

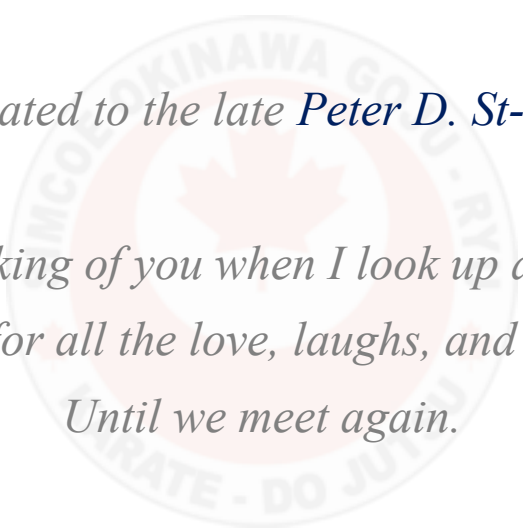
1,1,3,3-Tetramethyldisiloxane and potassium *tert*-butoxide as an unconventional reducing agent and its application in the synthesis and deconstruction of carbon–carbon bonds

By

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Dedicated to the late Peter D. St-Onge.

I'll be thinking of you when I look up at the stars.

Thanks for all the love, laughs, and support.

Until we meet again.

ABSTRACT

Over the past decade, the combination of hydrosilanes and Lewis bases have seen a renaissance with chemists uncovering the mechanistic intricacies that underlying their reactivity. Owing to the diverse mechanistic reactivity showcased by these reagent combinations, various reductive defunctionalization reactions including C–O, C–N, and C–C bond cleavage have been reported as practical synthetic methods. Further investigation of these reagent combinations led to the development of C–H and N–H silylation reactions in addition to hydrosilylation reactions earning their place as versatile synthetic multi-tools. Despite this synthetic versatility, chemists have yet to extend the list of transformations facilitated by hydrosilanes and Lewis bases to the synthesis of carbon-carbon bonds – a fundamental transformation in organic synthesis. This thesis outlines the discovery and application of 1,1,3,3-tetramethyldisiloxane (TMDSO) and potassium *tert*-butoxide (KO^tBu) as a unique reducing agent towards C–C bond cleavage and C–C bond formation.

Chapter Two of this dissertation outlines the serendipitous discovery and development of the reductive C(sp²)–CF₃ bond cleavage of 2-trifluoromethylpyridines. Using TMDSO and KO^tBu the reductive cleavage of C(sp²)–CF₃ bonds was demonstrated to be regioselective for C2 on trifluoromethylpyridines and trifluoromethylquinolines bearing alkyl, amino, aryl, and chloro substituents. A small mechanistic investigation unveiled that TMDSO and KO^tBu may display redox reactivity acting as a one-pot single-electron donor and hydrogen atom donor. The discovery of this redox reactivity manifold culminated in a hydroalkylation reaction discussed in chapter 3 of the dissertation.

Chapter Three of this dissertation builds on a discovery made towards the end of Chapter Two where under the same reaction conditions *trans*-stilbene could be hydroalkylated using an alkyl halide as an electrophile, representing the first instance of C(sp³)–C(sp³) bond formation facilitated by the combination of a hydrosilane and Lewis base. This transition-metal-free approach is used to functionalize mono, di, and trisubstituted aryl olefins bearing alkyl, aryl, and halogen substituents and primary and secondary alkyl halides as electrophiles. An in-depth mechanistic analysis pointed towards the formation of a benzylic radical via HAT from what is presumed to be a potassium dihydridosilicate to styrene, followed by a key reductive radical polar crossover step to transform the benzylic radical into a benzylic carbanion. A subsequent bimolecular nucleophilic substitution reaction between the benzylic carbanion and alkyl halide leads to the desired product.

Chapter Four of this dissertation highlights an unusual $C(sp^3)$ -H alkylation reaction facilitated by TMDSO and KO^tBu that was discovered at the end of chapter three. In this chapter, TMDSO and $KOtBu$ are used to facilitate the deprotonation and alkylation of weakly acidic $C(sp^3)$ -H bonds. A small scope of alkylpyridines, benzylic species, and dithiane were amenable to the reaction conditions. A unique feature of this reaction is the overalkylation of the intended product thought to occur through a subsequent deprotonation and alkylation step; this reactivity was exploited to synthesize novel spirocycles from alkylpyridines and dihaloalkanes. Control experiments, reaction kinetics, and substrate probes revealed the reaction proceeds through a key deprotonation step facilitated by a KH-like base derived from the hydrosilane, TMDSO.

This thesis concludes with chapter five highlighting the significance of this work by demonstrating the expansion of hydrosilane and Lewis base reactivity towards the synthesis of $C(sp^3)$ - $C(sp^3)$ bonds. This chapter also serves to frame the future of this reactivity based on the opinions of the dissertation author.

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Statement of Contributions

Unless otherwise noted, all work in this thesis is original and was conducted by the dissertation author. Chapter 2 saw assistance from Shajia I. Khan who led the optimization of the transformation, and who synthesized and purified starting materials and scope examples. Adam Cook conducted the variable time normalization analysis. All other work in chapter 2 was conducted by the author of this thesis. Hana Nugraha contributed to chapter 3, specifically in the early stages of the project where she screened various substrates to determine which were amenable to the reaction conditions. Further, she synthesized a substrate to test as a mechanistic probe. All other work in chapter 3 was conducted by the author of this dissertation. Finally, chapter 4 was conducted solely by the author of this dissertation. All rough drafts of the manuscripts and the accompanying supporting information were written by the author of this dissertation with revisions and editing from Professor Stephen G. Newman and the coauthors of the work. Specific contributions (ie. experiments, and their location within the chapter) are outlined in their respective chapter.

Claims to Original Research

Chapters 2 and 3 of this dissertation are originally published in the following journals:

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List of Abbreviations

2c–2e	2-center-2-electron bonding
3c–4e	3-center-4-electron bonding
BDE	bond dissociation energy
bp	boiling point
CDCl ₃	chloroform-d1
d	doublet
DCM	dichloromethane
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DMSO	dimethyl sulfoxide
DNB	dinitrobenzene
EI	electron impact
EPR	electron paramagnetic resonance
e.g.	for example
GCMS	gas chromatography–mass spectrometry
HAT	hydrogen-atom transfer
HDS	hydrodesulfurization
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HTE	high-throughput experimentation
Hz	Hertz
LAH	lithium aluminum hydride
Magn. Sector	magnetic sector

MeCN	acetonitrile
MHz	megahertz
MHAT	metal-hydride hydrogen atom transfer
m	multiplet
n-BuLi	n-butyllithium
NMR	nuclear magnetic resonance
pKa	acid dissociation constant
PFAS	polyfluoroalkyl substances
PhMe	toluene
PKIE	primary kinetic isotope effect
PMHS	polymethylhydrosiloxane
PMI	process mass intensity
ppm	parts per million
q	quartet
quin	quintet
RRPC	reductive radical polar crossover
s	singlet
SCE	saturated calomel electrode
SDS	safety data sheet
SET	single-electron transfer
S _N 2	bimolecular nucleophilic substitution
Stb	stilbene
TBAF	tetrabutylammonium fluoride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy radical

TEMPOL	4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilane
TMSCl	chlorotrimethylsilane
TMDSO	1,1,3,3-tetramethyldisiloxane
UV	ultraviolet
vTNA	variable time normalization analysis
V	volts
via	by way of
XAT	halogen atom transfer
XEC	cross-electrophile coupling
π^*	antibonding molecular orbital

Chapter 1 | Hydrosilanes and Lewis Bases: Properties and Reactivity in Organic Synthesis

1.1 | Chapter outline

The research in this dissertation is unified by the theme of hydrosilanes and Lewis base-mediated transformations in organic synthesis. This chapter serves to provide the reader with context necessary to understand the diverse reactivity that arises when mixing hydrosilanes and Lewis bases. A prerequisite to understanding these reactions, is to first understand the properties and reactivity that silicon displays when interacting with a Lewis base. This includes the topic of hypervalent silicon, its behaviour in solution, and its reactivity. Section 1.2 serves to introduce the properties associated with hypervalent silicon followed by its behaviour in solution. Section 1.3 summarizes the field of hydrosilane and Lewis base-mediated carbonyl hydrosilylation and reduction. Section 1.4 introduces the reader to the unconventional reactivity of hydrosilanes and Lewis bases and then elaborates on the mechanistic underpinnings that enable this reactivity. Chapter 1 then concludes by stating the overarching research goals associated with the dissertation research before transitioning into chapter 2.

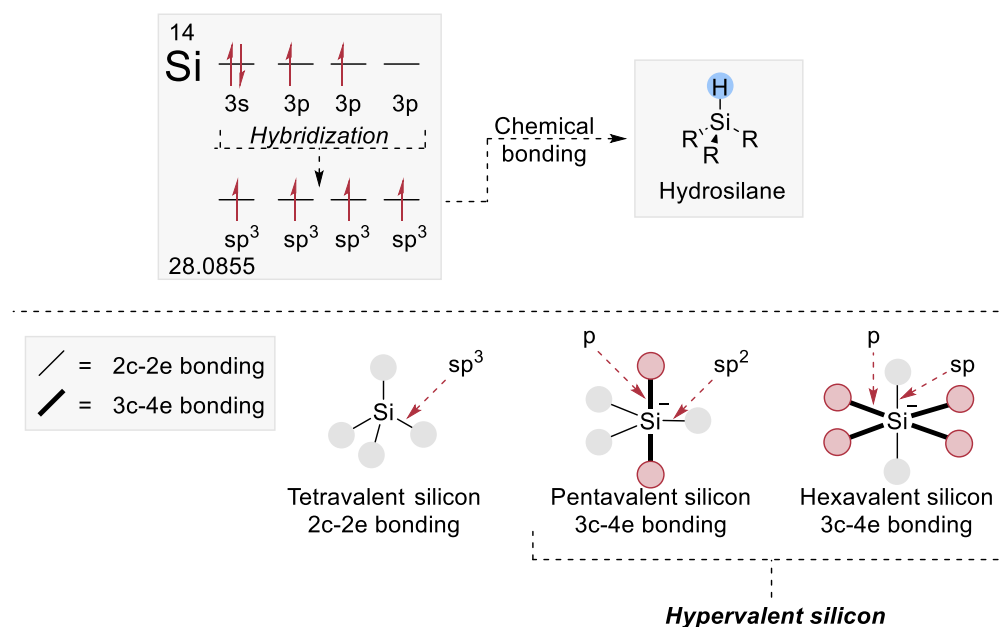
1.2 | Properties, behaviour, and reactivity of hydrosilanes and pentavalent hydrosilane complexes

1.2.1 | Hydrosilanes and pentavalent hydrosilane complexes

Like carbon, silicon has 4 valence electrons that can participate in chemical bonding. Tetravalent silicon – that is silicon bearing 4 bonds – possesses a tetrahedral geometry. Hydrosilanes are a subclass of tetravalent silicon compounds that contain at least one covalent Si-H bond and follow the general formula of $R_{(n-1)}SiH_n$ (**Figure 1.1**).^{1,2} Unlike carbon, silicon can accept electrons from Lewis bases interacting with them in a reversible fashion. Thus, to some extent, hydrosilanes may be considered Lewis acidic. Association of one Lewis base to silicon

results in the expansion of its valency from tetravalent silicon to pentavalent silicon.¹ Coordination of a second Lewis base to silicon results in a hexavalent species. Penta and hexavalent silicon are both examples of hypervalent silicon species.^{4,5} Accompanied by its change in valency, silicon's orbitals rehybridize to accommodate the additional electron density from the Lewis base. In pentavalent silicon 3 sp^2 hybridized orbitals engage in 2-center-2-electron bonding (2c–2e) with their substituents – that is, classical covalent bonding – whereas a p-orbital bonds with 2 substituents in what is referred to as 3-center-4-electron bonding (3c–4e). Substituents participating in 3c–4e bonding tend to be more polarized and further from the silicon center compared to substituents engaging in covalent bonding (2c–2e).¹ In hexavalent silicon, 2 sp hybridized orbitals participate in 2c–2e bonding while 2 p orbitals are engaged in 3c–4e bonding.^{4,5} Accompanied by silicon's expanded valence is a change in its properties and reactivity. Taking a hypervalent hydrosilane as an example, the silicon center is typically more electron dense and bears a partial or full negative charge, depending on the extent of electron donation from the Lewis base.⁶ This results in the lengthening of the silicon hydride bond rendering it hydridic, and more reactive than its tetravalent counterpart. Second pentavalent hydrosilane complexes typically, but not exclusively, assume a trigonal bipyramidal geometry – a consequence of orbital rehybridization – with the hydride substituent occupying either the axial or equatorial position.³ Whether hydride is present at the axial or equatorial position depends on both the substituents covalently bound to silicon and the Lewis base associated to silicon's 3d-orbital.^{3,7} Though it is thought that transfer of Si–H is more favourable from the apical site. Finally, while the substituents on hydrosilanes are purely covalent, the substituents in a pentavalent silicon complex have some ionic character which ultimately results in the dynamic behaviour exhibited by these complexes in solution.³

Figure 1.1: Chemical bonding and properties of tetravalent and hypervalent silicon



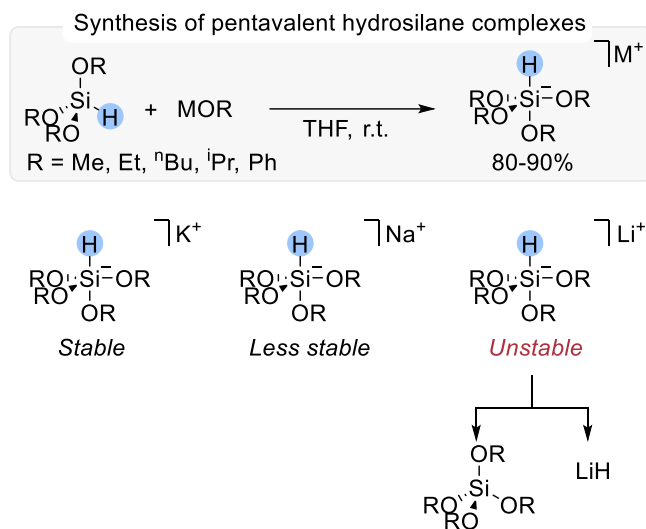
1.2.2 | Pentavalent hydrosilane complexes and their behaviour in solution

Pentavalent hydrosilane complexes are accessed in two ways: by mixing hydrosilanes with Lewis bases in solution or by synthesizing and isolating the complexes directly. Complexes formed with ionic Lewis bases carry full charges, whereas those formed with neutral Lewis bases carry partial charges. Early studies aimed to understand the behavior of these species in solution by focusing on their direct synthesis, isolation, and subsequent use.

The study and characterization of pentavalent hydrosilane complexes dates back to the early 1960s.⁶ Frye reported the first instance of a pentavalent alkoxy silane he coined as a triptych-siloxazolidine (**Figure 1.2**). This hydrosilane featured 3 alkoxy substituents bound to an amine that would coordinate to the silicon center through its nitrogen lone pair. Until this point, a stable pentavalent complex comprised of trialkoxysilanes and amines had yet to be reported. This was attributed to the steric penalty accompanied by coordination of an aliphatic amine to silicon

pentavalent hydrosilane complex. The authors noted their stability in solution was heavily associated with the counterion. Mixing lithium ethoxide (LiOEt) and triethoxysilane ((EtO)₃SiH) led to 40% formation of tetraethyl orthosilicate (Si(OEt)₄) and the desired complex [(OEt)₄SiH]Li⁺ whereas synthesizing the potassium analogue of the same complex led to exclusive formation of [(OEt)₄SiH]K⁺ in 85% yield.¹¹ The authors were unsuccessful in synthesizing [(OPh)₄SiH]Li⁺ suggesting the alkoxy substituents also influence the stability of these complexes. The decomposition pathway is thought to lead to the formation of lithium hydride (LiH) as a byproduct, which the authors propose as the driving force for decomposition.

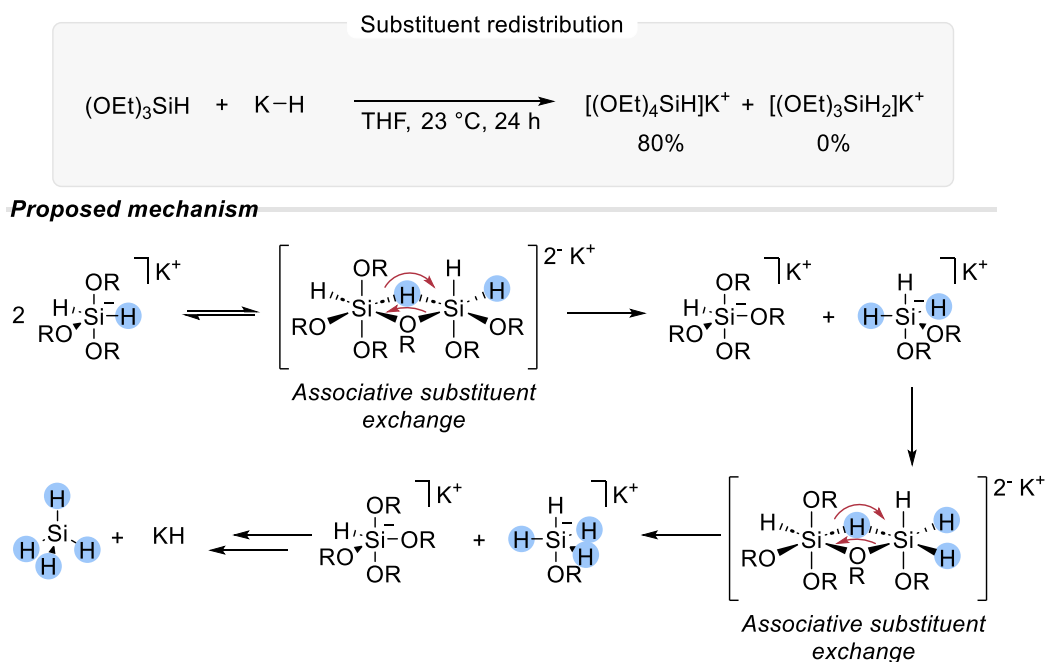
Scheme 1.1: Synthesis, stability, and decomposition of pentavalent hydrosilane complexes



Although pentavalent silicon species are stable in the solid-state, they readily undergo substituent exchange between pentavalent hydrosilane complexes. This exchange often produces a mixture of pentavalent hydrosilane species which vary depending on the type of substituents bound to silicon. In a follow up study, the authors investigated pentavalent potassium dihydrosilane complexes which, as their name suggests, follow the formula [(OR)₃SiH₂]K⁺ where R is an alkyl or phenyl substituent.¹¹ To their surprise many of these dihydrosilane complexes were

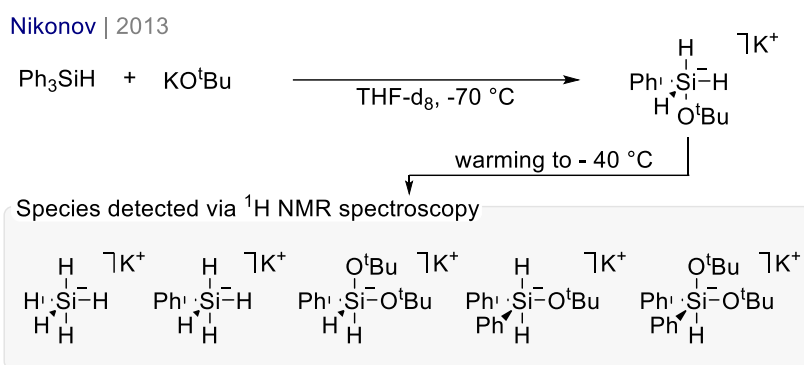
unstable in solution and would degrade into $[(\text{OR})_4\text{SiH}]\text{K}^+$, silane (SiH_4), and potassium hydride (KH) (**Scheme 1.2A**). The authors found that dihydrosilane complexes bearing methoxy (OMe) and ethoxy (OEt) substituents were unstable in solution, whereas complexes bearing bulkier isopropoxy (O^iPr) and sec-butoxy ($\text{O}^{\text{sec}}\text{Bu}$) substituents were resistant to degradation. This process is thought to proceed through an associative mechanism between pentavalent hydrosilane complexes leading to the formation of a dimeric intermediate bridged through hydride and alkoxy substituents (**Scheme 1.2B**).^{11,12} Increasing steric bulk around the alkoxy substituent prevents this decomposition pathway, which is attributed to a decreased rate of decomposition arising from an energetically disfavoured association between two pentavalent hydrosilane complexes. Furthermore, solvents are also known to influence the exchange of hydride groups which is attributed to solvent-induced geometry changes of these pentavalent complexes.

Scheme 1.2: Mechanism of substituent redistribution of alkoxy substituents in pentavalent hydrosilane complexes



The exchange of substituents around silicon isn't limited to only alkoxide and hydride substituents, but phenyl substituents are known to undergo a similar exchange pathway.¹³ ^{29}Si and ^1H nuclear magnetic resonance (NMR) experiments conducted in a study from 2013 showed at $-70\text{ }^\circ\text{C}$ the mixture of phenylsilane (PhSiH_3) and potassium *tert*-butoxide (KO^tBu) combine to form $[\text{PhSiH}_3\text{O}^t\text{Bu}]^-\text{K}^+$. Warming up this species to $-40\text{ }^\circ\text{C}$ leads to the exchange of hydride, phenyl, and *tert*-butoxide substituents producing a complicated mixture of species including $[\text{PhSiH}_4]^-\text{K}^+$, and $[\text{SiH}_5]^-\text{K}^+$, $[\text{PhSiH}_2(\text{OtBu})_2]^-\text{K}^+$, $[\text{Ph}_2\text{SiH}_2(\text{O}^t\text{Bu})]^-\text{K}^+$, and $[\text{Ph}_2\text{SiH}(\text{O}^t\text{Bu})_2]^-\text{K}^+$ (**Scheme 1.3**). It should be noted that alkyl substituents are not exchanged in a similar manner to hydride, alkoxy, or phenyl substituents.

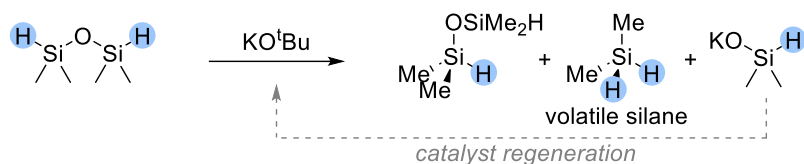
Scheme 1.3: Substituent exchange in aryl pentavalent hydrosilane complexes



Pentavalent complexes of hydrosiloxanes – a species of silane bearing Si–O–Si linkages as well as hydride substituents – are similarly known to be unstable in solution and undergo decomposition into multiple different species. In 2013 Nikonov and coworkers proposed the decomposition pathway of hydrosiloxanes where they undergo Lewis base-catalyzed decomposition into methylsilane (MeSiH_3) and a silicon gel like substance comprised of silicon oligomers and polymers (**Scheme 1.4**).¹³ The authors highlight that this represents an excellent way to access volatile silanes considering 1,1,3,3-tetramethyldisiloxane (TMDSO) and polymethylhydrosiloxane (PMHS) are the byproducts of direct synthesis. Furthermore, numerous

other hydrosilanes – particularly hydrosilanes bearing alkoxy substituents – are known to spontaneously produce SiH_4 which is a toxic and explosive gas.

Scheme 1.4: Lewis base-catalyzed decomposition of hydrosiloxanes



Although some pentavalent silicon complexes are stable in the solid state, they typically show dynamic reactivity in solution and produce various hydridic species. No mechanistic studies have been conducted to specifically understand which of these species is the active reducing agent and as a result it is generally accepted that they are all capable of facilitating transformations. These pentavalent complexes aren't often synthesized, isolated and used in reactions, rather chemists typically employ Lewis bases and hydrosilanes separately. Thus, the chemistry going forward in this dissertation will discuss hydrosilanes and Lewis bases separately rather than their complex, under the assumption that these pentavalent complexes form in solution.

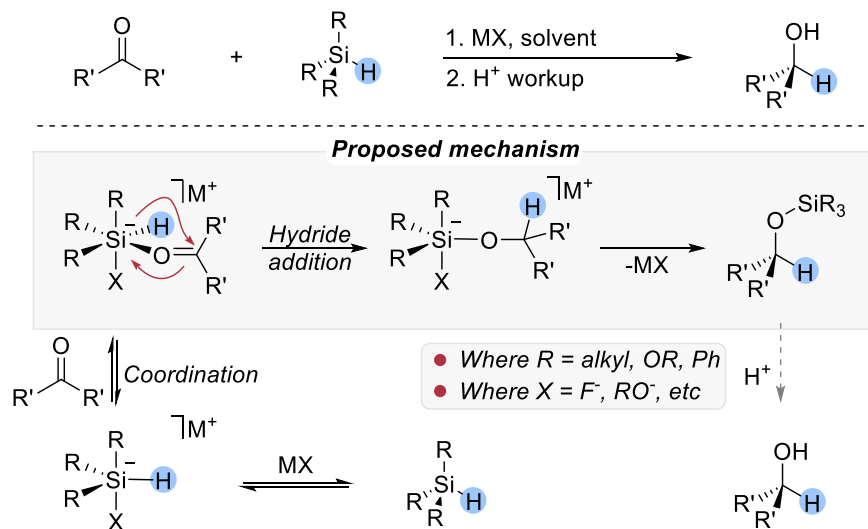
1.3 | Hydrosilane and Lewis base-mediated hydrosilylation of carbonyls

The hydrosilylation of carbonyls represents an important class of transformations seeing widespread use in industry for the preparation of silicon-containing materials. Typical hydrosilylation reactions employed transition metal catalysts and hydrosilanes to perform this transformation on ketones,^{14,15} imines,¹⁶ and nitriles.¹⁷ Equally as important are reduction reactions wherein acidic treatment of the silyl ether resulting from hydrosilylation will provide the corresponding alcohol. Typical hydride reductants used to reduce carbonyl species are sodium borohydride (NaBH_4), lithium aluminum hydride (LAH), and diisobutylaluminum hydride (DIBAL-H). While these have seen extensive use and continue to do so, they're not without their

shortcomings. For instance, they are sensitive to moisture which forces them to be stored under dry and often inert conditions. LAH, for instance, is so reactive it spontaneously ignites in air and has been documented countless times as starting fires.¹⁸ Better ways to improve the safe handling of LAH and related metal hydrides will likely see study well into the future. Hydrosilanes on the other hand are shelf-stable and typically less moisture sensitive than their metal hydride counterparts representing a safer, and in some ways, more practical alternative.

The hydrosilylation of carbonyls is thought to proceed through reversible formation of the pentavalent hydrosilane complex (**Scheme 1.5**). Subsequent association of the carbonyl lone pair to the silicon center affords a hexacoordinate hydrosilane complex. From there, hydride addition to the antibonding molecular orbital (π^*) of the carbonyl results in breaking of the π -C-O bond and formation of the Si-O bond.^{19, 20} Dissociation of the pentavalent silane complex affords the Lewis base and silyl ether which upon hydrolysis provides the corresponding alcohol, in the case of aldehydes and ketones. Esters and amides require two hydride equivalents to reduce down to the corresponding alcohol and amine, respectively.

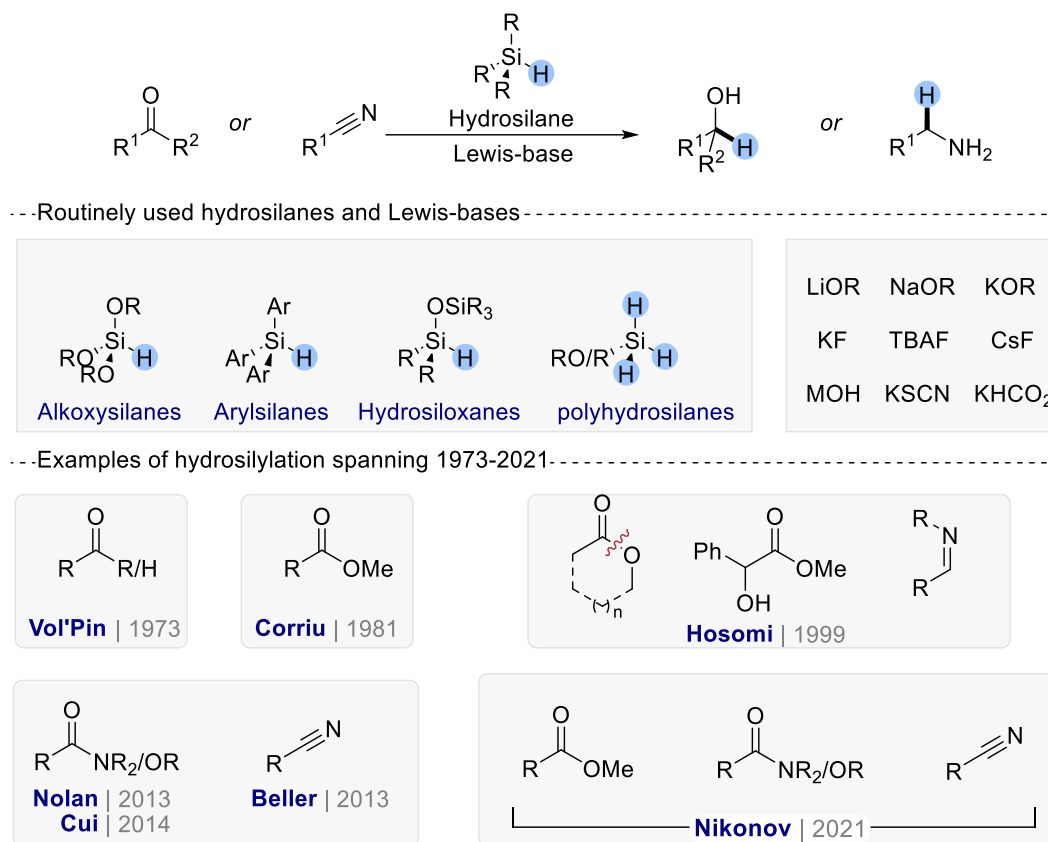
Scheme 1.5: General mechanism of carbonyl hydrosilylation



Hydrosilanes and Lewis bases are able to facilitate hydrosilylation in the absence of a transition metal catalyst. The earliest example goes back to Vol'pin who in 1973 reported the cesium fluoride (CsF)-catalyzed hydrosilylation of carbonyls using trialkylsilanes (**Figure 1.3**).²¹ Soon after this initial work it was found that arylsilanes reacted with carbonyls much more effectively than trialkylsilanes, and using various metal salts including CsF, potassium fluoride (KF), potassium formate (KHCO₂), and potassium thiocyanate (KSCN) with harder bases proving more effective.²³ Though many of these reactions were heterogeneous due to the poor solubility of these harder salts. The use of tetrabutylammonium fluoride (TBAF) and related fluoride salts that demonstrated higher solubility proved more efficient. Alternatively, the use of polar aprotic solvents such as hexamethylphosphoramide (HMPA) could be used to help solubilize these species improving their reactivity.²³ Indeed this area continued to see intense study showing the use of trialkoxysilanes,²⁴ and hydrosiloxanes,²⁵ in combination with metal salts to reduce carbonyls. The scope of carbonyl reduction also saw progress including work by Hosomi who showed lactones, imines, and α -hydroxy esters undergo reduction. Interestingly, the hydroxyl group present in α -hydroxy esters helped to direct hydride reactivity, presumably through association to silicon.²⁶ Developments of hydrosilane and Lewis base-mediated hydrosilylation were made well into the 2000s where Nolan in 2013 reported the hydrosilane-mediated reduction of esters and amides using catalytic KOH, PhSiH₃, and no solvent.²⁷ This marked the first instance of amides undergoing transition-metal free reduction down to the corresponding amine. Similar bodies of work from the groups of Cui and Beller disclosed similar hydrosilane-mediated amide reduction using PhSiH₃ as their hydrosilane and subsequent hydrolysis using acidic conditions, with Beller's conditions also being capable of reducing nitriles down to the amine.^{28,29} Finally, work by Nikonov

in 2021 identified general conditions using catalytic KO^tBu and (EtO)₃SiH at room temperature capable of reducing aldehydes, ketones, esters, amides, and nitriles down to alcohols and amines.³⁰

Figure 1.3: Fifty years of dedicated hydrosilylation studies



1.4 | Hydrosilanes and potassium alkoxides: unconventional reactivity and mechanisms

Section 1.3 highlights the unconventional reactivity – that this dissertation author will define as reactivity that diverges from the typical hydride reduction of carbonyl species – of hydrosilanes and Lewis bases particularly, but not exclusively, with the use of KO^tBu as a Lewis base additive. This unconventional reactivity as seen in section 1.1.3 went largely unnoticed as chemists focused their attention on the development of carbonyl hydrosilylation (see section 1.2). However, in 2013 this unconventional reactivity saw a renaissance with the discovery that

triethylsilane (Et_3SiH) and KO^tBu facilitate the reductive cleavage of C–O bonds in diaryl ethers.³¹ Given the unintuitive nature of this transformation, follow-up studies uncovered that this reducing agent can facilitate many transformations including C–N, C–S, C–C bond cleavage, and the silylation of N–H and C–H bonds. The ability for one reagent pair to facilitate so many different transformations is remarkable and naturally piqued the curiosity of chemists, which led to about a decade's worth of mechanistic studies devoted to uncovering how these reactions take place. These findings show that Et_3SiH and KO^tBu – commonly referred to as the Grubbs-Stoltz reagent – is a mechanistically intricate and diverse species. The author of this dissertation would argue there is great value in studying such a reagent pair, and more broadly related classes of reagents with the hopes of applying what is learned to organic synthesis. Herein lies a discussion on the reactivity and mechanistic underpinnings of these reagents.

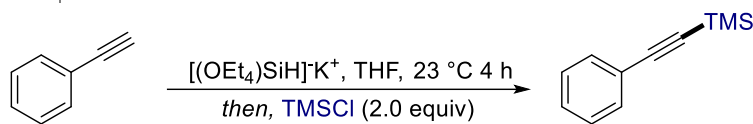
1.4.1 | Early developments of the unconventional reactivity of pentavalent hydrosilane complexes

1.4.1.1 | Early signs of basic reactivity of $[(\text{OEt})_4\text{SiH}]^-\text{K}^+$

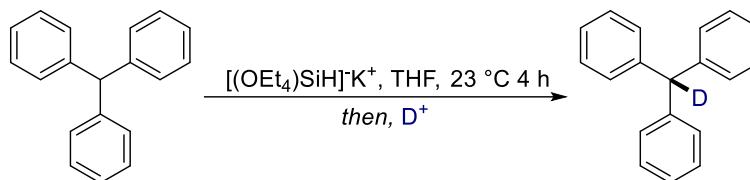
In preliminary work conducted by Corriu and coworkers, $(\text{OEt})_4\text{SiH}]\text{K}^+$ was shown to react with phenylacetylene and the mixture was then quenched by adding chlorotrimethylsilane (TMSCl) (**Scheme 1.6**).¹¹ The authors speculated that deprotonation of the terminal alkynes C–H bond occurred forming potassium acetylide. In a similar experiment, treating triphenylmethane with $[(\text{OEt})_4\text{SiH}]^-\text{K}^+$ followed by subsequent deuterolysis led to the formation of triphenylmethane- d_1 (Ph_3CD). The authors speculated that the highly polarized Si–H bond was responsible for the deprotonation taking place leading to the formation of hydrogen gas and tetraethyl orthosilicate as byproducts. These preliminary results highlighting the basic nature of pentavalent hydrosilane complexes never saw further development.

Scheme 1.6: Early examples of pentavalent hydrosilicates exhibiting basic reactivity

Corriu | 1991



Corriu | 1991

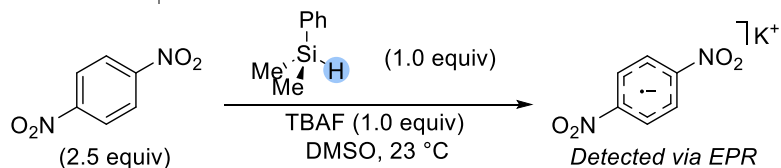


1.4.1.2 | Early redox reactivity of hydrosilanes and Lewis bases

In 1986, Tanner et al. set out to investigate whether the reduction of carbonyls by hydrosilanes and Lewis bases occurred through a heterolytic pathway or through single-electron processes.³² An in-depth mechanistic investigation pointed out a heterolytic pathway was responsible for hydrosilylation. Interestingly however, mixing of phenyldimethylsilane (Me_2PhSiH), TBAF and dinitrobenzene (DNB) resulted in the formation of a dinitrobenzene radical anion (**Scheme 1.7**).

Scheme 1.7: Single electron reduction of dinitrobenzene

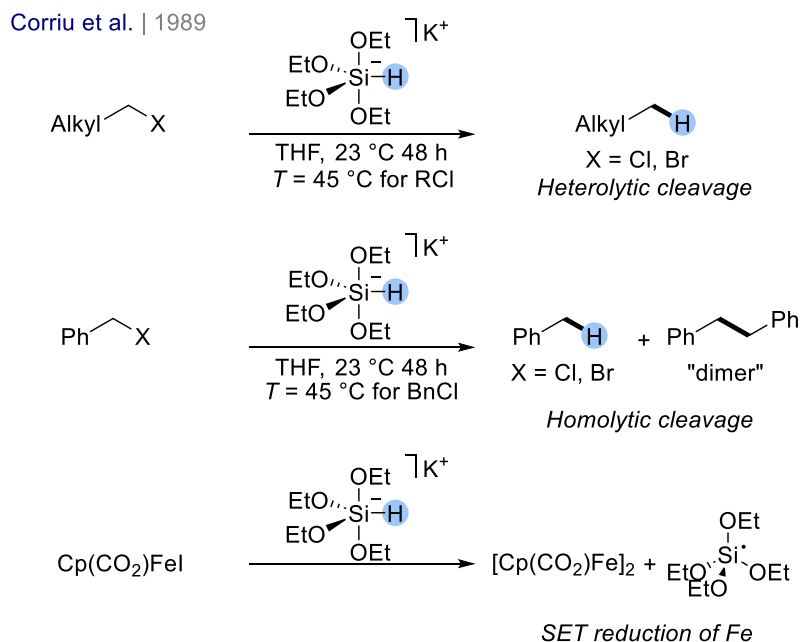
Tanner et al. | 1986



This radical anion was detected via electron-paramagnetic resonance (EPR) spectroscopy. Notably, this reactivity was not observed when mixing DNB with TBAF or Me_2PhSiH independently. This led the authors to speculate that $[(\text{Me}_2\text{PhSiHF})^-\text{TBA}]^+\text{K}^+$ was forming in solution and responsible for donating a single-electron to dinitrobenzene. A subsequent study in 1991

elaborated on the redox reactivity displayed by pentavalent hydrosilane species. In this work, alkyl and benzyl halides were shown to undergo reduction to the corresponding alkylbenzene when mixed with $[(\text{OEt})_4\text{SiH}]^-\text{K}^+$ (**Scheme 1.8**).³³ The authors investigated whether hydrodehalogenation was proceeding through a homolytic or heterolytic pathway through use of known radical probes. The results indicated that alkyl halides underwent hydrodehalogenation through an ionic reduction pathway, whereas benzyl halides were reduced shown to undergo reduction through a homolytic pathway. The authors speculated this occurred through single-electron transfer to the benzyl halide. Next, the authors found the reduction of η^5 -cyclopentadienyl(dicarbonyl)iodoiron(II) ($\text{Cp}(\text{CO}_2)\text{FeI}$) down to its dimer bis[η^5 -cyclopentadienyl-bis(carbonyl)iron] ($[\text{Cp}(\text{CO}_2)\text{Fe}]_2$) when mixed with $[(\text{OEt})_4\text{SiH}]^-\text{K}^+$. The reduction of iron (II) to iron (I) by this complex further demonstrated its redox behaviour.

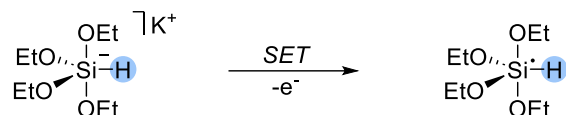
Scheme 1.8: Various reduction reactions facilitated by hypervalent silicon



The authors proposed the active single-electron donor to be $[(\text{OEt})_4\text{SiH}]^-\text{K}^+$ though no further or direct support for this was offered (**Scheme 1.9**). Notably while indirect evidence for a single-

electron donor was provided no direct evidence could substantiate the proposed reduction pathway. This will be brought into discussion in section 1.3.3. Despite these mechanistically intriguing reactions, they would wait for nearly 25 years before they saw application in the development of synthetic methods.

Scheme 1.9: Hypothesized single-electron donor



1.4.2 | The Grubbs-Stoltz reagent in reductive defunctionalization and intramolecular cyclization reactions

In 2013 Grubbs and Stoltz were studying transition metal-catalyzed reductive cleavage of C–O bonds in aryl ethers with the hopes of applying it to efficient biomass conversion (**Scheme 1.10A**).³¹ During their study of this transformation, they realized that the reaction proceeded in the absence of their transition metal catalyst, instead only requiring Et₃SiH and KO^tBu. This was a fascinating discovery at the time considering transition-metal-free aryl C–O reduction was unheard of; this led them to continue their study of this transformation with the hopes of providing a transition-metal-free alternative to C–O bond reductions for the synthetic community. A small scope showcasing the reduction of C–O bonds in diaryl ethers was synthesized along with a few alkyl-aryl ethers. In contrast to transition metal-catalyzed approaches, the alkyl C–O bond would be cleaved under Grubbs’s conditions – offering a complementary selectivity to existing methodologies.³⁴ An oligomeric ether containing six C–O bonds was used as a lignin-model and

underwent quantitative conversion suggesting this platform, with further development, may be applicable to lignin biomass conversion.

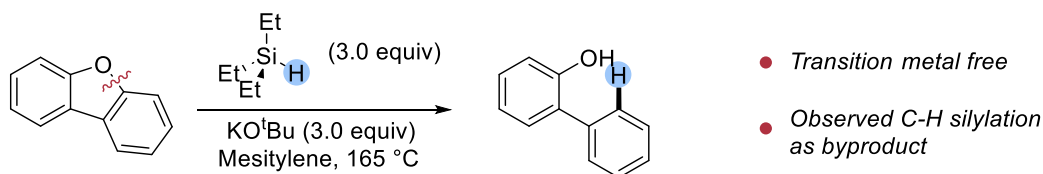
In a follow-up study Grubbs and Stoltz extended this reducing agent to the hydrodesulfurisation (HDS) of sulfur-heterocycles (**Scheme 1.10B**).³⁵ Diesel and other forms of petroleum often contain organosulfur impurities which lead to poisoning catalytic converters and the formation of sulfur-pollutants during fuel combustion.³⁶ The general protocol to remove these organosulfur impurities is through treatment of the sulfur-contaminated petroleum with hydrogen gas (H_2) and heterogeneous transition metal catalysts at high temperatures and pressures.³⁷ This treatment doesn't remove all sulfur impurities. Given the associated risks with heating petroleum – a fuel produced specifically for combustion... – in the presence of hydrogen gas at high pressures Grubbs and Stoltz set out to apply their reagent combination to desulfurize fuels with the hopes of providing a safer, cost-effective protocol. The reaction was first demonstrated on a scope of dibenzothiophenes, followed by non-heterocyclic aromatic sulfur species resulting in desulfurization of 71% and higher. The Grubbs-Stoltz reagent was then used to treat ultra-low sulfur diesel containing approximately 6.1 ppm of organosulfur impurities which led to the reduction of these impurities to ~ 2.3 parts per million (ppm) after 40 hours at 165 °C. This led to the method being considered for a HDS polishing technology. The authors conducted a density functional theory (DFT) study to investigate the mechanistic pathway for hydrodesulfurization and decided to also calculate the pathway for reductive C–O bond cleavage. The DFT showed that both the deoxygenation and desulfurization reactions proceed through nucleophilic addition of triethylsilyl radicals to the aromatic rings, followed by a sequence of intramolecular reactions culminating in reductive C–O bond cleavage in the case of aryl ethers, and hydrodesulfurization

of organic sulfides (**Scheme 1.10C**). The authors do not comment on the initial formation of this proposed triethylsilyl radical.

Scheme 1.10: The Grubbs-Stoltz reagent in deoxygenation and hydrodesulfurization reactions

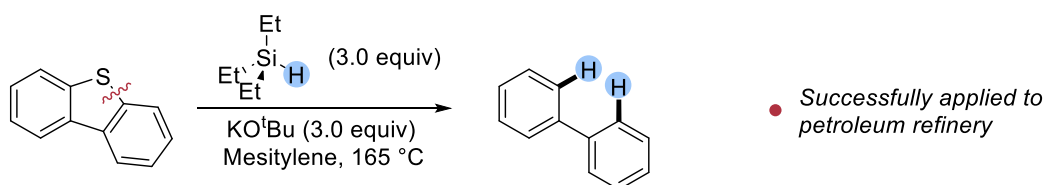
A. Reductive C-O bond cleavage of aryl ethers

Grubbs et al. | 2013

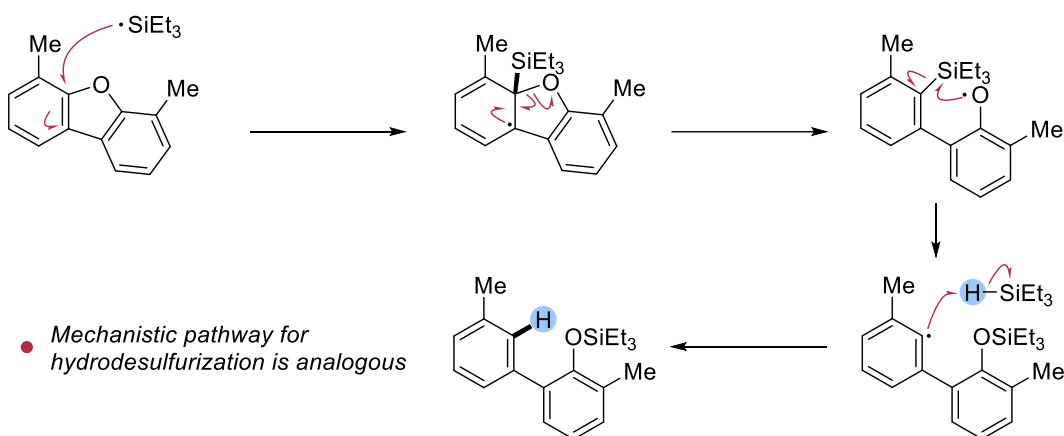


B. Hydrodesulfurization of organic sulfides

Grubbs et al. | 2017



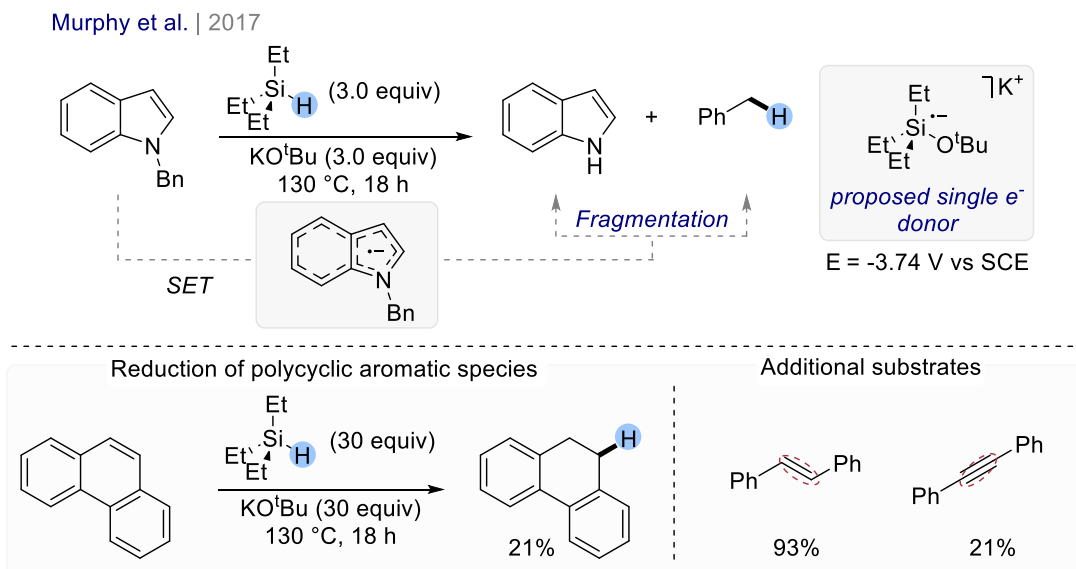
C. DFT-supported reaction mechanism



This curious reagent combination captured the attention of Professor John Murphy based in the University of Strathclyde who questioned the redox properties of the Grubbs-Stoltz reagent. The authors quickly discovered that the Grubbs-Stoltz reagent facilitates debenzylization of N-benzylindole (**Scheme 1.11**).³⁸ The single-electron reduction of N-benzylindole to indole and

toluene is typically performed using excess alkali metals in ammonia via the Birch-reduction.³⁹ This reaction proceeds through single-electron reduction of the indole to the indole radical anion followed by rapid fragmentation to the indolide and benzylic radical which lead to indole and toluene upon workup. The authors speculated that the triethylsilyl-tertbutoxy radical anion may act as a potent single-electron donor and used N-benzylindole as an electron acceptor to probe single-electron transfer. To question whether this was occurring the authors screened various N-benzylated indoles using the Grubbs-Stoltz reagent and observed significant debenylation in each case, providing experimental evidence of single-electron reduction taking place. A silicon radical anion, a pentavalent silicon complex, and silicide were all considered as candidates responsible for single-electron reduction of the N-benzyl indole. DFT calculations pointed towards prohibitively high activation energies and endergonic energetic barriers to SET from the pentavalent silicon complex, and silicide while the silicon radical anion showed a barrierless and exergonic energy profile. The calculated reduction potential of -3.74 V vs SCE in acetonitrile (MeCN) suggested the silicon radical anion to be a highly reducing single-electron donor, considerably higher than that of alkali metals. Direct experimental support of this reducing system to perform the Birch-reduction of polycyclic aromatic species, *trans*-stilbene, and diphenylacetylene further supported the silicon radical anion as being a valid single-electron donor, though direct hydride reduction of these systems was also deemed feasible based on calculated energetic barriers and could not be ruled out. Calling back to work by Tanner and Corriu; it's possible these transformations were being facilitated by a silicon radical anion (Scheme 1.7, Scheme 1.8).³²

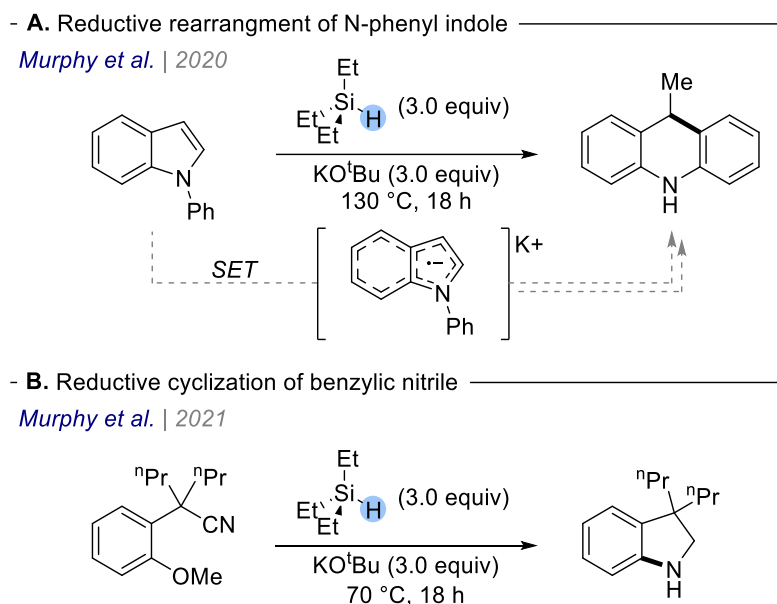
Scheme 1.11: Single-electron reduction of N-benzylindole and polycyclic aromatic species using the Grubbs-Stoltz reagent



Further studies building on the highly reducing nature of this silicon radical anion were undertaken using the Grubbs-Stoltz reagent. In a follow-up study, replacing N-benzylindoles with N-phenylindoles shut down the aforementioned radical fragmentation and instead the ring expansion to 9,10-dihydroacridines was observed (**Scheme 1.12A**).⁴⁰ A thorough mechanistic study including known mechanistic probes that test for the presence of radical anions and deuterium labelling experiments provided experimental evidence for silicon radical anion mediated single-electron reduction pathways leading to the 9,10-dihydroacridines. Given the complex nature of this reducing system, it's often challenging to propose a concrete mechanism as many feasible reactive intermediates are at play. Moreover, the barrier heights are in some instances of comparable magnitude further raising question as to which specific mechanism is operative. This is demonstrated in work featuring rearrangement reactions of benzonitriles and indolinenes where, yet another rigorous mechanistic study led the authors to propose the intermediacy of hydride donors, electron donors, hydrogen-atom donors, and silicon radicals

derived from the Grubbs-Stoltz reagent, all of which are potentially playing a role (**Scheme 1.12B**).⁴¹

Scheme 1.12: Reductive rearrangement reactions using the Grubbs-Stoltz reagent



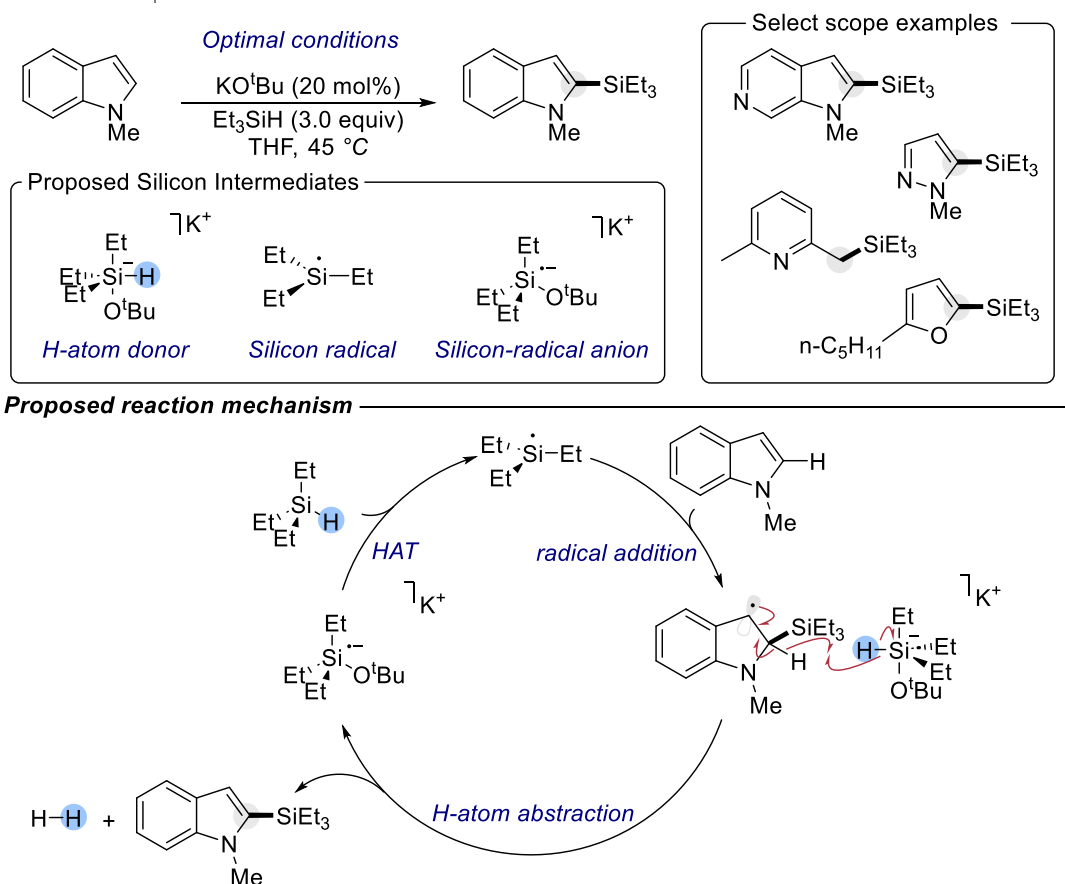
1.4.3 | Hydrosilanes and Lewis bases in C–H and N–H silylation reactions, and in the hydrosilylation of vinylarenes

Serving as a follow-up investigation to the reductive C–O bond cleavage of aryl ethers, Grubbs and Stoltz published the KO^tBu-catalyzed C–H silylation of heterocycles using Et₃SiH and KO^tBu (**Scheme 1.13**).⁴² This transformation is highly practical enabling access to heterocycles – which were previously out of scope using the current state-of-the-art transition metal-catalyzed protocols – such as indoles, pyridines, thiophenes, furans, pyrazoles, and more to undergo C(sp²)–H silylation. The method could also be extended to simple aryl C(sp²)–H and benzylic C(sp²)–H bonds albeit in slightly diminished yields, and derivatization of the silicon-handle showcased the high synthetic utility associated with this reagent pair. Given the clear synthetic utility of this method, an in-depth mechanistic study in collaboration with Kendall Houk to uncover the reaction

mechanism was undertaken.⁴³ The authors made a few noteworthy observations throughout this study. They began investigating counterion effects by using $\text{CsOH}\cdot\text{H}_2\text{O}$ and $\text{RbOH}\cdot x\text{H}_2\text{O}$ found like KOH, cesium cations (Cs^+) and rubidium cations (Rb^+) all promoted the reaction with K^+ leading to the highest yields whereas cations, including sodium cations (Na^+), lithium cations (Li^+), magnesium cations (Mg^{2+}), barium cations (Ba^{2+}), calcium cations (Ca^{2+}), aluminum cations (Al^{3+}) possessing smaller atomic radii could not promote the transformation. An induction period, which the authors attribute to formation of a pentavalent silicon complex, was measured for each base, with K^+ leading to the shortest of them all. Beyond that, the role of K^+ remained largely unknown which is consistent with many of the reports covering the Grubbs-Stoltz reagent.⁴⁴ Hydrogen gas evolution was detected using ^1H NMR spectroscopy and eudiometry, which was confirmed to come from the indole C–H bond at C2 and Et_3SiH through isotopic labelling experiments of Et_3SiH and the indole starting material. The use of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical probe helped the authors confirm the presence of triethylsilyl radicals through the corresponding radical adduct. Additionally, radical character on C3 of the indole was demonstrated through the observation of strain-driven cyclopropyl ring opening of a designer indole bearing a cyclopropyl ring at C3. Based on the data, the following mechanism was proposed: A triethylsilyl radical attacks C2 on the indole affording the benzylic radical on C3, subsequent hydrogen atom abstraction by a pentavalent silane complex affords the silylated indole, hydrogen gas, and a silicon radical anion which in the presence of Et_3SiH reacts to generate a new triethylsilyl radical alongside a pentavalent silicon hydride species. This study was published alongside an accompanying paper outlining an analogous ionic pathway for C–H silylation and cannot be ruled out leaving this mechanism up for debate.⁴⁵

Scheme 1.13: Radical C–H silylation of heterocycles

Grubbs et al. | 2017

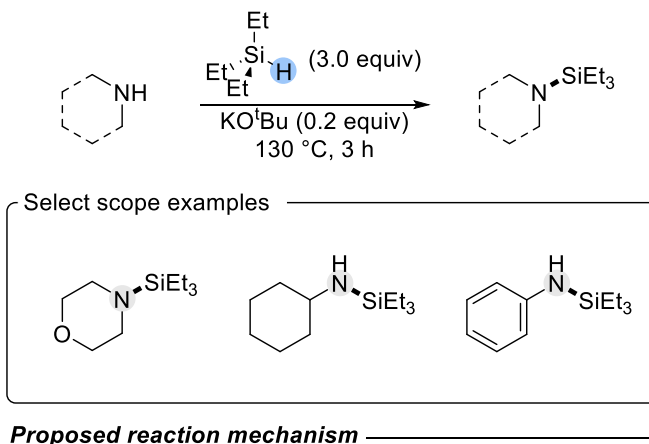


Another surprising reactivity manifold brought on by the Grubbs-Stoltz reagent was disclosed in 2019 showcasing the N–H silylation of amines.⁴⁶ The silylation of amines was accomplished using catalytic KO^tBu and stoichiometric Et₃SiH enabling the silylation of aniline, and both 1° and 2° aliphatic amines. A control experiment ruled out the direct deprotonation of the N–H bond using KO^tBu which prompted the authors to uncover the mechanism. Mechanistic and computational experiments corroborated their hypothesis that KH was the active catalyst responsible for deprotonating the amine. KH regeneration was proposed to occur through a key isomerization step (**Scheme 1.14**). One other instance of the Grubbs-Stoltz reducing agent creating basic conditions has seen computational support. In 2021, Murphy et al. conducted a study

surrounding the Truce-Smiles rearrangement of an ortho-tolylphenyl ether. DFT calculations supported a deprotonation pathway facilitated by the Si–H bond of a pentavalent silicon intermediate.⁴⁷

Scheme 1.14: Amine silylation using the Grubbs-Stoltz reagent

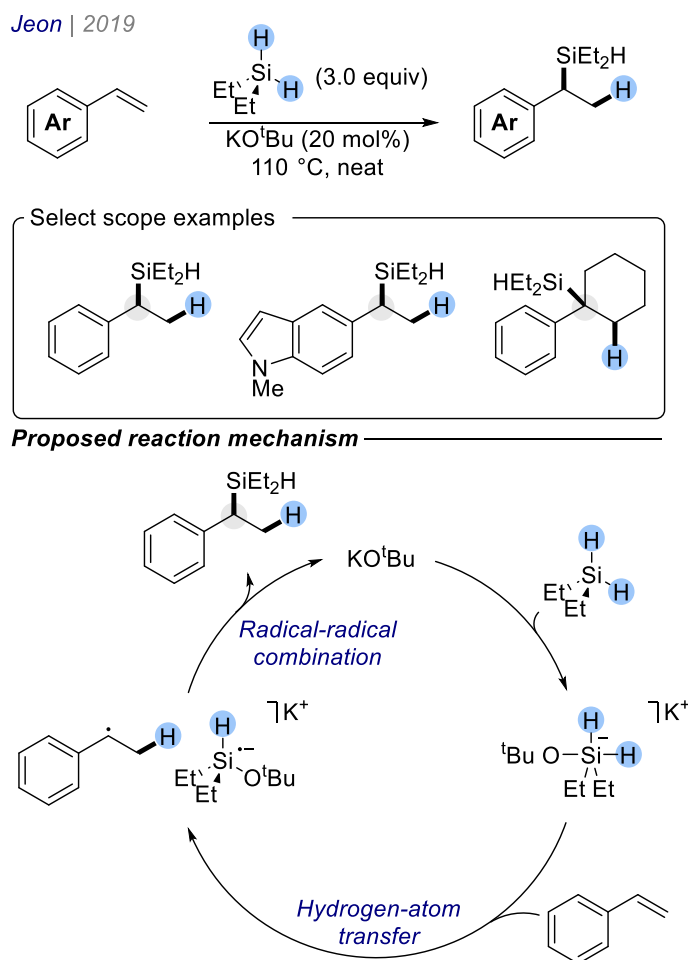
Murphy et al. | 2019



In 2019 work by Jeon showcased the use of diethylsilane (Et_2SiH_2) and potassium alkoxides as a powerful hydrogen atom donor capable of the hydrosilylation and polymerization of vinylarenes (**Scheme 1.15**).⁴⁸ This system was found to be distinct from the Grubbs-Stoltz reagent as Et_3SiH failed to perform the reaction. Despite this contrast, various hydrosilanes were shown to effectively facilitate polymerization and hydrosilylation including dialkylsilanes, siloxanes such as TMDSO, and arylsilanes clearly demonstrating a nuanced difference between

dialkyl and trialkylsilanes. Electron rich vinylarenes underwent smooth hydrosilylation with various examples of heterocycles in the scope. The authors conducted an in-depth mechanistic analysis of the reaction and through use of radical substrate probes found it to proceed through hydrogen atom-transfer from a pentavalent silicon complex to the corresponding benzylic radical and silicon radical anion. The authors propose a reversible dissociation of the silicon radical anion into KO^tBu and the silicon radical is followed by rapid radical combination furnishing the C–Si bond. Given that potassium is well known to associate to π -bonds of aromatic rings,⁴⁹ the authors speculated that π -cation interactions between potassium and styrene played a significant role in this transformation.⁵⁰ The authors had an interesting way of probing this reaction. Using TEMPO as an additive they observed 2,2,6,6-tetramethylpiperidin-1-ol (TEMPOL) indicating hydrogen atom transfer to TEMPO had taken place. Exclusion of styrene led to no formation of TEMPOL, however using 18-crown-6 – a known chelator of potassium cations – in place of styrene resulted in TEMPOL formation. This was interpreted to mean that the binding or chelating of the potassium cation leads to hydrogen-atom transfer taking place, thus the authors concluded that styrene was binding potassium through π -cation interactions.

Scheme 1.15: KO^tBu-catalyzed hydrosilylation of vinylarenes

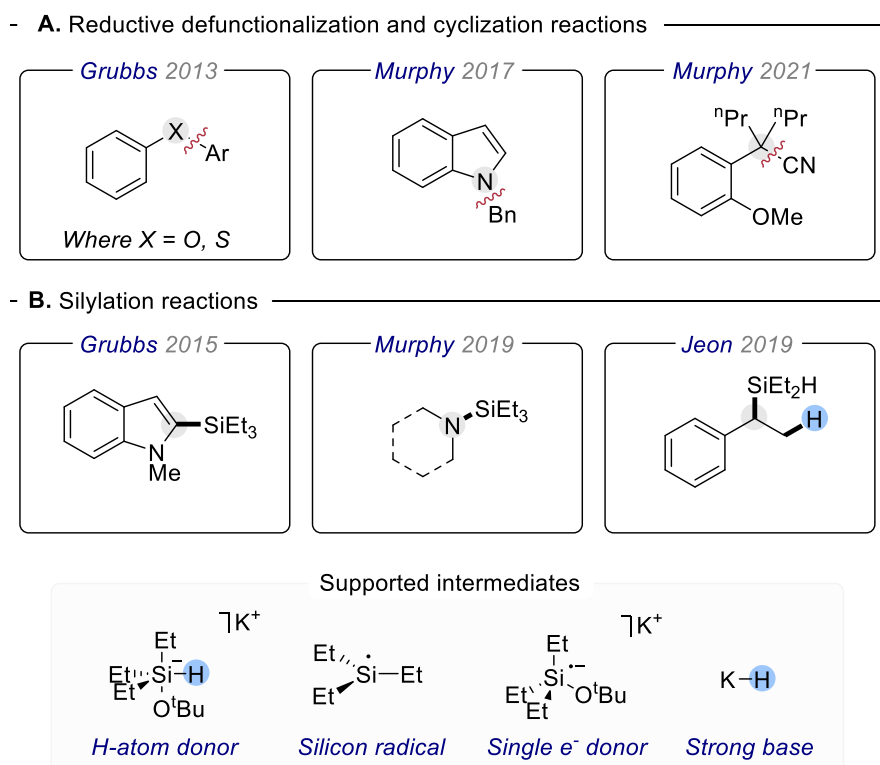


The use of hydrosilanes and Lewis bases has seen widespread application. The Grubbs-Stoltz reagent was used in the reductive C–O bond cleavage of diaryl ethers towards a cleaner, and practical alternative to the refinement of biomass conversion, the debenzoylation of N-benzyl indoles, and complex rearrangement reactions to construct heterocycles (**Scheme 1.16A**). Furthermore, the use of these powerful reducing systems in performing C–H silylation reactions of heteroarenes, N–H silylation of amines, and the hydrosilylation of vinylarenes - species which are of high value to the synthetic community - is significant (**Scheme 1.16B**). The widespread application of these reducing systems is a testament to their practicality as synthetic multi-tools

and should encourage further developments in this field. Further developments of this area would benefit from continued efforts towards understanding their reactivity.

It should be noted that while a lot of mechanistic insight had been gained from these studies, many unanswered questions remained: Outside of Jeon's work, the role of K^+ remains unclear with many reactions being shut down in the absence of K^+ . Similarly, some reactions are hydrosilane specific. Why is $KOtBu$ invoked as a catalyst in some reactions but stoichiometrically in others? In Jeon's catalytic silylation reaction Et_2SiH_2 promotes the transformation in high yields whereas introduction of Et_3SiH leads to a complete shut-down of the reaction. If one could understand these nuances, perhaps better control over these systems could be obtained.

Scheme 1.16: Summarizing the diverse reactivity of hydrosilanes and Lewis bases



1.5 | Research objectives

The extent of mechanistic diversity hydrosilanes and Lewis base combinations demonstrate is clearly profound and provides access to all kinds of reactive intermediates including radical anions, carbon-centered radicals, and more. This reactivity has led to the clear establishment of these species being powerful reducing agents capable of facilitating defunctionalization and silylation reactions. At the outset of this dissertation, no examples of hydrosilanes and Lewis base combinations mediating intermolecular carbon-carbon bond forming reactions had been reported. Given the development of synthetic methods to construct C–C bonds is an ongoing point of interest to the synthetic community, this was recognized as an important opportunity to develop complexity building reactions using hydrosilanes and Lewis bases. Thus, the primary goal of this dissertation was to:

Extend the breadth of hydrosilanes and Lewis base-mediated transformations to the synthesis of carbon-carbon bonds.

Chapter 2 of this dissertation outlines the discovery and development of an unintuitive and unexpected reductive de-trifluoromethylation reaction. The chapter begins with examples of C–CF₃ bond cleavage, followed by an introduction, discussion of the methodology, mechanism, and conclusions of the work.

Chapter 3 of this dissertation outlines the design and implementation of a hydroalkylation protocol. Of note, this work represents the first example of using hydrosilanes and Lewis base combinations to facilitate C(sp³)–C(sp³) bond formation. The chapter begins with an overview of existing hydroalkylation methodologies to provide the reader with context towards the hydroalkylation reaction featured in chapter 3. Next, the work is introduced followed by a discussion of the methodology, an in-depth mechanistic analysis, and conclusions.

Chapter 4 of this dissertation outlines a C–H alkylation protocol facilitated by TMDSO and KO^tBu. The chapter begins by discussing base-mediated C–H functionalization reactions with a particular emphasis on the mode of deprotonation. Following that the work is introduced followed by a discussion of the methodology, mechanistic analysis, and conclusions.

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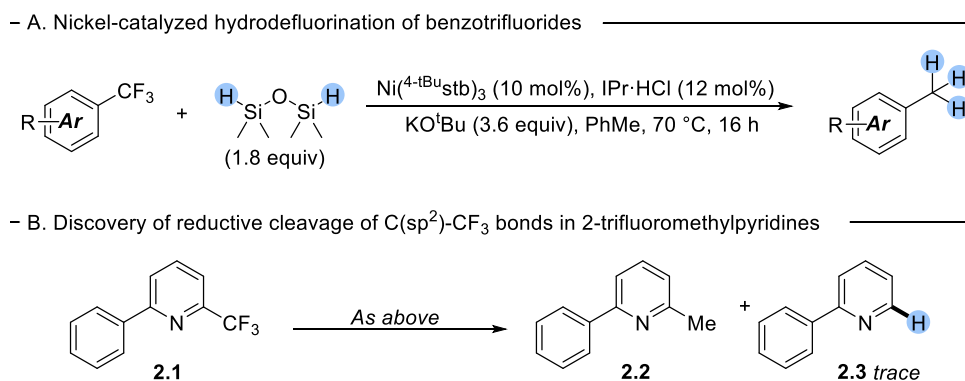
Chapter 2 | Reductive C–CF₃ Bond Cleavage of 2-Trifluoromethylpyridines

2.1 | Chapter outline

Chapter 1 demonstrated that hydrosilanes and Lewis bases are uniquely powerful reducing agents that are known to facilitate unexpected transformations. The dissertation author found himself studying this niche area of chemistry through serendipity while developing a nickel-catalyzed protocol for the hydrodefluorination of benzotrifluorides (**Scheme 2.1A**). During the scope evaluation of this transformation, it was discovered that substrate **2.1** underwent C–CF₃ bond cleavage leading to the formation of **2.3** in trace quantities (**Scheme 2.1B**). A quick investigation led the dissertation author to realize this transformation proceeds in the absence of the transition metal catalyst and using 1,1,3,3-tetramethyldisiloxane (TMDSO) and potassium *tert*-butoxide (KO^tBu) alone. This led to the development of a protocol to reductively cleave the C–CF₃ bonds in 2-trifluoromethylpyridines which is the primary topic of chapter 2.

Chapter 2 begins by providing the reader with a comprehensive evaluation of the existing protocols wherein C–CF₃ bond cleavage takes place. Next, the development of a protocol to cleave C–CF₃ bonds using TMDSO and KO^tBu will be discussed followed by its scope and a mechanistic analysis of the reaction. Finally, the chapter finishes with a conclusion of the research.

Scheme 2.1: Discovering the reductive C–CF₃ bond cleavage of 2-trifluoromethylpyridines



2.2 | Reuse permissions and contributions to research

The content of sections 2.4 (with the exception of 2.7.2, which is written for this dissertation), 2.5, 2.6, and 2.8 have been adapted with permission from the original manuscript and supporting information of “Reductive Cleavage of C(sp²)–CF₃ Bonds of 2-Trifluoromethylpyridines” by Piers St-Onge, Shajia I. Khan, Adam Cook, and Stephen G. Newman. {*Org. Lett.*, **2023**, 25, 1030-1034}. Copyright 2023 American Chemical Society. The dissertation author is the primary author of this work. Minimal changes have been made to the portions that were reproduced from the original manuscript. These changes unify the style and ensure consistent numbering of molecules, figures, tables, and schemes throughout this dissertation.

All other sections of chapter 2 are original and found only within this dissertation.

Contributions

The optimization of this reaction was conducted by Shajia I. Khan and presented in (**Table 2.1**). Shajia I. Khan synthesized select starting materials including **2.5**, **2.18**, **2.19**, **2.20**, and **2.31** and scope examples including **2.7**, **2.55**, **2.56**, **2.57**, **2.58**. with the remainder of the scope being synthesized, characterized, and isolated by the author of this dissertation. Adam Cook performed the variable time normalization analysis depicted in Section **2.6**, **Scheme 2.9A**. All other experiments were conducted by the dissertation author.

2.3 | Existing strategies to perform C–CF₃ bond cleavage

2.3.1 | The importance of hydrodefunctionalization reactions in organic synthesis

Hydrodefunctionalization reactions are of paramount importance to the synthetic community and see routine use in organic synthesis. Their applications are far-reaching and include the removal of protecting directing groups after the desired transformation has taken

place,^{1,2} and in the treatment and removal of persistent organic pollutants – a class of molecule defined by their ability to persist in the environment and bioaccumulate in humans and wildlife.³ Hydrodefunctionalization reactions are used in the controlled deconstruction of polymers – such as biomass – to materials that can be used in synthesis,⁴ the purification of petroleum fuels, (as previously discussed in chapter 1 section 1.3 of this dissertation),⁵ and generally in organic synthesis.

Given the importance of such reactions, it should come as no surprise that the number of strategies to perform hydrodefunctionalisation reactions is vast. There exist methods to reductively cleave nearly every functional group, if not all of them. The hydrodefunctionalization of C–C bonds, is significantly rarer in comparison though strategies to cleave C–C bonds in synthesis exist.⁶ Even more rare are the instances of reductive C–CF₃ bond cleaving reactions.

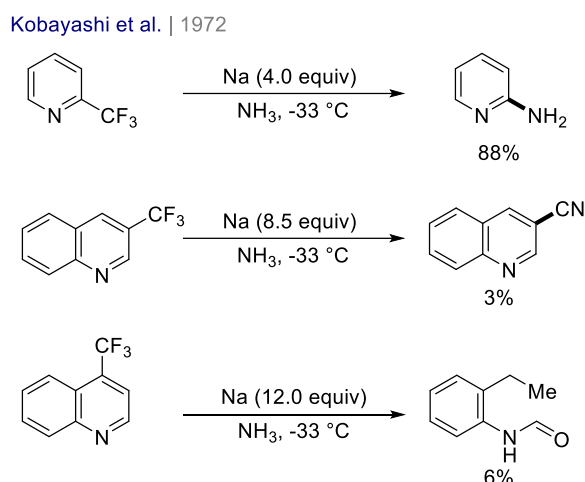
2.3.2 | The cleavage of C–CF₃ bonds

Polyfluoroalkyl substances – commonly referred to as PFAS – are chemically resistant to degradation and as a result tend to persist in the environment and even the human body.⁷ Considering their role in the body and environment is poorly understood their accumulation is viewed as an issue. Thus, there is some argument that the removal of trifluoromethyl groups, and longer perfluoroalkyl chains, is an important class of reaction. However, many instances of C–CF₃ bond cleavage have been discovered serendipitously rather than through intentional design and have led to studies founded in curiosity.

A study from 1972 outlined the C–CF₃ bond cleavage in 2-trifluoromethyl pyridines using sodium metal (Na) and liquid ammonia (NH₃) (**Scheme 2.2**).⁸ The authors proposed the mixing of sodium with ammonia produces sodium amide (NaNH₂) which undergoes a nucleophilic aromatic substitution (S_NAr) reaction with 2-trifluoromethylpyridine. The use of 2-trifluoromethylpyridine

as an electrophile resulted in the formation of 2-aminopyridine in 88% yield. However, the authors noted quinolines bearing a trifluoromethyl group at C3 and C4 to undergo different transformations under similar conditions. Positioning the trifluoromethyl group at C3 resulted in a 3% yield of 3-quinolinecarbonitrile whereas 4-trifluoromethyl quinoline underwent ring opening and hydrolysis. While this is not a reductive C–CF₃ bond cleaving reaction, its similarity to the reaction discussed in chapter 2 makes it worth mentioning.

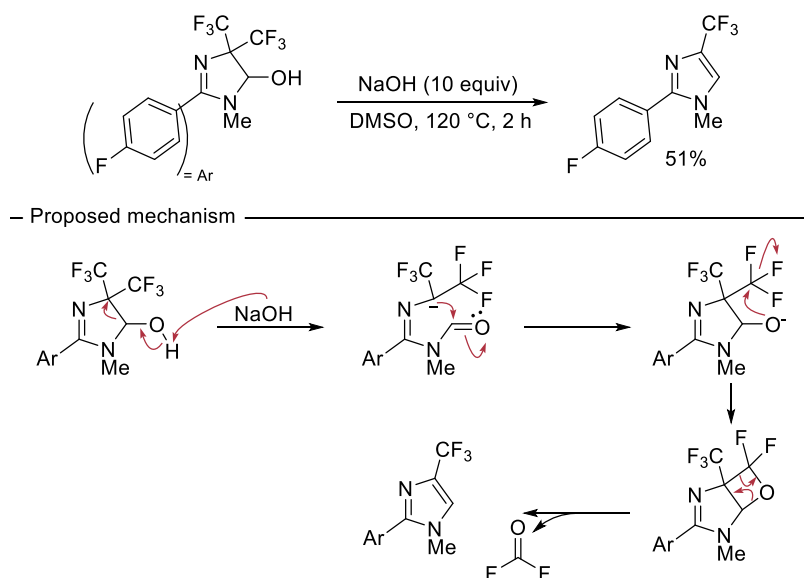
Scheme 2.2: Sodium metal and liquid ammonia mediated amination of C–CF₃ bonds



A group of researchers were studying bis-trifluoromethyl hydroxyimidazoline rings for their application in acetyl coenzyme-A cholesterol acyltransferase inhibition when they happened upon the unexpected reductive C–CF₃ bond cleavage of their target molecule (**Scheme 2.3**).⁹ They elected to study the transformation and found the de-trifluoromethylation to occur in the presence of various alkali-metal bases when stirred in dimethyl sulfoxide (DMSO) at high temperatures. The authors proposed the mechanism proceeded through base-induced ring opening, closing, and elimination of carbonyl fluoride resulting in the de-trifluoromethylated product.

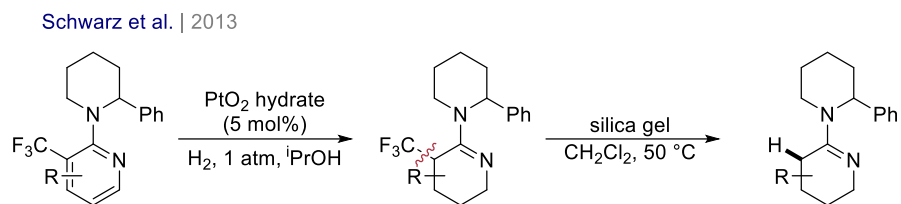
Scheme 2.3: Base induced reductive C–CF₃ bond cleavage

Boswell et al. | 1997



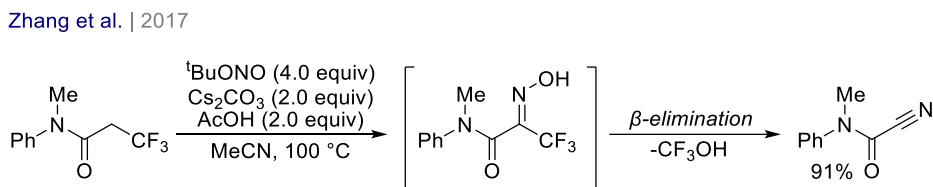
A study showcasing the directed ruthenium-catalyzed C–H mono-arylation of piperidines used covalently linked 3-trifluoromethylpyridine to direct C–H insertion.¹⁰ Towards the end of the study, the authors had hoped to remove the pyridine from the product molecule to demonstrate the practicality of their method when they accidentally discovered the reductive cleavage of the C–CF₃ bond (**Scheme 2.4**). Through hydrogenating the pyridine ring and subjecting it to column chromatography, reductive C–CF₃ bond cleavage took place affording the aliphatic analogue of their compound. The authors then intentionally tried to cleave the C–CF₃ bond by heating their substrate to 50 °C and stirring it with silica in dichloromethane (DCM) which ultimately resulted in de-trifluoromethylation.

Scheme 2.4: Silica gel mediated reductive C–CF₃ bond cleavage



In 2017 a research article outlining the transformation of trifluoropropanamides into cyanoformamides was found to proceed through a key C–CF₃ bond-breaking step (**Scheme 2.5**).¹¹ The reaction makes use of *tert*-butyl nitrite which the authors speculate acts as an electrophilic radical precursor and the source of nitrogen in the reaction. A possible mechanism was provided which showed the key C–CF₃ bond-cleaving step to proceed through β -elimination of a α -trifluoromethyl oxime producing trifluoromethanol and the cyanoformamide product.

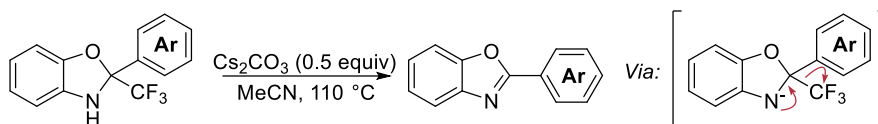
Scheme 2.5: C–CF₃ bond cleavage of trifluoropropanamides



Finally, a study in 2021 involving the synthesis of 2-arylbenzoxazoles featuring a key C–CF₃ bond-breaking step was published (**Scheme 2.6**).¹² The trifluoromethyl heterocycle was synthesized through condensation chemistry with trifluoroacetophenone and *ortho*-aminophenol positioning the CF₃ group adjacent to the benzoxazole nitrogen. This setup nicely for an aromaticity-driven C–CF₃ bond cleaving reaction which the authors believed to proceed through deprotonation of the N–H bond and aromaticity-driven trifluoromethyl anion expulsion. Their mechanism was supported by the detection of fluoroform (CF₃H) by ¹⁹F nuclear magnetic resonance spectroscopy (NMR).

Scheme 2.6: Aromaticity-driven trifluoromethyl anion expulsion

Xiong et al. | 2021



There are few similarities between the different methods and mechanisms by which C–CF₃ bond cleavage occurs, in fact the similarity between each strategy appears to be that each strategy to cleave C–CF₃ bonds is unique. Perhaps another commonality is many of these protocols were discovered by accident and pursued out of curiosity or the realization of their synthetic potential. With the growing interest in the removal of PFAS and the importance of late-stage defunctionalization reactions in organic synthesis, the intentional design of a general method to remove trifluoromethyl groups, and eventually perfluoro alkyl chains, could be viewed as important.

2.4 | Research goals

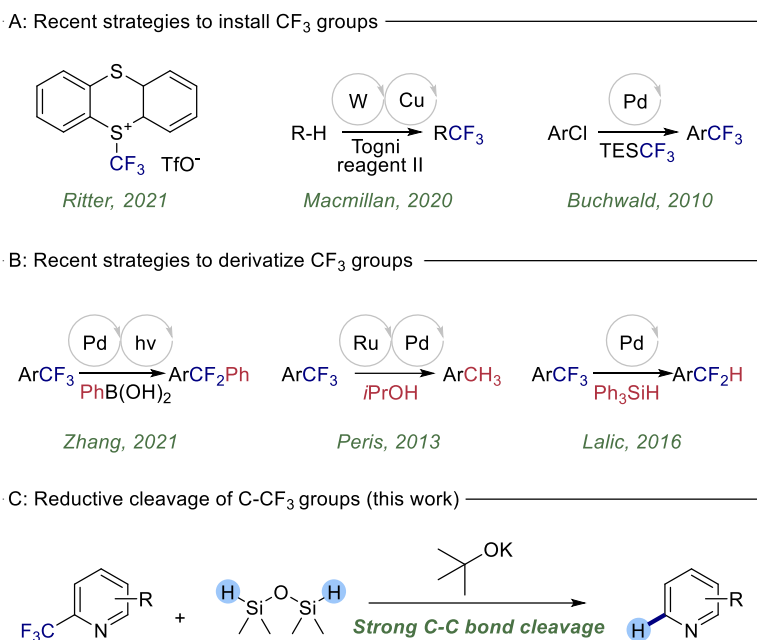
Following the discovery of the detrifluoromethylation reaction (section 2.1, **Scheme 2.1B**) and considering the many reports of interesting reactions mediated by hydrosilanes and Lewis bases outlined in section 1.3 of chapter 1, the dissertation author elected to study this transformation. The motivation to study this transformation was curiosity-driven with the hopes of identifying how this unusual transformation may be applied to organic synthesis, understanding the underlying mechanism, and applying the findings to the development of a new reaction. To reiterate section 2.2, the development and investigation of this reductive C(sp²)–CF₃ bond cleavage reaction was published in {*Org. Lett.*, **2023**, 25, 1030-1034} and is reproduced with permission in Sections 2.5-2.6, and 2.8 below.

2.5 | Reductive cleavage of C(sp²)-CF₃ bonds in trifluoromethylpyridines

Owing to their unique properties, trifluoromethyl groups have become an increasingly popular motif in the pharmaceutical industry.^{13,14} With an abundance of new methods available to introduce trifluoromethyl groups into molecules,¹⁵⁻¹⁷ (**Scheme 2.7A**) there is increasing attention on how such molecules can be harnessed. The activation of the C-F bonds of trifluoromethyl groups can be achieved to prepare difluoroalkyl (CF₂R), difluoromethyl (CF₂H), or methyl (CH₃) groups (**Scheme 2.7B**).¹⁸⁻²⁰ In contrast, the C-CF₃ bond is generally considered to be quite difficult to activate, and methods to cleave this linkage are rare.^{11,12,21} Such defunctionalization reactions are important to the synthetic community, for example to cleave directing/protecting groups² or to remove halogens from persistent organic pollutants.²²

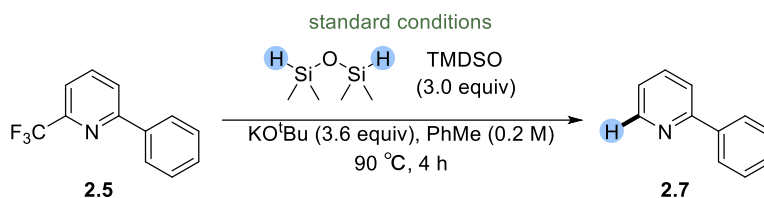
During our group's recent efforts on Ni-catalyzed reductive defunctionalization reactions,^{23,24} we observed the unexpected C-C bond cleavage of the CF₃ unit of 2-trifluoromethylpyridines in the presence of strong base and organosilane reducing agents. Control experiments revealed that the Ni catalyst was not involved in this chemistry, which could be achieved simply by heating substrate, tetramethyldisiloxane (TMDSO), and KO^tBu in toluene (**Scheme 2.7C**). Given the rarity of such C-C bond-cleaving reactions, the potential synthetic applications, the unusual reaction conditions, and the ambiguous mechanism by which the reaction occurred, we elected to optimize and study this transformation. In particular, there have been numerous reports recently about triethylsilane (Et₃SiH) and KO^tBu providing a powerful and unique combination for unusual C-C and C-H bond-cleaving reactions.²⁵⁻²⁹ To our knowledge, the unique behavior of TMDSO/KO^tBu has primarily been attributed to carbonyl bond reduction chemistry.³⁰⁻³² The results presented herein demonstrate this unusual defunctionalization reaction is general to diverse 2-substituted trifluoromethylpyridines and related heterocycles, providing a unique strategy to sever this strong bond.

Scheme 2.7: Synthesis, modification, and removal of trifluoromethyl groups



2.6 | Results and discussion

We began by investigating the reactivity of 2-trifluoromethylpyridines in the presence of mild and inexpensive silane reducing agents. Subjecting trifluoromethylpyridine **2.5** to TMDSO and KO^tBu in toluene at 90 °C provided the de-trifluoromethylated product **2.7** in 71 % yield (**Table 2.1, entry 1**). Excluding KO^tBu or TMDSO from the reaction mixture resulted in 0 % of the desired product (**2.7**) (**entry 2**) suggesting both are required for the transformation to occur. Trialkylsilanes such as Et₃SiH (**entry 3**) and triisopropylsilane ((iPr)₃SiH) (**entry 4**) were ineffective, contrasting related precedent that uses these reductants to cleave strong C–C and C–H bonds.^{25,33} Phenylsilane (PhSiH₃) (**entry 5**) and triethoxysilane ((EtO)₃SiH) (**entry 6**) facilitate the reaction, albeit in lower yields (**entries 5 & 6**). KO^tBu proved unique with other basic additives being ineffective (**entries 7-10**).^{25,34,35} Lastly, decreasing the loading of KO^tBu and TMDSO provided the desired product in 25 % yield (**entry 11**) showcasing that an excess of each reagent is required for appreciable yields.

Table 2.1: Optimization for the reduction of **2.5**

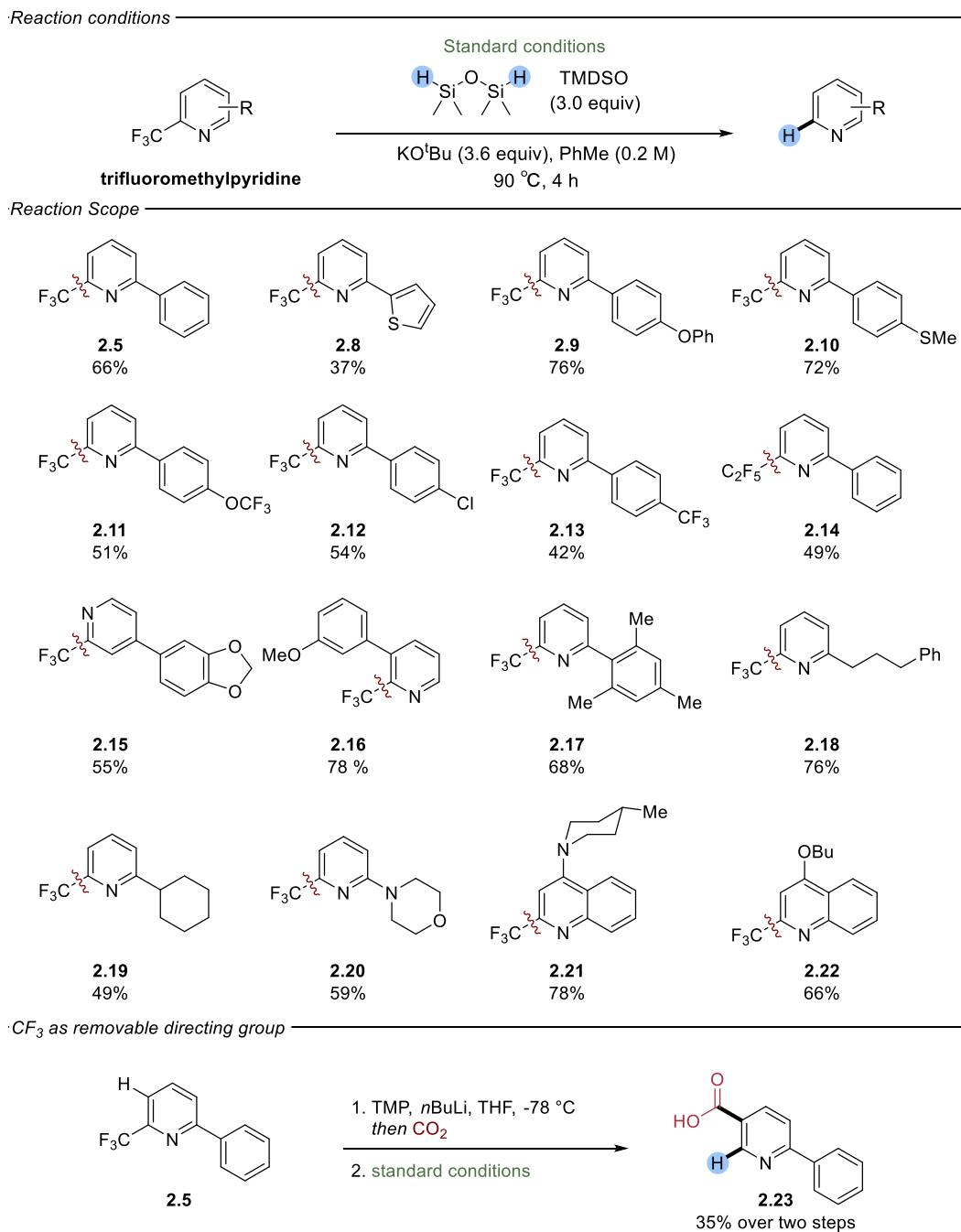
Entry	Change to standard conditions	% yield 2.7
1	None	71
2	Omit TMSO or KO ^t Bu	0
3	Replace TMSO with Et ₃ SiH	0
4	Replace TMSO with (iPr) ₃ SiH	0
5	Replace TMSO with PhSiH ₃	34
6	Replace TMSO with (EtO) ₃ SiH	57
7	Replace KO ^t Bu with Al(O ^t Bu) ₃	0
8	Replace KO ^t Bu with KOPh	0
9	Replace KO ^t Bu with NaO ^t Bu	0
10	Replace KO ^t Bu with CsF	0
11	1.0 equiv TMSO and KO ^t Bu, 80 °C	25

Standard conditions: substrate (0.20 mmol), TMSO (0.60 mmol), KO^tBu (0.72 mmol), PhMe (0.20 M), 90 °C, 4 h. % yields were calculated using ¹H NMR spectroscopy

With optimized conditions developed for a model substrate, a range of trifluoromethyl-containing heterocycles were tested (**Scheme 2.8**). Thiophene-bearing pyridine **2.8** was found to undergo de-trifluoromethylation in a modest 37% yield. Other potentially reducible functional

groups including a phenyl ether (**2.9**), thioether (**2.10**), trifluoromethyl ether (**2.11**), and chlorine (**2.12**), were tolerated, indicating that the reaction shows chemoselectivity for reduction of the trifluoromethyl C–C bond. A substrate bearing two trifluoromethyl groups was prepared and observed to undergo selective C–C cleavage at the pyridine 2-position (**2.13**), leaving the remote CF₃ group untouched. Additionally, no reactivity was observed when investigating substrates bearing the trifluoromethyl group at positions 3 or 4 on the pyridine ring (See section 2.7.1, Scheme 2.11A). A pentafluoroethyl group (C₂F₅) could also be reductively cleaved (**2.14**), demonstrating longer perfluoroalkyl-containing species are similarly reactive. 2,4-Disubstituted (**2.15**) and 2,3-disubstituted (**2.16**) pyridines were also selectively reduced, indicating that the reaction occurs independent of the substitution pattern around the pyridine ring. A substrate bearing a bulky mesityl group (**2.17**) was also reduced, suggesting that the steric profile of the nitrogen does not affect reactivity. In addition to aromatic groups, substitution with a linear alkane (**2.18**), cyclohexyl ring (**2.19**), or morpholine (**2.20**), on the pyridine ring were all well tolerated. Next, we explored other heterocyclic scaffolds. Trifluoromethyl quinolines bearing nitrogen (**2.21**) and oxygen (**2.22**) substituents were smoothly reduced. In contrast, trifluoromethyl-bearing pyrazoles and pyrimidines were out of scope (See Section 2.7.1, Scheme 2.11). We then sought to explore if the CF₃ group could be used as a removable directing group. Carboxylation of trifluoromethylpyridine **2.5** by directed metalation,³⁶ followed by reductive de-trifluoromethylation produced the nicotinic acid derivative **2.23** in 35% yield over two steps.

Scheme 2.8: Scope evaluation for reductive de-trifluoromethylation

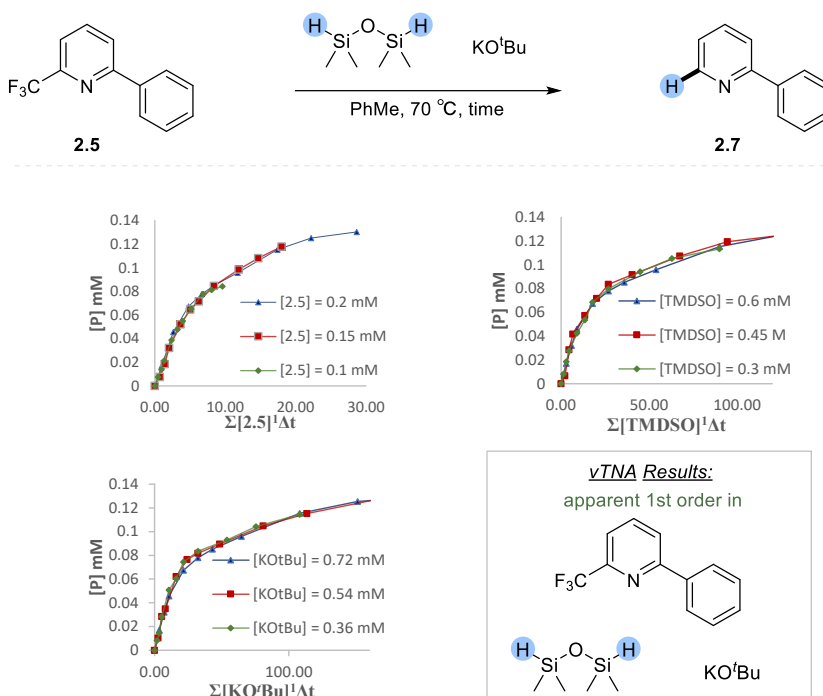


Standard conditions: substrate (0.20 mmol), TMSO (0.60 mmol), KO^tBu (0.72 mmol), PhMe (0.20 M), 90 °C, 4 h. % yields are isolated.

The combination of silanes and strong base are well-established to make a potent reducing agent, for example enabling ester and nitrile hydrosilylation.³⁰⁻³² More recently, alkylsilanes and KO^tBu in particular have been shown to facilitate diverse reduction, C–H functionalization, and rearrangement reactions.²⁵⁻²⁹ Extensive studies have uncovered a complicated network of mechanistic possibilities, including silyl radicals, radical anions, silicate hydride donors, and hydrogen atom donors.^{37,38} While the reaction described herein works well with TMDSO and fails with triethylsilane, we speculate that a similar set of potential reactive intermediates may be present.

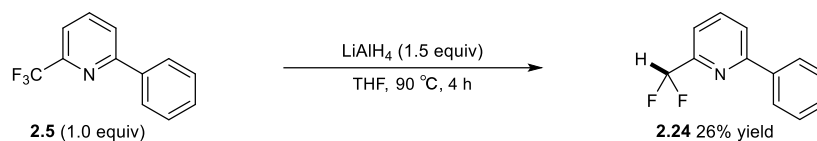
To gain insight into the mechanism operative in this unprecedented reductive de-trifluoromethylation, the reaction's kinetics were investigated using the variable time normalization analysis (vTNA) method with model substrate **2.5** (**Scheme 2.9**).^{39,40} The rate data is consistent with 1st order kinetics for all studied species – the substrate (**2.5**), TMDSO, and KO^tBu - though fractional orders (+/- 0.5) cannot be ruled out (**Scheme 2.9**). Silanes and alkoxides are known to interact to make hypervalent silicate species that are potent reducing agents.³⁰⁻³²

Scheme 2.9: Variable Time Normalization Analysis (vTNA)



Based on this precedent and the observed kinetic behavior, we speculated that such a species may be able to deliver hydride to the pyridine, ultimately cleaving the C–CF₃ bond. Indeed, reduction of electron-deficient heterocycles by hydride donors is well established, albeit most common with cationic substrates such as pyridiniums.⁴¹ However, when heating trifluoromethylpyridine **2.5** in the presence of lithium aluminum hydride, a strong hydride donor capable of reductive defunctionalization and pyridinium reduction,^{42–44} no evidence of C–C bond cleavage was observed (**Scheme 2.10**). Instead, difluoromethylpyridine **2.24** was the only identifiable product, isolated in 26% yield with 41% recovery of starting material. Notably, this species did not undergo C–C bond cleavage upon treatment with TMDSO/KO^tBu, suggesting it is not a reactive intermediate and that delivery of hydride may not be involved in the key step.

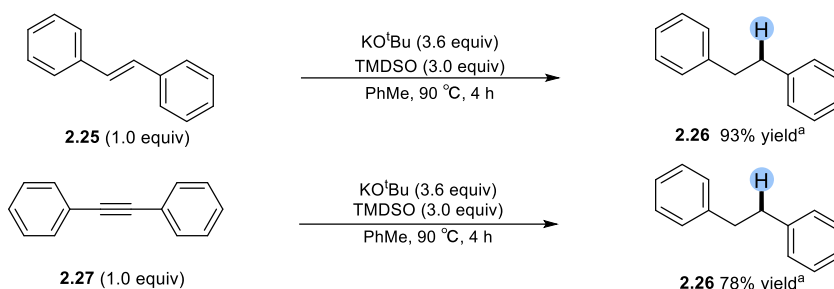
Scheme 2.10: Hydride reduction results in C–F cleavage instead of C–C cleavage



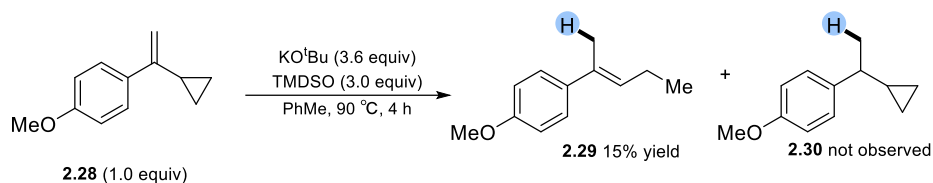
We next investigated if the combination of TMDSO/ KO^tBu would react with other potentially reducible systems.³⁷ Upon exposure of either trans-stilbene **2.25** or diphenylacetylene **2.27** to the standard reaction conditions, 1,2-diphenylethane **2.26** was formed in excellent yield (**Scheme 2.11A**). The cyclopropyl-containing styrene **2.28** could be similarly reduced, forming the corresponding ring-opened product **2.29** in 15% yield with no detection of ring retained products, suggesting a benzylic radical may be present (**Scheme 2.11B**). This suggests a pyridine radical anion could be a potential reactive intermediate. Such species are well precedented and have been found to bear significant spin density on N and C4, leading to dimerization at C4 in polar solvents,⁴⁵ though this side-product was never observed in our reaction. A density functional theory (DFT) calculation comparing a 2- CF_3 -pyridine radical anion to the parent compound suggests the presence of the CF_3 group may have a large impact on the singly occupied molecular orbital (SOMO), decreasing spin density on C4 and increasing it on C2. Furthermore, a deuterium labelling experiment was conducted using d_2 -TMDSO which resulted in 63% deuterium in the product pyridine exclusively at C2 (**Section 2.7.5, Scheme 2.14**).

Scheme 2.11: Mechanistic probes used to detect radical species

—A. TMDSO and KO^tBu mediated C-C π -bond reduction



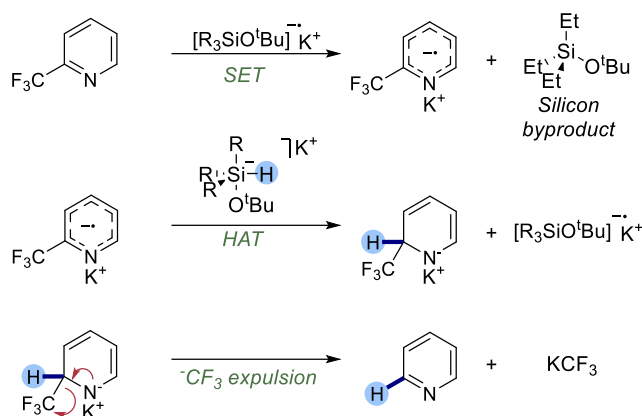
— B. Evidence of radical character in C-C π -bond reduction



^a % yields determined by calibrated GCMS. ^b Ar = 4-methoxyphenyl.

Based on the insight gained from the above experiments, we speculate that the reaction may proceed by a key single-electron transfer step (**Scheme 2.12**). As suggested by Murphy and co-workers in related reduction reactions featuring KO^tBu/Et₃SiH,³⁷ a silicon radical anion may be formed in situ from KO^tBu and TMDSO. This species could transfer an electron to the electron-deficient pyridine ring, generating a pyridine radical anion.⁴⁶⁻⁴⁸ The silane and alkoxide base may react by an equilibrium to form a hypervalent silicon hydride species that can react with the pyridine radical anion by H atom transfer forming a dearomatized pyridyl anion and the aforementioned silicon radical anion. Elimination of CF₃ may provide the product pyridine along with trifluoromethyl anion.

Scheme 2.12: A plausible mechanism for reductive de-trifluoromethylation



2.7 | Additional experimental results

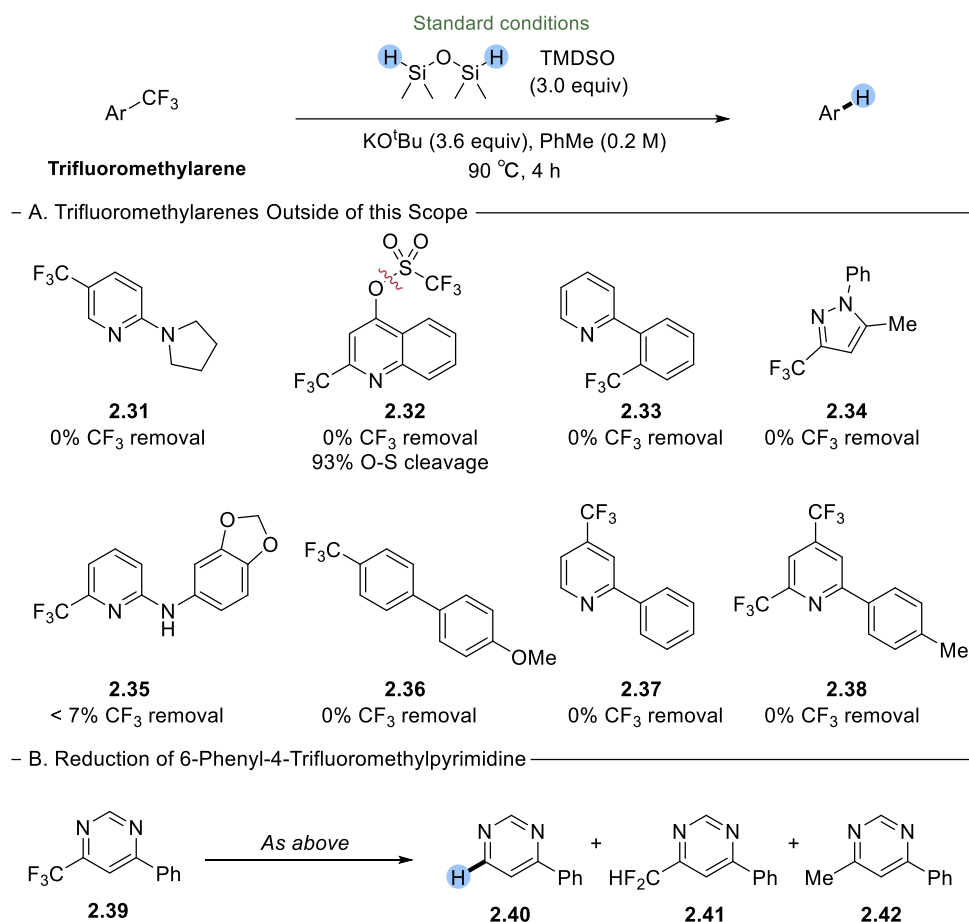
The written body of work found in sections 2.5 and 2.6 of chapter 2 was published as a letter with specific limitations on space, word, and page count as outlined by the publisher's requirements. As such, a large amount of relevant data and experiments that aided in formulating hypotheses surrounding this research in addition to understanding the strengths, weaknesses, and insight we gained has been left out. In this section additional experimental results outlining the limitations of the scope (Section 2.7.1), failed pyridine-derived mechanistic probes (Section 2.7.2), mechanistic probes used to support or refute the existence of potential reactive intermediates (Section 2.7.3), the fate of the CF_3 group (Section 2.7.4), and deuterium labelling experiments (Section 2.7.5) that are originally found in the supporting information are brought into discussion.

2.7.1 | Limitations of the scope

During the synthesis and isolation of scope examples, many substrates failed to undergo reductive C–C bond cleavage. Substrates **2.31**, **2.33**, **2.34**, **2.36**, **2.37**, **2.38** were unreactive towards C– CF_3 bond cleavage and were recovered in low yield. Substrate **2.32** was instead reduced to the

quinolinol and substrate **2.35** underwent reductive C–CF₃ bond cleavage in less than 7% yield. Difluoromethylpyridines were out of scope and thus were also ruled out as reactive intermediates. Two substrates in particular stood out among the rest. Substrate **2.38** retained its CF₃ groups despite 2-trifluoromethylpyridines being amenable to the reaction scope (**Scheme 2.13A**). This would suggest that substrates bearing CF₃ groups at C4 are unreactive towards C–CF₃ bond cleavage and that CF₃ groups at C4 shut down reactivity. One possibility is the additional CF₃ group changes the electronics of the species enough that an alternative reaction pathway ensues – this, however, is purely speculative. The second substrate was 6-phenyl-4-trifluoromethylpyrimidine. Firstly, when testing this species poor mass balance was obtained (**Scheme 2.13B**). Pyrimidines are more electrophilic than analogous pyridine species due to their second nitrogen atom.⁴⁹ Owing to their enhanced electrophilicity, species of pyrimidine are known to undergo semi-hydrogenation in the presence of sodium borohydride (NaBH₄) and lithium aluminum hydride (LAH).⁵⁰ It's possible that a species of pentavalent hydrosilanes could be reducing this pyrimidine in a similar fashion though no semi-hydrogenated species were detected when testing **2.39**. Secondly, within that small subset of material 3% C–CF₃ bond cleavage, 3% monodefluorination, and 3% exhaustive defluorination was found to occur indicating a competing reaction pathway is taking place.

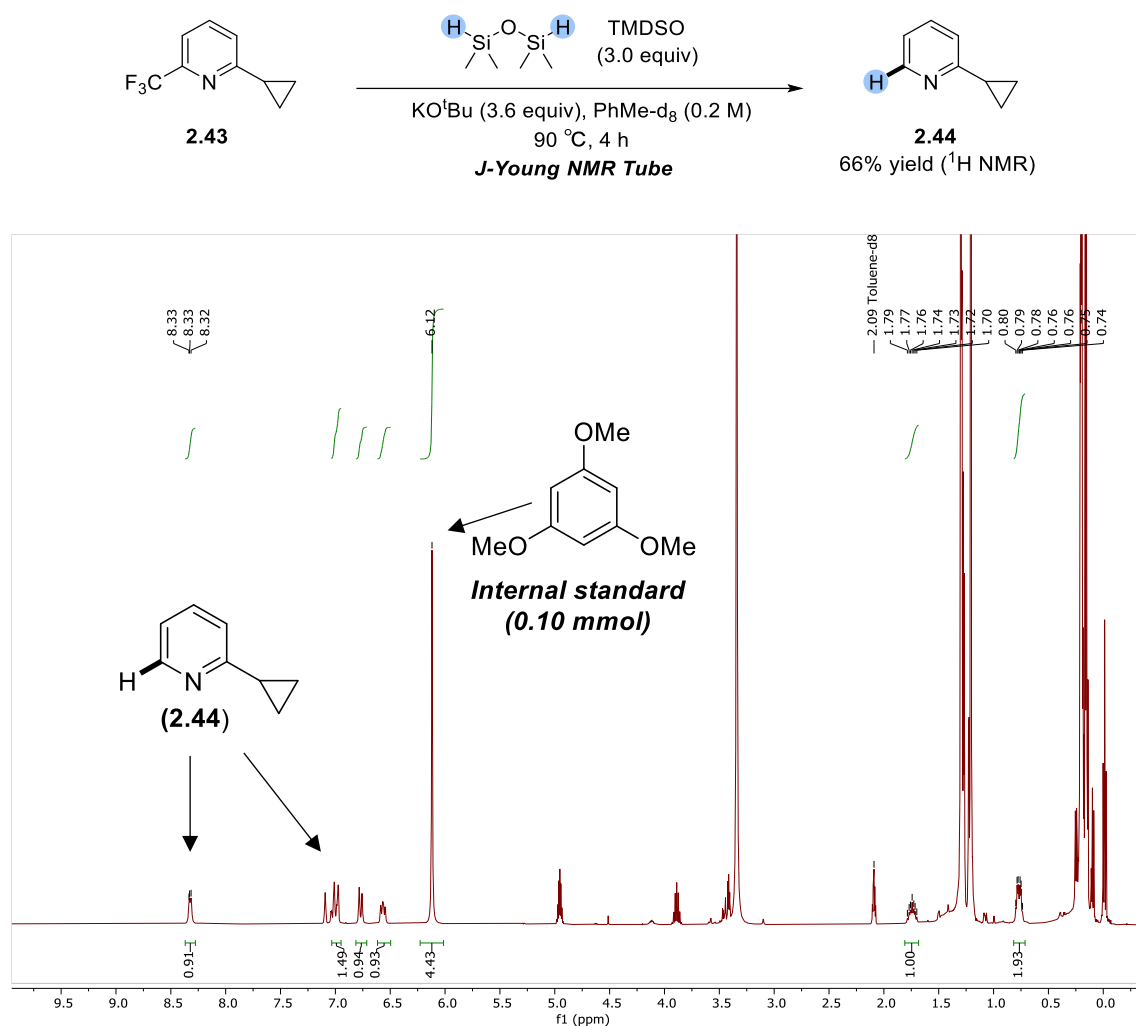
Scheme 2.13: Substrates beyond the scope of this transformation



2.7.2 | Failed substrate probes

It was hypothesized that a pyridine radical anion could be a feasible reactive intermediate based on work by Murphy and coworkers.³⁷ In order to probe this hypothesis **2.43** was used as a substrate in the de-trifluoromethylation reaction (**Figure 2.1**). Due to the high volatility of **2.43**, an NMR experiment was conducted and analyzed to determine whether any ring-opening had occurred. If a radical anion were present, ring-opening of the cyclopropane ring should be observed. However, ring-opening was not observed and instead **2.44** formed in 66% yield based on ¹H NMR spectroscopy. This experimental result could indicate that a pyridine radical anion is *not* present in the reaction, however since this substrate is not precededented as a substrate probe to test for radical anions this result was deemed inconclusive.

