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Facile Synthesis Of Tertiary Aliphatic Amine–Containing Cyclic Motif Via Neutral Aminyl Radical Cyclization

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FACILE SYNTHESIS OF TERTIARY ALIPHATIC AMINE–CONTAINING CYCLIC MOTIF VIA NEUTRAL AMINYL RADICAL CYCLIZATION

by

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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
AIBN	2,2'-azobis(2-methylpropionitrile)
BDE	bond dissocation energy
Bu_3SnH	tributyltin hydride
$(BzO)_2$	benzoyl peroxide
CH_2Cl_2	dichloromethane
DIBALH	diisobutylaluminium hydride
DMP	Dess–Martin periodinane
Et_3GeH	triethylgermanium hydride
Et_3SiH	triethylsilane
$(i\text{-Pr})_3SiH$	triisopropylsilane
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
NCS	*N*-chlorosuccinimide
PhEt	ethylbenzene
PhH	benzene
Ph(*i*-Pr)	cumene
PhMe	toluene
Ph_2MeSiH	methyldiphenylsilane
Ph_3SiH	triphenylsilane
TBACl	tetrabutylammonium chloride
TEA	triethylamine

TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TIPSH	triisopropylsilane
TMSCl	trimethylsilyl chloride
$(TMS)_3SiH$	tris(trimethylsilyl)silane
TsOH	*p*-toluenesulfonic acid

CHAPTER 1 BACKGROUND OF NITROGEN-CENTERED RADICALS

1.0 Introduction

Radical chemistry is one of the important tools in the synthetic community between 1980s and 1990s. During that time, majority of the efforts are concerning the reactions with carbon-centered radicals;[1] however, the chemistry of radical on a nitrogen atom center still remain largely unexplored.[2] Due to the prevalence of nitrogen atoms in natural products and pharmaceutical lead targets,[3] the development of nitrogen-centered radical chemistry for the synthesis of nitrogen atom-containing complex structures is highly desired. This chapter will describe the four common types of nitrogen-centered radicals, provide representative examples of their basic transformations, and compare known rate information about each radical.

1.1 Types of Nitrogen-Centered Radical

The common types of nitrogen-centered radicals are: amminium, amidyl, iminyl, and neutral aminyl radicals (**Figure 1**). As shown, the amminium radical contained a positive charge on the nitrogen atom, which enhanced the radical's reactivity.[2d] In the amidyl radical, the electron withdrawing nature of the carbonyl group also increases the reactivity of the *N*-centered radical.[2b] The iminyl radical is derived from imine, thus, the electron withdrawing nature of the C=N π system also increases the reactivity of the radical.[2c, 2f] Finally, the neutral aminyl radical contains a radical on the nitrogen atom and is expected to be the least reactive *N*-centered radical among the class.[2d]

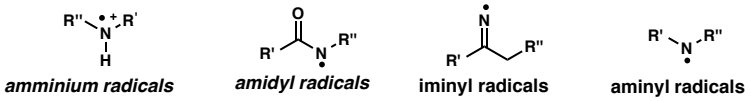
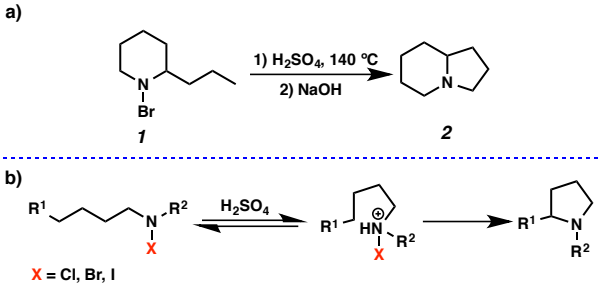


Figure 1. Four common types of *N*-centered radicals.

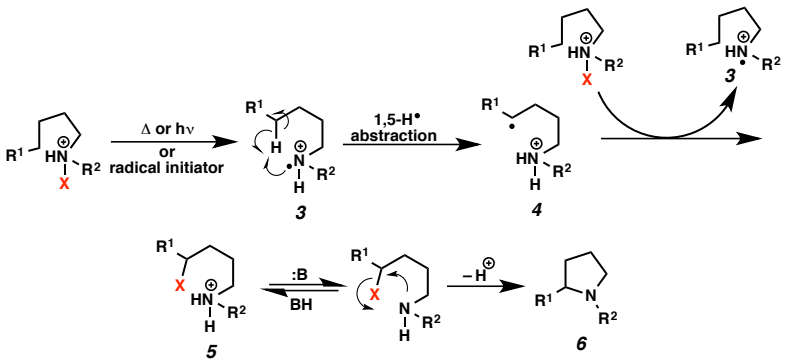
1.1.1 Amminium Radical

The earliest work on amminium radical was discovered by Hofmann in the 1880s. He treated 1-bromo-2-propylpiperidine (**1**) with hot sulfuric acid followed by a basic work-up, which afforded indolizidine (**2**) (**Scheme 1a**).[4] About three decades later, Loffler and Freytag using simple secondary amine substrates investigated this reaction further. Their investigation led to the discovery of a facile method for the preparation of pyrrolidines (**Scheme 1b**).[5] This latter become the well-known Hofmann-Loffler-Freytag reaction.



Scheme 1. Hofmann-Loffler-Freytag reaction.

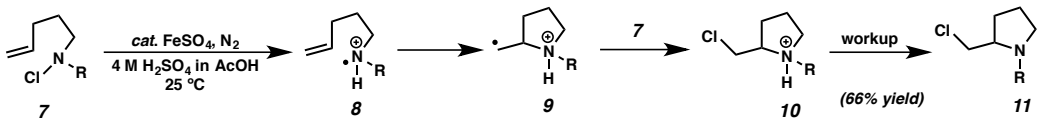
The mechanism for the Hofmann-Loffler-Freytag reaction is depicted in (**Scheme 2**). Initial homolysis of N–X bond under thermal or photochemical conditions gives the *N*-centered radical (**3**), which then undergoes an intramolecular 1,5-hydrogen atom abstraction to afford the alkyl radical (**4**). Upon halogen atom abstraction from another starting material, a halogenated amine (**5**) is generated, and it will undergoes substitution reaction by the amine in the presence of a base to deliver the pyrrolidine (**6**).



Scheme 2. Mechanism of Hofmann-Loffler-Freytag reaction.

In 1970, Surzur and Stella reported the intramolecular cyclization reaction of amminium radical with a terminal olefin in the presence of Fe(II).[6] The reaction proceeds via a different pathway than the Hofmann-Loffler-Freytag reaction (**Scheme 3**). Chloroamine (**7**) is protonated, and then undergoes an electron reduction by Fe(II) to give *N*-centered radical (**8**). The resulting amminium radical (**8**) reacts with the π-electrons on the terminal double bond to give the cyclic alkyl radical (**9**). Then this carbon-centered radical will abstract a chlorine atom from another protonated *N*-chloroamine (**7**) to propagate the radical chain and and delivers the cyclic ammonium ion (**10**). Deprotonation of (**10**) in the presence of a base during the workup provides the cyclic chloroamine (**11**).

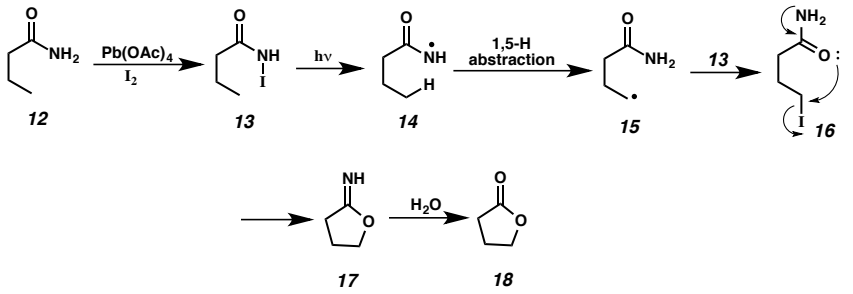
In the same seminal report, Surzur and Stella have shown that both Cu(I) and Ti(III) can also be used as reducing agents.[6] The best yield of the cyclic chloroamine (**11**) is obtained using titanium trichloride as reducing agent. However, the generation of amminium radical requires strong acidic solution thus limiting the synthetic value of this reaction.



Scheme 3. Cyclization of amminium radical with terminal olefin.

1.1.2 Amidyl Radical

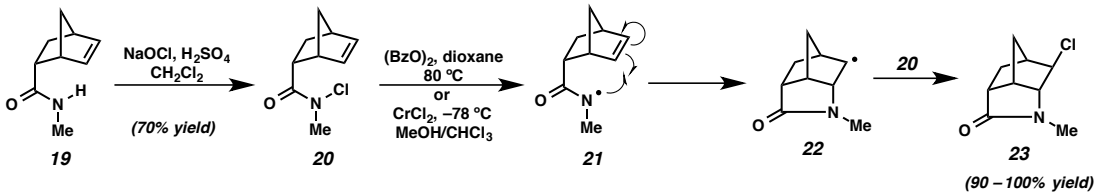
In amidyl radicals, the electron withdrawing carbonyl group adjacent to the *N*-centered radical makes the radical become more electrophilic than the aminyl radical.[2b] In 1965, Barton[7] and co-workers reported the preparation of lactone **18** from the butyramide **12** by treatment with lead tetra-acetate and iodine under photochemical conditions (**Scheme 4**). Upon photolysis, the weak N–I bond of the iodoamide (**13**) was homolytically cleaved to afford the amidyl radical (**14**). Similar to the Hofmann-Löffler-Freytag reaction, the *N*-centered radical underwent 1,5-hydrogen atom abstraction followed by I-atom abstraction to give the iodinated amide (**16**). The carbonyl oxygen then attacked the iodide intramolecularly in a S_N2 pathway to give the imine (**17**), which upon hydrolysis delivered the desired lactone (**18**).



Scheme 4. Preparation of lactone from iodoamide.

Later, Lessard[8] and Mackiewicz[9] extended Barton's work and reported the intramolecular cyclization of an amidyl radical with an olefin in the bicyclic system (**Scheme 5**). The chloroamide (**20**) can be initiated by either benzyl peroxide

under heated condition or with chromous chloride at –78 ºC to give the amidyl radical (**21**). Due to the strain enhanced nature of the bicyclic structure, it underwent rapids 5-*exo* cyclization of *N*-centered radical (**21**) with the olefin to give the secondary carbon radical (**22**). An abstraction of a chlorine atom from chloroamide **20** then afforded the lactam (**23**) in excellent yield.



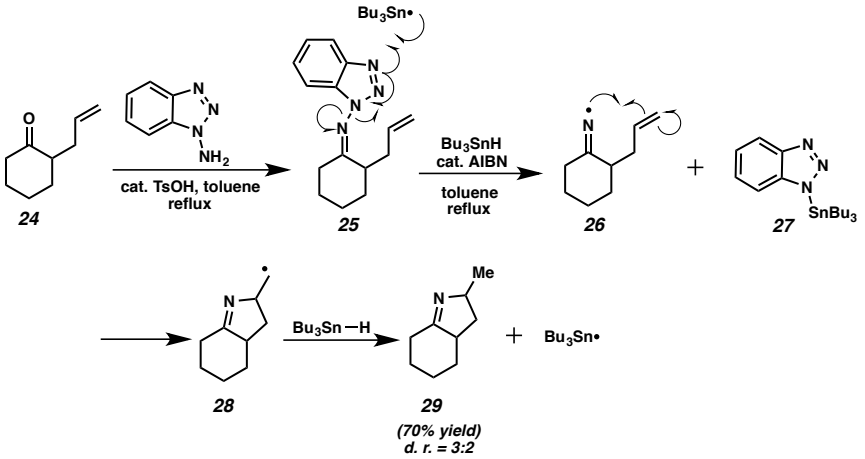
Scheme 5. Cyclization of amidyl radical with olefin in a strained system.

Furthermore, generations of amidyl radicals from homolytically cleavage of N–N bond,[10] N–S bond,[11] N–C bond,[12] and N–H[13] bond are also known. It is noteworthy that the homolysis of N–H bond reported by Forrester, requires harsh condition in the presence of a strong oxidizing agent. Therefore, this approach limited the scope of the reaction because many substrates cannot tolerate the harsh condition.

1.1.3 Iminyl Radical

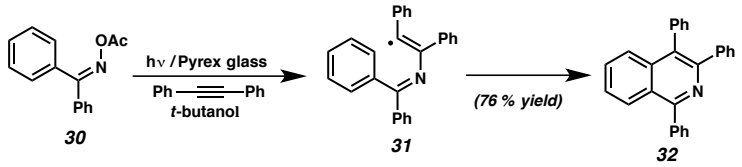
The sp^2 character of the iminyl nitrogen atom increased the electrophilicity of the *N*-centered radical relative to all aminyl radical. One of the earliest reports concerning the intramolecular cyclization of iminyl radical with a terminal olefin was reported by Kaim and Meyer (**Scheme 6**).[14] First, allyl ketone **24** was condensed with *N*-aminobenzotriazole to afford iminobenzotriazole **25**. Treatment with AIBN initiator in the presence of tributyltin hydride generates a stannyl radical. Addition of this radical to the benzotriazole induces homolytic

cleavage of the exocyclic N–N bond to form iminyl radical **26** and stannyl triazole **27**. Intramolecular cyclization of iminyl radical **26** with the pendant olefin gives primary alkyl radical **28**. H–atom abstraction from tributyltin hydride afforded the pyrroline product (**29**) and propagates the radical chain.



Scheme 6. Preparation of pyrroline from iminyl radical.

In 2006, Alonso[15] and co-workers reported the conversion of acyloximes to isoquinolines (**Scheme 7**). Homolysis of N–O bond in the acyloxime **30** was induced photolytically. Subsequent addition of the iminyl radical to diphenylethyne afforded vinylic radical **31**. Intramolecular addition to the phenyl ring followed by rearomatization delivered isoquinoline **32** in good yield (**32**).

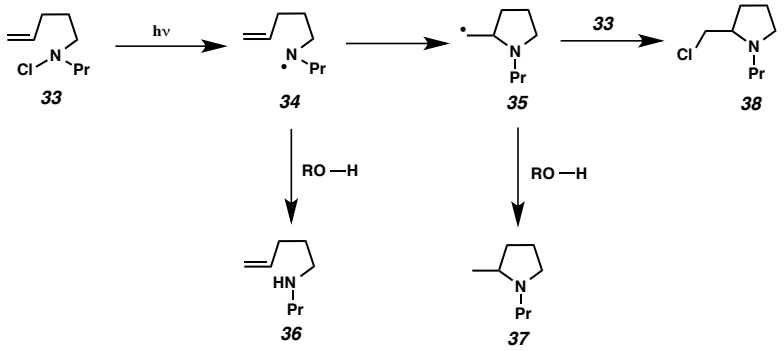


Scheme 7. Intermolecular cyclization of iminyl radical with alkyne.

1.1.4 Neutral Aminyl Radicals

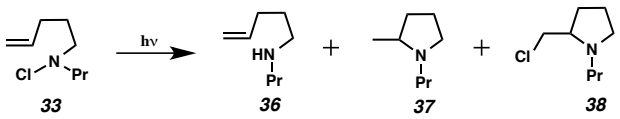
Among the different types of *N*-centered radicals, the neutral aminyl radical is known to be less reactive toward cyclization.[2d] The earlier work on

intramolecular cyclization of alkenylaminyl radical to prepare pyrrolidine was reported by Surzur and co-workers in 1970 (**Scheme 8**).[16] They investigate the cyclization of a secondary chloroamine (**33**) under the condition of photolysis in both acidic and alcoholic solvents. Their results have shown that the alkenylaminyl radical (**34**) and the primary carbon radical (**36**) can be trapped by the hydrogen atom from the alcoholic solvent to afford the reduced secondary amine (**35**) and 2-methylpyrrolidine (**37**) respectively.



Scheme 8. Cyclization of neutral aminyl radical with terminal olefin.

Under aqueous acetic acid conditions, the cyclization of aminyl radical (**34**) gave 2-chloromethylpyrrolidine (**38**) in 70% yield (**Table 1, Entry 1**). When the reaction is carried in methanol, only 37% yield of the desired product (**38**) is formed, and the major product (49% yield) is the 2-methylpyrrolidine (**37**) (**Entry 2**). These effects are even pronounced in isopropanol (**Entry 3**). The formation of reduction product **36** and reductive cyclization product **37** depend on the ability of the solvent to act as hydrogen atom donor, and the stronger the ability, the higher the conversion to each product.



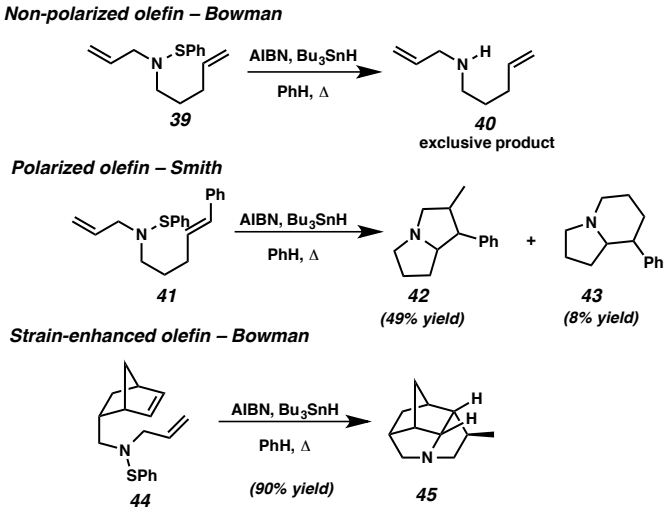
33 *36* *37* *38*

Entry	*Solvent*	*Yield (%)*	*36* :	*37* :	*38*
1)	AcOH–H_2O (1 : 1)	70	0	0	100
2)	MeOH	72	14	49	37
3)	*i*PrOH	62	29	61	10

Table 1. Solvent effect on aminyl radical cyclization.

Seminal work from Newcomb, [17] Suginome, [18] Tsanaktsidis, [19] and Bowman [20] have provided a much deeper insight into the mechanism of cyclization reaction of alkyl radicals. One noteworthy reactivity trend of aminyl radicals in the cyclization reaction with pendant olefins relates to the electronic properties of the olefin (**Scheme 9**). Initially, Bowman reported the tandem cyclization of sulfenamide precursor (**39**) initiated by AIBN under thermal conditions.[20c] Due to faster intermolecular trapping of an alkyl aminyl radical than cyclization onto an unactivated terminal, he obtained exclusively the reduced amine product (**40**). On the other hand, Smith and Shroff have shown that under the same reaction conditions, the tandem cyclization onto phenyl-substituted oelfin **41** gave moderate yield of 5-*exo*-trig product (**42**) along with a small amount of 6-*endo*-trig product (**43**).[21] This result suggests that increasing the polarization on the olefin increases the rate of the cyclization reaction of aminyl radicals. In this case, the electron withdrawing nature of the phenyl group on (**41**) lowers the LUMO energy of the π-bond, improving the overlap with the SOMO of the *N*-centered radical. Later, Bowman had investigated the tandem cyclization reaction of aminyl radical on a bridged bicyclic sulfenamide precursor (**44**).[20d] In this case, the LUMO of the olefin on the strained bicyclic ring system is also in lower energy. The geometry of the sulfenamide precursor (**44**) brings the

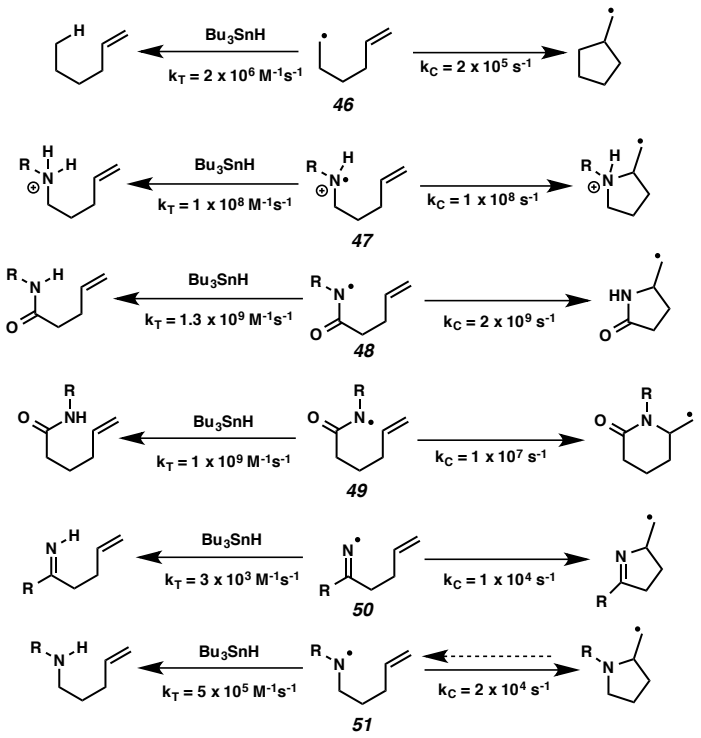
resulting aminyl radical in close orientation with the olefin, which increases the rate of the cyclization to afford the polycyclic pyrrolizidine (**45**) in 90% yield.



Scheme 9. Early examples of tandem cyclization of aminyl radical with olefins.

