, 82.4, 28.7

IR (neat) 3341, 2924, 1711, 2599, 1493, 1454, 1375, 1284, 1260, 1238, 1155, 1055, 970, 834, 792, 743, 700, 647, 598 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{10}H_{13}ClO_2$ $[M]^+$: 200.0604, found 200.0614.



5e

4-chloro-3-ethoxy-2-methylphenol (5e). The title compound was prepared according to General Procedure A, using 3-ethoxy-2-methylcyclohex-2-enone (154.2 mg, 1.00 mmol) and tosyl chloride (400. mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 179 mg (96% yield)

2nd run: 174 mg (93% yield)

3rd run: 173 mg (93% yield)

TLC (SiO_2) R_f = 0.44 in 20% EtOAc in hexanes, $KMnO_4$ stain

mp 89–91 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.6 Hz, 1H), 6.51 (d, *J* = 8.6 Hz, 1H), 4.87 (s, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H)

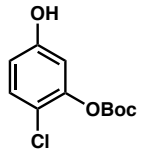
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 127.0, 119.7, 119.6, 111.4, 109.5, 69.0, 15.5, 9.4

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 127.4, 111.7

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 127.4, 111.7, 69.2 (–), 16.0, 10.0

IR (neat) 3313, 2979, 2925, 1589, 1478, 1454, 1388, 1362, 1320, 1219, 1109, 1075, 1021, 948, 888, 846, 814, 757, 715, 676, 653, 614 cm^{-1}

HRMS (EI$^+$) *m/z* calc'd for $C_9H_{11}ClO_2$ [M]$^+$: 186.0448, found 186.0452



5f

***tert*-Butyl (2-chloro-5-hydroxyphenyl) carbonate (5f).** The title compound was prepared according to General Procedure A, using *tert*-butyl (3-oxocyclohex-1-en-1-yl) carbonate (212.2 mg, 1.00 mmol) and tosyl chloride (400. mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 167 mg (68% yield)

2nd run: 164 mg (67% yield)

3rd run: 163 mg (67% yield)

TLC (SiO_2) R_f = 0.48 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

mp 95–97 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 2.8 Hz, 1H), 6.61 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.45 (s, 1H), 1.57 (s, 9H)

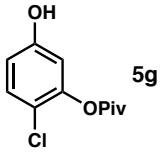
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 151.1, 147.3, 130.5, 118.2, 114.5, 111.0, 84.6, 27.6

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 130.9, 114.8, 111.4

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 130.9, 114.8, 111.4, 28.0

IR (neat) 3411, 3002, 2971, 2930, 1731, 1612, 1588, 1492, 1438, 1369, 1283, 1256, 1241, 1145, 1068, 951, 875, 851, 804, 778, 754, 650, 593 cm^{-1}

HRMS (EI$^+$) *m/z* calc'd for $C_{11}H_{13}ClO_4$ [M]$^+$: 244.0502, found 244.0505



5g

2-chloro-5-hydroxyphenyl pivalate (**5g**). The title compound was prepared according to General Procedure A, using 3-oxocyclohex-1-en-1-yl pivalate (196.3 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% Et_2O in CH_2Cl_2), the title compound was isolated as a white solid.

1st run: 119 mg (52% yield)

2nd run: 123 mg (54% yield)

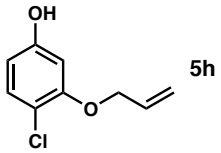
TLC (SiO_2) R_f = 0.50 in 5% EtOAc in CH_2Cl_2, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 1H), 6.61 (dd, J = 8.7, 2.8 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H), 5.50 (br. s, 1H), 1.39 (s, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 155.2, 147.5, 130.4, 118.1, 114.2, 111.1, 39.3, 27.1

IR (neat) 3396, 2962, 2925, 2853, 1727, 1601, 1484, 1455, 1365, 1396, 1328, 1299, 1284, 1162, 1139, 1127, 1055, 1030, 962, 937, 906, 809, 761, 693, 652, 599, 563 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{11}H_{13}ClO_3$ $[M]^+$: 228.0553, found 228.0553.



5h

3-(Allyloxy)-4-chlorophenol (5h). The title compound was prepared according to General Procedure A, using 3-(allyloxy)cyclohex-2-enone (152.2 mg, 1.00 mmol) and tosyl chloride

(400. mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 169 mg (92% yield)

2nd run: 168 mg (91% yield)

3rd run: 171 mg (93% yield)

TLC (SiO_2) R_f = 0.42 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 1H), 6.46 (d, *J* = 2.7 Hz, 1H), 6.37 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.05 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H), 5.46 (ddd, *J* = 17.3, 3.1, 1.6 Hz, 1H), 5.31 (ddd, *J* = 10.6, 2.8, 1.4 Hz, 1H), 4.98 (s, 1H), 4.56 (dt, *J* = 5.1, 1.5 Hz, 2H)

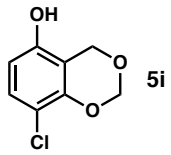
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 154.8, 132.4, 130.4, 118.0, 114.6, 108.1, 102.0, 69.7

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 132.4, 130.4, 108.1, 101.9

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 132.6, 130.4, 117.8 (–), 108.0, 102.0, 69.9 (–)

IR (neat) 3371, 2924, 1588, 1488, 1446, 1422, 1292, 1172, 1133, 1100, 1062, 1009, 929, 826, 795, 758, 658, 623, 563 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_9ClO_2$ $[M]^+$: 184.0291, found 184.0292.



5i

8-Chloro-4H-benzo[d][1,3]dioxin-5-ol (5i). The title compound was prepared according to General Procedure A, using 7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one[60] (154.2 mg, 1.00

mmol) and tosyl chloride (400. mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 142 mg (76% yield)

2nd run: 139 mg (75% yield)

3rd run: 138 mg (74% yield)

TLC (SiO_2) R_f = 0.58 in 20% EtOAc in hexanes, $KMnO_4$ stain

mp 162–164 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, J = 8.6 Hz, 1H), 6.31 (d, J = 8.6 Hz, 1H), 5.31 (s, 2H), 4.87 (s, 2H), 4.82 (s, 1H)

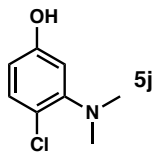
^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 149.2, 128.0, 113.2, 110.6, 91.5, 63.0

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 127.7, 107.4

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 127.7, 107.6, 91.3 (–), 62.6

IR (neat) 3343, 2925, 1619, 1604, 1492, 1473, 1459, 1443, 1408, 1342, 1291, 1224, 1202, 1160, 1132, 1063, 1031, 974, 920, 911, 781, 671, 640, 627, 595 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_7ClO_3$ $[M]^+$: 186.0084, found 186.0090



5j

4-chloro-3-(dimethylamino)phenol (**5j**). The title compound was prepared according to General Procedure A, using 3-(dimethylamino)cyclohex-2-en-1-one (139.2 mg, 1.00 mmol) and tosyl

chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 3% MeOH in CH_2Cl_2), the title compound was isolated as a white solid.

1st run: 90 mg (38% yield)

2nd run: 99 mg (42% yield)

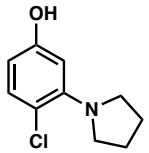
TLC (SiO_2) R_f = 0.42 in 3% MeOH in CH_2Cl_2, $KMnO_4$ stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.6 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 6.42 (dd, J = 8.6, 2.8 Hz, 1H), 5.91 (br. s, 1H), 2.75 (s, 6H); δ_C (126 MHz, CDCl3) 155.2, 151.0, 131.1, 119.3, 110.3, 107.6, 43.6

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 151.0, 131.1, 119.3, 110.3, 107.6, 43.6

IR (neat) 3168, 2956, 2791, 2670, 2601, 1595, 1497, 1478, 1446, 1408, 1306, 1244, 1148, 1120, 1049, 1035, 981, 884, 847, 804, 756, 706, 657, 638 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_{10}ClNO$ $[M+H]^+$: 172.0526, found 172.0529.



5k

4-chloro-3-(pyrrolidin-1-yl)phenol (**5k**). The title compound was prepared according to General Procedure A, using 3-(pyrrolidin-1-yl)cyclohex-2-enone**Error! Bookmark not defined.** (165.2 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 3% MeOH in CH_2Cl_2), the title compound was isolated as a white solid.

1st run: 185 mg (94% yield)

2nd run: 187 mg (95% yield)

3rd run: 186 mg (94% yield)

TLC (SiO_2) R_f = 0.55 in 1% MeOH in CH_2Cl_2, $KMnO_4$ stain

mp 61–63 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8 Hz, 1H), 6.23 (d, J = 2.7 Hz, 1H), 6.06 (dd, J = 8.8, 2.7 Hz, 1H), 5.40 (s, 1H), 3.23 (t, J = 6.5 Hz, 4H), 2.00 (comp. m, 4H)

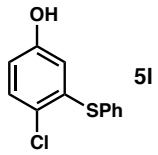
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 148.9, 131.7, 106.1, 98.8, 95.4, 47.7, 25.4

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 132.0, 107.7, 104.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 132.0, 107.7, 104.8, 51.4 (–), 25.5 (–)

IR (neat) 3249, 2964, 2867, 2510, 1588, 1567, 1501, 1486, 1460, 1420, 1348, 1300, 1272, 1214, 1175, 1156, 1052, 1034, 994, 912, 876, 814, 793, 780, 665, 629 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{10}H_{12}BrNO$ $[M]^+$: 242.0181, found 242.0174



5l

4-chloro-3-(phenylthio)phenol (**5l**). The title compound was prepared according to General Procedure A, using 3-(phenylthio)cyclohex-2-en-1-one (204.3 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a white solid.

1st run: 90 mg (38% yield)

2nd run: 99 mg (42% yield)

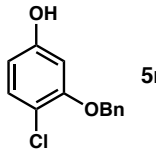
TLC (SiO_2) R_f = 0.52 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.41 (m, 3H), 7.22 (d, J = 8.6 Hz, 1H), 6.58 (dd, J = 8.6, 2.9 Hz, 1H), 6.33 (d, J = 2.9 Hz, 1H), 4.68 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.2, 134.1, 131.8, 130.4, 129.7, 128.8, 123.9, 115.7, 114.2

IR (neat) 3257, 2922, 1594, 1565, 1462, 1431, 1421, 1327, 1256, 1222, 1129, 1106, 1024, 930, 913, 893, 864, 807, 745, 796, 706, 685, 648cm^{-1}

HRMS (EI$^+$) *m/z* calc'd for $C_{12}H_9ClOS$ $[M]^+$: 236.0063, found 236.0068.



5m

3-(benzyloxy)-4-chlorophenol (5m). The title compound was prepared according to General Procedure A, using 3-(benzyloxy)cyclohex-2-enone (202.3 mg, 1.00 mmol) and tosyl chloride (400. mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 218 mg (93% yield)

2nd run: 223 mg (95% yield)

3rd run: 220 mg (94% yield)

TLC (SiO_2) R_f = 0.58 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

mp 65–66 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.50 (d, J = 2.5 Hz, 1H), 6.37 (dd, J = 2.5 Hz, J = 8.6 Hz, 1H), 5.12 (s, 2H), 4.84 (s, 1H)

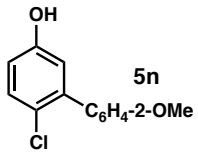
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 154.9, 136.2, 130.4, 128.6, 128.0, 127.0, 114.8, 108.2, 102.3, 70.7

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 130.4, 128.7, 128.0, 127.0, 108.2, 102.2

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 130.5, 128.6, 128.0, 127.0, 108.2, 102.3, 70.7 (–)

IR (neat) 3305, 3028, 2931, 1609, 1584, 1486, 1456, 1449, 1378, 1357, 1327, 1286, 1213, 1169, 1133, 1064, 1014, 1000, 965, 842, 826, 793, 767, 734, 692, 660, 616, 555 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{13}H_{11}ClO_2$ $[M]^+$: 234.0448, found 234.0450



4-chloro-3-(dimethylamino)phenol (**5n**). The title compound was prepared according to General Procedure A, using 2'-methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (202.3 mg, 1.00 mmol) and tosyl chloride (400 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexane), the title compound was isolated as a light yellow oil.

1st run: 87 mg (38% yield)

2nd run: 91 mg (39% yield)

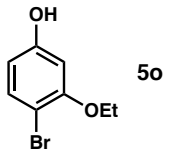
TLC (SiO_2) R_f = 0.38 in 10% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.30 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.23 (d, *J* = 2.0Hz, 1H), 7.04 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 5.53 (s, 1H), 3.82 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 150.7, 139.1, 130.6, 129.2, 129.0, 128.3, 122.7, 120.8, 117.3, 111.2, 109.5, 55.5

IR (neat) 3508, 2935, 2834, 1597, 1582, 1566, 1476, 1462, 1424, 1306, 1260, 1241, 1179, 1120, 1049, 1025, 900, 875, 812, 788, 751, 712, 639, 586, 561 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{13}H_{11}ClO_2$ $[M]^+$: 234.0448, found 234.0449.



5o

4-Bromo-3-ethoxyphenol (5o). The title compound was prepared according to General Procedure A, using 3-ethoxycyclohex-2-enone (140.2 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 191 mg (88% yield)

2nd run: 183 mg (85% yield)

3rd run: 187 mg (87% yield)

TLC (SiO_2) R_f = 0.36 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

mp 58–60 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 6.32 (dd, J = 8.5, 2.7 Hz, 1H), 4.97 (s, 1H), 4.04 (q, J = 7.0 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H)

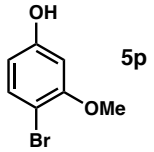
^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 155.9, 133.3, 108.4, 102.6, 101.3, 64.7, 14.6

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 133.6, 109.0, 101.0

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 133.1, 108.4, 101.2, 65.0 (–), 14.6

IR (neat) 3300, 2977, 2933, 2898, 1600, 1586, 1490, 1435, 1391, 1342, 1289, 1255, 1223, 1183, 1122, 1106, 1041,1025, 987, 815, 696, 633, 621 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_9BrO_2$ $[M]^+$: 215.9786, found 215.9789



4-Bromo-3-methoxyphenol (5p). The title compound was prepared according to General Procedure A, using 3-methoxycyclohex-2-enone (126.6 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 178 mg (88% yield)

2nd run: 175 mg (86% yield)

TLC (SiO_2) R_f = 0.35 in 20% EtOAc in hexane, *p*-anisaldehyde stain

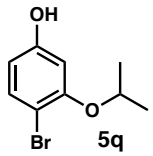
mp 85–86 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 1H), 6.46 (d, J = 2.7 Hz, 1H), 6.33 (dd, J = 8.5, 2.7 Hz, 1H), 4.92 (s, 1H), 3.86 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 156.0, 133.3, 108.4, 102.2, 100.3, 56.2

IR (neat) 3455, 2930, 1608, 1583, 1481, 1457, 1421, 1315, 1296, 1261, 1225, 1192, 1157, 1129, 1041, 1021, 947, 821, 791, 728, 622 cm^{-1}

HRMS (EI^+) *m/z* calc'd for for $C_7H_7BrO_2$ $[M]^+$: 201.9629, found 201.9631.



4-bromo-3-isopropoxyphenol (5q). The title compound was prepared according to General Procedure A, using 3-isopropoxycyclohex-2-en-1-one (154.2 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a light yellow oil.

1st run: 202 mg (88% yield)

2nd run: 204 mg (88% yield)

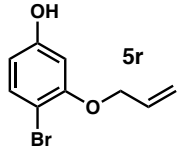
TLC (SiO_2) R_f = 0.50 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 2.5 Hz, 1H), 6.32 (dd, J = 8.5, 2.6 Hz, 1H), 4.84 (s, 1H), 4.50 (hept, J = 6.1 Hz, 1H), 1.38 (d, J = 6.1 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 155.3, 133.4, 108.7, 104.1, 103.3, 72.0, 22.0

IR (neat) 3374, 2977, 2925, 1582, 1481, 1449, 1384, 1373, 1291, 1264, 1185, 1104, 1035, 996, 918, 827, 796, 738, 698, 623, 607 cm^{-1}

HRMS (EI^+) *m/z* calc'd for for $C_9H_{11}BrO_2$ $[M]^+$: 229.9942, found 229.9951.



3-(Allyloxy)-4-bromophenol (5r). The title compound was prepared according to General Procedure A, using 3-(allyloxy)cyclohex-2-enone (152.2 mg, 1.00 mmol) and tosyl bromide (494

mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 193 mg (84% yield)

2nd run: 196 mg (86% yield)

3rd run: 198 mg (86% yield)

TLC (SiO_2) R_f = 0.40 in 11% EtOAc in hexanes

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 6.34 (dd, J = 8.5, 2.7 Hz, 1H), 6.04 (m, 1H), 5.48 (dd, J = 17.3, 1.5 Hz, 1H), 5.32 (dd, J = 10.6, 1.4 Hz, 1H), 4.97 (s, 1H), 4.56 (dt, J = 4.8, 1.5 Hz, 2H)

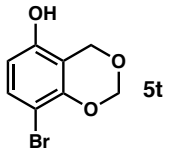
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 155.6, 133.4, 132.3, 118.0, 108.7, 102.8, 101.7, 69.6

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 133.4, 132.2, 109.2, 102.0

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 133.4, 132.2, 118.1 (–), 109.2, 102.0, 69.7 (–)

IR (neat) 3498, 2922, 1586, 1484, 1422, 1297, 1252, 1152, 1118, 1045, 999, 966, 926, 832, 783, 652, 642, 616, 607, 589, 681, 560, 552 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_9BrO_2$ $[M]^+$: 227.9786, found 227.9785



5t

8-Bromo-4H-benzo[d][1,3]dioxin-5-ol (**5t**). The title compound was prepared according to General Procedure A, using 4,6,7,8-tetrahydro-5*H*-benzo[*d*][1,3]dioxin-5-one (154.2 mg, 1.00

mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as white solid.

1st run: 199 mg (86% yield)

2nd run: 203 mg (88% yield)

TLC (SiO_2) R_f = 0.36 in 20% EtOAc in hexanes

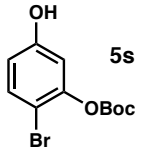
mp 158–159 °C

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.39 (d, J = 8.7 Hz, 1H), 5.27 (s, 2H), 4.71 (s, 2H)

^{13}C NMR (126 MHz, DMSO-d_6) δ 153.8, 150.0, 130.9, 111.2, 109.2, 98.5, 91.5, 63.0

IR (neat) 3349, 2949, 2922, 2870, 1615, 1599, 1487, 1470, 1455, 1443, 1407, 1338, 1287, 1260, 1225, 1197, 1158, 1122, 1063, 1030, 973, 917, 892, 779, 725, 700, 671, 601 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_7BrO_3$ $[M]^+$: 229.9579, found 229.9579.



2-bromo-5-hydroxyphenyl *tert*-butyl carbonate (5s). The title compound was prepared according to General Procedure A, using *tert*-butyl (3-oxocyclohex-1-en-1-yl) carbonate (221.2 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 211 mg (73% yield)

2nd run: 217 mg (75% yield)

TLC (SiO_2) R_f = 0.46 in 20% EtOAc in hexane, *p*-anisaldehyde stain

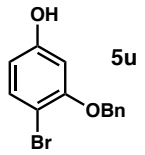
mp 106–107 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.54 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.67 (s, 1H), 1.58 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 151.2, 148.5, 133.4, 115.1, 106.4, 84.8, 27.6

IR (neat) 3411, 2999, 2968, 2926, 1731, 1607, 1587, 1487, 1452, 1437, 1395, 1373, 1367, 1283, 1256, 1239, 1206, 1146, 1059, 949, 875, 851, 776, 754, 728, 687, 591cm^{-1}

HRMS (EI^+) *m/z* calc'd for for $C_{11}H_{13}BrO_4$ $[M]^+$: 287.9997, found 288.001.



3-(benzyloxy)-4-bromophenol (5u). The title compound was prepared according to General Procedure A, using 3-(benzyloxy)cyclohex-2-en-1-one (202.3 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 245 mg (88% yield)

2nd run: 234 mg (84% yield)

TLC (SiO_2) R_f = 0.44 in 20% EtOAc in hexane, *p*-anisaldehyde stain

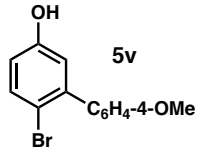
mp 50–52 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.36 (m, 4H), 6.48 (d, *J* = 2.6 Hz, 1H), 6.34 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.12 (s, 2H), 4.90 (s, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 155.7, 136.2, 133.4, 128.6, 127.9, 126.9, 109.0, 102.9, 102.2, 70.7

IR (neat) 3253, 2920, 2856, 1582, 1498, 1440, 1383, 1362, 1292, 1270, 1236, 1210, 1119, 1078, 1051, 1026, 975, 903, 821, 793, 731, 693, 636, 620 cm^{-1}

HRMS (EI^+) *m/z* calc'd for for $C_{13}H_{11}BrO_2$ $[M]^+$: 277.9942, found 277.9948.



6-bromo-4'-methoxy-[1,1'-biphenyl]-3-ol (5v). The title compound was prepared according to General Procedure A, using 4'-methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (202.3 mg, 1.00 mmol) and tosyl bromide (494 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 128 mg (46% yield)

2nd run: 123 mg (74% yield)

TLC (SiO_2) R_f = 0.52 in 20% EtOAc in hexane, *p*-anisaldehyde stain

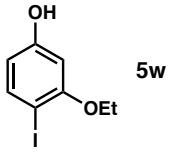
mp 67–68 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 1H), 7.34 (m, 2H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.02 (m, 3H), 5.55 (s, 1H), 3.83 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 151.7, 139.9, 131.4, 130.6, 129.1, 123.2, 120.9, 117.2, 111.3, 108.8, 55.5

IR (neat) 3499, 2935, 2834, 1702, 1582, 1561, 1498, 1473, 1435, 1420, 1401, 1374, 1305, 1258, 1240, 1179, 1120, 1056, 1040, 1023, 898, 873, 810, 788, 751, 707, 634, 582, 555 cm^{-1}

HRMS (EI^+) *m/z* calc'd for for $C_{13}H_{11}BrO_2$ $[M]^+$: 277.9942, found 277.9951.



5w

3-Ethoxy-4-iodophenol (5w). The title compound was prepared according to General Procedure A, using 3-ethoxycyclohex-2-enone (140.2 mg, 1.00 mmol) and tosyl iodide (592 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 194 mg (73% yield)

2nd run: 191 mg (72% yield)

3rd run: 185 mg (70% yield)

TLC (SiO_2) R_f = 0.40 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

mp 78–80 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 1H), 6.36 (d, *J* = 2.6 Hz, 1H), 6.25 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.24 (s, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H)

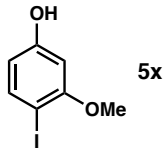
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 157.0, 139.3, 109.6, 100.7, 75.3, 64.9, 14.7

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 139.0, 109.2, 100.7

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 139.5, 109.8, 100.7, 65.3 (–), 14.7

IR (neat) 3237, 2976, 2932, 1600, 1572, 1482, 1453, 1394, 1348, 1287, 1272, 1173, 1125, 1106, 1038, 1017, 990, 892, 820, 801, 666, 627, 609, 576 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_9IO_2$ $[M]^+$: 263.9648, found 263.9649.



5x

3-Methoxy-4-iodophenol (5x). The title compound was prepared according to General Procedure A, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol) and tosyl iodide (592 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 175 mg (70% yield)

2nd run: 180 mg (72% yield)

TLC (SiO_2) R_f = 0.42 in 20% EtOAc in hexane, *p*-anisaldehyde stain

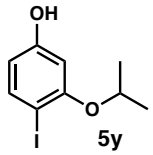
mp 90–91 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 6.26 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.00 (s, 1H), 3.84 (s, 3H); δ_C (126 MHz, $CDCl_3$) 159.1, 157.2, 139.3, 109.5, 99.7, 74.4, 56.2

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 157.2, 139.3, 109.5, 99.7, 74.4, 56.2

IR (neat) 3246, 2930, 1604, 1576, 1471, 1447, 1422, 1331, 1290, 1261, 1214, 1189, 1162, 1128, 1039, 1013, 946, 826, 800, 666, 626, 603 cm^{-1}

HRMS (EI$^+$) *m/z* calc'd for $C_7H_7IO_2$ [M]$^+$: 249.9491, found 249.9494.



5y

3-Isopropoxy-4-iodophenol (5y). The title compound was prepared according to General Procedure A, using 3-isopropoxycyclohex-2-en-1-one (154.2 mg, 1.00 mmol) and tosyl iodide (592 mg, 2.10 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a colorless oil.

1st run: 181 mg (65% yield)

2nd run: 175 mg (63% yield)

TLC (SiO_2) R_f = 0.44 in 20% EtOAc in hexane, *p*-anisaldehyde stain

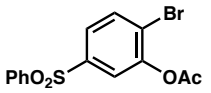
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 2.6 Hz, 1H) 6.25 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.28 (s, 1H), 4.46 (septet, *J* = 6.1 Hz, 1H), 1.37 (d, *J* = 6.1 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 156.9, 139.4, 109.9, 102.6, 77.1, 72.3, 22.0

IR (neat) 3346, 2976, 2929, 1700, 1575, 1474, 1441, 1384, 1373, 1288, 1261, 1184, 1164, 1122, 1103, 997, 917, 827, 793, 696, 628, 605 cm^{-1}

HRMS (EI$^+$) *m/z* calc'd for $C_7H_7IO_2$ [M]$^+$: 249.9491, found 249.9494.

5.2.5. Procedures and Experimental Data for Phenoxide Trapping Reactions



8

2-Bromo-5-(phenylsulfonyl)phenyl acetate (Scheme 8). A 25 mL round bottom flask was charged with 2-bromo-5-(phenylsulfonyl)phenol (**3r**, 31.3 mg, 0.100 mmol, 1.00 equiv) and 4-(dimethylamino)pyridine (0.6 mg, 0.005 mmol, 5 mol %), Et_3N (21 μL, 0.15 mmol, 1.5 equiv) and dichloromethane (6 mL). Acetic anhydride (11.3 μL, 0.120 mmol, 1.20 equiv) was added dropwise (*Note: slight exotherm*). The reaction mixture stirred at room temperature vented to air with a needle for 16 h. At this time, analysis by TLC indicated full conversion to a single new product. Water (5 mL) was added to the reaction mixture and the resulting biphasic mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were washed with brine (1 x 5 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 8:1 hexanes/EtOAc then 4:1 hexanes/EtOAc) to afford the ester product in as a white solid (31 mg, 87% yield).

TLC (SiO_2) R_f = 0.44 in 25% EtOAc in hexanes, *p*-anisaldehyde stain

mp 114–116 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.66 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 2.37 (s, 3H)

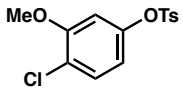
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 148.7, 142.1, 140.7, 134.4, 133.6, 129.5, 127.7, 126.1, 123.1, 122.6, 20.6

^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 134.4, 133.6, 129.5, 127.7, 126.2, 123.0

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 134.4, 133.6, 129.5, 127.7, 126.2, 123.0, 20.8

IR (neat) 3092, 1767, 1583, 1461, 1452, 1386, 1365, 1309, 1188, 1150, 1101, 1075, 1034, 1008, 959, 936, 891, 842, 823, 759, 738, 719, 692, 686, 662, 604, 583 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{14}H_{11}BrO_4S$ $[M]^+$: 353.9561, found 353.9574



9a

4-Chloro-3-methoxyphenyl 4-methylbenzenesulfonate (9a). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), and additional tosyl chloride (400. mg, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as white solid (271 mg, 87% yield).

TLC (SiO_2) R_f = 0.68 in 20% EtOAc in hexanes, $KMnO_4$ stain

mp 63–65 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 6.45 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.79 (s, 3H), 2.45 (s, 3H)

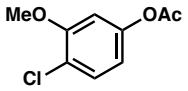
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 145.6, 130.2, 129.8, 128.6, 114.7, 107.1, 56.2, 21.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 130.7, 130.2, 129.0, 115.1, 107.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 130.7, 130.2, 129.0, 115.1, 107.5, 125.8, 22.2

IR (neat) 3087, 3008, 2948, 1598, 1577, 1487, 1442, 1406, 1371, 1296, 1272, 1212, 1189, 1177, 1136, 1119, 1091, 1066, 1033, 1026, 1017, 945, 859, 848, 821, 810, 791, 720, 705, 685, 656, 632, 612, 559 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{14}H_{13}ClO_4S[M]^+$: 312.0223, found 312.0229



9b

4-Chloro-3-methoxyphenyl acetate (9b). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), and acetyl chloride (AcCl, 0.15 mL, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After adding AcCl, the mixture was stirred at room temperature for 10 min and then quenched as described. After purification by flash chromatography (SiO_2, 1.2% EtOAc in hexanes), the title compound was isolated as a white solid (82% yield).

TLC (SiO_2) R_f = 0.42 in 5% EtOAc in hexanes, $KMnO_4$ stain

mp 35–37 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 8.5, 2.4 Hz, 1H), 3.88 (s, 3H), 2.30 (s, 3H)

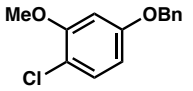
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 155.4, 150.0, 130.2, 119.5, 114.1, 106.2, 56.2, 21.1

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 130.7, 114.8, 106.7

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 130.7, 114.8, 106.7, 56.6, 21.4

IR (neat) 3090, 3021, 2957, 1758, 1600, 1584, 1484, 1469, 1444, 1407, 1370, 1277, 1251, 1205, 1189, 1148, 1065, 1025, 957, 886, 838, 811, 757, 708, 628, 604, 588 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_9ClO_3[M]^+$: 200.0240, found 200.0242



9c

4-(Benzyloxy)-1-chloro-2-methoxybenzene (9c). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), and benzyl bromide (BnBr, 359 mg, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After adding BnBr, the mixture stirred at room temperature for 10 min and then quenched as described. After purification by flash chromatography (SiO_2, 3% EtOAc in hexanes), the title compound was isolated as a white solid (142 mg, 57% yield).

TLC (SiO_2) R_f = 0.48 in 6% EtOAc in hexanes, $KMnO_4$ stain

mp 30–32 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 5H), 7.28 (d, J = 8.7 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.53 (dd, J = 8.7, 2.7 Hz, 1H), 5.05 (s, 2H), 3.86 (s, 3H)

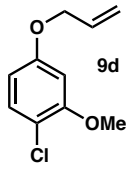
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 155.7, 136.6, 130.1, 128.7, 128.2, 127.6, 114.4, 106.1, 100.9, 70.4, 56.0

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 130.6, 129.1, 128.6, 128.0, 106.6, 101.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 130.6, 129.1, 128.6, 128.0, 106.6, 101.3, 70.7 (–), 56.2

IR (neat) 3084, 3014, 2980, 2936, 2873, 1880, 1587, 1490, 1453, 1445, 1407, 1381, 1306, 1280, 1171, 1193, 1130, 1064, 1009, 954, 912, 841, 819, 759, 727, 699, 680, 627 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{14}H_{13}ClO_2[M]^+$: 248.0604, found 248.0607



4-(Allyloxy)-1-chloro-2-methoxybenzene (9d). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (316.5 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), allyl bromide (254.1 mg, 2.10 mmol, 2.10 equiv) (354 mg, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After adding allyl bromide, the mixture stirred at room temperature for 10 min and then quenched as described. After purification by flash chromatography (SiO_2, 2.5% EtOAc in hexanes), the title compound was isolated as a light yellow oil (85 mg, 43% yield).

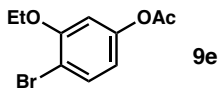
TLC (SiO_2) R_f = 0.44 in 5% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 1H), 6.53 (d, J = 2.7 Hz, 1H), 6.42 (dd, J = 8.7, 2.7 Hz, 1H), 6.03 (ddd, J = 17.2, 10.6, 5.3 Hz, 1H), 5.41 (dd, J = 17.2, 1.5 Hz, 1H), 5.30 (dd, J = 10.6, 1.4 Hz, 1H), 4.50 (dd, J = 5.3, 1.5 Hz, 2H), 3.85 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 155.6, 132.9, 130.0, 117.9, 114.2, 106.0, 100.7, 69.1, 56.0

IR (neat) 2939, 1735, 1583, 1490, 1463, 1447, 1424, 1408, 1306, 1280, 1258, 1198, 1166, 1126, 1068, 1023, 925, 832, 820, 787, 749, 685, 627 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{10}H_{11}ClO_2$ $[M]^+$: 198.0448, found 198.0448.



4-Bromo-3-ethoxyphenyl acetate (9e). A 25 mL round bottom flask was charged with 4-bromo-3-ethoxyphenol (**5o**, 259 mg, 1.00 mmol, 1.00 equiv) and 4-(dimethylamino)pyridine (6

mg, 0.05 mmol, 5 mol %), Et_3N (209 μL, 1.50 mmol, 1.50 equiv) and dichloromethane (10 mL). Acetic anhydride (113 μL, 1.20 mmol, 1.20 equiv) was added dropwise (*Note: slight exotherm*). The reaction mixture stirred at room temperature vented to air with a needle for 20 h. At this time, analysis by TLC indicated full conversion to a single new product. Water (10 mL) was added to the reaction mixture and the resulting biphasic mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 20:1 hexanes/EtOAc) to afford the ester product in as a white solid (232 mg, 90% yield).

TLC (SiO_2) R_f = 0.54 in 10% EtOAc in hexanes, $KMnO_4$ stain

mp 32–34 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 6.59 (dd, J = 8.5, 2.4 Hz, 1H), 4.05 (q, J = 7.0 Hz, 2H), 2.27 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H)

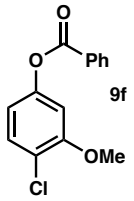
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 155.8, 150.7, 133.2, 114.6, 108.6, 107.2, 64.9, 21.0, 14.5

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 133.6, 115.0, 107.7

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 133.6, 115.0, 107.7, 65.3 (–), 21.6, 15.0

IR (neat) 2985, 2937, 2898, 1748, 2595, 1580, 1481, 1467, 1454, 1437, 1410, 1391, 1363, 1275, 1255, 1204, 1160, 1120, 1109, 1047, 1032, 1014, 984, 917, 884, 843, 822, 796, 746, 691, 606, 586, 558 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{10}H_{11}BrO_3$ $[M]^+$: 257.9892, found 257.9897



4-(Benzyloxy)-1-chloro-2-methoxybenzene (9f). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), and benzoyl chloride (295 mg, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After adding benzoyl chloride, the mixture stirred at room temperature for 10 min and then quenched as described. After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid (194 mg, 74% yield).

TLC (SiO_2) R_f = 0.52 in 10% EtOAc in hexanes, $KMnO_4$ stain

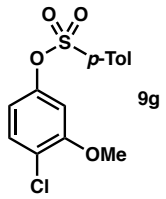
mp 72–74 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 7.4 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.40 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 2.5 Hz, 1H), 6.79 (dd, J = 10.1, 2.85 Hz, 1H), 3.90 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 155.5, 150.3, 133.8, 130.3, 130.2, 129.1, 119.6, 114.3, 106.4, 56.2

IR (neat) 3027, 2950, 1730, 1598, 1483, 1465, 1446, 1407, 1350, 1314, 1293, 1279, 1245, 1193, 1154, 1121, 1080, 1047, 1001, 942, 885, 837, 803, 792, 744, 708, 682, 652, 607, 564 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{14}H_{11}ClO_3$ $[M]^+$: 262.0397, found 262.0400.



4-Chloro-3-methoxyphenyl 4-methylbenzenesulfonate (9g). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), and additional tosyl chloride (400. mg, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as white solid (271 mg, 87% yield).

TLC (SiO_2) R_f = 0.68 in 20% EtOAc in hexanes, $KMnO_4$ stain

mp 63–65 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 6.45 (dd, J = 8.6, 2.6 Hz, 1H), 3.79 (s, 3H), 2.45 (s, 3H)

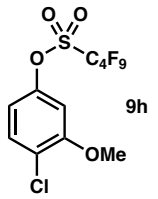
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 145.6, 130.2, 129.8, 128.6, 114.7, 107.1, 56.2, 21.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 130.7, 130.2, 129.0, 115.1, 107.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 130.7, 130.2, 129.0, 115.1, 107.5, 125.8, 22.2

IR (neat) 3087, 3008, 2948, 1598, 1577, 1487, 1442, 1406, 1371, 1296, 1272, 1212, 1189, 1177, 1136, 1119, 1091, 1066, 1033, 1026, 1017, 945, 859, 848, 821, 810, 791, 720, 705, 685, 656, 632, 612, 559 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{14}H_{13}ClO_4S[M]^+$: 312.0223, found 312.0229



4-Chloro-3-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (9h). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (634 mg, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a colorless oil (75% yield).

TLC (SiO_2) R_f = 0.57 in 20% EtOAc in hexanes, $KMnO_4$ stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.5 Hz, 1H), 6.85 (comp. m, 2H), 3.93 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 148.5, 130.8, 122.7, 113.6, 105.8, 56.5

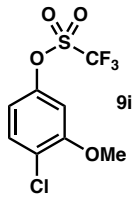
^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 131.2, 114.0, 106.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 131.2, 114.0, 106.2, 56.8

^{19}F NMR (376 MHz, $CDCl_3$) δ –81.1 (t, J = 9.4 Hz), –109.2 (t, J = 13.4 Hz), –121.3 (s), –126.3 (t, J = 12.3 Hz)

IR (neat) 2919, 1604, 1581, 1487, 1466, 1448, 1427, 1407, 1352, 1294, 1272, 1224, 1198, 1142, 1071, 1029, 1010, 945, 851, 793, 748, 738, 718, 698, 685, 651, 618, 586 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{11}H_6ClF_9O_4S[M]^+$: 439.9532, found 439.9530



4-chloro-3-methoxyphenyl trifluoromethanesulfonate (9i). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), trifluoromethanesulfonyl chloride (354 mg, 2.10 mmol, 2.10 equiv) as the trapping electrophile. After adding trifluoromethanesulfonyl chloride, the mixture stirred at room temperature for 10 min and then quenched as described. After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a light yellow oil (58 mg, 20% yield).

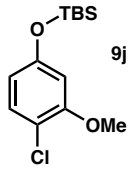
TLC (SiO_2) R_f = 0.50 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.4 Hz, 1H), 6.84 (m, 2H), 3.93 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 148.3, 130.8, 122.7, 119.9, 113.6, 105.8, 56.5

IR (neat) 2947, 1603, 1581, 1486, 1423, 1407, 1296, 1274, 1244, 1205, 1137, 1120, 1069, 1027, 943, 850, 830, 803, 719, 677, 627, 598, 565 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_8H_6ClF_3O_4S$ $[M]^+$: 289.9627, found 289.9630.



tert-**butyl(4-chloro-3-methoxyphenoxy)dimethylsilane (9j).** The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (316.5 mg, 1.00 mmol), tosyl chloride (400. mg, 2.10 mmol), *tert*-butylchlorodimethylsilane (354 mg, 2.10 mmol, 2.10

equiv) as the trapping electrophile. After adding trifluoromethanesulfonyl chloride, the mixture stirred at room temperature for 10 min and then quenched as described. After purification by flash chromatography (SiO_2, 1% EtOAc in hexanes), the title compound was isolated as a light yellow oil (224 mg, 82% yield).

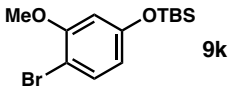
TLC (SiO_2) R_f = 0.50 in 2.5% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 6.38 (dd, J = 8.5, 2.6 Hz, 1H), 3.85 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 155.4, 130.0, 114.6, 112.5,105.0, 55.9, 25.6, 18.2, –4.4

IR (neat) 3411, 2930, 2857, 1731, 1589, 1490, 1471, 1447, 1407, 1370, 1301, 1254, 1202, 1167, 1148, 1068, 1030, 975, 875, 837, 778, 754, 729, 711, 689, 675, 650, 593 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{13}H_{21}ClO_2Si$ $[M]^+$: 272.0999, found 272.0994.



9k

(4-Bromo-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane (9k). The title compound was prepared according to General Procedure D, using 3-methoxycyclohex-2-enone (126.2 mg, 1.0 mmol), tosyl bromide (494 mg, 2.10 mmol), and a solution of TBSCl (317 mg, 2.10 mmol, 2.10 equiv) in THF (3 mL) as the trapping electrophile. After purification by flash chromatography (SiO_2, 1% EtOAc in hexanes), the title compound was isolated as a colorless oil (227 mg, 71% yield).

TLC (SiO_2) R_f = 0.6 in 2.5% EtOAc in hexanes, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 2.6 Hz, 1H), 6.35 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.85 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 156.2, 133.0, 113.2, 105.0, 103.0, 56.0, 25.6, 18.2, –4.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 133.4, 113.7, 105.4

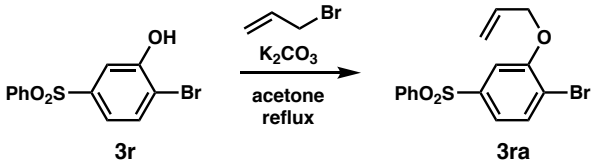
^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 133.4, 113.7, 105.4, 56.2, 25.7, –4.2

IR (neat) 2955, 2929, 2857, 1586, 1484, 1471, 1446, 1403, 1298, 1253, 1202, 1168, 1119, 1051, 1025, 975, 938, 834, 778, 701, 669, 637, 596 cm^{-1}

GCMS (*m/z*): 318.1 (23%), 261.0 (68%), 180.1 (100%), 165.0 (22%), 151.1 (11%), 137.0 (16%), 73.1 (15%), 63.1 (17%)

5.2.6. Procedures and Experimental Data for Synthetic Applications

Claisen Rearrangement (Scheme 5a):[61]



2-(Allyloxy)-1-bromo-4-(phenylsulfonyl)benzene (3ra). To a room temperature solution of 2-bromo-5-(phenylsulfonyl)phenol (**3r**, 313.2 mg, 1.00 mmol, 1.00 equiv) and potassium carbonate (276 mg, 2.00 mmol, 2.00 equiv) in acetone (5 mL) was added allyl bromide (104 μL, 1.20 mmol, 1.20 equiv). The resulting mixture was heated to reflux and stirred for 16 h. The mixture was cooled and then filtered through a short pad of Celite and washed with EtOAc. The filtrate

was concentrated and the residue was purified by flash chromatography (SiO_2, 8:1 hexanes/EtOAc) to afford the allyl aryl ether as white solid (331 mg, 94% yield).

TLC (SiO_2) R_f = 0.56 in 10% EtOAc in hexane, $KMnO_4$ stain

mp 123–125 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.91 (s, 1H), 7.67 (d, 1H, J = 8.2 Hz), 7.58 (m, 1H), 7.51 (m, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.03 (ddt, *J* = 17.1, 10.4, 5.1 Hz, 2H), 5.49 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.34 (dd, *J* = 10.6, 1.3 Hz, 1H), 4.67 (d, *J* = 5.1 Hz, 1H);

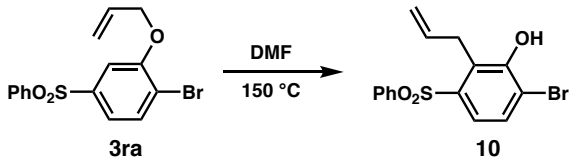
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 141.7, 141.2, 134.2, 133.4, 131.5, 129.3, 127.5, 120.9, 118.6, 118.4, 111.7, 70.0

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 134.6, 133.8, 131.9, 129.8, 128.0, 121.3, 112.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 134.6, 133.8, 131.9, 129.8, 128.0, 121.3, 119.0 (–), 112.2, 70.4 (–)

IR (neat) 3096, 3074, 2923, 1581, 1475, 1457, 1445, 1395, 1363, 1317, 1293, 1268, 1250, 1150, 1102, 1075, 1029, 1016, 997, 979, 937, 905, 862, 828, 764, 728, 703, 689, 621, 597, 578 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{15}H_{13}BrO_3S$ $[M]^+$: 351.9769, found 351.9772



3ra 10

2-Allyl-6-bromo-3-(phenylsulfonyl)phenol (10). An oven-dried 15 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was charged with 2-(allyloxy)-1-

bromo-4-(phenylsulfonyl)benzene (**3ra**,35.3 mg, 0.100 mmol, 1.00 equiv) and dry *N*,*N*-dimethylformamide (DMF, 5 mL). The mixture was then heated to 150 °C for 20 h. After cooling to room temperature, the mixture was diluted with EtOAc (10 mL), washed with water (3 x 5 mL), brine (1 x 10 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 15:1 hexanes/EtOAc) to afford the product as light yellow oil (24.5 mg, 69% yield).

TLC (SiO_2) R_f = 0.42 in 10% EtOAc in hexane, $KMnO_4$ stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.57 (m, 2H), 7.50 (m, 2H), 5.85 (s, 1H), 5.58 (m, 1H), 4.83 (m, 2H), 3.71 (d, *J* = 6.0 Hz, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 141.4, 139.8, 133.6, 133.2, 130.0, 129.2, 127.5, 127.1, 122.3, 116.8, 116.2, 31.3, 29.7

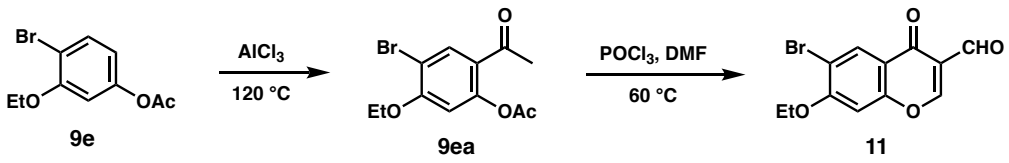
^{13}C DEPT-90 NMR (101 MHz, $CDCl_3$) δ 133.6, 133.3, 130.1, 129.2, 127.5, 122.4

^{13}C DEPT-135 NMR (101 MHz, $CDCl_3$) δ 133.6, 133.3, 130.1, 129.2, 127.5, 122.4, 116.2 (–), 31.3 (–)

IR (neat) 3425, 3080, 2923, 1637, 1574, 1446, 1426, 1305, 1244, 1151, 1077, 997, 917, 876, 843, 808, 753, 722, 686, 613, 567 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{15}H_{13}BrO_3S$ $[M]^+$: 351.9769, found 351.9771

Fries Rearrangement (Scheme 5d):[62]



1-(5-Bromo-4-ethoxy-2-hydroxyphenyl)ethanone (9ea). To an oven-dried 20 mL round bottom flask under N_2 atmosphere containing stirred neat 4-bromo-3-ethoxyphenyl acetate (**9e**, 259 mg, 1.00 mmol, 1.00 equiv) was added powdered anhydr $AlCl_3$ (266.7 mg, 2.00 mmol, 2.00 equiv) was added in small portions (*Note: exotherm—use caution*). The mixture was then heated to 120 °C for 6 h. After cooling to room temperature, ice (approximately 5 g) was added and the mixture was stirred for 20 min. The mixture was diluted with EtOAc (20 mL) and then the phases were separated. The aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 20:1 hexane/EtOAc) to afford the product as a white solid (184 mg, 71% yield).

TLC (SiO_2) R_f = 0.5 in 11% EtOAc in hexanes, $KMnO_4$ stain

mp 108–110 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 6.38 (s, 1H), 4.09 (q, J = 7.0 Hz, 2H), 2.53 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 164.2, 161.2, 134.6, 114.4, 101.2, 65.1, 26.2, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 135.1, 101.7

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 135.1, 101.7, 65.7 (–), 26.6, 14.5

IR (neat) 2987, 2895, 1622, 1598, 1564, 1488, 1469, 1424, 1405, 1382, 1361, 1308, 1273, 1249, 1198, 1105, 1074, 1041, 958, 894. 879, 843, 811, 749, 742, 709, 683, 644, 587, 572 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{10}H_{11}BrO_3$ $[M]^+$: 257.9892, found 257.9894

6-Bromo-7-ethoxy-4-oxo-4H-chromene-3-carbaldehyde (11). An oven-dried 10 mL round bottom flask under N_2 atmosphere containing a stirred solution of 1-(5-bromo-4-ethoxy-2-hydroxyphenyl)ethanone (**9ea**, 25.9 mg, 0.100 mmol, 1.00 equiv) and dry *N*,*N*-dimethylformamide (DMF, 1.0 mL) was thoroughly cooled to 0 °C in an ice/water bath. To the reaction mixture was added neat $POCl_3$ (49 μL, 0.52 mmol, 5.2 equiv) slowly over 1 min. The ice/water bath was removed and the mixture was further stirred at room temperature for 20 min and then heated to 60 °C for 20 h. After TLC indicated complete consumption of starting material, the mixture was cooled to ambient temperature and then ice (approximately 5 g) was added and the mixture was stirred for 2 h. Water (10 mL) was added to the reaction and then the mixture was extracted with EtOAc (5 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 4:1 hexane/EtOAc) to afford the product as a white powder (26 mg, 86% yield).

TLC (SiO_2) R_f = 0.52 in 20% EtOAc in hexanes, $KMnO_4$ stain

mp 189–191 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.46 (d, *J* = 10.6 Hz, 2H), 6.90 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 1.56 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4, 174.2, 160.1, 156.8, 130.2, 120.3, 119.3, 111.9, 109.5, 100.9, 65.8, 14.2

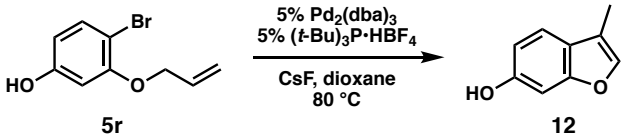
^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 188.7, 160.5, 130.7, 101.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 188.7, 160.5, 130.7, 101.5, 66.3 (–), 14.7

IR (neat) 3066, 2979, 2881, 1696, 1646, 1613, 1548, 1486, 1465, 1436, 1391, 1343, 1288, 1256, 1238, 1217, 1163, 1122, 1105, 1028, 908, 949, 889, 845, 823, 813, 777, 764, 722, 648, 591 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{12}H_9BrO_4$ $[M]^+$: 295.9684, found 295.9689

Mizoroki–Heck Cyclization (12):[63]



3-Methylbenzofuran-6-ol (12). In a dry N_2 atmosphere glovebox, a 50 mL Schlenk tube was charged with 3-(allyloxy)-4-bromophenol (**5r**, 22.9 mg, 0.10 mmol, 1.00 equiv), $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol, 5 mol %), [(*t*-Bu)$_3$PH][BF_4] (1.5 mg, 0.0050 mmol, 5 mol %), and CsF (30.4 mg, 0.200 mmol, 2.00 equiv). Dry dioxane (1.0 mL) was added via syringe, the tube was sealed, removed from the glovebox, and the mixture was then heated to 80 °C and stirred for 16 h at which time analysis by TLC (5% EtOAc/hexanes) indicated complete consumption of the aryl bromide. The mixture was cooled and then diluted with EtOAc (10 mL), filtered through a short pad of silica gel with copious washing (EtOAc). The filtrate was concentrated and the residue was then purified by flash chromatography (SiO_2, 20:1 hexane/EtOAc) to afford the product as white solid.

1st run: 13.2 mg (89% yield)

2nd run: 13.6 mg (92% yield)

TLC (SiO_2) R_f = 0.56 in 2% EtOAc in hexane, *p*-anisaldehyde stain

mp 82–84 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 1H), 7.31 (s, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.81 (s, 1H), 2.21 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 153.4, 140.5, 122.8, 119.6, 115.4, 111.2, 98.3, 29.7, 7.9

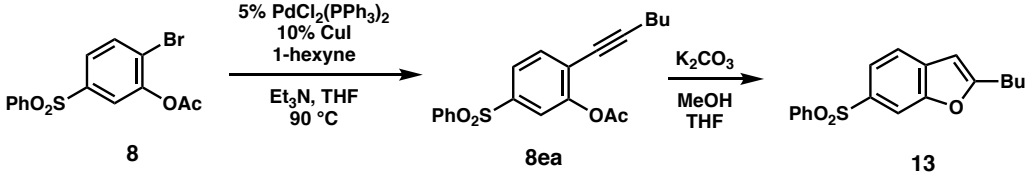
^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.7, 120.2, 111.5, 98.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.7, 120.2, 111.5, 98.8, 8.5

IR (neat) 3164, 2921, 2853, 1626, 1605, 1484, 1456, 1390, 1344, 1307, 1279, 1232, 1137, 1128, 1078, 1066, 943, 834, 809, 796, 774, 742, 663, 626, 598, 586 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_9H_8O_2$ $[M]^+$: 148.0524, found 148.0525

Sonogashira Coupling (13):[64]



2-(Hex-1-yn-1-yl)-5-(phenylsulfonyl)phenyl acetate (8a). An oven-dried 15 mL round bottom flask was charged with dry Et_3N (0.20 mL, 1.5 mmol, 15 equiv) under N_2. To the flask 2-bromo-5-(phenylsulfonyl)phenyl acetate (**8**, 35.5 mg, 0.100 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.0050 mmol, 5.0 mol %), CuI (2 mg, 0.01 mmol, 10 mol %), and hex-1-yne (9 mg, 0.11 mmol, 1.10 equiv) were added sequentially under positive N_2 pressure. The reaction mixture was heated to 90 °C for 6 h, at which time analysis by TLC (20% EtOAc/hexanes) indicated complete consumption of the aryl bromide. The reaction mixture was cooled to ambient temperature and diluted with Et_2O (10 mL). The resulting mixture was washed with saturated aq

NH_4Cl solution (2 x 5 mL) and brine (1 x 5 mL). The organic layer was dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo to a dark brown oil. The residue was purified by flash chromatography (SiO_2, 10% EtOAc in hexanes) to afford the product as a yellow oil (33.4 mg, 94% yield).

TLC (SiO_2) R_f = 0.35, 10% EtOAc in hexanes, $KMnO_4$ stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 7.9 Hz, 2H), 7.69 (m, 2H), 7.54 (m, 4H), 2.43 (t, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.56 (m, 2H), 1.45 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 151.6, 141.1, 141.0, 133.8, 133.4, 129.4, 128.4, 127.7, 124.9, 123.6, 121.6, 100.0, 74.7, 30.4, 21.8, 20.7, 19.2, 13.5

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 133.8, 133.4, 129.4, 127.7, 124.9, 121.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 133.8, 133.4, 129.4, 127.7, 124.9, 121.6, 74.7 (–), 30.4 (–), 21.8 (–), 20.7, 19.2 (–), 13.5

IR (neat) 2962, 2925, 2858, 1591, 1574, 1448, 1420, 1305, 1287, 1244, 1222, 1170, 1142, 1118, 1088, 1049, 1024, 997, 981, 949, 918, 876, 842, 805, 787, 760, 748, 729, 693, 625, 610, 587, 558 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{20}H_{20}O_4S$ $[M]^+$: 314.0977, found 314.0992

2-Butyl-6-(phenylsulfonyl)benzofuran (13). In a 20 mL round bottom flask, a suspension of K_2CO_3 (28.0 mg, 2.05 mmol, 0.205 equiv) in MeOH (0.7 mL) and THF (0.6 mL) was cooled to 0 °C in an ice/water bath. A solution of 2-(hex-1-yn-1-yl)-5-(phenylsulfonyl)phenyl acetate (**8a**, 35.7 mg, 0.100 mmol, 1.00 equiv) in THF (0.5 mL) was added dropwise. The resulting heterogeneous mixture was stirred vigorously at room temperature vented to air with a needle for

20 h, at which time TLC indicated complete consumption of the starting material. The reaction mixture was decanted into a separatory funnel containing CH_2Cl_2 (10 mL) and the resulting mixture was washed with saturated aqueous NH_4Cl solution (1 x 5 mL). The organic layer was then dried over anhyd Na_2SO_4, filtered though cotton, and concentrated in vacuo to a brown solid. The residue was purified by flash chromatography (SiO_2, 5% EtOAc in hexanes) to afford the product as white solid (28 mg, 88% yield).

TLC (SiO_2) R_f = 0.6 in 10% EtOAc in hexanes, $KMnO_4$ stain

mp 83–85 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.76 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.51 (m, 4H), 6.43 (s, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.72 (m, 2H), 1.41 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 153.6, 142.3, 135.9, 133.7, 132.8, 129.1, 127.4, 121.9, 120.7, 110.8, 102.1, 29.5, 28.2, 22.2, 13.7

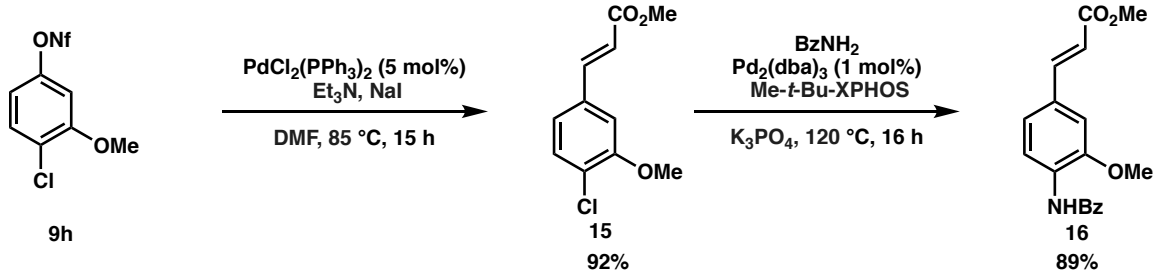
^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 133.3, 129.6, 127.9, 122.4, 121.1, 111.3, 102.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 133.3, 129.6, 127.8, 122.3, 121.1, 111.3, 102.6, 29.8, 28.7 (–), 22.6 (–), 14.1

IR (neat) 2963, 2926, 2858, 1591, 1574, 1463, 1448, 1420, 1340, 1305, 1244, 1222, 1170, 1142, 1119, 1088, 1049, 1024, 997, 981, 949, 918, 876, 841, 806, 788, 760, 748, 729, 693, 625, 610, 588, 558 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{18}H_{18}O_3S$ $[M]^+$: 314.0977, found 314.0979

Sequential Heck/Buchwald–Hartwig Reaction :



(*E*)-Methyl 3-(4-chloro-3-methoxyphenyl)acrylate (15). The title compound was prepared according to following procedure: In a dry N_2 atmosphere glovebox, to a mixture of 4-chloro-3-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**9h**, vide supra, 1.32 g, 3.00 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (105 mg, 0.0150 mmol, 5 mol%), NaI (44.9 mg, 0.30 mmol, 10 mol%), Et_3N (1.7 mL, 12 mmol, 4.0 equiv), and dry DMF (10.0 mL) in 50 mL Schlenk tube was added dropwise methyl acrylate (0.54 mL, 6.0 mmol, 2.0 equiv), the tube was sealed and removed from the glove box. The mixture was then heated to 85 °C and stirred for 15 h at which time analysis by TLC (11% EtOAc/hexanes, R_f = 0.40, $KMnO_4$ stain) indicated complete consumption of the starting material. The mixture was cooled, diluted with EtOAc (40 mL), and then filtered through a short pad of silica gel with copious washing (EtOAc). The filtrate was concentrated and the residue was then purified by flash chromatography (SiO_2, 15:1 hexane/EtOAc) to afford the product as white solid (209 mg, 92% yield).

TLC (SiO_2) R_f = 0.40 in 11% EtOAc in hexanes, $KMnO_4$ stain

mp 85–87 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.04 (s, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 155.2, 143.8, 134.2, 130.5, 124.7, 121.2, 118.4, 110.8, 56.1, 51.8

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 144.2, 131.0, 121.6, 118.9, 111.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 144.2, 131.0, 121.6, 118.9, 111.3, 56.6, 52.2

IR (neat) 3067, 2952, 2923, 2843, 1704, 1633, 1590, 1574, 1487, 1461, 1443, 1435, 1411, 1321, 1309, 1279, 1261, 1236, 1178, 1136, 1064, 1030, 977, 925, 858, 798, 763, 711, 672, 599, 572 cm^{-1}

GCMS (*m/z*): 226 (76%), 195 (100%), 152 (28%), 132 (42%), 89 (47%), 63 (24%)

(*E*)-Methyl 3-(4-benzamido-3-methoxyphenyl)acrylate (16). The title compound was prepared according to following procedure: In a dry N_2 atmosphere glovebox, an oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (1.8 mg, 2.0 μmol, 1.0 mol%), tetramethyl di-*t*-BuXPhos (2.4 mg, 5.0 μmol, 2.5 mol%), benzamide (73 mg, 0.60 mmol, 3.0 equiv), K_3PO_4 (50.9 mg, 0.240 mmol, 1.20 equiv), (*E*)-methyl 3-(4-chloro-3-methoxyphenyl)acrylate (**SI15**, 45.3 mg, 0.200 mmol, 1.00 equiv) and *t*-BuOH (1.0 mL). The tube was sealed and removed from glovebox. The mixture was heated to 120 °C with stirring for 16 h at which time TLC analysis (25% EtOAc/hexanes, R_f = 0.35, $KMnO_4$ stain) indicated complete consumption of the starting material. The mixture was cooled, diluted with EtOAc (10 mL), and then filtered through a short pad of silica gel with copious washing (EtOAc). The filtrate was concentrated and the residue was then purified by flash chromatography (SiO_2, 4:1 hexane/EtOAc) to afford the product as light yield solid (55.4 mg, 89% yield).

TLC (SiO_2) R_f = 0.35 in 25% EtOAc in hexanes, $KMnO_4$ stain

mp 151–153 °C

^{1}H NMR (500 MHz, d_6-DMSO) δ 9.44 (s, 1H), 7.95 (comp. m, 3H), 7.61 (comp. m, 2H), 7.52 (comp. m, 3H), 7.32 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 16.0 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H)

^{13}C NMR (126 MHz, d_6-DMSO) δ 167.2, 165.4, 151.2, 144.8, 134.7, 132.3, 131.4, 129.7, 129.0, 127.9, 123.3, 122.0, 117.5, 110.9, 56.5, 51.8

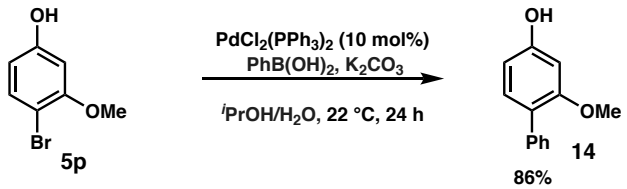
^{13}C DEPT-90 NMR (126 MHz, d_6-DMSO) δ 145.3, 132.7, 129.4, 128.4, 123.8, 122.5, 118.0, 111.3

^{13}C DEPT-135 NMR (126 MHz, d_6-DMSO) δ 145.3, 132.7, 129.4, 128.4, 123.8, 122.5, 118.0, 111.3, 57.0, 52.4

IR (neat) 3430, 3063, 2951, 2846, 1699, 1667, 1641, 1590, 1523, 1502, 1481, 1458, 1438, 1411, 1347, 1315, 1297, 1268, 1235, 1186, 1165, 1136, 1102, 1075, 1035, 982, 943, 893, 859, 794, 781, 737, 703, 687, 679, 618, 591, 578 cm^{-1}

GCMS (*m/z*): 311 (23%), 280 (1.5%), 105 (100%), 77 (35%), 51 (5%).

Suzuki–Miyaura Cross-Coupling (14):



Solid $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol, 10 mol%) was added to a stirred solution of 4-bromo-3-methoxyphenol (20.3 mg, 0.1 mmol, 1.0 equiv), phenylboronic acid (12.2 mg, 0.1 mmol, 1.0

equiv), and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv) in water (0.35 mL) and isopropanol (1.5 mL) at room temperature under an N_2 atmosphere. The contents were stirred for 20 min and then the reaction mixture was slowly heated to reflux. After 24 h, TLC indicated completion of the reaction. The solvents were removed under reduced pressure, then add di-water 10 mL, the mixture was extracted with EtOAc (2 x 5.0 mL) and washed with water, the organic layer was separated, dried over Na_2SO_4, solvent removed under reduced pressure and the obtained crude product was purified by flash chromatography using silica gel with hexane/ethyl acetate (40:1 then 6:1) as eluent to deliver the product (**14**) as a white solid (17.2 mg, 86% yield).

mp 90–91 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 6.53 (s, 1H), 6.49 (d, *J* = 10.3 Hz, 1H), 5.14 (s, 1H), 3.78 (s, 3H)

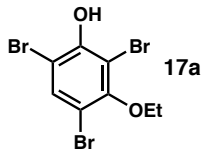
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 156.1, 138.3, 131.5, 129.4, 128.0, 126.5, 123.5, 107.3, 99.4, 55.6, 29.7

IR (neat) 3323, 2927, 1610, 1592, 1511, 1485, 1467, 1454, 1421, 1362, 1337, 1288, 1245, 1193, 1160, 1127, 1116, 1074, 950, 913, 831, 825, 809, 761, 723, 693, 626, 587, 562 cm^{-1}

HRMS (EI^+) *m/z* calc'd for $C_{13}H_{12}O_2$ $[M]^+$: 200.0837, found 200.0838.

5.2.7. Procedures and Experimental Data for 2,4,6-Tribromoresorcinols Resorcinols

An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with substrate ketone (1.00 mmol, 1.00 equiv), HMPA (210 μL, 215 mg, 1.2 mmol, 1.2 equiv), and dry THF (8 mL) and then cooled to 0 °C in an ice/water bath. A solution of LiHMDS (1.00 M in THF, 4.00 mL, 4.00 equiv) was added dropwise over 4 min. After stirring the mixture for 1 h, the reaction system was cooled to –78 °C. DABCO•$2Br_2$ (2.2 mmol, 2.2 equiv) was added one-portion. After 30 min at –78 °C (the mixture changed color from yellow to green and then yellow), a solution of LiHMDS (1.00 M in THF, 1.00 mL) was added dropwise over 1 min. When the addition was complete, the mixture was warmed to room temperature over 20 min at which time TLC indicated complete consumption of the dihalogenated intermediate (R_f ~0.3 in 4:1 hexanes/EtOAc, visualized with *p*-anisaldehyde stain). The reaction was quenched with a saturated aq NH_4Cl solution (10 mL) and then EtOAc (20 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.



2,4,6-Tribromo-3-ethoxyphenol (**17a**). The title compound was prepared according to General Procedure above, using 3-ethoxycyclohex-2-enone (140.2 mg, 1.00 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 356 mg (95% yield)

2nd run: 349 mg (93% yield)

TLC (SiO_2) R_f = 0.52 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

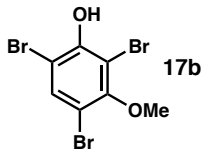
mp 108–110 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 5.92 (s, 1H), 4.08 (q, J = 7.0 Hz, 2H), 1.49 (t, J = 7.0 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 149.9, 134.1, 108.5, 107.1, 104.6, 69.7, 15.5

IR (neat) 3336, 3076, 2975, 2924, 1545, 1441, 1178, 1030, 868 cm^{-1}

HRMS (EI^+) *m/z* calc'd $C_8H_7Br_3O_2$ $[M]^+$: 371.7996, found 371.7993



2,4,6-Tribromo-3-methoxyphenol (**17b**). The title compound was prepared according to General Procedure above, using 3-methoxycyclohex-2-enone (126.2 mg, 1.00 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 356 mg (95% yield)

2nd run: 349 mg (93% yield)

TLC (SiO_2) R_f = 0.44 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

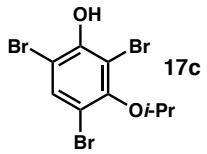
mp 100–101 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 5.94 (s, 1H), 3.88 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 150.0, 134.2, 108.2, 106.8, 104.9, 60.7

IR (neat) 3421, 2941, 1452, 1436, 1394, 1271, 1213, 1038, 949, 853, 685 cm^{-1}

HRMS (EI^+) *m/z* calc'd $C_7H_5Br_3O_2$ $[M]^+$: 357.7840, found 357.7839



2,4,6-Tribromo-3-isopropoxyphenol (**17c**). The title compound was prepared according to General Procedure above, using 3-isopropoxycyclohex-2-en-1-one (154.2 mg, 1.00 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 346 mg (89% yield)

2nd run: 354 mg (91% yield)

TLC (SiO_2) R_f = 0.44 in 20% EtOAc in hexanes, *p*-anisaldehyde stain

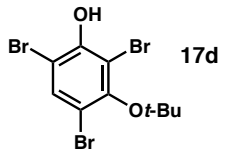
mp 55–57 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 5.95 (s, 1H), 4.71 (heptet, J = 6.2 Hz, 1H), 1.38 (d, J = 6.2 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 149.9, 134.4, 109.0, 107.9, 104.1, 77.7, 25.5

IR (neat) 3406, 3083, 2980, 2934, 2870, 1559, 1466, 1437, 1176, 1137, 1035, 927, 908, 686 cm^{-1}

HRMS (EI^+) *m/z* calc'd $C_9H_9Br_3O_2$ $[M]^+$: 385.8153, found 385.8151



2,4,6-tribromo-3-(tert-butoxy)phenol (**17d**). The title compound was prepared according to General Procedure above, using 3-(*tert*-butoxy)cyclohex-2-en-1-one (168.3 mg, 1.00 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 346 mg (89% yield)

2nd run: 354 mg (91% yield)

TLC (SiO_2) R_f = 0.38 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

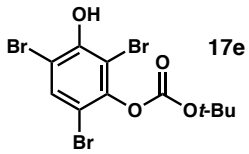
mp 46–47 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 5.95 (br. s, 1H), 1.55 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 149.8, 134.4, 110.9, 109.7, 104.1, 87.4, 30.4

IR (neat) 3467, 3067, 2974, 2929, 1439, 1366, 1307, 1145, 838, 753, 680, 608 cm^{-1}

HRMS (EI^+) *m/z* calc'd $C_{10}H_{11}Br_3O_2$ $[M]^+$: 399.8309, found 399.8290



17e

(2,4,6-tribromo-3-hydroxyphenyl) carbonate (**17e**)**.** The title compound was prepared according to General Procedure above, *tert*-butyl (3-oxocyclohex-1-en-1-yl) carbonate (212.3 mg, 1.00 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 375 mg (84% yield)

2nd run: 357 mg (80% yield)

TLC (SiO_2) R_f = 0.48 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

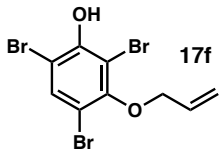
mp 86–87 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.05 (br. s, 1H), 1.57 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 149.1, 146.1, 133.9, 108.1, 107.3, 106.6, 27.6

IR (neat) 3372, 3084, 2994, 2971, 1747, 1550, 1448, 1219, 1137, 1085, 858, 690 cm^{-1}

HRMS (EI^+) *m/z* calc'd $C_{11}H_{11}Br_3O_4$ $[M]^+$: 343.7683, found 343.7690



3-(allyloxy)-2,4,6-tribromophenol (**17f**). The title compound was prepared according to General Procedure above, 3-(allyloxy)cyclohex-2-en-1-one (152.2 mg, 1.00 mmol). After purification by flash chromatography (SiO_2, 5% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 348 mg (90% yield)

2nd run: 340 mg (88% yield)

TLC (SiO_2) R_f = 0.50 in 10% EtOAc in hexanes, *p*-anisaldehyde stain

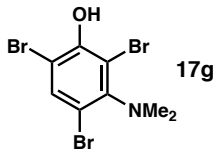
mp 64–65 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 6.15 (ddd, J = 17.1, 10.6, 5.9Hz, 1H), 5.93 (s, 1H), 5.46 (dd, J = 17.1, 1.3Hz, 1H), 5.31 (d, J = 10.6 Hz, 1H), 4.54 (d, J = 5.9 Hz, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 149.9, 134.2, 132.6, 119.1, 108.6, 107.2, 104.9, 74.3

IR (neat) 3408, 3070, 1408, 1356, 1308, 1175, 1164, 1041, 940, 683 cm^{-1}

HRMS (EI^+) *m/z* calc'd $C_9H_7Br_3O_2$ $[M]^+$: 383.7996, found 383.8004



17g

2,4,6-tribromo-3-(dimethylamino)phenol (**17g**). The title compound was prepared according to General Procedure above, 3-(dimethylamino)cyclohex-2-en-1-one (152.2 mg, 1.00 mmol). After purification by flash chromatography (SiO_2, 50% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 348 mg (90% yield)

2nd run: 340 mg (88% yield)

TLC (SiO_2) R_f = 0.35 in 50% EtOAc in hexanes, *p*-anisaldehyde stain

mp 90–91 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.95 (br. s, 1H), 2.86 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 148.8, 134.8, 115.2, 114.4, 105.8, 41.7

IR (neat) 3479, 2913, 2790, 1668, 1426, 1386, 1328, 1191, 1158, 1023, 760, 681 cm^{-1}

HRMS (EI^+) *m/z* calc'd $C_8H_8Br_3NO$ $[M]^+$: 371.8234, found 371.8236

5.3. γ-Hydroxylation of Vinylogous Esters

5.3.1. General Information for γ-Hydroxylation of Enones

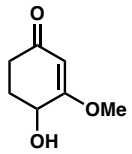
Unless otherwise stated, reactions were performed in oven-dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous dichloromethane, pentane, toluene, and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying column[53] on a Pure Process Technology system. Molecular sieves (MS) were purchased from Aldrich and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted. Hexamethylphosphoramide (HMPA) was purchased from Chem-Impex International, Inc., distilled over CaH_2 prior to use, and stored over 4 Å MS under argon atmosphere. Lithium bis(trimethylsilyl)amine (HMDS) was purchased from Alfa Aesar. Starting materials, including 1,3-diketones, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. Vinylogous ester substrates were prepared according to literature procedures.[57] Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[3] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz),

integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0).

5.3.2. General Procedure for γ-Hydroxylated Products

An oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with substrate ketone (0.50 mmol, 1.00 equiv), hexamethylphosphoramide (HMPA, 218 μL, 224 mg, 1.25 mmol, 2.50 equiv), and dry THF (3 mL) and then cooled to –78 °C. A solution of LiHMDS (1.00 M in THF, 0.99 mL, 0.99 equiv) was added dropwise over 3 min. A solution of Davis oxaziridine[65] (0.75 mmol, 1.50 equiv) in THF (2.0 mL, then the vial was rinsed with 1.0 mL and added to the reaction) was added dropwise over 5 min. After 1h at –78 °C, TLC indicated complete consumption of starting material. The mixture was then warmed to room temperature over 20 min. The reaction was quenched with a saturated aq NH_4Cl solution (5.0 mL) and then EtOAc (10.0 mL) was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 5.0 mL). The combined organic phases were washed with brine (1 x 10 mL), dried over anhyd Na_2SO_4, filtered through cotton, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

5.3.3. Experimental Data for γ-Hydroxylation of Enones (19)



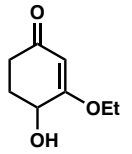
19a

4-hydroxy-3-methoxycyclohex-2-enone (19a) The title compound was prepared according to the general procedure, using **3-methoxycyclohex-2-enone** (63.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless oil (66.8 mg, 94% yield).

TLC (SiO_2) R_f = 0.40 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 4.50 (dd, *J* = 8.1, 4.8 Hz, 1H), 3.78 (s, 3H), 2.60 (m, 1H), 2.32 (m, 2H), 2.04 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 176.1, 102.1, 66.8, 56.2, 34.0, 29.4



19b

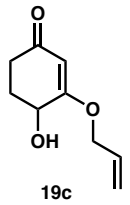
3-ethoxy-4-hydroxycyclohex-2-enone (19b) The title compound was prepared according to the general procedure, using **3-ethoxycyclohex-2-enone** (70.1 mg, 0.50 mmol). After purification by

flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless oil (73.4, 94% yield).

TLC (SiO_2) R_f = 0.40 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.46 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.96 (d, *J* = 7.0 Hz, 2H), 2.59 (dt, *J* = 16.8, 5.5 Hz, 1H), 2.32 (m, 2H), 2.03 (tdd, *J* = 10.4, 5.7, 2.6 Hz, 1H), 1.43 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 175.4, 102.4, 66.8. 64.9, 33.9, 29.4, 14.0



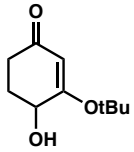
19c

3-(allyloxy)-4-hydroxycyclohex-2-enone (19c) The title compound was prepared according to the general procedure, using 3-(allyloxy)cyclohex-2-enone (76.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless oil (70.6, 94% yield).

TLC (SiO_2) R_f = 0.40 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.38 (m, 3H), 4.48 (2H), 2.60 (m, 1H), 2.31 (m, 2H), 2.03 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 174.9, 130.8, 119.7, 102.9, 69.7, 66.7, 33.8, 29.4



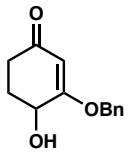
19d

3-(tert-butoxy)-4-hydroxycyclohex-2-enone (19d) The title compound was prepared according to the general procedure, using 3-(tert-butoxy)cyclohex-2-enone (84.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless oil (31.3, 34% yield).

TLC (SiO_2) R_f = 0.42 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (m, 1H), 4.34 (dd, *J* = 8.3, 4.7 Hz, 1H), 2.56 (dt, *J* = 6.5, 3.4 Hz, 1H), 2.30 (m, 2H), 1.98 (m, 1H), 1.52 (d, *J* = 5.5 Hz, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 172.7, 105.5, 82.6, 67.6, 33.8, 29.1, 28.1



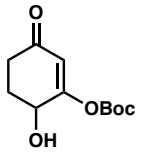
19e

3-(benzyloxy)-4-hydroxycyclohex-2-enone (19e) The title compound was prepared according to the general procedure, using 3-(benzyloxy)cyclohex-2-enone (101.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless oil (72.0, 66% yield).

TLC (SiO_2) R_f = 0.44 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (s, 1H), 4.91 (s, 2H), 4.48 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.60 (m, 1H), 2.33 (td, *J* = 8.4, 4.9 Hz, 1H), 2.26 (m, 1H), 2.02 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.0, 175.5, 134.5, 128.8, 128.0, 103.1, 71.0, 66.6, 33.8, 29.4



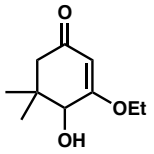
19f

tert-butyl (6-hydroxy-3-oxocyclohex-1-en-1-yl) carbonate (19f) The title compound was prepared according to the general procedure, using tert-butyl (3-oxocyclohex-1-en-1-yl) carbonate (106.3 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (81.0 mg, 71% yield).

TLC (SiO_2) R_f = 0.45 in 50% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (s, 1H), 4.35 (m, 1H) 2.54 (m, 1H), 2.30 (m, 2H), 1.98 (m, 1H), 1.53 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 172.7, 126.4, 109.6, 105.5, 67.7, 33.9, 29.1, 28.1



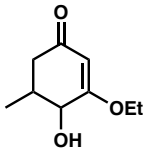
19g

3-ethoxy-4-hydroxy-5,5-dimethylcyclohex-2-enone (19g) The title compound was prepared according to the general procedure, using 3-ethoxy-5,5-dimethylcyclohex-2-enone (84.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (110.9, 78% yield).

TLC (SiO_2) R_f = 0.45 in 50% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.08 (s, 1H), 3.92 (q, J = 7.0 Hz, 1H), 2.39 (d, J = 16.5, 1H), 2.17 (d, J = 16.0 Hz, 1H), 1.39 (t, J = 7.0 Hz, 3H), 1.10 (s, 3H), 1.03 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 174.5, 101.2, 74.8, 65.0, 48.6, 37.2, 26.8, 21.5, 14.0



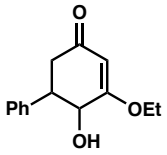
19h

3-ethoxy-4-hydroxy-5-methylcyclohex-2-enone (19h) The title compound was prepared according to the general procedure, using 3-ethoxy-5-methylcyclohex-2-enone (77.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (51.1 mg, 60% yield).

TLC (SiO_2) R_f = 0.35 in 50% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.08 (t, *J* = 7.2 Hz, 1H), 3.92 (m, 2H), 2.53 (m, 1H), 2.44 (d, *J* = 6.3 Hz, 1H), 2.30 (dt, *J* = 6.1, 3.3 Hz, 1H), 2.15 (m, 1H), 1.41 (t, *J* = 8.5 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 175.4, 102.0, 72.6, 69.8, 65.1, 64.8, 43.0, 40.1, 36.2, 33.3, 18.0, 15.4, 14.0



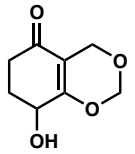
19i

5-ethoxy-6-hydroxy-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (19i) The title compound was prepared according to the general procedure, using 5-ethoxy-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (108.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (69.8, 62% yield).

TLC (SiO_2) R_f = 0.50 in 30% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.29 (m, 3H), 5.42 (d, *J* = 6.1 Hz, 1H), 4.64 (t, *J* = 7.8 Hz, 1H), 3.99 (dtd, *J* = 10.3, 6.8, 3.3 Hz, 2H), 3.32 (m, 1H), 2.65 (ddd, *J* = 21.1, 9.6, 5.6 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 175.0, 140.2, 128.8, 127.6, 127.4, 102.3, 77.4, 77.1, 76.9, 71.4, 65.4, 47.4, 42.5, 14.0



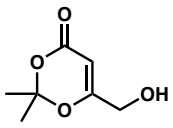
19j

8-hydroxy-4,6,7,8-tetrahydro-5H-benzo[d][1,3]dioxin-5-one (19j) The title compound was prepared according to the general procedure, using 4,6,7,8-tetrahydro-5H-benzo[d][1,3]dioxin-5-one (77.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (78.3 mg, 92% yield).

TLC (SiO_2) R_f = 0.35 in 30% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (d, *J* = 5.5, 1H), 5.19 (d, *J* = 5.5 Hz, 4.47 (t, *J* = 6.0 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 1H), 2.62 (m, 1H), 2.30 (m, 2H), 2.04 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7, 168.4, 111.7, 91.9, 65.3, 62.5, 32.2, 29.1



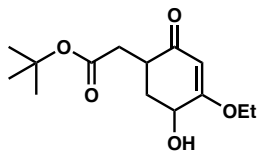
19k

6-(hydroxymethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (19k) The title compound was prepared according to the general procedure, using 2,2,6-trimethyl-4H-1,3-dioxin-4-one (71.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (65.6, 83% yield).

TLC (SiO_2) R_f = 0.54 in 30% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (s, 1H), 4.18 (s, 2H), 1.70 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 107.1, 91.8, 60.7, 24.9



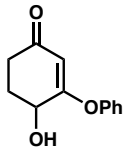
19l

***tert*-butyl 2-(4-ethoxy-5-hydroxy-2-oxocyclohex-3-en-1-yl)acetate (19l)** The title compound was prepared according to the general procedure, using tert-butyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate (127.2 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (101.4, 75% yield).

TLC (SiO_2) R_f = 0.54 in 30% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.34 (t, J = 3.5 Hz, 1H), 3.92 (t, J = 7.0 Hz, 2H), 3.09 (m, 1H), 2.69 (dd, J = 5, 11 Hz, 1H), 2.33 (dd, J = 7.5, 9.0 Hz, 1H), 2.17 (m, 1H), 2.05 (m, 1H), 1.44 (s, 9H), 1.38 (t, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 174.0, 171.7, 102.1, 80.6, 66.0, 64.7, 37.3, 35.5, 34.6, 28.1, 14.0



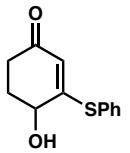
19m

4-hydroxy-3-phenoxycyclohex-2-enone (19m) The title compound was prepared according to the general procedure, using 3-phenoxycyclohex-2-enone (94.2 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (50.0 mg, 49% yield).

TLC (SiO_2) R_f = 0.30 in 50% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 2H), 5.09 (s, 1H) 4.73 (m, 1H), 2.62 (m, 1H), 2.38 (m, 2H), 2.14 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 176.1, 152.4, 130.2, 126.5, 121.2, 105.6, 66.4, 33.9, 29.4



19n

4-hydroxy-3-(phenylthio)cyclohex-2-enone (19n) The title compound was prepared according to the general procedure, using 3-(phenylthio)cyclohex-2-enone (102.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (95.7, 87% yield).

TLC (SiO_2) R_f = 0.50 in 30% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 5H). 5.38 (s, 1H), 4.64 (m, 1H) 2.63 (m, 1H). 2.34 (m, 2H), 2.16 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.3, 169.7, 135.5, 130.3, 130.1, 127.7, 120.8, 68.5, 34.2, 31.7

5.4. γ-Dihaloalkylation of Vinylogous Esters

5.4.1. General Information for γ-Dihaloalkylation of Vinylogous Esters

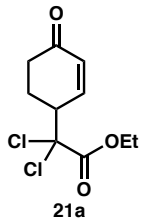
Unless otherwise stated, reactions were performed in oven-dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous dichloromethane, pentane, toluene and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[53] on a Pure Process Technology system. Molecular sieves (MS) were purchased from Aldrich and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted. 1,2-Dichloroethene was purchased from Chem-Impex International, Inc., distilled over CaH_2 prior to use, and stored over 4 Å MS under N_2 atmosphere. Sodium hydride (NaH) was purchased as 60% dispersion in mineral oil from Acros and used as received. Sodium bicarbonate ($NaHCO_3$) was purchase from Fischer Chemical and used as received. Starting materials, including 2-cyclohexen-1-one, were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. N,N,N',N'',N''-Pentamethyldiethylenetriamine (PMDTA) was purchased from Aldrich and used as received. Copper (II) trifluoromethanesulfonate was purchased from Aldrich and stored in a glovebox. Starting materials were made according to the literature procedures.3-9 Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion

temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with p-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[57] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me4Si (δ 0.0). Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Bruker Avance DRX-400 at 376 MHz and are reported relative to the external standard F_3CCO_2H (δ –76.53 ppm). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model 6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). LC/MS analyses were performed on Agilent 1200 liquid chromatography system interfaced with an Agilent 6300 ion trap mass selective detector. TBS-dienol ethers were synthesized by enolization with LiHMDS or by soft enolization according to our previous publication.[49]

5.4.2. General Procedure for Synthesis of Dihaloester Compounds

Anhydrous $Cu(OTf)_2$ (6.8 mg, 0.01875 mmol, 7.5 mol%) and $NaHCO_3$ (21 mg, 0.25 mmol, 1.0 equiv) were added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. Then the vial was sealed with a septum cap and then evacuated and backfilled with dry N_2 (three cycles). Anhydrous 1,2-dichloroethane (1 mL) and *N*, *N*, *N'*, *N''*, *N''*-pentamethyldiethylenetriamine (7.8 μL, 0.0375 mmol, 15 mol%) were injected into the vial via syringe and the mixture was stirred at 22 °C for 10 min. The α-halo compound (0.375 mmol, 1.5 equiv) and TBS dienol ether (0.25 mmol, 1.0 equiv) were injected to the vial sequentially via syringe. The mixture was warmed to 80 °C and stirred. After the reaction was complete (monitored by TLC, typically after 22 h), the mixture was cooled to room temperature, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography on silica gel. Specific quantities of reagents, procedural variations, and purification conditions may be found below in the entry containing the characterization data.

5.4.3. Experimental Data for γ-Dihaloalkylation of Vinylogous Esters



21a

ethyl 2,2-dichloro-2-(4-oxocyclohex-2-en-1-yl)acetate (21a) The title compound was prepared according to the general procedure using **tert-butyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane** (52.6 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2 20% EtOAc in hexane), the title compound was isolated as a colorless oil (55.3 mg, 88 % yield).

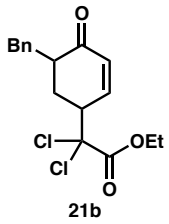
TLC (SiO_2) R_f = 0.35 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 10.4 Hz, 1H), 6.16 (d, *J* = 10.4 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.59 (m, 1H), 2.62 (m, 1H), 2.45 (m, 1H), 2.29 (m, 1H), 2.08 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 164.9, 131.3, 64.4, 48.7, 36.3, 25.1, 13.9

IR (neat) 2982, 2939, 1757, 1740, 1684, 1619, 1448, 1368, 1296, 1237, 1183, 1095, 1017, 932, 833, 785, 749, 691, 640 cm^{-1}

GC/MS (*m/z*): 215.0 (3%), 187.0 (20%), 179.0 (28%), 156.0 (37%), 141.0 (17%), 133.0 (44%), 115.0 (26%), 95.0 (100%), 85.0 (26%), 77.0 (62%), 68.0 (42%), 51.1 (51%)



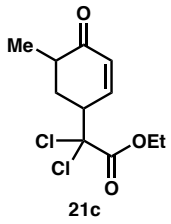
21b

ethyl 2-(5-benzyl-4-oxocyclohex-2-en-1-yl)-2,2-dichloroacetate (21b) The title compound was prepared according to the general procedure using **((6-benzylcyclohexa-1,3-dien-1-yl)oxy)(*tert*-butyl)dimethylsilane** (75.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 µL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (53.0 mg, 62% yield).

TLC (SiO_2) R_f = 0.35 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 5H), 7.05 (m, 1H), 6.20 (d, J = 10.5, 1H), 4.26 (m, 2H), 3.69 (m, 1H), 3.02 (m, 1H), 2.81 (m, 1H), 2.68 (m, 1H), 2.02 (m, 1H), 1.96 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 164.7, 149.9, 145.2, 138.2, 130.5, 129.0, 128.6, 126.7, 86.7, 64.4, 46.3, 45.0, 36.1, 27.1, 27.9, 25.7, 13.7



21c

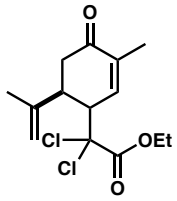
ethyl 2,2-dichloro-2-(5-methyl-4-oxocyclohex-2-en-1-yl)acetate (21c) The title compound was prepared according to the general procedure using ***tert*-butyldimethyl((6-methylcyclohexa-1,3-**

dien-1-yl)oxy)silane (56.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (20.0 mg, 30% yield).

TLC (SiO_2) R_f = 0.35 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (m, 1H), 6.10 (d, J = 10.3 Hz, 1H), 4.39 (m, 2H), 3.63 (m, 1H), 2.69 (m, 1H), 2.23 (m, 1H), 2.03 (m, 1H), 1.38 (s, 3H), 1.21 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 164.9, 144.8, 130.2, 86.6, 64.3, 44.9, 39.0, 31.3, 25.7, 16.0, 13.9



21d

ethyl 2,2-dichloro-2-((6*S*)-3-methyl-4-oxo-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)acetate (21d) The title compound was prepared according to the general procedure using **(*S*)-*tert*-butyldimethyl((2-methyl-5-(prop-1-en-2-yl)cyclohexa-1,3-dien-1-yl)oxy)silane** (66.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (47.3 mg, 62% yield).

TLC (SiO_2) R_f = 0.30 in 20% EtOAc in hexane, *p*-anisaldehyde stain

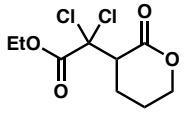
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 4.77 (d, *J* = 12.2 Hz, 2H), 4.23 (dtd, *J* =

44.6, 7.1, 3.6 Hz, 2H), 3.61 (dt, *J* = 4.7, 2.3 Hz, 1H), 3.02 (t, *J* = 6.9 Hz, 1H), 2.52 (m, 2H), 1.84 (s, 3H), 1.66 (s, 3H), 1.33 (t, *J* = 5.0 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 165.0, 143.8, 140.0, 138.3, 115.1, 87.7, 63.9, 49.7, 45.0, 41.0, 25.6, 19.2, 16.0, 13.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.4, 50.1, 45.4, 26.0, 19.6, 14.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.4, 115.5, 64.3, 50.1 (–), 45.4 (–), 41.4 (–), 26.0 (–), 19.6 (–), 16.4 (–), 14.0 (–)



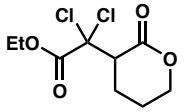
21e

ethyl 2,2-dichloro-2-(2-oxotetrahydro-2*H*-pyran-3-yl)acetate (21e) The title compound was prepared according to the general procedure using ***tert*-butyl((3,4-dihydro-2*H*-pyran-6-yl)oxy)dimethylsilane** (53.6 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (12.2 mg, 19% yield).

TLC (SiO_2) R_f = 0.50 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (m, 1H), 4.35-4.32 (m, 2H), 2.55 (dt, *J* = 6.9, 3.4 Hz, 1H), 1.90 (m, 3H), 1.38 (m, 4H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 161.9, 69.5, 65.6, 62.8, 29.8, 29.7, 22.3, 19.1, 13.7



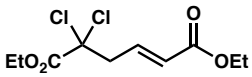
21f

ethyl 2,2-dichloro-2-(2-oxotetrahydro-2*H*-pyran-3-yl)acetate (**21f)** The title compound was prepared according to the general procedure using **((3,4-dihydro-2*H*-pyran-6-yl)oxy)trimethylsilane** (53.6 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (12.8 mg, 20% yield).

TLC (SiO_2) R_f = 0.50 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (m, 1H), 4.35-4.32 (m, 2H), 2.55 (dt, *J* = 6.9, 3.4 Hz, 1H), 1.90 (m, 3H), 1.38 (m, 4H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 161.9, 69.5, 65.6, 62.8, 29.8, 29.7, 22.3, 19.1, 13.7



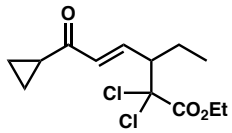
21g

diethyl (*E*)-5,5-dichlorohex-2-enedioate (**21g)** The title compound was prepared according to the general procedure using **(*Z*)-*tert*-butyl((1-ethoxybuta-1,3-dien-1-yl)oxy)dimethylsilane** (57.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (55.2 mg, 82% yield).

TLC (SiO_2) R_f = 0.45 in 50% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (m, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 4.30 (m, 2H), 4.10 (m, 2H), 3.29 (d, *J* = 7.0 Hz, 2H), 1.30 (m, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 165.2, 139.2, 127.1, 81.6, 64.0, 90.6, 25.6, 14.1, 13.8



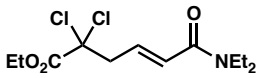
21h

ethyl (*E*)-2,2-dichloro-6-cyclopropyl-3-ethyl-6-oxohex-4-enoate (**21h)** The title compound was prepared according to the general procedure using ***tert*-butyl(((1*Z*,3*E*)-1-cyclopropylhexa-1,3-dien-1-yl)oxy)dimethylsilane** (63.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (29.3 mg, 40% yield).

TLC (SiO_2) R_f = 0.35 in 50% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (t, *J* = 9.5 Hz, 1H), 6.30 (d, *J* = 15.5 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 3.05 (m, 1H), 2.15 (m, 1H) 1.83 (m, 1H), 1.59 (1H), 1.32 (t, J = 9.0 Hz, 3H), 1.09 (m, 2H), 0.93 (t, *J* = 3.0 Hz, 2H) 0.85 (m, 2H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 165.2, 140.6, 135.2, 87.1, 64.0, 56.3, 26.0, 25.6, 23.2, 18.9, 13.8, 11.8, 11.5

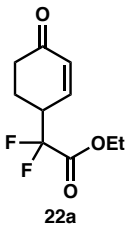


21i

ethyl (*E*)-2,2-dichloro-6-(diethylamino)-6-oxohex-4-enoate (**21i)** The title compound was prepared according to the general procedure using **(*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-*N*,*N*-diethylbuta-1,3-dien-1-amine** (63.9 mg, 0.25 mmol, 1.0 equiv) and ethyl 2,2,2-trichloroacetate (52.3 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 18 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (6.73 mg, 10% yield).

TLC (SiO_2) R_f = 0.45 in 50% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 15 Hz, 1 H), 6.23 (d, *J* = 15 Hz, 1H), 4.36 (m, 2H), 3.41 (m, 4H), 3.34 (d, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.23 (m, 6H)



22a

ethyl 2,2-difluoro-2-(4-oxocyclohex-2-en-1-yl)acetate (22a) The title compound was prepared according to the general procedure using **tert-butyl(cyclohexa1,3-dien-1-yloxy)dimethylsilane** (52.6 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2 difluoroacetate (48.1 μL, 0.375 mmol,1.5 equiv) at 80 °C for 26 h. After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless oil (48.9 mg, 90% yield).

TLC (SiO_2) R_f = 0.35 in 20% EtOAc in hexane, *p*-anisaldehyde stain

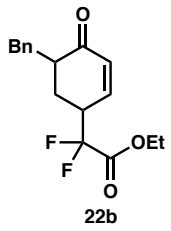
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, *J* = 10.4 Hz, 1H), 6.16 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.24 (m, 1H), 2.60 (m, 1H), 2.40 (m, 1H), 2.18 (m, 1H), 1.99 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 162.9 (t, *J* = 37.8 Hz), 143.0, 132.0, 115.4 (t, *J* = 252 Hz), 63.3, 41.4, 41.2, 41.0, 35.9, 22.2, 13.9

^{19}F NMR (376 MHz, $CDCl_3$) δ –109.87 (dd, *J* = 261.3, 12.5 Hz, 1F), –112.05 (dd, *J* = 261.2, 15.7 Hz, 1F)

IR (neat) 2923, 1759, 1687, 1419, 1391, 1374, 1285, 1148, 1098, 1076, 1019, 891, 851, 783, 744, 636 cm^{-1}

GC/MS (*m/z*): 218.0 (1%), 198.0 (3%), 145.0 (14%), 117.0 (100%), 95.0 (46%), 68.0 (42%), 51.0 (6%)



22b

ethyl 2-(5-benzyl-4-oxocyclohex-2-en-1-yl)-2,2-difluoroacetate (22b) The title compound was prepared according to the general procedure using **((6-benzylcyclohexa-1,3-dien-1-yl)oxy)(tert-butyl)dimethylsilane** (75.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5%

EtOAc in hexane), the title compound was isolated as a colorless oil (54.8 mg, 71% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.30 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

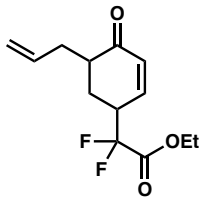
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.90 (dd, *J* = 10.3, 2.2 Hz, 1H), 6.20 (dd, *J* = 10.3, 2.4 Hz, 1H), 4.25 (m, 2H), 3.31 (m, 1H), 3.11 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.81 (m, 1H), 2.61 (dd, *J* = 13.8, 10.7 Hz, 1H), 1.96 (m, 1H), 1.83 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 162.9, 141.7, 138.3, 131.7, 128.9, 128.6, 126.6, 116.2 (d, *J* = 252 Hz), 63.3, 45.4, 38.2 (t, *J* = 22.3 Hz), 35.6, 24.9, 13.8

^{19}F NMR (376 MHz, $CDCl_3$) δ –107.84 (dd, *J* = 258.9, 11.1 Hz, 1F), –112.24 (dd, *J* = 258.9, 18.6 Hz, 1F)

IR (neat) 2929, 1759, 1736, 1679, 1603, 1496, 1453, 1390, 1373, 1242, 1177, 1143, 1043, 1011, 851, 786, 766, 732, 699, 593 cm^{-1}

GC/MS (*m/z*): 308.1 (3%), 279.1 (1%), 259.1 (2%), 197.0 (6%), 185.1 (10%), 169.0 (6%), 157.0 (2%), 143.0 (4%), 107.0 (23%), 91.1 (100%), 77.0 (5%), 65.0 (8%), 51.0 (4%)



22c

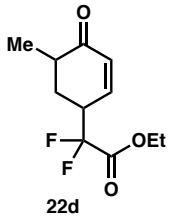
ethyl 2-(5-allyl-4-oxocyclohex-2-en-1-yl)-2,2-difluoroacetate (22c) The title compound was prepared according to the general procedure using **((6-allylcyclohexa-1,3-dien-1-yl)oxy)(*tert*-butyl)dimethylsilane** (62.5 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification

indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (32.3 mg, 50% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.30 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 10.5 Hz, 1H), 6.17 (dd, *J* = 8.0, 2.0 Hz, 1H) 5.76 (m, 1H), 5.14 (m, 1H), 5.12 (m, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 3.30 (m, 1H), 2.62 (m, 1H), 2.50 (m, 1H), 2.13 (m, 4H), 1.40 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 141.64, 141.61, 136.1, 134.9, 133.4, 132.2, 131.7, 130.9, 129.6, 119.3, 118.9, 117.7, 116.7, 63.37, 63.32, 47.0, 46.2, 43.2, 39.33, 39.29, 34.0, 33.7, 27.3, 25.5, 25.3, 14.0



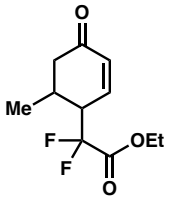
22d

ethyl 2,2-difluoro-2-(5-methyl-4-oxocyclohex-2-en-1-yl)acetate (22d) The title compound was prepared according to the general procedure using **((6-allylcyclohexa-1,3-dien-1-yl)oxy)(*tert*-butyl)dimethylsilane** (62.5 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (30.2 mg, 48% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.30 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.14 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.39 (m, 2H), 3.29 (ddt, *J* = 10.6, 5.4, 2.8 Hz, 1H), 2.67 (q, *J* = 6.5 Hz, 1H), 2.16 (m, 1H), 1.95 (dd, *J* = 13.4, 6.6 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 141.4, 131.5, 63.3, 38.4, 38.3, 28.7, 15.4, 14.0



22e

ethyl 2,2-difluoro-2-(6-methyl-4-oxocyclohex-2-en-1-yl)acetate (22e) The title compound was prepared according to the general procedure with *tert*-butyldimethyl((5-methylcyclohexa-1,3 dien-1-yl)oxy)silane (56.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (36.7 mg, 63% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.25 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

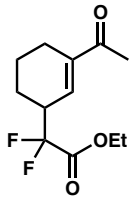
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 10.3, 3.5 Hz, 1H), 6.17 (d, *J* = 10.3 Hz, 1H), 4.36 (app. q, *J* = 7.1 Hz, 2H), 2.98 (m, 1H), 2.63 (dd, *J* = 16.6, 4.6 Hz, 1H), 2.39 (m, 1H), 2.22 (dd, *J* = 16.7, 8.3 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 163.2, 141.7, 131.9, 115.8 (t, J = 264.6), 63.4, 47.1 (t, J = 21.5 Hz), 43.8, 29.3, 20.5, 13.9

^{19}F NMR (376 MHz, $CDCl_3$) δ –105.81 (dd, J = 261.6, 13.1 Hz, 1F), –107.66 (dd, J = 261.6, 14.5 Hz, 1F)

IR (neat) 2963, 2924, 2854, 1760, 1737, 1682, 1461, 1393, 1198, 1164, 1127, 1093, 1075, 1048, 1010, 856, 749, 637, 568 cm^{-1}

GC/MS (*m/z*): 232.0 (1%), 212.1 (2%), 169.0 (2%), 159.0 (8%), 138.0 (4%), 124.0 (6%), 109.1 (100%), 89.0 (23%), 79.1 (6%), 68.0 (38%), 51.1 (4%)

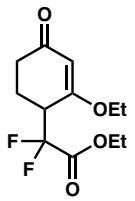


22f

ethyl 2-(3-acetylcyclohex-2-en-1-yl)-2,2-difluoroacetate (22f) The title compound was prepared according to the general procedure using **(*E*)-*tert*-butyl(1-(cyclohex-2-en-1-ylidene)ethoxy)dimethylsilane** (59.6 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (29.6 mg, 48% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.45 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (s, 1H), 4.38 (q, *J* = 6.6 Hz, 3H), 2.35 (s, 3H), 2.14 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.67 (m, 4H)



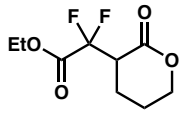
22g

ethyl 2-(3-acetylcyclohex-2-en-1-yl)-2,2-difluoroacetate (22g) The title compound was prepared according to the general procedure using **(*E*)-*tert*-butyl(1-(cyclohex-2-en-1-ylidene)ethoxy)dimethylsilane** (59.6 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (29.6 mg, 48% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.45 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (s, 1H), 4.38 (q, *J* = 6.6 Hz, 3H), 2.35 (s, 3H), 2.14 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.67 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 145.1, 142.8, 140.0, 132.77, 132.73, 63.1, 62.6, 41.8, 41.65, 41.48 (t, *J* = 88.4 Hz), 26.4, 25.4, 22.7, 22.6, 21.61, 21.46, 21.38, 20.4, 14.1, 14.0



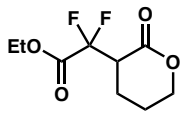
22h

ethyl 2,2-difluoro-2-(2-oxotetrahydro-2*H*-pyran-3-yl)acetate (22h) The title compound was prepared according to the general procedure using ***tert*-butyl((3,4-dihydro-2*H*-pyran-6-yl)oxy)dimethylsilane** (60.3 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (17.8 mg, 32% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.55 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (m, 5H), 3.07 (td, *J* = 7.0, 4.1 Hz, 1H), 2.71 (td, *J* = 6.8, 3.6 Hz, 1H), 2.00 (m, 2H), 1.38 (dt, *J* = 9.4, 7.3 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 68.7, 68.2, 62.8, 62.4, 23.5, 22.4, 21.4, 20.7, 14.0, 13.7



22i

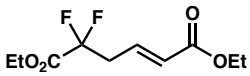
ethyl 2,2-difluoro-2-(2-oxotetrahydro-2*H*-pyran-3-yl)acetate (22i) The title compound was prepared according to the general procedure using **((3,4-dihydro-2*H*-pyran-6-yl)oxy)trimethylsilane** (43.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate

(48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (2.77 mg, 5% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.55 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (m, 5H), 3.07 (td, *J* = 7.0, 4.1 Hz, 1H), 2.71 (td, *J* = 6.8, 3.6 Hz, 1H), 2.00 (m, 2H), 1.38 (dt, *J* = 9.4, 7.3 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 68.7, 68.2, 62.8, 62.4, 23.5, 22.4, 21.4, 20.7, 14.0, 13.7



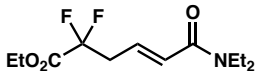
22j

diethyl (*E*)-5,5-difluorohex-2-enedioate (22j) The title compound was prepared according to the general procedure using **(*Z*)-*tert*-butyl((1-ethoxybuta-1,3-dien-1-yl)oxy)dimethylsilane** (57.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (18.9 mg, 32% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.32 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (m, 1H), 6.00 (d, J = 16 Hz, 1H), 4.33 (m, 2H), 4.20 (m, 2H), 2.98 (m, 2H), 1.34 (m, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 163.5, 163.3m 163.0 (t, *J* = 127 Hz), 136.1, 136.0, 133.0 (t, *J* = 21.5 Hz), 127.4, 114.4, 63.1, 60.6, 37.5, 37.3, 37.1 (t, *J* = 96 Hz), 25.8, 25.7, 25.6, 14.1, 13.9



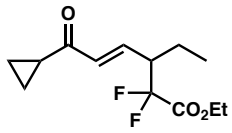
22k

ethyl (*E*)-6-(diethylamino)-2,2-difluoro-6-oxohex-4-enoate (22k) The title compound was prepared according to the general procedure using **(*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-*N*,*N*-diethylbuta-1,3-dien-1-amine** (63.4 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (13.2 mg, 20% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.45 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (m, 1H), 6.24 (dd, *J* = 14.9, 1.6 Hz, 1H), 4.34 (d, *J* = 7.1 Hz, 1H), 3.42 (m, 5H), 1.21 (m, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 165.8, 141.1, 131.3, 127.1, 121.9, 116.07, 115.99, 62.1, 42.1, 40.7, 18.2, 14.8, 13.2



22l

ethyl (*E*)-6-cyclopropyl-3-ethyl-2,2-difluoro-6-oxohex-4-enoate (22l) The title compound was prepared according to the general procedure using ***tert*-butyl(((1*Z*,3*E*)-1-cyclopropylhexa-1,3-dien-1-yl)oxy)dimethylsilane** (63.1 mg, 0.25 mmol, 1.0 equiv) and ethyl 2-bromo-2,2-difluoroacetate (48.1 μL, 0.375 mmol, 1.5 equiv) at 80 °C for 24 h. Crude ^{1}H NMR prior to purification indicated a single diastereomer. After purification by flash chromatography (SiO_2, 12.5% EtOAc in hexane), the title compound was isolated as a colorless oil (9.78 mg, 15% yield), comprising a single diastereomer (based on ^{1}H NMR of purified material).

TLC (SiO_2) R_f = 0.40 in 12.5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (dd, J = 9.5, 6.5 Hz, 1H), 6.32 (d, J = 15.5 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 2.86 (m, 1H), 2.16 (m, 1H), 1.83 (1H0 1.35 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 3.0 Hz, 3H), 0.95 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 163.5, 138.57, 138.54, 135.2, 117.8, 115.8, 113.7, 63.0, 49.37, 49.20, 49.02, (t, *J* = 88 Hz) 20.0, 18.9, 13.9, 11.5, 11.4

PART TWO

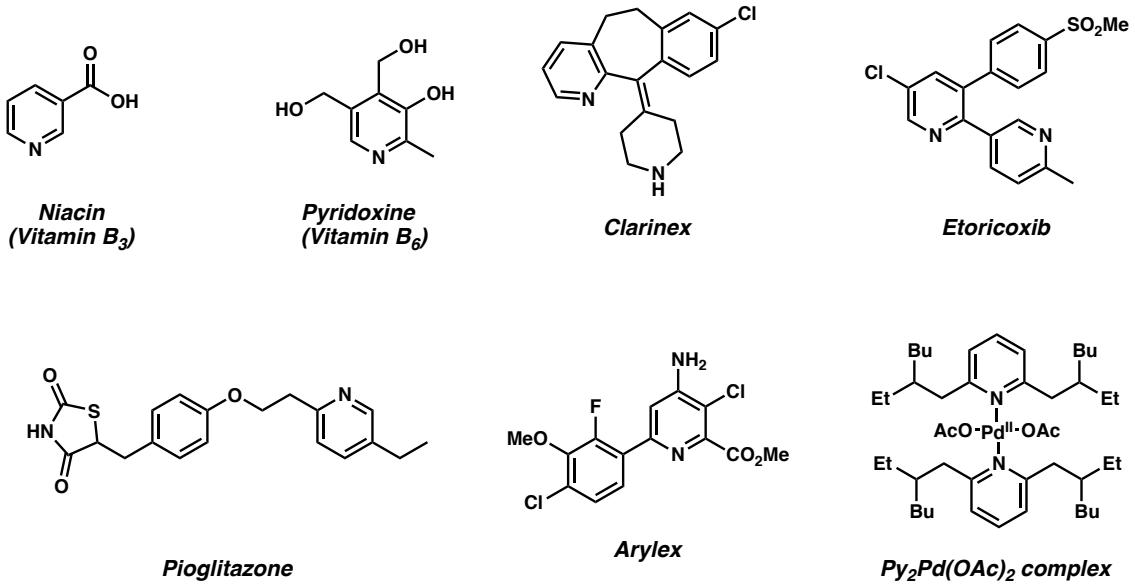
Synthesis of Sterically Demanding Pyridines

6. Introduction

6.1. Previous Methods to Access Pyridines

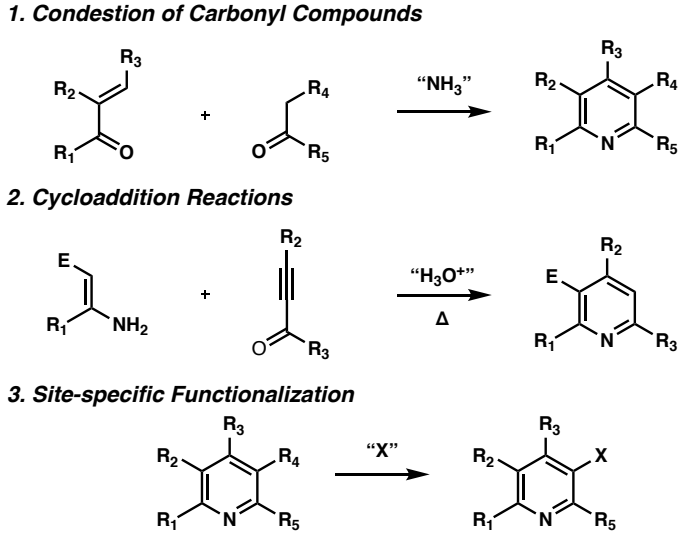
Although the pyridine ring may be simple in structure, arguably it is regarded as one of the most important heteroaromatic structures (Scheme 55). It is naturally occurring in many vital compounds such as the vitamins niacin and pyridoxine (vitamins B_3 and B_6, respectively).[66] Other well recognized pharmaceutical drugs, such as, the antihistamine Clarinex, the Cox-2 inhibitor Etoricoxib, and the anti-diabetic Pioglitazone all contain the pyridine motif.[66] Pyridines are also important components in herbicides, best represented by Dow's leading agriculture product, Arylex.[67] In terms of synthetic applications, research groups such as the Yu group have also utilized substituted pyridines as ligands for first and second-row transition metal ligands to form reactive complexes capable of innovative transformations.[68]

Scheme 55: Common Pyridines



Owing to the importance of pyridines, various methodologies dedicated to the synthesis of this valuable heterocycle have been developed. Their prevalence in medicinal and agrichemical compounds have made them popular target molecules in the synthetic community. Therefore, only three of the most general approaches to access these common structural motifs will be discussed (Scheme 56, 1→3). The first method relies on utilizing functionalized precursors to construct the pyridine ring, often times through the condensation of carbonyl compounds. The second is the less explored method of cycloaddition reactions. Lastly, the synthesis of a desired pyridine may rely on the site-specific functionalization of an existing pyridine.[69] Since there are countless of examples in literature of the latter strategy, it should be noted that only ring-construction reactions will be discussed below as oppose to ring functionalization.

Scheme 56: General approaches for pyridine synthesis

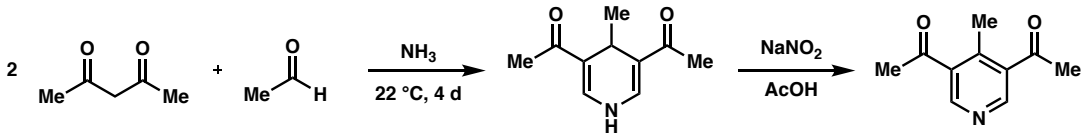


The first strategy has been the focus of several groups that have pioneered protocols involving carbonyl compounds and the use of ammonia/ammonia equivalents. For over a century now, this has been the common route to access substituted pyridines, resulting in a number of classical

named reactions including the Hantzsch dihydropyridine (pyridine) synthesis,[70] the Chichibabin pyridine synthesis,[71] the Bohlmann–Rahtz synthesis,[72] and the Kröhnke pyridine synthesis (Scheme 57).[73] The methods developed by Hantzsch and Chichibabin, although reliable, require the use of ammonia, which is a significant hazard to researchers' health. Also, the Bohlmann–Rahtz synthesis requires harsh reaction conditions given that the dehydration step occurs under vacuum. Unlike the Hantzsch synthesis, the Kröhnke method does not require a separate oxidation step. However, the condensation of acylmethylpyridinium salts with α,β-unsaturated ketones still requires the same nitrogen source, ammonia. Among classical pyridine synthesis, the Bönnemann cyclization stands out for its innovative [2 + 2 + 2] cycloaddition of alkynes and nitriles.[74] Though most of their reported yields were over 90%, they found that the scope of the nitrile and alkyne components limited the transformation. Overall, these classical approaches suffer from common limitations such as the employment of pre-functionalized starting materials and regioselectivity issues.

Scheme 57: Previous methods to access pyridines

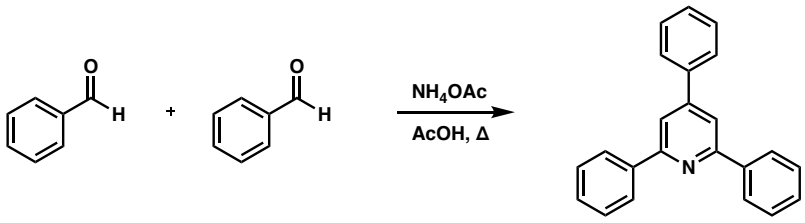
Hantzsch Dihydropyridine (Pyridine) Synthesis (1881)



51% yield

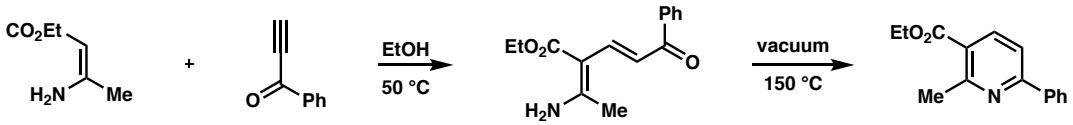
83% yield

Chichibabin Pyridine Synthesis (1906)



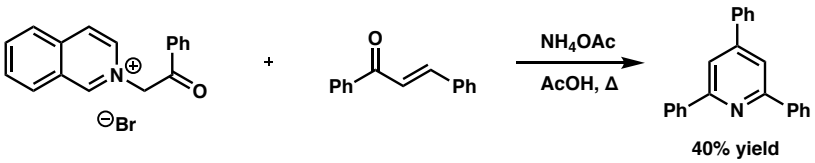
68% yield

Bohlmann-Rahtz Pyridine Synthesis (1957)



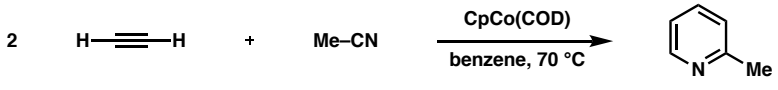
90% yield

Kröhnke Pyridine Synthesis (1961)



40% yield

Bönnemann Cyclization (1978)



93% yield

6.2. Pyridine Synthesis via Ring Expansion of Pyrrole: The Ciamician–Dennstedt Rearrangement

As outlined in Part 1, our work has been primarily focused on the chemical transformations attainable via reactions of diene systems in dienolate intermediates with a variety of electrophiles. Next, we wanted to investigate the reactivity of the heterocylic diene equivalent, pyrrole (Scheme 58). Although it may not be obvious, and we inherently wouldn't classify pyrroles as dienes, the structure and nucleophilicity of pyrrole is seemingly similar to the dienes employed in Part 1.

Scheme 58: Pyrrole nomenclature

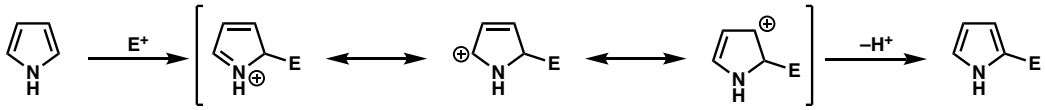
pyrrole
1*H*-pyrrrole

We were interested in studying the reactivity of pyrroles, specifically the reactivity of the diene system. Despite only having 4π-systems, pyrroles react similar to that of 6π-systems, such as benzene or aniline. Although pyrrole is aromatic, it differs from other 6π-systems, in that both of the lone pair electrons are contributing to the aromatic system. As part of the delocalized π electron system, the lone pairs are consequently not available for bonding to a proton. Protonation of the nitrogen in pyrrole is very unfavorable as it would destroy aromaticity. In the presence of a stronger acid, however, protonation of the nitrogen atom is inevitable resulting in the loss of aromatic character originally present (Scheme 59). The pyrrolium cation (pk_a –3.8) can be considered a very strong acid, and thus pyrrole is not all basic.[75] The high reactivity of the protonated species is akin to classical diene systems. However, these species are unstable and prone to polymerization.[76] As a result, pyrroles work well in electrophilic substitution reactions, even better than benzene as the ring is more electron rich due to donation by nitrogen.

Scheme 59: Protonation of pyrrole

The increased reactivity at the C-2 and C-5 (α-positions) of pyrroles is well credited to the stabilized resonance contributors that result in the presence of an electrophile (Scheme 60). For that reason, there are two general ways in which pyrroles can react, either directly with a strong electrophile or via a cycloaddition reaction. The former has been well studied and to that end, there is a wide range of transformations including, nitration, halogenation, sulfonation, acylation, and alkylation reactions.[77]

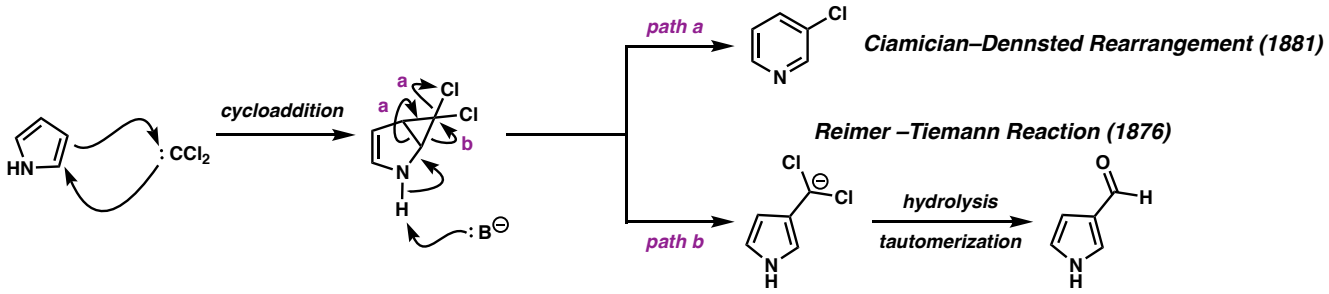
Scheme 60: Reactivity of pyrroles with electrophiles



One intriguing reaction featuring pyrroles that we were particularly interested in is the Ciamician and Dennstedt rearrangement reaction.[78] In 1881, Ciamician and Dennstedt reported a ring-expansion reaction of pyrrole in the presence of chloroform in an alkaline solution leading to 3-chloropyridine (Scheme 61). The transformation proceeds via cyclopropanation of one of the π-bonds of a pyrrole with *in situ* formed dichlorocarbene and subsequent base-induced ring opening (path a). Prior to Ciamician and Dennstedt's work, Reimer and Tiemann reported the formylation of pyrroles via formation of the same dichloro[3.1.0]cyclopropane adduct.[79] However, the rearrangement step differs from Ciamician and Dennstedt's report as it occurs via cleavage of the exocyclic bond, followed by hydrolysis of the dichloromethyl moiety to generate

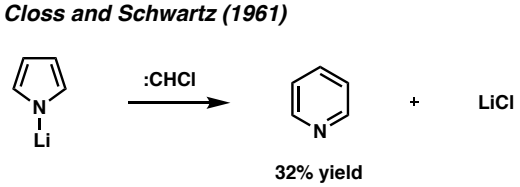
the formylation product (path b). It should be noted, that Reimer and Tiemann observed both potential products along with several byproducts all in poor yield.

Scheme 61: Addition of dichlorocarbene to pyrroles



Although very efficient, the Ciamician–Dennsted was under utilized within the synthetic community until about the 1960s. Closs and Schwartz reinvigorated interest in the reaction with their attempt to diversify the reagents required for the rearrangement to occur (Scheme 62).[80] They reported the formation of pyridine upon the addition of methylithium to a solution of pyrrole in methylenechloride. Notably, their approach employs the formation of a monochlorocarbene species under highly basic conditions. Unfortunately, their interest was short-lived as this was their sole example.

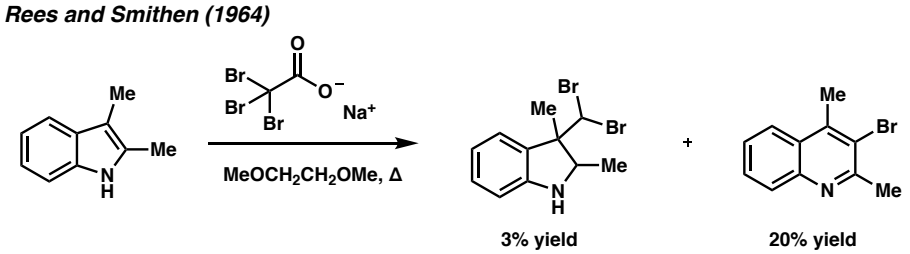
Scheme 62: Closs and Schwartz ring expansion of lithiated pyrrole



In 1964, Rees and Smithen pursued a similar goal by utilizing a different dihalocarbene precursor, such as sodium tribromoacetate (Scheme 63).[81] Lamentably, the reaction products

were isolated as a mixture of isomers in very poor yield. Nevertheless, they expanded the substrate scope of the transformation to produce quinolines from substituted indoles.

Scheme 63: Rees and Smithen of substituted indole



More recently, several groups have made exhaustive efforts to improve and develop optimal reaction conditions for the Ciamician–Dennstedt rearrangement. Specifically, flash vacuum pyrolysis of chloroform with pyrroles,[82] pyrazoles,[83] indoles,[84] or imidazoles[85] has been reported. Also, in terms of carbene scope, phenyl(trichloromethyl)mercury has also been implemented as a dichlorocarbene precursor.[5] Additionally, dichlorocarbenes have also been generated under electrochemical conditions for the synthesis of 3-chloroquinolines from indoles, albeit in poor to fair yields.[86] However, the employment of harsh reactions conditions and low reaction yields deter widespread use of these methods.

6.3. Summary

Although much attention has been focused on the synthesis of key heterocyclic building block pyridine, the majority of methods are still dependent on pre-functionalized starting materials, employ a hazardous nitrogen source, and result in low reaction yields and regioselectivity. Moreover, the methods discussed are also limited to simpler and often, only symmetrical

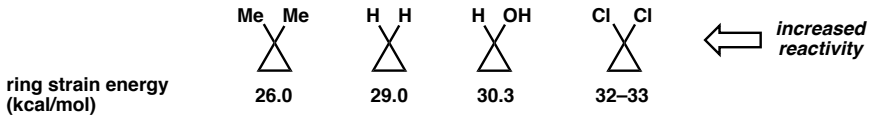
pyridines. Therefore, a safe and modular method to access highly substituted pyridines in a general and efficient manner remains a significant challenge to overcome.

7. Ciamician–Dennstedt Rearrangement of Sterically Hindered Pyrroles

7.1. Reaction Development

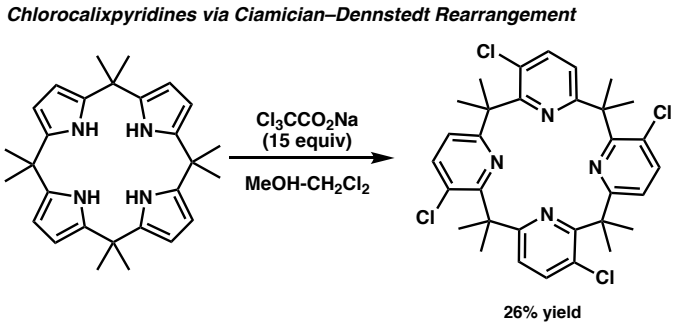
We inferred that the Ciamician–Dennstedt reaction is facilitated by the ring strain present in cyclopropane intermediate (*vide infra*). It is well known that [3.1.0] ring systems open at a rate 200 times faster than the analogous [4.1.0] ring systems. [87] Apparently, relief of strain appears to be the main driving force for ring expansion (Scheme 64). Hence, we believed increasing the substitution pattern of the pyrrole system might result in enhanced reactivity. Thus, we aimed to develop an efficient Ciamician–Dennstedt reaction of sterically congested pyrroles to generate a broad scope of substituted 3-halopyridines. Ultimately, this will provide a solution to the long-standing synthetic challenge of preparing sterically encumbered pyridines. These moieties are particularly prized for applications where non-nucleophilic bases are required.

Scheme 64: Ring strain in cyclopropanes



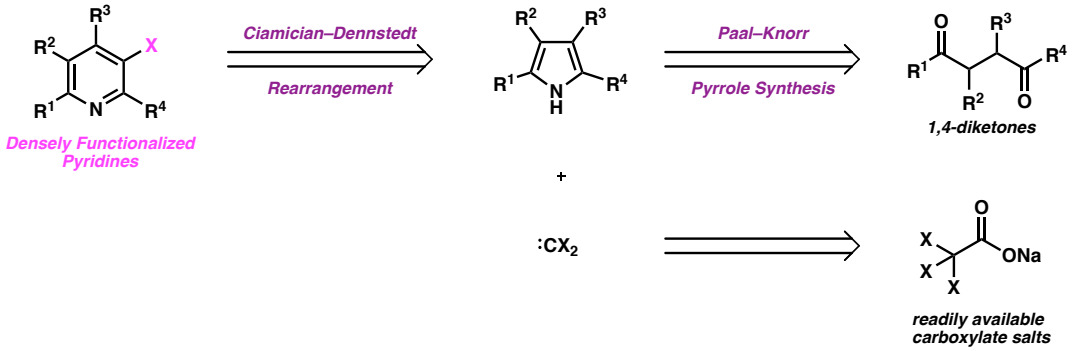
To the best of our knowledge, there is only one example of a Ciamician–Dennstedt reaction of bulky pyrroles. In 1998, Sessler and co-workers reported a ring-exapnsion of calix[4]pyrroles with sodium trichloroacetate, which produced all four constitutional isomers chlorocalixpyridines (Scheme 65).[88] Although very promising, the rearrangement has yet to be utilized for the synthesis of other sterically encumbered halopyridines.