Figure 2.1: Probing the intermediacy of a pyridine radical anion in a J. Young NMR tube

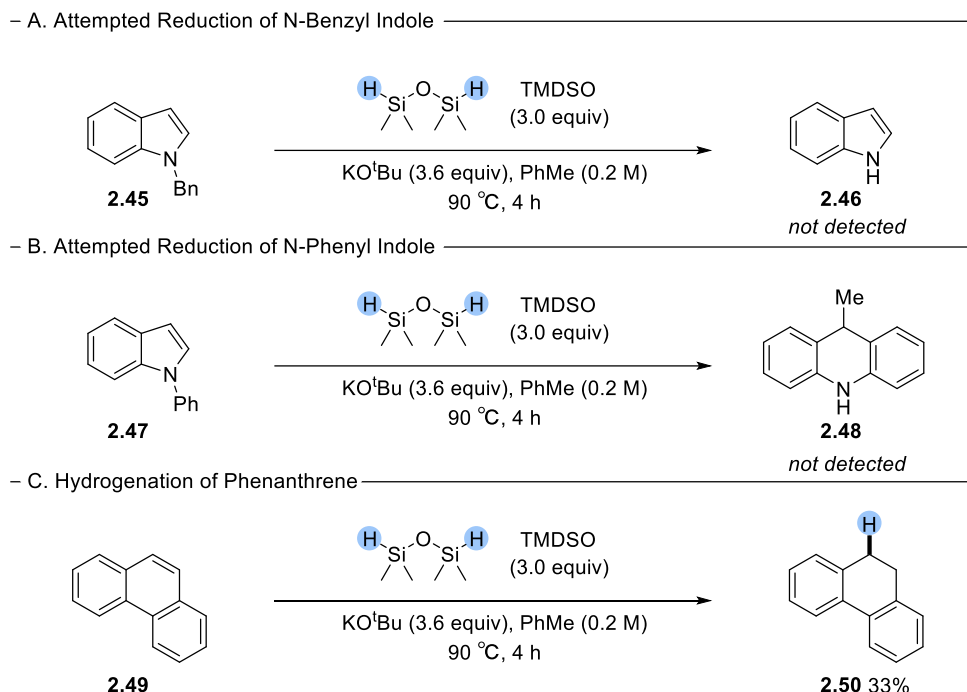


2.7.3 | Additional substrate probes

In 2017 Murphy and coworkers investigated the redox properties of silicon radical anions thought to arise from the Grubbs-Stoltz reagent (See chapter 1, Section 1.3.2). The author of this dissertation speculated whether a similar reactive intermediate was present under the reaction conditions and began to test substrate probes invoked by Murphy and coworkers. N-benzyl indole (**2.45**) - which is known to undergo radical fragmentation after accepting an electron via SET – was tested.^{37,51} No fragmentation products derived from the indolyl radical anion were detected

and instead starting material was recovered (**Scheme 2.14A**). It was later discovered that the combination of TMDSO and KO^tBu is basic enough to deprotonate weakly acidic C–H species with an acid dissociation constant (*pK*_a) of up to approximately 35 (see chapter 4, section 4.5.4). It's possible the deprotonation of the benzylic C–H bond occurs followed by its protonation upon workup. Murphy and coworkers showed that the Grubbs-Stoltz reagent can transform N-phenylindoles into the corresponding acridine and proposed SET to be a major pathway.⁵² When testing **2.47** in under the standard reaction conditions no acridine (**2.48**) had been detected and therefore no evidence of SET had been gathered (**Scheme 2.14B**). This result could suggest SET is not operative under the reaction conditions. The hydrogenation of phenanthrene was then used to support a radical anion (**Scheme 2.14C**). Testing phenanthrene led to the formation of **2.50** in 33% yield which was interpreted as proceeding through a Birch-reduction pathway.³⁷ The author of this dissertation regrets this conclusion because the reduction of this species could in theory occur through hydride transfer or, based on a follow-up study discussed in chapter 3 of this dissertation, could proceed through hydrogen atom transfer. Even now, the mechanism of hydrogenation remains unknown as it was never fully elucidated.

Scheme 2.14: Investigating N-benzylindole, N-phenylindole, and phenanthrene as potential single-electron acceptors

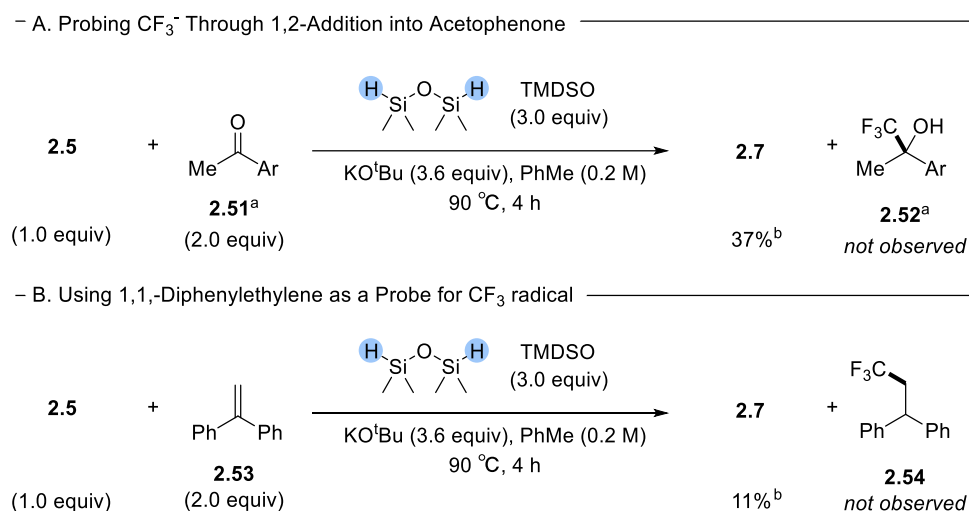


2.7.4 | Destination getaway for a trifluoromethyl group

Several attempts to uncover the mechanism for trifluoromethyl expulsion were made, however no concrete conclusion could be made. It was speculated that the loss of CF_3 groups could occur through an anionic or radical pathway. Trifluoromethyl anions are known to add into aryl ketones through a 1,2-addition pathway resulting in α -trifluoromethyl benzyl alcohol.⁵³ To probe whether a CF_3 anion was a feasible pathway, *para*-methylacetophenone (**2.51**) was added to the reaction (**Scheme 2.15A**). No 1,2-addition product could be identified and unsurprisingly **2.51** underwent hydrosilylation instead. This data is inconclusive and the experiment unsuccessful likely because there is significantly more hydride in solution than there is trifluoromethyl anion, assuming the anionic pathway is operative. It's been demonstrated that trifluoromethyl radicals can undergo Giese-like addition with vinylarenes.⁵⁴ Whether CF_3 radical was being formed as a transient byproduct of C– CF_3 bond cleavage was brought into question. To test this hypothesis,

1,1-diphenylethylene (**2.53**) was introduced to the standard conditions and observed no product that would have indicated CF₃ radical (**Scheme 2.15B**). Instead, the hydrogenation of 1,1-diphenylethylene was observed as is consistent with the hydrogenation of *trans*-stilbene and diphenylacetylene (**Scheme 2.11**). Thus, the pathway by which CF₃ expulsion occurs remains unknown. Further experimentation utilizing designer CF₂–Ar substrates could be conducted to help elucidate the mechanism of CF₃ expulsion.

Scheme 2.15: Attempts at in-situ capture of trifluoromethyl anions and radicals



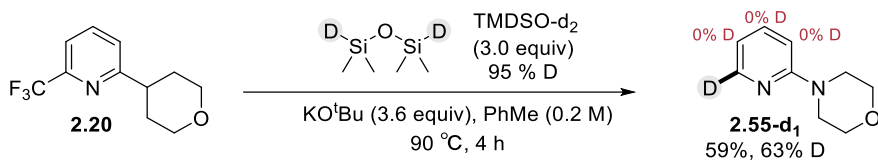
^a Ar = *p*-methylphenyl, ^b % yields were calculated using ¹H NMR spectroscopy

2.7.5 | Deuterium labelling experiment

To interrogate where the hydrogen atom on the product derives from, pyridine **2.20** was subjected to the standard conditions while employing 95% deuterium enriched TMSO-d₂. The ¹H NMR experiment was performed with an extended relaxation time of 30 seconds to ensure a more uniform integration in both the NMR spectrum of the pure sample and the crude reaction mixture (**Scheme 2.16**). Deuterium was detected exclusively at the 2-position on the pyridine ring with 63% D incorporation. With 6 equivalents of potentially active hydrogen atoms in the 3 equivalents of d₂-TMSO, one explanation for the significant amount of proton found in the

product could be due to a large kinetic isotope effect (KIE). Another possibility is an alternative hydrogen atom source such as the solvent, toluene (PhMe).

Scheme 2.16: Deuterium labelling of 2-trifluoromethyl-6-morpholinopyridine



2.8 | Conclusions

In summary, we have developed a protocol for the reductive de-trifluoromethylation of pyridines and related heterocycles. The reaction conditions were chemoselective for C–C cleavage at the 2-position of these heteroaromatic rings, leaving distal trifluoromethyl groups untouched. The combination of KO^tBu and TMDSO was found to be particularly important for this unusual defunctionalization, with kinetic analyses showing positive order in both these components as well as the pyridine substrate. Mechanistic evidence suggests the reaction proceeds by the formation of a powerful reducing agent capable of single-electron transfer to the electron-deficient π -system. Most importantly, this work represents a new and unusual strong bond cleavage method using silicon-hydride/base, a reagent combination that continues to find surprising new applications.

2.9 | Subsequent advances

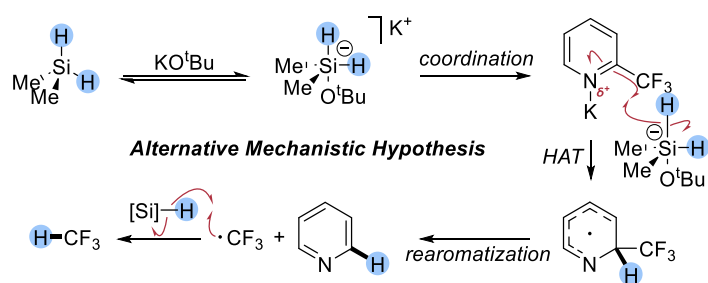
To date, no significant advances have been made in this area of research since the publication of this work. However, conclusions regarding the mechanism of C– CF_3 bond cleavage have been revised based on data acquired during the study of a hydroalkylation reaction presented in chapter 3 of this dissertation. In section 2.4 – which was taken directly from the original publication – a plausible mechanism had been included which suggested TMDSO and KO^tBu acts as a one-pot single-electron donor and hydrogen atom donor. While this reducing combination—TMDSO and KO^tBu —is still regarded as being a one-pot single-electron donor and hydrogen atom

donor (see chapter 3 of this dissertation), the de-trifluoromethylation protocol is not likely to proceed through a radical anion. It is now the opinion of the dissertation author that the mechanism of this transformation should be considered inconclusive given the lack of highly convincing evidence to support a pyridine radical anion as a reactive intermediate. The reduction of *trans*-stilbene and diphenyl acetylene were invoked as mechanistic probes to support a SET pathway (Section 2.6, **Scheme 2.11**). This was based on work by Murphy and coworkers who made a convincing argument that the Grubbs-Stoltz reagent is reducing these species via SET or hydride delivery, which remains a strong conclusion.³⁷ However, not only does Et₃SiH fail to promote the reductive C–CF₃ bond cleavage of 2-trifluoromethylpyridines— suggesting while TMDSO bears similarities it is a distinct hydrosilane – but in a follow-up study by Newman and coworkers it was found that vinylarenes undergo hydrogen-atom transfer (HAT) in the presence of TMDSO and KO^tBu which would suggest *trans*-stilbene does not undergo SET under our conditions.⁵⁵ This same argument can be made for the reductive ring-opening of **2.28** (**Scheme 2.11**). Additionally, *even if* *trans*-stilbene and diphenylacetylene were to undergo SET under the standard conditions for de-trifluoromethylation it still only provides indirect evidence since *trans*-stilbene and pyridine are significantly differently from one another and can thus react significantly different from one another.

An alternative mechanism for the transformation is outlined as follows: Association of KO^tBu to a hydrosilane—that is likely dimethylsilane (see chapter 3 of the dissertation)—leading to the reversible formation of a pentavalent potassium complex (**Scheme 2.17**). Pyridine may coordinate to the potassium in the pentavalent hydrosilane complex which brings the complex into close proximity to the trifluoromethylpyridine substrate. Polarity-matched hydrogen atom transfer to C2 on the pyridine ring dearomatizes the substrate affording a pyridyl radical which may

undergo rapid re-aromatization facilitating trifluoromethyl radical ejection. The trifluoromethyl radical likely undergoes hydrogen atom abstraction with a hydrosilanes species be that a tetravalent or pentavalent species. The author of this dissertation would like to highlight that while this serves as an alternative mechanism *it is purely speculative* as significant evidence to support such a proposal is lacking.

Scheme 2.17: An alternative mechanistic hypothesis for reductive de-trifluoromethylation

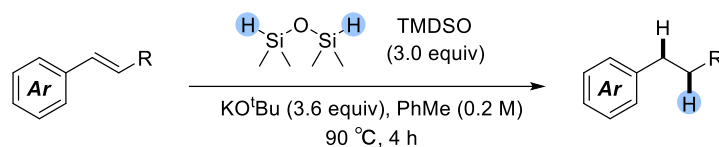


A full mechanistic understanding will depend on resolving several outstanding questions about this transformation.

2.10 | Future directions

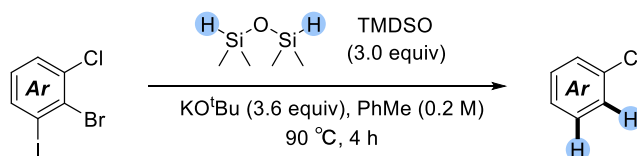
One promising direction to focus on is the hydrogenation of vinylarenes (**Scheme 2.18**). Using the standard conditions for de-trifluoromethylation *trans*-stilbene and diphenylacetylene are hydrogenated in high yield using TMDSO and KO^tBu as a reducing agent (**Scheme 2.11**). With enough effort, this could become a convenient method to hydrogenate related π -systems and potentially as a way to deuterate vinylarenes using TMDSO- d_2 . Moreover, the study of the underlying mechanism by which hydrogenation proceeds could lead to future developments in TMDSO and KO^tBu mediated hydrofunctionalization reactions.

Scheme 2.18: Hydrogenation of vinylarenes



As was stated in section 2.1 the applications of hydrodefunctionalization reactions are far reaching and can be applied to many problems. Given the highly reducing nature of TMDSO and KO^tBu , the extension of this reaction to the reductive defunctionalization of other functional groups would be a strong and promising future direction. More specifically, it was noticed in this reaction that aryl chlorides (see section 2.6, **Scheme 2.8**) are tolerated quite nicely, thus one could envision tailoring the system to the selective hydrodehalogenation of $\text{C}(\text{sp}^2)\text{-Br}$ and $\text{C}(\text{sp}^2)\text{-I}$ bonds in multi-halogenated species (**Scheme 2.19**). Furthermore employing TMDSO-d_2 as the reducing agent could be used to install deuterium at specific locations using this method. Although there are existing methods to perform this transformation one could argue TMDSO and KO^tBu would be a low-cost alternative strategy.^{56,57}

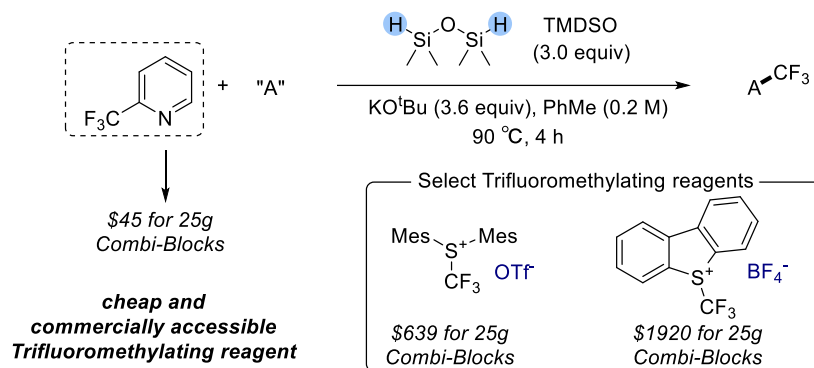
Scheme 2.19: Selective hydrodehalogenation of polyhalogenated species



A more unique and niche extension of the system lies in trying to utilize trifluoromethylpyridines as trifluoromethylating reagents (**Scheme 2.20**). Trifluoromethylation is an ongoing area of interest which continues to see development.^{58,59} Despite there being many ways to perform this class of reaction the existing trifluoromethylating reagents are not without their limitations. A major limitation of the existing trifluoromethylating reagents is their high cost or a time-demanding synthesis. For instance, the Mes-Umemoto reagent is ~ \$639 for 25g on combi-block

which is cheap compared to the Umemoto reagent which sells for \$1920 for 25g from the same vendor. 2-Trifluoromethylpyridine, on the other hand, costs \$45 for 25g.⁶⁰ The caveat is in order to harness 2-trifluoromethylpyridines one must first investigate the mechanism by which C–CF₃ bond cleavage occurs. Nonetheless, this remains a strong future direction of the work.

Scheme 2.20: Harnessing 2-trifluoromethylpyridine as a trifluoromethylating reagent



2.11 | Experimental

2.11.1 | General experimental details

Unless stated otherwise, reactions were set up outside the glovebox under an atmosphere of N₂ using oven dried glassware. Column chromatography was performed manually and in some cases via Combi-flash Rf automated chromatography both using Silicycle F60 40-63 μm silica gel. Thin-layer chromatography was performed using aluminum-backed EMD Millipore Silica Gel 60 F₂₅₄ pre-coated plates. A UV lamp was used to visualize TLC plates.

2.11.2 | Instrumentation

GCMS data was obtained using an Agilent Technologies 7890B GC with a 30 m x 0.25 mm HP-5 column. Accurate mass data (EI) was obtained from an Agilent 5977A GC/MSD using MassWorks 4.0 from CERNO Bioscience.⁶¹ HRMS-EI data was obtained using a Kratos concept magnetic sector electron impact mass spectrometer. ¹H, ¹³C, and ¹⁹F NMRs were obtained using a Bruker Avance II 500 MHz spectrometer, a Bruker Avance II 400 MHz spectrometer or a Bruker

Avance I 300 MHz spectrometer. ^1H NMR yields were determined using trimethoxybenzene as an internal standard. ^1H NMR spectra were calibrated using CDCl_3 (7.26 ppm), ^{13}C NMR spectra were calibrated using CDCl_3 (77.00 ppm). Reported NMR data is as follows: chemical shift (δ ppm), multiplicity (where s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants in Hz (where applicable), and relative proton integration. Melting points were measured using a Fisher-Johns melting point apparatus, the crystalline substance was placed between two glass slides and observed through a magnification lens.

2.11.3 | Materials

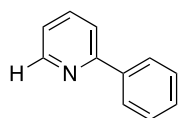
Organic solvents were degassed using nitrogen and were then filtered through a PureSolv solvent purification system (SPS) to remove water. Unless otherwise noted, starting materials were purchased from Combi-blocks and used as received. Potassium tert-butoxide (KO^tBu) (trace metal grade 99.8 %) was purchased from Oakwood chemicals. 1,1,3,3-Tetramethyldisiloxane (TMDSO), triethoxysilane, triethylsilane, triisopropylsilane, potassium fluoride, cesium fluoride, and aluminum tert-butoxide were purchased from Sigma Aldrich. Triphenylsilane, 2-chloro-6-trifluoromethylpyridine, 3-bromo-2-trifluoromethylpyridine, 5-bromo-2-trifluoromethylpyridine, 4-chloro-2-trifluoromethylpyridine, *N*-benzylindole were purchased from Combi-blocks. Details regarding the synthesis and NMR spectra of isolated starting materials, and additional experiments can be located in the supporting information available for free through the publication website (<https://doi.org/10.1021/acs.orglett.3c00258>). The NMR spectra for products synthesized according to the general procedure (*vide infra*) can be found in the appendix.

2.11.4 | Experimental procedures and characterization data

Optimization procedure: To an oven-dried 8 mL screw cap vial equipped with a stir bar was weighed **1** (0.1 mmol) and the corresponding base. The vial was capped with a plastic screw cap equipped with a Teflon/silicone septum and then purged under a positive pressure of N_2 for 10

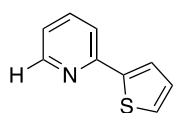
minutes. Once sufficiently purged, solvent was added via syringe through the septum followed by silane. The N₂ source was removed, the reaction was placed in an oil bath, and heated to the desired reaction temperature. After 4 hours the screw cap vial was removed from the oil bath, cooled to room temperature, and the reaction mixture was diluted with ethyl acetate. Then, 0.5 mL of a 0.2 (M) solution of 1,3,5-trimethoxybenzene in toluene – as an internal standard – was added to the crude reaction mixture which was then filtered through silica gel using a fritted funnel with EtOAc and concentrated using a rotary evaporator. The crude residue was then dissolved in CDCl₃ and submitted for analysis by ¹H NMR spectrometer. NMR yields were determined by integrating the peak at ~ 8.70 ppm, which corresponds to the proton located ortho to the nitrogen in **2.7**, relative to the peak at 6.08 ppm on 1,3,5-trimethoxybenzene.

General Procedure: Reductive de-trifluoromethylation of 2-trifluoromethylpyridines. To an oven dried 8 mL screw cap vial equipped with a stir bar was weighed the trifluoromethyl pyridine derivative (0.2 mmol), and KO^tBu (0.72 mmol). The vial was sealed with a screw cap equipped with a septum and then purged under a positive pressure of N₂ for 10 minutes. Once purged using a balloon filled with N₂, PhMe (1.0 mL) was added via syringe through the septum followed by TMSO (106.0 μL). The N₂ source was removed, the reaction was placed in an oil bath set to 90 °C. After 4 hours the reaction vessel was removed from the oil bath, cooled to room temperature, and diluted with ethyl acetate. The reaction mixture was filtered through silica gel using a fritted funnel with ethyl acetate, concentrated under reduced pressure, and purified via column chromatography.

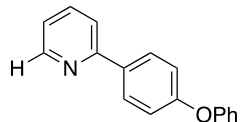


2-Phenylpyridine (2.7): Compound **2.7** was prepared from substrate **2.5** according to general procedure C. The crude residue was purified via automated column chromatography using a gradient of 0-10% EtOAc:hexanes to afford a pale-yellow oil.

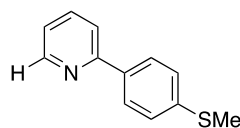
(20.5 mg, 66% yield). Characterization data matched previously reported data.⁶² **¹H NMR** (400 MHz, CDCl₃): 8.71-8.69 (m, 1H), 8.01-7.98 (m, 2H), 7.78-7.62 (m, 2H), 7.51-7.40 (m, 3H), 7.24 (ddd, *J* = 6.7, 4.8, 2.0, Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): 157.6, 149.8, 139.5, 136.9, 129.1, 128.9, 127.1, 122.3, 120.7.



2-(2-Thienyl)pyridine (2.56): Compound **2.56** was prepared from substrate **2.9** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-30% EtOAc:hexanes to afford a colorless oil. (11.9 mg, 37% yield). Characterization data matched previously reported data.⁶³ **¹H NMR** (400 MHz, CDCl₃): δ_H 8.62 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.90 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.73-7.61 (m, 3H), 7.40 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ_C 153.6, 149.7, 142.2, 136.9, 126.5, 126.4, 126.3, 123.7, 122.0, 120.5.

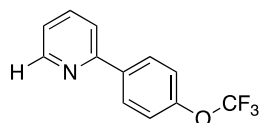


2-(4-Phenoxyphenyl)-pyridine (2.57): Compound **2.57** was prepared from substrate **2.10** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-10% EtOAc:hexanes to afford a white solid. (37.4 mg, 76% yield). Characterization data matched previously reported data.⁶⁴ **¹H NMR** (400 MHz, CDCl₃): 8.68 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 8.00-7.96 (m, 2H), 7.76-7.68 (m, 2H), 7.39-7.34 (m, 2H), 7.21 (ddd, *J* = 7.2, 4.8, 1.4, Hz, 1H), 7.22-7.05 (m, 5H); **¹³C NMR** (100 MHz, CDCl₃): 158.4, 157.0, 157.0, 149.7, 136.9, 134.5, 130.0, 128.6, 123.7, 121.9, 120.3, 119.3, 119.0.

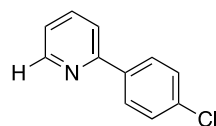


2-(4-Thiomethoxyphenyl)-pyridine (2.58): Compound **2.58** was prepared from substrate **2.11** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-10% EtOAc:hexanes to afford an off-white solid. (30.0 mg, 72% yield). Characterization data matched previously reported data.⁶⁵ **¹H**

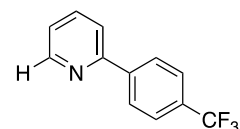
NMR (400 MHz, CDCl₃): δ_H 8.68-8.66 (m, 1H), 7.95-7.91 (m, 2H), 7.75-7.67 (m, 2H), 7.35-7.32 (m, 2H), 7.20 (ddd, J = 6.9, 4.8, 1.6 Hz, 1H), 2.52 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ_C 156.9, 149.7, 140.0, 136.9, 136.0, 127.3, 126.5, 122.1, 120.2, 15.6.



2-(4-Trifluoromethylphenyl)-pyridine (2.59): Compound **2.59** was prepared from substrate **2.12** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-20% EtOAc:hexanes to afford a white solid. (24.4 mg, 51% yield). Characterization data matched previously reported data.⁶² **¹H NMR** (400 MHz, CDCl₃): δ_H 8.69 (ddd, J = 4.8, 1.9, 1.0 Hz, 1H), 8.04-8.01 (m, 2H), 7.79-7.75 (m, 1H), 7.70 (dt, J = 8.0, 1.2 Hz, 1H), 7.32 (dq, 8.9, 1.1 Hz, 2H), 7.27-7.24 (m, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ_C 156.2, 150.2 (q, J = 1.9 Hz), 149.9, 138.1, 137.1, 128.5, 122.6, 121.2, 120.62 (q, J = 257.4 Hz), 120.60.

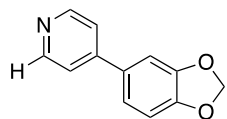


2-(4-Chlorophenyl)-pyridine (2.60): Compound **2.60** was prepared from substrate **2.13** according to general procedure C. The crude residue was purified via automated column chromatography using a gradient of 0-10% EtOAc:hexanes to afford a white solid. (20.4 mg, 54% yield). Characterization data matched previously reported data.⁶² **¹H NMR** (400 MHz, CDCl₃): δ_H 8.70-8.68 (m, 1H), 7.96-7.92 (m, 2H), 7.78-7.68 (m, 2H), 7.46-7.43 (m, 2H), 7.25-7.23 (m, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ_C 156.4, 149.9, 137.9, 137.0, 135.3, 129.1, 128.3, 122.5, 120.5.



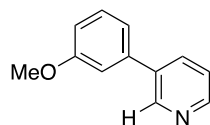
2-(4-Trifluoromethylphenyl)-pyridine (2.61): Compound **2.61** was prepared from substrate **2.14** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-10% EtOAc:hexanes to afford a colorless oil. (18.7 mg, 42% yield). Characterization data matched previously reported data.⁶² **¹H NMR** (400 MHz, CDCl₃): δ_H 8.74-8.72 (m, 1H), 8.11 (d, J = 8.2

Hz, 2H), 7.82-7.72 (m, 4H), 7.30 (ddd, $J = 6.7, 4.8, 1.6$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 156.0, 150.0, 142.8, 137.2, 131.0 (q, $J = 32.4$ Hz), 127.3, 125.8 (q, $J = 3.8$ Hz), 124.3 (q, $J = 271.4$ Hz), 123.1, 121.0; $^{19}\text{F NMR}$ (376 MHz, CDCl_3): δ_{F} 62.6.



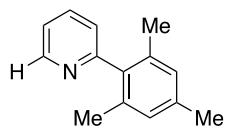
4-(3,4-Methylenedioxyphenyl)-pyridine (2.62): Compound **2.62** was

prepared from substrate **2.15** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 20-60% EtOAc:hexanes to afford a white solid. (39.8 mg, 55% yield). Characterization data matched previously reported data.⁶⁶ $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.61-8.60 (m, 2H), 7.43-7.41 (m, 2H), 7.15-7.10 (m, 2H), 6.91 (dd, $J = 8.0, 0.4$ Hz, 1H), 6.03 (s, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 150.3, 148.7, 148.6, 148.1, 132.3, 121.4, 121.1, 109.0, 107.3, 101.6.



3-(3-Methoxyphenyl)-pyridine (2.63): Compound **2.63** was prepared from

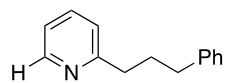
substrate **2.16** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 10-30% EtOAc:hexanes to afford a yellow oil. (28.8 mg, 78% yield). Characterization data matched previously reported data.⁶⁷ $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.87-8.82 (m, 1H), 8.60-8.58 (m, 1H), 7.86 (ddd, $J = 7.9, 2.4, 1.6$ Hz, 1H), 7.41-7.34 (m, 2H), 7.16 (ddd, $J = 7.6, 1.7, 0.9$ Hz, 1H), 7.10 (dd, $J = 2.6, 1.6$ Hz, 1H), 6.95 (ddd, $J = 8.3, 2.6, 1.0$ Hz, 1H), 3.87 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 160.2, 148.7, 148.4, 139.4, 136.7, 134.6, 130.3, 123.7, 119.7, 113.5, 113.1, 55.5.



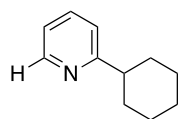
2-(2,4,6-Trimethylphenyl)pyridine (2.64): Compound **2.64** was prepared

from substrate **2.17** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-10% EtOAc:hexanes via combiflash to afford a colorless oil. (26.6 mg, 68% yield). Characterization data matched previously reported data.⁶⁸ $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.71 (ddd, 4.9, 1.9, 1.0 Hz, 1H), 7.74 (td, $J = 7.7, 1.9$ Hz,

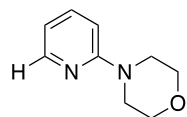
1H), 7.25-7.21 (m, 2H), 6.93 (s, 2H), 2.32 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 160.2, 149.8, 137.9, 137.5, 136.3, 135.8, 128.4, 124.8, 121.6, 21.2, 20.2.



2-(3-Phenylpropyl)-pyridine (2.65): Compound **2.65** was prepared from substrate **2.18** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-20% EtOAc:hexanes to afford a colorless oil. (29.8 mg, 76% yield). Characterization data matched previously reported data.⁶⁹ ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.52 (ddd, $J = 4.9, 1.9, 1.0$ Hz, 1H), 7.57 (td, $J = 7.7, 1.9$ Hz, 1H), 7.28-7.24 (m, 2H), 7.19-7.16 (m, 3H), 7.14-7.07 (m, 2H), 2.84-2.80 (m, 2H), 2.69-2.65 (m, 2H), 2.10-2.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 162.0, 149.2, 142.2, 136.6, 128.6, 128.4, 125.9, 123.0, 121.2, 37.9, 35.7, 31.6.

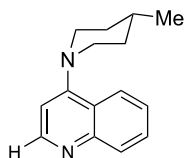


2-Cyclohexylpyridine (2.66): Compound **2.66** was prepared from substrate **2.19** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-10% EtOAc:hexanes to afford a volatile, colorless liquid. (32.3 mg, 49% yield). Characterization data matched previously reported data.⁷⁰ ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.52-8.52 (m, 1H), 7.60 (t, $J = 7.7$ Hz, 1H), 7.15 (d, $J = 7.9$, 1H), 7.09 (ddd, $J = 7.5, 4.9, 1.2$ Hz, 1H), 2.70 (tt, $J = 11.9, 3.4$ Hz, 1H), 1.97-1.93 (m, 2H), 1.88-1.83 (m, 2H), 1.78-1.72 (m, 1H), 1.57-1.46 (m, 2H), 1.45-1.36 (m, 2H), 1.34-1.23 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 166.5, 149.0, 136.8, 121.24, 121.22, 46.6, 33.1, 26.7, 26.2.

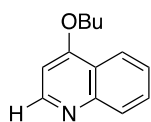


4-(2-Pyridinyl)morpholine (2.55): Compound **2.55** was prepared from substrate **2.19** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 0-20% EtOAc:hexanes to afford a colorless oil (19.1 mg, 59% yield). Characterization data matched previously reported data.⁷¹ ^1H NMR (400

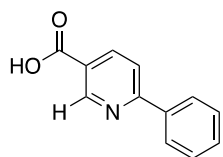
MHz, CDCl₃): δ_H 8.21-8.19 (m, 1H), 7.50 (ddd, J = 8.8, 7.1, 2.0 Hz, 1H), 6.68-6.62 (m, 2H), 3.84-3.81 (m, 4H), 3.51-3.48 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ_C 159.7, 148.1, 137.7, 114.0, 107.1, 66.9, 45.8.



4-(4-Methyl-1-piperidinyl)-quinoline (2.67): Compound **2.67** was prepared from substrate **2.20** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 40-60% EtOAc:hexanes to afford a brownish-orange oil (35.3 mg, 78% yield). ¹H NMR (400 MHz, CDCl₃): δ_H 8.68 (d, J = 5.0 Hz, 1H), 8.00 (ddd, J = 16.0, 8.4, 1.3 Hz, 2H), 7.62 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.45 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 6.80 (d, J = 5.0 Hz, 1H), 3.59-3.55 (m, 2H), 2.79 (td, J = 11.8, 2.3 Hz, 2H), 1.84-1.78 (m, 2H), 1.65-1.49 (m, 3H), 1.05 (d, J = 6.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ_C 157.9, 150.8, 149.6, 129.9, 129.0, 125.1, 124.0, 123.8, 108.7, 53.0, 34.5, 31.1, 22.0. **HRMS (EI-Magn. Sector)** m/z : Calcd for C₁₅H₁₈N₂ [M]⁺ 226.14172; Found: 226.14436.

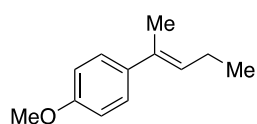


4-Butoxy-quinoline (2.68): Compound **2.68** was prepared from substrate **2.21** according to general procedure C. The crude residue was purified via column chromatography using 100% EtOAc to afford a red oil. (26.7 mg, 66% yield). Characterization data matched previously reported data.⁷² ¹H NMR (400 MHz, CDCl₃): δ_H 8.72 (d, J = 5.2 Hz, 1H), 8.22 (ddd, J = 8.3, 1.5, 0.6 Hz, 1H), 8.03-8.01 (m, 1H), 7.68 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.49 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 6.70 (d, J = 5.2 Hz, 1H), 4.18 (t, J = 6.4 Hz, 2H), 1.95-1.88 (m, 2H), 1.63-1.54 (m, 2H), 2.04 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ_C 161.9, 151.5, 149.3, 129.8, 129.0, 125.6, 122.0, 121.7, 100.8, 68.3, 31.1, 19.5, 14.0.



6-Phenyl-3-pyridinecarboxylic acid (2.23): Compound **2.23** was prepared from substrate **2.5** according to general procedure C. The crude residue was

purified via column chromatography using a gradient of 5%-15% MeOH:DCM to afford a beige solid. (14.0 mg, 35% yield). Characterization data matched previously reported data.⁷³ **¹H NMR** (400 MHz, d₆-acetone): δ_H 9.24 (d, J = 2.1 Hz, 1H), 8.40 (dd, J = 8.3, 2.2 Hz, 1H), 8.22-8.20 (m, 2H), 8.08 (d, J = 8.3 Hz, 1H), 7.56-7.47 (m, 3H); **¹³C NMR** (100 MHz, d₆-acetone): δ_C 166.6, 161.0, 151.7, 139.1, 138.9, 130.8, 129.7, 129.4, 128.1, 120.5

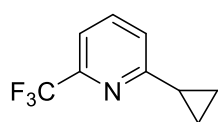


1-Methoxy-4-[(1E)-methyl-1-buten-1-yl]benzene (2.29): Compound **2.29**

was prepared from substrate **2.28** according to general procedure C. The crude residue was purified via column chromatography using a gradient of 2%-10% DCM:Hexanes to afford a yellow oil. (5.4 mg, 15% yield). Characterization data matched previously reported data.⁷⁴ **¹H NMR** (400 MHz, CDCl₃): δ_H 7.32 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.69 (td, J = 7.1, 1.4 Hz, 1H), 3.81 (s, 3H), 2.19 (quin, J = 7.4 Hz, 2H), 2.00 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ_C 158.5, 136.7, 133.5, 128.9, 126.7, 113.6, 55.4, 22.2, 15.8, 14.4.

The following protocol was adapted from a literature protocol.⁷⁶ To an oven-dried round-bottom flask equipped with stir bar was added 2-chloro-6-trifluoromethylpyridine (1.0 equiv), THF (0.17 M), and NMP (1.8 M). The round-bottom flask was covered with a septum and shipped out of the glovebox. While stirring, cyclopropylmagnesium bromide (1.5 equiv) was added through the septum under a positive pressure of N₂ gas. The reaction mixture was allowed to stir for 10 minutes and was then quenched with saturated ammonium chloride and diluted with diethyl

ether. A liquid-liquid extraction was performed using diethyl ether, the organic layer was washed with brine, and dried over sodium sulfate. The organic layer was filtered and concentrated via rotary evaporation and the crude residue was purified via column chromatography.



2-Cyclopropyl-6-trifluoromethylpyridine (2.43): Compound **2.43** was prepared from 2-chloro-6-trifluoromethylpyridine and cyclopropylmagnesium bromide. The crude residue was purified via column chromatography using a gradient of 0%-10% DCM:Hexanes to afford a yellow oil. (80.5 mg, 43% yield). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.67 (td, $J = 7.8, 0.7$ Hz, 1H), 7.39 (dd, $J = 7.7, 1.0$ Hz, 1H), 7.27 (d, $J = 8.1$ Hz, 1H), 2.09 (tt, $J = 8.0, 4.9$ Hz, 1H), 1.11-1.01 (m, 4H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 164.2, 147.8 (q, $J = 34.1$ Hz), 137.0, 123.9, 121.7 (q, $J = 274.2$ Hz), 116.9 (q, $J = 2.9$ Hz), 17.3, 10.7 ppm. **¹⁹F NMR** (376 MHz, CDCl₃): δ_F 68.3 ppm.

2.11.5 | Procedure for variable-time normalization analysis and associated data

Procedure for Variable-Time Normalization Analysis (vTNA): Kinetic data for this reductive C–CF₃ cleavage reaction was obtained for compound **2.5**. All individual kinetic experiments were performed according to the general reaction conditions, varying the amount of base, silane or substrate added. Ten reactions were set up in parallel and stopped after 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, 90 min, 150 min, 210 min and 300 min. Yields were obtained via ¹H-NMR using 1,3,5-trimethoxybenzene as internal standard. The method of variable time normalization analysis was conducted on the obtained yield vs. time data based on the method described by Burés and co-workers in order to determine the observed rate equation.⁴⁰ Standard reaction conditions were 0.200 M trifluoromethyl-pyridine (**2.5**), 0.600 M TMDSO, and 0.720 M KO^tBu. **Figure 2.2** was generated by varying the [substrate], setting it to 0.200 M (standard conditions), 0.150 M or 0.100 M while keeping all else constant. **Figure 2.3** was generating by varying [TMDSO], setting it to 0.600 M (standard conditions), 0.450 M or 0.300 M while keeping all else constant. **Figure 2.4** was generated by varying [KO^tBu], setting it to 0.720 M (standard conditions), 0.540 M or 0.360 M while keeping all else constant.

Results of the vTNA experiments for the C–CF₃ cleavage reaction indicate a near-first order dependence on substrate, base and silane, suggesting that each of these three species are involved in the rate-determining step or the steps immediately preceding it. It should be noted that vTNA provides the practitioner with approximate orders of the studied reaction components. To obtain greater accuracy and certainty with respect to the order of each studied reaction component initial rate measurements are required.

Note* After the publication of this work, work by Mimi Hii pointed out an error in an assumption made during our vTNA analysis.⁷⁶ The vTNA data in **tables 2.5-2.10** had been processed

incorrectly; the concentration of KO^tBu and TMDSO are held constant throughout the reaction which is inappropriate as they are not catalytic species in this transformation. The corrected data is shown below in **tables 2.11-2.12**. The developers of the autovTNA calculator determined the best overlay *using our original data* to be: [TMDSO]^{0.97}, [KO^tBu]^{0.83}, and [**2.5**]^{1.04}. I used the autovTNA calculator to determine the best overlay *using our revised data* in **tables 2.11-2.12** which showed the following orders: [TMDSO]^{0.825}, [KO^tBu]^{0.694}, and [**2.5**]^{1.05}. We felt the change in order was small enough that our conclusions remain unchanged, especially considering vTNA is used to obtain approximate rate data. That being said, we regret this error in the original publication and are happy we could correct it.

Figure 2.2: Graphs depicting apparent first-order overlay of 2.5

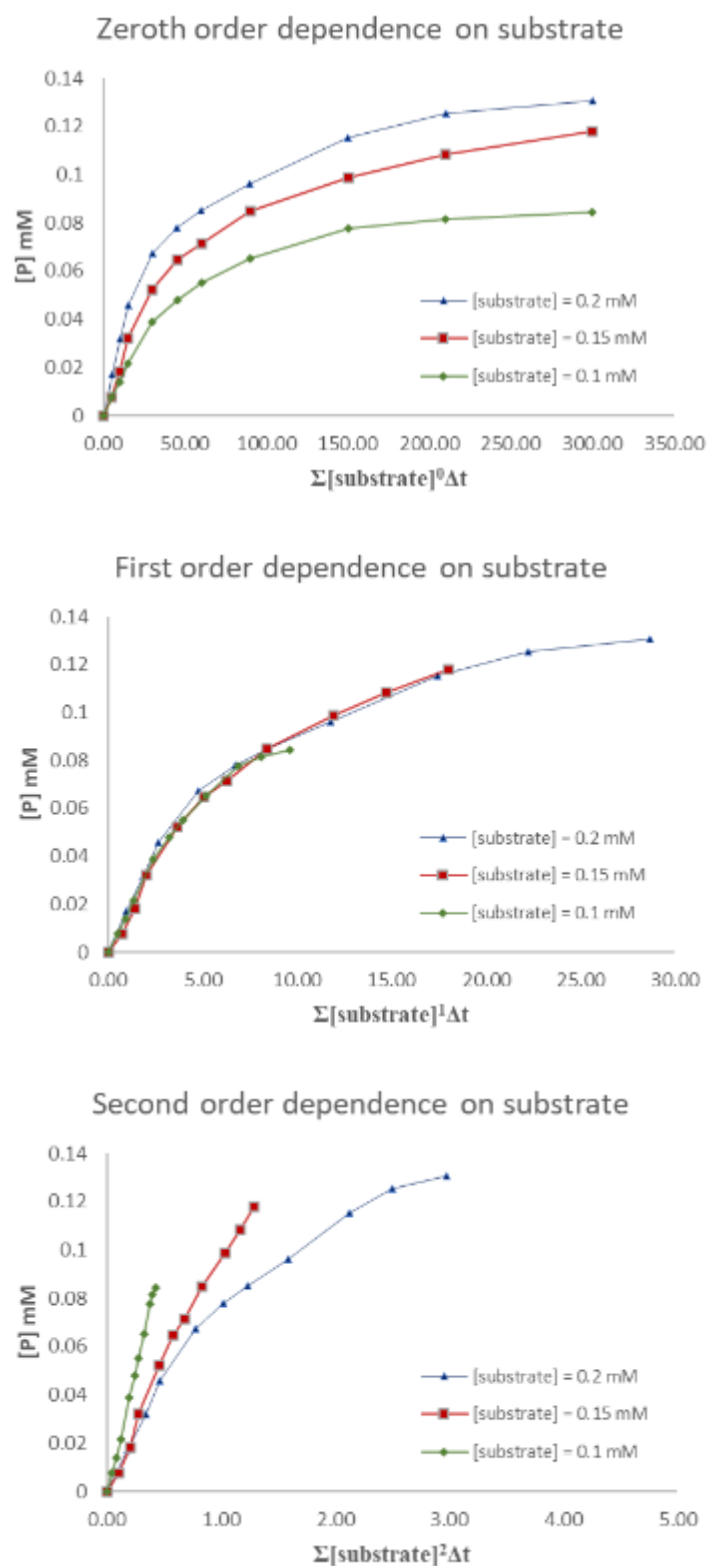


Figure 2.3: Graphs depicting apparent first-order overlay of TMDSO

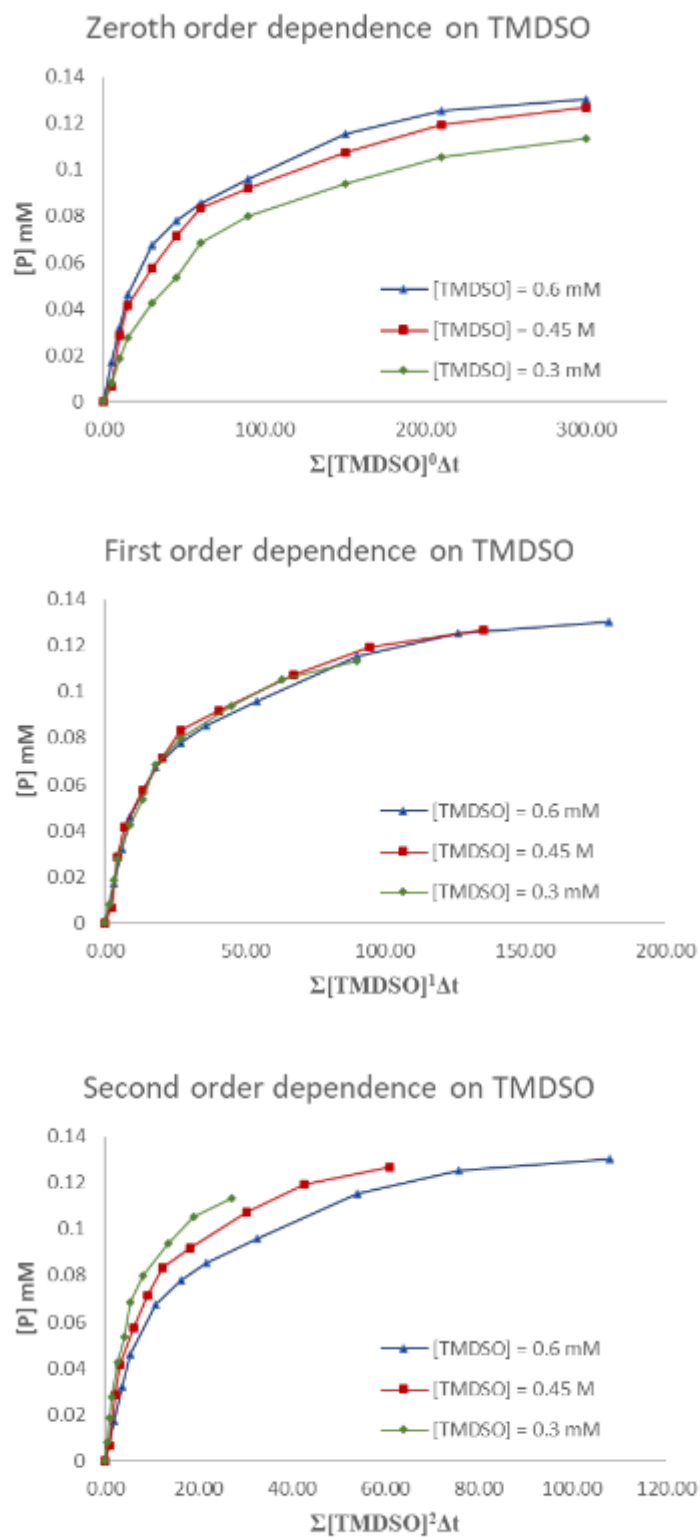


Figure 2.4: Graphs depicting apparent first-order overlay of KO^tBu

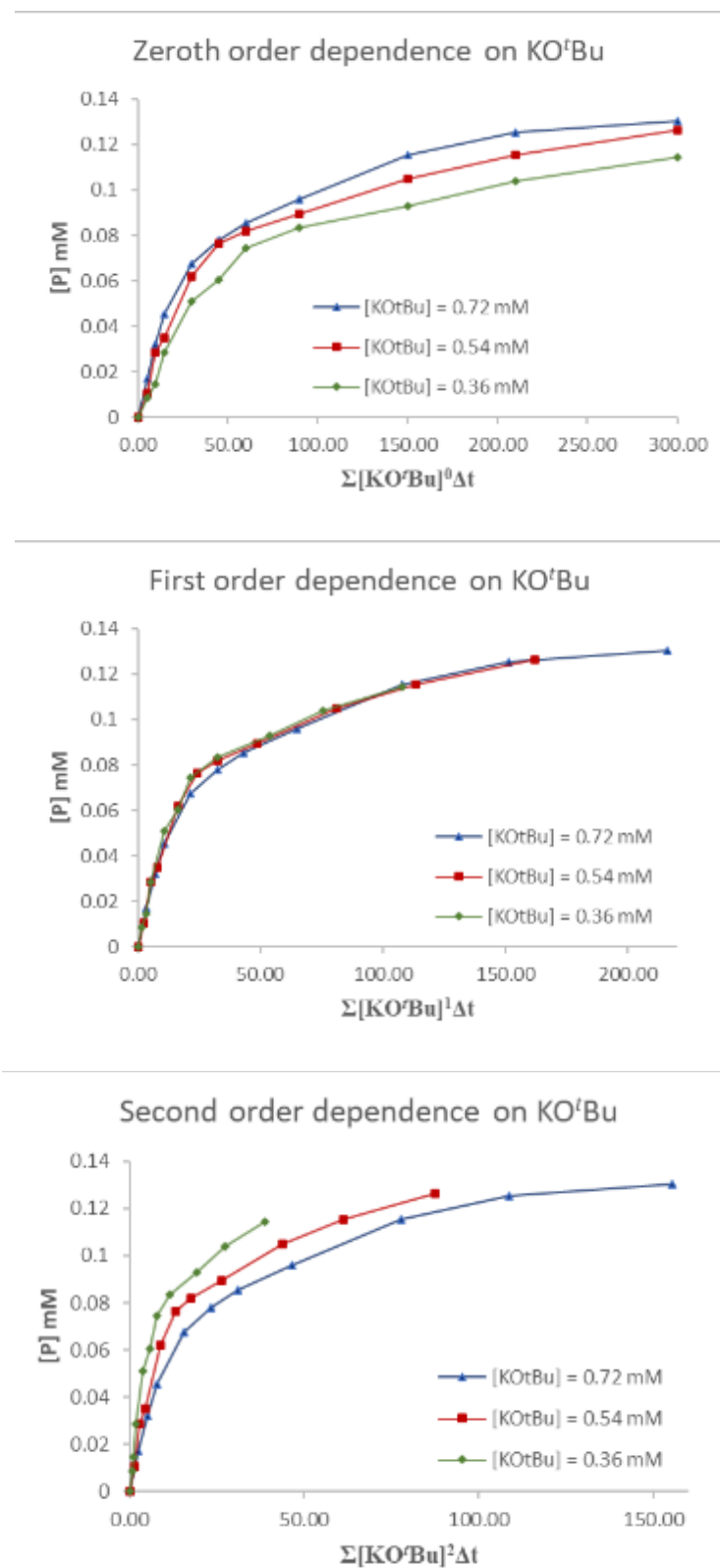


Table 2.2: Raw vTNA data for 1st order overlay of 2.5

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[A] (M)	[P] (M)	t (h)	tA	[A] (M)	[P] (M)	t (h)	tA	[A] (M)	[P] (M)
0	0.00	0.200	0	0	0.00	0.100	0	0	0.00	0.150	0
5	0.96	0.183	0.0170	5	0.48	0.092	0.00759	5	0.73	0.142	0.00764
10	1.83	0.168	0.0321	10	0.93	0.086	0.0139	10	1.42	0.132	0.0185
15	2.64	0.154	0.0458	15	1.34	0.079	0.0214	15	2.04	0.118	0.0321
30	4.79	0.133	0.0674	30	2.39	0.061	0.0389	30	3.66	0.098	0.0522
45	6.70	0.122	0.0779	45	3.23	0.052	0.0479	45	5.03	0.085	0.0647
60	8.48	0.115	0.0853	60	3.96	0.045	0.0549	60	6.26	0.078	0.0716
90	11.76	0.104	0.0959	90	5.16	0.035	0.0653	90	8.41	0.065	0.0848
150	17.42	0.085	0.1154	150	6.86	0.022	0.0779	150	11.91	0.051	0.0986
210	22.20	0.075	0.1253	210	8.08	0.019	0.0815	210	14.70	0.042	0.1083
300	28.69	0.070	0.1305	300	9.61	0.016	0.0844	300	18.02	0.032	0.1180

Table 2.3: Raw vTNA data for 0th order overlay of 2.5

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[A] (M)	[P] (M)	t (h)	tA	[A] (M)	[P] (M)	t (h)	tA	[A] (M)	[P] (M)
0	0.00	0.200	0	0	0.00	0.100	0	0	0.00	0.150	0
5	5.00	0.183	0.0170	5	5.00	0.092	0.00759	5	5.00	0.142	0.00764
10	10.00	0.168	0.0321	10	10.00	0.086	0.0139	10	10.00	0.132	0.0185
15	15.00	0.154	0.0458	15	15.00	0.079	0.0214	15	15.00	0.118	0.0321
30	30.00	0.133	0.0674	30	30.00	0.061	0.0389	30	30.00	0.098	0.0522
45	45.00	0.122	0.0779	45	45.00	0.052	0.0479	45	45.00	0.085	0.0647
60	60.00	0.115	0.0853	60	60.00	0.045	0.0549	60	60.00	0.078	0.0716
90	90.00	0.104	0.0959	90	90.00	0.035	0.0653	90	90.00	0.065	0.0848
150	150.00	0.085	0.1154	150	150.00	0.022	0.0779	150	150.00	0.051	0.0986
210	210.00	0.075	0.1253	210	210.00	0.019	0.0815	210	210.00	0.042	0.1083
300	300.00	0.070	0.1305	300	300.00	0.016	0.0844	300	300.00	0.032	0.1180

Table 2.4: Raw vTNA data for 2nd order overlay of 2.5

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[A] (M)	[P] (M)	t (h)	tA	[A] (M)	[P] (M)	t (h)	tA	[A] (M)	[P] (M)
0	0.00	0.200	0	0	0.00	0.100	0	0	0.00	0.150	0
5	0.18	0.183	0.0170	5	0.05	0.092	0.00759	5	0.11	0.142	0.00764
10	0.34	0.168	0.0321	10	0.09	0.086	0.0139	10	0.20	0.132	0.0185
15	0.47	0.154	0.0458	15	0.12	0.079	0.0214	15	0.28	0.118	0.0321
30	0.78	0.133	0.0674	30	0.19	0.061	0.0389	30	0.45	0.098	0.0522
45	1.02	0.122	0.0779	45	0.24	0.052	0.0479	45	0.58	0.085	0.0647
60	1.23	0.115	0.0853	60	0.28	0.045	0.0549	60	0.68	0.078	0.0716
90	1.59	0.104	0.0959	90	0.32	0.035	0.0653	90	0.83	0.065	0.0848
150	2.12	0.085	0.1154	150	0.37	0.022	0.0779	150	1.04	0.051	0.0986
210	2.50	0.075	0.1253	210	0.40	0.019	0.0815	210	1.17	0.042	0.1083
300	2.97	0.070	0.1305	300	0.42	0.016	0.0844	300	1.29	0.032	0.1180

Table 2.5: Raw vTNA data for 1st order overlay of TMDSO

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)
0	0.00	0.600	0	0	0.00	0.300	0	0	0.00	0.450	0
5	3.00	0.600	0.017	5	1.50	0.300	0.008	5	2.25	0.450	0.00647
10	6.00	0.600	0.03213	10	3.00	0.300	0.01842	10	4.50	0.450	0.02849
15	9.00	0.600	0.04575	15	4.50	0.300	0.02753	15	6.75	0.450	0.04173
30	18.00	0.600	0.06742	30	9.00	0.300	0.04245	30	13.50	0.450	0.05741
45	27.00	0.600	0.07794	45	13.50	0.300	0.05356	45	20.25	0.450	0.07164
60	36.00	0.600	0.08529	60	18.00	0.300	0.06853	60	27.00	0.450	0.08364
90	54.00	0.600	0.09592	90	27.00	0.300	0.07984	90	40.50	0.450	0.09174
150	90.00	0.600	0.1154	150	45.00	0.300	0.0942	150	67.50	0.450	0.1074
210	126.00	0.600	0.125342	210	63.00	0.300	0.1053	210	94.50	0.450	0.1194
300	180.00	0.600	0.13047	300	90.00	0.300	0.1134	300	135.00	0.450	0.1267

Table 2.6: Raw vTNA data for 0th order overlay of TMDSO

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)
0	0.00	0.600	0	0	0.00	0.300	0	0	0.00	0.450	0
5	5.00	0.600	0.017	5	5.00	0.300	0.008	5	5.00	0.450	0.00647
10	10.00	0.600	0.03213	10	10.00	0.300	0.01842	10	10.00	0.450	0.02849
15	15.00	0.600	0.04575	15	15.00	0.300	0.02753	15	15.00	0.450	0.04173
30	30.00	0.600	0.06742	30	30.00	0.300	0.04245	30	30.00	0.450	0.05741
45	45.00	0.600	0.07794	45	45.00	0.300	0.05356	45	45.00	0.450	0.07164
60	60.00	0.600	0.08529	60	60.00	0.300	0.06853	60	60.00	0.450	0.08364
90	90.00	0.600	0.09592	90	90.00	0.300	0.07984	90	90.00	0.450	0.09174
150	150.00	0.600	0.1154	150	150.00	0.300	0.0942	150	150.00	0.450	0.1074
210	210.00	0.600	0.125342	210	210.00	0.300	0.1053	210	210.00	0.450	0.1194
300	300.00	0.600	0.13047	300	300.00	0.300	0.1134	300	300.00	0.450	0.1267

Table 2.7: Raw vTNA data for 2nd order overlay of TMDSO

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)
0	0.00	0.600	0	0	0.00	0.300	0	0	0.00	0.450	0
5	1.80	0.600	0.017	5	0.45	0.300	0.008	5	1.01	0.450	0.00647
10	3.60	0.600	0.03213	10	0.90	0.300	0.01842	10	2.03	0.450	0.02849
15	5.40	0.600	0.04575	15	1.35	0.300	0.02753	15	3.04	0.450	0.04173
30	10.80	0.600	0.06742	30	2.70	0.300	0.04245	30	6.08	0.450	0.05741
45	16.20	0.600	0.07794	45	4.05	0.300	0.05356	45	9.11	0.450	0.07164
60	21.60	0.600	0.08529	60	5.40	0.300	0.06853	60	12.15	0.450	0.08364
90	32.40	0.600	0.09592	90	8.10	0.300	0.07984	90	18.23	0.450	0.09174
150	54.00	0.600	0.1154	150	13.50	0.300	0.0942	150	30.38	0.450	0.1074
210	75.60	0.600	0.125342	210	18.90	0.300	0.1053	210	42.53	0.450	0.1194
300	108.00	0.600	0.13047	300	27.00	0.300	0.1134	300	60.75	0.450	0.1267

Table 2.8: Raw vTNA data for 1st order overlay of KO^tBu

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)
0	0.00	0.720	0	0	0.00	0.360	0	0	0.00	0.540	0
5	3.60	0.720	0.017	5	1.80	0.360	0.008313	5	2.70	0.540	0.01039
10	7.20	0.720	0.03213	10	3.60	0.360	0.01448	10	5.40	0.540	0.02849
15	10.80	0.720	0.04575	15	5.40	0.360	0.028384	15	8.10	0.540	0.03495
30	21.60	0.720	0.06742	30	10.80	0.360	0.050924	30	16.20	0.540	0.062174
45	32.40	0.720	0.07794	45	16.20	0.360	0.060475	45	24.30	0.540	0.076451
60	43.20	0.720	0.08529	60	21.60	0.360	0.074389	60	32.40	0.540	0.08174
90	64.80	0.720	0.09592	90	32.40	0.360	0.08357	90	48.60	0.540	0.08947
150	108.00	0.720	0.1154	150	54.00	0.360	0.092946	150	81.00	0.540	0.1048
210	151.20	0.720	0.125342	210	75.60	0.360	0.1042	210	113.40	0.540	0.1153
300	216.00	0.720	0.13047	300	108.00	0.360	0.11443	300	162.00	0.540	0.1264

Table 2.9: Raw vTNA data for 0th order overlay of KO^tBu

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)
0	0.00	0.720	0	0	0.00	0.360	0	0	0.00	0.540	0
5	5.00	0.720	0.017	5	5.00	0.360	0.008313	5	5.00	0.540	0.01039
10	10.00	0.720	0.03213	10	10.00	0.360	0.01448	10	10.00	0.540	0.02849
15	15.00	0.720	0.04575	15	15.00	0.360	0.028384	15	15.00	0.540	0.03495
30	30.00	0.720	0.06742	30	30.00	0.360	0.050924	30	30.00	0.540	0.062174
45	45.00	0.720	0.07794	45	45.00	0.360	0.060475	45	45.00	0.540	0.076451
60	60.00	0.720	0.08529	60	60.00	0.360	0.074389	60	60.00	0.540	0.08174
90	90.00	0.720	0.09592	90	90.00	0.360	0.08357	90	90.00	0.540	0.08947
150	150.00	0.720	0.1154	150	150.00	0.360	0.092946	150	150.00	0.540	0.1048
210	210.00	0.720	0.125342	210	210.00	0.360	0.1042	210	210.00	0.540	0.1153
300	300.00	0.720	0.13047	300	300.00	0.360	0.11443	300	300.00	0.540	0.1264

Table 2.10: Raw vTNA data for 2nd order overlay of KO^tBu

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)
0	0.00	0.720	0	0	0.00	0.360	0	0	0.00	0.540	0
5	2.59	0.720	0.017	5	0.65	0.360	0.008313	5	1.46	0.540	0.01039
10	5.18	0.720	0.03213	10	1.30	0.360	0.01448	10	2.92	0.540	0.02849
15	7.78	0.720	0.04575	15	1.94	0.360	0.028384	15	4.37	0.540	0.03495
30	15.55	0.720	0.06742	30	3.89	0.360	0.050924	30	8.75	0.540	0.062174
45	23.33	0.720	0.07794	45	5.83	0.360	0.060475	45	13.12	0.540	0.076451
60	31.10	0.720	0.08529	60	7.78	0.360	0.074389	60	17.50	0.540	0.08174
90	46.66	0.720	0.09592	90	11.66	0.360	0.08357	90	26.24	0.540	0.08947
150	77.76	0.720	0.1154	150	19.44	0.360	0.092946	150	43.74	0.540	0.1048
210	108.86	0.720	0.125342	210	27.22	0.360	0.1042	210	61.24	0.540	0.1153
300	155.52	0.720	0.13047	300	38.88	0.360	0.11443	300	87.48	0.540	0.1264

Table 2.11: Corrected raw vTNA data for TMDSO

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)	t (h)	tA	[TMDSO] (M)	[P] (M)
0	0.00	0.600	0	0	0.00	0.300	0	0	0.00	0.450	0
5	3.22	0.583	0.017	5	1.80	0.292	0.008	5	2.55	0.444	0.00647
10	6.37	0.568	0.03213	10	3.56	0.282	0.01842	10	5.03	0.422	0.02849
15	9.45	0.554	0.04575	15	5.27	0.272	0.02753	15	7.42	0.408	0.04173
30	18.46	0.533	0.06742	30	10.21	0.258	0.04245	30	14.39	0.393	0.05741
45	27.24	0.522	0.07794	45	14.94	0.246	0.05356	45	21.15	0.378	0.07164
60	35.89	0.515	0.08529	60	19.46	0.231	0.06853	60	27.71	0.366	0.08364
90	52.95	0.504	0.09592	90	28.10	0.220	0.07984	90	40.53	0.358	0.09174
150	86.22	0.485	0.1154	150	44.54	0.206	0.0942	150	65.48	0.343	0.1074
210	118.66	0.475	0.125342	210	60.16	0.195	0.1053	210	89.60	0.331	0.1194
300	166.67	0.470	0.13047	300	82.64	0.187	0.1134	300	124.90	0.323	0.1267

Table 2.12: Corrected raw vTNA data for KO^tBu

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)	t (h)	tA	[KOtBu] (M)	[P] (M)
0	0.00	0.720	0	0	0.00	0.360	0	0	0.00	0.540	0
5	3.56	0.703	0.017	5	1.78	0.352	0.008313	5	2.67	0.530	0.01039
10	7.03	0.688	0.03213	10	3.52	0.346	0.01448	10	5.28	0.512	0.02849
15	10.44	0.674	0.04575	15	5.22	0.332	0.028384	15	7.82	0.505	0.03495
30	20.39	0.653	0.06742	30	10.02	0.309	0.050924	30	15.19	0.478	0.062174
45	30.10	0.642	0.07794	45	14.58	0.300	0.060475	45	22.25	0.464	0.076451
60	39.68	0.635	0.08529	60	18.97	0.286	0.074389	60	29.16	0.458	0.08174
90	58.56	0.624	0.09592	90	27.40	0.276	0.08357	90	42.80	0.451	0.08947
150	95.42	0.605	0.1154	150	43.71	0.267	0.092946	150	69.37	0.435	0.1048
210	131.40	0.595	0.125342	210	59.39	0.256	0.1042	210	95.16	0.425	0.1153
300	184.69	0.590	0.13047	300	81.96	0.246	0.11443	300	132.89	0.414	0.1264

2.12 | References

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Chapter 3 | The Hydroalkylation of Vinylarenes from In-Situ Generation of Benzylic Nucleophiles Using 1,1,3,3-Tetramethyldisiloxane and Potassium *tert*-Butoxide.

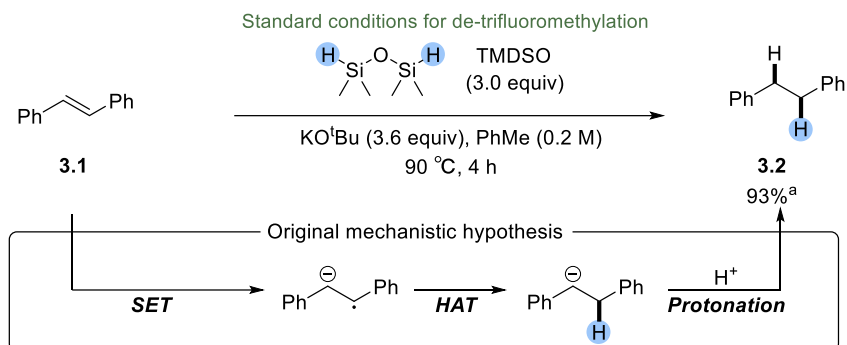
3.1 | Chapter outline

Towards the end of the work disclosed in chapter 2 of this dissertation, we discovered that *trans*-stilbene (**3.1**) could be reduced in 93% yield using only TMDSO and KO^tBu under the conditions used for the reductive C–CF₃ bond cleavage of 2-trifluoromethylpyridines (**Scheme 3.1A**). Based on the original mechanistic hypothesis outlined in chapter 2, we hypothesized the reaction proceeded through single-electron transfer (SET) to *trans*-stilbene, resulting in a radical anion. Subsequent hydrogen atom transfer (HAT) might afford a benzylic carbanion that is protonated during the workup. We questioned whether this presumed radical anion or benzyl anion could be exploited to achieve a hydrofunctionalization reaction by introducing an alkyl halide to intercept the carbanion (**Scheme 3.1B**). To probe this hypothesis, *trans*-stilbene (**3.1**) was combined with (**3.3**), TMDSO, and KO^tBu which led to the formation of **3.4** in 72% yield, and ultimately the initial discovery of the hydroalkylation reaction outlined in chapter 3.

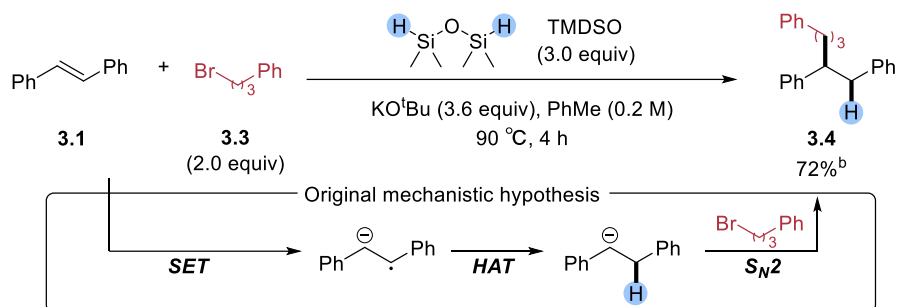
Chapter 3 begins with an introduction aiming to contextualize the field of intermolecular hydroalkylation reactions. Next a discussion about the optimization, scope of this hydroalkylation protocol and in-depth mechanistic analysis will be covered. The chapter finishes with a conclusion and proposes future directions of this research.

Scheme 3.1: Design and discovery of the hydroalkylation of *trans*-stilbene

– A. Hydrogenation of *trans*-stilbene



– B. Design of a hydroalkylation reaction



^a% yield determined by calibrated GC-MS. ^b% yield calculated using ¹H NMR spectroscopy

3.2 | Reuse permissions and contributions to research

The content of Sections 3.5 (with the exception of 3.5.4.1, which is written for this dissertation), 3.6, 3.8, and 3.9 have been adapted with permission from the original manuscript and supporting information of “Hydroalkylation of Vinylarenes by Transition-Metal-Free In Situ Generation of Benzylic Nucleophiles Using Tetramethyldisiloxane and Potassium *tert*-Butoxide” by Piers St-Onge, Hana Nugraha and Stephen G. Newman. {*Angew. Chem. Int. Ed.*, **2025**, 64, e202421077}. This material is licensed under the **Creative Commons Attribution–NonCommercial 4.0 International License (CC BY-NC 4.0)** (<https://creativecommons.org/licenses/by-nc/4.0/>). The dissertation author is the primary author of this work. Minimal changes have been made to the portions that were reproduced from the original manuscript. These changes unify the style and ensure consistent numbering of molecules, figures, tables, and schemes throughout this dissertation.

All other sections of chapter 3 are original and found only within this dissertation.

Contributions

Hana Nugraha synthesized substrate **3.41** to be tested as a mechanistic probe. She also conducted the screening of substrates **3.61**, **3.66**, **3.67**, **3.74**, **3.75**, and **3.80**. Much of her contribution to this project was in the preliminary screening of scope examples to gain an understanding of what substrates would be amenable to the hydroalkylation reaction before optimized conditions had been decided upon. As a result of this, many of the scope examples she synthesized and isolated were lower yielding and were synthesized and reisolated by the author of this dissertation. This includes substrates **3.7**, **3.9**, **3.10**, **3.16**, **3.28**, **3.29**, **3.32**. However, while she is not responsible for the isolation and % yields of the aforementioned compounds *as they appear in the published article*, her contributions were considered substantial because her work gave the

author of this dissertation a head-start in the synthesis and isolation of scope examples. The author of this dissertation would like to express his deep gratitude for Hana Nugraha's contribution to the work. All other experiments were conducted by the author of this dissertation.

3.3 | The hydroalkylation of olefins: A practical method to synthesize $C(sp^3)-C(sp^3)$ bonds.

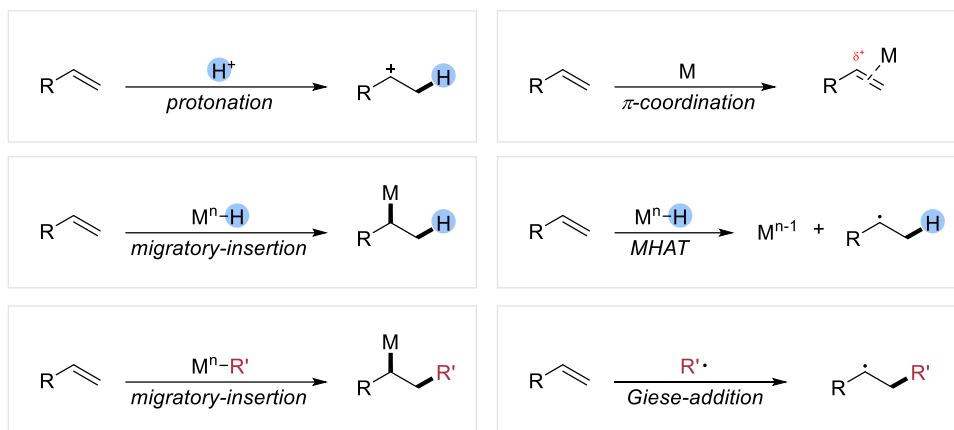
3.3.1 | Hydroalkylation reactions in synthetic organic chemistry

The development of methods to synthesize $C(sp^3)-C(sp^3)$ bonds remains a fundamental goal in organic synthesis. The discovery that molecules with a 3-dimensional structure see more clinical success, on average, than their flat counterparts has fueled this area of research leading to the development of various different $C(sp^3)-C(sp^3)$ bond forming transformations.¹ Hydroalkylation reactions involve the functionalization of an olefin or alkyne wherein a C-H bond and $C(sp^3)-C(sp^3)$ bond of an alkyl substituent are installed at the expense of a π -bond. Although many hydrofunctionalization reactions of various unsaturated functional groups exist, chapter 3 of this dissertation focuses on the hydroalkylation of olefins, as such section 3.3 serves to outline and discuss the hydroalkylation olefins. *This section will only cover the hydroalkylation of olefins, the hydroalkylation of other π -species will not be discussed in this section. Hydrofunctionalization reactions that do not classify as a hydroalkylation reaction will not be discussed.* Given that many olefins are commercially and synthetically available, this class of reaction presents an attractive approach to synthesize $C(sp^3)-C(sp^3)$ bonds while building molecular complexity.² Many dedicated efforts towards the development of hydroalkylation reactions have been undertaken. This section highlights 3 key strategies, namely: transition metal-catalyzed hydroalkylation reactions, photoredox-catalyzed hydroalkylation reactions, and emerging electrochemical hydroalkylation reactions.

3.3.2 | Transition metal-catalyzed hydroalkylation reactions

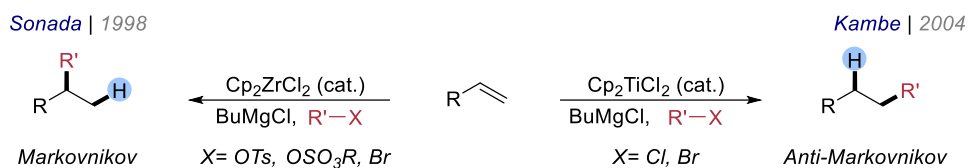
A highly utilized strategy to perform hydroalkylation reactions is through use of transition metal catalysis. Transition metal-catalyzed hydroalkylation reactions are known to proceed through many pathways which depend on a multitude of factors, including which transition metal is used, the electronics of an olefin, the source of hydrogen, and the acidity of the reaction conditions.³⁻⁵ Some more common key steps that are seen in transition metal-catalyzed hydroalkylation reactions include protonation of the olefin or coordination of the olefin to a Lewis acid and subsequent trapping with a carbon nucleophile, migratory insertion of a metal hydrogen or metal alkyl substituent, metal-hydride hydrogen atom transfer (MHAT), and the radical-addition of a carbon-centered radical to an olefin. (**Scheme 3.2**). In the ionic, 2-electron pathway, metal hydride or metal alkyl species first associate with the olefin which then inserts between the M–H or M–C bond to furnish a new C–H or C–alkyl bond and a C–metal bond. The oxidation state of the metal in this case remains unchanged. Under the single-electron manifold, hydroalkylation can proceed through (MHAT) or the radical-addition of a carbon-centered radical followed by the quenching of the incipient radical. As its name implies, MHAT describes the transfer of a hydrogen atom from a metal species to an olefin.⁶ The product is a carbon-centered radical that can be captured by the metal resulting in what is formally a two-step migratory insertion. Alternatively, the radical can engage in reactions with other species in solution. In order for MHAT to take place the M–H bond dissociation energy (BDE) needs to be low enough to react with the olefin species.⁷ Typically, MHAT leads to Markovnikov or branched product selectivity while the latter strategy gives rise to anti-Markovnikov or linear selectivity.

Scheme 3.2: Common key steps for transition metal-catalyzed hydroalkylation reactions



Some of the earliest examples of olefin hydroalkylation make use of zirconium hydride catalysis to install alkyl substituents at the benzylic position of vinylarenes (**Scheme 3.3**).⁸ These systems utilized alkyl bromides, tosylates, and sulfates as alkylating agents and alkyl Grignard reagents as a source of hydride for the transition metal catalyst. Notably, the substrate scope was limited to functional groups that are resistant to unwanted reactions with the Grignard species. A follow up from 2001 extended this chemistry to the difunctionalization of olefins.⁹ Examples of titanium-catalyzed hydroalkylation reactions have also been reported and make for synthetically viable strategies to access anti-Markovnikov hydroalkylation products. In this instance, alkyl electrophiles are transformed into carbon centered radicals from the titanium catalyst and undergo radical-addition onto electron deficient olefins followed by quenching of the incipient radical.¹⁰ Notably, this leads to an inverted regioselective outcome when compared to the zirconium-catalyzed reaction. Later Lin and coworkers reported a robust titanium-catalyzed hydroalkylation strategy making use of alkyl chlorides as radical precursors.⁵

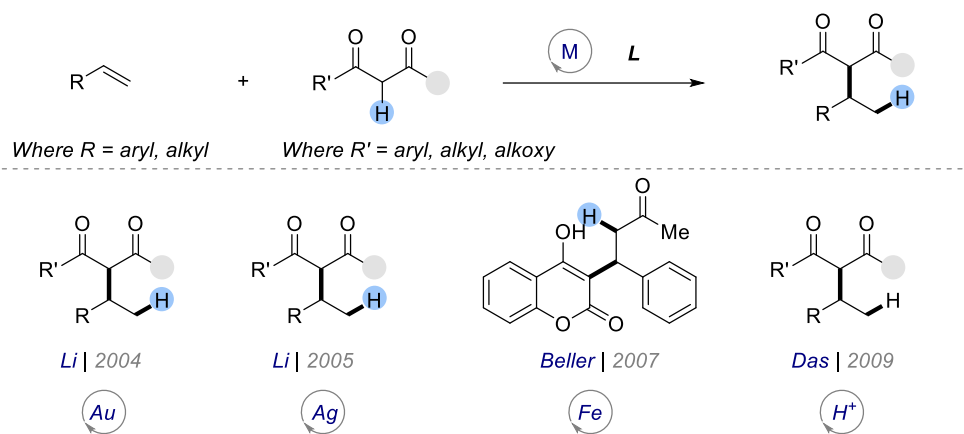
Scheme 3.3: Zirconium and titanium-catalyzed hydroalkylation reactions



Brønsted and Lewis acid-catalyzed hydroalkylation reactions have seen extensive study in the literature and are among the most popular transition metal-catalyzed hydroalkylation strategies. This class of hydroalkylation reaction proceeds through the activation of an olefin through either protonation by a strong acid or via coordination of the π -bond to a Lewis acidic metal center. This leads to positive charge accumulation on the more substituted position of the olefin, which can react with a carbon-based nucleophile. In an early example of the Lewis acid-catalyzed hydroalkylation of styrenes, a gold(III) precatalyst was used in tandem with 1,3-diketones as weak nucleophiles (Scheme 3.4).¹¹ Using a 5 mol% catalyst loading of AuCl_3 , the authors reported a scope of 15 examples bearing chlorine, methoxy, and methyl functional groups on the styrene ring. Acyclic and cyclic 1,3-diketones were featured in the scope, with two examples of quaternary carbon centers being formed in moderate to high yields. This was the first instance of a gold-catalyzed hydroalkylation reaction being reported in the literature. Shortly thereafter, the Li group demonstrated the same reaction could be facilitated using $\text{Ag}(\text{OTf})_3$ as a Lewis acid-catalyst; the authors highlighted the reversibility of the C–C bond forming step.¹² A similar styrene hydroalkylation strategy was later reported by Beller and coworkers, who utilized FeCl_3 as an earth-abundant catalyst alternative to gold.¹³ The authors demonstrated the applicability of this protocol to the synthesis of biologically relevant molecules by synthesizing warfarin—an anticoagulant medication—from 4-hydroxycoumarin and benzylideneacetone. In a Brønsted acid-catalyzed hydroalkylation strategy disclosed by Das and coworkers, Amberlyst-15—an acidic ion-exchange resin—was used as a heterogeneous catalyst.¹⁴ The reaction proceeds through

protonation of the homobenzylic position and subsequent nucleophilic addition of the 1,3-diketone-derived enolate to the resulting benzylic carbocation. The authors report high yields and short reaction times of 15–40 minutes, with a scope featuring methyl and chloro substituents on the aromatic ring of styrene. This class of intermolecular hydroalkylation continued to be studied using gold^{15,16} and iridium, with a particular emphasis on the use of unactivated alkenes.^{17,18}

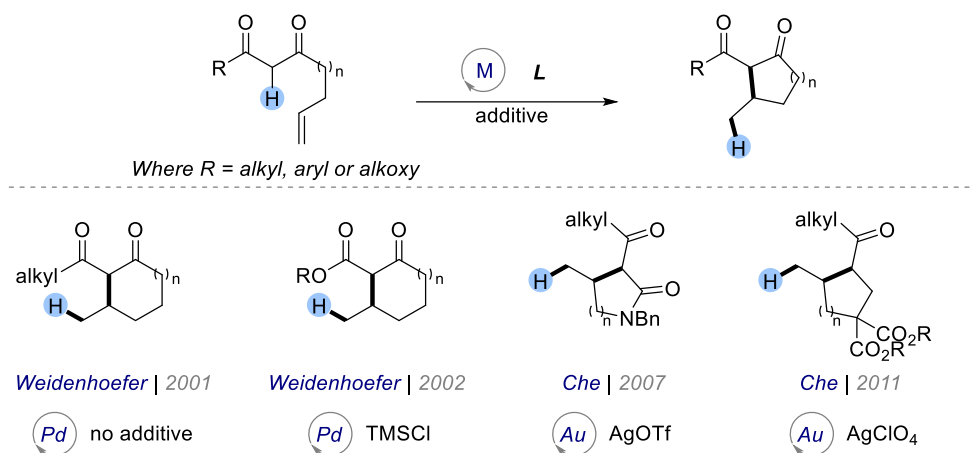
Scheme 3.4: Intermolecular Lewis and Brønsted acid-catalyzed hydroalkylation reactions



Intramolecular variants were more heavily investigated than their intermolecular counterparts. In 2001, Widenhoefer and coworkers developed an intramolecular hydroalkylation reaction between an unactivated olefin and a pendant 1,3-diketone using $PdCl_2(CH_3CN)_2$ as a catalyst (Scheme 3.5).¹⁹ The reaction proceeds at room temperature and requires 12–36 hours to reach completion; the products were predominantly aliphatic 2-acylcyclohexanones. The authors noted lower yields and longer reaction times when using β -keto esters as substrates, which they attributed to a higher equilibrium ratio between keto:enol tautomers when compared to 1,3-diketones. This scope limitation was addressed in a follow-up study by using $(CH_3)_3SiCl$ to generate the silyl enol ether of the β -keto esters removing the problem of the intrinsic higher keto:enol ratio observed with β -keto esters.²⁰ Using $(CH_3)_3SiCl$ as an additive led to shorter reaction times, allowing for a more feasible hydroalkylation strategy to access ester-bearing

carbocycles. The Widenhoefer group continued their study of palladium-catalyzed intramolecular hydroalkylation reactions into the mid-2000s,^{21,22} and in 2005 conducted an in-depth mechanistic investigation which led the authors to conclude palladium operates as a Lewis acid-catalyst.²³ Shortly after the advent of palladium-catalyzed intramolecular hydroalkylation reactions gold-catalyzed variants made their way into the spotlight. In 2007, Che and coworkers utilized a gold(I) precatalyst alongside a catalytic silver(I) additive to facilitate the intramolecular hydroalkylation of β -keto amides.²⁴ The authors utilized terminal unactivated olefins to synthesize five- and six-membered nitrogen-containing heterocycles in high yields, proceeding through a 5-exo-trig cyclization. Of particular note, this method allowed for the synthesis of spirocycles and highly substituted lactams – two classes of medically relevant substrates. In 2011, the authors extended their focus to an intramolecular hydroalkylation reaction of α -ketones, resulting in spirocycles and fused carbocycles.²⁵ This was the first example of a gold-catalyzed intramolecular hydroalkylation reaction using α -ketones without the use of additives. Deuterium labeling experiments pointed toward a reversible C–C bond-forming step. An asymmetric variant was later disclosed by Gandon featuring a gold/silver catalyst to access lactams in high ee and modest d.r.²⁶ The synthesis of carbocycles, heterocycles, and spirocyclic frameworks clearly illustrates that intramolecular Lewis acid-catalyzed hydroalkylation reactions are excellent for the rapid construction of molecular complexity.

Scheme 3.5: Intramolecular Lewis acid-catalyzed hydroalkylation reactions

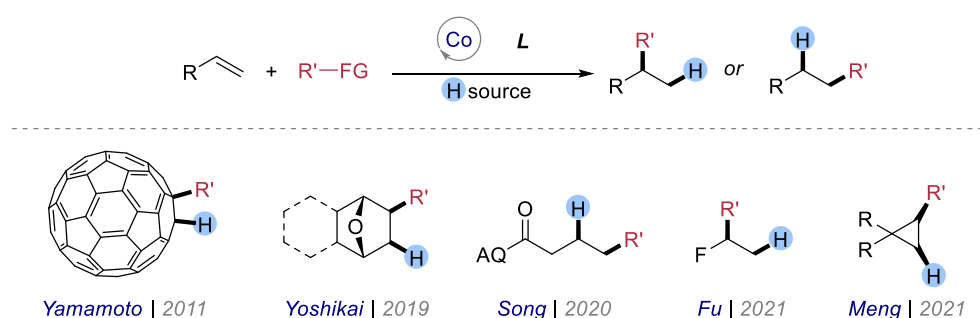


Many hydroalkylation reactions proceed via the radical-like addition of a carbon-centered radical onto an olefin. An example of this published by Baran and coworkers features an iron-catalyzed hydroalkylation reaction that makes use of electron-donating olefins as carbon-centered radical precursors and phenylsilane as a reductant.²⁷ In this work the iron(III) hydride donates its hydrogen atom via MHAT to an electron rich olefin to generate a carbon-centered radical which then undergoes radical addition with the electron-poor olefin to furnish the key C–C bond. This represents an attractive strategy to synthesize compounds bearing electron-rich and electron-poor motifs separated by 3-4 carbons. However, the use of electronically biased species limits the applicability of this transformation.

Cobalt hydroalkylation reactions represent a large proportion of hydroalkylation strategies which have been shown to proceed through ionic and single-electron pathways (**Scheme 3.6**).^{4,28} Cobalt is thus a diverse and powerful metal for hydroalkylation reactions. An early example was reported in 2011 wherein a cobalt-catalyzed hydroalkylation of fullerenes was disclosed.²⁹ This work uses cobalt to reduce alkyl halides to carbon-centered radicals which directly attack the fullerene π -bonds generated a stabilized radical. This stabilized radical on fullerene is then reduced to a carbanion and quenched using water as a mild proton source. About a decade later, the area of

cobalt-catalyzed hydroalkylation reactions saw high development. In 2020 Song and coworkers reported the cobalt-catalyzed hydroalkylation of unactivated olefins using oximes as radical precursors.³⁰ This work features Daugulis's aminoquinoline as a covalent chelator to direct regioselectivity towards the anti-Markovnikov product. Homo-enolate chemistry found its way into cobalt catalysis with several strategies forming cobalt-homoenolates as alkylating reagents derived from cyclopropanols.³¹⁻³³ Cobalt-catalyzed hydroalkylation of fluoroalkenes,³⁴ glycosides,^{35,36} and cyclopropenes³⁷ all saw development providing the synthetic community a convenient way to access fluorinated compounds, alkyl-sugar molecules, and functionalized cyclopropanes. Interestingly, each of these protocols made use of box ligands and alkyl electrophiles.

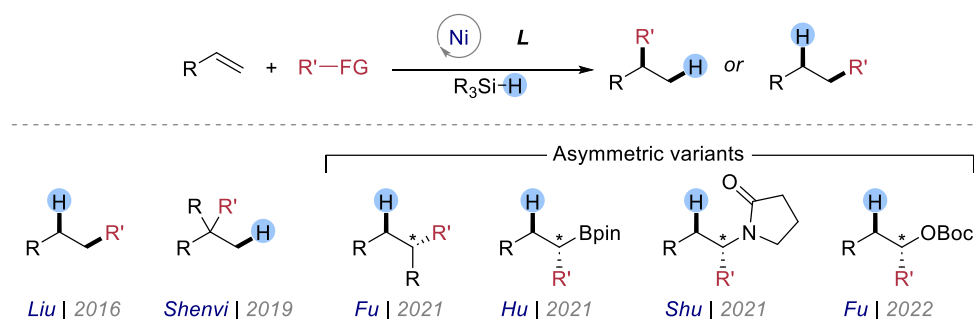
Scheme 3.6: Cobalt-catalyzed hydroalkylation strategies



Nickel has also emerged as a highly useful metal in hydroalkylation reactions (**Scheme 3.7**).³⁸ In 2016 a nickel-catalyzed anti-Markovnikov hydroalkylation reaction of unactivated olefins was reported by Liu and coworkers.³⁹ The transformation made use of unactivated primary and secondary alkyl iodides in a scope that was broadly applicable to various different functional groups. This represents a phenomenal strategy to hydroalkylate complex molecules – this was demonstrated by the authors when the hydroalkylation of cinchonidine and calciferol could be undertaken in high yields and high regio/chemoselectivity. Soon after its development a dual transition metal-catalyzed approach was reported by Shenvi and coworkers.⁴⁰ This work featured

the powerful combination of manganese and nickel to transform trisubstituted olefins into quaternary carbon centers – a challenging motif to access. Each metal served its own purpose; manganese was responsible for MHAT while nickel would engage the resulting carbon-centered radical in cross coupling with the alkyl halide. Not long after this many reports of nickel-catalyzed asymmetric hydroalkylation protocols of aliphatic olefins,⁴¹ vinyl boronates,⁴² enamides,⁴³ and vinyl esters,⁴⁴ made their way into the literature. Each of these transformations relies on the use of chiral ligands to introduce point chirality into the product molecules, which in some cases resulted in the formation of two or more contiguous stereocenters in high diastereoselectivity. Notably, each of the aforementioned strategies use hydrosilanes as reductants. Various other transition metal-catalyzed hydroalkylation strategies exist including methods using palladium, copper, and gold.³

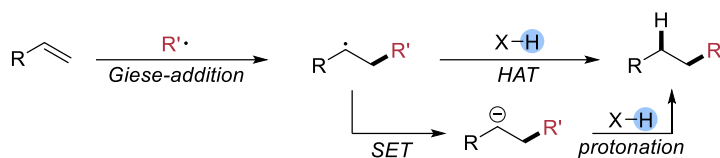
Scheme 3.7: Nickel-catalyzed hydroalkylation reactions



3.3.3 | Photochemical radical hydroalkylation strategies

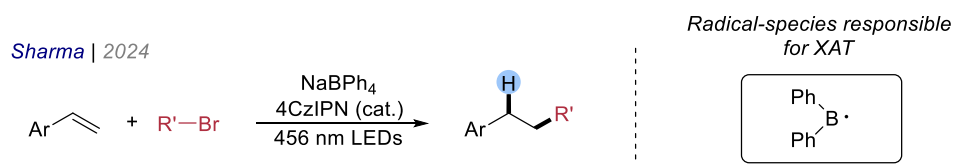
Photoredox catalysis provides another valuable approach to perform hydroalkylation reactions. A common step in photoredox-catalyzed hydroalkylation reactions is the radical-addition of a carbon-centered radical to an olefin.⁴⁵⁻⁴⁷ This carbon-centered radical can react further through hydrogen-atom transfer, or by single-electron reduction to a carbanion which may be protonated in-situ or upon workup (**Scheme 3.8**).

Scheme 3.8: Giese-like addition and subsequent reactivity: a common hydroalkylation pathway



The regioselective outcome of radical-addition onto an olefin is largely governed by radical stabilization and as such the regioselective outcome tends to favour the more stable radical. However, electron-deficient olefins tend to undergo radical-addition much more rapidly than their electron-rich counterparts indicating some electronic or steric influence on the transition state.⁴⁸ Thus, existing photoredox-catalyzed radical hydroalkylation strategies tend to be anti-Markovnikov selective. Perhaps the biggest difference between the various photoredox-catalyzed hydroalkylation strategies is how carbon-centered radicals are formed. One such strategy is halogen atom transfer (XAT). As its name implies, XAT involves the abstraction of a halogen atom from carbon to a given radical species and is a popular strategy to generate carbon-centered radicals for hydroalkylation reactions (**Scheme 3.9**).⁴⁹ Sharma and coworkers capitalized on XAT using sodium tetraphenylborate ($NaBPh_4$) under photocatalytic conditions.⁴⁶ They showed $NaBPh_4$ could be transformed into a boryl radical that engages in halogen atom transfer with alkyl bromides leading to an alkyl radical. This alkyl radical then undergoes radical-addition with styrene affording a benzylic radical that is quenched via HAT.

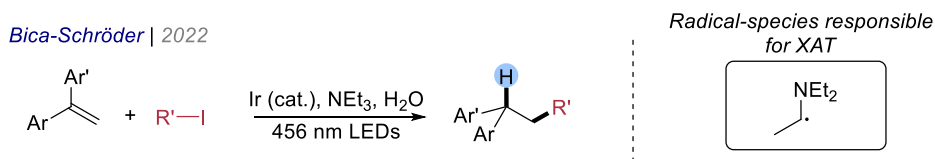
Scheme 3.9: Boryl radical-mediated photocatalytic hydroalkylation of aryl olefins



A similar hydroalkylation protocol featuring boryl radical anions used in XAT has been reported but does not require a photocatalyst and instead only blue light irradiation.⁴⁷ Another powerful way

to perform XAT is through use of α -amino radicals, which are generated through the single electron oxidation of a trialkyl amine. This can be accomplished under photocatalytic conditions. Oxidation of the amine to the radical cation enhances the acidity of the adjacent C–H bond which in the presence of base can afford the desired α -amino radical.⁵⁰ In 2024 Bica-Schröder and coworkers reported the iridium-catalyzed hydroalkylation of aryl alkenes (**Scheme 3.10**). This work featured the use of triethylamine as an α -amino radical precursor which engages in XAT with alkyl iodides to generate the key radical species of this transformation.⁴⁵ A related hydroalkylation study was reported earlier this year that proceeds through a similar mechanism but instead uses tributylamine as the α -amino radical precursor. This work specifically focused on the hydroalkylation of methyleneisoidolinones.⁵¹ In each of these cases, the radical species responsible for XAT is generated through SET with the active photocatalyst.

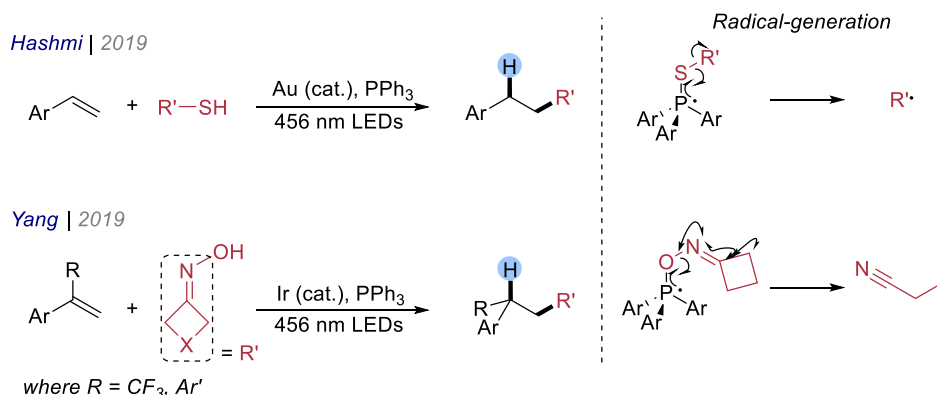
Scheme 3.10: α -amino radical-mediated photocatalytic hydroalkylation of aryl olefins



As previously stated, other strategies to access carbon-centered radicals have been used in hydroalkylation protocols. For instance, in 2019 Hashmi reported the use of thiols as radical precursors engaging them in the radical hydroalkylation of vinylarenes (**Scheme 3.11**).⁵² A photoactive gold catalyst was used to oxidize the thiol to a radical cation, which would undergo nucleophilic addition by phosphine affording a phosphoranyl radical species primed to undergo α -scission releasing a carbon-centered radical and phosphine sulfide. Yang and coworkers disclosed an iridium-catalyzed radical hydroalkylation of vinylarenes uses cyclic oximes as radical precursors.⁵³ In contrast to work by Hashmi, the iridium photocatalyst oxidizes the phosphine to

the phosphonium radical cation which then undergoes nucleophilic attack by the oximes hydroxyl group. α -scission of the phosphoranyl radical drives ring-opening of the oximes 4-membered cycle leading to a linear carbon-centered radical bearing a terminal nitrile functionality. representing a practical way to introduce alkyl chains bearing internal heteroatoms onto olefin scaffolds. Each makes clever use of phosphoranyl radicals to transform substrates with exceedingly high reduction potentials into carbon-centered radicals. This clever strategy circumvents the need for highly reducing conditions.⁵²⁻⁵⁴

Scheme 3.11: Phosphoranyl radical-mediated photocatalytic hydroalkylation reactions of activated olefins



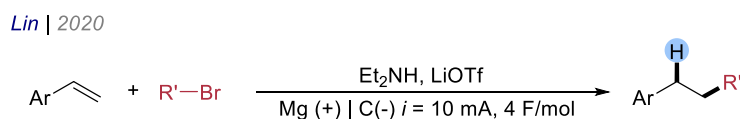
Outside of these strategies the use of substrates that undergo visible light-mediated bond homolysis,⁵⁵ H-atom abstraction,⁵⁶ and single-electron reduction,⁵⁷ to generate carbon-centered radicals primed for radical-addition have been reported.

3.3.4 | Electrochemical hydroalkylation reactions

Electrochemistry has received recognition as a powerful platform to perform organic synthesis due to the ability to fine-tune the potential of a given system.⁵⁸ Electrons may be used directly which obviates the need for a stoichiometric redox reagent which is accompanied by unwanted side-products. Furthermore, it's found synergy with transition metal catalysis and

photoredox catalysis allowing for transformations that are otherwise exceedingly challenging to perform.^{59,60} Naturally, such a tool has been applied in the hydroalkylation of olefins. Using alkyl bromides as radical precursors Lin and coworkers developed an anti-Markovnikov selective electrochemical hydroalkylation reaction (**Scheme 3.12**).⁶¹ In this work, styrenes were amenable to the reaction conditions, including a few non-styrene olefins demonstrating its use as a highly practical transformation. The use of electrochemical conditions allows for the direct reduction of alkyl bromides to the corresponding radical, a pathway which is otherwise challenging to perform. Following radical-addition of the radical to the olefin subsequent anodic reduction of the benzylic radical produces a benzylic carbanion which is protonated upon workup. Their follow-up study, although a dicarbofunctionalization reaction rather than hydroalkylation, makes use of two electrophiles in one pot and capitalizes on the tunability of the electrochemical potential to selectively engage one electrophile in single-electron reduction, and the other in polar alkylation chemistry.⁶²

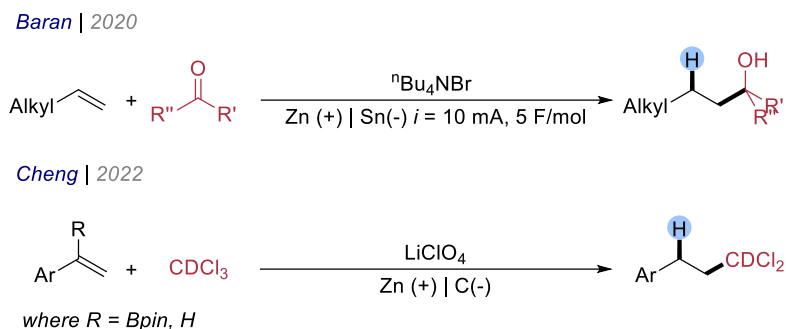
Scheme 3.12: Electrochemical hydroalkylation of aryl olefins using alkyl halides as radical precursors



In a report from 2020, Baran and coworkers showcase the electrochemical hydroalkylation of aliphatic olefins using a (+)Zn/(-)Sn electrode (**Scheme 3.13**).⁶³ Ketones are reduced to their ketyl radical and undergo radical-addition to the olefin affording the anti-Markovnikov product. It should be noted that many strategies to engage ketones in hydroalkylation reactions through a ketyl radical pathway have been reported.⁶⁴⁻⁶⁶ Cheng reported an interesting hydroalkylation protocol making use of chloroform-d₁ (CDCl₃) as a radical precursor under electrochemical conditions.⁶⁷ In addition to hydroalkylation products, deuterio-chlorocyclopropane rings can be constructed.

While electrochemical hydroalkylation reactions remain in their infancy, electrochemistry offers a great deal of potential (*Bud um, Tss!*) towards organic synthesis.

Scheme 3.13: Electrochemical hydroalkylation of alkyl and aryl olefins



The hydroalkylation of olefins is a well defined and established field dominated by transition metal and photoredox catalysis. Although many significant advances have been made this area is not without its limitations. In cases where alkyl halides are used, a limited number of protocols utilizing alkyl chlorides as electrophiles have been reported, with virtually no accounts that proceed through a polar displacement of the C–Cl bond being reported. While this may appear unimportant, on larger scales the identity of the halogen or leaving group becomes significant considering heavier halogens – Br, I – produce heavier waste streams and a larger overall process mass intensity (PMI). Coupled with the greater abundance and stability of alkyl chlorides compared to their bromide and iodide congeners, this presents a significant area for improvement. We also noted many of the transition metal-catalyzed protocols made use of hydrosilanes as a reductant. Given that many transition metal-catalyzed reactions are sensitive to air the application of these protocols require special equipment making their use somewhat less general and/or accessible. Thus, there exists some argument for a strategy that can answer these leading to an alternative hydroalkylation strategy.

3.4 | Research goals: Design and development of a hydroalkylation reaction

After discovering the initial hit outlined in **Scheme 3.1** we considered whether this transformation would be desirable. We reviewed the existing hydroalkylation methods in the literature (*vide supra*) noting that few reports of protocols functionalize the benzylic position using alkyl electrophiles. Furthermore, methods that do establish a C–C bond at the benzylic position typically make use of organometallic alkylating reagents,⁷ or display poor functional group tolerance.⁸ We also made the observation that while many protocols make use of alkyl bromides, and iodides, few examples utilize unactivated primary and secondary alkyl chlorides as alkylating reagents. We also noted many of the transition metal-catalyzed protocols made use of hydrosilanes as a reductant. We thought that under our conditions we could make use of alkyl chlorides as electrophiles and obviate the need for a transition metal catalyst, ultimately offering a complementary hydroalkylation strategy. Furthermore, the low cost associated with our reducing agent (~\$2 for 1 gram) makes this an ideal strategy to synthesize C(sp³)–C(sp³) bonds at cost. Finally, the final and more exciting reason to study this transformation was to uncover the underlying reaction mechanism with the hopes of learning more about this unconventional, and exciting reagent combination. To reiterate section 3.2 the development and investigation of this discovered hydroalkylation reaction was published in {*Angew. Chem. Int. Ed.*, **2025**, 64, e202421077} and is reproduced with permission in Sections 3.5-3.6, and 3.8-3.9 below.

Section 3.5 | In situ generation of benzylic nucleophiles using tetramethyldisiloxane and potassium *tert*-butoxide

The combination of hydrosilanes and metal alkoxides enables a diverse array of transformations. The Grubbs-Stoltz reagent pair – Et₃SiH/KO^tBu – is particularly powerful, with seminal reports demonstrating it is capable of a range of reductive C–C,⁶⁸ C–O,⁶⁹ C–S,⁷⁰ and C–N⁷¹ bond-cleaving reactions (**Scheme 3.14A**). On the other hand, its use in complexity-building reactions is less

common, with exceptions including C–H silylation developed by Grubbs and Stoltz,⁷² cyclization and intramolecular rearrangements developed by Murphy,^{68,73} and the KO^tBu-catalyzed hydrosilylation of vinylarenes developed by Jeon.⁷⁴ The versatility of this reagent pair is attributed to its ability to generate numerous possible reactive intermediates in situ, with mechanistic evidence that the combination of hydrosilane and alkoxide can become a strong base, a hydride donor, a hydrogen atom donor, a single-electron donor, and a source of silicon radicals.^{71,75} While these reactive intermediates have been controlled to facilitate a range of interesting reactions, to our knowledge, no intermolecular, complexity-building C–C bond-forming reactions have been reported.

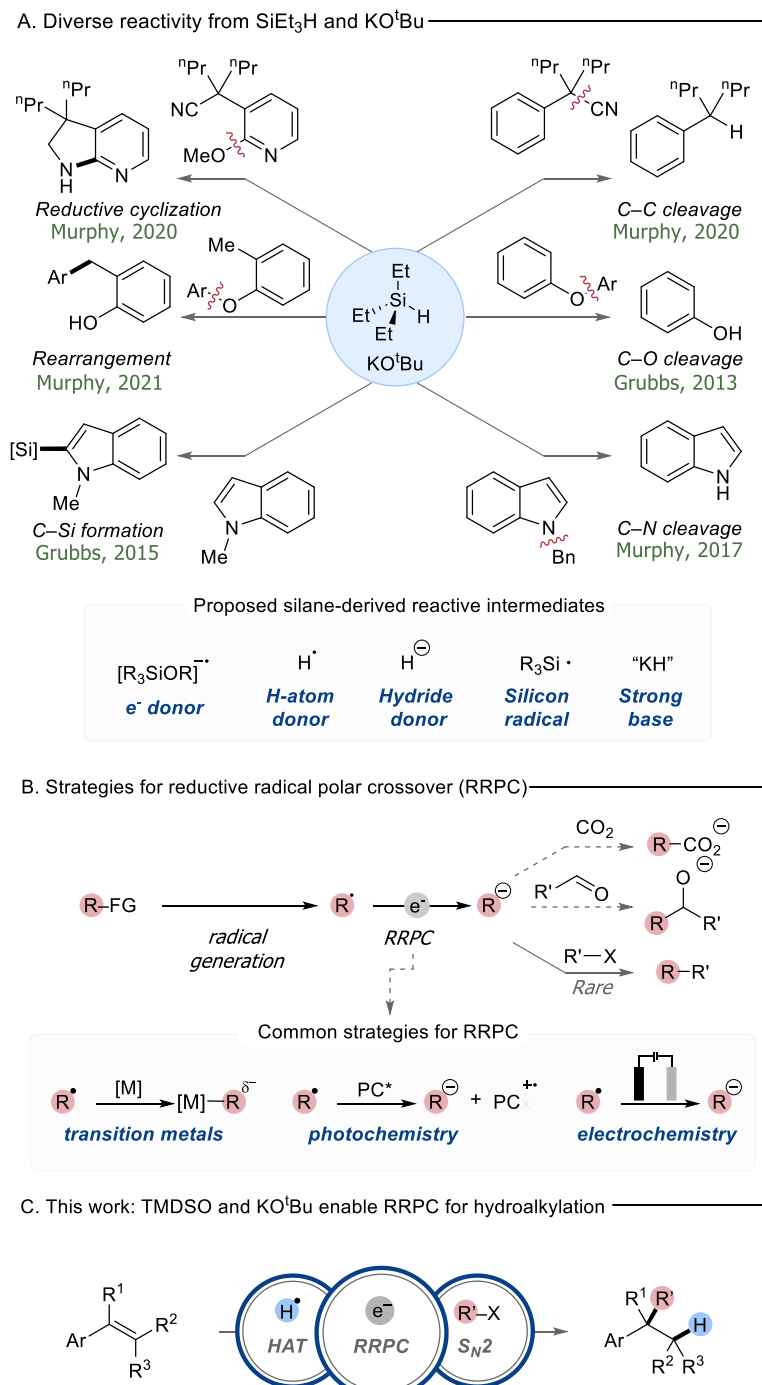
Our group contributed to the growing number of applications of hydrosilanes and alkoxides when we discovered that the Ar–CF₃ bond of 2-trifluoromethylpyridines can be reductively cleaved.⁷⁶ 1,1,3,3-Tetramethyldisiloxane (TMDSO) was found to be uniquely effective, contrasting the more common observation that triethylsilane (Et₃SiH) is needed in similar reductive defunctionalization reactions. The mechanism was thought to occur by a sequence of single-electron transfer (SET) and hydrogen-atom transfer (HAT) events to the pyridine π -system, formally delivering H[–] over two steps. Taking inspiration from Jeon’s seminal discovery in alkene hydrosilylation,⁷⁴ we hypothesized that simple alkenes such as styrene might be able to accept a hydrogen atom and electron, forming stabilized anions via reductive radical polar crossover (RRPC), which might be then harnessed for C–C bond formation.

RRPC is a powerful strategy that exploits some of the most useful aspects of both radical and anionic chemistry.^{77,78} Three strategies to carry out RRPC are particularly common – the use of photoredox catalysis, electrochemistry, or stoichiometric transition metals – all of which are capable of generating radicals and subsequently reducing them to anions or polarized C–M bonds

(Scheme 3.15B).^{62,79-86} Notably, these anions are most commonly used to attack electrophilic π -bonds such as ketones.^{87,88} Examples of alkylation via substitution reactions with alkyl halides are limited mainly to intramolecular examples, presenting a limitation in our ability to exploit these in-situ generated anions.^{89,90}

In an attempt to understand this gap, a recent mechanistic study by König and co-workers elaborated upon the rarity of such intermolecular bimolecular nucleophilic substitution (S_N2) reactions, who suggested that carbanions formed via RRPC are highly basic and prone to deprotonate the weakly acidic solvents (e.g., acetonitrile) often used in this chemistry, hindering development of challenging substitution reactions.⁹¹ In contrast, our previous work on using TMDSO/ KO^tBu as both an electron and hydrogen atom donating system was carried out in toluene, which we speculated could provide a distinct synthetic advantage to exploiting in situ formed carbanions. Furthermore, methods that feature this reagent pair are usually operationally simple and inexpensive, providing practical advantages over more complex approaches to both RRPC and to transition metal-catalyzed hydroalkylation.^{40,92,93} Herein, we disclose our findings that TMDSO and KO^tBu can enable the hydroalkylation of diverse styrenes and related vinylarenes (Scheme 3.16C). Simple conditions are used, demonstrating these reactions can be achieved without the need for photochemistry, electrochemistry, or transition metals. Mechanistic studies are consistent with an RRPC pathway, where styrene accepts both a radical and an electron to form a reactive carbanion that can undergo subsequent S_N2 -type alkylation.

Scheme 3.14: Triethylsilane mediated reactions, reductive radical polar crossover strategies, and Lewis base/silane-mediated RRPC for hydro-alkylation.

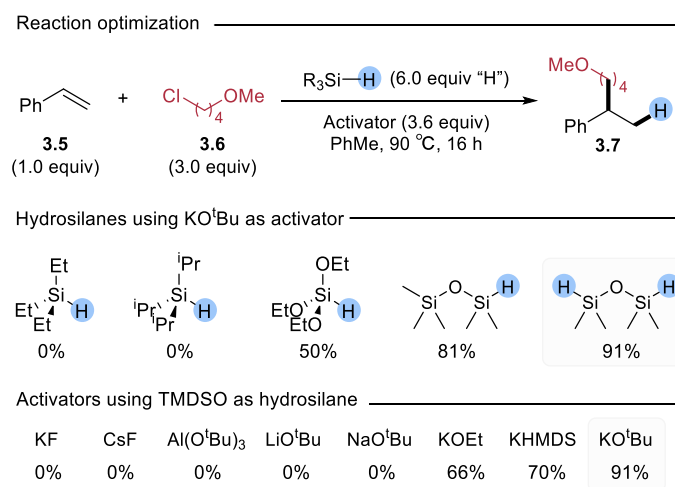


Section 3.6 | Results and discussion

Section 3.6.1 | Reaction optimization

Our study began with the reaction of styrene **3.5** with alkyl chloride **3.6** to prepare hydroalkylation product **3.7** (Scheme 3.15). Use of the Grubbs-Stoltz reagent was unsuccessful, despite its prevalence in the hydrosilane/alkoxide literature. Similarly, triisopropylsilane led to no product formation. Switching to triethoxysilane and pentamethyldisiloxane led to yields of 50% and 81%, respectively. The optimal reaction conditions identified TMDSO as the hydrosilane and KO^tBu as the basic activator. With toluene as a solvent, stirring at 90 °C for 16 h resulted in the formation of **3.7** in 91% yield. While some related hydrosilanes were also effective (see Table 3.2, section 3.7.1), TMDSO was ultimately selected due to the low cost (<\$1 USD/gram)⁹⁴, high yield, and broad availability. Various bases and fluoride salts were also screened as activators. KO^tBu was identified as the only high yielding choice, with potassium ethoxide (KOEt) and potassium hexamethyldisilazide (KHMDs) proving modestly effective.

