Intramolecular Cope-Type Hydroamination of Alkenes and Alkynes Using Hydrazides

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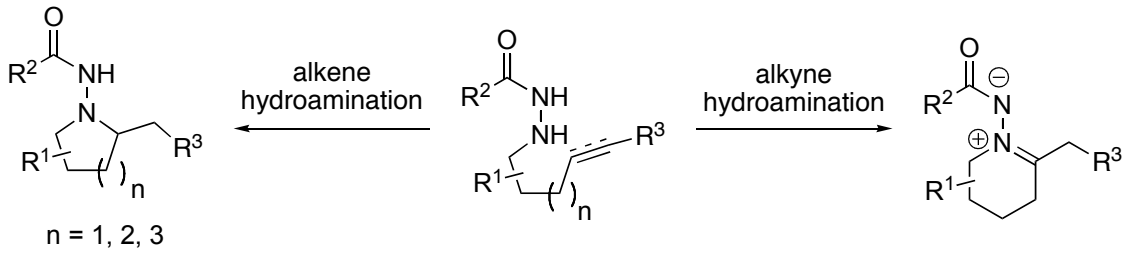
Abstract



Nitrogen-containing molecules are ubiquitous in both natural products and pharmaceutical drugs, thus an efficient method for the formation of these motifs is of great importance. Hydroamination, that is the addition of an N-H bond across an unsaturated carbon-carbon bond of an alkene or alkyne, stands out as a potential approach to obtain such molecules. To date, most research in this area relies on transition-metal catalysis to enable such reactivity. In efforts directed towards metal-free alternatives, we have developed a simple, metal-free hydroamination of alkenes using hydrazides. Further investigation into the corresponding reactivity of alkynes with hydrazides has provided access to novel azomethine imine products. In Chapter 2, expansion of the substrate scope with respect to the intramolecular hydroamination of alkenes using hydrazides, as well as studies directed towards elucidation of the mechanism of this reaction will be presented. The intramolecular hydroamination of alkynes using hydrazides and methods to access and isolate the azomethine imine products formed will be discussed in Chapter 3.

Acknowledgements

As I'm sitting here writing my thesis, I still can't believe that I'm at this point! It seems crazy to think that I've been in university for 7 years now… When I decided to do my Master's, I knew that it would be a challenge, but I was excited to be ending one chapter and starting another.

The last 2 years have been a whirlwind, there were many moments when I wasn't sure if I had made the right choice, when truthfully, I wasn't sure whether I would make it through. But what helped me were the people… My supervisor André Beauchemin, by far the most passionate chemist that I've ever met, was full of support, encouragement and who was always there to push me beyond limits that I thought were unreachable. To Jean, who trained me when I first started in the lab, I will never forget to run a TLC before rotovaping ever again!! I thank Isabelle and Francis, who both suffered through incessant questioning, whether it be about a lab prep or the latest group meeting question that I could not for the life of me comprehend, and who provided unwaivering friendship along the way. To Christian, my fellow labmate… I will always remember our mutual love for Micheal Jackson, your great music mixes and your dancing (which is much better than mine!). Pete, I am very grateful for our friendship, we've struggled through our master's together (me more than you)… you've always been there to listen, to help and you were always willing to have a few beers and just hang out. To the rest of the group, past and present; Matt, Toni, Jenn, Joe, Nick, Tom, Sandrine, Amy, Hao… thanks for all of the amazing memories.

Last, but not least… to my family. Mom and Dad, you have both given me so much, so many words of wisdom, so much support, you've made me the person that I am today yet always given me the freedom to live my life my way… thanks for always believing in me and reminding me to have the confidence to believe in myself. To Chris, I will be forever grateful to have you in my life, you've been my rock through countless difficult times and my partner in crime through all the good ones!! Aimee, Ryan and Kristy, Nana, Blake and Debbie and the Pierces, you've all had a part in helping me get to where I am today, thank you!

And with that said… I now look forward to the next chapter, whatever that will bring!

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Abbreviations

aq.	aqueous
calcd	calculated
cat.	catalyst or catalyzed
$CHCl_3$	chloroform
CO_2	carbon dioxide
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DMF	dimethylformamide
GC/MS	gas chromatography/mass spectrometry
ee	enantiomeric excess
equiv.	molar equivalents
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Δ	heat
HRMS	High Resolution Mass Spectrometry
h	hours
HCl	hydrochloric acid
H_2O	water
i-PrOH	isopropanol
i-Pr	isopropyl

KIE	kinetic isotope effect
$KMnO_4$	potassium permanganate
LiHMDS	lithiumhexamethyldisilizane
MHz	megahertz
mL	milliliters
M	molarity
MeCN	acetonitrile
MeOH	methanol
mg	milligrams
min	minutes
mmol	millimolar
n-BuOH	normal butanol
n-Bu	normal butyl
n-PrOH	normal propanol
NMR	Nuclear Magnetic Resonance
$PhCH_3$	toluene
$PhCF_3$	α,α,α,-trifluorotoluene
ppm	parts per million
quant.	quantitative
R_f	rate of flow (coelution coefficient)
r.t.	room temperature
t-butanol	tertiary butanol
t-Bu	tertiary butyl

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
TS	transition state
μL	microlitre
μm	micromolar
μw	microwave
vs	versus

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Chapter 1: General Hydroamination Reactivity

Chapter 1: General Hydroamination Reactivity

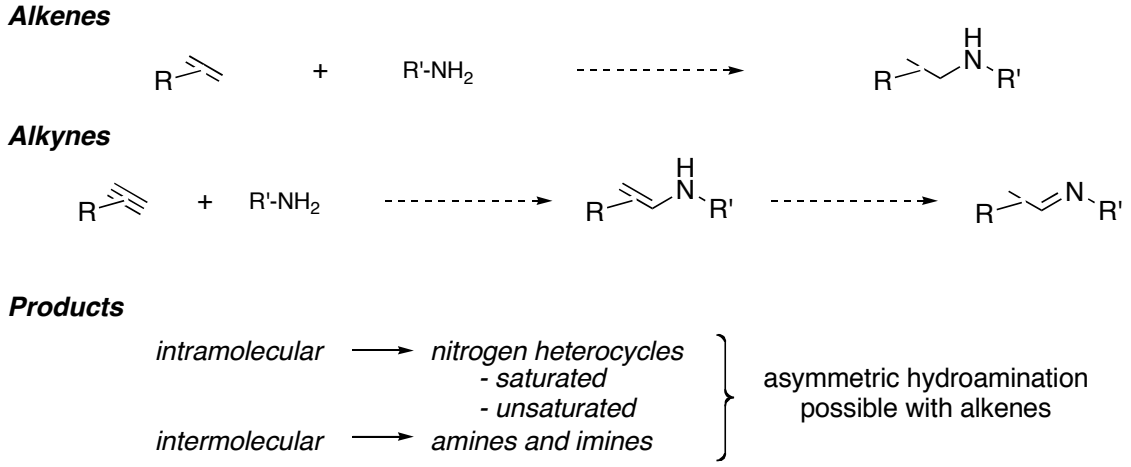
1.1. Hydroamination as a Desirable Synthetic Transformation

Due to the prevalence of nitrogen-containing molecules in both natural products and pharmaceuticals, efficient methods for the formation of these motifs is of great importance.[1] Hydroamination, that is the addition of an N-H bond across an unsaturated carbon-carbon bond of an alkene or alkyne stands out as a potentially general approach to obtain such molecules. Recent investigations into hydroamination reactivity have shown this potential.[2] Amines and imines can be attained through the conversion of alkenes and alkynes respectively and both saturated and unsaturated nitrogen heterocycles can be generated by intramolecular hydroamination (Scheme 1.1). In addition, when carried out asymmetrically on alkenes, access to chiral amines and heterocycles becomes possible. However, hydroamination reactivity still presents many challenges and remains underdeveloped and underutilized in synthesis.

[1] (a) Duggers, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Proc. Res. Dev.* **2005**, *9*, 253. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

[2] For selected reviews see (a) Minatti, A.; Muniz, K. *Chem. Rev.* **2007**, *36*, 1142. (b) Severin, R.; Doye, S. *Chem. Rev.* **2007**, *36*, 1407. (c) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Pohlki, F.; Doye, S. *Chem. Rev.* **2003**, *32*, 104. (f) Molander, G. E.; Romero, J. A. C. *Chem. Rev.* **2002**, *102*, 2161. (g) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *8*, 344. (h) Beller, M.; Briendl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, *10*, 1579. (i) Muller, T. E.; Beller, M. *Chem Rev.* **1998**, *98*, 675. (j) Johannsen, M.; Jorgenson, K. A. *Chem. Rev.* **1998**, *98*, 1689.

Scheme 1.1: Synthetic Potential of Hydroamination



1.2. Overview of Hydroamination Methods in Literature

One of the main problems encountered in hydroamination chemistry is caused by the electrostatic repulsion between the electron-rich π bond and the nitrogen lone pair. This interaction results in a high activation energy, making it more difficult for the reaction to proceed.[3] Several approaches to circumvent this issue, such as acid and base-catalyzed hydroamination and transition metal catalysis, have been reported in the literature.

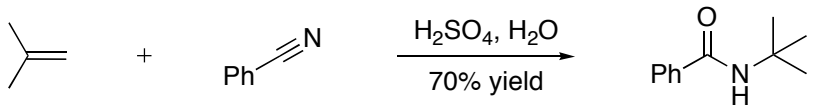
1.2.1. Acid-Catalyzed Hydroamination

Acid-catalyzed reactions, which require high temperatures and provide low yields, were first reported by Hickinbottom in 1932 in an attempt to overcome this

[3] Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306.

activation issue.[4] Such reactions are specific and dependent on amine basicity, as the nitrogen atom can buffer the effect of the acid and prevent protonation of the π bond. In these cases, the nitrogen atom also loses its nucleophilicity as it becomes protonated.[5]

Despite these issues, examples of the intermolecular and intramolecular hydroamination of alkenes and alkynes has been shown to proceed with the use of catalytic amounts of acid in combination with deactivated nitrogen nucleophiles.[6] The Ritter amination, an intermolecular hydroamination, relies on acid catalysis. In such processes, protonation of the alkene **(1.1)** with strong acid allows for attack by the nitrile **(1.2)**, forming the Markovnikov product **(1.3)** in reasonable yield (Equation 1.1).[7]

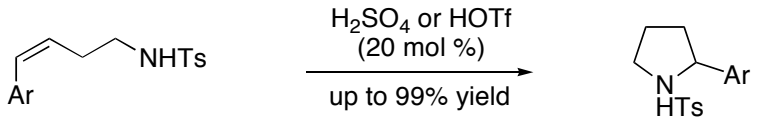


1.1 **1.2** **1.3** **(1.1)**

Most acid-catalyzed hydroamination reactions require the use of biased systems, using alkenes that are strained or highly reactive that generate a stable carbocation and nitrogen nucleophiles that are less-basic and thus slightly deactivated. Schlummer and Hartwig reported that in the presence of substoichiometric quantities of triflic acid, the intramolecular hydroamination of aminoalkenes **(1.4)** provided access to the respective

[4] (a) Hickinbottom, W. J. *J. Chem. Soc.* **1932**, 2646. (b) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 319. (c) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 1981.
[5] For a review see: Krimen L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.
[6] (a) Muller, T. E.; Berger, M.; Grosche, M.; Herdtweck, E.; Schmidtchen, F. P. *Organometallics* **2001**, *20*, 4384 (b) Penzien, J.; Su, R. Q.; Muller, T. E. *J. Mol. Catal. A: Chem.* **2002**, *182*, 489 (c) Mizuno, N.; Tabata, M.; Uematsu, T.; Iwamoto, M. *J. Catal.* **1994**, *146*, 249.
[7] (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045 (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.

pyrrolidines **(1.5)** and piperidines (Equation 1.2).[8] However, tosylation of the amine was preferred in order to reduce the basicity of the amine, thus preventing its protonation.



1.4 **1.5** **(1.2)**

Although examples have been reported, acid-catalyzed hydroaminations are restricted in substrate scope and have limited compatibility with regard to functional groups.

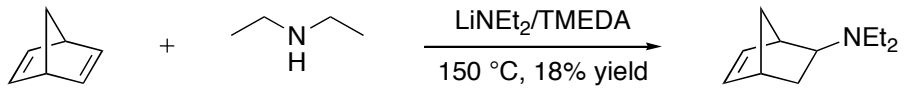
1.2.2. Base-Catalyzed Hydroamination

Base-catalyzed hydroamination has also been reported in the literature as a possible solution, but again this method presents several limitations. Functional group tolerance is decreased as only groups that are less acidic than the amine are allowed, and biased alkenes are typically used.[9]

Lemkuhl obtained hydroamination products upon the reaction of 2,5-norbornadiene **(1.6)** with diethylamine (**1.7,** Equation 1.3) when using lithium diethylamide in combination with tetramethylethylenediamine.[9c] It was observed that

[8] Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.
[9] For examples of base-catalyzed hydroamination see: (a) Horrillo-Martinez, P.; Hultsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311. (b) Pez, G. P.; Galle, J. E. *Pure Appl. Chem.* **1985**, *57*, 1917. (c) Lehmkukl, H.; Reinehr, D. J. *Organomet. Chem.* **1973**, *55*, 215. (d) Takabe, K.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 222.

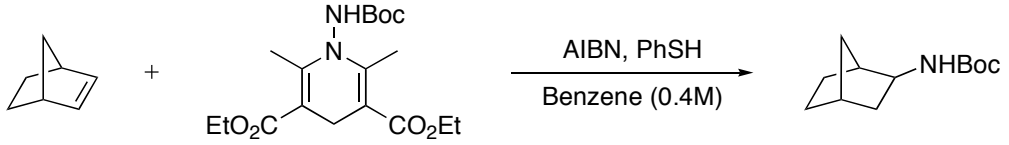
under similar conditions, when 2,5-norbornadiene was replaced by styrene, the reaction required lower temperatures and higher yields were produced.[10]



1.6 **1.7** **1.8** **(1.3)**

1.2.3. Radical-Based Hydroamination

Alternatively, methods based on free radicals have also been presented and display complementary reactivity. Guin and coworkers were initially able to show a radical hydroamination process when norbornene **(1.9)** was refluxed in benzene in the presence of their radical-transfer-hydroamination reagent **1.10**, as well as azobisisobutyronitrile (AIBN) and PhSH, to afford the hydroamination product **1.11** in 54% yield (Equation 1.4).[11]



1.9 **1.10** **1.11** **(1.4)**

It was determined that the use of Et_3B/O_2 as the initiator provided slightly increased yields, and that this radical hydroamination reaction was amenable to various

[10] Schlott, R. J.; Falk, J. C.; Narducy, K. W. *J. Org. Chem.* **1972**, *37*, 4243.
[11] Guin, J.; Frolich, R.; Studer, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 779.

aliphatic, cyclic and substituted alkenes, affording the anti-Markovnikov hydroamination products in good yields. In further studies, it was shown that vicinal diamines could be obtained with good selectivity through the hydroamination of chiral enecarbamates.[11]

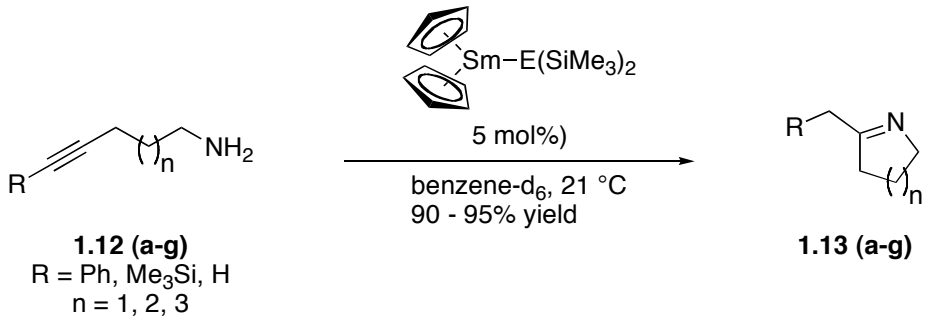
1.2.4. Transition-Metal Catalyzed Hydroamination

To date, the majority of progress that has been made with respect to hydroamination involves the use of transition-metal catalysts to lower the activation energy of the reaction.[12] The use of lanthanide and early metal-based catalysts in intramolecular situations has been shown to be successful, but this methodology is air and moisture sensitive and is limited in terms of functional group compatibility.[13]

In 1996, Li and Marks reported the samarium-catalyzed hydroamination of aliphatic and aromatic aminoalkynes **(1.12 a-g)**, which yielded the corresponding pyrrolizindines and indolizidines **(1.13 a-g)** as products (Equation 1.5).[13e]

[12] For selected reviews, see : (a) Severin, R.; S. Doye, *Chem. Soc. Rev.* **2007**, *32*, 1407. (b) Matsunaga, S.; *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 778. (c) Hultzsch, K.C., *Adv. Synth. Catal.* **2005**, *347*, 367. (d) Alonso, F.; Beletskaya, I.. P.; Yus, M., *Chem. Rev.* **2004**, *104*, 3079. (e) Roesky, P. W.; Müller, T. E., *Angew. Chem. Int. Ed.* **2003**, *42*, 2708. (f) Pohlki, F.; Doye, S., *Chem. Soc. Rev.* **2003**, *32*, 104. (g) Nobis, M.; Drießen-Hölscher, B., *Angew. Chem. Int. Ed.* **2001**, *40*, 3983. (h) Brunet, J.-J.; Neibecker, D., in *Catalytic Heterofunctionalization*, ed. A. Togni, H. Grützmacher, WILEY-VCH, Weinheim, **2001**, pp 91-141. (i) Müller, T. E.; Beller, M., *Chem. Rev.* **1998**, *98*, 675.

[13] For examples of lanthanide-catalysed hydroamination see: (a) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (b) Rastatter, M.; Zulys, A.; Roesky, P. W. *Chem. Eur. J.* **2007**, *13*, 3606. (c) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584. (d) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (e) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 707.



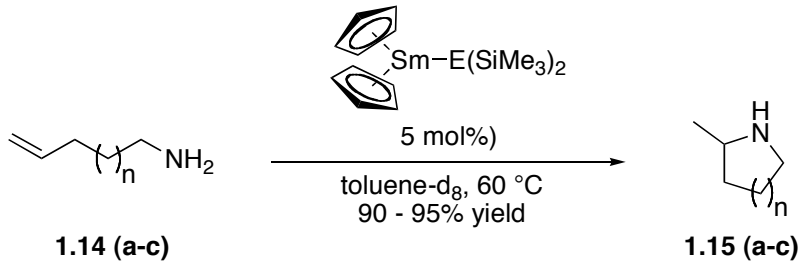
1.12 (a-g)
R = Ph, Me_3Si, H
n = 1, 2, 3

1.13 (a-g)

(1.5)

A range of aminodiolefins and aminoalkenalkynes were also used in such organlanthanide-catalyzed reactions to afford similar compounds, and majority of the bicyclizations took place with regioselectivities greater than 95%.[13e]

Alkenes were also subjected to cyclizations with the aid of samarium-catalysis, however they typically required heating at elevated temperatures. Pyrrolidines, piperidines and azepan rings were successfully accessed through this methodology (Equation 1.6).[14]



1.14 (a-c)

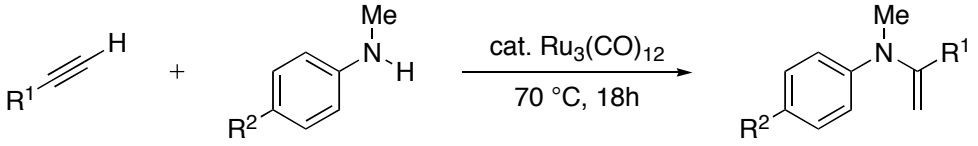
1.15 (a-c)

(1.6)

[14] (a) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108 (b) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.

More recently, the use of late transition metals has demonstrated an increased tolerance of functional groups and has provided insight into the thermodynamic problems associated with intermolecular hydroaminations.[3,15]

The first ruthenium-catalyzed intermolecular hydroamination of alkynes was developed by Uchimara.[16] In this report, it was shown that in the presence of $Ru_3(CO)_{12}$, terminal alkynes would participate in a hydroamination reaction with aromatic amines (Equation 1.7).[3]



(1.7)

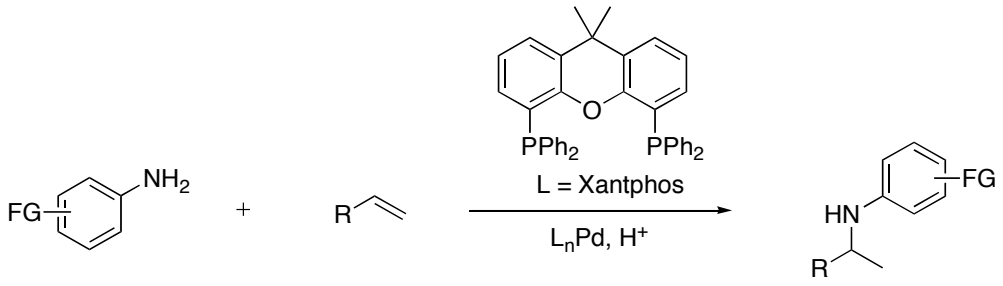
1.16 (a-d) **1.17 (a-b)** **1.18 (aa-db)**
R^1 = Ph, *p*-MeC_6H_4, *p*-FC_6H_4, cyclohex-1-enyl
R^2 = H, Me
76-85% yield

The intermolecular hydroamination of alkenes is generally more difficult than the corresponding intramolecular reaction, due to the increased energy required for this transformation to occur. Often, methods for the intermolecular hydroamination of alkenes thus use reactive alkenes, such as norbornene and styrene. With the help of late-transition metals, these processes can be achieved much more easily. Hartwig was able to catalyze the intermolecular hydroamination reaction of styrene-based alkenes with

[15] For examples of late transition metal-catalyzed hydroamination see: (a) Johns, A. M.; Utsunomiya, M.; Incarrito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (c) Brouwer, C.; He, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1744. (d) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314. (e) Brunet, J.-J.; Chu, N.-C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, 4711. (f) Liu, C.; Bender, C. F.; Han, X.; Widenhoefer, R. A. *Chem. Commun.* **2007**, 3607. (g) Widenhoefer, R. A.; Han, X. *Eur. J. Org.Chem.* **2006**, 4555.
[16] Uchimaru, Y. *Chem. Commun.* **1999**, 1133.

aniline derivatives, using palladium.[15] This reaction was able to tolerate a large range of functionalities, which likely would not have been possible with other forms of catalysis.[15]

These conditions were improved upon for the hydroamination of vinylarenes and dienes using palladium-complexes of Xantphos (Equation 1.8).[15a]

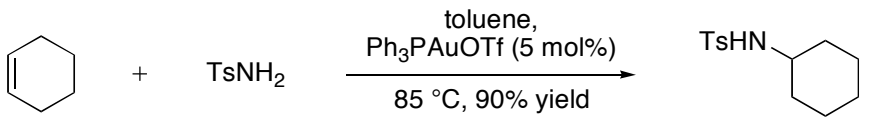


1.19 **1.20** R = Ar,vinylic **1.21** **(1.8)**

These advanced catalysts are much more reactive for the hydroamination of vinylarenes and dienes than catalysts that have previously been reported. These reactions occur selectively and in the presence of a diverse array of functionalities, such as nitro, nitrile, ester, amide, carboxylic acid, phenolic, hydroxyl and enolizable keto groups.[15a]

Hartwig has been instrumental in studies related to the thermodynamics associated with the addition of amines to olefins for catalytic hydroamination processes. Through the direct measurement of equilibrium constants, these reactions have been shown to be exothermic and nearly ergoneutral.[3] Knowing that the reaction yield is largely controlled by thermodynamics, the conditions can be tailored to give good yields. It is an appreciation of these thermodynamic issues that has allowed for the discovery of catalysts for the intermolecular hydroamination of alkenes that lack high ring strain.

Despite progress made with respect to hydroamination, there remain limited examples of the intermolecular hydroamination of unactivated alkenes. In preliminary experiments, Zhang and He tested the reaction between cyclohexene and an assortment of nitrogen nucleophiles, finding that *N*-cyclohexyl-*p*-toluenesulfonamide **(1.24)** could be prepared in 90% yield via the reaction of $TsNH_2$ **(1.23)** with cyclohexene **(1.22)** with catalytic $Ph_3PAuOTf$ (Equation 1.9).[15b]



1.22 **1.23** **1.24** **(1.9)**

This reaction works well for an assortment of olefins, including terminal alkenes. Intramolecular alkene hydroamination was also examined, and several *N*-tosylated amino olefins were efficiently cyclized under these conditions to give pyrrolidines.[15b] This methodology has since been extended to 1,3-dienes, producing allylic amine products that are important intermediates in synthesis and appear in many natural products.[15c] However, it is likely that these reactions simply involve catalysis via the *in situ* generation of acid.[17] Enantioselective variations of such techniques have also been presented but intermolecular examples remain rare. [18,19]

Although the formation of C-N bonds can be achieved using the hydroamination processes outlined above, most of these methods remain limited in substrate scope and

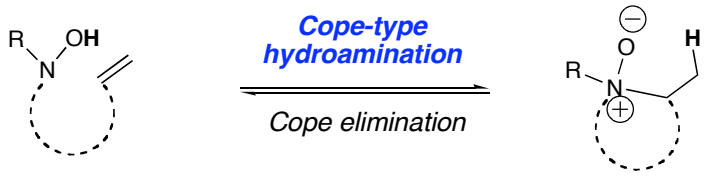
[17] (a) Zigang, Li.; Zunliang, Z.; Brouwer, C.; Cai-Guang, Y.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.
[18] Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.
[19] Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.

functional group compatibility. These restrictions thus continue to stimulate further investigation of such hydroamination reactions, in pursuit of an improved route.

1.3. Cope-Type Hydroamination

A unique approach for the hydroamination of alkenes and alkynes is the Cope-type hydroamination (Scheme 1.2).[20] The Cope-type hydroamination has not gained much attention as a hydroamination strategy, but it is the microscopic reverse of the Cope elimination and a concerted hydroamination strategy.[20]

Scheme 1.2: Cope-Type Hydroamination

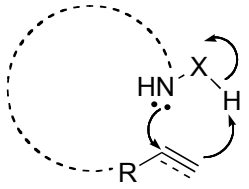


The Cope-type hydroamination involves the addition of an N-H bond across an unsaturated carbon-carbon bond using a bi-functional reagent, such as hydroxylamine or hydrazine. In doing so, a new carbon-nitrogen and a new carbon-hydrogen bond are formed. Although the Cope-type hydroamination was initially proposed to proceed

[20] In the literature, such reactions are also referred to as "reverse Cope cyclizations" or reverse Cope eliminations. For a review see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

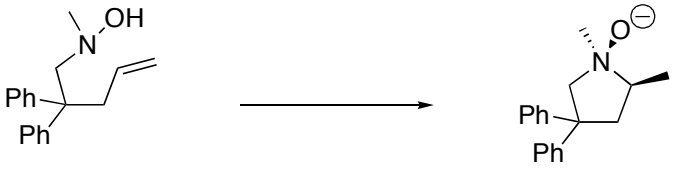
through a radical mechanism,[21] further studies revealed findings that can only be rationalized by a concerted mechanism (Scheme 1.3).[22]

Scheme 1.3: Concerted Mechanism of Cope-Type Hydroamination



X = NH or O

Ciganek isolated a single diastereomer **(1.26)** from the cyclization of a methyl-substituted **(1.25)** hydroxylamine (Equation 1.10).[22b] Analysis of the pyrrolidine compound obtained **(1.26)** revealed a cis relationship between the β-methyl substituent and the *N*-oxide. This led Ciganek to assume that the nitrogen and hydrogen atoms had been delivered via the same face, indicating that the process was concerted.

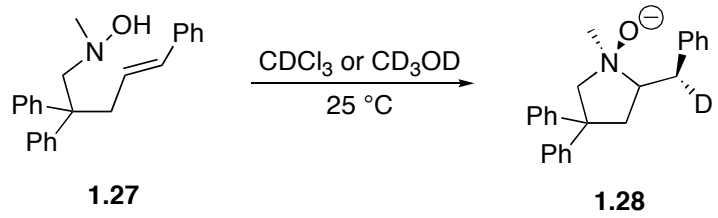


1.25 **1.26** **(1.10)**

[21] (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

[22] (a) Black, D.; St, C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317. (b) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. (c) Ciganek, E. Jr.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795. (d) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803. (e) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139. (f) Oppolzer, W. *Gazz. Chim. Ital.* **1995**, *125*, 207.

To supply proof for this assumption, Ciganek synthesized hydroxylamine **1.27** and transformed it to the corresponding deuterated methyl-substituted hydroxylamine by treatment with $CDCl_3$ or CD_3OD. After isolation of the *N*-oxide (**1.28**), it was determined that the deuterium transfer was consistent with a concerted mechanism (Equation 1.11).[22b]

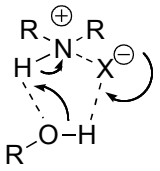


1.27 **1.28** **(1.11)**

Due to the fact that the Cope-type hydroamination occurs via a concerted mechanism, this method is significantly different than other techniques found in the literature. Following the concerted step, a proton transfer takes place, thus the reaction can be facilitated by protic solvents,[22b,c,23] affording the desired hydroamination product. This reaction can occur under mild conditions and it is also worth noting that the concerted pathway allows for a high degree of predictability.

[23] (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47,* 1410. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *52*, 17893.

Scheme 1.4: Proton Transfer Following Hydroamination

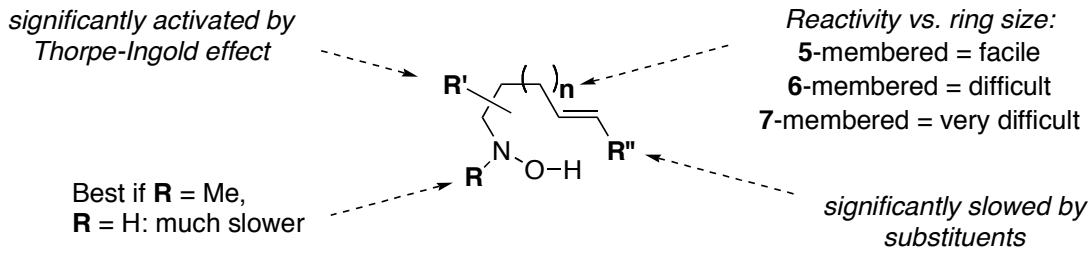


X = NH or O

1.3.1. Intramolecular Cope-Type Hydroamination

The Cope-type hydroamination, despite its appeal as a simple and attractive route to access nitrogen-containing heterocycles, is seldom used. This can be explained by observing the features of the reactivity of alkenes in the intramolecular Cope-type hydroamination.

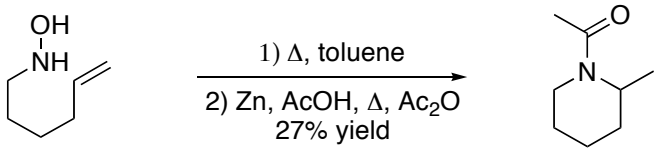
Scheme 1.5: General Features of the Intramolecular Cope-Type Hydroamination [20]



As shown in Scheme 1.5, alkyl substitution on the nitrogen atom is required to increase reactivity, but this limits the scope of the reaction due to the formation of a less stable product. Also, formation of five-membered rings via the Cope-type hydroamination is much more successful, whereas the formation of six and seven-

membered rings is much more difficult and examples of such cases are rare. Unfortunately, similar reactivity trends are also reported for other hydroamination methodologies.

Nevertheless, in 1976 House reported the cyclization of six-membered hydroxylamine **1.29** to give the analagous piperidine.[24] This was followed by N-O bond cleavage and the product was then isolated as the amide **1.30** (Equation 1.12). House mentioned that in comparison to the cyclization of 5-membered rings, 6-membered variants required harsher reaction conditions, including higher temperatures and that decreased yields were observed.[24]



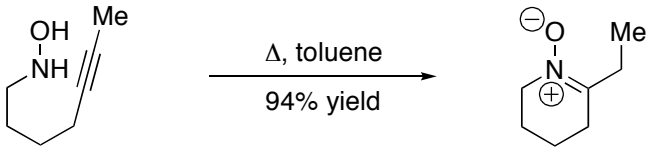
1.29 **1.30** **(1.12)**

In addition, hydroamination is considerably activated by the Thorpe-Ingold effect. That is, when the size of the substituents is increased, the reaction is enhanced. Moreover, substitution on the alkene or alkyne significantly slows the rate of the Cope-type hydroamination, restricting the use of this site in other synthetic strategies.

Despite these challenges, the Holmes group presented an example in 1994, where they were able to produce the six-membered ring *N*-oxide **1.32** through a hydroxylamine

[24] (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

alkyne cyclization (Equation 1.13).[25] Even though distal substitution of the alkyne renders these cyclizations much more difficult, Fox was able to demonstrate examples of 5-, 6- and 7-membered cyclizations which proceeded to give the corresponding substituted *N*-oxides in good yields.[25] It should be noted that for alkynes, cyclizations to form 6-membered rings occur faster than that of the parent five- or seven-membered substrates.

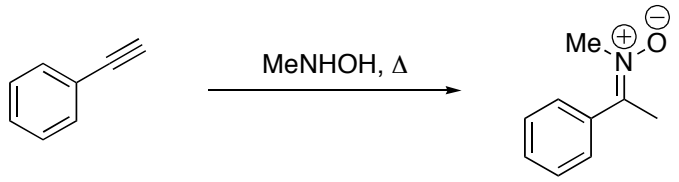


1.31 **1.32** **(1.13)**

1.3.2. Intermolecular Cope-Type Hydroamination

In order to further probe the limitations of the Cope-type hydroamination strategy, intermolecular reactions must be discussed. The intermolecular hydroamination of aryl acetylenes **(1.33)** with *N*-alkylhydroxylamines to afford nitrone intermediates **(1.34)** was described by Padwa (Equation 1.14).[26] The nitrone intermediate could subsequently participate in a [3 + 2] cycloaddition reaction, giving a mixture of products.

[25] Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3379.
[26] Padwa, A.; Wong, S. K. *J. Org. Chem*. **1986**, *51*, 3125.



1.33 **1.34** **(1.14)**

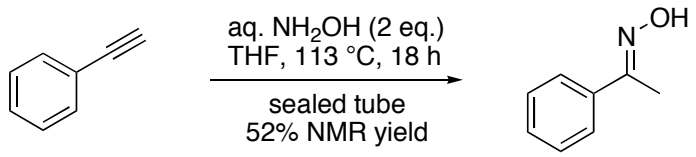
Instances of the intermolecular Cope-type hydroamination of alkenes are even more elusive. The first case of such reactivity was reported by Laughlin in 1973. He reacted several olefins with *N,N*-methylhydroxylamine.[27] This reaction produced a complex mixture of products, but it was determined that some of the compounds produced had to originate from a Cope-type hydroamination.

It is a combination of these features that has limited the use of the Cope-type hydroamination as a useful synthetic strategy. It is worth noting however that similar issues arise in most hydroamination reactions, including transition-metal catalyzed approaches. Cope-type hydroamination reactions generally require similar conditions and temperatures with regards to the other methods previously mentioned. It is of importance to the Beauchemin research group to continue investigations into this Cope-type hydroamination, and to focus efforts on improving the reactivity of such transformations.

[27] Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

1.3.3. Previous Work by the Beauchemin Research Group on Hydroxylamines

The first example of intermolecular Cope-type hydroamination reactivity observed by our group involved alkynes and hydroxylamines. Alkynes are generally more reactive than alkenes due to the low stability of their π bond, and they were therefore preferred for preliminary studies. In an initial lead, it was shown that phenylacetylene **(1.35)**, when heated with aqueous hydroxylamine in a sealed tube, generated the *E*-oxime **1.36** in 52% NMR yield (Equation 1.15).[23b]

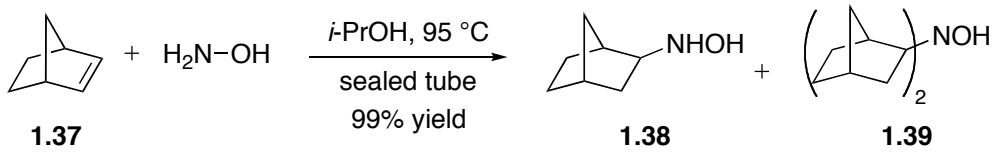


1.35 **1.36** **(1.15)**

Optimization of this reaction was performed including a solvent scan, and it was observed that alcoholic solvents such as *i*-PrOH were optimal for this transformation, facilitating the proton transfer step. The scope of this reaction was subsequently developed, demonstrating that the conditions were amenable to terminal alkynes, alkylacetylenes, enynes and alkynes bearing hydroxyl, pyridine and other common protecting groups. The reaction also worked well with various steric and electronic substitution patterns on the arene ring.[23]

Having achieved such good results with alkynes, the group then turned its focus to the hydroamination of alkenes, a more challenging task. Norbornene was used in the initial experiments, as its strained structure renders it more reactive. It was found that the

reaction was quite sensitive to solvent and concentration, however good results were obtained with almost exclusive with the use of alcoholic solvents.[23b] When run in *i*-PrOH, the reaction between aqueous hydroxylamine and norbornene **(1.37)** produced a good combined yield of the mono- and bis-hydroamination products (**1.38 and 1.39**, Equation 1.16**)**.[23b]



1.37 **1.38** **1.39** **(1.16)**

Selectivity for the monohydroamination product could be achieved with use of excess hydroxylamine. A range of strained alkenes, including styrene and vinylarenes with free hydroxyl/nitro groups were well tolerated and an unconjugated allylphenol also displayed reactivity, albeit in lower yield.[23b]

Even though significant progress has been made using hydroxylamines in the Cope-type hydroamination, these reagents can be sensitive and prone to decomposition. More convenient reagents would thus be ideal to broaden the scope of this reactivity.

1.3.4. Previous Work by the Beauchemin Research Group Using Hydrazines

Following the results obtained for the intermolecular hydroamination of aqueous hydroxylamine with alkynes and alkenes, it was believed that hydrazines could be a

possible alternative for such transformations and provide access to valuable products. Three different categories of hydrazines were considered: unactivated hydrazines, activated hydrazines and Lewis/Brϕnsted acid activated hydrazines (Figure 1.1).

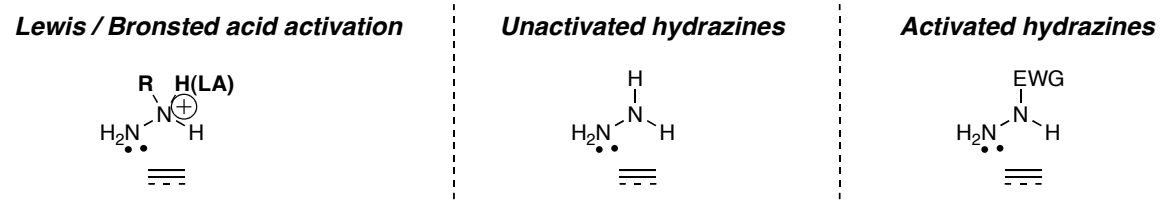
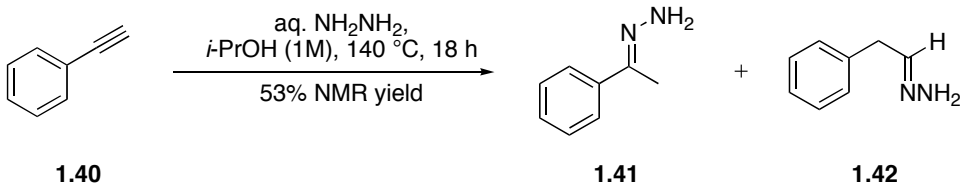


Figure 1.1: Three Different Types of Hydrazines

Assuming that the intermolecular Cope-type hydroamination occurs through a concerted mechanism, it was considered that the use of substituted hydrazines (or hydroxylamines) could destabilize the transition state and lead to a change in regioselectivity. In initial trials, Mrs. Pamela Cebrowski was able to demonstrate that the reaction of aqueous hydrazine with phenylacetylene **(1.40)** lead to a 53% NMR yield as a 2.5:1 mixture of regioisomers, with the anti-Markovnikov hydrazone **1.42** being favored (Equation 1.17).[28]



1.40 **1.41** **1.42** **(1.17)**

[28] Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492.

Optimization of this lead result was performed with methylhydrazine ($MeNHNH_2$) and this led to both increased conversions and regioselectivities. Using phenylacetylene, a solvent scan demonstrated reactivity in many solvents, however the best results were obtained using high concentrations in protic solvents such as *i*-PrOH. This supports the idea that protic solvents can facilitate the proton transfer step following hydroamination. With the optimal conditions in hand, the substrate scope was evaluated. The hydroamination of aromatic acetylenes and heterocyclic acetylenes proceeded in good yields and substitution of the arene ring was well tolerated. It should be noted that the linear hydrazones were derivatized in order to allow their isolation by column chromatography.

1.4. Conclusion

Hydroamination is a potentially general approach to access many types of nitrogen heterocycles which are important scaffolds in organic synthesis and the pharmaceutical industry. There are several strategies to obtain hydroamination products, including acid/base catalysis, radical methodology and transition-metal catalysis. The Cope-type hydroamination is an alternative to these approaches, it is metal-free and uses bifunctional reagents such as hydroxylamines in order to carry out the desired transformation. The Beauchemin group has shown the synthetic potential of hydroxylamines in the Cope-type hydroamination, however these reagents can be less than ideal to work with. In order to expand the scope of this reactivity, more suitable reagents were necessary. Hydrazines were a promising option, displaying

hydroamination reactivity and increased stability. However, derivatization of the products obtained from the use of hydrazines was required for their isolation. Due to the stability of hydrazides, both on the bench and thermally, investigations into their use for the Cope-type hydroamination were initated.

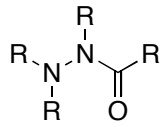
Chapter 2: Intramolecular Cope-Type Hydroamination of Alkenes[29]

[29] A portion of this chapter has been published: Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, 131, 8740.

Chapter 2: Intramolecular Cope-Type Hydroamination of Alkenes

2.1. Introduction

Hydrazides are derivatives of hydrazines that share a common functional group, characterized by a nitrogen-nitrogen covalent bond, which is substituted with four groups, one of which is an acyl group (Figure 2.1). Hydrogens, alkyl or aryl groups make up the remaining substituents.



R = H, alkyl, aryl

Figure 2.1: General Hydrazide Structure

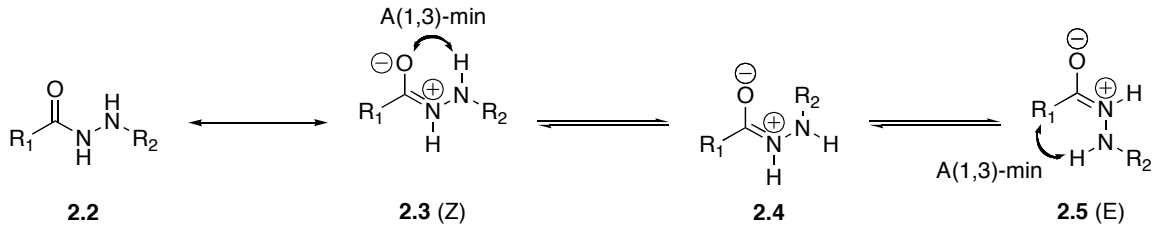
Hydrazides are an old class of molecules that have been known in chemistry since 1850, when the first example was reported.[30] Since then, a variety of *N*-unsubstituted, mono- and disubstituted acylhydrazines have become commercially available. Hydrazides have also been used to perform many chemical transformations, and have found use as intermediates to access important organic molecules, pharmaceutical candidates, polymers, dyestuffs and photographic products.[31]

[30] Schofer, K.; Schwan, J. *Prak. Chem*. **1850**, *51*, 185.
[31] Hydazine and its Derivatives, in *Kirk-Othmer Encyclopedia Chemical Technology*, 4th edn., vol. 13, John Wiley & Sons, New York, **1995**.

2.1.1. Structural Characteristics of Hydrazides

The structural properties of hydrazides can be compared to those of amides (Scheme 2.1). As found in amides, the lone pair of the nitrogen in hydrazides is delocalized onto the carbonyl, forming a partial double bond between the carbon and nitrogen bond. In such compounds, the geometry adopted is trigonal planar and positioned to reduce the amount of 1,3-allylic strain.[32] Due to their partial double bond character, hydrazides can exist in two conformations, as both Z and E isomers. In general, if the nitrogen atoms of a hydrazide are fully substituted, they prefer to adopt the E conformation. However, if the size of the carbonyl substituent is increased (R_1), a mixture of E and Z isomers can be observed.[33]

Scheme 2.1: E and Z Isomers and Minimization of 1,3-allylic Strain

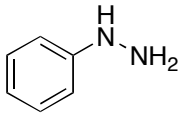


2.2 **2.3** (Z) **2.4** **2.5** (E)

[32] Broeker, J.; Hoffman, R. W.; Houk, K. N. *J. Prak. Chem*. **1991**, *113*, 5006.
[33] (a) Knapp, S.; Toby, B. H.; Sebastian, M.; Krogh-Jespersen, K.; Potenza, J. A. *J. Org. Chem.* **1981**, *46*, 2490. (b) Ghelfi, F.; Parsons, A. F. *J. Org. Chem.* **2000**, *65*, 6249.

2.1.2. Use of Hydrazides

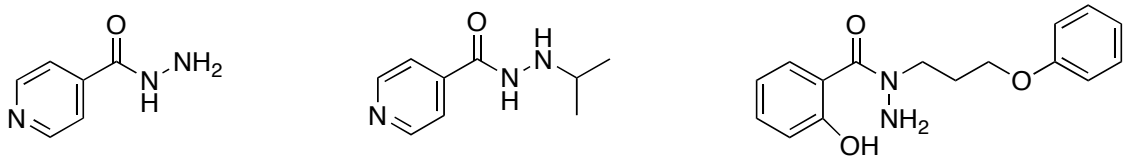
A number of mono- and disubstituted hydrazines are used as reagents in organic chemistry, including the oldest hydrazine compound, phenylhydrazine (**2.6,** Figure 2.2). Phenylhydrazine played a key role in the formation of crystalline derivatives of carbohydrates and it also became the model for other hydrazine analogues that were commonly used in qualitative tests for the identification of carbonyl compounds.[34]



2.6

Figure 2.2: Structure of phenylhydrazine

As mentioned previously, the hydrazide moiety presents itself in many pharmaceutical agents. Examples of a few pharmaceuticals containing this functional group are shown below (Figure 2.3).