Scheme 65: Chlorocalixpyridines via Ciamician–Dennstedt rearrangement



The overall objective of this chemistry was to create a modular synthesis to achieve customizable polysubstituted pyridines in a highly efficient and selective manner (Scheme 66). By appending diverse functional groups on the 1,4-diketones and then subjecting them to the Paal–Knorr protocol,[89] we could produce a number of substituted pyrrole precursors within reasonable time and ease. Inspired by Sessler's report, we aim to employ dihalocarbene sources derived from from readily available carboxylate salts to promote the Ciamician–Dennstedt rearrangement of sterically hindered pyridines.

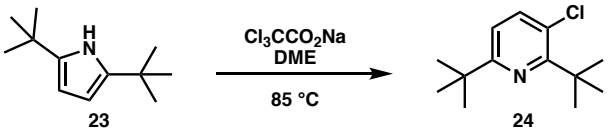
Scheme 66: Strategy for synthesis of 3-chloropyridines



7.2. Optimization of the Reaction Conditions

We began our initial investigation by utilizing conventional Ciamician–Dennstedt reaction conditions for the ring expansion of 2,5-di-*tert*-butyl-1*H*-pyrrole **23** to furnish 3-chloro-2,6-di-tertbutlypyridine (DTBP-Cl) **24** (Scheme 67). Expectedly, utilizing a variety of traditional alkoxide/alcohol protocols yielded poor results. At this point, we sought alternative dihalocarbene sources. Among the economical and commercially available dihalocarboxylate salts tested, success was only found with sodium trichloracetate. Additionally, pyrroles were also exposed to dihalocarboxylic acids along with a variety of bases in anticipation of the salt forming *in situ*. Unfortunately, only a trace amount of product was observed in these cases. Therefore, we continued our optimization studies with the use of the inexpensive trichloroacetate salt.

Scheme 67: Optimization of reaction conditions



23 24

[Pyrrole]	% yield
0.5 M	44%
0.625 M	58%
0.75 M	60%
0.8 M	61%
0.85 M	67%
1.0	59%

Pyrrole 1.0 equiv
Cl_3CCO_2Na 6.0 equiv

Cl_3CCO_2Na equiv	% yield
3.0	37%
3.5	58%
6.0	67%
6.5	78%
7.0	79%
7.5	73%
7.5*	45%
7.7	83%
8.0	75%

1.0 equiv Pyrrole
0.8 M Pyrrole
*with diglyme at 162 °C

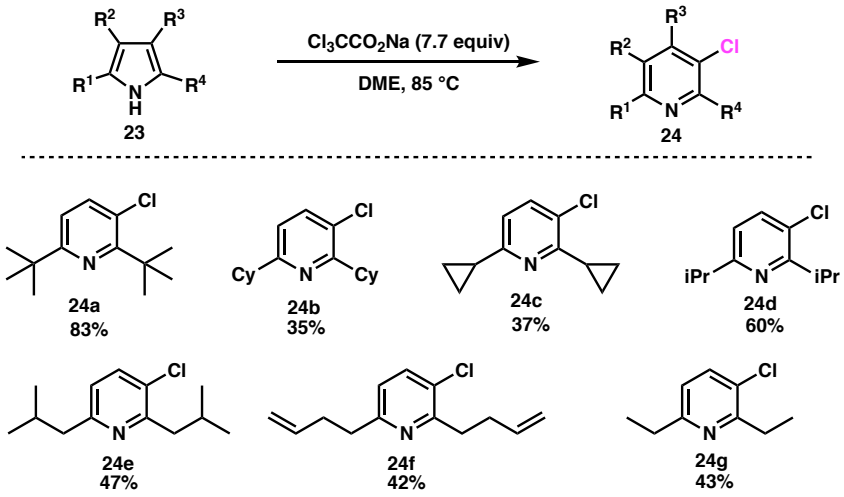
At the beginning stages of the optimization process, we found that the trichloroacetate salt was insoluble in nearly all solvents we tested. Among those screened, we found some success with the use of 1,2-dimethoxyethane (DME) and diglyme. Ultimately, when compared, DME was the

optimal solvent for the transformation. As for the equivalence of the trichloroacetate salt, we were able to observe a general trend. Increased equivalents of the salt resulted in higher yields obtained for the desired 3-chloropyridine, reaching a plateau after 7.7 equivalents. Lastly, we tested the effect of solvent concentration and it was found that 0.80 M resulted in 83% isolated yield of **24**.

7.3. Scope and Limitations

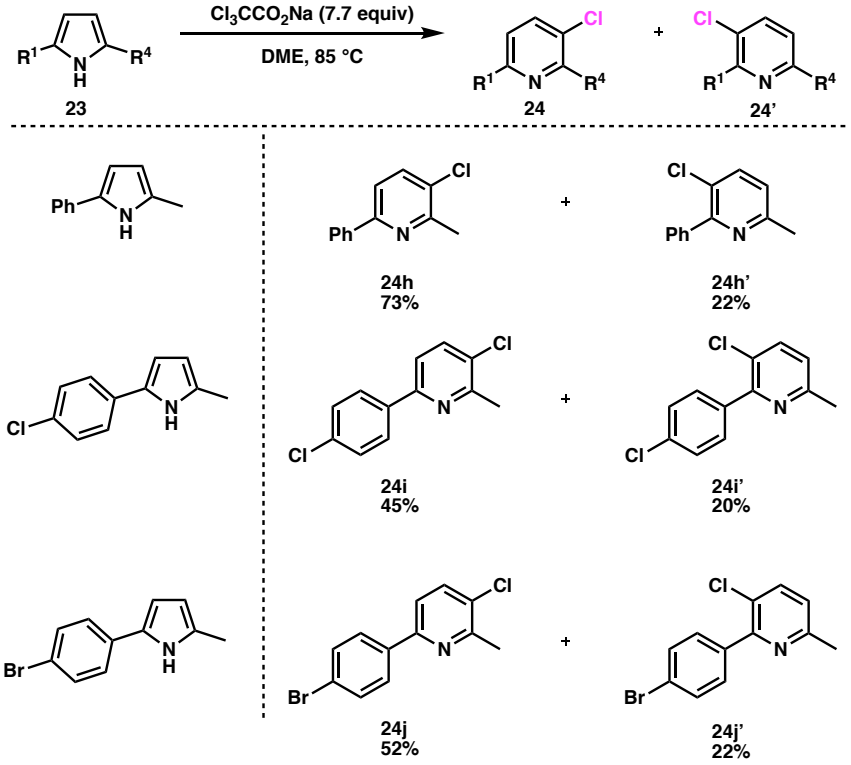
Our exploration of the substrate scope began with symmetrical pyrroles (Scheme 68). We were able to obtain fair to good yields for a number of substituted pyridines (**24b–g**). Pyrroles possessing 2,6-di-substituted cycloalkanes reacted well, producing **24b–c** in respectable yields. Likewise, substrates containing acyclic aliphatic chains resulted in their corresponding pyridine products in good yields (**24d–g**) under our reaction conditions. Notably, a pyrrole substrate with a competitive reacting site (alkene attachment), furnished the desired product in a highly selective manner (**24f**). Overall, these results were very encouraging as past reports to utilize bulky pyrroles for the Ciamician–Dennstedt rearrangement failed to produce such yields under mild conditions.

Scheme 68: Scope of symmetrical 2,6-disubstituted-3-chloropyridines



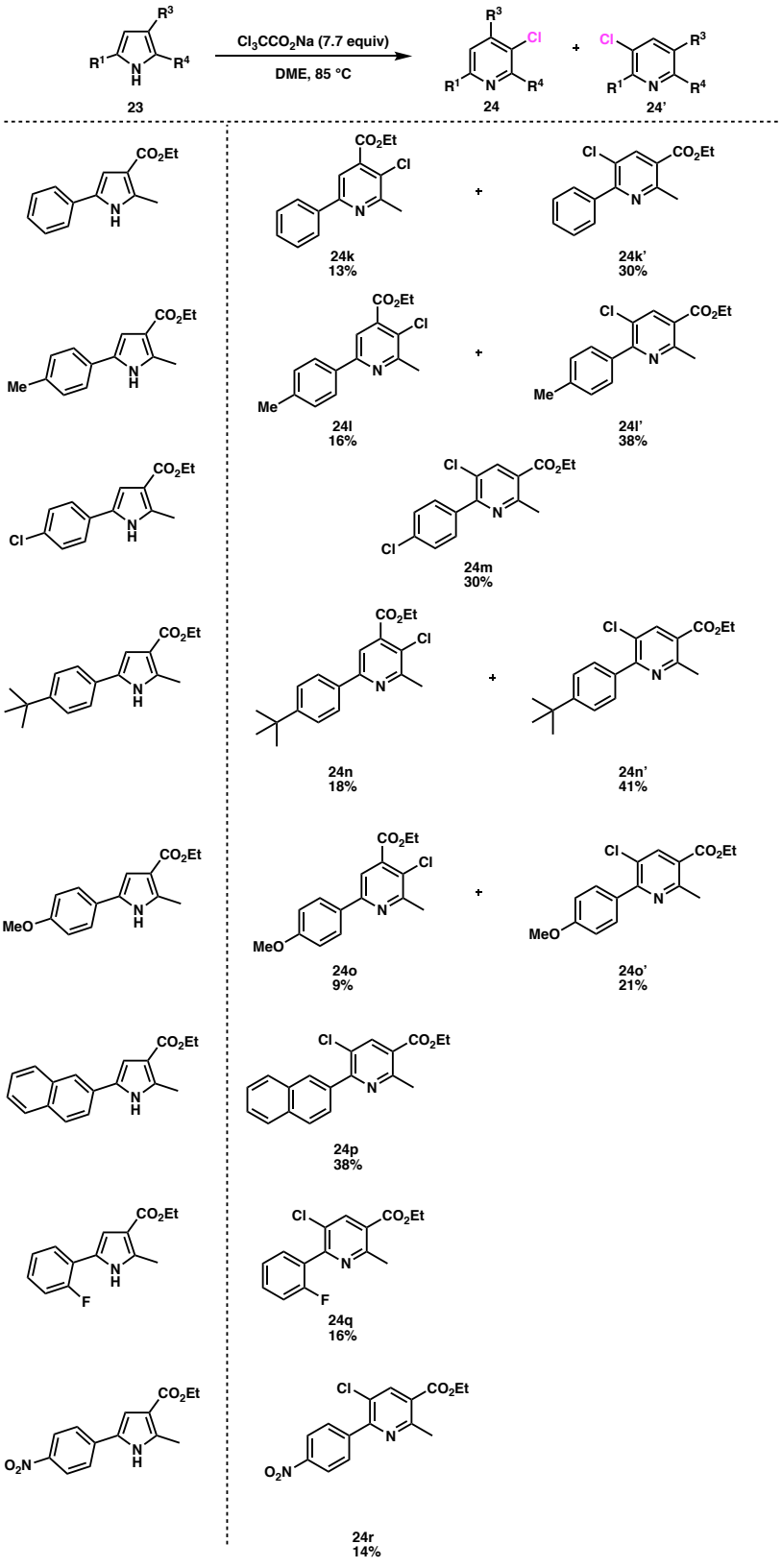
Next, unsymmetrical pyrroles were tested under our reaction conditions (Scheme 69). In these cases, we observed both isomers. We noted a general trend in which the carbene added preferentially on the least hindered double bond of the pyrrole. Separation of both isomers proved to be facile via column chromatography.

Scheme 69: Scope of unsymmetrical 2,6-disubstituted-3-chloropyridines



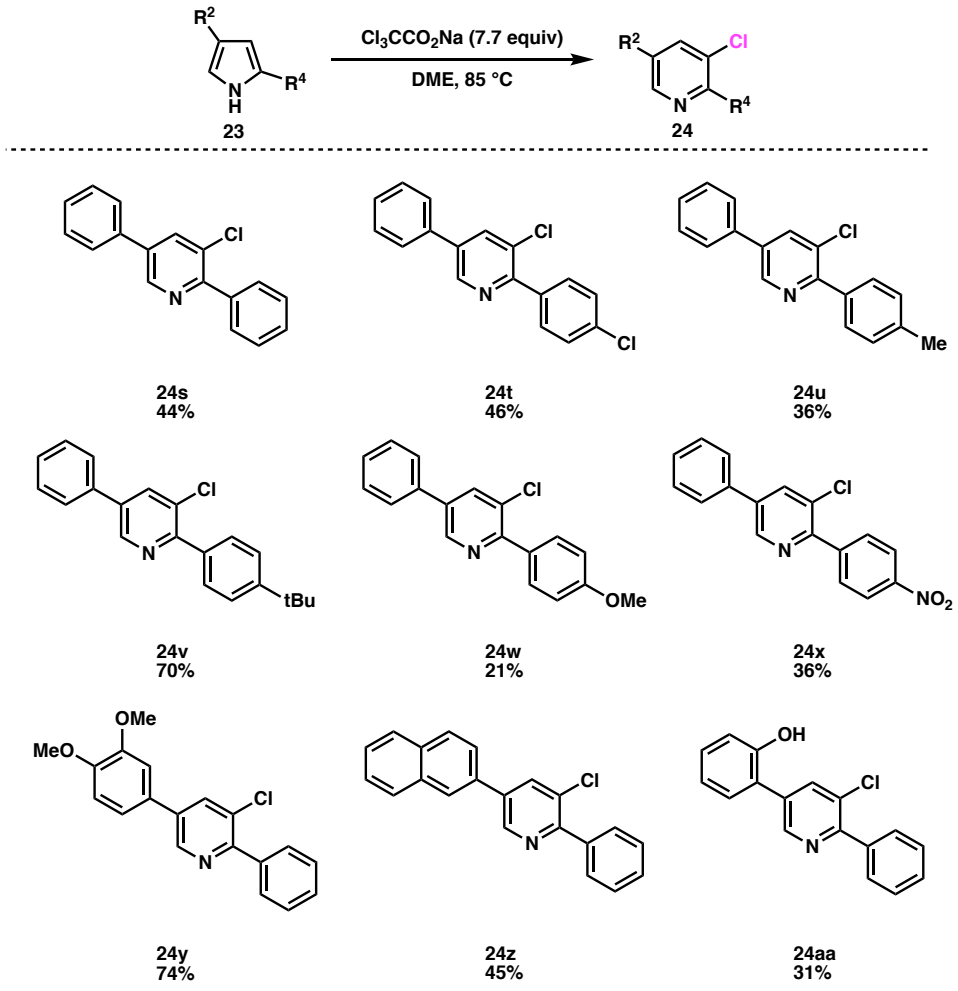
A variety of trisubstituted pyrroles containing an ester moiety were tested (Scheme 70). In most cases, 5-chloropyridines were obtained as the major product. To our delight, both isomers were isolable via column chromatography. Interestingly, it was found that 3-ester-pyrroles containing an electron-withdrawing arene substituent at the 5-postion resulted in the formation of 5-chloropyridines as the sole regioisomer (**24m,p,q–r**), albeit in low efficiency. However, the reaction was most efficient with alkyl substituents at the 2-postion and with electron-rich arenes at the 5-position (**24k–l,n**).

Scheme 70: Scope of ester halopyridines

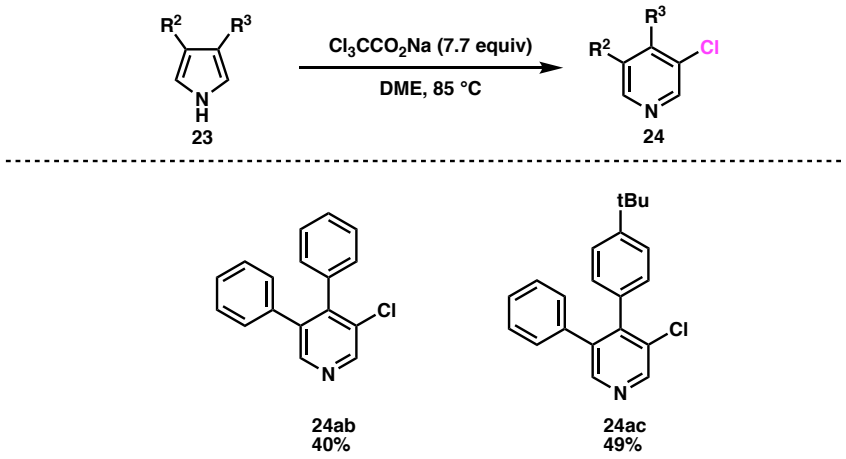


Our studies also included the exploration of 2,3-disubstituted pyrroles (Scheme 71) and 3,4-disubstituted pyrroles (Scheme 72). For the former case, the substrate scope was found to be quite broad; 2,3-disubstituted pyrroles possessing both electron-withdrawing groups and electron-donating groups all reacted well (**24–aa**). As for the latter, 3,4-disubstituted pyrroles worked, however, the substrate scope was limited (**24ab–24ac**).

Scheme 71: Scope of 3-chloro-2,5-disubstituted pyridines



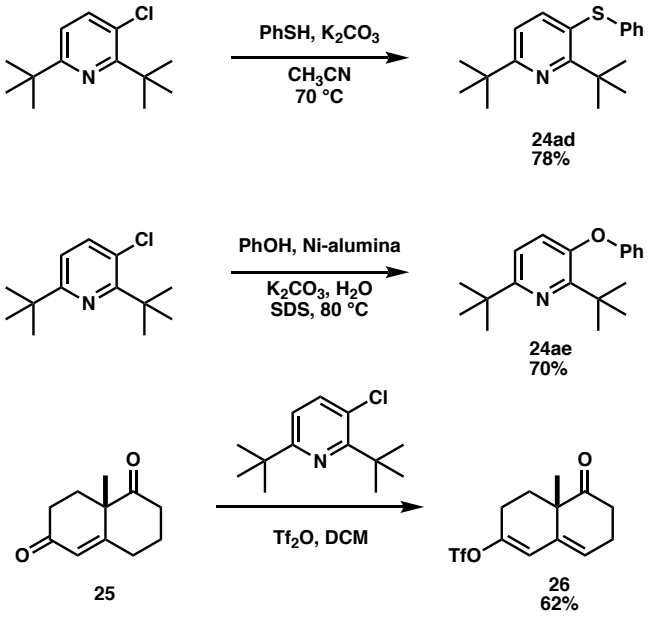
Scheme 72: Scope of 3-chloro-4,5-disubstituted pyridines



7.4. Synthetic Applications

In order to explore the prospect of heterocyclic synthesis, we employed 3-chloropyridine **24a** in a few synthetic transformations (Scheme 73). Nucleophilic aromatic substitution of **24a** with thiophenol generated **24ad** in 71% yield.[90] Next, etherification of **24a** with phenol resulted in diaryl ether **24ae** in good yield utilizing recyclable alumina-supported nickel nanoparticles.[91] These transformations are also encouraging when considering the possibility of forming solid-supported reagents. Lastly, we attempted to use **24a** as a non-nucleophilic hindered base in the enolization of the Wieland–Miescher ketone, which proceeded successfully (**25→26**). [92]

Scheme 73: Synthetic applications of 3-chloropyridine



7.5. Summary

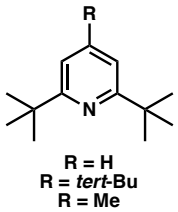
In summary, we present an expansion on the Ciamician–Dennstedt rearrangement reaction. Although first reported in 1881, it is widely underutilized in the synthetic chemistry community. This lack of precedence served to encourage our efforts to explore and expand upon the reaction with the aim of producing a broader scope under mild conditions. Past methods that feature the Ciamician–Dennstedt rearrangement have been limited to the use of excess dihalocarbene precursor and low yields with only few examples. With our efficient protocol, we have provided a wide scope of halopyridines with commercially available carboxylate salts. Notably, our protocol provides expeditious access to sterically hindered pyridines, which are synthetically difficult to obtain. Moreover, our Ciamician–Dennstedt rearrangement method allows us to access largely sterically encumbered polysubstituted halopyridines from customizable pyrroles. Thus, the halogen installed on the pyridine opens a wide array of possibilities for future chemical manipulation.

8. Discovery of 2,6-bis(2-methoxypropan-2-yl)pyridine as a Highly Efficient Base

8.1. Uses of 2,6-di-*t*-butylpyridine as a base

Our methodology for the synthesis of 3-chloropyridines inspired us to delve further into the area of heterocyclic chemistry. We were particularly interested in the common base, 2,6-di-*t*-butylpyridine (DTBP). Brown and Kanner introduced 2,6-di-*t*-butyl-4-alkyl-pyridine and its derivatives[93] as non-nucleophilic mild bases in 1953 (Scheme 74). Since then, syntheses of these bases have been scarcely reported, despite their widespread use.

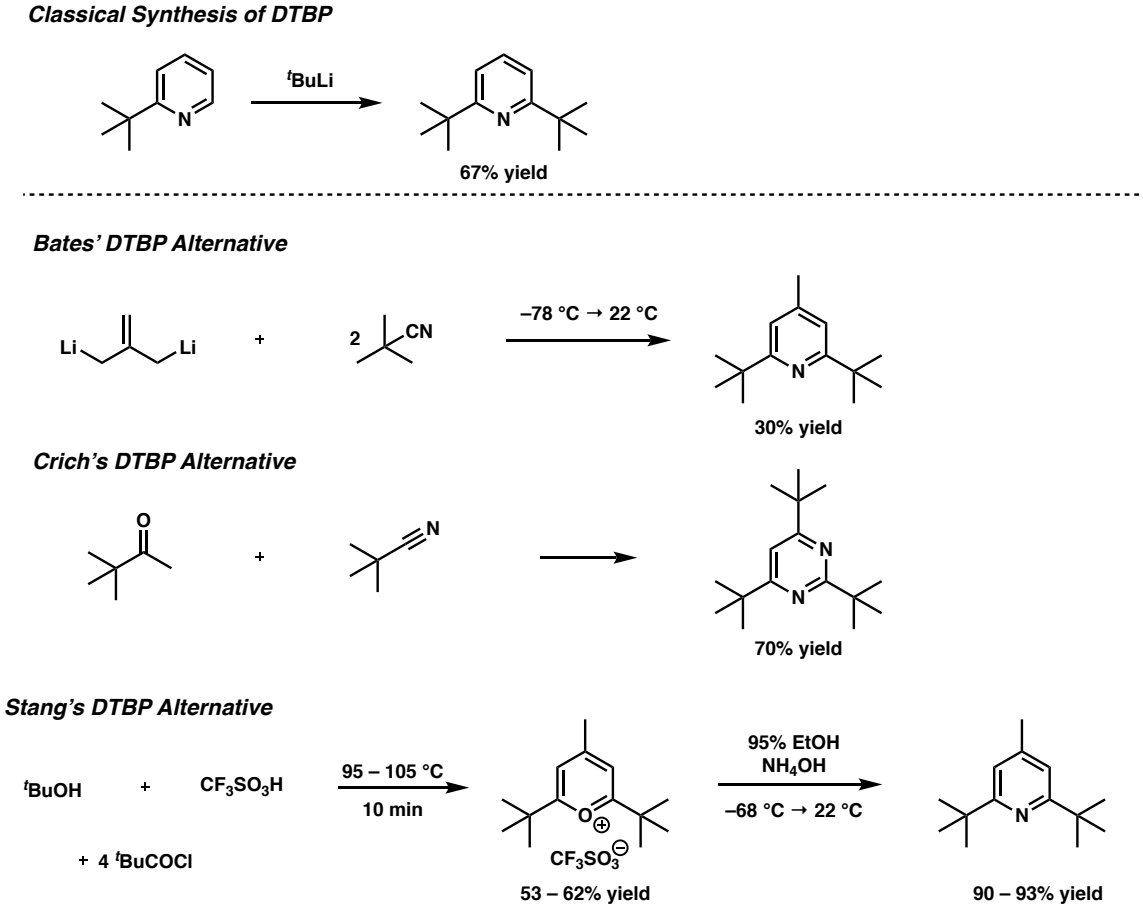
Scheme 74: 2,6-di-*tert*-butylpyridine derivatives



Of the aforementioned syntheses, the classical method to synthesize DTBP and a few notable alternatives are highlighted below (Scheme 75). The Brown group first reported the synthesis of DTBP from 2-*t*-butylpyridine and excess ^{t}BuLi.[93] Since then, other groups have reported multiple, one-pot or sequential additions of *tert*-butylmetal reagents or anionic equivalents to pyridine or substituted pyridines in order to access these bases.[94] Specifically, Bates' synthesis of 2,6-di-*t*-butyl-4-methylpyridine, the condensation of dilithio isobutylene with two equivalents of pivalonitrile, is low yielding and therefore, limited to small-scale synthesis.[95] More recently, the Crich group reported that 2,4,6-tri-*t*-butylpyrimidine (TTBP) serves as an "admirable" replacement for DTBP.[96] Crich's method was readily scaled to provide 90g batches in a one-pot, chromatography-free sequence. Although effective, Crich's protocol required 6 full days for the completion of the reaction. Although reliable, these methods also use large excesses of the

nucleophile, rendering them less than optimal for batch scale up protocols. Moreover, these methods often feature low reaction scope and reaction yields. It should be mentioned, however, that alternative methods toward the formation of DTBP derivatives that do not involve hard nucleophiles and/or highly basic reagents have been reported. Typically, these approaches have involved the formation of the cationic *tert*-butylpyrylium intermediates, followed by treatment with ammonia to afford the desired DTBP base.[97] Among these, Stang's method is the most direct approach reported to date.[98] Their protocol allows for the production of up to ~65 g batches of 2,6-di-*t*-butyl-4-methylpyridine and though it reduces the cost a DTBP alternative, there is still room for improvement with respect to the scope of the transformation and the multi-step synthesis of their. It is apparent that an efficient method to allow customization of DTBP analogues from economical, commercially available reagents is highly warranted.

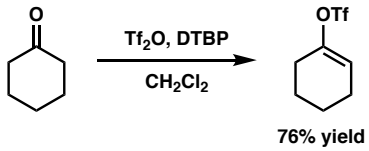
Scheme 75: Previous to access DTBP and DTBP alternatives



Our developed Ciamician–Dennstedt rearrangement protocol, outlined in Chapter 7, provided an economical alternative to the costly 2,6-di-*t*-butylpyridine[99] and other derivatives. DTBP, in particular, has many properties that enable it to participate in a number of unique transformations. For one, DTBP has high basicity in the gas phase,[100] but is known as a weak base in aqueous solution,[101] this low basicity is credited to steric hindrance of solvation.[102] Though, it should be noted that this is highly solvent dependent. As a result, DTBP forms an HCl salt readily but does not react with MeI or BF_3.[101a,b]

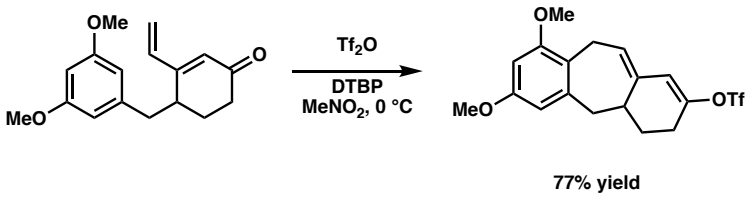
Our desire to find an alternative and more efficient pyridine base stemmed from the general utility DTBP has in synthetic chemistry. It is known to play a number of different roles depending on the reaction conditions and overall transformation. It is most widely known as a weak, hindered, non-nucleophilic base. More notably, DTBP has been widely employed as the catalyst for enolization and addition reactions. In 1980, the Stang group reported a single-step improved synthesis of primary and other vinyl trifluoromethanesulfonates with the use of DTBP (Scheme 76).[103]

Scheme 76: Enolization of cyclohexanone



The Trauner group has also used DTBP in their development of a new variant of the Friedel–Crafts reaction to yield 3-aryl enol triflates (Scheme 77).[104] Thus, DTBP may facilitate inter- and intramolecular reactions to form enol triflates.

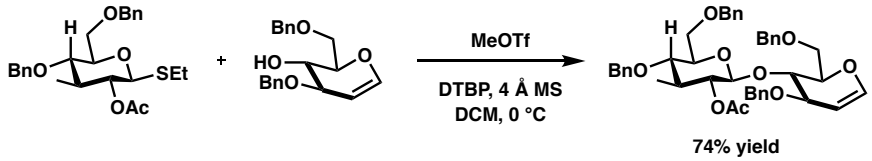
Scheme 77: Intramolecular cyclization



DTBP has also been an integral component to stabilize *O*-glycosidic bonds by removing the liberated acid in *O*-alkylation of carbohydrates using Lewis acids such as methyl triflate, as shown by the Danishefsky group (Scheme 78).[105] They found DTBP to be especially advantageous for the coupling of glycal derived thioethyl glycosyl donors with more complex

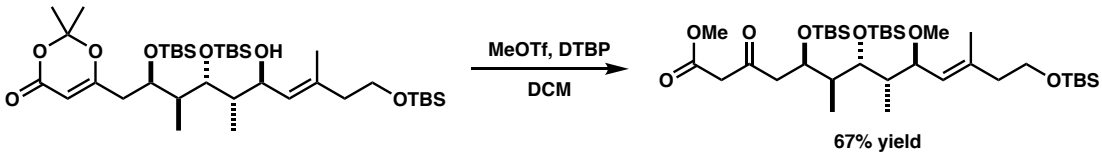
glycal acceptors that required longer reaction times as the new linkage degraded with prolonged exposure to acid.

Scheme 78: Synthesis of glycosyl thioethyl donors from glycal precursors



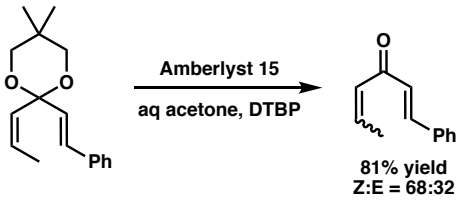
Additionally, DTBP was found to be an instrumental base for the synthesis of alkyl ethers, where triflates of saturated alcohols are used as alkylating agents. This approach has proven particularly useful in natural product synthesis as seen in the case of the aglycone of callipeltoside A, where a one-pot *O*-methylation/deprotection reaction was achieved (Scheme 79).[106]

Scheme 79: One-pot protection/deprotection reaction



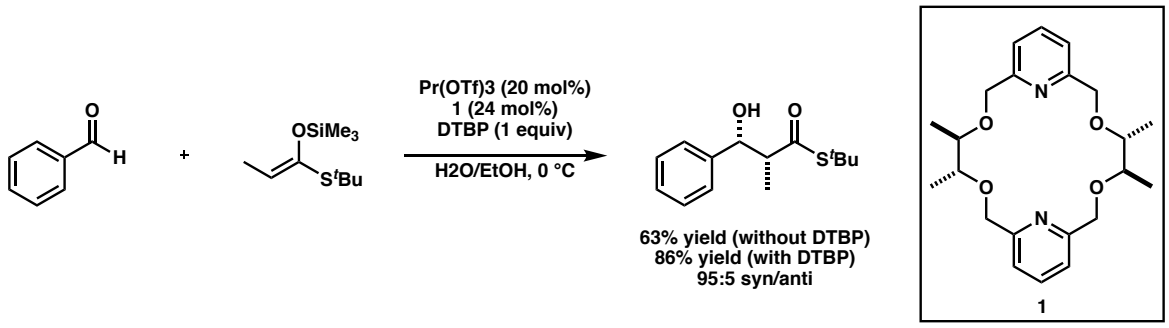
DTBP has been used as a proton scavenger to prevent acid-catalyzed side reactions or nucleophilic reactions. For example, the Isaka group utilized Amberlyst 15 pre-treated with DTBP to obtain the desired dienones (Scheme 80).[107]

Scheme 80: Hydrolysis of dienone acetals



In 2003, the Kobayashi group illustrated the importance of DTBP for their catalytic asymmetric aldol reaction protocol (Scheme 81).[108] They utilized chiral bis-pyridino-18-crown-6 rare earth metal triflate complexes to prepare aldol adducts in good to high yields and stereoselectivities. In their work, they discovered a vast improvement when DTBP was utilized concurrently with their reaction conditions. They postulated that DTBP suppressed the hydrolysis of the silyl enol ethers required to ultimately afford the aldol adduct.

Scheme 81: Kobayashi's asymmetric aldol reaction



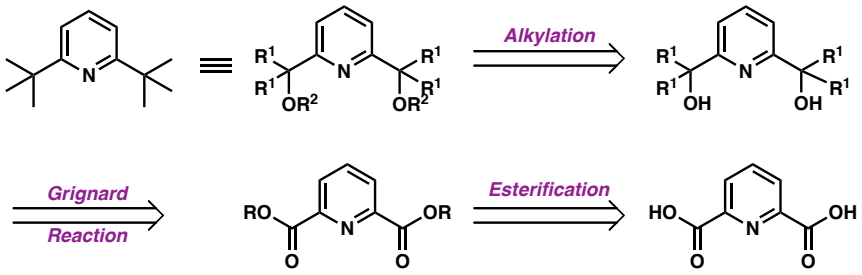
The usefulness of 2,6-di-*t*-butylpyridine in synthetic chemistry is what has primarily driven our search to find an alternative compound that could perform comparatively. At the same time, we hope to provide an efficient and economical solution to make this alternative base accessible for research purposes. Our goal is to offer more options when transformations require sterically hindered, non-nucleophilic pyridine bases to yield optimal results in both method development and natural product synthesis.

8.2. Reaction Development

Our strategy to design a substitute for the useful pyridine base, DTBP, was centered on finding a reliable, atom economical, and cost-effective protocol (Scheme 82). We aimed to utilize common starting materials and reagents that would be present in most laboratories. We reasoned

that we could mimic the steric bulk around the pyridine ring by adding substituted alkyl groups via sequential Grignard addition[109]/etherification[110] of readily available 2,6-dipyridylester to furnish bis-tertiary pyridyl ether **27**. The diester pyridine could be easily attained via esterification conditions of the inexpensive and abundant 2,6-pyridinedicarboxylic acid. Notably, our method will allow the development of a toolbox of bulky and tunable pyridines that could be beneficial to the synthetic community.

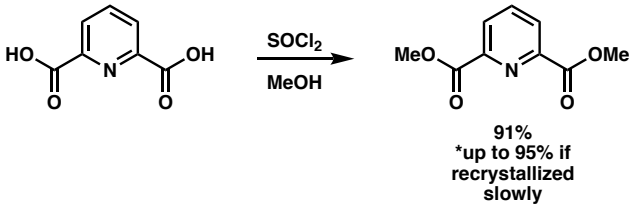
Scheme 82: Retrosynthetic analysis of DTBP analogues



8.3. Optimization of the Reaction Conditions

The development of our protocol began with the synthesis of dimethyl 2,6-pyridinedicarboxylate. Fortunately, the conditions for this step have been well established and we did not deviate from the known method (Scheme 83).[111] Alternatively, the diester may be easily purchased from a variety of chemical vendors at a reasonable price.[112]

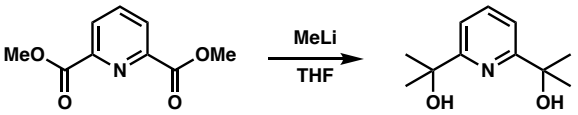
Scheme 83: Esterification of 2,6-pyridinedicarboxylic acid.



The second step of our proposed synthesis involved the addition of alkyl groups on the pyridine ring in order to increase the steric bulk, thereby mimicking the reactivity of DTBP. We initially

turned to known methods, such as addition of alkyl lithium reagents.[113] Our attempts with MeLi gave fair yields of the desired pyridine alcohol (Scheme 84). However, we noted the best conditions are when the reaction was conducted under cryogenic temperatures, which is not ideal for multi-gram synthesis. Additionally, we rationalized that organomagnesium halides offer more versatility than alkyl lithium reagents due to commercial availability and the milder reaction conditions employed.

Scheme 84: Reaction with MeLi

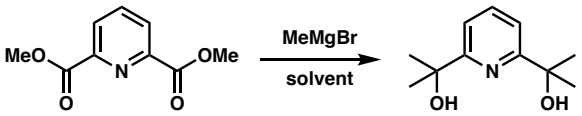


temperature	% yield
22 °C	35%
0 °C	48%
–78 °C	71%

Details: 5.0 equiv MeLi, 0.11 M ester

Thus, our optimization studies continued with the use of simple organomagnesium halides, primarily MeMgBr.[114] Several reaction parameters such as the solvent, temperature, and equivalents of Grignard were varied and tested (Scheme 85). Other solvents screened, such as THF and DCM, proved to be ineffective. We found that the dropwise addition of the Grignard reagent was effective and provided fair yields of the product. Given that the nature of Grignard reactions is exothermic, we also tested reactions at lower temperatures. Our initial screen measured the threshold of the equivalents required for the transformation. We concluded that 6.0 equiv of MeMgBr at 0 °C provided the desired product in excellent yield.

Scheme 85: Optimization of Grignard reaction

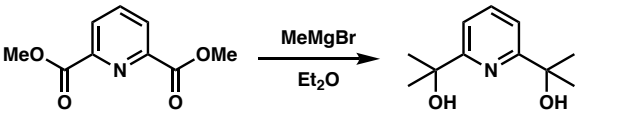


MeMgBr	solvent	temperature	% yield
2.04 equiv	Et_2O	22 °C	36%
2.04 equiv	Et_2O	–78 °C	39%
4.0 equiv	Et_2O	22 °C	48%
4.8 equiv	1:1 THF/DCM	22 °C	54%
5.0 equiv	THF	22 °C	39%*
5.0 equiv	DCM	22 °C	61%*
5.0 equiv	Et_2O	22 °C	63%
6.0 equiv	Et_2O	22 °C	82% (column)
7.0 equiv	Et_2O	22 °C	73%
8.0 equiv	Et_2O	22 °C	sm + pdt
9.0 equiv	Et_2O	22 °C	sm + pdt
10.0 equiv	Et_2O	22 °C	82%
6.0 equiv	Et_2O	0 °C	84%
6.0 equiv	Et_2O	–78 °C	mixture
6.0 equiv	THF	22 °C	mixture
6.0 equiv	DCM	22 °C	mixture
6.0 equiv	Et_2O*	0 °C	76%
6.0 equiv	Et_2O**	0 °C	mixture
6.0 equiv	Et_2O	0 °C	85% (recrystallized)

1.0 equiv ester, 0.17 M ester
*Done with 0.11M ester (previously used with MeLi)
**Quenched with MeI, no alcohol pdt observed

With scalability in mind, we also sought to find comparable reaction conditions that would require less solvent (Scheme 86). Unfortunately, any effort to make the reaction more concentrated resulted in lower yields or incomplete reactions. Therefore, our conditions remained as previously stated.

Scheme 86: Concentration optimization

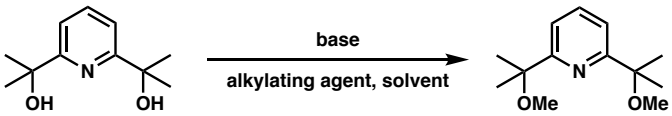


Et_2O	% yield
0.17 M	85%
0.25 M	72%
0.5 M	pdt + sm
1.0 M	70% + sm
2.0 M	59%

1.0 equiv ester
6.0 equiv MeMgBr

The final step of our synthesis was alkylation via Williamson ether synthesis. Once more, we sought to find reaction conditions involving low-cost materials. To this end, we screened many inexpensive common bases such as K_2CO_3, NaOH, and LiOH (Scheme 87). Simultaneously, we screened protic and polar aprotic solvents, as they are known to aid alkylation reactions. After many unfruitful results, we observed product formation with the use of stronger bases such as KO^{t}Bu and hydride bases.

Scheme 87: Optimization of alkylation reaction



K_2CO_3	alkylating agent	solvent	% yield
2.0 equiv	Me_2CO_3	acetone	0%
3.0 equiv	Me_2CO_3	acetone	0%
4.0 equiv	Me_2CO_3	acetone	0%
2.0 equiv	Me_2CO_3	THF	0%
2.0 equiv	MeI	acetone	0%
2.0 equiv	MeI	THF	0%

All done at reflux except last 2 entries

NaOH	alkylating agent	solvent	% yield
2.56 equiv	Me_2CO_3	EtOH	0%
2.56 equiv	Me_2SO_4	EtOH	0%

LiOH	alkylating agent	solvent	% yield
1.0 equiv	Me_2CO_3	THF	0%
2.0 equiv*	Me_2CO_3	THF	0%
2.0 equiv	Me_2CO_3	THF**	0%
2.0 equiv	Me_2CO_3	DMF**	0%
3.3 equiv	Me_2CO_3	THF	0%
2.0 equiv	Me_2CO_3	EtOH**	0%
2.0 equiv	Me_2SO_4	THF	0%

*2.0 equiv of alcohol
**Also tried reaction at reflux

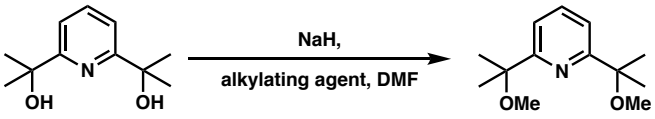
base	alkylating agent	solvent	% yield
DBU	Me_2CO_3	DMF	0%
KO^tBu	MeI	DMF	23%**
KO^tBu	MeI	THF	3%
KH	MeI	DMF	28%***
NaH	MeI	DMF	74%

**Also tried at reflux with no increase in yield
***Done at 0 °C

We discovered that NaH was the optimal base to utilize for our alkylation reaction. Therefore, we tested its performance with previously tested alkylating agents (Scheme 88). However, employment of dimethylcarbonate and dimethylsulfate failed to produce any desirable product. It is also known that Williamson ether reactions are often facilitated with the addition of crown ether additives.[115] Thus, 15-crown-5 ether was employed in DMF and THF. However, neither case resulted in better yields. Similar to the Grignard addition step, we were interested in

decreasing the amount of solvent needed for the transformation. Again, we observed optimal results with the low concentration herein reported.

Scheme 88: Optimization for alkylation reaction with NaH



equiv	alkylating agent	solvent	% yield
2.0 equiv	Me_2CO_3	DMF	0%
4.0 equiv	Me_2CO_3	DMF	0%
2.0 equiv	Me_2SO_4	DMF	10%
4.0 equiv	Me_2SO_4	DMF	0%

Details: 1.0 equiv alcohol, 2.0 equiv NaH, 0.138 M alcohol

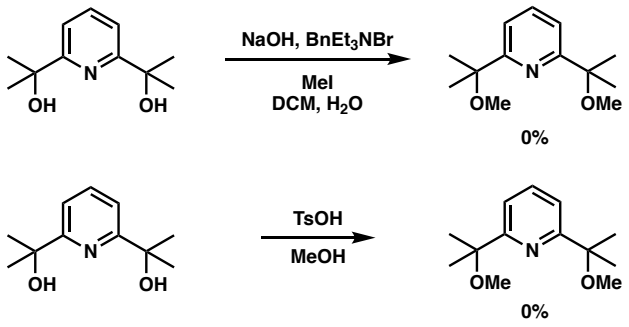
additive	solvent	% yield
15-c-5	DMF	40%
15-c-5	THF	63%
none	DMSO	8%

[alcohol]	% yield*
0.138 M	74%
1.0 M	53%
2.0 M	61%

Details: 1.0 equiv alcohol. 2.0 equiv NaH, 2.0 equiv MeI
*Reactions without additive

Lastly, we tested several unconventional alkylation conditions (Scheme 89). Among those tested were with ammonium salts and under acidic conditions.[116] These reaction parameters also proved unsuccessful. At this point, we were satisfied with the previous results utilizing NaH and MeI to generate the desired pyridine ether in 74% yield.

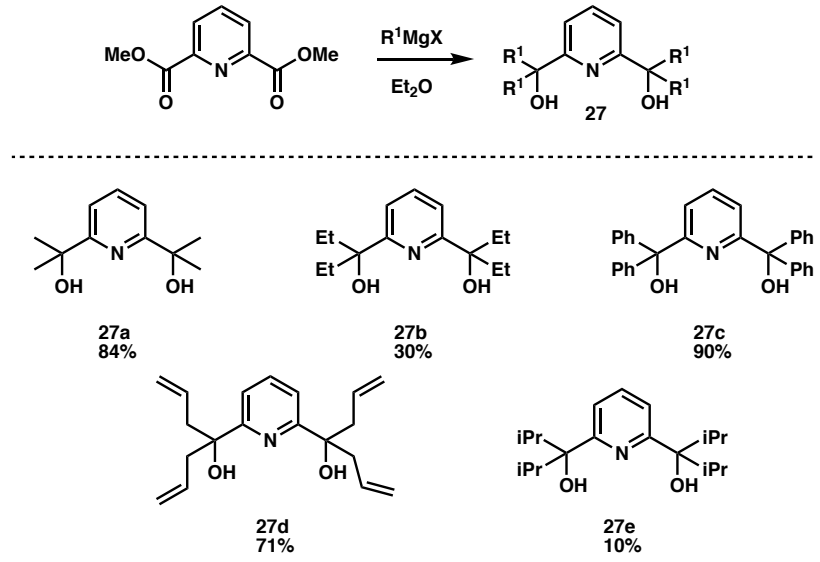
Scheme 89: Unconventional alkylation methods



8.4. Scope and Limitations

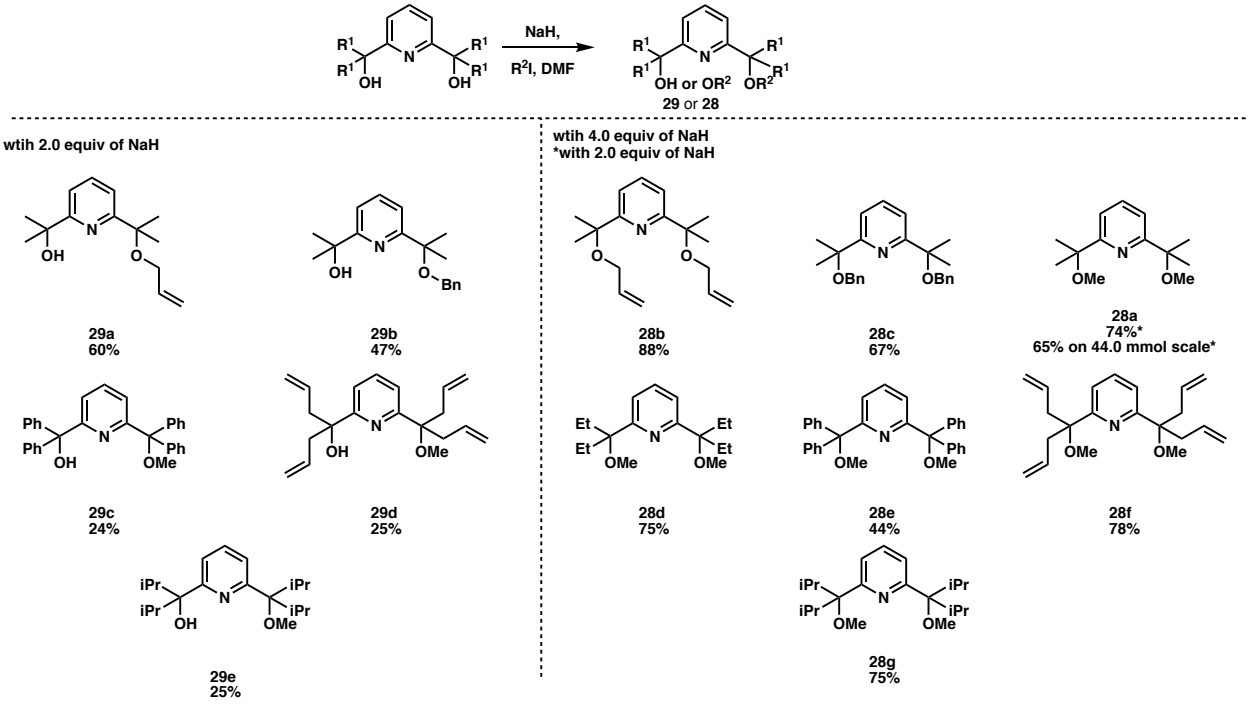
With the optimal synthesis in hand, we set out to expand the scope of the DTBP analogues. With a series of Grignard reagents, we were able to produce a variety of pyridine alcohols possessing tertiary aliphatic and benzylic pyridyl alcohols (Scheme 90). Interestingly, we only observed a decrease in efficiency with the cases in which more sp^3 character would exist nearby the nitrogen center of the pyridine ring.

Scheme 90: Scope of pyridine alcohols



Upon expanding our protocol to generate a variety of pyridine ethers, we observed an unusual trend (Scheme 91). Under our standard conditions, we observed the monoalkylated product solely for most of the alcohols. Remarkably, our etherification protocol was not limited to methylation, as benzylation and allylation was achieved in good yields. In order to drive the reaction to achieve double alkylation, it was found that increasing the equivalence of base resulted in the formation of the desired dialkylated product in fair to excellent yield. We were also able to show the scalability of our protocol with a 44.0 mmol reaction that did not suffer a dramatic decrease in reaction efficiency (Scheme 92).

Scheme 91: Scope of pyridine ethers

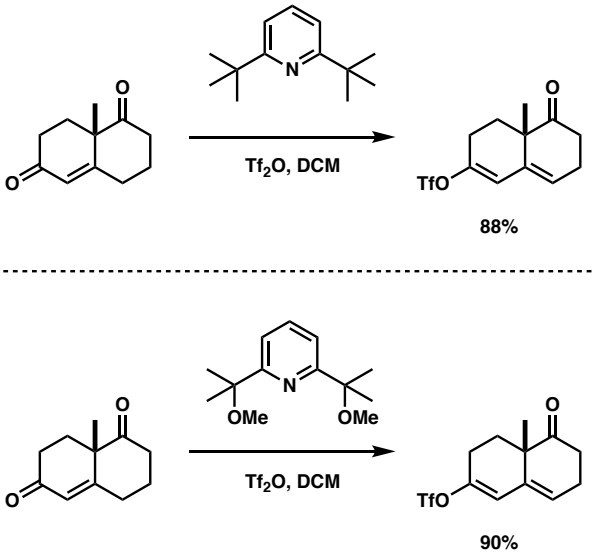


Scheme 92: Large scale synthesis of 2,6-bis(2-methoxypropan-2-yl)pyridine

8.5. Synthetic Applications

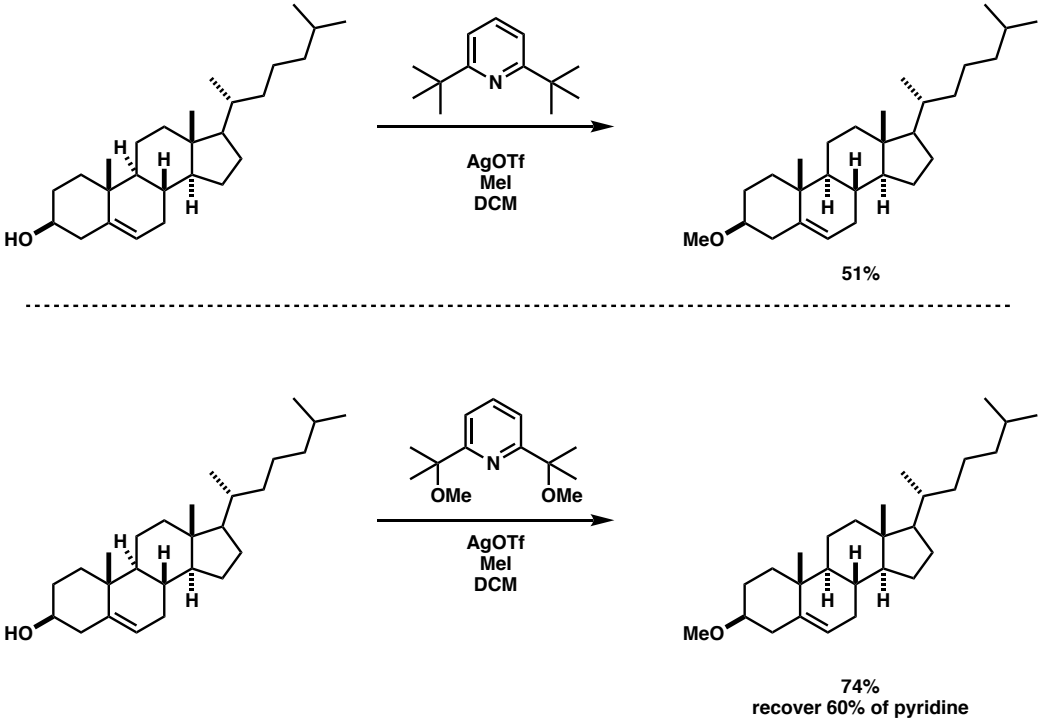
With the ideal synthesis of 2,6-bis(2-methoxypropan-2-yl)pyridine achieved (**27a**), we were able to apply **27a** as a base to a number of useful synthetic transformation in order to compare its reaction efficiency to that of DTBP. For instance, the triflation of the Wieland–Miescher ketone occurs in optimal yield of 88% with DTBP. However, a comparable yield, 90%, was also achieved using our alternative pyridine (Scheme 93).

Scheme 93: Triflation of Wieland–Miescher ketone



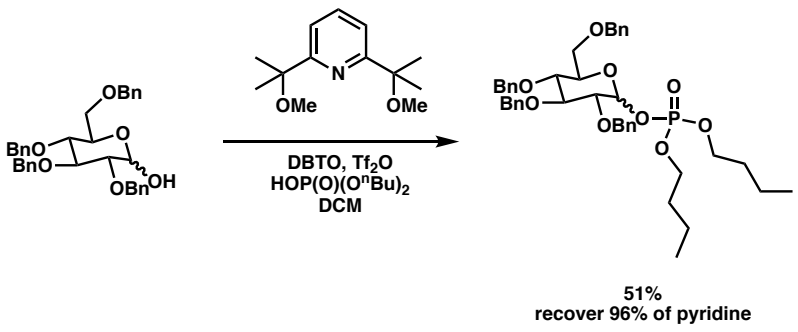
Gratifyingly, employment of **27a** as a base for the etherification of cholesterol in the presence of silver triflate resulted in methylated cholesterol in 74% yield (Scheme 94). In contrast, Roof and co-workers reported 51% yield of the methylated cholesterol when DTBP was employed. This comparison study highlights that **27a** is significantly more efficient than DTBP for triflation of natural products.[117] Moreover, an added advantage of our employing of **27a**, is that it can be easily recovered (60%) via column chromatography.

Scheme 94: Silver triflate assisted etherification of alcohols



We have also proven our generated pyridine base is highly efficient and useful for the synthesis of glycosyl-1-phosphates via dehydrative glycosylation. The Gin group was able to provide an array of these products with dialkyl phosphate acceptors and DTBP.[118] We are able to synthesize a new glycosyl-1-phosphate derivative with the use of dibutyl phosphate in the presence of **27a**, quite efficiently (Scheme 95). Once more, we are able to recover 96% of our pyridine **27a**.

Scheme 95: Dehydrative phosphorylation mediated by **27a**



8.6. Proton Affinity

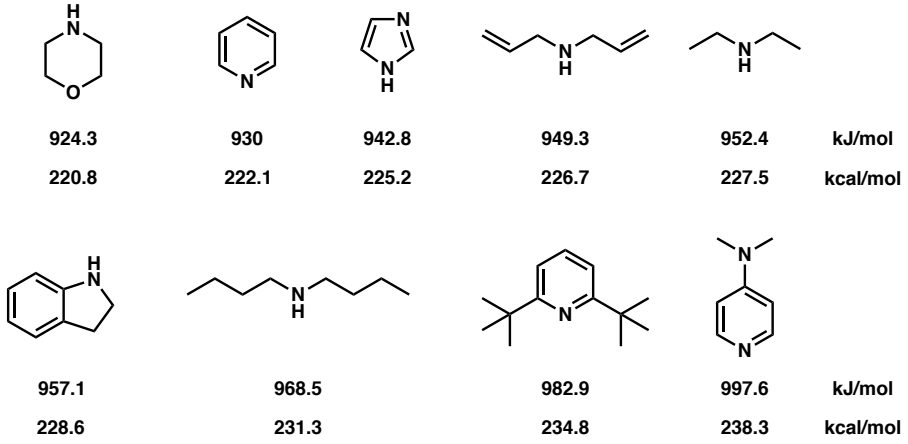
To gain further insight into the DTBP analogues, we examined the intrinsic properties and reactivity in the gas phase. Specifically, we focused on measuring the proton affinity (PA) of the analogues. Proton affinity measurements are utilized to measure the enthalpy change (ΔH, $\Delta G = (\Delta H - T\Delta S)$ of deprotonation/protonation reactions. Deprotonation reactions (eq. 1) exhibit positive enthalpy changes (ΔH_{acid}) ranging from 314 to 417 kcal/mol (eq. 1). This measurement is known as the gas phase acidity. On the other hand, gas phase proton affinity is defined as the negative enthalpy change of protonation reactions, ranging from 130 to 291 kcal/mol (eq. 2).[119] Lower values of gas phase proton affinity correspond to higher acidity, while higher value of proton affinity corresponds to higher basicity.

$$HA \rightarrow H^+ + A^- \quad \text{eq. 1}$$
$$B + H^+ \rightarrow HB^+ \quad \text{eq. 2}$$

Herein, we present the first experimental results characterizing the basicity of the pyridine analogues synthesized. We utilized the kinetic method to determine the proton affinity values of these analogues. The kinetic method has been used previously to study the thermochemical properties for a variety of diverse molecules.[120] The kinetic method is based on the competitive fragmentation of proton-bound complex ions (hetero-dimers) by either metastable decomposition or collision-induced dissociation (CID). This method was employed to determine the proton affinity of a number of DTBP analogues relative to a series of reference bases (Scheme 96) according to previously established methods.[121] Proton-bound dimer ions were allowed to undergo CID with nitrogen buffer gas at varying activation energies. The dimers were introduced into a high-resolution quadrupole ion trap mass spectrometer by electrospraying solutions of the DTBP analogues in dry methanol and a reference base (with acetic acid). To determine the most

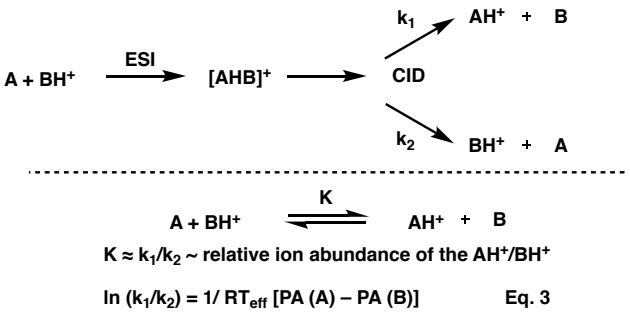
basic site, the non-covalently bound dimers were then subjected to collision-induced dissociation (CID) in order to verify which retained the proton more often.

Scheme 96: Experimentally determined PAs of representative reference bases



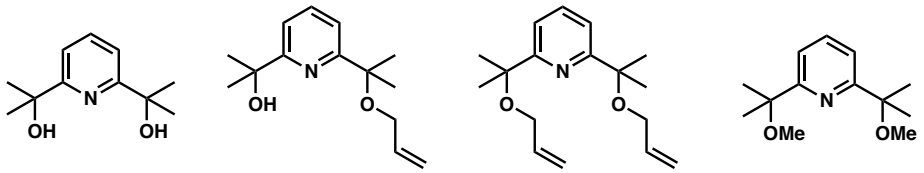
Cooks and co-workers first developed the kinetic method in the 1970s.[122] To simplify, this method uses kinetic information to study the thermochemical properties in the gas phase. Cooks' kinetic method essentially compares two competitive reactions (Scheme 97). AH^+ represents the compound with unknown basicity and BH^+ represents a series of reference bases. If compound A has a higher PA, the proton-bound dimer would split into AH^+ and B, and vice versa. The ratios of rate constants (k_1/k_2) of the two dissociation pathways are represented by the ratio of the relative ion abundance of AH^+/BH^+. The basicity of the sample is compared to the reference base by calculation of eq. 3. From these calculations, a plot of the natural log of the ratio of product ion intensities versus the known PA values of the reference bases is generated. At last, the intercept of this best-fit line corresponds to the proton affinity of the sample.

Scheme 97: CID of proton-bound complex of acid and reference base



All of the pyridine DTBP analogues were tested using Cooks' kinetic method. Strong relative ion abundances were obtained for four substrates discussed below. Fortunately, our success allowed us to calculate the proton affinity values for the three types of derivatives we focused on: dihydroxyl pyridines, mono-ether pyridines, and diether pyridines (Scheme 98).

Scheme 98: Pyridine analogues used in Cooks kinetic method study



27a	29a	2bb	28a	
956.9	930.5	944.3	953.9	kJ/mol
228.7	222.4	225.7	228.0	kcal/mol

The calculated proton affinity values for the DTBP analogues fell in the range of 222–229 kcal/mol. Analysis of the data yields a PA of 228.7 kcal/mol for our standard dihydroxyl pyridine using the simple kinetic method. The calculated PA for the mono-ether is 222.4 kcal/mol. As for the two diethers, the allyl and methyl substrates were found to have PAs 225.7 and 228.0 kcal/mol, respectively. From our study, we can conclude that the DTBP analogues we prepared are less basic than DTBP itself but more basic than unsubstituted pyridine. Therefore,

our pyridines are ideal candidates for chemical transformations that require sterically hindered non-nucleophilic weak bases.

8.7. Summary

In summary, we are able to provide an efficient route towards the synthesis of an economical alternative to the costly 2,6-di-*tert*-butyl pyridine (DTBP). It was found that 2,6-bis(2-methoxypropan-2-yl)pyridine, **27a**, was a significantly more efficient base compared to DTBP for triflation of ketones and etherification of alcohols. Moreover, the facile recovery of **27a** is an appealing feature of our reagent in terms of recyclability. All the starting materials involved in our short and practical synthesis are found in most common laboratories and are quite inexpensive. Lastly, proton affinity studies disclosed that the synthesize pyridines analogs are less basic than DTBP but more basic than pyridine. Overall, we believe pyridine **27a** and its analogs are great alternatives to expensive DTBP and we envision that they will become widely employed bases in future synthetic methodologies and natural product synthesis.

9. Experimental Section

9.1. General Information

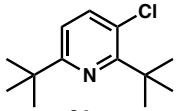
Unless otherwise stated, reactions were performed in oven-dried glassware under a N_2 atmosphere using dry, deoxygenated solvents. Anhydrous dichloromethane, pentane, toluene, and THF (BHT-free) were purchased from Aldrich, degassed with argon, and dried by passage through activated drying columns[53] on a Pure Process Technology system. Grignard reagents/MeLi were purchased from Aldrich, Alfa Aesar, Acros or Oakwood Chemical. Sodium hydride (NaH) was purchased as 60% dispersion in mineral oil from Acros and used as received. Starting materials, including were purchased from Aldrich, Alfa Aesar, or Oakwood Chemical and used as received. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[57] was performed using Silicycle SiliaFlash® P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift

relative to Me_4Si (δ 0.0). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}).

9.2. Procedure and Experimental Data for Halopyridine Products

General Procedure for synthesis of Halopyridine Products

Sodium trichloroacetate (3.85 mmol, 7.7 equiv) and substituted pyrrole (0.50 mmol, 1.0 equiv) was added to an oven-dried 20 mL vial equipped with a magnetic stirring bar. Then, the vial was capped and then evacuated and backfilled with nitrogen (three cycles). The flask was charged with 1,2-dimethoxyethane (0.63 mL) and heated to 85 °C. After stirring for 1 hour, the reaction mixture was cooled to room temperature. The mixture was maintained at room temperature for 10 min at which point TLC indicated the consumption of starting material (visualized with *p*-anisaldehyde). The reaciton was quenched with H_2O (3 mL) and then EtOAc (3 mL) added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered through cotton, and concetrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product. Specific quantities of reagents, procedural variations, and purification conditions may be found below in the entry containing the characterization data.



24a

2,6-di-*tert*-butyl-3-chloropyridine (24a) The title compound was prepared according to the General Procedure, using 2,5-di-*tert*-butyl-1*H*-pyrrole (89.5 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 100% hexanes), the title compound was isolated as a colorless liquid (93.7 mg, 83% yield).

TLC (SiO_2) R_f = 0.95 in 100% hexanes, *p*-anisaldehyde stain

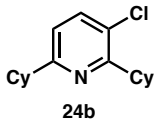
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 1.55 (s, 9H), 1.38 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 161.5, 138.8, 127.3, 117.3, 77.3, 77.0, 76.7, 39.5, 37.6, 30.1, 28.8

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 139.2, 117.7, 30.5, 29.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 139.2, 117.7, 30.5, 29.2

IR (neat) 2955.63, 2929.39, 2903.27, 2869.48, 1572.78, 1557.21, 1478.30, 1421.00, 1363.26, 1143.51, 1033.28, 851.04, 780.52 cm^{-1}



24b

3-chloro-2,6-dicyclohexylpyridine (24b) The title compound was prepared according to the General Procedure, using **2,5-dicyclohexyl-1*H*-pyrrole** (115.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 100% hexanes), the title compound was isolated as a colorless liquid (48.6 mg, 35% yield).

TLC (SiO_2) R_f = 0.35 in 100% hexanes, *p*-anisaldehyde stain

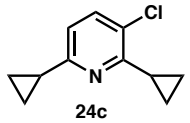
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 3.18 (m, 1H), 2.68 (m, 1H), 1.84 (m, 16H), 1.40 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 161.2, 136.6, 127.2, 118.8, 45.8, 42.0, 32.9, 31.3, 26.6, 26.5

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 136.9, 119.2, 46.2, 42.4, 33.3, 31.7, 27.0, 26.9. 26.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 136.9, 119.2, 45.2, 42.3, 33.3 (–), 31.7 (–), 27.0 (–), 26.9 (–), 26.5 (–)

IR (neat) 2922.75, 2850.63, 1742.13, 1566.63, 1447.01, 1237.74, 1024.98, 843.99, 823.12 cm^{-1}



24c

3-chloro-2,6-dicyclopropylpyridine (24c) The title compound was prepared according to the General Procedure, using **2,5-dicyclopropyl-1*H*-pyrrole** (73.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 100% hexanes), the title compound was isolated as a colorless liquid (35.8 mg, 37% yield).

TLC (SiO_2) R_f = 0.50 in 100% hexanes, *p*-anisaldehyde stain

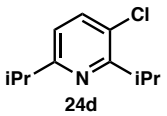
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 2.47 (m, 1H), 1.93 (m, 1H), 1.06 (m, 2H), 0.96 (m, 4H), 0.91 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 157.9, 135.7, 126.9, 118.8, 16.5, 13.2, 9.8, 9.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 136.9, 119.2, 16.9, 13.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 136.1, 119.2, 16.5, 13.2, 9.8 (–), 9.6 (–)

IR (neat) 3089.22, 3006.95, 2925.65, 2853.95, 1905.63, 1738.73, 1683.21, 1566.24, 1454.95, 1165.33, 1059.58, 936.40, 814.81cm^{-1}



24d

3-chloro-2,6-diisopropylpyridine (24d) The title compound was prepared according to the General Procedure, using **2,5-diisopropyl-1*H*-pyrrole** (75.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 2.5% EtOAc in hexane), the title compound was isolated as a colorless liquid (58.7 mg, 60% yield).

TLC (SiO_2) R_f = 0.35 in 5% EtOAc in hexane, *p*-anisaldehyde stain

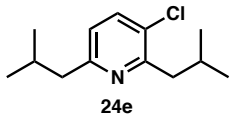
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 3.55 (m, 1H), 3.03 (m, 1H), 1.32 (d, J = 2.2 Hz, 6H), 1.30 (d, J = 2.2 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 161.9, 136.6, 127.0, 118.7, 35.8, 31.8, 22.5, 21.2

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.0, 119.1, 36.2, 32.2, 22.9, 21.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.0, 119.1, 36.2, 32.2, 22.9, 21.6

IR (neat) 3368.33, 2970.62, 2869.01, 1662.97, 1567.49, 1469.77, 1360.40, 1145.67, 1029.15, 834.42 cm^{-1}



24e

3-chloro-2,6-diisobutylpyridine (24e) The title compound was prepared according to the General Procedure, using **2,5-diisobutyl-1*H*-pyrrole** (89.7 mg, 0.50 mmol). After purification

by flash chromatography (SiO_2, 2.5% EtOAc in hexane), the title compound was isolated as a colorless liquid (53.1 mg, 47% yield).

TLC (SiO_2) R_f = 0.35 in 5% EtOAc in hexane, *p*-anisaldehyde stain

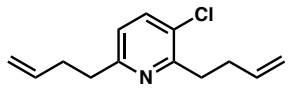
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 2.80 (d, *J* = 7.5 Hz, 2H), 2.60 (d, *J* = 7.5 Hz, 2H), 2.19 (m, 1H), 2.06 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 6H), 0.91 (d, *J* = 6.5 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 157.8, 136.5, 129.9, 128.5, 121.8, 105.6, 46.9, 43.9, 37.3, 29.3, 29.2, 28.3, 22.4, 22.3, 22.2

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.0, 122.2, 106.0, 29.3, 29.2, 28.3, 22.4, 22.3, 22.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.0, 122.2, 106.0, 29.3 (–), 29.2 (–), 28.3, 22.4, 22.3, 22.2

IR (neat) 2955.27, 2927.52, 2868.71, 1675.32, 1568.58, 1441.17, 1384.34, 1141.78, 1087.83, 1031.25, 839.15, 807.67 cm^{-1}



24f

2,6-di(but-3-en-1-yl)-3-chloropyridine (24f) The title compound was prepared according to the General Procedure, using **2,5-di(but-3-en-1-yl)-1*H*-pyrrole** (87.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 2.5% EtOAc in hexane), the title compound was isolated as a colorless liquid (46.6 mg, 42% yield).

TLC (SiO_2) R_f = 0.40 in 5% EtOAc in hexane, *p*-anisaldehyde stain

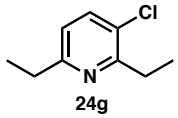
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.91 (m, 2H), 5.04 (m, 4H), 3.03 (t, *J* = 8.0 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.51 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 157.6, 137.8, 137.6, 136.8, 128.2, 121.4, 115.2, 114.9, 37.0, 34.8, 33.7, 32.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.2, 138.0, 137.2, 121.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.2, 115.6, 115.4, 37.4 (–), 35.2 (–), 34.1 (–), 32.7 (–)

IR (neat) 3077.03, 2926.19, 2853.56, 1702.93, 1640.18, 1569.92, 1440.35, 1259.94, 1138.77, 1040.08, 993.43, 909.82, 825.31 cm^{-1}



24g

3-chloro-2,6-diethylpyridine (24e) The title compound was prepared according to the General Procedure, using **2,5-diethyl-1*H*-pyrrole** (61.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 2.5% EtOAc in hexane), the title compound was isolated as a colorless liquid (36.5 mg, 43% yield).

TLC (SiO_2) R_f = 0.35 in 5% EtOAc in hexane, *p*-anisaldehyde stain

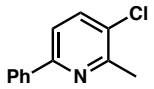
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 2.95 (q, *J* = 7.5 Hz, 2H), 2.80 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 159.4, 136.9, 127.7, 120.4, 30.9, 29.0, 14.0, 12.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.3, 120.8, 110.0, 31.3, 29.4, 14.4, 13.1

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.3, 120.8, 31.3, 29.4 (–)

IR (neat) 2963.27, 2931.99, 2873.80, 1738.10, 1548.91, 1462.30, 1378.26, 1260.08, 1092.10, 1019.44, 802.56 cm^{-1}



24h

3-chloro-2-methyl-6-phenylpyridine (24h) The title compound was prepared according to the General Procedure, using **2-methyl-5-phenyl-1*H*-pyrrole** (78.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (74.3 mg, 73% yield).

TLC (SiO_2) R_f = 0.52 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 65–69 °C

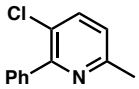
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 7.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 (m, 4H), 2.73 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 154.9, 138.6, 137.0, 129.8, 129.0, 128.8, 126.8, 118.9, 23.0

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.4, 129.4, 129.2, 127.2, 119.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.4, 129.4, 129.2, 127.2, 119.3, 23.4

IR (neat) 3058.72, 2925.07, 2357.70, 1956.81, 1905.91, 1814.98, 1569.74, 1428.78, 1380.45, 1043.47, 829.30 cm^{-1}



24h'

3-chloro-6-methyl-2-phenylpyridine (24h') The title compound was prepared according to the General Procedure, using **2-methyl-5-phenyl-1*H*-pyrrole** (78.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (22.4 mg, 22% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

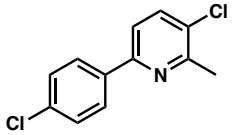
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (m, 3H), 7.47 (m, 3H), 7.11 (d, J = 8.5 Hz, 1H), 2.62 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 138.1, 131.9, 129.3, 128.6, 128.0, 127.1, 122.8, 24.1

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.5, 129.7, 129.0, 123.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 138.5, 129.7, 129.0, 128.4, 123.2, 24.5

IR (neat) 3057.61, 2923.62, 1736.76, 1567.57, 1429.23, 1378.64, 1227.53, 1138.40, 1020.93, 818.52 cm^{-1}



24i

3-chloro-6-(4-chlorophenyl)-2-methylpyridine (24i) The title compound was prepared according to the General Procedure, using **2-(4-chlorophenyl)-5-methyl-1*H*-pyrrole** (95.8 mg,

0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (53.6 mg, 45% yield).

TLC (SiO_2) R_f = 0.52 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 90–92 °C

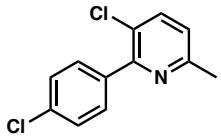
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 1H), 7.45 (m, 4H), 2.71 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 153.6, 137.1, 136.9, 135.2, 130.1, 128.9, 128.1, 118.7, 22.9

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.4, 129.3, 128.5, 119.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.4, 129.3, 128.5, 119.0, 23.3

IR (neat) 3067.62, 2924.28, 2852.13, 2359.38, 2341.50, 1914.33, 1667.57, 1580.40, 1432.50, 1238.40, 1079.18, 773.83 cm^{-1}



24i'

3-chloro-2-(4-chlorophenyl)-6-methylpyridine (24i') The title compound was prepared according to the General Procedure, using **2-(4-chlorophenyl)-5-methyl-1*H*-pyrrole** (95.8 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (23.8 mg, 20% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 78–80 °C

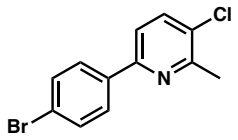
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.46 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 4H), 2.61 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 154.4, 138.2, 136.9, 134.8, 130.8, 128.3, 127.1, 123.1, 24.1

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.6, 131.2, 128.7, 123.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 138.6, 131.2, 128.7, 123.5, 110.0, 24.5

IR (neat) 3057.66, 2921.55, 2361.27, 1903.65, 1779.06, 1658.86, 1564.65, 1433.50, 1177.82, 1012.61, 989.03, 826.76 cm^{-1}



24j

6-(4-bromophenyl)-3-chloro-2-methylpyridine (24j) The title compound was prepared according to the General Procedure, using **2-(4-bromophenyl)-5-methyl-1*H*-pyrrole** (118.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (73.5 mg, 52% yield).

TLC (SiO_2) R_f = 0.52 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 106–108 °C

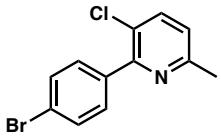
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H) 2.71 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 153.6, 137.4, 137.1, 131.9, 130.2, 128.4, 123.5, 118.6, 22.9

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.4, 132.3, 128.8, 119.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 155.9, 153.6, 137.4, 137.1, 131.9, 130.2, 128.4, 123.5, 118.6, 22.9

IR (neat) 3062.79, 3015.58, 2924.66, 2850.89, 1914.99, 1585.89, 1428.53, 1238.70, 1047.78, 973.53, 854.77 cm^{-1}



24j'

2-(4-bromophenyl)-3-chloro-6-methylpyridine (24j') The title compound was prepared according to the General Procedure, using **2-(4-bromophenyl)-5-methyl-1*H*-pyrrole** (118.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (31.1 mg, 22% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 77–79 °C

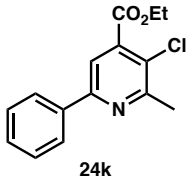
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.62 (m, 5H), 7.12 (d, *J* = 8.5 Hz, 1H), 2.61 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 154.4, 138.2, 137.3, 131.2, 131.1, 127.0, 123.2, 123.1, 24.1

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.2, 131.6, 131.5, 123.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 156.8, 154.4, 138.2, 137.3, 131.2, 131.1, 127.0, 123.2, 123.1, 109.6, 24.1

IR (neat) 3053.55, 2993.36, 2920.70, 2853.60,1919.81, 1902.61, 1590.94, 1433.93, 1377.02, 1179.39, 1008.78, 989.95, 824.20 cm^{-1}



24k

ethyl 3-chloro-2-methyl-6-phenylisonicotinate (24k) The title compound was prepared according to the General Procedure, using **ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate** (114.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (17.9 mg, 13% yield).

TLC (SiO_2) R_f = 0.55 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 45–47 °C

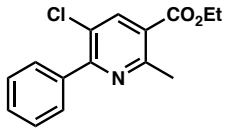
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.0 Hz, 2H), 7.83 (s, 1H), 7.48 (m, 3H), 4.49 (q, J = 7.0 Hz, 2H), 2.79 (s, 3H), 1.37 (t, J = 7.5 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 157.8, 154.8, 139.1, 137.8, 129.4, 128.8, 126.9, 118.2, 62.3, 23.5, 14.2

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 129.8, 129.2, 127.3, 118.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 129.8, 129.2, 127.3, 118.6, 62.7 (–), 23.9, 14.6

IR (neat) 3202.33, 2989.70, 1728.20, 1584.98, 1437.41, 1332.54, 1284.49, 1163.80, 1110.23, 1025.33, 924.93, 806.36 cm^{-1}



24k'

ethyl 5-chloro-2-methyl-6-phenylnicotinate (24k') The title compound was prepared according to the General Procedure, using **ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate** (114.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (41.4 mg, 30% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

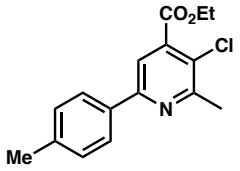
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.45 (m, 3H), 4.40 (q, J = 7.0 Hz, 2H), 2.88 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 157.9, 140.2, 137.5, 129.4, 129.3, 128.8, 128.0, 127.0, 124.7, 61.5, 24.5, 14.2

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.6, 129.8, 128.4

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.5, 129.83, 129.67, 128.4, 61.9, 24.9

IR (neat) 3061.56, 2980.95, 2934.77, 2905.19, 1723.86, 1576.97, 1537.96, 1432.93, 1247.54, 1087.03, 1021.66, 931.78, 867.15 cm^{-1}



24l

ethyl 3-chloro-2-methyl-6-(*p*-tolyl)isonicotinate (24l) The title compound was prepared according to the General Procedure, using **ethyl 2-methyl-5-(*p*-tolyl)-1*H*-pyrrole-3-carboxylate** (121.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (23.2 mg, 16% yield).

TLC (SiO_2) R_f = 0.55 in 5% EtOAc in hexane, *p*-anisaldehyde stain

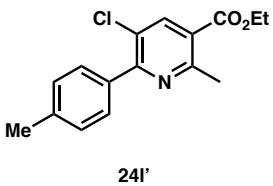
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 7.0 Hz, 2H), 7.80 (s, 1H), 7.30 (d, J = 7.5 Hz, 2H), 4.48 (q, J = 6.9 Hz, 2H), 2.77 (s, 3H), 2.43 (s, 3H), 1.46 (m, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 157.6, 154.8, 139.5, 139.0, 135.0, 129.5, 128.8, 126.7, 126.4, 117.8, 77.3, 77.1, 76.8, 62.2, 23.5, 21.3, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 129.9, 127.1, 118.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 129.9, 127.1, 118.2, 62.6, 21.7, 14.6

IR (neat) 3030.24, 2980.77, 2922.41, 2858.76, 1734.15, 1613.72, 1546.02, 1279.14, 1179.62, 1048.48, 1018.33, 935.65, 820.93 cm^{-1}



24l'

ethyl 5-chloro-2-methyl-6-(*p*-tolyl)nicotinate (24l') The title compound was prepared according to the General Procedure, using **ethyl 2-methyl-5-(*p*-tolyl)-1*H*-pyrrole-3-carboxylate** (121.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (55.1 mg, 38% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 38–40 °C

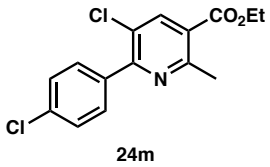
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.43 (q, J = 7.0 Hz, 2H), 2.89 (s, 3H), 2.44 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 158.0, 157.8, 140.2, 139.4, 134.7, 129.4, 128.8, 126.9, 124.5, 61.5, 24.5, 21.4, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.6, 129.8, 129.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.6, 129.8, 129.2, 61.9 (–), 24.9, 21.8, 14.7

IR (neat) 3083.98, 3027.97, 2975.07, 2921.28, 2970.18, 1725.79, 1578.03, 1434.68, 1392.90, 1285.80, 1252.53, 1088.76, 1022.20, 817.39 cm^{-1}



24m

ethyl 5-chloro-6-(4-chlorophenyl)-2-methylnicotinate (24m) The title compound was prepared according to the General Procedure, using **ethyl 5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate** (131.9 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (46.5 mg, 30% yield).

TLC (SiO_2) R_f = 0.52 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 79–82 °C

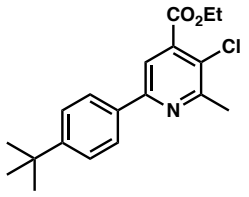
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 4.44 (q, *J* = 7.0 Hz, 2H), 2.88 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 157.9, 156.7, 140.3, 135.9, 135.5, 130.9, 129.0, 128.4, 128.1, 126.9, 125.1, 117.9, 61.7, 24.5, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.7, 131.3, 129.4, 128.8, 128.5, 118.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.7, 131.3, 129.4, 128.7, 128.5, 118.3, 62.1 (–), 24.9, 14.3

IR (neat) 3084.85, 2975.59, 2932.47, 1722.44, 1593.48, 1491.54, 1287.73, 1088.22, 826.46 cm^{-1}



24n

ethyl 6-(4-(*tert*-butyl)phenyl)-3-chloro-2-methylisonicotinate (24n) The title compound was prepared according to the General Procedure, using **ethyl 5-(4-(*tert*-butyl)phenyl)-2-methyl-1*H*-pyrrole-3-carboxylate** (142.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (29.9 mg, 18% yield).

TLC (SiO_2) R_f = 0.55 in 5% EtOAc in hexane, *p*-anisaldehyde stain

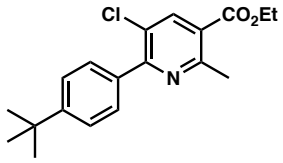
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.82 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 4.49 (q, *J* = 7.0 Hz, 2H), 2.78 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H), 1.39 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 157.6, 154.9, 152.7, 140.2, 139.0, 135.1, 126.6, 125.8, 117.9, 62.2, 34.8, 31.3, 23.5, 14.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.2, 139.0, 135.1, 126.6, 125.8, 117.9, 31.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.2, 139.0, 135.1, 126.6, 125.8, 117.9, 62.2 (–), 31.3, 23.5, 14.7

IR (neat) 2962.66, 2904.80, 2869.09, 1727.79, 1581.76, 1375.25, 1284.45, 1017.10, 909.30, 839.84 cm^{-1}



24n'

ethyl 6-(4-(*tert*-butyl)phenyl)-5-chloro-2-methylnicotinate (24n') The title compound was prepared according to the General Procedure, using **ethyl 5-(4-(*tert*-butyl)phenyl)-2-methyl-1*H*-pyrrole-3-carboxylate** (142.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (68.1 mg, 41% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

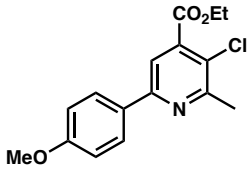
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 4.44 (t, *J* = 7.0 Hz, 2H), 2.89 (s, 3H), 1.45 (t, *J* = 7.5 Hz, 3H), 1.39 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 158.0, 157.8, 152.5, 140.2, 134.7, 129.2, 126.9, 125.1, 124.5, 61.5, 34.8, 31.3, 24.5, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.6, 129.6, 125.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.2, 129.6, 125.5, 61.5 (–), 31.6, 24.9

IR (neat) 2962.89, 2904. 47, 2869.27, 1725.09, 1578.99, 1435.01, 1366.01, 1243.96, 1083.71, 1019.18, 909.12, 866.11 cm^{-1}



24o

ethyl 3-chloro-6-(4-methoxyphenyl)-2-methylisonicotinate (24o) The title compound was prepared according to the General Procedure, using **ethyl 5-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate** (129.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (13.8 mg, 9% yield).

TLC (SiO_2) R_f = 0.55 in 5% EtOAc in hexane, *p*-anisaldehyde stain

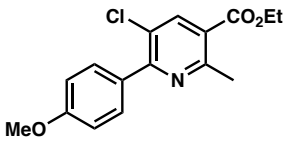
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 9.0 Hz, 2H), 7.76 (s, 1H), 7.02 (m, 3H), 4.47 (q, J = 7.0 Hz, 2H), 3.89 (s, 3H), 2.87 (s, 2H), 1.28 (t, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 157.9, 156.7, 155.9, 140.4, 134.6, 131.1, 130.1, 117.4, 113.5, 111.1, 61.6, 56.4, 24.5, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.4, 134.6, 131.1, 130.1, 117.4, 113.5, 111.1

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.4, 134.6, 130.1, 117.4, 61.6 (–), 56.4, 24.5, 14.3

IR (neat) 2979.70, 2956.69, 2928.16, 2851.35, 2838.50, 1724.60, 1607.49, 1512.96, 1393.32, 1246.74, 1175.35, 1028.73, 932.95, 833.95 cm^{-1}



24o'

ethyl 5-chloro-6-(4-methoxyphenyl)-2-methylnicotinate (24o') The title compound was prepared according to the General Procedure, using **ethyl 5-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate** (129.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a white solid (32.1 mg, 21% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 120–122 °C

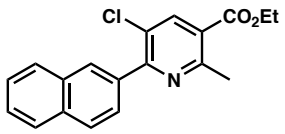
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.08 (d, J = 2.5 Hz, 1H), 7.83 (dd, J = 8.6, 2.0 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 2.87 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 157.9, 155.9, 140.4, 134.6, 130.4, 124.7, 111.4, 111.1, 61.6, 56.4, 24.5, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.8, 135.0, 132.2, 130.4, 127.4, 117.8, 112.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.4, 134.6, 130.4, 56.8, 24.9, 14.7

IR (neat) 2924.41, 2848.50, 2359.56, 2341.43, 1723.72, 1599.62, 1503.80, 1374.46, 1253.19, 1113.77, 1016.90, 947.71, 813.80 cm^{-1}



24p

ethyl 5-chloro-2-methyl-6-(naphthalen-2-yl)nicotinate (24p) The title compound was prepared according to the General Procedure, using **ethyl 2-methyl-5-(naphthalen-2-yl)-1*H*-pyrrole-3-carboxylate** (139.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (61.9 mg, 38% yield).

TLC (SiO_2) R_f = 0.52 in 5% EtOAc in hexane, *p*-anisaldehyde stain

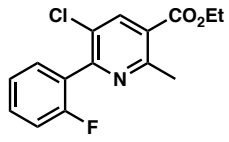
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.32 (s, 1H), 7.94 (m, 6H), 4.45 (q, J = 7.0 Hz, 3H), 2.93 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 157.95, 157.92, 140.3, 133.6, 132.8, 129.4, 128.7, 127.73, 127.69, 127.3, 127.0, 126.62, 126.45, 126.32, 124.2, 118.4, 61.6, 24.5, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.7, 129.8, 129.16, 129.11, 128.99, 128.1, 127.36, 127.20, 127.01, 126.85, 126.71, 124.6, 118.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.7, 129.8, 129.16, 129.11, 128.99, 128.1, 127.36, 127.20, 127.01, 126.85, 126.71, 124.6, 118.8, 62.0 (–), 24.5, 14.3

IR (neat) 3057.79, 2979.27, 2958.96, 2928.11, 2870.93, 2854.47, 1723.70, 1614.73, 153840, 1391.93, 1244.04, 1184.11, 1018.12, 966.00, 819.06 cm^{-1}



24q

ethyl 5-chloro-6-(2-fluorophenyl)-2-methylnicotinate (24q) The title compound was prepared according to the General Procedure, using **ethyl 5-(2-fluorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate** (121.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a colorless liquid (23.5 mg, 16% yield).

TLC (SiO_2) R_f = 0.58 in 5% EtOAc in hexane, *p*-anisaldehyde stain

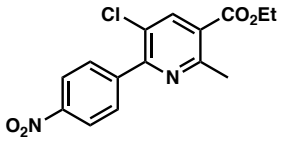
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.32 (s, 1H), 7.56 (m, 4H), 4.45 (q, J = 7.0 Hz, 3H), 2.93 (s, 3 H), 1.29 (t, J = 7.5 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 140.3, 134.9, 133.6, 132.8, 129.5, 128.7, 127.7, 127.0, 126.3, 118.4 61.6, 24.5, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.3, 134.9, 133.6, 132.8, 129.5, 128.7, 127.7, 127.0, 126.3, 118.4

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.3, 134.9, 133.6, 132.8, 129.5, 128.7, 127.7, 127.0, 126.3, 118.4, 61.6, 24.5, 14.3

IR (neat) 3057.05, 2926.51, 2853.64, 1724.24, 1578.23, 1436.02, 1392.23, 1241.91, 1183.79, 1102.30, 1018.60, 905.93, 818.66 cm^{-1}



24r

ethyl 5-chloro-2-methyl-6-(4-nitrophenyl)nicotinate (**24r)** The title compound was prepared according to the General Procedure, using **ethyl 2-methyl-5-(4-nitrophenyl)-1*H*-pyrrole-3-carboxylate** (137.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 0.5→2% EtOAc in hexane), the title compound was isolated as a yellow solid (22.5 mg, 14% yield).

TLC (SiO_2) R_f = 0.60 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 89–91 °C

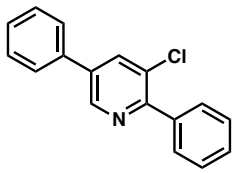
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.34 (m, 2H), 8.18 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 4.45 (q, J = 7.0 Hz, 3H), 2.90 (s, 3 H), 1.47 (t, J = 7.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 158.3, 155.1, 148.1, 140.5, 139.0, 135.5, 129.1, 127.1, 124.8, 124.0, 61.8, 24.4, 14.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 140.9, 135.9, 129.5, 125.2, 124.4, 118.7

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 140.9, 135.9, 129.5, 125.2, 124.4, 24.8, 14.6

IR (neat) 3088.23, 2920.49, 2850.16, 1727.66, 1521.73, 1351.23, 1254.84, 1092.76, 1024.54, 892.71 cm^{-1}



24s

3-chloro-2,5-diphenylpyridine (**24s)** The title compound was prepared according to the General Procedure, using **2,4-diphenyl-1*H*-pyrrole** (109.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (58.5 mg, 44% yield).

TLC (SiO_2) R_f = 0.40 in 5% EtOAc in hexane, *p*-anisaldehyde stain

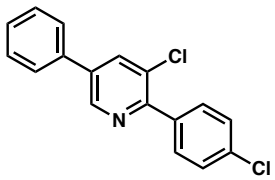
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.03 (d, J = 7.5 Hz, 2H), 7.75 (s, 1H), 7.53 (m, 8H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 149.8, 148.2, 138.2, 129.6, 129.3, 129.2, 128.9, 128.8, 128.5, 127.1, 126.9, 122.2, 120.4, 117.2

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 150.2, 129.2, 128.9, 128.8, 128.5, 127.1, 126.9, 122.2, 120.4, 117.2

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 150.2, 129.6, 129.3, 129.2, 128.9, 128.8, 128.5, 127.1, 126.9, 122.2

IR (neat) 3057.74, 3028.08, 2360.13, 2156.21, 1735.87, 1588.61, 1441.13, 1366.66, 1213.78, 1014.77, 986.05, 867.39 cm^{-1}



24t

3-chloro-2-(4-chlorophenyl)-5-phenylpyridine (**24t)** The title compound was prepared according to the General Procedure, using **2-(4-chlorophenyl)-4-phenyl-1*H*-pyrrole** (126.9 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a white solid (69.0 mg, 46% yield).

TLC (SiO_2) R_f = 0.45 in 5% EtOAc in hexane, *p*-anisaldehyde stain

mp 98–100 °C

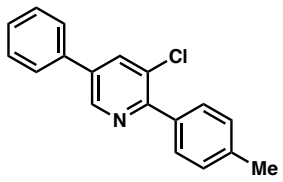
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.75 (s, 1H), 7.54 (m, 8H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 149.8, 148.4, 136.7, 135.5, 129.05, 129.01, 128.92, 128.52, 128.37, 128.1, 127.1, 122.0, 120.7, 117.0

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 150.2, 131.2, 129.7, 129.45, 129.41, 129.32, 128.92, 128.77, 128.75, 128.5, 127.5, 122.4

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 150.2, 131.2, 129.7, 129.45, 129.41, 129.32, 128.92, 128.77, 128.75, 128.5, 127.5, 122.4

IR (neat) 3085.43, 3060.79, 3033.55, 2922.96, 2851.19, 1979.10, 1777.72, 1594.85, 1493.70, 1282.57, 1102.32, 867.50 cm^{-1}



24u

3-chloro-5-phenyl-2-(*p*-tolyl)pyridine (**24u)** The title compound was prepared according to the General Procedure, using **4-phenyl-2-(*p*-tolyl)-1*H*-pyrrole** (116.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (50.4 mg, 36% yield).

TLC (SiO_2) R_f = 0.45 in 5% EtOAc in hexane, *p*-anisaldehyde stain

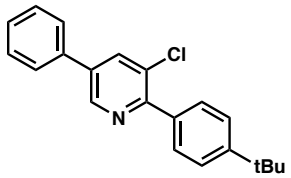
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.00 (m, 2H), 7.72 (d, J = 4.5 Hz, 1H), 7.52 (m, 6H), 7.31 (d, J = 8.0 Hz, 1H), 2.44 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 149.7, 148.1, 139.4, 136.99, 136.97, 135.4, 129.6, 129.2, 128.97, 128.86, 128.47, 128.45, 127.12, 127.00, 126.98, 126.8, 121.9, 120.1, 116.8, 21.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 150.0, 129.6, 129.2, 128.97, 128.86, 128.47, 128.45, 127.12, 127.00, 126.98, 126.8, 121.9, 120.1, 116.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 150.0, 129.6, 129.2, 128.97, 128.86, 128.47, 128.45, 127.12, 127.00, 126.98, 126.8, 121.9, 120.1, 116.8, 21.3

IR (neat) 3057.07, 3030.75, 2960.68, 2925.77, 2866.40, 1738.03, 1585.87, 1458.15, 1382.72, 1240.02, 1056.97, 908.02 cm^{-1}



24v

2-(4-(*tert*-butyl)phenyl)-3-chloro-5-phenylpyridine (24v) The title compound was prepared according to the General Procedure, using **2-(4-(*tert*-butyl)phenyl)-4-phenyl-1*H*-pyrrole** (137.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (112.6 mg, 70% yield).

TLC (SiO_2) R_f = 0.45 in 5% EtOAc in hexane, *p*-anisaldehyde stain

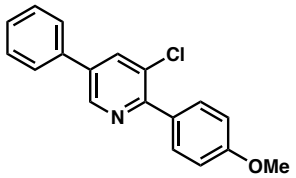
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.73 (s, 1H), 7.54 (m, 10H), 1.40 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 152.6, 149.7, 148.0, 137.0, 135.4, 129.2, 128.98, 128.83, 128.45, 128.42, 127.1, 126.8, 126.6, 125.8, 121.9, 120.1, 116.9, 77.3, 77.0, 76.8, 34.7, 31.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 150.1, 129.9, 129.6, 128.8, 127.5, 127.2, 126.2, 122.3, 120.5, 117.3, 31.7

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 135.4, 129.2, 128.98, 128.83, 128.45, 128.42, 127.1, 126.8, 126.6, 125.8, 121.9, 120.1

IR (neat) 3058, 3029.51, 2959.79, 2924.79, 2854.95, 2360.22, 2340.68, 1737.77, 1585.88, 1995.65, 1258.65, 1108.58, 1000.80, 919.91, 820.60 cm^{-1}



24w

3-chloro-2-(4-methoxyphenyl)-5-phenylpyridine (**24w)** The title compound was prepared according to the General Procedure, using **2-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole** (124.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (31.1 mg, 21% yield).

TLC (SiO_2) R_f = 0.58 in 5% EtOAc in hexane, *p*-anisaldehyde stain

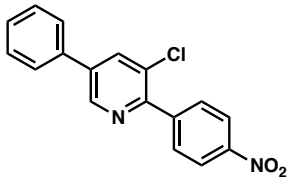
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.68 (m, 1H), 7.51 (m, 6H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 129.00, 128.94, 128.4, 127.1, 114.35, 114.35, 111.90, 111.90, 56.40, 56.40, 55.42, 55.42

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 150.0, 132.2, 129.7, 129.3, 128.90, 128.75, 127.5, 121.9, 114.74, 114.57, 112.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 129.3, 128.9, 114.7, 112.3, 56.8, 55.8

IR (neat) 2923.80, 2851.94, 2359.93, 2341.64, 1586.77, 1458.15, 1367.08, 1256.59, 1212.75, 1031.99, 812.21 cm^{-1}



24x

3-chloro-2-(4-nitrophenyl)-5-phenylpyridine (**24x)** The title compound was prepared according to the General Procedure, using **2-(4-nitrophenyl)-4-phenyl-1*H*-pyrrole** (132.1 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (55.9 mg, 36% yield).

TLC (SiO_2) R_f = 0.60 in 5% EtOAc in hexane, *p*-anisaldehyde stain

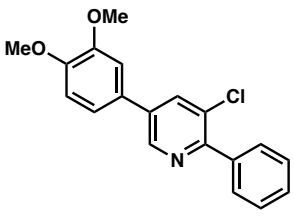
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.89 (t, *J* = 8.5 Hz, 3H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.50 (m, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 138.7, 129.6, 129.3, 128.8, 128.0, 126.9, 119.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 139.1, 130.0, 129.6, 129.2, 128.3, 127.3, 120.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 139.1, 130.0, 129.7, 129.2, 128.3, 127.3, 120.0

IR (neat) 3059.96, 3033.32, 2924.02, 2852.78, 2359.61, 2341.92, 1775.90, 1601.74, 1440.22, 1111.40, 919.19, 831.55 cm^{-1}



24y

3-chloro-5-(3,4-dimethoxyphenyl)-2-phenylpyridine (**24y)** The title compound was prepared according to the General Procedure, using **4-(3,4-dimethoxyphenyl)-2-phenyl-1*H*-pyrrole** (139.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (120.5 mg, 74% yield).

TLC (SiO_2) R_f = 0.58 in 5% EtOAc in hexane, *p*-anisaldehyde stain

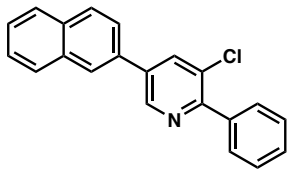
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.09 (d, J = 8Hz, 1 H), 7.88 (t, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 1H), 7.50 (m, 5H), 4.30 (s, 3H), 4.29 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 155.2, 138.7, 138.5, 138.2, 129.6, 129.3, 128.8, 128.3, 128.0, 127.8, 126.9, 119.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 139.1, 129.7, 129.2, 128.4, 128.2, 127.3, 120.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 139.1, 129.7, 129.2, 128.4, 128.2, 127.3, 120.0

IR (neat) 3060.45, 3032.57, 2956.99, 2926.71, 3856.99, 2776.30, 1732.90, 1557.79, 1448.44, 1229.69, 1047.50, 916.72 cm^{-1}



24z

3-chloro-5-(naphthalen-2-yl)-2-phenylpyridine (**24z)** The title compound was prepared according to the General Procedure, using **4-(naphthalen-2-yl)-2-phenyl-1*H*-pyrrole** (134.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (71.1 mg, 45% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

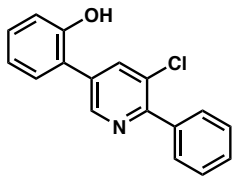
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 6.6, 1.1 Hz, 2H), 7.88 (m, 3H), 7.69 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.49 (m, 6H), 7.29 (t, *J* = 0.8 Hz, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 129.6, 129.3, 128.8, 127.9, 126.9, 119.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 139.1, 130.0, 129.7, 129.2, 128.3, 127.3, 120.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 139.1, 130.0, 129.7, 129.2, 128.3, 127.3, 120.0, 110.0

IR (neat) 3086.04, 3059.43, 3033.51, 2921.50, 2849.53, 2359.45, 2341.93, 1722.67, 1601.33, 1449.36, 1371.41m 1047.44, 917.78, 831.25 cm^{-1}



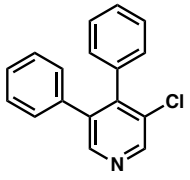
24aa

2-(5-chloro-6-phenylpyridin-3-yl)phenol (**24aa)** The title compound was prepared according to the General Procedure, using **2-(5-phenyl-1*H*-pyrrol-3-yl)phenol** (58.8 mg, 0.25 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (21.8 mg, 31% yield).

TLC (SiO_2) R_f = 0.55 in 5% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 7.5 Hz, 1H), 7.88 (t, J = 7.5 Hz, 3H), 7.70 (d, J = 8.0 Hz, 1H), 7.50 (m, 6H)

IR (neat) 3059.54, 2925,05, 2854.04, 2094.97, 1563.24, 1425.81, 1362.33, 1111.87, 1029.59, 918.05, 831.61 cm^{-1}



24ab

3-chloro-4,5-diphenylpyridine (**24ab)** The title compound was prepared according to the General Procedure, using **3,4-diphenyl-1*H*-pyrrole** (109.6 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (53.1 mg, 40% yield).

TLC (SiO_2) R_f = 0.45 in 5% EtOAc in hexane, *p*-anisaldehyde stain

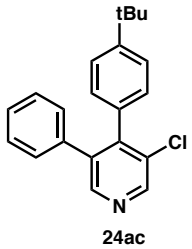
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.5 Hz, 2H), 7.80 (t, *J* = 8.5 Hz, 3H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.50 (m, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 155.2, 138.7, 138.5, 138.2, 129.6, 129.3, 128.8, 128.5, 128.0, 126.9, 119.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 139.1, 130.0, 129.67, 129.2, 128.4, 127.3, 127.3, 120.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 139.1, 130.0, 129.7, 129.2, 127.3, 120.0

IR (neat) 3059.14, 3032.63, 2924.91, 2852.11, 1887.43, 1731.79, 1583.02, 1425.06, 1370.81, 1144.05, 1047.53, 864.33cm^{-1}



24ac

4-(4-(*tert*-butyl)phenyl)-3-chloro-5-phenylpyridine (**24ac)** The title compound was prepared according to the General Procedure, using **3-(4-(*tert*-butyl)phenyl)-4-phenyl-1*H*-pyrrole** (137.7 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 1% EtOAc in hexane), the title compound was isolated as a colorless liquid (78.9 mg, 49% yield).

TLC (SiO_2) R_f = 0.50 in 5% EtOAc in hexane, *p*-anisaldehyde stain

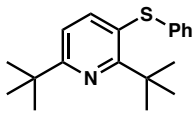
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.5 Hz, 1H), 7.63 (t, J = 9.0 Hz, 2H), 7.52 (m, 5H), 1.40 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 155.5, 155.2, 152.4, 138.6, 135.73, 135.57, 132.0, 130.1, 129.43, 129.35, 128.8, 128.49, 128.44, 128.41, 128.36, 128.27, 128.17, 128.05, 126.82, 126.67, 126.2, 125.85, 125.76, 125.68, 125.4, 31.3, 20.9

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 132.4, 129.7, 126.1, 125.3, 119.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 139.0, 132.4, 129.7, 127.1, 126.6, 126.1, 125.3, 119.5

IR (neat) 2962.35, 2904.22, 2867.84, 2227.59, 1606.59, 1433.29, 1242.37, 1010.91, 9-8.30, 837.14 cm^{-1}



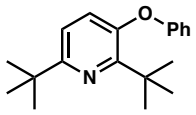
24ad

2,6-di-*tert*-butyl-3-(phenylthio)pyridine (**24ad)** The title compound was prepared according to known procedures,[3] using **2,6-di-*tert*-butyl-3-chloropyridine** (135.5 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 100% hexanes), the title compound was isolated as a colorless liquid (116.5 mg, 78% yield).

TLC (SiO_2) R_f = 0.65 in 100% hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 3H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 1.56 (s, 9H), 1.40 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 161.5, 138.9, 137.1, 129.1, 127.5, 127.28, 127.17, 117.3, 39.5, 37.6, 30.1, 29.8, 28.8



24ae

2,6-di-*tert*-butyl-3-phenoxypyridine (**24ae)** The title compound was prepared according to known procedures,[4] using **2,6-di-*tert*-butyl-3-chloropyridine** (135.5 mg, 0.50 mmol). After purification by flash chromatography (SiO_2, 100% hexanes), the title compound was isolated as a colorless liquid (99.2 mg, 70% yield).

TLC (SiO_2) R_f = 0.48 in 100% hexanes, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 9.0 Hz, 1H), 7.25 (m, 2H), 7.09 (d, *J* = 9.5 Hz, 1H), 6.91 (m, 3H), 1.52 (s, 9H), 1.36 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 165.1, 161.5, 156.0, 138.8, 129.6, 120.3, 117.3, 115.3, 30.1, 28.7, 21.1

9.3. Synthesis of 2,6-di-t-butylpyridine Analogues

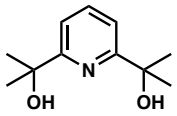
General Procedure for Synthesis of Pyridine Alcohols

Dimethyl 2,6-pyridinedicarboxylate (10.0 mmol, 1.0 equiv.) is placed in an oven-dried 100-mL round bottom flask equipped with a magnetic stirrer bar coated with Teflon, fitted with a nitrogen inlet and a rubber septum. The flask was evacuated and backfilled with nitrogen (three cycles). The flask was charged with dry diethyl ether (59.0 mL, 0.17M) and cooled to 0°C in an ice-water bath. After which, a solution of Grignard reagent (60.0 mmol, 6.0 equiv.) is added dropwise via a dropping funnel. The resulting mixture was then allowed to stir overnight and warm to room temperature. The reaction started as an orange colored solution and progressed to a pale yellow. The progress of the reaction was followed by TLC analysis on silica gel with 50% EtOAc-hexane as eluent and visualization with *p*-anisaldehyde. The ester starting material has R_f = 0.50 (UV-active, white) and the alcohol product has Rf = 0.67 (UV-active, white). Upon completion, the reaction was quenched with 100.0 mL of aqueous saturated NH_4Cl at 0°C in an ice-water bath via a dropping funnel and then 15.0 mL of ethyl acetate was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 10.0 mL). The combined organic phases were washed with water (1 x 10.0 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated on the rotary evaporator. The residue was purified by

flash chromatography on silica gel to afford the desired product with 20% ethyl acetate-hexanes solvent system. The desired resulting product is dried under vacuum.

General Procedure for Synthesis of Pyridine Ethers

The corresponding pyridine alcohol (5.0 mmol, 1.0 equiv.) and sodium hydride (60% in mineral oil, 2.0 or 4.0 equiv.) was placed in a 100-mL round bottom flask equipped with a magnetic stirrer bar coated with Teflon, fitted with a nitrogen inlet and a rubber septum. Synthesis of diethers required 4.0 equiv of base and alkylating agent, mono pyridine ethers required only 2.0 equiv. The flask was evacuated and backfilled with nitrogen (three cycles). The flask was charged with dry dimethylformamide (36.0 mL, 0.138 M), and the solution was allowed to stir for 15 minutes. After which, methyliodide (2.0 or 4.0 equiv) was added dropwise to the reaction flask via syringe over 5-10 minutes at 0°C in an ice-water bath. The resulting mixture was then allowed to stir overnight (6 hours is required). The reaction undergoes several color changes, ultimately turning into a clear orange colored solution. The progress of the reaction was followed by TLC analysis on silica gel with 20% EtOAc-hexane as eluent and visualization with *p*-anisaldehyde. The alcohol starting material has R_f = 0.16 (UV-active, white) and the ether product has R_f = 0.71 (UV-active, white). Upon completion, the reaction was quenched with water and then 15.0 mL of ethyl acetate was added. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 15.0 mL). The combined organic phases were washed with water (1 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated on the rotary evaporator. The residue was purified by flash chromatography on silica gel to afford the desired product. The desired resulting product is dried under vacuum.



27a

2,2'-(pyridine-2,6-diyl)bis(propan-2-ol) (27a) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Alcohols,** using dimethyl 2,6-pyridinedicarboxylate (1.95 g, 10.0 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a white solid (1.64 g, 84% yield).

TLC (SiO_2) R_f = 0.67 in 50% EtOAc in hexane, *p*-anisaldehyde stain

mp 85–87 °C

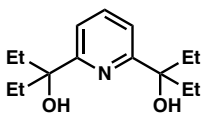
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (t, *J* = 8 Hz, 1H), 7.33 (d, *J* = 8 Hz, 2H), 4.34 (s, 2H), 1.57 (s, 12H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 138.0, 116.7, 72.3, 30.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.4, 117.1, 31.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 138.4, 117.1, 31.0

IR (neat) 2994.83 cm-1, 2967.44, 2927.13, 1576.00, 1451.44, 1421.03, 1401.59, 1375.99, 1365.92, 1356.10, 1293.24, 1228.50, 1182.19, 1152.36, 1127.59, 1077.97, 995.72, 961.57, 895.08, 853.75, 821.60, 786.68, 760.14, 631.93, 578.04 cm^{-1}



27b

3,3'-(pyridine-2,6-diyl)bis(pentan-3-ol) (27b) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Alcohols,** using dimethyl 2,6-pyridinedicarboxylate (1.95 g, 10.0 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless liquid (0.78 g, 30% yield).

TLC (SiO_2) R_f = 0.65 in 50% EtOAc in hexane, *p*-anisaldehyde stain

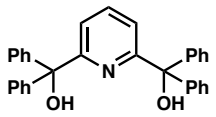
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (t, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 2H), 4.27 (s, 2H), 1.86 (q, J = 7.5 Hz, 8H), 0.66 (t, J = 7.5 Hz, 12H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 137.4, 117.7, 34.6, 7.6

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.8, 118.1, 35.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.8, 118.1, 35.1, 8.0

IR (neat) 3414.73, 2964.97, 2935.70, 2878.08, 1728.03, 1577.48, 1456.71, 1395.88, 1373.57, 1324.21, 1302.94, 1275.38, 1252.25, 1237.95, 1213.02, 1163.48, 1138.25, 1122.90, 1104.58, 1087.09, 1053.93, 1042.57, 999.61, 967.16, 947.37, 939.81, 905.30, 888.33, 846.96, 815.99, 794.29, 779.10, 755.37, 735.18, 710.07, 699.75, 684.01, 667.25, 642.28, 633.17, 612.23, 594.11, 586.60, 574.33, 566.83, 559.02, 553.42 cm^{-1}



27c

pyridine-2,6-diylbis(diphenylmethanol) (27c) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Alcohols,** using dimethyl 2,6-

pyridinedicarboxylate (1.95 g, 10.0 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a white solid (3.99 g, 90% yield).

TLC (SiO_2) R_f = 0.64 in 50% EtOAc in hexane, *p*-anisaldehyde stain

mp 119–120 °C

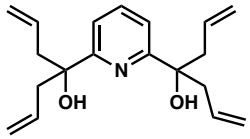
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 15 Hz, 20H), 7.12 (d, J = 7.5 Hz, 2H), 5.11 (s, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 145.8, 137.0, 128.2, 128.0, 127.5, 122.0, 81.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.4, 128.6, 128.4, 127.9, 121.9

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.4, 128.6, 128.4, 127.9, 121.9

IR (neat) 3053.95, 3023.03, 2945.41, 2851.41, 2828.02, 2040.22, 1959.22, 1888.94, 1811.87, 1738.31, 1568.67, 1491.60, 1443.66, 1316.07, 1259.12, 1181.87, 1093, 1073.05, 1030.51, 925.40, 856.30, 553.11 cm^{-1}



27d

4,4'-(pyridine-2,6-diyl)bis(hepta-1,6-dien-4-ol) (27d) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Alcohols,** using dimethyl 2,6-pyridinedicarboxylate (1.95 g, 10.0 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a colorless liquid (2.12 g, 71% yield).

TLC (SiO_2) R_f = 0.60 in 50% EtOAc in hexane, *p*-anisaldehyde stain

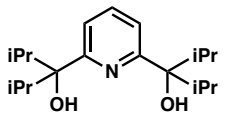
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (t, *J* = 8Hz, 1H), 7.27 (d, *J* = 7.5Hz, 2H), 5.58 (m, 4H), 4.97 (m, 8H), 4.05 (s, 2H), 2.63 (m, 8H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 137.2, 133.3, 118.4, 118.2, 76.0, 46.0

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.6, 133.7, 118.6, 46.4

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.6, 133.7, 118.6, 46.4

IR (neat) 3419.26, 3075.14, 3008.05, 2978.70, 2931.24, 2907.16, 1736.97, 1639.72, 1591.05, 1413.44, 1242.96, 994.96, 911.89, 816.54, 757.52, 631.40 cm^{-1}



27e

3,3'-(pyridine-2,6-diyl)bis(2,4-dimethylpentan-3-ol) (27e) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Alcohols,** using dimethyl 2,6-pyridinedicarboxylate (1.95 g, 10.0 mmol). After purification by flash chromatography (SiO_2, 20% EtOAc in hexane), the title compound was isolated as a yellow solid (0.31 g, 10% yield).

TLC (SiO_2) R_f = 0.55 in 50% EtOAc in hexane, *p*-anisaldehyde stain

mp 80–85 °C

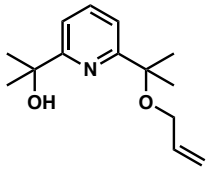
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (t, *J* = 8 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 2.35 (m, 4H), 0.80 (dd, *J* = 24, 7 Hz, 24H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 136.1, 119.0, 80.4, 34.3, 17.4, 16.7

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 136.5, 119.4, 34.7, 17.1

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 136.5, 119.4, 34.7, 17.8, 17.1

IR (neat) 3423.58, 3225.09, 2961.98, 2934.86, 2907.54, 2874.97, 1724.99, 1588.60, 1577.65,1461.40, 1409.65, 1381.22, 1260.68, 1167.08, 996.88, 805.33, 687.52 cm^{-1}



29a

3,3'-(pyridine-2,6-diyl)bis(2,4-dimethylpentan-3-ol) (29a) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **2,2'-(pyridine-2,6-diyl)bis(propan-2-ol)** (0.98 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (0.71 g, 60% yield).

TLC (SiO_2) R_f = 0.55 in 20% EtOAc in hexane, *p*-anisaldehyde stain

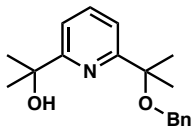
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, *J* = 8 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 5.92 (m, 1H), 5.39 (s, 1H), 5.29 (d, *J* = 17.5 Hz, 1H), 5.12 (d, *J* = 10.5, 1H), 3.80 (s, 2H), 1.58 (s, 6H), 1.51 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 163.2, 137.6, 135.4, 117.9, 116.6, 115.8, 78.8, 71.4, 64.4, 30.7, 27.1

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.0, 135.8, 118.3, 117.0, 64.8, 31.0, 27.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 138.0, 135.8, 118.3, 117.0, 116.6, 64.8 (–), 31.0, 27.5

IR (neat) 3420.51, 2976.31, 2929.78, 2861, 93, 2360.10, 1577.37, 1469.13, 1371.49, 1172.99, 1030.59, 919.51, 816.88 cm^{-1}



29b

2-(6-(2-(benzyloxy)propan-2-yl)pyridin-2-yl)propan-2-ol (29b) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **2,2'-(pyridine-2,6-diyl)bis(propan-2-ol)** (0.98 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a white solid (0.67 g, 47% yield).

TLC (SiO_2) R_f = 0.52 in 20% EtOAc in hexane, *p*-anisaldehyde stain

mp 51–53 °C

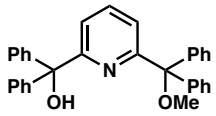
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (t, *J* = 3.5 Hz, 1H), 7.60 (d, *J* = 3.5 Hz, 1H), 7.38 (m, 4H), 7.28 (m, 2H), 5.50 (s, 1H), 4.42 (s, 2H), 1.73 (s, 6H), 1.60 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 163.2, 139.2, 137.7, 128.3, 127.3, 118.2, 116.8, 79.0, 71.5, 65.3, 30.8, 27.2

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 138.1, 128.7, 127.7, 118.6, 117.2, 31.2, 27.6

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 138.1, 128.8, 127.7, 118.6, 117.2, 65.7 (–), 31.2, 27.6

IR (neat) 3413.75, 2975.23, 2929.38, 1738.08, 1577.21, 1453.01, 1358.60, 1170.03, 1058.36, 964.66, 846.30 cm^{-1}



29c

(6-(methoxydiphenylmethyl)pyridin-2-yl)diphenylmethanol (29c) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **pyridine-2,6-diylbis(diphenylmethanol)** (2.21 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a white solid (0.55 g, 24% yield).

TLC (SiO_2) R_f = 0.55 in 20% EtOAc in hexane, *p*-anisaldehyde stain

mp 85–90 °C

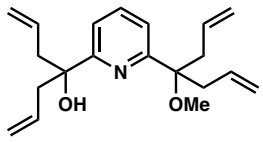
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.0 Hz, 1H), 7.67 (t, J = 7.0 Hz, 1H), 7.45 (m, 4H), 7.30 (m, 16H), 7.01 (d, J = 7.0 Hz, 1H), 5.90 (s, 1H), 3.18 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 161.9, 146.3, 142.9, 142.9, 137.3, 129.2, 128.3, 127.9, 127.7, 127.3, 127.2, 120.5, 120.4, 87.4, 81.1, 52.5

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.7, 129.6, 128.7, 128.3, 128.1, 127.7, 127.6, 120.9, 120.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.7, 129.6, 128.7, 128.3, 128.1, 127.7, 127.6, 120.9, 120.8, 52.9

IR (neat) 3427.49, 3056.74, 2980.36, 2937.74, 2826.80, 1736.74, 1572.19, 1444.58, 1371.52, 1240.39, 1088.78, 1000.03, 909.11 cm^{-1}



29d

4-(6-(4-methoxyhepta-1,6-dien-4-yl)pyridin-2-yl)hepta-1,6-dien-4-ol (29d) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **4,4'-(pyridine-2,6-diyl)bis(hepta-1,6-dien-4-ol)** (1.50 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (0.39 g, 25% yield).

TLC (SiO_2) R_f = 0.50 in 20% EtOAc in hexane, *p*-anisaldehyde stain

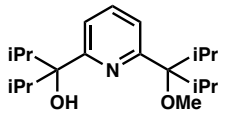
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, *J* = 8 Hz, 1H), 7.433 (d, *J* = 8 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 5.58 (m, 4H), 4.96 (m, 8H), 3.27 (s, 3H), 2.77 (m, 4H), 2.62 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 160.7, 136.8, 133.6, 133.1, 119.6, 117.9, 117.8, 117.7, 82.2, 75.6, 49.9, 46.2, 40.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.2, 134.0, 133.5, 120.0, 118.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.2, 134.0, 133.5, 120.0, 118.4, 118.30, 118.13, 50.4, 50.3, 46.6, 40.8

IR (neat) 3074.69, 3008.11, 2936.39, 2911.85, 2828.80, 2359.54, 2341.65, 1639.81, 1588.52, 1577.04, 1431.60, 1388.10, 1075.59, 992.48, 910.56 cm^{-1}



29e

3-(6-(3-methoxy-2,4-dimethylpentan-3-yl)pyridin-2-yl)-2,4-dimethylpentan-3-ol (29e) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **3,3'-(pyridine-2,6-diyl)bis(2,4-dimethylpentan-3-ol)** (1.54 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (0.40 g, 25% yield).

TLC (SiO_2) R_f = 0.48 in 20% EtOAc in hexane, *p*-anisaldehyde stain

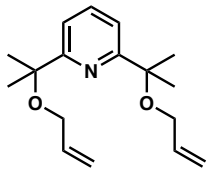
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (t, J = 7.5 Hz, 1H), 7.536 (d, J = 8 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 5.83 (s, 1H), 3.53 (s, 3H), 2.80 (m, 2H), 2.29 (m, 2H), 0.92 (d, J = 7 Hz, 4H), 0.83 (m, 20H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 158.9, 135.6, 121.5, 120.7, 117.9, 85.9, 79.5, 52.5, 34.4, 31.3, 30.9, 18.2, 18.0, 17.9, 17.6, 17.5, 16.9

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 136.0, 121.9, 121.1, 118.3, 34.9, 31.7, 31.3, 18.4, 18.1, 17.9, 17.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 136.0, 121.9, 118.3, 52.9, 34.8, 31.7, 31.3, 18.6, 18.4, 18.3, 18.0, 17.9, 17.3

IR (neat) 3374.12, 2963.90, 2936.22, 2875.95, 2835.02, 2359.66, 1742.13, 1577.84, 1453.98, 1380.85, 1079.28, 804.87 cm^{-1}



28b

2,6-bis(2-(allyloxy)propan-2-yl)pyridine (28b) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **2,2'-(pyridine-2,6-diyl)bis(propan-2-ol)** (0.98 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (1.10 g, 88% yield).

TLC (SiO_2) R_f = 0.65 in 20% EtOAc in hexane, *p*-anisaldehyde stain

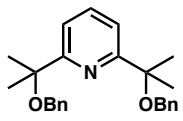
^{1}H NMR (500 MHz, $CDCl_3$) δ (500 MHz, $CDCl_3$) δ 7.63 (t, J = 8 Hz, 1H), 7.41 (d, J = 7.5 Hz, 2H), 5.94 (m, 2H), 5.31 (d, J = 17.5 Hz, 2H), 5.12 (d, J = 10 Hz, 2H), 3.84 (d, J = 5 Hz, 4H), 1.58 (s, 12H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 136.6, 135.7, 117.4, 115.6, 79.2, 64.3, 27.1

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.0, 136.1, 117.8, 116.0, 64.7, 27.5

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.0, 136.1, 117.8, 116.0, 64.8 (–), 27.4

IR (neat) 3079.26, 2978.33, 2931.33, 2860.31, 1728.95, 1646.59, 1577.03, 1467.07, 1451.76, 1355.64, 1237.83, 1168.35, 1060.99, 918.22, 818.66, 756.34 cm^{-1}



28c

2,6-bis(2-(benzyloxy)propan-2-yl)pyridine (28c) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **2,2'-(pyridine-2,6-diyl)bis(propan-2-ol)** (0.98 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (1.26 g, 67% yield).

TLC (SiO_2) R_f = 0.64 in 20% EtOAc in hexane, *p*-anisaldehyde stain

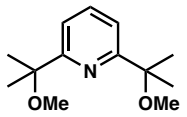
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 8 Hz, 2H), 7.49 (m, 8H), 7.38 (t, J = 7 Hz, 2H), 4.53 (s, 4H), 1.83 (s, 12H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 139.6, 136.8, 128.4, 127.4, 127.3, 117.9, 79.5, 65.4, 27.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.2, 128.8, 127.8, 127.7, 118.3, 27.7

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.2, 128.8, 127.7, 118.3, 65.8 (–), 27.7, 27.7

IR (neat) 3088.52, 3063.48, 3030.08, 2929.86, 2862.31, 1725.93, 1576.91, 1452.83, 1356.03, 1308.96, 1166.90, 1058.29, 886.34, 731.34 cm^{-1}



28a

2,6-bis(2-methoxypropan-2-yl)pyridine (28a) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **2,2'-(pyridine-2,6-diyl)bis(propan-2-ol)** (0.98 g, 5.0 mmol). Only 2.0 equiv of base and alkylating agent required. After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (0.83 g, 74% yield).

TLC (SiO_2) R_f = 0.71 in 20% EtOAc in hexane, *p*-anisaldehyde stain

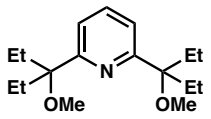
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 2H), 3.18 (s, 6H), 1.55 (s, 12H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 137.0, 117. 9, 79.3, 51.2, 26.9

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 136.9, 117.9, 26.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.0, 117.8, 51.2, 26.9

IR (neat) 2976.26, 2932.98, 2825.28, 1577.01, 1461.61, 1409.87, 1370.86, 13657.05, 1293.36, 1239.01, 1175.11, 1073.25, 994.80, 926.58, 818.94, 757.05, 604.37, 574.02 cm^{-1}



28d

2,6-bis(3-methoxypentan-3-yl)pyridine (28d) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **3,3'-(pyridine-2,6-diyl)bis(pentan-3-ol)** (1.26 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (1.05 g, 75% yield).

TLC (SiO_2) R_f = 0.69 in 20% EtOAc in hexane, *p*-anisaldehyde stain

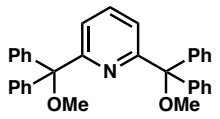
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8 Hz, 2H), 3.20 (s, 6H), 1.96 (m, 8H), 0.61 (t, *J* = 7.5 Hz, 12H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 135. 3, 118.8, 83.4, 49.2, 27.9, 7.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 135.7, 119.2, 28.3

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 135.7, 119.2, 49.56, 49.54, 28.28, 28.25, 7.7

IR (neat) 2965.52, 2935.95, 2877.36, 2826.45, 1581.51, 1459.11, 1448.62, 1338.47, 1187.33, 1169.10, 1149.45, 1138.44, 1075.61, 1055.83, 994.89, 940.81, 819.54, 793.36, 775.78, 756.23, 591.81, 585.02, 575.84, 564.62, 551.34 cm^{-1}



28e

2,6-bis(methoxydiphenylmethyl)pyridine (28e) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **pyridine-2,6-diylbis(diphenylmethanol)** (2.22 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a white solid (1.04 g, 44% yield).

TLC (SiO_2) R_f = 0.65 in 20% EtOAc in hexane, *p*-anisaldehyde stain

mp 185–187 °C

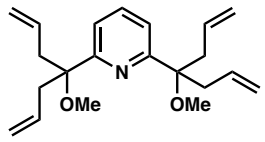
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.65 (m, 2H), 7.25 (m, 20H), 3.05 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 143.1, 136.9, 129.5, 127.3, 126.7, 118.6, 87.3, 52.3

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 137.3, 129.9, 127.7, 127.1, 119.0

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 137.3, 129.9, 127.7, 127.1, 119.0, 52.7

IR (neat) 3053.95, 3023.03, 2945.41, 2851.40, 2828.02, 2040.22, 1888.94, 1811.87, 1738.31, 1558.67, 1443.66, 1093.87, 1073.05, 925.40, 768.20, 675.22. 635.55 cm^{-1}



28f

2,6-bis(4-methoxyhepta-1,6-dien-4-yl)pyridine (28f) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **4,4'-(pyridine-2,6-diyl)bis(hepta-1,6-dien-4-ol)** (1.50 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (1.28 g, 78% yield).

