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Main Group-Catalyzed Carbon to Carbon Bond-Forming Reactions of Dicoordinate Carbocations

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Main Group-Catalyzed Carbon to Carbon Bond-Forming Reactions of Dicoordinate Carbocations

A dissertation submitted in partial satisfaction of the

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in Chemistry

by

Alex Levon Bagdasarian

2019

ABSTRACT OF THE DISSERTATION

Main Group-Catalyzed Carbon to Carbon Bond-Forming

Reactions of Dicoordinate Carbocations

by

Alex Levon Bagdasarian

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2019

Professor Hosea Martin Nelson, Chair

This dissertation focuses on the development of catalytic Carbon to Carbon (C–C) bond forming reactions of dicoordinate carbocations. The unique reactivity described herein focuses on the use of ionizable groups and appropriate counter anions to facilitate productive reactions of high-energy cationic intermediates. The first chapter discusses the exploration of phenyl carbocations, generated from aryl fluorides under silylium-weakly coordinating anion (WCA) catalysis, in the context of hydrocarbon functionalization. Chapter two describes the discovery of C–H insertion and reductive Friedel-Crafts reactions of vinyl carbocations generated from vinyl triflates and silylium-WCA salts. Chapter three describes a novel approach to generating vinyl cations using Lithium Lewis acids. Interestingly, these vinyl carbocations are formed under basic conditions, with lithium hexamethyldisilazide (LiHMDS) as the Lewis acid precursor. Chapter four describes two new catalytic manifolds using urea-based organocatalysts. In one instance, the

urea catalyst directly ionizes the vinyl triflate through a hydrogen-bonding interaction to promote intra molecular C–H insertion reactions. In another case, urea organocatalysts combined with LiHMDS, result in novel lithium-urea catalyst that promote Friedel-Crafts reactions of vinyl triflates. In summary, these studies have resulted in the development of new catalytic methods using main-group catalysis for the formation of C–C bonds.

The dissertation of Alex Levon Bagdasarian is approved.

Alexander Michael Spokoyny

Patrick G. Harran

Neil Kamal Garg

Hosea Martin Nelson, Committee Chair

University of California, Los Angeles

2019

"*Do not let schooling interfere with your education."*

–Mark Twain

To my Parents, Varouj and Sylvia, and my Sisters, Ani and Nareen.

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LIST OF ABBREVIATIONS

α	alpha
Å	angstrom
β	beta
γ	gamma
m/z	mass to charge ratio
μ	micro
π	pi
Ac	acetyl, acetate
AcOH	acetic acid
AIBN	azobisisobutyronitrile
app.	apparent
aq.	aqueous
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
Bn	benzyl
br	broad
Bu	butyl
i-Bu	isobutyl
n-Bu	butyl (linear)
t-Bu	*tert*-butyl
t-BuOH	*tert*-butyl alcohol
°C	degrees Celsius
calcd	calculated
cat.	catalytic
Cbz	carboxybenzyl
cod	1,5-cyclooctadiene
d	doublet
dba	dibenzylideneacetone
dr	diastereomeric ratio
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DIC	*N,N*′-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine

dme	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
equiv	equivalent
Et_3N	triethylamine
ESI	electrospray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared (spectroscopy)
J	coupling constant
L	liter
LDA	Lithium diisopropylamide
m	meta
m	multiplet or milli
min	minute(s)
mol	mole(s)
mp	melting point
M	molecular mass
Me	methyl
MHz	megahertz
MS	molecular sieves
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Ns	nosyl
[O]	oxidation
OTf	trifluoromethanesulfonate (triflate)
ppts	para-toluenesulfonic acid
pH	hydrogen ion concentration in aqueous solution
PMHS	polymethylhydrosiloxane

ppm	parts per million
Ph	phenyl
Pr	propyl
i-Pr	isopropyl
PSI	Pounds per square inch
q	quartet
quint.	quintet
R_f	retention factor
s	singlet
sat.	saturated
sext.	sextet
t	triplet
trig	trigonal
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
WCA	weakly coordinating anion

ACKNOWLEDGMENTS

I would like to begin by thanking the person that made all the science presented here possible, Professor Hosea Nelson. I first met Hosea during my visitation weekend at UCLA, as it turned out he had only started his career at UCLA the day before. I unknowingly met him on top of the bomb shelter with several other students and we began to converse about a series of random topics. His charisma that weekend (and still to this day) was contagious and motivating. Eventually as we all parted ways, he urged all of his to, "see his poster." It was only then that I realized he was actually a professor of Chemistry and not a prospective graduate student. Later that year, in July, I came to UCLA to set up Hosea's new lab space, beginning with scrubbing monkey bars in hoods that were caked with years of chemical research. After prepping the laboratory space we began unboxing new glassware, chemicals, instruments and other lab essentials. As the first student to join the lab I had the unique experience of setting up the foundations of a laboratory that has become (in my unbiased opinion) extremely successful. For this experience I am eternally grateful.

Hosea also shaped who I am as a scientist today. He always stresses the importance of using "hypothesis-driven inquiry" to make novel discoveries and address scientific problems that are fundamentally intriguing. More often than not, these discoveries happen serendipitously. This motto has tremendously shaped my scientific thought process. For a large portion of my early graduate career Hosea worked in the hood next to me, he gave "hands-on training" a new meaning. He could do a chemical operation in his hood (without looking) while correcting me on my poor laboratory technique. I received a tremendous amount of mentorship and guidance while we shared a bay and that experience is irreplaceable. Along the way, he instilled four basic research rules to abide by for success, that have equally influenced me: 1) rely on yourself more

than others (or a rendition thereof), 2) bet on yourself, 3) the best experiment is the one you can do now, 4) don't let emotion influence a decision (or a rendition thereof). These have taught me to exhibit my own due diligence with science, have confidence in my abilities, run experiments frequently, and let data drive research. I believe these guidelines, along with many things I learned along the way, are responsible for my graduate career success.

Along with scientific support, Hosea was also a huge supporter of me regarding personal development, growth, and well-being. I remember during my first year it was approaching Thanksgiving time and I was not sure if graduate students typically took time off for the holidays (especially the first class of students in an assistant professor's lab!). When he asked me what I was doing for the holiday, I told him I was staying in lab. He laughed. The next thing I knew he was dropping me off at my family's home in Cupertino while he was heading to Frisco. He did this multiple times during my graduate school and I am forever grateful that he not only encouraged me to visit my family frequently, but he even drove me there! Hosea—you really have no idea how thankful I am to you for the years of mentorship and guidance you have given me. The experience has been priceless and I have learned more in the past four years (about chemistry/science, life, and even cars) than I have in my entire life. I will always see you as not only a phenomenal mentor, but also a true friend.

I would next like to thank a series of faculty members who have made my graduate school a more complete experience. Firstly, my committee members: Profs. Alex Spokoyny, Patrick Harran, and Neil Garg. You have all been instrumental in my development as a chemist. Alex always had great scientific advice that helped me achieve many of my milestones during my graduate career. Professor Harran's Organic Synthesis II course was undoubtedly one of my favorite courses at UCLA. His ability to communicate the intricacies of organic chemistry is

something I aspire to be able to do. And last but certainly not least, Neil. Neil has always been a second mentor to me. He was always willing to take time out of his busy day to impart his wisdom. At times this advice was priceless and I am extremely thankful to have had somebody so willing to share their knowledge with me.

I would also like to thank Professor Vince Lavallo (UC Riverside) for many discussions of science, life, and gardening. I will always remember our joint camping trips as times of great fun and discussion. I would also like to thank Vince for the donation of our initial carborane cluster library that resulted in our labs first discovery, and early success. I would also like to thank Professor Ken Houk for several collaborations from his group that resulted in greater scientific insight.

My pathway towards graduate school, in particular synthetic organic chemistry, would never have come to realization without my experience at UC Davis (y'ags) and my undergraduate advisor Professor Mark Kurth. After several interviews for undergraduate research positions where I was told that as a Division I athlete I would not have enough time for research, I met Mark. In preparation for our meeting, I had come up with numerous reasons as to why he should take me and how athletics would not interfere with research. I walked into his office, he introduced himself and immediately told me the project I would start on, who would be my mentor, and proceeded to take me to the lab space. To my surprise, not once, did he bring up athletics, what others said was a setback. He took me under his guidance and I am forever grateful to him for his mentorship. During this time I also had the opportunity to meet Professor Makhluf Hadadin (American University of Beirut), who was very inspirational in my development as a chemist. I must also thank my graduate student mentor, Dr. Huy Nguyen, as

well as the other graduate students that motivated me to pursue a career in chemistry, Dr. Keith Coffman, Dr. Kelli Gottlieb, and Dr. Teresa Palazzo.

I also must acknowledge the people who helped in much of the "grunt" work that went into this thesis, the graduate students in the Nelson lab. My graduate school success is inextricably linked to my amazing lab mates who are second to none; I challenge anyone to find better colleagues. I will wait.

I would first like to thank Brian Shao, a fellow graduating lab mate. Brian was there with me from day one and stuck it with me through the end. When I say day one, this includes my undergraduate career at UC Davis. While Brian and I were the same major, took all the same classes, knew mutual friends, we never met each other until UCLA. I first met Brian the summer before our first year and we have been sharing memories ever since. Brian is a phenomenal scientist and an even better friend. Only he understands what it "used to be like" in the early days of the Nelson lab. I thank him for his resilience throughout graduate school as it helped fuel mine. I could always go to you when I had science, slide-formatting, writing, and other related questions; thank you for making yourself available to me, it will never be forgotten. Y'ags.

I must also thank Sydnee (Syd) Green. Although we never worked on any projects together, she undoubtedly brought a new flavor to the Nelson lab that made my (and others) experience infinitely better. I first "met" Syd at UC Davis during my senior year where we knowingly and unknowingly had several classes together. I was very surprised when I saw her at UCLA recruitment weekend because I immediately recognized her from UC Davis, I hope I can take some credit in recruiting her to come to UCLA. Syd is an extremely talented chemist, a tenacious explorer of chemical space, and an incredible person. When I hear talk of people that can "light up a room" the first person I think of is Syd. Thank you for always listening to me,

expressing your opinion freely, and supporting me unconditionally throughout my graduate school experience. Your loyalty and selflessness resulted in all of my best memories from my time at UCLA. I will never forget that and I am eternally grateful. Y'ags.

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I would like to thank Jessica Burch, who came in as a first year and absolutely killed it with her discoveries in terpene cyclization reactions. Jessica came in and turned "spectroscopic nightmares" into useful methods for making natural products, not an easy feat by any means!

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to explain things in a way that I could understand, for this I am very grateful. I always enjoyed our times at Shamishiri drinking doogh, Persian snapping, and solving escape rooms. Sepand Jan, thank you for being an amazing colleague, but more importantly, an amazing friend.

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I would like to thank the post-doctoral scholars who had a tremendous influence on my bench technique. First I need to thank Dr. Jonny Gordon, who began the lab with Hosea, Brian and me. Jonny was always on-deck for any questions I had and was always willing to show me new techniques in organic synthesis that I have adopted to this day. I also must thank Dr. Matt Asay, our resident inorganic chemist. Matt expanded my horizons greatly upon his arrival showing me the benefits of liquid nitrogen, schlenk flasks, and various inorganic techniques. Thank you Jonny and Matt for giving me hands-on training to improve upon my bench skills.

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parents, Varouj and Sylvia, thank you for teaching me the importance of sacrifice, hard work, and determination. You both have been role models for me. I can not help but to think that I am involved in the sciences because of your careers as engineers. I am incredibly proud to call you my parents and you have made very large shoes for me to fill in, but I will certainly do my best! To my sisters, Ani and Nareen, you guys have been awesome pillars of support for me during the past four years. Although I have missed a lot of family events due to my schooling, you guys always made me feel like I was there through play-by-plays or FaceTime. You guys kept me going and made sure that I understood the importance of work-life balance, especially when things would get carried away. I love you all so much, this is for you.

BIOGRAPHICAL SKETCH

Education:

University of California, Los Angeles, CA

• Ph.D. in Organic Chemistry, anticipated Fall 2019, Advisor: Hosea M. Nelson

University of California, Davis, CA

• B.S. in Pharmaceutical Chemistry, 2015

Professional and Academic Experience:

Graduate Research Assistant: University of California, Los Angeles, CA

• July 2015 – present; Advisor: Prof. Hosea M. Nelson

• Discovered novel C–C bond forming reactions by means of reactive phenyl and vinyl carbocations under various modes of catalysis.

Undergraduate Research Assistant: University of California, Davis, CA

• March 2013 – July 2015; Advisor: Prof. Mark J. Kurth

• SAR studies for Cystic Fibrosis and developing novel heterocyclic methodologies.

Honors and Awards:

• Christopher S. Foote Fellowship, UCLA, (2018–2019)

• Ernest F. Hare, Jr. Memorial Scholarship, UCLA, (2019)

• Dissertation Year Fellowship, UCLA, (2019)

• Association of College Water Polo Coaches Academic Award, UCD, (2013–2015)

• Western Water Polo Association All-Academic Award, UCD, (2013–2015)

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Brian Shao, Tyler R. Benton, Chloé G. Williams, Steven P. Fisher, Vincent Lavallo, K. N. Houk, Hosea M. Nelson. *J. Am. Chem. Soc.* **2019**, *141*, 9140–9144.

2. **Teaching an old carbocation new tricks: intermolecular C–H insertion reactions of vinyl cations.** Stasik Popov, Brian Shao, Alex L. Bagdasarian, Tyler R. Benton, Luyi Zou, Zhongyue Yang, K. N. Houk, Hosea M. Nelson. *Science* **2018**, *361*, 381–387.
3. **Arylation of hydrocarbons enabled by organosilicon reagents and weakly coordinating anions.** Brian Shao,[†] Alex L. Bagdasarian,[†] Stasik Popov, Hosea M. Nelson. *Science* **2017**, *355*, 1403–1407.
4. **One-pot synthesis of benzo[4,5]imidazo[2,1-a]isoquinolines and isoquinolino[3,4-b]quinoxalines via tandem cyclization strategies.** Alex L. Bagdasarian, Huy H. Nguyen, Teresa A. Palazzo, James C. Fettinger, Makhluf J. Haddadin, Mark J. Kurth. *J. Org. Chem.* **2016**, *81*, 3924–3928.
5. **Heterocycle-to-heterocycle route to quinoline-4-amines: reductive heterocyclization of 3-(2-nitrophenyl)isoxazoles.** Keith C. Coffman, Vy Duong, Alex L. Bagdasarian, James C. Fettinger, Makhluf J. Haddadin, Mark J. Kurth. *Eur. J. Org. Chem.* **2014**, *34*, 7651–7657.
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CHAPTER ONE

Strategies for Catalytic Carbon–Carbon Bond-Forming Reactions of Dicoordinate Carbocations

1.1 Abstract

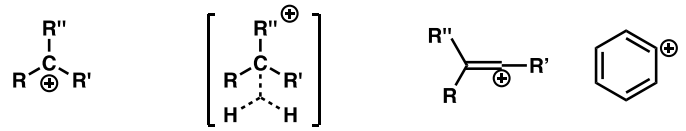
Carbocations have long been heralded as reactive intermediates of great synthetic importance. From their significance in biological processes to their implementation and exploitation in synthetic organic chemistry, the unique reactivity of these fleeting species has allowed for the development of previously inaccessible synthetic methods. Dicoordinate carbenium ions, a subclass of carbocations, have been highly underutilized largely due to their inherent instability. The focus of this chapter is to summarize the use of catalytic methods for C–C bond-forming reactions of dicoordinate carbocations. The works described herein provide preliminary data and precedent for the studies reported in later chapters.

1.2 Introduction

Carbocations have a rich history embedded in physical organic chemistry and organic synthesis. [1–3] Worthy to note are the contributions of George Olah to the field of carbocation research. His use of "magic acid" ($SbF_5/HFSO_3$) solutions to stabilize these intermediates and study their reactivity properties led to his eventual reception of the Nobel Prize in 1994. It was also during this time that Olah coined the words "carbenium" (**1.1**) and "carbonium" (**1.2**) ions (Fig. 1.1).[4] The major distinction between these two classes is that "carbonium" ions display hypervalent (three center two electron) nonclassical bonding while "carbenium" ions are

traditionally tricoordinate, electron-deficient carbon centers. In conjunction with this nomenclature, another class of carbocations dubbed "dicoordinate carbocations" (**1.3**) consists of an electron deficient carbon center that is disubstituted. Examples include vinyl and phenyl carbocations. Although tri- and dicoordinate carbocations are under the same branch as "carbenium" ions, they possess markedly different reactivity profiles.

Figure 1.1. Relevant classes of carbocations



1.1 *carbenium* ***1.2*** *carbonium* ***1.3*** *dicoordinate carbocation*

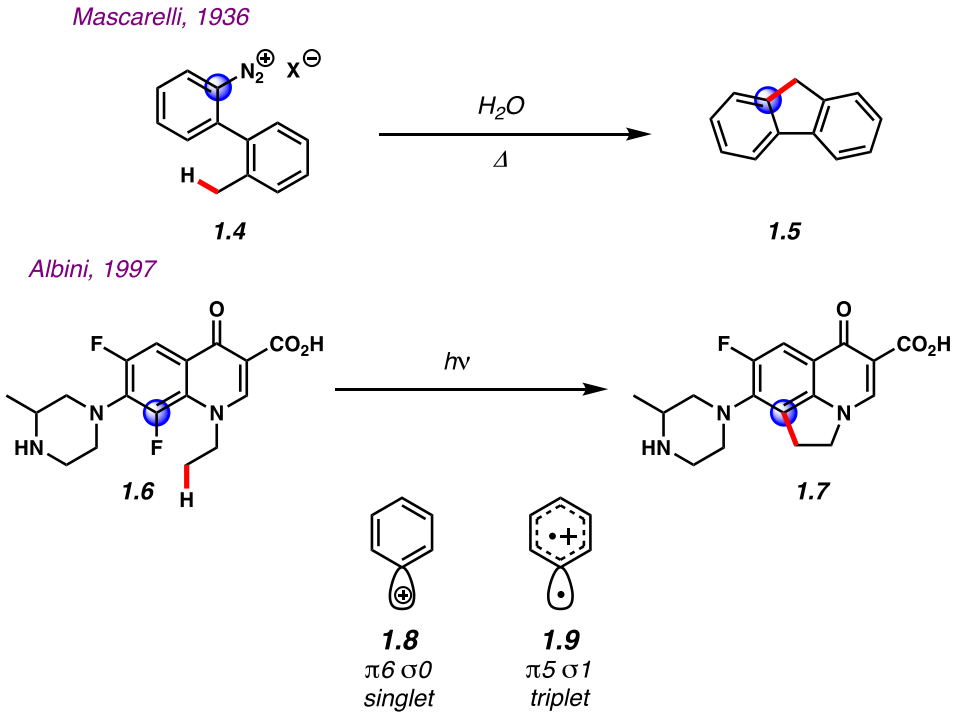
Tricoordinate carbocations are more frequently employed in organic chemistry compared to their dicoordinate counterparts. From a practical perspective, commercial cationic reagents such as trityl (Ph_3C^+) salts are readily available. From a design perspective, they aid in retrosynthetic analysis as synthons used in designing synthetic routes.[5] On the other hand, dicoordinate cations are much less encountered as synthons or intermediates in organic synthesis.[6] In vinyl and phenyl cations, the charge is more concentrated to a single electrophilic carbon site that lacks stabilizing substituents. Comparatively, trityl cations are more stable than a dicoordinate carbocations due to the extended π system that allows for a delocalized cationic charge. Other obstacles thwarting further applications of dicoordinate cations are methods to access these high-energy intermediates are limited compared to tricoordinate carbenium ions. In an effort to address these limitations, several key advancements have been made on the subject of dicoordinate cations, from their generation to developing catalytic examples of their reactivity in forging new C–C bonds.

1.3 Phenyl Carbocations

While related in their dicoordinate nature, phenyl carbocations have been highly elusive intermediates compared to their vinyl carbocation counterpart. One limitation to accessing these high-energy intermediates is, not surprisingly, the barrier for ionization.[7] In most cases, vinyl carbocations that have neighboring sp^3-hybridized carbons are readily able to adopt linear sp-geometry to help stabilize the cationic charge in an isolated p-orbital.[8] In contrast, phenyl carbocations are restricted in their endohedral geometry, inherently limiting their propensity for ionization. This typically limits the modes of ionization to use of relatively harsh conditions.

In a seminal report from Mascarelli in 1936, biaryldiazonium salt **1.4**, under thermolytic conditions, could be converted to fluorene (**1.5**, Fig. 1.2).[9] While the underlying mechanism of this reaction was not fully understood at the time, several decades of investigations concluded that functionalization of the methyl group was attributed to a C–H insertion event from a transient phenyl cation.[10] Building off of these results, Albini studied the reactivity of phenyl cations formed *via* photochemical irradiation (**1.6** → **1.7**).[11] An advantage of this strategy is the use of a halide leaving group as well as the ability to harness both singlet and triplet phenyl cations. Upon initial excitation, the singlet phenyl cation is generated and can subsequently undergo either C–X cleavage to form a π^6-σ^0 cation (**1.8**) or an intersystem crossing to form the triplet cation (π^5-σ^1) (**1.9**). These singlet and triplet cations have analogous reactivity profiles to singlet and triplet carbenes.[12] Key to this reactivity is the electronic structure of the cation with either orthogonal occupied and unoccupied orbitals or singly occupied orthogonal orbitals. Although providing impressive insight to the nature of these cationic intermediates, these methods were seldom applied in organic synthesis.

Figure 1.2. Phenyl carbocations

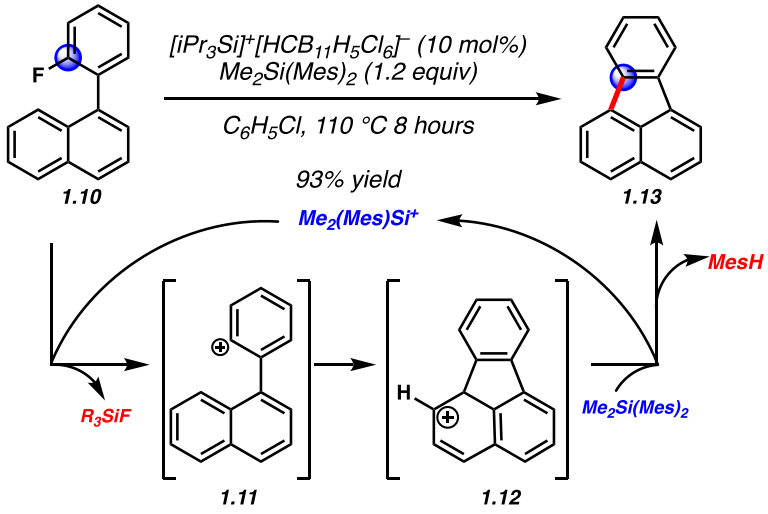


1.4 Catalytic Applications of Phenyl Carbocations

While ample mechanistic studies have been conducted on phenyl carbocations, their catalytic applications in organic synthesis are sparse. The first example of catalytic reactions of phenyl carbocations was reported in 2011 by Siegel and coworkers. In this report, aryl fluorides were converted to polyaromatic products *via* an intramolecular Friedel-Crafts addition under silylium-weakly coordinating anion (WCA) catalysis (Fig. 1.3).[13] This strategy relies on the thermodynamics of Si–F bond formation and the hyper Lewis acidic silylium ion for productive C–C bond formation. Another important aspect of this system is the use of *mono*-carborane $[HCB_{11}H_5Cl_6]^-$, a non-nucleophilic and non-basic anion to impart kinetic persistence to carbocations.[14] The catalytic process begins with triisopropyl silylium abstracting fluoride of aryl substrate **1.10** to give cation **1.11**. This then undergoes an intramolecular Friedel-Crafts addition to furnish Wheland intermediate **1.12**. Rearomatization of this intermediate furnishes the desired

product (**1.13**) and the resulting acid protonates the Me_2Mes_2Si base. Here the neutralization of the generated proton is coupled to the formation of anew catalytically active silylium species through protodesilylation of the silylium base. Aromatization of the mesitylene ring results in an active silylium-WCA catalyst and an equivalent of mesitylene. While this reaction demonstrated a new mode of generating phenyl carbocations catalytically, the method was limited in the formation of intramolecular arene-arene bonds. Siegel further expanded on this methodology by demonstrating the application of aryl fluorides in C–H insertion reactions.[15] The use of biaryl fluorides with pendant alkyl chains (**1.14**) allow for productive benzylic functionalization reactions. Here, this class of substrates allows for the synthesis of fluorene (**1.5**), analogous to Mascarelli's synthesis in the 1930's.

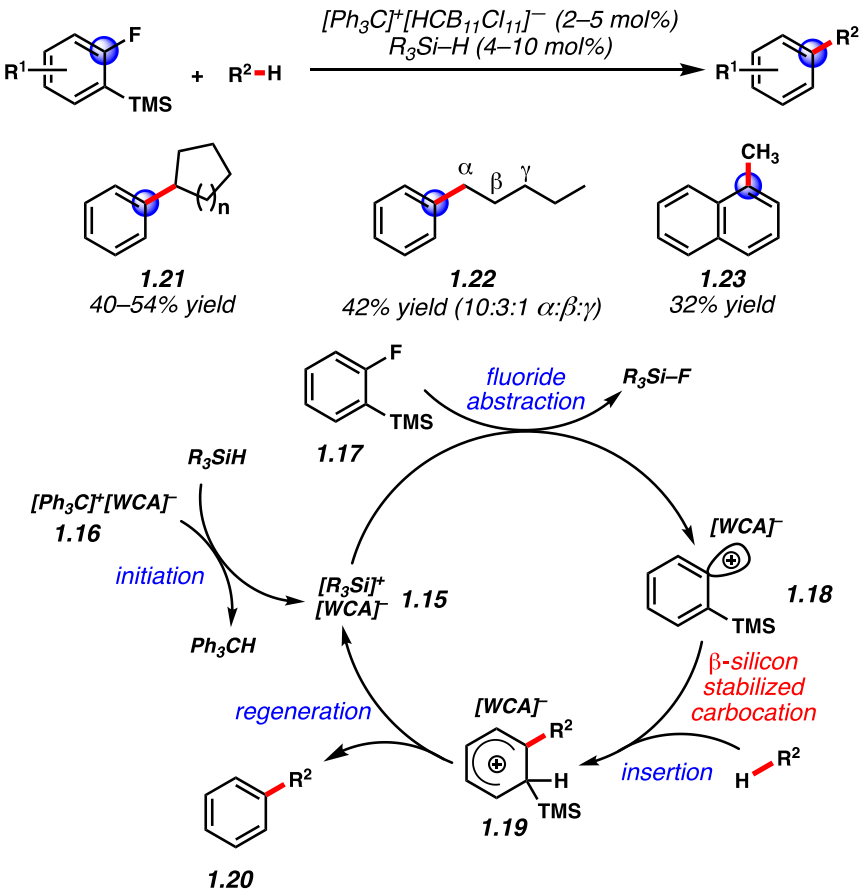
Figure 1.3. Siegel's Intramolecular Friedel-Crafts Reaction



Nelson and coworkers contributed with a breakthrough in 2017 to the field of carbocation chemistry by utilizing *o*-fluorotrimethylsilyl benzenes, under silylium catalysis, to promote intermolecular Friedel-Crafts and alkane C–H functionalization reactions (Fig. 1.4).[16] While this report does rely on the use of harsh silylium ions, the crux of this method is the incorporation of the *ortho* trimethylsilyl group that 1) lowers the barrier for ionization due to the β-silicon effect

and 2) serves to regenerate the active silylium species. This C–C bond-forming protocol offers several advances from Siegel's seminal work. Rather than isolating the reactive silylium-WCA salt, the catalyst is formed *in-situ* from the corresponding trityl-WCA precatalyst and a silane. Additionally, this transformation does not require stoichiometric bases and allows for reactions to occur under milder conditions. These improvements allow for Lewis basic functional groups such as halogens and ethers to be tolerated considering the hyper Lewis acidic nature of silylium ions. Mechanistically, this reaction proceeds with the initial formation of the active silylium-WCA catalyst **1.15** from a Bartlett-Condon-Schneider (BCS) hydride transfer of the corresponding trityl precatalyst **1.16**.[17] A fluoride (**1.17**) is then abstracted from the aryl substrate, generating the β-silicon stabilized phenyl carbocation **1.18** that reacts with a hydrocarbon to yield Wheland intermediate **1.19**. The concomitant release of product (**1.20**) and regeneration of active catalyst is achieved *via* loss of the TMS group. Cyclic hydrocarbons were also well tolerated, giving alkylated arenes (**1.21**) in 40–54% yields. Impressively, these reactive phenyl carbocations undergo intermolecular C–H insertion into linear alkanes with exquisite primary C–H bond selectivity. For example, arylated pentane isomers (**1.22**) are formed in a 10:3:1 ratio, in a combined 42% yield. Furthermore, under slightly modified conditions, methylnaphthalene (**1.23**) was synthesized from methane gas and the corresponding aryl fluoride in 32% isolated yield.

Figure 1.4. Catalytic Intermolecular C-H Insertion Reactions of Phenyl Cations

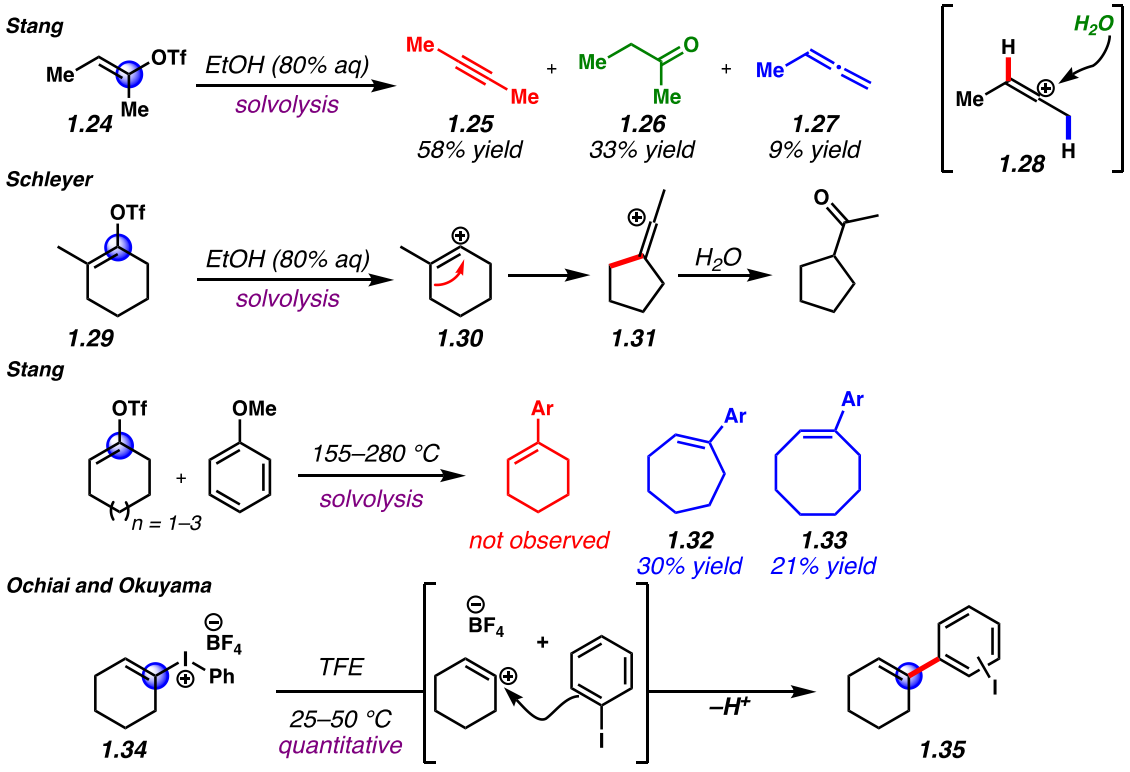


1.5 Early Studies of Dicoordinate Vinyl Cations

Vinyl carbocations, while related to phenyl carbocations in their dicoordinate nature, are more readily accessible than phenyl cations. Vinyl cations have been heavily studied from a computational and physical organic perspective for nearly a century. Since the initial proposal from Jacobs, substantial knowledge gaps have been filled during this time.[18] The reactivity of vinyl cations was validated early on by Hannack, Stang, Schleyer, and others, who elaborated on the trifluoromethanesulfonate (triflate or OTf) leaving group as a potent nucleofuge. The culmination of their studies demonstrated the intermediacy of vinyl cations through solvolytic reactions, wherein the resulting cation is either deprotonated or quenched by a solvent molecule. In Stang's seminal solvolysis example using butenyl triflate **1.24**, three major products were

observed: alkyne **1.25**, ketone **1.26**, and allene **1.27** (Fig. 1.5).[19] Each of these products are derived from a singular vinyl cation (**1.28**). The linearity of a vinyl cation (*sp*-hybridized) was further validated when substituted variants (**1.29**) were subjected to solvolytic conditions, resulting in ionization to the corresponding cyclic vinyl cation (**1.30**) and subsequent ring-contraction rearrangements to afford exocyclic linear cation **1.31**.[20] Their desire for linearity was further validated when Stang studied their solvolytic reactivity in trapping the resulting carbocation with a nucleophilic anisole. As expected, smaller cyclohexene derived triflates were unreactive while larger seven and eight-member triflates were arylated in moderate yield (**1.32** and **1.33**).[21] In efforts to make the ionization of the vinyl cation precursors more facile, Okuyama and Ochiai developed the use of vinyl iodosyl tetrafluoroborates (**1.34**) substrates that are 10^6 times more reactive than the corresponding triflate.[22] Under solvolytic conditions, ion-pair (**1.30**) is generated and the nucleofuge recombines making a mixture of Friedel-Crafts isomers (**1.31**). This development allowed for milder reaction conditions while still giving access to the high-energy cationic intermediates. In addition to designing substrates such that barriers for ionization are lowered, one can envision lowering these barriers through traditional means such as catalyst design and screening.

Figure 1.5. Early studies of dicoordinate vinyl cations

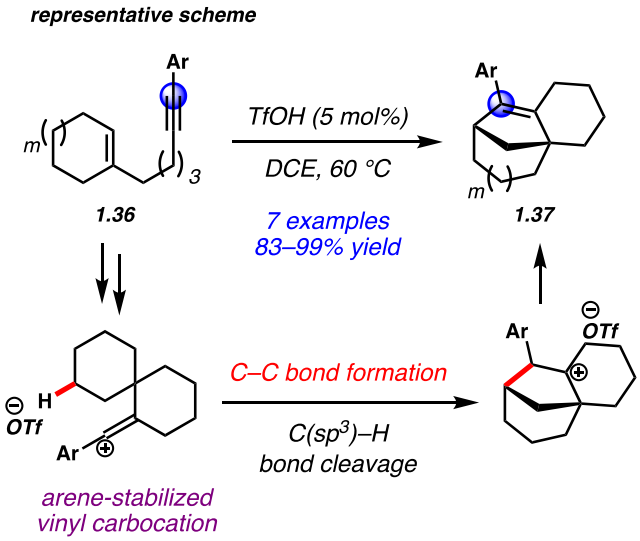


1.6 Catalytic Applications of Vinyl Carbocations

While many stoichiometric (solvolytic) reactions of vinyl carbocations exist, only recently have methods for catalytic applications come to fruition. In 2010, Yamamoto and Jin demonstrated that vinyl cations catalytically generated from their corresponding enyne (**1.36**) can undergo intramolecular C–C bond forming reaction *via* C(sp^3)–H cleavage to give tetracyclic scaffolds (**1.37**) (Fig. 1.6).[23] In these examples, however, the use of super acids triflic acid (TfOH) or triflimide (Tf_2NH) was imperative for cyclization. This is likely due to the inherent stability of the respective conjugate bases (OTf^- and NTf_2^-) that allow for the cationic intermediates to have kinetic persistence.[24, 25] More amenable acids such as TFA and *p*-TsOH resulted in no product formation. It is also worthy to note that Lewis acidic $AuClPPh_3/AgX$ (X = OTf, SbF_6, or NTf_2) combinations worked moderately well. Although limited in scope, this method offered a new catalytic use of alkynes as vinyl cation precursors for C–C bond

formation. Mechanistically, the C–H cleavage can be envisioned to occur by a C–H insertion mechanism. At the time, the only other example of a vinyl cation C–H insertion reaction had been reported by Metzger in 2006, under stoichiometric conditions.[26]

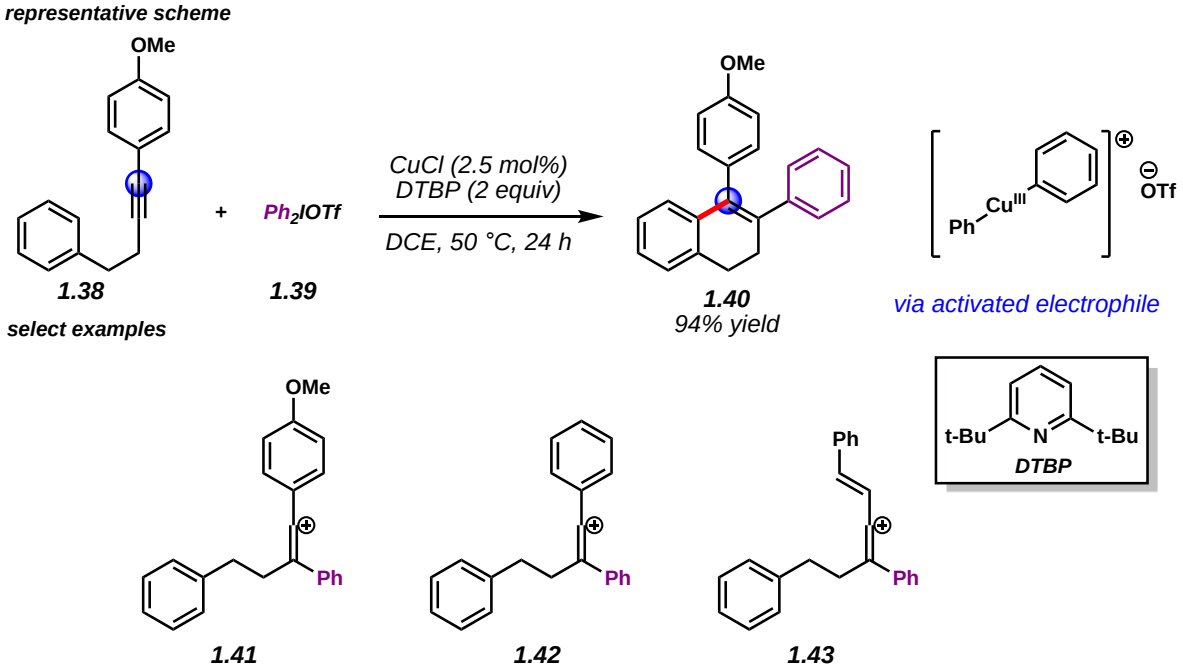
Figure 1.6. Yamamoto and Jin's acid-catalyzed cyclization



In an effort to expand on the utility of vinyl cations, Gaunt and coworkers developed copper-mediated carboarylation reaction of alkynes (**1.38**) in the presence of hypervalent iodine (**1.39**) (Fig. 1.7).[27] While hypervalent iodine reagents have traditionally been used as electrophiles, upon a formal oxidative addition by Cu(I), the electrophilicity of the aryl group is enhanced such that the alkyne participates in C–C bond formation. This generates the intermediate vinyl cation, followed by an intramolecular Friedel-Crafts addition to furnish **1.40**. This method largely relies on the use of strong electron-donor substituents on the alkyne moiety to stabilize the incipient styrenyl vinyl cation prior to intramolecular trapping. While a strongly contributing resonance structure of an oxocarbenium/ketene can be drawn when a PMP group is used (**1.41**), other substituents on the alkyne such as phenyl (**1.42**) and styrene (**1.43**) were also tolerated, although with limited scope. Nonetheless, this method provided an early example

where the generation of vinyl cations can be mediated by sub-stoichiometric amounts of a transition metal. It is also worth noting that Niggemann and coworkers developed a similar reaction in 2015 under calcium-catalysis using benzylic alcohols in place of hypervalent iodine reagents.[28]

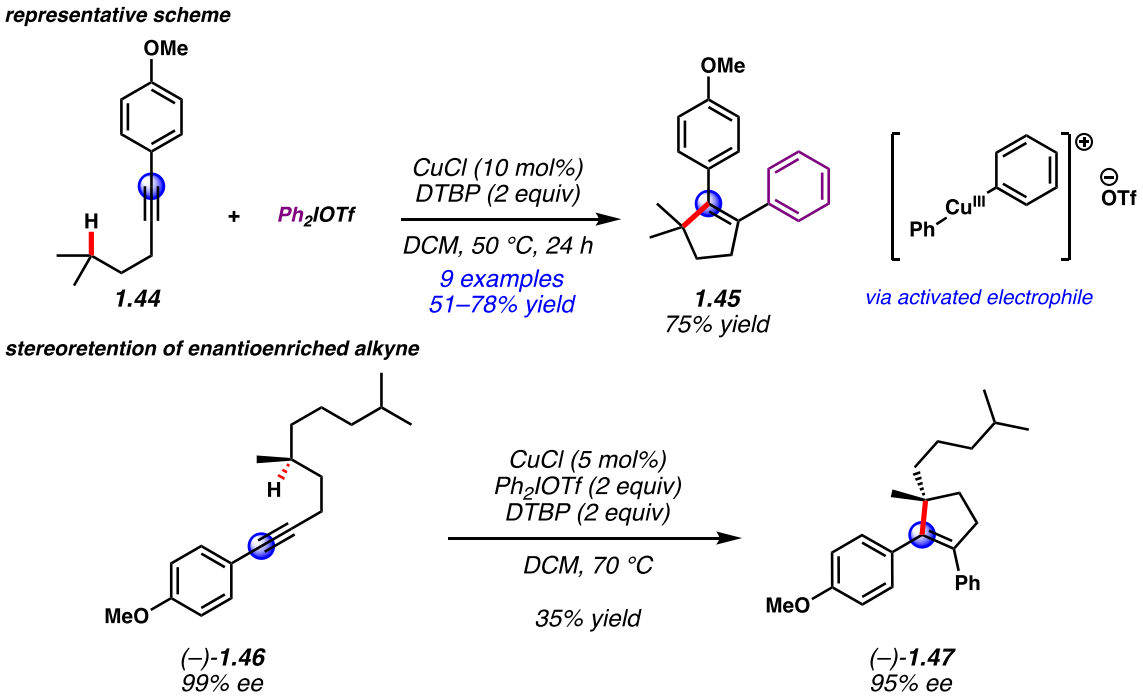
Figure 1.7. Gaunt's copper-catalyzed carboarylation



Under a similar strategy of copper catalysis and hypervalent iodine reagents, Gaunt disclosed another application of copper-catalyzed vinyl cation generation.[29] In the model substrate **1.44**, it was shown that **1.45** can be formed when the propargylic benzyl group is replaced with an alkyl chain (Fig. 1.8). Upon generation of the incipient vinyl carbocation *via* arylation of the alkyne, a new C–C bond is formed between the vinyl carbocation and an inert 2° or 3° C–H bond of the alkyl chain. The authors attribute this reactivity to a concerted 1,5-hydride shift that is reminiscent of a carbene C–H insertion pathway. In order to rule out a stepwise hydride shift followed by recombination, enantioenriched starting material **1.46** was subjected to

the reaction conditions. Although low yielding, the desired product (**1.47**) was obtained with near complete enantio-retention, suggestive of a concerted pathway.

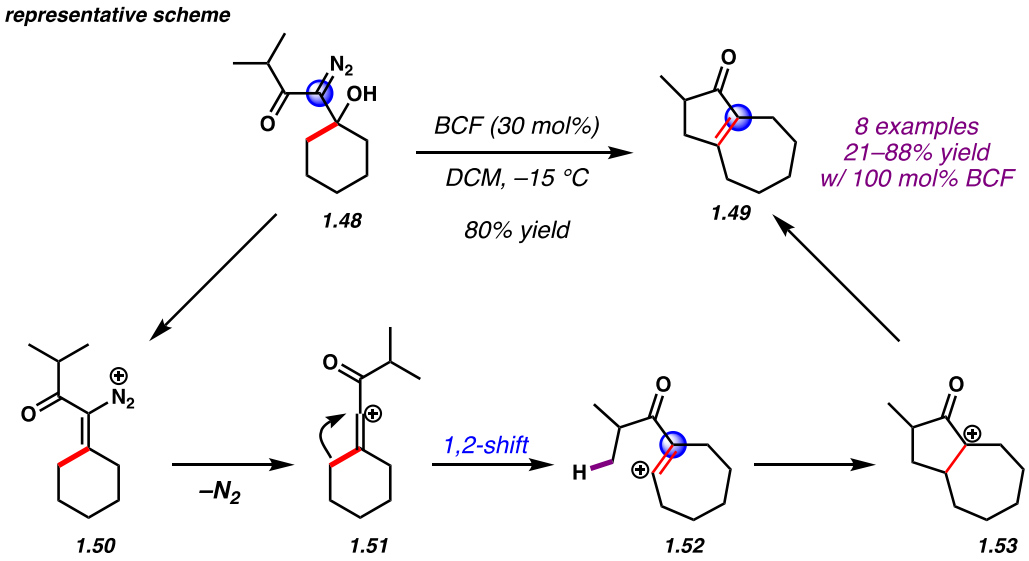
Figure 1.8. Gaunt's copper-catalyzed cyclopentene synthesis



In 2017, Brewer and coworkers showed that substoichiometric quantities of $B(C_6F_5)_3$ (BCF) could be utilized in conjunction with β-hydroxy-α-diazo ketones (**1.48**) to afford cyclopentene derivatives (**1.49**) (Fig. 1.9).[30] While the scope of this particular reaction is inherently limited, it offers a novel entry into *in-situ* generated vinyl carbocations using a main-group catalyst. Beginning with hydroxyketone **1.49**, dehydroxylation of the tertiary alcohol to give vinyl diazonium **1.50**. Subsequent extrusion of dinitrogen gives rise to vinyl cation **1.51**. The α-keto vinyl cation, due to the withdrawing nature of the ketone, undergoes a subsequent ring expansion sequence to give cyclic cycloheptenyl vinyl cation **1.52**. With pendant alkyl groups, this vinyl cation engages in a C–C bond-forming reaction through a C–H insertion pathway to give cyclopentenone **1.53**. Although catalytic applications of BCF were studied, the

reaction worked best under stoichiometric conditions as reported by Padwa.[31] Complimentary to traditional transition-metal catalyzed C–H insertions processes, the use of main-group reagents in this setting allows for the synthesis of biologically relevant cyclopentenone scaffolds.[32]

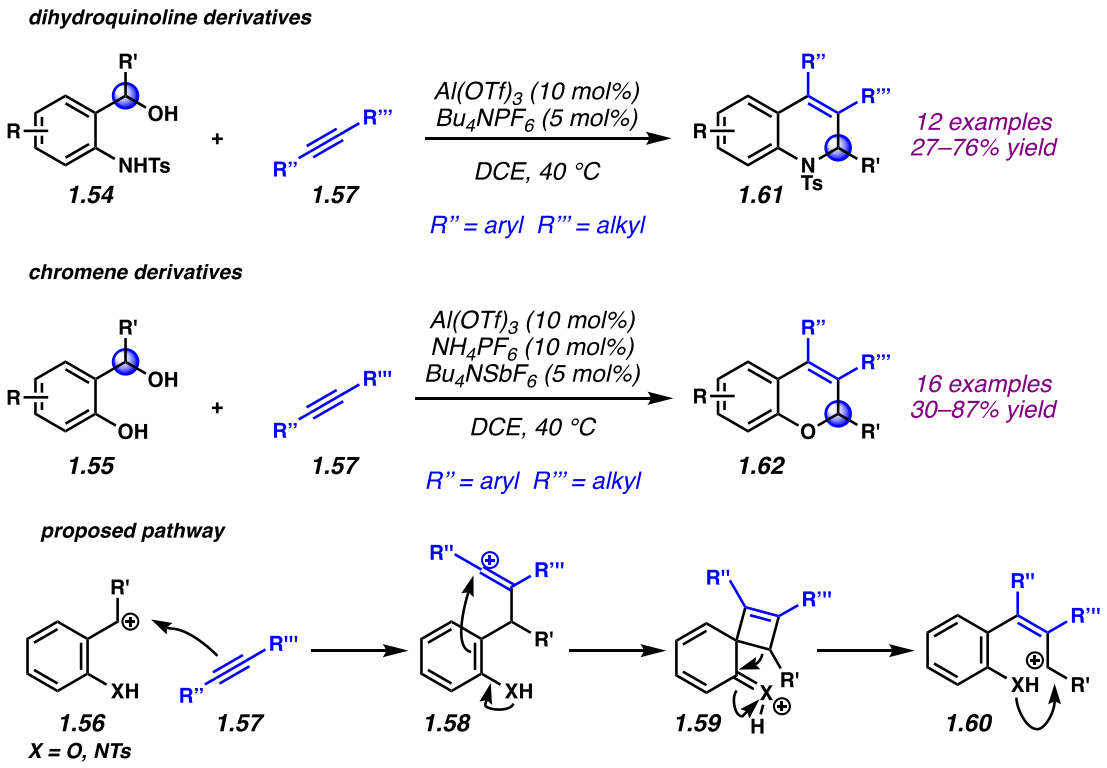
Figure 1.9. Brewer's main-group catalyzed C–H insertion of vinyl cation



Niggemann and coworkers demonstrated further applications of main-group catalysts and vinyl carbocations to make dihydroquinolines and chromene derivatives.[33] In their system, vinyl cations, generated from phenols and anilines with substituted alkynes, were shown to undergo C–C bond-formation in the presence of an aluminum-based catalyst. In this elegant example, benzylic alcohols (**1.54** or **1.55**) undergo heterolytic C–O cleavage to give benzylic carbocations (**1.56**) that are quenched by nucleophilic addition of an alkyne moiety (**1.57**) (Fig. 1.10). The *in-situ* generated vinyl cation (**1.58**) undergoes an intramolecular Friedel-Crafts addition *via* an *ipso* substitution giving spirocycle **1.59**. Interestingly, this ipso substitution allows for a unique *1,3*-aryl shift to provide a formal sp^2-sp^3 C–C insertion process and an allylic carbocation **1.60**. In the final step, the pendant nucleophile adds into the allylic position, giving rise to either dihydroquinoline or chromene products **1.61** and **1.62**, respectively. Critical to the success of this

method is the use of the weakly coordinating counter anions such as SbF_6 or PF_6, derived from the corresponding ammonium salts. Due to the nature of the reactive cationic intermediates, appropriate counter anions are an attractive approach to further elaborating these reactive species.

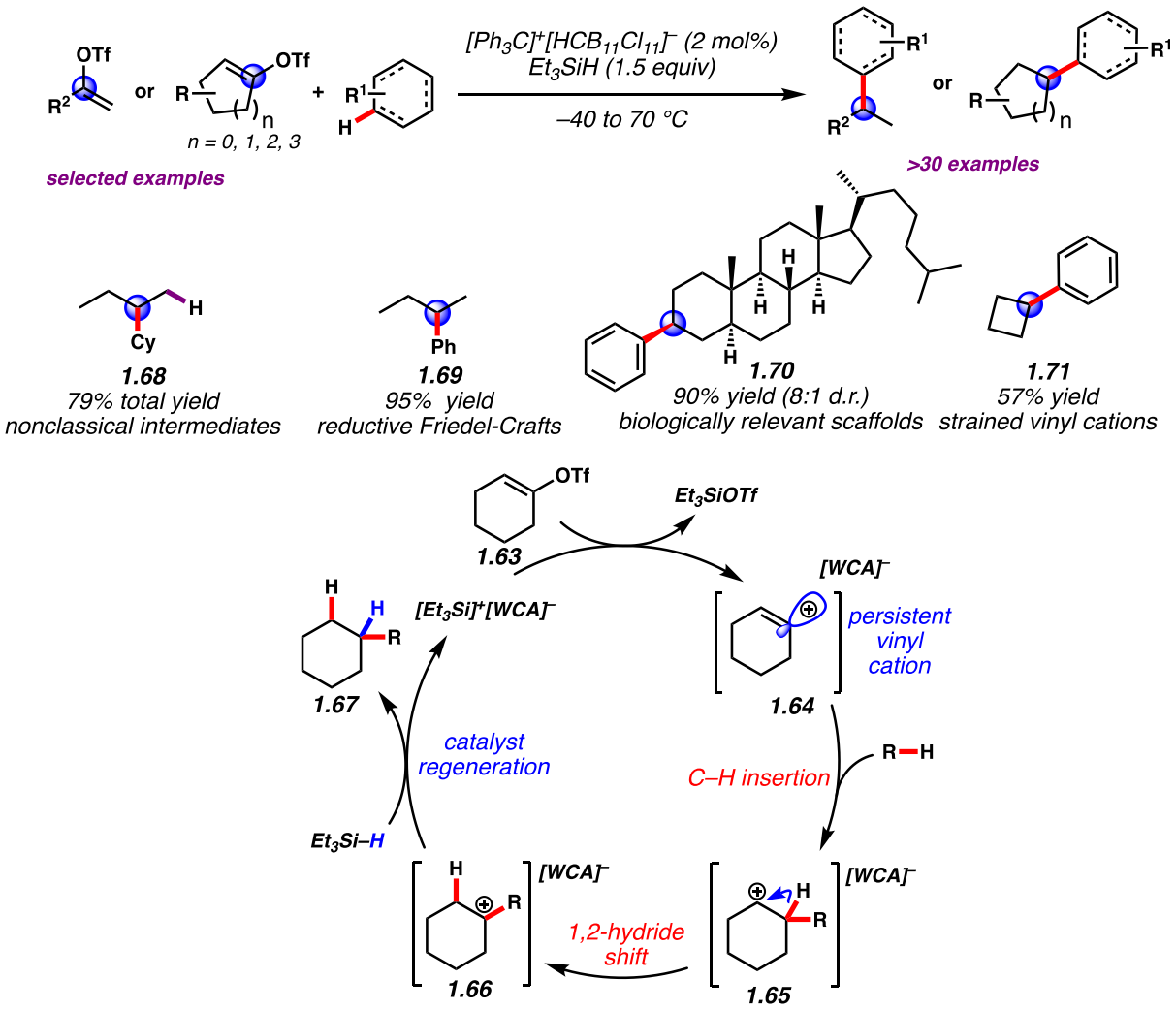
Figure 1.10. Niggeman's aluminum-catalyzed vinyl cation cyclization



In 2018, Nelson and coworkers took the concept of using weakly coordinating anions further by using *mono*-carborane anions, paired with silylium Lewis acids, to catalyze the formation of vinyl carbocations.[34] In this report vinyl triflates (**1.63**) were converted to vinyl carbocations through heterolytic cleavage by means of forming Et_3SiOTf and a kinetically persistent vinyl cation-WCA ion pair (**1.64**). The cationic species then undergoes an intermolecular C–H insertion reaction to give 2° cation **1.65** and subsequent hydride migration afforiding 3° cations **1.66**. The tertiary carbocation is then reduced to give the alkylated product

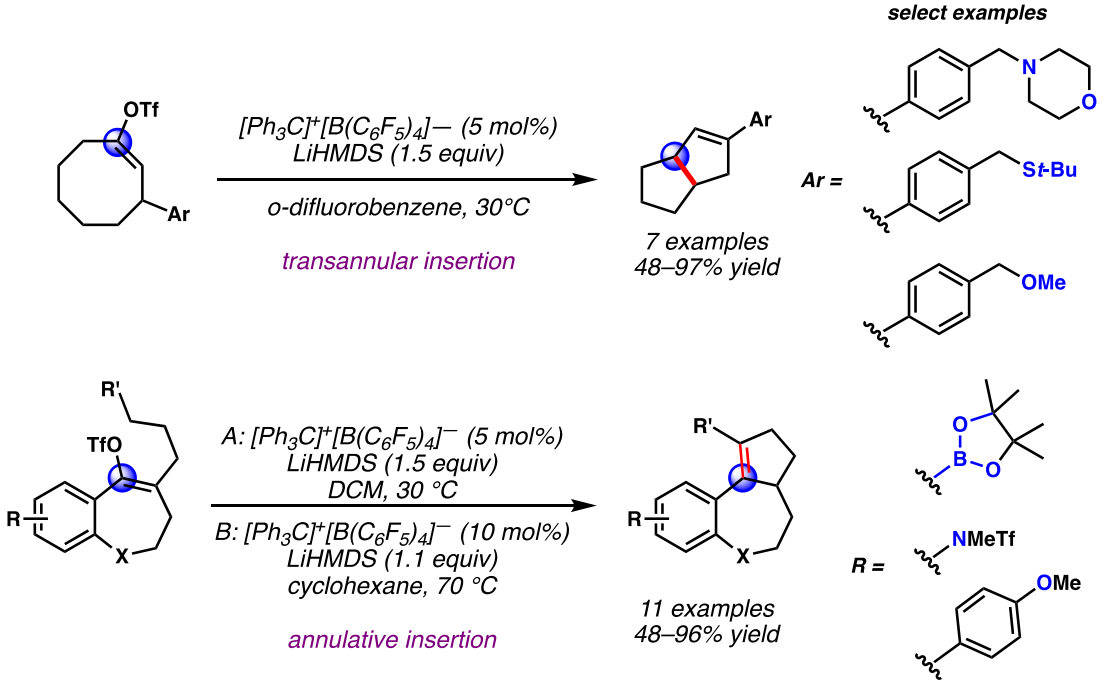
1.67 and regenerate the active catalyst. These intermediates show enhanced reactivity profiles where inert C–H bonds of hydrocarbons such as cyclohexane are readily functionalized in good to excellent yields. Interestingly the use of linear vinyl triflates highlights the unique nature of these reactive species in that both vinylic position can be functionalized due to the nonclassical nature of these intermediates (**1.68**). Complete fidelity of functionalization at the C–OTf site was attained using aromatic nucleophiles including electron rich and deficient arenes, giving arylated linear alkanes (**1.69**). This allowed for the synthesis unique products such as steroid derivatives (**1.70**) and aryl cyclobutenes (**1.71**).

Figure 1.11. Catalytic Intermolecular C–H Insertion and Reductive Friedel-Crafts Reactions of VInyl Cations



Shortly following this report, Nelson and coworkers disclosed another advancement where lithium Lewis acids, derived from LiHMDS, paired with weakly coordinating anions allowed for productive ionization of vinyl triflates that underwent intramolecular C–H insertion reactions.[35] 3-Arylcyclooctene triflates (**1.72**) were readily converted to bicyclic cores (**1.73**) and alkylated benzosuberone derivatives (**1.74**) undergo insertion into 1° C–H bonds to give tricyclic products (**1.75**) in good to excellent yield (Fig. 1.12). In using a milder Lewis acid, the functional group tolerance was greatly improved allowing for functional groups such as methyl ethers, morpholines, and other heteroatoms to be present. Analogous to the previously disclosed silylium methodology, in this case, the catalyst is now regenerated *via* a terminal deprotonation as opposed to hydride delivery. While many strategies to generate vinyl cations previously, including several examples shown here, rely on Brønsted acidic conditions, this represents the first example of generating these intermediates under basic conditions. Additionally, commercially available $[Ph_3C]^+[B(C_6F_5)_4]^-$ proved to be a superior catalyst to the exotic *mono*-carborane weakly coordinating anion.

Figure 1.12. Li-Catalyzed C–H Insertion of Vinyl Cations Under Basic Conditions



1.7 Conclusion and Outlook

In summary, reactive dicoordinate cations have displayed remarkable reactivity profiles, despite being only recently employed in catalytic reactions. Unlike their tricoordinate relatives, there are limited methods for generating high-energy dicoordinate species, thus hindering their application in synthesis. While several advancements have been made, specifically in the use of milder Lewis acids, catalyst design will continue to be an area of great focus in order to develop chemistry better suited for the broader community. Future research directions should also address broader functional group tolerance such as heterocyclic substrates as well as asymmetric variants where applicable.

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CHAPTER TWO

Arylation of Hydrocarbons Enabled by Organosilicon Reagents and Weakly Coordinating Anions

Adapted from: Brian Shao[†], Alex L. Bagdasarian[†], Stasik Popov, and Hosea M. Nelson

Science **2017**, *355*, 1403–1407.

2.1 Abstract

Over the past 80 years, phenyl cation intermediates have been implicated in a variety of C–H arylation reactions. Although these examples have inspired several theoretical and mechanistic studies, aryl cation equivalents have received limited attention in organic methodology. Their high-energy and promiscuous reactivity profiles have hampered applications in selective, intermolecular processes. Herein, we report a reaction design that overcomes these challenges. Specifically, we find that β-silicon-stabilized aryl cation equivalents, generated *via* silylium-mediated fluoride activation, undergo insertion into sp^3 and sp^2 C–H bonds. This reaction manifold provides a framework for the catalytic arylation of hydrocarbons, including simple alkanes such as methane. This process uses low loadings of earth-abundant catalysts (1 to 5 mol%) and occurs under mild conditions (30 to 100 °C).

2.2 Introduction

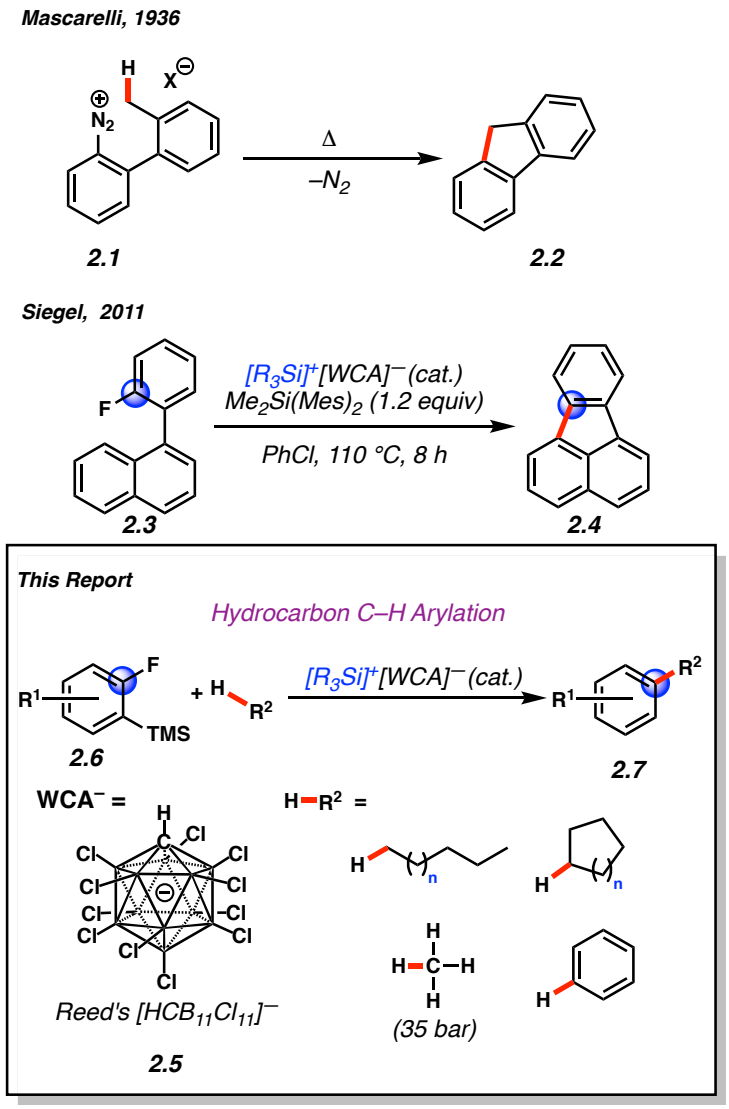
In 1891, Merling unknowingly sparked the field of synthetic carbocation chemistry with his synthesis of an aromatic tropylium ion.[1] Since then carbocations have been fundamental in

the field of organic chemistry as a field of scientific and practical endeavor.[2] Conceptually, carbenium ions serve as synthons, guiding the design of retrosynthetic analyses and elucidating the selection of synthetic equivalents.[3] Practically, they are equally important, as stabilized carbocations are routinely generated and employed in standard synthetic transformations.[4] On the other hand, carbocations that are divalent, and/or not stabilized by resonance donating groups or hyperconjugation, are not easily manipulated or employed in routine transformations.[5] Although exquisite fundamental studies of these more reactive species have revealed remarkable reactivity profiles[6], studies aimed at methodological advances in this area are rare.[7, 8] This is particularly true for phenyl cations. Their reactive nature has not only thwarted characterization in the condensed phase, but their mere existence as reactive intermediates remains challenged by some.[9–11]

Despite their controversial nature, we sought to discover a phenyl cation equivalent that could be used in catalytic, intermolecular C–H arylation reactions. We were inspired by seminal reports of analogous reactivity over the last 80 years. In the 1930s, Mascarelli reported that the thermolysis of aryl diazonium salt **2.1** led to the formation of fluorene (**2.2**), presumably *via* C–H insertion of a phenyl cation intermediate (Fig. 1).[12] Furthermore, reports from Albini's group suggest that photo-generated phenyl cations participate in intramolecular C–H insertion reactions.[13, 14] Siegel and coworkers recently proposed the intermediacy of phenyl cations in the silylium-mediated, intramolecular Friedel–Crafts reaction of aryl fluorides (**2.3**) to form poly aromatic hydrocarbons (**2.4**).[15, 16] Finally, Reed has presented evidence for incipient aryl cations, where the structure of a phenyl halonium salt of *undeca*chlorinated monocarba-*closo*-dodecaborate anion (**2.5**) was elucidated by X-ray crystallography.[17] Despite these fundamental breakthroughs, catalytic, intermolecular reactions of phenyl cation equivalents have been elusive.

Considering these seminal efforts, as well as the frontier molecular orbital analogy that can be made with singlet carbene species[18, 19], we pursued application of phenyl cation equivalents in catalytic, intermolecular C–H functionalization reactions. We report the successful execution of using trimethylsilylarylfluorides (**2.6**) to forge C–C bonds with sp^2 and sp^3 C–H bonds to give alkylated arenes (**2.7**).

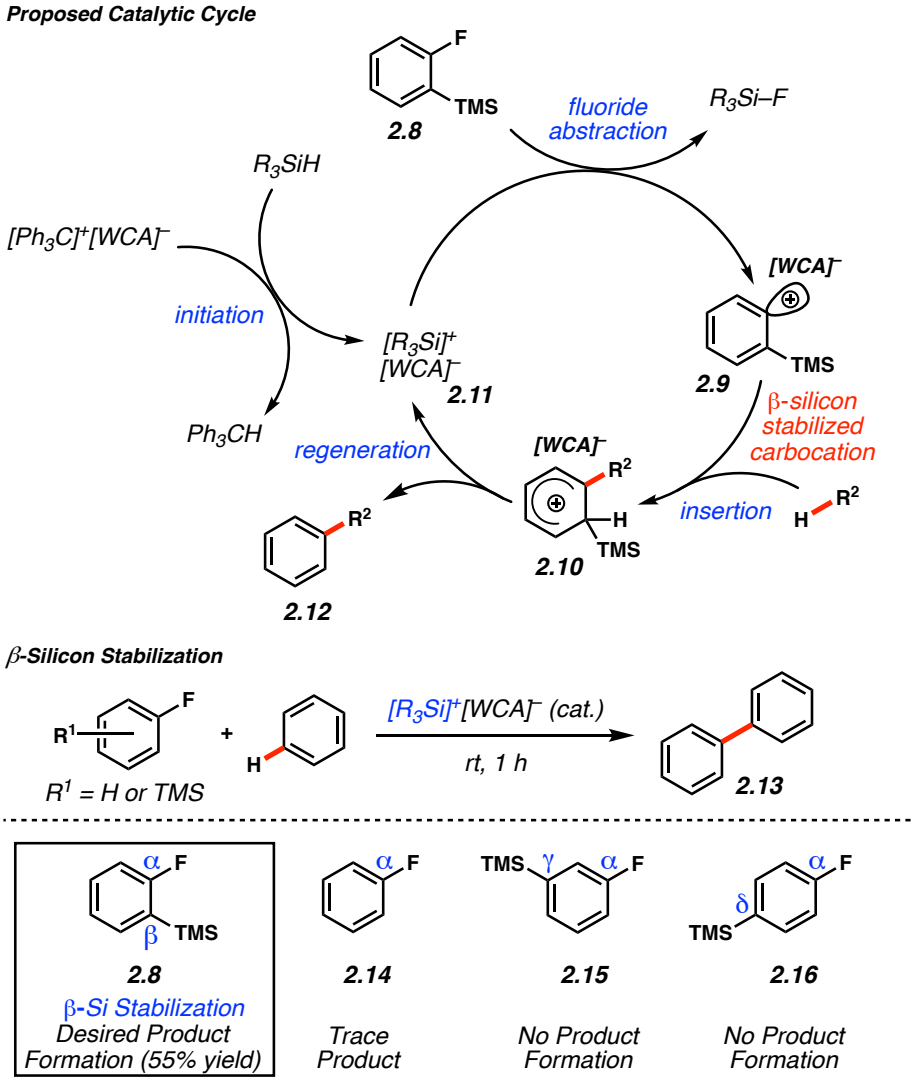
Figure 2.1. Reactions of phenyl carbocations



2.3 The Proposal of a Phenyl Carbocation Equivalent

We envisioned that β-silylated aryl fluorides (**2.8**, Fig. 2) would be particularly well suited as phenyl cation precursors for several reasons. First, we anticipated that β-silicon stabilization would lower the barrier for fluoride abstraction and temper the σ-electrophilicity of the phenyl cation equivalent (**2.9**).[20–24] Second, we envisioned that silicon substitution would enhance the nucleophilicity of the arene π-system, perhaps improving the insertion reactivity of cation **2.9**.[25] Finally, we hypothesized that elimination of the β-silicon group from a reactive intermediate such as arenium **2.10** could regenerate the key reactive silicon species.

Figure 2.2. Proposed cycle and importance of β-silicon



Taking into account these reagent-design concepts, we envisioned the cationic chain process depicted in Figure 2. Here a substochiometric silylium-carborane initiator (**2.11**)[26], generated *via* Bartlett–Condon–Schneider hydride transfer[27], could abstract a fluoride from fluoroarene **2.8** to generate phenyl cation **2.9**. Subsequent insertion into the hydrocarbon C–H bond would then yield β-silicon stabilized Wheland intermediate **2.10**. Elimination of trimethylsilylium would then afford C–H arylation product **2.12**. Importantly, this elementary step would generate the active trimethylsilylium-carborane salt that proceeds through the cycle in a manner analogous to classic Brønsted acid catalysis.[28]

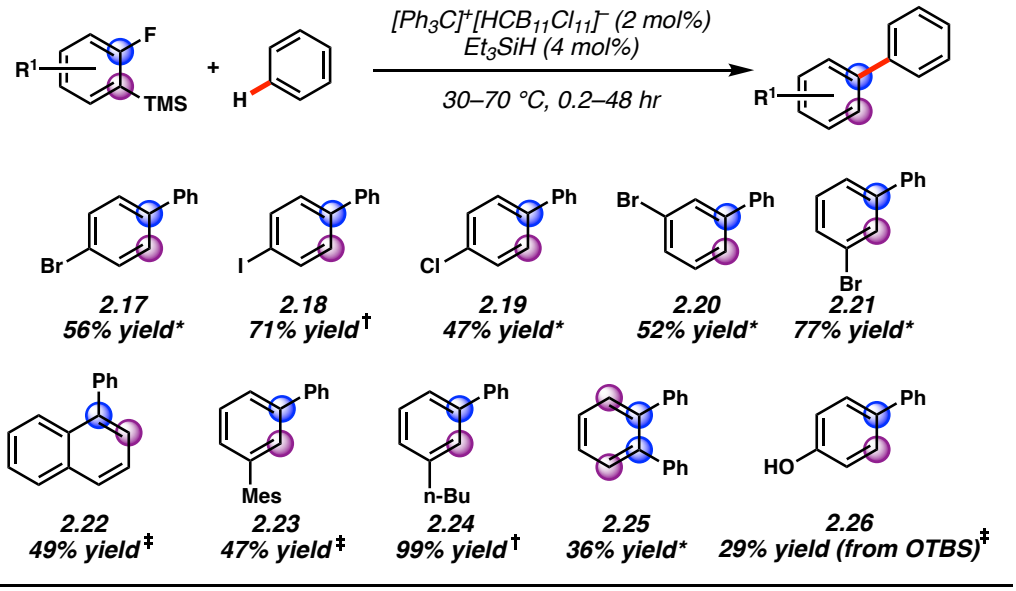
2.4 The Realization of Fluorotrimethylsilylarenes as Phenyl Carbocation Precursors

After a short examination of reaction conditions[29], we found that exposure of fluoride **2.8** to 1 mol% of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ and 2 mol% of triethylsilane in benzene solvent resulted in the facile formation of biphenyl (**2.13**) in 55% yield, at 30 °C in 1 hour. Application of these reaction conditions to fluorobenzene (**2.14**) only resulted in trace product **2.13**, and use of *meta*- and *para*-silylated aryl fluorides **2.15** and **2.16**, respectively, did not result in product formation.

With this initial finding in hand, we investigated the scope of this arylation reaction (Table 2.1). We were pleased to observe selective C–F functionalization in the presence of weaker carbon-halogen (C–X) bonds, similar to previous reports from Ozerov and coworkers.[30] Specifically, products **2.17**–**2.20** highlight the fluorophilicity of the silylium-carborane catalyst. In these cases, weaker C–X bonds that have less steric encumbrance than the C–F bond do not undergo ionization. This selectivity stands in stark contrast to many traditional reactions of aryl halides where reactivity often trends with bond dissociation energies (BDEs).[31, 32] To further

investigate this unusual selectivity and to separate β-silicon effects from fluorophilicity, we exposed (2-bromo-6-fluorophenyl)trimethylsilane (substrate for **2.21**) to our reaction conditions.

Table 2.1. C–H arylation reactions of phenyl carbocations



*Yield determined by: *GC-FID, †NMR, ‡isolation*

Remarkably, *m*-bromobiphenyl (**2.21**) was formed in good yield, supporting our claim of halide selectivity. Polycyclic aromatic fluorides were competent under the reaction conditions as well, as demonstrated by the formation of 1-phenylnaphthalene (**2.22**) in 49% yield. Additionally, aryl and alkyl substitution were tolerated under the reaction conditions providing phenylated aromatics (**2.23–2.24**) in moderate to excellent yields (47–99%). Consecutive arylation of difluorides was also possible as demonstrated by the formation of *o*-terphenyl (**2.25**), albeit in a diminished 36% yield. Finally, the presence of heteroatom donor substituents, typically incompatible with silylium catalysis, provided 29% yield of the desired phenol derivative **2.26**. It is worthy to note that in cases where the yields were moderate, we observed several byproducts, including simple fluoroarenes resulting from protodesilylation of the starting materials (presumably arising from highly-acidic arenium intermediates), as well as double arylation

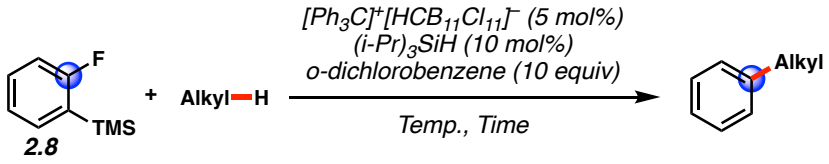
products resulting from a second arylation event. Throughout our scope studies, some general reactivity trends were apparent. Positional selectivity was preserved in all cases, including those with lower yields. Halide substituents required higher reaction temperatures whereas alkyl/aryl substituents allowed faster, lower temperature arylation. These observations are consistent with the intermediacy of a cationic aryl species.

2.5 Hydrocarbon C–H Functionalization Using Phenyl Carbocations

Bolstered by these results, we began our investigation into the arylation of alkanes. After optimization of reaction conditions[29], we found that cyclohexane could be phenylated by aryl fluoride **2.8** in 41% yield (Table 2.2, entry 1). We were surprised to find that this alkane arylation reaction proceeded at 60 °C in two hours. Likewise, cyclopentane underwent smooth arylation under similar conditions in 54% yield (Table 2.2, entry 2). Cycloheptane could also be arylated in 40% yield (Table 2.2, entry 3). With these results in hand, we set out to investigate reactivity with acyclic alkanes. We were pleased to find that *n*-hexane underwent arylation to yield all three phenylhexane isomers in 40% overall yield (Table 2.2, entry 4). This C–H arylation reaction displayed terminal selectivity, with an α:β:γ ratio of 5:2:1. In a similar fashion, *n*-pentane also underwent terminal-selective arylation to yield phenylpentane isomers in 42% yield with a 10:3:1 ratio (Table 2.2, entry 5). An earlier report of direct, terminal selective arylation of saturated hydrocarbons required zeolite catalysts at > 200 °C, and delivered < 5% yield.[33] The terminal C–H bonds of alkanes, though kinetically more accessible, have higher BDEs than their internal counterparts (98 kcal/mol for terminal vs. 93–95 kcal/mol for internal).[34] Given our ability to arylate the strongest of C–H bonds (Table 2.2, entries 4 and 5), and the longstanding interest in hydrocarbon gas functionalization, we became intrigued by the

prospect of arylating methane gas (C–H bond BDE ~105 kcal/mol).[32, 35, 36] Initial experiments were thwarted by deleterious arylation of solvent. After optimization[29], we found that use of C_6F_6 solvent allowed for the arylation of methane in 32% yield, at low temperatures (60 °C) and synthetically relevant pressures (35 bar) (Table 2.2.1). The conversion of naphthalene **2.27** to 1-methylnaphthalene (**2.28**) serves as a rare example of methane gas functionalization using main group catalysis.[37]

Table 2.2. Arylation of hydrocarbon C–H bonds



2.8

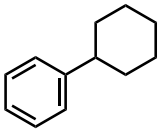
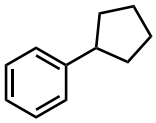
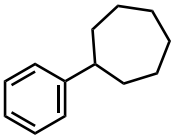
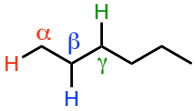
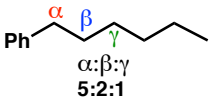
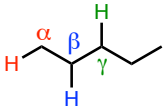
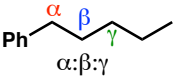
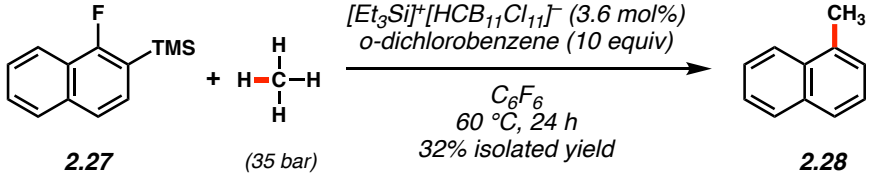
Entry	Alkane	Temp. (°C)	Time (hours)	Product	Yield (%)
1		60	2		41*
2		70	1		54†
3		100	9		40†‡
4		60	8	 α:β:γ 5:2:1	40* α:β:γ 26:9:5
5		60	8	 α:β:γ 10:3:1	42* α:β:γ 30:10:2

Table 2.2.1. Arylation of methane C–H bonds



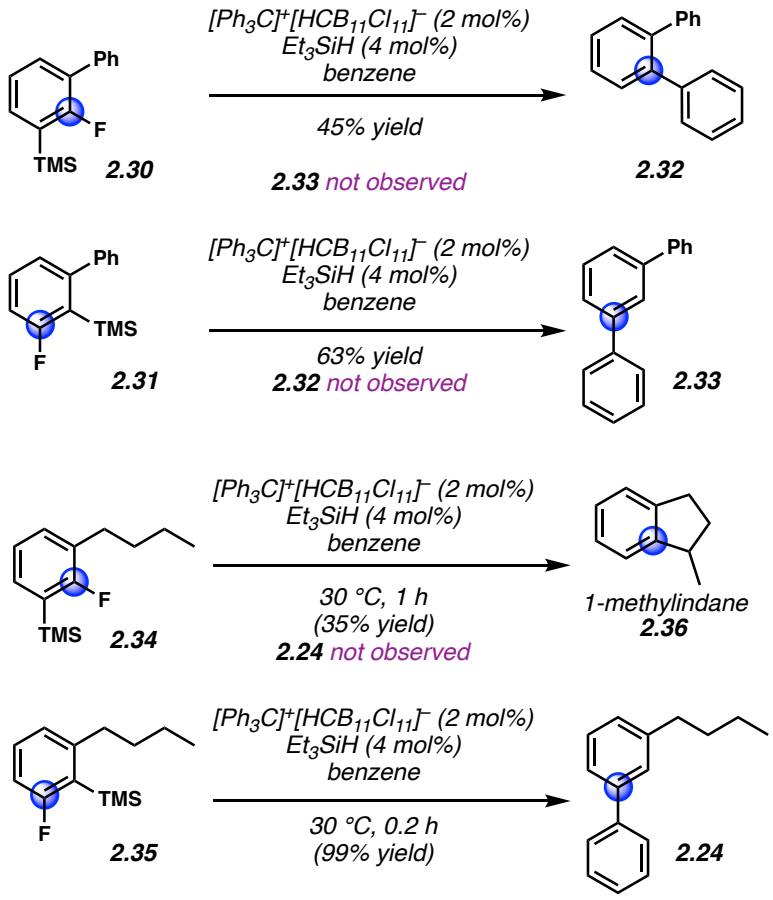
2.27 (35 bar) **2.28**

*Yield determined by: *GC-FID, †NMR, ‡reaction was performed in absence of o-dichlorobenzene.*

2.6 Mechanistic Studies

Several experiments were performed to probe the nature of the reactive intermediate. Arynes, as well as their transition metal complexes, have been shown to undergo C–H insertion reactions;[38, 39] however, intermolecular insertion into sp^3 C–H bonds has not been reported.[40, 41] The different products observed in Table 1, **2.17** vs. **2.20**, which would presumably go through an identical aryne intermediate (Fig. 3, **2.29**, R = Ph), is suggestive that an aryne intermediate is not active. To better understand the site-selectivity and probing of an aryne intermediate, biarylfluorosilanes **2.30 and 2.31** were synthesized. Under the reaction conditions, these would presumably go through an identical intermediate, resulting in the same products. To our desire, the use of **2.30** led to *o*-terphenyl (**2.32**), while **2.31** gave *m*-terphenyl (**2.33**). Importantly, the incorporation of an aryl group is only detected at the fluorine-bound carbon, further suggesting an aryne intermediate is not operative. As a further means of investigation, we prepared butyl derivative **2.34** (Fig. 3). The intermediacy of aryne **2.29** (R = butyl) would lead to the formation of biaryl **2.24** from both fluorides **2.34** and **2.35**. However, unlike the arylation reactivity observed for **2.35** (i.e. **2.35** → **2.24**), compound **2.24** (Fig. 3) was not observed in the reaction of butyl derivative **2.34** (Fig. 3). Instead, we observed rapid intramolecular C–H insertion to form 1-methylindane (Fig. 3, **2.36**) in 35% yield (43% after optimization).[29] These entries suggest that an electrophilic site is localized to the C–F carbon.

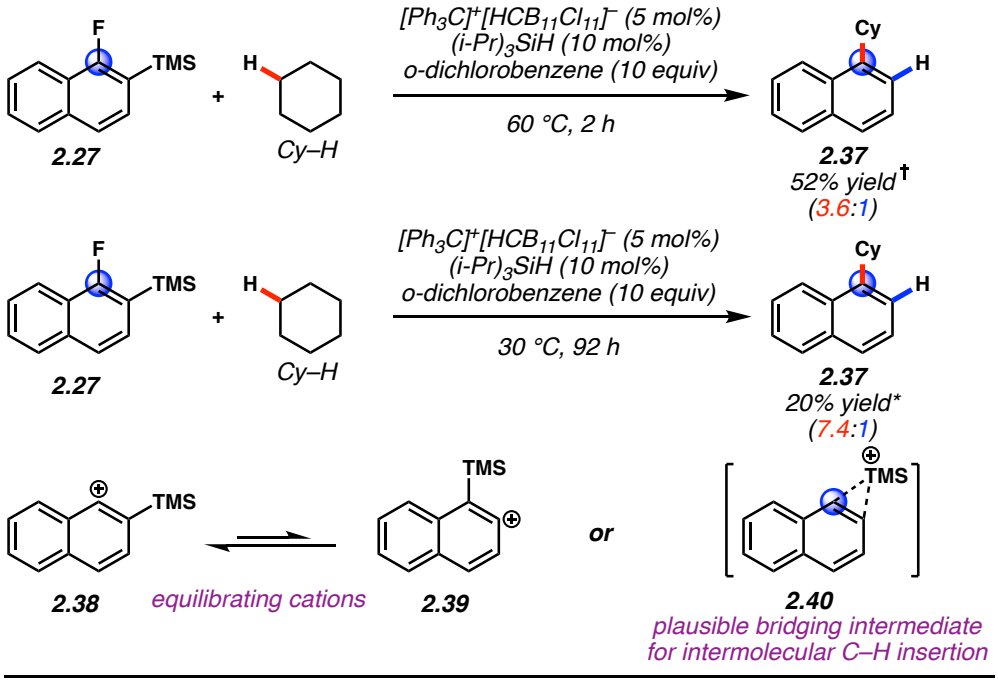
Figure 2.3. Disproving the intermediacy of an aryne



In further efforts to validate the active intermediate, a study of intermolecular C–H insertion reactions of substituted fluorotrimethylsilyl derivatives was undertaken (Figure 2.4.). The use of 1-fluoro-2-trimethylsilyl naphthalene (**2.27**) in cyclohexane under standard alkylation conditions gave rise to an interesting 3.6 to 1 selectivity of C–H functionalization, favoring the original C–F site in an overall 52% yield of naphthylcyclohexane **2.37**. Contrary to our previous results demonstrating complete fidelity at the C–F site in the context of Friedel-Crafts alkylation, this result necessitated further exploration. In decreasing the temperature to ambient conditions, although in a diminished 20% yield, the C–F selectivity can be improved to 7.4 to 1 selectivity. These results suggest that there exists a possibility that there could be equilibrating cationic

intermediates along the pathway. This makes sense especially when given an insertion reaction pathway that has a comparatively larger barrier (Friedel-Crafts vs. insertion) would allow for an equilibration of intermediates (**2.38** and **2.39**) or possibly an unsymmetrical silyl bridging intermediate (**2.40**) wherein the degree of bridging is under kinetic control. These observations also do not rule out the possibility of an unsymmetrical silylium-dicarbenoid species analogous to the silver complex proposed by Lee and coworkers.[39] Thus, while we draw the reactive intermediate **2.9** as a formal carbocation, it is possible that a free phenyl cation is not operative. One could also envision a species analogous to Reed's phenyl chloronium salt[17], wherein the β-trimethylsilyl group enhances reactivity through steric buttressing or electronic perturbation.

Figure 2.4. Investigating the intermediate for intermolecular C–H insertion



*Yield determined by: *GC-FID, †NMR*

2.7 Conclusion

In closing, we have developed a methodology to generate aryl cation equivalents that engage in the catalytic, intermolecular C–H arylation of arenes and alkanes using main group

catalysis. Reagents were designed wherein β-silicon substitution facilitated C–F bond activation and catalyst turnover. Furthermore, the hyper-fluorophilicity of the silylium-carborane catalyst mediates selective functionalization of C–F bonds in the presence of weaker C–X bonds. This selectivity trend is complementary to transition metal-catalyzed cross-coupling reactions and traditional nucleophilic substitution reactions. More fundamentally, this work represents an exciting paradigm in catalysis, where strong bonds (C–F and C–H) are directly engaged in C–C bond-forming cross-coupling reactions.

2.8 Experimental Section

2.8.1 Materials and Methods

Unless otherwise stated, all reactions were performed in an MBraun glovebox under nitrogen atmosphere with < 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and allowed to cool *in vacuo* before use. All liquid substrates were either dried over CaH_2 or filtered through dry neutral aluminum oxide. Solid substrates were dried over P_2O_5. All solvents were rigorously dried before use. Benzene, *o*-dichlorobenzene, and toluene were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. Cyclohexane (Sigma-Aldrich), fluorobenzene (Sigma-Aldrich), and *n*-hexane (Oakwood) were distilled over potassium. Chlorobenzene (Fisher Scientific), cycloheptane (Alfa Aesar) and *o*-difluorobenzene (Oakwood) were distilled over sodium. Cyclopentane (Matheson Cole and Bell) was filtered through dry neutral aluminum oxide. Pentane (Sigma-Aldrich) was distilled over sodium-potassium alloy. Hexafluorobenzene (Oakwood) was dried over CaH_2 and stored in a glovebox. All solvents were stored over 4 Å molecular sieves. Triethylsilane (Oakwood) and triisopropylsilane (AK Scientific) were dried over CaH_2 and stored inside a glovebox over 4 Å

molecular sieves. *Closo*-carborane anions, including $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$, were prepared according to literature procedure. Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230–400 mesh) was used for flash chromatography. NMR spectra were recorded on a Bruker AV-300 (^1H, ^{19}F), Bruker AV-400 (^1H, ^{13}C, ^{19}F), Bruker DRX-500 (^1H), and Bruker AV-500 (^1H, ^{13}C). ^1H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) and CD_2Cl_2 (5.32 ppm). Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.0 ppm). GC spectra were recorded on an Agilent 6850 series GC using an Agilent HP-1 (50 m, 0.32 mm ID, 0.25 mm DF) column. GCMS spectra were recorded on a Shimadzu GCMS-QP2010 using a Restek XTI-5 (50 m, 0.25 mm ID, 0.25 mm DF) column. Reactions incorporating methane gas were conducted using a Parr Model 5000 Multiple Reactor system. The system was operated *via* a 4871 process controller and SpecView version 2.5. All pressures were reported from the SpecView interface at room temperature. IR Spectra were recorded on a Perkin Elmer 100 spectrometer and are reported in terms of absorption frequency (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on a Waters (Micromass) GCT Premier spectrometer and are reported as follows: m/z (% relative intensity).

2.8.2 Experimental Procedures

Synthesis of substrates for Table 2.1, 2.2, 2.2.1 and Figure 2.3 are reported in the adapted article.

2.8.3 Aryl Insertion Reactions

2.8.3.1 Optimization Table for Aryl Insertion Reaction

In our studies, we optimized our reaction conditions for anion, silane, concentration, and temperature using **2.8** in benzene.

Anion	% Cat. Loading	Conc.	Silane	Temperature	Yield
$[HCB_{11}H_5Cl_6]$	5 mol%	0.1 M	iPr_3SiH (10 mol%)	70 °C	41%
$[HCB_{11}H_5Br_6]$	5 mol%	0.1 M	Et_3SiH (10 mol%)	70 °C	0%
$[HCB_{11}Me_5Br_6]$	5 mol%	0.1 M	Et_3SiH (10 mol%)	70 °C	0%
$[HCB_{11}Cl_{11}]$	1 mol%	0.02 M	Et_3SiH (2 mol%)	30 °C	55%
$[HCB_{11}Cl_{11}]$	2 mol%	0.1 M	Et_3SiH (4 mol%)	30 °C	49%
$[HCB_{11}Br_{11}]$	5 mol%	0.1 M	Et_3SiH (10 mol%)	30 °C	31%
$[(C_6F_5)_4B]$	5 mol%	0. 1M	Et_3SiH (10 mol%)	30 °C	27%

Table 2.3. Optimization of (2-fluorophenyl)trimethylsilane substrate in benzene.

2.8.3.2 Initial Investigation of Aryl Fluorides

Outlined below are our initial experiments evaluating the reactivity of aryl fluorides in both the presence and absence of the trimethylsilyl group. We also conducted control experiments using a previously reported silylium-catalyzed C–F functionalization method.[15] Our experiments below support the need for an *ortho*-trimethylsilyl group for our catalytic system.

2.8.3.2.1 Fluorobenzene Control

Described below is the application of fluorobenzene using our optimized conditions.

$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 1.1 μmol, 0.02 equiv) and triethylsilane (0.5 μL, 2.2 μmol, 0.04 equiv) were stirred in benzene (3 mL) to form a colorless solution (0.02 M) before the addition of fluorobenzene (9.5 μL, 0.054 mmol, 1 equiv). Reaction was stirred at 30 °C. After 5 days, GC-FID showed formation of biphenyl. Addition of nonane (9.7 μL, 0.054 mmol, 1 equiv) as an internal standard showed < 5% yield of biphenyl (Fig. 2.6).

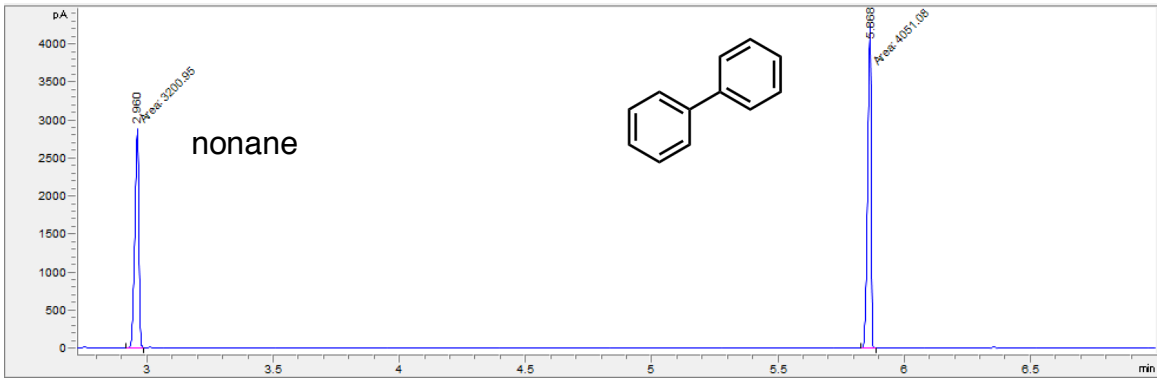


Figure 2.5. GC trace for internal standard nonane and biphenyl in 1:1 ratio.

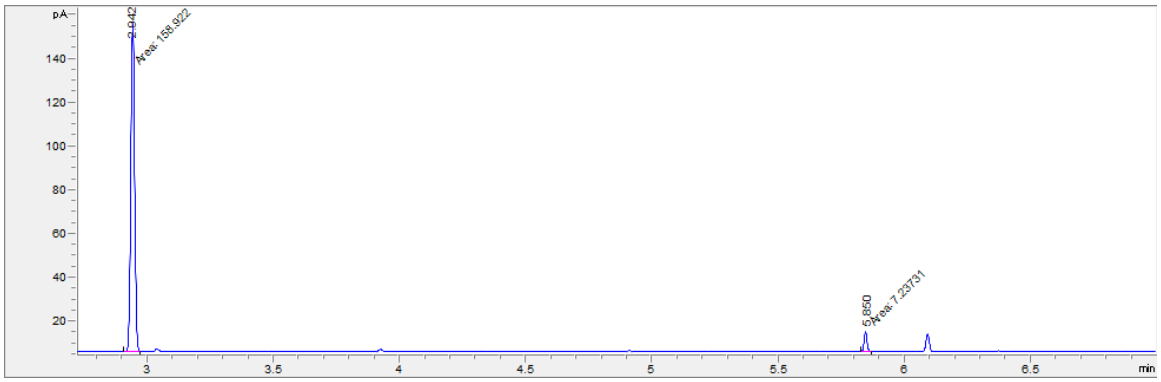


Figure 2.6. GC trace for internal standard nonane in fluorobenzene control reaction.

2.8.3.2.2 Application of Conditions from Reference 15

Described below is the application of fluorobenzene with a previously reported silylium-catalyzed C–F functionalization for the intermolecular formation of biphenyl.

Fluorobenzene (9.5 µL, 0.1 mmol, 1 equiv), dimethyldimesitylsilane (25.6 mg, 0.09 mmol, 0.9 equiv) and $[i\text{Pr}_3\text{Si}]^+[\text{HCB}_{11}\text{H}_5\text{Cl}_6]^-$ (5.3 mg, 0.01 mmol, 0.1 equiv)were dissolved in benzene (1 mL). The reaction was then stirred at 30 °C. After 13 hours, GC-FID spectra showed formation of biphenyl in < 5% yield (Fig. 2.7).

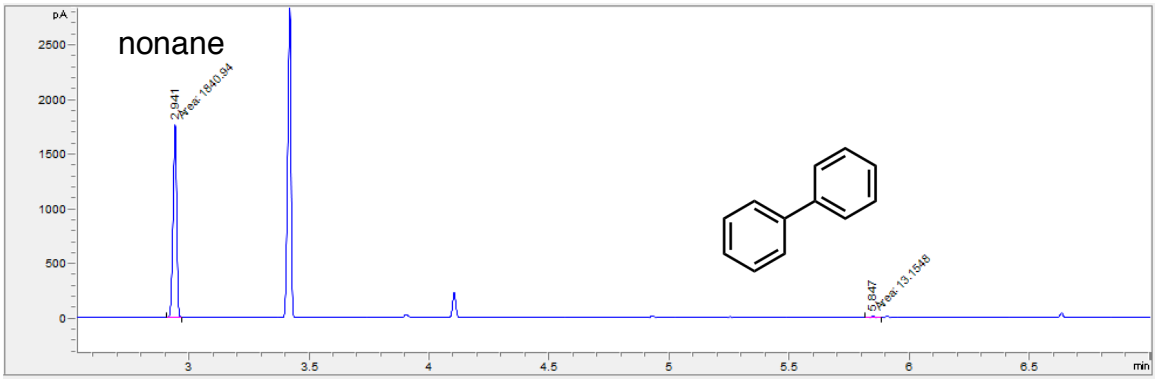


Figure 2.7. GC trace for application of reference 15 conditions to fluorobenzene at 30 °C.

2.8.3.2.3 Positional Effects of the Silyl Group

Outlined below are a series of experiments probing the reactivity of our substrate in varying the position of the trimethylsilyl group relative to the aryl C–F carbon. The experiments below support the need for a trimethylsilyl group *ortho* to the aryl C–F carbon to generate the desired product in catalytic fashion.

$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.5 mg, 3.3 μmol) and triethylsilane (1 μL, 6.6 μmol,) were stirred in benzene (1.5 mL) to form a colorless solution. This solution was partitioned equally into three separate vials before aryl fluorides **2.8**, **2.15**, and **2.16** (0.054 mmol) were added in their respective reactions. Reactions were then stirred at 30 °C for 2 hours before addition of nonane (9.7 μL, 0.054 mmol, 1 equiv) as an internal standard. As shown below, no formation of biphenyl was observed when using *meta*- or *para*- trimethylsilyl aryl fluorides (Figs. 2.9 and 2.10). The *ortho*-trimethylsilyl aryl fluoride was the only positional isomer that afforded biphenyl in 47% yield (Fig. 2.11).

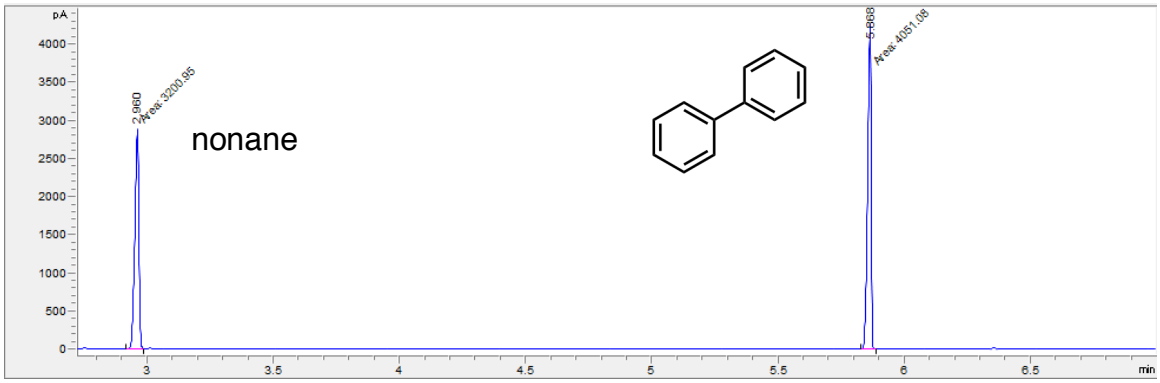


Figure 2.8. GC trace for internal standard nonane and biphenyl in 1:1 ratio.

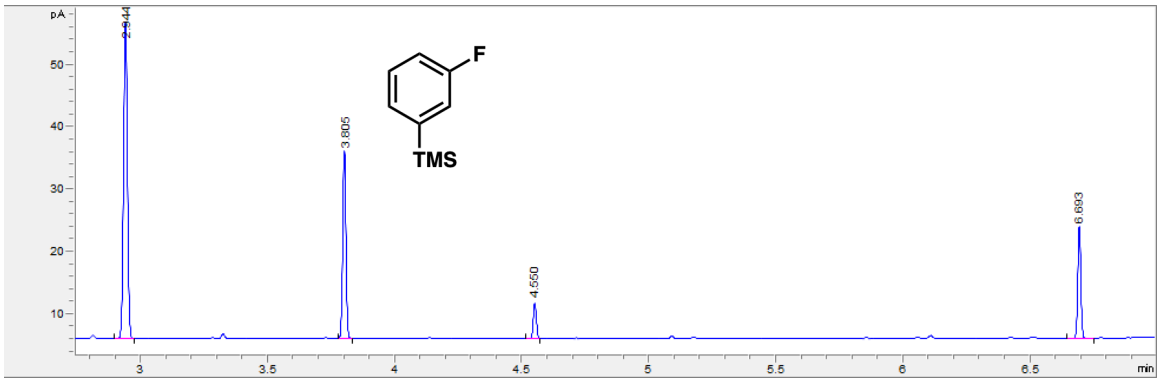


Figure 2.9. GC trace for internal standard nonane and **2.15** after 2 hour reaction time.

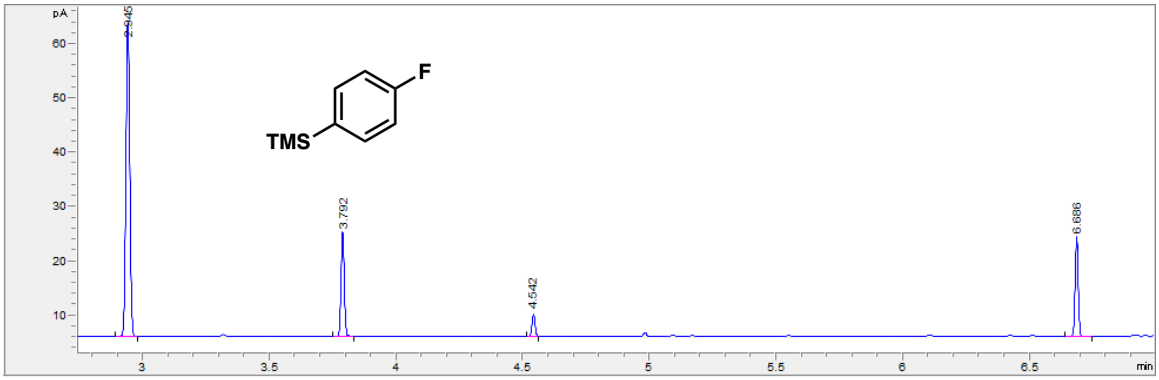


Figure 2.10. GC trace for internal standard nonane and **2.16** after 2 hour reaction time.

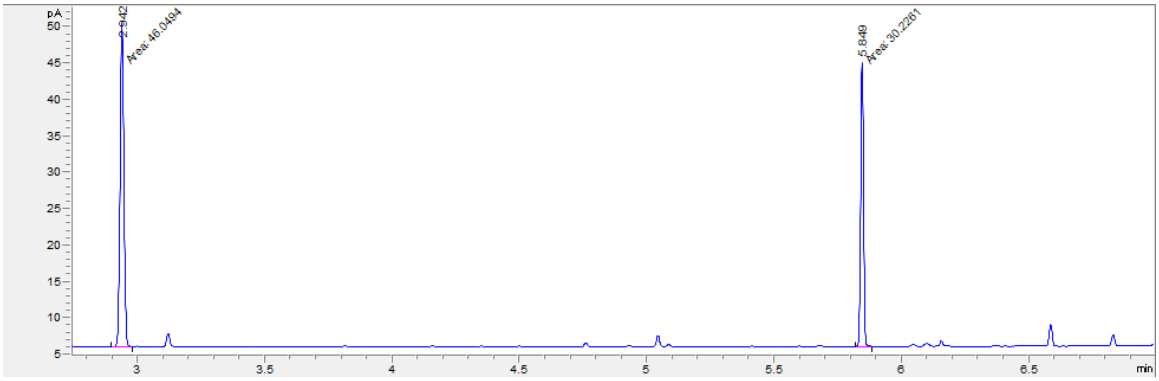
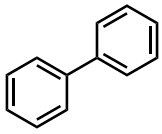


Figure 2.11. GC trace for internal standard nonane and **2.8** after 2 hour reaction time showing formation of biphenyl in 47% yield.

2.8.3.3 General Procedure for Intermolecular Aryl Insertion Reactions

$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 1.1 μmol, 0.02 equiv) and triethylsilane (0.5 μL, 2.2 μmol, 0.04 equiv) were stirred in benzene (0.5 mL) to form a colorless solution (0.1 M) before the addition of aryl fluoride substrate (0.054 mmol, 1 equiv). Substrates were stirred between 30–70 °C for 0.2–9 hours (see individual substrates for reaction conditions). Reactions were monitored by GC-

FID spectra. If previously heated, reactions were cooled to room temperature before volatiles were rotary evaporated and purified by flash column or preparatory thin layer chromatography.



Biphenyl (2.13). Synthesized according to general procedure 2.8.3.3 with a modified 1 mol% catalyst loading and 0.02 M concentration. Catalyst loading was achieved by taking 0.55 mL from a freshly prepared stock solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.5 mg) and triethylsilane (0.5 µL) in benzene (2 mL). Additional benzene was added to reach a total volume of 3 mL before aryl fluoride **2.8** (9.1 mg, 0.054 mmol, 1 equiv) was added to the colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.54 µmol, 0.01 equiv) and triethylsilane (1.1 µmol, 0.02 equiv) in benzene. Reaction was stirred at 30 °C for 1 hour to afford **2.13** in 55% yield (GC) as shown in Fig. 2.13.

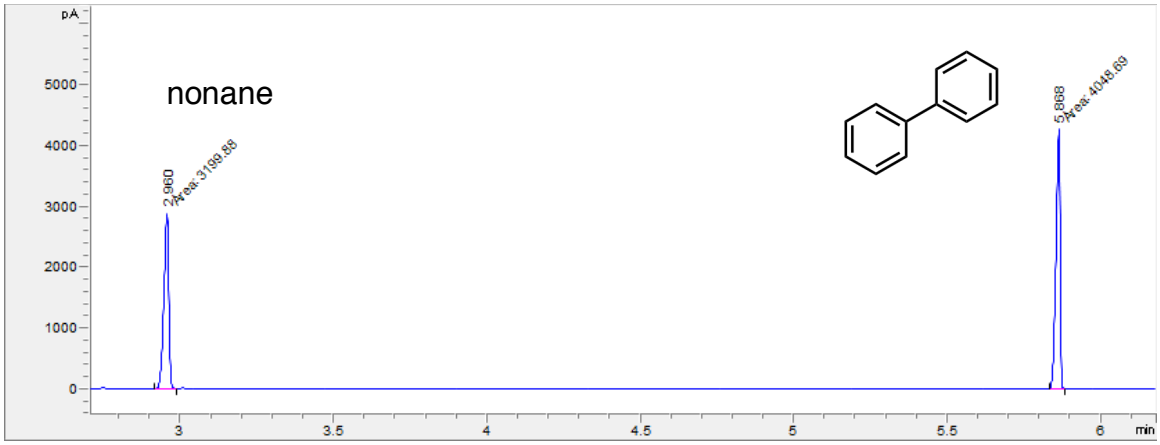


Figure 2.12. GC trace for internal standard nonane and **2.13** in 1:1 ratio.

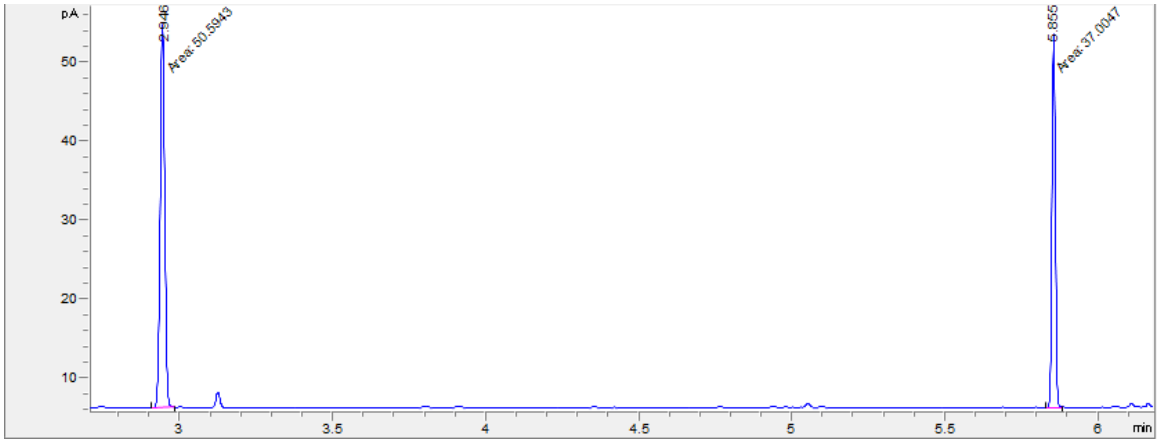


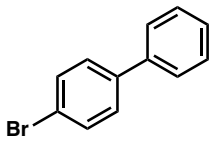
Figure 2.13. GC trace for yield shown for **2.13**.

2.8.3.4 Scope of Fluorotrimethylsilyl Arene Electrophiles

Described below is the characterization and procedure for the scope described in Table 2.1.

General Procedure

$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 1.1 µmol, 0.02 equiv) and triethylsilane (0.5 µL, 2.2 µmol, 0.04 equiv) were stirred in benzene (0.5 mL) to form a colorless solution (0.1 M) before the addition of aryl fluoride substrate (0.054 mmol, 1 equiv). Substrates were stirred between 30–70 °C for 0.2–9 hours (see individual substrates for reaction conditions). Reactions were monitored by GC-FID spectra. If previously heated, reactions were cooled to room temperature before volatiles were rotary evaporated and purified by flash column or preparatory thin layer chromatography.



4-bromobiphenyl (2.17). 2.17 was synthesized according to general procedure described in 2.8.3.4. The corresponding aryl fluoride (13.4 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 µmol, 0.02 equiv) and triethylsilane (2.2 µmol, 0.04 equiv), and was

stirred at 60 °C for 1 hour to give **2.17** in 56% yield (GC) as shown in Fig. 2.15. Crude product was purified by flash column chromatography (hexanes) to give **2.17** as a white solid (5.8 mg, 46%). NMR Spectra match those reported in literature.[42]

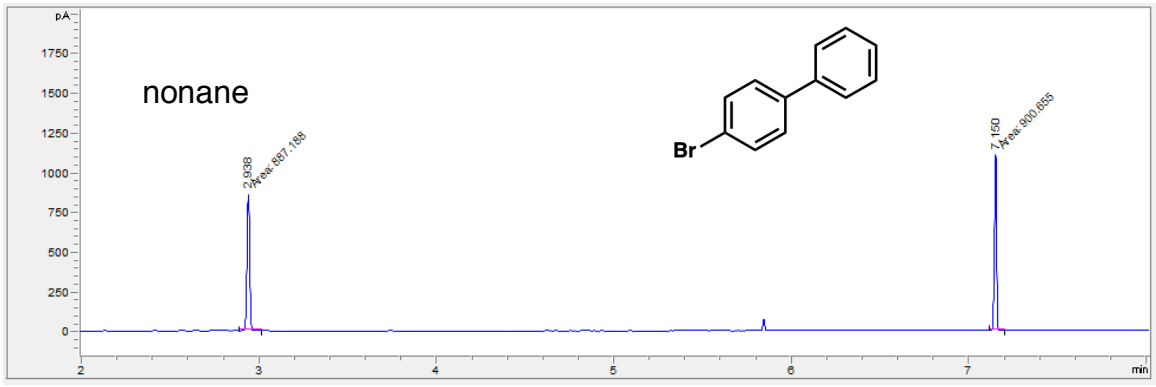


Figure 2.14. GC trace for internal standard nonane and **2.17** in 1:1 ratio.

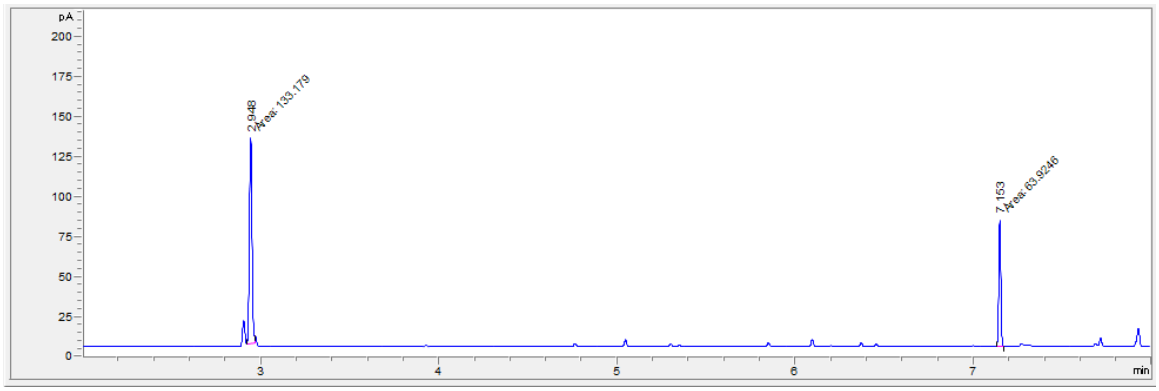
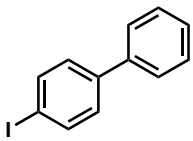
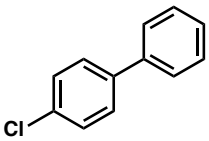


Figure 2.15. GC trace showing formation of **2.17** in 56% yield.



4-iodobiphenyl (2.18). 2.18 was synthesized according to general procedure described in 2.8.3.4. The corresponding aryl fluoride (15.9 mg, 0.054 mmol) was added to a colorless solution

of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv) and was stirred at 70 °C for 1 hour to give **2.18** in 71% yield (NMR). Crude product was purified by preparatory thin layer chromatography (hexanes) to give **2.18** as a white solid (7.8 mg, 52%). NMR Spectra match those reported in literature.[43]



4-chlorobiphenyl (2.19). 2.19 was synthesized according to general procedure described in 2.8.3.4. The corresponding aryl fluoride (11.0 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 70 °C for 9 hours to give **2.19** in 47% yield (GC) as shown in Fig. 2.17. Crude product was purified by column chromatography (hexanes) to give **2.19** as a white solid (4.1 mg, 40%). NMR Spectra match those reported in literature.[44]

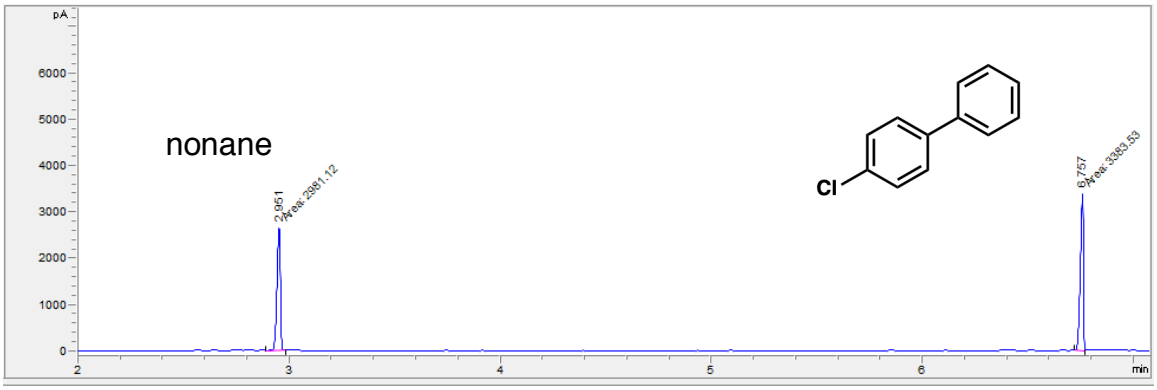


Figure 2.16. GC trace for internal standard nonane and **2.19** in 1:1 ratio.

