Intramolecular Cope-Type Hydroamination of Alkenes in the Synthesis of Alkaloids: Total Synthesis of (±)–Coniine and (±)–Desbromoarborescidine A and Studies on a Novel Amination Strategy Towards Manzamine A

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Abstract

Intramolecular hydroamination represents a potentially general, simple strategy to access various nitrogen heterocycles. While important progress has been accomplished in recent years, six-membered ring formation via alkene hydroamination is typically difficult and limited to terminal alkenes, suggesting that only 2-methylpiperidines can be accessed reliably with current methods. As part of the Beauchemin group efforts on metal-free concerted hydroamination methods, the first part of this thesis describes the development of a Cope-type hydroamination-Meisenheimer rearrangement (CHMR) sequence that is applicable in inter- and intramolecular reactions. Data acquired from optimization on a difficult substrate (coniine) and the successful application of the CHMR sequence to the syntheses of *N*-norreticuline and 10-desbromoarborescidine are reported.

The amination of alkenes is surprisingly scarcely used in the synthesis of complex alkaloids despite its potential for the construction of structurally challenging molecules while avoiding functional group interconversions. Hence, the second part of this thesis describes the studies on a novel amination sequence, consisting of an intermolecular Diels-Alder followed by an intramolecular hydroamination reaction, in the efforts towards the synthesis of biologically active and structurally complex Manzamine A. As such, the synthesis of the model substrates, including the development of a novel family of aminodienes, as well as the assessment of their reactivity towards [4+2] cycloadditions is reported.

Acknowledgments - Remerciements

First, I would like to thank André. Merci de m’avoir laissée trouver ma voie, tout en me ramenant dans le droit chemin lorsque je m’égarais. Les cinq ans passés sous ta supervision m'ont permis de redécouvrir la chimie sous un autre angle. Merci de m'avoir encouragée, conseillée et donné multiples opportunités de me dépasser. Je ne regretterai jamais de m'être jointe au groupe.

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`Would you tell me, please, which way I ought to go from here?'

`That depends a good deal on where you want to get to,' said the Cat.

`I don't much care where--' said Alice.

`Then it doesn't matter which way you go,' said the Cat.

`--so long as I get SOMEWHERE,' Alice added as an explanation.

`Oh, you're sure to do that,' said the Cat, `if you only walk long enough.'

Lewis Carroll

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List of Abbreviations

Å	angstrom (10^{-10} meters)
Ac	acetyl
AIBN	2,2-azo bisisobutyronitrile
Alloc	allyl formate
aq.	aqueous
Ar	aryl
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
°C	degree Celsius
CHMR	Cope-type hydroamination-Meisenheimer rearrangement
cis	on the same side
Cy	cyclohexyl
δ	chemical shift in parts per million
Δ	reflux
D, d	deuterium, deuterated (in solvents), doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyridine
DMF	dimethylformamide

DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E	*German,* entgegen
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
g	gram
G	Gibbs free energy
h	hour
H-bond(ing)	hydrogen bond(ing)
HRMS	high-resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
L	liter
LDA	lithium diisopropyl amide
m	meta
M	molar
Me	methyl
μW	microwave irradiation
mg	milligram
mL	milliliter
mmol	millimol
min	minute

Ms	methanesulfonyl
MS	molecular sieves
n	neo
N	Normal (concentration)
N-O bond	nitrogen-oxygen bond
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
[O]	oxidation
o	ortho
p	para
Pd/C	Palladium on carbon
Ph	phenyl
Pr	propyl
R	generic group
R	*latin*, right
Red-Al	sodium bis(2-methoxyethoxy) aluminium hydride
RT	room temperature
S	*latin*, left
sat.	saturated
SM	starting material
SN1 or SN2	nucleophilic substitution first order; or second order
t, tert	tertiary
TBAF	tetrabutyl ammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
trans	on opposite side
Ts	*para*-toluenesulfonyl
UV	ultra-violet
vs.	versus
X	heteroatom or pseudohalide
Z	*German*, zusammen

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1 Introduction

1.1 *The Hydroamination Reaction*

1.1.1 General Reactivity

The amine functionality is omnipresent in biologically active molecules, both in natural products and in compounds used in medicinal chemistry. Therefore, the development of effective C-N bond forming reactions that can be applied to a variety of molecules is of major importance. Many methods have been and are still applied to the incorporation of the nitrogen moiety within a molecule's backbone.[1] Among those, the hydroamination of π-systems stands out as an efficient method that has had a beneficial impact on synthetic strategies in recent years.[2]

As depicted in Scheme 1.1, a hydroamination reaction is the formal addition of a nitrogen-hydrogen bond across a π−system, such as an alkene or alkyne. The hydroamination of alkenes leads to amine-containing molecules, while the same reaction on alkynes will lead to the formation of enamine and imine moieties. Effecting the hydroamination reaction on substituted alkenes can generate chiral molecules containing up to two additional stereocenters. Furthermore, when done in an intramolecular fashion, the result of the hydroamination reaction is a saturated or unsaturated, nitrogen-containing heterocycle. Such products are of great interest for eventual application in the synthesis of natural products or analogs thereof where, up to recent years, the hydroamination method had only been scarcely used.[3]

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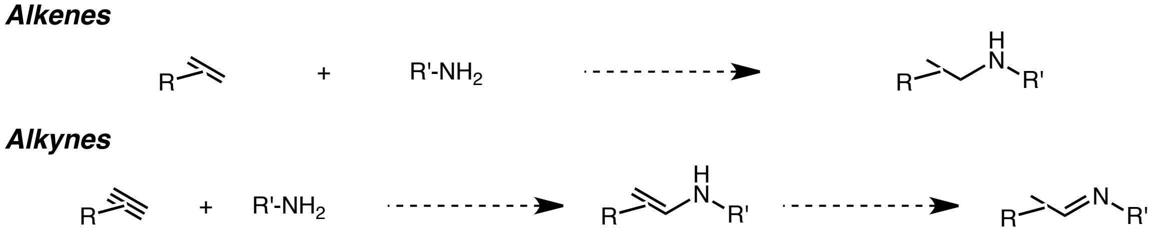
[1] a) Duggers, R. W.; Ragan, J. A.; Brown Rippin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253. b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

[2] Recent reviews: a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. b) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407.

[3] Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003***, 125*, 15878.



Scheme 1.1– The hydroamination reaction

1.1.2 Limitations

Despite many recent advances in the field, the hydroamination reaction still faces many challenges preventing its wider application in total synthesis: the reactivity of alkenes and alkynes has a high activation energy due to the repulsive forces forming between the nitrogen's lone pair and the π-bond electrons of the unsaturated substrate when coming into close proximity. Because of this elevated activation energy, high temperatures are needed to allow uncatalyzed reactions to proceed, sometimes leading to thermal decomposition of the starting material. Finally, the Hartwig group proved that the thermodynamics of the intermolecular hydroamination reaction were close to neutral, rendering the complete conversion of the starting materials into the products difficult (Eq. 1.1).[4] The reaction of styrene or substituted derivatives with *N*-methylaniline, *m*- or *p*-anisidine under palladium catalysis demonstrated that the hydroamination reaction was exothermic, but nearly thermoneutral due to the counter effect of the entropy term.

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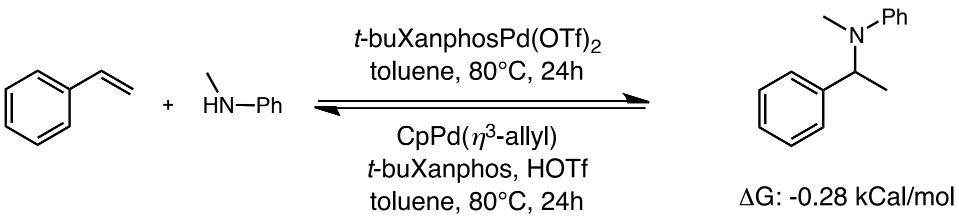
[4] Hartwig, J.F.; Ridder, A.; Sakai, N.; Johns, A.M. *J. Am. Chem. Soc.* **2006**, *128*, 9306.

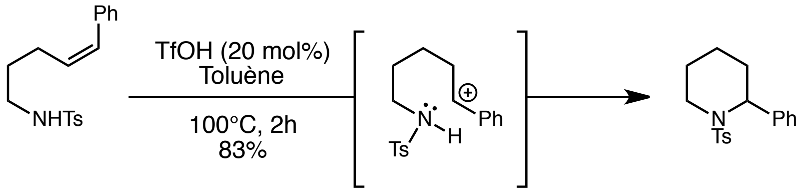


(1.1)

1.1.3 Catalysis of the Intramolecular Hydroamination Reaction

1.1.3.1 Acid Catalysis

The acid catalysis of the hydroamination reaction has been achieved with limited results because of the buffering nature of the nucleophilic amine. The first efficient example of six-membered rings cyclization via acid-catalyzed intramolecular hydroamination was accomplished by the Hartwig group. The reaction consisted of a tosyl-substituted nitrogen cyclizing onto a phenyl-substituted alkene. The electron-poor nature of the nitrogen efficiently minimized its protonation while the phenyl help to stabilize the carbocation formed upon protonation of the alkene under acidic conditions (Eq. 1.2).[5]



(1.2)

More recently, the Toste group catalyzed enantioselective hydroamination cyclizations with the help of chiral dithiophosphoric acids. Although the reaction is specific to the cyclization of five-membered rings, this new type of reactivity allowed for high yields and enantiomeric excesses. Their sequence involved the addition of the chiral catalyst onto the substrate's diene or allene moiety, allowing for a diastereoselective hydroamination reaction to take

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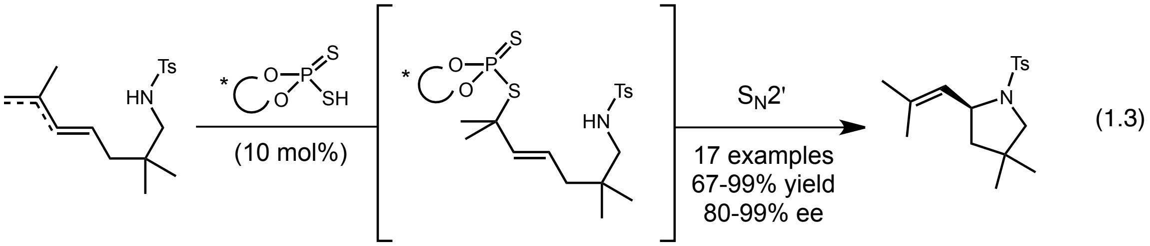
[5] Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

place. The nitrogen addition onto the alkene efficiently regenerated the chiral catalyst by S_N2' type displacement (Eq. 1.3).[6]



(1.3)

1.1.3.2 Metal Catalysis

The metal catalyzed intramolecular hydroamination of alkene derivatives has mostly been investigated for the formation of five-membered rings. Operating with different mechanisms, both early- and late-transition metals proved efficient to catalyze this transformation.[7,8,9,10,11] A rare example of metal-catalyzed six-membered ring cyclization was effected by a hydrated iron (III) catalyst. As with acid catalyzed cyclizations, a phenyl-stabilized alkene was used, affording the desired product in 94% yield (Eq. 1.4).[12] Zirconium and rhodium have also

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[6] a) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245. b) For a highlight, see Dion, I.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8233.