1.2 Kinetic Rate Constant of *N*-Centered Radicals

A good way in aiding the design of radical reaction is to have a thoughtful understanding of the rate of the radical cyclization versus trapping with a hydrogen atom donor. Synthetic chemists can establish the best experimental parameters with the knowledge concerning the rate of radical species that can undergoes different mechanistic pathway. The kinetic studies reported by Newcomb and co-workers[22] delineated the rate constants for *N*-centered radicals in the cyclization reaction as well as the rate for premature hydrogen atom abstraction (**Scheme 10**).



Scheme 10. Rate constant for the reaction of *N*-centered radicals.

As shown in **Scheme 10**, the primary carbon radical (**46**) is included in the list for the purpose of comparison. The rate of cyclization of amminium radical **47** is 500 times faster than the carbon radical (**46**), and the tendency for amminium radical **47** to abstract a hydrogen atom is only 50 times faster than the carbon radical. This suggests that the desired cyclization process is favored over the premature hydrogen atom abstraction.

As expected, amidyl radical **48** is very reactive toward the 5-*exo*-trig cyclization process. The rate for the cyclization is 10,000 times faster than the carbon radical (**46**) and the rate for the hydrogen atom abstraction is only 650 times faster. When amidyl radical **49** undergoes 6-*exo*-trig cyclization, the rate of the reaction became 200 times slower compared to the 5-*exo*-trig cyclization in the case of amidyl radical **48**. Despite the rates of cyclization is different but the

rate of hydrogen atom abstraction for amidyl radical **48** and **49** are very similar. Therefore, it is difficult for amidyl radical **49** to overcome the premature hydrogen atom abstraction.

The cyclization rate of iminyl radical **50** is reported to be 20 times slower than the primary carbon radical (**47**), but the rate of hydrogen atom abstraction is about 667 times slower than the carbon radical (**47**). This suggests that the desired cyclization is more favorable than the premature hydrogen atom abstraction in iminyl radical **62**. Therefore, the tendency of the iminyl radical (**62**) to undergoes premature hydrogen atom is minimized.

When considering the neutral aminyl radical (**51**), the cyclization is 10 times slower than the carbon radical (**47**) and the rate for the aminyl radical (**51**) to abstract a hydrogen atom is happened to be only 4 times slower than the carbon radical (**47**). Therefore, it is more likely for the aminyl radical to undergoes premature hydrogen atom abstraction than the desired cyclization process. Furthermore, the results on cyclization of aminyl radical **51** with terminal olefin reported by Bowman suggests that the ring closure step may be reversible.[20b]

1.3 Conclusion

In summary, the four common types of *N*-centered radicals are amminium, amidyl, iminyl and aminyl radicals. These *N*-centered radicals were generated from the corresponding radical precursors under thermal or photochemical condition. The chemistry of amminium radical was discovered by Hofmann and later was known as the Hofmann-Loffler-Freytag reaction. This reaction served as a facile method to prepare the pyrrolidine from simple secondary amines.

However, generation of amminium radical required strong acids which limited its synthetic values. The preparation of lactam from intramolecular cyclization of amidyl radical with strained olefin was reported by Lessard and Mackiewicz. In addition, iminyl and aminyl can be used to prepare pyrroline and pyrrolidine respectively via intramolecular cyclization with terminal olefin.

Based on the kinetic studies on *N*-centered radicals, amidyl radical undergoes cyclization with terminal olefin faster than the other three types radicals. In the reaction of aminyl radical with terminal olefin, the rate constant suggests that the competition between the desired cyclization and premature hydrogen atom abstraction is unfavorable.

CHAPTER 2 RECENT PUBLISHED WORK ON AMINYL RADICAL FROM THE STOCKDILL LAB

2.1 Introduction

Tertiary amine–containing polycyclic motifs are prevalent in natural products and pharmaceutical lead targets.[3] In particular, alkaloids isolated from tree of the genus *Daphniphyllum*, contain a tertiary aliphatic amine at the ring junction seems intriguing and challenging within the synthetic community. These alkaloids possess biological activity such as cytotoxicity, antioxidant, and tubulin inhibition.[23] Kobayashi[24] and Zhang[25] elucidated the structure of daphnicyclidin A and daphniyunnine C respectively (**Figure 2**), however, the complete total syntheses of these two alkaloids have not been reported.

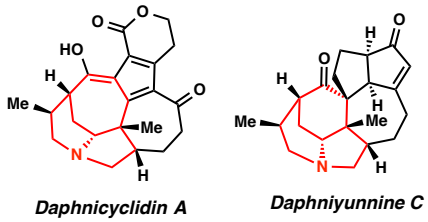


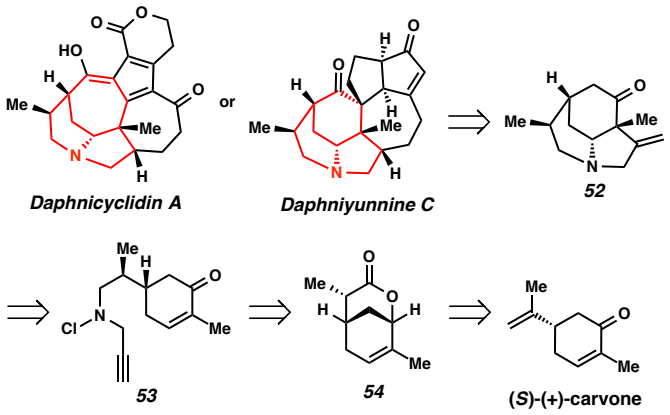
Figure 2. *Daphniphyllum* alkaloids with polycyclic rigid framework.

Inspired by these natural products, one focus in the Stockdill lab is the development of neutral aminyl radical chemistry in the synthesis of tertiary aliphatic amine–containing cyclic cores via a tandem cyclization. As discussed in the previous chapter, neutral aminyl radicals are known to be less efficient toward cyclization than the other three types of *N*-centered radicals.[26] However, the chemistry of neutral aminyl radicals is less known in the literature. We sought to understand more about this type of *N*-centered radicals by probing their reactivity. On the other hand, amidyl, iminyl, and amminium radicals all possess

some drawbacks in the synthesis of *Daphniphyllum* alkaloids. For example, these alkaloids generally contain aliphatic amines, thus, cyclization of amidyl and iminyl radicals must be followed by conversion of amides or imines to the saturated amine, reducing their overall utility. Furthermore, the amminium radical is usually generated under strong acidic conditions, thus limiting their synthetic value.

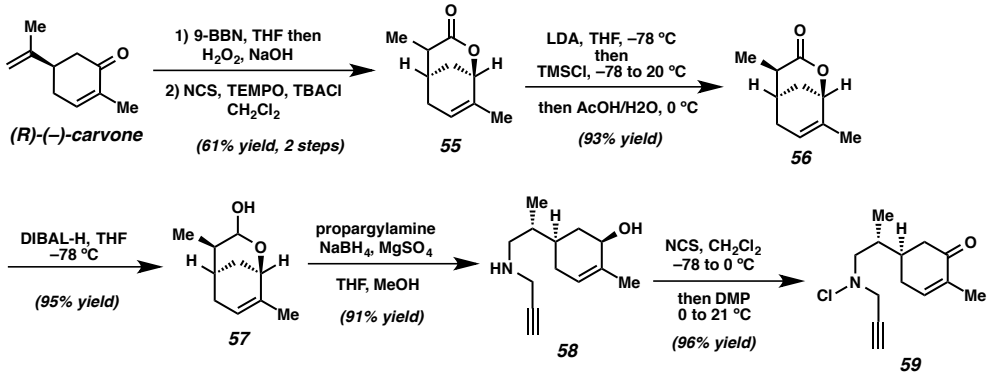
2.2 Synthesis of the Tricyclic Core of *Daphniphyllum* Alkaloids

Members in our lab attempted to efficiently prepare the tertiary aliphatic amine containing-tricyclic core of *Daphniphyllum* alkaloids in order to use it as a building block for the syntheses of daphnicyclidin A and daphniyunnine C. As shown in **Scheme 11**, both daphnicyclidin A and daphniyunnine C were envisioned to be accessible from the tricyclic core (**52**). The tricyclic core was realized could be prepared from the aminyl radical precursor (**53**) via an intramolecular tandem cyclization. Furthermore, the aminyl radical precursor can be elaborated from the bicyclic lactone (**54**), which was known to be prepared from readily available (*S*)-(+)-carvone in 3 steps.[27]



Scheme 11. Retrosynthetic analysis of *Daphniphyllum* alkaloids.

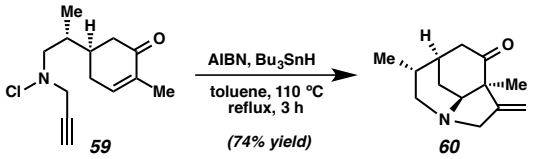
In 2014, the Stockdill lab has applied the chemistry of aminyl radical cyclization in the synthesis of tertiary aliphatic amine–containing tricyclic core **52**.[28] The preparation of aminyl radical precursor is started from readily available (*R*)-(–)-carvone (**Scheme 12**). Hydroboration of carvone followed by oxidation using NCS and TEMPO afforded the bicyclic lactone (**55**) as 1:1 ratio of diastereomers. Epimerization of the both diastereomers using LDA gave the resulting product (**56**) as a single diastereomer. Then reduction of lactone **56** followed by reductive amination of resulting aldehyde with propargylamine gave the secondary amine (**58**). To prepare the *N*-chloro radical precursor, the secondary amine (**58**) was first treated with NCS and then a sequential oxidation of allylic alcohol with Dess-Martin periodinane delivered the chloroamine radical precursor (**59**).



Scheme 12. Synthesis of aminyl radical precursor.

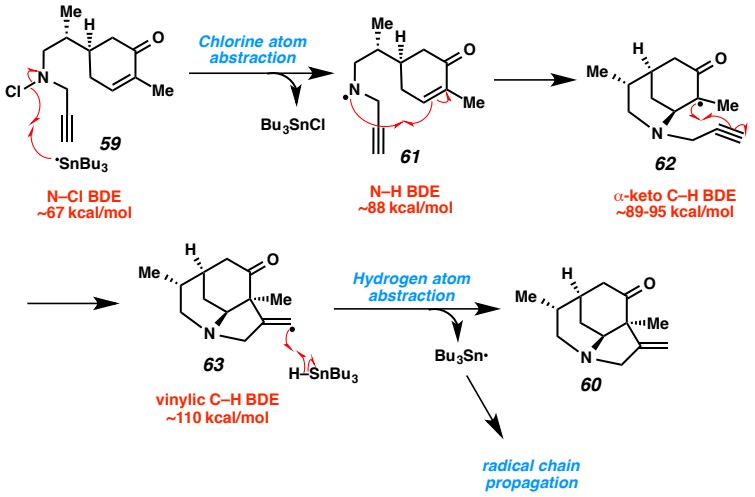
The electron withdrawing nature of the carbonyl group on the enone will increase the polarization on the olefin, which favors the cyclization between the aminyl radical and the olefin.[20d, 21] For this reason, members in the Stockdill's lab had chosen to investigate the tandem cyclization of the aminy radical with enone

substrate (**Scheme 13**). The best reaction condition was refluxing chloroamine **59** with AIBN and Bu_3SnH in toluene for 3 hours.[28]



Scheme 13. Tandem cyclization of aminyl radical with cyclic enone.

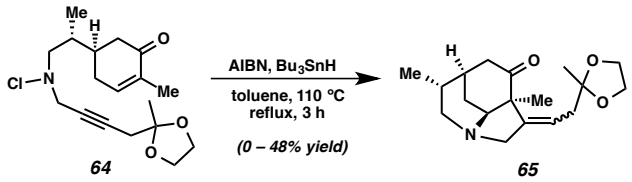
Homolytic cleavage of the weak N–Cl bond was resulted from chlorine radical abstraction by the tributyltin radical (**Scheme 14**). The resulting aminyl radical **61** undergoes an intramolecular 6-*exo*-trig radical cyclization with enone to afford the tertiary carbon radical (**62**). This tertiary carbon radical will then undergoes an intramolecular 5-*exo*-dig cyclization with terminal alkyne tether to give the vinylic radical (**63**). Lastly, hydrogen atom abstraction from the Bu_3SnH propagates the radical chain process and delivers the tertiary amine-containing tricyclic core **60**.



Scheme 14. Mechanism of aminyl radical cyclization to prepare tricyclic core.

Later, Dr. Ibrahim, a postdoctoral fellow in the Stockdill lab, investigated the tandem cyclization of aminyl radical on a substrate that contains a tethered

internal alkyne (**Scheme 15**). Under the same reaction condition as in the case of **59**, the yield for the preparation of tricyclic core **65** from **64** is very inconsistent and usually poor.



Scheme 15. Aminyl radical cyclization on internal alkyne substrate.

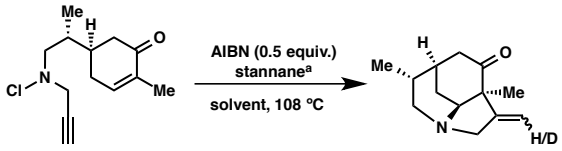
Then Dr. Ibrahim discovered that using triisopropylsilane as a hydrogen atom donor in the radical reaction gave better yields than tributyltin hydride. After extensive solvent screening, Dr. Ibrahim revealed that the radical cyclization reaction is much cleaner in THF. The best condition was heating **64** in THF at 100 ºC with TIPSH and AIBN inside a sealed tube for 3 hours. After optimization of the purification technique, the yield of the isolated product **65** increased to 68%.

2.3 Solvent Studies in the Aminyl Radical Cyclization

During the course of optimization of the cyclization of chloroamine **59**, Dr. Ibrahim obtained only 21% yield of the cyclized product (**60**) in benzene (versus 61% yield at the same temperature in toluene).[28] The low yield of the cyclized product (**60**) in benzene is presumably due to the radical chain termination process by addition of radical intermediate to benzene during the reaction. It is known from the literature that addition of alkyl radical to benzene is common and the cyclohexadienyl radical is unreactive toward abstraction of hydrogen atom from tributyltin hydride.[29] Thus, this leads to the inhibition of radical propagation process.

Because the radical cyclization is more efficient in toluene, it seemed likely that toluene was serving as a hydrogen atom donor. The cyclization of **59** in toluene gave the best yield when 0.5 equivalent of AIBN is employed. Higher loading of radical initiator suggested that the radical chain pathway is not propagated.[29] This result indicates that the benzylic radical is forming in the reaction and then undergoes dimerization[29] which terminated the radical chain process.

To shed light on the role of toluene in the aminyl radical cyclization, the Stockdill group conducted experiments with deuterium labeled toluene and stannane.[30] The results from their deuterium labeling study are shown in **Table 2**. A solution of AIBN and stannane was added dropwise to a heated solution of chloroamine **59** in toluene over 1 hour, followed by heating until the chloroamine is fully consumed.



59 *60*

entry	solvent	stannane	(equiv.)	isolated yield (%)	observed MS intensities (m/z)[b] 206	207	208
1	PhMe	–	–	9	100	15	1
2	PhMe	Bu_3Sn–H	2	74	100	15	1
3	PhMe	Bu_3Sn–D	2	65	100	32	5
4	d_8–PhMe	Bu_3Sn–H	2	46	100	93	15
5	d_8–PhMe	Bu_3Sn–D	2	26	17	100	17
6[a]	PhMe	Bu_3Sn–D	2	54	100	51	7
7	PhMe	Bu_3Sn–D	*4*	*39*	*100*	*54*	*8*

[a]The reagents were added all at once at the begining of the reaction. [b]Calculated m/z for $C_{13}H_{19}NO$: 205 (100%), 206 (14.7%), 207 (1.2%), for $C_{13}H_{18}DNO$: 206 (100%), 207 (14.7%), 208 (1.2%).

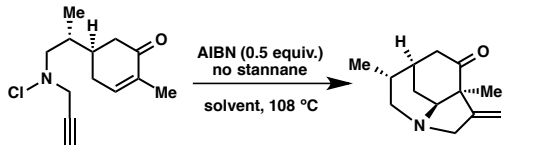
Table 2. Deuterium labeled toluene and stannane experiment.

In the absence of a deuterium source, the observed isotope distribution of the cyclized product (**60**) is consistent with the value of calculated natural isotope

abundance (**Entry 1 and 2**). Switching to the deuterated stannane, the intensity of 207 m/z and 208 m/z increased slightly, indicating the incorporation of deuterium (**Entry 3**). When the reaction was carried in d_8–toluene with stannane, the yield of cyclized product **60** decreased, but the amount of deuterium incorporation increased significantly (**Entry 4**). This suggested that the vinylic radical (**63**) in **Scheme 14** abstracts hydrogen atom from the toluene more often than from stannane because the concentration of stannane is lower than toluene. Instead of slow addition, reagents were added all together at the beginning. They observed slightly decrease of the yield of the product (**60**), but the amount of deuterium incorporation increased (**Entry 3 versus Entry 6**). This results indicates that when the concentration of stannane is increased in reaction mixture it will compete with toluene. Moreover, doubling the loading of stannane while maintaining slow addition of the reagents led to a similar amount of deuterium incorporation as **Entry 6**, but the yield of the cyclized product (**60**) is decreased (**Entry 7**).

The Stockdill lab also investigated the aminyl radical cyclization in the absence of stannane.[30] They conduct the experiment of radical cyclization of (**59**) in four different aromatic hydrocarbon solvents (**Table 3.**) In each case, the solvent serves as the hydrogen atom donor, given its ability to generate a resonance stabilized benzylic radical. The AIBN was added at the start of the reaction and the reaction mixture was heated for 5 hours. As shown in **Table 4**, the isolated yield of the cyclized product (**60**) increased as the BDE of the benzylic C–H bond in the solvent decreased. This suggested that the interaction

between the vinylic radical (**63**) (vinylic C–H ~110 kcal/mol) and hydrogen atom donor with lower BDE is more favored. However, the decrease in the BDE of the benzylic C–H bond also leads to the formation of reduced amine side product (resulted from H· abstraction by **61**, N–H bond ~88 kcal/mol). This correlates with the kinetic rate of aminyl radical[22] in which the premature hydrogen atom abstraction by the *N*-centered radical is in competition with the cyclization.



59 *60*

entry	solvent	BDE (kcal/mol)	isolated yield (%)
1	PhMe	88	9
2	*o*-xylene	87	30
3	PhEt	85	42
4	Ph(*i*-Pr)	83	49

Table 3. Aminyl radical cyclization under stannane free.

2.4 Conclusion

In summary, the Stockdill lab has successfully employed the chemistry of aminyl radical in preparing the tertiary aliphatic amine containing-tricyclic core of *Daphniphyllum* alkaloids via a tandem cyclization. The tertiary aliphatic amine–containing tricyclic core (**60**) was prepared from a known lactone in 6 steps. Dr. Ibrahim discovered that tandem cyclization of internal alkyne substrate works best in THF using silane as hydrogen atom source. The deuterium labeling experiments of toluene and stannane indicates that toluene can serve as a hydrogen atom donor, given its ability to generate a resonance stabilized benzylic radical. On the other hand, increasing the concentration of stannane in the reaction mixture leads to the competition of stannane with toluene.

Furthermore, the experiment conducted under stannane free condition suggest that the weaker the hydrogen bond of the solvent, the greater of its potential to donate the hydrogen atom.

CHAPTER 3 INTRAMOLECULAR MONOCYCLIZATION OF AMINYL RADICAL WITH OLEFINS

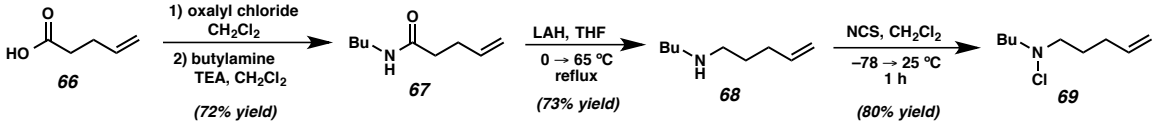
3.1 Introduction

As discussed in the previous chapter, Dr. Ibrahim discovered aminyl radical cyclization with an internal alkyne works best in THF using silane as hydrogen atom source. This discovery inspired him to investigate different types of silanes in the aminyl radical cyclization. Since stannanes are toxic and cause problems in purification, Dr. Ibrahim anticipated that silanes could be a hydrogen atom donor alternative. When I joined the Stockdill lab in 2015, I worked on the monocyclization of aminyl radical with olefins that have different polarization. Initially, I was working with Dr. Ibrahim and Dr. Joarder in identifying the best stannane free hydrogen atom donor for monocyclization of aminyl radical with terminal olefin. Then I investigate the monocyclization on the olefin that has greater polarization than terminal olefin, such as the styrenyl substrate. In this chapter, the discrepancy between the cyclization of aminyl radical with terminal olefin and styrenyl will be discussed.

3.2 Monocyclization With Terminal Olefin

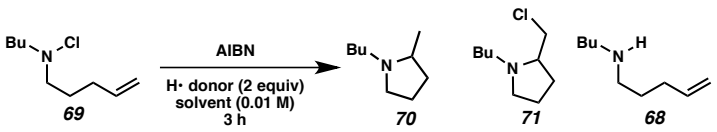
In order to quickly identify the best hydrogen atom donor, we choose to investigate the radical cyclization on simple alkenylamine substrate because the preparation is simple. The synthesis of chloroamine radical precursor **69** by Dr. De Joarder is shown in **Scheme 16**. Treatment of pentenoic acid **66** with oxalyl chloride followed by butylamine gave the amide (**67**). Reduction of amide using lithium aluminum hydride in refluxing THF afforded the alkenylamine (**68**). Then

the amine was treated with *N*-chlorosuccinimide at –78 ºC followed by warming to room temperature over 1 hour and delivered the chloroamine (**69**).