TLC (SiO_2) R_f = 0.68 in 20% EtOAc in hexane, *p*-anisaldehyde stain

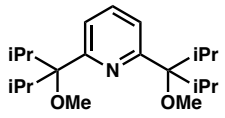
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 5.56 (m, 4H), 4.97 (m, 8H), 3.28 (s, 6H), 2.78 (m, 8H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 135.9, 133.6, 119.2, 117.3, 82.3, 49.8, 40.4

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 136.3, 134.0, 119.56, 119.53, 117.69, 117.62, 40.8

^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 136.3, 134.0, 119.6, 117.7, 50.2, 40.8

IR (neat) 3074.65, 3007.66, 2978.39, 2936.69, 2915.17, 2827.21, 1833.42, 1741.31, 1640.01, 1577.01, 1450.14, 1286.80, 1075.01, 990.88, 910.30, 758.42, 630.13 cm^{-1}



28g

2,6-bis(3-methoxy-2,4-dimethylpentan-3-yl)pyridine (28g) The title compound was prepared according to the **General Procedure for Synthesis of Pyridine Ethers,** using **3,3'-(pyridine-2,6-diyl)bis(2,4-dimethylpentan-3-ol)** (1.54 g, 5.0 mmol). After purification by flash chromatography (SiO_2, 10% EtOAc in hexane), the title compound was isolated as a colorless liquid (1.26 g, 75% yield).

TLC (SiO_2) R_f = 0.60 in 20% EtOAc in hexane, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 3.52 (s, 6H), 2.80 (m, 4H), 0.88 (dd, J = 7.0 Hz, 24H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 134.3, 120.7, 86.1, 52.3, 30.9, 18.2, 17.9

^{13}C DEPT-90 NMR (126 MHz, $CDCl_3$) δ 134.7, 121.1, 31.3

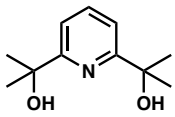
^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$) δ 134.7, 121. 1, 121.0, 52.7, 31.3, 18.5, 18.3

IR (neat) 2964.97, 2936.04, 2876.19, 2833.36, 1577.02, 1445.53, 1383.39, 1188.07, 1078.35, 1013.66, 994.64, 977.82, 808.34, 758.00, 731.32 cm^{-1}

9.4. Gas Phase Studies of 2,6-di-*t*-butylpyridine Analogues

General Information

MS analysis was carried out in "Targeted MS mode" in triplicate analysis with an Agilent 6545 quadrupole time-of-flight (Q-TOF) mass spectrometer in positive ion mode, tuned for Fragile Ions. The sample was injected via syringe pump at a flow rate of 0.60 μL/min. Instrument parameters were as followed: gas temp at 325 °C, gas flow of 5 l/min, nebulizer at 20 psig, sheath gas temperature at 275 °C, sheath gas flow of 12, VCap at 3600, nozzle volage at 2000 V, fragmentor at 120, skimmer1 at 65, and octopoleRFpeak at 750. Mass range was set from 50 – 500 m/z. MS scan rate was 1.00 spectra/scan. MS/MS scan rate was 1.00 spectra/scan.



27a

	Reference Base	PA (kJ/mol)
A	Pyridine	930
B	Bu_2NH	968.5
C	Indoline	957.1
D	Et_2NH	952.4
E	Morpholine	924.3
	Average	**946.46**

Voltage	Pyridine (m/z)	27a (m/z)	Complex (m/z)	Ratio of 27a/Ref base	Ln(Ratio)	Avg
3V	109.95	562.36	711.25	5.114688495	1.632116497	
	168.83	506.59	698.47	3.000592312	1.098809706	
	80.89	535.44	704.55	6.619359624	1.889998632	1.540308278
5V	148.14	512.46	628.31	3.459295261	1.241064887	
	136.39	525.57	634.28	3.853435003	1.348964959	
	146.21	435.74	613.6	2.98023391	1.092001791	1.227343879
10V	124.21	403.23	581.21	3.246356976	1.177533437	
	243.69	340.08	573.3	1.395543518	0.333283958	
	171.99	424.73	526.53	2.469504041	0.904017337	0.804944911

Voltage	Bu_2NH (m/z)	27a (m/z)	Complex (m/z)	Ratio of 27a/Ref base	Ln(Ratio)	Avg
3V	33178.84	85.58	5060.47	0.002579355	-5.960215991	
	33675.32	125.56	5313.05	0.003728547	-5.591736772	
	34878.17	107.51	5584.92	0.003082444	-5.782032545	-5.777995103
5V	40156.1	81.05	1772.44	0.002018373	-6.20546339	
	38534.64	104.03	1558.08	0.002699649	-5.914633537	
	37206.14	93.95	1513.61	0.002525121	-5.981466355	-6.033854427
10V	37797.1	85.45	884	0.002260755	-6.09205625	
	40005.17	129.97	888.66	0.00324883	-5.72946032	
	40929.02	90.05	837.17	0.00220015	-6.119229554	-5.980248708

Voltage	Indoline (m/z)	27a (m/z)	Complex (m/z)	Ratio of 27a/Ref base	Ln(Ratio)	Avg
3V	213.77	2330.01	605.18	10.89961173	2.388727168	
	231.1	2483.92	637.68	10.74824751	2.374742719	
	227.21	2338.37	567.85	10.2916685	2.331334684	2.364934857
5V	374.72	2488.01	554.24	6.639650939	1.893059393	
	263.51	2404.68	527.63	9.125573982	2.2110808	
	302.79	2137.51	575.69	7.059381089	1.954357383	2.019499192
10V	559.24	2209.3	546.59	3.950540019	1.373852283	
	676.97	2366.25	540.51	3.495354299	1.251434744	
	565.92	2315.54	467.67	4.091638394	1.408945475	1.344744167

Voltage	Et_2NH (m/z)	27a (m/z)	Complex (m/z)	Ratio of 27a/Ref base	Ln(Ratio)	Avg
3V	4762533.31	3169558.18	45070.48	0.665519373	-0.407187532	
	4825539.67	3218579.53	47101.02	0.666988513	-0.404982455	
	4832650.94	3212818.67	46333.74	0.664814966	-0.408246524	-0.406805503
5V	4776207.74	3181321.05	45833.02	0.666076775	-0.406350337	
	5146183.59	3460559.37	49252.77	0.672451596	-0.396825146	
	4798146.73	3201873.04	46044.01	0.667314532	-0.404493782	-0.402556421
10V	4809680.31	3199599.31	46582.62	0.665241576	-0.407605032	
	4971857.92	3323135.31	977128.81	0.668389034	-0.402884889	
	5085805.75	3407467.23	48961.39	0.669995552	-0.400484206	-0.403658042

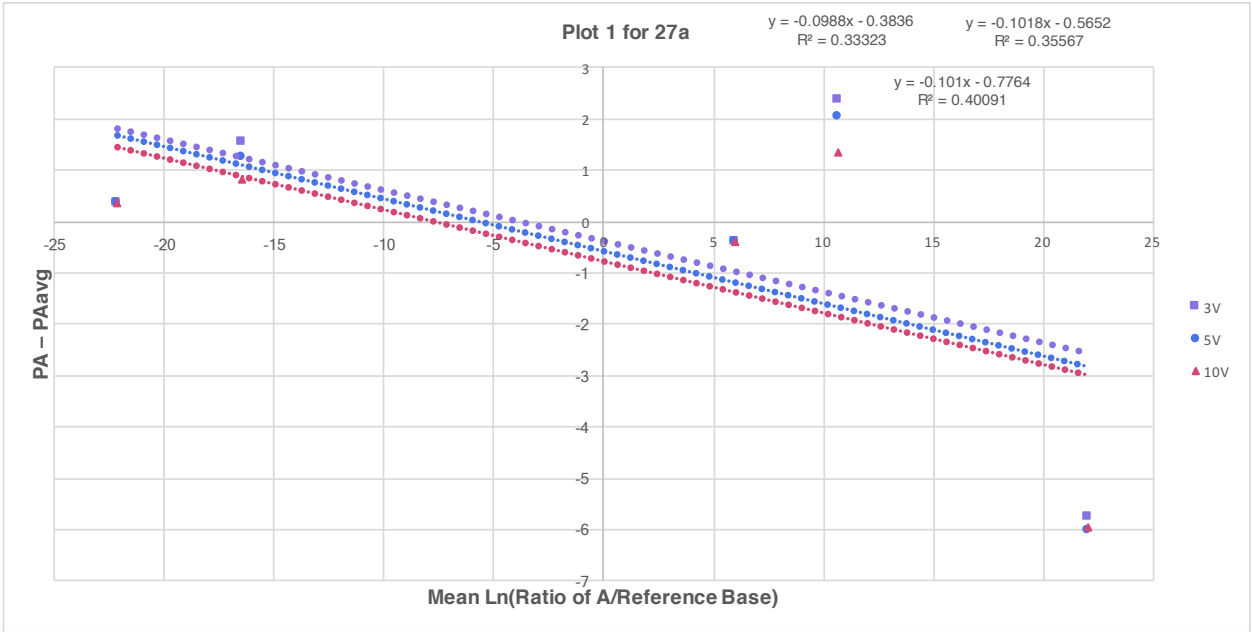
Voltage	Morpholine (m/z)	27a (m/z)	Complex (m/z)	Ratio of 27a/Ref base	Ln(Ratio)	Avg
3V	1739918.67	2503494.41	120491.26	1.438857145	0.363849149	
	1747443.13	2509841.71	123945.78	1.436293787	0.362066036	
	1774648.38	2540412.54	125049.19	1.431501907	0.358724178	0.361546454
5V	1681666.33	2426313.34	120012.97	1.442803068	0.366587796	
	1640708.26	2363999.58	115758.09	1.440840909	0.365226907	
	1661318.46	2378537.5	117813.51	1.43171677	0.358874263	0.363562989
10V	1667961.21	2390602.46	116862.92	1.433248235	0.359943361	
	1755451.24	2496672.49	123416.95	1.422239726	0.352232901	
	1807658.97	2552565.65	127114.73	1.412083635	0.345066369	0.35241421

3V	$PA-PA_{avg}$ (x)	Mean LnRatio (y)
A	-16.46	1.540308278
B	22.04	-5.777995103
C	10.64	2.364934857
D	5.94	-0.406805503
E	-22.16	0.361546454

5V	$PA-PA_{avg}$ (x)	Mean LnRatio (y)
A	-16.46	1.227343879
B	22.04	-6.033854427
C	10.64	2.019499192
D	5.94	-0.402556421
E	-22.16	0.363562989

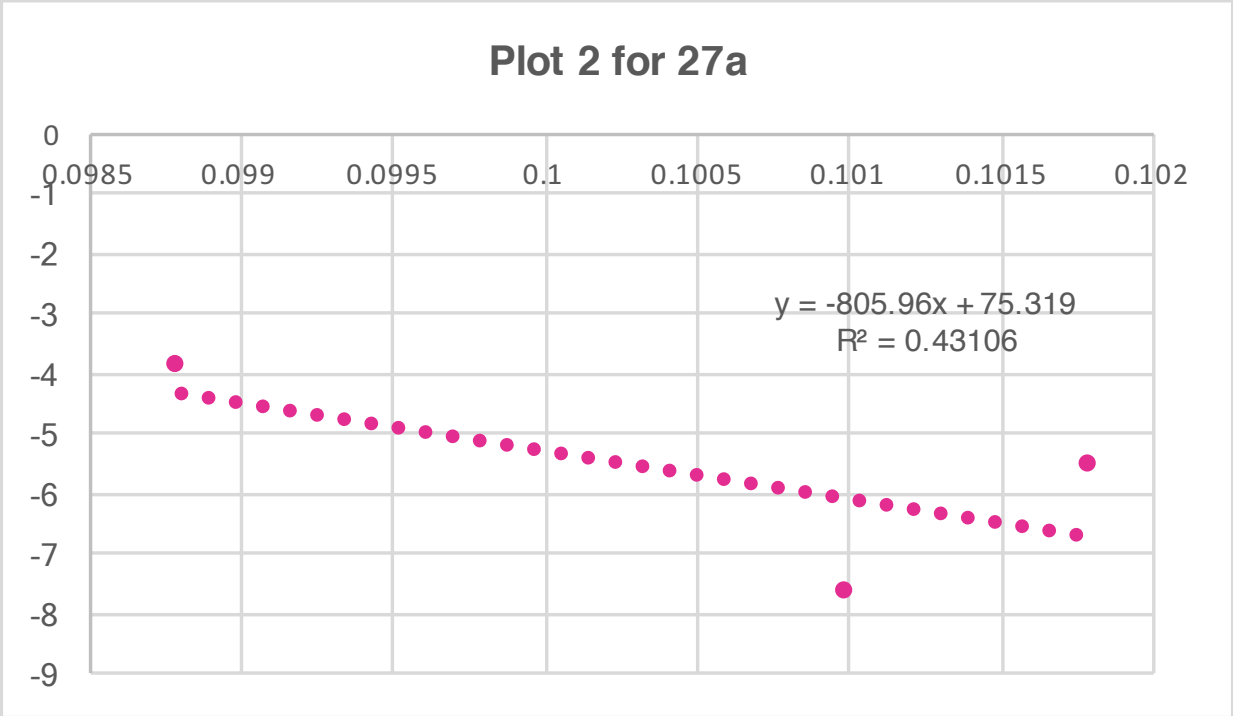
10V	PA-PA$_{avg}$ (x)	Mean LnRatio (y)
A	-16.46	0.804944911
B	22.04	-5.980248708
C	10.64	1.344744167
D	5.94	-0.403658042
E	-22.16	0.35241421

The first plot (plot 1) is of the natural log of the ratio of product ion intensities from collision-induced dissociation of the proton-bound dimer. Plot 1 for 27a was generated using data collected at 3, 5 and 10 V. Average of x–intercepts was used to calculate apparent PA of sample.

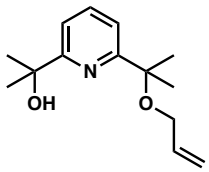


		3V	5V	10V	Average
X–intercept	**–b/m**	-3.882591093	-5.552062868	-7.687128713	-5.707260891
Apparent PA of 27a	**PA + (–x–int)**	933.8825911	974.0520629	964.7871287	**957.6 kJ/mol**
				Calculated PA	**228.7 kcal/mol**

The intercepts of the best-fit lines from plot 1 are plotted in a second plot (plot 2) against the negative slope of those lines for the different activation energies. The quantity [PA(A) – PA$_{avg}$] is obtained from the slope of the best-fit line to the data in plot 2.



x–int	y–int
0.0988	-3.882591093
0.1018	-5.552062868
0.101	-7.687128713



29a

	Base	PA (kJ/mol)
A	DMAP	997.6
B	Bu_2NH	968.5
C	Et_2NH	952.4
D	DTBP	982.9
E	$Allyl_2NH$	949.3
F	Morpholine	924.3

Voltage	DMAP (m/z)	29a (m/z)	Complex (m/z)	Ratio of 29a/Ref base	Ln(Ratio)	Avg
3V	74.43	0.78	1361.29	0.010479645	-4.558320446	
	94.37	3.83	1561.38	0.040584932	-3.204358423	
	61.31	21.69	1614.58	0.353775893	-1.039091637	-2.933923502
5V	72.26	4.38	1259.97	0.060614448	-2.803222001	
	45.14	3.52	1099.82	0.077979619	-2.551307782	
	49.29	11.51	1119.51	0.233515926	-1.454504998	-2.26967826
10V	77.94	13.6	928.68	0.1744932	-1.745869507	
	53.16	11.11	989.48	0.208991723	-1.56546063	
	54.77	10.09	929.04	0.184224941	-1.691597764	-1.667642634

Voltage	Bu_2NH (m/z)	29a (m/z)	Complex (m/z)	Ratio of 29a/Ref base	Ln(Ratio)	Avg
3V	231.49	171.8	13592.6	0.742148689	-0.298205666	
	216.63	98.62	13380.62	0.455246272	-0.786916748	
	198.34	138.12	13009.51	0.696379954	-0.361859857	-0.482327424
5V	205.8	78.28	13073.24	0.380369291	-0.966612681	
	281.12	80.34	12681.82	0.28578543	-1.252513996	
	198.86	80.5	12620.95	0.404807402	-0.904343875	-1.041156851
10V	316.3	52.5	12741.74	0.165981663	-1.795877961	
	296.15	53.38	12726.21	0.180246497	-1.713429939	
	296.13	75.77	13183.05	0.255867356	-1.363096111	-1.62413467

Voltage	Et_2NH (m/z)	29a (m/z)	Complex (m/z)	Ratio of 29a/Ref base	Ln(Ratio)	Avg
3V	139763.19	11145914.13	19837.92	79.74856706	4.378878774	
	138532.24	11106820.08	19959.15	80.17498367	4.384211542	
	136917.53	10950773.05	19422.92	79.9807961	4.381786557	4.381625624
5V	141136.8	11214028.85	20202.5	79.45503122	4.375191217	
	146066.96	11670083.79	20544.87	79.8954383	4.380718758	
	140422.01	11211910.25	20035.78	79.8443937	4.380079662	4.378663212
10V	138317.21	10967777.69	19159.3	79.29438202	4.373167282	
	144848.65	11430619.72	20678.5	78.91423027	4.36836157	
	150267.23	11807859.2	21267.95	78.5790701	4.36410538	4.368544744

Voltage	DTBP (m/z)	29a (m/z)	Complex (m/z)	Ratio of 29a/Ref base	Ln(Ratio)	Avg
3V	107800.5	11686435.74	114548.44	108.407992	4.685901813	
	108378.76	11625416.23	112899.55	107.2665551	4.675316906	
	112889.64	12075437.26	117952.31	106.9667443	4.672517986	4.67791223
5V	113071.55	12040868.8	116448.82	106.4889338	4.668041072	
	112911.91	12103858.73	116431.32	107.1973606	4.674671627	
	107145.36	11622589.17	108902.50	108.4749649	4.686519409	4.67641070
10V	104776.22	11408460.14	107689.16	108.8840592	4.690283639	
	109453.24	11642341.89	111167.17	106.3681796	4.666906468	
	109610.14	11678502.75	111355.36	106.5458246	4.66857517	4.67525509

Voltage	$Allyl_2NH$ (m/z)	29a (m/z)	Complex (m/z)	Ratio of 29a/Ref base	Ln(Ratio)	Avg
3V	1848644.77	9196556.91	51928.32	4.974756134	1.604376351	
	1860394.29	9219164.96	51783.21	4.955489817	1.600496016	
	1911832.37	9497397.21	52674.73	4.967693486	1.602955645	1.602609337
5V	1908788.01	9487073.88	52671.67	4.970208232	1.603461737	
	2030369.28	10039920.02	56005.06	4.94487388	1.59835146	
	1976358.19	9774839.37	54283.19	4.945884516	1.59855582	1.600123006
10V	2006847.86	9922622.9	55367.79	4.944382231	1.598252029	
	2033144.09	10075414.54	56154.71	4.955583123	1.600514845	
	2008732.32	9969085.97	55516.8	4.962874282	1.601985065	1.600250646

Voltage	Morpholine (m/z)	29a (m/z)	Ratio of 29a/Ref base	Ln(Ratio)	Avg
3V	38931.23	12189735.42	313.1094348	5.746552761	
	41604.32	12714862.98	305.6140079	5.722322894	
	40311.18	12455191.17	308.9760997	5.733263927	5.734046527
5V	38902.6	12035103.86	309.365026	5.734521894	
	39389.14	12117513.25	307.6358928	5.728916917	
	40725.92	12514276.57	307.2803897	5.727760652	5.730399821
10V	42496.82	12671483.33	298.1748594	5.697680091	
	39226.78	12108479.93	308.678916	5.73230163	
	40238.11	12326532.89	306.3397583	5.724694807	5.718225509

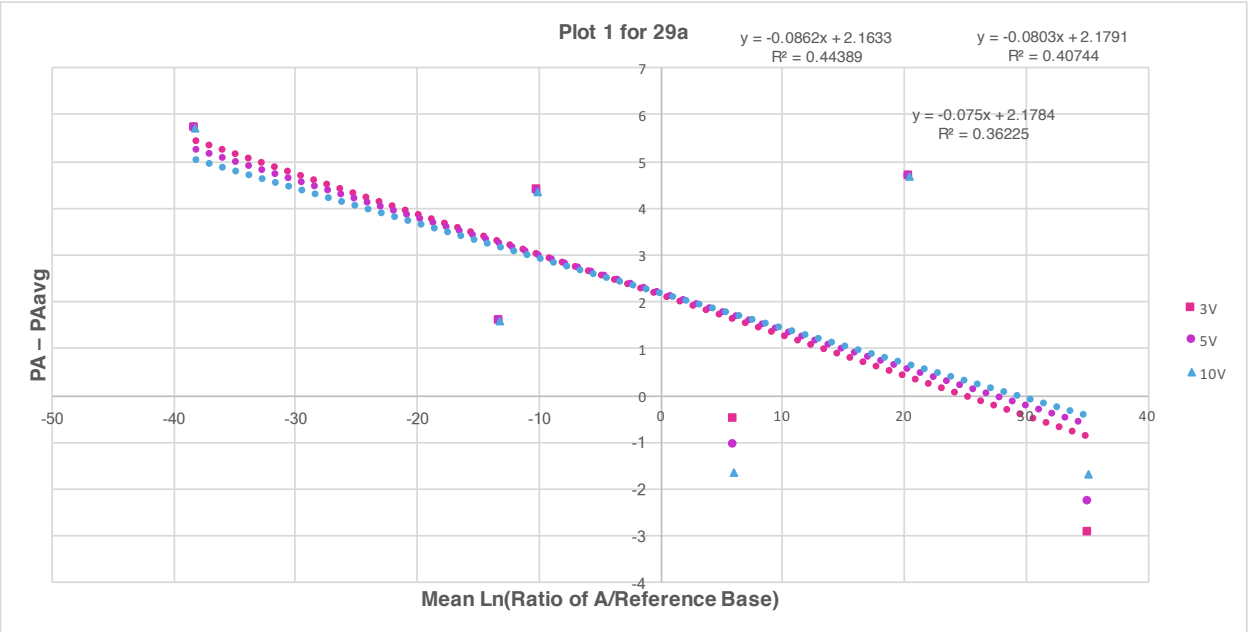
*complex observed but not recorded

3V	PA-PA$_{avg}$ (x)	Mean LnRatio (y)
A	35.1	-2.933923502
B	6	-0.482327424
C	-10.1	4.381625624
D	20.4	4.677912235
E	-13.2	1.602609337
F	-38.2	5.734046527

5V	PA-PAavg (x)	Mean LnRatio (y)
A	35.1	-2.26967826
B	6	-1.041156851
C	-10.1	4.378663212
D	20.4	4.676410702
E	-13.2	1.600123006
F	-38.2	5.730399821

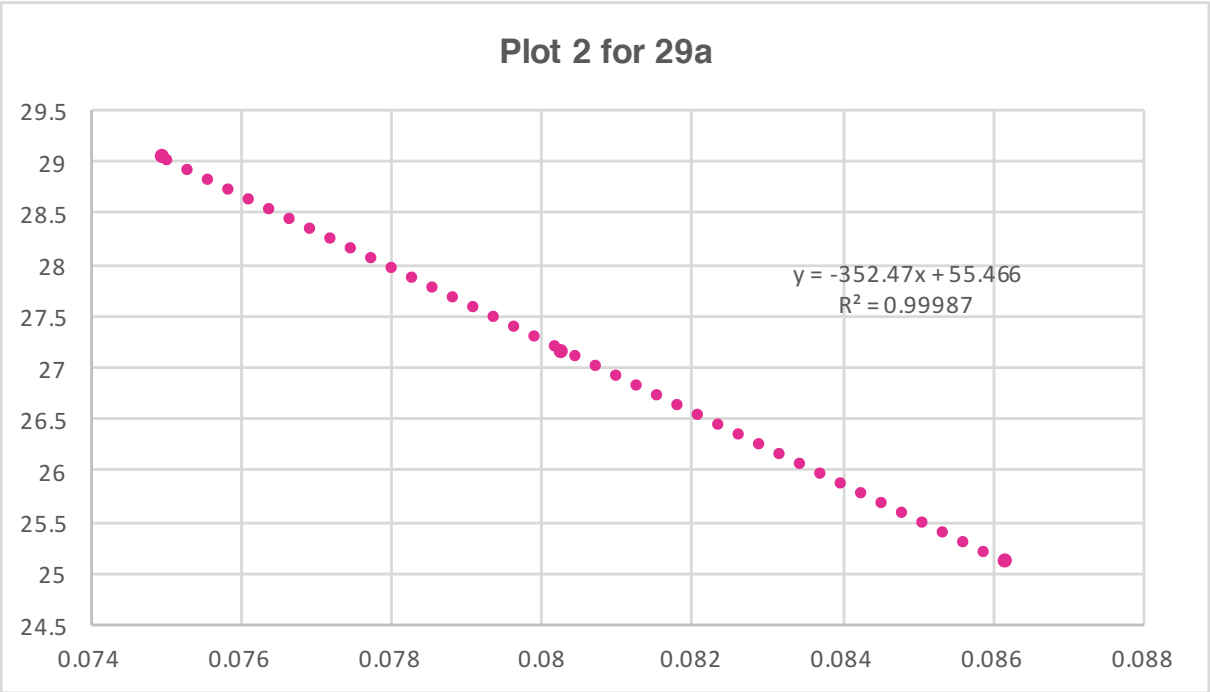
10V	PA-PAavg (x)	Mean LnRatio (y)
A	35.1	-1.667642634
B	6	-1.62413467
C	-10.1	4.368544744
D	20.4	4.675255093
E	-13.2	1.600250646
F	-38.2	5.718225509

The first plot (plot 1) is of the natural log of the ratio of product ion intensities from collision-induced dissociation of the proton-bound dimer. Plot 1 for 29a was generated using data collected at 3, 5 and 10 V. Average of x–intercepts was used to calculate apparent PA of sample.

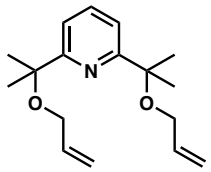


		3V	5V	10V	Average
X–intercept	**–b/m**	25.0962877	27.1369863	29.04533333	27.09286911
Apparent PA of 29a	**PA + (–x–int)**	972.5037123	941.3630137	923.3546667	**945.7 kJ/mol**
				Calculated PA	**225.9 kcal/mol**

The intercepts of the best-fit lines from plot 1 are plotted in a second plot (plot 2) against the negative slope of those lines for the different activation energies. The quantity [PA(A) – PA_{avg}] is obtained from the slope of the best-fit line to the data in plot 2.



x–int	y–int
0.0862	25.0962877
0.0803	27.1369863
0.075	29.04533333



28b

	Base	PA (kJ/mol)
A	DMAP	997.6
B	Bu_2NH	968.5
C	Et_2NH	952.4
D	Morpholine	924.3
E	Imidazole	942.8
	Average	**957.12**

Voltage	DMAP (m/z)	28b (m/z)	Complex (m/z)	Ratio of 28b/Ref base	Ln(Ratio)	Avg
3V	15.47	2.32	170.52	0.149967679	-1.897335479	
	6.29	7.93	145.52	1.26073132	0.231691965	
	6.7	11.88	130.66	1.773134328	0.572748788	-0.364298242
5V	13.37	9.34	134.4	0.698578908	-0.358707139	
	12.52	8.47	136.39	0.676517572	-0.390796857	
	6.33	18.66	165.65	2.947867299	1.081081959	0.110525988
10V	18.89	13.15	136.13	0.696135521	-0.362210923	
	15.11	4.26	123.8	0.281932495	-1.266087616	
	17.5	18.73	148.51	1.070285714	0.067925636	-0.520124301

Voltage	Bu_2NH (m/z)	28b (m/z)	Complex (m/z)	Ratio of 28b/Ref base	Ln(Ratio)	Avg
3V	29.5	29.41	525.66	0.996949153	-0.003055511	
	25.55	16.32	590.66	0.638747554	-0.448245967	
	18.53	17.88	485.06	0.964921749	-0.035708271	-0.162336583
5V	25.17	24.12	422.04	0.958283671	-0.042611437	
	26.25	18.33	377.89	0.698285714	-0.359126927	
	39.15	25.68	366.76	0.655938697	-0.421687944	-0.274475436
10V	41.84	6.33	298.44	0.151290631	-1.888552584	
	46.58	9.27	282.64	0.199012452	-1.614387885	
	23.91	6.97	270.24	0.291509829	-1.232681557	-1.578540675

Voltage	Et_2NH (m/z)	28b (m/z)	Complex (m/z)	Ratio of 28b/Ref base	Ln(Ratio)	Avg
3V	114900.61	15426435.25	27297.52	134.25895	4.899770398	
	117056.66	15468097.33	27472.06	132.1419672	4.883876854	
	120166.29	15934022.99	29098.11	132.5997748	4.887335379	4.890327544
5V	122466.55	16095843.8	28998.93	131.4305318	4.878478437	
	119703.14	15763604.94	27825.18	131.6891515	4.880444233	
	117962.93	15604640.85	27160.04	132.2842765	4.884953217	4.881291962
10V	120490.13	15842425.56	28070.98	131.4831809	4.878878942	
	126114.32	16354185.72	28530.48	129.6774682	4.865050354	
	130478	16481857.92	29655.32	126.319057	4.838810905	4.8609134

Voltage	Morpholine (m/z)	28b (m/z)	Complex (m/z)	Ratio of 28b/Ref base	Ln(Ratio)	Avg
3V	40782.17	17437052.47	41510.98	427.5655874	6.058107697	
	40699.12	17244055.38	40795.41	423.6960254	6.049016277	
	39665.34	17168854.52	41162.24	432.8427418	6.070374479	6.05916615
5V	40384.66	17409406.36	42142.79	431.089586	6.066315925	
	42787.91	17651663.39	43139.32	412.5385743	6.022329715	
	42566.71	17637946.45	42650.52	414.3601056	6.026735416	6.03846035
10V	41540.04	17302229.88	42414.04	416.519336	6.031932886	
	41412.55	17320219.62	41813.8	418.2360086	6.036045887	
	43474.45	17736769.2	43584.59	407.9814512	6.011221711	6.02640016

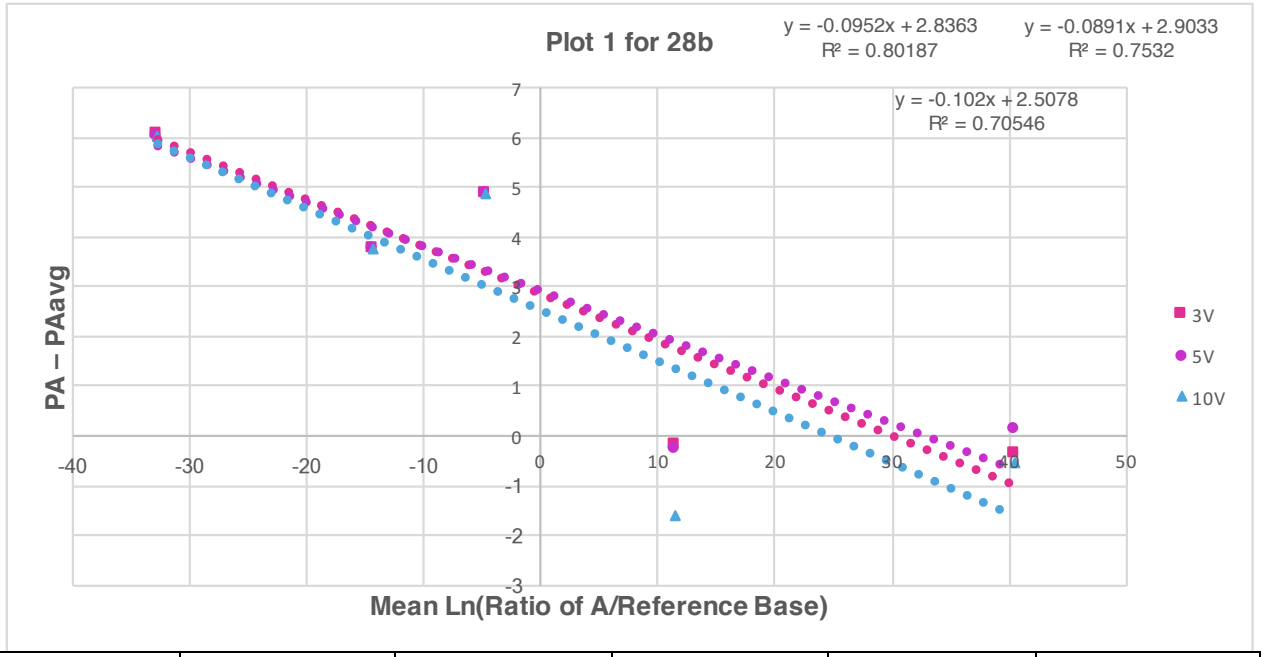
Voltage	Imidazole (m/z)	28b (m/z)	Complex (m/z)	Ratio of 28b/Ref base	Ln(Ratio)	Avg
3V	403438.37	17218813.58	255789.83	42.68015851	3.75373414	
	401002.26	17120158.36	251349.63	42.69342113	3.754044836	
	385540.46	16700890.03	240404.56	43.3181255	3.76857115	3.758783376
5V	385890.15	16683916.18	237627.92	43.2348848	3.766647688	
	393092.9	16803720.86	238817.92	42.74745451	3.75530965	
	391765.38	16822907.82	237698.67	42.94128241	3.759833657	3.760596998
10V	400482.02	17041663.15	243240.22	42.55287953	3.750747527	
	411056.39	17344751.72	247354.85	42.19555307	3.742314838	
	392148.29	16816480.23	236492.05	42.88296203	3.758474592	3.750512319

3V	PA-PA_{avg} (x)	Mean LnRatio (y)
A	40.48	-0.364298242
B	11.38	-0.162336583
C	-4.72	4.890327544
D	-32.82	6.059166151
E	-14.32	3.758783376

5V	PA-PA_{avg} (x)	Mean LnRatio (y)
A	40.48	0.110525988
B	11.38	-0.274475436
C	-4.72	4.881291962
D	-32.82	6.038460352
E	-14.32	3.760596998

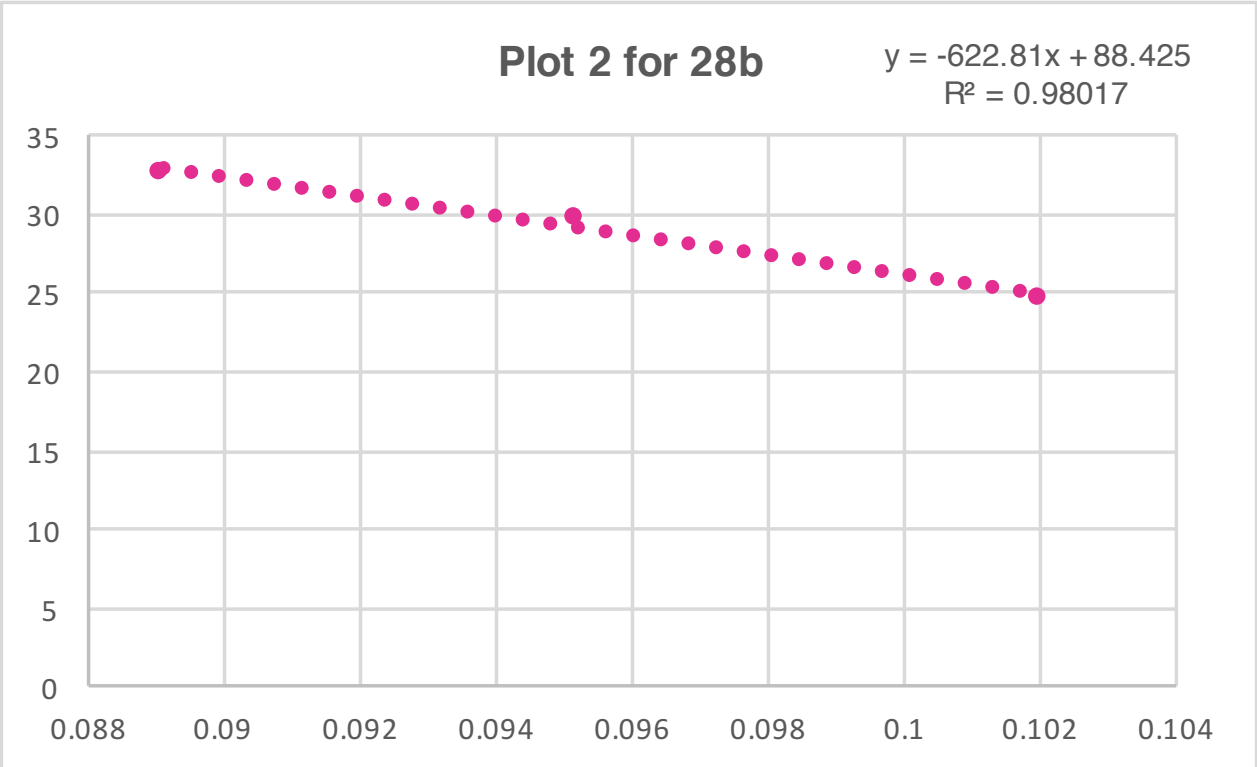
10V	PA-PA_{avg} (x)	Mean LnRatio (y)
A	40.48	-0.520124301
B	11.38	-1.578540675
C	-4.72	4.8609134
D	-32.82	6.026400161
E	-14.32	3.750512319

The first plot (plot 1) is of the natural log of the ratio of product ion intensities from collision-induced dissociation of the proton-bound dimer. Plot 1 for 28b was generated using data collected at 3, 5 and 10 V. Average of x–intercepts was used to calculate apparent PA of sample.

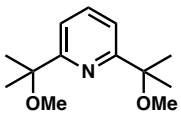


		3V	5V	10V	Average
X–intercept	**–b/m**	29.79306723	32.58473625	24.58627451	28.988026
Apparent PA of 28b	**PA + (–x–int)**	967.8069328	935.9152637	927.8137255	**943.8 kJ/mol**
				Calculated PA	**225.7 kcal/mol**

The intercepts of the best-fit lines from plot 1 are plotted in a second plot (plot 2) against the negative slope of those lines for the different activation energies. The quantity [PA(A) – PA_{avg}] is obtained from the slope of the best-fit line to the data in plot 2.



x–int	y–int
0.0952	29.79306723
0.0891	32.58473625
0.102	24.58627451



28a

	Base	PA (kJ/mol)
A	DMAP	997.6
B	Bu_2NH	968.5
C	Et_2NH	952.4
D	$Allyl_2NH$	949.3
E	Morpholine	924.3
	Average	**958.42**

Voltage	DMAP (m/z)	28a (m/z)	Complex (m/z)	Ratio of 28a/Ref base	Ln(Ratio)	Avg
3V	24.7	35.41	3819.31	1.433603239	0.360191022	
	48.66	24.08	4159.97	0.49486231	-0.703475717	
	42.26	29.73	4052.97	0.70350213	-0.351684375	-0.231656357
5V	42.76	19.85	3305.6	0.464218896	-0.767399079	
	41.81	48.69	3734.97	1.164553934	0.152338125	
	48.98	33.57	3760.19	0.685381788	-0.377779241	-0.330946732
10V	43.18	22.26	3174.5	0.515516443	-0.662586079	
	70.68	15.51	3266.09	0.219439728	-1.51667767	
	42.19	34.41	3186.48	0.815596113	-0.203836006	-0.794366585

Voltage	Bu_2NH (m/z)	28a (m/z)	Complex (m/z)	Ratio of 28a/Ref base	Ln(Ratio)	Avg
3V	126.29	27.6	11658.95	0.21854462	-1.520765077	
	141.65	15.86	11660.53	0.111966114	-2.18955901	
	168.29	18.71	11046.66	0.111177135	-2.196630541	-1.968984876
5V	189.85	18.87	11363.73	0.099394259	-2.308660927	
	188.61	14.67	11920.14	0.077779545	-2.553876799	
	156.35	18.45	10365.51	0.118004477	-2.137032713	-2.333190147
10V	182.49	11.69	10393.28	0.064058305	-2.747961602	
	256.93	16.48	10745.93	0.064141984	-2.74665615	
	247	36.56	11434.71	0.148016194	-1.91043359	-2.468350447

Voltage	Et_2NH (m/z)	28a (m/z)	Complex (m/z)	Ratio of 28a/Ref base	Ln(Ratio)	Avg
3V	151362.14	8367154.25	113977	55.27904303	4.012393868	
	151605.60	8271068.95	107041.07	54.55648703	3.999236624	
	153352.71	8358537.74	110885.51	54.50531484	3.998298217	4.00330957
5V	157812.33	8640876.85	11545.81	54.75413011	4.002852802	
	154389.97	8411642.25	112496.49	54.48308753	3.997890333	
	159891.44	8702770.95	113072.52	54.42924868	3.996901669	3.999214935
10V	169205.87	9145210.72	117930.86	54.04783368	3.989869463	
	166753	9168841.8	119083.46	54.98456879	4.007052578	
	171297.32	9348422.59	121621.51	54.57424897	3.999562141	3.998828061

Voltage	$Allyl_2NH$ (m/z)	28a (m/z)	Complex (m/z)	Ratio of 28a/Ref base	Ln(Ratio)	Avg
3V	2060722.04	8878671.86	41715.72	4.308524725	1.460595554	
	2123545.06	9069431.95	43866.7	4.270892161	1.451822742	
	2109358.83	8960473.18	43484.15	4.24796059	1.446439007	1.452952434
5V	2059854.54	8767821.88	41872.33	4.256524774	1.448453047	
	2033227.81	8617845.56	41586.91	4.238504666	1.444210534	
	2045046.27	8635494.74	41904.02	4.222640273	1.44046059	1.444374723
10V	2064426.29	8709527.75	42408.26	4.218861091	1.439565208	
	2176619.24	9174368.22	44607.98	4.214962384	1.438640667	
	2172270.93	9167058.44	44126.81	4.220034579	1.439843322	1.439349732

Voltage	Morpholine (m/z)	28a (m/z)	Complex (m/z)	Ratio of 28a/Ref base	Ln(Ratio)
3V	63410.33	12853728.48	202.707169	5.31176242	
	63785.85	12762819.44	200.0885689	5.298760113	
	64837.02	12835893.44	197.9716748	5.288123964	5.299548832
5V	64391.97	12686889.05	197.0259498	5.283335445	
	63756.31	12528455.32	196.5053392	5.280689602	
	66962.14	12803430.64	191.2040242	5.253341048	5.272455365
10V	68322.4	13161175.65	192.6333918	5.260788858	
	67457.67	13079708.68	193.8950557	5.267317063	
	65308.41	12601835.88	192.9588529	5.262476969	5.26352763

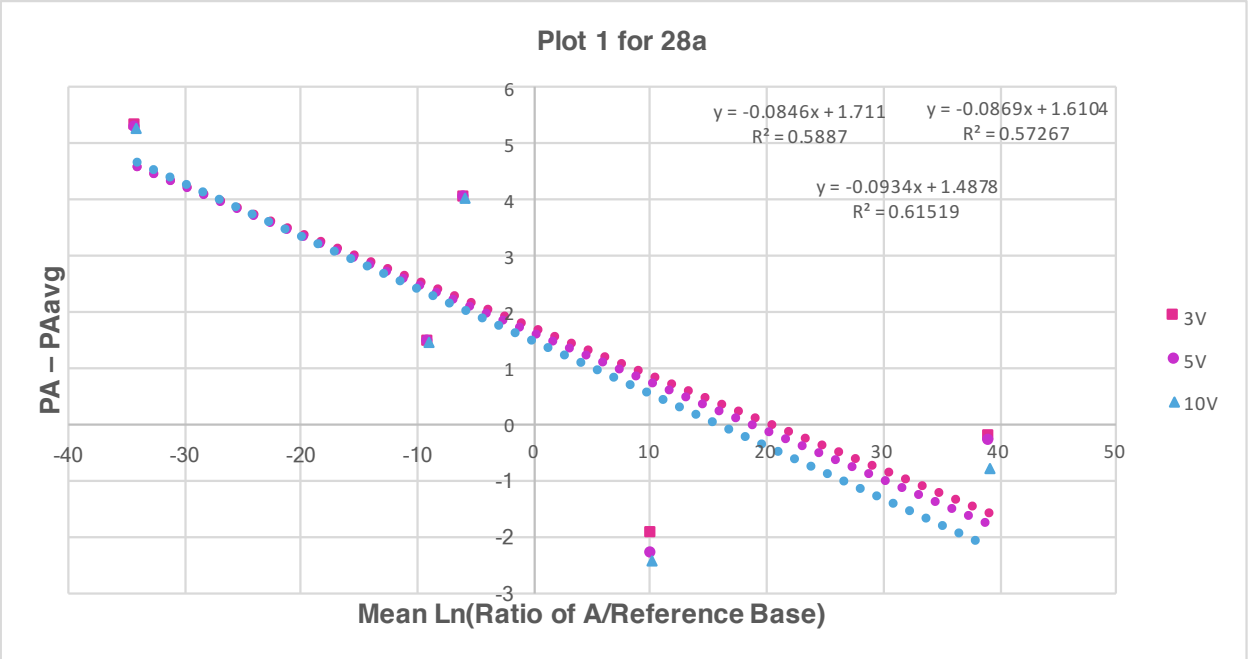
*complex observed but not recorded

3V	$PA-PA_{avg}$ (x)	Mean LnRatio (y)
A	39.18	-0.231656357
B	10.08	-1.968984876
C	-6.02	4.00330957
D	-9.12	1.452952434
E	-34.12	5.299548832

5V	PA-AvgPA (x)	Mean LnRatio (y)
A	39.18	-0.330946732
B	10.08	-2.333190147
C	-6.02	3.999214935
D	-9.12	1.444374723
E	-34.12	5.272455365

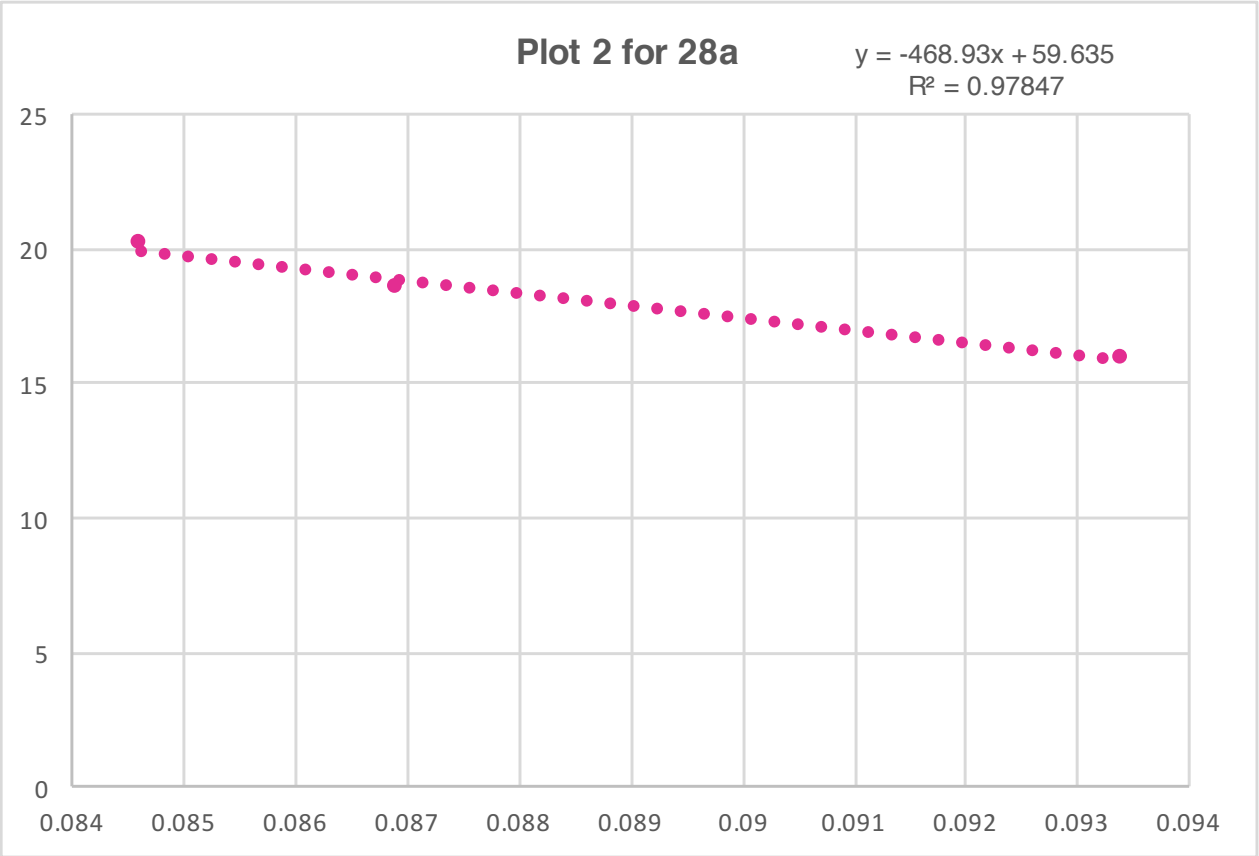
10V	PA-AvgPA (x)	Mean LnRatio (y)
A	39.18	-0.794366585
B	10.08	-2.468350447
C	-6.02	3.998828061
D	-9.12	1.439349732
E	-34.12	5.26352763

The first plot (plot 1) is of the natural log of the ratio of product ion intensities from collision-induced dissociation of the proton-bound dimer. Plot 1 for 28a was generated using data collected at 3, 5 and 10 V. Average of x–intercepts was used to calculate apparent PA of sample.



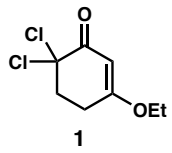
		3V	5V	10V	Average
X–intercept	**–b/m**	20.22458629	18.53164557	15.92933619	18.22852268
Apparent PA of 28a	**PA + (–x–int)**	977.3754137	949.9683544	936.4706638	**954.6 kJ/mol**
				Calculated PA	**228.0 kcal/mol**

The intercepts of the best-fit lines from plot 1 are plotted in a second plot (plot 2) against the negative slope of those lines for the different activation energies. The quantity [PA(A) – PA_{avg}] is obtained from the slope of the best-fit line to the data in plot 2.



x–int	y–int
0.0846	20.22458629
0.0869	18.53164557
0.0934	15.92933619

APPENDICES



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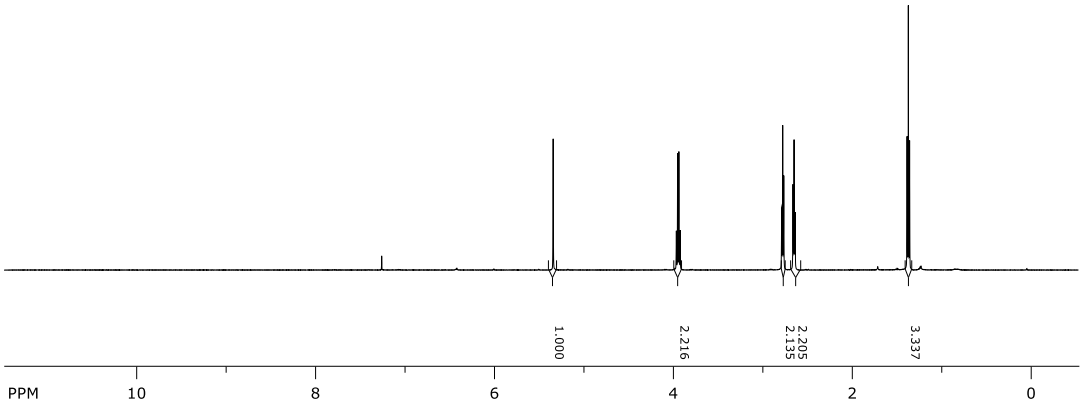
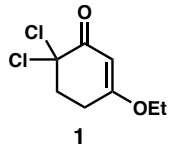


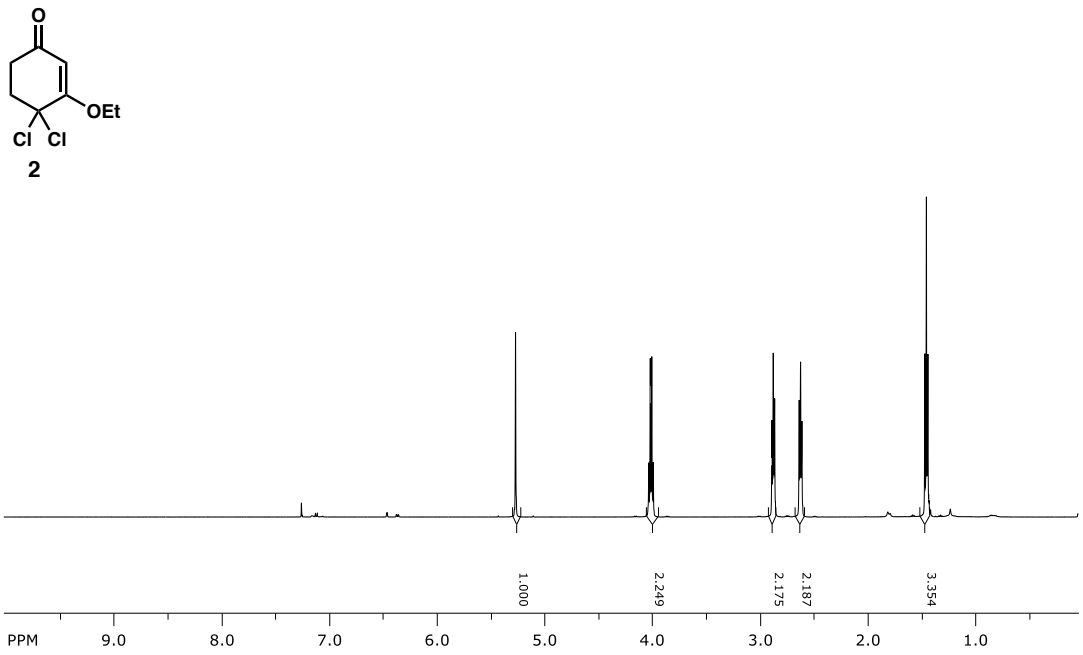
^{1}H NMR (500 MHz, $CDCl_3$)

cxh2-m-148-3B.002.esp



1

^{13}C NMR (126 MHz, $CDCl_3$)



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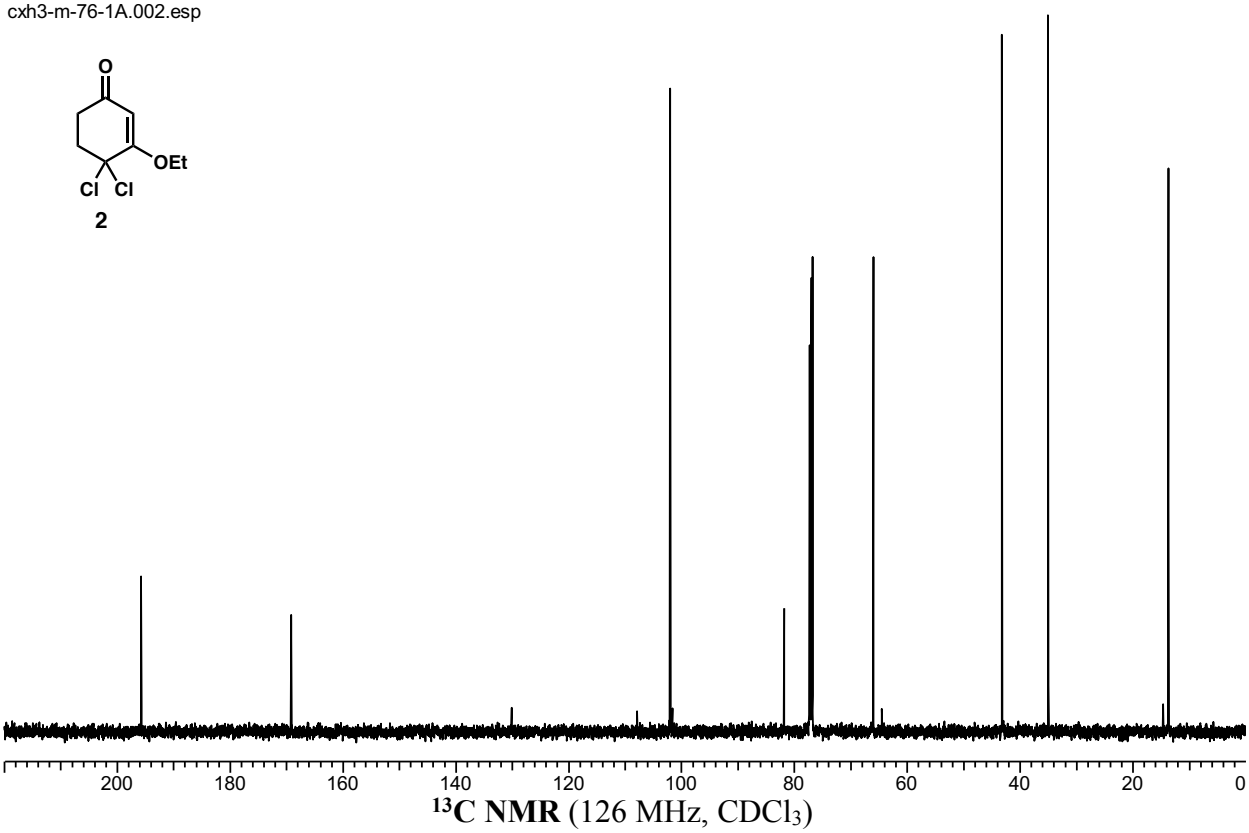
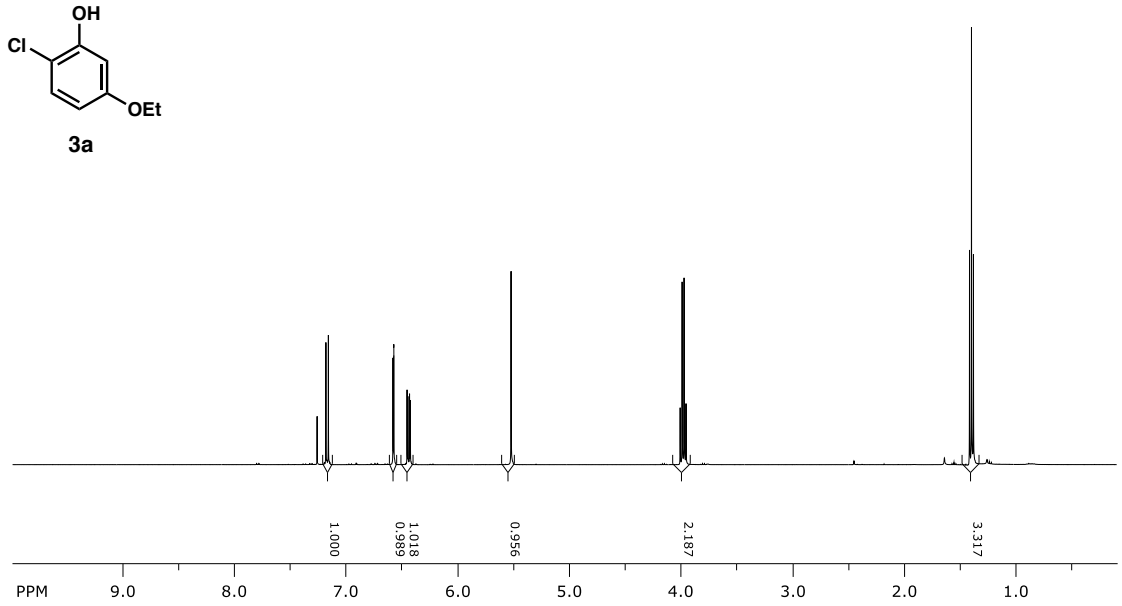
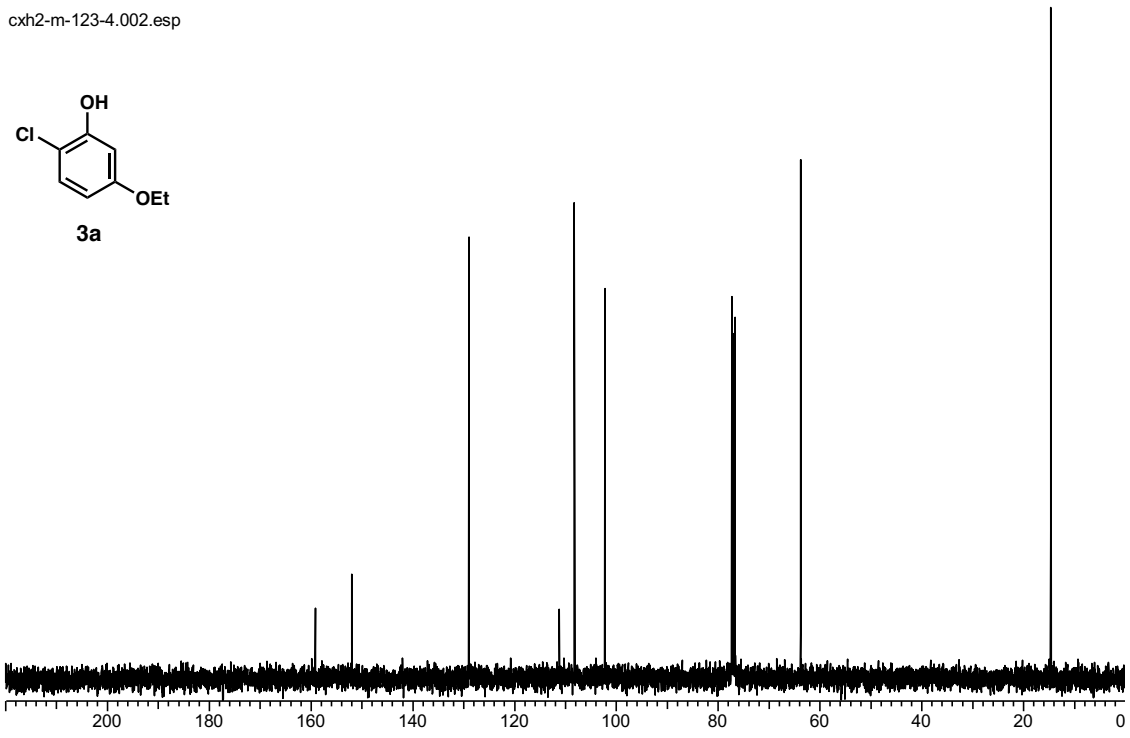


^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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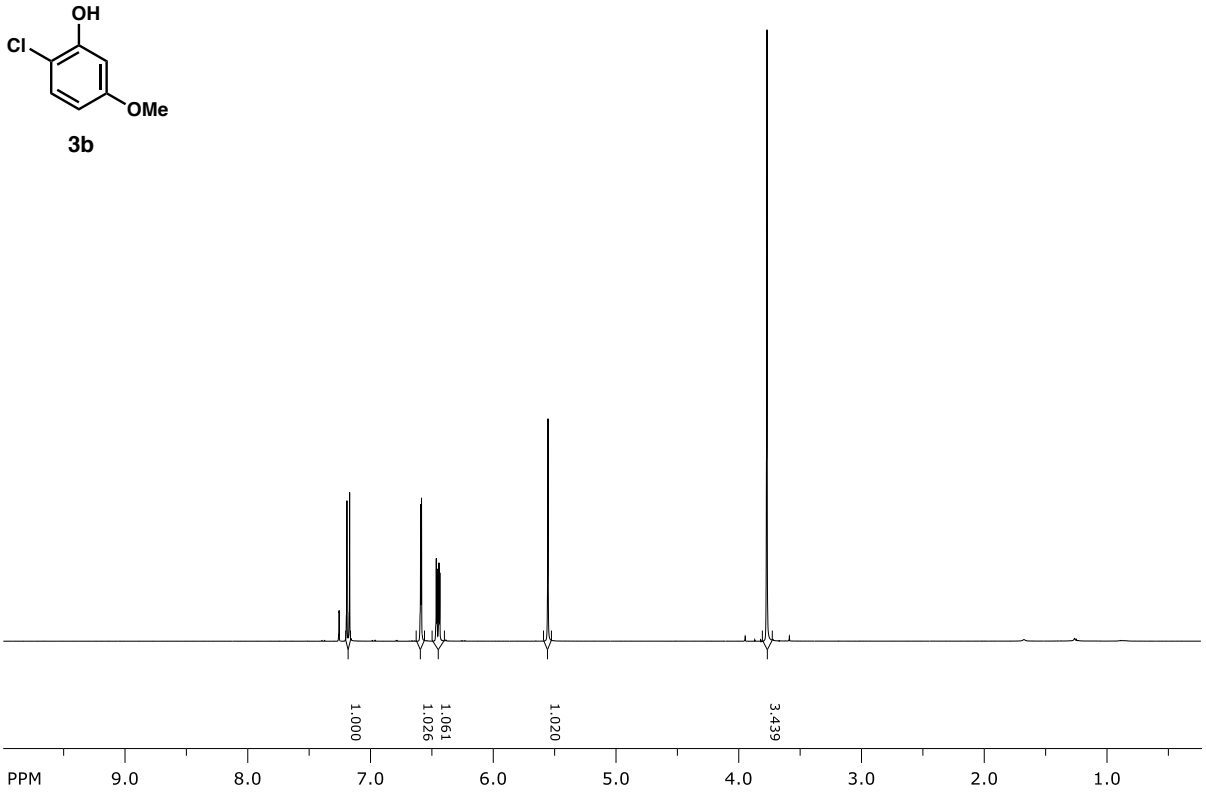
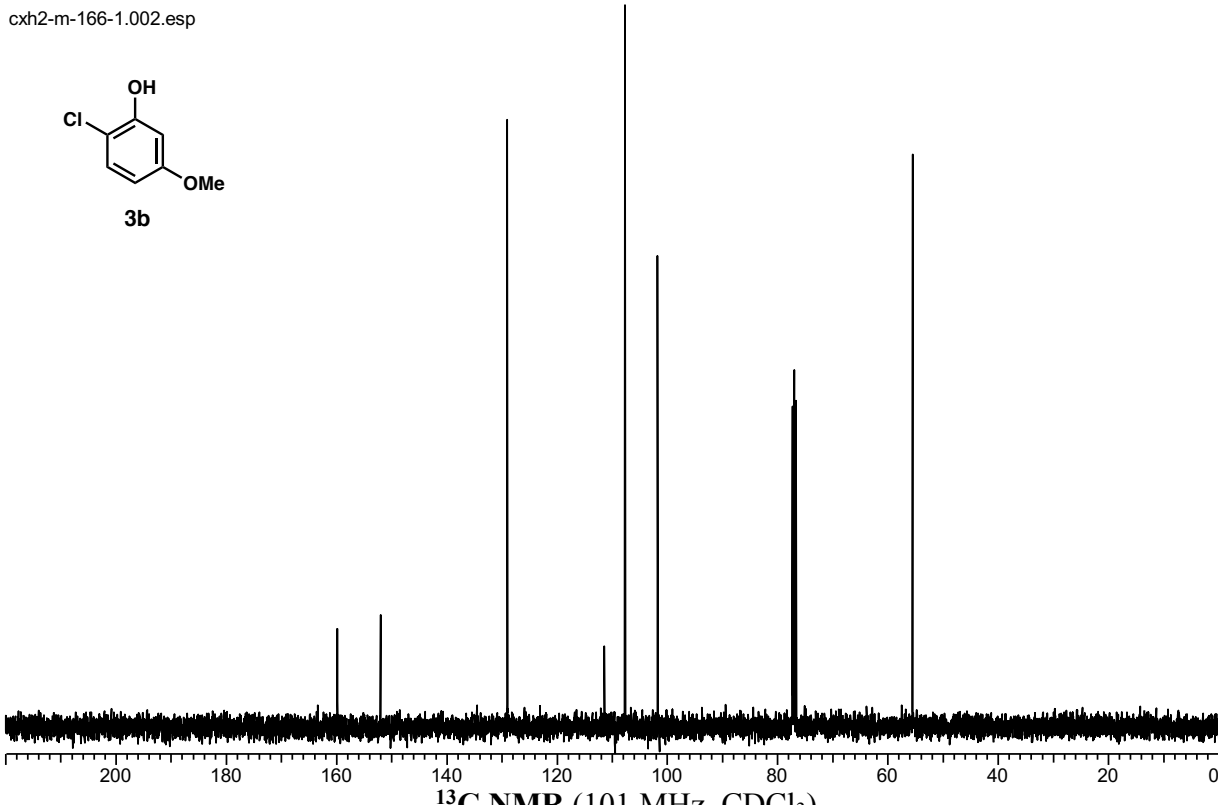
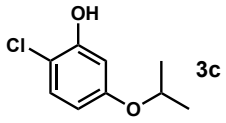


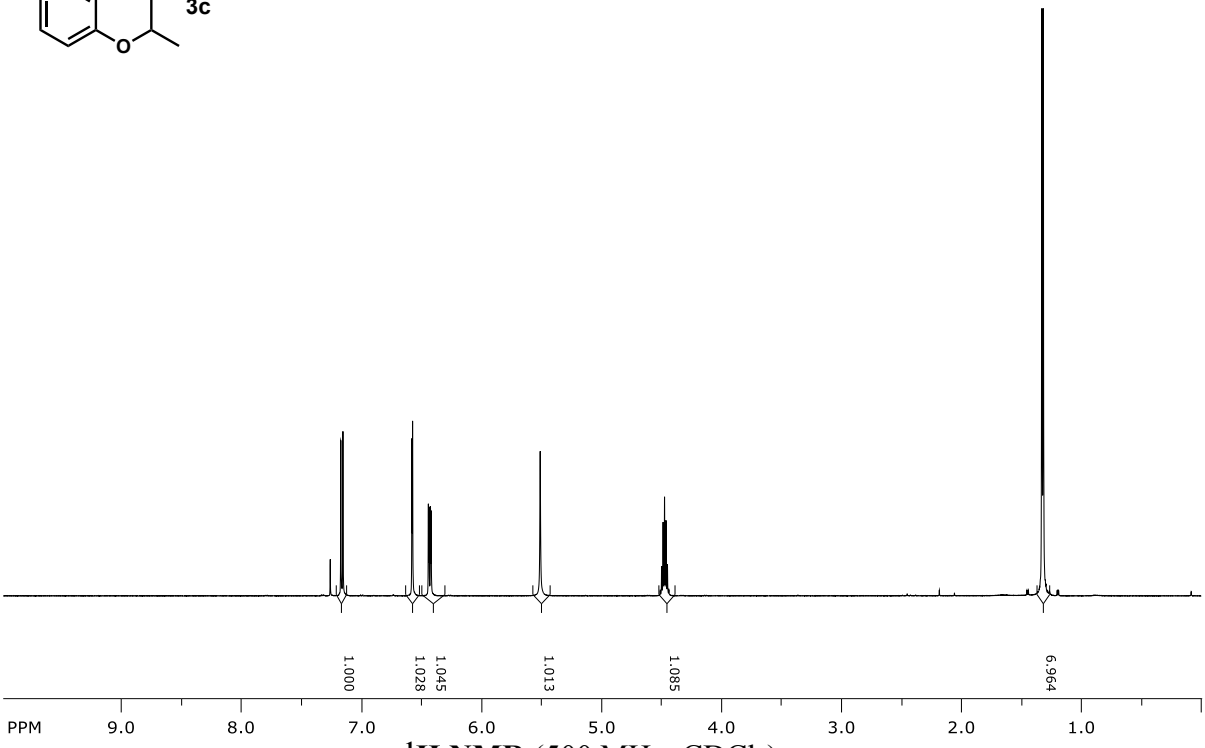
^{1}H NMR (400 MHz, $CDCl_3$)



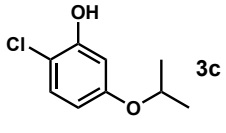
^{13}C NMR (101 MHz, $CDCl_3$)



3c



^{1}H NMR (500 MHz, $CDCl_3$)



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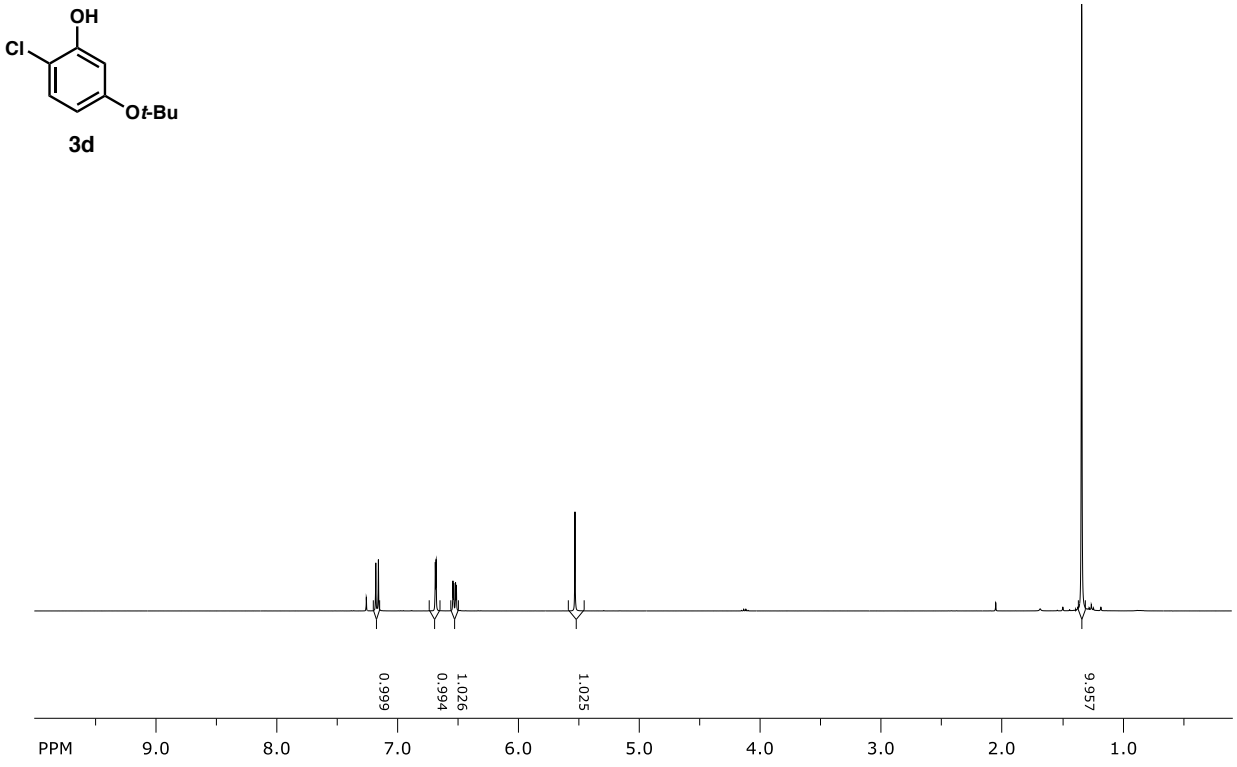
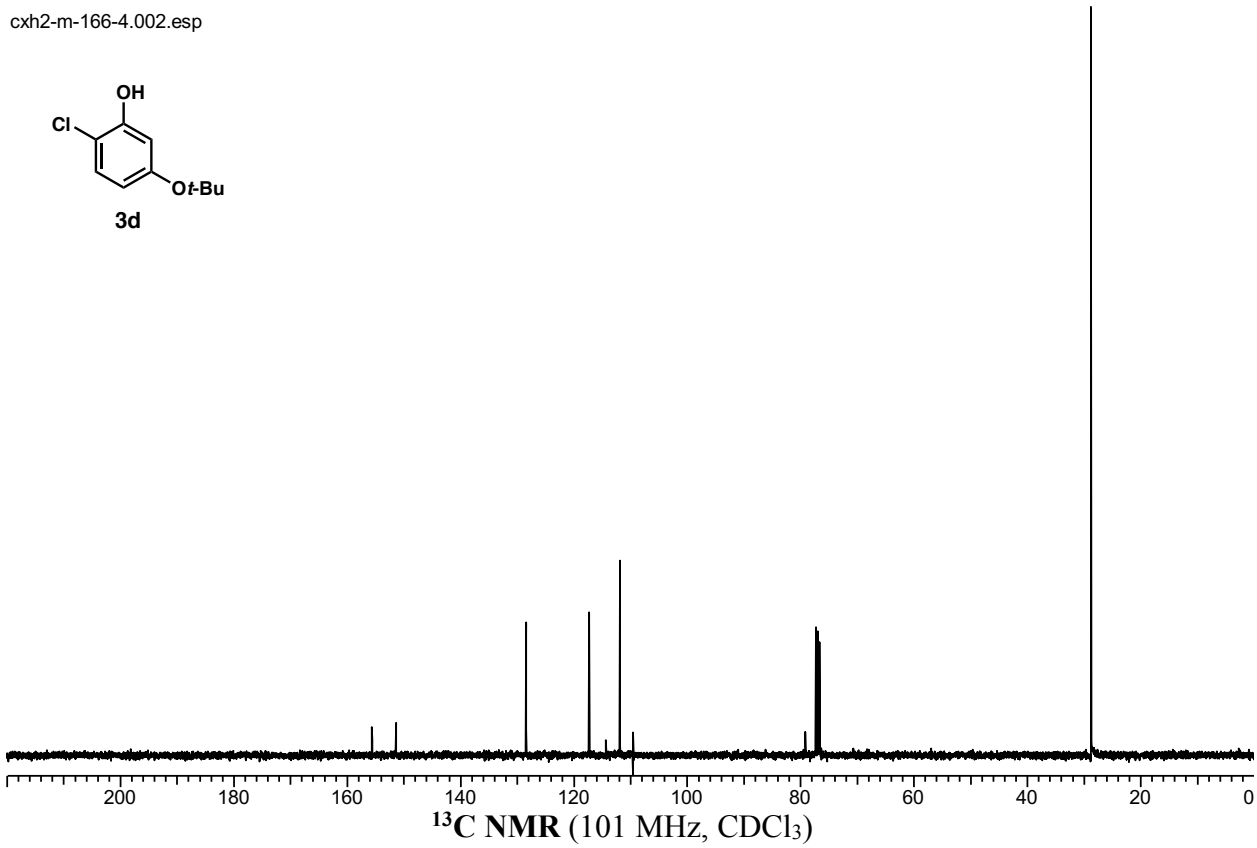
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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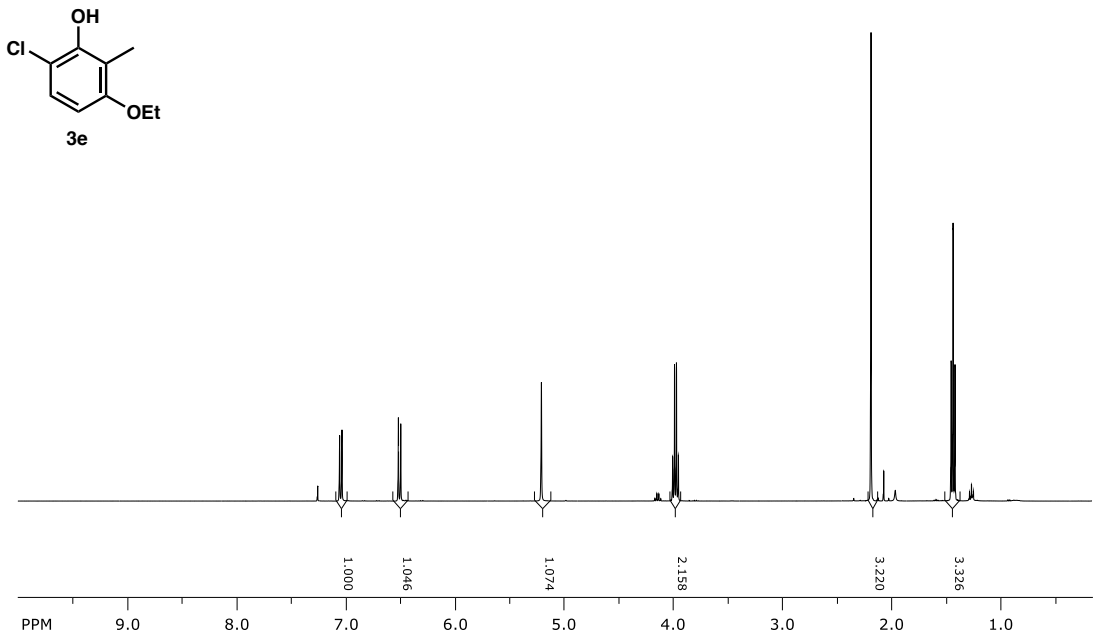

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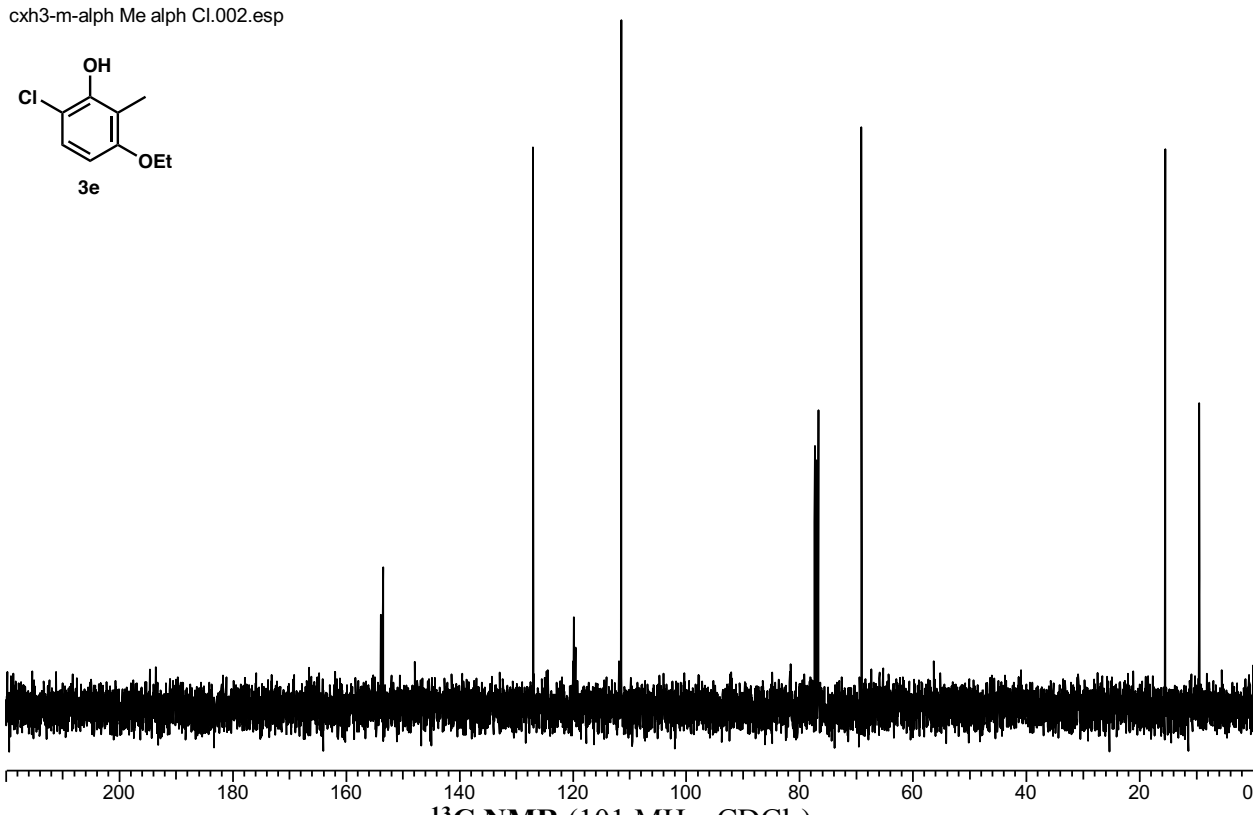

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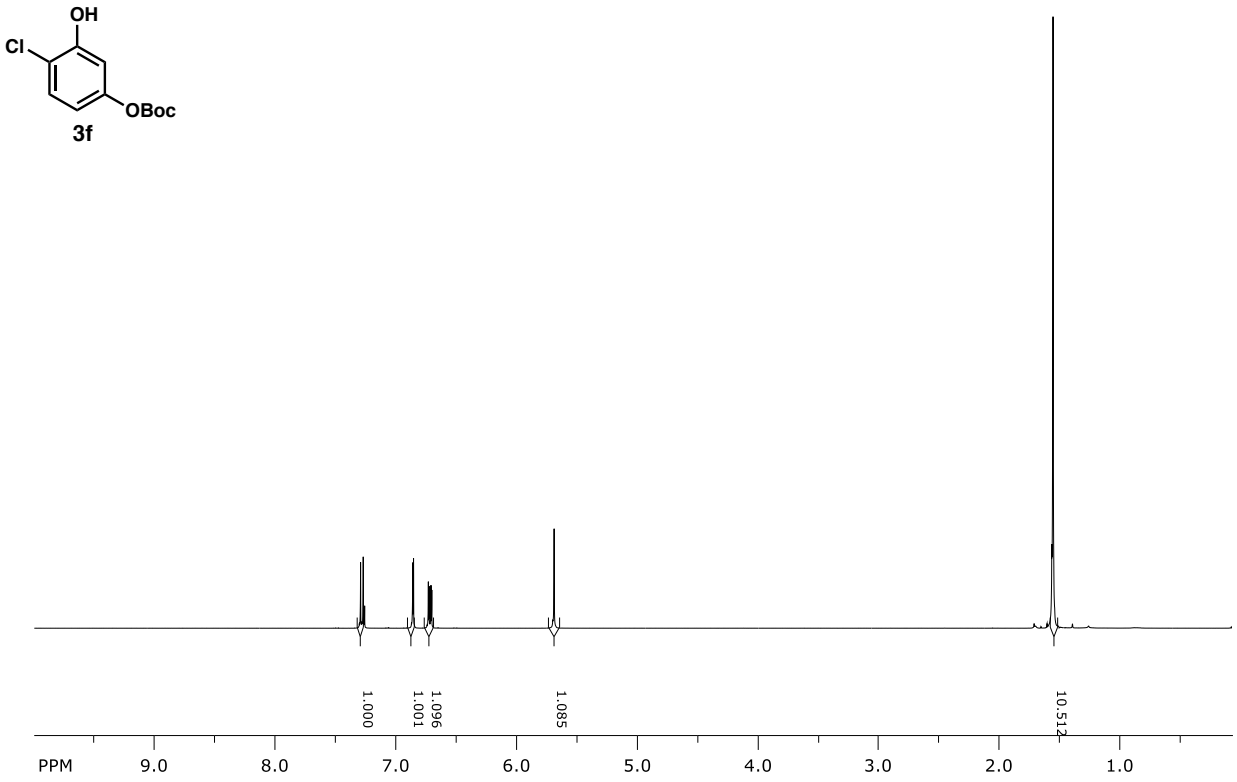
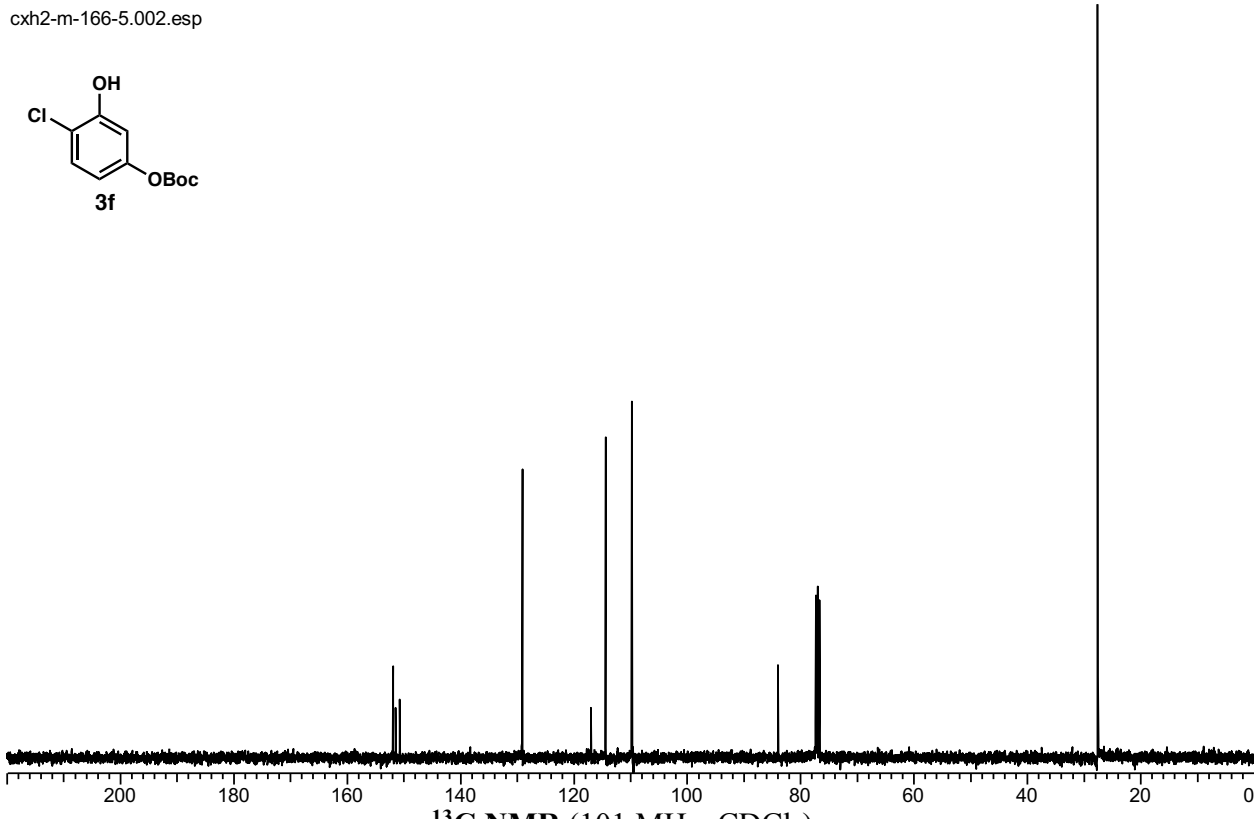


^{1}H NMR (400 MHz, $CDCl_3$)



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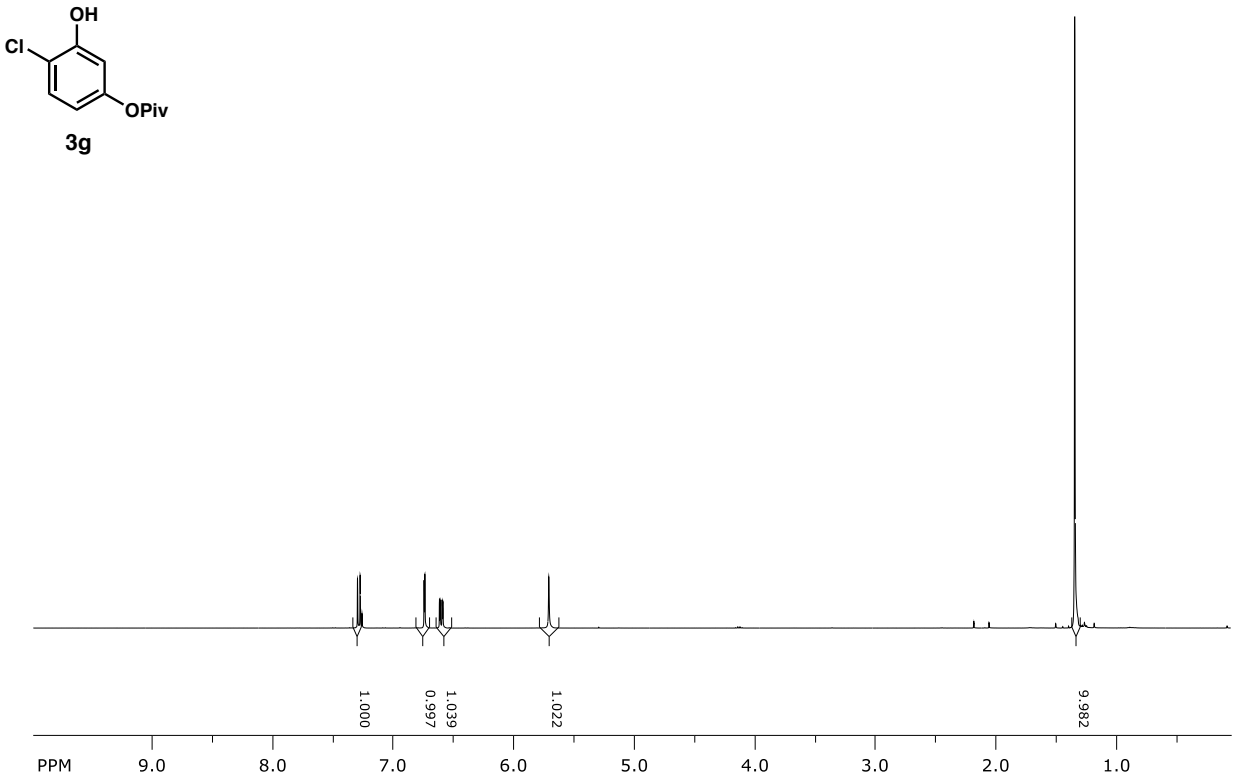
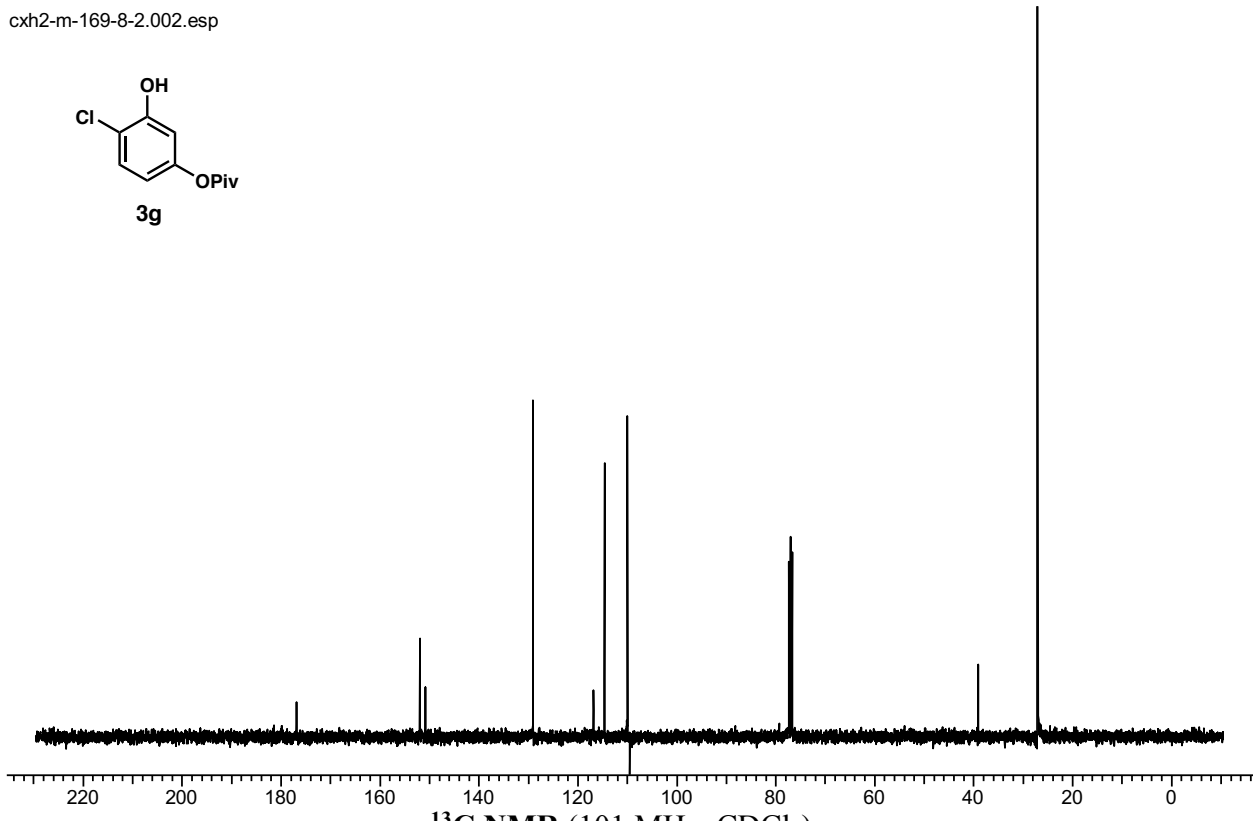
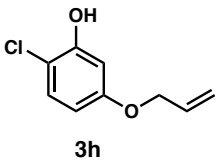


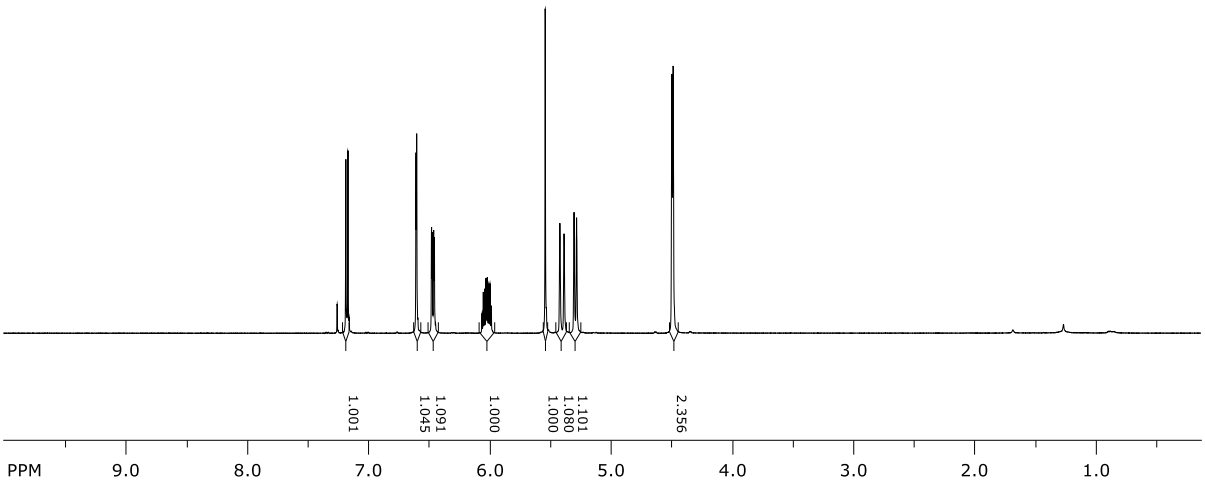
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

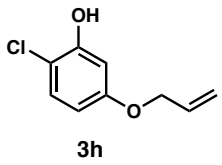


3h



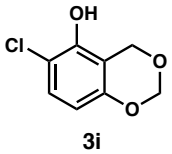
^{1}H NMR (500 MHz, $CDCl_3$)

cxh2-m-168-1.002.esp

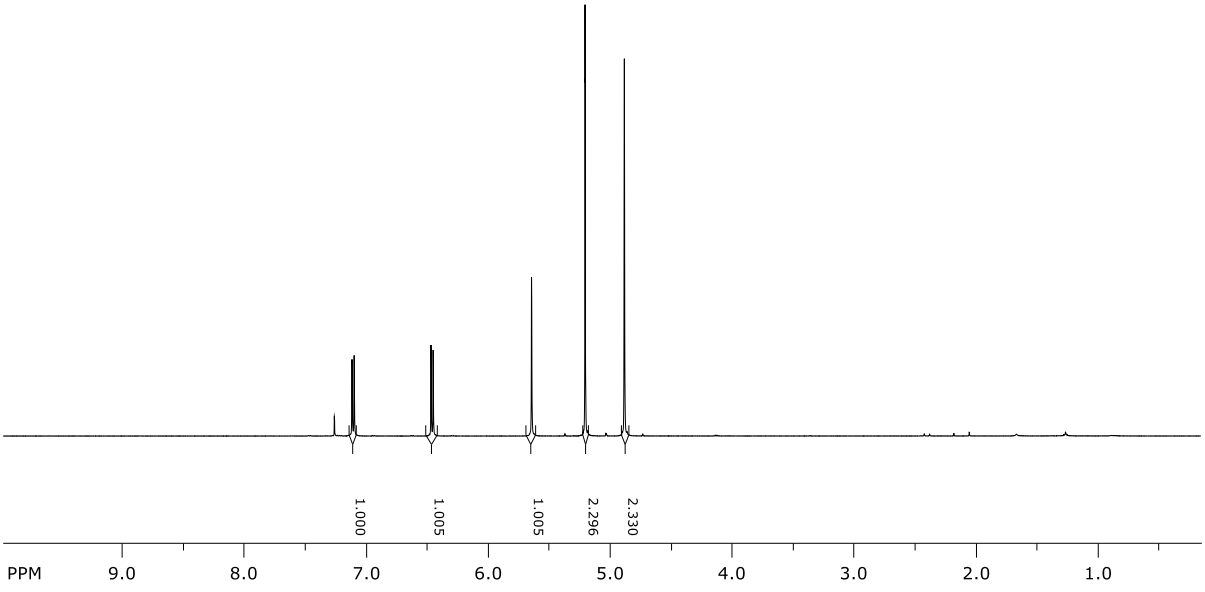


3h

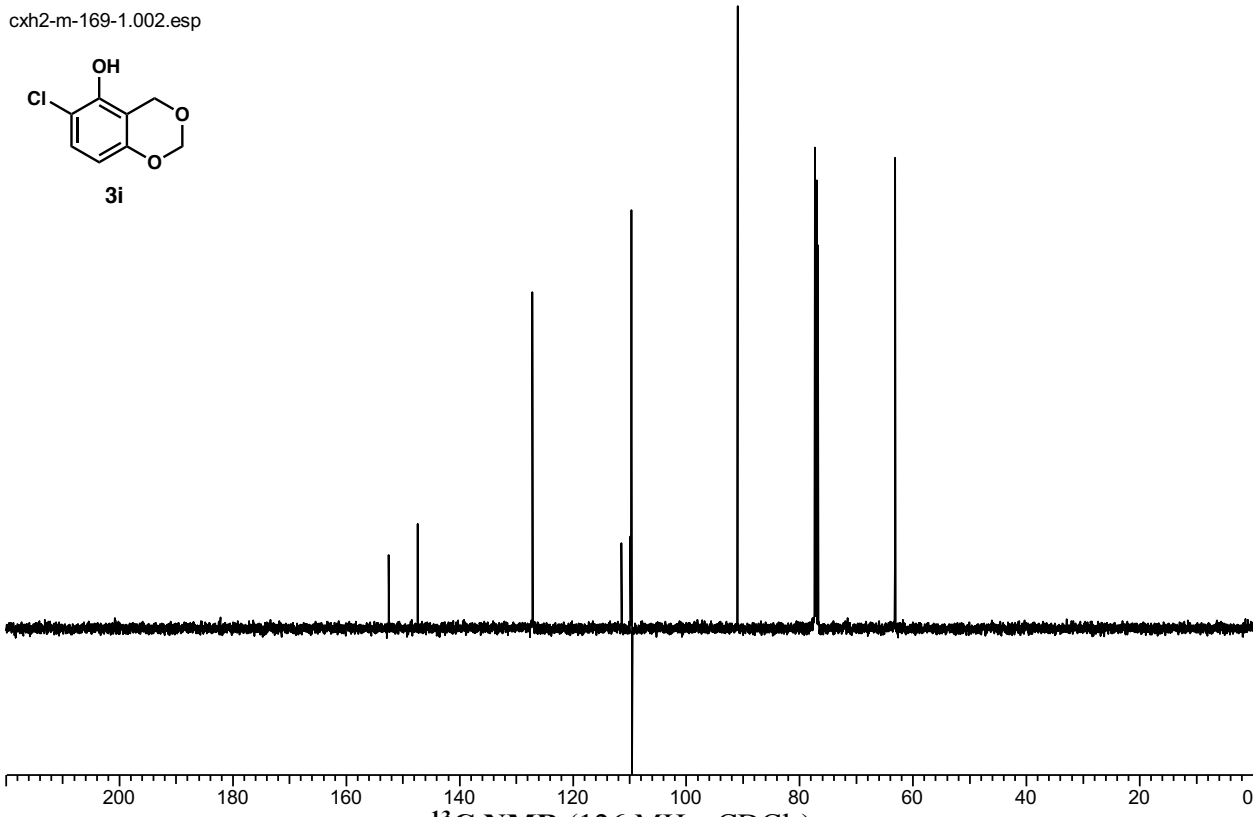
^{13}C NMR (126 MHz, $CDCl_3$)



3i

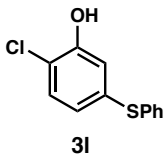


^{1}H NMR (500 MHz, $CDCl_3$)

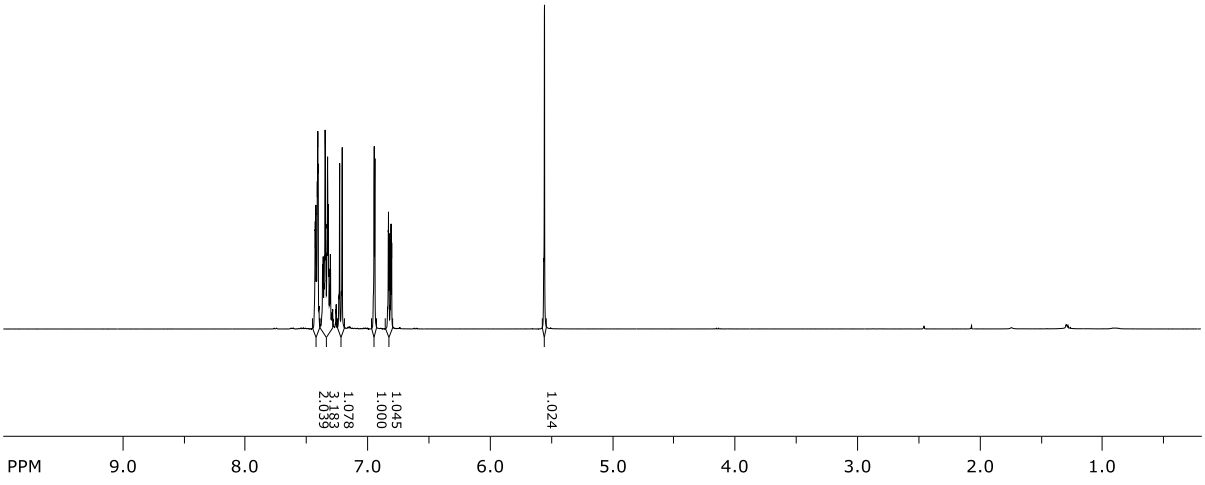


3i

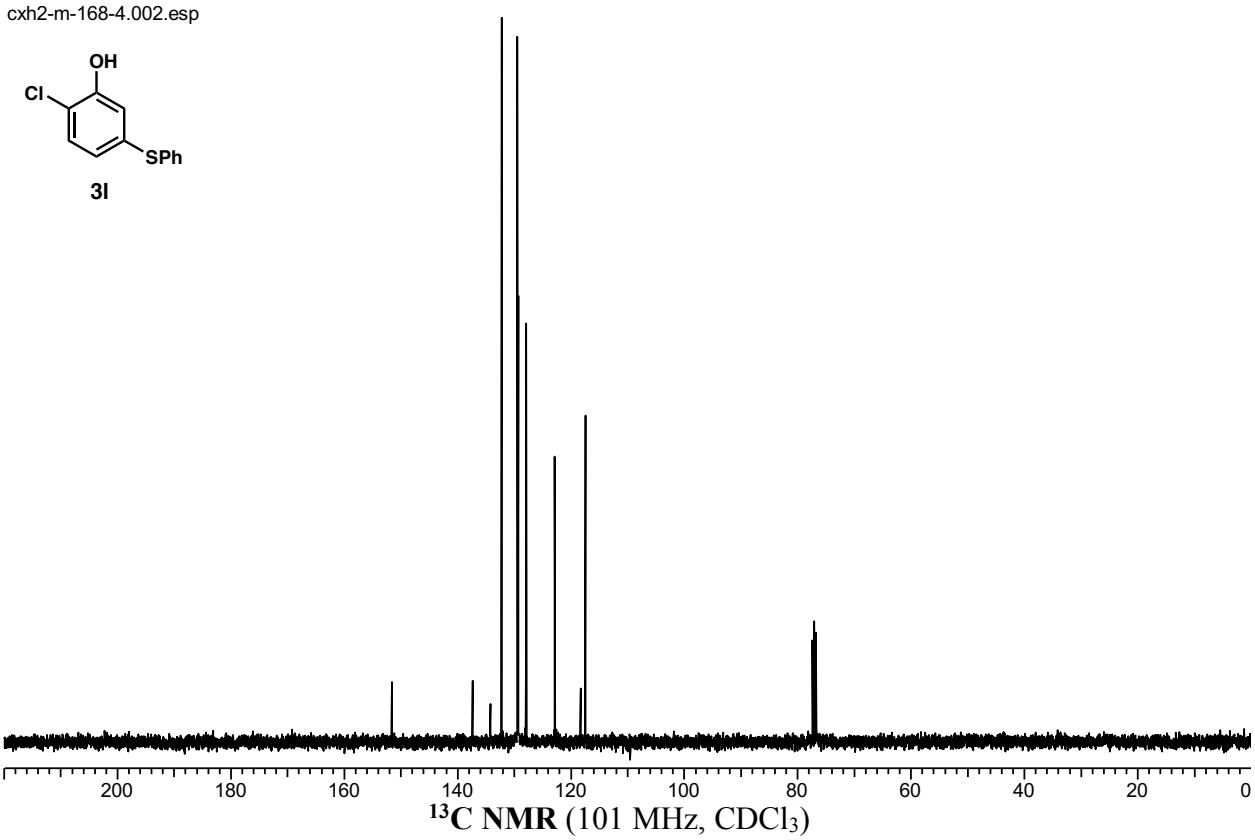
^{13}C NMR (126 MHz, $CDCl_3$)



3l

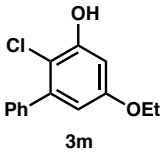


^{1}H NMR (400 MHz, $CDCl_3$)

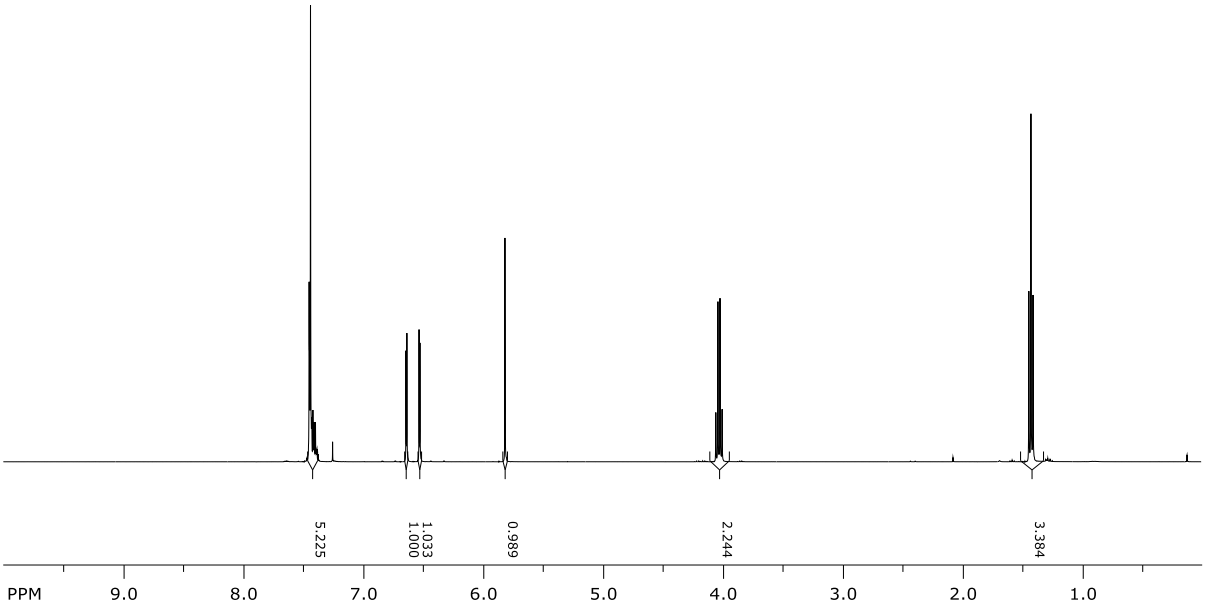


3l

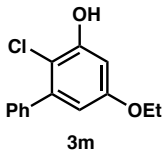
^{13}C NMR (101 MHz, $CDCl_3$)



3m

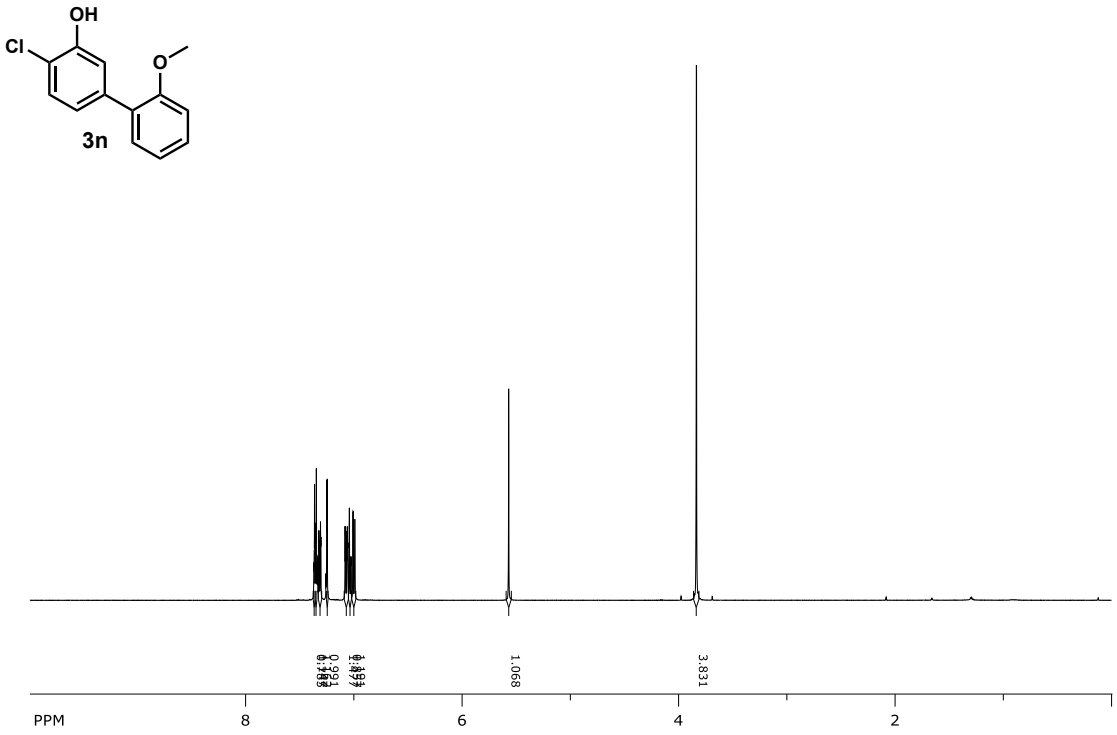


^{1}H NMR (400 MHz, $CDCl_3$)

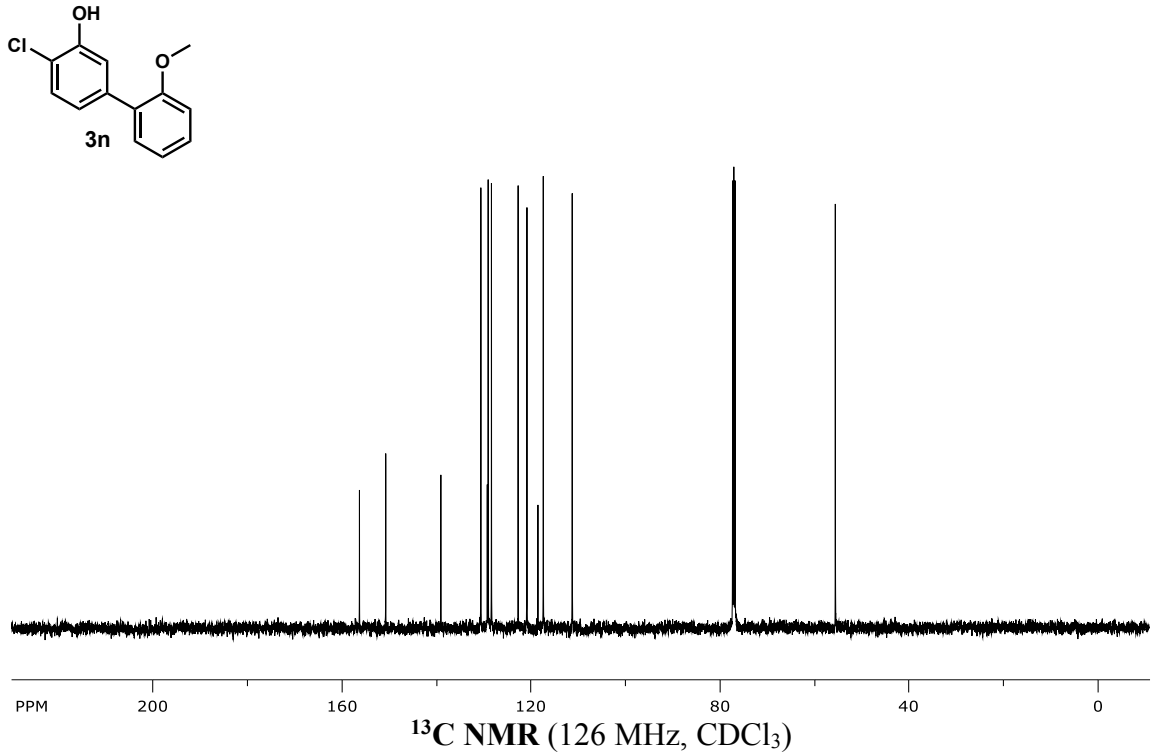


3m

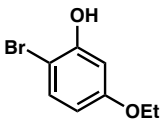
^{13}C NMR (101 MHz, $CDCl_3$)



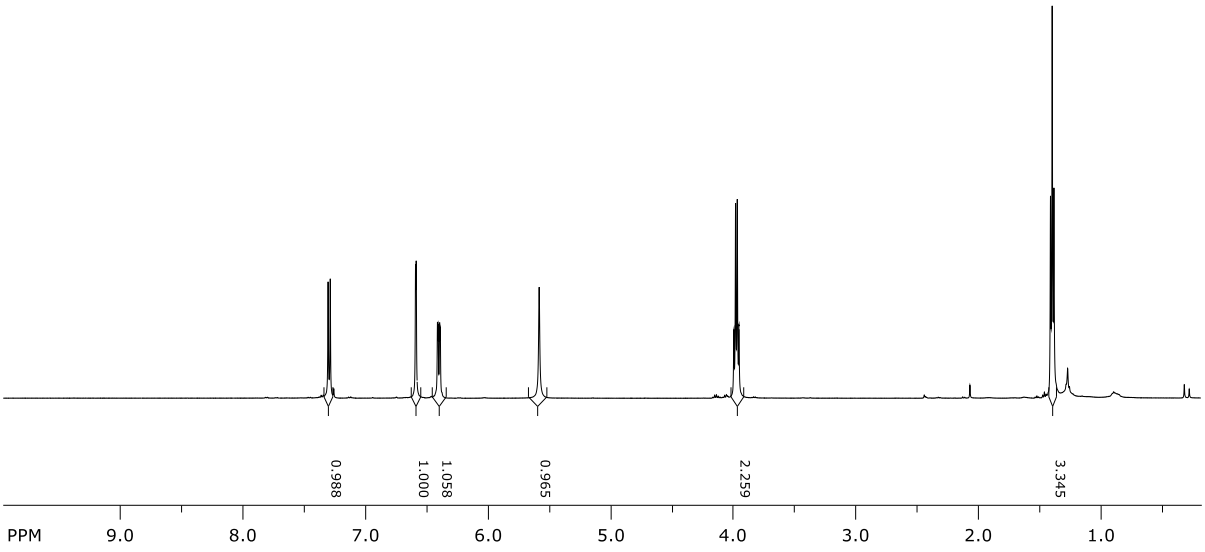
^{1}H NMR (500 MHz, $CDCl_3$)



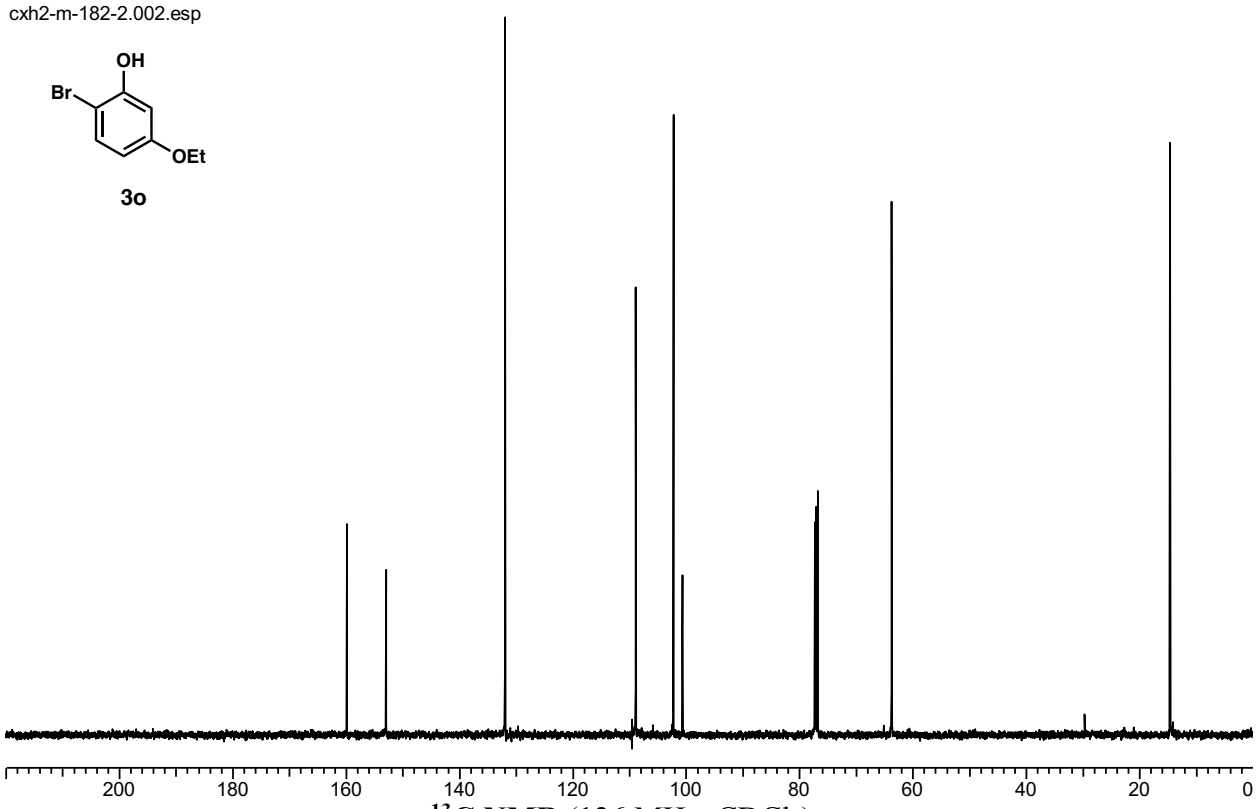
^{13}C NMR (126 MHz, $CDCl_3$)



3o

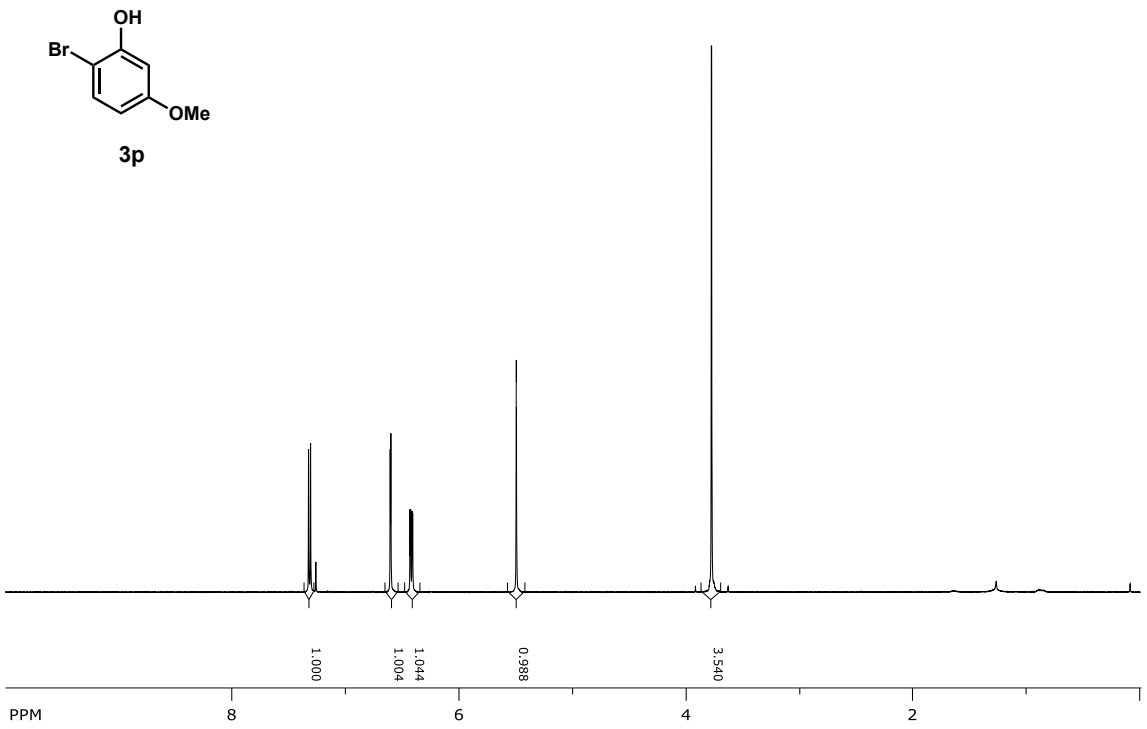


^{1}H NMR (500 MHz, $CDCl_3$)

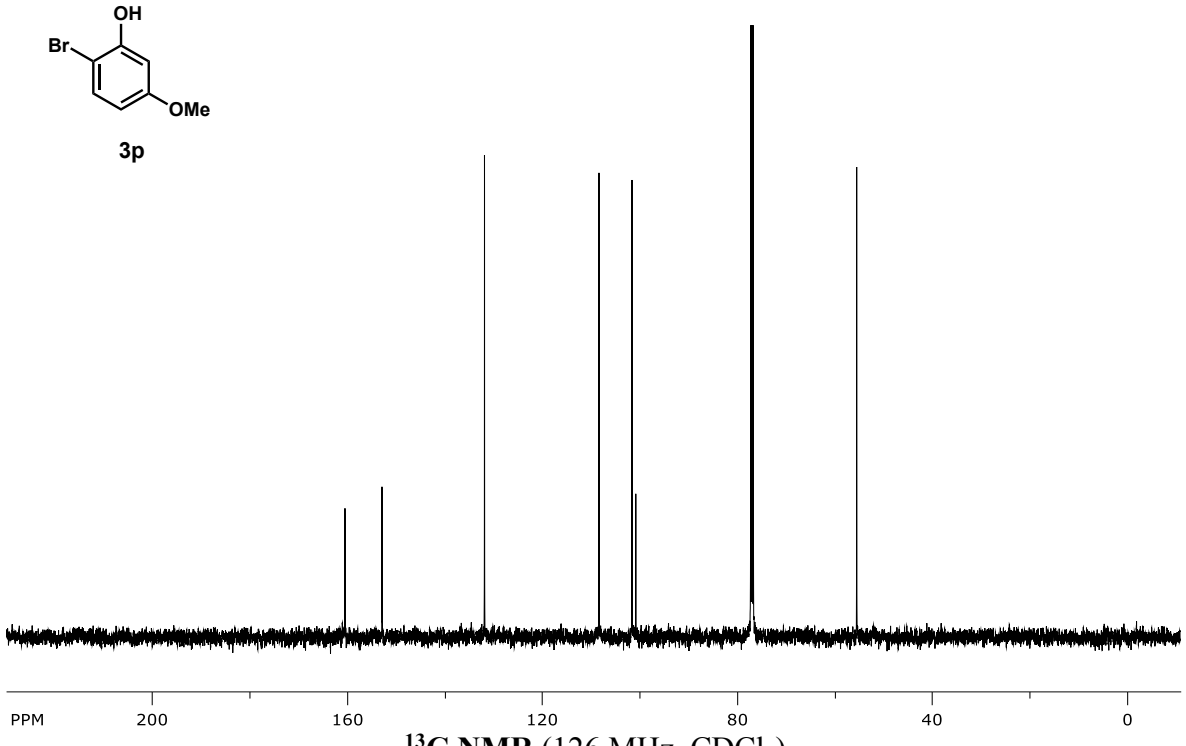


3o

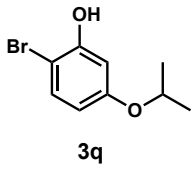
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