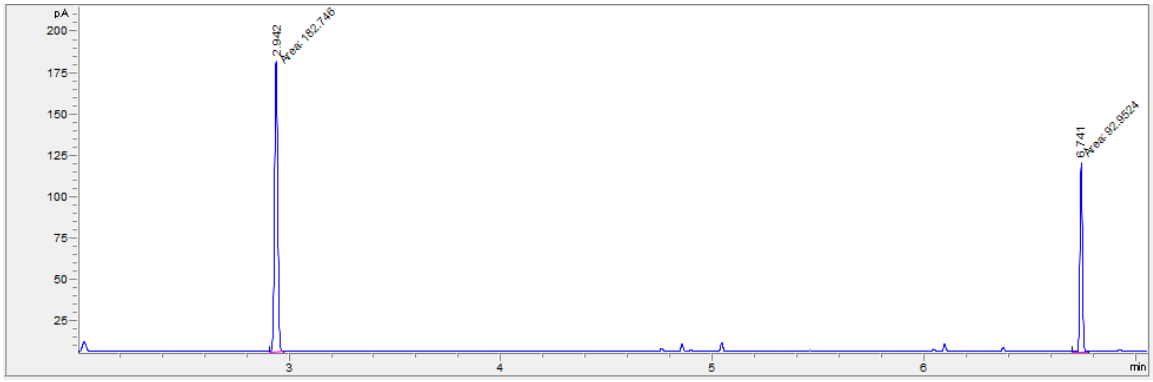
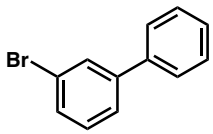


Figure 2.17. GC trace showing formation of **2.19** in 47% yield.



3-bromobiphenyl (2.20 and **2.21).** 3-bromobiphenyl was synthesized from two different substrates according to general procedure 2.8.3.4.

For **2.20**, the corresponding aryl fluoride (13.4 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 µmol, 0.02 equiv) and triethylsilane (2.2 µmol, 0.04 equiv), and was stirred at 60 °C for 1 hour to give **2.20** in 52% yield (GC) as shown in Fig. 2.19.

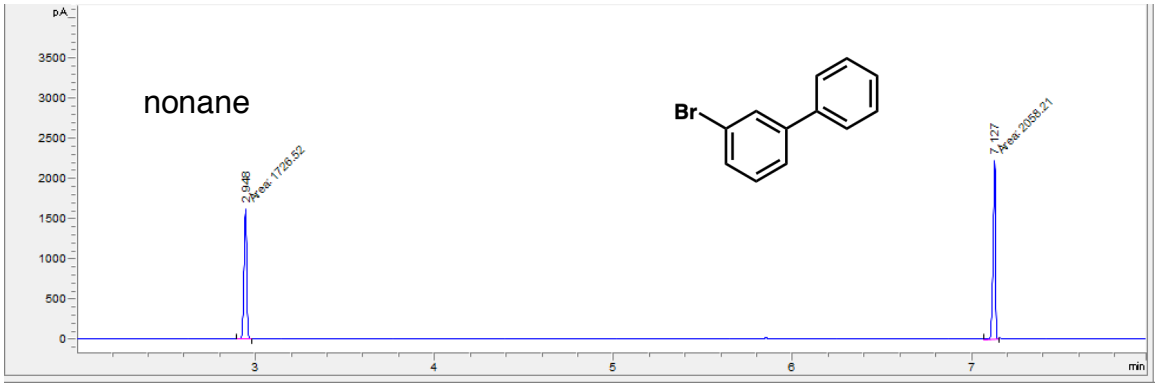


Figure 2.18. GC trace for internal standard nonane and **2.20** in 1:1 ratio.

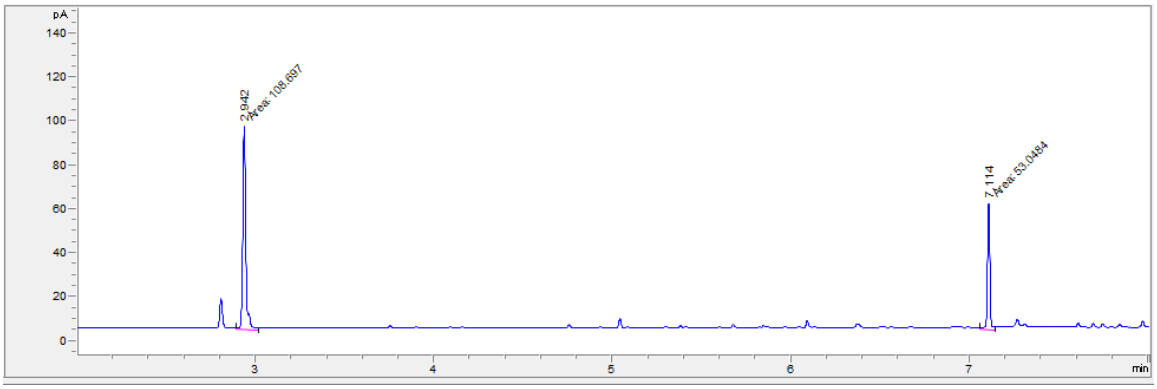


Figure 2.19. GC trace showing formation of **2.20** in 52% yield.

Similarly, the corresponding aryl fluoride (13.4 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 µmol, 0.02 equiv) and triethylsilane (2.2 µmol, 0.04 equiv) and was stirred at 60 °C for 1 hour to give **2.21** in 77% yield (GC) as shown in Fig. 2.20. Crude product was purified by preparatory thin layer chromatography (hexanes) to give **2.21** as a white solid (7.4 mg, 59%). NMR Spectra match those reported in literature.[45]

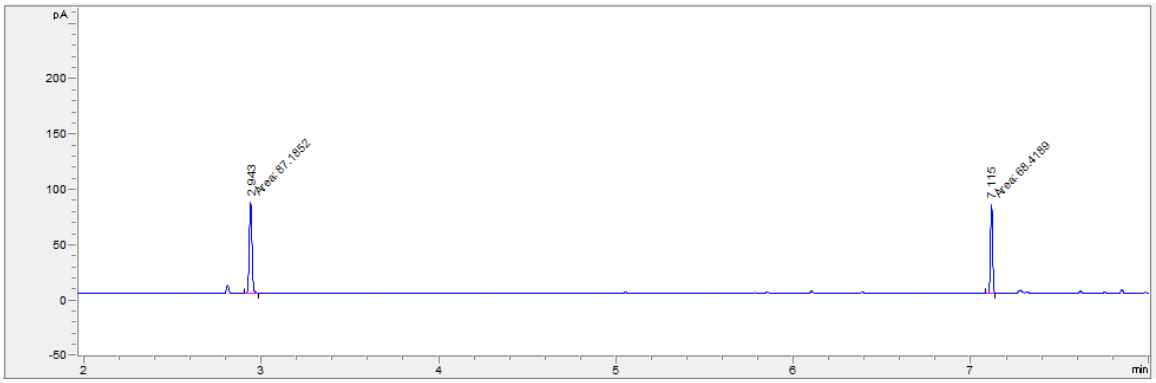
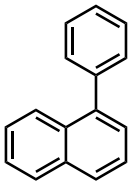
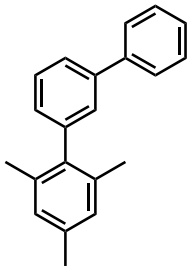


Figure 2.20. GC trace showing formation of **2.21** in 77% yield.



1-phenylnaphthalene (2.22). 2.22 was synthesized according to general procedure described in 2.8.3.4. The corresponding aryl fluoride (11.8 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 30 °C for 1 hour. Crude product was purified by preparatory thin layer chromatography (hexanes) to give **2.22** as a colorless oil (5.4 mg, 49%). NMR Spectra match those reported in literature.[46]

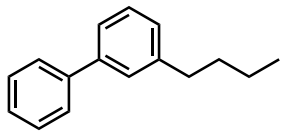


3-mesitylbiphenyl (2.23). 2.23 was synthesized according to general procedure described in 2.8.3.4. The corresponding aryl fluoride (15.5 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 30 °C for 1 hour. Crude product was purified by flash column chromatography (9:1 pentane:dichloromethane) to give **2.23** as a colorless oil (6.9 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.62 (m, 2H), 7.59 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.52–7.41 (m, 4H), 7.38–7.31 (m, 1H), 7.14 (dt, J = 7.5, 1.5 Hz, 1H), 6.98 (s, 2H), 2.36 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 141.1, 141.0, 138.9, 136.6, 136.0, 128.8, 128.7, 128.2, 128.1, 128.0, 127.3, 127.1, 125.2, 21.0, 20.8.

FTIR (Neat Film NaCl): 3059, 3030, 2952, 2919, 2867, 1946, 1880, 1803, 1730, 1471, 850, 757 cm^{-1}.

HR-MS (GC-CI): Calculated for $C_{21}H_{20}$: 272.1565; measured: 272.1575.

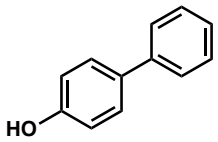


3-butylbiphenyl (2.24). 2.24 was synthesized according to general procedure described in 2.8.3.4. The corresponding aryl fluoride (12.1 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 30 °C for 0.2 hours to give **2.24** in 99% yield (NMR). Crude product was purified by flash column chromatography (hexanes) to give **2.24** as a colorless oil (10.6 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.60 (m, 2H), 7.51–7.41 (m, 4H), 7.38 (td, *J* = 7.4, 5.2 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 2.72 (t, *J* = 7.7 Hz, 2H), 1.74–1.65 (m, 2H), 1.49–1.38 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 141.5, 141.2, 128.7, 128.6, 127.4, 127.3, 127.2, 127.1, 124.5, 35.8, 33.7, 22.4, 14.0.

FTIR (Neat Film NaCl): 3059, 3029 2956, 2928, 2857, 1889, 1873, 1799, 1600, 1479, 754, 697 cm^{-1}.

HR-MS (GC-CI): Calculated for $C_{16}H_{18}$: 210.1409; measured: 210.1404.



4-hydroxybiphenyl (2.26). 2.26 was synthesized according to general procedure described in 2.8.3.4 with a slight modification. The corresponding aryl fluoride (16.1 mg, 0.054 mmol) was

added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv) and was stirred at 60 °C for 48 hours. After cooling to room temperature, the reaction was quenched with a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with Et_2O (3 x 1 mL) and combined organic layers were rotary evaporated. Crude product was purified by flash column chromatography (4:1 hexanes:ethyl acetate) to give **2.26** as a white solid (2.3 mg, 29%). NMR Spectra match those reported in literature.[47]

2.8.4 Alkane Insertion Reactions

2.8.4.1 Optimization Table for Intermolecular Alkane C–H Insertion

We optimized our reaction conditions for anion, silane, and additive using **2.8** in cyclohexane.

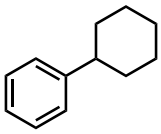
Anion (5 mol%)	Silane (10 mol%)	Additive	Time	Yield
$[HCB_{11}H_5Cl_6]$	iPr_3SiH	*o*-$C_6H_4Cl_2$ (10 equiv)	120 hr	32%
$[HCB_{11}Cl_{11}]$	Et_3SiH	*o*-$C_6H_4Cl_2$ (10 equiv)	8 hr	24%
$[HCB_{11}Cl_{11}]$	iPr_3SiH	*o*-$C_6H_4Cl_2$ (10 equiv)	2 hr	41%
$[HCB_{11}Cl_{11}]$	iPr_3SiH	$Me_2(Mes)_2Si$ (1 equiv)	9 hr	37%
$[HCB_{11}Cl_{11}]$	iPr_3SiH	*o*-$C_6H_4F_2$ (10 equiv)	2 hr	27%
$[HCB_{11}Cl_{11}]$	iPr_3SiH	none	22 hr	38%
$[(C_6F_5)_4B]$	iPr_3SiH	none	36 hr	18%

Table 2.4. Optimization of (2-fluorophenyl)trimethylsilane substrate in cyclohexane.

2.8.4.2 General Procedure for Intermolecular Alkane C–H Insertion

$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.0 mg, 2.7 μmol, 0.05 equiv) and triisopropylsilane (1.1 μL, 5.4 μmol, 0.1 equiv) were stirred in *o*-dichlorobenzene (60 μL, 0.54 mmol, 10 equiv) to give a colorless solution. Alkane solvent (1 mL), followed by aryl fluoride **2.8** (0.054 mmol, 1 equiv), were

added respectively to give a 0.05 M solution. The reaction was then heated between 60–100 °C for 1–9 hours (see individual substrates for reaction conditions). Reaction was monitored by GC-FID. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous sodium bicarbonate and the organic layers were concentrated *via* rotary evaporation and purified by flash column chromatography (hexanes or pentane).



Phenylcyclohexane (**Table 2.2, entry 1**)**.** Synthesized according to general procedure 2.8.4.2. Aryl fluoride **2.8** (9.1 mg, 0.054 mmol) was added to a solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.0 mg, 2.7 µmol, 0.05 equiv), triisopropylsilane (1.1 µL, 5.4 µmol, 0.1 equiv), *o*-dichlorobenzene (60 µL, 0.54 mmol, 10 equiv), and cyclohexane (1 mL). Reaction was stirred at 60 °C for 2 hours to give phenylcyclohexane in 41% yield (GC) as shown in Fig. 2.22. Crude product was purified by flash column chromatography (pentane) to give phenylcyclohexane as a colorless oil. NMR Spectra match those reported in literature.[48]

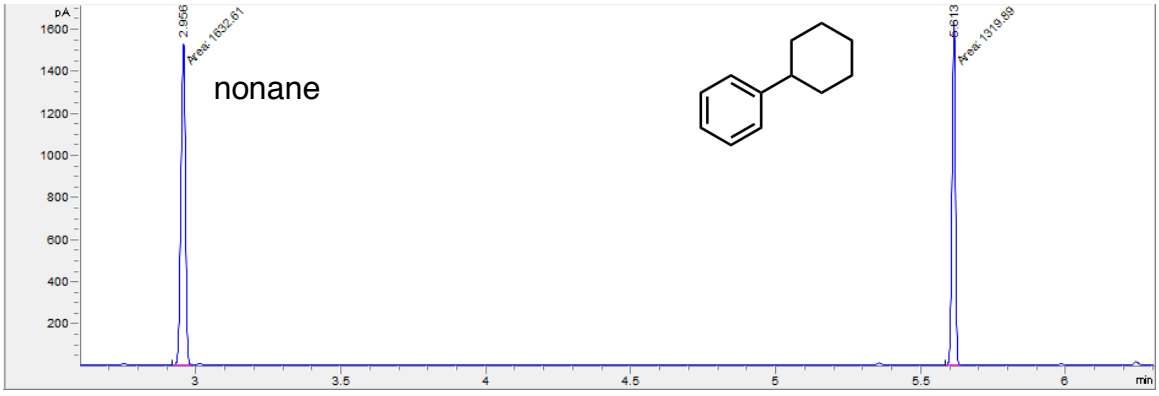


Figure 2.21. GC trace for internal standard nonane and phenylcyclohexane in 1:1 ratio.

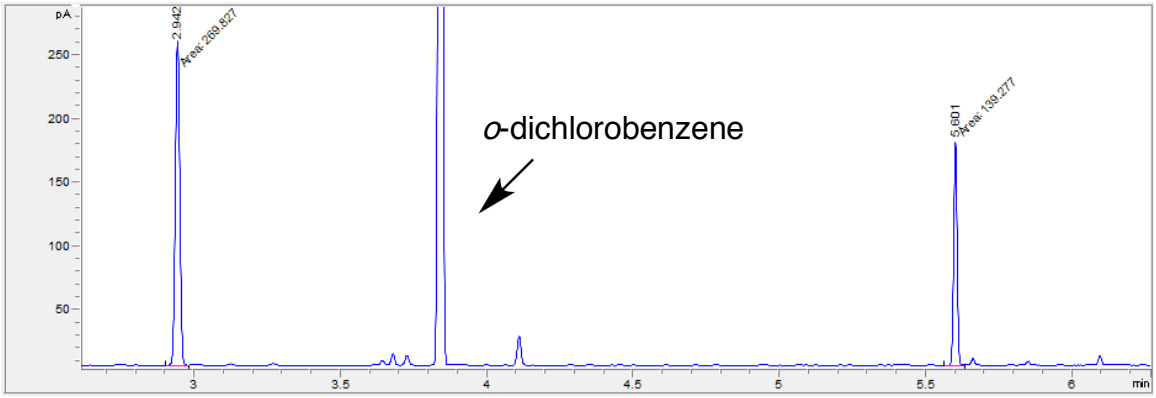
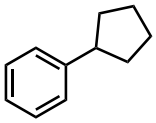
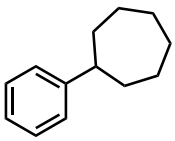


Figure 2.22. GC trace showing formation of phenylcyclohexane in 41% yield.

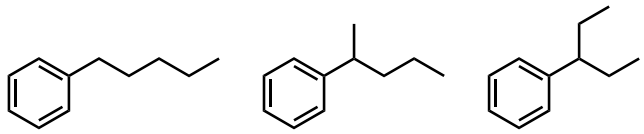


Phenylcyclopentane (Table 2.2, entry 2). Synthesized according to general procedure 2.8.4.2. Aryl fluoride **2.8** (0.054 mmol, 9.1 mg) was added to a solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.0 mg, 2.7 μmol, 0.05 equiv), triisopropylsilane (1.1 μL, 5.4 μmol, 0.1 equiv), *o*-dichlorobenzene (60 μL, 0.54 mmol, 10 equiv), and cyclopentane (1 mL). Reaction was stirred at 70 °C for 1 hour to give phenylcyclopentane in 54% yield (NMR). Crude product was purified by flash column chromatography (pentane) to give phenylcyclopentane as a colorless oil. NMR Spectra match those reported in literature.[49]



Phenylcycloheptane (Table 2.2, entry 3). Synthesized according to general procedure 2.8.4.2 excluding *o*-dichlorobenzene. Aryl fluoride **2.8** (0.054 mmol, 9.1 mg) was added to a solution of

$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.0 mg, 2.7 μmol, 0.05 equiv), triisopropylsilane (1.1 μL, 5.4 μmol, 0.1 equiv), and cycloheptane (1 mL). Reaction was heated at 100 °C for 9 hours to give phenylcycloheptane in 40% yield (NMR). Crude product was purified by flash column chromatography (hexanes) to give phenylcycloheptane as a colorless oil (3.4 mg, 36%). NMR Spectra match those reported in literature.[49]



Phenylpentane isomers (Table 2.2, entry 4). Synthesized according to general procedure 2.8.4.2. Aryl fluoride **2.8** (0.054 mmol, 9.1 mg) was added to a solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.0 mg, 2.7 μmol, 0.05 equiv), triisopropylsilane (1.1 μL, 5.4 μmol, 0.1 equiv), *o*-dichlorobenzene (60 μL, 0.54 mmol, 10 equiv), and *n*-pentane (1 mL). Reaction was heated at 60 °C for 8 hours to give phenylpentane isomers in 42% overall yield (GC) as shown in Figs. 2.25, 2.27, and 2.29. Crude product was purified by flash column chromatography (hexanes) to give phenylpentane isomers as a colorless oil. Calculated GC yields were: 1-phenylpentane (30%) shown in Fig. 2.25, 2-phenylpentane (10%) shown in Fig. 2.27, 3-phenylpentane (2%) shown in Fig. 2.29. NMR Spectra match those reported in literature.[50–52]

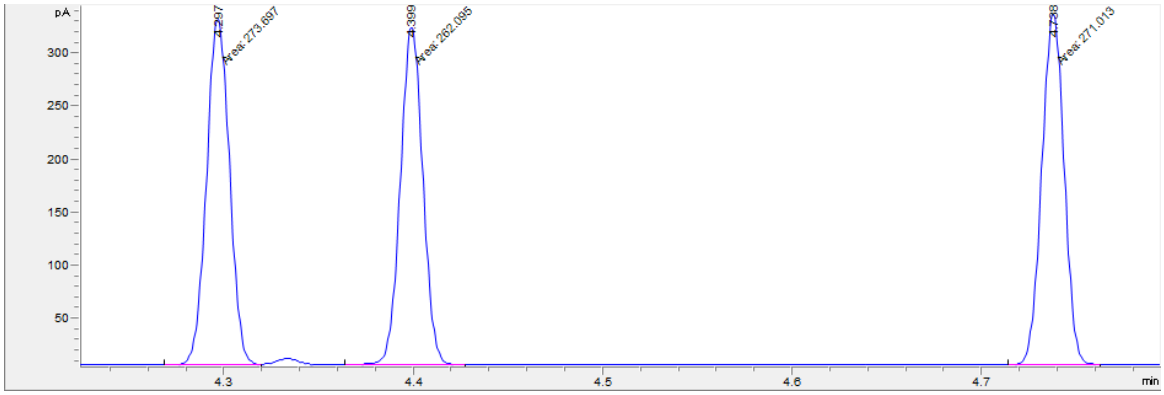


Figure 2.23. GC trace for a 1:1:1 ratio of phenylpentane isomers.

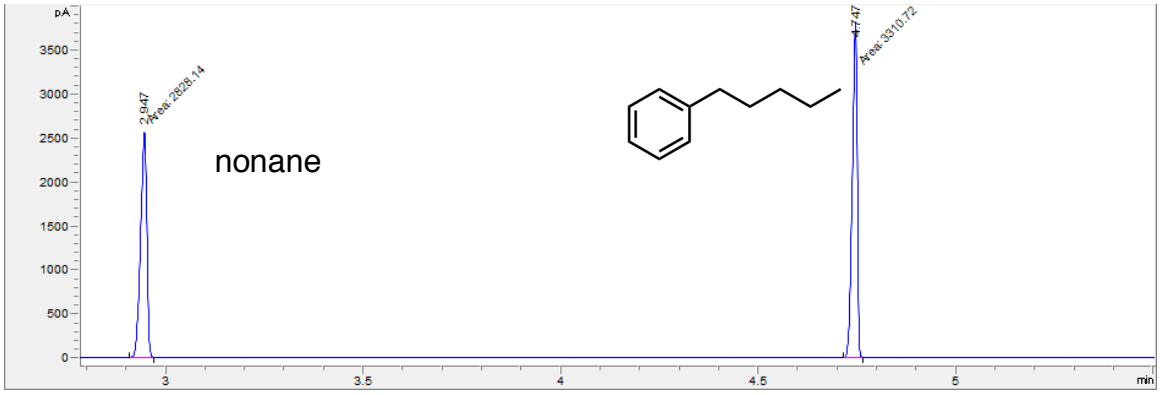


Figure 2.24. GC trace for internal standard nonane and 1-phenylpentane in 1:1 ratio.

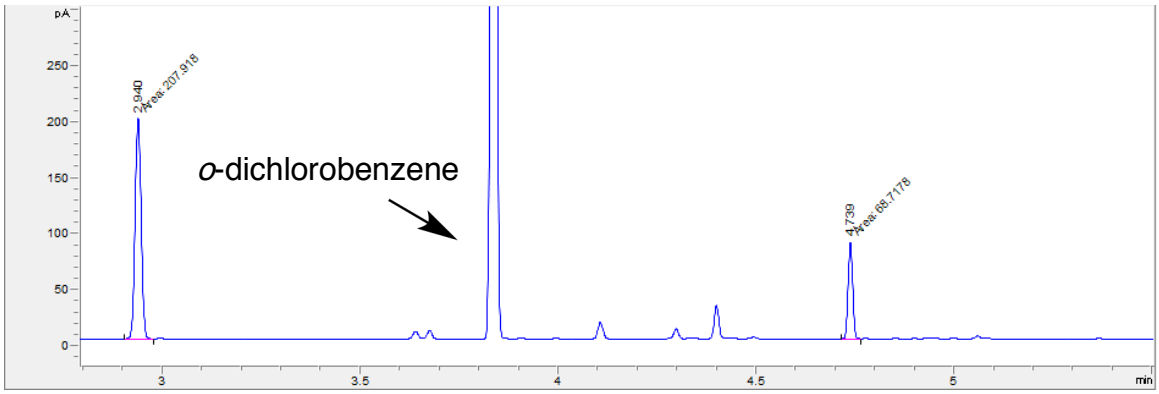


Figure 2.25. GC trace showing formation of 1-phenylpentane from **2.8** in 30% yield.

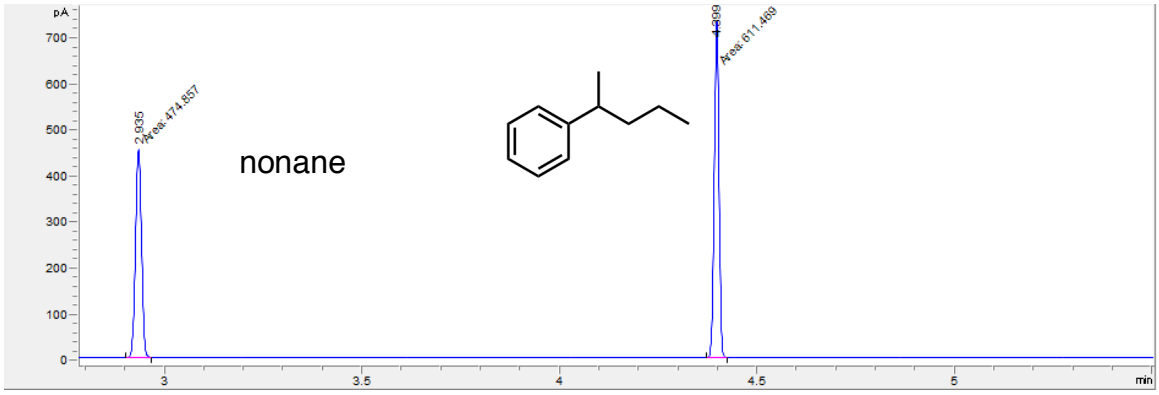


Figure 2.26. GC trace for internal standard nonane and 2-phenylpentane in 1:1 ratio.

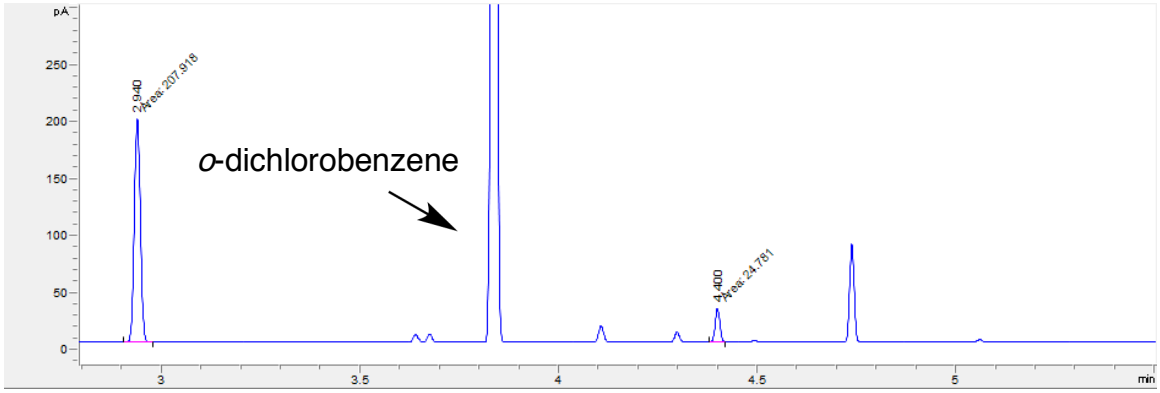


Figure 2.27. GC trace showing formation of 2-phenylpentane from **2.8** in 10% yield.

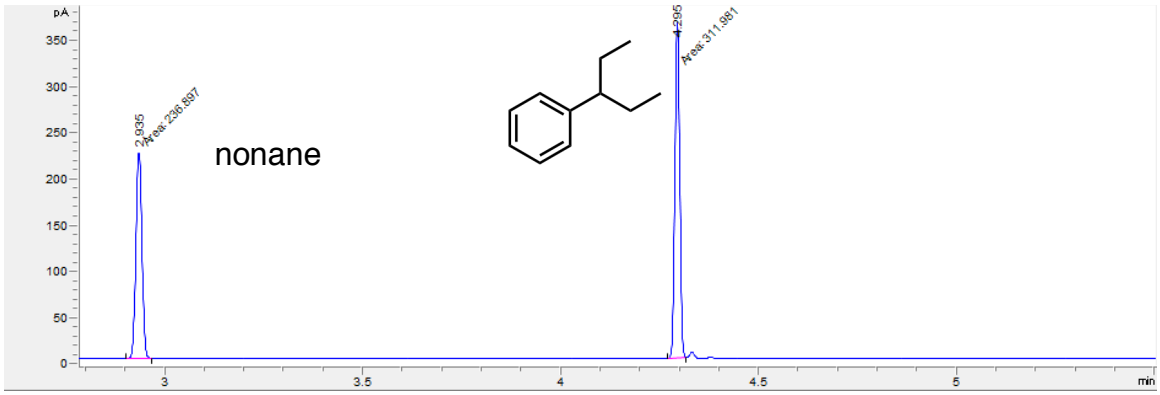


Figure 2.28. GC trace for internal standard nonane and 3-phenylpentane in 1:1 ratio.

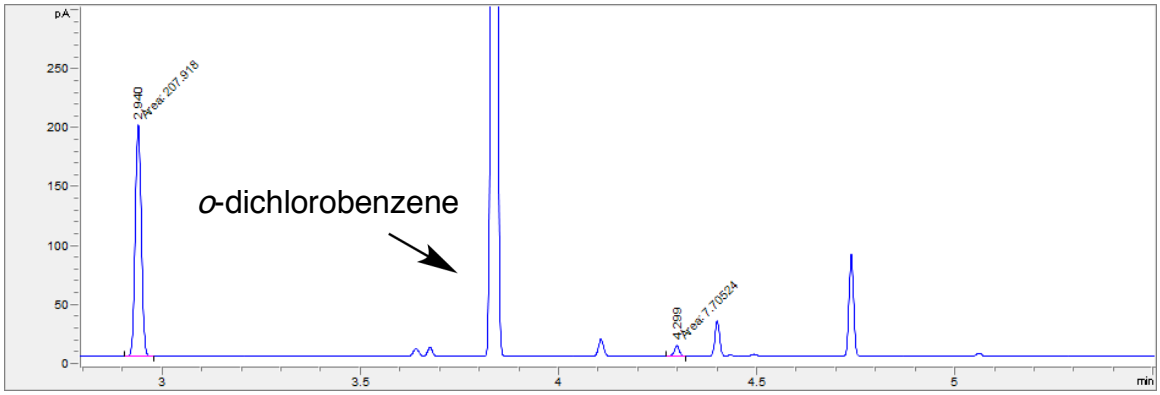
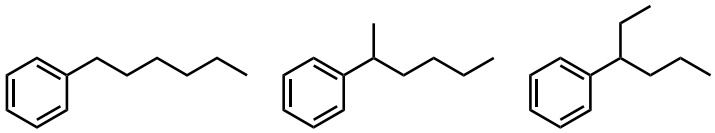


Figure 2.29. GC trace showing formation of 3-phenylpentane from **2.8** in 2% yield.



Phenylhexane isomers (Table 2.2, entry 5). Synthesized according to general procedure 2.8.4.2. Aryl fluoride **2.8** (0.054 mmol, 9.1 mg) was added to a solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.0 mg, 2.7 μmol, 0.05 equiv), triisopropylsilane (1.1 μL, 5.4 μmol, 0.1 equiv), *o*-dichlorobenzene (60 μL, 0.54 mmol, 10 equiv), and *n*-hexane (1 mL). Reaction was heated at 60 °C for 8 hours to give phenylhexane isomers in 40% overall yield (GC) as shown in Figs. 2.32, 2.34, and 2.36. Crude product was purified by flash column chromatography (hexanes) to give phenylhexane isomers as a colorless oil. The error associated with the 3-phenylhexane calibration curve was shown to be greater than the theoretical yield. Yield of 3-phenylhexane was then calculated by using 1-phenylhexane and 2-phenylhexane as reference, taking into account the integral ratio of 1 for all isomers shown in Fig. 2.30. Calculated yields were: 1-phenylhexane (26%) shown in Fig. 2.32, 2-phenylhexane (9%) shown in Fig. 2.34, 3-phenylhexane (5%) shown in Fig. 2.36. NMR Spectra match those reported in literature.[53, 54]

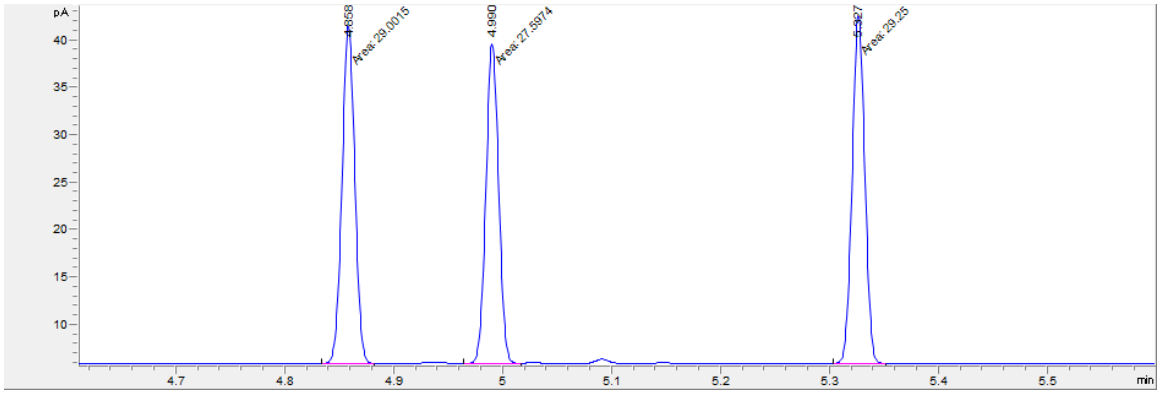


Figure 2.30. GC trace for a 1:1:1 ratio of phenylhexane isomers.

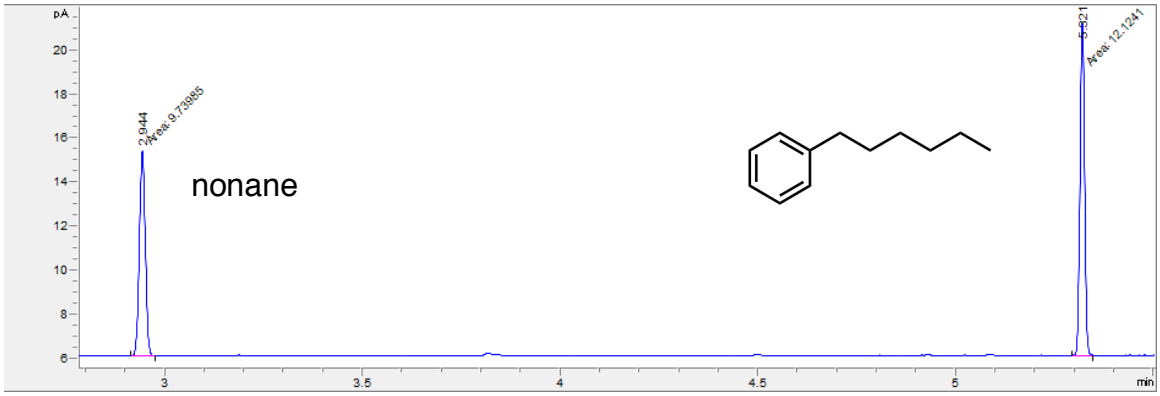


Figure 2.31. GC trace for internal standard nonane and 1-phenylhexane in 1:1 ratio.

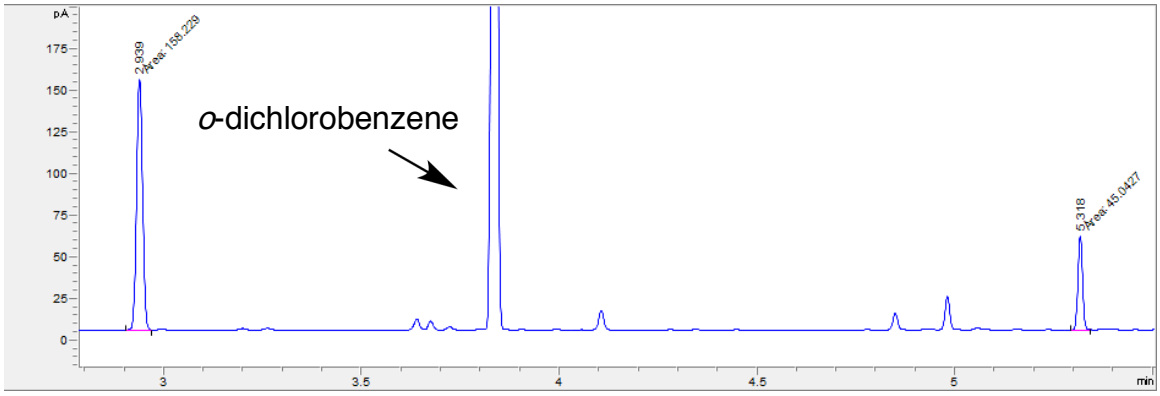


Figure 2.32. GC trace showing the formation of 1-phenylhexane from **2.8** in 26% yield.

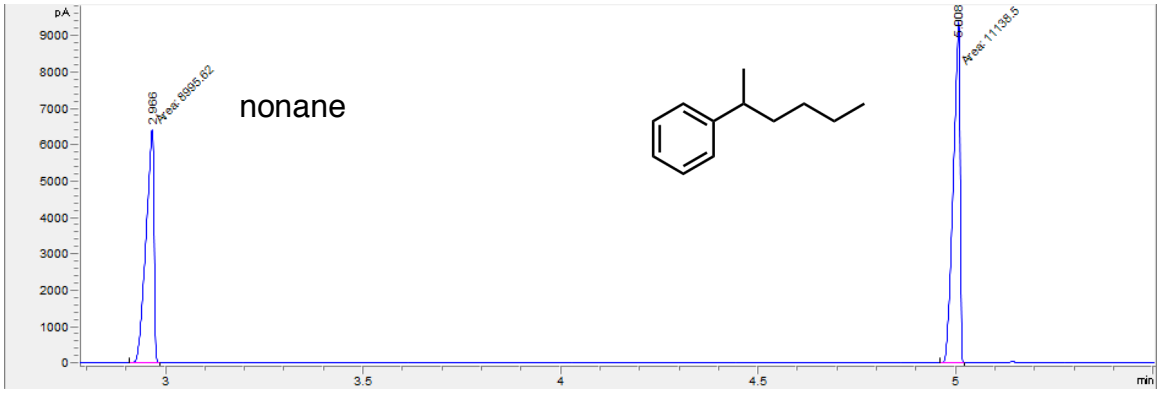


Figure 2.33. GC trace for internal standard nonane and 2-phenylhexane in 1:1 ratio.

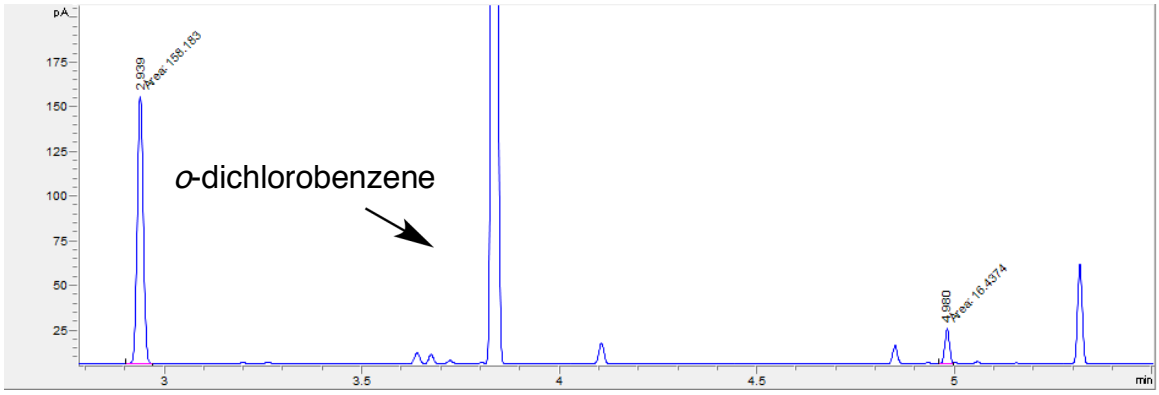


Figure 2.34. GC trace showing the formation of 2-phenylhexane from **2.8** in 9% yield.

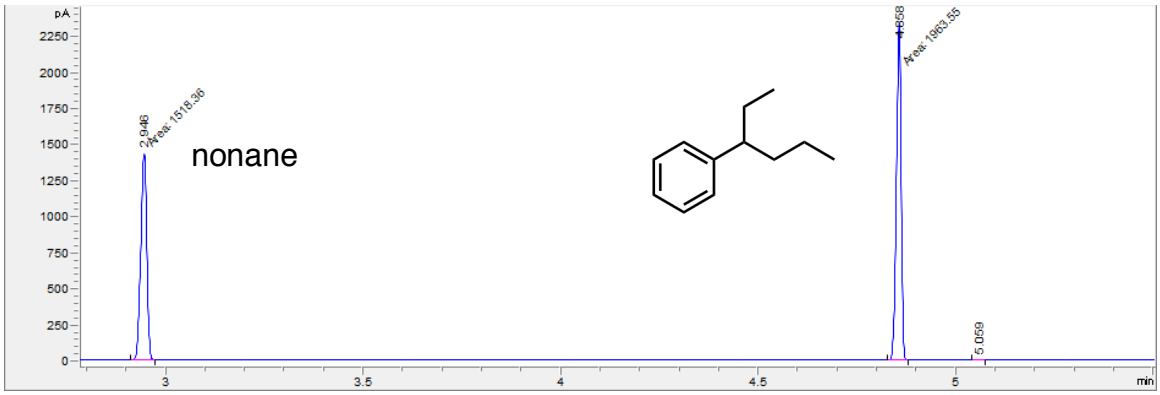


Figure 2.35. GC trace for internal standard nonane and 3-phenylhexane in 1:1 ratio.

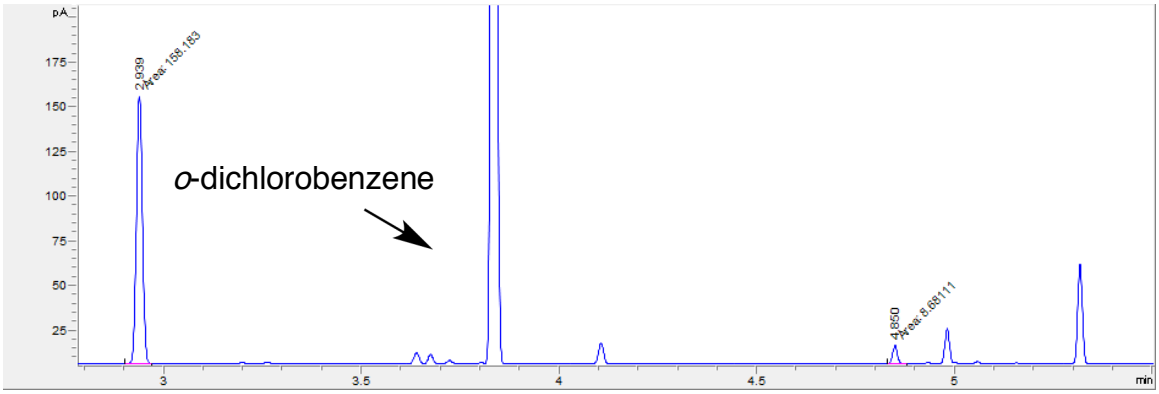


Figure 2.36. GC trace showing formation of 3-phenylhexane from **2.28**. The error associated with the 3-phenylhexane calibration curve was shown to be greater than the theoretical yield.

2.8.5 Methane Reaction

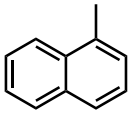
Described below is the general procedure for the catalytic arylation of methane.

2.8.5.1 Optimization Table for Methane Insertion Reaction

In our studies, we optimized our reaction conditions for catalyst and solvent. Below in Table 2.5, we summarize our key observations.

Catalyst (5 mol%)	Solvent	Silane (10 mol%)	Yield
$[Ph_3C][HCB_{11}Cl_{11}]$	*o*-$C_6H_4Cl_2$	iPr_3SiH	0%
$[Et_3Si][HCB_{11}Cl_{11}]$*	C_6F_6	none	32%
$[Ph_3C][HCB_{11}Cl_{11}]$	C_6H_5Cl	iPr_3SiH	0%
$[Ph_3C][HCB_{11}Cl_{11}]$	*o*-$C_6H_4F_2$	iPr_3SiH	0%
$[Ph_3C][HCB_{11}Cl_{11}]$	C_6F_6	iPr_3SiH	22%
$[Ph_3C][HCB_{11}Cl_{11}]$	C_6H_5F	iPr_3SiH	0%

Table 2.5. Optimization of (1-fluoronaphthalen-2-yl)trimethylsilane **2.29** for the insertion reaction with methane. * 3.6 mol% catalyst loading.



1-methylnaphthalene (2.28). Prior to the reaction, the reactor was purged with argon three times at room temperature and heated to 160 °C. After reaching 160 °C, the reactor was purged with argon three times and heated at this temperature for 12 hours. The vessel was then cooled to 25 °C and purged with argon three times.

Inside a glovebox, $[Et_3Si]^+[HCB_{11}Cl_{11}]^-$ (2.5 mg, 3.92 μmol, 0.036 equiv) was dissolved in *o*-dichlorobenzene (0.12 mL, 1.08 mmol, 10 equiv). Hexafluorobenzene (1 mL), followed by aryl fluoride **2.27** (23.6 mg, 0.108 mmol, 1 equiv), were added respectively to give a 0.1 M suspension. The reaction was sealed and brought out to assemble in the reactor. Pressure vessel was assembled under a stream of argon as fast as possible to avoid exposure to air (<1 minute). Once sealed, the vessel was purged with argon three times, flushed with methane, then purged with methane three times. The reactor was then pressurized with methane to 35 bar and heated to 60 °C for 24 hours. After cooling to room temperature, the reaction mixture was diluted in hexanes, concentrated by rotary evaporation and purified by flash column chromatography (pentane) to give **2.28** as a colorless oil (4.9 mg, 32%). NMR Spectra match those reported in literature.[55]

Low yields are attributed to protodesilylation of **2.27** during the reaction as shown in Fig. S50. This is likely due to adventitious water introduced upon assembly of the reactor.

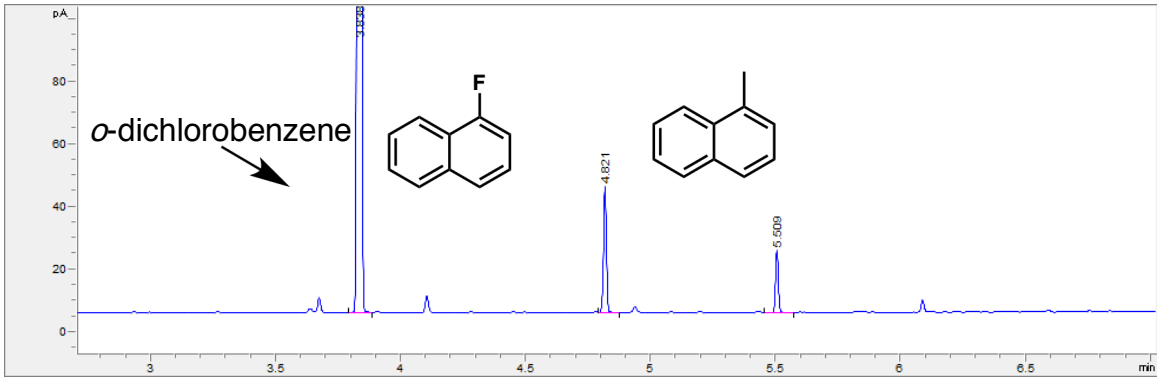


Figure 2.37. GC trace for crude methane insertion reaction showing both **2.30** and the major byproduct 1-fluoronaphthalene.

2.8.6 Mechanistic Studies

Described below is an outline of the mechanistic studies undertaken.

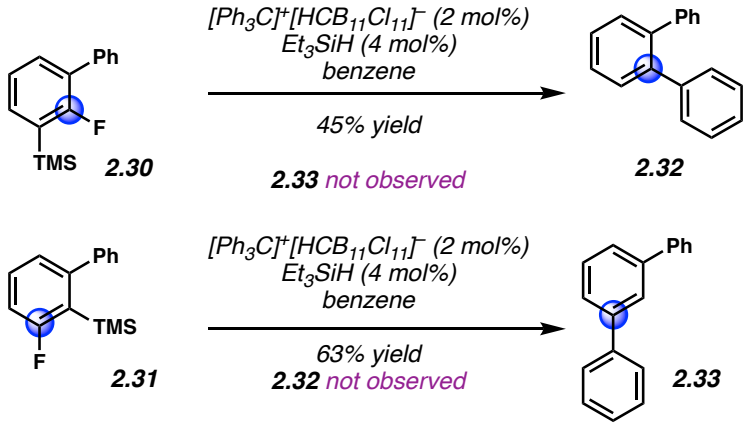
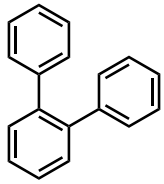


Figure 2.38. Mechanistic studies using **2.30** and **2.31**.



***o*-terphenyl (2.32). 2.32** was synthesized according to general procedure 2.8.3.4. **2.30** (13.2 mg, 0.054 mmol, 1 equiv) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 µmol, 0.02 equiv) and triethylsilane (2.2 µmol, 0.04 equiv), and was stirred at 70 °C for 36 hours to give

2.32 in 45% yield (GC) as shown in Figure 2.40. Crude product was purified by flash column chromatography (hexanes) to give **2.32** as a white solid (4.4 mg, 35%). NMR Spectra match those reported in literature.[56]

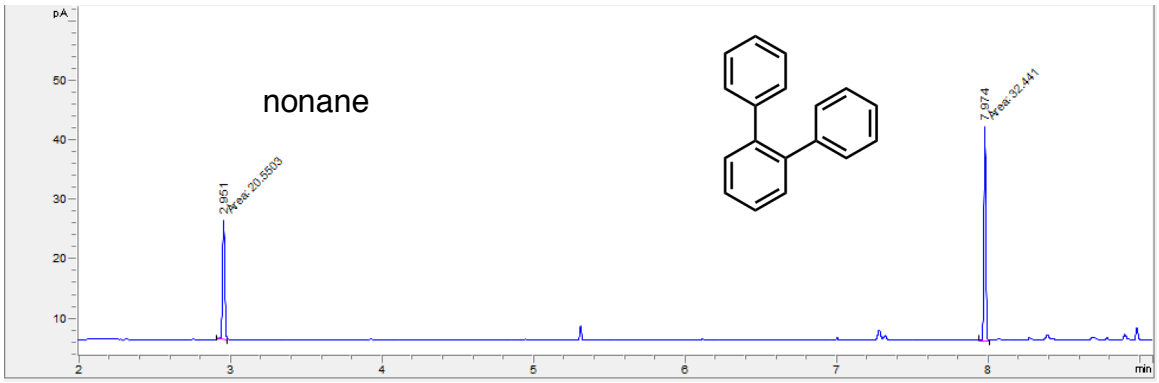


Figure 2.39. GC trace for internal standard nonane and **2.32** in 1:1 ratio.

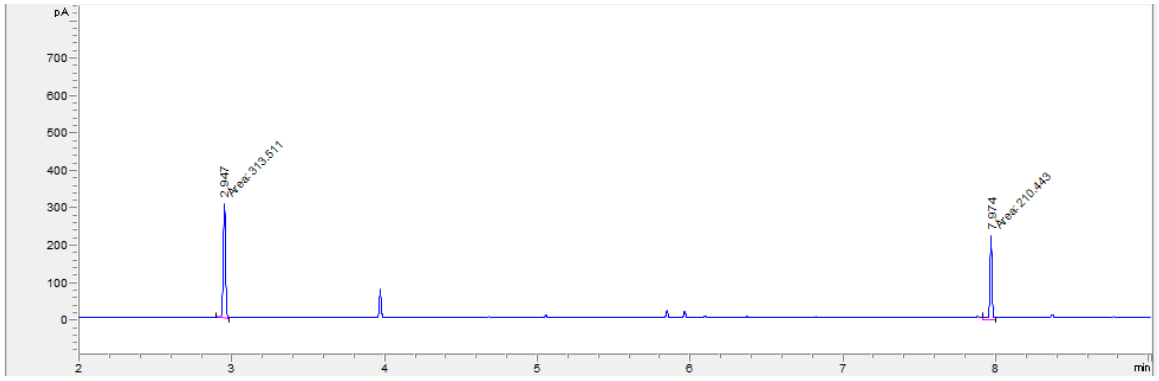
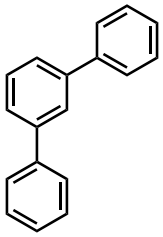


Figure 2.40. GC trace showing formation of **2.32** from **2.30** in 45% yield.



***m*-terphenyl (2.33). 2.33** was synthesized according to general procedure 2.8.3.4. **2.31** (13.2 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 µmol, 0.02 equiv)

and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 30 °C for 1 hour to give **2.33** in 63% yield (GC) as shown in Fig. 2.42. Crude product was purified by flash column chromatography (hexanes) to give **2.33** as a white solid (7.0 mg, 56%). NMR Spectra match those reported in literature.[57]

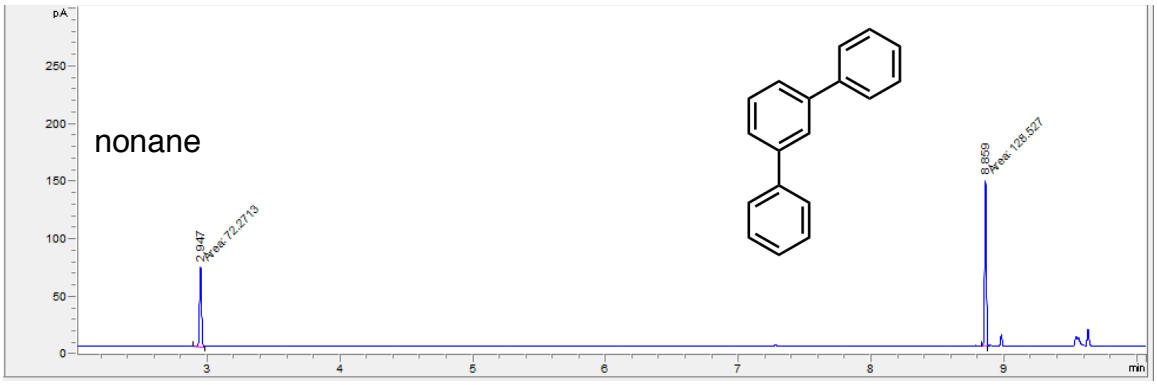


Figure 2.41. GC trace for internal standard nonane and **2.33** in 1:1 ratio.

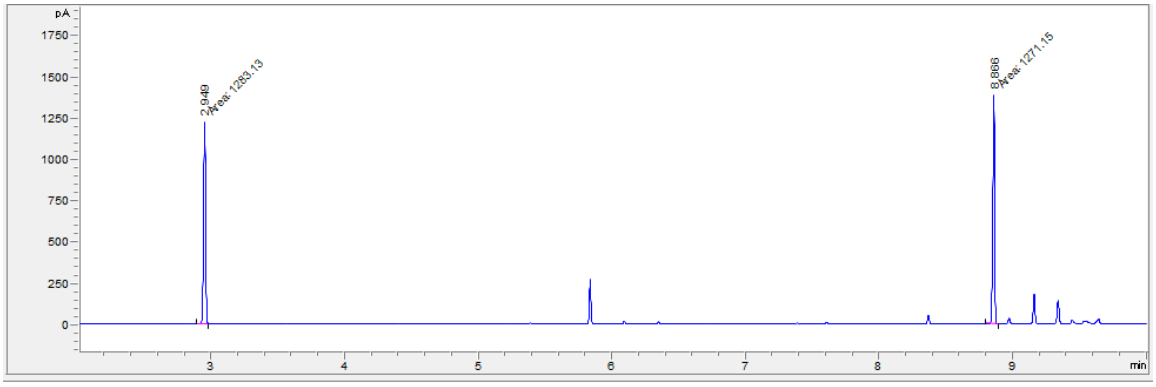


Figure 2.42. GC trace showing formation of **2.33** from **2.31** in 63% yield.

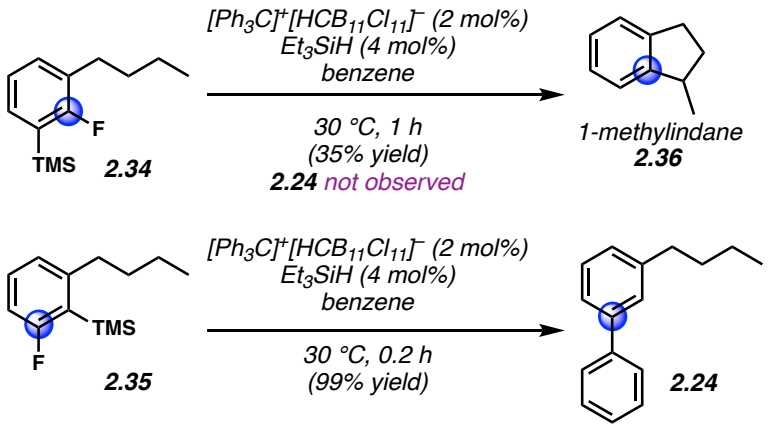
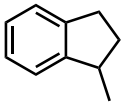


Figure 2.43. Mechanistic studies using **2.34** and **2.35**.



1-methylindane (2.36). $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (4 mg, 5 µmol, 0.04 equiv) and triethylsilane (1.8 µL, 11 µmol, 0.09 equiv) were dissolved in fluorobenzene (1 mL) to give a colorless solution before addition of aryl fluoride **2.34** (27.5 mg, 0.12 mmol, 1 equiv). Reaction was stirred at 30 °C for 2 hours to give **2.36** in 43% yield (GC) as shown in Fig. S26. After volatiles were rotary evaporated, the crude product was purified by flash column chromatography (pentane) to give **2.36** as a colorless oil (5.8 mg, 36%). NMR Spectra match those reported in literature.[58]

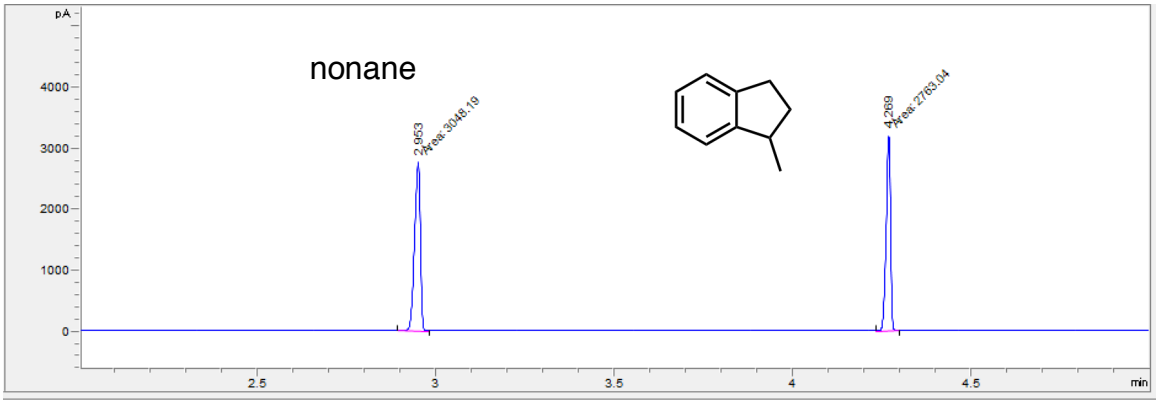


Figure 2.44. GC trace for internal standard nonane and **2.36** in 1:1 ratio.

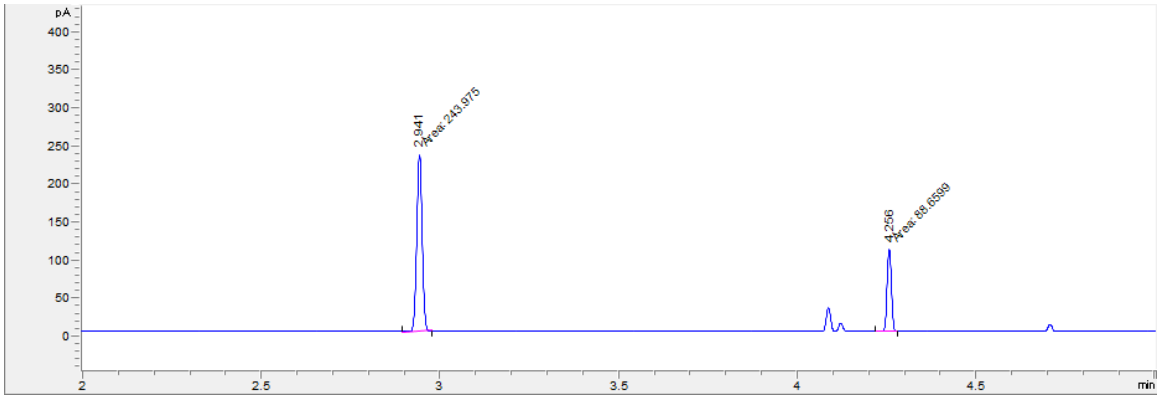
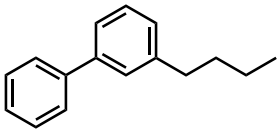


Figure 2.45. GC trace showing formation of **2.36** from **2.34** in 43% yield.



3-butylbiphenyl (2.24). 2.24 was synthesized according to general procedure 2.8.3.4. **2.35** (12.1 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 30 °C for 0.2 hours to give **2.24** in 99% yield (NMR). Crude product was purified by flash column chromatography (hexanes) to give **2.24** as a colorless oil (10.6 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.60 (m, 2H), 7.51–7.41 (m, 4H), 7.38 (td, J = 7.4, 5.2 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 2.72 (t, J = 7.7 Hz, 2H), 1.74–1.65 (m, 2H), 1.49–1.38 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 141.5, 141.2, 128.7, 128.6, 127.4, 127.3, 127.2, 127.1, 124.5, 35.8, 33.7, 22.4, 14.0.

FTIR (Neat Film NaCl): 3059, 3029 2956, 2928, 2857, 1889, 1873, 1799, 1600, 1479, 754, 697 cm^{-1}.

HR-MS (GC-CI): Calculated for $C_{16}H_{18}$: 210.1409; measured: 210.1404.

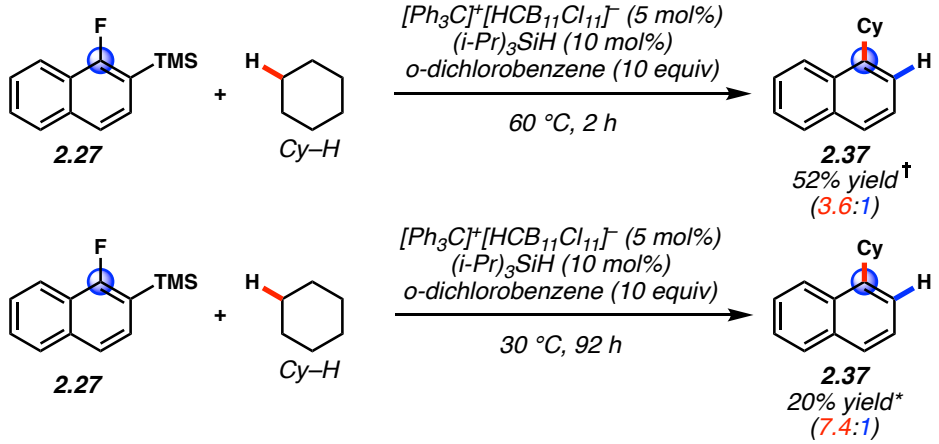
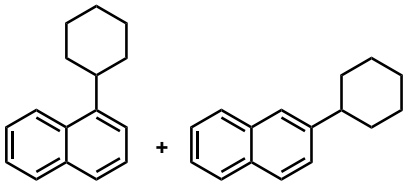


Figure 2.46. Mechanistic studies using **2.27** in intermolecular C–H insertion.



1-Cyclohexylnapthalene and **2-Cyclohexylnaphthalene** (**2.37** and **2.37.1**) **2.37** and **2.37.1** were synthesized according to general procedure 2.8.3.2. **2.27** (12.1 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 60 °C for 2 hours to give **2.37** and **2.37.1** in 52% yield (NMR). Diagnostic peaks were identified according to NMR spectra reported in literature.[59, 60]

Similarly, **2.37** and **2.37.1** were synthesized according to general procedure 2.8.3.2. **2.27** (12.1 mg, 0.054 mmol) was added to a colorless solution of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.1 μmol, 0.02 equiv) and triethylsilane (2.2 μmol, 0.04 equiv), and was stirred at 30 °C for 92 hours to give **2.37** and **2.37.1** in 20% yield (GC).

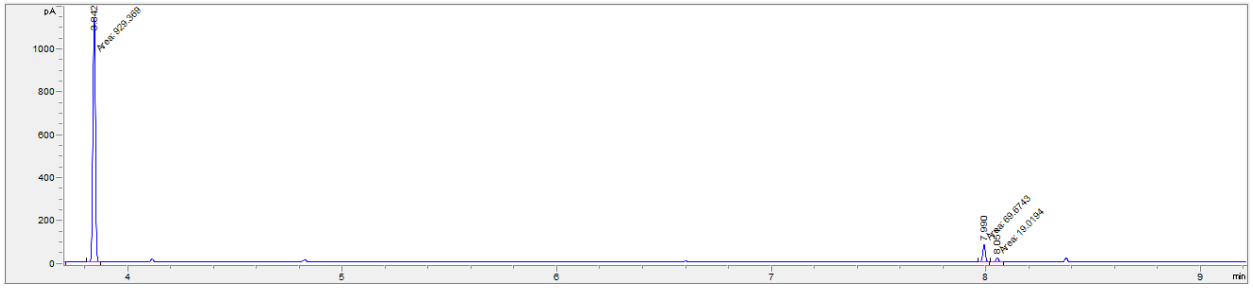


Figure 2.47. GC trace of reaction at 60 °C showing formation of **2.37** from **2.37.1** in 52% yield.

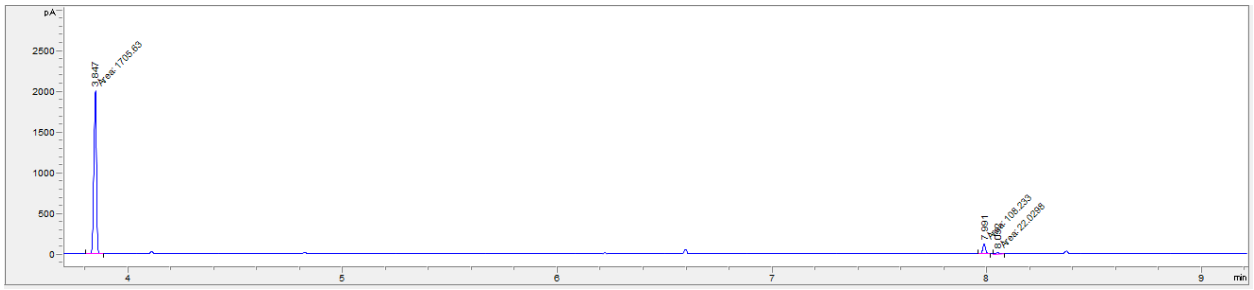


Figure 2.48. GC trace of reaction at 30 °C showing formation of **2.37** from **2.37.1** in 20% yield.

2.9 Alternative Reactive Intermediates

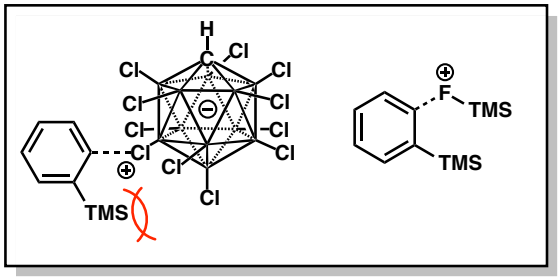


Figure 2.49. Halonium salts as alternatives to **2.9**.

2.10 Spectra Relevant to Chapter Two:

Arylation of Hydrocarbons Enabled by Organosilicon Reagents and Weakly Coordinating Anions

Adapted from: Brian Shao[†], Alex L. Bagdasarian[†], Stasik Popov, and Hosea M. Nelson

Science, **2017**, *355*, 1403–1407.

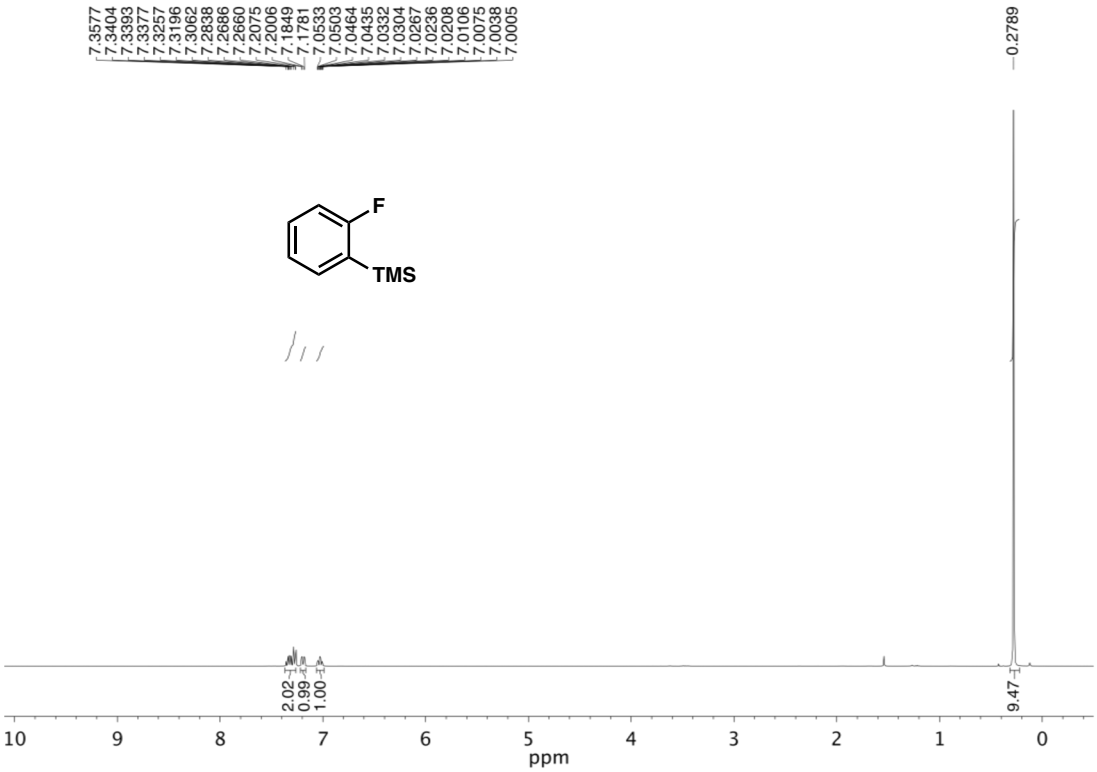


Figure 2.50. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.8**.

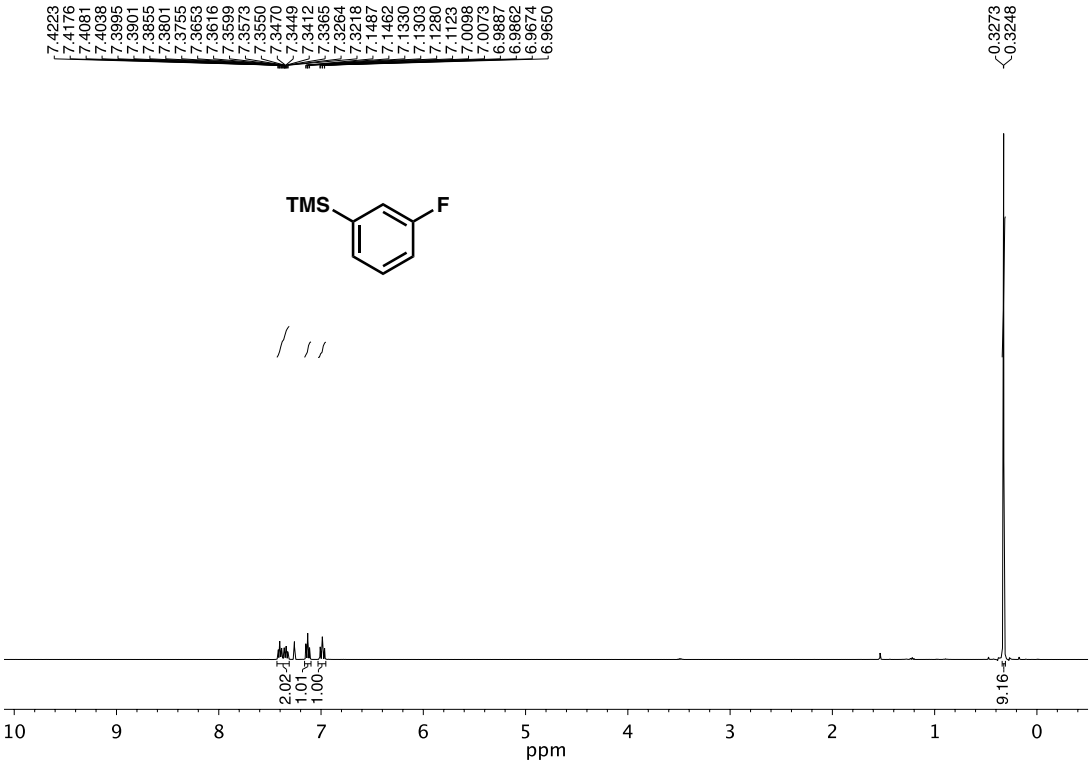


Figure 2.51. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.15**.

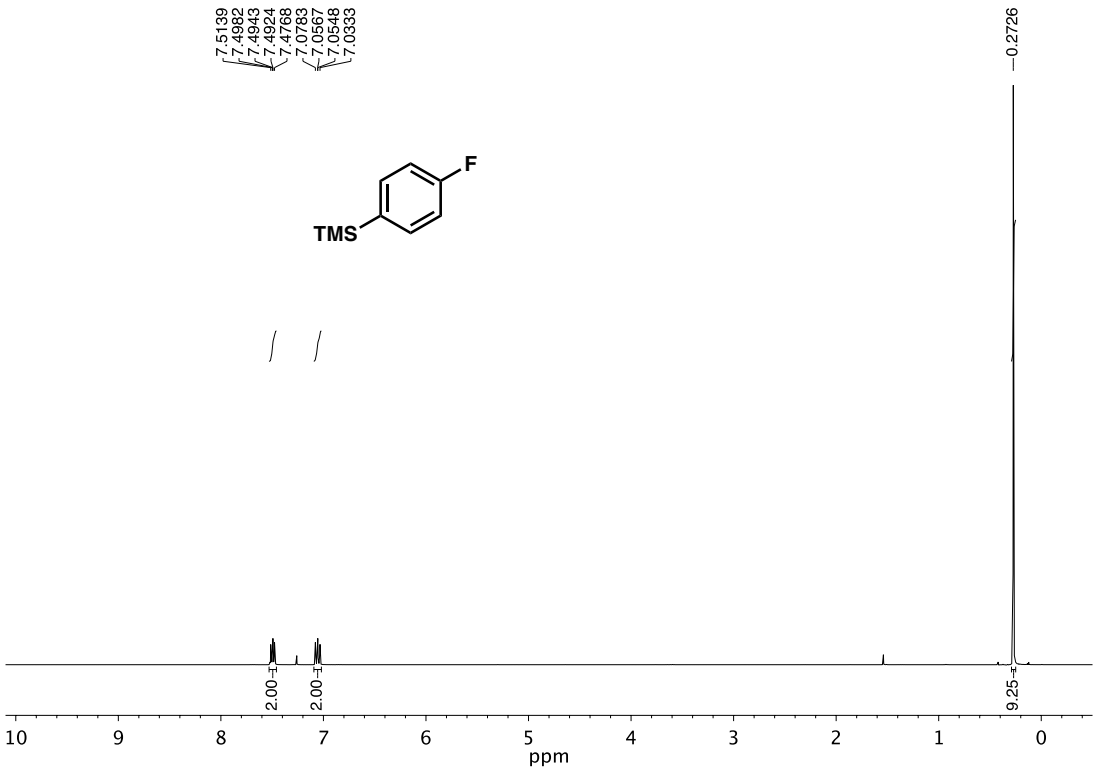


Figure 2.52. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.16**.

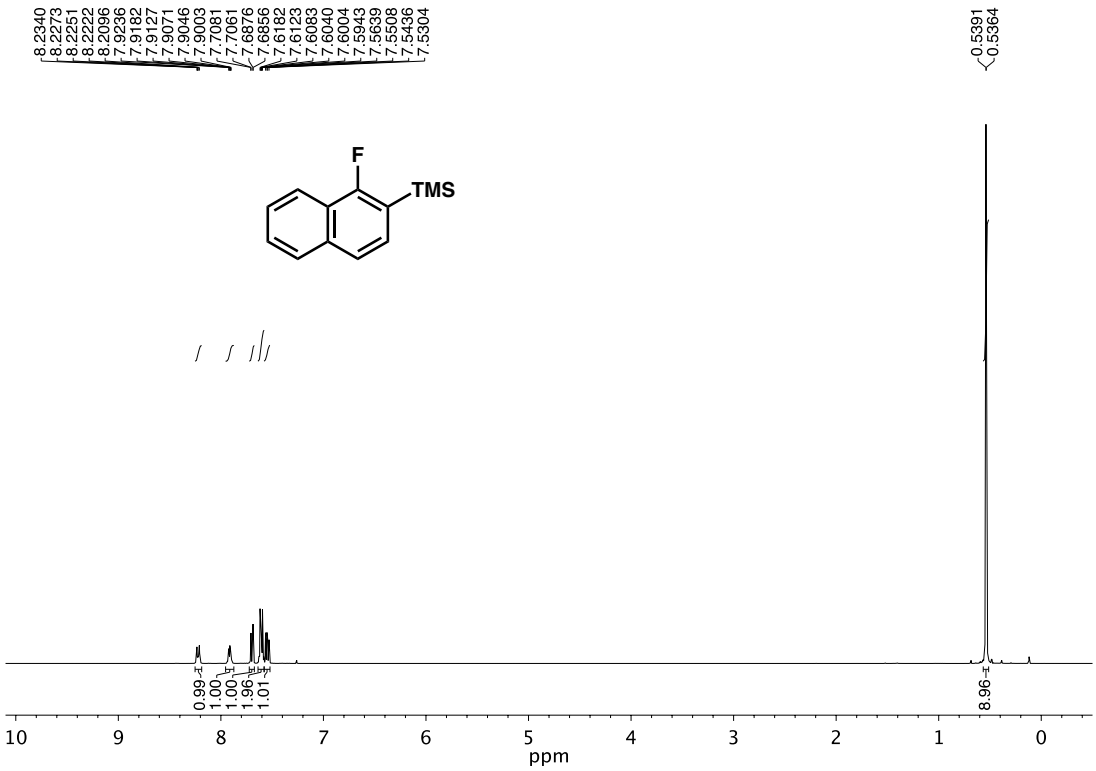


Figure 2.53 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.27**.

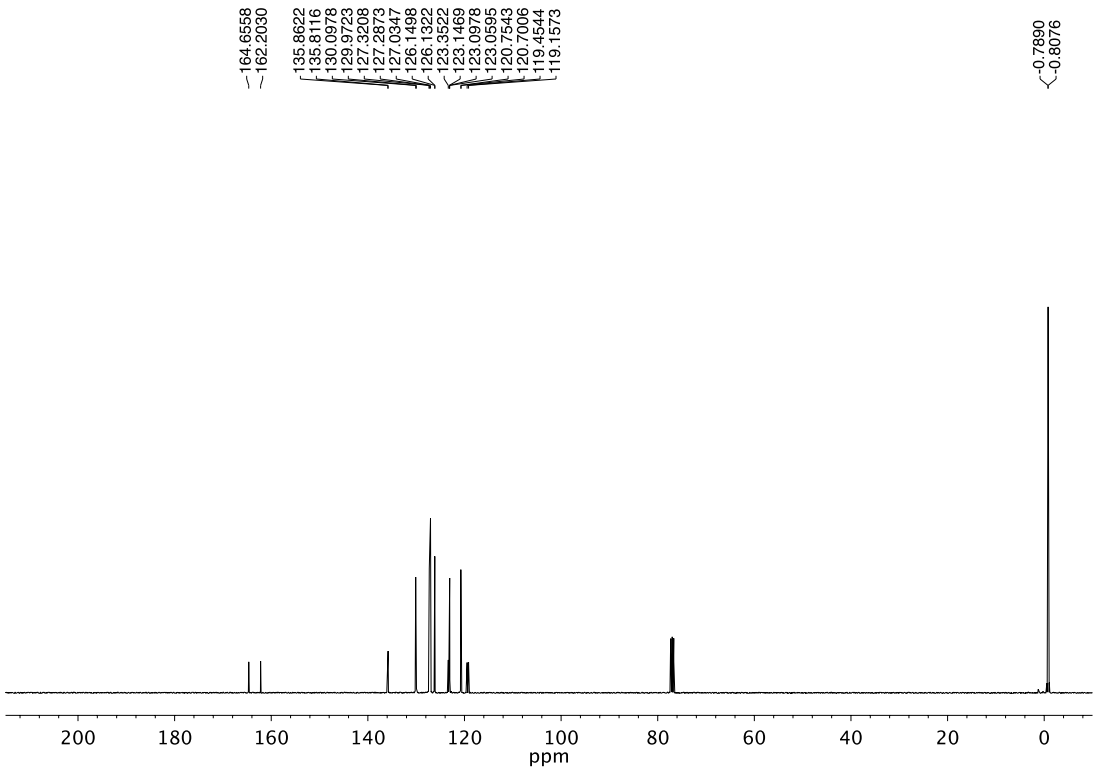


Figure 2.54. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.27**.

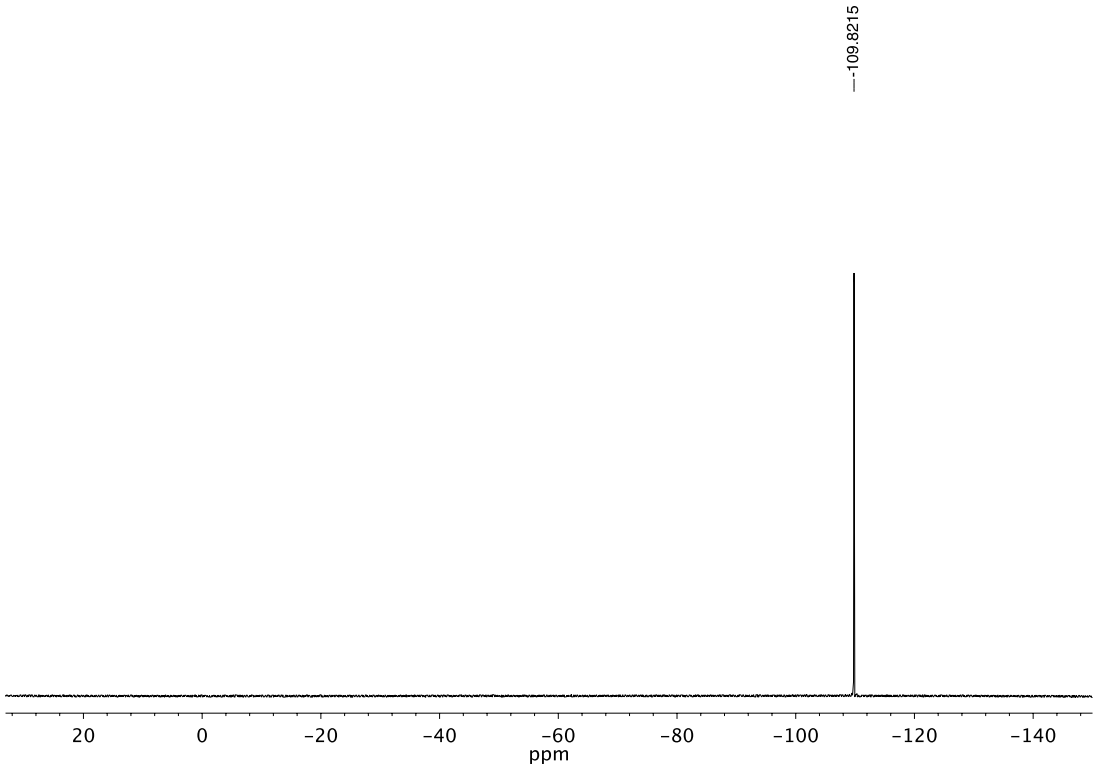


Figure 2.55. ^{19}F NMR (376 MHz, $CDCl_3$) of compound **2.27**.

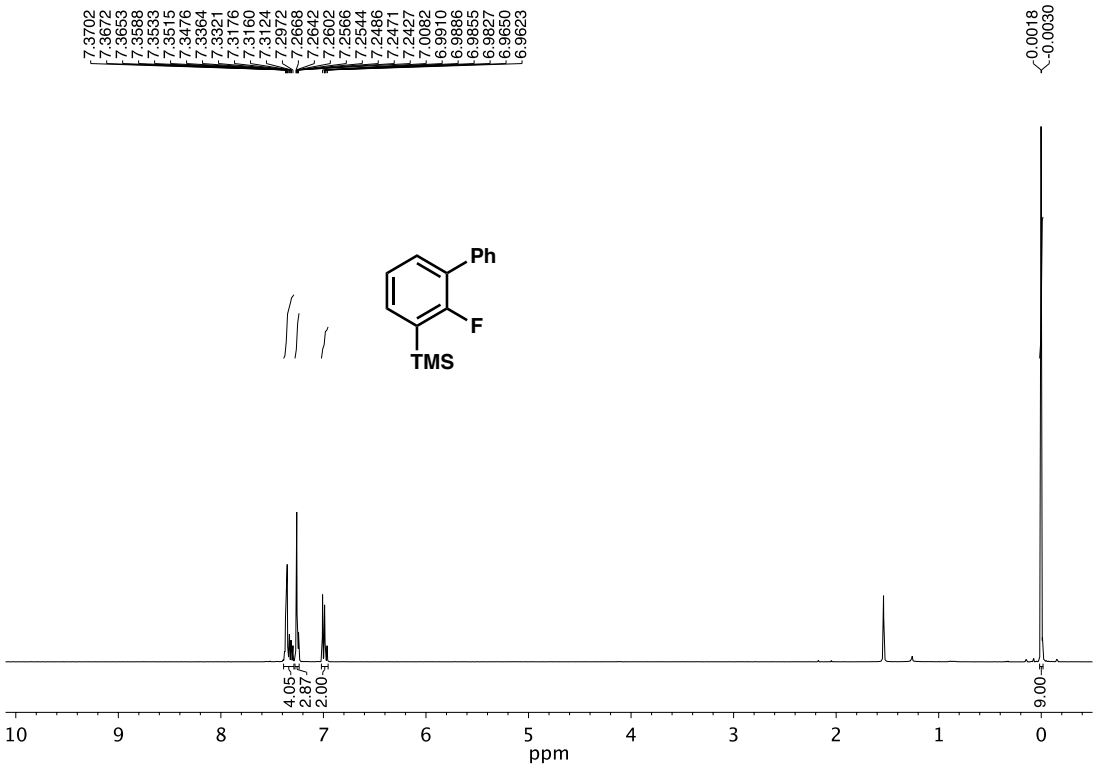


Figure 2.56. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.30**.

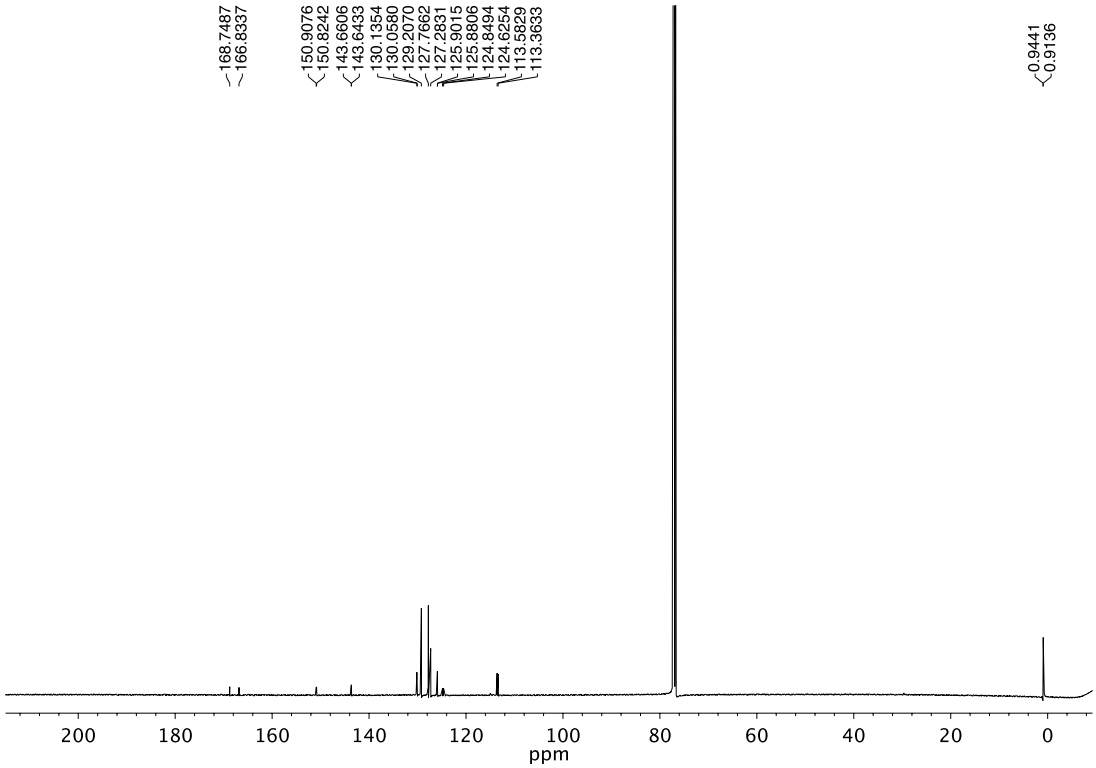


Figure 2.57. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.30**.

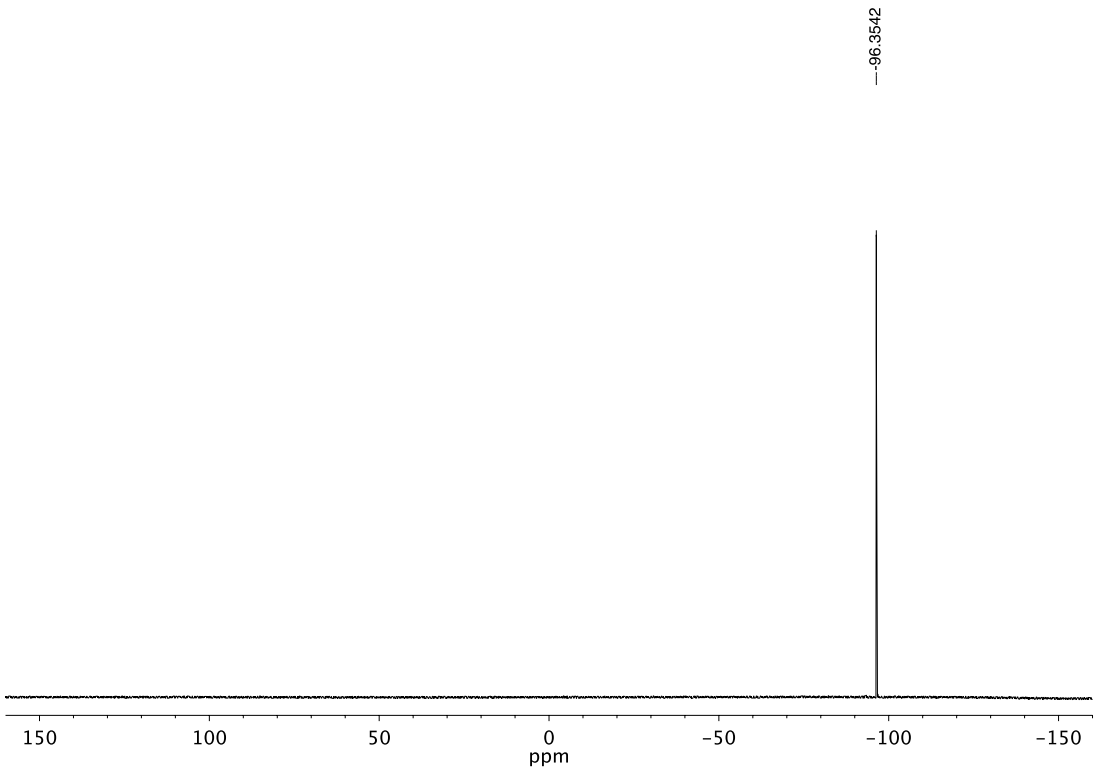


Figure 2.58. ^{19}F NMR (376 MHz, $CDCl_3$) of compound **2.30**.

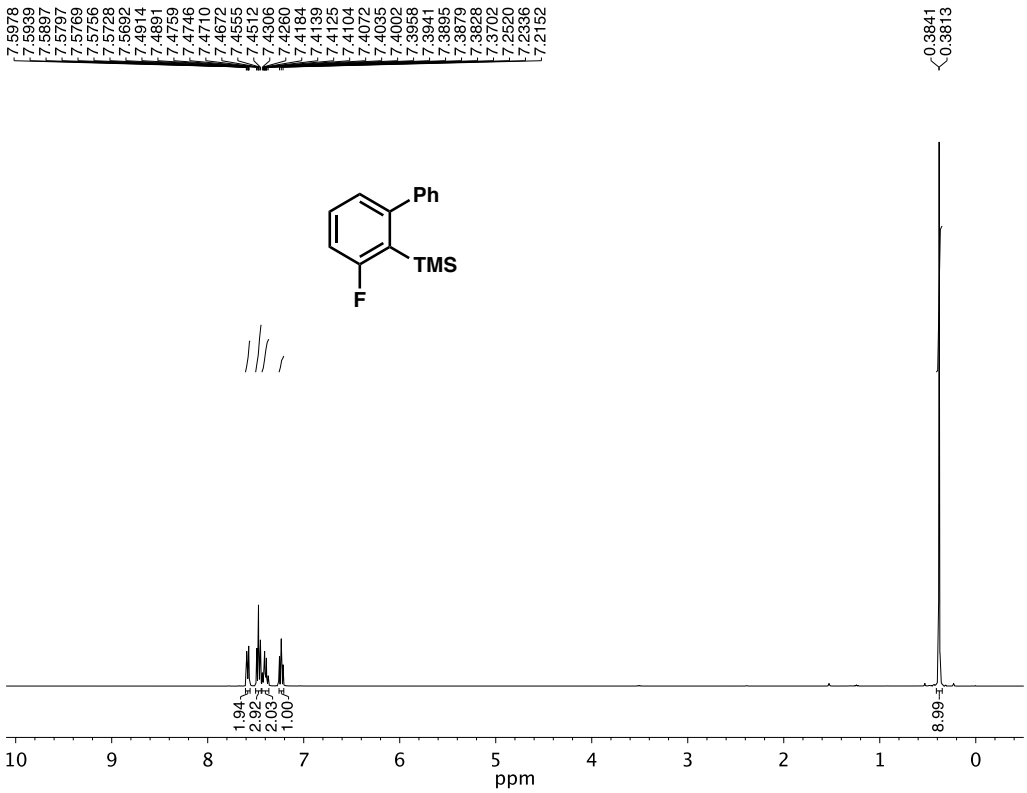


Figure 2.59. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.31**.

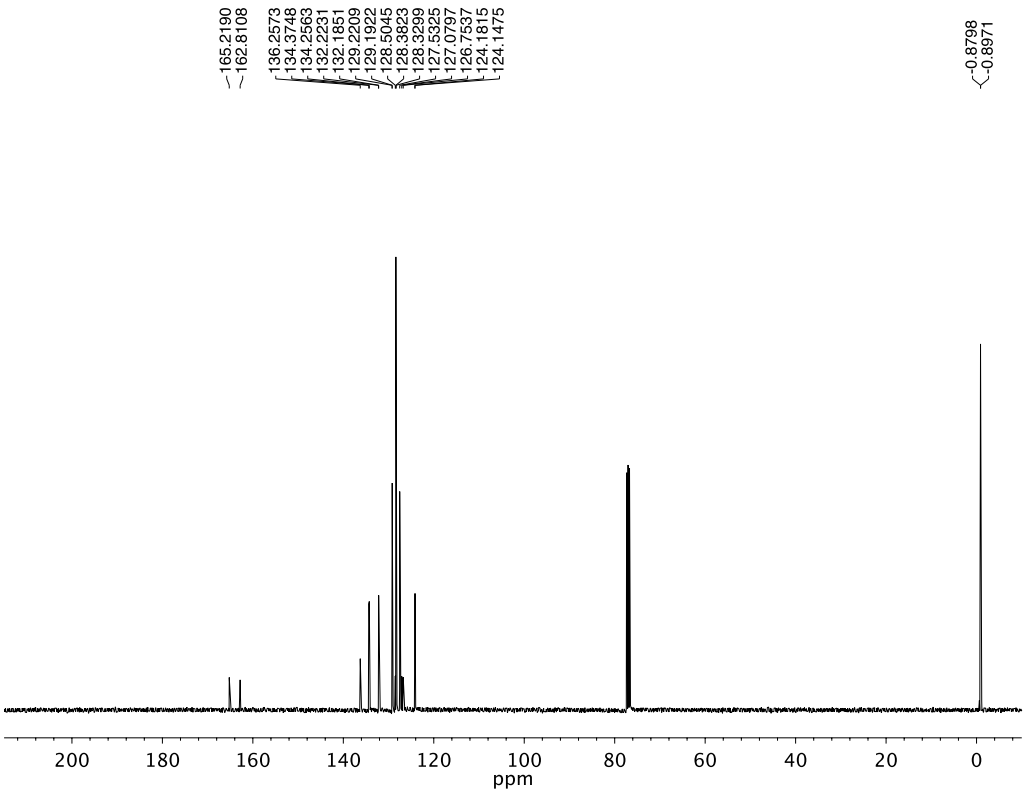


Figure 2.60. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.31**.

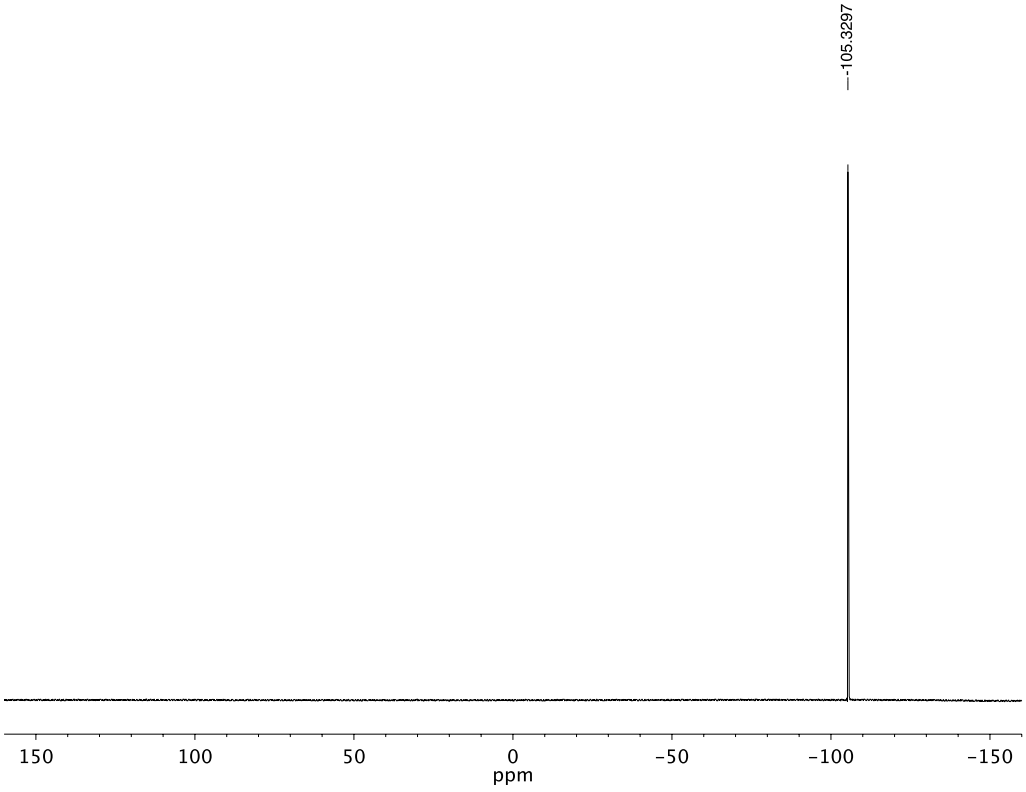


Figure 2.61. ^{19}F NMR (376 MHz, $CDCl_3$) of compound **2.31**.

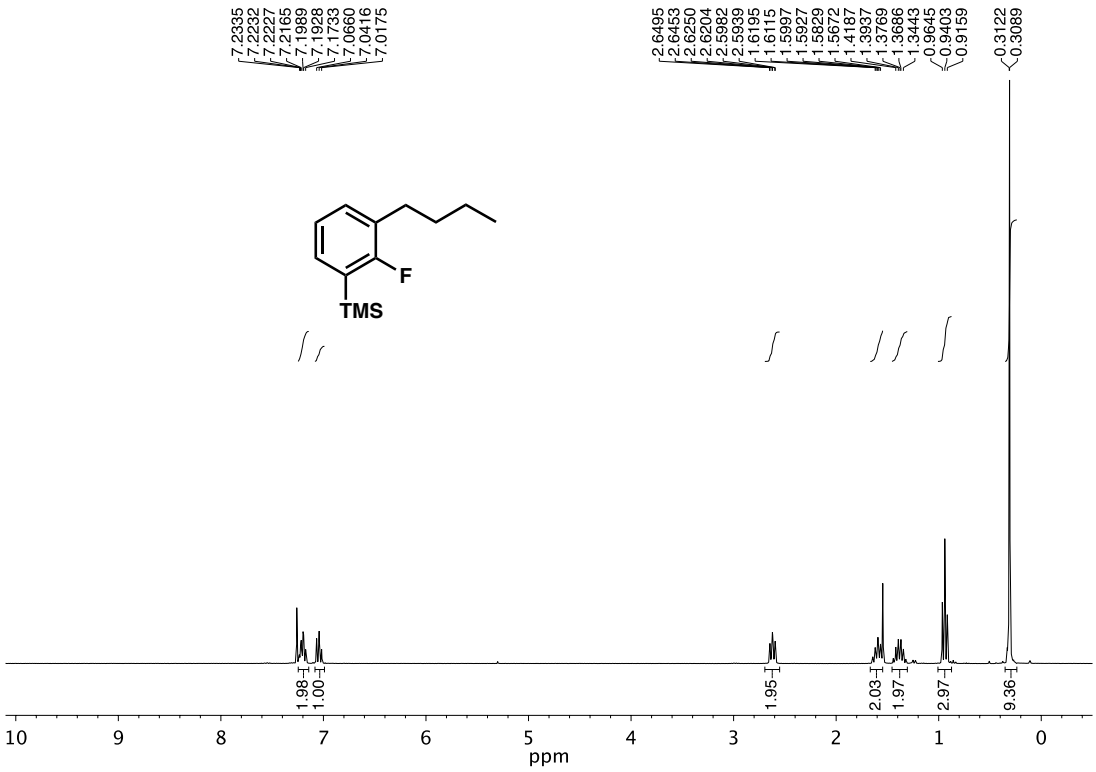


Figure 2.62. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.34**.

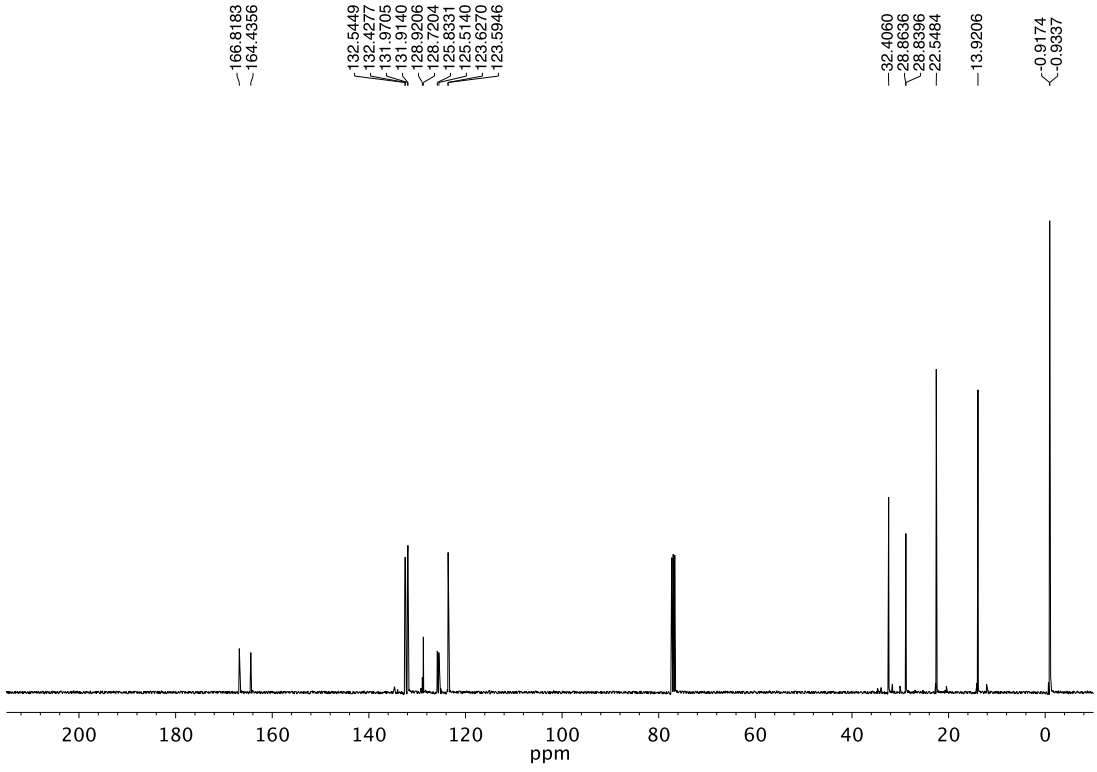


Figure 2.63. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.34**.

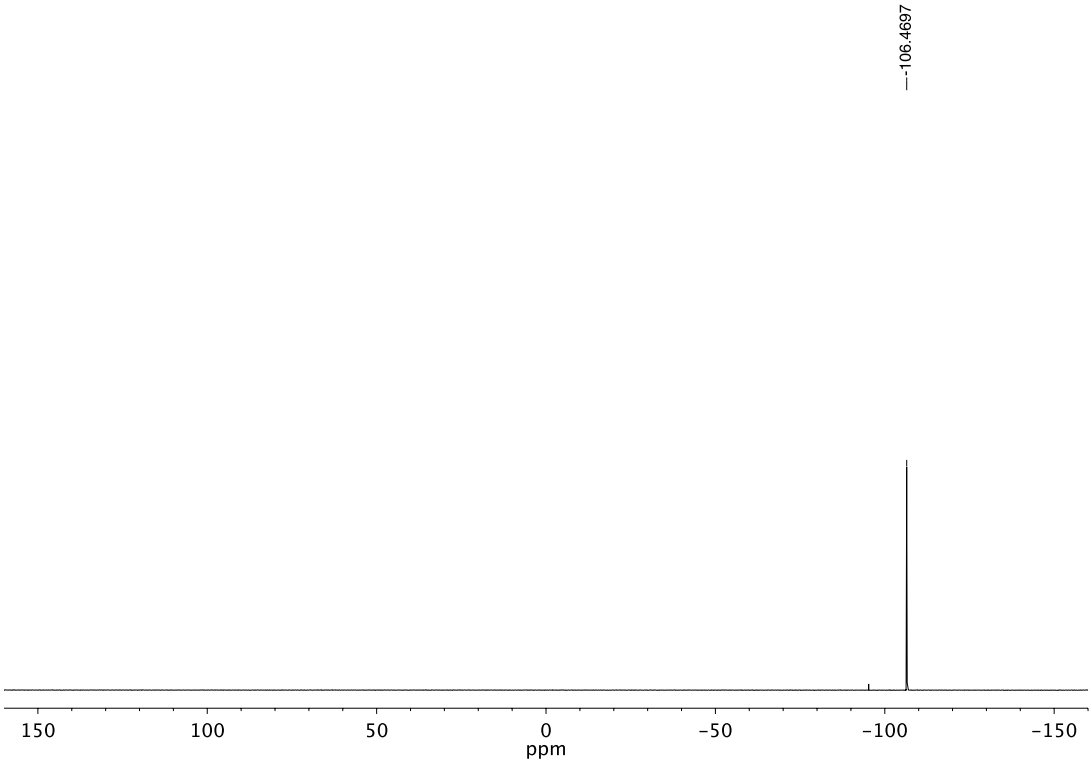


Figure 2.64. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **2.34**.

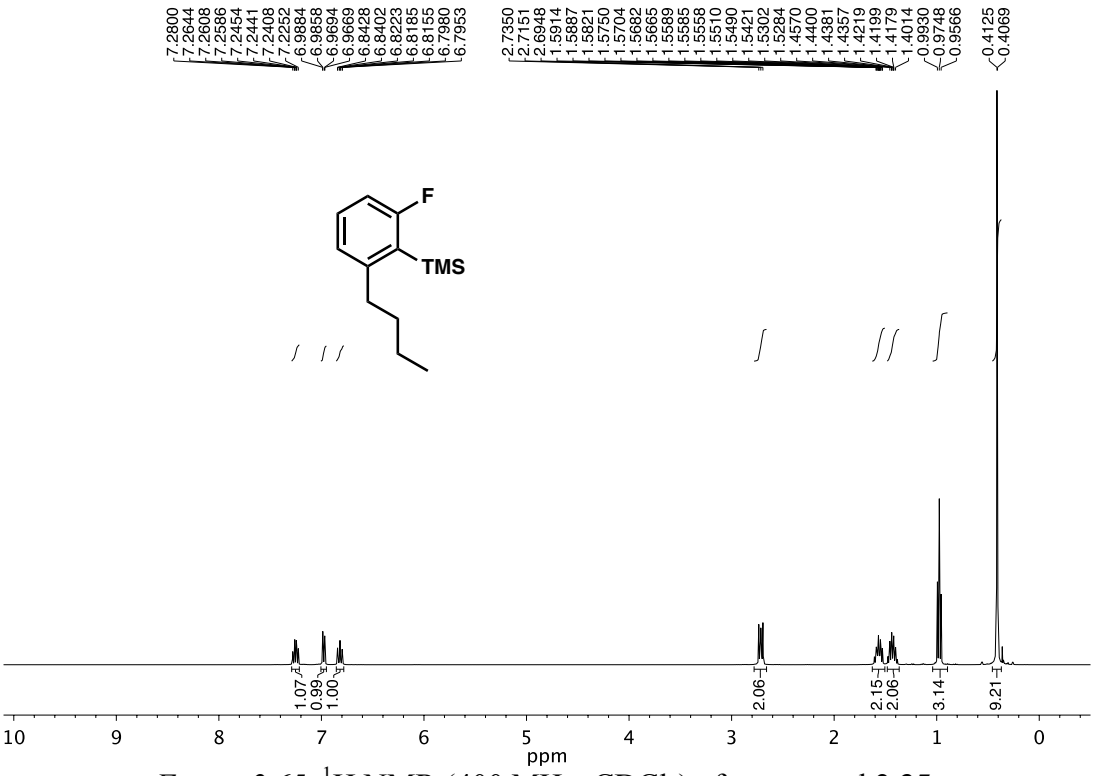


Figure 2.65. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.35**.

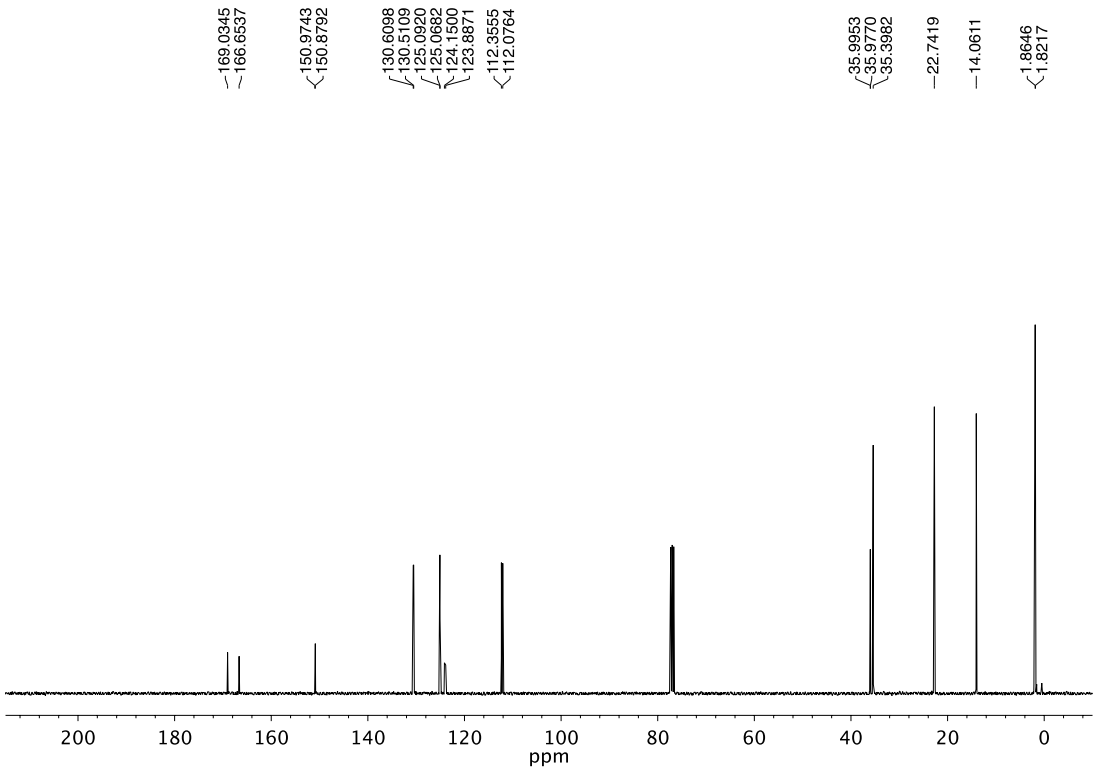


Figure 2.66. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.35**.