2.7
Isoniazid

2.8
Iproniazid

2.9

Figure 2.3: Hydrazides used as Pharmaceuticals

[34] Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205.

Isoniazid (**2.7**) used in combination with other drugs, functions as a strong anti-tuberculosis agent.[35] Iproniazid (**2.8**), while being used as an anti-tuberculosis medication, showed an affect on the central nervous system and it is now used as an antidepressant. *N*-(2-Hydroxybenzoyl)-*N*-(2-hydroxy-3-phenoxypropyl)hydrazine (**2.9**) discovered by the Burke group, is used as a potent HIV integrase inhibitor.[36] In recent years, it has also been observed that hydrazides may be promising drug candidates for the treatment of Alzheimer's disease.[37] Hydrazides have also been used as protecting groups,[38] cross linkers[39] and ligands.[40]

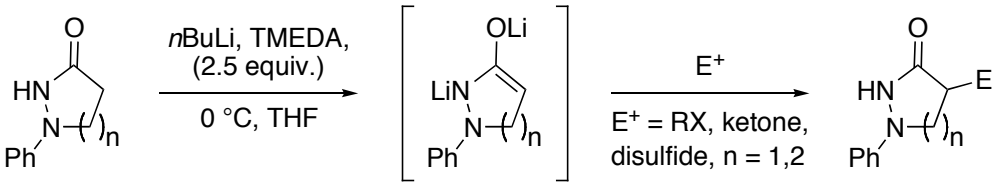
2.1.3. General Reactivity of Hydrazides

The structural characteristics of hydrazides are similar to those of amides, and the presence of this amide-like functionality can allow for enolate chemistry. Despite this, the reactivity of hydrazides depends on their structure and there are no accounts of enolate formation related to acyclic hydrazides.[41] However, it has been reported that new carbon-carbon bonds can be formed through the reaction of the enolates of substituted cyclic hydrazides with electrophiles.[41] When phenidone **2.10a** (n = 1) or pyridazinone **2.10b** (n = 2) were treated with 2.5 equivalents of an *n*-butyllithium-*N,N,N,N'*-tetramethyl-ethylenediamine complex, dianions **2.11a** and

[35] Seydel, J. K.; Schaper, K.-J.; Wempe, E.; Cordes, H. P. *J. Med. Chem.* **1976**, *19*, 483.
[36] Zhao, H.; Neamati, N.; Sunder, S.; Hong, H.; Wang, S.; Milne, G. W. A.; Pommier, Y.; Burke, T. R. *J. Med. Chem.* **1997**, *40*, 937.
[37] Pickhardt, M.; Larbig, G.; Khlistunova, I.; Coksezen, A.; Meyer, B.; Mandelkow, E.-M.; Schmidt, B.; Mandelkow, E. *Biochemistry* **2007**, *46*, 10016.
[38] Cheung, H. T.; Blout, E. R. *J. Org. Chem.* **1965**, *30*, 315.
[39] Ansell, S. M.; Tardi, P. G.; Buchowsky *Bioconjuguate Chem.* **1996**, *7*, 490.
[40] Kost, D.; Kalikhman, I. *Acc. Chem. Res.* **2009**, *42*, 303.
[41] Licandro, E.; Perdicchia, D. *Eur. J. Org. Chem.* **2004**, 665.

2.11b were generated.[42] Upon reaction with various electrophiles, pyrazolidinones **2.12a** and pyridazinones **2.12a** were accessed (Scheme 2.2).

Scheme 2.2: Reactivity of Substituted Cyclic Hydrazides as Enolates



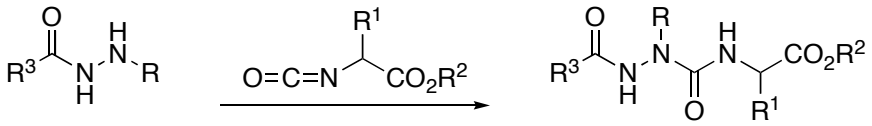
2.10 (a-b) **2.11 (a-b)** **2.12 (a-b)**

Azapeptides are a class of peptides in which the α-CH group of one or more amino acid residues in the peptide chain is replaced by a nitrogen atom (Figure 2.4).[41] The advantages to this structural modification are that azapeptides are more resistant to enzymes, they show increased bioavailability and absorption and due to this they have become of synthetic interest.[41]

Figure 2.4: Structure of Peptides versus Azapeptides

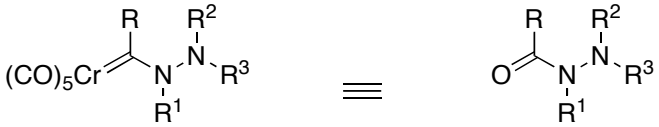
[42] Hlasta, D. J.; Casey, F. B.; Ferguson, E. W.; Gangell, S. J.; Heimann, M. R.; Jaegar, E. P.; Kullnig, R. K.; Gordon, R. J. *J. Med. Chem.* **1991**, *34*, 1560.

The most common method to form the azaamino acid/amino acid linkage required for an azapeptide is via the addition of hydrazines or hydrazides **2.13** to α-isocyanato esters **2.14** or fatty acids (Equation 2.1).[43]



2.13 **2.14** **(2.1)**

Alkyl(hydrazino)carbene complexes, categorized as heteroatom-stabilized Fischer-type carbene complexes have emerged in the literature recently. These metallahydrazides have the general structure of compound **2.15** and are directly related to the hydrazide analogues **2.16** (Equation 2.2).[41]

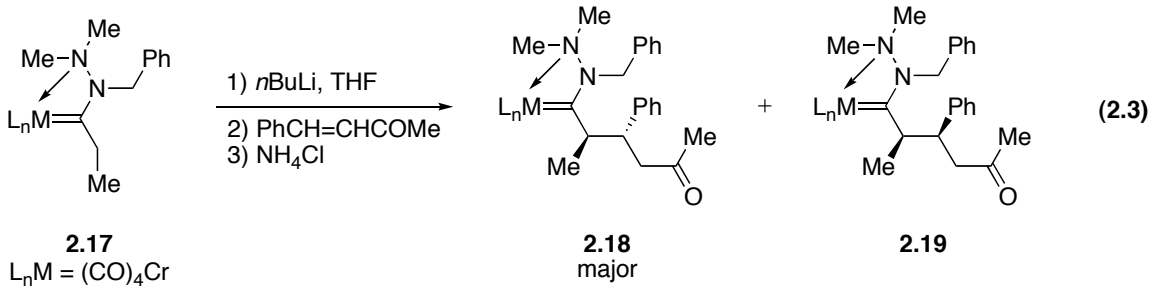


2.15 **2.16** **(2.2)**

These carbene complexes can be deprotonated with strong base, because the hydrogen atoms located at the α-position with respect to the carbene carbon atom are acidic. The anions obtained, can then be reacted with a range of electrophiles.[41] The highly diastereoselective Michael addtion of Fischer-type alkyl(hydrazine)carbene complex **2.17** to afford substituted hydrazides has been reported.[44] At -78 °C, the anion of complex **2.17** adds to the enone (step 2) in a 1,4-regioselective manner to give

[43] Gante, J. *Synthesis* **1989**, 405.
[44] Licandro, E.; Perdicchia, D.; Maiorana, S.; Baldoli, C.; Graiff, C.; Tiripicchio, A. *J. Organomet. Chem.* **2003**, *684*, 170.

complexes **2.18** and **2.19** in greater than 98% diasteromeric exess (Equation 2.3).[44] Highly diastereoslective aldol-type addition reactions with aromatic and aliphatic aldehydes to give functionalized hydrazides have also been reported using the same alkyl(hydrazine)carbene complexes.[44]



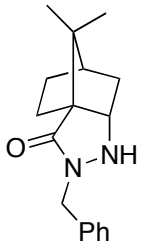
2.17
$L_nM = (CO)_4Cr$

2.18
major

2.19

(2.3)

More recently, Lemay and Ogilvie made use of a camphor based hydrazide as a catalyst for enantioselective Diels-Alder reactions.[45] The camphor-derived hydrazide (Figure 2.5) allowed the reaction to proceed with ee's ranging from 3% to 82%.



2.20

Figure 2.5: Camphor-Based Hydrazide Used in Enantioselective Diels-Alder Reactions

[45] (a) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *93*, 1793. (b) Lemay, M.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 463.

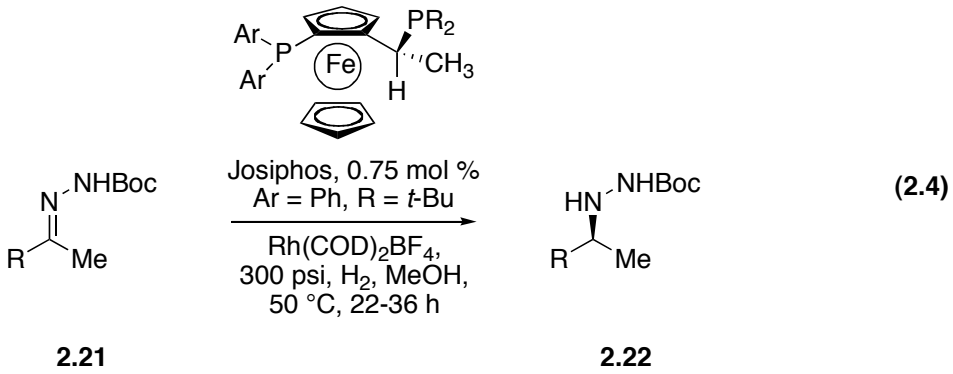
2.2. Methods to Prepare Hydrazides

Due to the potential of hydrazides in synthesis as well as their prevalence in pharmaceuticals, thousands of hydrazides or derivatives thereof are commercially available.[46] For those hydrazides that are not commercially available, several techniques for their synthesis have been outlined in the literature and depend on their substitution patterns (mono, di, tri).[34,41] The following sections will provide an overview on the synthesis of mono- and di-substituted hydrazides as this is relevant to put in context the hydroamination reactivity presented in Chapters 2 and 3.

2.2.1. Reduction of Hydrazones

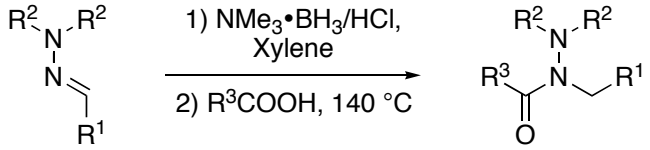
Hydrazones formed from aldehydes and ketones are useful as protecting groups, in the identification of other compounds, as well as for the synthesis of hydrazines and hydrazides via reduction of their C=N bond.[34] For example, Merck Research Laboratories has developed the enantioselective catalytic hydrogenation of hydrazones **2.21**, which provides Boc-protected hydrazines **2.22** as shown in Equation 2.4.[47] The Josiphos ligand proved to be the best catalyst in this case, and following optimization good selectivity was achieved and the enantioselectivity for a variety of hydrazones ranged from and 73-91%.[47]

[46] Based on Aldrich search "hydrazide", 2932 are currently available.
[47] Yoshikawa, N.; Lushi, T.; McWilliams, C.; Ramasamy, D.; Sheppard, R. *Org. Lett.*, **2010**, *12*, 276.



2.21 **2.22** **(2.4)**

Another "one-pot" synthesis of mono- and disubstituted hydrazides via reduction of the corresponding hydrazones, followed by acylation of the obtained hydrazine has been published.[48] The entire reaction from aldehyde to hydrazide is performed in "one-pot"; the hydrazone **2.23** is formed in a xylene solution and a borane•trimethylamine complex in addition to hydrochloric acid are used for the reduction step. Upon addition of an aromatic or aliphatic carboxylic acid, the hydrazide **2.24** is obtained (Equation 2.5).[48]



2.23 **2.24** **(2.5)**

This "one-pot" method to access hydrazides has several advantages, including high yields, few by-products, simple purification, short reaction times and the use of reagents that are readily available and compatible with larger-scale industrial processes.[41]

[48] Perdicchia, D.; Licandro, E.; Maioranan, S.; Baldoli, C.; Giannini, C. *Tetrahedron* **2003**, *59*, 7733.

Several other agents have been employed in the reduction of the C=N bonds of hydrazones, including catecholborane,[49] diborane in THF,[50] amberlyst-15(H^+)-LiCl-$NaBH_4$,[51] and milder reducing agents such as trimethylsilane in the presence of trifluroracetic acid,[52] $NaBH_4$ and $NaCNBH_3$ have also been shown to reduce hydrazones to the corresponding hydrazines or hydrazides under acidic conditions.[34,53]

The addition of other nucleophiles to hydrazones is also very common and provides a robust alternative to reduction based methods to access alpha-branched hydrazides. Numerous enantioselective procedures are available in the literature including Jang's indium-mediated catalytic enantioselective allylation of *N*-Benzoylhydrazones.[54,55]

2.2.2. Other Methods for the Synthesis of Hydrazides

Substituted hydrazides can also be synthesized via alkylation. Katritzky's benzotriazole method is useful for the preparation of disubstituted hydrazides.[56] In this approach, the β-nitrogen atom of unsubstituted and β-monosubstituted hydrazides **2.25** can be alkylated with hydroxymethyltriazole to afford the mono- or bis adducts **2.26**.

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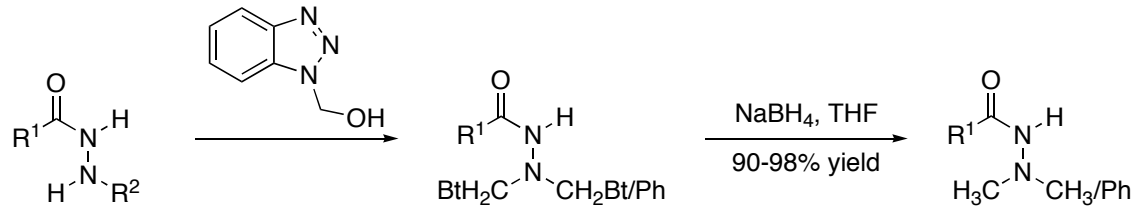
[49] Kabalka, G. W.; Baker, J. D.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512.
[50] Ghali, N. I.; Venton, D. L. *J. Org. Chem.* **1981**, *46*, 5414.
[51] Baruah, B.; Dutta, M. P.; Boruah, A.; Prajapati,, D.; Sandhu, J. S. *Synlett* **1999**, *4*, 409.
[52] (a) Wu, P.-L.; Peng, S.-U.; Magrath, J. *Synthesis*, **1995**, 435. (b) Wu, P.-L.; Peng, S.-U.; Magrath, J. *Synthesis* **1996**, 249.
[53] Calabretta, R.; Gallina, C.; Giordano. C. *Synthesis* **1991**, 536.
[54] Kim, S. J.; Jang, D. O. *J. Am. Chem. Soc.* **2010**, *132*, 12186.
[55] For other examples of catalytic asymmetric allylation of imine derivative see: (a) Kargbo, R.; Takahashi,Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc.* **2007**, *129*, 3846. (b) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767. (c) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315.
[56] Katritzky, A. R.; Chander Rao, M. S. *J. Chem. Soc. Perkin Trans. 1*, **1989**, 2297.

These β-mono- or disubstitituted adducts can then be reduced with $NaBH_4$, to form β-methyl hydrazides **2.27** in high yield (Scheme 2.3).[56]

Scheme 2.3: Synthesis of Alkylated Hydrazides Using Benzotriazole



2.25
R^1 = Ph, OEt,
R^2 = H, Ph

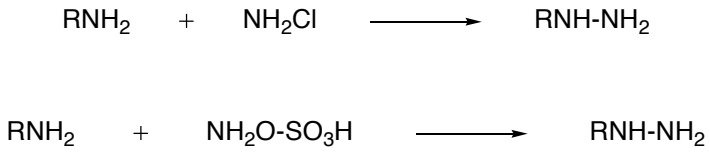
2.26
R = H, Ph

2.27

Amination reactions, such as that between chloramines and primary amines afford alkylhydrazines as products, according to the Raschig procedure shown in Scheme 2.4.[34] Other substituted hydrazines, such as *tert*-butyl hydrazine is made using this methodology, and hydroxylamine-*O*-sulfonic acid also reacts with amines to give similar products (Scheme 2.4).[57] In both cases, chloramine and hydroxylamine-*O*-sulfonic acid act as the electrophile.

[57] Huddleston, P. R.; Coutts, I. G. C. in *Comprehensive Organic Functional Group Transformations*, Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Ed; Pergamon/Elsevier: Oxford, **1995**, vol. 2, pp. 371-383.

Scheme 2.4: Amination of Amines to Give Hydrazines and Hydrazides



The Raschig method provides access to monosubstituted hydrazines and hydrazides and many other amines, including secondary and aromatic amines react well using this approach to give 1,1-alkyl/aryl derivatives.[34,57]

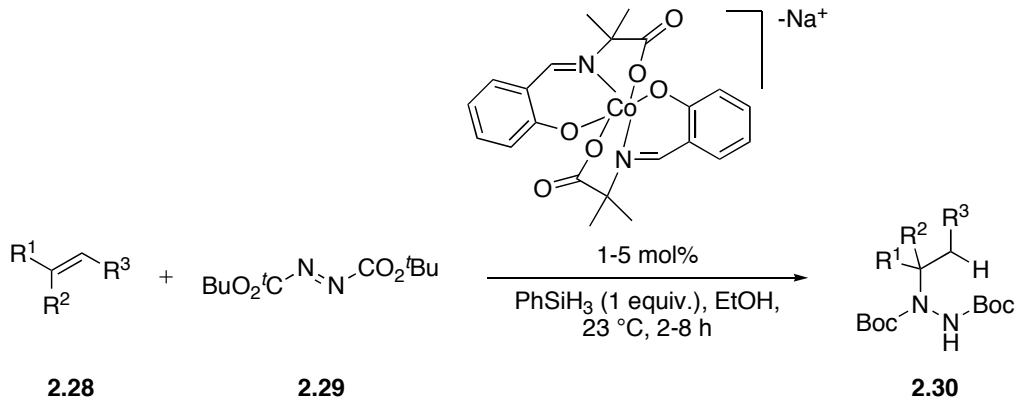
2.3. Hydrohydrazination Reactions

The hydroamination of alkenes has been studied extensively, however, there have been new developments in the related amination reaction of alkenes with hyrazines and hydrazides, termed hydrohydrazination.

In the previous section, methods to access hydrazides were discussed, however no approach to *N*-alkylhydrazides through the direct functionalization of olefin C=C bonds had been reported. Carriera has recently reported a process in which reaction of an olefin **2.28** with di-*tert*-butyl azodicarboxylate **2.29**, in the presence of $PhSiH_3$, and a Co(III) catalyst furnishes Markovnikov hydrazides **2.30** from a variety of olefins in 62-94% yield (Equation 2.6).[58] It was shown that a range of cobalt complexes could catalyze this hydrohydrazination reaction, and that a broad range of cyclic and acylic olefins could be

[58] Waser, J.; Carriera, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676.

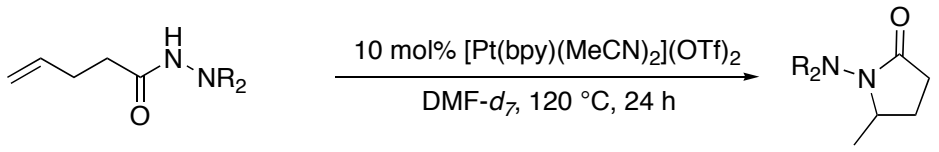
cyclized in good yield using 1-5 mol% of the Co-complex.[58] Since this discovery, Carriera has identified a new manganese-complex that catalyzes these hydrohydrazination reactions with much higher reactivity and a larger scope than the previous Cobalt complexes.[59]



2.28 **2.29** **2.30** **(2.6)**

Michael has very recently reported an intramolecular hydrohydrazination reaction of alkenyl hydrazides performed using platinum catalysis.[60] When alkenyl hydrazide **2.31** was treated with 10 molar % of $Pt(bpy)Me_2$, cyclization of the hydrazide to a single regioisomer of *N*-aminopyrrolidinone **2.32** occurred selectively (Equation 2.7). After studies with a range of Pt complexes, it was found that the highest conversion (95-100%) was obtained using $[Pt(bpy)(MeCN)_2](OTf)_2$ as the catalyst.[60] Alkenyl hydrazides with various protecting groups were amenable to this reaction, as well as alkenyl hydrazides with different electronic and substitution patterns.

[59] (a) Waser, J.; Carriera, E. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4099. (b) Waser, J.; Carriera, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.
[60] Hoover, J. M.; DiPasquale, A.; Mayer, J. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 5043.



(2.7)

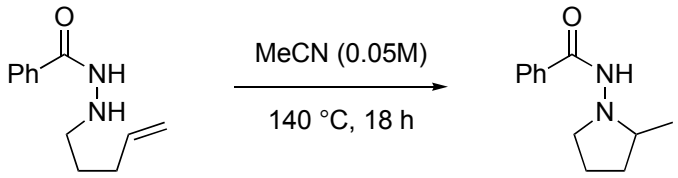
2.31
NR_2 = NHAc, NHPhtal, NHBz, NHTFA, NHCbz, NHBoc, NHTs, NHPh, $NHMe_2$

2.32

2.4. Towards Intramolecular Hydroamination using Hydrazides

As previously mentioned, the Beauchemin Research Group has been interested in using concerted hydroamination reactivity of hydroxylamines to address challenges in this dynamic research field. Despite developing the more difficult intermolecular reactivity, it was noticed that hydroxylamines were not ideal reagents due to their thermal instability. It was envisioned that hydrazides may function well in such Cope-type hydroaminations, and studies into their potential reactivity were initiated.

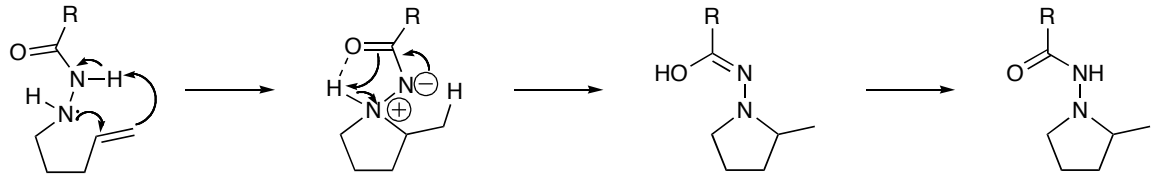
In order to confirm the predicted reactivity of hydrazides in the Cope-type hydroamination, a simple system was first investigated. It was found that upon heating phenyl hydrazide **2.33** at 140 °C for 18 hours, the desired product **2.34** was formed in 70% yield (Equation 2.8).



2.33 **2.34** **(2.8)**

For hydroxylamines, important solvent effects have been observed and explained the importance of the proton transfer step.[23] Thus, both protic and aprotic, as well as polar and non-polar solvents were investigated in this system. Optimization of this reaction performed by Mr. Jean-Grégoire Roveda, including solvent and temperature scans, demonstrated that the best results (93% yield) were obtained using ∝,∝,∝-trifluorotoluene as the solvent and heating the reaction at 120°C. The reaction also proved efficient in a variety of solvents (*i*-PrOH, $PhCH_3$, DMF, dioxane, MeCN, H_2O), suggesting the possible involvement of the hydrazide group as a facilitator in the proton transfer step. This is illustrated in Scheme 2.5 and has been confirmed by density fuctional theory.

Scheme 2.5: Hydrazide Group as a Facilitator in Proton Transfer Step

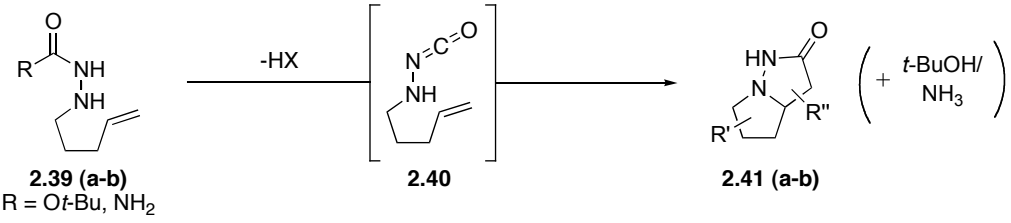


2.35 **2.36** **2.37** **2.38**

What now became of interest was whether the substrate scope of such intramolecular hydroamination reactions with hydrazines could be expanded. In order to

show diversity in such a reaction, various functional groups on the carbonyl moiety needed to be explored. It was shown that both *tert*-butyl and pyridyl hydrazides also afforded the respective hydroamination products albeit at higher temperatures.

Interestingly, when studying the reactivity of carbazates (oxygen-substitued reagents, **2.39a**) under similar conditions, a mixture of both hydroamination and aminocarbonylation products were obtained. Further studies into this reactivity revealed that at higher temperatures (180-200 °C), aminocarbonylation is favored over hydroamination (Equation 2.9). Such results indicate that hydrazides have the potential to selectively produce either hydroamination or aminocarbonylation products, depending upon the reaction conditions.[29] Similar results were seen for semicarbazide (nitrogen-containing, **2.39b**) analogues and extensions of this aminocarbonylation reactivity are currently underway in the Beauchemin lab. The current working hypothesis is that such reactions involve an aminoisocyanate intermediate (**2.40**, Equation 2.9).



2.39 (a-b) R = O*t*-Bu, NH_2 **2.40** **2.41 (a-b)** **(2.9)**

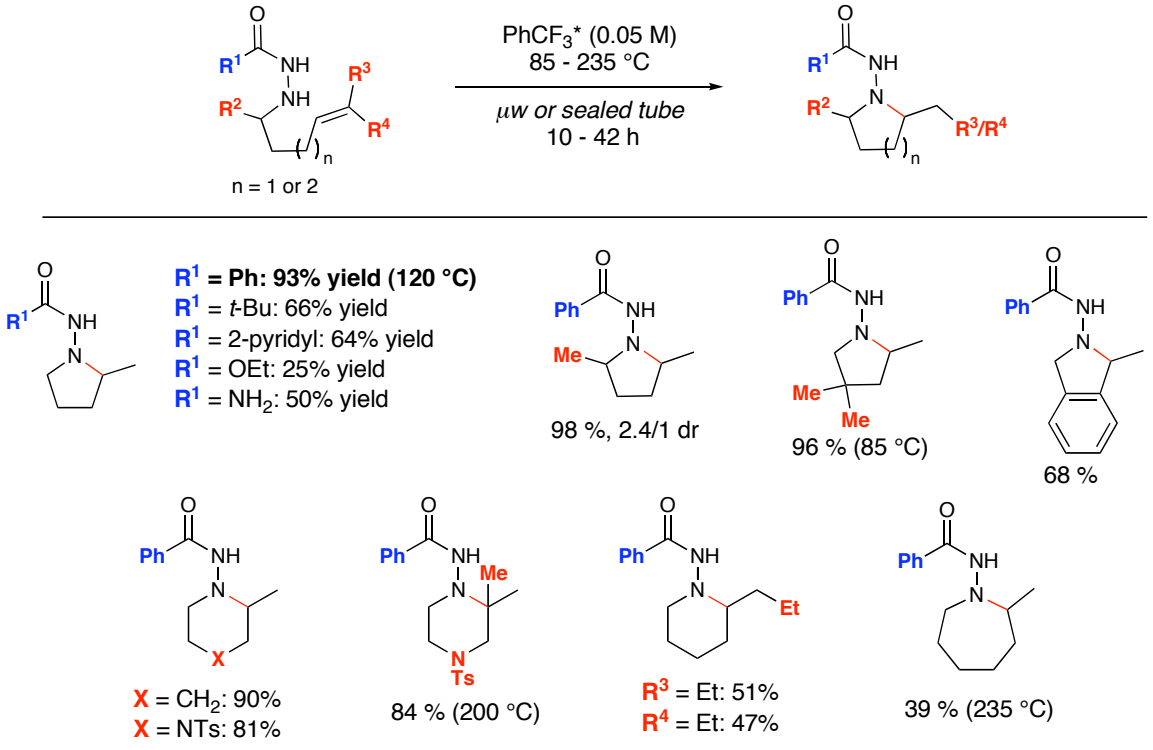
A preliminary substrate scope for the intramolecular hydroamination reactivity of hydrazides was previously developed by a colleague, Jean-Gregoire Roveda.[61,29] He has

[61] Roveda, J.-G. *Hydrazides as Tunable Reagents for Alkene Hydroamination and Aminocarbonylation*. (MSc. Thesis, University of Ottawa, 2010).

demonstrated that hydrazides show a broad applicability to the hydroamination reaction by successfully cyclizing phenyl, *tert*-butyl, pyridyl, oxygen and nitrogen-substituted hydrazides (Table 2.1) upon heating.

Table 2.1: Intramolecular Hydroamination of Alkenes Using Hydrazides

Substrate Scope



The reactivity of benzoic hydrazides has been of interest and it was determined that intramolecular hydroamination products could be attained through the cyclization of such substrates. Studies have revealed that both primary and secondary hydrazides react under similar conditions and five, six and seven-membered nitrogen-containing rings have been efficiently produced using such methods. The more facile thermal cyclizations involve temperatures ranging from 70 to 120 °C for five-membered substrates and go up

to 235 °C to achieve the most difficult six-membered cyclizations. Heteroatoms can also be tolerated, as both a morpholine and two piperazines have been formed. The preliminary substrate scope for this reactivity is shown in Table 2.1 above.

In efforts to continue investigations into the intramolecular hydroamination of hydrazides and to highlight the use of the Cope-type hydroamination in synthesis, further expansion of this reaction's substrate scope is currently in progress.

2.5. Project Objectives

Studies into the intramolecular Cope-type hydroamination of alkenes using hydrazides were in progress at the time that I joined the Beauchemin Research Group. Mr. Jean-Grégoire Roveda had already shown that hydrazides were indeed amenable to hydroamination and he was actively examining the substrate scope of this reaction. It was my goal to aid him in these investigations by preparing additional substrates that could illustrate the synthetic potential of this Cope-type hydroamination strategy.

The mechanism of the intramolecular Cope-type hydroamination using hydroxylamines had been studied previously, and the reaction was proven to proceed in a concerted manner. It became of interest whether the corresponding reaction with hydrazides was operating through a similar mechanism. In parallel to developing the substrate scope for these reactions, kinetic studies were undertaken in order to shed light on the mechanism of action of these transformations.

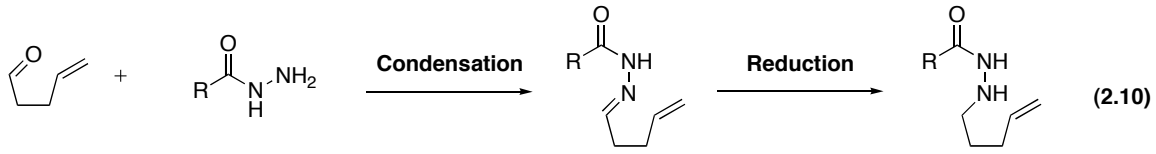
2.6. Preparation of Substrates

Upon beginning this project, no viable method had been developed to synthesize alkenylhydrazides, that is, hydrazides with an alkenyl chain on the terminal amine. Hansen had previously demonstrated that a mono-boc protected hydrazine could be accessed in 85% yield via the reaction of boc-hydrazine and 1-bromo-3-phenyl propane.[62] Following this procedure, a colleague, Mr. Jean-Grégoire Roveda, was able to synthesize various alkylated hydrazides but in low to moderate yields.

Typically sulfonates are better alkylating agents than bromides, thus it was thought that this revision may enhance the yields obtained. Unfortunately this was not the case, as the yields of the alkenylhydrazides obtained using but-3enyl-4-methylbenzenesulfonate according to Sirrett's procedure[63] were even lower than those previously obtained. Having observed low reactivity and poor yields, a different route for the preparation of the substrates was of great importance.

As an alternative, an approach that involved reduction of the hydrazone was investigated (Equation 2.10). Simple condensation of an aldehyde (**2.42**) with a hydrazide (**2.43**) provides the hydrazone (**2.44**), which can be reduced to the desired hydrazide (**2.45**).

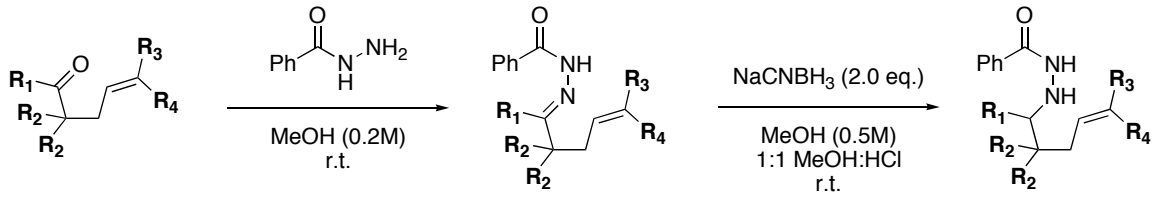
[62] Hansen, T. K. *Tetrahedron* **1999**, *40*, 9119.
[63] Ashley, J. N.; Collins, M. D.; Sirett, N. E. *J. Org. Chem.* **1999**, *183*, 897.



2.42 **2.43** R = alkyl, aryl **2.44** **2.45** **(2.10)**

Table 2.2 summarizes the results for this approach with five-membered ring precursors. The hydrazones and the hydrazides were all obtained in reasonable yields using this methodology. It was observed that with secondary hydrazones (entry 1), the increase in the steric hindrance prevented the formation of the undesired dialkylation product. Entries 2 and 3 were synthesized from the corresponding commercially available alcohols and entry 4 from commercially available 2,2-dimethylpent-4-enal.

Table 2.2: Synthesis of Five-Membered Ring Precursors



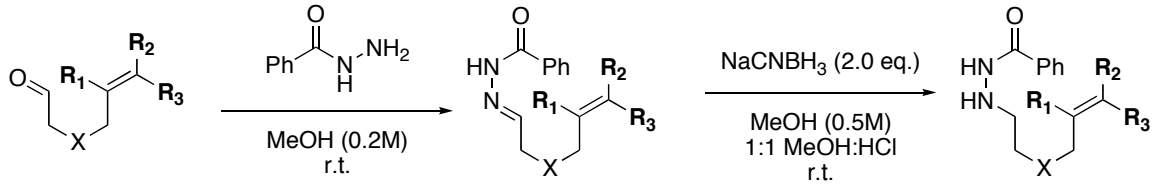
2.46 (a-d) **2.47 (a-d)** **2.48 (a-d)**

Entry	R^1	R^2	R^3	R^4	Hydrazone yield (%)	Reduction Yield (%)
1[a]	Me	H	H	H	86 (**2.47a**)	90 (**2.48a**)
2	H	H	Me	H	69 (**2.47b**)	42 (**2.48b**)
3	H	H	H	Me	63 (**2.47c**)	48 (**2.48c**)
4[a]	H	Me	H	H	100 (**2.47d**)	52 (**2.48d**)

[a]These substrates were synthesized by Jean-Grégoire Roveda.

The following 6-membered ring cyclization precursors were synthesized via the same method previously described. The hydrazone (**2.50**) and hydrazide (**2.51**) were isolated in varying yields shown in Table 2.3.

Table 2.3: Synthesis of Six-Membered Ring Precursors



2.49 **2.50** **2.51**

Entry	R^1	R^2	R^3	X	Hydrazone yield (%)	Reduction Yield (%)
1[a]	H	H	H	O	69 (**2.50**)	77 (**2.51**)

[a] This cyclization precursor was synthesized by Jean-Grégoire Roveda

Again, it was noted that reduction of primary hydrazones in the six-membered ring precursors gave moderate yields. This can be explained by the fact that dialkylation of the hydrazide is a competitive pathway during the reduction of the hydrazone to the hydrazide.

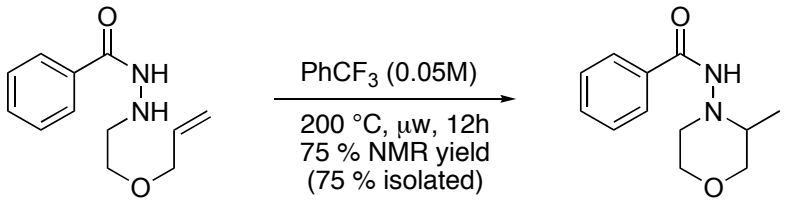
2.7. Synthesis of Additional Hydroamination Products from Benzoic Hydrazides

In order to demonstrate the value of metal-free hydroamination in synthesis and to provide a more robust alternative to our hydroamination/[2,3]-rearrangement sequence,[64] the Beauchemin group has invested considerable time into forming additional substrates via the intramolecular Cope-type hydroamination. After discovering that benzoic hydrazides participated successfully in such reactions, the scope of this metal-free hydroamination approach was explored and established, probing the generality with respect to ring size, alkene substitution and the presence of heteroatoms. An attractive feature of hydrazides, is that in contrast to hydroxylamines, these reactants are typically bench stable, crystalline and more stable upon heating.

To further probe the scope of the Cope-type hydroamination using hydrazines, the presence of heteroatoms in the substrate were considered. It was of interest whether oxygen- and nitrogen-containing reagents could be amenable to hydroamination. Such reagents could provide access to appealing morpholine and piperazine derivatives, respectively.

Utilizing the optimized conditions determined in previous hydroamination reactions, it was found that upon heating hydrazide **2.52** in trifluorotoluene in the microwave at 200 °C for 12 hours, the desired hydroamination product **2.53** was obtained in good NMR yield (Equation 2.11).

[64] Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bedard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874.

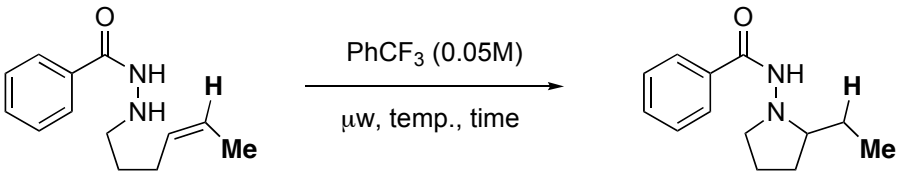


2.52 **2.53** **(2.11)**

Purification of the crude product was achieved using flash chromatography, yielding 75% of the pure morpholine hydroamination derivative. These results provide further proof that the Cope-type hydroamination is broad in scope and that the functional group compatibility of the reaction can be expanded. This work also shows that the Cope-type hydroamination is agreeable with substrates that contain heteroatoms, increasing its usefulness as a synthetic strategy.

Another possibility to increase the substrate scope for such hydroamination reactivity is substitution of the terminal double bond. It has been shown that substitution of the distal alkene renders cyclization more difficult with hydroxylamines and such cyclizations are rarely reported for methods involving transition metal catalyts.[20] Thus, a substrate with a Z-alkene configuration and a terminal methyl group was studied next. The results of which are shown in Table 2.4 below.

Table 2.4: Optimization of Cyclization onto cis-Alkene with Terminal Substitution



2.54 **2.55**

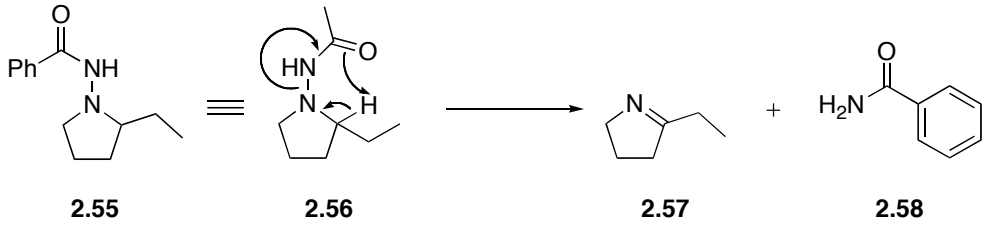
Entry	Temperature (°C)	Time (h)	NMR Yield (%)[a]
1[b]	160	16	5
2[b]	190	20	58
3	200	10	23
4	190	5	57
5	160	5	28
6	175	5	53
7	**175**	**10**	**75[c]**

[a] NMR yield using 1,2-dimethoxybenzene as an internal standard
[b] These reactions were preformed in a sealed tube and heated in a wax bath
[c] Isolated yield

The best trial for the hydroamination reaction was heating the alkylhydrazide in trifluorotoluene at 175 °C for 10 hours in the microwave (entry 7). Under these conditions, a 75% NMR yield of the alkylhydrazide to the desired hydroamination product was observed. Purification by chromatography provided pyrrolidine **2.55** as a white solid in 75% yield. It is worth noting that 10% of starting material remained following the reaction. The remaining mass difference can be accounted for by the formation of an unwanted imine side product (**2.57**), which is highly volatile and evaporates upon heating. Upon formation of the desired hydroamination product (**2.55**), elimination of the benzamide moiety affords this "oxidative" Cope-type hydroamination product (**2.57**, Equation 2.12).[65] The formation of this product has been confirmed by GC/MS and ^{1}H NMR, and further studies have been undertaken by Mr. Francis Loiseau

[65] This is referred to as an "oxidative" Cope-type hydroamination with respect to the alkene.

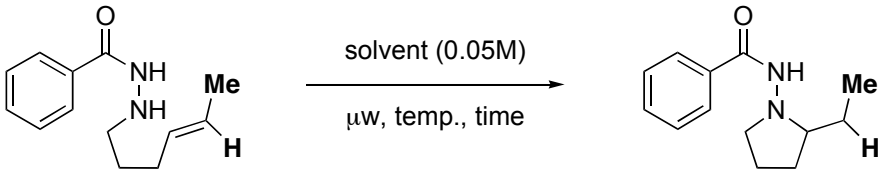
and Mr. Michael Raymond to optimize this reactivity.



2.55 **2.56** **2.57** **2.58** **(2.12)**

It was of interest to determine whether the same hydroamination product **2.55** obtained above could be accessed from both the cis and the trans hydrazide substrates. Thus, cyclization of the trans analogue **2.59** was undertaken next. As performed previously, the trans alkylhydrazide was submitted to a range of hydroamination conditions (Table 2.5).

Table 2.5: Optimization of Cyclization onto trans-Alkene with Terminal Substitution



2.59 **2.55**

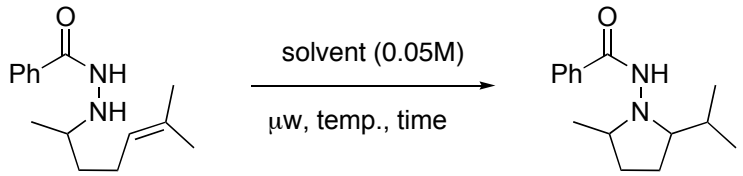
Entry	Solvent	Temperature (°C)	Time (h)	NMR Yield (%)
1	**$PhCF_3$**	**175**	**10**	**61**
2	*n*-PrOH	175	5	45
3	*i*-PrOH	175	5	35

4	*t*-BuOH	175	5	42
5	*t*-BuOH	175	10	59
6	*t*-BuOH	200	10	51

When submitted to the optimized conditions found for the cis alkylhydrazide, the trans alkylhydrazide showed a lower conversion, with only 61% of the hydrazide converting to the desired hydroamination product (versus 75% for the cis analogue). Protic solvents such as alcohols have been shown to increase the conversions of other hydroamination reactions, by helping in the proton transfer step.[24b] In an attempt to increase our conversions, such thinking was applied here, and various alcoholic solvents (*n*-PrOH, *i*-PrOH and *t*-BuOH) were scanned. Although no higher conversion was achieved, the results obtained using alcohols as solvents were promising. In some cases, using *t*-BuOH (entries 5 and 6), conversions similar to the best result were obtained. In these instances, the amount of recovered starting material was significant as well (up to approximately 30% in some cases).

Due to the fact that substitution at the distal position of the alkene has been known to be difficult (see previously mentioned trends in Scheme 1.5),[20] the reactivity of a di-substituted alkene in our reaction became of interest. With this hydrazide in hand, the hydroamination step was attempted and the results of which are summarized in Table 2.6 below.

Table 2.6: Optimization of Hydroamination for gem-Dimethyl Substrate



2.60 **2.61**

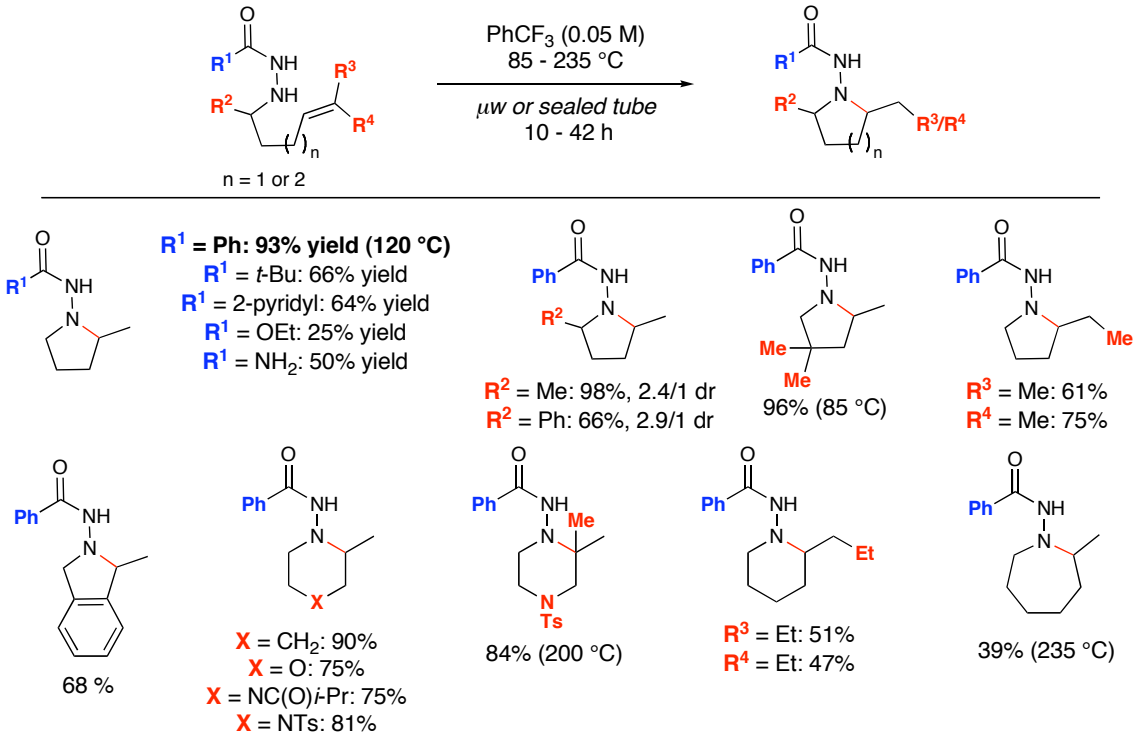
Entry	Solvent	Temperature (°C)	Time (h)	NMR Yield (%)	Starting Material (%)
1	$PhCF_3$	175	12	12	56
2	*t*-BuOH	200	10	21	32
3	*i*-PrOH	180	20	31	40

From the above results, we can see that similar conditions for the hydroamination reaction do not provide good yields in the case of this gem-dimethyl substituted alkene. This is consistent with previous findings regarding substitution at the distal position of the alkene in intramolecular Cope-type alkene hydroamination using hydroxylamines.[20] Although we were unable to attain sufficient yields for this substrate, this study provided us with information regarding the limitations of our methodology, creating an area for improvement in the future.