Scheme 3.15: Reaction optimization for the hydroalkylation of styrene



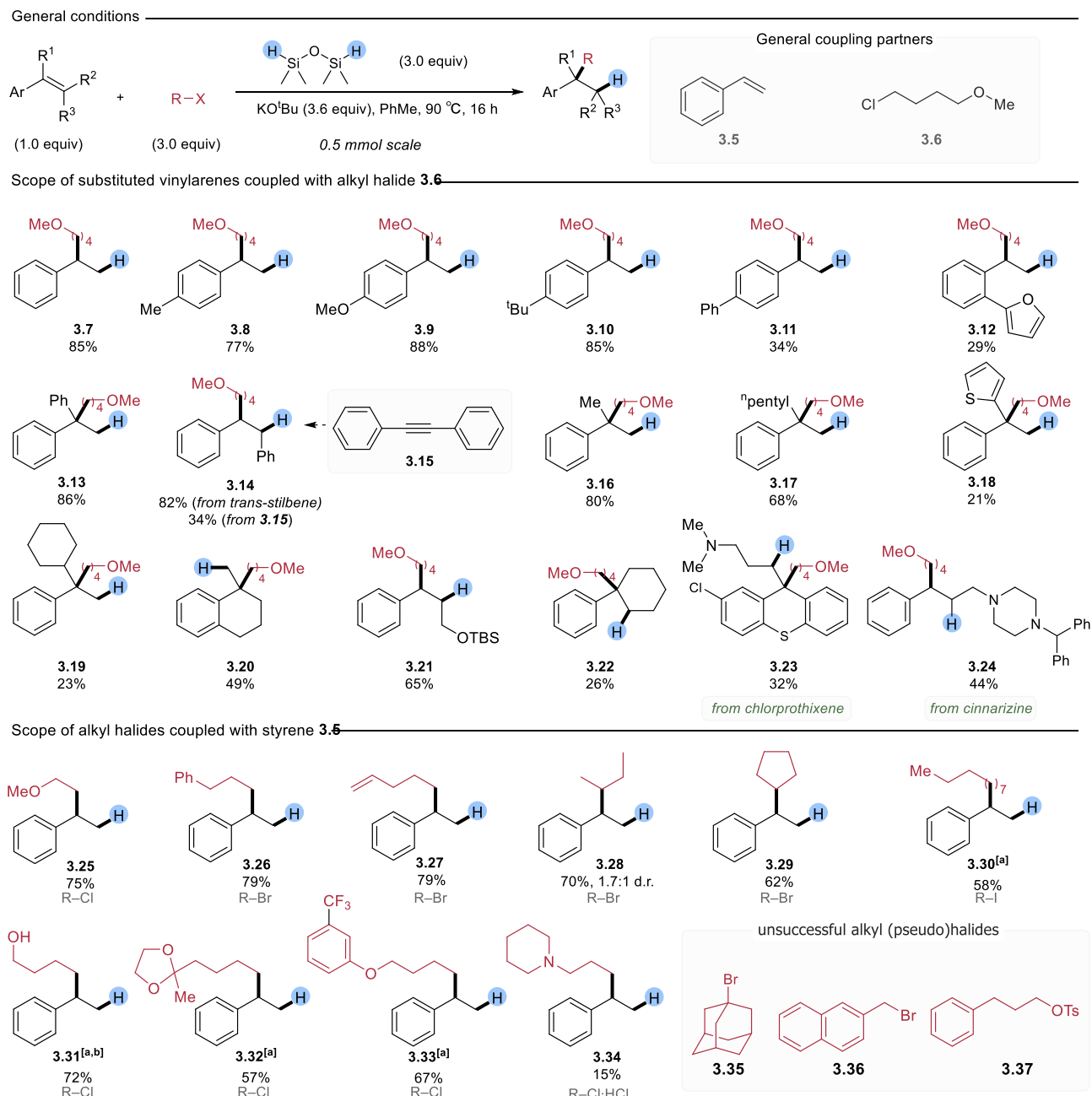
Section 3.6.2 | Reaction scope

Towards evaluating the reaction scope, the substitution pattern of the styrene aryl ring was first investigated using alkyl halide **3.6** as a common electrophile (**Scheme 3.16**). Reaction with the parent styrene **3.5** (0.5 mmol scale) provided **3.7** in 85% isolated yield. Hydroalkylation of 4-methylstyrene, 4-methoxystyrene, and 4-tert-butylstyrene led to similar yields of products **3.8-3.10**, respectively. When using 4-phenylstyrene, hydroalkylation product **3.11** was obtained in just 34% yield alongside a dimeric styrene-derived side product (See **Scheme 3.25**, section 3.7.4.2). An ortho-substituted furan-containing styrene could also be hydroalkylated to give **3.12** in 29% yield. Next, the viability of carrying out hydroalkylation on di- and tri- substituted olefins was explored. Using alkyl chloride **3.6**, 1,1-diphenylethylene was efficiently hydroalkylated to provide **3.13** in 86% yield. Trans-stilbene behaved similarly to give **3.14**. The same product could be obtained from diphenylacetylene **3.15** in 34% yield, indicating that alkynes are also viable reactants. α -Methyl styrene was hydroalkylated to give **3.16** in 80% yield, demonstrating access to benzylic quaternary carbon centers. Larger substituents were detrimental to the outcome, with α -pentyl substituted styrene giving **3.17** in 68% yield, α -thienylstyrene producing **3.18** in 21%, and α -cyclohexyl styrene giving **3.19** in 23% yield. Similarly, α -substituted bicyclic styrene led to a modest 49% yield of **3.20**. While free alcohols were not tolerated, TBS-protected cinnamyl alcohol provided hydroalkylated product **3.21** in 65% yield. Next, a cyclic trisubstituted olefin was tested which led to a 26% yield of **3.22**. We then turned our attention towards vinylarene-containing bioactive molecules as substrates. The antipsychotic drug chlorprothixene underwent hydroalkylation to afford **3.23** in 32% yield. Similarly, the antihistamine cinnarizine gave **3.24** in 44% yield, demonstrating applicability to these heterocycle-containing molecules.

Lastly, we sought to investigate the scope of the alkyl halides using styrene as a representative coupling partner. A range of primary and secondary alkyl chlorides, bromides, and an alkyl iodide

reacted comparably, giving **3.25-3.30** in 58-79% yield. Alkyl chlorides bearing a TBS-protected alcohol, acetal, and aryl ether were also tolerated, giving **3.31-3.33** in 57-72% yield. In contrast, hydroalkylation to form **3.34** from the corresponding amine-containing alkyl chloride (as its hydrochloride salt) proceeded with a low isolated yield of 15%. Tertiary alkyl halides such as bromoadamantane **3.35** and π -activated alkyl halides such as naphthyl bromide **3.36** gave no evidence of product formation, with reductive hydrodehalogenation being observed as the main side product. Alkyl tosylate **3.37** was also not tolerated and was instead found to be deprotected to reveal free alcohol. In general, highly electron-deficient styrenes were also ineffective substrates. A discussion of these and other unsuccessful examples is provided in section 3.7.3.

Scheme 3.16: Scope of styrenes, vinylarenes, and alkyl halides for hydroalkylation



Section 3.6.3 | Mechanistic investigation

The reactivity of hydrosilanes and alkoxide bases has been the subject of numerous studies, and the diversity of transformations that have been developed alongside pathways that have been proposed is exceptional.⁷⁴ Regarding the functionalization of alkenes, Jeon and coworkers

demonstrated the KO^tBu-catalyzed the hydrosilylation of styrenes using diethylsilane. They proposed the reaction is initiated by the transfer of an H atom from silicon to the alkene, revealing a silicon radical anion that recombines with the benzyl radical.⁷⁶ Murphy and coworkers have proposed related silicon radical anions to be potent single-electron donors.⁷¹ This precedent, alongside our own work on pyridine reductive defunctionalization,⁷⁶ suggests that styrene hydroalkylation might occur by sequence of HAT and SET steps. Nonetheless, the plethora of potential reactive intermediates that hydrosilanes and alkoxides can generate means many other pathways might be possible, and several related questions about how the reaction proceeds were unanswered. We thus set out to carry out a mechanistic study to understand the role and nature of the silane reducing agent, the nature of any styrene-derived reactive intermediates, and the pathway for the C–C bond-forming event.

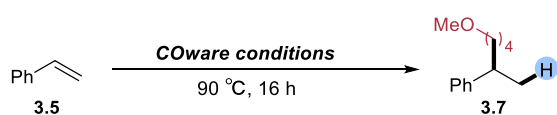
When TMDSO is added to a stirring mixture of KO^tBu and substrate, rapid gas formation occurs followed by an immediate color change. Since oligomeric hydrosilanes have been shown to decompose into volatile monomers by the action of Lewis bases,^{76,95} we speculated that this gas may be the active reducing agent in our hydroalkylation. We thus carried out our reaction in COWare –two-well glassware specifically designed for generating gases in one well and delivering them to the other where they may then enter solution and react (**Scheme 3.17A**). KO^tBu and TMDSO were added to Well A and styrene **3.5**, alkyl halide **3.6**, and additional KO^tBu were added to Well B, which contained no TMDSO. Well A rapidly formed gas when KO^tBu and TMDSO were combined, and shortly after, Well B changed color. After heating for 16 hours at 90 °C, the contents of Well B were worked-up and hydroalkylation product **3.7** was obtained in 59% yield. ¹H NMR analysis of the KO^tBu and TMDSO mixture shows the formation of SiMe₂H₂ (bp = -19.6 °C), which is likely the gas observed and the active reductant that transfers into Well B. Although

the possibility of TMDSO (bp = 70.5 °C) transferring cannot be ruled out, we suspect it is unlikely due to formation of silicon oligomers occurring exclusively in well A, as detected via GCMS (see section 3.7.4.4). Dimethylsilane (Me_2SiH_2) is gaseous, non-abundant, and challenging to handle, preventing us from directly confirming it is an effective reagent for hydroalkylation. We speculated that Et_2SiH_2 might be a suitable alternative as a stoichiometric reductant considering it is a commercially available liquid (bp = 56 °C). While TMDSO gives 91% yield of the hydroalkylated product **3.7** in the reaction of styrene **3.5** with alkyl chloride **3.6**, diethylsilane (Et_2SiH_2) is less effective, providing **3.7** in 68% yield (**Scheme 3.17B**). Notably, no gas evolution is observed in this reaction. In comparison, Et_3SiH gives no observable product formation, suggesting a subtle but impactful difference between dialkyl and trialkyl hydrosilanes.

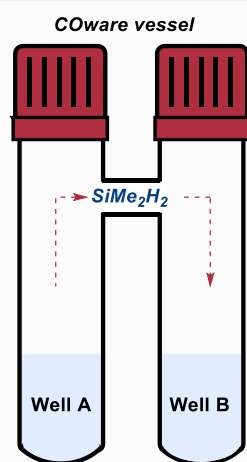
A common byproduct observed throughout our scope evaluation was the corresponding styrene hydrosilylation product. Given that benzylsilanes are known to act as carbon-centered nucleophiles in the presence of Lewis bases,⁹⁶ we were curious if these were side-products or intermediates on the reaction pathway. We thus prepared benzylsilane **3.40** and subjected it to a mixture of KO^tBu and alkyl chloride **3.8** (**Scheme 3.17C**). Hydroalkylation product **3.9** was not detected, suggesting that the direct reaction of the hypervalent silicate anion with alkyl halide is not operative. Interestingly, inclusion of TMDSO in the reaction led to a 42% yield of **3.9** alongside substantial recovery of the starting benzylsilane, indicating that there is a viable mechanism for these intermediates to undergo hydroalkylation, though it does not appear to be the dominant pathway.

Scheme 3.17: Investigating TMDSO and its role as the reducing agent

A. Investigating role of TMDSO and KO^tBu in COWare



Change to COWare conditions	% yield 3.7
None	59
20 mol% KO ^t Bu in well B	3
20 mol% KO ^t Bu in well A	84
Omit KO ^t Bu in well A or B	0



COWare conditions

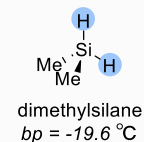
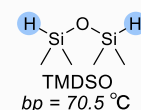
Well A

KO^tBu (3.6 equiv)
 TMDSO (3.0 equiv)
 PhMe

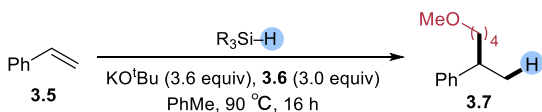
Well B

KO^tBu (3.6 equiv)
3.5 (1.0 equiv)
3.6 (3.0 equiv)
 PhMe

Boiling points

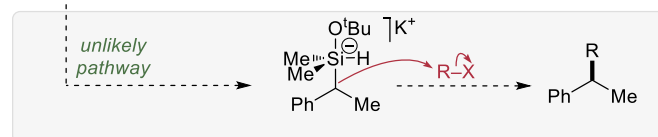
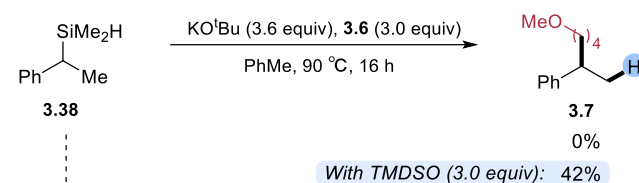


B. Reinvestigating the choice of silane



Silane	% yield 3.7
TMDSO (3.0 equiv)	91
Et ₂ SiH ₂ (3.0 equiv)	68
Et ₃ SiH (6.0 equiv)	0

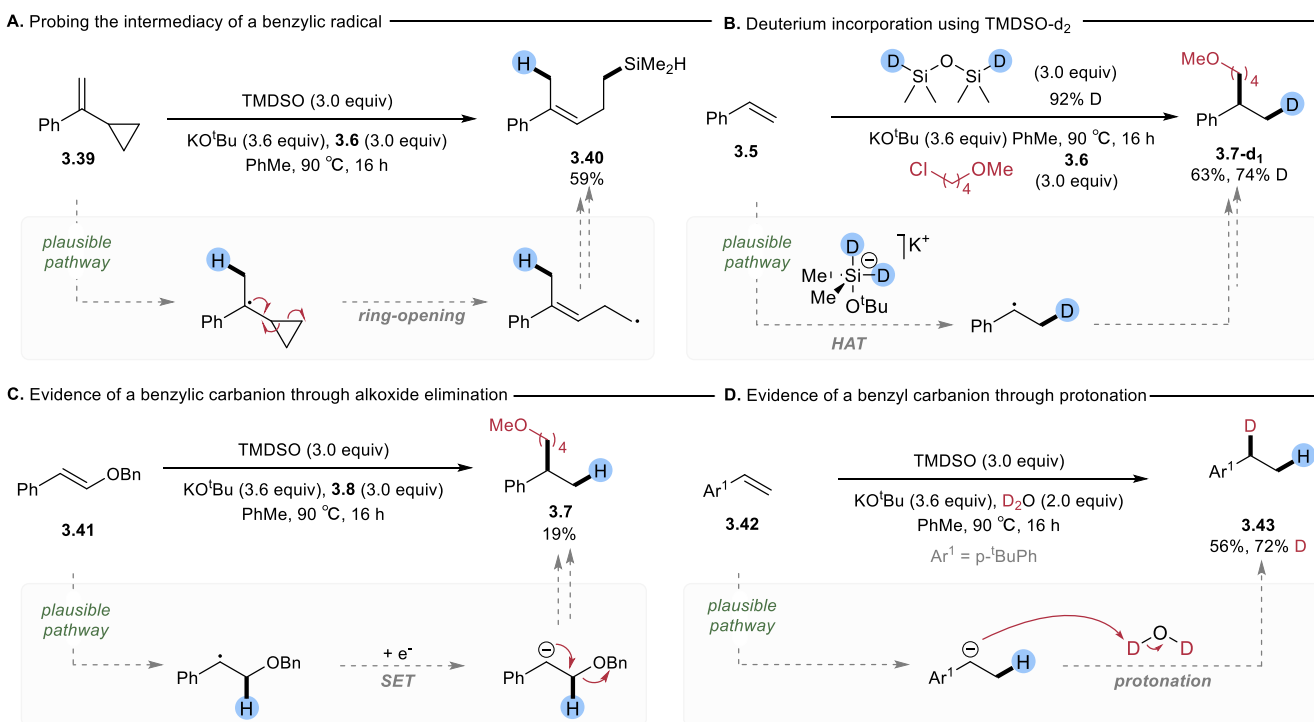
C. Investigating benzyl silane as plausible reactive intermediate



We next sought to probe if the reaction might proceed via a radical intermediate. When cyclopropane-substituted styrene **3.39** was subjected to the standard conditions, ring opened alkylsilane **3.40** was observed in 59% yield, suggesting a reactive styrene intermediate is formed that has radical character in the benzylic position (**Scheme 3.18A**). When TMDSO-*d*₂ (92% D) was used as a reagent in the reaction of styrene **3.5** and alkyl chloride **3.6**, hydroalkylated product **3.7-d**₁ was obtained in 63% yield with 74% deuteration observed exclusively at the homobenzylic position (**Scheme 3.18B**). When considered alongside key precedent from Jeon and co-workers,⁷⁴ these observations are consistent with a mechanism that involves transfer of a hydrogen atom from an activated silane complex to the styrene resulting in the formation of a benzylic radical,⁷⁴ and inconsistent with a mechanism wherein silane transfers a hydride anion to styrene, directly forming

a benzylic anion.⁹⁷ To probe if anionic intermediates might be present, vinyl ether-substituted styrene **3.41** was subjected to the standard reaction conditions (**Scheme 3.18C**). Deoxygenated product **3.7** was formed in 19% yield, which might arise from a benzylic carbanion intermediate that eliminates alkoxide, forming styrene in-situ, which may then go on to react further.⁶¹ Next, styrene **3.42** was subjected to the reaction conditions using 2 equivalents of D₂O in place of the alkyl electrophile. Styrene reduction product **3.43** was obtained in 56% yield with 72% deuteration exclusively at the benzylic position, consistent with the formation of a carbanion intermediate (**Scheme 3.18D**). Notably, running the reaction in d₈-toluene also resulted in substantial deuterium incorporation, suggesting solvent may also react as a proton source (see **Scheme 3.26B**, Section 3.7.4.3). Further experiments for investigating the reactivity at the homobenzylic position indicate that no radical or anionic character develops at this carbon, consistent with a benzyl radical and/or anion as a key reactive intermediate instead of a styrene radical anion (see section 3.7.5.2).

Scheme 3.18: Probing potential reactive intermediates

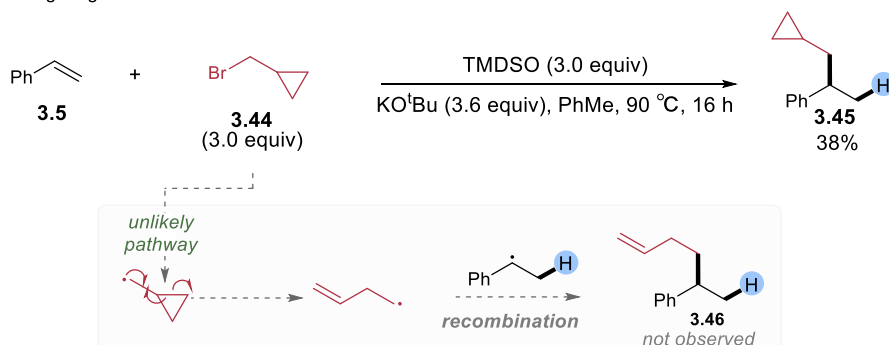


We next sought to probe the key C–C bond forming step. While we originally hypothesized that an S_N2 process may be operative, there is precedent for hydrosilanes and Lewis bases to form single-electron donors and silicon radicals that could potentially react with alkyl halides to make alkyl radicals via SET or halogen-atom transfer.^{49,71} To rule out this possibility under our reaction conditions and to probe the C–C bond forming step further, we used bromomethylcyclopropane **3.44** as an electrophile. When coupled with styrene, hydroalkylation proceeded smoothly to give **3.45** in 38% yield with no evidence of ring-opened product **3.46** that might be suggestive of an alkyl radical intermediate (**Scheme 3.19A**).

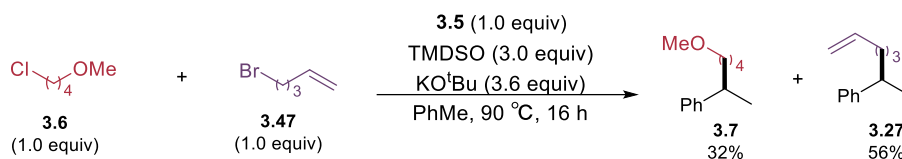
Lastly, competition experiments were run with various organohalides (**Scheme 3.19B**). When using both a primary alkyl chloride **3.6** and alkyl bromide **3.47**, the reaction shows modest preference for reaction with the alkyl bromide to give **3.27**. Similarly, competition between a primary (**3.47**) and secondary (**3.48**) alkyl bromide showed preferential reactivity with the primary substrate (**Scheme 3.19C**). Lastly, a primary (**3.47**) and a benzylic (**3.36**) alkyl bromide were used in a competition experiment (**Scheme 3.19D**). Here, only the product derived from the primary alkyl bromide formed, and the benzylic bromide substrate was found to degrade into methyl naphthalene, suggesting that this electrophile is too active and might react directly with KO^tBu/TMDSO. Overall, this data is most consistent with an S_N2 pathway for C–C bond formation.

Scheme 3.19: Differentiating between a radical-radical cross coupling and competition experiments to probe an S_N2 mechanism

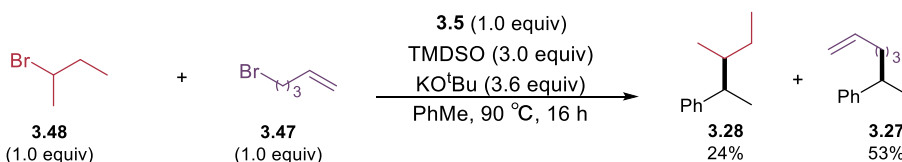
A. Investigating a radical-radical recombination mechanism



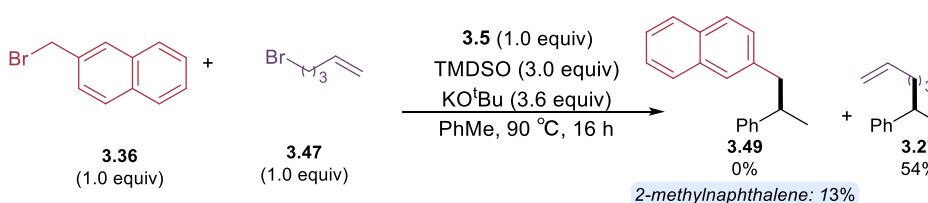
B. Alkyl chloride versus alkyl bromide



C. 1° alkyl bromide versus 2° alkyl bromide



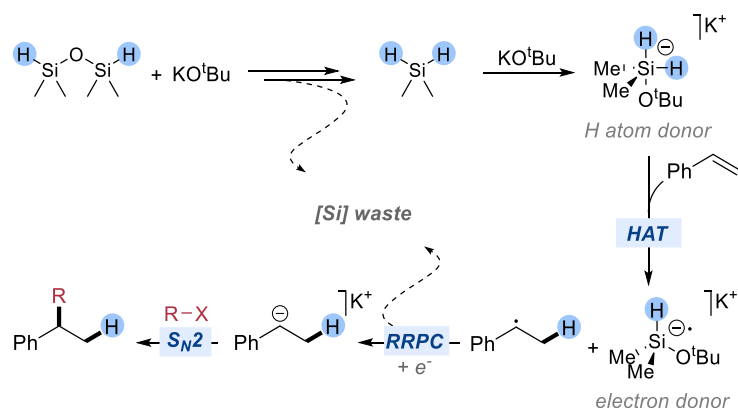
D. 1° alkyl bromide versus benzylic alkyl bromide



These experimental findings, in addition to mechanistic studies of related systems,^{71,74,75} allow a plausible mechanism to be proposed (**Scheme 3.20**). First, KO^tBu catalyzes the decomposition of TMSO into Me₂SiH₂ and various silicon oligomers.⁹⁵ The Me₂SiH₂ combines with KO^tBu to make a silicate anion that transfers a hydrogen atom to styrene, generating a benzylic radical alongside a silicon radical-anion. Notably, our reaction succeeds only when using potassium-bases and fails with LiO^tBu, and NaO^tBu, suggesting a cation- π interaction may be critical for this step.^{74,76} The styrene radical and silicon radical anion react further via radical polar cross-over,⁷¹

affording a benzyl potassium nucleophile. The additional hydride in the silicon by-product may be reactive via HAT with another molecule of styrene or may be an unreactive waste product. The benzylic carbanion undergoes an S_N2 reaction with the alkyl halide, furnishing the hydroalkylated product. While this pathway is consistent with experimental results, several unanswered questions remain. For example, the underlying difference between trialkyl and dialkylsilanes, the relevance of benzylsilanes as reactive intermediates, and the divergence of our hydroalkylation and Jeon's hydrosilylation⁷⁴ warrant further investigation.

Scheme 3.20: Proposed reaction mechanism



3.7 | Additional experimental results

The written body of work found in section 3.5 and 3.6 of chapter 3 was published as a research article with specific limitations on space, word, and page count as outlined by the publisher's requirements. As such, a large amount of relevant data and experiments that aided in formulating hypotheses surrounding this research in addition to understanding the strengths, weaknesses, and insight we gained has been left out. In this section additional experimental results outlining additional reaction optimization data (Section 3.7.1), scalability and safety of this reaction (Section 3.7.2), scope limitations (Section 3.7.3), common byproducts of the reaction (Section 3.7.4), and additional mechanistic experiments (Section 3.7.5) are discussed.

3.7.1 | Additional reaction optimization data

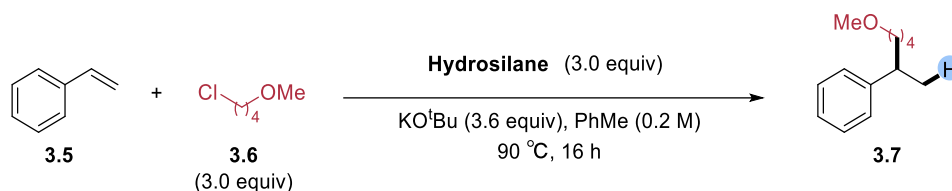
Various different metal salts were screened during the optimization of this reaction (**Table 3.1**). Similar to observations made in chapter 2 of this dissertation, sodium (**entry 7**), lithium (**entry 8**), aluminum (**entry 10**), and cesium salts (**entries 5 & 6**) failed to promote the hydroalkylation reaction. Potassium salts with Lewis basic counterions including KO^tBu (**entry 2**), KHMDS (**entry 4**), and KOEt (**entry 9**) led to much higher yields with KO^tBu proving the highest overall yield of **3.7**. Notably, the use of potassium hydroxide (KOH) (**entry 3**) led to a low yield of 7% which we attribute to the sample being wet. Finally, 18-crown-6 – a known chelator of potassium ions (K⁺) – was used alongside KO^tBu which ultimately shut down the reaction further demonstrating that K⁺ is a necessary reaction component (**entry 11**).

Table 3.1: Screening various Lewis basic metal salts

Entry	activator	% yield 3.7
1	no activator	0
2	KO ^t Bu (3.6 equiv)	91
3	KOH (3.6 equiv)	7
4	KHMDS (3.6 equiv)	70
5	Cs ₂ CO ₃ (3.6 equiv)	0
6	CsF (3.6 equiv)	0
7	NaO ^t Bu (3.6 equiv)	0
8	LiO ^t Bu (3.6 equiv)	0
9	KOEt (3.6 equiv)	66
10	Al(O ^t Bu) ₃ (1.2 equiv)	0

Various different hydrosilanes were screened during the optimization of this reaction (Table 3.2). Phenyl (entry 3), diphenyl (entry 5), and triphenylsilanes (entry 6) all led to high yields of **3.7**. Hydrosiloxanes (entries 10-12) and triethoxysilane (entry 7) also produced low to high yields of **3.7**. However, trialkylsilanes (entries 8 & 9) proved to be totally unreactive in the hydroalkylation reaction leading to the recovery of **3.5** and **3.6** with no detection of **3.7**. Finally, a phenyldialkylsilane was used (entry 4) which led to merely 6% of **3.7**.

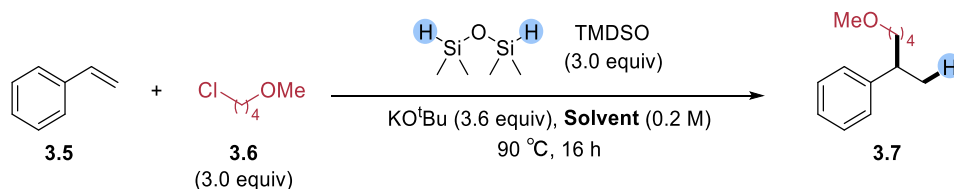
Table 3.2: Screening various hydrosilanes



Entry	hydrosilane	% yield 3.7
1	no hydrosilane	0
2	1,1,3,3-tetramethyldisiloxane (3.0 equiv)	91
3	phenylsilane (2.0 equiv)	79
4	phenyldimethylsilane	6
5	diphenylmethylsilane	81
6	triphenylsilane (6.0 equiv)	71
7	Triethoxysilane (6.0 equiv)	50
8	Triethylsilane (6.0 equiv)	0
9	triisopropylsilane (6.0 equiv)	0
10	PMHS (6.0 equiv)	28
11	pentamethyldisiloxane (6.0 equiv)	81
12	hexamethyltrisiloxane (3.0 equiv)	93

We screened different solvents during the optimization of this reaction (**Table 3.3**). The use of acetonitrile (**entry 3**) and dichloromethane (**entry 4**) resulted in no product formation; in fact they appeared to react violently with TMDSO and KO^tBu. Tetrahydrofuran (THF) led to a low yield of 32% (**entry 2**). Benzene (**entry 5**), 1,4-dioxane (**entry 6**), and benzotrifluoride (**entry 7**) were also screened as solvents and found to be suitable alternative to toluene (PhMe) providing yields ranging from 72-81%. This became an important observation later on in the project as 1,4-dioxane was used in place of PhMe to avoid a solvent-derived byproduct that complicated product isolation (**Scheme 3.26**).

Table 3.3: Screening various solvents in the hydroalkylation reaction

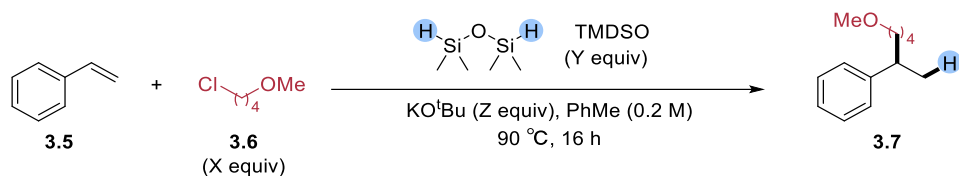


Entry	solvent	% yield 3.7
1	PhMe	91
2	THF	32
3	CH ₃ CN	0
4	CH ₂ Cl ₂	0
5	benzene	72
6	1,4-dioxane	74
7	PhCF ₃	81

Many different ratios of **3.8**:KO^tBu:TMDSO were screened to simultaneously learn which ratio was optimal while ruling out the possibility of catalytic TMDSO and KO^tBu (**Table 3.4**). This data served to highlight that TMDSO is not a catalyst, and the reaction yield depends

significantly on the ratio of **3.6**:KO^tBu:TMDSO. Overall, a ratio of 1: 1.2: 1 of **3.6**:KO^tBu:TMDSO was identified as being optimal.

Table 3.4: Screening optimal stoichiometry of **3.6**, TMDSO, and KO^tBu



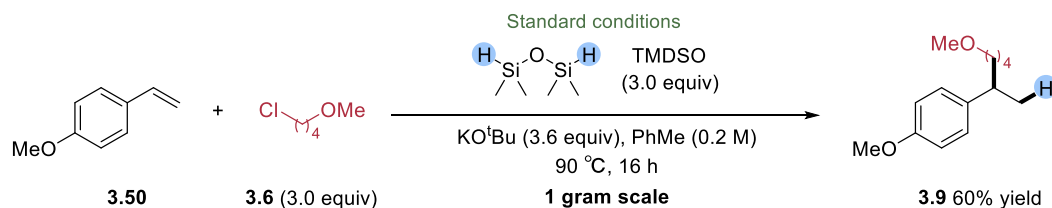
Entry	3.6	KO ^t Bu	TMDSO	% yield 3.7
1	3.0 equiv	3.6 equiv	3.0 equiv	91
2	2.0 equiv	2.0 equiv	2.0 equiv	83
3	2.0 equiv	2.0 equiv	0.5 equiv	18
4	2.0 equiv	2.0 equiv	1.0 equiv	61
5	1.0 equiv	2.0 equiv	0.5 equiv	16
6	1.0 equiv	2.0 equiv	2.0 equiv	76
7	2.0 equiv	1.0 equiv	2.0 equiv	52
8	2.0 equiv	2.0 equiv	1.0 equiv	33
9	1.0 equiv	1.0 equiv	1.0 equiv	67
10	1.2 equiv	2.0 equiv	2.0 equiv	67

3.7.2 | Reaction scale-up and safety considerations

The dissertation author attempted to scale the hydroalkylation of **3.50** to demonstrate the practicality of this method. The reaction was conducted on a 1-gram scale in a round bottom flask using TMDSO as the hydrosilane of choice (**Scheme 3.21**). This resulted in a 60% yield of **3.9**. When running the same experiment on a 0.5 mmol scale product **3.9** was isolated in 88% which would suggest the reaction requires modification to ensure a reproducible yield on larger scales. It should be noted that this reaction was performed in 1-dram vials on a 0.5 mmol scale thus one could argue the scale up should be performed in a pressurized sealed reactor. The author of this dissertation decided against this for several reasons. The first being the exact pressure of the reactor is unknown, and using the ideal gas-law to calculate an approximate pressure suggested it was unsafe and would therefore be unwise to perform. Furthermore, the safety data sheet (SDS) of SiMe_2H_2 states the gas is extremely flammable and potentially explosive.⁹⁸ Finally, the boiling point of SiMe_2H_2 is approximately $-20\text{ }^\circ\text{C}$ and the reaction takes place at $90\text{ }^\circ\text{C}$ which is significantly higher than its boiling point. Thus, the reaction was conducted in a round bottom flask with a nitrogen filled balloon as a failsafe. Several reasons could be attributed to the low yield of this transformation in a round bottom flask such as a change in headspace, the impact on the headspace partial pressure and the stirring as a function of the flask shape, and heating of the sample.

If one wishes to scale up the reaction the author of this dissertation would recommend switching to a less volatile silane that had been demonstrated to facilitate this transformation, such as Ph_2SiH_2 , and optimizing accordingly.

Scheme 3.21: Reaction scale-up (Left: dropwise addition of TMDSO, right: dropwise addition of **3.6**)



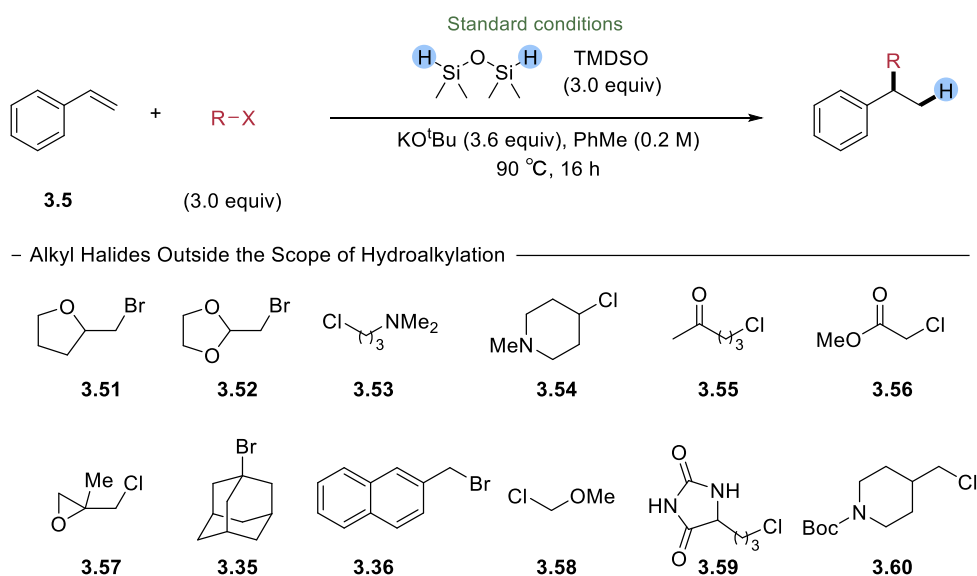
3.7.3 | Limitations of the scope

During the scope investigation many styrenes, vinylarenes, and alkyl halides were tested. Many of these examples failed to undergo the hydroalkylation reaction, and for various different reasons.

Alkyl halides that failed to undergo hydroalkylation are found below (**Scheme 3.22**). Alkyl halides bearing tetrahydrofuran and dioxolane rings (**3.51**, and **3.52**) adjacent to the carbon-halogen bond underwent a side reaction we attribute to reductive ring opening. Alkyl halides

bearing aliphatic tertiary amines **3.53** and **3.54** were out of scope. Substrates bearing hydride sensitive functional groups including ketone (**3.55**), ester (**3.56**), and epoxide (**3.57**) led to intractable mixtures of products which we attribute to hydride reduction. In the case of carbonyl containing species it is suspected that hydrosilylation occurs and the resulting silylethers are incorporated into the silicon oligomers. Activated electrophiles **3.35**, **3.36**, and **3.58** underwent hydrodehalogenation which is consistent with early work by Corriu.⁹⁹ Finally in some cases the reaction would not occur and the starting alkyl halide could be recovered **3.59** & **3.60**.

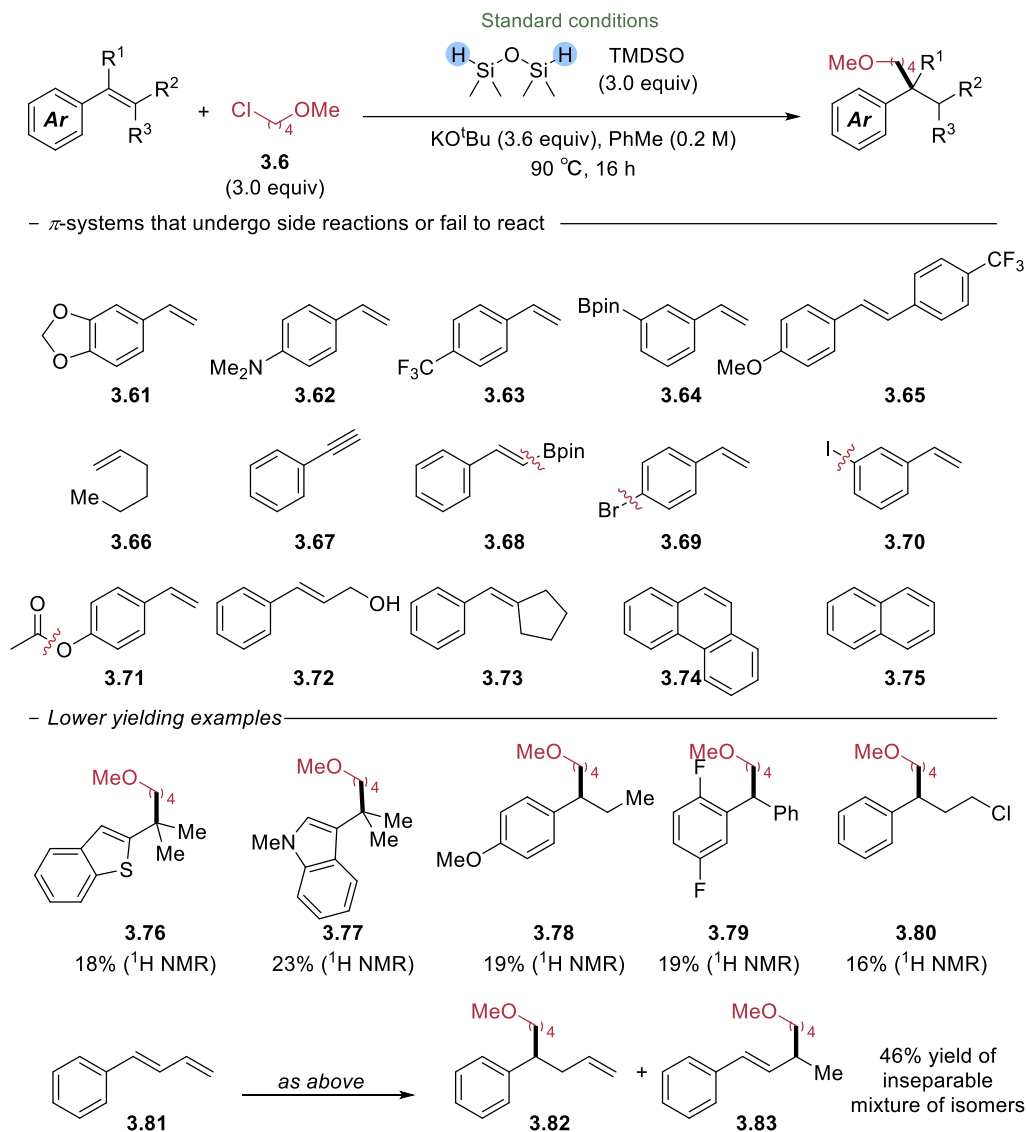
Scheme 3.22: Scope of failed alkyl halide coupling partners



Vinylarenes and related π -systems that either failed to undergo hydroalkylation *or* reacted in low yield can be found below (**Scheme 3.23**). Substrates **3.61-3.66** failed to undergo hydroalkylation, and instead led to their recovery. Phenylacetylene (**3.67**) decomposed under the conditions, it's possible the alkyne terminus having an acid dissociation constant (pKa) of approximately 26 could have been deprotonated leading to its decomposition – this however, is speculative. Substrates **3.68-3.71** underwent hydrodefunctionalization at their respective C–B, C–Br, C–I, and C–O bonds. Cinammyl alcohol led to an intractable mixture of products, and it is

speculated that it was incorporated into the silicon oligomers through reaction with KO^tBu. The hydroalkylation products of phenanthrene and naphthalene were only detected in trace quantities (<< 1%) and the substrates are essentially unreactive. Various species (**3.76-3.80**) reacted in low yields ranging from 16-23% based on calculated yields using ¹H NMR spectroscopy. Substrates **3.76** and **3.77** were too difficult to separate from unidentified impurities, while others (**3.78-3.80**) were simply low yielding and could potentially be improved through substrate specific optimization. The testing of **3.81** led to a 46% yield of regioisomers **3.82** and **3.83**.

Scheme 3.23: Scope of low yielding and failed π -systems



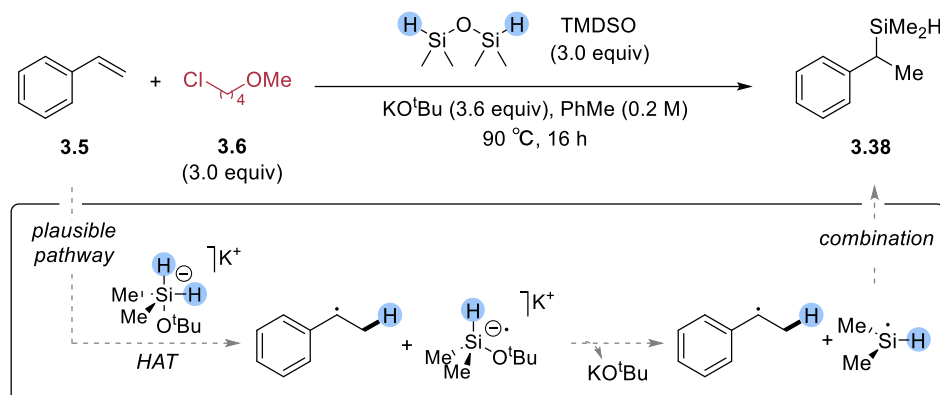
3.7.4 | Common byproducts and mass balance of the hydroalkylation reaction

Several common byproducts were routinely detected throughout the course of this study. Hydrosilylation was frequently observed as a competing byproduct, the formation of **3.84** - a styrene-derived dimer, alkylation of the solvent **3.85**, and the formation of silicon oligomers. The origin of these byproducts was a point of interest and were thus considered further.

3.7.4.1 | Hydrosilylation as a competing byproduct

Throughout the course of the study, benzylsilane was a commonly observed byproduct present in quantities ranging from ~ 0-10% depending on the styrene used in the reaction (**Scheme 3.24**). Hydrosilylated byproducts are consistent with the proposed mechanism. Hydrosilylation may occur in the same manner as observed by Jeon and co-workers,⁷⁴ wherein association of KO^tBu to in-situ generated dimethylsilane activates the Si–H bond such that hydrogen atom transfer to styrene **3.5** may occur generating the benzylic radical alongside a silicon radical anion. KO^tBu may then dissociate leading to a silicon radical which, due to its close proximity, will immediately combine with the benzyl radical producing the C–Si bond alongside regenerated KO^tBu.

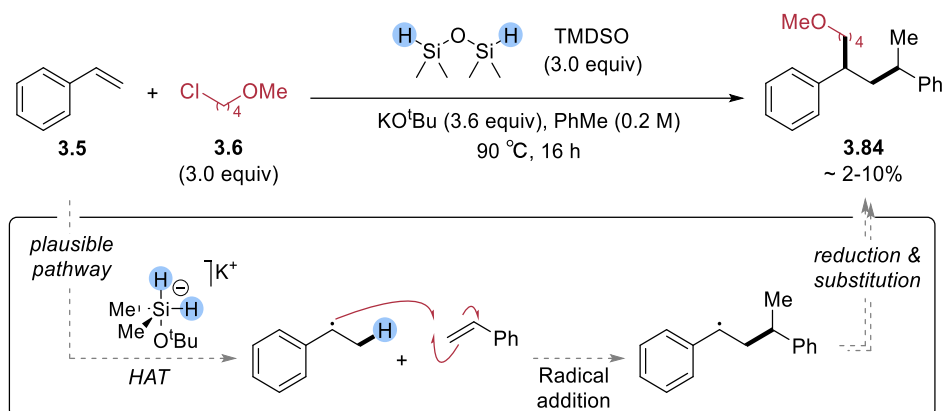
Scheme 3.24: Benzylsilane as a common byproduct and a plausible mechanism for its formation



3.7.4.2 | Formation of the styrene-derived dimer

A side product of the hydroalkylation reaction we referred to as a dimer (**3.84**) was observed in virtually every scope example (**Scheme 3.25**). Although the mechanism of its formation was not studied, it likely arises from radical or anionic addition of a benzylic radical – that formed from HAT to styrene – to another styrene molecule followed by subsequent RRPC and alkylation. The amount of the dimer varied based on the electronics of the aromatic ring, but never exceeded 10 % yield.

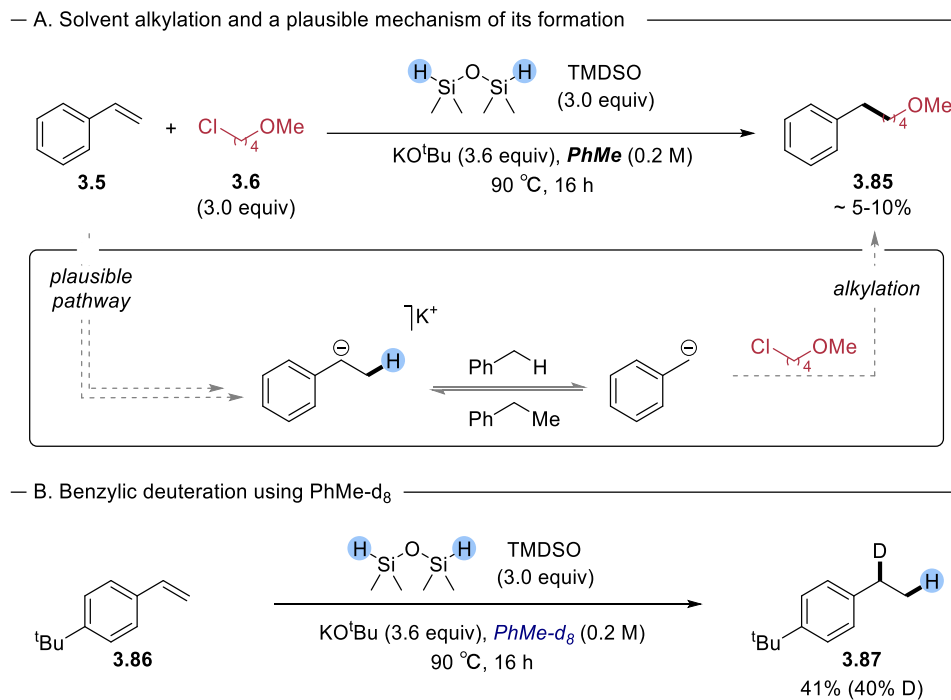
Scheme 3.25: Styrene-derived dimer as a common byproduct and a plausible mechanism for its formation



3.7.4.3 | The origin of solvent alkylation

As mentioned above in section 3.5.2 a commonly observed byproduct of the reaction was **3.85** – the formation of which was attributed to solvent alkylation. Given that C–C bond formation likely proceeds through an S_N2-reaction between an in-situ generated benzylic carbanion and an alkyl halide (**Scheme 3.26**) the solvent impurity was hypothesized to arise from a similar pathway. This would imply the formation of a benzylic carbanion from toluene which led the dissertation author to question its origin. One possibility was that the styrene-derived benzylic carbanion was deprotonating toluene which could go on to react in a subsequent alkylation step. To probe this hypothesis, *para*-tertbutyl styrene was tested using PhMe-d₈ as the solvent and in the absence of the alkyl electrophile. Product **3.87** was identified in 41% yield and 40% deuteration at the benzylic position. It was concluded this byproduct likely arises from deprotonation of PhMe-d₈.

Scheme 3.26: Solvent alkylation as a common byproduct and a plausible mechanism for its formation



3.7.4.4 | The origin of the silicon oligomers

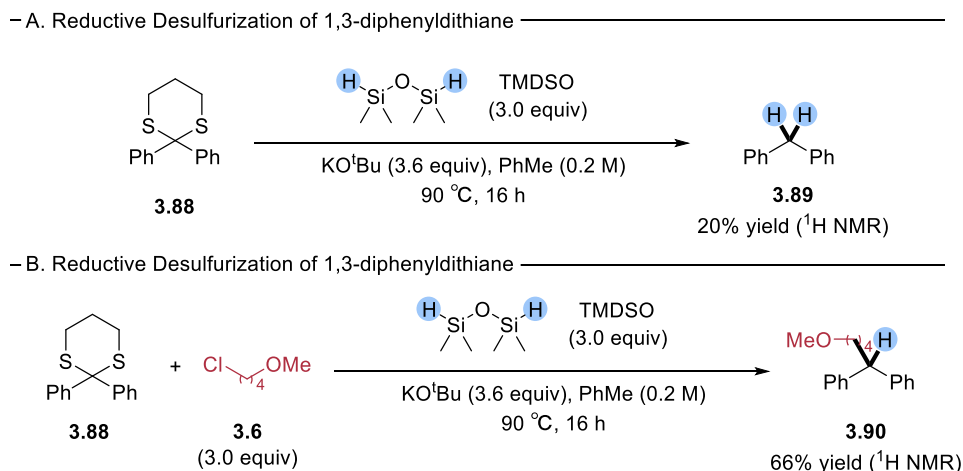
The silicon oligomers were consistently observed as a byproduct. Their formation stems from the KO^tBu -catalyzed decomposition of TMSO into dimethylsilane.⁹⁵ Although this did not receive dedicated study, a few observations were noted: First, silicon oligomers were formed in significant quantities regardless of the loading of KO^tBu . As a result of this, the oligomers often complicated separation as they would co-elute with most samples during column chromatography. In addition to the significant quantities of oligomers, there appeared to be a large variety in the species of oligomer which spanned an undefined degree of polymerization. This was crudely approximated by the GCMS data for each sample, a representative chromatogram is depicted in the experimental section of chapter 3 (see **section 3.11**).

3.7.5 | Additional mechanistic data

3.7.5.1 | A substrate probe for single-electron transfer

A key reductive radical polar crossover step is thought to be responsible for transforming a benzylic radical into a benzylic carbanion via SET. The author of this dissertation wanted to provide evidence for single-electron transfer taking place and looked to utilize a substrate prone to single-electron reduction as a mechanistic probe. 1,3-diphenyldithianes are known to undergo single-electron reduction to the corresponding diphenylmethane when exposed to organic super-electron donors or visible light absorbing potassium dimsyl salts.^{100,101} Testing 1,3-diphenyldithiane (**3.88**) resulted in its reduction to diphenylmethane (**3.89**) in 20% yield (**Scheme 3.27A**). This could indicate a SET pathway is operative but is insufficient to say with certainty that SET is taking place. Interestingly conducting the same experiment with inclusion of the alkyl electrophile **3.6** resulted in the reductive alkylation of 1,3-diphenyldithiane affording **3.90** in 66% yield (**Scheme 3.27B**). Notably, KO^tBu used alone did not facilitate either of these transformations.

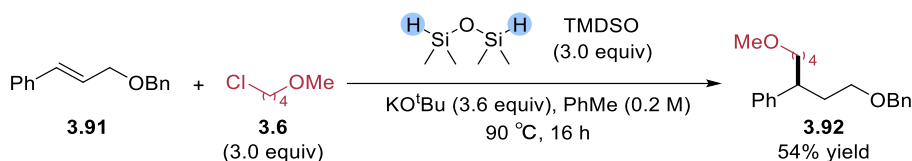
Scheme 3.27: Reductive desulfurization and alkylation of 1,3-diphenyldithiane



3.7.5.2 | Probing for reactivity at the homobenzylic position

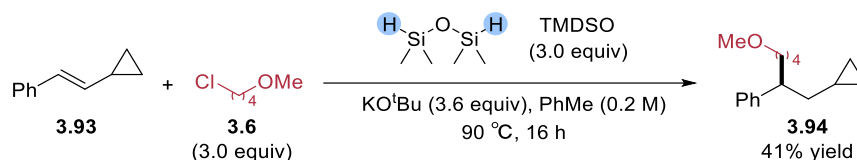
In the initial hypothesis outlined in Section 3.1 it was speculated that *trans*-stilbene could be transformed into a radical anion. The first indication that this was incorrect came from the regioselective outcome of the reaction. It was noted that C–C bond formation only occurred at the benzylic position rather than the homobenzylic position. Since radical anions of olefins are nucleophilic at the homobenzylic position it was realized this was an unlikely reactive intermediate. In order to be thorough, further experiments were conducted to rule out a radical anion as a potential reactive intermediate. Substrate **3.91** was synthesized to act as a probe for negative charge accumulation at the homobenzylic position. If this does occur, C–O bond cleavage should be observed and would provide evidence for an olefin-derived radical anion. This however was not observed, and instead the hydroalkylated product (**3.92**) was obtained in 54% yield which aligned with the observed product regioselectivity of the reaction scope (**Scheme 3.28**).

Scheme 3.28: Probing for homobenzylic carbanion character



The formation of a homobenzylic radical was then brought into question. To do this, β -cyclopropyl styrene **3.93** was synthesized and tested. Hydroalkylated product **3.94** was observed in 41% yield, with the remainder of mass balance consisting of unreacted **3.93** and some hydrosilylated product (**Scheme 3.29**). No ring opening was observed, and thus it was concluded there is likely no radical character at the homobenzylic position. This is likely a result of the benzylic position being more stabilized during hydrogen atom transfer versus the homobenzylic position, which also serves to explain the regioselective outcome of the reaction.

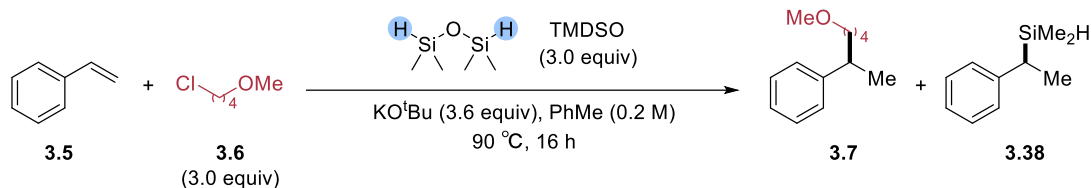
Scheme 3.29: Probing for homobenzylic radical character



3.7.5.3 | Why does hydroalkylation outcompete hydrosilylation?

A perplexing question faced throughout this study was how these reaction conditions differed when compared to work by Jeon and coworkers.⁷⁴ In their work, KO^tBu catalyzes the hydrosilylation of styrenes using Et₂SiH₂ as the silylating agent of choice, though notably it worked with TMSO. This question was approached by considering the differences between the reaction conditions for the hydroalkylation reaction and Jeon's conditions for hydrosilylation and by manipulating one variable at a time with the hopes of identifying *where* our reaction diverges from that reported by Jeon (**Table 3.5**). If no parameters are changed, 0% hydrosilylation is observed under our conditions (**entry 1**). Note that hydrosilylation does occur when using other styrenes in approximately 5%. Removal of solvent led to no hydrosilylation and 35 % hydroalkylation, indicating concentration does not play a role (**entry 2**). Removal of the alkyl halide or the alkyl halide and the solvent similarly produced no hydrosilylation (**entries 3 & 4**). Using 20 mol% of KO^tBu resulted in 13% hydroalkylation and 5% hydrosilylation (**entry 4**). Finally, using 20 mol% of KO^tBu and removal of the alkyl halide led to a 10% yield of the hydrosilylated product (**entry 6**). The only parameter that appeared to impact the amount of hydrosilylation that occurred was KO^tBu. We concluded that the amount of KO^tBu present in the reaction dictates how much hydrosilylation takes place despite not being able to reproduce yields obtained in Jeon's hydrosilylation work.

Table 3.5: Parameters influencing hydroalkylation selectivity

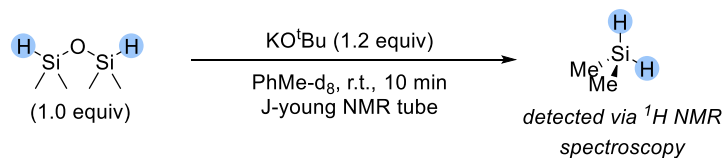


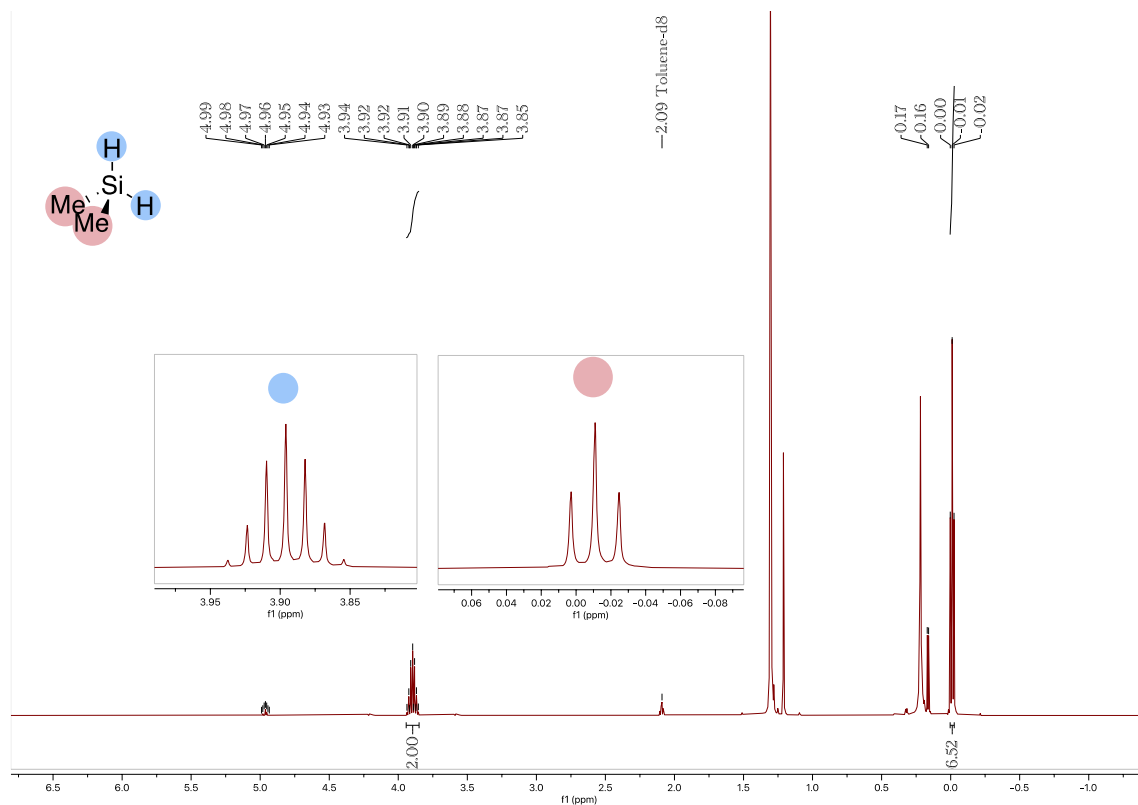
Entry	Change to above conditions	% Yield 3.7	% Yield 3.38
1	none	91	0
2	remove solvent	35	0
3	remove alkyl halide	0	0
4	remove solvent, remove alkyl halide	0	0
5	KO ^t Bu (20 mol%)	13	5
6	KO ^t Bu (20 mol%) and remove alkyl halide	0	10

3.7.5.4 | Identifying dimethylsilane via ¹H NMR spectroscopy

To further confirm the formation of SiMe₂H₂ in the reaction TMSO and KO^tBu were mixed in a J. Young tube and submitted for analysis by ¹H NMR spectroscopy (**Figure 3.1**). While SiMe₂H₂ was successfully identified. Notably, however, no signs of pentavalent hydrosilanes were detected suggesting its formation to be disfavored at room temperature.

Figure 3.1: ¹H NMR of dimethylsilane





3.8 | Conclusions

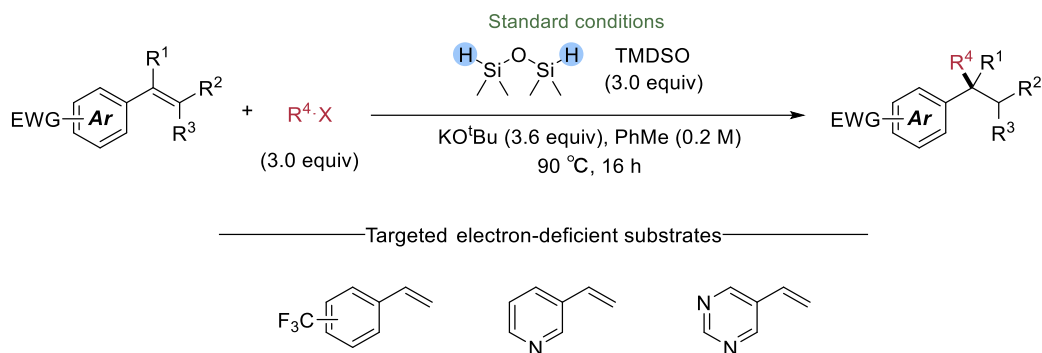
In conclusion, we have developed a regioselective vinylarene hydroalkylation reaction using TMDSO and KO^tBu as readily available reagents. Mechanistic studies are consistent with the reaction proceeding by both a benzyl radical and benzyl anion intermediate, which suggests the TMDSO/KO^tBu reagent pair is capable of donating both a hydrogen atom and an electron, ultimately enabling a powerful radical polar crossover reaction that proceeds without using photochemistry, electrochemistry, or transition metals. This reaction represents a rare example of RRPC being used for alkylation reactions via substitution chemistry and is the first report of a hydrosilane-alkoxide base-mediated intermolecular C(sp³)–C(sp³) bond formation. Further studies are currently underway to capitalize on this unique reducing system for the discovery, design, and development of novel transformations.

3.9 | Future directions of the work

3.9.1 | Direct extension of vinylarene hydroalkylation

Many future directions stemming from the research conducted in chapter 3 can be envisioned. Chapter 3 features a thoroughly investigated mechanism which strongly supports the proposed intermediate species such as a benzylic radical and carbanion. While the author of this dissertation is confident in assigning identities to the proposed reactive intermediates, many unanswered questions remain and could benefit this work through further study. For instance, electron rich olefins undergo hydroalkylation in modest to high yields, while many electron-withdrawing vinylarenes were either unreactive towards the transformation or underwent undesired side reactions (**Scheme 3.23**). Further studies could serve to identify the reason behind this electronic preference and ideally lead to a solution to extend this method to the hydroalkylation of electron deficient vinylarenes (**Scheme 3.30**).

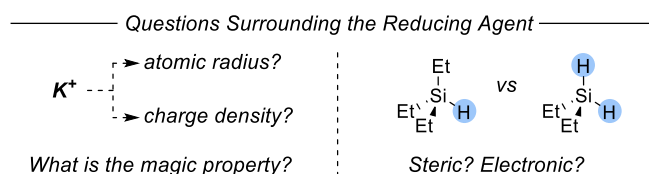
Scheme 3.30: Extending the scope of hydroalkylation to electron-deficient vinylarenes



While some effort was taken to understand the active reducing agent of this transformation, the role of potassium remained unknown. A related set of conditions published by Jeon and coworkers hints at potassium cations participating in π -cation interactions with the π -bonds of styrene. While potassium cations may be playing a similar role under our conditions, more research needs to be conducted in order to confidently state its role. Not only would this benefit this body

of work, but potentially many others who have noted the same curious observation that potassium is essential in these reactions. On the other hand, it was also questioned why trialkylsilanes do not facilitate the hydroalkylation reaction. The fact that dialkylsilanes are perfectly viable in this transformation, while trialkylsilanes completely shut down the reaction hints at a significant difference between their reactivity. It could be a steric factor, or alternatively the second hydrogen atom bound to silicon may play an unknown role in this transformation. Either way, this would be an exciting, and likely insightful, topic to explore (**Scheme 3.31**).

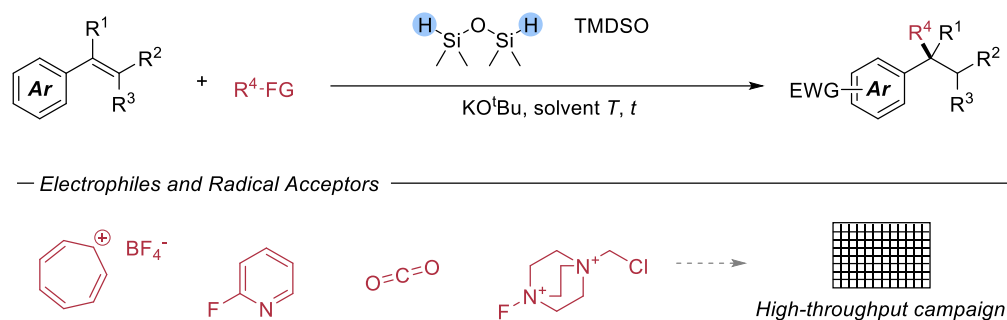
Scheme 3.31: Unanswered questions surrounding the reducing agent



3.9.2 | The development of alternative hydrofunctionalization reactions

Hydroalkylation reactions represent one class of reaction within the broader set of hydrofunctionalization reactions. A special feature of this transformation is the ability to access both a benzylic radical and a benzylic carbanion from a vinylarene. This opens the door to engaging radical acceptors in reactivity with a benzylic radical and electrophiles in a reaction with a benzylic carbanion (**Scheme 3.32**). Various different electrophiles – such as tropylium tetrafluoroborate, 2-fluoropyridines, carbon dioxide and selectfluorTM – could be envisioned in engaging in hydrofunctionalization reactions with vinylarenes. An interesting way to explore this chemistry would be through the high-throughput experimentation guided discovery and optimization. This would extend the breadth of this systems hydrofunctionalization chemistry, and it could potentially be streamlined using high-throughput experimentation (HTE).

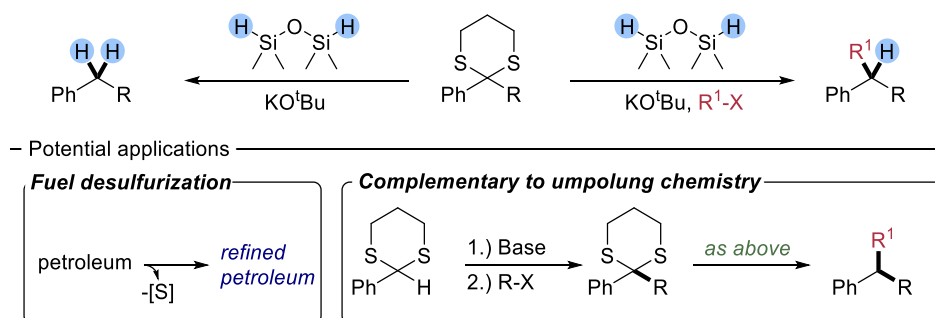
Scheme 3.32: Exploring other electrophiles in hydrofunctionalization reactions



3.9.3 | Other directions conceived during the study of the hydroalkylation reaction

Another promising direction builds upon the hydrodesulfurization and reductive alkylation of 1,3-diphenyldithiane – an observation made during the mechanistic investigation (**Scheme 3.27**). Desulfurization is an ongoing area of research housing clear applications in the petroleum industry.¹⁰² Furthermore, dithianes are often used as protecting groups of carbonyls and are engaged in umpolung reactivity such as in the Corey-Seebach reaction. In essence, the hydrodesulfurization and reductive alkylation of aryl dithianes could be a synthetically useful transformation (**Scheme 3.33**). Extension of this to the reductive alkylation of dioxolanes and related species could be envisioned as well. Not only are these reactions attractive from an organic synthesis standpoint, but one stands to gain a deeper glimpse into the inner workings of TMDSO and KO^tBu through a mechanistic investigation.

Scheme 3.33: Hydrodesulfurization and reductive alkylation of 1,3-aryldithianes



3.10 | Experimental

3.10.1 | General experimental details

Unless stated otherwise, reactions were set up outside the glovebox under an atmosphere of N₂ using oven dried glassware. Column chromatography was performed manually and in some cases via Combi-flash Rf automated chromatography both using Silicycle F60 40-63 μ m silica gel. Thin-layer chromatography was performed using aluminum-backed EMD Millipore Silica Gel 60 F₂₅₄ pre-coated plates. A UV lamp was used to visualize TLC plates.

3.10.2 | Instrumentation

GCMS data was obtained using an Agilent Technologies 7890B GC with a 30 m x 0.25 mm HP-5 column. Accurate mass data (EI) was obtained from an Agilent 5977A GC/MSD using MassWorks 4.0 from CERNO Bioscience.¹⁰³ HRMS-EI data was obtained using a Kratos concept magnetic sector electron impact mass spectrometer. ¹H, ¹³C, and ¹⁹F NMRs were obtained using a Bruker Avance II 500 MHz spectrometer, or a Bruker Avance II 400 MHz spectrometer. ¹H NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. ¹H NMR spectra were calibrated using CDCl₃ (7.26 ppm), ¹³C NMR spectra were calibrated using CDCl₃ (77.00 ppm). Reported NMR data is as follows: chemical shift (δ ppm), multiplicity (where s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants in Hz (where applicable), and relative proton integration. Melting points were measured using a Fisher-Johns melting point apparatus, with crystalline substances placed between two glass slides and observed through a magnification lens.

3.10.3 | Materials

Organic solvents were degassed using nitrogen and were then filtered through a Puresolv solvent purification system (SPS) to remove water. Unless otherwise noted, starting materials were purchased from Combi-blocks and used as received. Potassium tert-butoxide (KO^tBu) (trace metal

grade 99.8 %) was purchased from Oakwood chemicals. 1,1,3,3-Tetramethyldisiloxane (TMDSO), triethylsilane, triethylsilane, triisopropylsilane, potassium fluoride, cesium fluoride, and aluminum tert-butoxide were purchased from Sigma Aldrich. Details regarding the synthesis of starting materials, nuclear magnetic resonance spectra of starting materials, and additional experiments can be located in the supporting information available for free through the publication website (<https://doi.org/10.1002/anie.202421077>). Compound **3.88** was synthesized according to a literature procedure.¹⁰⁴

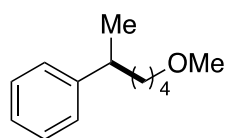
3.10.4 | Experimental procedures and characterization data

Reaction Optimization: To an oven dried 8 mL screw cap vial equipped with a stir bar was added the corresponding base/additive. The vial was then sealed with a plastic screw cap and pierceable Teflon/silicone septum. The reaction vessel was purged using a balloon filled with N₂ for 3-5 minutes. Solvent was taken directly from a solvent purification system and added through the septum using a syringe. Styrene **1a** (0.2 mmol) was then added, followed by the corresponding hydrosilane species and then alkyl halide **2a**. The N₂ balloon was then removed and the reaction vessel was placed in an oil bath that had been preheated to the desired temperature and allowed to stir for the indicated time. Once complete, the reaction mixture was removed from the oil bath, diluted with EtOAc while hot, cooled to room temperature, and then 1,3,5-trimethoxy benzene was weighed and added as a solid internal standard. The solution was then filtered through silica with EtOAc using a 15 mL glass fritted funnel and subsequently concentrated using a rotary evaporator. The crude residue was then dissolved in CDCl₃ and analyzed via ¹H NMR. The % yield of the product was determined by integrating the peak at 2.68 ppm, which corresponds to the benzylic proton in **3** relative to the peak at 6.08 ppm on 1,3,5-trimethoxybenzene.

General Procedure: The Hydroalkylation of Vinylarenes. To an oven dried 4 mL screw cap vial equipped with a stir bar was added the corresponding base/additive. The vial was then sealed with a plastic screw cap and pierceable Teflon/silicone septum. The reaction vessel was purged using a balloon filled with N₂ for 3-5 minutes. PhMe (1.25 mL, 0.4 M) was taken directly from a solvent purification system and added through the septum using a syringe. The corresponding olefin (0.5 mmol) was then added, followed by TMDSO (1.5 mmol) and the alkyl halide coupling partner (1.5 mmol). The N₂ balloon was then removed from the septum and the reaction vessel was placed in an oil bath that had been preheated to 90 °C and allowed to stir for 16 hours. Once complete, the reaction mixture was removed from the oil bath, diluted with EtOAc, and cooled to room temperature. The solution was then filtered through silica with EtOAc using a 15 mL glass fritted funnel and subsequently concentrated using a rotary evaporator. The crude residue was then purified using flash column chromatography.

Optionally, to facilitate purification, prior to chromatography the crude mixture was sometimes transferred to an 8 mL reaction tube equipped with a stir bar. TBAF (1.0 M solution in THF, 0.7 mL) was then added to the crude residue, which was then heated to 70 °C for 2 hours to breakdown silicon oligomers. After 2 hours, the solution was cooled to room temperature and filtered through silica with EtOAc using a 15 mL glass fritted funnel and concentrated using a rotary evaporator.

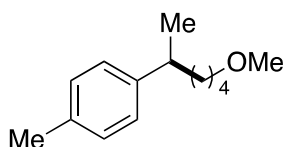
Alternatively, HCl (1.0 M solution in H₂O, 1.0 mL) can be used in place of TBAF.



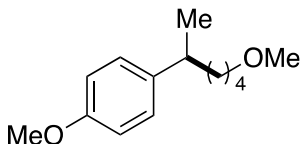
1-Methoxy-5-methyl-5-butylbenzene (3.7): Product **3.7** was prepared from 1-chloro-4-methoxybutane and styrene according to the General Procedure.

The crude material was purified via automated column chromatography using a gradient of 0- >10% of EtOAc in hexanes to afford **3.7** as a colorless oil (81.9 mg, 85%). ¹H NMR (400 MHz, CDCl₃): δ_H 7.32-7.27 (m, 2H), 7.20-7.16 (m, 3H), 3.32 (t, *J* = 6.7 Hz, 2H), 3.31 (s, 3H), 2.68 (sext,

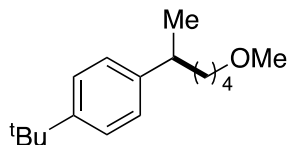
$J = 7.0$ Hz, 1H), 1.63-1.51 (m, 4H), 1.37-1.13 (m, 2H), 1.24 (d, $J = 6.9$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 147.9, 128.4, 127.1, 125.9, 73.0, 58.7, 40.1, 38.4, 29.9, 24.4, 22.4 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{13}\text{H}_{20}\text{O}$: 192.1509; found: 192.1546. Spectral accuracy: 98.3%



1-Methoxy-5-methyl(4'-methyl)-5-butylbenzene (3.8): Product **3.8** was prepared from 1-chloro-4-methoxybutane and 4-methylstyrene according to the General Procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **3.8** as a colorless oil (79.4 mg, 77%). ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.12-7.06 (m, 4H), 3.32 (t, $J = 6.5$ Hz, 2H), 3.30 (s, 3H), 2.65 (sext, $J = 6.5$ Hz, 1H), 2.32 (s, 3H), 1.60-1.50 (m, 4H), 1.36-1.15 (m, 2H), 1.22 (d, $J = 7.0$ Hz, 3H) ppm. ; ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 144.8, 135.3, 129.1, 127.0, 73.0, 58.7, 39.6, 38.5, 29.9, 24.5, 22.6, 21.1 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1665; found: 206.1671. Spectral accuracy: 95.0%



1-Methoxy-5-methyl-(4'-methoxy)-5-butylbenzene (3.9): Product **3.9** was prepared from 1-chloro-4-methoxybutane and 4-methoxystyrene according to the General Procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **3.9** as a colorless oil (94.5 mg, 85%). ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.12-7.08 (m, 2H), 6.86-6.82 (m, 2H), 3.79 (s, 3H), 3.32 (t, $J = 6.9$ Hz, 2H), 3.30 (s, 3H), 2.64 (sext, $J = 7.1$ Hz, 1H), 1.59-1.50 (m, 4H), 1.35-1.16 (m, 2H), 1.21 (d, $J = 6.9$ Hz, 3H) ppm.; ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 157.8, 139.9, 127.9, 113.8, 73.0, 58.6, 55.3, 39.2, 38.6, 29.9, 24.4, 22.6 ppm. **HRMS (EI-Magn. Sector) m/z :** Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2$: 222.1625; found: 222.1630.



1-Methoxy-5-methyl-(4'-tertbutyl)-5-butylbenzene (3.10): Product

3.10 was prepared from 1-chloro-4-methoxybutane and 4-tertbutylstyrene

according to the General Procedure. The crude material was purified via

automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford

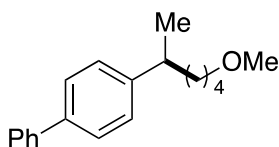
3.10 as a colorless oil (109.3 mg, 88%). ¹H NMR (400 MHz, CDCl₃): δ_H 7.30 (d, *J* = 8.3 Hz, 2H),

7.11 (d, *J* = 8.2 Hz, 2H), 3.33 (t, *J* = 6.7 Hz, 2H), 3.30 (s, 3H), 2.66 (sext, *J* = 7.1 Hz, 1H), 1.63-

1.50 (m, 4H), 1.31 (s, 9H), 1.22 (d, *J* = 6.9 Hz, 3H) ppm ; ¹³C NMR (100 MHz, CDCl₃): δ_C 148.6,

144.8, 126.7, 125.3, 73.0, 58.7, 39.5, 38.5, 34.5, 31.6, 29.9, 24.5, 22.3 ppm. **Accurate Mass (EI-**

Quadrupole) *m/z*: Calcd for C₁₇H₂₈O: 248.2135; found: 248.2166. Spectral Accuracy: 97.5%



1-Methoxy-5-methyl-(4'-phenyl)-5-butylbenzene (3.11): Product **3.11**

was prepared from 1-chloro-4-methoxybutane and 4-phenylstyrene

according to the General Procedure. The crude material was purified via

automated column chromatography using an eluent of 2% EtOAc:hexanes to afford **3.11** as a

colorless oil (45.8 mg, 34%). ¹H NMR (400 MHz, CDCl₃): δ_H 7.60-7.58 (m, 2H), 7.54-7.51 (m,

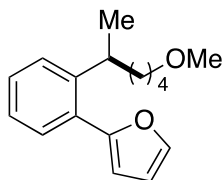
2H), 7.45-7.41 (m, 2H), 7.34-7.30 (m, 1H), 7.27-7.24 (m, 2H), 3.34 (t, *J* = 6.6 Hz, 2H), 3.31 (s,

3H), 2.73 (sextet, *J* = 7.1 Hz, 1H), 1.66-1.53 (m, 4H), 1.41-1.21 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ_C 147.0, 141.3, 138.9, 128.8, 127.5, 127.2, 127.14, 127.1, 73.0,

58.7, 39.8, 38.4, 29.9, 24.5, 22.4 ppm. **Accurate Mass (EI-Quadrupole)** *m/z*: Calcd for C₁₉H₂₄O:

268.1822; found: 268.1836. Spectral Accuracy: 98.0%



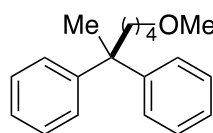
1-Methoxy-5-methyl-(2'-Furyl)-5-butylbenzene (3.12): Product **3.12** was

prepared from 1-chloro-4-methoxybutane and 2-furylstyrene according to the

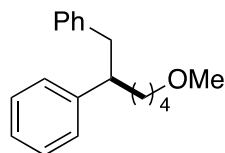
General Procedure. The crude material was purified via automated column

chromatography using a gradient of 0->3% of EtOAc in hexanes to afford **3.12** as a colorless oil

(37.5 mg, 29%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.52-7.51 (m, 1H), 7.49-7.47 (m, 1H), 7.37-7.31 (m, 2H), 7.24-7.20 (m, 1H), 6.49 (dd, $J = 3.3, 1.8$ Hz, 1H), 6.42 (dd, $J = 3.3, 0.8$ Hz, 1H), 3.31 (t, $J = 6.6$ Hz, 2H), 3.30 (s, 3H), 3.21 (sext, $J = 7.0$ Hz, 1H), 1.73-1.64 (m, 1H), 1.61-1.54 (m, 1H), 1.53-1.47 (m, 2H), 1.37-1.16 (m, 2H), 1.25 (d, $J = 6.9$ Hz, 3H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 154.1, 146.0, 142.0, 130.4, 129.3, 128.6, 126.3, 125.7, 111.1, 108.4, 72.9, 58.6, 38.1, 34.9, 29.8, 24.3, 22.4 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_2$: 258.1614; found: 258.1636. Spectral accuracy: 98.7%

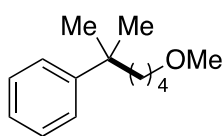


1-Methoxy-5-methyl-5-phenyl-5-butylbenzene (3.13): Product **3.13** was prepared from 1-chloro-4-methoxybutane and 1,1-diphenylethylene according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 3% EtOAc:hexanes to afford **3.13** as a colorless oil (115.2 mg, 86%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.28-7.24 (m, 4H), 7.20-7.14 (m, 6H), 3.30 (t, $J = 6.7$ Hz, 2H), 3.28 (s, 3H), 2.13-2.09 (m, 2H), 1.64 (s, 3H), 1.56 (p, $J = 7.7$ Hz, 2H), 1.19-1.11 (m, 2H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 149.9, 128.1, 127.5, 125.7, 72.9, 58.7, 46.4, 41.8, 30.5, 27.7, 21.5 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{19}\text{H}_{24}\text{O}$: 268.1822; found: 268.1807. Spectral accuracy: 97.4%



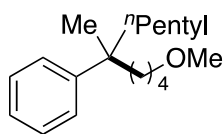
1-Methoxy-5-benzyl-5-butylbenzene (3.14): Product **3.14** was prepared from 1-chloro-4-methoxybutane and *trans*-stilbene (and from diphenylacetylene **10a**) according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 3% EtOAc:hexanes to afford **3.14** as a colorless oil (110.1 mg, 82% from *trans*-stilbene) (45.2 mg, 34% from diphenylacetylene **3.15**). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.28-7.09 (m, 8H), 7.04-7.01 (m, 2H), 3.28-3.24 (m, 5H), 2.90-2.82 (m, 2H), 2.84-2.77 (m, 1H), 1.75-1.59 (m, 2H), 1.57-1.41 (m, 2H), 1.24-1.16 (m, 2H) ppm.

^{13}C *NMR* (100 MHz, CDCl_3): δ_{C} 145.2, 140.9, 129.3, 128.3, 128.2, 127.9, 126.1, 125.9, 72.9, 58.6, 48.1, 44.0, 35.5, 29.8, 24.2 ppm. **HRMS (EI-Magn. Sector)** m/z : Calcd for $\text{C}_{19}\text{H}_{24}\text{O}$: 268.1822; found: 268.1819. Spectral accuracy: 96.5%



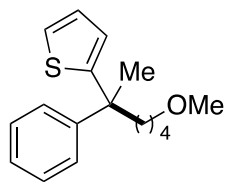
1-Methoxy-5,5-dimethyl-5-butylbenzene (3.16): Product **3.16** was prepared from 1-chloro-4-methoxybutane and α -methylstyrene according to the General

Procedure. The crude material was purified via automated column chromatography using a gradient of 0->2% of EtOAc in hexanes to afford **3.16** as a colorless oil (82.5 mg, 80%). ^1H *NMR* (400 MHz, CDCl_3): δ_{H} 7.35-7.28 (m, 4H), 7.19-7.15 (m, 1H), 3.29 (t, J = 6.6 Hz, 2H), 3.29 (s, 3H), 1.65-1.61 (m, 2H), 1.49 (dq, J = 8.0, 6.7 Hz, 2H), 1.31 (s, 6H), 1.16-1.08 (m, 2H) ppm. ^{13}C *NMR* (100 MHz, CDCl_3): δ_{C} 149.7, 128.1, 125.9, 125.5, 73.0, 58.6, 44.7, 37.8, 30.5, 29.0, 21.5 ppm. **HRMS (EI-Magn. Sector)** m/z : Calcd for $\text{C}_{14}\text{H}_{22}\text{O}$: 206.1612; found: 206.1554.



1-Methoxy-5-pentyl-5-methyl-5-butylbenzene (3.17): Product **3.17** was prepared from 1-chloro-4-methoxybutane and α -pentylstyrene according to the

General Procedure. The crude material was purified via automated column chromatography using a gradient of 0->2% of EtOAc in hexanes to afford **3.17** as a colorless oil (89.7 mg, 68%). ^1H *NMR* (400 MHz, CDCl_3): δ_{H} 7.29-7.24 (m, 4H), 7.17-7.11 (m, 1H), 3.28-3.25 (m, 5H), 1.71-1.62 (m, 2H), 1.56-1.42 (m, 4H), 1.25 (s, 3H), 1.21-1.07 (m, 6H), 1.03-0.86 (m, 2H), 0.80 (t, J = 6.9 Hz, 3H) ppm. ^{13}C *NMR* (100 MHz, CDCl_3): δ_{C} 148.3, 128.1, 126.5, 125.3, 73.0, 58.7, 43.5, 43.4, 40.9, 32.8, 30.5, 24.1, 24.0, 22.7, 21.0, 14.2 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{18}\text{H}_{30}\text{O}$: 262.2291; found: 262.2310. Spectral accuracy: 97.0%.



1-Methoxy-5-thienyl-5-methyl-5-butylbenzene (3.18): Product **3.18** was

prepared from 1-chloro-4-methoxybutane and α -thiophenylstyrene according

to the General Procedure. The crude material was purified via automated

column chromatography using an eluent of 5% EtOAc:hexanes to afford **3.18** as a colorless oil

(28.9 mg, 21%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.29-7.26 (m, 2H), 7.21-7.17 (m, 1H), 7.16-7.14

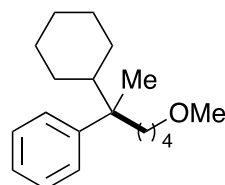
(m, 1H), 6.91 (dd, $J = 5.1, 3.5$ Hz, 1H), 6.79 (dd, $J = 3.5, 1.2$ Hz, 1H), 3.31 (t, $J = 6.6$ Hz, 2H),

3.29 (s, 3H), 2.23-2.06 (m, 2H), 1.73 (s, 3H), 1.61-1.53 (m, 2H), 1.38-1.14 (m, 2H) ppm. $^{13}\text{C NMR}$

(100 MHz, CDCl_3): δ_{C} 155.9, 148.8, 128.2, 126.8, 126.3, 126.2, 123.8, 123.5, 72.8, 58.7, 45.1,

43.5, 30.3, 28.5, 21.6 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{17}\text{H}_{22}\text{OS}$: 274.1386;

found: 274.1391. Spectral accuracy: 98.6%



1-Methoxy-5-methyl-5-cyclohexyl-5-butylbenzene (3.19): Product **3.19** was

prepared from 1-chloro-4-methoxybutane and α -cyclohexylstyrene according

to the General Procedure. The crude material was purified via automated

column chromatography using a gradient of 0->2% of EtOAc in hexanes to afford **3.19** as a

colorless oil (31.6 mg, 23%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.30-7.22 (m, 4H), 7.17-7.12 (m,

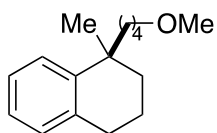
1H), 3.28-3.23 (m, 2H), 3.26 (s, 3H), 1.83-1.73 (m, 2H), 1.83-1.70 (m, 3H), 1.67-1.58 (m, 4H),

1.51-1.42 (m, 3H), 1.21 (s, 3H), 1.19-1.03 (m, 4H), 1.01-0.78 (m, 3H) ppm. $^{13}\text{C NMR}$ (100 MHz,

CDCl_3): δ_{C} 148.0, 127.9, 127.0, 125.2, 73.0, 58.6, 49.6, 44.0, 40.0, 30.7, 28.1, 27.9, 27.5, 27.3,

27.0, 21.1, 19.4 ppm. **HRMS (EI-Magn. Sector) m/z :** Calcd for $\text{C}_{19}\text{H}_{30}\text{O}$: 274.2320; found:

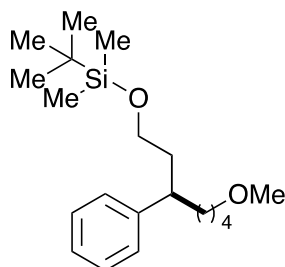
274.2344:



1-Methyl-1-(5'-methoxy)butyl, 2,3,4-trihydronaphthalene (3.20): Product

3.20 was prepared from 1-chloro-4-methoxybutane and 1,2,3,4-tetrahydro-1-methylene-naphthalene according to the General Procedure. The crude

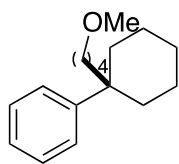
material was purified via automated column chromatography using an eluent of 2% EtOAc:hexanes to afford **3.20** as a colorless oil (57.5 mg, 49%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.26-7.24 (m, 1H), 7.15-7.11 (m, 1H), 7.08-7.02 (m, 2H), 3.33 (td, J = 6.6, 1.9 Hz, 2H), 3.30 (s, 3H), 2.74 (t, J = 6.2 Hz, 2H), 1.85-1.69 (m, 4H), 1.57-1.48 (m, 4H), 1.38-1.27 (m, 1H), 1.25 (s, 3H), 1.19-1.08 (m, 1H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 145.3, 136.9, 129.2, 126.8, 125.9, 125.3, 73.0, 58.7, 43.5, 36.9, 35.4, 30.9, 30.6, 30.4, 21.2, 19.7 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₁₇H₂₂OS: 232.1822; found: 232.1820. Spectral accuracy: 98.5%



1-Methoxy-5-(2'-tertbutyldimethylethoxysilyl)-5-butylbenzene

(3.21): Product **3.21** was prepared from 1-chloro-4-methoxybutane and cinnamyl-tertbutyldimethylsilanol according to the General Procedure.

The crude material was purified via automated column chromatography using an eluent of 3% EtOAc:hexanes to afford **3.21** as a colorless oil (109.4 mg, 65%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.29-7.25 (m, 2H), 7.19-7.12 (m, 3H), 3.49-3.44 (m, 1H), 3.41-3.35 (m, 1H), 3.29 (dt, 6.7, 1.1 Hz, 2H), 3.28 (s, 3H), 2.68 (tt, J = 9.8, 5.3 Hz, 1H), 1.90-1.85 (m, 1H), 1.78-1.43 (m, 5H), 1.29-1.10 (m, 2H), 0.86 (s, 9H), -0.03 (d, J = 1.6 Hz, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 145.5, 128.4, 127.9, 126.1, 73.0, 61.3, 58.6, 42.2, 39.9, 36.9, 29.8, 26.1, 24.3, 18.4, -5.2 (d, J = 1.8 Hz) ppm. **HRMS (EI-Magn. Sector)** m/z : Calcd for C₁₆H₂₇O₂Si [M-C₄H₉]⁺: 279.1783; found: 279.1785.



1-Phenyl-(5'-methoxy)-1-butylcyclohexane (3.22): Product **3.22** was prepared

from 1-chloro-4-methoxybutane and phenylcyclohexene according to the General

Procedure. The crude material was purified via automated column

chromatography using a gradient of 0->2% of EtOAc in hexanes to afford **3.22** as a colorless oil

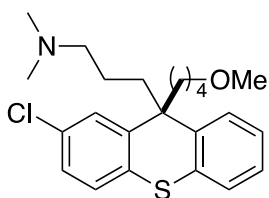
(32.0 mg, 26%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.31 (d, J = 4.2 Hz, 4H), 7.16 (septet, J = 4.2

Hz, 1H), 3.25 (s, 3H), 3.23 (t, J = 6.7 Hz, 2H), 2.08 (dd, J = 13.8, 6.4 Hz, 2H), 1.62-1.49 (m, 6H),

1.46-1.34 (m, 6H), 1.03-0.95 (m, 2H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 147.2, 128.2, 127.0,

125.2, 73.0, 58.6, 41.3, 36.3, 30.4, 26.8, 22.5, 20.2 ppm. **Accurate Mass (EI-Quadrupole) m/z :**

Calcd for C₁₇H₂₂OS: 246.1978; found: 246.1912. Spectral accuracy: 98.4%



1-Methoxy-5-butylchlorprothixene (3.23): Product **3.23** was prepared

from 1-chloro-4-methoxybutane and chlorprothixene according to the

General Procedure. The crude material was purified via column

chromatography using a gradient of 90->95% of acetone in EtOAc to afford **3.23** as a yellow oil

(65.2 mg, 32%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.42-7.40 (m, 2H), 7.24-7.11 (m, 5H), 3.26-3.22

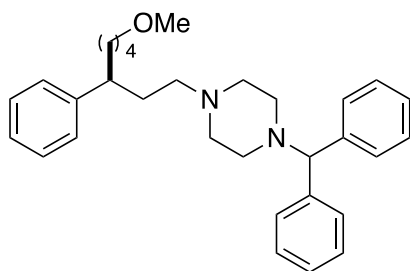
(m, 5H), 2.15 (t, J = 7.1 Hz, 2H), 2.10 (s, 6H), 2.08-1.98 (m, 4H), 1.46 (pentet, J = 7.0 Hz, 2H),

1.25-1.18 (m, 2H), 1.14-1.06 (m, 2H) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ_C 139.5, 136.7, 131.8,

131.0, 130.3, 127.7, 127.6, 127.0, 126.6, 126.4, 126.0, 72.6, 59.8, 58.7, 48.0, 45.5, 40.5, 38.4, 29.9,

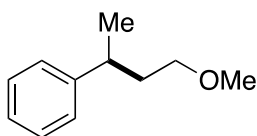
22.6, 21.2 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for C₂₃H₃₀ClNOS: 403.1731; found:

403.1764. Spectral accuracy: 97.7%



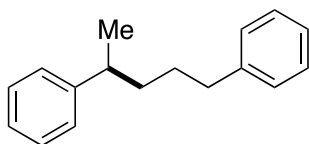
4-Chloromethoxybutylcinnarrizine (3.24): Product **3.24** was prepared from 1-chloro-4-methoxybutane and cinnarrizine according to the General Procedure. The crude material was purified via automated column chromatography using a gradient

of 0->40% of EtOAc in DCM to afford **3.24** as a yellow oil (100.0 mg, 44%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.42-7.40 (m, 4H), 7.30-7.24 (m, 6H), 7.20-7.13 (m, 5H), 4.21 (s, 1H), 3.28 (s, 3H), 3.28 (t, $J=6.7$ Hz, 2H), 2.57-2.27 (m, 8H), 2.24 (ddd, $J=12.0, 10.6, 5.5$ Hz, 1H), 2.11 (ddd, $J=12.1, 10.5, 4.9$ Hz, 1H), 1.61-1.69 (m, 1H), 1.78-1.70 (m, 1H), 1.68-1.43 (m, 5H), 1.30-1.11 (m, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ_C 145.5, 142.9, 128.5, 128.4, 128.0, 127.7, 127.0, 126.1, 76.4, 72.9, 58.6, 57.0, 53.6, 52.0, 44.4, 37.1, 33.9, 29.8, 24.2 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₃₁H₄₀N₂O: 456.3135; found: 456.3132. Spectral accuracy: 97.0%



1-Methoxy-3-Phenyl-3-methylbenzene (3.25): Product **3.25** was prepared from 1-chloro-2-methoxyethane and styrene according to the General

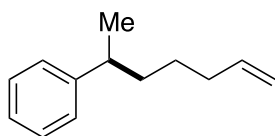
Procedure. The crude material was purified via automated column chromatography using an eluent of 3% EtOAc:hexanes to afford **3.25** as a colorless oil (61.3 mg, 75%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.32-7.28 (m, 2H), 7.22-7.18 (m, 3H), 3.32-3.20 (m, 2H), 3.32 (s, 3H), 2.87 (sextet, $J=6.8$ Hz, 1H), 1.89-1.82 (m, 2H), 1.28 (d, $J=7.0$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ_C 147.1, 128.5, 127.1, 126.1, 71.0, 58.7, 38.1, 36.6, 22.4 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₁₁H₁₆O: 164.1196; found: 164.1143. Spectral accuracy: 97.3%



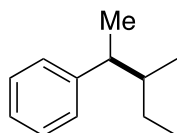
1,4-diphenyl-pentane (3.26): Product **3.26** was prepared from 1-bromo-3-phenylpropane and styrene according to the General procedure. The crude material was purified via automated column

chromatography using an eluent of 100% hexanes to afford **3.26** as a colorless oil (88.6 mg, 79%).

¹H NMR (400 MHz, CDCl₃): δ_H 7.32-7.25 (m, 4H), 7.22-7.14 (m, 6H), 2.73 (sext, $J=7.0$ Hz, 1H), 2.60 (dt, $J = 7.0, 1.9$ Hz, 2H), 1.71-1.46 (m, 4H), 1.26 (d, $J = 6.9$ Hz, 3H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 147.7, 142.8, 128.5, 128.4, 128.44, 128.36, 127.1, 126.0, 125.7, 40.0, 38.1, 36.1, 29.7, 22.5 ppm. **Accurate Mass (EI-Quadrupole) m/z** : Calcd for C₁₇H₂₀: 224.1560; found: 224.1532. Spectral Accuracy: 98.9%

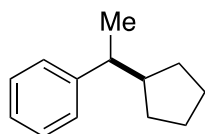


6-Hepten-2-ylbenzene (3.27): Product **3.27** was prepared from 5-bromopentene and styrene according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 100% hexanes to afford **3.27** as a colorless oil (68.5 mg, 79%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.32-7.28 (m, 2H), 7.21-7.16 (m, 3H), 5.77 (ddt, $J = 17.0, 10.1, 6.7$ Hz, 1H), 5.00-4.90 (m, 2H), 2.69 (sext, $J = 7.1$ Hz, 1H), 2.05-2.00 (m, 2H), 1.62-1.56 (m, 2H), 1.42-1.25 (m, 2H), 1.25 (d, $J = 7.0$ Hz, 3H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 147.9, 139.1, 128.4, 127.1, 125.9, 114.5, 40.0, 38.0, 34.0, 27.2, 22.4 ppm. **Accurate Mass (EI-Quadrupole) m/z** : Calcd for C₁₃H₁₈: 174.1403; found: 174.1442. Spectral accuracy: 98.4%



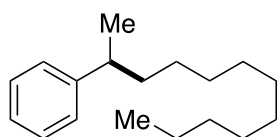
(3-Methyl-2-pentanyl)benzene (3.28): Product **3.28** was prepared from 2-bromobutane and styrene according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 100% pentane to afford **3.28** as an inseparable mixture of diastereomers in a ratio of 1.7:1 and as a colorless oil (56.8 mg, 70%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.31-7.26 (m, 2H), 7.20-7.15 (m, 3H), 2.58 (sextet, $J=7.2$ Hz, 1H), 1.61-1.48 (m, 1H), 1.36-1.29 (m, 1H), 1.25 (minor diastereomer, d, 1.22H), 1.21 (major diastereomer, d, $J = 7.1$ Hz, 2.10H), 1.17-0.95 (m, 1H), 0.91-0.82 (m, 5H), 0.73 (d, $J = 6.7$ Hz, 1H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C major diastereomer: 147.5, 128.2, 127.8, 125.7, 44.7, 40.9, 27.7, 17.8, 15.8, 11.8 ppm; minor diastereomer: 146.9, 128.1, 128.0, 125.8, 44.9, 40.9, 26.5,

19.0, 17.0, 11.5 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $C_{12}H_{18}$: 162.1403; found: 162.1399. Spectral accuracy: 99.1%



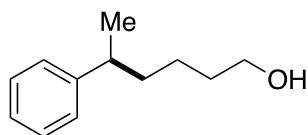
(1-Cyclopentylethyl)benzene (3.29): Product **3.29** was prepared from

bromocyclopentane and styrene according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 100% hexanes to afford **3.29** as a colorless oil (54.0 mg, 62%). **1H NMR** (400 MHz, $CDCl_3$): δ_H 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 2.44-2.40 (m, 1H), 2.00-1.86 (m, 2H), 1.69-1.63 (m, 1H), 1.58-1.50 (m, 2H), 1.48-1.34 (m, 2H), 1.25 (d, $J = 6.9$ Hz, 3H), 1.22-1.17 (m, 1H), 1.06-0.96 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 148.2, 128.3, 127.4, 125.8, 47.7, 46.3, 31.9, 31.6, 25.5, 25.3, 21.6 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $C_{13}H_{18}$: 174.1403; found: 174.1395. Spectral accuracy: 98.6



2-Phenyldodecane (3.30): Product **3.30** was prepared from 1-iodododecane

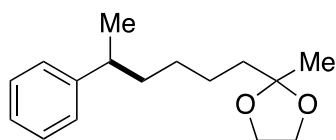
and styrene according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 100% hexanes to afford **3.30** as a colorless oil (71.5 mg, 58%). **1H NMR** (400 MHz, $CDCl_3$): δ_H 7.33-7.28 (m, 2H), 7.21-7.17 (m, 3H), 2.68 (sext, $J = 7.2$ Hz, 1H), 1.60-1.54 (m, 2H), 1.32-1.24 (m, 19H), 0.92-0.88 (m, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 148.2, 128.4, 127.1, 125.9, 40.1, 38.6, 32.1, 29.9, 29.81, 29.78, 29.7, 29.5, 27.9, 22.8, 22.5, 14.3 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $C_{18}H_{30}$: 246.2342; found: 246.2377. Spectral accuracy: 98.9



5-Phenyl-5-methyl-1-hexanol (3.31): Product **3.31** was prepared from

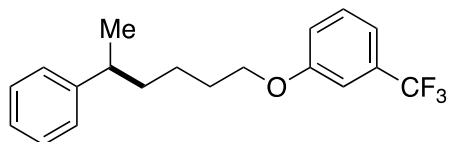
1-chloro-4-tertbutyldimethylsilyloxybutane and styrene according to the General Procedure. The crude material was worked up using TBAF (0.7 mL, 1.0 M in THF) and then purified via automated column chromatography using a gradient of 0->5% of EtOAc in

hexanes to afford **3.31** as a colorless oil (64.2 mg, 72%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.31-7.27 (m, 2H), 7.20-7.16 (m, 3H), 3.59 (q, J = 6.4 Hz, 2H), 2.69 (sextet, J = 7.0 Hz, 1H), 1.67-1.48 (m, 4H), 1.37-1.27 (m, 1H), 1.24 (d, J = 7.0 Hz, 3H), 1.20-1.12 (m, 1H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 147.7, 128.5, 127.1, 126.0, 63.1, 40.1, 38.3, 33.0, 24.0, 22.5 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₁₂H₁₈O: 178.1352; found: 178.1342. Spectral accuracy: 98.0%



2-(5-Phenyl-hexyl)-2-methyl-[1,3]dioxolane (3.32): Product **3.32**

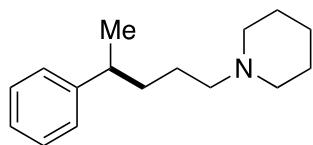
was prepared from 2-(4-Chloro-butyl)-2-methyl-[1,3]dioxolane and styrene according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 2% EtOAc:hexanes to afford **3.32** as a colorless oil (71.1 mg, 57%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.31-7.26 (m, 2H), 7.20-7.16 (m, 3H), 3.95-3.87 (m, 4H), 2.67 (sextet, J = 7.0 Hz, 1H), 1.61-1.54 (m, 4H), 1.41-1.30 (m, 2H), 1.29 (s, 3H), 1.23 (d, J = 6.9 Hz, 3H), 1.26-1.13 (m, 2H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 147.9, 128.4, 127.1, 125.9, 110.3, 64.7, 40.0, 39.3, 38.5, 28.1, 24.3, 23.9, 22.5 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for H₂₄C₁₆O₂: 248.1771; found: 248.1764. Spectral accuracy: 98.4%



5-Phenyl-hexyl-(3-trifluoromethyl)phenylether (3.33):

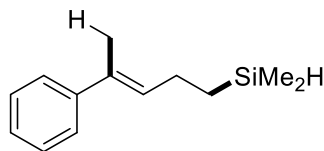
Product **3.33** was prepared from **S2** and styrene according to the General Procedure. The crude material was purified via automated column chromatography using an eluent of 2% EtOAc:hexanes to afford **3.33** as a colorless oil (108.0 mg, 67%). **¹H NMR** (500 MHz, CDCl₃): δ_H 7.36 (t, J = 8.0 Hz, 1H), 7.31-7.28 (m, 2H), 7.20-7.17 (m, 4H), 7.09-7.08 (m, 1H), 7.02 (dd, J = 8.3, 2.5 Hz, 1H), 3.93 (td, J = 6.5, 2.2 Hz, 2H), 2.72 (sext, J = 7.0 Hz, 1H), 1.83-1.72 (m, 2H), 1.68-1.61 (m, 2H), 1.48-1.38 (m, 1H), 1.37-1.30 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H) ppm. **¹³C NMR** (125 MHz, CDCl₃): δ_C 159.3, 147.6, 132.0, 131.8, 130.0, 128.5, 127.1, 126.1, 118.1, 117.3 (q, J = 4.0 Hz), 111.3 (q, J = 4.0 Hz), 68.3,

40.1, 38.2, 29.3, 24.3, 22.5 ppm. ^{19}F NMR (470 MHz, CDCl_3): δ_{F} 62.68 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{H}_{21}\text{C}_{19}\text{F}_3\text{O}$: 322.1539; found: 322.1519. Spectral accuracy: 99.2%



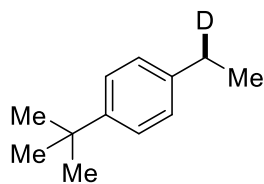
4-Phenyl-N-pentylpiperidine (3.34): Product **3.34** was prepared from 3-chloropropylpiperidine hydrochloride and styrene according to the

General Procedure and employing 4 equivalents of KO^tBu . The crude material was purified via automated column chromatography using a gradient of 0->40% of DCM in EtOAc to afford **3.34** as a colorless oil (17.8 mg, 15%). ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.30-7.26 (m, 2H), 7.19-7.14 (m, 3H), 2.68 (sext, $J = 7.0$ Hz, 1H), 2.23 (ddd, $J = 8.9, 6.1, 2.7$ Hz, 2H), 1.58-1.52 (m, 7H), 1.51-1.32 (m, 5H), 1.24 (d, $J = 6.9$ Hz, 3H), 0.92-0.82 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 147.7, 128.4, 127.1, 126.0, 59.6, 54.6, 40.1, 36.5, 25.9, 25.1, 24.5, 22.5 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{16}\text{H}_{25}\text{N}$: 231.1982; found: 231.1956. Spectral accuracy: 97.7%



Dimethyl(4-phenylpent-3-en-1-yl)silane (3.40) was prepared from 1-chloro-4-methoxybutane and the corresponding styrene according to the General Procedure. The crude material was purified via column

chromatography using an eluent of 100% hexanes to afford **3.40** as a colorless oil (47.9 mg, 59%). The characterization of this species matches the literature.⁷⁶ ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.39-7.36 (m, 2H), 7.32-7.29 (m, 2H), 7.23-7.19 (m, 1H), 5.80 (tq, $J = 7.2, 1.5$ Hz, 1H), 3.91 (heptet, $J = 7.1$ Hz, 1H), 2.27 (q, $J = 7.5$ Hz, 2H), 2.03 (s, 3H), 0.80-0.75 (m, 2H), 0.11 (d, $J = 3.7$ Hz, 6H) ppm.



α -Deutero-4-tert-butylethylbenzene (3.43) was prepared the

corresponding styrene according to the General Procedure and using D₂O

(2.0 equiv) instead of an alkyl halide. The crude material was purified via

automated column chromatography using an eluent of 100% hexanes to afford **3.43** as a colorless

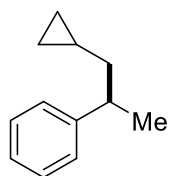
oil (45.9 mg, 56%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.35-7.33 (m, 2H), 7.18-7.15 (m, 2H), 2.68-

2.60 (m, 1.28H), 1.34 (s, 9H), 1.28-1.24 (m, 3H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 148.5,

141.3 (d, J = 3.1 Hz), 127.6, 125.3, 34.5, 31.6, 28.4, 28.1 (t, J = 19.6 Hz), 15.6 ppm. **Accurate**

Mass (EI-Quadrupole) m/z : Calcd for C₁₇H₁₇D: 163.1466; found: 163.1444 Spectral accuracy:

97.2%



(2-Cyclopropyl-1-methylethyl)benzene (3.45) was prepared from

bromomethylcyclopropane and styrene according to the General Procedure. The

crude material was purified via automated column chromatography using an eluent

of 100% hexanes to afford **3.45** as a colorless oil (30.7 mg, 38%). **¹H NMR** (400 MHz, CDCl₃):

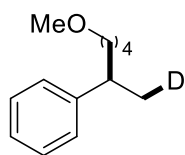
δ_H 7.31-7.26 (m, 2H), 7.23-7.15 (m, 3H), 2.83 (h, J = 7.1 Hz, 1H), 1.59 (dddd, J = 13.8, 7.6, 6.3,

1.3 Hz, 1H), 1.37-1.32 (m, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.61-0.55 (m, 1H), 0.43-0.30 (m, 2H),

0.07—0.07 (m, 2H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ_C 148.1, 128.4, 128.3, 127.2, 125.9, 43.9,

40.6, 22.0, 9.6, 4.9, 4.5 **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₁₂H₁₆: 160.1247; found:

160.1294 Spectral accuracy: 98.1%



Synthesis of 1-methoxy-5-deutero-methyl-5-butylbenzene (3.7-d₁):

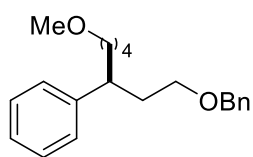
Compound **3.7-d₁** was synthesized according to the General Procedure and using

TMDSO-d₂, styrene, and 1-chloro-4-methoxy butane. The crude material was

purified via automated column chromatography using an eluent of 2% hexanes:EtOAc to afford

3.7-d₁ as a colorless oil (24.1 mg, 63%). **¹H NMR** (400 MHz, CDCl₃): δ_H 7.32-7.27 (m, 2H), 7.20-

7.16 (m, 3H), 3.32 (t, $J = 6.7$ Hz, 2H), 3.31 (s, 3H), 2.67 (pent, $J = 7.0$ Hz, 1H), 1.63-1.51 (m, 4H), 1.37-1.13 (m, 2H), 1.24 (d, $J = 6.9$ Hz, 2.26H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 147.9, 128.4, 127.1, 125.9, 73.0, 58.7, 40.1, 38.4, 29.9, 24.4, 22.4 ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 15.6 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{13}\text{H}_{19}\text{DO}$: 193.0996; found: 193.1012 Spectral accuracy: 97%



1-Methoxy-5-(2'-benzyloxy)ethyl-5-butylbenzene (3.92) was prepared

from 1-chloro-4-methoxybutane and styrene **3.92** according to the General

Procedure. The crude material was purified via automated column

chromatography using a gradient of 0-2% EtOAc:hexanes to afford **3.92** as a colorless oil (84.6

mg, 54%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.35-7.24 (m, 7H), 7.20-7.12 (m, 3H), 4.43-4.36 (m,

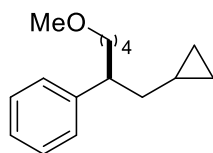
2H), 3.37-3.31 (m, 1H), 3.30-3.36 (m, 5H), 3.25-3.21 (m, 1H), 2.72 (tt, $J = 10.0, 5.2$ Hz, 1H), 2.05-

1.97 (m, 1H), 1.87-1.76 (m, 1H), 1.68-1.57 (m, 2H), 1.56-1.43 (m, 2H), 1.29-1.09 (m, 2H) ppm.

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 145.3, 138.7, 128.46, 128.45, 127.84, 127.79, 127.6, 126.1, 73.1,

72.9, 68.6, 58.6, 42.6, 37.0, 36.9, 29.8, 24.3 ppm. **HRMS (EI-Magn. Sector) m/z :** Calcd for

$\text{C}_{21}\text{H}_{28}\text{O}_2$: 312.2135; found: 312.2180.