Scheme 16. Preparation of *N*-butyl-*N*-chloropent-4-en-1-amine.

The monocyclization of chloroamine **69** under stannane free condition was shown in **Table 4**. When $(i\text{-Pr})_3SiH$ was used as hydrogen atom donor, the best condition was heating in THF at 100 ºC. This result is consistent with the earlier discovery by Dr. Ibrahim in the internal alkyne substrate (**Entry 1 – 4**). Switching to thiols, the radical reaction gave exclusively the reduced amine product (**68**) (**Entry 5 and 6**). The ratio distributions of the products were similar when phenylsilane is used (**Entry 4 vs. 7**). However, the ratio of the desired pyrrolidine (**70**) increased in the case of $(TMS)_3SiH$, its Si–H bond is slightly weaker (~84 kcal/mol) (**Entry 8**). In the absence of a hydrogen atom donor, the radical reaction proceed to give more of the chlorinated pyrrolidine (**71**) (**Entry 8 vs. 9**). This suggested that the isobutyronitrile radical (from AIBN) could either abstract a chlorine atom directly from **69**, or it could abstract a hydrogen atom from the THF solvent leading to chlorine atom abstraction by the tetrahydrofuran radical. When there is no hydrogen atom or AIBN in the reaction, the ratio distribution of product **70** and **71** decreased but the reduced amine (**68**) increased (**Entry 9 vs 10**). Furthermore, heating the reaction at 130 ºC in the absence of a hydrogen atom donor gave about 1 : 3 ratio of **71** and **68**. The best silane that we have identified in the monocyclization of chloroamine **68** is $(TMS)_3SiH$.

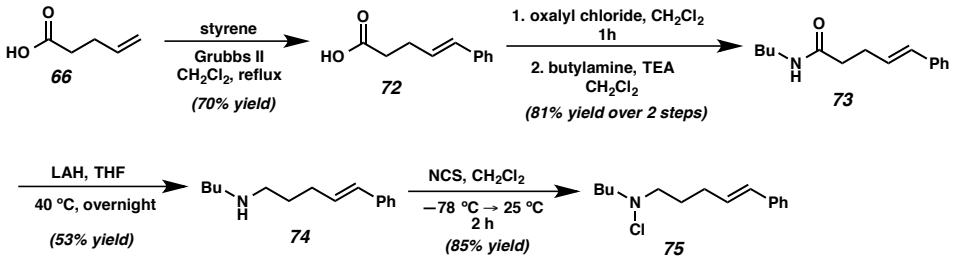


entry	H· donor	AIBN (equiv)	Solvent	Temp. (ºC)	Ratio (GCMS) *69*	*70*	*71*	*68*
1	$(i\text{-Pr})_3SiH$	0.2	Ph-CF_3	100	0	2	0	98
2	$(i\text{-Pr})_3SiH$	0.2	toluene	100	58	2	3	37
3	$(i\text{-Pr})_3SiH$	0.2	PhH	100	33	0	24	43
4	$(i\text{-Pr})_3SiH$	0.2	THF	100	0	40	17	43
5	*t*-BuSH	0.2	THF	100	0	0	0	100
6	PhSH	0.2	THF	100	0	4	0	96
7	$PhSiH_3$	0.2	THF	100	0	43	14	42
8	$(TMS)_3SiH$	0.2	THF	100	0	64	9	27
9	none	0.2	THF	100	0	50	25	24
10	none	none	THF	100	0	37	18	45
11	none	0.2	THF	130	0	0	23	77

Table 4. Monocyclization of *N*-butyl-*N*-chloropent-4-en-1-amine.

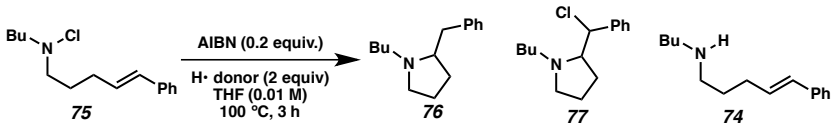
3.3 Monocyclization With Styrenyl

According to the earlier work reported by Bowman,[20b] the cyclization of aminyl radical with styrenyl favored the cyclization reaction. Therefore, we are anticipating the monocyclization of aminyl radical with styrenyl should provide better yield than the cyclization with terminal olefin. I prepared the chloroamine **75** as shown in **Scheme 17**. Olefin metathesis of pentenoic acid **66** with styrene using Grubbs II catalyst gave the phenylpentenoic acid (**72**). Treatment of the carboxylic acid with oxalyl chloride followed by butylamine gave the amide (**73**). Reduction of amide using lithium aluminum hydride in THF at 40 ºC afforded the amine (**74**). The amine was treated with *N*-chlorosuccinimide at –78 ºC followed by warming to room temperature over 2 hours and delivered the styrene substituted chloroamine (**75**).



Scheme 17. Preparation of styrenyl chloroamine.

The results for the monocyclization of aminyl radical with styrenyl are summarized in **Table 5**. During the course of the study, no chloroamine **75** starting material was observed in the reaction. When the cyclization reaction proceed in the presence of $(TMS)_3SiH$, the major product that observed is the reduced amine (**74**) (**Entry 1**). This result is not in agreement with the monocyclization of terminal olefin as discussed in the previuos section. Despite extensive screening of different silyl hydrogen atom donors (**Entry 2–8**), the ratio of the desired pyrrolidine (**76**) does not improve further. When switching to stannane, the radical reaction gave exclusively the desired product (**76**).

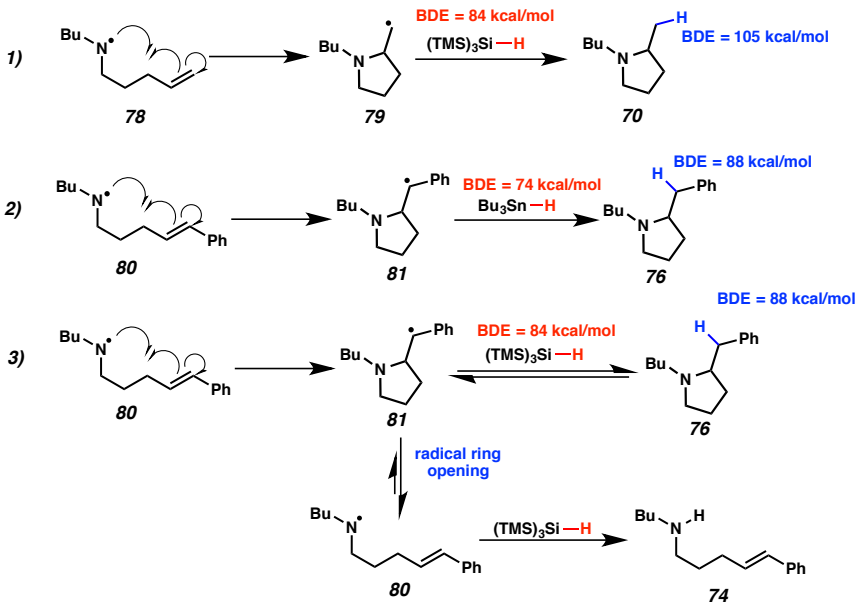


Entry	H donor	Ratio (GCMS) 76	77	74
1	$(TMS)_3SiH$	4	7	89
2	$(i\text{-}Pr)_3SiH$	2	15	83
3	Et_3SiH	1	6	93
4	Hanstzsch ester	3	1	96
5	Et_3GeH	5	9	86
6	Ph_3SiH	2	5	93
7	Ph_2MeSiH	3	11	86
8	cyclohexadiene	2	4	94
9	Bu_3SnH	100	0	0

Table 5. Monocyclization of styrenyl substrate.

To understand the discrepancy between the optimal H–atom donor for monocyclization with a terminal olefin and with styrenyl, a correlation based on

the BDE of the $(TMS)_3SiH$ and Bu_3SnH is proposed (**Scheme 18**). From our observation, the monocyclization is favored when the difference of BDE between the H–atom donor and the final C–H bond is around 14 to 20 kca/mol. The cyclization of aminyl radical **78** with terminal olefin proceeds to favor the formation of pyrrolidine **70** and the difference of BDE between the Si–H (84kcal/mol) [31] and the C–H bond (105 kcal/mol)[31] is about 20 kcal/mol. Presumably, this difference in the BDE gap is sufficient to drive the formation of cyclized product. For the same reason, the monocyclization of aminyl radical **80** with styrenyl favored pyrrolidine **76** because the BDE difference between the stannane and benzylic C–H bond is 14 kcal/mol. However, the BDE of $(TMS)_3SiH$ (Si–H bond, ~84 kcal/mol) is too similar to the benzylic hydrogen (~88 kcal/mol).[31] Therefore, after the hydrogen atom abstraction, it is possible for the reverse reaction of **76** to compete, leading to the radical ring opening of **81** to give aminyl radical **80**. Then the aminyl radical abstracted a hydrogen atom from the $(TMS)_3SiH$ to afforded the reduced amine (**74**).



Scheme 18. Bond dissocation energy rationale.

At this stage, we have no solid evidence to support our hypothesis and the correlation of the BDE shown in **Scheme 18** is based upon our experimental observations. We are currently collaborating with Professor Bernhard Schlegel in our department to understand the details of the monocyclization using computational analysis.

3.4 Conclusion

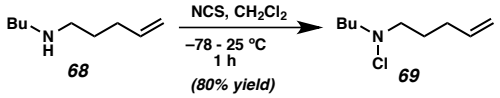
In summary, we have discovered that intramolecular monocyclization of aminyl radical with terminal olefin can proceed to afford the pyrrolidine using silanes as hydrogen atom donor. The best condition was heating the reaction in THF at 100 ºC with $(TMS)_3SiH$ and AIBN. However, under the same condition, the cyclization of styrenyl substrate provide exclusively the reduced amine product. Presumably, the BDE of $(TMS)_3SiH$ (84 kcal/mol) is too similar to the benzylic hydrogen (~88 kcal/mol). Therefore, it is possible for the $(TMS)_3Si\cdot$ to abstract the benzylic hydrogen atom from the cyclized product, leading to the ring

opening of the resulting benzylic radical. This will led the reaction back to the aminyl radical, which upon abstracting a hydrogen atom from the $(TMS)_3SiH$ to afforded the reduced amine. The computational analysis on the monocyclization of aminyl radical with terminal olefin and with styrenyl is currently undergoing in our lab.

3.5 Experimental Section

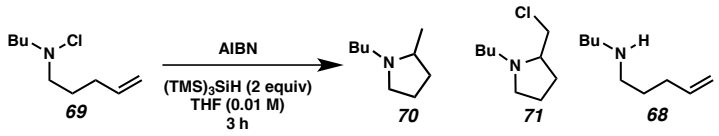
Unless otherwise specified, all commercially available reagents were purchased from Aldrich and used without further purification. Anhydrous THF, PhH, PhMe, DMF, DMSO, CH_2Cl_2 were passed through a commercial solvent purification system (2 columns of alumina) and used without further drying. Triethylamine and Hünig's base were distilled over CaH_2 immediately prior to use. Unless otherwise noted, all reactions were performed in flame-dried glassware under 1 atm of pre-purified anhydrous N_2 or argon gas. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury-400 MHz instrument with a multinuclear broadband probe at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to residual solvent peaks (as established by Stoltz, et. al. in Organometallics 2010, 29, 2176). All ^{13}C spectra are recorded with complete proton decoupling. Thin layer chromatography was performed using glass-backed SiliaPlate™ TLC Plates (cat. # TLG-R10011B-323) cut to the desired size then visualized with short-wave UV lamps and $KMnO_4$, CAM, PMA, or Anisaldehyde stains. Compounds **67** (DDJ–IV–34) and **68** (DDJ–IV–039) were prepared by Dr. De Joarder and the procedure for compound **68** was adapted from the literature.[32]

3.5.1 Preparation of Terminal Olefin Substrate



Chloroamine 69. To a solution of **68** (200 mg, 1.42 mmol, 1.0 equiv) in CH_2Cl_2 (5.7 mL, 0.25 M) at –78 ºC was added NCS (208 mg, 1.56 mmol, 1.1 equiv). The resulting mixture was continuing stirred at –78 ºC and allowed to warm to ambient temperature over 1 h. At this time, the reaction mixture was diluted with 18 mL of pentane and flashed through a plug of silica (2.5% ether/pentane) to afford 0.2 g of **69** as clear liquid (80% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 5.81 (td, *J* = 16.8, 6.6 Hz, 1H), 5.03 (d, *J* = 17.1 Hz, 1H), 4.97 (d, *J* = 10.4 Hz, 1H), 2.93 (t, *J* = 7.1 Hz, 4H), 2.11 (dd, *J* = 14.3 Hz, 7.0 Hz, 2H), 1.82–1.72 (m, 2H), 1.70–1.59 (m, 2H), 1.41–1.31 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 138.27, 115.12, 64.30, 63.65, 31.00, 30.14, 27.15, 20.18, 14.09. Spectra data were consistent with those previous reported in the literature.[33]

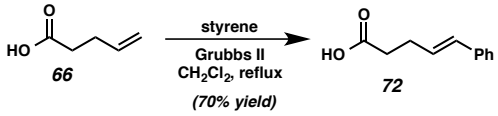
3.5.2 Procedure for Monocyclization With Terminal Olefin.



To a Biotage microwave tube wrapped with aluminum foil was added **69** (32 mg, 0.184 mmol, 1.0 equiv), and AIBN (6 mg, 0.037 mmol, 0.2 equiv). Then the tube was sealed with the septum followed by evacuated one cycle in Schlenk line and backfilling with argon. After evacuation, $(TMS)_3SiH$ (91 mg, 0.368 mmol, 2.0 equiv) and THF (20.4 mL, 0.01M) were added via syringe to the sealed tube

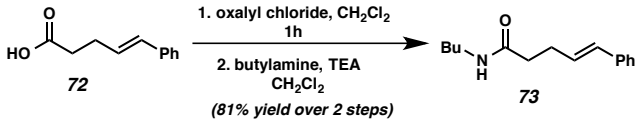
under argon. Finally, the sealed tube was merged into a pre-heated oil bath at 100 ºC for 3 hours. The reaction was cooled to ambient temperature and the solvent was concentrated. The crude was diluted with diethyl ether (10 mL) and washed with 10% HCl (2 x 10 mL). The layers were separated and the aqueous layer was basified to pH 13 with 3 M NaOH. Then the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to afford mixture of **70**, **71**, and **68**. Compounds **70** and **68** have similar R_f value in 5% MeOH/CH_2Cl_2 so we did not isolated them. The ratio distribution was determined by GCMS (QP2010 SE, Shimadzu). However, no internal standard was employed, so the results can only be interpreted qualitatively.

3.5.3 Preparation of Styrenyl Substrate



Carboxylic Acid 72. To a solution of Grubbs II catalyst (85 mg, 0.1 mmol, 0.02 equiv) in CH_2Cl_2 (17.0 mL, 0.29 M) was added pent-4-enoic acid (**66**) (500 mg, 5.0 mmol, 1.0 equiv) and styrene (1.04 g, 10.0 mmol, 2.0 equiv) via syringe under argon. Then the reaction flask was equipped with a reflux condenser and the resulting mixture was allowed to reflux at 50 ºC for 13 h. At this time, the reaction was cooled to ambient temperature and concentrated under vacuum to give dark green solid. The crude solid was dissolve in EtOAc (17 mL) and washed with $NaHCO_3$ (3 x 34 mL). The combined aqueous layers were acidified to pH 1 with 10% HCl at 0 ºC, and then the aqueous layer was extracted with

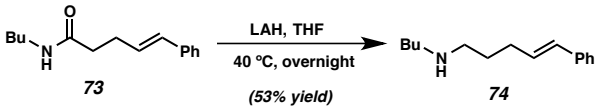
EtOAc (2 x 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to afford 678 mg of **72** as light purple solid (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 5H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.27 – 6.17 (m, 1H), 2.58-2.54 (m, 4H); ^{13}C NMR (101MHz, $CDCl_3$) δ 179.32, 137.38, 131.31, 128.65, 128.13, 127.35, 126.22, 33.91, 28.05. Spectra data were consistent with those previous reported in the literature.[34]



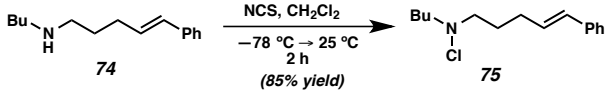
Amide 73. To a solution of **72** (87 mg, 0.494 mmol, 1.0 equiv) in CH_2Cl_2 (1.2 mL, 0.4 M) at 0 ºC was added oxalyl chloride (125 mg, 0.99 mmol, 2 equiv) and one drop of DMF via syringe. The reaction mixture was warmed to ambient temperature and stirred for 2 h. Then the reaction was concentrated under vacuum and the residue was used in next step without further purification.

To a round bottom flask was added the residue in CH_2Cl_2 (1.65 mL, 0.3 M) under argon. The resulting mixture was cooled to 0 ºC followed by addition of *N*–butyl amine (47 mg, 0.642 mmol, 1.3 equiv) and TEA (65 mg, 0.642 mmol, 1.3 equiv) drop wise via a syringe. Then the reaction was warmed to ambient temperature and stirred for 15 h. At this time, the reaction was quenched with 2 mL of water and extracted with CH_2Cl_2 (1x 5mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography on silica (0–30% ethyl acetate/hexane) collected 89 mg of **73** as white solid. (81% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36–7.16 (m, 5H), 6.43 (d, *J* = 15.8 Hz, 1H),

6.20 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.55 (s, 1H), 3.25 (q, *J* = 6.8 Hz, 2H), 2.55 (q, *J* = 7.3 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.51–1.40 (m, 2H), 1.37–1.24 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 172.17, 137.44, 131.09, 128.92, 128.62, 127.25, 126.13, 39.37, 36.57, 31.85, 29.19, 20.18, 13.85. Spectra data were consistent with those previous reported in the literature.[19d]

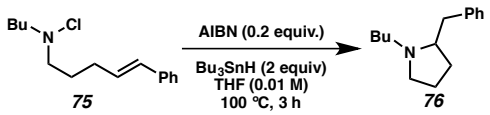


Amine 74. To a solution of **73** (115 mg, 0.50 mmol, 1.0 equiv) in THF (2.5 mL, 0.20 M) at 0 ºC was added LAH (46 mg, 1.24 mmol, 2.5 equiv). The resulting mixture was allowed to warm to ambient temperature and then stirred at 40 ºC with a septum under argon for 20 h. At this time, the reaction was quenched with 3 M NaOH at 0 ºC. The solution was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography on silica (0–7% MeOH/CH_2Cl_2) collected 57 mg of **74** as an oil (53 % yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.31–7.14 (m, 5H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.8 Hz, 1H), 2.70–2.56 (m, 4H), 2.26 (q, *J* = 7.3, 6.8 Hz, 2H), 1.72–1.58 (m, 2H), 1.50 – 1.23 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 137.20, 131.69, 128.64, 128.02, 127.36, 126.17, 47.97, 47.51, 30.22, 28.10, 25.67, 20.22, 13.66. Spectra data were consistent with those previous reported in the literature.[19d]



Chloroamine 75. To a solution of **74** (56 mg, 0.26 mmol, 1.0 equiv) in CH_2Cl_2 (1.03 mL, 0.25 M) at –78 ºC was added NCS (38 mg, 0.28 mmol, 1.1 equiv). The resulting mixture was stirred at -78 ºC and allowed to warm to ambient temperature over 1 h. At this time, the reaction mixture was diluted with 7 mL of pentane and flashed through a plug of silica (2.5% ether/pentane) to afford 55 mg of **75** as clear liquid (85% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.37 – 7.17 (m, 5H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.00 – 2.89 (m, 4H), 2.34 – 2.23 (m, 2H), 1.91–1.80 (m, 2H), 1.71 – 1.59 (m, 2H), 1.43–1.30 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 137.80, 130.59, 130.16, 128.64, 127.08, 126.09, 64.35, 63.63, 30.26, 30.16, 27.64, 20.19, 14.10.