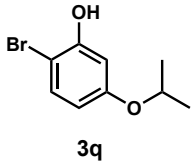


^{13}C NMR (126 MHz, $CDCl_3$)



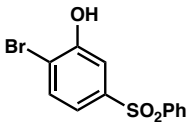
3q

^{1}H NMR (500 MHz, $CDCl_3$)

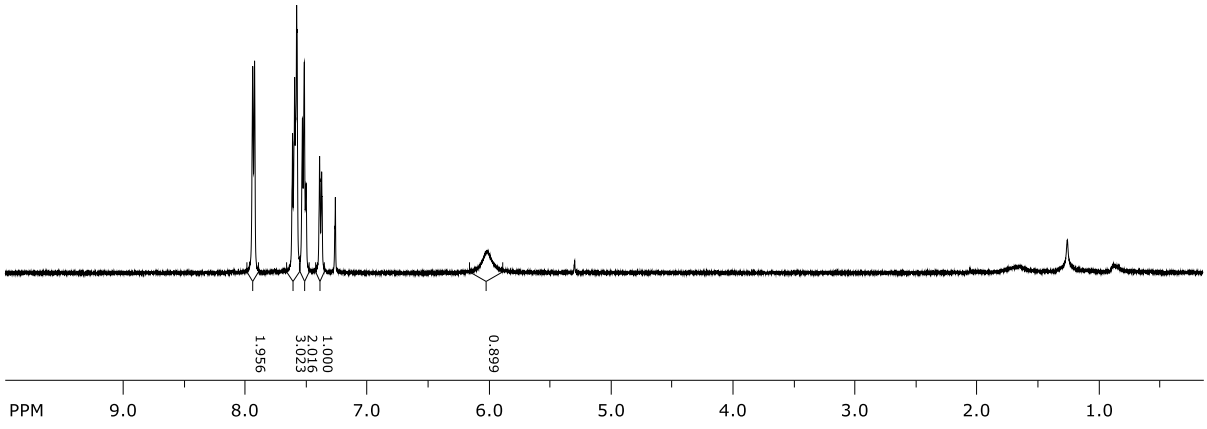


3q

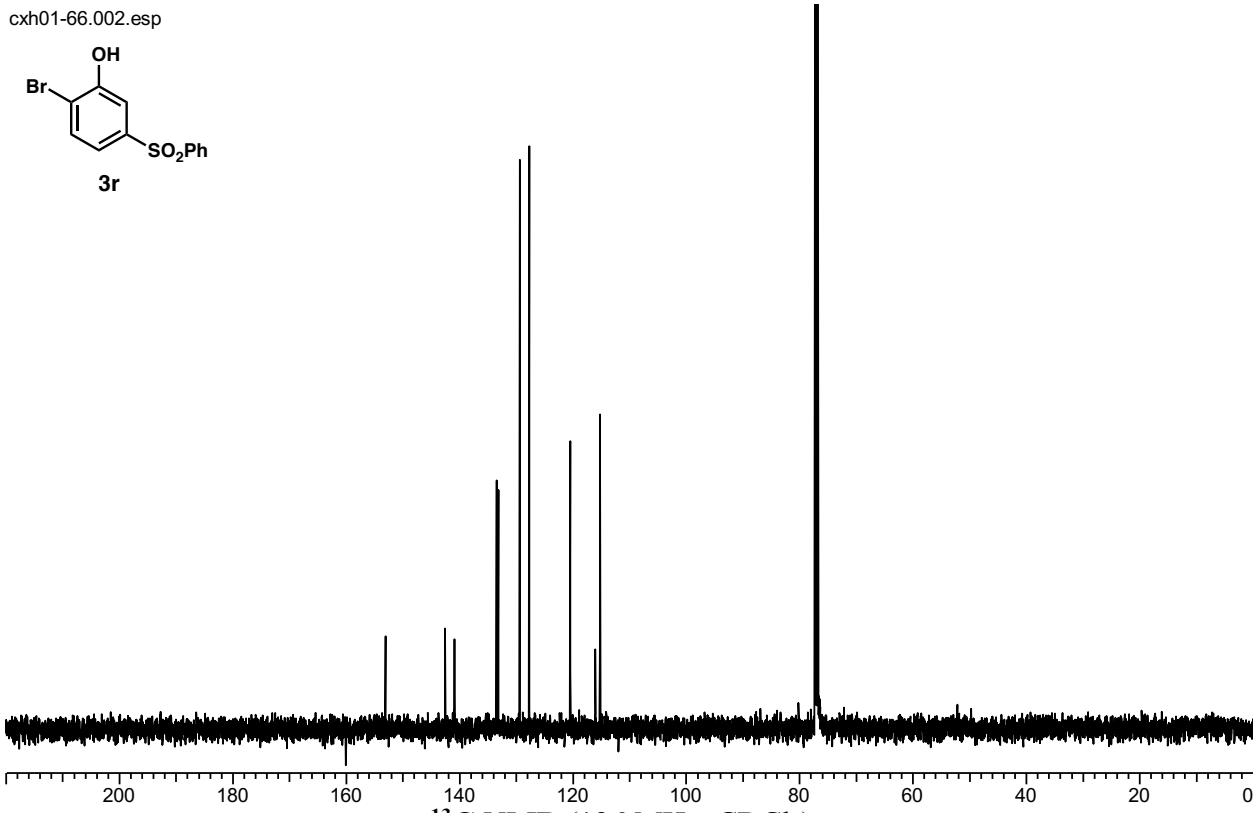
^{13}C NMR (126 MHz, $CDCl_3$)



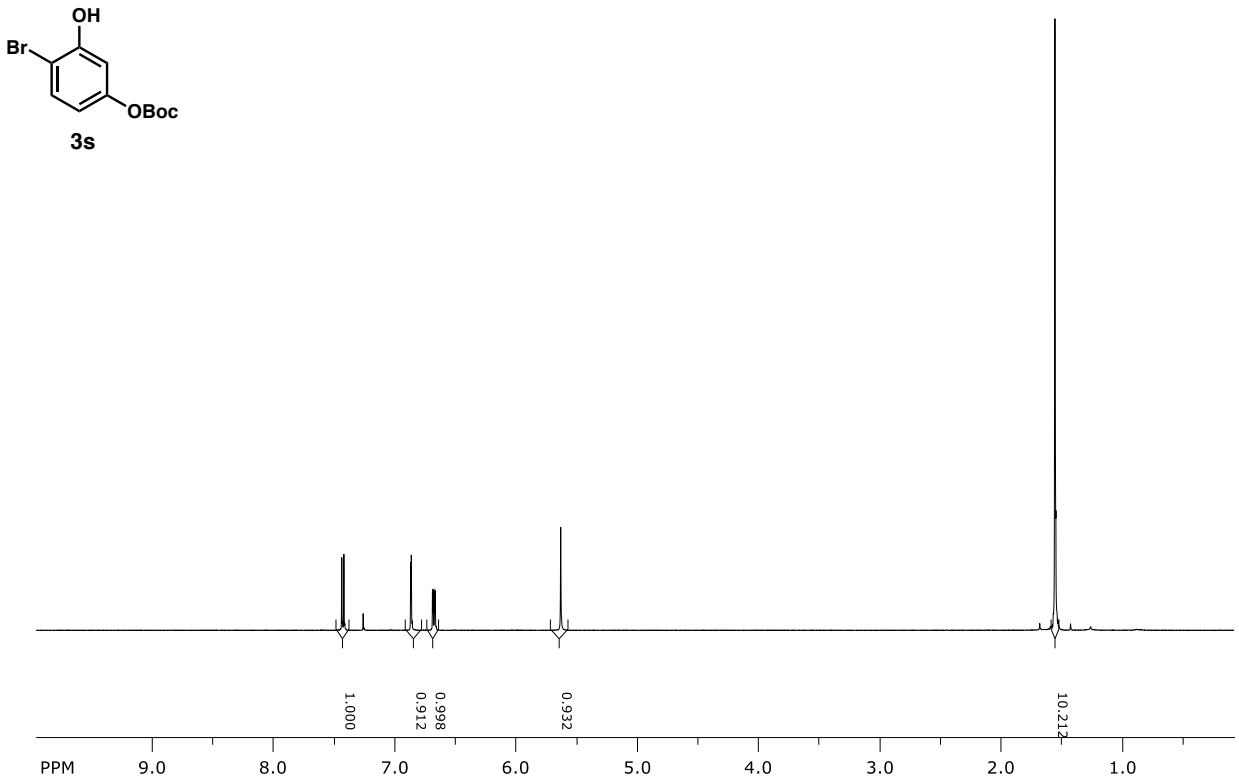
3r



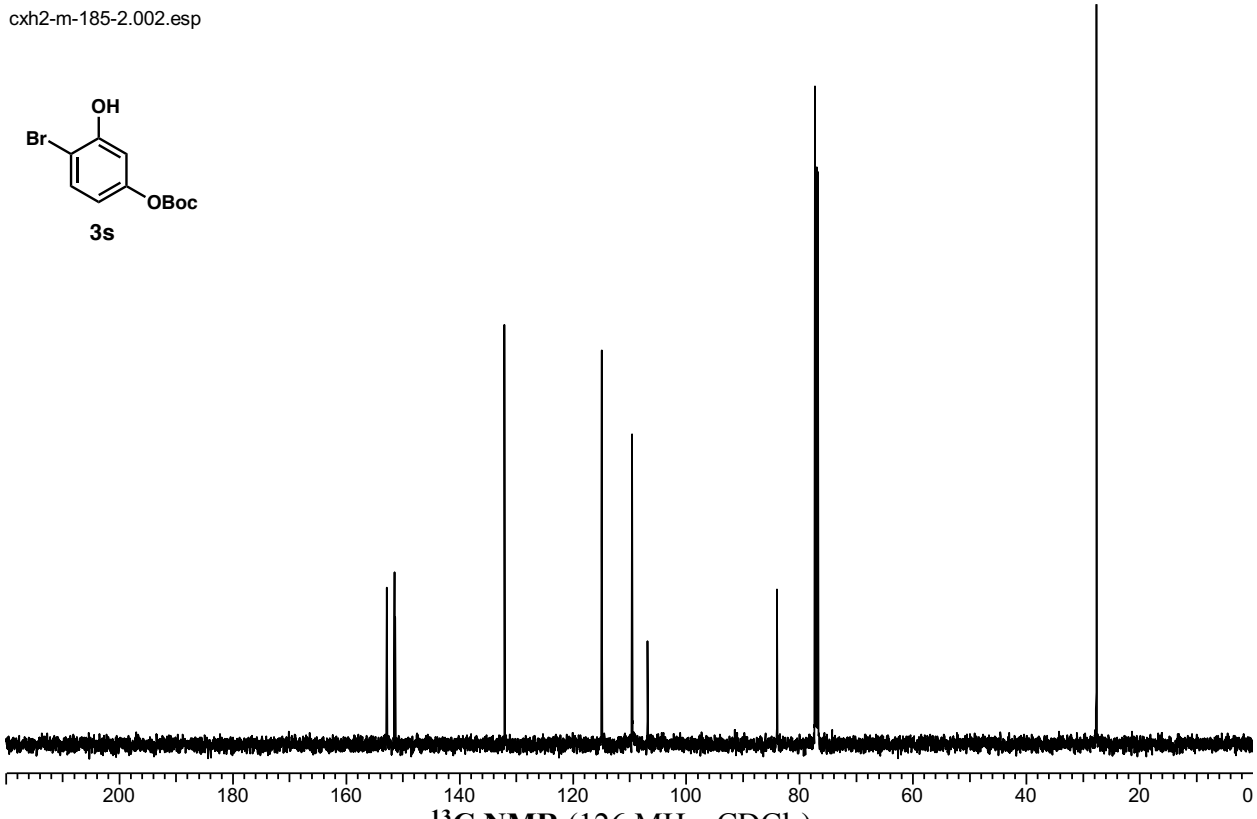
^{1}H NMR (500 MHz, $CDCl_3$)



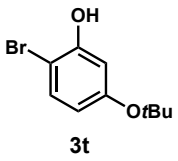
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



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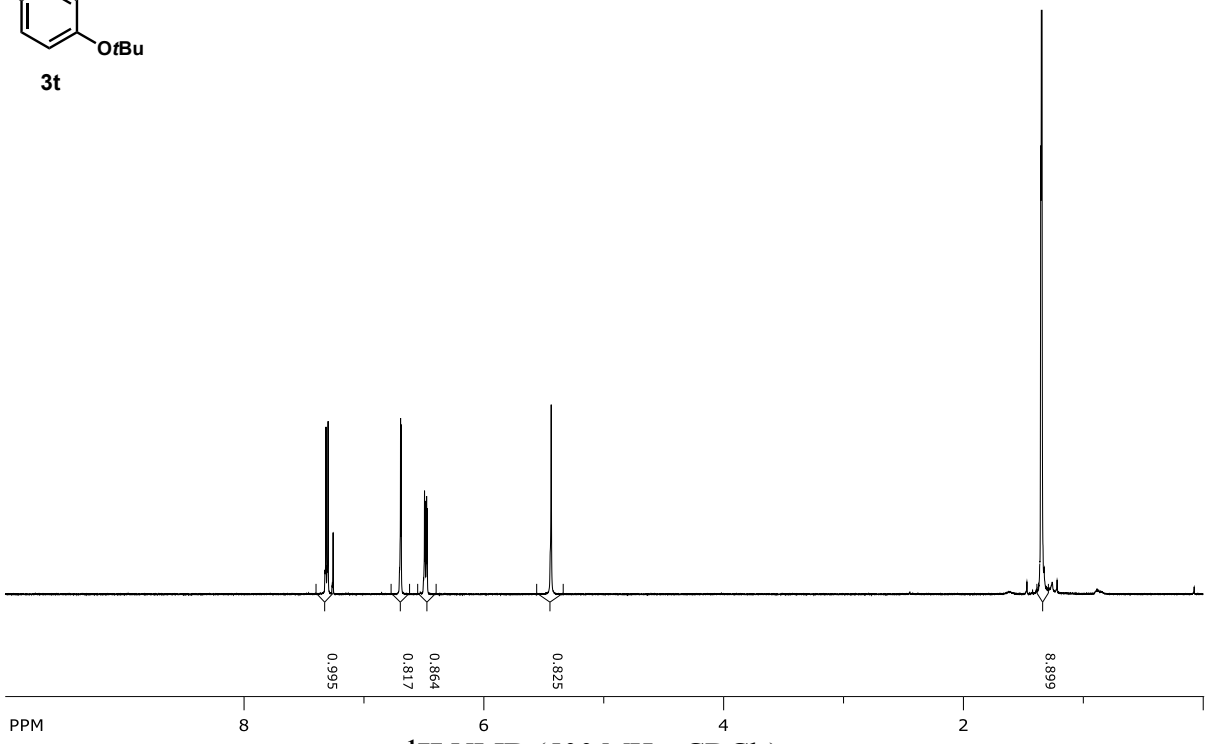
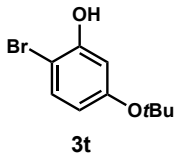
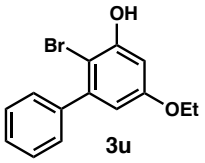


^{1}H NMR (500 MHz, $CDCl_3$)



3t

^{13}C NMR (126 MHz, $CDCl_3$)



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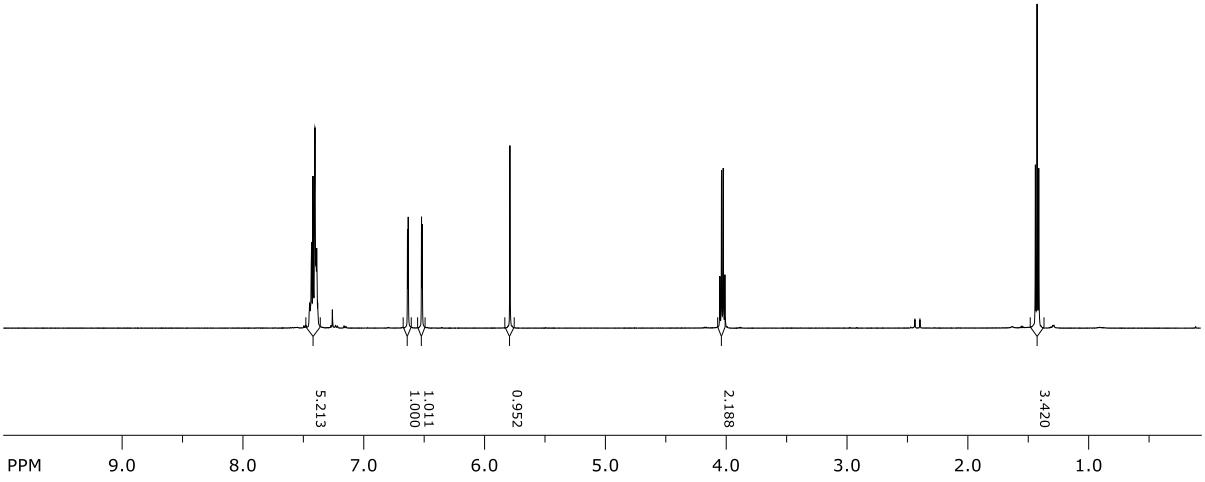
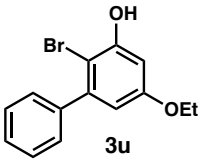


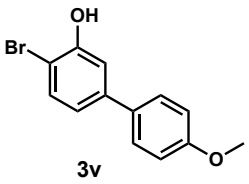
^{1}H NMR (500 MHz, $CDCl_3$)

cxh2-m-184-5.002.esp



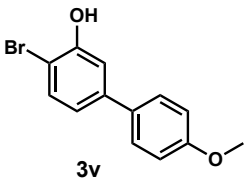
3u

^{13}C NMR (126 MHz, $CDCl_3$)



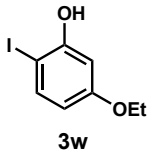
3v

^{1}H NMR (500 MHz, $CDCl_3$)



3v

^{13}C NMR (126 MHz, $CDCl_3$)



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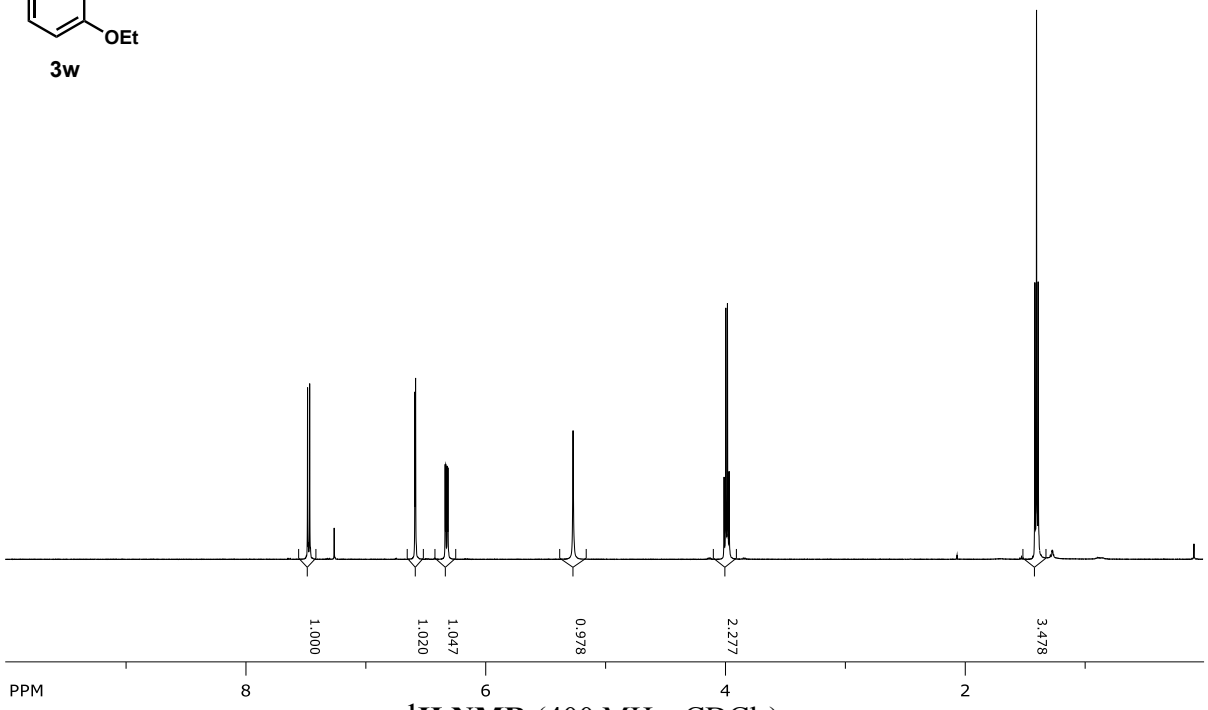
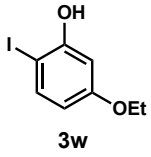


^{1}H NMR (400 MHz, $CDCl_3$)



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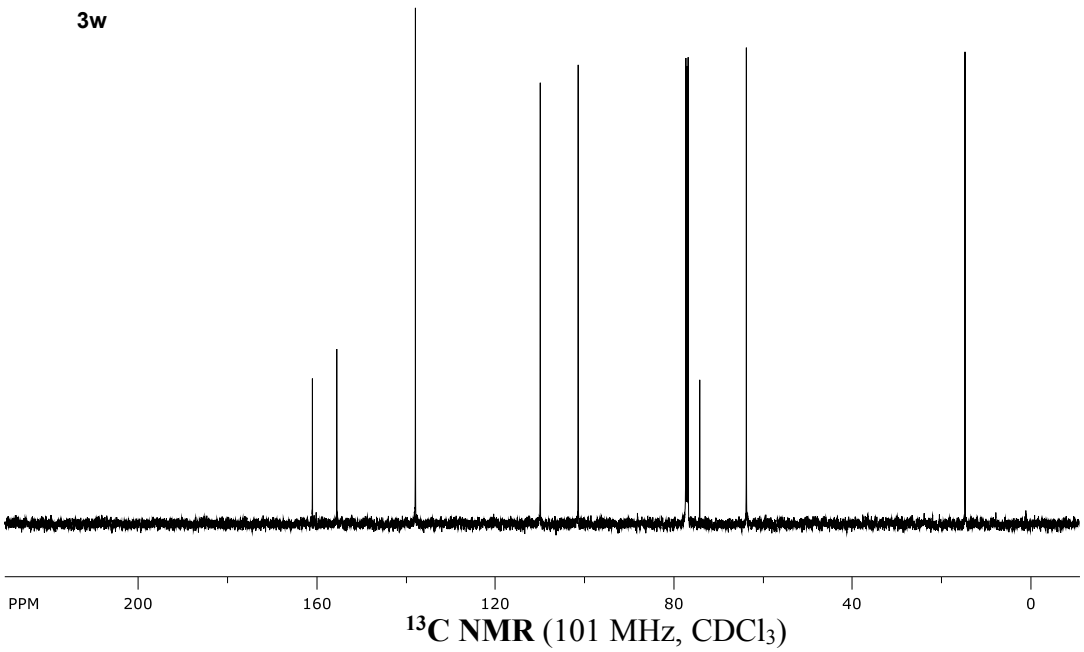
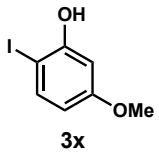
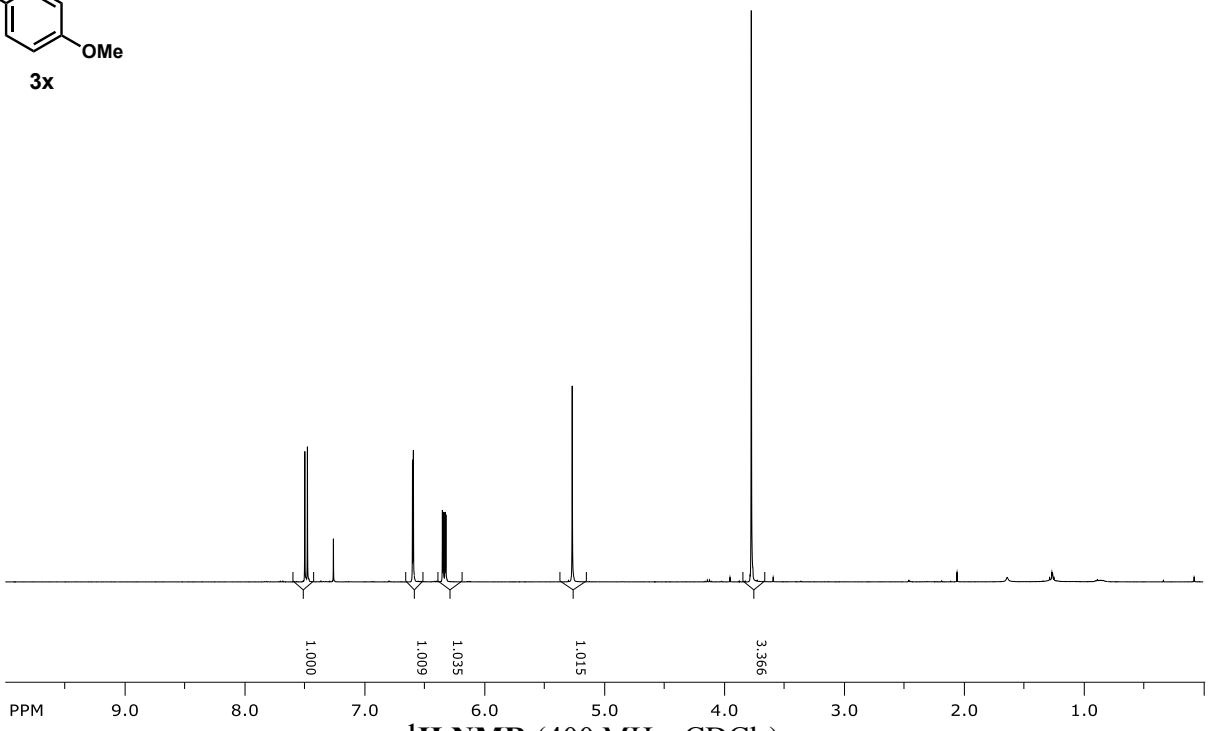


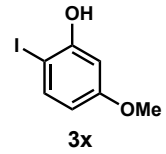
^{13}C NMR (101 MHz, $CDCl_3$)



3x

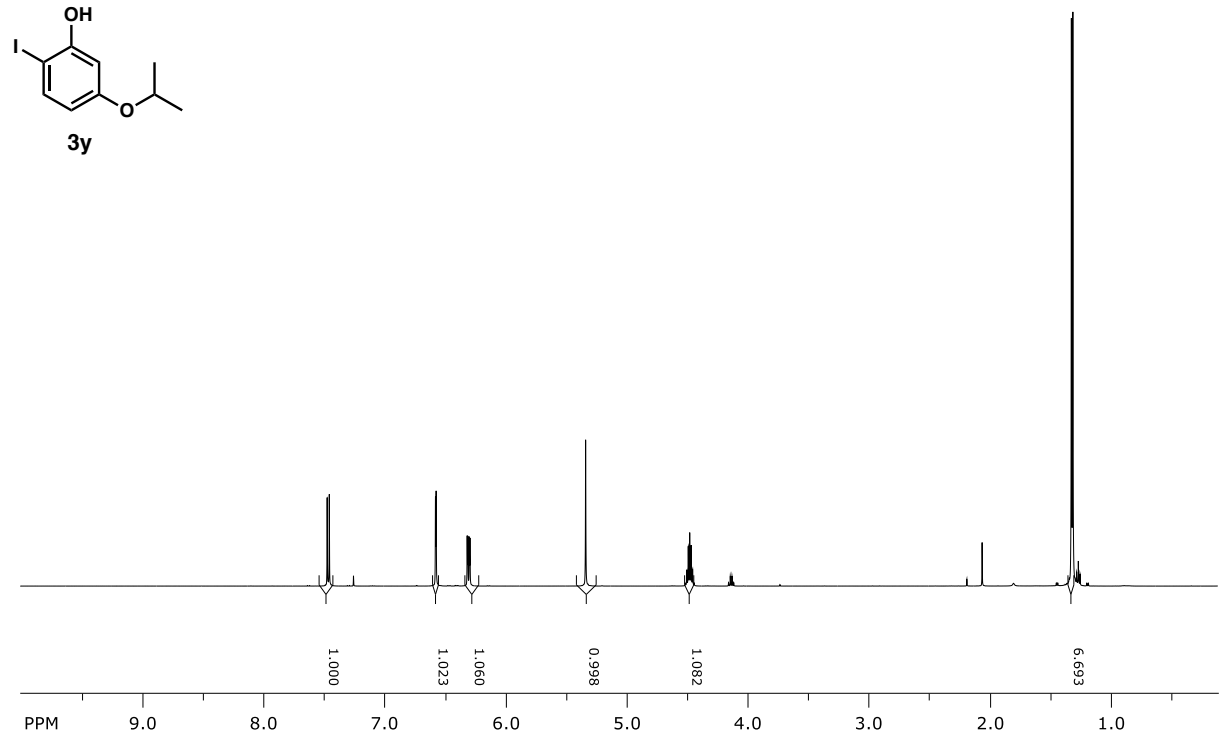


^{1}H NMR (400 MHz, $CDCl_3$)

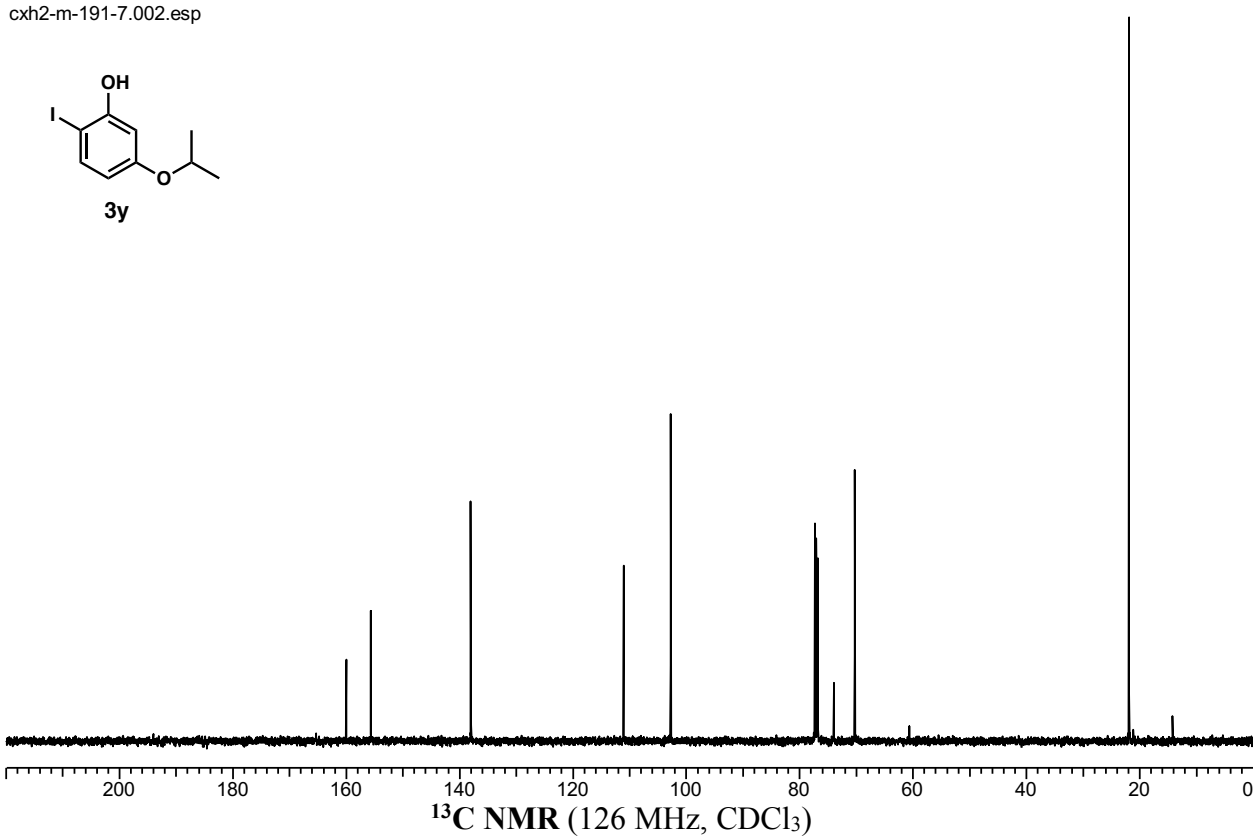


3x

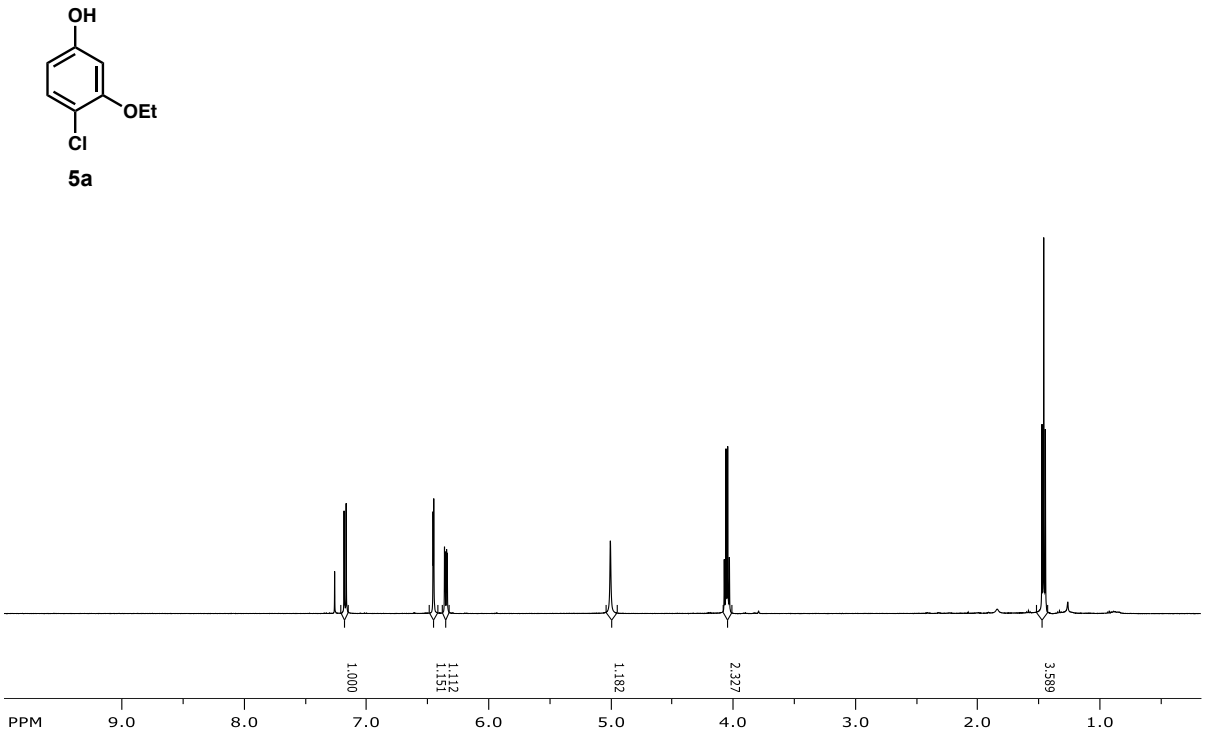
^{13}C NMR (101 MHz, $CDCl_3$)



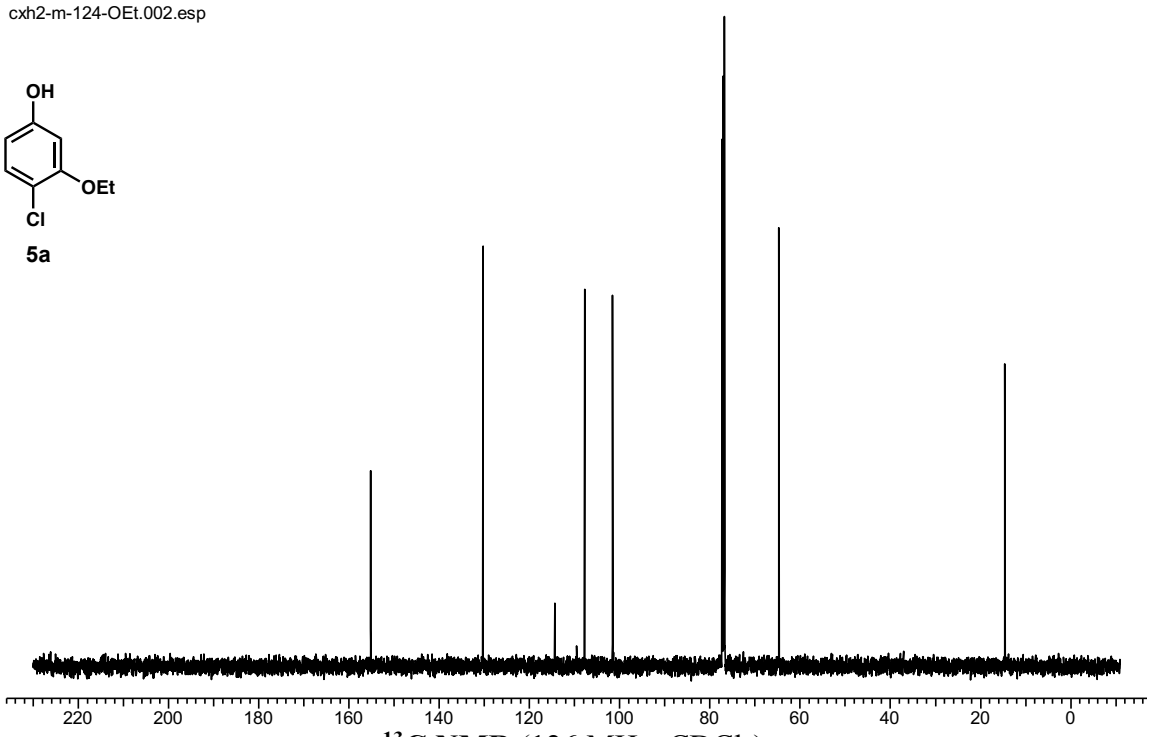
^{1}H NMR (500 MHz, $CDCl_3$)



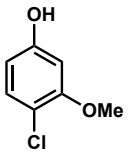
^{13}C NMR (126 MHz, $CDCl_3$)



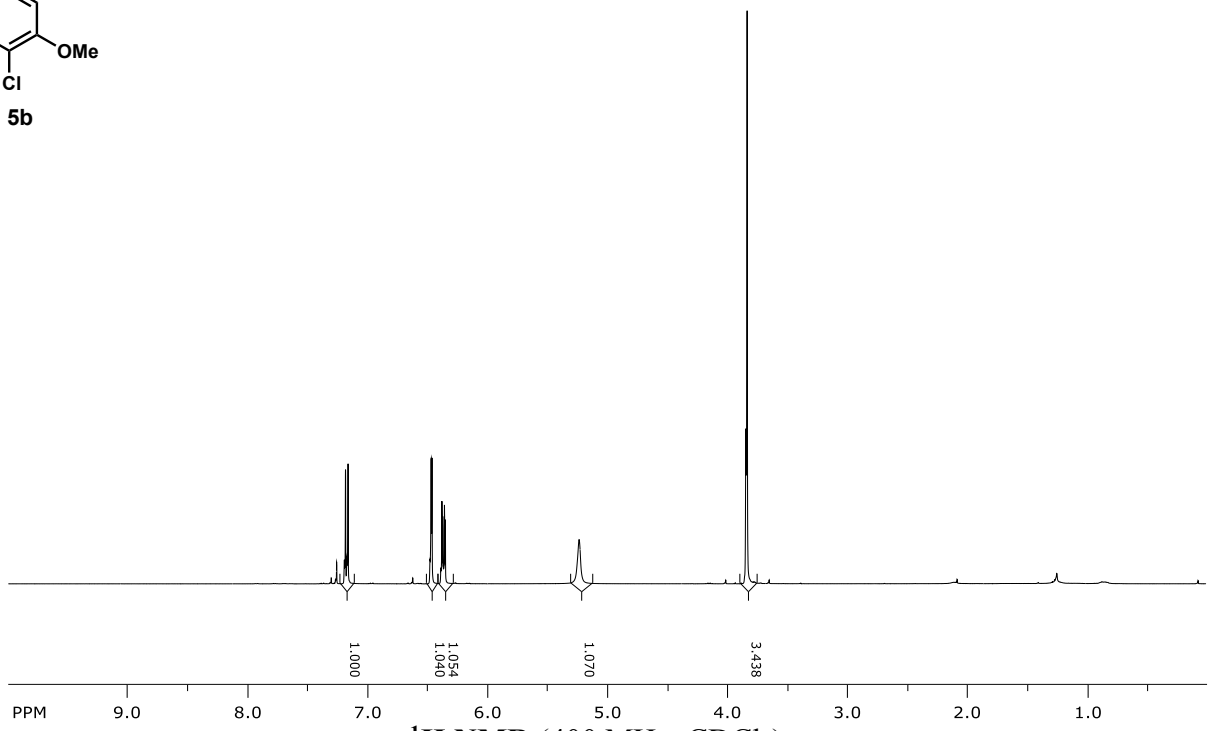
^{1}H NMR (500 MHz, $CDCl_3$)



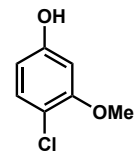
^{13}C NMR (126 MHz, $CDCl_3$)



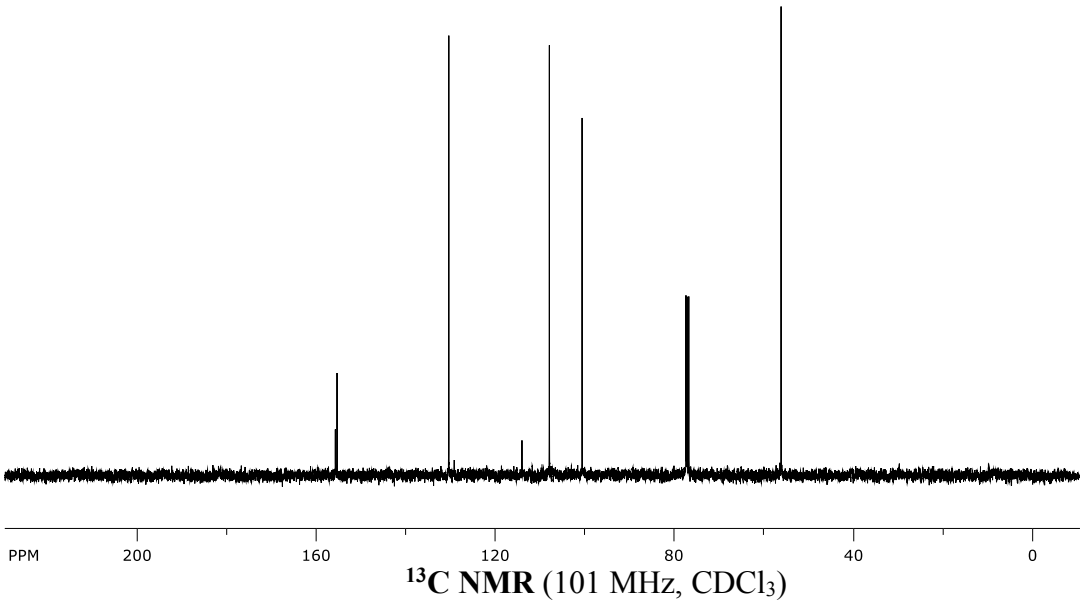
5b



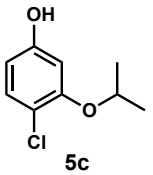
^{1}H NMR (400 MHz, $CDCl_3$)



5b

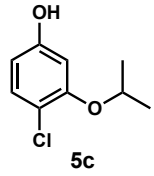


^{13}C NMR (101 MHz, $CDCl_3$)



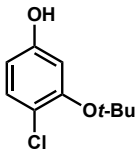
5c

^{1}H NMR (400 MHz, $CDCl_3$)

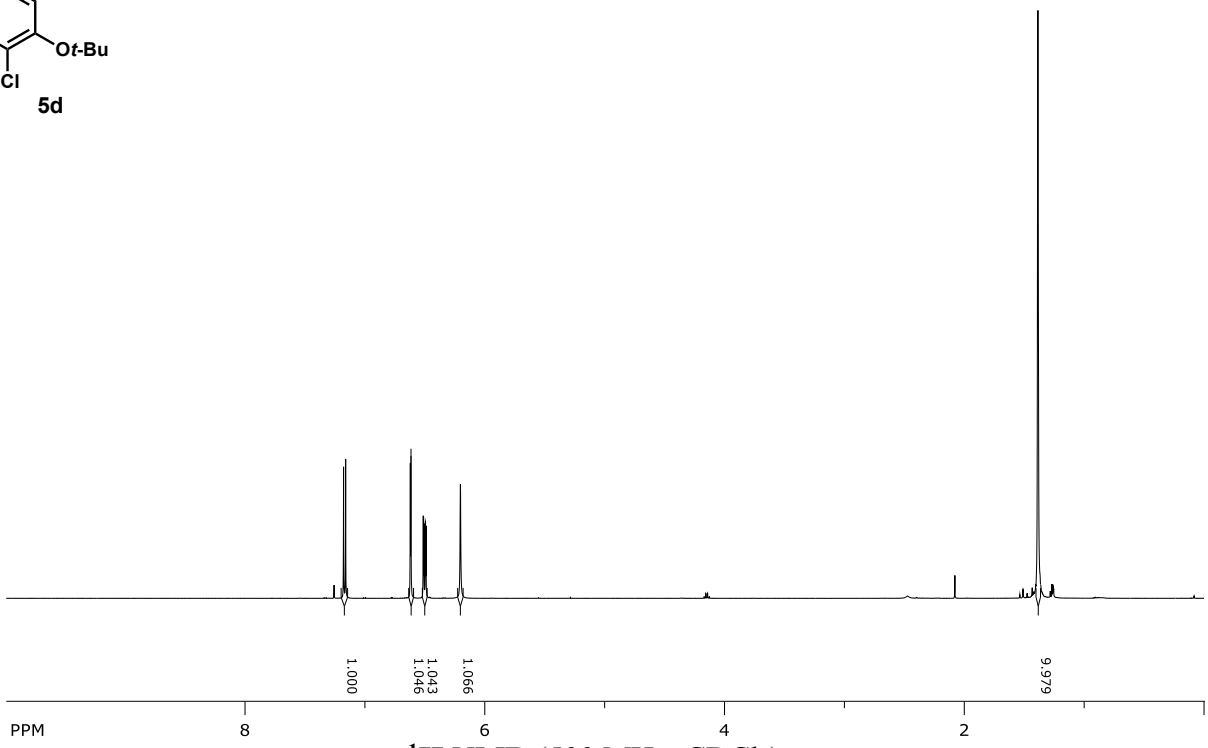


5c

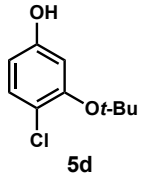
^{13}C NMR (101 MHz, $CDCl_3$)



5d

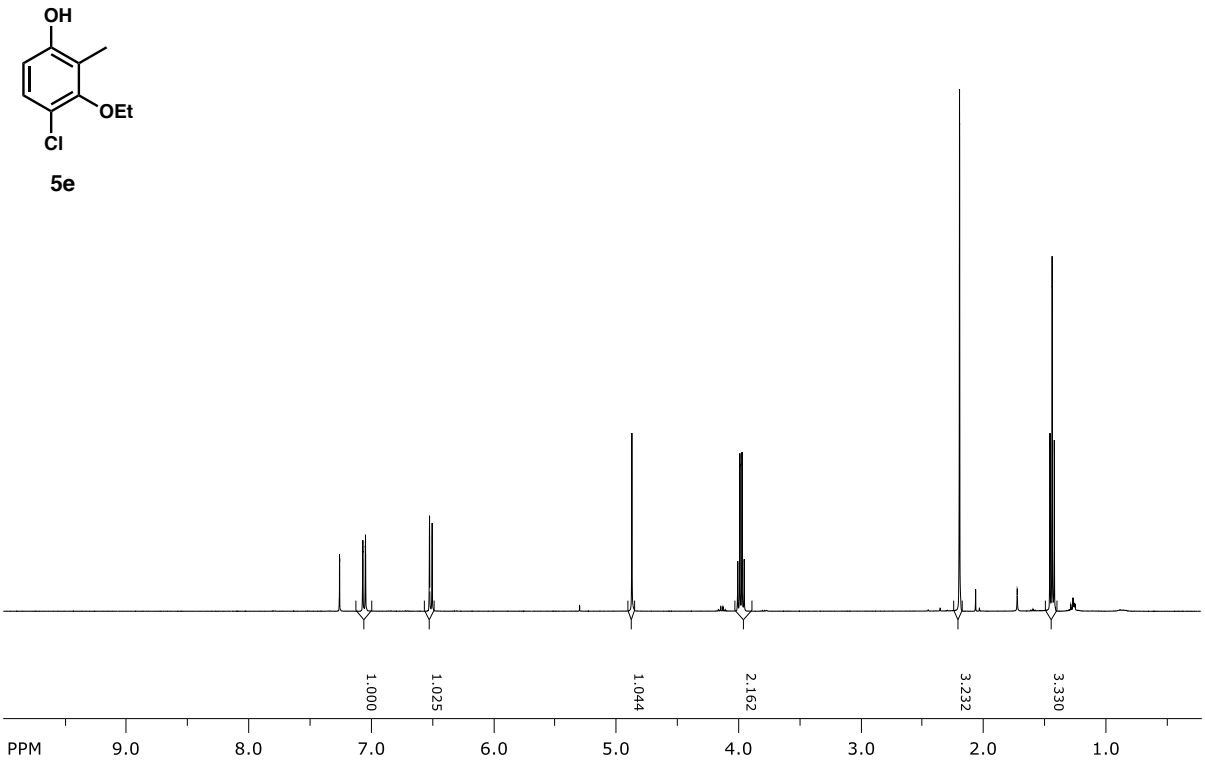


^{1}H NMR (500 MHz, $CDCl_3$)

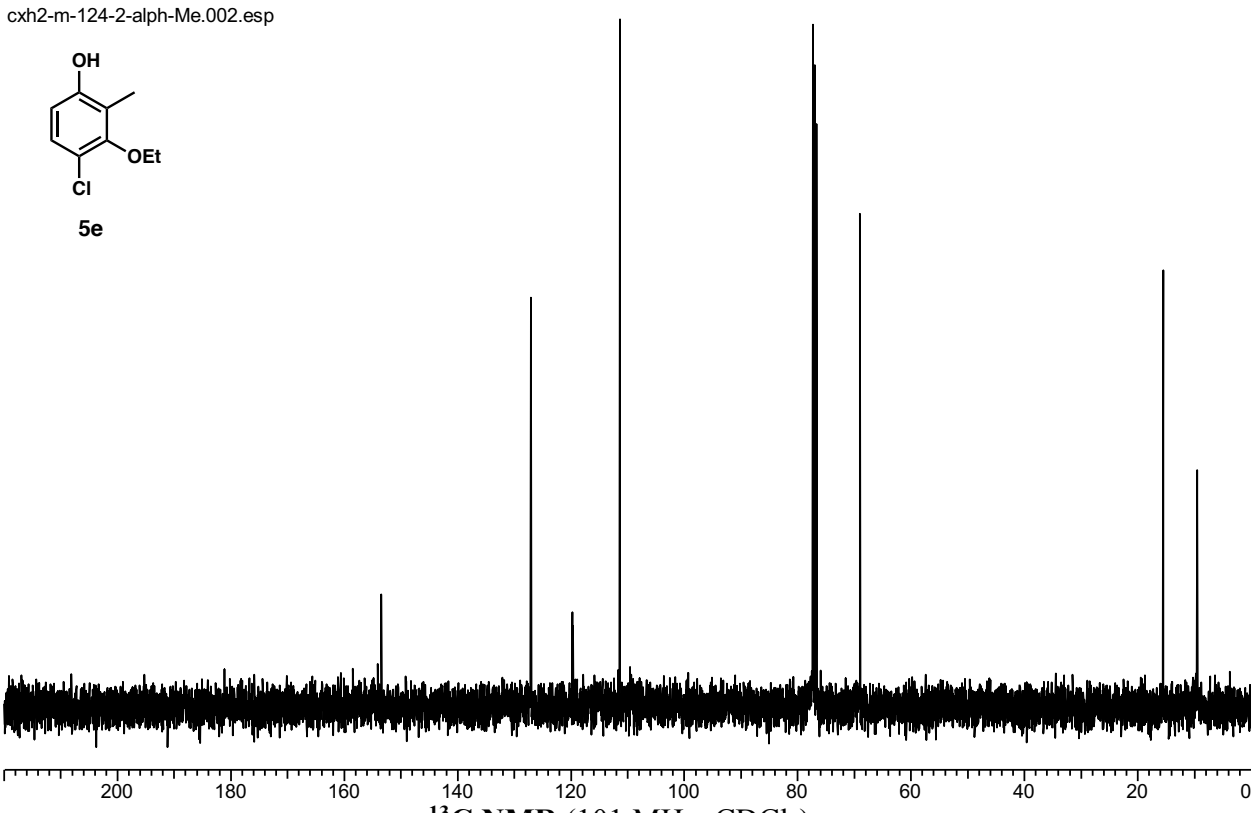


5d

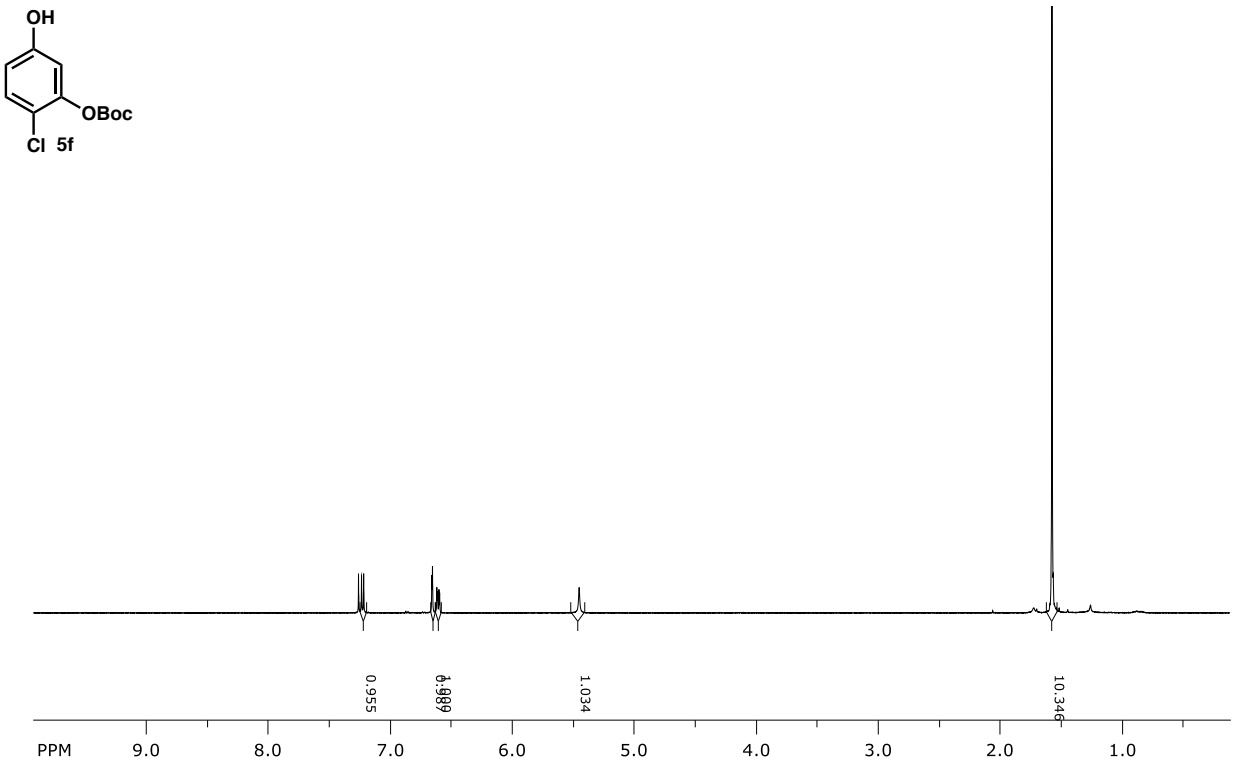
^{13}C NMR (126 MHz, $CDCl_3$)



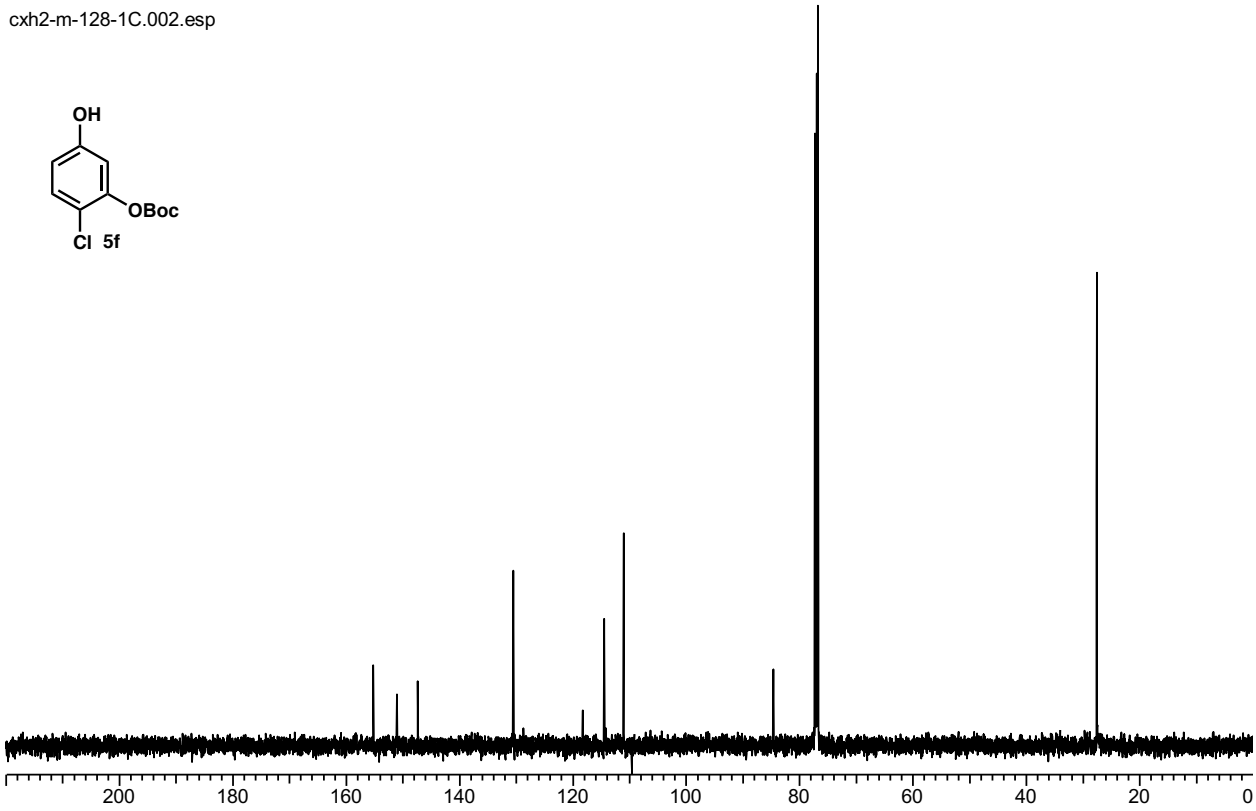
^{1}H NMR (400 MHz, $CDCl_3$)



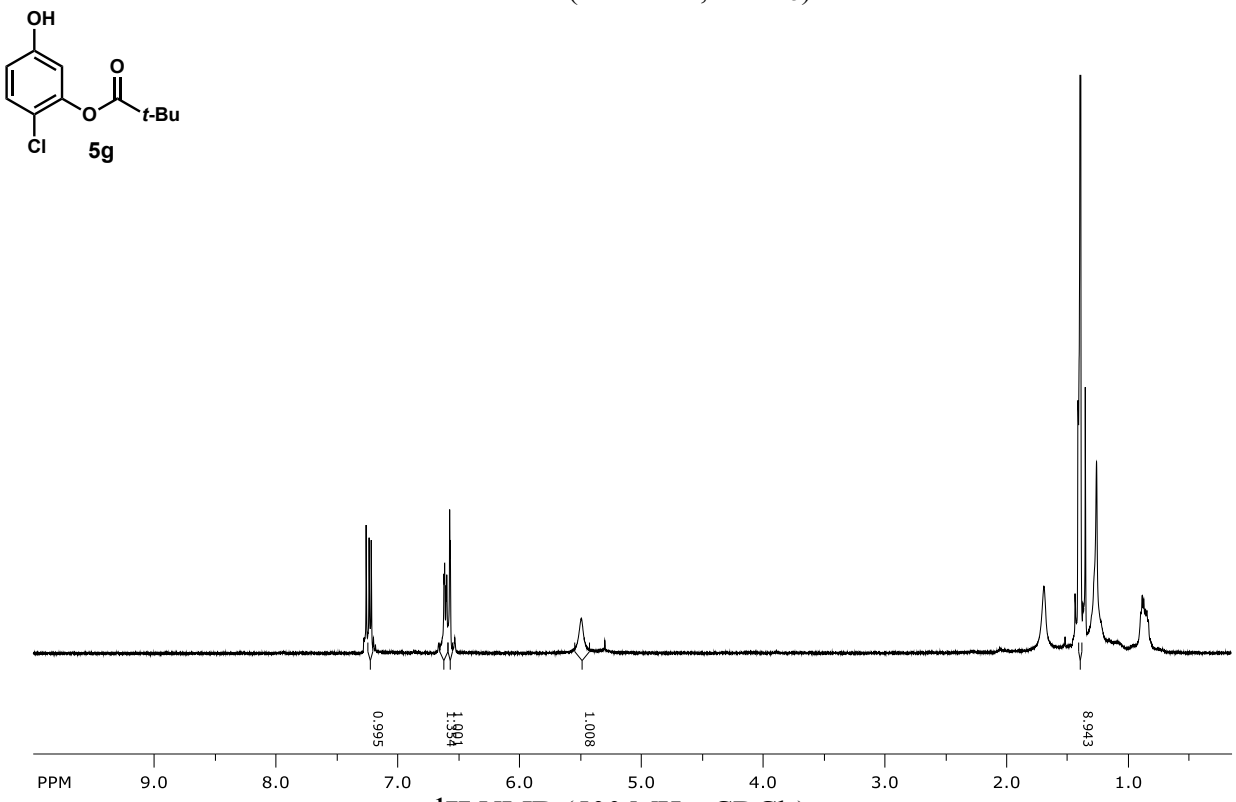
^{13}C NMR (101 MHz, $CDCl_3$)



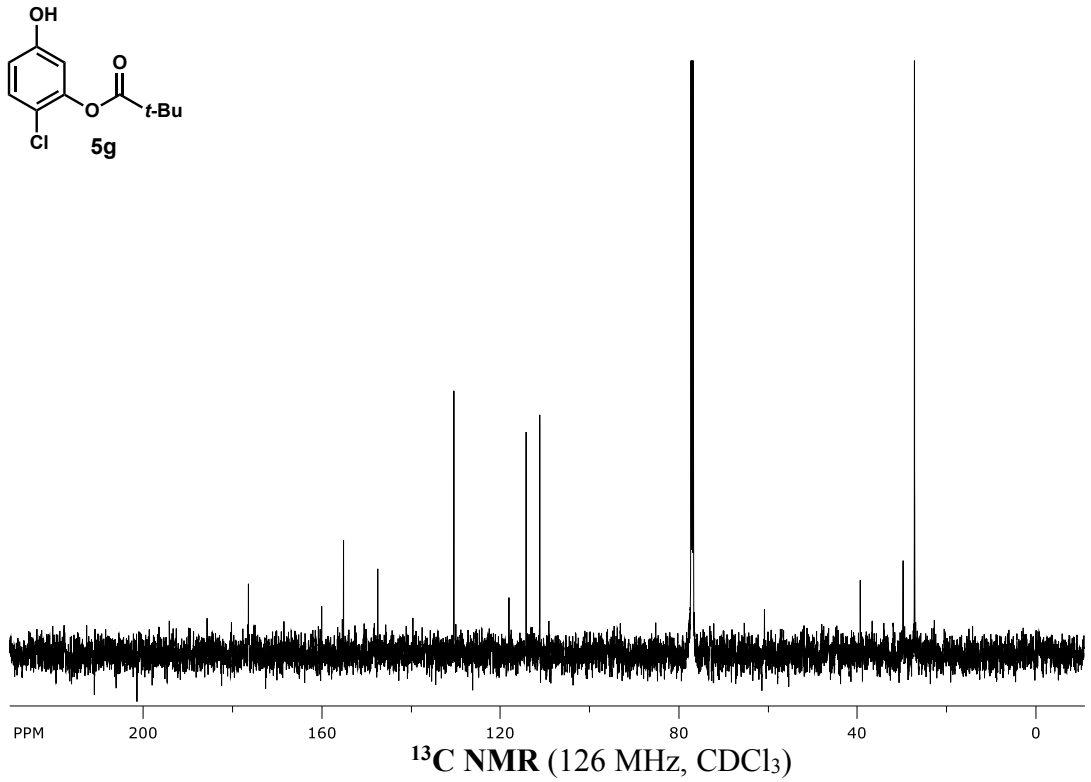
^{1}H NMR (500 MHz, $CDCl_3$)



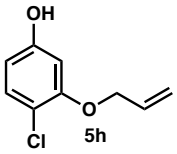
^{13}C NMR (126 MHz, $CDCl_3$)

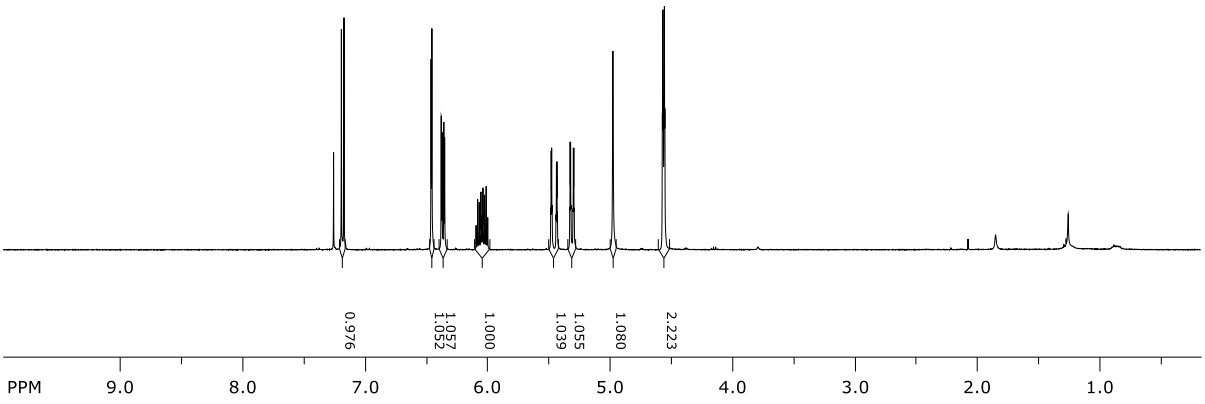


^{1}H NMR (500 MHz, $CDCl_3$)

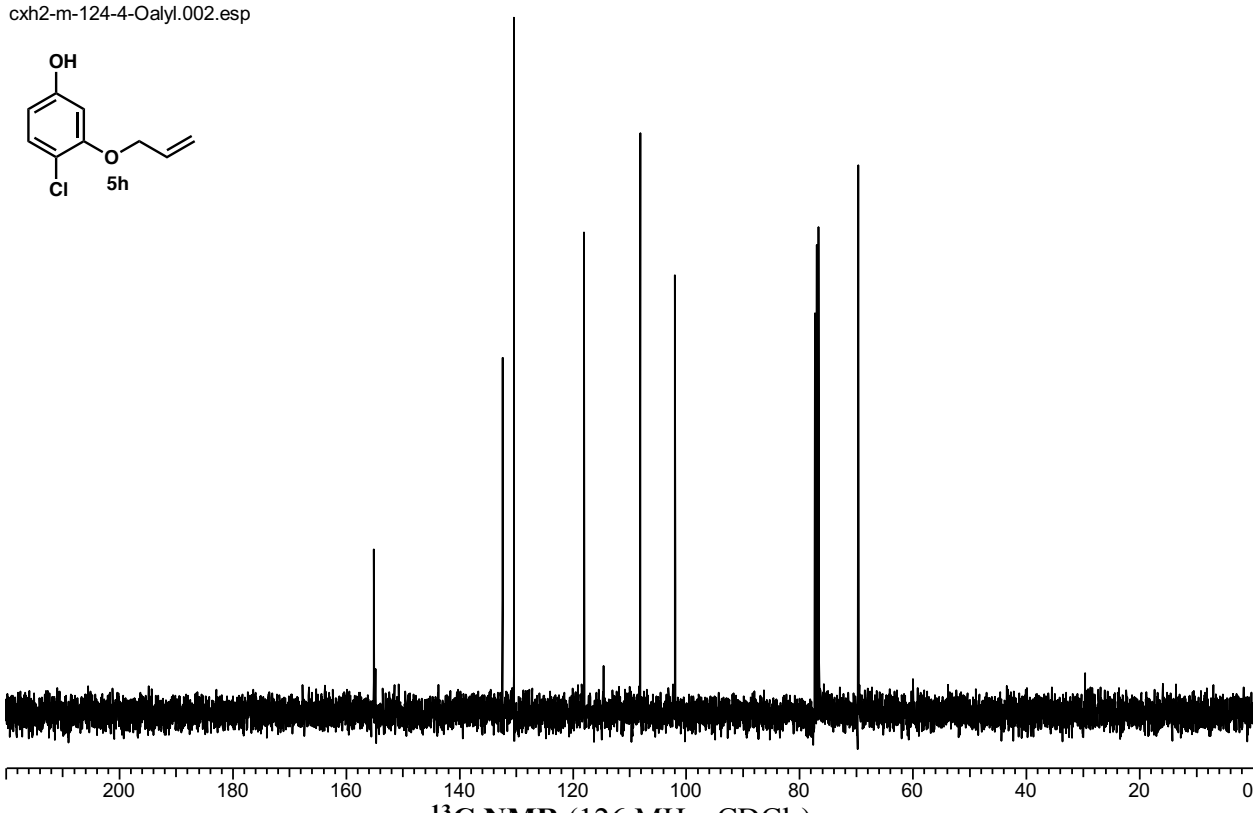


^{13}C NMR (126 MHz, $CDCl_3$)

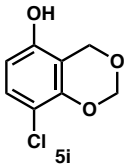




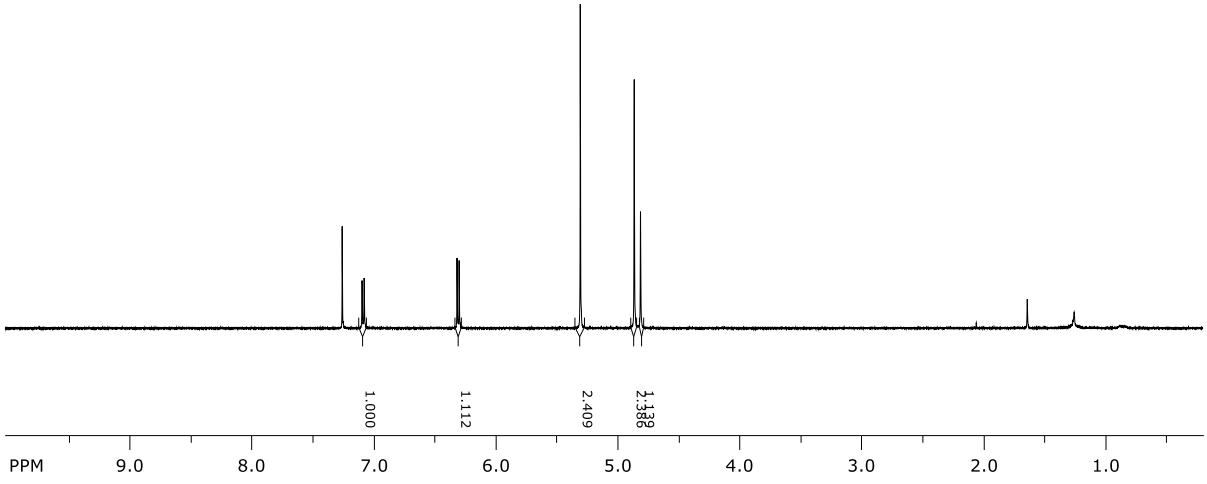
^{1}H NMR (500 MHz, $CDCl_3$)



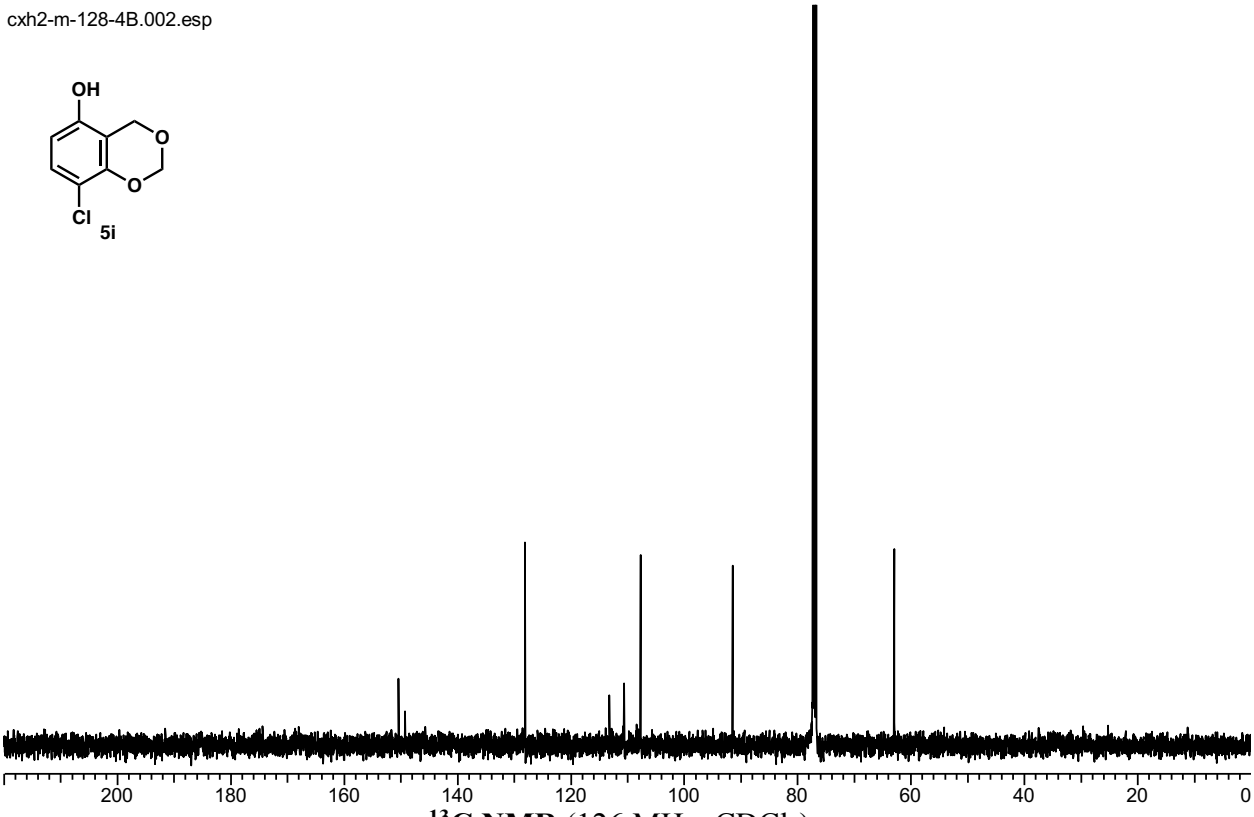
^{13}C NMR (126 MHz, $CDCl_3$)



5i

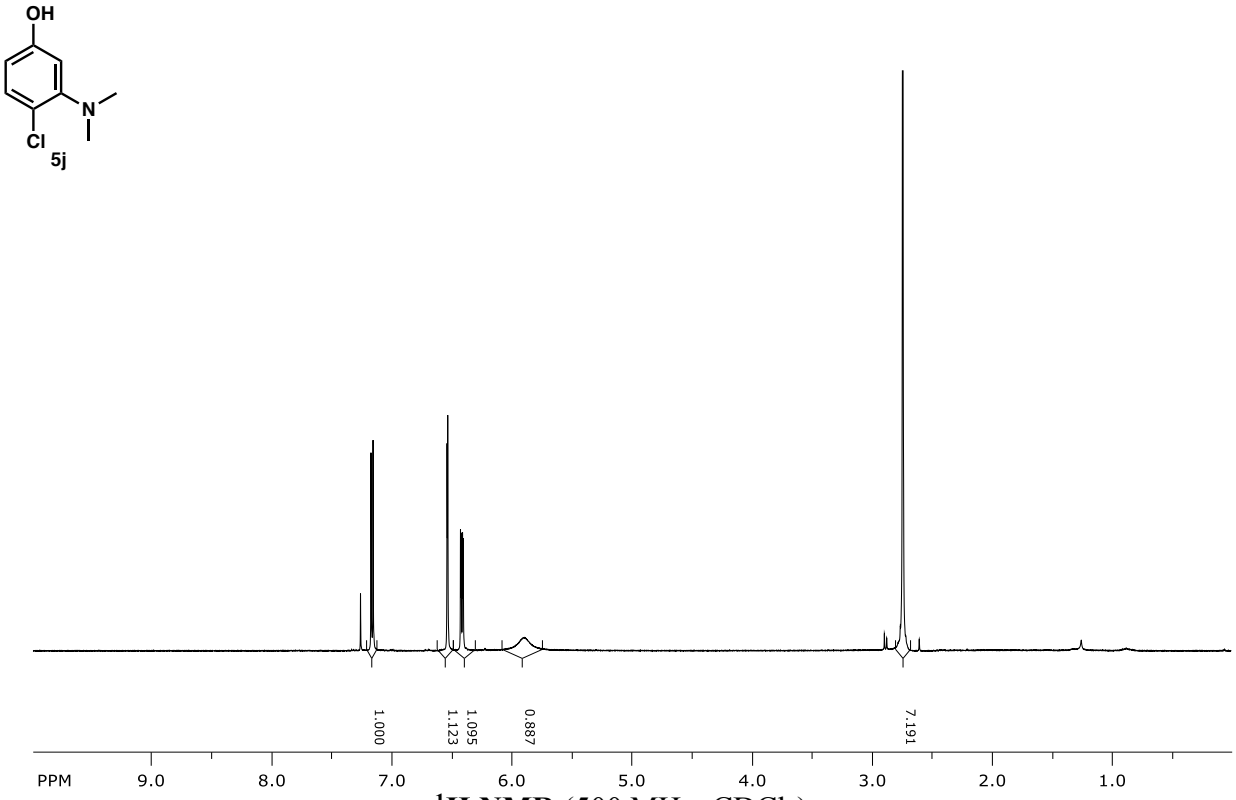


^{1}H NMR (500 MHz, $CDCl_3$)

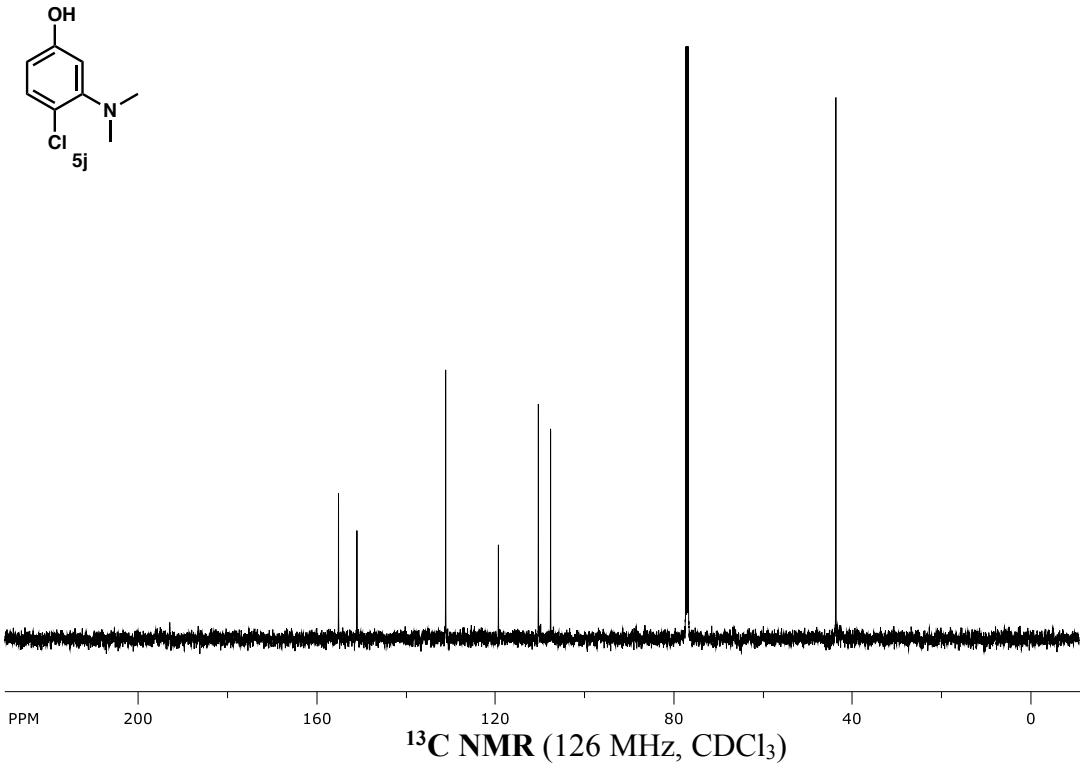


5i

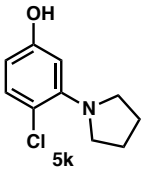
^{13}C NMR (126 MHz, $CDCl_3$)

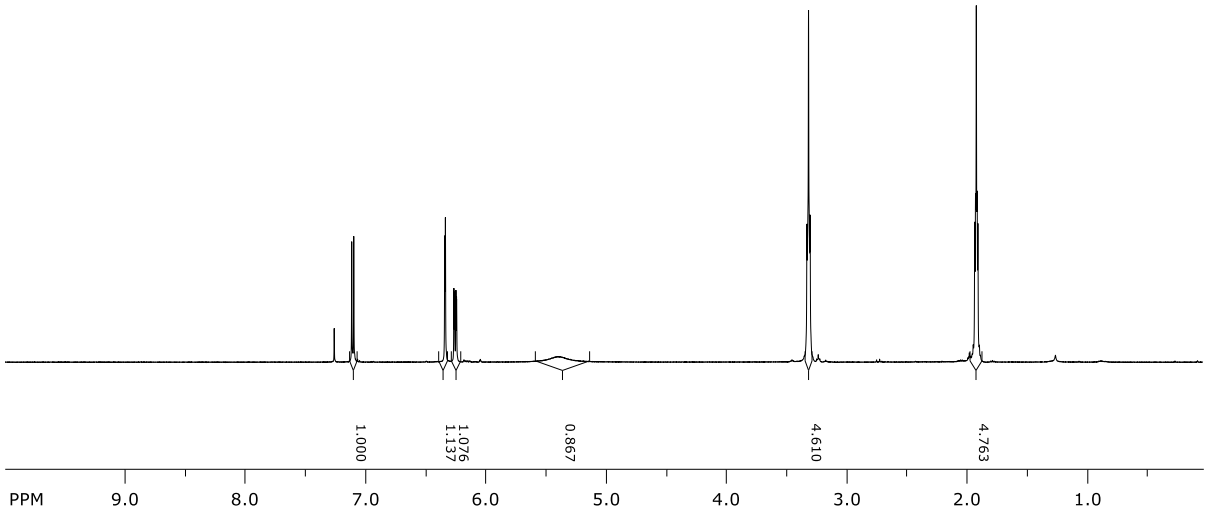


^{1}H NMR (500 MHz, $CDCl_3$)

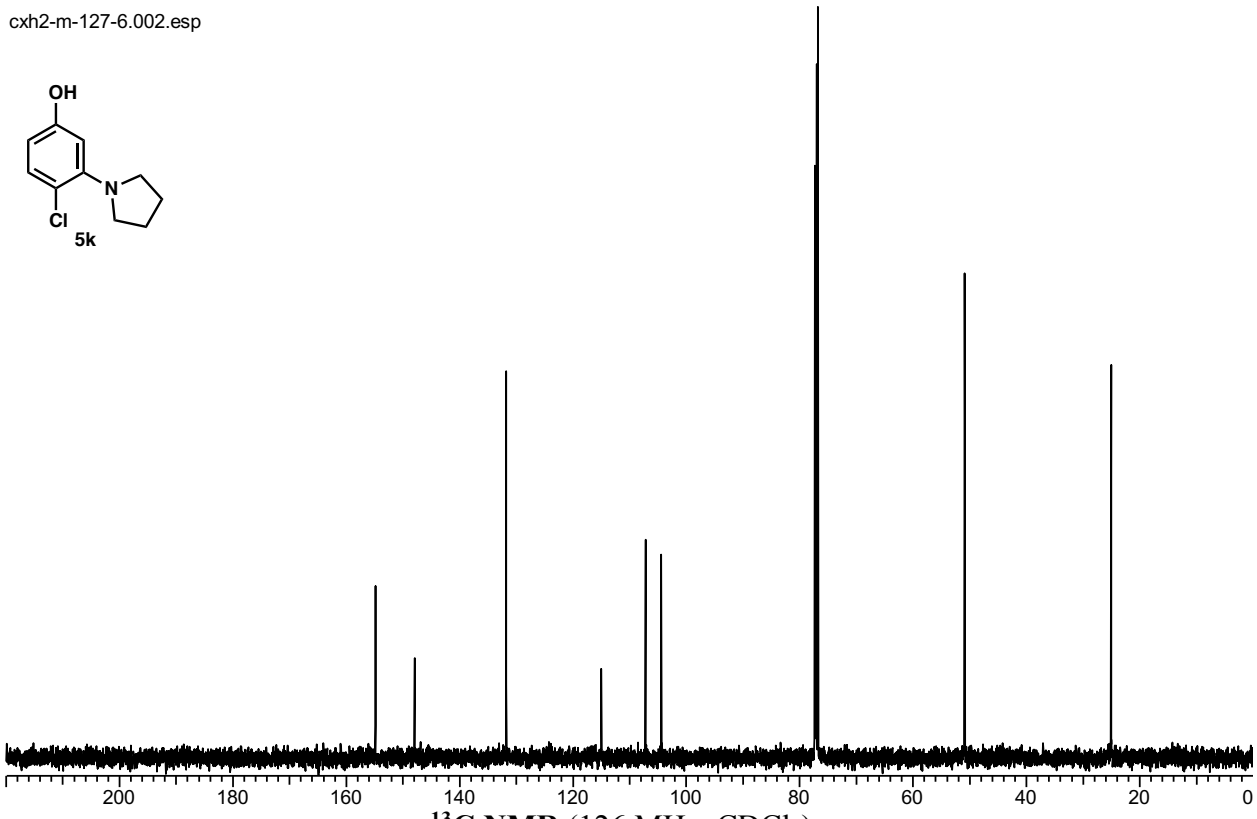


^{13}C NMR (126 MHz, $CDCl_3$)

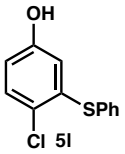


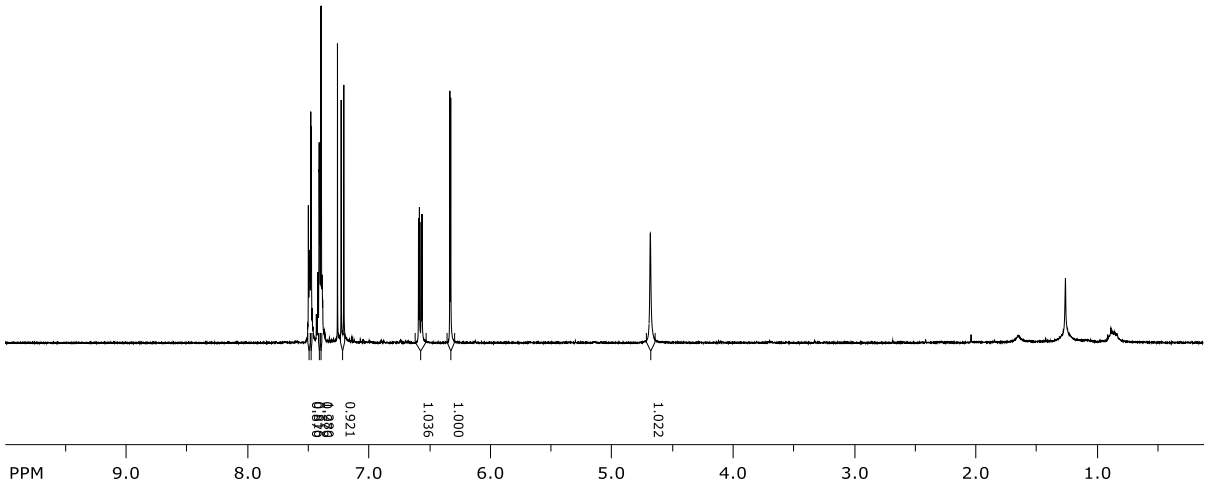


^{1}H NMR (500 MHz, $CDCl_3$)

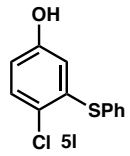


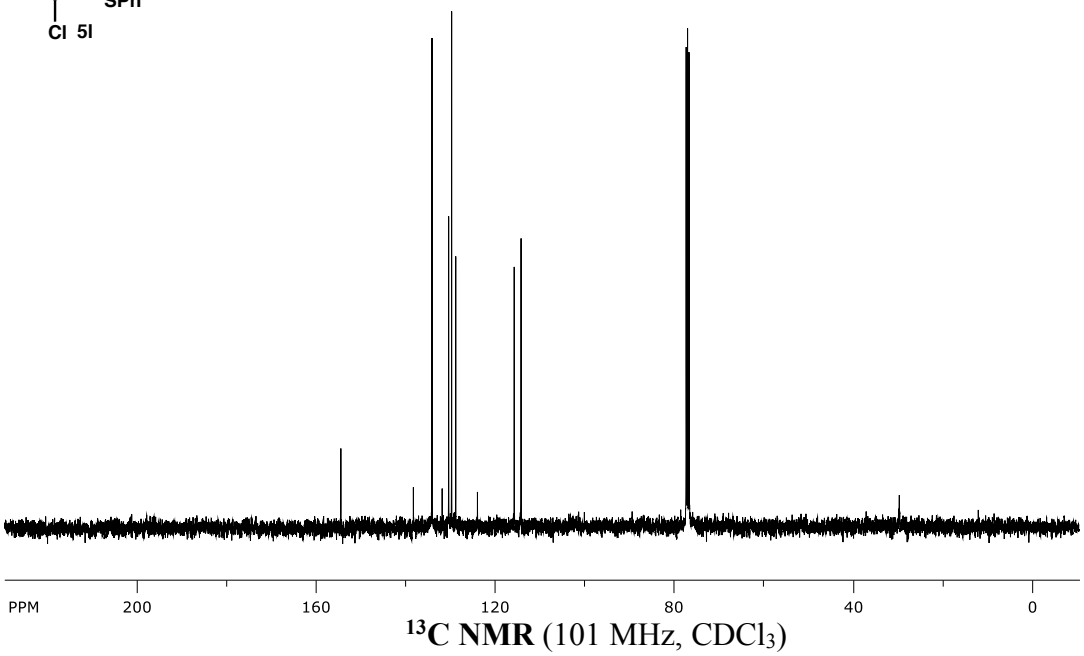
^{13}C NMR (126 MHz, $CDCl_3$)



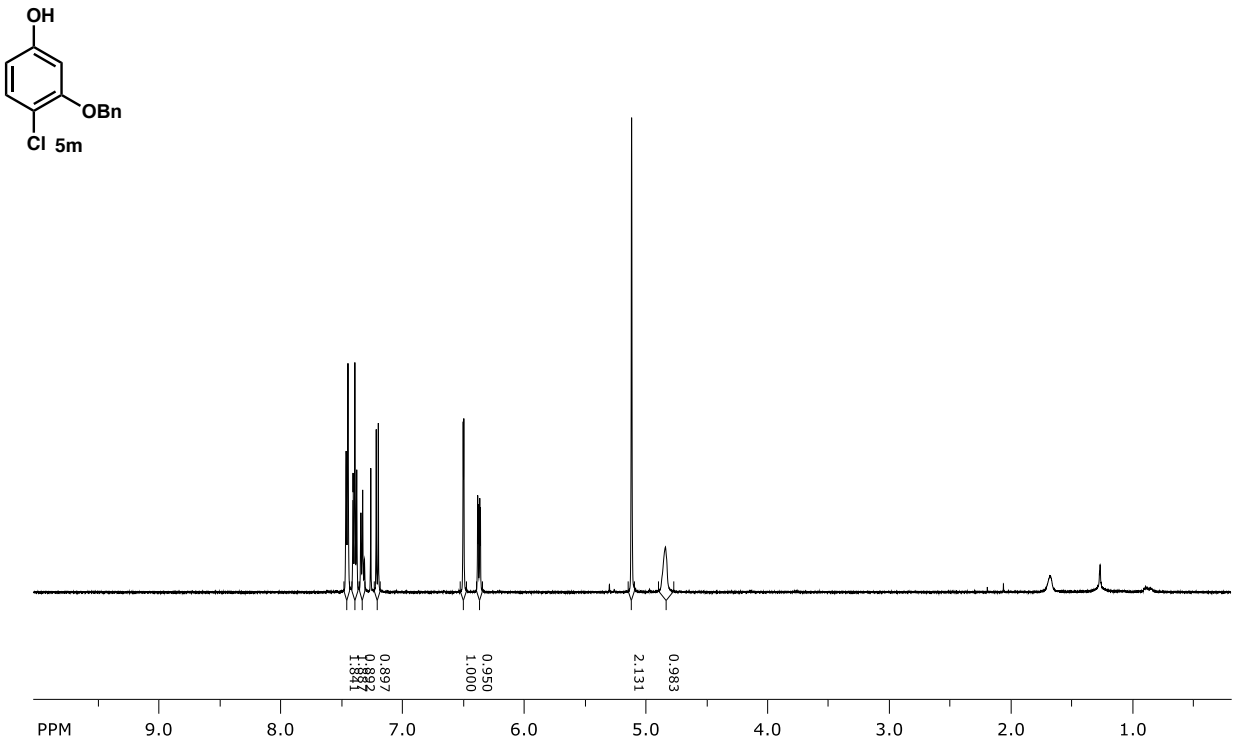


^{1}H NMR (400 MHz, $CDCl_3$)

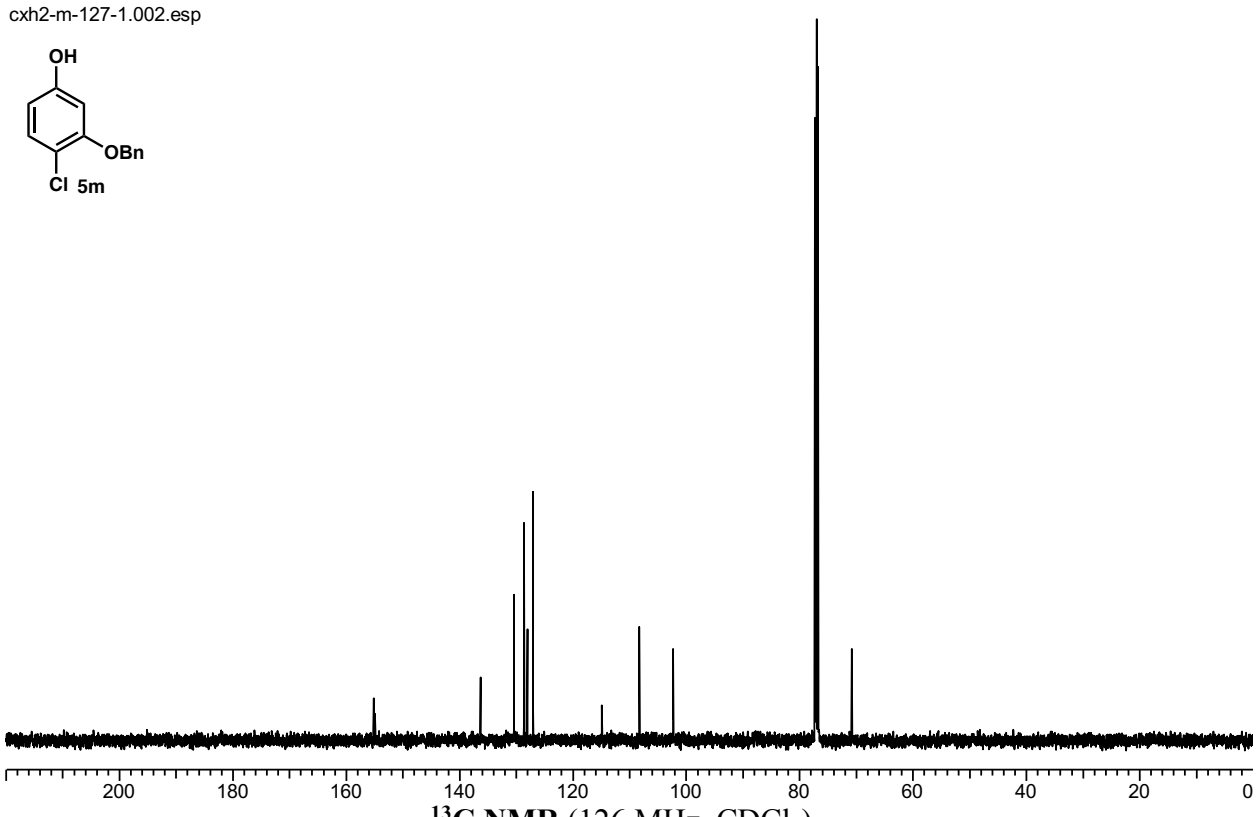




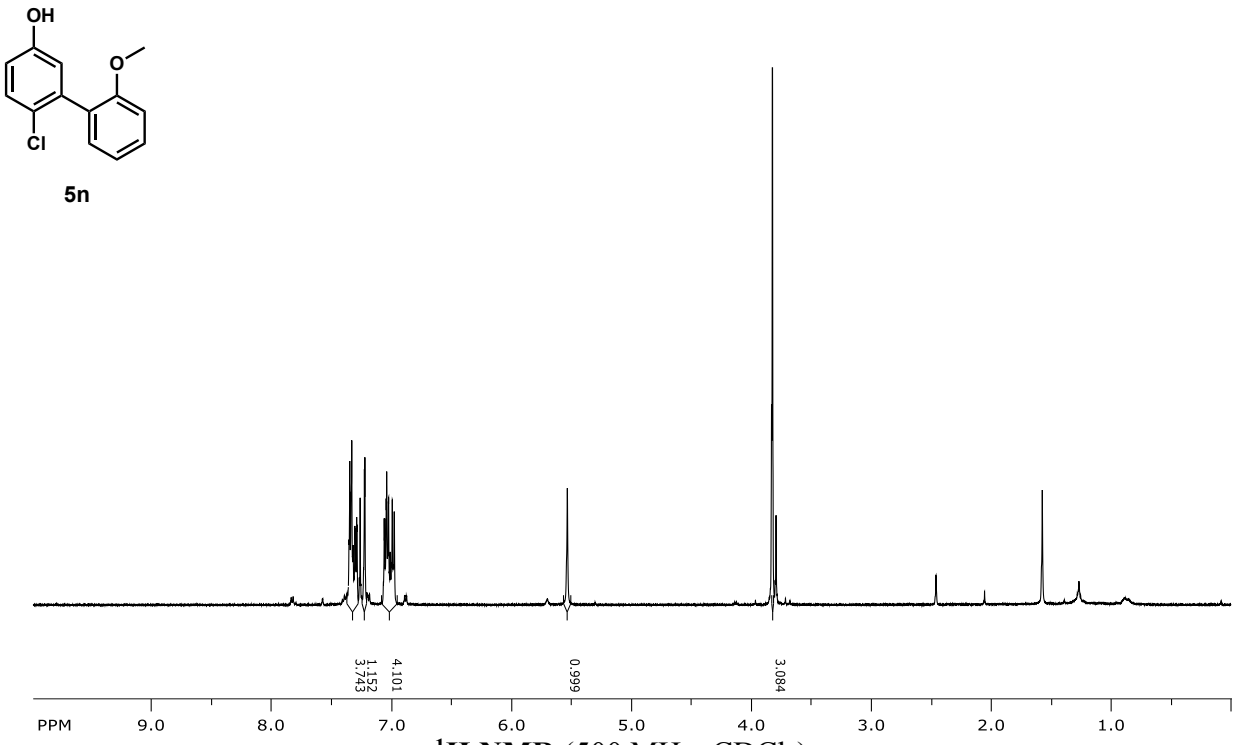
^{13}C NMR (101 MHz, $CDCl_3$)



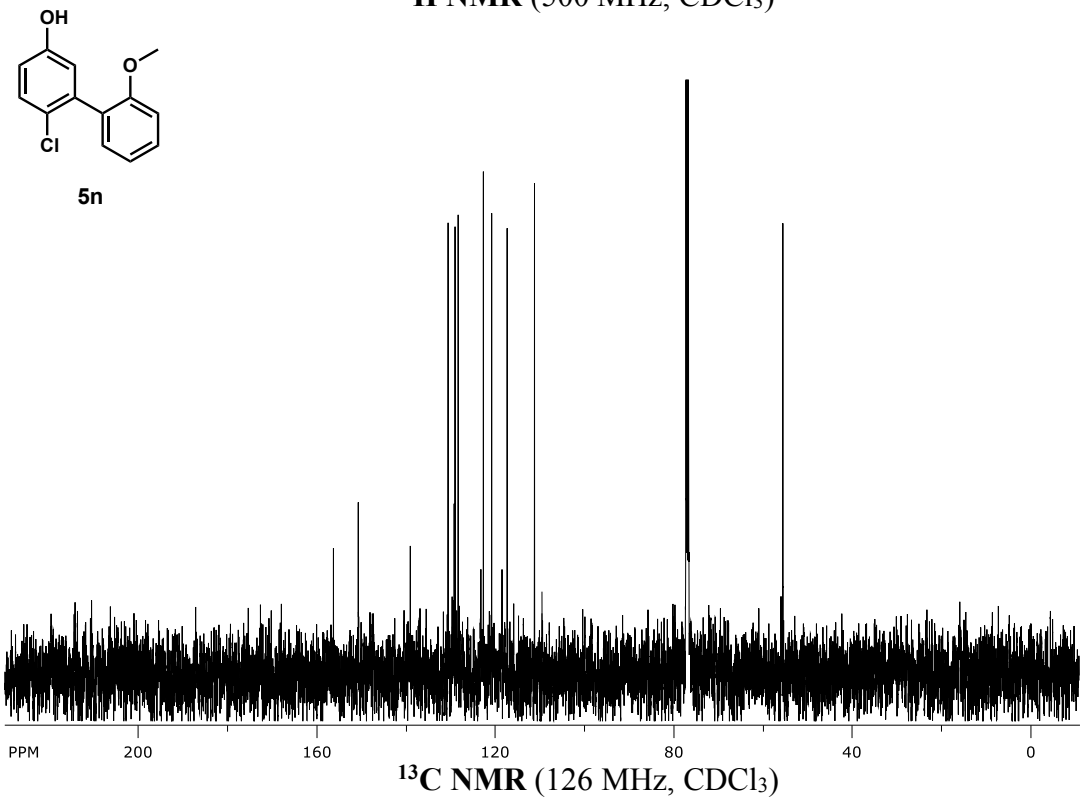
^{1}H NMR (500 MHz, $CDCl_3$)



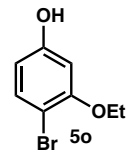
^{13}C NMR (126 MHz, $CDCl_3$)

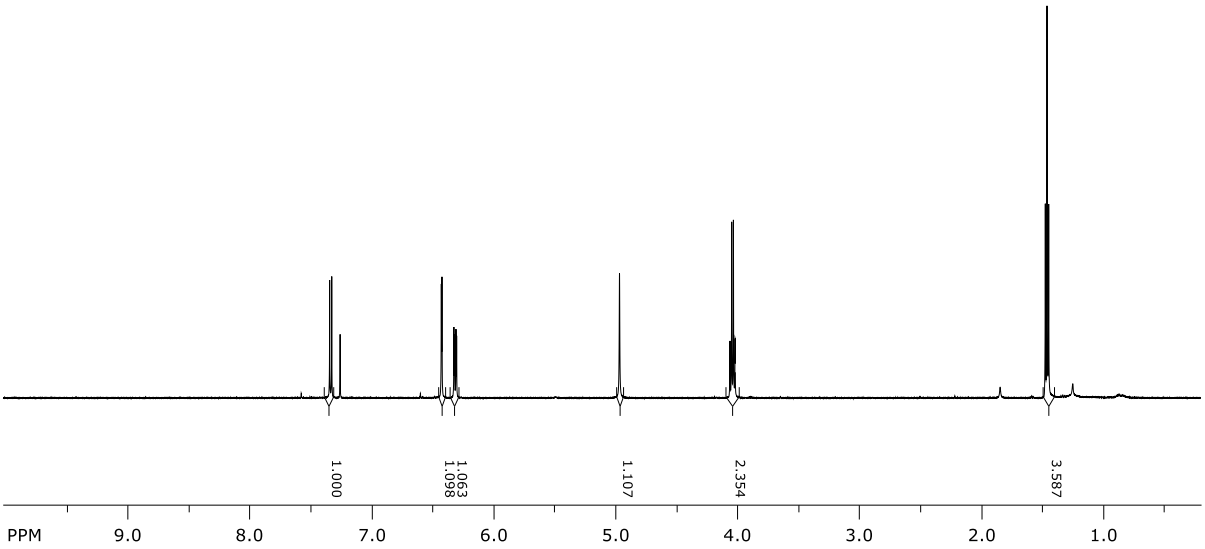


^{1}H NMR (500 MHz, $CDCl_3$)

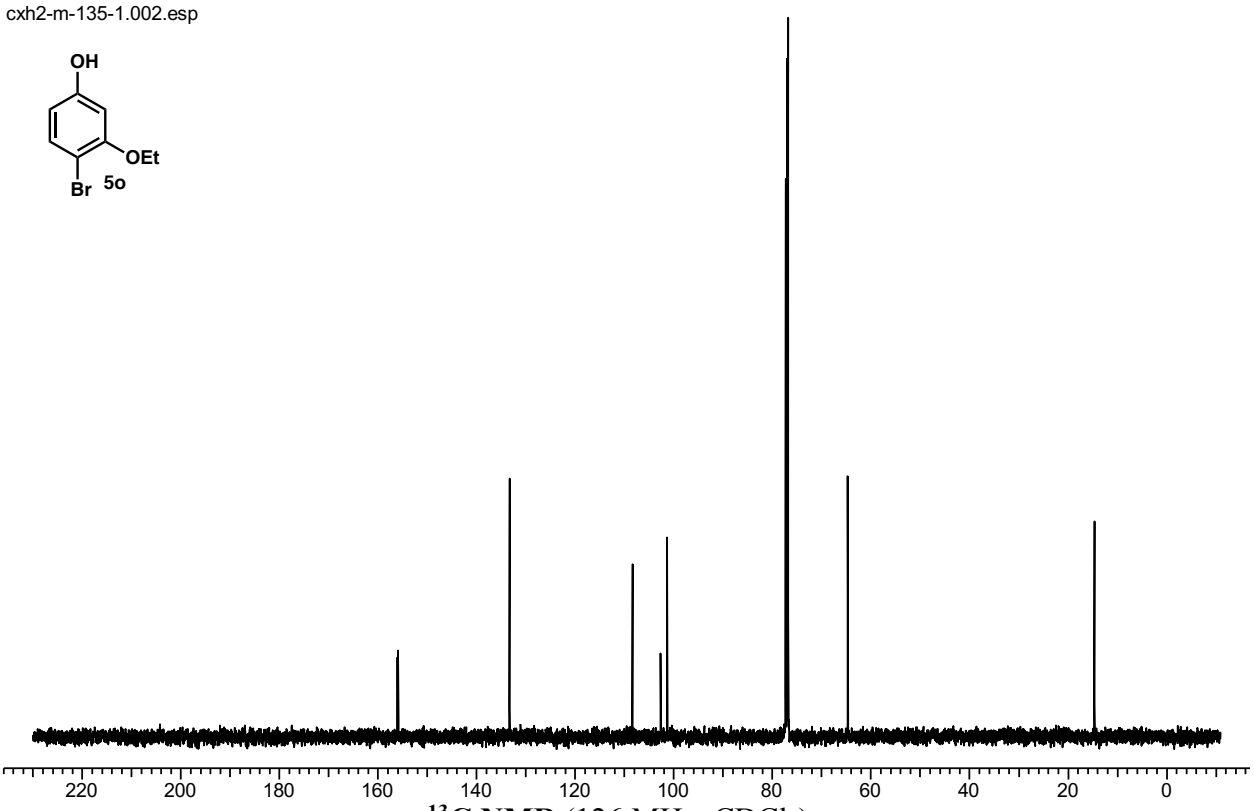


^{13}C NMR (126 MHz, $CDCl_3$)

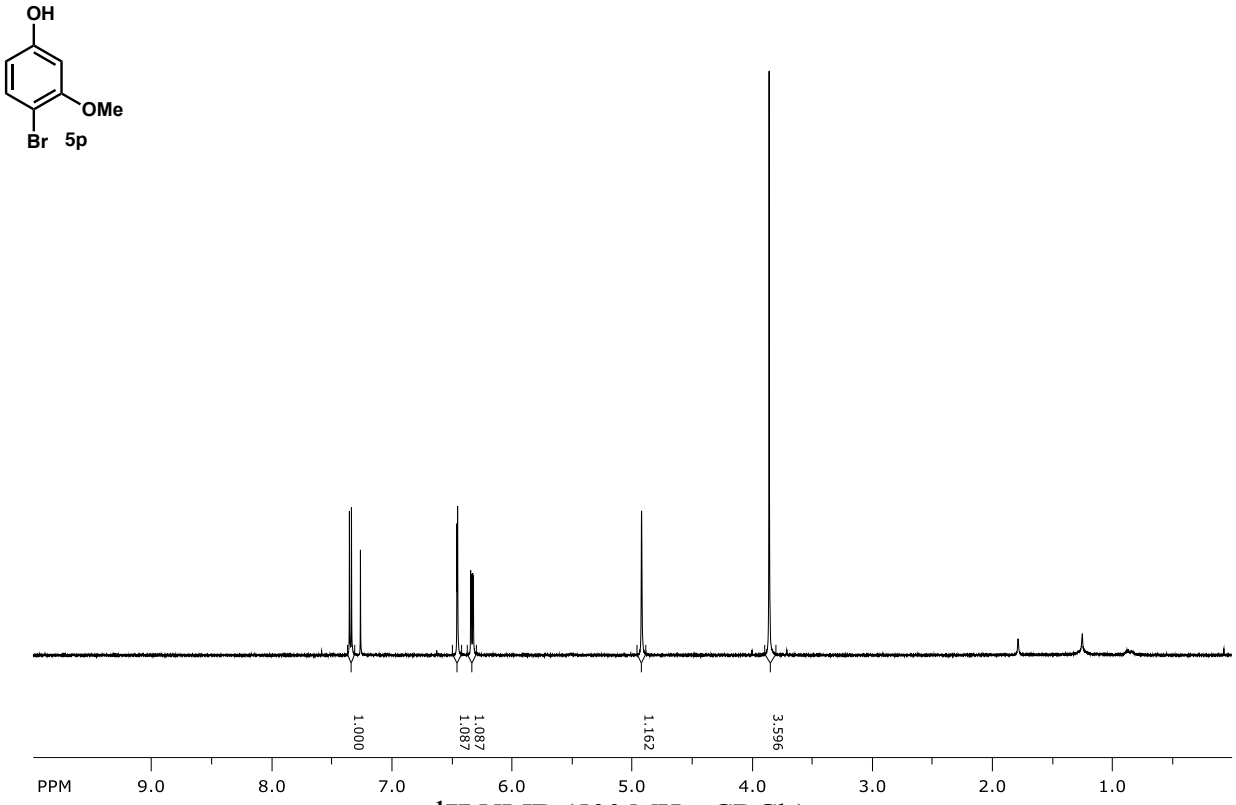




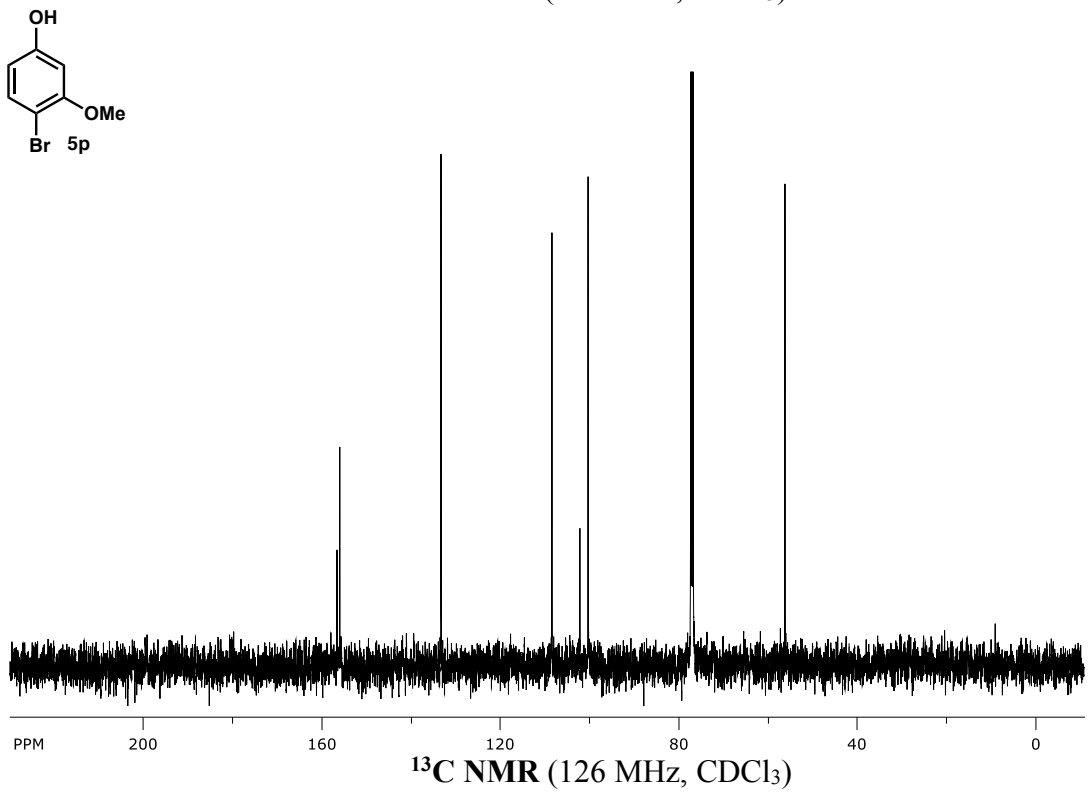
^{1}H NMR (500 MHz, $CDCl_3$)



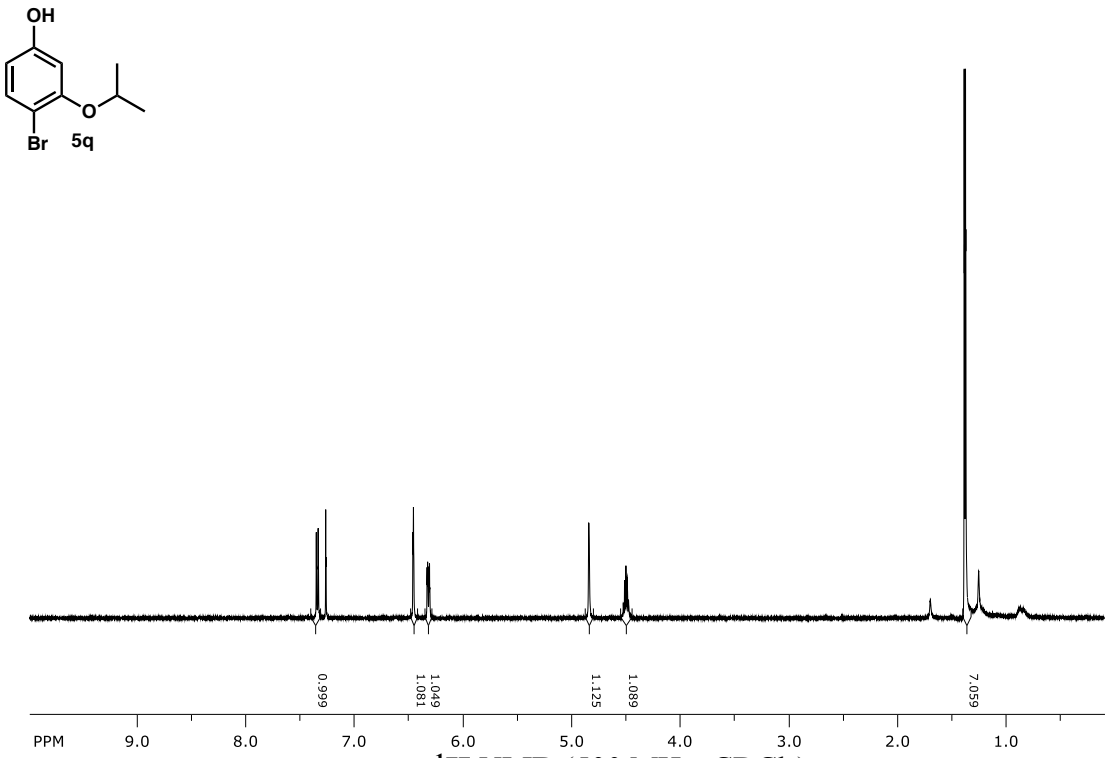
^{13}C NMR (126 MHz, $CDCl_3$)



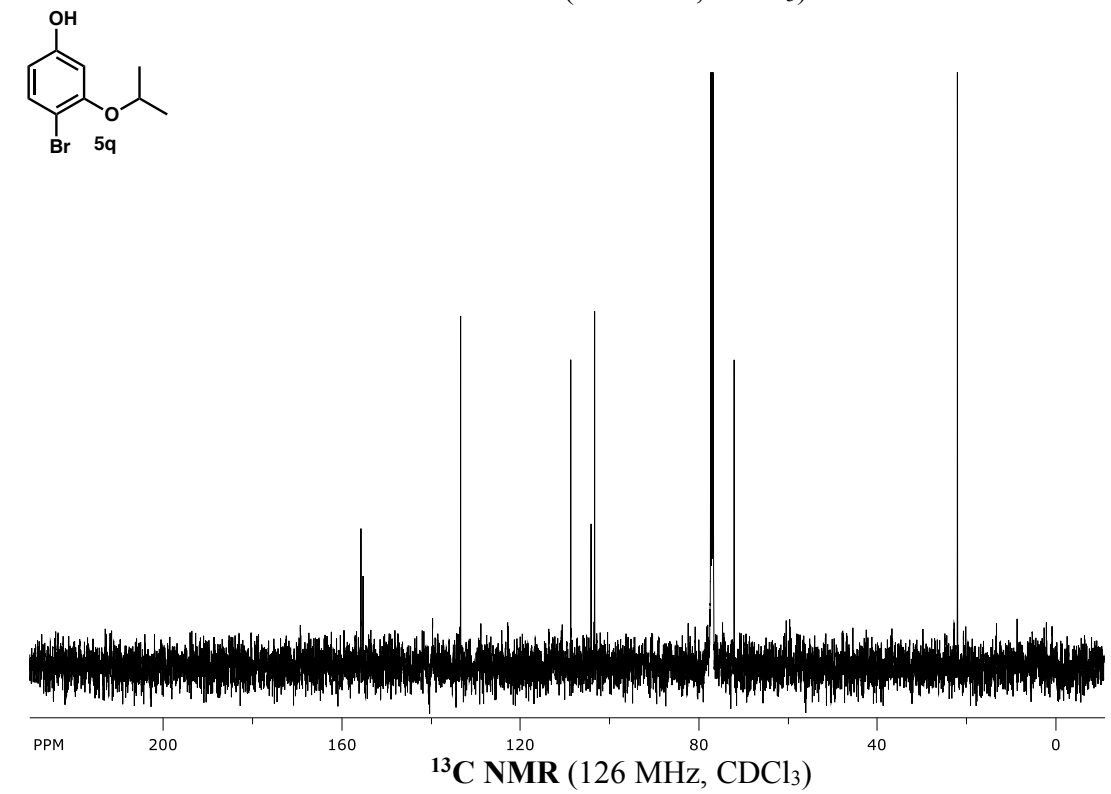
^{1}H NMR (500 MHz, $CDCl_3$)



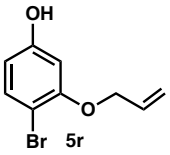
^{13}C NMR (126 MHz, $CDCl_3$)

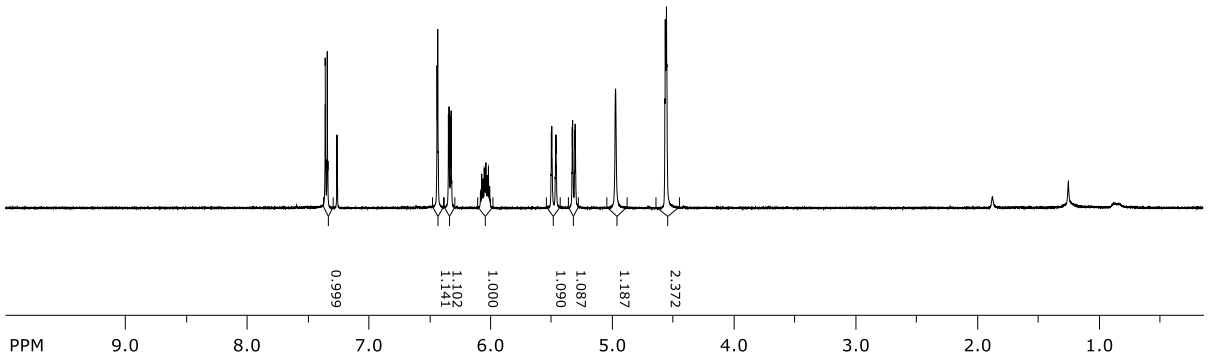


^{1}H NMR (500 MHz, $CDCl_3$)

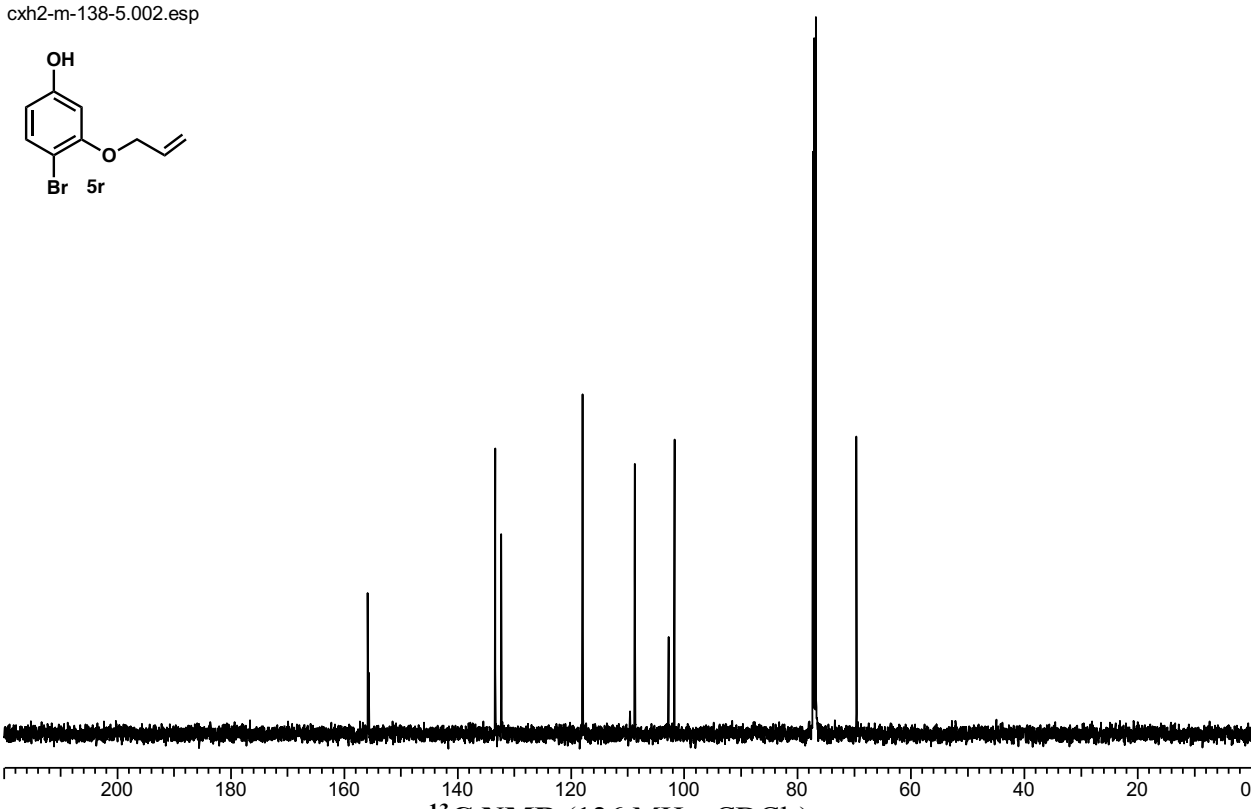


^{13}C NMR (126 MHz, $CDCl_3$)

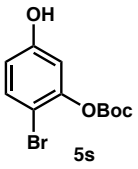




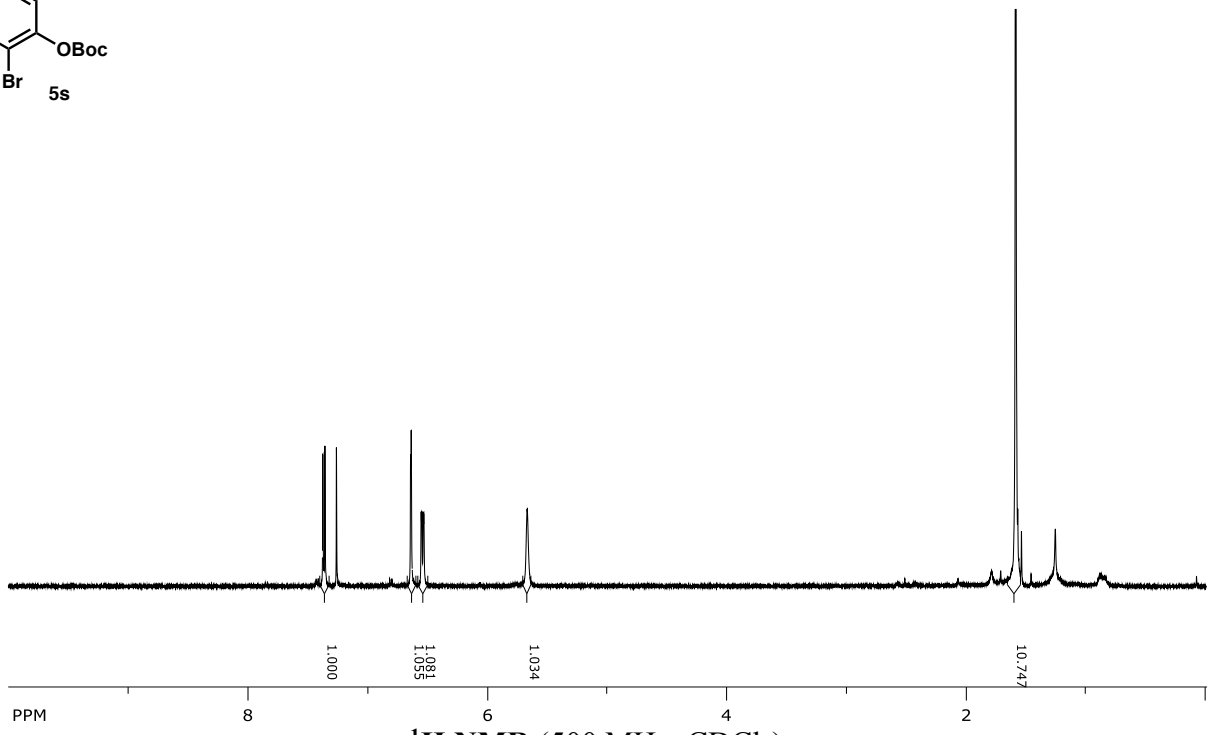
^{1}H NMR (500 MHz, $CDCl_3$)