1-Methoxy-5-methylenecyclopropyl-5-butylbenzene (3.94) was prepared

from 1-chloro-4-methoxybutane and the corresponding styrene according to the

General Procedure. The crude material was purified via automated column

chromatography using an eluent of 2% EtOAc:hexanes to afford **3.94** as a colorless oil (47.9 mg,

41%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.30-7.26 (m, 2H), 7.20-7.15 (m, 3H), 3.30 (dt, $J = 6.9,$

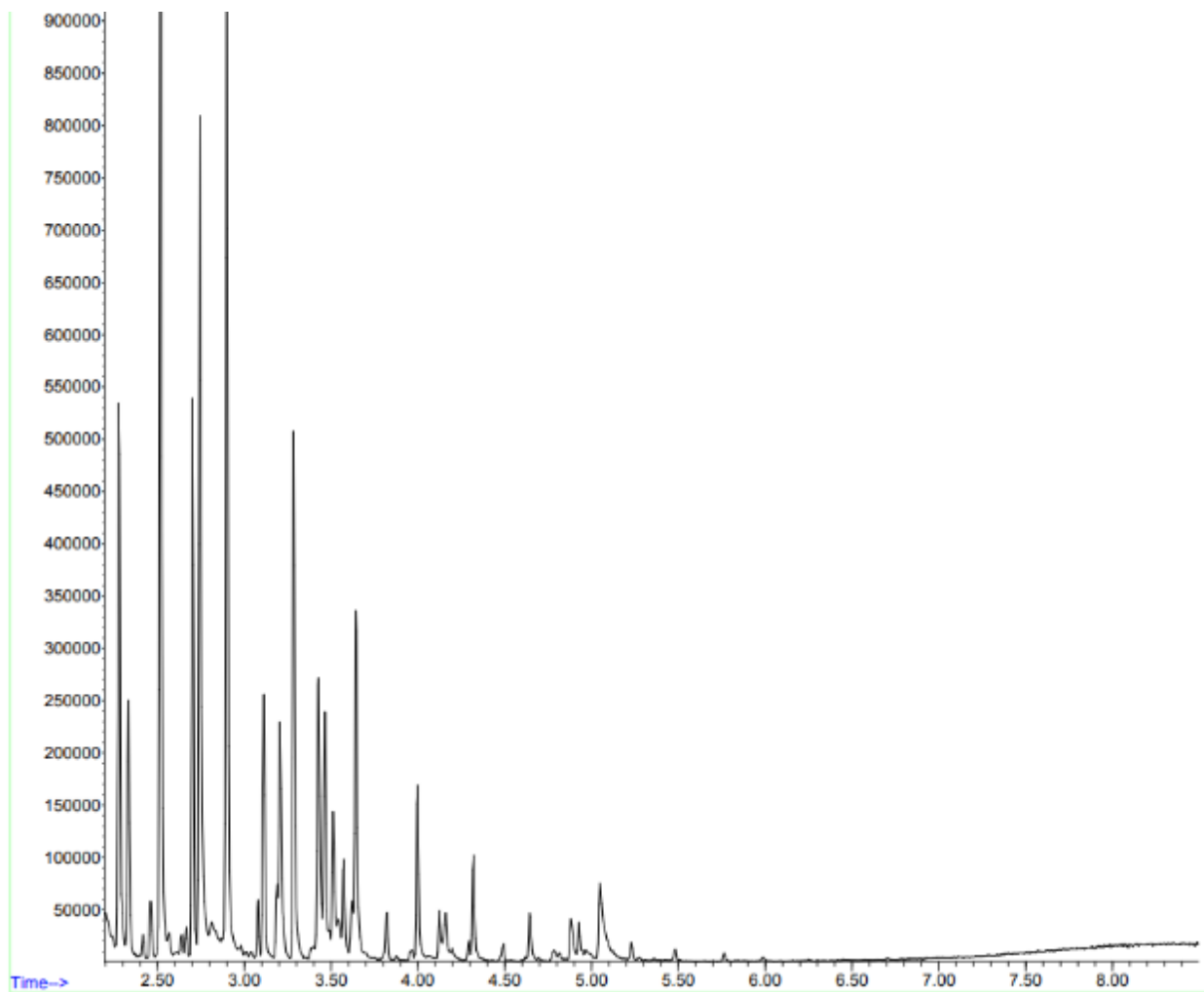
1.9 Hz, 2H), 3.29 (s, 3H), 2.67-2.60 (m, 1H), 1.74-1.46 (m, 5H), 1.35-1.14 (m, 3H), 0.55-0.45 (m,

1H), 0.39-0.26 (m, 2H), 0.01- -0.11 (m, 2H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 146.3, 128.3,

127.9, 125.9, 73.0, 58.7, 46.6, 42.5, 36.3, 29.9, 24.3, 9.5, 4.8, 4.7 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $C_{16}H_{24}O$: 232.1822; found: 232.1816. Spectral accuracy: 99.3%.

Procedure for the COware Reaction. To an oven dried Coware vessel equipped with a stir bar in each well was added the corresponding base/additive (1.8 mmol). The vial was then sealed with the red screw caps equipped with a pierceable Teflon/silicone septum. Each well of the reaction vessel was purged using a balloon filled with argon for 3-5 minutes. PhMe (1.25 mL, 0.4 M) was taken directly from a solvent purification system and added through the septum using a syringe to each well. The corresponding olefin (0.5 mmol) was then added into well B, followed by TMDSO (1.5 mmol) into well A and the alkyl halide coupling partner (1.5 mmol) into well B. The balloon filled with argon was then removed from the septum, and the reaction vessel was carefully placed in an oil bath that had been preheated to 90 °C and allowed to stir for 16 hours. Once complete, the reaction mixture was removed from the oil bath, diluted with EtOAc while hot, and cooled to room temperature. The solution was then filtered through silica with EtOAc using a 15 mL glass fritted funnel, concentrated using a rotary evaporator, and analyzed via GCMS and NMR spectroscopy. Percent yields were determined using 1H NMR spectroscopy with 1,3,5-trimethoxy benzene as an internal standard.

A Sample Chromatogram of a typical reaction is depicted below as an example to emphasize both the quantity and variety of silicon oligomers formed in each reaction:



Silicon oligomers as detected by GCMS analysis.

3.11 | References

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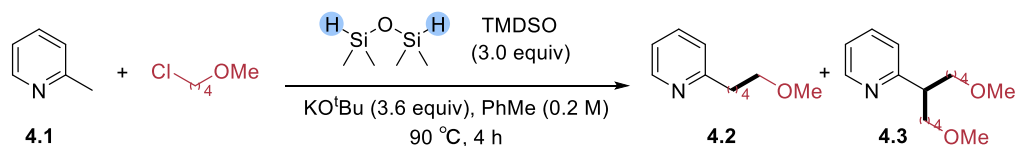
Chapter 4 | Deprotonation and Alkylation of Weakly Acidic C(sp³)–H Bonds Using 1,1,3,3-Tetramethyldisiloxane and Potassium *tert*-Butoxide.

Section 4.1 | Chapter outlook

In the previous chapter, the hydroalkylation of vinylarenes using alkyl halides as electrophiles and the combination of 1,1,3,3-tetramethyldisiloxane (TMDSO) and potassium *tert*-butoxide (KO^tBu) was discussed. As mentioned in section 3.7.4.3 a common byproduct of the reaction was the alkylation of toluene (PhMe), the reaction solvent. Although it proved to be a nuisance during the purification of samples the author of this dissertation questioned whether such a reaction could be targeted. A quick literature search revealed that hydrosilanes and Lewis bases are known to exhibit basic reactivity and are capable of deprotonating weakly acidic C–H bonds (see chapter 1 section 1.4.1.1 for more information). Yet no examples of C–H alkylation reactions facilitated by hydrosilanes and Lewis bases exist. Following this observation was the discovery that TMDSO and KO^tBu can facilitate the alkylation of 2-picoline (**4.1**) resulting in the formation of **4.2** and dialkylated product **4.3** (**Scheme 4.1**). This chapter explores this unexpected reaction as its main topic, where TMDSO and KO^tBu mediate C–H alkylations.

This section begins with a comprehensive analysis of established strong base-mediated C–H functionalization reactions, followed by the optimization of a TMDSO and KO^tBu mediated C–H alkylation reaction. In the next section, a scope examination is conducted, applications of the method are explored, and the underlying mechanism is discussed. This chapter ends with a conclusion and discussion of promising future directions of this research.

Scheme 4.1: Discovery of a C–H alkylation reaction



Section 4.2 | Reuse permissions and contributions to research

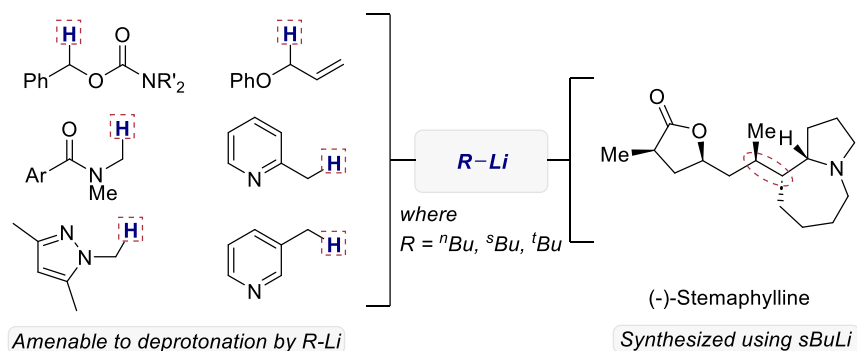
All of this research is original and has not yet been published in the literature. The content of this chapter was conducted solely by the dissertation author.

4.3 | The deprotonation and functionalization of weakly acidic C(sp³)-H bonds

4.3.1 | Alkylolithiums: A double-edged sword in C-H functionalization reactions

The deprotonation and alkylation of C-H bonds is a fundamental transformation in organic synthesis. Given their abundance and resistance to most transformations, the direct use of C-H bonds in organic synthesis is highly desirable. As a result, this transformation has found broad application in routine organic synthesis and notably in the total synthesis of complex natural products, where alkylolithiums serve as powerful reagents.^{1,2} Typical C-H deprotonation reactions are facilitated by *n*-butyllithium (*n*-BuLi) – a unimetal superbases with an acid dissociation constant (pK_a) of approximately 52 making it capable of deprotonating some of the most unreactive C-H bonds (**Scheme 4.2**).³

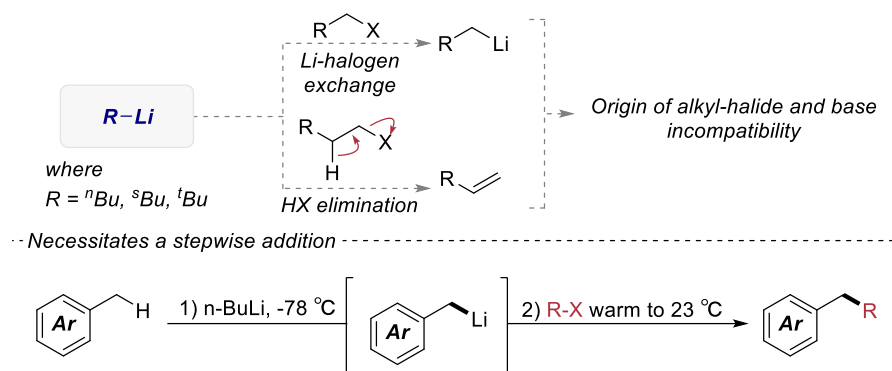
Scheme 4.2: Alkylolithiums in deprotonation reactions



Related bases, *sec*-butyllithium (*s*-BuLi) and *tert*-butyllithium (*t*-BuLi) see routine use as well. Although *n*-BuLi is without a doubt a staple in the synthetic organic chemist's toolbox, its highly reactive nature presents some chemoselectivity challenges.⁴ For instance, lithium-halogen exchange and the E2-elimination of alkyl halides often lead to undesired side products which we

will refer to as: base-alkyl halide incompatibility (**Scheme 4.3**). This frames n-BuLi as a double-edged sword in organic synthesis. The desired chemoselective outcome can be achieved through use of a step-wise protocol wherein treatment of the C–H bond with n-BuLi precedes addition of the alkyl halide electrophile. Further chemo- and regioselectivity can be obtained using cryogenic temperatures. In addition to its high reactivity resulting in the formation of unwanted side products its reactivity presents danger to the synthetic organic chemist as it can ignite upon exposure to the atmosphere. Clever solutions have also been designed and implemented to provide a more convenient way to handle these species and improve their shelf-stability through a clever immobilization strategy.⁵ Given the chemoselectivity challenges associated with n-BuLi and related alkyllithiums milder alternatives are often used when deprotonating species with a pKa range of 26–34.

Scheme 4.3: Undesired side reactions of alkyllithiums



4.3.2 | Alternative bases in contemporary C–H alkylation reactions

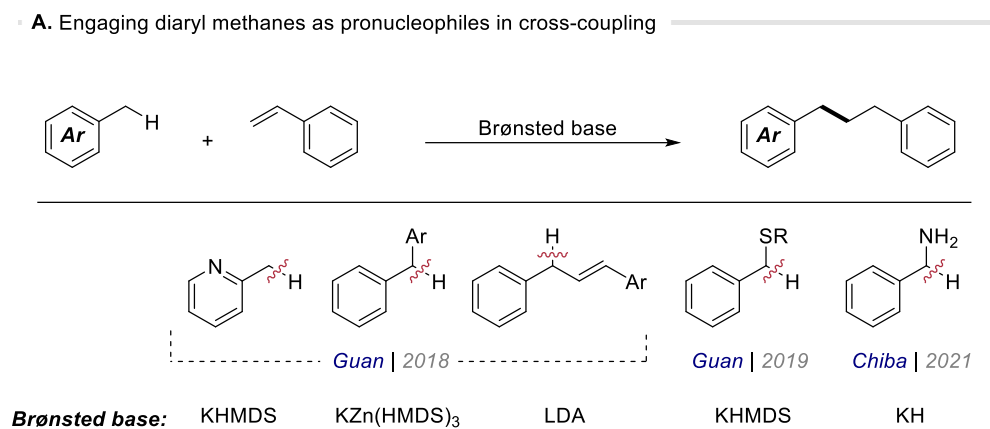
Contemporary base-mediated C–H alkylation reactions typically do not involve the use of alkyl halides as electrophiles and instead invoke electrophilic olefins as alkylating agents. Of course, these reactions could also be, and typically are, defined as Brønsted-base mediated hydroalkylation reactions. Given this section contextualizes chapter 4 regarding base mediated C–

H alkylation, these reactions will be analyzed through the lens of C–H alkylation with a particular emphasis on the deprotonation and the basic species at hand.

Pioneering work was conducted by Pines in the 1950s-1970s who used alkali metals to catalyze the addition of benzylic C–H species onto olefins, providing the alkylated product.^{6,7} Contemporary variants of this transformation make use of alkali metal salts; three concurrent examples of which were published by Guan in 2018. The authors found 2 and 4-alkylpyridines could undergo potassium hexamethyldisilazide (KHMDs)-catalyzed C–H alkylation in the presence of vinylarenes (**Scheme 4.4**). The authors suggest the weakly acidic species is reversibly deprotonated by KHMDs, generating pyridyl potassium in low, but synthetically useful, concentrations.⁸ Note that the base-vinylarene compatibility under these conditions allow for alkylation to take place without degradation of the alkylating agent. The use of diphenylmethanes – a common motif in drug molecules – as pronucleophiles was reported in a similar transformation, instead using a bimetallic hexamethyldisilazide (KZn(HMDs)₃).⁹ The authors propose the active catalyst is comprised of a diphenylmethane potassium zincate species thought to be generated through reaction of the initial base and the diphenylmethane substrate. Similar reactions utilize symmetric 1,3-diarylpropenes,¹⁰ and weakly acidic sulfides,¹¹ as pronucleophiles in analogous reactions. An intriguing variant of the same reaction was later reported and made use of potassium hydride (KH) as a stoichiometric Brønsted-base.¹² In this transformation, benzylamines are used as pronucleophiles which is interesting for two reasons. First, the benzylic C–H bond is several orders of magnitude less acidic than diphenylmethane. The second and more interesting observation is that metal hydride bases tend to deprotonate N–H and O–H bonds more readily than C–H bonds. The authors propose the amine N–H bond is deprotonated by KH but can then deprotonate the benzylic position leading to the benzyl potassium species responsible for

alkylation. The authors noted counterion effects dictated product selectivity wherein use of sodium hydride (NaH) and lithium hydride (LiH) resulted in N–H alkylation, while KH produced the desired product arising from C–H alkylation. An interesting counterion effect is observed where potassium bases lead to the desired C-alkylation whereas sodium and lithium provide N–H alkylation. A density functional theory (DFT) analysis of the reaction showed coordination of styrene to potassium in the key alkylation step to have a reasonable barrier, which the authors speculated was responsible for governing C-alkylation. While these strategies are powerful in their own right, if we are to consider them as alkylation reactions of benzylic C–H bonds, they are inherently limited to olefins bearing anion-stabilizing substituents as alkylating agents. Thus, alternative electrophiles as alkylating agents could broaden the allowed scope.

Scheme 4.4: Brønsted-base mediated benzylic C–H alkylation

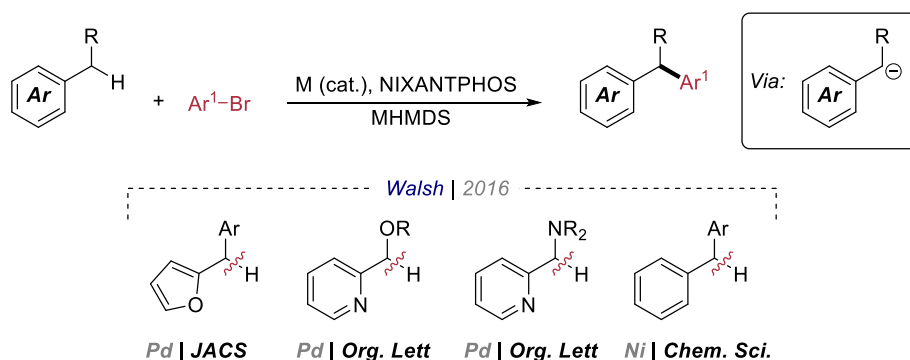


4.3.3 | Alternative bases in benzylic C–H arylation

Strong bases have played a central role in transition metal-catalyzed C–H arylation reactions. The Walsh group recognized KHMDS as a privileged base and spearheaded its application in the transition metal-catalyzed C–H arylation of weakly acidic species. In 2016, they reported the palladium-catalyzed cross coupling of 2-pyridylmethyl silyl ethers,¹³ benzyl furans,¹⁴ azaarylmethylamines,¹⁵ and the nickel-catalyzed arylation of diarylmethanes (Scheme 4.5).¹⁶ In

each of these systems, 4,6-Bis(diphenylphosphino)phenoxazine (NiXANTPHOS) served as the ligand with a metal hexamethyldisilazide as the base. The authors proposed the base reversibly deprotonates the target C–H bond which is then intercepted by the transition metal catalyst as a nucleophilic cross coupling partner. Notably, the pKa of these species range anywhere from ~30–35 allowing a small but synthetically relevant concentration of benzylic carbanion to form in solution.

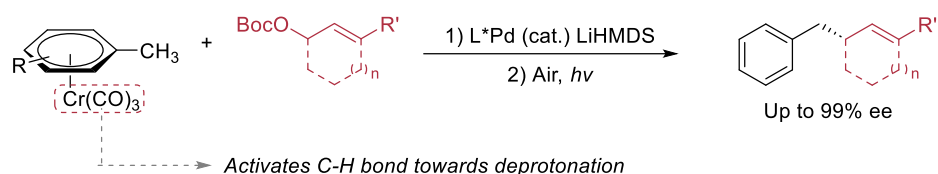
Scheme 4.5: Engaging diarylmethanes as pronucleophiles in cross coupling reactions



In 2016, Walsh and coworkers directed their attention towards targeting toluene derivatives as pronucleophiles, and recognized their high pKa of approximately 41 as an immense challenge.¹⁷ The authors noted that chromium tricarbonyl (Cr(CO)₃) can strongly associate to the π -bonds of aromatic rings in an η -6 fashion to form stable isolable (toluene)chromium tricarbonyl complexes.¹⁸ The electron withdrawing properties of the transition metal bound to the aromatic ring helps to stabilize negative charge accumulation at the benzylic position, effectively lowering the pKa of the benzylic C–H bond.¹⁸ Walsh and coworkers leveraged this effect to engage toluene as a pronucleophile in a palladium-catalyzed asymmetric allylation reaction, using lithium hexamethyldisilazide (LiHMDS) as the base (**Scheme 4.6**).¹⁷

Scheme 4.6: Engaging (toluene)chromium tricarbonyl complexes as pronucleophiles in a palladium-catalyzed asymmetric allylation reaction

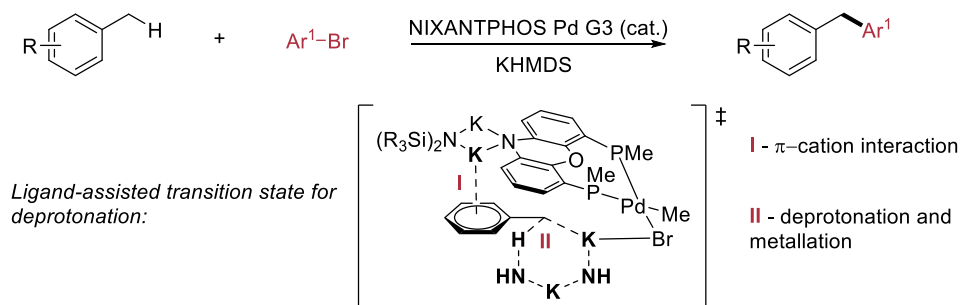
Walsh | 2016



The chromium complex could be removed from the product molecules with minimal erosion of the chirality center. In a follow-up study, the Walsh group demonstrated free toluenes could be used directly as pronucleophiles, obviating the need to synthesize the (toluene)chromium tricarbonyl complex (**Scheme 4.7**).¹⁹ The authors proposed the barrier to benzylic deprotonation was lowered through association of the aromatic ring to potassium from KHMDS in a π -cation interaction. A DFT analysis showed the NiXANTPHOS ligand places the potassium cation into close proximity with the aromatic ring on toluene aiding in the deprotonation step.

Scheme 4.7: Harnessing toluenes as pronucleophiles in transition metal-catalyzed arylation via ligand-assisted deprotonation

Walsh | 2018

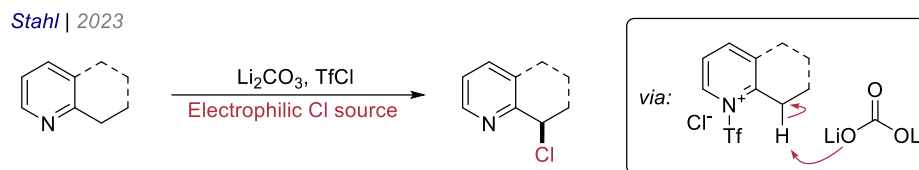


4.3.4 | Base-mediated benzylic C–H oxidation

This theme of assisting a weaker base to facilitate the deprotonation of robust C–H bonds is not unique to metal hexamethyldisilazides. In a recent report by Stahl, alkyl pyridines were chlorinated at their pyridylic C–H bonds using a synergistic combination of Lewis acids and weak

bases (**Scheme 4.8**).²⁰ Association of pyridine lone-pair to the Lewis acid induces a more facile deprotonation of alkyl substituents at the resonant C2, C4, and C6 positions of the pyridine ring. While this strategy enables the facile deprotonation of the pyridylic C-H bond using a very weak base, the scope is inherently limited to pyridine and its related heterocycles.

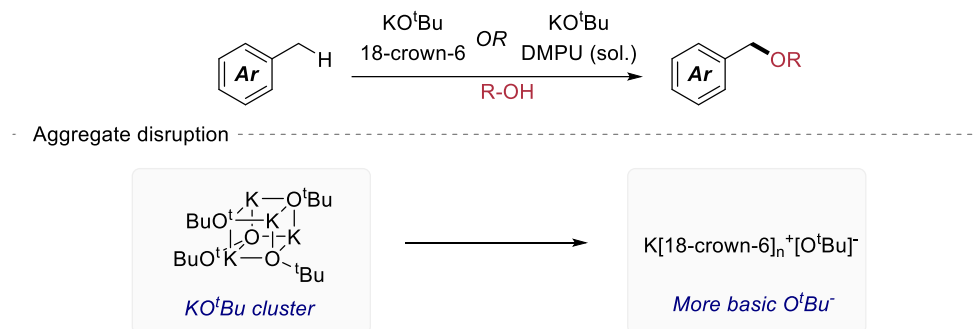
Scheme 4.8: Electrophilic chlorination of pyridine through lone-pair activation



Another approach is to manipulate the strength of the base, rather than the substrate. Work by Bandar and coworkers leverages the basicity enhancement of KO^tBu for the deprotonation of weakly acidic C-H bonds in a clever benzylic etherification reaction driven by Le-Chatelier's principle (**Scheme 4.9**).²¹ The authors used Stoichiometric 18-crown-6 or solvent quantities of N,N-dimethylpropyleneurea (DMPU) to render *tert*-butoxide more basic leading to a more reactive alkoxide. These additives are thought to sequester K⁺ from *tert*-butoxide (O^tBu⁻) rendering it significantly more basic. This approach culminated in a deprotonation strategy capable of targeting pyridine and non-pyridine substrates as it doesn't require the nitrogen heteroatom for activation. Examples of dimethylsulfoxide (DMSO) being used to enhance the basicity of cesium hydroxide (CsOH),²² and KO^tBu,²³ have been reported by Knochel and coworkers.

Scheme 4.9: Basicity enhancement of KO^tBu through aggregate disruption

Bandar | 2024



4.3.5 | Where are the contemporary base-mediated C–H alkylation reactions?

Although metal-hexamethyldisilazide, metal-alkoxides, and metal-hydrides have seen extensive use in deprotonation reactions, no examples utilizing them alongside alkyl halides in C(sp³)–H alkylation reactions have been reported. Generally speaking, the deprotonation and alkylation of weakly acidic C(sp³)–H bonds is accomplished using stepwise treatment with alkyllithiums followed by the addition of an alkyl halide. However, section 4.2.1 mentions numerous limitations ascribed to the unimetal superbase. The dissertation author wishes to return to this notion of base and alkyl halide incompatibility, highlighting the missed opportunities that stem from it. For example, the development of a C–H alkylation protocol that enables in-situ dialkylation through use of a dielectrophile is not feasible with stepwise protocols. The development of such a method would enable rapid access to spirocycles residing in unexplored chemical space. Another missed opportunity concerns the use of transiently stable carbanions – species that are short-lived in solution. Many of these transiently stable species decompose faster than they can react in the classical stepwise protocol using alkyllithiums.⁴ A solution to these key challenges lies in identifying a strong base that is compatible with alkyl halides. Given the clear synthetic opportunity these reactions present it begs the questions, where are the contemporary base-mediated C(sp³)–H alkylation reactions?

Section 4.4 | Research goals

As mentioned in Section 4.2 (*vide supra*) the high reactivity associated with n-BuLi can result in poor chemo and regioselectivity and has led to the use of functional-group tolerant bases to perform C–H functionalization reactions. Despite this, all the existing base-mediated C–H alkylation reactions – that use alkyl halides as electrophiles – involve stoichiometric deprotonation and subsequent quenching with the alkyl halide. Given its compatibility with alkyl halides, the use of TMDSO and KO^tBu to perform the C–H alkylation of weakly acidic species could be envisioned and would thereby obviate the need for a one-step protocol. A hopeful side-effect of studying this transformation would be to engage weakly acidic species in dialkylation reactions – a current limitation in organic synthesis. Finally, the dissertation author was intrigued by the role played by TMDSO in this transformation and hoped to uncover it. Herein lies the C–H alkylation of weakly acidic C–H bonds using TMDSO and KO^tBu as an alkylhalide compatible base.

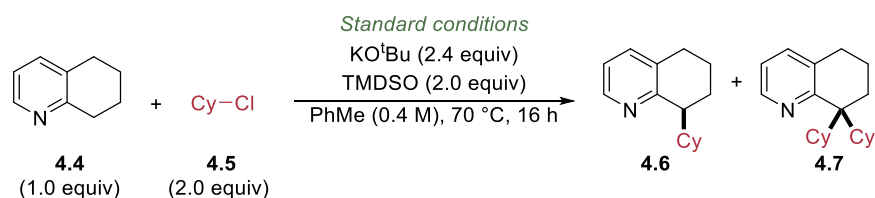
Section 4.5 | Results and discussion

4.5.1 | Reaction optimization

The study began with optimizing the C–H alkylation of 5,6,7,8-tetrahydroquinoline (**4.4**) using **4.5** as an electrophile to form **4.6** and **4.7** (Table 4.1). The dissertation author identified **4.4** (1.0 equiv), **4.5** (2.0 equiv), TMDSO (2.0 equiv), KO^tBu (2.4 equiv) in PhMe, at 70 °C as being the optimal reaction conditions (Table 4.1, entry 1); the findings of the reaction optimization are discussed herein. Swapping KO^tBu for KHMDS led to a high yield of 79% (entry 2). Owing to its low cost, KO^tBu was kept as the optimal base noting KHMDS as a suitable alternative if needed. Using potassium ethoxide (KOEt) resulted in the formation of **4.6** in 51% yield and **4.7** in 23% yield (entry 3). KHMDS has been shown to facilitate the deprotonation and functionalization of weakly acidic C–H bonds well above its pK_a which is thought to be a result of π -cation interactions.^{17,19} Surprisingly, using KO^tBu or KHMDS in the absence of TMDSO resulted in no

product detection and the recovery of **4.4** (entry 4). This suggested that not only are KO^tBu and KHMDS incapable of facilitating this transformation on their own, but also that TMDSO likely plays a key role in this transformation. The use of sodium *tert*-butoxide (NaO^tBu) or sodium hexamethyldisilazide (NaHMDS) similarly led to recovered starting material hinting at a key role played by K⁺ (entry 5). Increasing the temperature led to diminished yields of **4.6** and higher quantities of **4.7** (entries 6-8). Etheral solvents including tetrahydrofuran (THF) and 1,4-dioxane led to significantly higher amounts of **4.7** reaching 18% and 20%, respectively (entries 9 & 10). Finally, in-line with chapters 2 and 3 of this dissertation trialkylsilanes were ineffective when used in place of TMDSO (entries 11 & 12).

Table 4.1: Key parameters screened in the C–H alkylation reaction



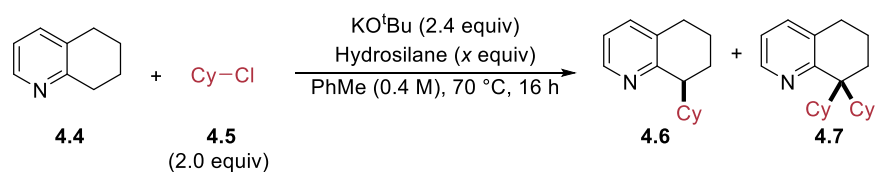
Entry	Change to Standard Conditions	% yield 4.6	% yield 4.7
1	none	85	3
2	KHMDS instead of KO ^t Bu	79	0
3	KOEt instead of KO ^t Bu	51	23
4	KHMDS or KO ^t Bu without TMDSO	0	0
5	NaO ^t Bu or NaHMDS instead of KO ^t Bu	0	0
6	80 °C instead of 70 °C	60	12
7	90 °C instead of 70 °C	64	13
8	100 °C instead of 70 °C	55	15

9	1,4-dioxane instead of PhMe	54	20
10	THF instead of PhMe	47	18
11	ⁱ Pr ₃ SiH (4.0 equiv)	0	0
12	Et ₃ SiH (4.0 equiv)	0	0

% yields were calculated using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Numerous hydrosilanes were screened in the reaction (**Table 4.2**). Using TMDSO led to an 85% yield of **4.6**, with only 3% dialkylation occurring. Testing related alkoxy silanes and analogues of TMDSO led to diminished yields of **4.6** and similarly low quantities of the dialkylated product **4.7** (**entries 2-4**). Triphenylsilane (Ph₃SiH) and phenyldimethylsilane (PhMe₂H) similarly produced moderate yields of **4.6** in 50% and 52%, respectively, with small quantities of **4.7** being formed (**entries 6-7**). Overall, the identity of the silane doesn't appear to contribute heavily to the amount of **4.7** formed in the reaction.

Table 4.2: Hydrosilanes screened in the C–H alkylation reaction



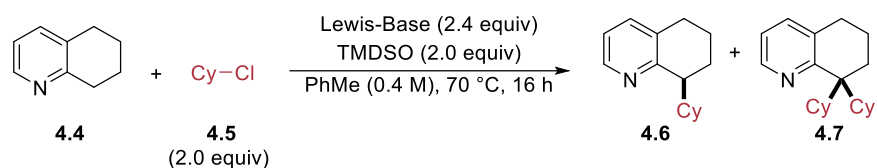
Entry	Hydrosilane	% yield 4.6	% yield 4.7
1	omit TMDSO	0	0
2	TMDSO (2.0 equiv)	85	3
3	(EtO) ₃ SiH (4.0 equiv)	35	trace

4	Me ₃ SiOSiH ₂ OSiMe ₃ (2.0 equiv)	65	6
5	Me ₃ SiOSiMe ₂ H (4.0 equiv)	71	trace
6	PhSiH ₃ (1.5 equiv)	50	3
7	PhSiMe ₂ H (4.0 equiv)	52	0

% yields were calculated using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Numerous Lewis bases were screened in the reaction (**Table 4.3**). Removal of the Lewis base led to no reaction (**entry 1**). Using potassium hydroxide (KOH) led to a low yield of **4.6** which the dissertation author attributes to trace water being present in the KOH (**entry 2**). KH was used alongside TMDSO and led to a 6% yield of **4.6** and no signs of **4.7** being formed in the transformation (**entry 3**). Interestingly, using KH in the absence of TMDSO resulted in 21% of **4.6** with no dialkylation taking place (**entry 4**). Metal fluoride salts (**entries 5 & 6**) and lithium Lewis bases were unreactive (**entries 7 & 8**).

Table 4.3: Lewis bases screened in the C–H alkylation reaction



Entry	Lewis base (2.4 equiv)	% yield 4.6	% yield 4.7
1	Omit the Lewis base	0	0
2	KOH	5	0
3	KH	6	0
4	Omit TMDSO and use KH	21	0
5	KF	0	0

6	CsF	0	0
7	LiHMDS	0	0
8	LiO ^t Bu	0	0

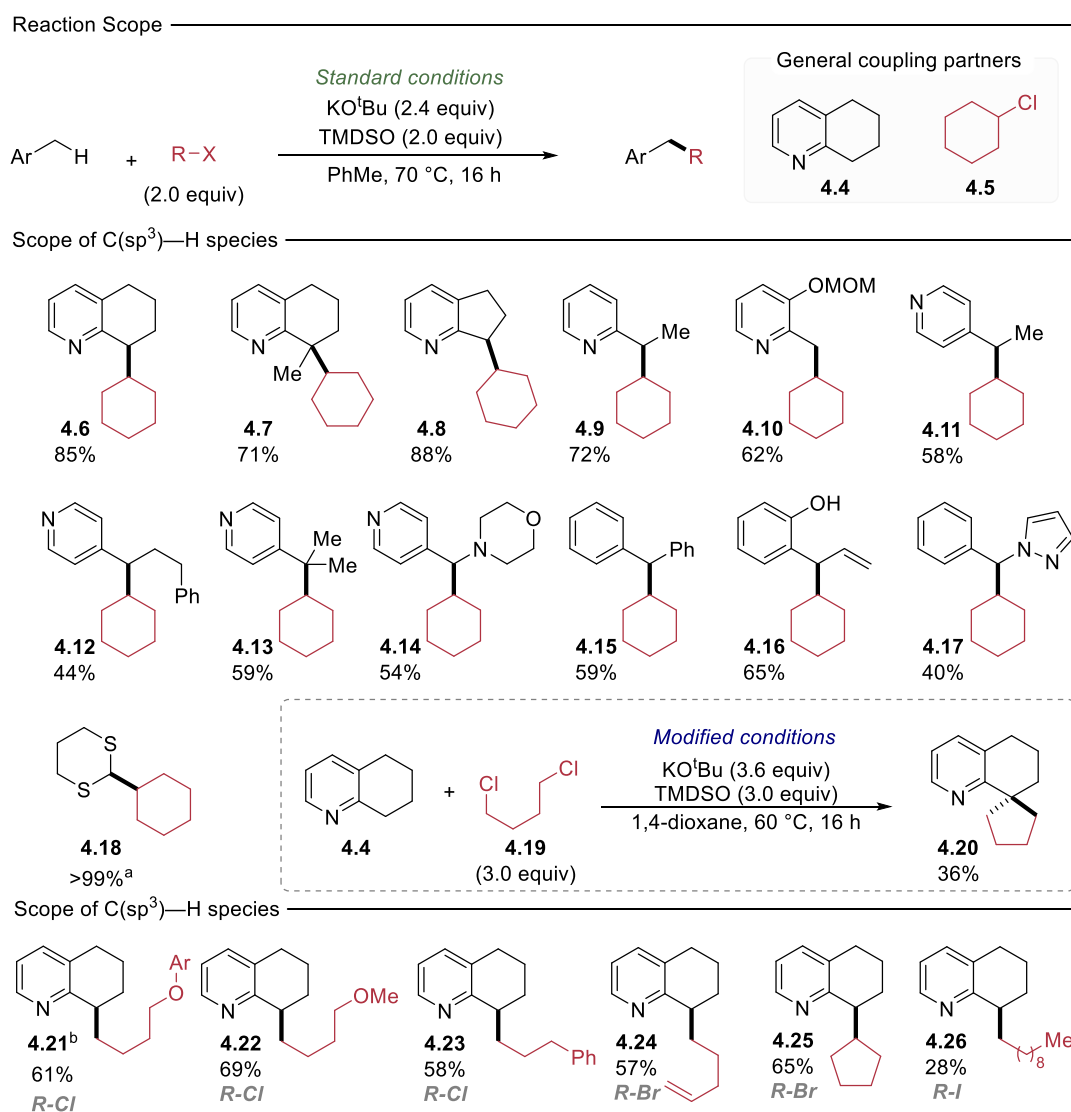
% yields were calculated using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

4.5.2 | Reaction scope

Having optimized the reaction using 5,6,7,8-tetrahydroquinoline **4.5** as the target substrate, the scope investigation began with the exploration of related alkylpyridine species as substrates (**Scheme 4.10**). Pyridylic methine C–H bonds could be alkylated, affording **4.7** in 71% yield and furnishing a quaternary carbon center. Alkylation of a 6,5 fused bicyclic pyridine scaffold proceeded smoothly resulting in 88% of **4.8**. Investigating acyclic alkylpyridines showed 2-ethylpyridine (**4.9**) to undergo alkylation in 73% yield and MOM-protected 2-picoline (**4.10**) in a slightly diminished yield of 62%. 4-Alkylpyridines were amenable to the reaction conditions albeit in much lower yields to their 2-alkyl substituted counterparts providing **4.11–4.14**, in yields of 44–59%. Non-pyridine scaffolds were then explored. Simple diphenylmethane was alkylated in 59% yield (**4.15**), and 2-allylphenol underwent regioselective benzylic alkylation in 65% yield (**4.16**). Notably, the phenol was left untouched and the alkene terminus – which typically undergoes alkylation from the corresponding allyl lithium analogue – did not react.²⁴ Benzylpyrazole could be alkylated producing (**4.17**) albeit in a significantly lower yield of 40%. The low yields could be attributed to C–N bond cleavage as hydrosilanes and Lewis bases are well precedented to reduce such functional groups.²⁵ Finally, alkylation of 1,3-dithiane produced **4.18** in near quantitative yield. A slight modification of our standard conditions enabled the in-situ dialkylation of **4.4** producing spirocycle **4.20** in 37% yield.

By investigating the scope of alkyl halides, it was found that alkyl chlorides bearing aryl and alkyl ethers underwent C–H alkylation smoothly producing **4.21** and **4.22** in yields of 61% and 69%. Alkyl halides bearing a primary substitution were used in this reaction to synthesize **4.23–4.25** resulting in modest yields of 57–65%. Lastly, the use of iododecane led to **4.26** in a low yield of 28% and large quantities of decane detected via gas chromatography-mass spectrometry (GCMS) indicating hydrodehalogenation had taken place.

Scheme 4.10: Reaction scope of weakly acidic C(sp³)–H arenes and alkyl halides

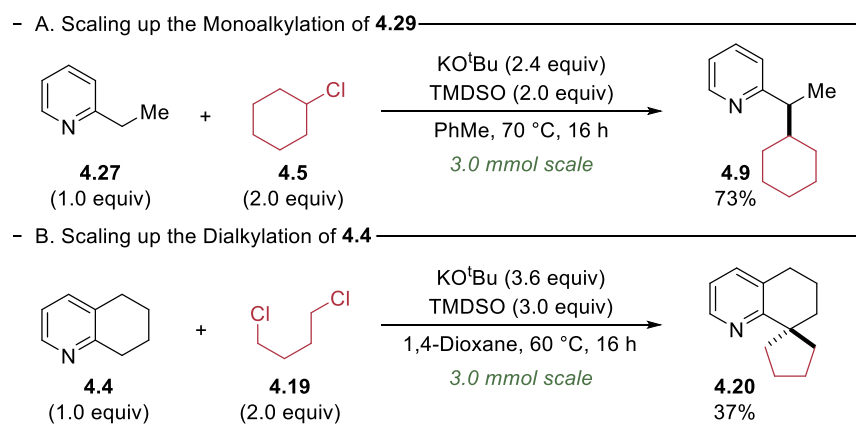


Standard conditions: Substrate (0.2 mmol), alkyl halide (0.4 mmol), TMSO (0.4 mmol), and KO^tBu (0.48 mmol) in PhMe (0.4 M), % yields are isolated. ^aUsed TMSO (3.0 equiv) and KO^tBu (3.6 equiv). ^bAr = 2-naphthyl.

4.5.3 | Reaction scale-up and safety considerations

To demonstrate the applicability of this synthetic method, the reaction was scaled up. The synthesis of **4.9** was scaled up from 0.2 mmol to 3.0 mmol to compare the two yields. Based on the findings in section 3.7.2 of chapter 3 that suggests the reaction yield is impacted by the headspace and pressure, this scale up was conducted in a pressure tube. This resulted in a 73% yield when conducted on a 3 mmol, consistent with yield obtained on a 0.2 mmol scale (**Scheme 4.10**). It was noted in section 3.7.2 of chapter 3 that scaling up this reaction is dangerous owing to the intense evolution of dimethylsilane (Me_2SiH_2) that occurs and its associated properties.²⁶ The author stands by these comments on safety and conducted this experiment in a pressure tube with the following justifications: this reaction is performed at a lower temperature, with a lower loading of TMDSO and KO^tBu , and was conducted on a lower scale (3 mmol here vs 8 mmol in chapter 3). The scale-up was conducted with the use of a blast shield. Following the successful synthesis of **4.27**, the synthesis of **4.20** was scaled up following the same protocol but with slightly modified conditions (**Scheme 4.11**).

Scheme 4.11: Reaction scale-up

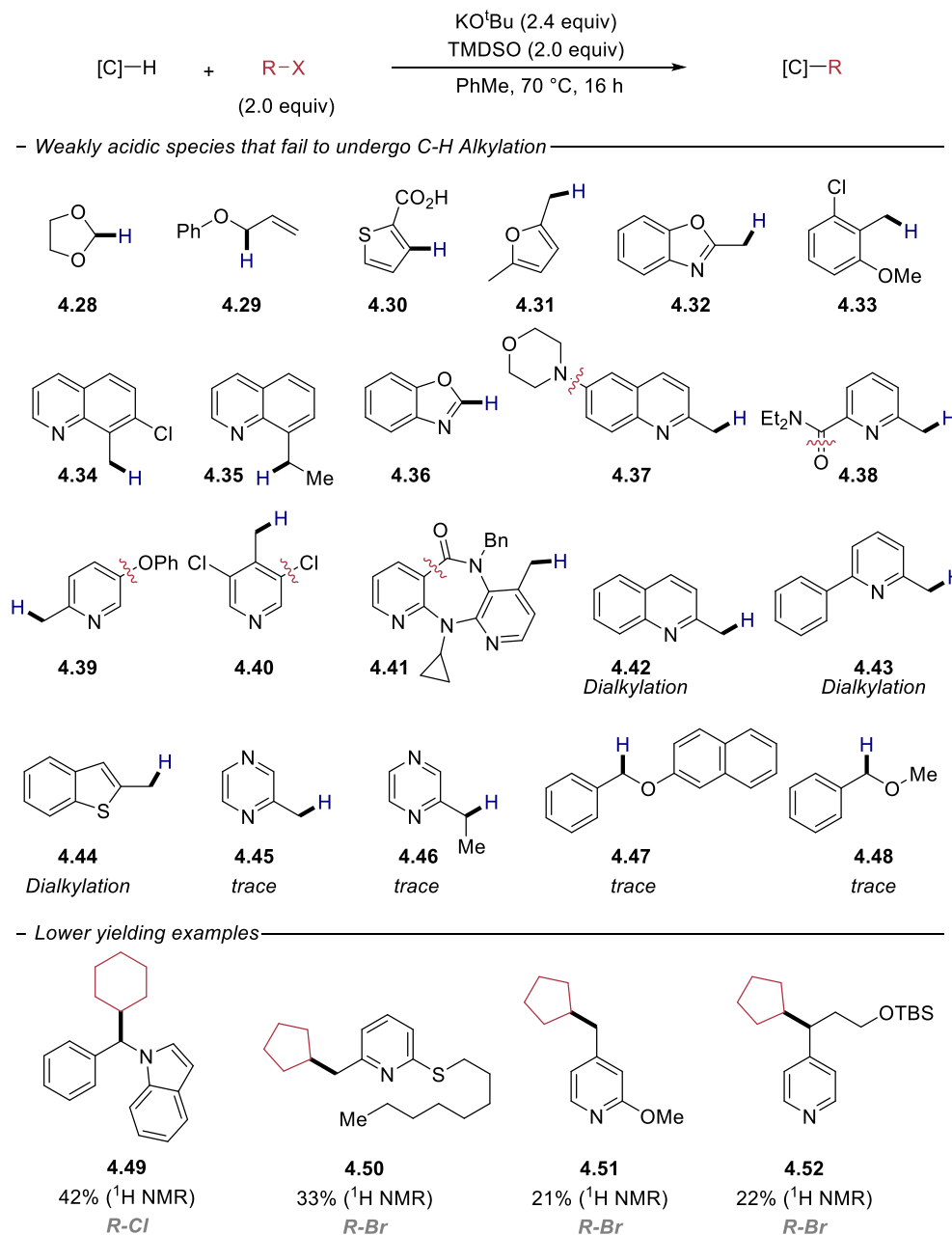


4.5.4 | Limitations of the scope

Throughout the scope investigation many weakly acidic C–H containing species and electrophiles were tested. Many of these examples led to reactions with undesirable outcomes and will be discussed in this section.

When investigating which weakly acidic C–H bonds could be alkylated, many substrates including **4.28-4.36** failed to undergo the C–H alkylation reaction and instead led to their recovery (**Scheme 4.12**). Many compounds were found to undergo C–H alkylation alongside undesired side reactions (**4.37-4.41**). Substrate **4.37** underwent hydrodeamination, **4.4** led to a mixture of several products attributed to hydride reduction of the amide, **4.39** underwent hydrodeoxygenation of its phenoxide substituent, **4.40** underwent hydrodechlorination, and **4.41** decomposed through an unidentified pathway. Many substrates were reactive towards C–H alkylation and underwent dialkylation as the major product **4.42-4.44**, while other substrates were reactive but only in trace quantities (**4.45-4.48**). Finally, select substrates underwent monoalkylation in lower yields **4.49-4.52** with **4.49** being particularly challenging to separate.

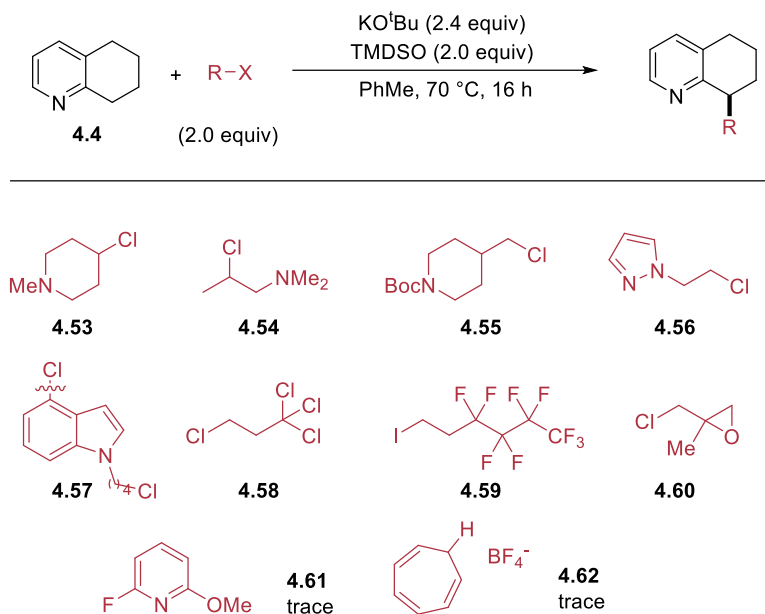
Scheme 4.12: Failed or otherwise challenging examples of weakly acidic species to isolate



A small subset of alkyl electrophiles was tested in the C–H alkylation reaction leading to undesirable outcomes (**Scheme 4.13**). Substrates **4.53–4.56** all shut down the reaction which we attribute to the Lewis basic nature of amines. Substrate **4.57** was reactive under the conditions but also underwent hydrodechlorination leading to a mixture of products. Substrates **4.58–4.60** were

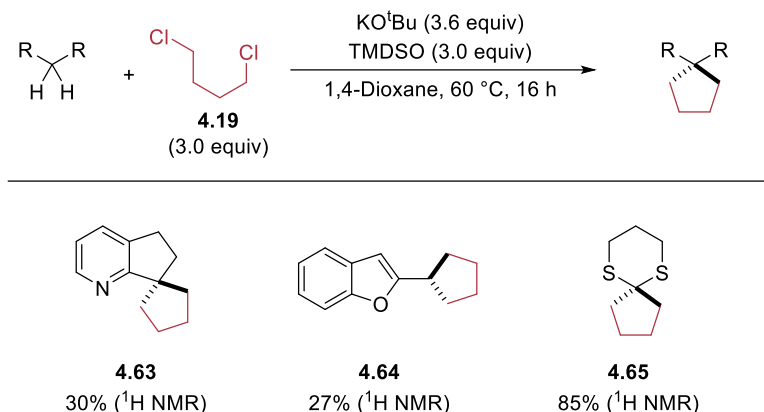
not recovered after the reaction likely due to volatility or decomposition. Finally, substrates **4.61** and **4.62** reacted in trace yield to afford the C–H arylation and C–H tropylation products, respectively.

Scheme 4.13: Electrophiles that failed to undergo C–H alkylation



The development of an in-situ dialkylation reaction to synthesize spirocycles from weakly acidic C–H species is a highly attractive reaction. After synthesizing and isolating product **4.20** in 37% yield other substrates were screened to determine which species were amenable to the dialkylation reaction (**Scheme 4.14**). Products **4.63** and **4.64** were formed in low yields of 30% and 27%, respectively, while product **4.65** could be synthesized in 85%. Although these are low yielding, apart from product **4.65**, this represents an exciting direction to take this chemistry and nonetheless serves to highlight the potential had from the compatibility of TMDSO and KO^tBu with alkyl halides. This will be further elaborated upon as a future direction (see section 4.6.1).

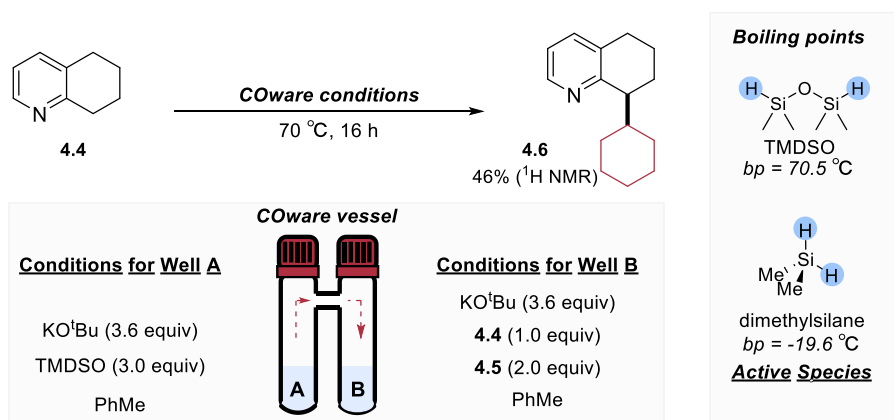
Scheme 4.14: Preliminary substrate screening of in-situ dialkylation



4.5.5 | COware experiment

Based on the findings outlined in section 3.6.3 of chapter 3, the author of this dissertation wanted to confirm that Me₂SiH₂ was not only forming in the reaction, but that it was the species of hydrosilanes responsible for the C–H alkylation taking place. To do this, **4.6** was synthesized by mixing KO^tBu, TMDSO, and PhMe in well A of the COware apparatus and **4.4**, **4.5**, KO^tBu, and PhMe in well B (Scheme 4.15). Product **4.6** was detected in 46% yield based on ¹H NMR spectroscopy and it was concluded that Me₂SiH₂ is the hydrosilane species responsible for reactivity.

Scheme 4.15: Confirming the formation of Me₂SiH₂ using COware

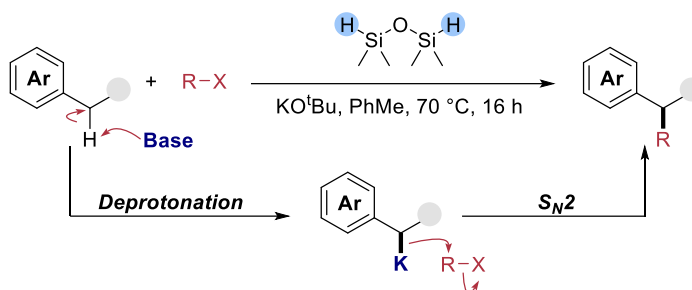


4.5.6 | Mechanistic investigation

4.5.6.1 | Substrate probes: identifying a reactive intermediate

At the beginning of the mechanistic investigation, it was hypothesized that the reaction proceeds through deprotonation of the weakly acidic C–H bond to form an organopotassium species which can engage in an S_N2 reaction with the alkyl electrophile (**Scheme 4.16**).

Scheme 4.16: Mechanistic hypothesis



This hypothesized was investigated by synthesizing and using 2-pyridyl potassium (**4.66**) as a nucleophile in the reaction which led to the formation of **4.67** in 21% yield (**Scheme 4.17**). Comparing this to the standard reaction conditions and using **4.68**, a similar yield of 29% was obtained. This result indicates a high likelihood that organopotassium species are reactive intermediates of this transformation and form through deprotonation of the pyridylic proton.

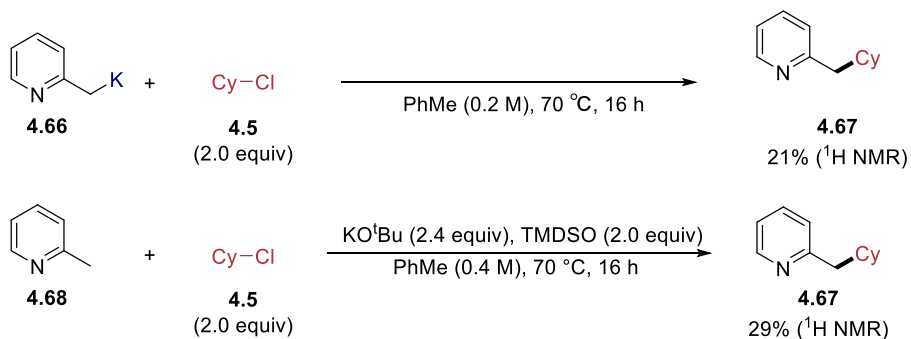
Next, pyridylsilane was considered as a plausible intermediate. Silylation of aromatic and benzylic C–H bonds is known to occur in the presence of hydrosilanes and Lewis bases.²⁷ Furthermore, benzylsilanes and Lewis basic metal salts have been used as pronucleophiles in arylation reactions.²⁸ To test this hypothesis **4.69** was subjected to the reaction conditions and **4.70** was isolated in 70% yield, alongside 7% de-silylation confidently ruling out its role as an intermediate in the reaction (**Scheme 4.17B**).

There are many instances of KO^tBu facilitating benzylic C–H functionalization with evidence that these transformations proceed through a benzylic radical intermediate.^{29,30} To

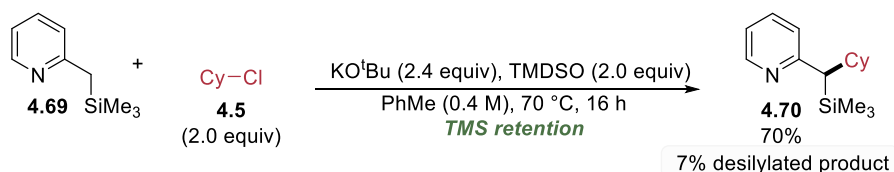
investigate the possibility of an operative analogous mechanism cyclopropyl-ring bearing substrate **4.71** was tested (**Scheme 4.17C**). No ring-opened products were detected and instead **4.72** was isolated as the sole product in 48% yield. Taken together this data best supports the formation of pyridyl potassium as a reactive intermediate, which is suspected to form through deprotonation. Taking it a step further, substrate **4.73** was tested as a single diastereomer and afforded product **4.74**. 2D NMR analysis showed stereoinversion occurred at the alkyl halide carbon, which is consistent with an S_N2 mechanism, further strengthening the hypothesis outlined in (**Scheme 4.17D**).

Scheme 4.17: Probing reactive intermediates

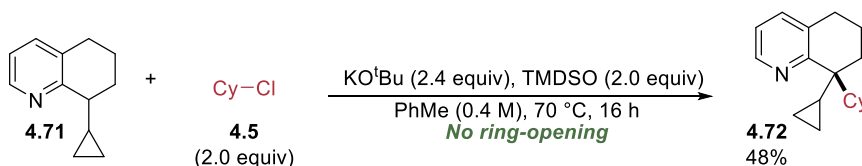
A. Comparing our conditions to the direct use of pyridyl potassium



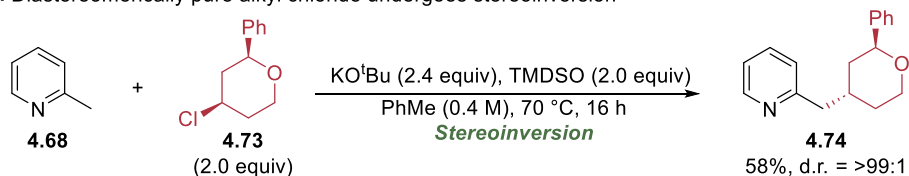
B. Probing benzylsilane as a reactive intermediate



C. Probing a benzylic radical as a reactive intermediate



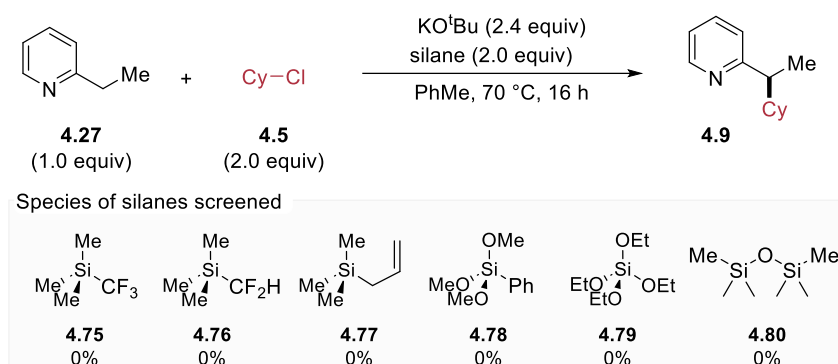
D. Diastereomerically pure alkyl chloride undergoes stereoinversion



4.5.6.2 | Investigating the role of TMDSO and KO^tBu

Based on the gathered evidence from testing substrate probes, it was speculated the reaction proceeds through deprotonation of the pyridylic position. However, it was noted early on that KO^tBu doesn't facilitate this transformation on its own and instead requires TMDSO. The identity of the active base, and the role played by Me₂SiH₂ – the active hydrosilane in this transformation (see **Scheme 4.16**) – was therefore questioned. Many examples of pyridine functionalization have been facilitated through the activation of the nitrogen lone-pair, which brings into question whether Me₂SiH₂ was acting as a Lewis acid in this transformation.³¹⁻³³ To answer this question, various silanes were screened as Lewis acids resulting in no formation of **4.9** (**Scheme 4.18**). A noteworthy observation is only hydrosilanes can facilitate this transformation. Using silanes **4.75-4.80** led to no C–H silylation. Worth highlighting is the failure of **4.79** and **4.80** to promote the transformation when their hydrosilanes counterparts – triethoxysilane ((EtO)₃SiH) and TMDSO – enable C–H alkylation in moderate to high yield (see **Table 4.2**).

Scheme 4.18: Screening silanes as mild Lewis acids



Next, the possibility that Me₂SiH₂ enhances the basicity of KO^tBu through disruption of its aggregates was considered. In non-polar solvents, KO^tBu aggregates forming a tetramer which has a pK_a of approximately 17. Known chelators of potassium ions (K⁺) including DMSO, DMPU, and 18-crown-6 are proposed to disrupt the KO^tBu tetramer and sequester K⁺, rendering *tert*-

butoxide significantly more reactive.^{34,35} One hypothesis is that Me_2SiH_2 sequesters K^+ rendering *tert*-butoxide more basic. To test this hypothesis the synthesis of **4.6** was attempted using known aggregate disruptors DMSO, DMPU and 18-crown-6, as substitutes for TMDSO (**Table 4.4**). No formation of **4.6** occurred using any of these species, and instead **4.4** was recovered. It was therefore concluded that *if* Me_2SiH_2 is enhancing the basicity of KO^tBu it is occurring through a pathway distinct from that of aggregate disruption.

Table 4.4: Investigating additives as alternatives to TMDSO

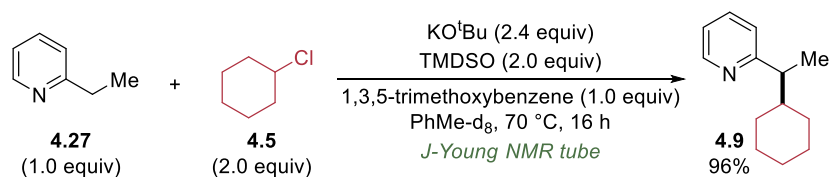


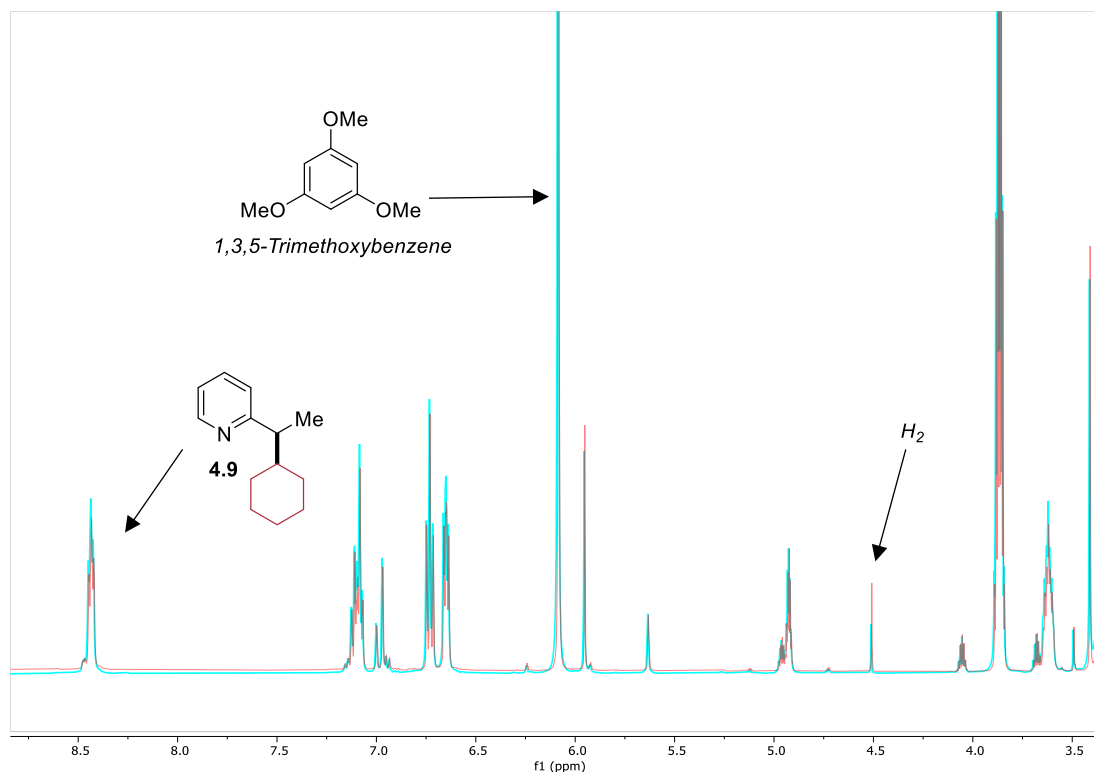
Entry	Change to the conditions above	% yield 4.6
1	none	85
2	DMSO (2.0 equiv) instead of TMDSO	0
3	Omit TMDSO, and using DMSO as solvent	0
4	DMPU (2.0 equiv) instead of TMDSO	0
5	Omit TMDSO, and using DMPU as solvent	0
6	18-crown-6 (2.0 equiv) instead of TMDSO	0

The importance of the Si–H bond of the hydrosilane was then brought into question rather than the silicon center itself. It’s been noted that hydrosilanes and Lewis bases can exhibit highly basic reactivity and – in the case of metal dihydridosilicate species – are suspected to decompose into the corresponding metal hydride based on research conducted in the early 1990s.³⁶ Moreover,

recent work by Murphy and coworkers demonstrated the Grubbs-Stoltz reagent was capable of reacting with amines to generate KH as an N–H silylation catalyst.³⁷ It was hypothesized that the Si–H bond, if reactive, would produce H₂ gas through the deprotonation of the pyridylic C–H bond. To investigate this, the alkylation of 2-ethylpyridine (**4.27**) was performed in a J. Young NMR tube and the reaction mixture was analyzed via ¹H nuclear magnetic resonance (NMR) spectroscopy (**Figure 4.1**). Formation of **4.9** was detected in 96% based on ¹H NMR yield alongside the detection of hydrogen gas (H₂) at 4.51 ppm – in agreement with literature values.³⁸ Degassing the NMR tube and analyzing the mixture resulted in a significant drop of the peak at 4.51 ppm (**Figure 4.1**). Notably, however, conducting the same experiment with the exclusion of **4.27** and **4.5** led to H₂ gas detection indicating that H₂ gas evolution may also occur as a byproduct of heating TMDSO and KO^tBu, making this result inconclusive (see Section 4.7.5.1).

Figure 4.1: H₂ gas evolution detected via ¹H NMR spectroscopy (Zoomed in)





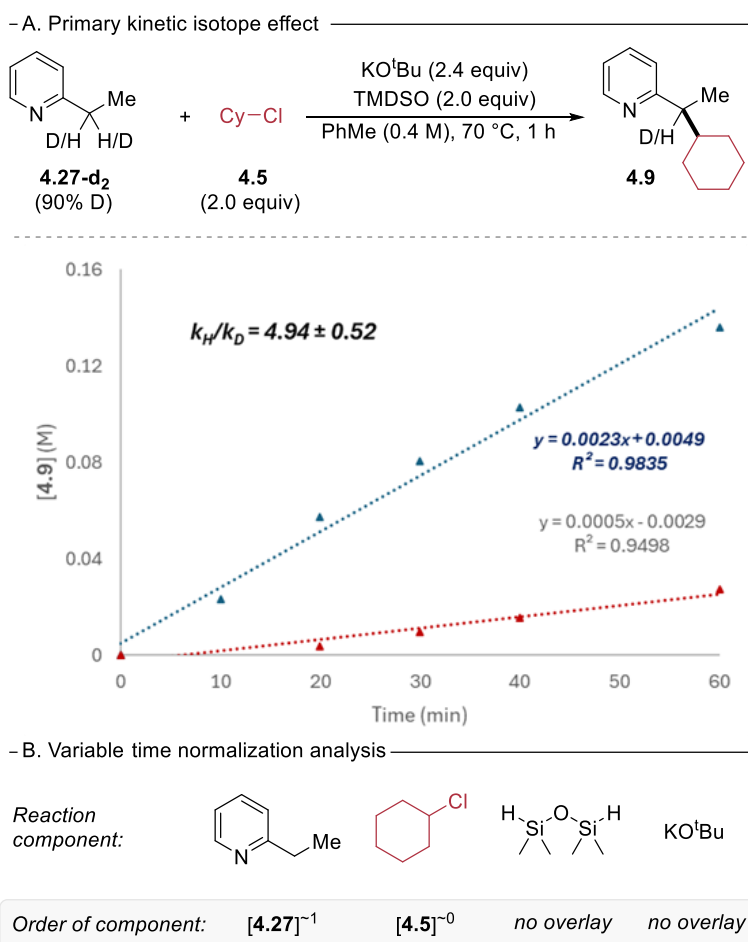
The pressurized spectrum is shown in red, whereas the degassed spectrum is shown in blue.

4.5.6.3 | Reaction kinetics: PKIE, vTNA, and alkyl halide decomposition kinetics

Following the mechanistic probes and the analysis of the role played by TMDSO and KO^tBu, the dissertation author was interested in studying the reaction kinetics of this transformation. Using 90% deuterium enriched **4.27-d₂** as a substrate, a primary kinetic isotope effect (PKIE) was measured (**Scheme 4.19A**). Measurement by independent rates indicated a large kinetic isotope effect of 4.94 ± 0.52 suggesting that deprotonation of **4.27** occurs *at or before* the rate determining step of the reaction. It should be noted that the true kinetic isotope effect (KIE) is likely to be larger given that **4.27-d₂** was enriched up to 90%, leaving 10% protium at the reactive site. Next, kinetic data was gathered, and variable time normalization analysis (vTNA) was applied at an attempt to determine the approximate order of each reaction component. (**Scheme 4.19B**). The vTNA was conducted, and an autovTNA calculator developed by Hii and coworkers was used to identify the best possible overlay for each reaction component.³⁹ The best overlay found for **4.27** and **4.5** were 1.037 and 0.286, respectively, which is approximated to a 1st order dependence

in **4.27** and a 0th order dependence in **4.5**. Under this approximation, the data indicates that **4.27** is likely involved at the rate determining step (RDS) of the reaction, while substrate **4.5** is not and does not likely appear in the rate equation. Taking the large PKIE into account, this data indicates a rate-determining deprotonation of **4.27**. Unfortunately, no reasonable overlay could be identified for TMDSO and KO^tBu and thus their participation in the rate determining step is unknown.

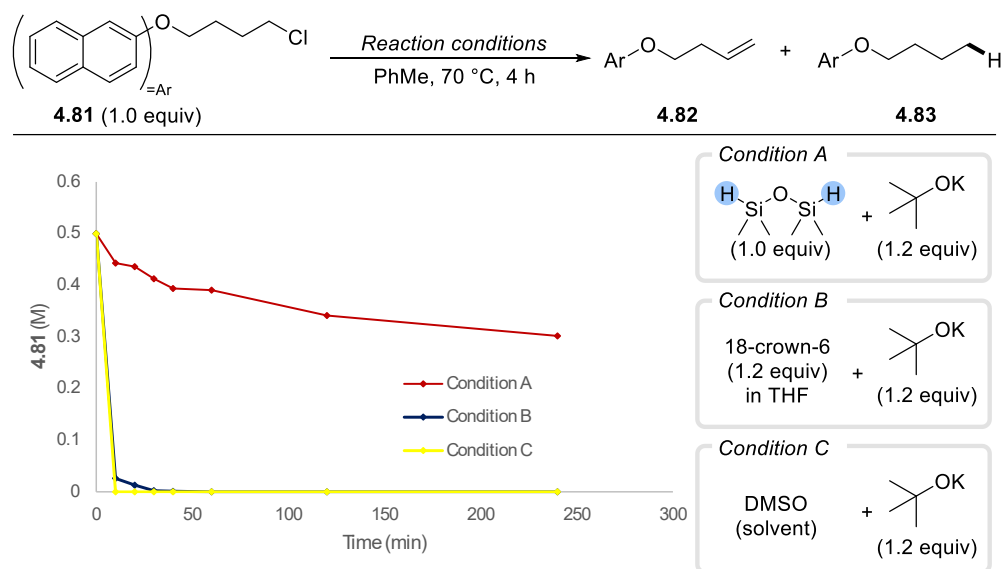
Scheme 4.19: Kinetic analysis: PKIE and vTNA



Alkyl halides are known to undergo E2-elimination with strong bases at elevated temperatures. Given that the conditions employ both a hydrosilane and a strong base, the stability of the alkyl halide was questioned and the dissertation author elected to monitor its concentration over time in the presence of TMDSO and KO^tBu. The concentration profile of the same alkyl

halide was compared to other kinetic runs utilizing KO^tBu and additives that are known to enhance the basicity of KO^tBu. Primary alkyl chloride **4.81** was selected for this study because it undergoes the desired transformation to give **4.21** in 61% yield under the standard conditions. The concentration of **4.81** was followed over time under three different conditions (**Scheme 4.20**). Under the standard conditions, **4.81** slowly underwent hydrodehalogenation, with only **4.83** being detected, consistent with earlier reports of hydrosilane- and Lewis base-mediated hydrodehalogenation of alkyl halides.³⁶ When 18-crown-6 (condition B) or DMSO (condition C) was combined with KO^tBu, **4.81** underwent near-quantitative consumption within 10 minutes (**Scheme 4.20**). Under these conditions, elimination to give **4.82** was the major byproduct, in addition to products derived from elimination of the naphtholate. No formation of **4.83** was detected. These observations suggest the reason that 18-crown-6 and DMSO do not facilitate the desired C–H alkylation reaction (see **Table 4.4**) is due to competitive base-induced alkyl halide degradation. By contrast, TMDSO places KO^tBu in a “Goldilocks” zone — the active base is sufficiently reactive to promote C–H alkylation but mild enough to tolerate the alkyl halide electrophile.

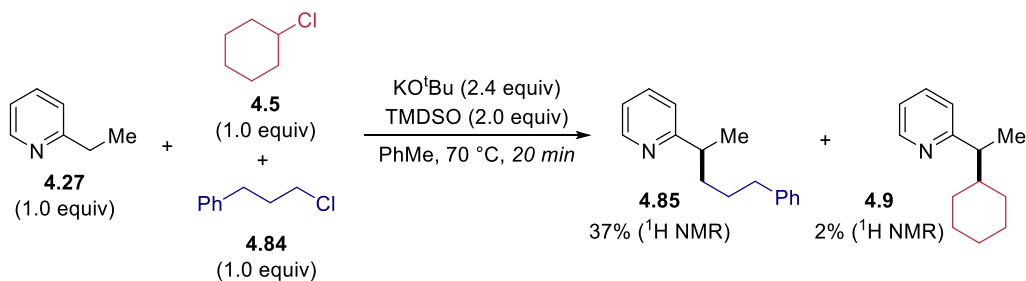
Scheme 4.20: Monitoring base-induced alkyl halide decomposition over time



4.5.6.4 | Competition experiment

The relative rate of reactivity between a primary and secondary alkyl halide as an electrophile was then brought into question. A competition experiment was conducted using a secondary cyclic alkyl chloride (**4.5**) and a primary acyclic alkyl chloride (**4.84**). Product **4.85** was detected in 37% yield when compared to **4.9** forming in a mere 2% (**Scheme 4.21**). This indicates a near 20-fold difference in relative rates of reactivity between the two alkyl halides.

Scheme 4.21: Competition experiment

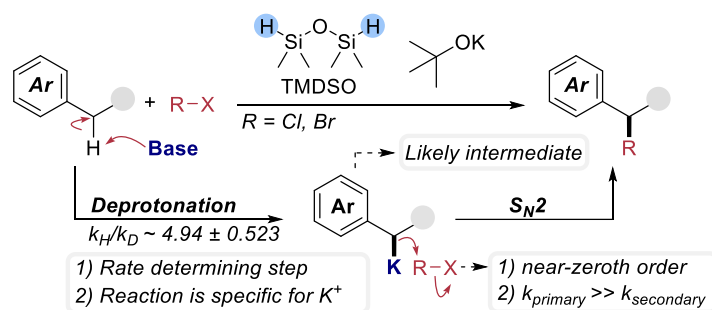


4.5.6.5 | Proposed reaction mechanism

Drawing on the data described thus far, a mechanism can be proposed (**Scheme 4.22**). The reaction likely proceeds through deprotonation of the weakly acidic C–H bond to generate an

organopotassium species which can engage in a subsequent S_N2 reaction with the alkyl electrophile. A large PKIE of 4.94 ± 0.52 and a near-zeroth-order dependence on the alkyl halide electrophile and a positive first-order dependence on 2-ethylpyridine indicates that deprotonation is likely the rate-determining step. Based on the evidence suggesting the Si–H bond in TMDSO is essential for reactivity, and the many reports of pentavalent hydrosilanes species producing KH, it is currently speculated that KH is the active base in this transformation.³⁶ Further experimentation, however, is required to confidently assign an identity to the species of active base.

Scheme 4.22: Proposed reaction mechanism



Section 4.6 | Conclusion

In conclusion an in-situ C–H alkylation of weakly acidic $C(sp^3)$ –H containing species has been developed. Various substrates including 2-alkyl pyridines, 4-alkyl pyridines, and select benzylic species were alkylated in low to high yields using alkyl chlorides, bromides, and iodides as electrophiles. The reaction was applied to spirocyclization of 5,6,7,8-tetrahydroquinoline (**4.4**) using 1,4-dichlorobutane (**4.19**) as a dielectrophile, showcasing these systems unique compatibility with alkyl halides can be applied in organic synthesis. Mechanistic data is consistent with a rate-determining deprotonation step followed by alkylation of an organopotassium species. Although the active base wasn't fully characterized, it is suspected that TMDSO and $KOtBu$ react to release solubilized KH and thus represents a convenient alternative to the direct handling of KH.

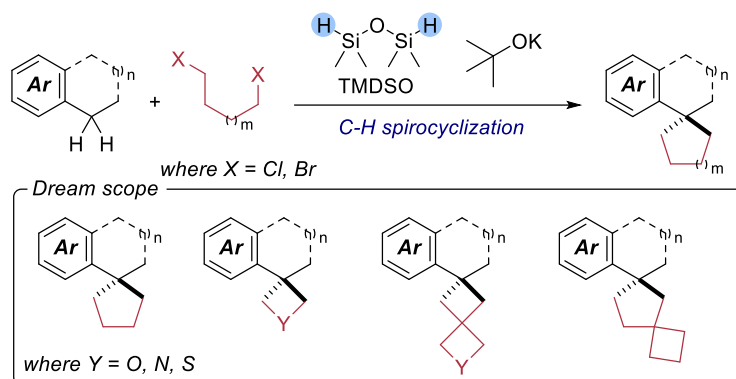
Further studies to uncover the identity of the active base and further exploit this chemistry are underway.

4.6.1 | Future directions

Calling back to the introduction of chapter 4; the notion of base and alkyl halide compatibility would unlock useful synthetic transformations. Given the rarity of strong bases that are compatible with alkyl halides and that TMDSO and KO^tBu possess such a quality, the future directions should capitalize on this.

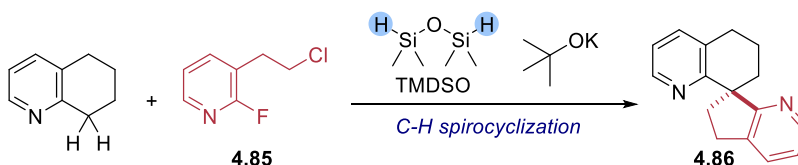
Given the importance of spirocycles to the medicinal chemistry sphere, methods to garner access to these species is of great importance.^{40,41} While there are numerous ways to synthesize spirocycles in the literature, many of these transformations are labour intensive requiring multiple synthetic steps.⁴² Moreover, many of these transformations hinge on the deprotonation of enolizable protons and require the preinstallation of a tethered reactive functional group rather than forming two bonds in one step.⁴³⁻⁴⁵ Irrespective of this, the use of dihaloalkanes and bases to perform spirocyclization at positions bearing a pK_a of 30 or greater are exceedingly rare if not unheard of. Given the synthesis of **4.20** in 37% yield using preliminary conditions for C–H dialkylation, one can envision the use of TMDSO and KO^tBu to synthesize spirocycles from weakly acidic benzylic C–H bonds (**Scheme 4.23**). Initial screening shown in **Scheme 4.14** suggests these conditions are not specific to pyridylic C–H bonds and could be applied to many other weakly acidic C–H species. Furthermore, derivatization of these products would provide rapid access to functionalized spirocycles. This reaction, if developed, would be a powerful synthetic methodology to synthesize spirocycles from abundant materials in a single step.

Scheme 4.23: In-situ C–H dialkylation of weakly acidic species



Another exciting direction would be to investigate dielectrophiles bearing two different species of electrophile on either end (**Scheme 4.24**). For instance, substrate **4.85** bearing an alkyl halide tethered to 2-fluoropyridine could be envisioned to undergo in-situ alkylation and a nucleophilic aromatic substitution reaction ($\text{S}_{\text{N}}\text{Ar}$) reaction to afford a the corresponding spirocycle **4.86**. Not only would this provide access to more interesting spirocycles and thus be of synthetic importance, but it would provide the opportunity for an in-depth mechanistic analysis of the reaction and therefore offers the chance for a deeper mechanistic understanding of TMDSO and KO^tBu .

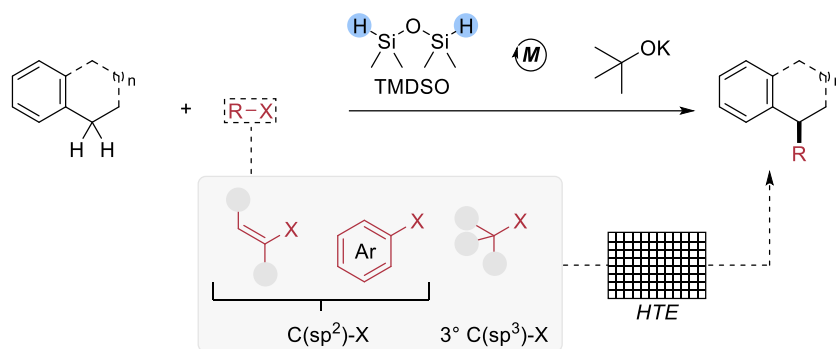
Scheme 4.24: In-situ C–H dialkylation of weakly acidic species using asymmetric dielectrophiles



The transition metal-catalyzed C–H monofunctionalization of weakly acidic species has been thoroughly investigated by Walsh and coworkers.¹³⁻¹⁷ Another direction of this research would be to utilize TMDSO and KO^tBu as a base to engage weakly acidic species in transition

metal-catalyzed C–H cross coupling reactions (**Scheme 4.25**). This would enable electrophiles that are unable to react in a direct alkylation reaction to be cross coupled with the weakly acidic species. For instance, an interesting class of electrophile to target could be tertiary alkyl halides, species bearing activated C(sp²)-O and C(sp³)-O bonds – species that cannot undergo direct substitution in C-H alkylation protocol discussed in chapter 4. The latter examples would provide a means to engage more abundant species in C-H functionalization reactions. This direction of research would benefit from high-throughput experimentation to identify which electrophiles would be suitable in the cross-coupling reaction.

Scheme 4.25: Synergistic TMDSO/KO^tBu and transition metal-catalyzed C–H difunctionalization of weakly acidic species



Section 4.7 | Experimental

4.7.1 | General experimental details

Unless stated otherwise, reactions were set up outside the glovebox under an atmosphere of N₂ using oven dried glassware. Column chromatography was performed manually and in some cases via Combi-flash Rf automated chromatography both using Silicycle F60 40-63 μm silica gel. Thin-layer chromatography was performed using aluminum-backed EMD Millipore Silica Gel 60 F₂₅₄ pre-coated plates. A UV lamp was used to visualize TLC plates.

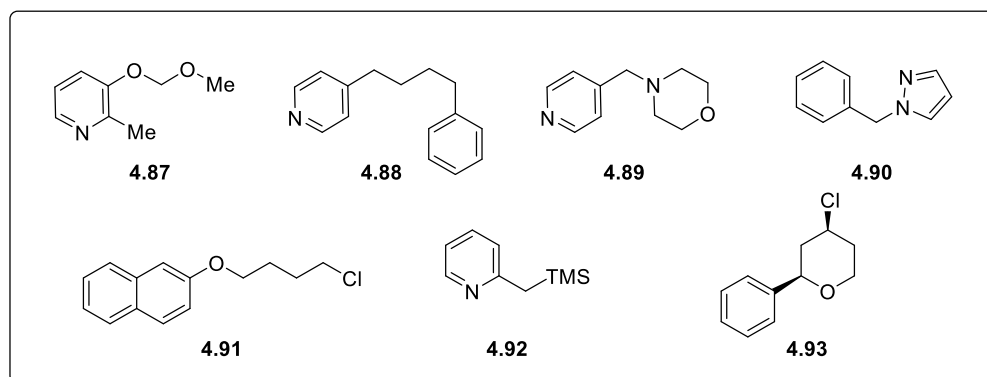
4.7.2 | Instrumentation

GCMS data was obtained using an Agilent Technologies 7890B GC with a 30 m x 0.25 mm HP-5 column. Accurate mass data (EI) was obtained from an Agilent 5977A GC/MSD using MassWorks 4.0 from CERNO Bioscience.⁴⁶ HRMS-EI data was obtained using a Kratos concept magnetic sector electron impact mass spectrometer. ¹H, ¹³C, and ¹⁹F NMRs were obtained using a Bruker Avance II 500 MHz spectrometer, or a Bruker Avance II 400 MHz spectrometer. ¹H NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. ¹H NMR spectra were calibrated using CDCl₃ (7.26 ppm) or PhMe-d₈ (2.09 ppm), ¹³C NMR spectra were calibrated using CDCl₃ (77.00 ppm). Reported NMR data is as follows: chemical shift (δ ppm), multiplicity (where s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants in Hz (where applicable), and relative proton integration.

4.7.3 | Materials

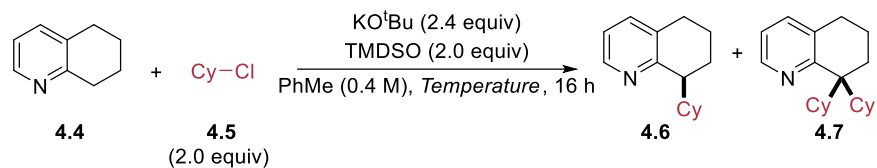
Organic solvents were degassed using nitrogen and were then filtered through a Puresolv solvent purification system (SPS) to remove water. Unless otherwise noted, starting materials were purchased from Combi-blocks and used as received. Potassium tert-butoxide (KO^tBu) (trace metal grade 99.8 %) was purchased from Oakwood chemicals. 1,1,3,3-Tetramethyldisiloxane (TMDSO), triethylsilane, triethylsilane, triisopropylsilane, potassium fluoride, and cesium fluoride were purchased from Sigma Aldrich. The following starting materials were synthesized according to literature protocols: **4.87**,⁴⁷ **4.88**,⁴⁸ **4.89**,¹⁶ **4.90**,⁴⁹ **4.91**,⁵⁰ **4.92**,⁵¹ **4.93**⁵² (**Figure 4.2**):

Figure 4.2: Starting materials synthesized according to literature protocols



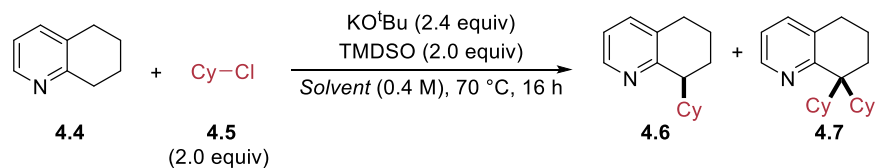
4.7.4 | Reaction optimization

Reaction Optimization: Reaction optimization was conducted in an N₂ filled glovebox. To an oven dried 1 dram screw cap vial equipped with a stir bar was added the corresponding base/additive. Next solvent (0.4 M) was added to the vial followed by **4.4** (0.2 mmol), and **4.5** (0.4 mmol). The hydrosilane was added and the vial was quickly sealed with a plastic screw cap and pierceable Teflon/silicone septum. The reaction vessel was placed in an oil bath that had been preheated to the desired temperature and allowed to stir for the indicated time. Once complete, the reaction mixture was removed from the oil bath and allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc, and then 1,3,5-trimethoxy benzene was added as a stock solution in PhMe. The solution was then filtered through silica with EtOAc using a 15 mL glass fritted funnel and subsequently concentrated using a rotary evaporator. The crude residue was then dissolved in CDCl₃ and analyzed via ¹H NMR spectroscopy. The % yield of the product was determined by integrating the peak at 8.42 ppm, which corresponds to the proton at C2 of **4.6** relative to the peak at 6.08 ppm on 1,3,5-trimethoxybenzene.

Table 4.5: Temperatures screened in the C–H alkylation reaction

Entry	Temperature °C	% yield 4.6	% yield 4.7
1	70	85	3
2	60	65	8
2	50	63	6
3	40	55	4
4	80	60	12
5	90	64	13
6	100	55	15

% yields were calculated using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

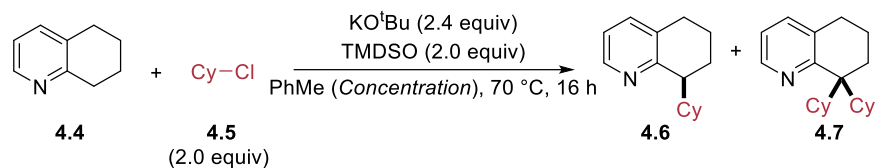
Table 4.6: Solvents screened in the C–H alkylation reaction

Entry	Solvent	% yield 4.6	% yield 4.7
1	PhMe	85	3
2	1,4-Dioxane	54	20
2	1:1 PhMe:1,4-Dioxane	56	16

3	THF	47	18
4	Benzene	65	Trace
5	CPME	61	15

% yields were calculated using ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Table 4.7: Concentrations screened in the C–H alkylation reaction

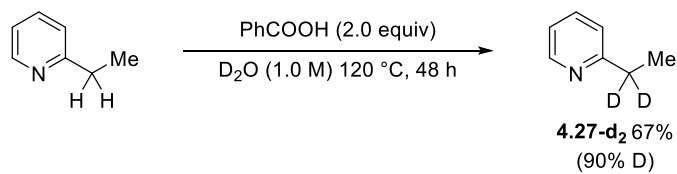


Entry	Concentration (M)	% yield 4.6	% yield 4.7
1	0.4	85	3
2	0.6	65	13
2	0.8	68	7
3	1.0	51	11
4	0.2	62	8
5	neat	38	9

% yields were calculated using ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

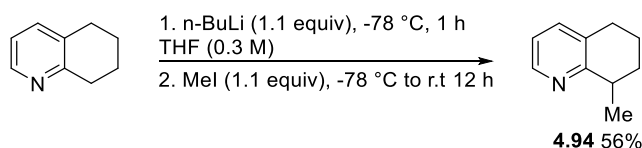
4.7.5 | Starting material synthesis

Synthesis of 2-(α,α -deutero)ethylpyridine:

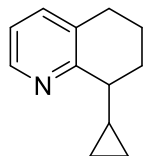


2-(α,α -deutero)ethylpyridine (**4.27-d₂**) was prepared according to a modified literature protocol.⁵³ To a oven dried pressure flask equipped with a stir bar was added benzoic acid (10.0 mmol), D₂O (5.0 mL), and 2-ethylpyridine (5.0 mmol). The reaction vessel was sealed, placed into a preheated 120 °C oil bath and stirred for 48 hours. The mixture was allowed to cool to ambient temperature, quenched with aqueous NaHCO₃, extracted with ethyl acetate, and dried over Na₂SO₄. The reaction was then filtered and concentrated to afford pure **4.27-d₂** as a beige oil (364.6 mg, 67%, 90% D). ¹H NMR (400 MHz, CDCl₃): δ_H 8.45 (d, J = 4.0 Hz, 1H), 7.53 (td, J = 7.7, 1.9 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.03 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 2.74 (qt, J = 7.7, 2.2 Hz, 0.11H), 1.22 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 163.5, 149.1, 136.6, 122.2, 121.1, 30.8 (t, J = 19.4 Hz), 13.9 ppm.

Synthesis of 8-Methyl-5,6,7,8-tetrahydroquinoline:



8-Methyl-5,6,7,8-tetrahydroquinoline (**4.94**) was prepared according to a modified literature protocol.⁵⁴ An oven dried round bottom flask equipped with a stir bar was purged using an N₂ balloon and a septum. Dry THF (0.3M) was taken from an SPS and added to the flask, followed by 5,6,7,8-tetrahydroquinoline (**4.4**) (3.0 mmol). The reaction vessel was submerged in an acetone/dry ice bath and cooled to -78 °C. n-BuLi (3.3 mmol) was added dropwise to the mixture and stirred for 1 hour. After 1 hour, iodomethane (3.3 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with H₂O, extracted with ethyl acetate, washed with brine, and dried over Na₂SO₄. The solution was filtered, concentrated, and the product isolated by automated column chromatography using a gradient of 0->20% of EtOAc in hexanes to afford **4.94** as a pale-yellow oil (248.5 mg, 56%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.39 (d, J = 4.8 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.01 (dd, J = 7.7, 4.7 Hz, 1H), 3.01 (sext, J = 6.8 Hz, 1H), 2.82-2.69 (m, 2H), 2.06-1.98 (m, 1H), 1.92-1.83 (m, 1H), 1.78-1.60 (m, 2H), 1.37 (d, J = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 161.3, 146.83, 146.8, 137.03, 137.0, 132.1, 121.0, 35.6, 31.3, 29.5, 21.5, 20.1 ppm.



8-Cyclopropyl-5,6,7,8-tetrahydroquinoline (4.95): Product **4.95** was prepared from 5,6,7,8-tetrahydroquinoline (3.0 mmol) and bromocyclopropane (3.3 mmol) according to the same procedure as **4.94**.⁵⁴ The crude material was purified via automated column chromatography using a gradient of 0->15% of EtOAc in hexanes to afford **4.95** as a yellow oil (370 mg, 71%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.42-8.41 (m, 1H), 7.37-7.35 (m, 1H), 7.07-7.02 (m, 1H), 2.85-2.70 (m, 2H), 2.31-2.26 (m, 1H), 2.03-1.85 (m, 3H), 1.82-1.74 (m, 1H), 1.06-0.97 (m, 1H), 0.68-0.55 (m, 2H), 0.47-0.40 (m, 1H), 0.28-0.21 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 160.1, 146.8, 136.9, 132.1, 121.3, 44.8, 29.0, 28.9, 19.7, 17.3, 5.5, 2.9 ppm.

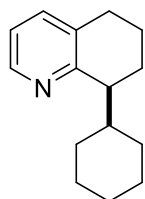
4.7.6 | General procedure and characterization data

General Procedure: The C-H alkylation of weakly acidic species. The synthesis of scope examples was conducted in an N₂ filled glovebox. To an oven dried 1 dram screw cap vial equipped with a stir bar was added KO^tBu (0.48 mmol). Next PhMe (0.4 M) was added to the vial followed by the weakly acidic species (0.2 mmol), and the desired alkyl halide (0.4 mmol). Note, if any other species were solid, they were be added before the addition of PhMe. TMDSO (0.4 mmol) was added to the mixture and the vial was quickly sealed with a plastic screw cap and pierceable Teflon/silicone septum. The reaction vessel was placed in an oil bath that had been preheated to the desired temperature and allowed to stir for the indicated time. Once complete, the reaction mixture was removed from the oil bath and allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc and filtered through silica gel with EtOAc using a 15 mL glass fritted funnel and subsequently concentrated using a rotary evaporator. The crude residue was then purified using flash column chromatography.

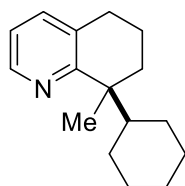
Optionally, to facilitate purification, prior to chromatography the crude mixture was sometimes treated with TBAF (1.0 M solution in THF, 0.7 mL). The mixture was then heated to 70 °C for 2 hours to breakdown the silicon oligomers. After 2 hours, the solution was cooled to room

temperature and filtered through silica with EtOAc using a 15 mL glass fritted funnel and concentrated using a rotary evaporator.

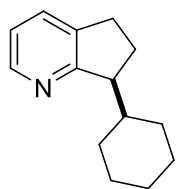
C–H Alkylation Product Characterization:



8-Cyclohexyl-5,6,7,8-tetrahydroquinoline (4.6): Product **4.6** was prepared from 5,6,7,8-tetrahydroquinoline (**4.4**) and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.6** as a colorless oil (36.9 mg, 85%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.42 (d, $J = 4.7$ Hz, 1H), 7.32-7.30 (m, 1H), 7.00-6.97 (m, 1H), 2.86-2.81 (m, 1H), 2.77-2.65 (m, 2H), 3.38-2.31 (m, 1H), 1.95-1.89 (m, 2H), 1.77-1.60 (m, 6H), 1.41-0.97 (m, 7H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 160.0, 146.8, 136.6, 133.5, 120.5, 46.0, 41.5, 31.7, 29.7, 27.9, 27.1, 26.9, 26.89, 24.2, 21.8 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{15}\text{H}_{21}\text{N}$: 215.1669; found: 215.1745. Spectral accuracy: 97.3%

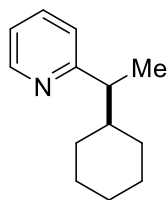


8-Methyl-8-Cyclohexyl-5,6,7,8-tetrahydroquinoline (4.7): Product **4.7** was prepared from **4.94** and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.7** as a colorless oil (32.5 mg, 71%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.43-8.41 (m, 1H), 7.28-7.26 (m, 1H), 6.94 (dd, $J = 7.6, 4.6$ Hz, 1H), 2.68-2.65 (m, 2H), 2.12 (tt, $J = 11.7, 3.2$ Hz, 1H), 1.90-1.75 (m, 4H), 1.72-1.52 (m, 4H), 1.29 (s, 3H), 1.21-0.85 (m, 6H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 164.4, 147.1, 136.5, 132.8, 120.2, 47.2, 42.5, 31.3, 30.3, 28.1, 27.7, 27.2, 27.1, 27.0, 19.6 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{16}\text{H}_{23}\text{N}$: 229.1825; found: 229.1816. Spectral accuracy: 97.5%

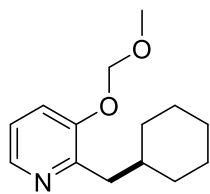


7-cyclohexyl-6,7-dihydro-5H-cyclopenta[b]pyridine (4.8): Product **4.8** was prepared from 6,7-Dihydro-5H-cyclopenta[b]pyridine and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.8** as white solid (35.3 mg, 88%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.36 (d, $J = 5.0$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 6.99 (dd, $J = 7.5, 4.9$ Hz, 1H), 3.09 (ddd, $J = 9.0, 6.2, 4.4$ Hz, 1H), 2.90-2.76 (m, 2H), 2.16-2.07 (m, 1H), 2.02-1.90 (m, 2H), 1.81-1.71 (m, 2H), 1.67-1.62

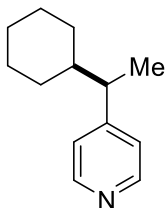
(m, 2H), 1.31-0.99 (m, 6H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 164.4, 147.1, 136.5, 132.8, 120.2, 47.2, 42.5, 31.3, 30.3, 28.1, 27.7, 27.2, 27.1, 27.0, 19.6 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{14}\text{H}_{19}\text{N}$: 201.1545; found: 201.1512. Spectral accuracy: 96.0%



2-(1-cyclohexylethyl)pyridine (4.9): Product **4.9** was prepared from 2-ethylpyridine (**4.27**) and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.9** as a colorless oil (420.3 mg, 72%). Characterization data matched previously reported data.⁵⁵ ^1H NMR (400 MHz, CDCl_3): 8.52 (d, $J = 4.5$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.07 (d, $J = 7.7$ Hz, 2H), 2.61 (quin, $J = 7.3$ Hz, 1H), 1.87-1.83 (m, 1H), 1.73-1.69 (m, 1H), 1.63-1.55 (m, 3H), 1.35-1.31 (m, 1H), 1.24 (d, $J = 7.1$ Hz, 3H), 1.20-1.06 (m, 3H), 0.99-0.84 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 166.4, 149.0, 136.3, 122.5, 121.1, 47.9, 43.4, 31.8, 30.3, 26.7, 26.6, 26.5, 17.6 ppm

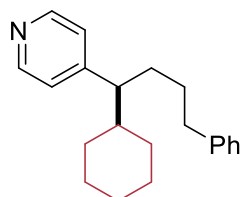


3-methoxymethoxy-2-(cyclohexylmethyl)pyridine (4.10): Product **4.10** was prepared from 3-methoxymethoxy-2-methylpyridine (**4.87**) and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->30% of EtOAc in hexanes to afford **4.10** as a yellow oil (29.2 mg, 62%). ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.16 (d, $J = 4.8$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.04 (dd, $J = 8.3, 4.7$ Hz, 1H), 5.18 (s, 2H), 3.47 (s, 3H), 2.72 (d, $J = 7.2$ Hz, 2H), 1.83-1.75 (m, 1H), 1.70-1.58 (m, 5H), 1.25-1.12 (m, 3H), 1.08-0.98 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 152.1, 151.8, 141.9, 121.6, 120.7, 94.4, 56.2, 40.0, 38.0, 33.4, 26.7, 26.4 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2$ $[\text{M}-\text{H}^+]$: 234.1489; found: 234.1544. Spectral accuracy: 96.6%

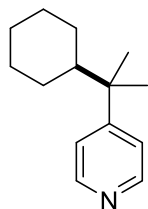


4-(1-cyclohexylethyl)pyridine (4.11): Product **4.11** was prepared from 4-ethylpyridine and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 10->40% of EtOAc in hexanes to afford **4.11** as a yellow oil (22.1 mg, 58%). ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.41 (d, $J = 6.1$ Hz, 2H), 7.01 (d, $J = 6.1$ Hz, 2H), 2.37 (quin, $J = 7.2$ Hz, 1H), 1.79-1.74 (m, 1H), 1.70-1.65 (m, 1H), 1.57-1.54 (m, 2H), 1.39-1.29 (m, 2H), 1.15 (d, $J = 7.1$ Hz, 3H), 1.11-0.99 (m, 3H), 0.91-0.69 (m, 2H) ppm. ^{13}C NMR (100 MHz,

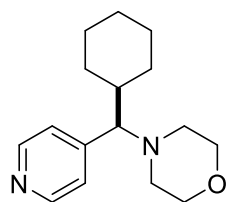
CDCl₃): δ_C 156.4, 149.4, 123.5, 45.6, 43.7, 31.4, 30.4, 26.5, 26.46, 18.1 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₁₃H₁₉N: 189.1528; found: 189.1512. Spectral accuracy: 98.0%



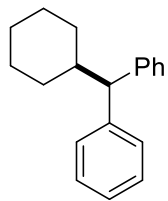
1-phenyl-4-cyclohexyl-(pyridin-4-yl)-butane (4.12): Product **4.12** was prepared from 5,6,7,8-tetrahydroquinoline (**4.88**) and chlorocyclohexane according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 10->30% of EtOAc in hexanes to afford **4.12** as a yellow oil (25.8 mg, 44%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.47 (d, J = 6.1 Hz, 2H), 7.26-7.22 (m, 2H), 7.17-7.13 (m, 1H), 7.08-7.00 (m, 4H), 2.69-2.45 (m, 2H), 2.32 (ddd, J = 11.3, 7.5, 4.1 Hz, 1H), 1.87-1.76 (m, 2H), 1.75-1.69 (m, 1H), 1.65-1.54 (m, 3H), 1.48-1.29 (m, 4H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 154.2, 149.4, 142.3, 128.43, 128.4, 125.9, 124.3, 51.9, 42.9, 36.0, 31.6, 31.3, 31.0, 29.5, 26.6, 26.55, 26.5 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₂₁H₂₇N: 293.2138; found: 293.2224. Spectral accuracy: 98.4%



4-(1-cyclohexylisopropyl)pyridine (4.13): Product **4.13** was prepared from 4-isopropylpyridine and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 10->40% of EtOAc in hexanes to afford **4.13** as a yellow oil (23.7 mg, 58%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.49-8.47 (m, 2H), 7.23-7.21 (m, 2H), 1.73-1.66 (m, 2H), 1.64-1.58 (m, 1H), 1.51-1.41 (m, 2H), 1.23 (s, 6H), 1.18-1.02 (m, 4H), 0.95-0.85 (m, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 160.1, 149.0, 122.0, 48.7, 40.9, 27.9, 27.1, 26.6, 24.7 ppm. **Accurate Mass (EI-Quadrupole)** m/z : Calcd for C₁₄H₂₁N: 203.1707; found: 203.1669. Spectral accuracy: 98.8%



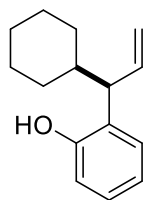
4-(cyclohexyl(pyridin-4-yl)methyl)morpholine (4.14): Product **4.14** was prepared from 4-morpholinopyridine (**4.89**) and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 70->100% of EtOAc in hexanes to afford **4.14** as a red oil (28.1 mg, 54%). Characterization data matched previously reported data.⁵⁶ ¹H NMR (400 MHz, CDCl₃): δ_H 8.52 (d, J = 4.3 Hz, 2H), 7.07 (d, J = 4.1 Hz, 2H), 3.67-3.64 (m, 4H), 3.05 (d, J = 7.7 Hz, 1H), 2.33-2.31 (m, 4H), 1.90-1.88 (m, 2H), 1.75-1.48 (m, 4H), 1.29-0.97 (m, 3H), 0.84-0.68 (m, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 149.4, 147.0, 124.7, 74.8, 67.3, 50.6, 37.2, 31.0, 28.7, 26.8, 26.5, 26.2 ppm.



(diphenylmethyl)cyclohexane (4.15): Product **4.15** was prepared from diphenylmethane and chlorocyclohexane (**4.5**) according to the general procedure.

The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.15** as a white solid (29.4 mg,

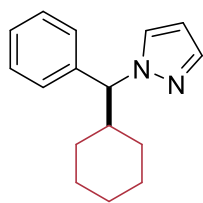
59%). Characterization data matched previously reported data.⁵⁷ $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 7.26-7.19 (m, 8H), 7.12-2.08 (m, 2H), 3.45 (d, $J = 10.9$ Hz, 1H), 2.08 (qt, $J = 10.9$, 3.2 Hz, 1H), 1.66-1.54 (m, 5H), 1.25-1.09 (m, 3H), 0.88-0.79 (m, 2H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_C 144.6, 128.5, 128.3, 126.0, 59.7, 41.4, 32.3, 26.7, 26.5 ppm.



2-(1-cyclohexylallyl)-phenol (4.16): Product **4.16** was prepared from 2-allylphenol and chlorocyclohexane (**4.5**) according to the general procedure. The crude material

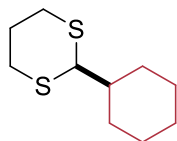
was purified via automated column chromatography using a gradient of 0->20% of EtOAc in hexanes to afford **4.16** as a pink oil (27.9 mg, 43.3%). $^1\text{H NMR}$ (400 MHz,

CDCl_3): δ_H 7.12-7.06 (m, 2H), 6.90 (td, $J = 7.5$, 1.3 Hz, 1H), 6.76 (dd, $J = 8.0$, 1.3 Hz, 1H), 6.09-6.00 (m, 1H), 5.10-5.08 (m, 1H), 5.06-5.05 (m, 1H), 4.75 (br. s, 1H), 1.98-1.91 (m, 1H), 1.79-1.60 (m, 4H), 1.50-1.44 (m, 1H), 1.30-1.08 (m, 3H), 1.02-0.81 (m, 2H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_C 153.4, 140.3, 129.7, 129.2, 127.1, 121.1, 116.1, 115.5, 50.8, 40.8, 31.7, 31.5, 26.7, 26.53, 26.51 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: 216.1532; found: 216.1509. Spectral accuracy: 97.1%

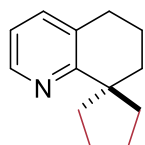


1-(1-phenylcyclohexyl)pyrazole (4.17): Product **4.17** was prepared from benzylpyrazole (**4.90**) and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->20% of EtOAc in hexanes to afford **4.17**

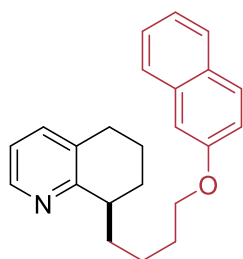
as an orange solid (19.6 mg, 40%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 7.53 (d, $J = 1.8$ Hz, 1H), 7.46-7.43 (m, 3H), 7.34-7.30 (m, 2H), 6.21 (t, $J = 2.1$ Hz, 1H), 4.82 (d, $J = 10.7$ Hz, 1H), 2.43 (qt, $J = 11.0$, 3.4 Hz, 1H), 1.72-1.65 (m, 3H), 1.46-1.35 (m, 2H), 1.28-1.14 (m, 4H), 1.01-0.84 (m, 2H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_C 139.6, 139.1, 128.8, 128.7, 128.0, 105.2, 72.7, 42.1, 30.7, 30.5, 26.5, 26.0, 25.8 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2$: 240.1621; found: 240.1625. Spectral accuracy: 98.8%



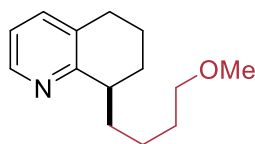
2-Cyclohexyl-1,3-dithiane (4.18): Product **4.18** was prepared from 1,3-dithiane and chlorocyclohexane (**4.5**) according to the general procedure but using KO^tBu (3.6 equiv) and TMSO (3.0 equiv). The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.18** as a colorless oil (40.1 mg, >99%). Characterization data matched previously reported data.⁵⁸ ¹H NMR (400 MHz, CDCl₃): δ_H 4.04 (d, J = 5.4 Hz, 1H), 2.92-2.82 (m, 4H), 2.12-2.07 (m, 1H), 1.91-1.62 (m, 7H), 1.30-1.11 (m, 5H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 55.5, 43.3, 31.1, 30.6, 26.6, 26.4, 26.3 ppm.