3.5.4 Procedure for Monocyclization With Styrenyl



To a Biotage microwave tube wrapped with aluminum foil was added **75** (86 mg, 0.34 mmol, 1.0 equiv) and AIBN (11 mg, 0.07 mmol, 0.2 equiv). Then the tube was sealed with the septum followed by evacuated one cycle in Schlenk line and backfilling with argon. After evacuation, Bu_3SnH (200 mg, 0.69 mmol, 2.0 equiv) and THF (38.0 mL, 0.01M) were added via syringe to the sealed tube under argon. Finally, the sealed tube was merged into a pre-heated oil bath at 100 ºC for 3 hours. The reaction was cooled to ambient temperature and the solvent was concentrated under vacuum. The crude was

injected into GCMS (QP2010 SE, Shimadzu) and the only product observed is compound **76**. Flash chromatography on 10% K_2CO_3/silica (0–5% MeOH/CH_2Cl_2) collected 43 mg of **76** as an oil (58% yield). For **Entry 1–8** in **Table 5**, the ratio between **74**, **76**, and **77** were determined by GCMS (QP2010 SE, Shimadzu). However, no internal standard was employed, so the results can only be interpreted qualitatively. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 (m, 5H), 3.25 – 3.15 (m, 1H), 3.06 (d, *J* = 9.4 Hz, 1H), 2.95 – 2.83 (m, 1H), 2.53 – 2.38 (m, 2H), 2.20–2.08 (m, 2H), 1.85–1.25(m, 8H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 140.32, 129.28, 128.30, 125.97, 66.65, 54.72, 54.29, 41.04, 31.12, 30.50, 21.99, 21.08, 14.23. Spectra data were consistent with those previous reported in the literature.[19d]

CHAPTER 4 TANDEM CYCLIZATION OF AMINYL RADICAL WITH ENONE AND STYRENYL

4.1 Introduction

In the previous chapter, we investigated the mononcyclization of aminyl radical with unactivated olefin and with polarized olefin under different types of H–atom donors. The discrepancy between using silanes and stannane for monocyclization driven us to investigated the tandem cyclization under same reaction conditions. Additionally, the successful work with the tandem cyclization using $(i\text{-Pr})_3SiH$, discovered by Dr. Ibrahim, inspired us to extend the reaction scope. The results in **Table 3** show that tandem cyclization of aminyl radicals can proceed in hydroaromatic solvents in the absence of stannane.[30] The drawback is that as the BDE of benzylic C–H bond decreases, the reaction favors the formation of both cyclized product and reduced amine. The undesired reduced amine side product is resulted from the premature hydrogen atom abstraction by the *N*-centered radical.

In order to overcome the premature hydrogen atom abstraction, we question whether the solvent is likely to donate an H–atom to the aminyl radical and the relative rate of cyclization vs. trapping (formation of N–H or C–H bond). Dr. Ibrahim has found that the tandem cyclization using $(i\text{-Pr})_3SiH$ in THF provide a much cleaner reaction to afford the desired cyclized product. The BDE of the C–H bond in THF is about 92 kcal/mol,[35] which is higher than the BDE of N–H bond (~88 kcal/mol).[35] This suggests that H–atom abstraction by the aminyl radical from THF is unlikely to occur. At the same time, it is possible for THF to

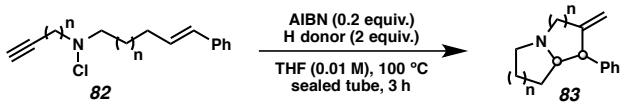
donates H–atom to the vinylic radical (vinylic C–H ~110 kcal/mol)[31] because the BDE difference is about 18 kcal/mol. Taken together, we hypothesized that tandem cyclization of aminyl radical with polarized olefin in THF can minimized the premature hydrogen atom abstraction and favor the cyclization. This chapter covered the tandem cyclization of aminyl radical with styrenyl and enone to prepare tertiary aliphatic amine–containing bicyclic motifs.

4.2 Tandem Cyclization With Styrenyl

The undergraduate student in our lab, Greg Rosenhauer, conducted experiments on the tandem cyclization of chloroamine **82** using silanes as hydrogen atom donor (**Table 6**). In some cases, the reaction gave the reduced amine product and the purification became difficult because all the compounds eluted similarly on the silica gel. Thus, acid–base workup was implemented and the yield was calculated as the combined amine products.

As shown in **Table 6**, tandem cyclization of **82a** using $(TMS)_3SiH$ proceed to give only the desired pyrrolizidine **83a** with no other side product (**Entry 1**). When swtiching to $(i\text{-}Pr)_3SiH$, trace amount of reduced amine product **84a** is observed (**Entry 2**). In the tandem cyclization of (**82b**), the amount of the reduced amine increased (**Entry 1 vs. 3**). Presumably during the second cyclization step, the 6-*exo*-dig cyclization is slower than the 5-*exo*-dig which leads to the reverse radical ring opening to give the reduced amine (**84b**). This result correlates with the correlation of BDE shown in **Scheme 18**, the BDE of benzylic C–H bond is similar with Si–H bond. In the cyclization of (**82c**), there was no reduced amine product observed (**Entry 3 vs. 4**). However, the slower 6-

exo-trig cyclization resulted in lower yield of the indolizidine (**83c**) compares to pyrrolizidine (**83a**) (**Entry 1 vs 4**). Suprisingly, the 6-*exo*-trig cyclization of **82d** afforded more of the quinolizidine product (**83d**) than the 5-exo-trig cyclization of **82b** (**Entry 3 vs. 5**).



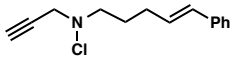
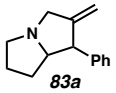
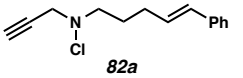
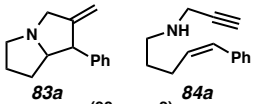
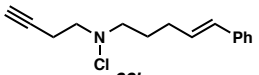
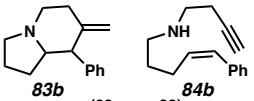
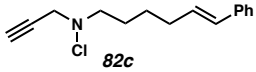
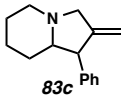
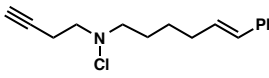
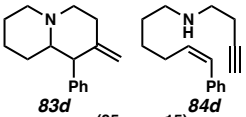
entry	starting material	H donor	products ratio (GCMS)	combined yield (%)
1	 *82a*	$(TMS)_3SiH$	 *83a*	62
2	 *82a*	$(i\text{-}Pr)_3SiH$	 *83a* (98 : 2) *84a*	61
3	 *82b*	$(TMS)_3SiH$	 *83b* (68 : 32) *84b*	60
4	 *82c*	$(TMS)_3SiH$	 *83c*	48
5	 *82d*	$(TMS)_3SiH$	 *83d* (85 : 15) *84d*	57

Table 6. Tandem cyclization with styrenyl.

4.3 Tandem Cyclization With Enone

In order to improve the yield of the aminyl radical cyclization, we have investigated the tandem cyclization with enone substrate. Since enone is more electron withdrawing than phenyl, the addition of aminyl radical to enone should be more favored. I am working together with another graduate student in our lab, Hansamali Sirinimal, in the investigation of tandem cyclization of aminyl radical with enone. In this project, Hansamali is working toward the cascade of 5-*exo*-trig /5-*exo*-dig cyclization to prepare pyrrolizidines **85** (**Figure 3**). Meanwhile, I was

working on the cascade cyclization of 6-*exo*-trig/5-*exo*-dig to prepare indolizidine **86**.

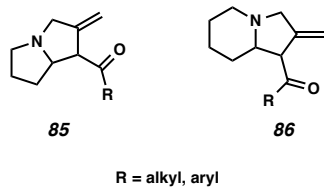
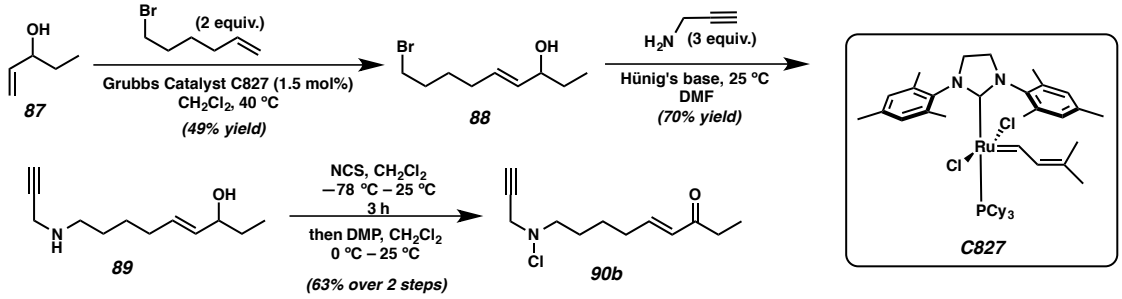


Figure 3. Ketone-substituted pyrrolizidine and indolizidine motif.

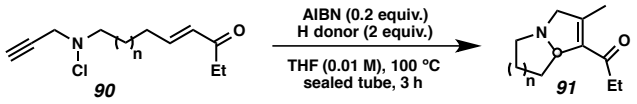
I prepare the aminyl radical precursor for the tandem cyclization from readily available allylic alcohol (**87)** (**Scheme 19**). The synthesis begin with cross metathesis of allylic alcohol **87** with 6-bromohexene using Grubbs catalyst C827 to deliver the cross-coupled product (**88**). Then *N*-alkylation of propargylamine with bromide **88** gave the secondary amine (**89**). To avoid the amine undergoes intramolecular conjugate addition with enone, the nitrogen was first chlorinate with NCS followed Dess-Martin oxidation of the allylic alcohol in one pot to afforded the chloroamine (**90b**).

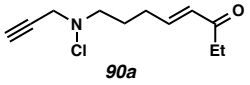
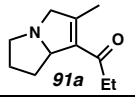
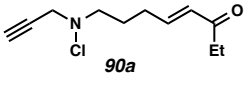
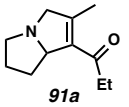
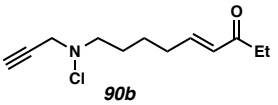
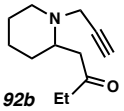
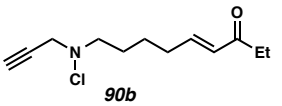
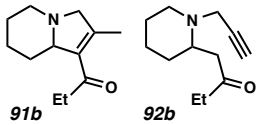
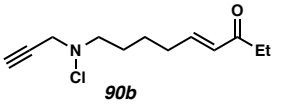
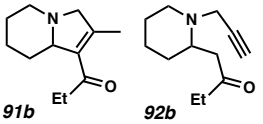


Scheme 19. Preparation of the chloroamine enone substrate.

The results for the tandem cyclization with enone substrate is summarized in **Table 7**. When $(TMS)_3SiH$ is used, Hansamali was able to isolate the resonance stablized pyrrolizidine (**91a**) in good yield (**Entry 1**). The yield for the pyrrolizidine improved further when switch to $(i\text{-}Pr)_3SiH$ (**Entry 2**). Compared to

the styrenyl, the high yielding of the pyrrolizidine (**91a**) denote that the greater polarization of the enone favors the cyclization process. However, during my attempt to prepare the indolizidine, the tandem cyclization with enone gave exclusively the monocyclized product (**92b**) (**Entry 3 and 4**). When replacing the silanes with stannane, the ratio of indolizidine (**91b**) increased but the major porduct is still (**92b**) (**Entry 5**). Since the 6-*exo*-trig is slower than 5-*exo*-trig cyclization, the tandem cyclization of **90b** might require longer time than **90a**. However, heating the cyclization reaction at 100 ºC using stannane for 15 hours gave the same result as heating for 3 hours.



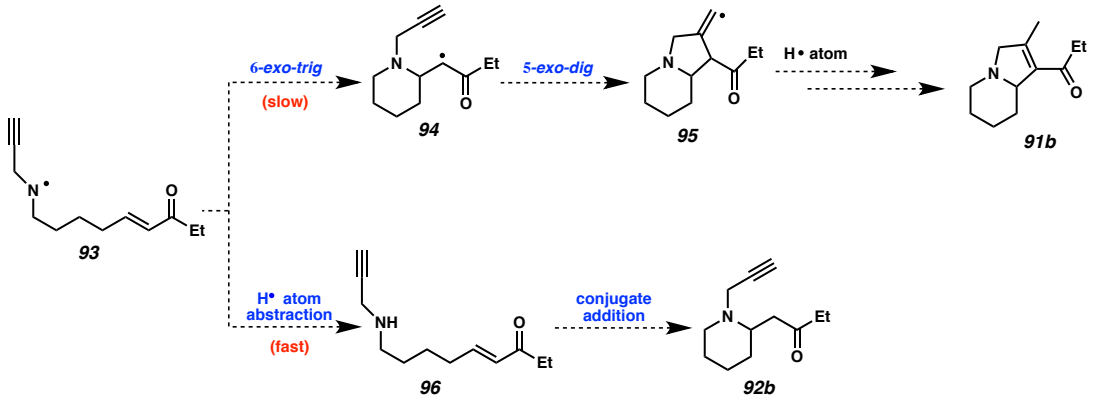
entry	starting material	H donor	product(s) ratio (GCMS)	isolated yield
1	 *90a*	$(TMS)_3SiH$	 *91a*	70 %
2	 *90a*	$(i\text{-}Pr)_3SiH$	 *91a*	80 %
3	 *90b*	$(TMS)_3SiH$	 *92b*	33 %
4	 *90b*	$(i\text{-}Pr)_3SiH$	 *91b* (4 : *92b* 96)	---
5[a]	 *90b*	Bu_3SnH	 *91b* (24 : *92b* 76)	---

[a]Heating the reaction at 100 °C for 15 h gave the same result.

Table 7. Tandem cyclization of enone substrate.

Despite the difference between the tandem cyclization of (**90a**) and (**90b**) is only in the first step of cyclization, but there is a wide disparity in yield of (**91a**)

and (**91b**). One possibility is that due to the slow 6-*exo*-trig cyclization, the premature H–atom abstraction competed with the cyclization pathway and leads to the linear secondary amine (**96**) (**Scheme 20**). Then the amine will undergoes conjugate addition to the enone and afforded the monocyclized product (**92b**).[36] In this case, the aminyl radical (**93**) is consumed in the step of premature hydrogen atom abstraction. Therefore, heating the reaction for 15 hours does not improve the coversion of **91b**.



Scheme 20. Proposed competing pathway of 6-*exo*-trig cyclization.

4.4 Conclusion

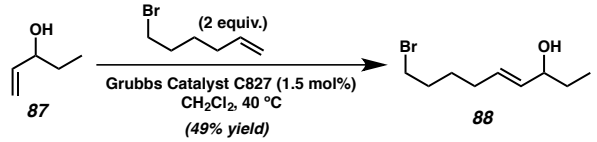
The undergraduate student in our lab, Greg Rosenhauer, had shown that silane is compatible in the tandem cyclization of aminyl radical with styrenyl. Although the reaction proceed to give the pyrrolizidine, indolizidine, and quinolizidine in good yields, the undesired reduced amine is still formed in some cases. On the other hand, Hansamali Sirinimal and I work together in the tandem cyclization of aminyl radical with enone. The tandem cyclization with enone in preparing the pyrrolizidine gave higher yields than in the case with styrenyl. This suggest that the greater polarization of enone favored the cyclization reaction more. However, in the tandem cyclization of preparing indolizidine, the reaction

gave exclusively the monocyclized product which resulted from the conjugate addition of amine. One possibility is that because the 6-*exo*-trig is slower than the 5-*exo*-trig cyclization, the predominate pathway in the reaction became the hydrogen atom abstraction by the *N*-centered radical. In this case, despite the electron withdrawing nature of enone, the cyclization process still cannot overcome the premature hydrogen atom abstraction.

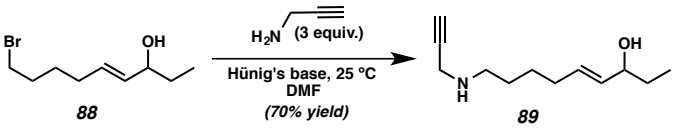
4.5 Experimental Section

Unless otherwise specified, all commercially available reagents were purchased from Aldrich and used without further purification. Anhydrous THF, PhH, PhMe, DMF, DMSO, CH_2Cl_2 were passed through a commercial solvent purification system (2 columns of alumina) and used without further drying. Triethylamine and Hünig's base were distilled over CaH_2 immediately prior to use. Unless otherwise noted, all reactions were performed in flame-dried glassware under 1 atm of pre-purified anhydrous N_2 or argon gas. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury-400 MHz instrument with a multinuclear broadband probe at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to residual solvent peaks (as established by Stoltz, et. al. in Organometallics 2010, 29, 2176). All ^{13}C spectra are recorded with complete proton decoupling. IR data was obtained on a PerkinElmer FT-IR spectrometer. Thin layer chromatography was performed using glass-backed SiliaPlate™ TLC Plates (cat. # TLG-R10011B-323) cut to the desired size then visualized with short-wave UV lamps and $KMnO_4$, CAM, PMA, or Anisaldehyde stains.

4.5.1 Preparation of Enone Substrate

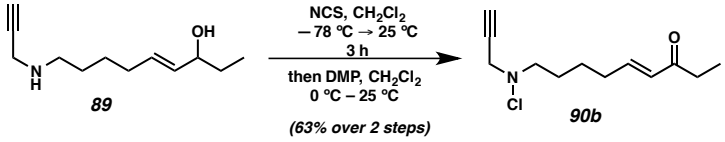


Bromide 88. To a solution of catalyst C827 (173 mg, 0.21 mmol, 0.015 equiv) in CH_2Cl_2 (68.3 mL, 0.20 M) was added **87** (1.20 g, 13.9 mmol, 1.0 equiv) and 6-bromo-1-hexene (4.51 g, 27.9 mmol, 2 equiv) via syringe under argon. Then the reaction flask was equipped with a reflux condenser and the resulting mixture was heated at 40 ºC for 20 h. At this time, the reaction was cooled to ambient temperature and concentrated under vacuum. Flash chromatography on silica (0 – 15% ethyl acetate/hexane) collected 1.52 g of **88** as brown liquid (49% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 5.70 – 5.58 (m, 1H), 5.48 (dd, J = 15.5, 7.0 Hz, 1H), 4.04 – 3.91 (m, 1H), 3.41 (t, J = 6.7 Hz, 2H), 2.08 (q, J = 7.0 Hz, 2H), 1.87 (dt, J = 14.9, 6.7 Hz, 2H), 1.63 – 1.45 (m, 4H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 133.59, 131.33, 74.51, 33.82, 32.31, 31.41, 30.29, 27.78, 9.91; IR (neat) 3352, 2962, 2932, 2859, 1456, 1249, 965, 645, 561 cm^{-1}.



Amine 89. To a solution of **88** (284 mg, 1.29 mmol, 1.0 equiv) in DMF (2.08 mL, 0.62 M) was added successively Hünig's base (0.86 mL, 1.5 M) and propargylamine (213 mg, 3.87 mmol, 3.0 equiv) at ambient temperature. The resulting mixture was stirred at ambient temperature for 19 h. At this time, the

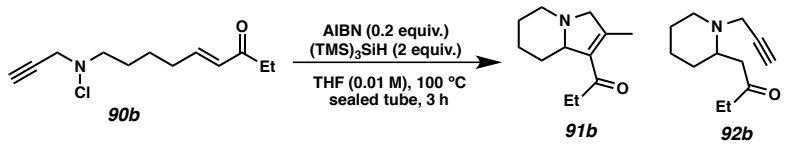
reaction was diluted with ethyl acetate (10mL) and washed with water. The layers were separated and the aqueous layer was back–extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica (0–5% MeOH/CH_2Cl_2) afforded 175 mg of **89** as dark liquid (70% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 5.69 – 5.55 (m, 1H), 5.44 (dd, J = 15.4, 7.1 Hz, 1H), 3.94 (q, J = 6.6 Hz, 1H), 3.41 (d, J = 2.3 Hz, 2H), 2.68 (td, J = 7.1, 3.4 Hz, 2H), 2.20 (d, J = 2.3 Hz, 1H), 2.06 (dq, J = 13.6, 6.8 Hz, 2H), 1.48 (tdd, J = 30.1, 14.3, 6.2 Hz, 6H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 133.32, 131.80, 82.21, 74.51, 71.48, 48.50, 38.21, 32.11, 30.27, 29.29, 26.94, 9.94; IR (neat) 3305, 2960, 2928, 2856, 1455, 1330, 1112, 966, 734, 627, 646 cm^{-1}.



Chloroamine 90b. To a solution of **89** (100 mg, 0.51 mmol, 1.0 equiv) in CH_2Cl_2 (2.56 mL, 0.20 M) at –78 ºC was added NCS (75.3 mg, 0.56 mmol, 1.1 equiv). The resulting mixture was stirred at –78 ºC and allowed to warm to 0 ºC over 3 h. At this time, DMP (326 mg, 0.77 mmol, 1.5 equiv) was added into the reaction mixture at 0 ºC. The resulting mixture was allowed to warm to ambient temperature and stirred for 14 h. Then the reaction was diluted with 10 mL of 40% ether/hexane and purified by flash chromatography on silica (40% ether/hexane) to afford 85 mg of **90b** as clear liquid (63% yield over 2 steps). ^{1}H

NMR (400 MHz, Chloroform-d) δ 6.81 (dt, J = 15.9, 6.9 Hz, 1H), 6.12 (dd, J = 15.8, 7.5 Hz, 1H), 3.81 (d, J = 2.3 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H), 2.55 (q, J = 7.3 Hz, 2H), 2.41 (t, J = 2.3 Hz, 1H), 2.24 (q, J = 6.9 Hz, 2H), 1.72 – 1.47 (m, 4H), 1.09 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 201.22, 146.39, 130.45, 74.97, 61.61, 52.77, 33.41, 32.18, 27.44, 25.28, 8.27; IR (neat) 3296, 3260, 2939, 2863, 1697, 1671, 1629, 1358, 1203, 979, 662 cm^{-1}.