[7] Ti: a) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959. b) Muller, C.; Loos, C.; Schulenberg, N.; Doye, S. *Eur. J. Org. Chem.* **2006**, 2499. c) Muller, C.; Saak, W.; Doye, S. *Eur. J. Org. Chem.* **2008**, 2731. d) Bergman, R.G.; Johnson, J. S. *J. Am. Chem. Soc*. **2001**, *123*, 2923.

[8] Pt: Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127,* 1070.

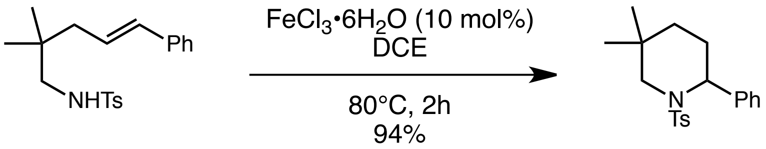
[9] Pd: Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39,* 5421.

[10] Au: a) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006***, 128,* 9066. b) Patil, N. T.; Lutete, L. M.; Nishina, N.; Yamamoto, Y. *Tet. Lett.* **2006***, 47*, 4749. c) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007***, 129,* 2452.

[11] Other metals: a) Lauterwasser, F.; Hayes, P. G.; Brase, S.; Piers, W. E.; Schafer, L. L. *Organometallics* **2004**, *23*, 2234. b) Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344.

[12] Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem. Int. Ed.* **2006**, *45,* 2938.

been investigated by the Livinghouse and Schaffer groups leading to the formation of piperidines in up to 92% yield (Eq. 1.5).[13]



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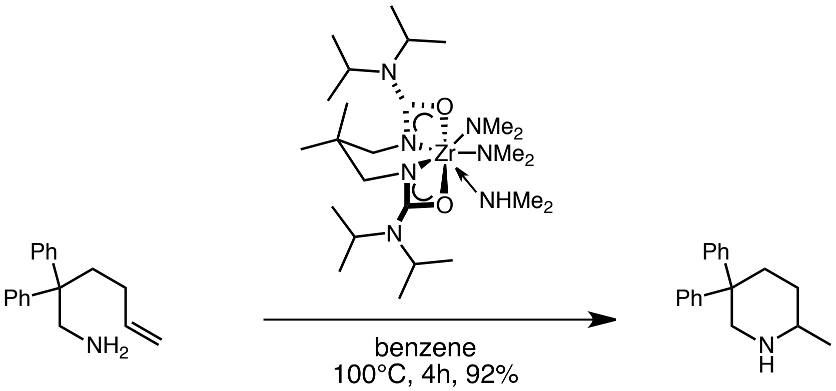

(1.5)

Marks and coworkers have done extensive research on the hydroamination of both allenes and alkenes using lanthanide catalysts, the later with the help of the Thorpe-Ingold effect (Eq. 1.6).[14] Schulz has also investigated similar reactions with chiral ligands.[15]

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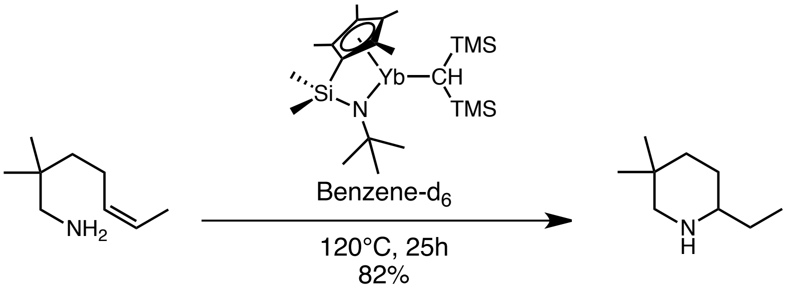
[13] a) Kim, H.; Lee, P. H.; Livinghouse, T. *Chem. Commun.* **2005**, 5205. b) Leitch, D. C.; Platel, R. H.; Schafer, L. L. *J. Am. Chem. Soc.* **2011**, *133*, 15453. c) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246. d) Liu, Z.; Yamamichi, H.; Madrahimov, S. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133,* 2772.

[14] a) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998***, 120,* 4871. b) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *Organometallics* **1999***, 18*, 1949. c) Ryu, J-S.; Marks, T. J.; McDonald, F. E. *J. Org. Chem.* **2004***, 69,* 1038. d) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007***, 129*, 4253. e) Ryu, J.-S.; Marks, T. J. MacDonald, F. E. *Org. Lett.* **2001***, 3,* 3091.

[15] Riegert, D.; Collin, J.; Meddour, A.; Schulz, E.; Trifonov, A. *J. Am. Chem. Soc.* **2006***, 71*, 2514.



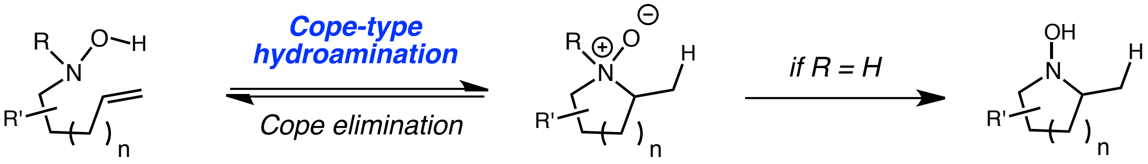
(1.6)

The scope of the hydroamination reaction, even when catalyzed, is still limited, and most methods are based on complex metal catalysts, which are often air and water sensitive or substrate specific.

1.2 *Intramolecular Cope-Type Hydroamination*

1.2.1 Overview

A different approach to address the challenges posed by the hydroamination reaction is the Cope-type hydroamination (Scheme 1.2). Known for over thirty-five years,[16,17] this reverse reaction of the Cope elimination shows similar reactivity to the transition metal catalyzed reactions and displays good yields with both alkenes and alkynes.



Scheme 1.2 – Cope-type hydroamination mechanism

Application of the Cope-type hydroamination to alkenes and alkynes involves the use of a bifunctional reagent, such as a hydroxylamine (X=O) or a hydrazide (X=N), which reacts in

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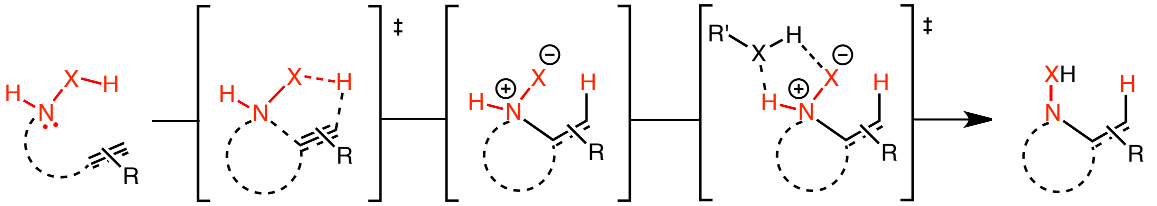
[16] Laughlin, R. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

[17] For a review on Cope-type hydroamination, see Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

a concerted way (Scheme 1.3).[18] As the nucleophile attacks the π-system, the alkene deprotonates the XH group resulting in the charged *N*-oxide intermediate. Unless proton transfer is possible, the intermediate will reverse to the starting material via Cope elimination. Otherwise, an intermolecular proton transfer will provide the desired product.[19] Such a concerted transition state efficiently prevents the formation of a carbocation intermediate, normally observed with acid catalysis of the hydroamination reaction, hence allowing high predictability of the reaction outcome. The bifunctional reagents can be used for the hydroamination of various π-systems, providing synthetically useful yields of the desired product.



Scheme 1.3 – Cope-type hydroamination transition state

1.2.2 Early Reports of Reactivity

Using thermal activation, the Oppolzer group was among the first to observe the reverse Cope elimination as a side reaction (Eq. 1.7).[20] They isolated the five-membered ring cyclized hydroamination product while investigating nitrone cycloadditions.

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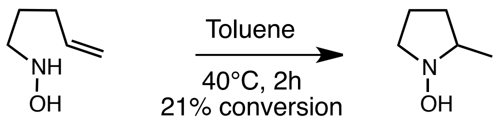
[18] Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

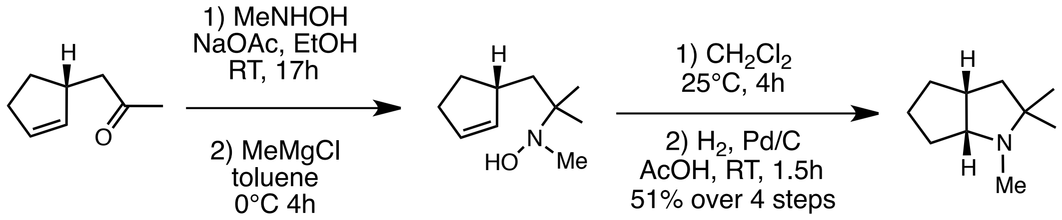
[19] Recent results in the Beauchemin group suggest that the proton transfer might have a lower activation energy than previously calculated. Stabilization of the charged intermediate would be the limiting factor. see: Loiseau, F. Ph.D. Thesis, University of Ottawa, ON, 2012.

[20] 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. c) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, 4391.

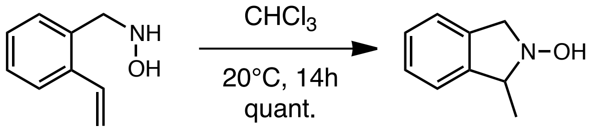


(1.7)

The scope of the Cope-type hydroamination reaction was later broadened by Ciganek with the synthesis of [5,5]-bicyclic alkaloids (Scheme 1.4)[21] and by Knight and coworkers with the synthesis of *N*-hydroxyisoindolines (Eq. 1.8).[22]

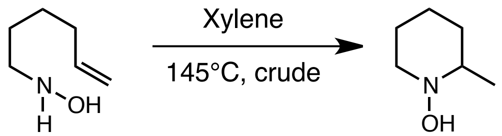


Scheme 1.4 – Ciganek's synthesis of bicyclic alkaloids via Cope-type hydroamination



(1.8)

Ciganek further contributed to the field knowledge by demonstrating the effect of nitrogen substitution on the cyclization process.[20a,23] His results showed that a monosubstituted hydroxylamine requires more elevated temperatures than its methylated analogue in order to cyclize (Eq. 1.9 and Eq. 1.10).