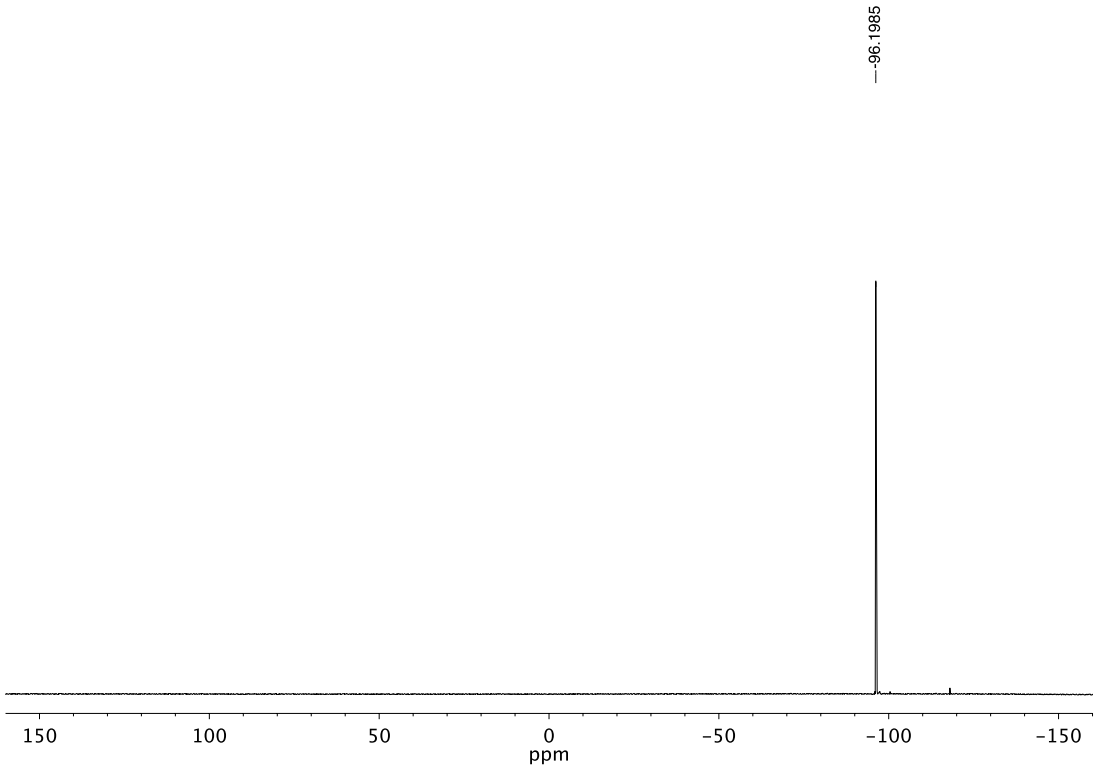


Figure 2.67. ^{19}F NMR (376 MHz, $CDCl_3$) of compound **2.35**.

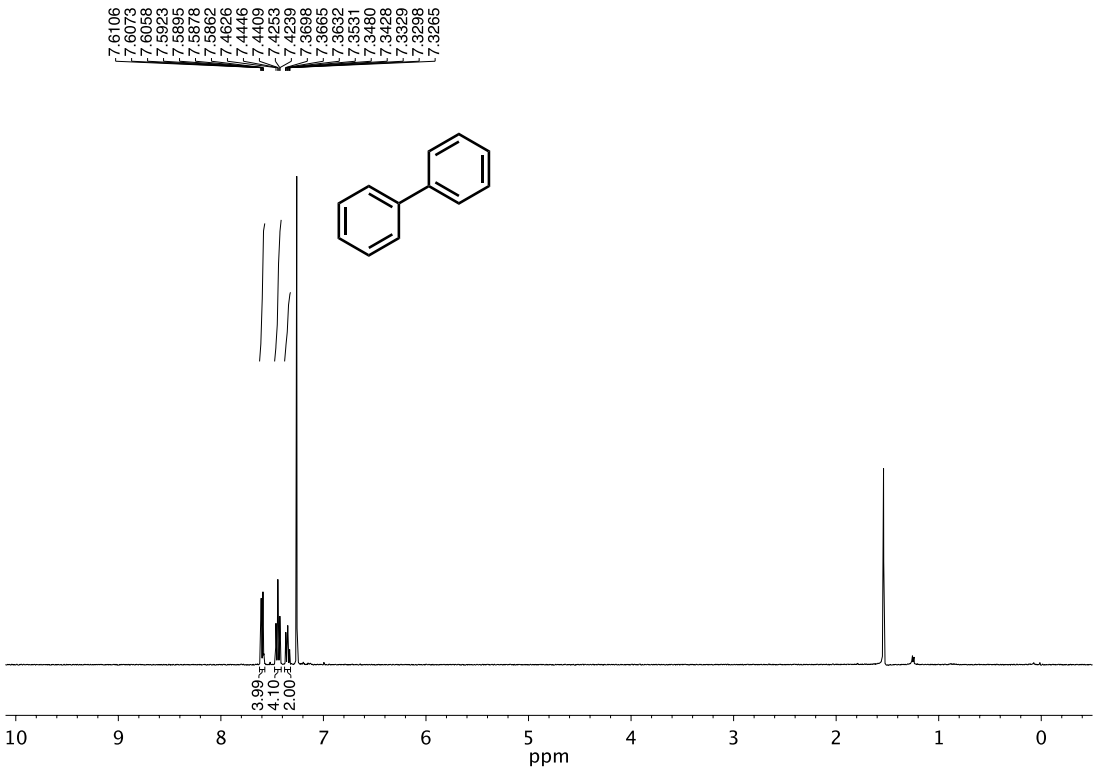


Figure 2.68. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.13**.

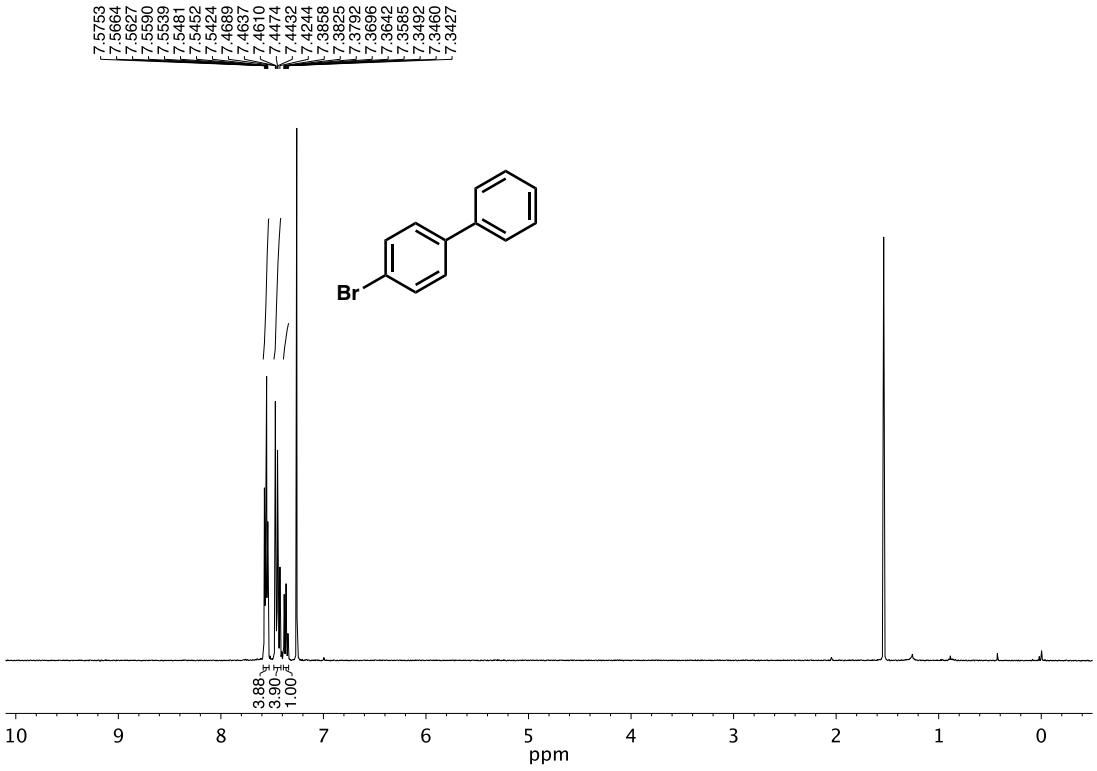


Figure 2.69. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.17**.

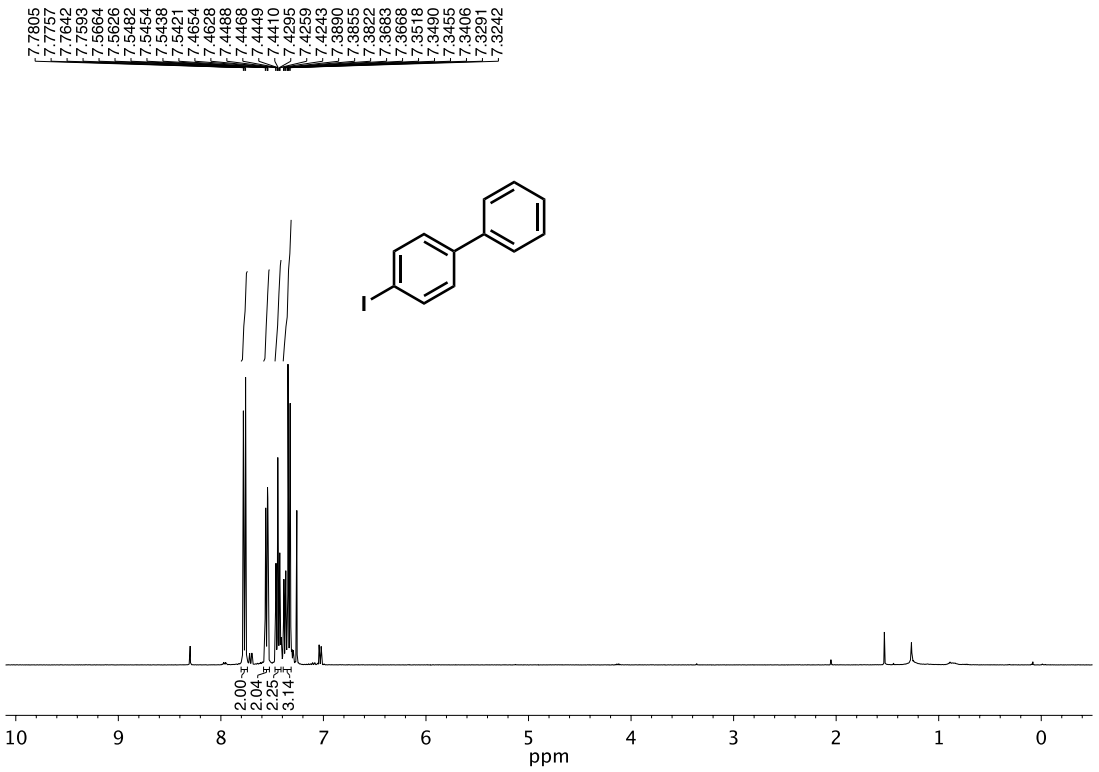


Figure 2.70. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.18**.

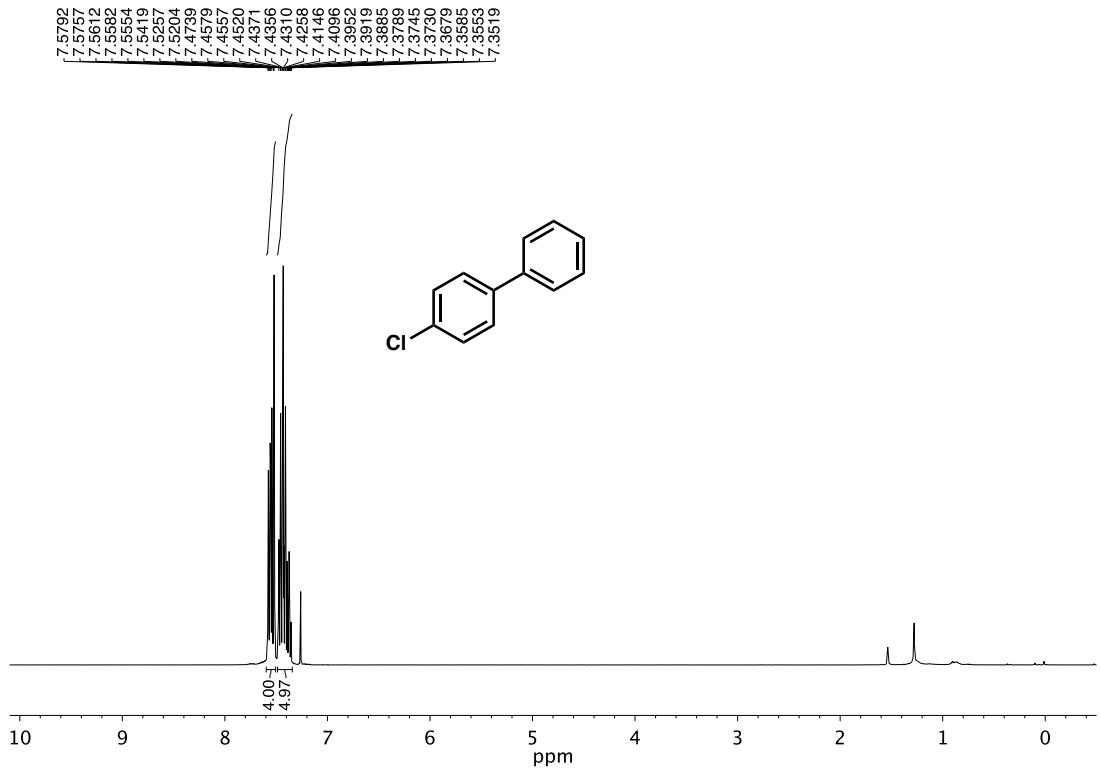


Figure 2.71. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.19**.

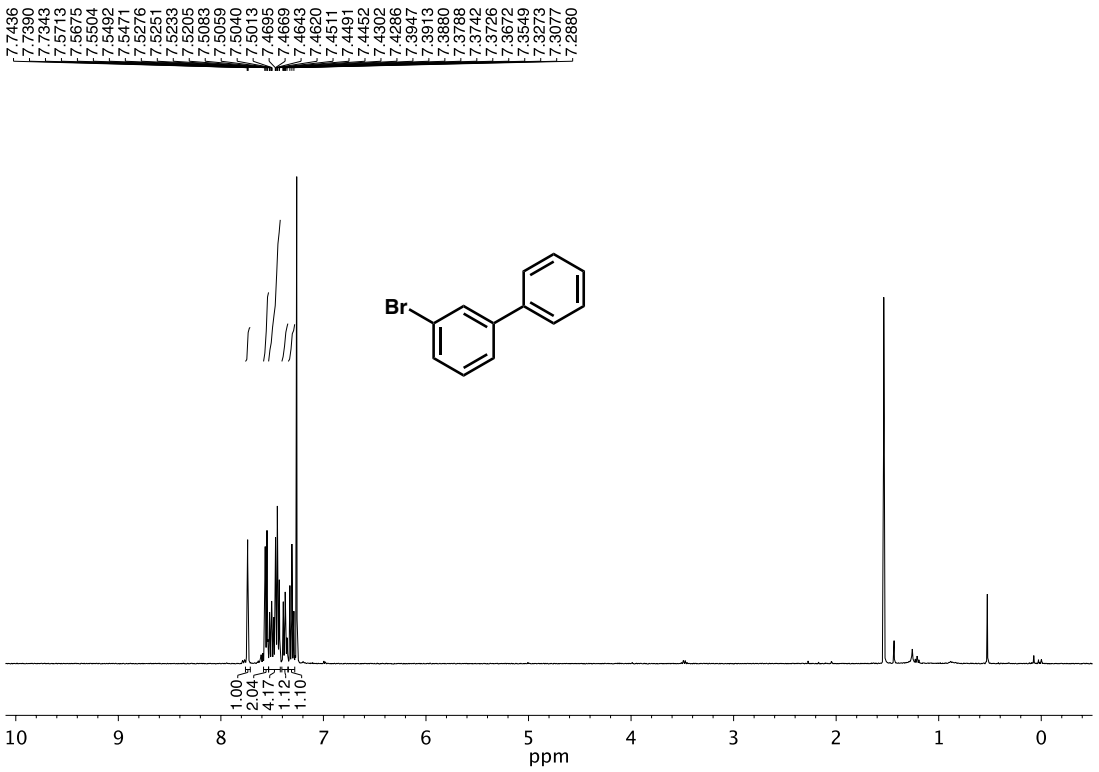


Figure 2.72. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.20**, **2.21**.

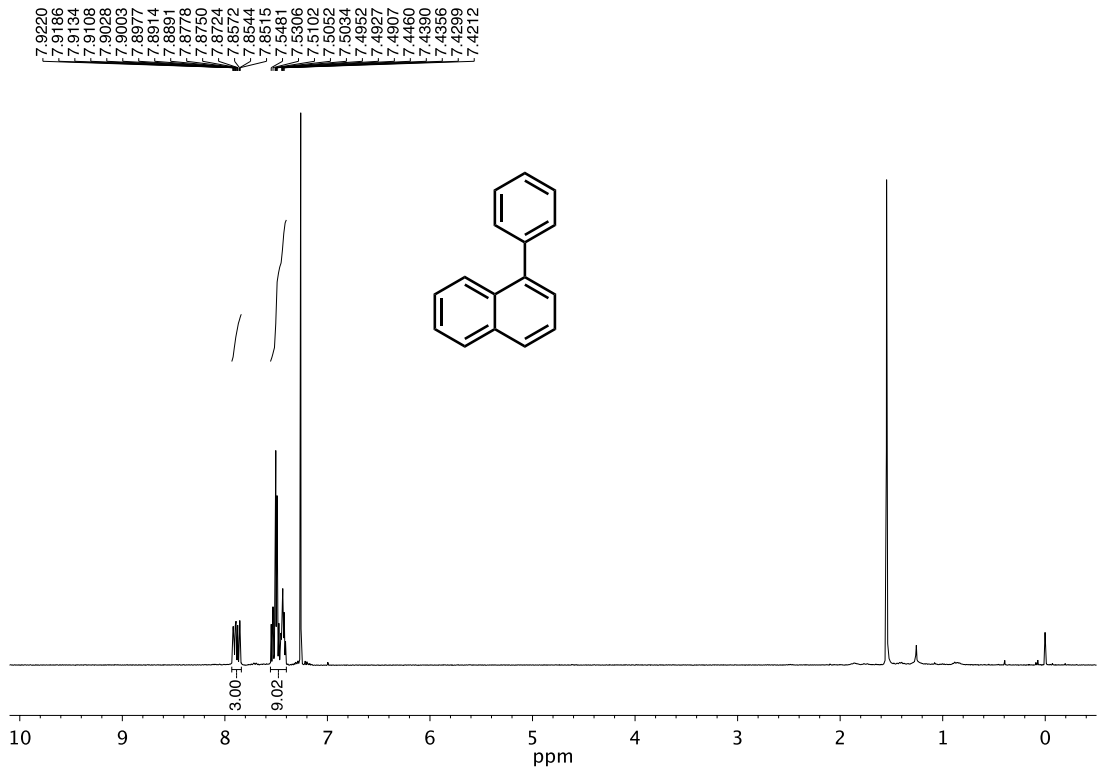


Figure 2.73. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.22**.

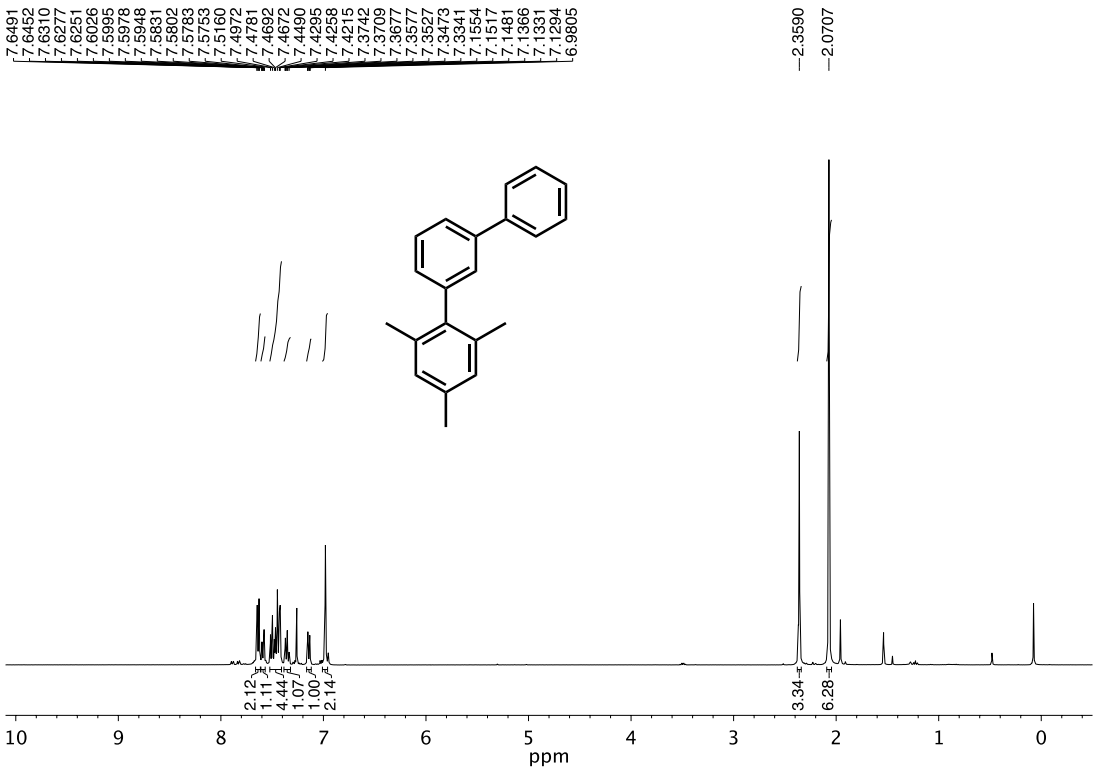


Figure 2.74. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.23**.

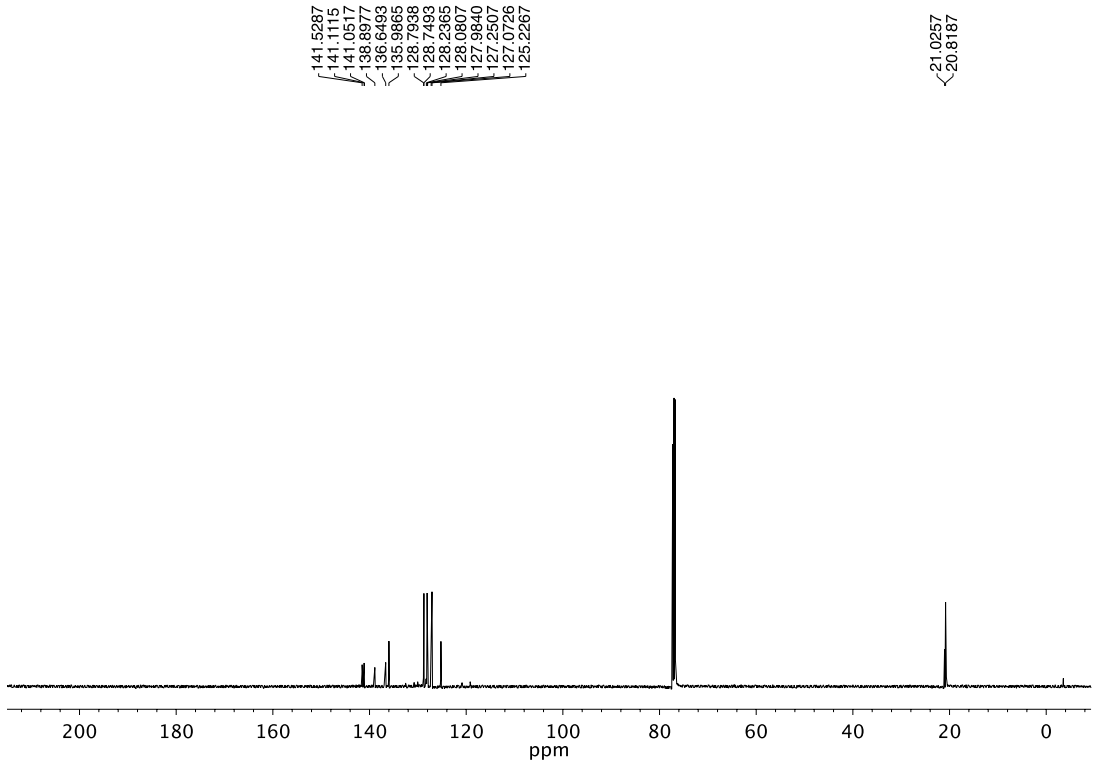


Figure 2.75. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.25**.

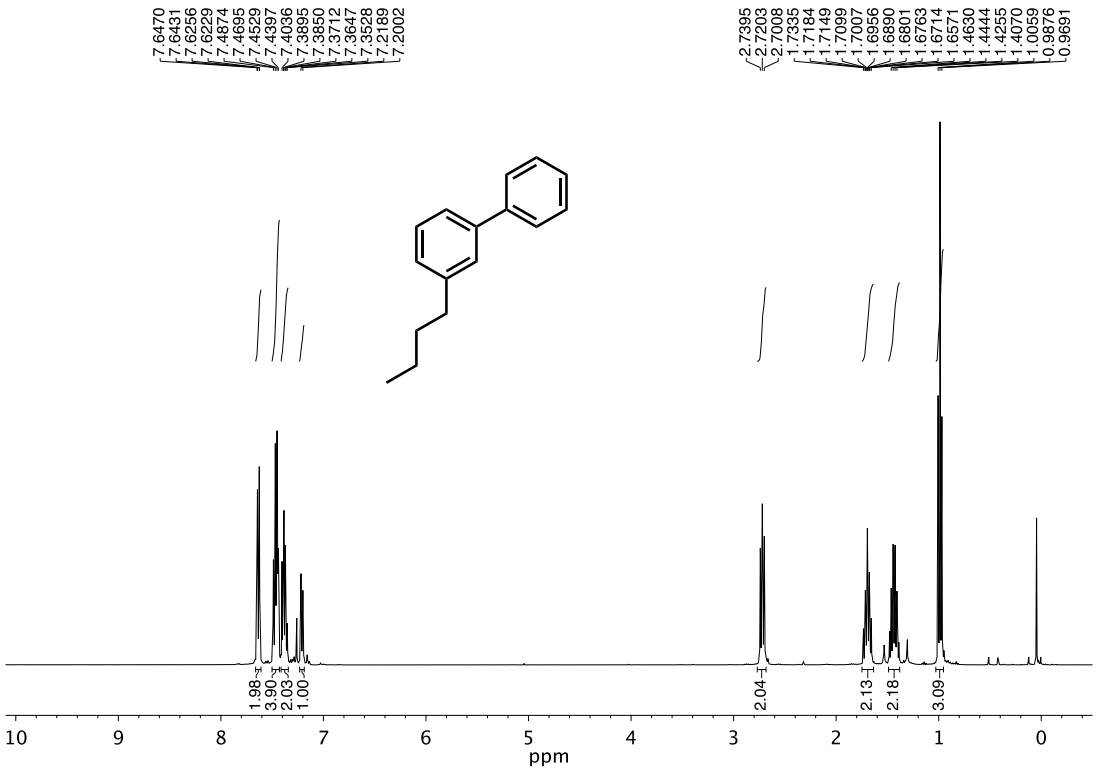


Figure 2.76. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.24**.

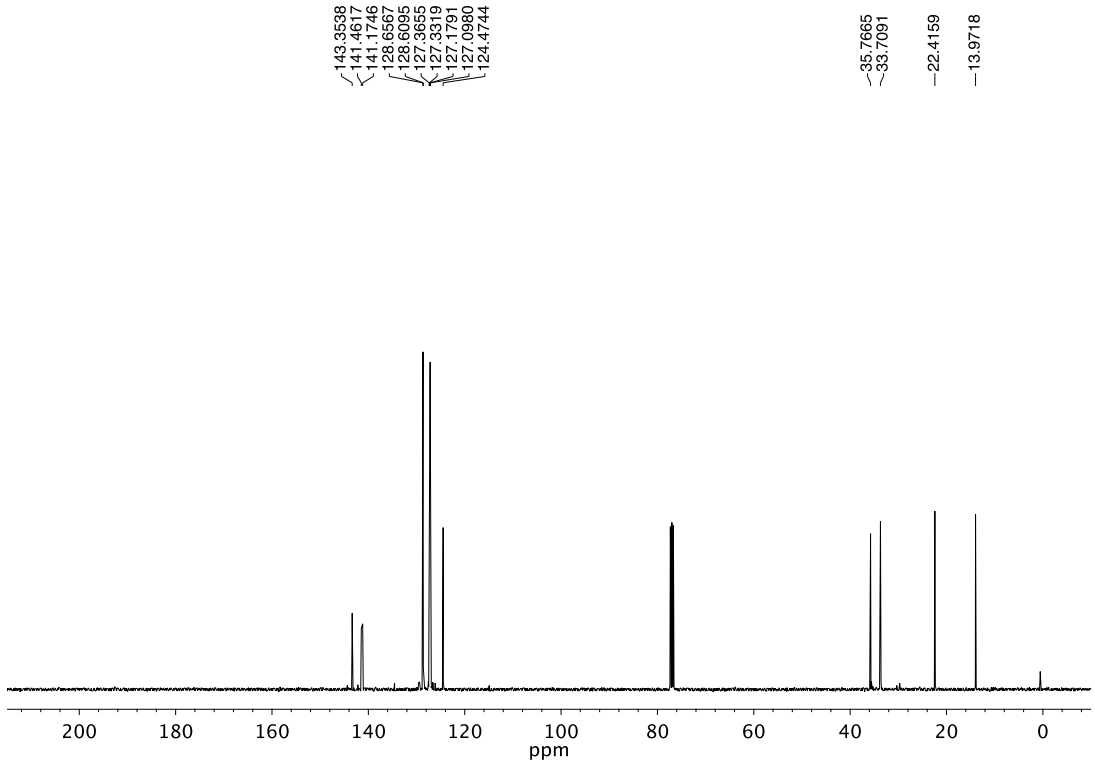


Figure 2.77. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2.24**.

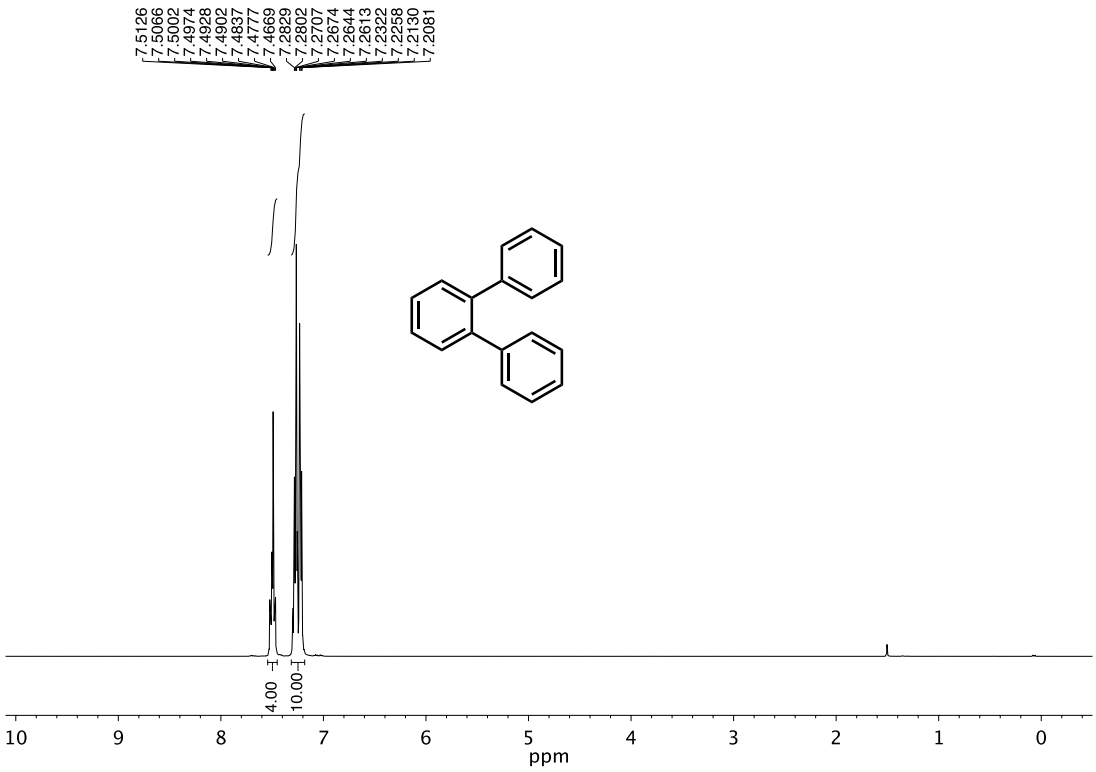


Figure 2.78. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.25**, **2.32**.

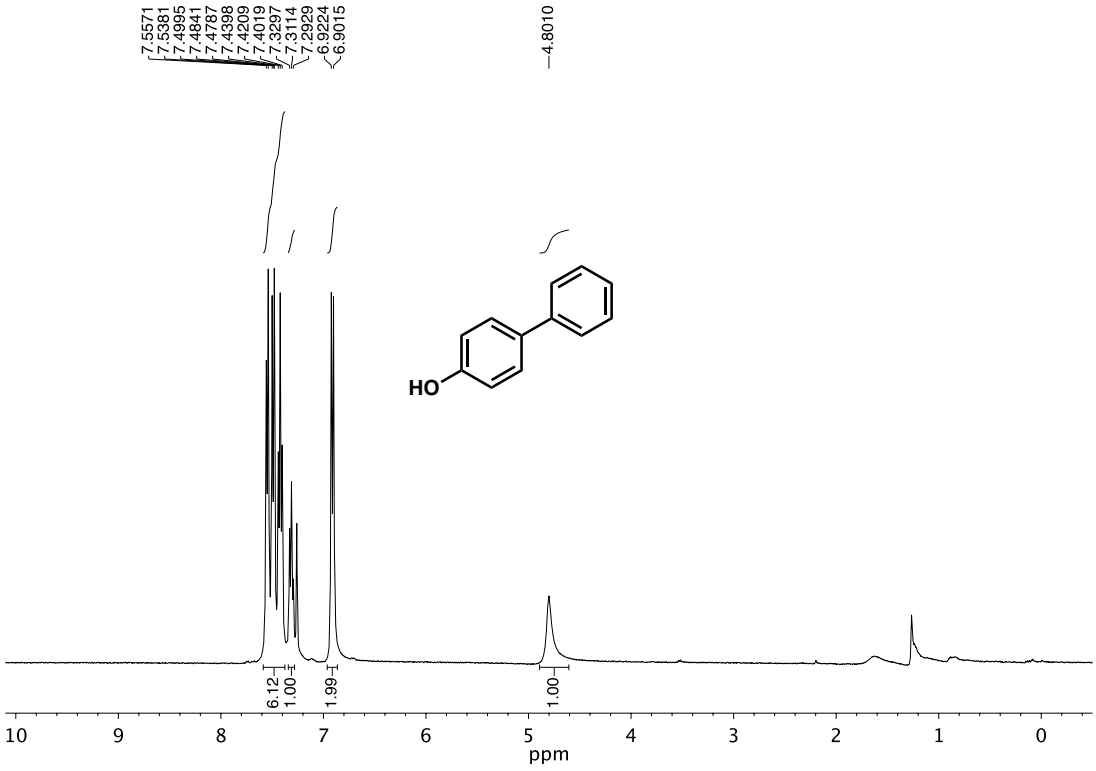


Figure 2.79. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.26**.

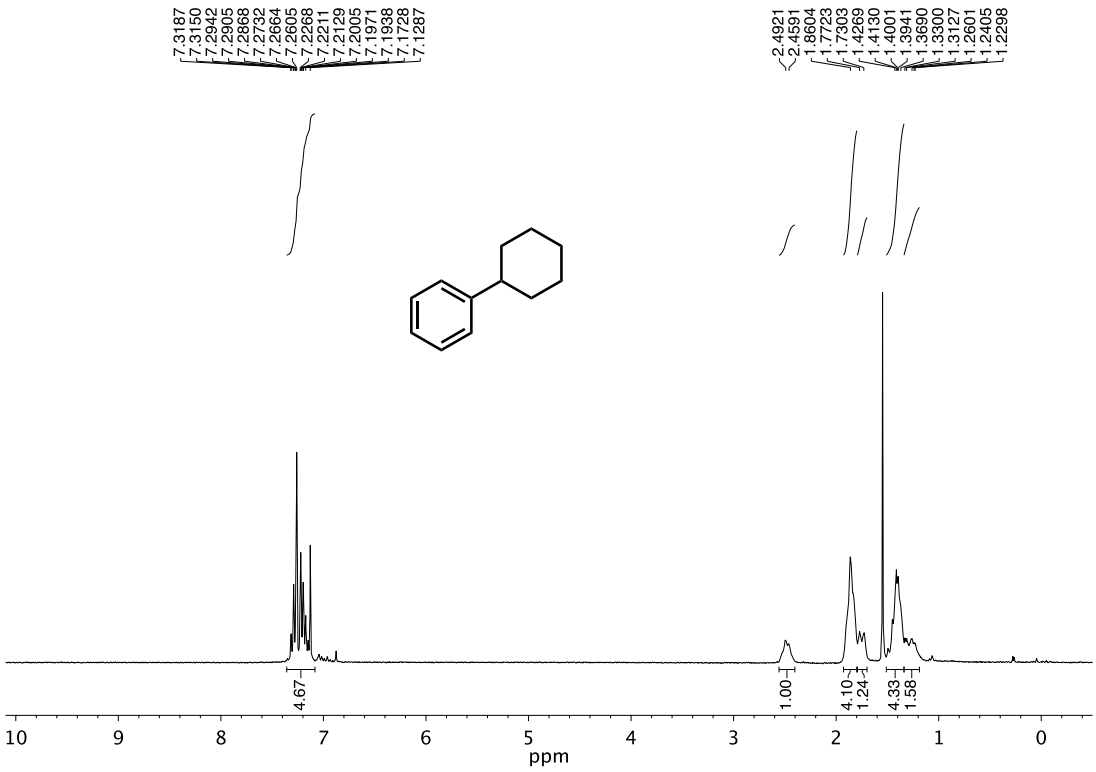


Figure 2.80. ^{1}H NMR (500 MHz, $CDCl_3$) of phenylcyclohexane.

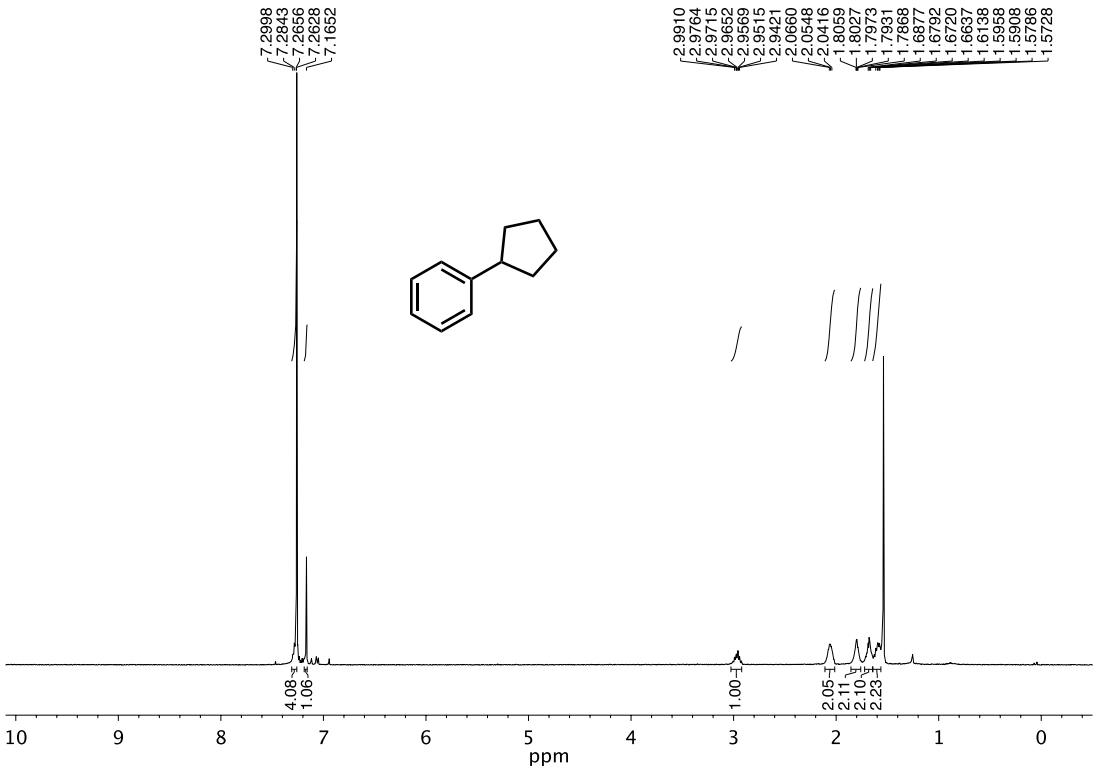


Figure 2.81. ^{1}H NMR (500 MHz, $CDCl_3$) of phenylcyclopentane.

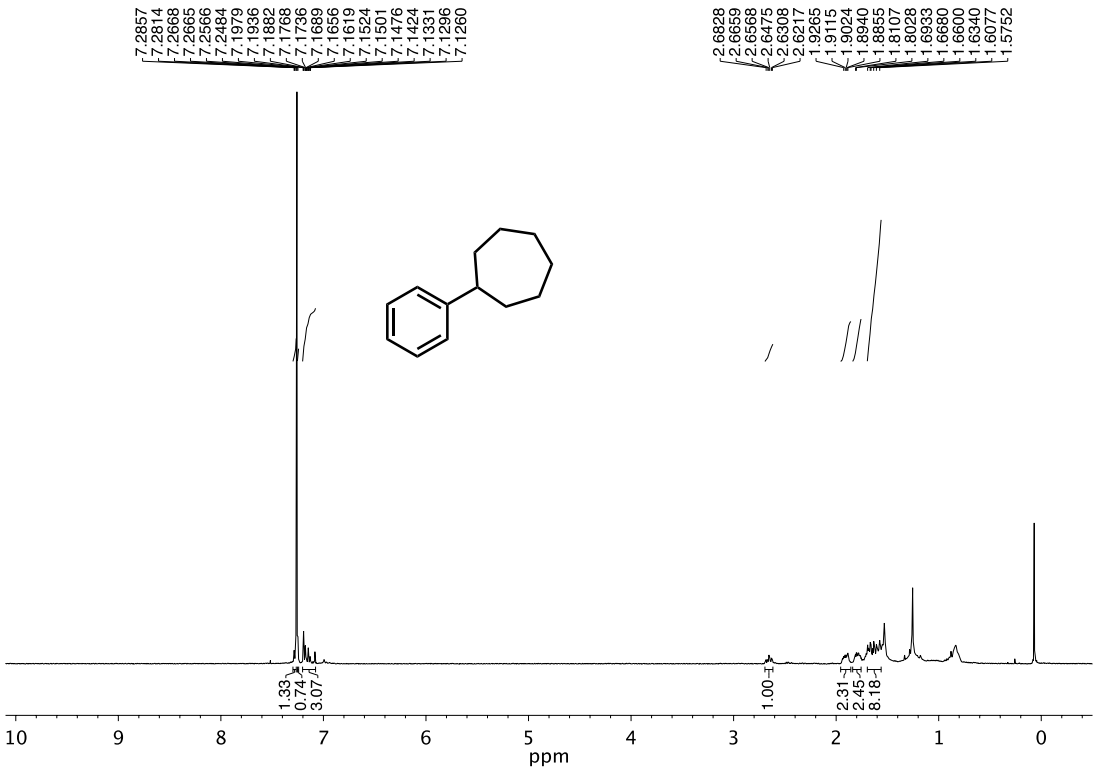


Figure 2.82. ^{1}H NMR (500 MHz, $CDCl_3$) of phenylcycloheptane.

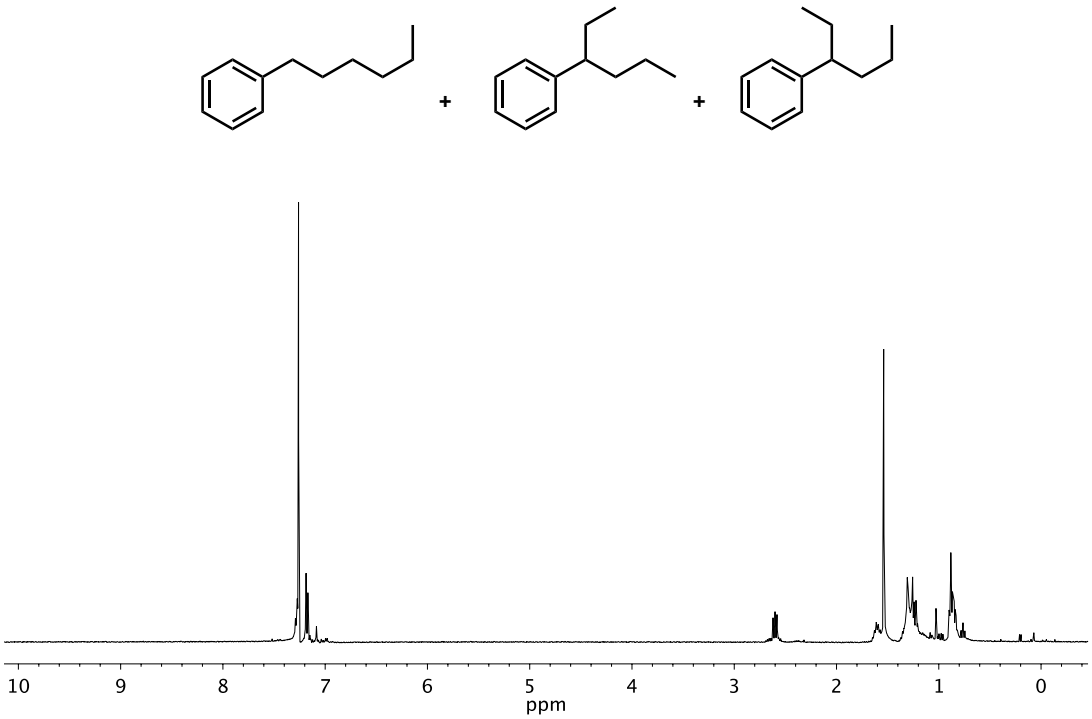


Figure 2.83. ^{1}H NMR (500 MHz, $CDCl_3$) of phenylhexane isomers.

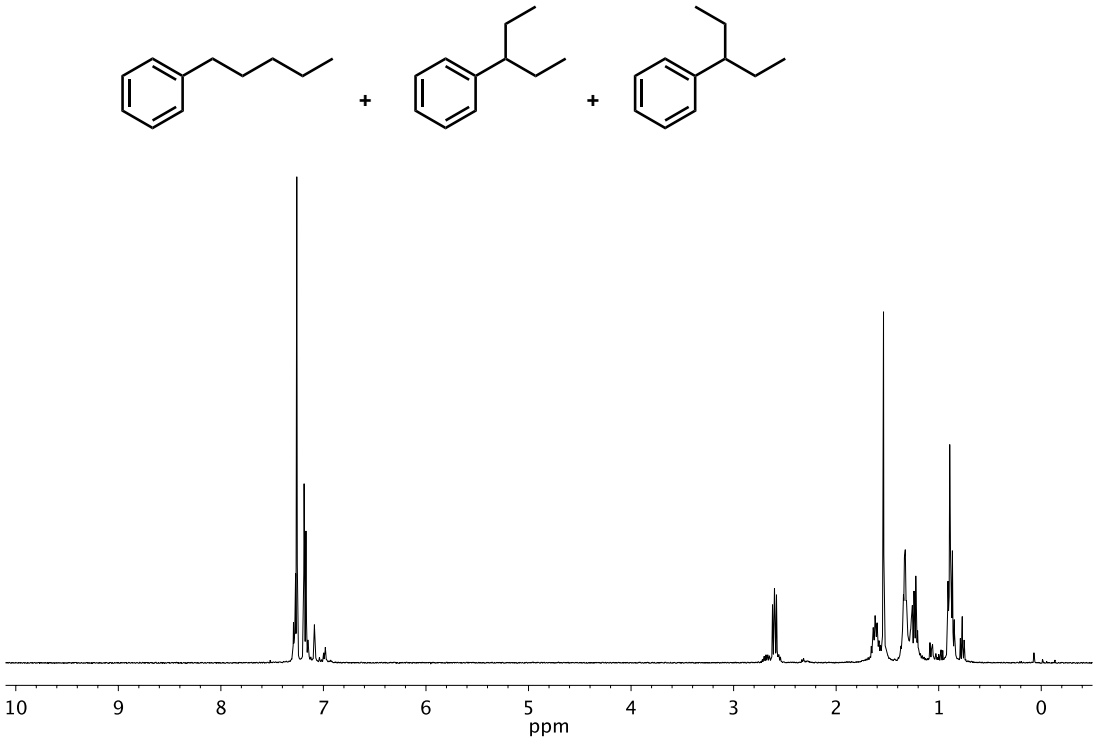


Figure 2.84. ^{1}H NMR (500 MHz, $CDCl_3$) of phenylpentane isomers.

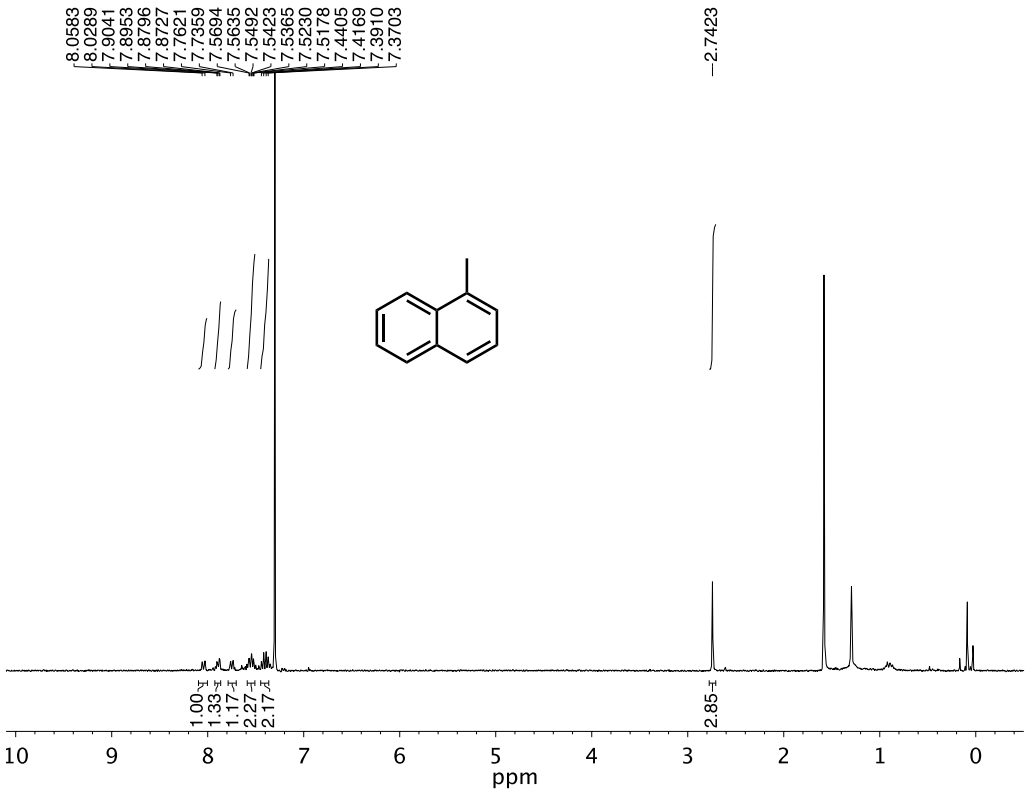


Figure 2.85. ^{1}H NMR (500 MHz, $CDCl_3$) of **2.28**.

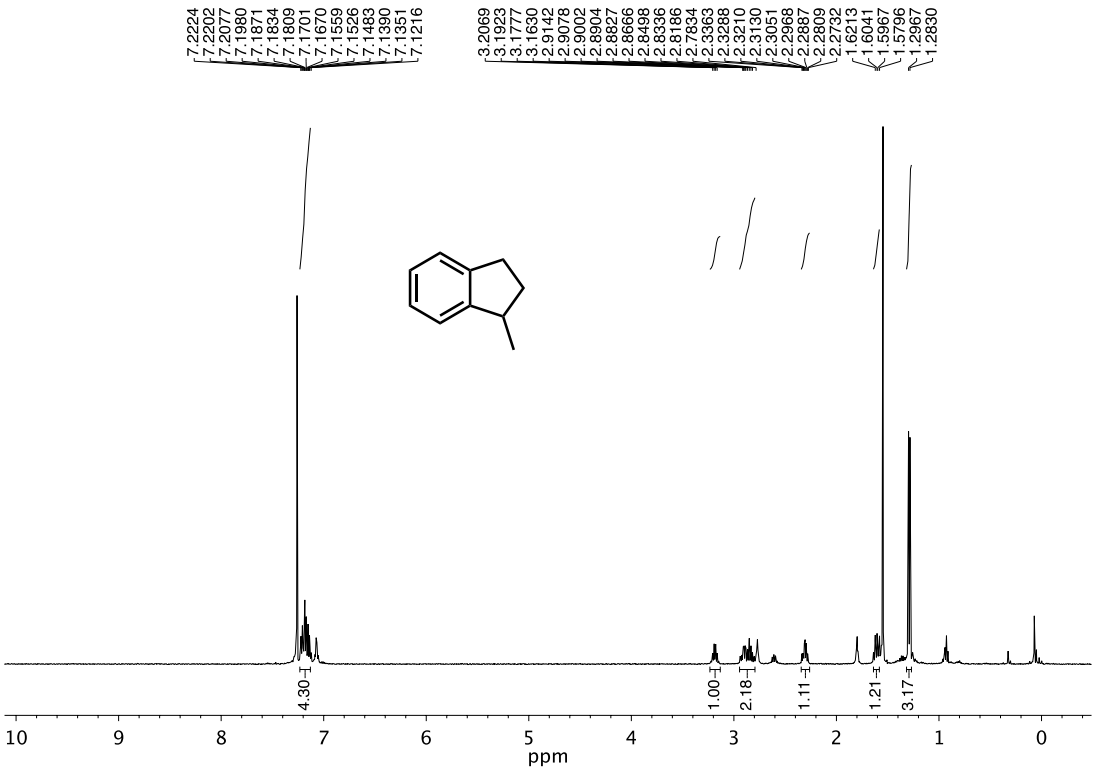


Figure 2.86. ^{1}H NMR (500 MHz, $CDCl_3$) of **2.36**.

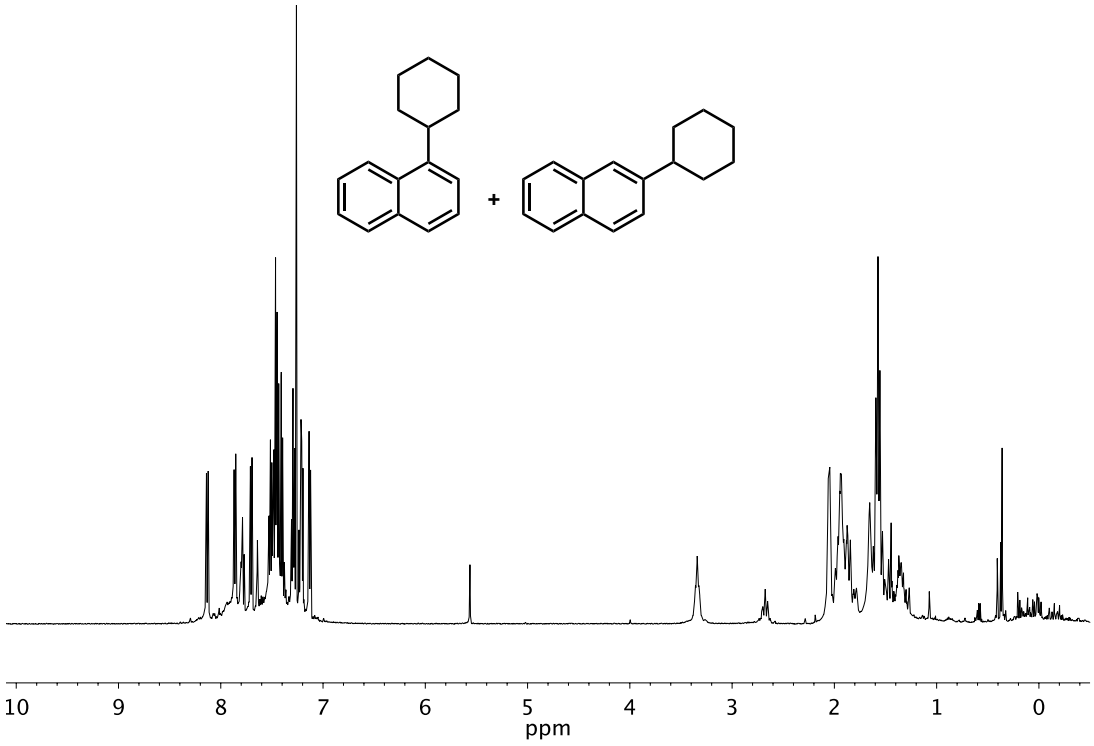


Figure 2.87. ^{1}H NMR (500 MHz, $CDCl_3$) of crude reaction showing **2.37** and **2.37.1**.

2.11 Notes and References

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CHAPTER THREE

Teaching an Old Carbocation New Tricks: Intermolecular C–H Insertion Reactions of Vinyl Carbocations

Adapted from: Stasik Popov, Brian Shao, Alex L. Bagdasarian, Tyler R. Benton, Luyi Zou, Zhongyue Yang, K. N. Houk, and Hosea M. Nelson

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3.1 Abstract

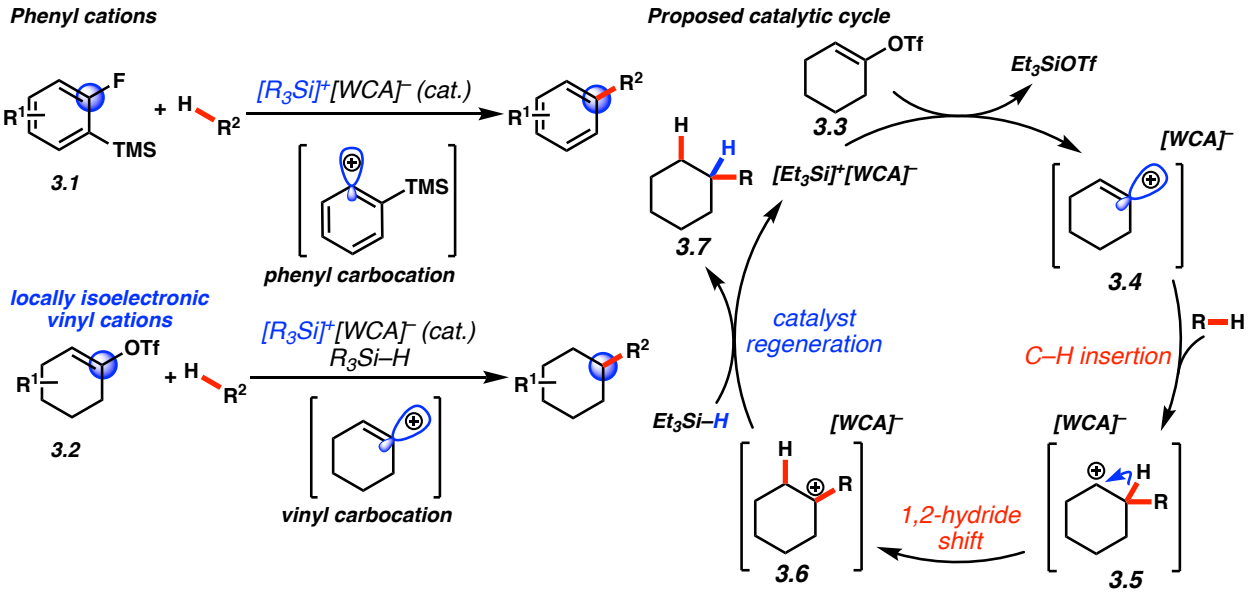
Vinyl carbocations have been the subject of extensive experimental and theoretical studies over the past five decades. Despite this long history in chemistry, the utility of vinyl cations in chemical synthesis has been limited, with most reactivity studies focusing on solvolysis reactions or intramolecular processes. Here, we report synthetic and mechanistic studies of vinyl cations generated through silylium/weakly coordinating anion (WCA) catalysis. We find that these reactive intermediates undergo intermolecular C–C bond forming reactions, including C–H insertion into unactivated sp^3 C–H bonds and reductive Friedel–Crafts reactions with arenes. Moreover, we conducted computational studies of these alkane C–H functionalization reactions and discovered that they proceed through nonclassical, ambimodal transition structures. This reaction manifold provides a framework for the catalytic functionalization of hydrocarbons using simple ketone derivatives.

3.2 Introduction

For more than a century, carbocations have played a central role in the chemical sciences, inspiring the development of broadly applied chemical reactions and a greater understanding of the fundamental properties of molecules.[1] This is especially true for dicoordinate vinyl cations. Beginning with Jacobs' proposal of a vinyl cation intermediate[2] and continued through the investigations by Grob[3], Hanack[4], Rappoport[5], Schleyer[6], Stang[7], and others[8–11], this class of reactive intermediates has been the subject of extensive theoretical and experimental studies. The structure and bonding of these cations has fascinated theorists, driving the development of computational techniques over the past five decades.[12–15] Vinyl cation intermediates have also been implicated in modern transition metal-catalyzed processes[16] and in classical acid-catalyzed reactions.[17] Despite this rich history and broad scientific relevance, most reactivity studies have focused on solvolysis reactions where the reactive vinyl cation is intercepted by heteroatom-containing solvent molecules.[18, 19]

Recently our group leveraged the reactivity of phenyl cations (**3.1**), a related class of dicoordinated carbocations, for catalytic C–C bond-formation *via* sp^3 C–H insertion (Fig. 3.1).[20] Inspired by this result, we hypothesized that locally isoelectronic vinyl cations (**3.2**) may display analogous C–H insertion reactivity. Despite their electronic similarity, C–H insertion reactions of vinyl cations are seldom found in the literature. This is particularly surprising given that vinyl carbocations have been extensively studied since the mid-20th century. The insertion of vinyl cations into methane C–H bonds has also been observed in the gas phase.[21] More recently, Metzger[22] and Brewer[23] have independently proposed the intramolecular C–H insertion of vinyl cations generated stoichiometrically from alkynes or diazo compounds in solution.

Figure 3.1. Extension towards locally isoelectronic vinyl cations



3.3 Proposal of Silylium-Catalyzed Generation of Vinyl Carbocations

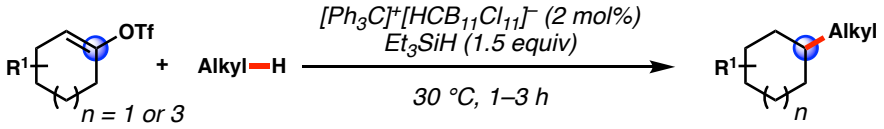
The solvolysis studies described above relied on polar solvents to facilitate thermal ionization of vinyl species bearing halide or pseudohalide leaving groups. This approach leads to attack of solvent on the cationic carbon center, leaving reactivity beyond the S_N1 manifold largely undiscovered. We drew on our phenyl cation studies to overcome this limitation by using silylium/monocarba-*closo*-dodecaborate salts (formed *in situ* through the reaction of triethylsilane with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$) in hydrophobic solvents to generate vinyl cations. Here the non-nucleophilic and non-basic properties of weakly coordinating anions (WCA), such as undecachlorinated monocarba-*closo*-dodecaborate anion $(HCB_{11}Cl_{11}^-)$[24], would enhance the Lewis acidity of the cationic silicon center allowing for mild ionization of vinyl triflates. In this scenario, silylium-mediated ionization of cyclohexenyl triflate (**3.3**) would generate a kinetically persistent vinyl cation/WCA ion pair (**3.4**). Insertion of this reactive dicoordinated cation (**3.4**) into an alkane C–H bond would lead to formation of alkyl carbocation **3.5**. A *1,2*-hydride shift

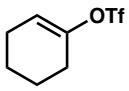
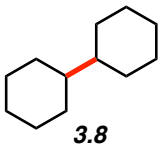
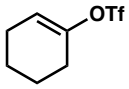
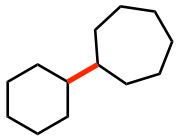
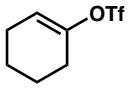
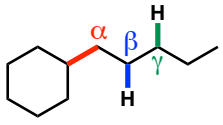
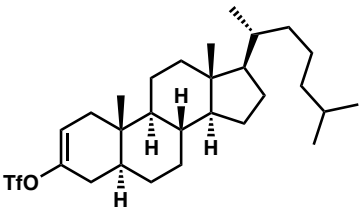
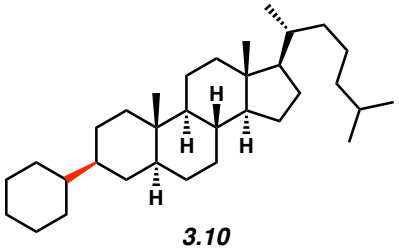
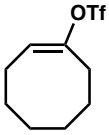
would lead to the more stable tertiary cation (**3.6**) that upon reduction by a sacrificial silane[25] would generate the functionalized hydrocarbon product **3.7**, and regenerate the silylium/carborane initiator. In its entirety, this process would enable the direct C–H alkylation of alkanes and arenes by simple ketone derivatives. Herein is discussed the successful execution of this mechanistic hypothesis, entailing intermolecular, reductive C–H alkylation mediated by silane and catalytic quantities of carborane salts.

We initiated our studies with cyclohexenyl triflate (**3.3**). We found early success when exposure of cyclohexenyl triflate (**3.3**) to 1.5 equivalents of triethylsilane and 2 mol% $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ in dried cyclohexane solvent at 30 °C resulted in the formation of cyclohexylcyclohexane (**3.8**; Table 3.1, entry 1) in 87% yield, after 90 minutes. Astounded by the remarkably mild conditions employed in this alkane alkylation reaction, we undertook a brief study of scope to further elucidate potential synthetic applications and to gain mechanistic insight. Inert C–H bonds, such as those of cycloheptane and *n*-pentane, also reacted efficiently with the cyclohexenyl cation, albeit with poor regioselectivity in the latter case, contrary to the selectivity displayed by the related phenyl carbocation (entries 2, 3).[20] Although cyclohexenyl triflates bearing substituents at the *2*- or *6*-positions led to complex mixtures of products, presumably due to non-productive unimolecular decompositions[26], other positions of the cyclohexenyl ring were tolerant of substitution. For example, exposure of the enol triflate derived from *5*α-cholestan-*3*-one (**3.9**, entry 4) to our reaction conditions led to formation of the alkylated steroid **3.10** in 88% yield and 15:1 diastereomeric ratio (*d.r.*)(relative stereochemistry determined by X-ray crystallography). Analogous to the previously reported ring-contraction reactions of medium-sized cyclic vinyl triflates[27], exposure of cyclooctenyl triflate (**3.11**) to our

optimized reaction conditions led to rapid transannular C–H insertion to yield bicyclo[*3.3.0*]octane (Table 1, entry 5).

Table 3.1. C–H insertion reactions of cyclic vinyl cations



Entry	Substrate	Solvent	Product	Yield (%), Time (h)
1	 ***3.3***	C_6H_{12}	 ***3.8***	87, 1.5
2	 ***3.3***	C_7H_{14}		88, 2
3	 ***3.3***	*n*-C_5H_{12}	 *21:36:11*	68, 1.5
4	 ***3.9***	C_6H_{12}	 ***3.10***	88, 3 (15:1 *d.r.*)
5	 ***3.11***	C_6H_{12}		91, 1

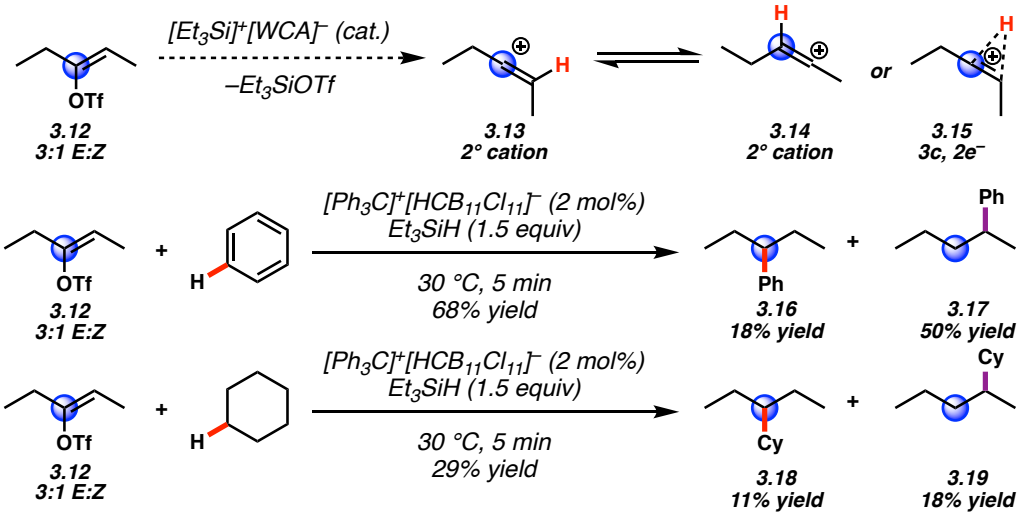
*Yield determined by: *GC-FID, † Isolation*

3.4 The Nonclassical Nature of the Vinyl Carbocation

Having established the catalytic, intermolecular C–H alkylation reactions of cyclic vinyl triflates, we extended our investigations to the reactivities of acyclic vinyl triflates. Acyclic vinyl cations have been the focus of previous experimental and theoretical studies of dicoordinated

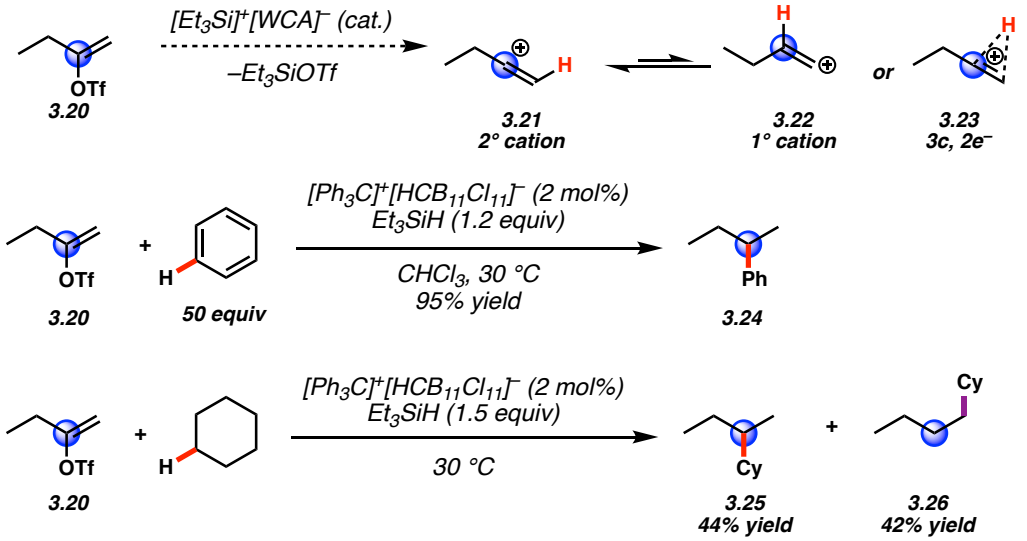
cations, as acyclic variants are generated under milder solvolytic conditions.[28] Moreover, depending on substitution, several studies support nonclassical ground-state bonding in vinyl cations, structures reminiscent of protonated alkynes.[29–31] In drawing parallels to the disparate selectivity of the napthyl cation C–H insertion selectivity (Fig. 2.4.), we reasoned that a similar discrimination may be operative. We hypothesized that use of pentenyl triflate **3.12** would be a suitable probe for mechanistic inquiry. Central to this hypothesis is addressing whether the vinyl cation would exist as two equilibrating electrophiles (**3.13** and **3.14**) or as a nonclassical ion (**3.15**) as proposed in physical organic studies. To our surprise, upon subjecting triflate **3.12** to benzene solvent under silylium catalysis, we observe a 68% yield of the combined products **3.16** and **3.17** in a 9:25 ratio, favoring the site not originally bearing the triflate. Furthermore, replacing benzene with cyclohexane as a nucleophile results in an 11:18 ratio of the cyclohexylated products **3.18** and **3.19**, maintaining the same selectivity. While in the previous phenyl cation case, use of an aromatic nucleophile maintained the site-selectivity exclusively at the site with the ionized group, in this example the fidelity was exchanged. While neither of the extended hypotheses could be validated entirely, both were still valid. One possibility is that nonclassical ion **3.15** is operative and the reactivity is determined by kinetic control. Another possibility is that cationic intermediates **3.13** and **3.14** are readily equilibrating due to a low barrier between two degenerate secondary vinyl cations and site-fidelity is determined by kinetic control.

Figure 3.2. Probing the intermediate for linear vinyl triflates



To further probe these surprising results, butenyl triflate **3.20** was chosen next as a model substrate (Fig. 3.3). In this event, ionization of butenyl triflate **3.20** would lead to secondary vinyl cation **3.21** that could be in equilibrium with primary cation **3.22**. While unlikely that a secondary vinyl cation would be in equilibrium with an exceedingly unstable primary cation, this model system offers the possibility to explore a ground-state nonclassical ion (**3.23**) *via* hydride-bridging. To our desire use of 50 equivalents of benzene in bulk chloroform solvent gave butylbenzene in 95% yield, maintaining site-specificity at the site originally baring the triflate. In an analogous study, exchanging benzene for cyclohexane resulted in a near 1 to 1 ratio for C–H insertion products **3.25** and **3.26**. This result is suggestive that a ground-state nonclassical ion is operative for C–H insertion reaction coordinate as a statistical distribution of cations **3.21** and **3.22** is unfavorable. With the barrier for attack of the arene π-system falling nearly 20 kcal/mol below the barrier for C–H insertion, it is reasonable to consider that an arene nucleophile is sufficiently reactive to attack the cation prior to intramolecular stabilization *via* hyperconjugation while insertion occurs on a stabilized nonclassical species.[32]

Figure 3.3. Reevaluated hypothesis for linear vinyl triflates

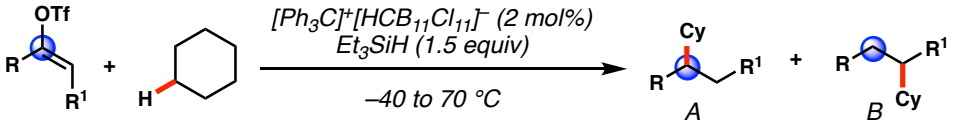


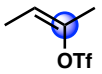
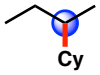
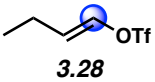
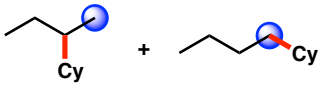
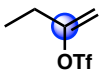
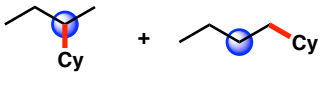
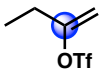
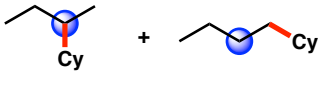
3.5 The Reactivity of Acyclic Vinyl Triflates

Having come to a deeper understanding of the nonclassical C–H insertion reactivity of acyclic vinyl cations, we extended our investigations to the reactivities of other acyclic vinyl triflates. Subjection of butenyl triflate **3.27** to the reaction conditions led to high-yielding reductive alkylation of cyclohexane, providing *2*-cyclohexylbutane (**3.25**) in 85% yield (Table 3.2, entry 1). Use of terminal triflate **3.28** (Table 3.2, entry 2) resulted in an identical product distribution to that of entry 2, albeit requiring extended reaction times. While primary vinyl cations are difficult to generate under solvolytic conditions[11], here the abstraction of the terminal triflate by silylium cation may provide a lower energy transition through favorable Si–O bond formation. Carrying out the reaction at –40 °C in chloroform solvent allowed for selective formation of *1*-cyclohexylbutane (**3.26**) (*ca.* 2:1) (Table 3.2, entry 3), compared to the statistical mixture formed under ambient conditions in the same time period (Table 3.2, entry 4). These results are consistent with our view of a nonclassical intermediate. In the absence of coordinating solvent, hyperconjugative stabilization may lead to a greater degree of bridging. As we increase the amount of chloroform solvent to attenuate hyperconjugative effects, stabilization of a more

classical 2° carbocation, instead of the energetically prohibitive 1° carbocation, would lead to terminal product **3.26**. The important observation of modulated product distributions in polar solvent (entry 3) implies that the product ratios of reactions that proceed through unsymmetrical nonclassical species can be dictated by experimental factors such as temperature or solvent that influence the degree of bridging.

Table 3.2. C–H insertion reactions of acyclic vinyl triflates



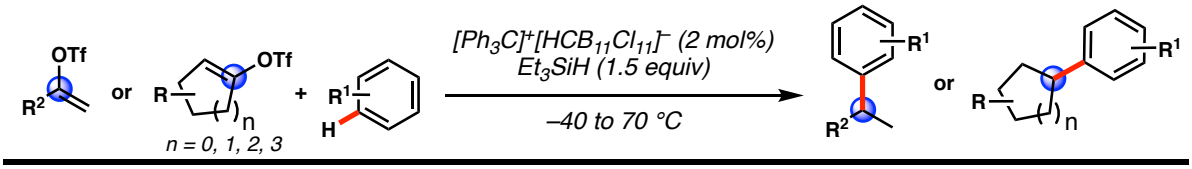
Entry	Substrate	Solvent	Temp. (°C)	Product	Yield (A, B) (%)
1	 ***3.27*** 2.5:1 E:Z	C_6H_{12}	30	 ***3.25***	*85*
2	 ***3.28*** 1:1.8 E:Z	C_6H_{12}	70	 ***3.25*** + ***3.26***	*16, 19*
3	 ***3.20***	$CHCl_3/C_6H_{12}$	–40	 ***3.25*** + ***3.26***	*17, 34*
4	 ***3.20***	C_6H_{12}	30	 ***3.25*** + ***3.26***	*40, 39*

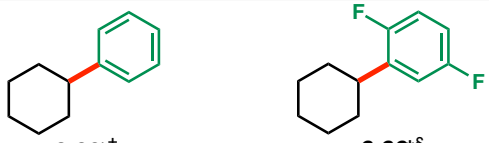
3.6 Reductive Friedel-Crafts Reactions of Vinyl Carbocations

Having established that vinyl triflates are competent vinyl cation precursors under silylium catalysis conditions, and that these reactive intermediates undergo efficient sp^3 C–H functionalization reactions, we sought to investigate their reactivity with arenes. It has been reported that cyclic vinyl cations are poor electrophiles in Friedel-Crafts arylation reactions.[33]

This finding has been attributed to the poor electrophilicity of vinyl cations[15] and to the slow ionization of vinyl cation precursors in arene solvents.[33] In early studies, cyclohexenyl triflates were completely unreactive towards arene nucleophiles, while larger ring size triflates participated in Friedel–Crafts reactions at elevated temperatures, albeit in poor yields.[33] We posited that use of silylium/carborane salts would allow for mild ionization of cyclic vinyl triflates in nonpolar solvents, allowing for facile Friedel–Crafts arylation reactions. We were pleased to find that with 4 equivalents of benzene in pentane solvent (1:22 molar ratio of benzene:pentane), cyclohexenyl triflate (**3.3**) underwent smooth reductive arylation to yield phenylcyclohexane (**3.29**) in 79% yield in 2 hours at room temperature (Fig. 3.4). In addition to benzene, electron-poor dihalogenated arenes underwent smooth, C–C bond formation to yield cyclohexylated haloarenes (**3.30**–**3.33**) in synthetically useful yields. Likewise, electron-rich arenes, such as mesitylene were competent nucleophiles giving sterically encumbered aryl alkanes (**3.34**). Cyclohexenyl triflates bearing substituents at the *4*- or *5*-positions could also be arylated (**3.35**–**3.37**), including the vinyl triflate of *5*α-cholestan-*3*-one which yielded an arylated steroid core (**3.38**) in 90% yield and 8:1 *d.r.*. Previously inaccessible from the corresponding triflate, the cyclopentenyl vinyl cation was successfully converted to phenyl cyclopentane (**3.39**) in 64% yield. Other ring sizes such as cycloheptenyl triflate undergoes smooth reductive alkylation with benzene reaction partners in 71% yield (**3.40**). Cyclobutenyl triflate participated in this reductive Friedel-Crafts alkylation to give phenyl cyclobutane (**3.41**) in 57% yield. The triflate derived from α-tetralone was reductively arylated in 43% yield, and acetophenone derived acyclic triflates were also arylated in 51 to 77% yield (**3.43** and **3.44**). Simple acyclic vinyl triflates were competent electrophiles for arylation by both electron-poor and electron-rich arenes, requiring as little as 10 equivalents of arene in chloroform solvent at –40 °C (**3.45**–**3.48**).

Table 3.3. Reductive Friedel-Crafts reactions of vinyl cations

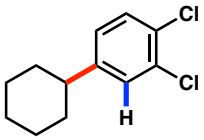




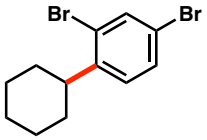
3.29*‡
4 equiv

3.30*§
10 equiv

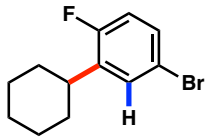
arene functionalization in pentane solvent



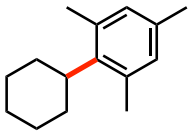
3.31
56% yield (47:9)§



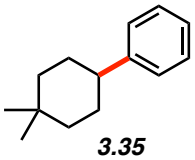
3.32
51% yield§



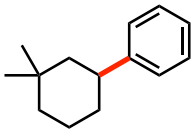
3.33
51% yield (43:8)§



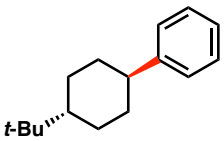
3.34
61% yield§



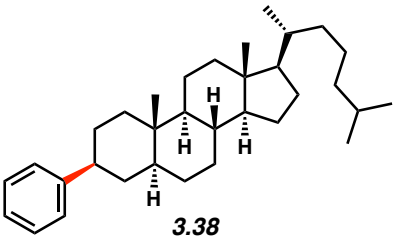
3.35
78% yield§



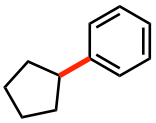
3.36
88% yield§



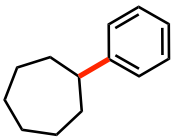
3.37
49% yield (9:1 *d.r.*)§



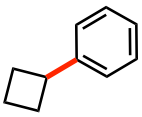
3.38
90% yield (8:1 *d.r.*)§



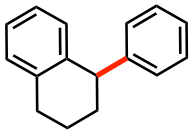
3.39
64% yield§



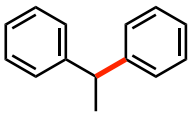
3.40
71% yield§



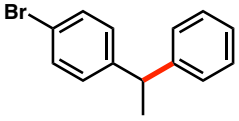
3.41
57% yield†§



3.42
43% yield§

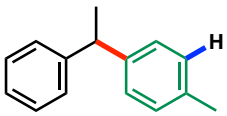


3.43
77% yield§

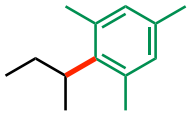


3.44
51% yield*§

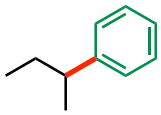
arene functionalization in chloroform solvent



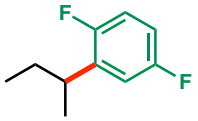
3.45, 66% yield (47:19)§
10 equiv



3.46, 80% yield§
10 equiv



3.47, 95% yield†‡
50 equiv



3.48, 46% yield†§
10 equiv

**1.2 equiv triethylsilane. †Triisopropylsilane used instead of triethylsilane. Yield determined by: ‡GC-FID, §NMR*

3.7 Conclusion

We have shown that vinyl cations, the subject of numerous computational and experimental studies, are now accessible from synthetically simple vinyl triflates using WCA salts under mild conditions. The non-nucleophilic nature of the WCA allows these unstabilized vinyl cations to engage in C–C bond forming reactions with alkanes and a variety of arenes, modes of reactivity that have been largely unreported despite extensive previous work. We find that the C–H insertion reactions of vinyl cations proceed through nonclassical ions, intermediates that are common in terpene biosynthesis[32] but rarely found in synthetic methodology. These findings lay the conceptual and experimental groundwork for further discoveries in the field of alkane C–H bond functionalization using ketone derivatives and WCA catalysis.

3.8 Experimental Section

3.8.1 Materials and Methods

Unless otherwise stated, all reactions were performed in an MBraun glovebox under nitrogen atmosphere with ≤ 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and dried *in vacuo* before use. All liquid substrates were either dried over CaH_2 or filtered through dry neutral aluminum oxide. Solid substrates were dried over P_2O_5. All solvents were rigorously dried before use. Benzene, *o*-dichlorobenzene, and toluene were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. Cyclohexane, fluorobenzene, and *n*-hexane were distilled over potassium. Chlorobenzene and *o*-difluorobenzene were distilled over sodium. Pentane was distilled over sodium-potassium alloy. Chloroform was dried over CaH_2 and stored in a glovebox. All solvents were stored over 4 Å molecular sieves. Triethylsilane and triisopropylsilane were dried over sodium and stored inside

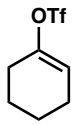
a glovebox. *Closo*-Carborane catalysts were prepared according to literature procedure. *n*-Butylcyclohexane and *n*-pentylcyclohexane were purchased from Alfa Aesar. Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. $AgNO_3$-Impregnated silica gel was prepared by mixing with a solution of $AgNO_3$ (150% v/w of 10% w/v solution in acetonitrile), removing solvent under reduced pressure, and drying at 120 °C. NMR spectra were recorded on a Bruker AV-300 (^1H, ^{19}F), Bruker AV-400 (^1H, ^{13}C, ^{19}F), Bruker DRX-500 (^1H), and Bruker AV-500 (^1H, ^{13}C). ^1H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) unless noted otherwise. Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.16 ppm) unless noted otherwise. GC spectra were recorded on an Agilent 6850 series GC using an Agilent HP-1 (50 m, 0.32 mm ID, 0.25 μm DF) column. GCMS spectra were recorded on a Shimadzu GCMS-QP2010 using a Restek XTI-5 (50 m, 0.25 mm ID, 0.25 μm DF) column. interface at room temperature. IR Spectra were record on a Perkin Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on a Waters (Micromass) GCT Premier spectrometer and are reported as follows: m/z (% relative intensity). Purification by preparative HPLC was done on an Agilent 1200 series instrument with a reverse phase Alltima C_{18} (5μ, 25 cm length, 1 cm internal diameter) column.

3.8.2 Experimental Procedures

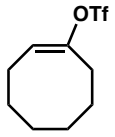
Substrate 3.12 was made according to literature.

Synthesis for substrates in Table 3.3 is reported in the adapted article.

3.8.2.1 Synthesis of Vinyl Triflates

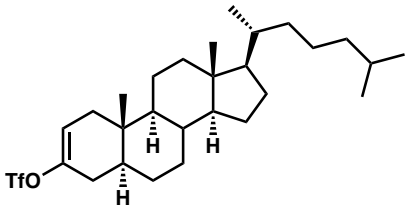


Cyclohex-1-en-1-yl trifluoromethanesulfonate (3.3). In a flame dried 1 L three-neck flask equipped with a dropping funnel, cyclohexanone (25.0 g, 255 mmol, 1.0 equiv) and freshly distilled anhydrous pyridine (22.2 g, 280 mmol, 1.1 equiv) were dissolved in anhydrous methylene chloride (400 mL). The solution was cooled to 0 °C. The dropping funnel was charged with a solution of triflic anhydride (79.0 g, 280 mmol, 1.1 equiv) in methylene chloride (160 mL). The solution was added dropwise to the reaction (~45 minutes). After addition ceased, the ice bath was removed and the reaction stirred for 16 hours. The volatiles were removed under reduced pressure and the crude material was suspended in petroleum ether and filtered. The supernatant was concentrated and the resulting oil was purified by vacuum distillation at 0.2 mmHg to give cyclohexenyl triflate (**3.3**) as a colorless oil (25.8 g, 44%). NMR data match those reported in literature.[35]

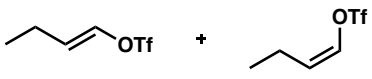


(*E*)-Cyclooct-1-en-1-yl trifluoromethanesulfonate (3.11). In a flame dried 250 mL round bottom flask, cyclooctanone (3.0 g, 23.8 mmol, 1.0 equiv) and freshly distilled 2-chloropyridine (3.0 g, 26.1 mmol, 1.1 equiv) were dissolved in anhydrous methylene chloride (90 mL). The

solution was cooled to 0 °C. Triflic anhydride (8.1 g, 28.5 mmol, 1.2 equiv) was added dropwise to the solution. After addition, the ice bath was removed and the reaction stirred for 16 hours. The reaction mixture was quenched with 0.5 M aqueous HCl (200 mL). The phases were separated and the aqueous layer was extracted with methylene chloride (2 x 100 mL). The combined organics were dried over magnesium sulfate, filtered and volatiles removed under reduced pressure to give the crude material as a purple oil. The product was purified by vacuum distillation (5 mmHg, 100 °C) to give triflate **(3.11)** as a colorless oil (3.2 g, 51%). NMR data match those reported in literature.[35]



***S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate (3.9).** Synthesized from 5a-cholestan-3-one according to reported literature. NMR data match those reported in literature.[36]



(E/Z)-But-1-en-1-yl trifluoromethanesulfonate (3.28). In a flame dried 500 mL round bottom flask, butyraldehyde (6.0 g, 83.2 mmol, 1.0 equiv) and freshly distilled 2-chloropyridine (10.4 g, 91.5 mmol, 1.1 equiv) were dissolved in anhydrous methylene chloride (300 mL). The solution was cooled to 0 °C. Triflic anhydride (28.2 g, 99.8 mmol, 1.2 equiv) was added dropwise to this solution. After addition, the ice bath was removed and the reaction was stirred at room

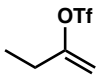
temperature overnight. The reaction was quenched with 0.5 M HCl. The phases were separated and the combined organic were dried over magnesium sulfate, filtered and volatiles removed under reduced pressure. The resulting oil was purified by vacuum distillation at 20 mmHg while heating at 60 °C to give triflate **3.28** as a brown oil (5.7 g, 30%). The distillate was brought into the glovebox and plugged through dry neutral alumina to afford the triflate **3.28** (1.8:1 Z:E mixture) as an off tan oil.

E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53–6.48 (m, 1H), 5.82 (dt, J = 11.8, 7.2 Hz, 1H), 2.09 (pd, J = 7.2, 1.6 Hz, 2H), 1.06 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, C_6D_6) δ –74.0; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 124.5, 118.8 (q, $^{1}J_{C–F}$ = 319 Hz), 20.3, 13.3.

Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53–6.48 (m, 1H), 5.27 (dt, J = 7.6, 5.6 Hz, 1H), 2.22 (pd, J = 7.6, 1.6 Hz, 2H), 1.04 (t, J = 7.6 Hz, 3H); ^{19}F NMR (376 MHz, C_6D_6) δ –74.4; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 122.6, 118.8 (q, $^{1}J_{C–F}$ = 319 Hz), 17.8, 13.3.

FTIR (Neat film NaCl): 2967, 1719, 1428, 1223, 1177, 1025, 766, 636, 578, 514.

HR-MS (GCT-LIFDI): Calculated for $C_5H_7F_3O_3S$: 204.0068; measured: 204.0075.



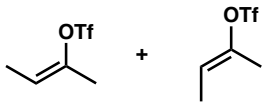
But-1-en-2-yl trifluoromethanesulfonate (3.20). To a 250 mL flame dried schlenk flask was condensed 1-butyne (5.00 g, 92.0 mmol, 1.1 equiv) at –78 °C. This was dissolved in anhydrous hexanes (92.0 mL) and the solution was warmed to –35 °C. Triflic acid (12.5 g, 83.0 mmol, 1.0 equiv) was added dropwise and the solution was allowed to slowly warm up to room temperature. After 2 hours of stirring, the reaction was quenched with saturated aqueous sodium bicarbonate (100 mL). The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 100 mL), dried over anhydrous potassium carbonate,

filtered and volatiles removed under reduced pressure (being careful of product volatility). The crude product was purified by vacuum distillation (25 mmHg, 50 °C) to give triflate **3.20** as a colorless oil (6.3 g, 37%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 5.34–5.11 (m, 2H), 2.44 (qt, J = 7.4, 1.0 Hz, 2H), 1.15 (t, J = 7.4 Hz, 3H); ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ –75.6; ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 158.8, 118.6 (q, $^{1}J_{C–F}$ = 318 Hz), 103.4, 26.8, 10.1.

FTIR (Neat film NaCl): 2986, 2950, 1670, 1415, 1249, 1202, 1138, 929, 848, 610, 506, 469.

HR-MS (GCT-LIFDI): Calculated for $C_5H_7F_3O_3S$: 204.0068; measured: 204.0065.



(*E*)-But-2-en-2-yl trifluoromethanesulfonate and **(*Z*)-but-2-en-2-yl trifluoromethanesulfonate (3.27).** In a 100 mL flame dried round bottom flask, triflate **3.20** (4.00 g, 19.6 mmol, 1 equiv) was dissolved in anhydrous methylene chloride (35 mL). Triflic acid (0.15 g, 0.98 mmol, 0.05 equiv) was added and the reaction stirred for 1 hour. The reaction was quenched with 5% aqueous sodium bicarbonate (35 mL). The layers were separated and the aqueous layer was extracted with pentane (3 x 20 mL). The volatiles were distilled off at 80 °C and then the product was purified by vacuum distillation (50 mmHg) to give triflate **3.27** as a 2.5:1 (*E:Z*) mixture of isomers (3.1 g, 78%).

Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (qd, J = 6.8, 0.8 Hz, 1H), 2.05 (br s, 3H), 1.71 (dq, J = 6.8, 1.6 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –75.0; ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 118.4 (q, $^{1}J_{C–F}$ = 318 Hz), 116.4, 19.6, 11.1.

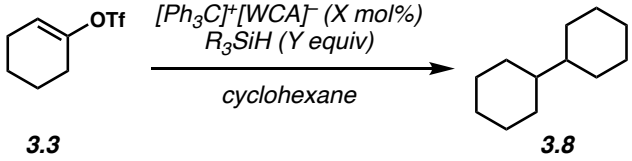
Minor Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (qd, J = 7.2, 0.8 Hz, 1H), 2.03 (br s, 3H), 1.69 (dq, J = 7.2, 1.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.2; ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 118.6 (q, $^{1}J_{C–F}$ = 318 Hz), 116.8, 15.7, 11.9.

FTIR (Neat film NaCl): 2934, 1710, 1412, 1245, 1201, 1135, 936, 876, 728, 632, 468.

HR-MS (GCT-LIFDI): Calculated for $C_5H_7F_3O_3S$: 204.0068; measured: 204.0065.

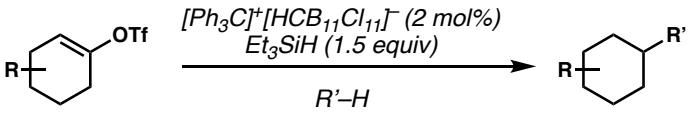
3.8.2.2 Catalytic C–H Insertion Reactions

This section outlines the optimization of the reaction shown below. All yields of bicyclohexyl (**3.8**) are GC yields.



Anion	% Cat. Loading	Conc.	Temp.	Silane	Yield
$[HCB_{11}Cl_{11}]$	2 mol%	0.1 M	30 °C	Et_3SiH (150 mol%)	87%
$[HCB_{11}Cl_{11}]$	2 mol%	0.1 M	30 °C	iPr_3SiH (150 mol%)	68%
$[HCB_{11}Cl_{11}]$	0 mol%	0.1 M	30 °C	Et_3SiH (120 mol%)	0%
$[HCB_{11}Cl_{11}]$	2 mol%	0.1 M	30 °C	none	0%
$[HCB_{11}H_5Cl_6]$	2 mol%	0.1 M	30 °C	Et_3SiH (150 mol%)	50%
$[HCB_{11}Br_{11}]$	2 mol%	0.1 M	30 °C	Et_3SiH (150 mol%)	69%
$[B(C_6F_5)_4]$	2 mol%	0.1 M	30 °C	Et_3SiH (150 mol%)	6%

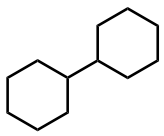
Table 3.4. Optimization of intermolecular alkylation reaction.



Scheme 3.1. General scheme for intermolecular C–H insertion reactions of vinyl triflates.

3.8.2.2.1 General Procedure

In a well-kept glovebox, H_2O, $O_2 \leq 0.5$ ppm, a dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.02 equiv) and this was suspended in alkane (0.1 M). Triethylsilane (1.5 equiv) along with a magnetic stirring bar were added to the mixture, and the resulting suspension stirred for 10 minutes. At this point, vinyl triflate (1.0 equiv) was added to the reaction and stirred for 0.16–12 hours at 30 °C (see substrates for specific details). Upon completion, the reaction mixture was passed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles removed under reduced pressure. Some substrates needed further purification by silica column chromatography (see below).



Bicyclohexyl (3.8, Table 3.1, entry 1). Synthesized according to general procedure 3.8.2.2.1. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv) and this was suspended in cyclohexane (0.5 mL, 4.63 mmol). Triethylsilane (12 mL, 0.075 mmol, 1.5 equiv) along with a magnetic stirring bar were added to the mixture and the resulting suspension stirred for 10 minutes. Cyclohexenyl triflate (**3.3**) (11.5 mg, 0.05 mmol, 1.0 equiv) was added to the reaction and stirred for 1.5 hours at 30 °C. Upon completion the reaction was plugged through silica and bicyclohexyl was obtained in 87% GC yield. The crude could be further purified by

flash column chromatography (hexanes) to give bicyclohexyl as a colorless oil. NMR spectra match those reported in literature.[37]

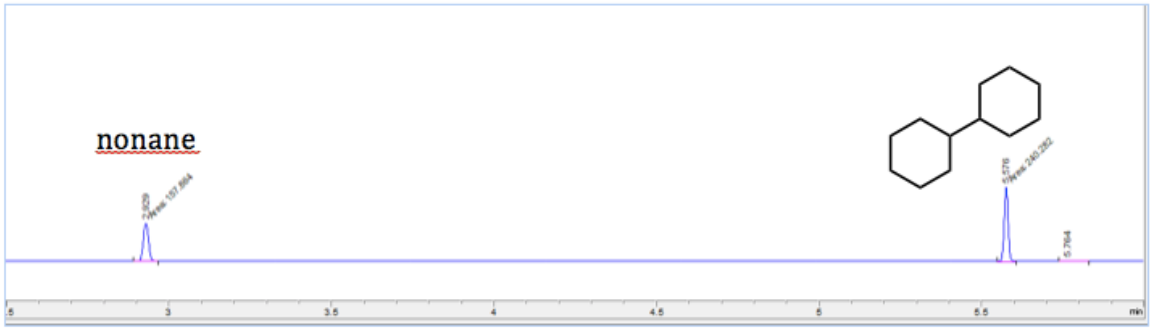


Figure 3.4. GC trace showing one to one mixture of nonane to bicyclohexyl.

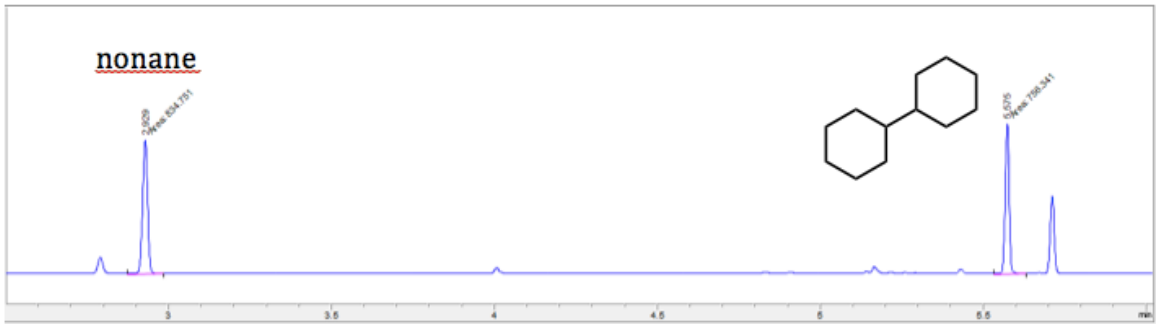
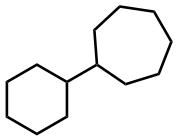


Figure 3.5. GC trace showing 87% yield of bicyclohexyl.



Cyclohexylcycloheptane (Table 3.1, entry 2). Synthesized according to general procedure 3.8.2.2.1. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv) and this was suspended in cycloheptane (0.5 mL). Triethylsilane (12 mL, 0.075 mmol, 1.5 equiv) along with a magnetic stirring bar were added to the mixture and the resulting suspension stirred

for 10 minutes. Cyclohexenyl triflate (**3.3**) (11.5 mg, 0.05 mmol, 1 equiv) was added to the reaction and stirred for 2 hours at 30 °C. Upon completion the reaction was plugged through silica and cyclohexylcycloheptane was obtained in 88% GC yield. The crude could be further purified by flash column chromatography (hexanes) to give cyclohexylcycloheptane as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74–1.68 (m, 2H), 1.68–1.52 (m, 9H), 1.50–1.43 (m ,2H), 1.42–1.3 4 (m, 2H), 1.32–1.07 (m, 7H), 1.06–0.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.0, 44.9, 31.5, 30.0, 28.6, 27.6, 27.2, 27.1.

FTIR (Neat film NaCl): 2918, 2850, 2670, 1448, 1349, 1263, 972, 893, 844.

HR-MS (GCT-LIFDI): Calculated for $C_{13}H_{24}$: 180.1878; measured: 180.1881.

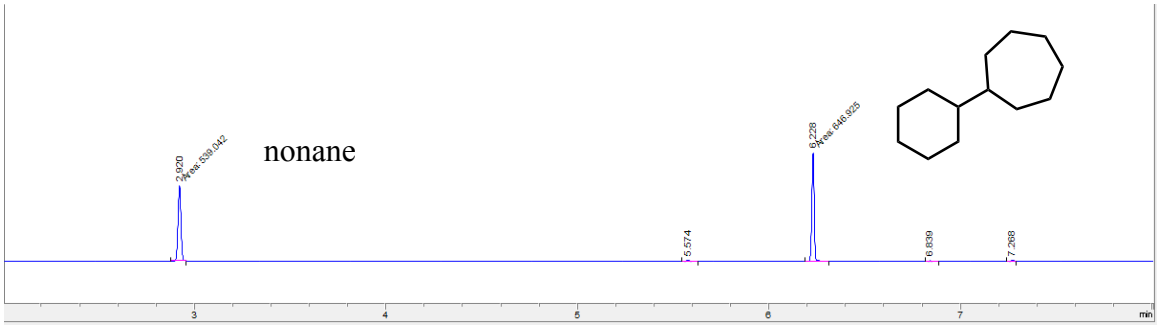


Figure 3.6. GC trace showing one to one mixture of nonane to cyclohexylcycloheptane.

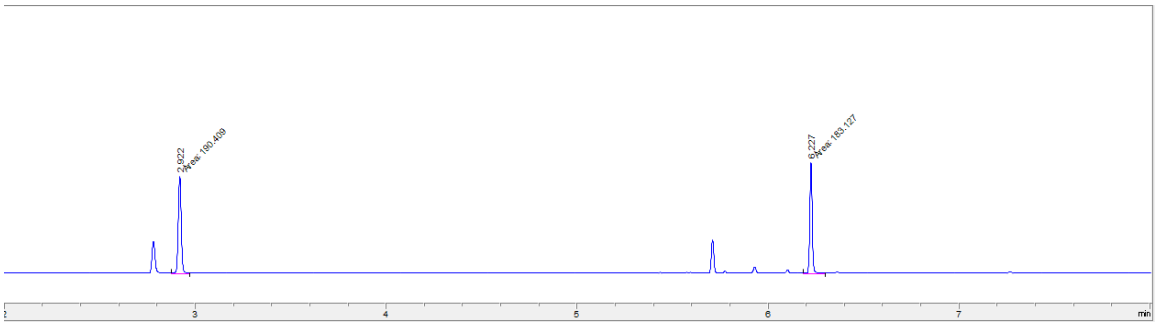
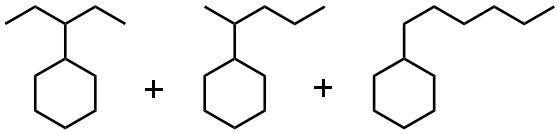
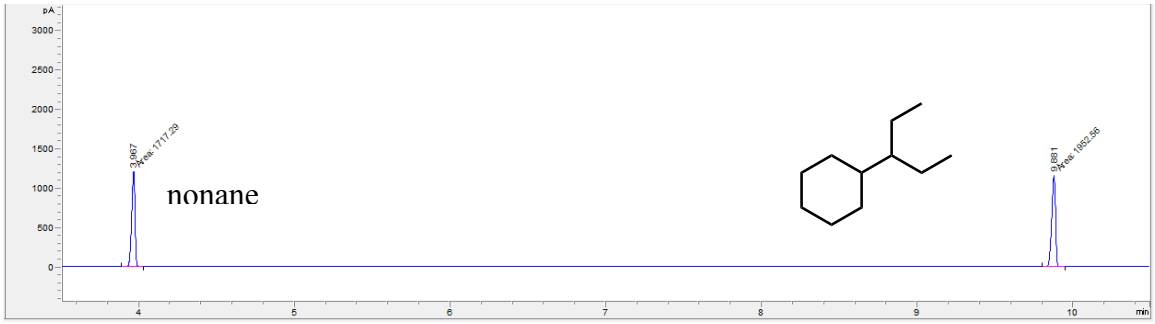
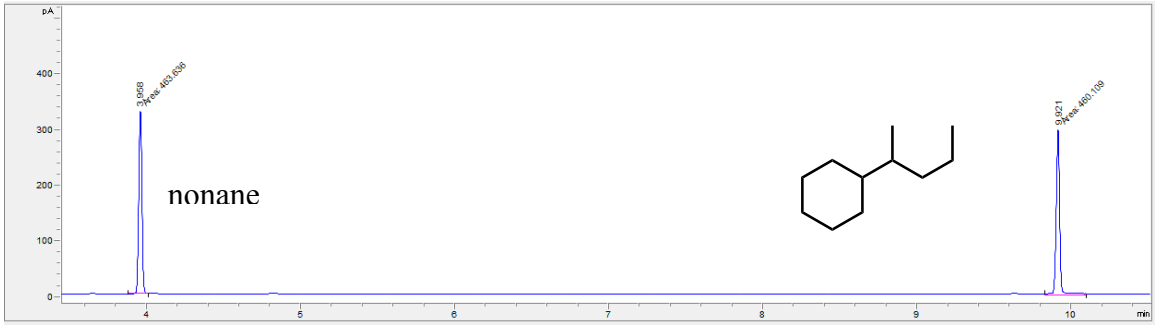


Figure 3.7. GC trace showing 88% yield of cyclohexylcycloheptane.



Pentylcyclohexane (Table 3.1, entry 3). Synthesized according to general procedure 3.8.2.2.1. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv) and this was suspended in pentane (0.5 mL). Triethylsilane (12 mL, 0.075 mmol, 1.5 equiv) along with a magnetic stirring bar were added to the mixture and the resulting suspension stirred for 10 minutes. Cyclohexenyl triflate (**3.3**) (11.5 mg, 0.05 mmol, 1.0 equiv) was added to the reaction and it stirred for 1.5 hours at 30 °C to give 11% of 3-cyclohexylpentane, 36% of 2-cyclohexylpentane and 21% of 1-cyclohexylpentane (GC). Upon completion the reaction was passed through silica and an inseparable mixture of the three isomers were obtained as a colorless oil (4.3 mg, 56%). The NMR data of this mixture matched those of the three authentic samples.





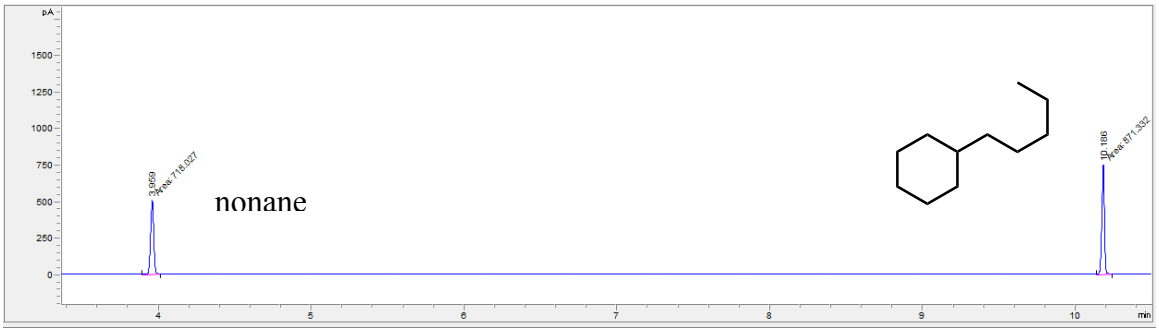


Figure 3.8. GC traces showing one to one mixture of nonane to 3-cyclohexylpentane (top), nonane to 2-cyclohexylpentane (middle), and nonane to 1-cyclohexylpentane (bottom).

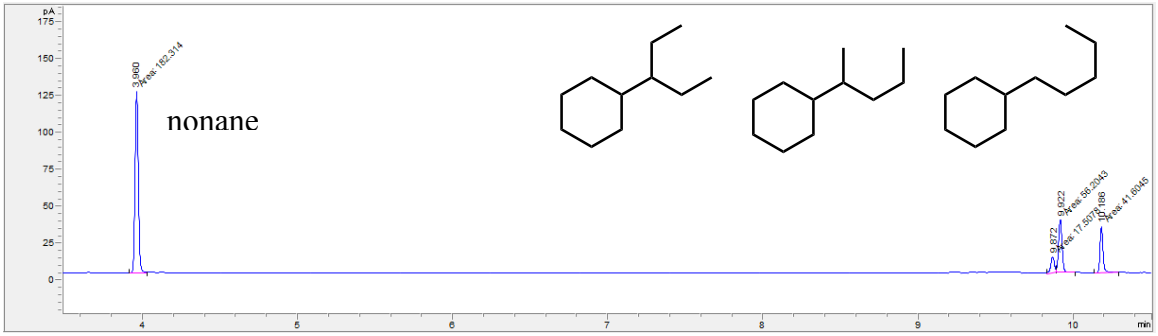
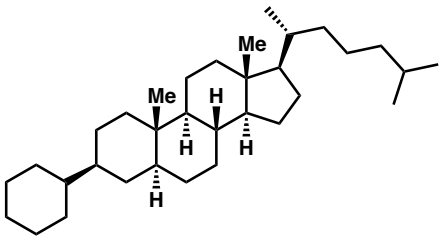


Figure 3.9. GC trace showing 11% of 3-cyclohexylpentane, 36% of 2-cyclohexylpentane and 21% of 1-cyclohexylpentane.



(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-Cyclohexyl-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene (3.10, Table 3.1, entry 4). Synthesized according to general procedure 3.8.2.2.1. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv) and this was suspended in cyclohexane (0.5 mL, 4.63 mmol). Triethylsilane (12 mL, 0.075 mmol, 1.5 equiv) along with a magnetic stirring bar were added to

the mixture and the resulting suspension stirred for 10 minutes. Triflate **3.9** (26.0 mg, 0.05 mmol, 1.0 equiv) was added to the reaction and it stirred for 3 hours at 30 °C. Upon completion the reaction was passed through silica and volatiles removed under reduced pressure to give product **3.10** as a white solid (19.5 mg, 88%). GC-FID analysis showed ~15:1 d.r. In order to assign the stereochemistry of the newly formed C–C bond, the material was crystallized by vapor diffusion in the following manner: ~3 mg of the material was dissolved in a minimal amount of cyclohexane in a small crystallization tube. This was placed into a 20 mL vial of acetone and the vial was capped. After 3 days, a crystal suitable for single crystal X-ray diffraction was grown.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79–0.66 (m, 4H), 0.83 (s, 3H), 0.96 (dd, J = 6.7, 2.3 Hz, 8H), 1.00 (d, J = 6.5 Hz, 3H), 1.37–1.04 (m, 22H), 1.49–1.37 (m, 4H), 1.69–1.56 (m, 3H), 1.85–1.70 (m, 7H), 1.95–1.86 (m, 1H), 2.05 (dt, J = 12.5, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.8, 56.5, 54.9, 47.0, 43.8, 43.6, 42.8, 40.3, 39.7, 39.1, 36.4, 36.2, 36.0, 35.7, 32.6, 32.4, 30.5, 30.4, 29.4, 28.4, 28.2, 27.1, 27.0, 25.8, 24.4, 24.0, 23.0, 22.7, 21.2, 18.8, 12.5, 12.3.

FTIR (Neat film NaCl): 2917, 2848, 1446, 1383, 1172, 930, 890.

HR-MS (GCT-LIFDI): Calculated for $C_{33}H_{58}$: 454.4539; measured: 454.4536.

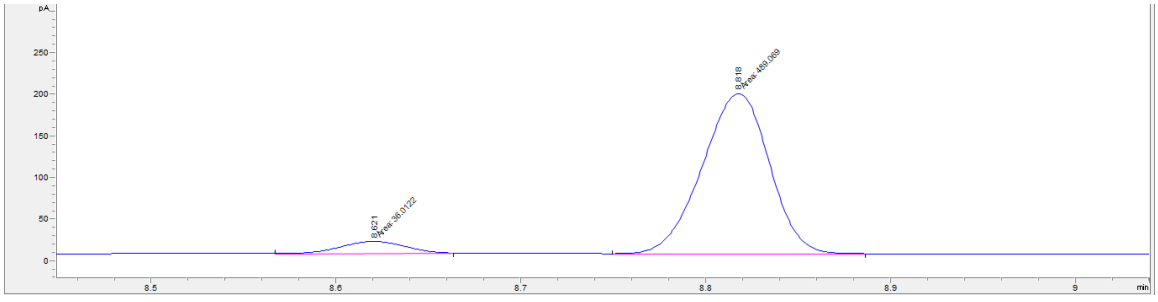
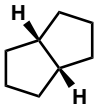


Figure 3.10. GC trace showing ~15:1 d.r. **3.10**.