4.5.2 Procedure for Tandem Cyclization With Enone

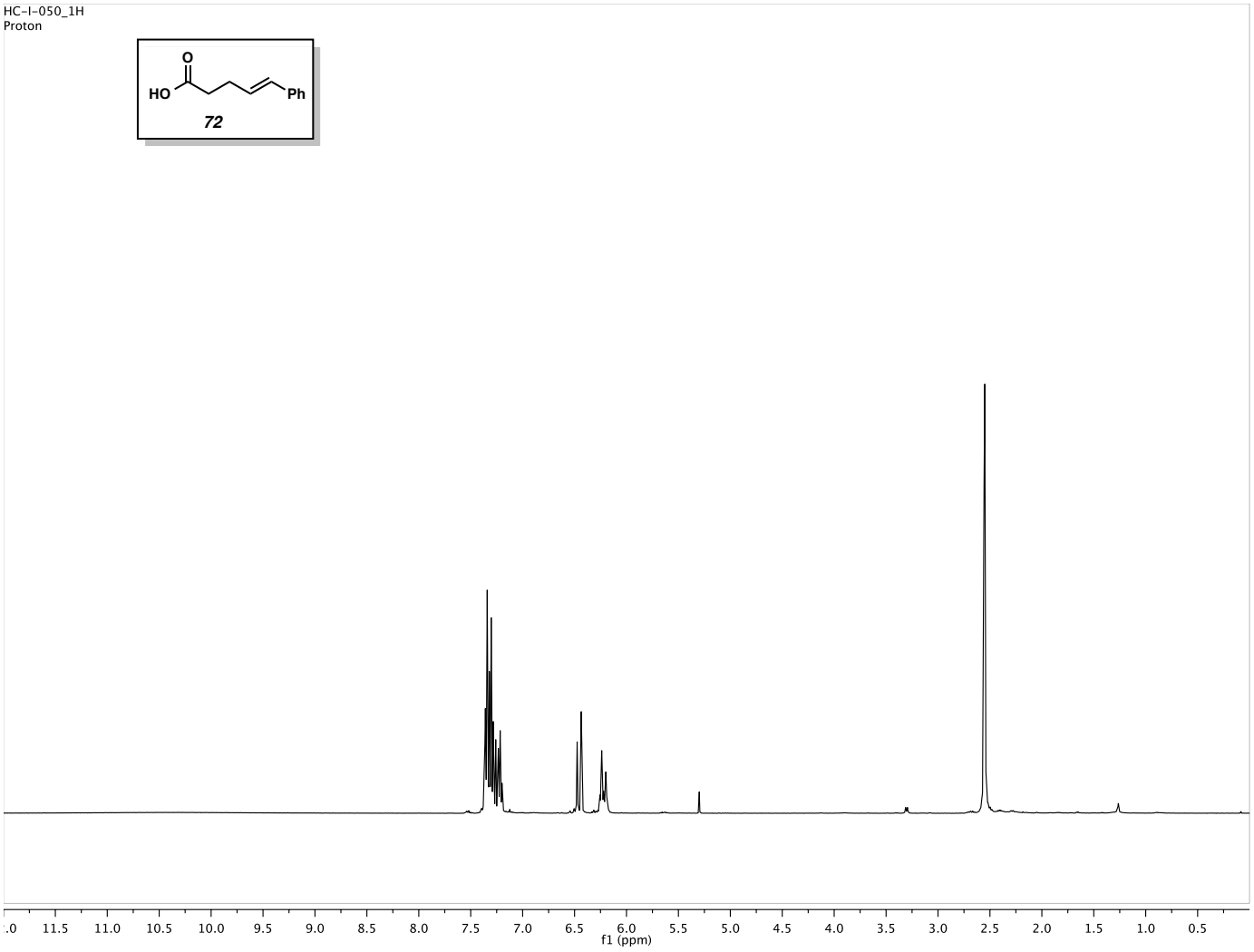


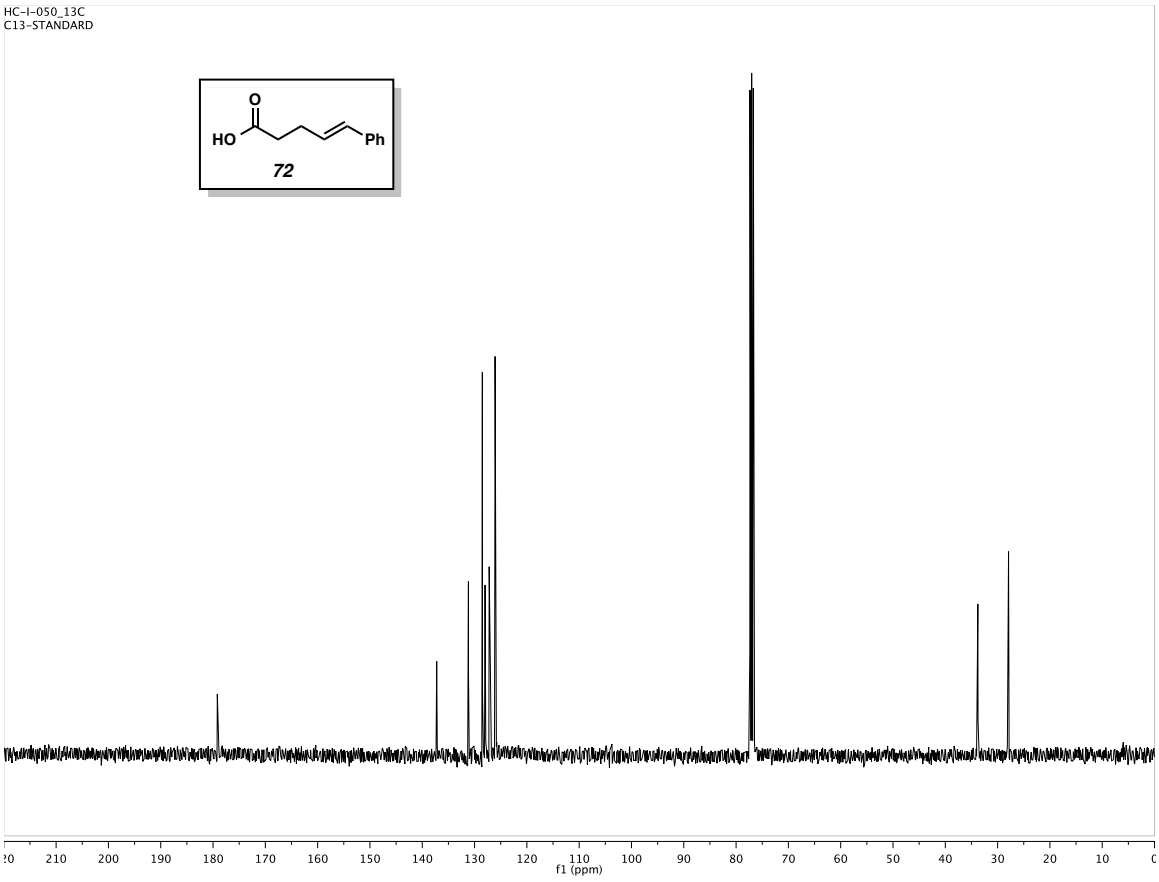
To a Biotage microwave tube wrapped with aluminum foil was added **90b** (40 mg, 0.18 mmol, 1.0 equiv) and AIBN (6 mg, 0.035 mmol, 0.2 equiv). Then the tube was sealed with the septum followed by evacuated one cycle in Schlenk line and backfilling with argon. After evacuation, $(TMS)_3SiH$ (87 mg, 0.351 mmol, 2.0 equiv) and THF (20.0 mL, 0.01 M) were added via syringe to the sealed tube under argon. Finally, the sealed tube was merged into a pre-heated oil bath at 100 ºC for 3 hours. The reaction was cooled to ambient temperature and the solvent was concentrated under vacuum. Flash chromatography on silica (0–3% $MeOH/CH_2Cl_2$) collected 11 mg of **92b** as yellow liquid (33% yield). Trace amount of **91b** was observed in TLC. For **Table 6** and **Table 7**, the ratio between the cyclized products and the reduced amines were determined by GCMS (QP2010 SE, Shimadzu). However, no internal standard was employed, so the results can only be interpreted qualitatively. ^{1}H NMR (400 MHz, Chloroform-d) δ 3.55 (dd, J = 17.5, 2.2 Hz, 1H), 3.28 (dd, J = 17.6, 2.3 Hz, 1H), 2.88 (d, J = 9.2

Hz, 1H), 2.83 – 2.71 (m, 2H), 2.57 – 2.31 (m, 4H), 2.23 (t, J = 2.3 Hz, 1H), 1.72 – 1.48 (m, 4H), 1.38 – 1.18 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ 210.36, 73.63, 55.68, 53.07, 45.89, 43.72, 37.02, 31.90, 25.96, 23.75, 7.88, 1.45; IR (neat) 3309, 2926, 2856, 1711, 1457, 1377, 1104, 1079, 658 cm^{-1}.

APPENDIX

^{1}H and ^{13}C NMR Spectra

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Ph
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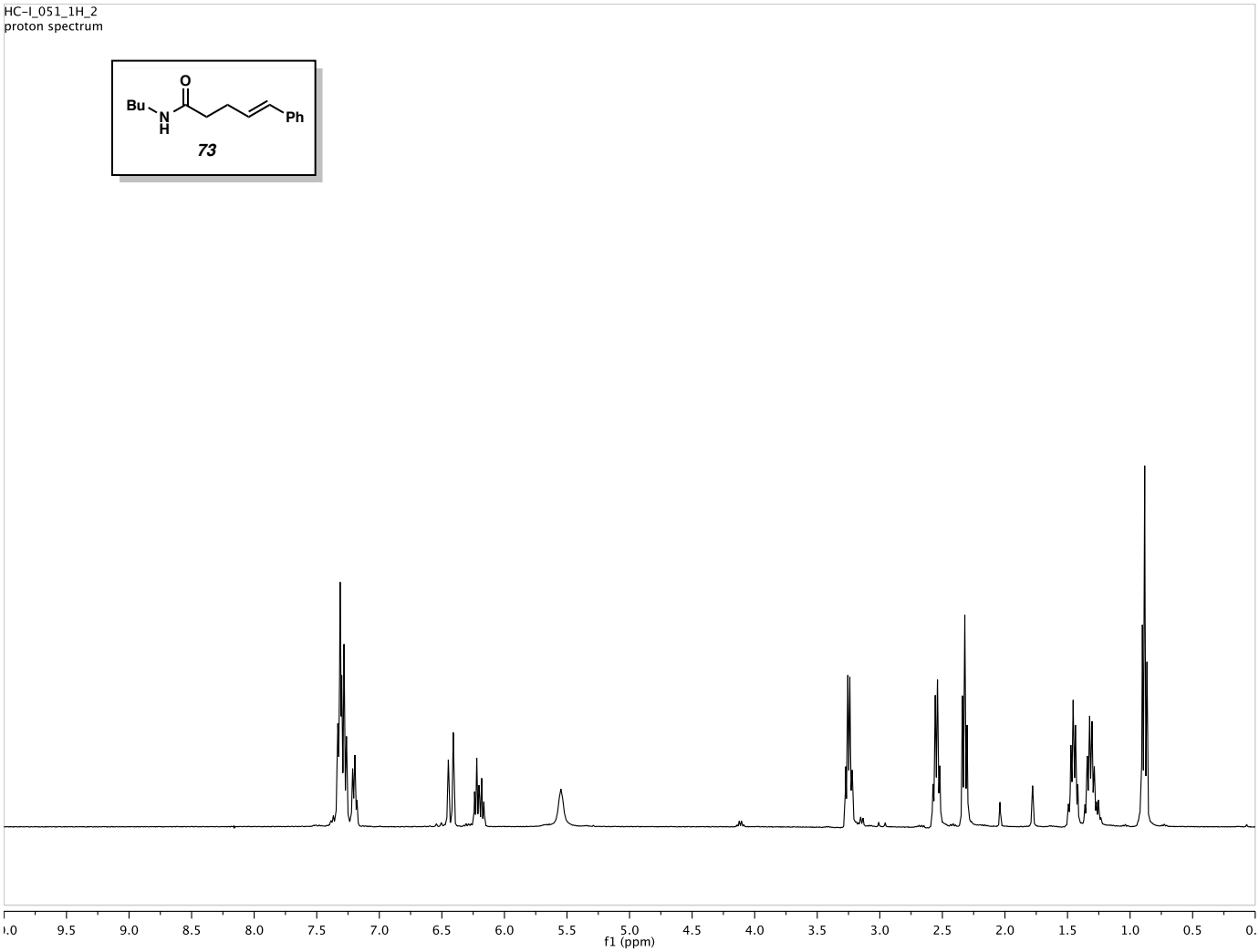
f1 (ppm)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proton spectrum
Bu
N
H
O
Ph
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9.5
9.0
8.5
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6.5
6.0
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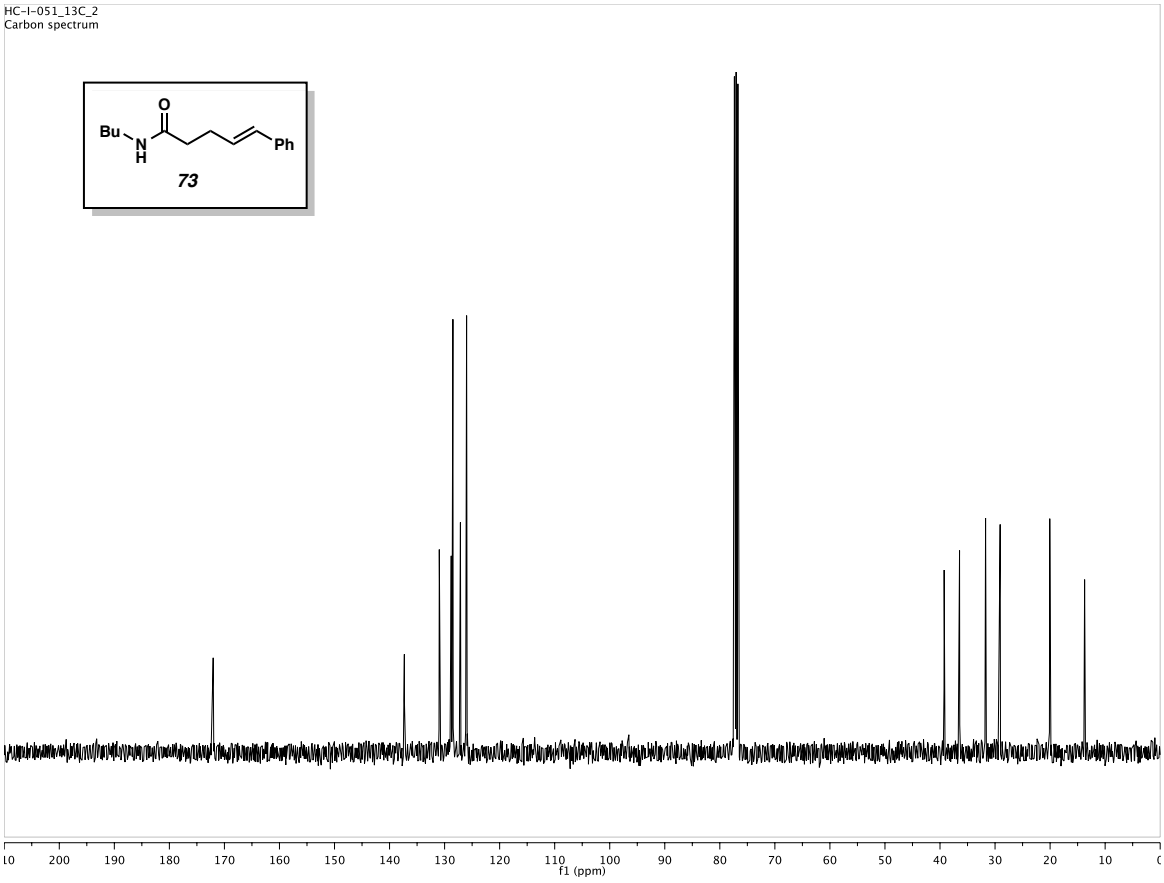
1.0
0.5
f1 (ppm)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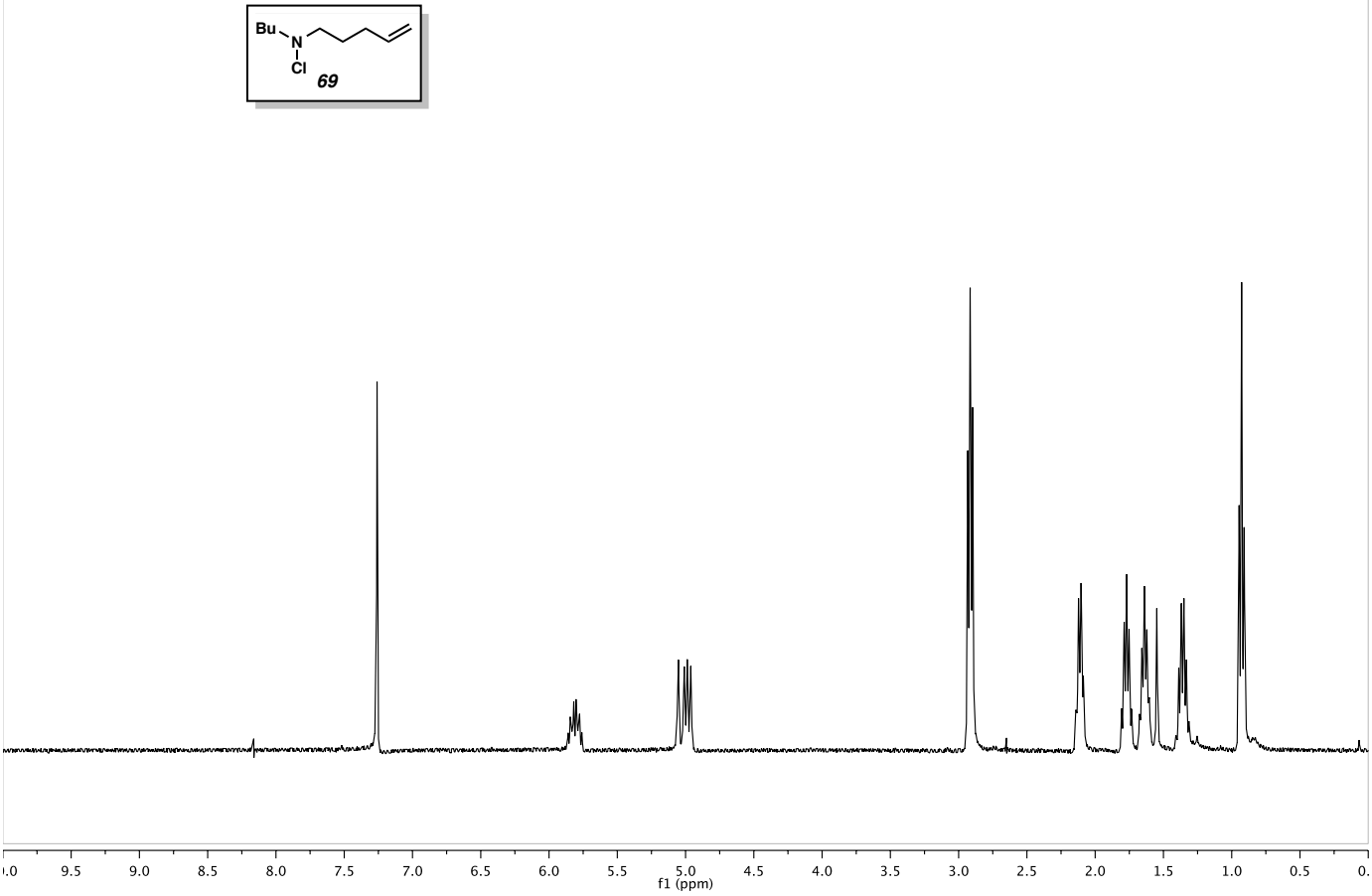
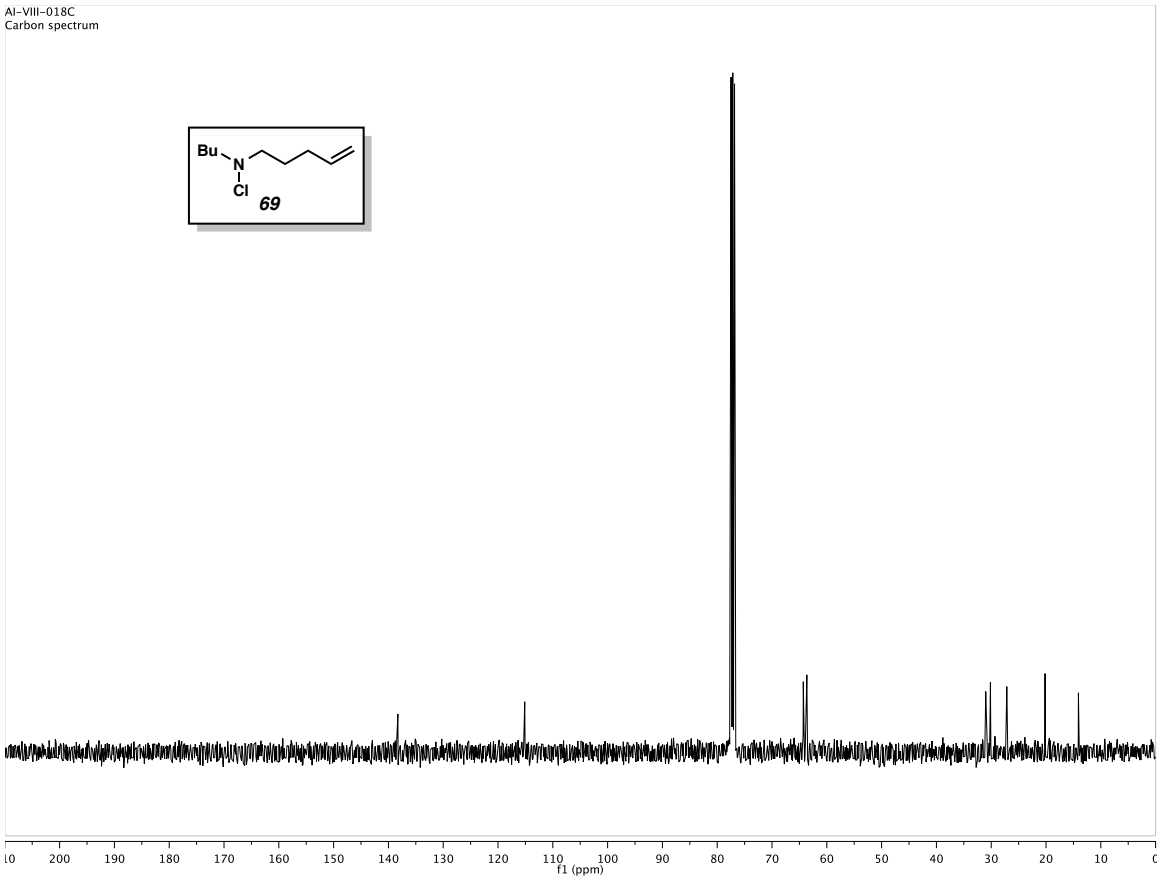
Carbon spectrum
Bu
N
H
O
Ph
73
f1 (ppm)