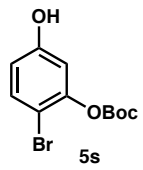
^{13}C NMR (126 MHz, $CDCl_3$)



5s

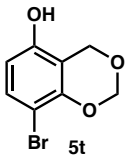


^{1}H NMR (500 MHz, $CDCl_3$)



5s

^{13}C NMR (126 MHz, $CDCl_3$)



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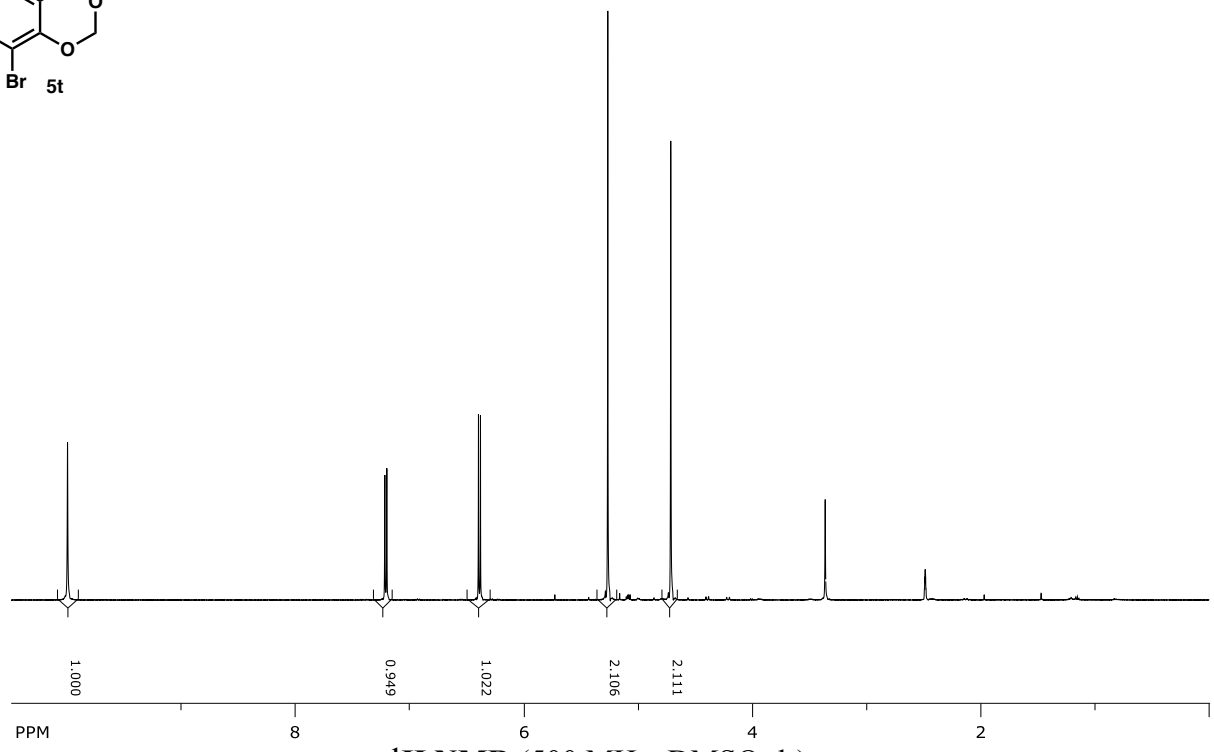
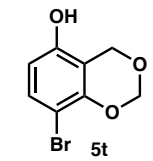


^{1}H NMR (500 MHz, DMSO-d_6)



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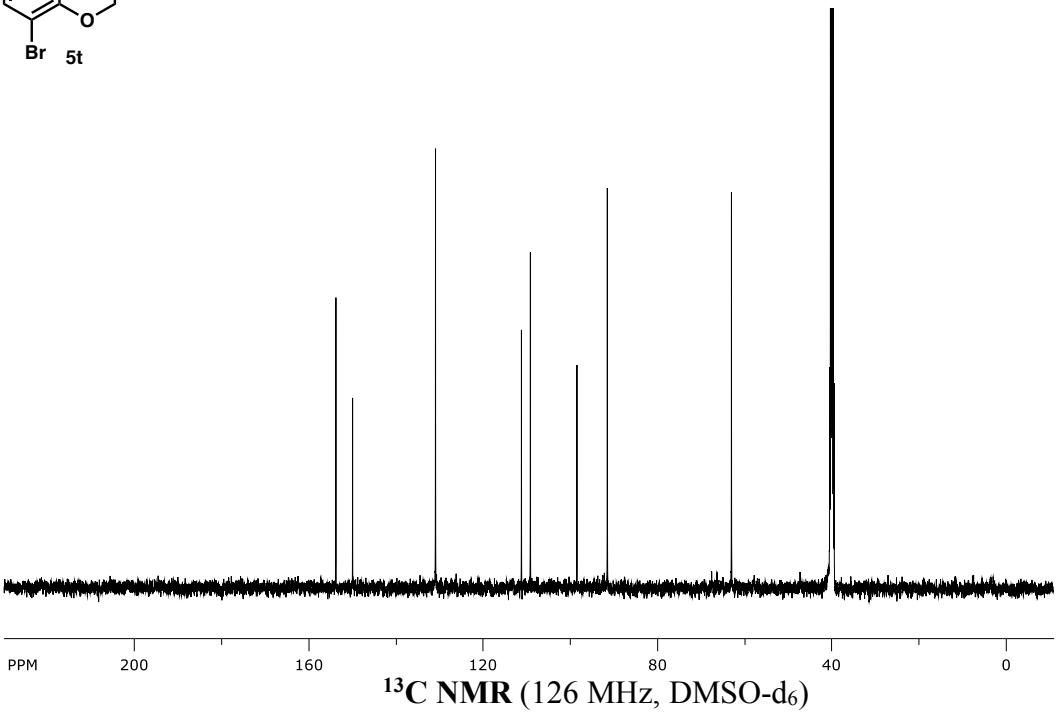
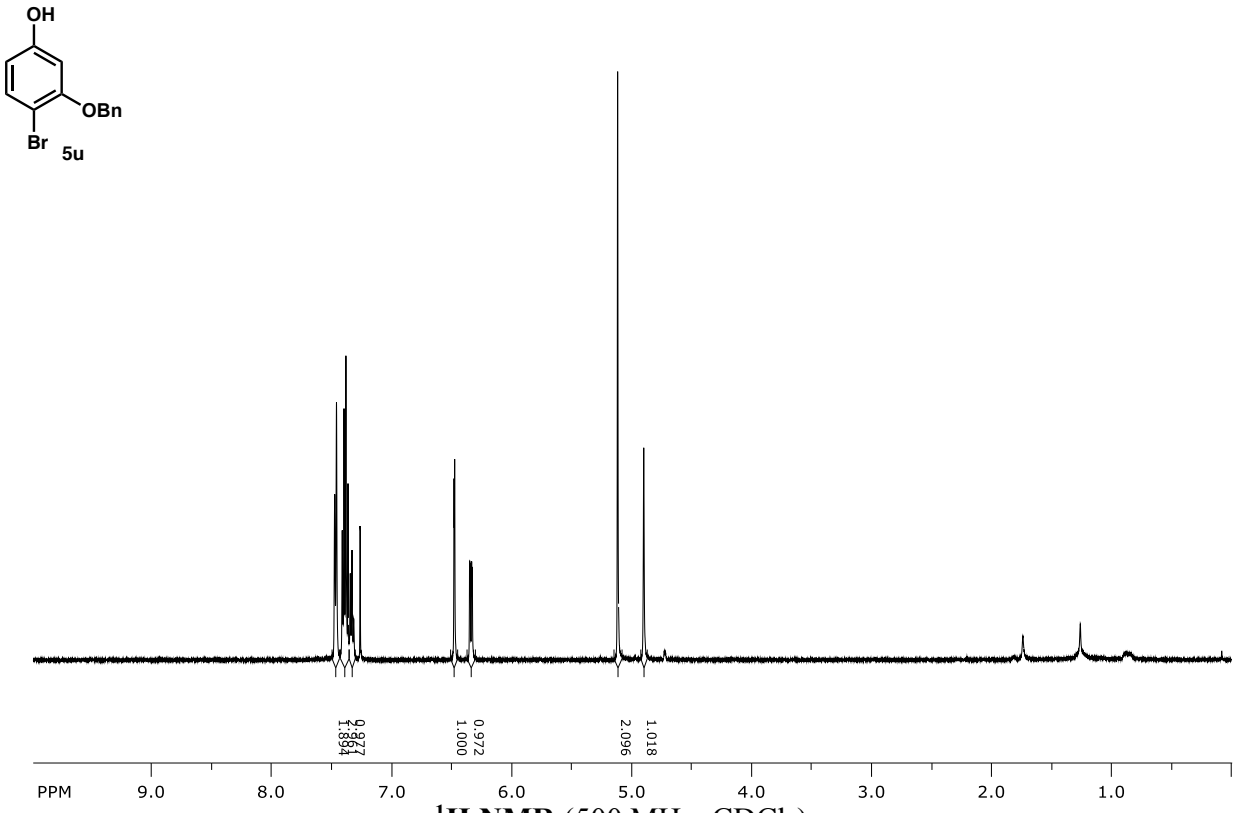
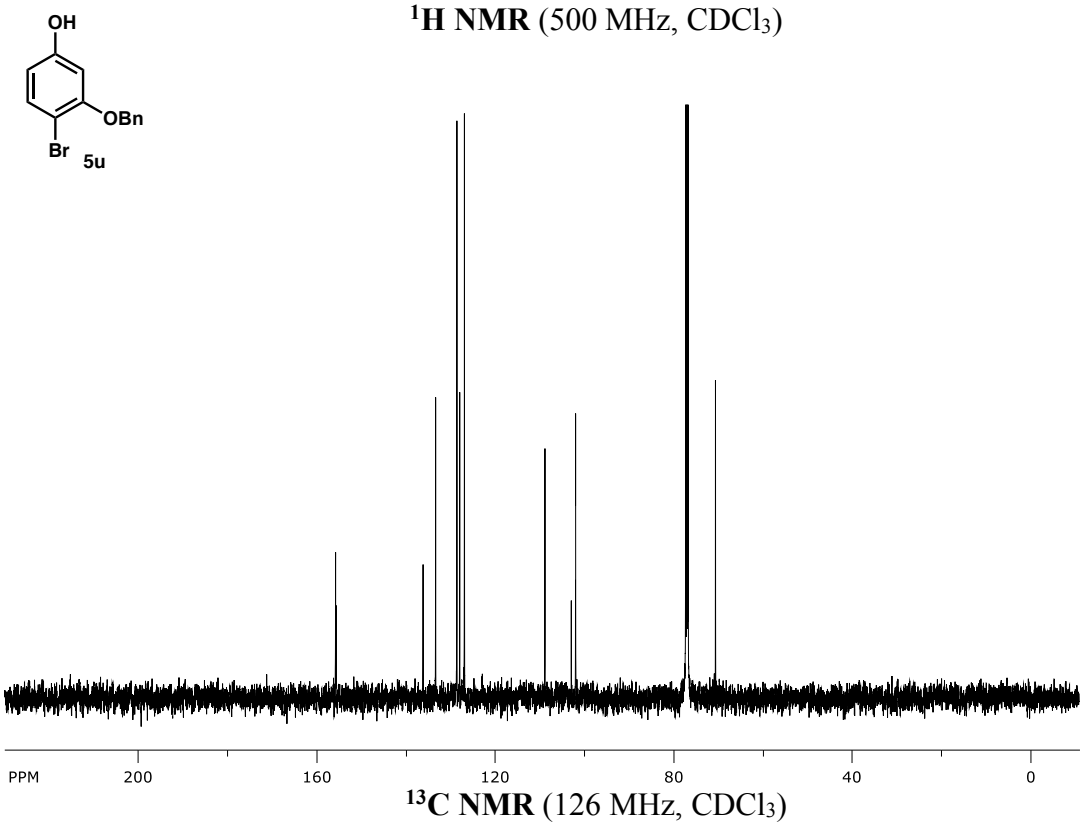


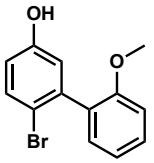
^{13}C NMR (126 MHz, DMSO-d_6)



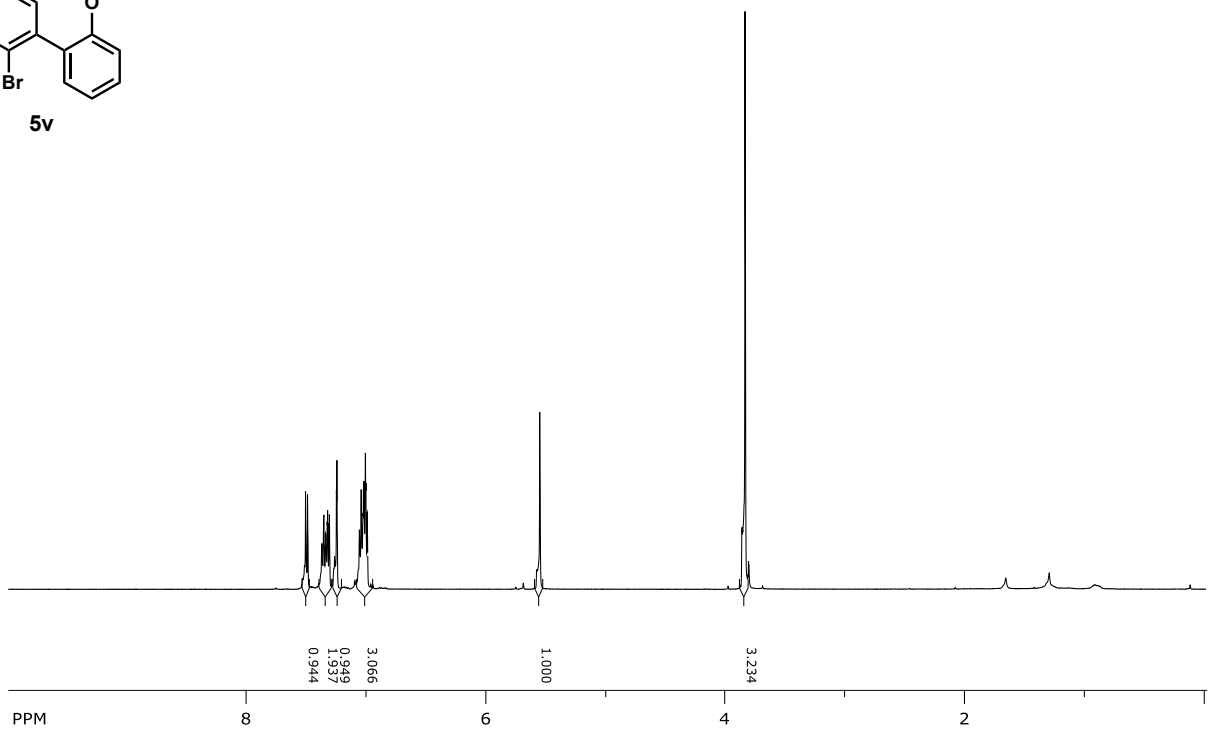
^{1}H NMR (500 MHz, $CDCl_3$)



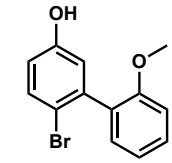
^{13}C NMR (126 MHz, $CDCl_3$)



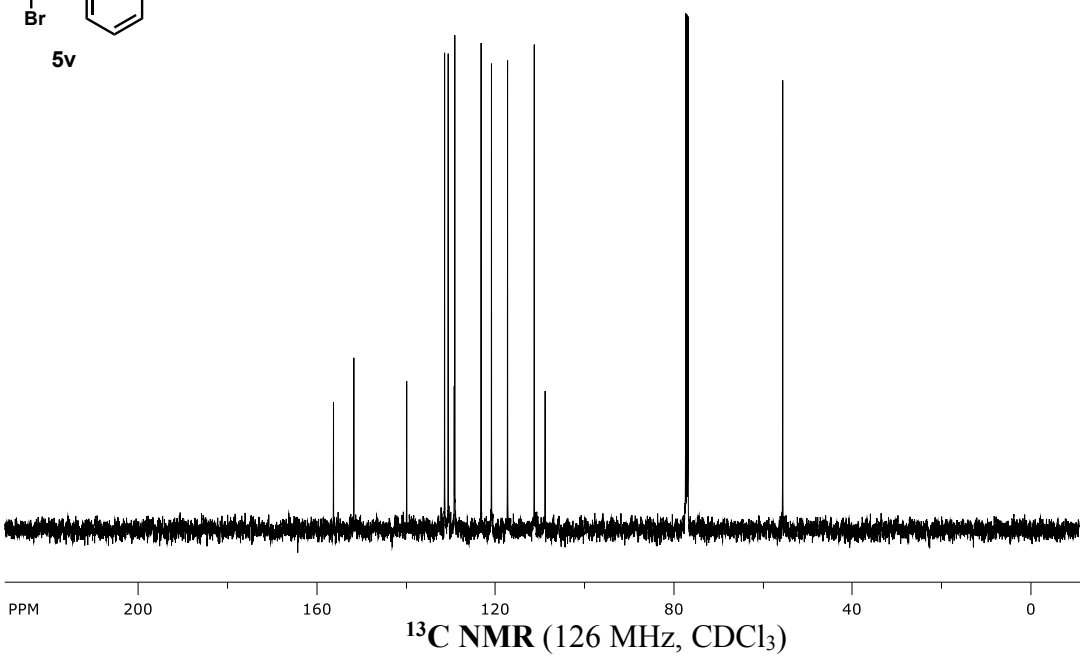
5v



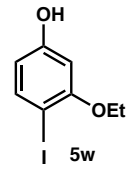
^{1}H NMR (500 MHz, $CDCl_3$)

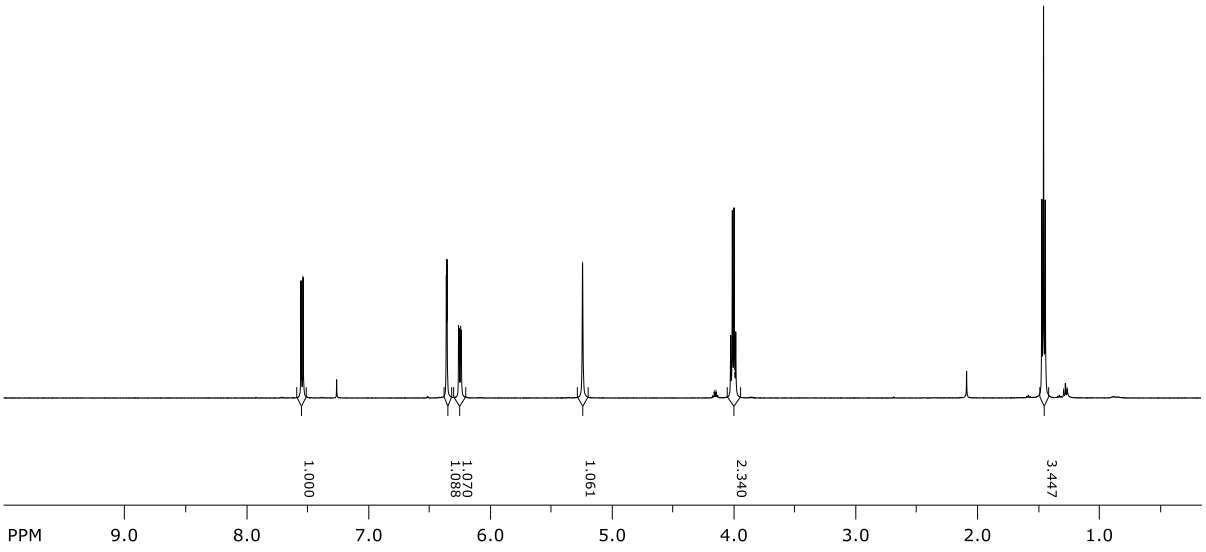


5v

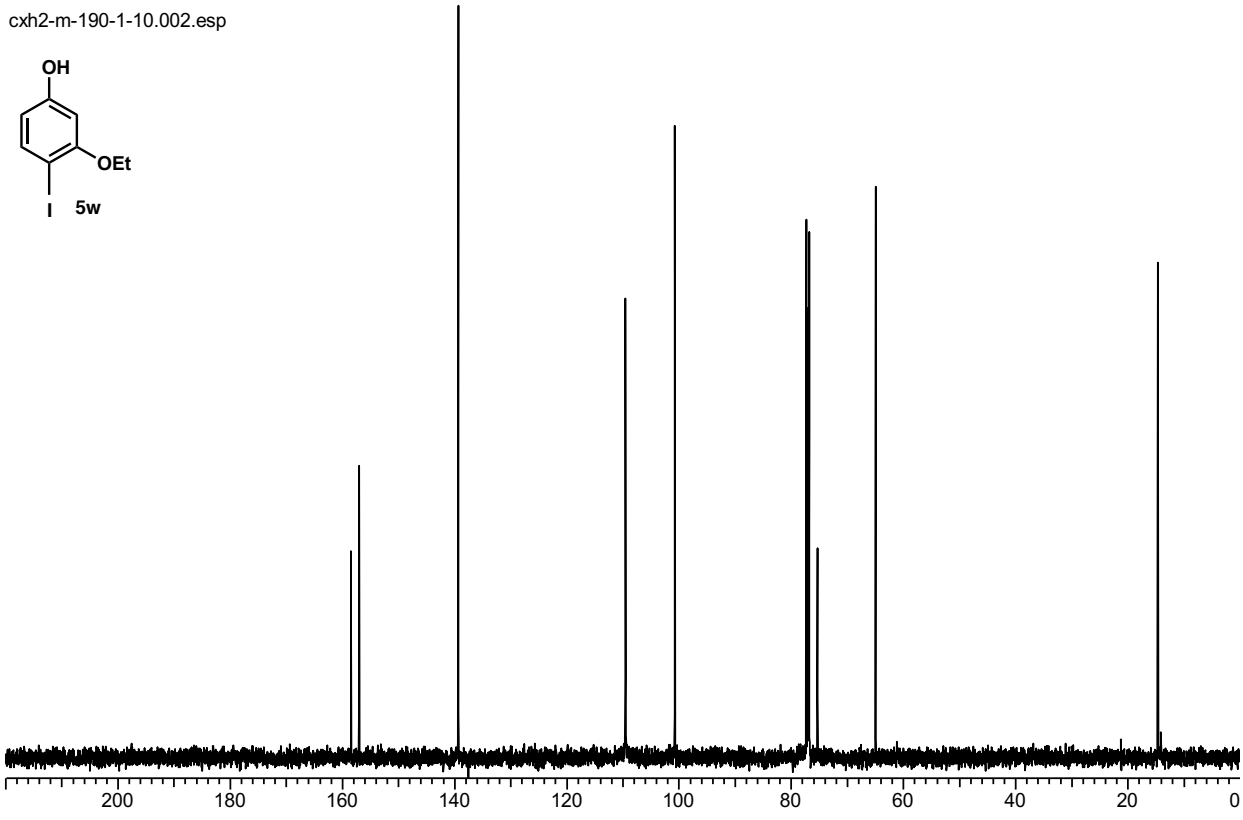


^{13}C NMR (126 MHz, $CDCl_3$)

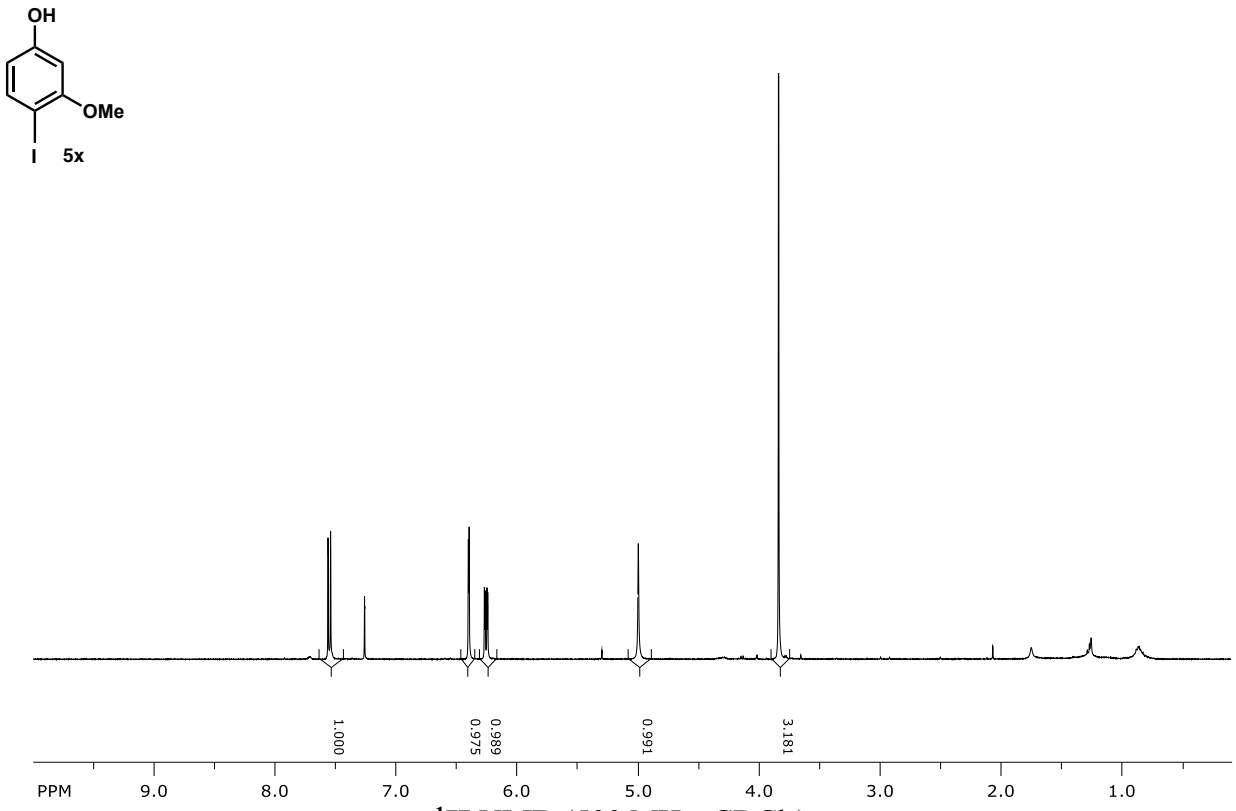




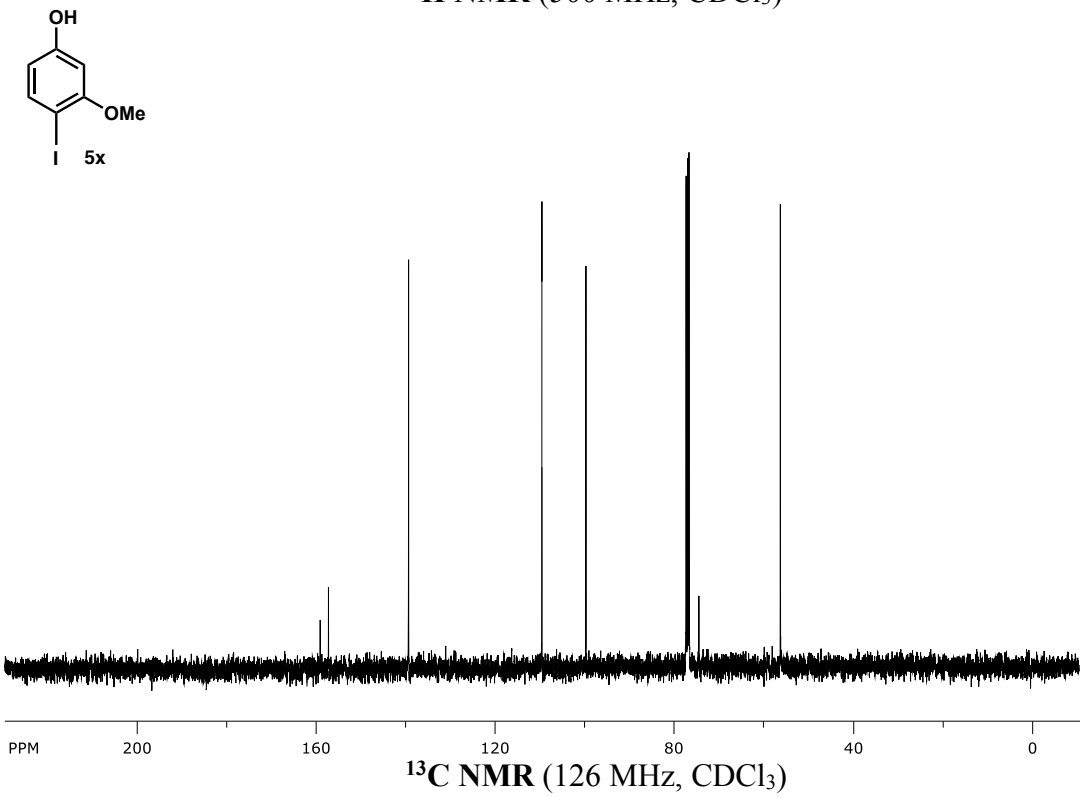
^{1}H NMR (500 MHz, $CDCl_3$)



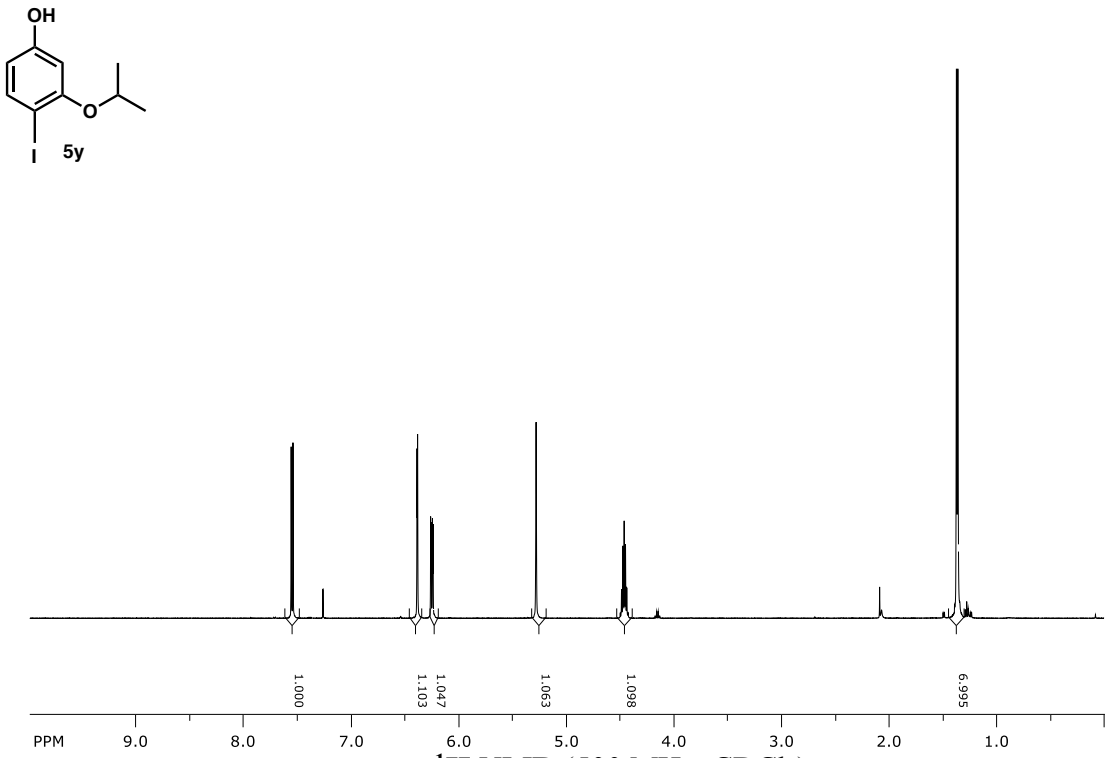
^{13}C NMR (126 MHz, $CDCl_3$)



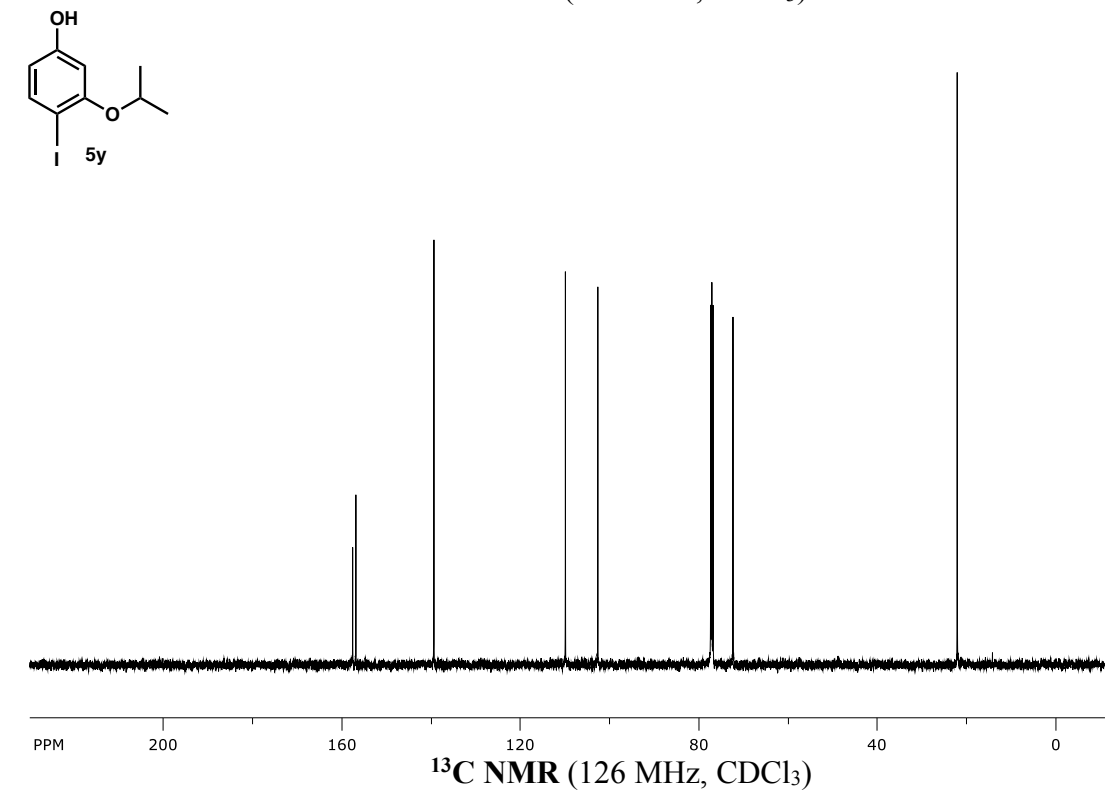
^{1}H NMR (500 MHz, $CDCl_3$)



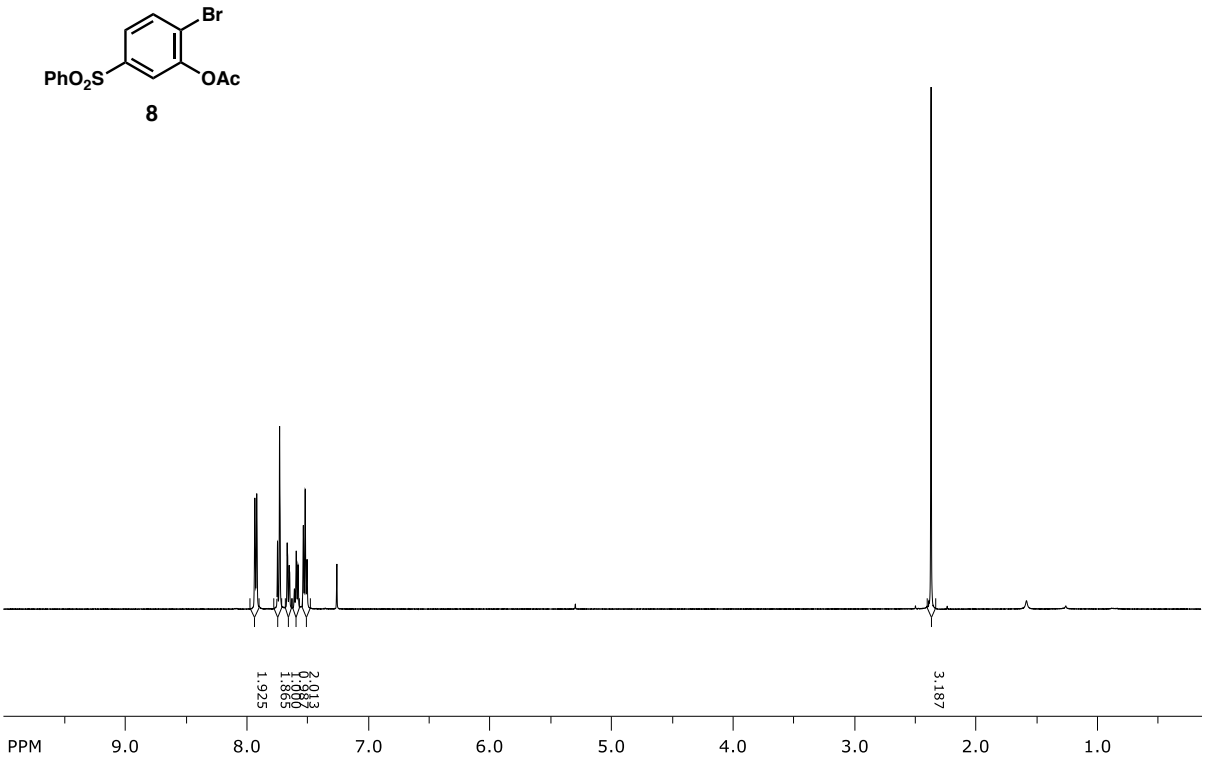
^{13}C NMR (126 MHz, $CDCl_3$)



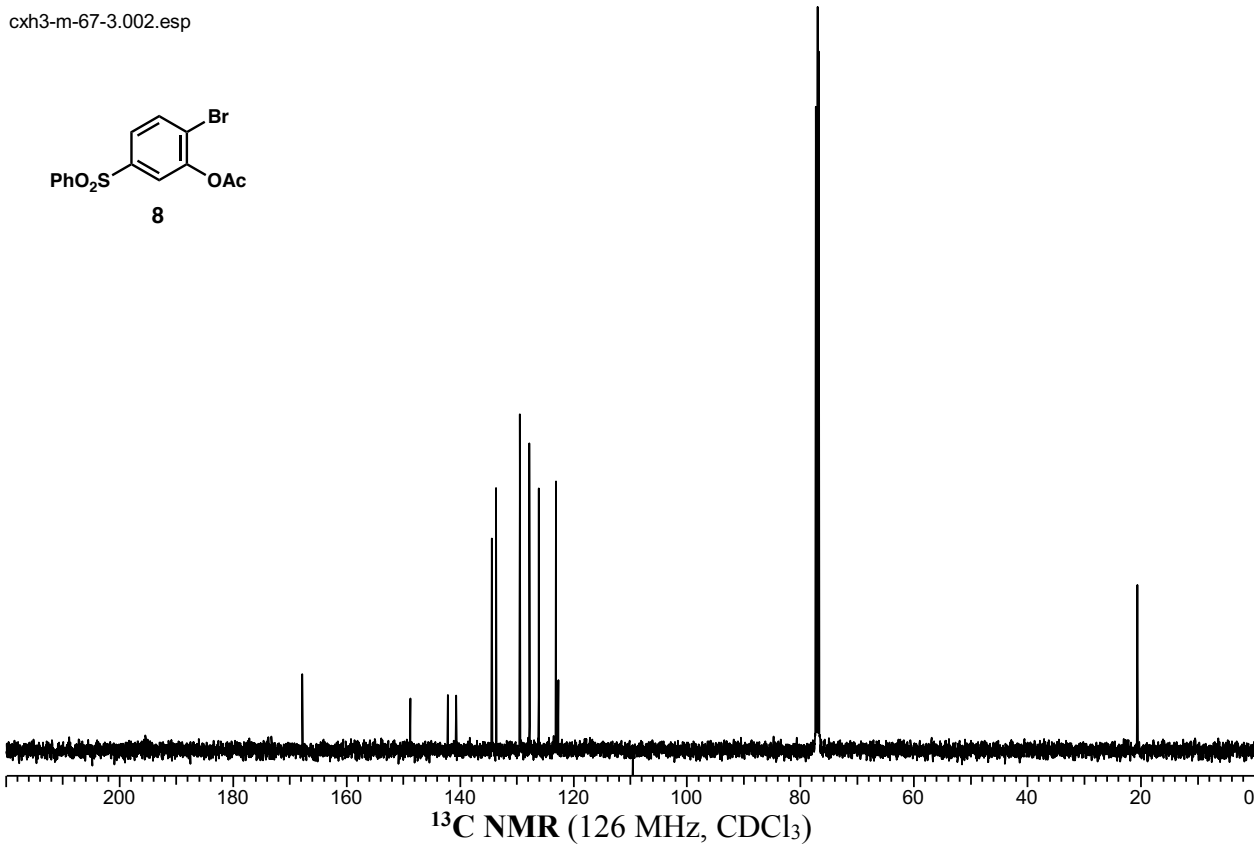
^{1}H NMR (500 MHz, $CDCl_3$)



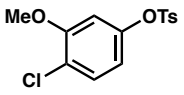
^{13}C NMR (126 MHz, $CDCl_3$)



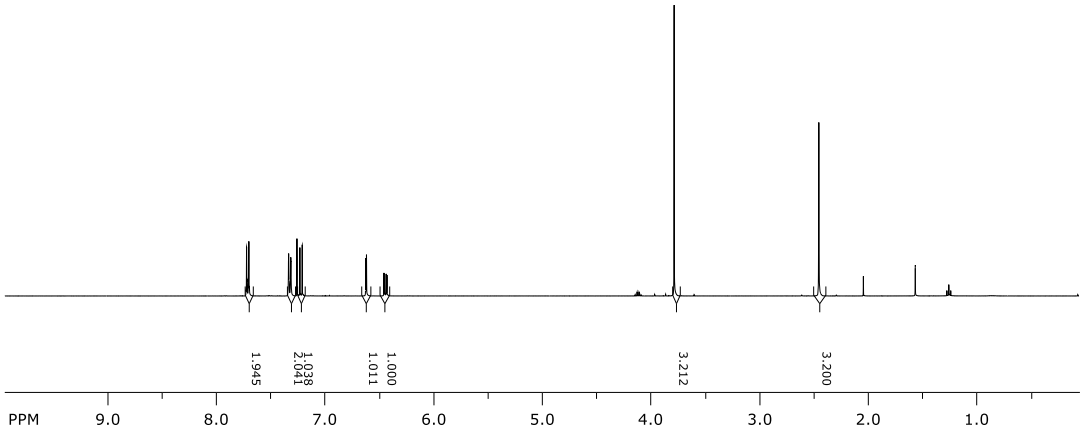
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)

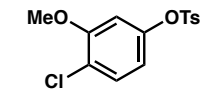


9a



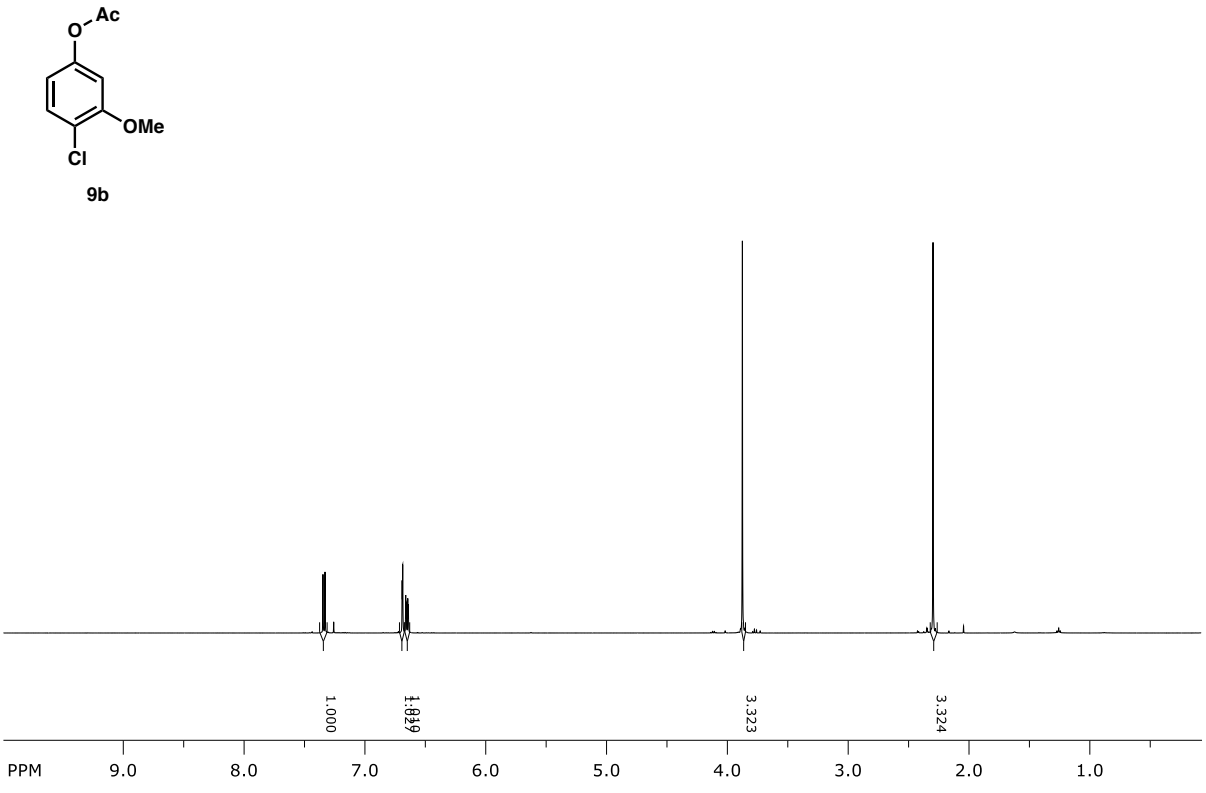
^{1}H NMR (400 MHz, $CDCl_3$)

cxh2-m-114-1.002.esp

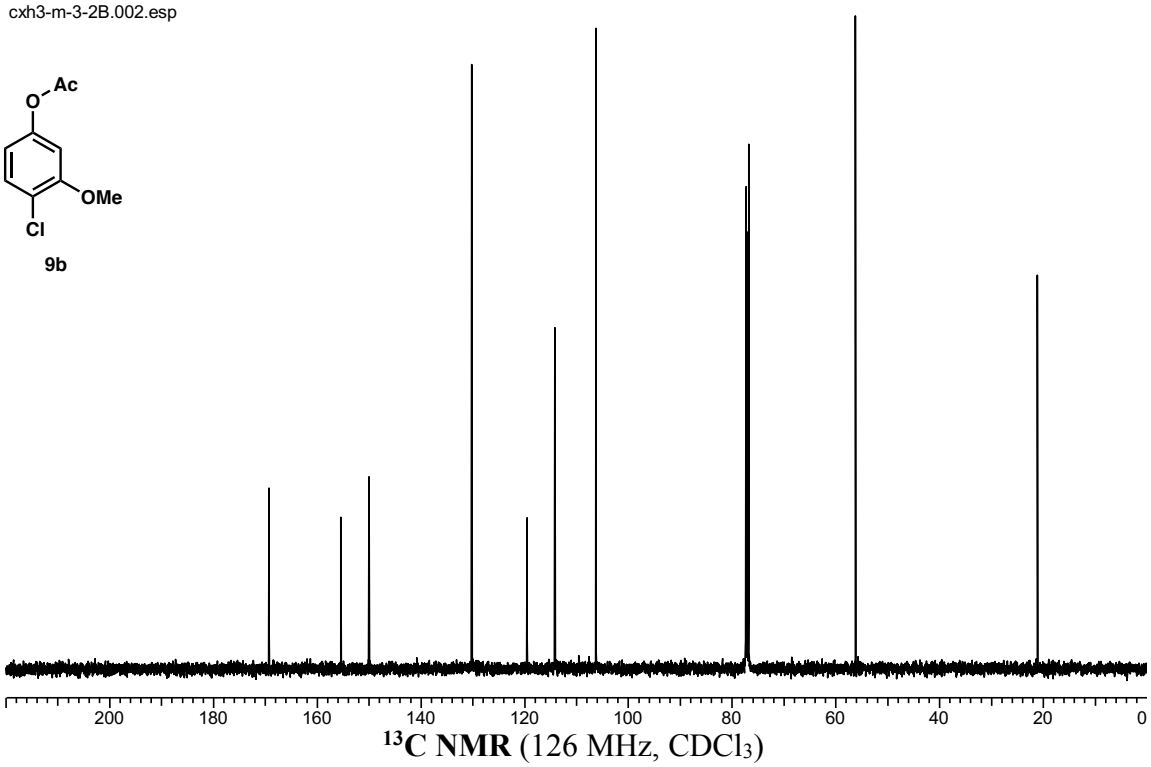


9a

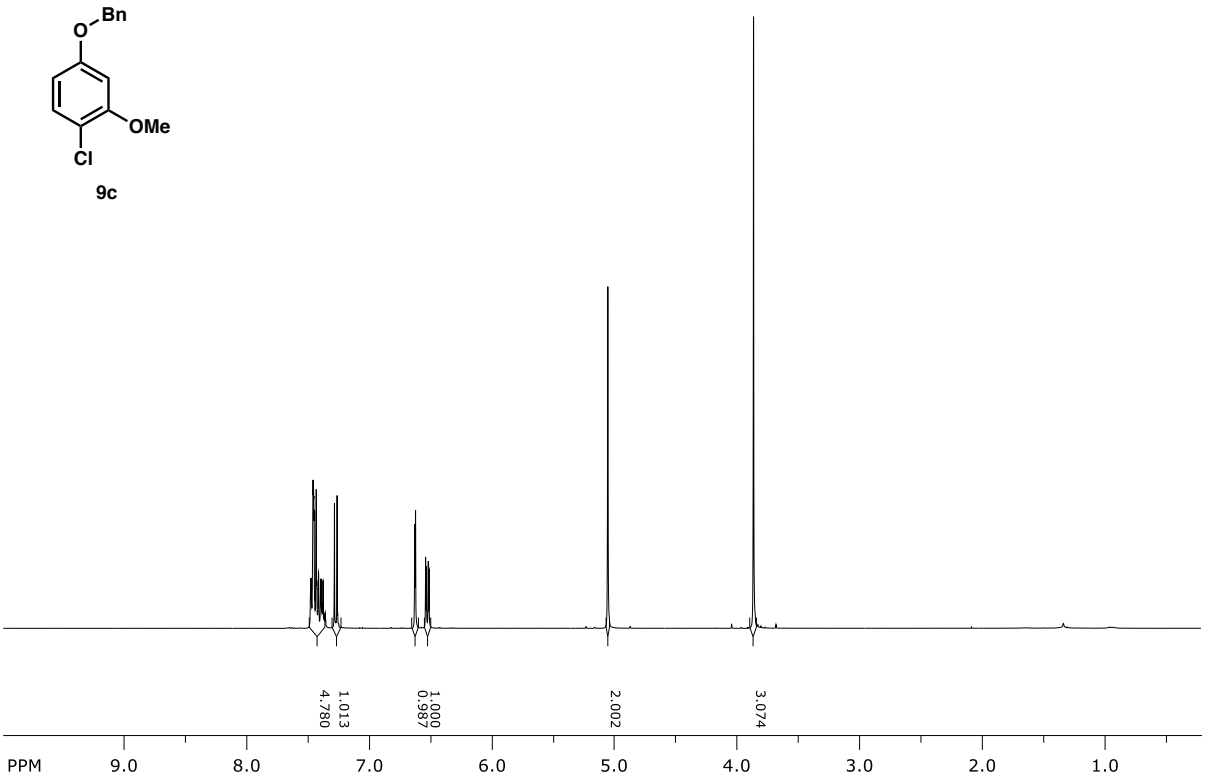
^{13}C NMR (101 MHz, $CDCl_3$)



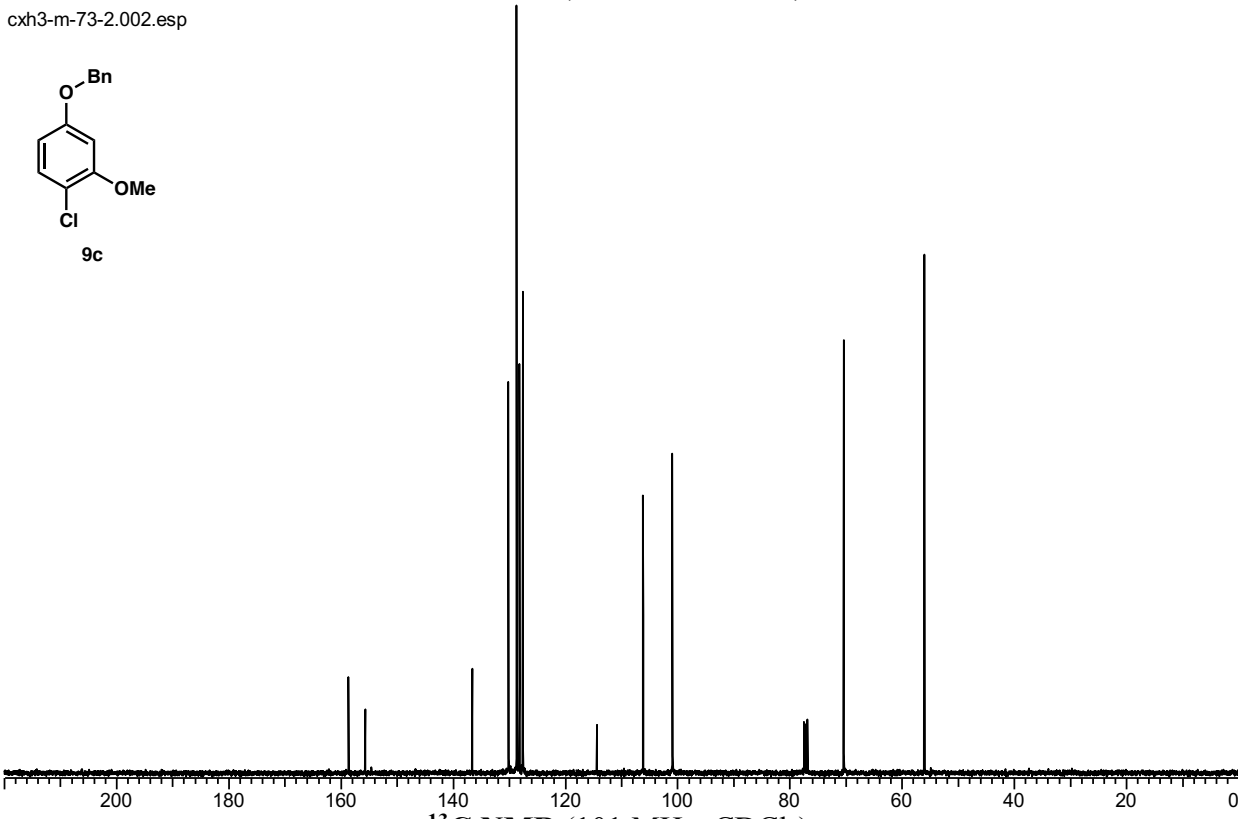
^{1}H NMR (500 MHz, $CDCl_3$)



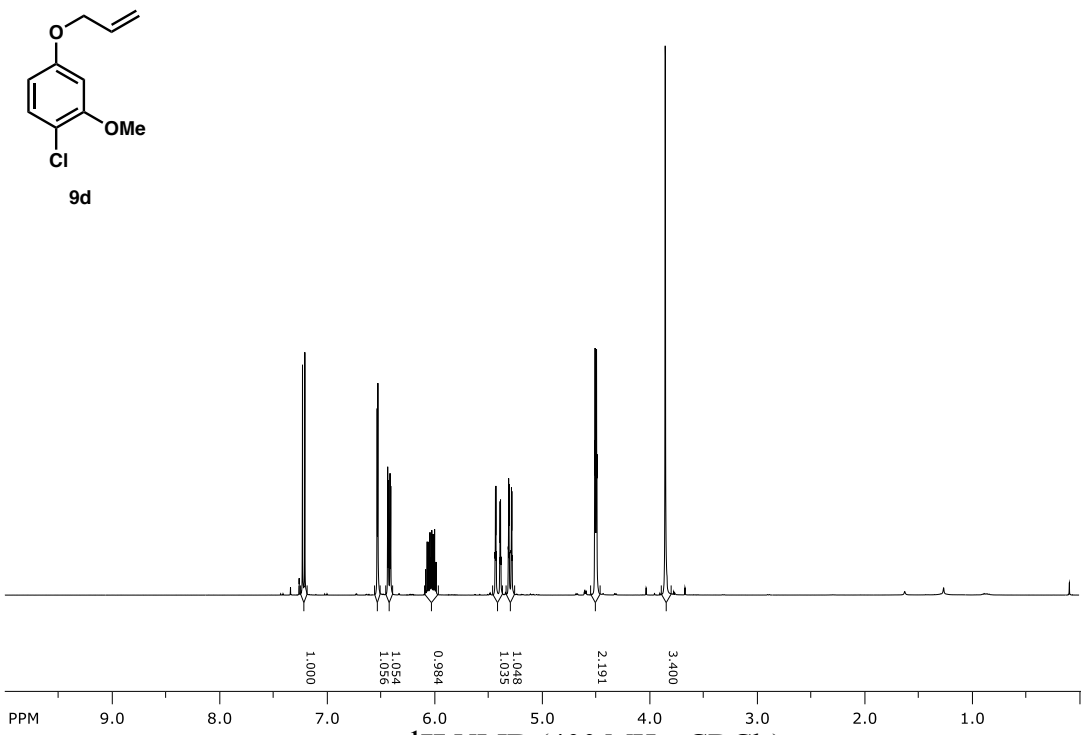
^{13}C NMR (126 MHz, $CDCl_3$)



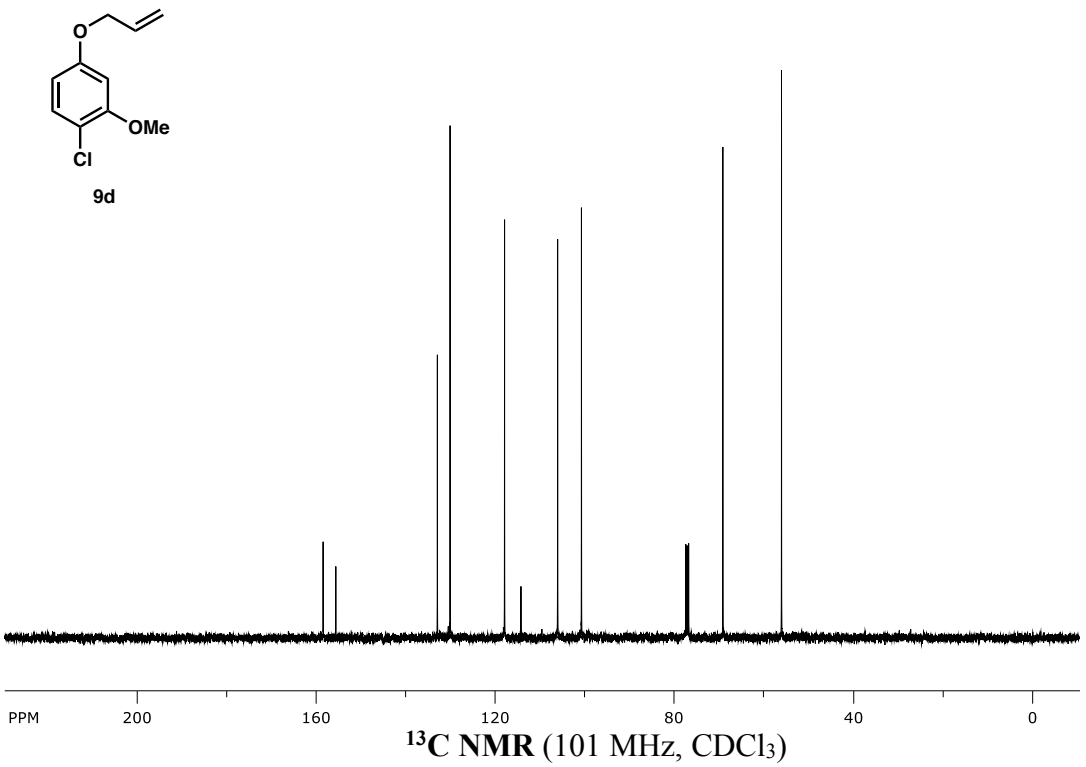
^{1}H NMR (400 MHz, $CDCl_3$)



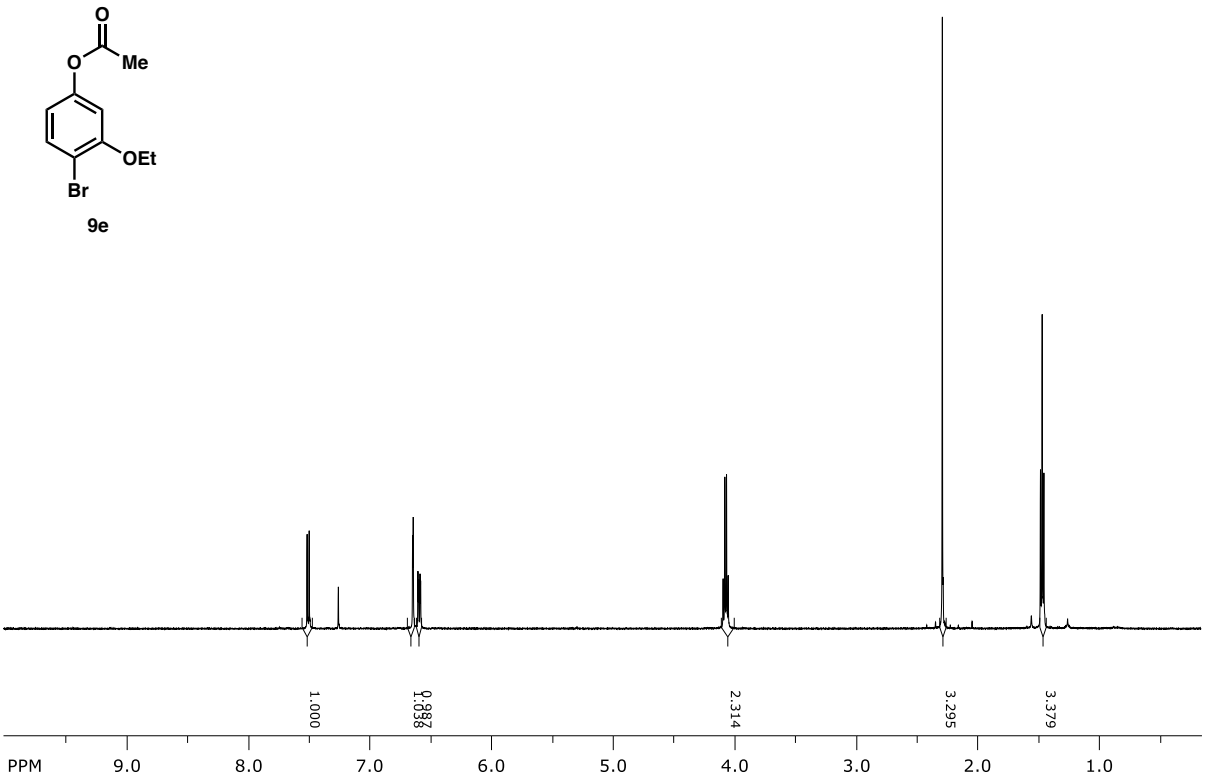
^{13}C NMR (101 MHz, $CDCl_3$)



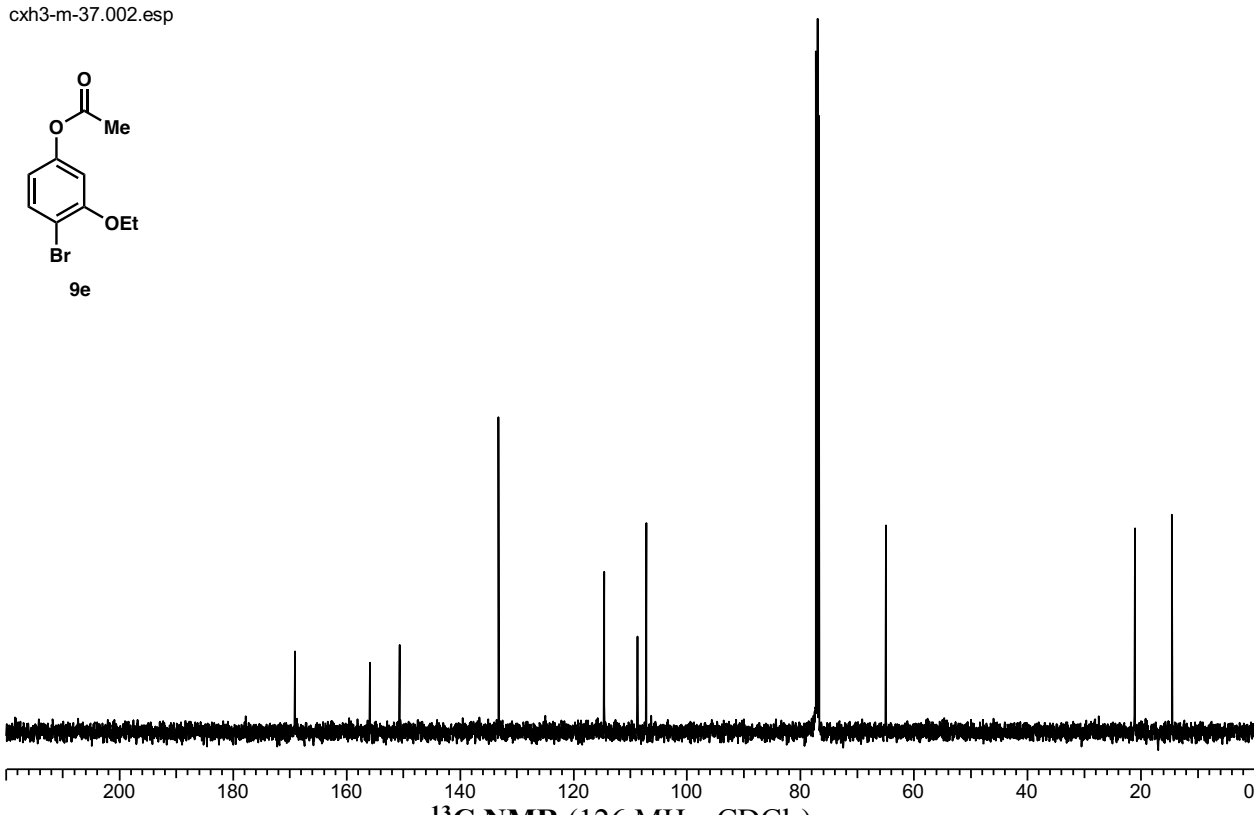
^{1}H NMR (400 MHz, $CDCl_3$)



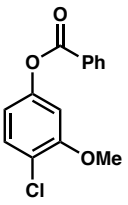
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

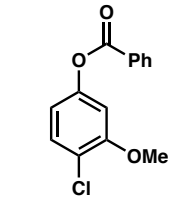


^{13}C NMR (126 MHz, $CDCl_3$)



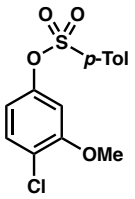
9f

^{1}H NMR (500 MHz, $CDCl_3$)

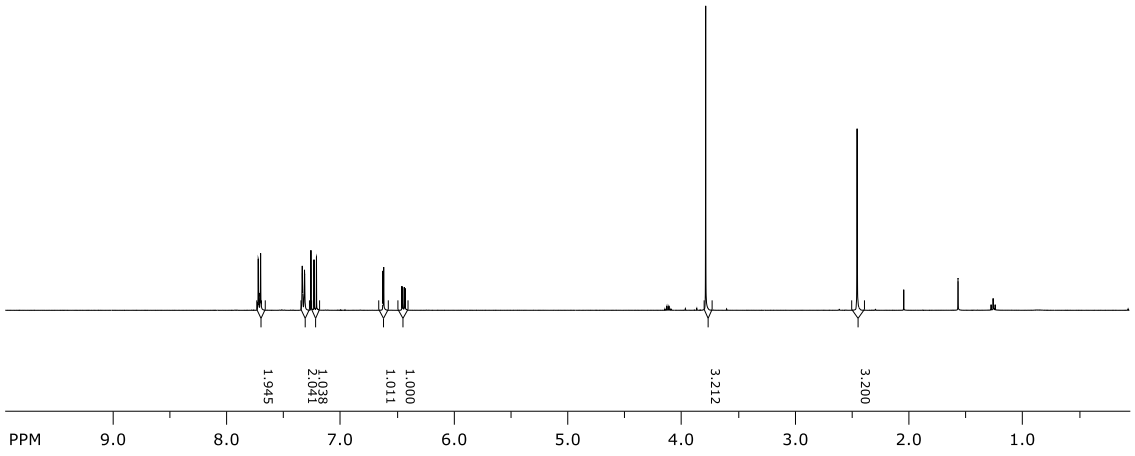


9f

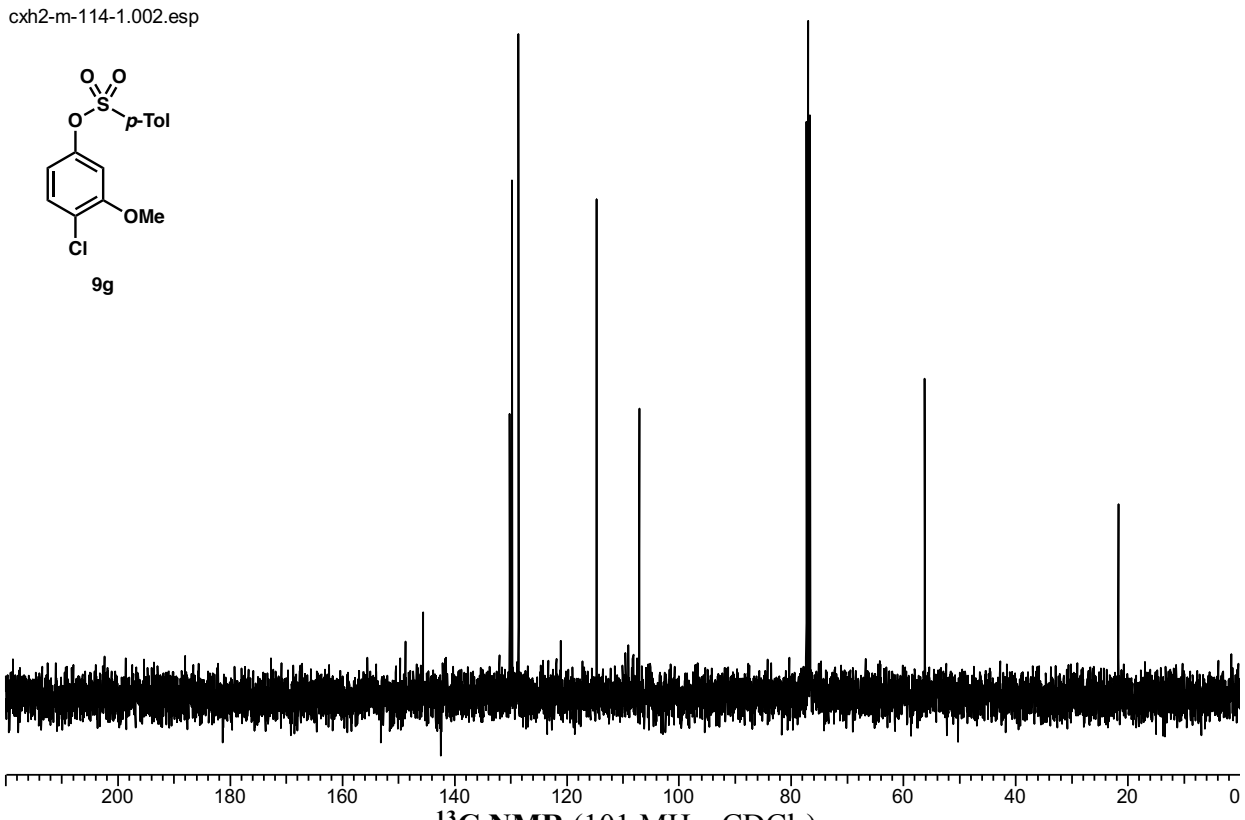
^{13}C NMR (126 MHz, $CDCl_3$)



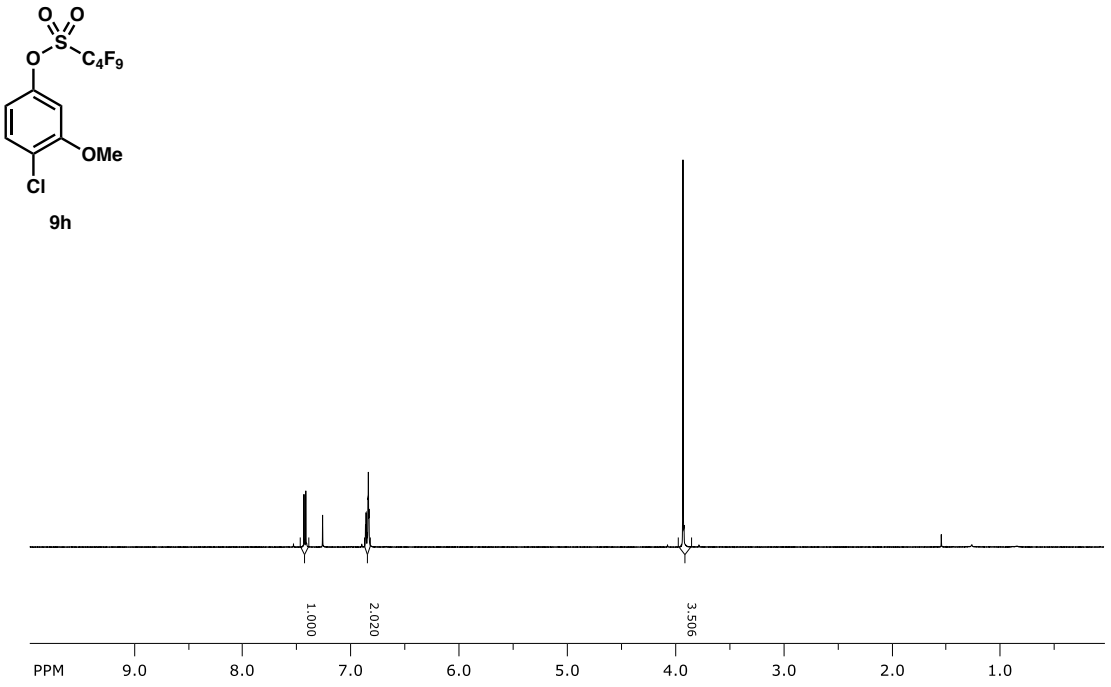
9g



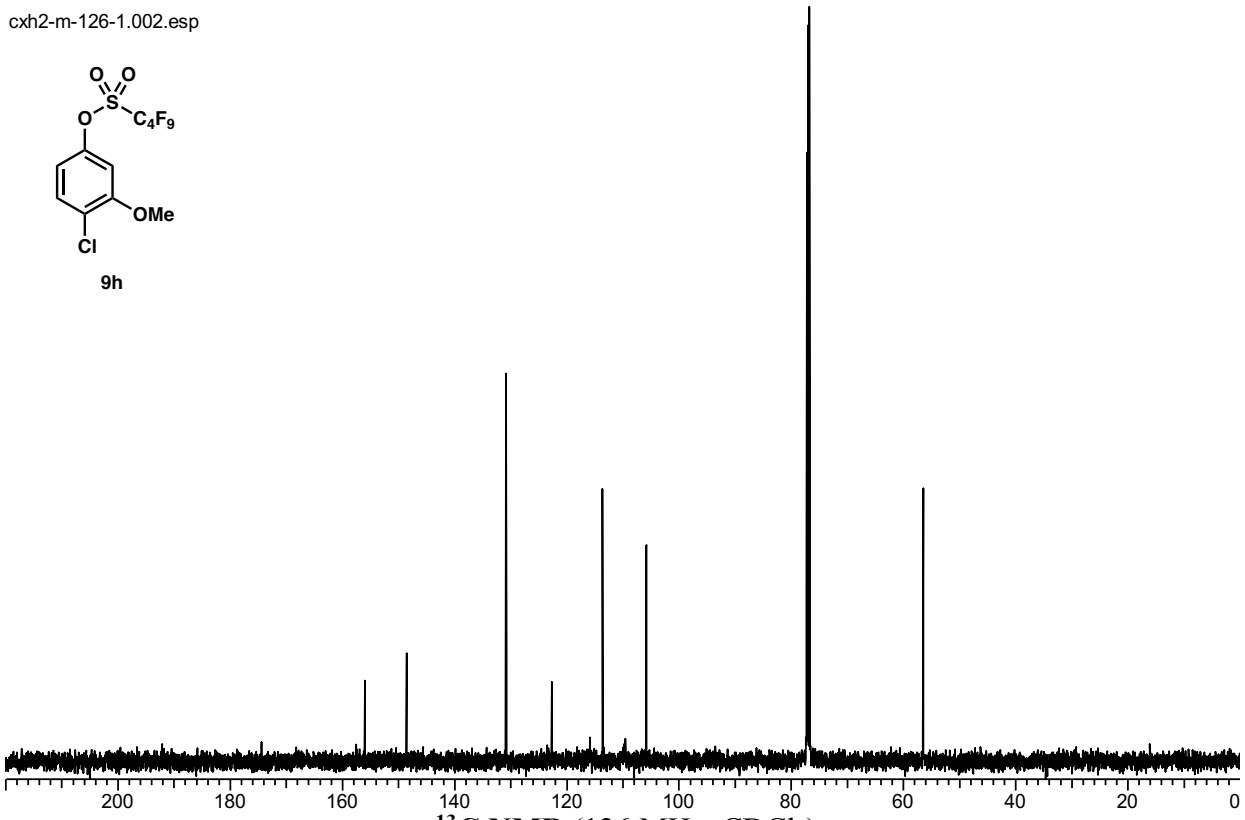
^{1}H NMR (400 MHz, $CDCl_3$)



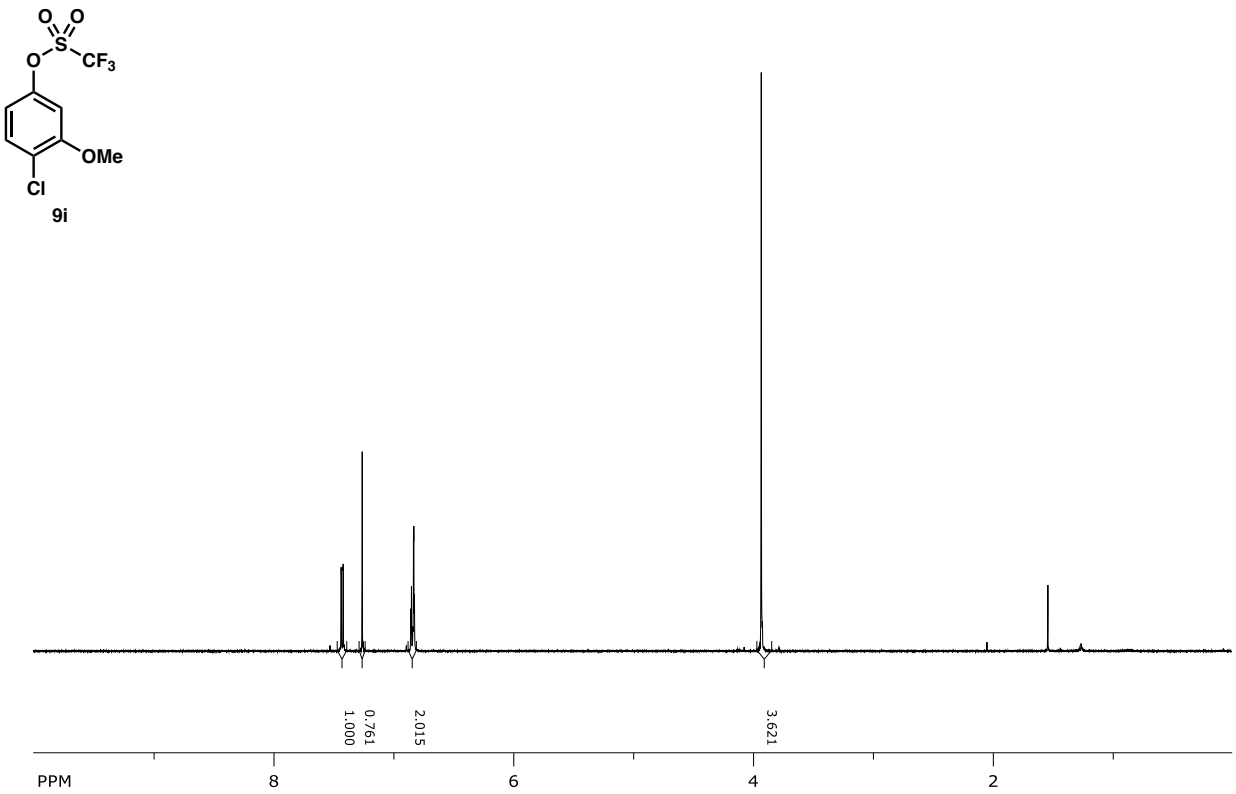
^{13}C NMR (101 MHz, $CDCl_3$)



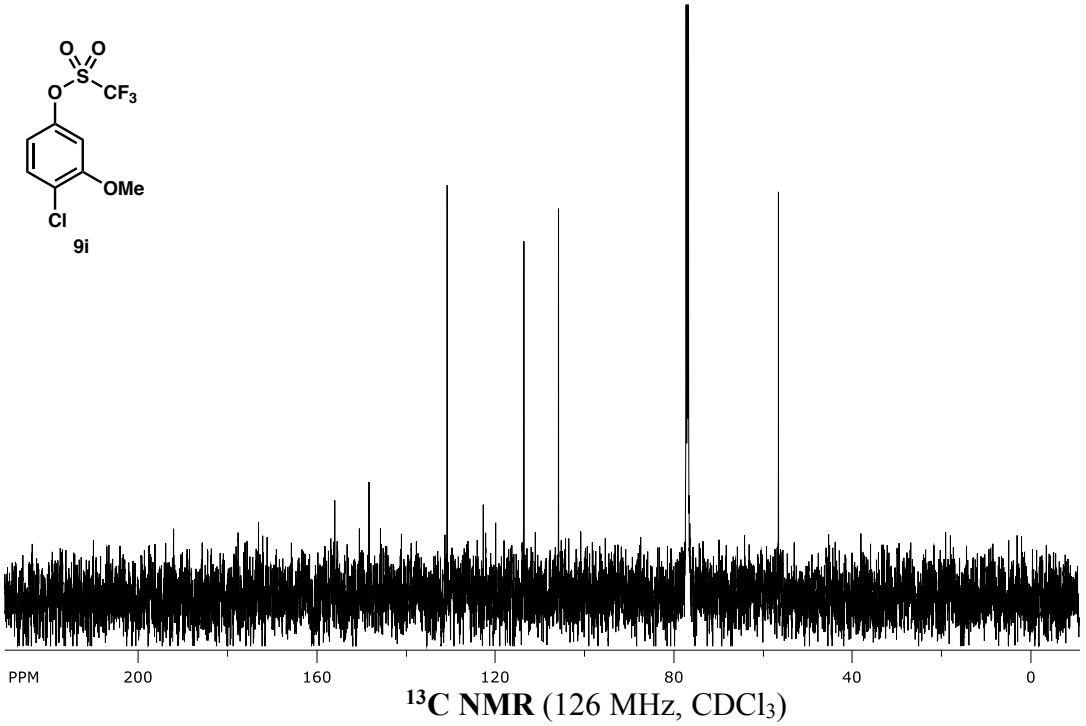
^{1}H NMR (500 MHz, $CDCl_3$)



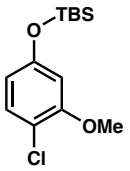
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

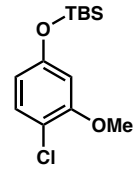


^{13}C NMR (126 MHz, $CDCl_3$)



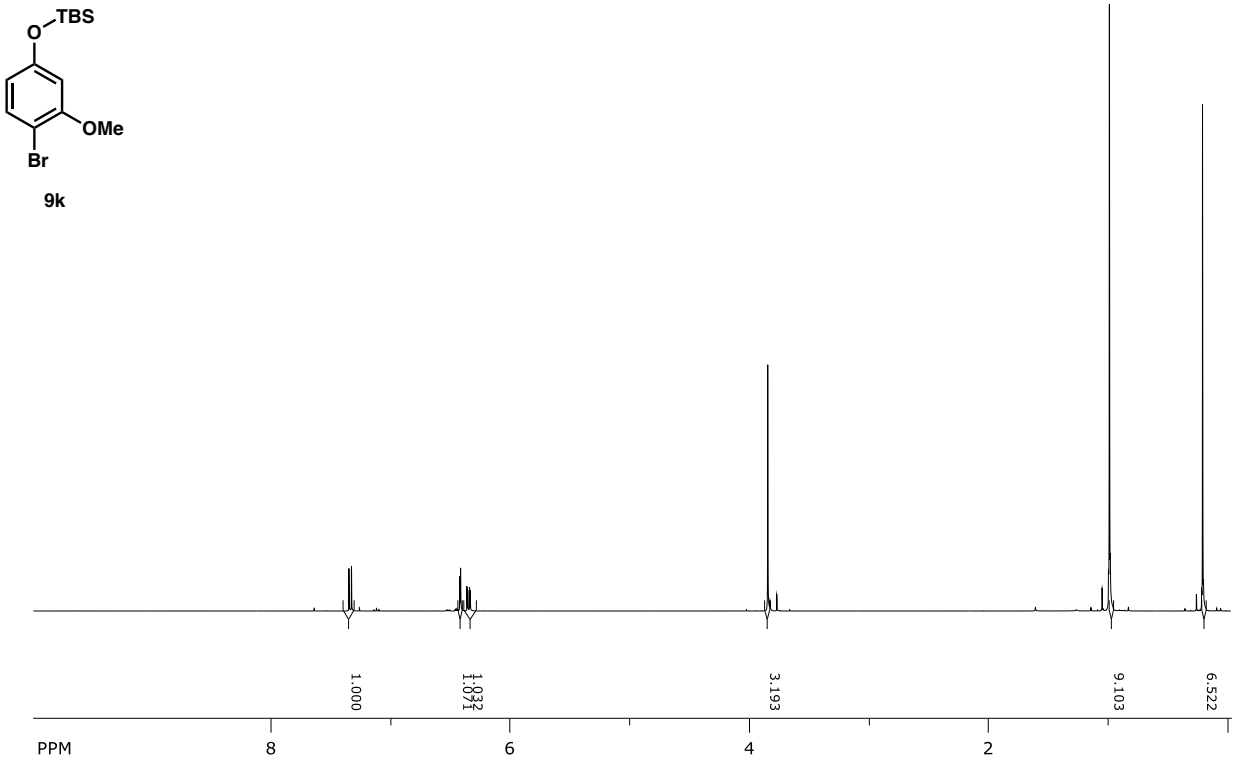
9j

^{1}H NMR (400 MHz, $CDCl_3$)

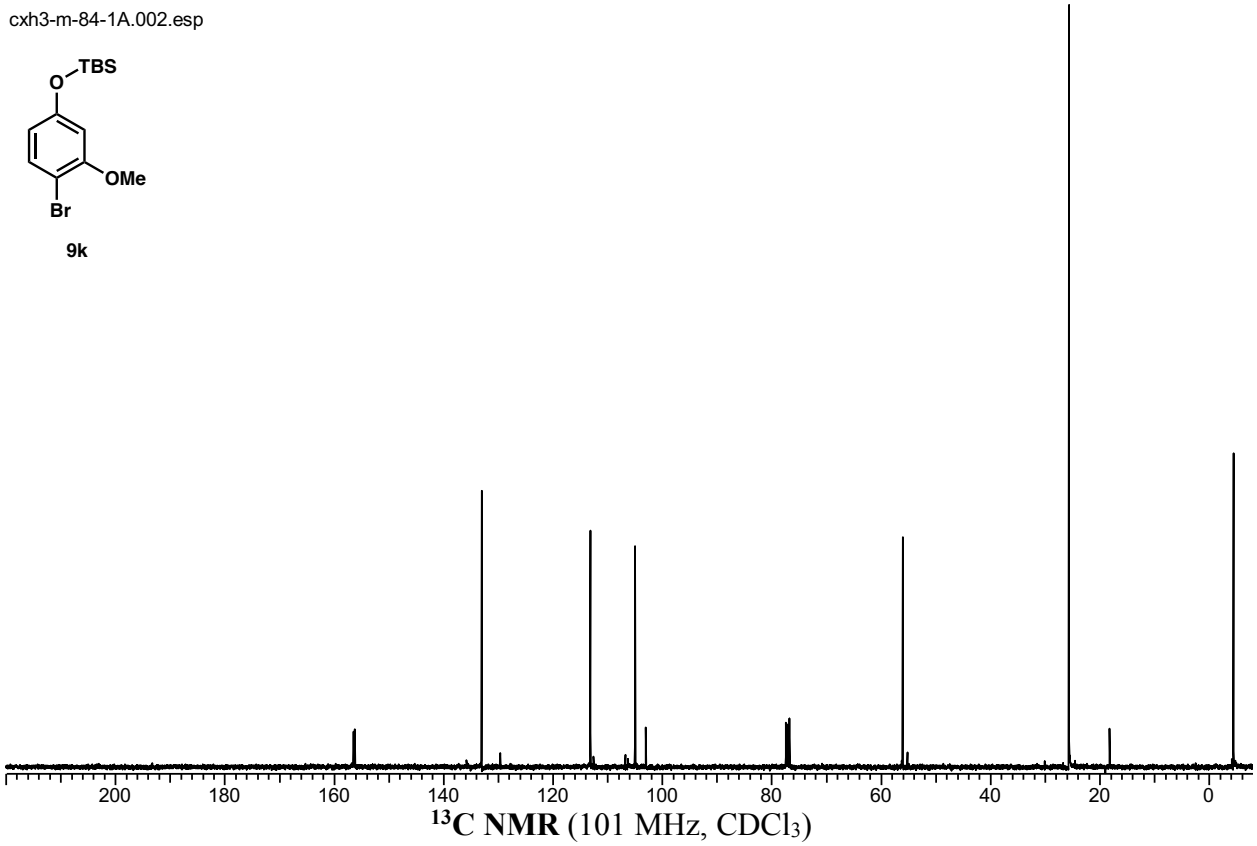


9j

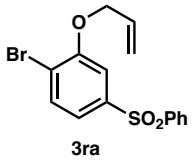
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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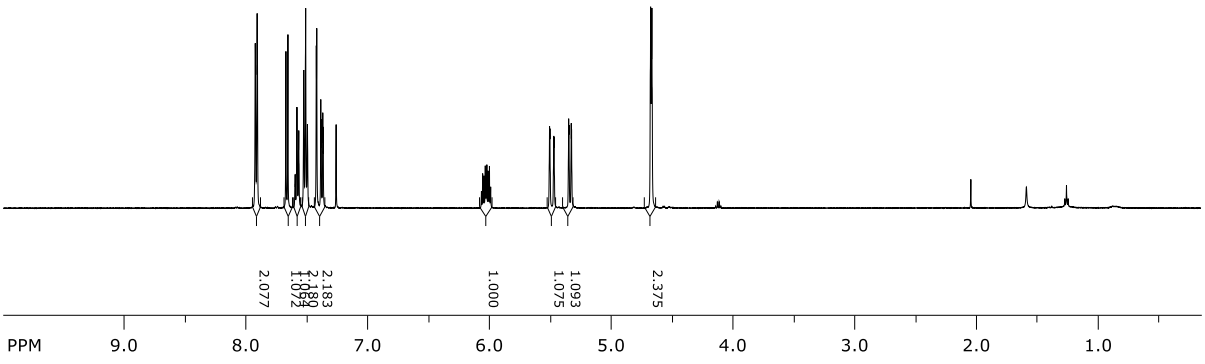
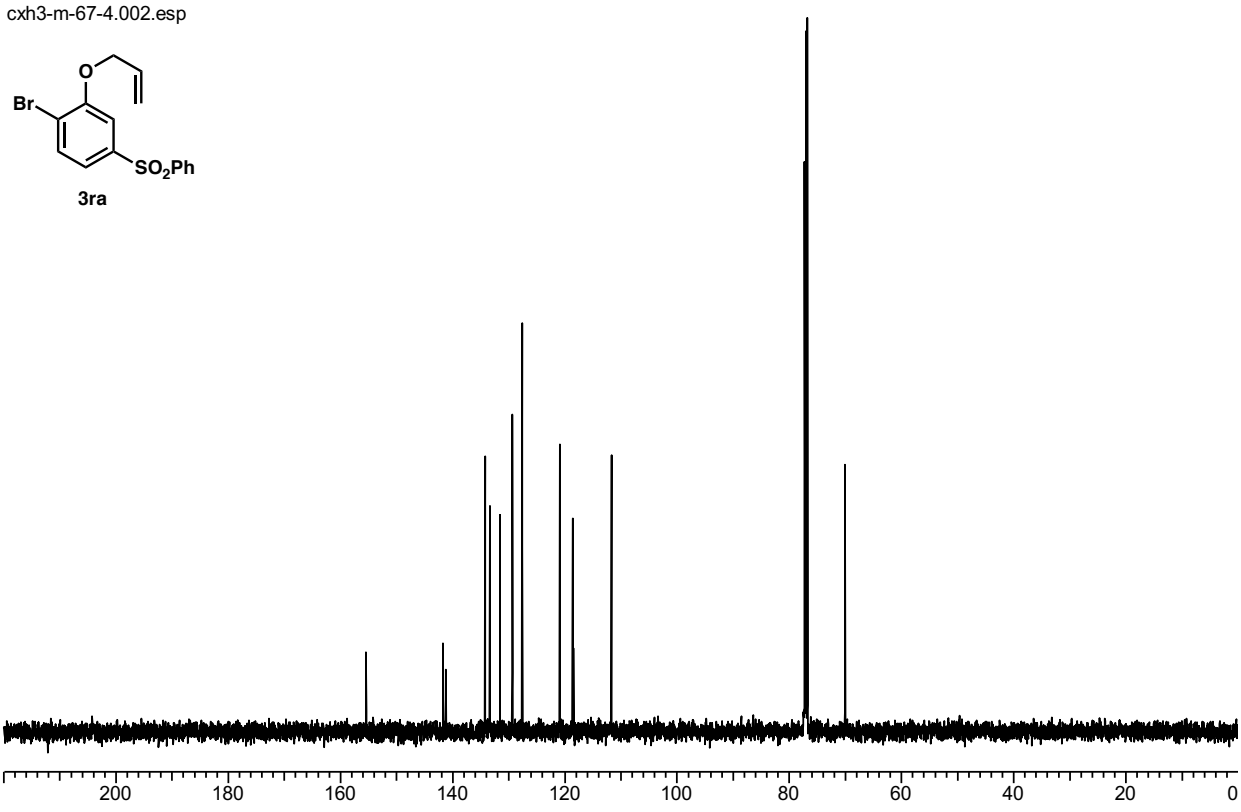
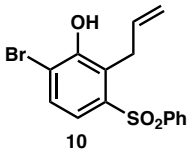


^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



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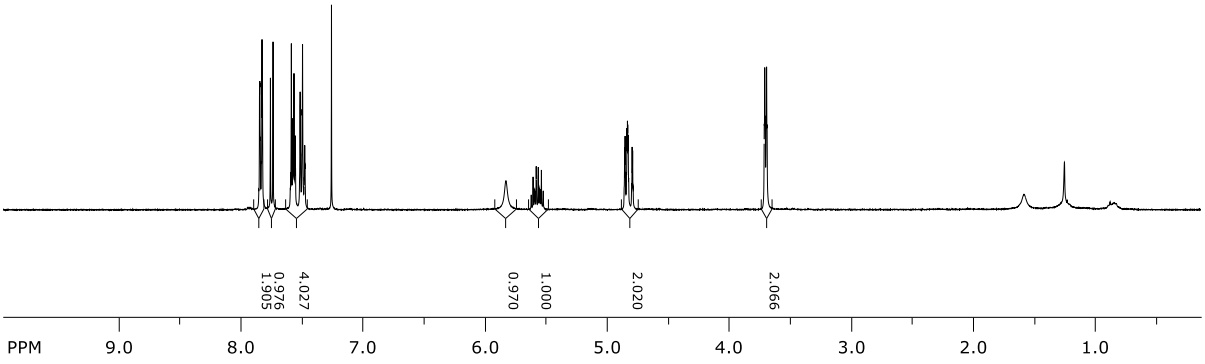
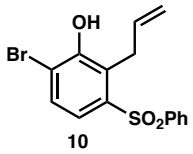


^{1}H NMR (400 MHz, $CDCl_3$)



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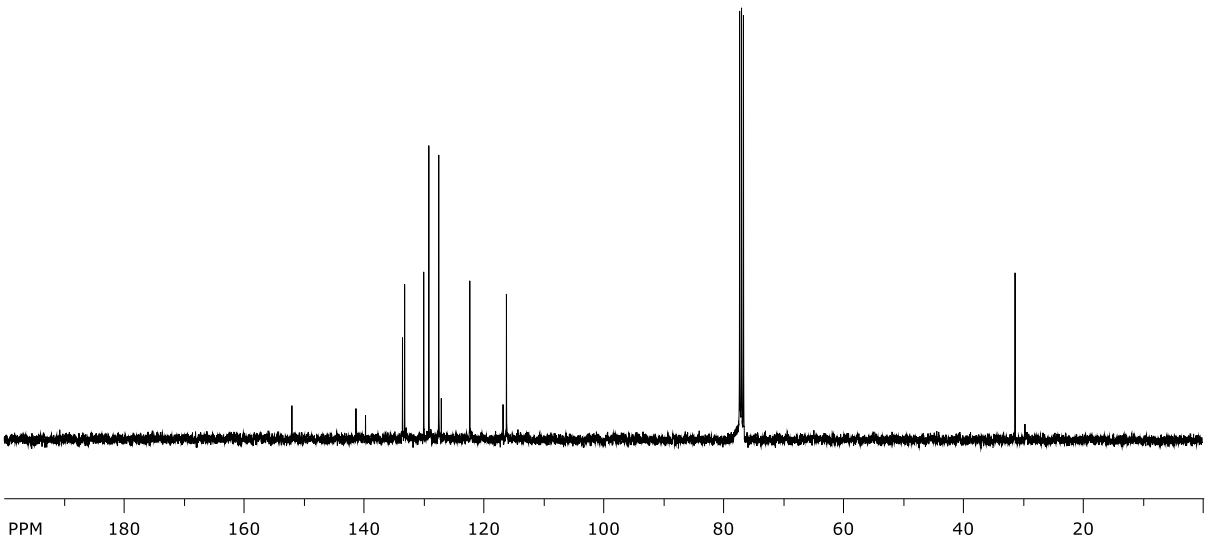
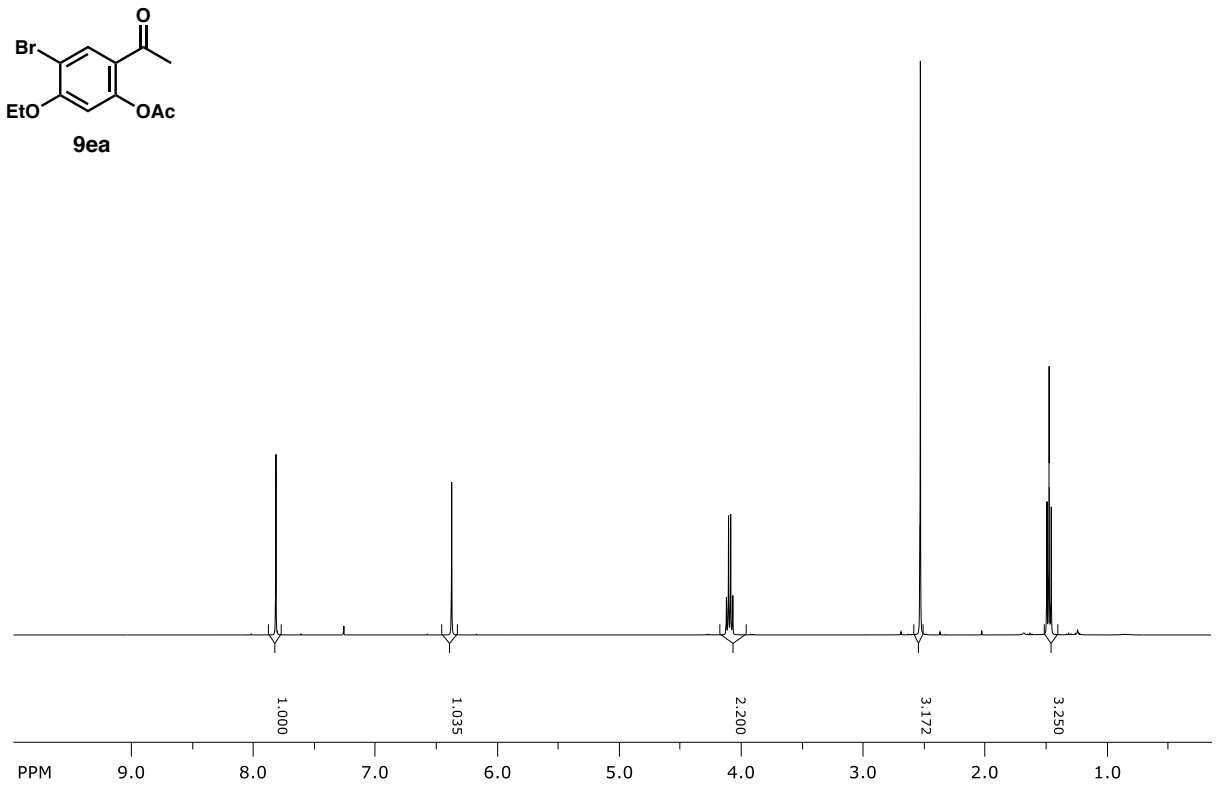
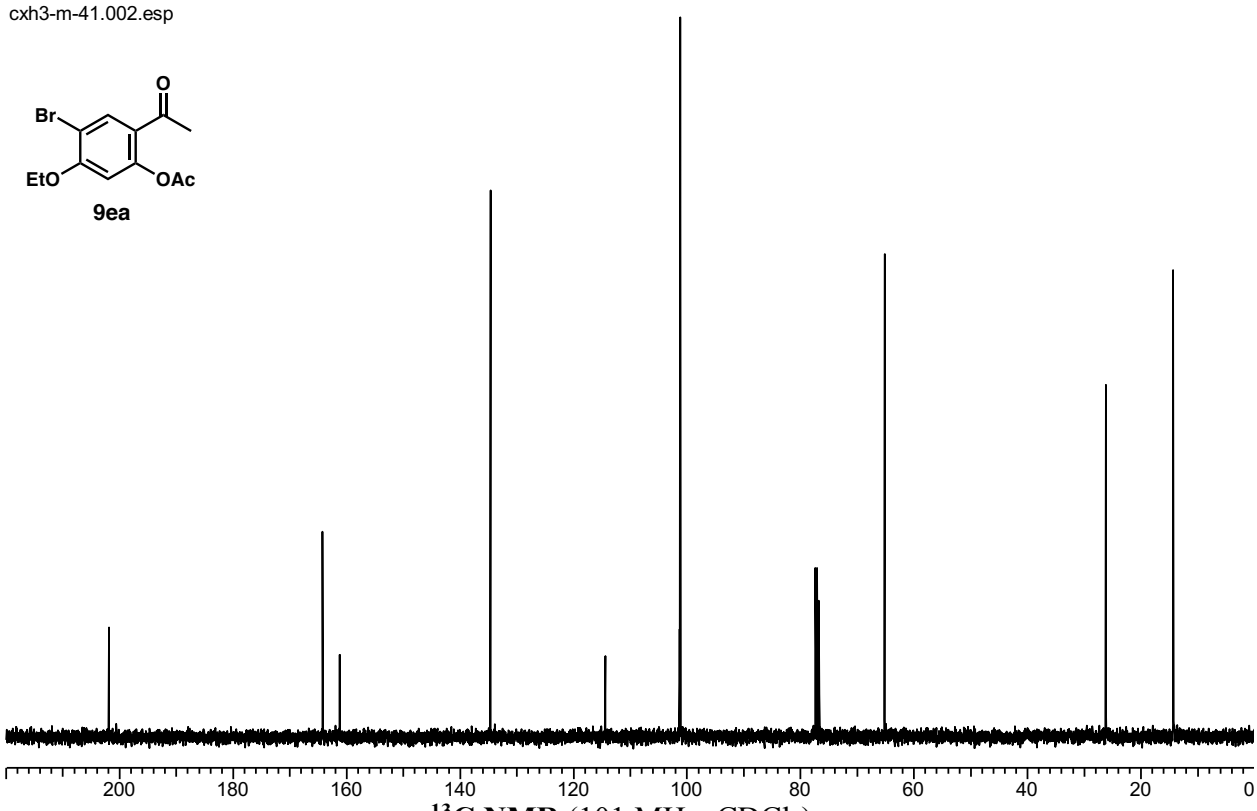


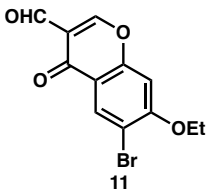
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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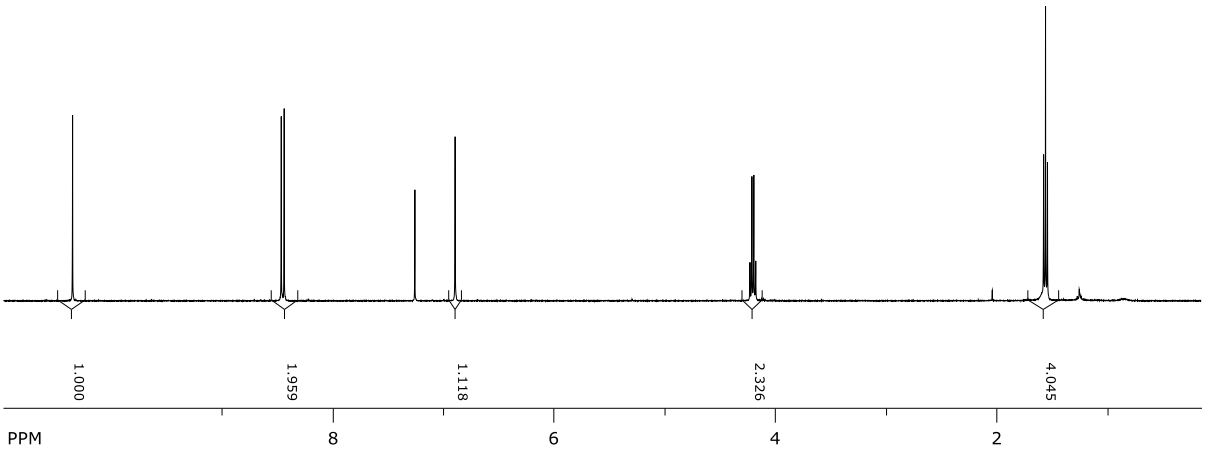
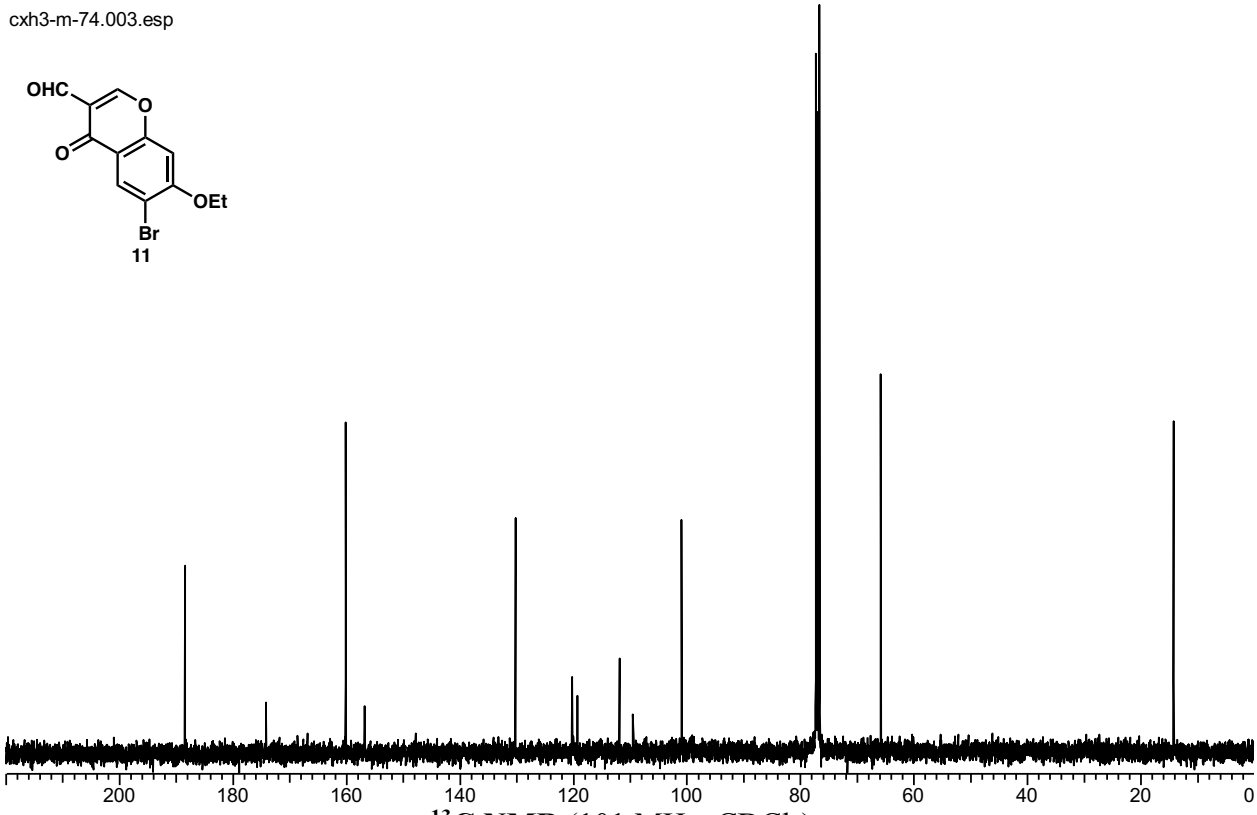
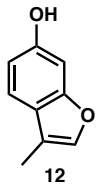


^{1}H NMR (400 MHz, $CDCl_3$)



11

^{13}C NMR (101 MHz, $CDCl_3$)



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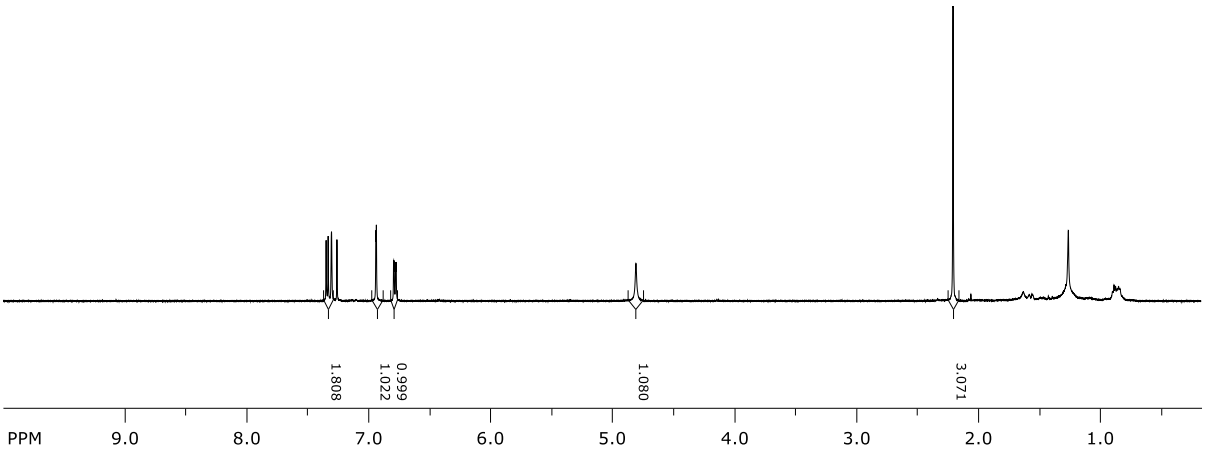
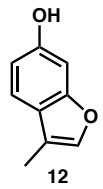


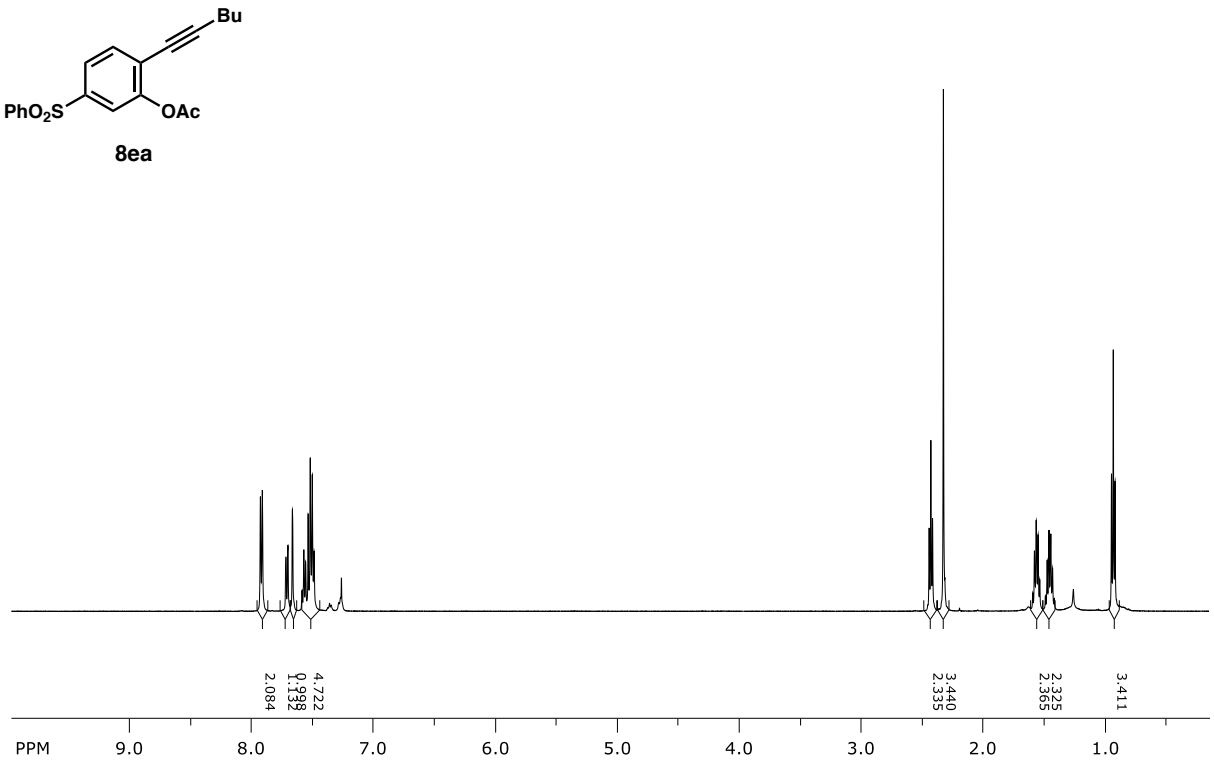
^{1}H NMR (500 MHz, $CDCl_3$)

cxh3-m-45-1-2.002.esp

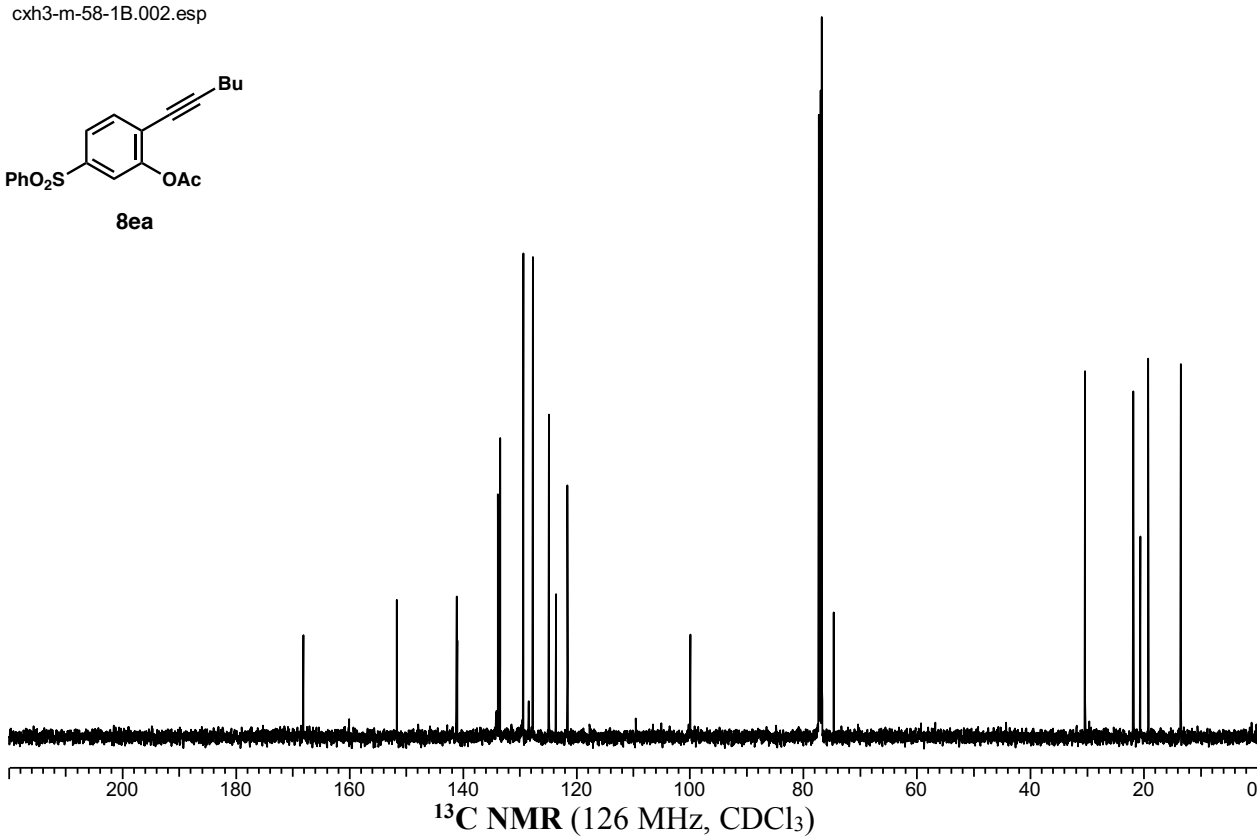


12

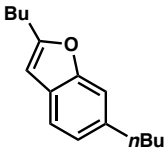
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



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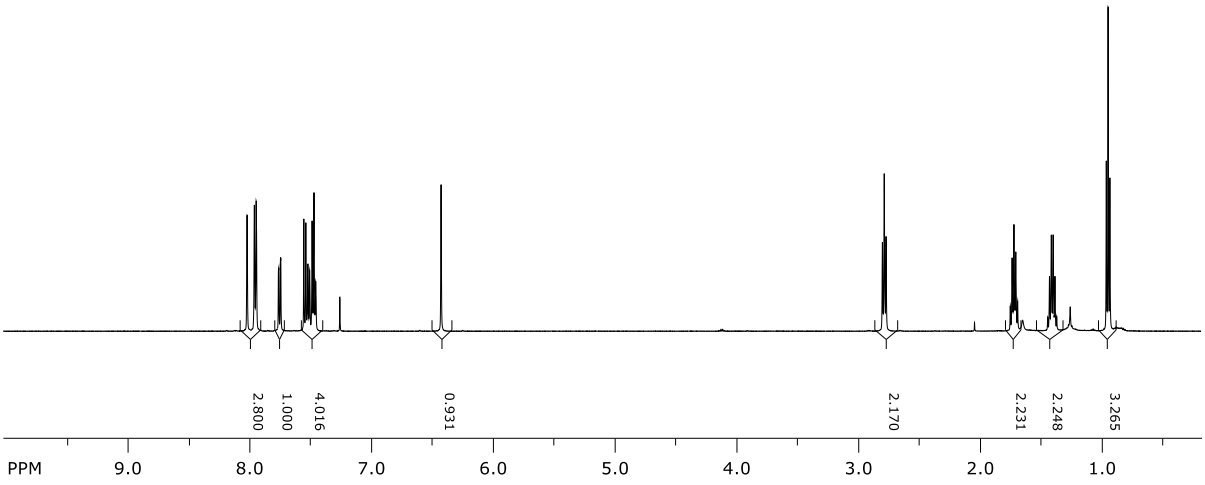
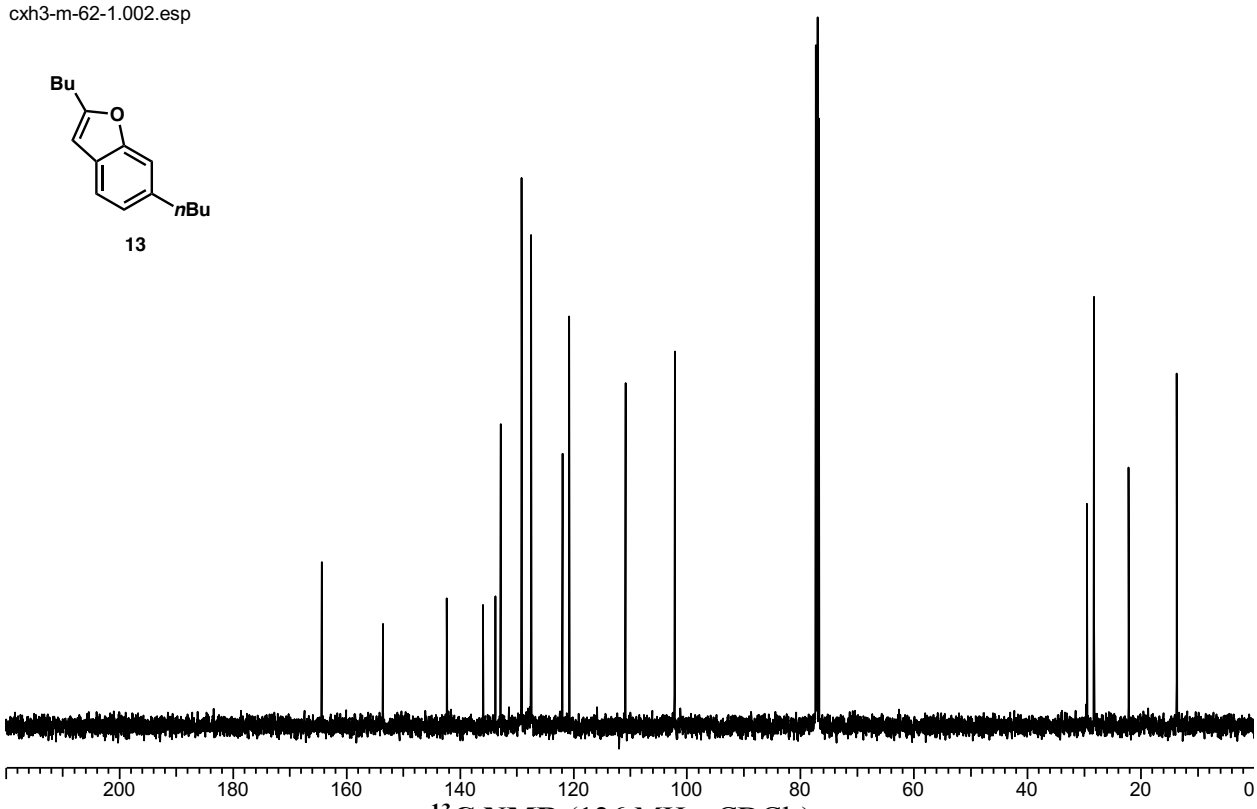
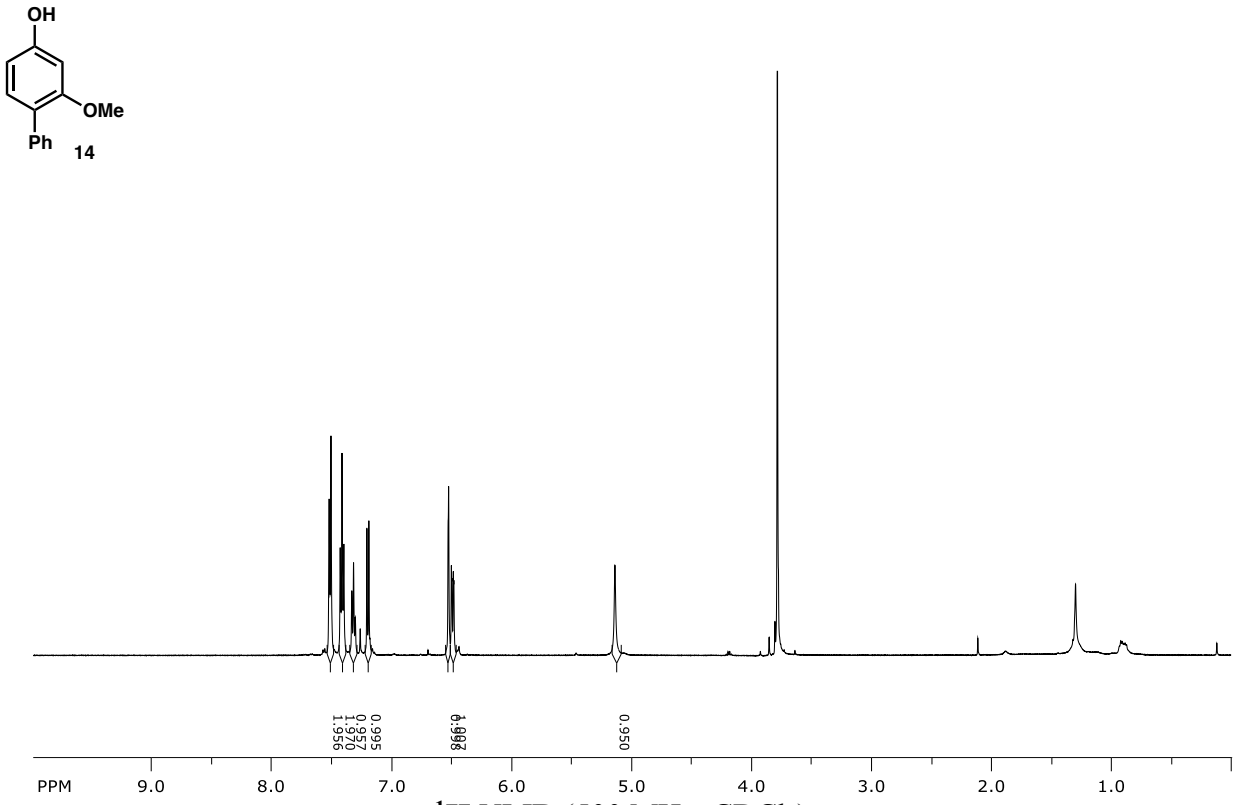