(1.9)

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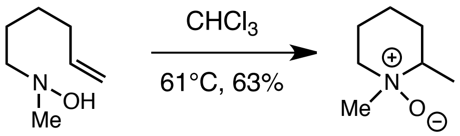
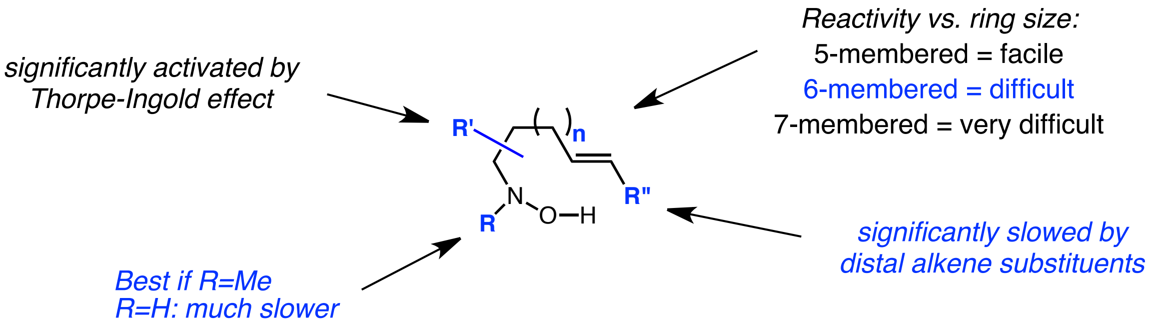
[21] Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803.
[22] Knight, D.W.; Leese, M.P. De Kimpe, N. *Tetrahedron Lett.* **2001**, *42*, 2597.
[23] Ciganek, E.; Read, Jr., J. M. *J. Org. Chem.* **1995**, *60*, 5795.



(1.10)

1.2.3 Reactivity Trends

It was found that the intramolecular Cope-type hydroamination of alkenes shows specific reactivity trends. While the cyclization of five-membered rings is the easiest to achieve, the formation of six-membered rings necessitates higher temperatures and might not proceed at all on certain substrates (Scheme 1.5).[17] Furthermore, examples of seven-membered rings are scarce. Other features of the intramolecular Cope-type hydroamination are the effects of substitution on the scaffold. One must note that substitutions on the carbon backbone leading to the Thorpe-Ingold effect significantly increase the reaction rate, while distal substitution of the alkene slows it down.[21] Finally, substitution of the nitrogen atom is of great importance: a di-substituted hydroxylamine nitrogen will undergo cyclization faster and at a lower temperature than its mono-substituted analogue. However, it will lead to a charged, high-energy *N*-oxide product that tends to revert to the starting material or to degrade.

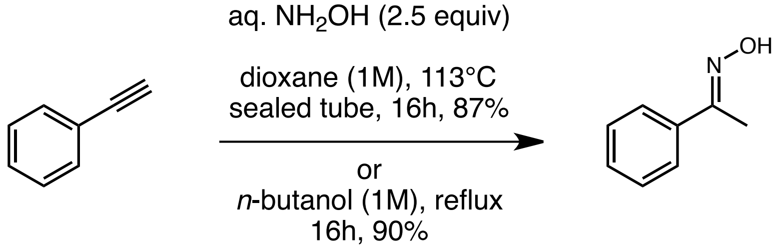


Scheme 1.5 – General features of intramolecular Cope-type hydroamination of alkenes[17]

1.2.4 Previous Results in the Beauchemin Group

Over the past few years, the Beauchemin group has been working on developing intermolecular and optimizing intramolecular Cope-type hydroamination reactions as a mean of facilitating the metal-free integration of nitrogen atoms onto molecules' backbones. The group focuses on both hydroxylamines and hydrazides as bifunctional moieties for Cope-type hydroamination.

The group's first Cope-type hydroamination hit was an intermolecular reaction of phenylacetylene using aqueous hydroxylamine in dioxane. Heating the reaction mixture in a sealed tube, under optimized conditions, provided acetophenone oxime in 87% isolated yield. Similar results were obtained under traditional reflux conditions (Eq. 1.11).[24]



(1.11)

Optimization of the intermolecular alkynes hydroamination showed that the reaction was most efficient in alcoholic solvents such as *i*-propanol. At the time, it was suggested that it was facilitating the high-energy proton transfer step of the reaction (Scheme 1.6). Various substitutions, electronic environments and protecting groups on both the alkyne and the hydroxylamine were well tolerated, as were unprotected hydroxy groups. The best reaction conditions for alkyne Cope-type hydroamination were then applied to less reactive alkene

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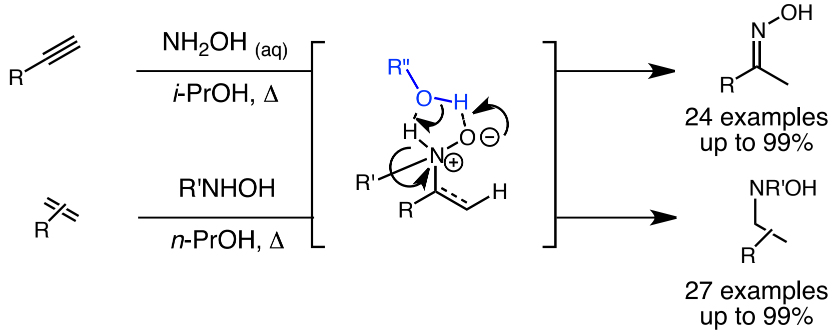
[24] a) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M-E.; Bédard, A-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893. b) Beauchemin, A. M.; Moran, J.; Lebrun, M-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.

substrates. With further optimization, these more challenging substrates could also be hydroaminated and produce excellent yields. First, the reaction of unsubstituted hydroxylamine (NH_2OH) was optimized in *i*-propanol. *n*-Propanol proved better for reactions with *N*-alkyl-hydroxylamines but required the use of sodium cyanoborohydride as a stabilizing additive to minimize the degradation of both the starting material and the final product. Finally, recent efforts have shown that *t*-BuOH is also an excellent solvent.[25]



Scheme 1.6 –Optimized intermolecular Cope-type hydroamination by the Beauchemin group

The insight obtained by the Beauchemin group from optimizing the Cope-type hydroamination reaction helped explain the field's previous limitations. It also allowed the development of conditions for a synthetically useful metal-free intermolecular Cope-type hydroamination reaction. From these results came the desire for optimization of the intramolecular Cope-type hydroamination and its application in the synthesis of biologically active molecules containing difficult to cyclize six-membered rings.

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[25] Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895.

2 Intramolecular Cope-Type Hydroamination Applied to the Synthesis of Alkaloids

2.1 Historic Background: Discovery and Isolation of Coniine

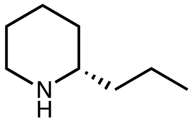
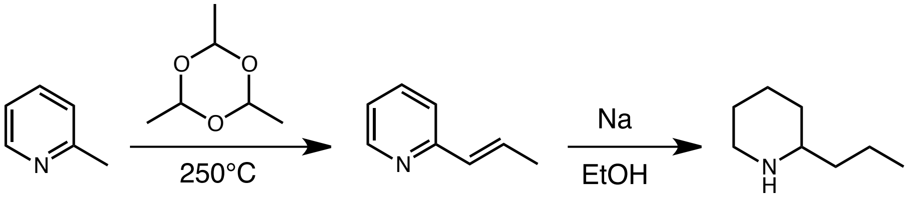


Figure 2.1 – (*S*)-Coniine

(*S*)-Coniine's first reported isolation was in 1827 by a scientist named Giesecke.[26] It was isolated from the poison hemlock called *Conium maculatum,* which had been known since antiquity. History reports that Greeks used a concoction of poison hemlock as a mean of executing criminals and it is hypothesized that its ingestion caused famous philosopher Socrates' death.[27] Coniine's empirical formula has been determined in 1881 by Hofmann[28] and the first reported synthesis by Ladenburg dates back to 1886. Racemic coniine was obtained by condensation at high temperature of 2-methylpyridine with paraldehyde, followed by reduction with sodium metal (Scheme 2.1).[29]



Scheme 2.1 – First reported synthesis of (±)-coniine

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[26] Giesecke *Arch. Pharm.* **1827**, *20*, 97.
[27] Vetter, J. *Food Chem. Tox.* **2004***, 42,* 1373.
[28] Hofmann, A. W. *Ber.* **1881**, *14*, 705.
[29] Ladenburg, A. *Ber.* **1886**, *19*, 439.

Over the years, it has been used for both toxic and therapeutic purposes, but its small therapeutic window prevented greater medicinal applications. Nowadays, poison hemlock can be found mainly in South Africa and the Mediterranean region and is known to be dangerous to both humans and animals. Its coniine content is the main cause of poisoned livestock from lethal hemlock ingestion.[30]

2.2 Previous Syntheses of Coniine

Coniine has been previously synthesized using many different strategies both original and effective. The principal difficulty in the synthesis of this molecule comes from its simple skeleton, which hinders the use of functional groups or forces their cleavage afterwards. In addition to the bare structure, the presence of a chiral center alpha to the nitrogen calls for means of stereocontrol during the synthesis. Finally, being volatile and highly toxic, coniine is usually isolated as a salt or with *N*-protecting groups.

2.2.1 Coniine via Reductive Amination

One method often used for the synthesis of coniine is the reductive amination. Oda and coworkers used this method in 1986 with the help of a chiral benzyl protective group to obtain the pure, naturally occuring (*S*)-coniine (Scheme 2.2).[31] This type of auxiliary was also used by the Hartley ($NaBH(OAc)_3$),[32] Shipmann ($NaBH(OAc)_3$),[33] Moody (H_2, Pd/C)[34] and Szymoniak ($NaBH(OAc)_3$)[35] groups with similar reductive amination methods. The

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[30] a) Reynolds, T. *Phytochemistry* **2005**, *66*, 1399. b) Lopez, T. A.; Cid, M. S.; Bianchini, M. L. *Toxicon* **1999**, *37*, 841.

[31] Kawaguchi, M.; Hayashi, O.; Sakai, N.; Hamada, M.; Yamamoto, Y.; Oda, J. *Agric. Biol. Chem*. **1986,** *50*, 3107.

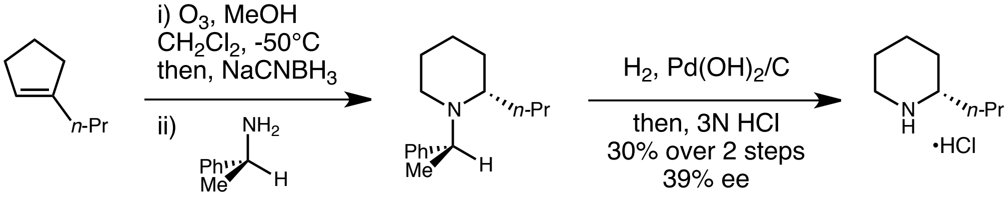
[32] Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley R. C. *Eur. J. Org. Chem.* **2006**, 4998.