(3a,6a)-Octahydropentalene (Table 3.1, entry 5). Synthesized according to general procedure 3.8.2.2.1. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol) and this was suspended in cyclohexane (0.5 mL, 4.63 mmol). Triethylsilane (12 mL, 0.075 mmol) along with a magnetic stirring bar were added to the mixture and the resulting suspension stirred for 10 minutes. Cyclooctenyl triflate (**3.11)** (18.0 mg, 0.07 mmol, 1.0 equiv) was added to the reaction and it stirred for 1 hours at 30 °C. The reaction was passed through silica in the glovebox and volatiles removed under reduced pressure to give (3a, 6a)-Octahydropentalene as a colorless oil (91% GC yield). NMR spectra match those reported in literature.[38]

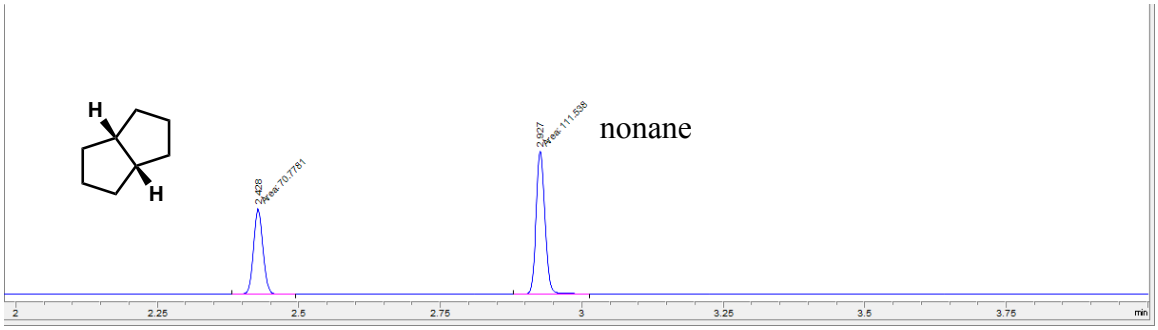


Figure 3.11. GC trace showing one to one mixture of nonane to (3a, 6a)-octahydropentalene.

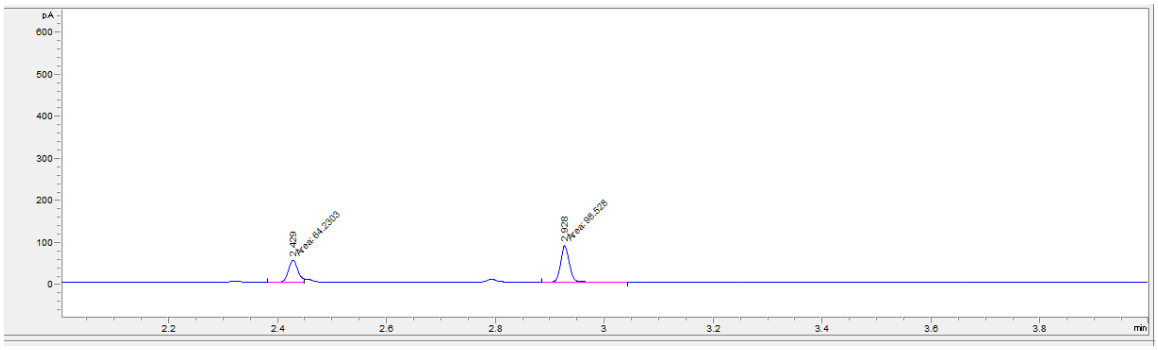
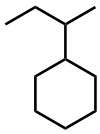


Figure 3.12. GC trace showing 91% yield of (3a, 6a)-octahydropentalene.



***sec*-Butylcyclohexane (3.25, Table 3.2, entry 1).** Synthesized according to a modified version of general procedure 3.8.2.2.1. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv) and this was suspended in cyclohexane (0.5 mL, 5.63 mmol). Triisopropylsilane (15 mL, 0.075 mmol, 1.2 equiv) along with a magnetic stirring bar were added to the mixture and the resulting suspension stirred for 10 minutes. Triflate **3.27** (10.2 mg, 0.05 mmol, 1.0 equiv) was added to the reaction and it stirred for 6 hours at 30 °C. Upon completion the reaction was passed through silica inside the glovebox and volatiles removed under reduced pressure. The crude product was further purified by silica column chromatography (hexanes) to give product **3.25** as a colorless oil. (85% GC yield). NMR spectra match those reported in literature.[39]

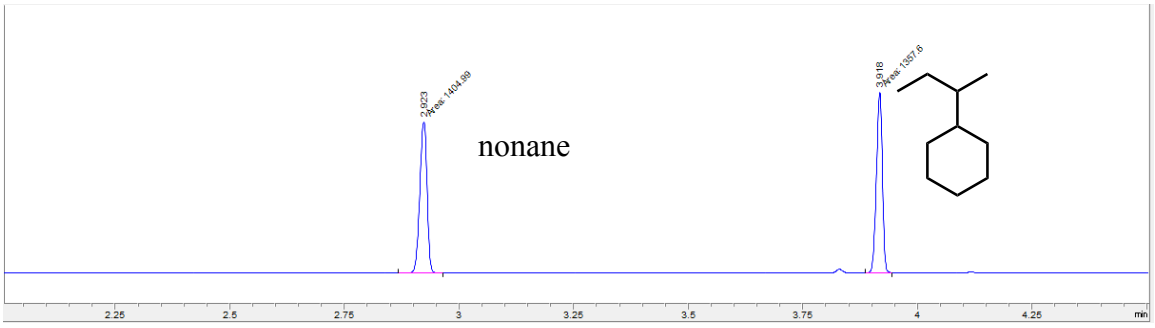


Figure 3.13. GC trace showing one to one mixture of nonane to *s*-butylcyclohexane.

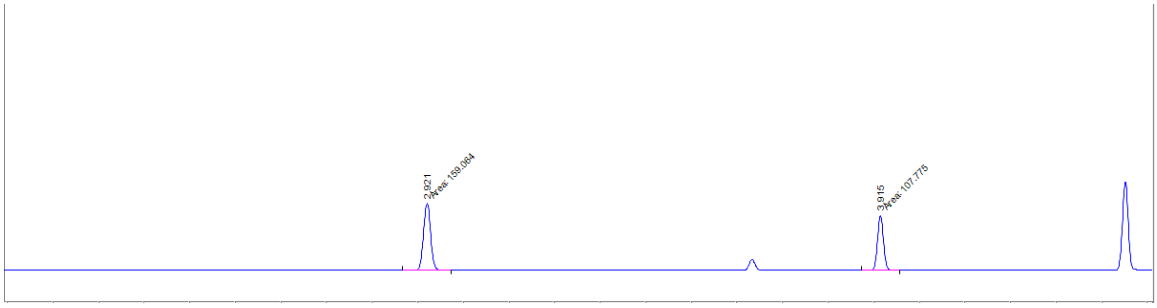
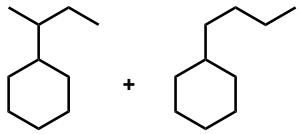


Figure 3.14. GC trace showing 85% yield of *s*-butylcyclohexane.



Butylcyclohexane (3.25, 3.26, Table 3.2, entry 2). A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv) and this was suspended in cyclohexane (0.5 mL). Triisopropylsilane (11.9 mg, 0.075 mmol, 1.5 equiv) was added the reaction along with a magnetic stir bar. After stirring the reaction for 5 minutes, triflate **3.28** (10.2 mg, 0.05 mmol, 1.0 equiv) was added and the reaction was heated to 70 °C. After 10 days, the reaction was cooled to room temperature and was passed through silica in the glovebox and volatiles removed under reduced pressure to give the ~1:1 mixture of product (16% *s*-butylcyclohexane, 19% *n*-butylcyclohexane GC yield).

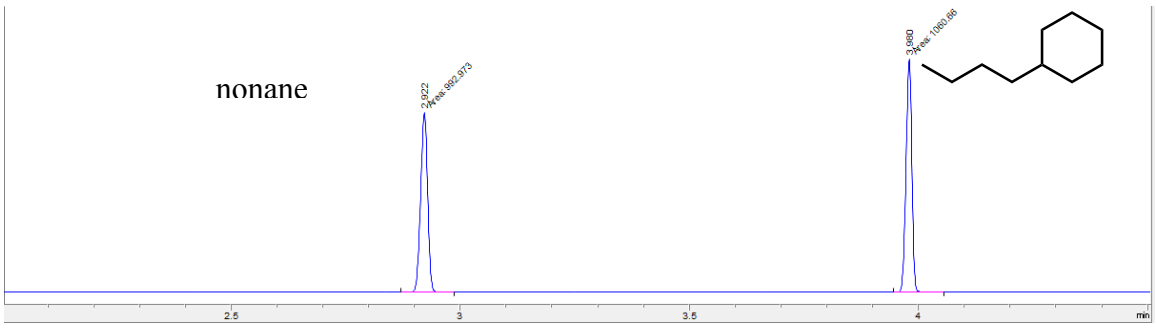


Figure 3.15. GC trace showing one to one mixture of nonane to *n*-butylcyclohexane.

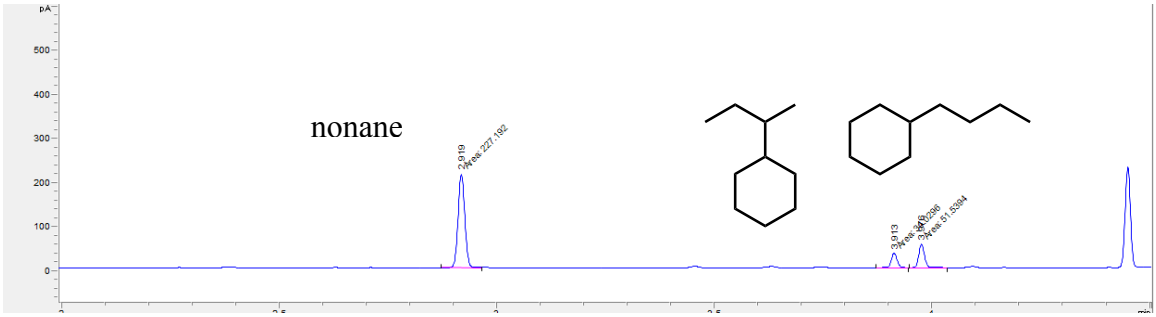
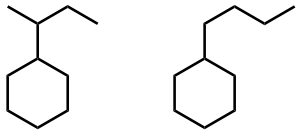


Figure 3.16. GC trace showing 16% yield of *sec*-butylcyclohexane and 19% yield of *n*-butylcyclohexane.



Butylcyclohexane (3.25, and **3.26, Table 3.2, entry 3).** A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.9 mg, 0.0025 mmol, 0.05 equiv) and this was dissolved in chloroform (3 mL) and hexanes (3 mL). Triflate **3.20** (10.2 mg, 0.05 mmol, 1.0 equiv) was added to the solution and it was cooled to –40 °C. Triethylsilane (12 mL, 0.075 mmol, 1.5 equiv) was quickly added and the reaction was stirred at –40 °C for 12 hours to give *n*-butylcyclohexane (**3.26,** 34% GC yield) and *s*-butylcyclohexane (**3.25**, 17% GC yield).

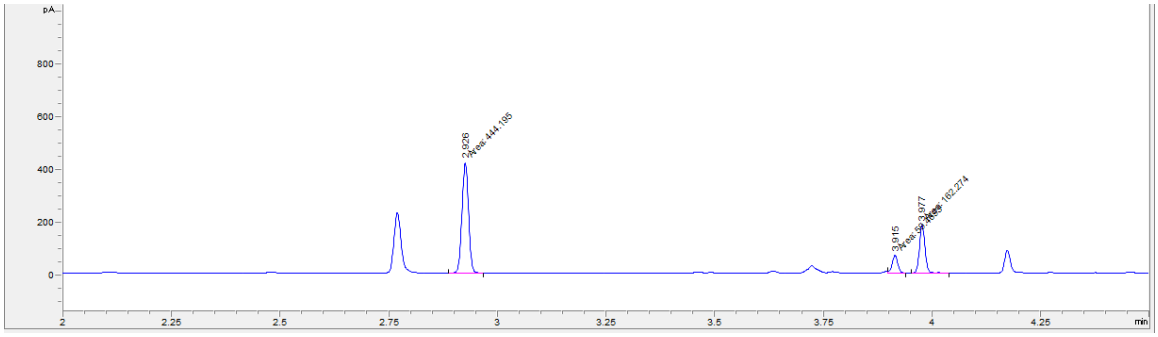
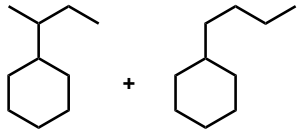


Figure 3.17. GC trace showing 17% yield of *s*-butylcyclohexane and 34% yield of *n*-butylcyclohexane.



Butylcyclohexane (3.25 and 3.26, Table 3.2, entry 4). Synthesized according to a modified version of general procedure 3.8.2.2.1. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv) and this was suspended in cyclohexane (9 mL). Triflate **3.20** (10.2 mg, 0.05 mmol, 1.0 equiv) was added to the reaction along with a magnetic stir bar. A solution of triethylsilane (12 ml, 0.075 mmol, 1.5 equiv) in cyclohexane (1 mL) was added portionwise to the reaction mixture over 10 minutes (100 mL every minute). 1 hour after the last addition of silane, the reaction was passed through silica in the glovebox and volatiles removed under reduced pressure to give the ~1:1 mixture of products *s*-butylcyclohexane **3.25** and *n*-butylcyclohexane **3.26** in 40% and 39% GC yields, respectively. The NMR spectra of the mixture matched the isolated NMR of the *s*-butylcyclohexane and the NMR of the commercial *n*-butylcyclohexane.[39]

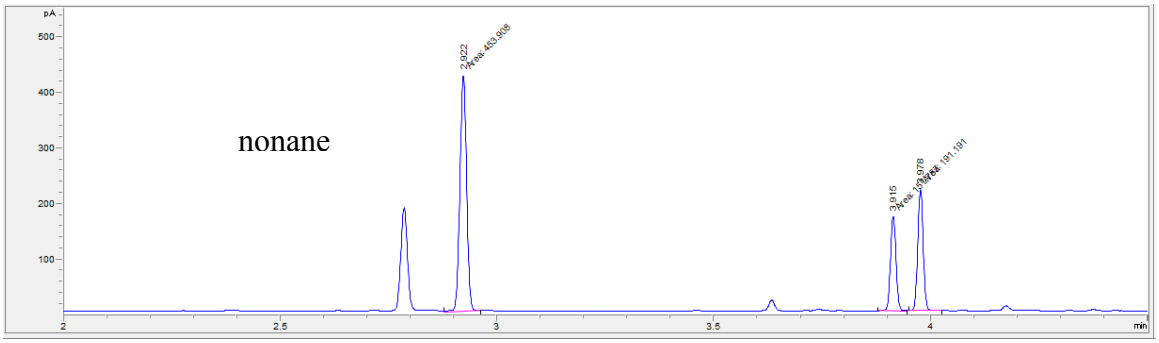
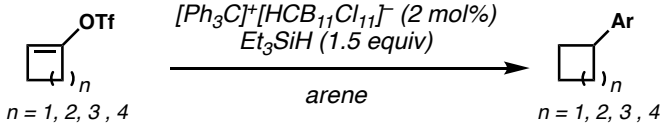


Figure 3.18. GC trace showing 40% yield of *s*-butylcyclohexane and 39% yield of *n*-butylcyclohexane.

3.8.2.3. Arene Alkylation Reactions

3.8.2.3.1 General Procedures for Intermolecular Reductive Friedel-Crafts Reactions.

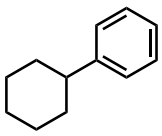


Scheme 3.2. General reaction scheme for intermolecular reductive Friedel-Crafts reactions.

General Procedure 3.A. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.02 equiv.) and this was dissolved in arene (enough to make a 0.1 M solution of vinyl triflate). Triethylsilane (1.5 equiv.) along with a magnetic stirring bar were added to the mixture and was shaken until it turned colorless. At this point, vinyl triflate (1.0 equiv.) was added to the reaction and it stirred for 0.1–48 hours at 30–75 °C (see substrates for specific details). Upon completion, the reaction mixture was pushed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles

removed under reduced pressure. Some substrates needed further purification by silica column chromatography (see below) or preparative high pressure liquid chromatography (HPLC).

General Procedure 3.B. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.02 equiv.) and this was dissolved in chloroform (enough to make a 0.1 M solution of vinyl triflate). Arene (10-50 equiv.) and vinyl triflate (1 equiv.) were added along with a magnetic stirring bar to the solution. The solution was cooled to –40 °C. At this point, silane (1.5 equiv.) was added to the reaction and it stirred at this temperature until completion (see substrates for specific details). Upon completion, the reaction mixture was pushed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles removed under reduced pressure. Some substrates needed further purification by silica column chromatography (see below) or preparative high pressure liquid chromatography (HPLC).



Phenylcyclohexane (3.29). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.002 mmol) and this was suspended in pentane (0.5 mL, 11.1 mmol). Triethylsilane (9.6 mL, 0.060 mmol), benzene (18 mL, 0.2 mmol, 4 equiv), and a magnetic stirring bar were added respectively to the mixture and stirred for 10 minutes. Cyclohexenyl triflate (**3.3**) (12.0 mg, 0.050 mmol) was added to the reaction and stirred for 2 hour at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed

under reduced pressure to give product **3.29** in 74% yield (GC). NMR spectra match those reported in literature.[20]

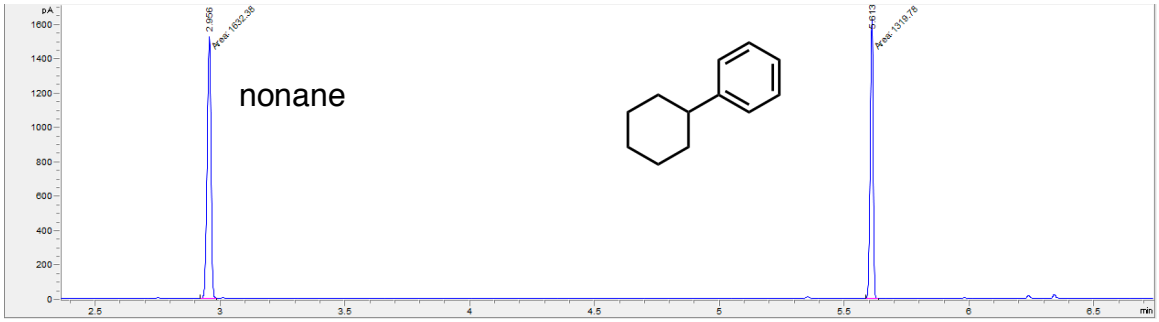


Figure 3.19. GC trace showing one to one mixture of nonane to phenylcyclohexane.

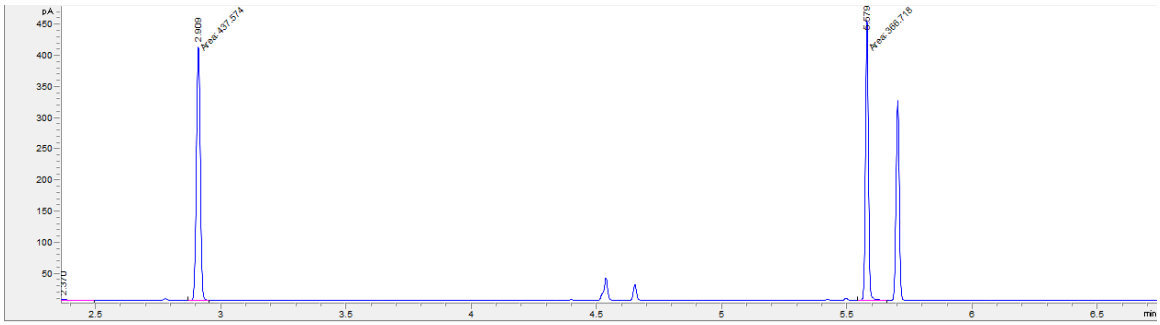
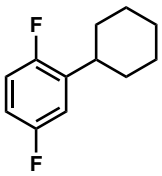


Figure 3.20. GC trace showing 74% yield of **3.29**.



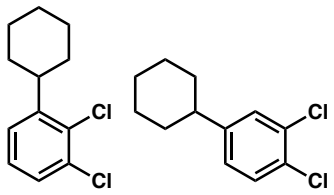
2-cyclohexyl-1,4-difluorobenzene (3.30). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (3.2 mg, 0.004 mmol) and this was suspended in pentane (0.5 mL) and 1,4-difluorobenzene (51 mL, 0.50 mmol). Triethylsilane (9.6 mL, 0.06 mmol) along with a magnetic stirring bar were added to the mixture and stirred for 10 minutes.

Cyclohexenyltriflate **(3.3**) (12.0 mg, 0.05 mmol) was added to the reaction and stirred for 3 hours at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to yield **3.30** in 49% yield (NMR). **3.30** was also synthesized as described above in 1,4-difluorobenzene solvent (0.5 mL). Crude material was purified by flash column chromatography (hexanes) to yield a colorless oil (22 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 – 6.88 (m, 2H), 6.83 – 6.78 (m, 1H), 2.84 (t, J = 10.8 Hz, 1H), 1.85 (br d, J = 10.5 Hz, 4H), 1.76 (br d, J = 12.9 Hz, 1H), 1.47 – 1.32 (m, 4H), 1.29 – 1.20 (m, 1H); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –119.4 (J = 17.7 Hz), –125.7 (J = 17.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9 (dd, $^{1}J_{C–F}$ = 240.8 Hz, $^{4}J_{C–F}$ = 2.3 Hz), 156.4 (dd, $^{1}J_{C–F}$ = 239.9 Hz, $^{4}J_{C–F}$ = 2.4 Hz), 136.3 (dd, $^{2}J_{C–F}$ = 17.4 Hz, $^{3}J_{C–F}$ = 7.0 Hz), 115.9 (dd, $^{2}J_{C–F}$ = 26.2 Hz, $^{3}J_{C–F}$ = 8.7 Hz), 114.1 (dd, $^{2}J_{C–F}$ = 24.0 Hz, $^{3}J_{C–F}$ = 5.5 Hz), 113.1 (dd, $^{2}J_{C–F}$ = 24.1 Hz, $^{3}J_{C–F}$ = 8.8 Hz), 37.1, 32.9, 26.7, 26.0.

FTIR (Neat film NaCl): 2928, 2854, 1625, 1596, 1493, 1450, 1425, 1232, 1178, 866, 810, 780, 731.

HR-MS (GCT-LIFDI): Calculated for $C_{12}H_{14}F_2$: 196.1064; measured: 196.1067.



~1:5 ratio

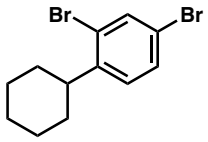
1,2-dichloro-4-cyclohexylbenzene (3.31). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^{+}[HCB_{11}Cl_{11}]^{-}$ (3.2 mg, 0.004 mmol) and this was suspended in 1,4-difluorobenzene (2 mL, 19.5 mmol). Triethylsilane (48 mL, 0.3 mmol) along with a

magnetic stirring bar were added to the mixture and stirred until colorless. Cyclohexenyltriflate (**3.3**) (46.0 mg, 0.20 mmol) was added the reaction and it stirred for 1 hour at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give product **3.31** as a mixture of isomers in 47% yield (NMR) and 9% yield (NMR). Crude material was further purified *via* flash column chromatography (hexanes) to give product **3.31** (mixture of isomers) as a colorless oil.

^{1}H NMR major isomer (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.03 (dd, J = 8.3, 1.9 Hz, 1H), 2.46 (dd, J = 10.2, 7.5 Hz, 1H), 1.84 (br d, J = 12.9 Hz, 4H), 1.75 (br d, J = 12.9 Hz, 1H), 1.41 – 1.33 (m, 4H), 1.28 – 1.19 (m, 2H); ^{13}C NMR major isomer (125 MHz, $CDCl_3$) δ 148.4, 132.2, 130.3, 129.6, 129.0, 126.5, 44.0, 34.4, 26.8, 26.1.

FTIR (Neat film NaCl): 2924, 2852, 1584, 1560, 1475, 1461, 1449, 1131, 1028, 671, 592.

HR-MS (GCT-LIFDI): Calculated for $C_{12}H_{14}Cl_2$: 228.0473; measured: 228.0473.

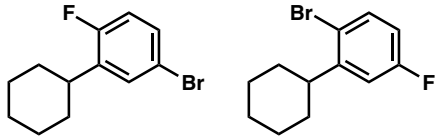


2,4-dibromo-1-cyclohexylbenzene (3.32). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol) and this was dissolved in 1,3-dibromobenzene (0.5 mL, 3.4 mmol). Triethylsilane (12 mL, 0.075 mmol) along with a magnetic stirring bar were added to the mixture and the resulting solution stirred for 10 minutes. Triflate **3.3** (12.0 mg, 0.05 mmol) was added to the reaction and stirred for 2 hours at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give product **3.32** in 51% yield (NMR). The crude product was further purified by reverse phase HPLC (9:1 acetonitrile:water) to give pure product as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.0 Hz, 2H), 7.38 (dd, *J* = 8.3, 2.0 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 2.90 (tt, *J* = 11.6, 3.0 Hz, 1H), 1.90 – 1.81 (m, 4H), 1.49 – 1.18 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 135.1, 130.8, 128.6, 125.1, 119.7, 43.0, 33.3, 26.9, 26.2.

FTIR (Neat film NaCl): 2924, 2851, 1730, 1577, 1551, 1465, 1448, 1379, 1083, 1033, 998, 812, 779, 720, 700, 553.

HR-MS (GCT-LIFDI): Calculated for $C_{12}H_{14}Br_2$: 317.9442; measured: 317.9455.



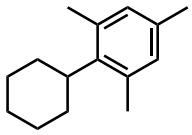
5.4:1

4-bromo-2-cyclohexyl-1-fluorobenzene (3.33). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol) and this was dissolved in 1,4-bromofluorobenzene (0.5 mL, 4.6 mmol). Triethylsilane (12 mL, 0.075 mmol) along with a magnetic stirring bar were added to the mixture and the resulting solution stirred for 10 minutes. Triflate **3.3** (12.0 mg, 0.05 mmol) was added to the reaction and stirred for 2 hours at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give product **3.33** as a mixture of isomers in 43% and 8% yield (NMR), respectively. The reaction mixture was purified by reverse phase HPLC (85:15 acetonitrile:water) to give the product **3.33** and a regioisomer as a mixture (~5:1 ratio) as a colorless oil. Major isomer was assigned by looking at the ^{13}C NMR and the HSQC. By ^{13}C NMR, the carbon on the fluorine and the carbons *ortho* to the fluorine could be assigned by their large $^{1}J_{C\text{-}F}$ and $^{2}J_{C\text{-}F}$ values respectively. Of the two carbons *ortho* to the fluorine, only one of them was attached to a hydrogen, meaning that the other position was cyclohexylated.

^{1}H NMR major isomer (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 6.5, 2.5 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.87 (dd, J = 9.9, 8.7 Hz, 1H), 2.85 – 2.77 (m, 1H), 1.87 – 1.80 (m, 4H), 1.79 – 1.72 (m, 1H), 1.44 – 1.36 (m, 4H), 1.30 – 1.21 (m, 1H); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ –119.4; ^{13}C NMR major isomer (125 MHz, $CDCl_3$) δ 159.8 (d, $^{1}J_{C–F}$ = 244.9 Hz), 137.0 (d, $^{2}J_{C–F}$ = 16.3 Hz), 130.9 (d, $^{3}J_{C–F}$ = 5.4 Hz), 130.0 (d, $^{3}J_{C–F}$ = 5.7 Hz), 117.1 (d, $^{2}J_{C–F}$ = 24.8 Hz), 116.7 (d, $^{4}J_{C–F}$ = 3.3 Hz), 37.2 (d, $^{3}J_{C–F}$ = 1.7 Hz, 33.0, 26.8, 26.2.

FTIR (Neat film NaCl): 2929, 2853, 1605, 1579, 1480, 1449, 1232, 1181, 1168, 1099, 1005, 869, 810, 612.

HR-MS (GCT-LIFDI): Calculated for $C_{12}H_{14}BrF$: 256.0263; measured: 256.0260.



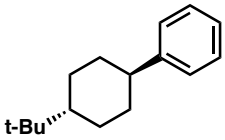
2-cyclohexyl-1,3,5-trimethylbenzene (3.34). Synthesized according to a modified procedure. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was suspended in perfluorohexanes (1.0 mL). Triethylsilane (24 mL, 0.15 mmol) and mesitylene (120 mg, 0.1 mmol) along with a magnetic stirring bar were added to the mixture and the resulting suspension stirred for 10 minutes. Triflate **3.3** (24.0 mg, 0.1 mmol) was added to the reaction and stirred for 3 minutes at 30 °C. The reaction mixture was quenched with anhydrous ether inside the glovebox and then plugged through silica inside the glovebox to give the crude material as a colorless oil in 61% NMR yield. The crude was further purified by reverse phase HPLC (85:15 acetonitrile:water) to give product **3.34** as a colorless oil.

^{1}H NMR (500 MHz, 57 °C, $CDCl_3$) δ 6.79 (s, 2H), 3.02 – 2.94 (m, 1H), 2.37 (s, 6H), 2.23 (s, 3H), 1.96 – 1.85 (m, 3H), 1.77 (br d, J = 12.3 Hz, 1H), 1.68 (br d, J = 13.1 Hz, 1H), 1.44 – 1.26

(m, 4H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 2H), 2.97 (tt, *J* = 12.4, 3.3 Hz, 1H), 2.51 – 2.29 (m, 6H), 2.24 (s, 3H), 1.96 – 1.83 (m, 4H), 1.80–1.74 (m, 1H), 1.71 – 1.65 (m, 2H), 1.45 – 1.23 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 136.3, 134.9, 131.3, 129.4, 41.4, 30.7, 27.9, 26.6, 21.8, 20.7.

FTIR (Neat film NaCl): 2924, 2851, 1612, 1483, 1448, 1369, 1261, 1025, 849, 572.

HR-MS (GCT-LIFDI): Calculated for $C_{15}H_{22}$: 202.1721; measured: 202.1727.

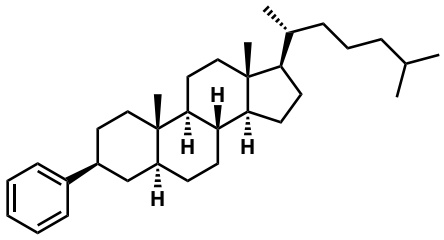


***anti*-4-(*tert*-Butyl)cyclohexyl)benzene (3.37).** Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was suspended in benzene (1 mL, 11.2 mmol). Triethylsilane (24 mL, 0.15 mmol) along with a magnetic stirring bar were added to the mixture and stirred until colorless. The corresponding triflate (29.0 mg, 0.10 mmol) was added to the reaction and stirred for 10 minutes at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give **3.37** as a mixture of diastereomers (44% NMR yield of *trans*, 5% NMR yield of *cis*).[40] The crude product was further purified by reverse phase prep HPLC (95:5 acetonitrile/water) to give the *trans* product **3.37** as a colorless oil (7.5 mg, 35%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.20 (m, 2H), 7.20 – 7.16 (m, 1H), 2.45 (tt, *J* = 12.2, 3.5 Hz, 1H), 1.99 – 1.87 (m, 4H), 1.45 (qd, *J* = 12.5, 2.6 Hz, 2H), 1.21 – 1.05 (m, 3H), 0.89 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 128.4, 127.0, 125.9, 47.92, 44.7, 34.9, 32.6, 27.9, 27.8.

FTIR (Neat film NaCl): 3061, 3027, 2937, 2921, 2855, 1602, 1493, 1479, 1448, 1364, 1232, 895, 755, 697, 532.

HR-MS (GCT-LIFDI): Calculated for $C_{16}H_{24}$: 216.1878; measured: 216.1889.

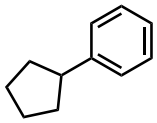


(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-3-phenylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene (3.38). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol) and this was suspended in benzene (0.5 mL, 5.6 mmol). Triethylsilane (12 mL, 0.075 mmol) along with a magnetic stirring bar were added to the mixture and the resulting suspension stirred for 10 minutes. Triflate **3.9** (26.0 mg, 0.05 mmol) was added to the reaction and stirred for 2 hours at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give product **3.38** as a diastereomeric mixture in 79% and 11% yield (NMR) of the major and minor diastereomers, respectively. The crude mixture was purified *via* silica column chromatography (hexanes) to give an inseparable mixture of diastereomers as a white solid (18.5 mg, 85% of mixture). Assignment of major isomer was based on key cross-peaks in ^{1}H COSY and ^{1}H NOESY spectroscopy experiments. From the major benzylic proton, adjacent protons were identified at 1.47 ppm and 1.72 ppm through COSY. The same peaks were observed in NOESY in addition to two peaks at 1.08 ppm and 1.26 ppm corresponding to 1,3-diaxial interactions of the benzylic proton. Through 2D HSQC and HMBC experiments, the cross-peak at 1.26 ppm was determined to be the *trans*-decalin proton.

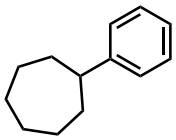
Major Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.27 – 7.24 (m, 2H), 7.22 – 7.18 (m, 1H), 2.58 (tt, *J* = 11.5, 5.0 Hz, 1H), 2.02 (dt, *J* = 12.5, 3.4 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.77 – 1.66 (m, 3H), 1.65 – 1.58 (m, 2H), 1.56 – 1.46 (m, 3H), 1.43 – 1.25 (m, 9H), 1.23 – 1.00 (m, 11H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 2.3 Hz, 3H), 0.90 (s, 3H), 0.89 (d, *J* = 2.3 Hz, 3H), 0.77 – 0.71 (m, 1H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 128.4, 127.0, 125.9, 56.8, 56.5, 54.8, 47.2, 45.0, 42.8, 39.7, 39.1, 36.8, 36.4, 36.0, 35.9, 35.7, 30.0, 28.2, 24.0, 23.0, 22.7, 18.9, 12.7, 12.3.

FTIR (Neat film NaCl): 3070, 3023, 2926, 2846, 1466, 1381, 757, 696, 513.

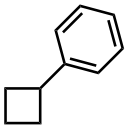
HR-MS (GCT-LIFDI): Calculated for $C_{33}H_{52}$: 448.4069; measured: 448.4058.



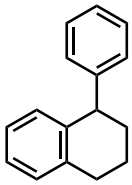
Phenylcyclopentane (3.39). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was suspended in benzene (1 mL, 11.2 mmol). Triethylsilane (24 mL, 0.15 mmol) along with a magnetic stirring bar were added to the mixture and stirred until colorless. Cyclopentenyl triflate (22.0 mg, 0.10 mmol) was added to the reaction and stirred for 6 days at 70 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give phenylcyclopentane (**3.39**) in 64% yield (NMR). The crude product was further purified by flash column chromatography (hexanes) to give phenylcyclopentane as a colorless oil (7.6 mg, 52%). NMR spectra match those reported in literature.[20]



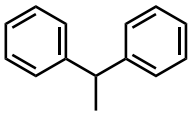
Phenylcycloheptane (3.40). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was suspended in benzene (1 mL, 11.2 mmol). Triethylsilane (24 mL, 0.15 mmol) along with a magnetic stirring bar were added to the mixture and stirred until colorless. Cycloheptenyl triflate (24.0 mg, 0.10 mmol) was added to the reaction and stirred for 1.5 hours at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give product **3.40** in 71% yield (NMR) with ~10% yield of (cyclohexylmethyl)benzene as a small inseparable side product. NMR data match those reported in literature.[20, 41]



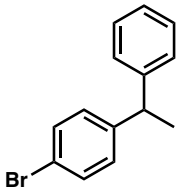
Phenylcyclobutane (3.41). Synthesized according to a modified general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol) and this was dissolved in benzene (10 mL, 112 mmol). Triisopropylsilane (15 mL, 0.075 mmol) along with a magnetic stirring bar were added to the mixture and stirred until colorless. Cyclobutenyl triflate (10.0 mg, 0.05 mmol) was added to the reaction and stirred for 0.5 hours at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give product **3.41** in 57% yield (NMR). The crude product was purified *via* silica column chromatography (hexanes) to give phenylcyclobutane as a colorless oil. NMR data match those reported in literature.[42]



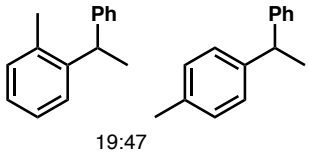
1-phenyl-1,2,3,4-tetrahydronaphthalene (3.42). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was suspended in benzene (1 mL, 11.2 mmol). Triethylsilane (24 mL, 0.15 mmol) along with a magnetic stirring bar were added to the mixture and stirred until colorless. The corresponding triflate (28.0 mg, 0.10 mmol) was added to the reaction and stirred for 2 days at 60 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give triflate **3.42** in 43% yield (NMR). Crude material was purified by flash column chromatography (hexanes) to give product **3.42** as a colorless oil (8.6 mg, 41.3%). NMR spectra match those reported in literature.[43]



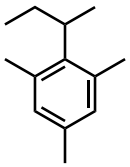
1,1-Diphenylethane (3.43). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was suspended in benzene (1 mL, 11.2 mmol). Triethylsilane (24 ,mL, 0.15 mmol) along with a magnetic stirring bar were added to the mixture and stirred until colorless. The corresponding triflate (29.0 mg, 0.10 mmol) was added to the reaction and stirred for 1 hour at 30 °C. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give triflate **3.43** in 77% yield (NMR). Crude material was further purified *via* flash column chromatography (hexanes) to give product **3.43** as a colorless oil (12.2 mg, 67%). NMR spectra match those reported in literature.[43]



1-bromo-4-(1-phenylethyl)benzene (3.44). Synthesized according to general procedure 3.A. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv.) and this was dissolved in benzene (0.5 mL). Triethylsilane (7.0 mg, 0.060 mmol, 1.2 equiv.) and 1-(4-bromophenyl)vinyl trifluoromethanesulfonate (10.2 mg, 0.05 mmol) were added along with a magnetic stirring bar to the solution and stirred for 2 hours. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure to give product **3.44** in 51% yield (NMR) as a colorless oil. NMR spectra match those reported in literature.[44]



1-methyl-4-(1-phenylethyl)benzene (3.45). Synthesized according to general procedure 3.B. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was dissolved in chloroform (1 mL). Toluene (92 mg, 1 mmol) and 1-phenylvinyl trifluoromethanesulfonate (25.2 mg, 0.1 mmol) were added along with a magnetic stirring bar to the solution. The solution was cooled to –40 °C. At this point, triethylsilane (17.4 mg, 0.15 mmol) was added to the reaction and stirred at –40 °C for 1 hour. The reaction mixture was warmed to room temperature and was plugged through silica in the glovebox and volatiles removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes) to give an inseparable mixture of products **3.45** in 47% and 19% yield, *para* and *ortho* isomers, respectively, as a colorless oil. NMR spectra match those reported in literature.[45, 46]

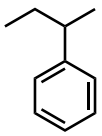


2-(*sec*-butyl)-1,3,5-trimethylbenzene (3.46). Synthesized according to general procedure 3.B. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was dissolved in chloroform (1 mL). Mesitylene (120 mg, 1 mmol) and but-1-en-2-yl trifluoromethanesulfonate (**3.20**) (20.4 mg, 0.1 mmol) were added along with a magnetic stirring bar to the solution. The solution was cooled to –40 °C. At this point, triethylsilane (17.4 mg, 0.15 mmol) was added to the reaction and it stirred at –-40 °C for 1 hour. The reaction mixture was warmed to room temperature and pushed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes) to give **3.46** as a colorless oil (80% NMR yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 2H), 3.14 (sex, J = 7.5 Hz, 1H), 2.32 (br s, 6H), 2.26 (s, 3H), 1.83 – 1.67 (m, 2H), 1.30 (d, J = 7.3 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 136.4, 134.8, 131.2, 129.6, 36.7, 28.4, 21.7, 20.8, 19.0, 13.3.

FTIR (Neat film NaCl): 2962, 2926, 2872, 1612, 1455, 1377, 850, 578.

HR-MS (GCT-LIFDI): Calculated for $C_{13}H_{20}$: 176.1565; measured: 176.1572.



***sec*-butylbenzene (3.47).** Synthesized according to a modified general procedure 3.B. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv.) and this was

dissolved in chloroform (0.4 mL). Benzene (195 mg, 2.5 mmol, 50 equiv.) and but-1-en-2-yl trifluoromethanesulfonate (**3.20**) (10.2 mg, 0.05 mmol) were added along with a magnetic stirring bar to the solution. Triisopropylsilane (11.9 mg, 0.075 mmol, 1.5 equiv.) was added dropwise to the reaction and stirred for 1 hour. The reaction was plugged through silica in the glovebox and volatiles removed under reduced pressure. The solution was brought out and volatiles removed under reduced pressure) to give product **3.47** in 95% yield (GC) as a colorless oil. NMR spectra match those reported in literature.[47]

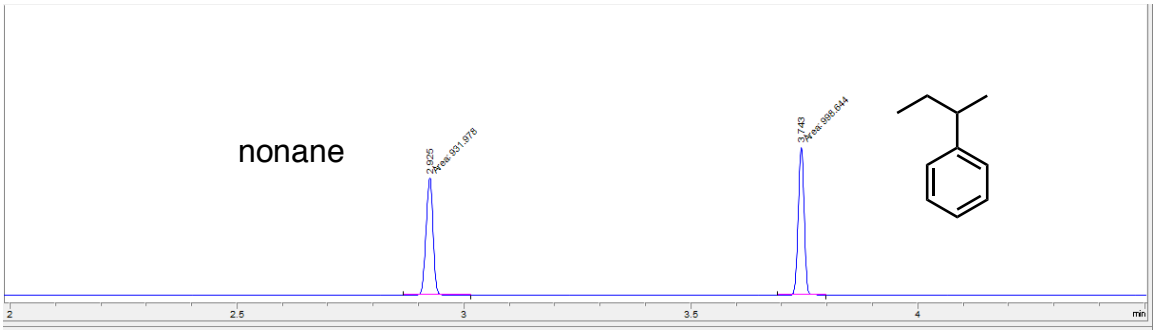


Figure. 3.21. GC trace of a 1:1 mixture of nonane to *s*-butylbenzene.

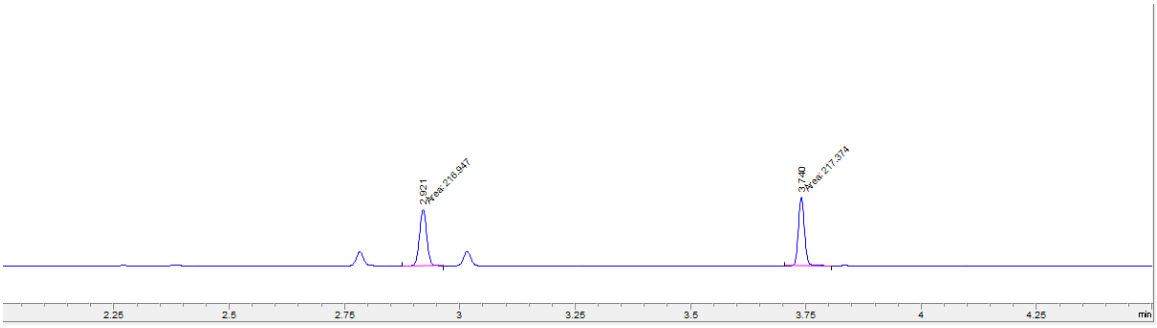
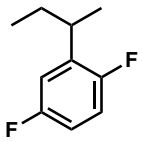


Figure 3.22. GC trace showing a 95% yield of *s*-butylbenzene.



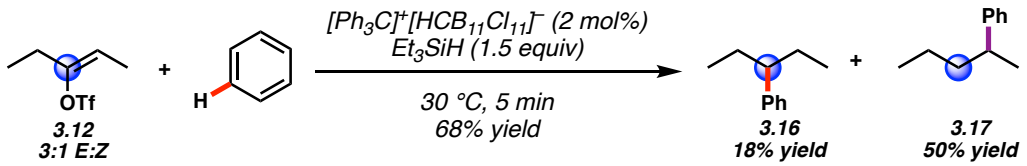
2-(*sec*-butyl)-1,4-difluorobenzene (3.48). Synthesized according to general procedure 3.B. A dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (1.6 mg, 0.002 mmol) and this was dissolved in chloroform (1 mL). 1,4-Difluorobenzene (114 mg, 1 mmol) and but-1-en-2-yl trifluoromethanesulfonate (**3.20**) (20.4 mg, 0.1 mmol) were added along with a magnetic stirring bar to the solution. The solution was cooled to –40 °C. At this point, triisopropylsilane (23.8 mg, 0.15 mmol) was added to the reaction and it stirred at –40 °C for 3 hours. The reaction mixture was warmed to room temparature and pushed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles removed under reduced pressure. The crude material was further purified by flash column chromatography (petroleum ether) with silver nitrate impregnated silica gel as a stationary phase to give product **3.48** as a colorless oil (46% NMR yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (td, J = 9.2, 4.6 Hz, 1H), 6.88 (ddd, J = 12.8, 6.2, 3.4 Hz, 1H), 6.85 – 6.79 (m, 1H), 3.00 – 2.93 (sex, J = 7.0, 2H), 1.60 (sex, J = 7.0 Hz, 2H), 1.22 (d, J = 7.0 Hz, 3H), 0.84 (t, J = 7.0, 3H); ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$) δ –119.5 (d, J = 17.8 Hz), –125.2 (d, J = 17.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9 (d, $^1J_{C–F}$ = 241.0 Hz), 156.7 (d, $^1J_{C–F}$ = 239.8 Hz), 136.0 (dd, $^2J_{C–F}$ = 17.5 Hz, $^3J_{C–F}$ = 6.9 Hz), 116.1 (dd, $^2J_{C–F}$ = 26.3 Hz, $^3J_{C–F}$ = 8.7 Hz), 114.2 (dd, $^2J_{C–F}$ = 13.8 Hz, $^3J_{C–F}$ = 5.6 Hz), 113.3 (dd, $^2J_{C–F}$ = 24.1 Hz, $^3J_{C–F}$ = 8.8 Hz), 34.1, 29.8, 20.4, 12.0.

FTIR (Neat film NaCl): 2963, 2931, 2875, 1596, 1496, 1464, 1415, 1380, 1180, 1165, 870, 810, 758, 731.

HR-MS (GCT-LIFDI): Calculated for $C_{10}H_{12}F_2$: 170.0907; measured: 170.0905.

3.8.2.4 Mechanistic Experiments



Scheme 3.3. Exploring the selectivity of reductive Friedel-Crafts reactions of vinyl triflates.

***3*-pentenylbenzene and 2-pentenylbenzene (3.16 and 3.17**) Synthesized according to general procedure 3.A. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.8 mg, 0.001 mmol, 0.02 equiv.) and this was dissolved in benzene (0.5 mL). Triethylsilane (7.0 mg, 0.060 mmol, 1.2 equiv.) and pentenyltriflate (**3.12**) (10.2 mg, 0.05 mmol) were added along with a magnetic stirring bar to the solution and stirred for 5 minutes. The reaction mixture was pushed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles removed under reduced pressure to give **3.16** and **3.17** in 18% yield and 50% yield (GC), respectively.

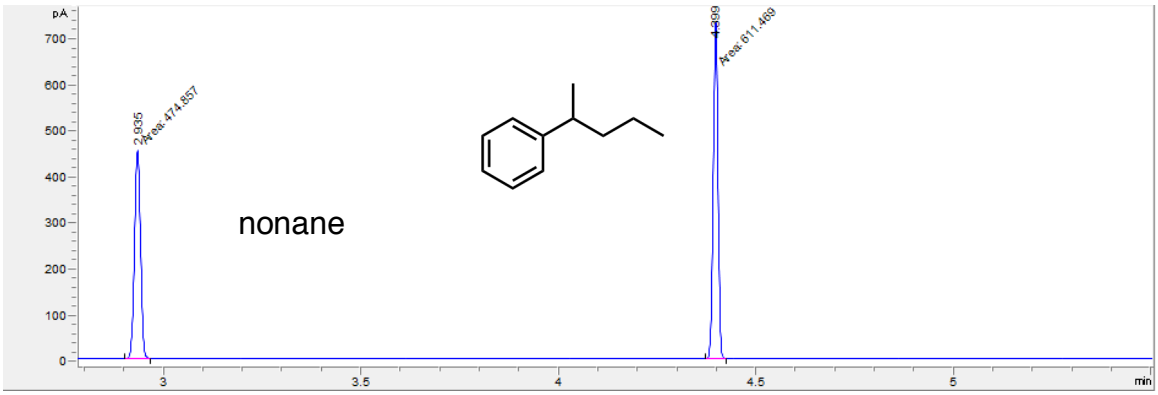


Figure 3.23. GC trace showing 1:1 mixture of *nonane* and 2-phenylpentane.

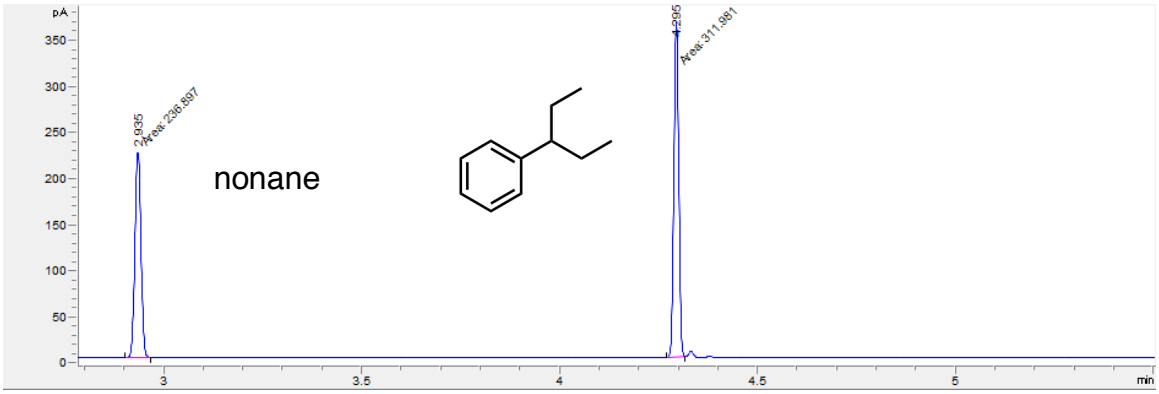


Figure 3.24. GC trace showing 1:1 mixture *nonane* and 3-phenylpentane.

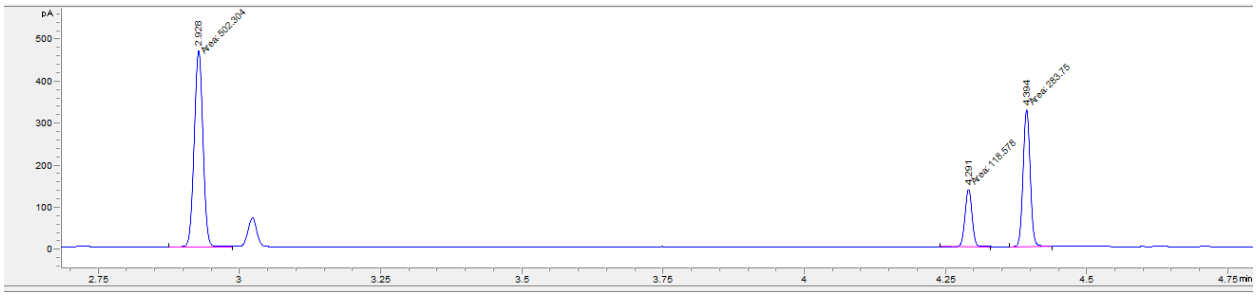
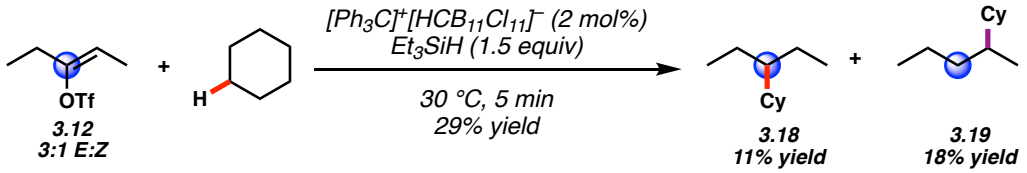


Figure 3.25. GC trace for reaction showing combined 68% yield.



Scheme 3.4. Exploring the selectivity of C–H insertion reactions of vinyl triflates.

***3*-pentenylcyclohexane and 2-pentenylcyclohexane (3.18 and 3.19**) Synthesized according to general procedure 3.A. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (2.3 mg, 0.003 mmol, 0.02 equiv.) and to the vial was added cyclohexane (0.32 mL). Triethylsilane (21.0 mg, 0.180 mmol, 1.2 equiv.) and pentenyltriflate (**3.12**) (33 mg, 0.15 mmol) were added along with a magnetic stirring bar to the solution and stirred for 5 minutes. The reaction mixture was pushed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles removed under reduced pressure. Crude material was further purified by flash column chromatography to give **3.18** and **3.19** as a mixture of isomers (4.6 mg, 29% yield).

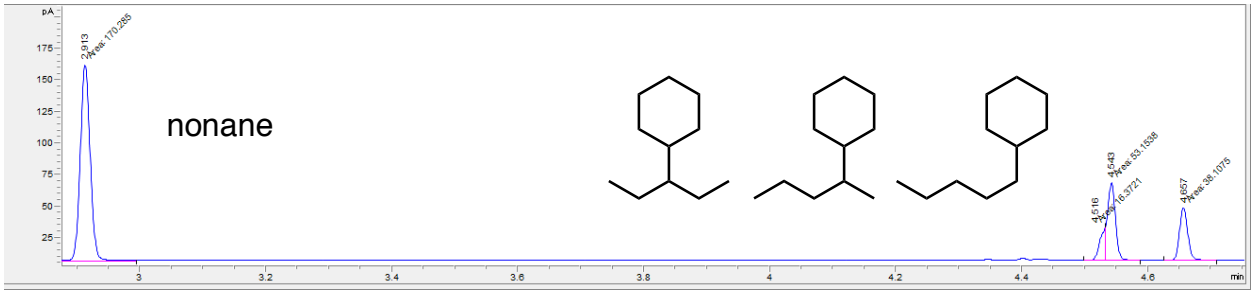


Figure 3.26. GC trace for internal standard *nonane* and cyclohexylpentane isomers.

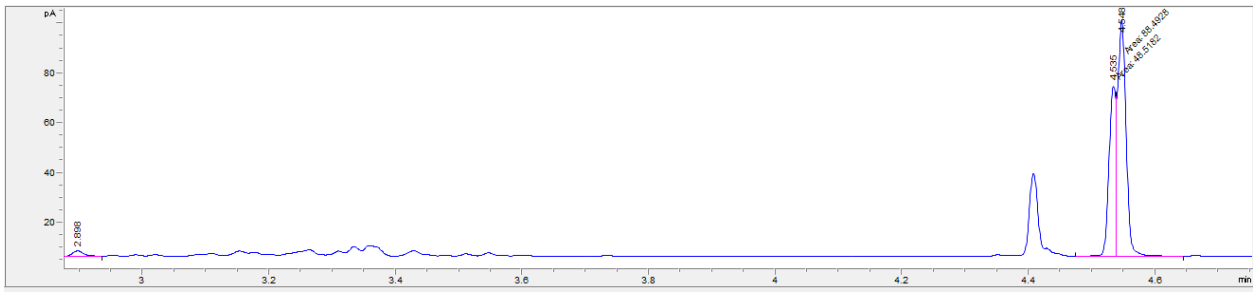


Figure 3.27. GC trace of reaction mixture showing formation of **3.18** and **3.19**.

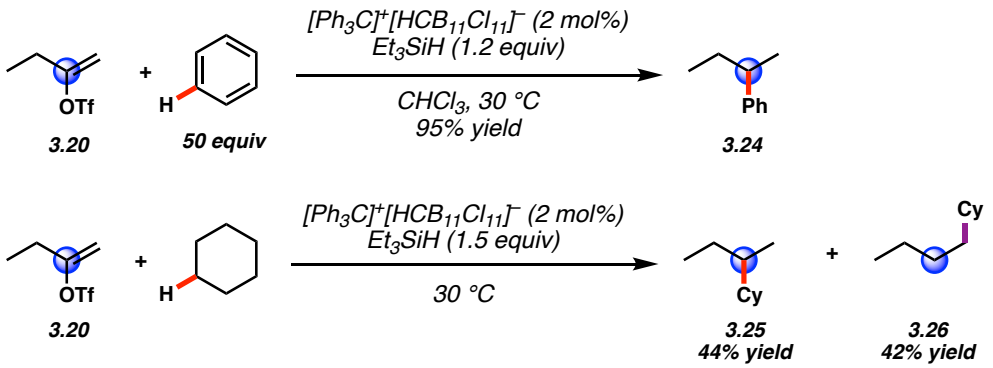
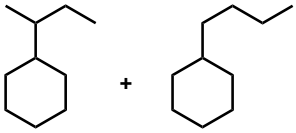
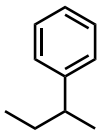


Figure 3.28. Improved mechanistic probe for C–C bond forming reactions of vinyl cations.



***sec*-butylbenzene (3.24).** See procedure outlined for synthesis of **3.47**.



Butylcyclohexane (3.25 and 3.26). See procedure outlined for synthesis of **Table 3.2**, **entry 4**.

3.9 Spectra Relevant to Chapter Three

Teaching an Old Carbocation New Tricks: Intermolecular C–H Insertion Reactions of Vinyl Carbocations

Adapted from: Stasik Popov, Brian Shao, Alex L. Bagdasarian, Tyler R. Benton, Luyi Zou, Zhongyue Yang, K. N. Houk, and Hosea M. Nelson

Science **2018**, *361*, 381–387.

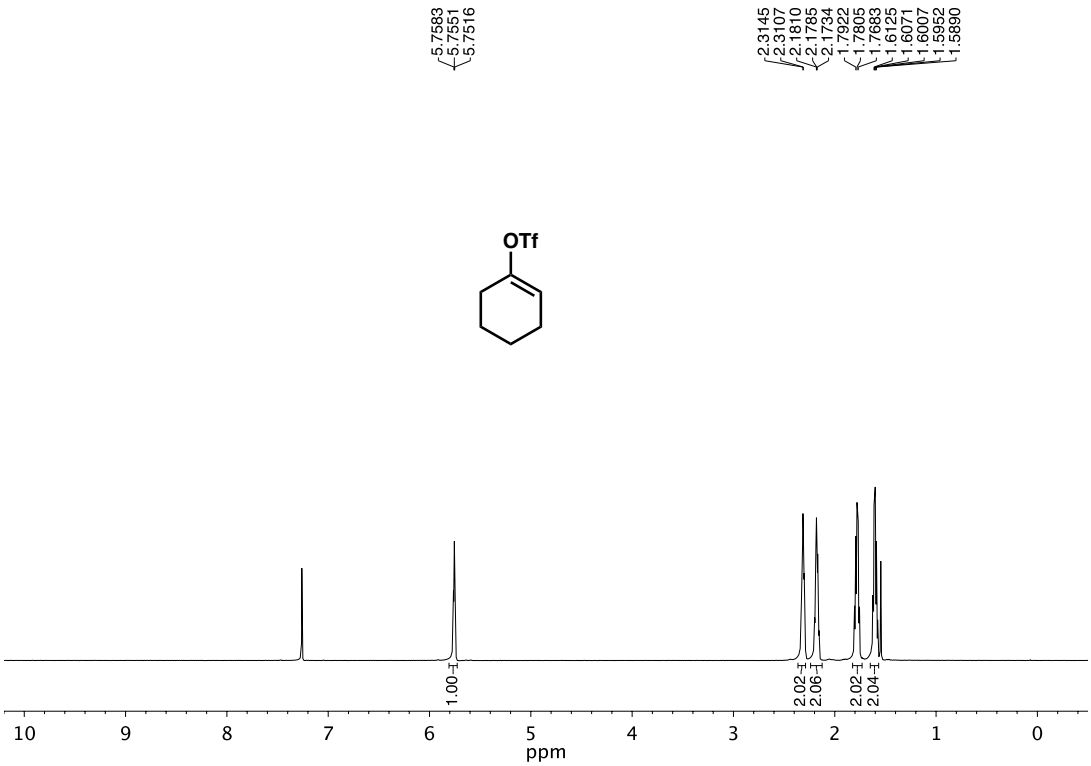


Figure 3.29. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.3**.

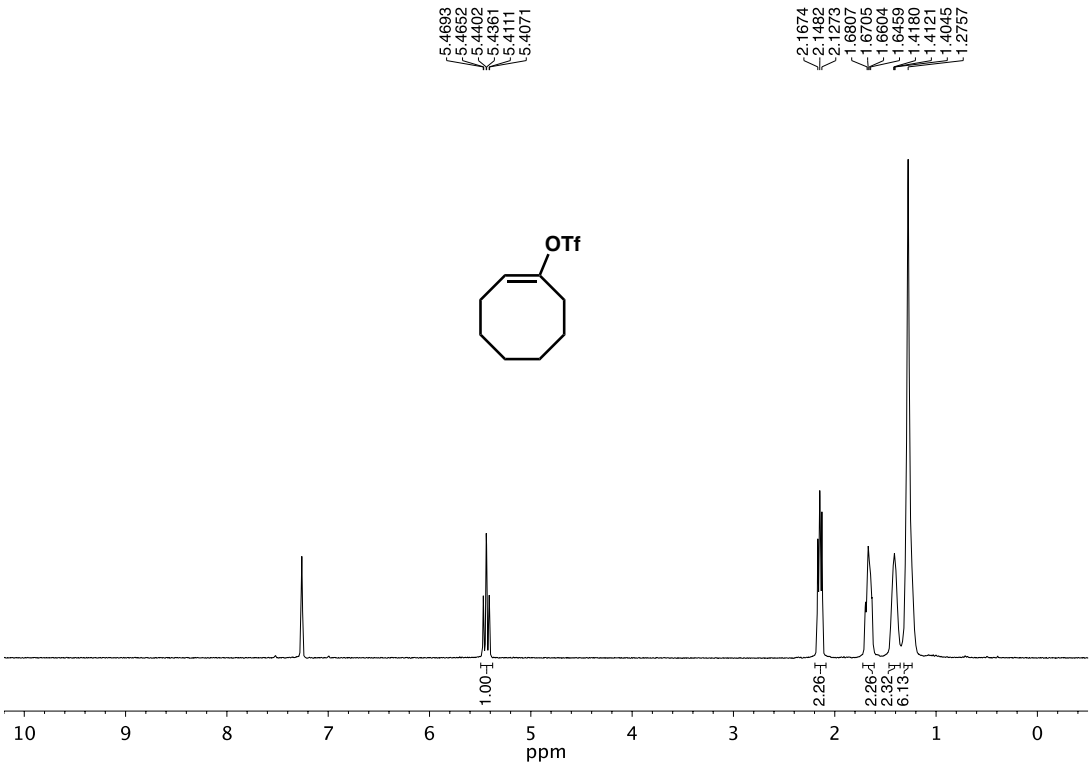


Figure 3.30. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.11**.

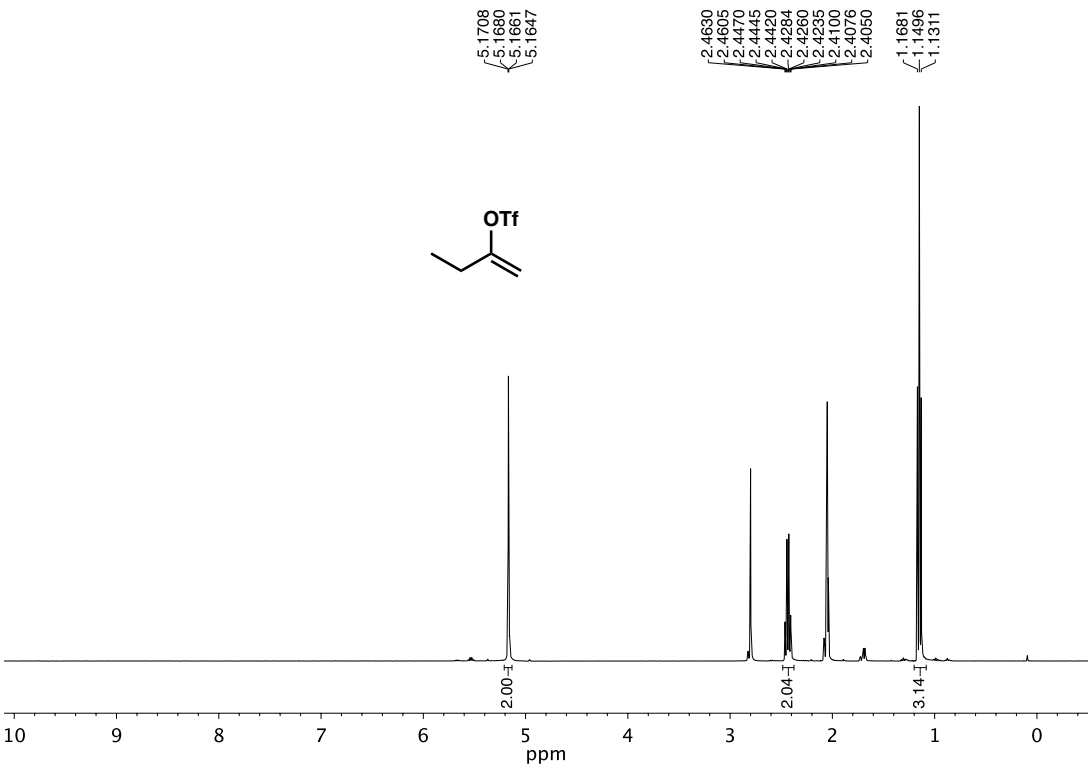


Figure 3.31. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.20**.

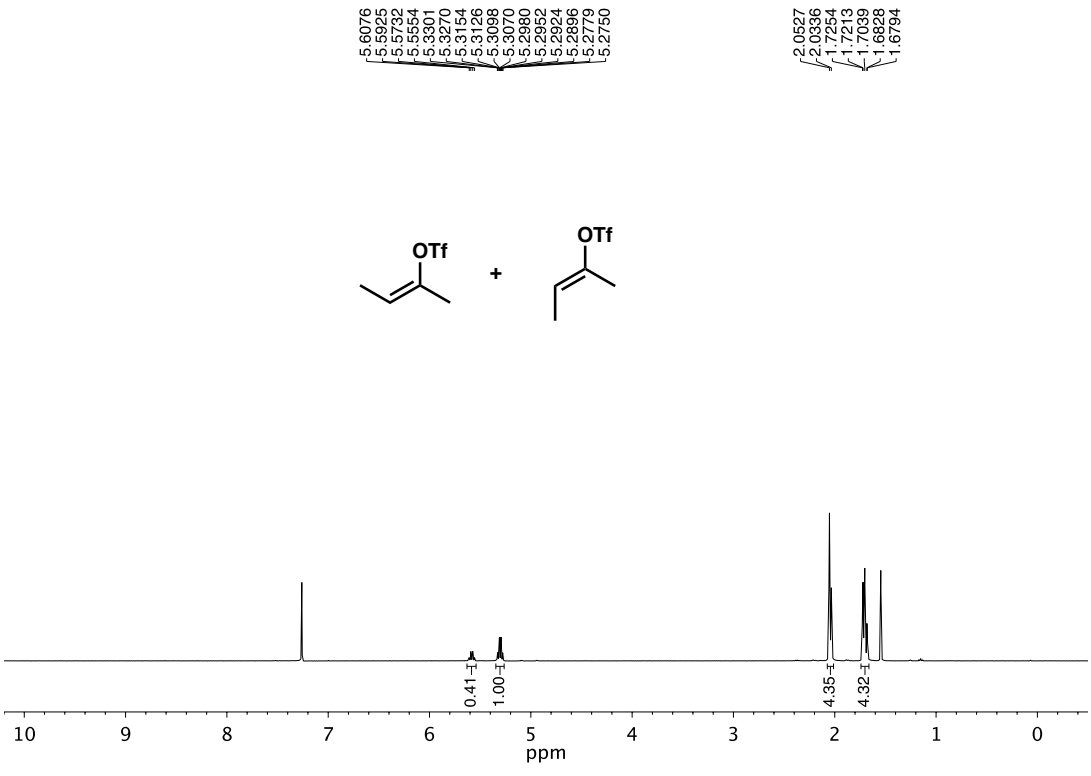


Figure 3.32. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.27**.

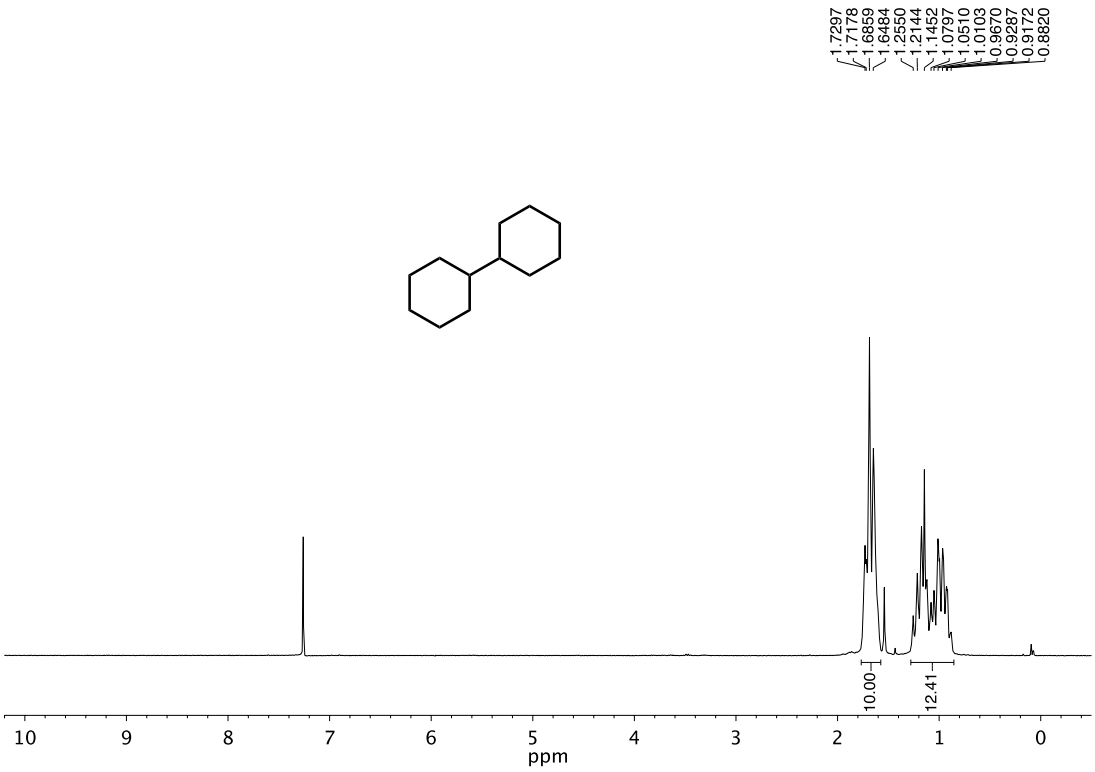


Figure 3.33. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.8**.

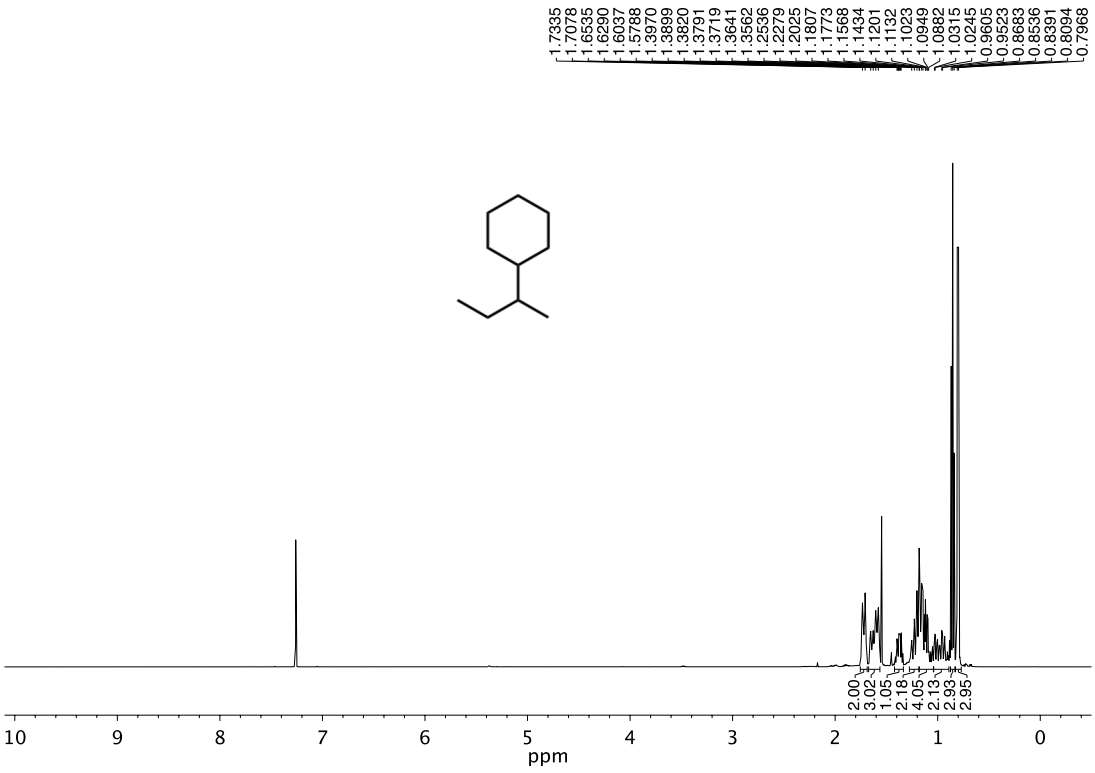


Figure 3.34. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.25**.

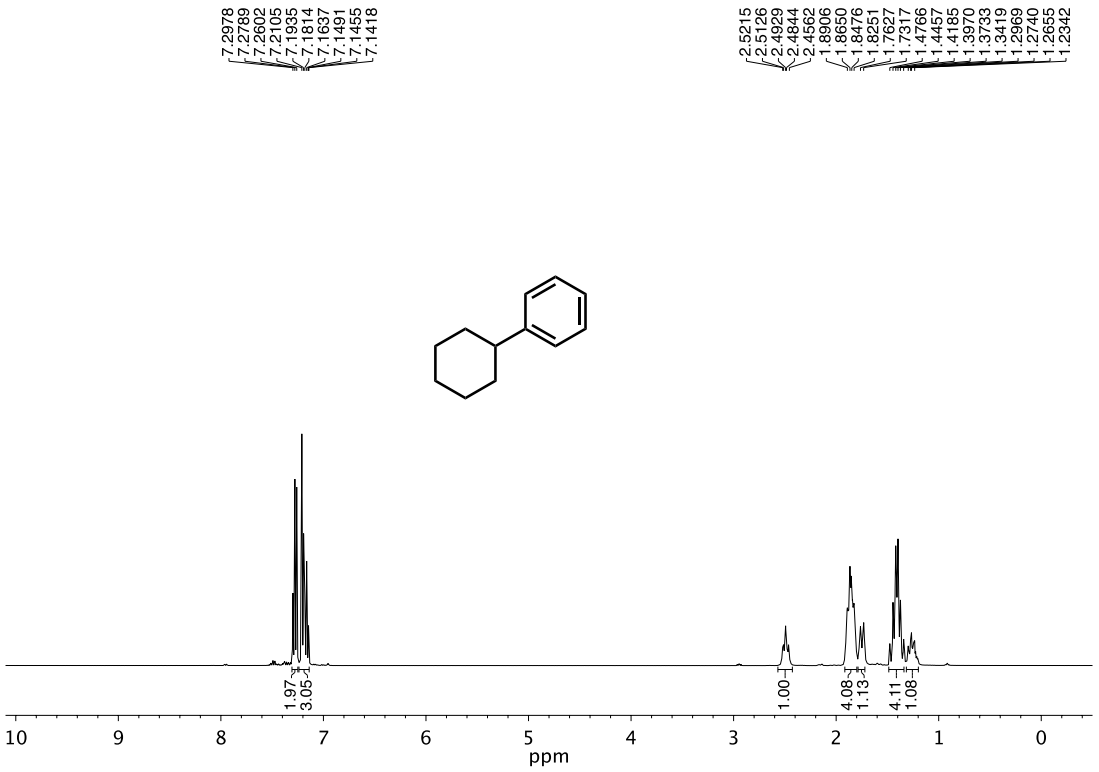


Figure 3.35. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.29**.

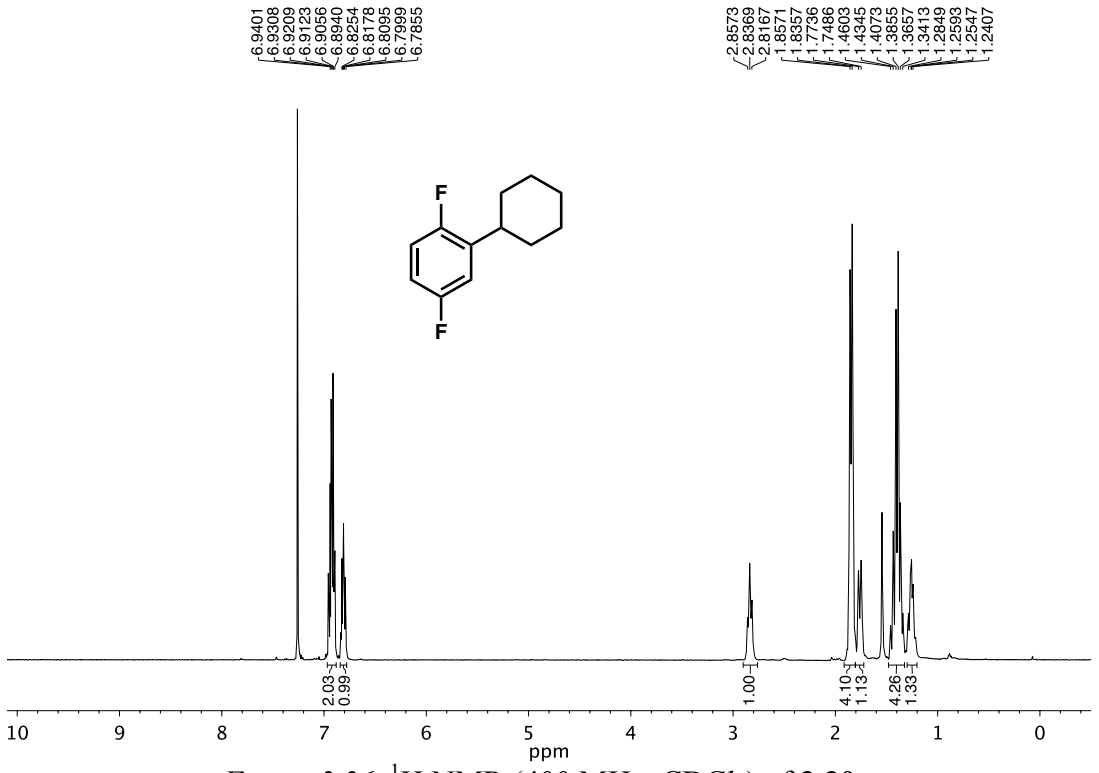


Figure 3.36. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.30**.

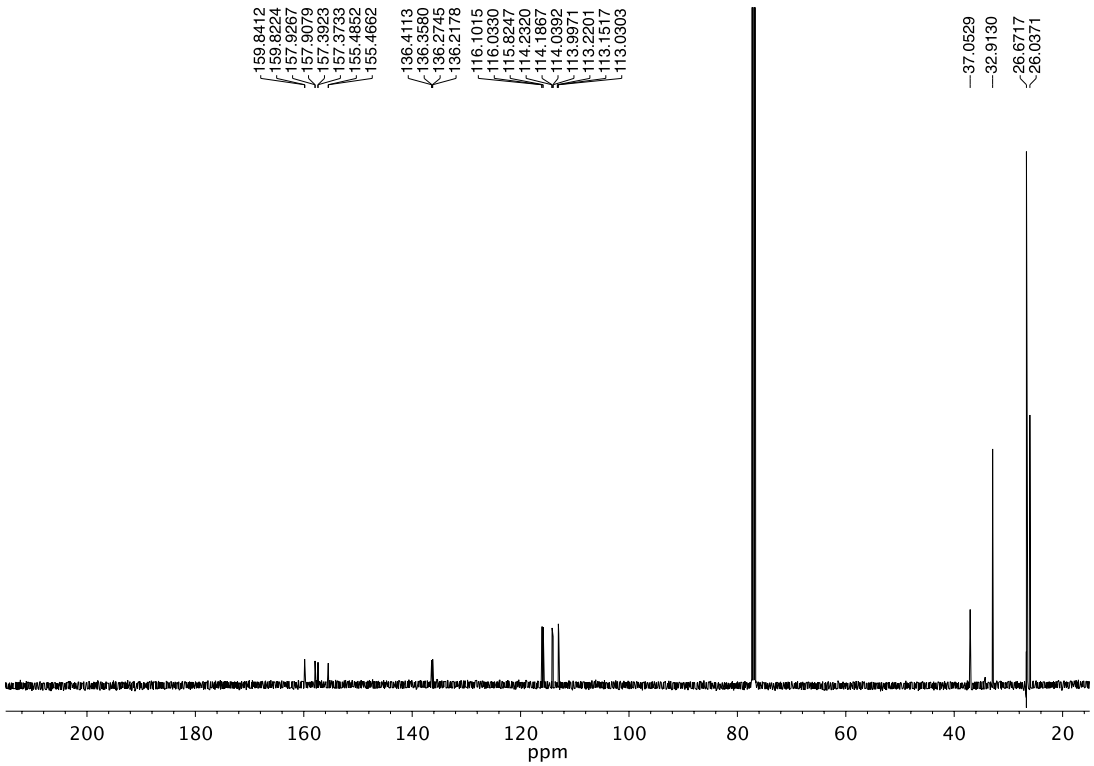


Figure 3.37. ^{13}C NMR (100 MHz, $CDCl_3$) of **3.30**.

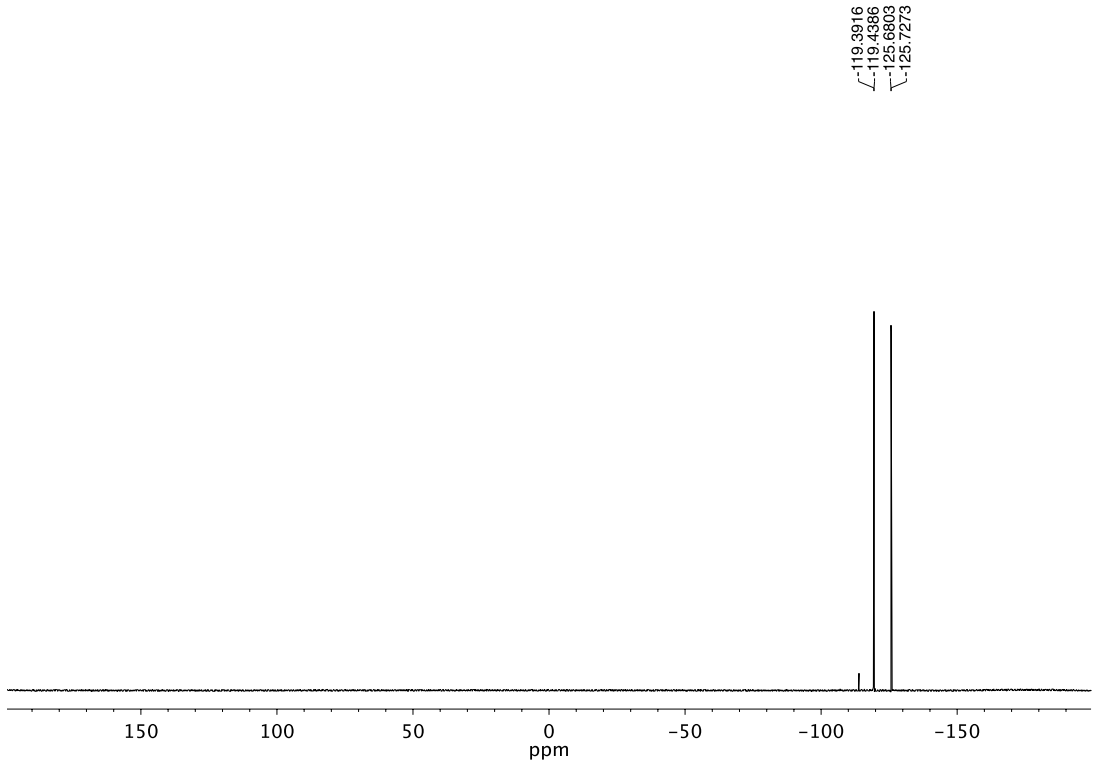


Figure 3.38. ^{19}F NMR (282 MHz, $CDCl_3$) of **3.30**.

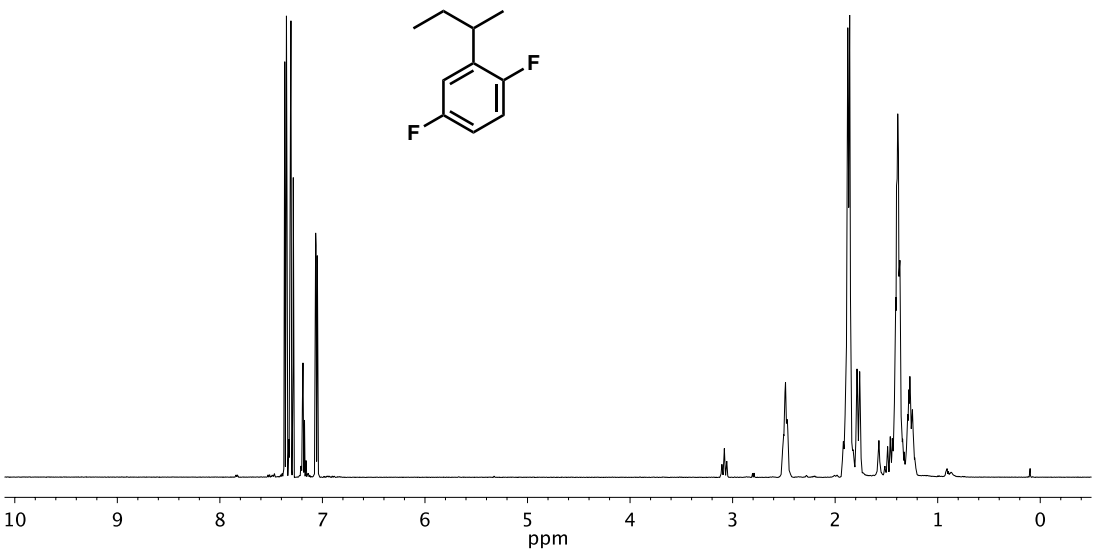


Figure 3.39. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.31**.

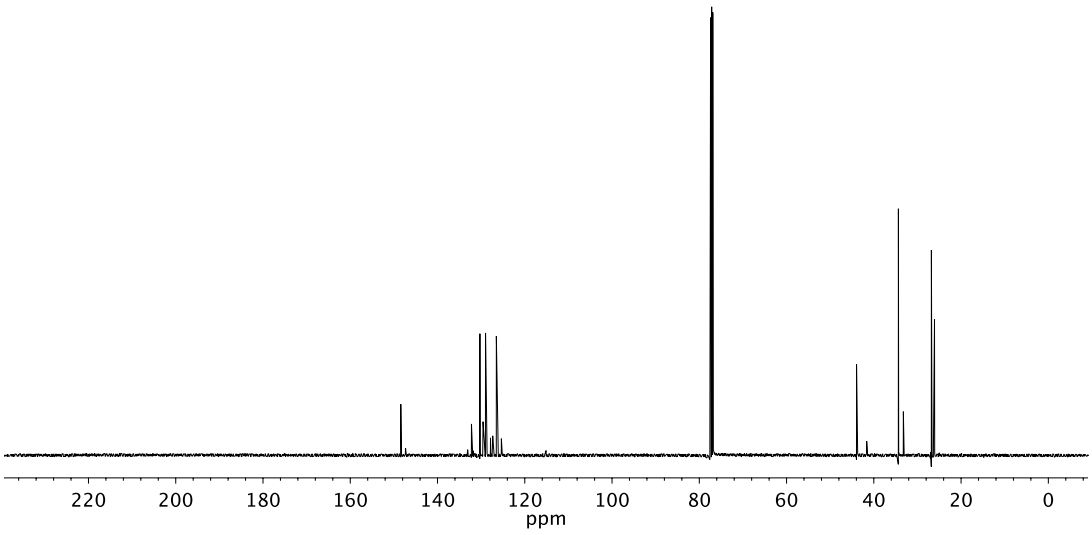


Figure 3.40. ^{13}C NMR (100 MHz, $CDCl_3$) of **3.31**.

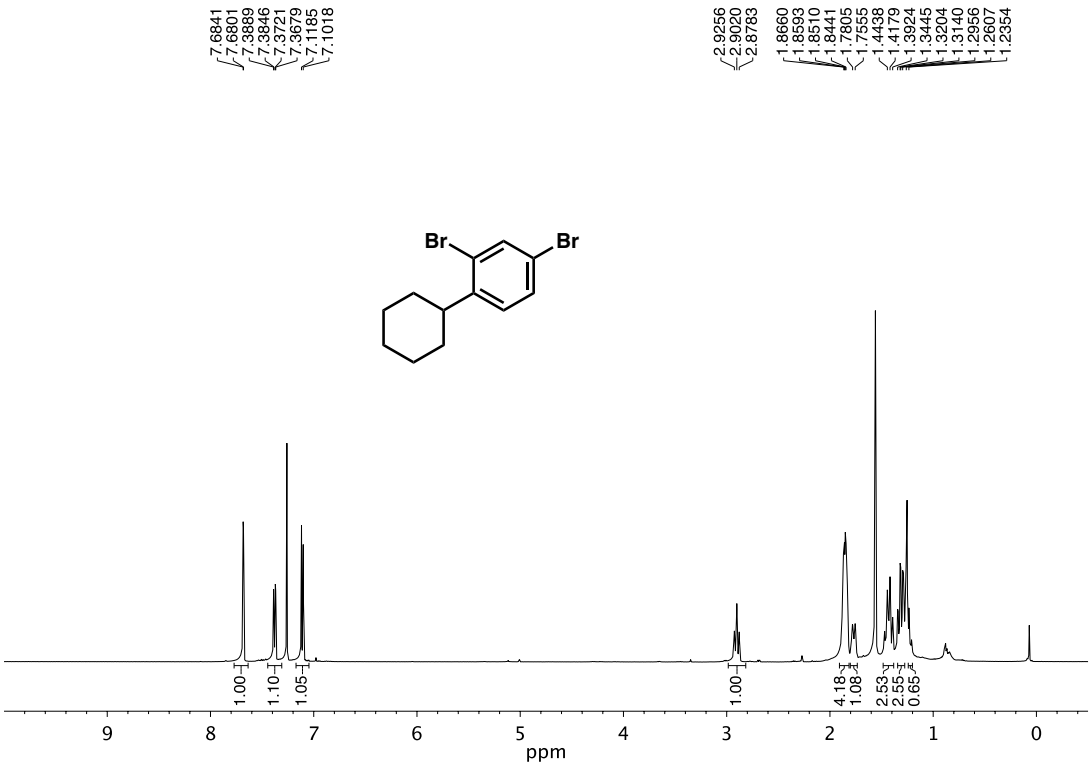


Figure 3.41. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.32**.

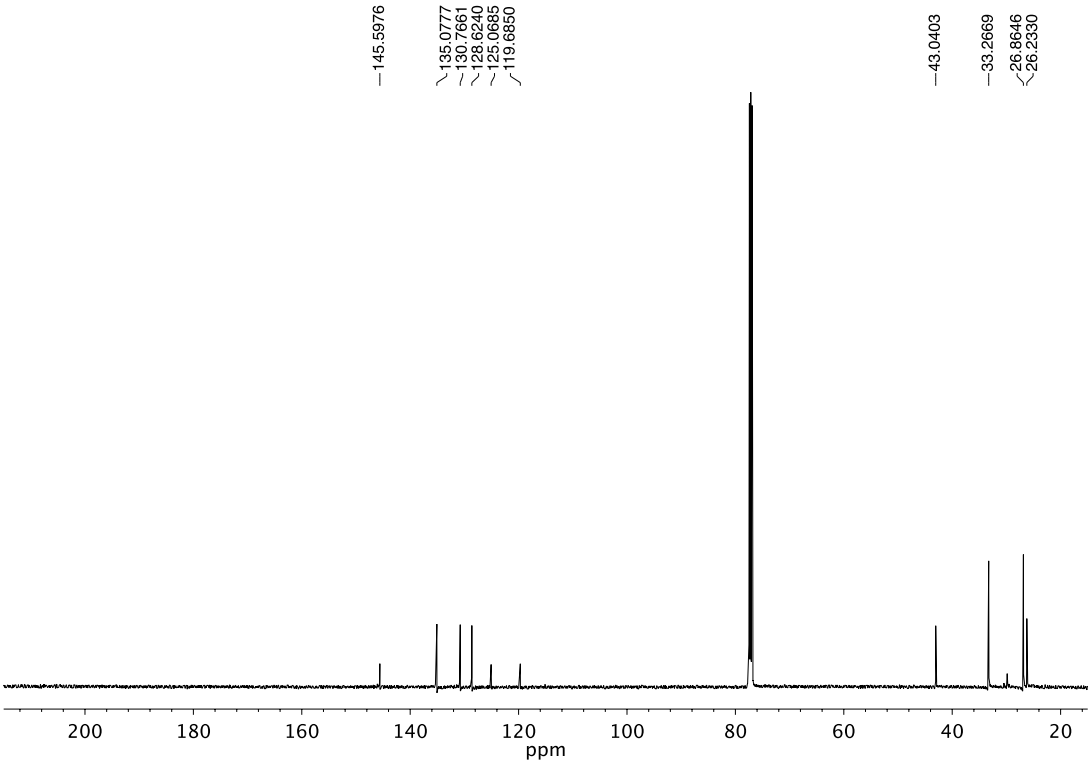


Figure 3.42. ^{13}C NMR (100 MHz, $CDCl_3$) of **3.32**.

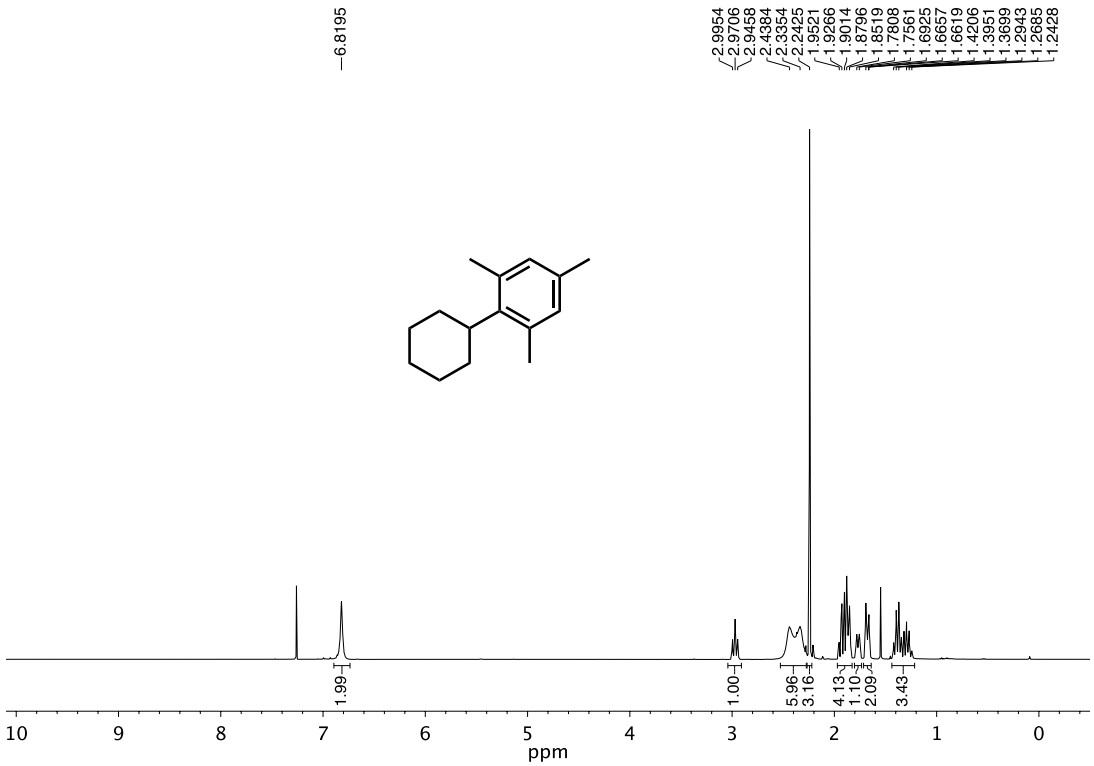


Figure 3.43. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.34**.

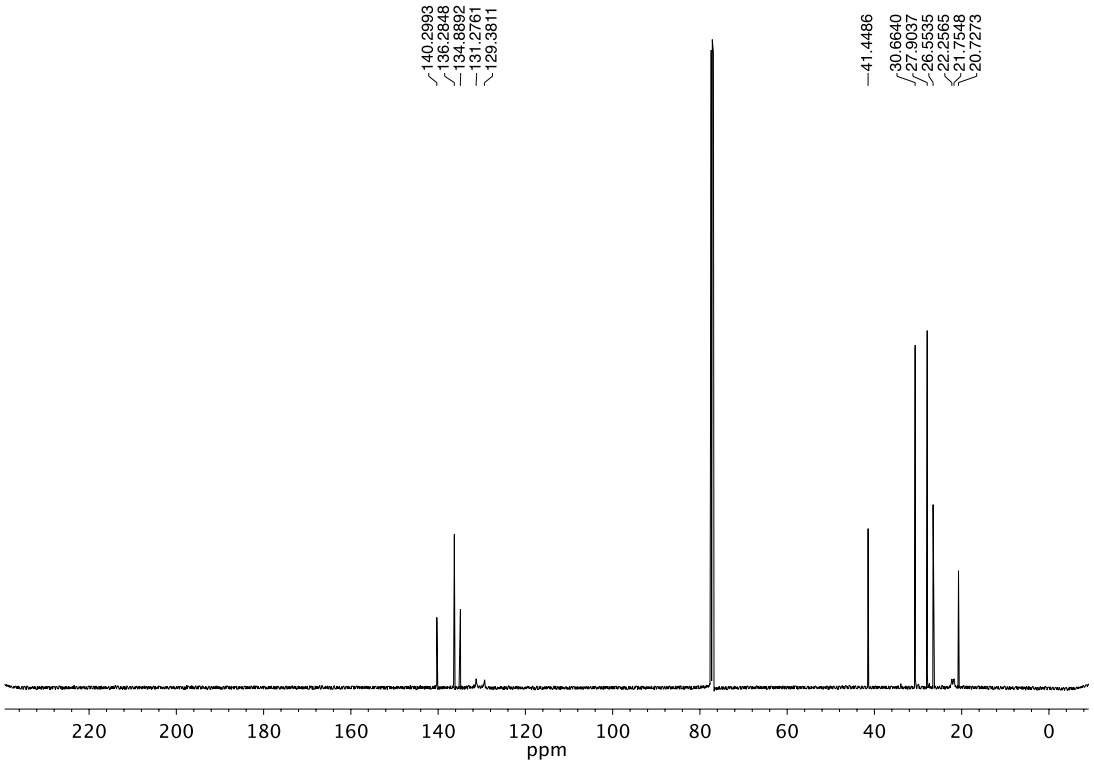


Figure 3.44. ^{13}C NMR (100 MHz, $CDCl_3$) of **3.34**.

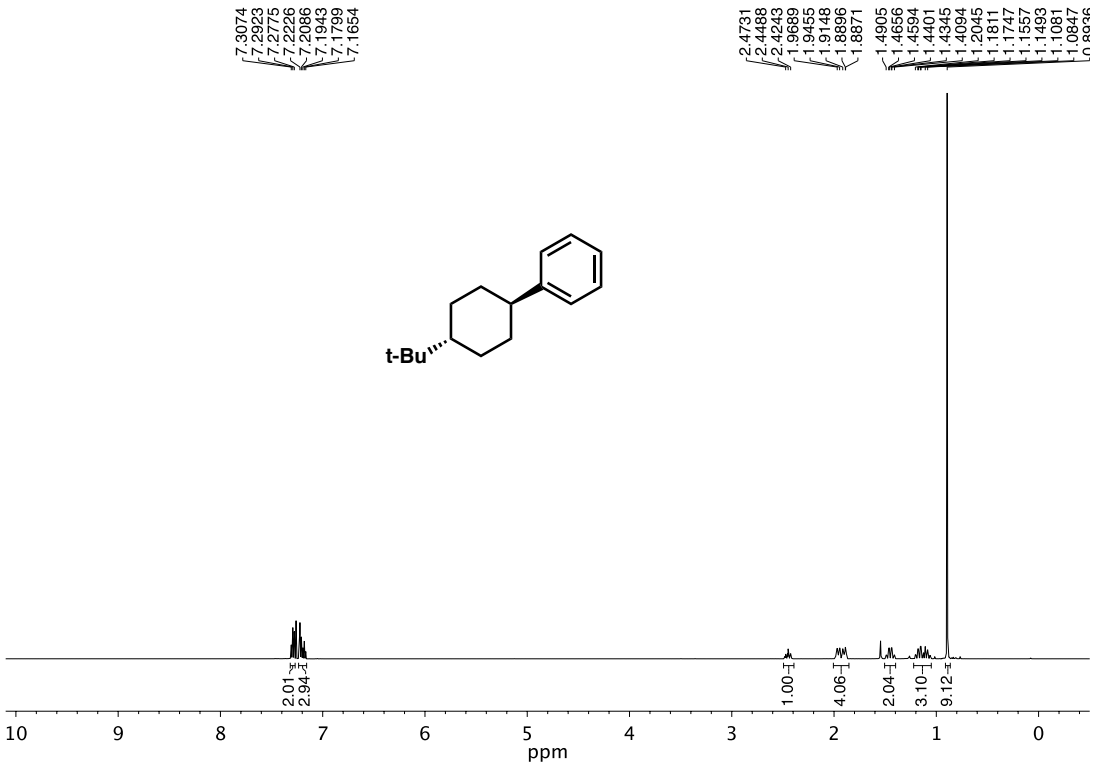


Figure 3.45. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.37**.

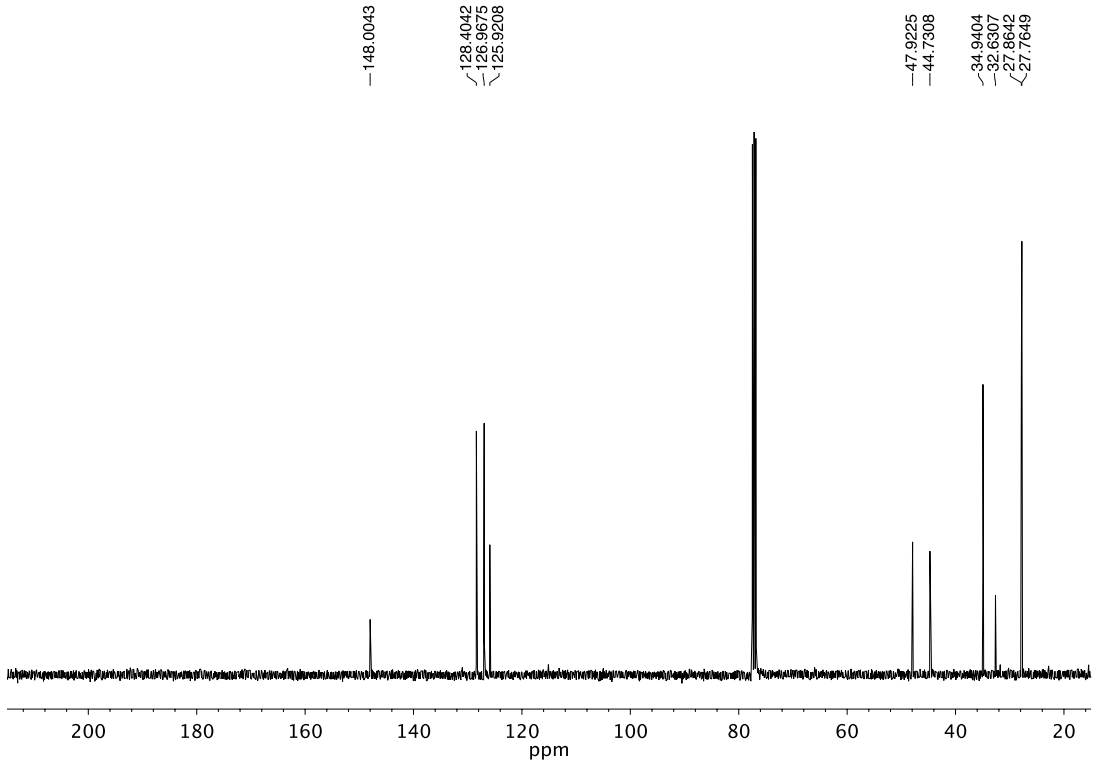


Figure 3.46. ^{13}C NMR (100 MHz, $CDCl_3$) of **3.37**.

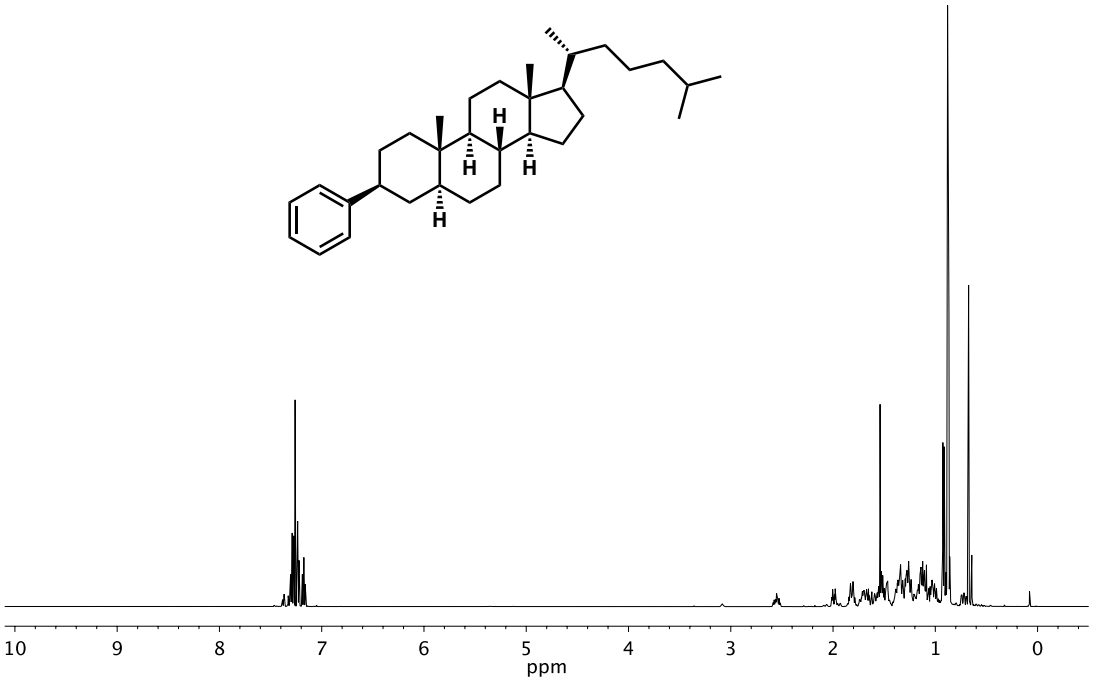


Figure 3.47. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.38**.

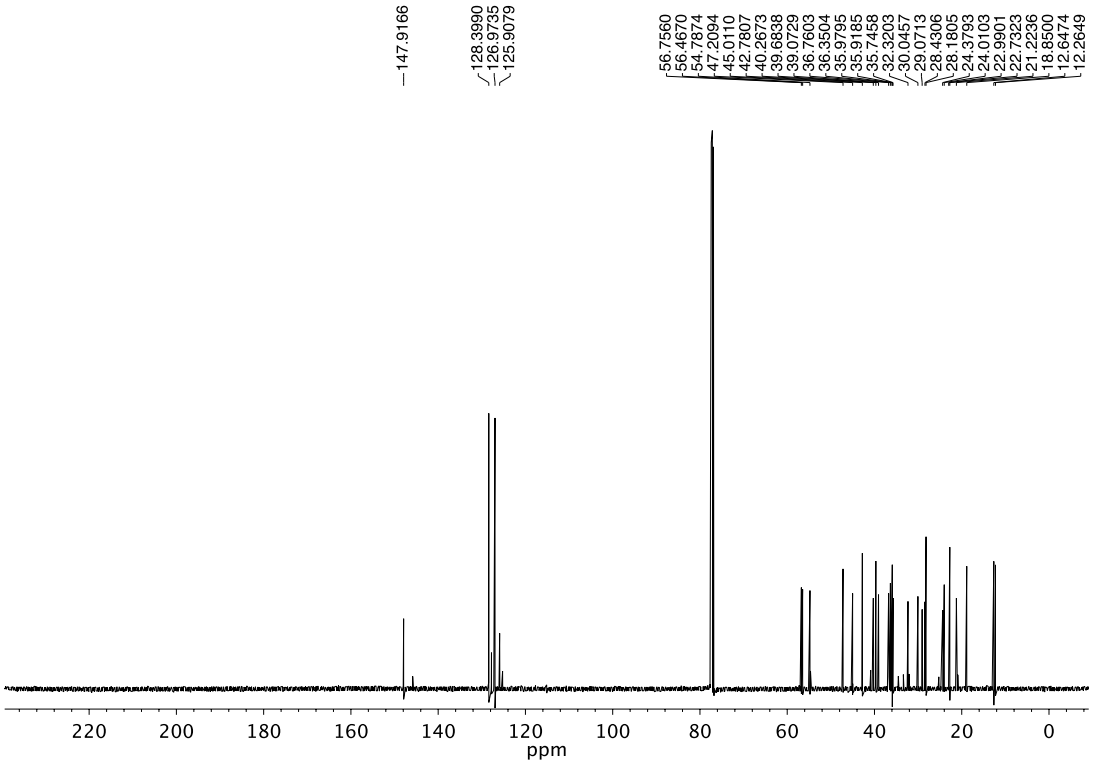


Figure 3.48. ^{13}C NMR (100 MHz, $CDCl_3$) of **3.38**.

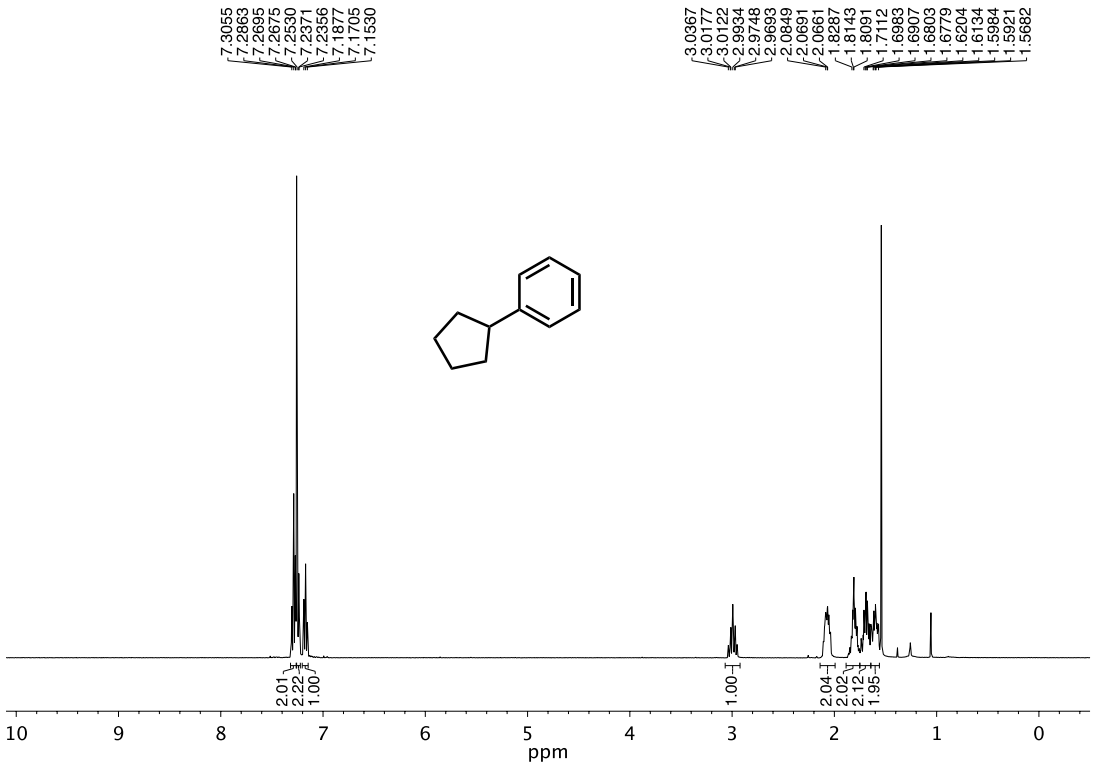


Figure 3.49. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.39**.

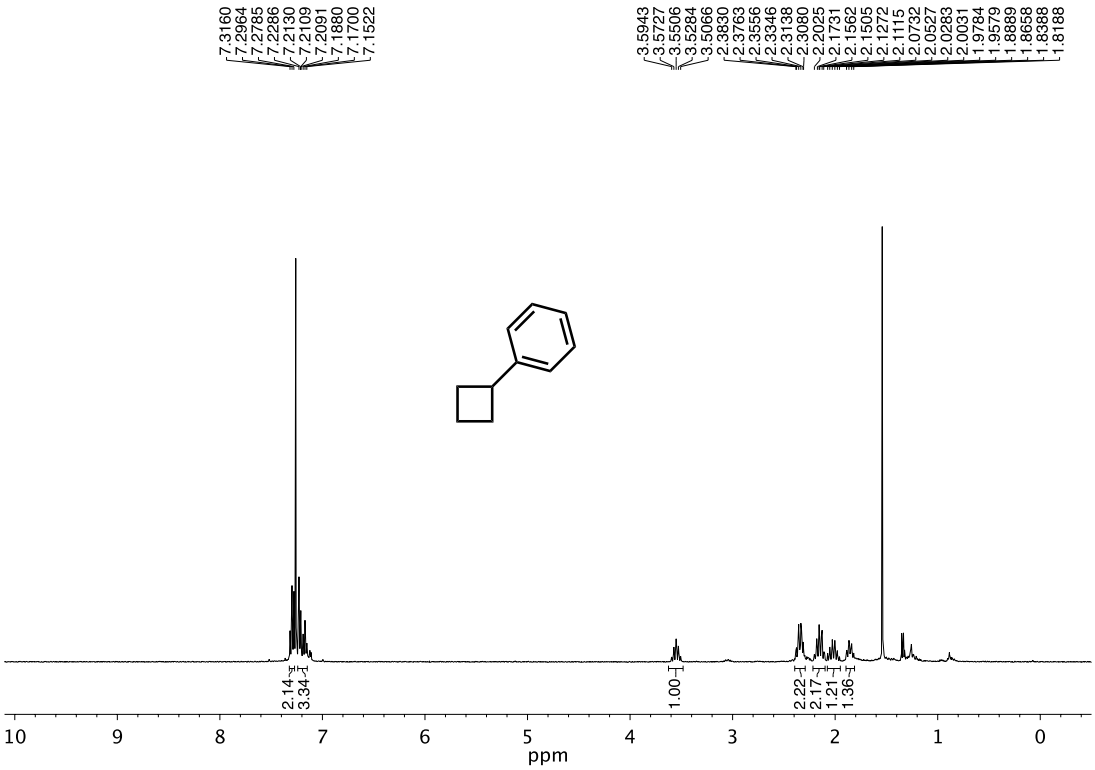


Figure 3.50. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.41**.