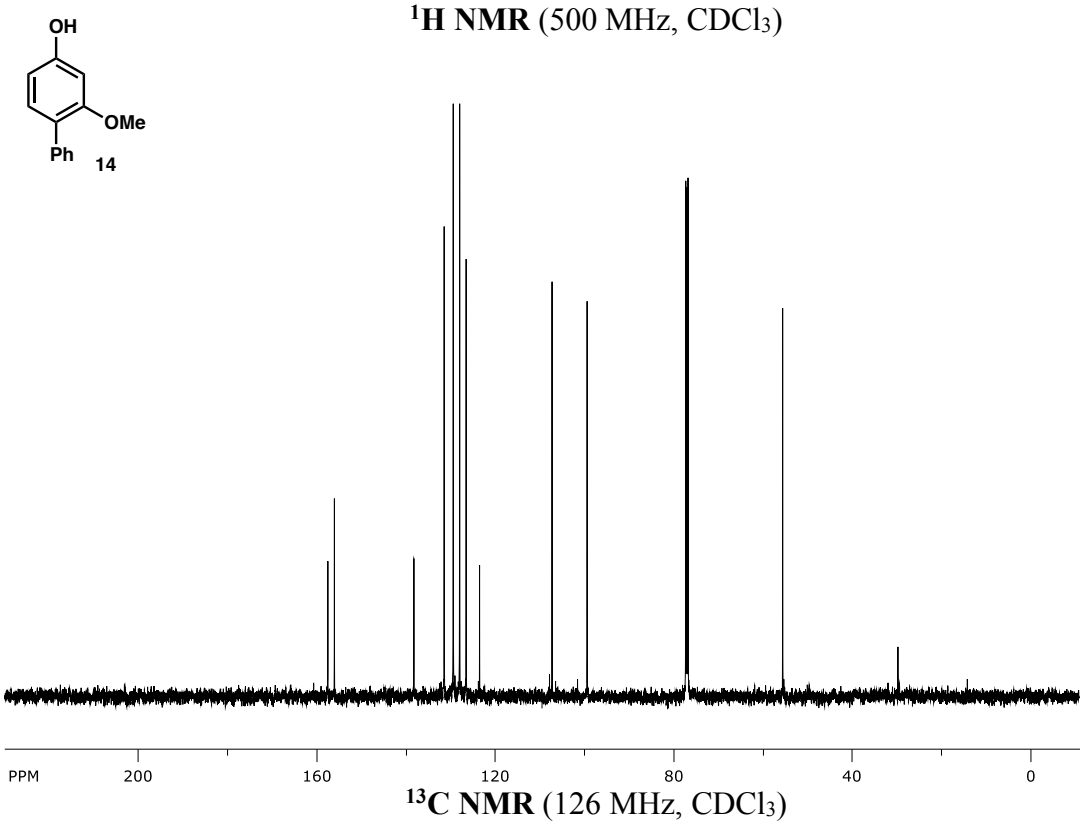
^{1}H NMR (500 MHz, $CDCl_3$)



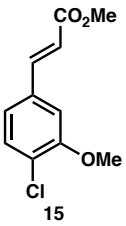
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



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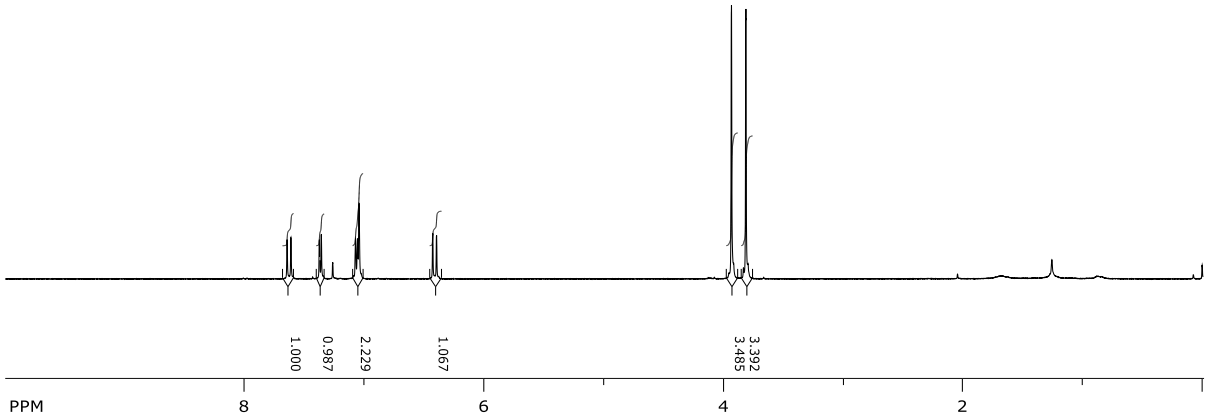
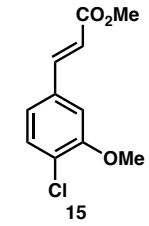


^{1}H NMR (500 MHz, $CDCl_3$)



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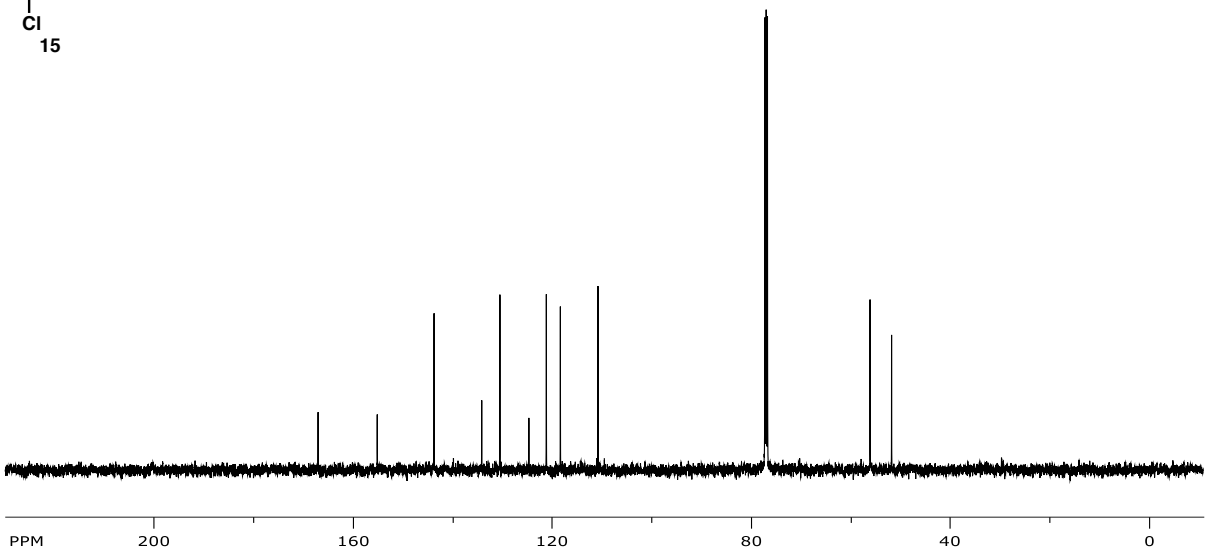
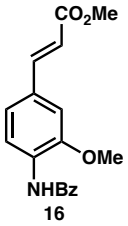


^{13}C NMR (126 MHz, $CDCl_3$)



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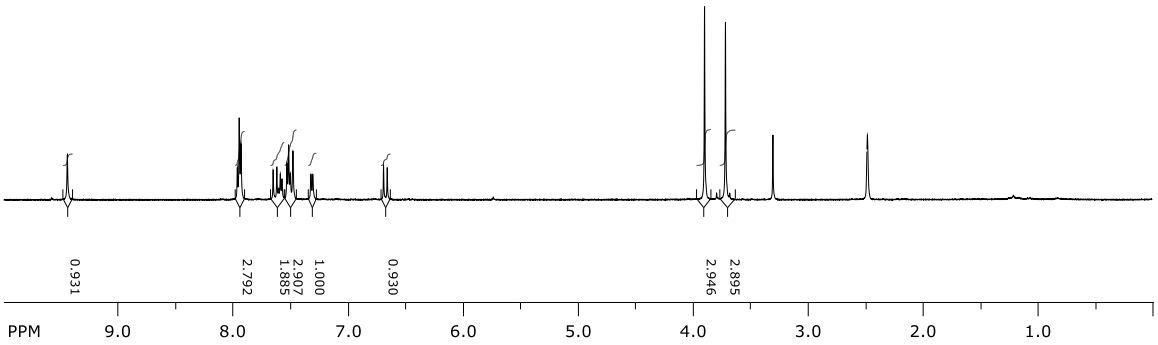
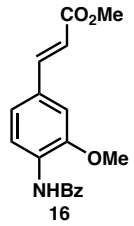


^{1}H NMR (500 MHz, *d*$_6$-DMSO)



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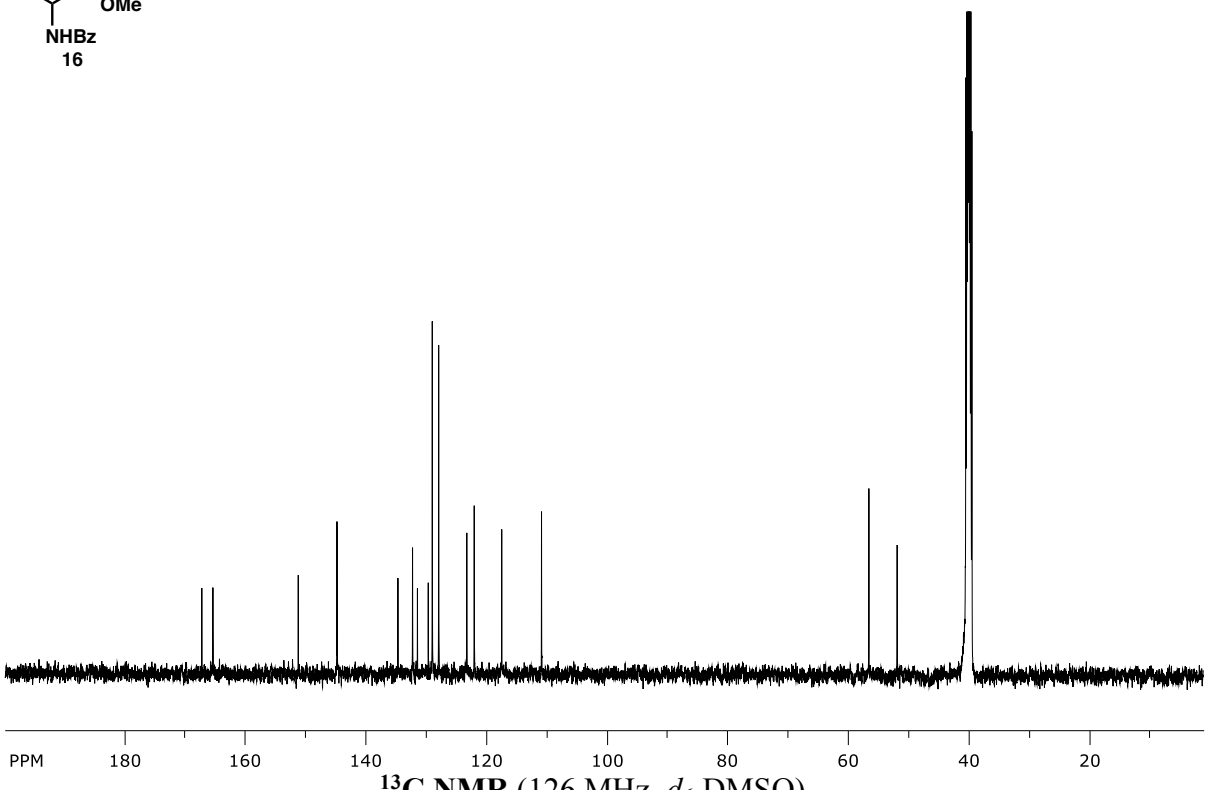
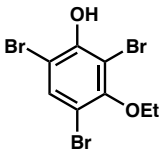
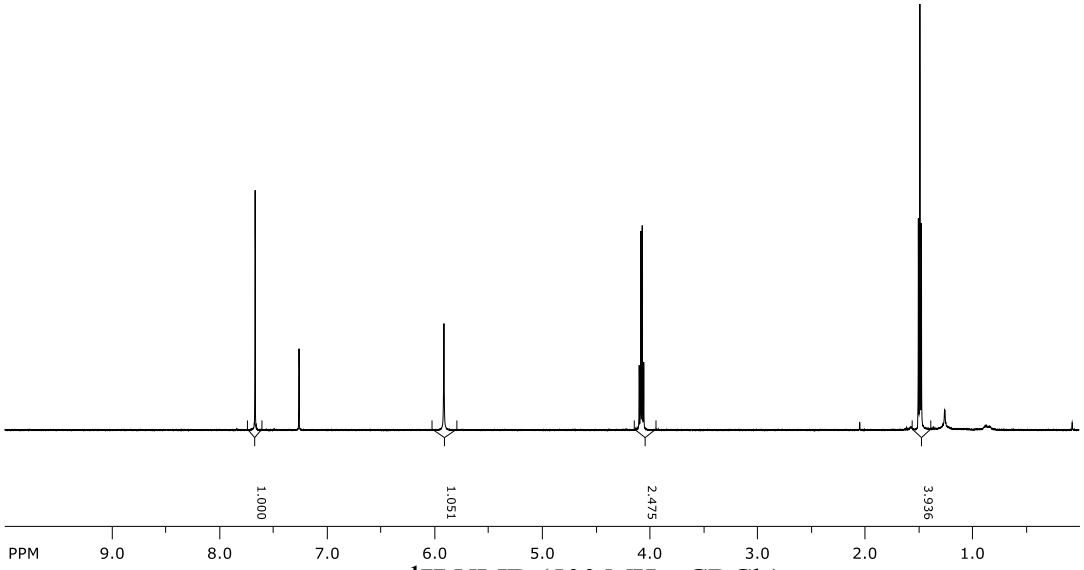


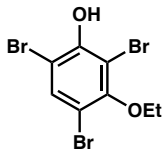
^{13}C NMR (126 MHz, *d*$_6$-DMSO)



17a

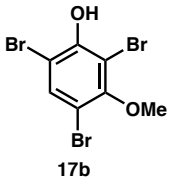


^{1}H NMR (500 MHz, $CDCl_3$)



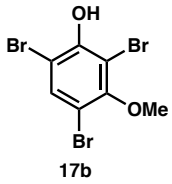
17a

^{13}C NMR (126 MHz, $CDCl_3$)



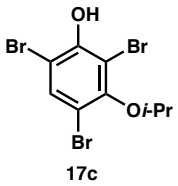
17b

^{1}H NMR (500 MHz, $CDCl_3$)



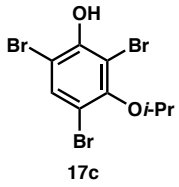
17b

^{13}C NMR (126 MHz, $CDCl_3$)



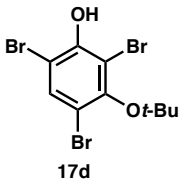
17c

^{1}H NMR (500 MHz, $CDCl_3$)



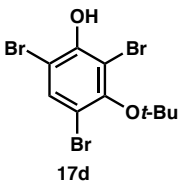
17c

^{13}C NMR (126 MHz, $CDCl_3$)



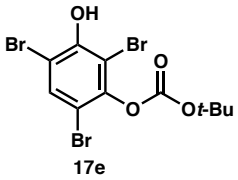
17d

^{1}H NMR (500 MHz, $CDCl_3$)



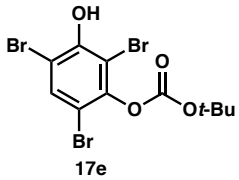
17d

^{13}C NMR (126 MHz, $CDCl_3$)



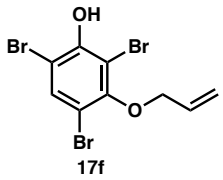
17e

^{1}H NMR (500 MHz, $CDCl_3$)

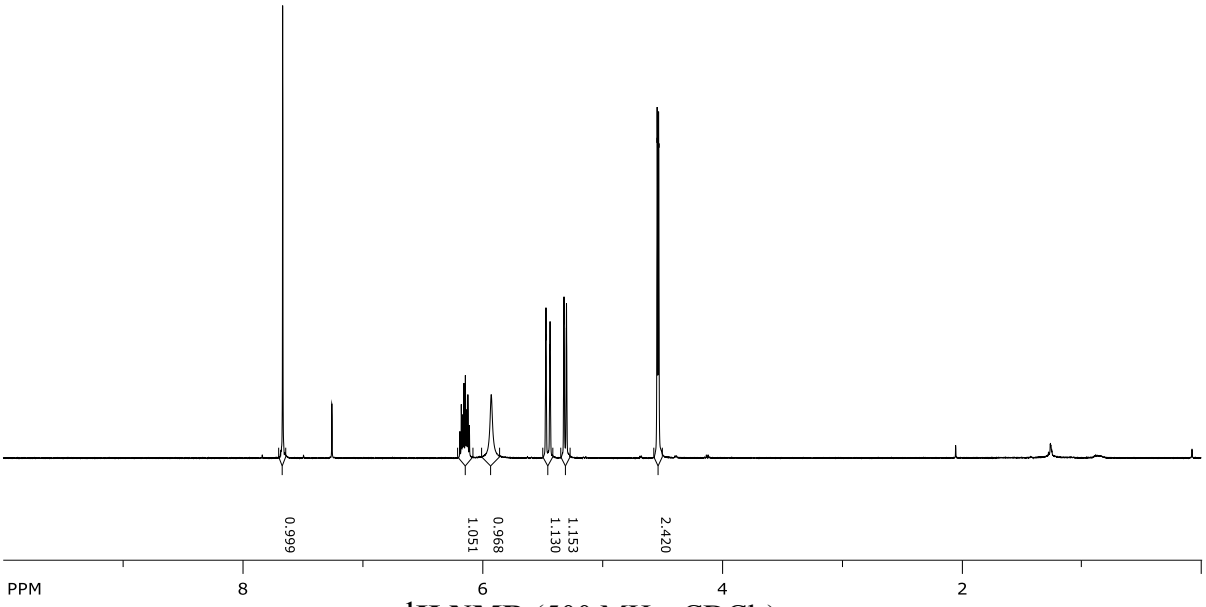


17e

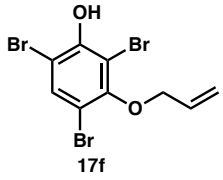
^{13}C NMR (126 MHz, $CDCl_3$)



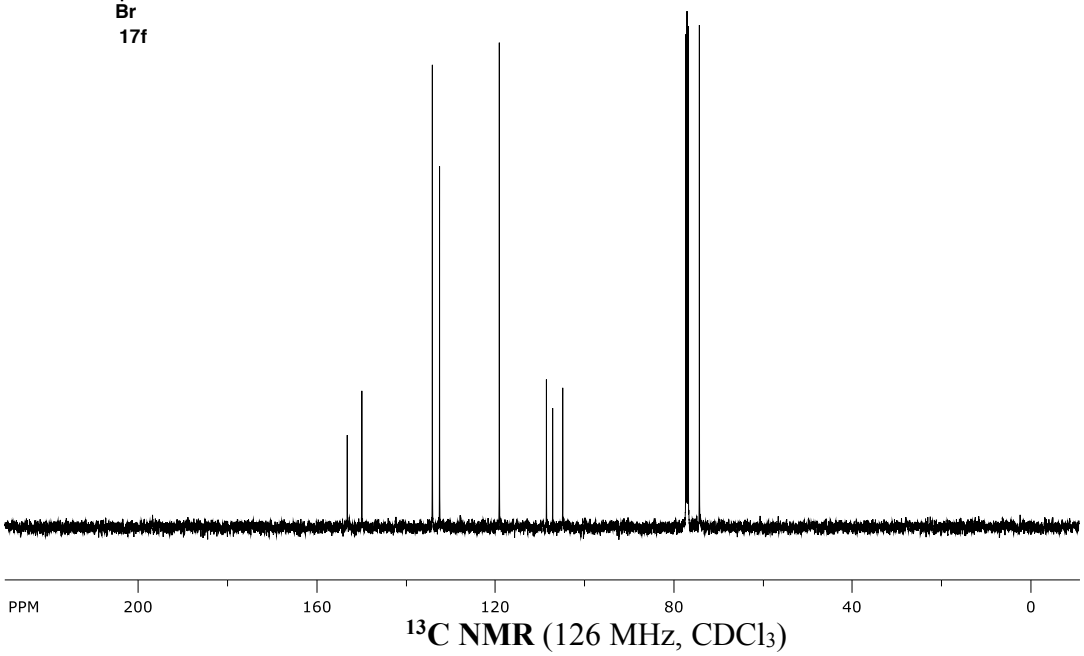
17f



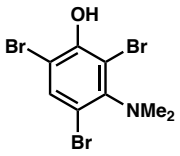
^{1}H NMR (500 MHz, $CDCl_3$)



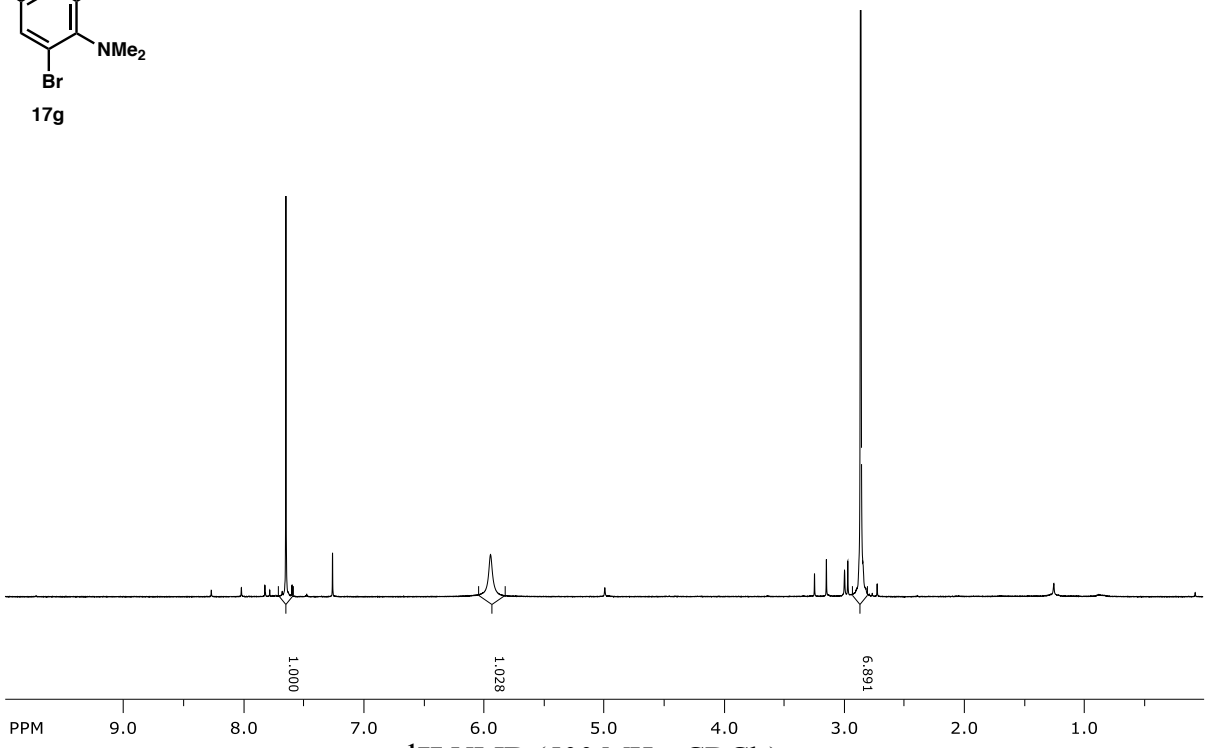
17f



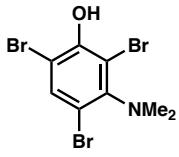
^{13}C NMR (126 MHz, $CDCl_3$)



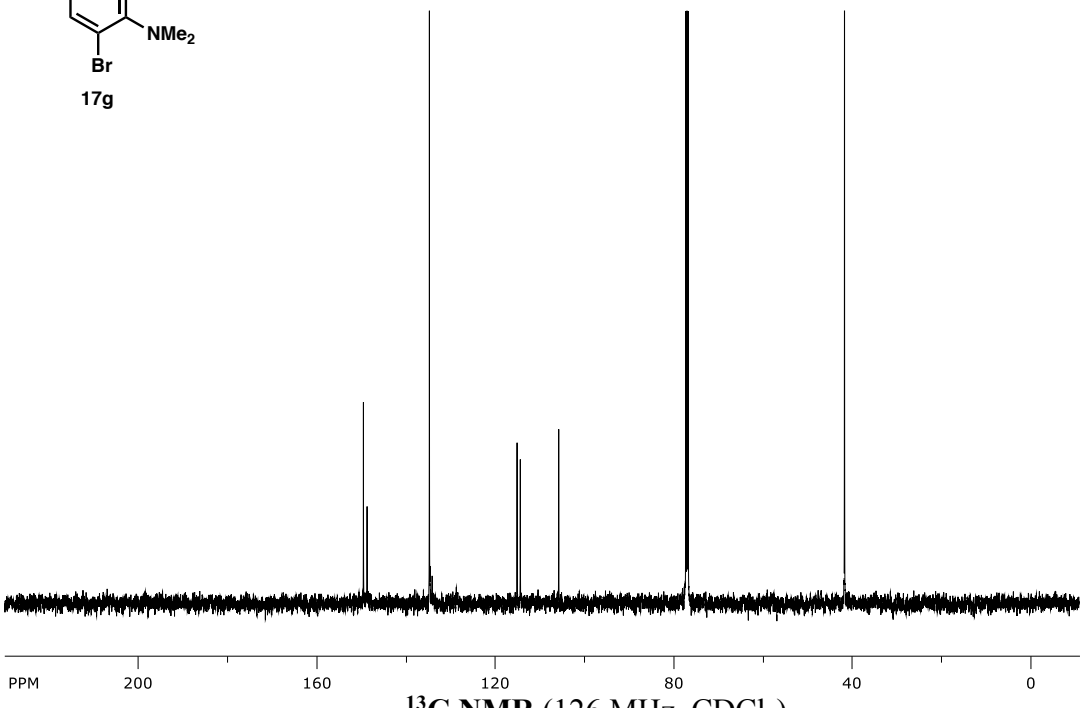
17g



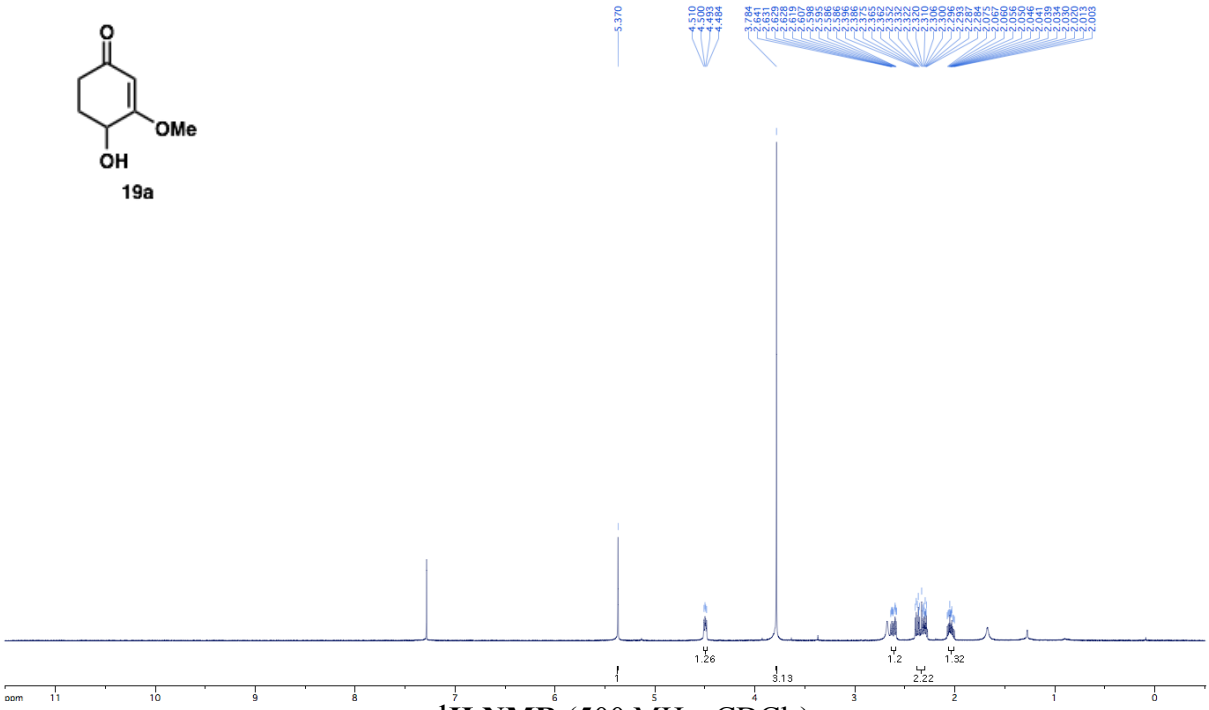
^{1}H NMR (500 MHz, $CDCl_3$)



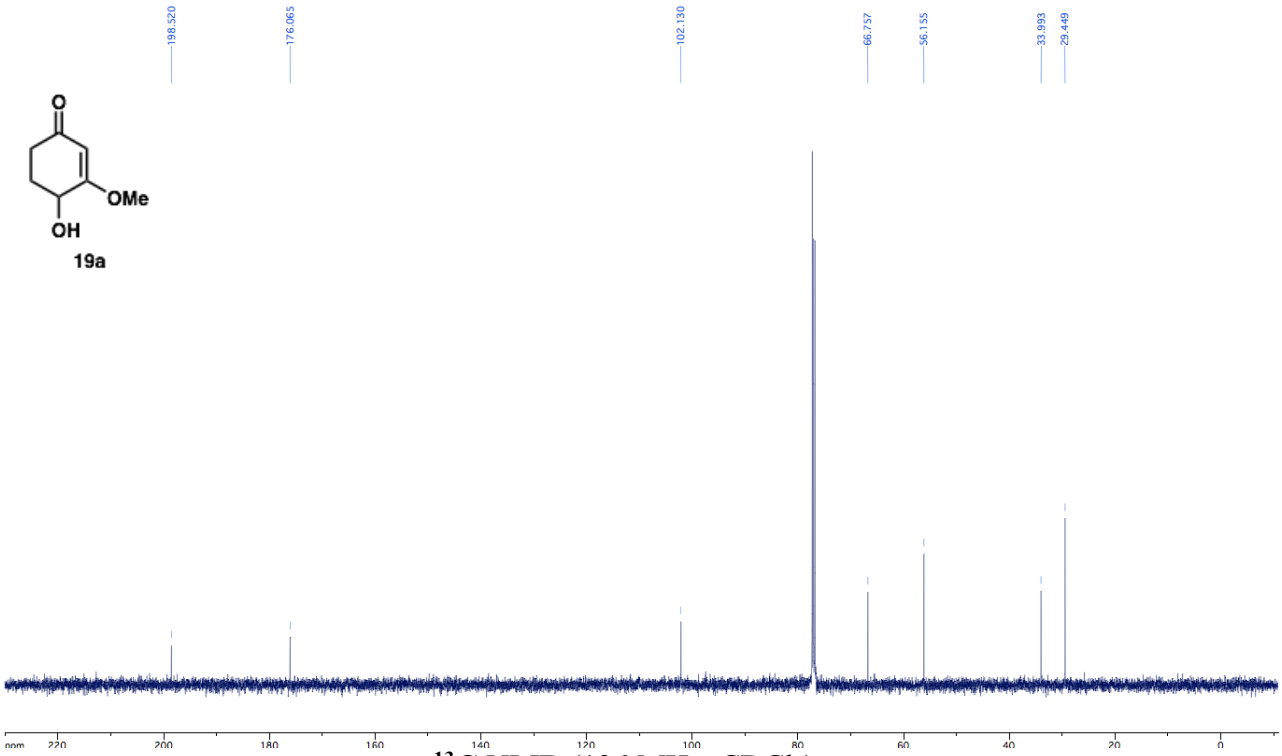
17g



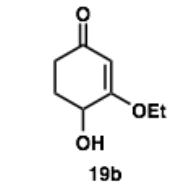
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

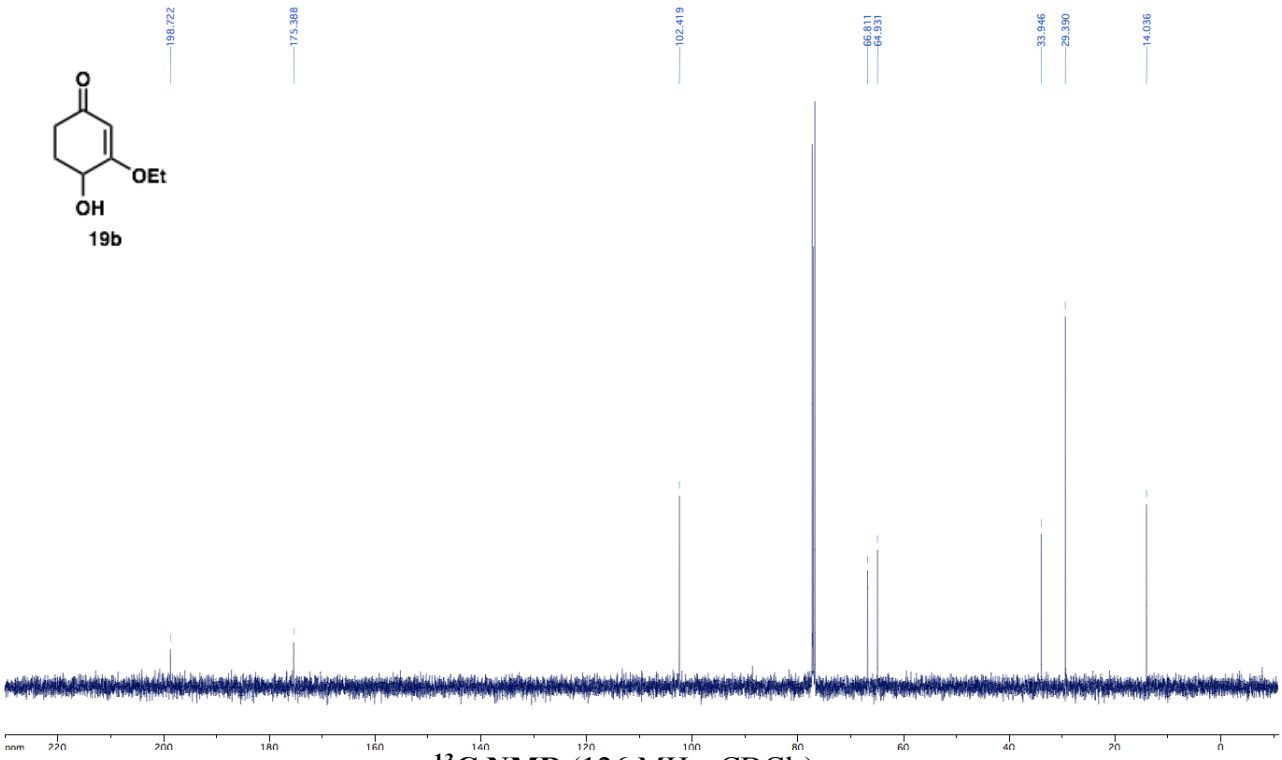


^{13}C NMR (126 MHz, $CDCl_3$)



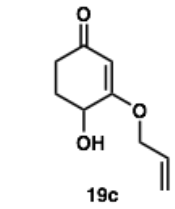
19b

^{1}H NMR (500 MHz, $CDCl_3$)

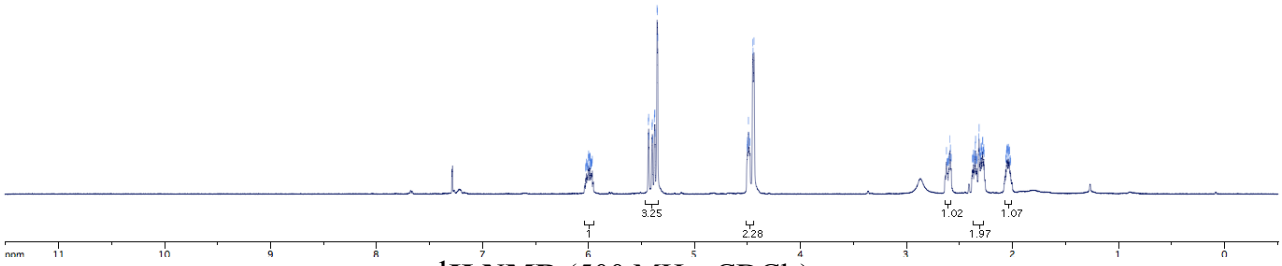


19b

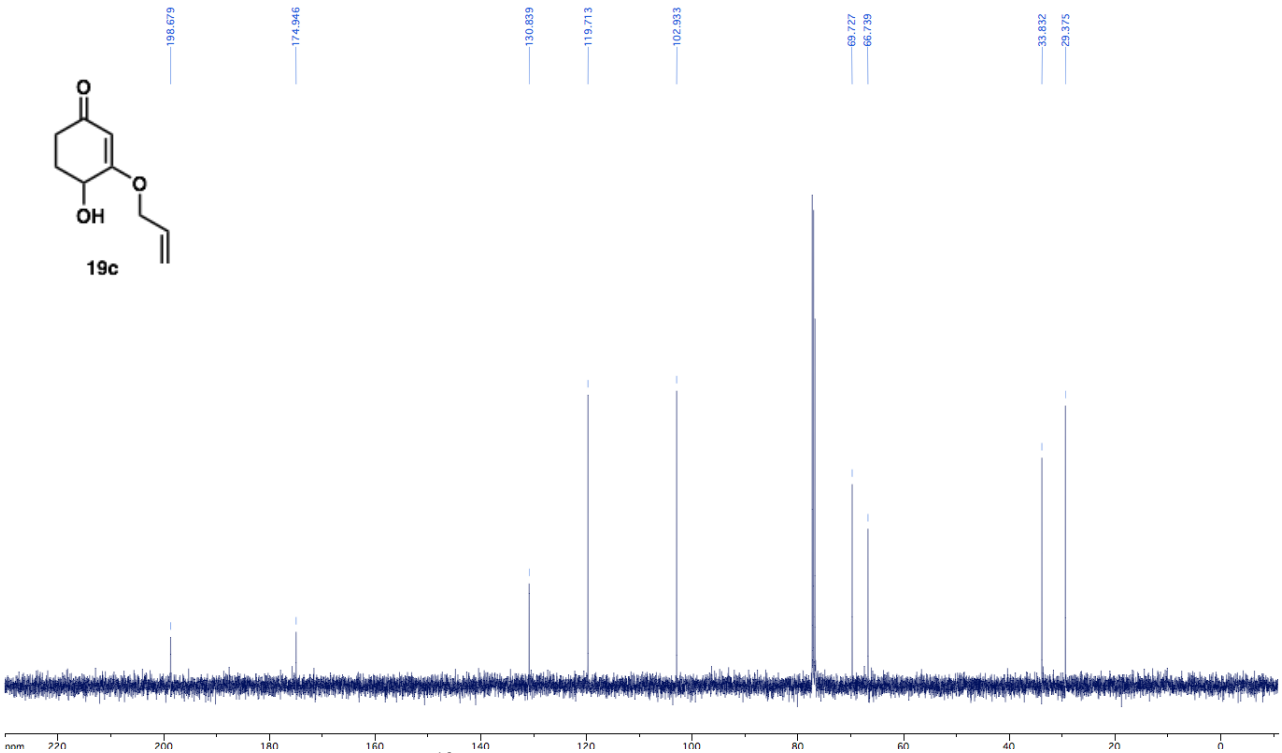
^{13}C NMR (126 MHz, $CDCl_3$)



19c

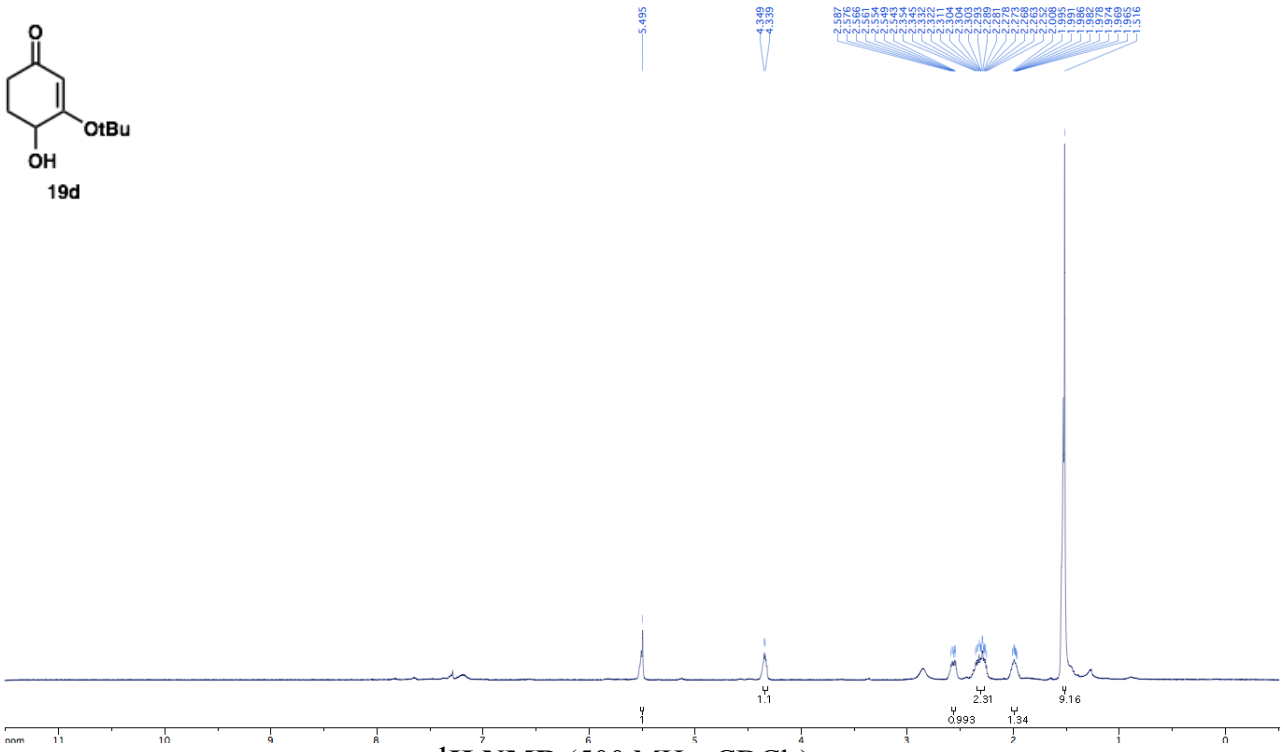


^{1}H NMR (500 MHz, $CDCl_3$)

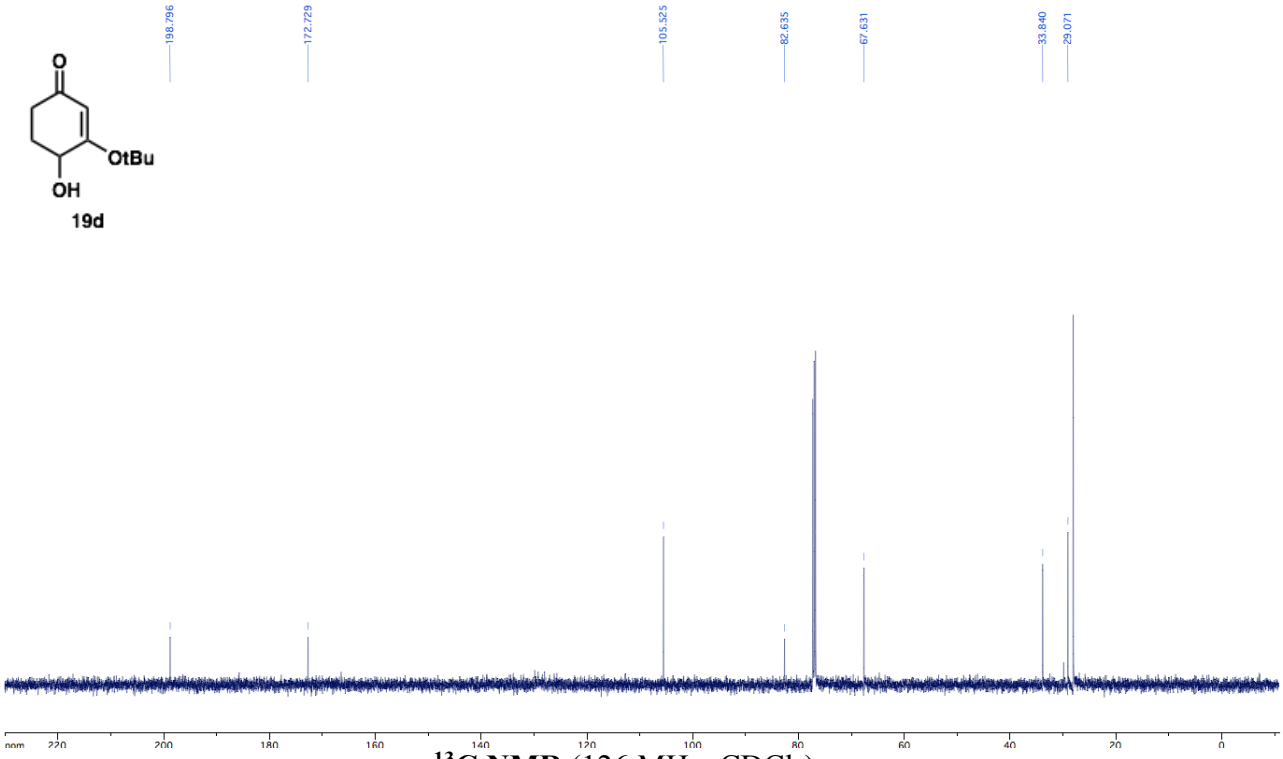


19c

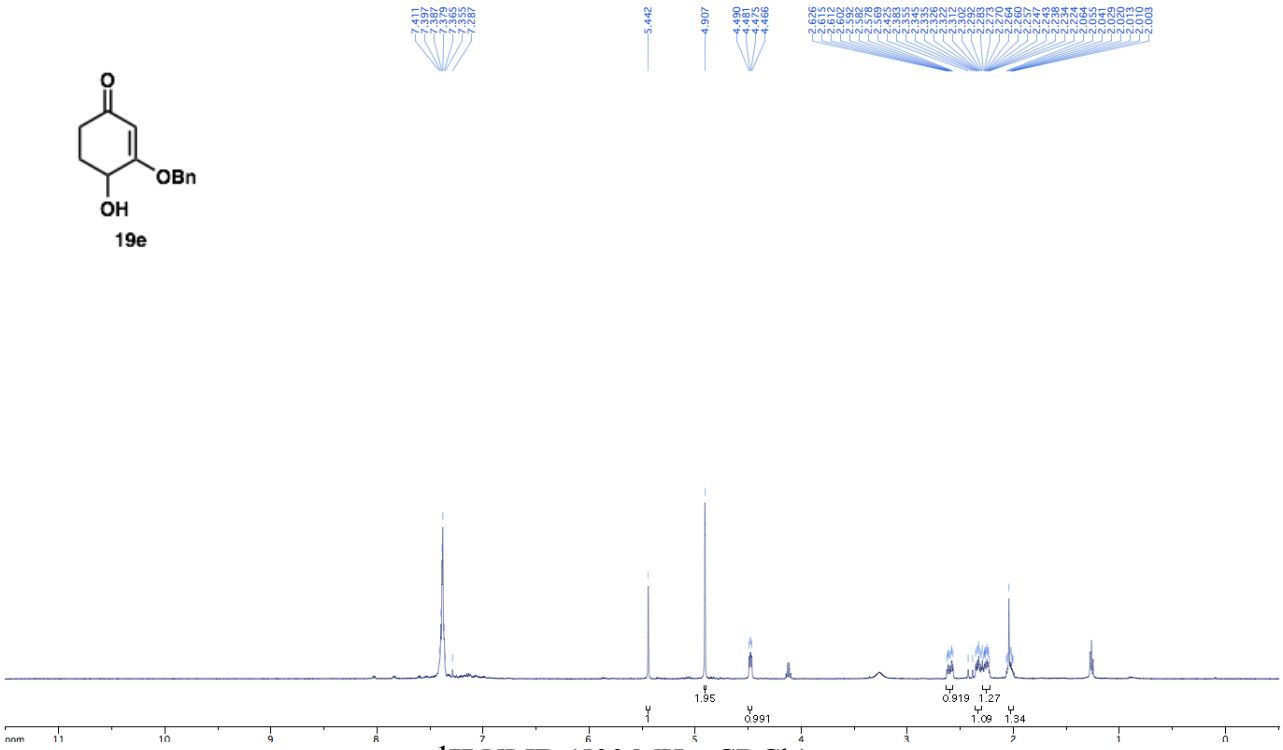
^{13}C NMR (126 MHz, $CDCl_3$)



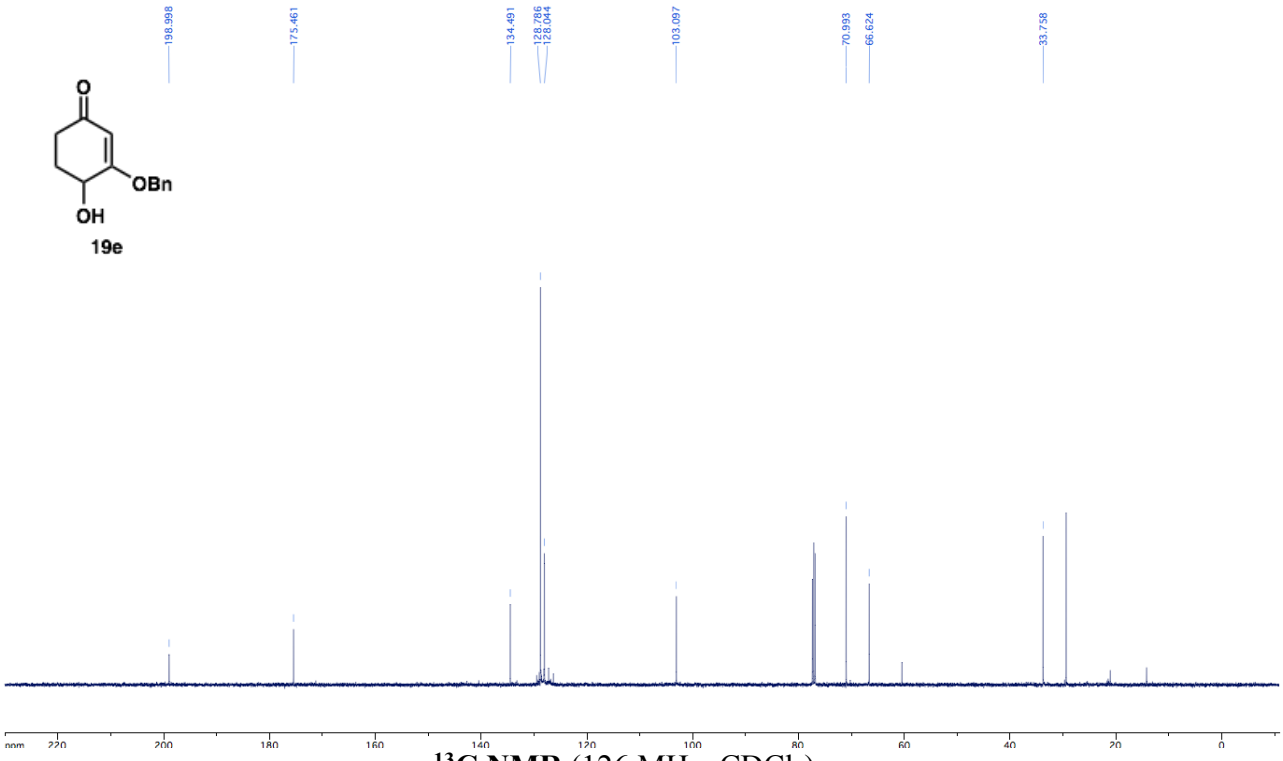
^{1}H NMR (500 MHz, $CDCl_3$)



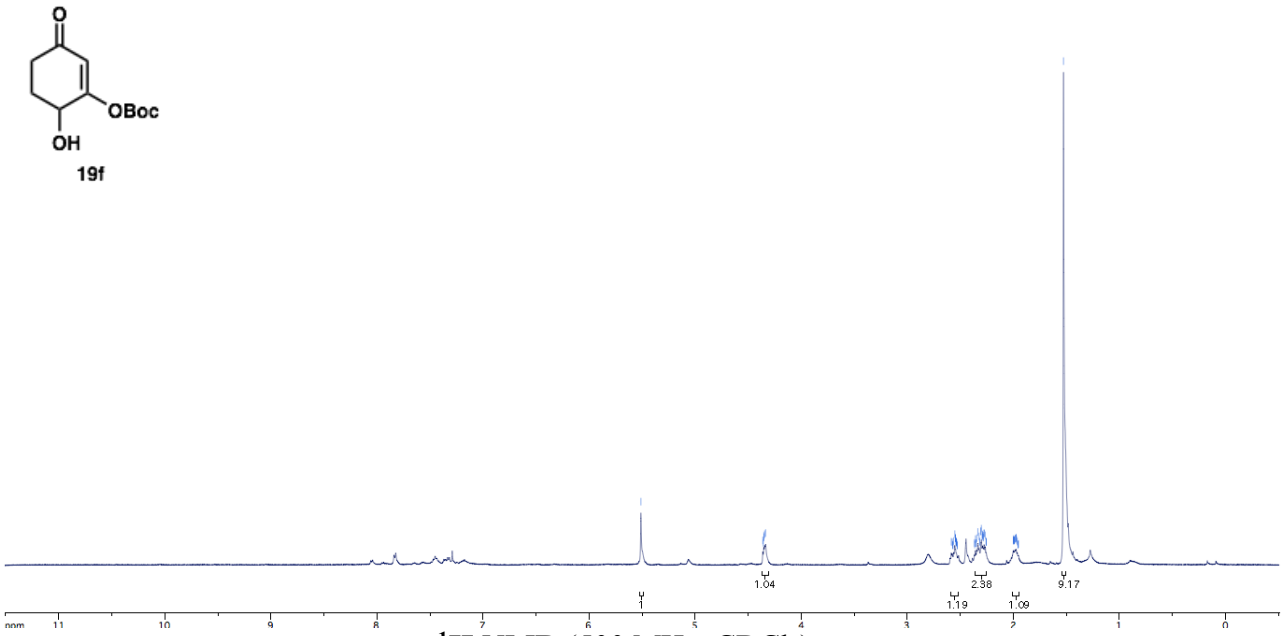
^{13}C NMR (126 MHz, $CDCl_3$)



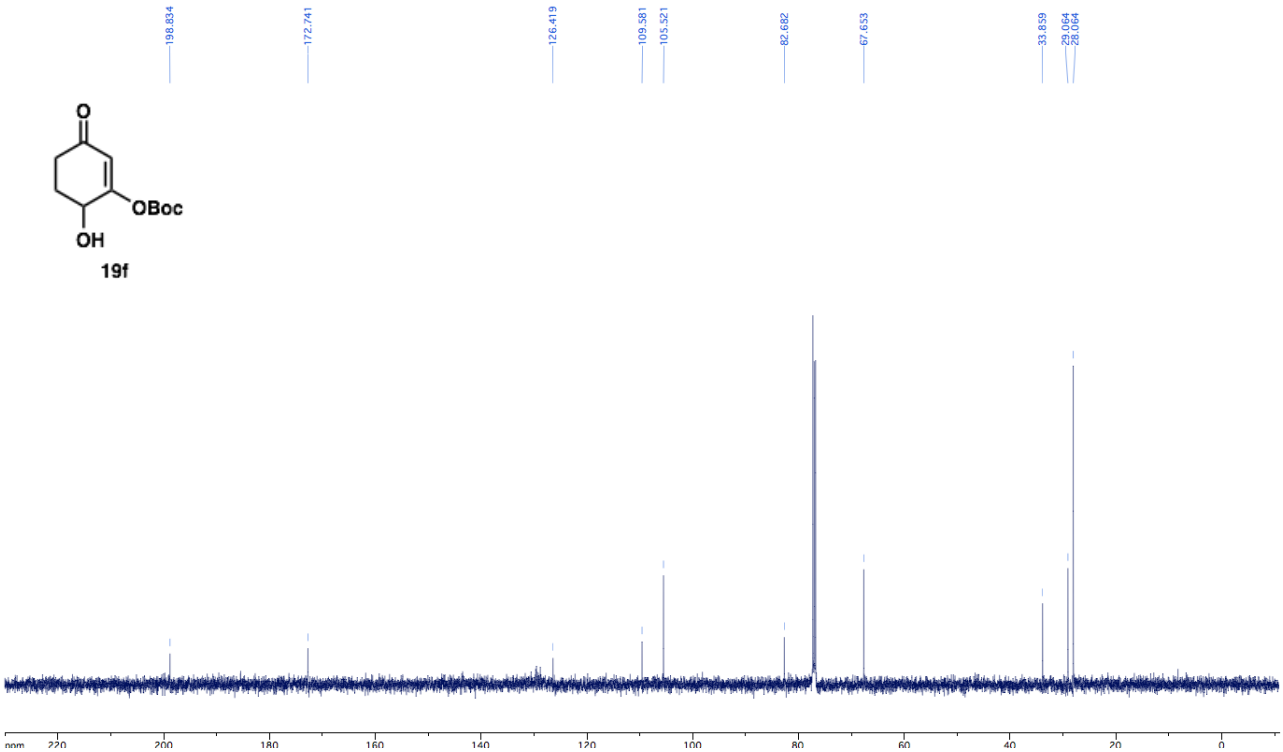
^{1}H NMR (500 MHz, $CDCl_3$)



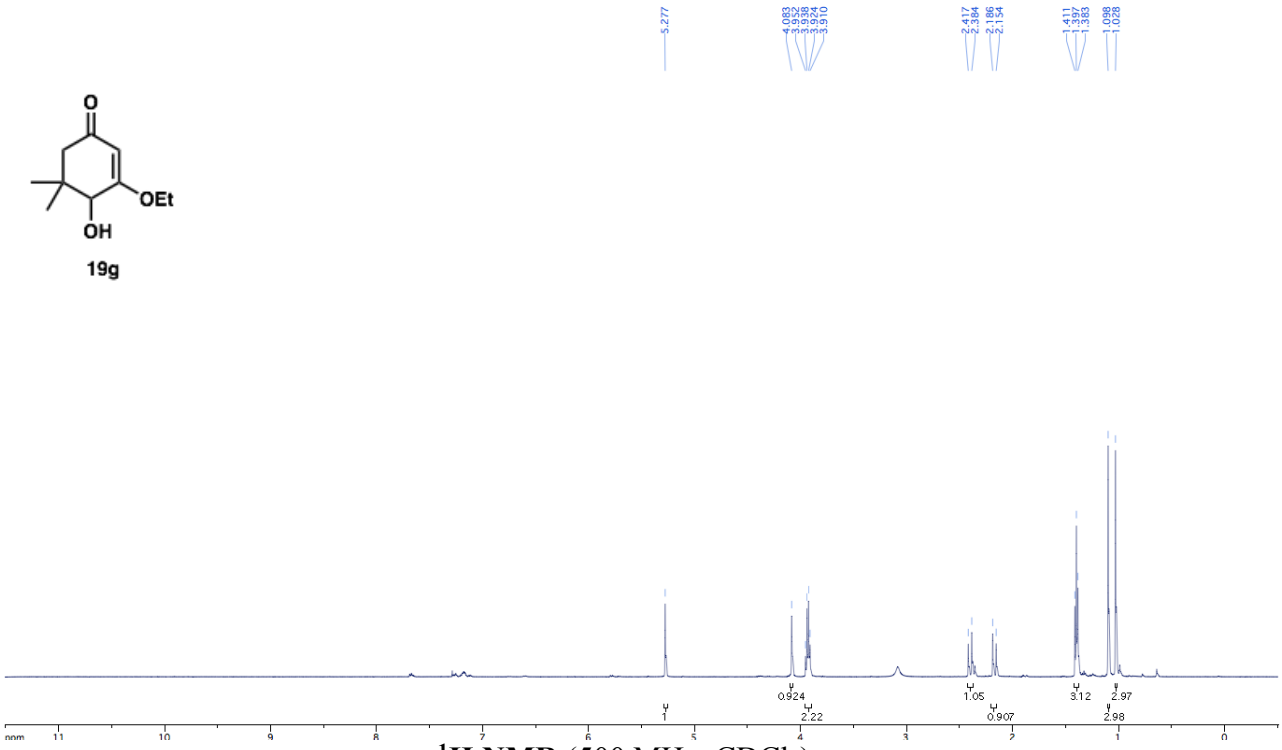
^{13}C NMR (126 MHz, $CDCl_3$)



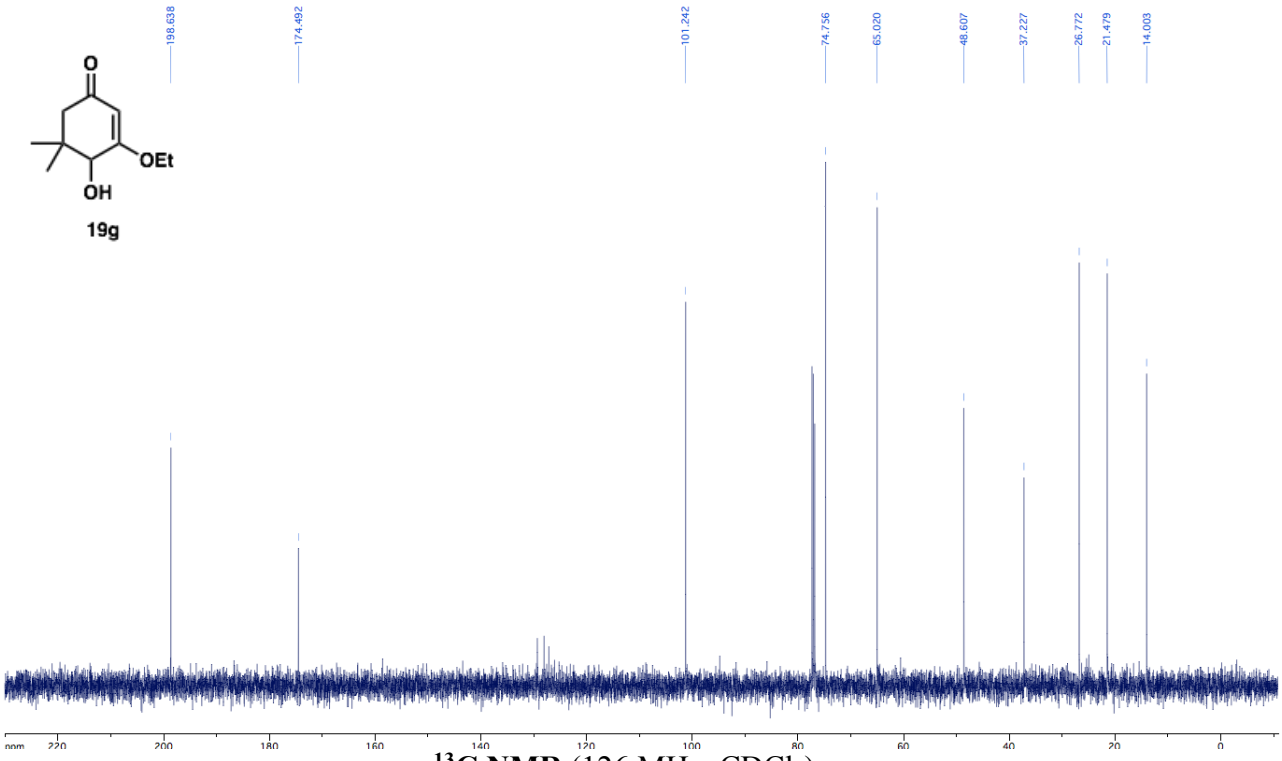
^{1}H NMR (500 MHz, $CDCl_3$)



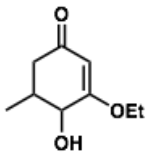
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

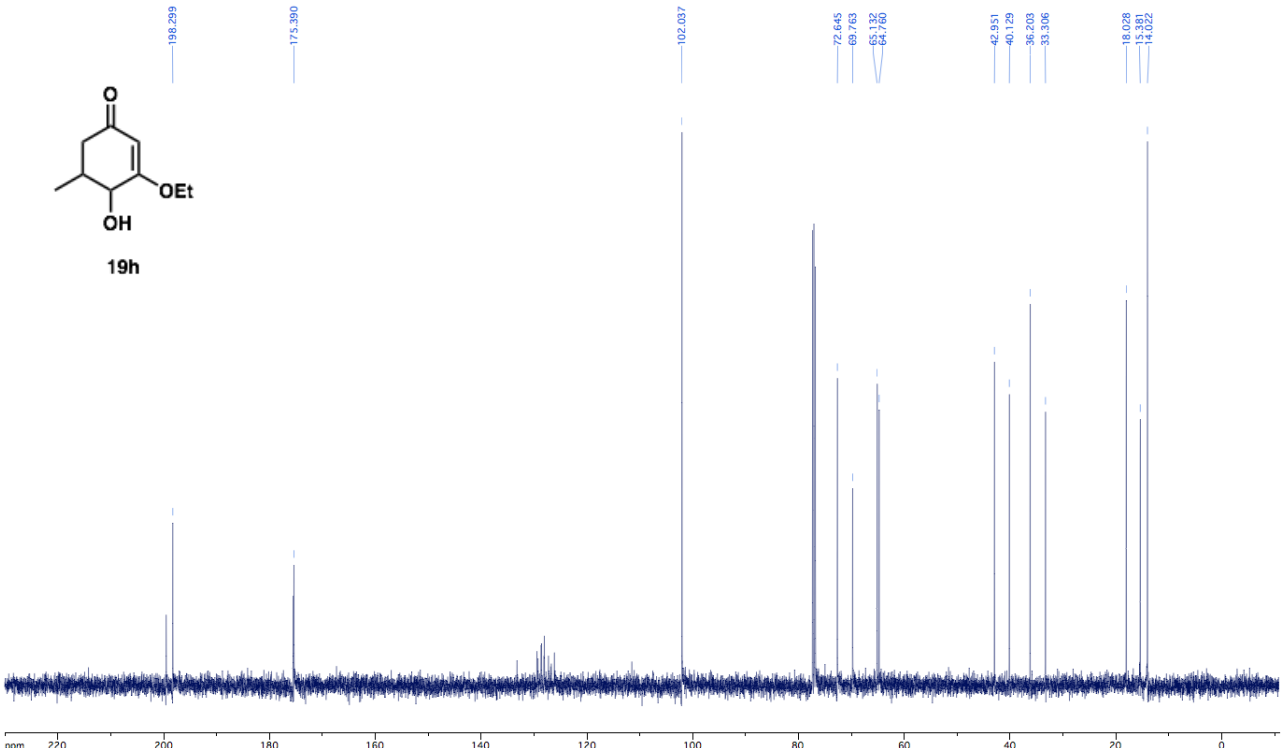


^{13}C NMR (126 MHz, $CDCl_3$)



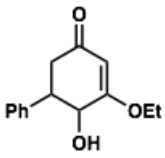
19h

^{1}H NMR (500 MHz, $CDCl_3$)



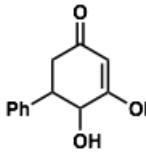
19h

^{13}C NMR (126 MHz, $CDCl_3$)



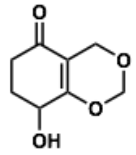
19i

^{1}H NMR (500 MHz, $CDCl_3$)

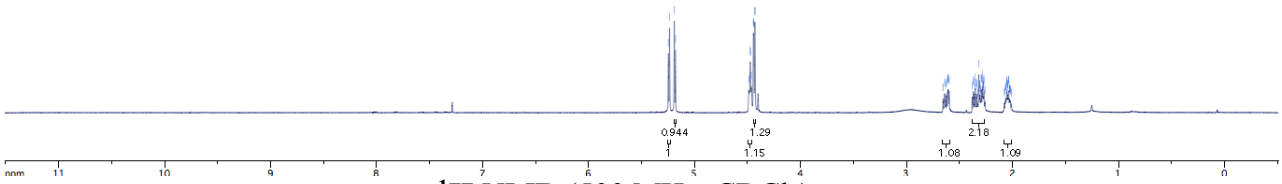


19i

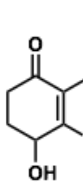
^{13}C NMR (126 MHz, $CDCl_3$)



19j

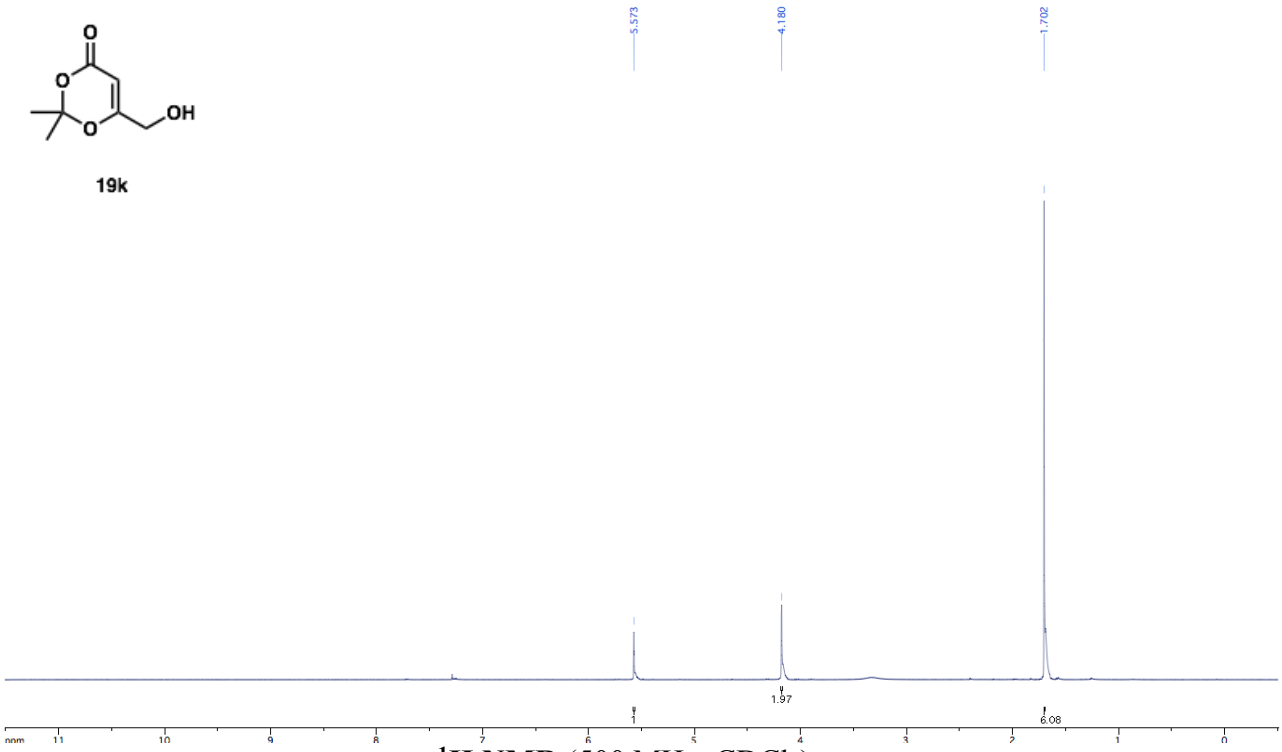


^{1}H NMR (500 MHz, $CDCl_3$)

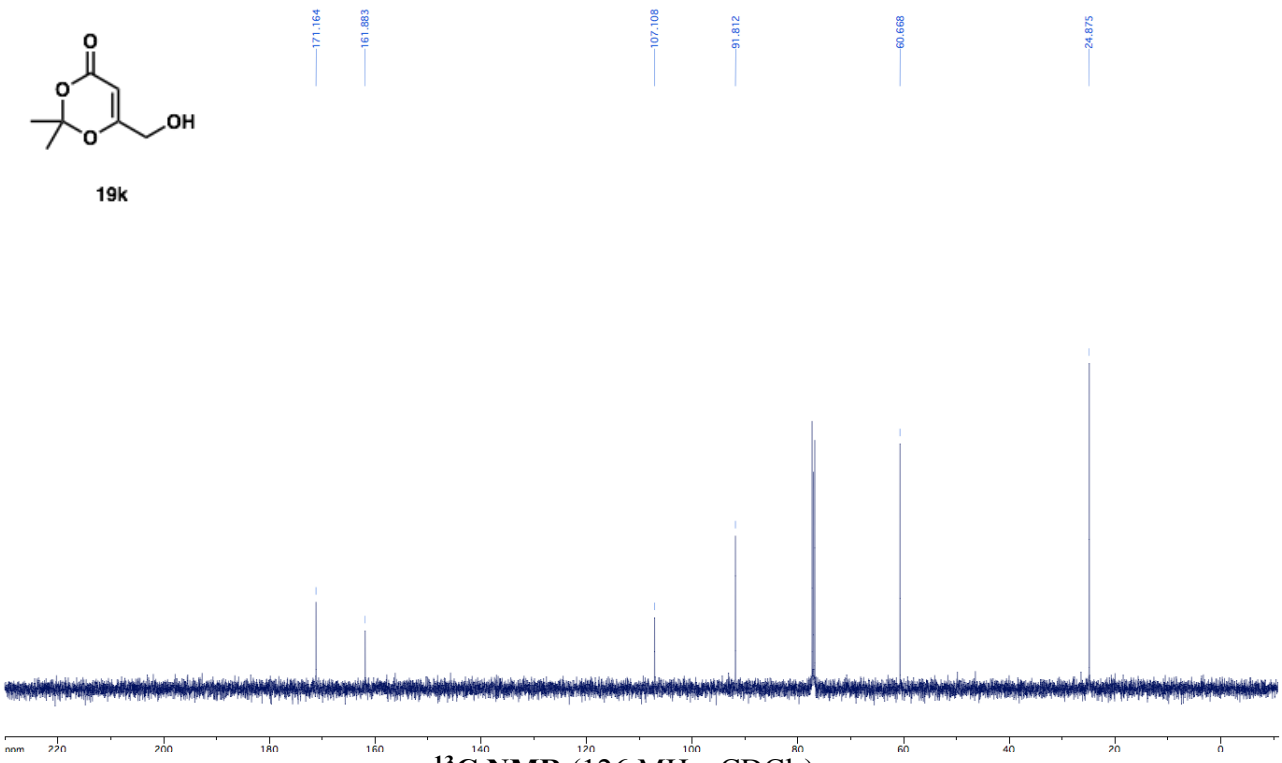


19j

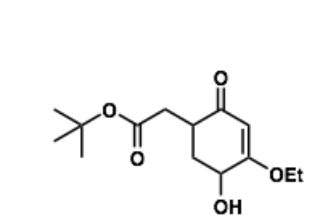
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

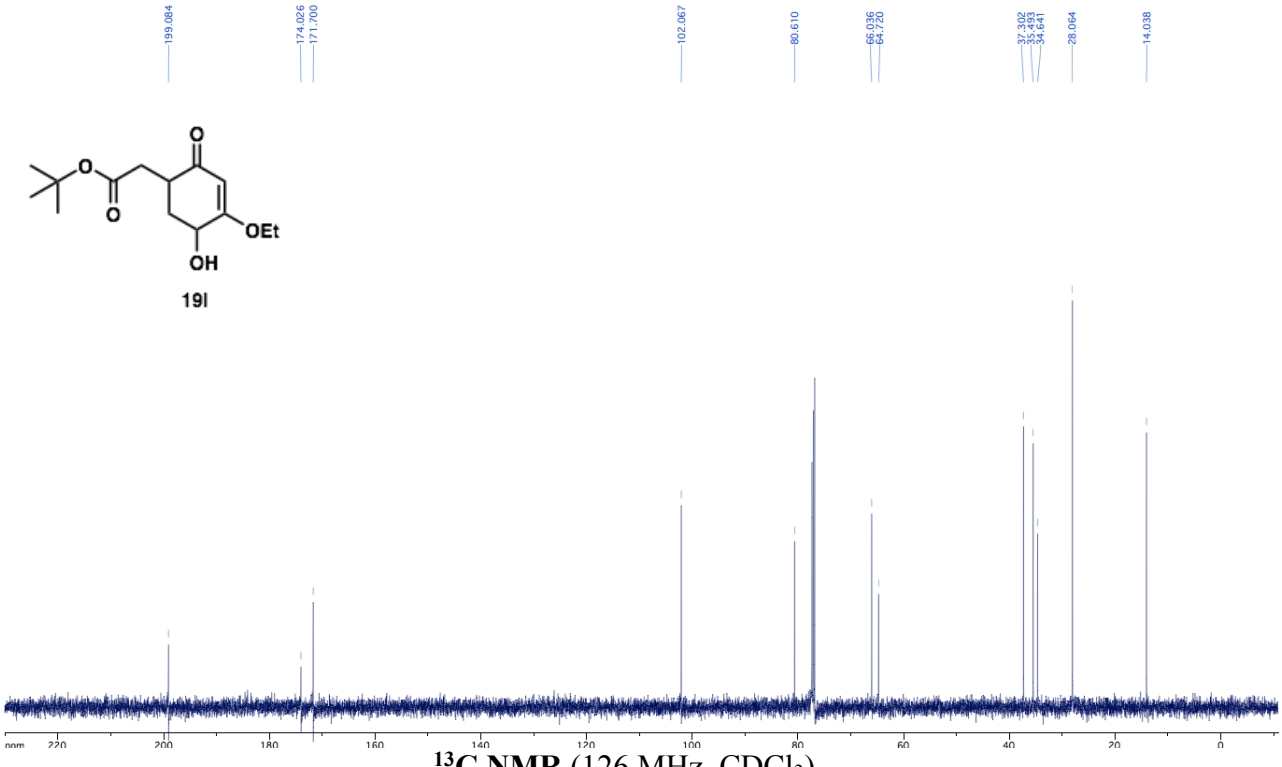


^{13}C NMR (126 MHz, $CDCl_3$)



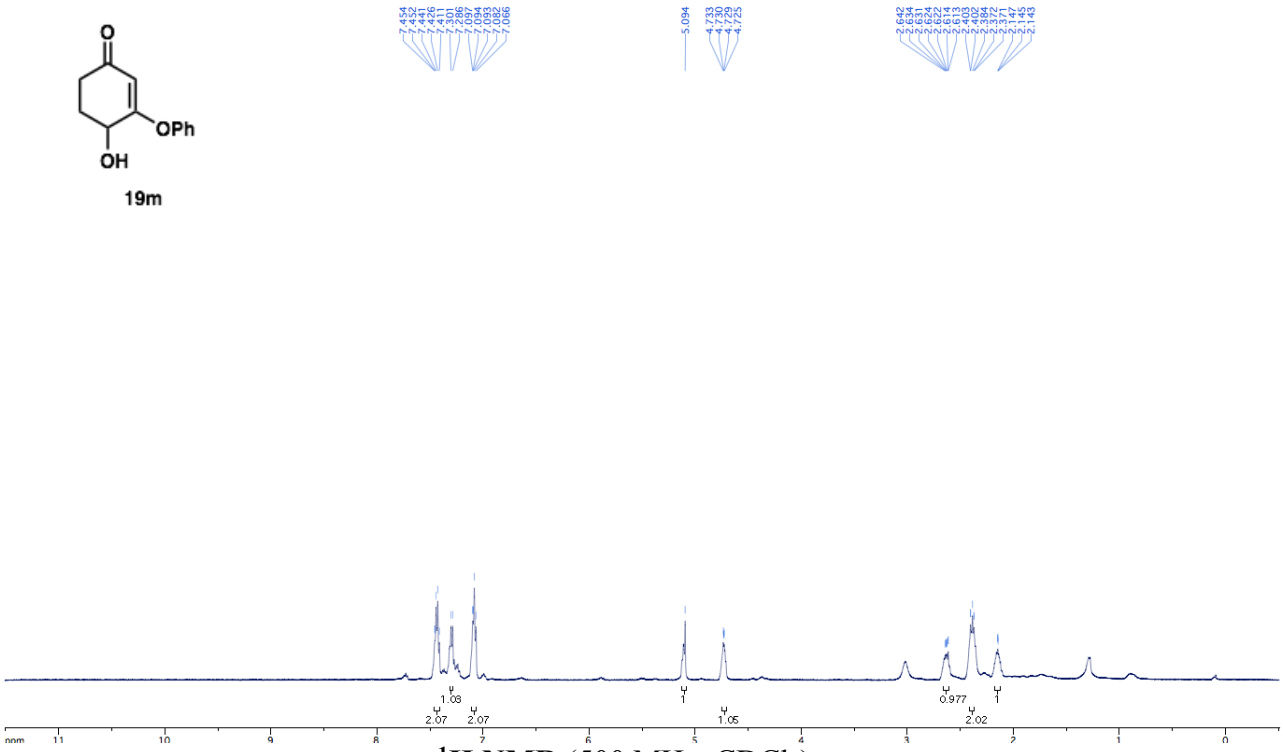
19l

^{1}H NMR (500 MHz, $CDCl_3$)

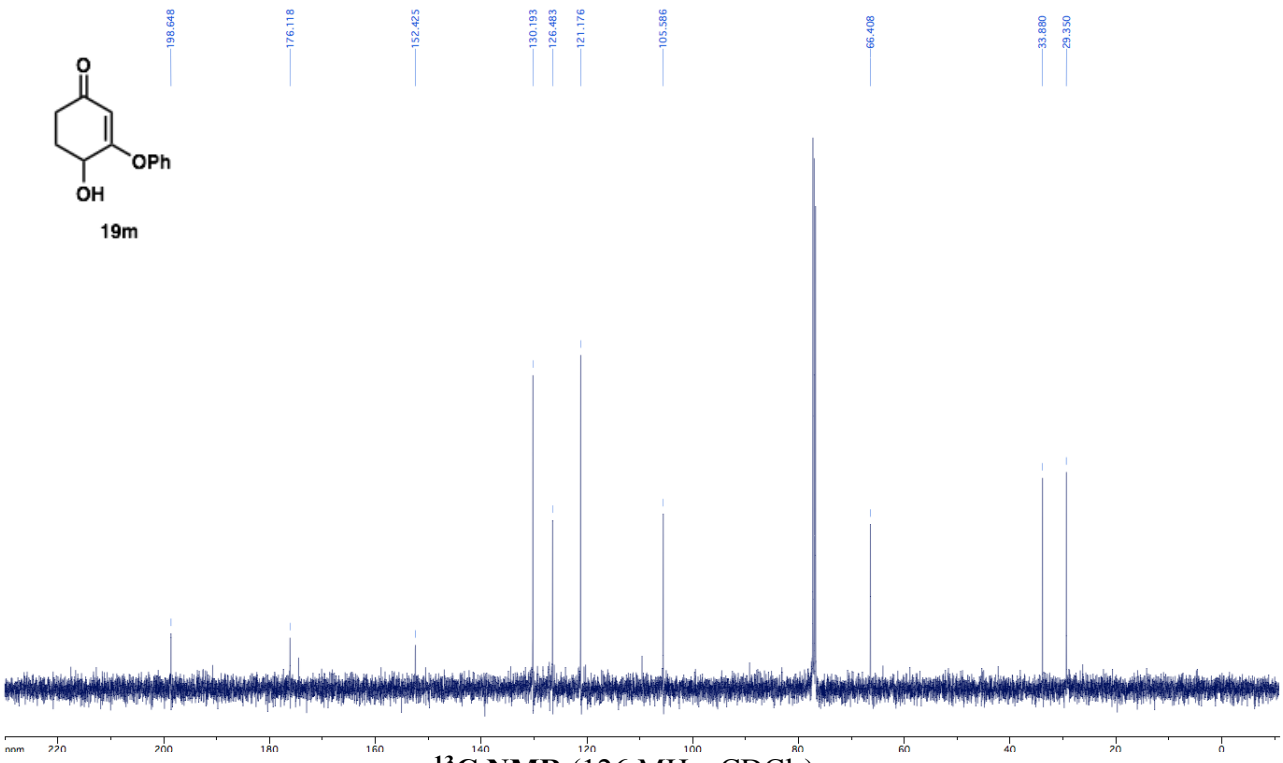


19l

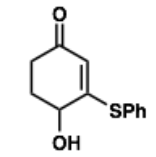
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

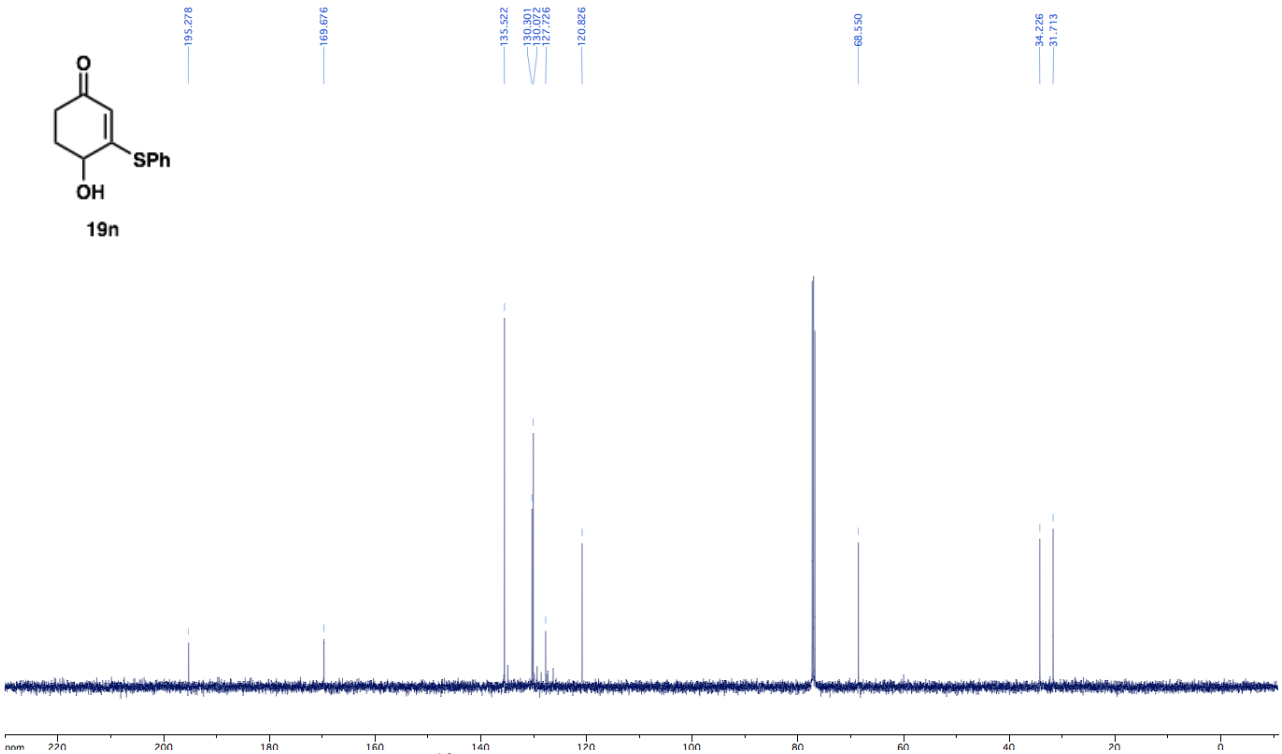


^{13}C NMR (126 MHz, $CDCl_3$)



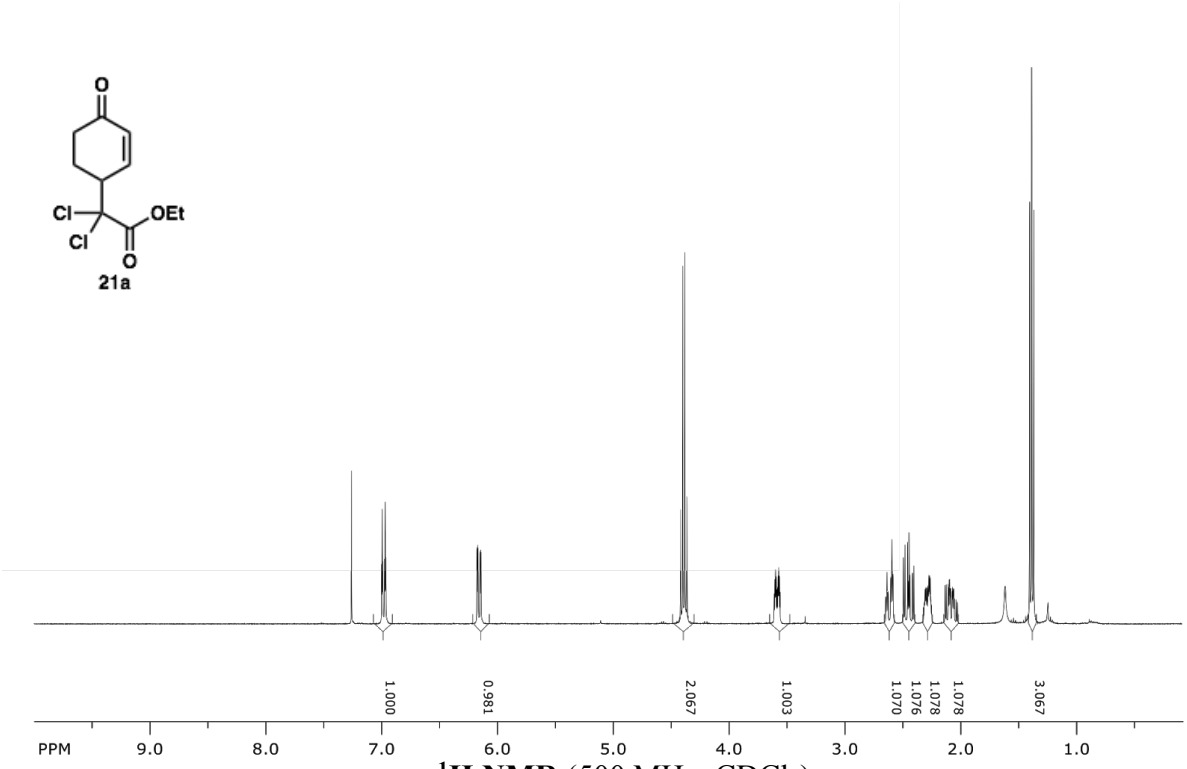
19n

^{1}H NMR (500 MHz, $CDCl_3$)

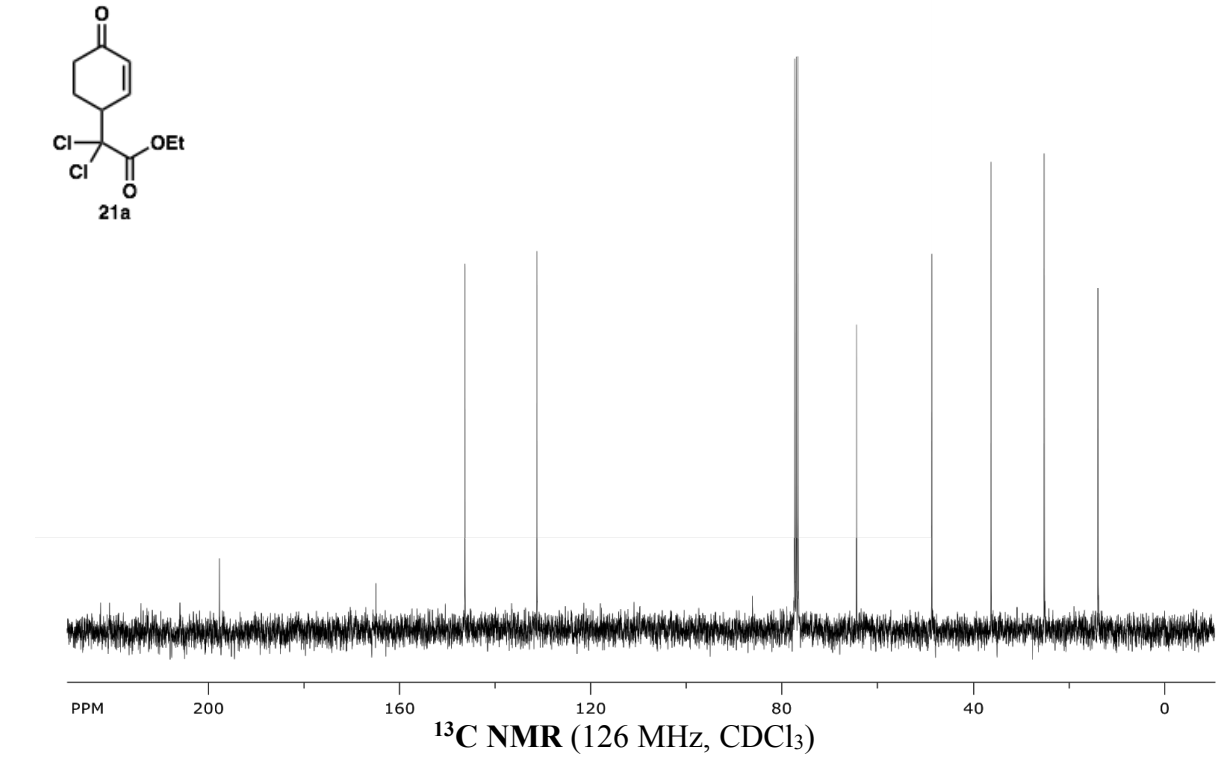


19n

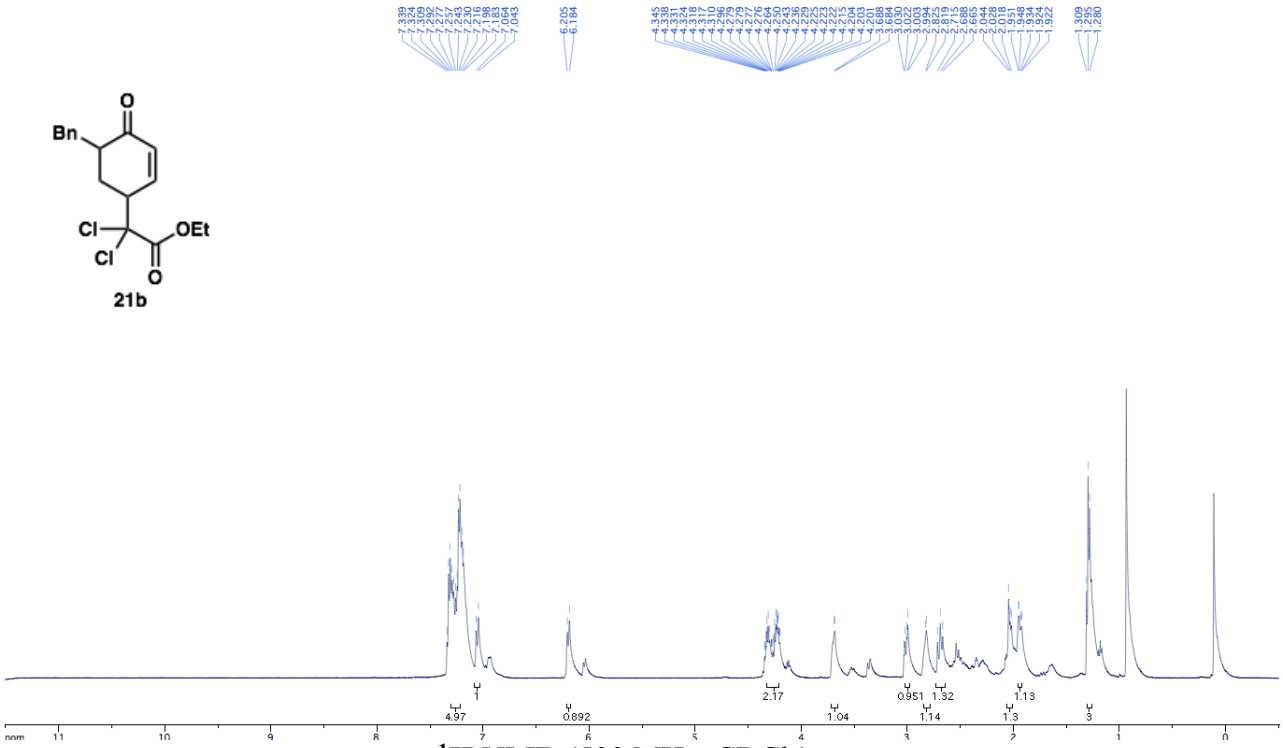
^{13}C NMR (126 MHz, $CDCl_3$)



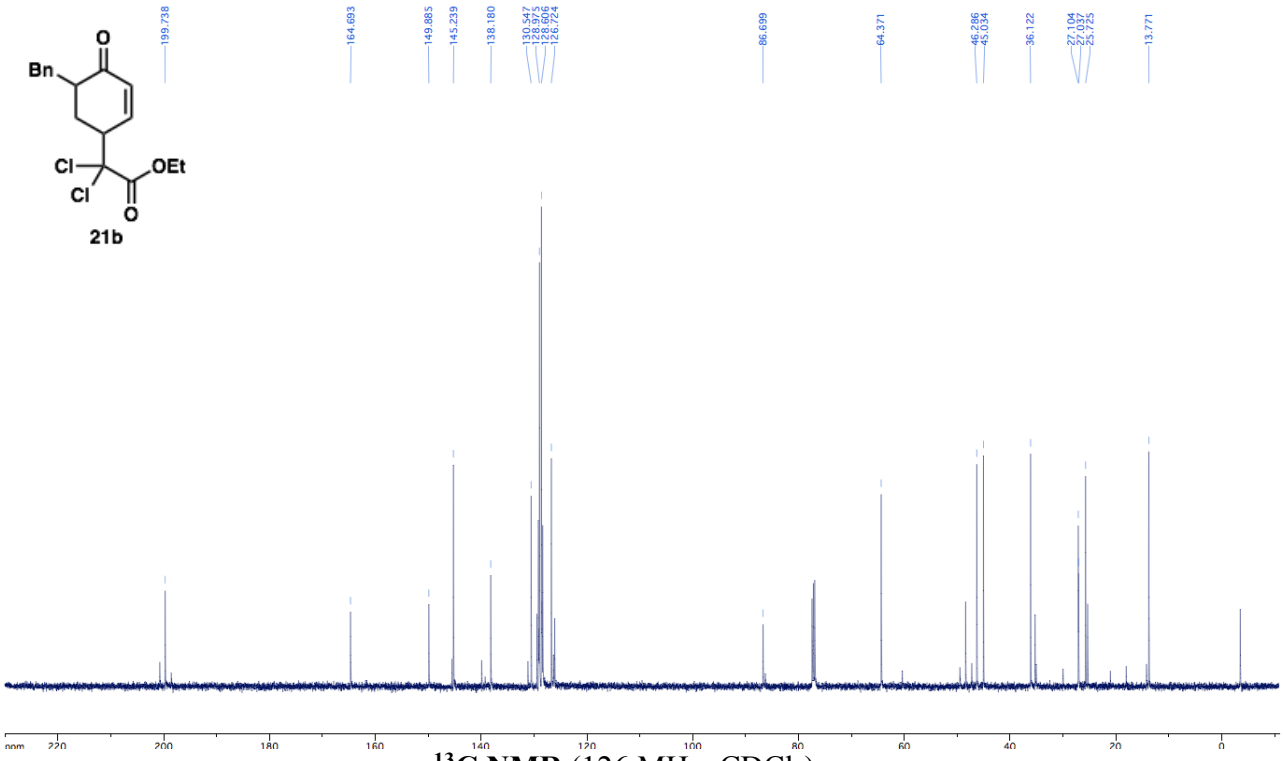
^{1}H NMR (500 MHz, $CDCl_3$)



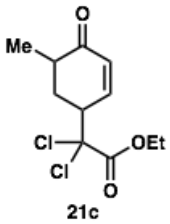
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

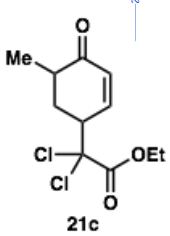


^{13}C NMR (126 MHz, $CDCl_3$)



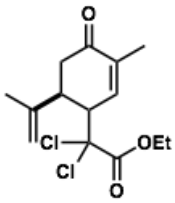
21c

^{1}H NMR (500 MHz, $CDCl_3$)



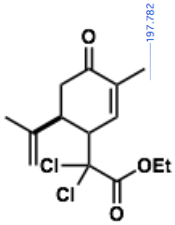
21c

^{13}C NMR (126 MHz, $CDCl_3$)



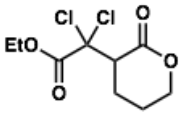
21d

^{1}H NMR (500 MHz, $CDCl_3$)

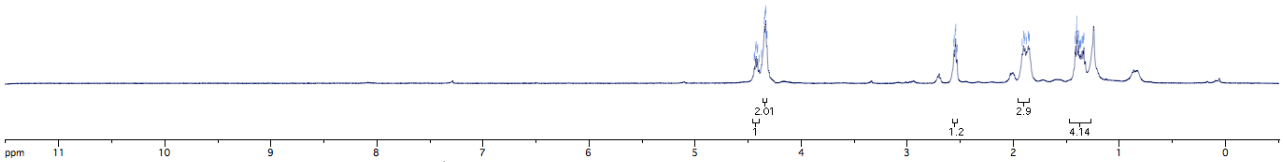


21d

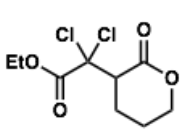
^{13}C NMR (126 MHz, $CDCl_3$)



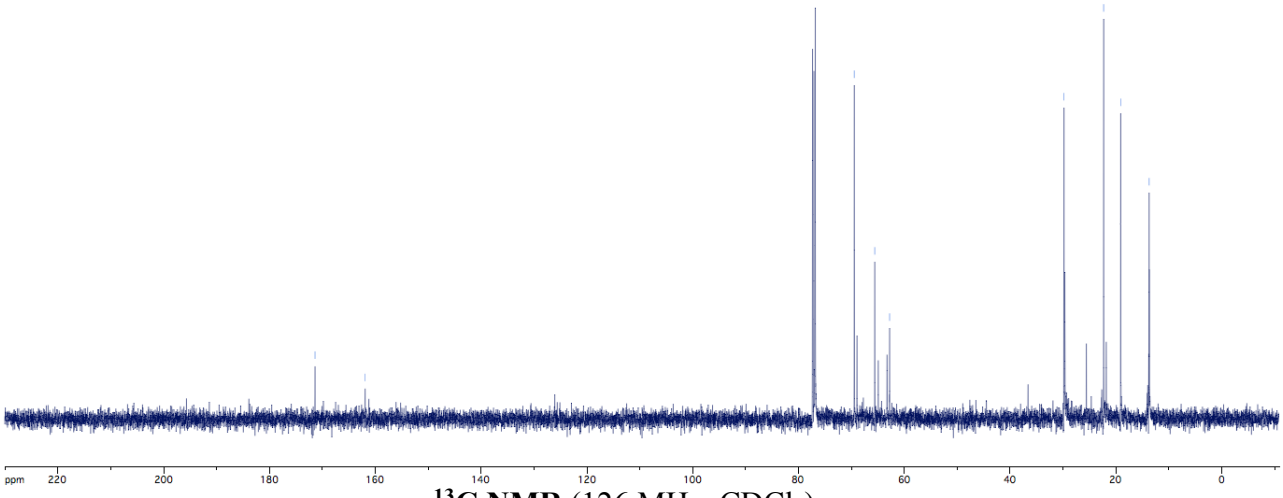
21e/f



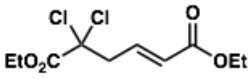
^{1}H NMR (500 MHz, $CDCl_3$)



21e/f

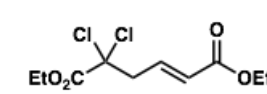


^{13}C NMR (126 MHz, $CDCl_3$)



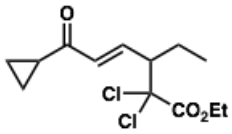
21g

^{1}H NMR (500 MHz, $CDCl_3$)



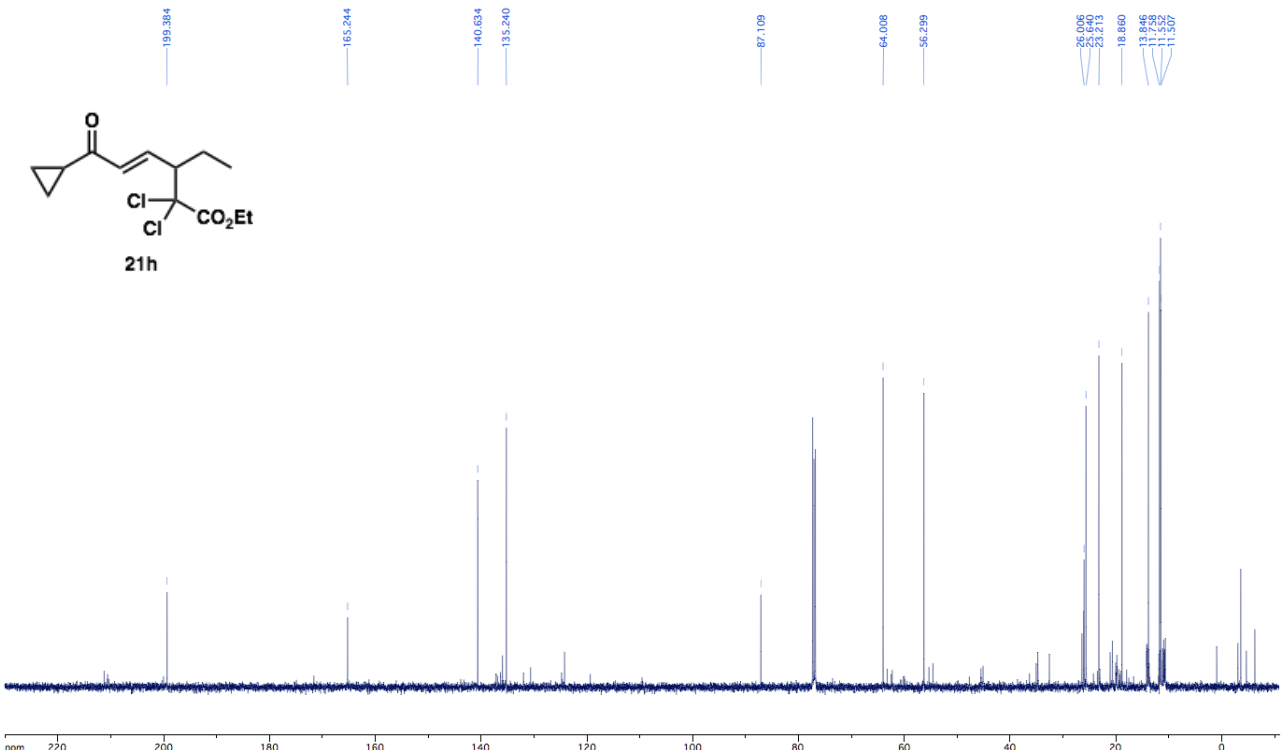
21g

^{13}C NMR (126 MHz, $CDCl_3$)



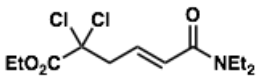
21h

^{1}H NMR (500 MHz, $CDCl_3$)



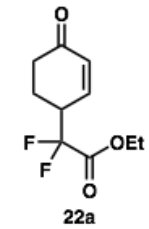
21h

^{13}C NMR (126 MHz, $CDCl_3$)



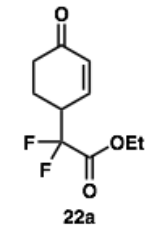
21i

^{1}H NMR (500 MHz, $CDCl_3$)

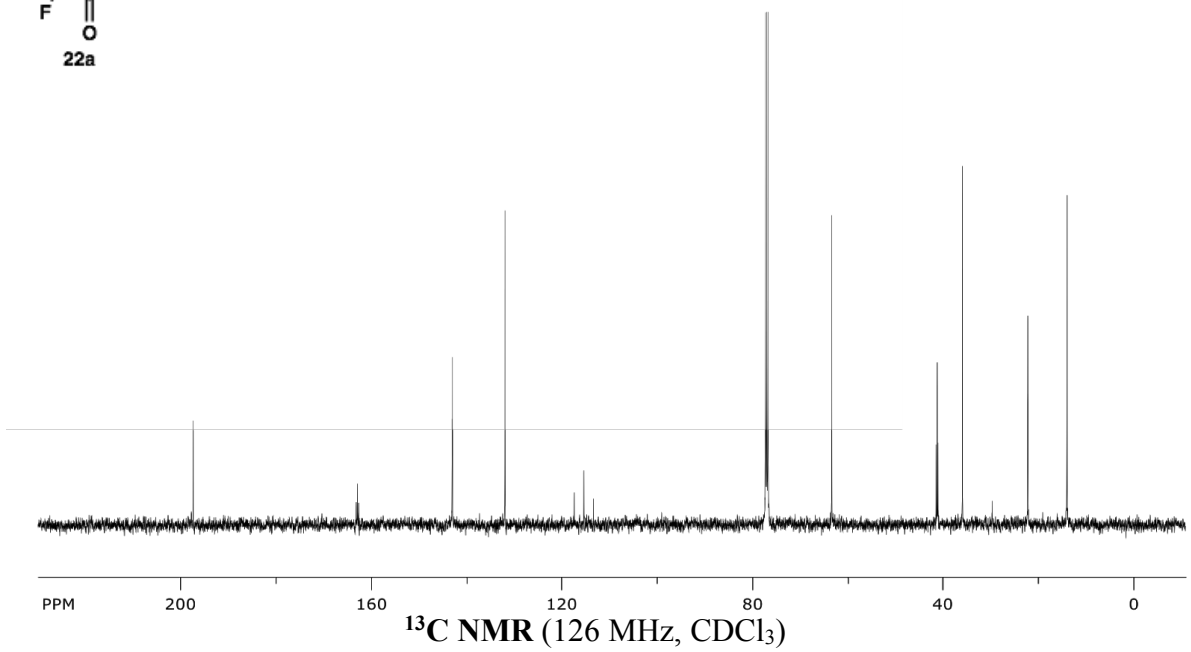


22a

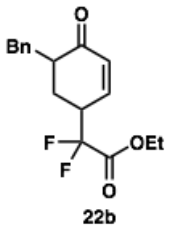
^{1}H NMR (500 MHz, $CDCl_3$)



22a

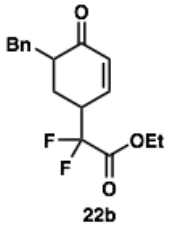


^{13}C NMR (126 MHz, $CDCl_3$)



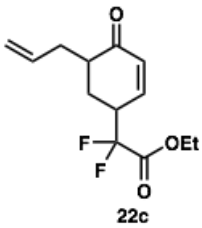
22b

^{1}H NMR (500 MHz, $CDCl_3$)

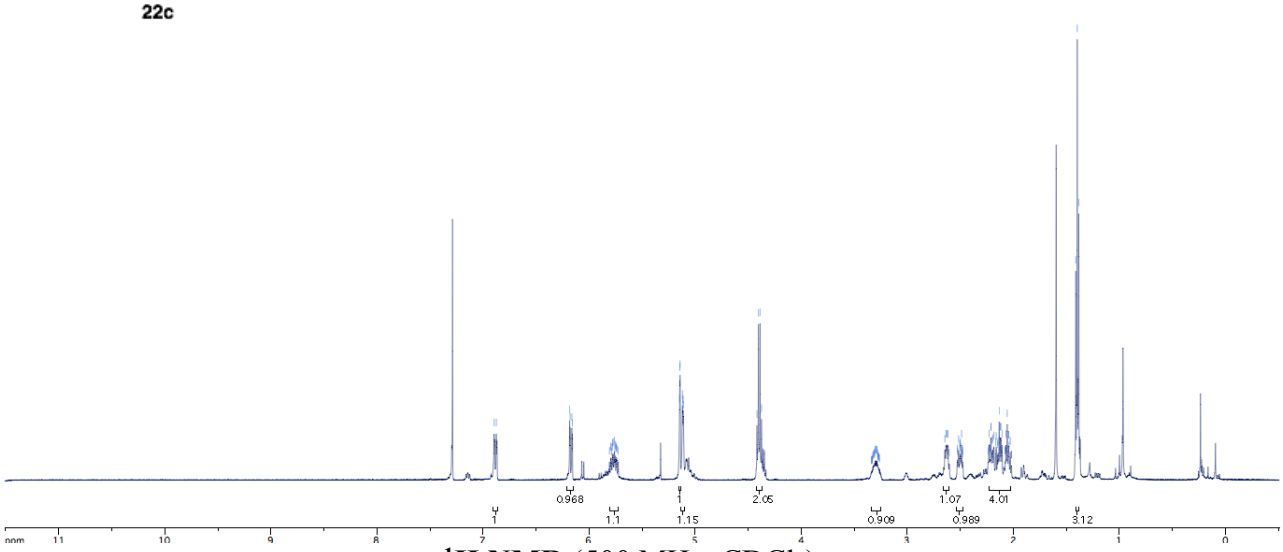


22b

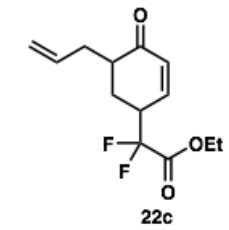
^{13}C NMR (126 MHz, $CDCl_3$)



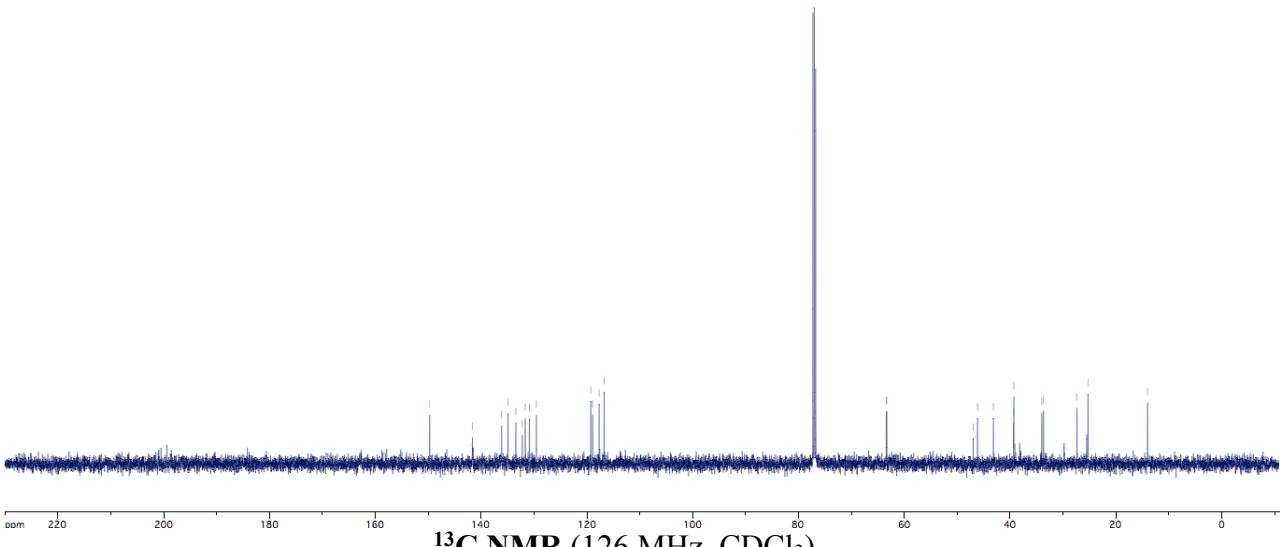
22c



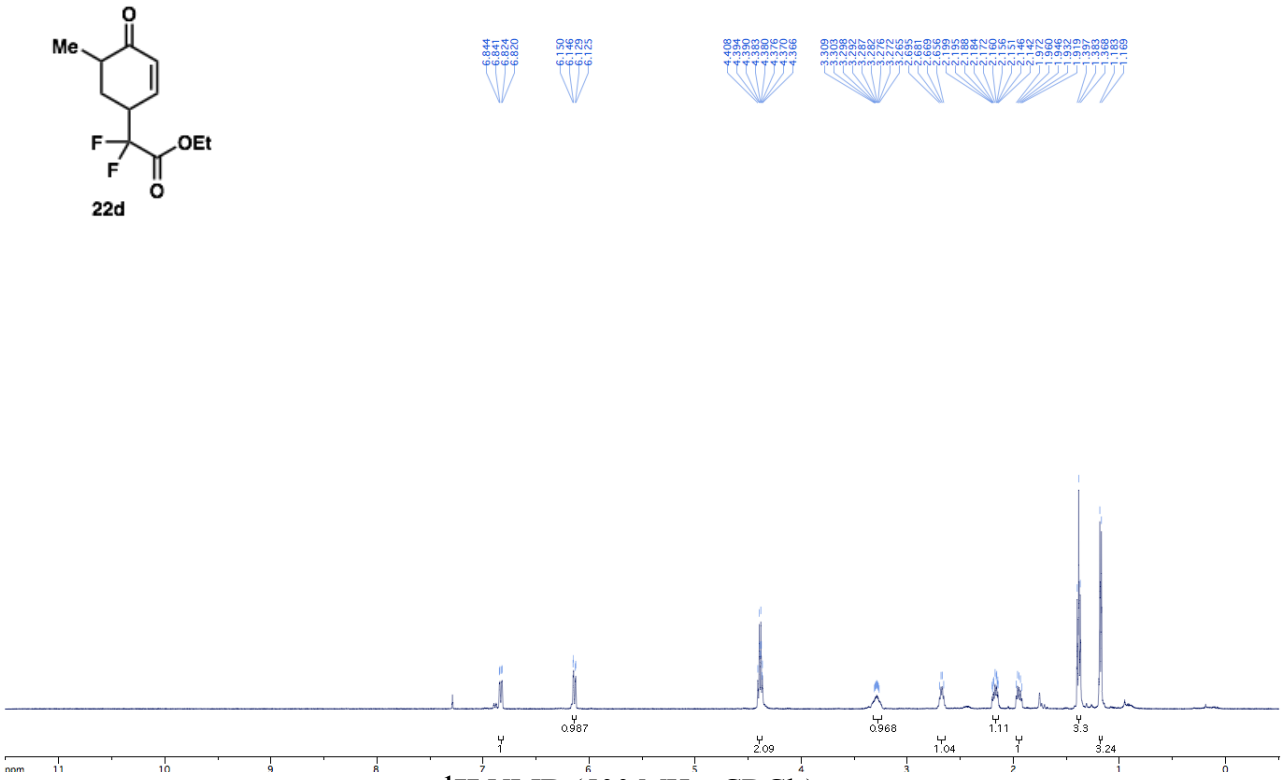
^{1}H NMR (500 MHz, $CDCl_3$)



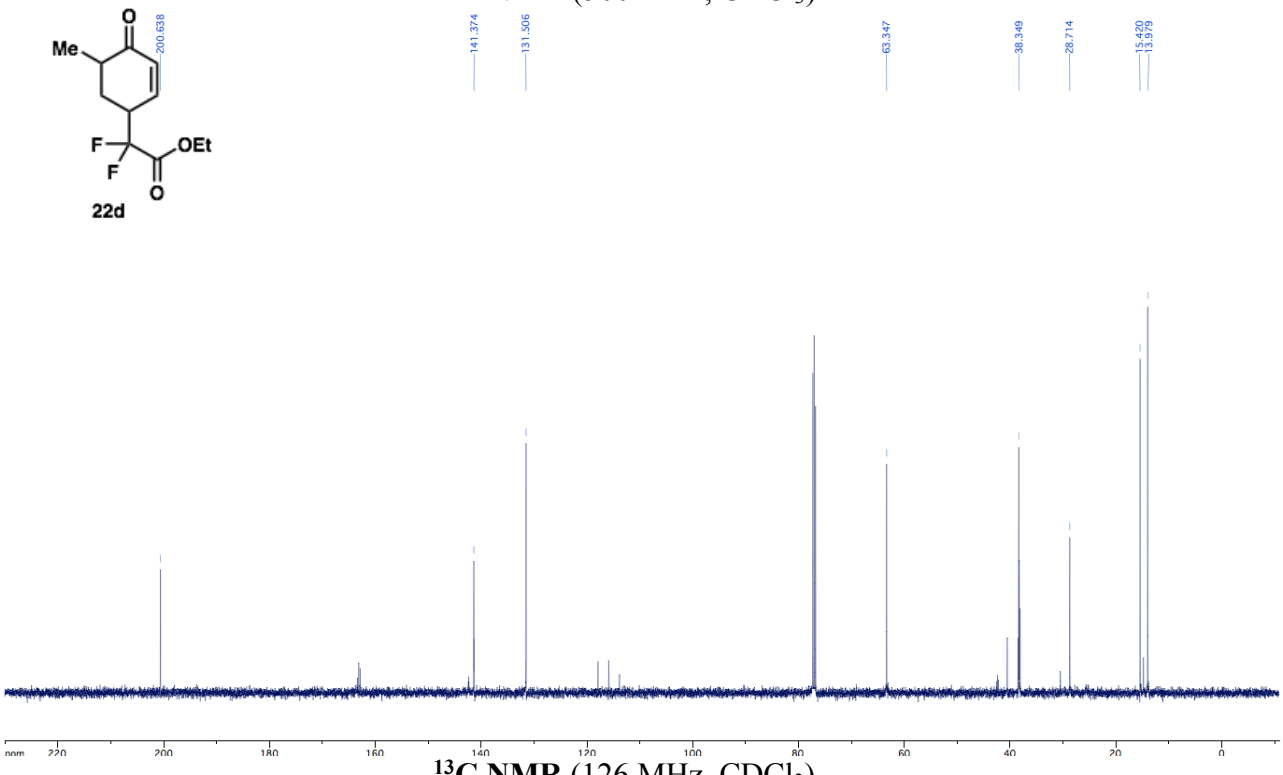
22c



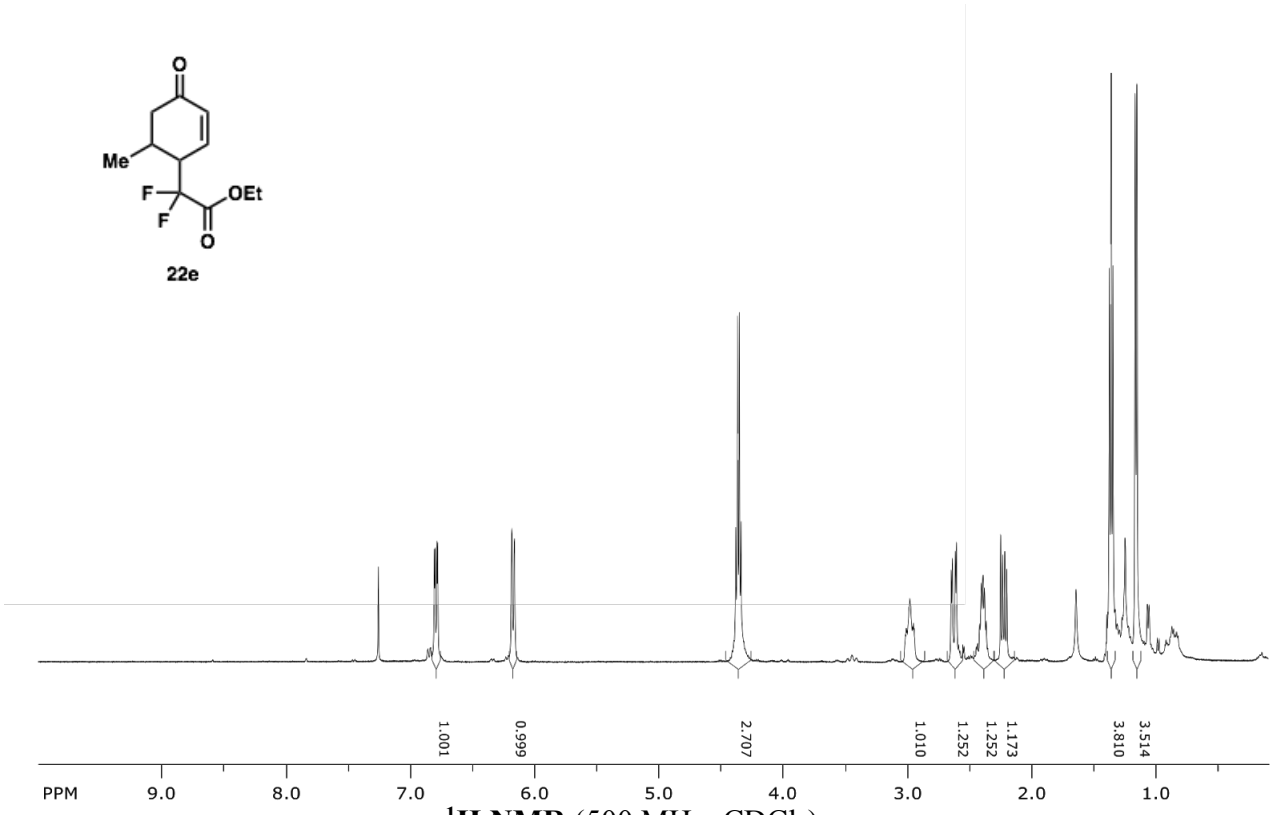
^{13}C NMR (126 MHz, $CDCl_3$)



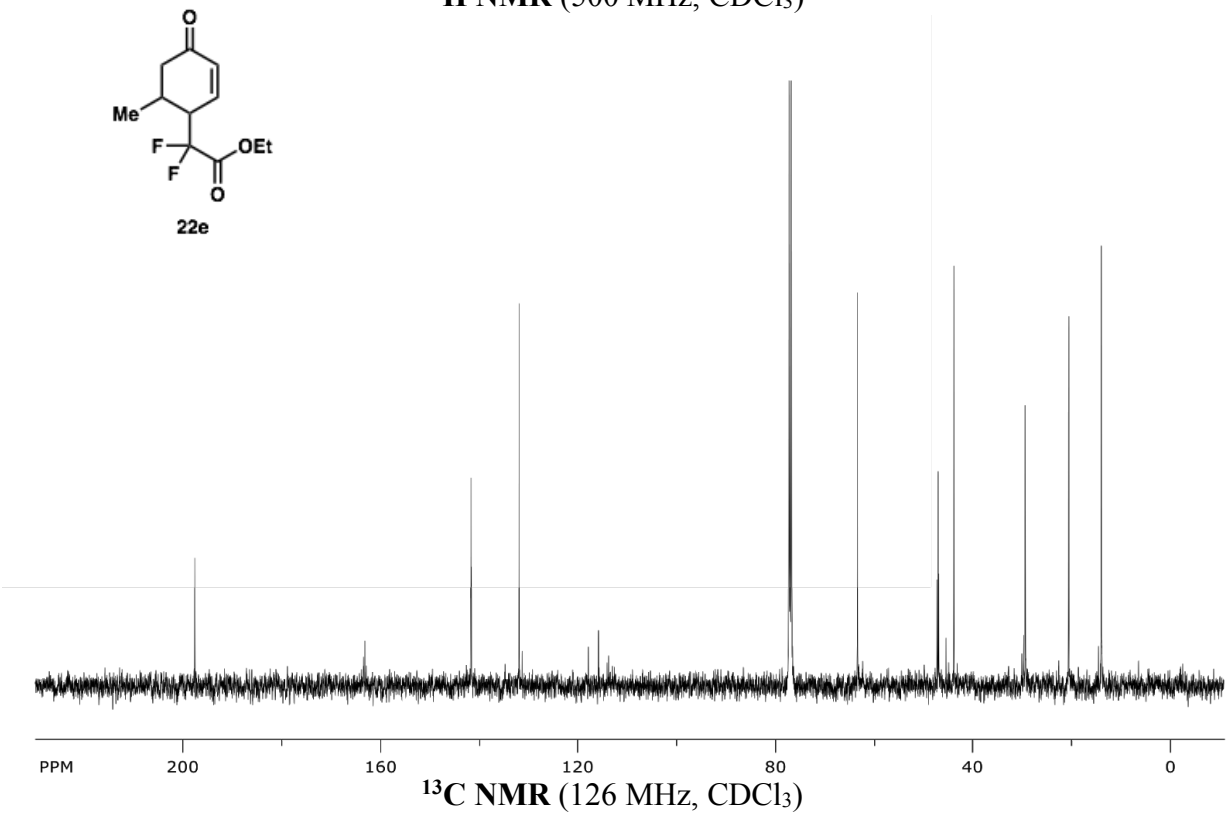
^{1}H NMR (500 MHz, $CDCl_3$)