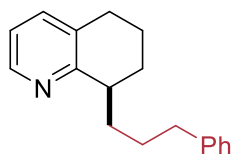
8H-spiro[cyclopentane-1,2'-5,6,7,8-tetrahydroquinoline] (4.20): Product **4.20** was prepared from 5,6,7,8-tetrahydroquinoline (**4.4**) and 1,4-dichlorobutane (**4.19**) according to the general procedure but using **4.19** (3.0 equiv), KO^tBu (3.6 equiv), TMSO (3.0 equiv), in 1,4-Dioxane at 60 °C. The crude material was purified via automated column chromatography using a gradient of 0->5% of EtOAc in hexanes to afford **4.20** as a colorless oil (13.7 mg, 37%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.35 (d, J = 6.5 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.91-6.87 (m, 1H), 2.69-2.66 (m, 2H), 2.13-2.06 (m, 2H), 1.87-1.79 (m, 2H), 1.73-1.63 (m, 6H), 1.62-1.55 (m, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 164.1, 147.3, 136.6, 132.1, 120.5, 48.5, 41.6, 36.5, 30.0, 25.6, 20.3 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for C₁₃H₁₇N: 187.1356; found: 187.1406. Spectral accuracy: 98.5%



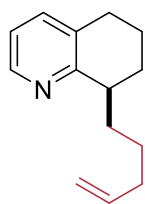
8-(4-(2-naphthyloxy)-1-butyl)-5,6,7,8-tetrahydroquinoline (4.21): Product **4.21** was prepared from 5,6,7,8-tetrahydroquinoline (**4.4**) and 4-(2-naphthyloxy)-1-chlorobutane (**4.91**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->20% of EtOAc in hexanes to afford **4.21** as a thick pale oil (40.6 mg, 61%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.42-8.40 (m, 1H), 7.77-7.71 (m, 3H), 7.42 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.37-7.30 (m, 2H), 7.16-7.13 (m, 2H), 7.02 (dd, J = 7.7, 4.7 Hz, 1H), 4.10 (t, J = 6.5 Hz, 2H), 2.96-2.90 (m, 1H), 2.82-2.69 (m, 2H), 2.18-2.10 (m, 1H), 2.03-1.84 (m, 4H), 1.81-1.60 (m, 5H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 160.6, 157.3, 146.8, 137.1, 134.8, 132.5, 129.4, 129.0, 127.7, 126.8, 126.4, 123.6, 121.0, 119.2, 106.7, 68.1, 40.8, 35.1, 29.6, 29.3, 27.5, 24.2, 20.0 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for C₁₃H₁₇N: 331.1931; found: 331.1984. Spectral accuracy: 99.1%



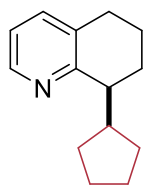
8-(4-methoxybutyl)-5,6,7,8-tetrahydroquinoline (4.22): Product **4.22** was prepared from 5,6,7,8-tetrahydroquinoline (**4.4**) and 1-chloro-4-methoxybutane according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->30% of EtOAc in hexanes to afford **4.22** as a colorless oil (30.5 mg, 69%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.37 (d, $J = 4.6$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 6.99 (dd, $J = 7.8, 4.6$ Hz, 1H), 3.38 (t, $J = 6.6$ Hz, 2H), 3.31 (s, 3H), 2.88-2.82 (m, 1H), 2.75-2.68 (m, 2H), 2.01-1.43 (m, 1H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 160.7, 146.8, 136.9, 132.3, 120.9, 73.0, 58.6, 40.8, 35.1, 30.0, 29.3, 27.4, 24.2, 19.9 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}$: 219.1704; found: 219.1618. Spectral accuracy: 97.5%



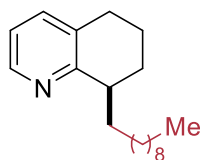
8-(3-phenylpropyl)-5,6,7,8-tetrahydroquinoline (4.23): Product **4.23** was prepared from 5,6,7,8-tetrahydroquinoline (**4.4**) and 1-bromo-3-phenylpropane according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->20% of EtOAc in hexanes to afford **4.23** as a colorless oil (29.1 mg, 58%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.40 (d, $J = 3.7$ Hz, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.29-7.25 (m, 2H), 7.20-7.14 (m, 3H), 7.02 (dd, $J = 7.7, 4.7$ Hz, 1H), 2.92 (dq, $J = 9.9, 5.2$ Hz, 1H), 2.78-2.69 (m, 3H), 2.65-2.57 (m, 1H), 2.14-2.06 (m, 1H), 2.00-1.93 (m, 1H), 1.88-1.57 (m, 6H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 160.6, 146.8, 143.0, 137.0, 132.4, 128.5, 128.4, 125.7, 120.9, 40.7, 36.4, 35.3, 29.7, 29.3, 27.5, 19.9 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{18}\text{H}_{21}\text{N}$: 251.1652; found: 251.1669. Spectral accuracy: 98.9%



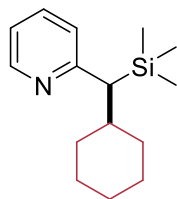
8-(pent-4-en-1-yl)-5,6,7,8-tetrahydroquinoline (4.24): Product **4.24** was prepared from 5,6,7,8-tetrahydroquinoline (**4.4**) and 5-bromo-pentene according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->20% of EtOAc in hexanes to afford **4.24** as a colorless oil (22.9 mg, 57%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 8.38 (d, $J = 4.7$ Hz, 1H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.00 (dd, $J = 7.6, 4.7$ Hz, 1H), 5.83 (ddt, $J = 16.9, 10.2, 6.6$ Hz, 1H), 5.02-4.90 (m, 2H), 2.88-2.83 (m, 1H), 2.75-2.71 (m, 2H), 2.16-1.91 (m, 4H), 1.89-1.81 (m, 1H), 1.78-1.67 (m, 2H), 1.60-1.46 (m, 3H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_{C} 160.8, 146.9, 139.2, 136.9, 132.3, 120.9, 114.4, 40.8, 35.0, 34.2, 29.3, 27.5, 27.0, 19.9 ppm. **Accurate Mass (EI-Quadrupole) m/z :** Calcd for $\text{C}_{14}\text{H}_{19}\text{N}$: 201.1548; found: 201.1512. Spectral accuracy: 97.0%



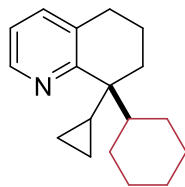
8-cyclopentyl-5,6,7,8-tetrahydroquinoline (4.25): Product **4.25** was prepared from 5,6,7,8-tetrahydroquinoline (**4.4**) and bromocyclopentane according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->20% of EtOAc in hexanes to afford **4.25** as a yellow oil (26.2 mg, 65%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.37 (d, *J* = 3.9 Hz, 1H), 7.32 (d, *J* = 6.6 Hz, 1H), 7.00 (dd, *J* = 7.6, 4.7 Hz, 1H), 2.92-2.88 (m, 1H), 2.82-2.68 (m, 2H), 2.52-2.42 (m, 1H), 1.99-1.87 (m, 2H), 1.84-1.75 (m, 1H), 1.73-1.44 (m, 8H), 1.25-1.13 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 160.8, 146.4, 136.7, 132.5, 120.8, 44.4, 44.0, 30.9, 29.1, 29.0, 25.6, 25.5, 25.2, 20.2 ppm. **Accurate Mass (EI-Quadrupole)** *m/z*: Calcd for C₁₄H₁₉N: 201.1612; found: 201.1512. Spectral accuracy: 98.8%



8-decyl-5,6,7,8-tetrahydroquinoline (4.26): Product **4.26** was prepared from 5,6,7,8-tetrahydroquinoline and chlorocyclohexane according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.26** as a yellow oil (15.2 mg, 28%). ¹H NMR (400 MHz, CDCl₃): δ_H ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 165.4, 149.1, 135.8, 123.1, 119.5, 47.7, 39.8, 34.2, 34.1, 26.8, 26.6, 26.5, -0.78 ppm. **Accurate Mass (EI-Quadrupole)** *m/z*: Calcd for C₁₉H₃₁N: 273.2519; found: 273.2451. Spectral accuracy: 98.8%

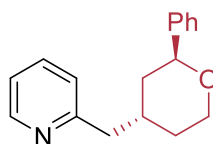


2-(trimethylsilyl-2-cyclohexylmethyl)pyridine (4.69): Product **4.69** was prepared from (2-picolyl)trimethylsilane (**4.92**) and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->10% of EtOAc in hexanes to afford **4.69** as a colorless oil (34.5 mg, 70%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.46 (d, *J* = 4.9 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 6.98-6.93 (m, 2H), 2.12-1.96 (m, 3H), 1.17-1.50 (m, 4H), 1.44-0.99 (m, 4H), 0.89-0.72 (m, 1H), -0.07 (s, 9H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 165.4, 149.1, 135.8, 123.1, 119.5, 47.7, 39.8, 34.2, 34.1, 26.8, 26.6, 26.5, -0.8 ppm. **Accurate Mass (EI-Quadrupole)** *m/z*: Calcd for C₁₅H₂₅NSi: 247.1751; found: 247.1826. Spectral accuracy: 98.1%



8-cyclopropyl-8-cyclohexyl-5,6,7,8-tetrahydroquinoline (4.71): Product **4.71** was prepared from 8-cyclopropyl-5,6,7,8-tetrahydroquinoline (**4.95**) and chlorocyclohexane (**4.5**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 0->100%

of DCM in hexanes to afford **4.71** as a thick colorless oil (24.6 mg, 48%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.37 (d, *J* = 4.6 Hz, 1H), 7.29-7.26 (m, 1H), 6.94 (dd, *J* = 8.5, 4.2 Hz, 1H), 2.76-2.68 (m, 2H), 2.40-2.34 (m, 1H), 2.11-1.95 (m, 2H), 1.85-1.74 (m, 3H), 1.67-1.55 (m, 4H), 1.25-0.98 (m, 5H), 0.43-0.31 (m, 2H), 0.20- -0.07 (m, 2H), -0.47- -0.51 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 160.5, 146.2, 136.3, 133.8, 120.4, 46.7, 44.2, 30.1, 29.5, 29.0, 27.43, 27.4, 27.3, 27.1, 21.2, 19.4, 3.8, -1.5 ppm. **Accurate Mass (EI-Quadrupole)** *m/z*: Calcd for C₁₈H₂₅N: 255.1982; found: 255.2028. Spectral accuracy: 97.5%



trans-4-picoly-2-phenyl-tetrahydropyran (4.73): Product **4.73** was prepared from 2-picoline and *cis*-4-chloro-2-phenyl-tetrahydropyran (**4.93**) according to the general procedure. The crude material was purified via automated column chromatography using a gradient of 20->30% of EtOAc in hexanes to afford **4.73** as a thick yellow oil (29.6 mg, 58%). ¹H NMR (400 MHz, CDCl₃): δ_H 8.48 (d, *J* = 4.9 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.28-7.14 (m, 5H), 7.10-7.04 (m, 2H), 4.72 (d, *J* = 9.1 Hz, 1H), 3.87-3.75 (m, 2H), 2.97 (d, *J* = 7.9 Hz, 2H), 2.43-2.37 (m, 1H), 1.92-1.85 (m, 1H), 1.77 (tt, *J* = 9.9, 4.8 Hz, 1H), 1.65-1.59 (m, 1H), 1.41-1.35 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ_C 160.8, 149.6, 142.6, 136.4, 128.4, 127.3, 126.2, 123.6, 121.3, 74.3, 63.3, 41.3, 36.6, 31.8, 30.1 ppm. **Accurate Mass (EI-Quadrupole)** *m/z*: Calcd for C₁₃H₂₀O: 253.1461; found: 253.1433. Spectral accuracy: 97.9%

Reaction Scale up: In a nitrogen filled glovebox, KO^tBu (6.8 mmol) was weighed into an oven dried 35 mL pressure tube equipped with a stir bar. PhMe (0.4 M) was added to the vial followed by 2-ethylpyridine (**4.27**) (3.0 mmol), and chlorocyclohexane (**4.5**) (6.0 mmol). TMDSO (6.0 mmol) was added to the mixture, and the pressure tube sealed with a screwcap equipped with a rubber O-ring. The reaction vessel was placed in an oil bath that had been preheated to 70 °C and allowed to stir for 16 hours. Once complete, the reaction mixture was removed from the oil bath and allowed to cool to ambient temperature. TBAF (6.0 mmol, 1.0 M sol. In THF) was added and the reaction stirred at 70 °C for 2 hours. The reaction was allowed to cool to ambient temperature, diluted with EtOAc and filtered through silica gel with EtOAc using a 30 mL glass fritted funnel

and subsequently concentrated using a rotary evaporator. The crude residue was then purified using flash column chromatography. (420.3 mg, 74%) (*vide supra for characterization data*).

Note* **4.20** was synthesized according to the same protocol and using modified conditions listed in **Scheme 4.10**.

COware procedure: The COware experiment was conducted in an N₂ filled glovebox. To an oven dried Coware vessel equipped with a stir bar in each well was added the corresponding base/additive (0.48 mmol). PhMe (0.5 mL, 0.4 M) was added to each well. Substrate **4.4** (0.2 mmol) was then added into well B, followed by the alkyl halide coupling partner **4.5** (0.4 mmol). TMDSO (0.40 mmol) was added to well A and the reaction quickly sealed using red screw caps equipped with a pierceable Teflon/silicone septum. The reaction vessel was carefully placed in an oil bath that had been preheated to 70 °C and allowed to stir for 16 hours. Once complete, the reaction mixture was removed from the oil bath and allowed to cool to ambient temperature. Both wells were diluted with EtOAc, and then 1,3,5-trimethoxy benzene was added to well B as a stock solution in PhMe. The solution was then filtered through silica with EtOAc using a 15 mL glass fritted funnel and subsequently concentrated using a rotary evaporator. The crude residue was then dissolved in CDCl₃ and analyzed via ¹H NMR spectroscopy. The % yield of the product was determined by integrating the peak at 8.42 ppm, which corresponds to the proton at C2 of **4.6** relative to the peak at 6.08 ppm on 1,3,5-trimethoxybenzene.

4.7.7 | Mechanistic experiments

4.7.7.1 | NMR experiments

NMR experiments were conducted in an N₂ filled glovebox. To an oven dried pressure graded J. Young NMR tube was added KO^tBu (0.24 mmol). Next PhMe-d₈ (0.4 M) was added to the NMR tube followed by 2-ethylpyridine (**4.27**) (0.1 mmol), and the chlorocyclohexane (**4.5**)

(0.2 mmol). TMDSO (0.2 mmol) was added to the mixture, and the J. Young NMR tube was quickly sealed with its Teflon cap. The reaction vessel was placed in an oil bath that had been preheated to the desired temperature and allowed to stir for the indicated time. Once complete, the reaction mixture was removed from the oil bath and allowed to cool to ambient temperature. The J. Young NMR tube was then placed into the NMR spectrometer for analysis. After analyzing the mixture, the J. Young NMR tube was removed from the spectrometer, degassed in a fumehood, and reinserted for further analysis (**Figure 4.3**).

Figure 4.3: Pressurized ^1H NMR spectrum using **4.27** (PhMe- d_8 , 500 MHz)

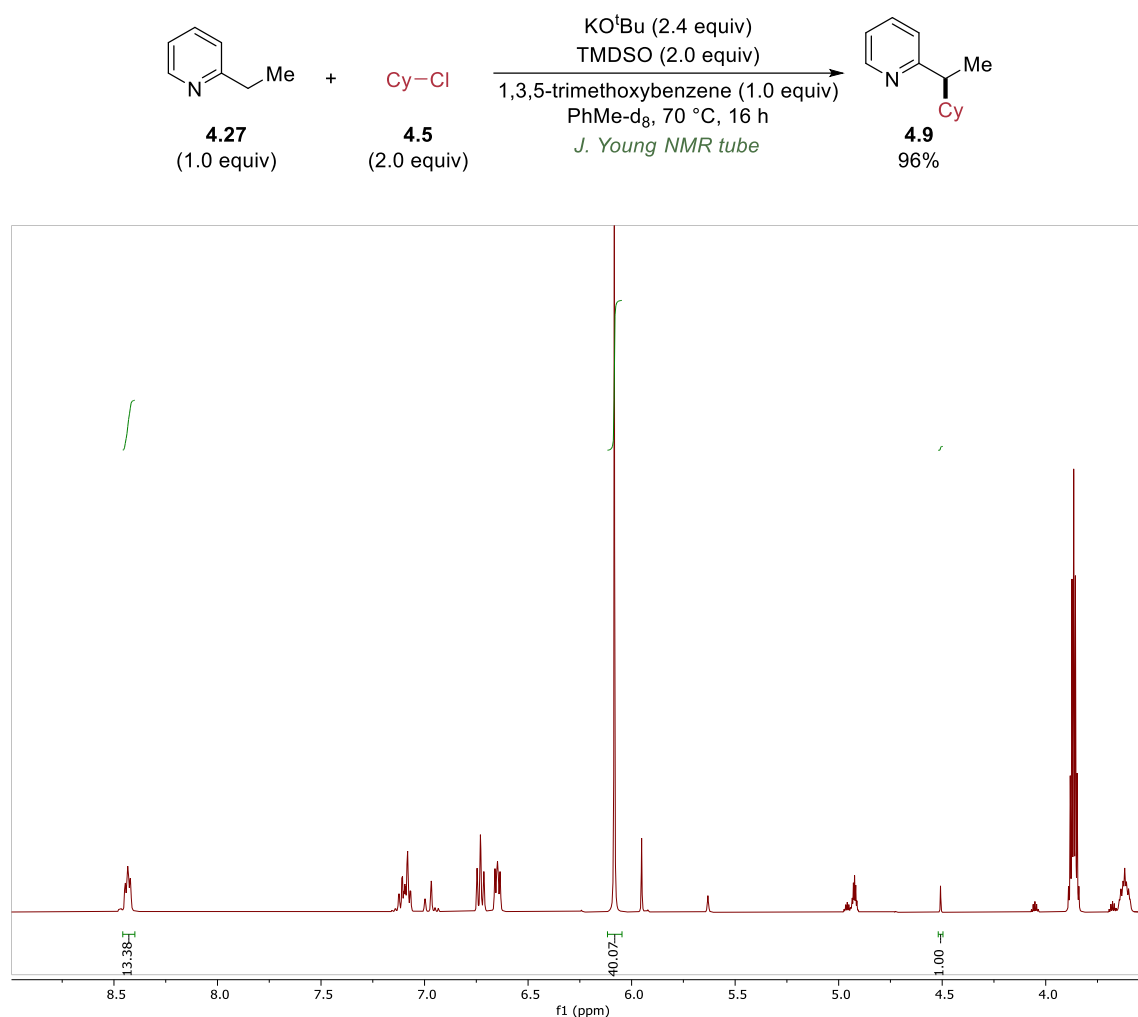
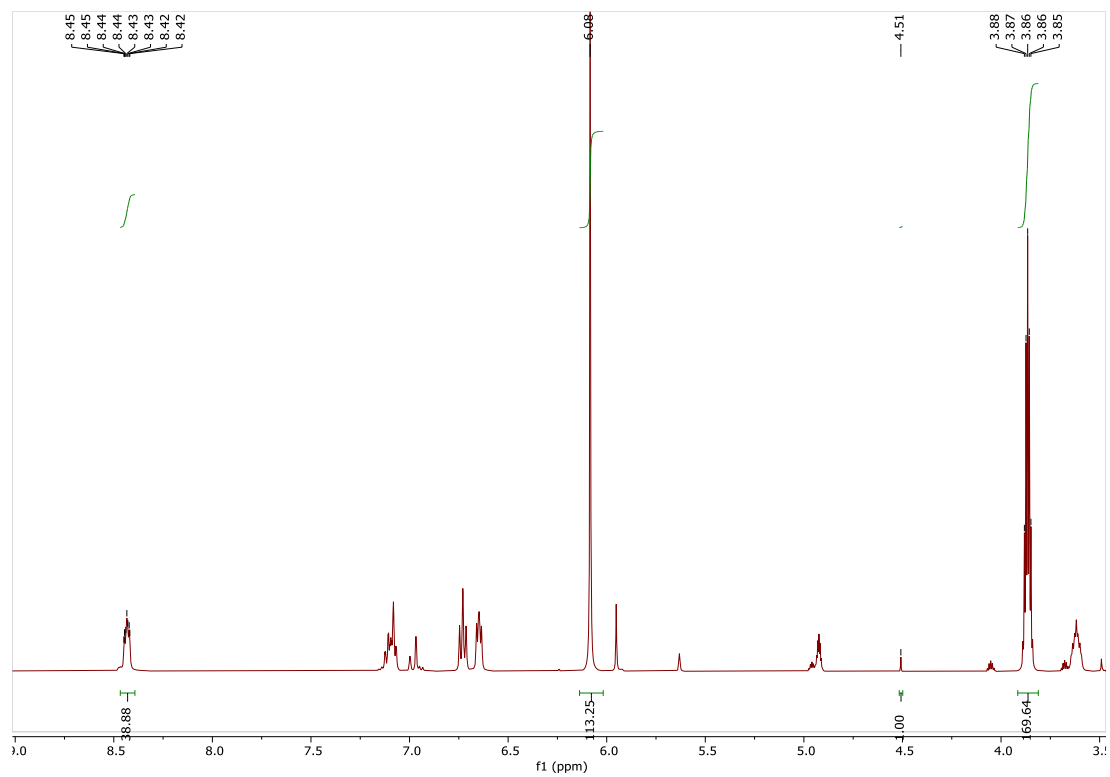


Figure 4.4: Degassed ^1H NMR spectrum using **4.27** (PhMe- d_8 , 500 MHz)



The same experiment was conducted using **4.27-d₂** to see whether formation of HD gas occurs. This was not observed, and instead only hydrogen gas evolution occurred (**Figure 4.5**). Analysis using ²D NMR spectroscopy further confirmed no formation of HD (**Figure 4.6**).

Figure 4.5: Pressurized ¹H NMR spectrum using **4.27-d₂** (PhMe-d₈, 500 MHz)

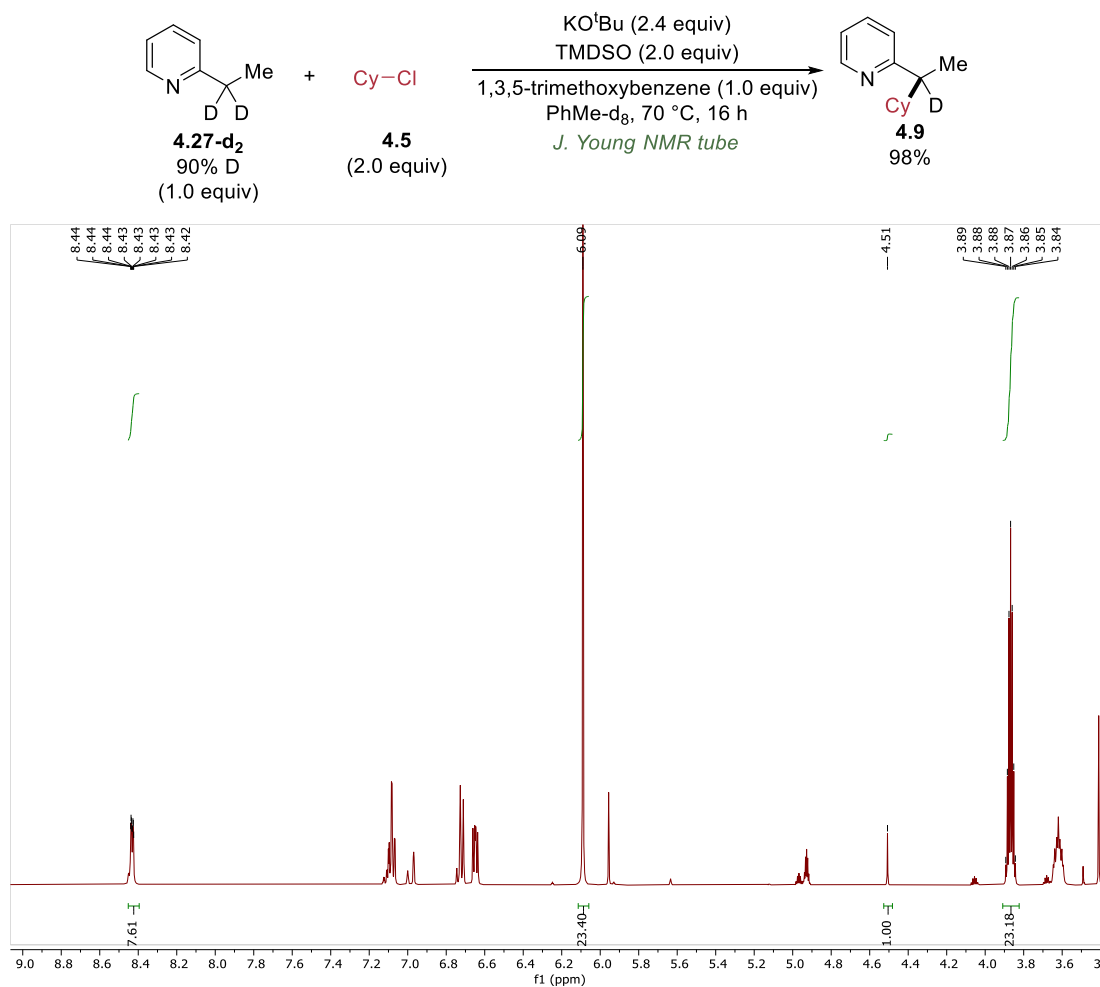
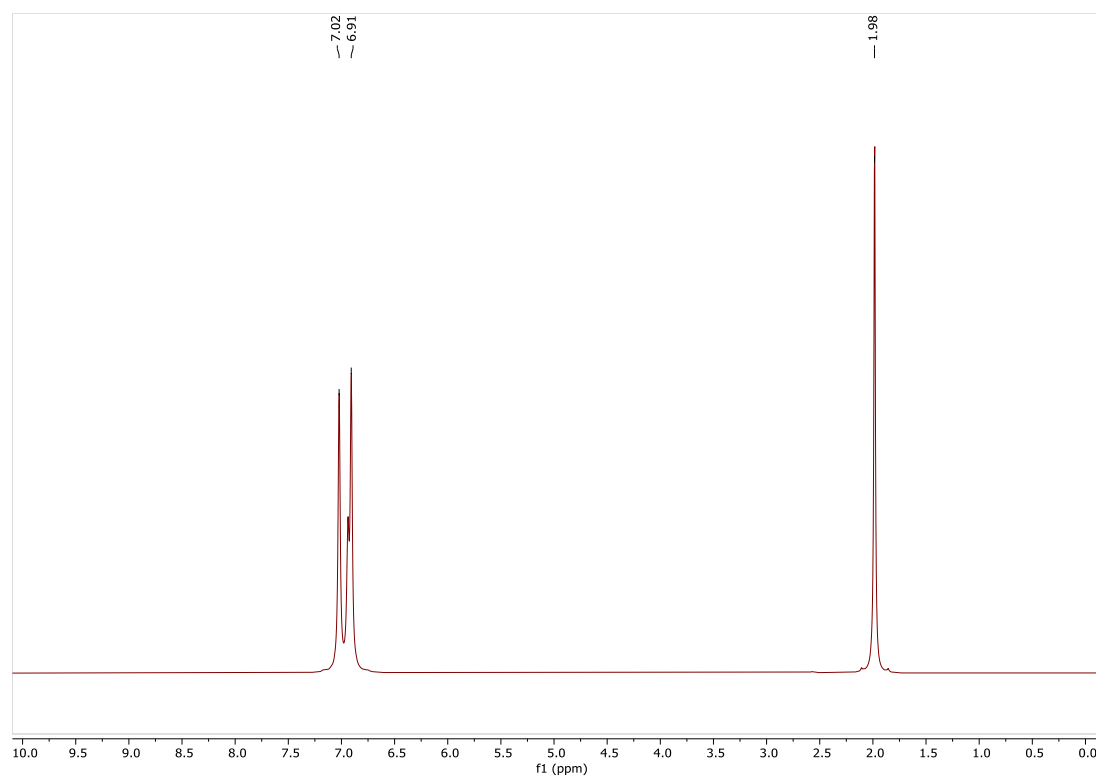
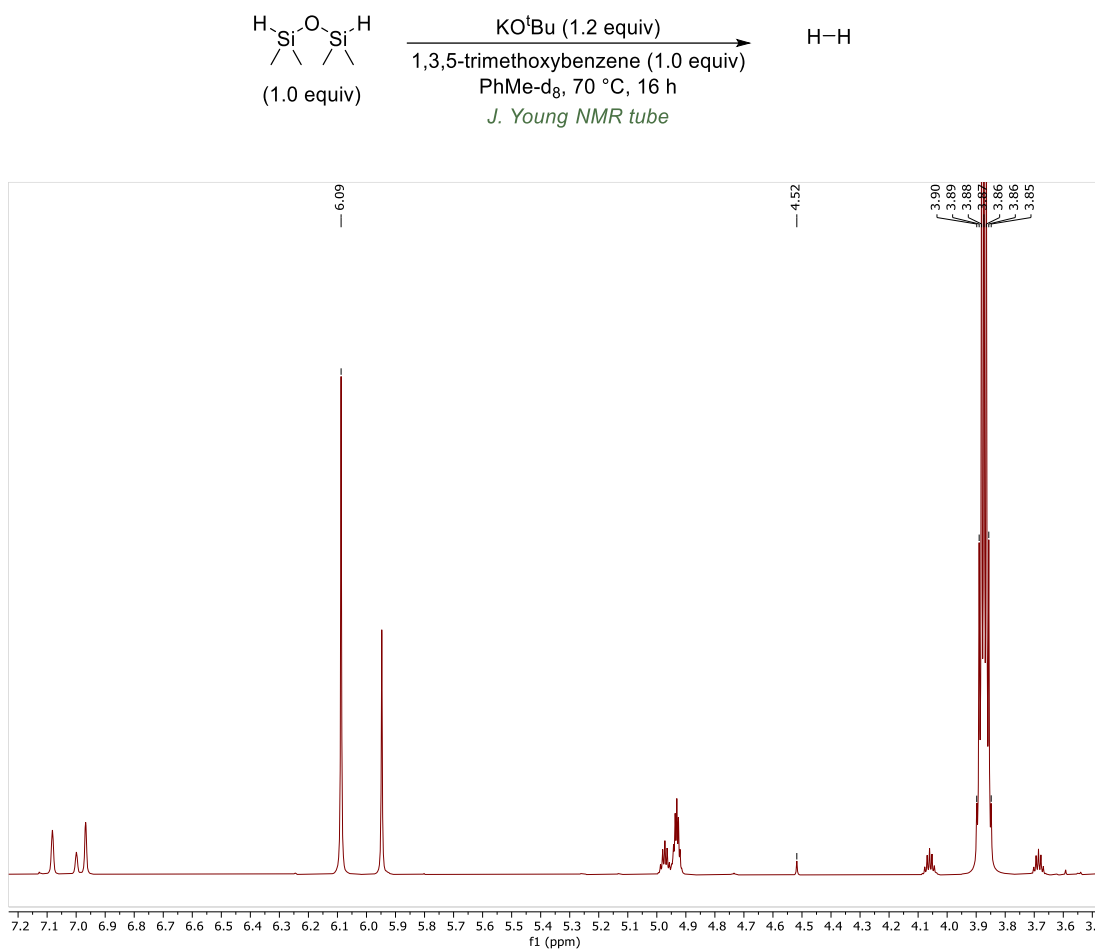


Figure 4.6: Pressurized ^2D NMR spectrum using **4.27-d₂** (PhMe-d₈, 500 MHz)



A final NMR experiment was conducted according to the procedure for NMR experiments using only TMSO and KO^tBu. H₂ gas evolution was observed indicating that H₂ evolution occurs when heating and mixing TMSO and KO^tBu together (**Figure 4.7**).

Figure 4.7: Pressurized ¹H NMR spectrum using only TMSO and KO^tBu (PhMe-d₈, 500 MHz)



4.7.7.2 | Procedures for vTNA and associated data

Procedure for Variable-Time Normalization Analysis (vTNA): Kinetic data for the C–H alkylation reaction was obtained for compound **4.27**. All individual kinetic experiments were performed according to the general reaction conditions, varying the amount of base, silane or substrate added. Nine reactions were set up in parallel and 10 μ L aliquots were taken using a microsyringe after 10 min, 20 min, 30 min, 40 min, 60 min, 120 min, 210 min, 300 min, 480 min, and 720 min. Yields were calculated using calibrated GCMS. The method of variable time normalization analysis was conducted on the obtained yield vs. time data based on the method described by Burés and co-workers in order to determine the observed rate equation.⁵⁹ Standard reaction conditions were 0.400 M 2-ethylpyridine (**4.27**), 0.800 M chlorocyclohexane (**4.5**), 0.800 M TMDSO, and 0.960 M KO^tBu. **Figure 4.8** was generated by varying the [**4.27**], setting it to 0.400 M (standard conditions), 0.200 M or 0.600 M while keeping all else constant. **Figure 4.9** was generated by varying [**4.5**], setting it to 0.800 M (standard conditions), 0.600 M or 1.00 M while keeping all else constant. As mentioned in section 4.5.6.3, no reasonable overlay could be obtained for TMDSO or KO^tBu and as a result their data has been omitted. Optimal overlay was determined using a vTNA calculator developed by Hii and coworkers.³⁹

Figure 4.8: Graph depicting apparent first-order overlay for 4.27

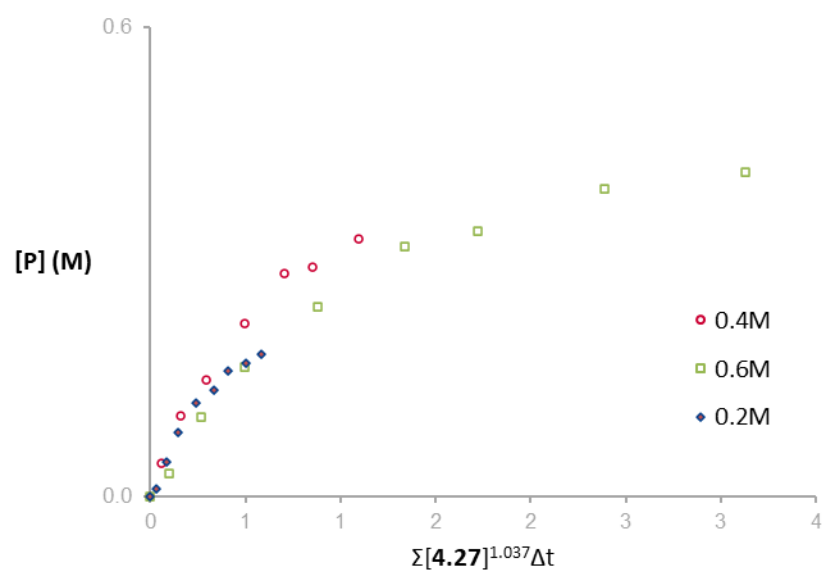


Figure 4.9: Graph depicting apparent near zeroth-order overlay of 4.5

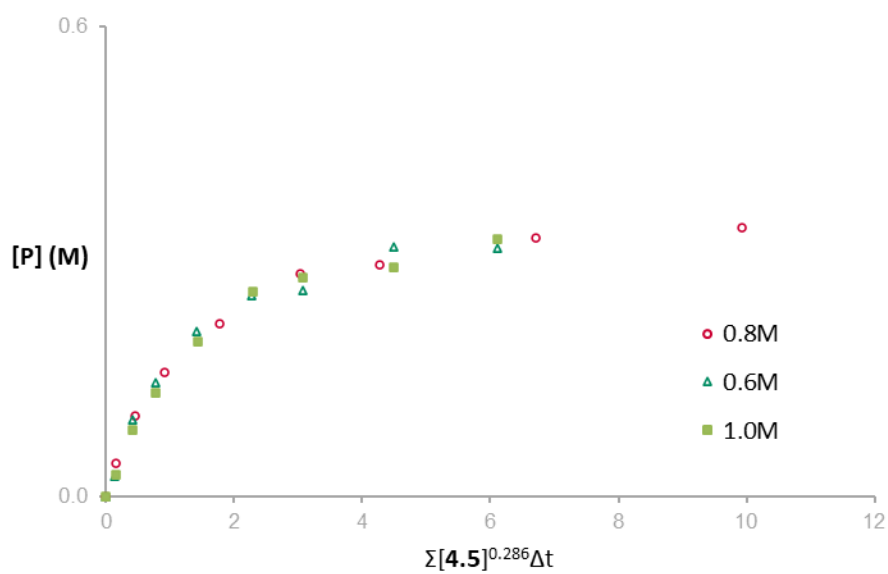


Table 4.8: Raw vTNA data for first-order overlay for 4.27

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[4.27] (M)	[P] (M)	t (h)	tA	[4.27] (M)	[P] (M)	t (h)	tA	[4.27] (M)	[P] (M)
0.00	0.00	0.400	0.000	0.00	0.00	0.200	0.000	0.00	0.00	0.600	0.000
0.17	0.06	0.347	0.042	0.17	0.03	0.187	0.010	0.17	0.10	0.571	0.029
0.50	0.16	0.297	0.103	0.50	0.08	0.155	0.045	0.50	0.27	0.499	0.101
1.00	0.29	0.251	0.149	1.00	0.15	0.118	0.082	1.00	0.50	0.435	0.165
2.00	0.50	0.179	0.221	2.00	0.24	0.081	0.119	2.00	0.88	0.357	0.243
3.50	0.70	0.115	0.285	3.50	0.34	0.064	0.136	3.50	1.34	0.280	0.320
5.00	0.85	0.106	0.294	5.00	0.41	0.040	0.160	5.00	1.72	0.260	0.340
8.00	1.10	0.070	0.330	8.00	0.50	0.030	0.170	8.00	2.39	0.207	0.393
12.00	1.32	0.056	0.344	12.00	0.58	0.018	0.182	12.00	3.13	0.185	0.415

Table 4.9: Raw vTNA data for near-zeroth order overlay for 4.5

Experiment 1				Experiment 2				Experiment 3			
t (h)	tA	[4.5] (M)	[P] (M)	t (h)	tA	[4.5] (M)	[P] (M)	t (h)	tA	[4.5] (M)	[P] (M)
0.00	0.00	0.800	0.000	0.00	0.00	0.600	0.000	0.00	0.00	1.000	0.000
0.17	0.17	0.758	0.042	0.17	0.17	0.575	0.025	0.17	0.17	0.973	0.027
0.50	0.47	0.697	0.103	0.50	0.45	0.503	0.097	0.50	0.49	0.916	0.084
1.00	0.92	0.641	0.159	1.00	0.85	0.455	0.145	1.00	0.98	0.868	0.132
2.00	1.78	0.579	0.221	2.00	1.63	0.390	0.210	2.00	1.93	0.803	0.197
3.50	3.05	0.515	0.285	3.50	2.76	0.344	0.256	3.50	3.32	0.738	0.262
5.00	4.28	0.505	0.295	5.00	3.86	0.337	0.263	5.00	4.69	0.720	0.280
8.00	6.73	0.470	0.330	8.00	6.01	0.281	0.319	8.00	7.41	0.707	0.293
12.00	9.94	0.456	0.344	12.00	8.79	0.283	0.317	12.00	11.01	0.672	0.328

4.7.7.3 | Other experimental procedures

Procedure for Measuring the Primary Kinetic Isotope Effect: The PKIE experiments were setup in an N₂ filled glovebox. To an oven dried 1 dram screw cap vial equipped with a stir bar was added KO^tBu (0.48 mmol). Next PhMe (0.4 M) was added to the vial followed by **4.27** or **4.27-d₂** (0.2 mmol), and chlorocyclohexane (**4.5**) (0.4 mmol). TMDSO (0.4 mmol) was added to the mixture, and the vial was quickly sealed with a plastic screw cap and pierceable Teflon/silicone septum. The reaction vessel was pierced with an N₂ filled balloon and placed into an oil bath that had been preheated to 70 °C. 10 µL aliquots were taken using a micro syringe at 10 min, 20 min, 30 min, 40 min, and 60 min and filtered through a small plug of silica directly into GC vials. The samples for each time point were then quantified by integrating the peak corresponding to product (**4.9**) and the internal standard, and the yields calculated using calibrated GCMS. Experiments were performed in triplicate for both **4.27** and **4.27-d₂**. The resulting data was then averaged across the three runs and plotted as concentration (M) against time (min) to obtain a primary kinetic isotope effect of $k_H/k_D = 4.94 \pm 0.52$.

Procedure for Monitoring Base-Mediated Alkyl Halide Decomposition: The reaction monitoring experiments were setup in an N₂ filled glovebox. To an oven dried 1 dram screw cap vial equipped with a stir bar was added KO^tBu (0.24 mmol). Next PhMe (0.4 M) was added to the vial followed alkyl chloride (**4.80**) (0.2 mmol). TMDSO (0.2 mmol) was added to the mixture, and the vial was quickly sealed with a plastic screw cap and pierceable Teflon/silicone septum. The reaction vessel was pierced with an N₂ filled balloon and placed into an oil bath that had been preheated to 70 °C. 10 µL aliquots were taken using a micro syringe at 10 min, 20 min, 30 min, 40 min, 60 min, 120 min, and 240 min and filtered through a small plug of silica directly into GC vials. The samples for each time point were then quantified by integrating the peak corresponding to the starting material (**4.80**) and the internal standard, and the yields calculated by calibrated GCMS. This

procedure was repeated using the same starting material **4.80** (0.2 mmol) for both conditions B (KO^tBu (0.24 mmol), 18-crown-6 (0.2 mmol), in THF (0.4M)) and conditions C ((KO^tBu (0.24 mmol) in DMSO (0.4M)). The resulting data was then plotted as concentration [M] against time (min) to obtain **Scheme 4.16**.

Procedure for Competition Experiment: The competition experiment was conducted in an N₂ filled glovebox. To an oven dried 1 dram screw cap vial equipped with a stir bar was added KO^tBu (0.48 mmol). Next PhMe (0.4 M) was added to the vial followed by **4.27** (0.2 mmol), **4.83** (0.2 mmol), and **4.5** (0.2 mmol). TMSO (0.40 mmol) was added, and the vial was quickly sealed with a plastic screw cap and pierceable Teflon/silicone septum. The reaction vessel was placed in an oil bath that had been preheated to the desired temperature and allowed to stir for the indicated time. Once complete, the reaction mixture was removed from the oil bath and allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc, and then 1,3,5-trimethoxy benzene was added as a stock solution in PhMe. The solution was then filtered through silica with EtOAc using a 15 mL glass fritted funnel and subsequently concentrated using a rotary evaporator. The crude residue was then dissolved in CDCl₃ and analyzed via ¹H NMR spectroscopy. The % yield of the products were determined using ¹H NMR spectroscopy.

Section 4.8 | References

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Chapter 5 | Concluding Remarks and Future Directions

Section 5.1 | Chapter outline

Chapter 5 begins with a summary of chapters 2, 3, and 4 followed by their strengths, weaknesses, and a blanket statement covering the overall contributions of this dissertation to the field of study. Following the conclusions is the future of this chemistry as viewed by the dissertation author.

Section 5.2 | Thesis summary

As highlighted in chapter 1, the combination of hydrosilanes and Lewis bases is known to facilitate hydrodefunctionalization reactions, silylation reactions, and intramolecular rearrangement reactions. This dissertation begins by recognizing the combination of hydrosilanes and Lewis bases is still an underappreciated synthetic multi-tool and had yet to be applied to the construction of carbon–carbon bonds – a fundamental goal and heavily researched area of synthetic organic chemistry. Taking note of these observations and again recalling chapter 1; the primary goal of this research was to:

Extend the breadth of hydrosilane and Lewis base-mediated transformations to the synthesis of carbon–carbon bonds.

Chapter 2 of this thesis was the first method to reduce C–CF₃ bonds in 2-trifluoromethylpyridines down to the corresponding C–H bond (**Scheme 5.1A**). The reaction showed substrate specificity for pyridines bearing a trifluoromethyl group at C2. The use of trifluoromethyl groups as removeable directing groups in the carboxylation of a pyridine ring was successfully demonstrated. The reaction displayed 1st order kinetics in 1,1,3,3-tetramethyldisiloxane (TMDSO), the substrate, and potassium *tert*-butoxide (KO^tBu). Deuterium labelling experiments confirmed that TMDSO delivers its hydrogen to the pyridine ring

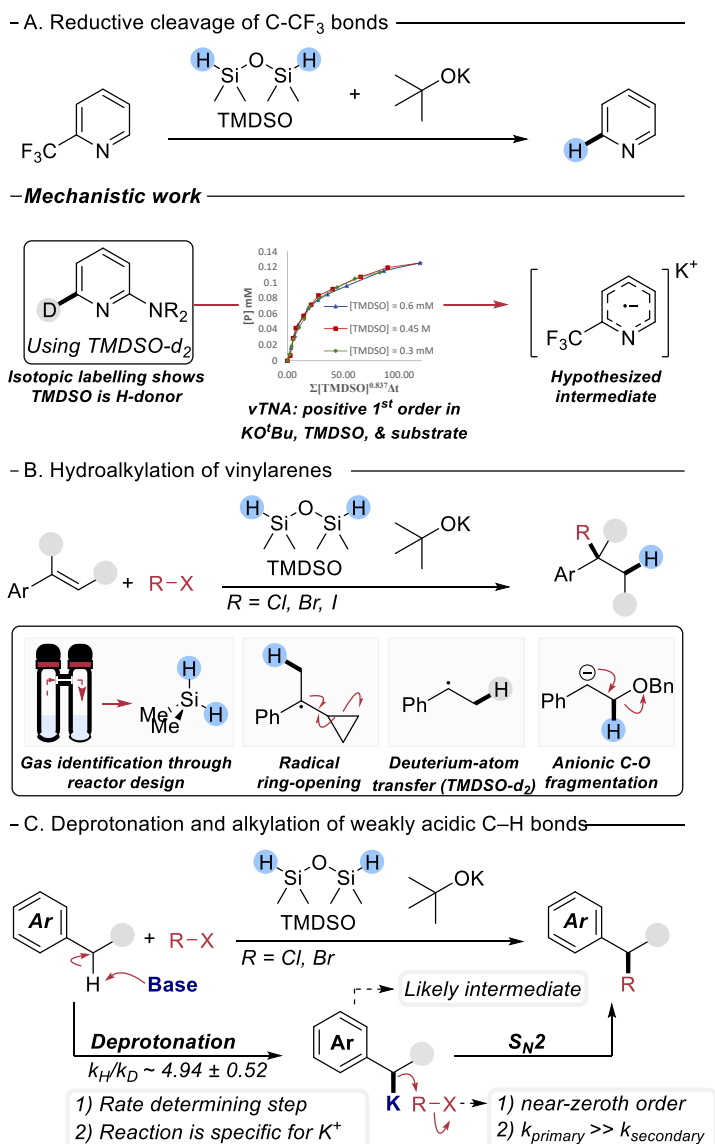
exclusively at C2. The mechanism by which C–CF₃ expulsion takes place remains unknown but ultimately led to the discovery of the hydroalkylation of vinylarenes.

Chapter 3 of this dissertation showcased the transition metal-free hydroalkylation of vinylarenes (**Scheme 5.1B**). The reaction features TMDSO and KO^tBu as a reductant with alkyl halides as the electrophile. Mono, di, and trisubstituted vinylarenes were amenable to the reaction, as were primary and secondary alkyl chlorides and bromides. Through reactor design, dimethylsilane (Me₂SiH₂) was identified as the gaseous reducing agent. The design and testing of substrate probes uncovered that the reaction likely proceeds through hydrogen atom transfer to the vinylarene, followed by a key reductive radical polar crossover (RRPC) step transforming the benzylic radical into a carbanion, and subsequent bimolecular nucleophilic substitution (S_N2) with the alkyl halide furnishing the C(sp³)–C(sp³) bond at the benzylic position. This work is an important first instance of using hydrosilanes and Lewis bases to synthesize C(sp³)–C(sp³) bonds through an intermolecular reaction.

Chapter 4 highlights the basic properties of TMDSO and KO^tBu in a C–H alkylation reaction (**Scheme 5.1C**). Many weakly acidic C–H-containing species including 2- and 4-alkylpyridines, benzylic species, and select heterocycles could be alkylated using TMDSO and KO^tBu as the base and alkyl halides as electrophiles. Notably, the product was found to be capable of undergoing further reactions which could result in dialkylation as a byproduct. This double alkylation could be harnessed to access spirocycles through use of a dielectrophile. A mechanistic study showed the reaction likely proceeds through rate-determining deprotonation of the weakly acidic C–H bond to afford an organopotassium nucleophile. Following deprotonation, an S_N2 with the alkyl electrophile can take place. Monitoring the degradation of the alkyl electrophile over time suggested that TMDSO and KO^tBu are basic enough to deprotonate weakly acidic C–H bonds and

are yet tolerant of alkyl halides. While the active base was never fully characterized, we suspect TMDSO and KO^tBu react to slowly release potassium hydride (KH) in solution and ultimately represent a convenient, safer, and more soluble alternative to the direct use of KH.

Scheme 5.1: Summary of the dissertation work in chapters 2-4



Section 5.3 | Contributions and conclusions

5.3.1 | Strengths of the dissertation research

Various aspects of the dissertation research can be highlighted as strengths. Analyzing the research through a synthetic organic chemist's point of view, TMDSO and KO^tBu are an inexpensive reagent pair costing approximately \$1/g for each reagent. Organic synthesis is inherently expensive to perform, thus it's imperative that cost-effective and commercially available reagents are made accessible to the synthetic organic chemist – after all, *we* have a tendency to use what is available to us. The low cost of TMDSO and KO^tBu is further proven to be valuable when considering chapters 2 and 3 provide a means to synthesize C(sp³)–C(sp³) bonds. The other advantage TMDSO and KO^tBu offer is their shelf stability and their low-oxygen sensitivity which allows for benchtop experimentation without the need for an inert atmosphere. This is a *huge* factor that governs whether a synthetic protocol gets used in the laboratory. For instance, many chemists don't have access to inert conditions to perform synthesis. Additionally, as the scale of a reaction increases the barrier to working under inert conditions is raised significantly.

Another area of this dissertation's strengths lies in the mechanistic studies of these transformations. The mechanistic study in chapter 3 was particularly informative and provided support for various reactive intermediates that were generated through use of the redox properties associated with hydrosilanes and Lewis bases. This mechanistic investigation culminated in the realization that TMDSO and KO^tBu are likely acting as a one-pot hydrogen atom donor and single-electron donor – a significant part of the conclusion made in chapter 3. The mechanistic study in chapter 4 hinted at a deprotonation and alkylation mechanism but also highlights the formation of a strong base in-situ. While the identity of the strong base remains elusive, we learned it is strong

enough to deprotonate species with an acid dissociation constant (pKa) of up to approximately 35 while ignoring the acidic C–H bonds in the alkyl halide, placing it in what could be considered as a Goldilocks zone that other bases seem to lie on the perimeter of.

5.3.2 | Weaknesses of the dissertation research

The weaknesses surrounding this research can be analyzed analogously to the strengths. Once again, taking the perspective of a synthetic organic chemist arguably the largest drawback to utilizing this reagent combination is the functional group incompatibility towards hydride sensitive functional groups. Esters, ketones, aldehydes, nitriles, carbamates, and related functional groups were almost invariably reduced in the reaction. While this can be overcome through use of protecting groups, it is an inherent limitation that is not ideal. Another unattractive feature of this reagent combination is the generation of gas in the reaction. Dimethylsilane is an extremely flammable, and potentially explosive gas that boils at -20 °C. Simply put, this is a dangerous material to work with. Furthermore, a build-up of pressure occurs within the reaction vessel and likely helps to keep dimethylsilane in solution where the reaction occurs making scaling up this transformation challenging. The use of diethylsilane (Et_2SiH_2) and related species may be a viable alternative but would likely require optimization and cost more. Next, is the generation of silicon oligomers. Across chapters 2-4, the separation of the desired product from the silicon oligomers presented a significant challenge as even after treatment with tetrabutylammonium fluoride (TBAF) or hydrochloric acid (HCl) some substrates required 1-3 separate purification steps. Also of note, is the low atom-economy associated with TMDSO. While its molecular weight is 134.32g/mol, only hydrogen is incorporated into the product which accounts for 1.5% of the reagents mass assuming *both* hydrogen atoms are used. The remainder of its constituents when combined with KO^tBu produce stoichiometric waste in the form of silicon oligomers as observed

using gas chromatography-mass spectrometry (GCMS). The last weakness the author would like to highlight is the low tunability of this system. Chapters 2-4 remark on how each of these transformations is transition metal free without acknowledging the advantages transition metal catalysis presents. In particular, the tunability of transition metal catalysis through ligand substitution is significant and indeed is responsible for why so many unprecedented transition-metal-catalyzed transformations can take place. Taking hydroalkylation reactions for example, while we have no way to impart chirality (as the current body of work exists) this is achievable, and demonstrated several times, through use of transition metal catalysis.¹⁻⁵

Mechanistically, the largest weaknesses of this dissertation research are tied to TMDSO and KO^tBu. No concrete explanation for why the potassium ion (K⁺) is a necessary reaction component can be offered. Speculation leads one to believe the unique property could be tied to the atomic radius or polarizability of K⁺, but this is not founded in gathered mechanistic evidence. Another weakness lies in the unanswered question: why does TMDSO facilitate these transformations while triethylsilane (Et₃SiH) does not? The dissertation author often draws on conclusions made about Et₃SiH to explain phenomena or mechanistic processes that occur while using TMDSO, despite noting their differences in reactivity. This is an important question to have answered. Next, we consider the species that arise from interactions between TMDSO and KO^tBu. While chapter 3 showed that TMDSO decomposes into Me₂SiH₂, the true identity of the active reducing agent is unknown. These questions if answered would provide significant insight towards the dissertation research and the broader field.⁶⁻⁸

5.3.3 | Final conclusions

Coming back to observations made in the introductory chapter of this dissertation. At the outset of this research, the author of this dissertation noticed the combination of hydrosilanes, and

Lewis bases had seen widespread use in hydrodefunctionalization reactions, silylation reactions, and intramolecular rearrangement reactions.⁹⁻¹¹ It was then asked: where are the C–C bond forming reactions? This led to the pursuit of the goal of extending the breadth of hydrosilanes and Lewis base-mediated transformations to the synthesis of carbon–carbon bonds.

This dissertation demonstrates that the redox and basic properties of these hydrosilanes and Lewis base mixtures can be used in complexity building reactions. Given the low cost, and ease with which they may be handled it's reasonable to say that these hydrosilanes and Lewis base mixtures are underappreciated as valuable synthetic multi-tools. Chapters 2-4 highlight this synthetic utility in what are the first instances of C–CF₃ bond cleavage and more importantly the construction of C(sp³)–C(sp³) bonds using these hydrosilane and Lewis base mixtures. Taking it deeper, TMDSO and KO^tBu are uniquely powerful at transforming vinylarenes, and benzylic C–H species– two classes of abundant compounds – into benzylic nucleophiles that may be engaged in organic synthesis. Furthermore, TMDSO and KO^tBu are unreactive towards alkyl electrophiles and yet highly reactive towards C–H bonds and π -bonds – properties that these strategies hinge upon. Overall, the author of this dissertation feels the work in this dissertation serves as the *beginning* of utilizing hydrosilanes and Lewis bases to construct carbon–carbon bonds and is hopeful to see further development of their reactivity.

Section 5.4 | New horizons in the chemistry of hydrosilanes and Lewis bases

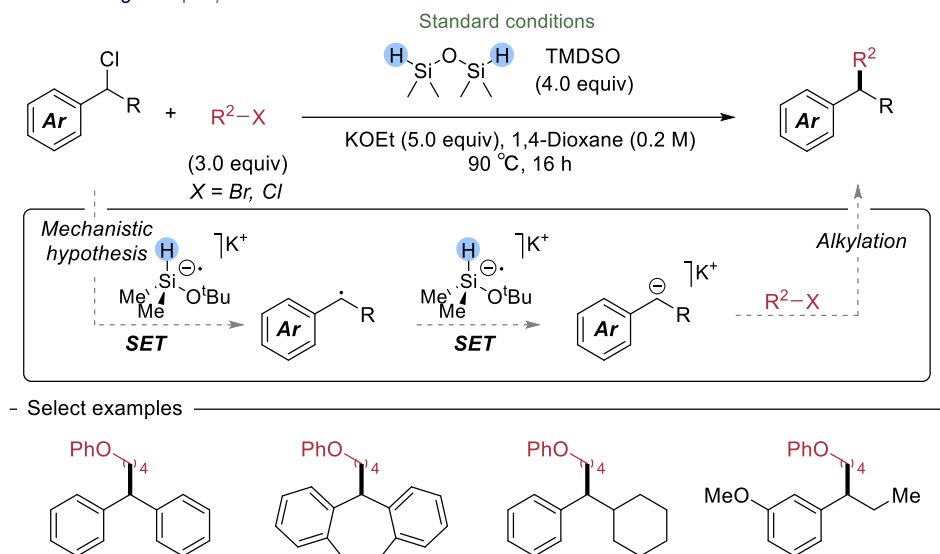
The future of hydrosilanes and Lewis bases will likely proceed through both intentional design and serendipitously as it has up until this point. What is meant by this is as long as chemists use hydrosilanes and Lewis base additives together in chemistry new and unexpected reactions facilitated by these reagent combinations will be discovered. However, the author of this dissertation is hopeful that recognition of the synthetic potential held by the mixture of

hydrosilanes and Lewis base combinations from existing work in the literature and the contents of this dissertation will inspire the intentional design of new transformations.

The next areas of research should utilize the strengths ascribed to TMDSO and KO^tBu. This reagent combination appears to be a powerful single-electron donor capable of reducing benzyl halides via single-electron transfer (SET), while also tolerating alkyl halides.^{7, 12, 13} Inspired by the work from the Lin group showcasing a cross-electrophile coupling (XEC) between alkyl halide prone to single-electron reduction and alkyl halides prone to substitution chemistry, Hana Nugraha – an MSc in the Newman lab and co-author on the manuscript from which chapter 3 is derived – designed an XEC reaction between benzyl chlorides and alkyl halides using TMDSO and KO^tBu (**Scheme 5.2**). The current mechanistic hypothesis is TMDSO and KO^tBu facilitate two subsequent single-electron transfer steps to the benzyl halide resulting in a benzylic carbanion capable of reacting with the alkyl halide in a substitution reaction. The scope is currently limited to secondary and tertiary benzyl chlorides bearing aryl and alkyl substituents. Primary benzyl halides undergo near quantitative dimerization, leading to poor yields of the cross-electrophile coupling product. Other alkyl halides bearing anion stabilizing substituents have been tested in the reaction including pinacol boronic esters (Bpin), and trimethylsilanes (TMS) but fail to react in the desired XEC. This is a highly fascinating and exciting reaction brought on by TMDSO and KO^tBu. Further studies will be conducted to improve the scope and elucidate the underlying mechanism.

Scheme 5.2: TMDSO and KO^tBu mediated cross-electrophile coupling (XEC)

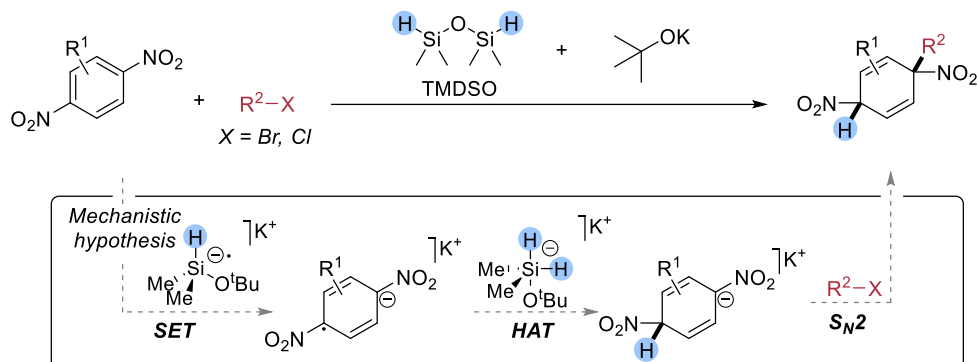
Newman & Nugraha | unpublished work



Another interesting direction of research that capitalizes on the redox reactivity of TMDSO and KO^tBu is the Birch-alkylation of electron deficient aromatic species. The Birch-alkylation of aromatic species is a highly utilized transformation in total synthesis providing a convenient way to transform aromatic molecules into olefins.¹⁴ The Birch-alkylation has also seen development in synthetic methods. Work by Landais and coworkers showcased the Birch-alkylation of biaryl species as a convenient means to selectively reduce one aromatic ring in the aromatic system.¹⁵ A later study by Vanderwal developed an auxiliary-controlled stereoselective Birch-alkylation of aromatic esters providing access to chiral cyclohexadienes – a highly versatile building block.¹⁶ The Birch-alkylation is a reaction with clear synthetic utility. The limitations of these reactions, however, is the use of highly reducing alkali metals that not only require handling at cryogenic temperatures but require careful and controlled quenching after the desired reaction has taken place. Based on early observations made by Tanner and coworkers, hydrosilanes and Lewis bases can reduce dinitrobenzene to the corresponding radical anion.¹⁷ One could thus envision the use

of hydrosilanes and Lewis bases to perform the Birch-alkylation of electron-deficient aromatic species (**Scheme 5.3**).

Scheme 5.3: TMDSO and KO^tBu might mediate the Birch-alkylation of dinitrobenzene



Overall, the transformations outlined in chapters 2, 3, and 4 are significantly different from one another with the unifying theme being the use of TMDSO and KO^tBu. As such, it is challenging to predict this chemistry's trajectory. In fact, high-throughput experimentation would be well suited towards discovering reactions using this reagent pair considering it is hard to predict what it is capable of. From a general standpoint the key features of this reagent combination are its tolerance of alkyl halides, redox properties, and its role as a strong base. Not only are these key features, but they operate synergistically with one another. The pursuit of novel transformations using these manifolds is unexplored territory which is surely going to bear fruit should anybody wander into it – and as J.R.R Tolkien once said:

Not all those who wander are lost.

Section 5.5 | References

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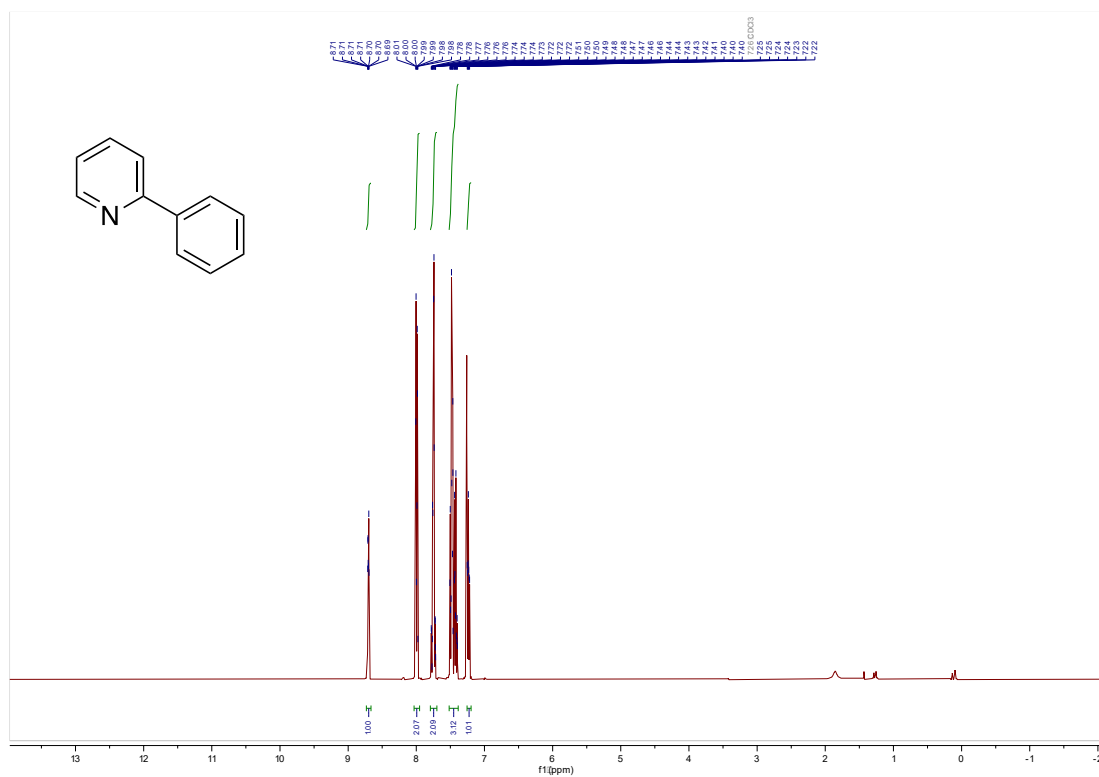
*For me, chemistry is a beautiful dance
matter moves in rhythm to the songs of kinetics and thermodynamics
sometimes unimaginably hot, other times unfathomably cold
we choose which partners partake in the dance and sometimes when we're lucky
a beautiful romance ensues*

*...Though more often than not, you wind up staying late to clean out
your glassware!*

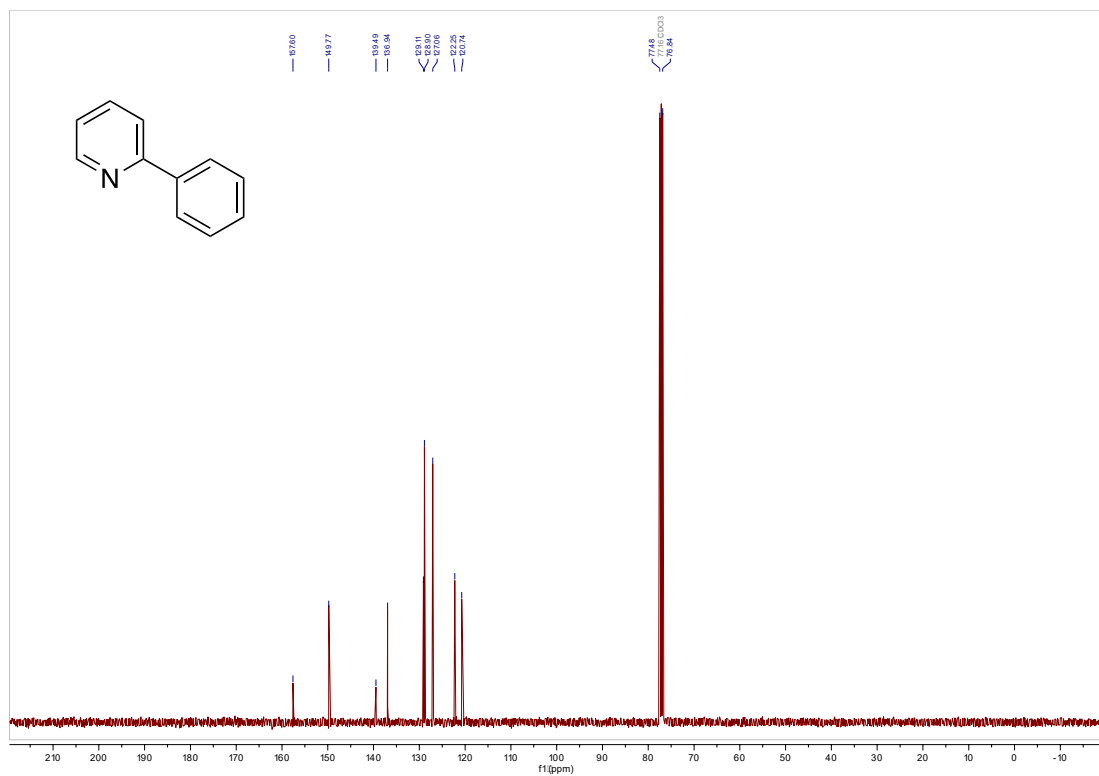
Thank you for reading my dissertation, I hope you enjoyed.

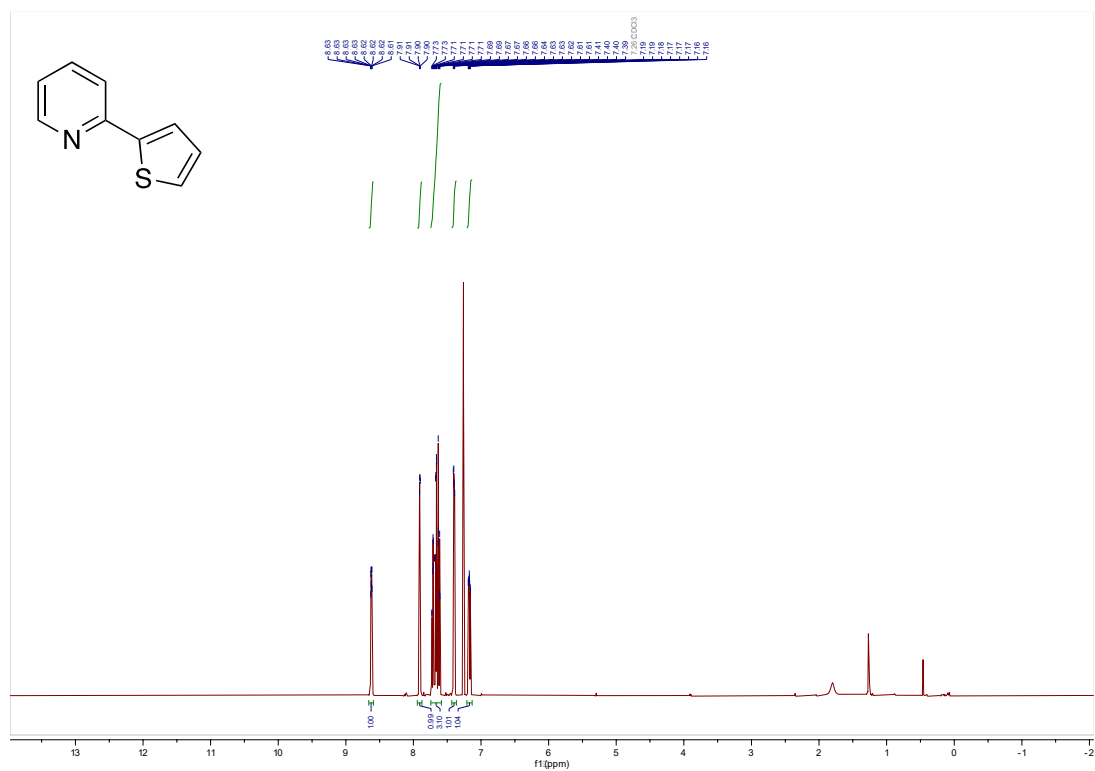
Appendix

NMR Spectra for Chapter 2:

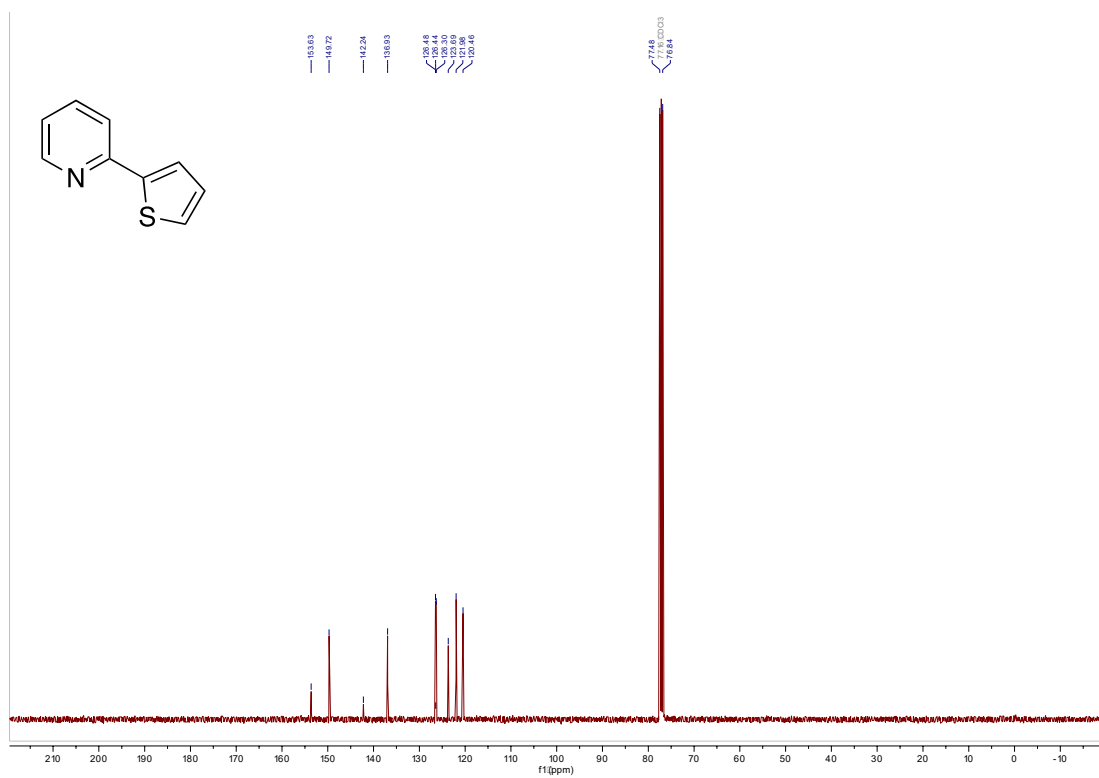
¹H NMR (400 MHz, CDCl₃) spectra of **2.7**

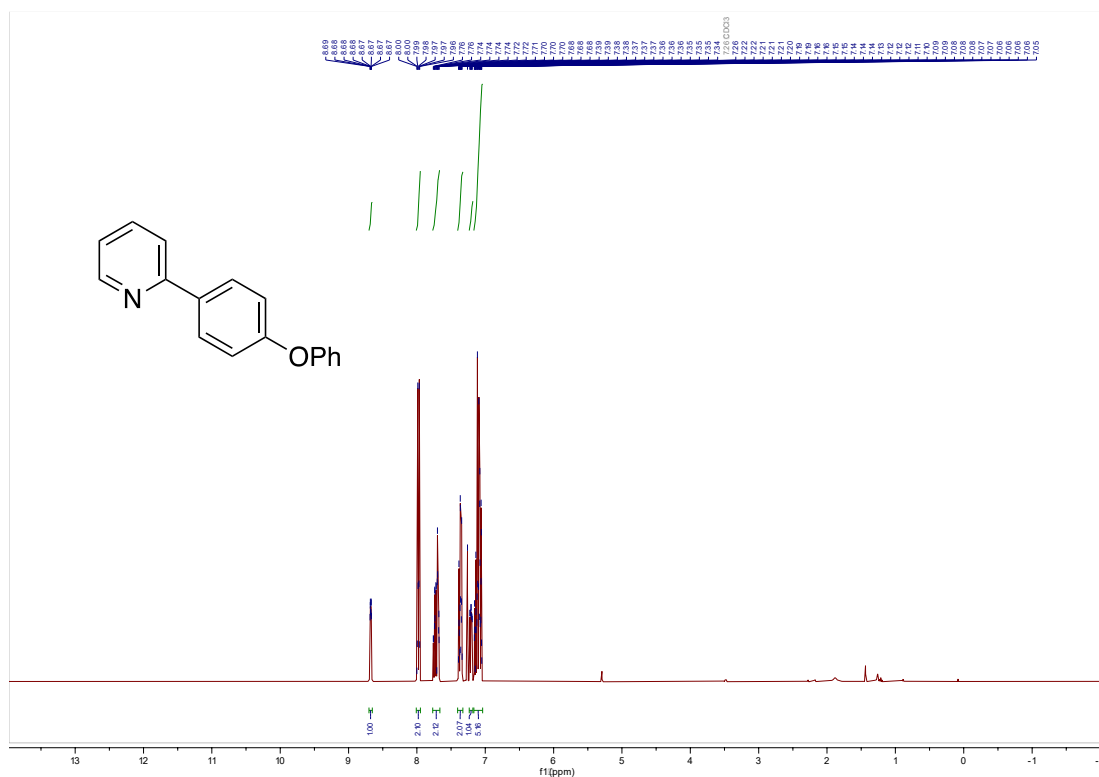
¹³C NMR (100 MHz, CDCl₃) spectra of **2.7**



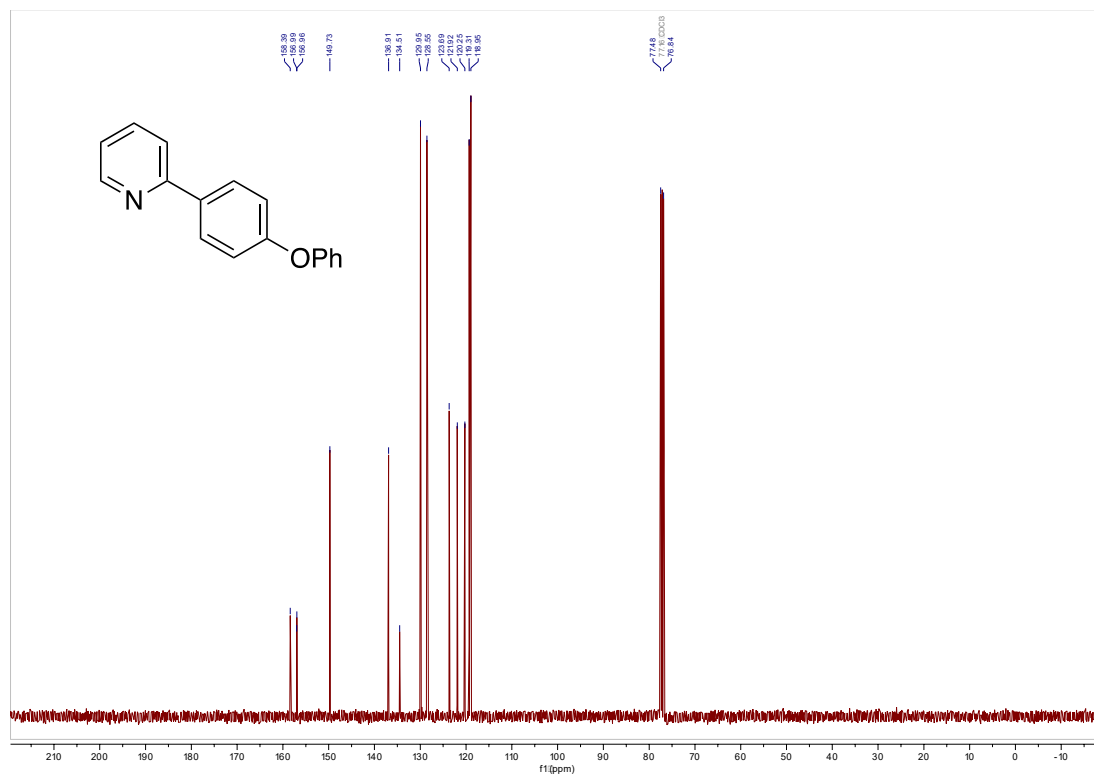
¹H NMR (400 MHz, CDCl₃) spectra of **2.56**

¹³C NMR (100 MHz, CDCl₃) spectra of **2.56**

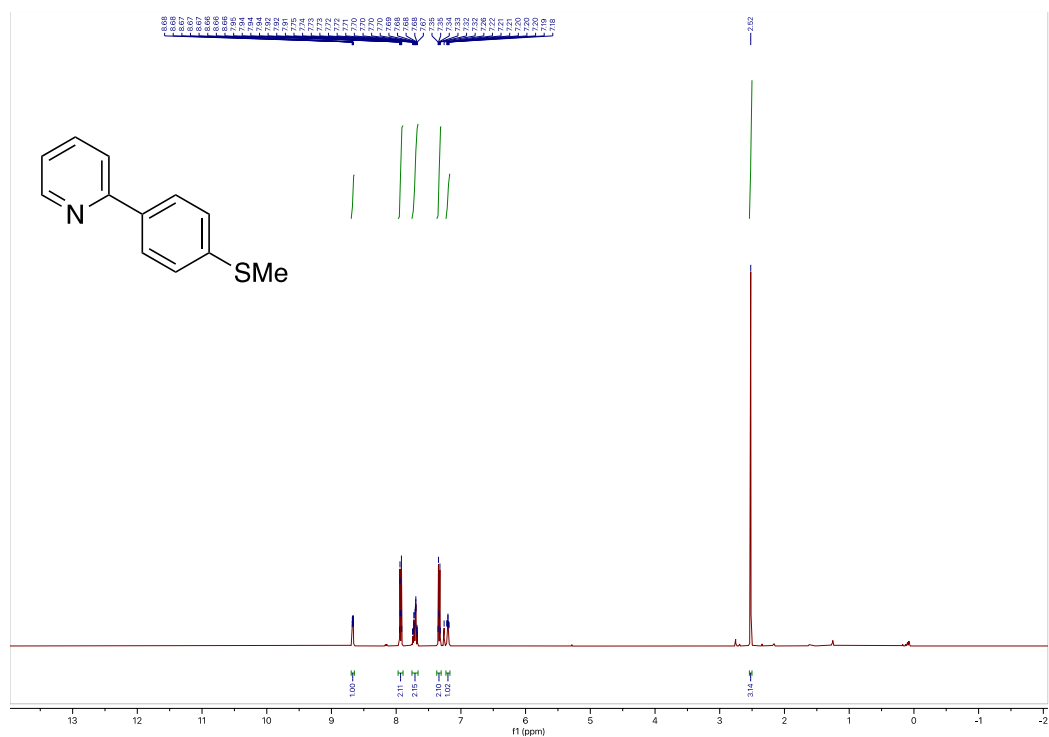


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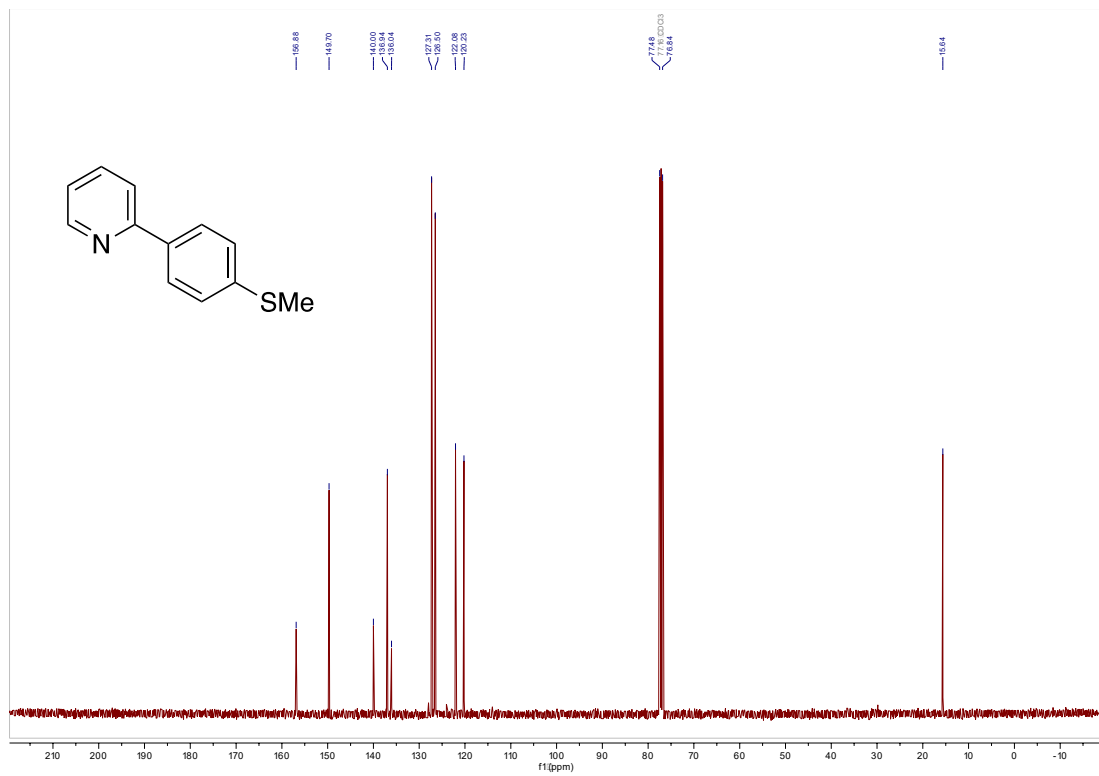
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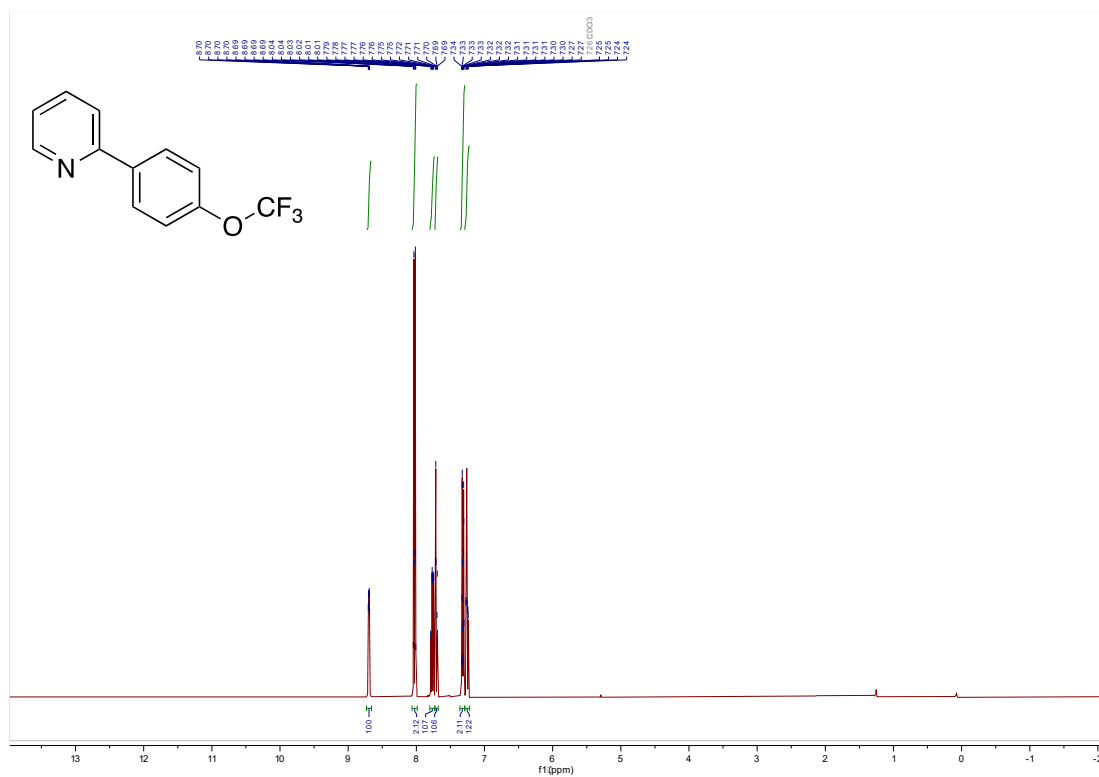
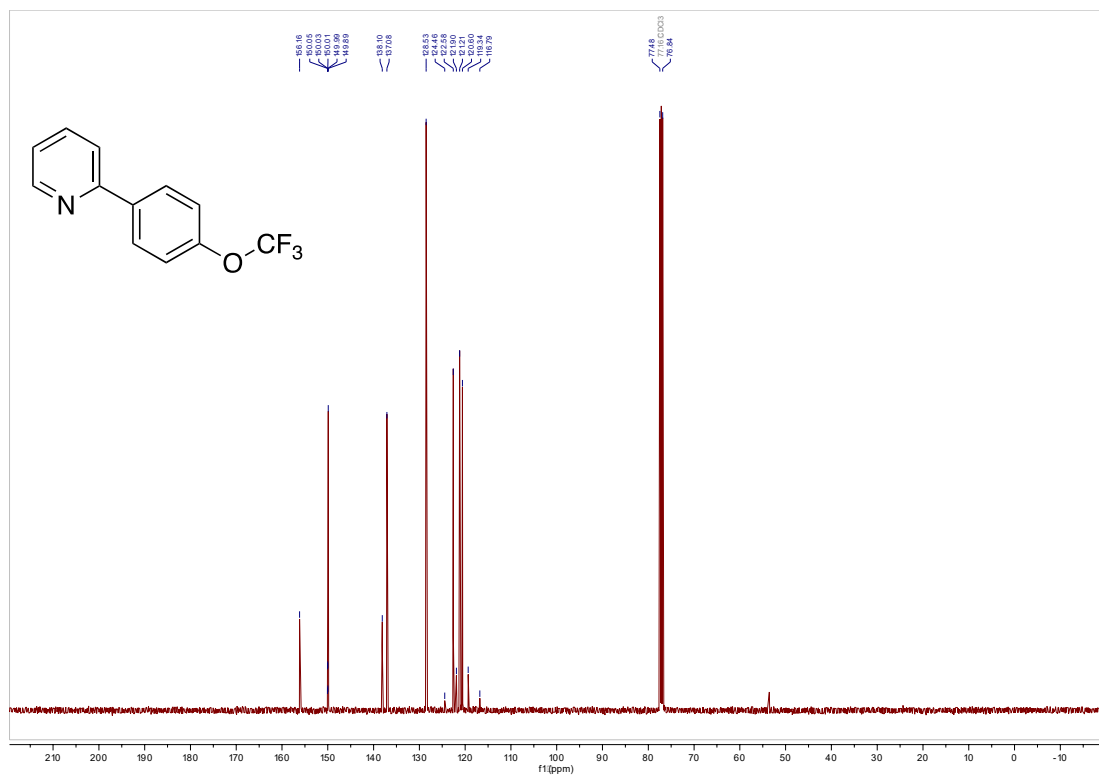


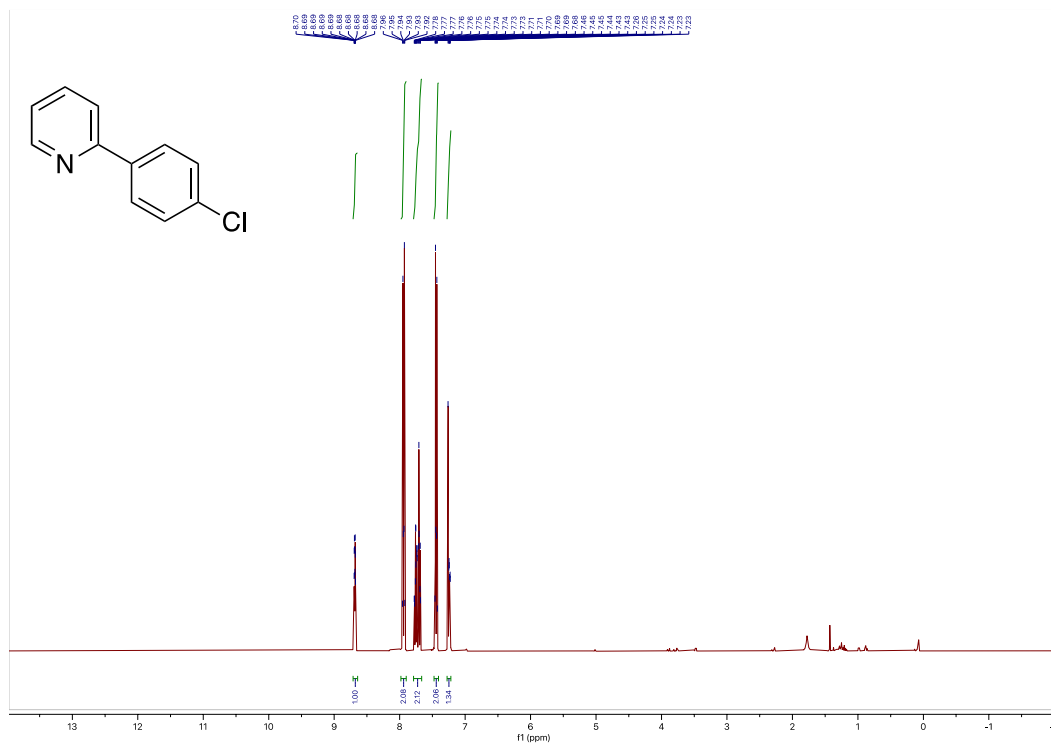
^1H NMR (400 MHz, CDCl_3) spectra of **2.58**



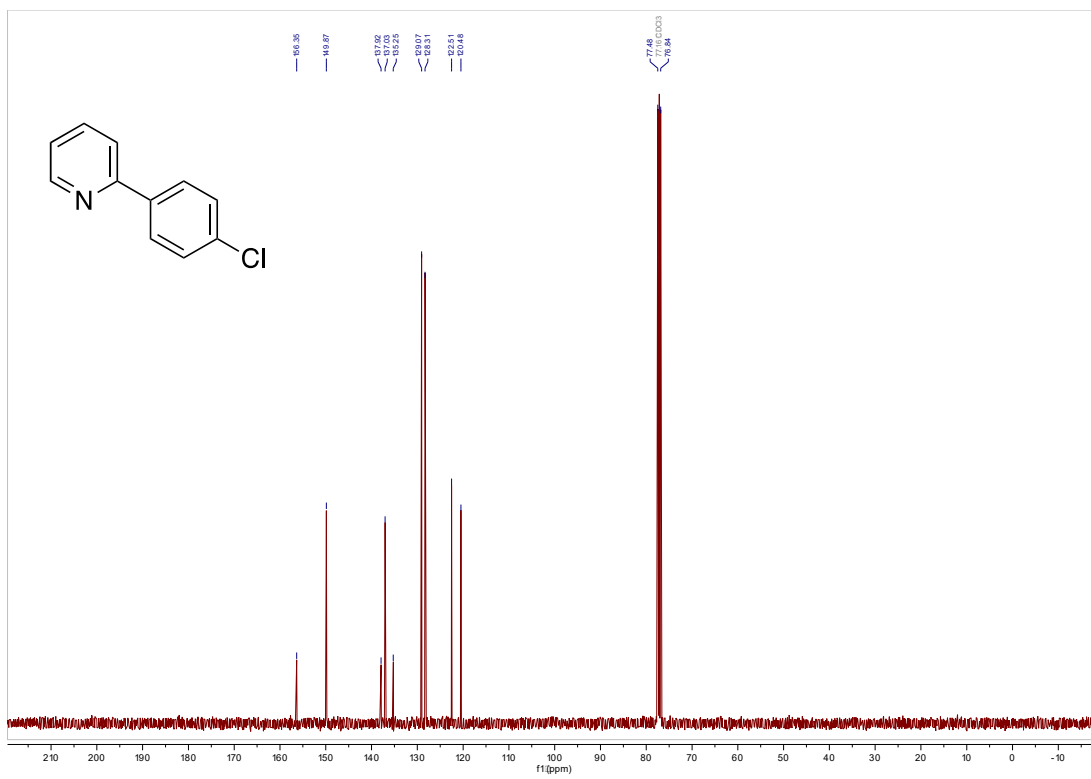
^{13}C NMR (100 MHz, CDCl_3) spectra of **2.58**



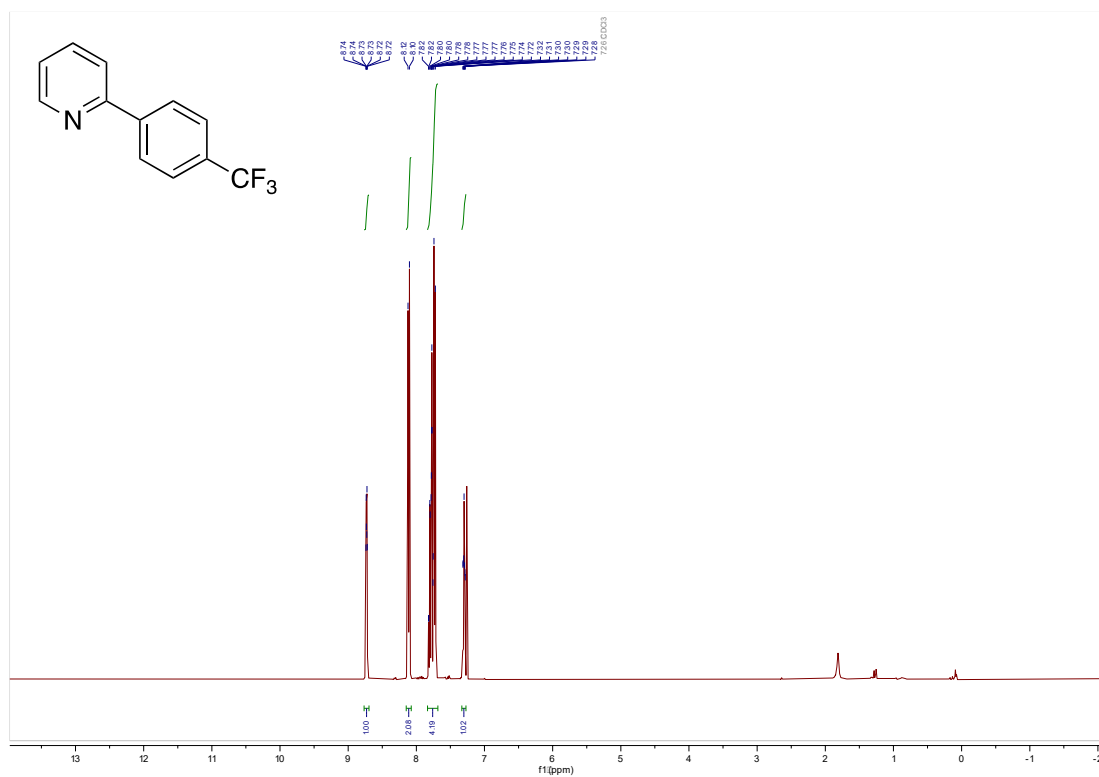
¹H NMR (400 MHz, CDCl₃) spectra of **2.59** ^{13}C NMR (100 MHz, CDCl_3) of **2.59**

¹H NMR (400 MHz, CDCl₃) spectra of **2.60**

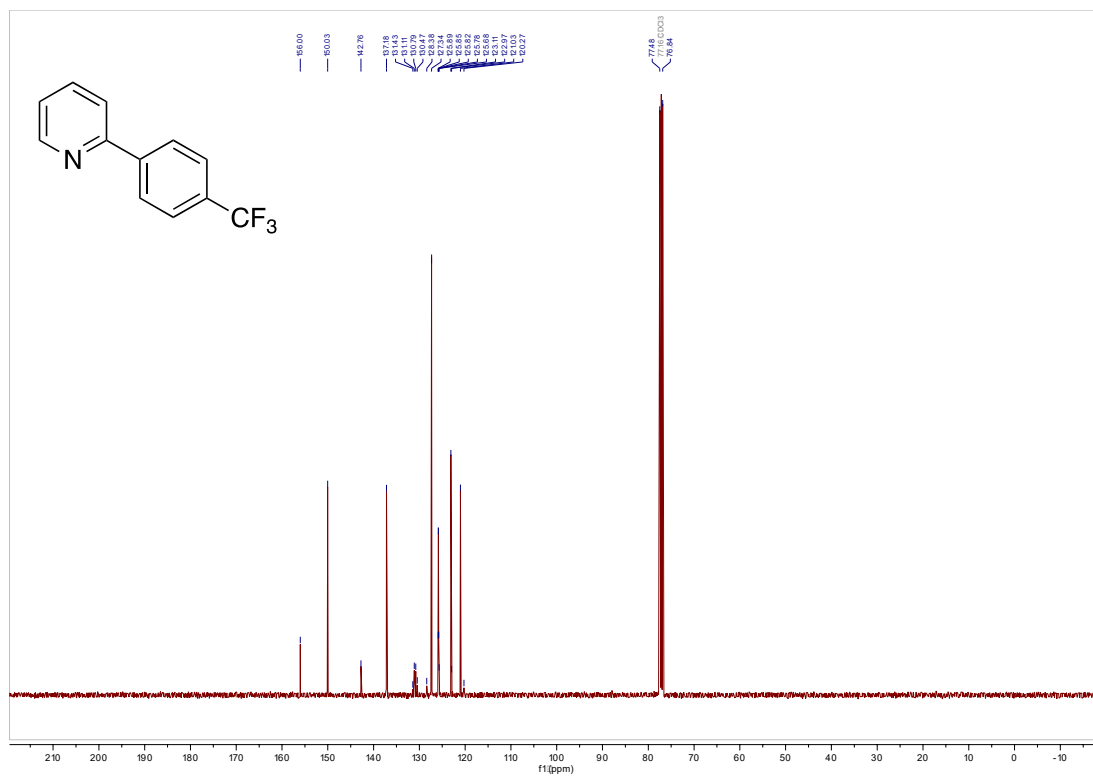
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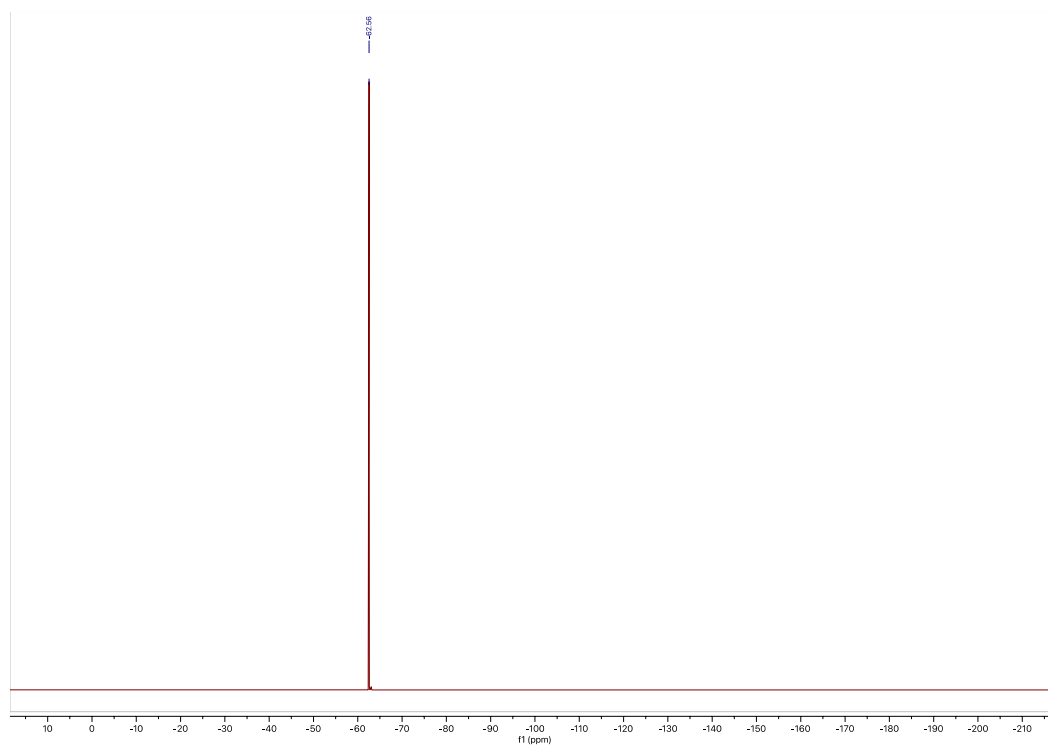
^1H NMR (CDCl_3 , 400 MHz) spectra of **2.61**



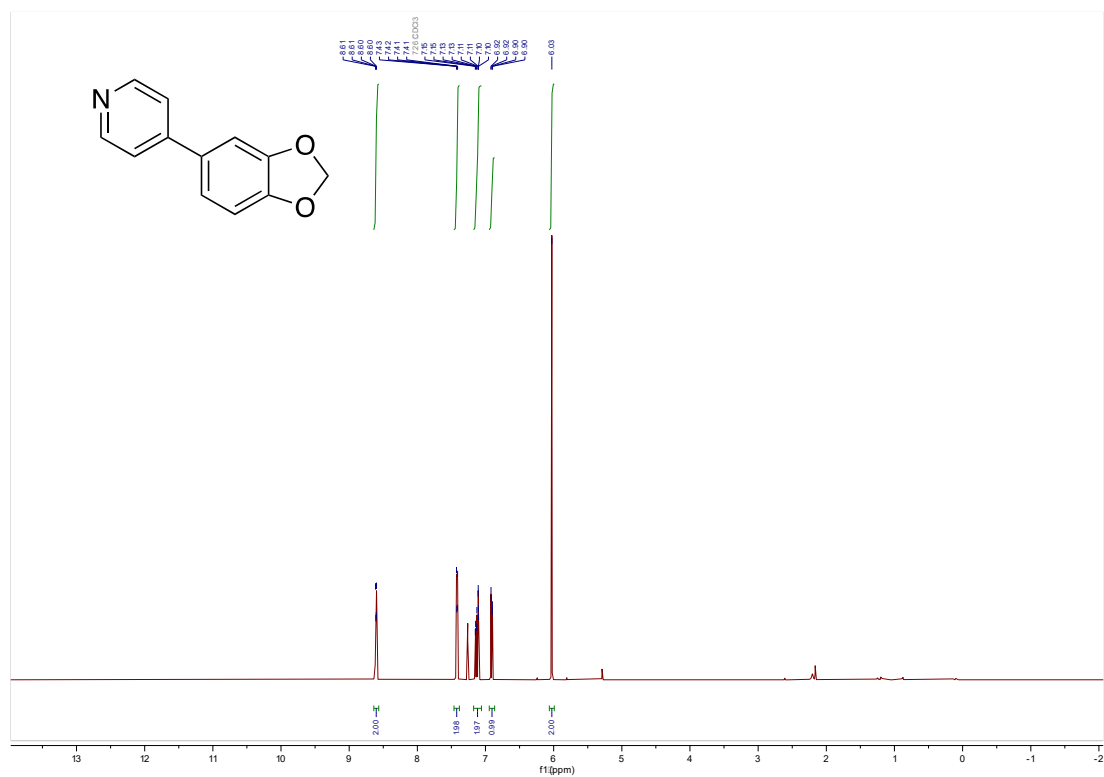
^{13}C NMR (CDCl_3 , 100 MHz) spectra of **2.61**



^{19}F NMR (CDCl_3 , 376 MHz) spectra of **2.61**



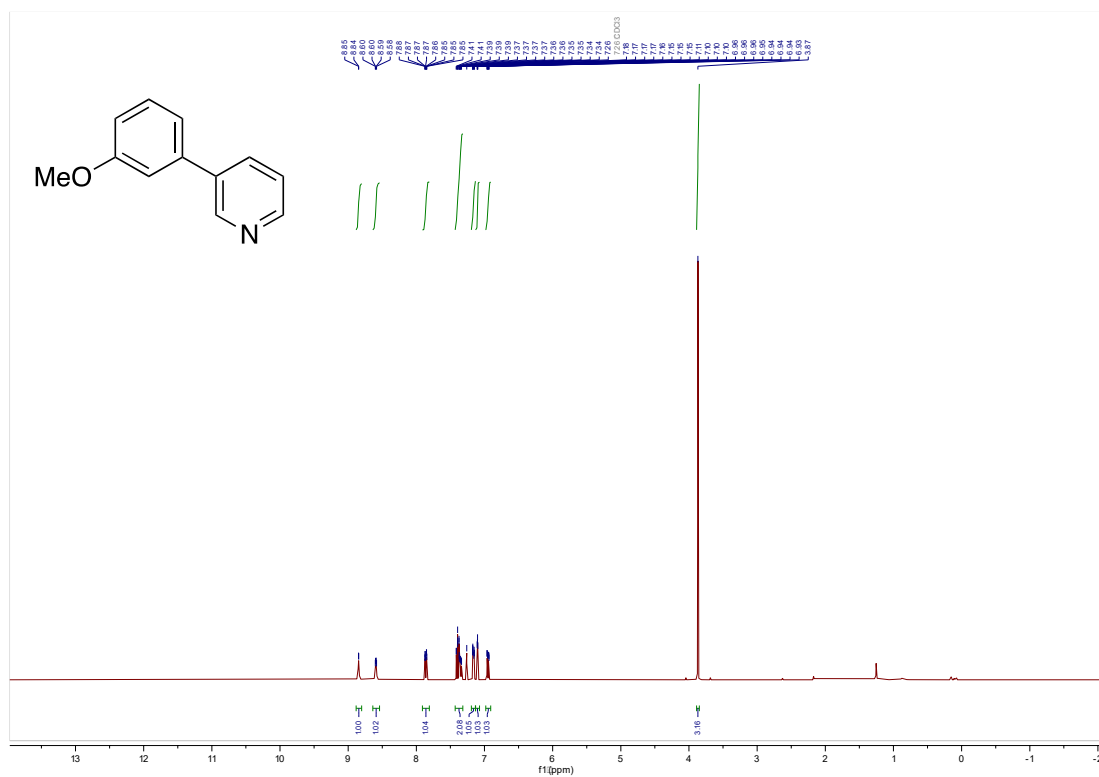
^1H NMR (400 MHz, CDCl_3) spectra of **2.62**