HC-I-025
proton spectrum

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N
Cl
69
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190
180
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90
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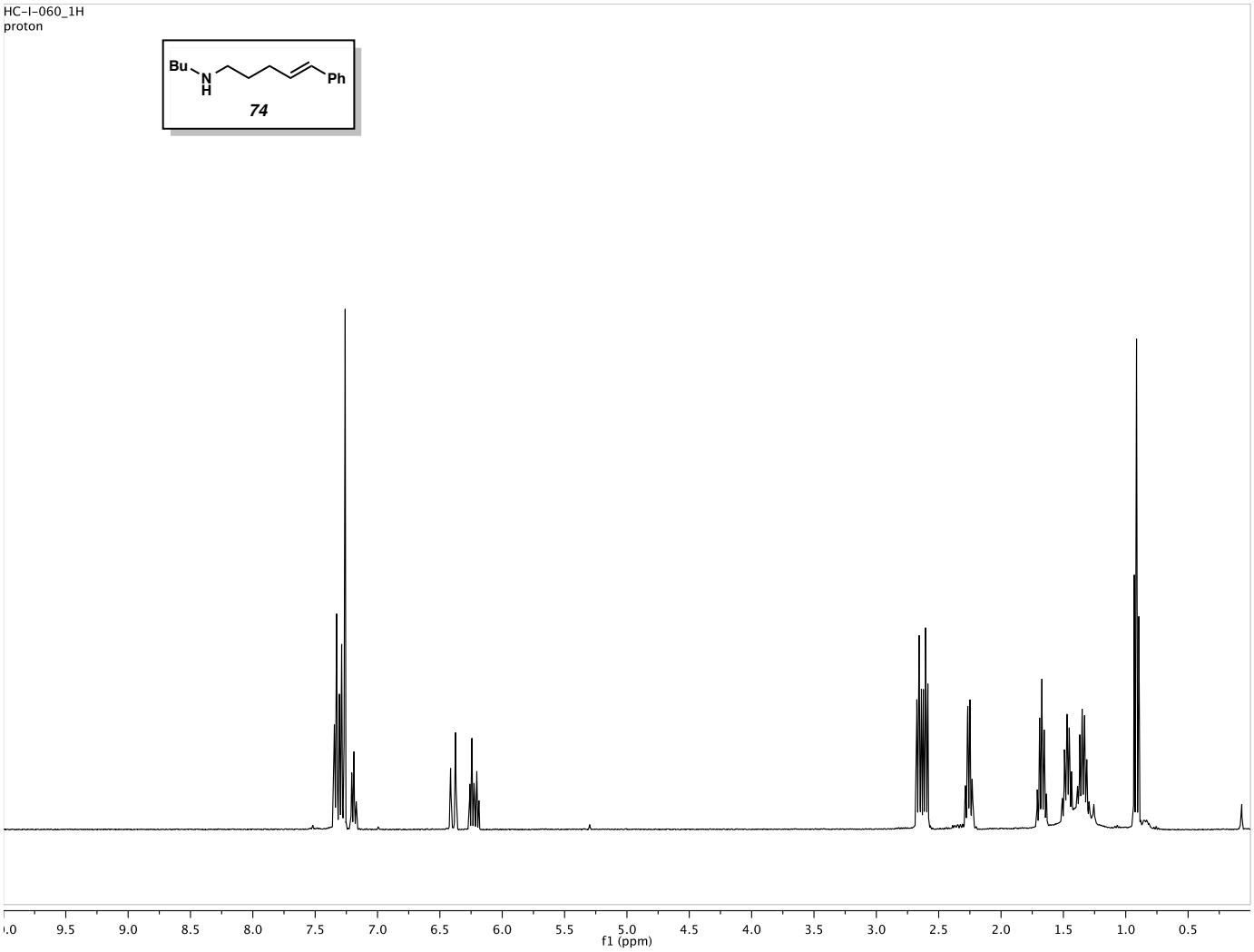
60
50
40
30
20
10
f1 (ppm)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H
Ph
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6.0
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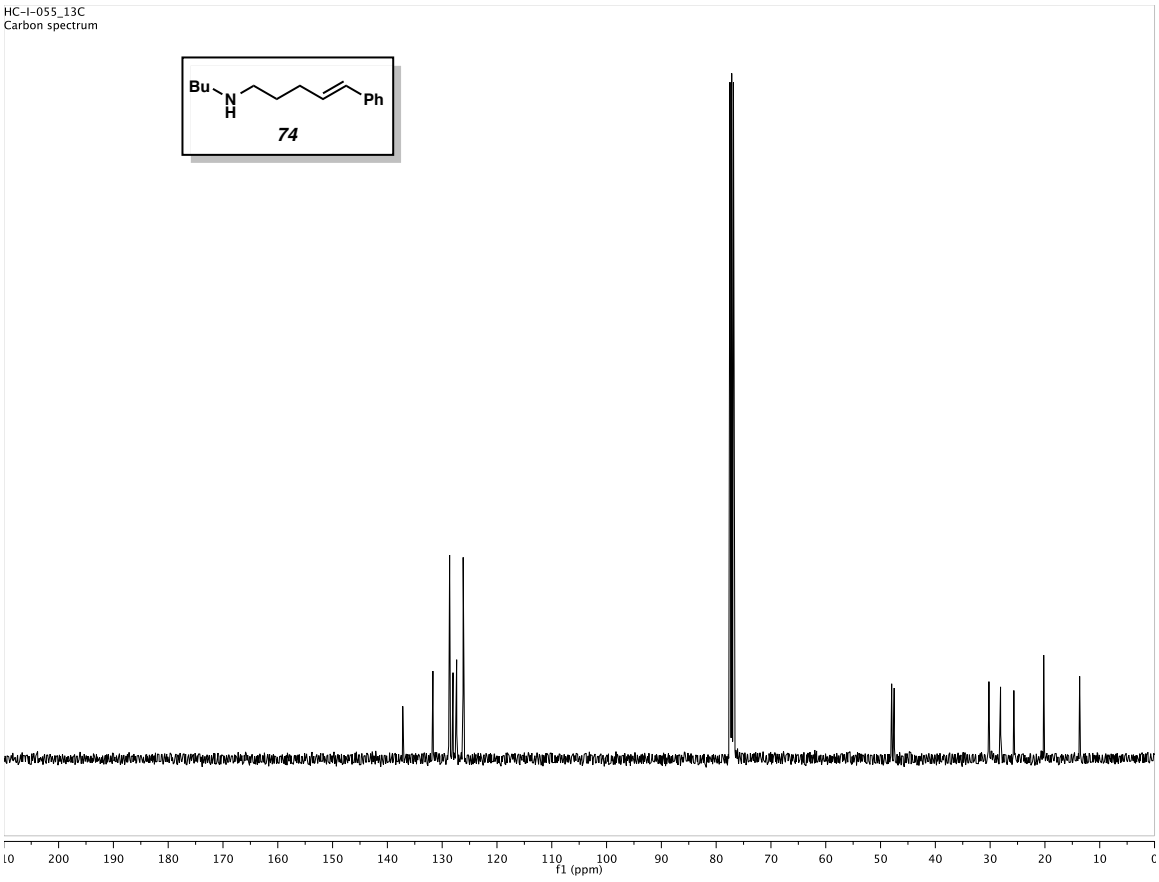
0.5
f1 (ppm)