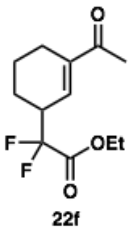
^{13}C NMR (126 MHz, $CDCl_3$)



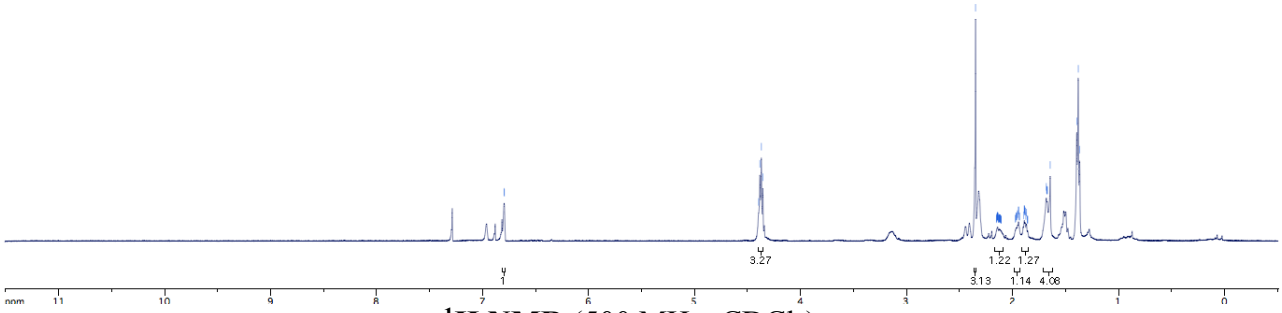
^{1}H NMR (500 MHz, $CDCl_3$)



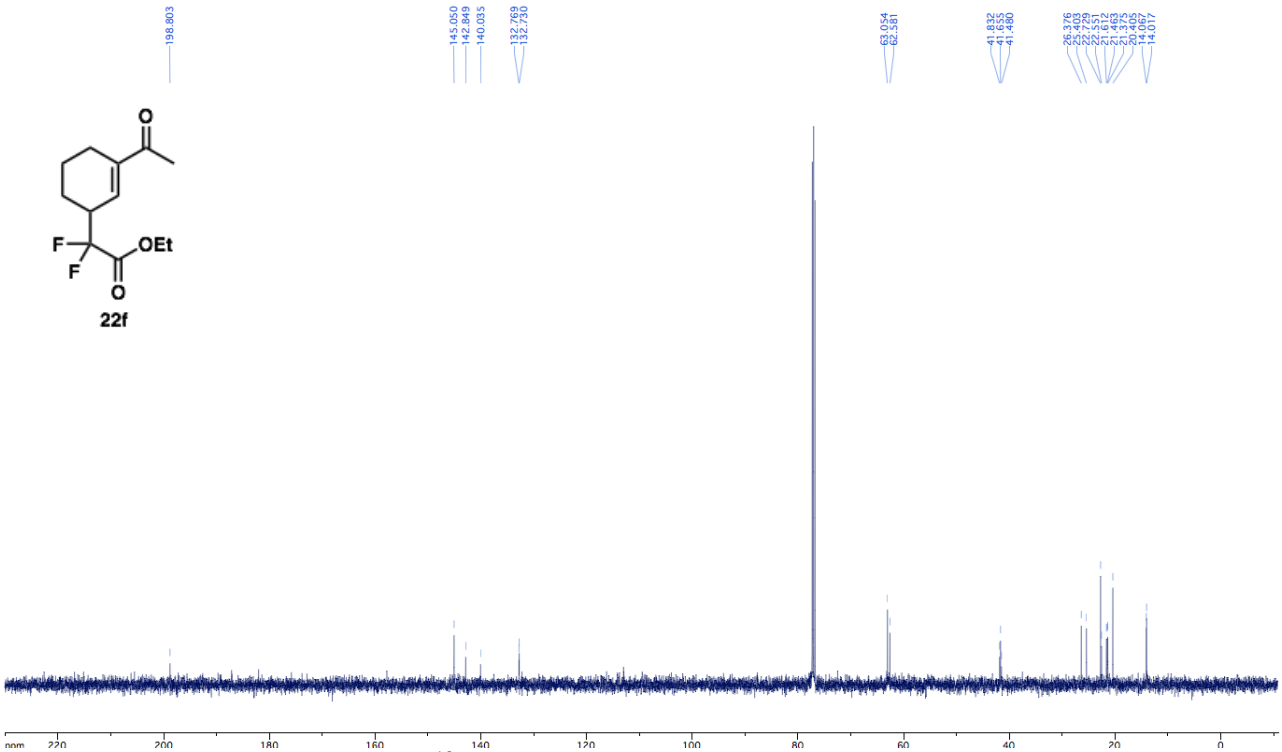
^{13}C NMR (126 MHz, $CDCl_3$)



22f

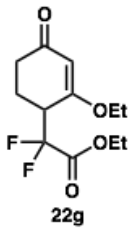


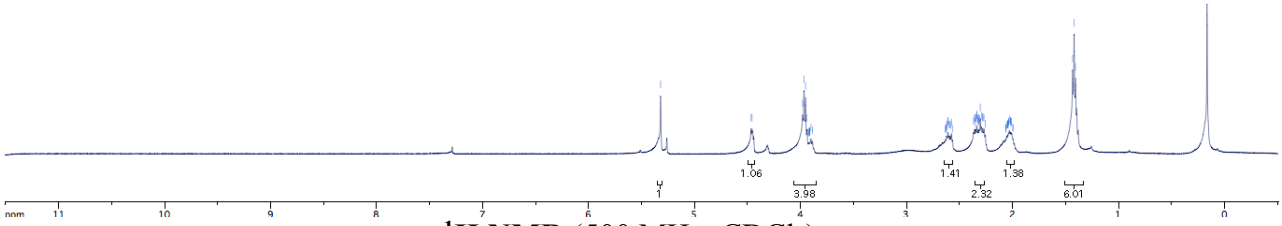
^{1}H NMR (500 MHz, $CDCl_3$)



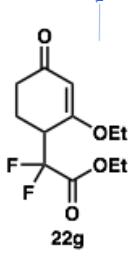
22f

^{13}C NMR (126 MHz, $CDCl_3$)

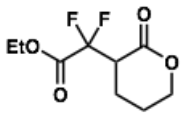




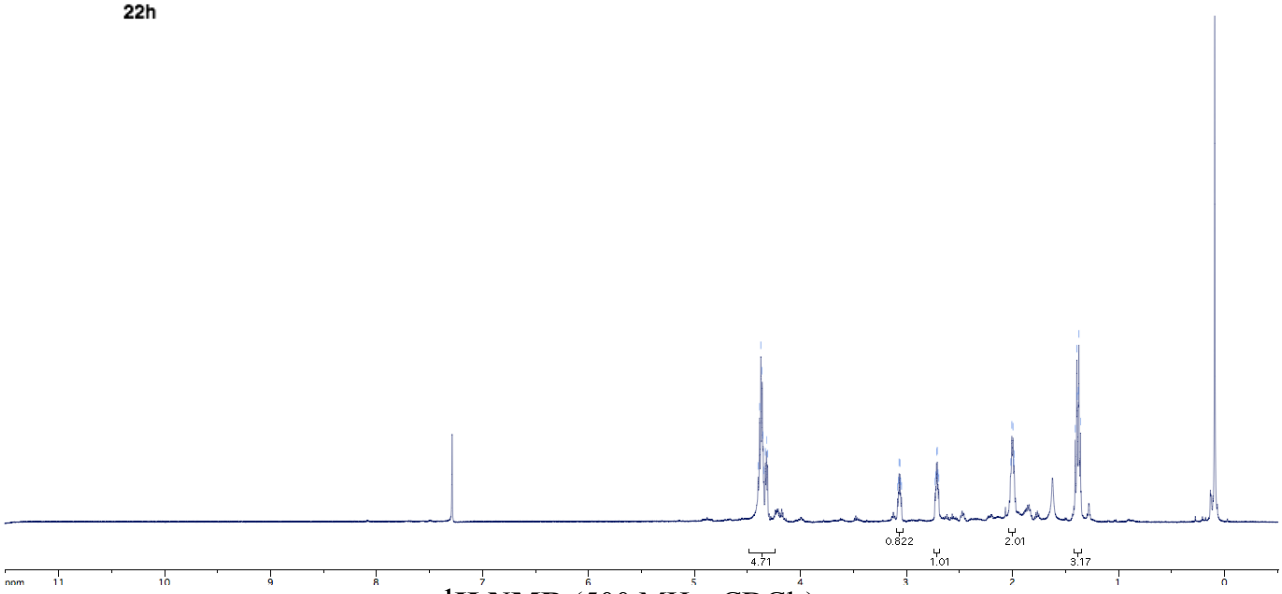
^{1}H NMR (500 MHz, $CDCl_3$)



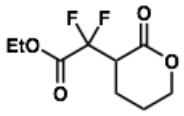
^{13}C NMR (126 MHz, $CDCl_3$)



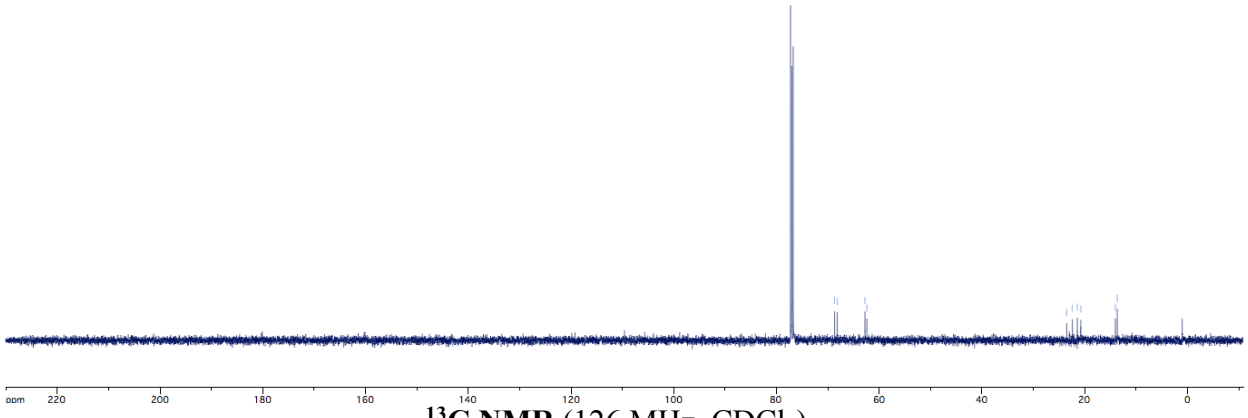
22h



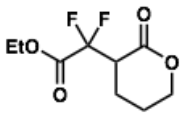
^{1}H NMR (500 MHz, $CDCl_3$)



22h

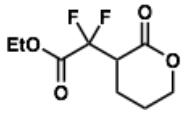


^{13}C NMR (126 MHz, $CDCl_3$)



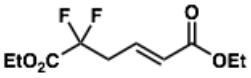
22i

^{1}H NMR (500 MHz, $CDCl_3$)



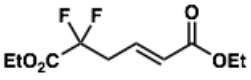
22i

^{13}C NMR (126 MHz, $CDCl_3$)



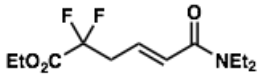
22j

^{1}H NMR (500 MHz, $CDCl_3$)



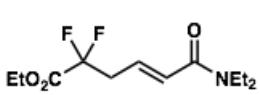
22j

^{13}C NMR (126 MHz, $CDCl_3$)



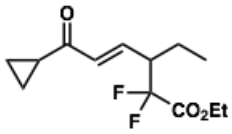
22k

^{1}H NMR (500 MHz, $CDCl_3$)



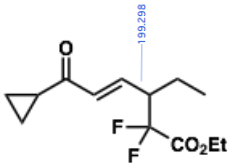
22k

^{13}C NMR (126 MHz, $CDCl_3$)



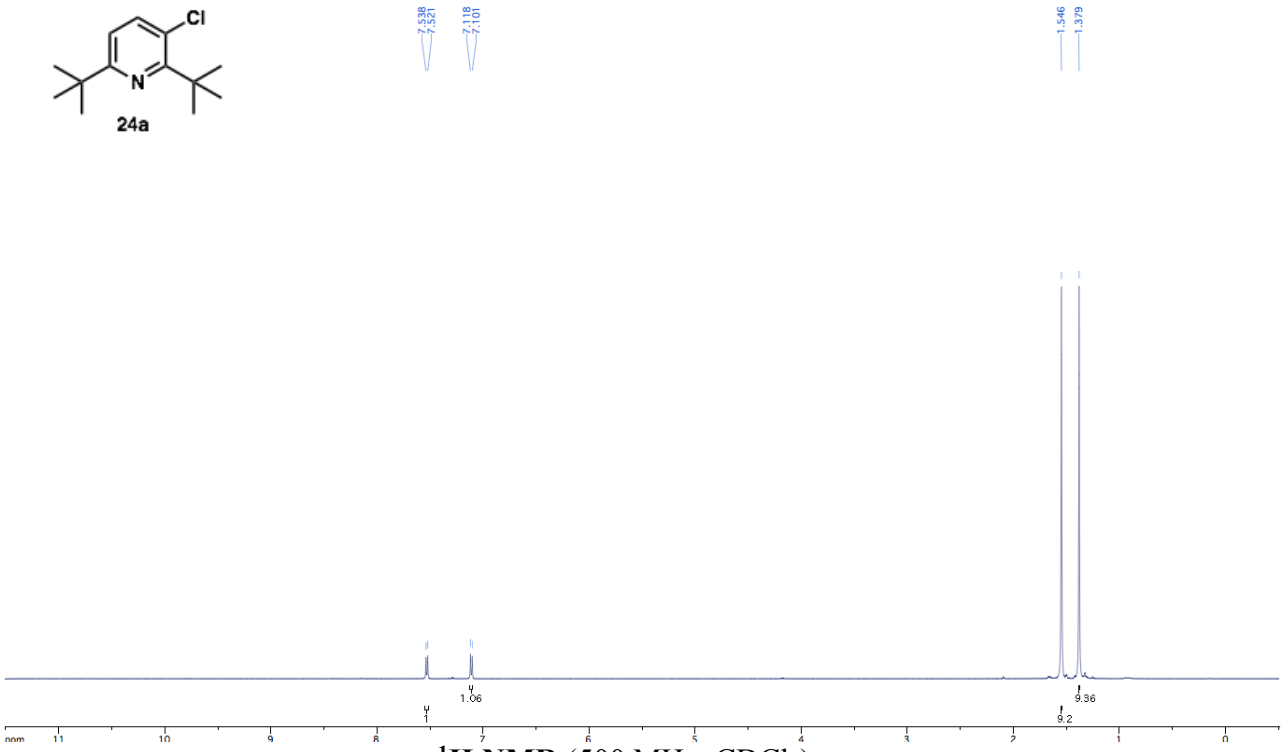
22l

^{1}H NMR (500 MHz, $CDCl_3$)

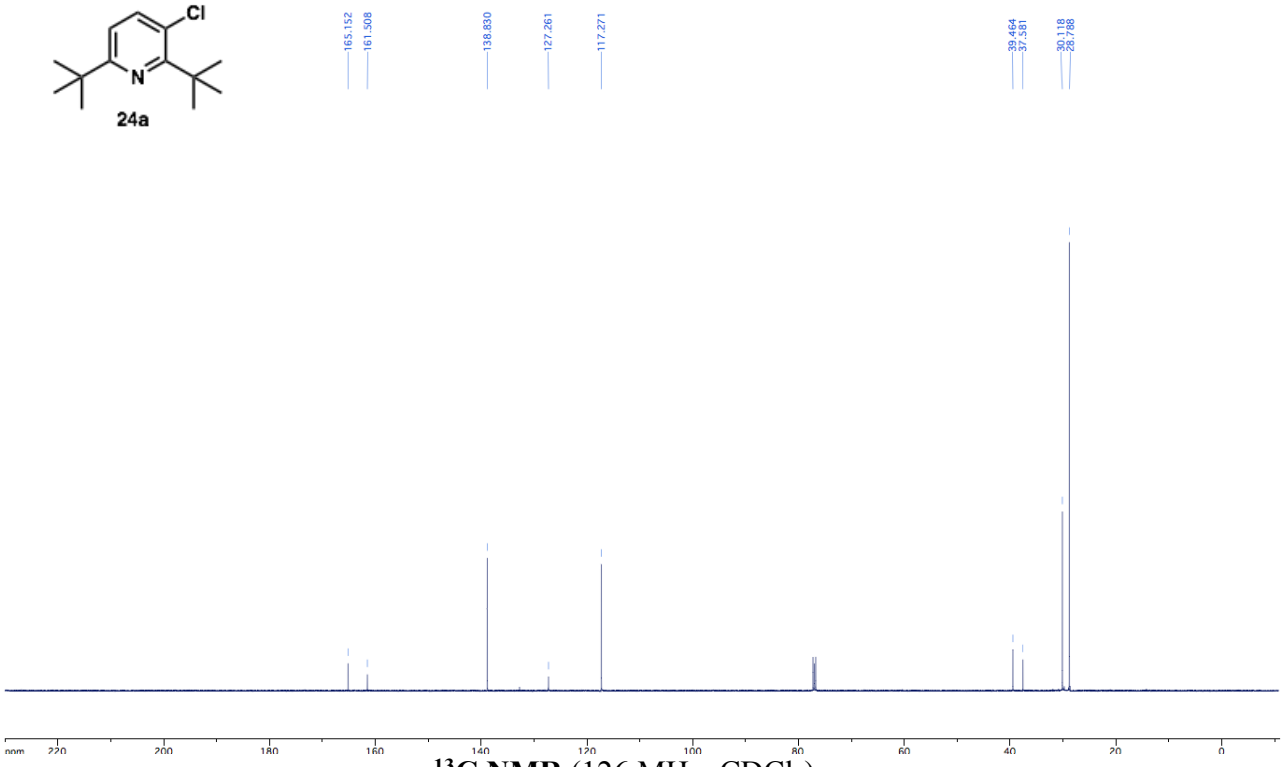


22l

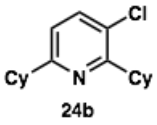
^{13}C NMR (126 MHz, $CDCl_3$)



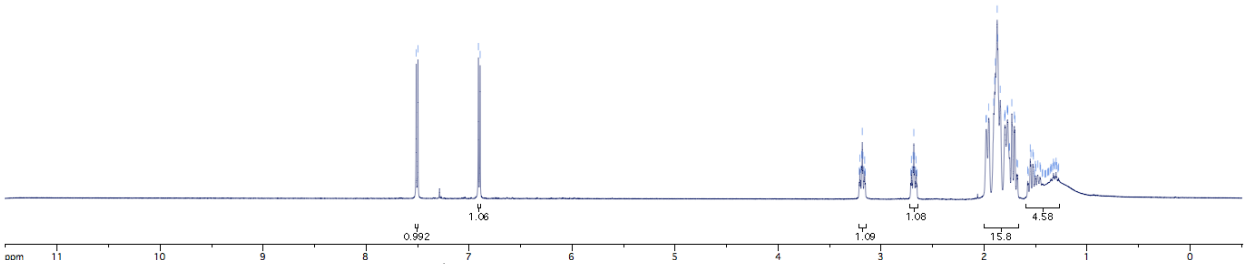
^{1}H NMR (500 MHz, $CDCl_3$)



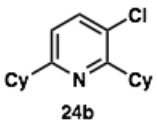
^{13}C NMR (126 MHz, $CDCl_3$)



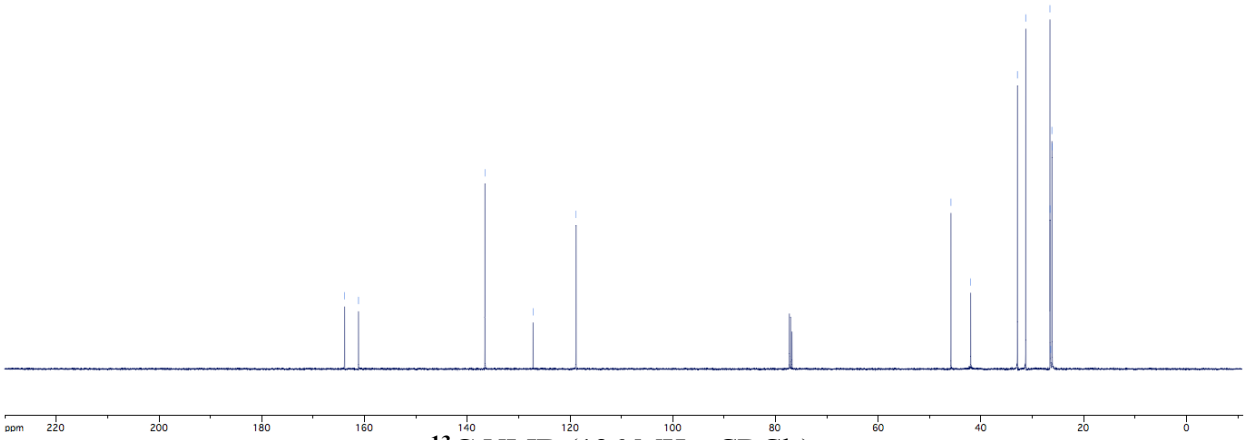
24b



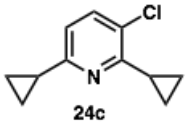
^{1}H NMR (500 MHz, $CDCl_3$)



24b

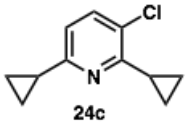


^{13}C NMR (126 MHz, $CDCl_3$)



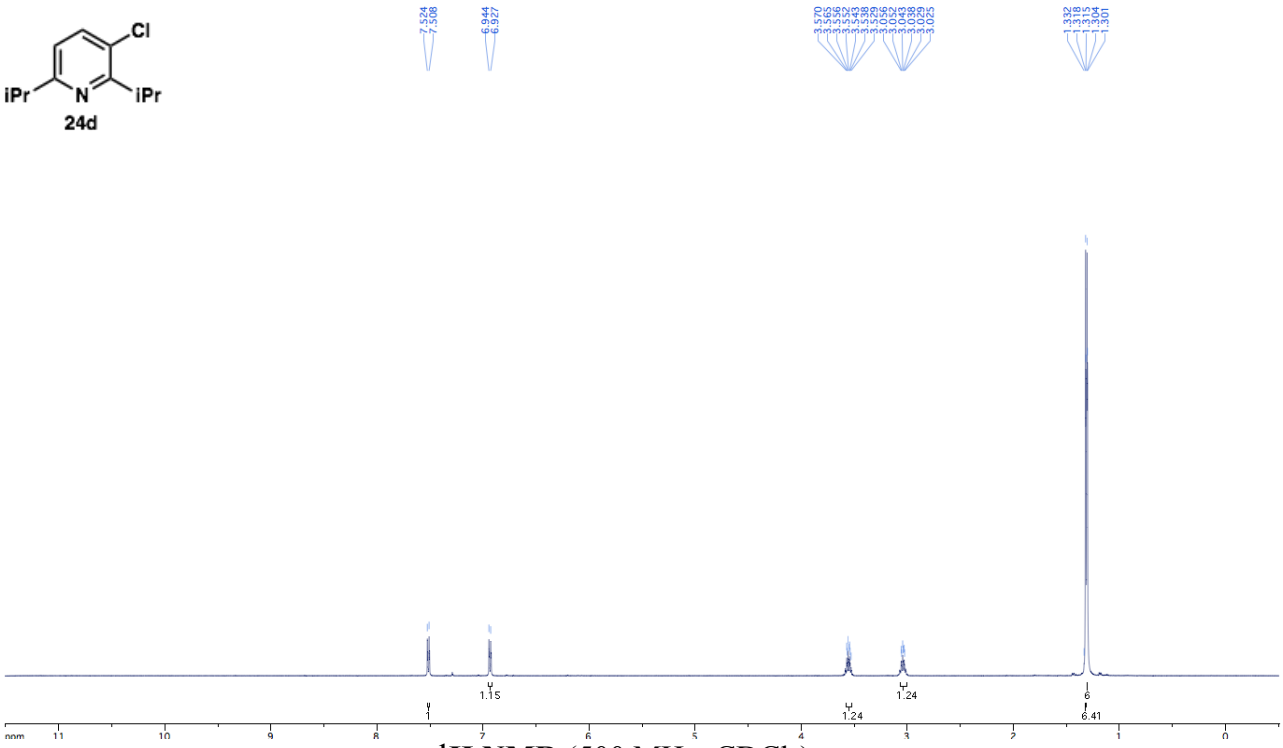
24c

^{1}H NMR (500 MHz, $CDCl_3$)

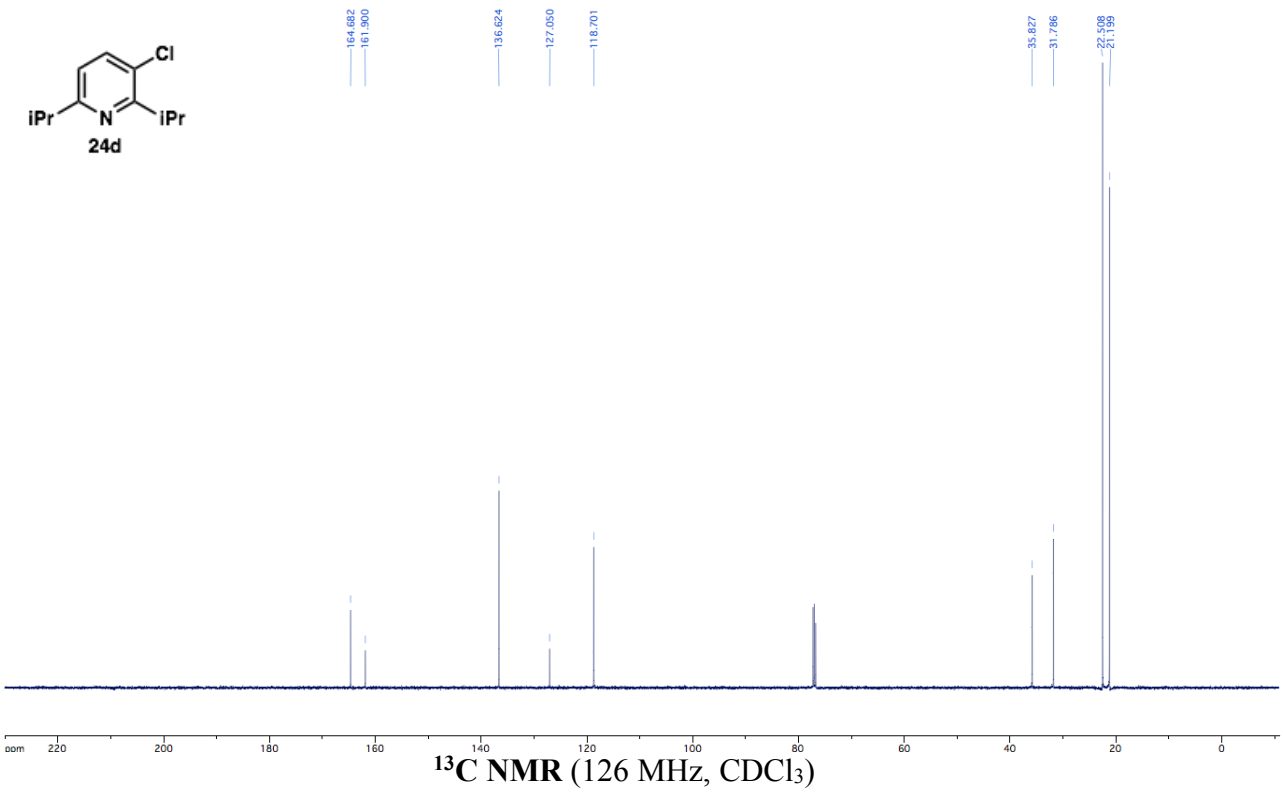


24c

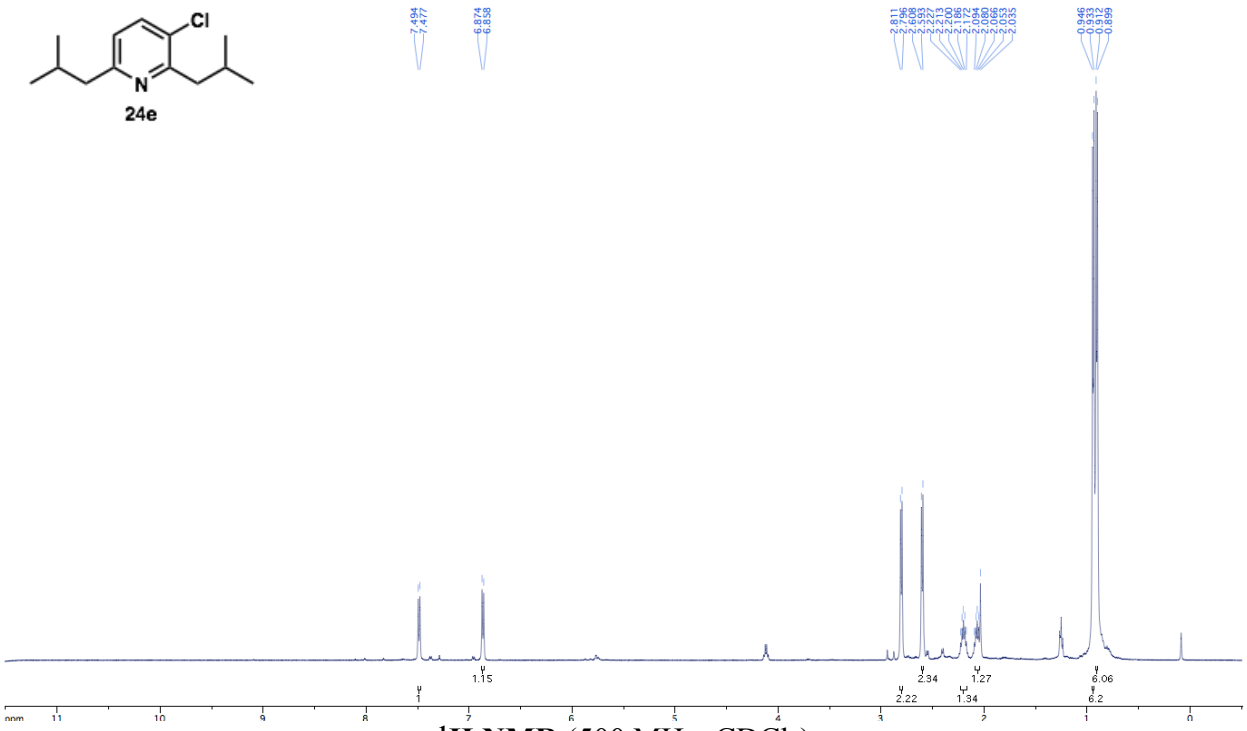
^{13}C NMR (126 MHz, $CDCl_3$)



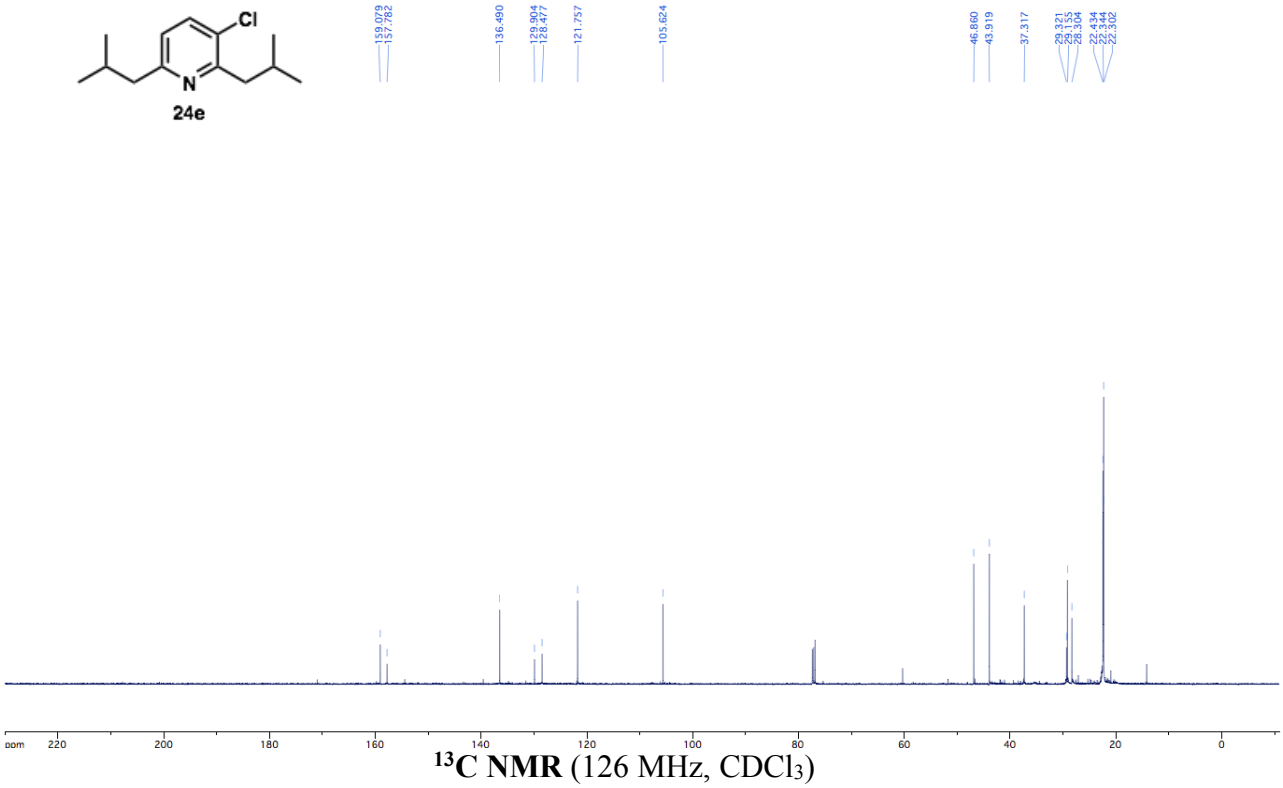
^{1}H NMR (500 MHz, $CDCl_3$)



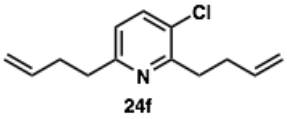
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

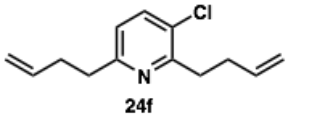


^{13}C NMR (126 MHz, $CDCl_3$)



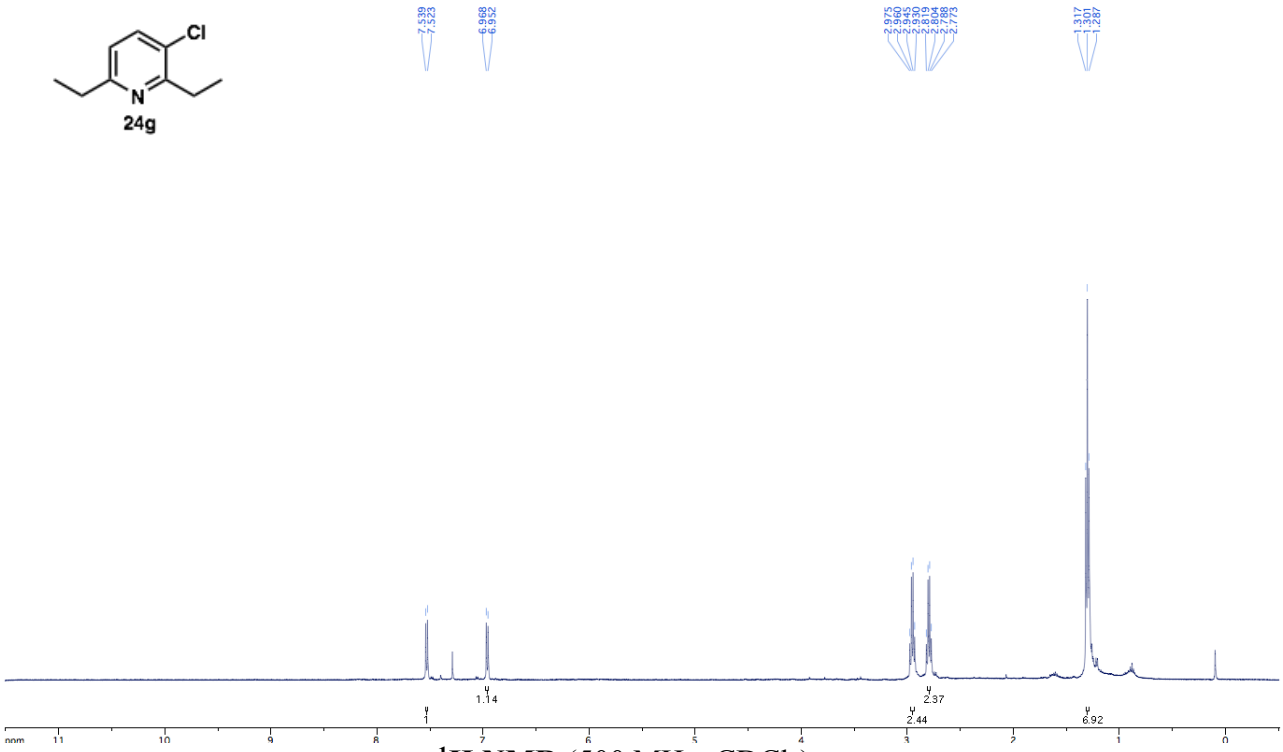
24f

^{1}H NMR (500 MHz, $CDCl_3$)

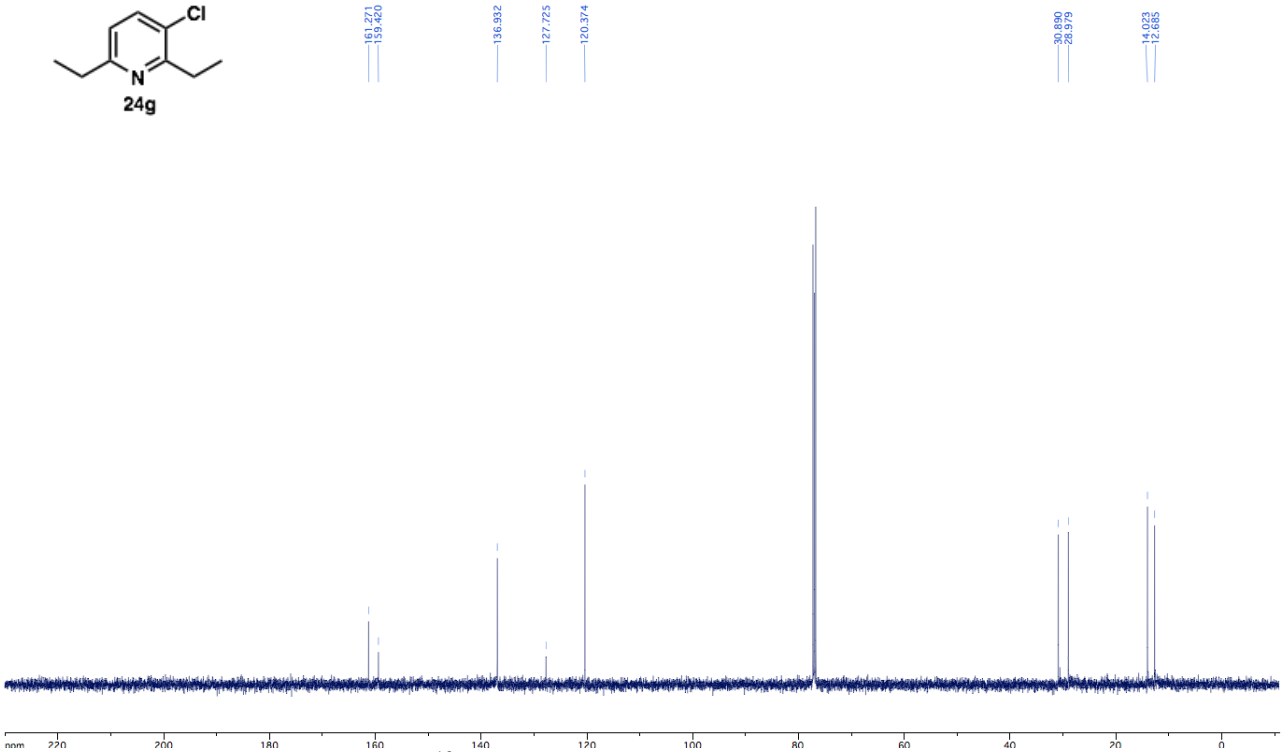


24f

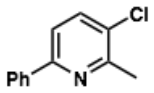
^{13}C NMR (126 MHz, $CDCl_3$)



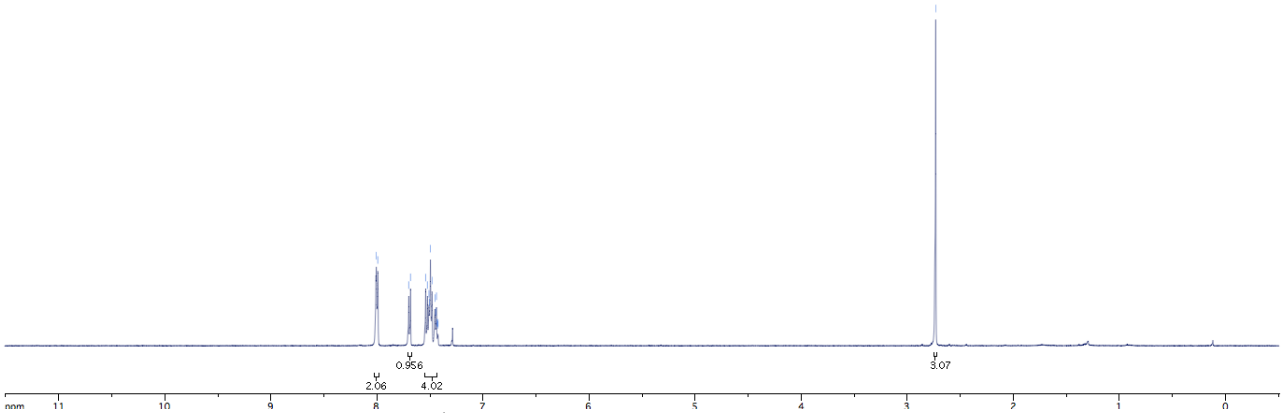
^{1}H NMR (500 MHz, $CDCl_3$)



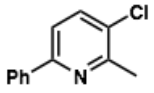
^{13}C NMR (126 MHz, $CDCl_3$)



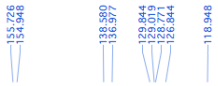
24h

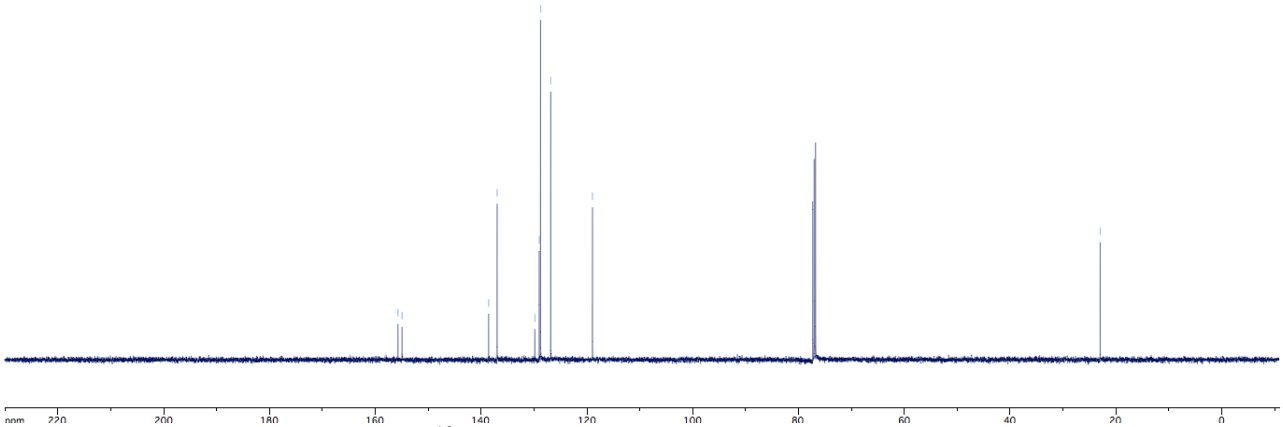


^{1}H NMR (500 MHz, $CDCl_3$)

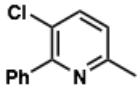


24h



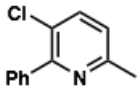


^{13}C NMR (126 MHz, $CDCl_3$)



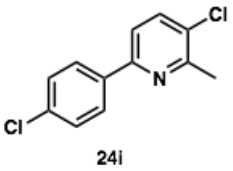
24h'

^{1}H NMR (500 MHz, $CDCl_3$)



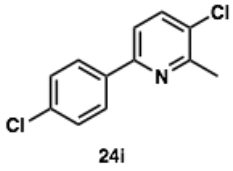
24h'

^{13}C NMR (126 MHz, $CDCl_3$)



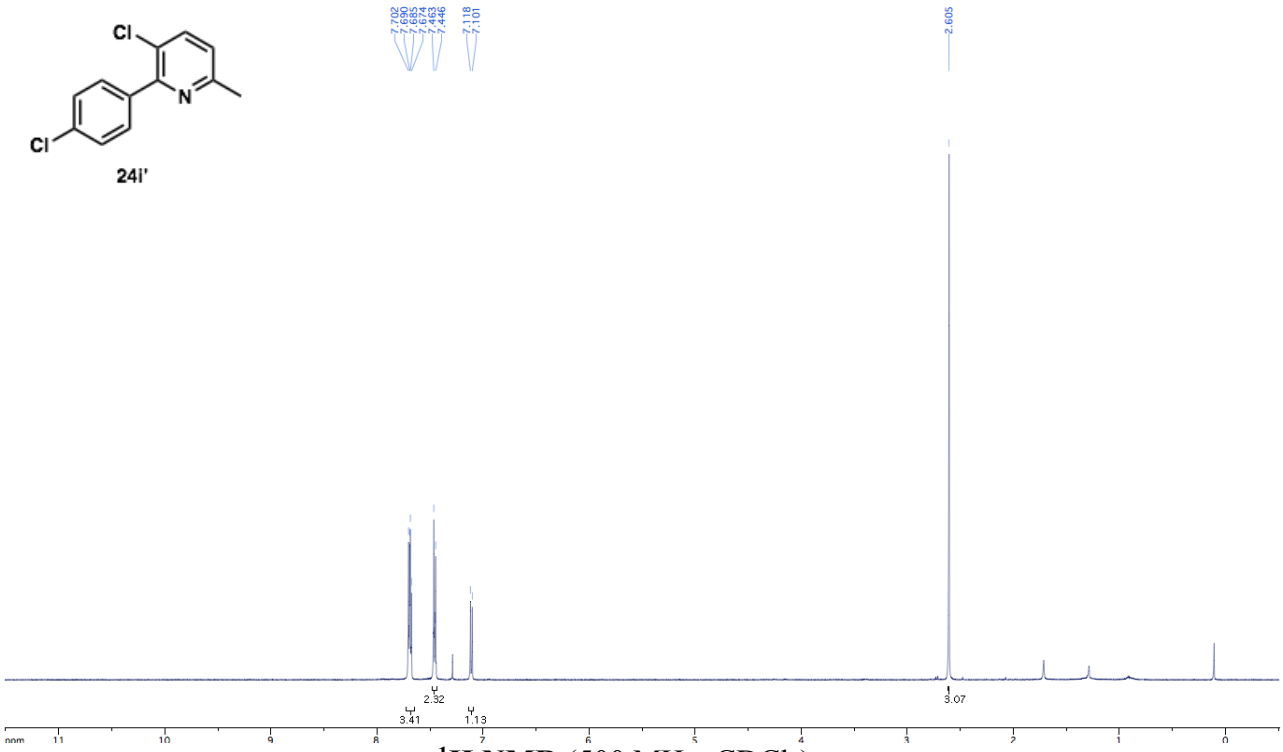
24i

^{1}H NMR (500 MHz, $CDCl_3$)

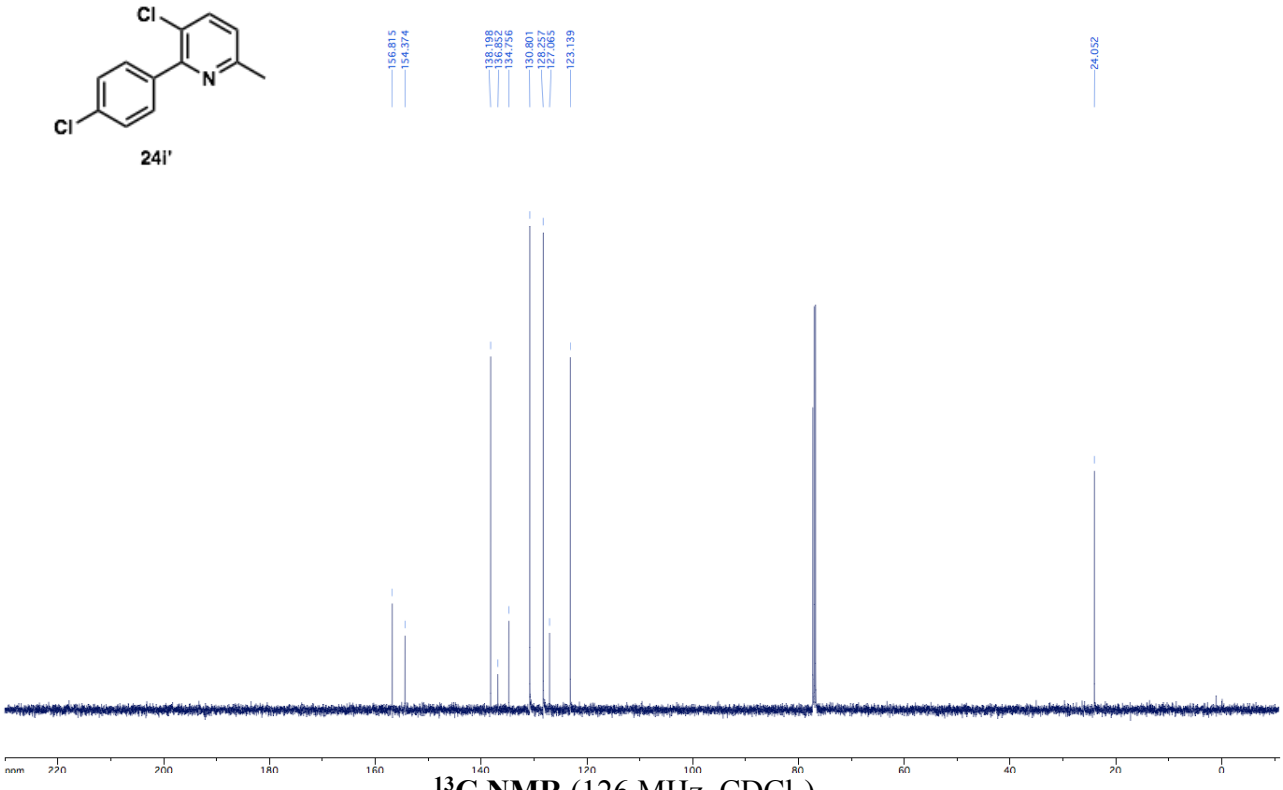


24i

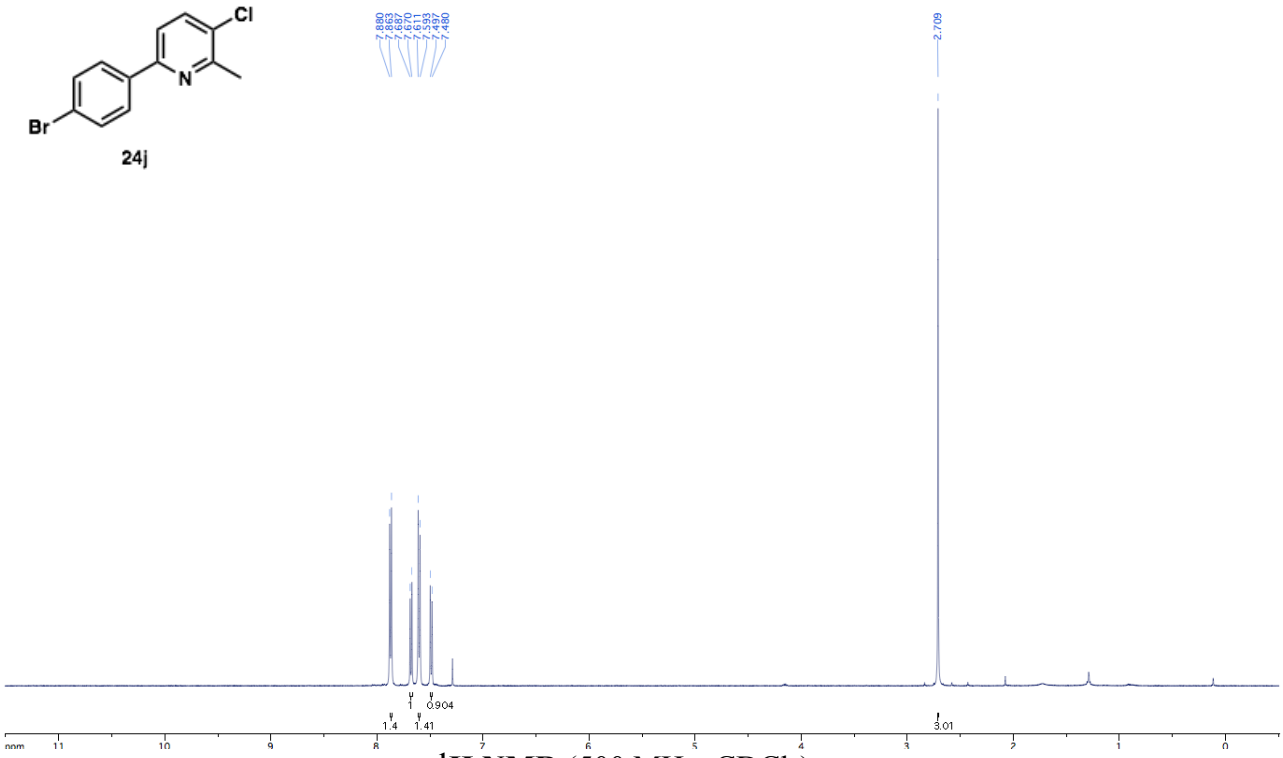
^{13}C NMR (126 MHz, $CDCl_3$)



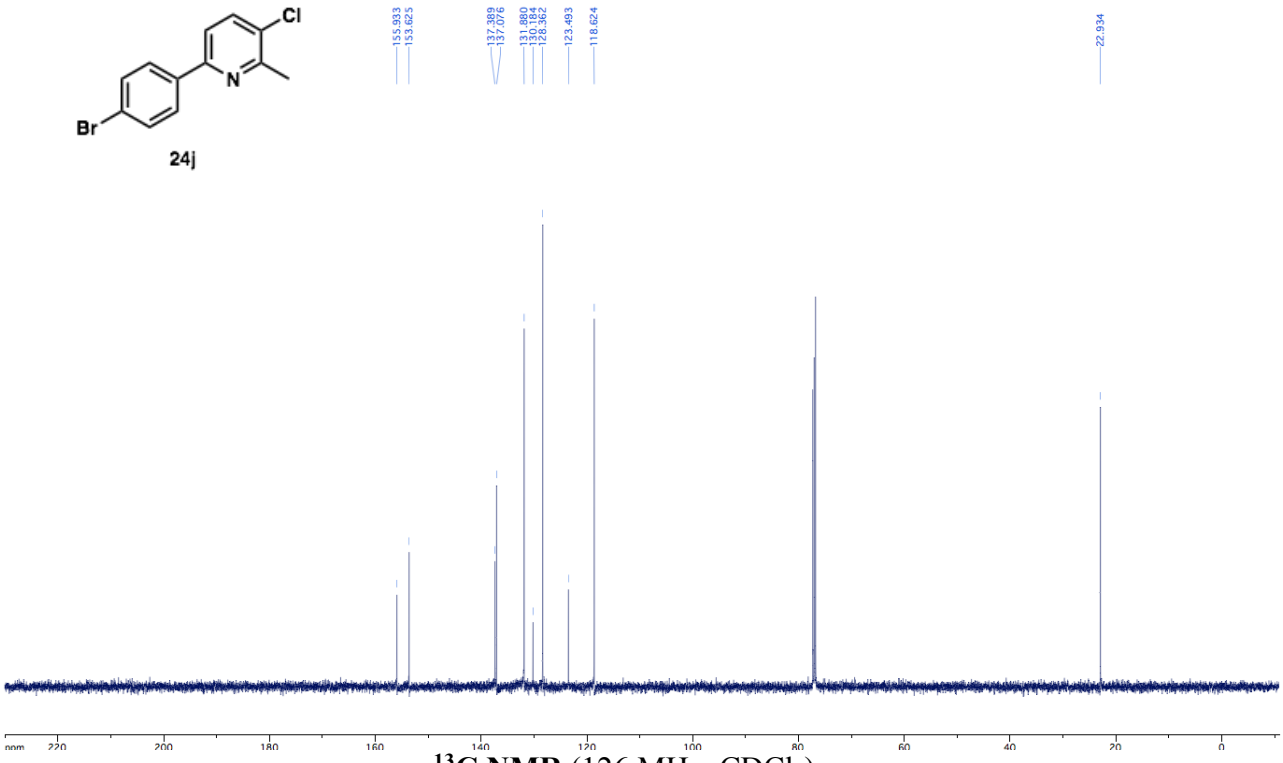
^{1}H NMR (500 MHz, $CDCl_3$)



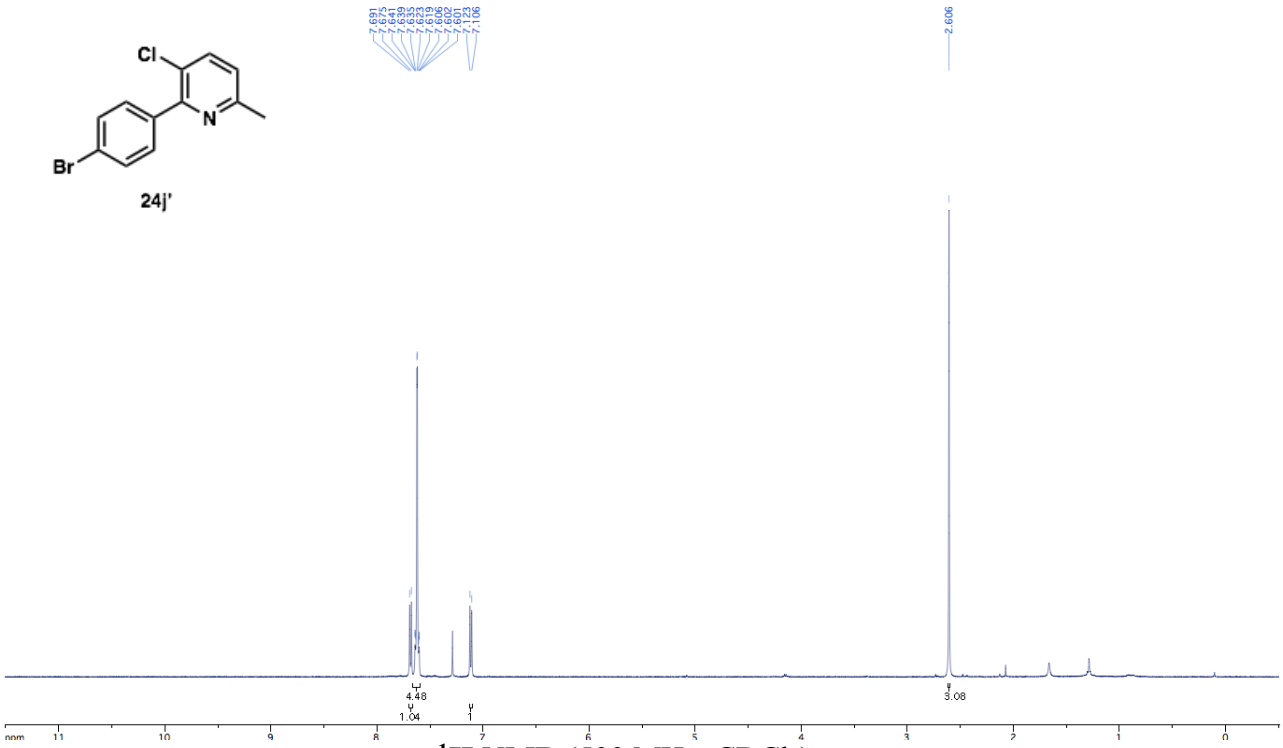
^{13}C NMR (126 MHz, $CDCl_3$)



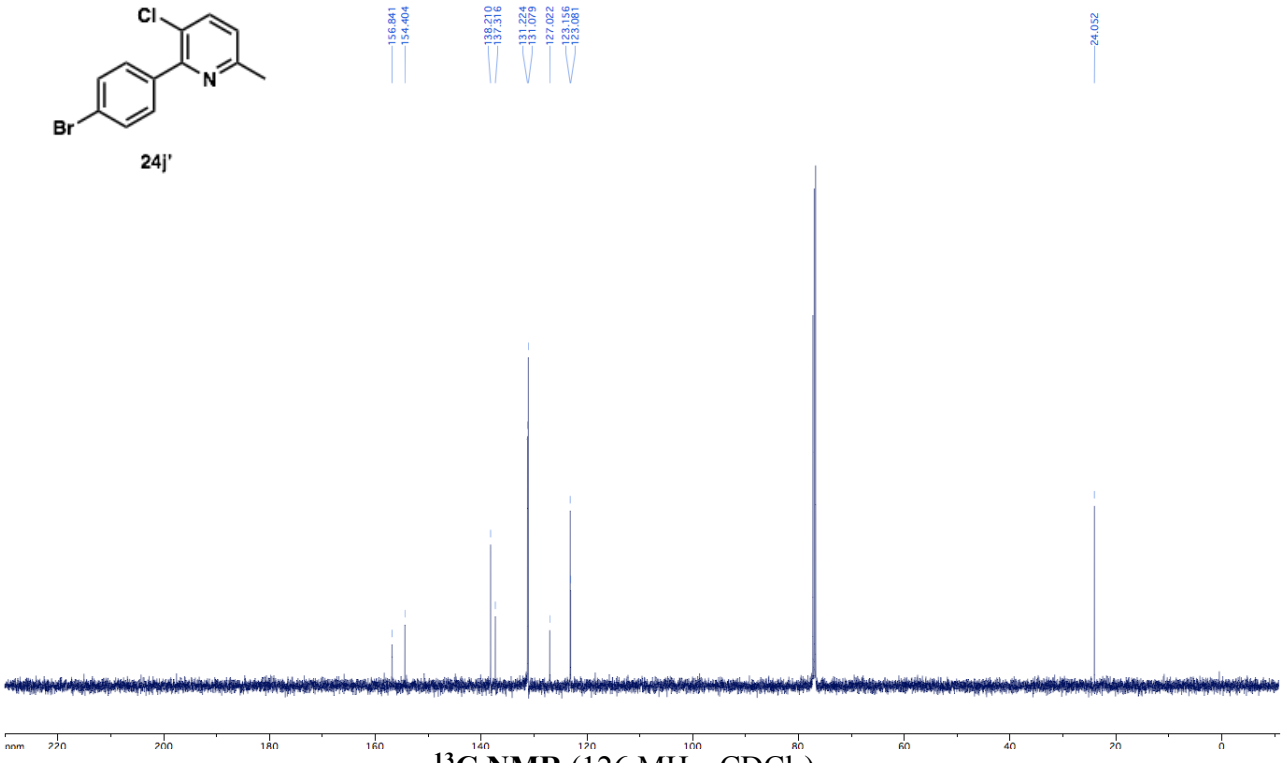
^{1}H NMR (500 MHz, $CDCl_3$)



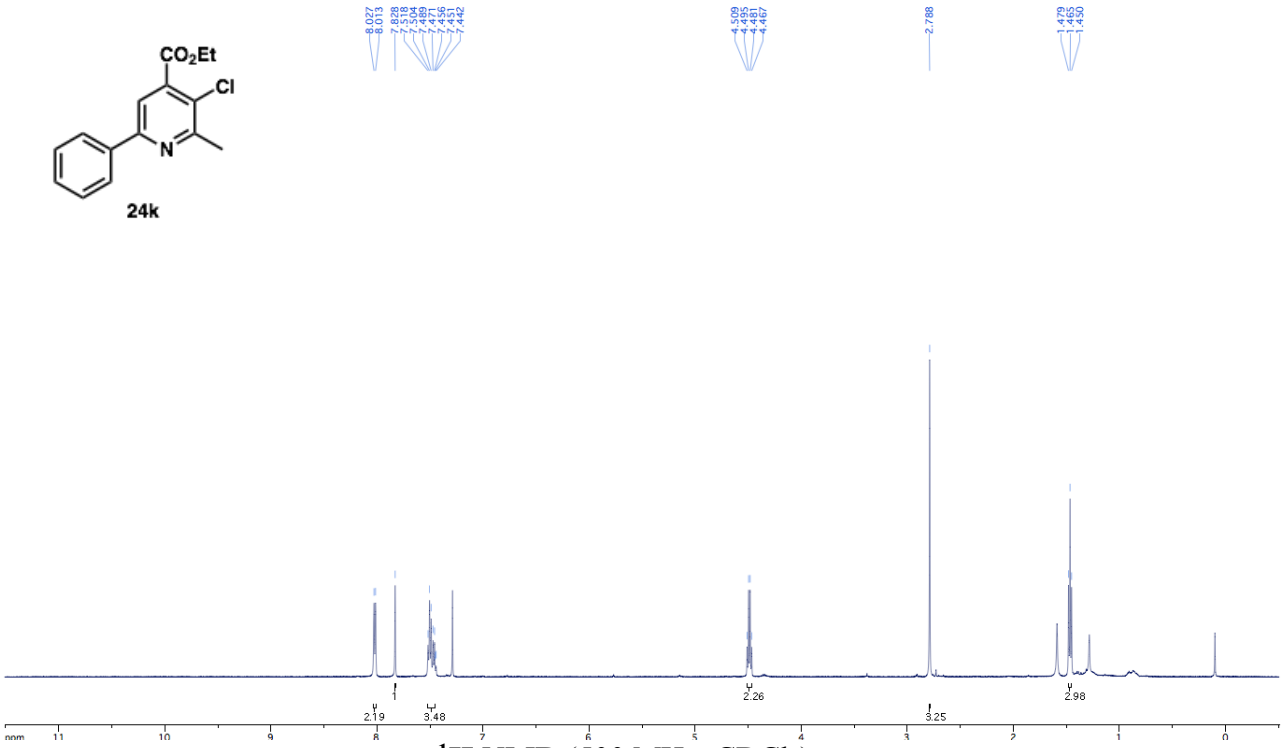
^{13}C NMR (126 MHz, $CDCl_3$)



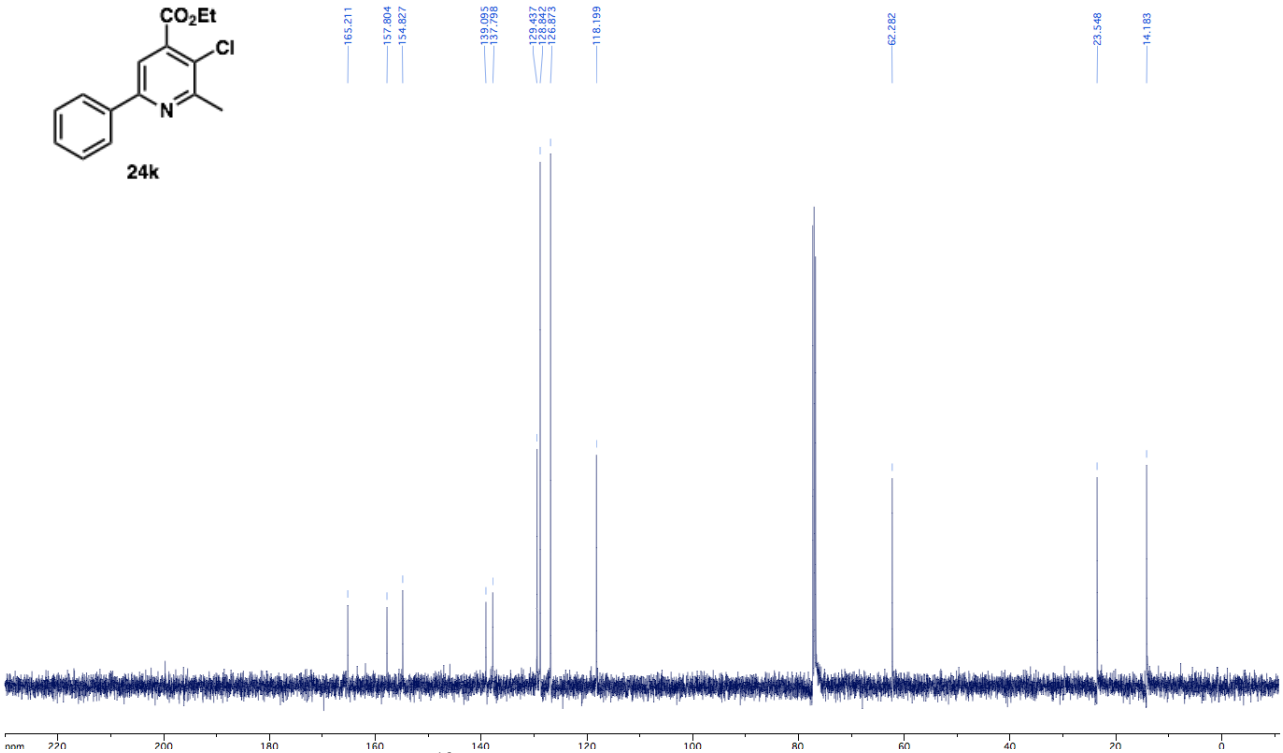
^{1}H NMR (500 MHz, $CDCl_3$)



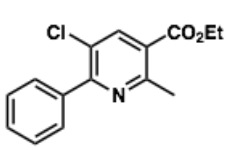
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

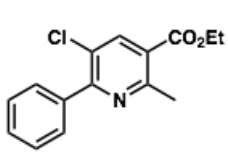


^{13}C NMR (126 MHz, $CDCl_3$)



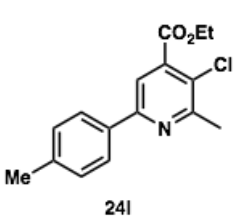
24k'

^{1}H NMR (500 MHz, $CDCl_3$)



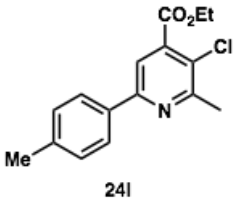
24k'

^{13}C NMR (126 MHz, $CDCl_3$)



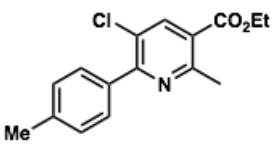
24l

^{1}H NMR (500 MHz, $CDCl_3$)



24l

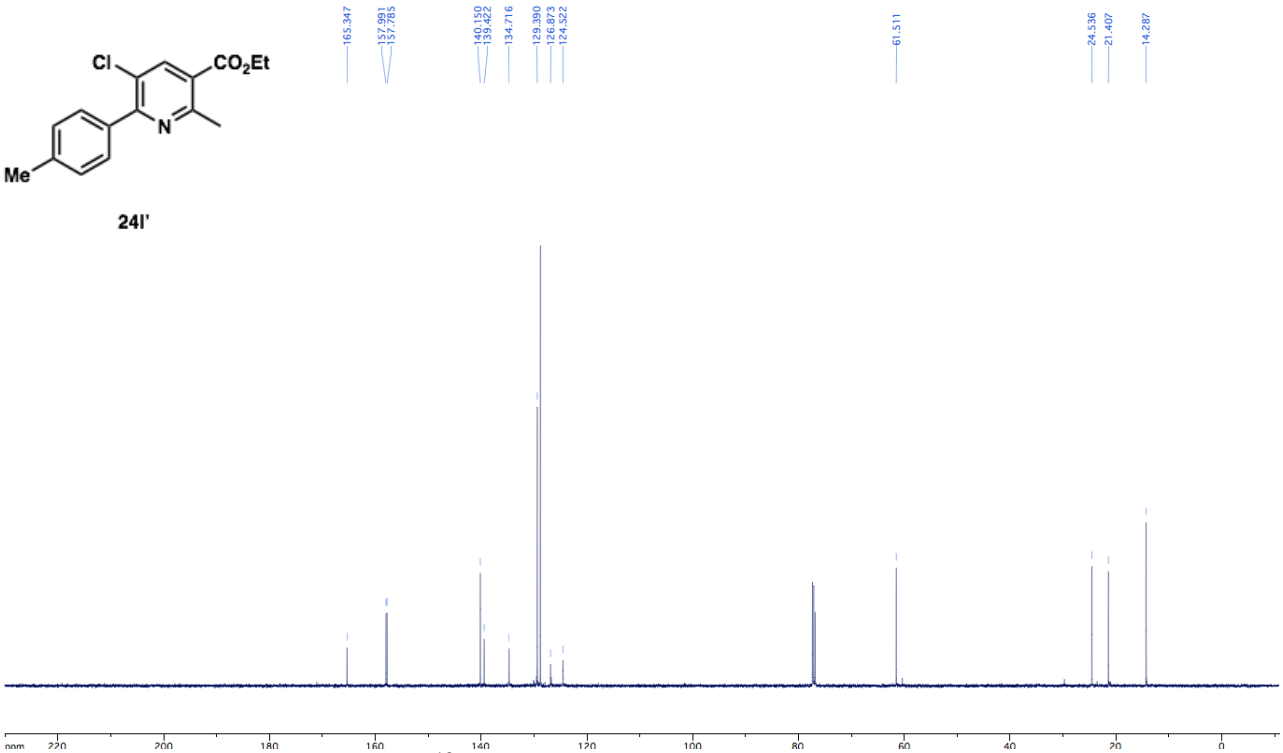
^{13}C NMR (126 MHz, $CDCl_3$)



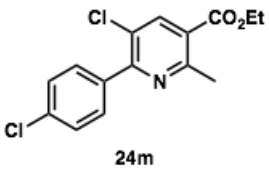
24l'

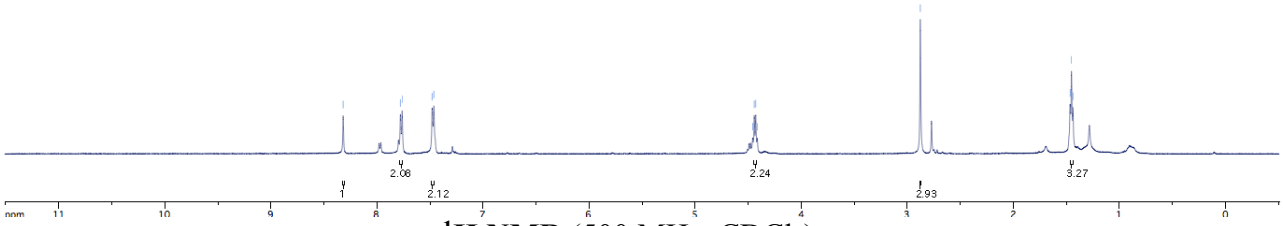
^{1}H NMR (500 MHz, $CDCl_3$)

24l'

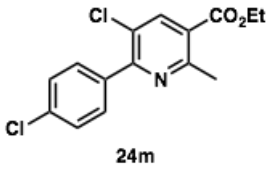


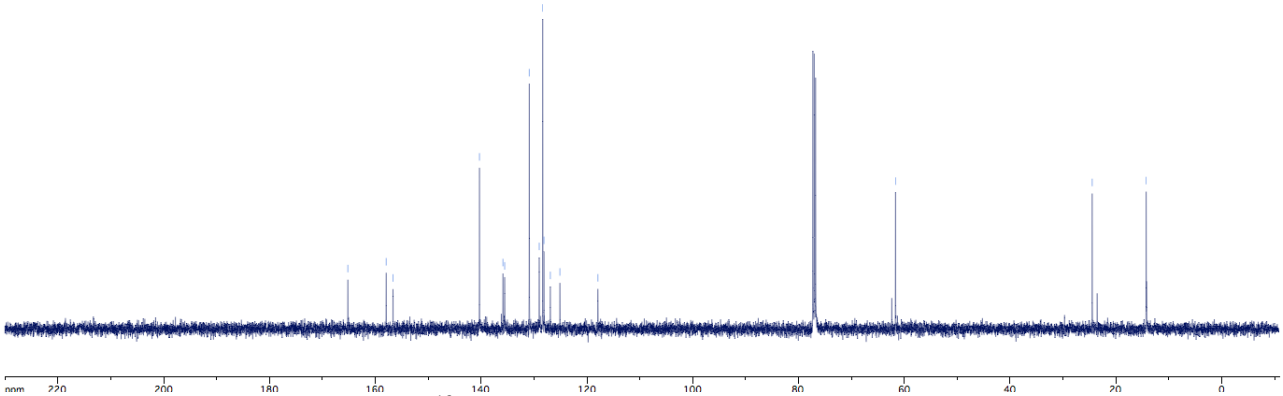
^{13}C NMR (126 MHz, $CDCl_3$)



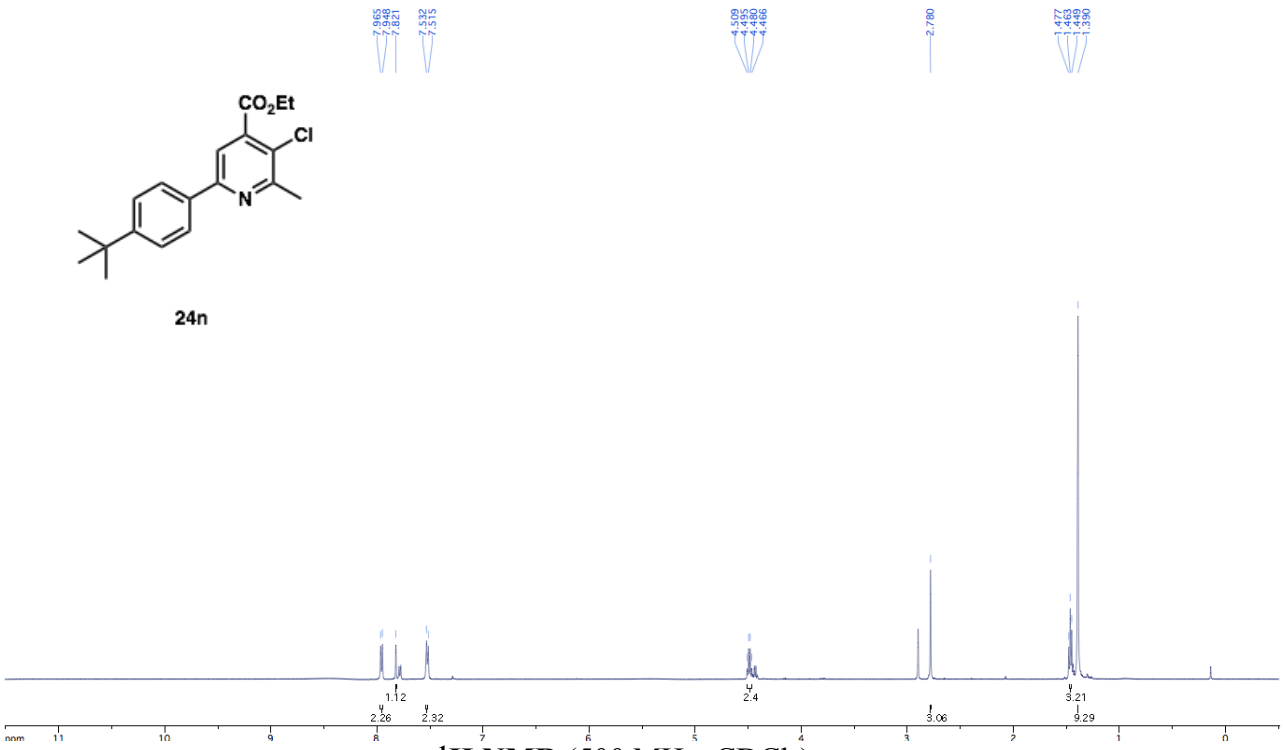


^{1}H NMR (500 MHz, $CDCl_3$)

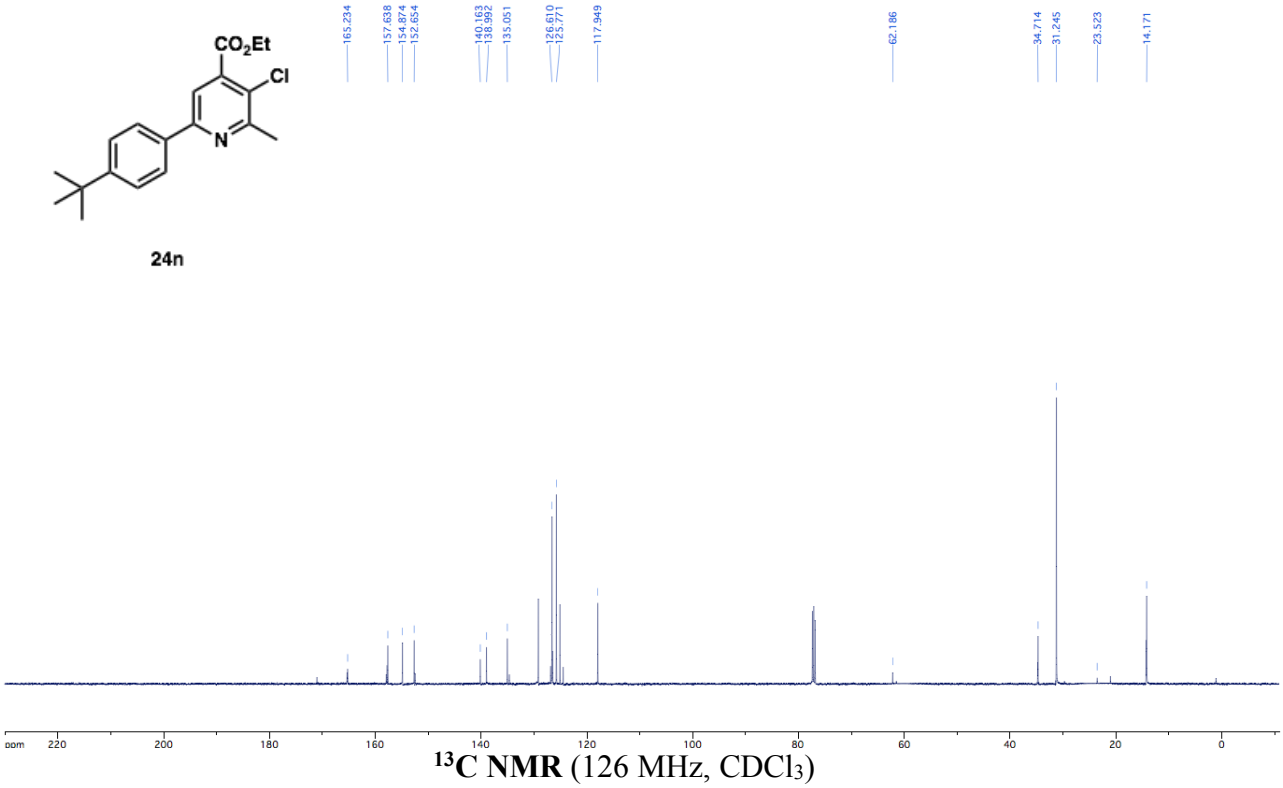




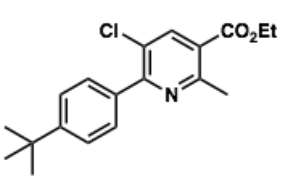
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

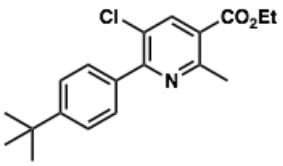


^{13}C NMR (126 MHz, $CDCl_3$)



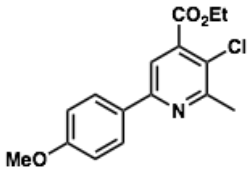
24n'

^{1}H NMR (500 MHz, $CDCl_3$)



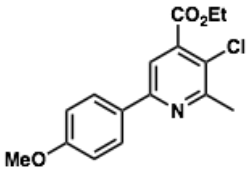
24n'

^{13}C NMR (126 MHz, $CDCl_3$)



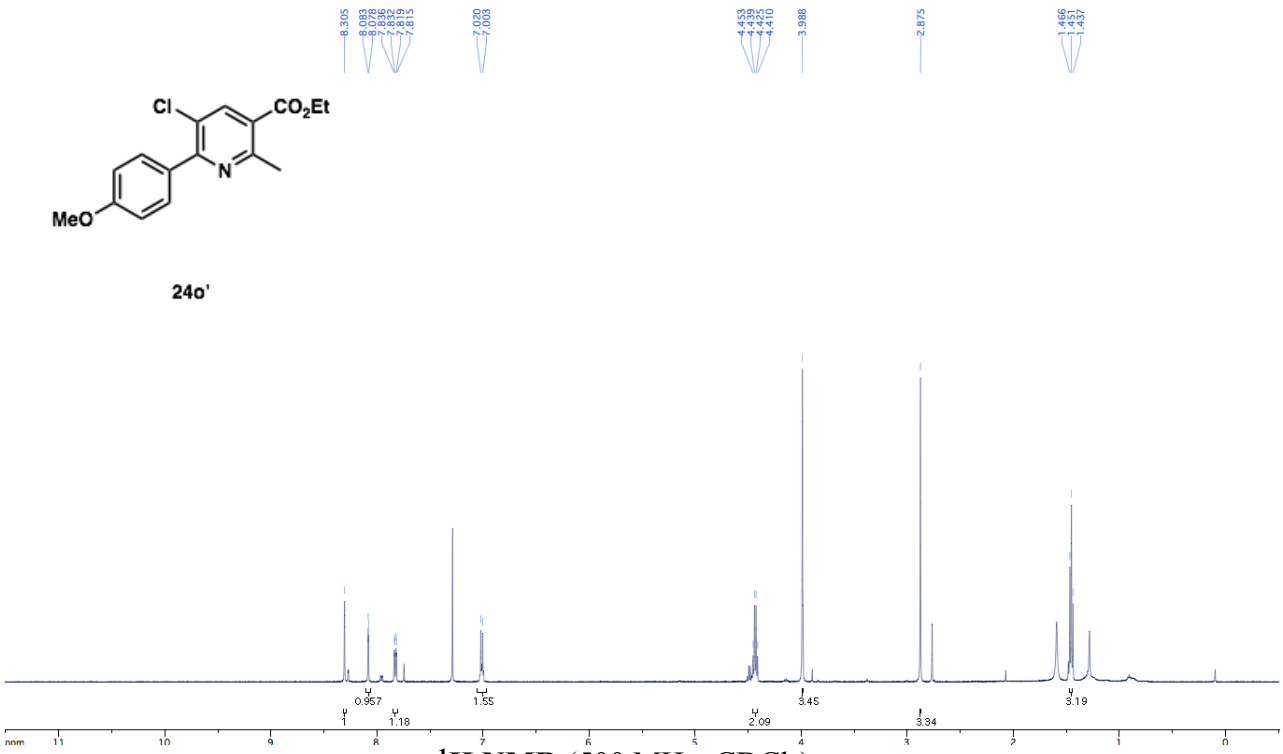
24o

^{1}H NMR (500 MHz, $CDCl_3$)



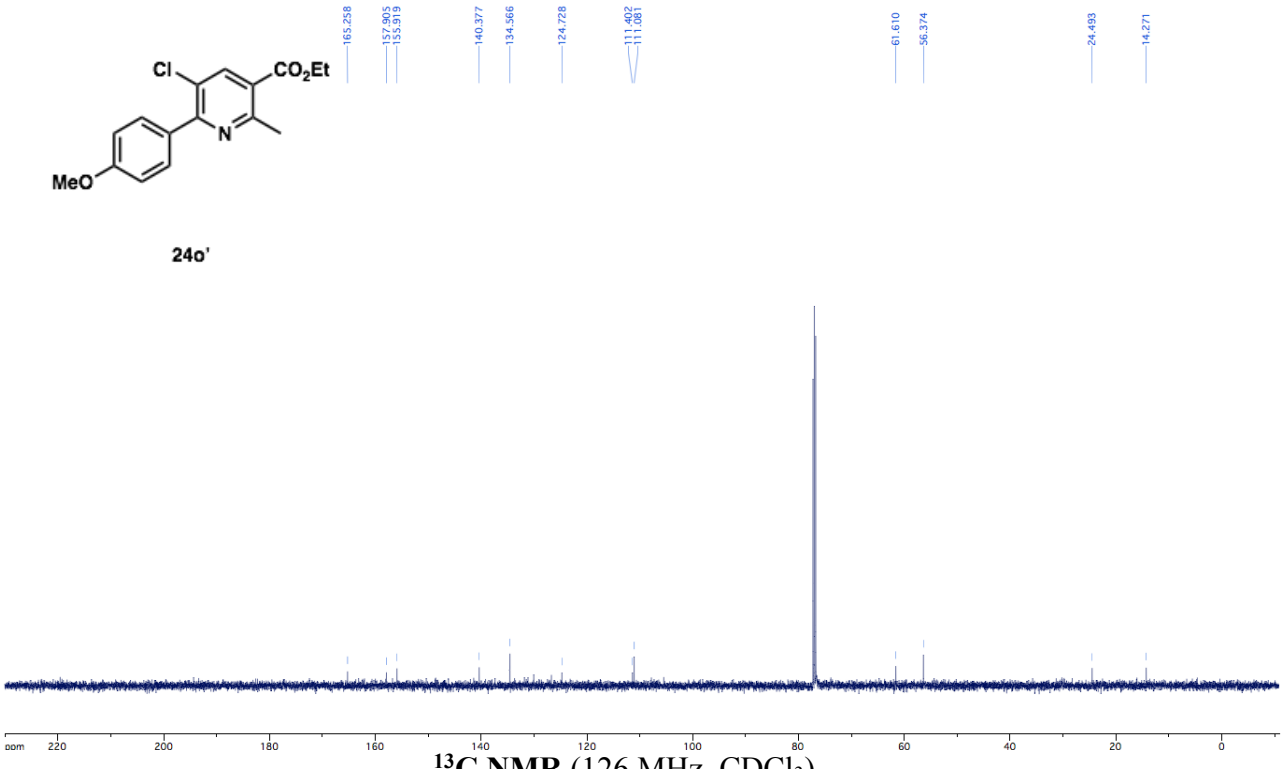
24o

^{13}C NMR (126 MHz, $CDCl_3$)



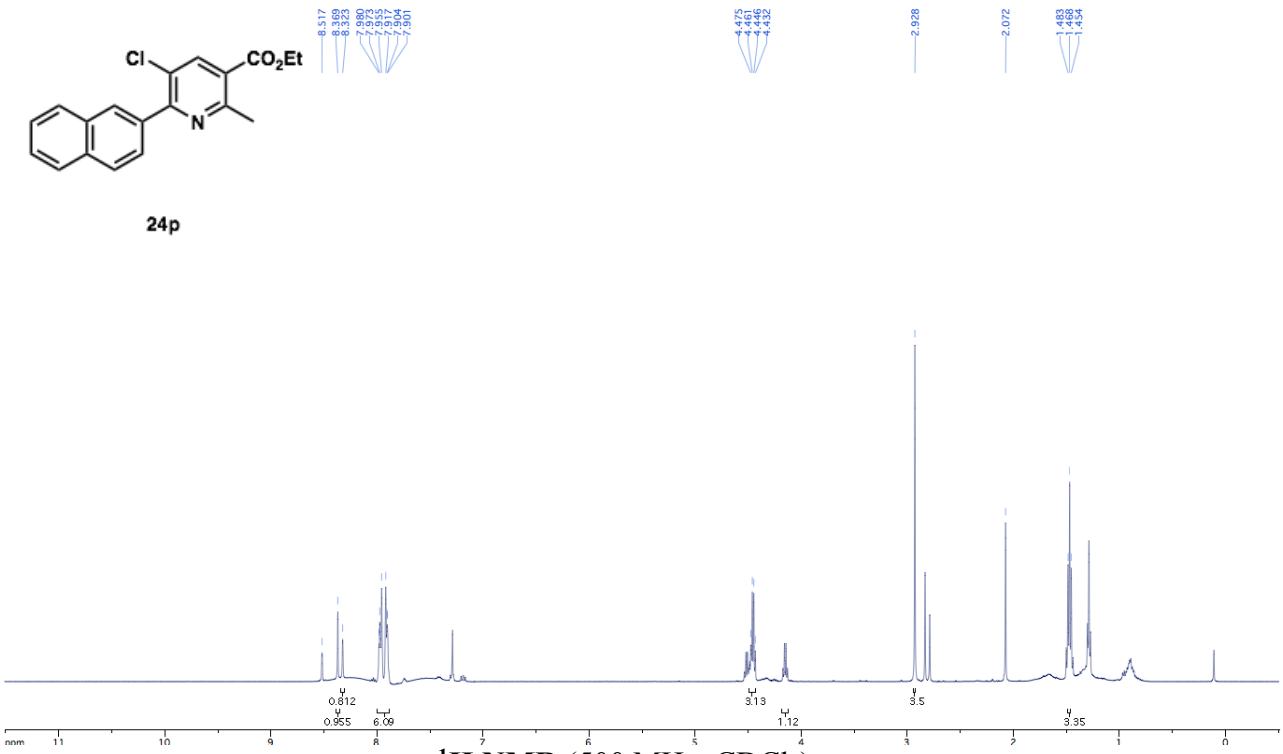
24o'

^{1}H NMR (500 MHz, $CDCl_3$)

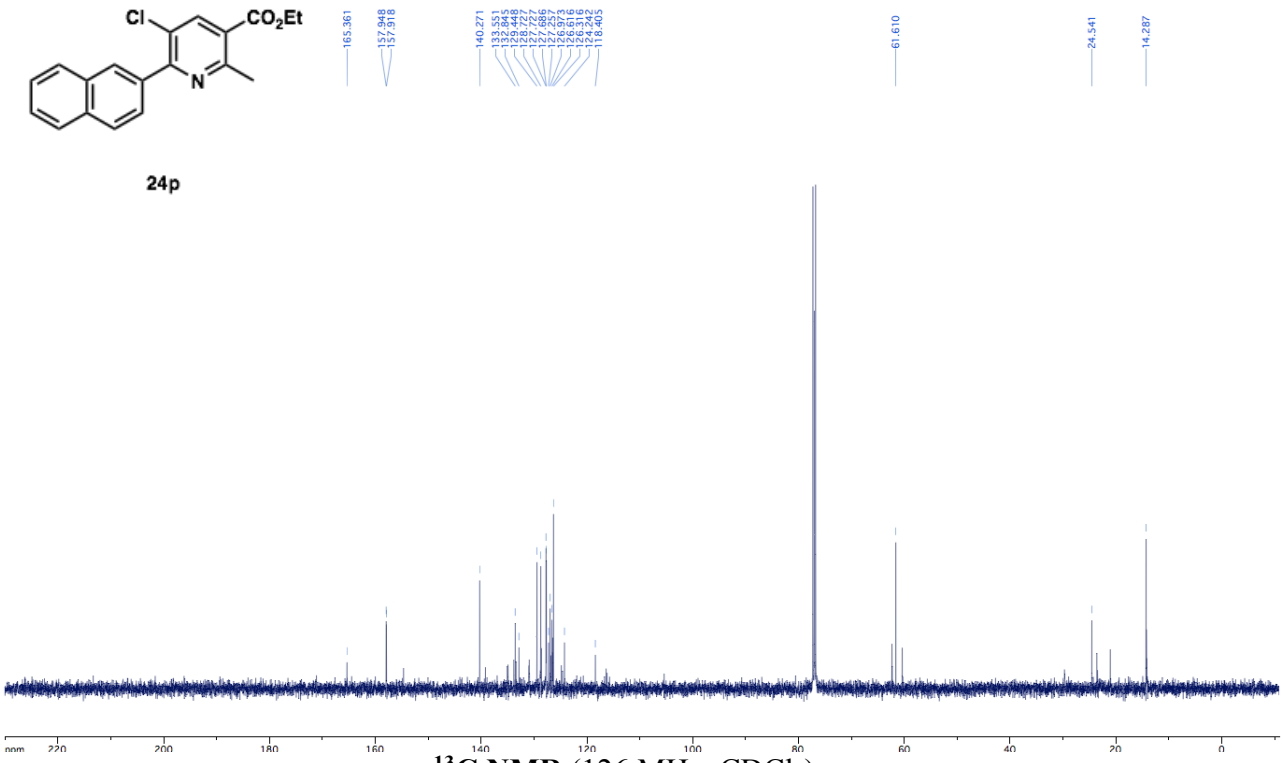


24o'

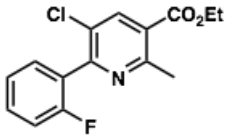
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

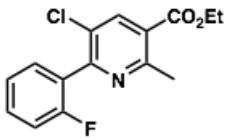


^{13}C NMR (126 MHz, $CDCl_3$)



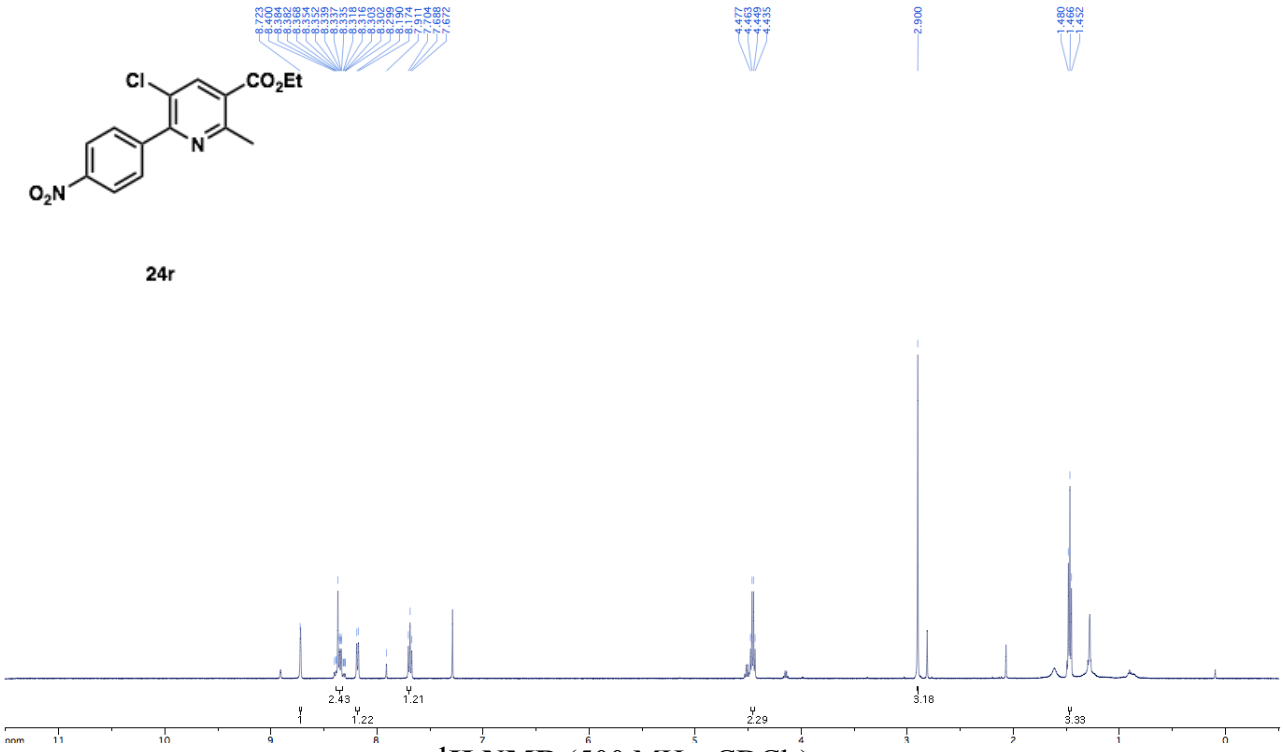
24q

^{1}H NMR (500 MHz, $CDCl_3$)

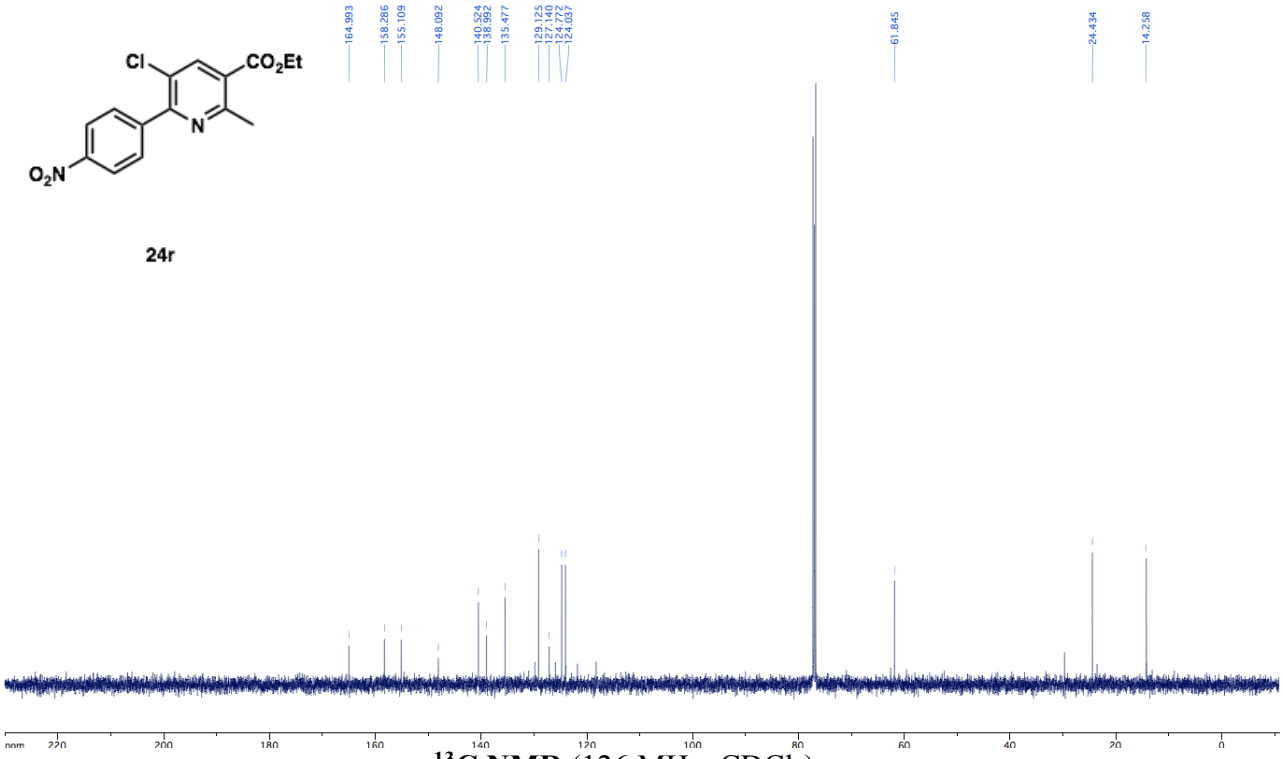


24q

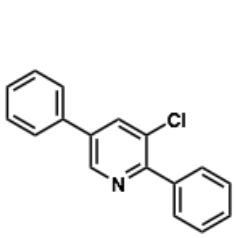
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

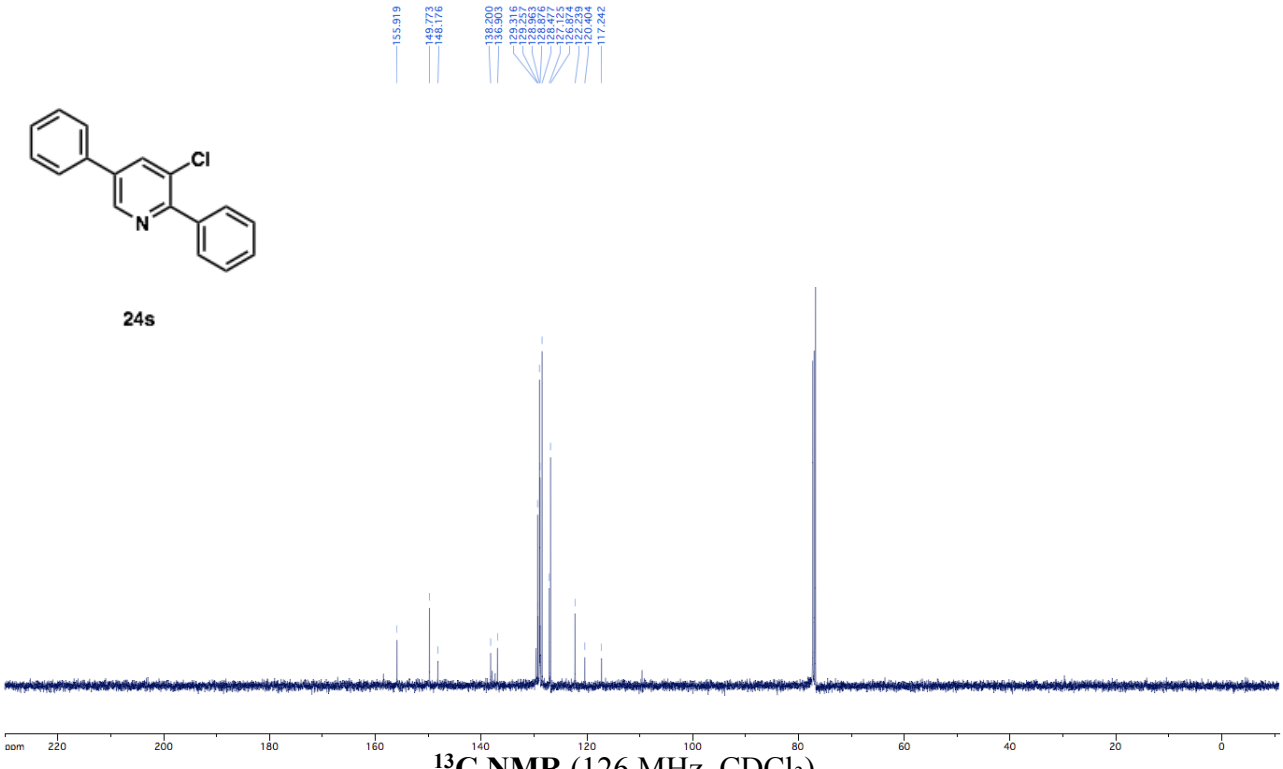


^{13}C NMR (126 MHz, $CDCl_3$)



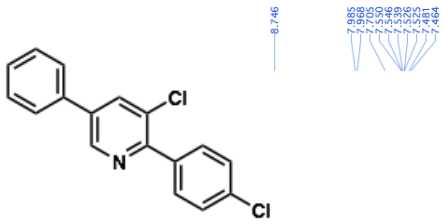
24s

^{1}H NMR (500 MHz, $CDCl_3$)



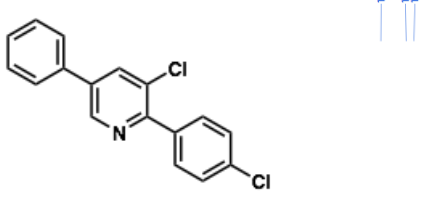
24s

^{13}C NMR (126 MHz, $CDCl_3$)



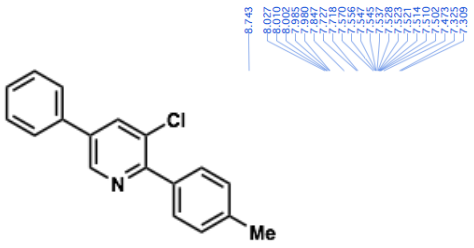
24t

^{1}H NMR (500 MHz, $CDCl_3$)



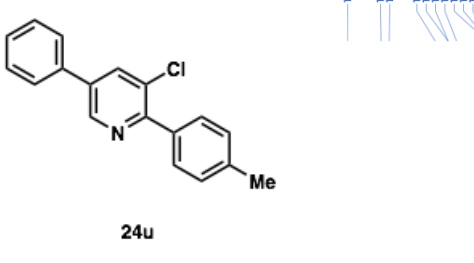
24t

^{13}C NMR (126 MHz, $CDCl_3$)



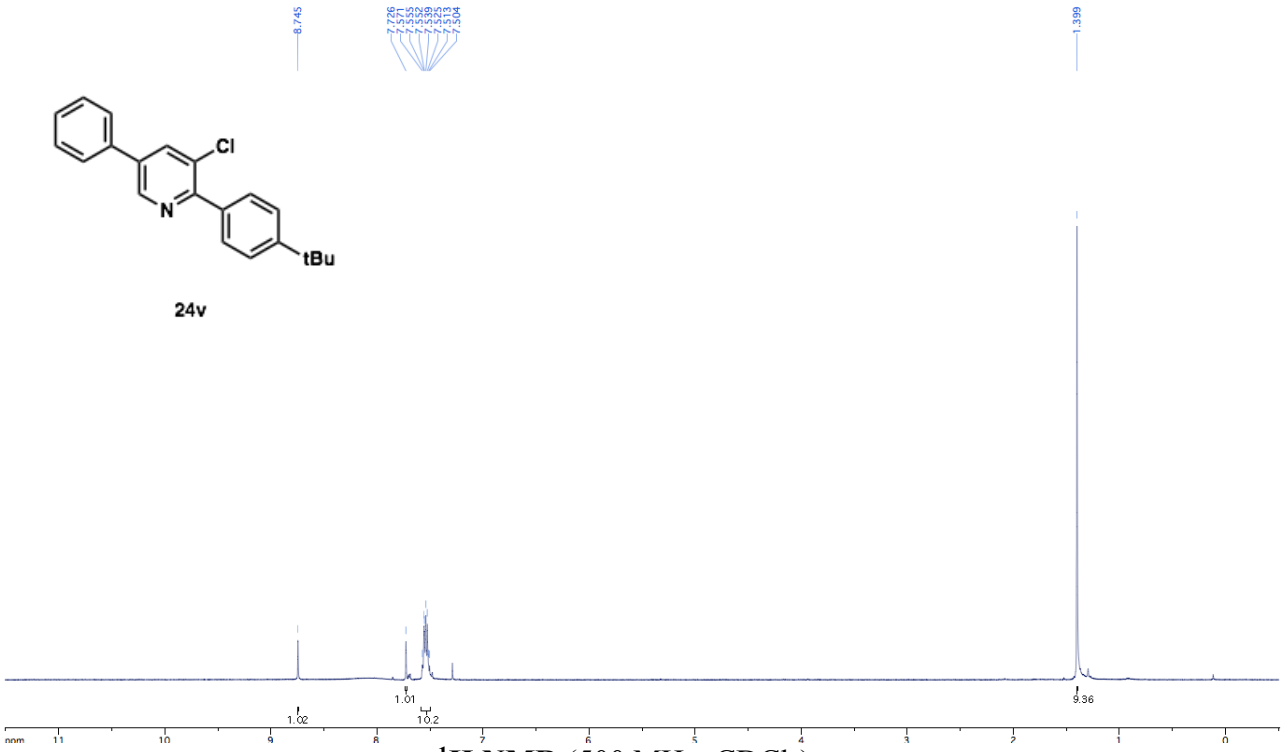
24u

^{1}H NMR (500 MHz, $CDCl_3$)



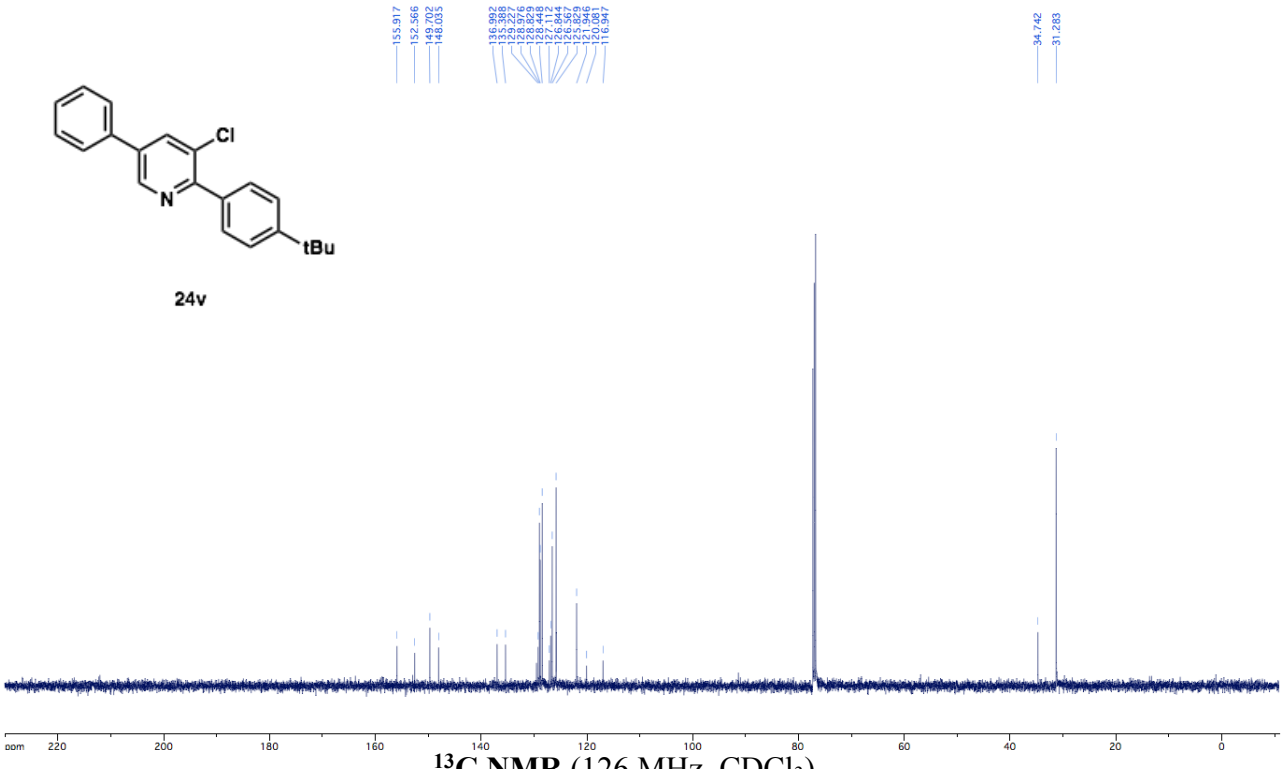
24u

^{13}C NMR (126 MHz, $CDCl_3$)



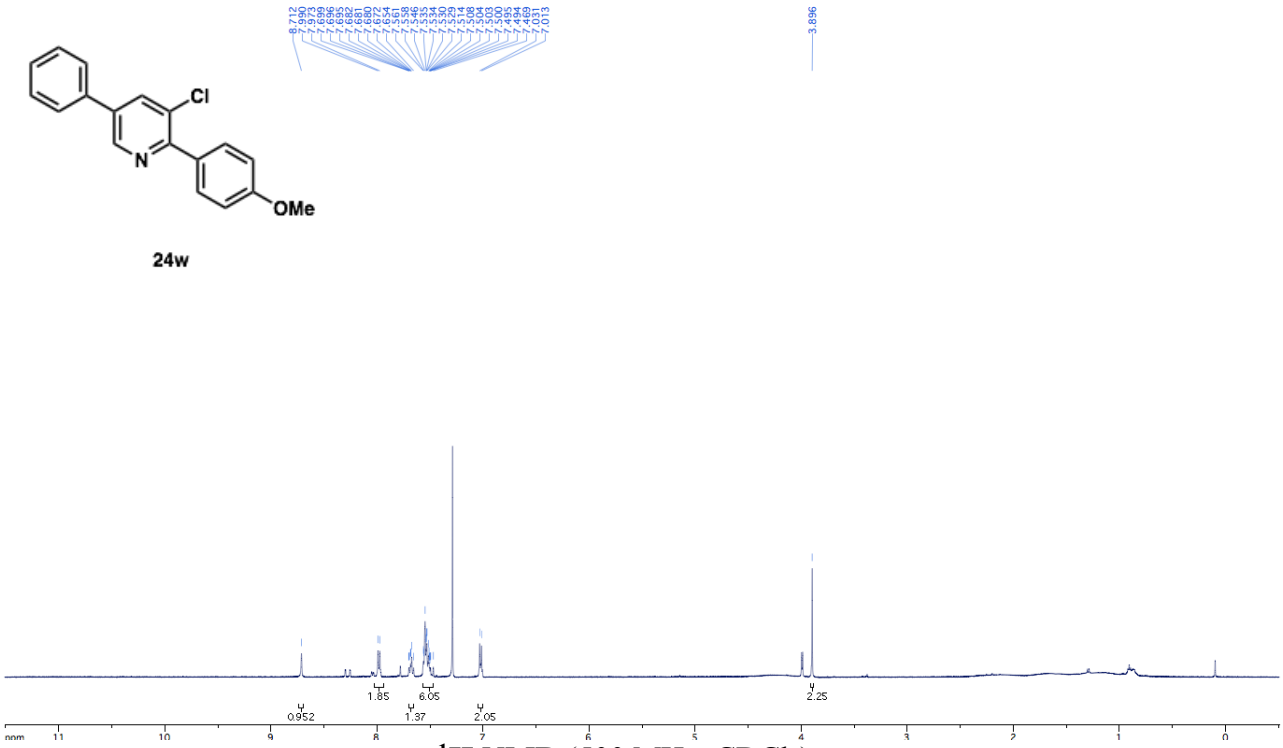
24v

^{1}H NMR (500 MHz, $CDCl_3$)

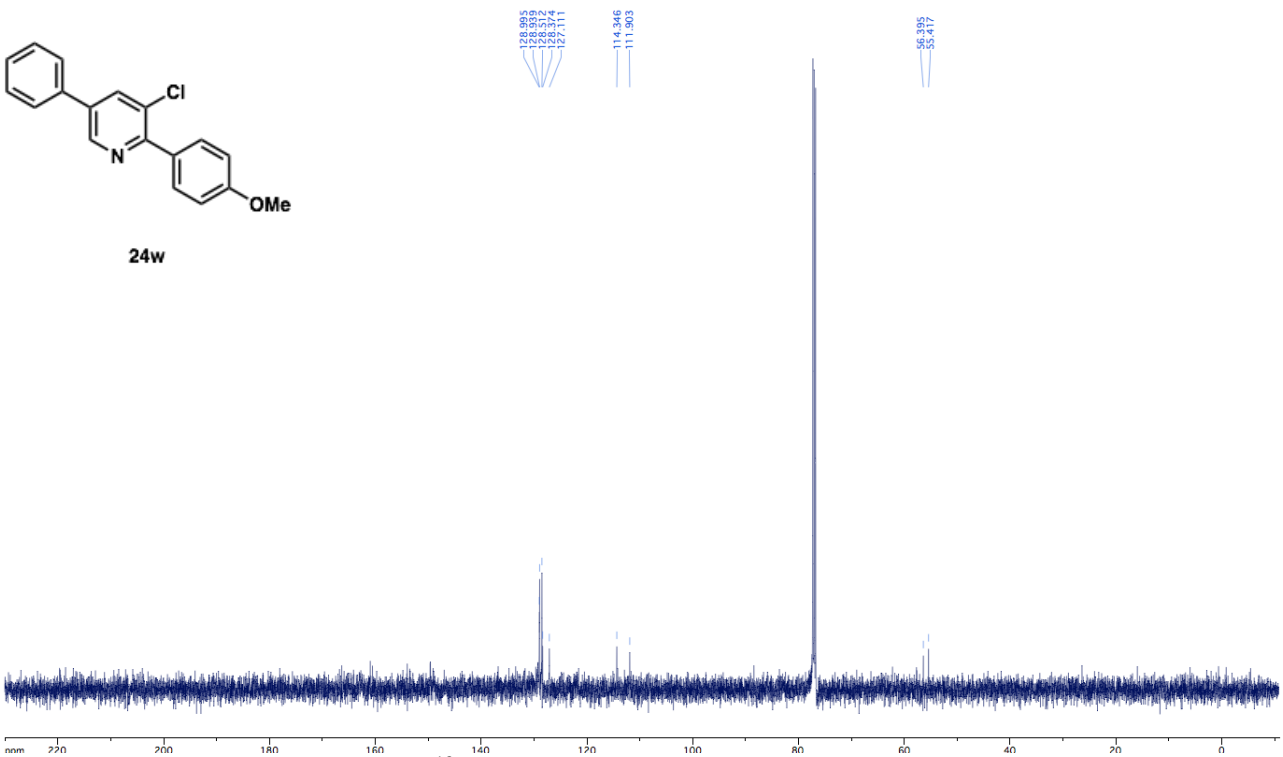


24v

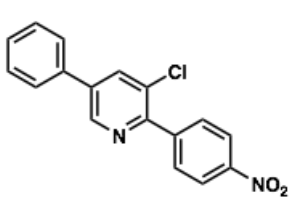
^{13}C NMR (126 MHz, $CDCl_3$)



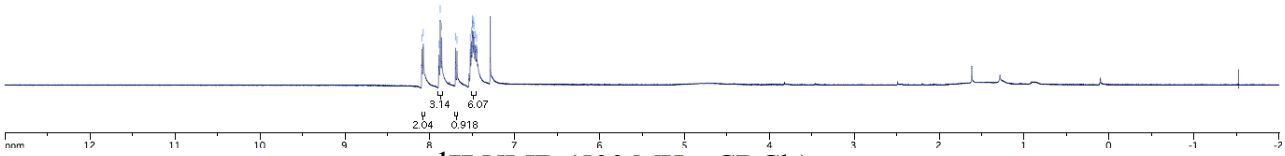
^{1}H NMR (500 MHz, $CDCl_3$)



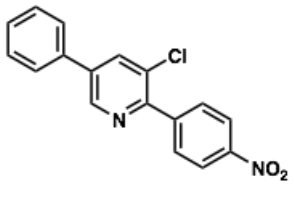
^{13}C NMR (126 MHz, $CDCl_3$)



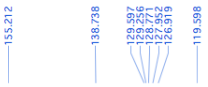
24x

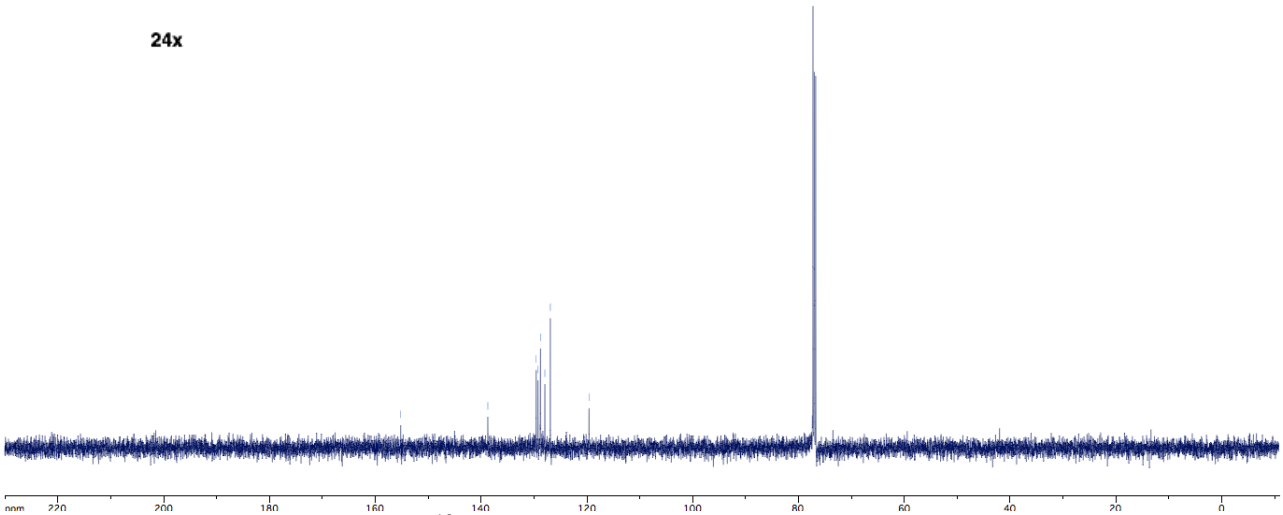


^{1}H NMR (500 MHz, $CDCl_3$)

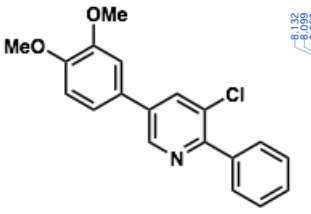


24x





^{13}C NMR (126 MHz, $CDCl_3$)



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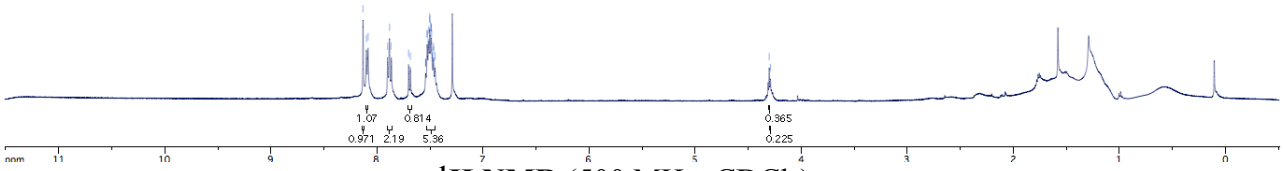
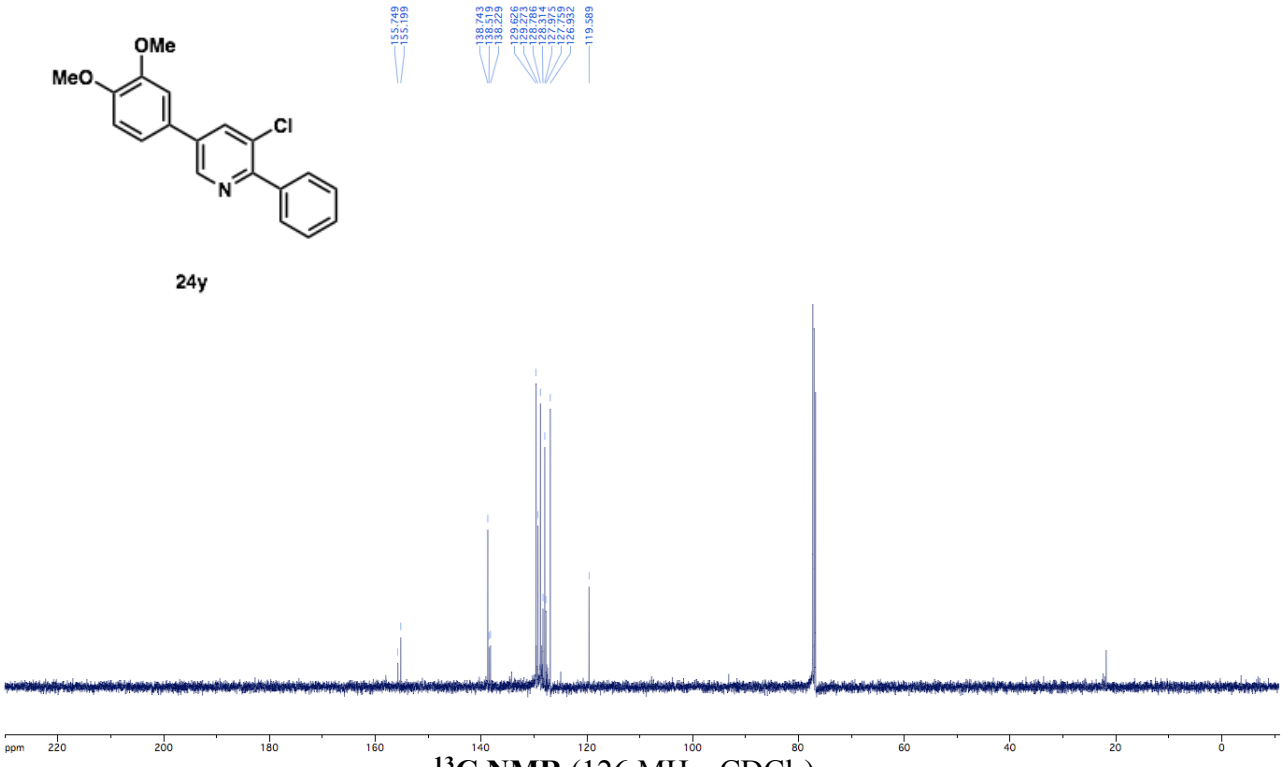