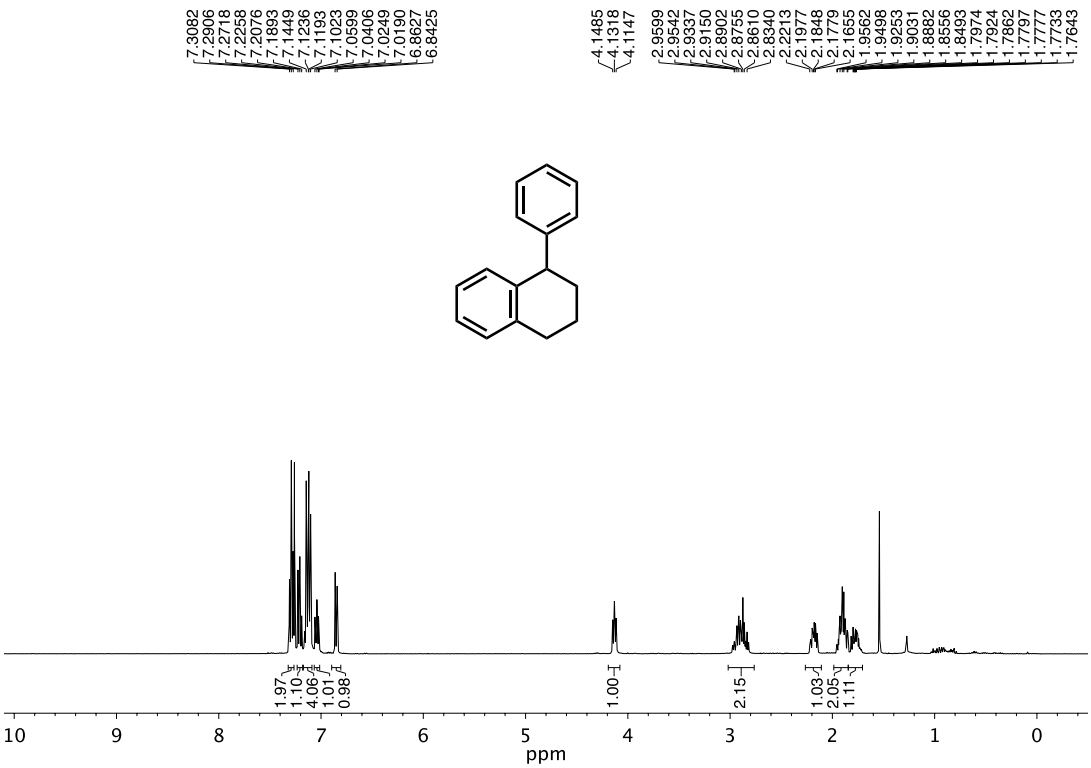


Figure 3.51. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.42**.

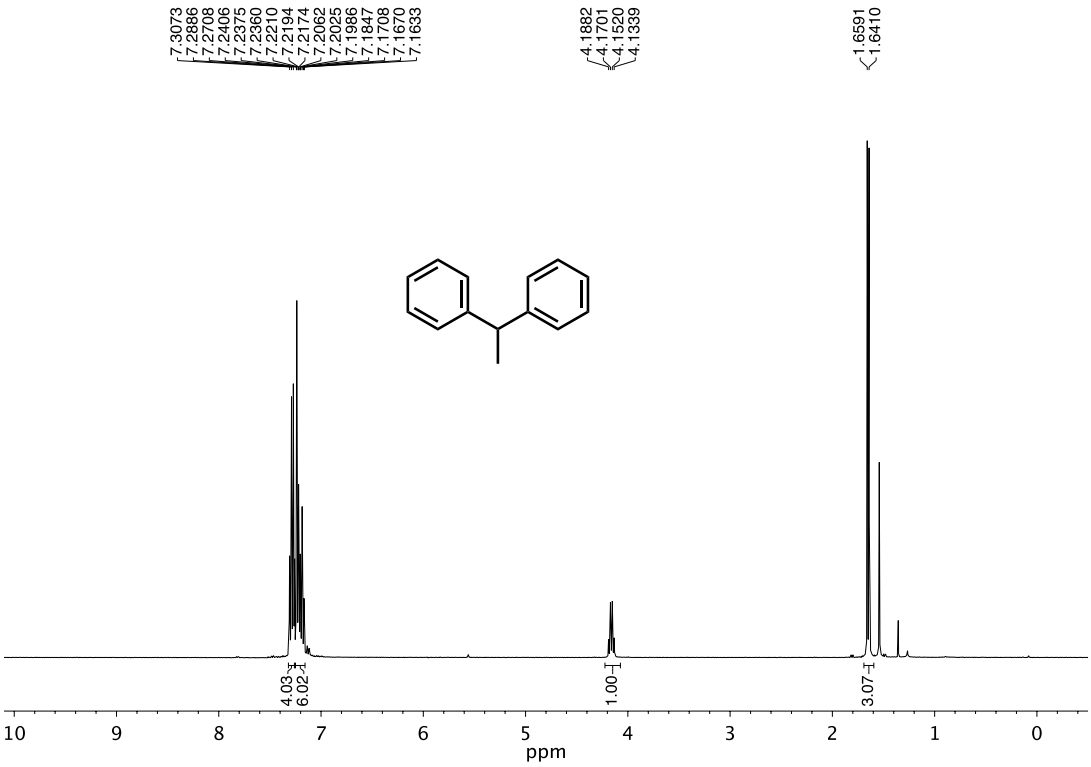


Figure 3.52. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.43**.

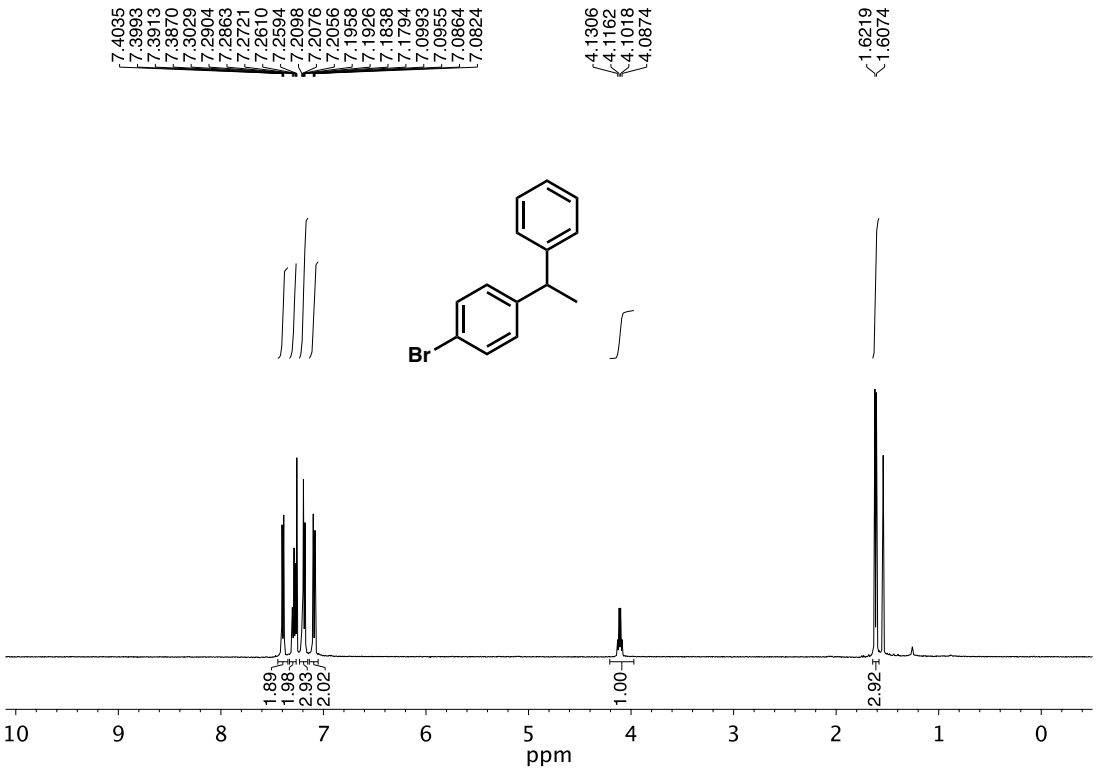


Figure 3.53. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.44**.

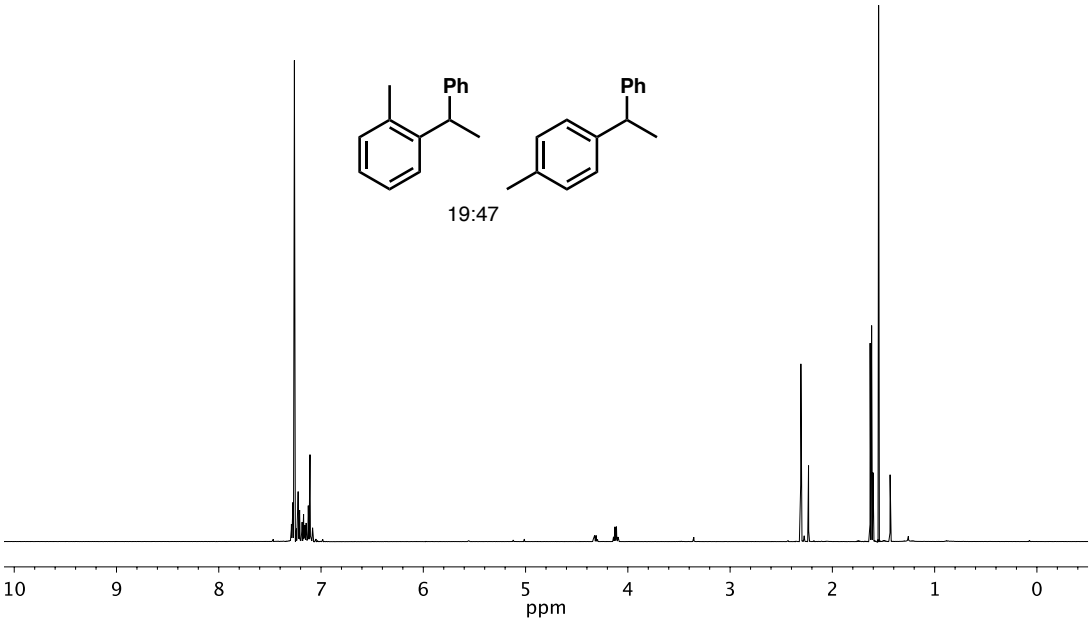


Figure 3.54. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.45**.

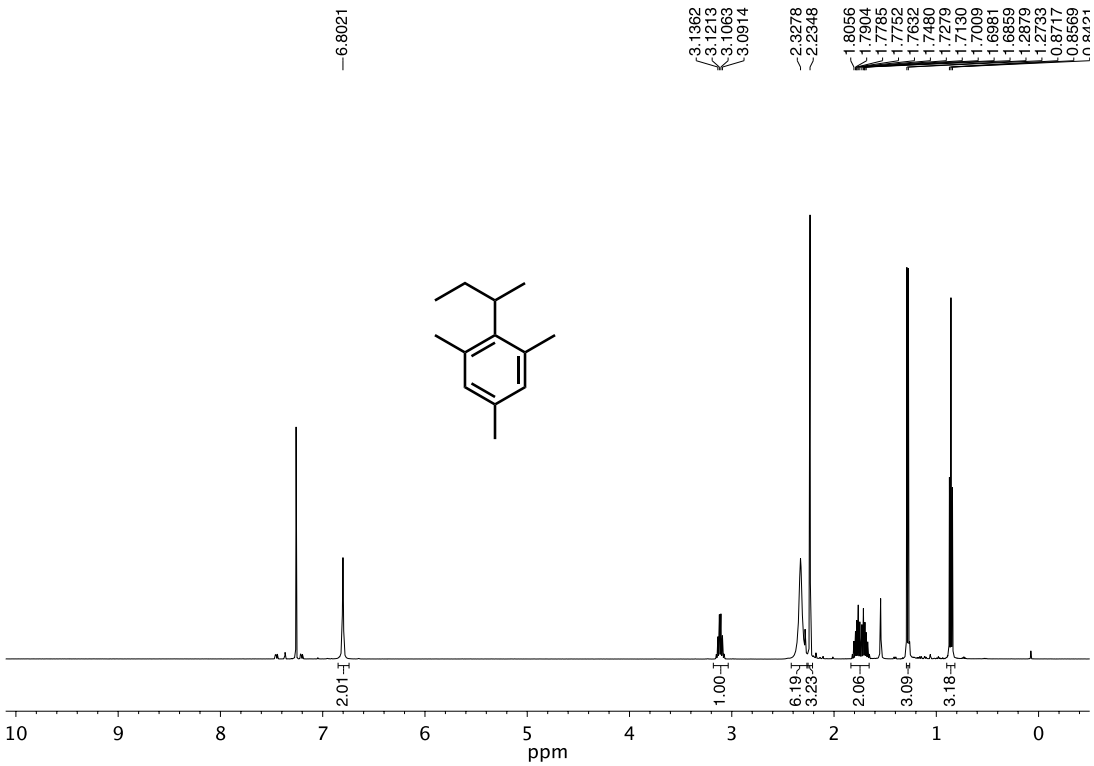


Figure 3.55. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.46**.

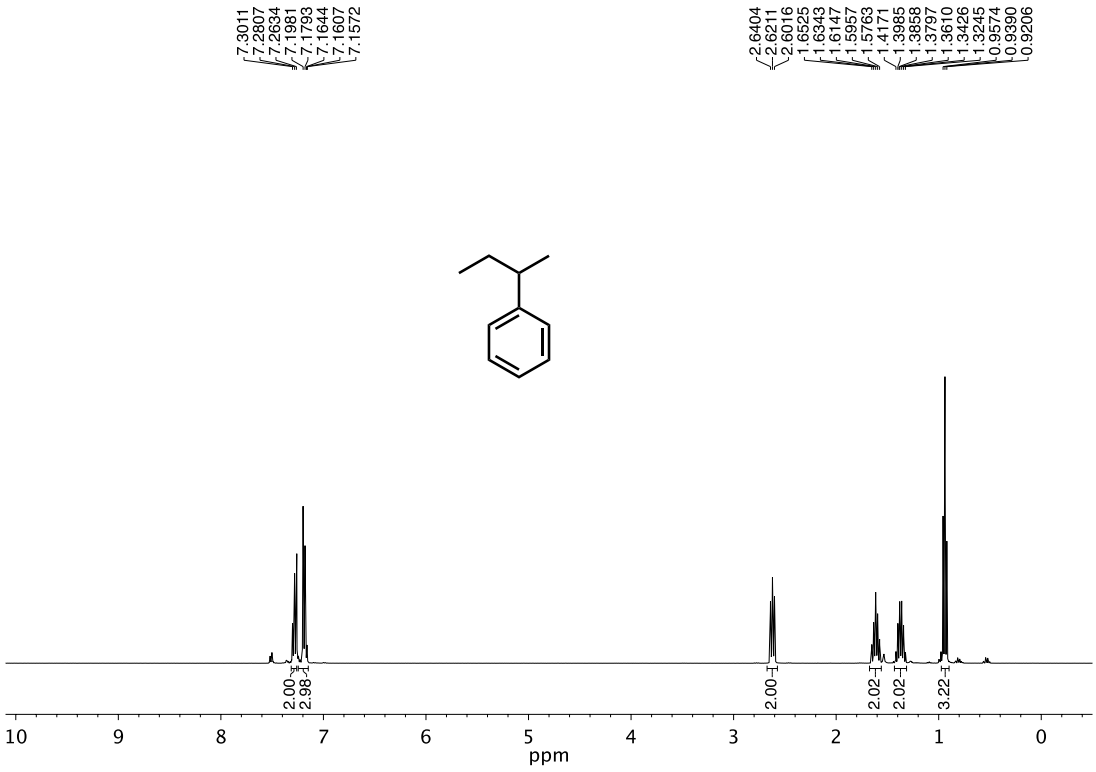


Figure 3.56. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.47**.

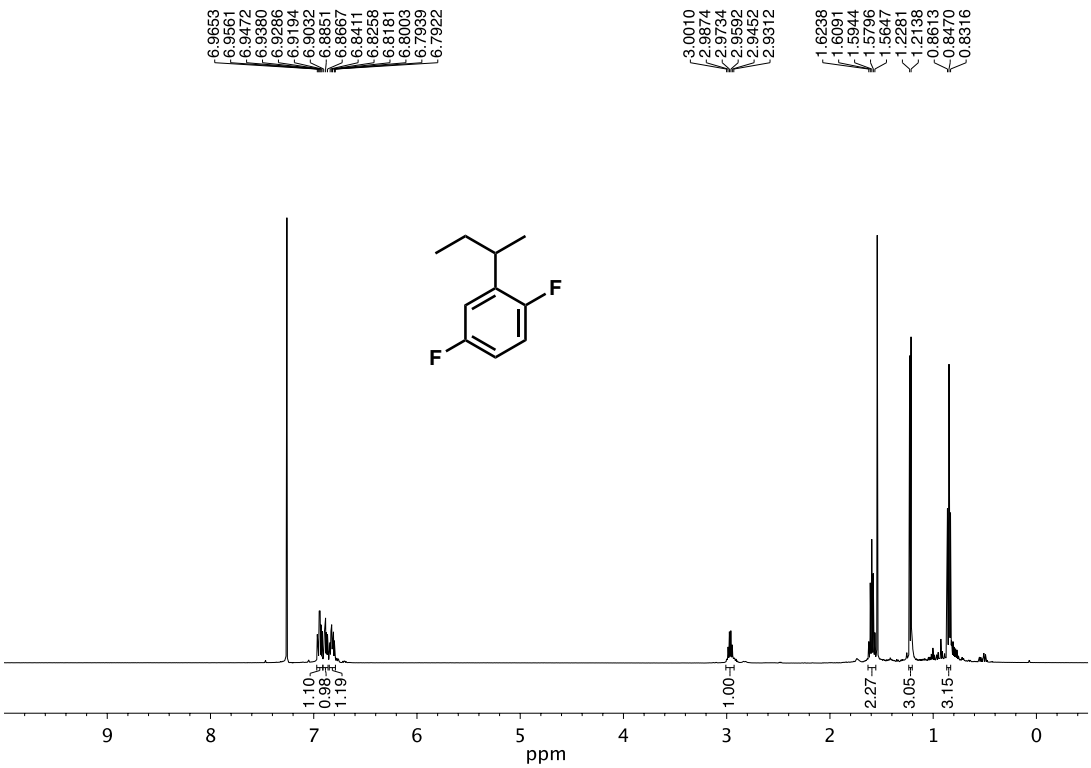


Figure 3.57. ^{1}H NMR (400 MHz, $CDCl_3$) of **3.48**.

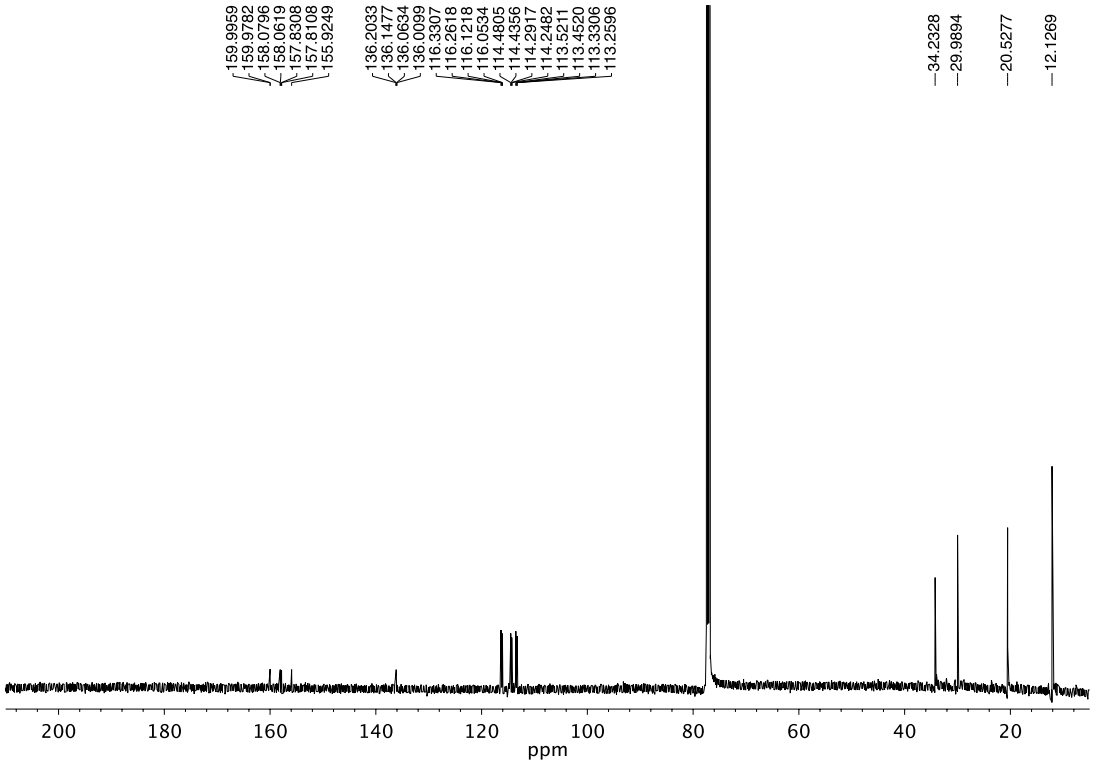


Figure 3.58. ^{13}C NMR (125 MHz, $CDCl_3$) of **3.48**.

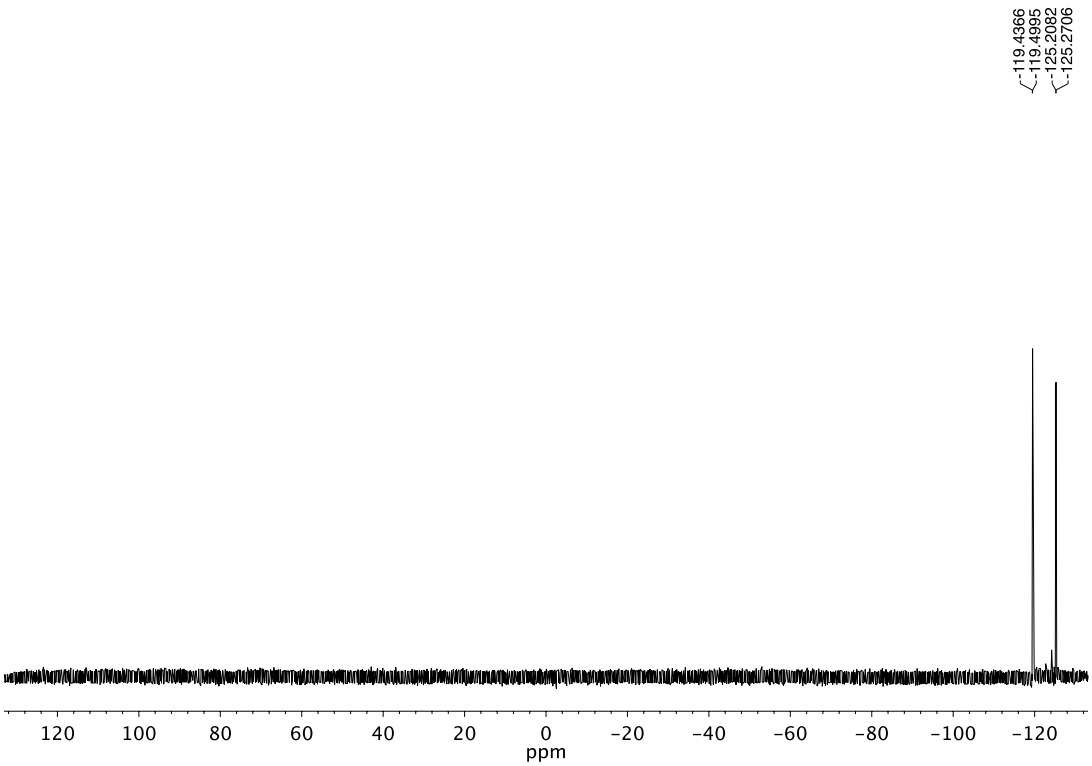


Figure 3.59. ^{19}F NMR (282 MHz, $CDCl_3$) of **3.48**.

3.10 Notes and References

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CHAPTER FOUR

Vinyl Carbocations Generated Under Basic Conditions and Their Intramolecular C–H Insertion Reactions

Adapted from: Benjamin Wigman, Stasik Popov, Alex L. Bagdasarian, Brian Shao, Tyler R. Benton, Chloé G. Williams, Steven P. Fisher, Vincent Lavallo, K. N. Houk, and Hosea M. Nelson

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4.1 Abstract

Here we report the surprising discovery that high-energy vinyl carbocations can be generated under strongly basic conditions, and that they engage in intramolecular sp^3 C–H insertion reactions through the catalysis of weakly coordinating anion salts. This approach relies on the unconventional combination of lithium hexamethyldisilazide base and the commercially available catalyst, triphenylmethylium tetrakis(pentafluorophenyl)borate. These reagents form a catalytically active lithium species that enables the application of vinyl cation C–H insertion reactions to heteroatom-containing substrates.

4.2 Introduction

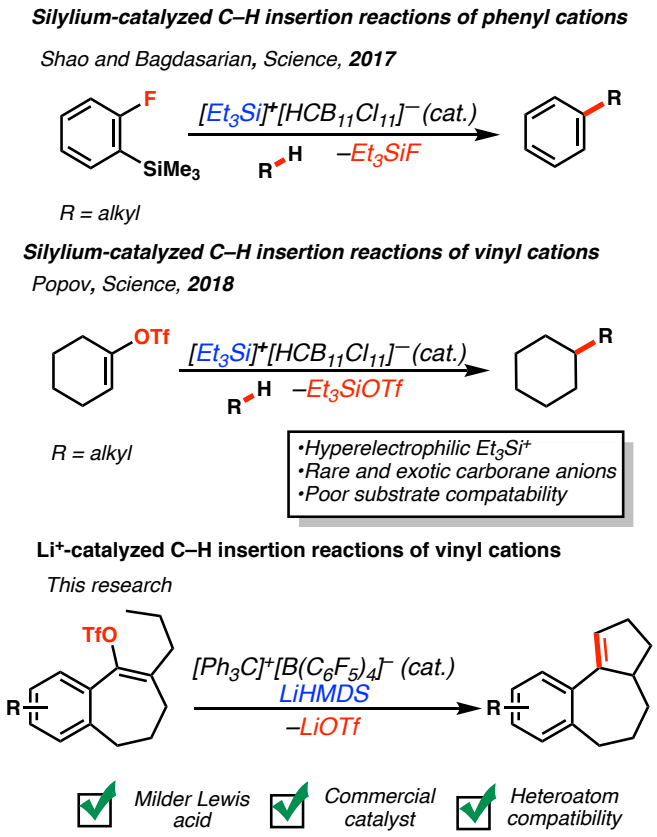
From the lessons learned about structure and bonding arising from the great classical vs. nonclassical ion debate of the mid-20th century, to the syntheses of pharmaceuticals and materials, carbocations have played a prominent role in the development of modern organic

chemistry.[1–3] Such species, which contain an electron deficient and positively charged carbon center, are typically generated under Brønsted acidic or Lewis acidic conditions, as exemplified by Norris, Kehrman and Baeyer's independent studies on the formation of the resonance stabilized triphenylmethyl (trityl) cation.[4–6] In the 1960s, elegant studies by Olah demonstrated that super acidic media, such as "magic acid," could be utilized to generate and characterize a variety of non-stabilized alkyl carbocations.[7] Later, Reed showed that when paired with appropriately robust and weakly coordinating anions (WCAs), savagely Lewis acidic silylium ions could be utilized to access, and in some cases isolate in crystalline form, a variety of otherwise reactive carbocations.[8,9] Even more reactive carbocations such as aryl or vinyl cations, are often generated in a similar fashion and have also found limited synthetic utility, save for the Balz-Schiemann and Sandmeyer reactions.[10,11] While Brønsted acidic and highly oxidizing "magic acid" and potent electrophiles like silylium ions are useful in generating such reactive carbocations for the conversion of hydrocarbons, they hinder the application of these strategies in the syntheses of heteroatom-rich complex molecules, such as those utilized for materials and pharmaceuticals.[12–14]

Recently, aryl and vinyl carbocations have been found to undergo fast and high yielding insertion reactions into unactivated sp^3 C–H bonds (Fig. 1).[15,16] In these systems the substrate scope was limited due to the electrophilicity of the silylium ion. In an effort to expand these C–H functionalization chemistries to additional synthetic applications, we posited that tempering the Lewis acidity of our active catalytic species would greatly expand the scope of vinyl carbocation C–H insertion reactions (Fig. 1). Here we report the discovery that high-energy vinyl carbocations can be generated under strongly basic conditions, and that they engage in intramolecular sp^3 C–H insertion reactions through the catalysis of weakly coordinating anions.

Importantly, this system features commercially available tetraarylborate salts instead of exotic carborane salts, and is demonstrated to be applicable to heteroatom containing substrates.

Figure 4.1. C–H insertion reactions of dicoordinate cations

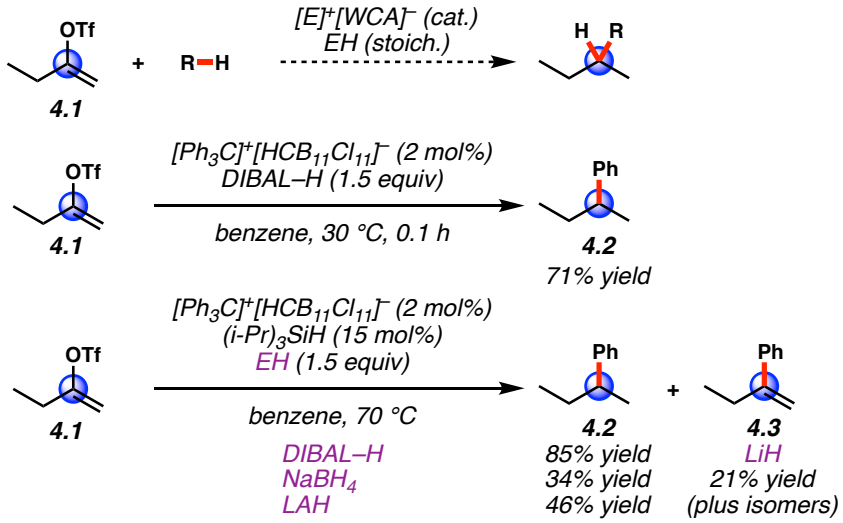


4.3 Use of Lithium Ions as Productive Lewis Acids for Vinyl Triflate Ionization

Inspired by work from Michl and others, we hypothesized that Li cations, paired with WCAs, could serve as Lewis acids capable of converting vinyl triflates into reactive vinyl cations.[17–19] To evaluate this hypothesis, we looked towards easily ionizable triflates such as butenyl triflate **4.1** (Fig. 4.2). In drawing analogies to trialkylsilanes in the previously disclosed methods, we considered using DIBAL-H (diisobutylaluminum hydride) as it has comparable hydricity and Lewis acidity to the related silicon species. To our delight, use of 1.5 equivalents of DIBAL-H with 2 mol% of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ in benzene solvent with butenyl triflate **4.1**

resulted in a high-yielding reductive Friedel-Crafts reaction. However, during further studies to expand on the functional group compatibility using DIBAL-H, we found alumenium cations to have a similar tolerance to silylium. In efforts to find a novel milder ionizing reagent, we opted to use a catalytic amount of $[R_3Si]^+[HCB_{11}Cl_{11}]^-$ in combination with a stoichiometric hydride donor that would serve to turn over the catalytic cycle. In this event DIBAL-H, $NaBH_4$, and LAH were all competent stoichiometric reductants delivering the reductively arylated product **4.2** in good to excellent yields (34–85% yield). To our surprise, use of lithium hydride (LiH) gave olefinic product **4.3** and **4.2** in 21% yield. This not only offers a milder Lewis acid for triflate ionization, but also the ability to install olefinic handles that could be modified late-stage, if desired.

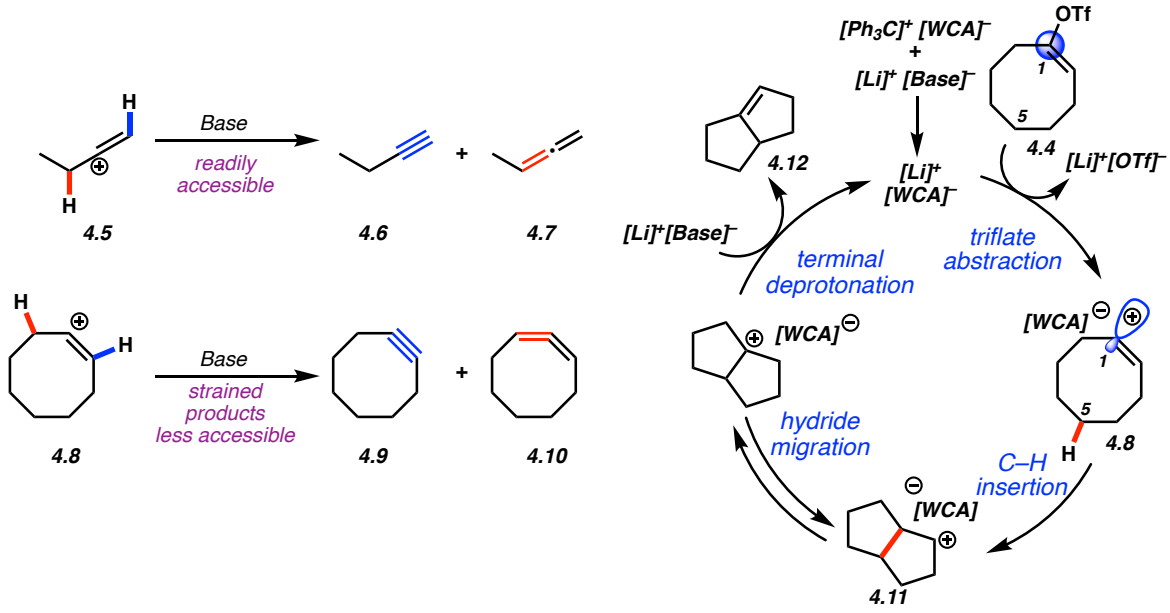
Figure 4.2. Discovery of new ionizing reagents



In order to limit the possibility of deprotonating the vinyl cation prior to productive C–C bond forming could occur we considered cyclooctenyl triflate **4.4** as it is easily ionized, but also cyclic and thus more difficult to deprotonate prematurely (Fig. 4.3). One can envision vinyl cation **4.5** under basic conditions readily delivering elimination products **4.6** and **4.7** while a cyclic vinyl cation (**4.8**) would have higher barriers to access analogous deprotonation products

4.9 and **4.10**. We postulated that the catalytic cycle would begin with nucleophilic attack of a lithium base on $[Ph_3C]^+[WCA]^-$ would yield the active $[Li]^+[WCA]^-$ catalyst (Fig. 4.3). $[Li]^+[WCA]^-$-mediated triflate abstraction would then afford a persistent vinyl cation **4.8** which would undergo transannular C–H insertion to form bicyclic secondary cation **4.11**. Lastly, we envisioned that deprotonation of this cation by a lithium base would generate alkene products **4.12** and concomitantly regenerate the active $[Li]^+[WCA]^-$ catalyst.

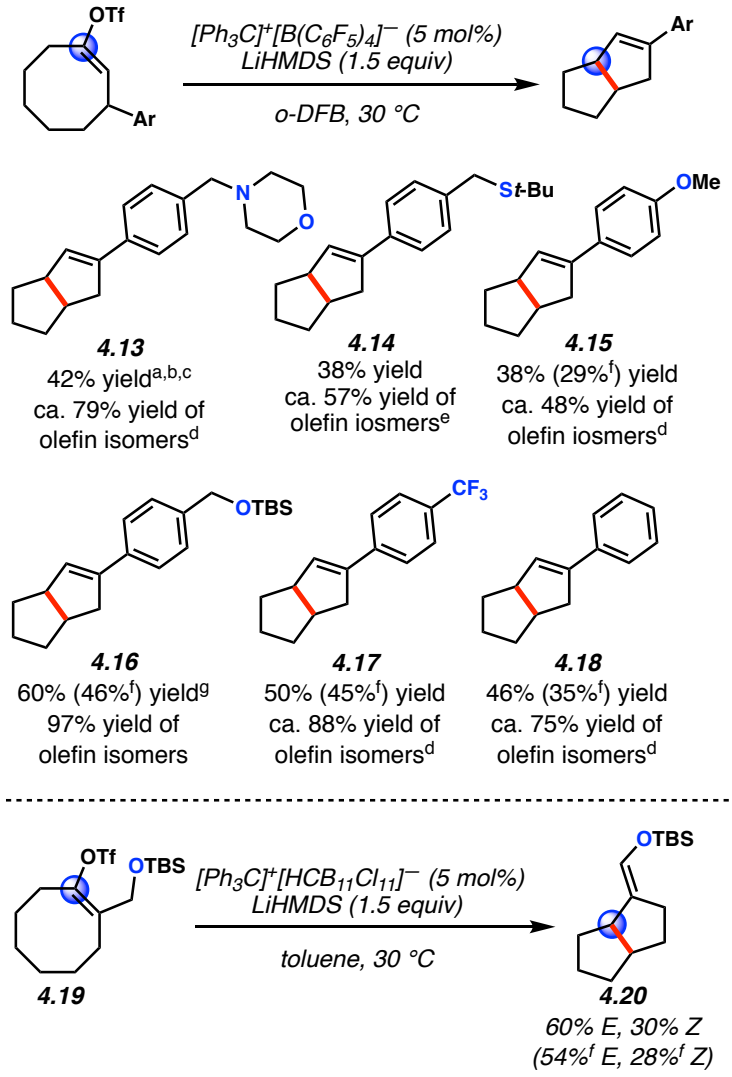
Figure 4.3. Deprotonation of vinyl cations and proposed catalytic cycle



Beginning with cyclooctenyl triflate **4.4**, a screen of several Li-bases, trityl salt catalysts, and general reaction conditions was undertaken. We were gratified to find that using a catalytic amount (5 mol%) of $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ and 1.5 equivalents of LiHMDS base in *o*-difluorobenzene (*o*-DFB) solvent produced a mixture of bicyclooctene products (**4.12**) in four hours, in a combined yield of 84% (Table 4.3). Remarkably, deleterious nucleophilic quenching or elimination products were not observed despite the utilization of the highly basic hexamethyldisilazide anion in the presence of a high-energy, reactive vinyl cation intermediate.

Pleasingly, commercially available $[Ph_3C]^+[B(C_6F_5)_4]^-$ was superior in this reaction, providing the bicyclooctene products (**4.12**) in 98% yield in 30 minutes at room temperature, obviating the need for the rarer $[HCB_{11}Cl_{11}]^-$ anion. Chlorinated solvents, which are traditionally unstable under silylium catalysis[20], were also competent media for these reactions, albeit providing the products in lower yield (Table 4.3). Moreover, unlike silylium-mediated reductive coupling conditions[15,16], here we generate olefinic products that can be further functionalized.[21,22] While our initial studies of Li^+ ion-generated vinyl cations demonstrated exquisite reactivity and conversion, we sought to validate our hypothesis that the use of Li^+ ions would improve the substrate compatibility of vinyl cation reactions. To explore the functional group tolerance, a variety of *3*-arylcyclooctenyl triflates were prepared (Table 4.1). We were pleased to find that benzylmorpholine derivative underwent conversion to bicyclic styrene **4.13**, in 42% yield after one hour. Similarly, heteroatom-containing thioethers and ethers were also competent under the reaction conditions (**4.14–4.16**, 38%, 38% and 60% yield of the depicted olefin isomer, respectively). An electron-deficient arene was tolerated, producing styrenyl trifluoromethyl derivative **4.17** in 50% yield. We also found that *3*-phenylcyclooctenyl triflate provided bicyclic styrene **4.18** in 46% yield. The overall efficiency of the transannular C–H insertion reactions was high, with the combined yields of the styrenyl, tri- and tetra- substituted olefin isomer products ranging from 48% to 97%.[23] In addition to *3*-aryl derived substrates, *2*-substituted vinyl triflate **4.19** yielded the silyl enol ether products **4.20** in 92% overall yield. These examples highlight the functional group tolerance of these newly discovered conditions, standing in stark contrast to the previously reported Lewis acid-mediated insertion reactions of vinyl cations.[11, 12, 16] In fact, when heteroatom containing substrates, (**4.13** and **4.15**), were subjected to the previously optimized silylium conditions, no reactivity was observed.[23]

Table 4.1. Cyclooctenyl triflate derivatives

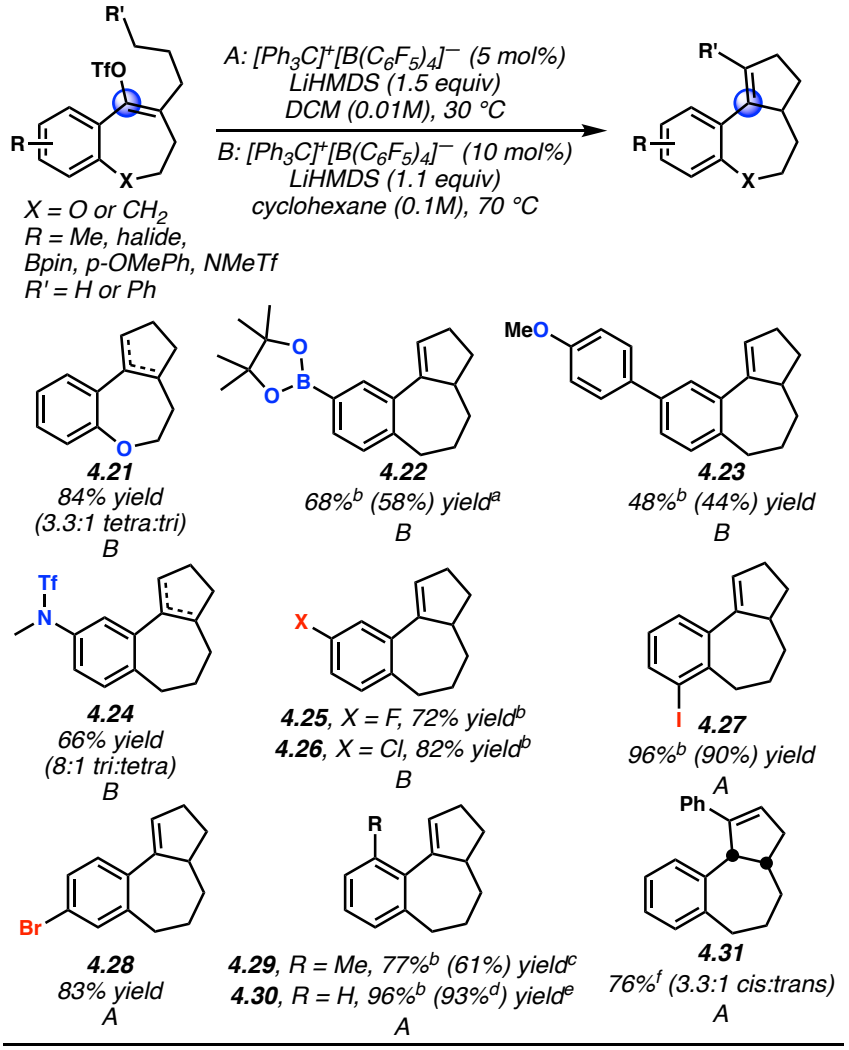


[a]3 equiv of LiHMDS. [b]Cyclohexane solvent. [c]70 °C. [d]Yield determined by GC-FID. [e]Yield determined by LCMS. [f]isolated yield. [g]DCM solvent.

Having demonstrated that cyclic vinyl triflates undergo transannular C–H insertion reactions under Li-WCA catalysis, we sought to further expand the scope of our method to annulation reactions. Benzosuberone-derived triflates with tethered alkyl chains stood out as potential candidates for several reasons: 1) The 7-membered ring triflate would have a low barrier for vinyl cation formation[24], 2) the possibility of insertion into 1° carbon C–H bonds could be probed, and 3) the large number of benzosuberone derivatives that have been identified

as potential therapeutics.[25] Gratifyingly, upon exposure to 10 mol% of $[Ph_3C]^+[B(C_6F_5)_4]^-$ and 1.1 equivalents of LiHMDS, propylbenzoxepinyl triflate affords tricycle **4.21** in 84% yield (3.3:1 isomer ratio) after two hours (Table 4.2). Further, 2-substituted pinacol boronic ester, anisole and protected aniline benzosuberone derivatives were successfully converted to their corresponding tricyclic styrene products (**4.22**–**4.24**) in 48 to 68% yield. Similarly, 2-halogenated benzosuberonyl triflates provided the desired styrene products **(4.25** and **4.26**) in 72 and 82% yield. Functionalization at other positions of the fused aryl system afforded tricyclic styrene products (**4.27**–**4.30**) in good to excellent yields (77–96%). These examples not only highlight the vastly improved heteroatom compatibility of these conditions, but also demonstrate the C–H insertion reactivity of benzylic vinyl cations into 1° C–H bonds. Finally, insertion into a benzylic 2° C–H bond was also possible, offering styrene **4.31** in 76% yield.

Table 4.2. Alkylated benzosuberone triflates



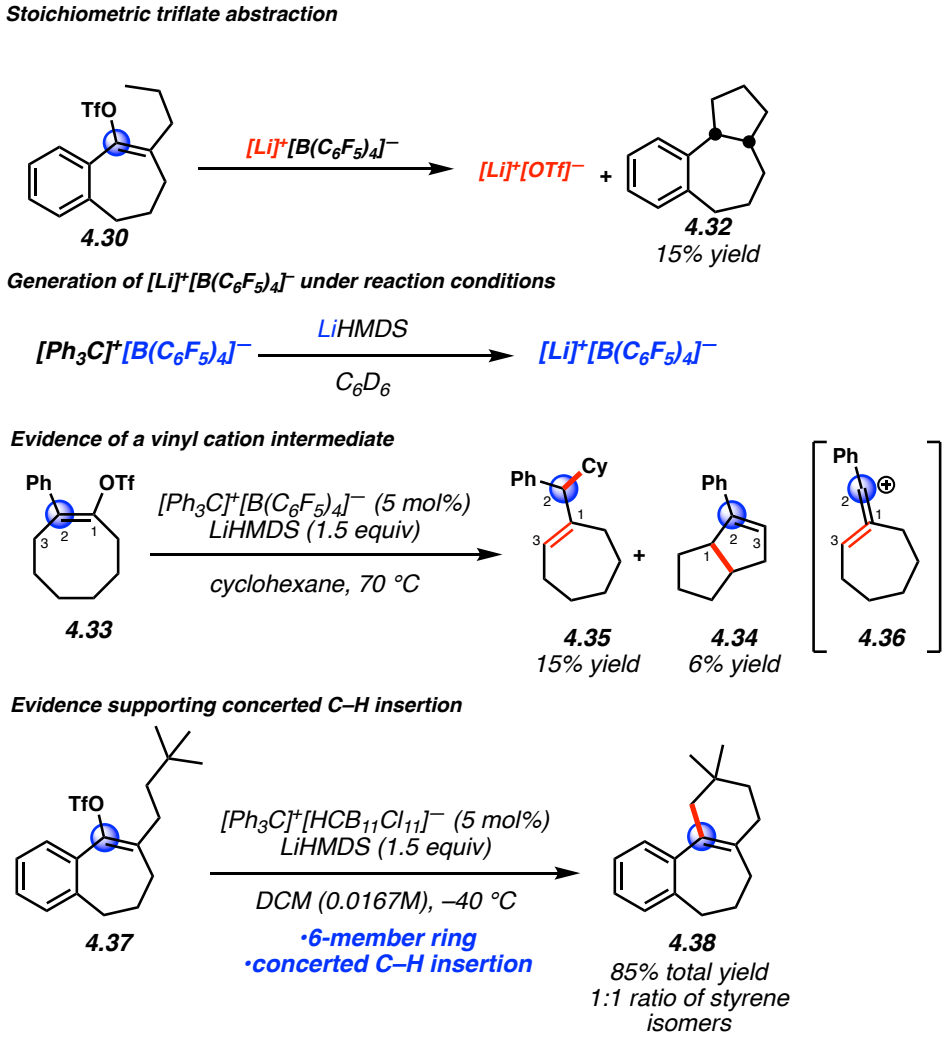
[a]30 °C. [b]Yield determined by NMR. [c]0.0167 M. [d]1 mmol [e][Ph3C]+[HCB11Cl11]– catalyst. [f]–40 °C.

With our scope studies in hand, we began our investigation into the mechanistic underpinnings of this transformation. Initially, because hexamethyldisilazane has been previously used as a silyl transfer reagent[26], we sought to discount the formation of silylium intermediates. In this regard, we found that NaHMDS and KHMDS were not competent under standard reaction conditions, supporting our hypothesis that Li^+ rather than Me_3Si^+ from HMDS is the active species (Table 4.3). Instead, we attribute this discrepancy in reactivity to the enhanced Lewis acidity of Li^+ ions compared to Na^+ and K^+ ions. From these observations, we

propose that the lithium ion is the active Lewis acid in our catalytic regime. To corroborate this mechanistic proposal, we treated triflate **4.30** with stoichiometric $[Li]^+[B(C_6F_5)]_4^-$, resulting in the formation of LiOTf and full consumption of the triflate starting material. Notably, we also observed the reduced tricycle **4.32** in 15% yield as well as other intractable mixtures of products.[23]

Additionally, we wanted to verify the *in situ* formation of a $[Li]^+[WCA]^-$ salt under our reaction conditions. Here we exposed $[Ph_3C]^+[B(C_6F_5)_4]^-$ to 1 equivalent of LiHMDS and observed rapid formation of $[Li]^+[B(C_6F_5)]_4^-$ by ^{7}Li, ^{11}B and ^{19}F NMR (Fig. 4.3). To confirm the intermediacy of a vinyl cation species in our system, we synthesized 2-phenyl vinyl triflate **4.33**, as 2-substituted cyclic vinyl cations have been previously reported to undergo ring-contractive rearrangement to exocyclic vinyl cations.[27,28] Under the reaction conditions, we observe formation of ring-contracted product **4.34** and transannular insertion product **4.35**. The cycloheptene derivative **4.34** is a result of C–H insertion into cyclohexane from the ring-contracted exocyclic vinyl cation **4.36**. Finally, to further validate our C–H insertion step, we looked to disprove the possibility of a *1,5*-hydride migration[29,30] given our selectivity in generating five-membered rings throughout our scope studies. Exposing *tert*-butyl derivative **4.37** to our reaction conditions yielded cyclohexene product isomers (**4.38**) in 85% yield and a 1:1 ratio. These observations disfavor a *1,5*-hydride migration pathway. Instead, these studies suggest a concerted (but possibly highly asynchronous) C–H insertion mechanism, where formation of a five-membered ring is based solely on kinetic preference.

Figure 4.4. Mechanistic Studies



4.4 Conclusion

Over a hundred years after Norris, Kehrman and Baeyer's pioneering studies on the formation of carbocations under Brønsted and Lewis acidic conditions, we show that it is possible to generate such species in highly basic media. Importantly, this catalytic regime represents a new strategy in synthetic chemistry where lithium bases can be utilized to fuel $[Li]^+[WCA]^-$ catalyzed, intramolecular C–H insertion reactions of carbocations. This study highlights the power of main group-catalyzed C–H functionalization reactions in a field dominated by transition metal-based systems. The commercial availability of the catalyst, the

simple reaction protocols described above and the resulting vast improvement in functional group compatibility, render this strategy an attractive approach to build molecules for academic as well as industrial pursuits.

4.5 Experimental Section

4.5.1 Materials and Methods

Unless otherwise stated, all reactions were performed in an MBraun glovebox under nitrogen atmosphere with ≤ 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and dried *in vacuo* before use. All liquid substrates were either dried over CaH_2 or filtered through dry neutral aluminum oxide. Solid substrates were dried over P_2O_5. All solvents were rigorously dried before use. Benzene, *o*-dichlorobenzene, and toluene were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. Cyclohexane, fluorobenzene, and *n*-hexane were distilled over potassium. Chlorobenzene was distilled over sodium. *o*-Difluorobenzene was distilled over CaH_2. Pentane was distilled over sodium-potassium alloy. Chloroform was dried over CaH_2 and stored in a glovebox. Triethylsilane and triisopropylsilane were dried over sodium and stored inside a glovebox. *Closo*-Carborane catalysts were prepared according to literature procedure. $[Li]^+[B(C_6F_5)_4]^-$ and $[K]^+[B(C_6F_5)_4]^-$ salts were synthesized according to literature procedure. Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography. $AgNO_3$-Impregnated silica gel was prepared by mixing with a solution of $AgNO_3$ (150% v/w of 10% w/v solution in acetonitrile), removing solvent under reduced pressure, and drying at 120 °C. NMR spectra were recorded on a Bruker AV-300 (^1H, ^{19}F),

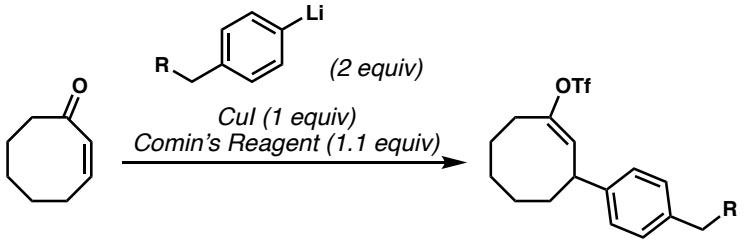
Bruker AV-400 (^{1}H, ^{13}C, ^{19}F), Bruker DRX-500 (^{1}H), and Bruker AV-500 (^{1}H, ^{13}C). ^{1}H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) unless noted otherwise. Data for ^{1}H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.0 ppm) unless noted otherwise. GC spectra were recorded on an Agilent 6850 series GC using an Agilent HP-1 (50 m, 0.32 mm ID, 0.25 mm DF) column. GCMS spectra were recorded on a Shimadzu GCMS-QP2010 using a Restek XTI-5 (50 m, 0.25 mm ID, 0.25 mm DF) column interface at room temperature. IR Spectra were record on a Perkin Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on a Waters (Micromass) GCT Premier spectrometer, a Waters (Micromass) LCT Premier, or an Agilent GC EI-MS, and are reported as follows: m/z (% relative intensity). Purification by preparative HPLC was done on an Agilent 1200 series instrument with a reverse phase Alltima C_{18} (5m, 25 cm length, 1 cm internal diameter) column.

4.5.2 Experimental Procedures

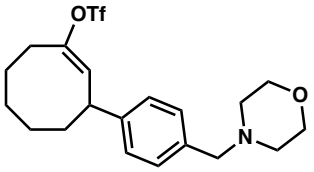
The synthesis of substrates in Table 4.2, Figure 4.3, are described in adapted article.

*The synthesis of substrates **4.1** and **4.4** are reported elsewhere.*[16]

4.5.2.1 Preparation of Vinyl Triflate Substrates



Scheme 4.1. Representative scheme for substrate synthesis *via* conjugate addition with copper.



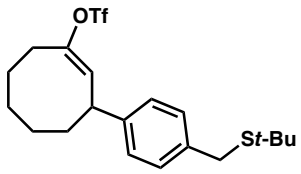
(*E*)-3-(4-(morpholinomethyl)phenyl)cyclooct-1-en-1-yl trifluoromethanesulfonate (4.39). To a degassed solution of 4-(4-bromobenzyl)morpholine (1.2 g, 4.8 mmol, 2.0 equiv) at –78 °C in THF (10 mL) was added a solution of 2.0 M *n*-BuLi in hexanes (2.5 mL, 2.0 equiv). After 30 minutes of stirring, this solution was cannula transferred to a degassed –78 °C solution of copper iodide in Et_2O (2.5 mL). The reaction was allowed to stir at –78 °C for 5 minutes before removing the cooling bath to stir at room temperature. Once the solution turned dark purple in color, the reaction was placed in a 0 °C bath. Cyclooct-2-en-1-one (300 mg, 2.4 mmol, 1.0 equiv) in Et_2O (5 mL) was added while maintaining this temperature. After 30 minutes of stirring, Comin's reagent (1.0 g, 2.5 mmol, 1.1 equiv) in THF (5 mL) was added and the reaction was allowed to warm to room temperature over 12 hours. The reaction was quenched by addition of saturated aqueous solution of ammonium chloride (20 mL) and extracted with Et_2O (3 x 20

mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (30% diethyl ether in hexanes) to yield 320 mg (31%) of light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.20 – 7.15 (m, 2H), 5.72 (d, *J* = 9.4 Hz, 1H), 3.70 (t, *J* = 4.7 Hz, 4H), 3.57 (ddd, *J* = 12.5, 9.5, 4.4 Hz, 1H), 3.47 (s, 2H), 2.75 (ddd, *J* = 15.7, 12.4, 3.3 Hz, 1H), 2.46 – 2.39 (m, 4H), 1.98 – 1.90 (m, 1H), 1.87 – 1.67 (m, 6H), 1.63 (s, 1H), 1.58 – 1.50 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 142.7, 136.2, 129.5, 126.9, 124.7, 122.3, 119.7, 117.2, 114.6, 67.0, 63.0, 53.6, 41.9, 37.8, 30.5, 27.5, 26.2, 25.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.2.

FTIR (Neat Film NaCl): 2829, 2855, 2806, 1678, 1513, 1455, 1414, 1206, 1143, 1117, 1037, 1008, 931, 867, 614 3093, 3027, 2934, 2856, 2805, 1512, 1453, 1332, 1264, 1118, 1008, 876, 827, 787, 614 cm^{-1}.

HRMS (GCT-LIFDI): Calculated for [$C_{20}H_{26}F_3NO_4S$ + H]: 434.1535; Measured: 434.1539.



(*E*)-3-(4-((*tert*-butylthio)methyl)phenyl)cyclooct-1-en-1-yl trifluoromethanesulfonate (4.40). To a degassed solution of 4-(4-bromobenzyl)(tert-butyl)sulfane (1.3g, 4.8 mmol, 2.0 equiv) at –78 °C in Et_2O (5 mL) was added a solution of 1.57 M *t*-BuLi in pentane (6.2 mL, 4.0 equiv). After 30 minutes of stirring, this solution was cannula transferred to a degassed –78°C solution of copper iodide (460 mg, 2.4 mmol, 1.0 equiv) in Et_2O (2.5 mL). The reaction was allowed to stir at –78 °C for 50 minutes before warming to 0 °C. After stirring at 0 °C for 5 minutes, cyclooct-2-en-1-one (300 mg, 2.4 mmol, 1.0 equiv) in Et_2O (5 mL) was added while maintaining

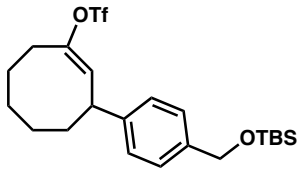
this temperature. After 30 minutes of stirring, Comin's reagent (1.0 g, 2.5 mmol, 1.1 equiv) in THF (5 mL) was added and the reaction was allowed to warm to room temperature over 36 hrs. The reaction was quenched by addition of saturated aqueous solution of ammonium chloride (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organics were washed with brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography (25% benzene in hexanes) to yield 265 mg (25%) of white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 5.71 (d, *J* = 9.4 Hz, 1H), 3.74 (s, 2H), 3.56 (ddd, *J* = 13.3, 9.4, 4.3 Hz, 1H), 2.75 (ddd, *J* = 15.5, 12.2, 3.4 Hz, 1H), 2.40 (dt, *J* = 15.8, 4.3 Hz, 1H), 1.93 (tt, *J* = 9.5, 3.8 Hz, 1H), 1.88 – 1.66 (m, 5H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 142.5, 137.1, 129.5, 127.3, 124.9, 118.6 (q, *J* = 320.0 Hz), 43.1, 42.1, 37.9, 33.1, 31.0, 30.7, 27.7, 26.3, 25.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.1.

FTIR (Neat film NaCl): 2928, 2860, 1678, 1513, 1457, 1415, 1365, 126, 1208, 1144, 1038, 1011, 982, 931, 871, 837, 732, 648, 608, 507.

HR-MS (GCT-LIFDI): Calculated for $C_{20}H_{27}F_3O_3S_2$: 436.1354; measured: 436.1335.

FTIR (Neat Film NaCl): 3045, 3005, 2933, 2857, 1678, 1613, 1514, 1414, 1248, 1209, 1144, 1039, 932, 871, 826, 607 cm^{-1}.



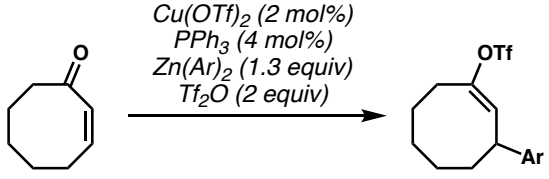
(*E*)-3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)cyclooct-1-en-1-yl trifluoromethanesulfonate (4.41). To a degassed solution of ((4-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (1.5 g, 4.8 mmol, 2.0 equiv) at –78 °C in Et_2O (5 mL) was added a solution of 1.57 M *t*-BuLi in pentane (6.2 mL, 4.0 equiv). After 30 minutes of stirring, this solution was

cannula transferred to a degassed –78 °C solution of copper iodide (460 mg, 2.4 mmol, 1.0 equiv) in Et_2O (2.5 mL). The reaction was allowed to stir at –78 °C for 50 minutes before warming to 0 °C. After stirring at 0 °C for 15 minutes, cyclooct-2-en-1-one (300 mg, 2.4 mmol, 1.0 equiv) in Et_2O (5 mL) was added while maintaining this temperature. After 45 minutes of stirring, Comin's reagent (1.0 g, 2.5 mmol, 1.1 equiv) in THF (5 mL) was added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated aqueous solution of ammonium chloride (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organics were washed with brine and dried with $MgSO_4$. The crude product was purified by flash column chromatography (25% chloroform in pentane) to yield 325 mg (28%) of yellow oil.

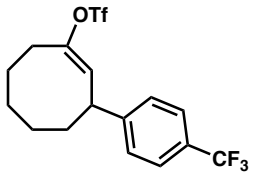
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 5.73 (d, J = 9.5 Hz, 1H), 4.72 (s, 2H), 3.57 (ddd, J = 13.2, 9.4, 4.3 Hz, 1H), 2.83 – 2.67 (m, 1H), 2.41 (dt, J = 15.6, 4.3 Hz, 1H), 2.02 – 1.89 (m, 1H), 1.87 – 1.65 (m, 4H), 0.94 (s, 10H), 0.10 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 142.4, 139.9, 126.8, 126.4, 124.8, 118.4 (q, J = 320.1 Hz), 64.6, 41.9, 37.8, 30.4, 27.5, 26.1, 25.9, 25.40, 18.4, –5.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.1.

FTIR (Neat film NaCl): 2930, 2858, 1416, 1248, 1210, 1145, 1092, 1039, 1009, 982, 932, 838, 777, 610, 507.

HR-MS (LCT-ESI): Calculated for [$C_{22}H_{33}F_3O_4SSi$ + Na]: 501.1719; Measured: 501.1700.



Scheme 4.2. Representative scheme for substrates synthesized *via* catalytic conjugate addition.



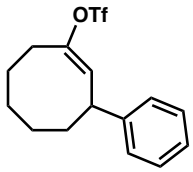
(*E*)-3-(4-(trifluoromethyl)phenyl)cyclooct-1-en-1-yl trifluoromethanesulfonate (4.42). A flame dried round bottom flask was charged with anhydrous $ZnCl_2$ (4.4 g, 32 mmol, 1.0 equiv) and anhydrous toluene (32 mL). After cooling the mixture to –30 °C, a 0.42 M aryl lithium solution (116 mL, 21 mmol, 1.3 equiv), made from reacting 1-bromo-4-(trifluoromethyl)benzene (8.9 mL, 64 mmol) in Et_2O (124 mL) with a solution of 2.63 M *n*-BuLi in hexanes (25 mL, 65 mmol) at –78 °C, was added dropwise. The reaction was then left to warm up to room temperature over 2 hours to yield a 0.18 M solution of diarylzinc by iodine titration.[4] To a separate flame dried schlenk flask was added $Cu(OTf)_2$ (116 mg, 0.32 mmol, 0.02 equiv), PPh_3 (169 mg, 0.64 mmol, 0.04 equiv) and anhydrous toluene (80 mL). Reaction was degassed and stirred for 30 minutes. Cyclooct-2-en-1-one (2.0 g, 16 mmol, 1.0 equiv) was added and the solution cooled to –30 °C. The solution of 0.18 M diarylzinc in Et_2O (116 mL, 21 mmol, 1.3 equiv) was then added dropwise. After 2 hours, the reaction was brought to 0 °C before adding Tf_2O (5.4 mL, 32 mmol, 2.0 equiv) and allowed to warm to room temperature over 12 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution (150 mL), extracted with Et_2O (3 x 100 mL), and the combined organics were dried over $MgSO_4$ filtered and concentrated. Crude product was purified by flash chromatography (hexanes) to yield 540 mg (8%) of colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.70 (d, *J* = 9.4 Hz, 1H), 3.65 (ddd, *J* = 13.1, 9.4, 4.3 Hz, 1H), 2.76 (ddd, *J* = 15.7, 12.3, 3.4 Hz, 1H), 2.43 (dt, *J* = 15.6, 4.2 Hz, 1H), 2.02 – 1.91 (m, 1H), 1.90 – 1.69 (m, 6H), 1.62 – 1.52 (m, 1H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 150.1, 147.7, 129.2, 129.0, 127.4, 125.7 (q, $J_{C–F}$ = 3.8 Hz), 125.6, 123.7, 123.0, 119.7, 117.2, 114.6, 42.2, 37.6, 30.5, 27.5, 26.1, 25.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.1, –64.5.

FTIR (Neat Film NaCl): 3060, 2933, 2859, 1679, 1619, 1415, 1326, 1210, 1124, 1070, 933, 606 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{16}H_{16}F_6O_3S$: 402.0724; Measured: 402.0745.



(*E*)-3-phenylcyclooct-1-en-1-yl trifluoromethanesulfonate (4.43). A flame dried round bottom flask was charged with anhydrous $ZnCl_2$ (4.2 g, 31 mmol, 1.0 equiv) and anhydrous toluene (31 mL). After cooling the mixture to –30 °C, a 1.0 M solution of PhMgBr in Et_2O (62 mL, 62 mmol, 2.0 equiv) was added dropwise. The reaction was then left to warm up to room temperature over 2 hours to yield a 0.47 M solution of diphenylzinc. To a separate flame dried schlenk flask was added $Cu(OTf)_2$ (64 mg, 0.18 mmol, 0.02 equiv), PPh_3 (93 mg, 0.35 mmol, 0.04 equiv) and anhydrous toluene (45 mL). After stirring for 30 minutes, cyclooct-2-en-1-one (1.1 g, 8.8 mmol, 1.0 equiv) was added and the solution cooled to –30 °C. The solution of 0.47 M diphenylzinc in Et_2O (30 mL, 11.5 mmol, 1.3 equiv) was then added dropwise. After 2 hours, the reaction was brought to 0 °C before adding Tf_2O (5 mL, 17.7 mmol, 2.0 equiv) and allowed to warm to room temperature over 12 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution (80 mL), extracted with Et_2O (3 x 60 mL) and the combined organics were dried over $MgSO_4$. After filtering and concentrating by rotary evaporation, the

crude product was purified by flash chromatography (hexanes) to yield 145 mg (5%) of colorless oil.

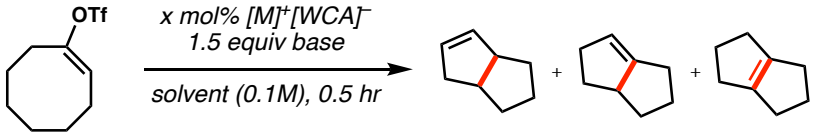
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.29 – 7.20 (m, 3H), 5.74 (d, *J* = 9.5 Hz, 1H), 3.59 (ddd, *J* = 12.1, 9.4, 4.4 Hz, 1H), 2.77 (ddd, *J* = 15.5, 12.2, 3.4 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.01 – 1.91 (m, 1H), 1.89 – 1.68 (m, 6H), 1.61 – 1.55 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 143.8, 128.8, 127.0, 126.7, 124.7, 122.3, 119.8, 117.2, 114.7, 42.3, 37.8, 30.5, 27.6, 26.2, 25.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.2.

FTIR (Neat Film NaCl): 3090, 3064, 2930, 2857, 1678, 1599, 1415, 1210, 1143, 932, 699, 605 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{15}H_{17}F_3O_3S$: 334.0850; Measured: 334.0848.

4.5.3 C–H Insertion Reactions Fueled by LiHMDS Base

4.5.3.1 Cyclooctenyl Triflate Derivatives



[M]$^+$[WCA]$^-$	% Cat. Loading	Temp.	Base	Solvent	Yield
$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$	5 mol%	30 °C	LiHMDS	*o*-DFB	90%
$[Ph_3C]^+[HCB_{11}Cl_{11}]^-$	5 mol%	30 °C	LiHMDS	DCM	59%
$[Ph_3C]^+[B(C_6F_5)_4]^-$	5 mol%	30 °C	LiHMDS	*o*-DFB	98%
$[Ph_3C]^+[B(C_6F_5)_4]^-$	0 mol%	30 °C	LiHMDS	*o*-DFB	0%
$[Ph_3C]^+[B(C_6F_5)_4]^-$	5 mol%	30 °C	NaHMDS	*o*-DFB	0%
$[Ph_3C]^+[B(C_6F_5)_4]^-$	5 mol%	30 °C	KHMDS	*o*-DFB	0%
$[Li]^+[B(C_6F_5)_4]^-$	5 mol%	30 °C	LiHMDS	*o*-DFB	84%

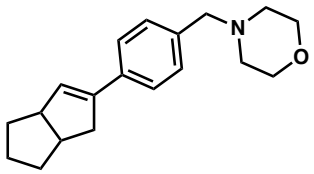
Table 4.3. Optimization of intramolecular C–H insertion reaction of cyclooctenyl triflate.

4.5.3.2 General Procedure for Transannular C–H Insertion Reactions

In a well kept glovebox, H_2O, $O_2 \leq 0.5$ ppm, a dram vial was charged with $[Ph_3C]^+[B(C_6F_5)_4]^-$ (0.05 equiv) and LiHMDS (1.5–3.0 equiv). Solids were stirred in solvent (0.1–0.017 M) for one minute before addition of cyclooctenyl triflate substrate. Reactions were stirred at 30–70 °C for 0.5–3.5 hours (see substrates for exact conditions). Reactions were monitored by GC-FID spectra unless noted otherwise. Upon completion, reactions were brought out of the glovebox, diluted with hexanes, and passed through a short plug of silica. Isolation of styrene products were

achieved by flash column, preparatory thin layer chromatography using silver impregnated silica or HPLC.

4.6.2.1.2 Insertion Reactions of Cyclooctenyl Triflate Derivatives

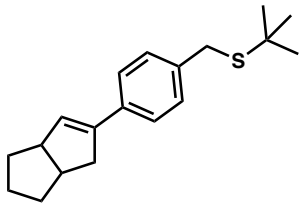


4-(4-(1,3a,4,5,6,6a-hexahydropentalen-2-yl)benzyl)morpholine (4.13). Synthesized according to general procedure 4.5.3.2. A dram vial charged with $[Ph_3C]^+[B(C_6F_5)_4]^-$ (1.2 mg, 1.25 mmol, 0.05 equiv) and LiHMDS (12.6 mg, 0.075 mmol, 3.0 equiv) was suspended in cyclohexane (0.25 mL, 0.017 M). After pre-stirring for one minute, the corresponding triflate **4.39** (10.8 mg, 0.025 mmol, 1.0 equiv) was added and stirred at 70 °C for 1 hour. Upon completion, reaction was diluted with hexanes (1 mL) and passed through a short plug of silica (1:1 hexanes:Et_2O) to yield **4.13** in 42% NMR yield. Crude product can be further purified by preparatory thin layer chromatography (10% methanol in ethyl acetate) using silver impregnated silica to give **4.13** as a colorless oil. Major byproducts observed are intractable mixtures of high molecular weight products likely due to oligomerization of the desired electron-rich styrene **4.13**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.9 Hz, 2H), 7.28 – 7.23 (m, 2H), 5.98 (q, J = 2.2 Hz, 1H), 3.70 (t, J = 4.6 Hz, 4H), 3.48 (s, 2H), 3.33 (tt, J = 8.5, 2.5 Hz, 1H), 2.99 (ddt, J = 16.2, 9.3, 2.0 Hz, 1H), 2.82 (ddq, J = 12.4, 8.3, 3.7 Hz, 1H), 2.53 – 2.36 (m, 4H), 1.83 – 1.67 (m, 3H), 1.51 (dt, J = 7.2, 4.6 Hz, 3H), 1.43 – 1.37 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 135.6, 129.8, 129.1, 126.1, 125.5, 67.0, 63.1, 53.5, 51.1, 41.4, 40.3, 35.8, 32.5, 25.3.

FTIR (Neat Film NaCl): 3093, 3027, 2934, 2856, 2805, 1512, 1453, 1332, 1264, 1118, 1008, 876, 827, 787 cm^{-1}.

HRMS (EI-MS): Calculated for $C19H_{25}NO$: 283.1936; Measured: 283.1934.

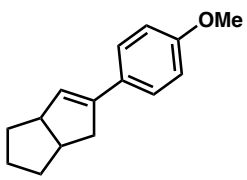


***tert*-butyl(4-(1,3a,4,5,6,6a-hexahydropentalen-2-yl)benzyl)sulfane (4.14).** Synthesized according to general procedure 4.5.3.2. A dram vial charged with $[Ph_3C]+[B(C_6F_5)_4]^-$ (2.3 mg, 2.50 mmol, 0.05 equiv) and LiHMDS (12.5 mg, 0.075 mmol, 1.5 equiv) was dissolved in *o*-difluorobenzene (0.5 mL). After pre-stirring for one minute, the corresponding triflate **4.40** (21.8 mg, 0.05 mmol 1.0 equiv) was added and stirred at 30°C for 0.5 hours. Upon completion, reaction was diluted with ether (1 mL) and passed through a short plug of silica (Et_2O) to yield **4.14**in 38% NMR yield. Crude product can be further purified by HPLC (10% water in acetonitrile) to give **4.14** as a white solid. The low yield observed is attributed to the instability of the products to silica chromatography.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 5.95 (q, *J* = 2.2 Hz, 1H), 3.74 (s, 1H), 3.31 (tq, *J* = 5.5, 2.7, 2.2 Hz, 1H), 2.97 (ddt, *J* = 16.1, 9.3, 1.9 Hz, 1H), 2.81 (dtdd, *J* = 9.4, 8.3, 4.2, 3.1 Hz, 1H), 2.39 (dtd, *J* = 16.2, 3.0, 1.8 Hz, 1H), 1.82 – 1.64 (m, 1H), 1.53 – 1.45 (m, 2H), 1.34 (s, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 137.0, 135.2, 129.7, 128.8, 125.7, 51.1, 42.8, 41.3, 40.3, 35.7, 33.20, 32.5, 30.9, 25.3.

FT-IR (neat film NaCl): 2929, 2859, 1511, 1458, 1415, 1363, 1161, 1052, 830, 756, 540 cm^{-1}.

HRMS (GCT-CI): Calculated for $C_{19}H_{26}S$: 286.1755; Measured: 286.1768.

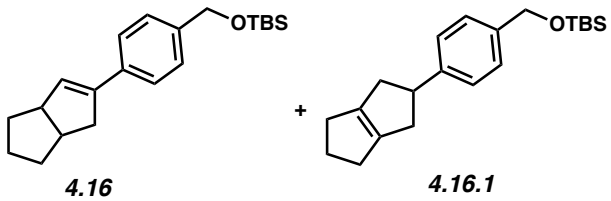


5-(4-methoxyphenyl)-1,2,3,3a,4,6a-hexahydropentalene (4.15). Synthesized according to general procedure 4.5.3.2. A dram vial charged with $[Ph_3C]^+[B(C_6F_5)_4]^-$ (1.2 mg, 1.25 mmol, 0.05 equiv) and LiHMDS (6.3 mg, 0.038 mmol, 1.5 equiv) was dissolved in *o*–difluorobenzene (1.5 mL, 0.017 M). After pre-stirring for one minute, the corresponding triflate (9.1 mg, 0.025 mmol, 1.0 equiv) was added and stirred at 30 °C for 1 hour. Upon completion, reaction was diluted with hexanes (1 mL) and passed through a short plug of silica to yield **4.15** in 38% NMR yield. Crude product can be further purified by flash column chromatography (50% benzene in hexanes) using silver impregnated silica to give **4.15** as a colorless oil in 29% yield (1.6 mg). Major byproducts observed are intractable mixtures of high molecular weight products likely due to oligomerization of the desired electron-rich styrene **4.15**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 6.88 – 6.80 (m, 2H), 5.85 (q, *J* = 2.2 Hz, 1H), 3.80 (s, 3H), 3.32 (td, *J* = 8.4, 7.5, 4.4 Hz, 1H), 2.97 (ddt, *J* = 16.1, 9.4, 2.0 Hz, 1H), 2.87 – 2.75 (m, 1H), 2.39 (dtd, *J* = 16.1, 3.0, 1.7 Hz, 1H), 1.82 – 1.64 (m, 2H), 1.55 – 1.46 (m, 3H), 1.45 – 1.37 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 140.2, 129.5, 127.8, 126.7, 113.6, 55.2, 51.12, 4.5, 40.3, 35.8, 32.6, 25.3.

FTIR (Neat Film NaCl): 3038, 2935, 2859, 1739, 1608, 1512, 1455, 1254, 1178, 1040, 825 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{15}H_{18}O$: 214.1358; Measured: 214.1353.



4.16 *4.16.1*

***tert*-butyl((4-(1,3a,4,5,6,6a-hexahydropentalen-2-yl)benzyl)oxy)dimethylsilane (4.16** and **4.16.1)** Synthesized according to general procedure 4.5.3.2. A dram vial charged with

$[Ph_3C]^+[B(C_6F_5)_4]^-$ (2.3 mg, 2.50 mmol, 0.05 equiv) and LiHMDS (12.5 mg, 0.075 mmol, 1.5 equiv) was dissolved in methylene chloride (0.5 mL). After pre-stirring for one minute, the corresponding triflate **4.41** (23.9 mg, 0.05 mmol 1.0 equiv) was added and stirred at 30°C for 0.5 hours. Upon completion, reaction was diluted with ether (1 mL) and passed through a short plug of silica (Et_2O) to yield **4.16** in 60% NMR yield. Crude product can be further purified by flash column chromatography using silver impregnated silica (10% benzene in pentane) to give 6.6mg (46%) of **4.16** as a colorless oil.

The tetrasubstituted isomer **4.16.1** could be isolated by preparatory thin layer chromatography (3:2 hexane:benzene) using silver impregnated silica to give **4.16.1** as a colorless oil.

Characterization of 4.16

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 0.7 Hz, 0H), 5.96 (q, *J* = 2.2 Hz, 1H), 4.72 (s, 1H), 3.32 (tt, *J* = 8.1, 2.5 Hz, 1H), 2.99 (ddt, *J* = 16.2, 9.4, 2.0 Hz, 1H), 2.91 – 2.70 (m, 1H), 2.41 (dtd, *J* = 16.2, 3.0, 1.8 Hz, 1H), 1.81 – 1.63 (m, 1H), 1.54 – 1.46 (m, 2H), 0.93 (s, 5H), 0.09 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 139.9, 135.3, 129.5, 125.9, 125.5, 64.8, 51.1, 41.4, 40.3, 35.8, 32.5, 25.9, 25.3, 18.4, –5.2.

FTIR(neat film NaCl): 2931, 2858, 1513, 1463, 1376, 1256, 1212, 1091, 1006, 838, 776, 667 cm^{-1}.

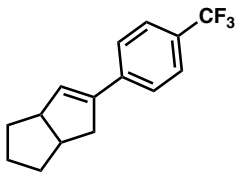
HRMS (GCT-CI): Calculated for $C_{21}H_{32}OSi$: 328.2222; Measured: 328.2227.

Characterization of 4.16.1

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 1H), 4.71 (s, 1H), 3.84 (tt, *J* = 8.9, 6.5 Hz, 1H), 2.74 – 2.54 (m, 1H), 2.39 – 2.10 (m, 2H), 0.94 (s, 2H), 0.10 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 144.7, 138.7, 126.7, 126.1, 64.8, 48.8, 38.5, 29.4, 28.1, 25.9, 18.4, –5.2.

FTIR (neat film NaCl): 2952, 2926, 2894, 2851, 1513, 1471, 1462, 1449, 1420, 1361, 1252, 1111, 1088, 835, 775 cm^{-1}.

HRMS (EI-MS): Calculated for [$C_{21}H_{32}OSi - C_4H_9$]: 271.1518; Measured: 271.1515.

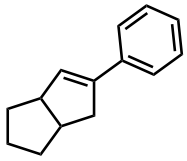


5-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydropentalene (4.17). Synthesized according to general procedure 4.5.3.2. A dram vial charged with $[Ph_3C]^+[B(C_6F_5)_4]^-$ (1.2 mg, 1.25 mmol, 0.05 equiv) and LiHMDS (6.3 mg, 0.038 mmol, 1.5 equiv) was dissolved in *o*–difluorobenzene (0.25 mL, 0.1 M). After pre-stirring for one minute, the corresponding triflate **4.42** (10.1 mg, 0.025 mmol, 1.0 equiv) was added and stirred at 30 °C for 1 hour. Upon completion, reaction was diluted with hexanes (1 mL) and passed through a short plug of silica to yield **4.17** in 50% NMR yield. Crude product can be further purified by flash column chromatography (hexanes) using silver impregnated silica to give **4.17** as a colorless oil. On 0.1 mmol scale, **4.17** was isolated in 45% yield (11.4 mg) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.53 – 7.47 (m, 2H), 6.11 (q, J = 2.2 Hz, 1H), 3.36 (tt, J = 8.6, 2.5 Hz, 1H), 3.01 (ddt, J = 16.1, 9.3, 2.0 Hz, 1H), 2.86 (dtdd, J = 9.3, 8.2, 4.3, 3.1 Hz, 1H), 2.42 (dtd, J = 16.2, 3.0, 1.7 Hz, 1H), 1.85 – 1.67 (m, 2H), 1.57 – 1.49 (m, 3H), 1.47 – 1.39 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 139.8, 132.6, 128.9, 128.6, 128.4, 128.1, 127.5, 125.7, 125.3, 125.1 (q, $J_{C–F}$ = 3.9 Hz), 123.2, 121.0, 51.2, 41.2, 40.3, 35.7, 32.4, 25.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.4.

FTIR (Neat Film NaCl): 3049, 2943, 2864, 1615, 1449, 1412, 1324, 1163, 1122, 1110, 1070, 1016, 832, 678, 599 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{15}H_{15}F_3$: 252.1126; Measured: 252.1129.



5-phenyl-1,2,3,3a,4,6a-hexahydropentalene (4.18). Synthesized according to general procedure 4.5.3.2. A dram vial charged with $[Ph_3C]^+[B(C_6F_5)_4]^-$ (1.2 mg, 1.25 mmol, 0.05 equiv) and LiHMDS (6.3 mg, 0.038 mmol, 1.5 equiv) was dissolved in *o*–difluorobenzene (1.5 mL, 0.017 M). After pre-stirring for one minute, the corresponding triflate **4.43** (8.4 mg, 0.025 mmol, 1.0 equiv) was added and stirred at 30 °C for 3.5 hours. Upon completion, reaction was diluted with hexanes (1 mL) and passed through a short plug of silica to yield **4.18** in 46% NMR yield. Crude product can be further purified by flash column chromatography (hexanes) using silver impregnated silica to give **4.18** as a colorless oil. On 0.1 mmol scale, **4.18** was isolated in 35% yield (7.1 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.17 (m, 1H), 5.99 (q, *J* = 2.2 Hz, 1H), 3.33 (tt, *J* = 8.5, 3.4 Hz, 1H), 3.01 (ddt, *J* = 16.2, 9.4, 2.0 Hz, 1H), 2.88 – 2.78 (m, 1H), 2.42 (dtd, *J* = 16.1, 3.0, 1.7 Hz, 1H), 1.83 – 1.66 (m, 2H), 1.54 – 1.48 (m, 3H), 1.47 – 1.38 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 136.6, 129.9, 128.2, 126.8, 125.6, 51.1, 41.3, 40.3, 35.8, 32.5, 25.3.

FTIR (Neat Film NaCl): 3066, 3031, 2929, 2859, 1734, 1679, 1494, 1448, 1211, 752, 692 cm^{-1}.

HR-MS (EI-MS): Calculated for $C_{14}H_{16}$: 184.1252; Measured: 184.1248.

4.5.4 Mass Balance of Alkene Isomer Products

In this section, GC-FID and GCMS spectra of crude reactions are shown to account for approximate mass balances of select substrates. GC-FID integrations for the styrenyl, tri- and tetra-substituted olefin products are assumed to have a coefficient of 1.

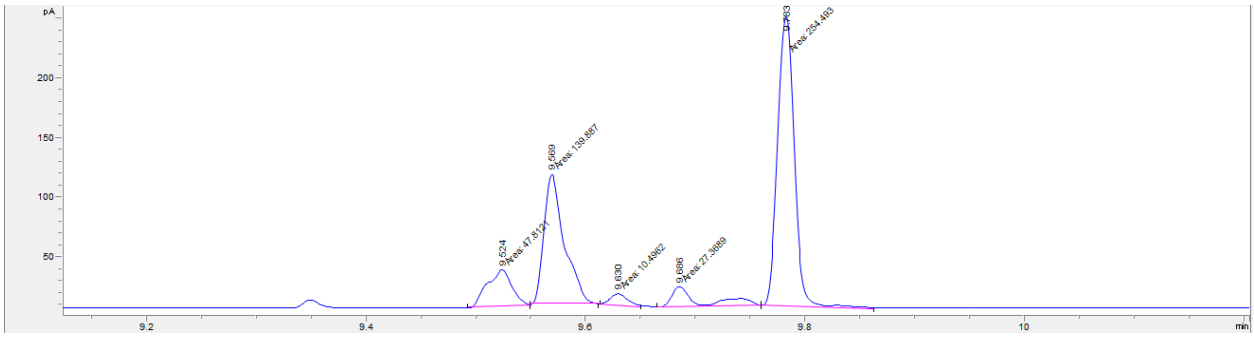
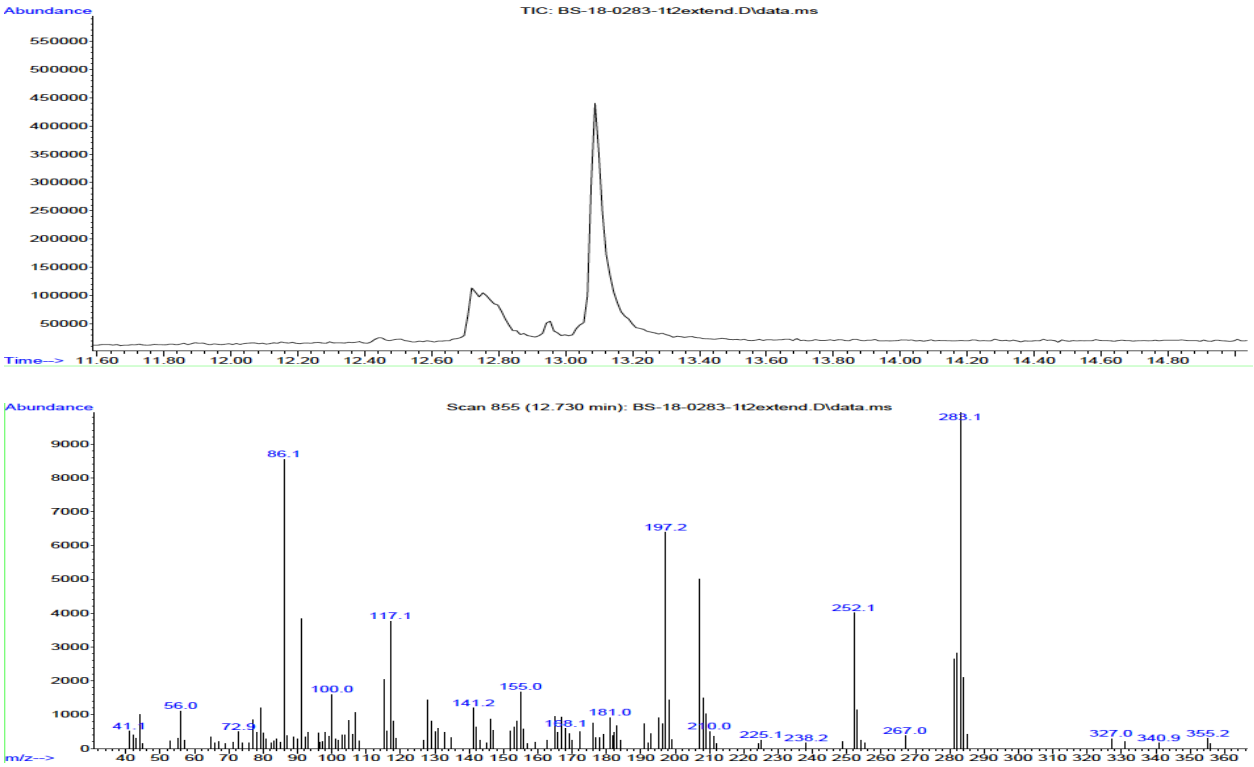


Figure 4.5. GC trace for crude reaction containing **4.13** showing a total of 79% yield.



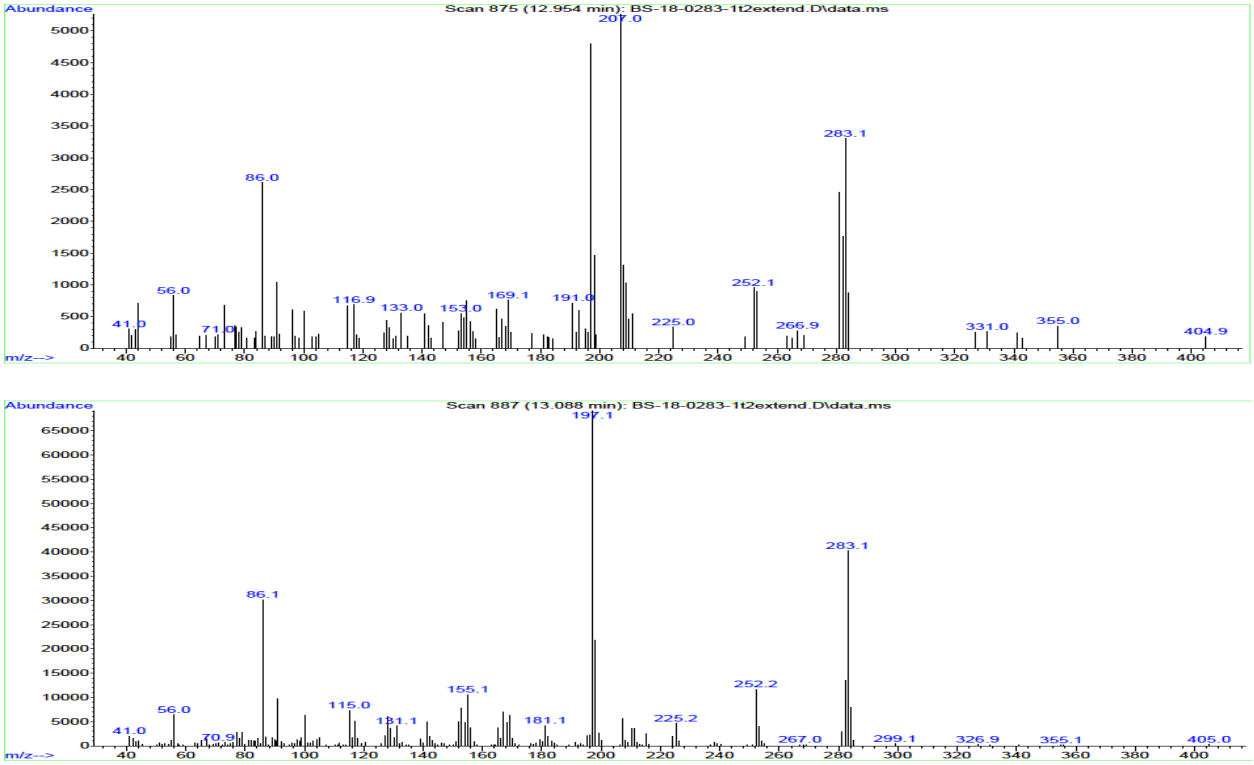


Figure 4.6. Mass spectrum of **4.13** with tri- and tetra-substituted alkene isomers.

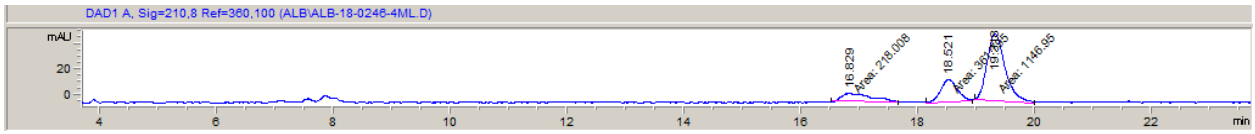


Figure 4.7. LC spectrum at 210 nm wavelength of crude reaction containing **4.14** showing a total of 57% yield.

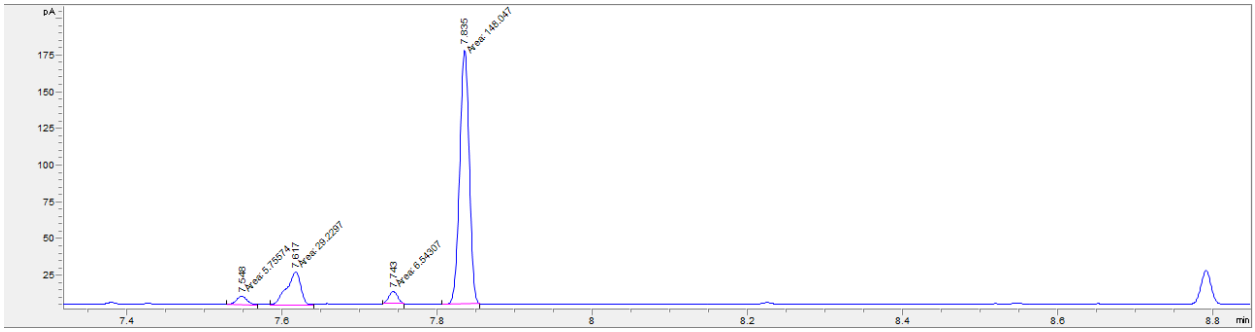


Figure 4.8. GC trace for crude reaction containing **4.15** showing a total of 48% yield.

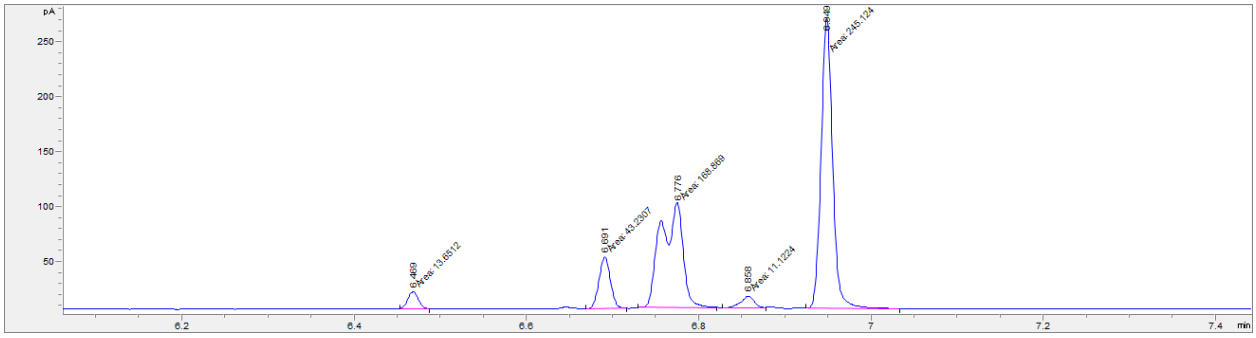
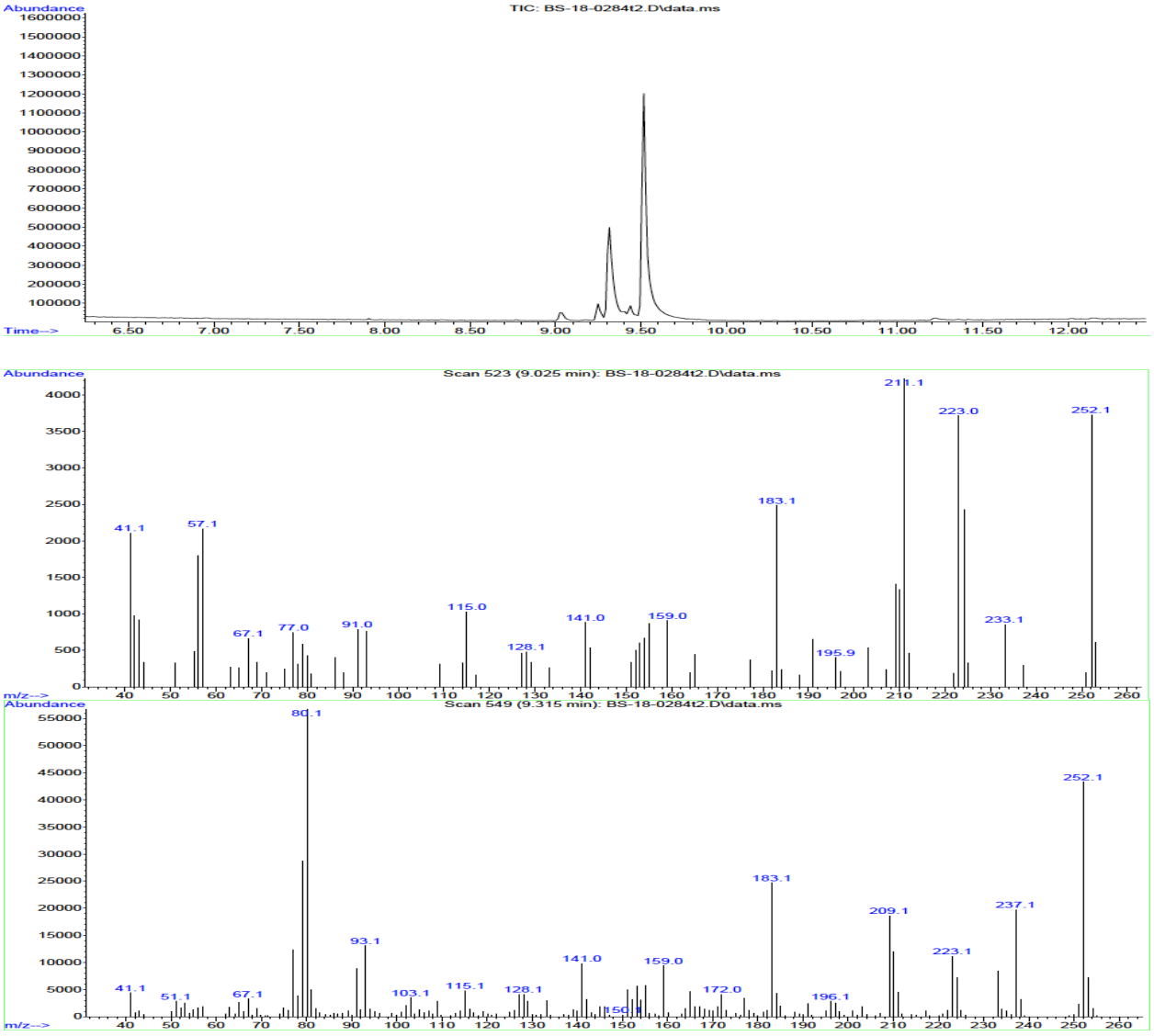


Figure 4.9. GC trace for crude reaction containing **4.17** showing a total of 88% yield.



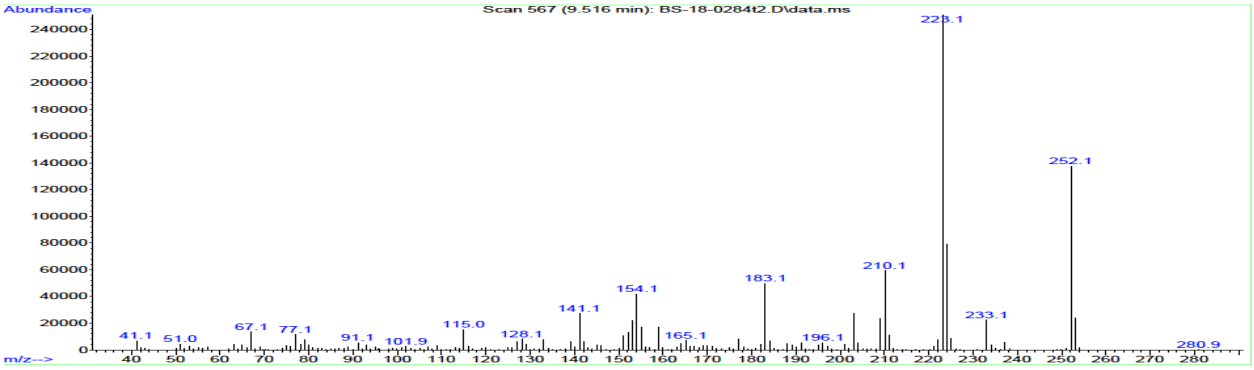


Figure 4.10. Mass spectrum of **4.17** with tri- and tetra-substituted alkene isomers.

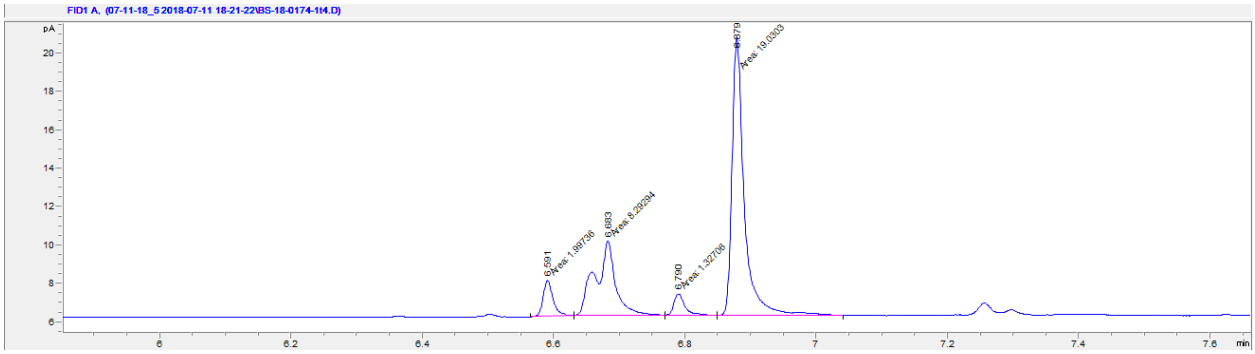


Figure 4.11. GC trace for crude reaction containing **4.18** showing a total of 75% yield.

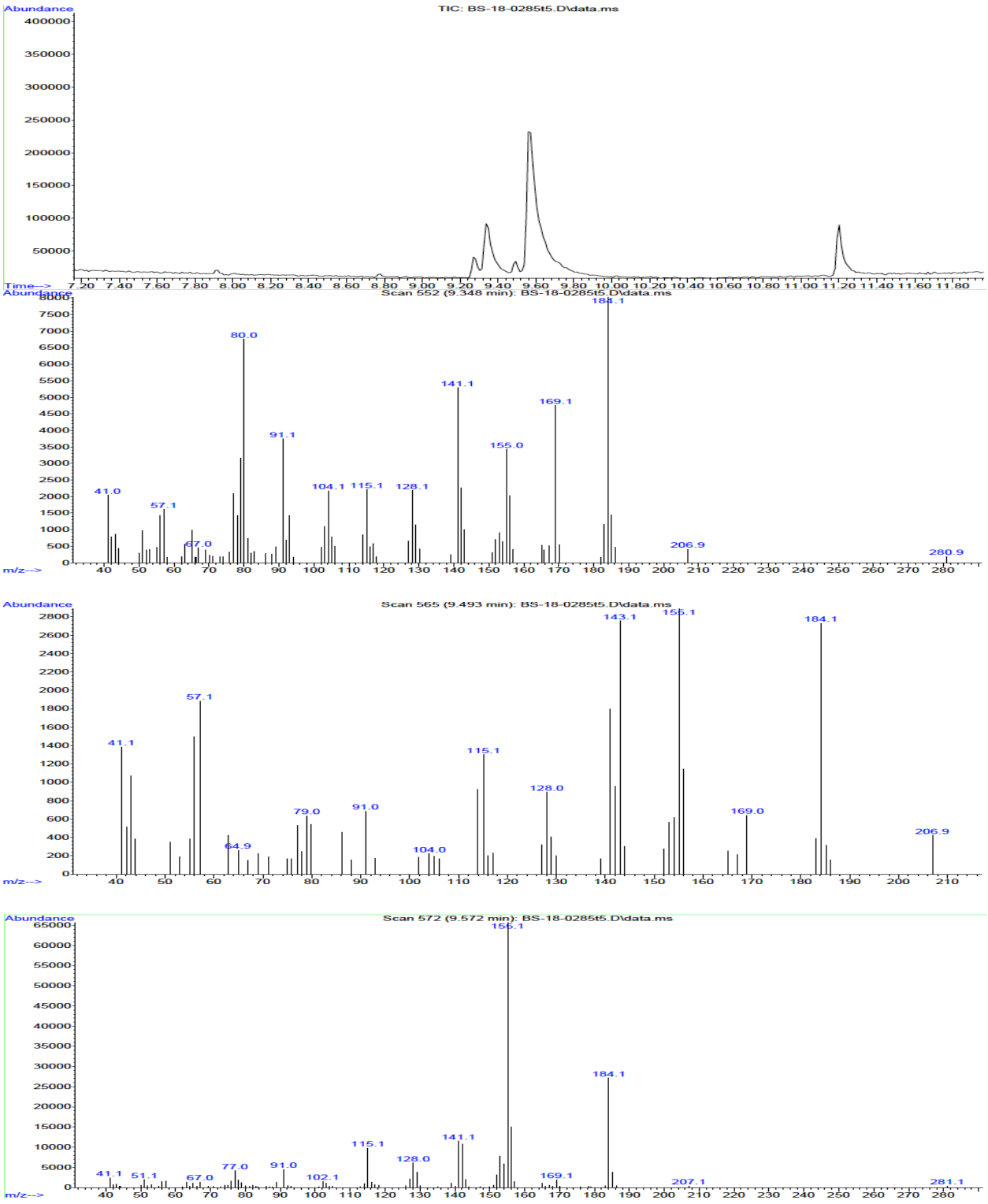


Figure 4.12. Mass spectrum of **4.18** with tri- and tetra-substituted alkene isomers.

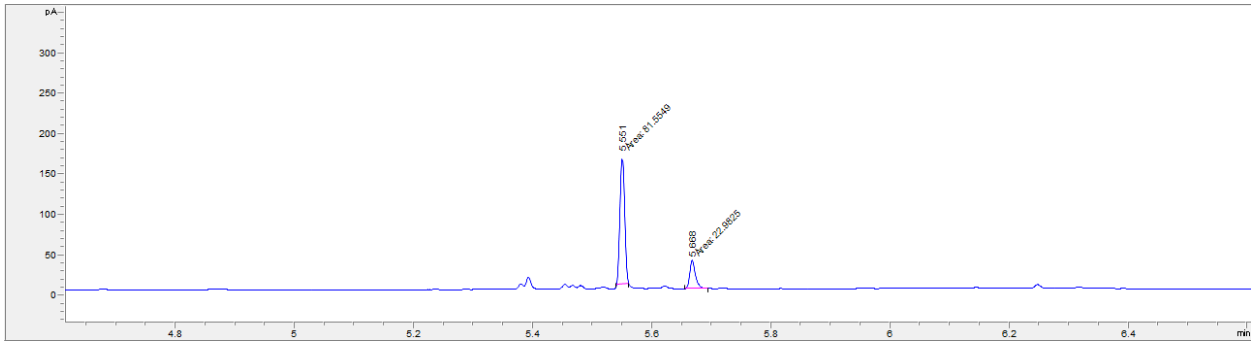


Figure 4.13. GC-FID spectrum of crude reaction containing **4.24** showing a total of 65% yield.

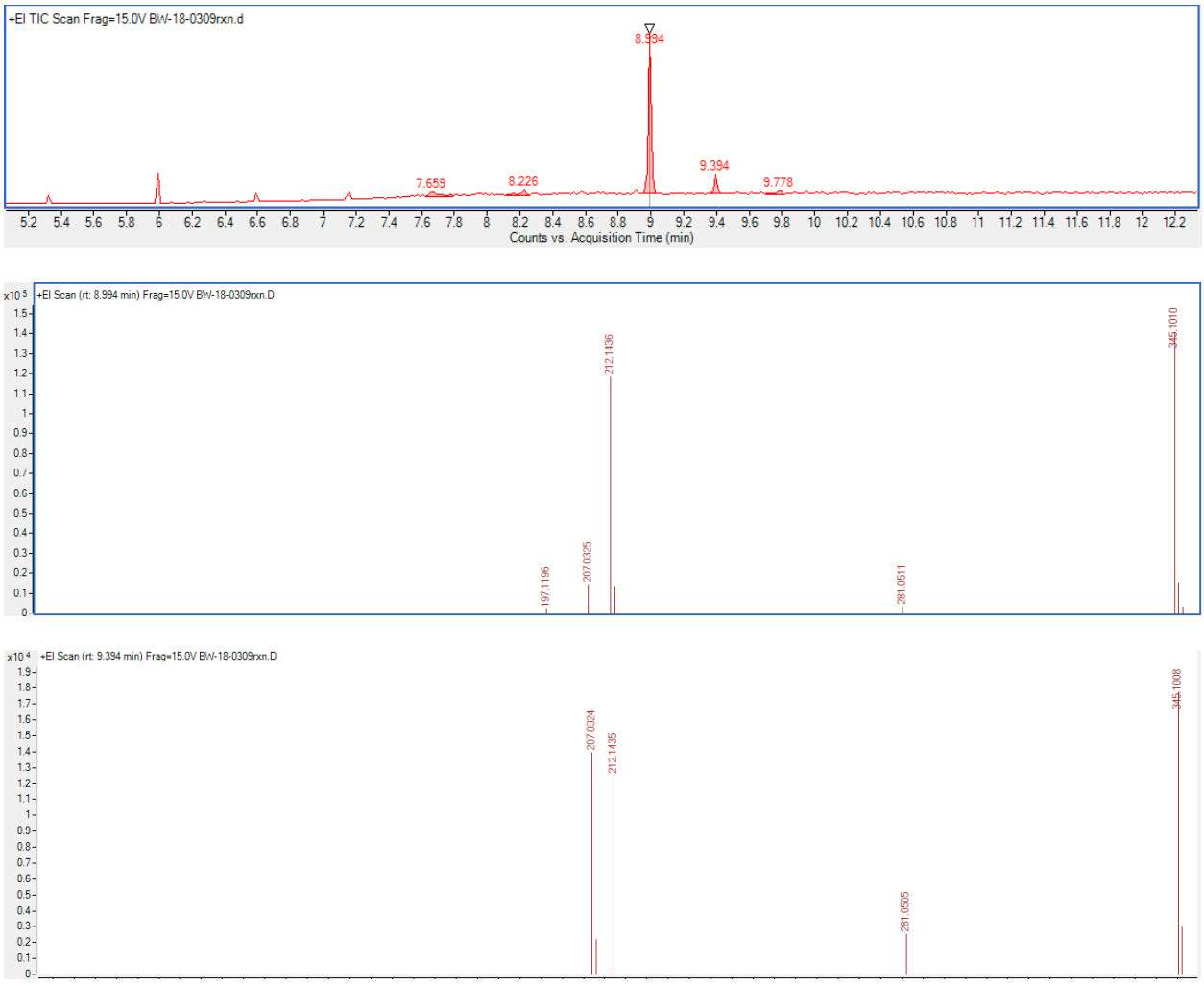


Figure 4.14. GC-MS trace of crude reaction containing **4.24**.

4.5.5 Traces of Initial Experiments Exploring Ionizing Agents in Figure 4.2

General procedure

In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with $[Ph_3C]^+[HCB_{11}Cl_{11}]^-$ (0.02 equiv.) and this was dissolved in arene (enough to make a 0.1 M solution of vinyl triflate). The respective metal hydride (1.5 equiv.) along with a magnetic stirring bar were added to the mixture (along with 0.15 equiv triisopropylsilane if applicable) and was shaken until it turned colorless. At this point, vinyl triflate (1.0 equiv.) was added to the reaction and it stirred for 0.1–168 hours at 30–70 °C. Upon completion, the reaction mixture was pushed through a short plug of silica gel inside the glovebox and washed with hexanes. The solution was brought out and volatiles removed under reduced pressure.

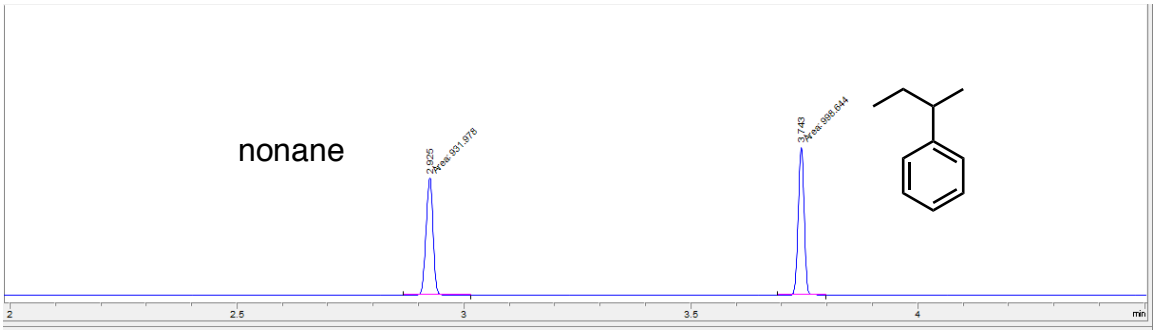


Figure 4.15. GC trace of a 1:1 mixture of nonane to *s*-butylbenzene.

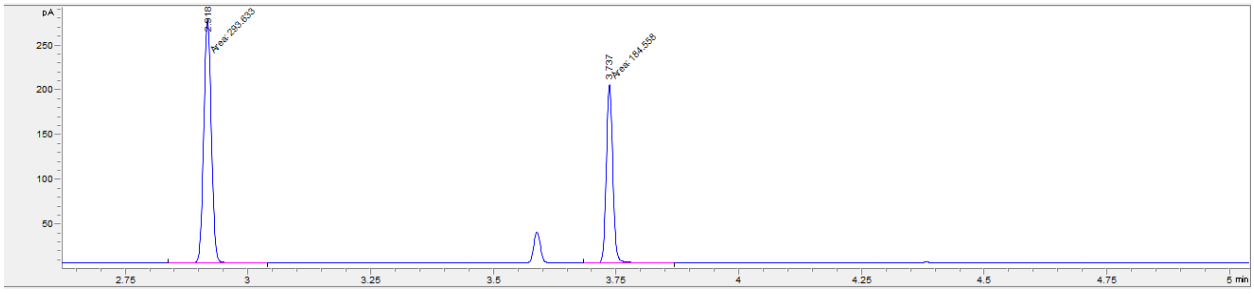


Figure 4.16. Use of DIBAL showing 71% yield of *s*-butylbenzene.