[33] Hayes, J. F.; Shipmann, M.; Twin, H. *Chem. Commun.* **2001**, 1784.

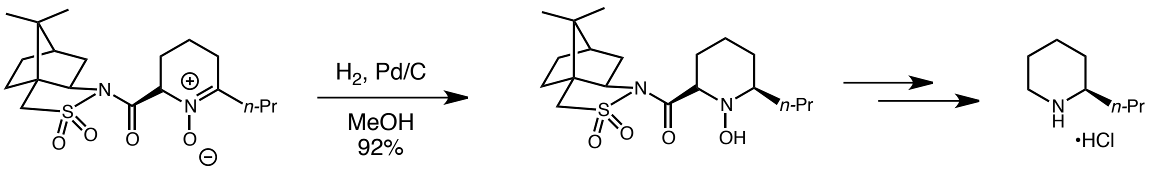
[34] Moody, C. J.; Lightfoot, A. P.; Gallagher, P.T. *J. Org. Chem.* **1997**, *62*, 746.

[35] Coia, N.; Mokhtari, N.; Vasse, J-L.; Szymoniak, J. *Org. Lett.* **2011***, 13*, 6292.

Oppolzer group also used a related approach by reducing a nitrone with hydrogenation on palladium, while employing a sultam acetal chiral auxiliary to obtain (*R*)-coniine (Scheme 2.3).[36]



Scheme 2.2 – Synthesis of (*S*)-coniine by reductive amination



Scheme 2.3 – Synthesis of (*R*)-coniine by reductive amination

Similar methods have been used with allylboron, allylsilicate reagents or hydrides combined with chiral ligands in order to add the propyl chain[37] or reduce the iminium enantioselectively.[38] More recently, some groups have been forming the iminium *in-situ* by reacting a δ−lactam with strong electrophiles.[39] The Huang group used triflic anhydride to afford the triflyl imidate, which was then trapped at -78°C with *n*-propyl magnesium bromide. An iminium was generated by expulsion of the triflate leaving group and final

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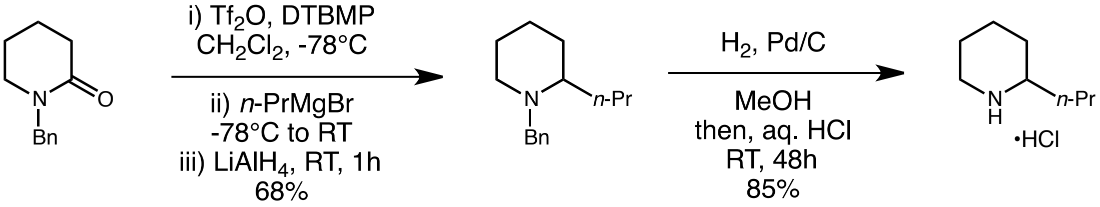
[36] Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015.

[37] a) Wu, R. T.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646. b) Airiau, E.; Girard, N.; Pizzeti, M.; Salvadori, J.; Taddei, M.; Mann, A. *J. Org. Chem.* **2010**, *75*, 8670.

[38] Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998***,* *63*, 6344.

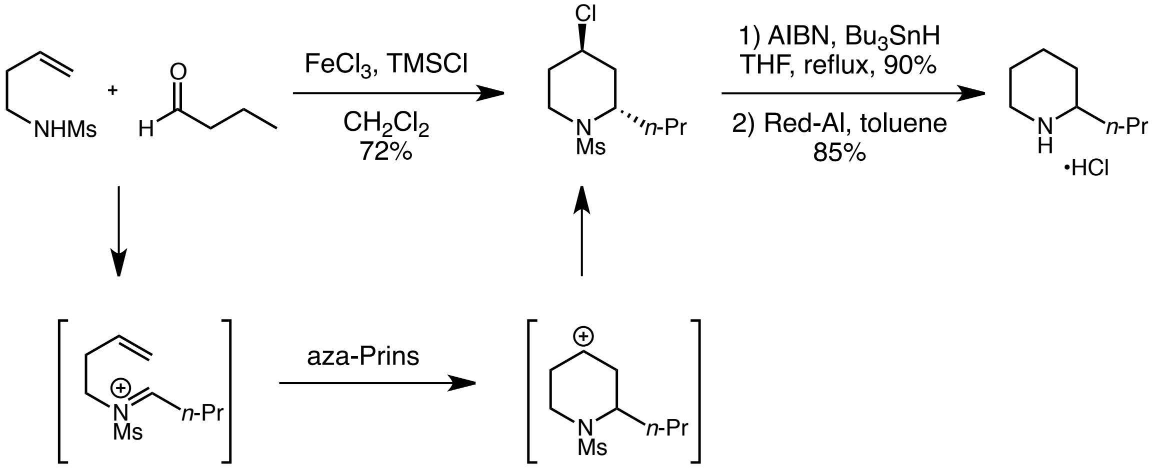
[39] a) Garnier, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008***,* *130*, 7449. b) Xiao, K-J.; Wang, Y.; Ye, K-Y.; Huang, P-Q. *Chem. Eur. J.* **2010**, *16*, 12792.

reduction was effected with lithium aluminum hydride (Scheme 2.4). Racemic coniine was obtained after cleavage of the benzyl protecting group.



Scheme 2.4– Synthesis of (±)-coniine by *in-situ* iminium formation and reduction

Intramolecular iminium-reducing reactions, such as aza-Prins,[40] have also been used for the synthesis of coniine (Scheme 2.5). The iminium, formed by condensation, was reduced by alkene addition. Trapping of the newly formed carbocation by the chloride counterion then quickly afforded the neutral product. Final reduction and deprotection provided coniine in 55% overall yield.



Scheme 2.5 – Synthesis of (±)-coniine by aza-Prins cyclization

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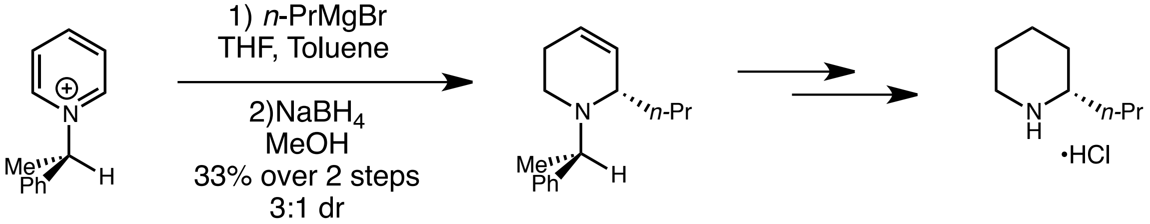
[40] Carballo, R. M.; Valdomir, G.; Purino, M.; Martin, V. S.; Padron, J. I. *Eur. J. Org. Chem.* **2010**, 2304.

The incorporation of the propyl chain of coniine can also be done by reduction or nucleophile addition at the alpha position of a pyridinium (Scheme 2.6). This method has been employed in the synthesis of coniine by the Marazano,[41] Comins,[42] Charette,[43] Kunz,[44] Das[45] and Feringa[46] groups.



Scheme 2.6 – Marazano's group synthesis of (*S*)-coniine by reduction of iminium

(*R*)-Coniine has also been shown to be efficiently obtained by formal displacement of a chiral oxygen with an allyl or alkyl moiety (Scheme 2.7).[47]

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[41] Guilloteau-Bertin, B.; Compere, D.; Gill, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, 1391.

[42] Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732.

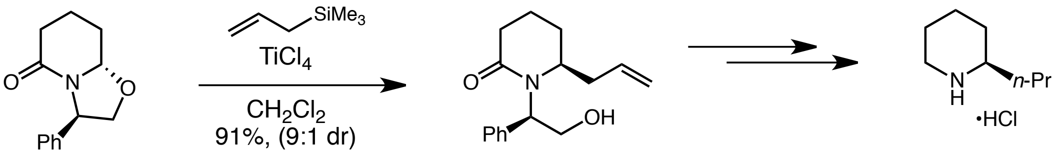
[43] Charette, A. B.; Grenon, M.; Lemire, A. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

[44] Klegraf, E.; Follmann, M.; Schollmeyer, D.; Kunz, H. *Eur. J. Org. Chem.* **2004**, 3346.

[45] a) Damodar, K.; Lingaiah, M.; Bhunia, N.; Das, B. *Synthesis* **2011**, 2478. b) Satyalakshmi, G.; Suneel, K.; Balaji, D.; Das, B. *Tetrahedron: Asymmetry* **2011**, *22*, 1000.

[46] Fernandez-Ibanez, M. A.; Macia, B.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 9339.

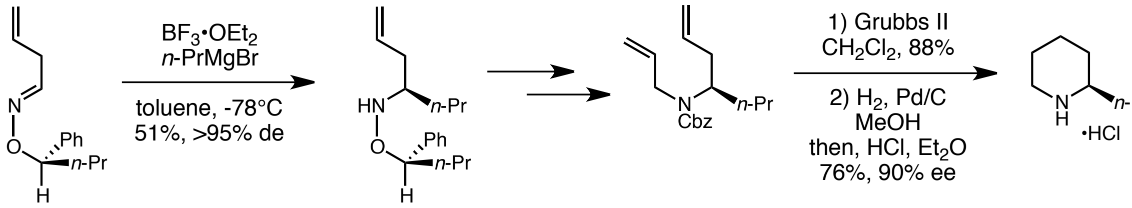
[47] a) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. b) Teran, J. L.; Gnecco, D.; Galindo, A.; Juarez, J.; Bernes, S.; Enriquez, R. G. *Tetrahedron: Asymmetry* **2001**, *12*, 357. c) Pandey, G.; Das, P. *Tetrahedron Lett*. **1997**, *38*, 9073. d) Xu, X.; Lu, J.; Li, R.; Ge, Z.; Dong, Y.; Hu, Y. *Synlett* **2004**, 122. e) Roa, L. F.; Gnecco, D.; Galindo, A.; Teran, J. L. Bernes, S. *Tetrahedron: Asymmetry* **2004**, *15,* 847. f) Arena, G.; Zill, N.; Salvadori, J.; Girard, N.; Mann, A.; Taddei, M. *Org. Lett.* **2011**, *13*, 2294.