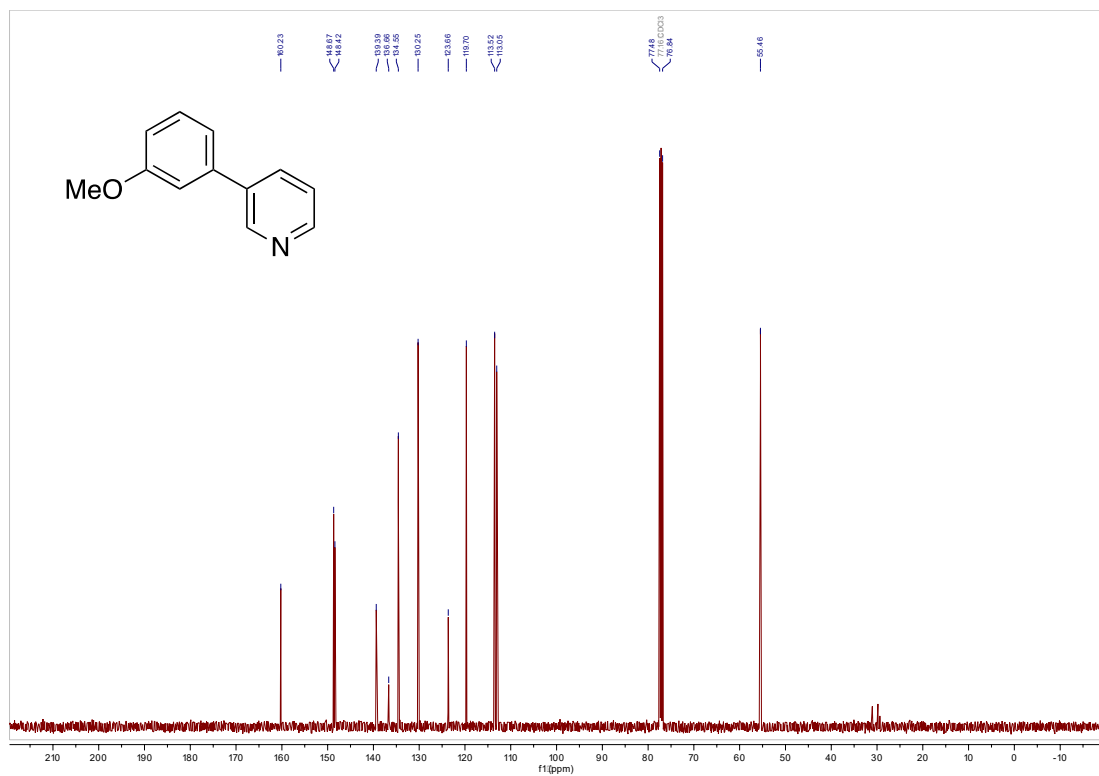
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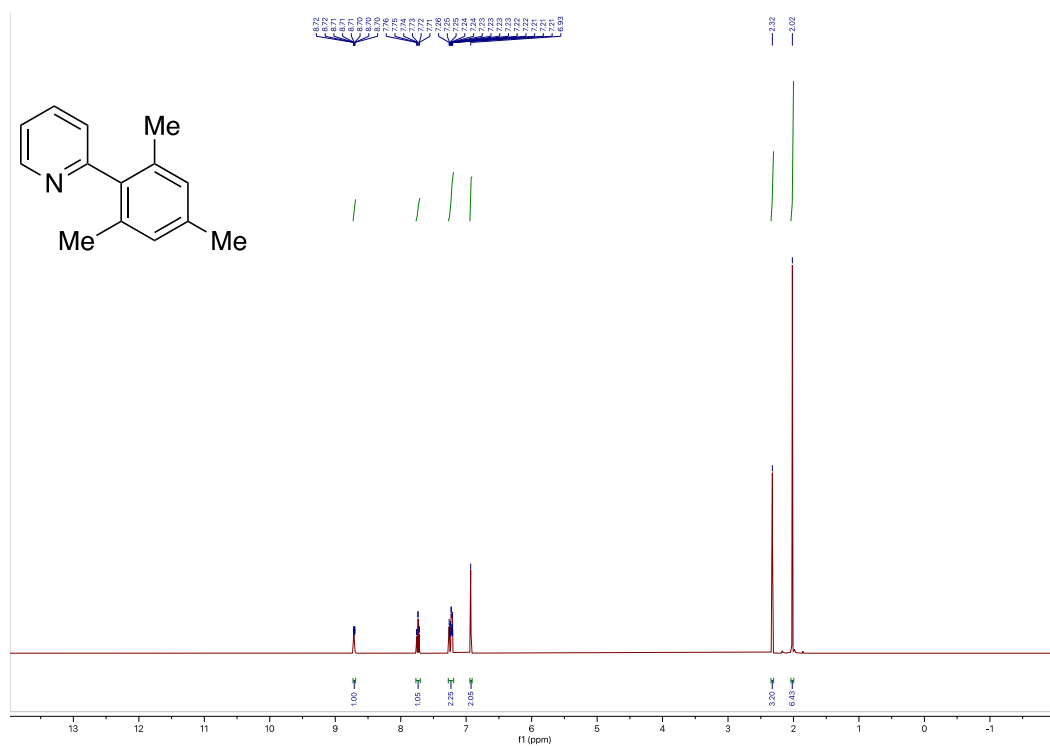
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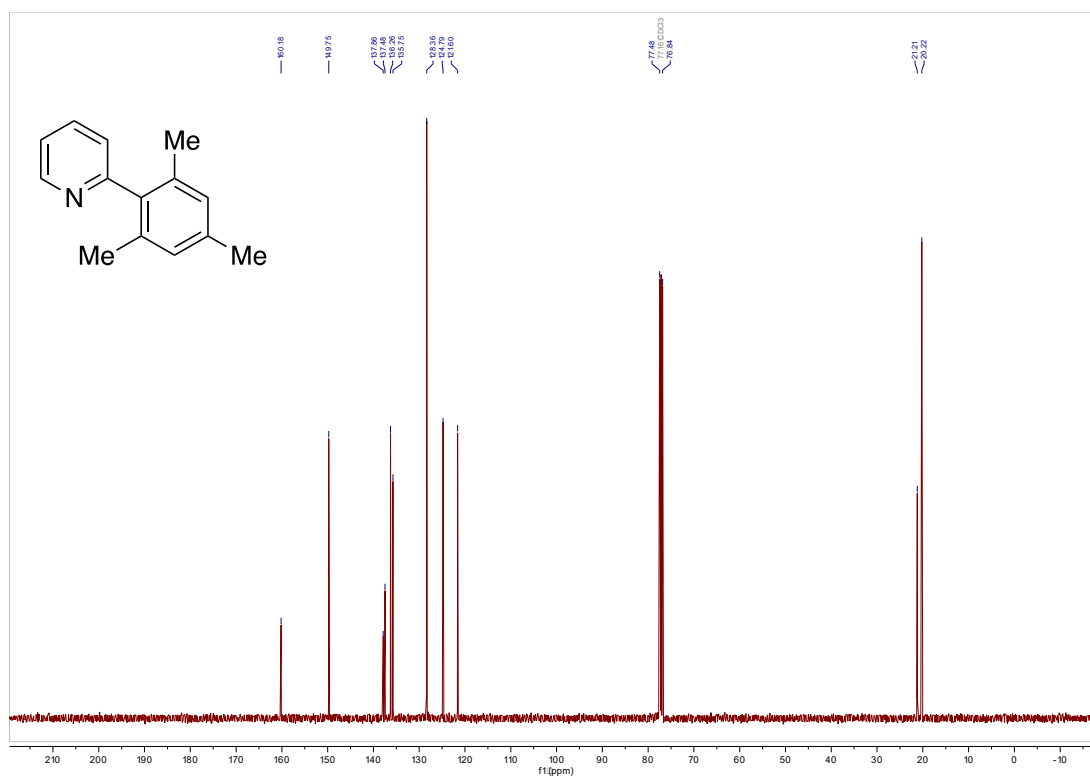
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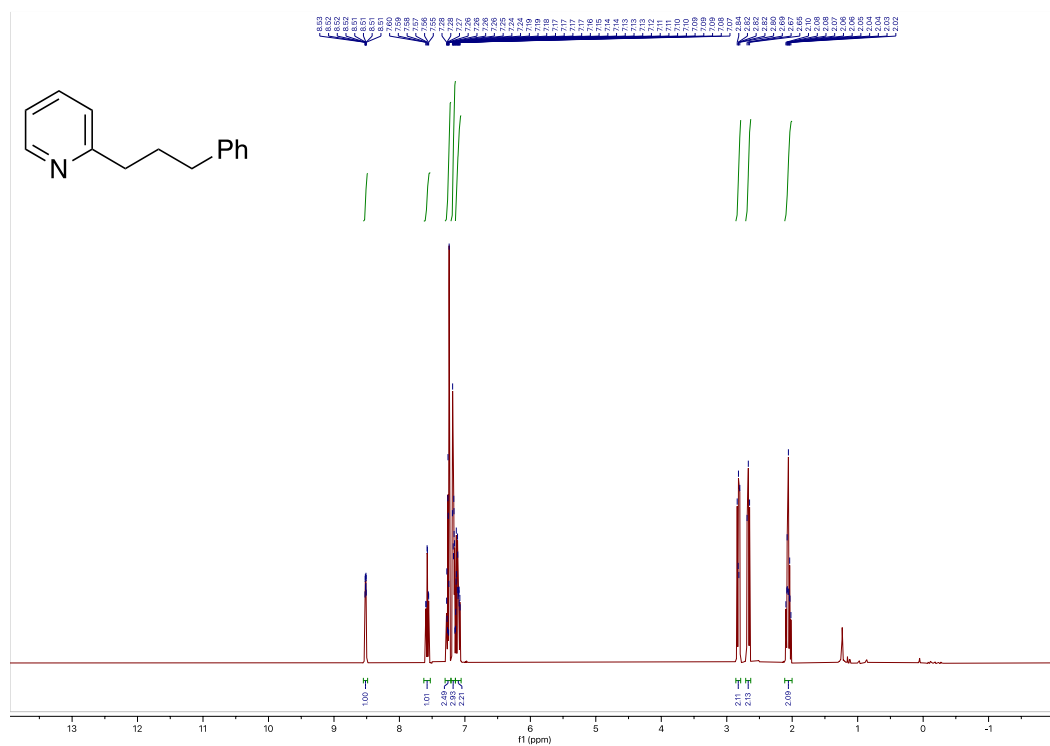
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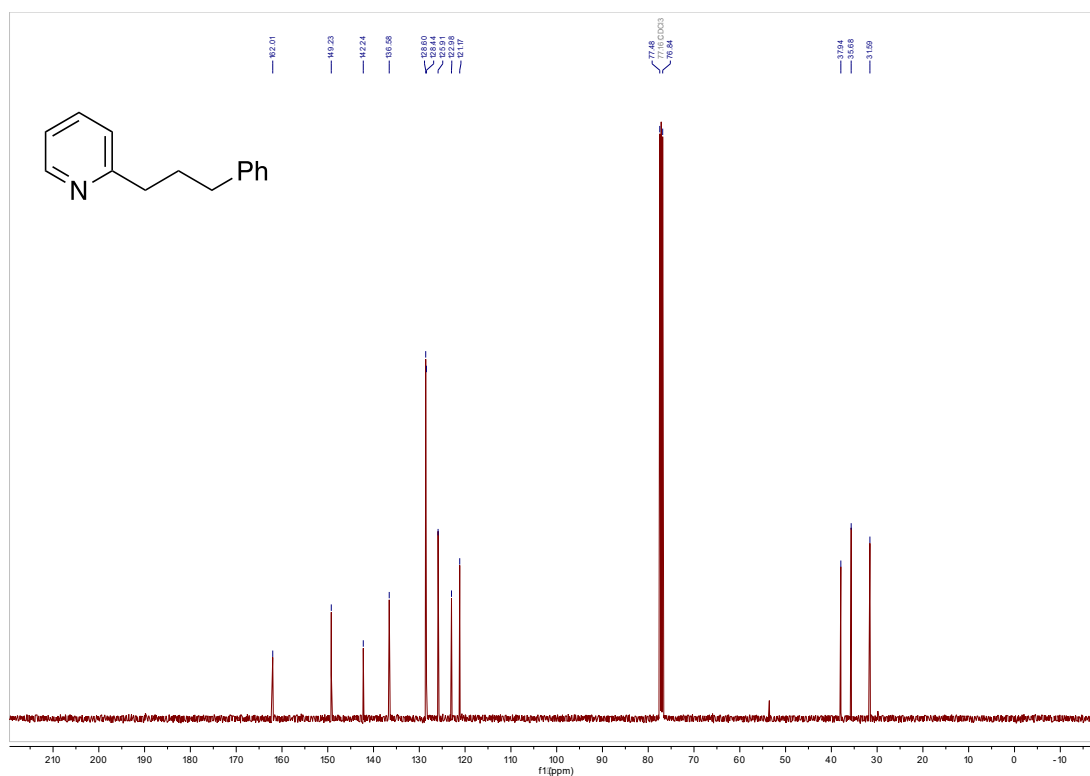
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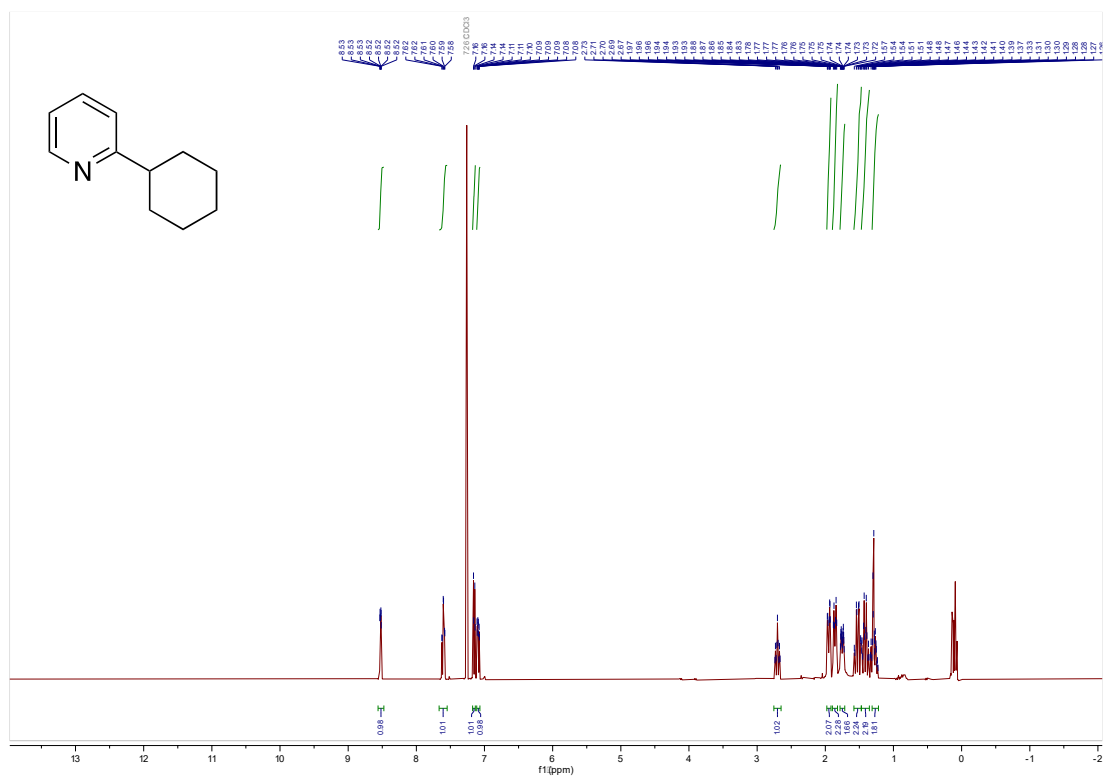
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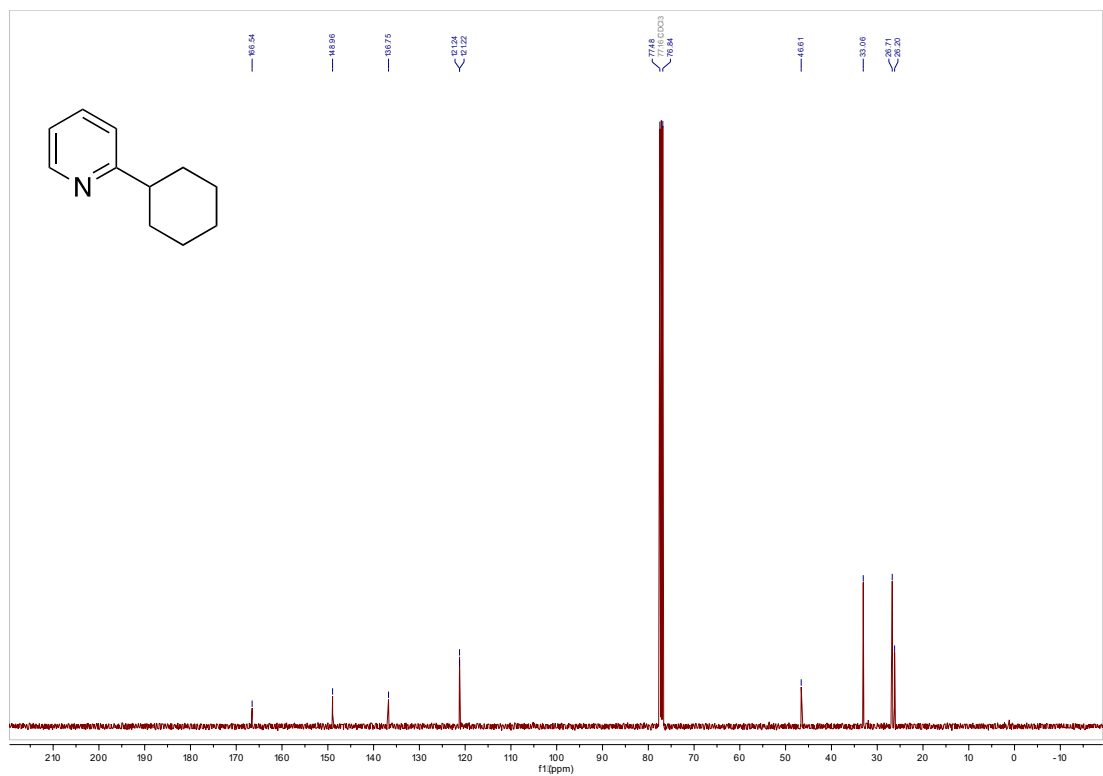
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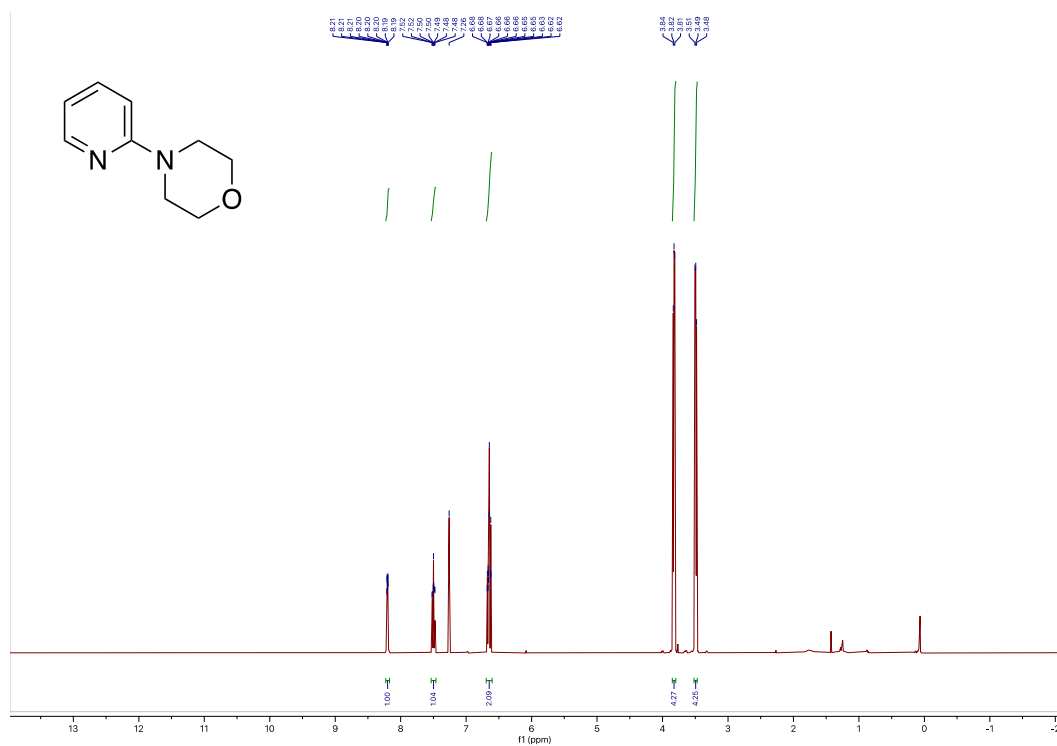
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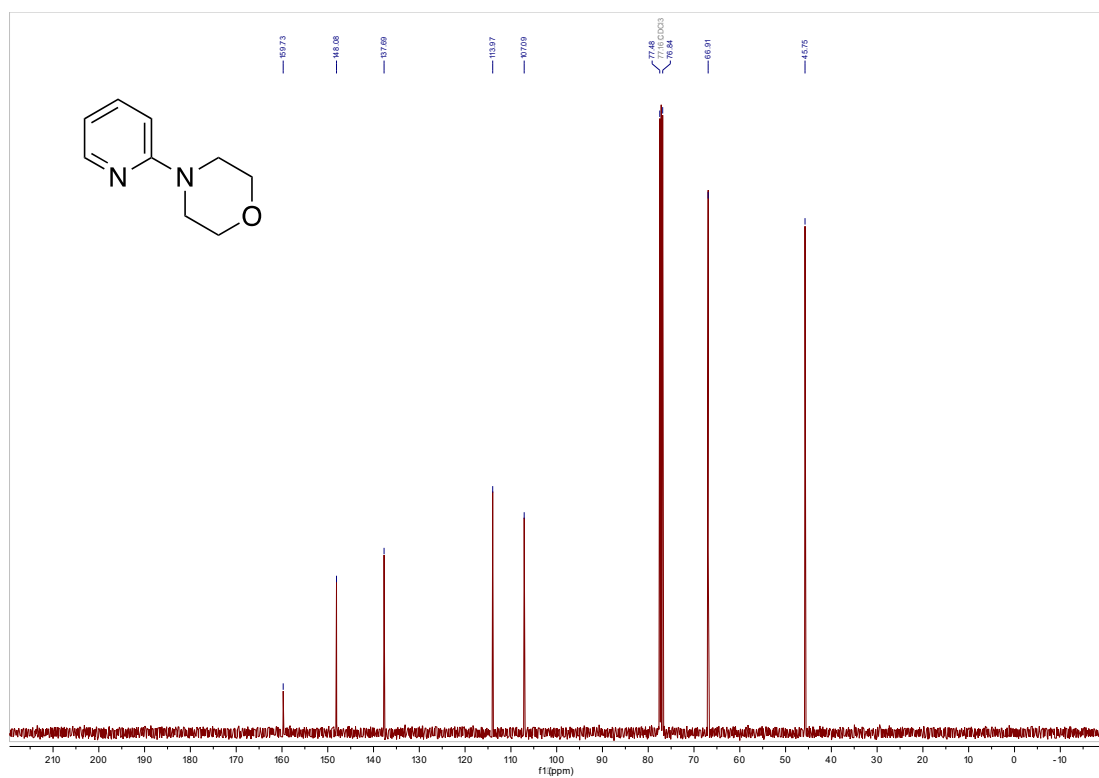
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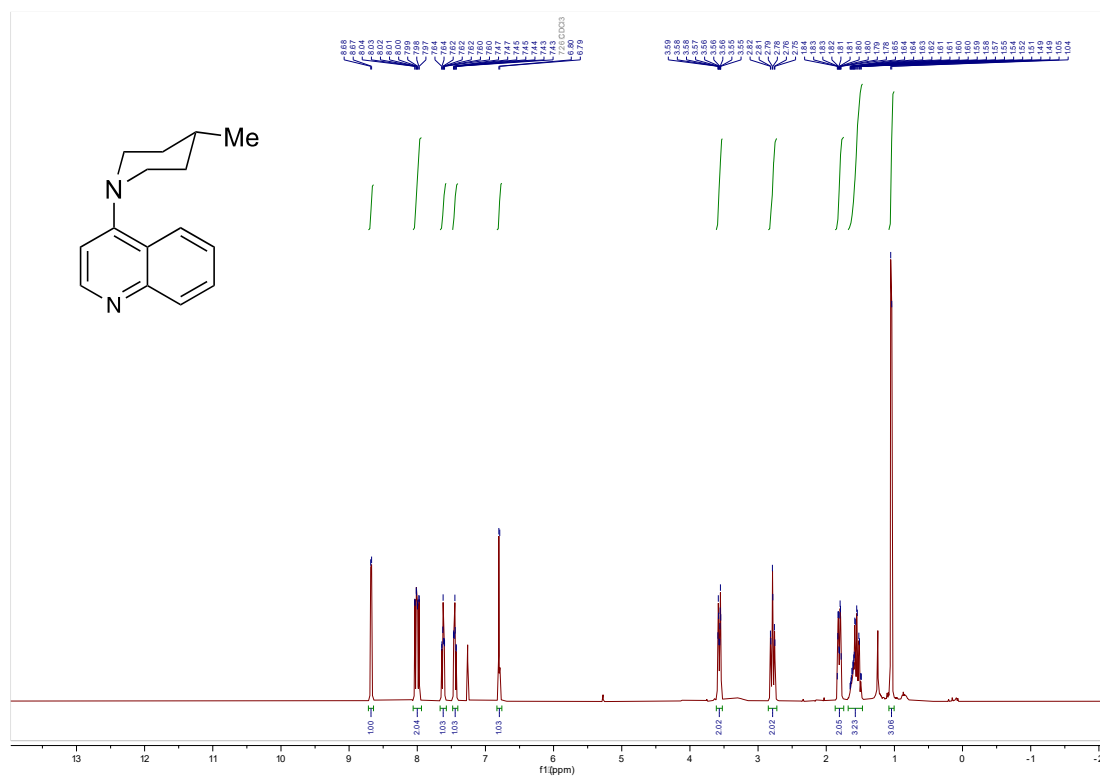
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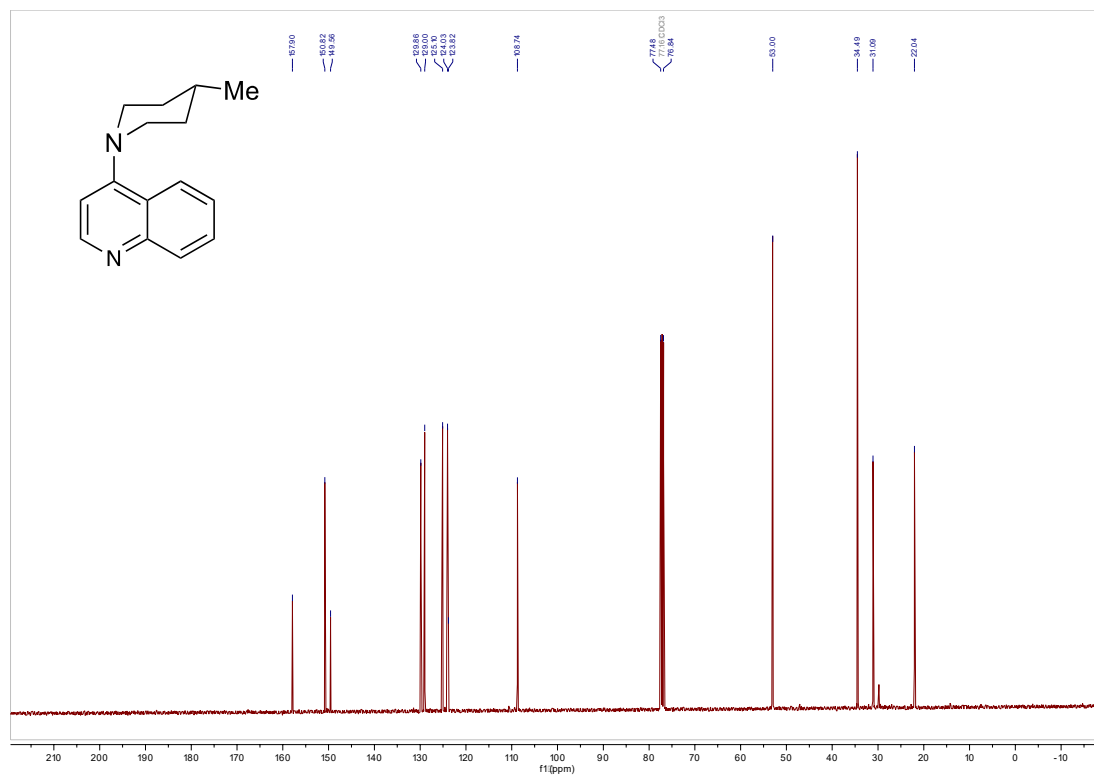
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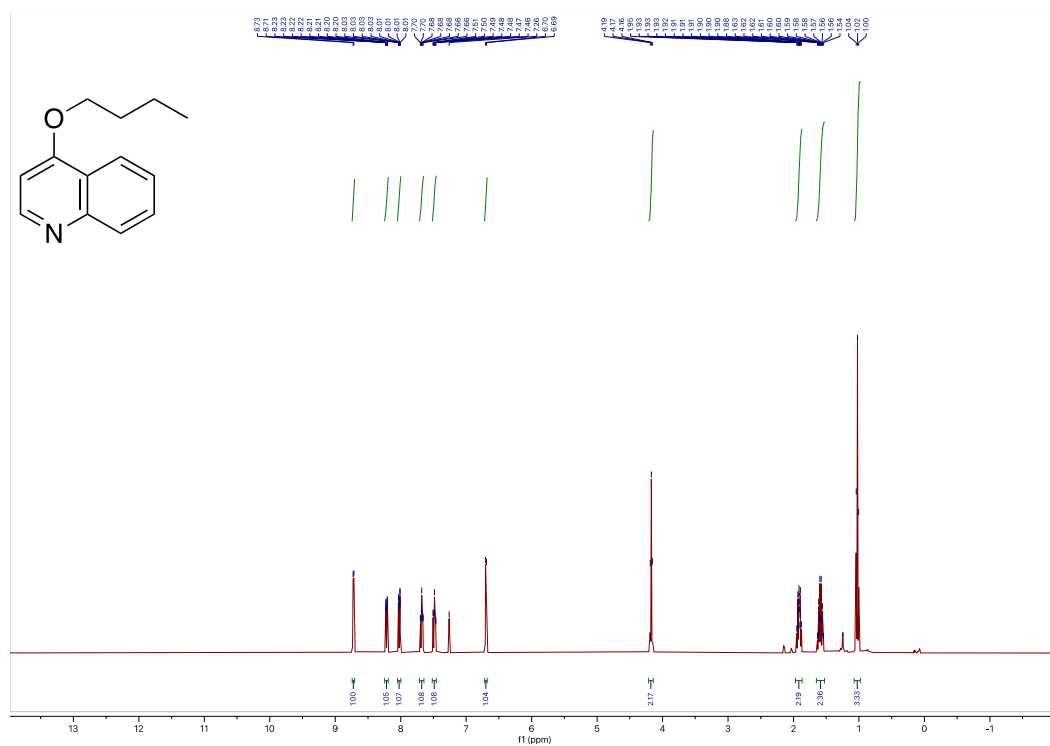
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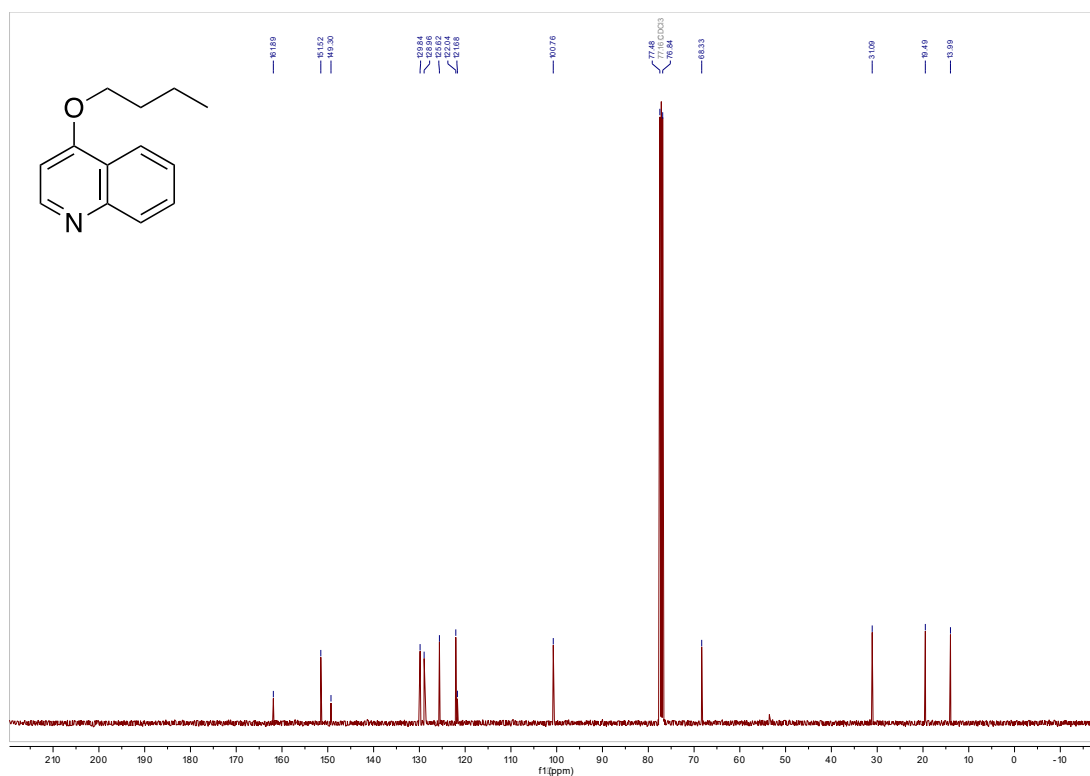
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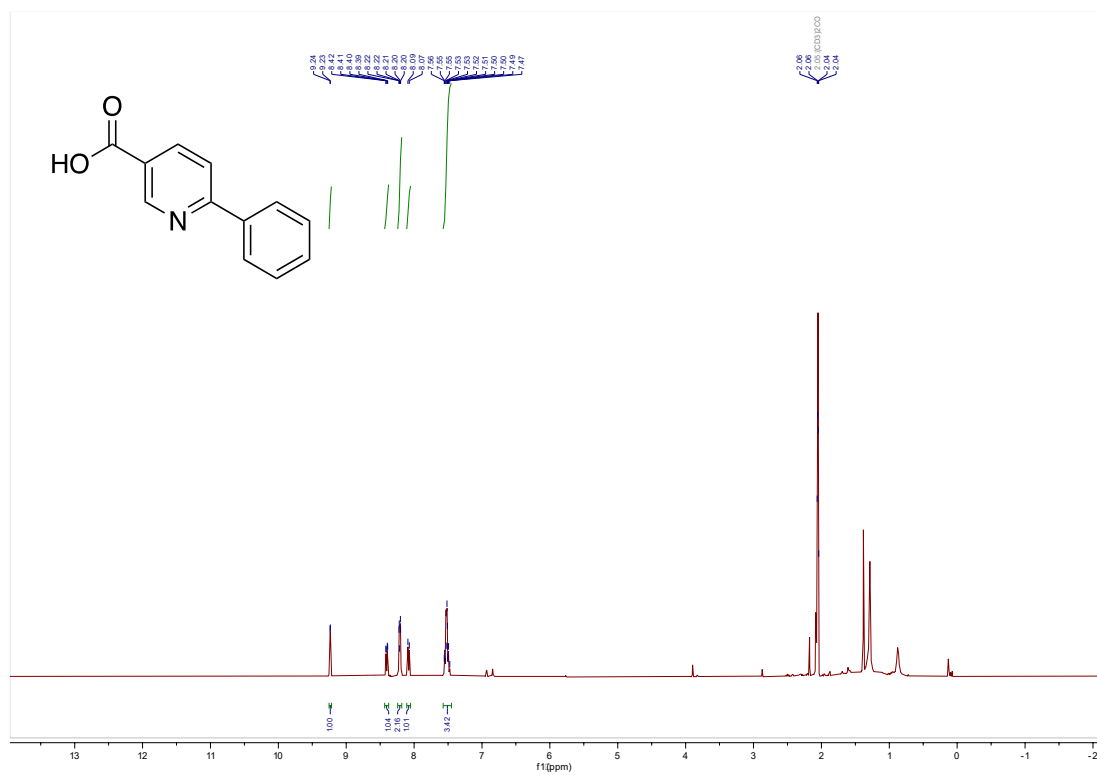
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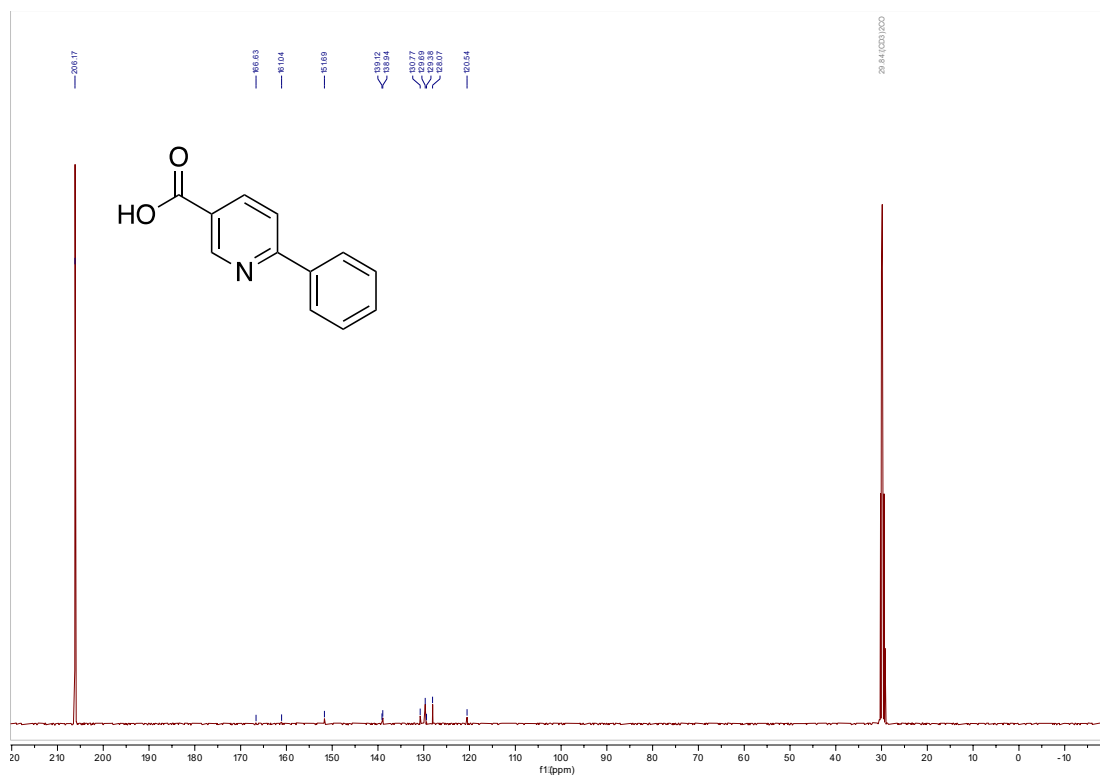
^{13}C NMR (100 MHz, CDCl_3) spectra of **2.68**



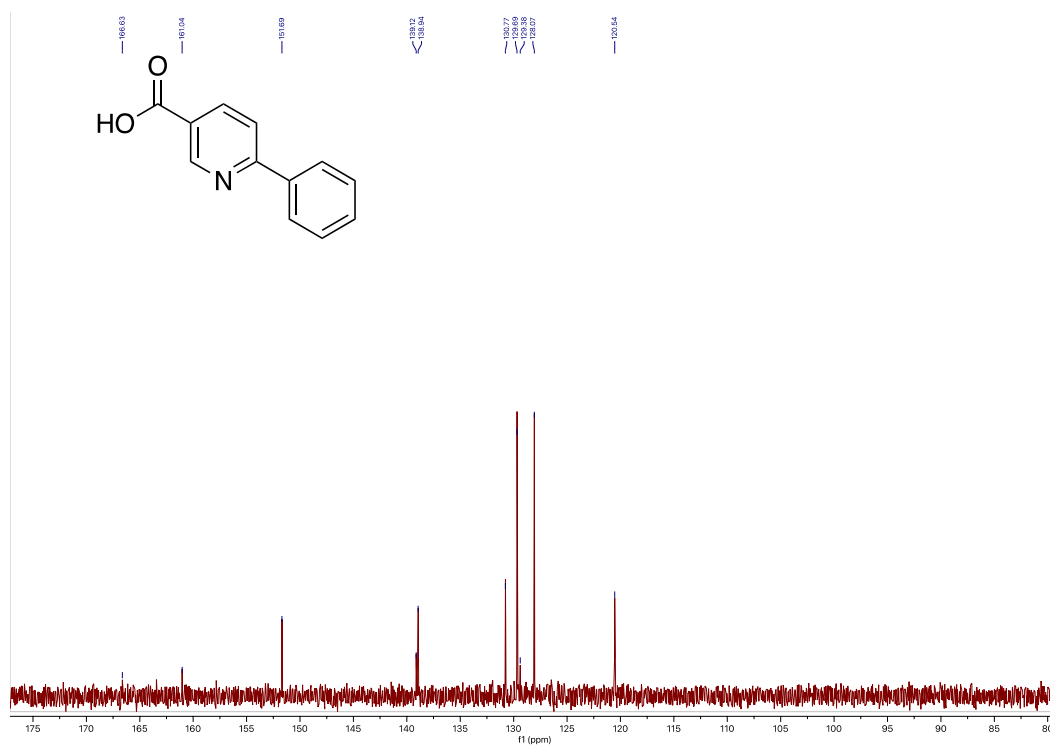
^1H NMR (400 MHz, d_6 -acetone) spectra of **2.23**



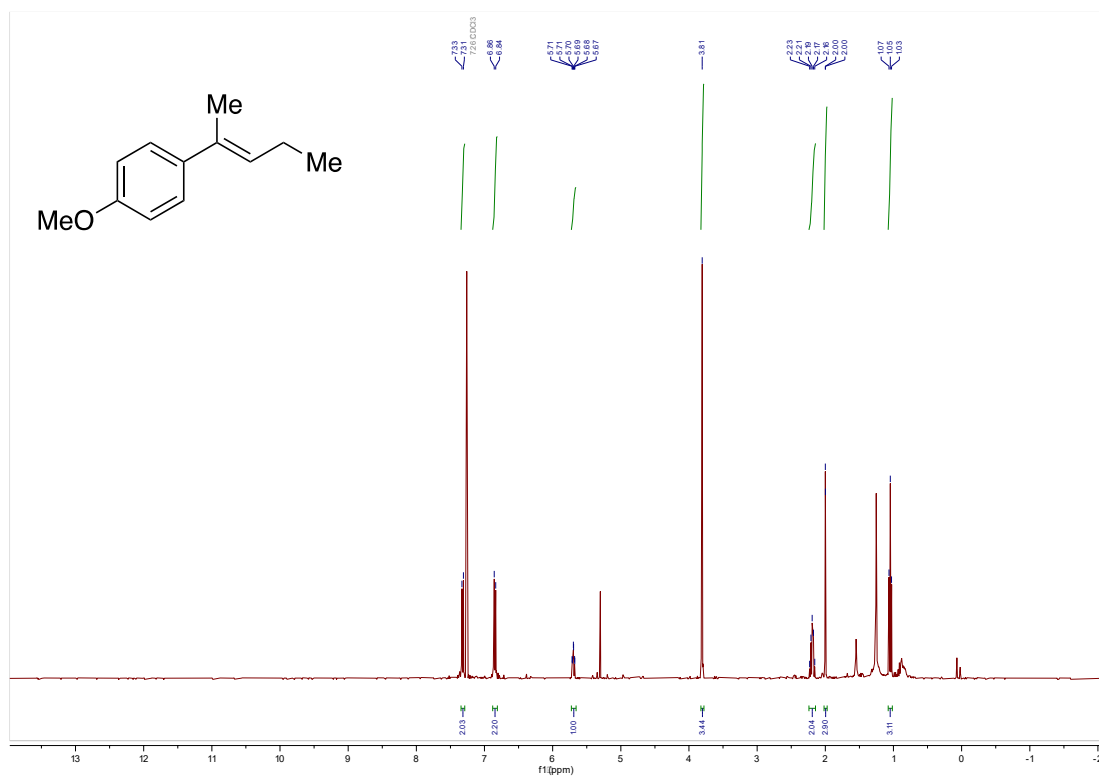
^{13}C NMR (100 MHz, d_6 -acetone) spectra of **2.23**



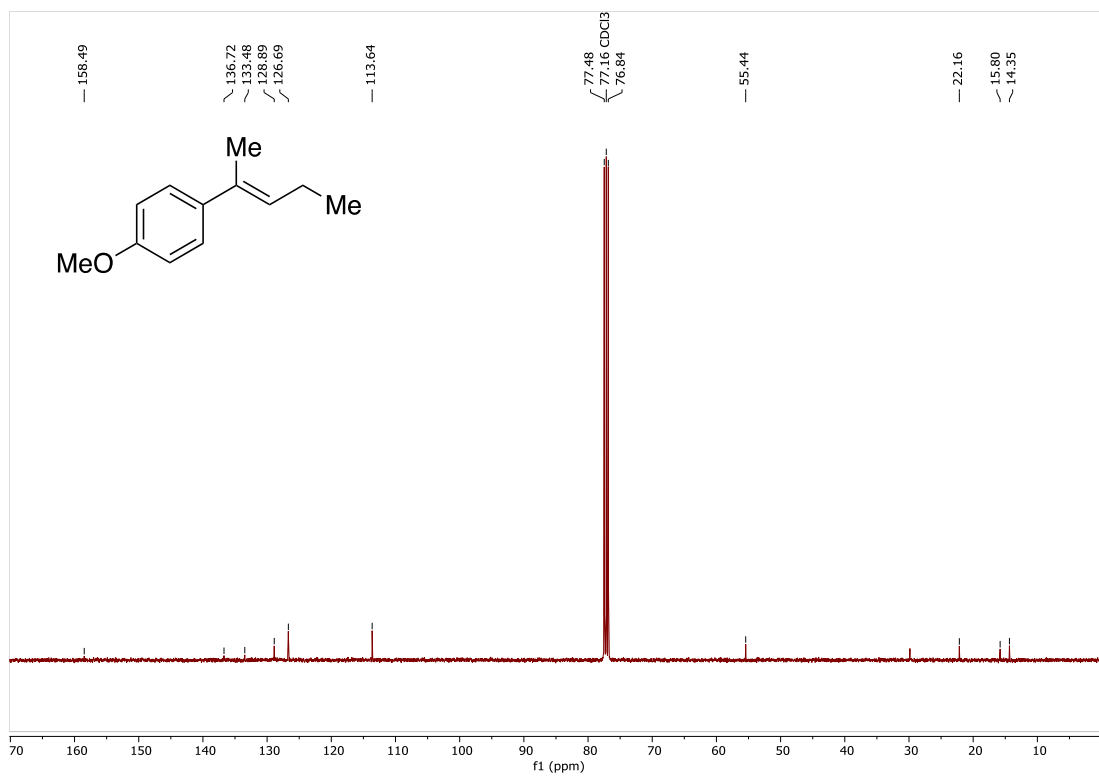
^{13}C NMR (100 MHz, d_6 -acetone, zoomed in) spectra of **2.23**



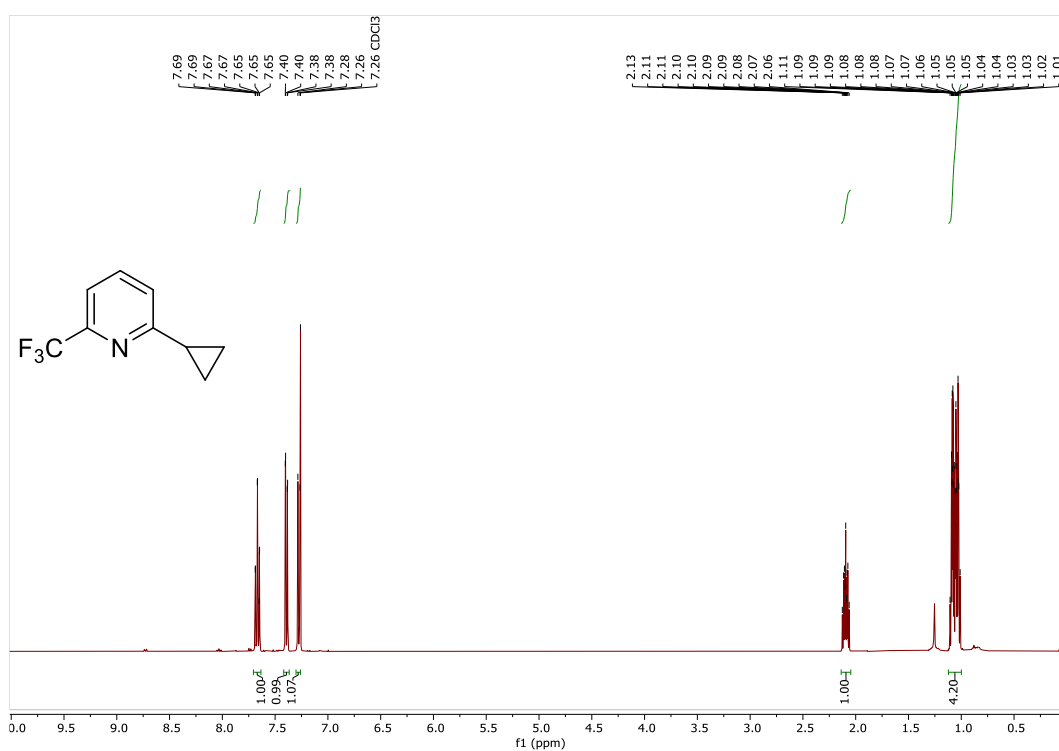
^1H NMR (400 MHz, CDCl_3) spectra of **2.29**



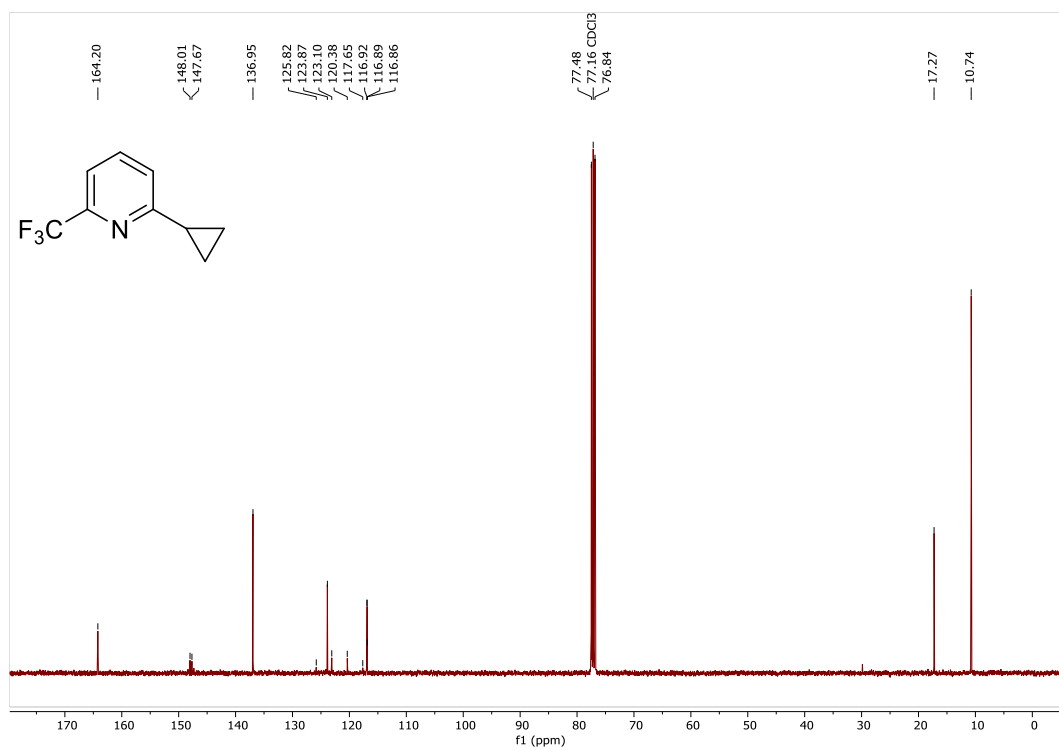
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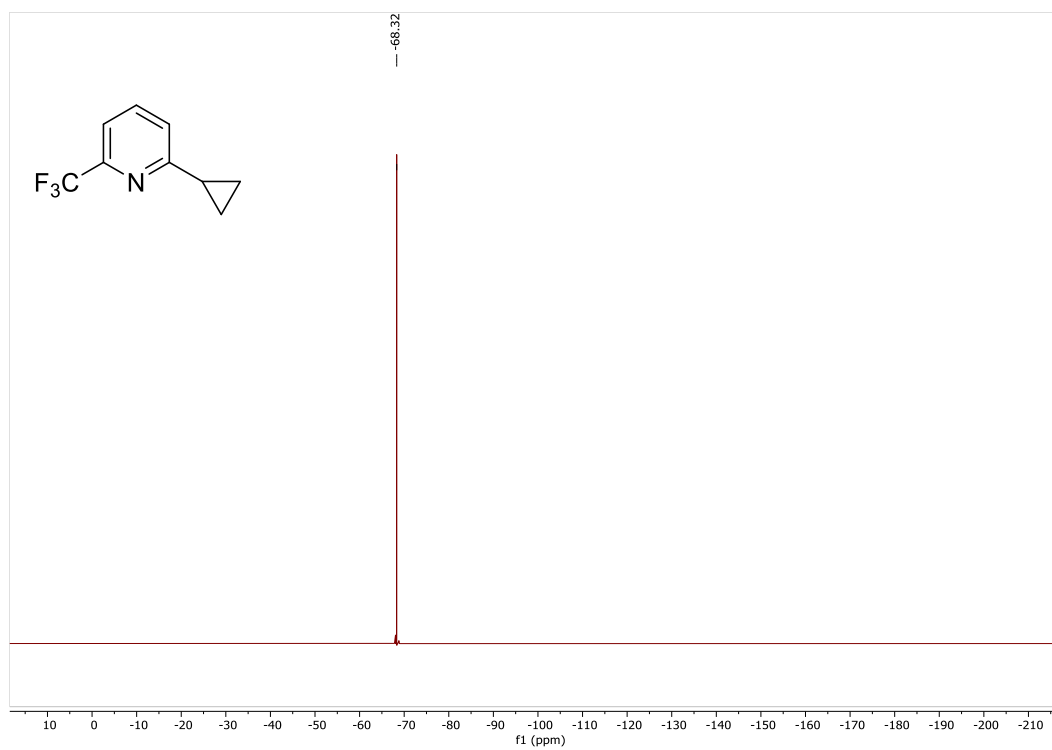
^1H NMR (400 MHz, CDCl_3) spectra of **2.43**



^{13}C NMR (100 MHz, CDCl_3) spectra of **2.43**

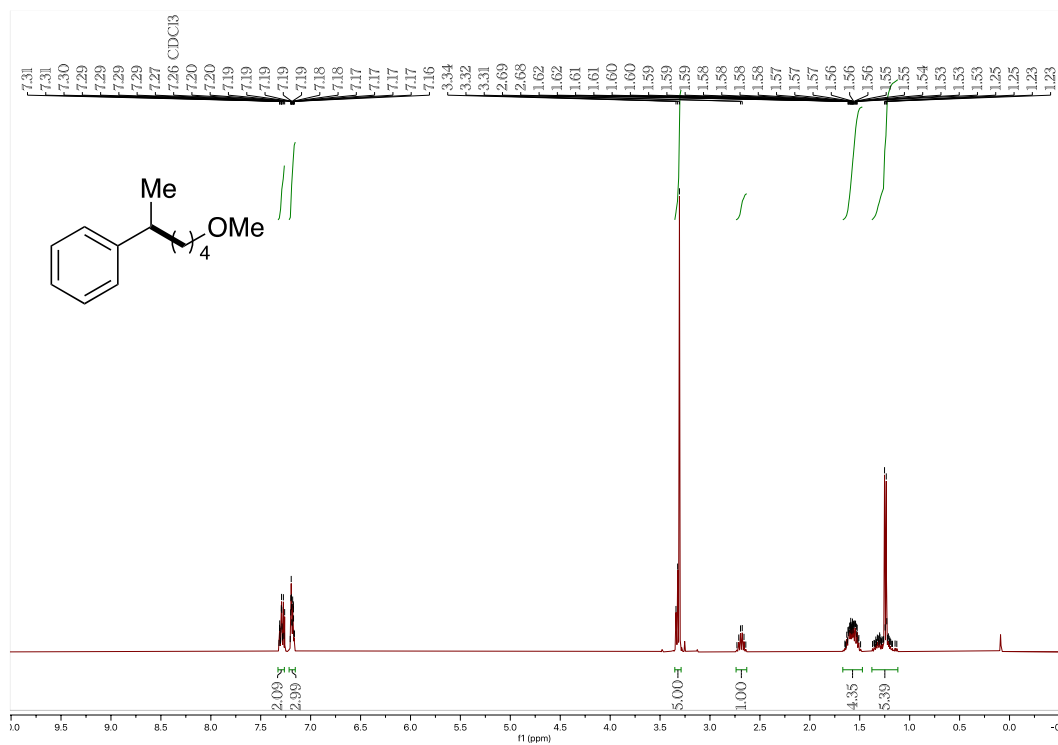


^{19}F NMR (376 MHz, CDCl_3) spectra of **2.43**

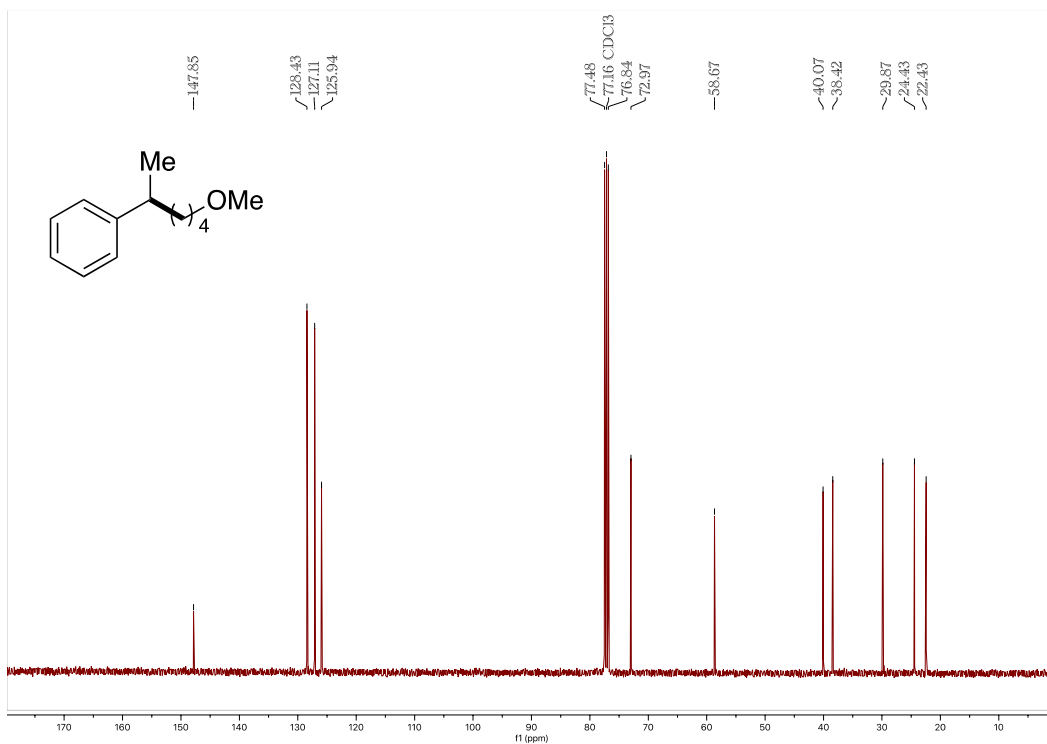


NMR Spectra for Chapter 3:

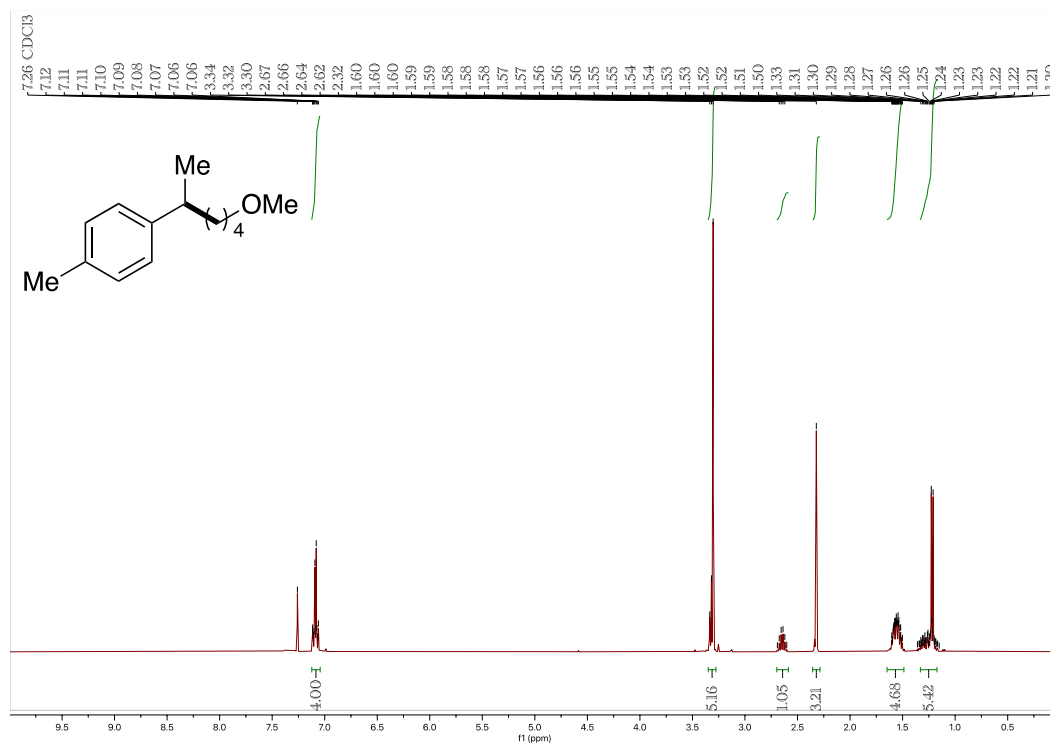
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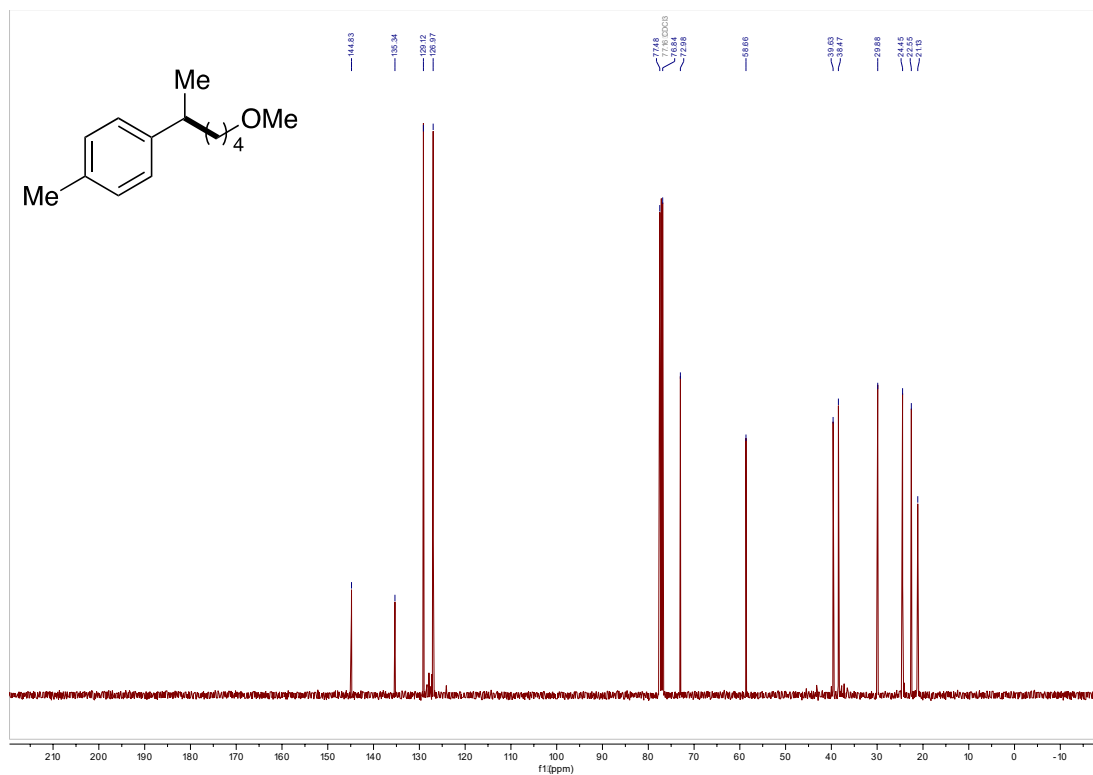
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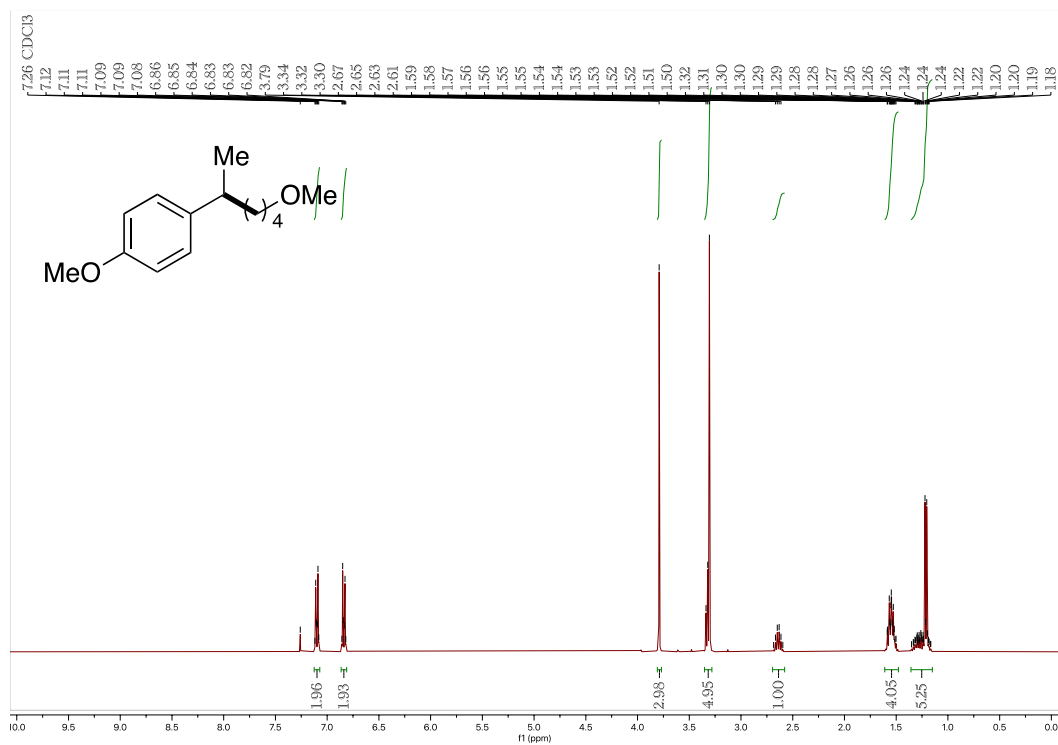
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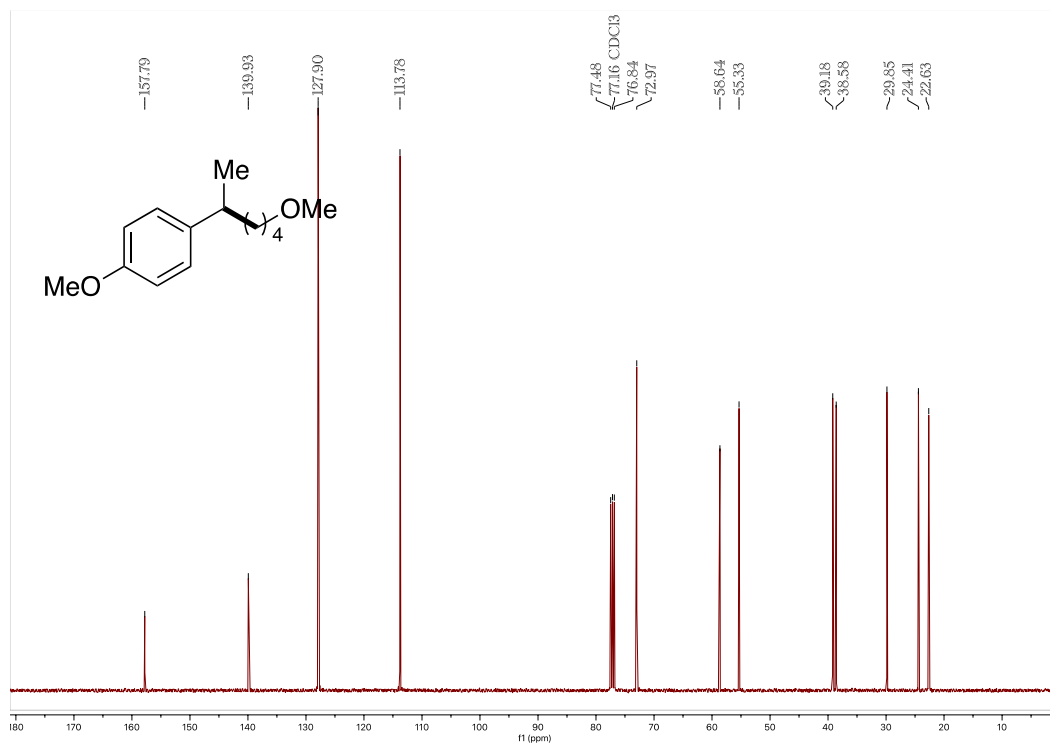
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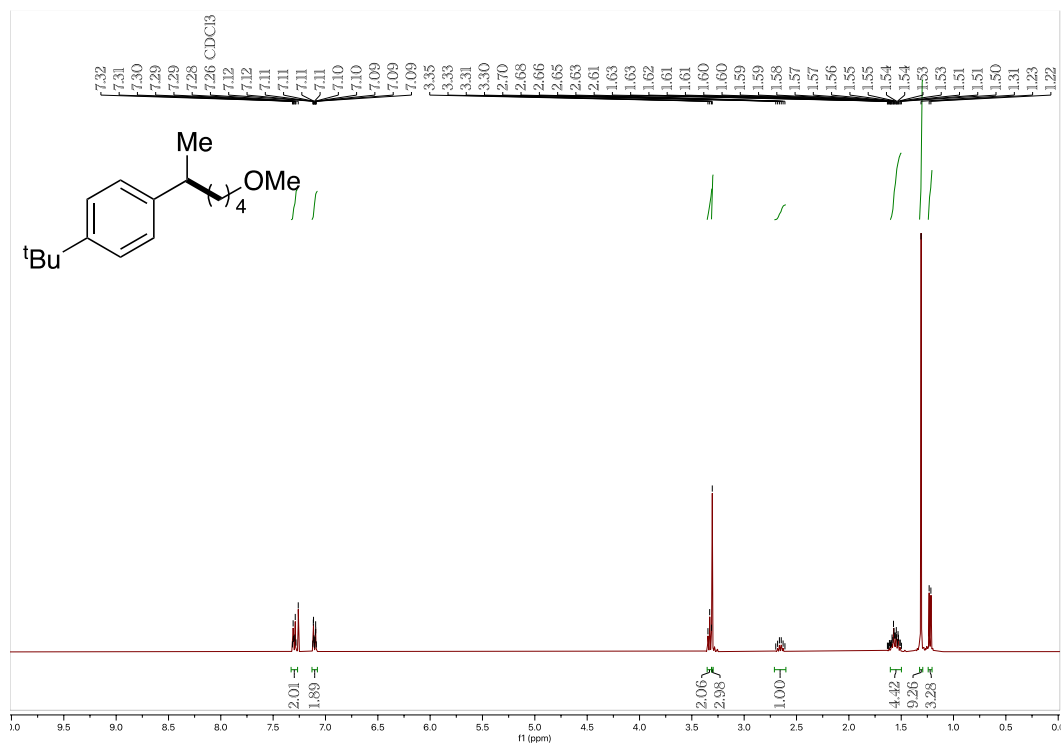
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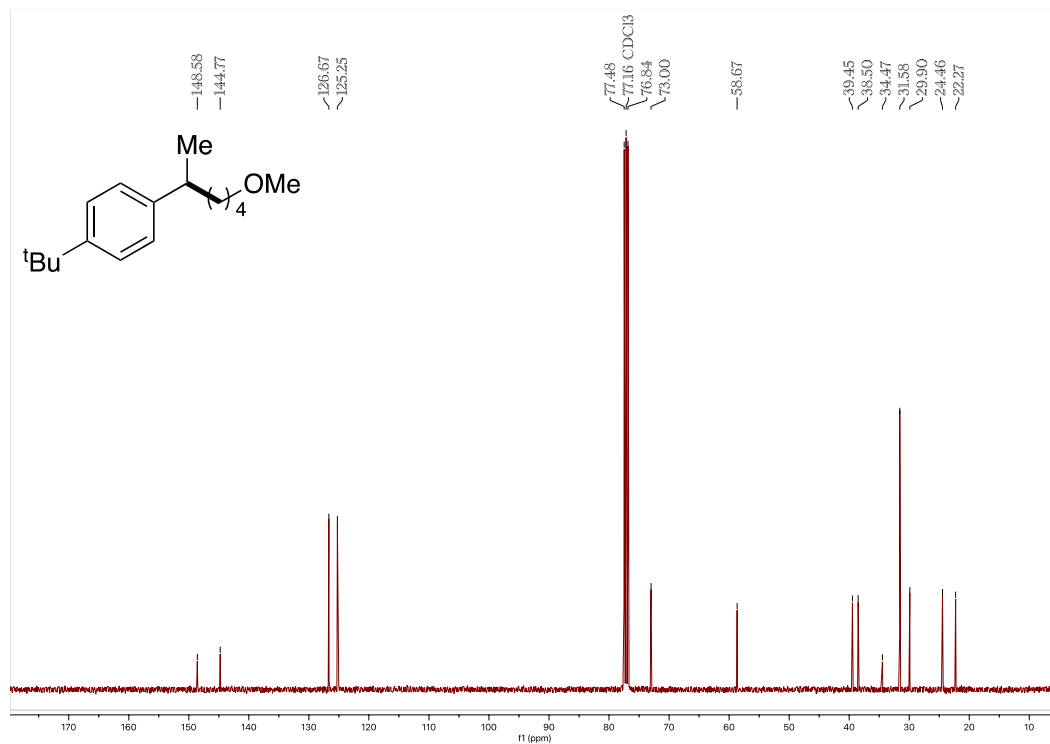
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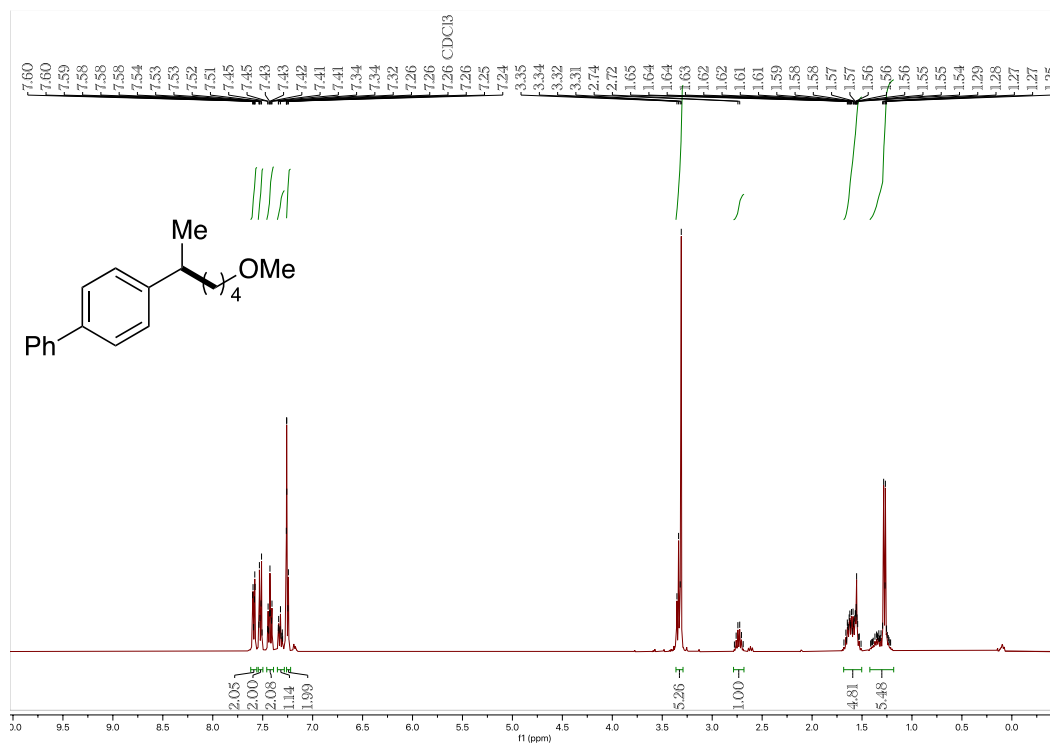
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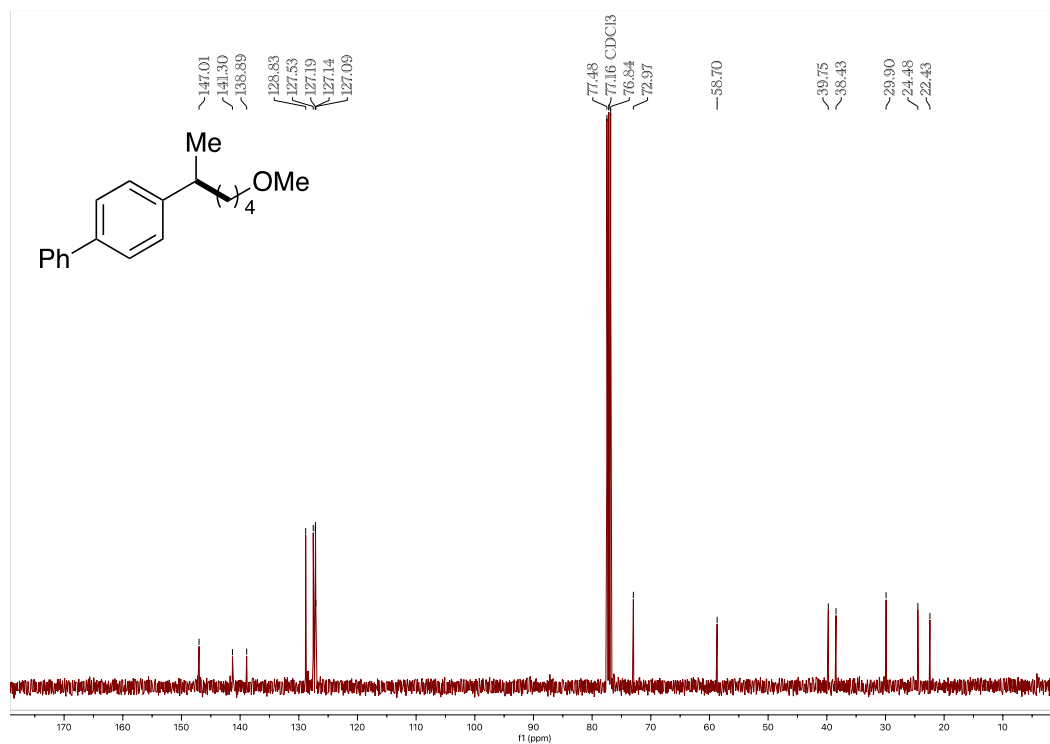
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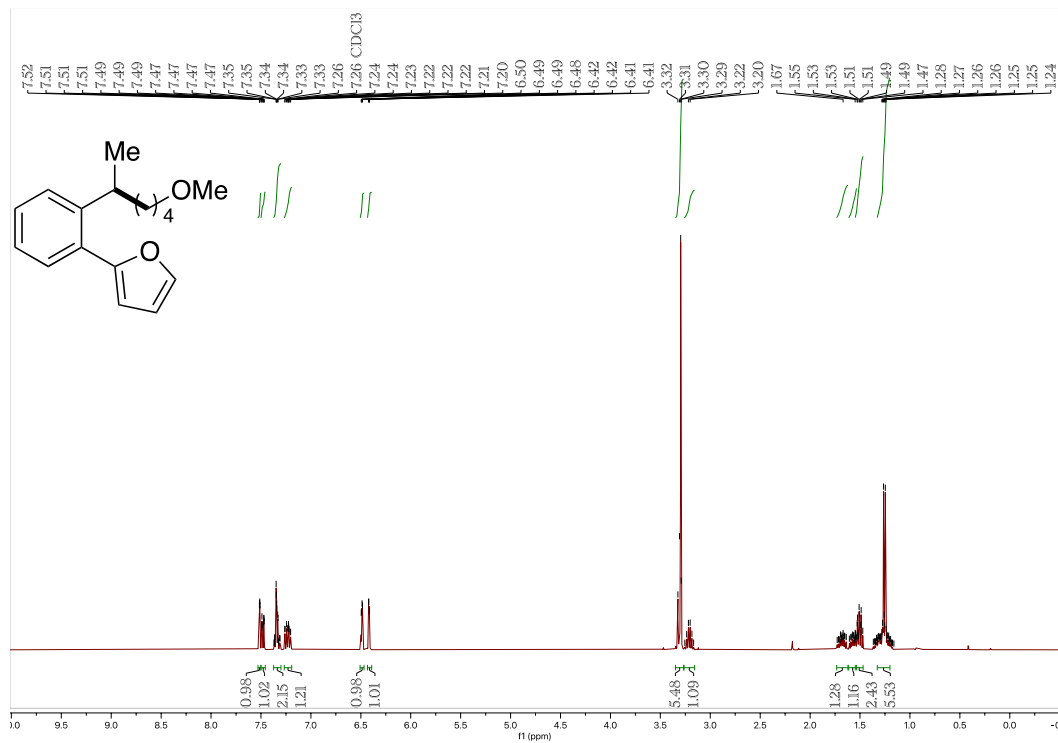
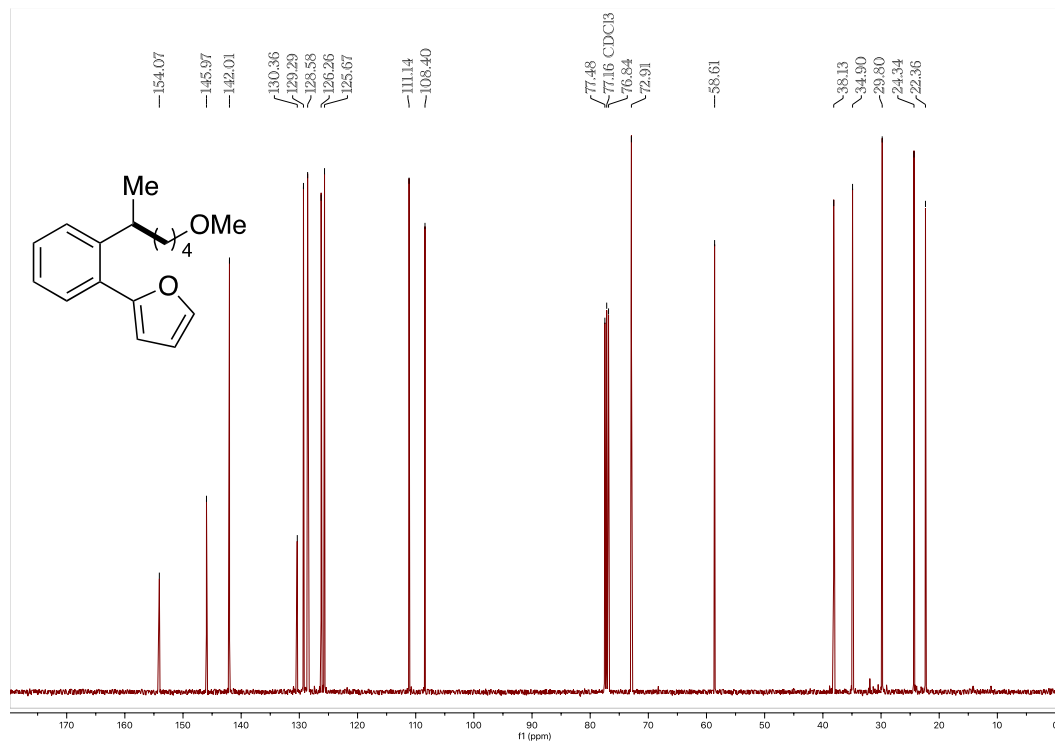


^1H NMR (400 MHz, CDCl_3) of **3.11**

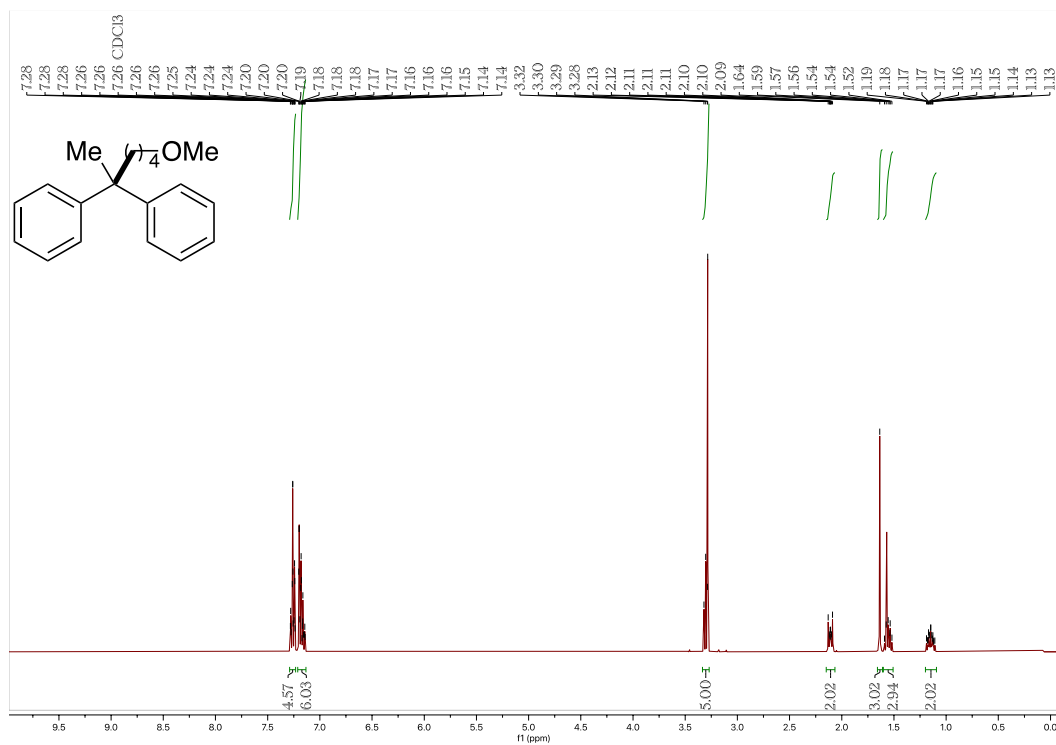


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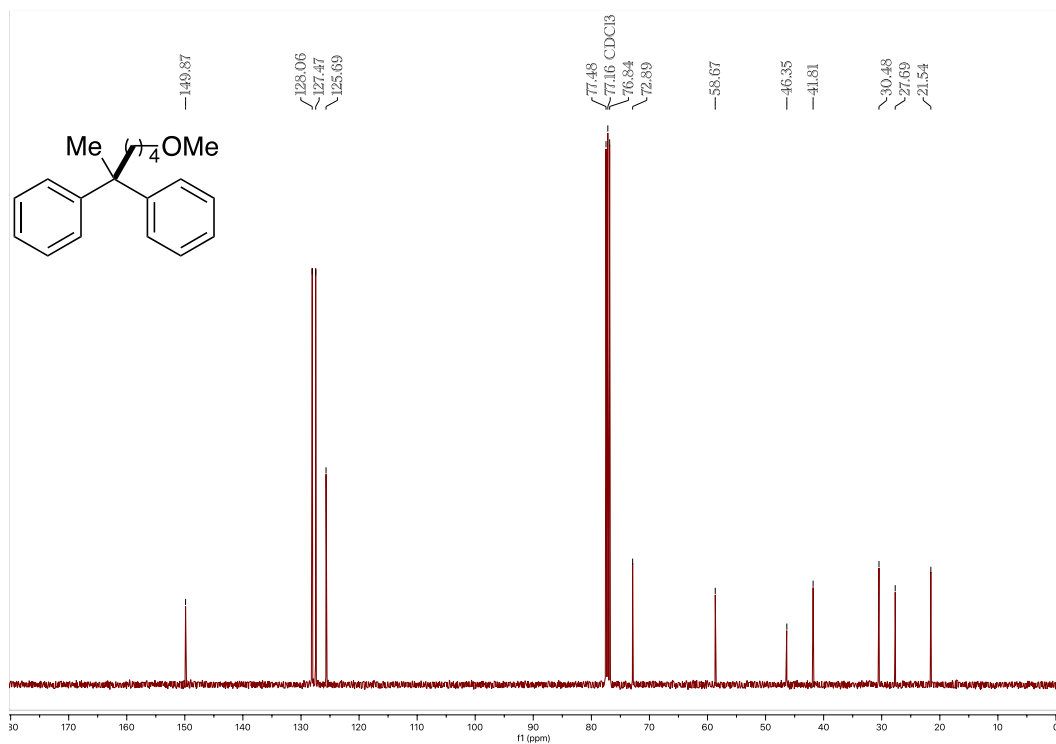


¹H NMR (400 MHz, CDCl₃) of **3.12**¹³C NMR (100 MHz, CDCl₃) of **3.12**

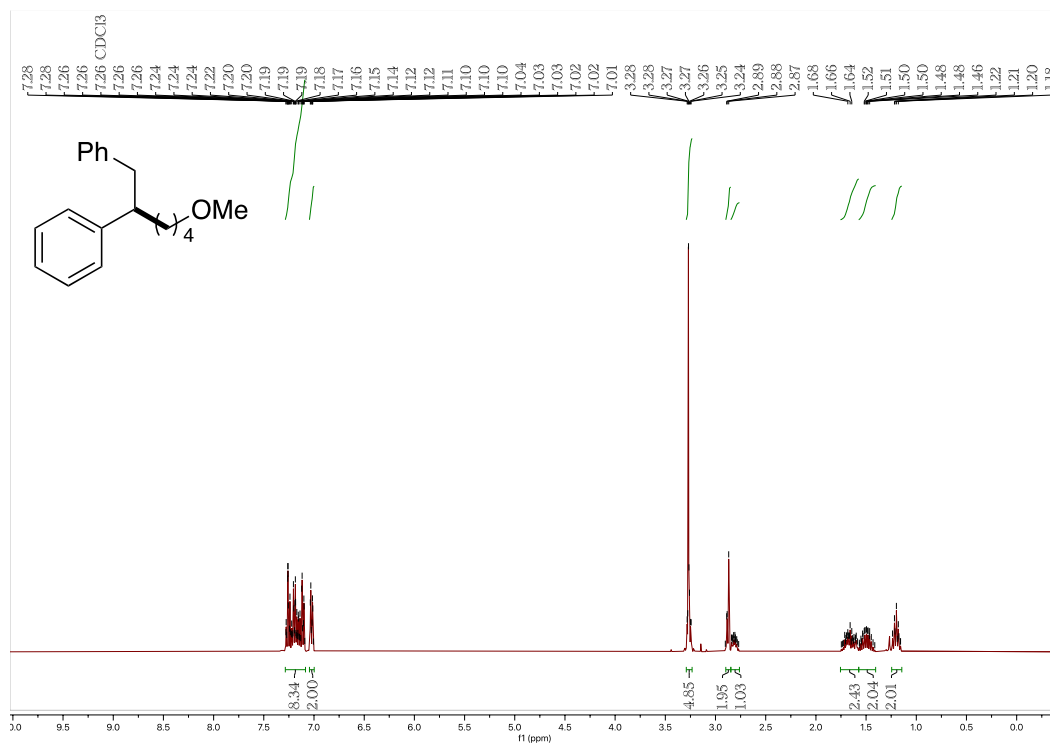
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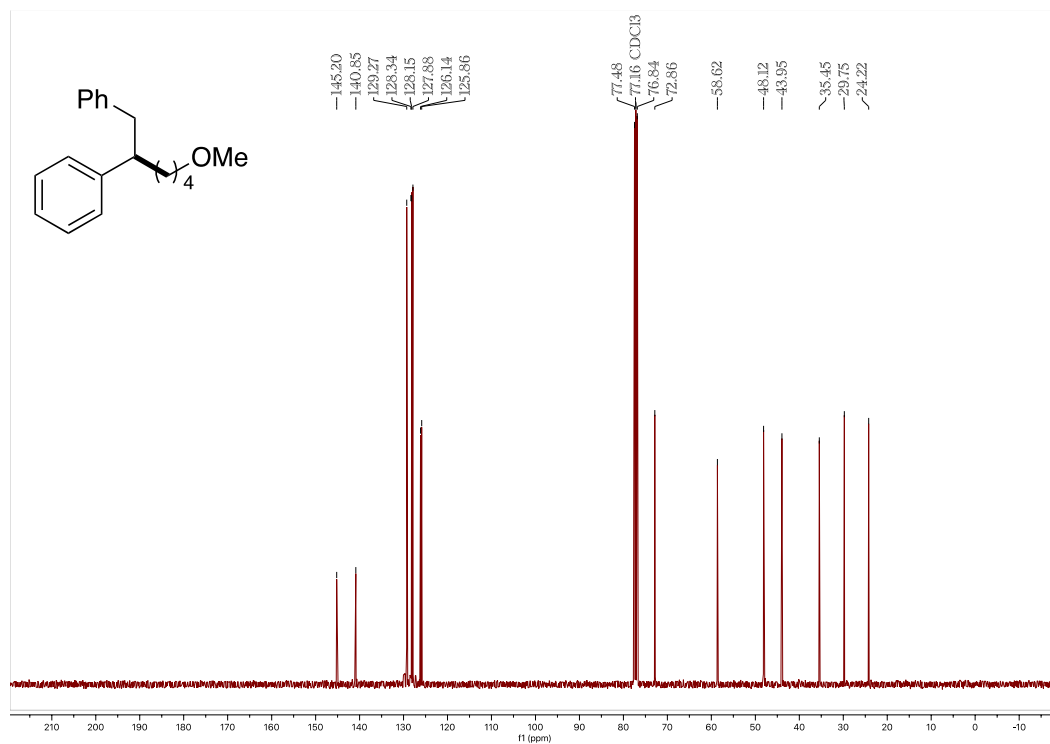
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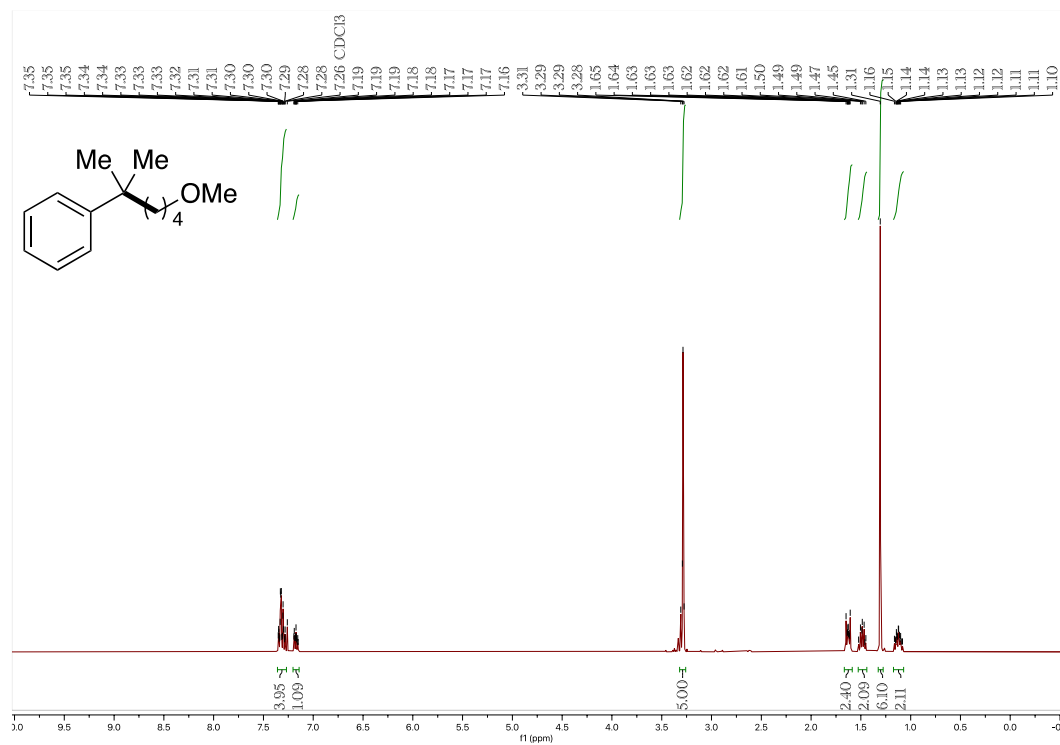
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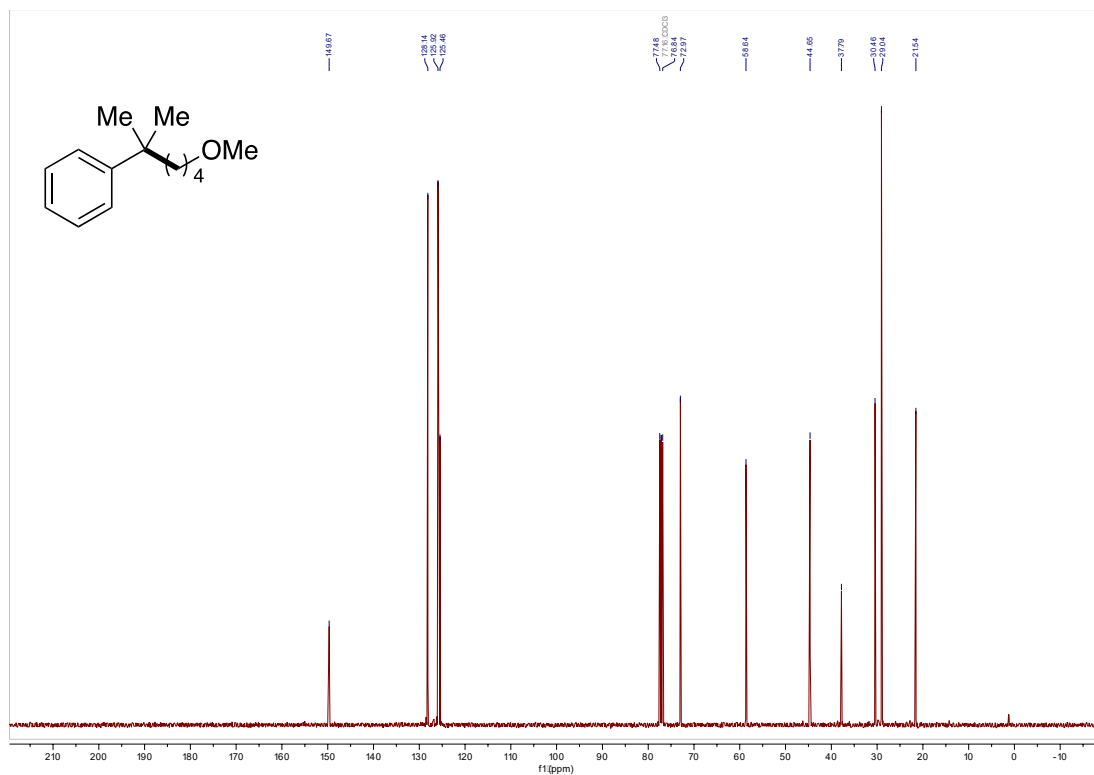
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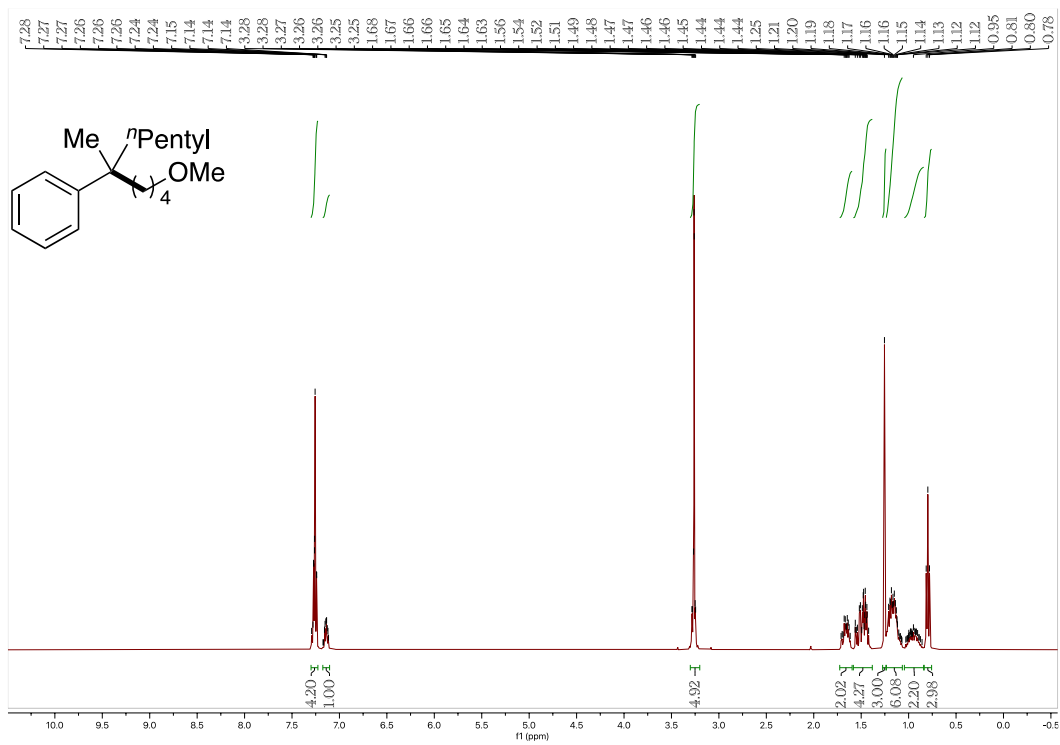
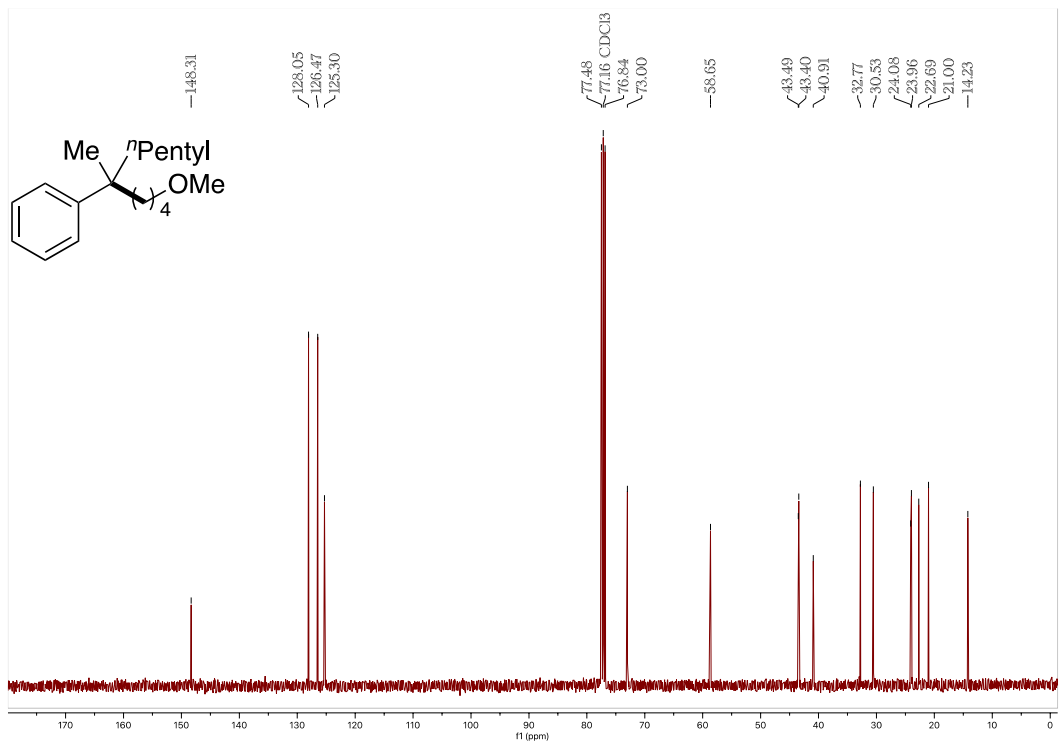


^1H NMR (400 MHz, CDCl_3) of **3.16**

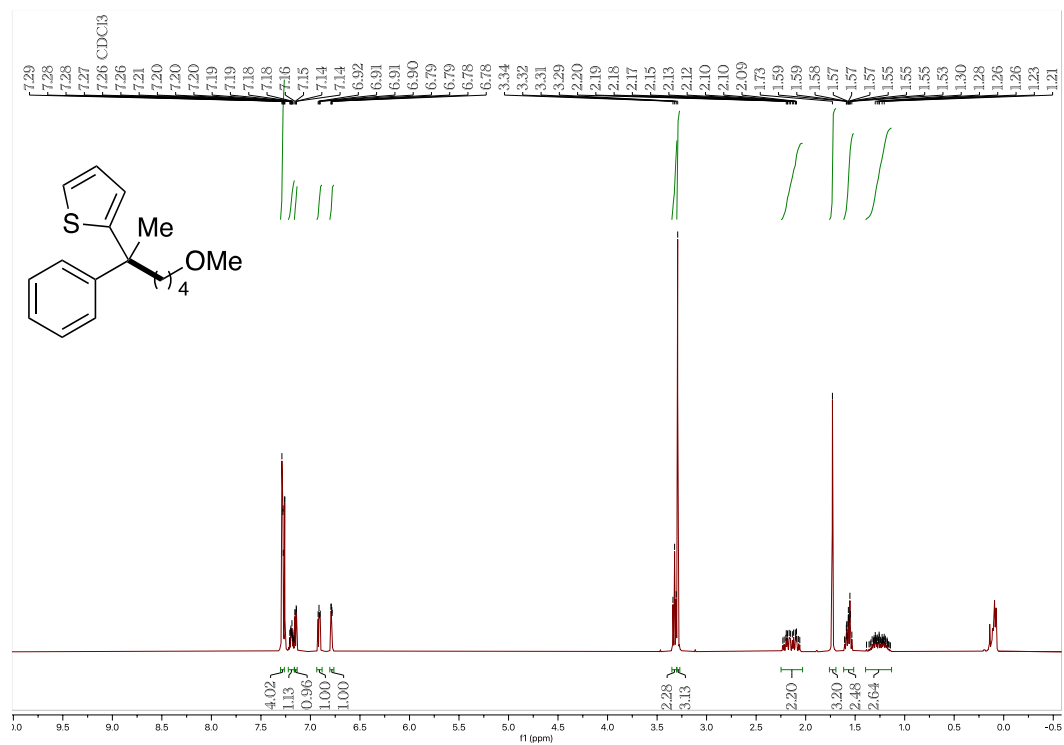


^{13}C NMR (100 MHz, CDCl_3) of **3.16**

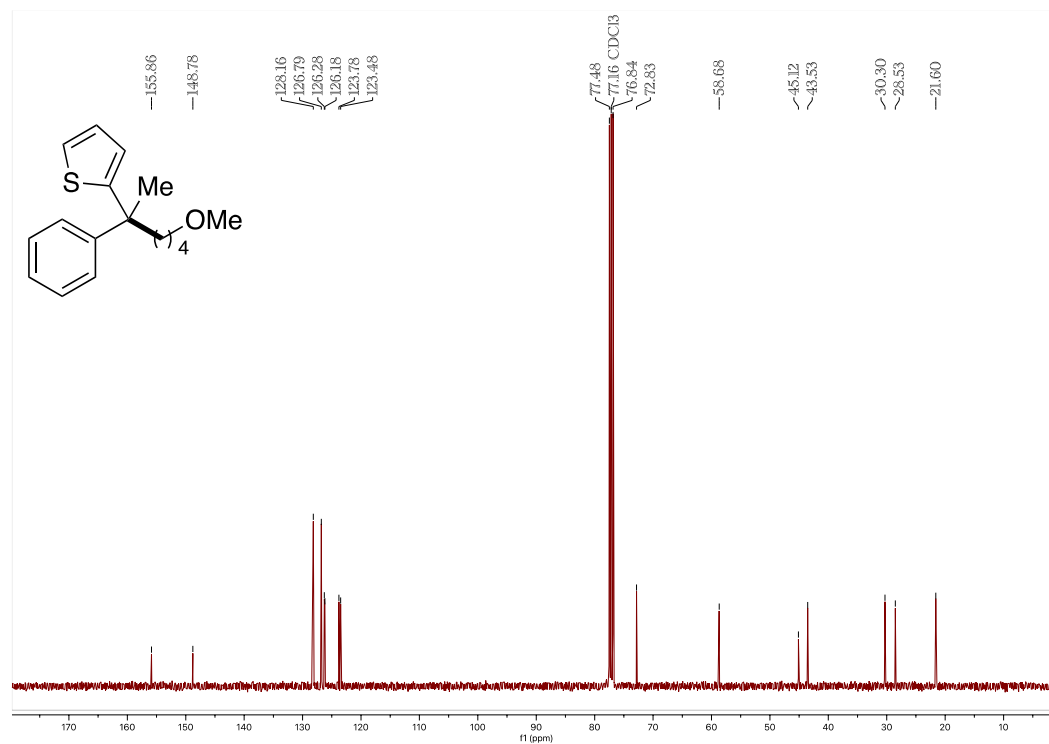


¹H NMR (400 MHz, CDCl₃) of **3.17** ^{13}C NMR (100 MHz, CDCl_3) of **3.17**

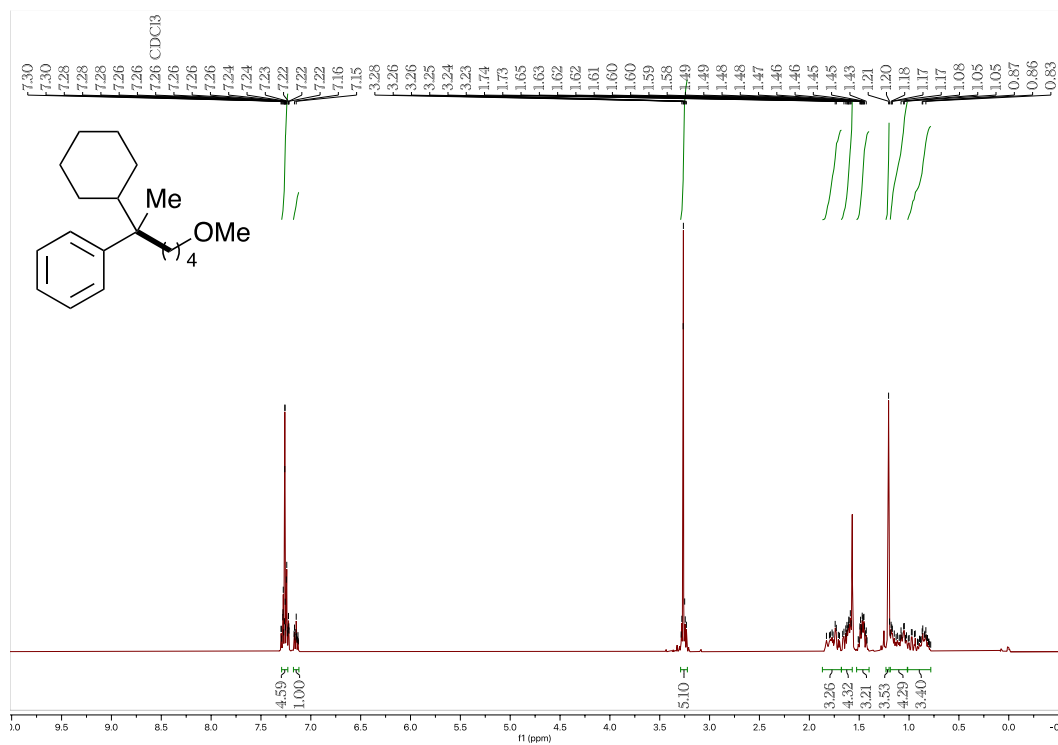
^1H NMR (400 MHz, CDCl_3) of **3.18**



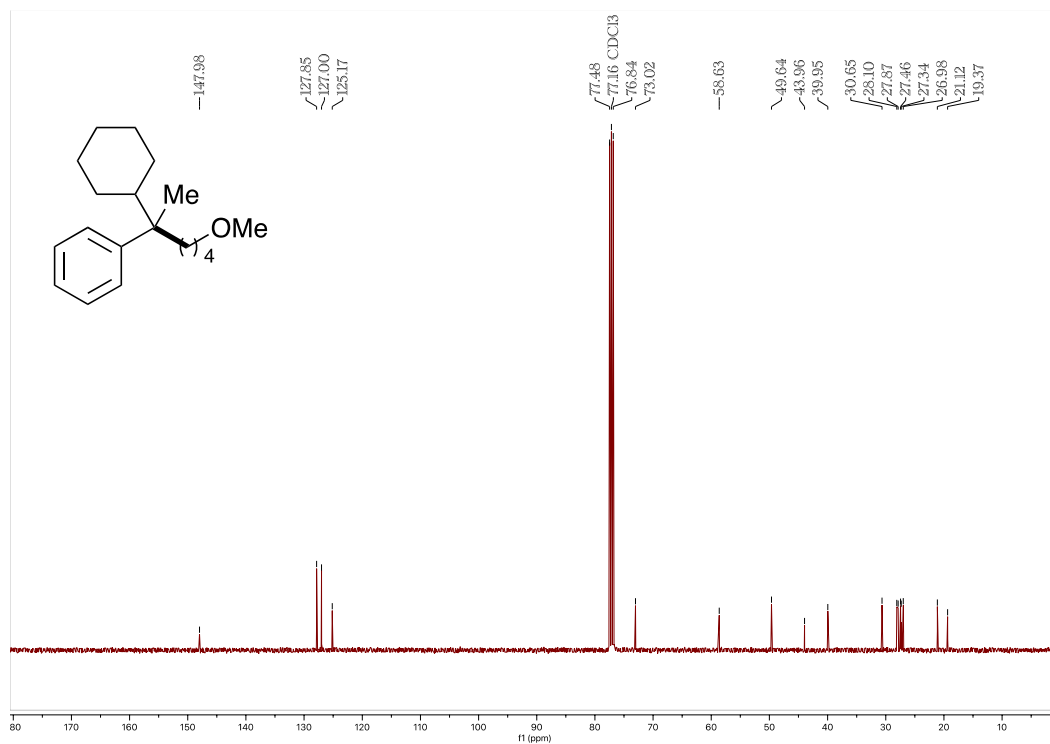
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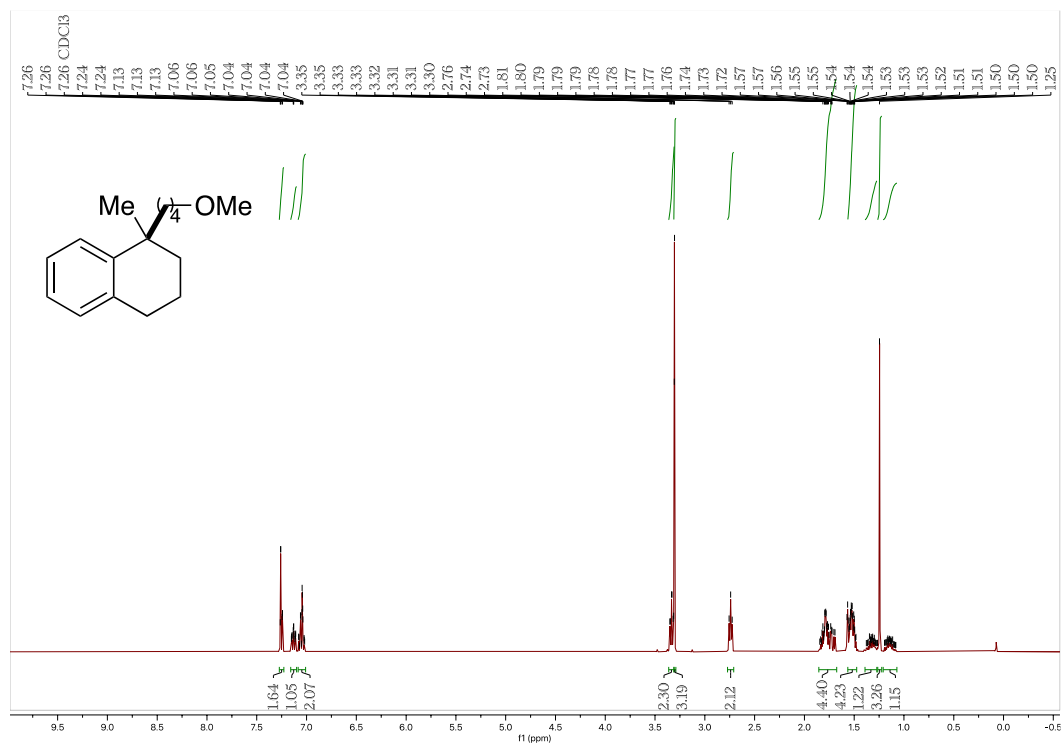
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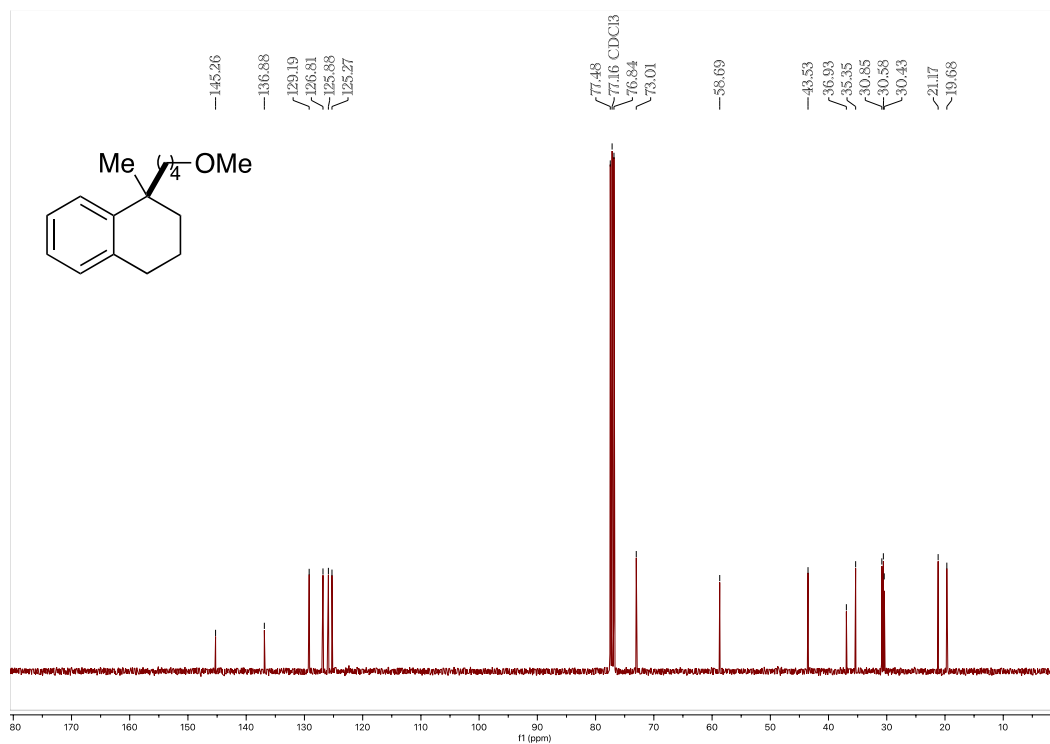
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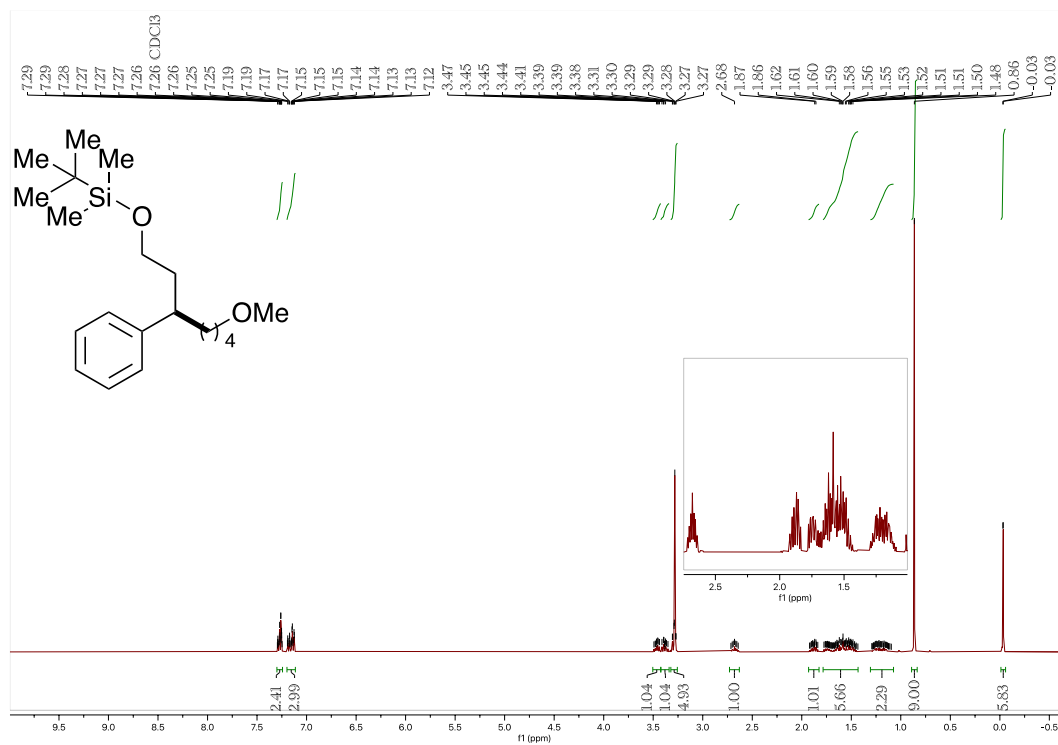
^1H NMR (400 MHz, CDCl_3) of **3.20**



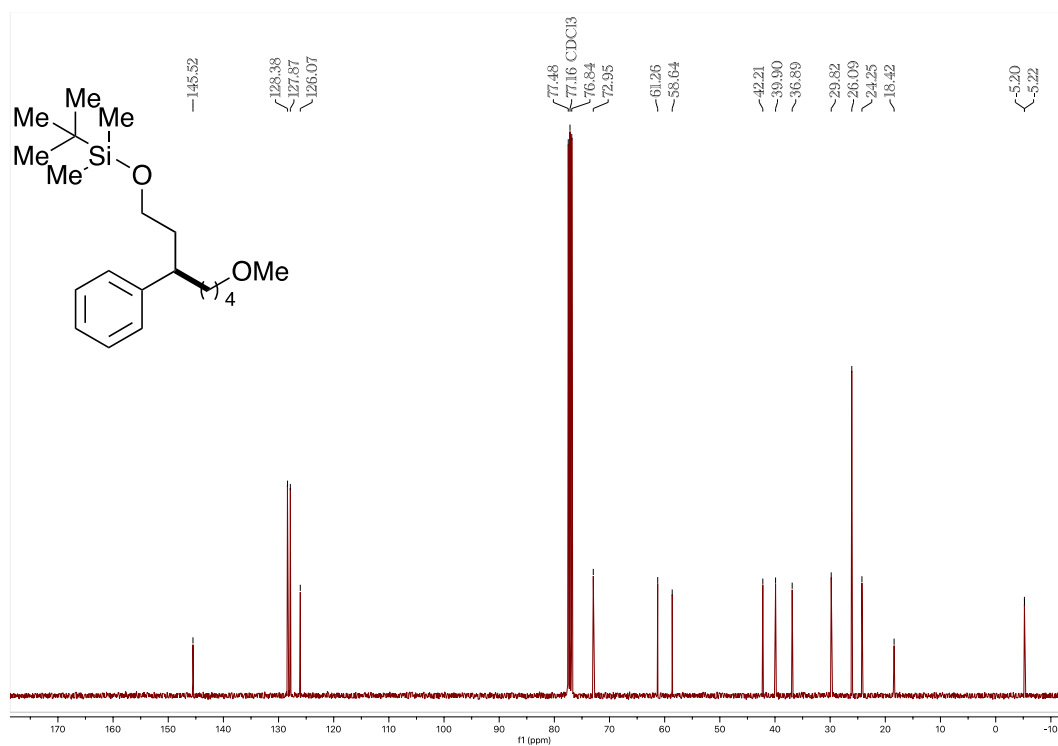
^{13}C NMR (100 MHz, CDCl_3) of **3.20**