^{1}H NMR (500 MHz, $CDCl_3$)



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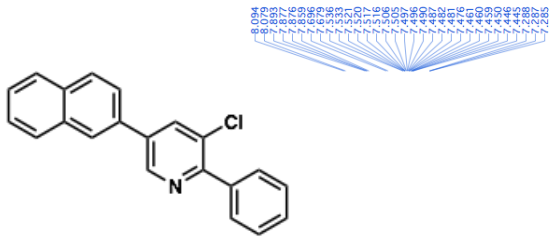
^{13}C NMR (126 MHz, $CDCl_3$)



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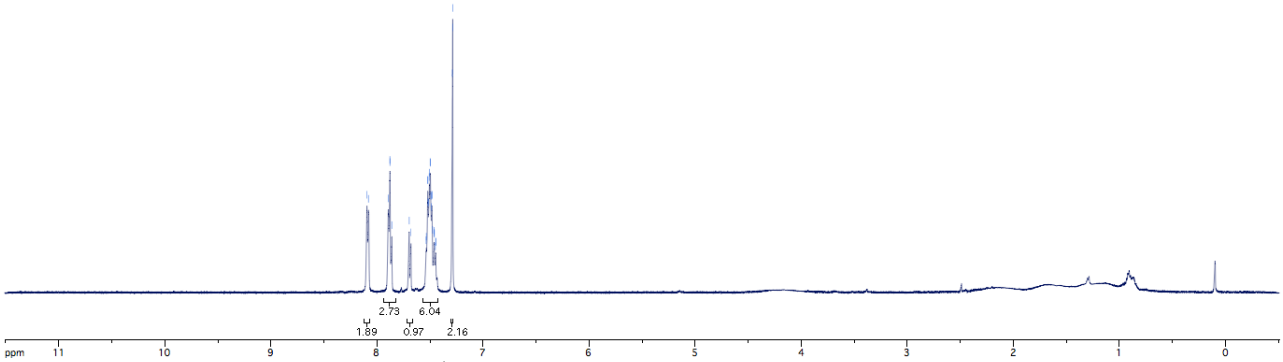
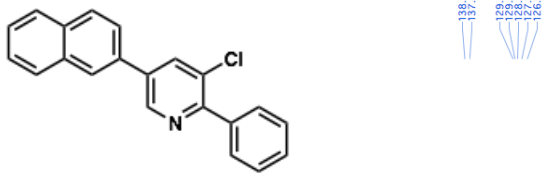
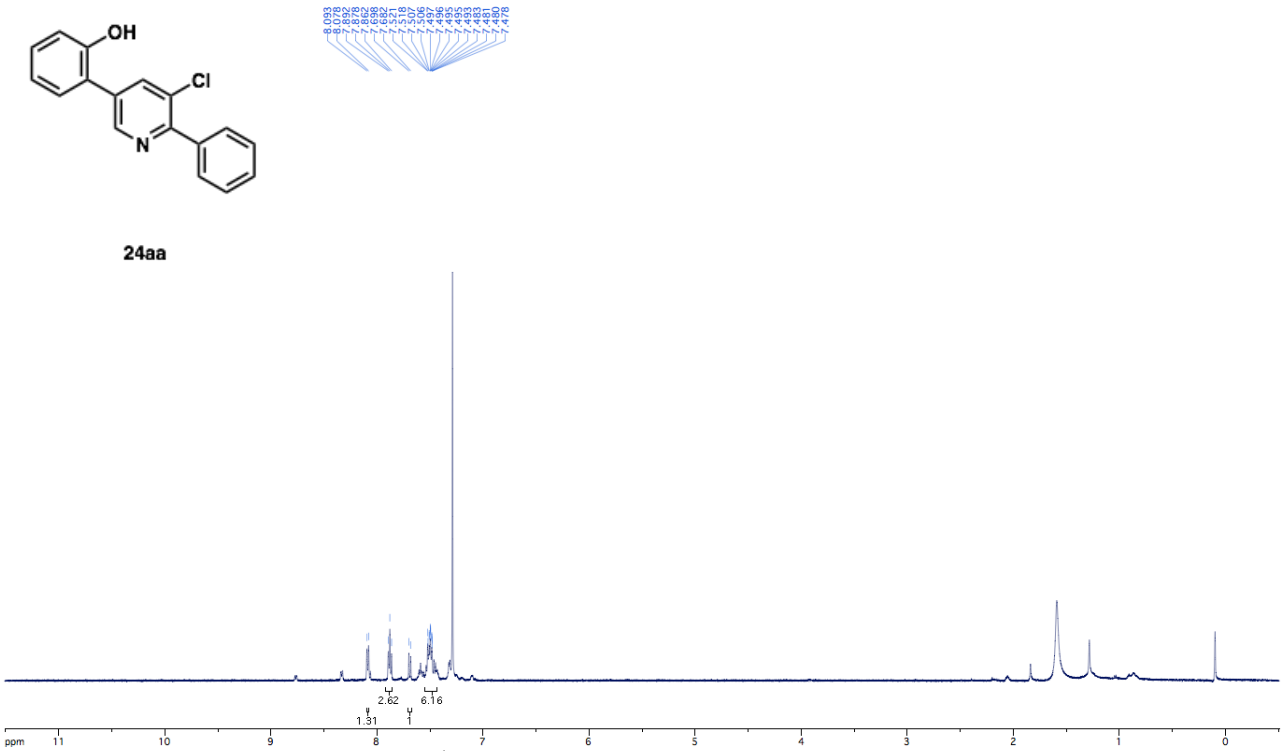


^{1}H NMR (500 MHz, $CDCl_3$)

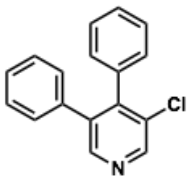


24z

^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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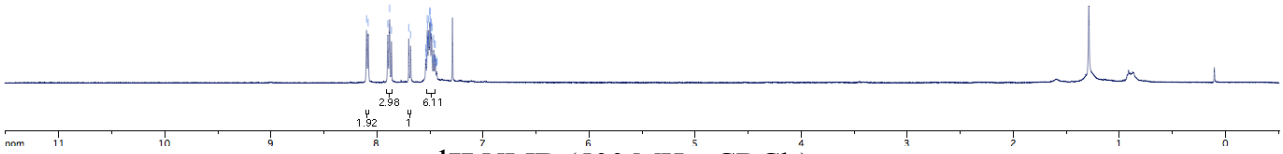
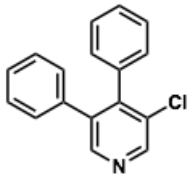


^{1}H NMR (500 MHz, $CDCl_3$)



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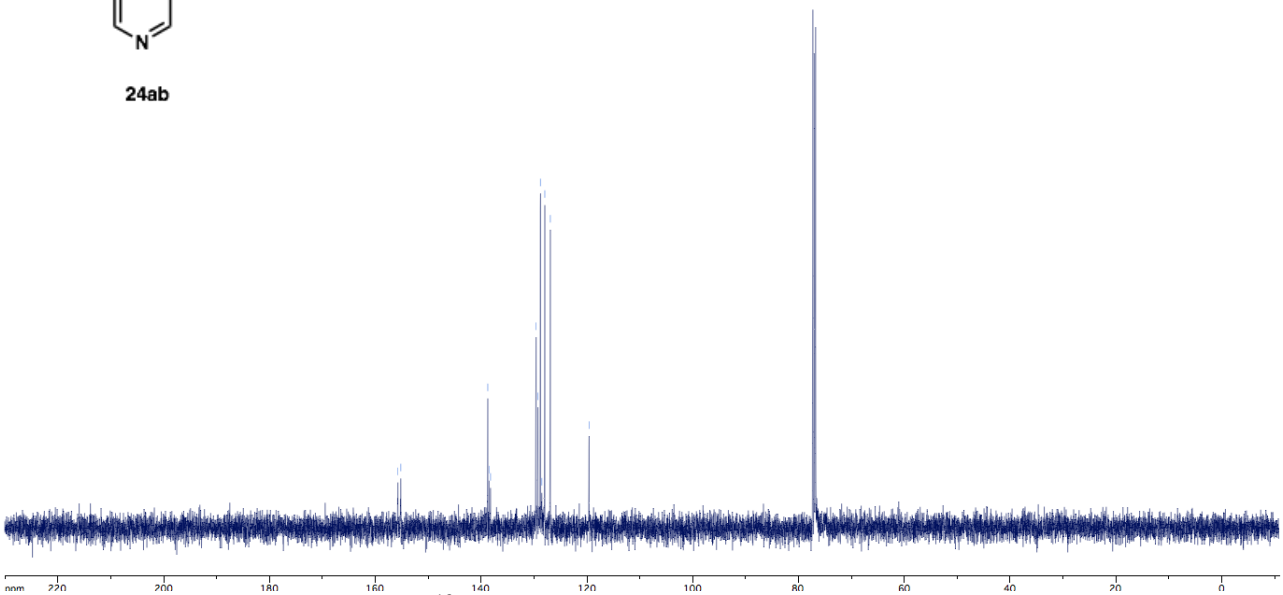
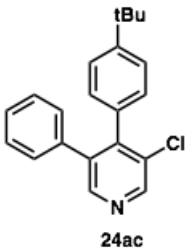
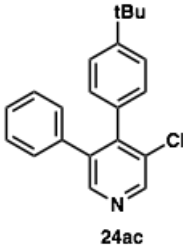


^{13}C NMR (126 MHz, $CDCl_3$)



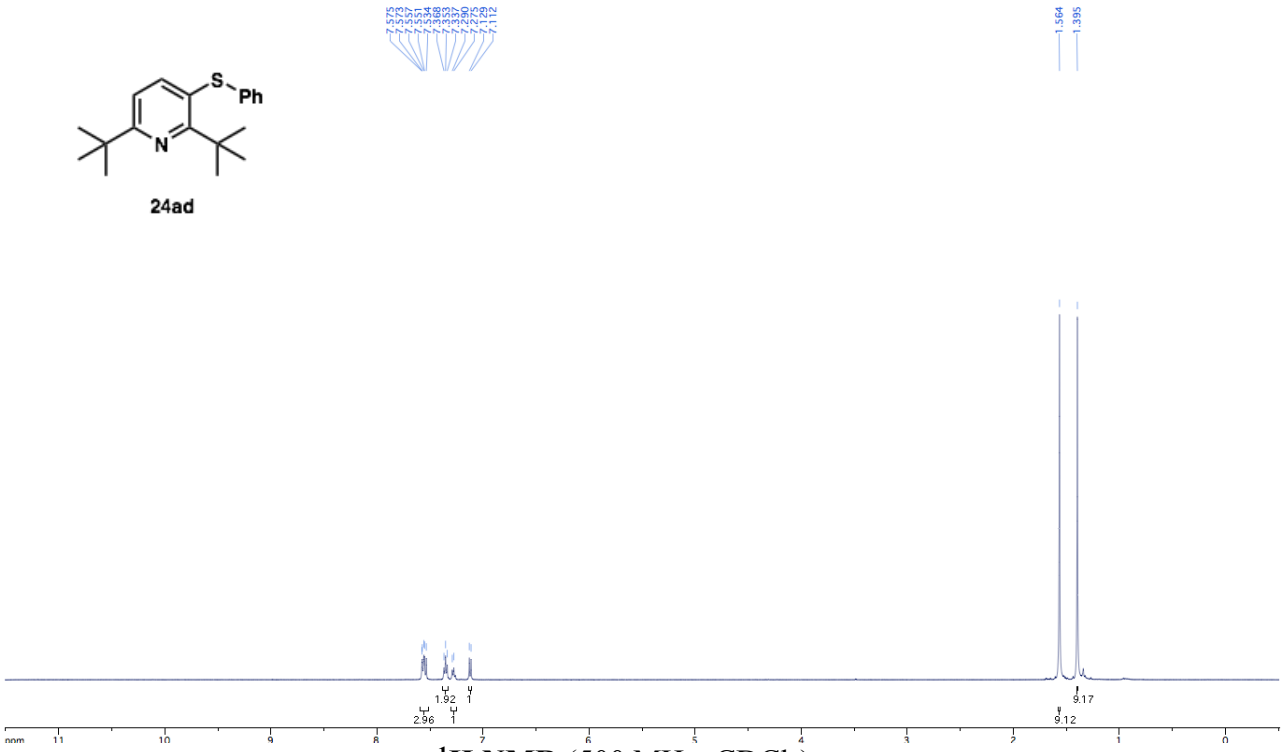
24ac

^{1}H NMR (500 MHz, $CDCl_3$)

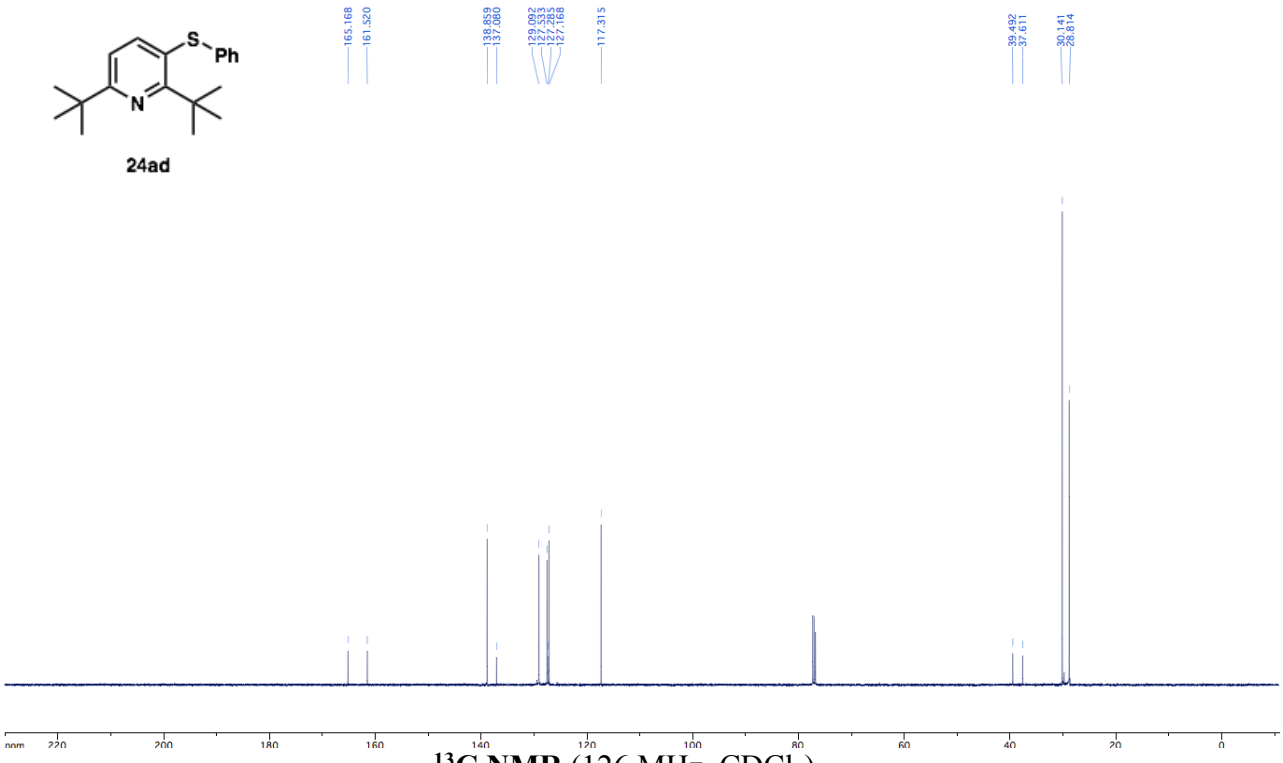


24ac

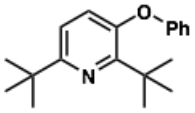
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

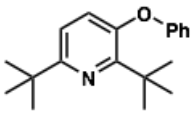


^{13}C NMR (126 MHz, $CDCl_3$)



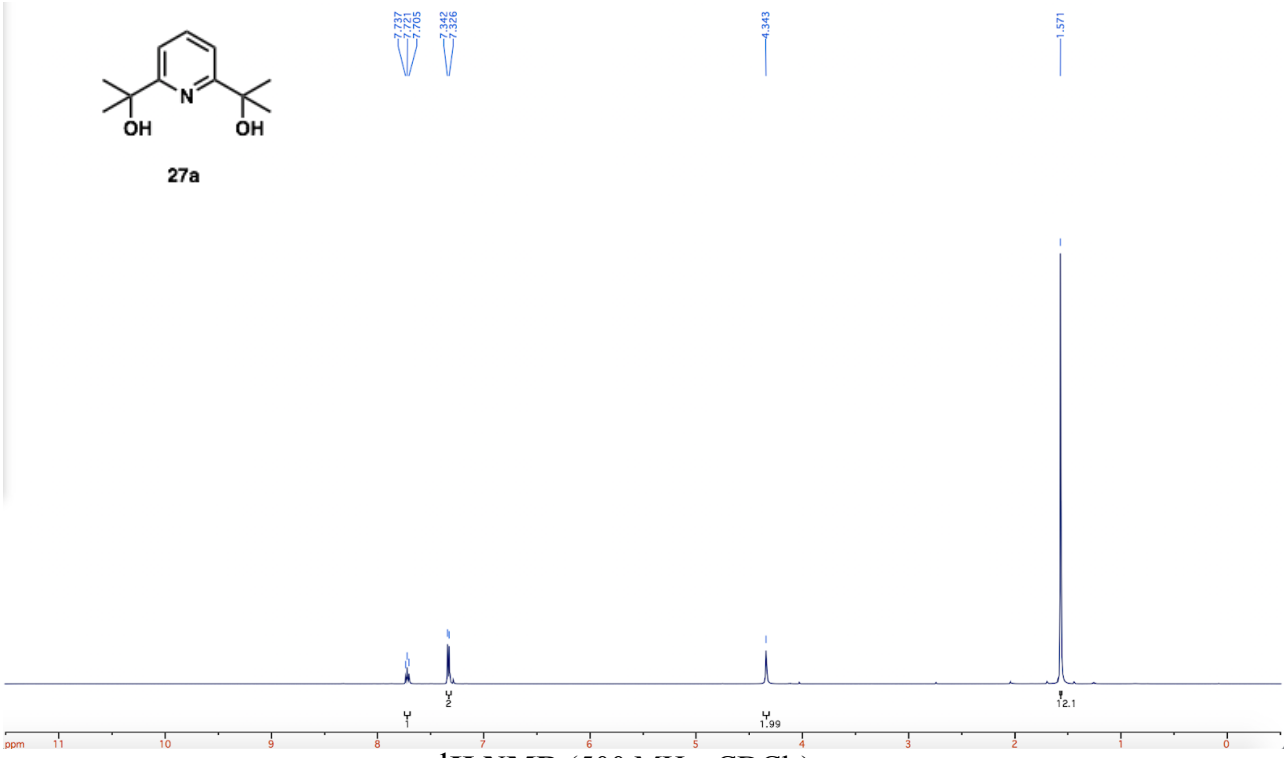
24ae

^{1}H NMR (500 MHz, $CDCl_3$)

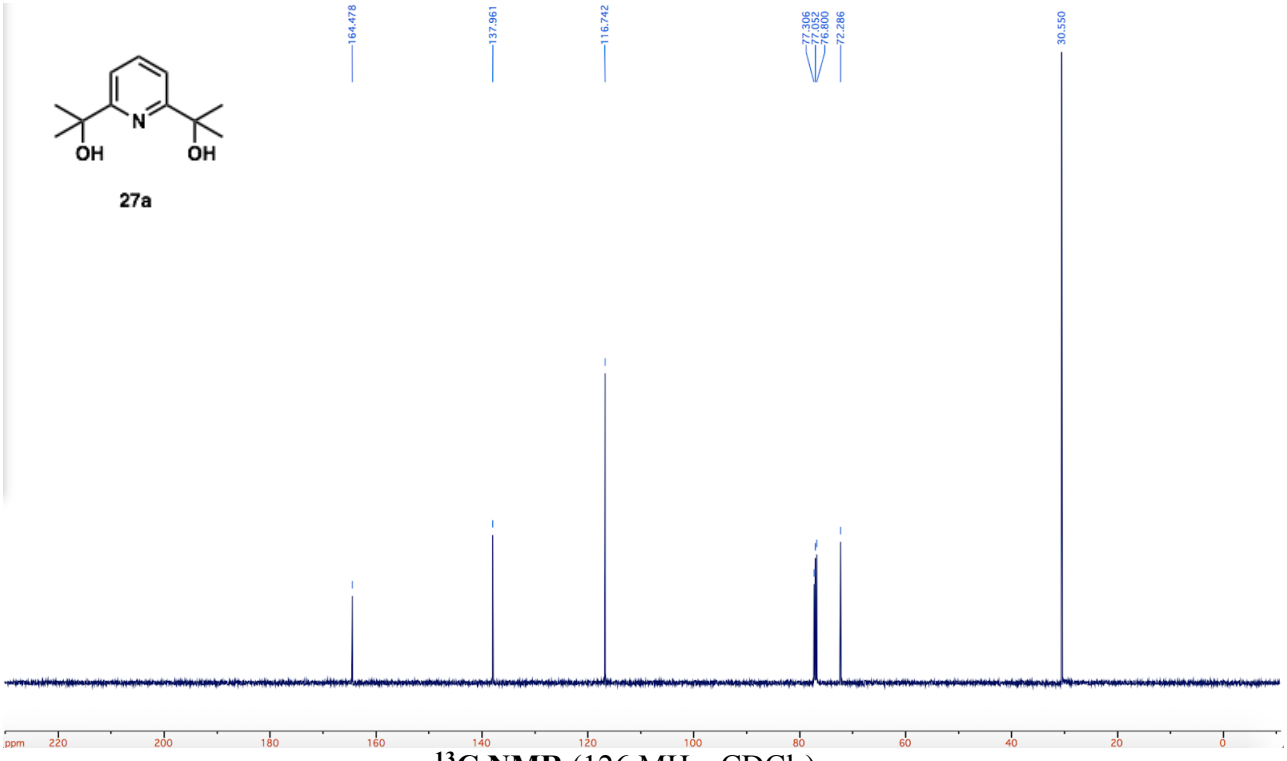


24ae

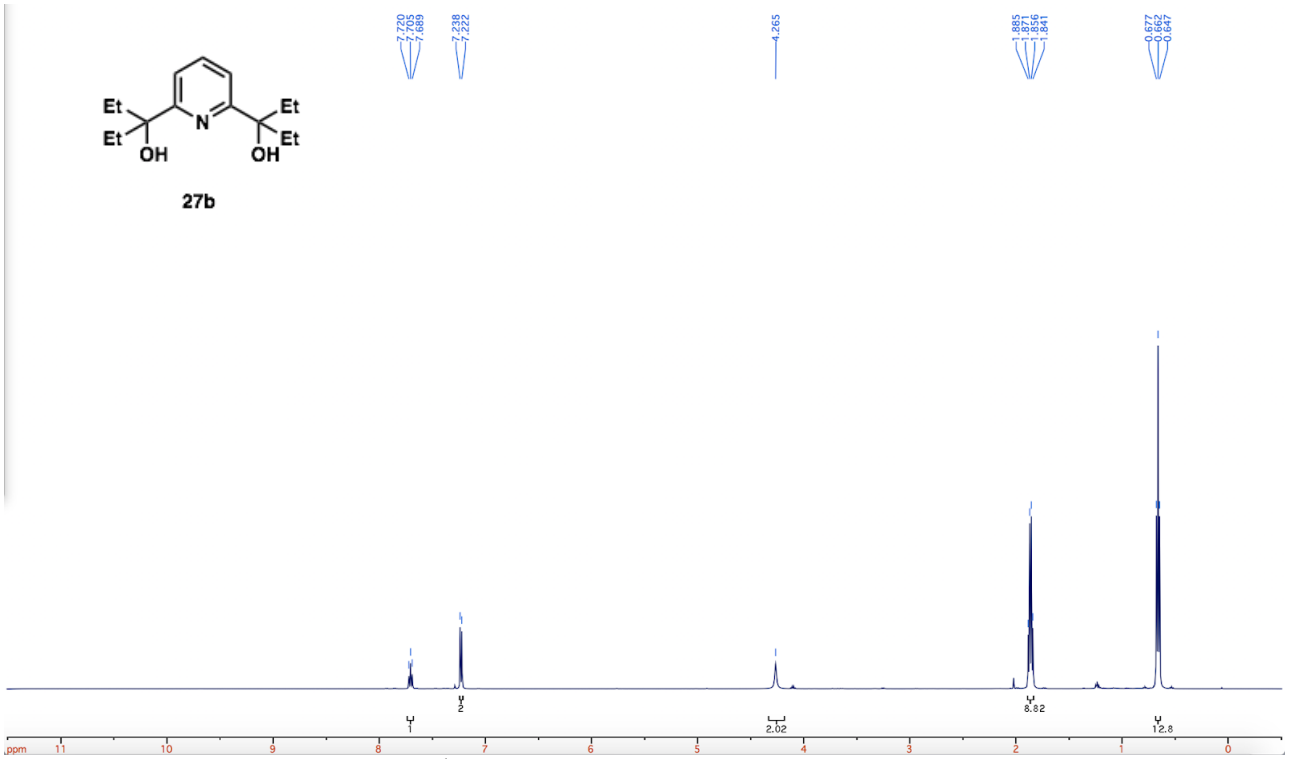
^{13}C NMR (126 MHz, $CDCl_3$)



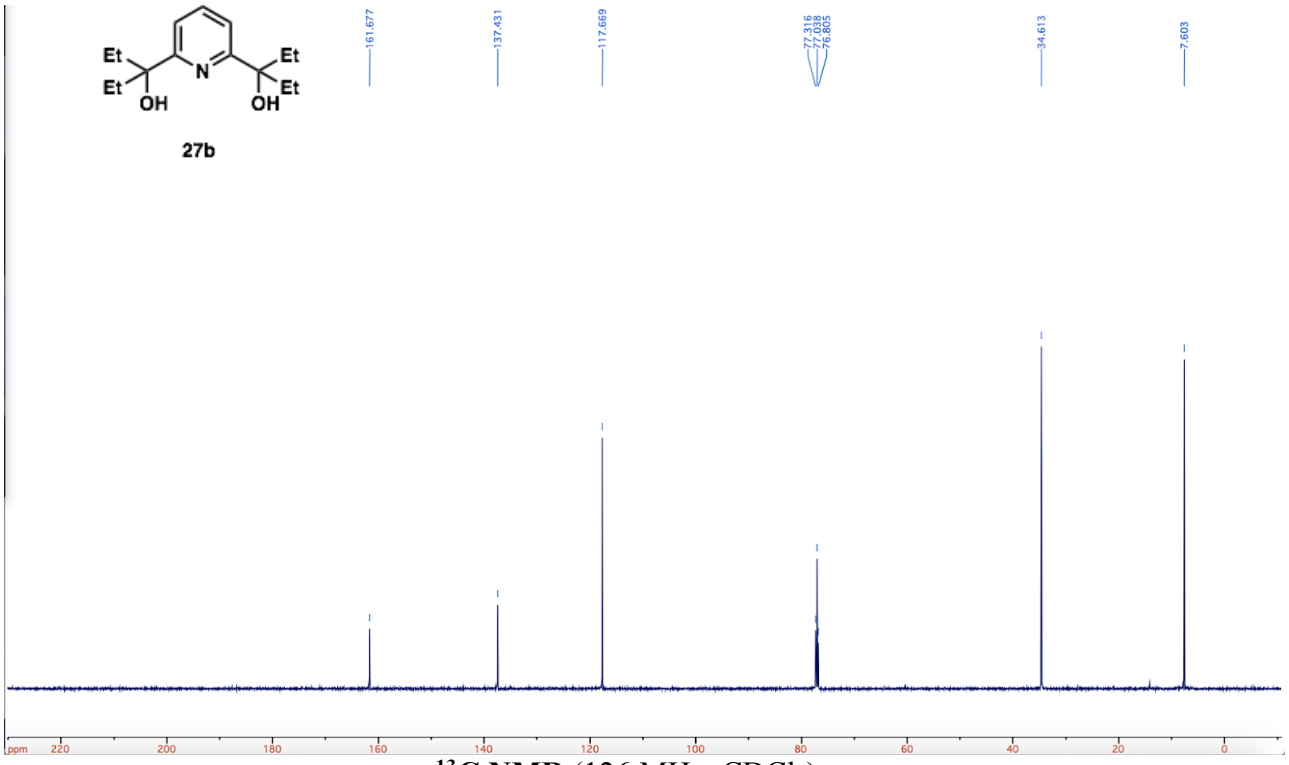
^{1}H NMR (500 MHz, $CDCl_3$)



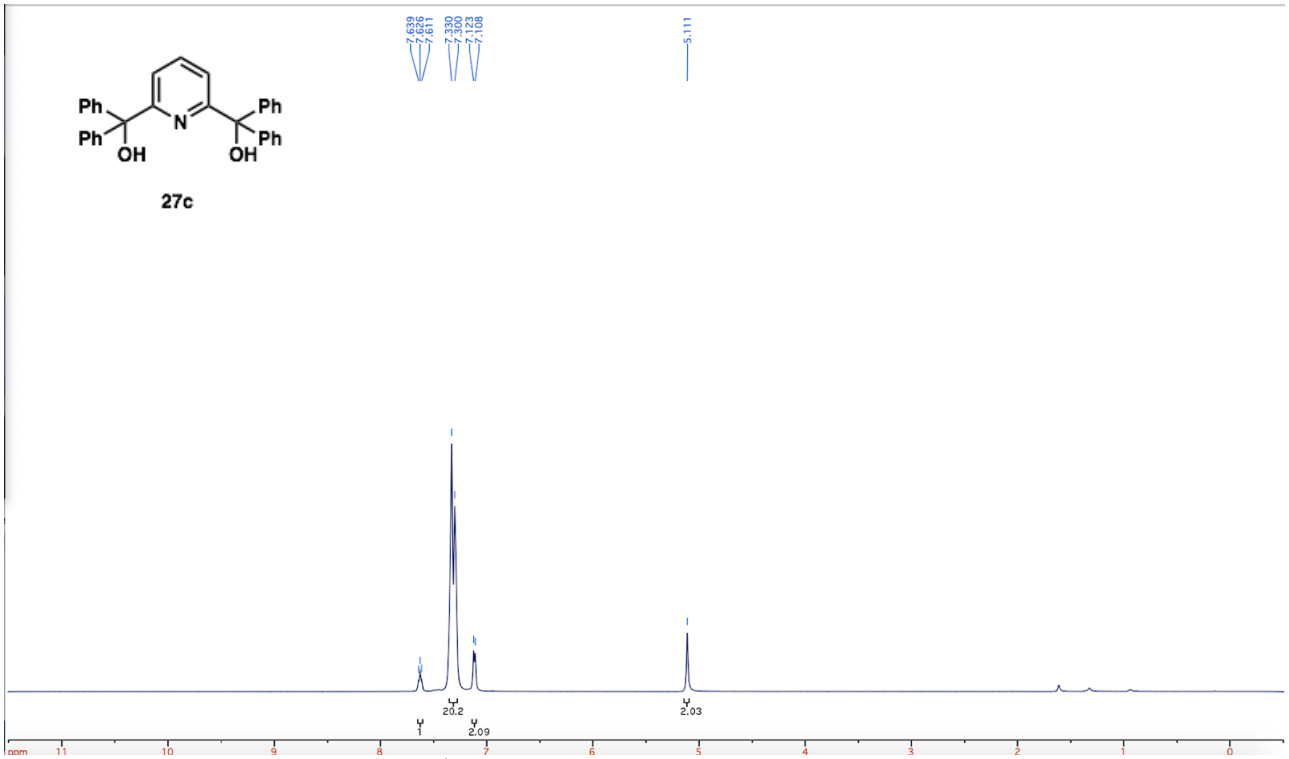
^{13}C NMR (126 MHz, $CDCl_3$)



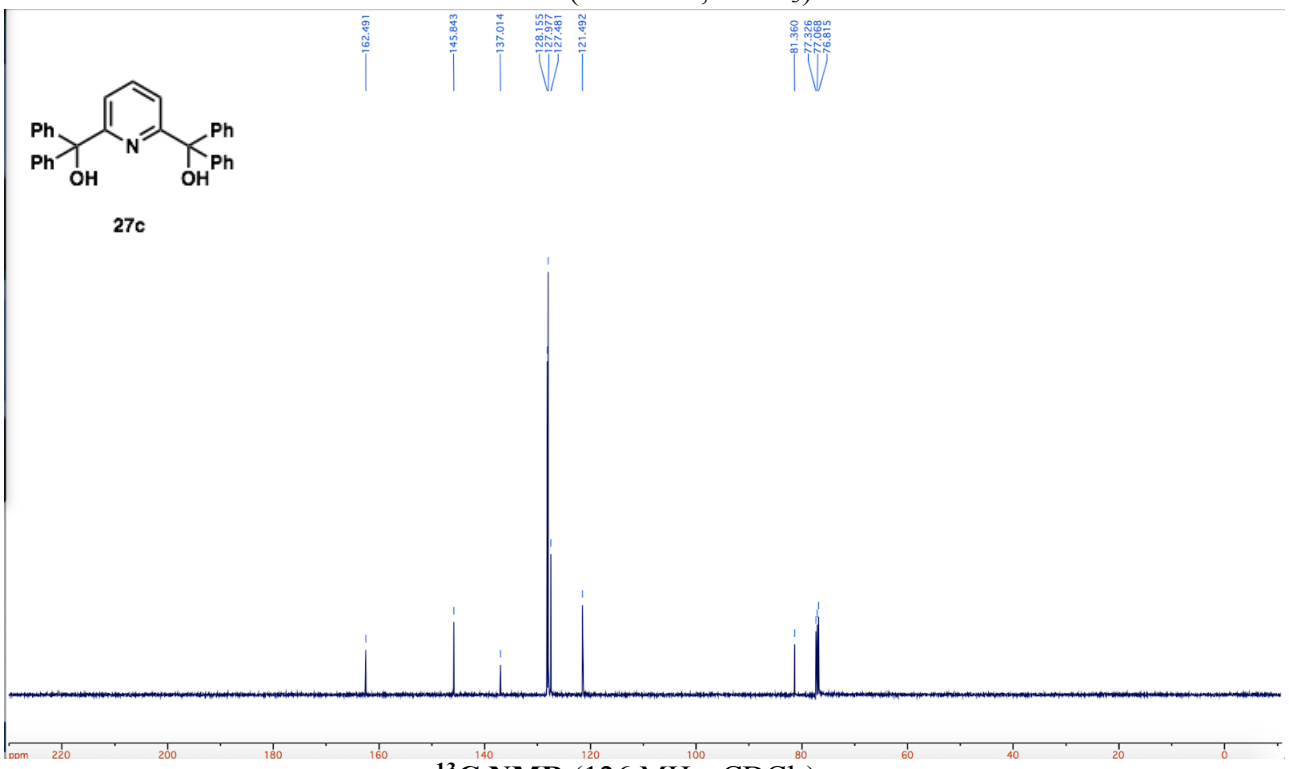
^{1}H NMR (500 MHz, $CDCl_3$)



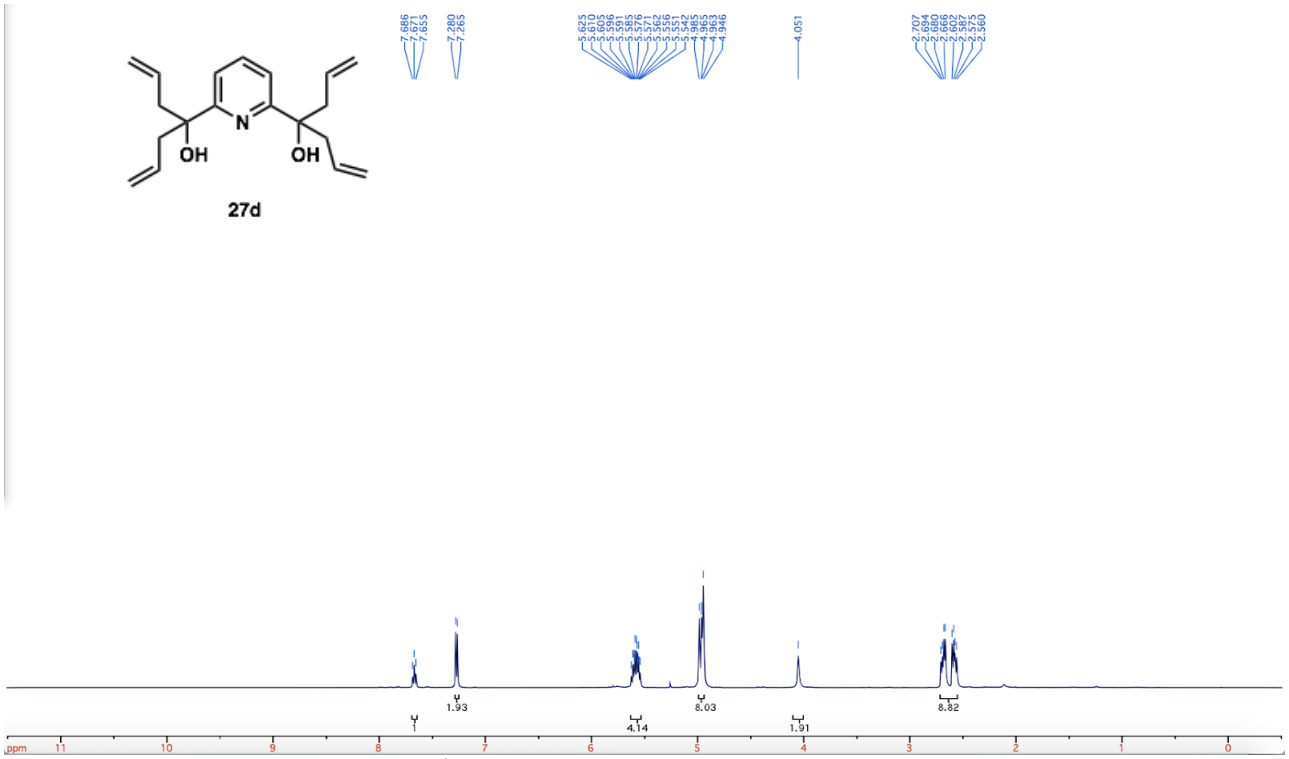
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



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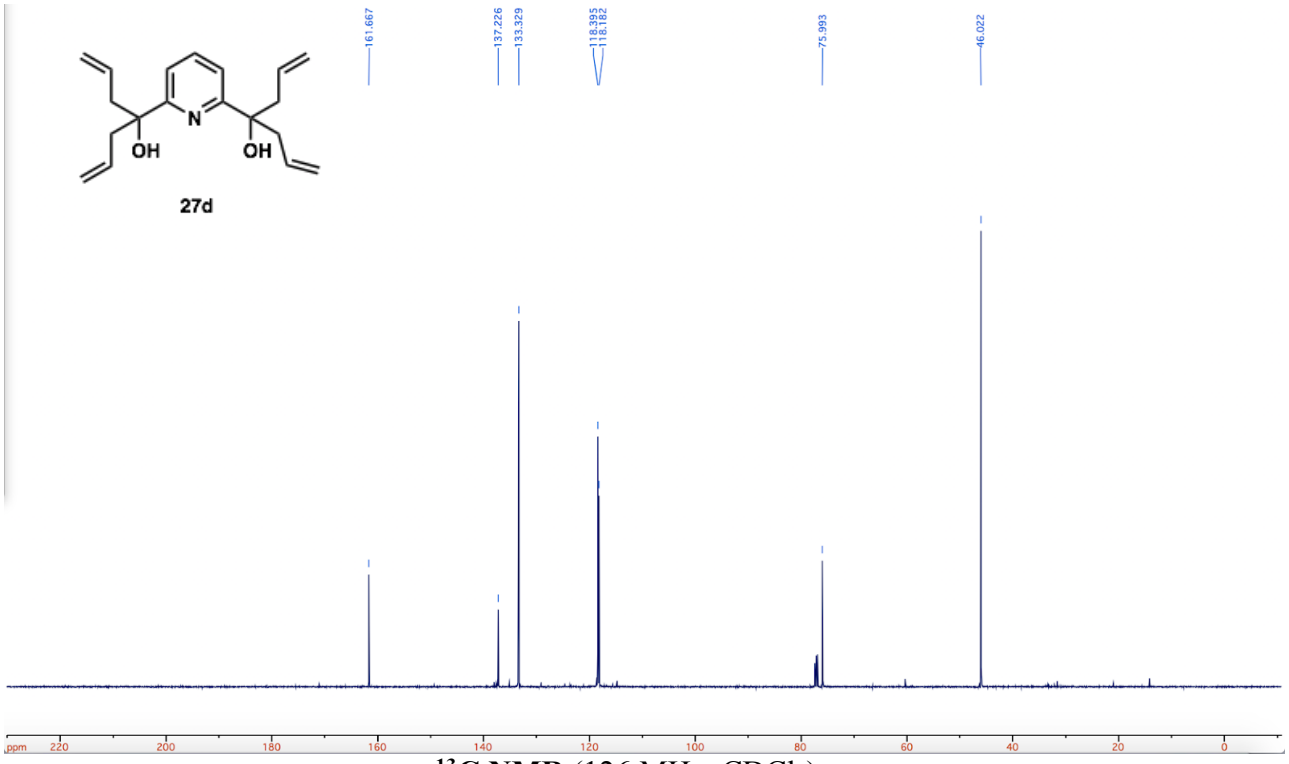

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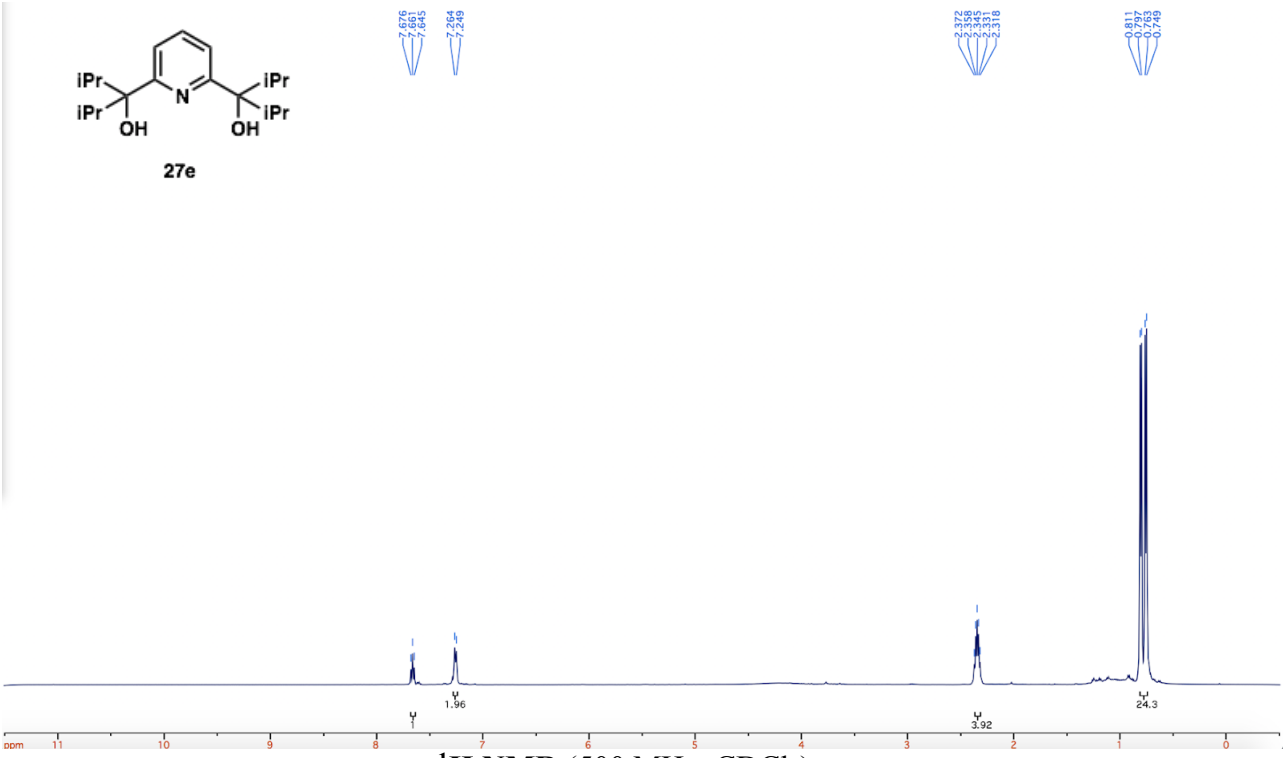
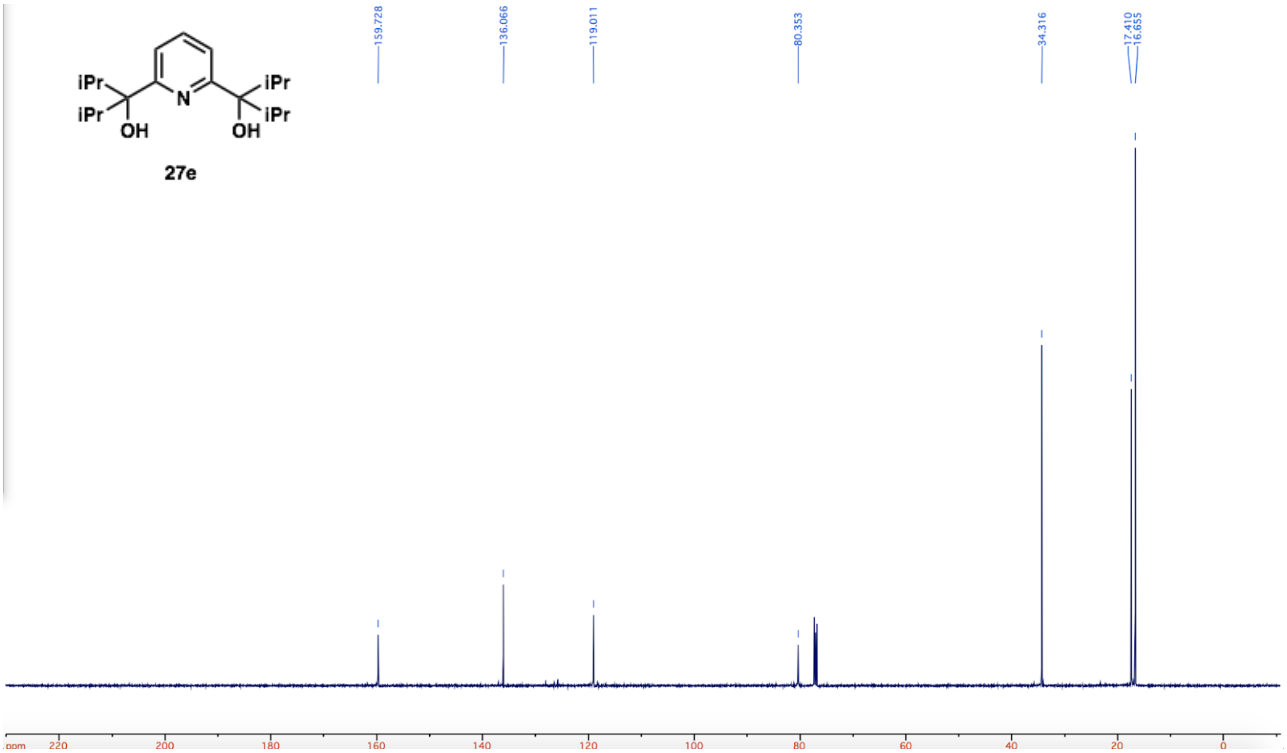


^{1}H NMR (500 MHz, $CDCl_3$)



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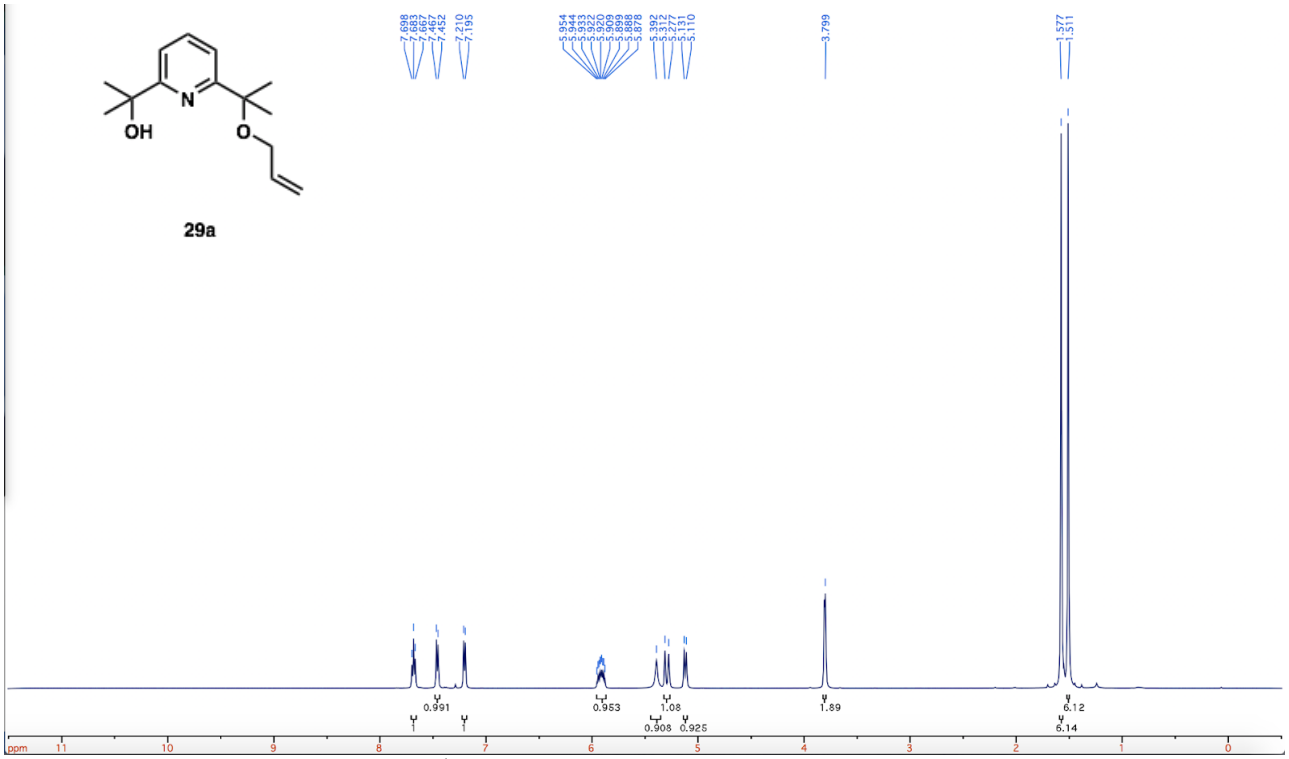
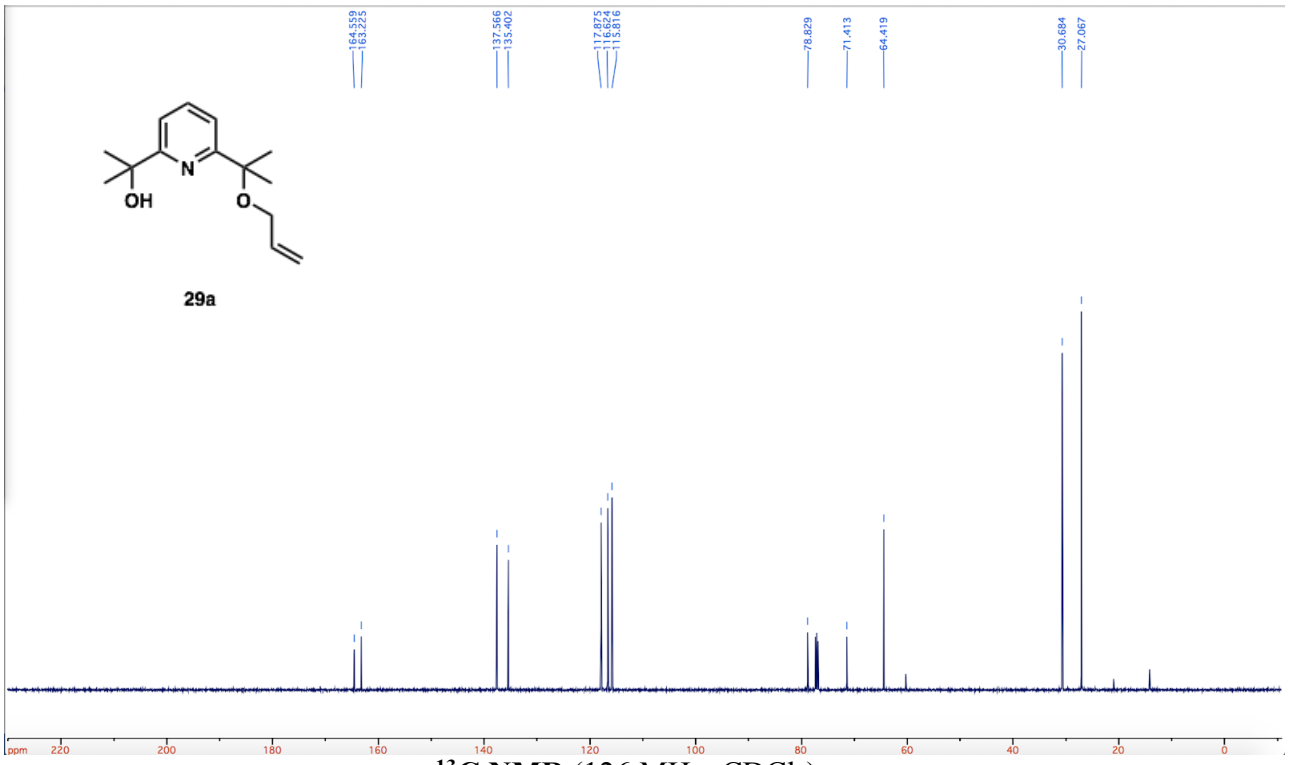


^{1}H NMR (500 MHz, $CDCl_3$)



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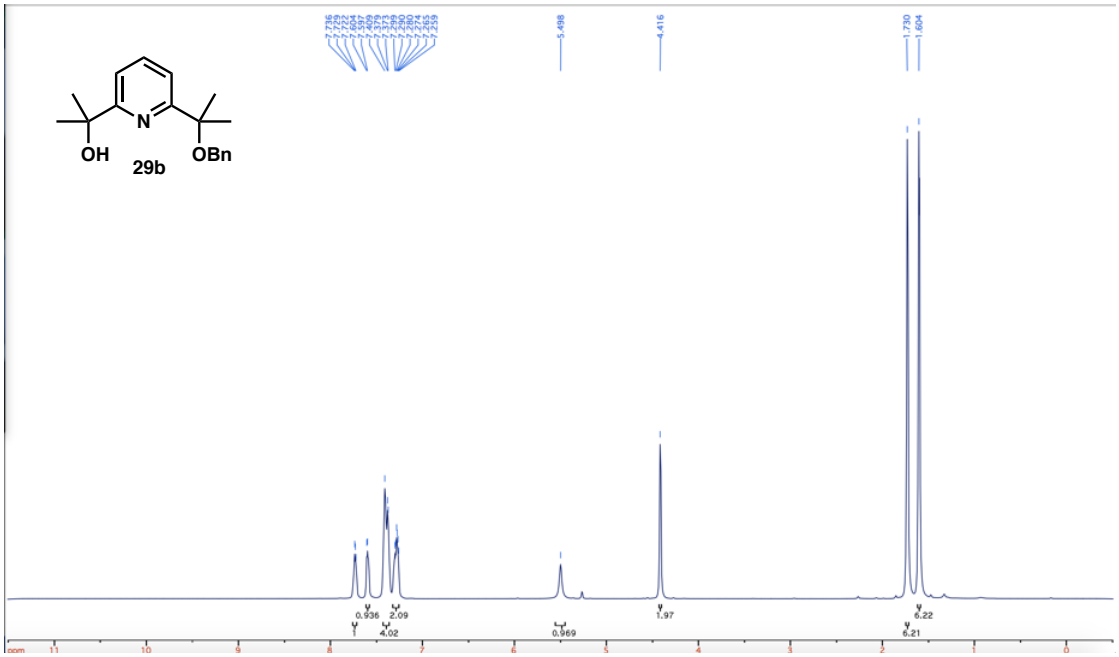

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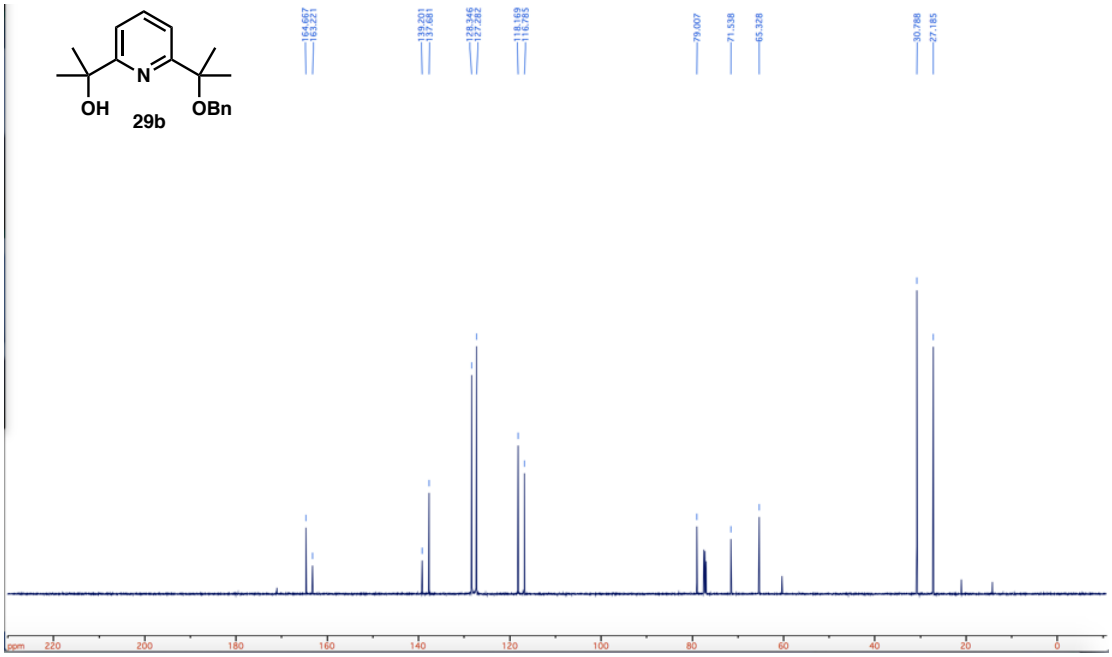

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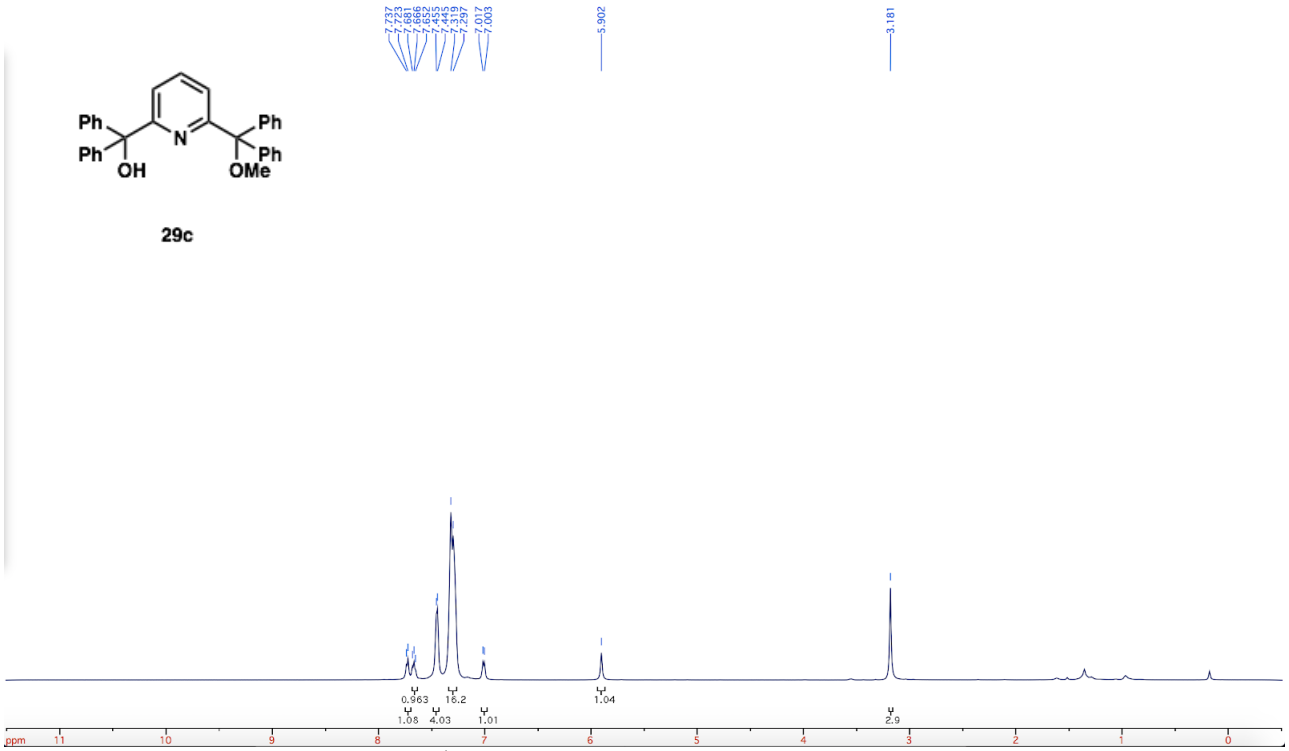
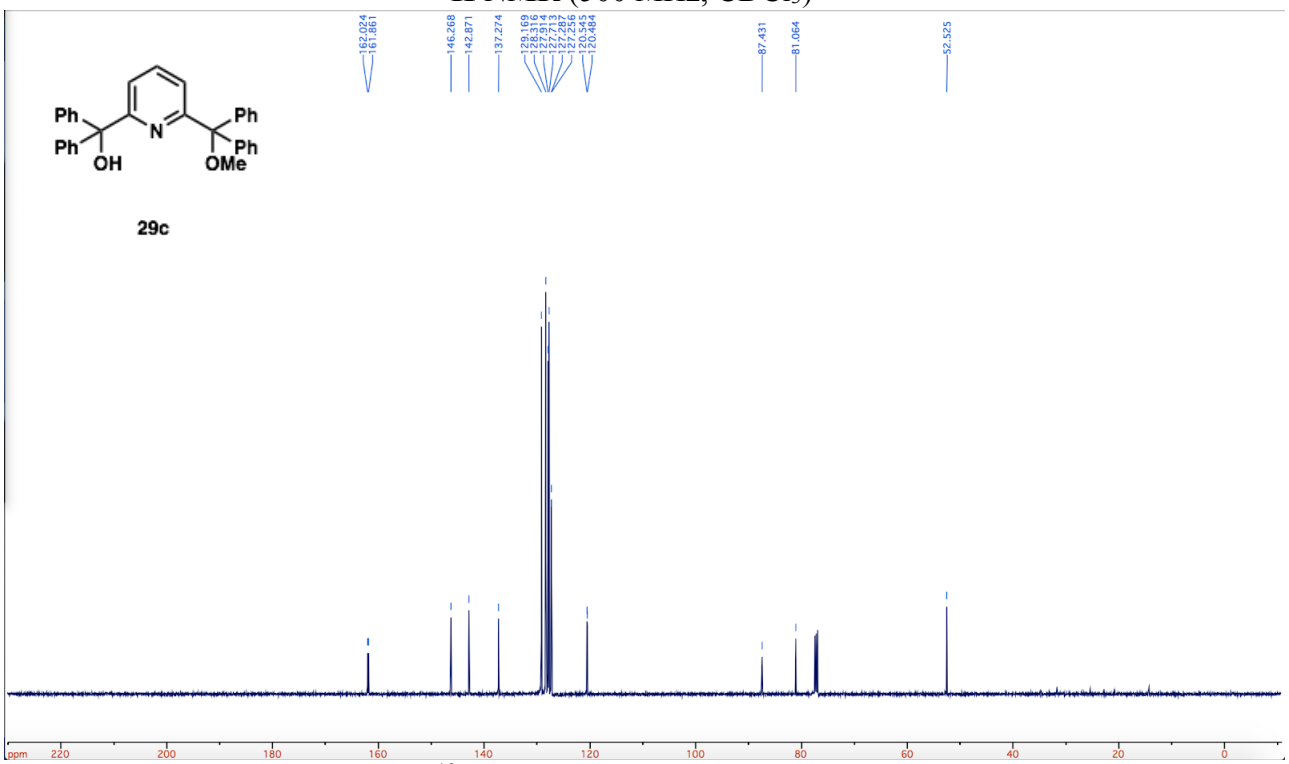
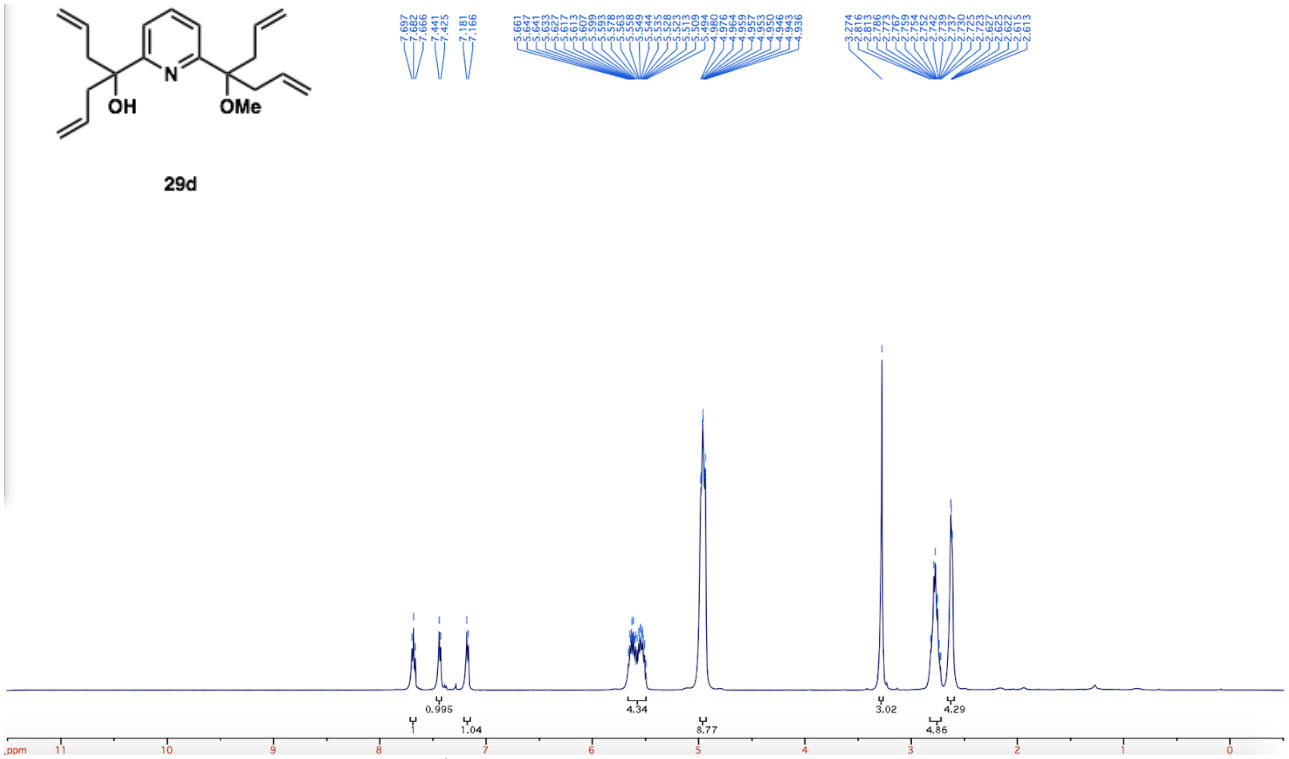


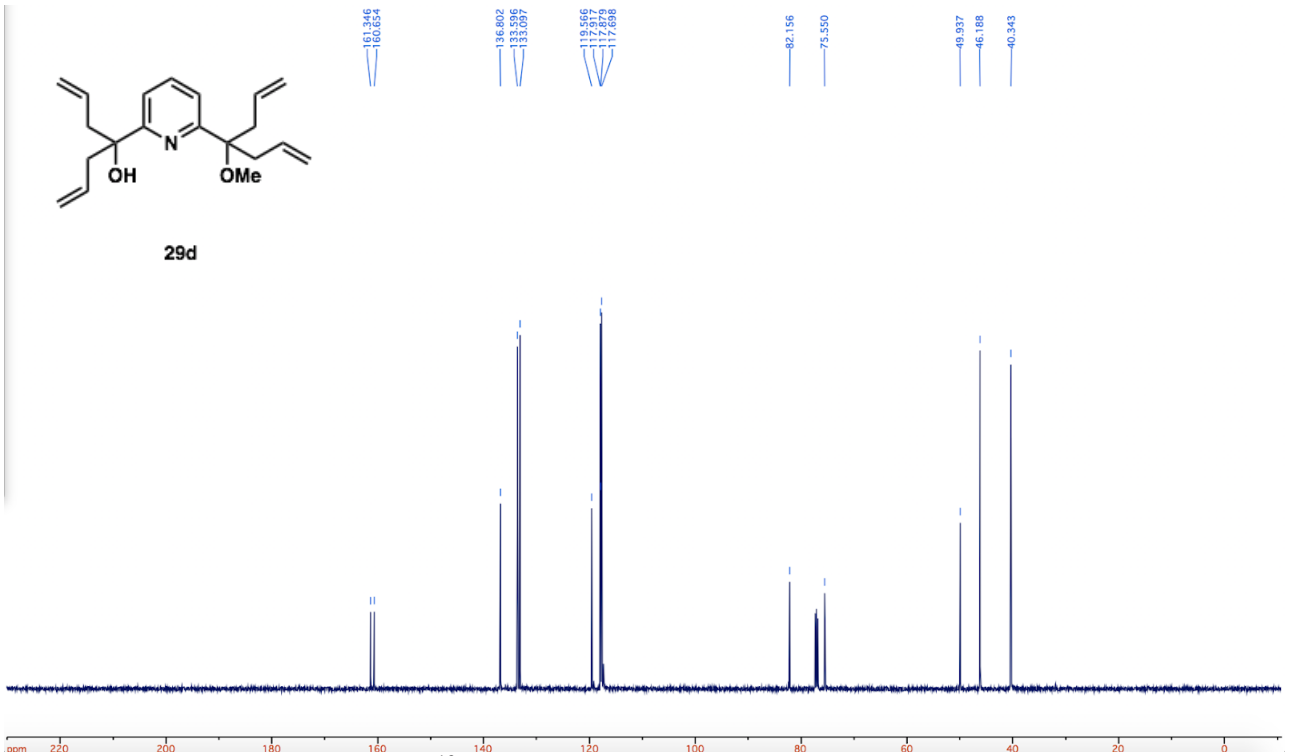
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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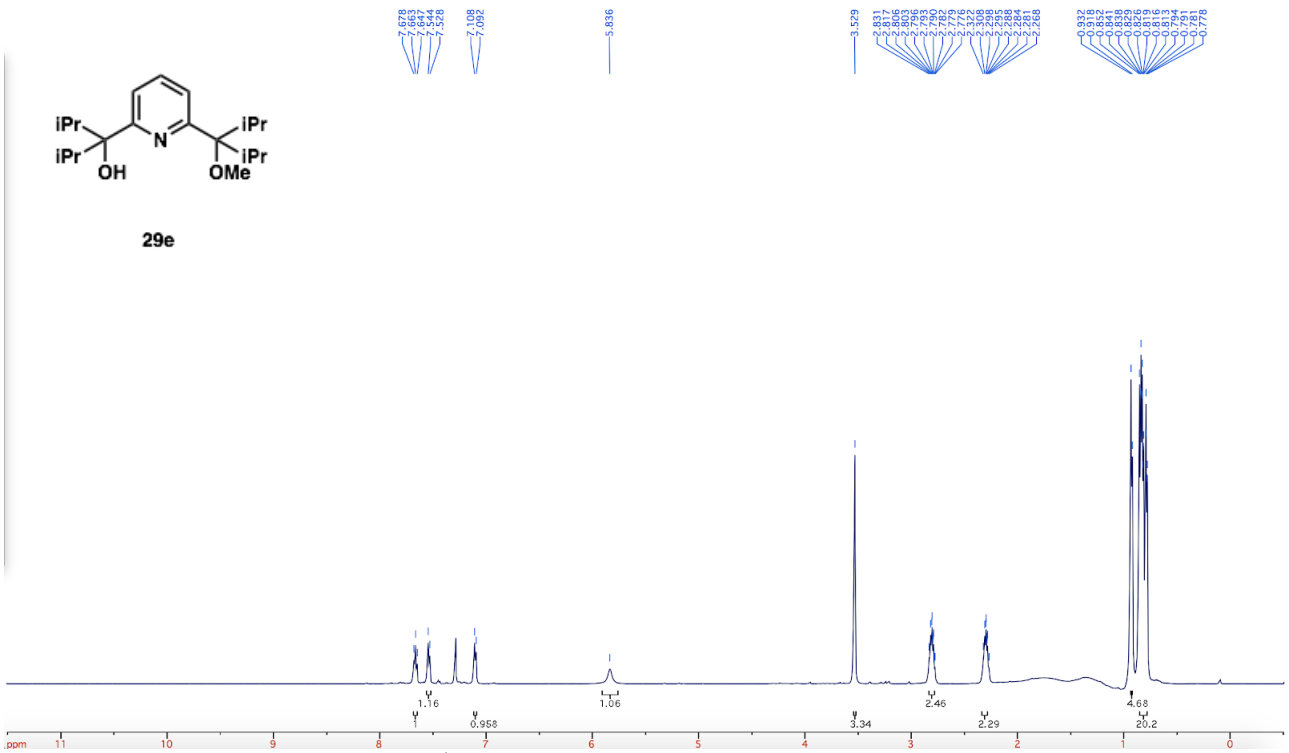
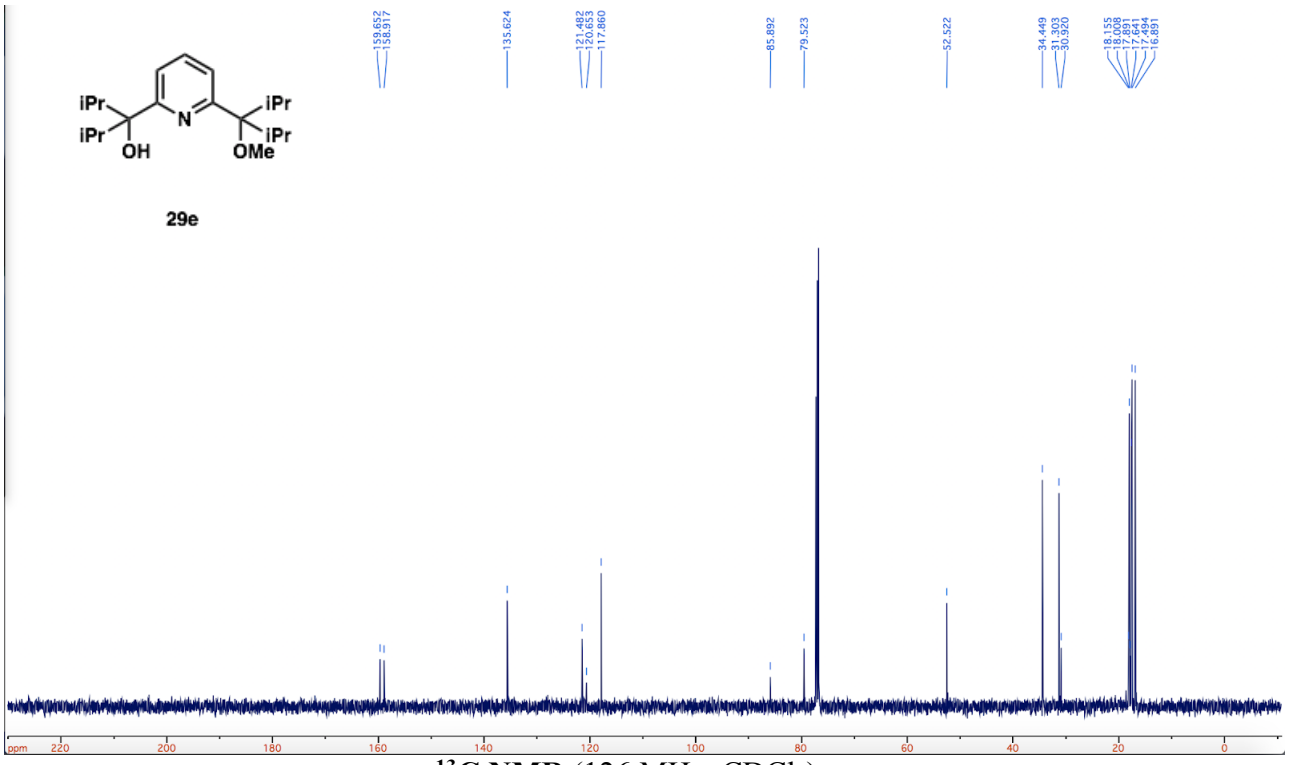
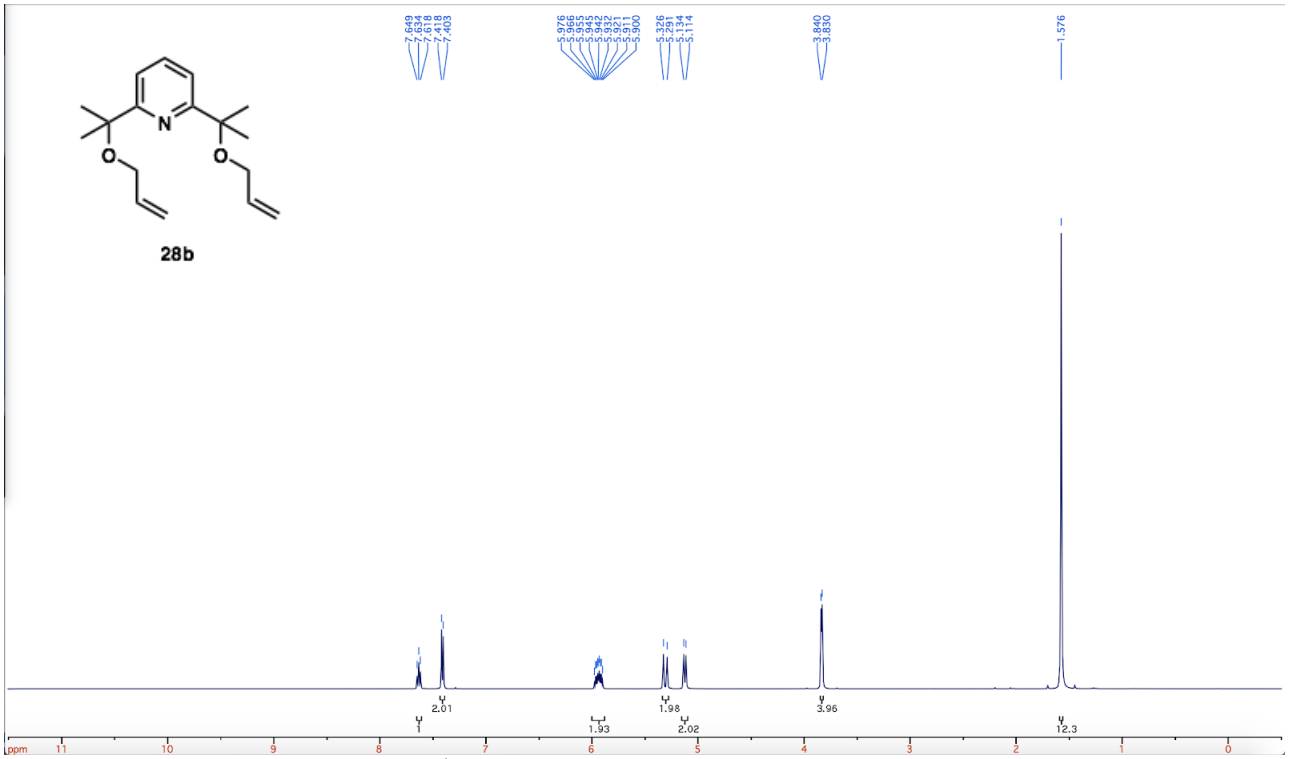


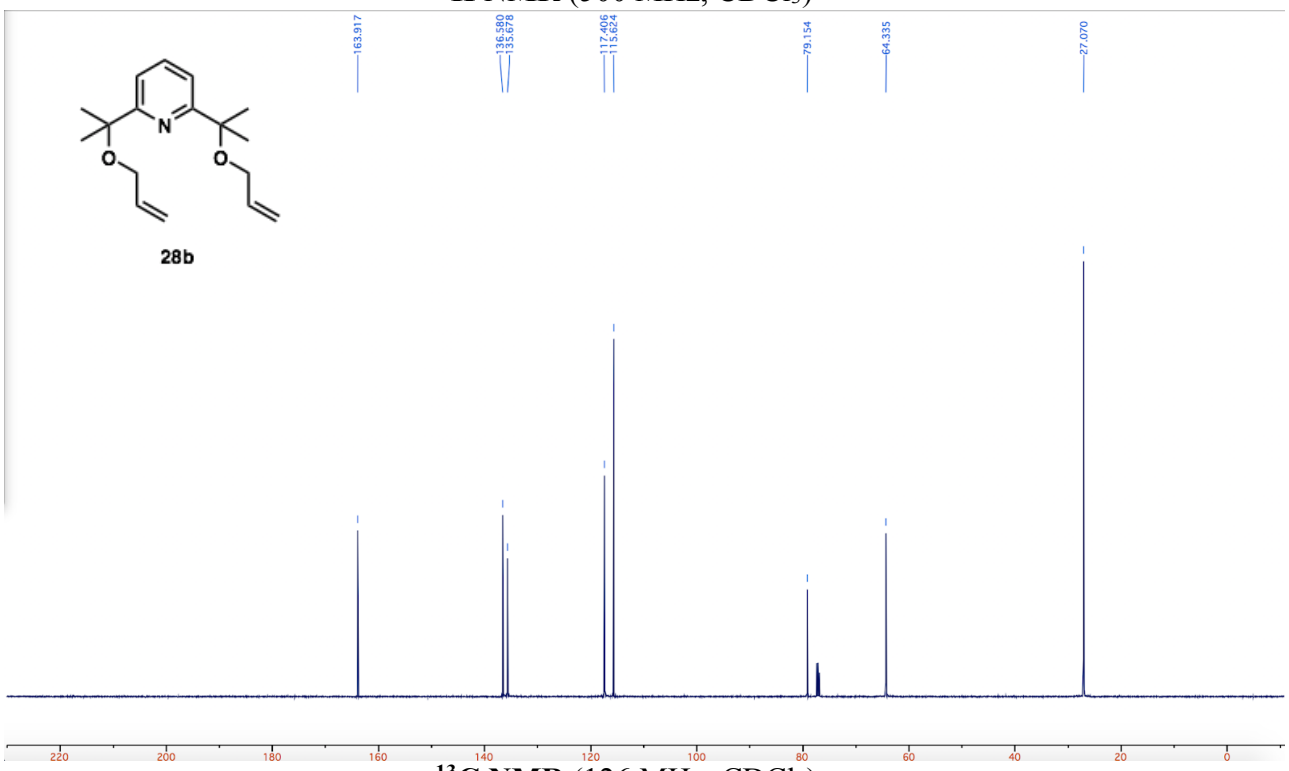
^{1}H NMR (500 MHz, $CDCl_3$)



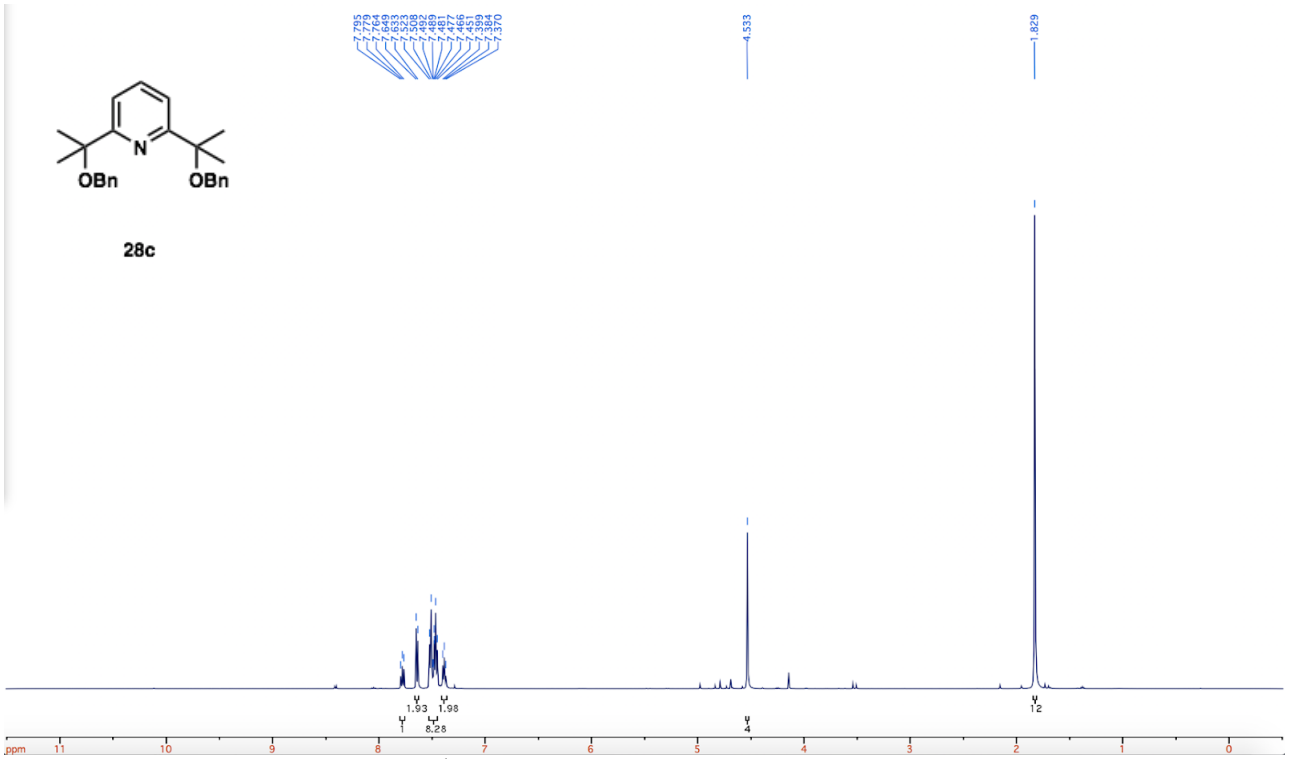
^{13}C NMR (126 MHz, $CDCl_3$)



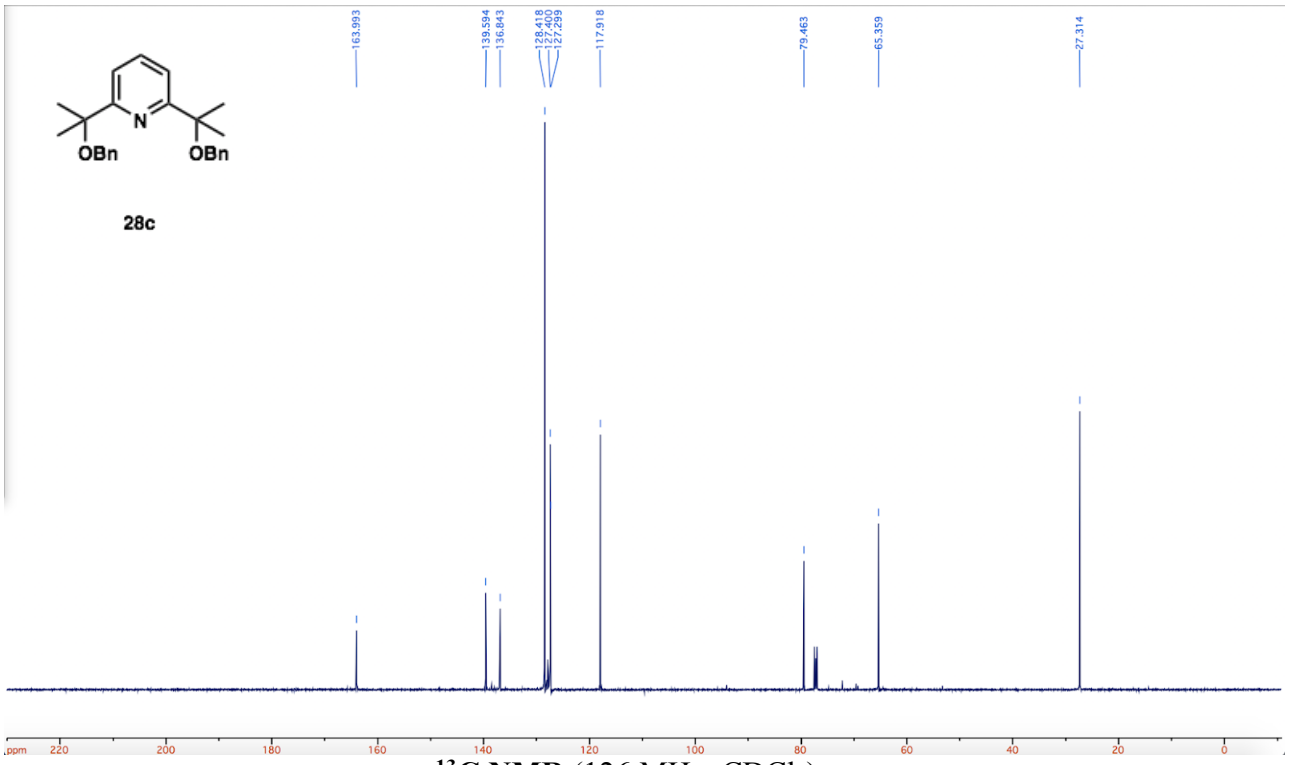
^{1}H NMR (500 MHz, $CDCl_3$)



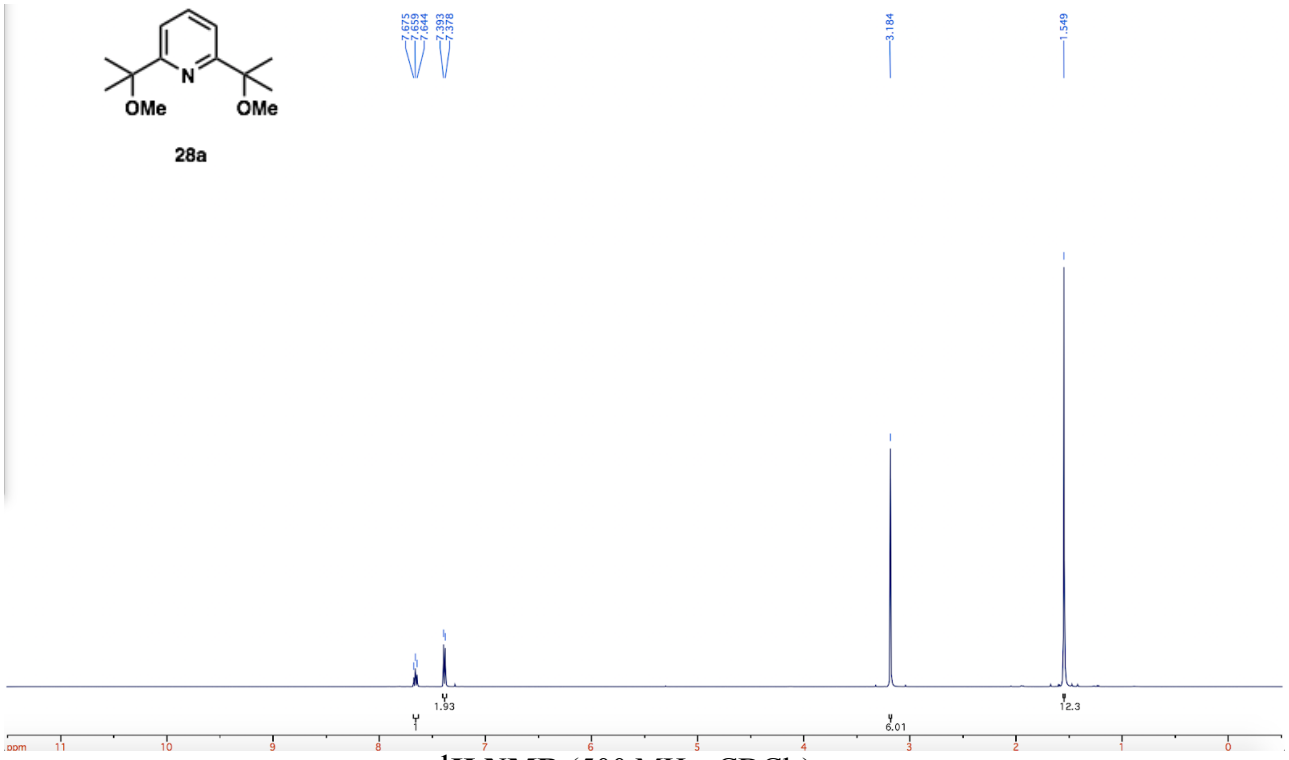
^{13}C NMR (126 MHz, $CDCl_3$)



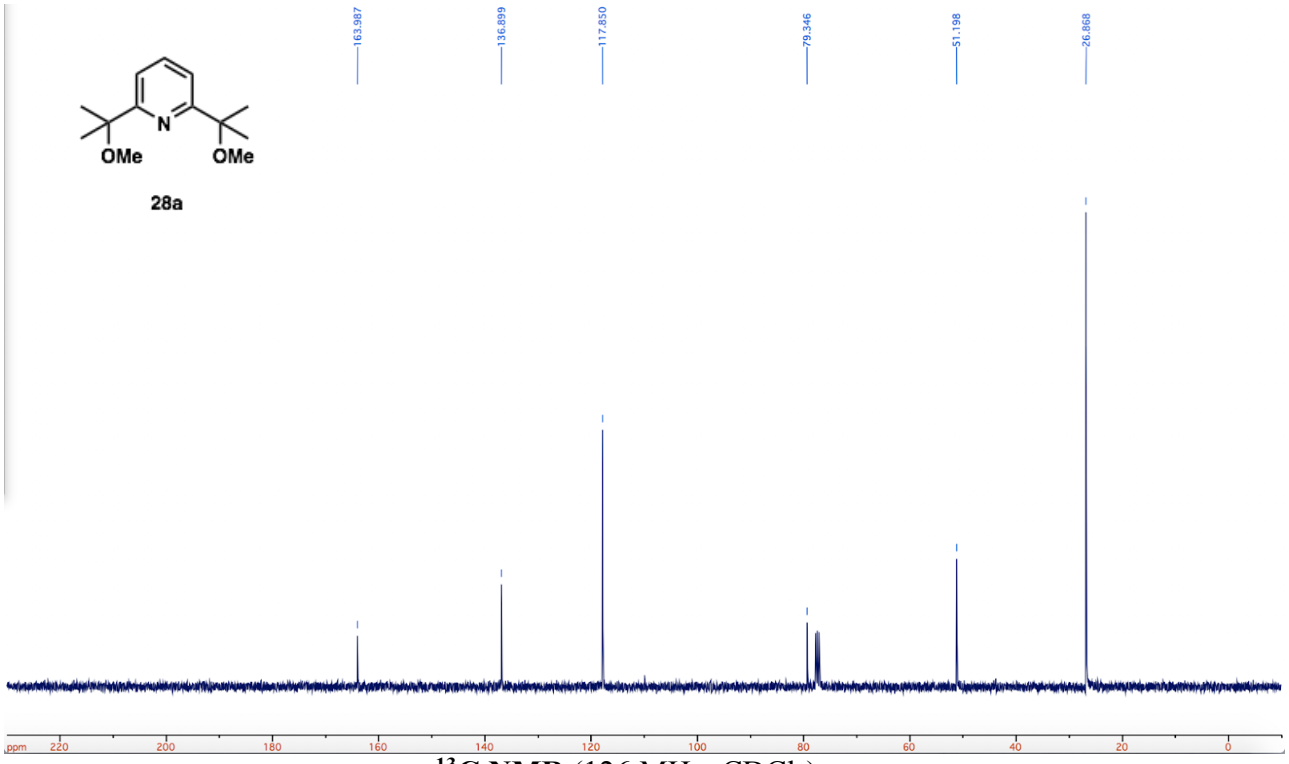
^{1}H NMR (500 MHz, $CDCl_3$)



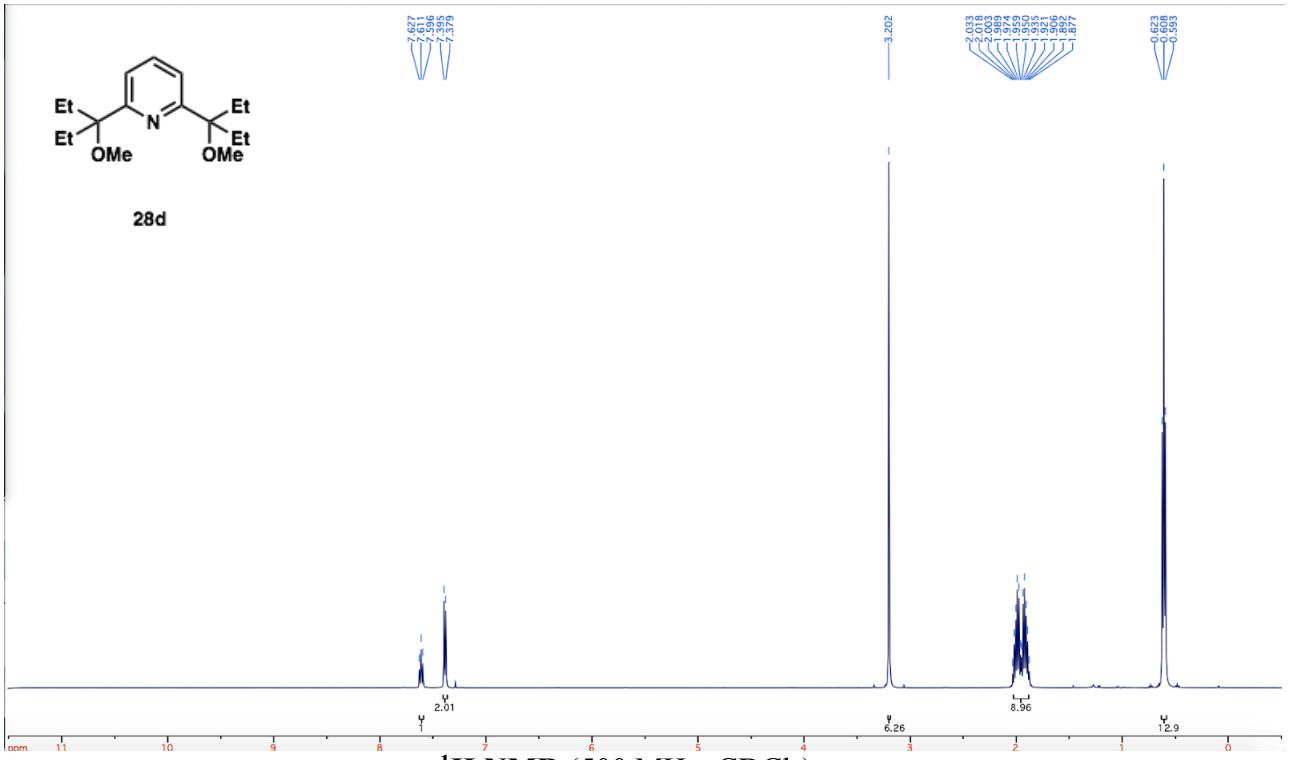
^{13}C NMR (126 MHz, $CDCl_3$)



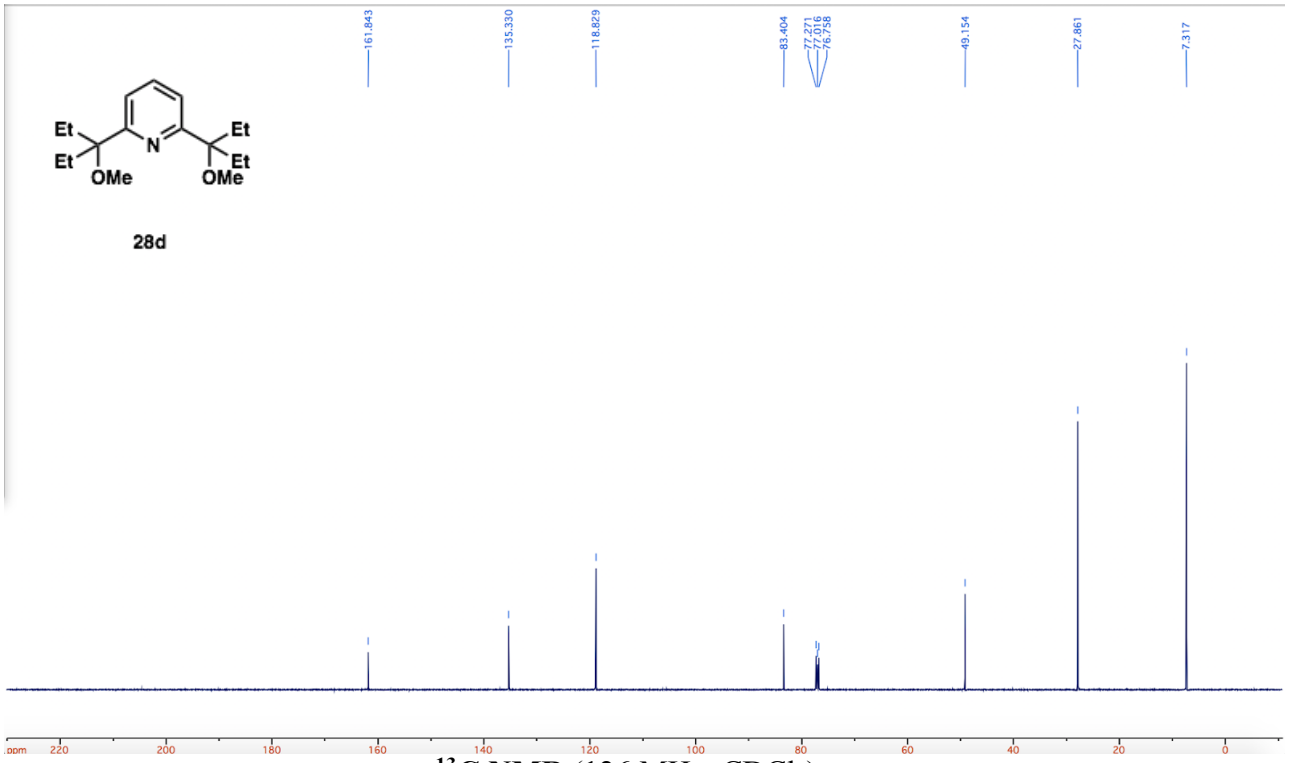
^{1}H NMR (500 MHz, $CDCl_3$)



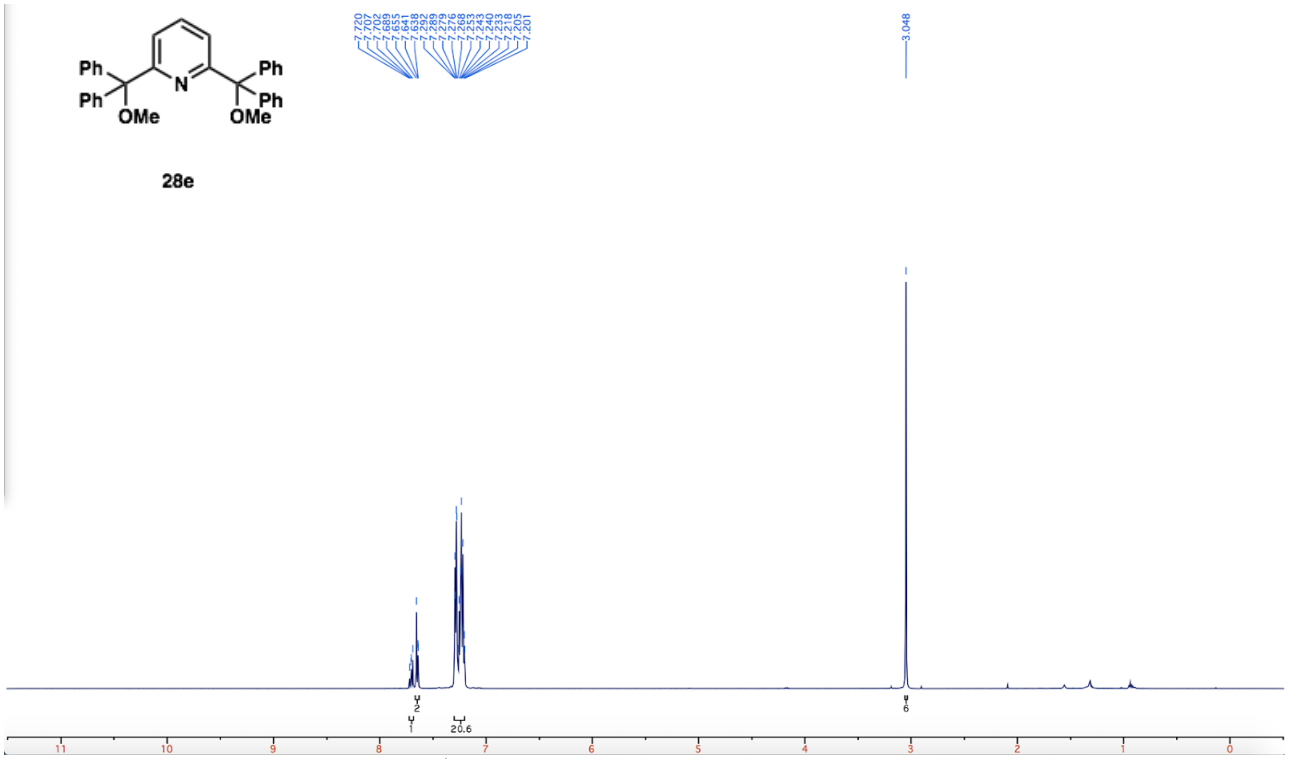
^{13}C NMR (126 MHz, $CDCl_3$)



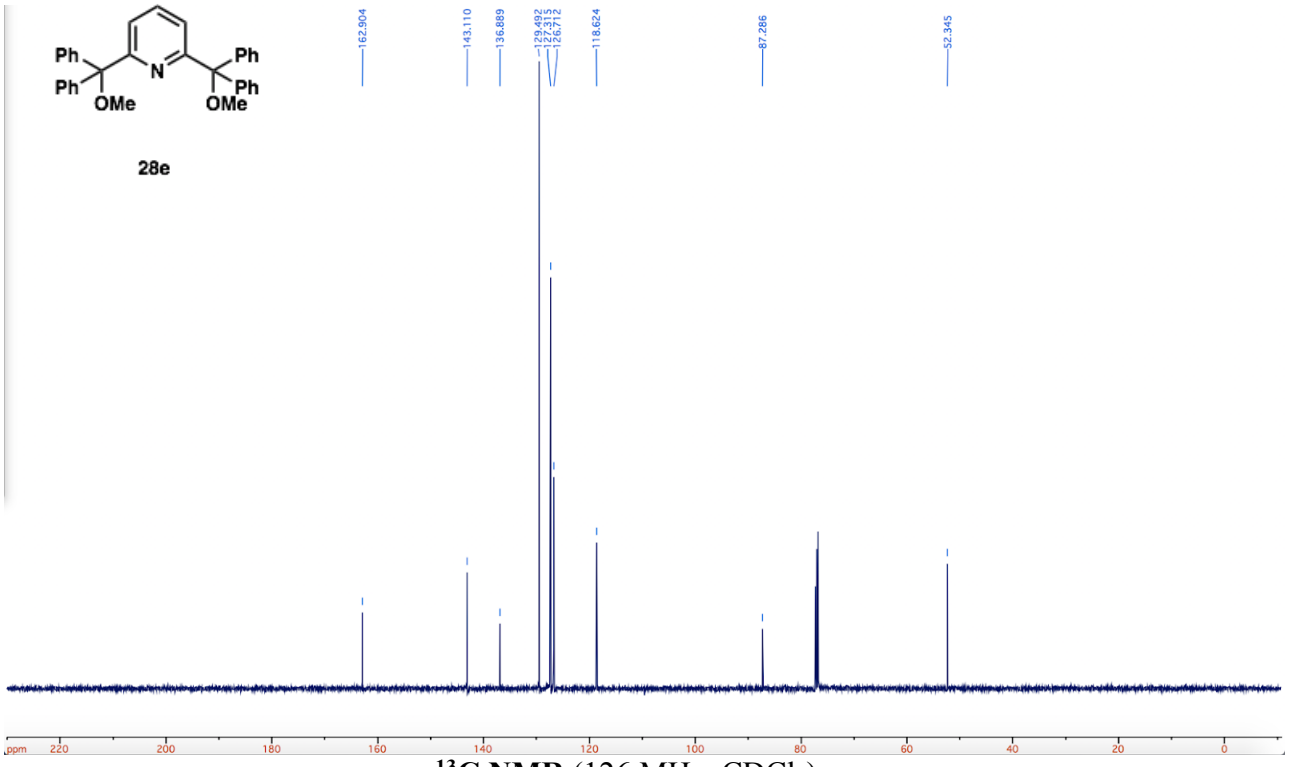
^{1}H NMR (500 MHz, $CDCl_3$)



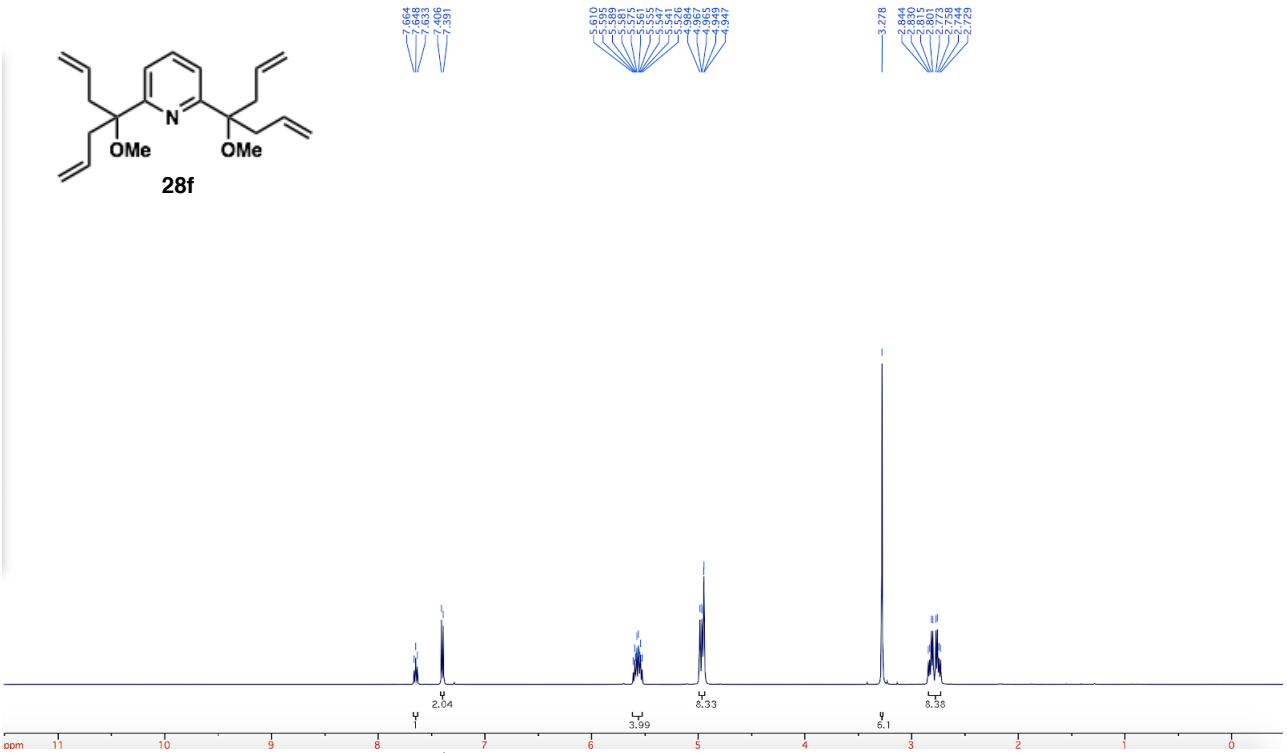
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



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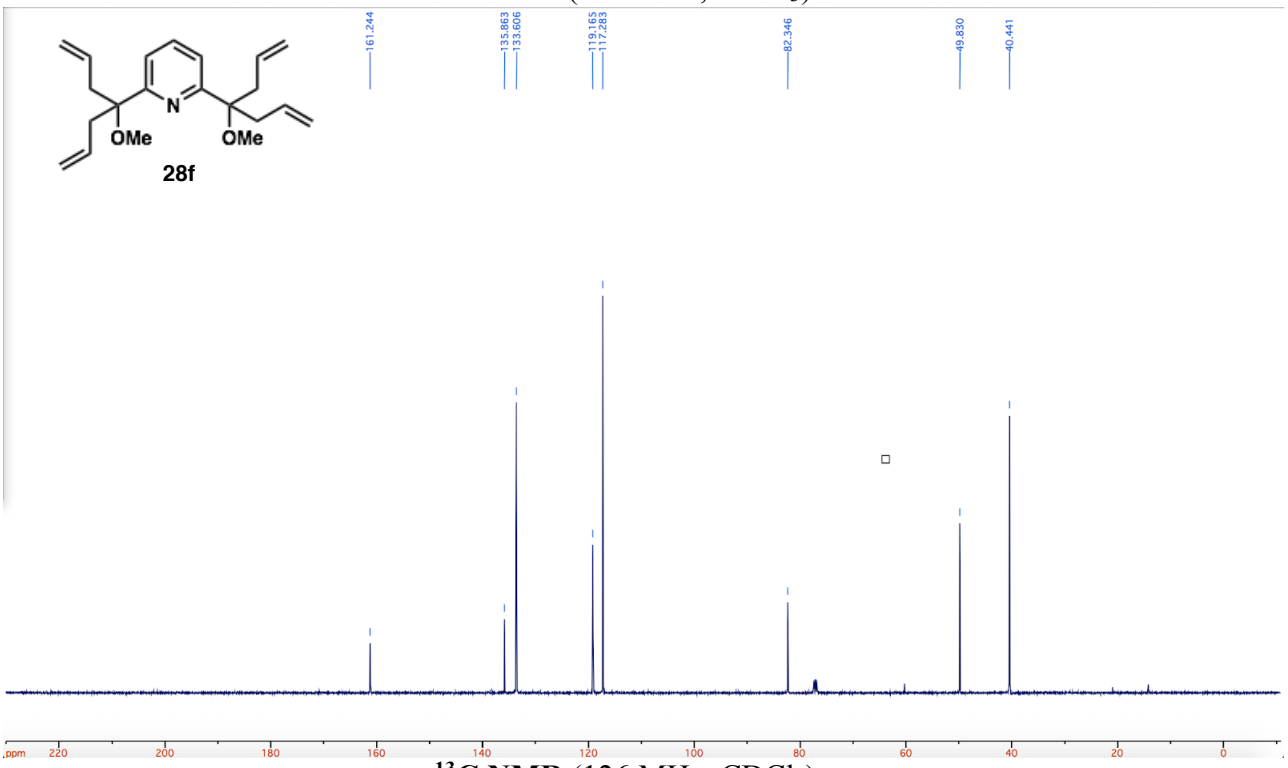

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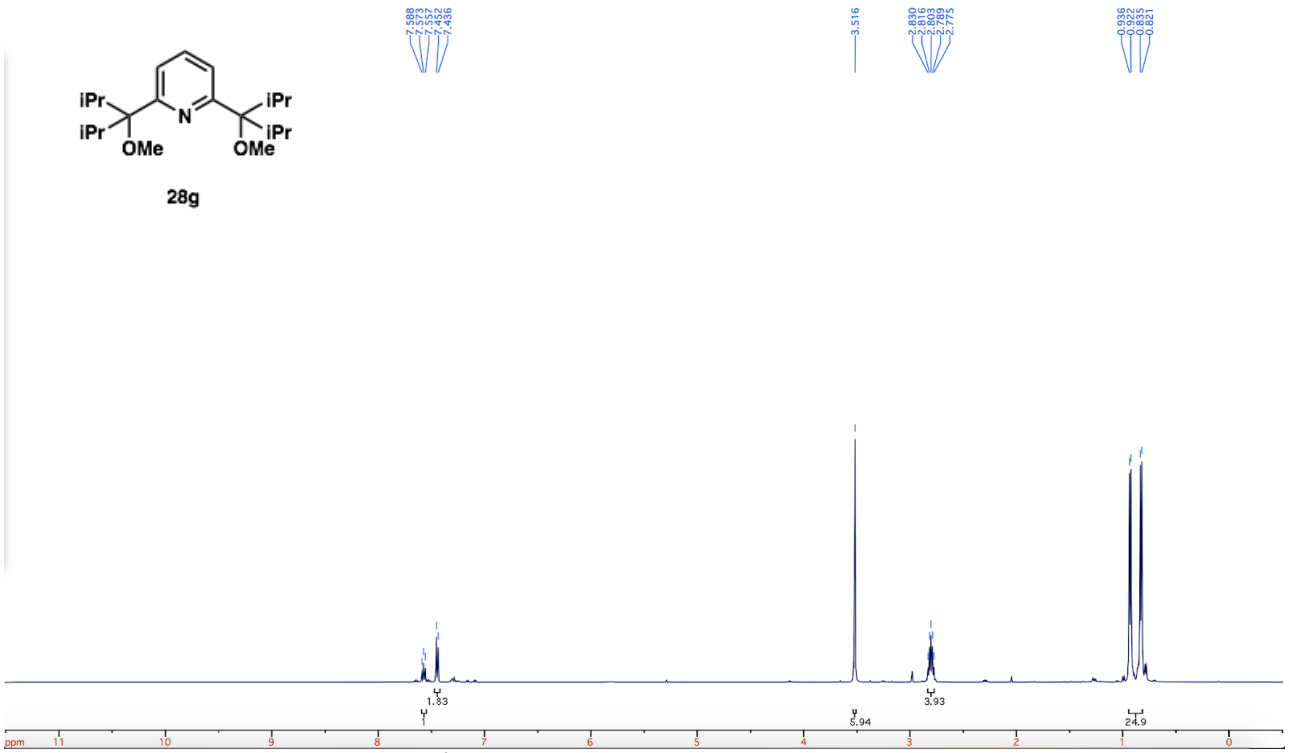
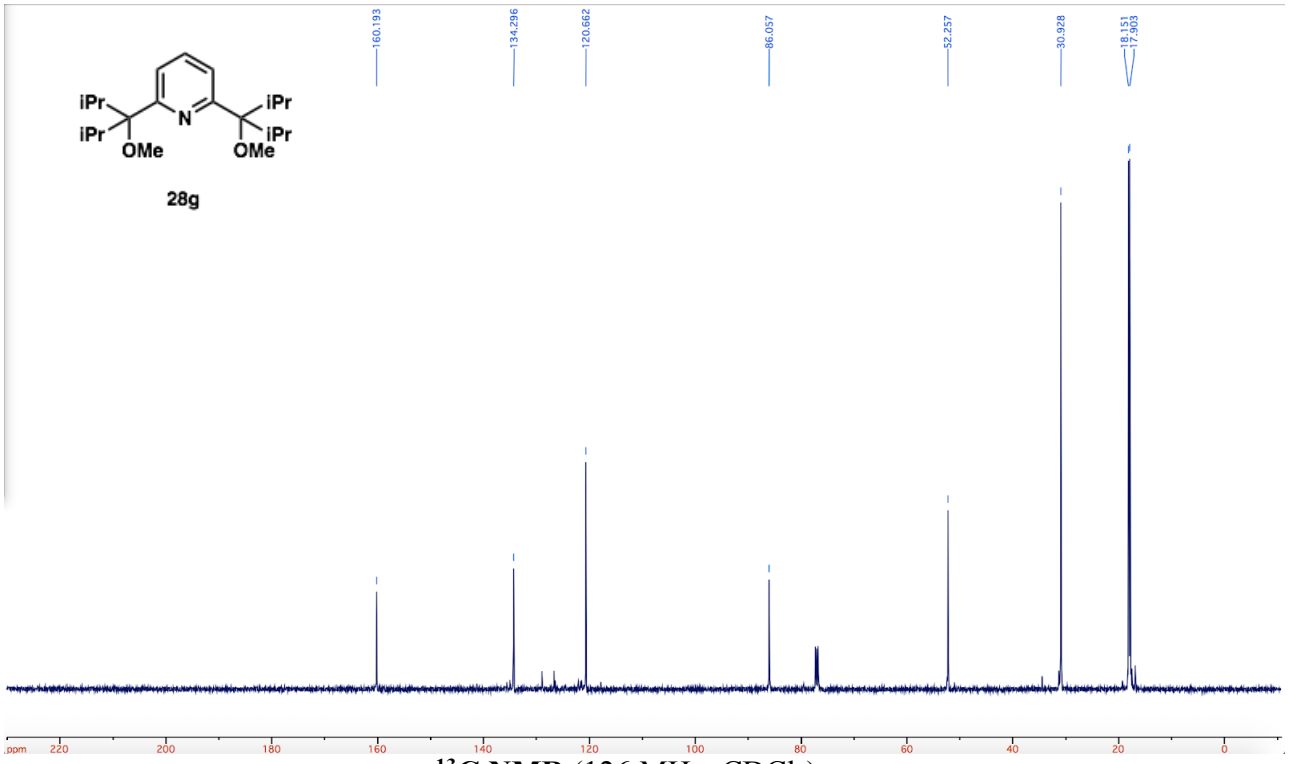


^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)

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Title: Regiodivergent Halogenation of Vinylogous Esters: One-Pot, Transition-Metal-Free Access to Differentiated Haloresorcinols

Author: Xiaohong Chen, Jenny S. Martinez, Justin T. Mohr

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jan 1, 2015

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Title:	Practical regioselective halogenation of vinylogous esters: synthesis of differentiated mono-haloresorcinols and polyhalogenated resorcinols
Author:	Xiaohong Chen,Xiaoguang Liu,Jenny S. Martinez,Justin T. Mohr
Publication:	Tetrahedron
Publisher:	Elsevier
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VITA

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Education

University of Illinois at Chicago – Chicago, IL (2012–Present)
Doctor of Philosophy in Chemistry

University of Illinois at Chicago – Chicago, IL (2008–2012)
Bachelor of Science in Chemistry

Research Experience

University of Illinois at Chicago – Chicago, IL (2012–Present)
Professor Justin T. Mohr (Research Advisor)

Graduate Research Assistant

- Developed a regiodivergent method to access halogenated resorcinol derivatives from readily available vinylogous esters using sulfonyl halides as halenium donors
- Developed an economical and efficient synthesis of 2,6-di-*t*-butylpyridine analogues
- Developed a methodology to access new sterically demanding halopyridines via the Ciamician–Dennstedt rearrangement
- Current work involves the γ–fluorination of cyclic enones and vinylogous esters

University of Illinois at Chicago – Chicago, IL (2010–2012)
Professor Duncan J. Wardrop (Research Advisor)

Undergraduate Research Assistant

- Research developing a reliable methodology to construct medium-sized rings under iodonium-mediated conditions by means of nitrenium ion intermediates

Awards

Freud Graduate Research Fellowship (2017)
Anhelo Project Dream Scholarship (2016)

University of Illinois at Chicago Graduate College Student Travel Presenter's Award (2015)
Herbert E. Paaren Summer Research Stipend (2010–2011)
Undergraduate Research Symposium Frances Seabright Award, the Aurum Iodide Chapter of
Iota Sigma Pi, the National Honor Society for Women in Chemistry (2010)
University of Illinois at Chicago Honors College Tuition Waiver (2010)
LINC TELACU Education Foundation Scholarship (2009)
HACEMOS: The Hispanic Employee Association of AT&T Scholarship (2008)
Camilla Heather Burke Memorial Scholarship (2008)

Work Experience

University of Illinois at Chicago – Chicago, IL (2012–Present)
Teaching Assistant for General, Organic, and Inorganic Chemistry

University of Illinois at Chicago – Chicago, IL (2013–2016)
Selected by department as instructor for Summer Enrichment Chemistry Workshop

Presentations

Cu-catalyzed γ-Alkylation of Enones and γ-Hydroxylation of Vinylogous Esters

Florida Heterocyclic and Synthetic Conference (2018)
University of Florida – Gainesville, FL

45th National Organic Symposium (2017)
University of California, Davis – Davis, CA

Access to Sterically Demanding Halopyridines via the Ciamician–Dennstedt Rearrangement

44th National Organic Symposium (2015)
University of Maryland – College Park, MD

Chicago Organic Symposium (2015)
University of Illinois at Chicago – Chicago, IL

AbbVie Scholars Symposium (2015)
AbbVie – Abbott Park, IL

Regioselective Halogenation of Vinylogous Esters: One-Step, Transition Metal-free Access to Differentiated Haloresorcinols

31st Annual H. C. Brown Lectures Poster Session (2014)
Purdue University – West Lafayette, IN

Publications

Chen, X.; Liu, X.; Martinez, J. S.; Mohr, J. T. "Practical Regioselective Halogenation of Vinylogous Esters: Synthesis of Differentiated mono-Haloresorcinols and Polyhalogenated Resorcinols" *Tetrahedron* **2016**, *72*, 3653–3665.

Chen, X.; Martinez, J. S.; Mohr, J. T. "Regiodivergent Halogenation of Vinylogous Esters: One-Step, Transition Metal-Free Access to Differentiated Haloresorcinols" *Org. Lett.* **2015**, *17*, 378–381.

Leadership Activities

Laboratory Safety Officer (2012–Present)
President of Chemistry Graduate Student Association (2012–2014)
President of Alternative Spring Break at UIC (2011–2012)

Service and Volunteer Activities

Academy Prep Center for Education – St. Petersburg, FL (2012)
Angel's Gate Animal Rehabilitation and Hospice – Delhi, NY (2011)
World Services for the Blind – Little Rock, AR (2011)
Jars of Clay – Atlanta, GA (2010)
Harvest Time International – Sanford, FL (2010)
Habitat for Humanity – Pontotoc, MS (2009)

Foreign Language Skills

Fluent in Spanish, Intermediate Italian

Cited Literature:

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