In collaboration with Mr. Jean-Grégoire Roveda, additional substrates were synthesized in order to expand the substrate scope of the intramolecular Cope-type hydroamination using hydrazides. The complete substrate scope is shown in Table 2.7

below. The extension of this reactivity to a broad range of substrates indicates its' potential utility in the field of organic synthesis.

Table 2.7: Complete Substrate Scope for the Intramolecular Hydroamination of Alkenes Using Hydrazides



2.8. Mechanistic Discussion

2.8.1. Introduction

To fully understand a chemical reaction, the mechanism, or the pathway by which the reaction proceeds must be known. Mechanistic studies are important once a chemical transformation has been somewhat studied, as insight into the mechanistic pathway can

unveil a deeper understanding, possibly allowing for improvements in reactivity, scope and applications of the chemical transformation. The mechanism of a specific reaction can be elucidated using several different techniques of kinetic studies, such as isotopic labeling, trapping of intermediates or through density functional theory (DFT).

2.8.2. Investigations into Intramolecular Cope-Type Hydroamination Using DFT

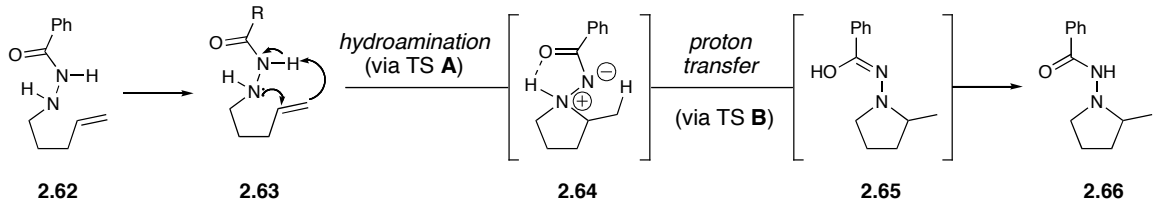
Density fuctional theory, or DFT, is a computational tool used in chemistry to examine the electronic structure of molecules. Using a function of electron density, the properties of a specific molecule in different environments can be determined. Such theoretical calculations allow for better insight into the process for a specific molecule to undergo a particular transformation. Such information proves useful when determining whether a reaction will proceed or which step in a reaction requires the most energy to occur. DFT also allows for the comparison of different molecules as substrates in the same reaction. That is, which molecule would more easily react under a certain set of conditions (which molecule has a lower activation energy). DFT is therefore quite useful in predicting chemical reactivity and also in supporting experimental results.

In order to gain further insight into the intramolecular hydroamination reactivity of alkenes using hydrazides and to support the pathway shown in Scheme 2.6, density functional theory studies were undertaken with Dr. Serge Gorelsky. All calculations were performed using the *Gaussian 03* program[66] in the gas phase at the

[66] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A. ; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi,

B3LYP[67]/TZVP[68] level of theory. Via DFT, the activation energies for a concerted, planar, 5-membered Cope-Type hydroamination transition state were calculated for the reaction of substrate **2.62**.

Scheme 2.6: Intramolecular Alkene Hydroamination Transition States



The activation energies for both transition states involving five and six-membered ring formation were determined to be 28.7 and 34.2 kcal/mol, respectively. In comparison, the activation energies calculated for the parent hydroxylamines were 22.9 and 27.2 kcal/mol, respectively. These results clearly agree with the experimental data, which indicates that higher temperatures (typically ~100 °C higher) are required for the Cope-type hydroamination of hydrazides.

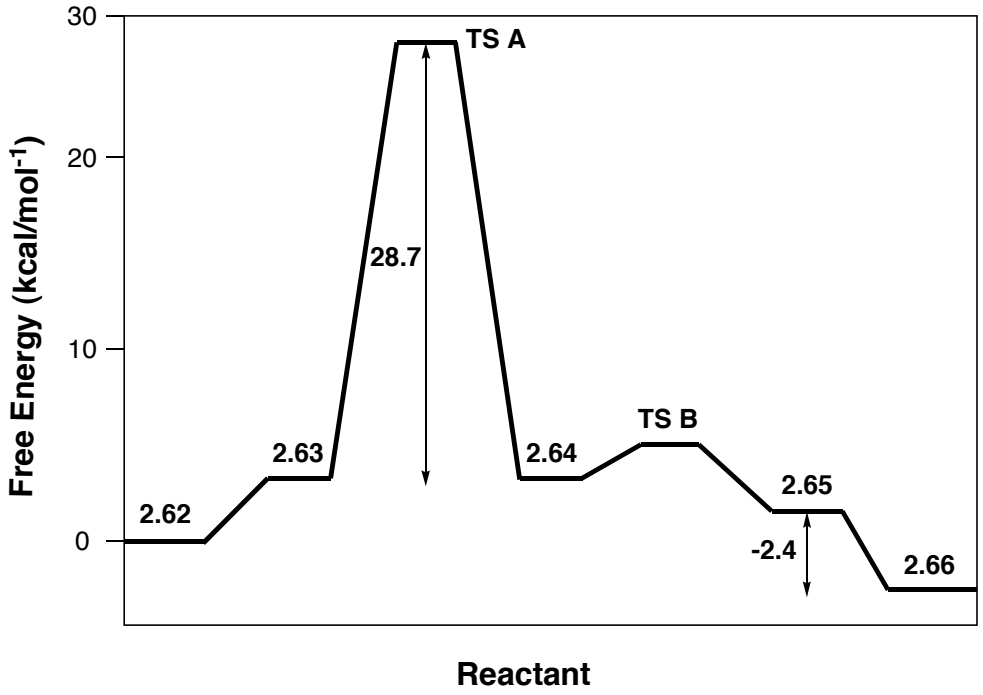
J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: 2003.

[67] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[68] Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.

Scheme 2.7 represents the free energy profile of this reaction. These calculations are consistent with a rate limiting hydroamination event and in agreement with the involvement of the hydrazide carbonyl moiety in the proton transfer step (**2.64,** TS **B**). Experimentally, the intramolecular hydroamination of hydrazides is compatible with many different solvents, and these calculations are in accord with this, indicating that the solvent is not involved in the proton transfer step.

Scheme 2.7: Free Energy of Reaction and Transition States for Intramolecular Cope-Type Hydroamination of Hydrazides via a 5-Membered Transition State



The activation energies needed for both transition states **A** and **B**, 28.7 and 5.2 kcal/mol, were also calculated and their transition state structures are shown in Scheme 2.8. TS structure **A** depicts a concerted asynchronous process and also supports

involvement of the hydrazide group in the proton transfer. From this, we can also deduce that the HOMO of the alkene interacts with the hydrogen atom first, followed by alignment of the N-H bond with the C=O π* orbital (LUMO). From these values, it is clear that the hydroamination step requires much more energy to proceed, indicating that this step is rate limiting. In comparison, the proton transfer step is remarkably facile.

Scheme 2.8: Transition State Structures for Hydroamination (A) and Proton Trafer (B)

A **B**

2.9. Kinetic Studies

2.9.1. Introduction

Reaction kinetics or chemical kinetics is the study of the rates of chemical processes. This includes the examination of how different conditions (e.g. temperature, time, etc.) can affect the rate of a chemical reaction. Knowledge of such changes in a chemical reaction can provide information about the reaction's mechanism. In addition,

information regarding the rate determining step of the reaction, the step whose rate determines the observed rate of product formation, can be obtained as well.

Isotope effects can provide information as to what bonds are broken or formed during a reaction. Substituting one isotope for another, can lead to a change in the overall rate of the reaction if the bond containing that isotope is broken during the rate determining step. When measuring kinetic isotope effects (KIE) for a reaction involving the substitution of a hydrogen with deuterium, the kinetic isotope effect can be expressed as:

$\mathbf{K_H/K_D}$, where K_H = rate with hydrogen and K_D = rate with deuterium

The size of the kinetic isotope effect provides information about the reaction mechanism. If K_H/K_D is greater than one, it can be concluded that the kinetic isotope effect is a result of a bond breaking or forming at the X-H/X-D bond. When K_H/K_D is less than one, the X-H/X-D bond was not involved in a bond breaking or forming step. The study of chemical kinetics and isotope effects is thus an exceptionally valuable tool in interpreting reaction mechanisms.

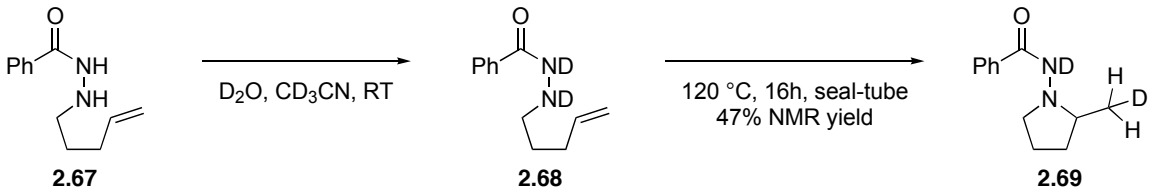
Although performing density functional theory calculations provided us with information about the hydroamination reactivity of hydrazides, it is still of great importance to discover details about how the reaction is proceeding. Previous work done by Oppolzer and Ciganek on intramolecular Cope-type hydromaminations with hydroxylamines provides strong evidence for a concerted process.[22] DFT calculations

into the mechanism of action for hydroxylamine derivatives previously done by the Beauchemin group were consistent with these findings.[23] It follows that the observed reactivity with hydrazides could occur via a similar concerted mechanism. In an attempt to prove this hypothesis, experimental studies have been developed.

2.9.2. Experimental Studies

In order to provide evidence for a concerted mechanism, it must be shown that the hydroamination step as well as the proton transfer step occur simultaneously. Initially, we proposed to do so using isotope effects. Taking a simple hydrazide (**2.67**) previously synthesized by Jean-Grégoire Roveda, which was known to cyclize via hydroamination in good yield, we planned to stir it in D_2O to form hydrazide **2.68**. It was anticipated that this would bring about an exchange between the hydrogen and deuterium atoms. Following exchange, the deuterated hydrazide **2.68** could be subjected to the optimized hydroamination conditions, to yield a hydroamination product in which one of the hydrogens on the methyl group had been substituted for a deuterium (**2.69**, Scheme 2.9). If successful, this deuterated product would show one less proton signal by ^{1}H NMR. Also, in comparing the rate of reaction between the hydrogen and the deuterium compounds, it could be determined whether this N-H/N-D bond was involved in the rate determining step of the reaction.

Scheme 2.9: Kinetic Studies on a Simple 5-Membered Substrate



2.67 **2.68** **2.69**

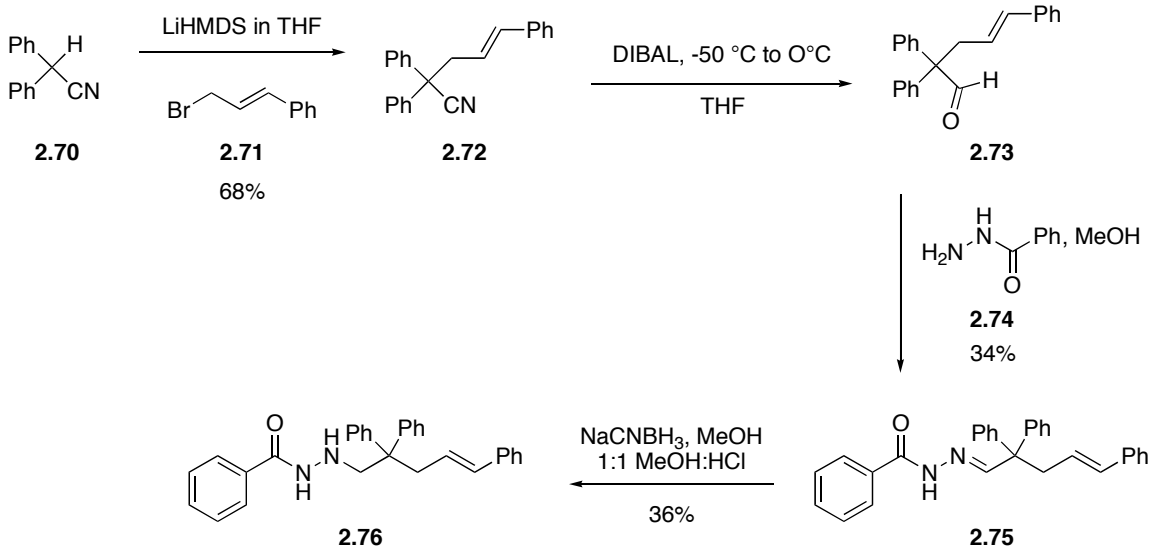
After carrying this out experimentally, it was noticed that there was a significant decrease in the hydroamination yield obtained by ^{1}H NMR. It was possible that the N-H bond was exchanging, and that deuterium was being incorporated, but we could not monitor this by NMR or isolate the deuterated product. Alternatively, a large kinetic isotope effect could exist in this case, and formation of the "H" hydroamination product could form preferentially over that of the "D" hydroamination product, despite the fact that only a small amount may remain following deuteration. After several trials, it was determined that perhaps this substrate would not readily exchange, and that a substrate more prone to cyclization might work more effectively.

2.9.3. Synthesis of E-Alkene for Kinetic Studies

Oppolzer and co-workers had done similar mechanistic studies using hydroxylamines.[22e,f] Looking at the substrate used in their studies, it was realized that a 1,2-di-substituted alkene could more easily prove that the hydroamination process was concerted. In Oppolzer's case, it is believed that the alkene's phenyl substituents were used due to the fact that they were less deactivating and its cyclization was also promoted by a Thorpe-Ingold effect. Based on this reasoning, a new substrate similar to that used

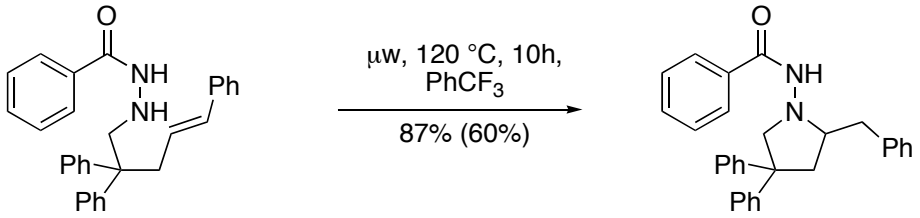
by Oppolzer, replacing the hydroxylamine moiety with our hydrazide functionality, was synthesized according to their procedures (Scheme 2.10).

Scheme 2.10: Synthesis of an Activated Substrate for Kinetic Studies



Alkylation of commercially available diphenylacetonitrile (**2.70**) with cinnamyl bromide (**2.71**) proceeded in 68% yield. The resulting nitrile (**2.72**) was reduced with diisobutylaluminum hydride and the crude product (**2.73**) was used directly in the next reaction due to the potential volatility of the aldehyde formed. From this point, following the procedure developed by Jean-Grégoire Roveda, the aldehyde was condensed with benzoic hydrazide **(2.74)** to form the hydrazone (**2.75**) in 34% yield. Upon reduction with $NaCNBH_3$, the hydrazide **2.76** was obtained (36% yield).

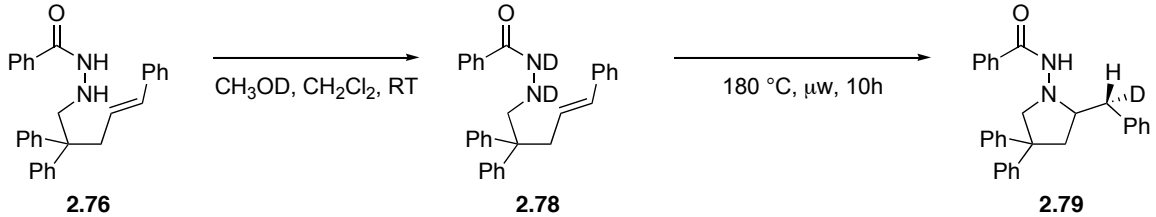
To verify that the hydroamination reaction would proceed, hydrazide **2.76** was submitted to microwave heating at 120 °C for 10 hours (Equation 2.13). After analyzing the ^{1}H NMR, an 87% NMR yield to the cyclized hydroamination product **2.77** was observed (60% isolated yield).



2.76 **2.77** **(2.13)**

With hydrazide **2.76** now in hand, we could return to the kinetic studies. Using similar reasoning as previously described, hydrazide **2.76** was stirred in deuterated methanol to induce exhange. It was observed that the substrate was not completely soluble in CH_3OD, therefore a few milliliters of dry CH_2Cl_2 were added to help solubilize the compound. Following the procedure for deuterium incorporation, the deuterated hydrazide **2.78** was submitted to the hydroamination conditions (μw for 10 hours), raising the temperature to 180 °C as it was expected that the deuterated product may be slower to react, as it is heavier than its hydrogen analogue (see Scheme 2.11).

Scheme 2.11: Deuterium Incorporation and Hydroamination With an Activated Substrate



2.76 **2.78** **2.79**

Following the reaction, a 30% NMR yield to the undeuterated hydroamination product was observed by ^{1}H NMR. This yield is significantly reduced in comparison to the results obtained upon submitting hydrazide **2.76** to the cyclization conditions (without stirring in a deuterium source), indicating that the presence of the deuterium slowed the rate of hydroamination. These results suggest that there is a large kinetic isotope effect, which would be consistent with involvement of the N-D bond in the rate determining step of the reaction. This, combined with the activation energy values obtained by DFT, imply that the hydroamination step is kinetically relevant. Although a numerical value for this kinetic isotope effect cannot be calculated to date, the information that we have gained from these kinetic studies has been of great importance.

2.9.4. Synthesis of Z-Alkene for Kinetic Studies

Synthesis of the cis-analogue of hydrazide **2.76** was the next logical step. It was expected that the cis alkene may be even more reactive towards deuterium incorporation / hydroamination (as it is less stable than its trans counterpart), and that using this substrate may provide us with better and more accurate results. The synthetic route to the Z-analogue is outlined below (Scheme 2.12).

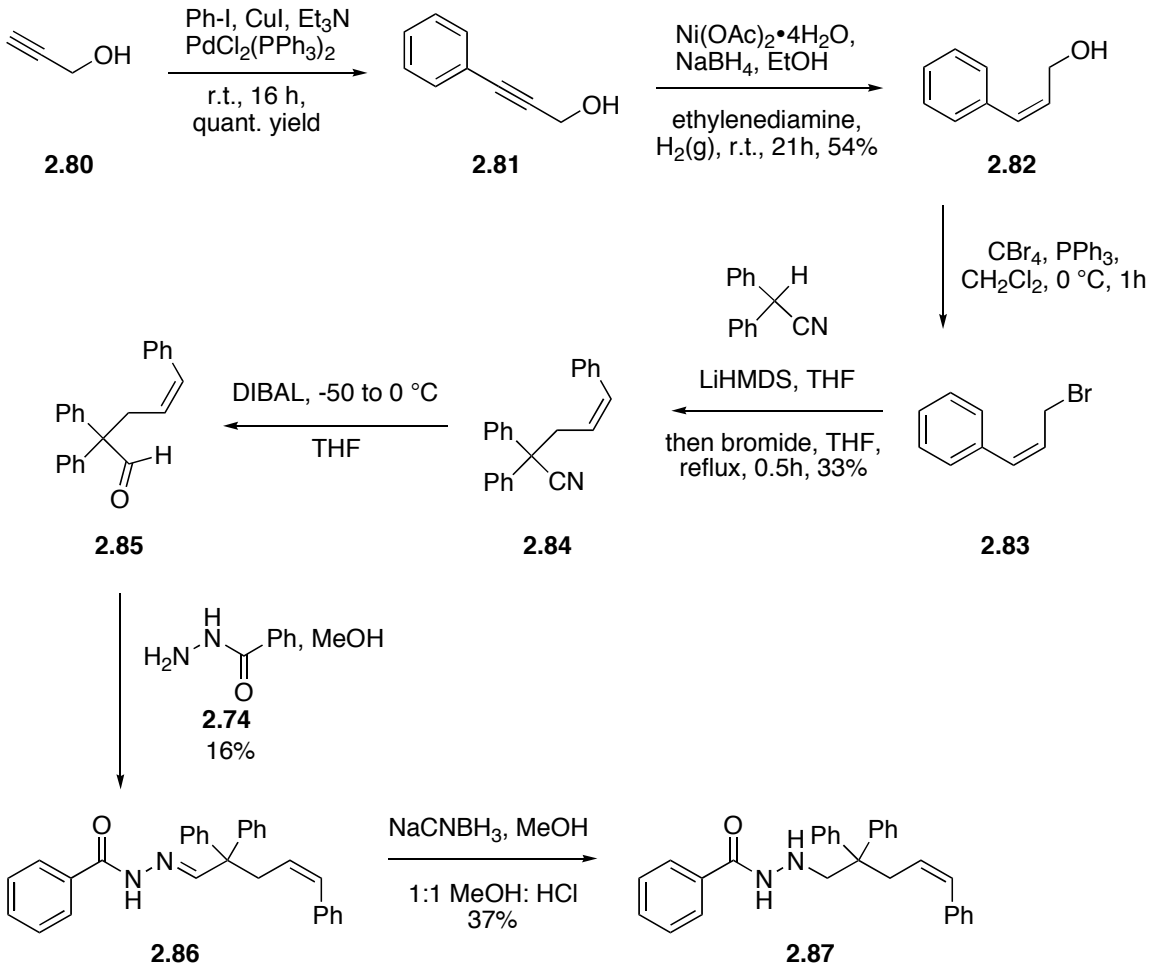
The synthesis of the Z-analogue begins with Sonogashira coupling of commercially available propargyl alcohol (**2.80**) with iodobenzene to give alkynol **2.81** in quantitative yield.[69] Reduction of alknyol **2.81** with $Ni(OAc)_2$ and ethylenediamine under a $H_{2(g)}$

[69] Lin, G.-Y.; Yang, C.-Y.; Lui, R.-S. *J. Org. Chem.* **2007**, *72*, 6753.

atmosphere provided Z-alkene **2.82** in 54% yield.[70] Bromination with CBr_4 and PPh_3 gave the corresponding bromide **2.83** which was used without further purification due to its tendency to isomerize.[71] From here, the synthesis followed the same steps as those outlined for the trans-analogue above. Alkylation of commercially available diphenylacetonitrile with bromide (**2.83**) proceeded in 33% yield.

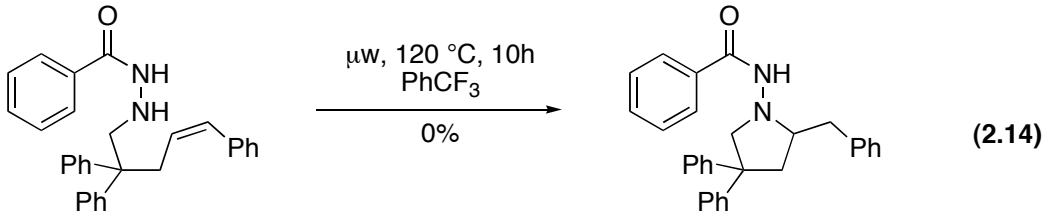
[70] Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.
[71] Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9909.

Scheme 2.12: Synthesis of Activated Z-Analogue for Kinetic Studies



The resulting nitrile (**2.84**) was reduced with diisobutylaluminum hydride and the crude product (**2.85**) was used directly in the next reaction due to the potential volatility of the aldehyde formed. The aldehyde was condensed with benzoic hydrazide to form the hydrazone (**2.86**) in 16%. Upon reduction with $NaCNBH_3$, the hydrazide **2.87** was obtained (37% yield).

To verify that the hydroamination reaction would proceed, hydrazide **2.87** was submitted to the microwave at 120 °C for 10 hours (Equation 2.14). After analyzing the ^{1}H NMR, it was concluded that no cyclized hydroamination product was obtained, and all starting material remained. Several attempts were made to cyclize hydrazide **2.87** (at elevated temperatures and reaction times) and unfortunately none of the desired hydroamination product was ever obtained. It is not understood as to why this Z-analogue would not cyclize, and the only explanation to date is that the cis conformation of the alkene must position the molecule in such a manner that it is not amenable to hydroamination.



2.87 **2.88** **(2.14)**

Although the mechanistic data that we have obtained from both DFT studies and isotopic labeling studies suggests that the intramolecular Cope-type hydroamination with hydrazides proceeds via a concerted mechanism, concrete proof has yet to be obtained. It has been proposed that mechanistic insight into this reaction could be obtained by using Singleton's method to calculate isotope effects based on ^{13}C natural abundance.[72] Efforts to elucidate and confirm the reaction mechanism for the intramolecular Cope-type hydroamination using hydrazides will continue to be a focus in the Beauchemin group.

[72] Singleton, D. A.; Thomas, A. A. *J. Chem. Soc.* **1995**, *117*, 9357.

2.10. Conclusions and Future Work

The Beauchemin group has been able to show that along with hydroxylamines, hydrazides are also amenable to the Cope-type hydroamination. The stability of hydrazides at elevated temperatures and their ease of synthesis make them a practical alternative in hydroamination reactions. Progress toward the synthesis of a range of substrates using metal-free alternatives to hydroamination has been made. Using this methodology, substrates including five, six and seven-membered nitrogen-containing heterocycles, morpholine and piperazine derivatives have been accessed. Motifs such as these are prevalent in both natural products and pharmaceuticals and access to them via Cope-type hydroamination may prove very useful in their synthesis.

Further insight into the hydroamination reactivity of hydrazides as well as the mechanism of action of this reaction would be a significant contribution to this field of chemistry. It is believed that the Cope-type hydroamination of alkenes using hydrazides proceeds through a concerted mechanism, much like hydroxylamines. Data in support of this position has been obtained through both density functional theory calculations and kinetic studies, but more definitive experimental support is still needed.

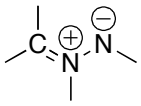
Extensions of the applicability of the Cope-type hydroamination in synthesis and continuation of the work outlined here is currently in progress.

Chapter 3: Intramolecular Cope-Type Hydroamination of Alkynes

Chapter 3: Intramolecular Cope-Type Hydroamination of Alkynes

3.1. Introduction

Azomethine imines belong to a class of organic compounds known as 1,3-dipoles. They are comprised of a central iminium bearing a positive charge that is bonded to a second nitrogen which carries a negative charge, thus making them a dipole (Figure 3.1).



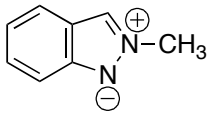
3.1

Figure 3.1: General Structure of Azomethine Imines

The discovery of 1,3-dipoles is intertwined with that of 1,3-dipolar cycloadditions, which are now used extensively in chemistry. The first 1,3-dipolar cycloaddition reaction was discovered by Buchner in 1888[73] and since, these reactions have evolved significantly and a variety of 1,3-dipoles have been discovered.[74] Many types of 1,3-dipoles have found applications in synthesis and this is arguably largely due to the key contributions made by Huisgen in the 1960's.[75,76]

[73] Buchner, E. *Ber. Dtsch. Chem. Ges.* **1988**, *21*, 2637.
[74] Huisgen, R. in *1,3-Dipolar Cucloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, **1984**, vol. 1, p. 1.
[75] Huisgen, R. *Angew. Chem.* **1963**, *75*, 604.
[76] Schantl, J. G. in *Science of Synthesis*; Padwa, A.; Bellus, D., Ed.; Thieme: New York, **2008**, vol. 27, p.731-824.

Azomethine imines went unrecognized until the 1960's, although there are some examples of this class of compounds that have been known for many years. One such example is 2-methylindazole (**3.2**, Figure 3.2), discovered in 1893.[77] Although this dipole is completely incorporated into an aromatic ring, it can still be categorized as an azomethine imine.



3.2

Figure 3.2: Known Azomethine Imine, 2-methylindazole

3.1.1. Structural Characteristics of Azomethine Imines

The structure of a 1,3-dipole has been described as an a-b-c system that can be categorized into two types, the allyl anion type and the propargyl/allenyl anion type.[78] Azomethine imines belong to the allyl anion type, which is characterized by an iminium centre (**atom b** in Figure 3.3).[79]

[77] Schad, P. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 216.
[78] Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
[79] Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.

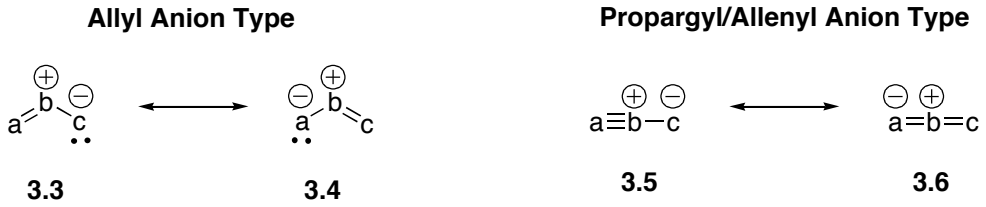
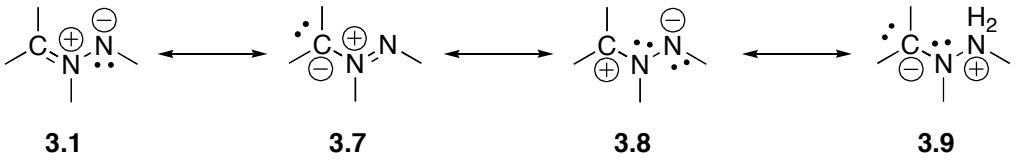


Figure 3.3: Types of 1,3-Dipoles

The allyl anion stabilization can be seen in the resonance structures shown in Scheme 3.1 below.[80] Due to the higher electronegativity of the nitrogen atom compared to that of the carbon, resonance structure **3.1** is most representative of the structure of azomethine imines.

Scheme 3.1: Resonance Structures of Azomethine Imines



3.1.2. Formation and Reactivity of Azomethine Imines

The potential applicability of azomethine imines in synthesis and their general reactivity remains largely unexplored.[74,76,78] In most instances, azomethine imines are intermediates that are subsequently trapped by reaction with dipoloraphiles to form five

[80] Grashey, R. in *1,3-Dipolar Cycloaddition Chemistry*; Padwa A., Ed.; Wiley: New York, **1984**, vol.1, p. 733.

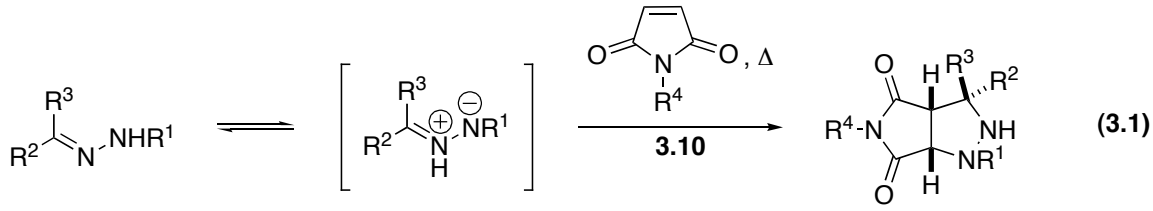
and six-membered heterocyclic rings. They can also react with nucleophiles and undergo other transformations to give rise to final products derived from azomethine imine precursors.[76]

There are four different subclasses of azomethine imines and each subclass is categorized by different structural characteristics as well as different reactivity. There are acylic azomethine imines, azomethine imines with two atoms (C and N or N and N) as part of a ring system and azomethine imines with all atoms incorporated into a ring system.[76] To date, no examples of azomethine imines with only one of the three required atoms embedded in a ring has been documented. [76]

3.1.2.1. Acylic Azomethine Imines

Acylic azomethine imines typically cannot be isolated as the products of reactions, but are common reaction intermediates. They are transformed into various products, usually by reacting with dipoloraphiles in inter- and intramolecular [3 + 2] cycloaddition reactions. For example, arylhydrazones (**3.10**) are assumed to react as azomethine imines (**3.11**) with *N*-arylmalemides (**3.11**) in a sealed tube at 140-150 °C in degassed aromatic solvents to afford tetrahydropyrrolo[3,4-c]pyrazole-4,6(1H,5H)-diones **3.12** (Equation 3.1).[81]

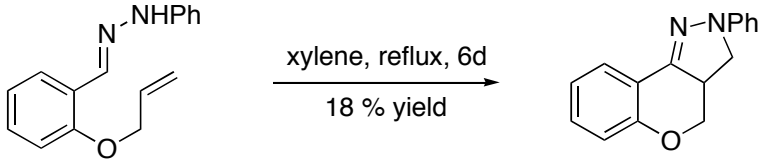
[81] (a) Grigg, R.; Dowling, M.; Jordan, M. W.; Sridharan, V.; Thianpatanagul, S. *Tetrahedron*, **1987**, *43*, 5873. (b) Kanemasa, S.; Tomoshige, N.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3944.



3.10 **3.11** **3.12** **(3.1)**

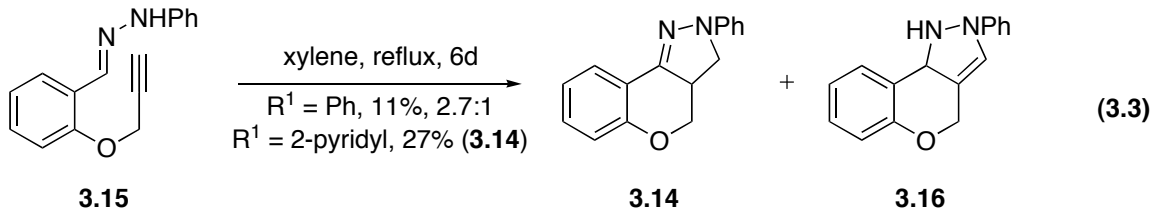
R^1 = Ph, CO_2Et, Me
R^2 = Ph, , 4-$MeOC_6H_4$, 2-pyridyl, CO_2Et, 2-thienyl, Ar
R^3 = H, Me
R^4 = Ph, 4-tol, Me

Grigg was also able to show that acyclic azomethine imines participate in intramolecular [3 + 2] cycloadditions with alkenes and alkynes. When 2-(allyloxy)benzaldehydephenylhydrazone **3.13** was heated, 2-phenyl-2,3,3a,4-tetrahydro[1]benzopyrano[4,3-c]-pyrazole **3.14** was obtained in low yield (Equation 3.2).[81a]



3.13 **3.14** **(3.2)**

The same product **3.14**, along with its regioisomer **3.16** (2.7:1 ratio), were obtained from heating the corresponding alkynyl hydrazone **3.15** under the same conditions (Equation 3.3).[81a] The yields of these reactions could be improved by substituting the phenyl group with a 2-pyridyl functionality.[81a]



3.15 **3.14** **3.16** **(3.3)**

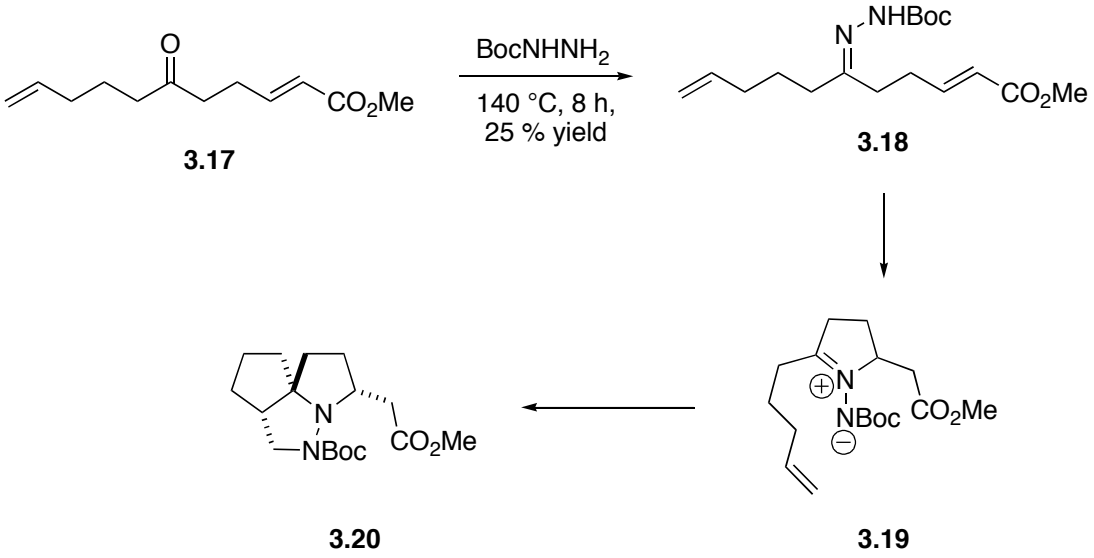
3.1.2.2. *C,N*-Cyclic Azomethine Imines

The second subclass of azomethine imines to be discussed are those that include both a carbon and a nitrogen atom in a ring. The properties and synthetic utility of these C,N-cyclic azomethine imines remains unknown, and examples are rare. Nevertheless, it was found that this type of azomethine imine functionality could be formed via heating a solution of methyl (2E)-6-oxoundeca-2,10-dienoate 3.17 with *tert*-butyl carbazate.[82] This reaction is thought to proceed via formation of the hydrazone 3.18, which then undergoes an intramolecular Michael addition to generate the azomethine imine 3.19. This is then followed by an intramolecular [3 + 2] cycloaddition to give the tricyclic pyrazole 3.20 (

Scheme 3.2).[82]

[82] Dolle, R. E.; Barden, M. C.; Brennan, P. E.; Ahmed, G.; Tran, V.; Ho, D. M. *Tetrahedron*, **1999**, *40*, 2907.

Scheme 3.2: Formation of C,N-Cyclic Azomethine Imine



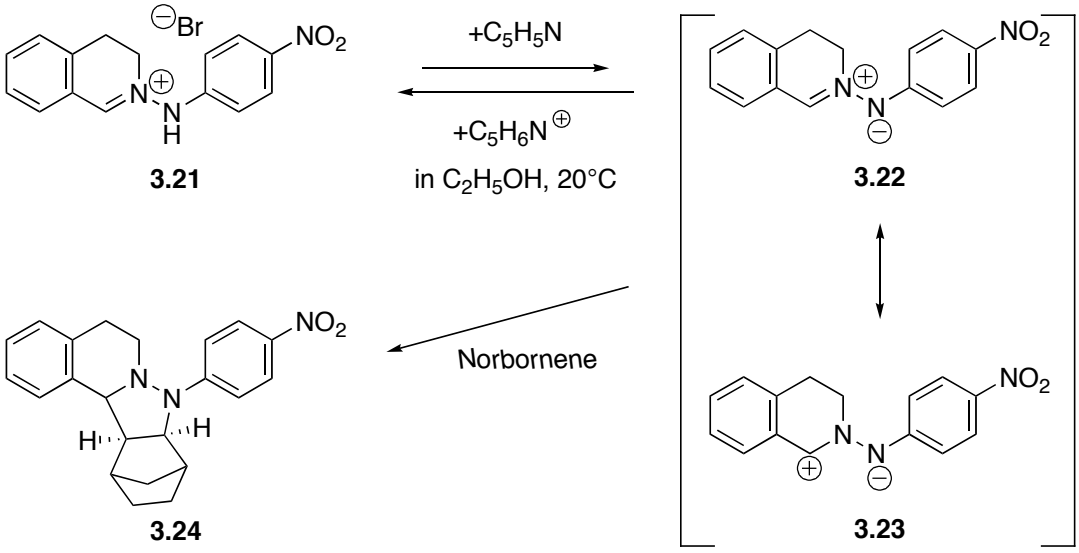
3.17 **3.18** **3.19** **3.20**

Deprotonation of *N*-arylamino-3,4-dihydroisoquinilinium salts, formed from 2-(β-bromoethyl)benzaldehyde and arylhydrazines,[83] yields azomethine imines of this type as well.[78] In the presence of pyridine for example (

[83] Schmitz, E. *Chem. Ber.* **1958**, *91*, 1495.

Scheme 3.3), the hydrazonium bromide 3.21 affords azomethine imine 3.22. Upon addition of norbornene, an almost quantitative yield of the corresponding cycloadduct 3.24 is obtained.[84] These 3,4-dihydroisoquinoline azomethine imines react so well with various alkenes that they can be used as analytical reagents to identify the presence of olefins.[78]

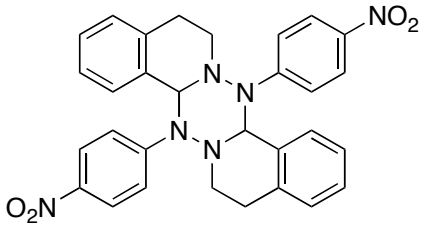
Scheme 3.3: Cycloaddition with 3,4-dihydroisoquinoline Azomethine Imines



In the absence of a dipolarophile, azomethine imine **3.22** exists as the

[84] Huisgen, R.; Grashey, R.; Laur, P.; Lietermann, H. *Angew. Chem*. **1960**, *72*, 416.

hexahydrotetrazine derivative **3.25** shown in below. Similar dimerization is observed for azomethine imines of this type that have a hydrogen, phenyl, *p*-chlorophenyl, benzyl, methyl, etc. on the anionic nitrogen.[83,85] It has been shown that these dimers dissociate at temperatures above 60 °C, providing a stable and convenient source of the respective azomethine imine.[83a]



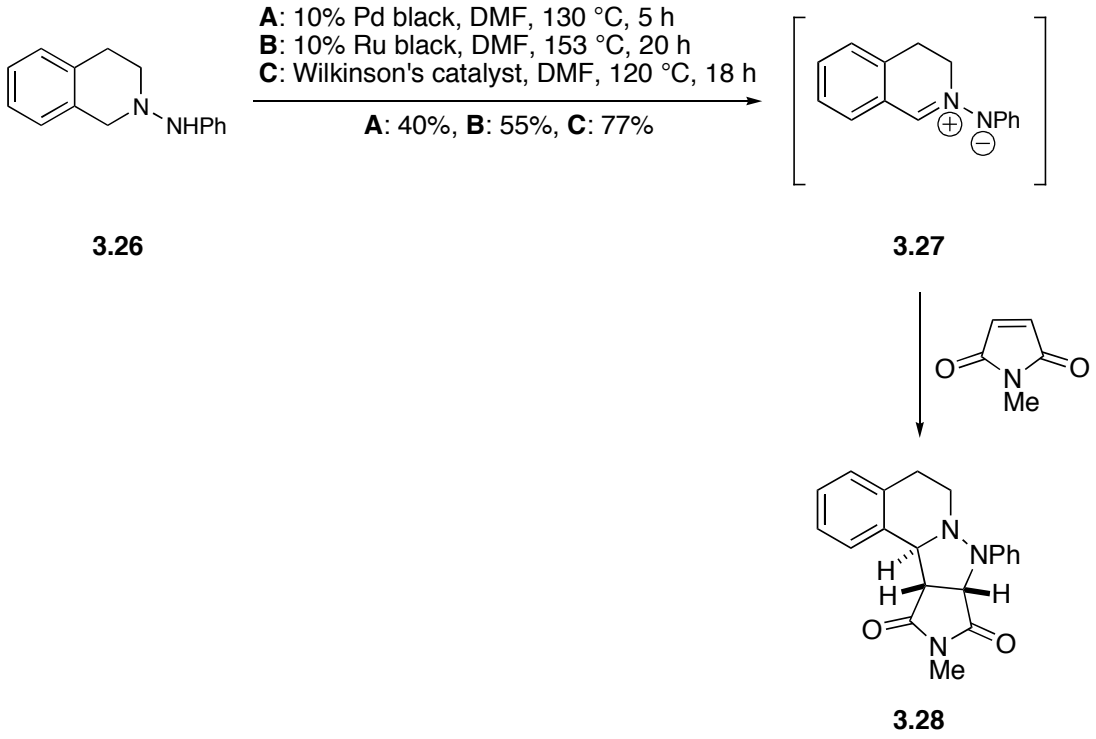
3.25

Figure 3.4: Dimer of Azomethine Imine 3.23

C,N-Cyclic azomethine imines can also be accessed through the catalytic dehydrogenation of amines. *N*-Phenyl-3,4-dihydroisoquinolin-2-(1H)-amine **3.26**, upon heating with palladium black or a similar catalyst in the presence of *N*-methylmaleimide, generates azomethine imine **3.27**, which reacts with the dipoloraphile yielding the cycloadduct **3.28** (Scheme 3.4).

Scheme 3.4: Catalytic Dehydrogenation to Yield Azomethine Imines

[85] Laur, P. Ph.D. Thesis, University of Munchen, **1962.**

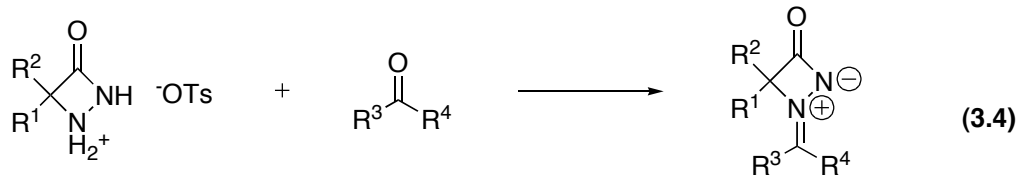


3.26 **3.27** **3.28**

3.1.2.3. *N,N*-Cyclic Azomethine Imines

The third category of azomethine imines incorporates both nitrogen atoms into the ring. Generally most azomethime imines with the N-N bond as part of the ring are accessed via the condensation of 1,2-disubstituted hydrazines that are integrated into four-, five- and six-membered rings.[76] Taylor and coworkers have shown that many 1-methylene-3-oxo-1,2-diazetidin-1-ium-2-ides **3.31** (azomethine imines) are available through the condensation of carbonyl compounds with 3-oxo-1,2-diazetidinium tosylates **3.29** (Equation 3.4).[86]

[86] Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567.