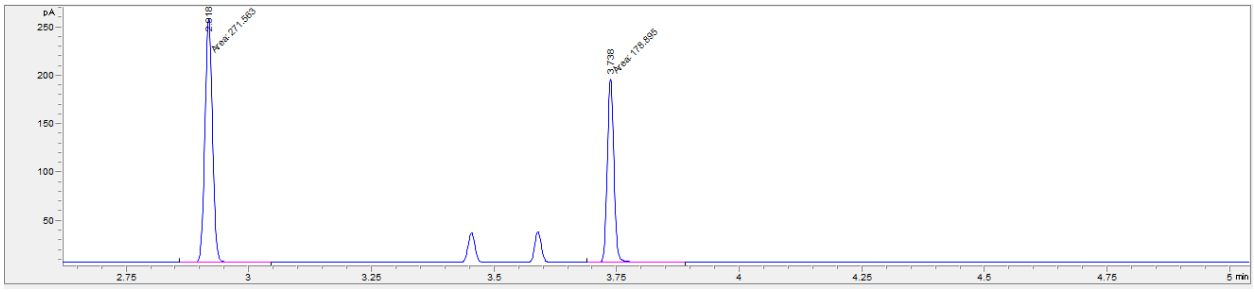


Figure 4.17. Use of DIBAL and TIPSH showing 85% yield of *s*-butylbenzene.

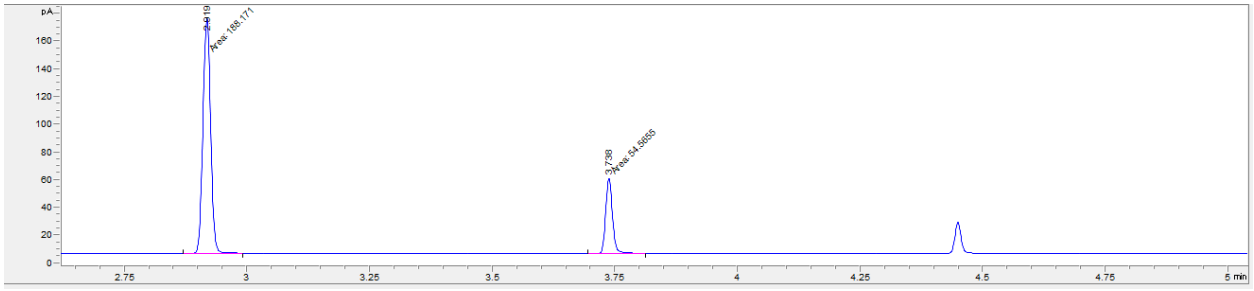


Figure 4.18. Use of $NaBH_4$ and TIPSH showing 34% yield of *s*-butylbenzene.

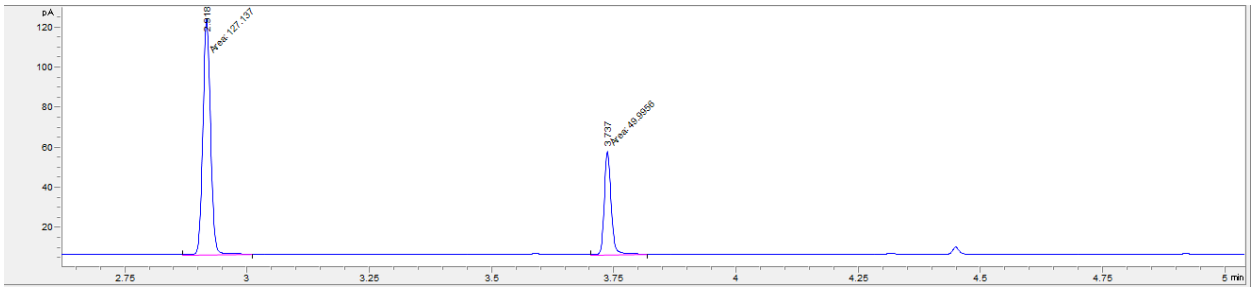


Figure 4.19. Use of LAH and TIPSH showing 46% yield of *s*-butylbenzene.

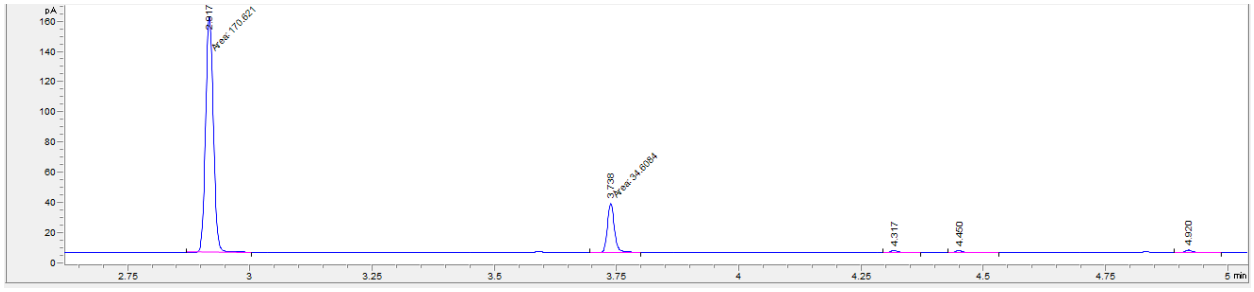


Figure 4.20. Use of LiH and TIPSH showing 21% yield of *s*-butylbenzene isomers.

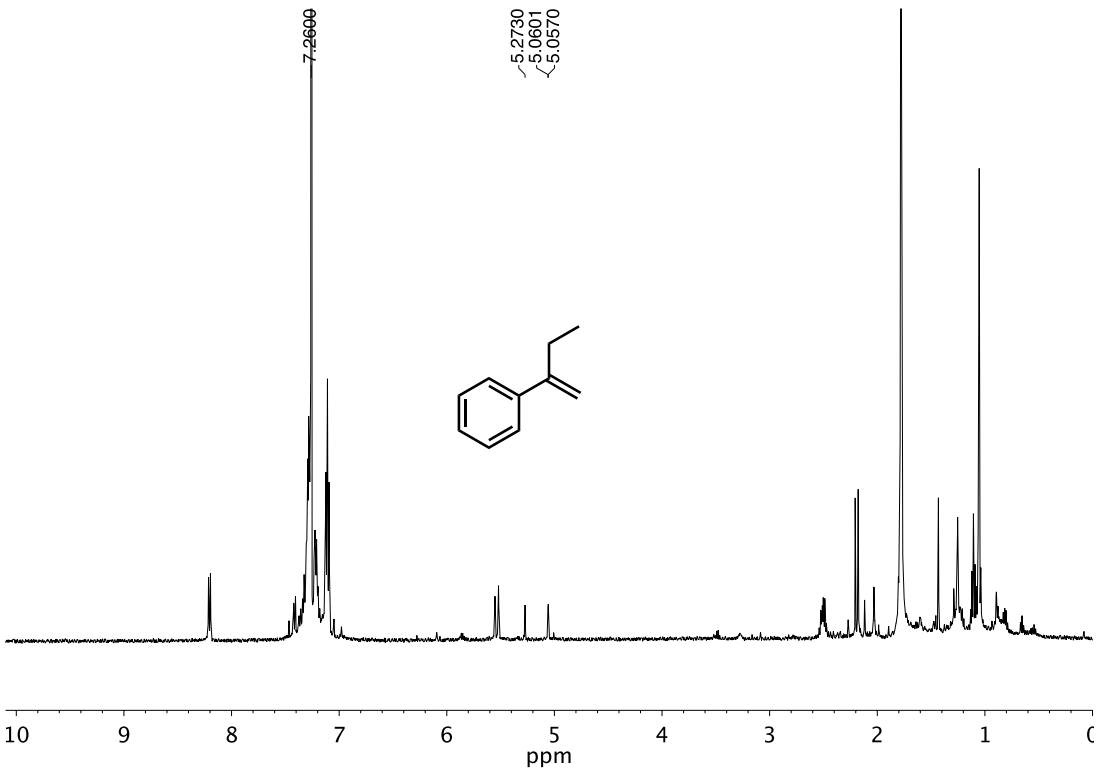


Figure 4.21. Closer observation of crude reaction mixture by NMR shows trace formation of unsaturated product **4.3**.

4.7 Spectra Relevant to Chapter Four:

Vinyl Carbocations Generated Under Basic Conditions and Their Intramolecular C–H Insertion Reactions

Adapted from: Benjamin Wigman, Stasik Popov, Alex L. Bagdasarian, Brian Shao, Tyler R. Benton, Chloé G. Williams, Steven P. Fisher, Vincent Lavallo, K. N. Houk, and Hosea M. Nelson

J. Am. Chem. Soc. **2019**, *141*, 9140–9144.

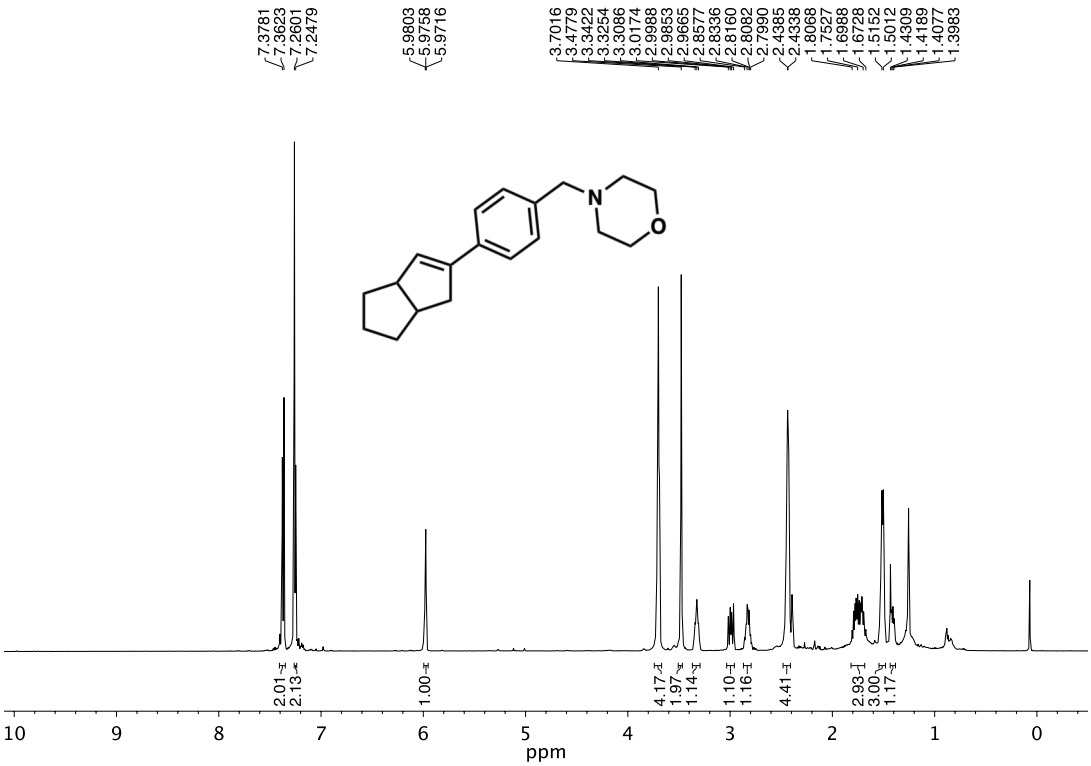


Figure 4.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.13**.

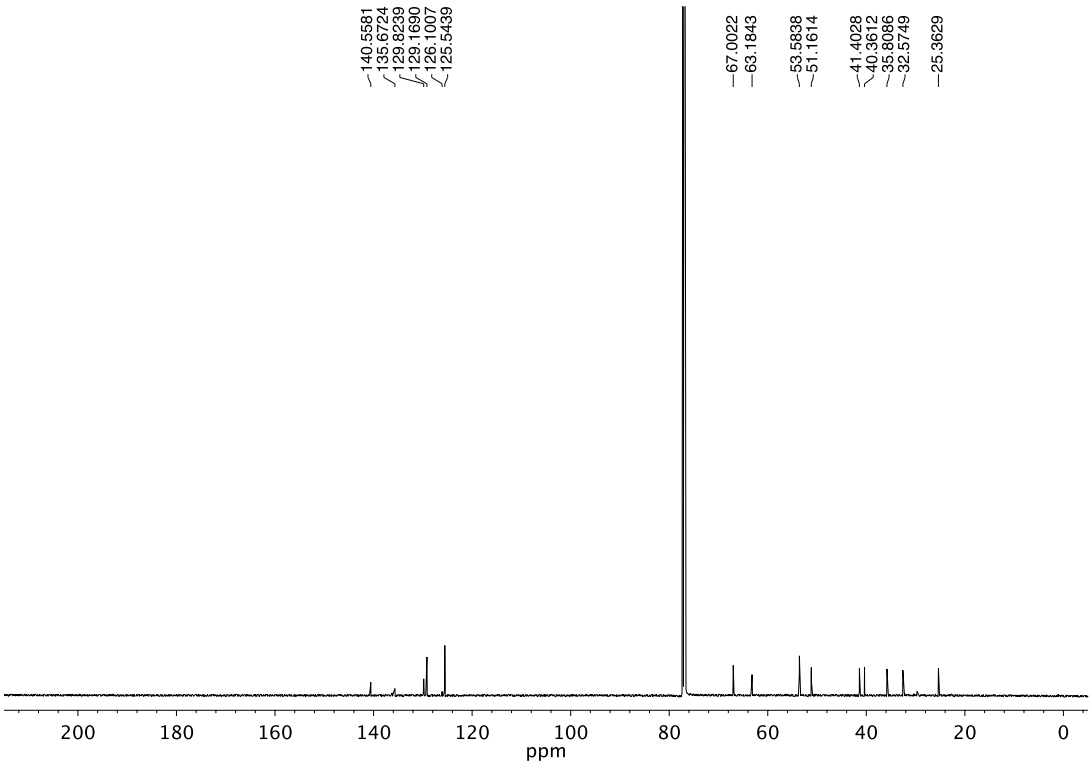


Figure 4.23. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.13**.

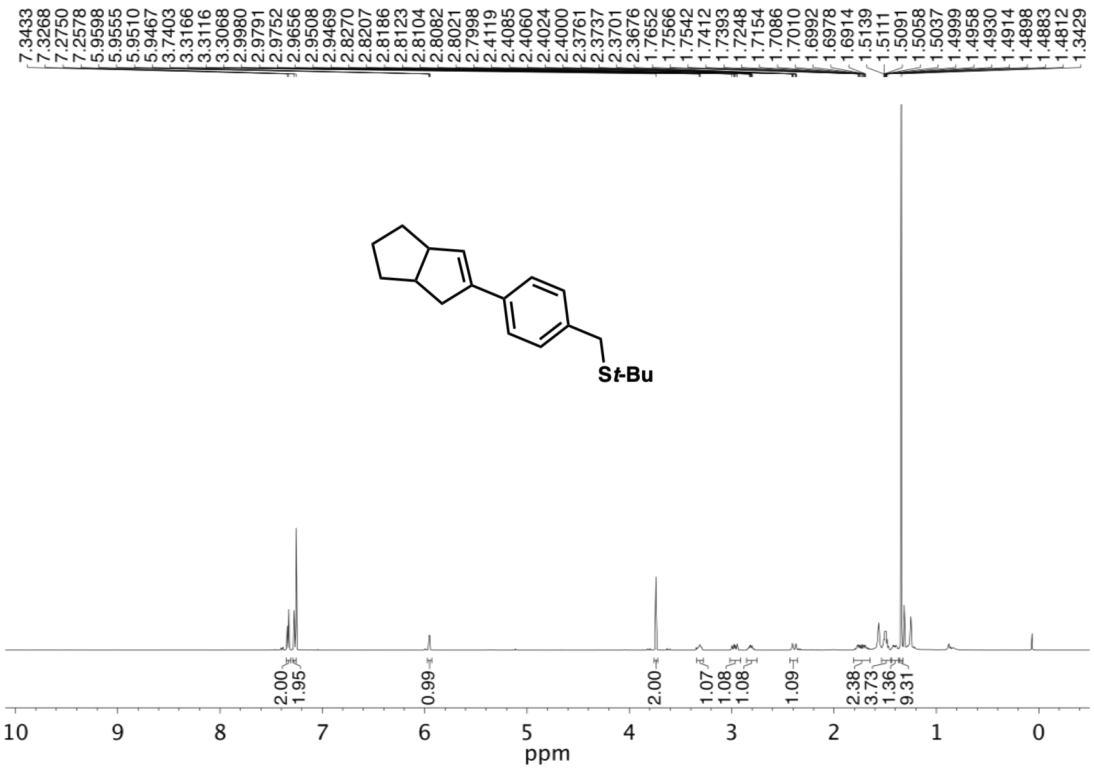


Figure 4.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.14**.

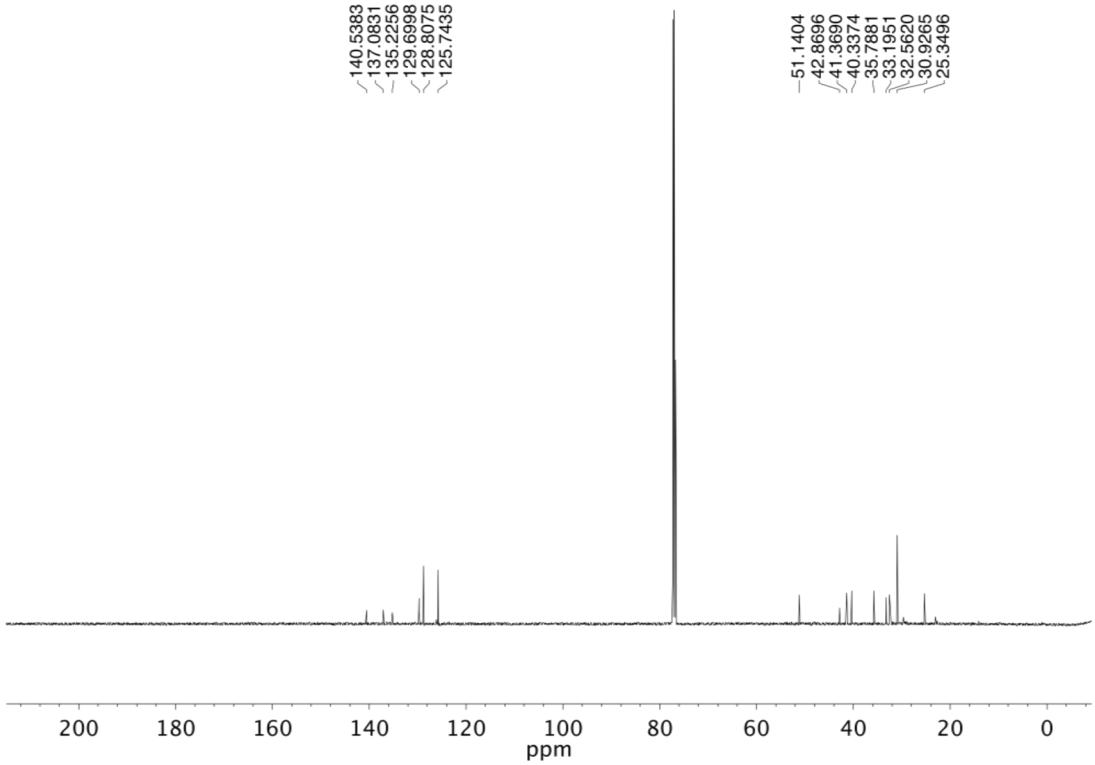


Figure 4.25. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.14**.

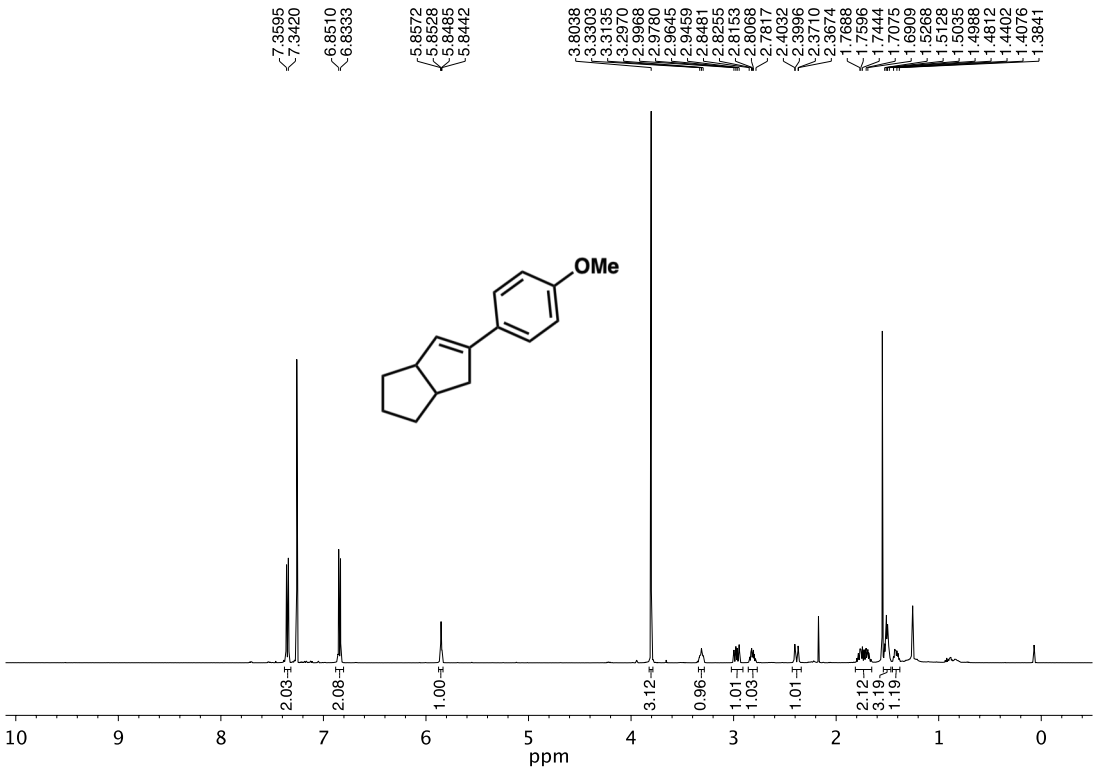


Figure 4.26. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.15**.

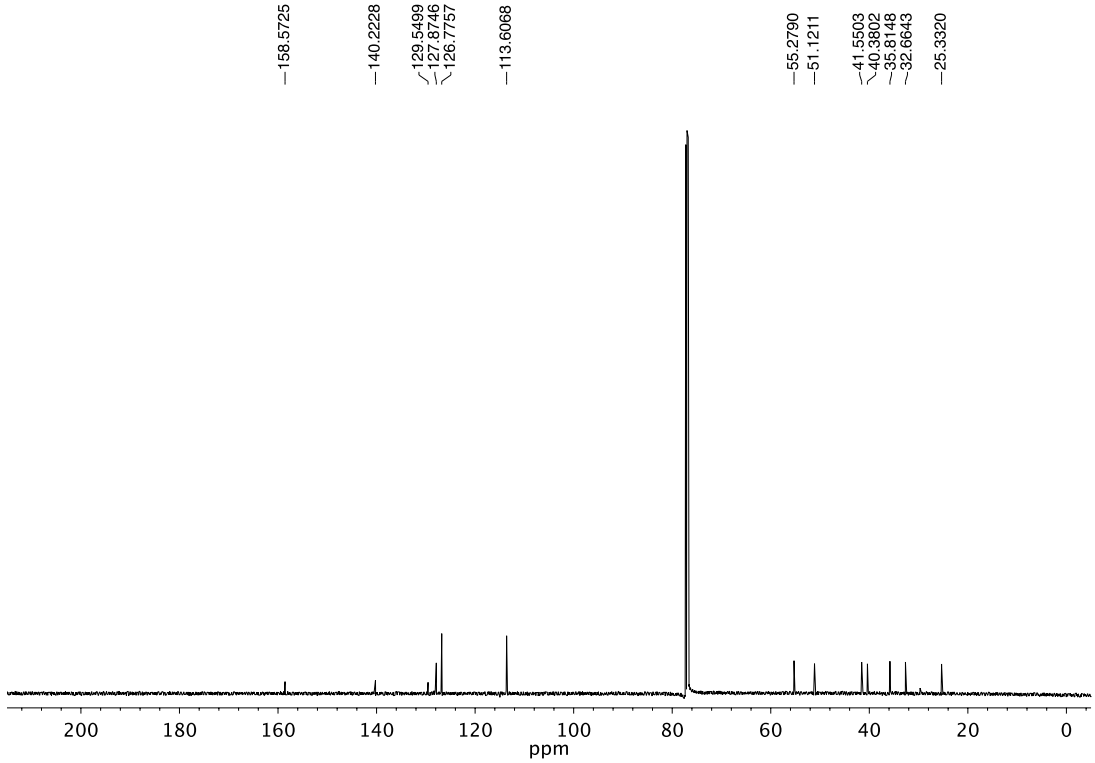


Figure 4.27. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.15**.

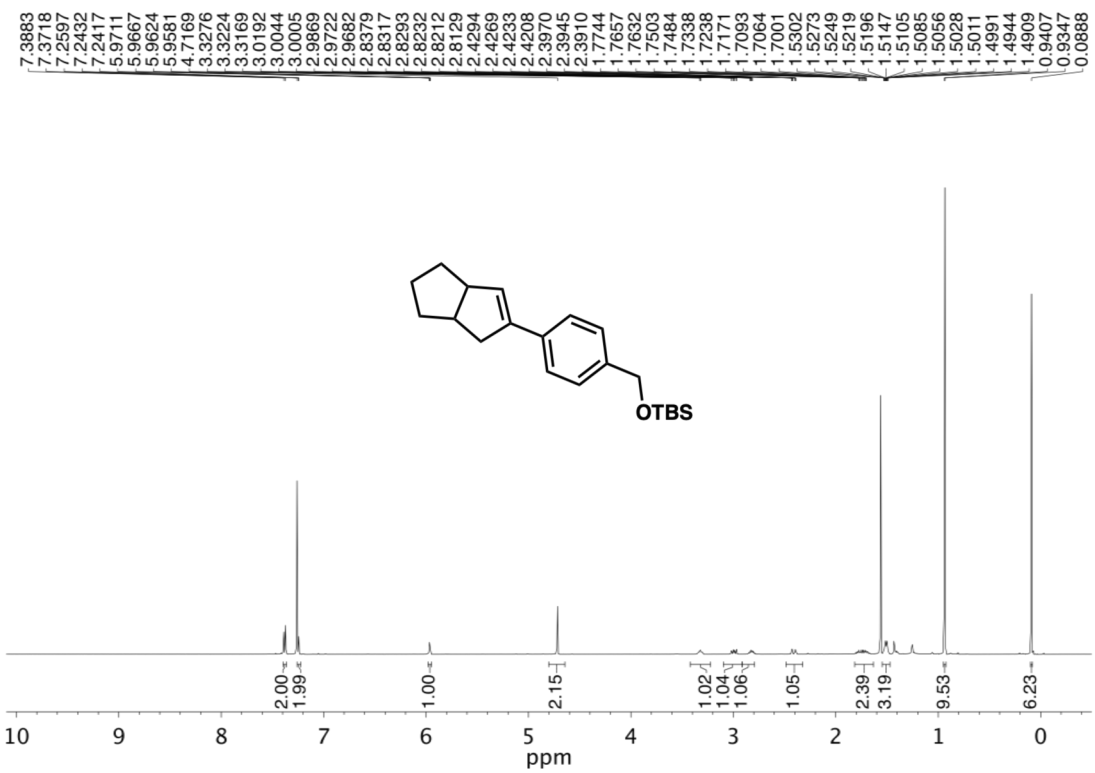


Figure 4.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.16**.

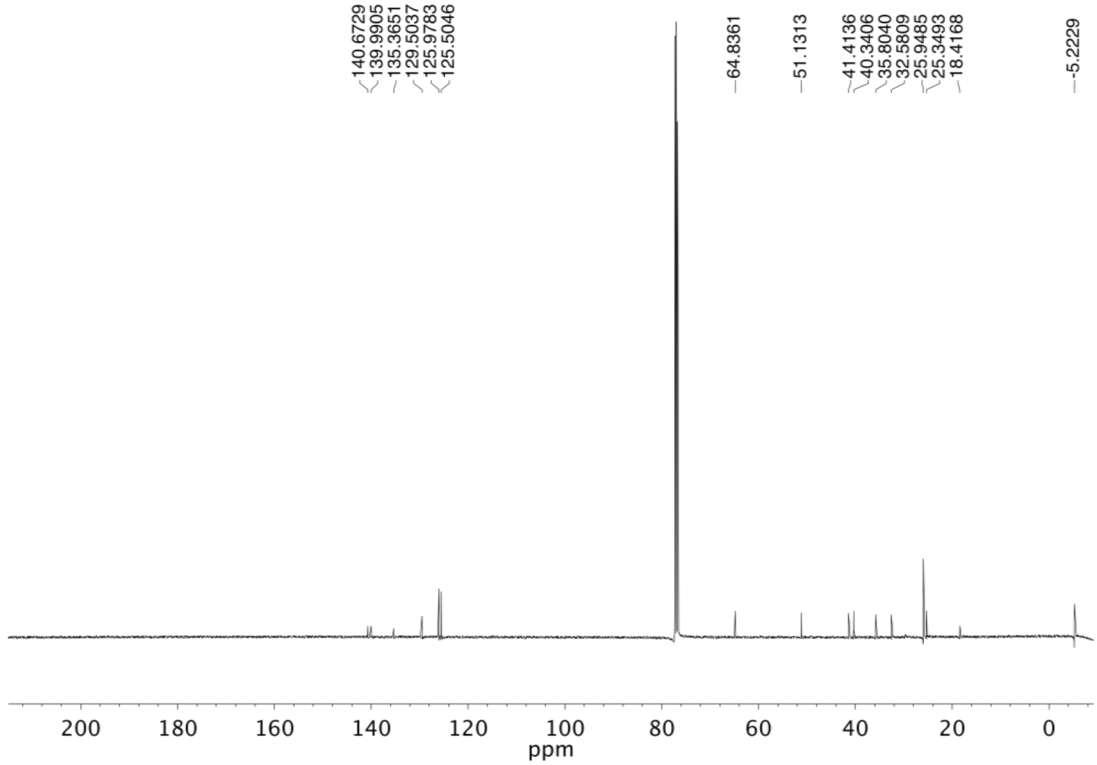


Figure 4.29. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.16**.

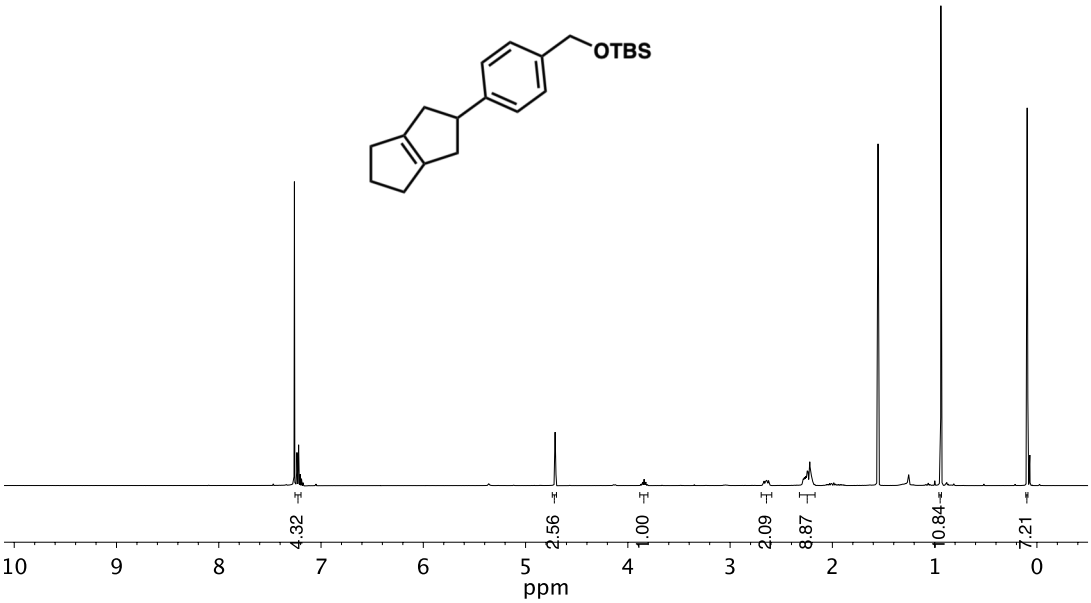


Figure 4.30. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.16.1**

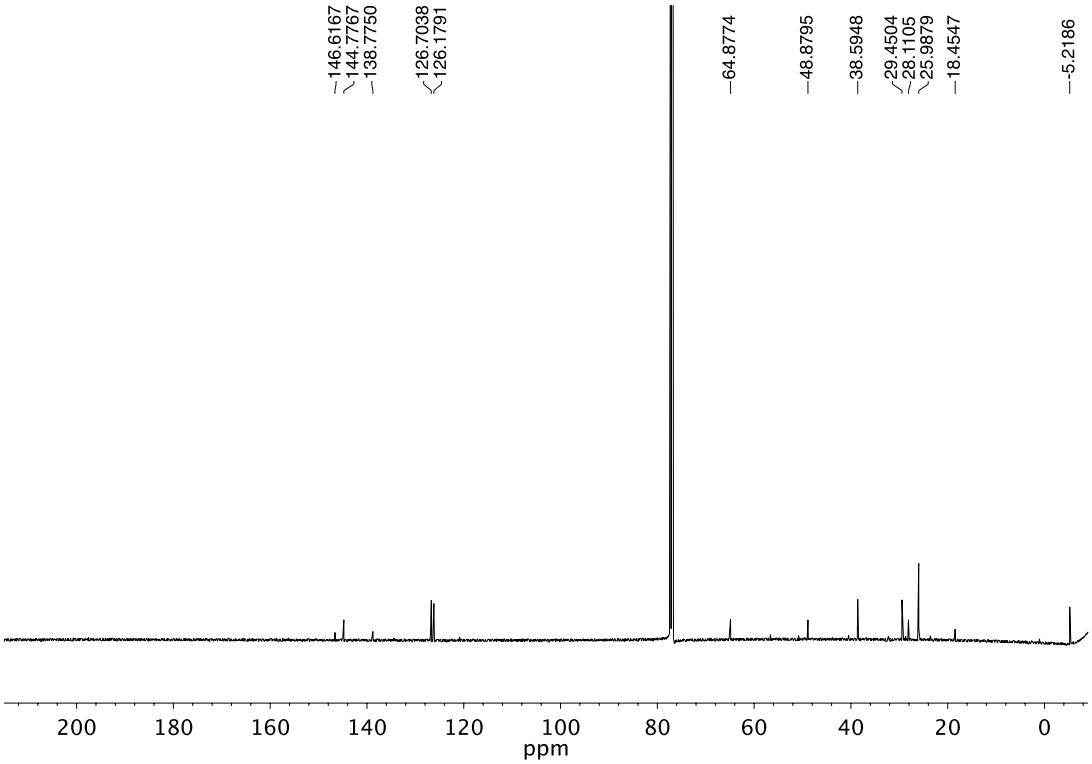


Figure 4.31. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.16.1**

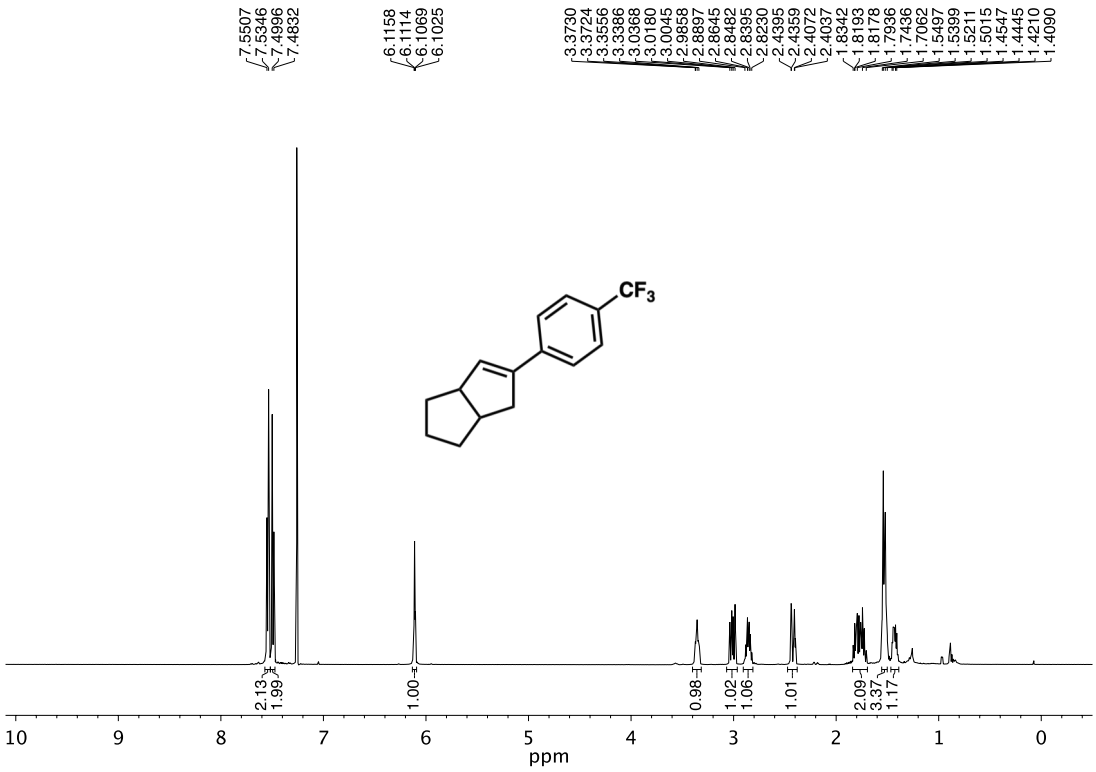


Figure 4.32. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.17**.

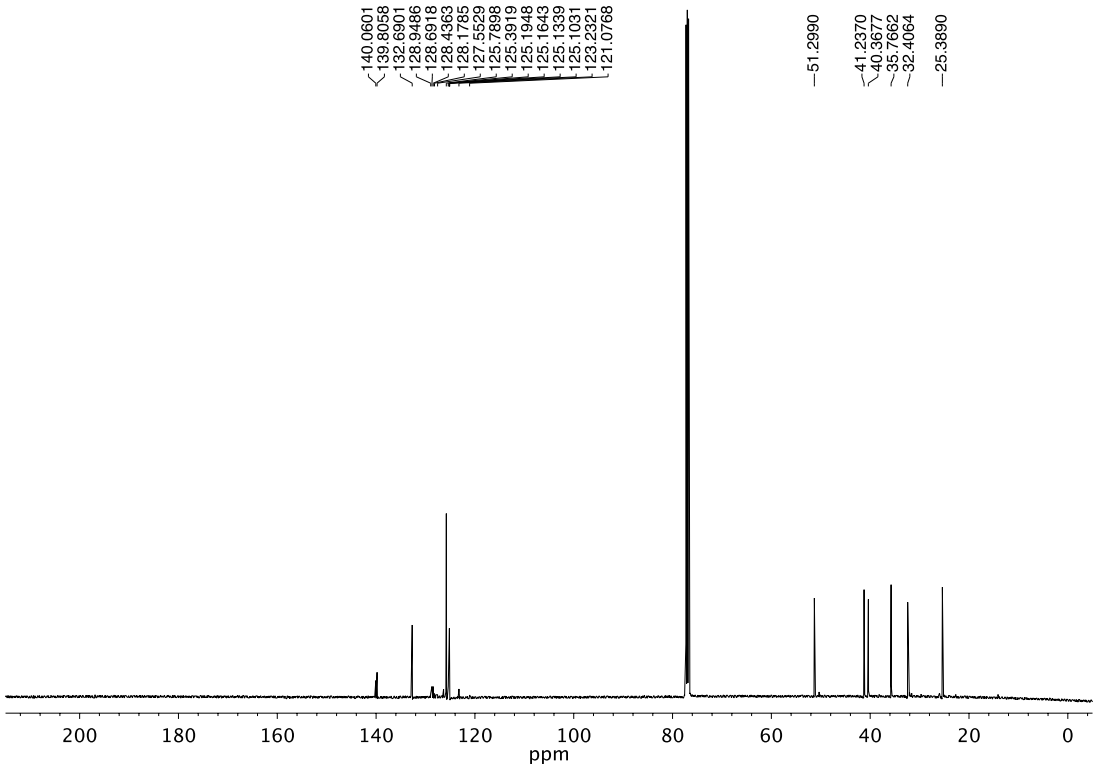


Figure 4.33. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.17**.

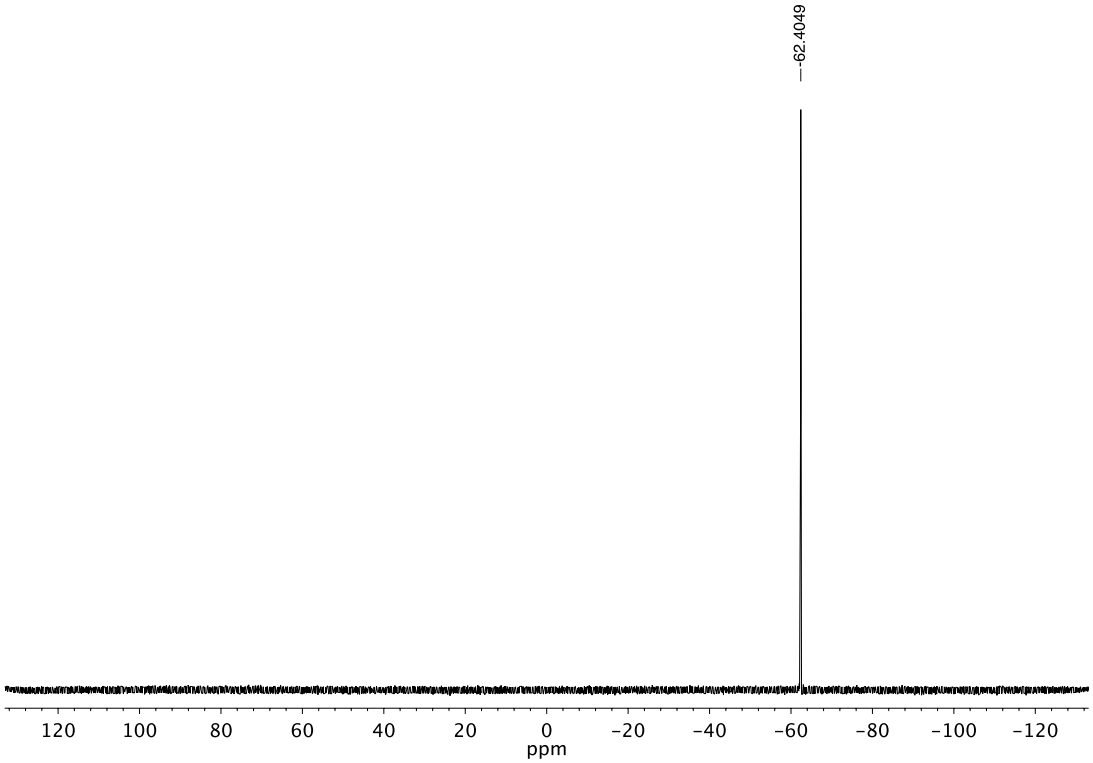


Figure 4.34. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **4.17**.

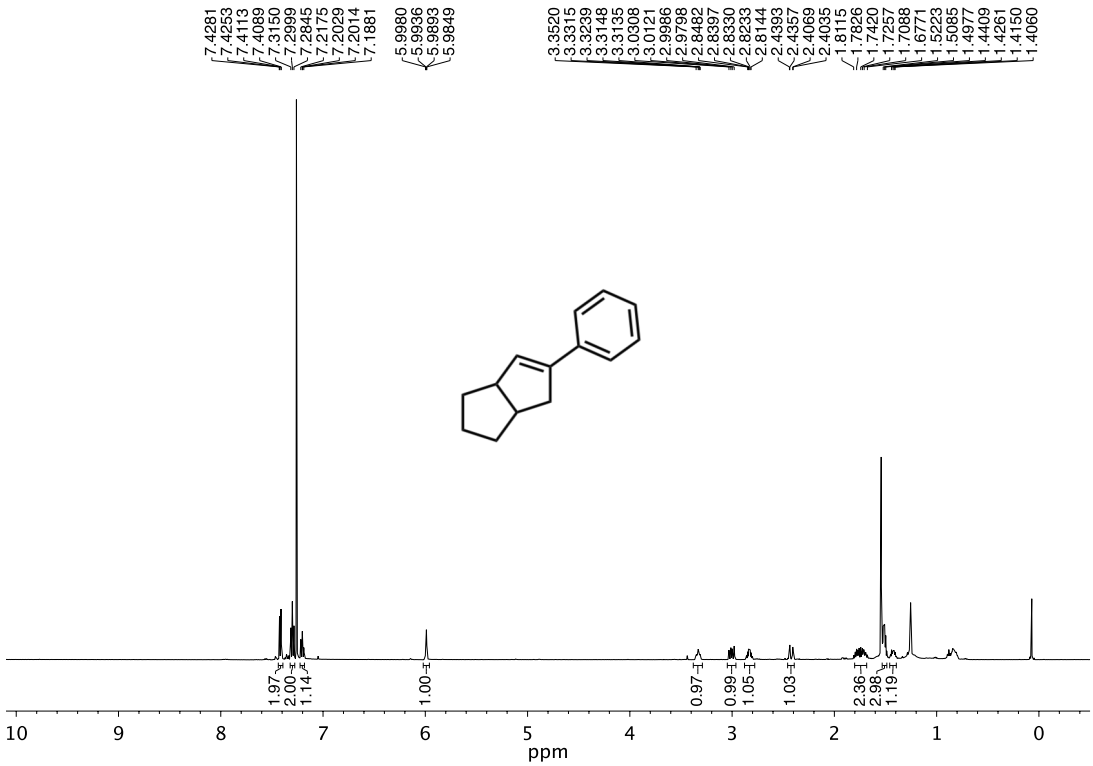


Figure 4.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.18**.

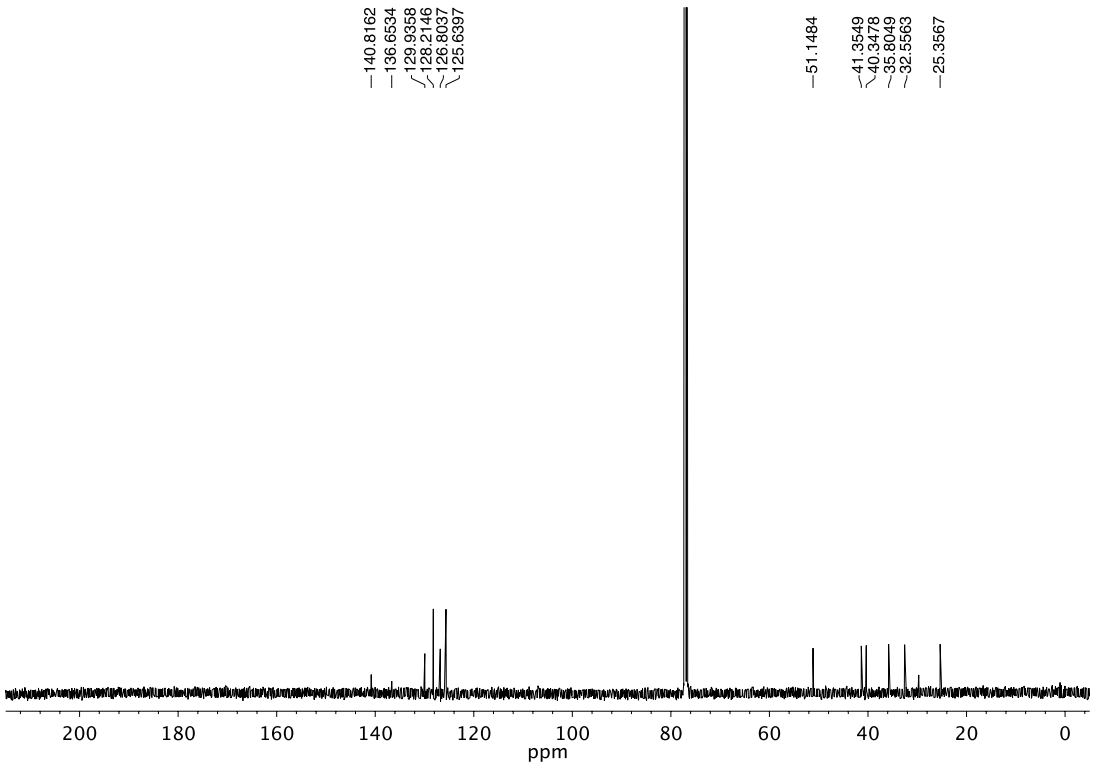


Figure 4.36. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.18**.

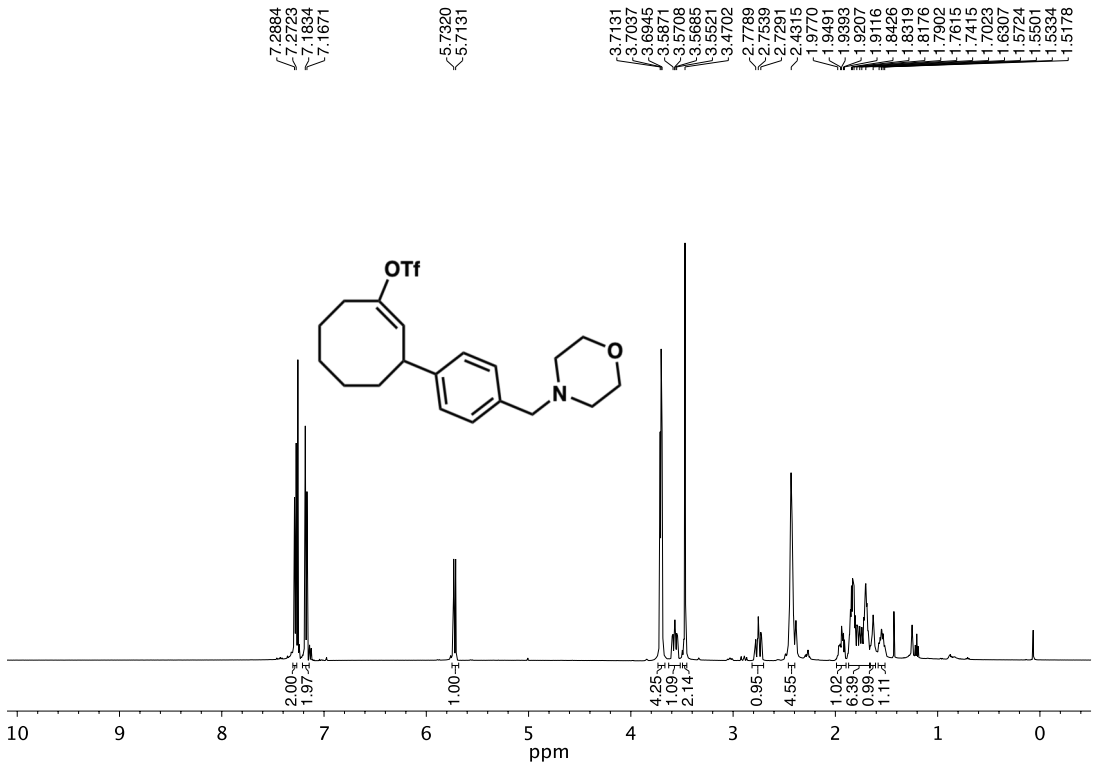


Figure 4.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.39**.

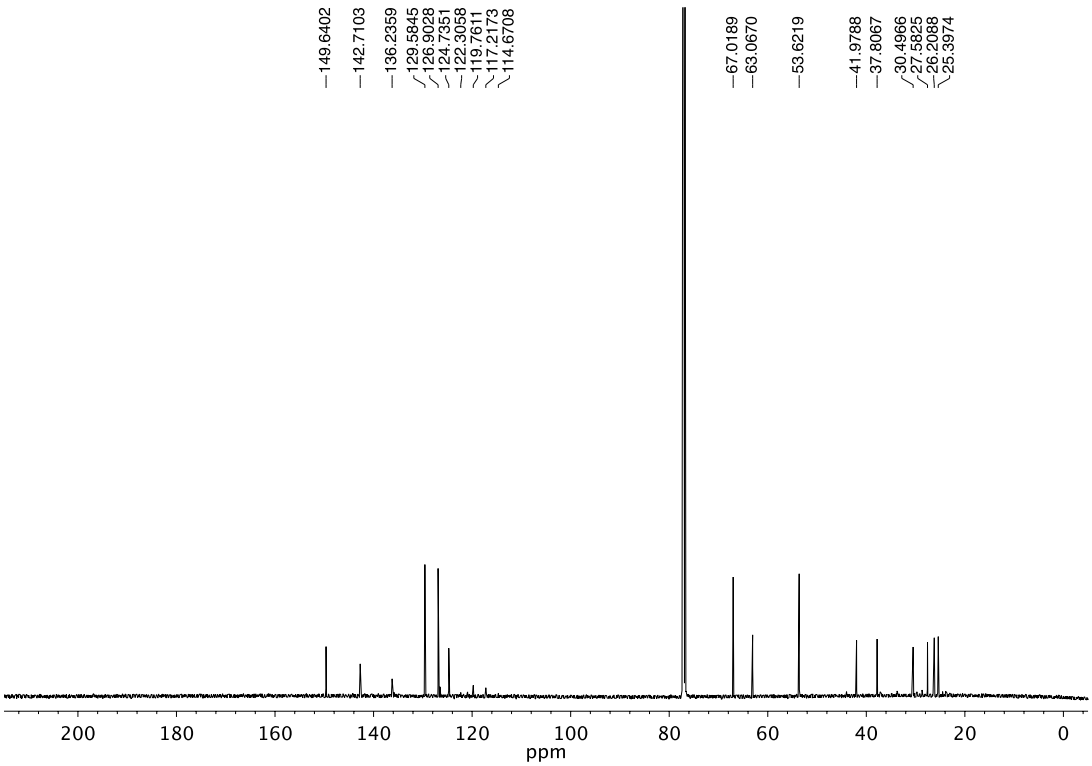


Figure 4.38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.39**.

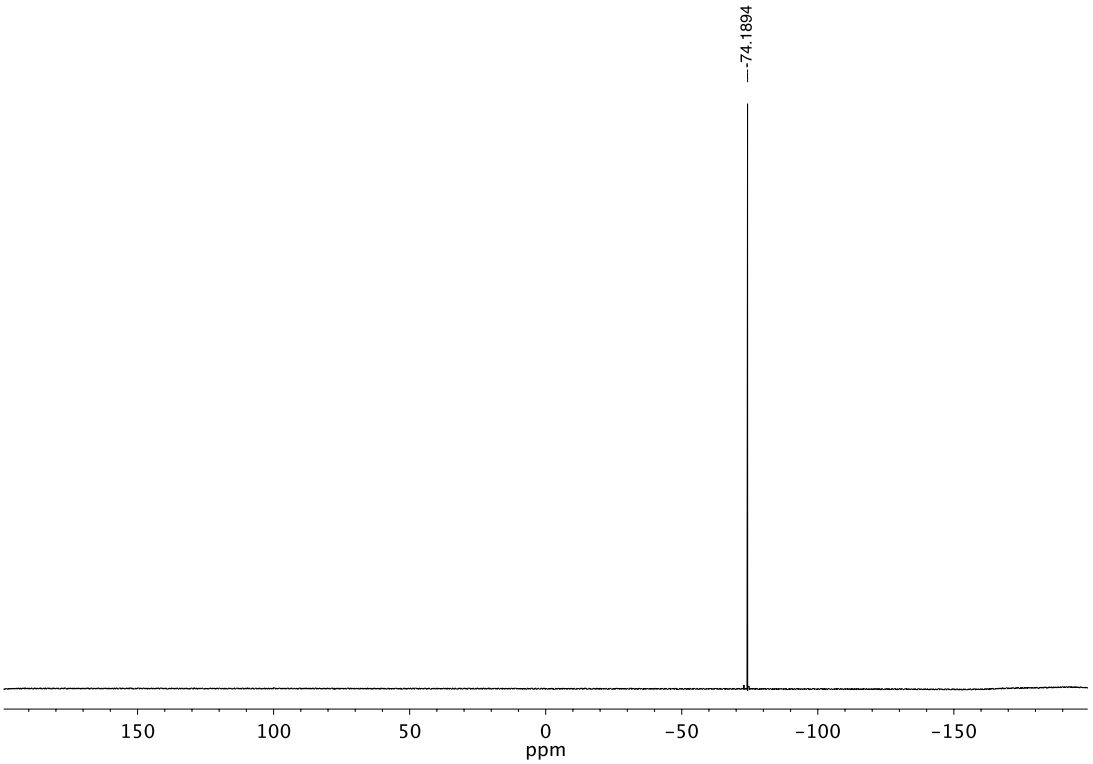


Figure 4.39. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **4.39**.

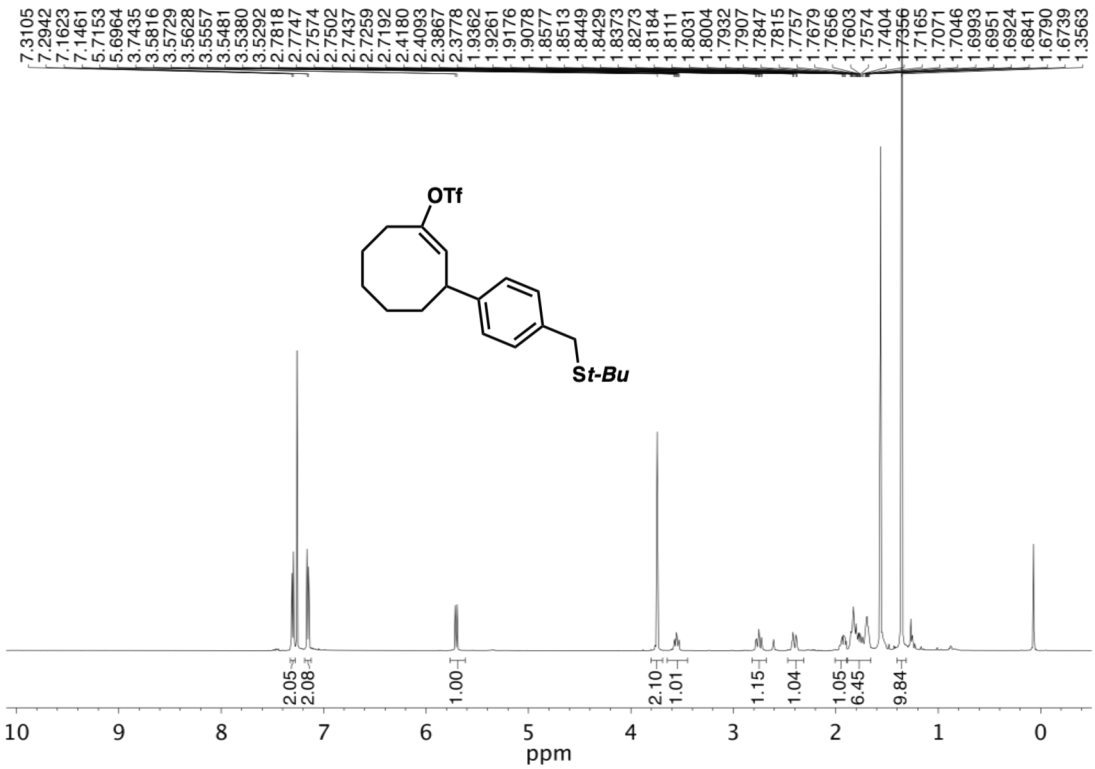


Figure 4.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.40**.

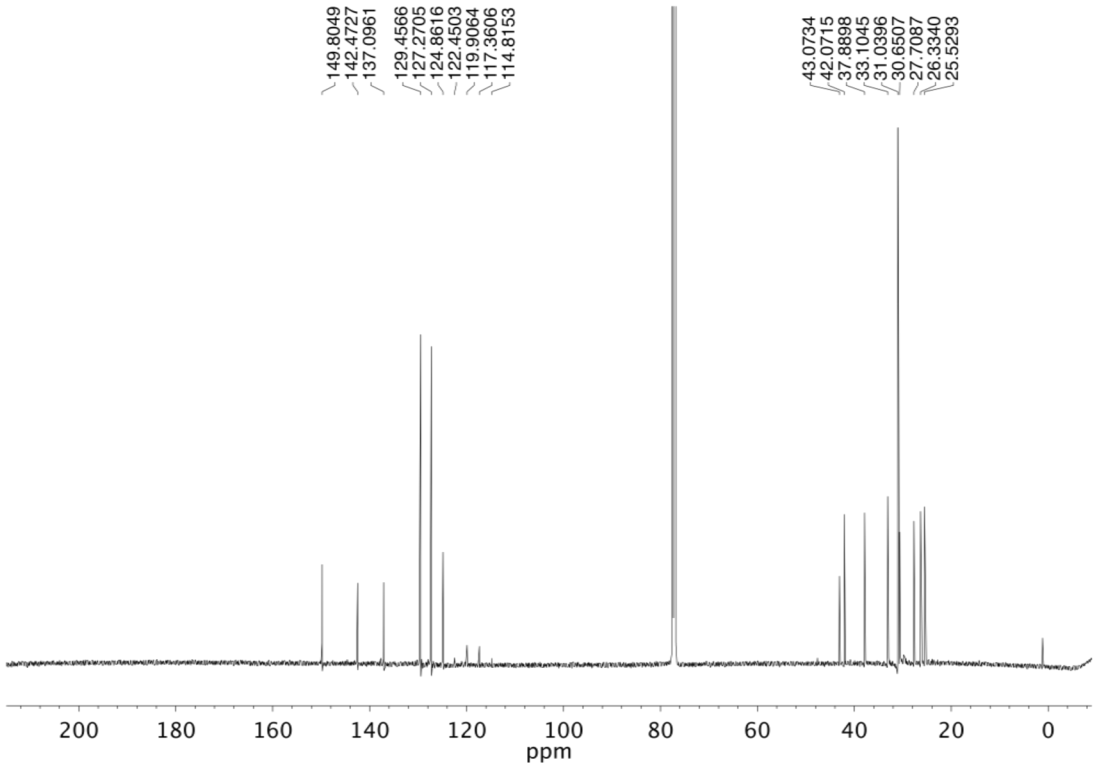


Figure 4.41. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.40**.

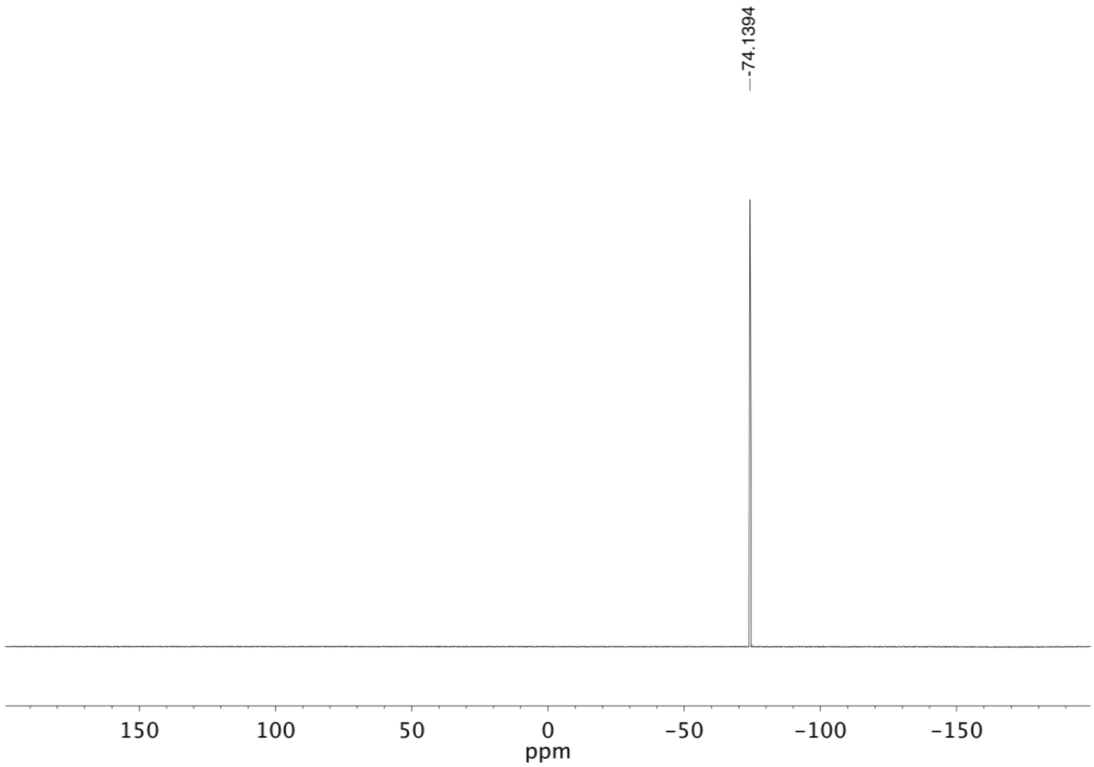


Figure 4.42. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **4.40**.

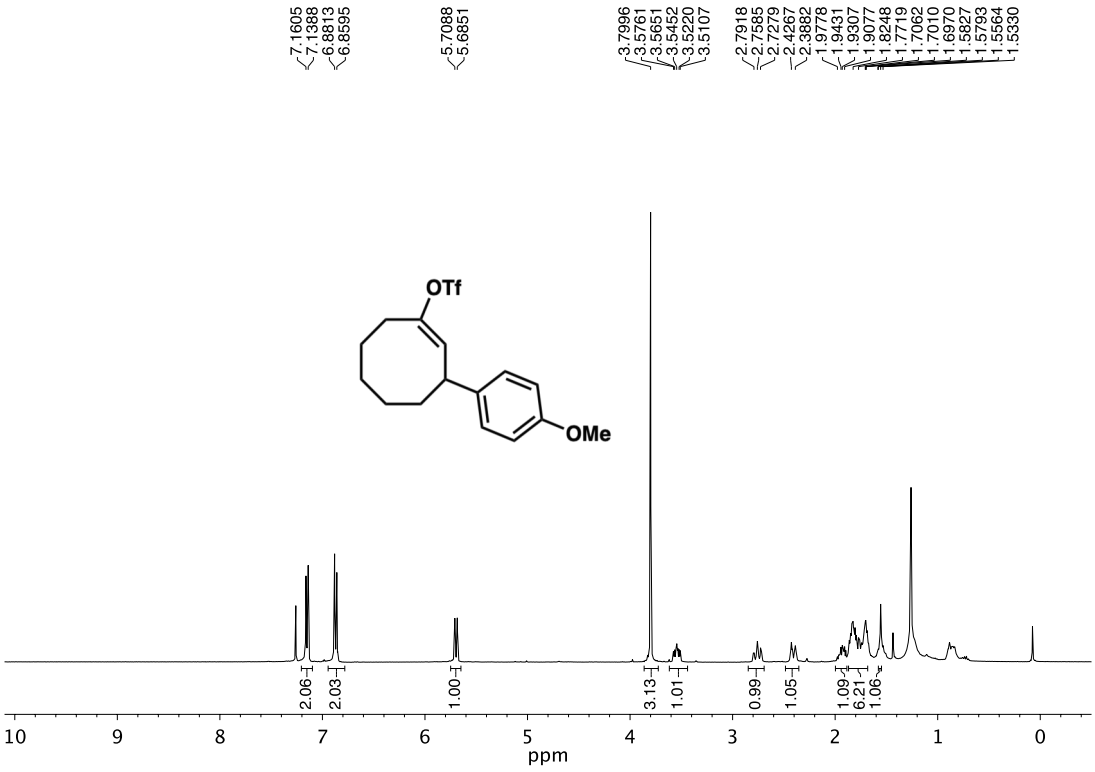


Figure 4.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.41**.

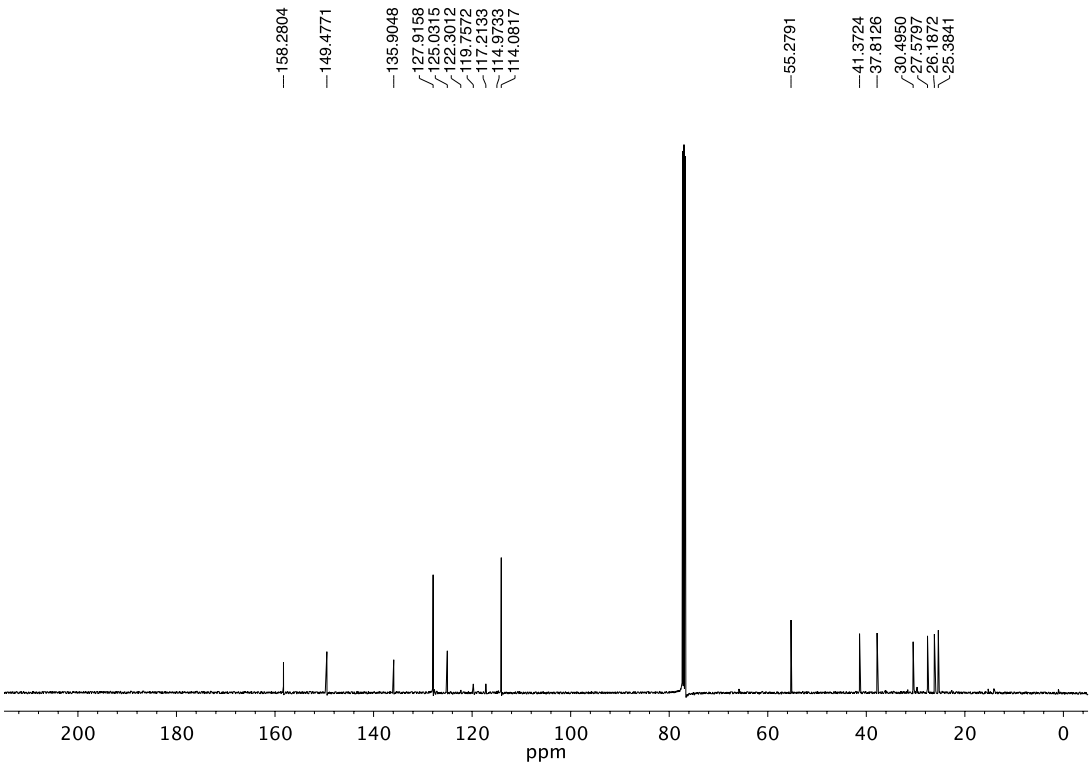


Figure 4.44. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.41**.

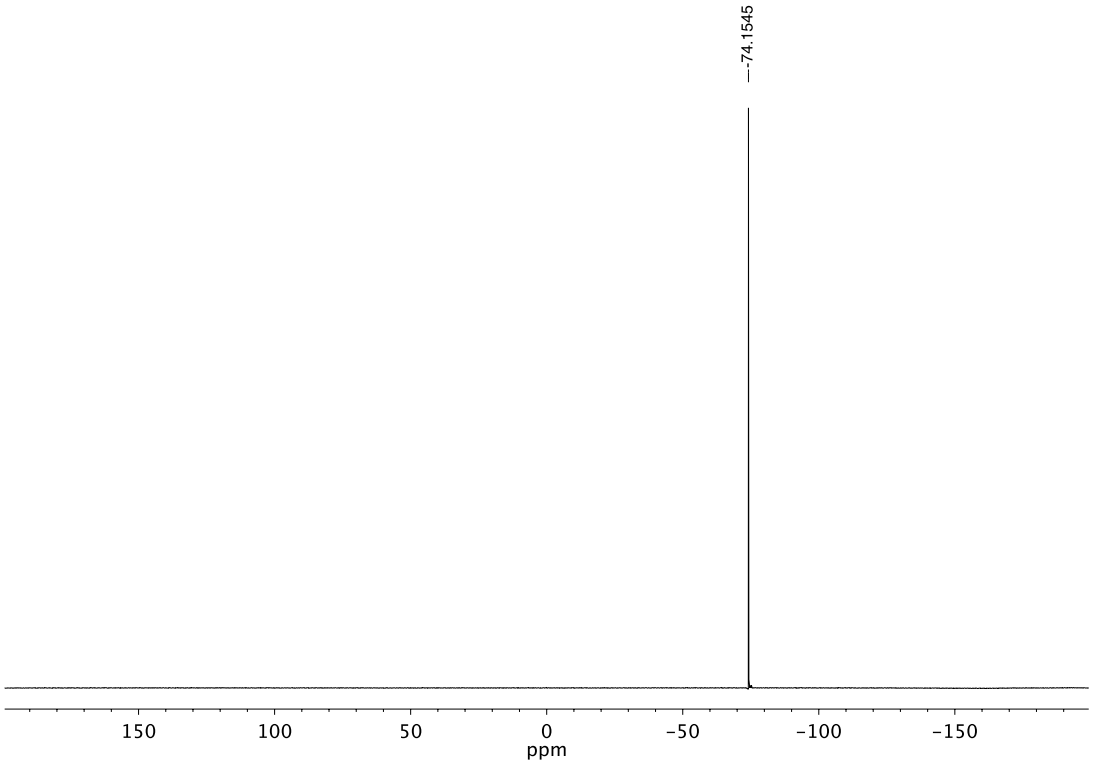


Figure 4.45. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **4.41**.

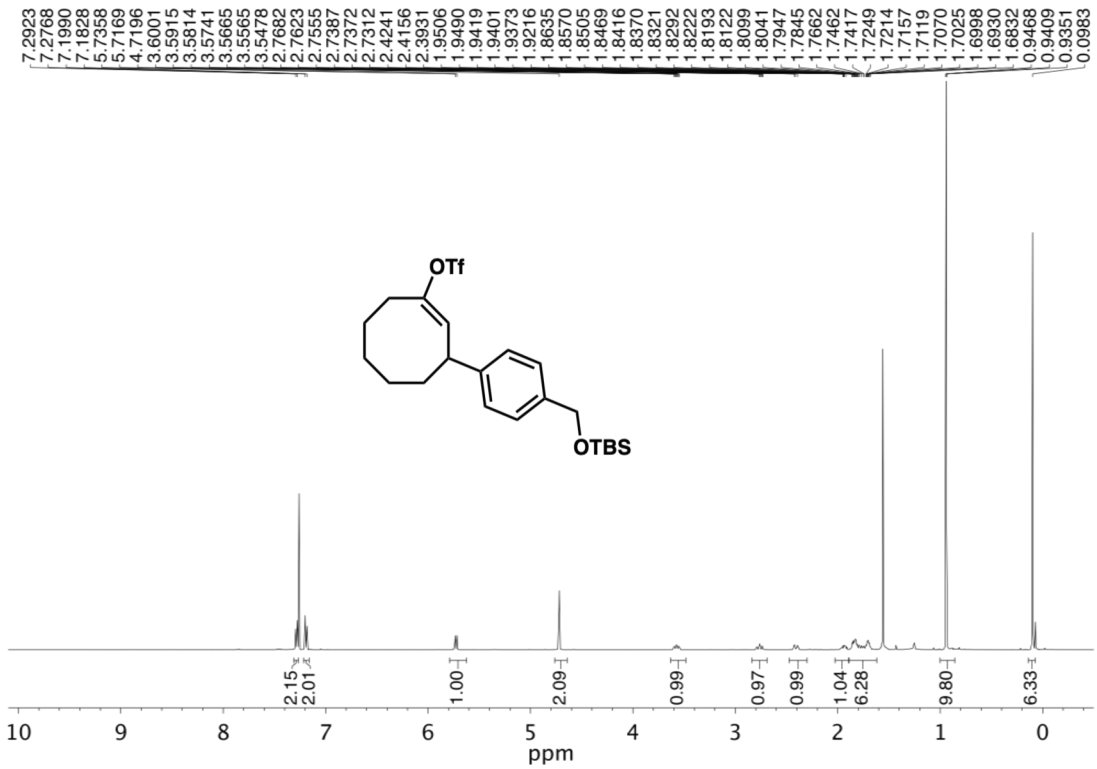


Figure 4.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.42**.

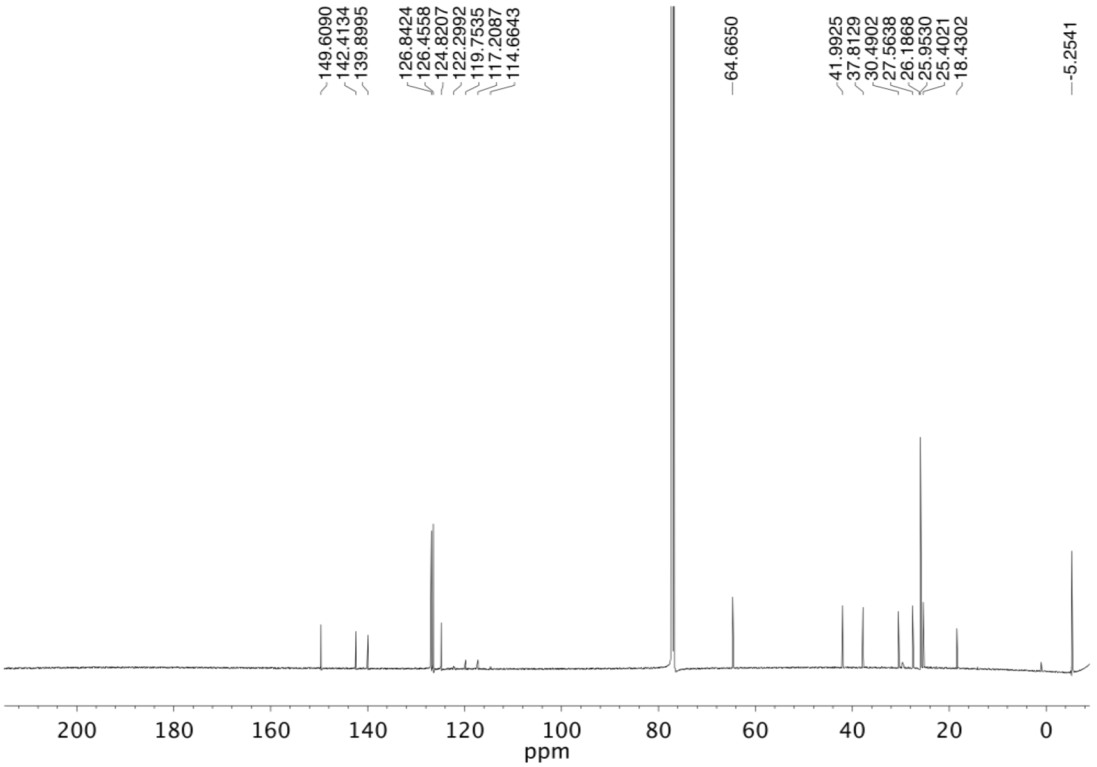


Figure 4.47. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.42**.

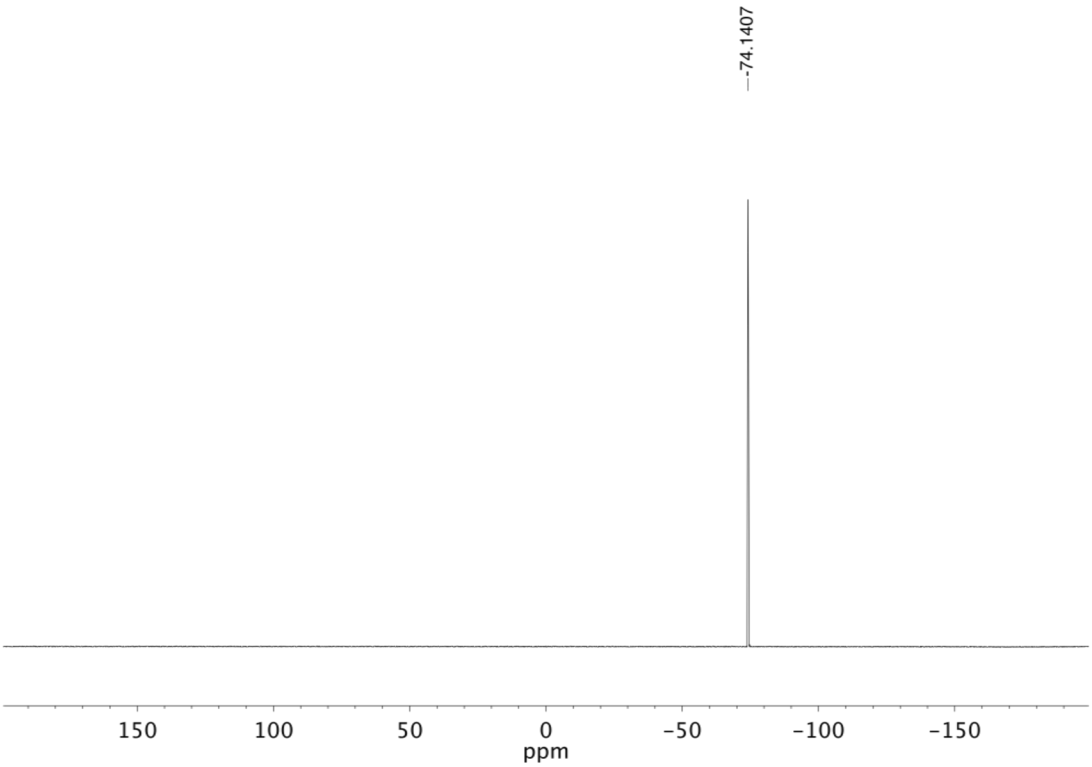


Figure 4.48. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **4.42**.

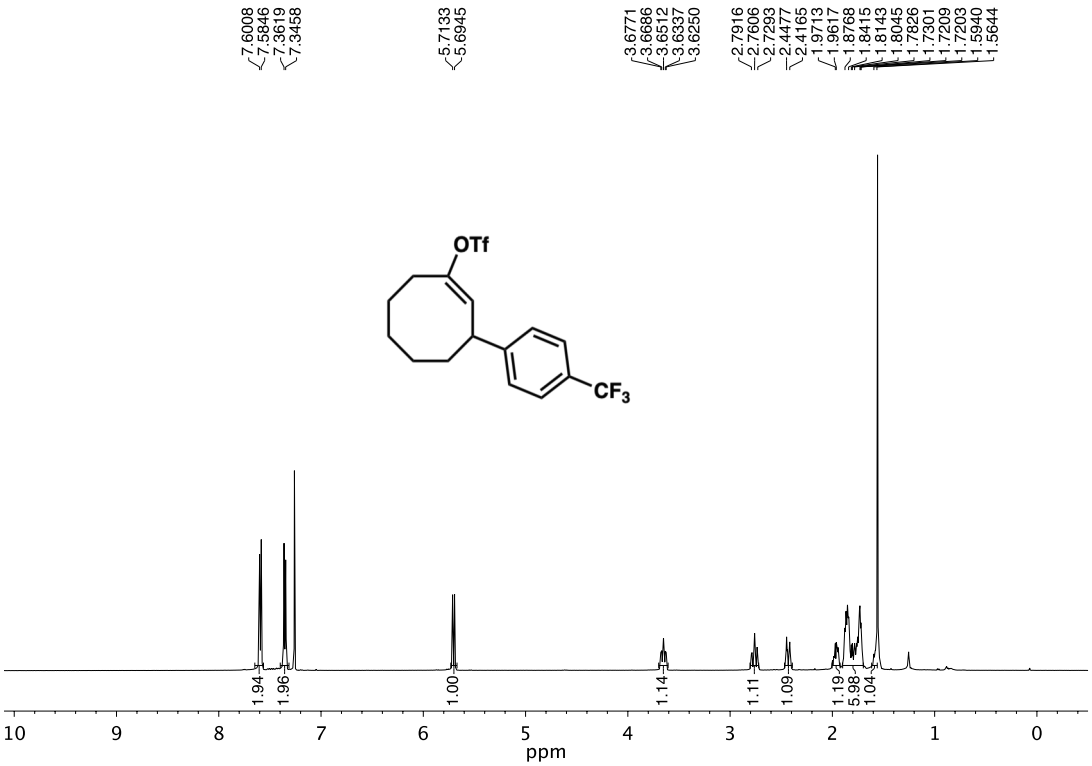


Figure 4.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.43**.

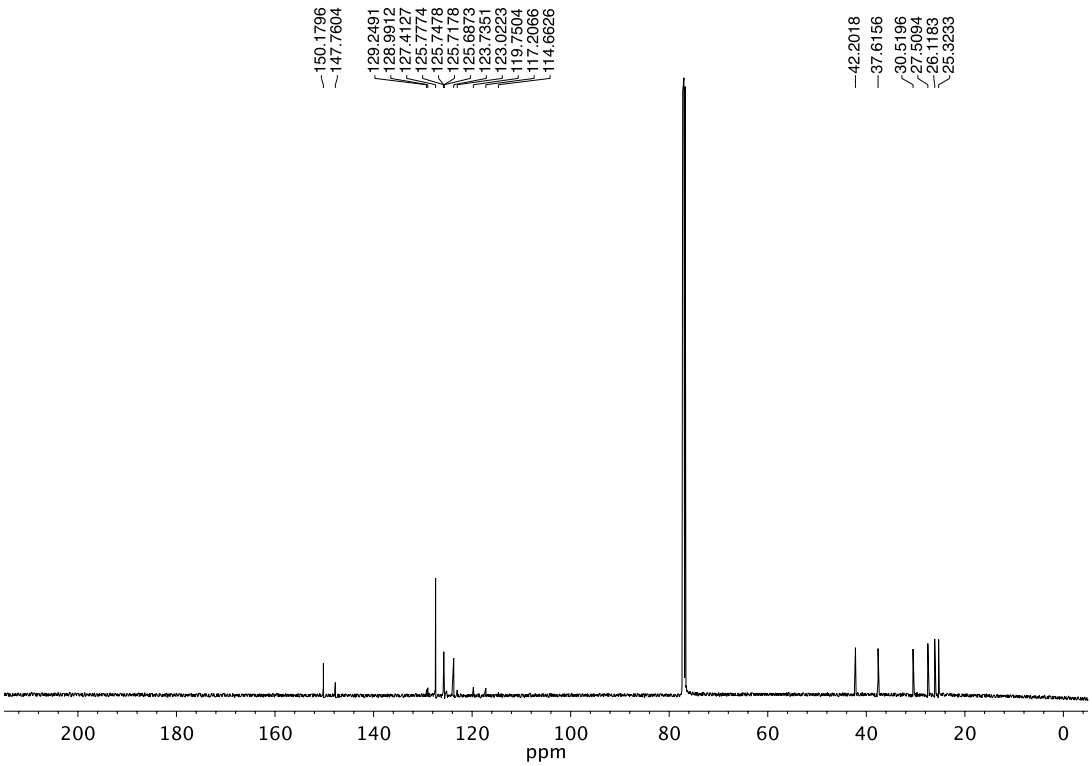


Figure 4.50. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.43**.

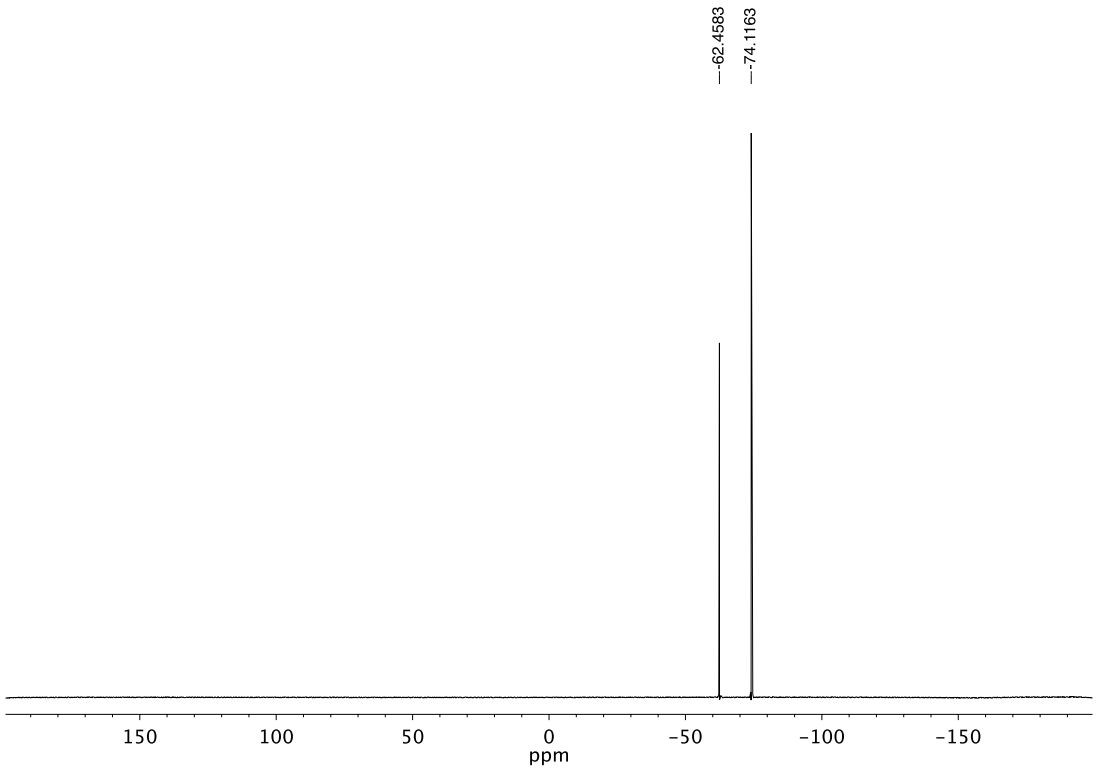


Figure 4.51. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **4.43**.

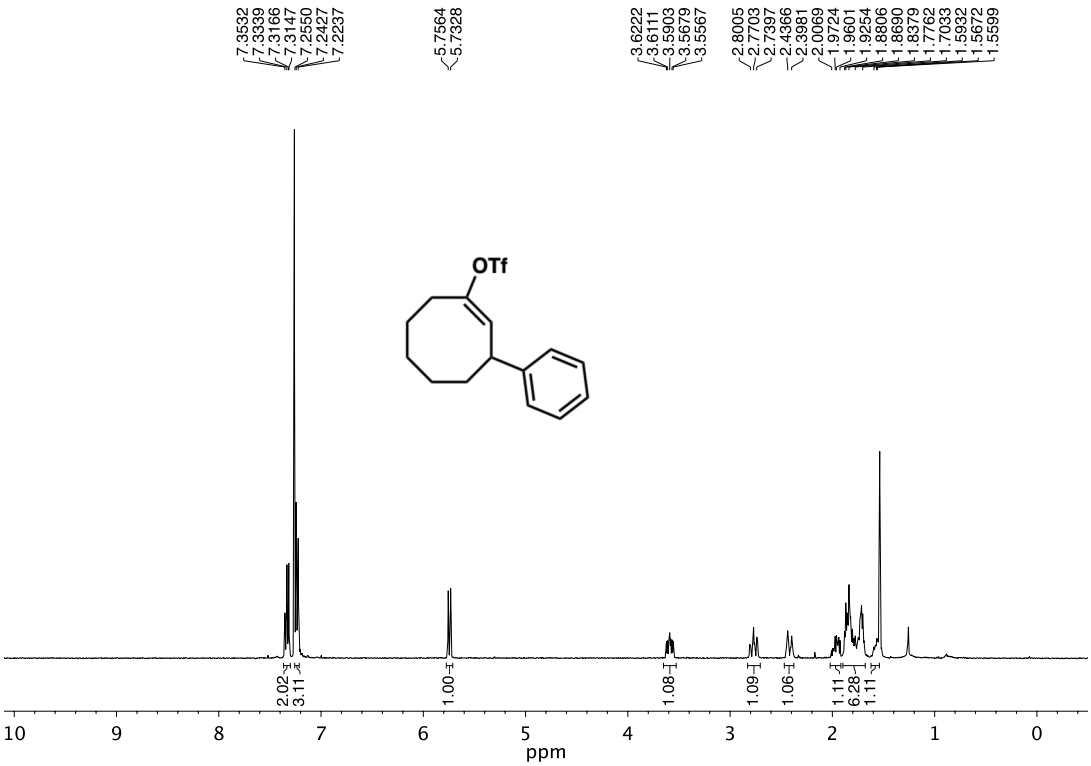


Figure 4.52. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.44**.

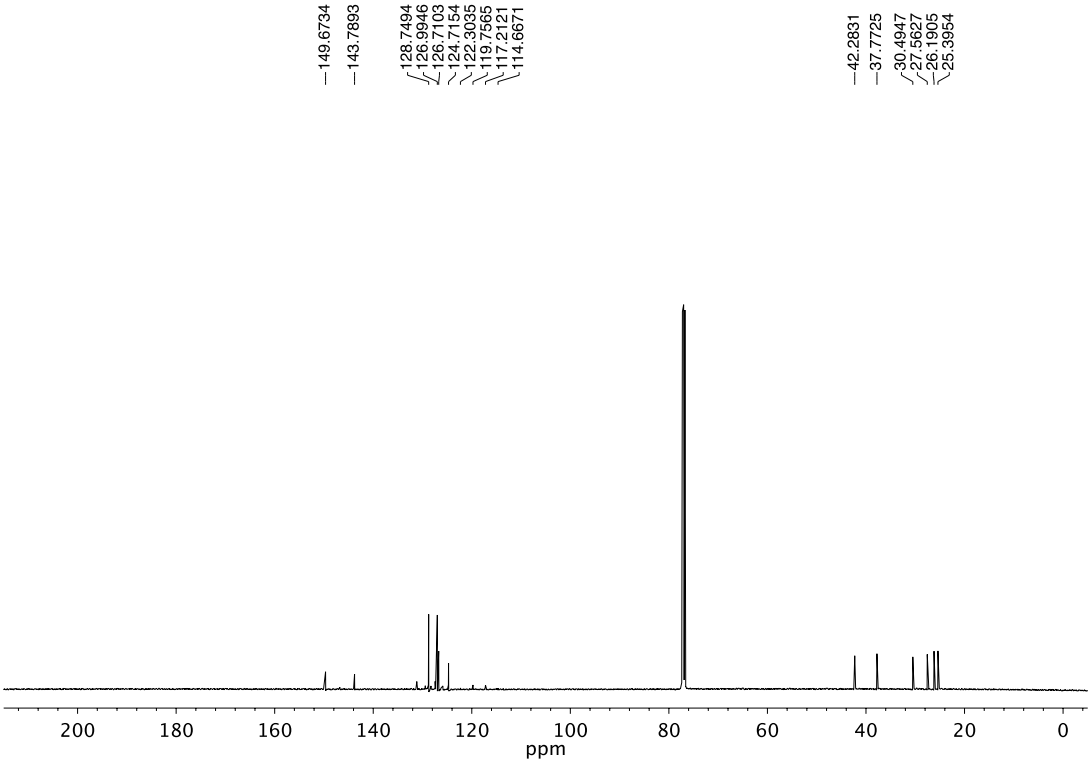


Figure 4.53. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.44**.

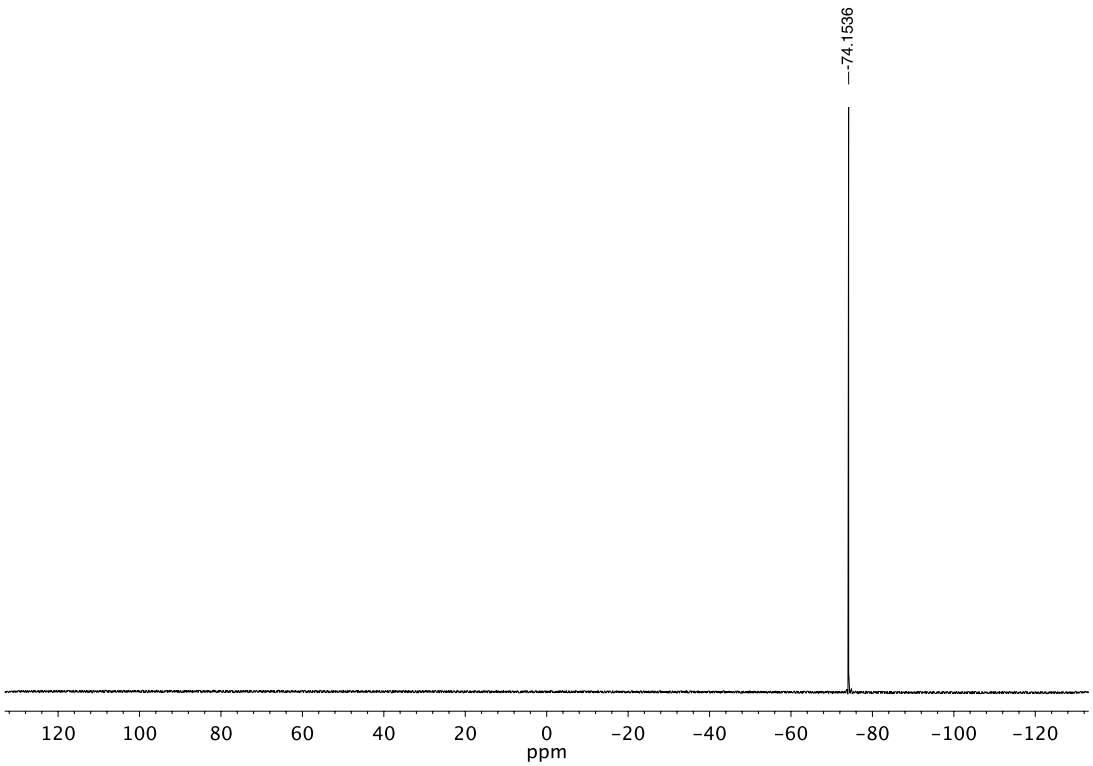


Figure 4.54. ^{19}F NMR (282 MHz, $CDCl_3$) of compound **4.44**.

4.8 Notes and References

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CHAPTER FIVE

Urea and Lithium/Urea Organocatalysts Catalyze C–C Bond-Forming Reactions of Vinyl Cations

Adapted from: Alex L. Bagdasarian, Stasik Popov, Benjamin Wigman, Wenjing Wei, Woojin Lee, Hosea M. Nelson

5.1 Abstract

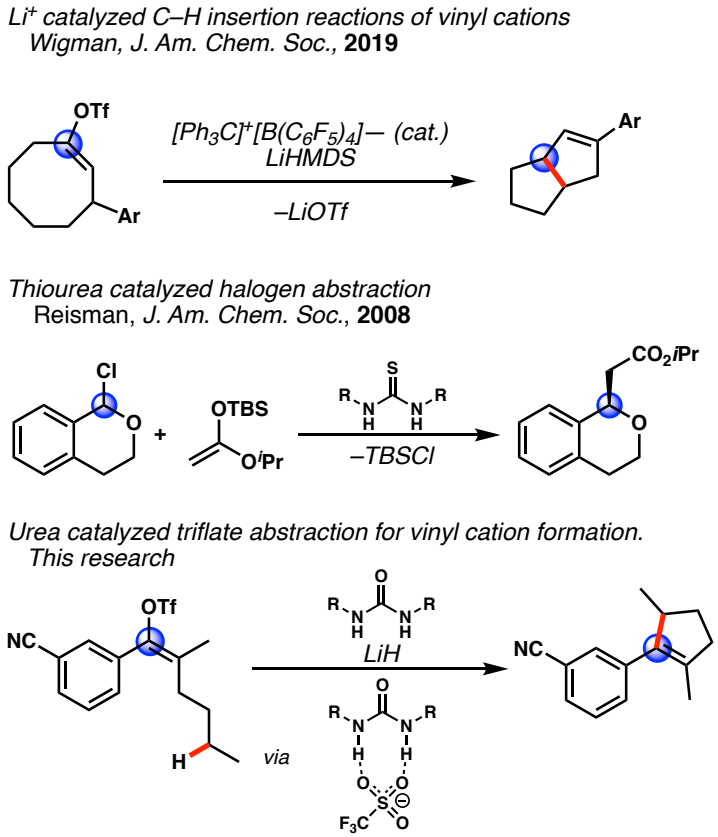
Herein we report the C–H insertion and Friedel–Crafts reactions of vinyl cations catalyzed by 3,5-bistrifluoromethylphenylurea and lithiated-urea organocatalysts. We introduce a new use for these privileged scaffolds where the combination of hydrogen bonding motifs with strong bases affords novel Li-Lewis acid catalysts. In the presence of vinyl triflates, these catalysts facilitate the generation of vinyl cations that undergo smooth C–C bond formation. We also demonstrate the applicability of using these hydrogen-bonding scaffolds to promote the ionization of vinyl triflates to promote intramolecular C–H functionalization reactions of inert C–H bonds.

5.2 Introduction

Forging C–C bonds via C–H insertion reactions has arisen as a transformation of great importance[1]. While the recent emergence of methods to convert C–H bonds to other functional groups rely heavily on the use of transition metal catalysis[2], our group has leveraged main group catalysis to generate reactive organic intermediates to undergo C–H functionalization.[3–5] Both of

these modes of reactivity have enabled the synthesis of molecules through unique mechanistic pathways. For example, vinyl cations have been recently shown to undergo facile C–H insertion reactions *via* nonclassical carbocations.[4] While this work was fundamentally insightful, the scope of those reactions was functional group limited. Recently, our group reported that lithium cations paired with weakly coordinating anions (WCAs) could generate vinyl cations from vinyl triflates and engage the former in C–H insertion reactions (Fig. 5.1).[5] The use of milder Li Lewis-acids allowed for greater functional group compatibility in the context of reactive carbocation chemistry. In efforts to further expand the scope of substrates, as well as catalysts capable of performing these unique transformations, we looked towards hydrogen/halogen bonding scaffolds. In these areas, these catalysts have found great success in promoting the discovery of new reactions.[6–7] Specifically, we were heavily inspired by the work of Jacobsen and coworkers generating cationic intermediates through hydrogen-bonding catalysis. In one study, Reisman demonstrated the use of chiral thiourea scaffolds to abstract activated benzyl chlorides to form oxocarbenium ions (Fig. 5.1).[8] Banik and coworkers 3later showed that similar squaramide moieties, combined with trimethylsilyl triflate (TMSOTf), enhance the electrophilicity of the silicon center *via* triflate binding.[9] Inspired by these studies, we sought to apply an analogous mode of ionization to vinyl triflates to provide vinyl cations competent for C–C bond forming reactions. Herein, we report the successful realization of this hypothesis and demonstrate that urea derived catalysts can be leveraged to perform C–H insertion and Friedel–Crafts reactions of vinyl cations (Fig. 5.1). Additionally we discovered that through the combination of urea scaffolds and lithium base, a novel Lithium-Urea complex is made that acts as a Li-Lewis acid catalyst capable of promoting C–H insertion and Friedel–Crafts reactions of vinyl carbocations.

Figure 5.1. Lewis acid catalyzed ionization of halides and pseudohalides.

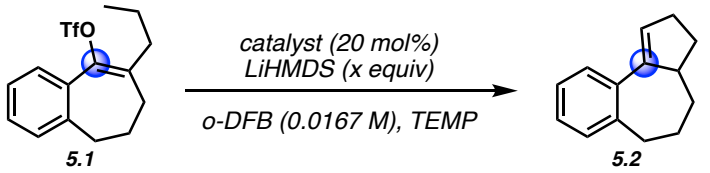


5.3 Discovery of Li-Urea Catalyst for the Ionization of Vinyl Triflates

We began our initial proof-of-concept screening efforts by exploring various hydrogen bond donor catalysts with our previously reported propylatedbenzosuberonyl triflate **5.1** (Table 5.1).[5] We hypothesized that the use of a pseudohalogen binding catalyst would abstract a triflate anion from a vinyl triflate, and the ensuing carbocation could undergo a C–H insertion/elimination sequence to give product **5.2**. Initially, the use of commercially available Schreiner's thiourea **5.3** gave neither conversion to the desired product **5.2** nor consumption of starting material **5.1**. With this result in hand, we rationalized that this class of substrates needed a stronger Lewis acid to better affect the ionization. Based on the inherent N–H acidity of these catalysts[10–11], and drawing from our previous work using lithium bases as precursors for lithium

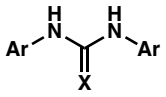
Lewis acids[5], we hypothesized the combination of these reagents could afford a competent Li-Urea Lewis acid. To our delight, we found that the addition of a stoichiometric amount of lithium hexamethyldisilazide (LiHMDS) resulted in a high yielding C–H insertion reaction, giving tricycle **5.2** in 78% yield (entry 2). The urea and squareamide analogs (**5.4** and **5.9** respectively) of Schreiner's catalyst were also competent catalysts for this transformation, yielding desired product in 96% and 72% yield, respectively (entries 4 and 5). This catalytic regime was also competent at lower temperatures and with lower equivalents of base (entries 6 and 7). Performing the reaction without Schreiner's catalyst gave essentially no yield of the desired product at lower temperatures, showcasing the necessity of both the hydrogen-bonding catalyst and lithium base (entry 3). Having found that urea catalyst **5.4** afforded the desired product in the highest yield, we next explored the effect of catalyst substitution on the product outcome. Probing monosubstituted trifluoromethyl urea catalysts (**5.5**–**5.7**) revealed the importance of a *meta*-trifluoromethyl group (79% yield for entry 9 vs. 3–9% yield for entries 8 and 10). Lastly, the N-methylated catalyst **5.8** delivered the desired product in a meager 19% yield, highlighting the importance of having both N–H hydrogen bond donors (entry 11).

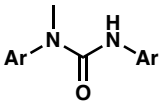
Table 5.1. Optimization table for C–H insertion.

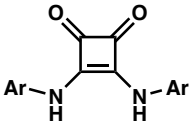


5.1 ***5.2***

entry	*cat.*	*LiHMDS equiv*	*Temp (°C)*	*yield*
1	***5.3***	*none*	*30*	*0%*
2	***5.3***	*1.5*	*30*	*78%*
3	***none***	*1.2*	*–40*	*1%*
4	***5.9***	*1.5*	*30*	*72%*
5	***5.4***	*1.5*	*30*	*96%*
6	***5.4***	*1.5*	*–40*	*93%*
7	***5.4***	*1.2*	*30*	*94%*
8	***5.5***	*1.2*	*30*	*3%*
9	***5.6***	*1.2*	*30*	*79%*
10	***5.7***	*1.2*	*30*	*9%*
11	***5.8***	*1.2*	*30*	*19%*







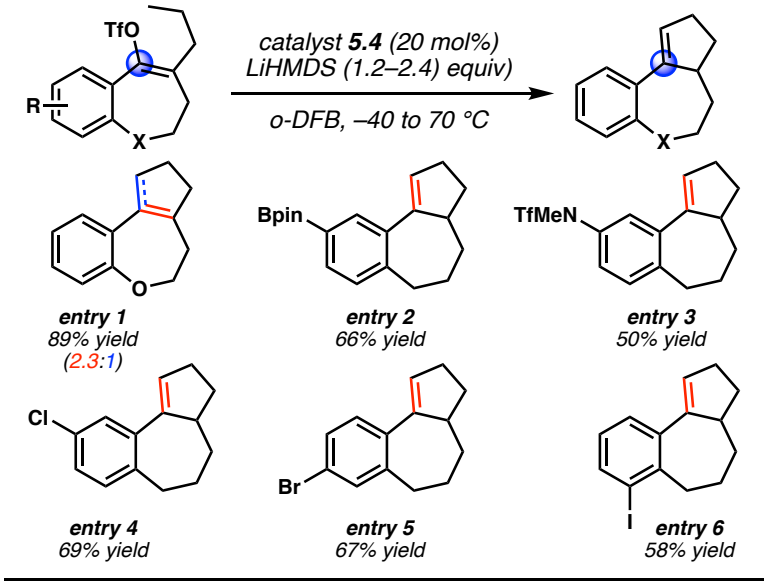
5.3: *X = S, Ar = 3,5-bis$CF_3C_6H_3$* ***5.8***: *Ar = 3,5-bis$CF_3C_6H_3$* ***5.9***: *Ar = 3,5-bis$CF_3C_6H_3$*
5.4: *X = O, Ar = 3,5-bis$CF_3C_6H_3$*
5.5: *X = O, Ar = 2-$CF_3C_6H_4$*
5.6: *X = O, Ar = 3-$CF_3C_6H_4$*
5.7: *X = O, Ar = 4-$CF_3C_6H_4$*

Yield determined by GC-FID.

Having discovered a novel mode of catalysis for C–H insertion reactions of propyl suberone **5.1**, we sought to explore the functional group compatibility and efficiency of this transformation. To investigate this, we screened a series of propyl suberone derivatives that had been previously reported to undergo C–H insertion reactions under lithium-weakly coordinating anion catalysis. By and large, the scope of propylated suberones was well tolerated. A benzoxepine core was readily synthesized under the conditions in 89% yield, albeit in a 2.3:1 mixture of olefin isomers (Figure 5.2, entry 1). Other heteroatom-containing pinacolboronates and protected anilines substrates were equally compatible, delivering tricyclic products in moderate yield (entries 2 and 3). Various halogenated arenes of differing substitution patterns were converted to the corresponding product in good to excellent yields (entries 4–6). Overall,

the efficiency and functional group tolerance of this catalytic manifold rivaled that of exotic lithium-weakly coordinating anion salts.

Figure 5.2. C–H insertion reactions of propylbenzosuberones.

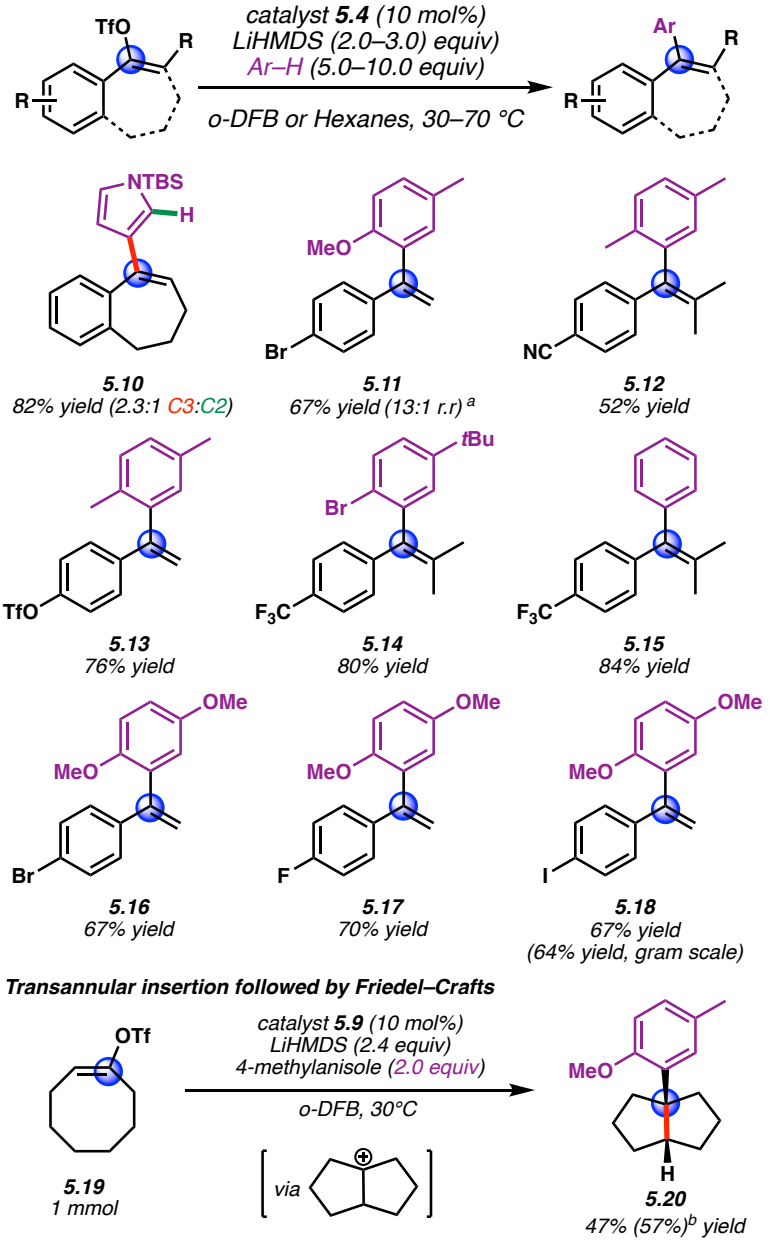


Yield determined by NMR.

To further develop the scope of this reaction, Li-urea catalyzed Friedel–Crafts reactions of vinyl cations were explored. Here, we decided to use the optimized reaction conditions from the insertion chemistry as a starting point for the Friedel– Crafts. We found a large range of both triflates and arenes to be tolerant of this transformation. A silylated pyrrole gave moderate selectivity to vinylation of the C3 position (Table 5.2, **5.10**), contrary to most Friedel–Crafts reactions which are C2 selective.[12] Halogenated, triflated or cyanoarenes were all well tolerated with anisoles and xylenes in moderate to good yields (52–76%, **5.11**–**5.13**). Trifluoromethylated vinyl triflate could react with benzene or the electron-deficient bromobenzene derivative yielding vinylated arenes in high yields (**5.14**–**5.15**). More electron rich aromatic nucleophiles, such as dimethoxybenzene, underwent smooth coupling with a variety of halogenated vinyl triflates in good yields (**5.16**–**5.18**). There was minimal decrease in efficiency when performing the reaction

on gram scale with the iodinated vinyl triflate, giving now 64% yield (**5.18**). Furthermore, cyclooctenyl triflate **5.19** was observed to undergo a C–H insertion, Friedel–Crafts cascade with 4-methylanisole giving alkylated arene **5.20** in 57% yield. Here, two new C–C bonds, a 5,5-fused ring system and a quaternary carbon center, were all forged in a single step. Notably, all of these reactions were performed on the bench and did not require scrupulous drying of substrates.

Table 5.2. Friedel-Crafts reactions of vinyl triflates.



5.10
82% yield (2.3:1 C3:C2)

5.11
67% yield (13:1 r.r) [a]

5.12
52% yield

5.13
76% yield

5.14
80% yield

5.15
84% yield

5.16
67% yield

5.17
70% yield

5.18
67% yield
(64% yield, gram scale)

5.19
1 mmol

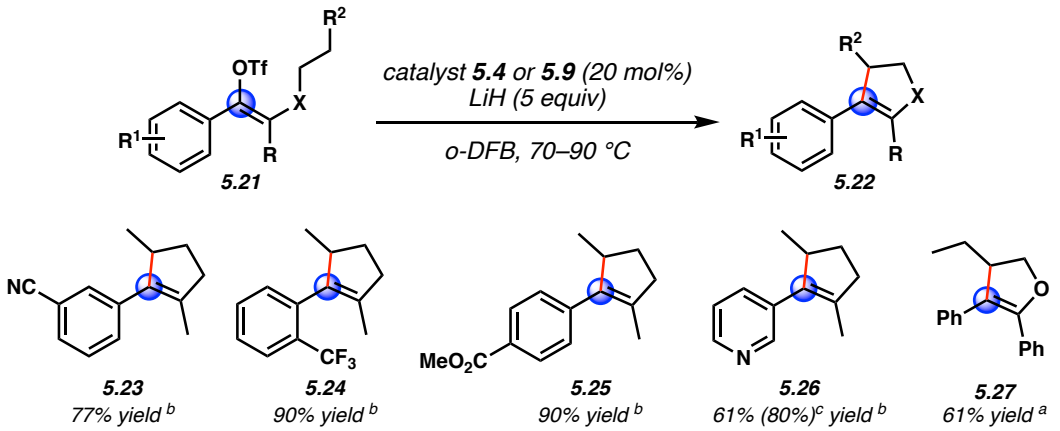
5.20
47% (57%)[b] *yield*

[a]*Catalyst **5.9** used instead.* [b] *Yield determined by GC–FID.*

5.4 Urea-Mediated C–H Insertion Reactions of Vinyl Triflates

While our initial studies of Li^+ ions paired with organocatalysts could generate vinyl cations to perform C–H insertion reactions, we sought to validate our hypothesis that these readily accessible organocatalysts were able to tolerate various functional groups in vinyl cation reactions. To explore the functional group tolerance, a variety of alkylated styrenyl triflates (**5.21**) were prepared (Figure 5.3). With the previously optimized conditions, we found that while LiHMDS was competent for most of these transformations, it made the expected product (**5.22**) as a mixture of olefin isomers in decreased yield.[13] After some brief optimization, we found that use of five equivalents of LiH resulted in high yielding reactions with excellent olefin selectivity. Under these newly-found conditions, we found that a variety of functional groups and substitutions were tolerated. A *meta*-nitrile, *ortho*-CF_3 and *para*-methylester were all well tolerated, delivering cyclopentenyl products **5.24** and **5.25** in 77%, 90% and 90% yield respectively. Pyridine derived triflates were also competent for this transformation delivering cyclopentenylpyridine **5.26** in 80% yield. Notably, the synthesis of heterocyclic dihydrofuran **5.27** was also possible from an appended butoxy benzoin derivative in 61% yield.