Scheme 2.7 – Synthesis of (*R*)-coniine by formal α-hydroxy displacement

2.2.2 Coniine via Ring Closing Metathesis

Another common coniine synthesis strategy is the ring closing metathesis (RCM). The first examples were reported by the Chang[48] and Moody[49] groups. The approach of the Moody group involved the use of a chiral benzylamine auxiliary, which allowed for the enantioselective introduction of the propyl chain. After functional groups interconversion, allylation of the amine afforded the metathesis precursor. The RCM was performed with good efficiency and provided, after nitrogen deprotection, (*R*)-coniine in 90% ee (Scheme 2.8).



Scheme 2.8 – Synthesis of (*R*)-coniine by RCM

The use of chiral auxiliaries combined with RCM was then further developed by many groups.[50] Wulff and coworkers reported the unique formation of a RCM precursor *en route*

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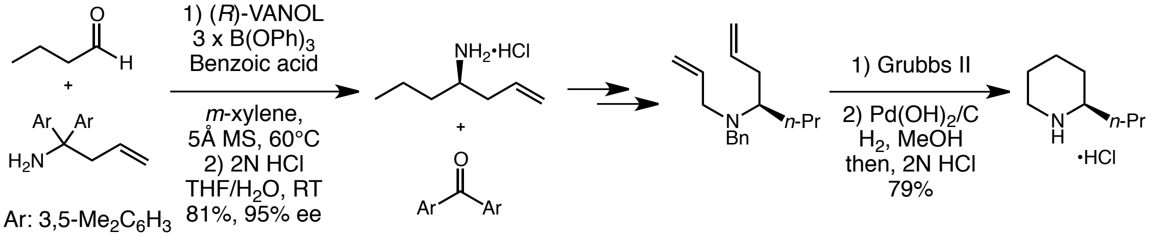
[48] Jo, E.; Na, Y.; Chang, S. *Tetrahedron Lett.* **1999**, *40*, 5581.

[49] a) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771. b) Hunt, J. C. A.; Laurent, P.; Moody, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2378.

[50] a) Pachamuthu, K.; Vankar, Y. D. *J. Organomet. Chem.* **2001**, *624*, 359. b) Kamareswaran, R.; Hassner, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2269. c) Davies, s. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, *1146.* d)

to coniine via an enantioselective [3,3]-rearrangement catalyzed by the chiral Brønsted acid (*R*)-VANOL (Scheme 2.9). Condensation of 1-butanal with a hindered homo-allylic amine, followed by rearrangement, provides a chiral amine, which after nitrogen allylation and protection yields the RCM precursor.[51]



Scheme 2.9 – Synthesis of (*R*)-coniine by enantioselective [3,3]-rearrangement and RCM

Both the Coldham[52] and Couture[53] groups have worked on the development of a methatesis strategy involving α,β-unsturated amides, while the Hoveyda[54] group specialized in RCM with chiral metathesis catalysts. In all those methods, the closing C=C bond is created β to the amine.

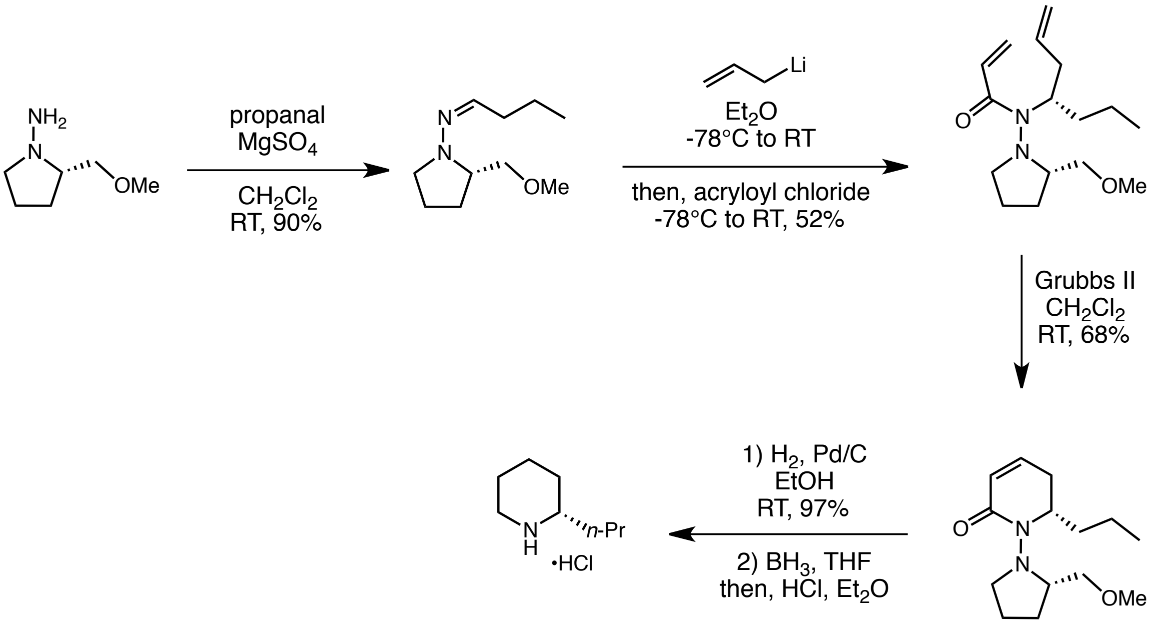
Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSeve, H.; Spino, C. *J. Org. Chem.* **2008**, *73*, 6239. e) Nomura, H.; Richards, C. J. *Org. Lett.* **2009***, 11,* 2892. f) Daly, M.; Gill, K.; Sime, M.; Simpson, G. L.; Sutherland, A. *Org. Biomol. Chem.* **2011***, 9*, 6761.

[51] Ren, H.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 5656.

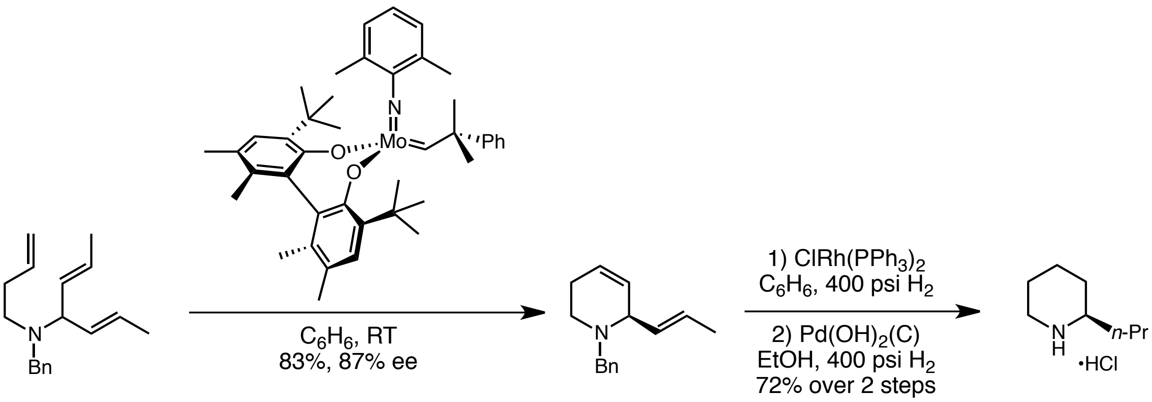
[52] Bensa, D.; Coldham, I.; Feinaugle, P.; Pathak, R. B.; Butlin, R. J. *Org. Biomol. Chem.* **2008**, *6*, 1410.

[53] Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007***, 9,* 2473.

[54] Sattely, E. S.; Cortez, A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526.



Scheme 2.10 – Synthesis of (*S*)-coniine by the Couture group



Scheme 2.11 – Synthesis of (*R*)-coniine by the Hoveyda group

2.2.3 Coniine via Diels-Alder Reactions

The Diels-Alder reaction has been employed by different groups in the synthesis of coniine. The use of an aza-Diels-Alder reaction in the synthesis of coniine was first developed by the Yamamoto group in 1993.[55] This approach was also used by the Kobayashi group in 2005

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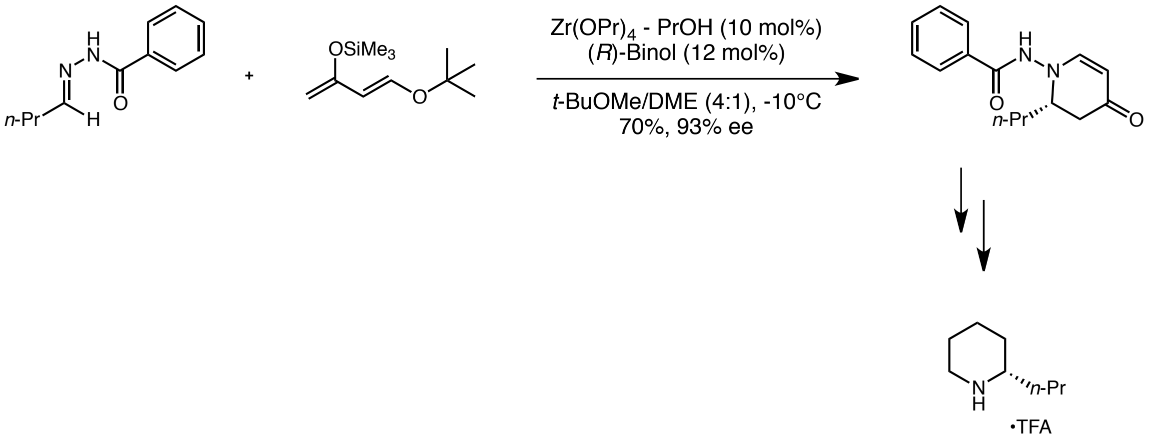
[55] Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.

(Scheme 2.12).[56] The later employed (*R*)-Binol as the chiral ligand for a zirconium-catalyzed enantioselective aza-Diels-Alder reaction.