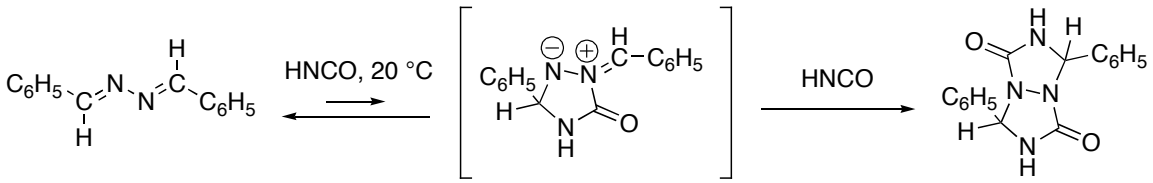
3.29 **3.30** **3.31** **(3.4)**

The reaction is followed by immediate work-up with sodium bicarbonate and works well with arylcarbaldehydes, hetarenecarbaldehydes and aliphatic ketones, but not with aliphatic aldehydes and aryl ketones.[86]

The crisscross addition, that is the addition of aldazines to multiple bonds, was first documented in 1917.[87] In 1963, Huisgen hypothesized that an azomethine imine 3.33 served as a key intermediate in this cycloaddition reaction **(**

Scheme **3.5**)[75] and the mechanistic pathway was later confirmed by isolation of the 1,3-dipole intermediate involved in the reaction of hexafluoroacetone azine with isobutene.[88]

Scheme 3.5: Crisscross Addition via an Azomethine Imine Intermediate

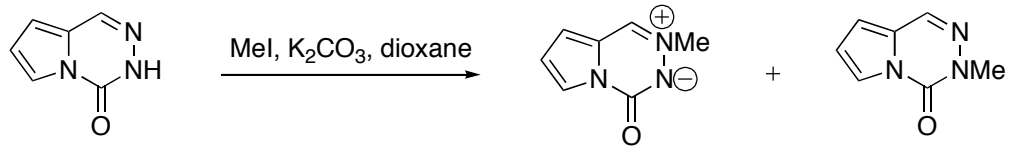


3.32 **3.33** **3.34**

[87] Wagner-Jauregg, T. *Synthesis* **1976**, 349.
[88] (a) Burger, K.; Thenn, W.; Gieren, A. *Angew. Chem. Int. Ed*. **1974**, *13*, 474. (b) Gieren, A.; Narayanan, P.; Burger, K.; Thenn, W. *Angew. Chem. Int. Ed.* **1974**, *13*, 475.

3.1.2.4. *C,N,N*-Cyclic Azomethine Imines

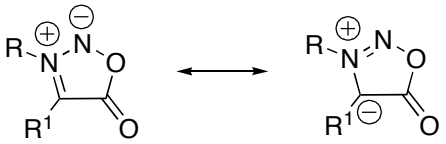
Examples of azomethine imines with all three atoms incorporated in the ring are rare. A product of this type was attained from the alkylation of pyrrolo[1,2-d](1,2,4)triazin-4(3H)-one **3.35**, which can occur at the α- and β-nitrogen atoms of the heterocyclic hydrazide moiety.[89] Azomethine imine **3.36** was obtained in good yield upon alkylation at the β-position in addition to the regioisomer **3.37** (Equation 3.5).[89] Other alkylated/phenylated azomethine imines were obtained in moderate to good yields using this methodology by varying the alkylating agent.



3.35 **3.36** 80% yield + **3.37** 16% yield **(3.5)**

Syndones, described as aromatic azomethine imines, were discovered in 1935,[90] and their structure shown in Equation 3.6 was not confirmed until 15 years later.[91] In the years that followed, their participation and usefulness in cycloaddition reactions was revealed.

[89] Sakai, N.; Funabashi, M.; Hamada, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron*, **1999**, *55*, 13703.
[90] Earl, J. C.; Mackney, A. W. *J. Chem. Soc.* **1935**, 899.
[91] Baker, W.; Ollis, W. D.; Poole, V. D. *J. Chem. Soc.* **1949**, 307.

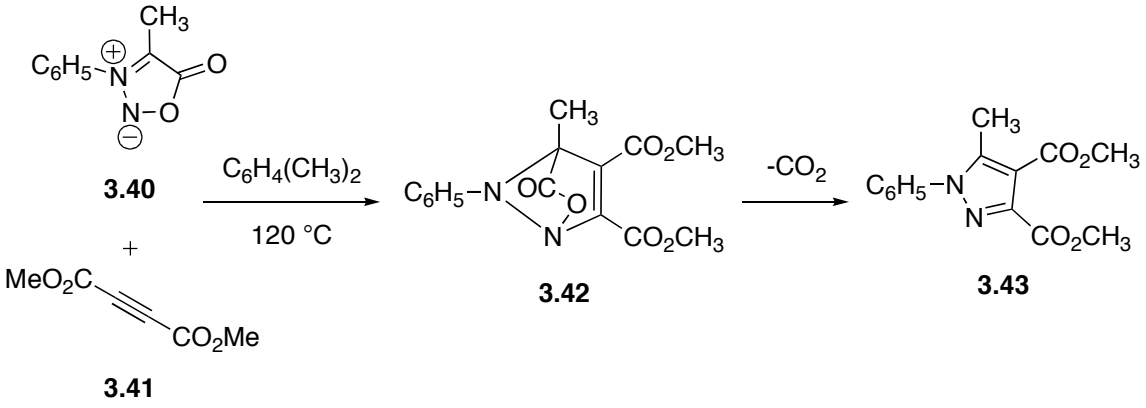


3.38 **3.39** **(3.6)**

When *N*-phenyl-*C*-methyl-syndone (3.40) was heated with dimethyl acetylenedicarboxylate (3.41) for one hour at 120 °C, a quantitative yield of dimethyl-1-phenyl-5-methyl-pyrazole-3,4-dicarboxylate (3.42) was obtained upon evolution of CO_2 gas (

Scheme **3.6**).[92]

Scheme 3.6: Generation of a C,N,N-Cyclic Syndone



3.40 **3.41** **3.42** **3.43**

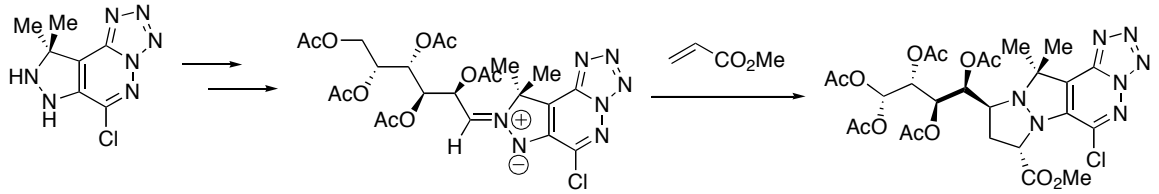
The scope of this reactivity is broad, as reactions of syndones with acetylene, 1-octyne, phenylacetylene, propargyl alcohol and phenylbenzoylacetylene all proceed in good yield.[92] This methodology is important as it unveiled a new synthetically useful preparation of pyrazoles.

[92] Huisgen, R.; Grashey, R.; Gotthardt, H.; Schmidt, R. *Angew. Chem. Int. Ed.* **1962**, *1*, 48.

3.1.3. Azomethine Imines in Asymmetic 1,3-Dipolar Cycloadditions

The use of azomethine imines in asymmetric 1,3-dipolar cycloaddition reactions has been limited and the focus in the past has been on the stereoselective synthesis of C-nucleosides using chiral azomethine imines. Chiral azomethine imines can be formed via dihydropyrazole derivatives through condensation with carbohydrate-derived aldehydes.[93] Such chiral azomethine imines can then undergo cycloaddition reactions to provide the nucleoside. Scheme 3.7 shows the formation of a nucleoside from the reaction of an azomethine imine and methyl acrylate. These 1,3-dipolar cycloaddition reactions were found to be highly stereoselective, showing greater than 95% diastereomeric excess in almost all of the cases.[93,94]

Scheme 3.7: Formation of C-Nucleoside via Cycloaddition of Azomethine Imine



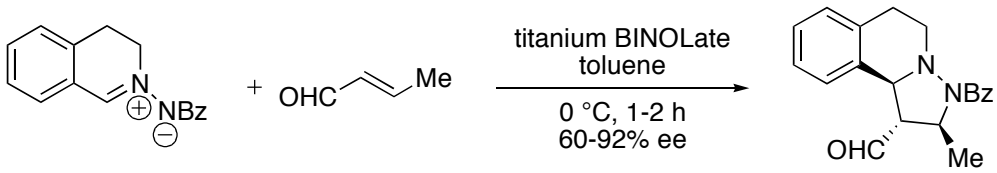
3.44 **3.45** **3.46**

Recent developments in the area of asymmetric 1,3-dipolar cycloadditions have indicated that azomethine imines could provide access to synthetically relevant

[93] Zlicar, M.; Stanovnik, V.; Tisler, M. *Tetrahedron* **1992**, *48*, 7695.
[94] (a) Zlicar, M.; Stanovnik, V.; Tisler, M. *J. Heterocycl. Chem.* **1993** *30*, 1209. (b) Stanovnik, V.; Jelen, B.; Zlicar, M. *Farmaco* **1993**, *48*, 231.

heterocycles.[95] Methods employing catalytic metallo- and organocatalysts have been achieved effectively, aiding asymmetric 1,3-dipolar cycloaddtions with a range of dipolarophiles.[95] Still, this reactivity has been limited to the use of *N,N'*-cyclic azomethine imines as the 1,3-dipole and this dramatically decreases its synthetic utility.

Maruoka recently reported the use of *C,N*-cyclic azomethine imine **3.47** with crotonaldehyde (**3.48**) in a highly enantioselective asymmetric 1,3-dipolar cycloaddition that is catalyzed by a titanium-BINOLate complex (Equation 3.7).[95] The corresponding cycloadduct **3.49** was formed in high yield with moderate to excellent selectivity in the presence of a catalyst formed using a 1:1 ratio of $Ti(O^iPr)_4$ and (*S*)-BINOL.



3.47 **3.48** **3.49** **(3.7)**

Investigation of other titanium-BINOLates using the same reaction conditions revealed that a 2:1 ratio of (*S*)-BINOL:$Ti(O^iPr)_4$ in toluene at 0 °C provided the cycloadduct **3.49** in 94% yield with excellent enantio- and diastereoselectivity.[95] In this reaction, 5-, 6- and 7-methyl substituents on the azomethine imine were well tolerated, in addition to azomethine imines with a variety of electron-withdrawing or electron-donating groups.[95] With respect to the α,β-unsaturated aldehyde, longer alkyl chains as well as an aromatic group were acceptable at the β-position and less reactive α,β-

[95] Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076.

disubstituted enals could also be used.[95] The absolute stereochemistry, determined by X-ray crystallography, confirmed the exoselective preference of this 1,3-dipolar cycloaddition.[95] This method was also applied to the development of *C,N*-cyclic azomethine imines that are not fused to an aromatic ring.

In summary, there are several categories of azomethine imines that differ in their structural properties as well as in their reactivity. Azomethine imines are very reactive species. Due to this they can be unstable and are usually used as intermediates in a reaction rather than being isolated in their pure form. It has been shown that electron-withdrawing groups can aid in stabilizing the negative charge,[96] but in most cases, azomethine imines are produced *in situ* and subsequently trapped.[80] Examples of the different types of azomethine imines as well as examples of their reactivity, including asymmetric variants have been discussed. Studies based on the formation and the synthetic potential of azomethine imines are in their infancy, thus the discovery of new classes or reactions of these compounds will present opportunities for growth in this field of chemistry.

3.2. Project Objectives

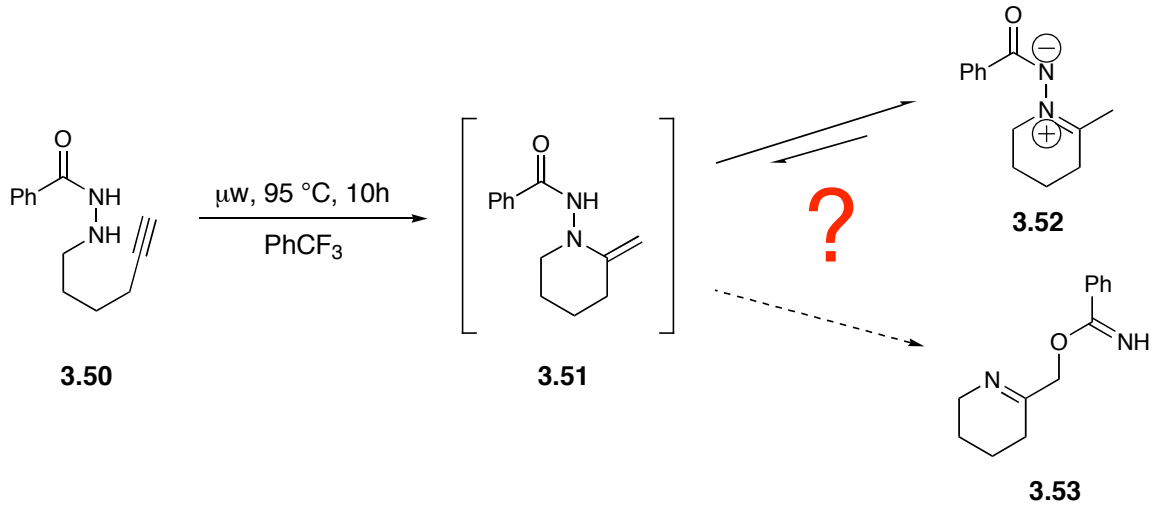
[96] Huisgen, R.; Fleischmann; Eckell, A. *Chem. Ber.* **1977**, *110*, 500.

In light of the good results obtained for the intramolecular hydroamination of alkenes using hydrazides, it was of interest to develop similar reactivity with alkynes. It has previously been shown that the intramolecular hydroamination of alkynes using hydroxylamines proceeds in good yields, providing a convenient route to endocyclic nitrones.[23] It was believed that analogous hydroamination reactivity should also occur with hydrazide derivatives.

3.3. Toward Intramolecular Hydroamination of Alkynes Using Hydrazides

It was hypothesized that alkynylhydrazide cyclization precursors could be synthesized using similar methodolody to that developed for the formation of alkenyl hydrazides. However, the type of products that could be attained upon submitting these alkynylhydrazides (**3.50**) to the optimized cyclization conditions was unknown, as it was envisioned that the hydroamination product **3.51** undergo a proton transfer to a more stable product, azomethine imine **3.52** or undergo a [3,3]-sigmatropic rearrangement to form **3.53** (Scheme 3.8).

Scheme 3.8: Proposed Products from the Intramolecular Hydroamination of Alkynes Using Hydrazides

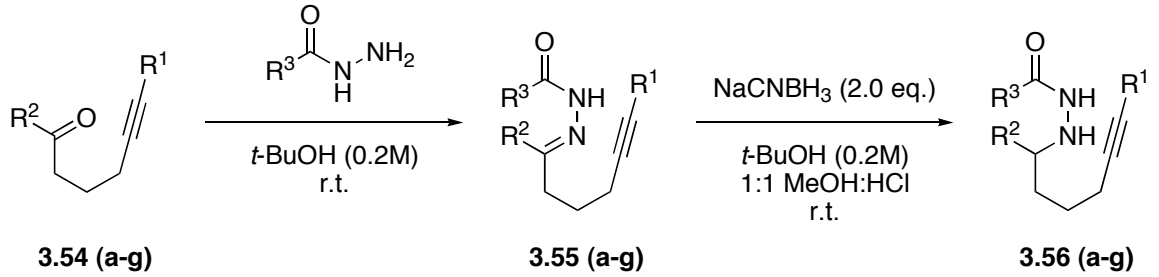


Throughout the course of these investigations, it was revealed that upon cyclization, novel azomethine imine products were being produced. In the following chapter, our method of accessing and isolating derivatives of these interesting compounds will be discussed.

3.3.1. Preliminary Substrate Scope for the Intramolecular Hydroamination of Alkynes using Hydrazides

To investigate the reactivity of alkynylhydrazides with regards to intramolecular hydroamination, several cyclization precursors were synthesized. Having previously developed good methodology for accessing the alkenyl cyclization precursors, the same procedure was used for alkynes. Table 3.1 summarizes the six-membered hydroamination precursors that have been synthesized to date.

Table 3.1: Synthesis of Six-Membered Ring Precursors



3.54 (a-g) **3.55 (a-g)** **3.56 (a-g)**

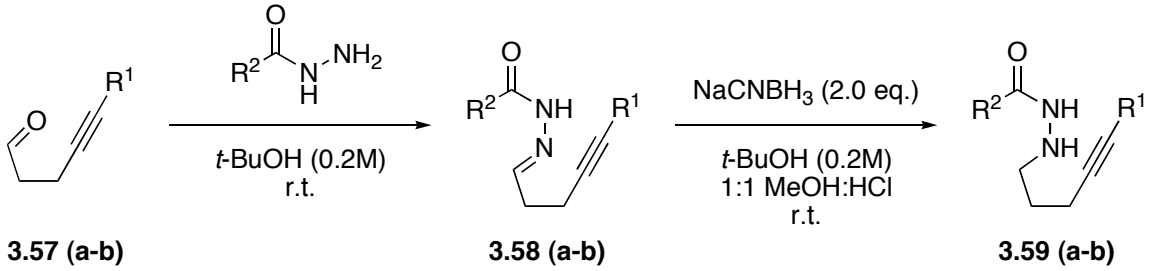
Entry	R^1	R^2	R^3	Reduction Yield (%)[a]
1	H	H	Ph	48 (**3.56a**)
2	H	H	$(CF_3)_2Ph$	57 (**3.56b**)
3	Ph	H	$(CF_3)_2Ph$	quant. (**3.56c**)
4	C_8H_9	H	$(CF_3)_2Ph$	56 **(3.56d)**
5[c]	C_6H_4Br	H	$(CF_3)_2Ph$	18 **(3.56e)**
6	H	Me	$(CF_3)_2Ph$	55 **(3.56f)**
7[c]	H	Bu	$(CF_3)_2Ph$	40 **(3.56g)**

[a] The yields reported are for the 2-step sequence; hydrazone formation and reduction of the hydrazone. [b] This hydrazone was formed in MeOH, and isolated by column chromatography in 63% yield prior to reduction. [c] These entries were synthesized by Ms. Sandrine Taing.

The hydrazides were all obtained in reasonable yields using this methodology. For entry 1, the hydrazone was formed in MeOH and isolated by column chromatography prior to reduction. All other hydrazones were not isolated in their pure form, but rather the hydrazide was accessed from the *in situ* reduction of the hydrazone in *t*-BuOH. Entries 1 and 2 were synthesized from the corresponding commercially available alcohols and entries 3-7 from the alkylated alcohols.

Using the same reductive amination procedure, five-membered hydroamination precursors were synthesized as well and are shown in Table 3.2. Again, the hydrazones **3.58** were not isolated, but directly reduced to the respective hydrazides **3.59**, which could be isolated by column chromatography in moderate yields.

Table 3.2: Synthesis of Five-Membered Precursors



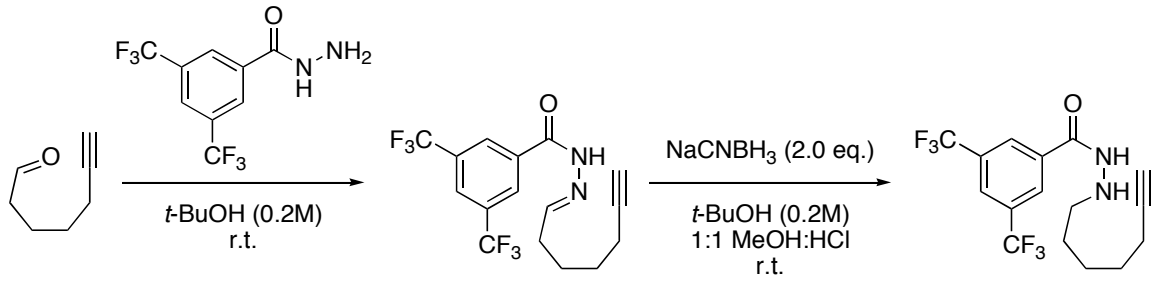
3.57 (a-b) **3.58 (a-b)** **3.59 (a-b)**

Entry	R^1	R^2	Reduction Yield (%)[a]
1	H	$(CF_3)_2Ph$	31 (**3.59a**)
2	Ph	$(CF_3)_2Ph$	38 (**3.59b**)

[a] The yields reported are for the 2-step sequence; hydrazone formation and reduction of the hydrazone

In addition to the five- and six-membered substrates, a seven-membered cyclization precursor was synthesized (Table 3.3). The hydrazone **3.61** was reduced *in situ* to give the hydrazide **3.62** in moderate yield.

Table 3.3: Synthesis of a Seven-Membered Precursor



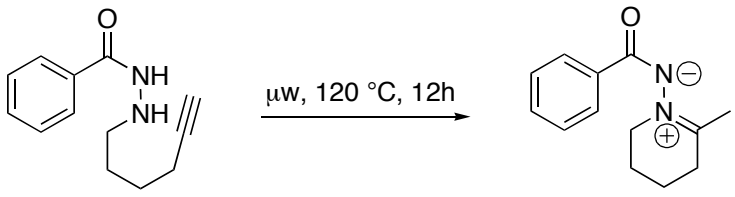
3.60 **3.61** **3.62**

Entry	R^1	R^2	Reduction Yield (%)[a]
1	H	$(CF_3)_2Ph$	42 (**3.62**)

[a] The yield reported is for the 2-step sequence; hydrazone formation and reduction of the hydrazone.

3.3.2. Intramolecular Hydroamination of Alkynes

To develop this Cope-type hydroamination reactivity with alkynes, a six-membered alkynyl hydrazide was first investigated. Upon heating hydrazide **3.56a** under the optimized hydroamination conditions found for alkenes (120 °C for 10 hours in $PhCF_3$), it was seen that all of the starting material was consumed by TLC (Equation 3.8).



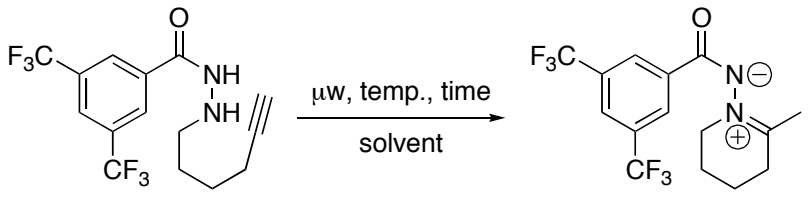
3.56a **3.63** **(3.8)**

This observation was also confirmed by ^1H NMR, but unfortunately several attempts to isolate the products formed were unsuccessful. Although we were unable to

isolate a pure product, information from the NMR's obtained suggested that dipolar azomethine imine product **3.63** was likely obtained. It was thought that the isolation issue might thus be due to the instability or decomposition of the product.

With isolation being an issue, the focus of the project turned to modifying the alknylhydrazide so that the product obtained following hydroamination would be stable. Previous studies had indicated that optimized electron withdrawing groups helped to stabilize the dipole structure developing in the transition state which lead to improved hydrohydrazidation chemistry.[96] Mr. Francis Loiseau and Mr. Michael Raymond had been having success using a 3,5-bis(trifluoromethyl)-substituted hydrazide in their studies on oxidative hydroamination, therefore it was believed that the use of this hydrazide moiety may be helpful. The results of these studies are outlined in Table 3.4.

Table 3.4: Optimization of 3,5-bistrifluoro-substitituted Alkynylhydrazide



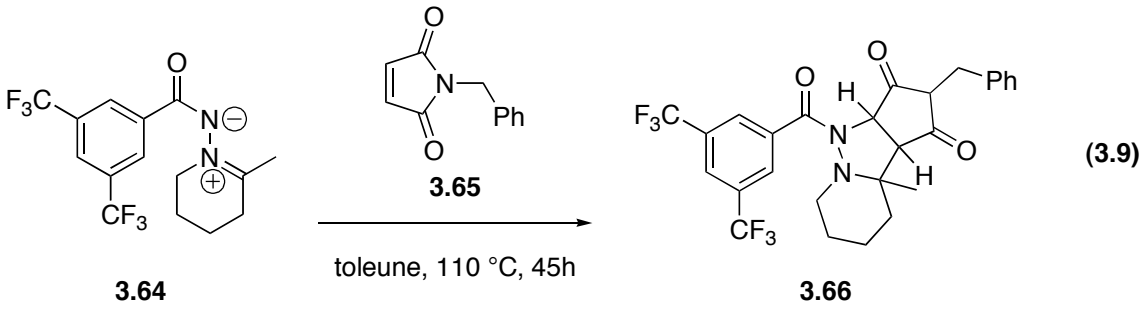
3.56b **3.64**

Entry	Solvent	Temperature (°C)	Time (h)	NMR Yield (%)
1	$PhCF_3$	90	10	41

2	$PhCF_3$	95	12	48
3	**$CDCl_3$**	**90**	**12**	**85**
4	d_6-DMSO	90	12	0

As it can be seen in entry 3, the best results were obtained when hydrazide **3.56b** was heated at 90 °C for 12 hours in deuterated chloroform. By running the reaction in $CDCl_3$, a ^1H NMR could be taken directly following the reaction, eliminating any loss or decomposition of the product upon evaporation. It was this solvent that allowed clear confirmation that it was in fact an azomethine imine that was generated upon the hydroamination of these alkynylhydrazides. The azomethine imine obtained was stable on silica gel, but unfortunately could not be obtained in the purity level required for characterization. It was also discovered that these azomethine imines were unstable and prone to decomposition upon sitting at room temperature overnight.

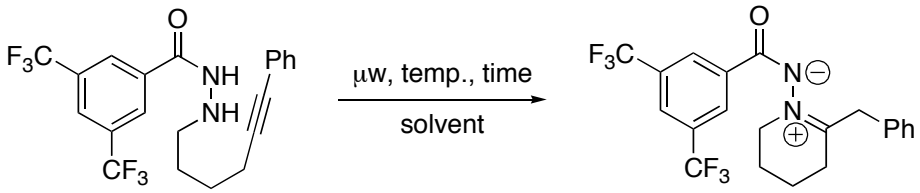
It is known from the literature that these azomethine imines participate in 1,3-dipolar cycloaddition reactions. In order to isolate a derivative of the azomethine imine in pure form and to provide further proof that the product generated was in fact azomethine imine **3.64**, it was trapped in a cycloaddition reaction using *N*-benzylmaleimide (**3.65**) as the dipolarophile (Equation 3.9). The desired cycloadduct **3.66** was obtained in 42% yield, confirming the presence of the azomethine imine starting material.



(3.9)

Next, it was of interest whether substitution at the terminal position of the alkyne could be tolerated, as this would be an important factor in the application of such substrates in synthesis. Hydrazide **3.56c**, with a phenyl substituent on the alkyne was thus investigated and optimization of the hydroamination conditions for this substrate can be seen in Table 3.5.

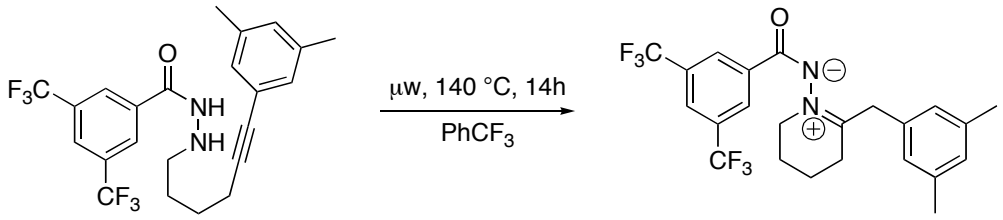
Table 3.5: Optimization of Terminally Substituted Alkyne for Hydroamination



Entry	Solvent	Temperature (°C)	Time (h)	NMR Yield (%)
1	$PhCF_3$	100	12	29
2	$PhCF_3$	120	14	76
3	**$PhCF_3$**	**140**	**14**	**81**
4	$CDCl_3$	110	16	76

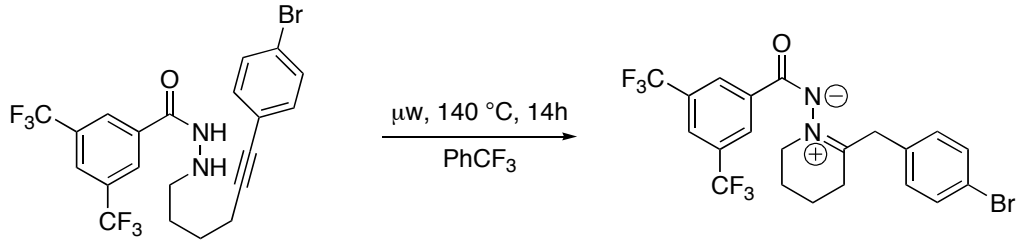
It was observed that as predicted, a substrate with substitution at the terminal alkyne would require increased temperatures to undergo hydroamination. The best results were obtained when hydrazide **3.56c** was heated in the microwave in $PhCF_3$ at 140 °C for 14 hours (entry 3). After several trials, the azomethine imine **3.67** was successfully isolated in a 72% yield when the cyclization was performed on a larger scale. It is believed that the phenyl functionality on the alkyne provides further stabilization, in addition to the 3,5-bistrifluoromethyl-moiety, and that this allowed isolation of the azomethine imine in good yield. Application of this isolation procedure on azomethine imine **3.64** (which could not be isolated previously) allowed for a 68% isolated yield of the desired product. With an optimized isolation process in hand, the focus of the project now turned to extension of the substrate scope.

Due to the fact that alkynlhydrazides with an aryl substituent on the alkyne seemed to produce stable azomethine imines, it was of interest to synthesize other substrates with various aryl functionalities. An alkynylhydrazide with a xylyl group at the distal position of the alkyne was formed, and when this hydrazide **3.56d** was submitted to the reaction conditions (140 °C for 14 hours), azomethine imine **3.68** was afforded in 91% yield (Equation 3.10).



3.56d **3.68** **(3.10)**

Substrates that prove to be the most useful synthetically are those that have functional groups that can be further modified in following reactions. The alkylhydrazide **3.56e** with a *p*-bromoaryl group on the alkyne was synthesized next, as it was understood that the bromo-group could prove useful in functional group transformations. This alkylhydrazide prepared by Ms. Sandrine Taing and cyclized to give azomethine imine **3.69** in 66% isolated yield (Equation 3.11).



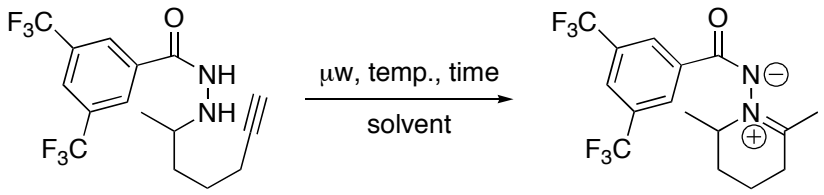
3.56e **3.69** **(3.11)**

Now that substitution at the distal position of the alkyne had been shown to proceed with a variety of different groups, the next step was to show that substitution at other positions on the ring could be tolerated. With this in mind, cyclization precursors with substitution at the position alpha to the ring nitrogen were made.

Using commercially available hex-5-yn-1-ol, oxidation to the corresponding aldehyde, followed by alkylation with MeMgBr provided the Me-alkylated alcohol,

which after another oxidation could be transformed in alkylhydrazide **3.56f** using the reduction amination approach. This alkylhydrazide was then submitted to the hydroamination conditions, and optimization of this process is shown in Table 3.6.

Table 3.6: Optimization of a Methyl-Substituted Alkyne for Hydroamination



3.56f **3.70**

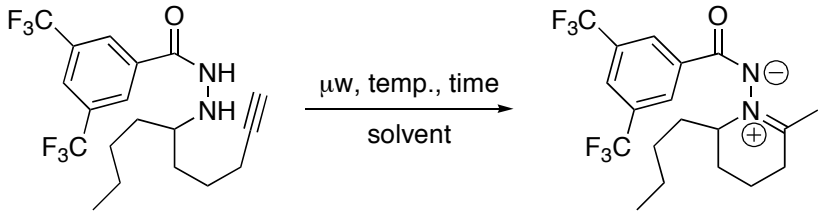
Entry	Solvent	Temperature (°C)	Time (h)	Isolated Yield (%)
1	$PhCF_3$	140	14	48
2	$PhCF_3$	120	14	66
3	**$PhCF_3$**	**110**	**14**	**91**

It was noted that an alkylhydrazide with substitution at the position alpha to the ring nitrogen is amenable to hydroamination. From these studies it can be seen that the best results were obtained when alkylydrazide **3.56f** was heated in the microwave at 110 °C for 14 hours, garnering azomethine imine **3.70** in 91% isolated yield.

Curious as to whether other substituents could be allowed at this position, the formation of additional alkynylhydrazides of this type were started. Ms. Sandrine Taing was able to synthesize alkynylhydrazide **3.56g** using the same procedure as outlined

above by substituting *n*-BuMgCl as the alkylating agent. Using similar hydroamination conditions, this alkylhydrazide was transformed to the respective azomethine imine **3.71** and optimization of this process is shown in Table 3.7 below.

Table 3.7: Optimization of a Butyl-Substituted Alkyne for Hydroamination



3.56g **3.71**

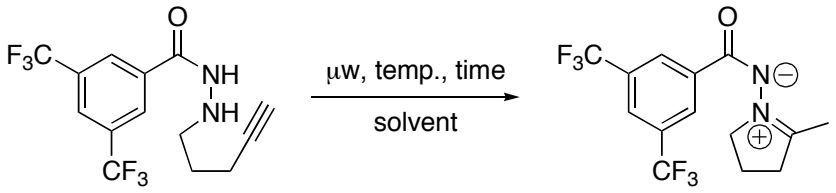
Entry	Solvent	Temperature (°C)	Time (h)	Isolated Yield (%)
1	$PhCF_3$	140	14	32
2	**$PhCF_3$**	**120**	**14**	**93**

This substrate shows that more bulky alkyl chains are well tolerated in this hydroamination reaction. The best trial was conducted in the microwave at 120 °C for 14 hours and afforded azomethine imine **3.71** in 93% isolated yield. Studies into other substituents at this position, including a phenyl group are currently underway.

With the promising results for the intramolecular hydroamination of 6-membered alkynlhydrazides, the focus now turned to demonstrating that other ring sizes could be used in these reactions. To do this, a 5-membered alkynlhydrazide **3.57a**, which could be

synthesized from commercially available 4-pent-yn-1-ol was first investigated and the results of which are summarized in Table 3.8.

Table 3.8: Optimization of a 5-Membered Alkyne for Hydroamination



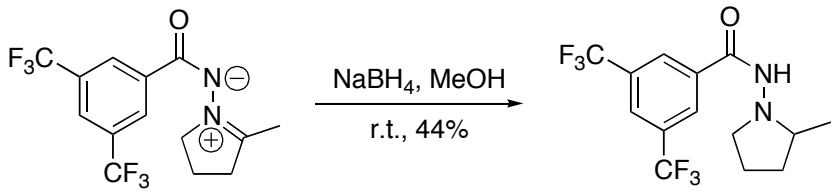
3.57a **3.72**

Entry	Solvent	Temperature (°C)	Time (h)	NMR Yield (%) (isolated yield)
1	$PhCF_3$	140	14	43 (10)
2	$PhCF_3$	140	14	45

This 5-membered alkynylhydrazide **3.57a** participated in the hydroamination reaction, producing a 45% NMR yield of azomethine imine **3.72**. However, attempts at isolating the azomethine imine by column chromatography proved difficult, resulting in only 10% isolated yield.

A strategy for the isolation of this azomethine imine was thus necessary. Given our previous experience with the isolation of hydrazides, reduction of the azomethine imine was attempted. Azomethine imine **3.72** was formed via the hydroamination of alkynylhydrazide **3.57a** in 45% NMR yield, and this was immediately subjected to $NaBH_4$ in methanol (Equation 3.12). The saturated analogue **3.73** was obtained in 44%

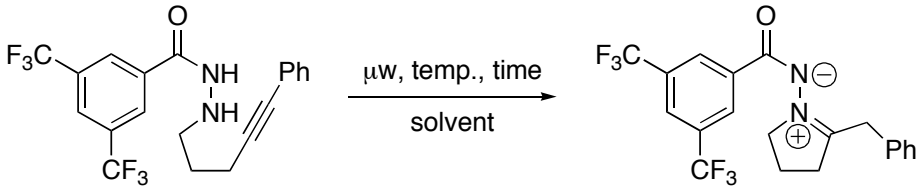
isolated yield, demonstrating that this is a successful method to derivatize azomethine imines to isolable species.



3.72 **3.73** **(3.12)**

In order to see if stable versions of five-membered azomethine imines could be obtained, it was rationalized that a phenyl group at the distal position of the alkyne might stabilize the azomethine imine, much like with the six-membered substrates. Thus, alkynlhydrazide **3.57b** was prepared, and the optimization of its use for hydroamination is presented in Table 3.9.

Table 3.9: Optimization of a 5-Membered Substrate with Phenyl Substitution for Hydroamination



3.57b **3.74**

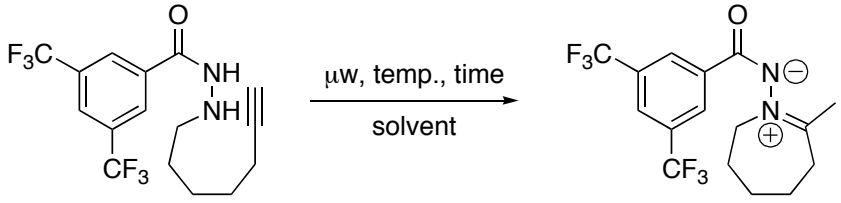
Entry	Solvent	Temperature (°C)	Time (h)	NMR Yield (%) (isolated yield)
1	$PhCF_3$	140	14	31

2	$PhCF_3$	160	14	60 (57)
3	**$PhCF_3$**	**150**	**14**	**67 (62)**

As hypothesized, the phenyl substituent on the alkyne of azomethine imine **3.74** allowed for its isolation, which could be due to the increased steric bulk and thus easier purification by chromatography, or alternatively by attenuating the reactivity of the product or other derived tautomers (see Scheme 3.8), or simply by preventing dimerization. The best results for this substrate were obtained when alknylhydrazide **3.57b** was submitted to the microwave at 150 °C for 14 hours, allowing for the isolation of azomethine imine **3.74** in 67% yield.

Next, a seven-membered cyclization precursor was synthesized, to verify whether larger ring sizes could partake in these intramolecular hydroamination reactions. Starting with commercially available heptynoic acid, this was reduced with $LiAlH_4$ to give hept-6-yn-1-ol in nearly quantitative yield. From here, hept-6-yn-1-ol was oxidized to the aldehyde, which was subsequently converted to the alkynylhydrazide, via the hydrazone in the usual manner. The alkynlhydrazide **3.62** was subjected to the hydroamination conditions, and the results of this are shown in Table 3.10.

Table 3.10: Optimization of a 7-Membered Alkyne for Hydroamination



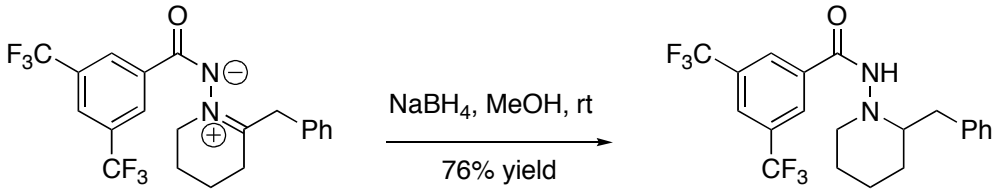
3.62 **3.75**

Entry	Solvent	Temperature (°C)	Time (h)	NMR Yield (%) (isolated yield)
1	$PhCF_3$	140	14	0
2	$PhCF_3$	190	14	0
3	**$PhCF_3$**	**170**	**14**	< 1 **(4)**

Cyclization of the seven-membered ring was challenging and we could not initially determine whether the desired azomethine imine **3.75** was being formed. When running the reaction at 140 °C for 14 hours in the microwave, no starting material was consumed and it was assumed that higher temperatures were required. With this in mind, the reaction was repeated at 190 °C for 14 hours, but a complex mixture of products was obtained, likely from some decomposition, and none of the azomethine imine could be isolated. The reaction was performed at 170 °C for 14 hours in the microwave in hope of eliminating some decomposition, but this still resulted in a complex mixture of products. Nevertheless, following column chromatography, 4% of azomethine imine **3.75** was isolated. Although this yield is quite low, this experiment demonstrates an important limitation to this methodology, that 7-membered rings may not be agreeable with the conditions needed for the intramolecular hydroamination of alkynes using hydrazides.

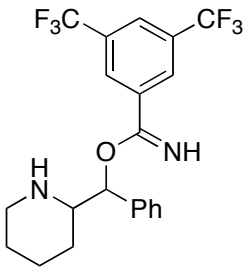
3.4. Derivatization of Azomethine Imines

Due to the fact that the azomethine imine products formed could not originally be isolated, considerable effort was invested into a strategy for their isolation and characterization. As shown previously, these azomethine imine products participate in 1,3-dipolar cycloadditions with dipolaraphiles such as *N*-phenylmaleimide (Equation 3.9). It was also believed that through a simple reduction with a borohydride species, that these azomethine imines could be converted to stable products. The reduction of azomethine imine **3.67** was attempted first (Equation 3.13). Reduction of the azomethine imine with both lithium borohydride and sodium borohydride were tried in parallel, and it was determined that the reaction with sodium borohydride was much cleaner, yielding 76% of the desired reduced compound (**3.76**).



3.67 **3.76** **(3.13)**

When the same procedure was used to reduce azomethine imine **3.64**, only 27% of the desired reduced compound was obtained. In this reaction, formation of a second product was clearly visible by TLC and ^{1}H NMR. It is possible that the side product may form from a [3,3]-sigmatropic rearrangement of the azomethine imine. The rearranged product **3.77** that is suspected to form in this reaction is shown in Figure 3.5 below.



3.77

Figure 3.5: Possible Side-Product Formed Upon Reduction of Azomethine Imine

3.5. Conclusions and Future Work

Recent results in our group had proven that hydrazides are useful in the Cope-type hydroamination of alkenes (Chapter 2). Such reagents are convenient, in that they are easy to synthesize and they are stable at high temperatures. Using similar methodology to that developed for the hydroamination of alkenes, this chapter highlights that the hydroamination of alkynes is possible using hydrazides. A variety of alkynylhydrazides cyclize to give hydroamination products in good yield, including internal alkynes. During this work, novel azomethine imine products were accessed, isolated and characterized and procedures to isolate derivatives of these compounds have been developed. The observation that bistrifluoromethyl substituents allow for the isolation of azomethine imines enabled the development of this reactivity and this may prove to be beneficial for other azomethine imines.

Currently in the Beauchemin group further investigations into the reactivity of alkynylhydrazides with respect to metal-free hydroamination are underway. Further expansion of the substrate scope of this reaction is in progress and in the future we hope

to be able to show the applicability of these intramolecular hydroamination reactions using hydrazides in organic synthesis.

Chapter 4: Experimental

Chapter 4: Experimental

4.1. General

All reactions were performed in oven-dried 0.5, 2, 5 or 20 mL Biotage seal tubes or flame-dried round bottom flasks, under an argon atmosphere unless otherwise noted. Microwave reactions were run in a Biotage Initiator microwave. Purification of reaction products was carried out by flash chromatography using Silicycle silica gel (40-60 μm), unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F_{254} (E. Merck), cut to size. Visualization was accomplished with UV light followed by staining with potassium permanganate solution and heating

^{1}H NMR spectra were recorded on Bruker Avance300 (300 MHz) and Bruker Avance400 (400 MHz) spectrometers at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm using solvent as the reference ($CDCl_3$ at 7.26 ppm or DMSO-d_6 at 2.50 ppm). Data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance300 (75 MHz) or Avance400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.52). Infrared (IR) spectra were obtained with neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). High-resolution

mass spectrometry (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70ev at the Ottawa-Carelton Mass Spectrometry Centre.

Unless otherwise noted, all commercial materials were purchased from commercial sources and used without further purification. Solvents used were freshly distilled prior to use unless otherwise noted: THF and ether over sodium; triethylamine and dichloromethane over calcium hydride; α,α,α-trifluorotoluene was dried over molecular sieves. Supporting information for previously reported compounds and precursors as well as the syntheses of (Z)-Hex-4-enal and (E)-Hex-4-enal can be found in a related publication.[29]

4.1.1. General Procedure for Formation of Aldehydes (Chapter 2)

The aldehyde was formed according to the preparation outlined by Mukai.[97] To a flame-dried round bottom flask charged with a magnetic stir bar, the alkenol (5.09 mmol) and dry Et_3N (20.4 mmol) were premixed in dry CH_2Cl_2 (0.33 M). To this, a solution of SO_3·Pyr (15.3 mmol) in DMSO (0.33 M) was added at 0 °C. The reaction solution was stirred at room temperature until judged to be complete by TLC. Upon completion, the reaction was quenched with a saturated solution of aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, washed with water and dried with Na_2SO_4. The unpurified

[97] Mukai, C.; Nomura, I.; Katagaki, S. *J. Org. Chem.* **2003**, *68*, 1376.

reaction mixture was concentrated under vacuum and used directly, without purification in the following step due to the volatility of the aldehyde.

4.1.2. General Procedure for Formation of the Hydrazone (Chapter 2)

The hydrazone was formed via the aldehyde according the Leighton's method.[98] The aldehyde (from the crude mixture, 6.08 mmol) and the hydrazide (5.53 mmol) were mixed in MeOH (0.20 M) containing a small quantity of Na_2SO_4. The reaction was stirred at room temperature until completion of the reaction was observed by TLC analysis. The reaction mixture was filtered, extracted with EtOAc, washed with water, dried with Na_2SO_4, concentrated under vacuum and purified by column chromatography to give the desired compound.