HC-I-055_13C
Carbon spectrum
Bu
N
H
Ph
74
200
190
180
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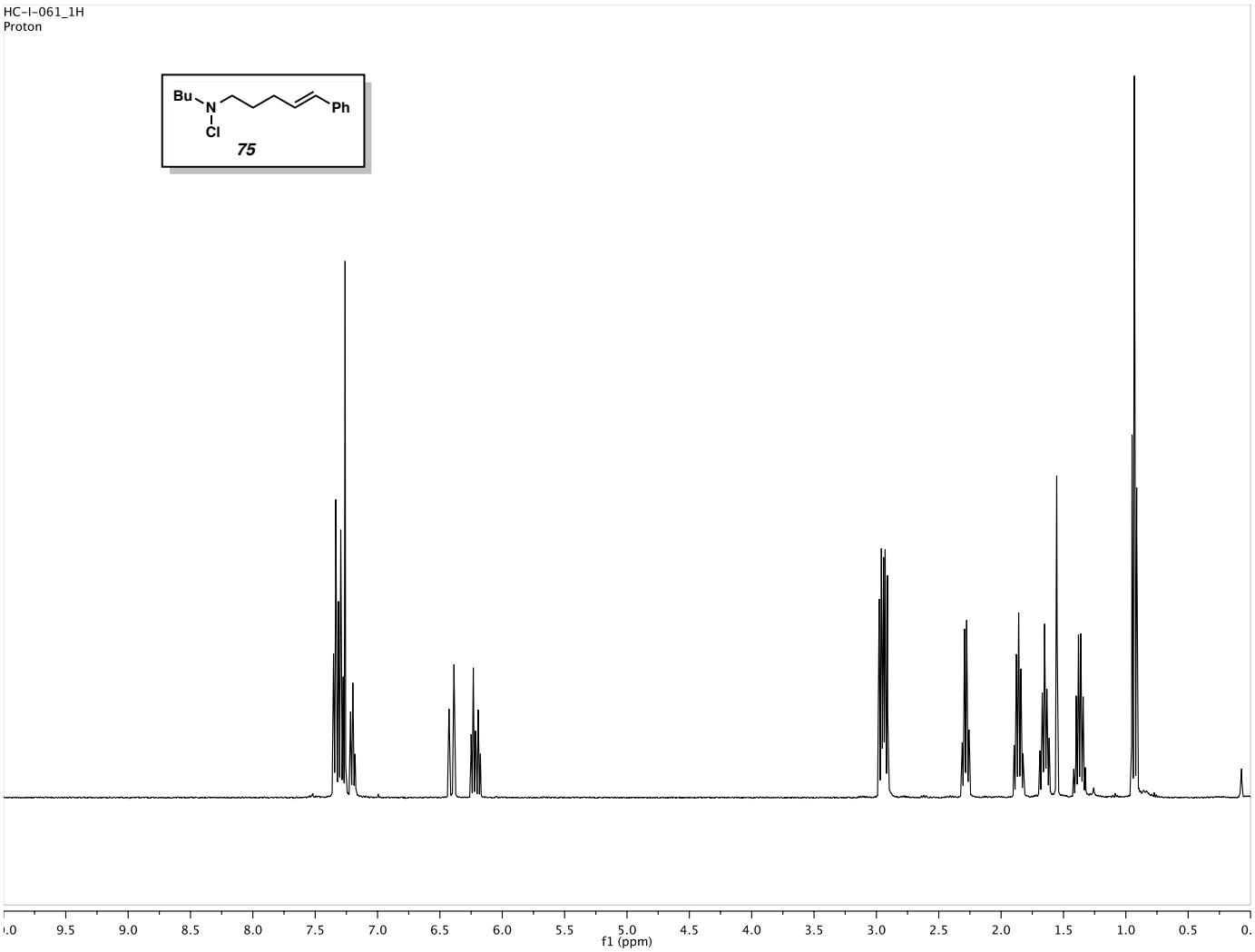
60
50
40
30
20
10
f1 (ppm)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Cl
Ph
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6.0
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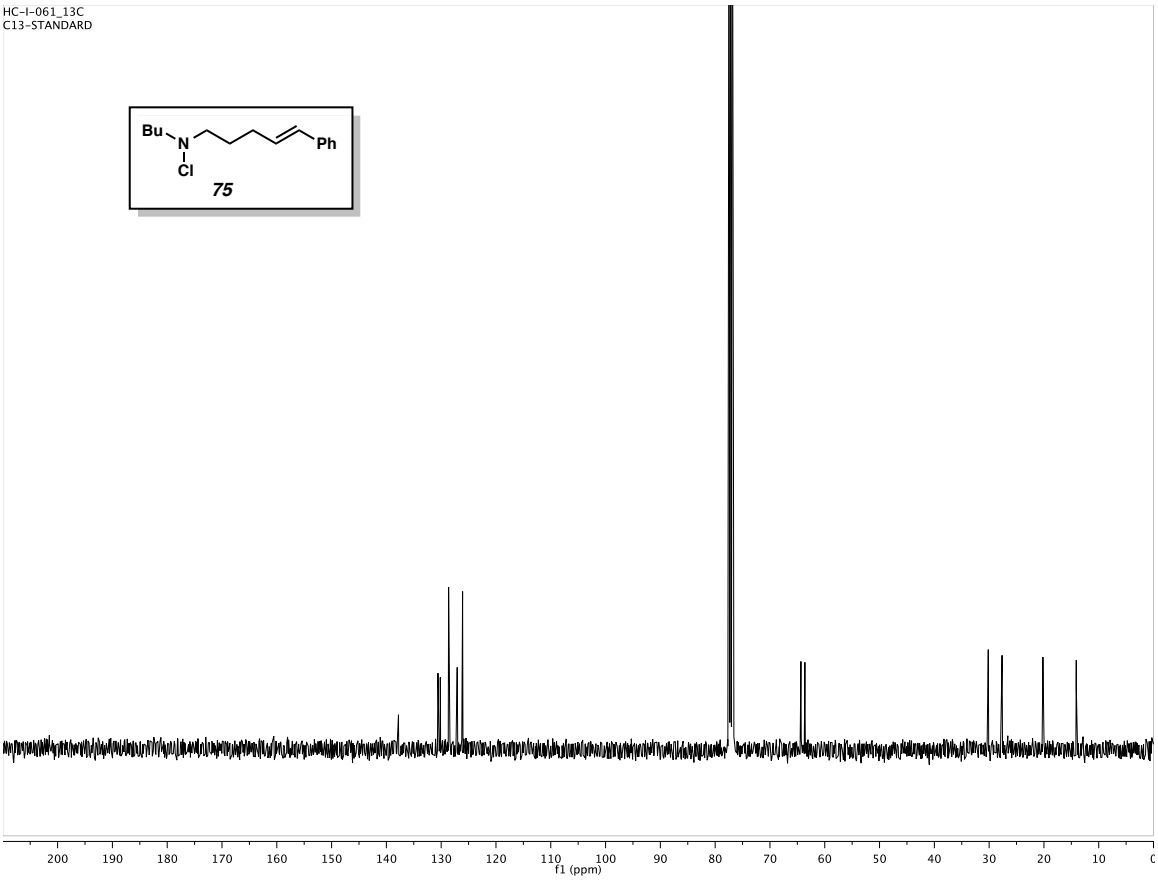
1.0
0.5
f1 (ppm)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C13-STANDARD
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N
Cl
Ph
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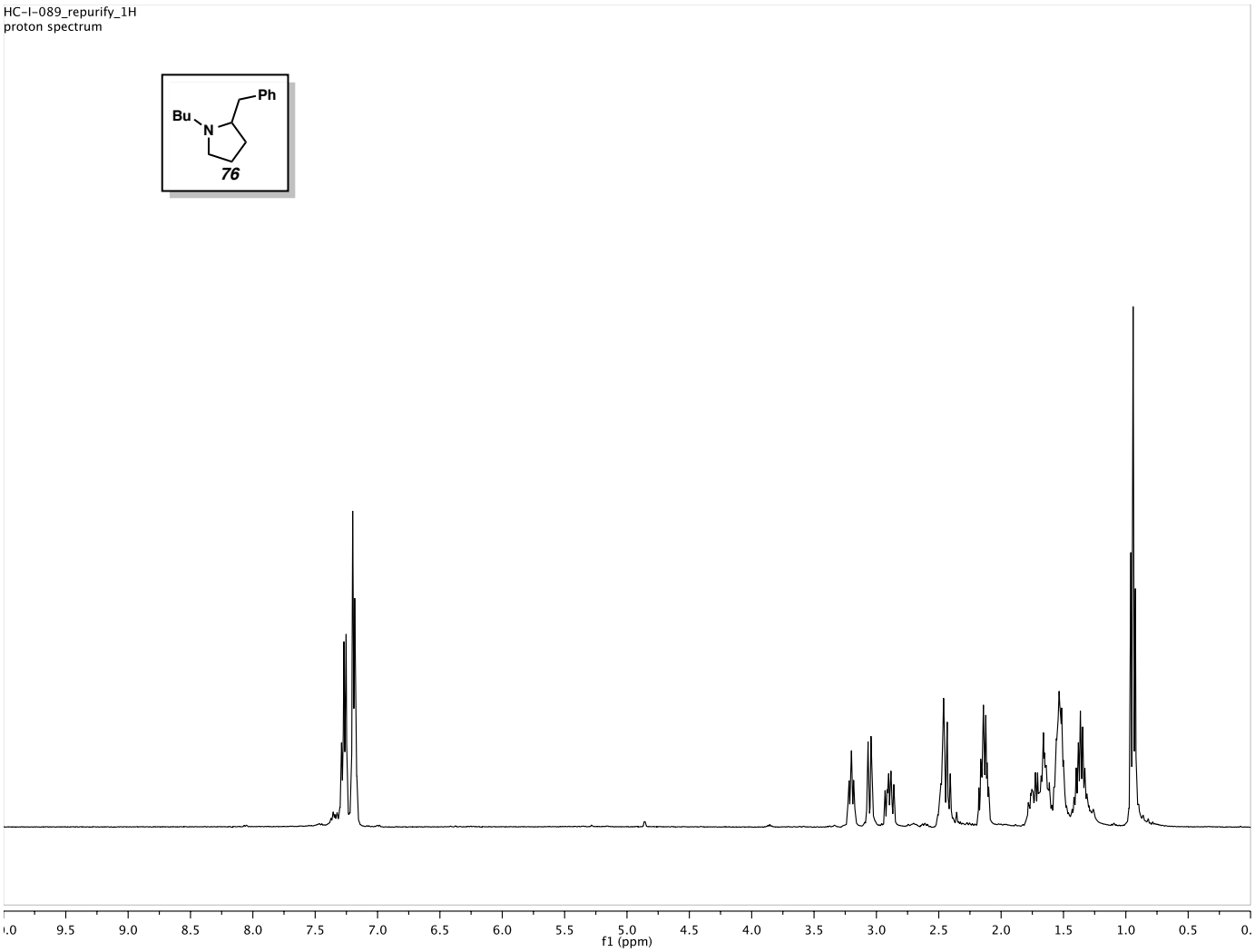
f1 (ppm)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proton spectrum
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6.0
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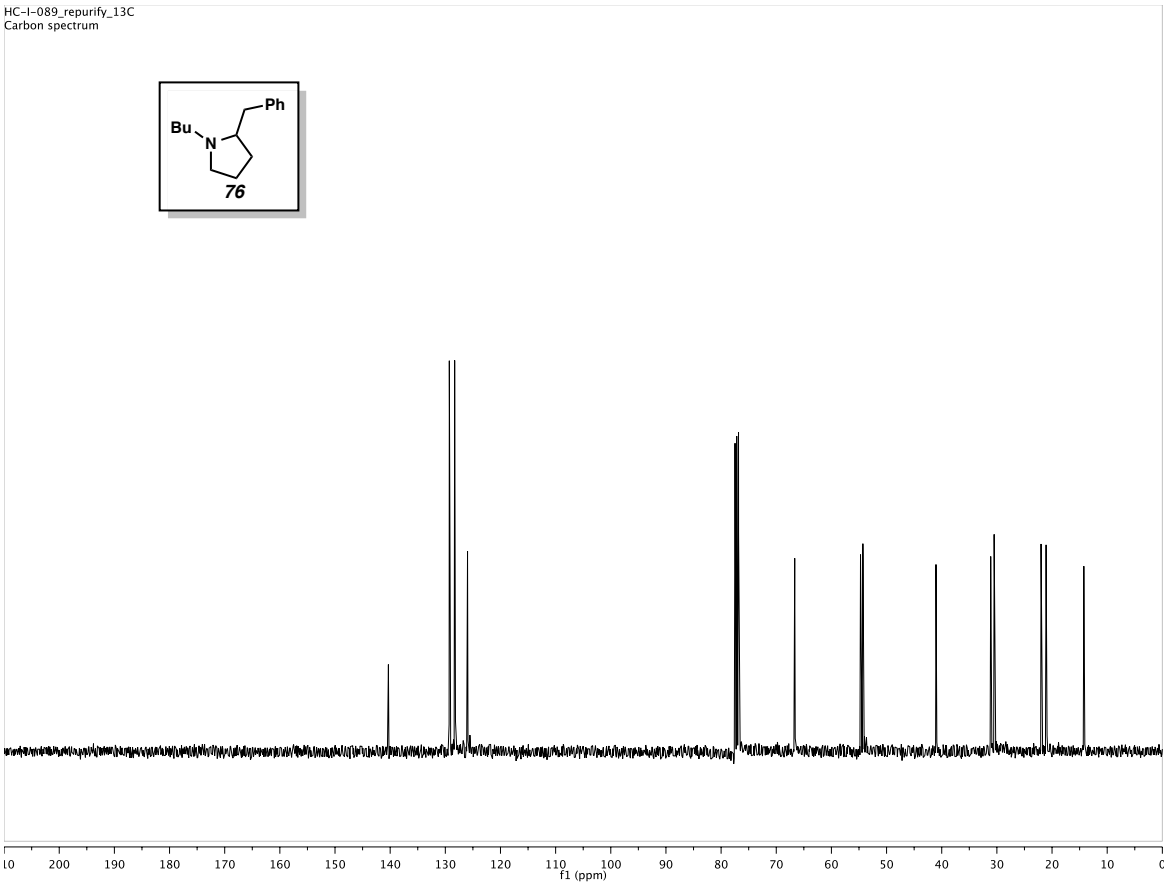
f1 (ppm)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Carbon spectrum
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N
Ph
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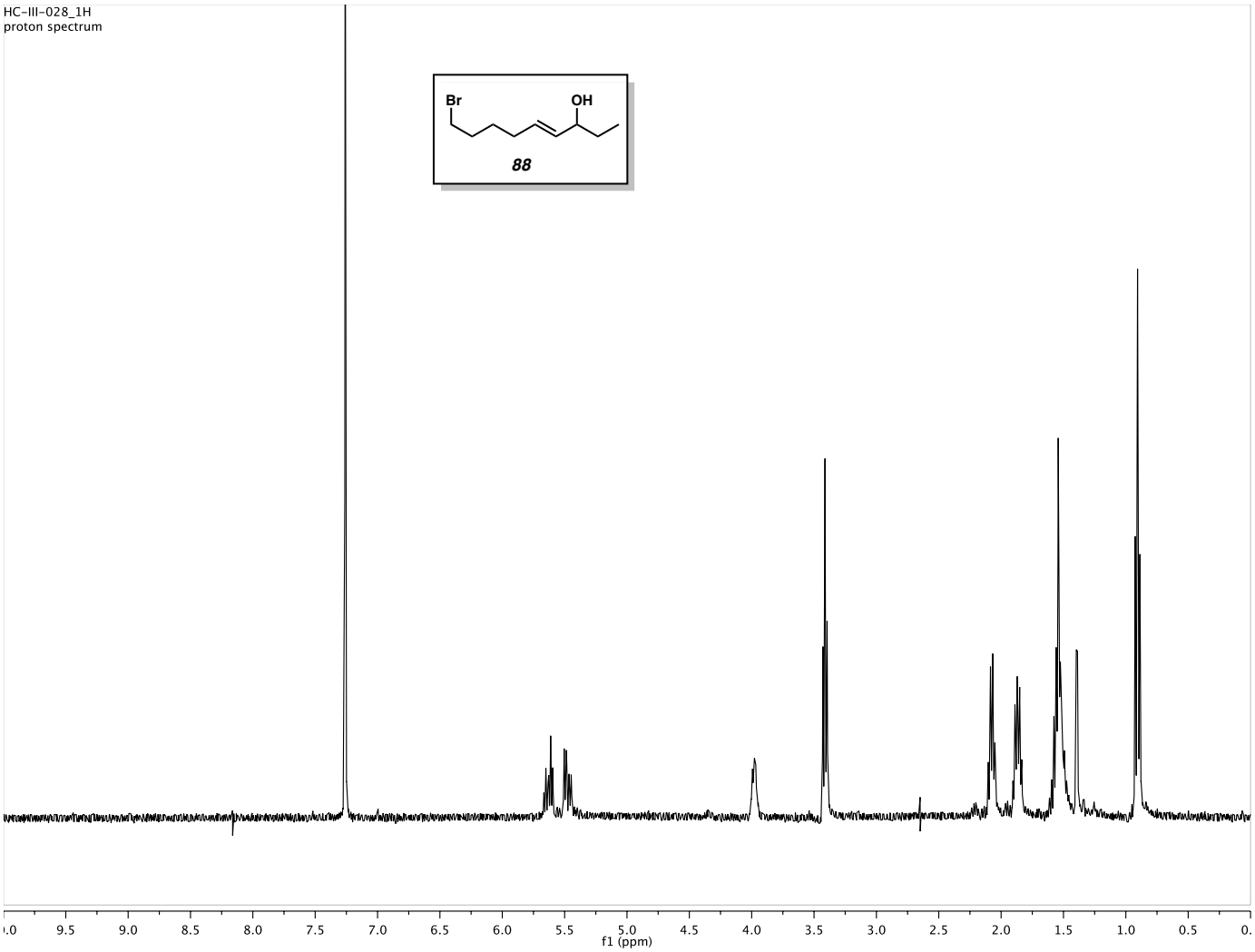
f1 (ppm)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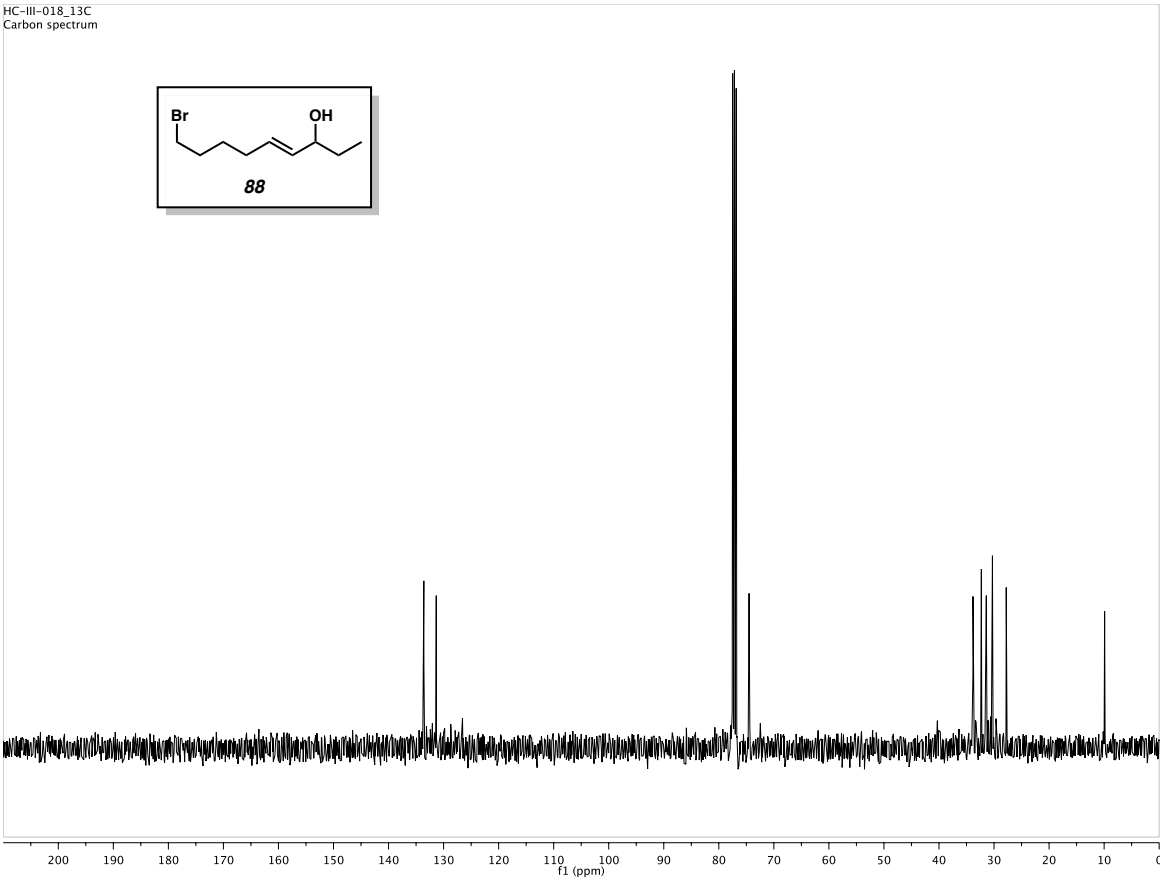
0.5
f1 (ppm)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Carbon spectrum
Br
OH
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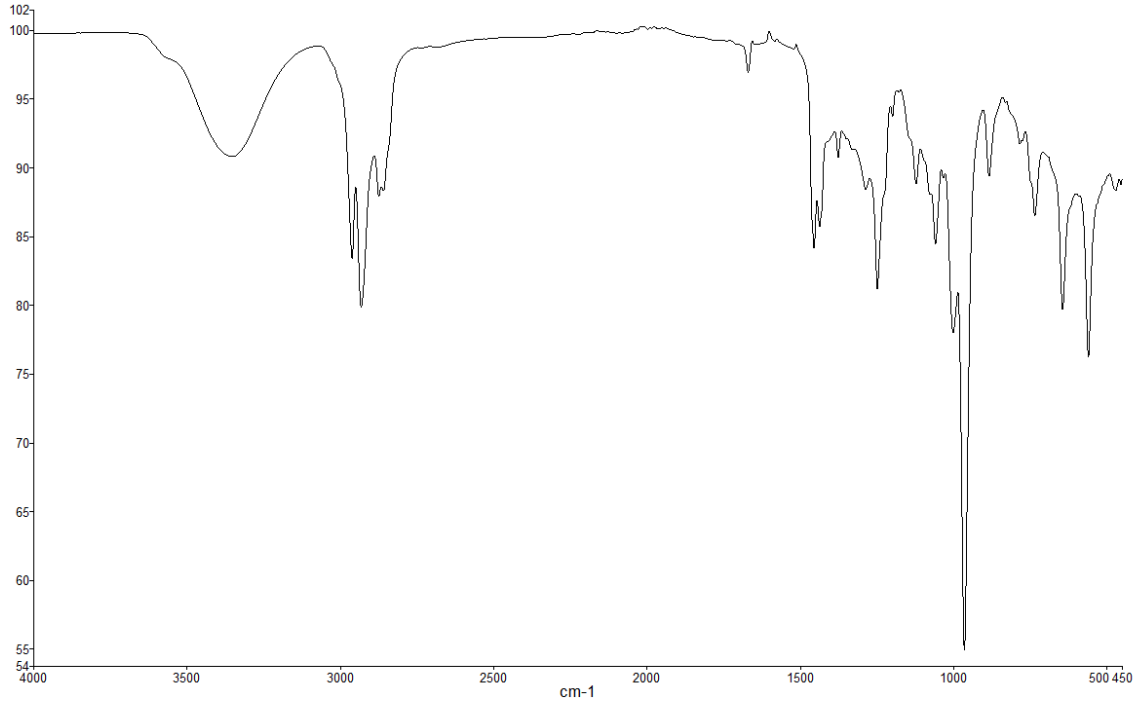
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70
65
60
55
54
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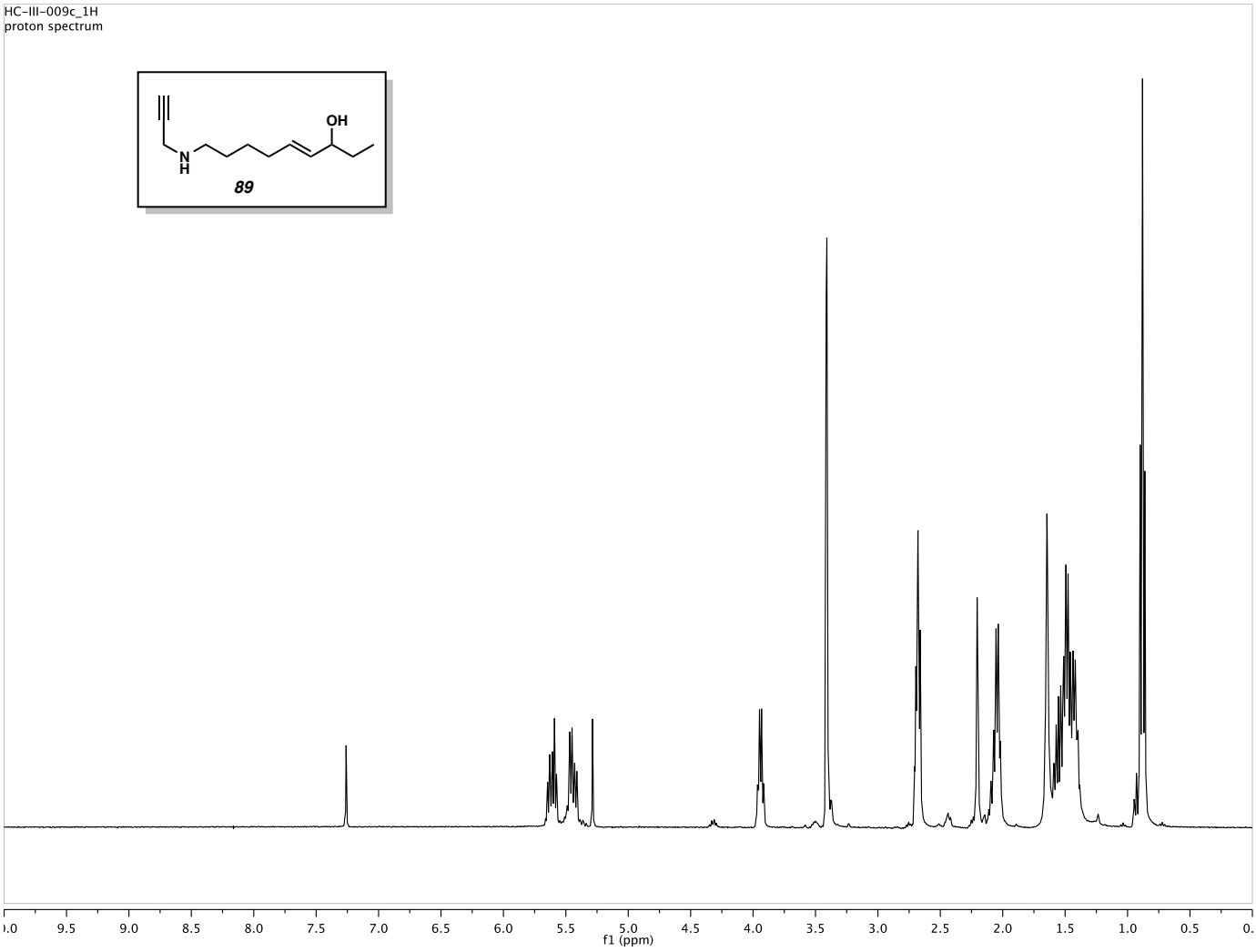
cm-1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OH
N
H
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6.0
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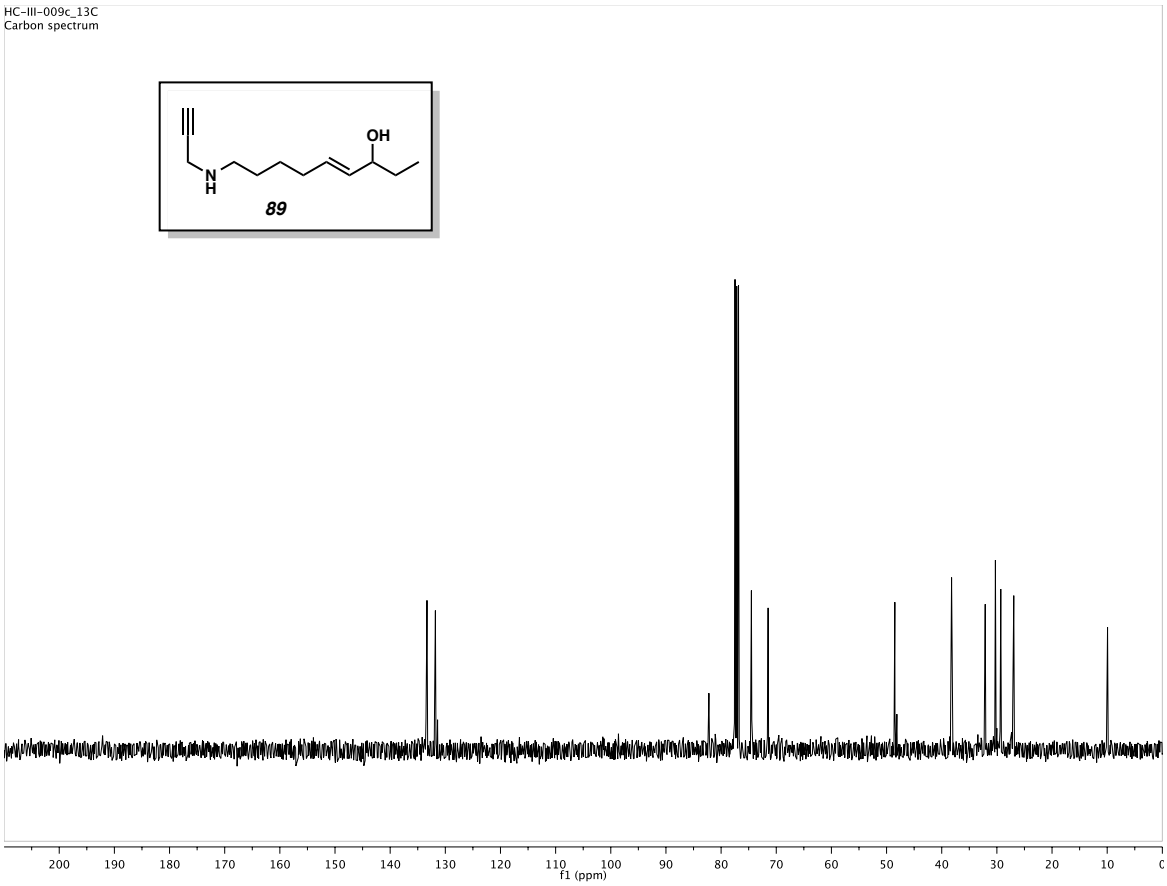
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H
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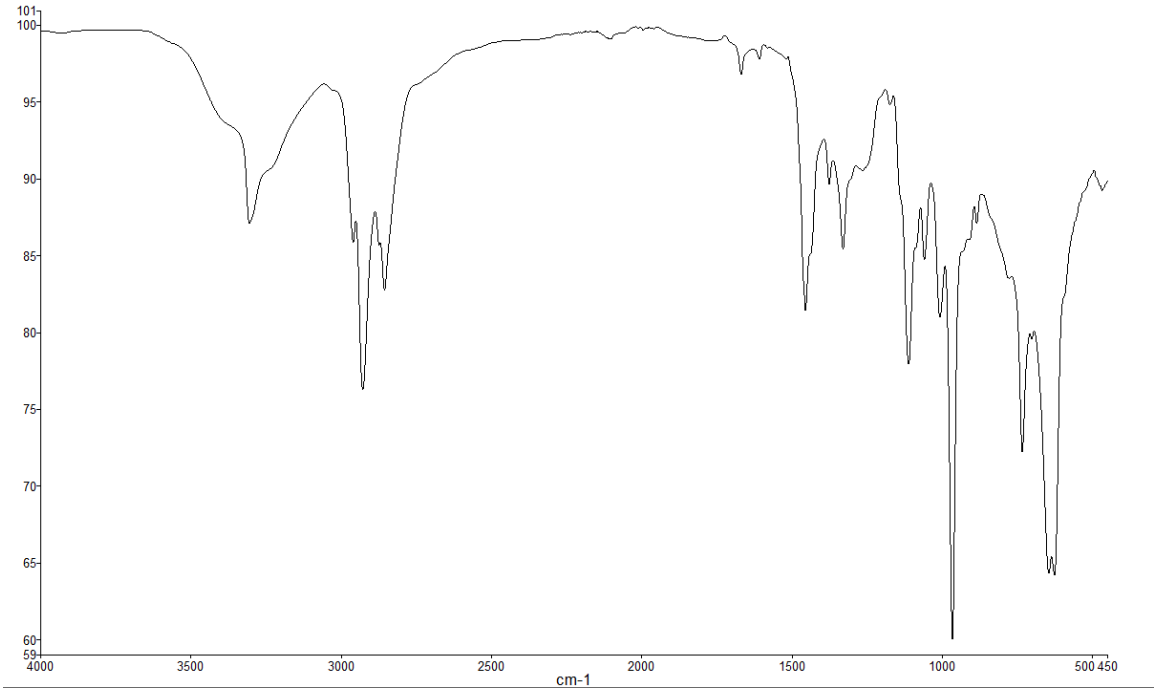
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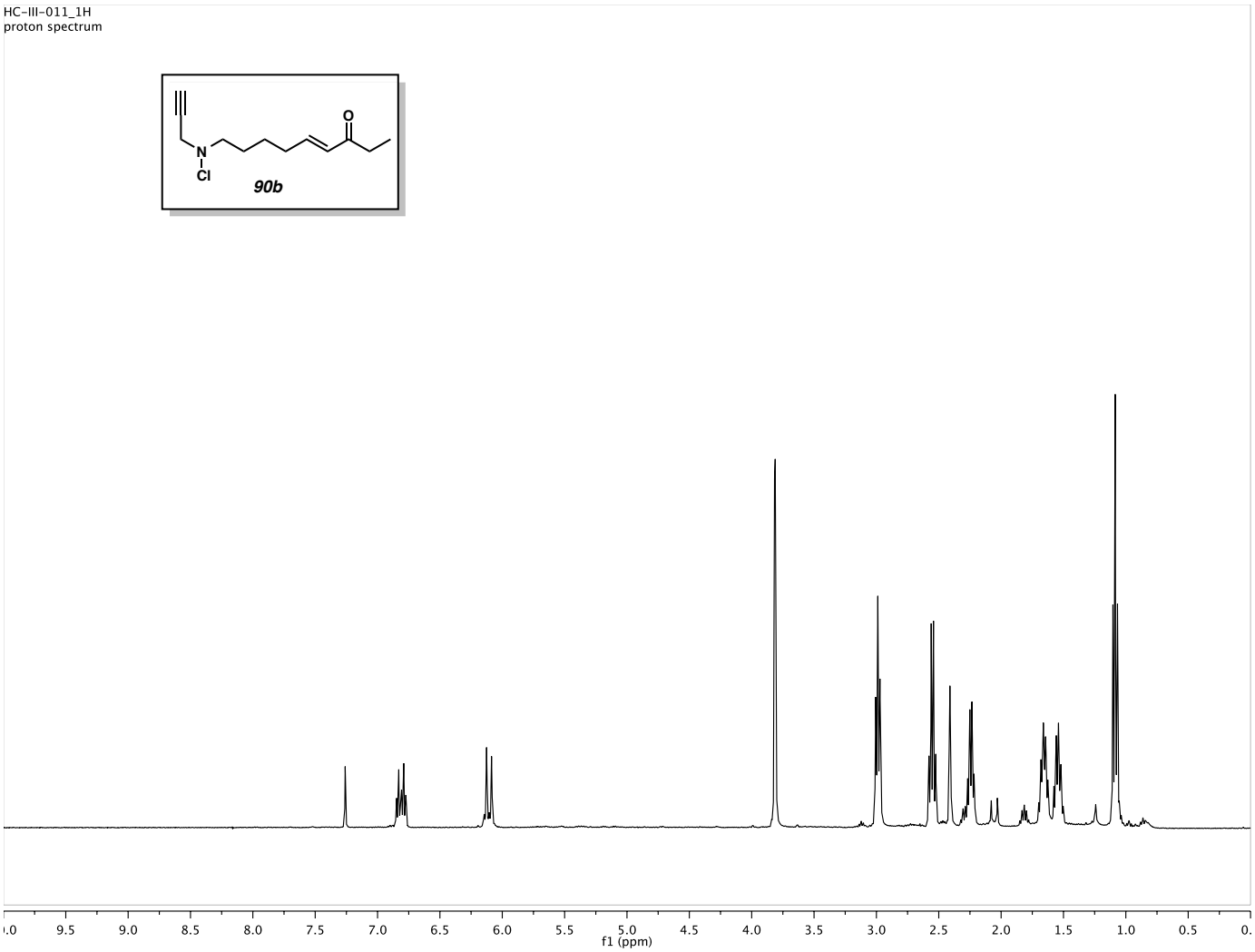
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Cl
90b
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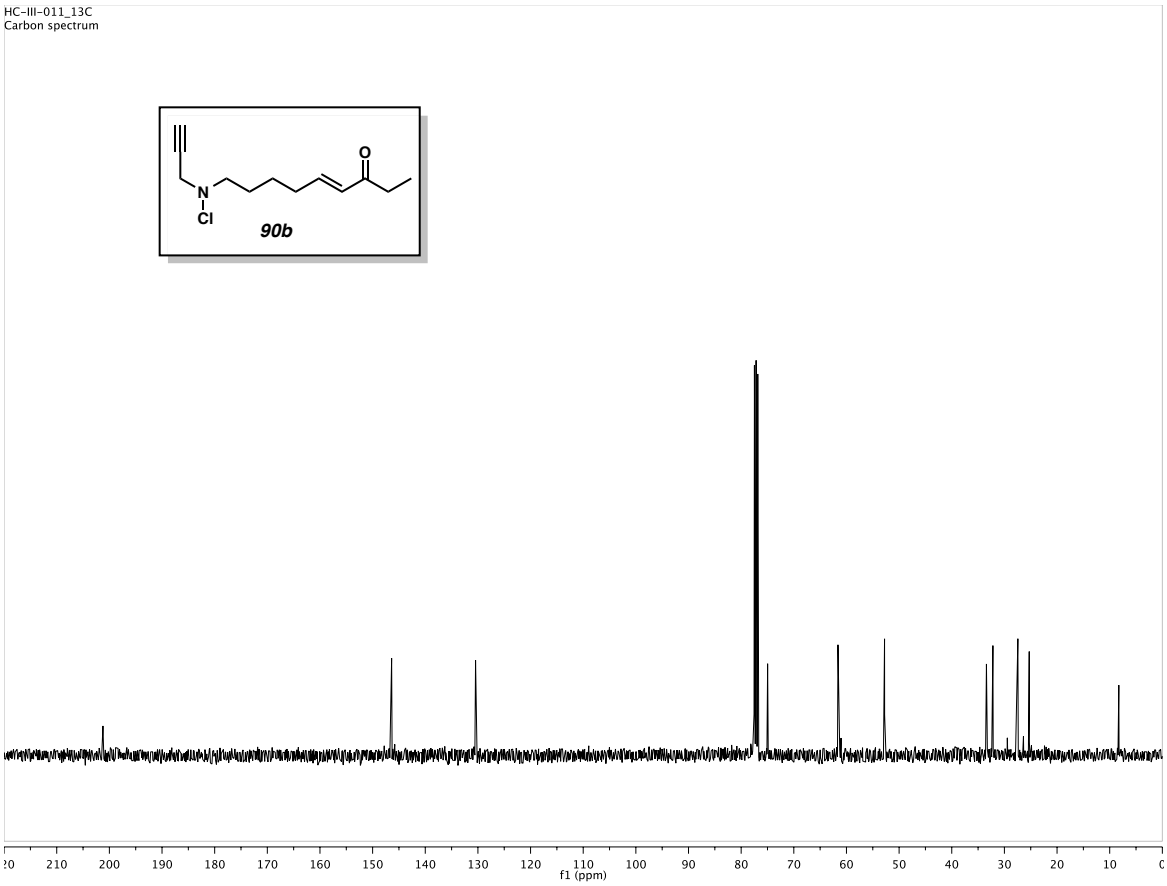
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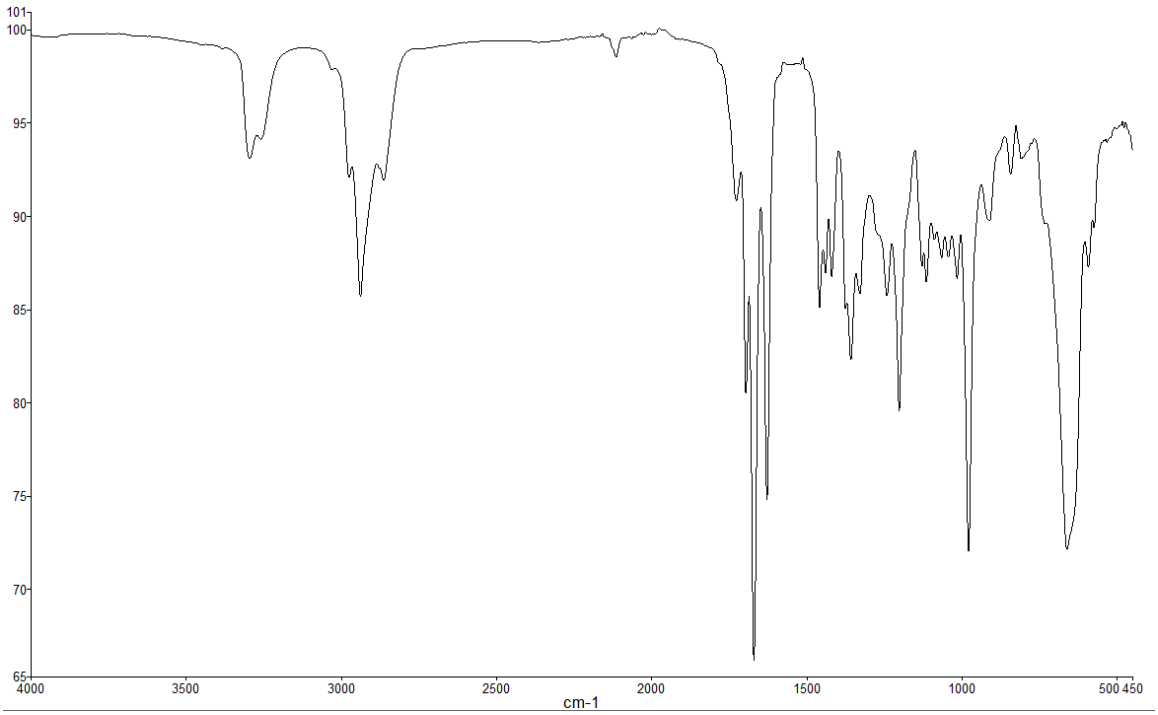
Carbon spectrum
O
N
Cl
90b
f1 (ppm)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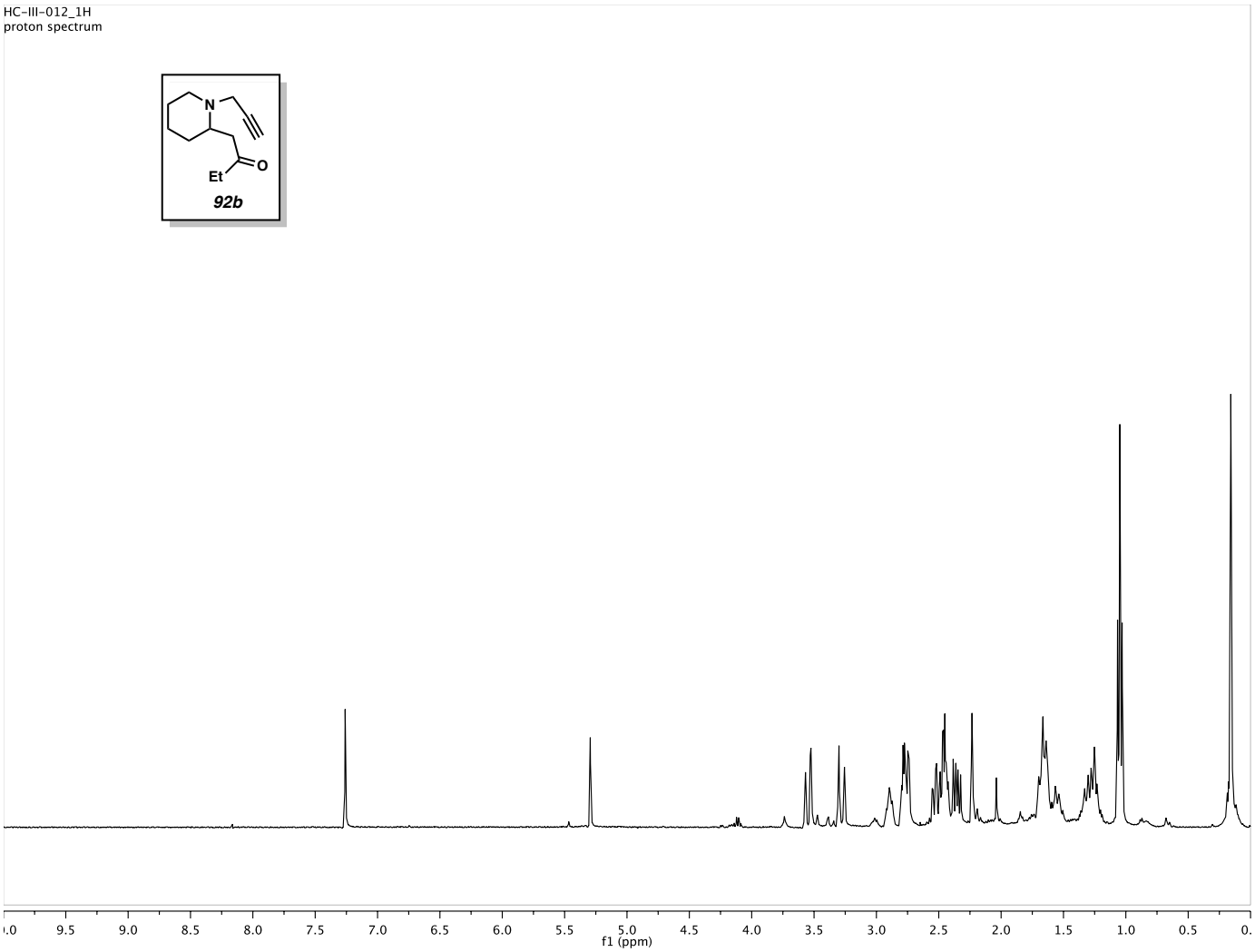
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proton spectrum
N
Et
O
92b
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9.0
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7.0
6.5
6.0
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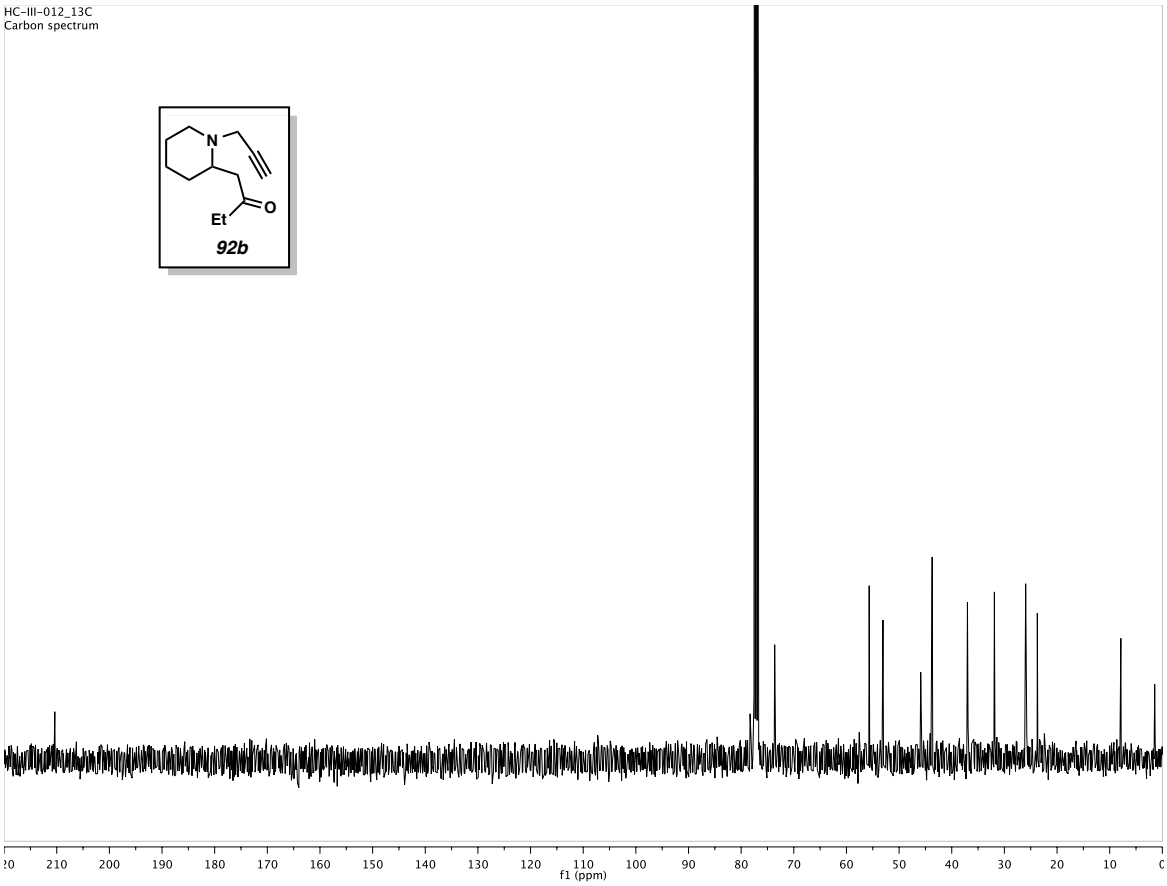
f1 (ppm)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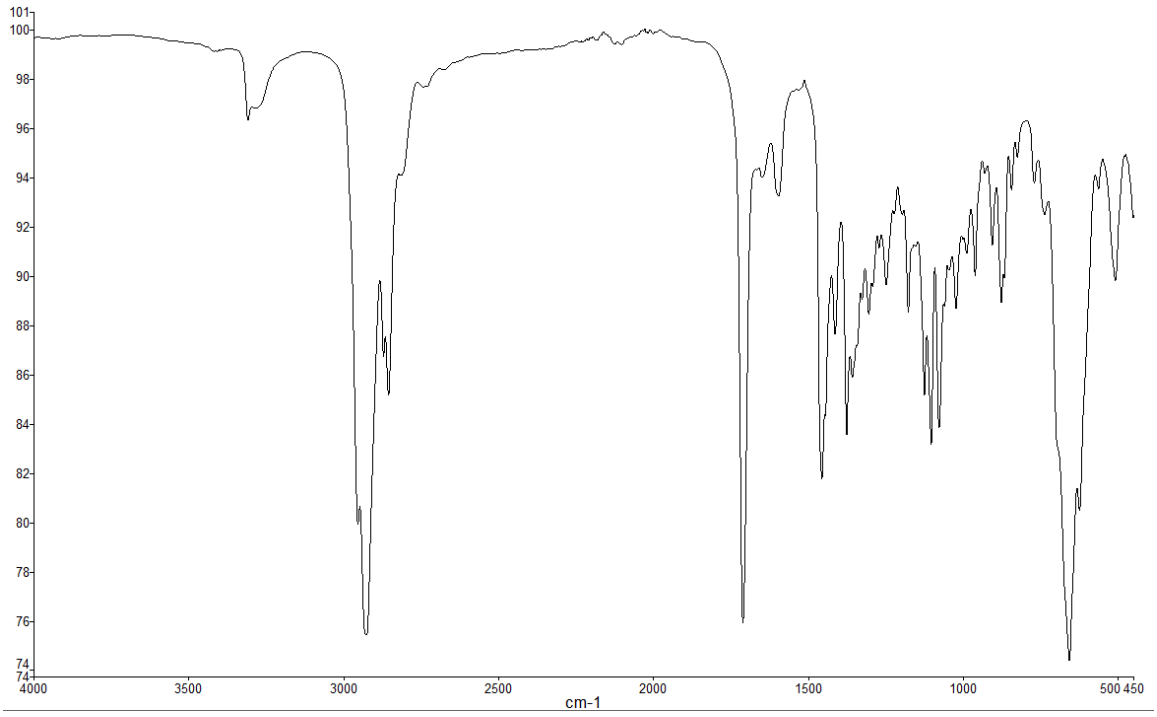
Carbon spectrum
N
Et
O
92b
f1 (ppm)