Scheme 2.12 – Synthesis of (*S*)-coniine by aza-Diels-Alder

Several chiral auxiliaries were used in order to obtain only one of coniine's enantiomers from the Diels-Alder reactions. A good example is the Kranke group's enantioselective synthesis of coniine employing carbohydrates as chiral auxiliaries (Scheme 2.13). This method afforded enantiomerically pure (*S*)-coniine in a 44% overall yield.[57]

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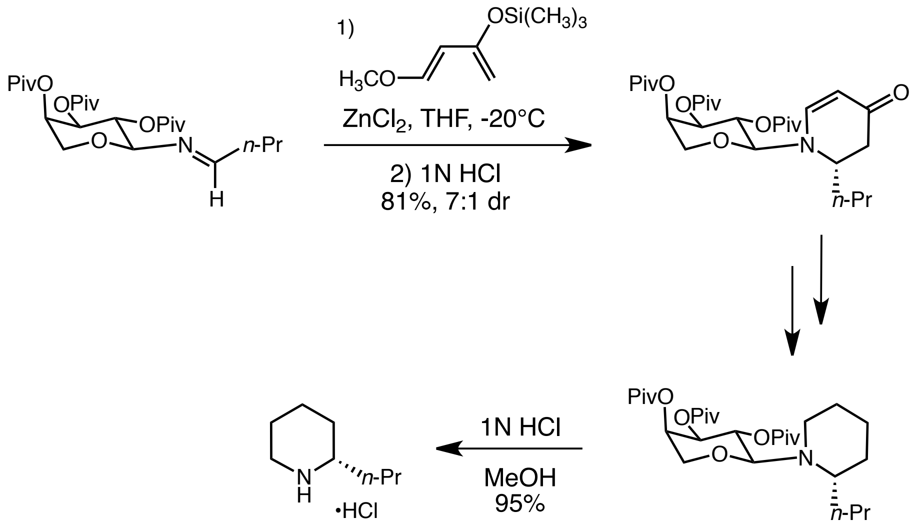
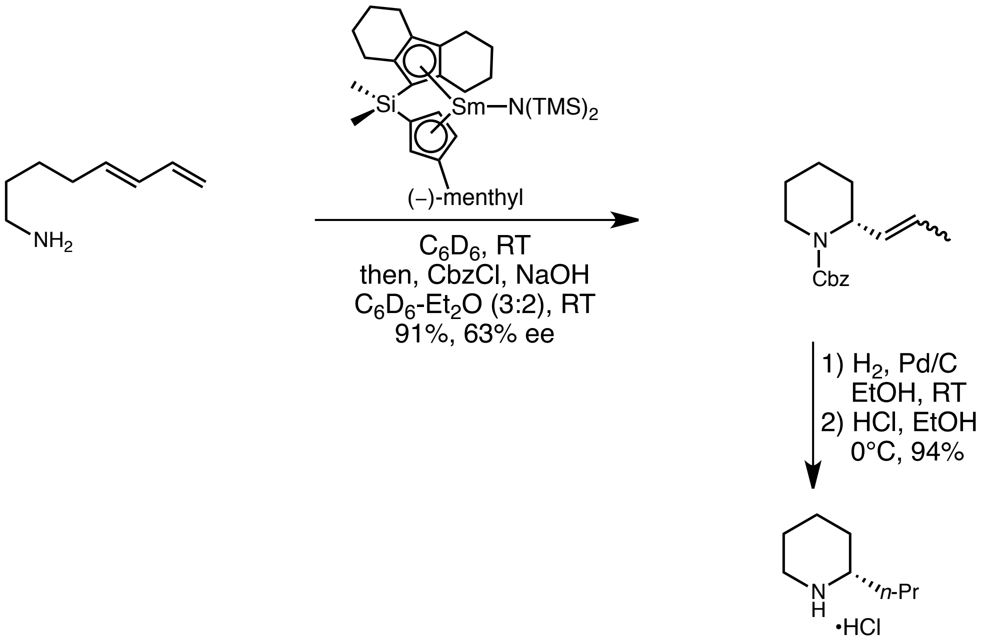
[56] Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005***, 46*, 1803.
[57] Kranke, B.; Kunz, H. *Can. J. Chem.* **2006***, 84*, 625.



Scheme 2.13 – The Kranke group approach to (*S*)-coniine by aza-Diels-Alder

2.2.4 Coniine via Hydroamination

Coniine has only been synthesized once through intramolecular hydroamination (Scheme 2.14). The synthesis was executed by the Marks group, which, with the help of a chiral samarium catalyst, afforded (*S*)-coniine in 63% ee and 86% yield from the diene precursor. Working with an activated alkene such as a diene or an allene, was necessary for Marks and coworkers as the nucleophile could not react efficiently on a simpler alkene under the reaction conditions.[3]



Scheme 2.14 – Synthesis of (*S*)-coniine by Samarium-catalyzed hydroamination

2.2.5 Coniine via Other Methods

Other methods have been used in order to close the six-membered ring of coniine. For example, the Mitsunobu reaction was employed by both the Knochel[58] and Singh[59] groups. In addition, the Wilkinson group developed an asymmetric hydrogenation using a (*R*)-Binap-$RuCl_2$ catalyst, affording (*R)*-coniine in good yield and high enantioselectivity (Scheme 2.15).[60]

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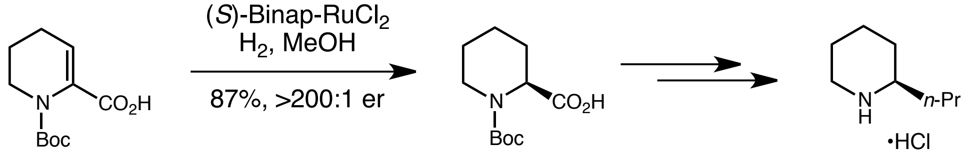
[58] a) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004***, 20*, 2324. b) Gommermann, N.; Knochel, P. *Chem. Eur. J.* **2006**, *12*, 4380.

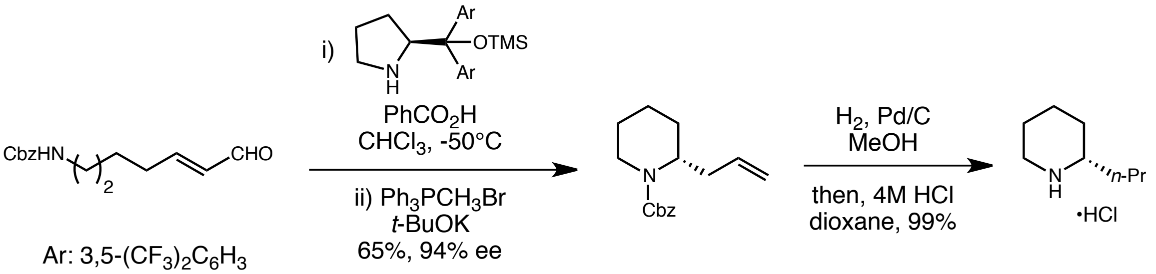
[59] Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2007**, *48,* 1907.

[60] Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155.



Scheme 2.15 – Synthesis of (*R*)-coniine by asymmetric hydrogenation

Other metals such as Pd[61] and Au[62] were used in order to activate nucleophilic allyl groups as a mean to install the *n*-propyl substituent. Using organocatalysis, the Fustero group published a synthesis of (*R*)-coniine from an enantioselective aza-Michael reaction using a Jorgensen-type catalyst (Scheme 2.16).[63]



Scheme 2.16 – Synthesis of (*S*)-coniine by aza-Michael addition

In addition, coniine has been synthesized by various other methodologies such as enzymatic kinetic resolution,[64] radical reactions and photocyclizations,[65] lithium amides cyclizations[66] and substitution[67] and finally with the use of Wenreib amides[68] or cyclic sulfates.[69]

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[61] Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2009***, 74*, 244.

[62] Mukherjee, P.; Widenhoefer, R. A. *Org. Lett.* **2011**, *13*, 1334.

[63] Fustero, S.; Jimenez, D.; Moscardo, J.; Catalan, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283.

[64] a) Nazabadioko, S.; Perez, R. J.; Brieva, R.; Gotor, V. *Tetrahedron: Asymmetry* **1998***, 9,* 1597. b) Angoli, M.; Barilli, A.; Lesma, G.; Passarella, D.; Riva, S.; Silvani, A.; Danieli, B. *J. Org. Chem.* **2003**, *68*, 9525. c) Passarella, D.; Barilli, A.; Belinghieri, F.; Fassi, P.; Riva, S.; Sacchetti, A.; Silvani, A.; Danieli, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2225.

2.3 Project Objectives

The focus of this project has been set on optimizing the difficult cyclization of saturated six-membered heterocycles using intramolecular Cope-type hydroamination. Based on the general features of the reactivity of alkenes (see section 1.2.3), coniine was selected as a substrate of choice for primary optimization. It was thought that this simple six-membered ring-containing molecule could come from an alkene substrate with distal substitution (Scheme 2.17). Considering the fact that the requisite substrate would lack of any beneficial Thorpe-Ingold effect, the proposed synthesis of coniine combined all the challenges known to the intramolecular Cope-type hydroamination of alkenes. Therefore it presented itself as the ideal target for the optimization of six-membered ring cyclization (see section 1.2.3).

2.4 Synthesis of Coniine via Cope-Type Hydroamination

2.4.1 Retrosynthetic Approach

The proposed retrosynthesis for the formation of coniine featured a Cope-type hydroamination reaction as the ring-closing step. The cyclization precursor hydroxylamine **2.1** could be obtained by means of a Mitsunobu reaction from alcohol **2.3**, which was provided from δ-valerolactone via a one-pot reduction/Wittig olefination. Another way of

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[65] a) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* **2006***, 128,* 7712. b) Friestad, G. K.; Marie, J. C.; Suh, Y.; Qin, J. *J. Org. Chem.* **2006**, *71*, 7016. c) Bois, F.; Gardette, D.; Gramain, J. C. *Tetrahedron Lett.* **2000**, *41*, 8769.

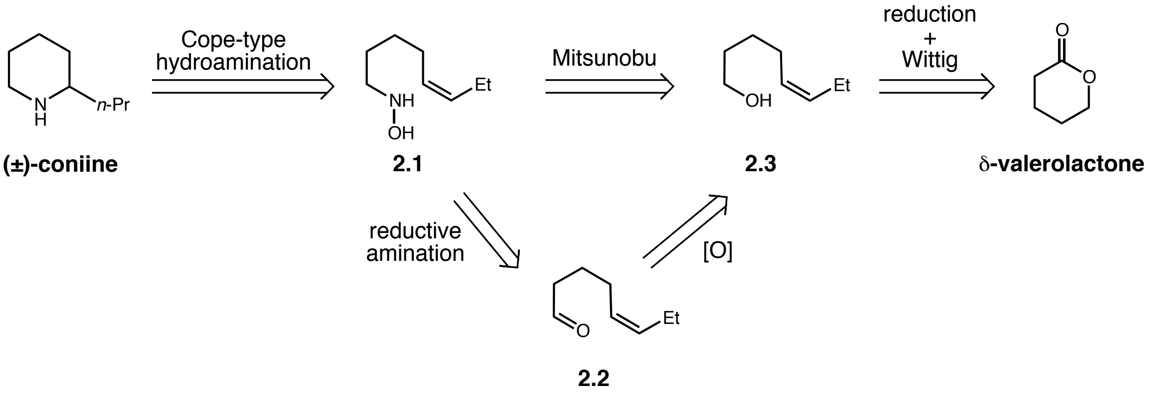
[66] a) Davies, S. G.; Hughes, D. G.; Price, P.D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567. b) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975.

[67] a) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216. b) Coldham, I.; Leonori, D. *J. Org. Chem.* **2010**, *75,* 4069.