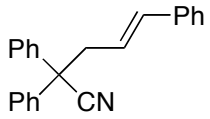
4.1.3. General Procedure for the Formation of Alkylhydrazides (Chapter 2)

The alkylhydrazide was prepared according to the method outlined by Lane.[99] To a flame-dried round-bottom flask charged with a magnetic stir bar, the respective hydrazone (1.60 mmol) and $NaCNBH_3$ (1.92 mmol) were combined in MeOH (0.050 M). A pinch of methyl orange was added to the solution to act as a pH indicator and the flask was capped with a septum. The reaction mixture was purged with argon while stirring at room temperature for 5 minutes. A solution of 1:1 MeOH:HCl was added dropwise until the pink color persisted for 30 minutes. The reaction mixture was then allowed to stir at

[98] Leighton, J. L.; Berger, R.; Duff, K. *J. Am. Chem. Soc.* **2004**, *126*, 5686.
[99] Lane, C. F. *Synthesis* **1975**, 135.

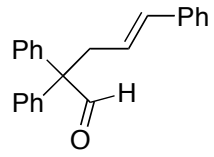
room temperature for 1 hour. Following this, the reaction was quenched with a 25% solution of NaOH until the pH of the solution was approximately 8. The solution was extracted with CH_2Cl_2, the organic phase was washed with a solution of 1:1 H_2O:Brine and dried with Na_2SO_4. After filtration, the solution was concentrated under vacuum and purified by column chromatography.

4.1.4. Preparation of Substrates (Chapter 2)

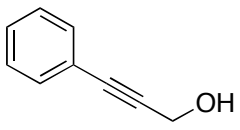


(E)-2,2,5-Triphenylpent-4-enenitrile (Scheme 2.10, 2.72). The alkylation product was formed from the corresponding nitrile according to the procedure outlined by Ciganek.[22c] To a solution of diphenylacetonitrile (2.14 g, 11.1 mmol) in dry THF (10.1 mL, 1.10 M) at room temperature, a 1.0 M solution of lithiumhexamethyldisilazide (2.28 g, 1.00 M) was added slowly. The reaction solution was heated at reflux (75 °C) for 0.5 hours. The reaction solution was cooled to room temperature and a solution of cinnamyl bromide (2.40 g, 12.2 mmol) in dry THF (3.38 mL, 3.60 M) was added. The reflux was resumed for 0.5 hours. Following this, the reaction solution was cooled to room temperature, diluted with water, extracted with ether and washed with water then brine. The organic phase was dried over $NaSO_4$ and concentrated to give a yellow solid. The crude solid was recrystallized from EtOAc to afford the title compound (2.33 g, 68% yield) as a light

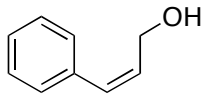
yellow solid. TLC R_f 0.40 in 10% EtOAc in hexanes. The spectral data was in agreement with that previously reported by Ciganek.[22c]



(E)-2,2,5-Triphenylpent-4-enal (Scheme 2.10, 2.73). The aldehyde was formed from the corresponding nitrile (E-2,2,5-triphenylpent-4-enenitrile) according to the procedure by Ciganek.[22] To a solution of the nitrile (1.30 g, 4.20 mmol) in dry THF (6.46 mL, 0.65 M), a 1.0 M solution of diisobutylaluminumhydride (8.40 mL, 1.0 M) was added at -50 °C. The reaction solution was warmed to room temperature and stirred for 75 minutes. Following completion, the reaction mixture was cooled to -55 °C and ethanol was added. The cooling bath was removed and replaced with an ice bath. A 10% HCl solution was added, and the reaction mixture was extracted with toluene, washed with 10% HCl and dried over Na_2SO_4. The crude mixture was concentrated under vacuum and used directly, without further purification due to the potential lability of the aldehyde. TLC R_f 0.51 in 10% EtOAc in hexanes.



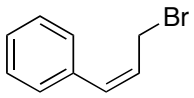
3-Phenylprop-2-yn-1-ol (Scheme 2.12, 2.81). The alkynol was prepared according to the procedure outlined by Lin.[100] To a solution of propargyl alcohol (1.50 g, 26.8 mmol) in Et_3N (78.7 mL, 0.34 M) was added iodobenzene (6.55 g, 32.1 mmol), CuI (0.103 g, 0.540 mmol) and $PdCl_2(PPh_3)_2$ (0.190 g, 0.270 mmol) and the reaction mixture was stirred at room temperature overnight (16 h). The reaction solution was washed with a saturated solution of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated to give a dark brown oil (quantitative yield). TLC R_f 0.30 in 30% EtOAc in hexanes. The spectral data was in agreement with that previously reported by Lin.[100]



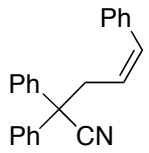
(Z)-3-Phenylprop-2-en-1-ol (cis-cinnamyl alcohol, Scheme 2.12, 2.82). Cis-cinnamyl alcohol was prepared according to the procedure outlined by Charette.[101] To a solution of $Ni(OAc)_2 \bullet 4H_2O$ (1.10 g, 4.54 mmol) in 95% ethanol (80.0 mL, 0.057 M), $NaBH_4$ (0.170 g, 4.54 mmol) was added slowly. The reaction was purged under $N_2(g)$ and stirred at room temperature for 5 minutes until a black precipitate formed. Following this, ethylenediamine (0.270 g, 4.54 mmol) was added and the reaction mixture was stirred for 20 minutes at room temperature. 3-phenylprop-2-yn-1-ol (3.00 g, 22.7 mmol) was added, the reaction was placed under a $H_2(g)$ atmosphere and stirred at room temperature for 21 hours. The reaction mixture was quenched with water, extracted with Et_2O, washed with

[100] Lin, G.-Y.; Yang, C.-Y.; Lui, R.-S. *J. Org. Chem.* **2007**, *72*, 6753.
[101] Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.

a saturated solution of $NaHCO_3$ and brine then dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (20% EtOAc in hexanes). The title compound was obtained as a yellow oil (1.62 g, 54%). TLC R_f 0.31 in 30% EtOAc in hexanes. The spectral data was in agreement with that recorded by Charette.[101]

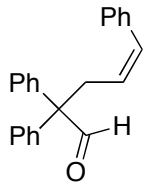


1-((Z)-3-Bromoprop-1-enyl)benzene (cis-cinnamyl bromide, Scheme 2.12, 2.83). Cis-cinnamyl bromide was prepared according to the procedure by Kirkland.[102] Cis-cinnamyl alcohol (1.00 g, 7.45 mmol) was dissolved in dry CH_2Cl_2 and the solution was cooled to 0 °C. To this, PPh_3 (3.50 g, 13.4 mmol) and CBr_4 (3.70 g, 11.2 mmol) were added and the reaction mixture was stirred at 0 ° C for 1 hour. The reaction mixture was concentrated under vacuum, redissolved in CH_2Cl_2 and filtered through a plug of silica. The solution was concentrated to give a yellow solid (1.00 g) which was used in the next reaction without further purification due to its' tendency to isomerize to the undesired trans product.[102]



[102] Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9909.

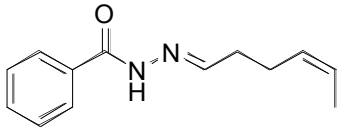
(Z)-2,2,5-Triphenylpent-4-enenitrile (Scheme 2.12, 2.84). The alkylation product was formed from the corresponding nitrile according to the procedure outlined by Ciganek.[22] To a solution of diphenylacetonitrile (0.370 g, 1.93 mmol) in dry THF (1.75 mL, 1.10 M), a 1.0 M solution of lithium hexamethyldisilazide (0.400 g, 1.00 M) was added slowly. The reaction solution was heated at reflux (75 °C) for 0.5 hours. The reaction solution was cooled to room temperature and a solution of cis-cinnamyl bromide (0.417 g, 2.12 mmol) in dry THF (0.590 mL, 3.60 M) was added. The reflux was resumed for 0.5 hours. Following this, the reaction solution was cooled to room temperature, diluted with water, extracted with ether and washed with water then brine. The organic phase was dried over $NaSO_4$ and concentrated. Purified by column chromatography (5% EtOAc in hexanes) to afford the title compound (0.195 g, 33% yield) as a white solid. TLC R_f 0.59 in 10% EtOAc in hexanes. The spectral data was in agreement with that previously reported by Ciganek.[22c]



(Z)-2,2,5-Triphenylpent-4-enal (Scheme 2.12, 2.85). The aldehyde was formed from the corresponding nitrile (Z-2,2,5-triphenylpent-4-enenitrile) according to the procedure by Ciganek.[22] To a solution of the nitrile (2.13 g, 6.88 mmol) in dry THF (10.6 mL, 0.65 M), a 1.0 M solution of diisobutylaluminum hydride (13.8 mL, 1.00 M) was added at -50 °C. The reaction solution was warmed to room temperature and stirred for 75 minutes.

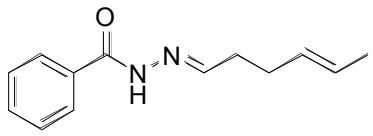
Following completion, the reaction mixture was cooled to -55 °C and ethanol was added. The cooling bath was removed and replaced with an ice bath. A 10% HCl solution was added, and the reaction mixture was extracted with toluene, washed with 10% HCl and dried over Na_2SO_4. The crude mixture was concentrated under vacuum and used directly, without further purification due to the potential volatility of the aldehyde. TLC R_f 0.54 in 10% EtOAc in hexanes.

4.1.5. Characterization of Hydrazones (Chapter 2)

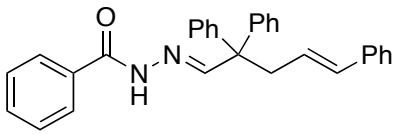


(9E)-*N*'-((Z)-Hex-4-enylidene)benzohydrazide (Table 2,2, Entry 3, 2.47c). Synthesized according to the general procedure using (Z)-hex-4-enal (from the crude mixture) and benzoic hydrazide (1.85 g, 13.6 mmol) in MeOH (68.0 mL, 0.20 M) with a small quantity of Na_2SO_4. The crude product was purified by flash chromatography (30% EtOAc in toluene with 1% Et_3N). The title compound was obtained as a white solid (1.86 g, 63% yield). TLC R_f 0.18 in 40 % EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 1H), 7.87-7.73 (m, 2H), 7.68-7.36 (m, 4H), 5.59-5.47 (m, 1H), 5.46-5.35 (m, 1H), 2.65-2.18 (m, 4H), 1.71-1.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (* denotes minor isomer) δ ppm 164.0 (C), *152.0 (CH), 152.0 (CH), 133.2 (CH), 132.0 (CH), *130.0 (CH), *129.0 (CH), 128.7 (CH), 128.4 (CH), *128.2 (CH), *127.6 (CH),

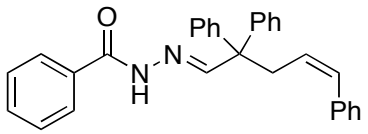
127.2 (CH), 125.4 (CH), *60.4 (CH_2), 32.2 (CH_2), *30.9 (CH_2), 24.0 (CH_2), *23.2 (CH_3), 12.8 (CH_3); IR (film) 3236, 2920, 2846, 1646, 1557, 1354, 1284, 1070, 801, 696 cm^{-1}; LRMS m/z (relative intensity): 105.0323 (100 %), 77.0407 (40.9 %), 51.0235 (11.3 %).



(9E)-*N*'-((E)-Hex-4-enylidene)benzohydrazide (Table 2,2, Entry 2, 2.47b). Synthesized according to the general procedure using (E)-hex-4-enal (from crude reaction mixture) and benzoic hydrazide (1.85 g, 13.6 mmol) in MeOH (68.0 mL, 0.20 M). The crude product was purified by flash column chromatography (50% EtOAc in toluene with 1% Et_3N). The title compound was obtained as a yellow solid (2.03 g, 69% yield). TLC R_f 0.14 in 20% EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 9.17 (s, 1H), 7.80 (d, *J* = 7.1 Hz, 1H), 7.64-7.35 (m, 4H), 5.59-5.32 (m, 2H), 2.32 (ddd, *J* = 19.1, 11.9, 6.2 Hz, 1H), 1.64 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (* denotes minor isomer) δ ppm 164.0 (C), 152.2 (CH), 133.2 (CH), 131.9 (CH), 131.9 (CH), *129.8 (CH), 129.3 (CH), 128.6 (CH), 127.2 (CH), *126.9 (CH), 126.4 (CH), 32.2 (CH_2), *29.8 (CH_2), 29.6 (CH_2), *28.8 (CH_2), 17.9 (CH_3); IR (film) 3068, 3028, 2915, 1695, 1682, 1649, 1572, 1562, 1439, 1359, 1286, 1084, 964, 692, 668 cm^{-1}; LRMS m/z (relative intensity): 105.0339 (100 %), 77.0399 (34.9 %).



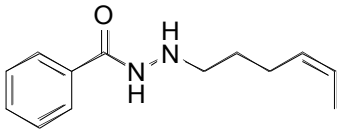
(9E)-*N*'-((E)-2,2,5-Triphenylpent-4-enylidene)benzohydrazide (Scheme 2.10, 2.75). Synthesized according to the general procedure using (E)-2,2,5-triphenylpent-4-enal (1.66 g, 5.31 mmol) and benzoic hydrazide (0.660 g, 4.83 mmol) in MeOH (24.2 mL, 0.20 M). A minimal amount of dry toluene was added to solubilize the aldehyde and the reaction was stirred at reflux (75 °C) until completion was observed by TLC analysis. The crude product was purified by flash column chromatography (20-40% EtOAc in hexanes). The title compound was obtained as a white jelly-like solid (0.71 g, 34% yield). TLC R_f 0.20 in 20% EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (s, 1H), 7.87 (dd, *J* = 7.5 Hz, 2H), 7.43-7.15 (m, 20H), 6.18-5.98 (m, 2H), 3.30 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.2 (C), 156.6 (CH), 143.2 (C), 137.7 (C), 132.9 (CH), 131.6 (CH), 130.0 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.5 (CH), 126.5 (CH), 126.2 (CH), 125.9 (CH), 77.2 (CH), 55.5 (C), 39.6 (CH_2); IR (film) 2919, 2850, 1995, 1577, 1083cm^{-1}; LRMS m/z (relative intensity): 183.0801 (44.7%), 182,0732 (59.4%), 165.0703 (23.6%), 117.0700 (50.1%), 106.0397 (37.9%), 77.0395 (100%), 51.0237 (31.9%).



(9E)-*N*'-((Z)-2,2,5-Triphenylpent-4-enylidene)benzohydrazide (Scheme 2.12, 2.86). Synthesized according to the general procedure using (E)-2,2,5-triphenylpent-4-enal (1.90 g, 6.08 mmol) and benzoic hydrazide (0.750 g, 5.53 mmol) in MeOH (27.7 mL,

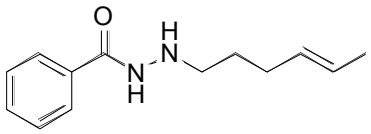
0.20 M). A minimal amount of dry toluene was added to solubilize the aldehyde and the reaction was stirred at reflux (75 °C) until completion was observed by TLC analysis. The crude product was purified by flash column chromatography (7.5% EtOAc in hexanes). The title compound was obtained as a white solid (0.37 g, 16% yield). TLC R_f 0.32 in 10% EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.81 (s, 1H), 7.36-7.13 (m, 20H), 6.40 (d, *J* = 11.8 Hz, 1H), 5.54 (m, 1H), 3.32 (dd, *J* = 6.8, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 139.2 (C), 137.6 (C), 137.2 (C), 132.4 (CH), 131.3 (CH), 130.0 (CH), 129.2 (CH), 128.8 (CH), 128.7 (C), 128.6 (CH), 128.3 (C), 128.2 (CH), 127.9 (CH), 127.4 (CH), 127.1 (CH), 126.7 (CH), 63.9 (C), 33.1 (CH_2); IR (film) 2920, 2852, 1996, 1085, 699 cm^{-1}; LRMS m/z (relative intensity): 183.0801 (44.7%), 182,0732 (59.4%), 165.0703 (23.6%), 117.0700 (50.1%), 106.0397 (37.9%), 77.0395 (100%), 51.0237 (31.9%).

4.1.6. Characterization of Alkylhydrazides



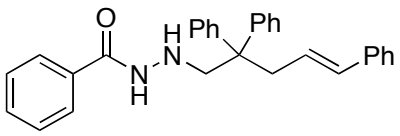
***N*'-((Z)-Hex-4-enyl)benzohydrazide (Table 2.2, Entry 3, 2.48c).** Synthesized according to the general procedure using (9E)-*N*'-((Z)-hex-4-enylidene)benzohydrazide (1.86 g, 8.61 mmol) and $NaCNBH_3$ (1.42 g, 20.7 mmol) in MeOH (17.2 mL, 0.50 M). The solution was concentrated under vacuum and purified by flash chromatography (15% EtOAc in toluene with 1% Et_3N). The title compound was obtained as a white solid

(0.890 g, 48% yield). TLC R_f 0.22 in 30 % EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 7.1 Hz, 2H), 7.55-7.47 (m, 1H), 7.46-7.39 (m, 2H), 5.52-5.42 (m, 1H), 5.42-5.32 (m, 1H), 2.94 (t, *J* = 7.3 Hz, 1H), 2.12 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.66-1.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (C), 132.8 (C), 131.8 (CH), 129.7 (CH), 128.6 (CH), 126.8 (CH), 124.5 (CH), 51.8 (CH_2), 27.8 (CH_2), 24.3 (CH_2), 12.7 (CH_3); IR (film) 3290, 3064, 3010, 2940, 2862, 1631, 1572, 1529, 1455, 1315, 1085, 1023, 887, 797, 688 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$ = 218.1419. Found 218.1409.

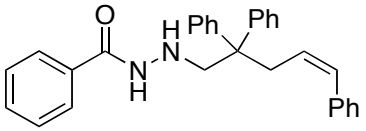


***N*'-((E)-Hex-4-enyl)benzohydrazide (Table 2.2, Entry 2, 2.48b).** Synthesized according to the general procedure using (9E)-*N*'-((E)-hex-4-enylidene)benzohydrazide (2.03 g, 9.39 mmol), $NaCNBH_3$ (1.55g, 22.5 mmol) in MeOH (18.8 mL, 0.50 M). The solution was concentrated under vacuum and purified by flash chromatography (15% EtOAc in toluene with 1% Et_3N). The title compound was obtained as a white solid (0.86 g, 42% yield). TLC R_f 0.24 in 30 % EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (br, 1H), 7.81-7.71 (m, 2H), 7.53-7.46 (m, 1H), 7.45-7.38 (m, 2H), 5.51-5.32 (m, 2H), 4.81 (br, 1H), 2.96-2.87 (m, 2H), 2.09-1.99 (m, 2H), 1.64-1.60 (m, 3H), 1.56 (dd, *J* = 14.8, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 132.9 (C), 131.8 (CH), 130.5 (CH), 128.6 (CH), 126.9 (CH), 125.5 (CH), 51.84 (CH_2), 30.1 (CH_2), 27.9 (CH_2), 17.9 (CH_3); IR (film) 3859, 3746, 3255, 3103, 3018, 2936, 2846, 1705, 1638,

1561, 1463, 1315, 1167, 1097, 1085, 1066, 961, 929, 692, 668 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$ = 218.1419. Found 218.1400.



***N*-((E)-2,2,5-Triphenylpent-4-enyl)benzohydrazide (Scheme 2.10, 2.76)**. Synthesized according to the general procedure using (9E)-*N*'-((E)-2,2,5-triphenylpent-4-enylidene)benzohydrazide (0.710 g, 1.73 mmol), $NaCNBH_3$ (0.280 g, 4.14 mmol) in MeOH (3.45 mL, 0.50 M). The solution was concentrated under vacuum and purified by flash chromatography (10-30% EtOAc in hexanes). The title compound was obtained as a white solid (quantitative yield). TLC R_f 0.59 in 30% EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.42-7.15 (m, 20H), 6.90 (s, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 5.74 (dt, *J* = 15.6, 15.0 Hz, 1H), 4.75 (s, 1H), 3.65 (s, 2H), 3.20 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.5 (C), 146.4 (C), 137.5 (C), 134.4 (C), 133.2 (CH), 132.5 (C), 131.6 (CH), 129.7 (CH), 129.9 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 126.7 (CH), 126.4 (CH), 126.3 (CH), 126.0 (CH), 58.8 (CH_2), 50.2 (C), 40.9 (CH_2); IR (film) 3059, 3025, 2922, 2854, 1599, 1493, 1447, 1067, 1036, 702 cm^{-1}; LRMS m/z (relative intensity): 342.1681 (25.9%), 341.1657 (92.6%), 325.1506 (15.8%), 205.1018 (21.4%), 193.0996 (25.7%), 192.0873 (22.4%), 165.0719 (19.4%), 149.0712 (100%), 105.0337 (61.9%), 91.0561 (35.3%), 77.0408 (20.3%).



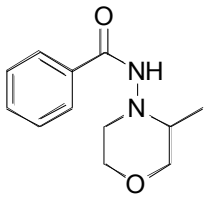
***N*'-((Z)-2,2,5-Triphenylpent-4-enyl)benzohydrazide (Scheme 2.12, 2.87).** Synthesized according to the general procedure using *N*'-((Z)-2,2,5-triphenylpent-4-enylidene)benzohydrazide (0.370 g, 0.860 mmol), $NaCNBH_3$ (0.140 g, 2.06 mmol) in MeOH (1.72 mL, 0.50 M). The solution was concentrated under vacuum and purified by flash chromatography (15% EtOAc in hexanes). The title compound was obtained as a yellow oil (0.135 g, 37% yield). TLC R_f 0.55 in 20 % EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.21 (m, 20H), 6.45 (d, *J* = 11.8 Hz, 1H), 5.85 (s, 1H), 5.46 (td, *J* = 11.9, 6.9 Hz, 1H), 4.16 (s, 2H), 3.27 (dd, *J* = 6.9, 1.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 144.9 (C), 143.8 (C), 137.4 (C), 131.1 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 68.6 (CH_2), 52.2 (C), 35.3 (CH_2); IR (film) 3059, 3025, 1599, 1493, 1447, 1067, 1037, 702 cm^{-1}; LRMS m/z (relative intensity): 205.0997 (13.4%), 198.0997 (16.2%), 197.0954 (100%), 105.0337 (69.7%), 91.0545 (36.3%), 77.0391 (12.7%).

4.1.7. General Procedure for Cope-Type Hydroamination of Alkenes (Chapter 2)

A flame-dried 5-20 mL Biotage Initiator microwave vial was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The hydrazide (1.00 equiv.) and α,α,α-trifluorotoluene (such that the concentration of the

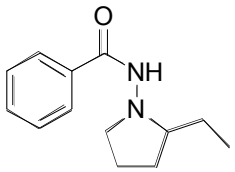
hydrazide was 0.05 M) were added to the microwave vial, while keeping it under an argon atmosphere. The septum was removed and the vial was quickly sealed with a microwave cap and heated in a Biotage Initiator microwave for 5-20 hours at 160-200 °C. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. The unpurified material was then again concentrated under reduced pressure and directly purified by silica gel chromatography to give the corresponding hydrohydrazidation product.

4.1.8. Characterization of Hydroamination Products via Alkenes (Chapter 2)

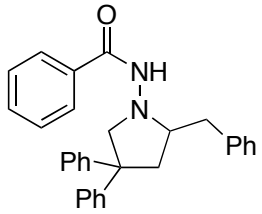


***N*-(3-Methylmorpholino)benzamide (Table 2.3, Entry 1, 2.51)**. Synthesized according to the general procedure (200 °C, 12h) using the corresponding hydrazide (0.220 g, 1.00 mmol). The crude mixture was concentrated under reduced pressure and purified by flash chromatography (3% MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.145 g, 66% yield). TLC R_f 0.36 in 100 % EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.72 (d, *J* = 7.3 Hz, 1H), 7.50-7.43 (m, 1H), 7.41-7.34 (m, 2H), 7.17 (br, 1H), 3.86-3.70 (m, 3H), 3.41-3.32 (m, 1H), 3.04 (dt, *J* = 10.6, 1.9 Hz, 1H), 2.97-2.82 (m,

2H), 1.02 (d, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ẟ ppm 166.2 (C), 133.6 (C), 131.5 (CH), 128.5 (CH), 127.0 (CH), 72.1 (CH_2), 66.6 (CH_2), 59.1 (CH), 55.8 (CH_2), 14.22 (CH_3); IR (film) 3488, 3230, 3065, 2972, 2858, 1652, 1542, 1303, 1117, 984, 904, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O_2$ $[M]^+$ = 220.1212. Found 220.1188.



***N*-(2-Ethylpyrrolidin-1-yl)benzamide (Table 2.4, 2.55).** Synthesized according to the general procedure (175 °C, 10h) using the corresponding hydrazide (0.200 g, 0.920 mmol). The crude mixture was concentrated under vacuum and purified by flash chromatography (75% Et_2O in pentane with 1% Et_3N). The title compound was obtained as a white solid (0.150 g, 75% yield). TLC R_f 0.51 in 100 % EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.75 (d, J = 7.0 Hz, 2H), 7.57-7.32 (m, 3H), 3.45 (dt, J = 8.5, 3.2 Hz, 1H), 2.83-2.66 (m, 2H), 2.10-1.66 (m, 4H), 1.65-1.36 (m, 2H), 0.90 (t, J = 7.5, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.9 (C), 134.3 (C), 131.9 (CH), 128.9 (CH), 127.4 (CH), 68.6 (CH), 56.3 (CH_2), 28.3 (CH_2), 26.5 (CH_2), 20.9 (CH_2), 11.0 (CH_3); IR (film) 3855, 3746, 3220, 3060, 2963, 2932, 2878, 1697, 1646, 1584, 1541, 1487, 1463, 1307, 1284, 1089, 941, 914, 688 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 218.1419. Found 218.1398.



***N*-(2-Benzyl-4,4-diphenylpyrrolidin-1-yl)benzamide (Equation 2.13, 2.77)**. Synthesized according to the general procedure (120 °C, 10h) using the corresponding E-hydrazide (0.030 g, 0.070 mmol). The crude mixture was concentrated under vacuum and purified by flash chromatography (30% EtOAc in hexanes). The title compound was obtained as a yellow oil (0.018 g, 60% yield). TLC R_f 0.49 in 30% EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.46-7.16 (m, 20H), 6.88 (s, 1H), 4.21 (d, J = 9.6 Hz, 1H), 3.80 (d, J = 9.6 Hz, 1H), 3.69 (q, J = 7.2 Hz, 1H), 3.00 (dd, J = 12.9, 8.4 Hz, 1H), 2.83 (dd, J = 13.4, 6.7 Hz, 1H), 2.66 (dd, J = 13.0, 7.6 Hz, 1H), 2.33 (dd, J = 12.9, 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.2 (C), 148.2 (C), 147.1 (C), 139.6 (C), 133.6 (C), 131.5 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.2 (CH), 126.0 (CH), 126.0 (CH), 66.6 (CH), 65.6 (CH_2), 52.1 (C), 43.1 (CH_2), 41.2 (CH_2); IR (film) in progress 3245, 3063, 3028, 1653, 1599, 1550, 1493, 1440, 1299, 1025, 744, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{30}H_{28}N_2O$ $[M]^+$: 432.2202. Found 432.2101.

4.2. General Procedure for Formation of Alkynylhydrazides (Chapter 3)

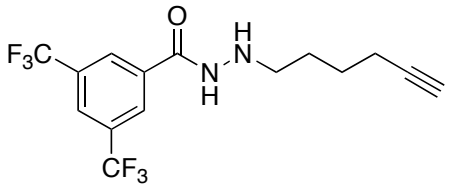
Aldehyde/Ketone Formation: To a flame-dried round bottom flask charged with a magnetic stir bar, the alcohol (15.3 mmol) and Et_3N (61.1 mmol) were premixed in CH_2Cl_2 (0.33 M). To this mixture, a solution of pyridine sulfur trioxide complex (45.8 mmol) in DMSO (46.3 mL, 0.33 M) was added at 0 °C. The mixture was vigorously stirred until complete by TLC, then quenched at 0 °C by addition of a saturated solution of NH_4Cl and extracted with dichloromethane. The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and concentrated to afford the crude aldehyde/ketone.

Hydrazone Formation: The corresponding aldehyde or ketone (10.2 mmol) was dissolved in *t*-BuOH (0.20 M) at 35 ºC. 3,5-bis(trifluoromethyl)benzohydrazide (10.2 mmol) and a small amount of Na_2SO_4 were added, and the reaction mixture was stirred under argon at 35 ºC. The reaction was monitored by TLC until consumption of the hydrazide was completed. The crude solution was then filtered over cotton, concentrated under reduced pressure and used directly in the reduction to the alkynylhydrazide.

Reduction of the Hydrazone: Performed via a modification of Lane's procedure.[99] The crude hydrazone solution was diluted further with *t*-BuOH (0.20 M) under argon. $NaCNBH_3$ (53.5 mmol) and a pinch of methyl orange were added to the solution. A mixture of 1:1 MeOH:HCl was added dropwise via syringe until the solution was a pink colour (pH < 3), while keeping vigorous stirring at 35 °C. The reaction was monitored visually, and extra 1:1 MeOH:HCl solution was added if the reaction lost its pink colour

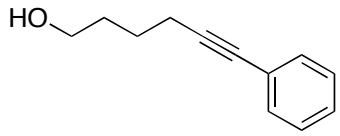
within the first 30 minutes. Upon completion by TLC (typically 1-2 hours), the reaction was quenched with dropwise addition of a 25% NaOH solution until the pH of the solution was approximately 8. The solution was extracted three times with CH_2Cl_2, the combined organic layers were washed with 1:1 H_2O:brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by column chromatography to give the corresponding alkynylhydrazide.

4.2.1. Characterization of Alkynlhydrazides (Chapter 3)

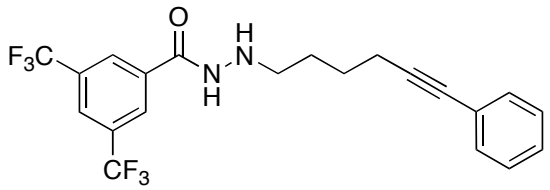


3,5-Bis(trifluoromethyl)-*N'*-(hex-5-ynyl)benzohydrazide (Table 3.1, Entry 2, 3.56b). Synthesized according to the general procedure using hex-5-yn-1-ol (1.50 g, 15.3 mmol). The crude was purified by flash chromatography on silica gel (50% Et_2O in pentane). The title compound was obtained as a pink solid (3.06 g, 57% yield). TLC R_f = 0.30 in 50% Et_2O in pentane; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.22 (s, 2H), 8.03 (s, 1H), 3.00 (t, *J* = 6.9 Hz, 2H), 2.26 (td, *J* = 6.7, 2.6 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.74-1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.5 (C), 134.9 (C), 132.4 (q, *J* = 34.0 Hz, 2C, C-CF_3), 127.3 (2C), 125.4 (CH), 122.8 (q, *J* = 273.1 Hz, 2C, CF_3), 84.1 (C), 68.7 (CH), 51.5 (CH_2), 26.7 (CH_2), 25.7 (CH_2), 18.2 (CH_2); IR (film) 3747, 2922, 2850, 1649,

1539, 1079 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{14}F_6N_2O$ $[M]^+$ = 352.1010. Found: 352.0996.



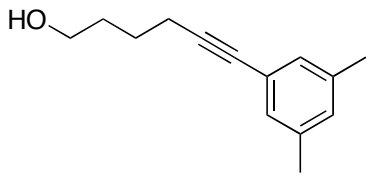
6-Phenylhex-5-yn-1-ol. To a solution of hex-5-yn-1-ol (1.00 g, 10.2 mmol) in Et_3N (30.0 mL, 0.34 M) was added iodobenzene (2.49 g, 12.2 mmol), CuI (0.038 g, 0.20 mmol) and $PdCl_2(PPh_3)_2$ (0.070 g, 0.010 mmol) and the reaction mixture was stirred at room temperature overnight (20 h). The reaction solution was washed with a saturated solution of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (40% EtOAc in hexanes). The title compound was obtained as a yellow oil (quantitative yield). TLC R_f 0.55 in 30% EtOAc in hexanes. The spectral data was in agreement with that previously reported in the literature.[103]



3,5-Bis(trifluoromethyl)-*N'*-(6-phenylhex-5-ynyl)benzohydrazide (Table 3.1, Entry 3, 3.56c). Synthesized according to the general procedure using 6-phenylhex-5-yn-1-ol

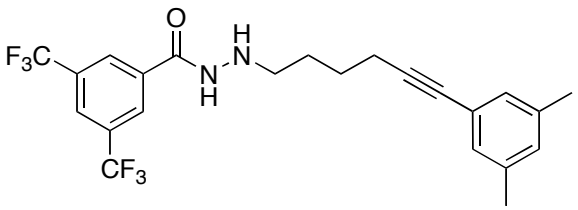
[103] Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076.

(1.87 g, 10.7 mmol). The crude was purified by flash chromatography on silica gel (20% EtOAc in hexanes). The title compound was obtained as a pink solid (quantitative yield). TLC R_f = 0.32 in 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.21 (s, 2H), 8.01 (s, 1H), 7.37-7.35 (m, 2H), 7.27-7.24 (m, 3H), 3.05 (t, *J* = 6.7 Hz, 2H), 2.47 (t, *J* = 6.5 Hz, 2H), 1.80-1.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.5 (C), 134.7 (C), 132.4 (q, *J* = 34.0 Hz, 2C, C-CF_3), 131.5 (2C), 128.2 (2C), 127.6 (CH), 127.3 (2C), 125.4 (CH), 123.7 (C), 122.7 (q, *J* = 273.3 Hz, 2C, CF_3), 89.5 (C), 81.1 (C), 51.7 (CH_2), 26.9 (CH_2), 26.0 (CH_2), 19.2 (CH_2); IR (film) 3751, 2918, 1702, 1649, 1082 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{21}H_{18}F_6N_2O$ $[M]^+$ = 428.1323. Found: 428.1307.



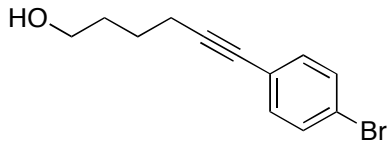
6-(3,5-Dimethylphenyl)hex-5-yn-1-ol. To a solution of hex-5-yn-1-ol (0.570 g, 5.78 mmol) in Et_3N (17.0 mL, 0.34 M) was added 5-iodo-*m*-xylene (1.61 g, 6.94 mmol), CuI (0.023 g, 0.020 mmol) and $PdCl_2(PPh_3)_2$ (0.041 g, 0.010 mmol) and the reaction mixture was stirred at room temperature overnight (16 h). The reaction solution was washed with a saturated solution of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (30% Et_2O in pentane). The title compound was obtained as a yellow oil (quantitative

yield). TLC R_f 0.35 in 30% Et_2O in pentane. The spectral data was in agreement with that previously reported in the literature.[104]

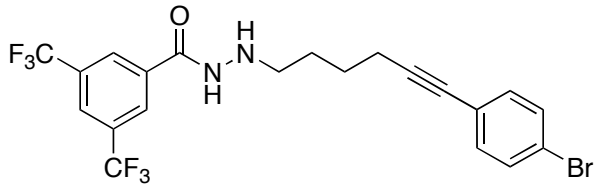


3,5-Bis(trifluoromethyl)-*N'*-(6-(3,5-dimethylphenyl)hex-5-ynyl)benzohydrazide (Table 3.1, Entry 4, 3.56d). Synthesized according to the general procedure using 6-(3,5-dimethylphenyl)hex-5-yn-1-ol (1.10 g, 5.84 mmol). The crude was purified by flash chromatography on silica gel (45% Et_2O in pentane). The title compound was obtained as a pink oil (1.48 g, 56% yield). TLC R_f = 0.25 in 40% Et_2O in pentane; ^{1}H NMR (300 MHz, $CDCl_3$) (as a mixture of conformers, * denotes minor conformer) δ ppm *8.43 (s, 2H), 8.20 (s, 1H), *8.05 (s, 1H), 8.01 (s, 1H), 7.00 (s, 2H), *6.96 (s, 2H), 3.04 (t, *J* = 6.8 Hz, 2H), 2.46 (t, *J* = 6.5 Hz, 2H), 2.25 (s, 6H), *2.23 (s, 6H), 1.79-1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) (as a mixture of conformers, * denotes minor conformer) δ ppm 164.5 (C), *163.5 (C), 137.7 (2C), 134.8 (C), 132.4 (q, *J* = 34.0 Hz, 2C, <u>C</u>-CF_3), *131.3, *129.7 (CH), 129.5 (CH), 129.2 (2C), *129.1, 127.3 (2C), 125.4 (CH), 123.3 (C), *122.9 (C), 122.8 (q, *J* = 272.9 Hz, 2C, <u>C</u>F_3), 121.4 (C), 88.7 (C), *87.4 (C), *82.1 (C), 81.3 (C), *57.4 (CH_2), 51.7 (CH_2), *27.0 (CH_2), 26.1 (CH_2), *25.3 (CH_2), 24.6 (CH_2), 21.0 (CH_3), *20.9, 19.2 (CH_2), *18.9 (CH_2); IR (film) 3465, 1645, 1280, 1136 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{23}H_{22}F_6N_2O$ $[M]^+$ = 456.1636. Found: 456.1652.

[104] Rizk, T.; Bilodeau, E.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8325.

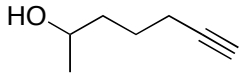


6-(4-Bromophenyl)hex-5-yn-1-ol.[105] To a solution of hex-5-yn-1-ol (1.00 g, 10.2 mmol) in Et_3N (30.0 mL, 0.34 M) was added 1-bromo-4-iodobenzene (3.46 g, 12.2 mmol), CuI (0.040 g, 0.020 mmol) and $PdCl_2(PPh_3)_2$ (0.070 g, 0.010 mmol) and the reaction mixture was stirred at room temperature overnight (16 h). The reaction solution was washed with a saturated solution of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (30% Et_2O in pentane). The title compound was obtained as a brown oil (1.95 g, 76% yield). TLC R_f 0.24 in 60% Et_2O in pentane. ^1H NMR (300 MHz, $CDCl_3$) 7.25 (dt, J = 8.9, 2.0 Hz), 3.71 (t, J= 6.2 Hz, 2H), 2.44 (t, J = 6.7 Hz, 2H), 1.72 (m, 4H), 1.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 132.9 (CH), 131.4 (CH), 122.8 (C), 121.6 (C), 91,1 (C), 79.9 (C), 62.4 (CH_2), 31.9 (CH_2), 24.9 (CH_2), 19.2 (CH_2); IR (film) 3371, 2941, 1486, 1072, 1011, 824 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}BrO$ $[M]^+$ = 252.0150. Found: 252.0165.



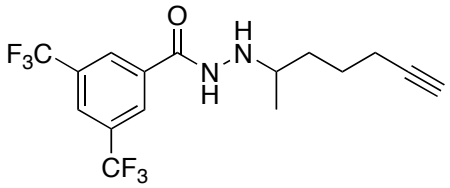
[105] This substrate was synthesized by Ms. Sandrine Taing.

***N'*-(6-(4-Bromophenyl)hex-5-ynyl)-3,5-bis(trifluoromethyl)benzohydrazide (Table 3.1, Entry 5, 3.56e).**[105] Synthesized according to the general procedure using 6-(4-bromophenyl)hex-5-yn-1-ol (1.95 g, 7.72 mmol). The crude was purified by flash chromatography on silica gel (20% Et_2O in pentane). The title compound was obtained as a white solid (0.480 g, 18% yield). TLC R_f = 0.22 in 30% Et_2O in pentane; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.22 (s, 2H), 8.03 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H), 2.46 (t, *J* = 6.0 Hz, 2H), 1.82-1.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.5 (C), 134.8 (C), 132.9 (2C), 132.4 (q, *J* = 33.9 Hz, 2C, <u>C</u>-CF_3), 131.4 (2C), 127.3 (2C), 125.4 (CH), 121.8 (q, *J* = 131.0 Hz, 2C, <u>C</u>F_3), 121.7 (C), 90.8 (C), 80.1 (C), 51.7 (CH_2), 27.0 (CH_2), 25.9 (CH_2), 19.2 (CH_2); IR (film) 3465, 1654, 1486, 1279, 1137, 1071, 1011, 908, 825, 682 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{21}H_{17}BrF_6N_2O$ $[M]^+$ = 506.0428. Found: 506.0332.



Hept-6-yn-2-ol. To a flame-dried round bottom flask, hex-5-yn-1-ol (1.00 g, 10.2 mmol) and Et_3N (5.68 mL, 40.8 mmol) were premixed in CH_2Cl_2 (30.9 mL, 0.33 M). To this mixture, a solution of pyridine sulfur trioxide complex (4.90 g, 30.6 mmol) in DMSO (30.9 mL, 0.33 M) was added at 0 °C. The mixture was vigorously stirred until complete by TLC, then quenched at 0 °C by addition of a saturated solution of NH_4Cl and extracted with dichloromethane. The combined organic extracts were washed with water,

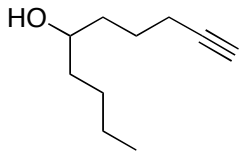
brine, dried and concentrated to afford the crude aldehyde as a yellow oil. To the crude aldehyde was added dry THF (25.5 mL, 0.40 M), and a 2.0 M solution of methylmagnesium bromide in THF (5.90 mL, 50.9 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature while stirring for 2 hours. The resulting solution was diluted with Et_2O, quenched with aqueous NH_4Cl, extracted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (40% Et_2O in pentane). The title compound was obtained as a yellow oil (quantitative yield). TLC R_f = 0.33 in 40% Et_2O in pentane. The spectral data was in agreement with that previously reported in the literature.[106]



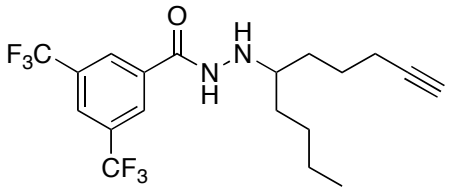
3,5-Bis(trifluoromethyl)-*N*'-(hept-6-yn-2-yl)benzohydrazide (Table 3.1, Entry 6, 3.56f). Synthesized according to the general procedure using hept-6-yn-2-one (10.2 mmol). The crude was purified by flash chromatography on silica gel (40% Et_2O in pentane). The title compound was obtained as a beige solid (1.38 g, 37% yield). TLC R_f = 0.36 in 40% Et_2O in pentane; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.22 (s, 2H), 8.02 (s, 1H), 3.18-3.08 (m, 1H), 2.25 (s, 2H), 1.95 (s, 1H), 1.75-1.47 (m, 4H), 1.13 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.6 (C), 134.9 (C), 132.4 (q, *J* = 34.0 Hz, 2C,

[106] Wu, Y.; Gao, J. *Org. Lett.* **2008**, *10*, 1533.

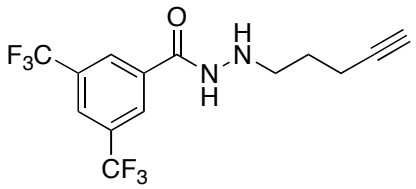
C-CF_3), 127.3 (2C), 125.3 (CH), 122.8 (q, J = 272.9 Hz, 2C, CF_3), 84.3 (CH), 68.7 (C), 55.5 (C), 33.3 (CH_2), 24.3 (CH_2), 18.5 (CH_2), 18.4 (CH_3); IR (film) 1637, 1379, 1276, 1136, 904, 676 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{16}F_6N_2O$ $[M]^+$- CH_3 = 352.1010. Found: 352.0960.



Dec-9-yn-5-ol.[105] To a flame-dried round bottom flask, hex-5-yn-1-ol (1.00 g, 10.2 mmol) and Et_3N (5.68 mL, 40.8 mmol) were premixed in CH_2Cl_2 (30.9 mL, 0.33 M). To this mixture, a solution of pyridine sulfur trioxide complex (4.90 g, 30.6 mmol) in DMSO (30.9 mL, 0.33 M) was added at 0 °C. The mixture was vigorously stirred until complete by TLC, then quenched at 0 °C by addition of a saturated solution of NH_4Cl and extracted with dichloromethane. The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a yellow oil. To the crude aldehyde (1.00 g, 10.2 mmol) was added THF (25.5 mL, 0.40 M), and a 2.0 M solution of butylmagnesium chloride in THF (25.5 mL, 50.9 mmol) at 0 °C. The solution was allowed to warm to room temperature while stirring for 2 hours. The resulting solution was diluted with Et_2O, quenched with a saturated solution of NH_4Cl, extracted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated. The unpurified ketone was used directly in the next reaction without further purification due to the instability of alkynol.

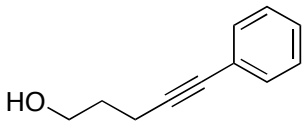


***N'*-(Dec-9-yn-5-yl)-3,5-bis(trifluoromethyl)benzohydrazide (Table 3.1, Entry 7, 3.56g).**[105] Synthesized according to general procedure B using dec-9-yn-5-one (1.55 g, 10.2 mmol). The crude was purified by flash chromatography (20% Et_2O in pentane). The title compound was obtained as a white solid (1.64 g, 40% yield). TLC R_f = 0.48 in 20% Et_2O in pentane; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (s, 2H), 8.00 (s, 1H), 7.72 (br s, 1H), 4.90 (br s, 1H), 2.97 (t, *J* = 5.5 Hz, 1H), 2.32-2.27 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.72-1.27 (m, 12H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (C), 135.0 (C), 132.4 (q, *J* = 33.4 Hz, 2C, <u>C</u>-CF_3), 127.2 (2C), 125.3 (CH), 122.8 (q, *J* = 279.3 Hz, 2C, <u>C</u>F_3), 84.6 (C), 68.7 (CH), 59.9 (CH), 32.0 (CH_2), 30.7 (CH_2), 27.9 (CH_2), 23.8 (CH_2), 22.9 (CH_2), 18.5 (CH_2), 14.0 (CH_3); IR (film) 1641, 1274, 1170, 1140, 911, 679 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{22}F_6N_2O$ $[M]^+$ = 408.1636. Found 408.1635.