cm-1

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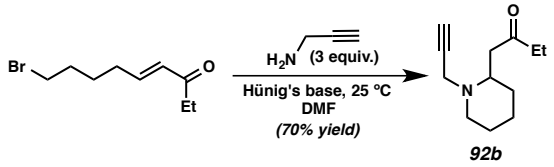
[36] The conjugate addition was observed in the following reaction:



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ABSTRACT

FACILE SYNTHESIS OF TERTIARY ALIPHATIC AMINE–CONTAINING CYCLIC MOTIF VIA NEUTRAL AMINYL RADICAL CYCLIZATION

by

HENG CHEN

MAY 2016

Advisor: Dr. Jennifer L. Stockdill

Major: Chemistry (organic)

Degree: Master of Science

Tertiary amine–containing cyclic motifs are prevalent in natural products and pharmaceutical lead targets. Inspired by these biological active molecules, one focus in our lab is the development of neutral aminyl radical chemistry in the synthesis of tertiary aliphatic amine–containing cyclic compounds. In this project, I investigated the mono- and tandem cyclization of aminyl radical with different types of olefins (terminal olefin, enone, and styrenyl). The effect of the hydrogen atom donor and the limitation of the reaction will be discussed.

AUTOBIOGRAPHICAL STATEMENT

Heng Chen was born in Fujian, China in 1991 and he moved to the United State with his parents at the age of ten. He received his B.S. in chemistry from Temple University in 2014. During his time in Temple, he worked at the laboratory of Professors Franklin Davis and Rodrigo Andrade on the total synthesis of alkaloids. In the transition between undergraduate and graduate studies, he was a summer intern at the medicinal chemistry department in Genentech, Inc. He began his graduate studies at Wayne State University working with Professor Jenn Stockdill. His graduate research is focus on development of aminyl radical chemistry in the synthesis of tertiary aliphatic amine–containing cyclic compounds. Heng began as an associate scientist II in the department of process chemistry at AbbVie in June 2016.