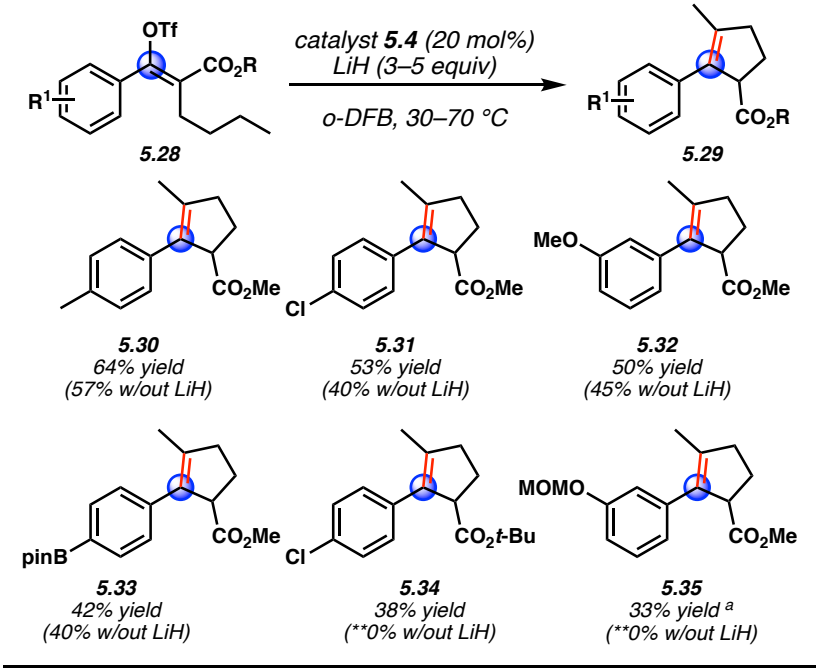
Figure 5.3. C–H insertion reactions of styrenyl triflates.



[a]Catalyst **5.9**. [b] Catalyst **5.4**. [c]Yield determined by NMR.

Inspired by the fact that the methyl ester triflate successfully afforded product **5.25**, we wondered if we could successfully perform C–H insertion reactions on triflates derived from butylated b-ketoesters (**5.28**) to afford aryl cyclopentene derivatives (**5.29**) (Figure 5.4). These substrates were also good candidates as the presence of heteroatoms in all substrates allows for the further development of broadly applicable scope in the context of reactive intermediate chemistry. Under the standard LiHMDS conditions, we found no conversion to the desired product, likely due to the electrophilicity of esters as well as recent reports describing ester functionalization with LiHMDS.[14–15] Remarkably, we found that simply by using urea catalyst **5.4**, without a Li-base, successful conversion of the *para*-methyl cyclopentenyl ester **5.30** was observed in 57% NMR yield. We also found that by using LiH in the reaction allowed for a slight increase in yield (64%). Halogen substituents, boronic esters and methyl ethers were also tolerated yielding the ester products **5.31**, **5.32**, and **5.33** in 42–53% yield. Notably, using LiH was important for substrates containing acid sensitive functional groups such as a *tert*-butyl ester or a methoxymethyl ether protected phenol, as the absence of LiH resulted in no desired product formation. In the presence of LiH, these substrates were successfully converted to their cyclized products **5.34** and **5.35** in 38% and 33% yield, respectively.

Figure 5.4. C–H insertion reactions of betaketo ester-derived vinyl triflate.



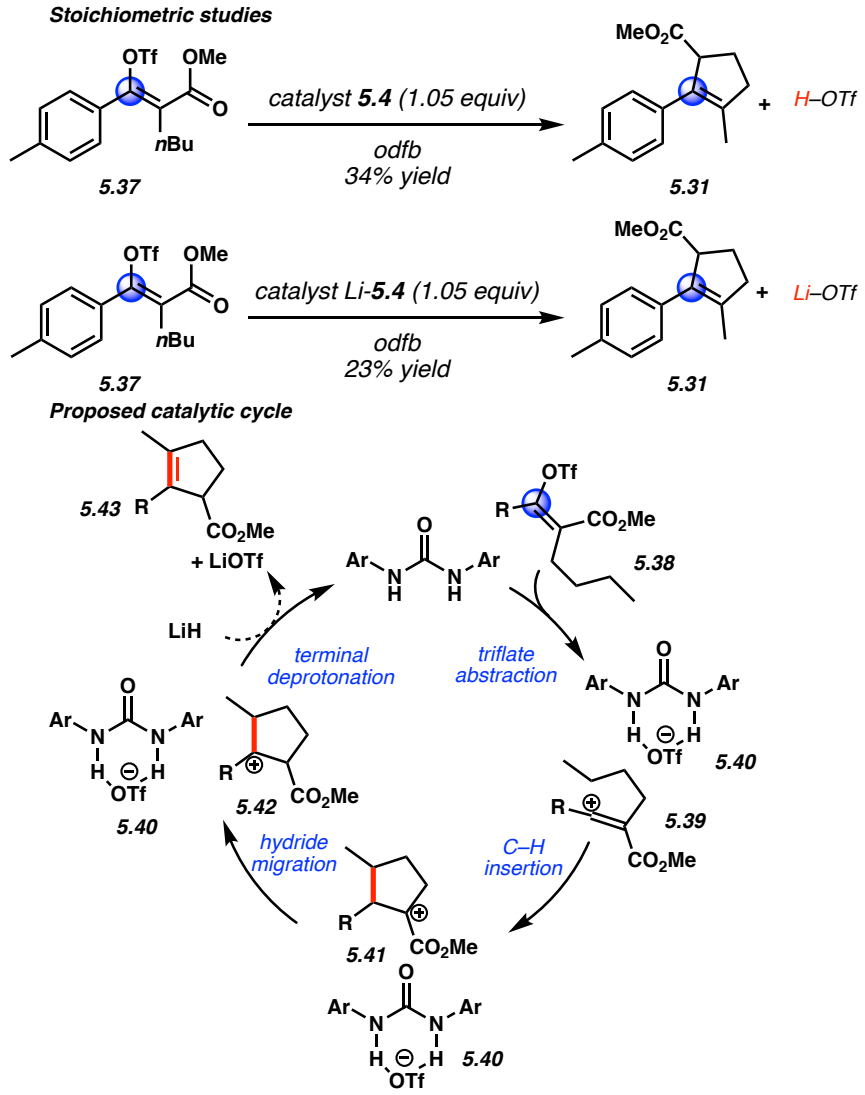
[a] *10 equiv LiH.*

5.5 Mechanistic Studies

With our scope studies in hand, we began our investigation into the mechanism of this transformation. Since the β-ketoester derived triflates could perform C–H insertion with or without added lithium salt, we decided to expose triflate **5.36** to a stoichiometric amount of urea (Fig. 5.5). This furnished the desired product (**5.30**) in 34% yield in only a few hours at room temperature. Furthermore, 38% yield of triflic acid was also observed as a byproduct.[13] Exposing the same substrate to a stoichiometric amount of lithiated urea, synthesized by stoichiometric deprotonation of urea **5.4** with LiHMDS, gave the desired product 23% yield as well as LiOTf. Due to the insolubility of lithium hydride in *o*-difluorobenzene, we presumably do not make the lithiated urea under the reaction conditions. However, with LiHMDS, we believe that the lithiated urea species is readily accessible[13]. For reactions using lithium hydride, we believe that the urea catalyst can abstract a triflate from **5.38**, giving benzylic cation **5.39** with an urea•triflate

counterion **5.40**. This can undergo an intramolecular insertion to give an a-ester cation **5.41**. This can then undergo a facile hydride shift to give benzylic cation **5.42**. If there is lithium hydride present in the reaction, this cation can then undergo deprotonation, concurrently forming LiOTf and regenerating the catalyst. In the case where there is no lithium hydride, it is presumed that the benzylic cation **5.42** can collapse to form the styrene product (**5.43**) as well as triflic acid. For the Friedel-Crafts reactions that are performed with LiHMDS, we believe that the mechanism is analogous to that previously reported by our group with the conjugate base of the urea acting as a counter anion.[5]

Figure 5.5. Mechanistic studies.



5.6 Conclusion

In conclusion, we have disclosed a unique application of hydrogen-bonding scaffolds, where 3,5-bistrifluoromethylphenyl urea and lithiated-3,5-bistrifluoromethylphenyl urea catalyze C–C bond forming reactions of vinyl cations from vinyl triflates. In the presence of these scaffolds, these reactive intermediates undergo facile C–H insertion and Friedel–Crafts reactions in good to excellent yield. Built on years of chemical research, this strategy has a unique facet in that these complexes can be used both as ionizing reagents and counter anions for lithium-Lewis acids.

5.7 Experimental Section

5.7.1 Materials and Methods

Unless otherwise stated, all reactions were performed in an MBraun or Vacuum Atmospheres glovebox under nitrogen atmosphere with ≤ 0.5 ppm O_2 levels. All glassware and stir-bars were dried in a 160 °C oven for at least 12 hours and dried *in vacuo* before use. All liquid substrates were filtered through dry neutral aluminum oxide. Solid substrates were dried over P_2O_5. All solvents were rigorously dried before use. Benzene, *o*-dichlorobenzene, and toluene were degassed and dried in a JC Meyer solvent system and stored inside a glovebox. Cyclohexane, fluorobenzene, and *n*-hexane were distilled over potassium. Pentane was distilled over sodium-potassium alloy. Chloroform, chlorobenzene and *o*-difluorobenzene were dried over CaH_2 and stored in a glovebox. Hydrogen-bonding catalysts were prepared according to original or modified literature procedures.[1] Preparatory thin layer chromatography (TLC) was performed using Millipore silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliaFlash P60 silica gel (230-400 mesh) was used for flash chromatography.

$AgNO_3$-Impregnated silica gel was prepared by mixing with a solution of $AgNO_3$ (150% v/w of 10% w/v solution in acetonitrile), removing solvent under reduced pressure, and drying at 120 °C. NMR spectra were recorded on a Bruker AV-300 (^1H, ^{19}F), Bruker AV-400 (^1H, ^{13}C, ^{19}F), Bruker DRX-500 (^1H), and Bruker AV-500 (^1H, ^{13}C). ^1H NMR spectra are reported relative to $CDCl_3$ (7.26 ppm) unless noted otherwise. Data for ^1H NMR spectra are as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet. ^{13}C NMR spectra are reported relative to $CDCl_3$ (77.0 ppm) unless noted otherwise. GC spectra were recorded on an Agilent 6850 series GC using an Agilent HP-1 (50 m, 0.32 mm ID, 0.25 mm DF) column. IR Spectra were record on a Perkin Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). High resolution mass spectra (HR-MS) were recorded on a Waters (Micromass) GCT Premier spectrometer, a Waters (Micromass) LCT Premier, an Agilent GC EI-MS, and are reported as follows: m/z (% relative intensity). Purification by preparative HPLC was done on an Agilent 1200 series instrument with a reverse phase Alltima C_{18} (5m, 25 cm length, 1 cm internal diameter) column.

5.7.2 Experimental Procedures

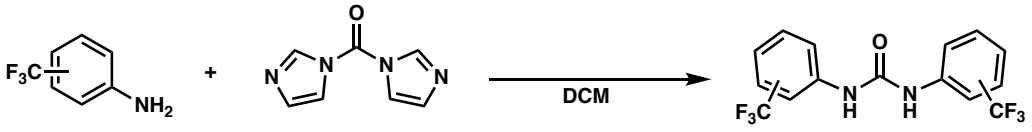
The synthesis of substrates in Figure 5.2 is reported elsewhere.[5]

Catalyst 5.3 [16]*, 5.9* [17] *synthesized according to literature procedure.*

Substrates 5.10 [18]*, 5.11* [4]*, 5.19* [4] *were synthesized according to literature procedure.*

5.7.2.1 Catalyst Synthesis

All catalysts were synthesized according to literature procedures or modified literature procedures. Prior to use in catalysis, the catalysts were heated under high vacuum, followed by drying over P_2O_5.

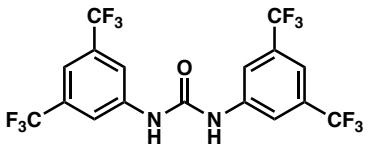


Scheme 5.1. Representative scheme for symmetric catalyst synthesis.

5.7.2.1.1 General Procedure

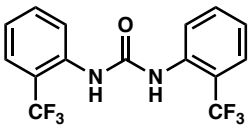
General procedure

To a stirring solution of CDI (1 equiv) in DCM (1.5 M) was added the respective aniline (2.1 equiv) in DCM (6.5 M). After stirring overnight a precipitate was formed and this was filtered and washed with minimal DCM to give the desired product. Note: the quality of CDI is important for this reaction. The use of lesser quality CDI did not result in productive precipitation of the desired product.



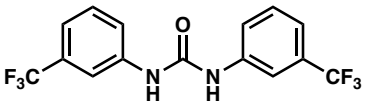
1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (5.4).

Synthesized according to general procedure. Spectra matches that reported in the literature.[19]



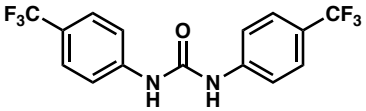
1,3-bis(2-(trifluoromethyl)phenyl)urea (5.5).

Synthesized according to general procedure. Spectra matches that reported in the literature.[21]



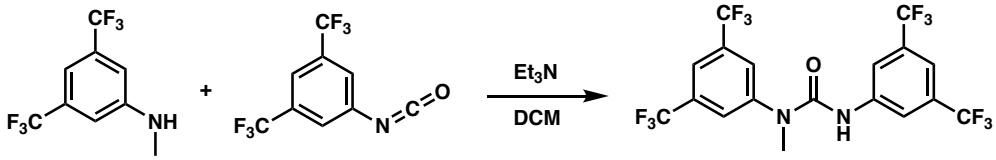
1,3-bis(3-(trifluoromethyl)phenyl)urea (5.6).

Synthesized according to general procedure. Spectra matches that reported in the literature.[22]

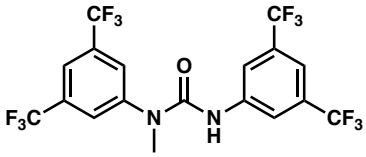


1,3-bis(4-(trifluoromethyl)phenyl)urea (5.7)

Synthesized according to general procedure. Spectra matches that reported in the literature.[23]



Scheme 5.2. Representative scheme for non-symmetric catalyst synthesis.



1,3-bis(3,5-bis(trifluoromethyl)phenyl)-1-methylurea (5.8). To a stirring solution of N-methyl-3,5-bis(trifluoromethyl)aniline (0.50g, 2.1 mmol, 1 equiv) in DCM (2 mL) was added triethylamine (0.29 mL, 2.1 mmol, 1 equiv) and 3,5-bis(trifluoromethyl)phenyl isocyanate (577 mg, 2.3 mmol, 1.1 equiv). The resulting solution was stirred overnight. The solution was diluted with DCM and the organic layer was washed with water and brine. The organics were dried over Na_2SO_4, filtered and concentrated. The resulting crude material was purified by column chromatography to give **5.8**.

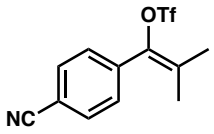
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 7.98 – 7.90 (m, 1H), 7.65 (d, J = 0.8 Hz, 0H), 3.43 (s, 3H).^{13}C NMR (126 MHz, DMSO-d_6) δ 154.1, 145.4, 142.0, 130.6 (q, J = 33.0 Hz), 130.5 (q, J = 32.7 Hz), 127.0, 123.3 (q, J = 273 Hz), 123.2 (q, J = 273 Hz), 119.6, 119.0, 114.9, 37.3.

5.7.2.2 Vinyl Triflate Synthesis

5.7.2.2.1 General Procedure

In a flame dried roundbottom flask, the starting ketone (1 equiv) was dissolved in THF to make a 0.413 M solution and this was cooled to –78 °C. To this solution was added a solution of NaHMDS (1.5 equiv, 1M solution in THF). This was warmed up to –40 °C for one hour before being cooled back down to –78 °C. Finally, a solution of $PhNTf_2$ (1 equiv, 1.65M in THF) was added dropwise and the reaction was allowed to warm up to r.t overnight. The reaction was quenched by addition of 1:9 *v/v* solution of methanol:ethyl acetate. The crude mixture was rotovapped and then suspended in 1:1 ether/pentane. The suspension was filtered and the solid

washed with pentane. The supernatant was concentrated giving the crude product. The crude was purified by flash column chromatography to give the pure vinyl triflate.



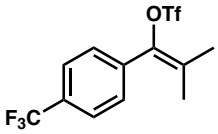
1-(4-cyanophenyl)-2-methylprop-1-en-1-yl trifluoromethanesulfonate (5.44).

Synthesized according to general procedure 5.7.2.2.1 starting from 4-isobutyrylbenzonitrile. Column chromatography was performed using 85:14.9:0.1 hexane:ethyl acetate:triethylamine. Product **5.44** was obtained as colorless oil (660 mg, 6.1 mmol, 36%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139. 4, 137.2, 132.2, 130.8, 130.1, 118.1, 118.1 (q, $^{1}J_{C–F}$ = 320.7 Hz), 113.1, 20.2, 19.2.^{19}F NMR (376 MHz, $CDCl_3$) δ –74.5.

FTIR (Neat film NaCl): 3067, 3000, 2952, 2865, 2231, 1608, 1504, 1412, 1242, 1206, 1138, 1081, 957, 855, 617, 595.

HR-MS (EI-MS): Calculated for $C_{12}H_{10}F_3NO_3S$: 305.0333; Measured: 305.0331.



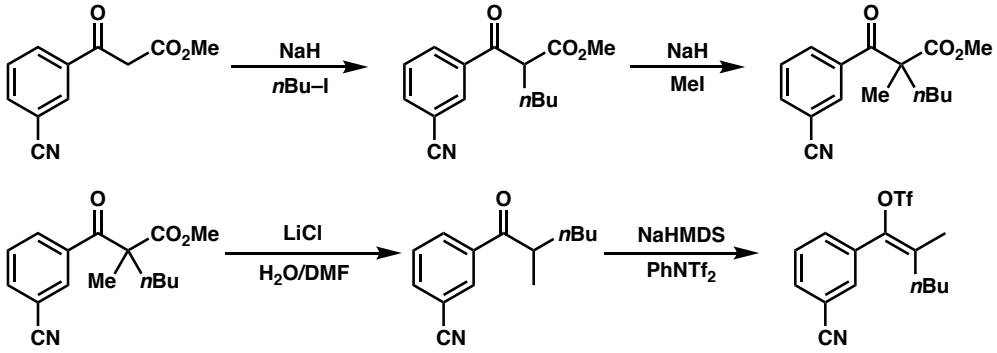
2-methyl-1-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl trifluoromethanesulfonate. (5.45).

Synthesized according to general procedure 5.7.2.2.1 starting from 2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-one. Triflate **5.45** (220 mg, 1.80 mmol) was obtained as a colorless oil in 35% yield. Chromatography was performed using 5% ether/hexanes as a solvent system on silica gel. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 8.1 Hz,

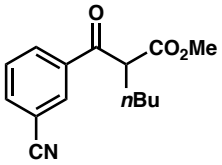
2H), 2.02 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 136.2, 131.2 (q, $^2J_{C–F}$ = 32.8 Hz), 130.0, 129.9, 125.4 (q, $^3J_{C–F}$ = 3.8 Hz), 123.7 (q, $^1J_{C–F}$ = 272.5 Hz), 118.1 (q, $^1J_{C–F}$ = 320.2 Hz), 20.2, 19.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ –180.0, –191.7.

FTIR (Neat film NaCl): 3002, 2928, 2867, 1619, 1416, 1326, 1212, 1138, 1067, 967, 858, 615.

HR-MS (EI-MS): Calculated for $C_{12}H_{10}F_6O_3S$: 348.0255; Measured: 348.0252.



Scheme 5.3. Representative scheme for synthesis of dialkyl styrenyl triflates.

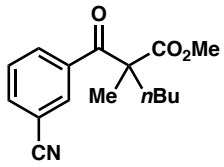


methyl 2-(3-cyanobenzoyl)hexanoate (5.46). To a schlenk flask was added NaH (2.0 g, 60% w/w, 49 mmol, 1.1 equiv) followed by THF (90 mL). The reaction mixture was cooled to 0 °C and to this was added the corresponding betaketoester (9.1 g, 45 mmol, 1 equiv). After H_2 evolution ceased, 1-iodobutane (20 mL, 179 mmol, 4 equiv) was added and the flask was sealed and heated to 120 °C for 48 hrs. Upon completion, reaction was quenched with water and the aqueous layer was extracted with EtOAc. The organics were then washed with water and brine.

The organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography to afford **5.46** (5.6g, 40% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 0.9 Hz, 1H), 8.22 – 8.16 (m, 1H), 7.86 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.63 (dd, *J* = 8.2, 7.5 Hz, 1H), 4.25 (t, *J* = 7.2 Hz, 1H), 3.69 (d, *J* = 0.7 Hz, 3H), 2.01 (qd, *J* = 7.1, 4.2 Hz, 2H), 1.33 (dd, *J* = 6.9, 3.3 Hz, 3H), 1.00 – 0.78 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.4, 169.9, 137.1, 132.5, 132.3, 129.9, 117.9, 113.5, 54.2, 29.8, 28.7, 22.6, 13.9.

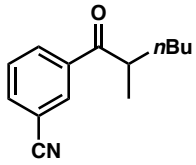
HRMS (CI-MS): Calculated for $[C_{15}H_{17}NO_3+H]^+$: 260.1287; Measured: 260.1282.



methyl 2-(3-cyanobenzoyl)-2-methylhexanoate (5.47). To a round bottom with NaH (1.9g, 60% w/w, 48 mmol, 2.2 equiv) in THF (43 mL) at 0 °C was added **5.46** (5.6g, 22 mmol, 1 equiv) dropwise. This was stirred at 0 °C until H_2 evolution ceased. To this iodomethane (4 mL, 65 mmol, 3 equiv) was added and subsequently warmed to room temperature. This was then heated to 80 °C overnight. Upon completion, the reaction was quenched with water and extracted with EtOAc. The combined organics were washed with water and brine. The organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (10% ether:hexanes) to give **5.47** (588 mg, 10% yield) as an oil.

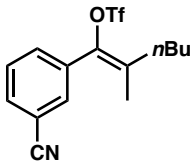
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.01 – 7.95 (m, 3H), 7.80 (dd, *J* = 7.6, 1.2 Hz, 3H), 7.55 (t, *J* = 7.8 Hz, 3H), 3.66 (s, 4H), 2.09 – 1.90 (m, 7H), 1.52 (s, 3H), 1.36 – 1.23 (m, 6H), 1.24 – 1.13 (m, 3H), 1.12 – 0.98 (m, 3H), 0.92 – 0.78 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8, 174.4, 136.7, 132.3, 132.2, 129.6, 118.0, 113.4, 57.2, 52.7, 36.1, 26.0, 23.1, 21.0, 13.9.

HRMS (CI-MS): Calculated for $[C_{16}H_{19}NO_3+H]^+$: 274.1443; Measured: 274.1455.



3-(2-methylhexanoyl)benzonitrile (5.48). To a solution of lithium chloride (1.73g, 41 mmol, 19 equiv) in DMF (61 mL) was added water (737 mL, 41 mmol, 19 equiv). To this mixture was added **5.47** (588 mg, 2.2 mmol, 1 equiv). The reaction was sealed and heated to 160 °C for 3 hrs. Upon completion, the reaction was diluted with water and extracted with 1:1 ether:hexanes mixture. The combined organics were washed with water (3 x) and brine (3 x), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (20% ether:hexanes) to give **5.48** (220 mg, 48% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.16 (dt, *J* = 8.0, 1.5 Hz, 2H), 7.83 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 2H), 3.40 (h, *J* = 6.7 Hz, 2H), 1.85 – 1.73 (m, 2H), 1.46 (dq, *J* = 14.4, 8.0, 7.3 Hz, 2H), 1.30 (dt, *J* = 6.1, 3.9 Hz, 4H), 1.21 (d, *J* = 6.7 Hz, 5H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 137.6, 135.8, 132.3, 132.1, 129.8, 118.2, 113.3, 41.0, 33.3, 29.6, 22.9, 17.1, 14.0.

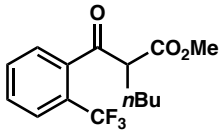


(*Z*)-1-(3-cyanophenyl)-2-methylhex-1-en-1-yl trifluoromethanesulfonate (5.49). To a round bottom flask was added **5.48** (220 mg, 1.0 mmol, 1 equiv) as a solution in dry THF (2.5 mL). This flask was cooled to –78 ºC, and to it was added a solution of NaHMDS (281 mg, 1.5 mmol,

1.5 equiv) as a solution in dry THF (2 mL) drop wise. This solution was allowed to stir for 30 minutes at –78 ºC. To the reaction was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (365 mg, 1.0 mmol, 1.0 equiv) as a solution in dry THF (0.6 mL). The reaction was allowed to warm to room temperature and stir overnight. The reaction was then cooled to –78 °C and was quenched by addition of MeOH in EtOAc (10% v/v). The solution was allowed to warm to room temperature and the combined organics were washed with water and brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated. The crude material was concentrated and purified by flash column chromatography (2.5% ether:hexanes) to give **5.49** as a clear oil (310 mg, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.65 (s, 1H), 7.62 – 7.57 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 2.07 – 2.00 (m, 3H), 1.99 (d, *J* = 0.8 Hz, 3H), 1.45 (tt, *J* = 7.7, 6.1 Hz, 3H), 1.27 – 1.16 (m, 3H), 0.88 – 0.77 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 134.7, 134.2, 133.2, 133.0, 129.6, 120.7 (q, $^1J_{C-F}$ = 320 Hz), 118.1, 113.0, 33.1, 29.9, 22.4, 16.5, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.64.

HRMS (EI-MS): Calculated for $C_{15}H_{16}F_3NO_3S$: 347.0803; Measured: 347.0797.



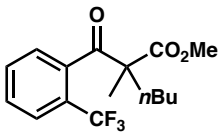
Methyl 2-(2-(trifluoromethyl)benzoyl)hexanoate (5.50). In a flame dried three neck flask was suspended sodium hydride (0.89 g, 22.3 mmol, 1.1 equiv, 60% dispersion in mineral oil) in anhydrous THF (41 mL). This suspension was cooled to 0 °C and to it was added methyl 3-oxo-3-(2-(trifluoromethyl)phenyl)propanoate (5.00 g, 20.3 mmol, 1.0 equiv). After bubbling stopped, *n*-butyliodide (14.9 g, 81.2 mmol, 4.0 equiv) was added and the reaction was refluxed for 24

hours. At this point it was cooled down to 0 °C and quenched with water (50 mL). This was then acidified with concentrated aqueous HCl. Ether (50 mL) was added and the layers were separated. Aqueous layer was extracted with ether (2 x 50 mL). Combined organics were washed with brine, dried over magnesium sulfate, filtered and concentrated to give crude product as orange oil. Crude was purified by silica column chromatography (7% ether/hexanes) to give pure product as yellow oil (3.24 g, 53%). The product existed as a 3:1 mixture of keto:enol tautomers. 4.04 (dd, J = 8.8, 5.7 Hz, 1H) and 3.67 (s, 3H) were characteristic peaks of the keto tautomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139. 4, 137.2, 132.2, 130.8, 130.1, 118.1, 118.1 (q, $^{1}J_{C–F}$ = 320.7 Hz), 113.1, 20.2, 19.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ –58.0 (keto), –59.8 (enol).

FTIR (Neat film NaCl): 2958, 2934, 2874, 2864, 1748, 1708, 1315, 1168, 1146, 770.

HR-MS (CI-MS): Calculated for $[C_{15}H_{17}F_3O_3+H]^+$: 303.1208; Measured: 303.1220.



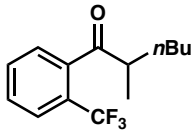
Methyl 2-methyl-2-(2-(trifluoromethyl)benzoyl)hexanoate (5.51). In a flame dried three neck flask was suspended sodium hydride (0.94 g, 23.6 mmol, 2.2 equiv, 60% dispersion in mineral oil) in anhydrous THF (21 mL). This suspension was cooled to 0 °C and to it was added ketoester **5.50** (3.24 g, 10.7 mmol, 1.0 equiv). After bubbling stopped, iodomethane (4.56 g, 32.2 mmol, 3.0 equiv) was added and the reaction was heated at 50 °C for 12 hours. At this point it was cooled down to 0 °C and quenched with water (20 mL). This was then acidified with concentrated aqueous HCl. Ether (20 mL) was added and the layers were separated. Aqueous layer was extracted with ether (2 x 20 mL). Combined organics were washed with brine, dried

over magnesium sulfate, filtered and concentrated to give crude product as dark red oil. Purified by flash column chromatography first with 25% ether/hexanes and then with 10% acetone/hexanes to give pure **5.51** as a light yellow oil (800 mg, 24%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 1H), 7.57 – 7.47 (m, 2H), 7.33 – 7.28 (m, 1H), 3.62 (s, 2H), 2.17 – 2.05 (m, 1H), 1.83 (ddd, J = 13.8, 12.5, 4.1 Hz, 1H), 1.46 (s, 3H), 1.38 – 1.27 (m, 2H), 1.16 – 1.07 (m, 1H), 0.89 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5, 173.1, 138.4 (q, $^{3}J_{C–F}$ = 2.6 Hz), 131.2, 129.8, 127.7 (q, $^{2}J_{C–F}$ = 32.3 Hz), 127.2 (q, $^{3}J_{C–F}$ = 4.8 Hz), 125.5, 123.3 (q, $^{1}J_{C–F}$ = 273.8 Hz), 59.9, 52.4, 36.4, 26.5, 23.0, 20.1, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –57.8.

FTIR (Neat film NaCl): 2957, 2930, 2873, 2862, 1739, 1705, 1460, 1448, 1313, 1169, 1132, 1036, 769.

HR-MS (CI-MS): Calculated for $[C_{16}H_{19}F_3O_3+H]^+$: 317.1364; Measured: 317.1354.



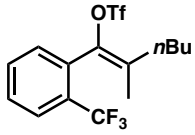
2-methyl-1-(2-(trifluoromethyl)phenyl)hexan-1-one (5.52). Ketoester **5.51** (800 mg, 2.53 mmol, 1.0 equiv.) was dissolved in AcOH (2.3 mL) in a 10 mL roundbottom flask. To this solution was added water (250 mg, 13.9 mmol, 5.5 equiv) and concentrated sulfuric acid (471 mg, 4.8 mmol, 1.9 equiv). This was refluxed open top at 110 °C for 12 hours. At this point the reaction was cooled to room temperature and diluted with 10 mL of water. Diethyl ether (15 mL) was added and the phases were separated. Aqueous was extracted with ether (2 x 15 mL). Combined organics were washed with water (1 x 30 mL), saturated aqueous sodium bicarbonate solution (5 x 30 mL) and brine (1 x 30 mL). The organics were then dried over magnesium

sulfate, filtered and concentrated to give crude as light orange oil. Purification by silica column chromatography (20% ether/hexanes) gave pure **5.52** as colorless oil (470 mg, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 7.4 Hz, 1H), 7.59 (dd, J = 7.6, 1.3 Hz, 1H), 7.55 (dd, J = 7.5, 1.3 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 3.08 (hex, J = 6.1 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.30 (dd, J = 9.5, 6.7 Hz, 1H), 1.40 – 1.26 (m, 5H), 1.16 (d, J = 6.9 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.8, 140.1 (q, $^3J_{C–F}$ = 2.3 Hz), 131.6, 130.0, 127.5 (q, $^2J_{C–F}$ = 32.2 Hz), 127.4, 126.9 (q, $^3J_{C–F}$ = 4.9 Hz), 123.6 (q, $^1J_{C–F}$ = 273.8 Hz), 45.7, 32.1, 29.3, 22.7, 15.9, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ –57.9.

FTIR (Neat film NaCl): 2966, 2935, 2875, 2862, 1703, 1313, 1169, 11366, 1169, 1063, 1036, 787.

HR-MS (CI-MS): Calculated for $[C_{14}H_{17}F_3O+H]^+$: 259.1310; Measured: 259.1318.



2-Methyl-1-(2-(trifluoromethyl)phenyl)hex-1-en-1-yl trifluoromethanesulfonate (5.53). Synthesized according to same procedure as **5.52** starting from 2-methyl-1-(2-(trifluoromethyl)phenyl)hexan-1-one. Column chromatography was performed using 95:5:0.1 hexane:diethyl ether:triethylamine. Product **5.53** was obtained as colorless oil and as a 3.8:1 mixture of *Z*:*E* isomers (260 mg, 1.8 mmol, 36%). The major isomer was determined by observing an NOE between the allylic methyl peak at 1.57 with aromatic protons.

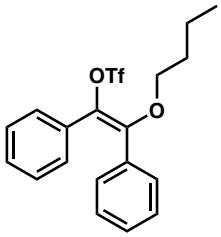
NMR Data for Major Isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.5, 1.4 Hz, 1H), 7.59 (td, J = 7.4, 1.6 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.53 – 7.48 (m, 1H), 2.46 (ddd, J = 13.4, 9.1, 7.0 Hz, 1H), 2.30 (ddd, J =

13.4, 8.9, 6.4 Hz, 1H), 1.57 (s, 3H), 1.55 – 1.49 (m, 2H), 1.48 – 1.36 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2, 135.1, 133.9, 131.8, 130.1, 130.1 (q, $^{2}J_{C–F}$ = 20.5 Hz), 126.56 (q, $^{3}J_{C–F}$ = 4.9 Hz), 123.5 (q, $^{1}J_{C–F}$ = 273.8 Hz), 118.0 (q, $^{1}J_{C–F}$ = 319.9 Hz), 31.7, 29.0, 22.5, 17.9, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.1, –75.3.

FTIR (Neat film NaCl): 2963, 2936, 2876, 1605, 1411, 1315, 1211, 1136, 1118, 846, 770, 606.

HR-MS (EI-MS): Calculated for $C_{15}H_{16}F_6O_3S$: 390.0724; Measured: 390.0730.

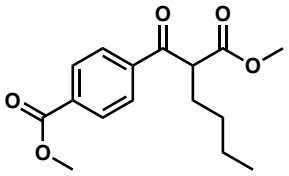


(*Z*)-2-butoxy-1,2-diphenylvinyl trifluoromethanesulfonate (5.54). To a flame dried flask was added NaHMDS (1.08 g, 5.9 mmol, 1.5 equiv) and anhydrous THF 20 ml, then cool the solution to –78 °C. 2-butoxy-1,2-diphenylethan-1-one (1.09 g, 3.9 mmol, 1 equiv) in 10 ml THF was added dropwise. Stir the solution at –78 °C for 30min and then warm up to 0 °C and keep at 0 °C for 30 min. 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.55 g, 4.3 mmol, 1.1 equiv) in 10 ml THF was added after the solution was cooled to –78 °C then warm up slowly to room temperature. Quench the reaction with 10 ml 1:5 MeOH/EA after 1 hour stirring at room temperature. The solvent was evaporated and the crude was purified by flash column chromatography (100:1 hexanes:ether) to yield of white solid in 59% yield.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.38 – 7.33 (m, 2H), 7.30 – 7.25 (m, 2H), 7.25 – 7.17 (m, 6H), 4.59 (dd, J = 9.8, 8.8 Hz, 1H), 4.23 (dd, J = 8.8, 7.0 Hz, 1H), 3.49 (dddd, J = 10.3, 8.9, 6.9, 3.5 Hz, 1H), 1.61 (dqd, J = 13.7, 7.6, 3.5 Hz, 1H), 1.45 – 1.35 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C

NMR (126 MHz, CD_2Cl_2) δ 150.1, 135.6, 132.0, 128.8, 128.4, 128.2, 128.0, 127.6, 126.3, 114.8, 73.3, 49.1, 25.5, 10.6. ^{19}F NMR (282 MHz, CD_2Cl_2) δ –75.29

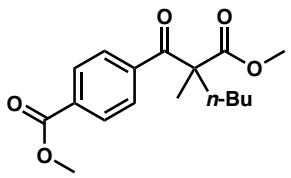
FTIR (Neat film NaCl): 3085, 3061, 3028, 2961, 2937, 2876, 1651, 1446, 1415, 1258, 1240, 1201, 1139, 1100, 1074, 1001, 986, 897,820, 768, 694, 647, 601, 569, 511.



methyl 4-(2-(methoxycarbonyl)hexanoyl)benzoate (5.55). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (1.3 g, 60% w/w, 33 mmol, 1.4 equiv) and then vacuum and backfilled with N_2 three times. To this was added THF (70 mL), and the solution as cooled to 0 ºC. To this was added portionwise the respective betaketoester (5.5 g, 23 mmol, 1 equiv) and stirred, 5 minutes, or until H_2 gas evolution had ceased. This solution was brought to reflux, and at 60 ºC the iodobutane (11 mL, 93 mmol, 4 equiv) was added in one portion. The solution was refluxed overnight, and upon full consumption of the starting material the solution was cooled to room temperature and quenched with water (30mL) and acidified with aqueous 1M HCl (5 mL). The aqueous layer was extracted with ether (3x45mL), dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash column chromatography (10% ethyl acetate:hexanes) to yield **5.55** as a white solid (3.56 g, 52% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.11 (m, 2H), 8.06 – 7.96 (m, 2H), 4.31 (t, J = 7.1 Hz, 1H), 3.95 (s, 3H), 3.68 (s, 3H), 2.02 (h, J = 7.3 Hz, 2H), 1.40 – 1.26 (m, 4H), 0.89 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.1, 170.5, 166.4, 139.8, 134.5, 130.3, 128.7, 54.7, 52.9, 52.8, 30.0, 29.0, 22.8, 14.1.

FTIR (Neat Film NaCl): 2956, 2873, 1729, 1590, 1436, 1405, 1279, 1230, 1194, 1109, 1015 cm^{-1}.

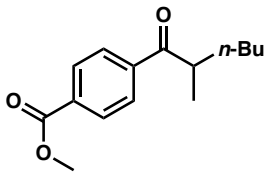


methyl 4-(2-(methoxycarbonyl)-2-methylhexanoyl)benzoate (5.56). To a 100mL round bottom flask was added NaH (1.1 g, 60% w/w, 26 mmol, 2.2 equiv) followed by dry THF (10 mL). The flask was cooled to 0 ºC and **5.55** (3.5 g, 12 mmol, 1 equiv) was added drop wise and allowed to stir for 15 minutes. To this was added MeI (2.2 mL, 36 mmol, 3 equiv) and allowed to stir for 48 hours. Upon full consumption of the starting material, the reaction was diluted with ether (10 mL), quenched with water (5 mL) and acidified with 1M HCl (3 mL). The aqueous layer was extracted with ether (3x 40mL), and the organics were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash column chromatography (10% ether:hexanes) to give **5.56** as a yellow oil (1.37 g, 37% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 2H), 7.90 – 7.78 (m, 2H), 3.94 (s, 3H), 3.63 (s, 3H), 2.01 (ddd, J = 9.8, 5.7, 3.6 Hz, 2H), 1.52 (s, 3H), 1.37 – 1.20 (m, 2H), 1.21 – 1.05 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 174.9, 166.4, 139.5, 133.7, 130.0, 128.5, 57.5, 52.8, 36.3, 26.2, 23.3, 21.3, 14.1.

FTIR (Neat Film NaCl): 2955, 2872, 1727, 1682, 1459, 1436, 1405, 1385, 1279, 1234, 1209, 1109, 970 cm^{-1}.

HRMS (CI-MS): Calculated for $[C_{17}H_{22}O_5+H]^+$: 307.1545; Measured: 307.1549.

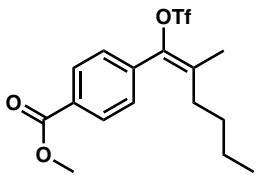


methyl 4-(2-methylhexanoyl)benzoate (5.57). To a 100mL Schlenk flask was added LiCl (3.76 g, 88.8 mmol, 20 equiv) and water (1.60 mL, 88.8 mol, 20 equiv) followed by wet DMF (10 mL). To this was added **5.56** (1.36 g, 4.4 mmol, 1 equiv), the Schlenk flask was sealed, and then heated to 150 ºC for 8 hours. The reaction was cooled and a 1:1 ratio of ether:water was added (20 mL). The aqueous layer was extracted with ether (4 x 70 mL). The combined organic layer was washed with water (5 x 10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash column chromatography (10% ether:hexanes) to yield **5.57** as a yellow oil (130 mg, 12% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H), 3.95 (d, J = 0.7 Hz, 3H), 3.45 (h, J = 6.7 Hz, 1H), 1.71 – 1.81 (m, 1H), 1.37 – 1.50 (m, 1H), 1.39 – 1.22 (m, 4H), 0.98 – 0.76 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.4, 166.6, 140.4, 133.9, 130.2, 128.4, 52.8, 41.3, 33.6, 29.8, 23.1, 17.3, 14.2.

FTIR (Neat Film NaCl): 2956, 2932, 2872, 2859, 1727, 1636, 1459, 1436, 1278, 1228, 1195, 1108, 971, 827, 722 cm^{-1}.

HRMS (CI-MS): Calculated for $[C_{15}H_{20}O_3+H]^+$: 249.1491; Measured: 249.1478.



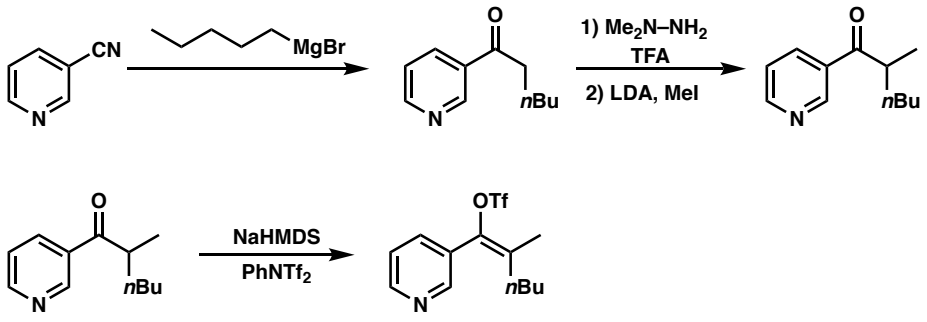
methyl (*E*)-4-(2-methyl-1-(((trifluoromethyl)sulfonyl)oxy)hex-1-en-1-yl)benzoate (5.58). To a 25 mL round bottom flask was added **5.57** (130 mg, 0.52 mmol, 1 equiv) as a solution in dry

THF (1mL). This flask was cooled to –78 ºC, and to it was added a solution of NaHMDS (144 mg, 0.79 mmol, 1.5 equiv) as a solution in dry THF (5 mL) drop wise. This solution was allowed to stir for 30 minutes at –78 ºC. To the reaction was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (206 mg, 0.58 mmol, 1.1 equiv) as a solution in dry THF (2 mL). The reaction was allowed to warm to room temperature and stir for 8h. The reaction was concentrated and suspended in 1:1 ether:hexanes (15 mL) and filtered. The solids were washed with cold 1:5 ether:hexanes. The filtrate was concentrated and purified by flash column chromatography (8% ether:hexanes) to give **5.58** as a clear oil (50 mg, 25% yield).

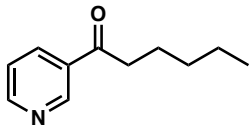
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 3.94 (s, 3H), 2.07 (t, J = 7.8 Hz, 2 H), 1.98 (s, 3H), 1.45 (p, J = 8.0, 7.5 Hz, 2H), 1.23 (q, J = 7.3 Hz, 2H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 141.3, 137.3, 133.9, 131.1, 129.9, 129.8, 118.3 (q, $^{1}J_{C–F}$ = 320.2 Hz),52.6, 33.4, 30.2, 22.6, 16.8, 14.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.66.

FTIR (Neat Film NaCl): 2959, 2938, 2865, 1728, 1414, 1279, 1210, 1141, 1104, 955, 868, 838, 706, 607 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{16}H_{19}F_3O_5S$: 380.0905; Measured: 380.0902.



Scheme 5.4. Synthetic scheme for the synthesis of pyridine-derived vinyl triflate.

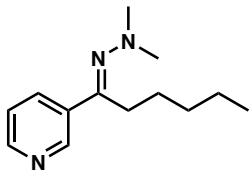


1-(pyridin-3-yl)hexan-1-one (5.59). A solution of 1-bromopentane (91.8 mmol, 1.125 equiv) in 200 mL of Et_2O was treated with magnesium (81.6 mmol, 1.00 equiv). The reaction was stirred for ~30 minutes until magnesium was fully dissolved. The solution was allowed to cool to room temperature after forming the Grignard reagent. The reagent was added into the solution of 3-cyanopyridine (81.6 mmol, 1.00 equiv) in Et_2O at 0 ℃ dropwise. After addition was completed, the reaction was warmed up to 40 ℃. Reaction was stirred for 16 hours. After cooling to room temperature, 2 M HCl (40 mL) was added to quench the reaction. The layers were separated and aqueous layer was refluxed at 140 ℃ for 2 hours. The reaction was cooled down to room temperature, and basified to pH 9 with saturated aqueous $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. The crude mixture was purified by column chromatography (15% acetone in hexanes) to afford pure ketone **5.59** as an oil (4.47 g, 31%).

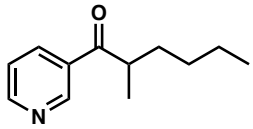
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (d, 1H), 8.77 (dd, J = 4.8, 1.7 Hz, 1H), 8.23 (dt, J = 8.0, 2.0 Hz, 1H), 7.42 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 2.98 (t, 2H), 1.81 – 1.71 (m, 2H), 1.37 (m, J = 5.9, 2.1 Hz, 4H), 0.94 – 0.89 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 153.3, 149.6, 135.3, 132.2, 123.6, 38.9, 31.4, 23.7, 22.5, 13.9.

FTIR (Neat film NaCl): 3050, 2957, 2931, 2872, 2861, 1689, 1585, 1467, 1419, 1373, 1294, 1243, 1215, 1119, 1044, 1025, 973, 801, 761, 704, 620.

HR-MS (EI-MS): Calculated for $C_{11}H_{15}NO$: 177.1154; Measured: 177.1147.



(*E*)-3-(1-(2,2-dimethylhydrazineylidene)hexyl)pyridine (5.60). To a flame dried 250 mL round bottom flask equipped with a Dean-Stark trap and reflux condenser was added 1-(pyridine-3-yl)hexan-1-one **5.59** (4.47 g, 25.2 mmol, 1.00 equiv). To this was added dry benzene (85 mL) followed by 1,1-dimethylhydrazine (3.53 mL, 45.4 mmol, 1.80 equiv) and trifluoroacetic acid (6 drops). The mixture was refluxed for 18 hours and subsequently cooled to room temperature. The crude reaction mixture was concentrated in vacuo and redissolved with diethyl ether (60 mL). The mixture was washed with saturated aqueous sodium bicarbonate solution (1 x 30 mL) and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude hydrazone **5.60**, which was used without further purification.



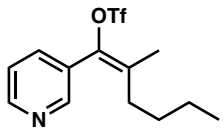
2-methyl-1-(pyridin-3-yl)hexan-1-one (5.61). To a flame dried 250 mL round bottom flask was added dry diisopropylamine (2.82 mL, 20.0 mmol, 1.10 equiv) followed by 60 mL of dry THF. The flask was brought to –78 °C and *n*-BuLi (11.2 mL, 1.87M in hexanes, 20.9 mmol, 1.15 equiv) was added dropwise. The mixture was allowed to stir for 30 minutes, warmed up to 0 ℃ for 30 minutes, and cooled back to –78 °C. To this was added a solution of hydrazone **5.60** (3.98 g, 18.1 mmol, 1.00 equiv) in anhydrous THF dropwise. This was allowed to stir at –78 °C for 30 minutes, allowed to warm up to 0 ℃ for 30 minutes, and then cooled back to –78 °C. To this was

added iodomethane (3.25 g, 22.7 mmol, 1.25 equiv) dropwise. The reaction was allowed to warm up to room temperature overnight. To the reaction was slowly added 2.5 M aqueous HCl solution (65 mL) and then heated to 50 °C for 1 hour. At this point, the hydrazone was fully hydrolyzed and the reaction was basified to pH 9 with saturated aqueous sodium bicarbonate. The crude reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. The crude mixture was purified by column chromatography (10% acetone in hexanes) to afford pure ketone **5.61** as an oil (1.22 g, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 1.2 Hz, 1H), 8.77 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.22 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.42 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H), 3.42 (hex, *J* = 6.8 Hz, 1H), 1.86 – 1.75 (m, 1H), 1.50 – 1.40 (m, 1H), 1.30 (m, *J* = 7.8 Hz, 4H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.89 – 0.84 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 153.2, 149.7, 135.7, 123.7, 41.1, 33.2, 29.5, 22.8, 16.9, 13.9.

FTIR (Neat film NaCl): 3046, 2958, 2931, 2859, 1684, 1584, 1459, 1417, 1376, 1237, 1208, 1116, 1043, 1025, 968, 823, 724, 702, 675, 618.

HR-MS (APCI): Calculated for $[C_{12}H_{17}NO+H]^+$: 192.1383; measured: 192.1377.

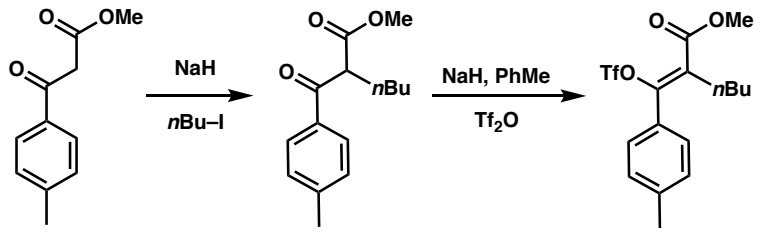


(*E*)-2-methyl-1-(pyridin-3-yl)hex-1-en-1-yl trifluoromethanesulfonate (5.62). Synthesized according to the same procedure as **5.49** starting from 2-methyl-1-(pyridin-3-yl)hexan-1-one **5.61**. Purified by column chromatography (first with 20% ether/hexanes and then 8% acetone/hexanes) to afford pure triflate **5.62** as yellow oil (530 mg, 26%).

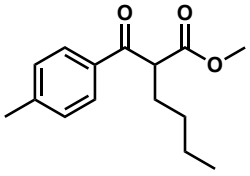
Assignment of the *E* configuration of this substrate was based on key cross peaks in ^{1}H NOESY experiments. There were key NOEs present between the two aromatic protons of pyridine (7.68, 8.61 ppm) and the allylic CH_2 protons (2.03-2.09 ppm). This led to the assignment of the (*E*)-isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.61 (d, *J* = 2.0 Hz, 1H), 7.68 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.35 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 2.09 – 2.03 (m, 2H), 2.00 (s, 3H), 1.50 – 1.40 (m, 2H), 1.24 (hex, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 150.3, 139.0, 137.0, 134.8, 128.9, 123.2, 118.1 (q, $^{1}J_{C-F}$ = 320.1 Hz), 33.1, 29.9, 22.3, 16.5, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.7.

FTIR (Neat film NaCl): 3033, 2961, 2933, 2865, 1588, 1567, 1411, 1207, 1140, 951, 847, 713, 607.
HR-MS (EI-MS): Calculated for $C_{13}H_{16}F_3NO_3S$: 323.0803; measured: 323.0796.



Scheme 5.5. Representative scheme for the synthesis of β–ketoester styrenyl triflates.



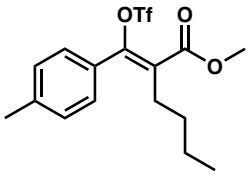
methyl 2-(4-methylbenzoyl)hexanoate (5.63). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (0.87 g, 60% w/w, 22 mmol, 1.4 equiv) and then vacuum and backfilled with N_2 three times. To this was added THF (45 mL), and the solution as

cooled to 0 ºC. To this was added portion wise the respective betaketoester (3.0 g, 16 mmol, 1 equiv) and stirred, 5 minutes, or until H_2 gas evolution had ceased. This solution was brought to reflux, and at 60 ºC the iodobutane (7.1mL, 62 mmol, 4 equiv) was added in one portion. The solution was refluxed overnight, and upon full consumption of the starting material the solution was cooled to room temperature and quenched with water (15 mL) and acidified with aqueous 1 M HCl (5 mL). The aqueous layer was extracted with ether (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash column chromatography (6% EtOAc:pentane) to yield **5.63** as a yellow oil (2.99 g, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.29 (t, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 2.42 (s, 3H), 2.11 – 1.86 (m, 2H), 1.41 – 1.27 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 142.1, 140.8, 131.3, 130.0, 128.3, 126.6, 50.0, 34.1, 33.5, 30.8, 25.7, 20.9, 14.6.

FTIR (Neat Film NaCl): 2955, 2930, 2872, 1738, 1679, 1606, 1455, 1434, 1281, 1252, 1230, 1182, 1121, 1010, 940, 823 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{15}H_{20}O_3$: 248.1412; Measured: 248.1401.

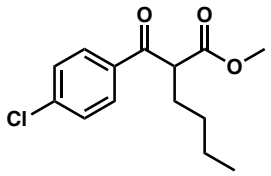


methyl (*Z*)-2-(*p*-tolyl(((trifluoromethyl)sulfonyl)oxy)methylene)hexanoate (5.64). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (170 mg, 60% w/w, 4.35 mmol, 1.8 equiv) followed by dry toluene (20 mL). To this was added dropwise **5.63** (600 mg, 2.4 mmol, 1 equiv). This was heated to 85 ºC for 1.5 hours. The reaction mixture was then cooled to 0 ºC and trifluoromethanesulfonic anhydride (0.57 mL, 3.4 mmol, 1.5 equiv). This was

allowed to stir at 0 ºC for 1h, and then warmed to r.t. overnight. The reaction was diluted with ether (15 mL), followed by addition of satd. aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with ether (3 x 20 mL). The organic layer was dried with Na_2CO_3, filtered, and concentrated. The crude oil was purified by column chromatography (6% ether:hexanes) to give **5.64** as a yellow oil (600 mg, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 2.34 – 2.23 (m, 2H), 1.56 (s, 3H), 1.41 (tdd, *J* = 9.9, 7.4, 3.9 Hz, 2H), 1.33 – 1.21 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 147.5, 140.9, 129.2, 129.0, 128.2, 128.1, 118.3 (q, $^1J_{C–F}$ = 320.2 Hz), 52.3, 30.6, 29.7, 22.2, 21.5, 13.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.55.

FTIR (Neat Film NaCl): 2960, 2934, 2875, 1731, 1421, 1302, 1208, 1139, 969, 842, 608 cm^{-1}.



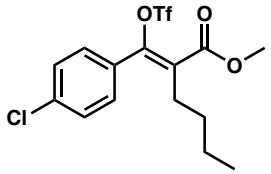
methyl 2-(4-chlorobenzoyl)hexanoate (5.65). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (0.71 g, 60% w/w, 18 mmol, 1.4 equiv) and then vacuum and backfilled with N_2 three times. To this was added THF (41 mL), and the solution as cooled to 0 ºC. To this was added portion wise the respective betaketoester (2.7 g, 13 mmol, 1 equiv) and stirred, 5 minutes, or until H_2 gas evolution had ceased. This solution was brought to reflux, and at 60 ºC the iodobutane (5.8 mL, 51 mmol, 4 equiv) was added in one portion. The solution was refluxed overnight, and upon full consumption of the starting material the solution was cooled to room temperature and quenched with water (15 mL) and acidified with aqueous 1 M HCl (5 mL). The aqueous layer was extracted with ether (3 x 25mL), dried over Na_2SO_4,

filtered, and concentrated. The crude oil was purified by flash column chromatography (6% ether:hexanes) to yield **5.65** as a clear oil (2.4 g, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 4.25 (t, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 2.14 – 1.83 (m, 2H), 1.42 – 1.17 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3, 170.6, 140.4, 134.9, 130.3, 129.4, 54.4, 52.8, 30.0, 29.0, 22.8, 14.1.

FTIR (Neat Film NaCl): 2957, 2932, 2872, 1741, 1686, 1589, 1435, 1400, 1280, 1228, 1178, 1093, 1011,954, 841 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{13}H_{15}ClO_3$: 254.0709; Measured: 254.0202.

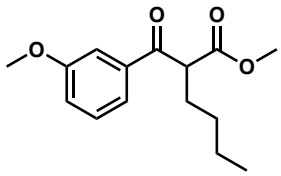


methyl (*Z*)-2-((4-chlorophenyl)(((trifluoromethyl)sulfonyl)oxy)methylene)hexanoate (5.66). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (160 mg, 60% w/w, 2.23 mmol, 1.8 equiv) followed by dry toluene (20 mL). To this was added dropwise **5.65** (600 mg, 4.0 mmol, 1 equiv). This was heated to 85 ºC for 1.5 hours. The reaction mixture was then cooled to 0 ºC and trifluoromethanesulfonic anhydride (0.57 mL, 3.4 mmol, 1.5 equiv). This was allowed to stir at 0 ºC for 1h, and then warmed to r.t. overnight. The reaction was diluted with ether (15 mL), followed by addition of satd. aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with ether (3 x 20 mL). The organic layer was dried with Na_2CO_3, filtered, and concentrated. The crude oil was purified by column chromatography (6% ether:hexanes) to give **5.66** as a clear oil (593 mg, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 3.89 (s, 3H), 2.43 – 2.16 (m, 2H), 1.48 – 1.35 (m, 2H), 1.30 – 1.20 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 146.2, 137.2, 130.9, 129.9, 129.7, 129.4, 118.3 (q, $^1J_{C–F}$ = 320.2 Hz), 52.8, 30.8, 30.1, 22.6, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.47.

FTIR (Neat Film NaCl): 2960, 2934, 2875, 1732, 1490, 1422, 1309, 1295, 1209, 1138, 1091, 1019, 970, 846, 605 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{15}H_{16}ClF_3O_5S$: 400.0359; Measured: 400.0412.



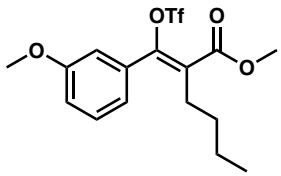
methyl 2-(3-methoxybenzoyl)hexanoate (5.67). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (0.81 g, 60% w/w, 20 mmol, 1.4 equiv) and then vacuum and backilled with N_2 three times. To this was added THF (40 mL), and the solution as cooled to 0 ºC. To this was added portion wise the respective betaketoester (3.0 g, 14 mmol, 1 equiv) and stirred, 5 minutes, or until H_2 gas evolution had ceased. This solution was brought to reflux, and at 60 ºC the iodobutane (6.5 mL, 58 mmol, 4 equiv) was added in one portion. The solution was refluxed overnight, and upon full consumption of the starting material the solution was cooled to room temperature and quenched with water (15 mL) and acidified with aqueous 1 M HCl (5 mL). The aqueous layer was extracted with ether (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash column chromatography (10% EtOAc:hexanes) to yield **5.67** as a yellow oil (2.92 g, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.51 (s, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 4.29 (t, J = 7.2 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 2.06 – 1.93 (m, 2H)

1.42 – 1.25 (m, 4H), 1.03 – 0.81 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.4, 170.9, 160.2, 137.9, 130.0, 121.4, 120.5, 113.0, 55.8, 54.4, 52.8, 30.1, 29.2, 22.8, 14.1.

FTIR (Neat Film NaCl): 2956, 2933, 2872, 2851, 2839, 1749, 1686, 1597, 1582, 1487, 1464, 1433, 1288, 1263, 1222, 1045, 785 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{16}H_{16}F_6O_3S$: 264.1362; Measured: 264.1373.

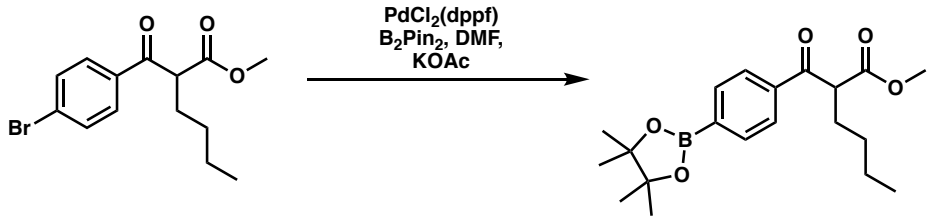


methyl (*Z*)-2-((3-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)methylene)hexanoate (5.68). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (95 mg, 60% w/w, 2.4 mmol, 1.8 equiv) followed by dry toluene (12 mL). To this was added dropwise **5.67** (350 mg, 1.3 mmol, 1 equiv). This was heated to 85 ºC for 1.5 hours. The reaction mixture was then cooled to 0 ºC and trifluoromethanesulfonic anhydride (0.34 mL, 2.0 mmol, 1.5 equiv). This was allowed to stir at 0 ºC for 1h, and then warmed to r.t. overnight. The reaction was diluted with ether (10 mL), followed by addition of satd. aqueous $NaHCO_3$ (8 mL). The aqueous layer was extracted with ether (3 x 15 mL). The organic layer was dried with Na_2CO_3, filtered, and concentrated. The crude oil was purified by column chromatography (10% ether:hexanes) to give **5.68** as a yellow oil (389 mg, 74% yield).

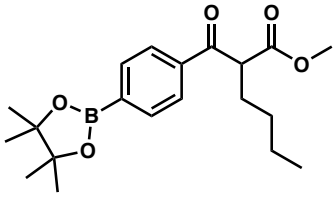
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.9 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 2.0 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 2.45 – 2.22 (m, 2H), 1.43 (tt, J = 7.8, 6.4 Hz, 2H), 1.26 (h, J = 7.3 Hz, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 159.8, 147.3, 132.5, 130.1, 129.0, 121.8, 118.3 (q, $^1J_{C–F}$ = 320.2 Hz), 116.8, 114.7, 55.7, 52.7, 30.9, 30.1, 22.6, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.52.

FTIR (Neat Film NaCl): 2959, 2934, 2875, 2842, 1732, 1599, 1420, 1291, 1244, 1205, 1138, 992, 890, 839, 614 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{16}H_{16}F_6O_3S$: 396.0854; Measured: 396.0853.



Scheme 5.6. Synthesis of aryl pinacolboronate from the corresponding aryl bromide.

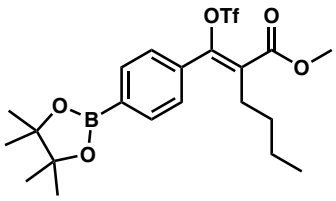


methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl)hexanoate (5.69). To a 50mL Schlenk flask was added bis(pinacolato)diboron (486 mg, 1.92 mmol, 1.2 equiv), $PdCl_2$(dppf) (234 mg, 0.32 mmol, 0.2 equiv), and KOAc (627 mg, 6.4 mmol, 4 equiv). The flask was vacuum evacuated and backfilled with N_2 three times. To the Schlenk flask was added a solution of methyl 2-(4-bromobenzoyl)hexanoate (500 mg, 1.60 mmol, 1 equiv) in degassed DMF (16 mL). The solution was heated to 90 ºC for 24 hours. Upon full consumption of the starting material, the reaction was quenched with saturated aqueous ammonium chloride (10mL). The aqueous layer was extracted with ether (4 x 40 mL). The organic layer was washed with water (5 x 10mL), dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash column chromatography (7 to 10% EtOAc:Hex) to yield **5.69** as a clear oil (381 mg, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 4.32 (t, *J* = 7.1 Hz, 1H), 3.67 (s, 3H), 2.18 – 1.86 (m, *J* = 7.2, 6.7 Hz, 2H), 1.35 (s, 12H), 1.33 – 1.30 (m, 4H), 0.92 – 0.85 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.6, 170.5, 138.1, 135.0, 127.5, 84.2, 54.1, 52.4, 29.7, 28.7, 22.5, 13.8. *Note*: Carbon attached to boron not seen due to relaxation on B. ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.60.

FTIR (Neat Film NaCl): 2978, 2982, 2957, 1741, 1686, 1508, 1459, 1399, 1358, 1329, 1275, 1142, 1123, 1088, 1018, 961, 855, 652 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{20}H_{29}BO_5$: 360.2108; Measured: 360.2111.

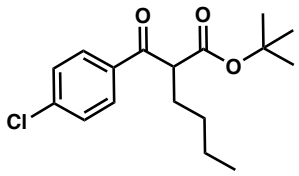


methyl (*Z*)-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(((trifluoromethyl)sulfonyl)oxy)methylene)hexanoate (5.70). To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (76 mg, 60% w/w, 1.90 mmol, 1.8 equiv) followed by dry toluene (10 mL). To this was added dropwise **5.69** (381 mg, 1.1 mmol, 1 equiv). This was heated to 85 ºC for 1.5 hours. The reaction mixture was then cooled to 0 ºC and trifluoromethanesulfonic anhydride (0.27 mL, 1.6 mmol, 1.5 equiv). This was allowed to stir at 0 ºC for 1h, and then warmed to r.t. overnight. The reaction was diluted with ether (10 mL), followed by addition of satd. aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ether (3 x 15 mL). The organic layer was dried with Na_2CO_3, filtered, and concentrated. The crude oil was purified by column chromatography (10% ether:hexanes) to give **5.70** as a clear oil (118 mg, 23% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 7.7 Hz, 2H), 3.89 (s, 3H), 2.29 (t, J = 7.7 Hz, 2H), 1.36 (s, 12H), 1.30 – 1.14 (m, 4H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 147.1, 134.8, 133.5, 128.8, 128.3, 118.3 (q, $^{1}J_{C–F}$ = 320.2 Hz), 84.2, 52.4, 30.5, 29.7, 24.9, 22.2, 13.6. *Note*: Carbon attached to boron not seen due to relaxation on B. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.5. ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.1.

FTIR (Neat Film NaCl): 2978, 2960, 2934, 2874, 1733, 1610, 1422, 1399, 1361, 1209, 1143, 1088, 962, 854, 658, 604 cm^{-1}.

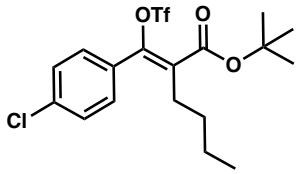
HRMS (EI-MS): Calculated for $C_{21}H_{28}BF_3O_7S$: 492.1600; Measured: 492.1598.



***tert*-butyl 2-(4-chlorobenzoyl)hexanoate (5.71).** To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (510 mg, 60% w/w, 13 mmol, 1.4 equiv) and then vacuum and backfilled with N_2 three times. To this was added THF (30 mL), and the solution as cooled to 0 ºC. To this was added drop wise the corresponding betaketoester (2.3 g, 9.0 mmol, 1 equiv) and stirred, 5 minutes, or until H_2 gas evolution had ceased. This solution was brought to reflux, and at 60 ºC the iodobutane (4.1 mL, 36 mmol, 4 equiv) was added in one portion. The solution was refluxed overnight, and upon full consumption of the starting material the solution was cooled to room temperature and quenched with water (10mL). The aqueous layer was extracted with ether (3x25mL), dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash column chromatography (4% ether:hexanes) to yield **5.71** as a yellow oil (1.28 g, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 4.13 (t, *J* = 7.1 Hz, 1H), 1.99 (q, *J* = 7.3, 6.9 Hz, 2H), 1.39 (s, 9H), 1.37 (m, 4H), 0.94 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.7, 169.3, 140.0, 135.2, 130.2, 129.2, 82.2, 55.9, 30.0, 28.7, 28.1, 22.9, 14.2.

FTIR (Neat Film NaCl): 2976, 2963, 2935, 2873, 1734, 1689, 1590, 1489, 1456, 1399, 1368, 1332, 1285, 1254, 1232, 1150, 1092, 1012, 841 cm^{-1}.

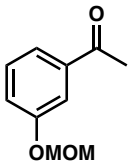


***tert*-butyl (*Z*)-2-((4-chlorophenyl)(((trifluoromethyl)sulfonyl)oxy)methylene)hexanoate (5.72).** To a 3-neck flask equipped with a reflux condenser and a stir bar was added NaH (120 mg, 60% w/w, 1.90 mmol, 1.8 equiv) followed by dry toluene (14mL). To this was added dropwise **5.71** (500 mg, 1.6 mmol, 1 equiv). This was heated to 85 ºC for 1.5 hours. The reaction mixture was then cooled to 0 ºC and trifluoromethanesulfonic anhydride (0.41 mL, 2.4 mmol, 1.5 equiv). This was allowed to stir at 0 ºC for 1h, and then warmed to r.t. overnight. To the reaction was added triethylamine (3 mL) to quench any remaining trifluoromethane sulfonic acid, diluted with ether (10 mL), followed by addition of satd. aqueous $NaHCO_3$. The aqueous layer was extracted with ether (3x20mL). The organic layer was dried with Na_2CO_3, filtered, and concentrated. The crude oil was purified by column chromatography on triethylamine deactivated silica gel (10% ether:hexanes + 0.5% triethylamine) to give **5.72** as a yellow solid (300 mg, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 2.30 – 2.15 (m, 2H), 1.58 (s, 9H), 1.47 – 1.36 (m, 2H), 1.30 – 1.23 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 165.1, 143.9, 137.0, 133.1, 131.5, 131.1, 129.3, 118.3 (q, $^1J_{C-F}$ = 320.2 Hz), 84.2, 30.4, 30.2, 28.2, 22.5, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.30.

FTIR (Neat Film NaCl): 2951, 2933, 2874, 1724, 1594, 1489, 1422, 1370, 1310, 1296, 1210, 1145, 1092, 1018, 969, 846, 606 cm^{-1}.

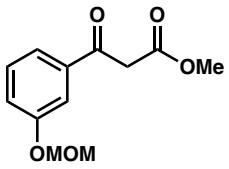


1-(3-(methoxymethoxy)phenyl)ethan-1-one (5.73). To a stirring solution of 3-hydroxyacetophenone (10.0g, 74 mmol, 1 equiv) in DCM (221 mL) at 0 °C was added diisopropylethylamine (26 mL, 147 mmol, 2 equiv). Subsequently bromo(methoxy)methane (7.2 mL, 88 mmol, 1.2 equiv) was added. This was allowed to stir at 0 °C for 30 minutes and then allowed to warm to room temperature. Upon completion, water was added to the reaction. The layers were separated and the organic layer was washed with 1M NaOH, followed by brine. The organic layer was dried with $MgSO_4$, filtered and concentrated. The crude oil was purified by column chromatography (10% EtOAc:Hex) to give **5.73** as an oil (9.8g, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.54 (m, 2H), 7.38 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.24 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 5.22 (s, 2H), 3.49 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 157.5, 138.6, 129.7, 122.1, 121.2, 115.7, 94.5, 56.2, 26.8.

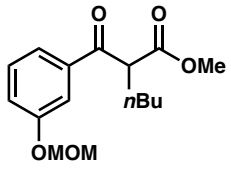
HRMS (EI-MS): Calculated for $C_{10}H_{12}O_3$: 180.0786; Measured: 180.0786.



methyl 3-(3-(methoxymethoxy)phenyl)-3-oxopropanoate (5.74). To a stirring solution of NaH (8.7g, 60%w/w, 218 mmol, 4 equiv) in THF (326 mL) was added dimethyl carbonate (13.7 mL, 163 mmol, 3 equiv) and then **5.73** (9.8g, 54 mmol, 1 equiv). This was then heated to 70 °C until complete conversion was observed. This was neutralized (pH 7) with 1 M HCl and then extracted with EtOAc. The organics were then washed with water and brine. The organics were dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by column chromatography (20% ether:hexanes) to give **5.74** as an oil (9.4g, 73% yield, 1.8:1 keto:enol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.47 (s, 1H), 7.61 (t, J = 2.1 Hz, 3H), 7.59 – 7.54 (m, 2H), 7.45 (t, J = 2.1 Hz, 1H), 7.43 – 7.38 (m, 4H), 7.33 (t, J = 8.0 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.14 (ddd, J = 8.2, 2.2, 1.2 Hz, 1H), 5.66 (s, 1H), 5.22 (s, 2H), 5.21 (s, 2H), 3.99 (d, J = 0.5 Hz, 5H), 3.80 (s, 1H), 3.76 (s, 3H), 3.49 (s, 7H), 3.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.1, 173.5, 171.2, 168.0, 157.6, 157.5, 137.4, 134.9, 130.0, 129.7, 122.2, 122.0, 119.7, 119.3, 115.9, 114.0, 94.5, 87.4, 56.2, 56.2, 52.6, 51.5, 45.9.

HRMS (EI-MS): Calculated for $C_{12}H_{14}O_5$: 238.0841; Measured: 238.0841.

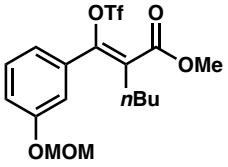


methyl 2-(3-(methoxymethoxy)benzoyl)hexanoate (5.75). To a stirring solution of NaH (1.7 g, 60% w/w, 43 mmol, 1.1 equiv) in THF (79 mL), at 0 ºC was added **5.74** (9.40 g, 39 mmol, 1 equiv) portion-wise. This was stirred at room temperature until H_2 gas evolution had ceased. To

the reaction mixture was added 1-iodobutane (29.0 g, 158 mmol, 4 equiv) at room temperature and then the reaction was heated to 60 ºC and refluxed overnight. Upon full consumption of the starting material, the solution was cooled to room temperature and quenched with water and neutralized with aqueous 1 M HCl. The aqueous layer was extracted with ether, dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash column chromatography to yield **5.75** as an oil (4.58 g, 39% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.63 – 7.58 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 3.0 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 0H), 5.21 (s, 3H), 4.28 (t, *J* = 7.2 Hz, 2H), 3.68 (s, 5H), 3.49 (s, 5H), 1.99 (p, *J* = 6.8 Hz, 3H), 1.37 – 1.29 (m, 3H), 0.89 (t, *J* = 7.0 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.0, 170.6, 157.7, 137.7, 129.9, 122.2, 121.7, 116.1, 94.6, 56.2, 54.2, 52.5, 29.9, 29.0, 22.6, 13.9.

HRMS (CI-MS): Calculated for $[C_{16}H_{22}O_5+H]^+$: 295.1545; Measured: 295.1532.



methyl (*Z*)-2-((3-(methoxymethoxy)phenyl)(((trifluoromethyl)sulfonyl)oxy)methylene) hexanoate (5.76). To a stirring solution of NaH (610 mg, 60% w/w, 15.3 mmol, 1.8 equiv) in toluene (8 mL) was added a solution of **5.75** (2.5g, 8.5 mmol, 1 equiv) in toluene (9 mL). After H_2 gas evolution ceased, the reaction was heated to 80 °C for 1 hr. The reaction mixture was then cooled to 0 °C and triflic anhydride (3.6g, 12.7 mmol, 1.5 equiv) was added and this was allowed to stir at 0 °C for 1 hr and then warmed to room temperature overnight. The reaction was diluted with diethyl ether followed by addition of satd. aqueous $NaHCO_3$. The aqueous layer was then extracted with ether (3 x 20 mL). The organics were dried over $MgSO_4$, filtered and

concentrated. The crude oil was purified by column chromatography (5% ether:hexanes) to give **5.76** as an oil (3.1g, 86% yield).

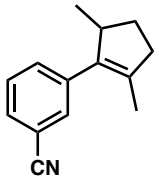
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (ddd, *J* = 8.2, 7.6, 0.6 Hz, 1H), 7.13 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 0H), 7.11 (t, *J* = 2.0 Hz, 1H), 7.05 (ddd, *J* = 7.6, 1.6, 1.1 Hz, 1H), 5.18 (s, 1H), 3.89 (s, 2H), 3.47 (s, 1H), 2.37 – 2.27 (m, 1H), 1.43 (tt, *J* = 7.8, 6.3 Hz, 1H), 1.27 (h, *J* = 7.3 Hz, 1H), 0.83 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 157.3, 147.0, 132.3, 129.8, 128.8, 122.7, 121.3 (q, *J* = 320.3 Hz), 118.8, 117.0, 94.6, 56.0, 52.5, 30.7, 29.9, 22.4, 13.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.58.

HRMS (EI-MS): Calculated for $C_{17}H_{21}F_3O_7S$: 426.0960; Measured: 426.0947.

5.7.2.3 Catalytic Reactions

5.7.2.3.1 General Procedure for Dialkyl Styrenyl Triflates

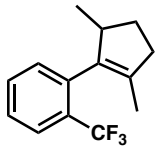
In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), an oven dried 1-dram vial with a magnetic stir bar was added urea catalyst **5.4** (0.005 mmol, 0.2 equiv) followed by LiH (0.075–0.125 mmol, 3–5 equiv). *o*-DFB (1.5 mL) was added and this was allowed to stir at room temperature for 5 minutes. To this was added the substrate (0.025 mmol, 1.0 equiv) and the reaction was heated to 70 °C. Upon completion of reaction, the mixture was diluted with ether and pushed through a pipette of silica gel. This was concentrated to give the crude material. The crude material was purified by silica flash chromatography to give the pure product.



3-(2,5-dimethylcyclopent-1-en-1-yl)benzonitrile (5.23) Synthesized according to general procedure 5.7.2.3.1 using triflate **5.49**, heating to 70 ºC for 24 hrs. The reaction vial was removed from the glove box, diluted with ether and plugged through silica gel with dichloromethane and concentrated. The crude oil was purified by flash column chromatography (2% ether:hexanes) to yield **5.23** as a clear oil (7.6 mg, 77% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dt, *J* = 7.1, 1.8 Hz, 0H), 7.47 – 7.45 (m, 0H), 7.45 – 7.39 (m, 1H), 3.15 (dddt, *J* = 8.5, 6.4, 4.3, 2.1 Hz, 0H), 2.59 – 2.45 (m, 0H), 2.44 – 2.31 (m, 0H), 2.22 (dddd, *J* = 12.8, 9.1, 8.2, 4.5 Hz, 0H), 1.79 – 1.64 (m, 1H), 1.52 – 1.40 (m, 0H), 0.92 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 138.8, 137.4, 132.9, 132.0, 129.6, 128.9, 119.3, 112.3, 43.3, 38.0, 31.4, 20.2, 15.4.

HR-MS (EI-MS): Calculated for $C_{14}H_{15}N$: 197.1205; Measured: 197.1204.



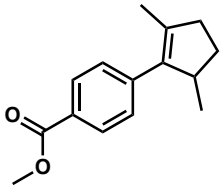
1-(2,5-dimethylcyclopent-1-en-1-yl)-2-(trifluoromethyl)benzene (5.24). Synthesized according to a slightly modified general procedure 5.7.2.3.1. To a 20 mL vial with a magnetic stir bar was added 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (9.6 mg, 0.02 mmol, 0.20 equiv). LiH (2.9 mg, 0.30 mmol, 3.0 equiv) was added followed by 1,2-difluorobenzene (6 mL). After a five minute prestir, vinyl triflate **5.53** (39.0 mg, 0.10 mmol, 1 equiv) was added. The reaction was heated to 70 °C. After 2 hours, the reaction was cooled to room temperature and removed

from the glovebox. The reaction was concentrated and then suspended in ether and pushed through a pad of silica. This was concentrated to give crude product as yellow solid. This was purified by silica flash column chromatography (3% ether/hexanes) to give cyclopentyl product **5.24** as colorless oil (21.6 mg, 90% yield, 0.90 mmol).

This compound exists as a mixture of rotamers at room temperature.

Major Rotamer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 1H), 7.53 – 7.45 (m, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 2.99 (s, 1H), 2.39 (t, J = 6.8 Hz, 2H), 2.22 (dtd, J = 12.3, 7.8, 6.1 Hz, 1H), 1.53 – 1.46 (m, 1H), 1.44 (s, 3H), 0.90 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 138.1 (q, $^3J_{C–F}$ = 2.5 Hz), 136.8, 132.3, 131.0, 128.9 (q, $^2J_{C–F}$ = 29.7 Hz), 126.5, 125.9 (q, J = 5.4 Hz), 124.3 (q, $^1J_{C–F}$ = 273.6 Hz), 44.6 (q, $^3J_{C–F}$ = 2.3 Hz), 36.7, 32.3, 19.9, 15.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.7.



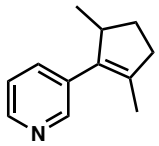
methyl 4-(2,5-dimethylcyclopent-1-en-1-yl)benzoate (5.25). Synthesized according to general procedure 5.7.2.3.1 using triflate **5.58**, heating to 70 ºC for 6h. The reaction vial was removed from the glove box and plugged through silica gel with ether and concentrated. The crude oil was purified by flash column chromatography (4% acetone:hexanes) to yield **5.25** as a clear oil (5.2 mg, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 3.91 (s, 2H), 3.16 – 3.23 (m, 1H), 2.46 – 2.54 (m, 1H), 2.33 – 2.41 (m, 1H), 2.22 (dtt, J = 12.9, 8.6, 4.5 Hz,

1H), 1.76 (s, 3H), 1.50 – 1.43 (m, 1H), 0.93 (d, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 143.5, 140.3, 137.2, 129.6, 128.6, 127.9, 52.3, 43.5, 38.4, 31.6, 20.5, 15.8.

FTIR (Neat Film NaCl): 2952, 2927, 2866, 2840, 1722, 1607, 1435, 1275, 1177, 1109, 1000, 857, 775, 709 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{16}H_{16}F_6O_3S$: 230.1307; Measured: 230.1299.



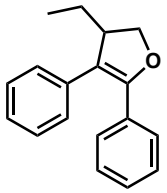
3-(2,5-dimethylcyclopent-1-en-1-yl)pyridine (5.26). Synthesized according to a slightly modified general procedure 5.7.2.3.1. To a 20 mL vial with a magnetic stir bar was added 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (9.6 mg, 0.02 mmol, 0.20 equiv). LiHMDS (56.5 mg, 0.34 mmol, 3.4 equiv) was added followed by cyclohexane (6 mL). After a five minute prestir, vinyl triflate **5.62** (32.3 mg, 0.10 mmol, 1 equiv) was added. The reaction was heated to 70 °C. After 4 hours, the reaction was cooled to room temperature and removed from the glovebox. The reaction was concentrated and then suspended in ether and pushed through a pad of silica. This was concentrated to give crude product as dark solid (80% NMR yield). This was purified by silica flash column chromatography (1% MeOH/DCM) and then another flash column chromatography (1:25:175 triethylamine:ethyl acetate:hexanes). This gave cyclopentyl product **5.26** as colorless oil (10.6 mg, 61% yield, 0.061 mmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.43 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 4.8, 1.7 Hz, 1H), 7.49 (dt, J = 7.8, 2.0 Hz, 1H), 7.25 (ddd, J = 7.8, 4.8, 0.9 Hz, 1H), 3.22 – 3.12 (m, 1H), 2.60 – 2.46 (m, 1H), 2.44 – 2.32 (m, 1H), 2.22 (dddd, J = 12.8, 9.0, 8.1, 4.7 Hz, 1H), 1.74 (dt, J = 2.2, 1.2 Hz,

3H), 1.48 (dddd, *J* = 12.8, 9.3, 6.8, 6.1 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.7, 147.2, 137.4, 137.1, 135.5, 133.8, 123.0, 43.2, 37.9, 31.4, 19.9, 15.1.

FTIR (Neat film NaCl): 3083, 3032, 2954, 2928, 2864, 2842, 1654, 1563, 1479, 1453, 1409, 1377, 1324, 1268, 1186, 1100, 1026, 1001, 957, 807, 716, 617.

HR-MS (EI-MS): Calculated for $C_{12}H_{15}N$: 173.1205; Measured: 173.1199.



3-ethyl-4,5-diphenyl-2,3-dihydrofuran (5.27). Synthesized according to a slightly modified general procedure 5.7.2.3.1. To an 1-dram vial with a magnetic stir bar in the glove box was added LiOtBu (9.0 mg, 0.11mmol, 1.5 equiv), 3,4-bis((3,5-bis(trifluoromethyl)phenyl)amino) cyclobut-3-ene-1,2-dione **5.9** (8.0 mg, 0.015mmol, 0.2 equiv), 1.5 ml DCE, 0.1 ml hexanes. This was allowed to prestir at room temperature for 1 hour. Then triflate **5.54** (30.0 mg, 0.075 mmol, 1 equiv) was added. The reaction was heated to 70 °C for 12 hours then 90 °C for another 12 hours. The reaction was diluted with ether and pushed through a pad of silica. The crude material was purified by silica flash chromatography (3% acetone/hexanes) to give pure **5.27** as colorless oil (11.5 mg, 61%, 0.046 mmol).

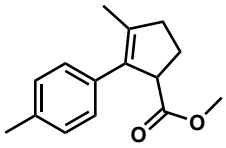
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.44 – 7.33 (m, 2H), 7.32 – 7.26 (m, 2H), 7.26 – 7.04 (m, 6H), 4.60 (dd, J = 9.8, 8.8 Hz, 1H), 4.24 (dd, J = 8.8, 7.0 Hz, 1H), 3.50 (dddd, J = 10.3, 9.0, 6.9, 3.5 Hz, 1H), 1.62 (dqd, J = 13.7, 7.5, 3.5 Hz, 1H), 1.47 – 1.36 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 150.0, 135.4, 131.8, 128.7, 128.3, 128.1, 127.9, 127.5, 126.1, 114.7, 73.2, 49.0, 25.4, 10.5.

FTIR (Neat film NaCl): 3079, 3055, 3025, 2959, 2929, 2873, 1950, 1886, 1808, 1650, 1601, 1497, 1446, 1365, 1233, 1094, 1067, 1016, 985, 950, 916, 761, 694, 674, 580, 493

HR-MS (EI-MS) Calculated for $C_{18}H_{18}O$: 250.1358; measured: 250.1354

5.7.2.3.2 General Procedure for β-Keto Ester Styrenyl Triflates

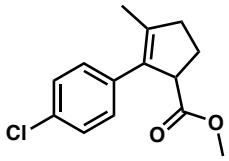
In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), an oven dried 1-dram vial with a magnetic stir bar was added urea catalyst **5.4** (0.2 equiv, 0.005 mmol) followed by LiH (0.075–0.125 mmol, 3–5 equiv). *o*-DFB (1.5 mL) was added and this was allowed to stir at room temperature for 5 minutes. To this was added the substrate (0.025 mmol, 1.0 equiv) and the reaction was heated to 70 °C. Upon completion of reaction, the mixture was diluted with ether and pushed through a pipette of silica gel. This was concentrated to give the crude material. The crude material was purified by silica flash chromatography to give the pure product.



methyl 3-methyl-2-(*p*-tolyl)cyclopent-2-ene-1-carboxylate (5.30). Synthesized according to a slightly modified general procedure 5.7.2.3.2. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with urea **5.4** (4.8 mg, 0.01 mmol, 0.2 equiv) and LiH (1.2 mg, 0.3 mmol, 3 equiv) followed by dry 1,2-difluorobenzene (3 mL). To this was added **5.64** (19 mg, 0.05 mmol, 1 equiv) and heated to 70 ºC for 3h. The reaction vial was removed from the glove box and plugged through silica gel with ether and concentrated. The crude oil was purified by flash column chromatography (2% ether:hexanes) to yield **5.30** as a yellow oil (7.4 mg, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 4H), 3.96 (dddd, *J* = 7.7, 5.8, 4.1, 2.1 Hz, 1H), 3.54 (s, 3H), 2.75 – 2.58 (m, 1H), 2.46 (dt, *J* = 16.2, 7.5 Hz, 1H), 2.26 (dtd, *J* = 13.0, 9.0, 5.4 Hz, 1H), 2.11 (ddt, *J* = 13.0, 9.2, 5.7 Hz, 1H), 1.82 (s, 3H).

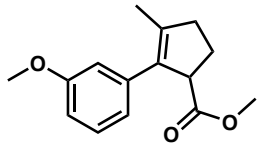
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 143.5, 140.3, 137.2, 129.6, 128.6, 127.9, 52.3, 43.5, 38.4, 31.6, 20.4, 15.8.



methyl 2-(4-chlorophenyl)-3-methylcyclopent-2-ene-1-carboxylate (5.31) Synthesized according to a slightly modified general procedure 5.7.2.3.2. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with urea catalyst **5.4** (4.8 mg, 0.01 mmol, 0.2 equiv) and LiH (1.2 mg, 0.3 mmol, 3 equiv) followed by dry 1,2-difluorobenzene (3 mL). To this was added **5.66** (20 mg, 0.05 mmol, 1 equiv) and heated to 70 ºC for 36h. The reaction vial was removed from the glove box and plugged through silica gel with ether and concentrated. The crude oil was purified by flash column chromatography (60% DCM:hexanes) to yield **5.31** as a clear oil (6.6 mg, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 3.94 (td, *J* = 6.4, 5.7, 2.5 Hz, 1H), 3.54 (s, 3H), 2.76 – 2.60 (m, 1H), 2.47 (dt, *J* = 15.9, 7.5 Hz, 1H), 2.37 – 2.18 (m, 1H), 2.21 – 2.02 (m, 1H), 1.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 140.6, 135.6, 133.0, 132.5, 129.6, 128.6, 54.9, 52.0, 39.0, 27.5, 15.7.

FTIR (Neat Film NaCl): 2950, 2844, 1734, 1491, 1434, 1337, 1251, 1194, 1165, 1092, 1013, 832 cm^{-1}.

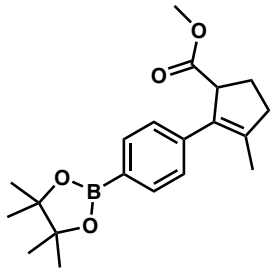


methyl 2-(3-methoxyphenyl)-3-methylcyclopent-2-ene-1-carboxylate (5.32). Synthesized according to general procedure 5.7.2.3.2. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with urea catalyst **5.4** (4.8 mg, 0.01 mmol, 0.2 equiv) and LiH (1.2 mg, 0.3 mmol, 3 equiv) followed by dry 1,2-difluorobenzene (3 mL). To this was added **5.68** (19.8 mg, 0.05 mmol, 1 equiv) and heated to 70 ºC for 5h. The reaction vial was removed from the glove box and plugged through silica gel with ether and concentrated. The crude oil was purified by flash column chromatography (2% acetone:hexanes) to yield **5.32** as a yellow oil (6.1 mg, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 1H), 6.81 (dt, *J* = 7.6, 1.3 Hz, 1H), 6.79 – 6.74 (m, 2H), 4.00 – 3.90 (m, 1H), 3.80 (s, 3H), 3.55 (s, 3H), 2.77 – 2.56 (m, 1H), 2.47 (dt, *J* = 16.0, 7.5 Hz, 1H), 2.27 (dtd, *J* = 12.9, 9.0, 5.3 Hz, 1H), 2.11 (ddt, *J* = 13.0, 9.3, 5.8 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 159.6, 140.1, 138.6, 134.0, 129.3, 120.8, 113.9, 112.4, 55.4, 55.0, 52.0, 39.0, 27.6, 15.8.

FTIR (Neat Film NaCl): 2950, 2842, 1733, 1599, 1577, 1487, 1454, 1432, 1339, 1287, 1231, 1165, 1047, 877, 788, 700 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{16}H_{16}F_6O_3S$: 246.1256; Measured: 246.1252.

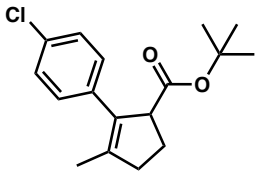


methyl 3-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopent-2-ene-1-carboxylate (5.33). Synthesized according to general procedure 5.7.2.3.2. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with urea catalyst **5.4** (2.4 mg, 0.005 mmol, 0.2 equiv) and LiH (0.6 mg, 0.15 mmol, 3 equiv) followed by dry 1,2-difluorobenzene (1.5 mL). To this was added **5.70** (12.3 mg, 0.025 mmol, 1 equiv) and heated to 70 ºC for 4h. The reaction vial was removed from the glove box and plugged through silica gel with ether and concentrated. The crude oil was purified by flash column chromatography (20% ether:hexanes) to yield **5.33** as a clear oil (3.5 mg, 41% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.08 – 3.92 (m, 1H), 3.51 (s, 3H), 2.76 – 2.61 (m, 1H), 2.55 – 2.41 (m, 1H), 2.27 (dtd, *J* = 13.0, 9.0, 5.2 Hz, 1H), 2.12 (ddt, *J* = 13.0, 9.2, 6.0 Hz, 1H), 1.82 (s, 1H), 1.34 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 140.5, 140.1, 134.8, 134.1, 127.6, 84.0, 54.9, 52.0j, 39.1, 27.6, 25.2, 15.7. *Note*: Carbon attached to boron not seen due to relaxation on B. ^{11}B NMR (161 MHz, $CDCl_3$) δ 30.78.

FTIR (Neat Film NaCl): 2977, 2955, 2928, 2854, 1735, 1609, 1435, 1398, 1361, 1822, 1276, 1165, 1144, 1091cm^{-1}.

HRMS (EI-MS): Calculated for $C_{20}H_{27}BO_4$: 342.2002; Measured: 342.1997.

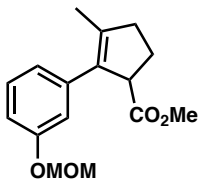


***tert*-butyl 2-(4-chlorophenyl)-3-methylcyclopent-2-ene-1-carboxylate (5.34).** Synthesized according to a slightly modified general procedure 5.7.2.3.2. In a well kept glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with urea catalyst **5.4** (4.8 mg, 0.01 mmol, 0.2 equiv) and LiH (1.2 mg, 0.15 mmol, 3 equiv) followed by dry 1,2-difluorobenzene (3 mL). To this was added **5.72** (22.1 mg, 0.050 mmol, 1 equiv) and heated to 70 ºC for 5h. The reaction vial was removed from the glove box and plugged through silica gel with ether and concentrated. The crude oil was purified by flash column chromatography (40% dichloromethane:hexanes followed by 3% acetone:hexanes) to yield **5.34** as a clear oil (5.6 mg, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 3.82 (bs, 1H), 2.61 – 2.68 (m, 1H), 2.40 – 2.48 (m, 1H), 2.26 – 2.02 (m, 1H), 1.79 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 139.9, 135.9, 133.6, 132.3, 130.0, 128.3, 80.5, 56.0, 38.9, 28.1, 26.9, 15.6.

FTIR (Neat Film NaCl): 2975, 2930, 2856, 1726, 1491, 1455, 1367, 1278, 1148, 1092, 1014, 833 cm^{-1}.

HRMS (EI-MS): Calculated for $C_{16}H_{16}F_6O_3S$: 292.1230; Measured: 292.1219.



methyl 2-(3-(methoxymethoxy)phenyl)-3-methylcyclopent-2-ene-1-carboxylate (5.35). Synthesized according to a slightly modified general procedure 5.7.2.3.2. In a well kept

glovebox, (H_2O, O_2 < 0.5 ppm), a dram vial was charged with the urea catalyst **5.4** (2.4 mg, 0.005 mmol, 0.2 equiv) and LiH (2.0 mg, 0.25 mmol, 10 equiv) followed by dry 1,2-difluorobenzene (1.5 mL). This mixture was sealed and heated to 70 °C for 30 minutes. After cooling to room temperature, to this was added **5.76** (10.7 mg, 0.025 mmol, 1 equiv) and heated to 90 ºC overnight. The reaction vial was removed from the glove box, diluted with ether, and plugged through silica gel with dichloromethane and concentrated. The crude oil was purified by flash column chromatography (90:5:5 hexanes:dichloromethane:ether) to yield **5.35** as a clear oil (2.5 mg, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (td, *J* = 7.7, 0.8 Hz, 1H), 6.91 (d, *J* = 1.1 Hz, 1H), 6.89 – 6.84 (m, 2H), 5.16 (s, 2H), 3.55 (s, 3H), 3.48 (s, 3H), 2.74 – 2.63 (m, 1H), 2.46 (dddd, *J* = 16.4, 9.0, 5.8, 1.4 Hz, 1H), 2.26 (dtd, *J* = 12.9, 9.0, 5.4 Hz, 1H), 2.11 (ddt, *J* = 13.0, 9.2, 5.8 Hz, 1H), 1.83 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 157.1, 140.0, 138.4, 133.5, 129.2, 121.8, 116.1, 114.5, 94.6, 56.1, 54.8, 51.8, 38.8, 27.4, 15.6.

5.8 Spectra Relevant to Chapter Five:

Urea and Lithium/Urea Organocatalysts Catalyze C–C Bond-Forming Reactions of Vinyl Cations

Adapted from: Alex L. Bagdasarian, Stasik Popov, Benjamin Wigman, Wenjing Wei, Woojin Lee, Hosea M. Nelson

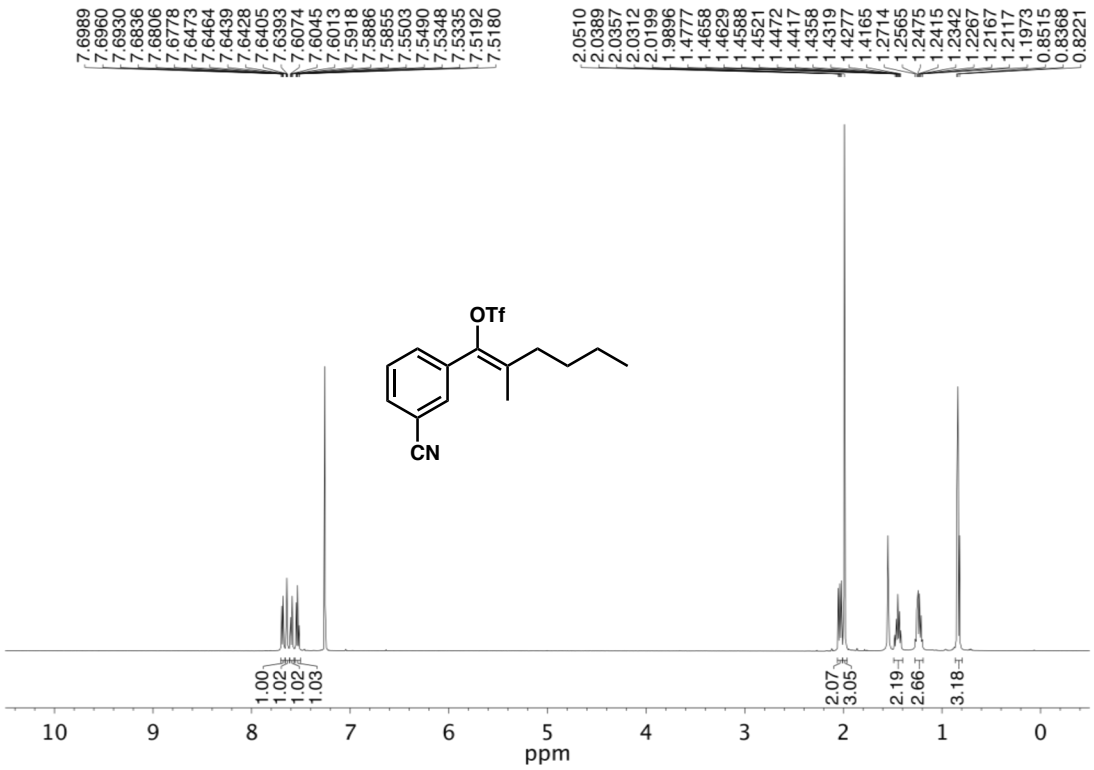


Figure 5.6. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.53**.

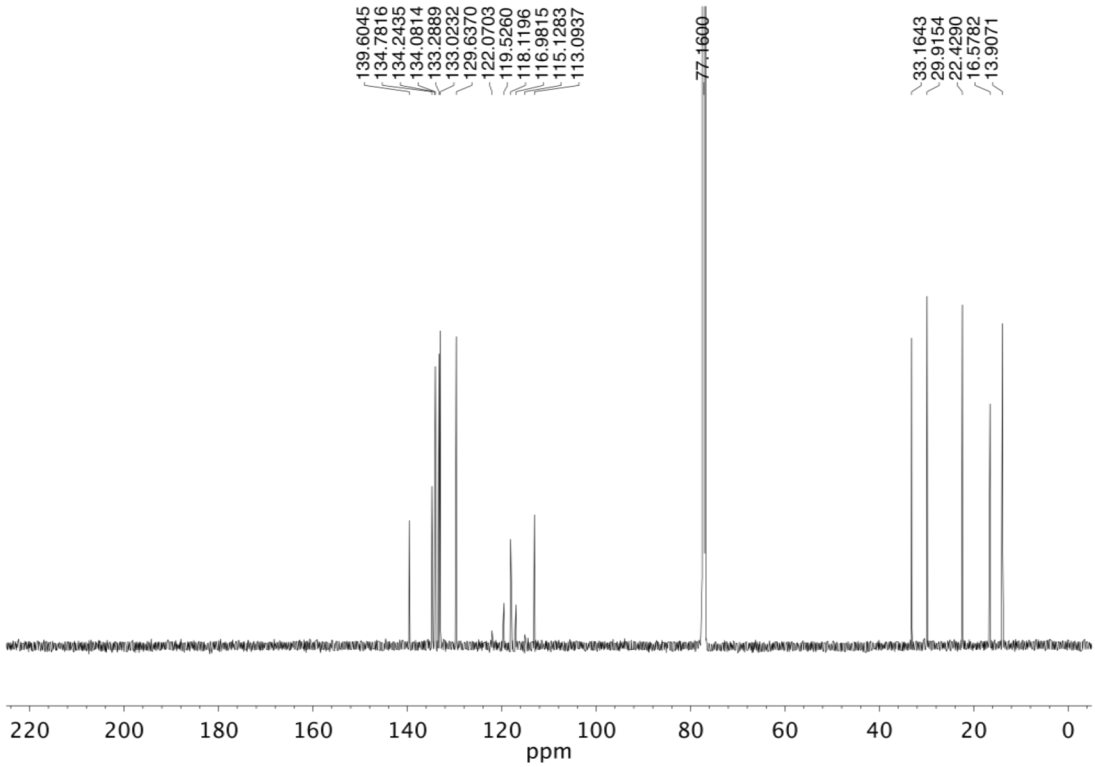


Figure 5.7. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.53**.

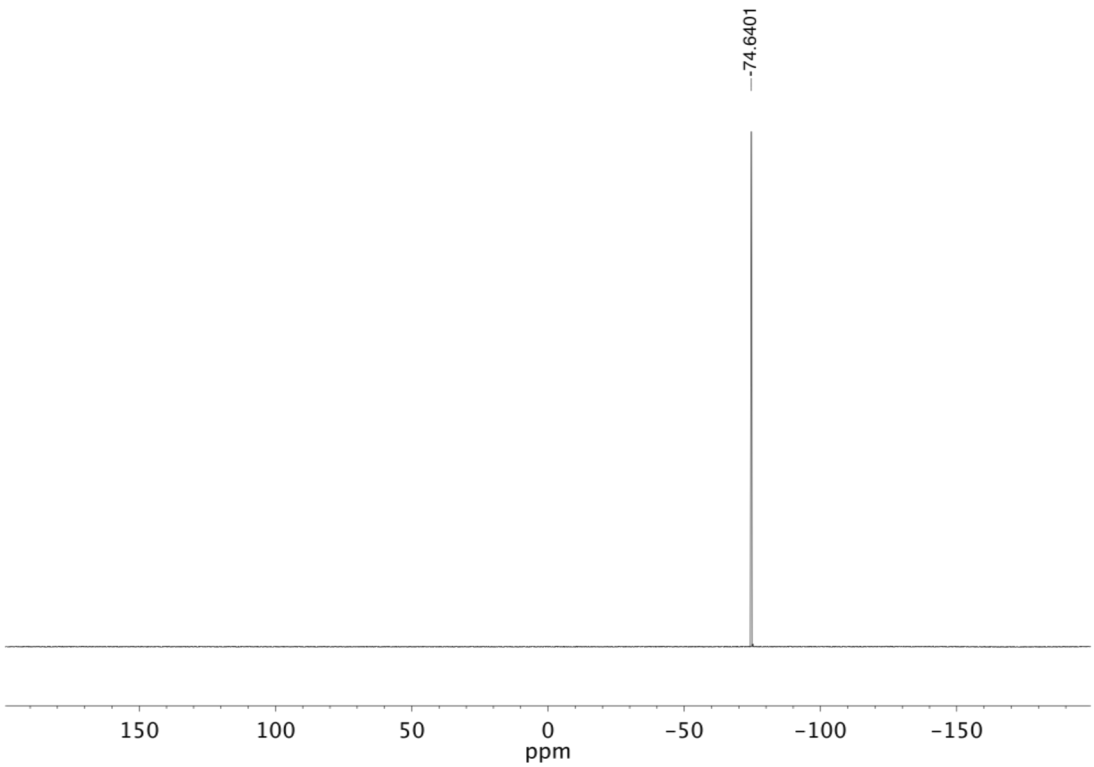


Figure 5.8. ^{19}F NMR (376 MHz, $CDCl_3$) of **5.53**.

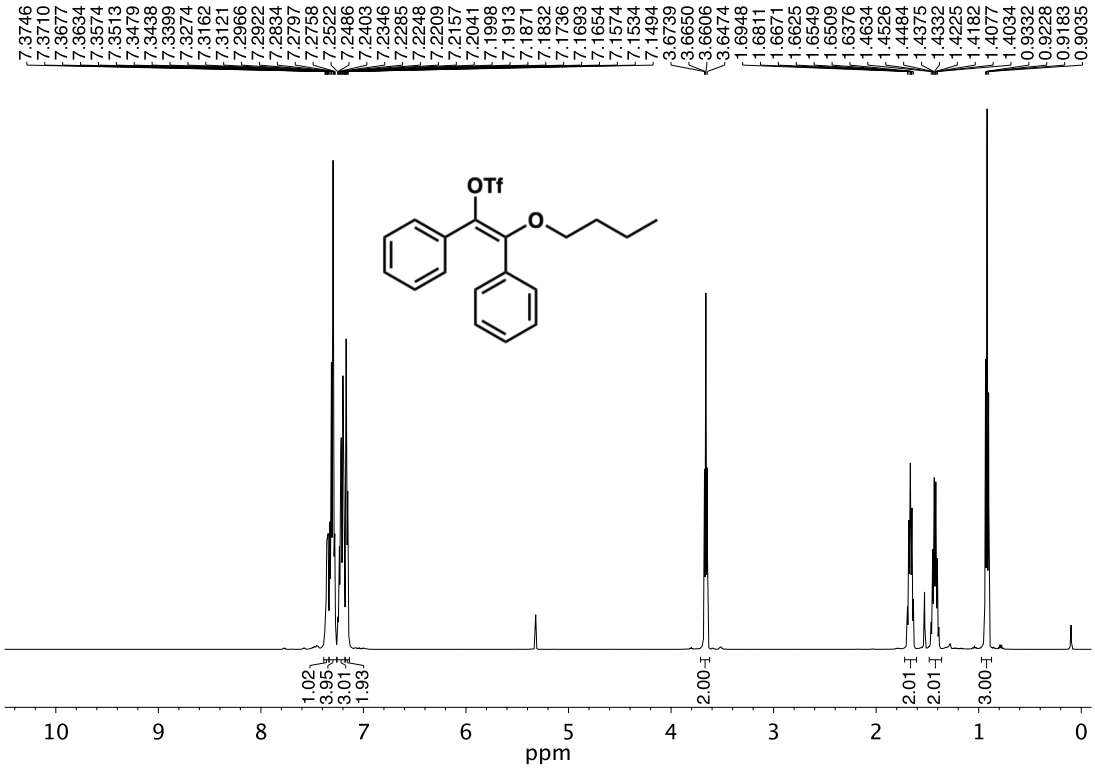


Figure 5.9. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.54**.

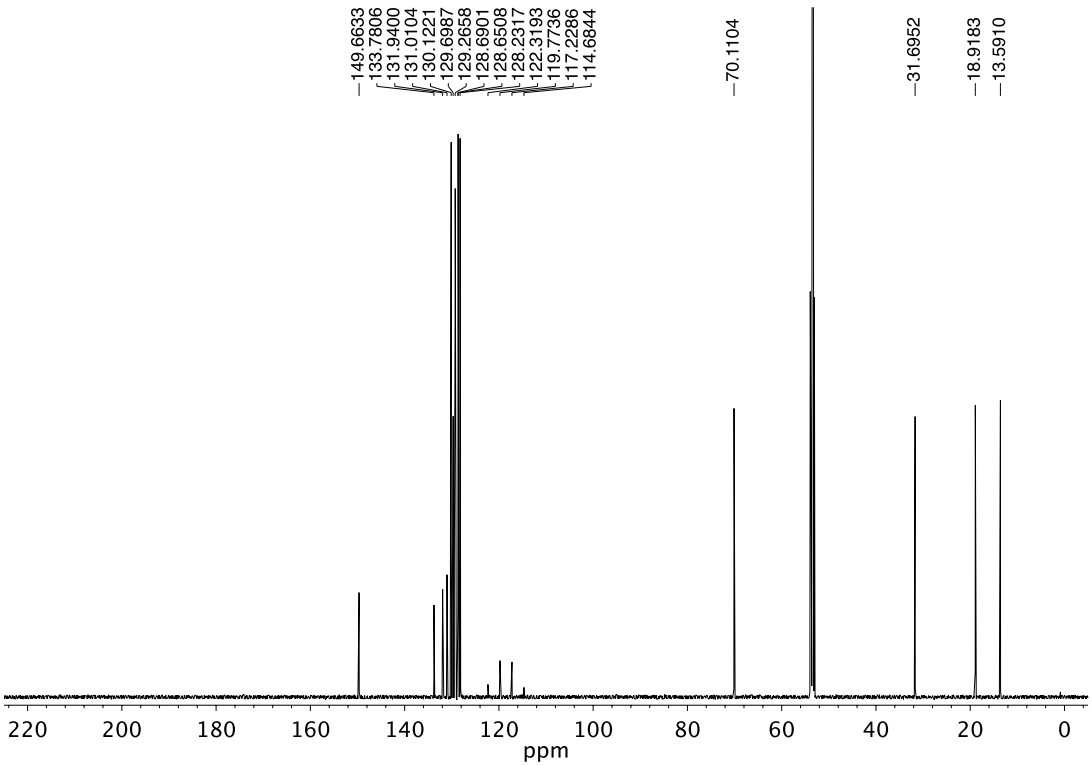


Figure 5.10. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.54**.

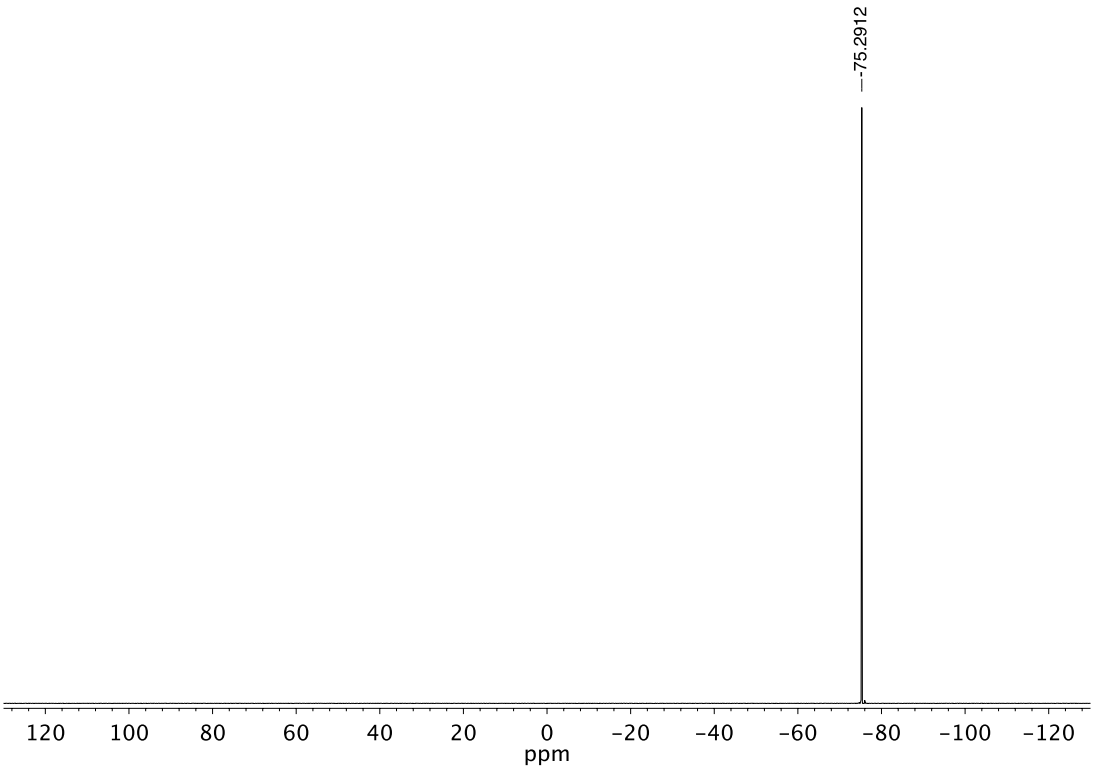


Figure 5.11. ^{19}F NMR (282 MHz, $CDCl_3$) of **5.54**.

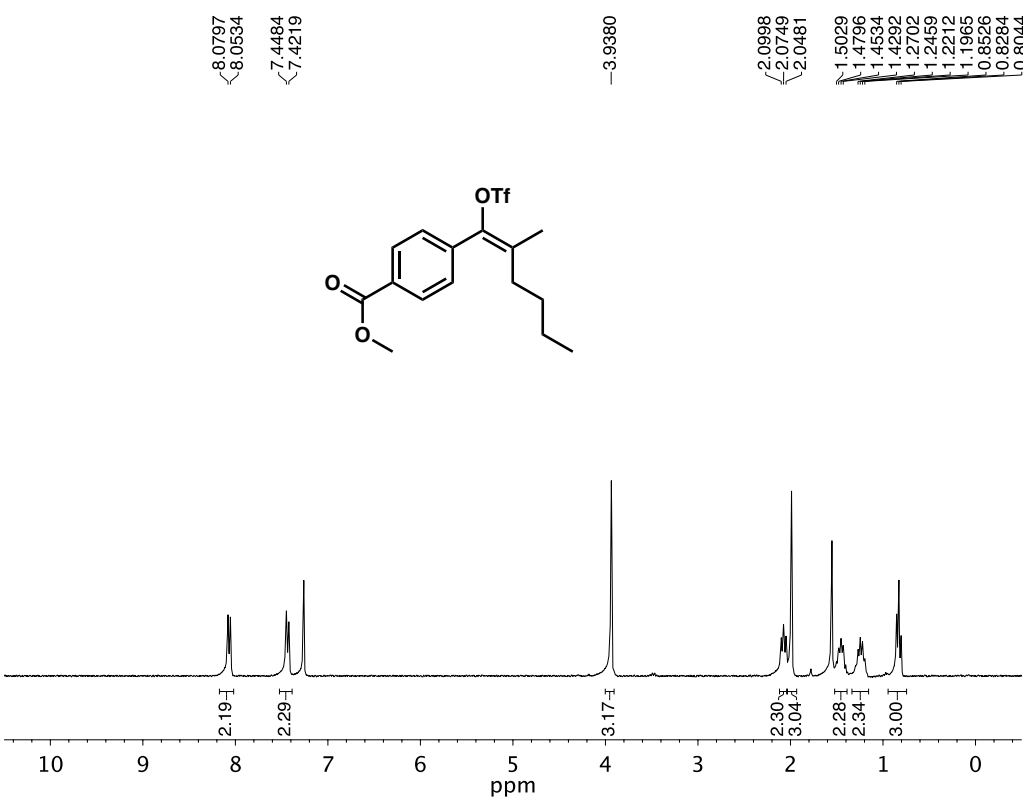


Figure 5.12. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.58**.