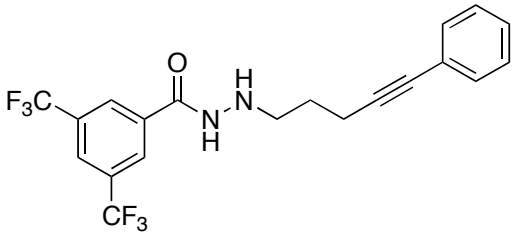
3,5-Bis(trifluoromethyl)-*N'*-(pent-4-ynyl)benzohydrazide (Table 3.2, Entry 1, 3.59a). Synthesized according to the general procedure using 4-pentyn-1-ol (1.50 g, 17.8 mmol).

The crude was purified by flash chromatography (40% Et_2O in pentane). The title compound was obtained as a pink solid (1.87 g, 31% yield). TLC R_f = 0.30 in 40% Et_2O in pentane; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.25 (s, 2H), 8.03 (s, 1H), 3.13 (t, *J* = 6.9 Hz, 2H), 2.35 (td, *J* = 7.0, 2.7 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.80 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.4 (C), 134.1 (C), 132.4 (q, *J* = 34.1 Hz, 2C, C-CF_3), 127.6 (2C), 125.7 122.8 (q, *J* = 272.8 Hz, 2C, CF_3), 83.3 (C), 69.4 (C), 50.9 (CH_2), 26.0 (CH_2), 16.0 (CH_2); IR (film) 2359, 1094 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{12}F_6N_2O$ $[M]^+$ = 338.0854. Found 338.0837.

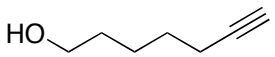


5-Phenylpent-4-yn-1-ol. To a solution of 4-pentyn-1-ol (1.00 g, 11.9 mmol) in Et_3N (35.0 mL, 0.34 M) was added iodobenzene (2.91 g, 14.3 mmol), CuI (0.046 g, 0.020 mmol) and $PdCl_2(PPh_3)_2$ (0.084 g, 0.010 mmol) and the reaction mixture was stirred at room temperature overnight (16 h). The reaction solution was washed with a saturated solution of $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (50% Et_2O in pentane). The title compound was obtained as a yellow oil (1.78 g, 94% yield). TLC R_f 0.35 in 50% Et_2O in pentane. The spectral data is in agreement with that previously reported in the literature.[107]

[107] Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442.

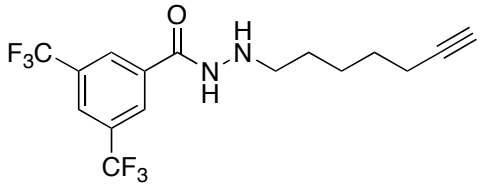


3,5-Bis(trifluoromethyl)-*N'*-(5-phenylpent-4-ynyl)benzohydrazide (Table 3.2, Entry 2, 3.59b). Synthesized according to the general procedure using 5-phenylpent-4-yn-1-ol (1.78 g, 11.9 mmol). The crude was purified by flash chromatography (40% Et_2O in pentane). The title compound was obtained as a pink oil (1.87 g, 38% yield). TLC R_f = 0.33 in 40% Et_2O in pentane; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.21 (s, 2H), 8.02 (s, 1H), 7.40-7.35 (m, 2H), 7.29-7.24 (m, 3H), 3.16 (t, *J* = 6.9 Hz, 2H), 2.56 (t, *J* = 6.9 Hz, 2H), 1.87 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.5 (C), 134.8 (C), 132.4 (q, *J* = 34.0 Hz, 2C, C-$\underline{C}F_3$), 131.5 (2C), 128.3 (2C), 127.7 (CH), 127.2 (2C), 127.2 (CH), 125.4 (CH), 123.5 (C), 122.8 (q, *J* = 273.3 Hz, 2C, $\underline{C}F_3$), 89.1 (C), 81.3 (C), 51.0 (CH_2), 27.0 (CH_2), 17.1 (CH_2); IR (film) 1649, 1284, 1139, 915, 756, 680 cm^{-1}; LRMS m/z (relative intensity): 323.0617 (37.1%), 241.0068 (100%), 173.1080 (90.5%), 145.0792 (29.6%), 129.0679 (24.9%), 128.0631 (56.7%), 115.0561 (81.9%).



Hept-6-yn-1-ol. To a flame-dried flask was added $LiAlH_4$ (0.600 g, 15.8 mmol) and Et_2O (52.7 mL, 0.150 M). The solution was cooled to 0 °C, then a solution of heptynoic acid (1.00 g, 7.90 mmol) in Et_2O (10.0 mL, 0.790 M) was added dropwise. The mixture

was allowed to cool to room temperature then stirred vigorously under argon for 1 hour. The reaction solution was quenched by dropwise addition of 1.0 M HCl, then extracted with Et_2O, dried over Na_2SO_4 and concentrated. The title compound was obtained as a yellow oil (0.880 g, 99% yield). TLC R_f = 0.27 in 30% Et_2O in pentane. The spectral data is in agreement with that previously reported in the literature.[108]



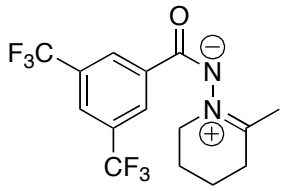
3,5-Bis(trifluoromethyl)-*N'*(hept-6-ynyl)benzohydrazide (Table 3,3, Entry 1, 3.62). Synthesized according to the general procedure using hept-6-yn-1-ol (0.880 g, 7.85 mmol). The crude was purified by flash chromatography (30% Et_2O in pentane). The title compound was obtained as a yellow oil (1.19 g, 42% yield). TLC R_f = 0.36 in 30% Et_2O in pentane; ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ ppm 7.83 (s, 2H), 7.51 (s, 1H), 2.27-2.25 (m, 2H), 1.89 (s, 1H), 1.56-1.54 (m, 2H), 1.00-0.78 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C) δ ppm 164.4 (C), 134.7 (C), 132.2 (q, J = 34.0 Hz, 2C, $\underline{C}$-CF_3), 127.3 (2C), 125.3 (CH), 122.8 (q, J = 273.7 Hz, 2C, $\underline{C}F_3$), 84.2 (C), 68.4 (C), 51.9 (CH_2), 28.1 (CH_2), 27.4 (CH_2), 26.0 (CH_2), 18.2 (CH_2); IR (film) 3310, 2949, 1641, 1280, 1174, 1132, 908, 679 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{16}F_6N_2O$ $[M]^+$ = 366.1167. Found 366.1162.

[108] Gung, B. W.; Gibeau, C.; Jones, A. *Tetrahedron*, **2005**, *16*, 3107.

4.2.2. General Procedure for Cope-Type Hydroamination of Alkynes (Chapter 3)

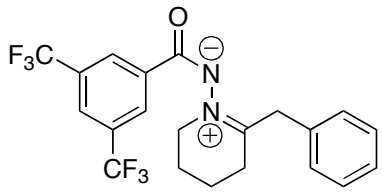
A flame-dried 5-20 mL Biotage Initiator microwave vial was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkynylhydrazide (1.00 equiv.) and α,α,α-trifluorotoluene (such that the concentration of the hydrazide was 0.05 M) were added to the microwave vial, while keeping it under an argon atmosphere. The septum was removed and the vial was quickly sealed with a microwave cap and heated in a Biotage Initiator microwave for 10-14 hours at 110-170 °C. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. The unpurified material was then again concentrated under reduced pressure and directly purified by silica gel chromatography to give the corresponding hydrohydrazidation product.

4.2.3. Characterization of Hydroamination Products via Alkynes (Chapter 3)



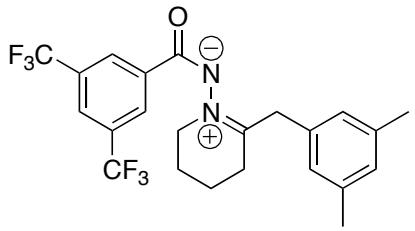
(3,5-Bis(trifluoromethyl)benzoyl(6-methyl-2,3,4,5-tetrahydropyridinium-1-yl) amide (Table 3.4, Entry 3, 3.64). Synthesized according to the general procedure (140 °C, 14h) using 3,5-bis(trifluoromethyl)-*N'*-(hex-5-ynyl)benzohydrazide (0.250 g, 0.710

mmol). The reaction mixture was isolated by column chromatography (2.5% MeOH in CH_2Cl_2). The title compound was obtained as a yellow oil (0.169 g, 68% yield). TLC R_f 0.29 in 5% MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.46 (s, 2H), 8.14 (s, 1H), 3.75 (t, *J* = 5.2 Hz, 2H), 2.82 (t, *J* = 6.0 Hz, 2H), 2.12 (s, 3H), 1.96-1.88 (m, 2H), 1.77-1.69 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 170.3 (C), 162.6 (C), 140.7 (C), 129.3 (q, *J* = 32.9 Hz, 2C, C-CF_3), 126.9 (2C), 124.5 (q, *J* = 273.0 Hz, 2C, CF_3), 121.3 (CH), 53.3 (CH_2), 39.5 (CH_3), 30.9 (CH_2), 20.8 (CH_2), 20.1 (C), 16.7 (CH_2); IR (film) 1649, 1276, 1132, 744, 680 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{14}F_6N_2O$ $[M]^+$ = 352.1010. Found: 352.0992.



(6-Benzyl-2,3,4,5-tetrahydropyridinium-1-yl)(3,5-bis(trifluoromethyl)benzoyl)amide (Table 3.5, Entry 3, 3.67). Synthesized according to the general procedure (140 °C, 14h) using 3,5-bis(trifluoromethyl)-*N'*-(6-phenylhex-5-ynyl)benzohydrazide (0.250 g, 0.584 mmol). The reaction mixture was isolated by column chromatography (2% MeOH in CH_2Cl_2). The title compound was obtained as a yellow oil (0.178 g, 72% yield). TLC R_f 0.27 in 2% MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of conformers, * denotes minor conformer) δ ppm 8.54 (br s, 2H), *8.41 (br s, 2H), *7.97 (br s, 1H), 7.87 (br s, 1H), 7.36-7.23 (m, 5H), 3.97 (br s, 4H), 2.50 (br s, 2H), 2.02-1.97 (m, 2H), 1.82-

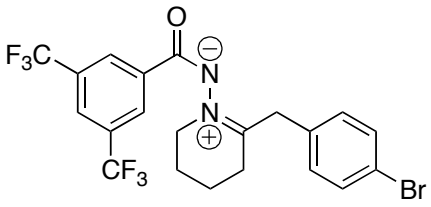
1.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 156.6 (C), 133.4 (C), 131.2 (q, J = 33.4 Hz, 2C, C-CF_3), 129.7 (2C), 129.1 (2C), 128.0 (2C), 127.8 (CH), 123.4 (q, J = 272.6 Hz, 2C, CF_3), 123.2 (CH), 54.6 (CH_2), 40.2 (CH_2), 30.1 (CH_2), 21.8 (CH_2), 17.8 (CH_2), missing two quaternary carbons;[109] IR (film) 2340, 1635, 1094 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{14}F_6N_2O$ $[M]^+$ = 428.1323. Found: 428.1326.



(3,5-Bis(trifluoromethyl)benzoyl(6-(3,5-dimethylbenzyl)-2,3,4,5-tetrahydropyridinium-1-yl)amide (Equation 3.10, 3.68). Synthesized according to the general procedure (140 °C, 14h) using 3,5-bis(trifluoromethyl)-*N'*-(6-(3,5-dimethylphenyl)hex-5-ynyl)benzohydrazide (0.250 g, 0.548 mmol). The reaction mixture was isolated by column chromatography (1-3% MeOH in CH_2Cl_2). The title compound was obtained as a yellow oil (0.229 g, 92% yield). TLC R_f 0.51 in 2% MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.56 (s, 2H), 7.89 (s, 1H), 6.93 (s, 1H), 6.86 (s, 2H), 4.00 (t, J = 5.5 Hz, 2H), 3.89 (s, 2H), 2.55 (t, J = 5.7 Hz, 2H), 2.29 (s, 6H), 2.22-1.98 (m, 2H), 1.82-1.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 138.7 (C), 133.2 (2C), 131.0 (q, J =

[109] Characterization for similar compounds show broad peaks corresponding to the molecule's quaternary carbons. Unfortunately, some compounds are missing some of these broad resonances despite acquisition of the spectra for 12h with significant sample quantity. However, all other data is compatible with the assigned structure.

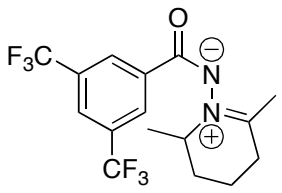
34.3 Hz, 2C, C-CF_3), 129.4 (CH), 128.1 (2C), 127.6 (2C), 125.3 (q, *J*= 272.7 Hz, 2C, CF_3), 123.2 (CH), 54.6 (CH_2), 40.1 (CH_2), 30.2 (CH_2), 21.8 (CH_2), 21.2 ($2CH_3$), 17.8 (CH_2), missing three quaternary carbons;[109] IR (film) 1706, 1660, 1276, 1177, 1136 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{14}F_6N_2O$ $[M]^+$ = 456.1636. Found: 456.1629.



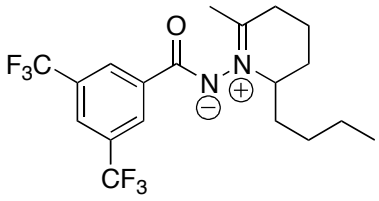
(3,5-Bis(trifluoromethyl)benzoyl(6-(4-bromobenzyl)-2,3,4,5-tetrahydropyridinium-1-yl)amide (Equation 3.11, 3.69).[105] Synthesized according to the general procedure A, heating for 14 hours at 140 °C using *N'*-(6-(4-bromophenyl)hex-5-ynyl)-3,5-bis(trifluoromethyl) benzohydrazide (0.250 g, 0.490 mmol). The reaction mixture was isolated by column chromatography (1% MeOH in CH_2Cl_2). The title compound was obtained as a light brown oil (0.170 g, 66% yield). TLC R_f 0.34 in 2% MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (s, 2H), 7.86 (s, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 3.95 (s, 2H), 3.88 (s, 2H), 2.45 (s, 2H), 1.98 (br s, 2H), 1.82-1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 132.5 (C), 132.1 (2C), 131.4 (2C), 131.0 (q, *J* = 33.2 Hz, 2C, C-CF_3), 127.9 (CH), 123.5 (q, *J* = 272.2 Hz, 2C, CF_3), 123.2 (C), 121.8 (C), 121.6 (C), 54.5 (CH_2), 39.6 (CH_2), 30.0 (CH_2), 21.7 (CH_2), 17.8 (CH_2), traces of chloroform present;[110] IR (film) cm^{-1} 682, 907, 1013, 1133, 1173, 1276, 1279,

[110] The traces of chloroform present in the spectrum were left due to the instability of the product formed.

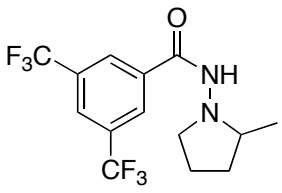
1489, 1568, 1626; HRMS (EI): Exact mass calcd for $C_{21}H_{17}BrF_6N_2O$ $[M]^+$: 506.0428. Found: 506.0422.



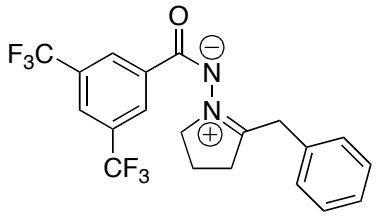
(3,5-Bis(trifluoromethyl)benzoyl(2,6-dimethyl-2,3,4,5-tetrahydropyridinium-1yl)amide (Table 3.6, Entry 3, 3.70). Synthesized according to the general procedure (110 °C, 14h) using 3,5-bis(trifluoromethyl)-*N'*-(hept-6-yn-2-yl)benzohydrazide (0.250 g, 0.682 mmol). The reaction mixture was isolated by column chromatography (2% MeOH in CH_2Cl_2). The title compound was obtained as a yellow oil (0.228 g, 91% yield). TLC R_f 0.26 in 2% MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (as a mixture of conformers, * denotes minor conformer) 8.55-8.06 (m, 3H), *4.45-4.42 (m, 1H), 4.10-4.03 (m, 1H), 2.83-2.81 (m, 2H), 2.12 (s, 3H), 2.07-1.73 (m, 2H), *1.65 (s, 3H), 1.36 (dd, *J* = 6.57 Hz, 3H), *1.05 (dd, *J* = 6.57 Hz, 3H), 1.25-1.23 (m, 2H), *0.86-0.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.4 (C), 141.3 (C), 130.1 (q, *J* = 32.7 Hz, 2C, C-CF_3), 128.1 (2C), 125.7 (q, *J* = 272.6 Hz, 2C, CF_3), 60.0 (CH), 32.4 (CH_2), *30.6 (CH_2), 28.1 (CH_2), 21.8 (CH_3), *21.4 (CH_3), *19.4 (CH_3), 18.8 (CH_3), 14.3 (CH_2); IR (film) 1280, 1136, 1082 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{14}F_6N_2O$ $[M]^+$ = 366.1167. Found: 366.1172.



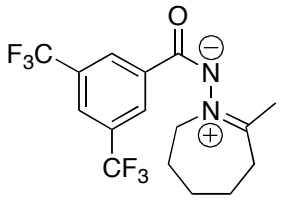
(3,5-Bis(trifluoromethyl)benzoyl(2-butyl-6-methyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (Table 3.7, Entry 2, 3.71).[105] Synthesized according to the general procedure (120 °C, 14h) using *N'*-(dec-9-yn-5-yl)-3,5-bis(trifluoromethyl)benzohydrazide (0.250 g, 0.610 mmol). The reaction mixture was isolated by column chromatography (1% MeOH in CH_2Cl_2). The title compound was obtained as a light brown oil (0.230 g, 93% yield). TLC R_f 0.30 in 1% MeOH in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.51 (s, 2H), 7.84 (s, 1H), 3.95-4.01 (m, 1H), 2.74 (br s, 2H), 2.20 (s, 3H), 2.19-1.95 (m, 3H), 1.94-1.77 (m, 2H), 1.75-1.57 (m, 1H), 1.47-1.24 (m, 4H), 0.84 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 171.3 (C), 165.1 (C), 139.8 (C), 130.8 (q, J = 33.1 Hz, 2C, <u>C</u>-CF_3), 128.2 (C), 123.2 (q, J = 272.3 Hz, 2C, <u>C</u>F_3), 123.0 (CH), 64.6 (CH), 32.5 (CH_2), 31.1 (CH_2), 28.4 (CH_2), 24.8 (CH_2), 22.2 (CH_2), 21.9 (CH_3), 14.1 (CH_2), 13.7 (CH_3), traces of chloroform present;[110] IR (film) 2964, 2937, 1626, 1576, 1318, 1278, 1173, 1131, 904, 681 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{22}F_6N_2O$ $[M]^+$ = 408.1636. Found: 408.1625.



***N*-(2-Methylpyrrolidin-1-yl)-3,5-bis(trifluoromethyl)benzamide (Equation 3.12, 3.73).** Synthesized according to the general procedure (140 °C, 14h) using 3,5-bis(trifluoromethyl)-*N'*-(pent-4-ynyl)benzohydrazide (0.250 g, 0.739 mmol). The reaction mixture was concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard, indicating the azomethine imine had been formed (45% NMR yield). Due to the instability of the azomethine imine, it was directly reduced to the corresponding saturated heterocycle to be isolated. The azomethine imine was dissolved in MeOH (7.50 mL, 0.100 M) and $NaBH_4$ (0.084 g, 2.22 mmol) was added. The reaction mixture was stirred under argon at room temperature for 2 hours. The reaction mixture was quenched with saturated solution of NH_4Cl, extracted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$, then brine, dried over Na_2SO_4 and concentrated. The reaction mixture was isolated by column chromatography (50% Et_2O in pentane). The title compound was obtained as a yellow oil (0.110 g, 44% yield, over 2 steps). TLC R_f 0.30 in 70% Et_2O in pentane. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.37-8.25 (m, 2H), 7.96 (s, 1H), 6.85 (br s, 1H), 3.51-2.63 (m, 3H), 2.10-1.63 (m, 4H), 1.24-1.22 (m, 2H), 0.99-0.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm (as a mixture of conformers, * denotes minor conformer) 144.6 (C), 131.9 (q, J = 31.6 Hz, 2C, $\underline{C}$-CF_3), 129.6 (C), 127.5 (2C), 124.3 (C), 122.9 (q, J = 272.8 Hz, 2C, $\underline{C}F_3$), 62.6 (CH), *56.5 (CH_2), 55.6 (CH_2), 30.3 (CH_2), *30.0 (CH_2), 20.5 (CH_2), *19.8 (CH_2), 17.7 (CH_3); IR (film) 1276, 1128, 1083 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{14}F_6N_2O$ $[M]^+$ = 340.2642. Found: 340.1016.



(5-Benzyl-3,4-dihydro-*2H*-pyrrolium-1-yl)(3,5-bis(trifluoromethyl)benzoyl)amide (Table 3.9, Entry 3, 3.74). Synthesized according to the general procedure (150 °C, 14h) using 3,5-bis(trifluoromethyl)-*N'*-(5-phenylpent-4-ynyl)benzohydrazide (0.250 g, 0.603 mmol). The reaction mixture was isolated by column chromatography (2% MeOH in CH_2Cl_2). The title compound was obtained as a yellow oil (0.153 g, 62% yield). TLC R_f 0.31 in 2% MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) (as a mixture of conformers, * denotes minor conformer) δ ppm 8.56 (s, 2H), *8.34 (s, 2H), *7.99 (s, 1H), 7.89 (s, 1H), 7.38-7.24 (m, 5H), 4.51 (s, 2H), 3.96 (s, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.28-2.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.3 (C), 133.0 (C) 133.0 (C), 131.0 (q, J = 33.3 Hz, 2C, $\underline{C}$-CF_3), 129.3 (2C), 129.2 (2C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 123.4 (q, J = 272.8 Hz, 2C, $\underline{C}F_3$), 121.6 (C), 60.2 (CH_2), 35.9 (CH_2), 34.4 (CH_2), 17.9 (CH_2), missing one quaternary carbon;[109] IR (film) 3393, 3207, 1668, 1280, 1178, 1132, 908, 699, 676 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{14}F_6N_2O$ $[M]^+$ = 414.1167. Found: 414.1258.



(3,5-Bis(trifluoromethyl)benzoyl)(7-methyl-3,4,5,6-tetrahydro-*2H*-azepinium-1-yl) amide (Table 3.10, Entry 3, 3.75). Synthesized according to the general procedure (170 °C, 14h) using 3,5-bis(trifluoromethyl)-*N'*(hept-6-ynyl)benzohydrazide (0.250 g, 0.683 mmol). The reaction mixture was isolated by column chromatography (1-5% MeOH in CH_2Cl_2). The title compound was obtained as a yellow oil (0.010 g, 4% yield). TLC R_f 0.34 in 1% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.29 (s, 2H), 7.93 (s, 1H), 2.95 (t, *J* = 6.6 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.13 (s, 3H), 1.67-1.50 (m, 4H), 1.49-1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.2 (C), 134.9 (C), 132.2 (q, *J* = 33.9 Hz, 2C, $\underline{C}$-CF_3), 127.4 (CH), 125.2 (CH), 122.2 (q, *J* = 273.1 Hz, 2C, $\underline{C}F_3$), 51.7 (CH_2), 43.4 (CH_2), 29.9 (CH_3), 27.6 (CH), 26.2 (CH_2), 23.3 (CH_2), missing one quaternary carbon;[109] IR (film) 1653, 1558, 1284, 1132, 1083 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{14}F_6N_2O$ $[M]^+$ = 366.1167. Found: 366.1178.

Appendix

Claims to Original Research:

1) Instrumental in expansion of the substrate scope for the intramolecular hydroamination of alkenes using hydrazides as well as preliminary mechanistic studies associated with this reaction.

2) Obtained initial results on the intramolecular hydroamination of alkenes using hydrazides, extensions of which are currently being investigated in the group.

3) Played a key role in the discovery and development of the substrate scope for the intramolecular hydroamination of alkynes using hydrazides, as well as in the isolation of the products formed.

Publications:

(1) ``*Hydrazides as Tunable Reagents for Alkene Hydroamination and Diamination*`` Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

Presentations:

(1) *"Hydrazides as Tunable Reagents for Alkene Hydroamination and Diamination"* Roveda, J-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

(2) "*Intramolecular Hydroamination of Alkenes and Alkynes Using Hydrazides"* Hunt, A. D.; Roveda, J.-G.; Gorelsky, S. I.; Beauchemin, A. M. *Keith Fagnou Organic Chemistry Symposium.* May 5-7, **2010** (poster).

(3) *"Intramolecular Hydroamination of Alkenes and Alkynes Using Hydrazides"* Hunt, A. D.; Roveda, J.-G.; Gorelsky, S. I.; Beauchemin, A. M. *QOMSBOC.* October 31, **2009** (poster).

(4) *"Intramolecular Hydroamination Reactivity Using Hydrazides: Scope and Potential Applicability"* Roveda, J.-G.; Hunt, A. D.; Gorelsky, S. I.; Beauchemin, A. M. *Synthesis Day.* June 5, **2009** (poster).

Appendix II: ^{1}H and ^{13}C Spectra

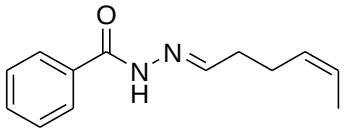
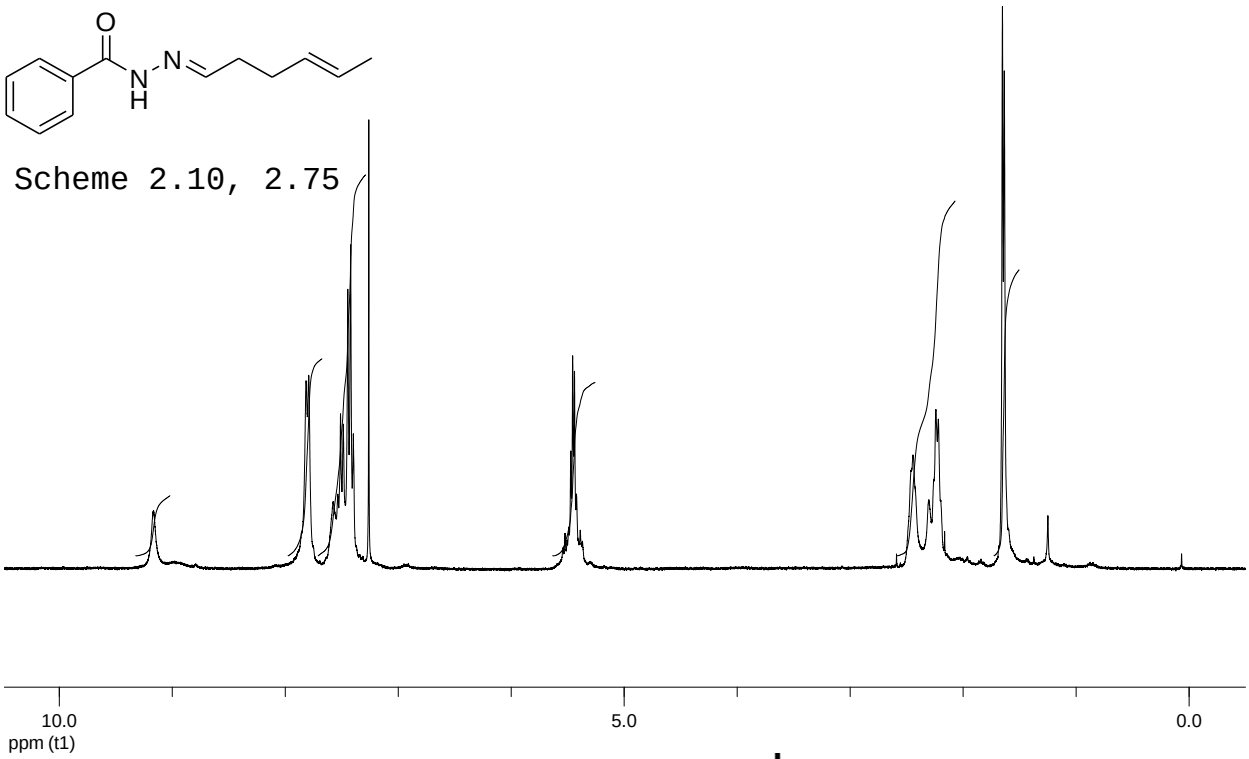
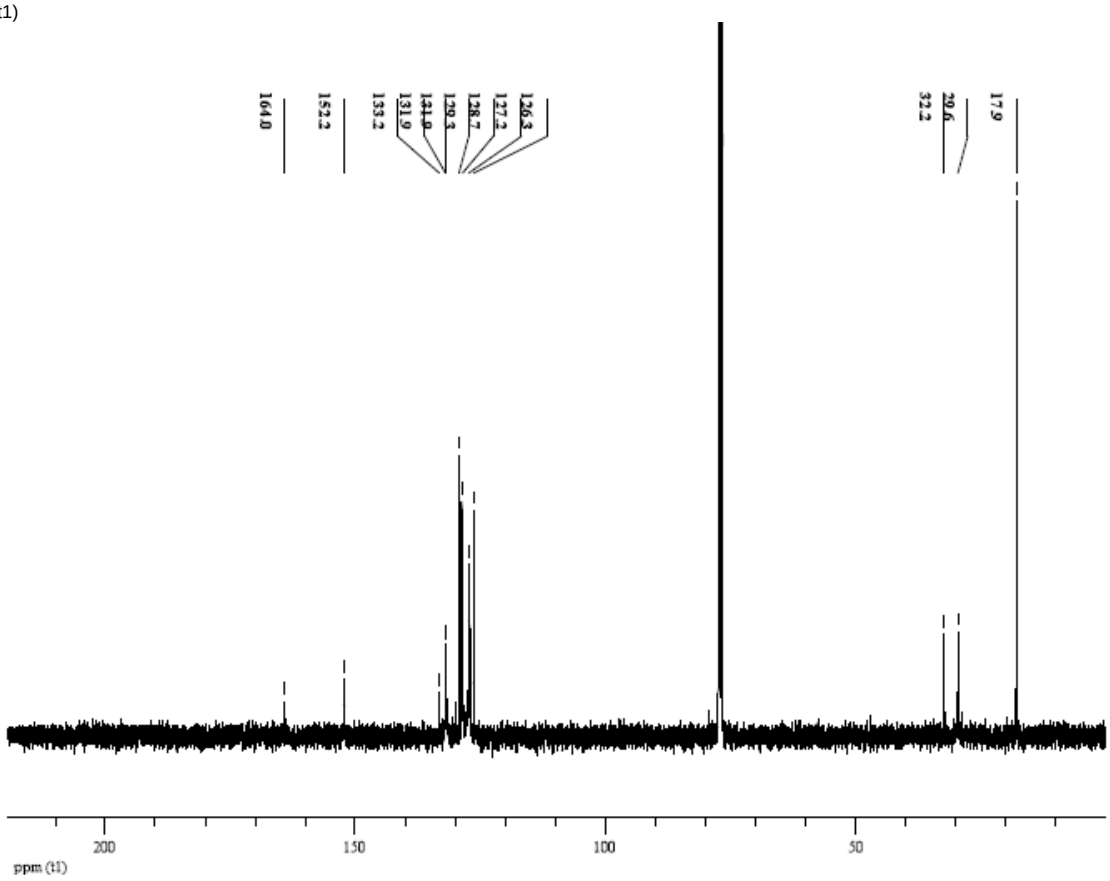
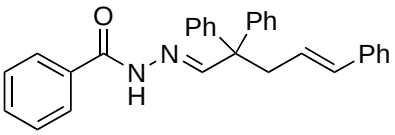


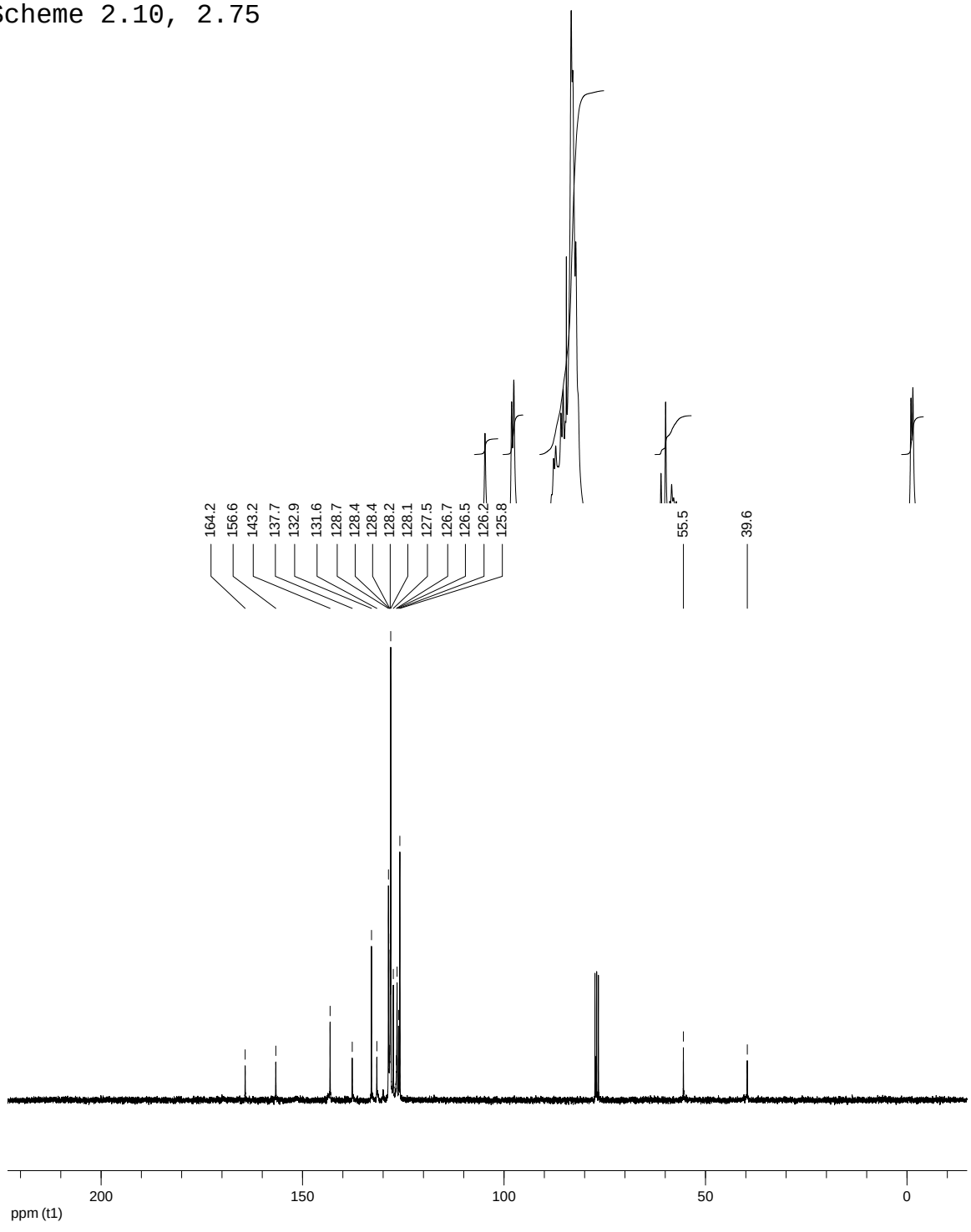
Table 2.2, Entry 2, 2.47b

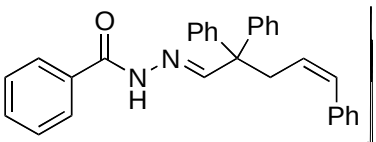

O
N
H
N
Scheme 2.10, 2.75
10.0
5.0
0.0
ppm (t1)


164.0
152.2
133.2
131.9
131.9
129.3
128.7
127.2
126.3
32.2
29.6
17.9
200
150
100
50
ppm (t1)

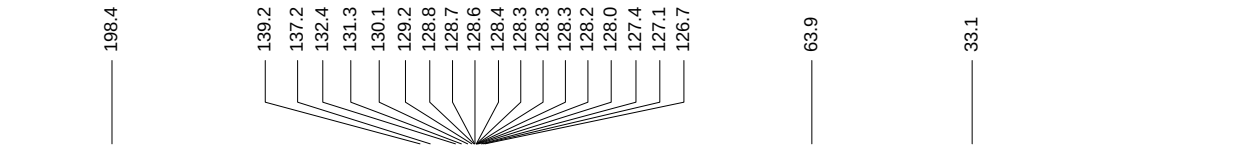


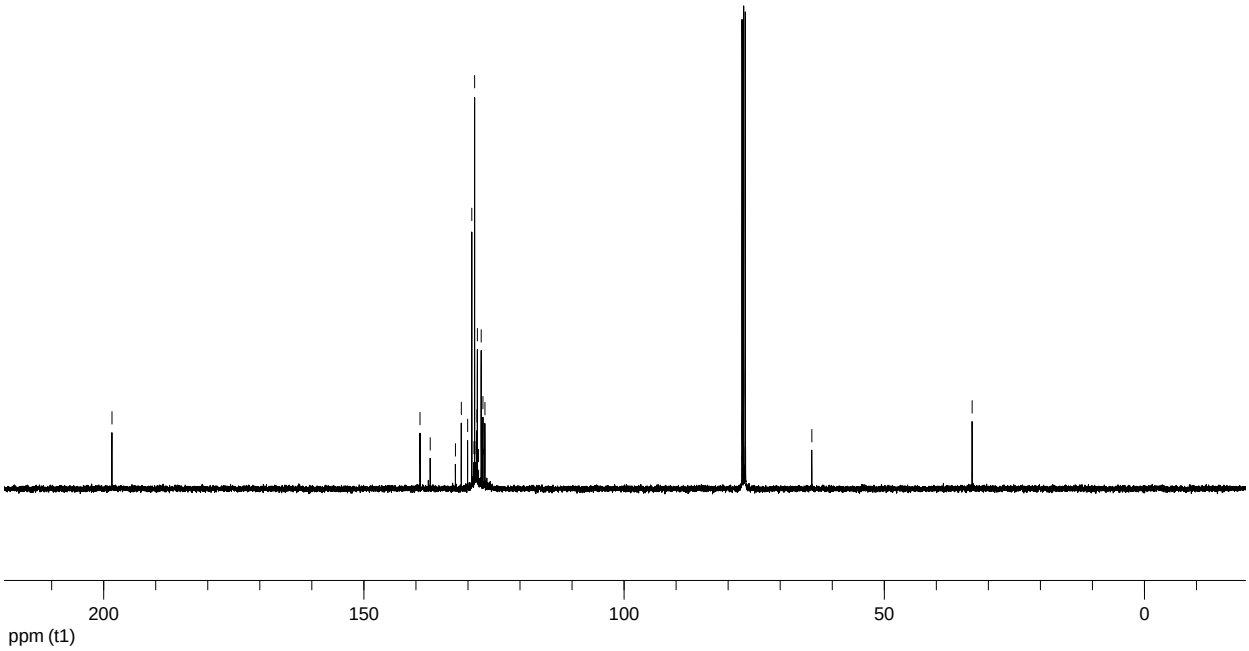
Scheme 2.10, 2.75





Scheme 2.12, 2.86





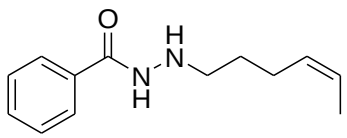
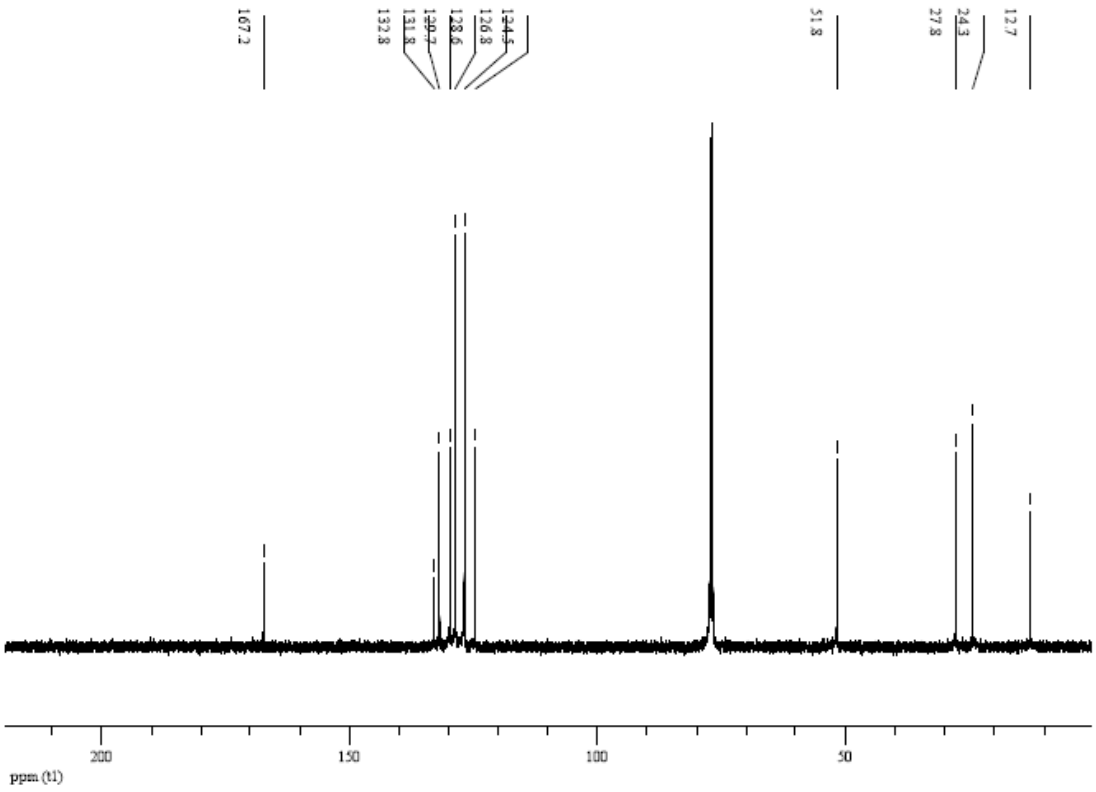


Table 2.2, Entry 3, 2.48c



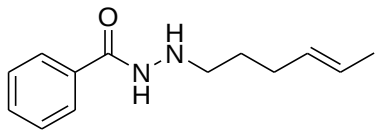
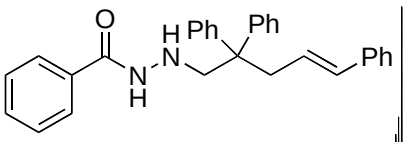
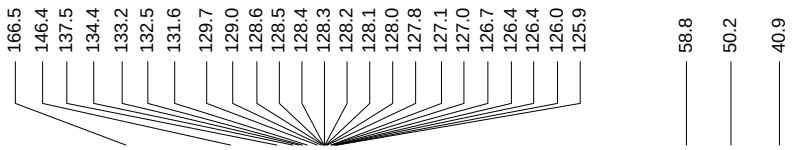
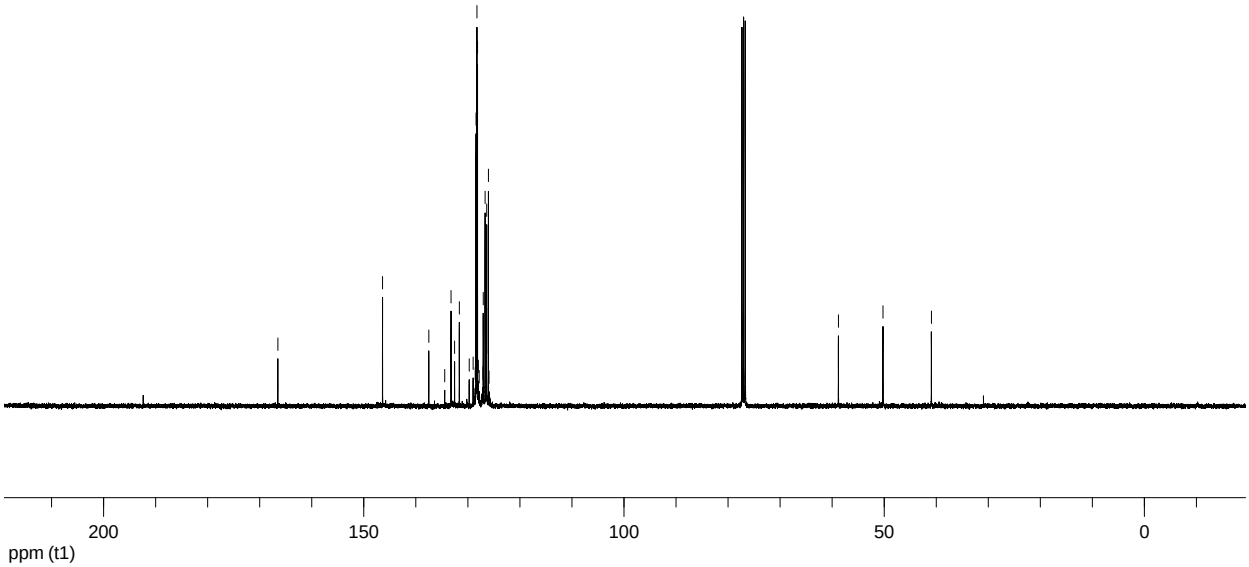