[68] Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004***, 2,* 1387.

[69] Eskici, M.; Gallagher, T. *Synlett* **2000**, 1360.

obtaining cyclization precursor **2.1** was through a reductive amination of the oxidized alcohol **2.3** (Scheme 2.17).



Scheme 2.17 – Retrosynthetic pathways towards coniine by Cope-type hydroamination

2.4.2 Synthesis of Hydroxylamine Cyclization Precursor

The first step of both considered synthetic pathways was a one-pot lactone reduction and Wittig olefination.[70] This sequence was first attempted as two separate steps. Unfortunately, the extraction following the DIBAL reduction step was problematic due to the oxophilicity of the aluminum salts. Irreproducible yields were obtained, even with treatment with Rochelle's salt. Thus a one-pot procedure was preferred and alcohol **2.3** was obtained in good yield. The cis and trans isomers could be separated by column chromatography over silver nitrate treated silica gel.[71] The major cis isomer (cis/trans = 7:1) was used for the subsequent optimization (Scheme 2.18). *N-tert*-Butyl carbamate-*O-tert*-butyl carbonate hydroxylamine (*bis*-Boc hydroxylamine) was then used in a Mitsunobu reaction to introduce

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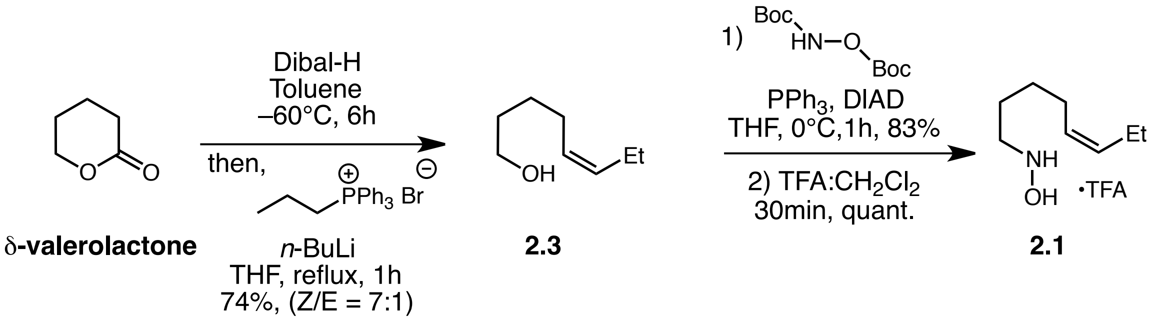
[70] a) Boland, W.; Ney, P.; Jaenicke, L. *Synthesis* **1980**, 1015. b) Andrus, M.B.; Li, W.; Keyes, R F. *J. Org. Chem.* **1997**, *62*, 5542.

[71] a) Li, T-S.; Li, J-T.; Li, H-Z. *Journal of Chromatography A* **1995**, *715*, 372. b) Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.

the hydroxylamine functionality onto the backbone of the molecule.[72] This reaction provided a *bis*-protected alkylhydroxylamine in good yield, which was then treated with trifluoroacetic acid (TFA) to quantitatively afford the deprotected product **2.1** as a TFA salt. The salt could be directly used in subsequent steps or neutralized by column chromatography using silica treated with triethylamine.



Scheme 2.18 – Synthesis of hydroamination precursor by Mitsunobu reaction

Hydroxylamine **2.1** could otherwise be obtained through oxidation of the alcohol **2.3**, followed by reductive amination (Scheme 2.19). The oxidation was performed under Parikh-Doering conditions to afford aldehyde **2.2** in 55% yield,[73] which was then reacted with aqueous hydroxylamine in *i*-propanol to afford oxime **2.4** in good yield. The reduction was then performed with sodium cyanoborohydride in MeOH. The acidity of the reaction was monitored with methyl orange (pKa = 3.7) and controlled by the addition of a hydrogen chloride solution in methanol to prevent enamine formation by deprotonation.[74,20b] This procedure afforded the desired hydrochloride salt hydroxylamine **2.1** in modest yield (44%).

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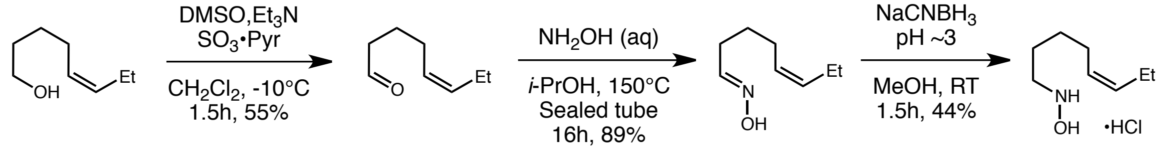
[72] a) Parry, R. J.; Tao, T.; Alemany, L. B. *Org. Lett.* **2003**, *5*, 1213. b) Knight, D.W.; Leese, M.P. *Tetrahedron Lett.* **2001**, *42*, 2593.

[73] a) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967***, 89*, 5505. b) Mukai, C.; Nomura, I.; Katagaki, S. *J. Org. Chem.* **2003**, 68, 1376.

[74] Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601.

The former synthetic pathway (see Scheme 2.18) providing greater quantity of the cyclization precursor in reproducible yields, it was kept as the main route towards hydroamination precursors.

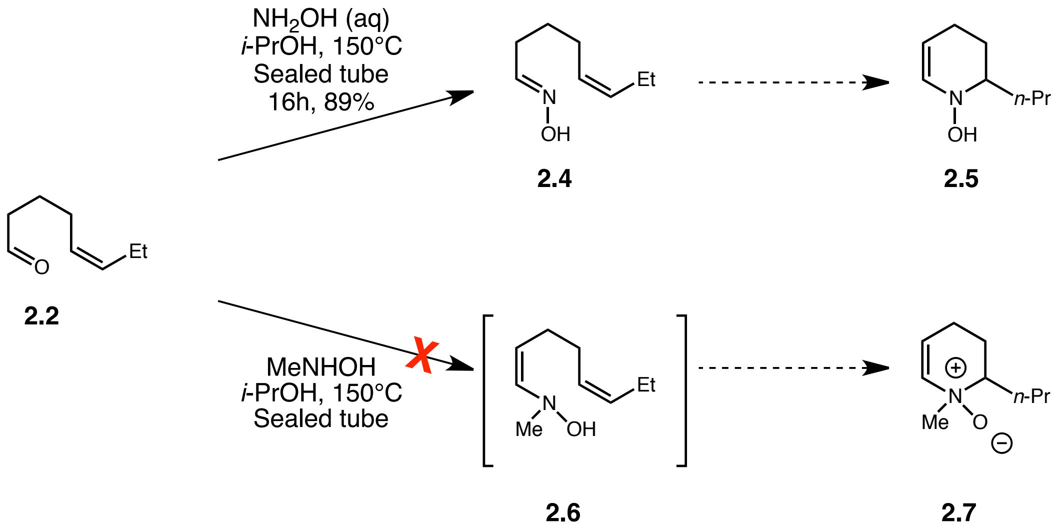


2.3 **2.2** **2.4** **2.1**

Scheme 2.19 – Synthesis of hydroamination precursor by reductive amination

2.4.3 Preliminary Cyclization Trials

The first attempted cyclizations were performed directly with aldehyde **2.2** in the presence of either hydroxylamine or methyl hydroxylamine in *i*-propanol. The goal was to form *in-situ* an oxime or hydroxylamine, which could then undergo Cope-type hydroamination. This would have afforded a coniine precursor via a new oxime-mediated Cope-type hydroamination. However, oxime **2.4** was the only product recovered (Scheme 2.20). This method was therefore used as an efficient mean for oximes formation and the Cope-type hydroamination reaction was attempted with the hydroxylamine cyclization precursor.

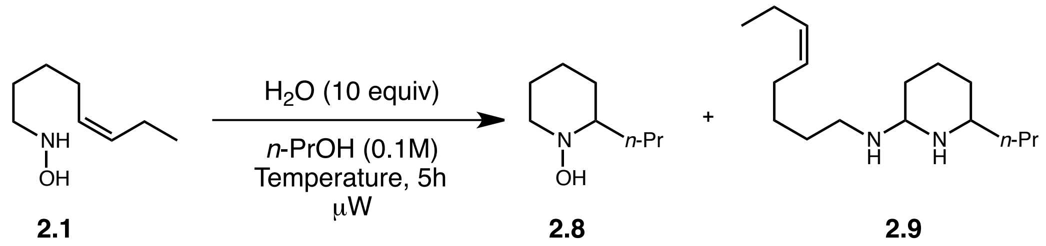


Scheme 2.20 – Preliminary cyclization trials

2.4.4 Cope-Type Hydroamination with Hydroxylamine Precursor

Based on previous results by Marie-Eve Lebrun and Joseph Moran (see section 1.2.4), cyclization of the free amine hydroxylamine substrate **2.1** was attempted in the standard conditions: it was heated by microwave irradiation, under argon, with *n*-propanol and water as solvent. Promising yields of the desired cyclized product were isolated in combination with proposed dimer **2.9** as a major product (Table 2.1, dimer yield in parenthesis). Salts of hydroxylamine's being more stable, their *in-situ* neutralization was attempted in a sealed tube in order to minimize thermal decomposition of the starting material. In addition, a greater solvent volume was used to minimize dimer formation, but no improvements came from these modifications (Table 2.2).

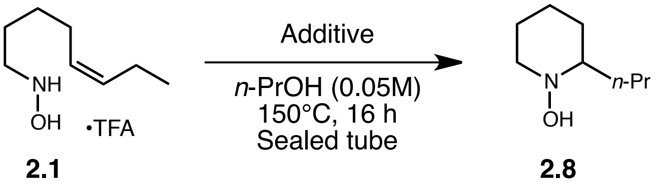
Table 2.1 – Cyclization attempts of hydroxylamine substrate.



Entry	Temperature	Yield %[a] **2.8**(**2.9**)
1	180°C	10(24)
2	140°C	11(18)
3	100°C	– [b]

[a] isolated yields [b] starting material recovered

Table 2.2 – *In-situ* neutralization of hydroxylamine salt in Cope-type hydroamination

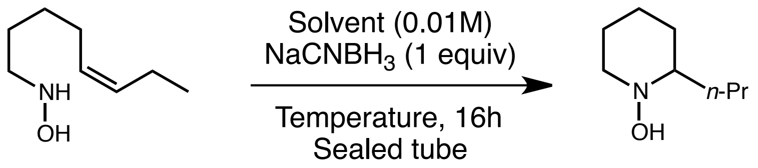


Entry	Additive	Yield [a] %
1	Et_3N	6
2	i-Pr_2EtN	–

[a] isolated yields

In order to improve the yield of the cyclization reaction, sodium cyanoborohydride was added as an additive. The beneficial effect of this additive had already been shown for the intermolecular Cope-type hydroamination (see section 1.2.4), presumably due to the stabilization of both starting materials and products under the reaction conditions. The addition of sodium cyanoborohydride to the reaction mixture greatly improved the yield of the Cope-type hydroamination (Table 2.3). The sealed tube cyclization in *n*-propanol, at 140°C, with this additive, provided coniine hydroxide in 23% yield, a two-fold increase from the original microwave cyclization attempts (see Table 2.1). The additive also allowed the reaction to proceed in a non-protic solvent, such as benzene, with similar results (Table 2.3, entry 3).