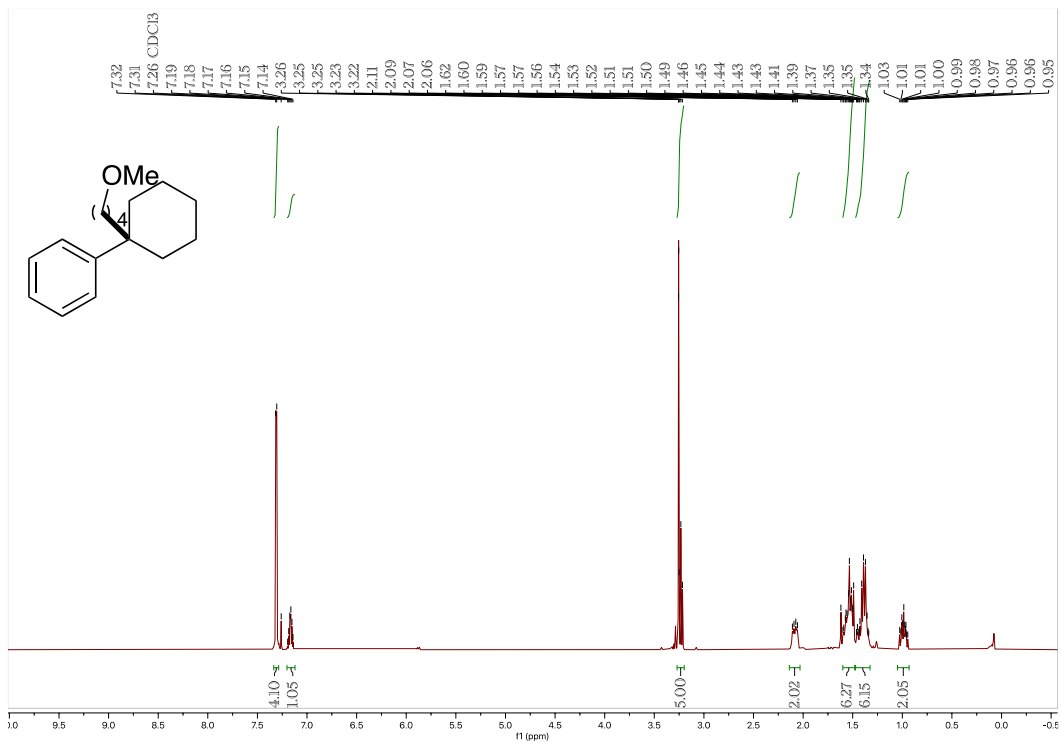
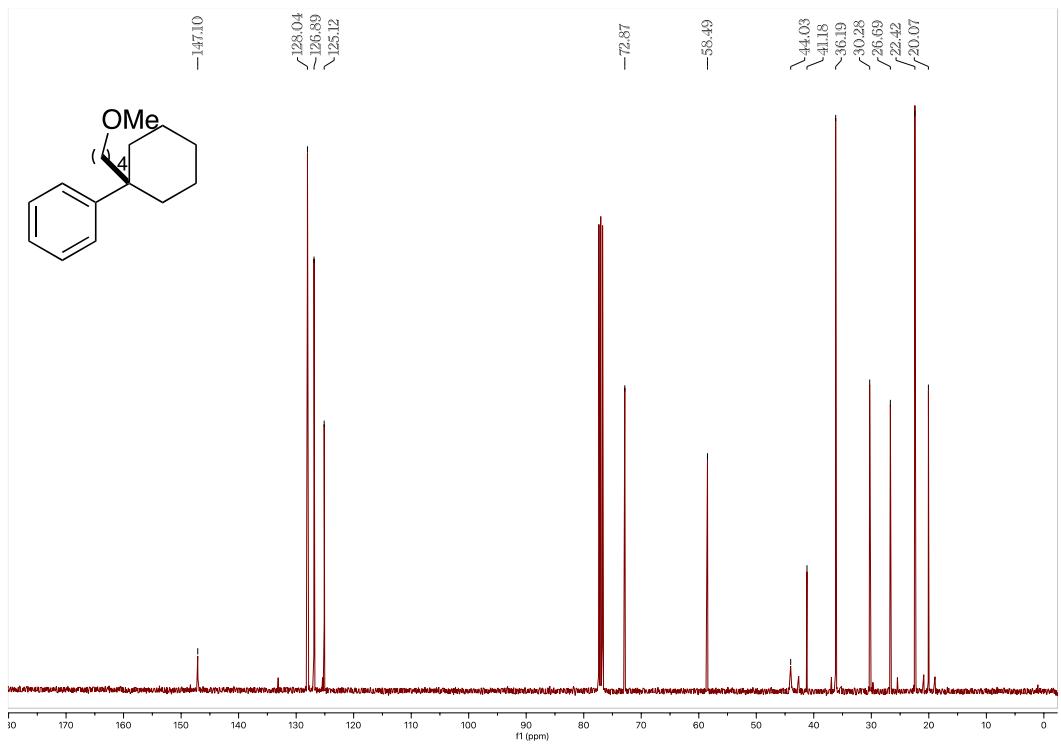


^1H NMR (400 MHz, CDCl_3) of **3.21**

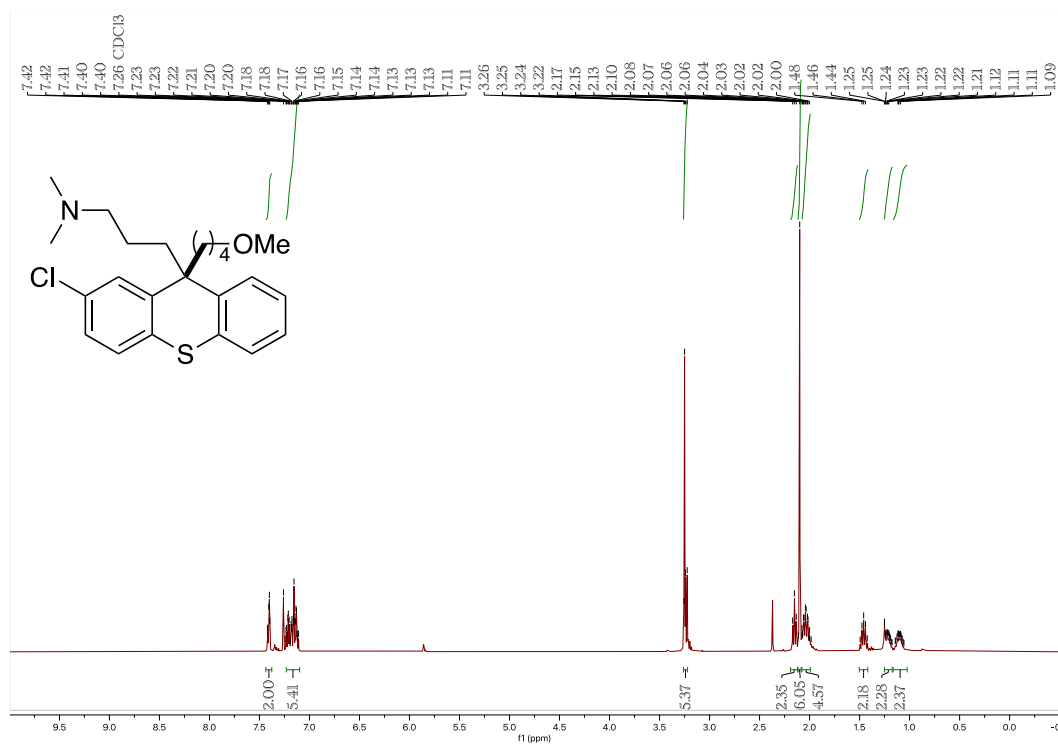


^{13}C NMR (100 MHz, CDCl_3) of **3.21**

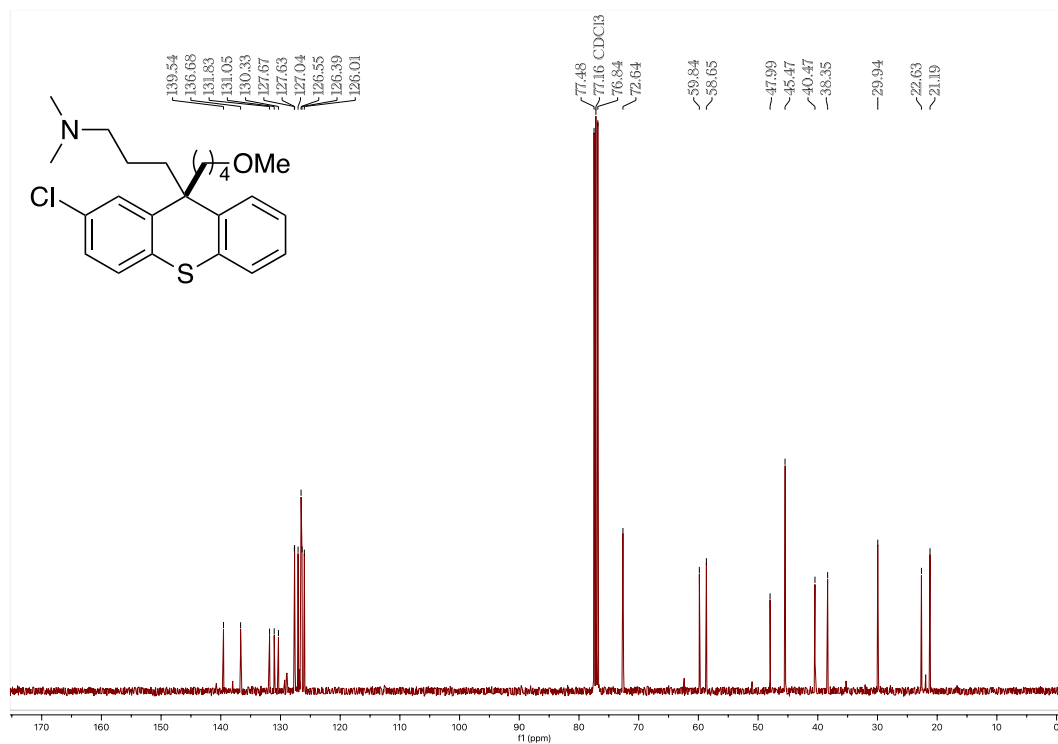


¹H NMR (400 MHz, CDCl₃) of **3.22**¹³C NMR (100 MHz, CDCl₃) of **3.22**

^1H NMR (400 MHz, CDCl_3) of **3.23**



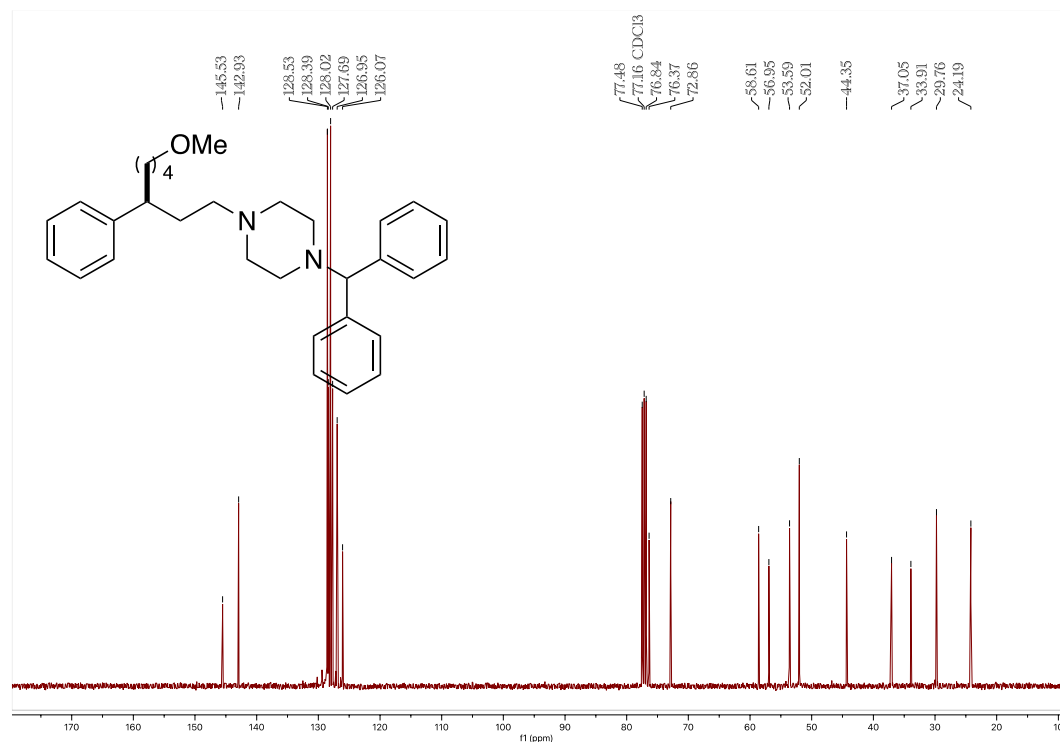
^{13}C NMR (100 MHz, CDCl_3) of **3.23**



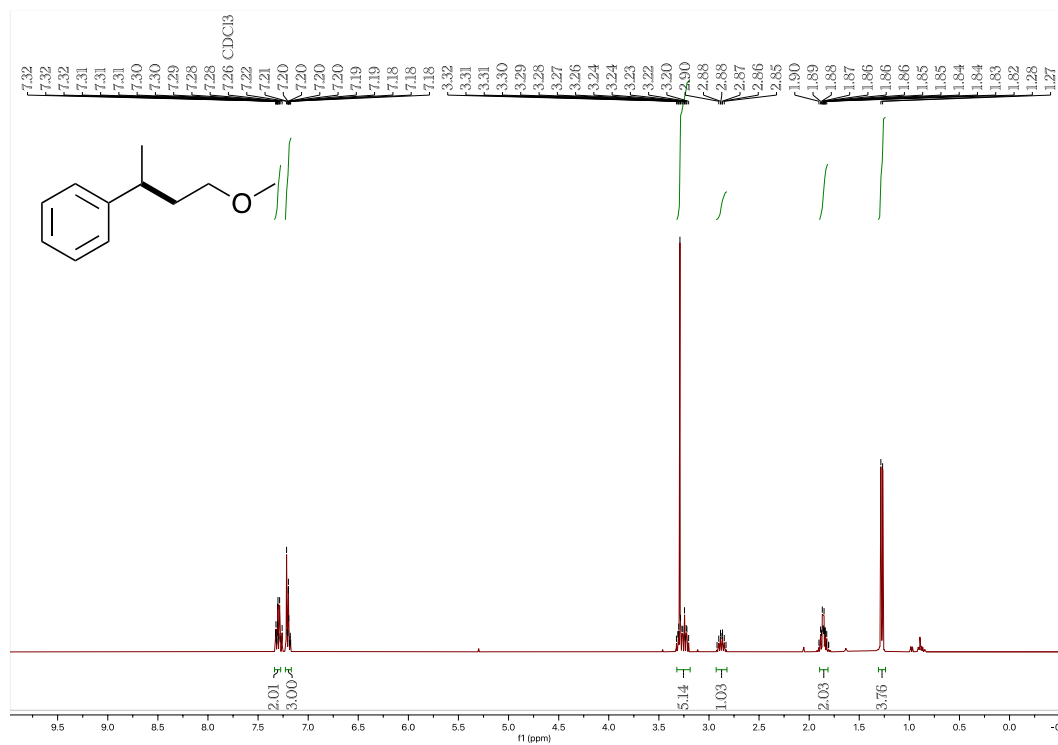
^1H NMR (400 MHz, CDCl_3) of **3.24**



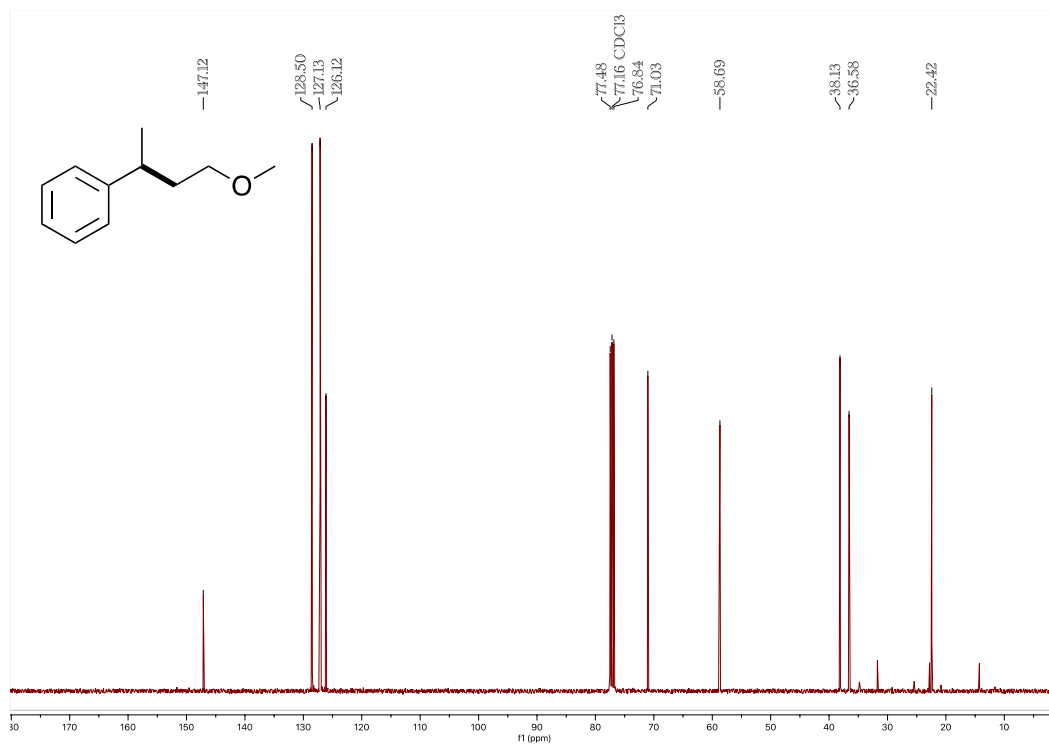
^{13}C NMR (100 MHz, CDCl_3) of **3.24**



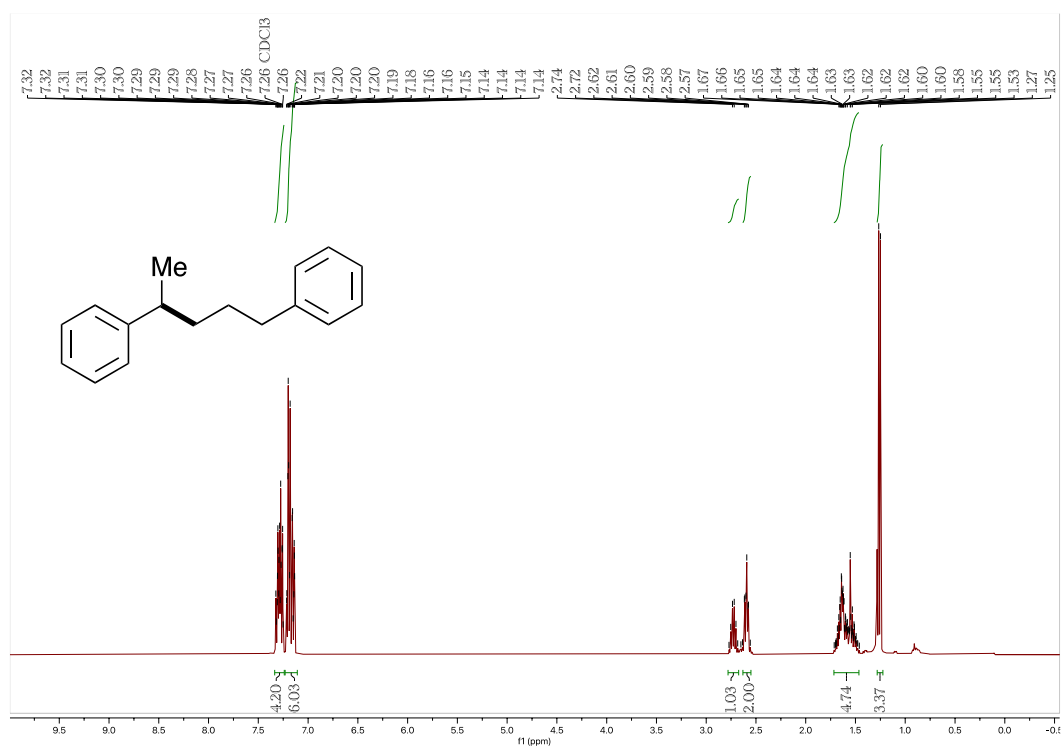
^1H NMR (400 MHz, CDCl_3) of **3.25**



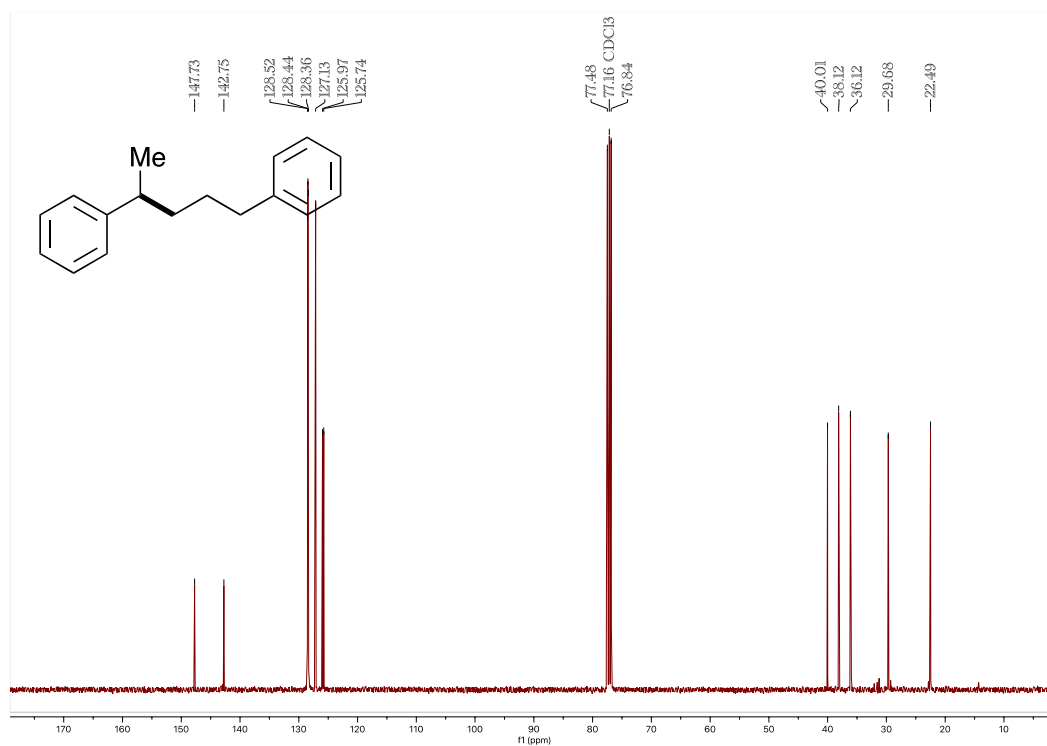
^{13}C NMR (100 MHz, CDCl_3) of **3.25**



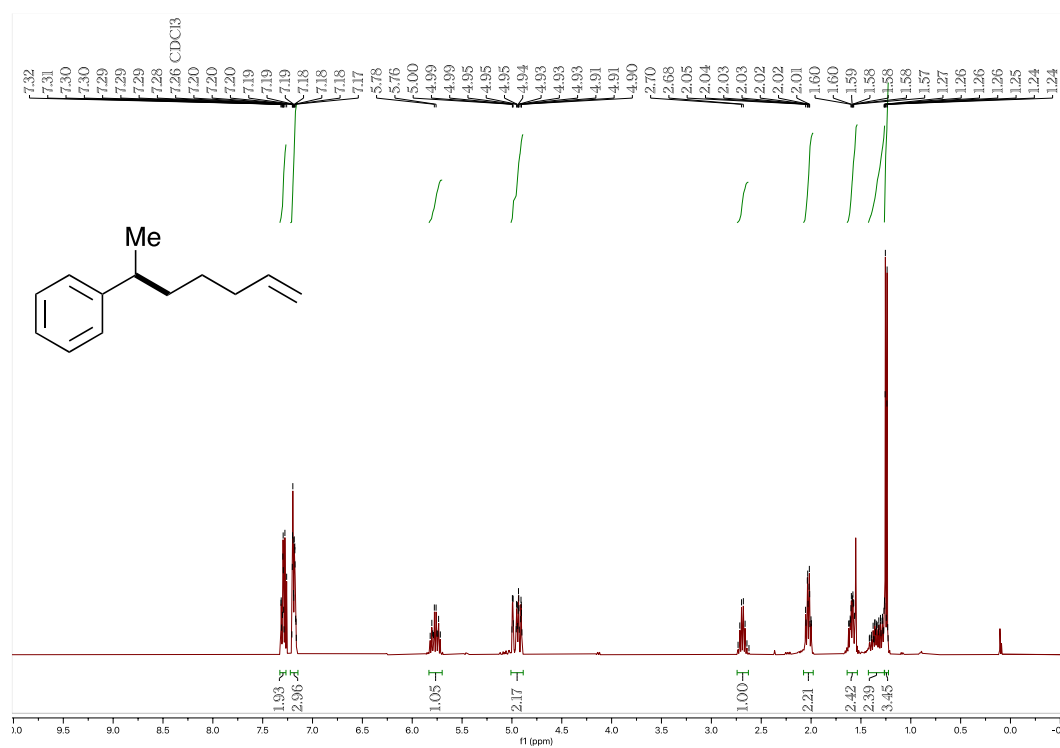
^1H NMR (400 MHz, CDCl_3) of **3.26**



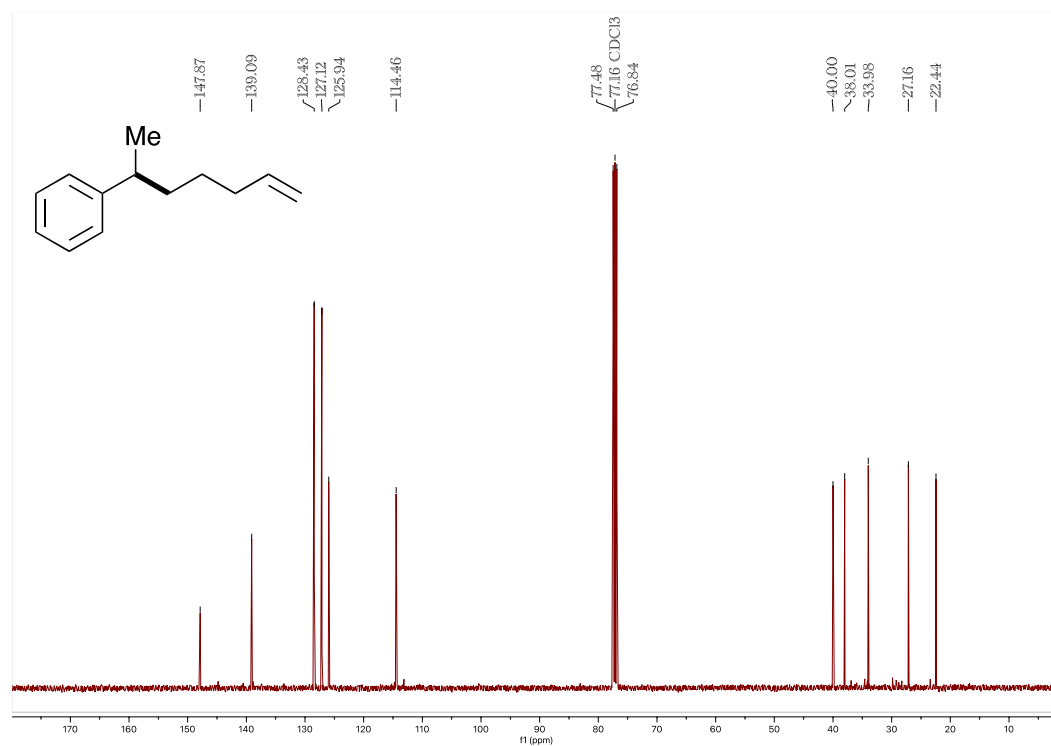
^{13}C NMR (100 MHz, CDCl_3) of **3.26**



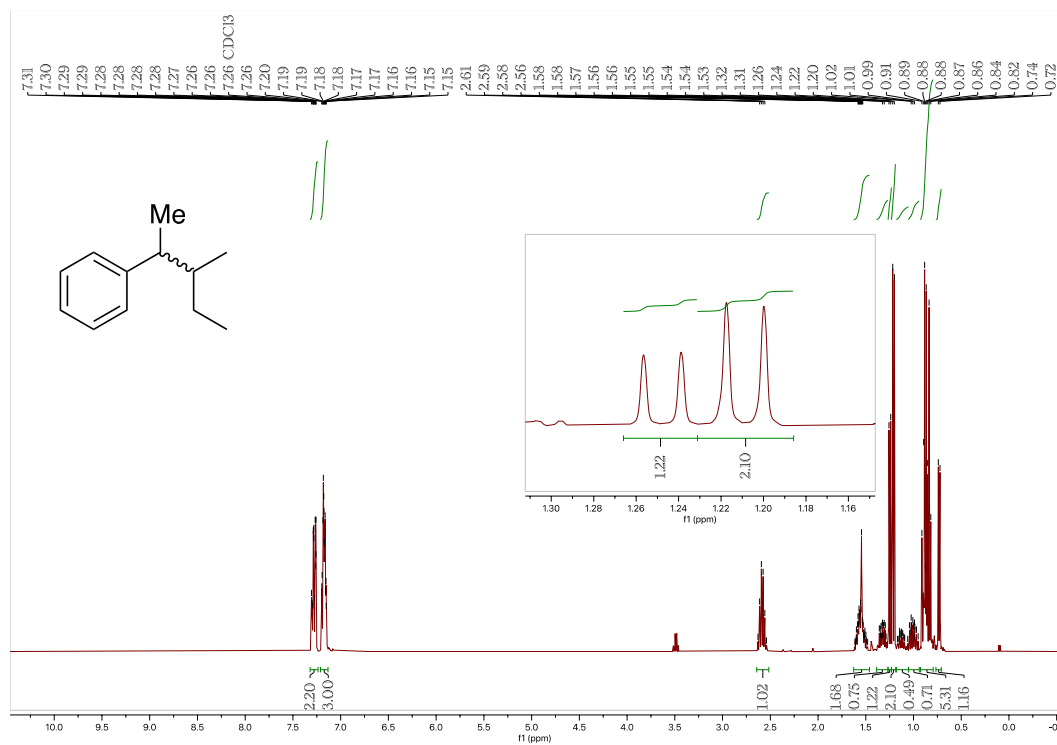
^1H NMR (400 MHz, CDCl_3) of **3.27**



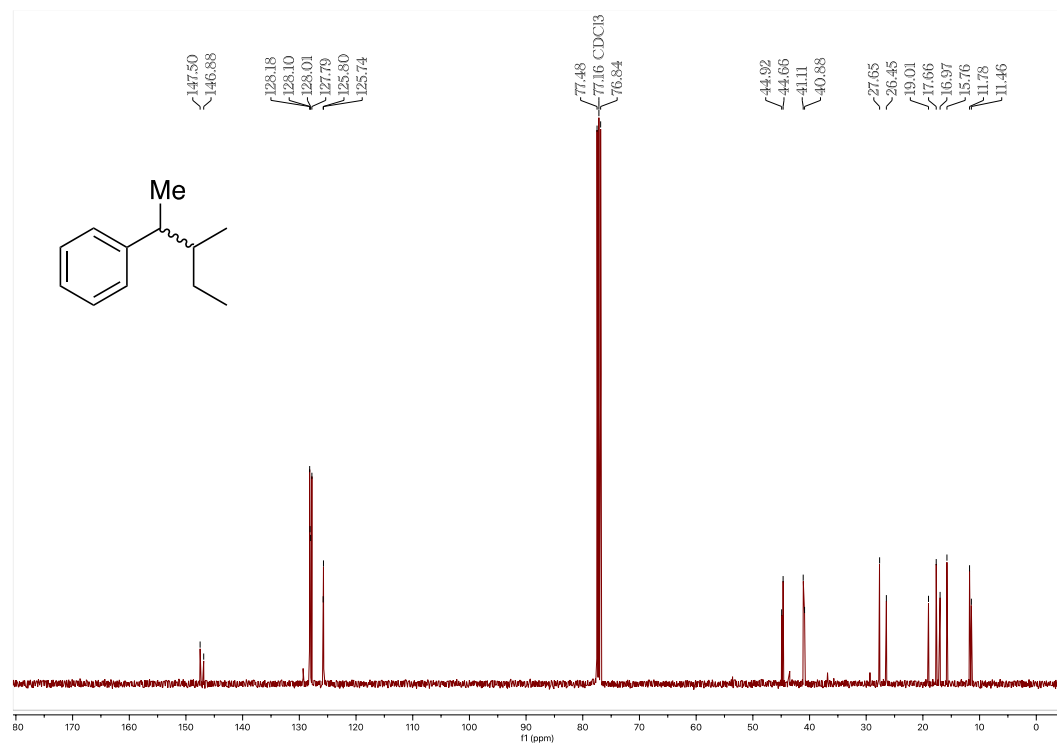
^{13}C NMR (100 MHz, CDCl_3) of **3.27**



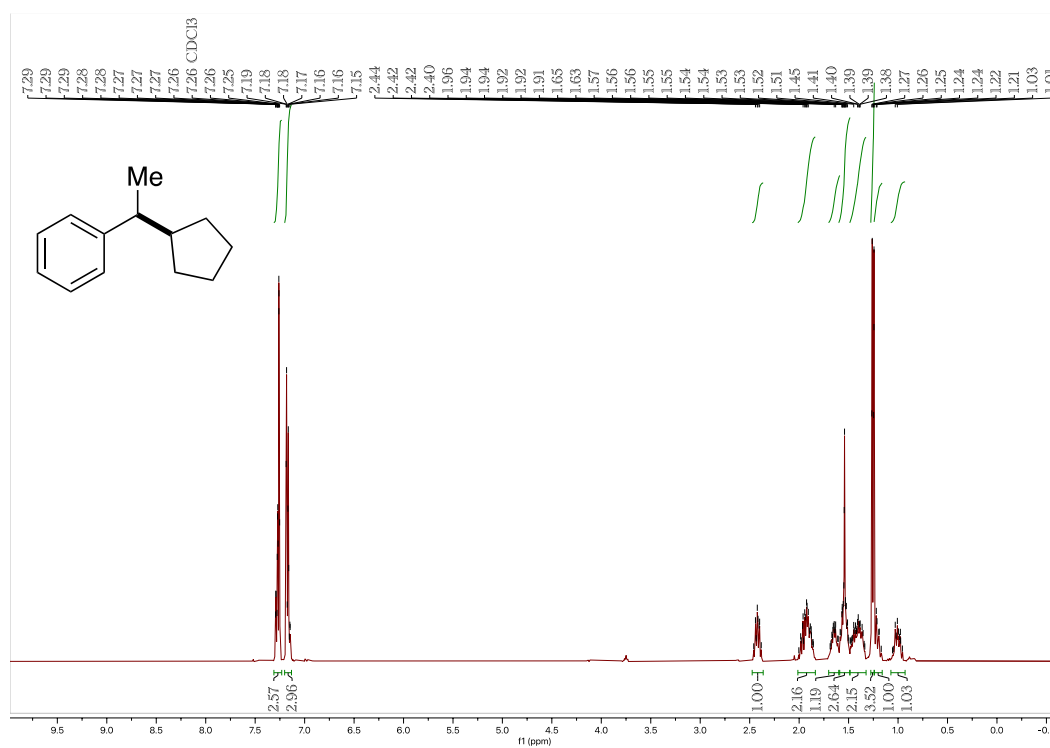
^1H NMR (400 MHz, CDCl_3) of **3.28**



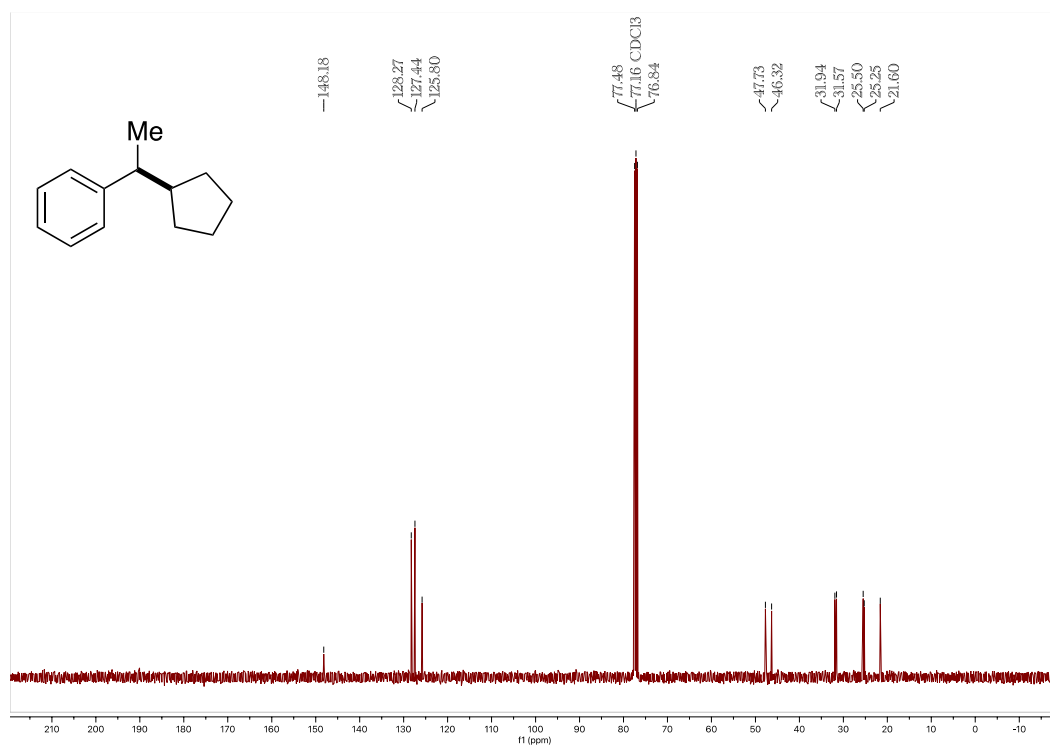
^{13}C NMR (100 MHz, CDCl_3) of **3.28**



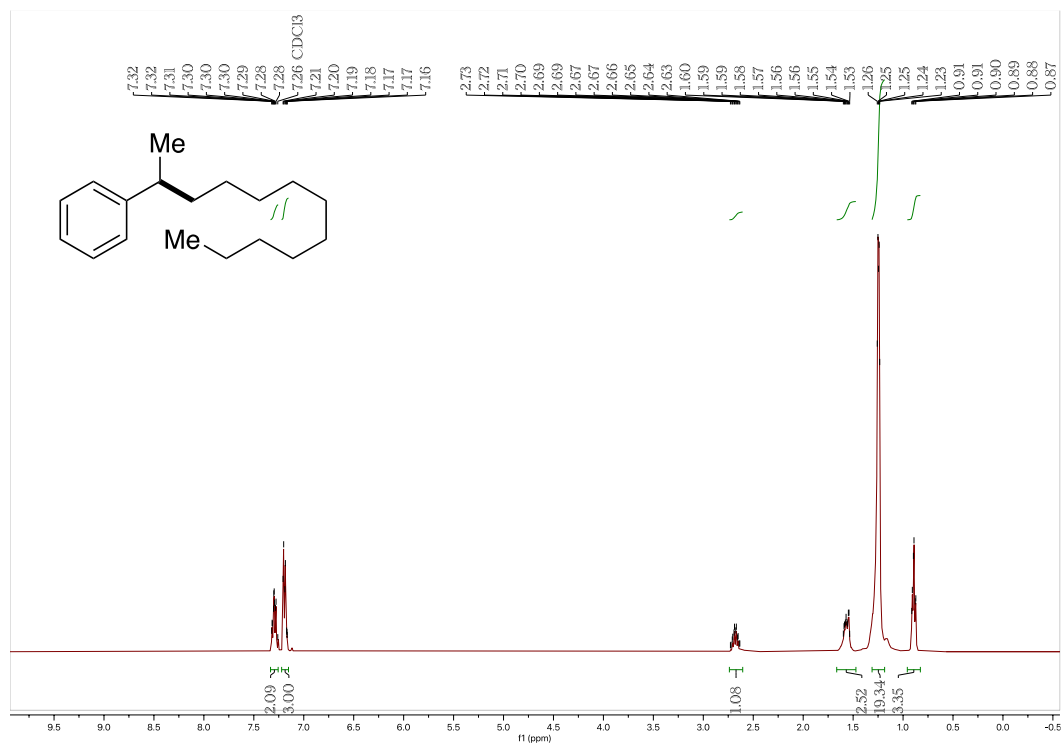
^1H NMR (400 MHz, CDCl_3) of **3.29**



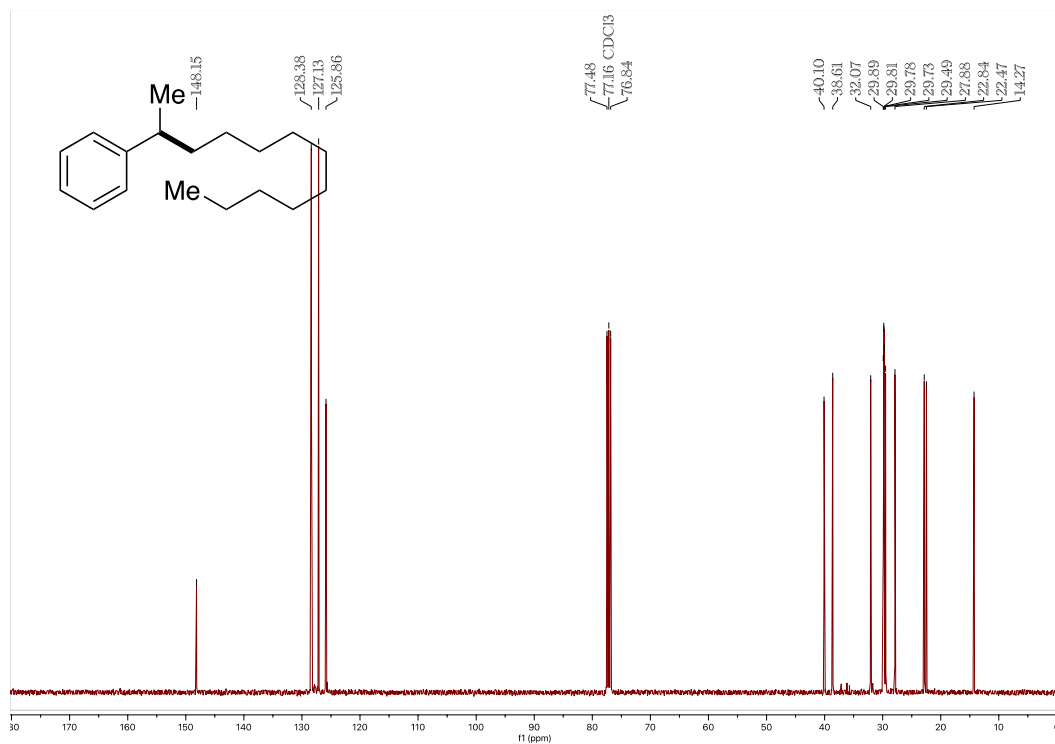
^{13}C NMR (100 MHz, CDCl_3) of **3.29**



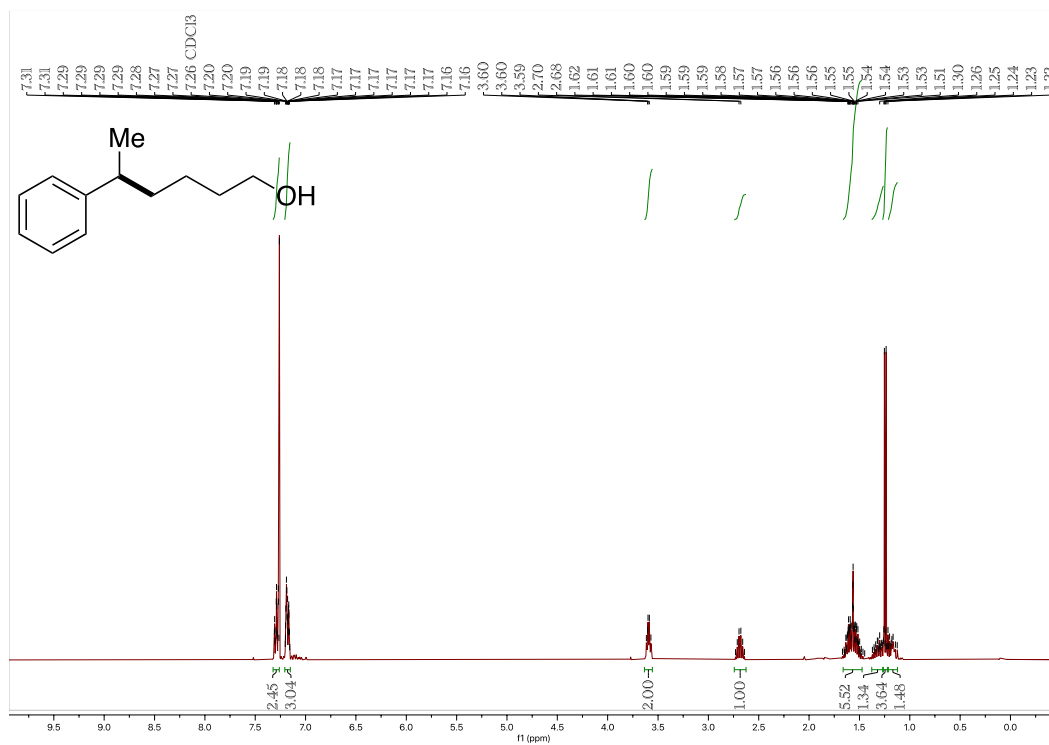
^1H NMR (400 MHz, CDCl_3) of **3.30**



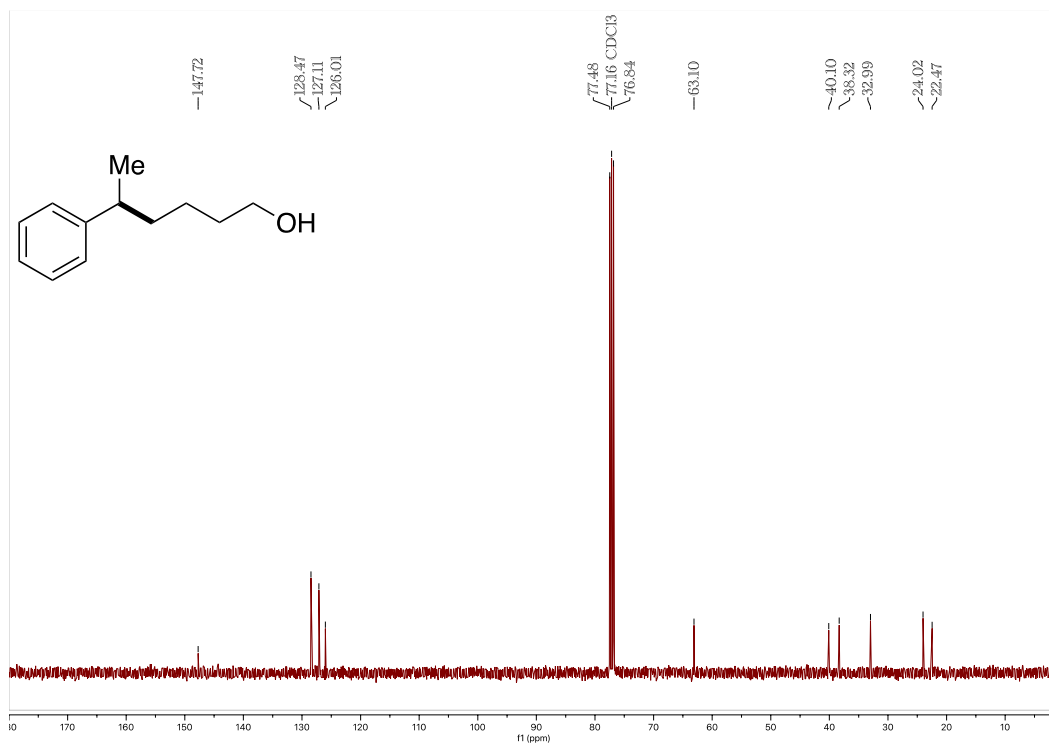
^{13}C NMR (100 MHz, CDCl_3) of **3.30**



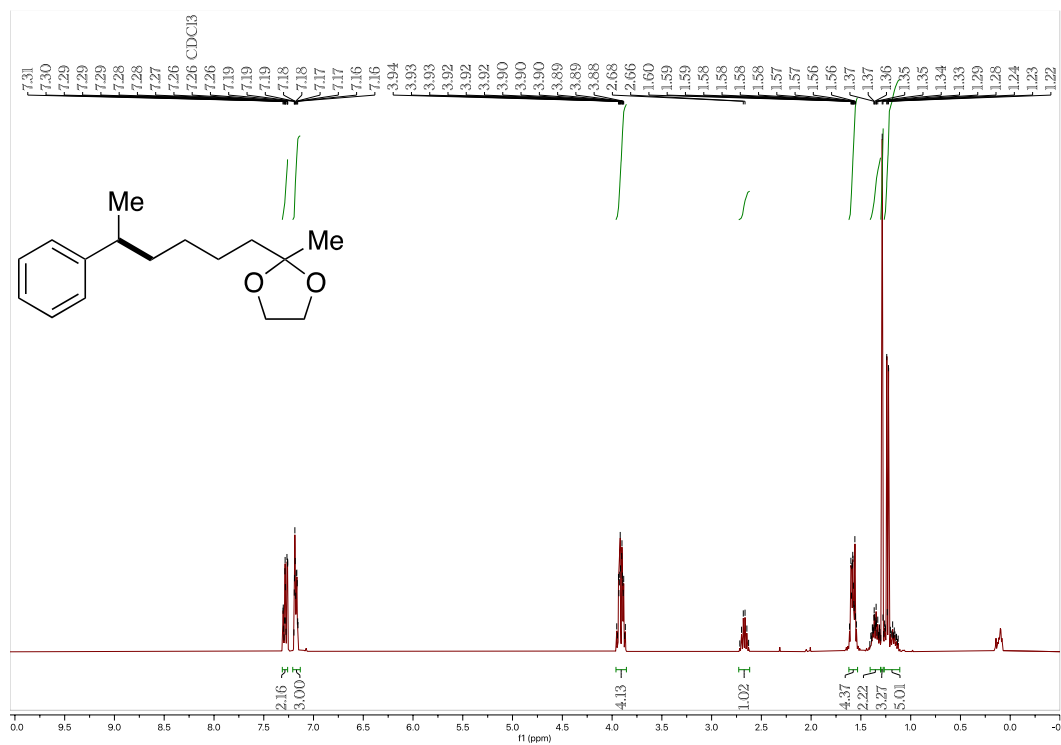
^1H NMR (400 MHz, CDCl_3) of **3.31**



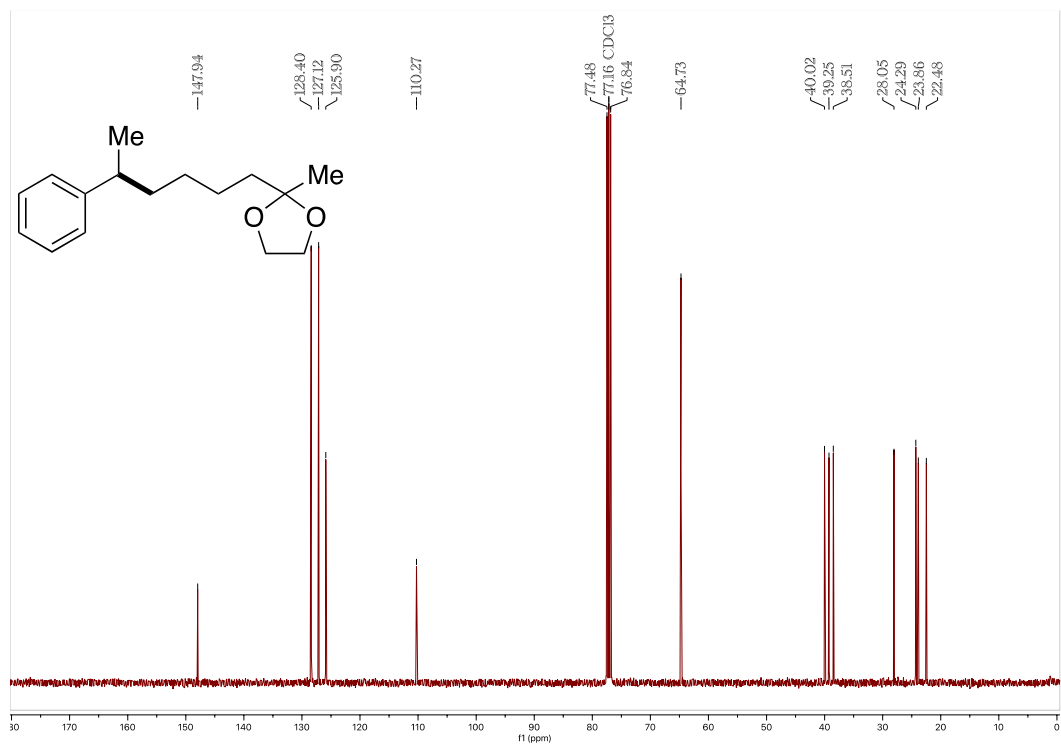
^{13}C NMR (100 MHz, CDCl_3) of **3.31**



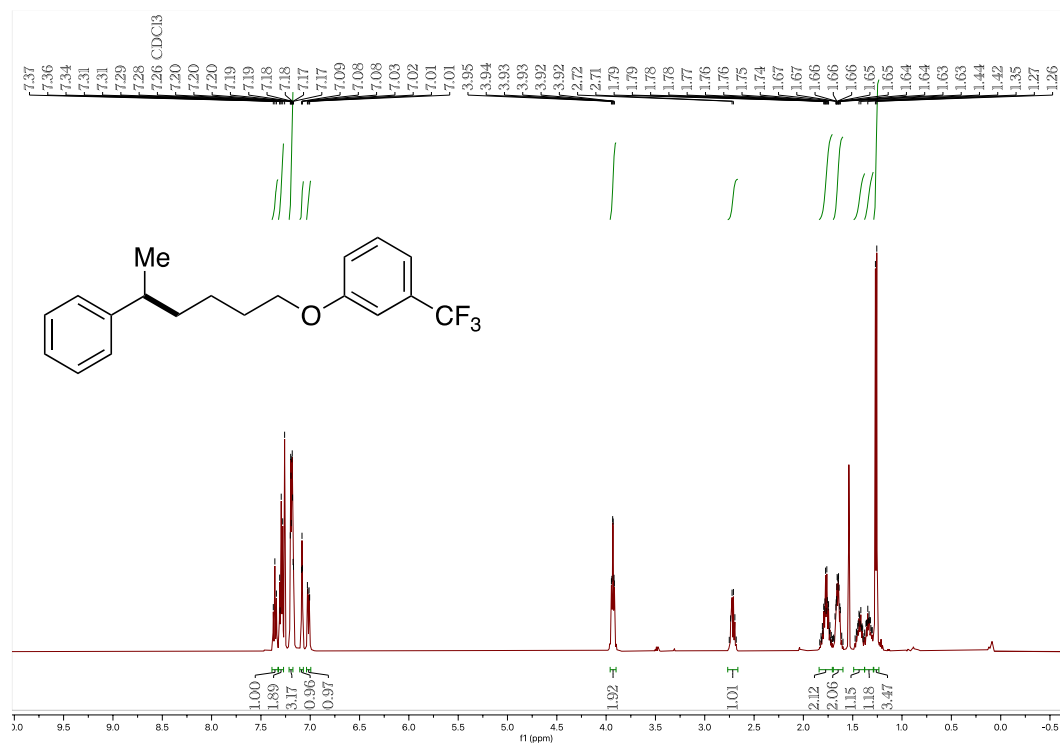
^1H NMR (400 MHz, CDCl_3) of **3.32**



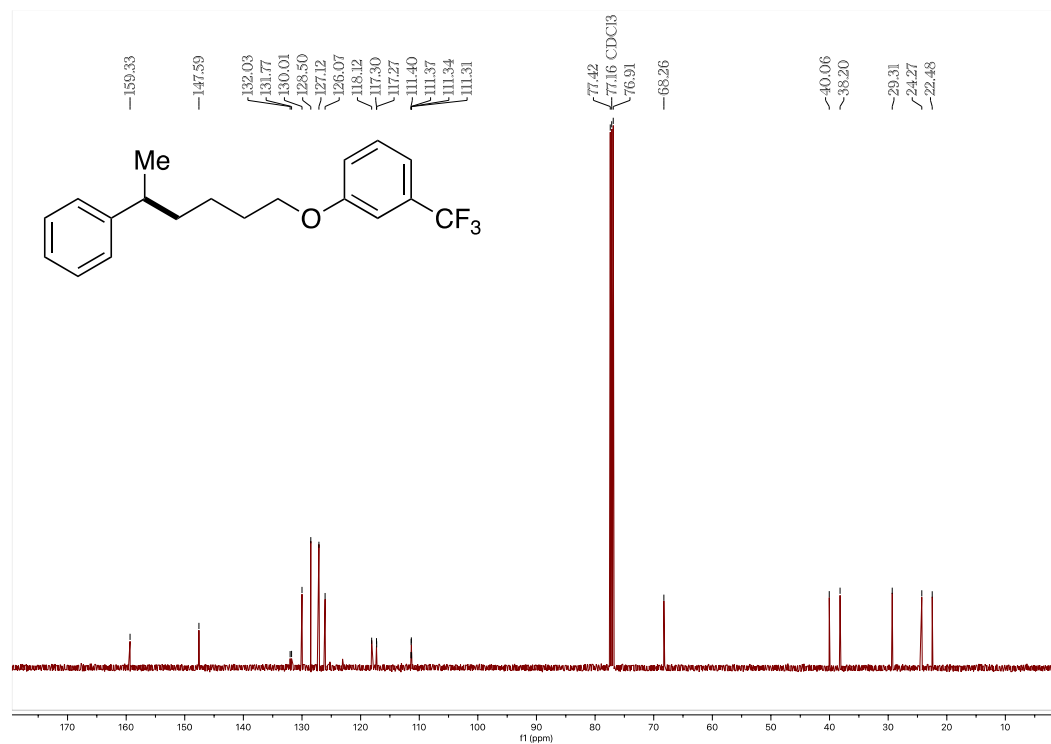
^{13}C NMR (100 MHz, CDCl_3) of **3.32**



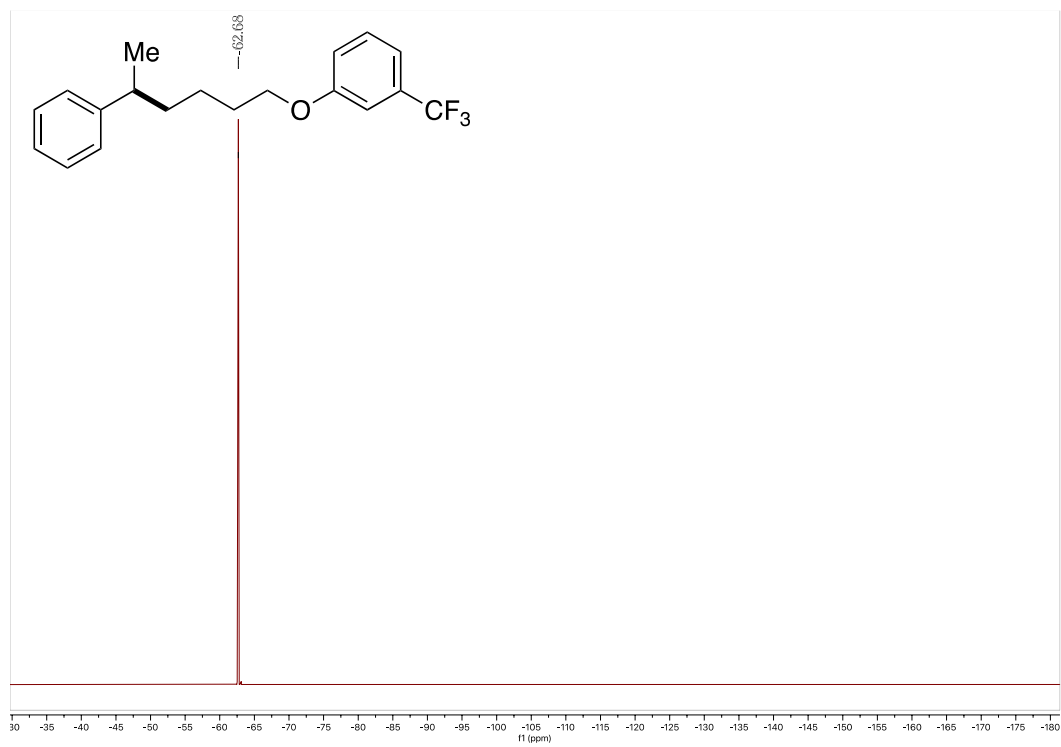
^1H NMR (500 MHz, CDCl_3) of **3.33**



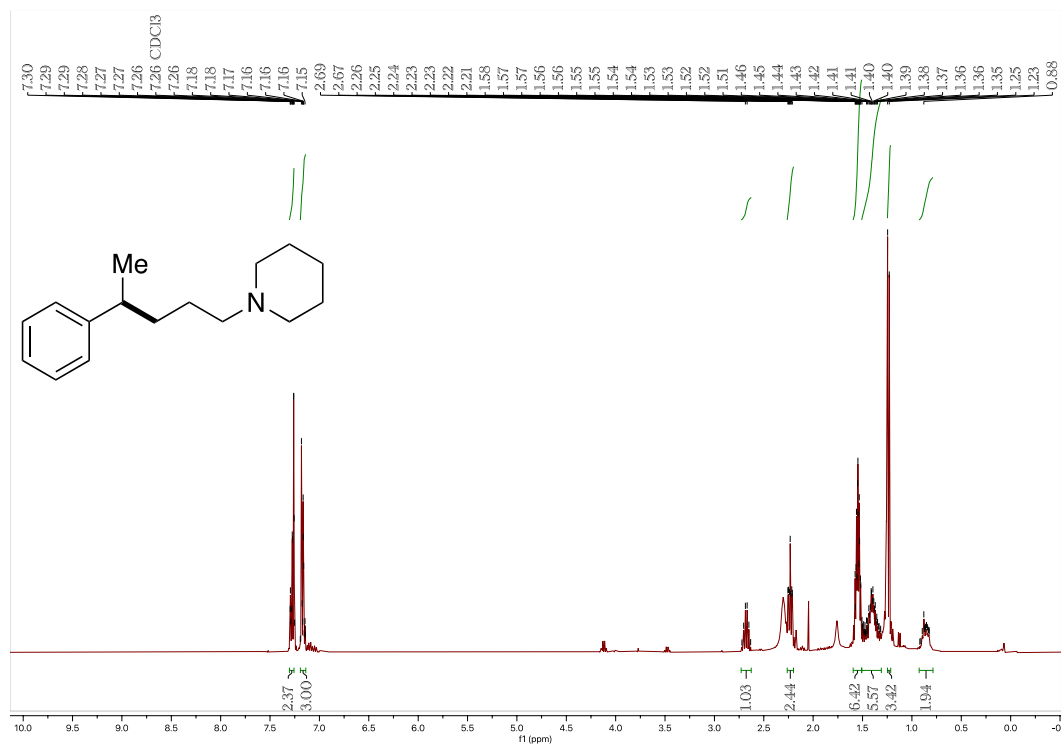
^{13}C NMR (125 MHz, CDCl_3) of **3.33**



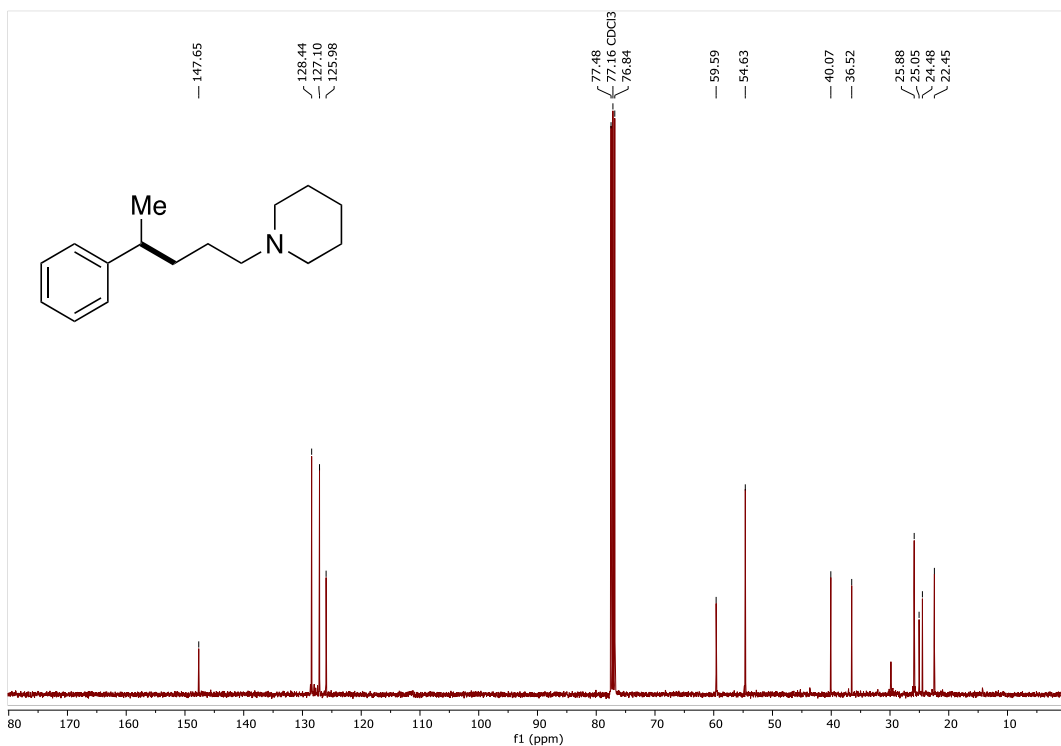
^{19}F NMR (470 MHz, CDCl_3) of **3.33**



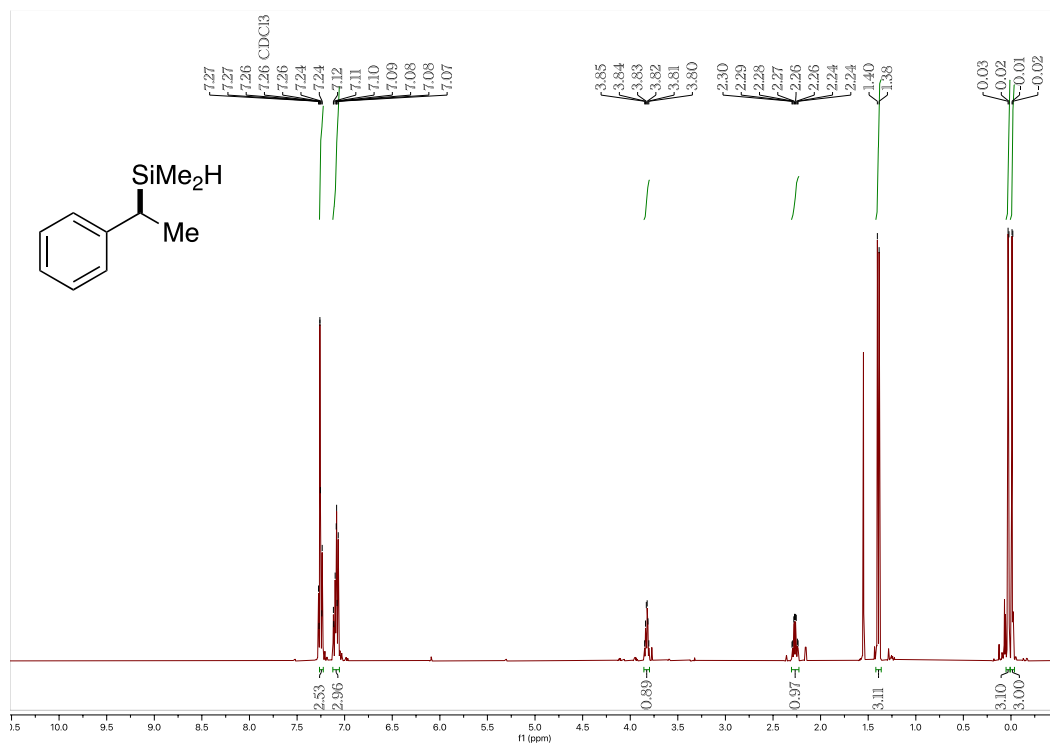
^1H NMR (400 MHz, CDCl_3) of **3.34**



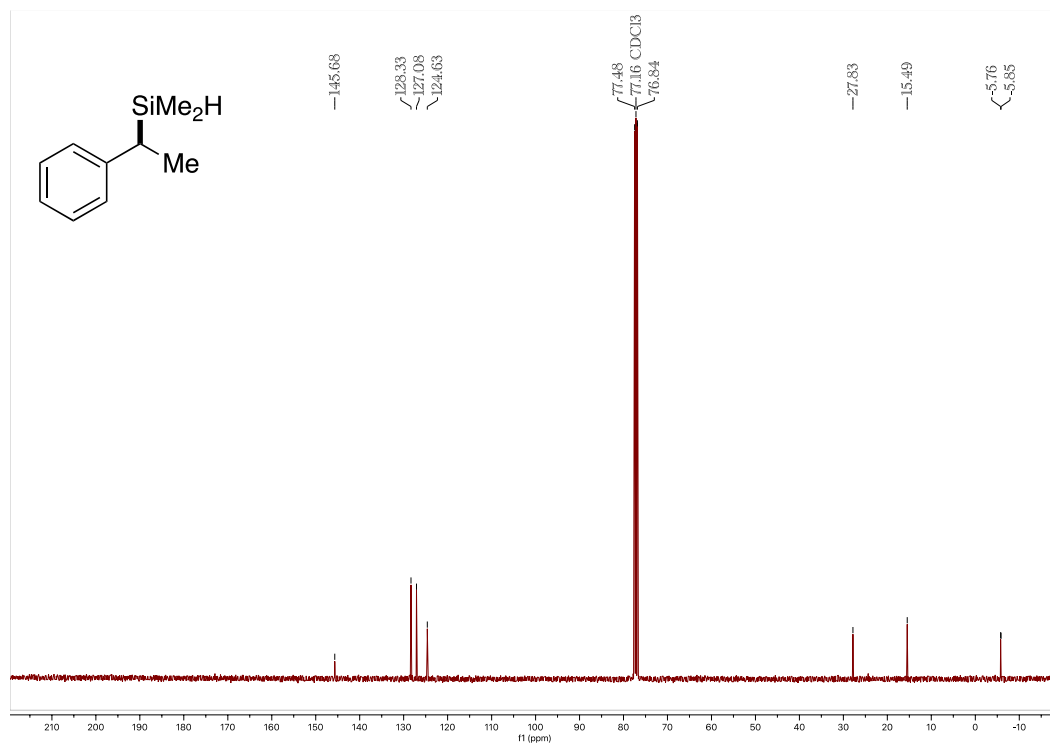
^{13}C NMR (100 MHz, CDCl_3) of **3.34**



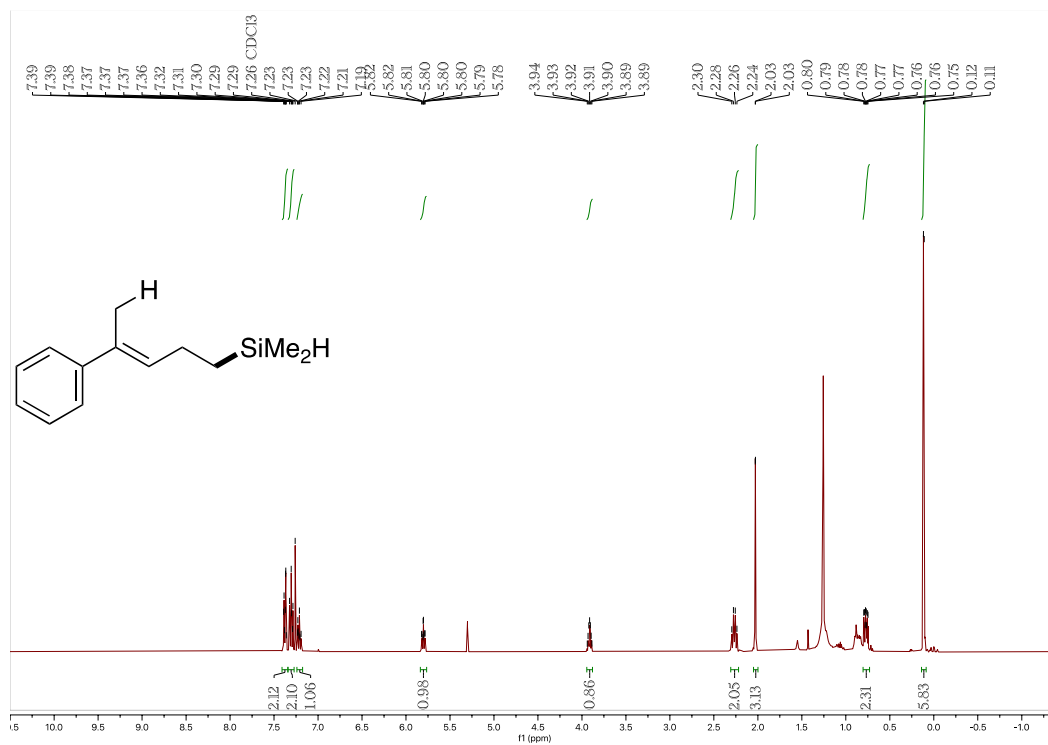
^{13}C NMR (100 MHz, CDCl_3) of **3.38**

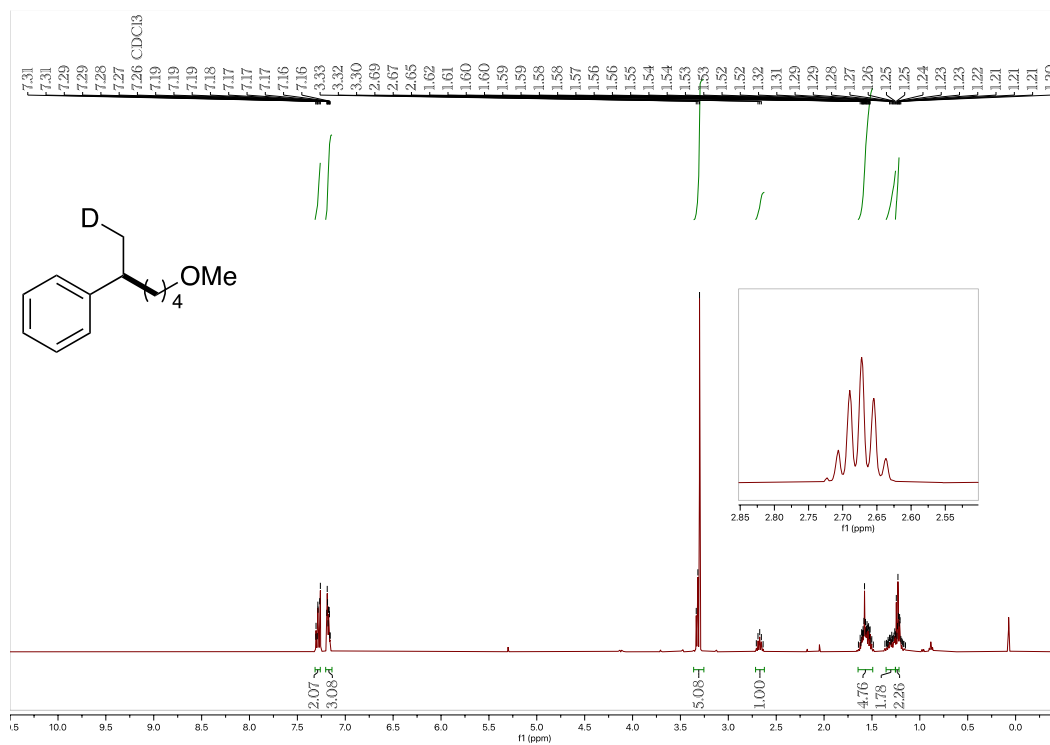
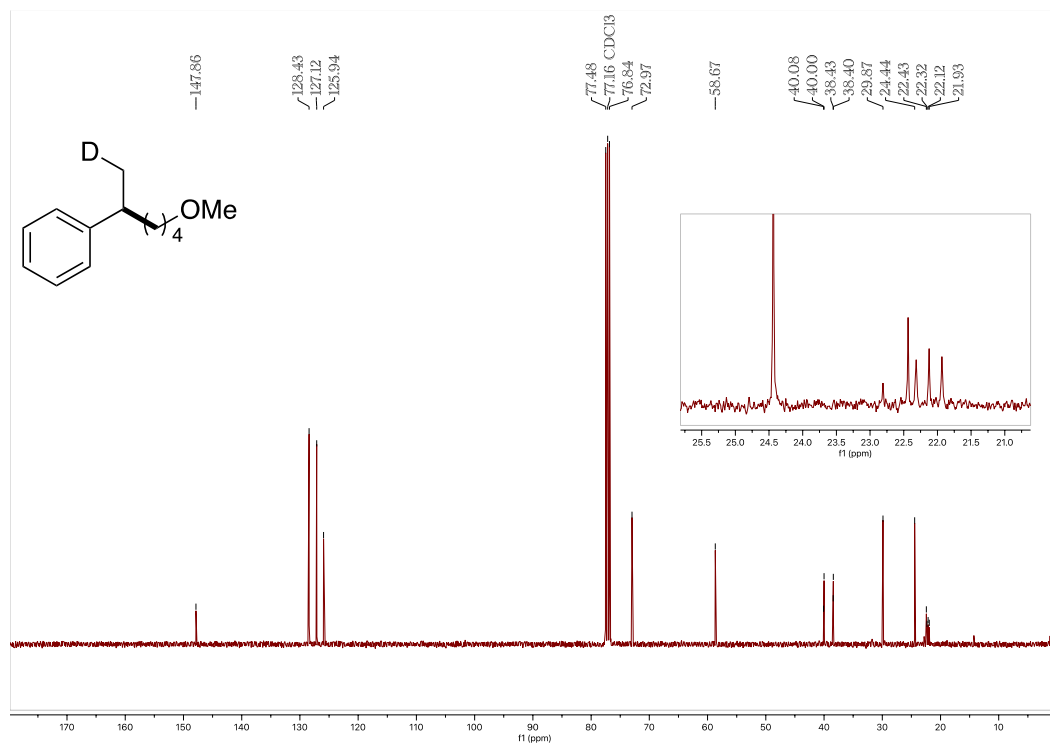


^{13}C NMR (100 MHz, CDCl_3) of **3.38**

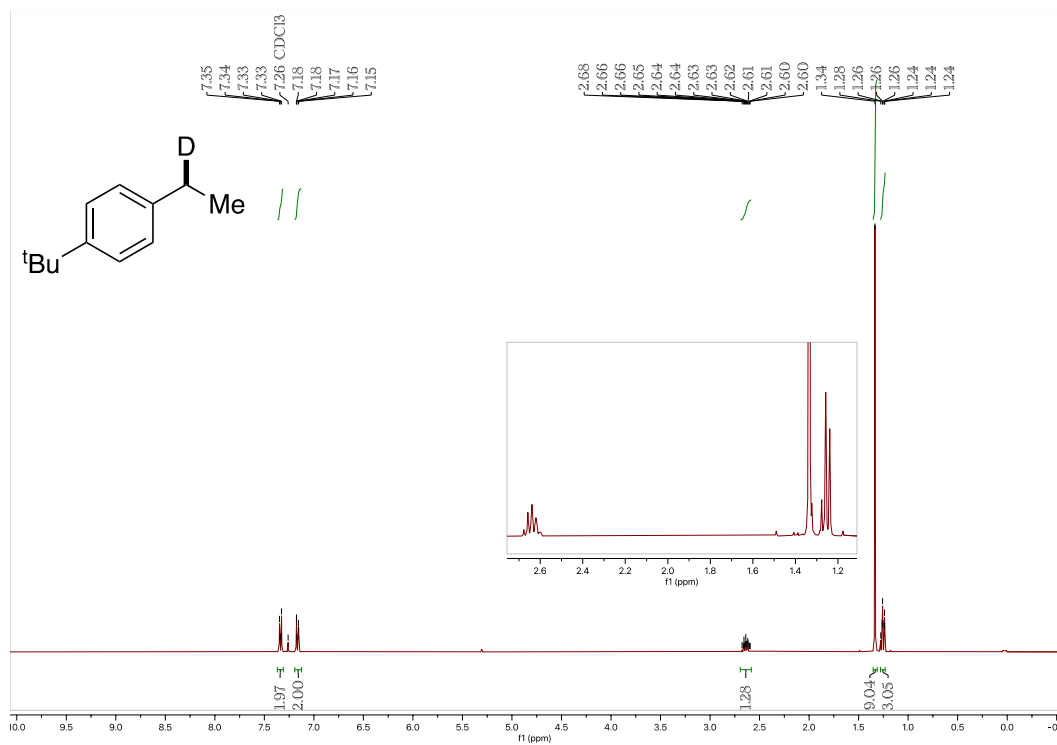


^1H NMR (400 MHz, CDCl_3) of **3.40**

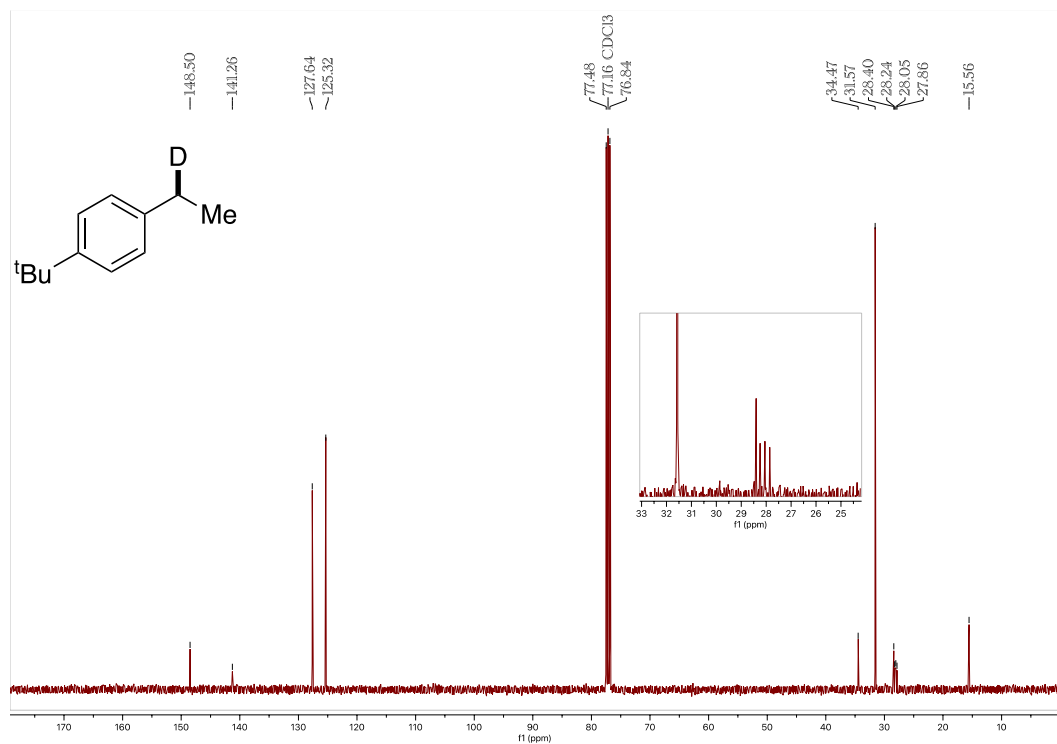


¹H NMR (400 MHz, CDCl₃) of **3.7-d₁** ^{13}C NMR (100 MHz, CDCl_3) of **3.7-d₁**

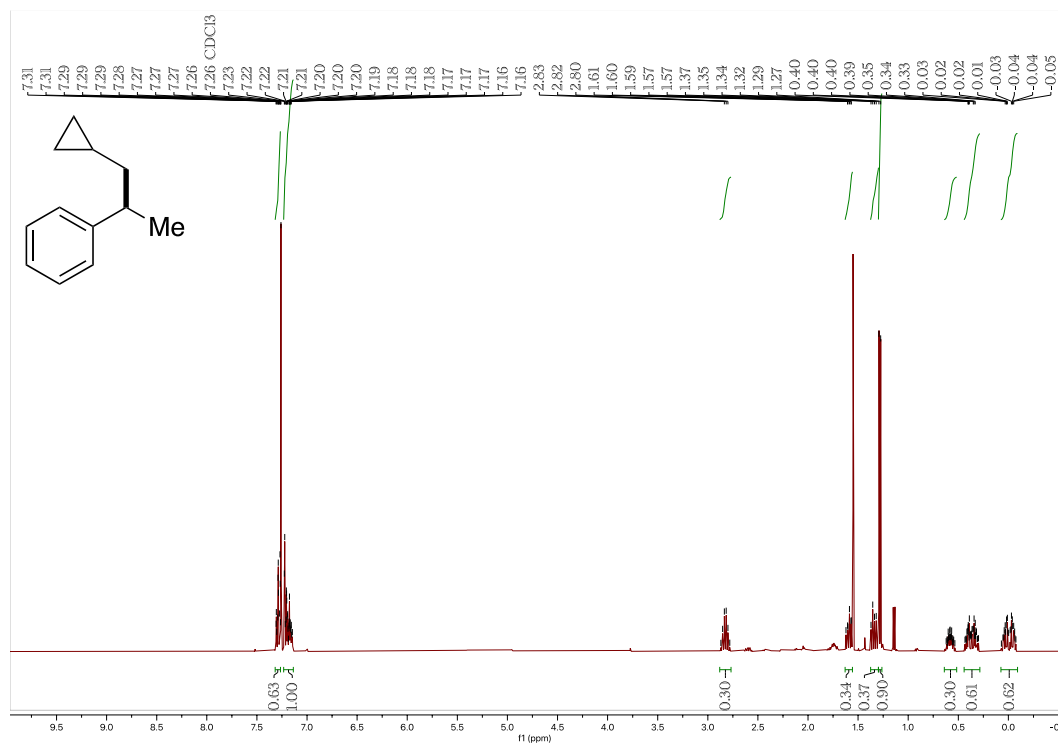
^1H NMR (400 MHz, CDCl_3) of **3.43**



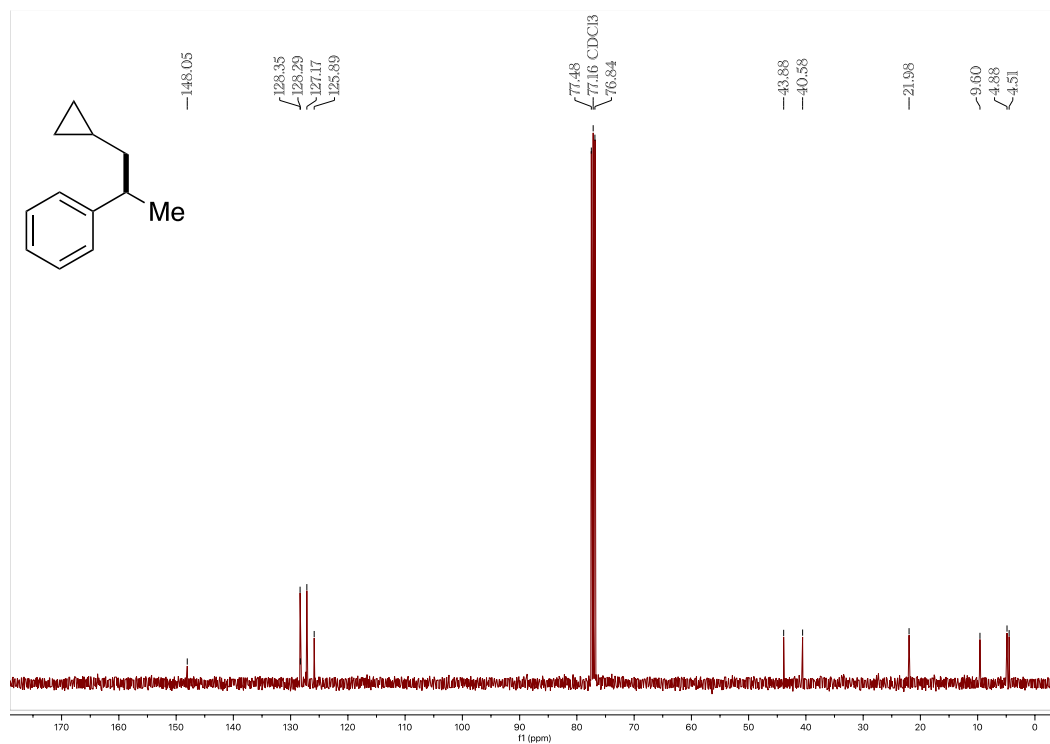
^{13}C NMR (100 MHz, CDCl_3) of **3.43**



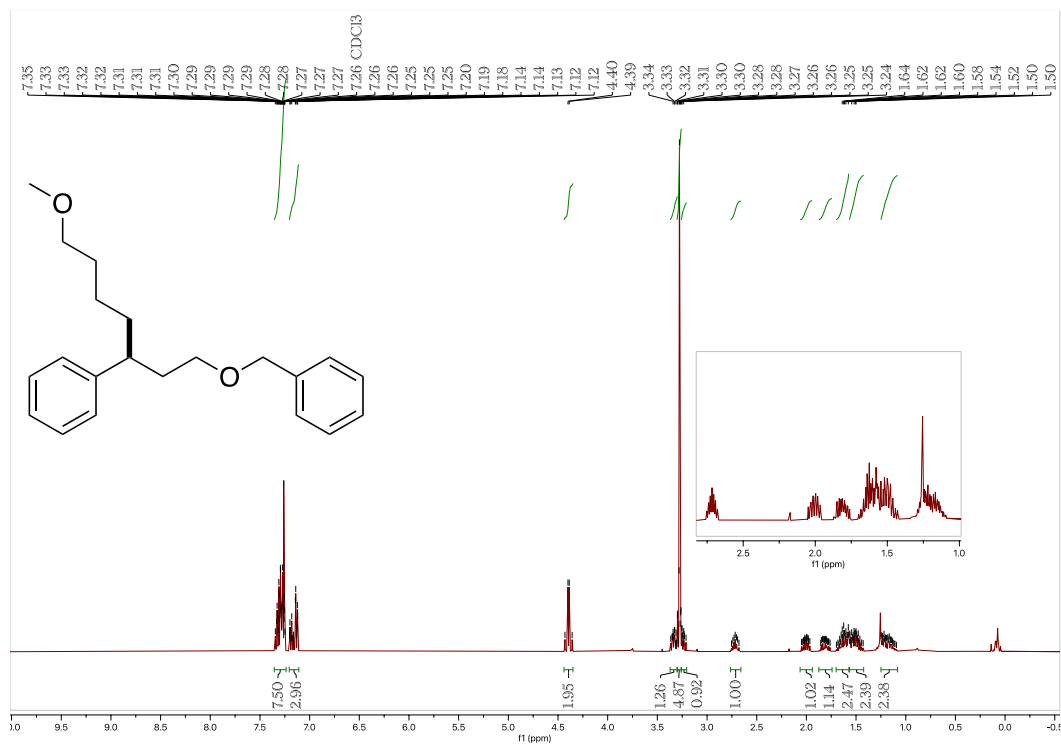
^1H NMR (400 MHz, CDCl_3) of **3.45**



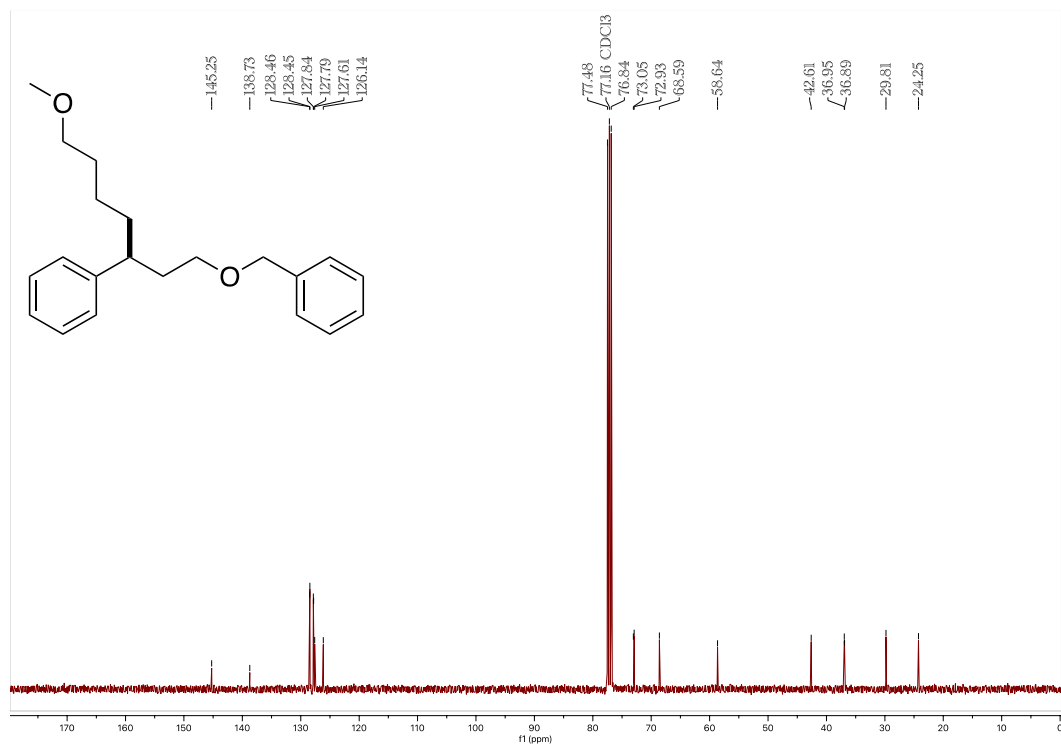
^{13}C NMR (100 MHz, CDCl_3) of **3.45**



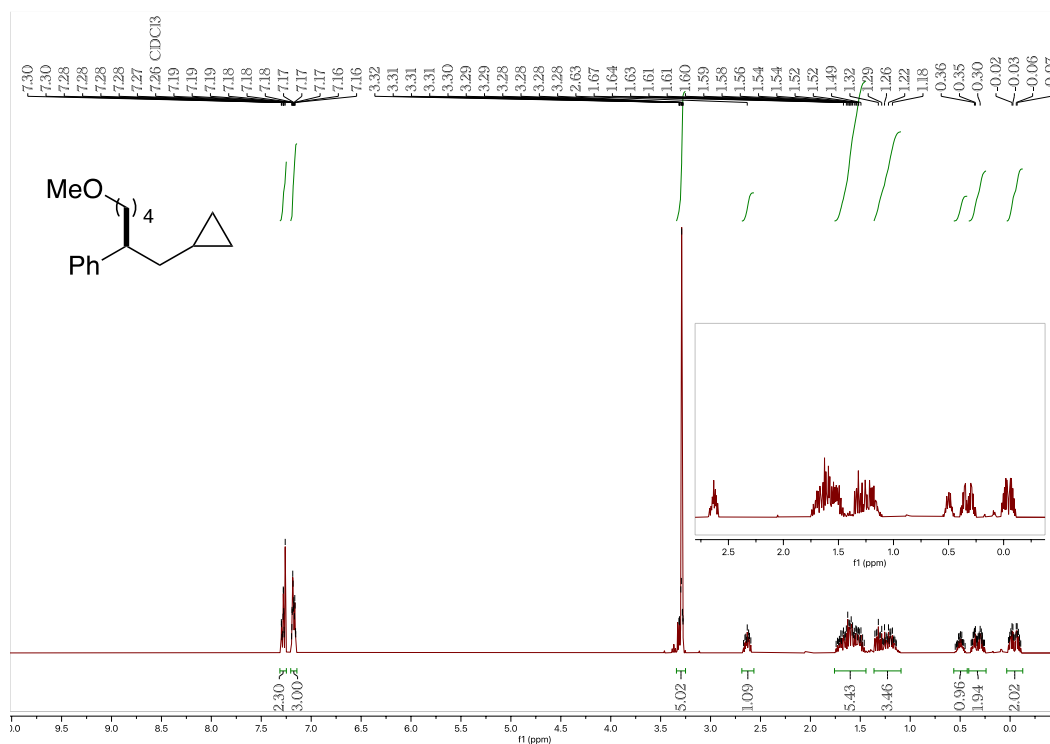
^1H NMR (400 MHz, CDCl_3) of **3.92**



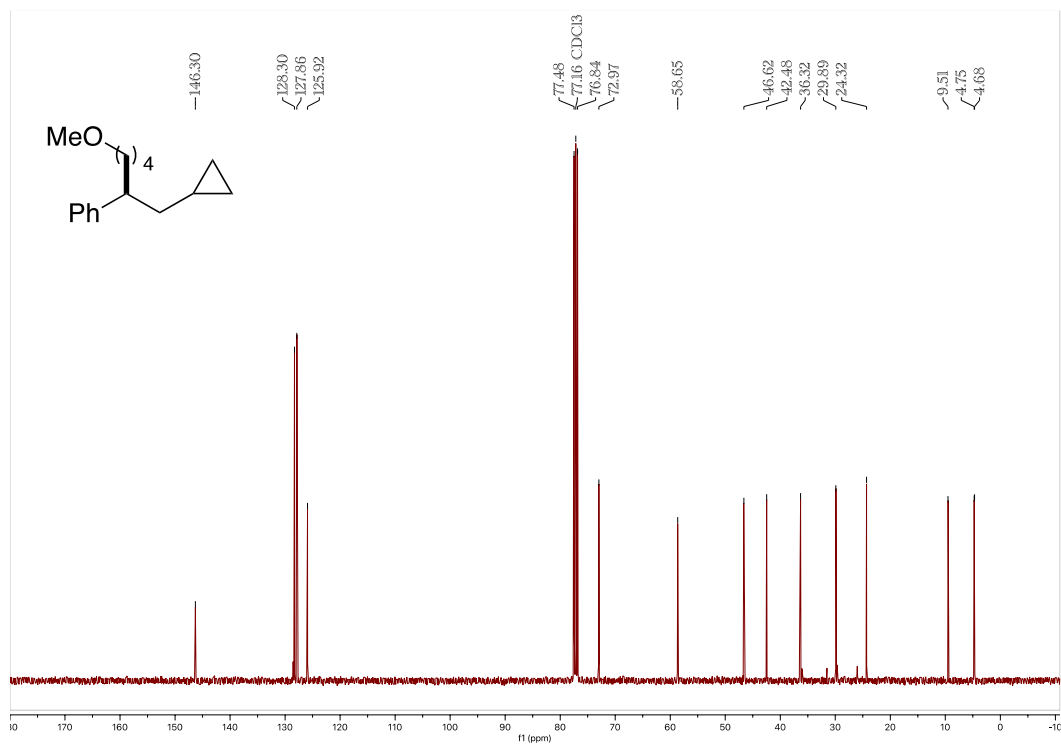
^{13}C NMR (100 MHz, CDCl_3) of **3.92**



^1H NMR (400 MHz, CDCl_3) of **3.94**

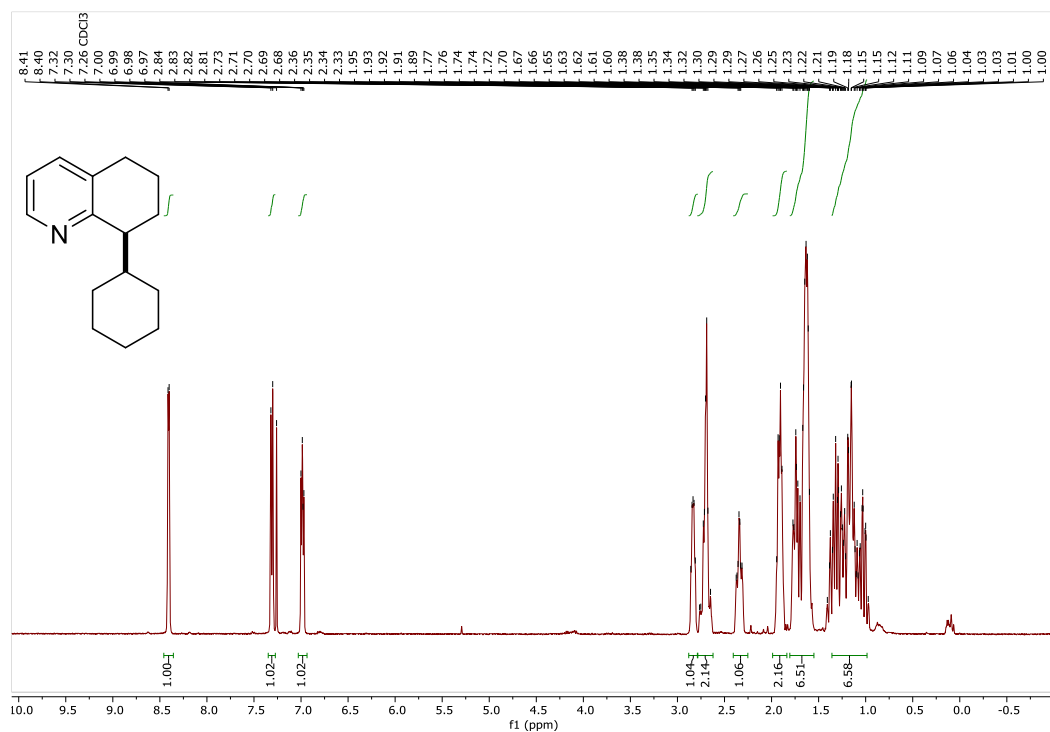


^{13}C NMR (100 MHz, CDCl_3) of **3.94**

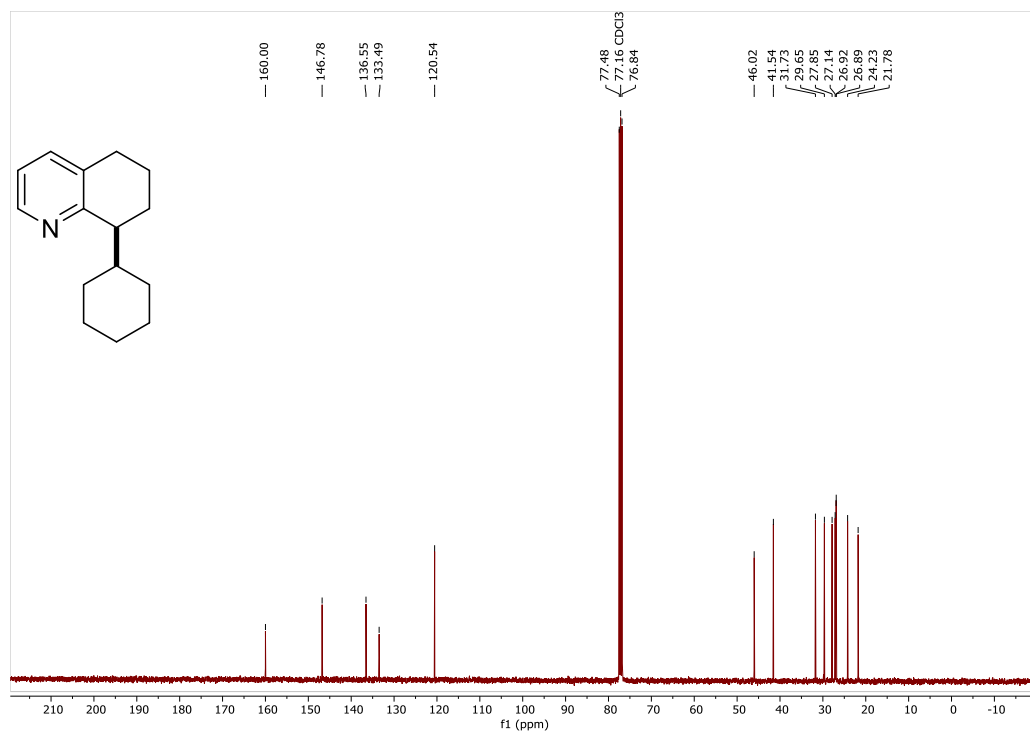


NMR Spectra for Chapter 4:

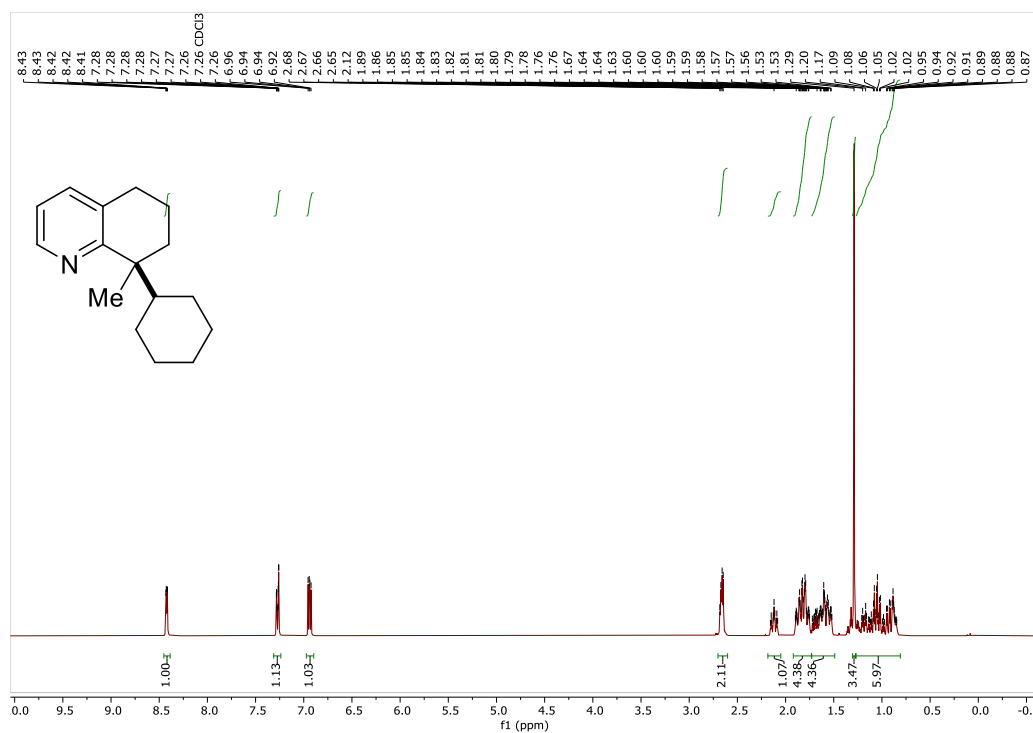
^1H NMR (400 MHz, CDCl_3) of **4.6**



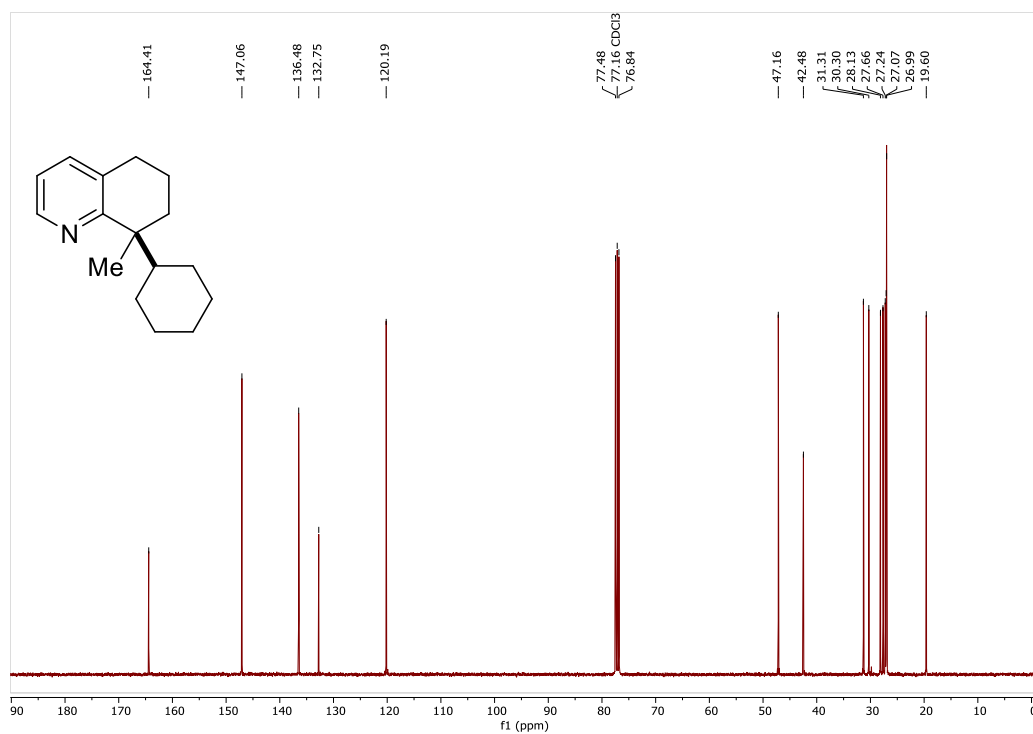
^{13}C NMR (100 MHz, CDCl_3) of **4.6**



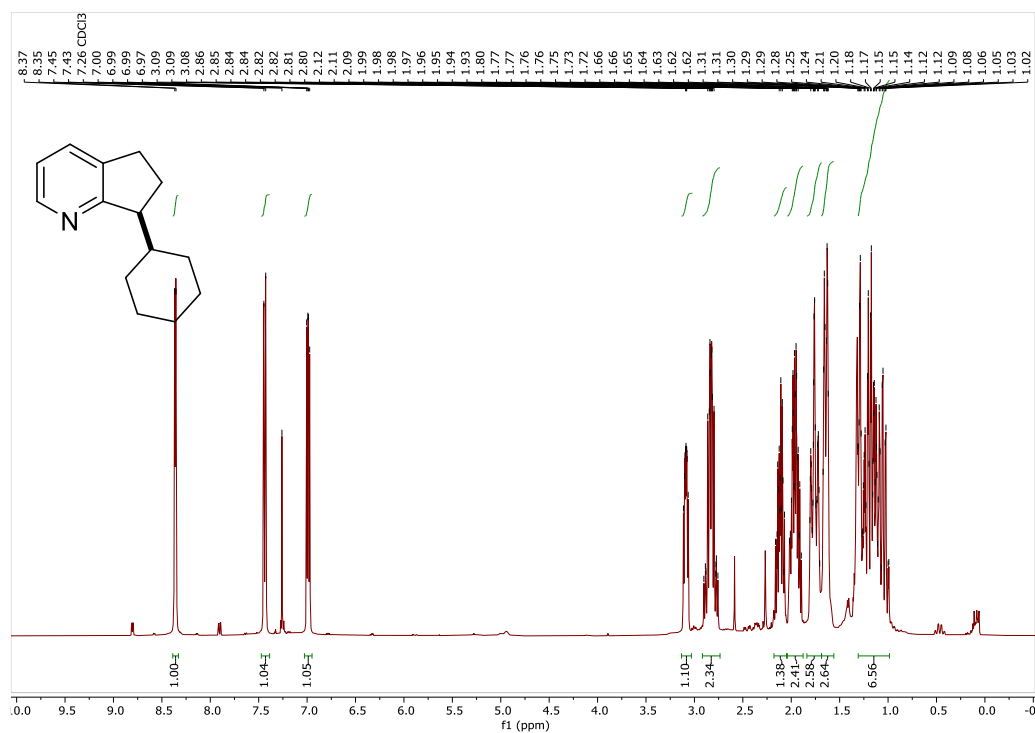
^1H NMR (400 MHz, CDCl_3) of **4.7**



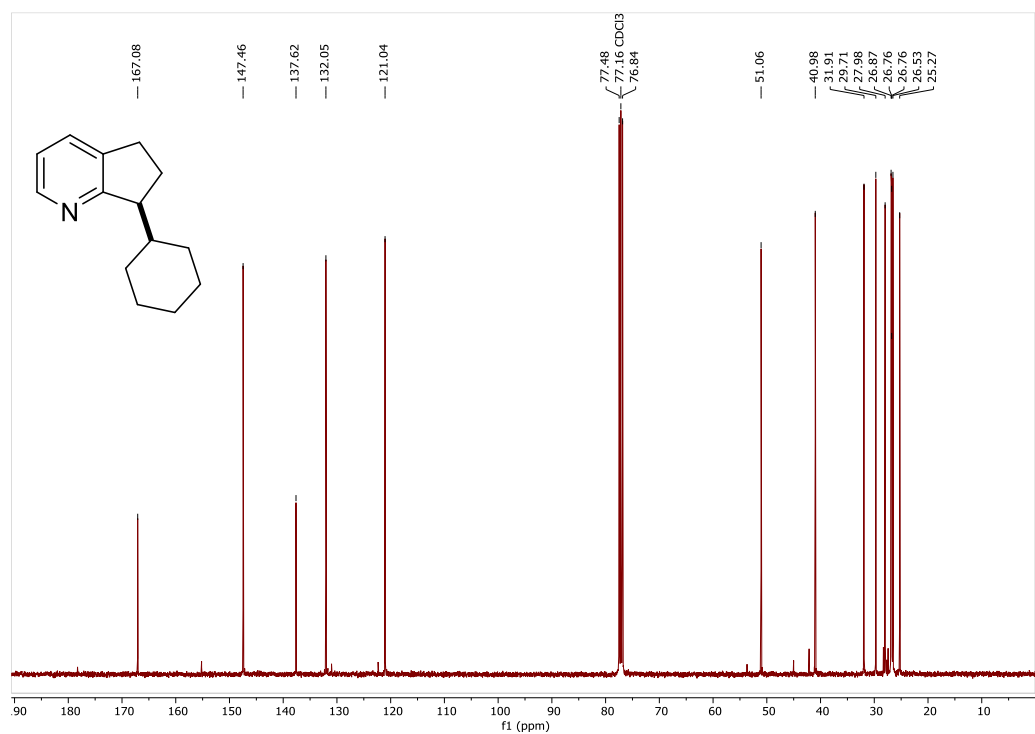
^{13}C NMR (100 MHz, CDCl_3) of **4.7**



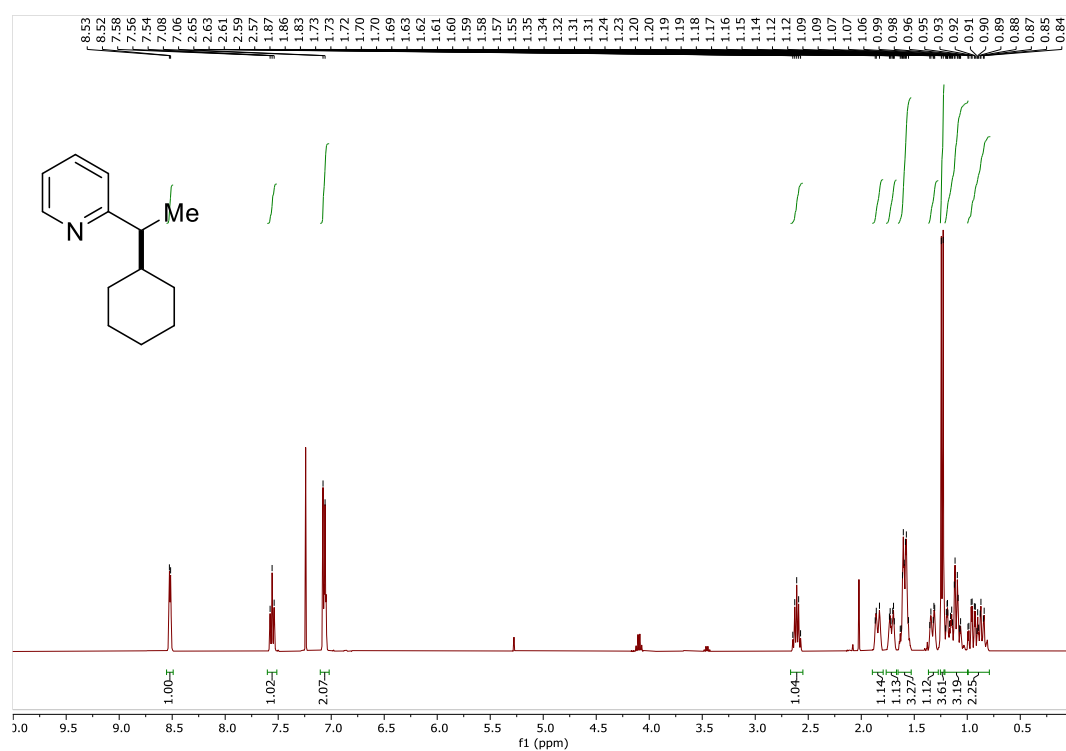
^1H NMR (400 MHz, CDCl_3) of **4.8**



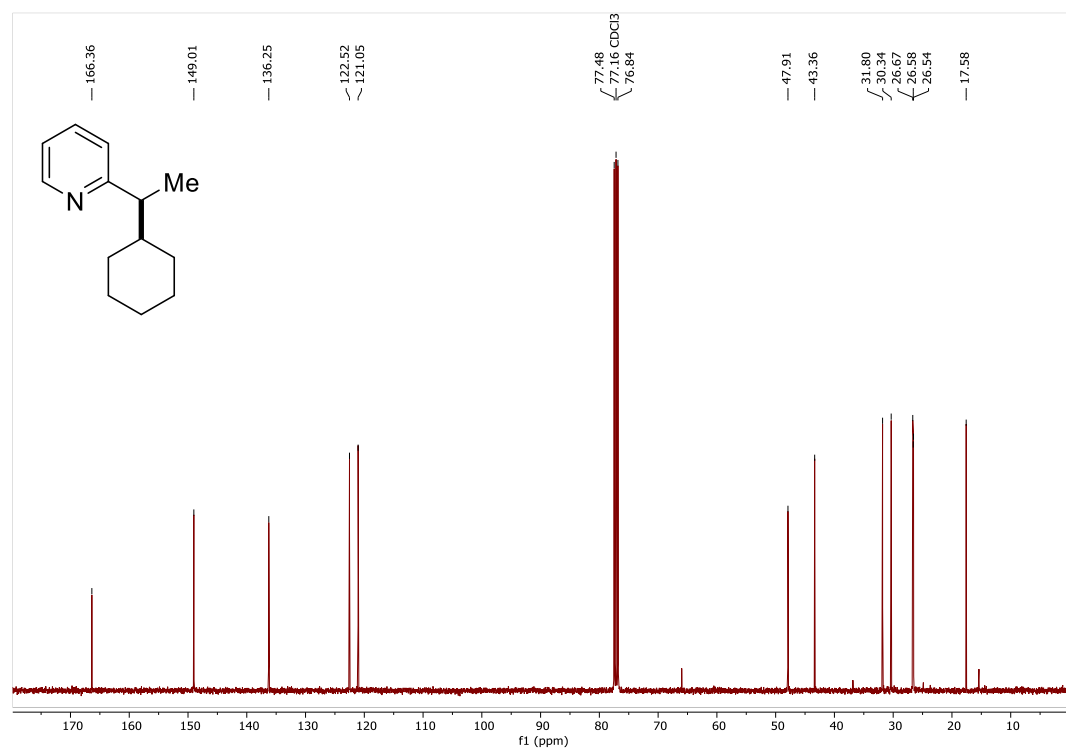
^{13}C NMR (100 MHz, CDCl_3) of **4.8**



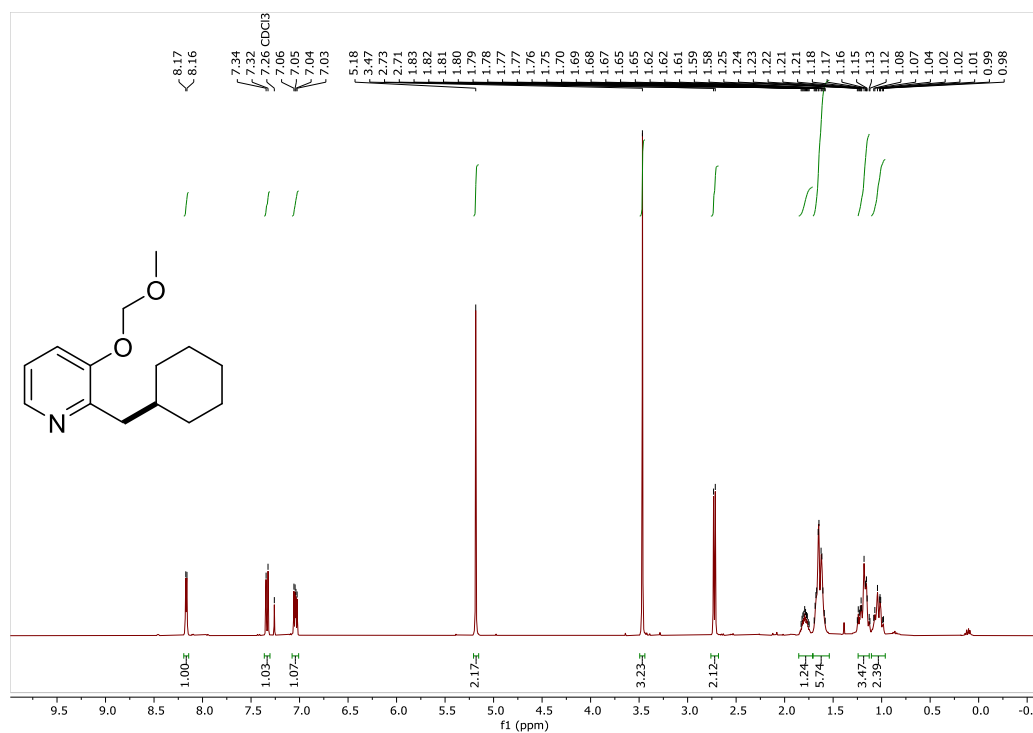
^1H NMR (400 MHz, CDCl_3) of **4.9**



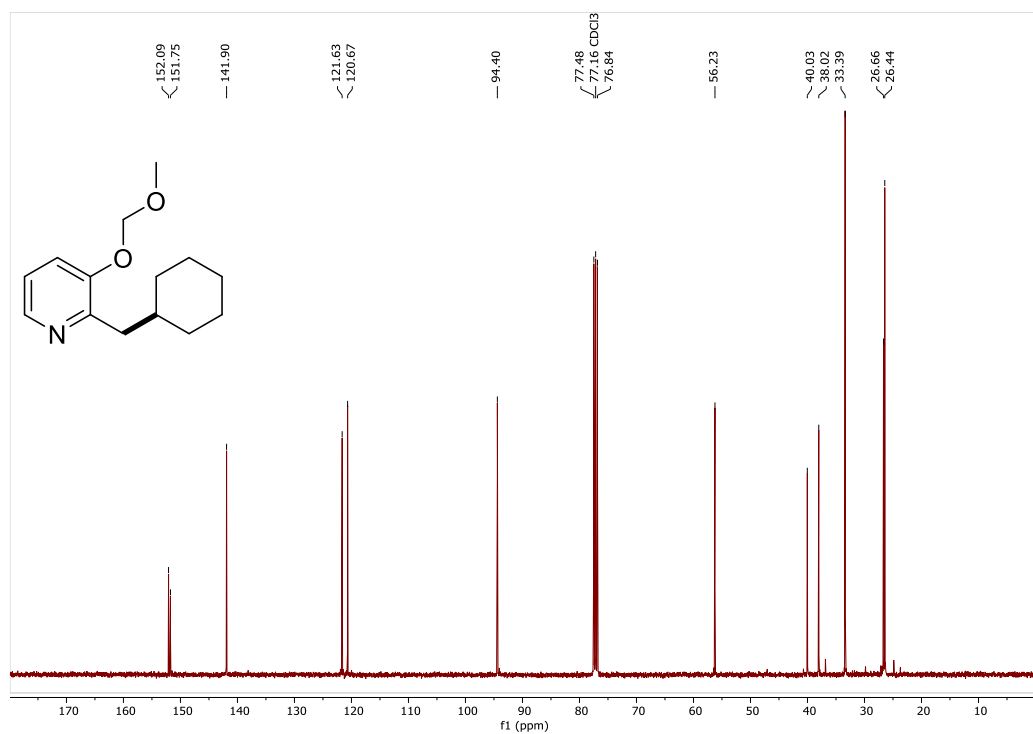
^{13}C NMR (100 MHz, CDCl_3) of **4.9**



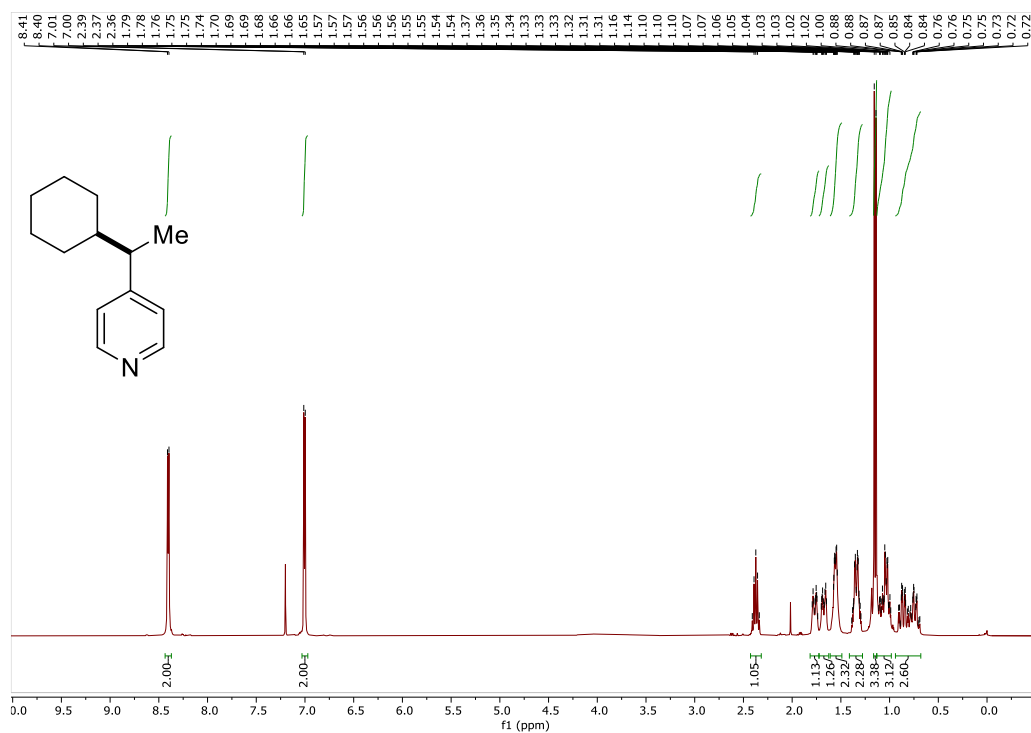
^1H NMR (400 MHz, CDCl_3) of **4.10**



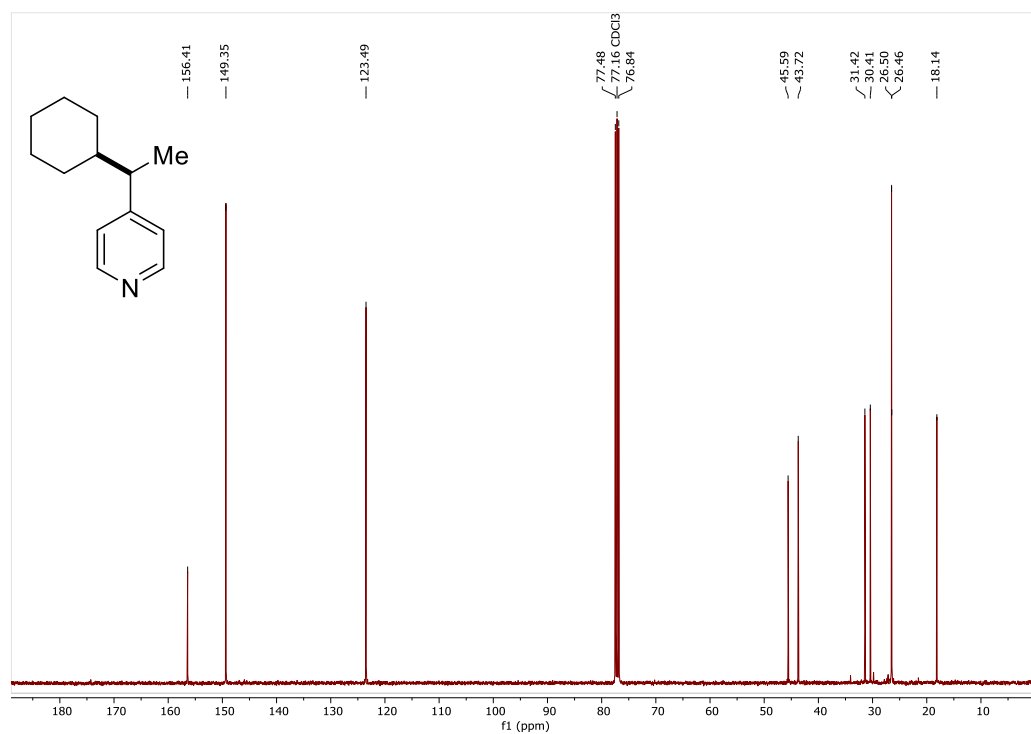
^{13}C NMR (100 MHz, CDCl_3) of **4.10**



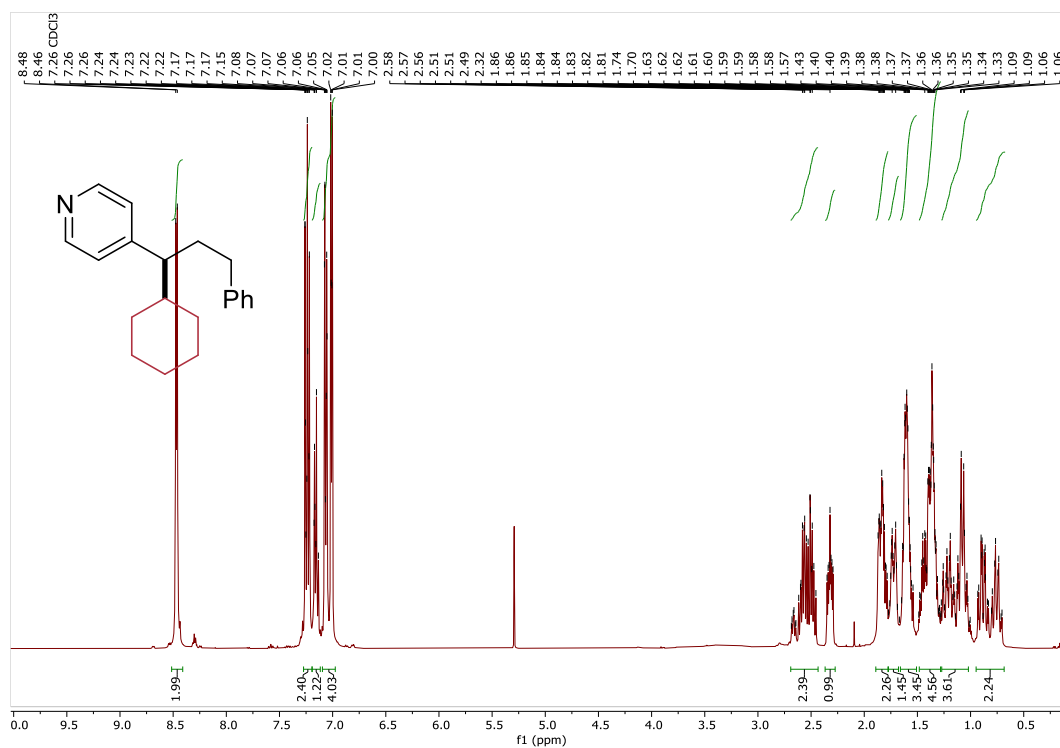
^1H NMR (400 MHz, CDCl_3) of **4.11**



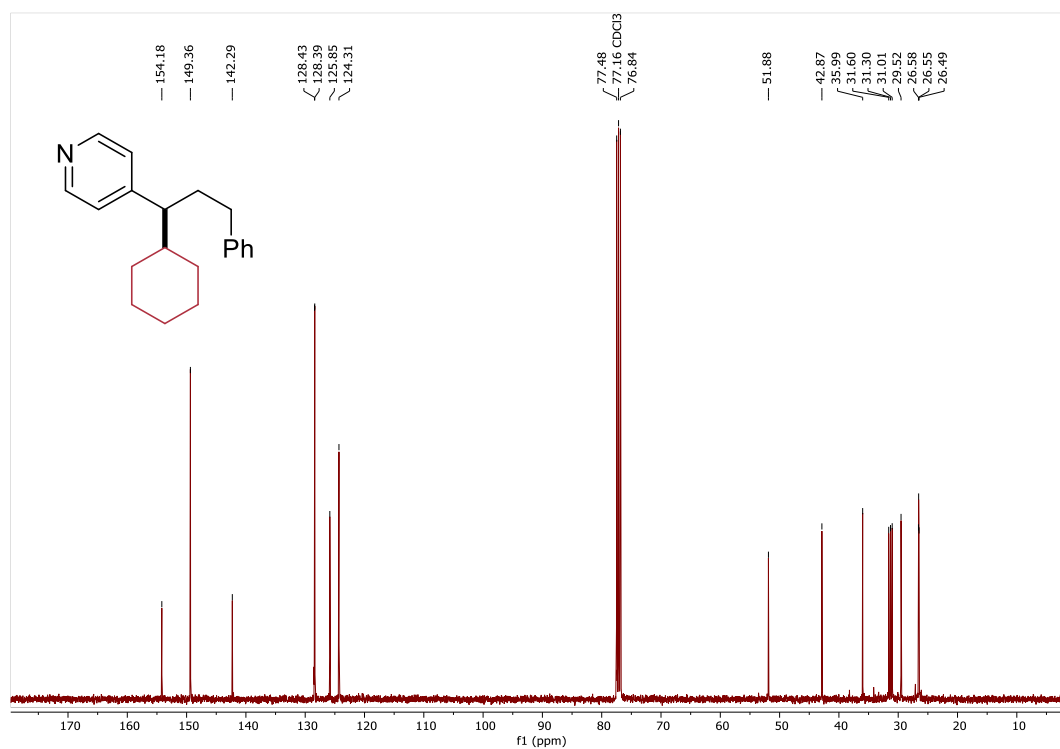
^{13}C NMR (100 MHz, CDCl_3) of **4.11**



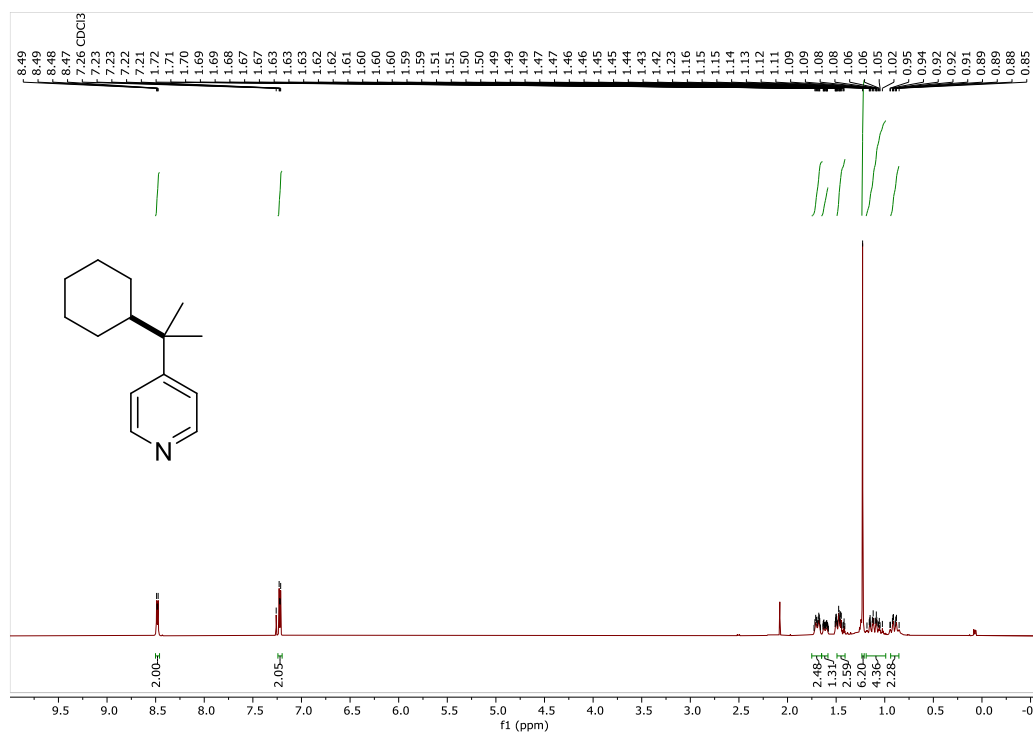
^1H NMR (400 MHz, CDCl_3) of **4.12**



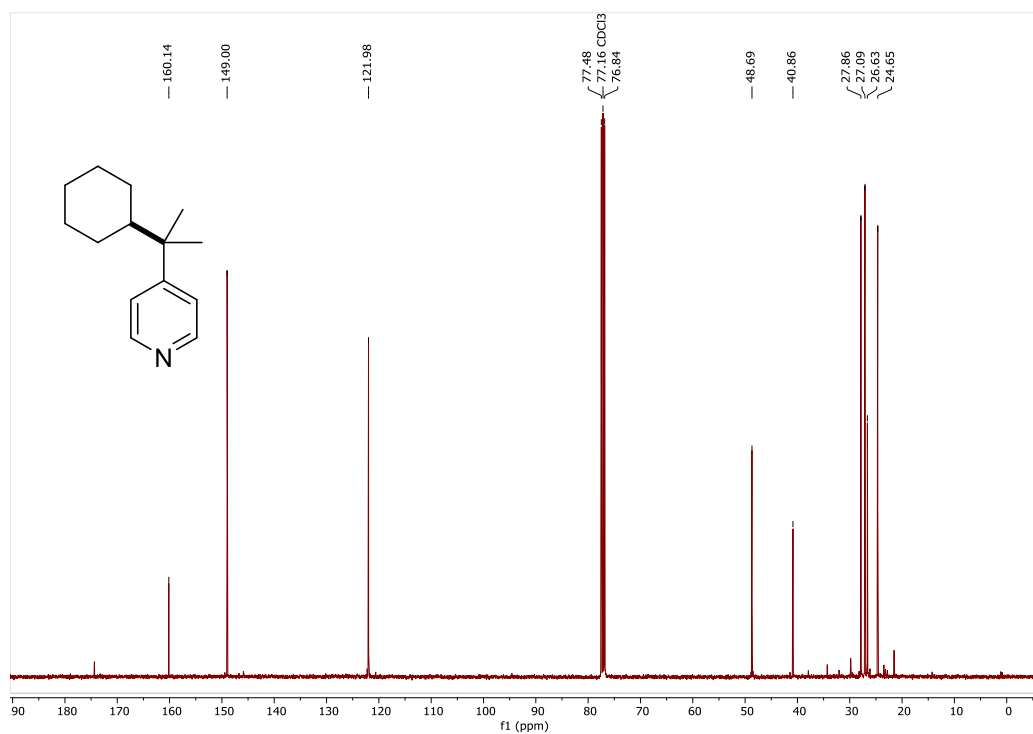
^{13}C NMR (100 MHz, CDCl_3) of **4.12**



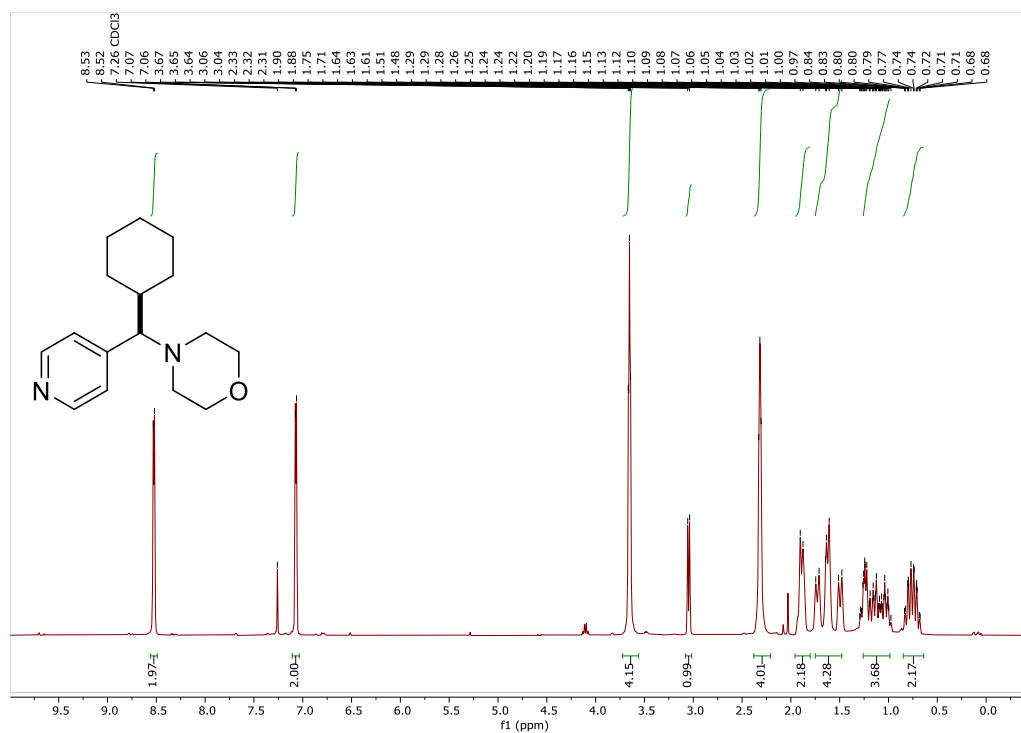
^1H NMR (400 MHz, CDCl_3) of **4.13**



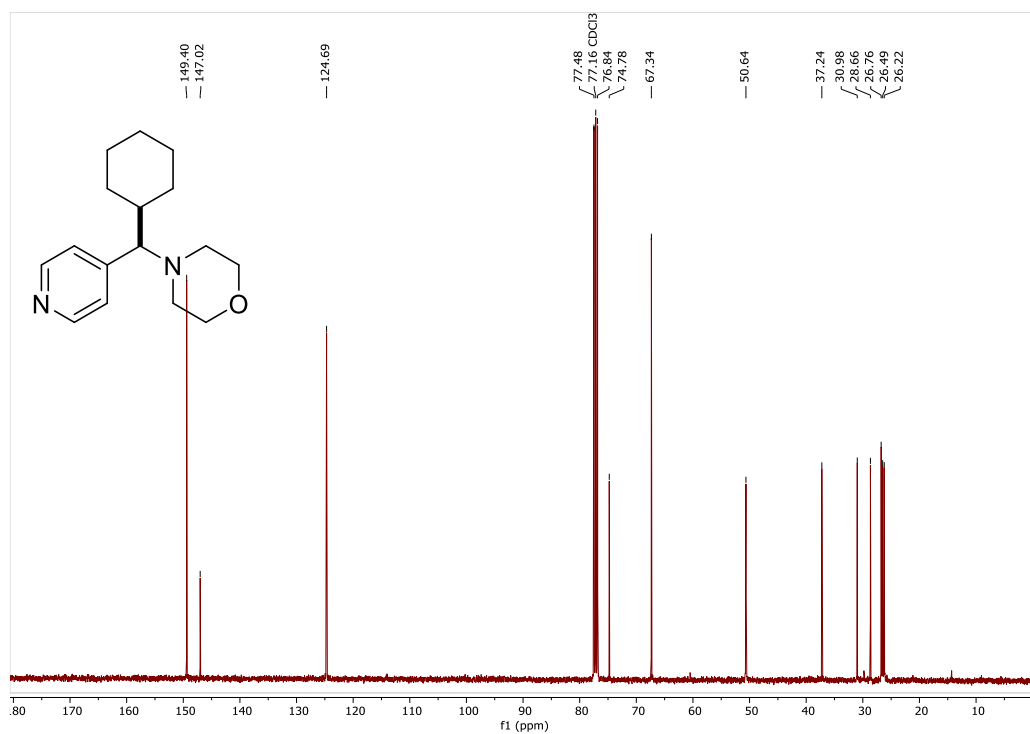
^{13}C NMR (100 MHz, CDCl_3) of **4.13**



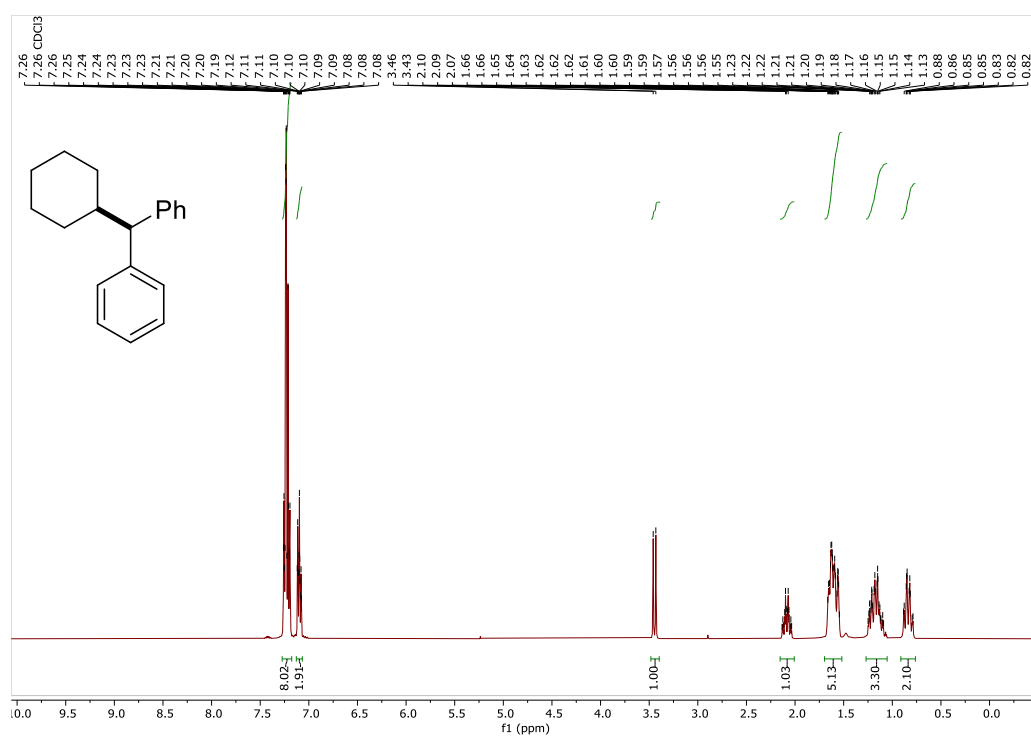
^1H NMR (400 MHz, CDCl_3) of **4.14**



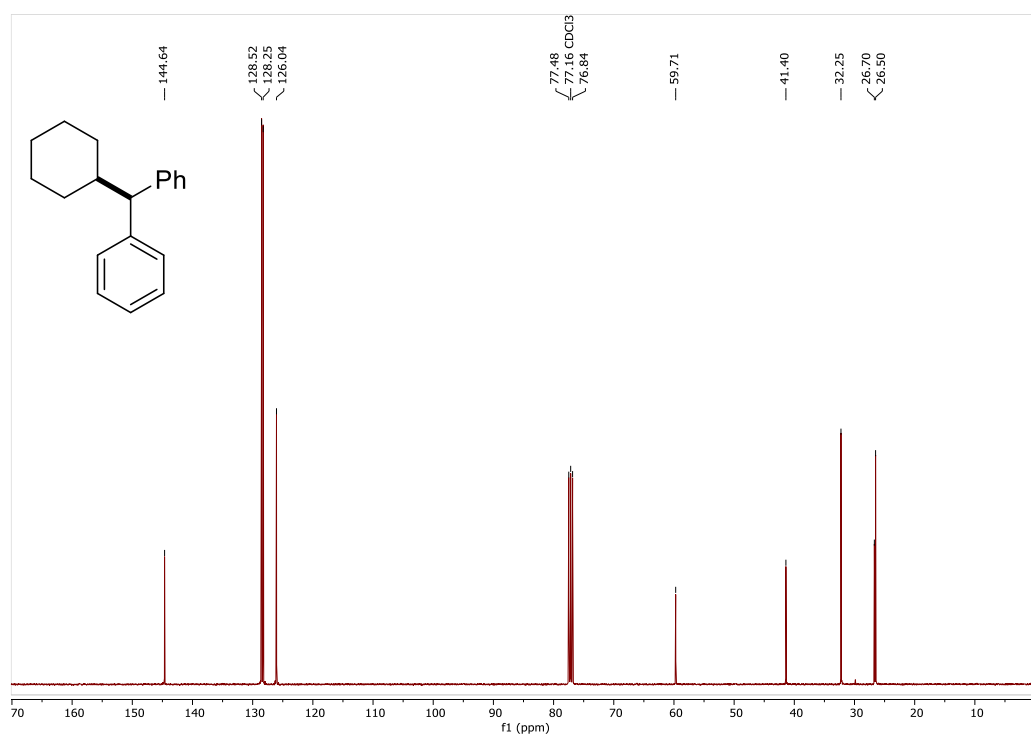
^{13}C NMR (100 MHz, CDCl_3) of **4.14**



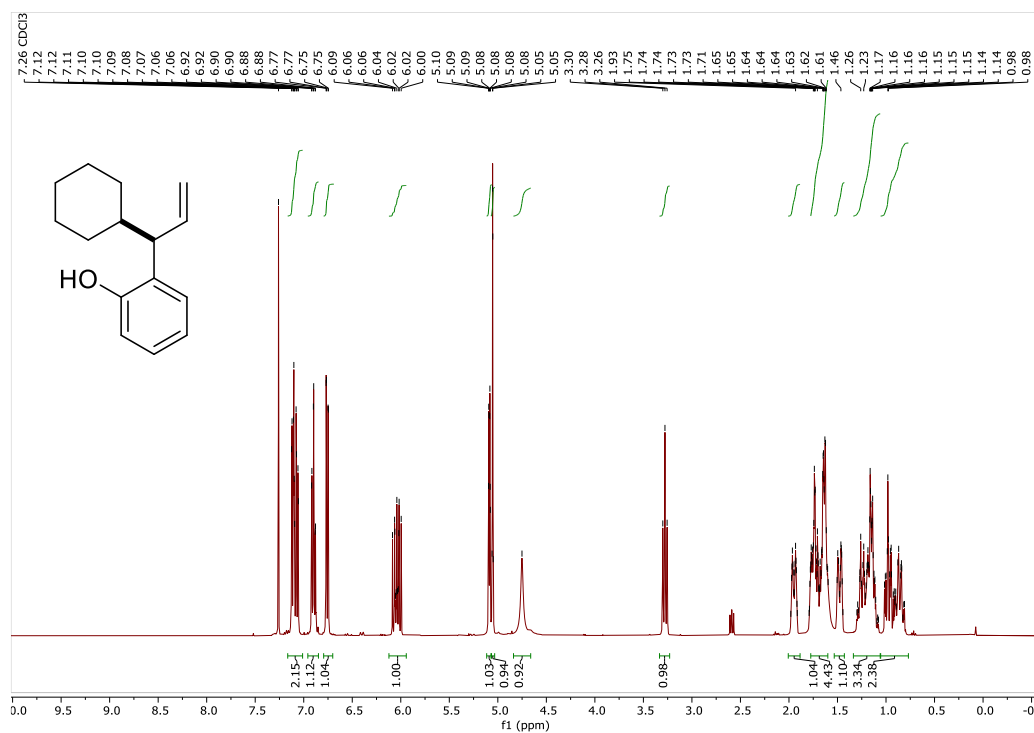
^1H NMR (400 MHz, CDCl_3) of **4.15**



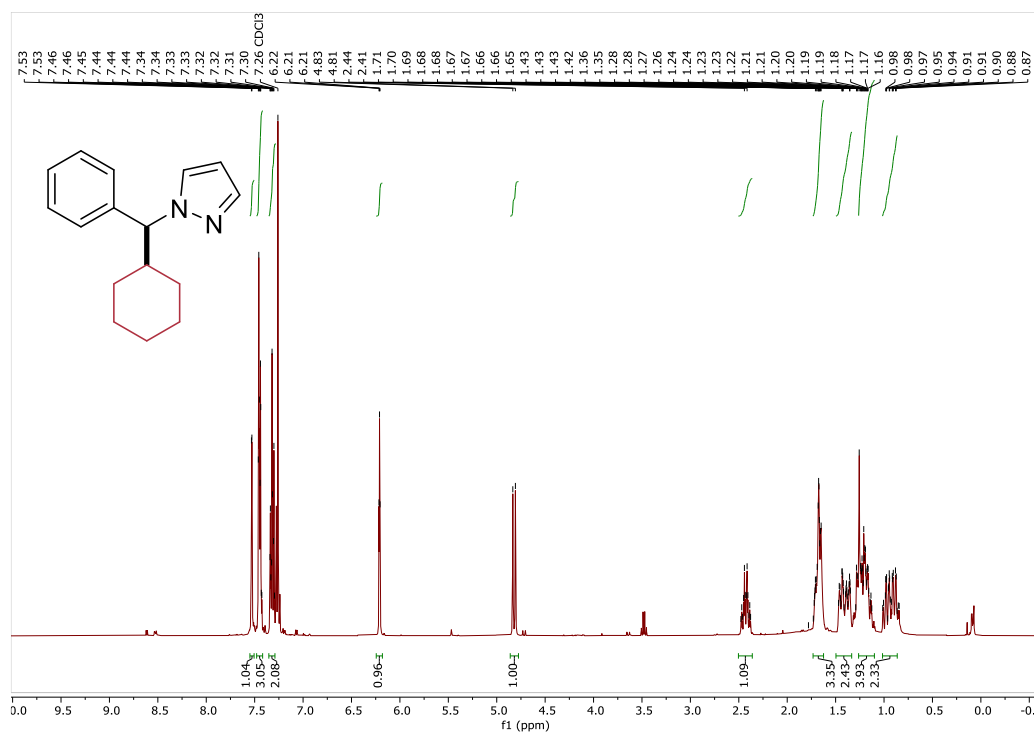
^{13}C NMR (100 MHz, CDCl_3) of **4.15**



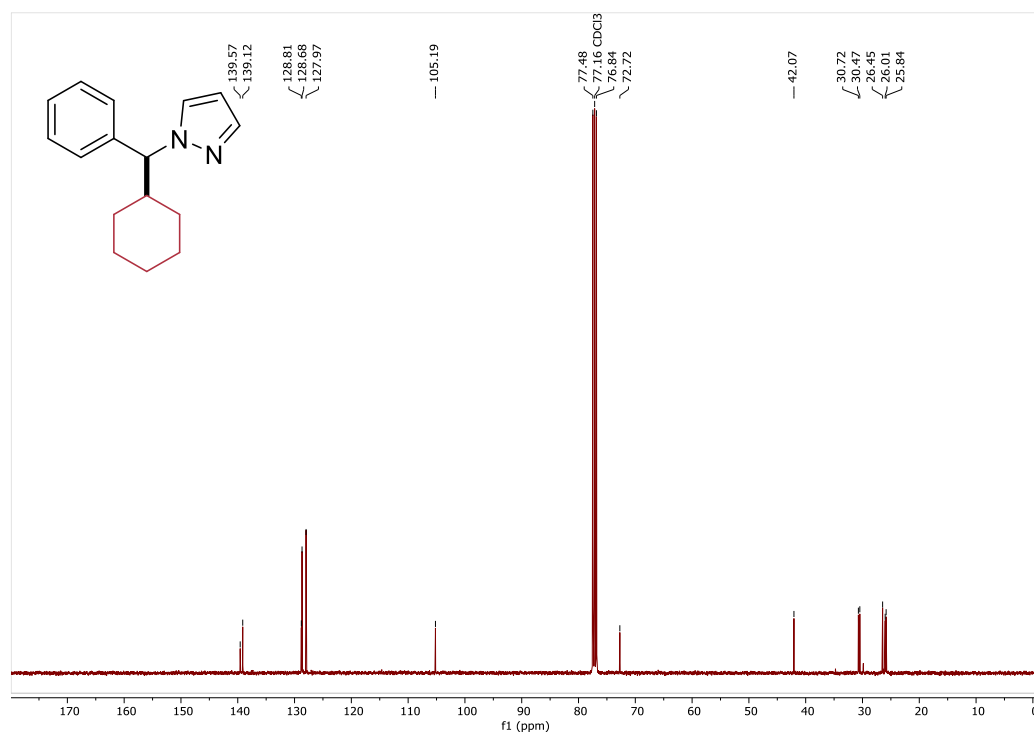
^1H NMR (400 MHz, CDCl_3) of **4.16**



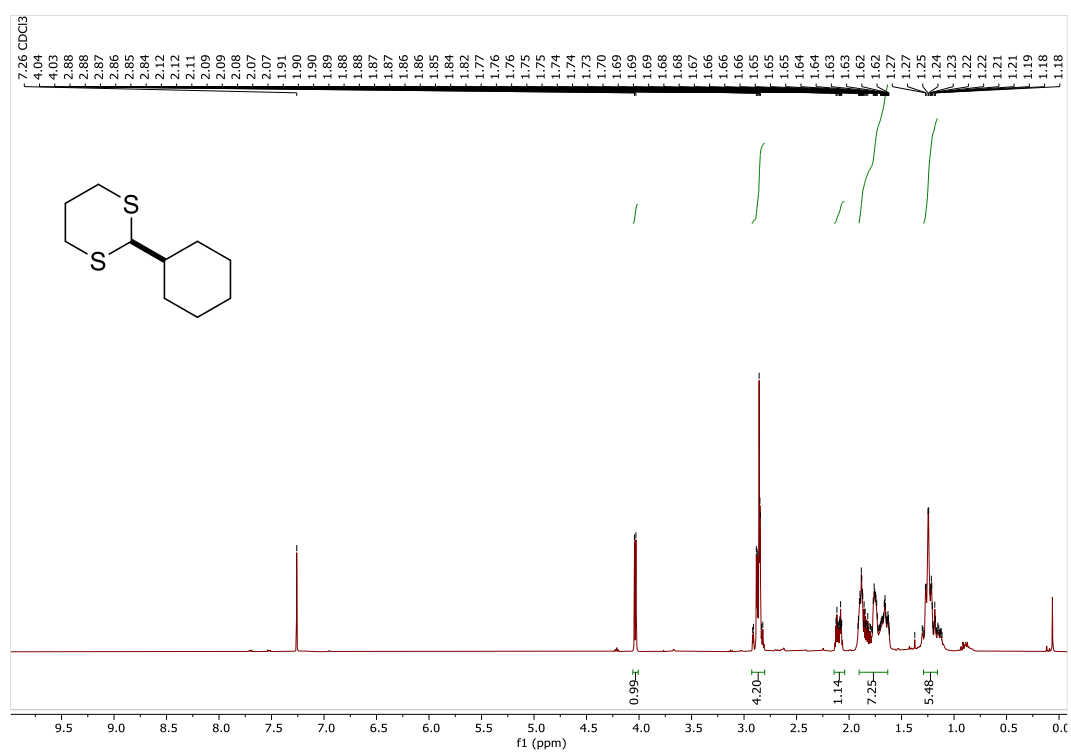
^1H NMR (400 MHz, CDCl_3) of **4.17**



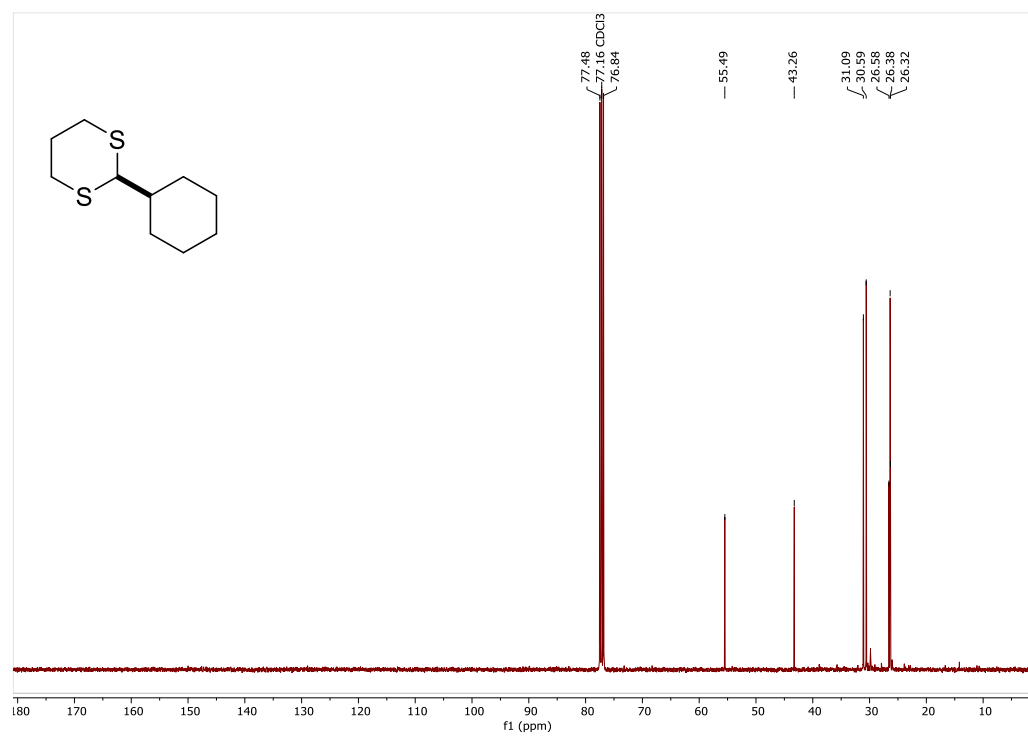
^{13}C NMR (100 MHz, CDCl_3) of **4.17**



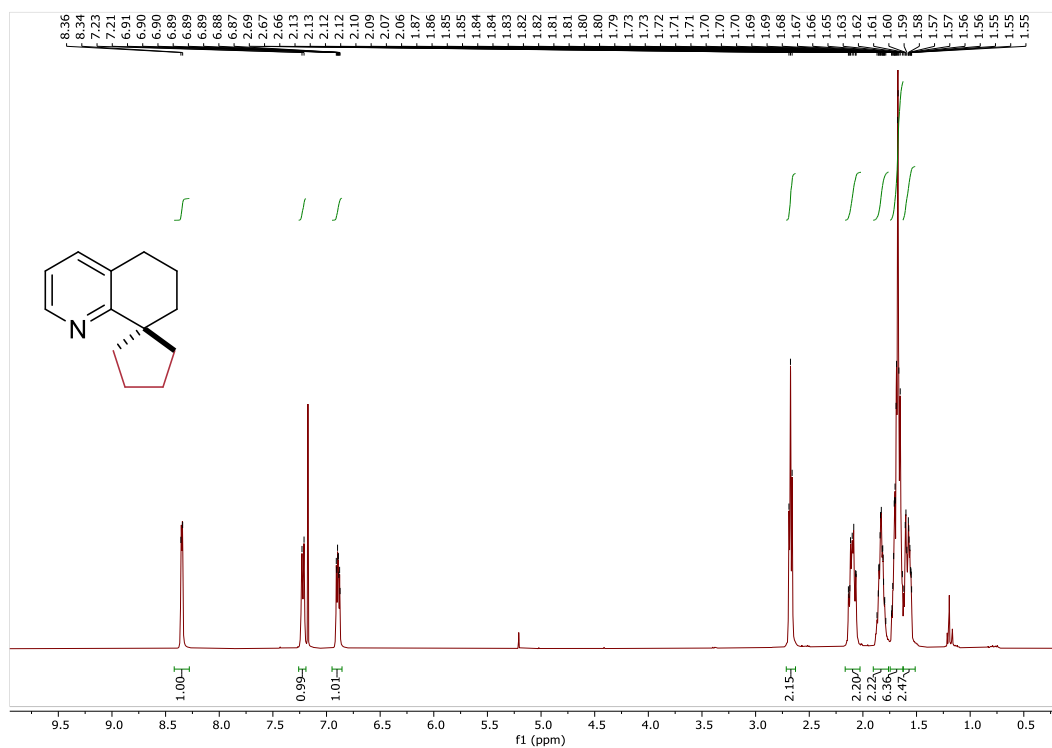
^1H NMR (400 MHz, CDCl_3) of **4.18**



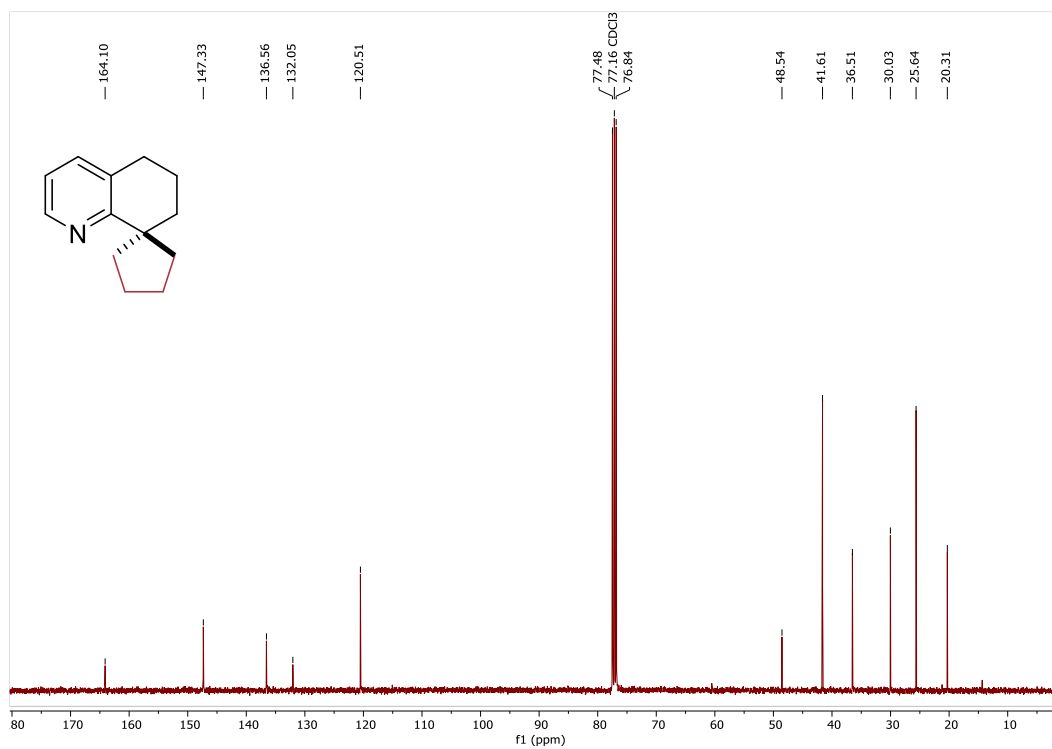
^{13}C NMR (100 MHz, CDCl_3) of **4.18**



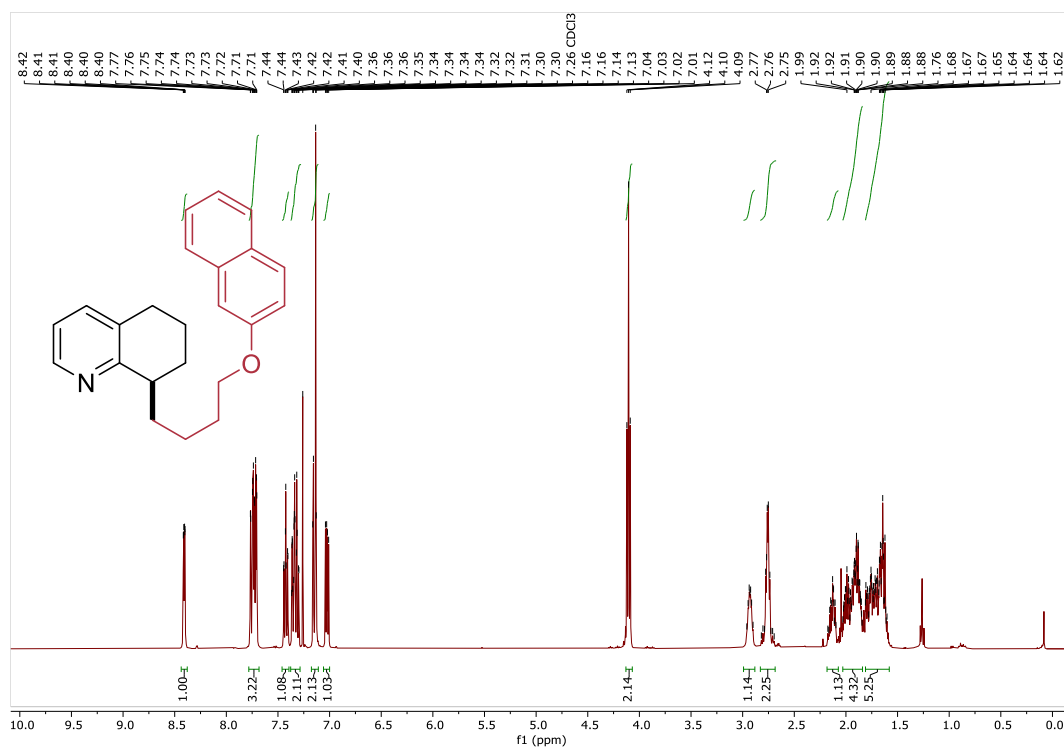
^1H NMR (400 MHz, CDCl_3) of **4.20**



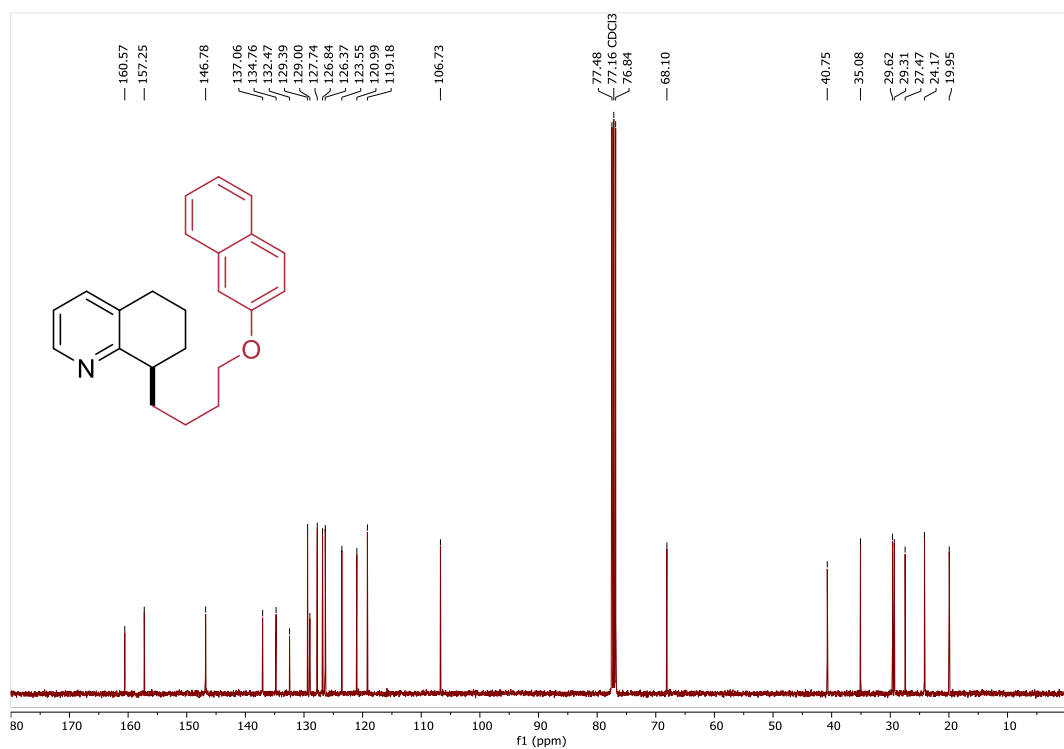
^{13}C NMR (100 MHz, CDCl_3) of **4.20**

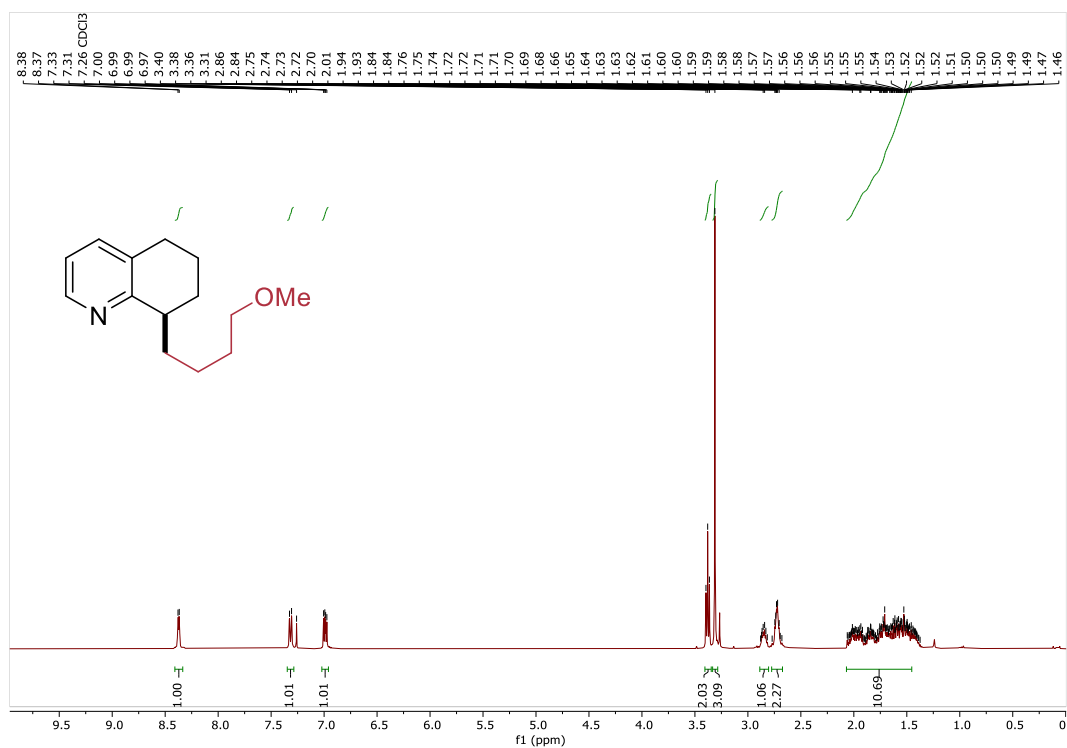
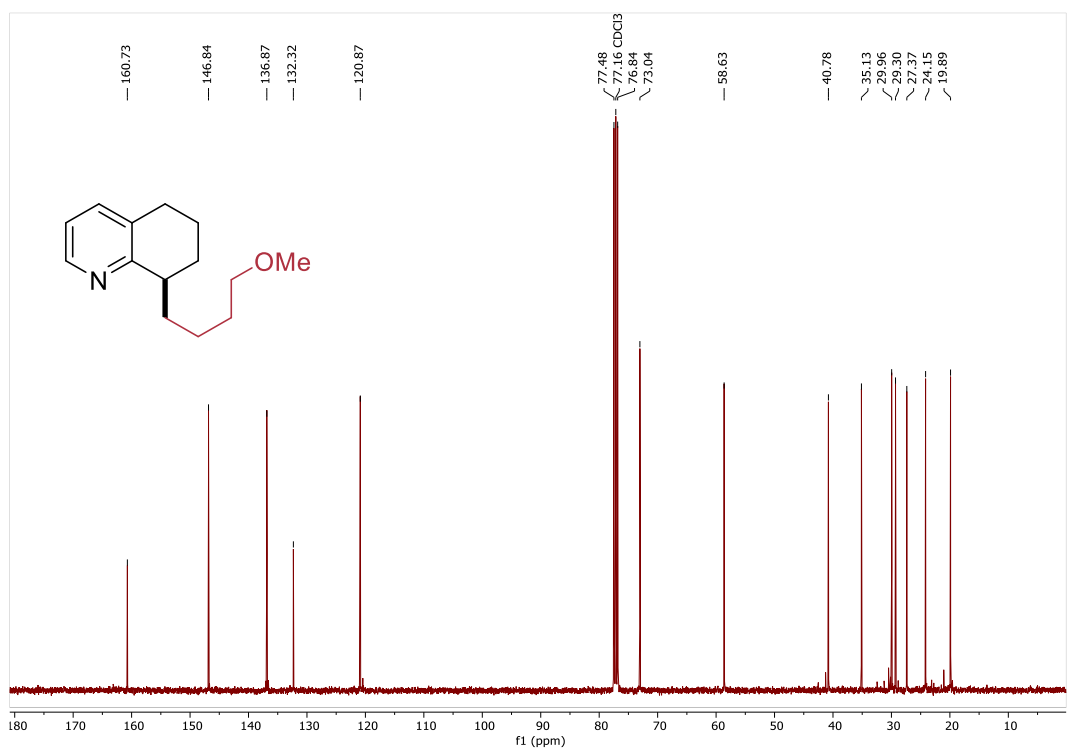


^1H NMR (400 MHz, CDCl_3) of **4.21**

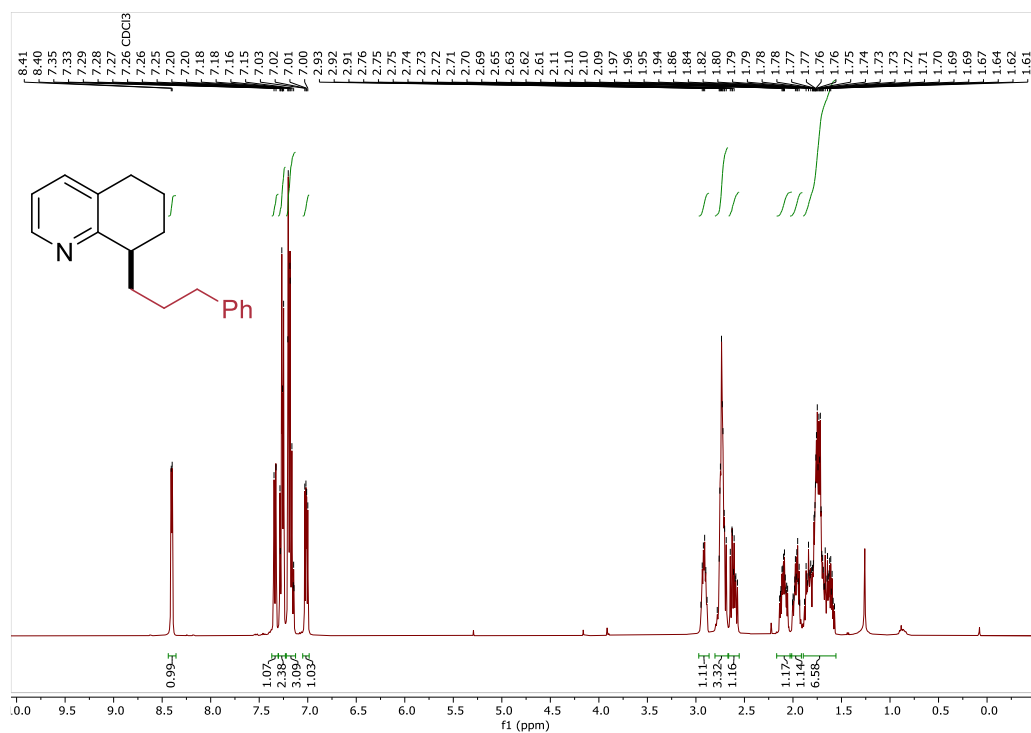


^{13}C NMR (100 MHz, CDCl_3) of **4.21**

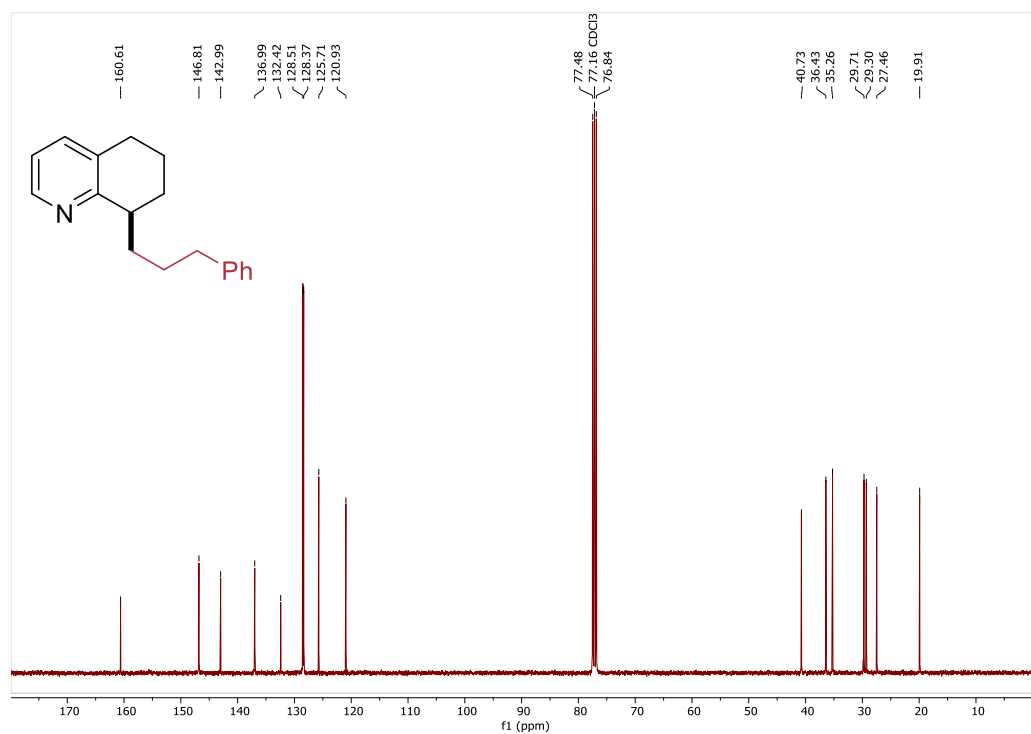


¹H NMR (400 MHz, CDCl₃,) of **4.22** ^{13}C NMR (100 MHz, CDCl_3) of **4.22**

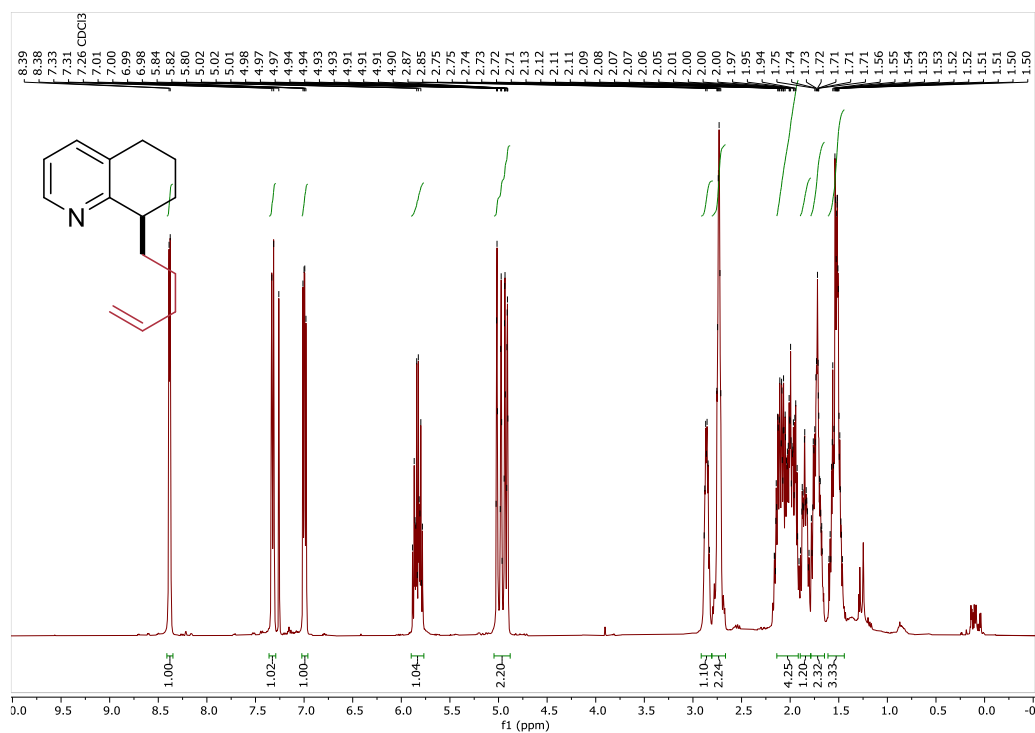
^1H NMR (400 MHz, CDCl_3) of **4.23**



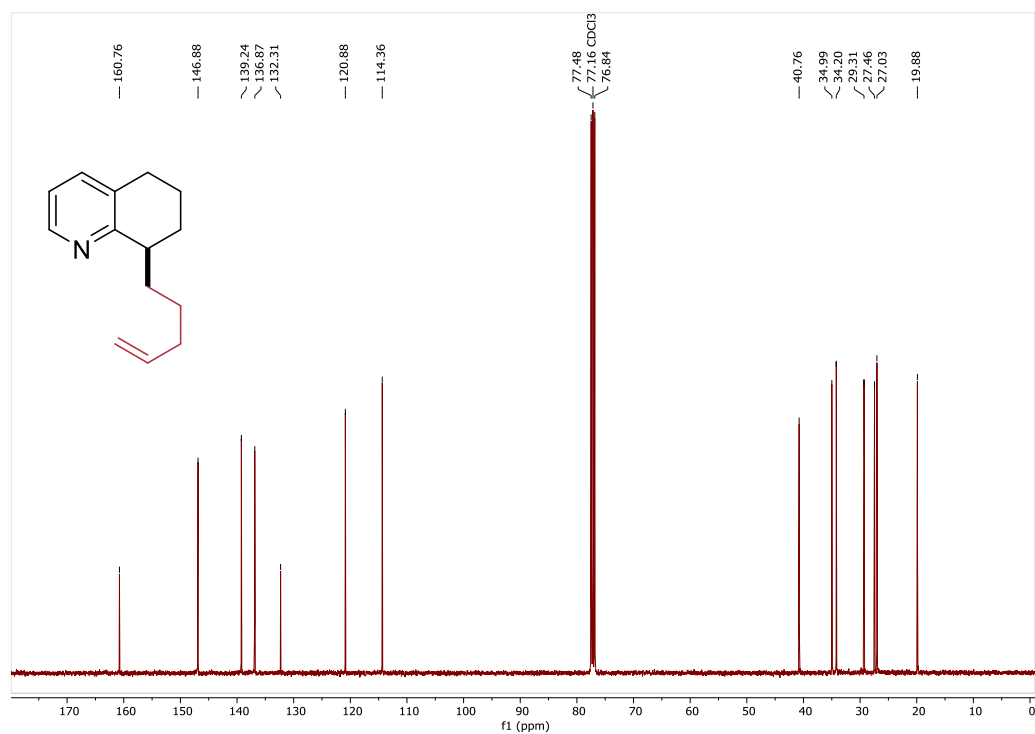
^{13}C NMR (100 MHz, CDCl_3) of **4.23**

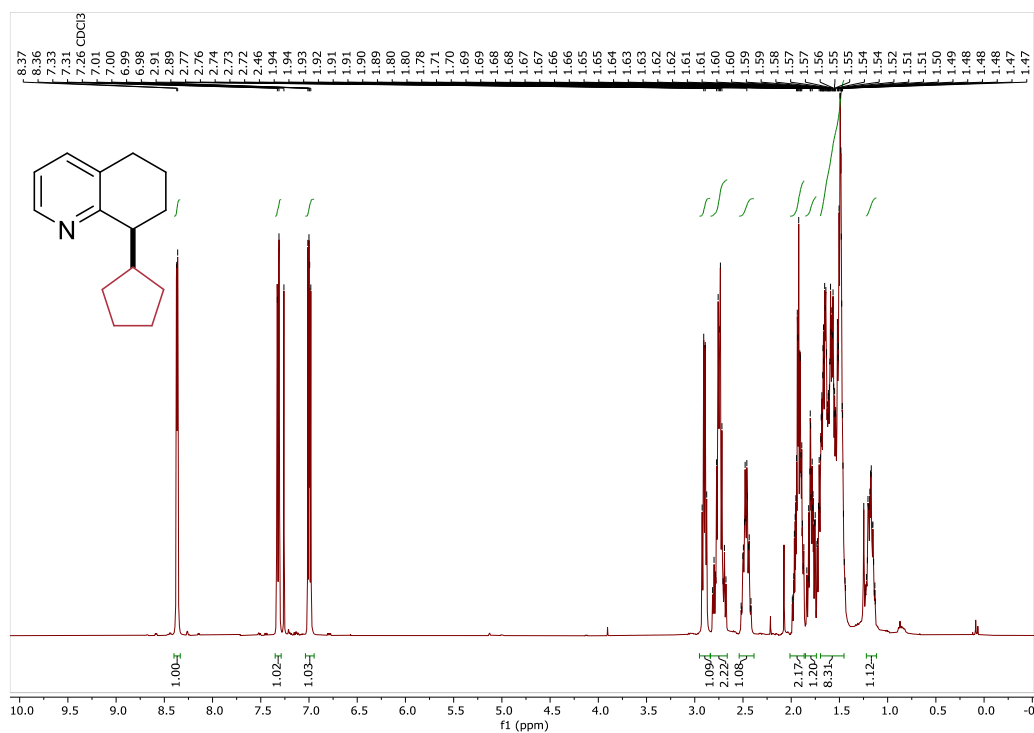
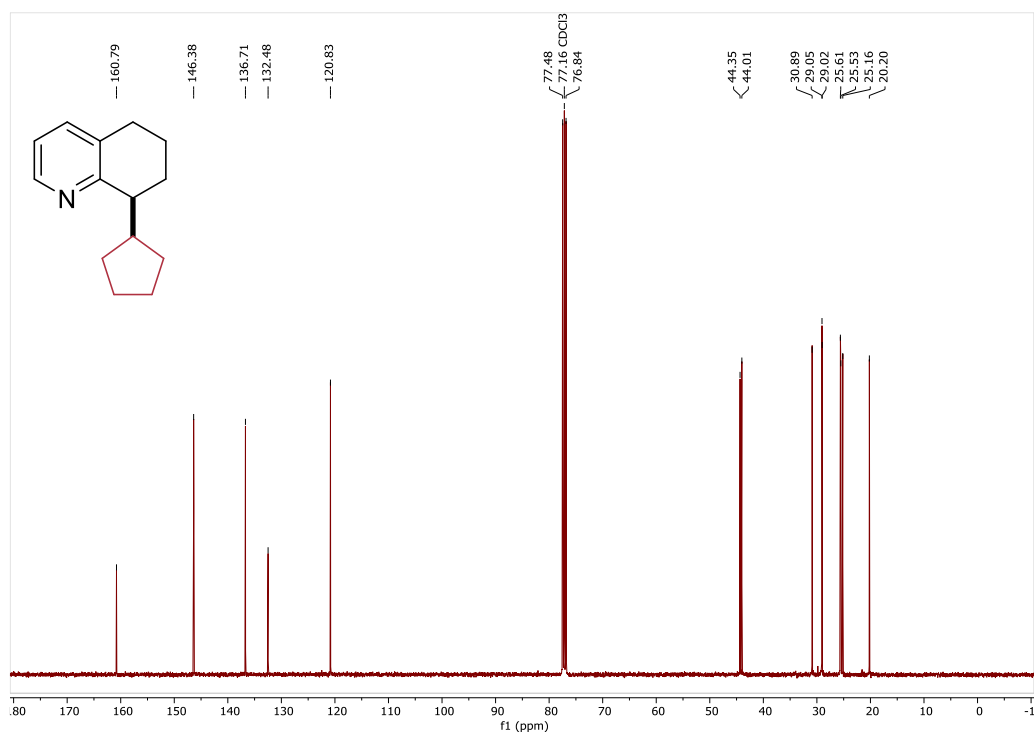


^1H NMR (400 MHz, CDCl_3) of **4.24**

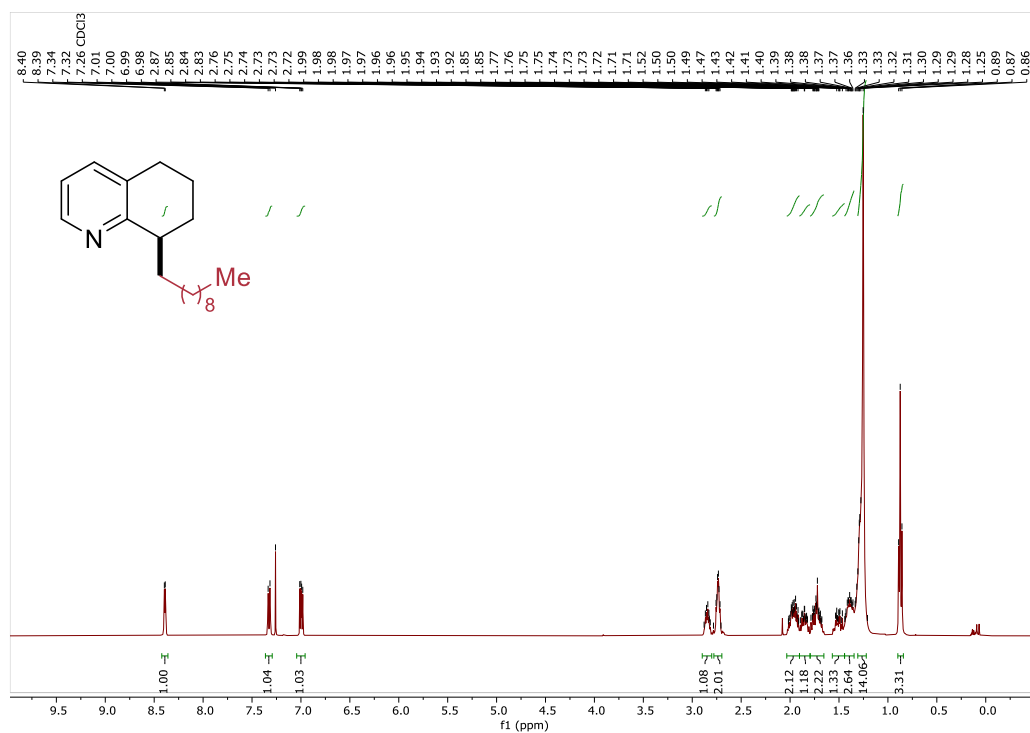


^{13}C NMR (100 MHz, CDCl_3) of **4.24**

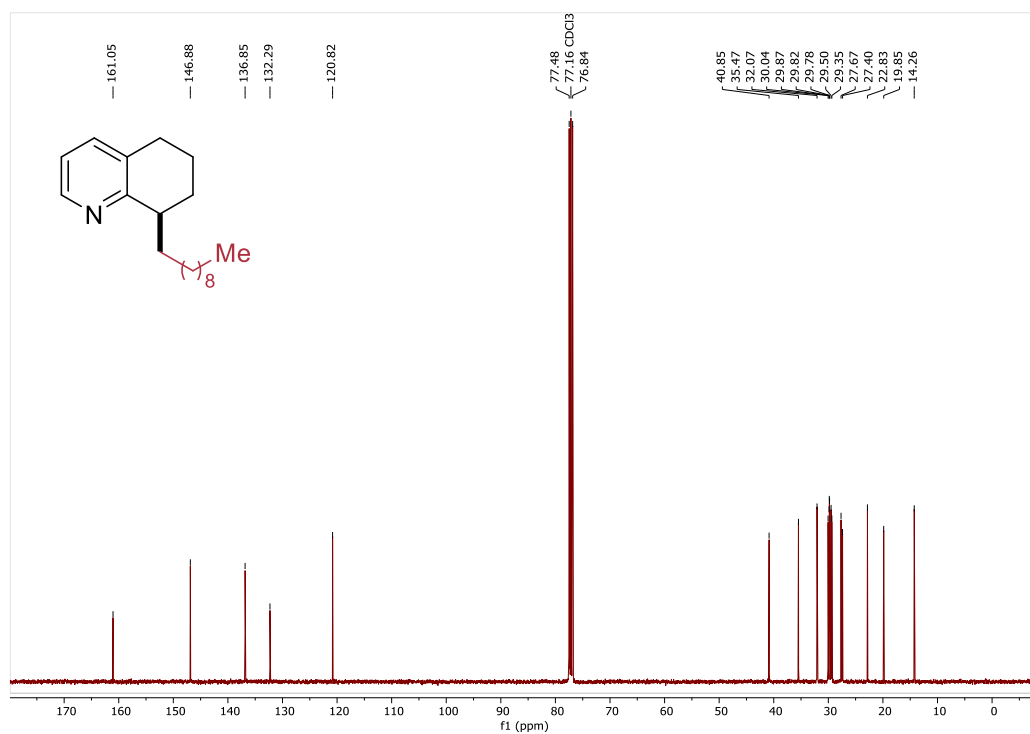


¹H NMR (400 MHz, CDCl₃,) of **4.25** ^{13}C NMR (100 MHz, CDCl_3) of **4.25**

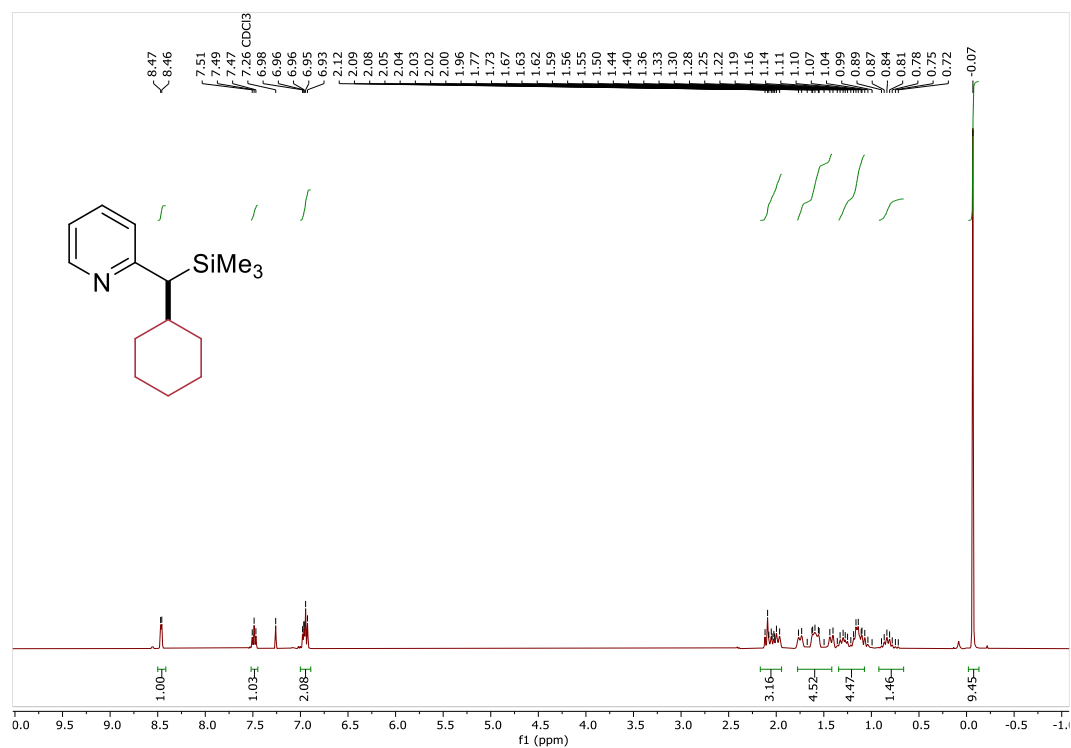
^1H NMR (400 MHz, CDCl_3) of **4.26**



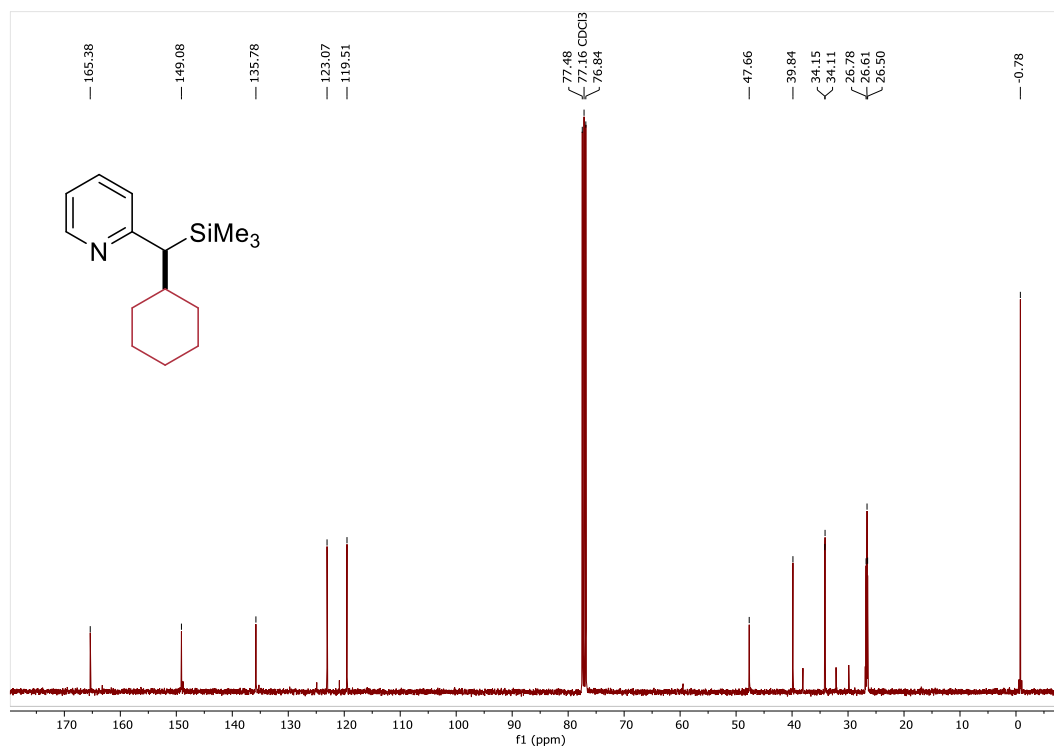
^{13}C NMR (100 MHz, CDCl_3) of **4.26**



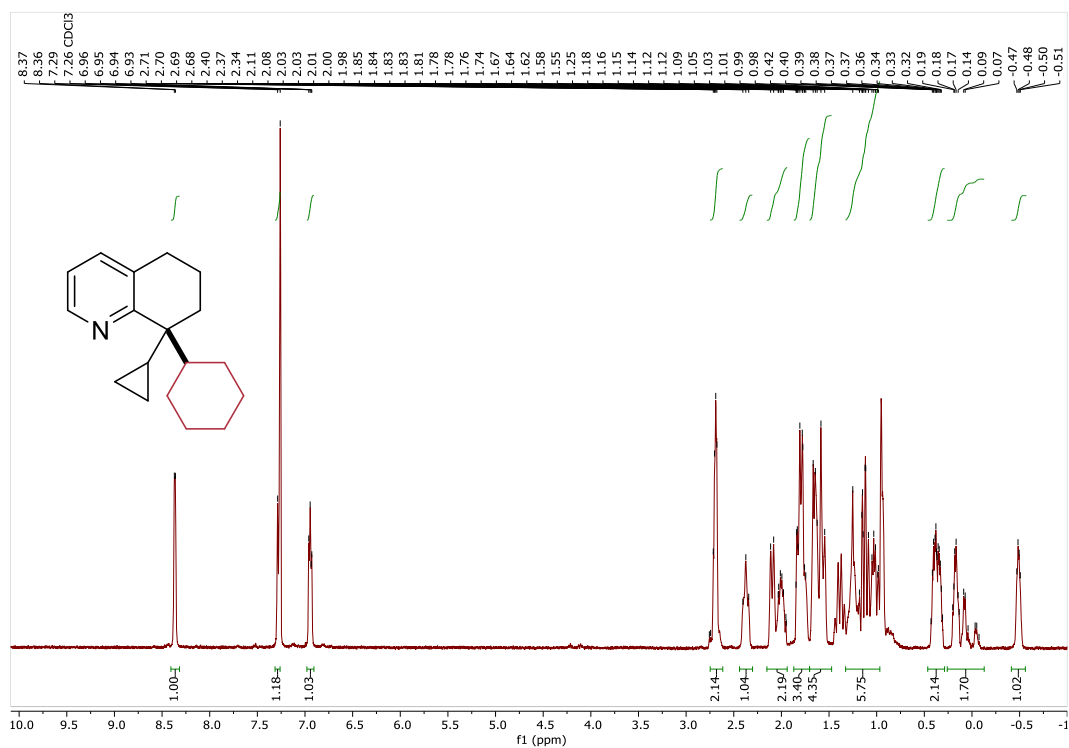
^1H NMR (400 MHz, CDCl_3) of **4.69**



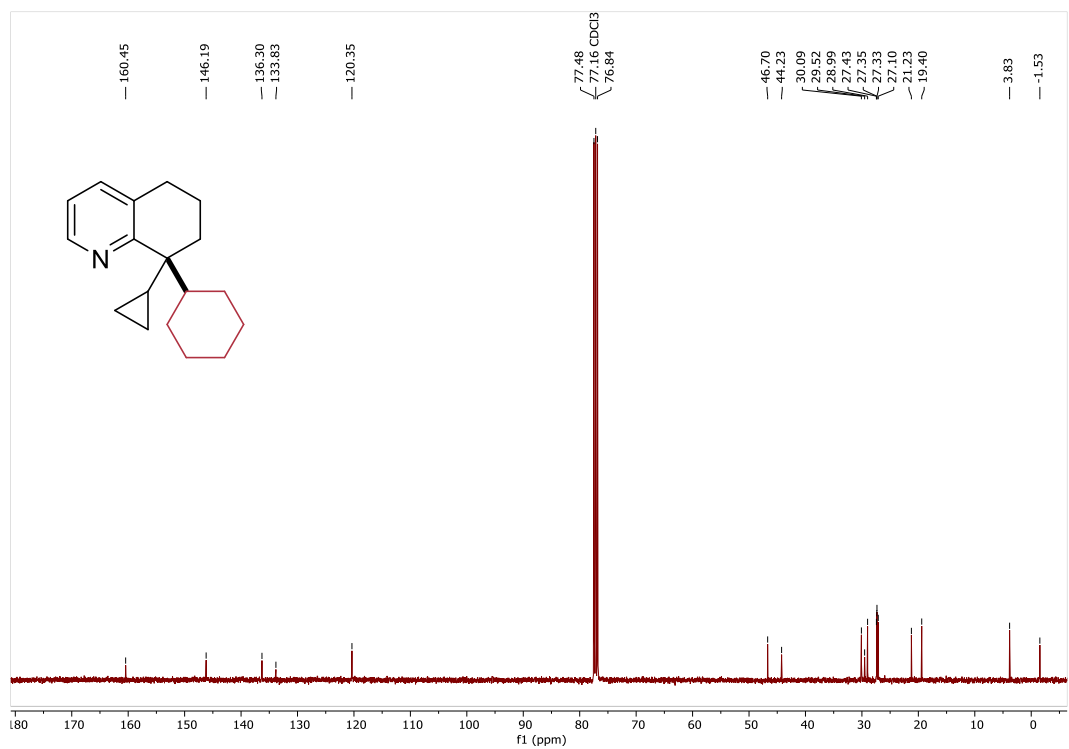
^{13}C NMR (100 MHz, CDCl_3) of **4.69**



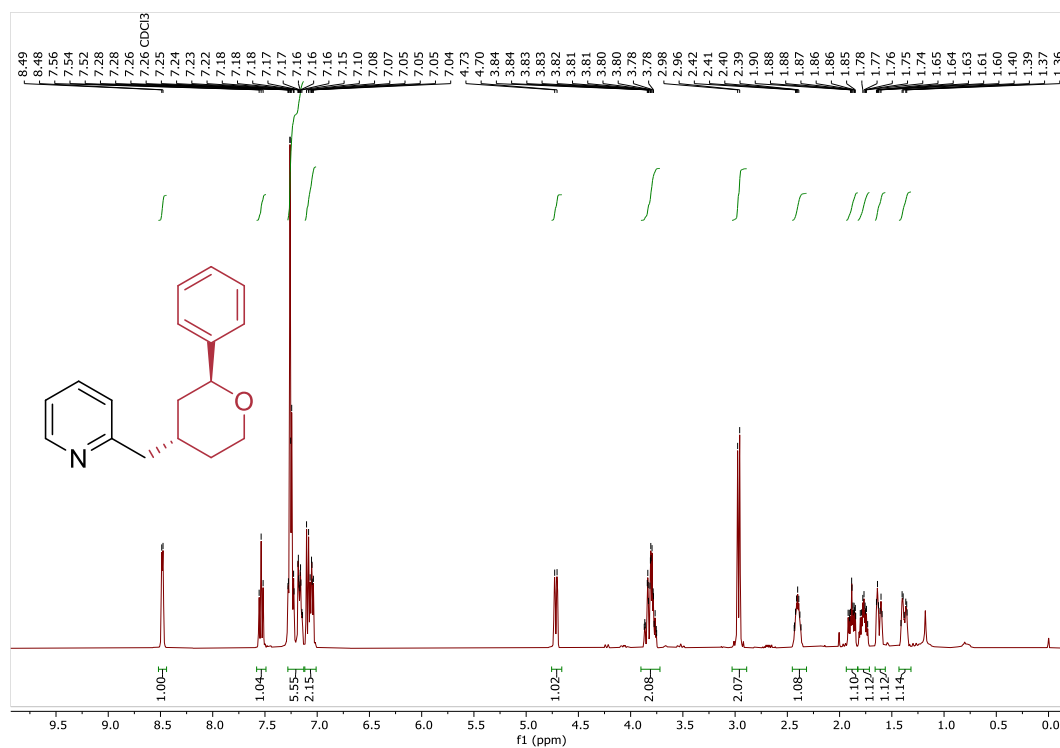
^1H NMR (400 MHz, CDCl_3) of **4.71**



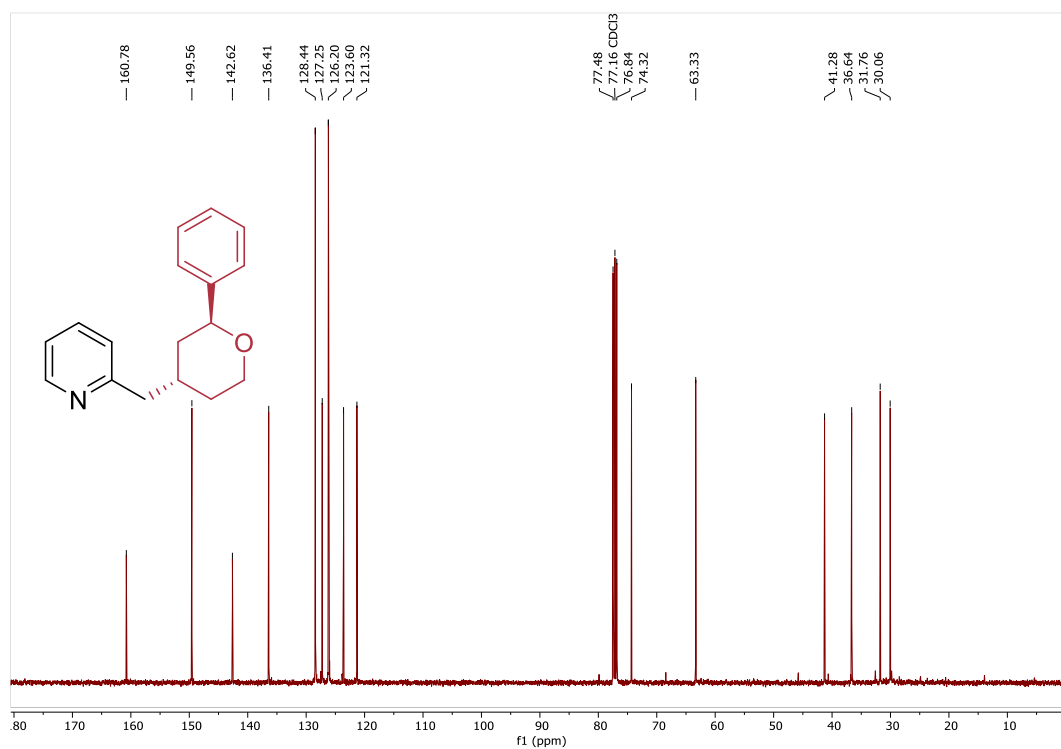
^{13}C NMR (100 MHz, CDCl_3) of **4.71**



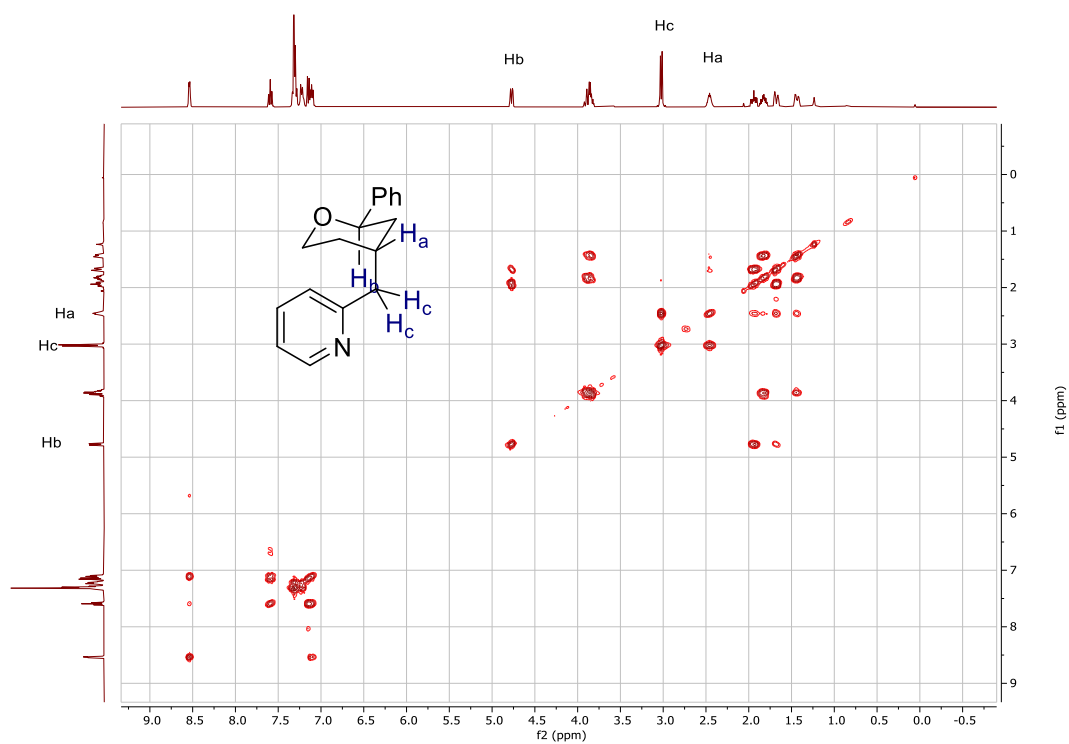
^1H NMR (400 MHz, CDCl_3) of **4.73**



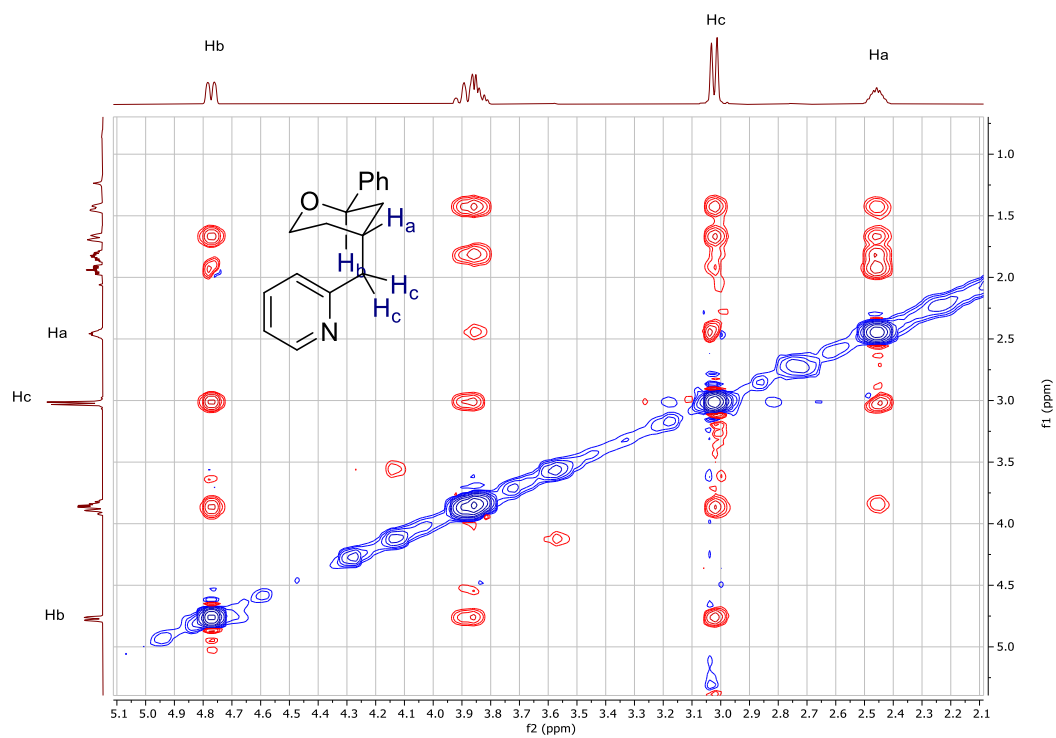
^{13}C NMR (100 MHz, CDCl_3) of **4.73**



COSY of **4.73**



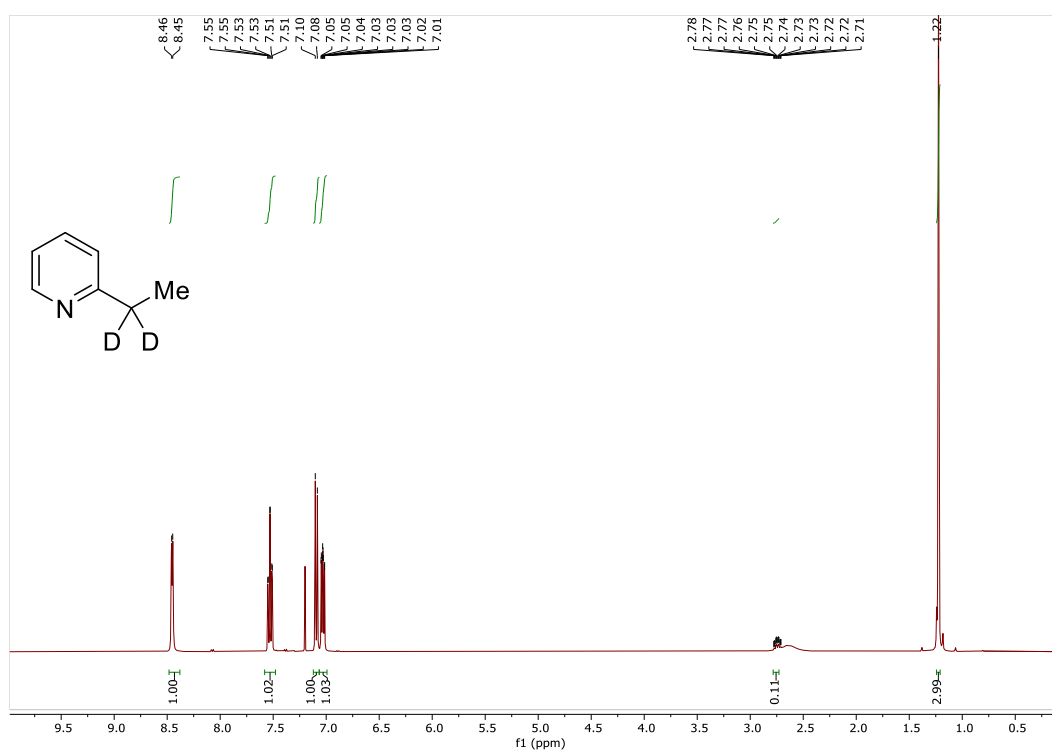
NOESY of **4.73**



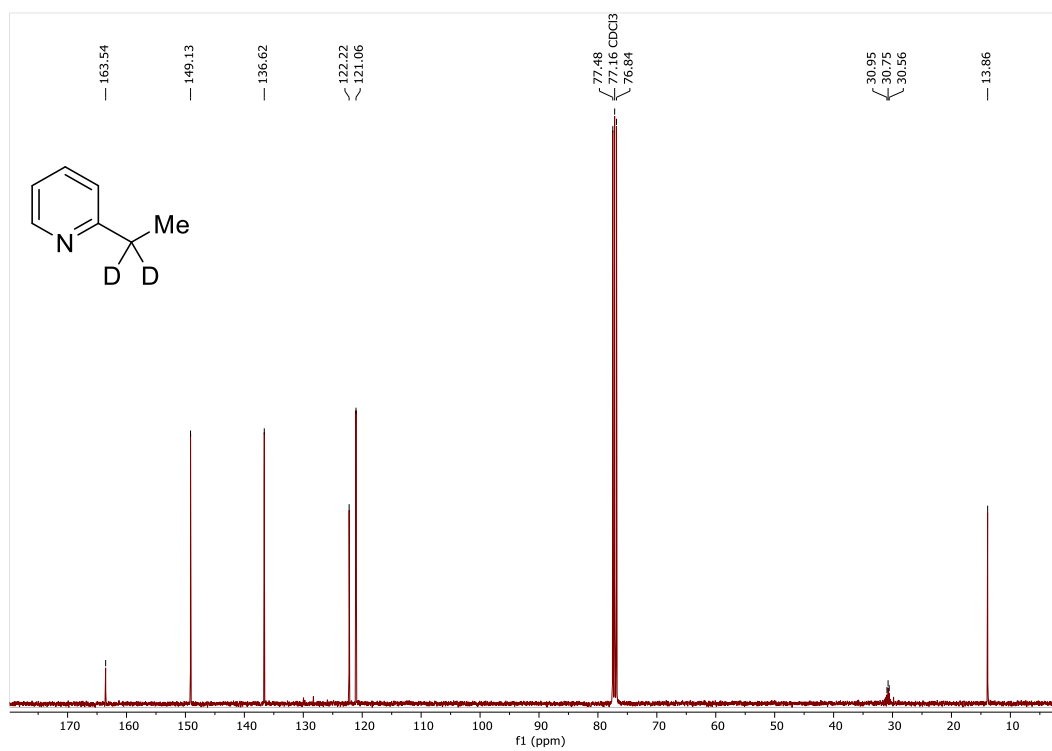
Ha shows an NOE with **Hc**, and no NOE with **Hb**

Hb shows an NOE with **Hc**, and no NOE with **Ha**

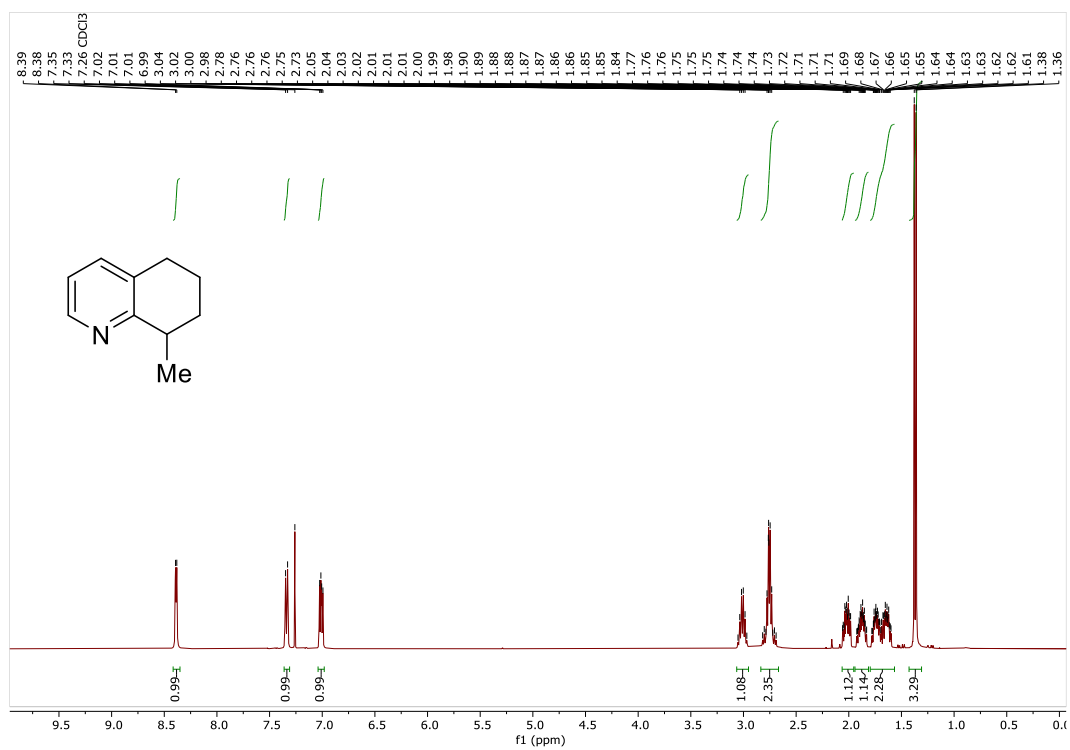
^1H NMR (400 MHz, CDCl_3) of **4.27-d₂**



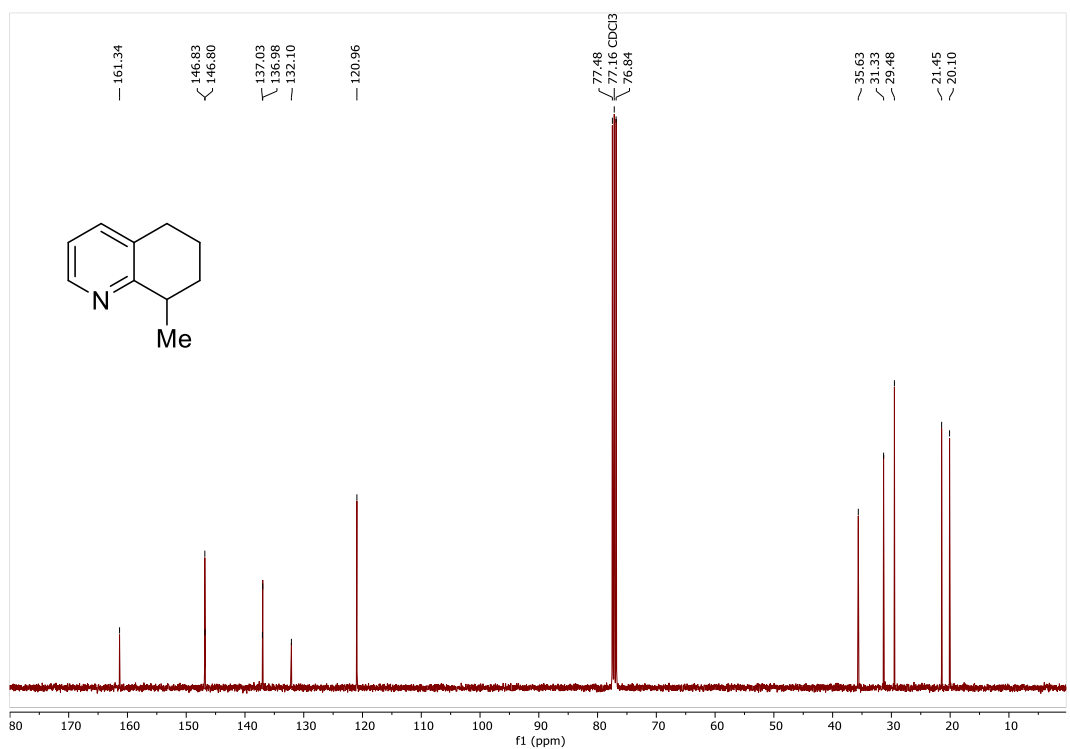
^{13}C NMR (100 MHz, CDCl_3) of **4.27-d₂**



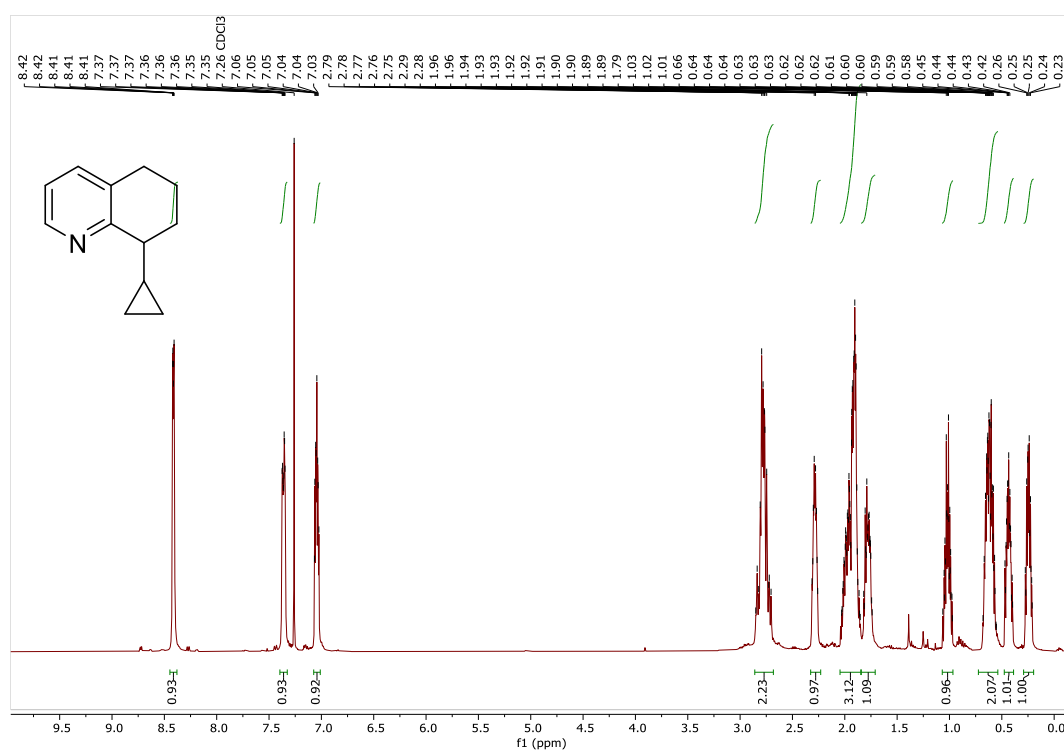
^1H NMR (400 MHz, CDCl_3) of **4.94**



^{13}C NMR (100 MHz, CDCl_3) of **4.94**



^1H NMR (400 MHz, CDCl_3) of **4.95**



^{13}C NMR (100 MHz, CDCl_3) of **4.95**