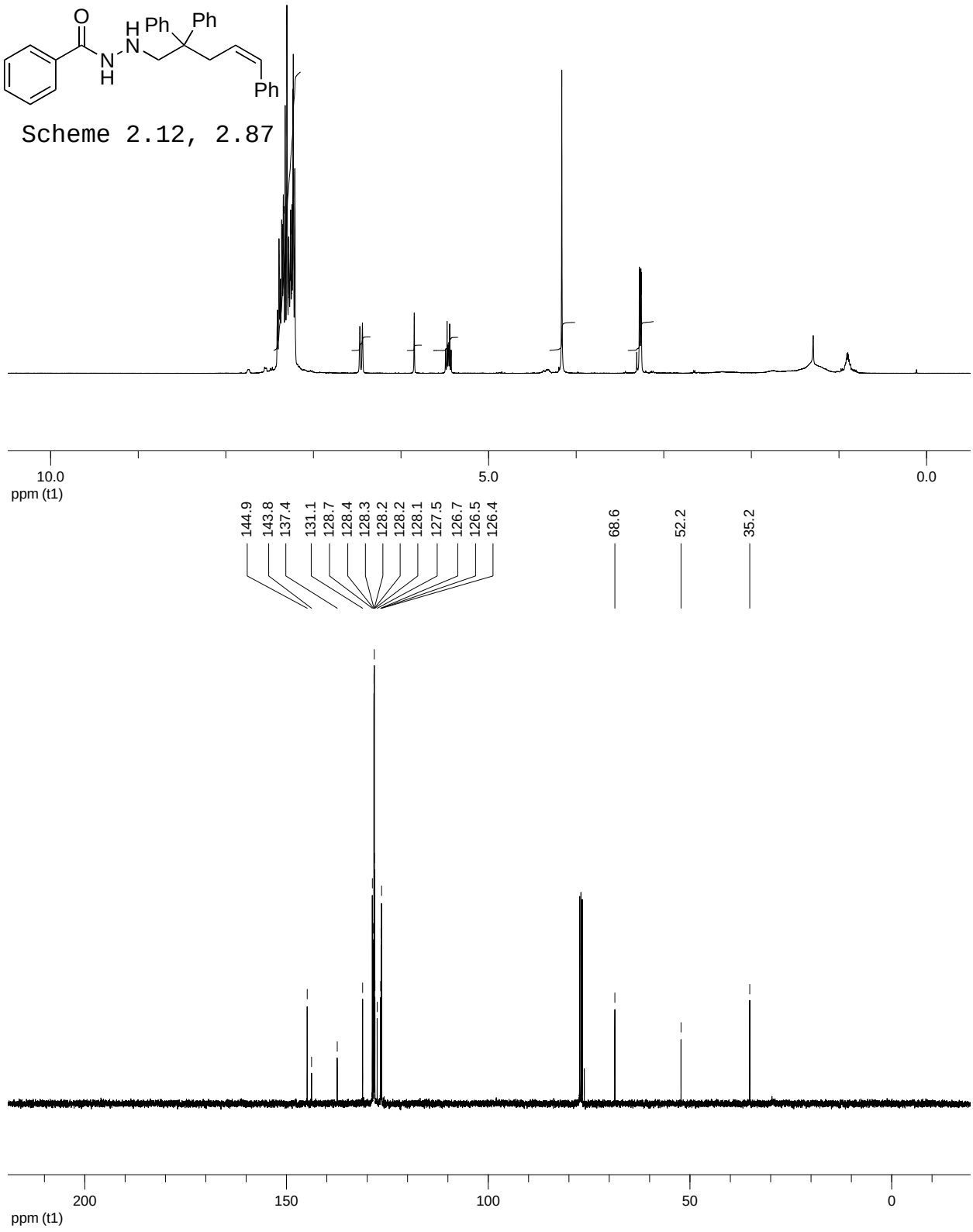
Table 2.2, Entry 2, 2.48b



Scheme 2.10, 2.76






Scheme 2.12, 2.87
10.0
5.0
0.0
ppm (t1)
144.9
143.8
137.4
131.1
128.7
128.4
128.3
128.2
128.2
128.1
127.5
126.7
126.5
126.4
68.6
52.2
35.2
200
150
100
50
0
ppm (t1)

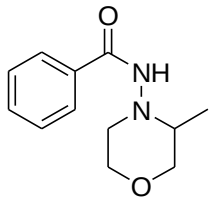
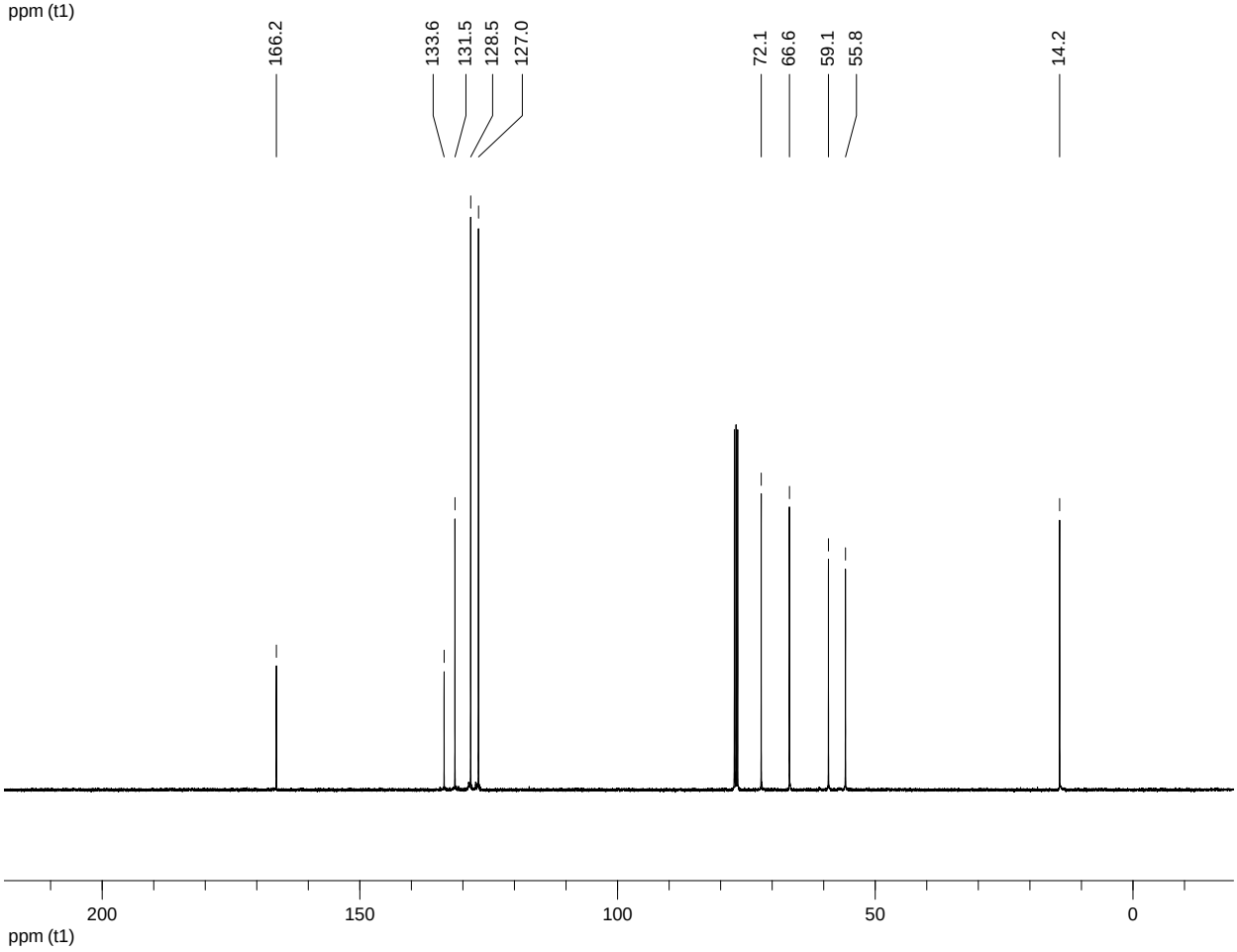


Table 2.3, Entry 1, 2.51



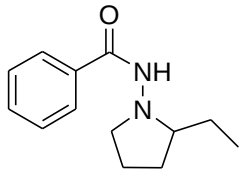
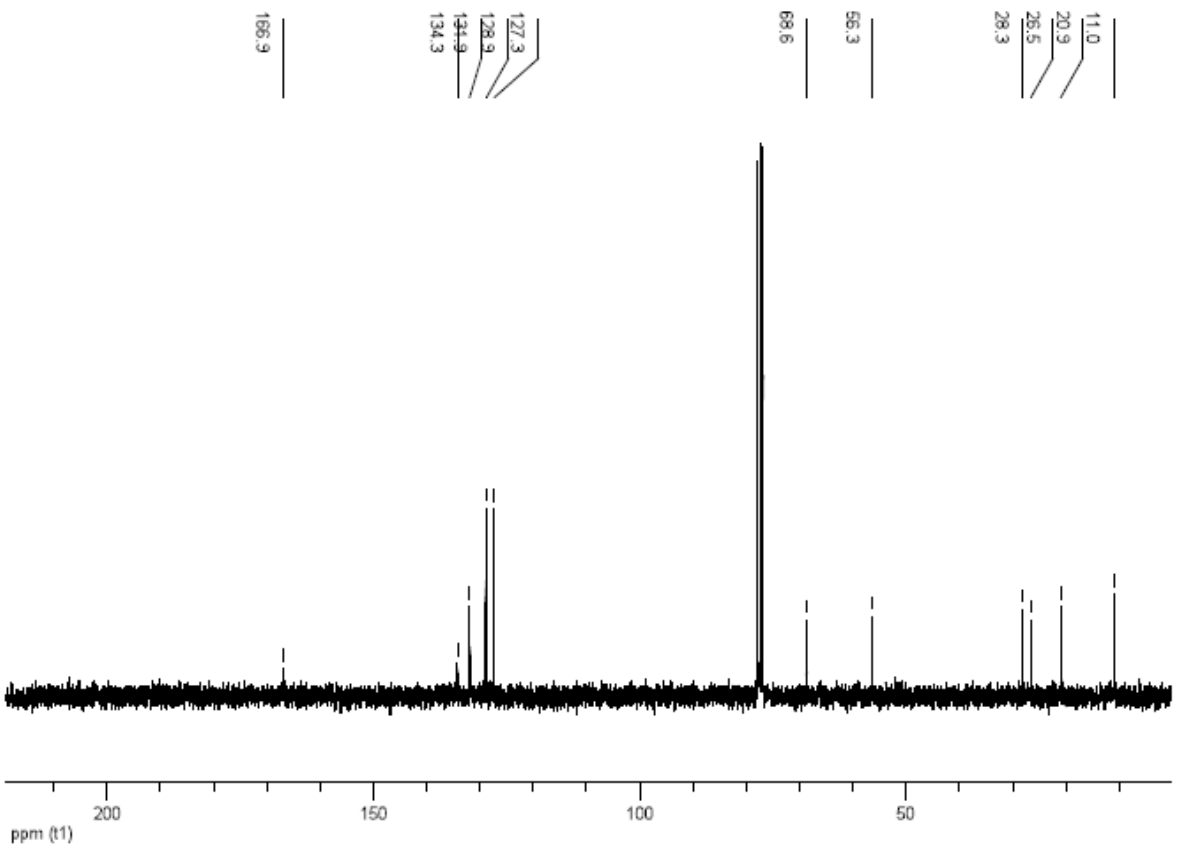
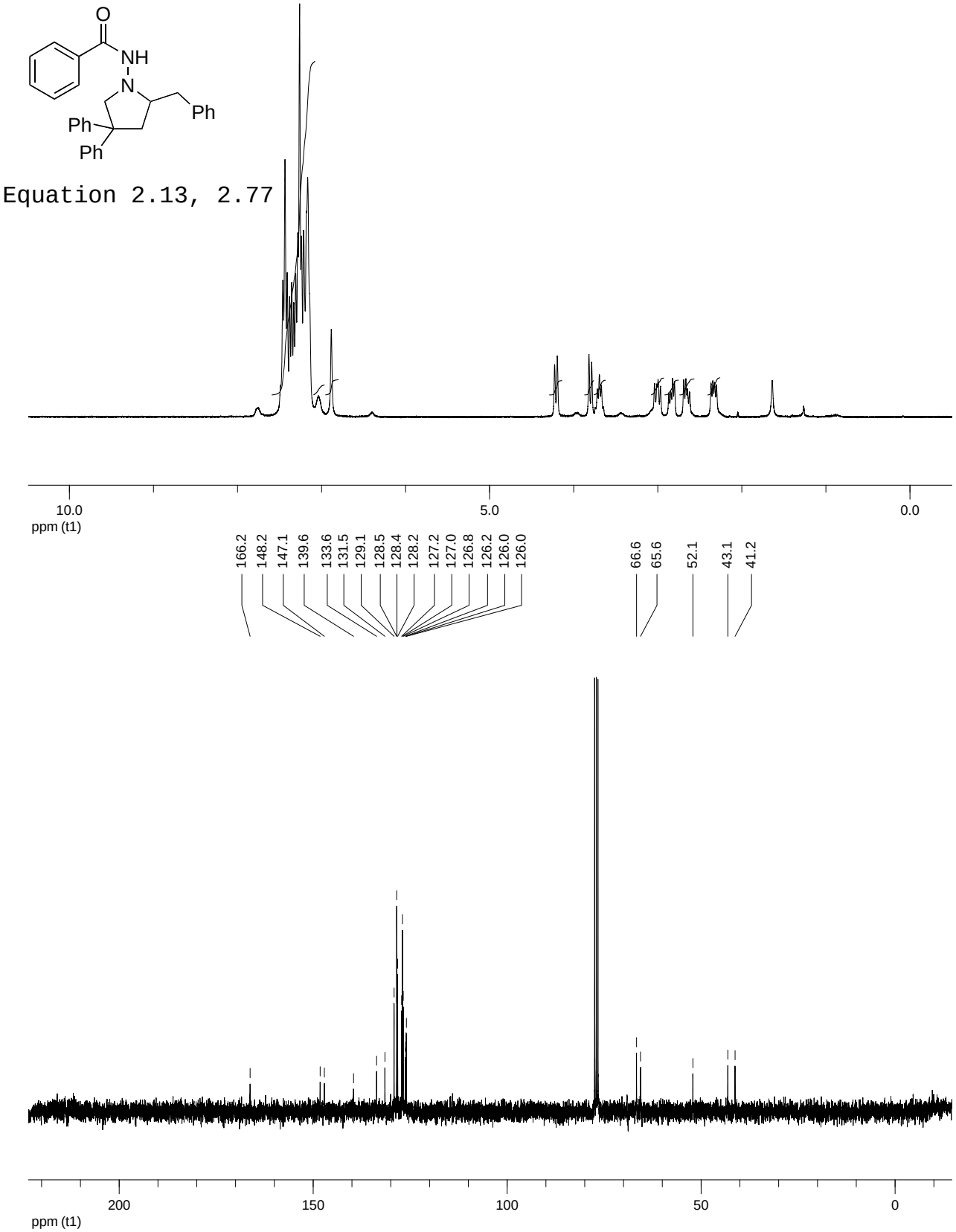

O
NH
N

Table 2.4, 2.55

10.0
5.0
0.0
ppm (t1)


166.9
134.3
131.9
128.9
127.3
68.6
56.3
28.3
26.5
20.9
11.0
200
150
100
50
ppm (t1)


O
NH
N
Ph
Ph
Ph
Equation 2.13, 2.77
10.0
5.0
0.0
ppm (t1)
166.2
148.2
147.1
139.6
133.6
131.5
129.1
128.5
128.4
128.2
127.2
127.0
126.8
126.2
126.0
126.0
66.6
65.6
52.1
43.1
41.2
200
150
100
50
0
ppm (t1)

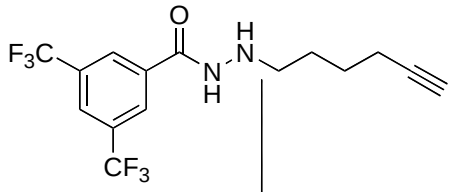
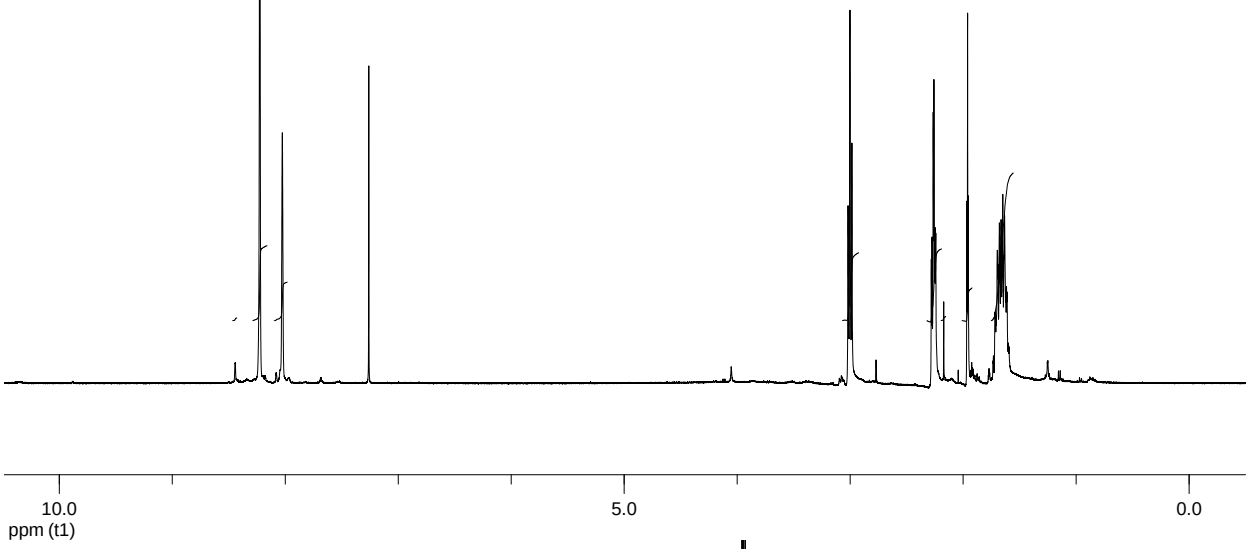
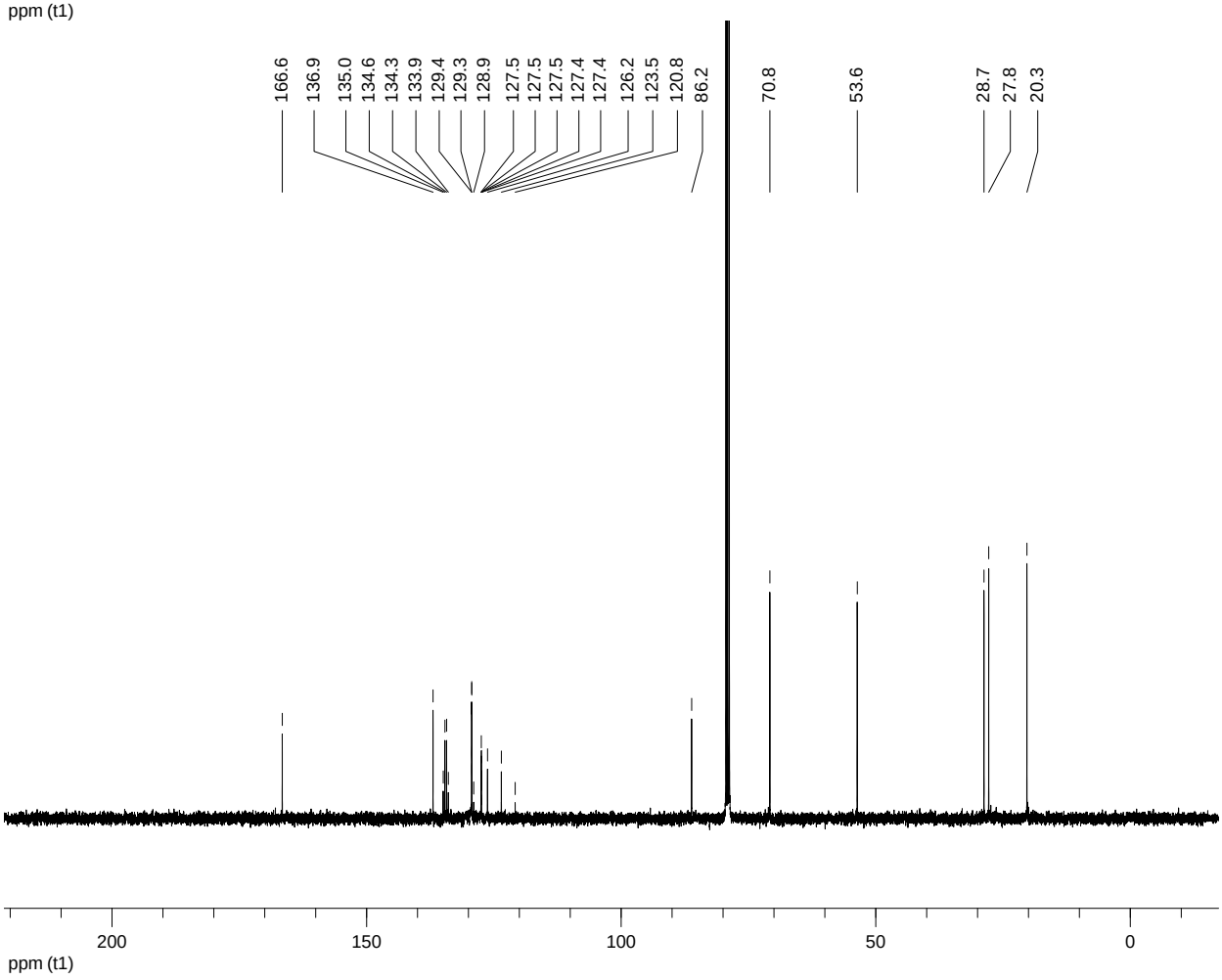


Table 3.1, Entry 2, 3.56b





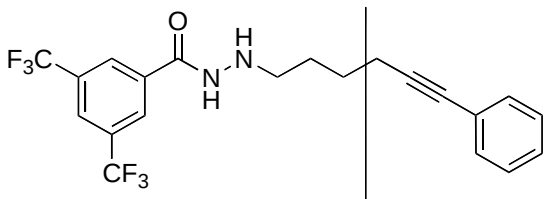
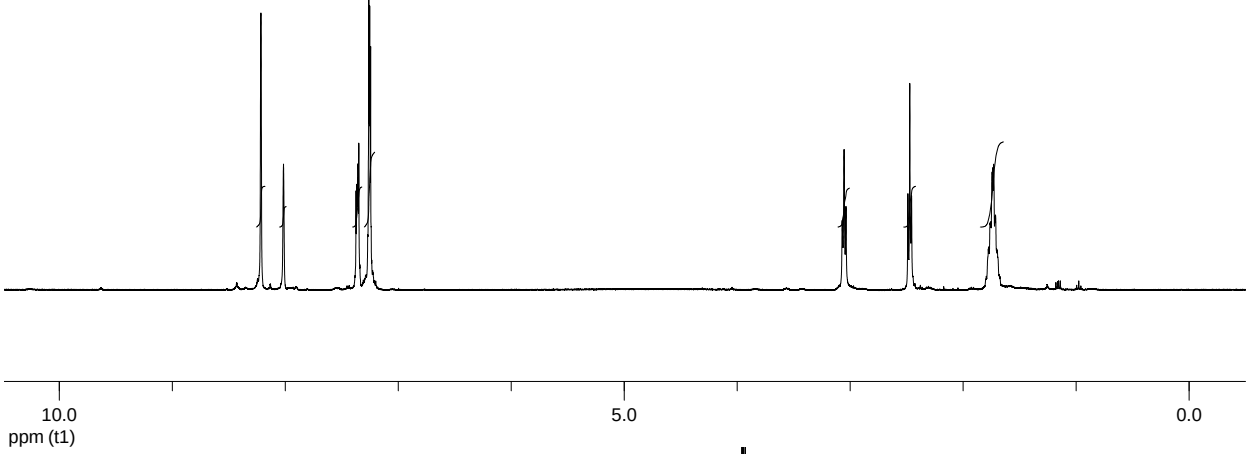
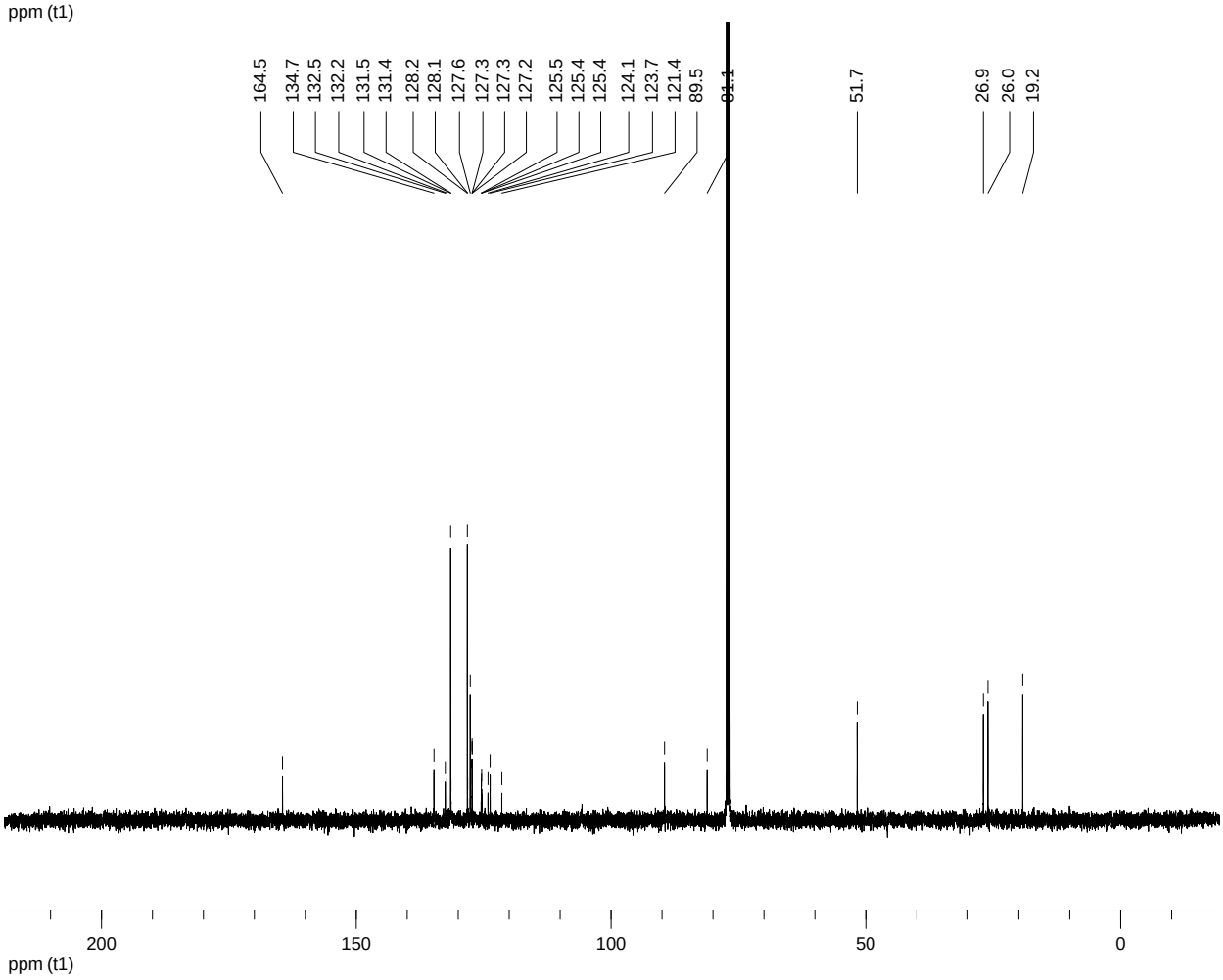


Table 3.1, Entry 3, 3.56c





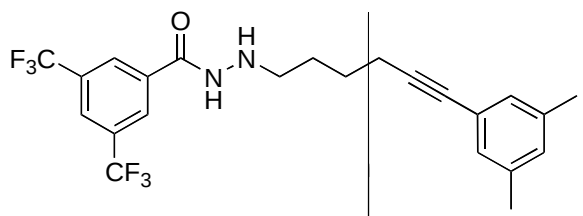
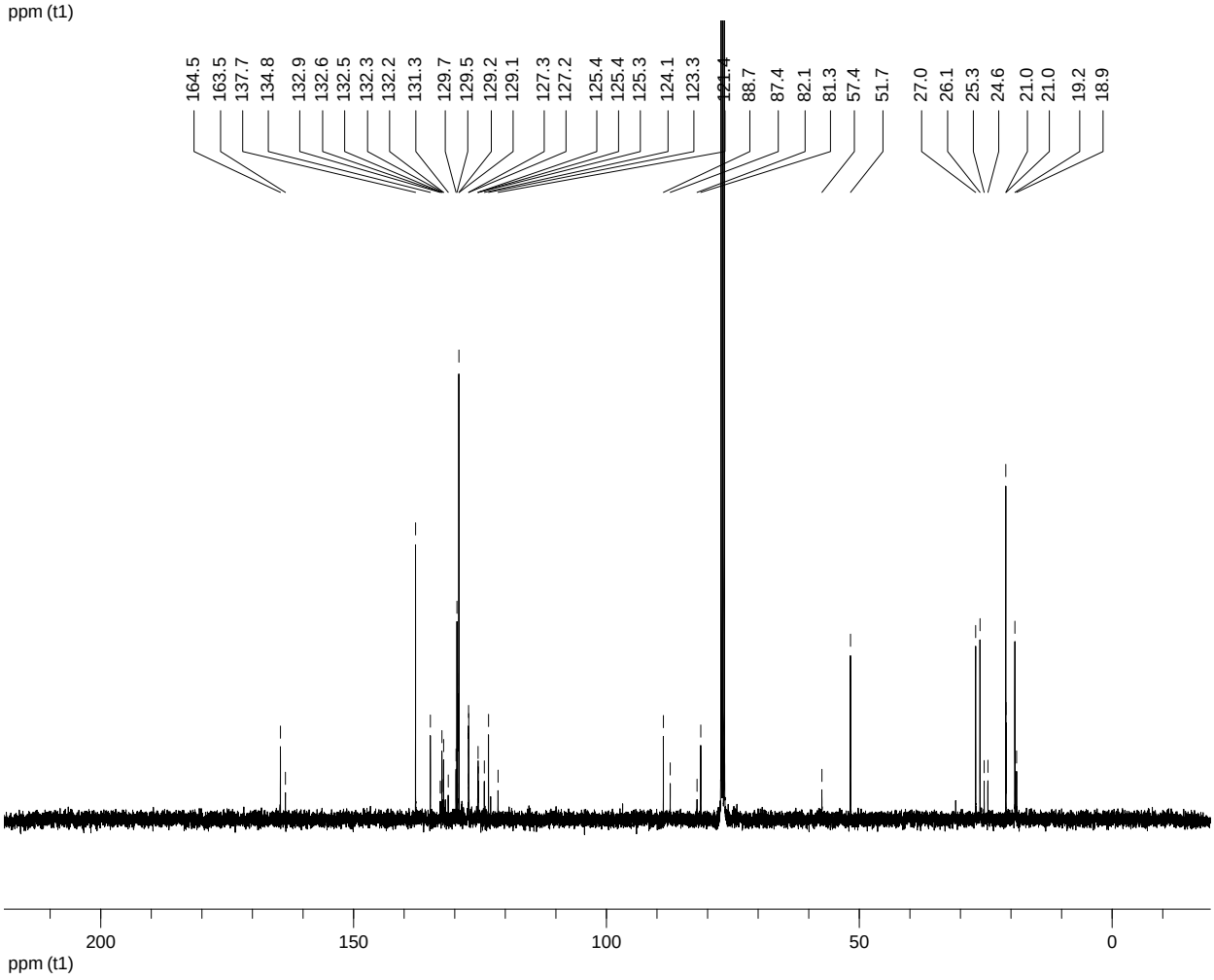
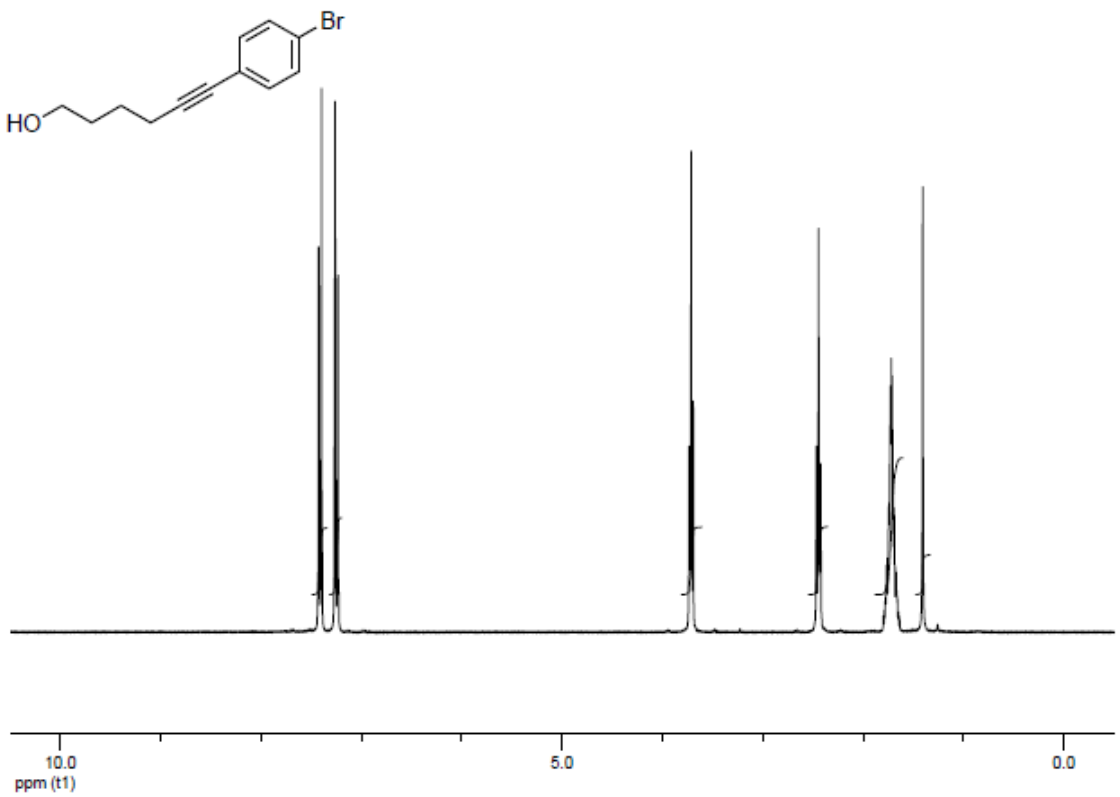
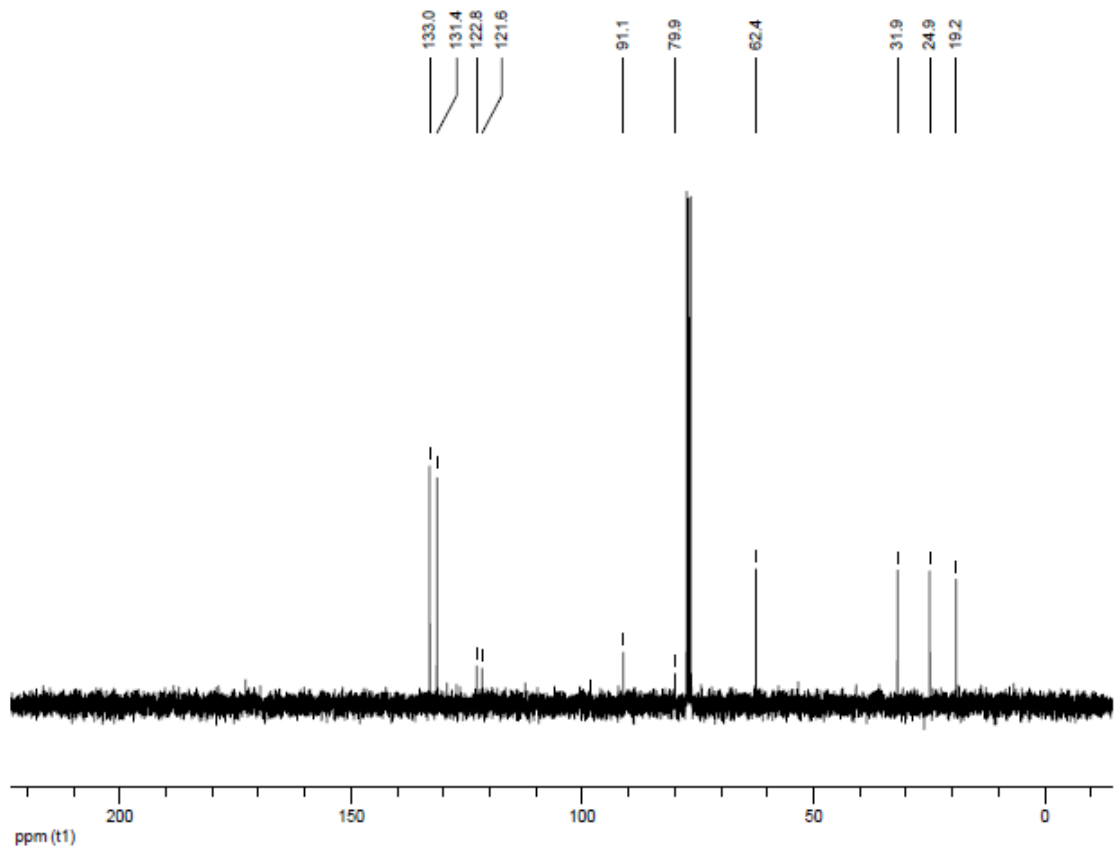


Table 3.1, Entry 4, 3.56d




Br
HO
10.0
ppm (t1)
5.0
0.0


133.0
131.4
122.8
121.6
91.1
79.9
62.4
31.9
24.9
19.2
200
150
100
50
0
ppm (t1)

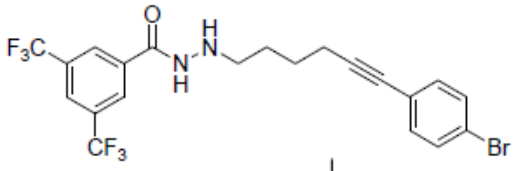
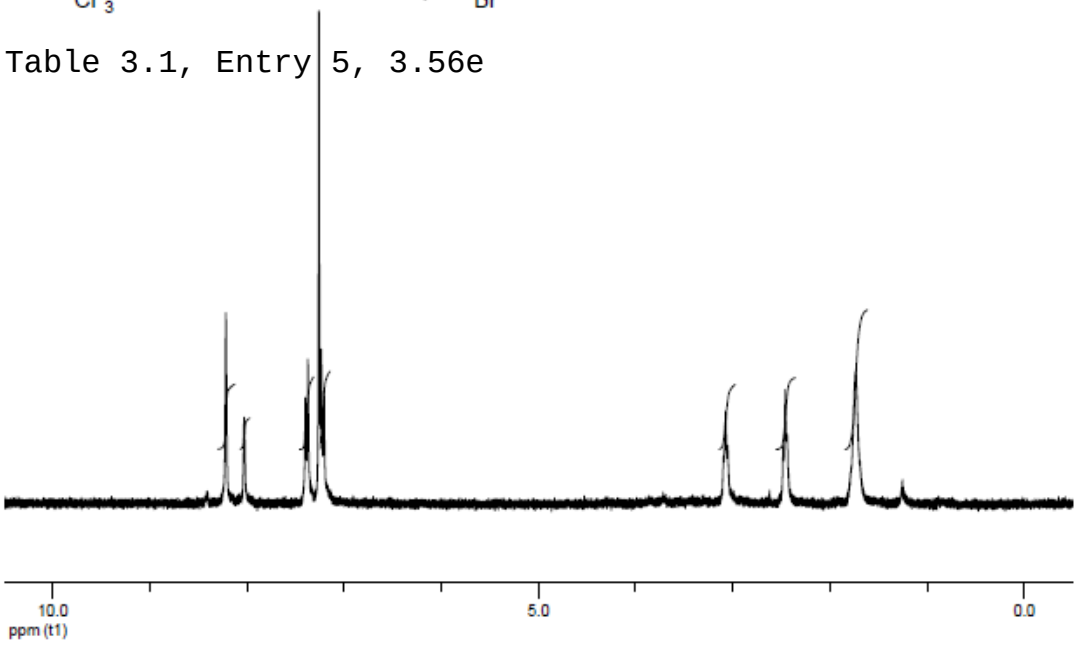
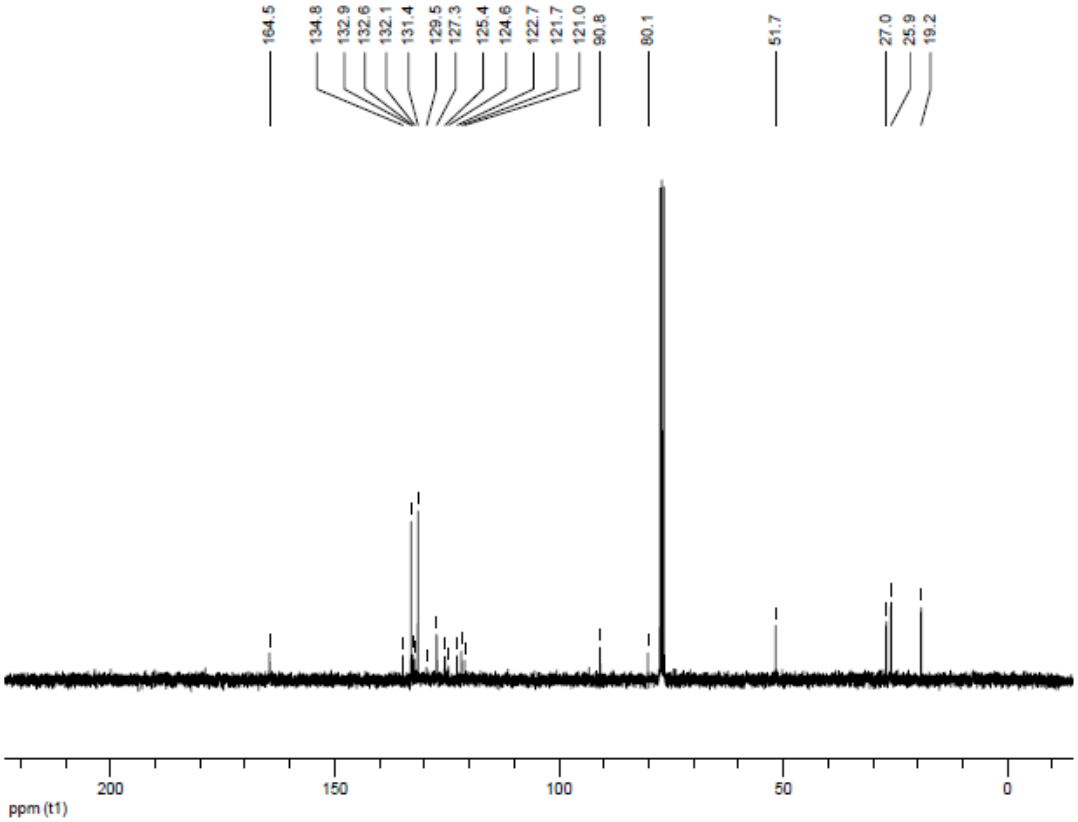


Table 3.1, Entry 5, 3.56e





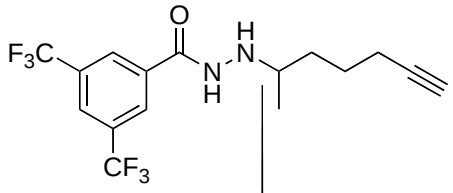
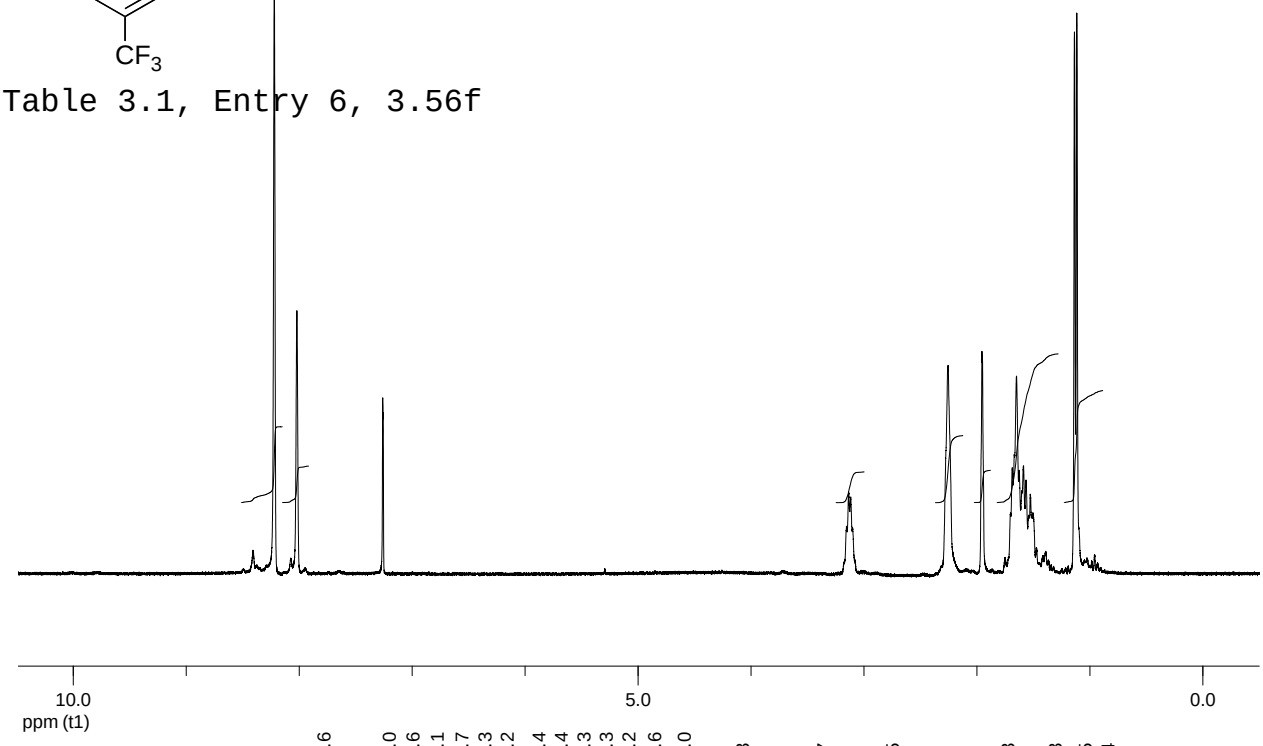
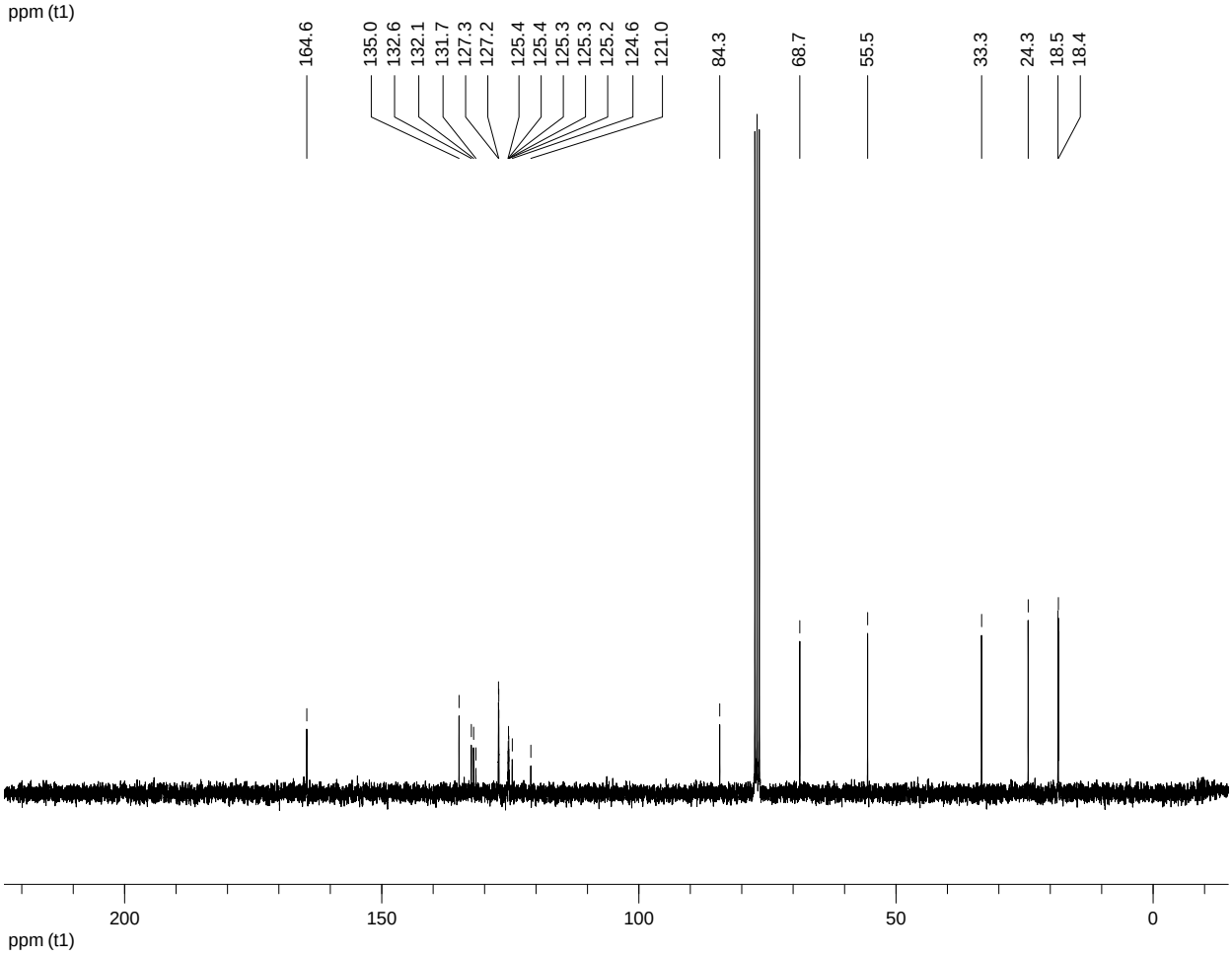