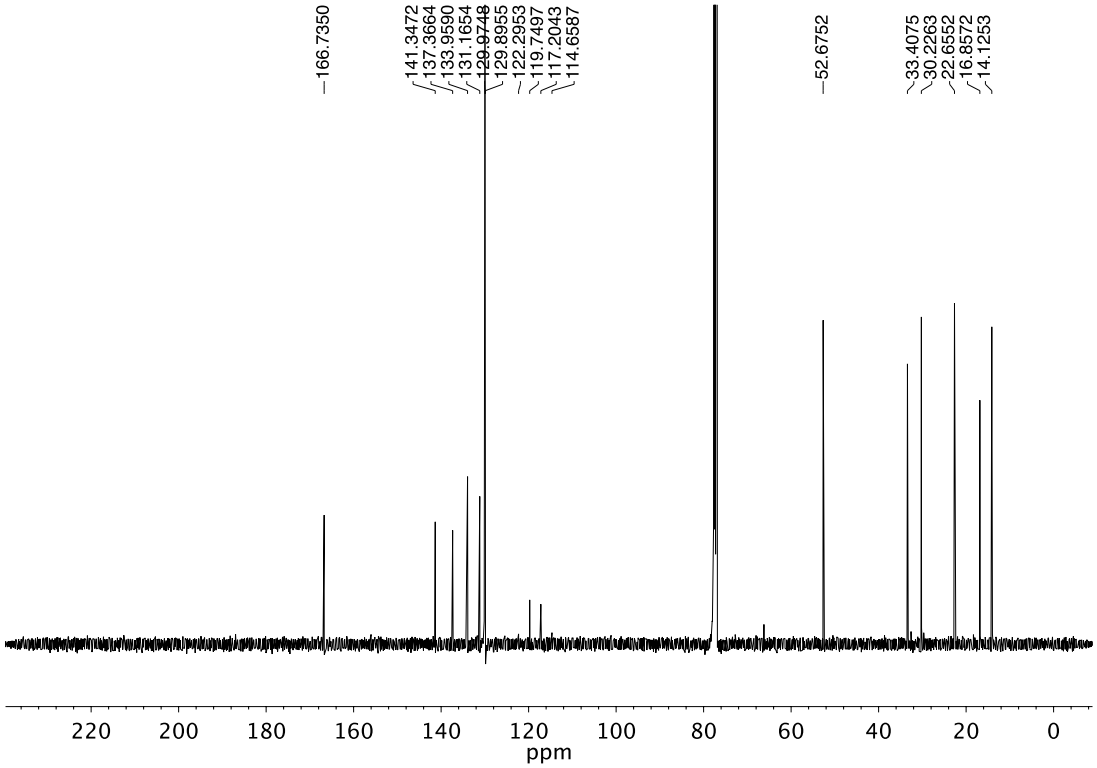


Figure 5.13. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.58**.

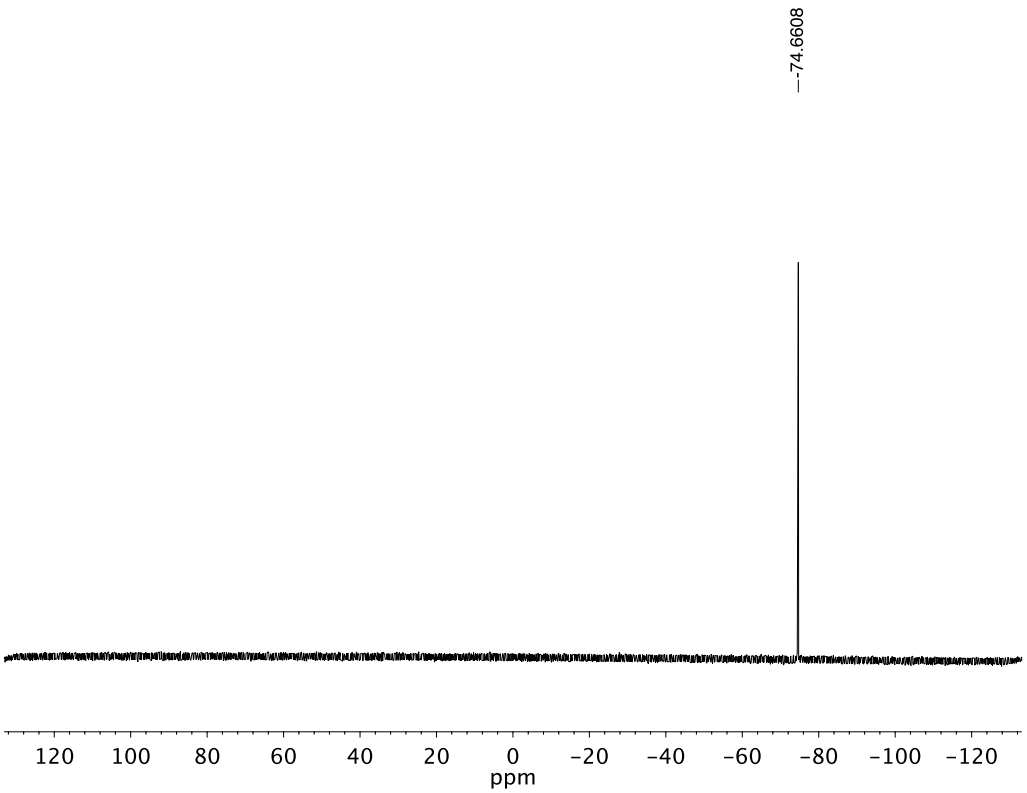


Figure 5.14. ^{19}F NMR (376 MHz, $CDCl_3$) of **5.58**.

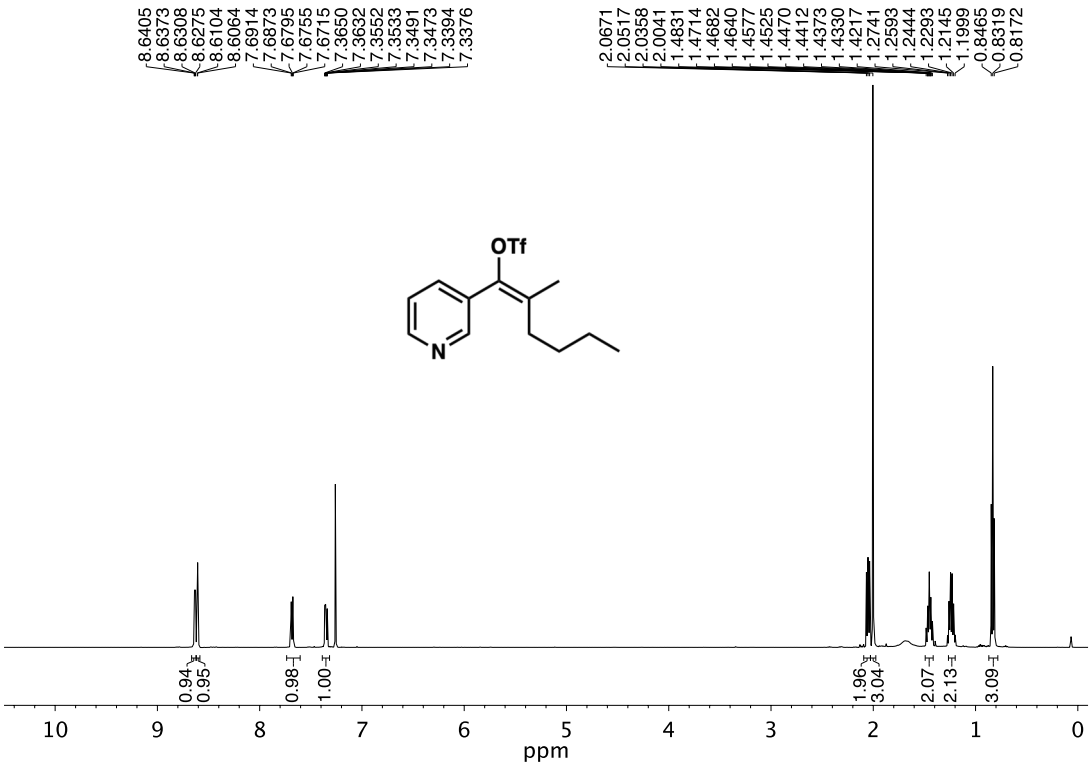


Figure 5.15. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.62**.

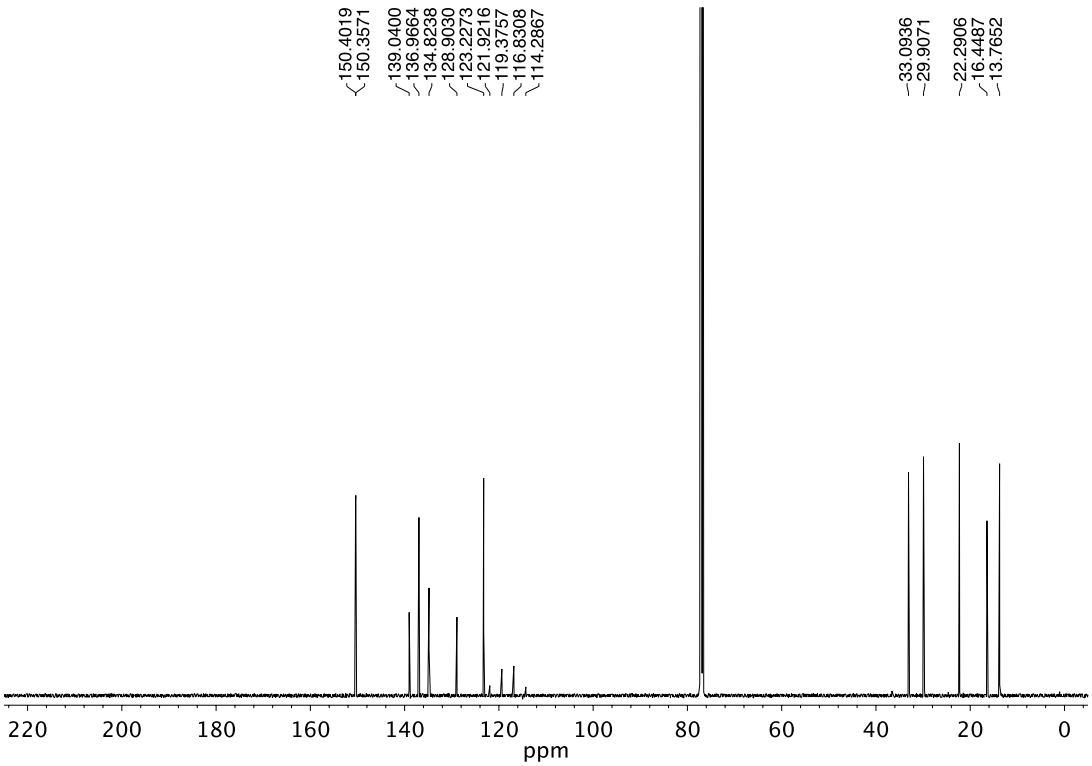


Figure 5.16. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.62**.

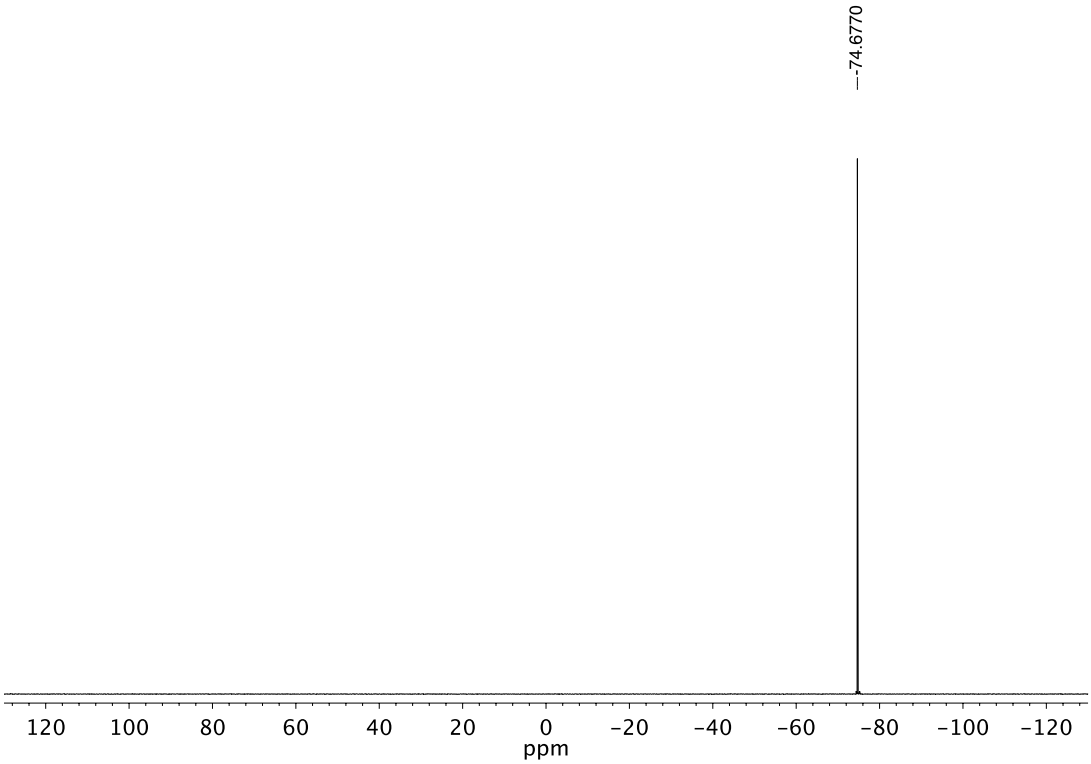


Figure 5.17. ^{19}F NMR (282 MHz, $CDCl_3$) of **5.62**.

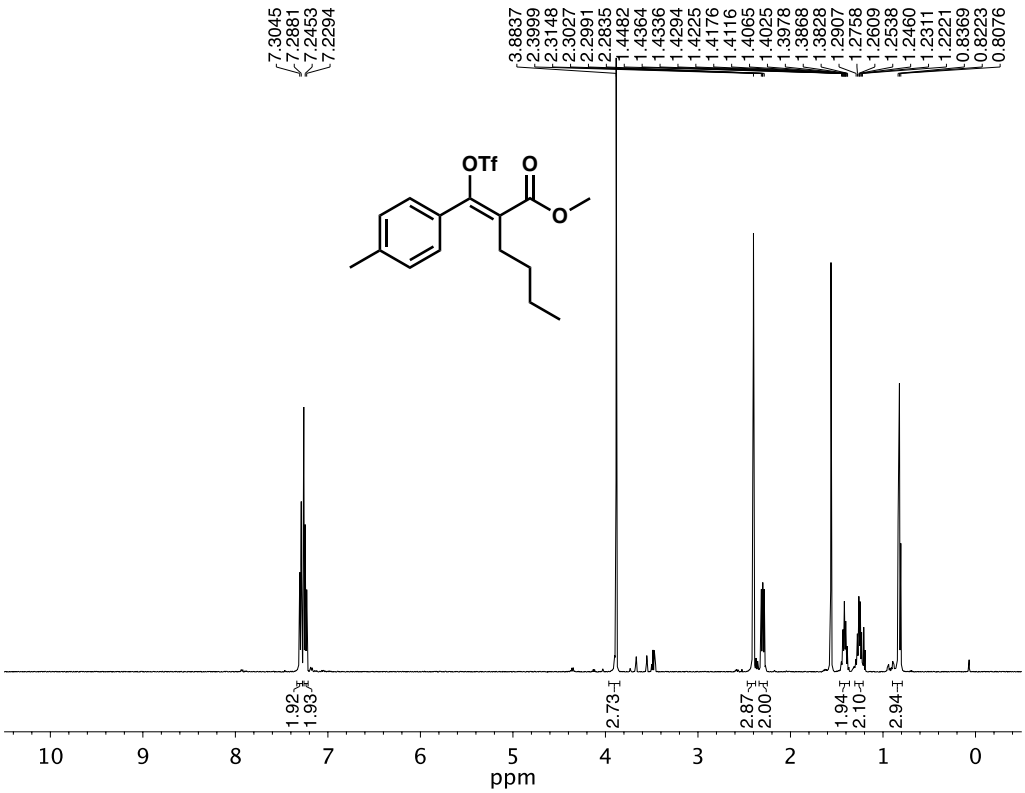


Figure 5.18. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.64**.

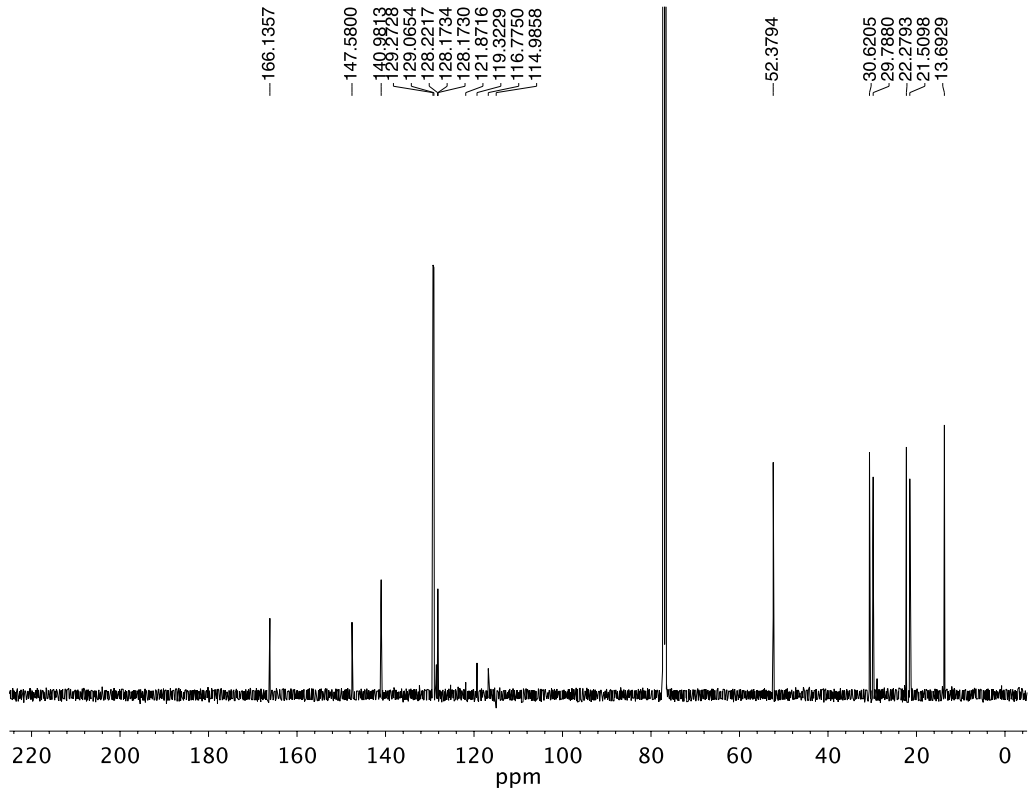


Figure 5.19. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.64**.

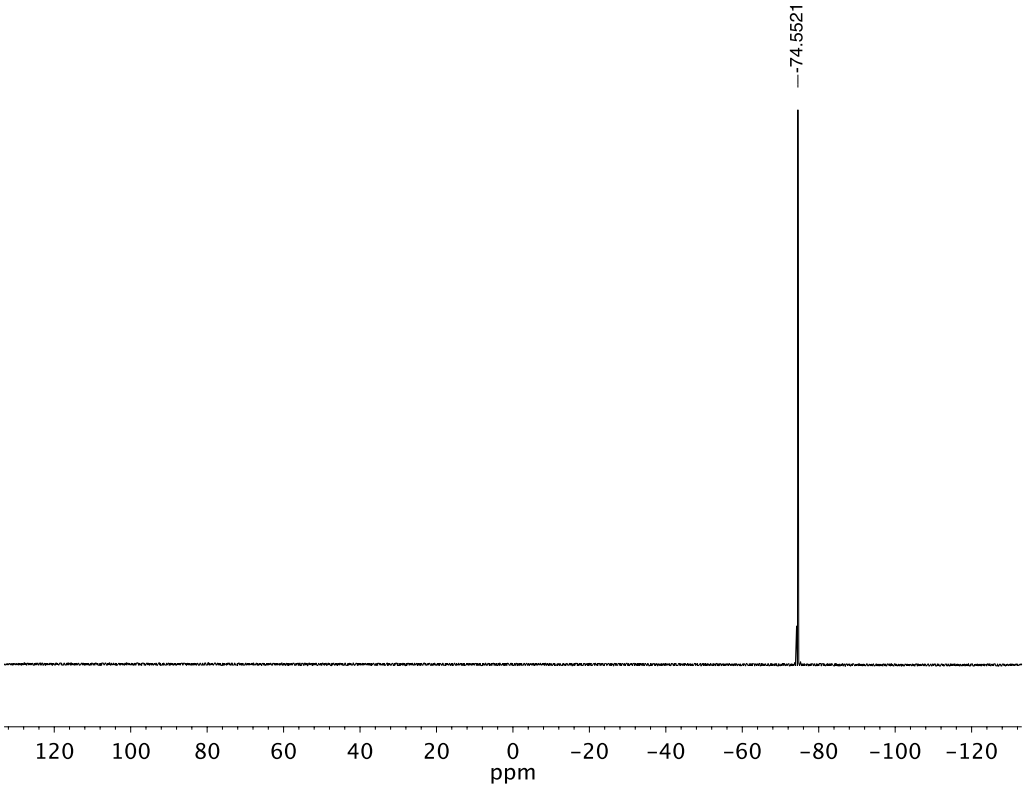


Figure 5.20. ^{19}F NMR (282 MHz, $CDCl_3$) of **5.64**.

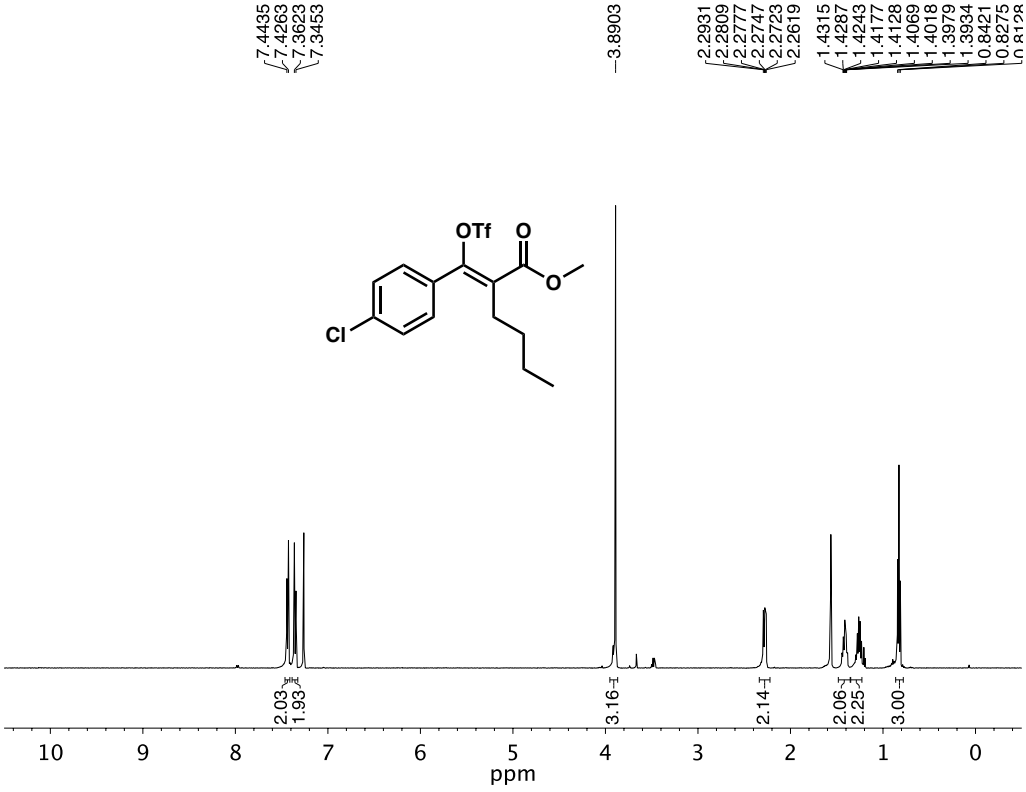


Figure 5.21. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.66**.

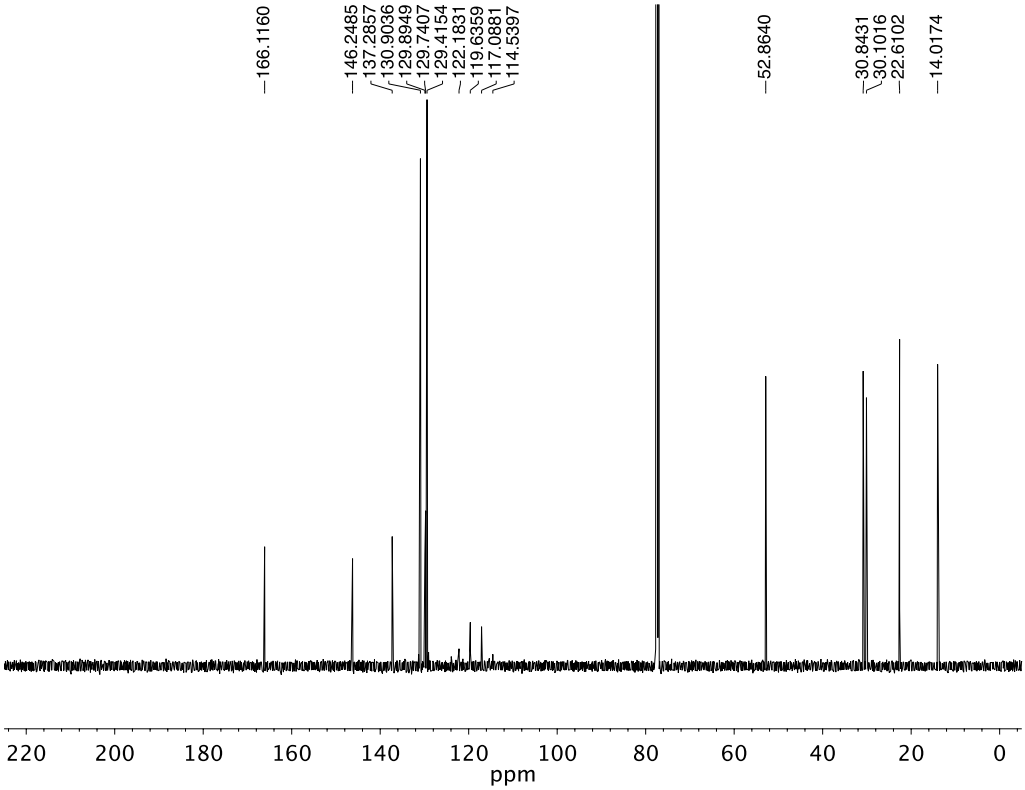


Figure 5.22. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.66**.

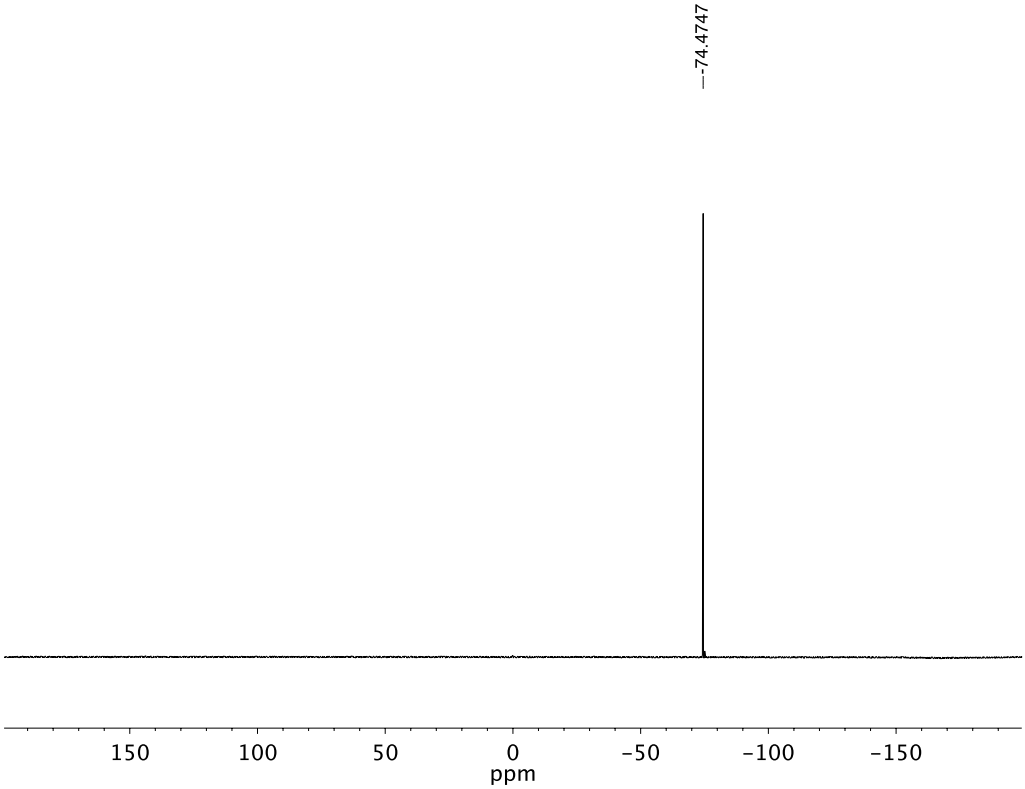


Figure 5.23. ^{19}F NMR (282 MHz, $CDCl_3$) of **5.66**.

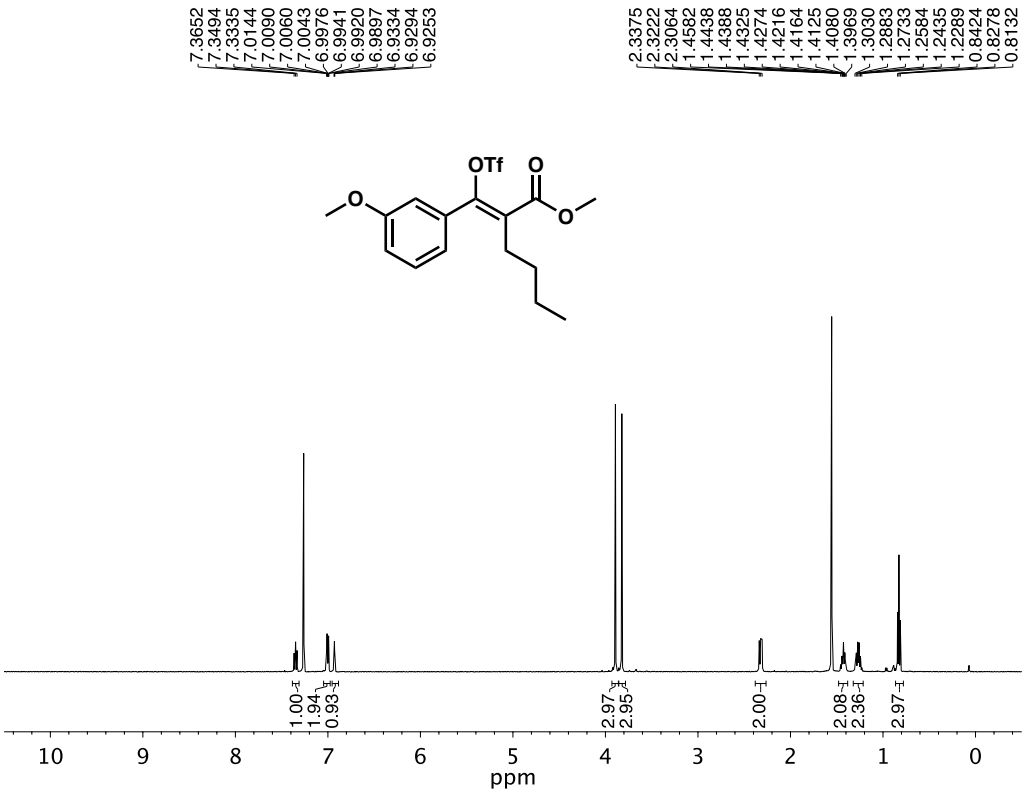


Figure 5.24. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.68**.

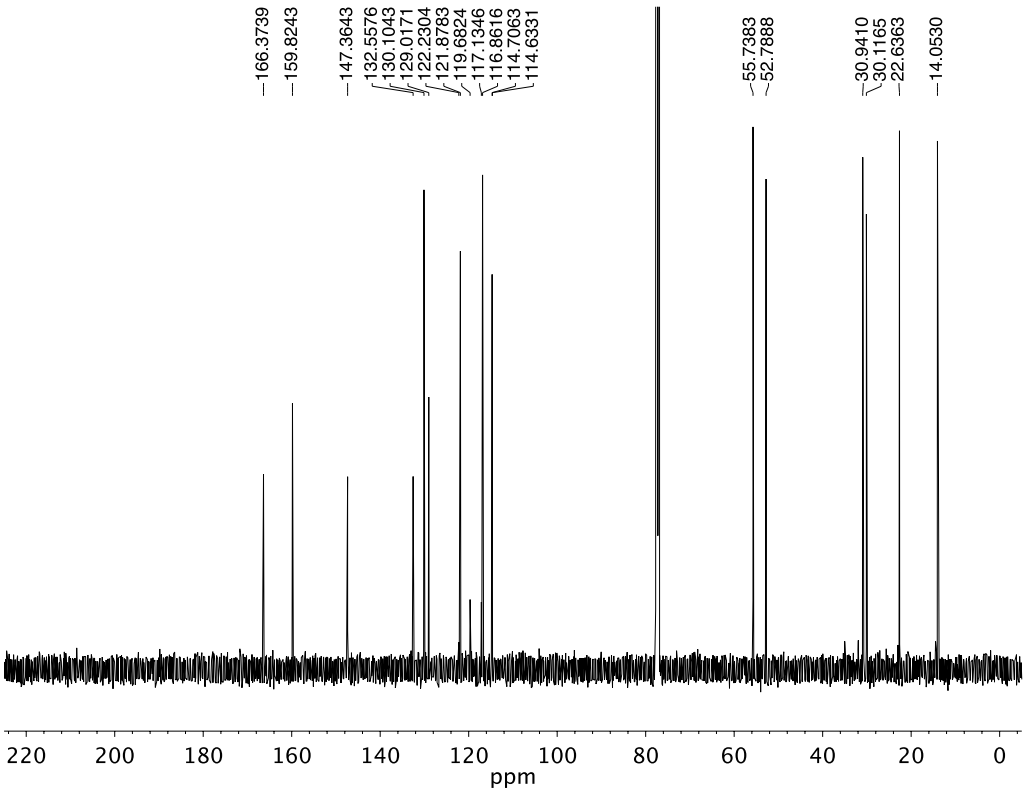


Figure 5.25. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.68**.

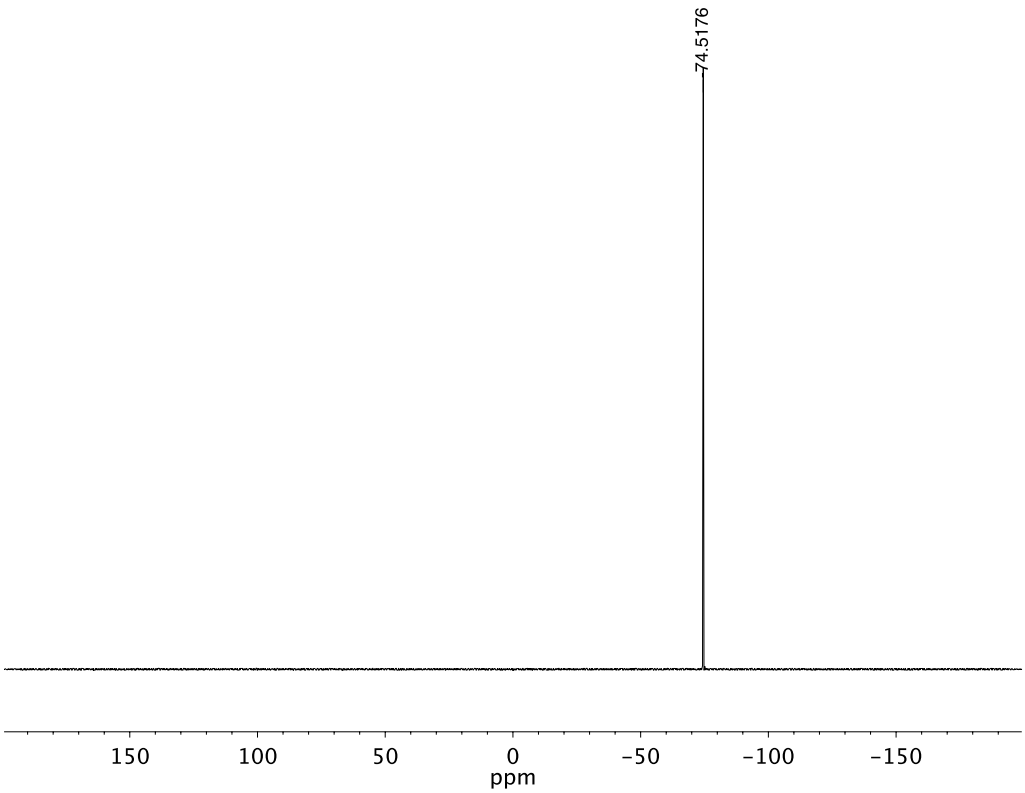


Figure 5.26. ^{19}F NMR (282 MHz, $CDCl_3$) of **5.68**.

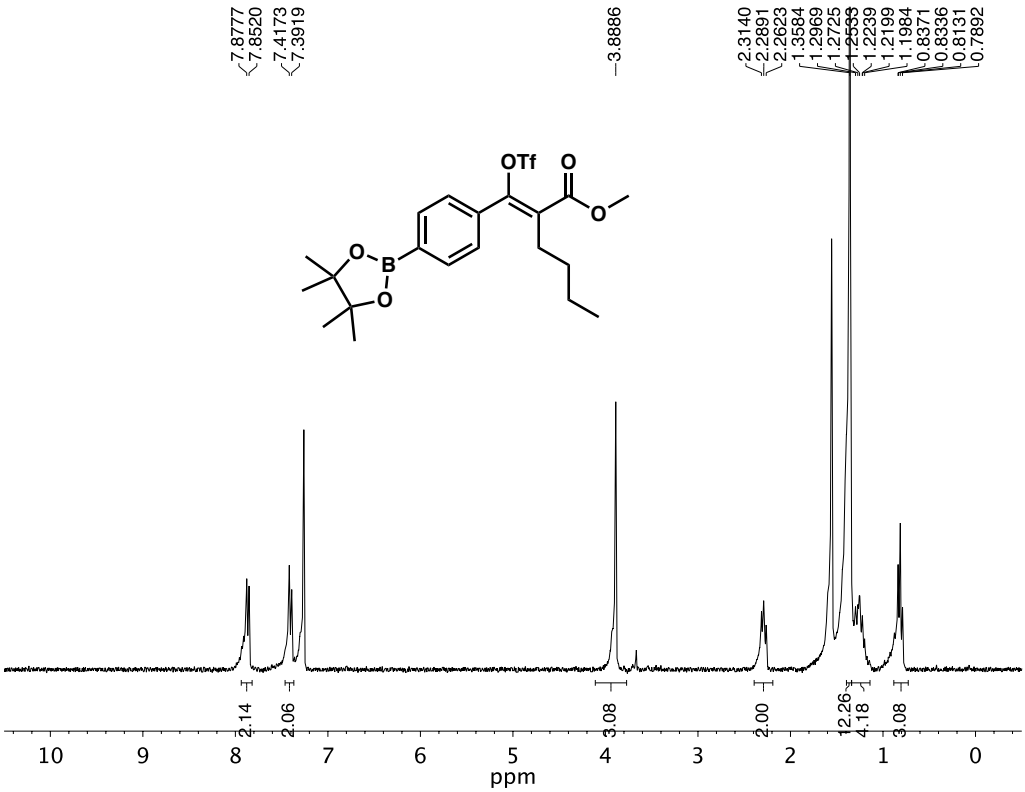


Figure 5.27. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.70**.

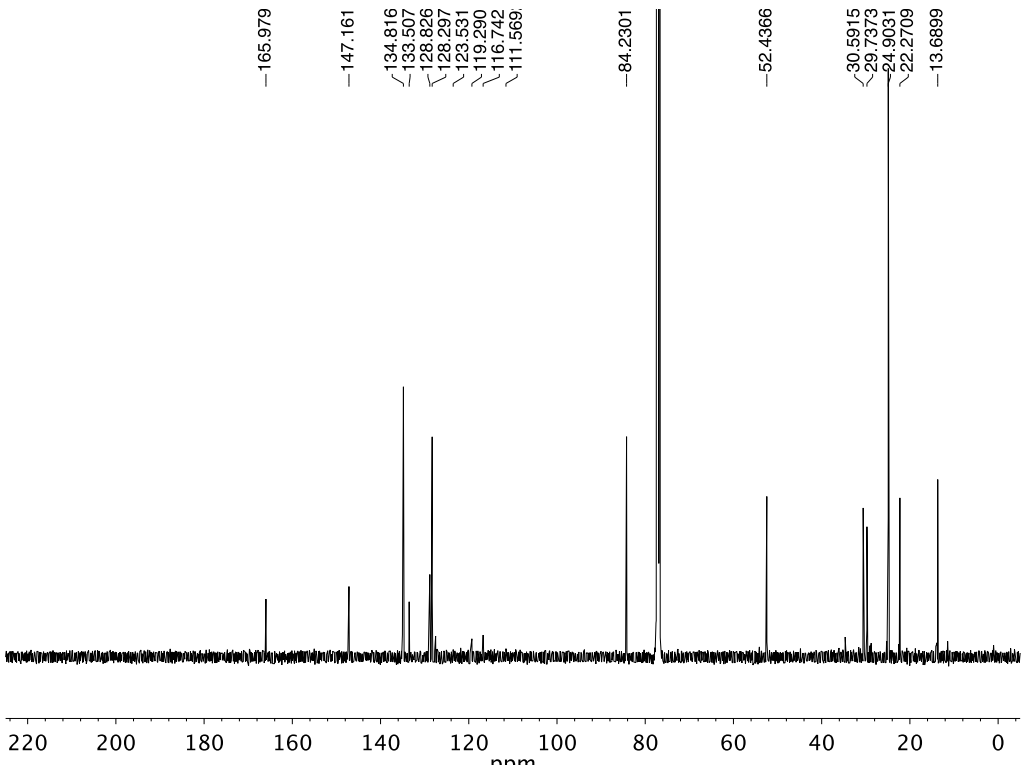


Figure 5.28. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.70**.

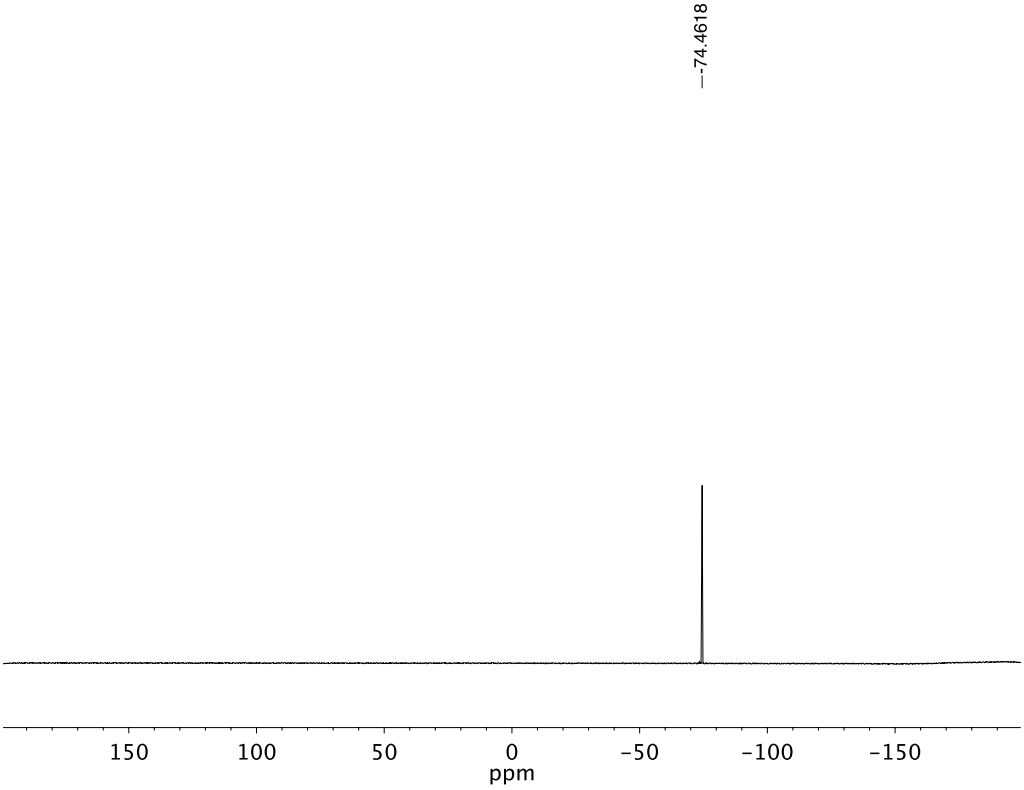


Figure 5.29. ^{19}F NMR (282 MHz, $CDCl_3$) of **5.70**.

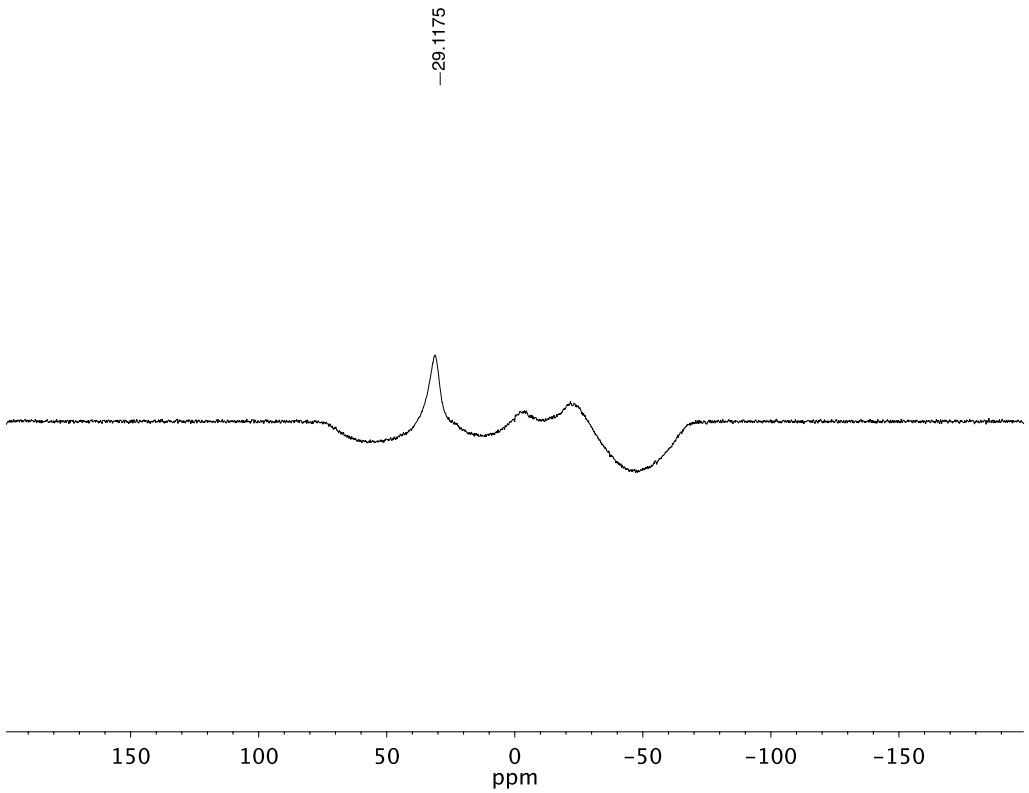


Figure 5.30. ^{11}B NMR (128 MHz, $CDCl_3$) of **5.70**.

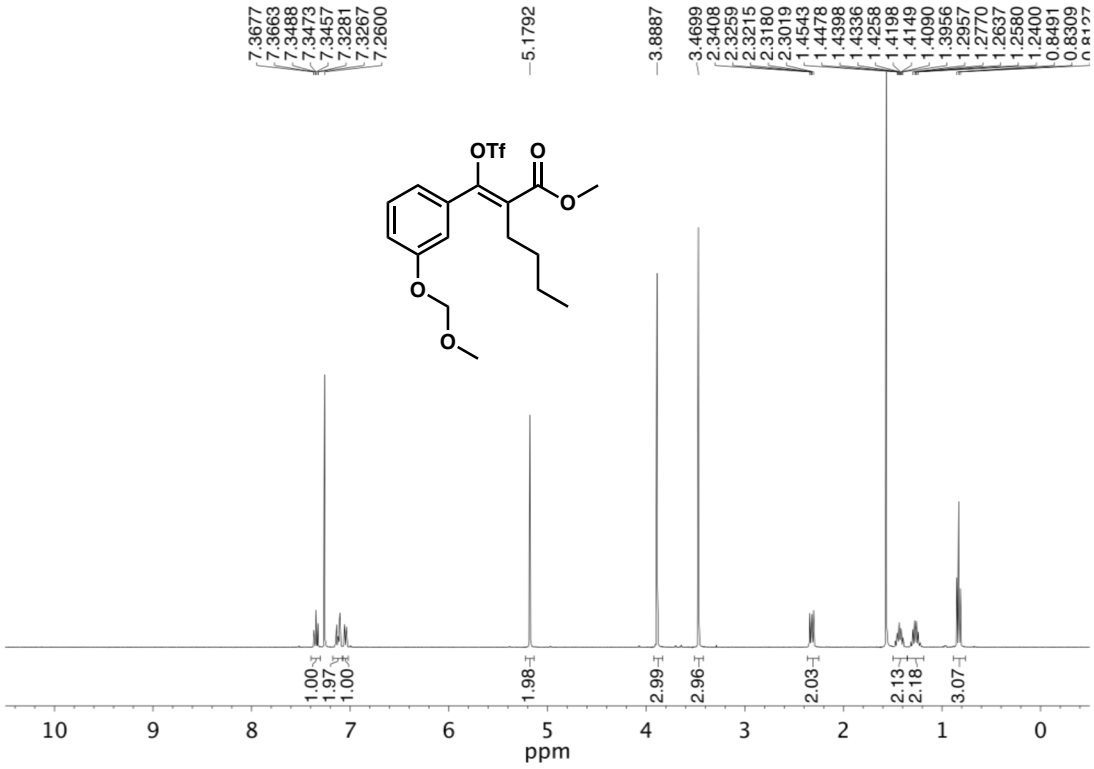


Figure 5.31. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.76**.

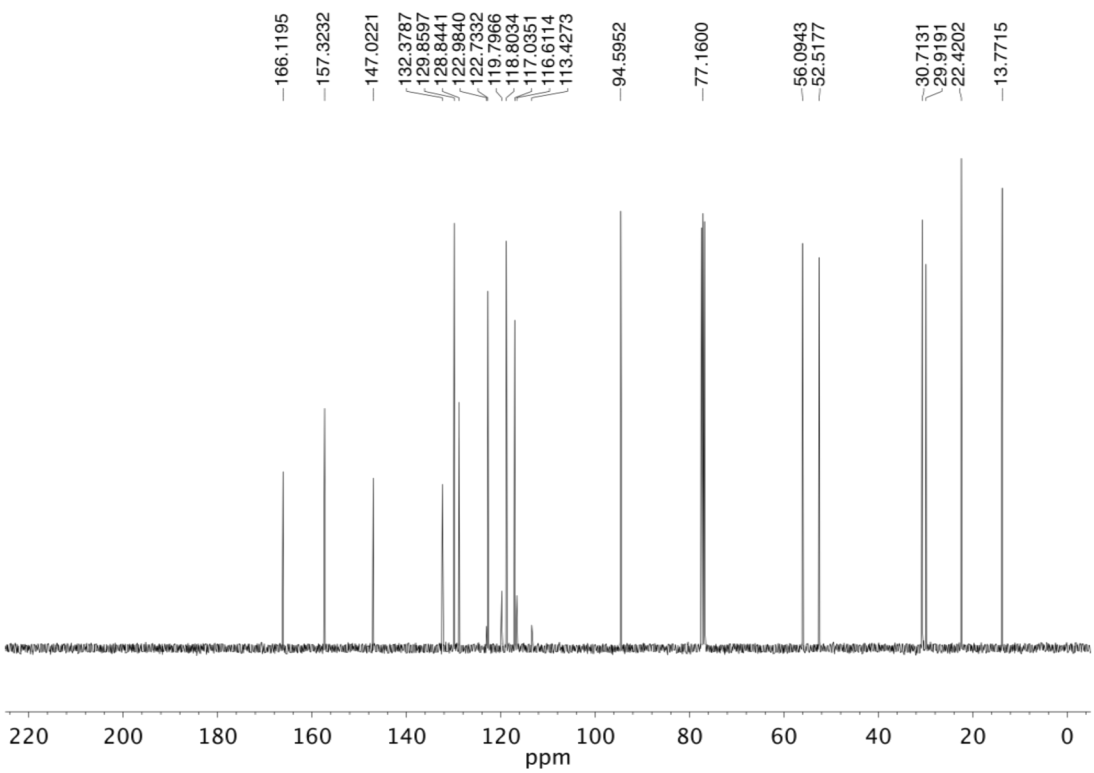


Figure 5.32. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.76**.

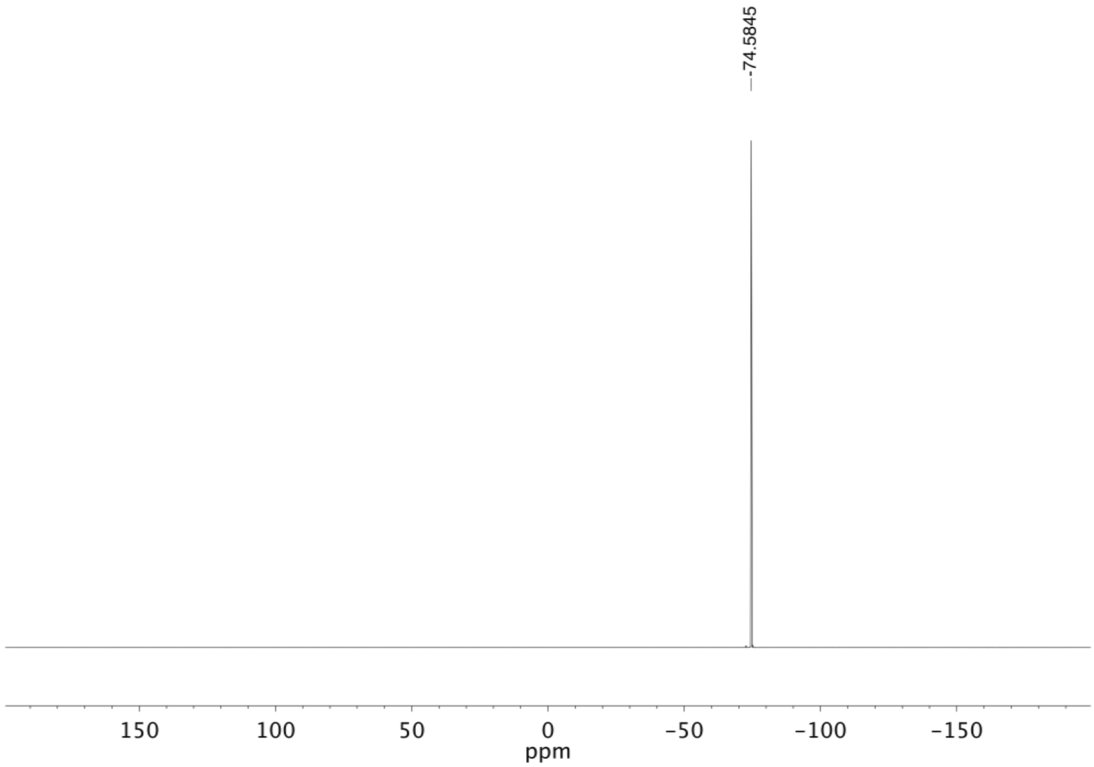


Figure 5.33. ^{19}F NMR (282 MHz, $CDCl_3$) of **5.76**.

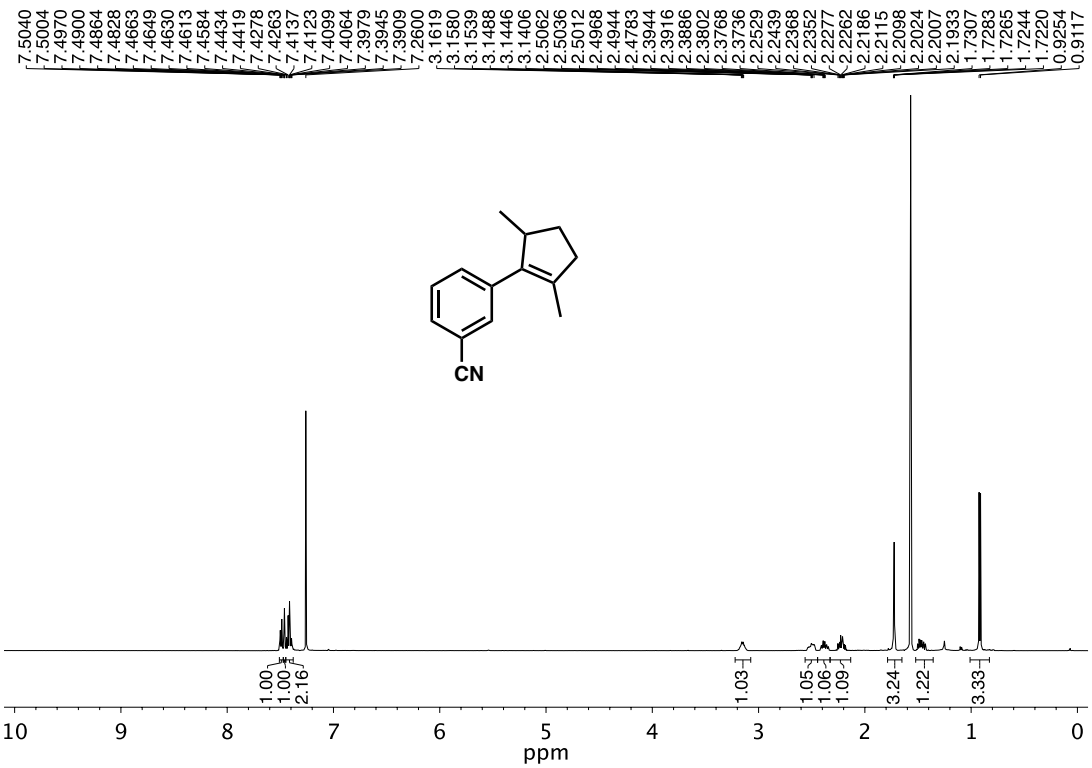


Figure 5.34. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.23**.

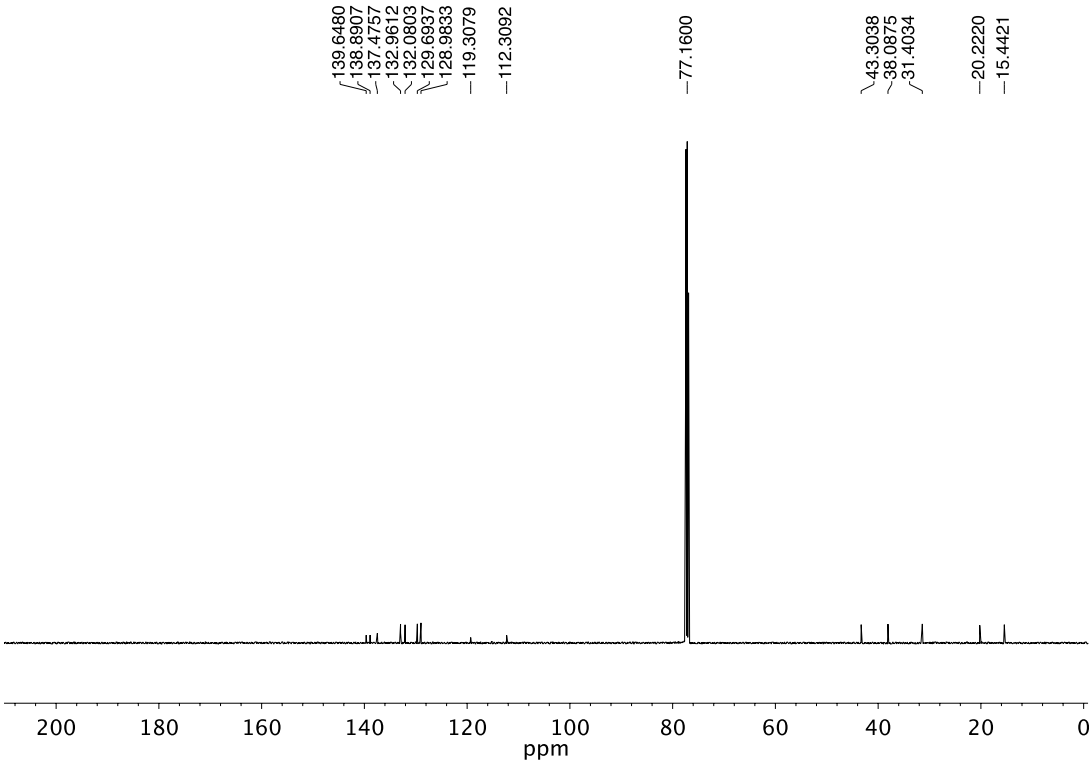


Figure 5.35. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.23**.

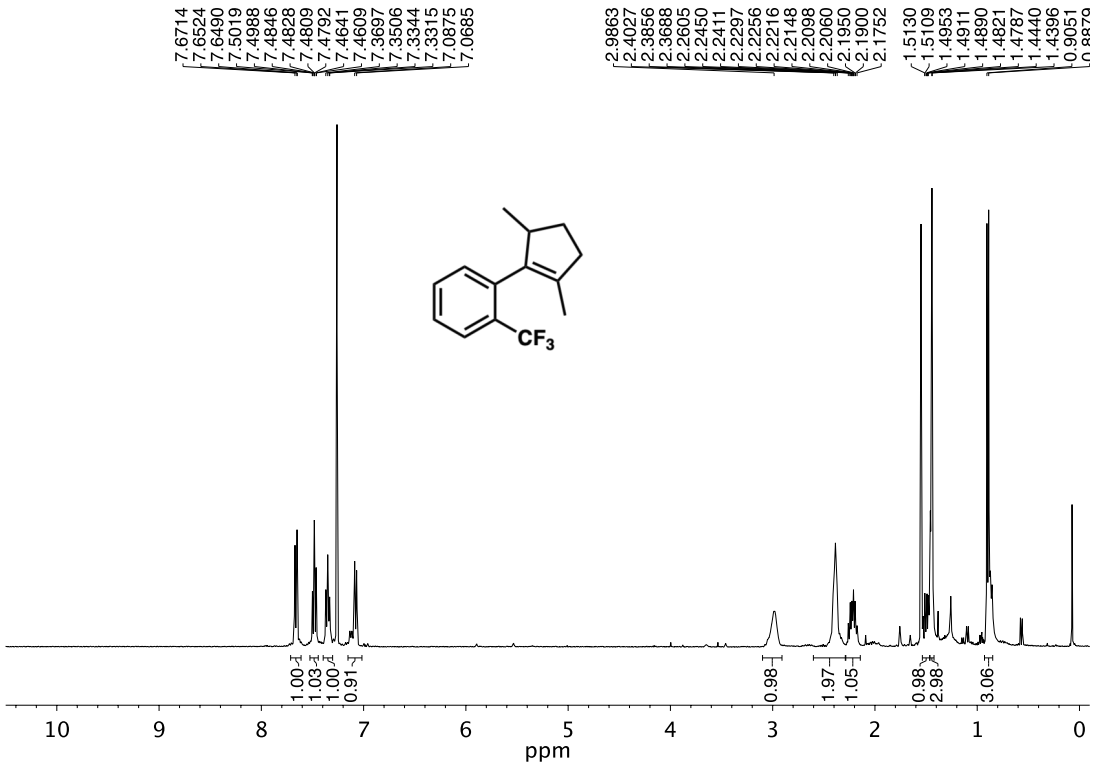


Figure 5.36. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.24**.

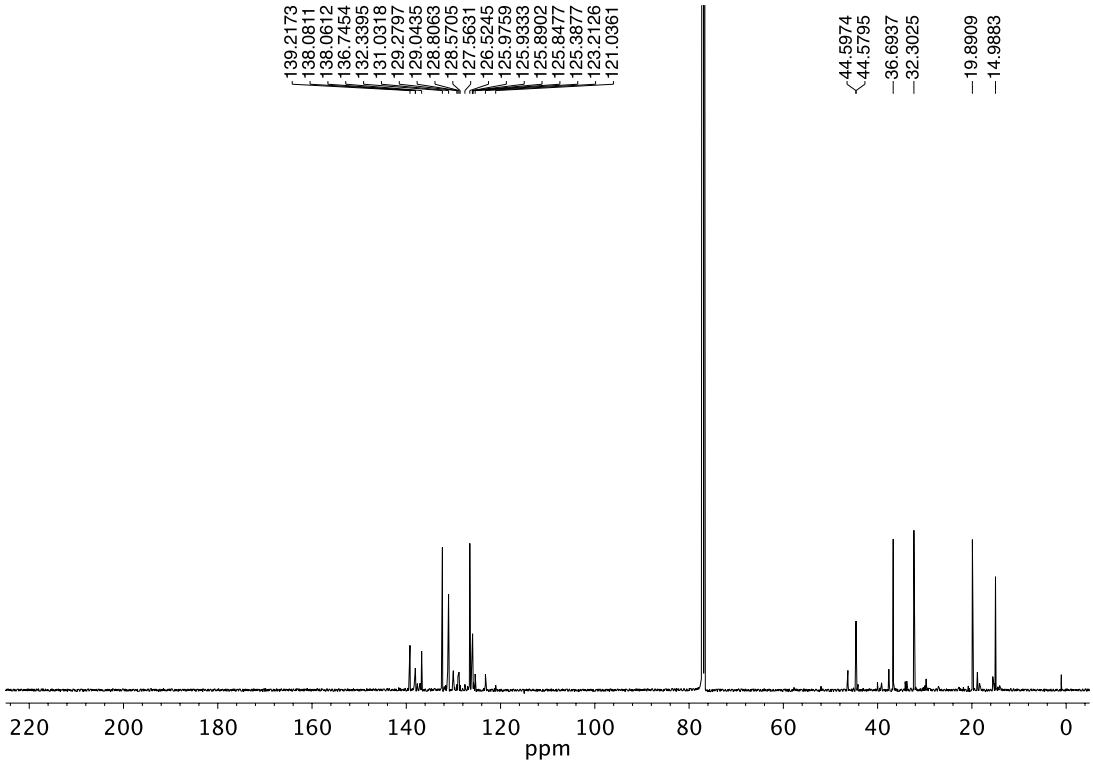


Figure 5.37. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.24**.

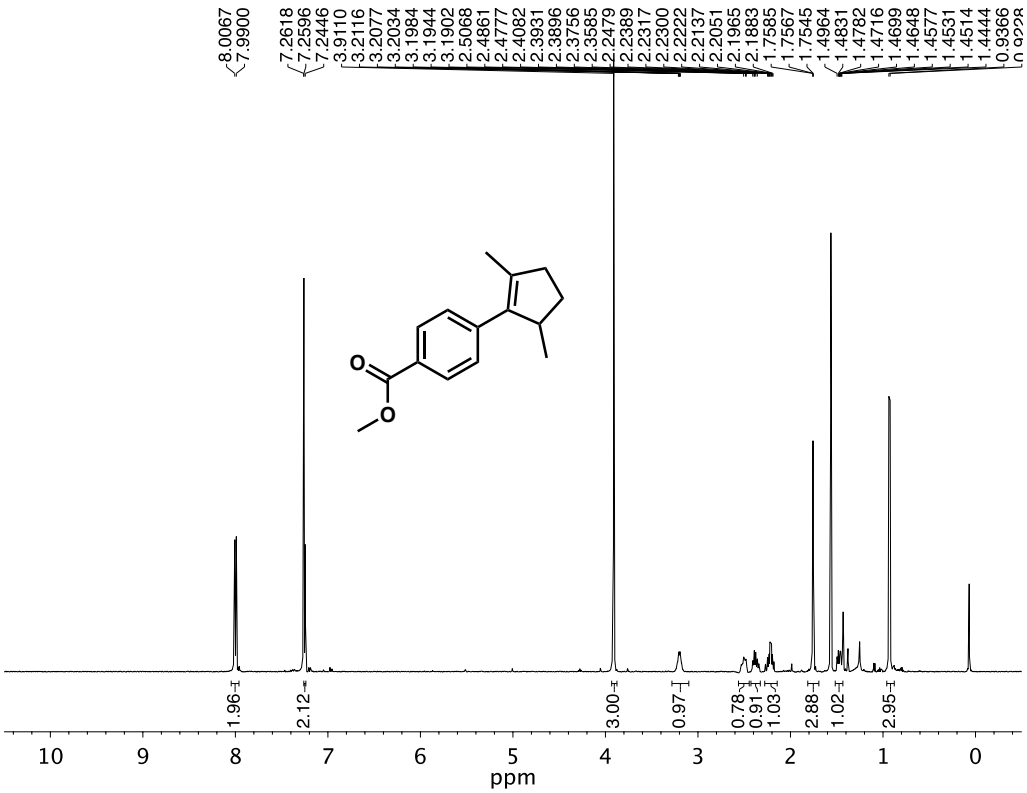


Figure 5.38. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.25**.

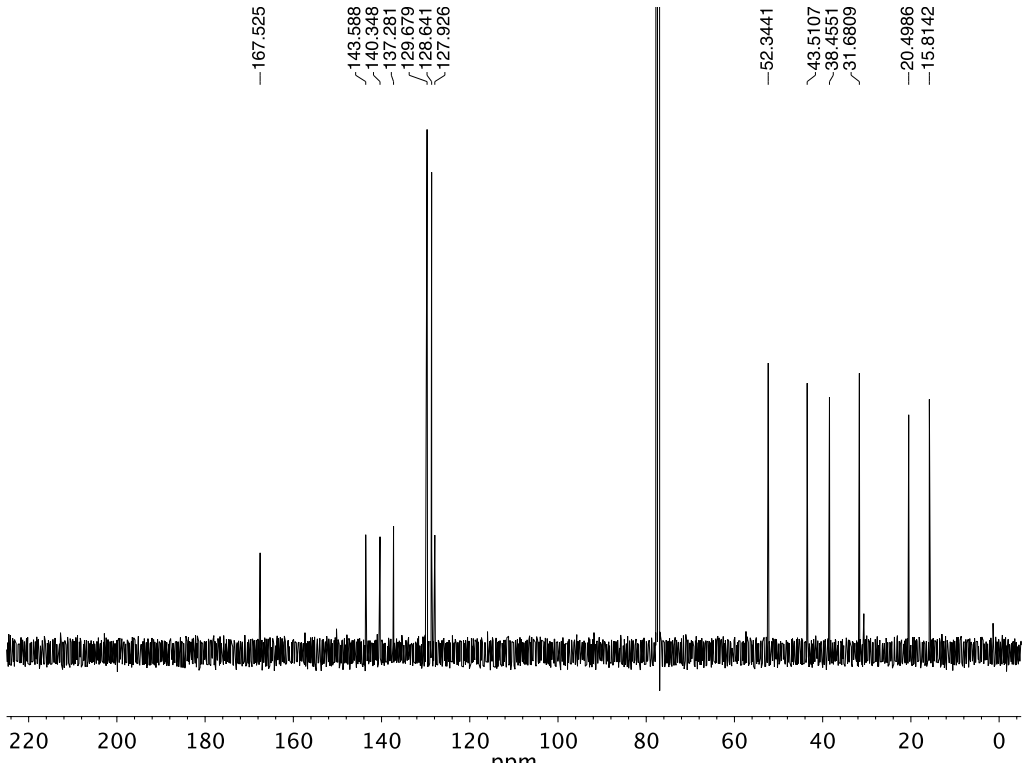


Figure 5.39. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.25**.

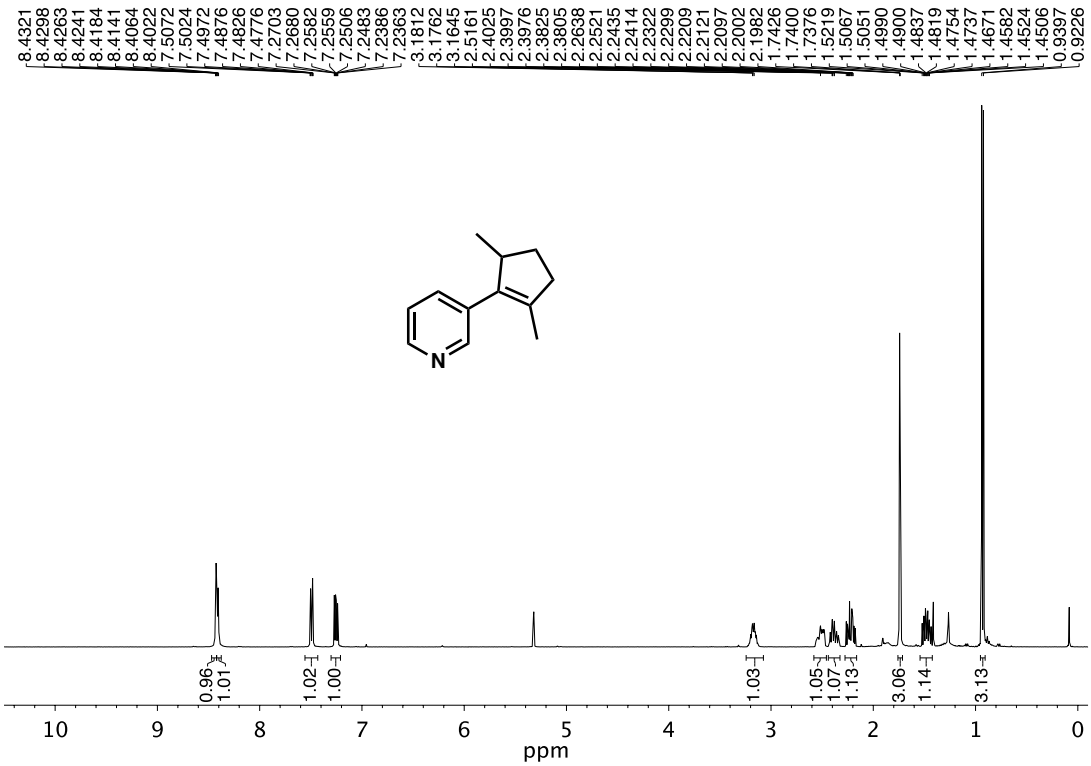


Figure 5.40. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.26**.

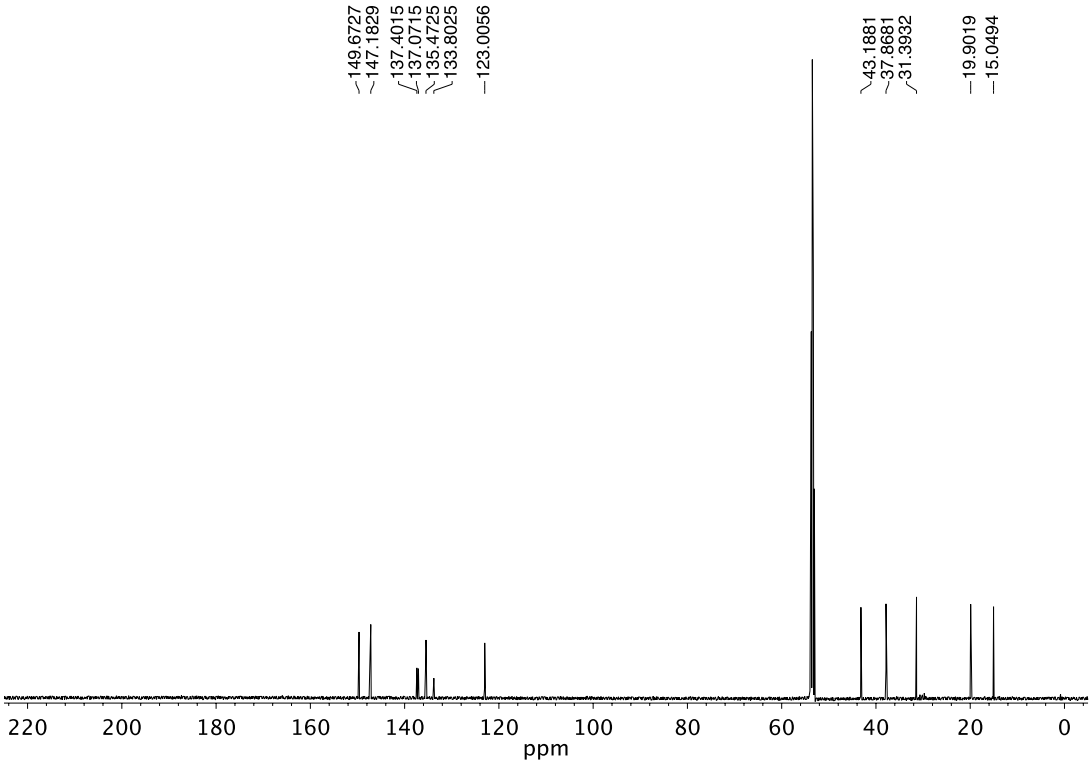


Figure 5.41. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.26**.

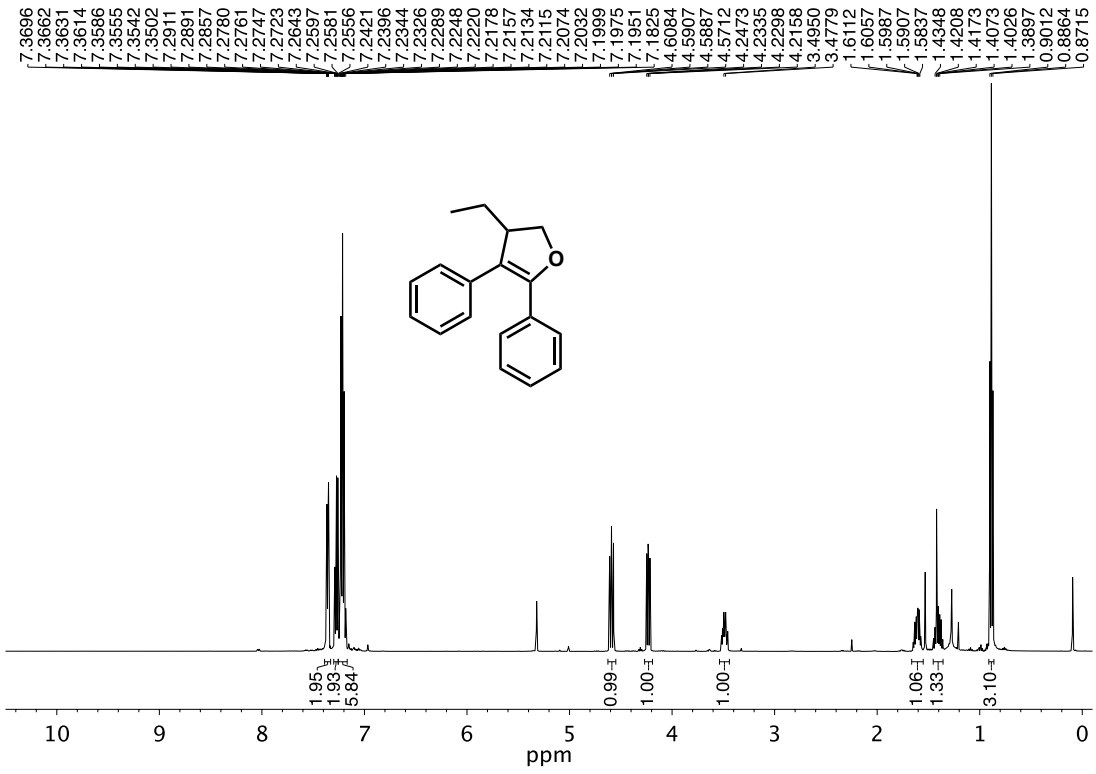


Figure 5.42. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.27**.

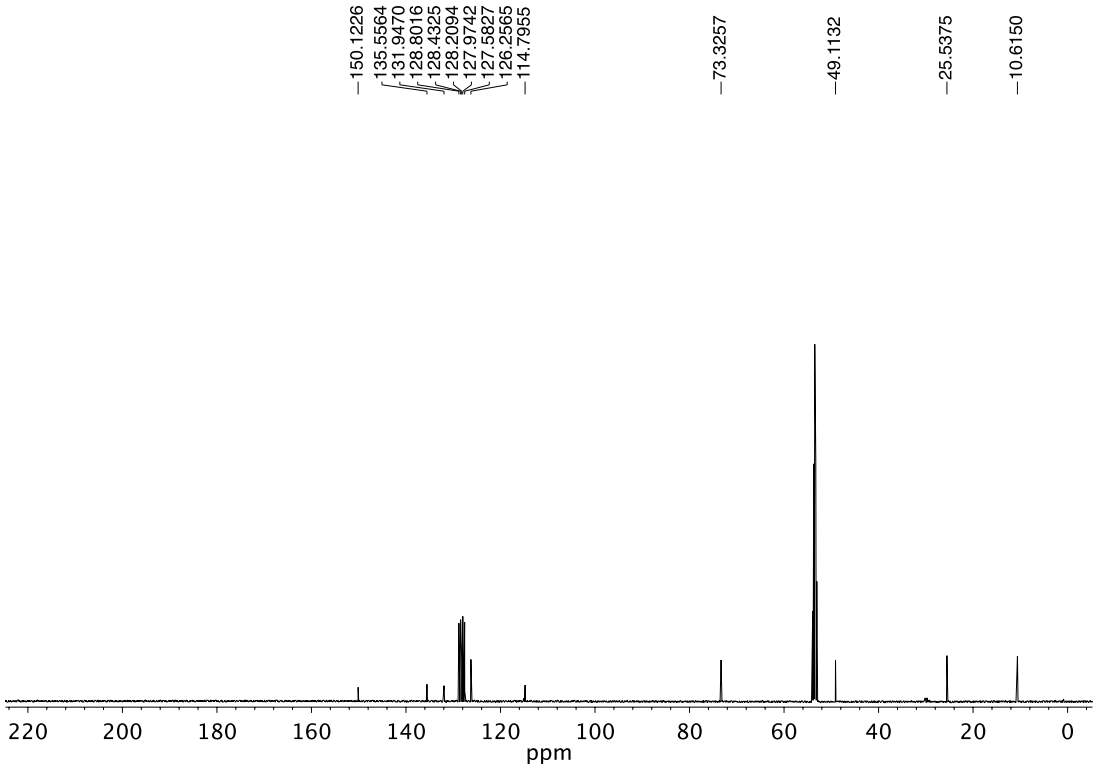


Figure 5.43. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.27**.

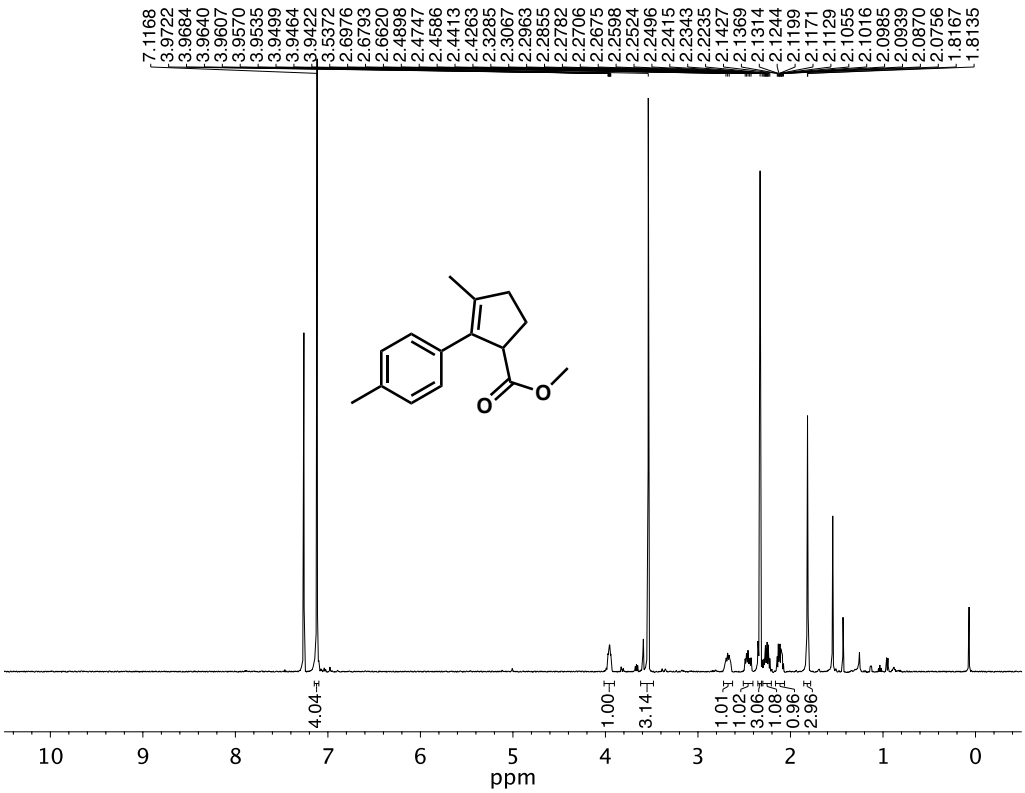


Figure 5.44. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.30**.

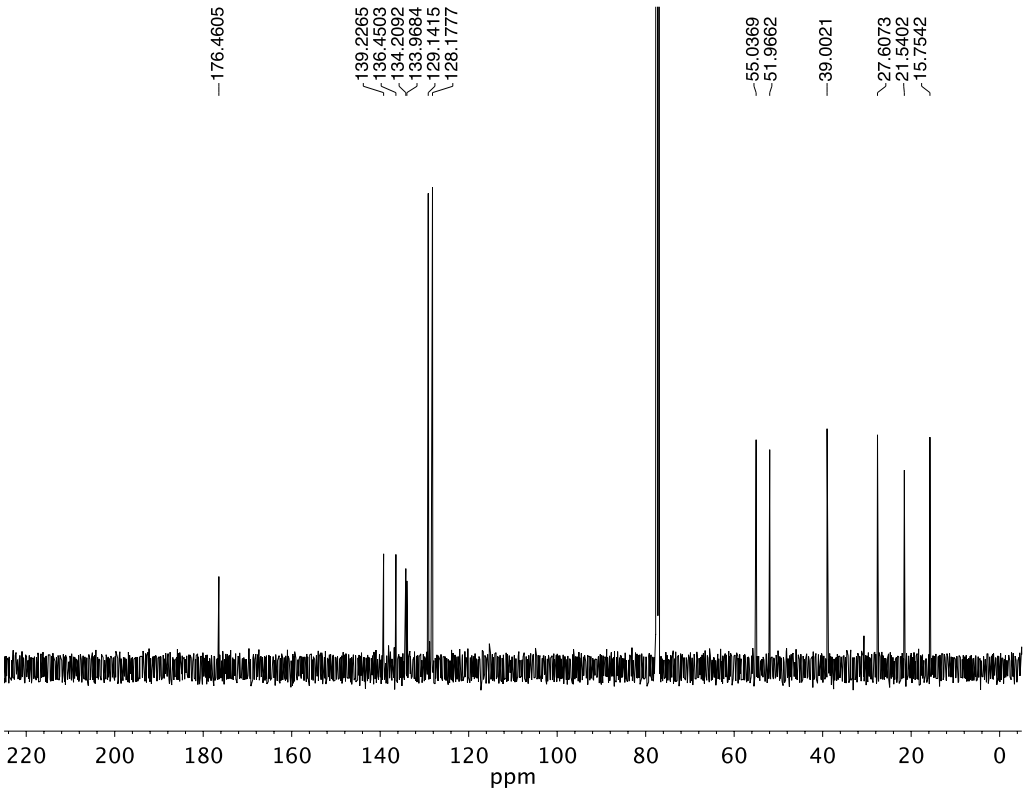


Figure 5.45. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.30**.

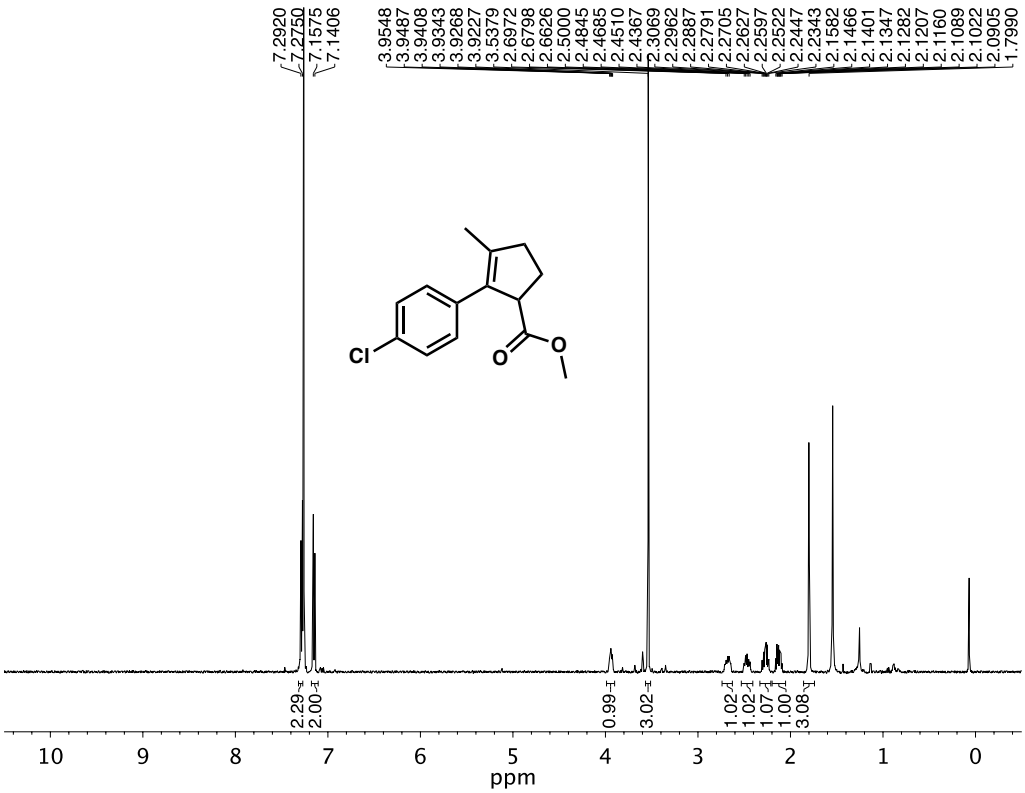


Figure 5.46. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.31**.

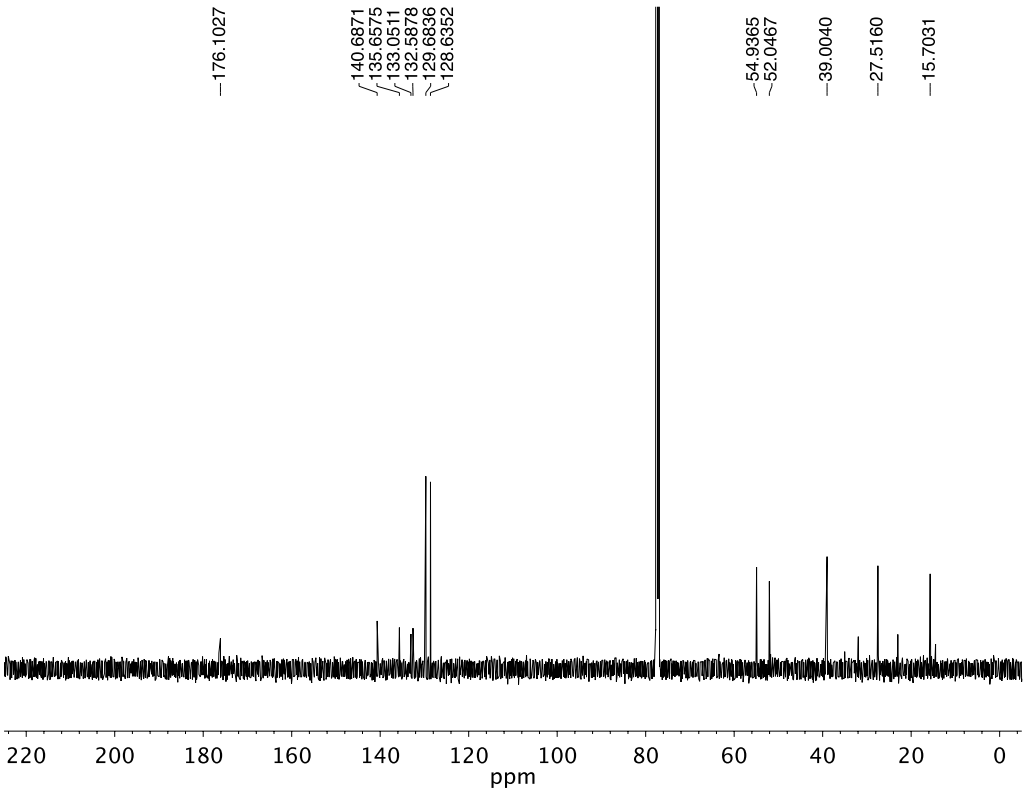


Figure 5.47. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.31**.

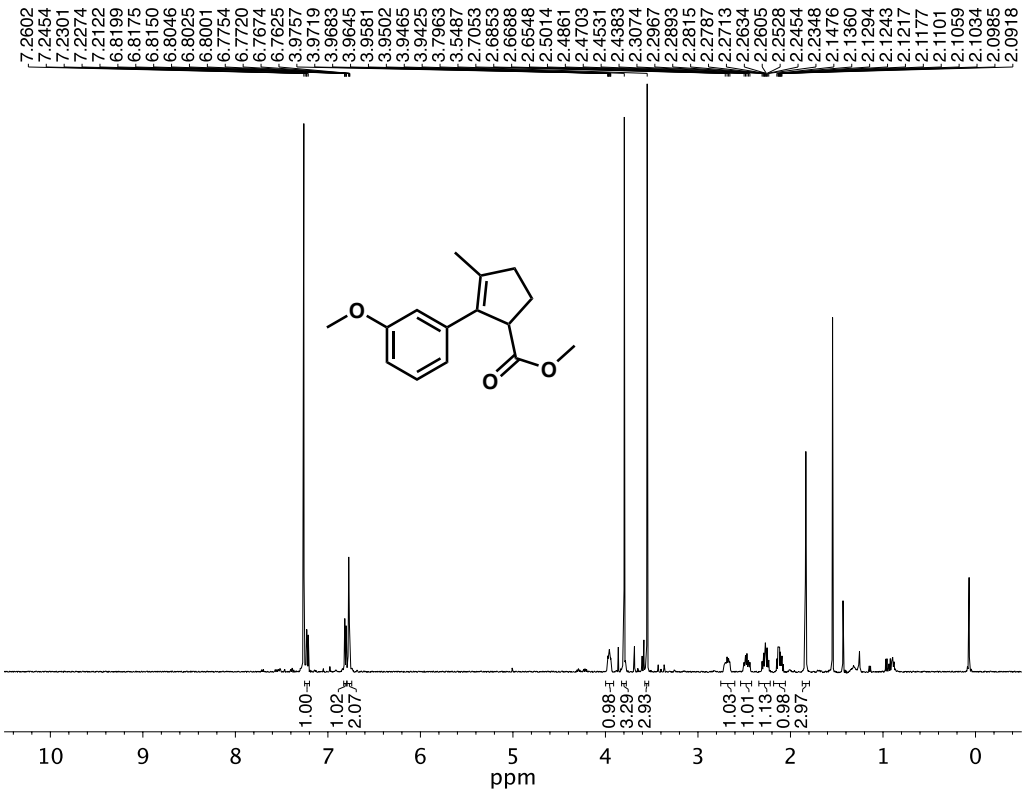


Figure 5.48. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.32**.

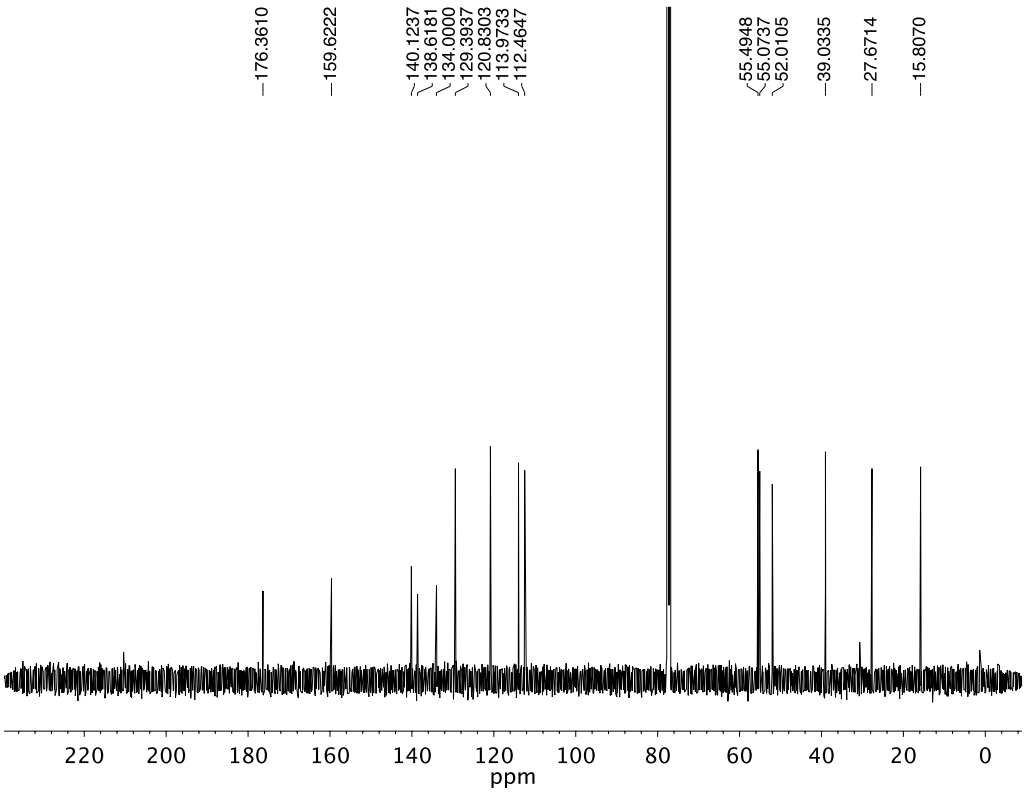


Figure 5.49. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.32**.

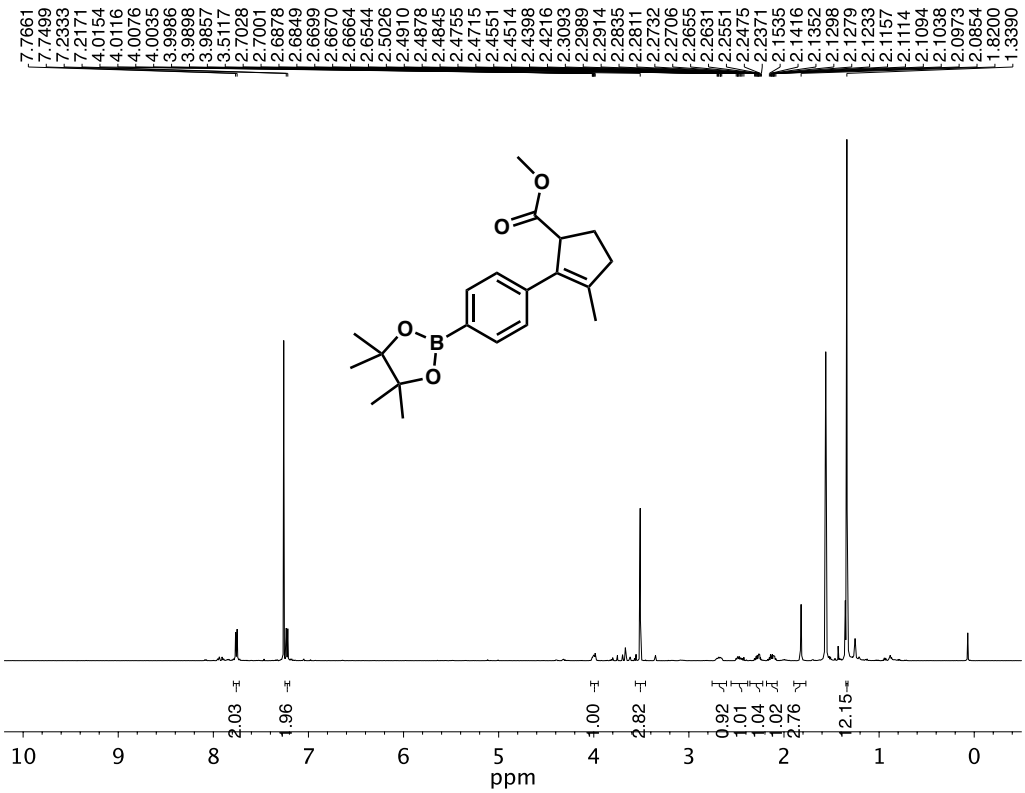


Figure 5.50. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.33**.

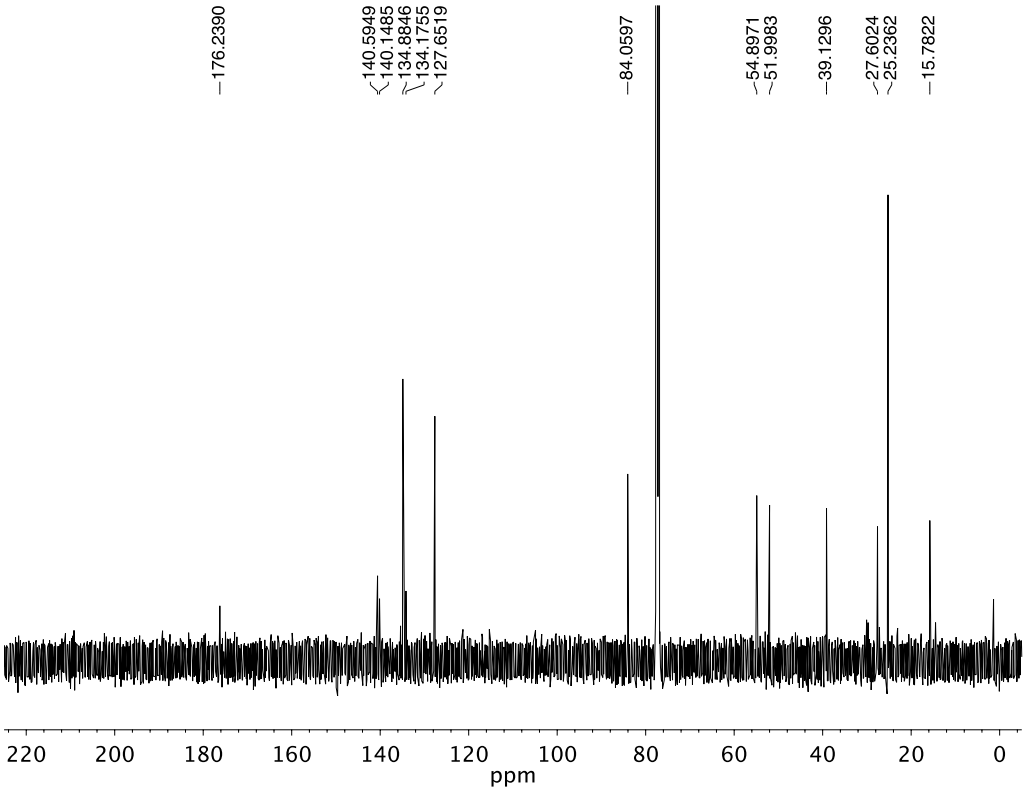


Figure 5.51. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.33**.

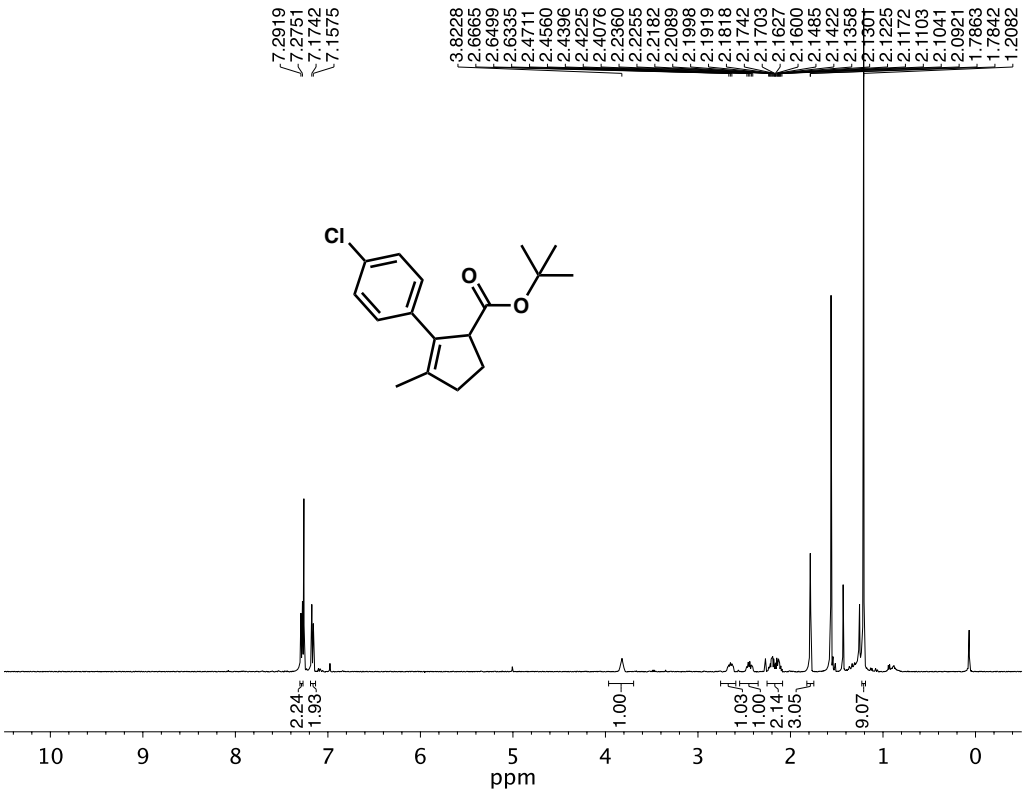


Figure 5.52. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.34**.

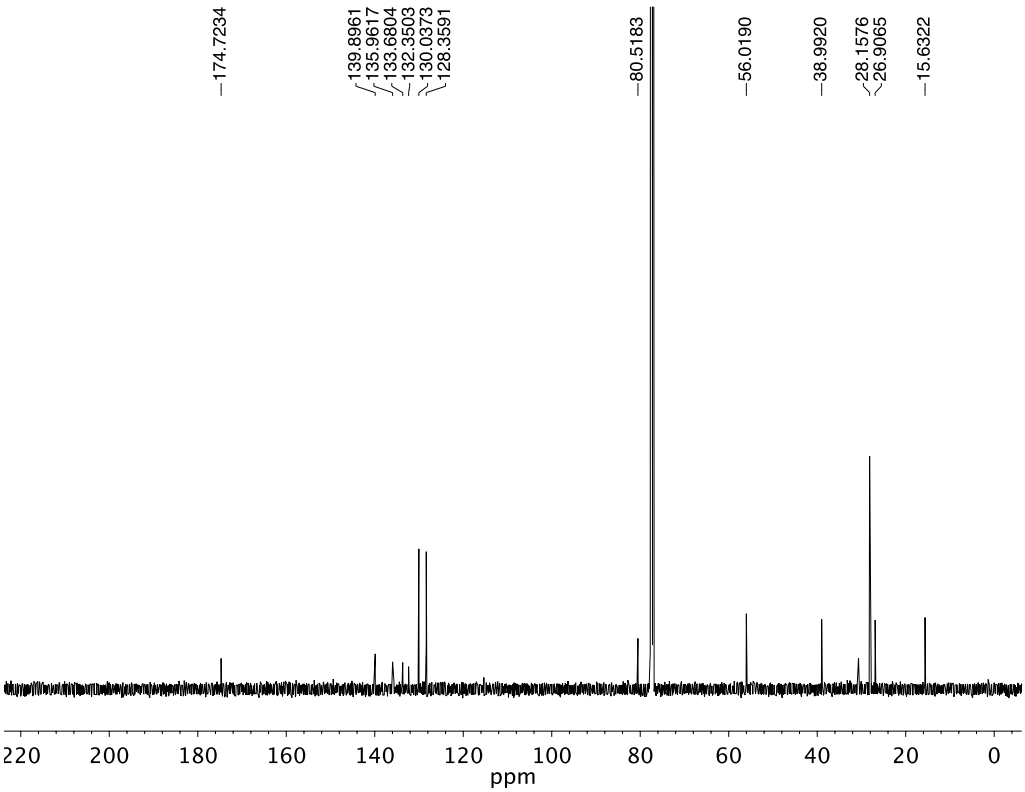


Figure 5.53. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.34**.

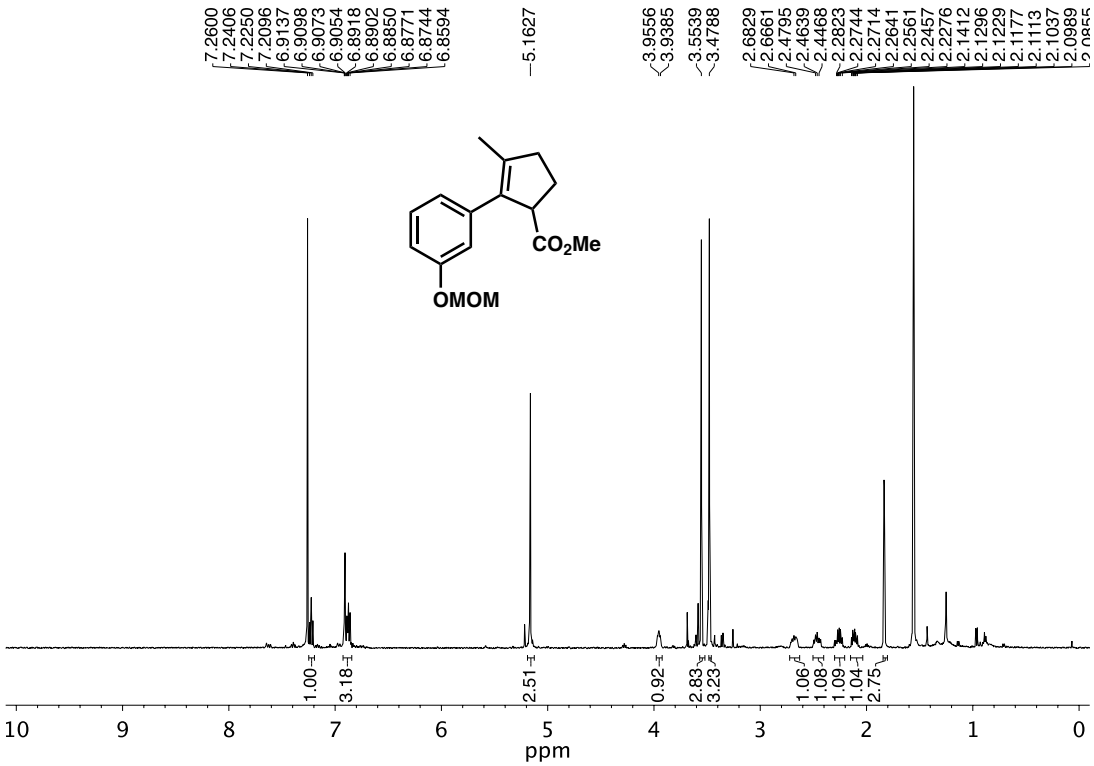


Figure 5.54. ^{1}H NMR (500 MHz, $CDCl_3$) of **5.35**.

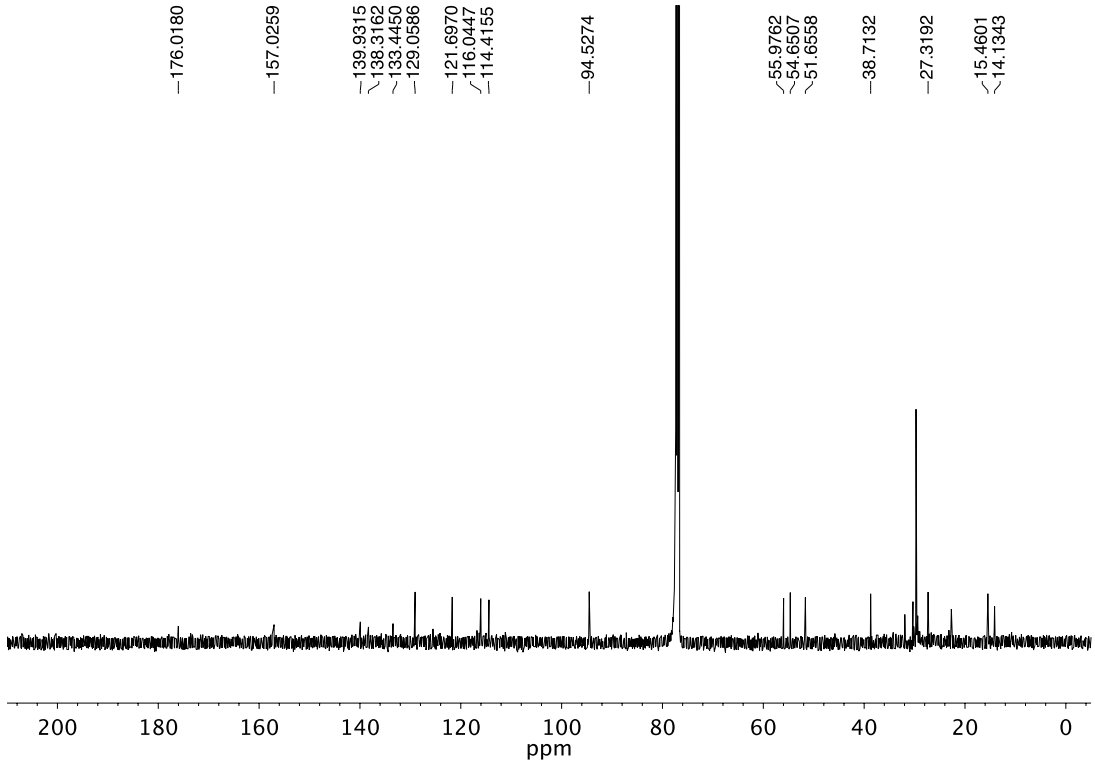


Figure 5.55. ^{13}C NMR (125 MHz, $CDCl_3$) of **5.35**.

5.9 Notes and References

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