Table 3.1, Entry 6, 3.56f





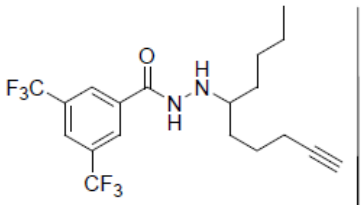
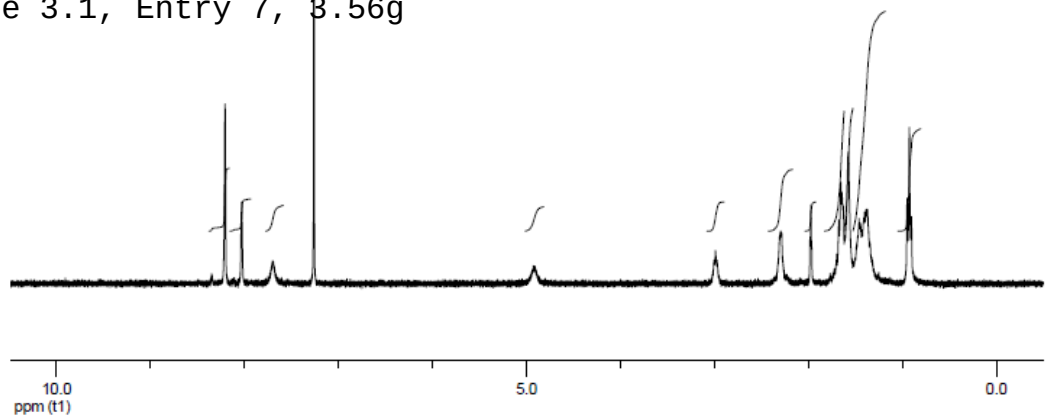
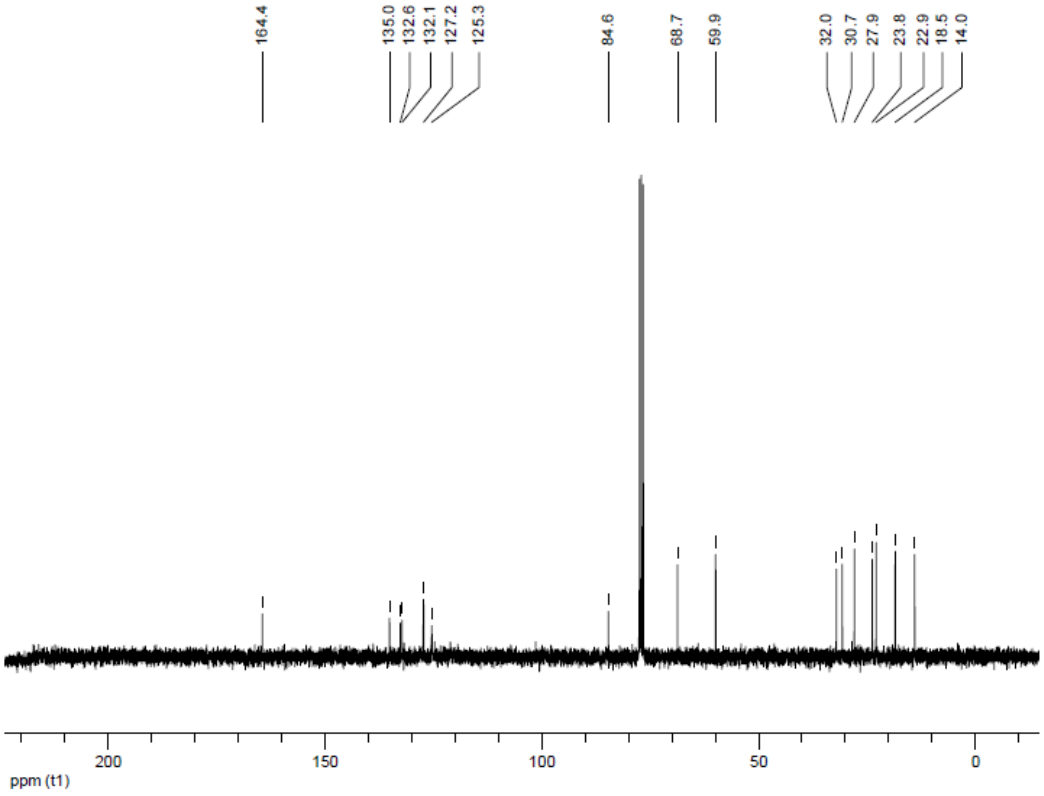


Table 3.1, Entry 7, 3.56g





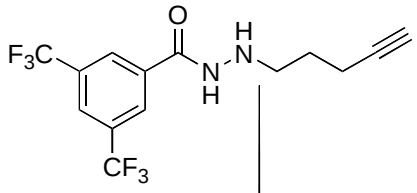
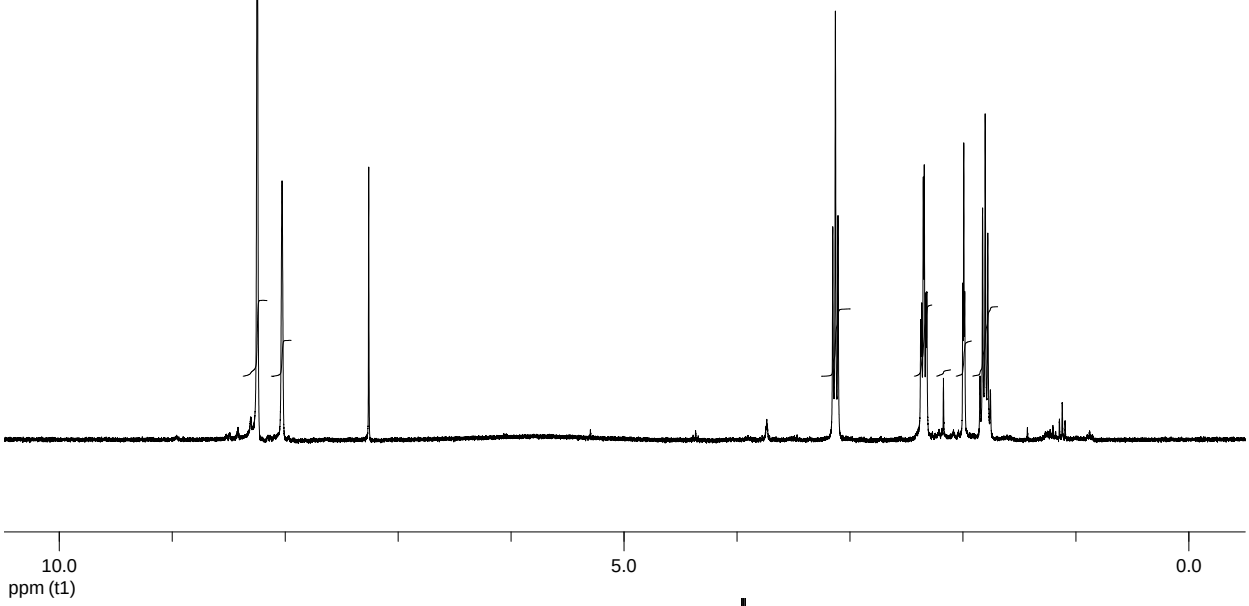
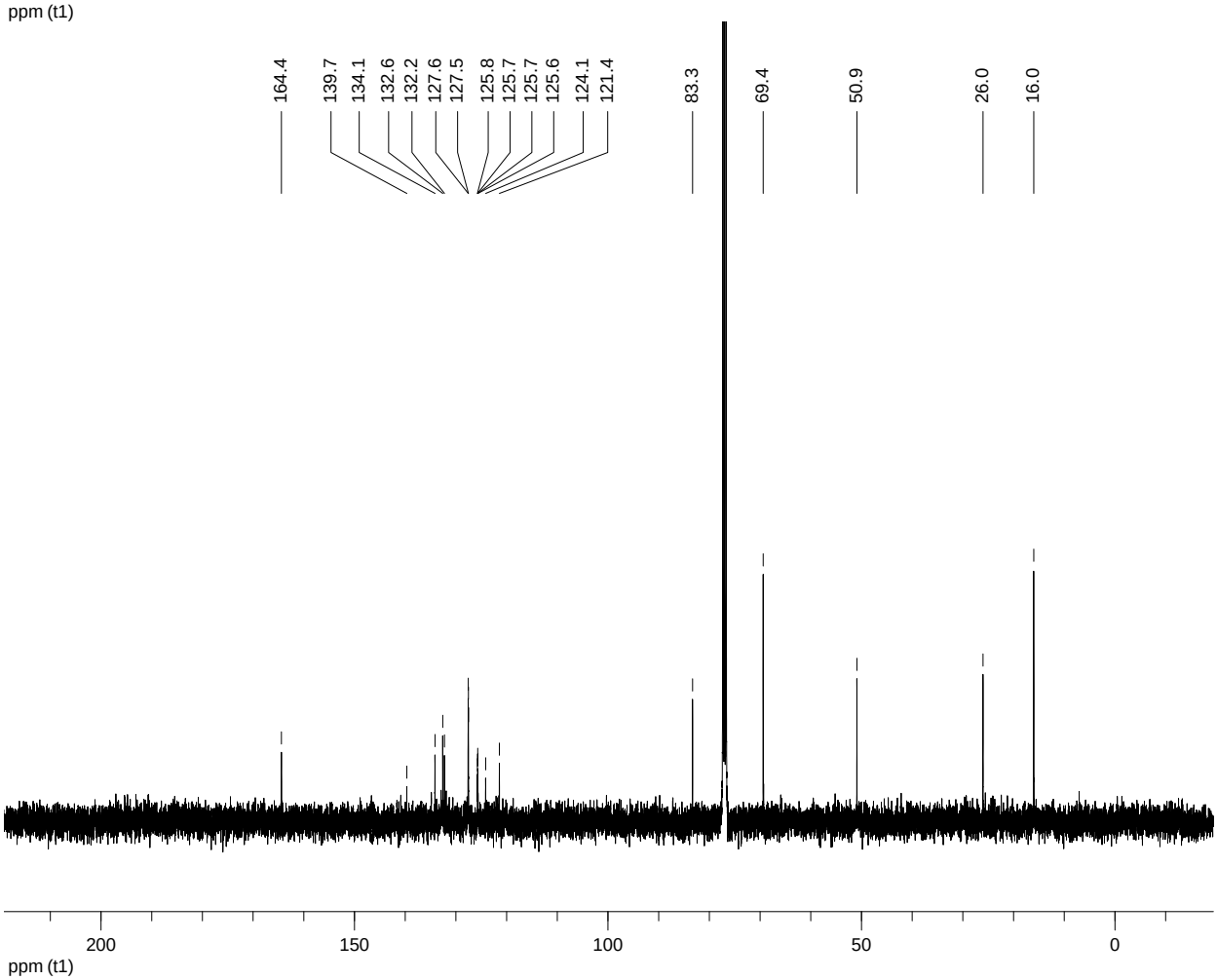


Table 3.2, Entry 1, 3.59a





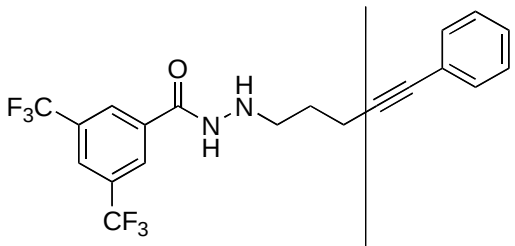
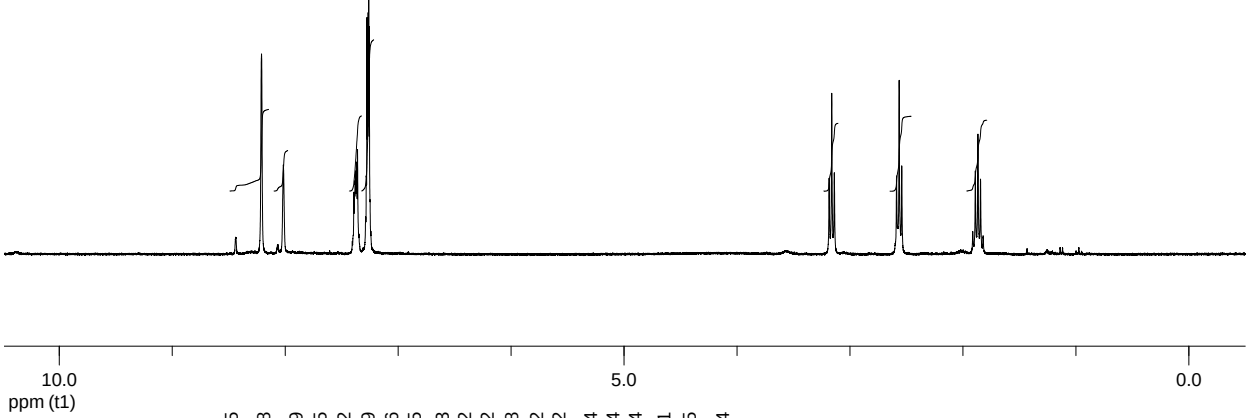
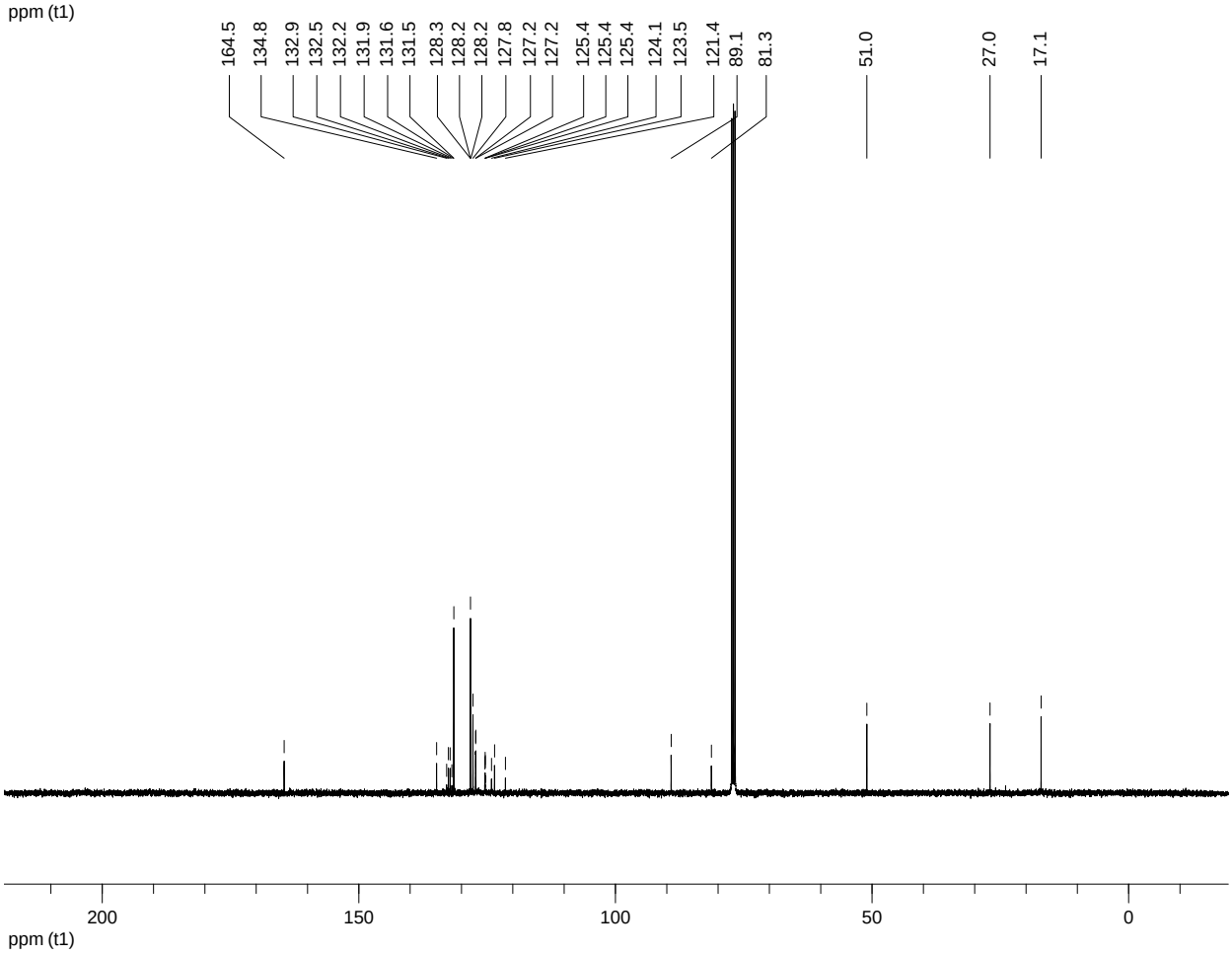
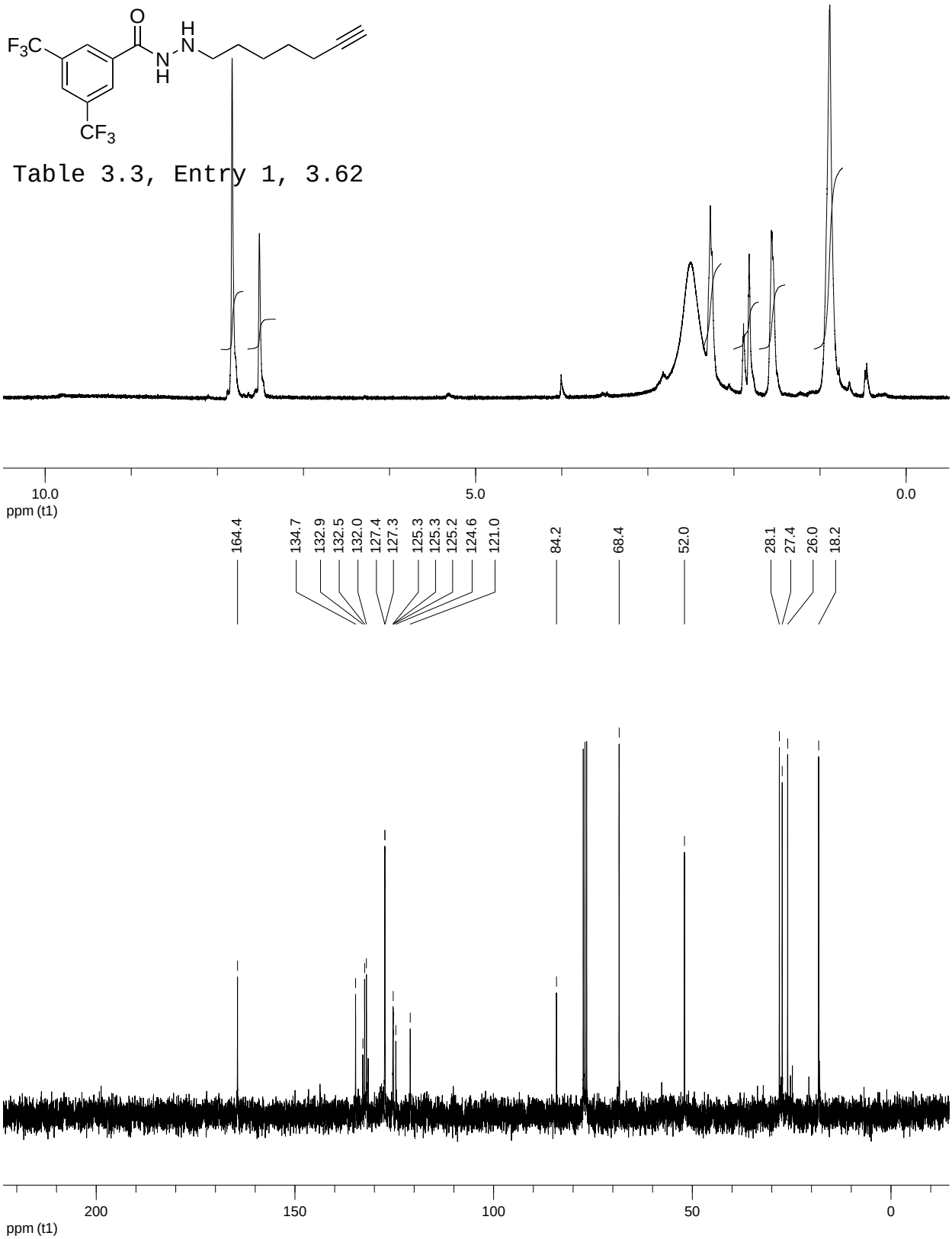


Table 3.2, Entry 2, 3.59b






O
H
N
F3C
N
H
CF3
Table 3.3, Entry 1, 3.62
10.0
5.0
0.0
ppm (t1)
164.4
134.7
132.9
132.5
132.0
127.4
127.3
125.3
125.3
125.2
124.6
121.0
84.2
68.4
52.0
28.1
27.4
26.0
18.2
200
150
100
50
0
ppm (t1)

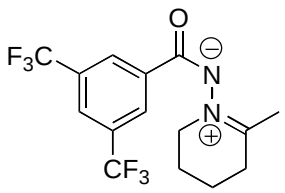
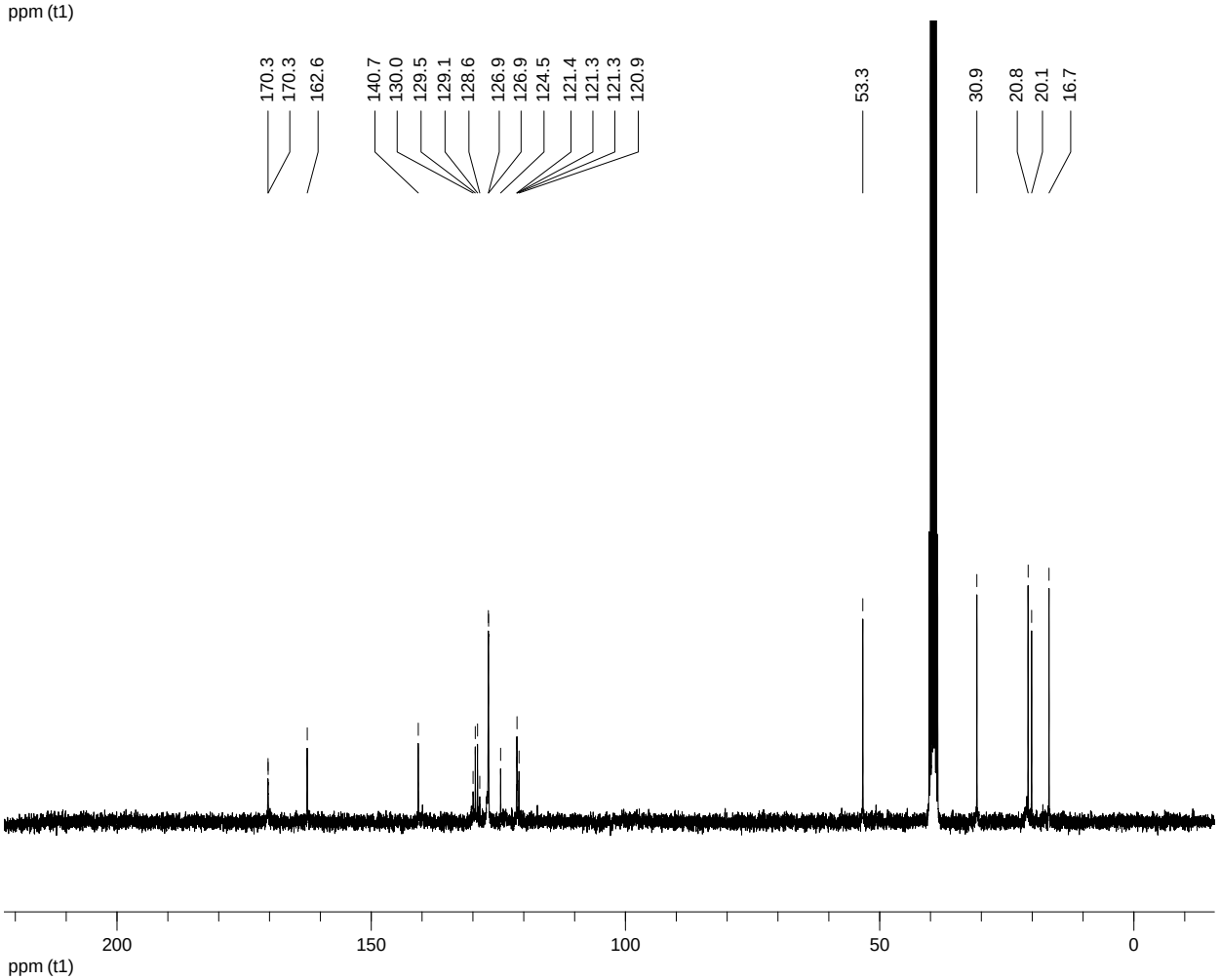


Table 3.4, Entry 3, 3.64



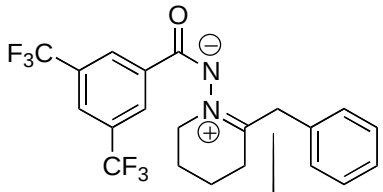
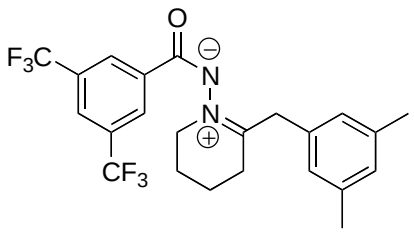
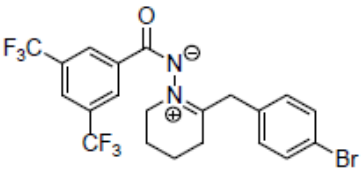


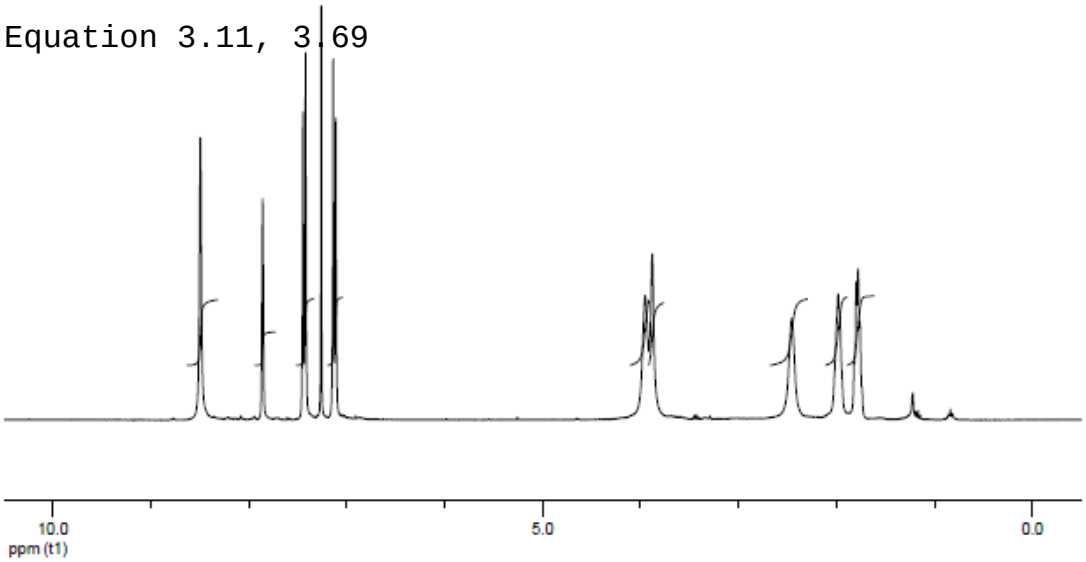
Table 3.5, Entry 3, 3.67

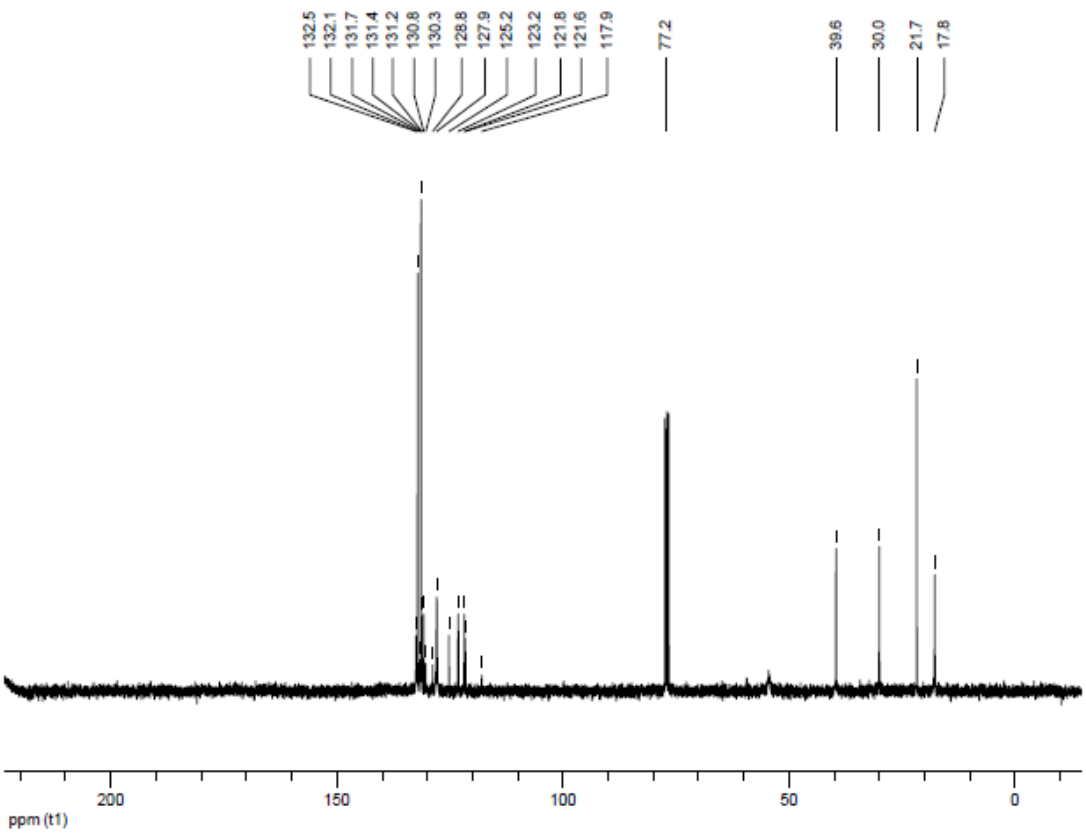


Equation 3.10, 3.68



Equation 3.11, 3.69





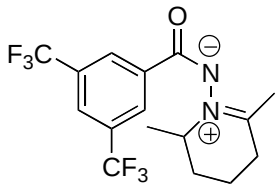
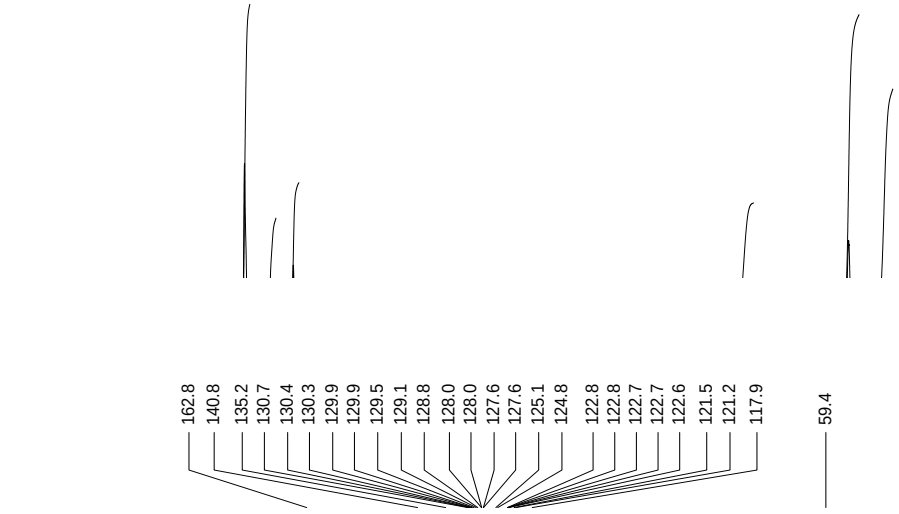
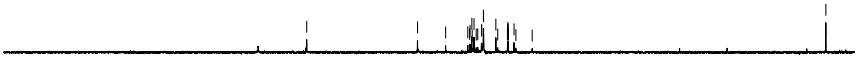


Table 3.6, Entry 3, 3.70





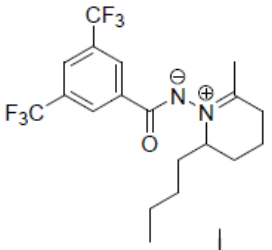
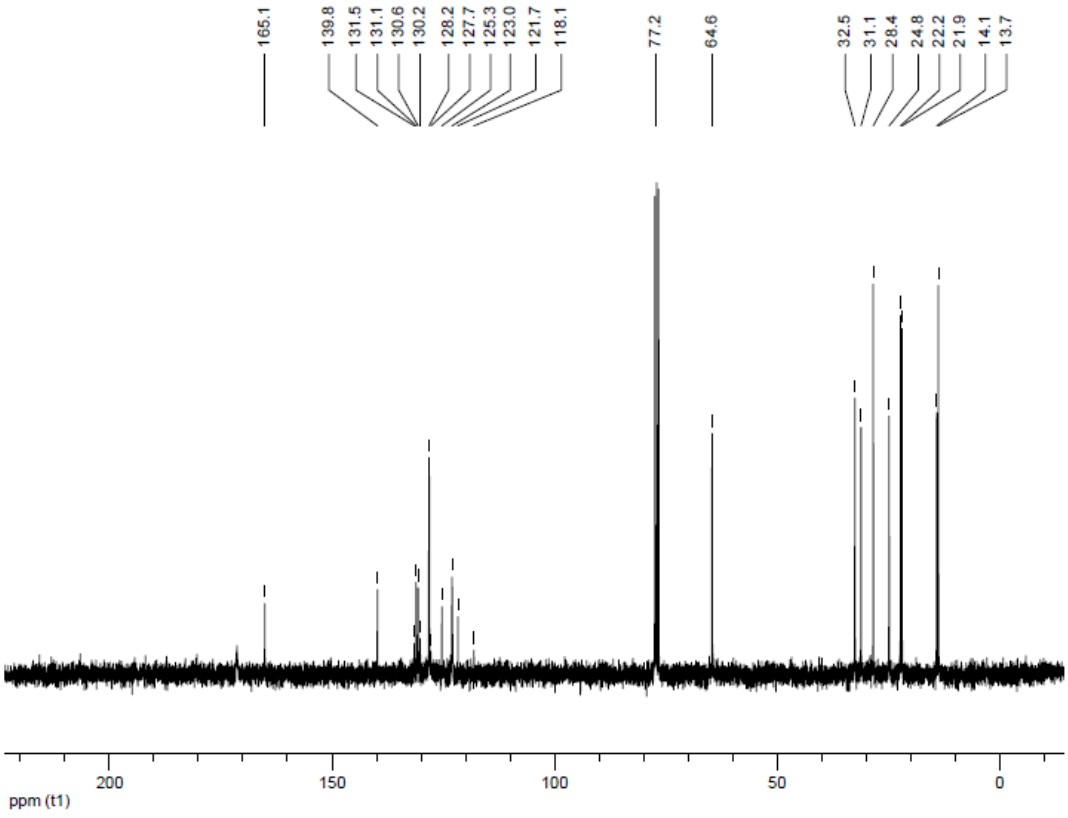
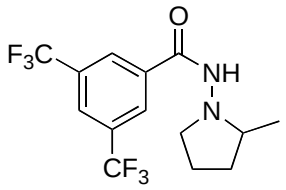


Table 3.7, Entry 2, 3.71





Equation 3.12, 3.73

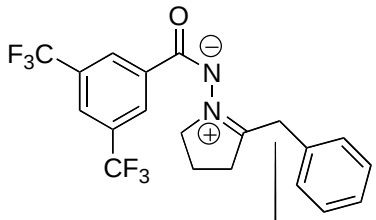
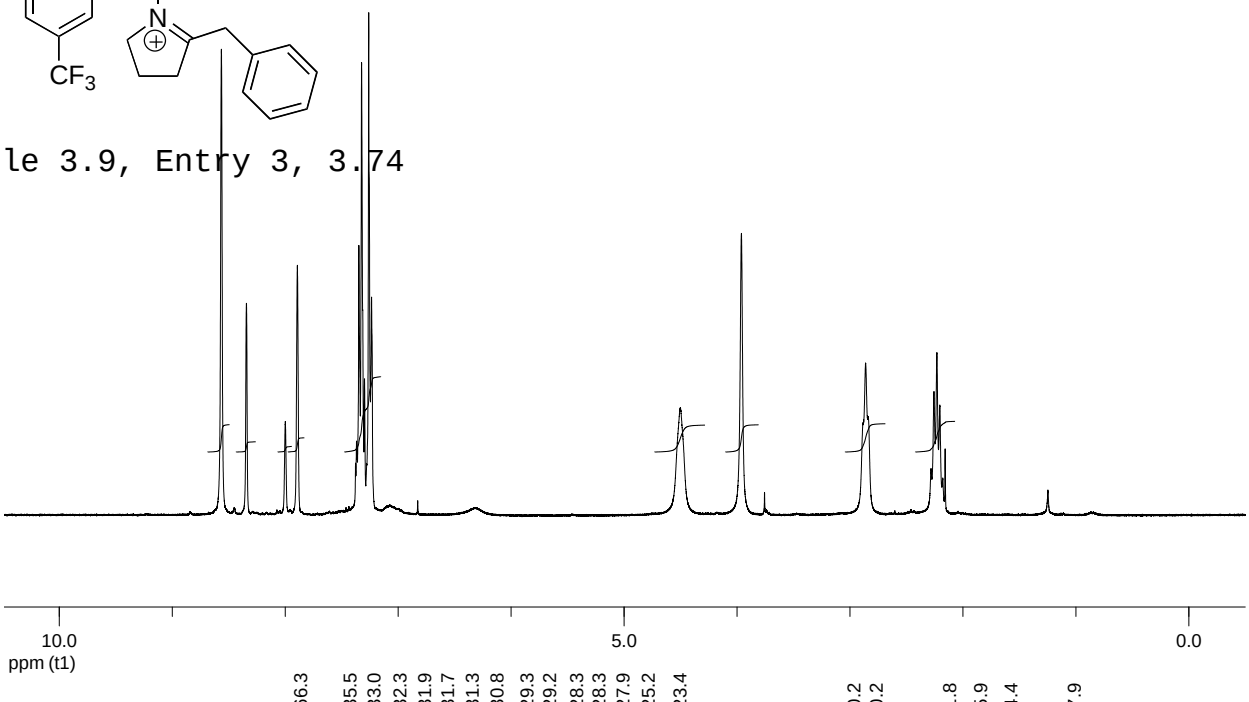
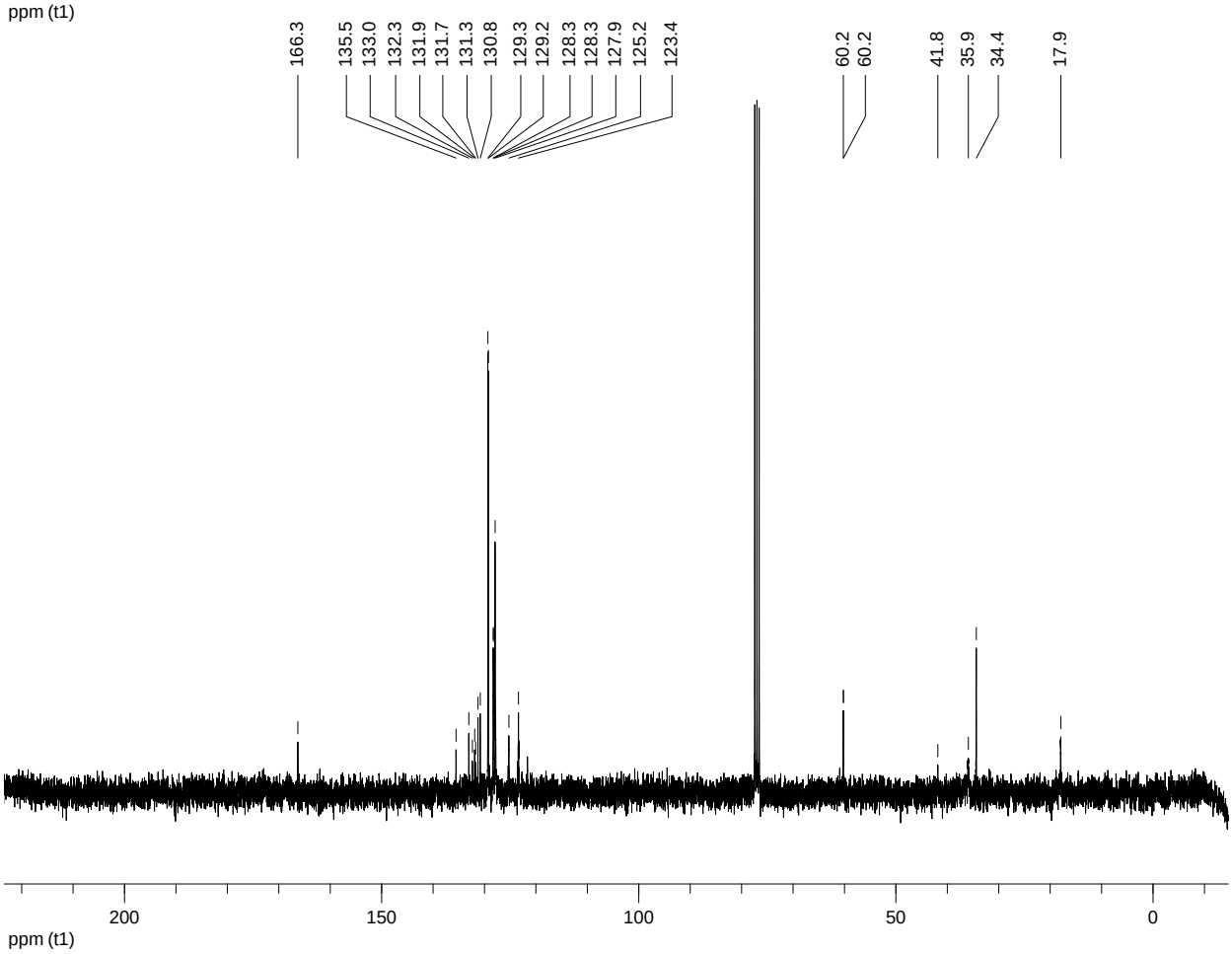


Table 3.9, Entry 3, 3.74





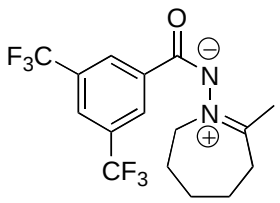


Table 3.10, Entry 3, 3.75