Table 2.3 – Cyclization attempts of hydroxylamine 2.1 with $NaCNBH_3$ additive



2.1 **2.8**

Entry	Solvent	Temperature	Yield [a] %
1	*n*-PrOH	140°C	23
2	*n*-PrOH	120°C	15 [b]
3	Benzene + 10 equiv H_2O	140°C	19

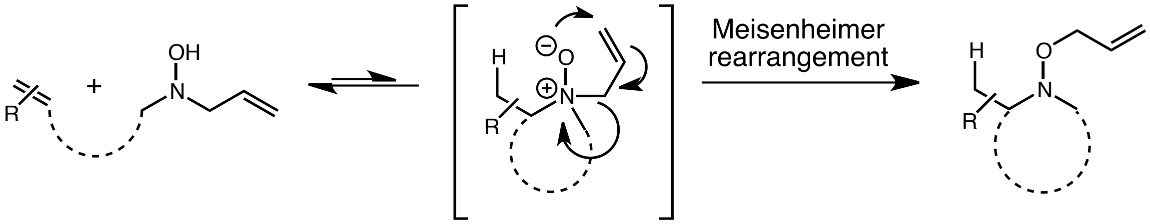
[a] isolated yields [b] 17% of starting material recovered

Despite the use of these optimized conditions, the yields obtained for the intramolecular Cope-type hydroamination of alkenes en route to six-membered rings were far from the ones observed for the intermolecular reaction. Furthermore, the reaction did not take place under the conditions described in the literature for the cyclization of difficult Cope-type hydroamination substrates.[23] Finally, the observed instability of hydroxylamine **2.1** suggested that a new method had to be developed.

2.4.5 Cope-Type Hydroamination-Meisenheimer Rearrangement Sequence

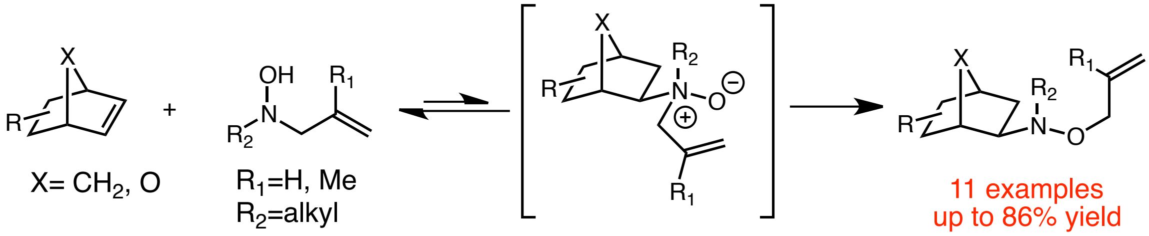
2.4.5.1 Intermolecular Precedents in the Beauchemin Group

In order to circumvent the challenge of thermoneutrality in the intermolecular hydroamination with alkenes (see section 1.1) and widen the application of intermolecular Cope-type hydroamination, the Beauchemin group turned their efforts towards the development of reaction sequences. The idea was to trap the charged intermediate formed by the reversible Cope-type hydroamination reaction using a second irreversible reaction to afford a more stable product. The first envisioned sequence involved a Meisenheimer rearrangement as the thermodynamic sink. By substituting the hydroxylamine starting material with an allyl group, the usual proton transfer step following the Cope-type hydroamination could be replaced by the Meisenheimer rearrangement (Scheme 2.21). Upon the initial hydroamination reaction, the negative charge formed onto the oxygen would attack the allyl moiety and trigger a [2,3] rearrangement, thereby relieving the positive charge on the nitrogen. The use of a more stable di-substituted hydroxylamine as the starting material would also prevent substrate degradation under the reaction conditions. Furthermore, an intramolecular rearrangement should allow for the use of a wider variety of solvents, since no proton transfer would be involved in the sequence.



Scheme 2.21 – Cope-type hydroamination-Meisenheimer rearrangement (CHMR) sequence

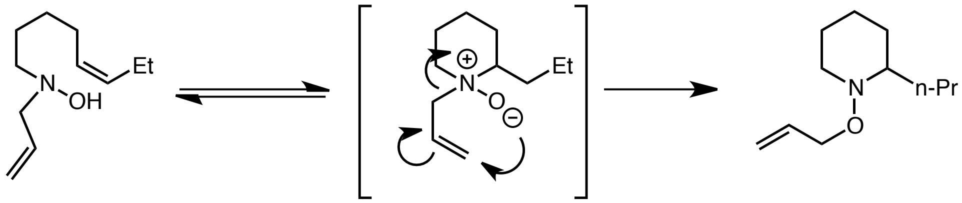
Results from Joffré Bourgeois' experiments on norbornene and derivatives showed that the Cope-type hydroamination-Meisenheimer rearrangement (CHMR) sequence was viable, but that an undesired Cope-type hydroamination reaction could occur on the allyl group. The allyl was therefore substituted for a methylallyl group (see section 2.4.5.5 for optimization), which helped provide multiple hydroamination products on various strained and activated alkenes in both protic and aprotic solvents (*n*-PrOH and benzene) (Scheme 2.22).[75]



Scheme 2.22 – Intermolecular CHMR sequence

2.4.5.2 CHMR Sequence Applied to the Cyclization of Six-Membered Rings

By applying the previously described CHMR sequence to the difficult cyclization of six-membered rings via intramolecular Cope-type hydroamination, it was hoped to provide a higher yielding key step. As previously stated (see section 2.4.5.1), the incorporation of the CHMR sequence to the synthesis of coniine would help stabilize both starting material and cyclized product. The [2,3]-Meisenheimer rearrangement would allow for thermodynamic draining of the reversible hydroamination reaction by neutralization of the charged intermediate **2.11**, providing higher quantities of the cyclized product.



2.10 **2.11** **2.12**

Scheme 2.23 – Application of the sequence to the synthesis of coniine

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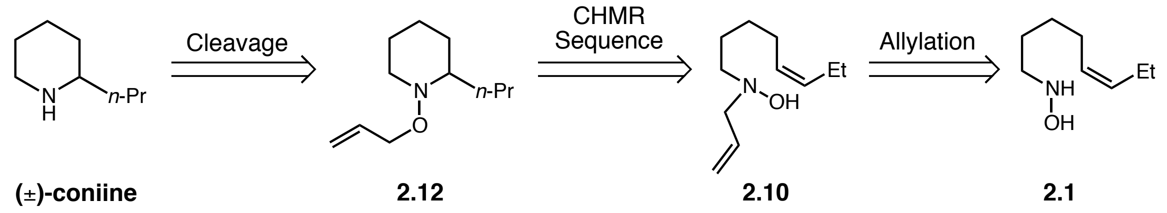
[75] Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874.

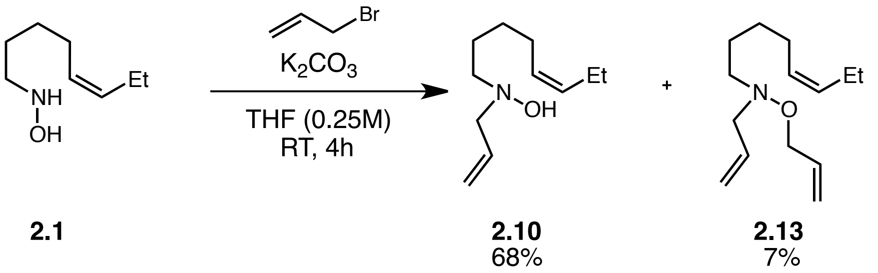
2.4.5.3 Synthesis of the Allylated Cyclization Precursor

Nitrogen allylation of hydroxylamine **2.1** for the synthesis of coniine was determined as a way to obtain CHMR sequence precursor **2.10** (Scheme 2.24).



Scheme 2.24 – Retrosynthetic analysis of coniine with CHMR sequence incorporation

A quick optimization of the newly developed allylation reaction revealed that an excess of allyl bromide and base was needed. The allylation of hydroxylamine **2.1** was accomplished using potassium carbonate and allyl bromide in THF, affording desired product **2.10** in 68% yield. The major side product of the reaction, hydroxylamine **2.13**, was the result of bis-allylation of the starting material and was obtained in 7% yield (Eq. 2.1).

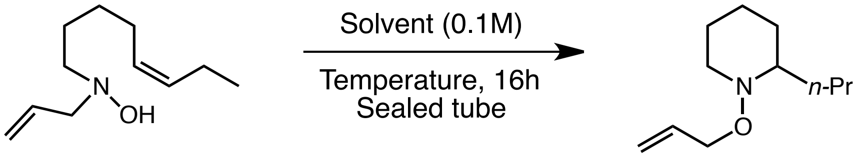


(2.1)

2.4.5.4 CHMR Sequence Optimization

With the allylated precursor in hand, the cyclization was attempted under various conditions (Table 2.4). No reaction was observed in DMSO or THF, while higher temperatures were needed in order to obtain the desired product in benzene. The highest yield was obtained with deoxygenated solvents (Table 2.4, entry 6). The major side products isolated were characterized and identified as dimer **2.9** (see section 2.4.4), bis-allylated precursor **2.13** (see section 2.4.5.3) and de-allylated product **2.8** (Figure 2.2).

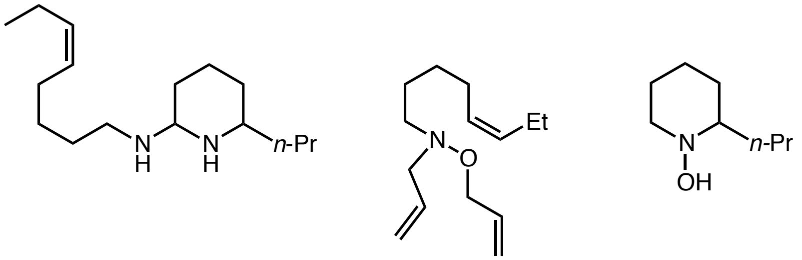
Table 2.4 – Primary cylization optimization with allylated hydroxylamines



2.10 **2.12**

Entry	Solvent	Temperature °C	Yield [a] %
1	DMSO-d_6	RT	–
2	DMSO-d_6	150	–
3	THF	120	–
4	C_6D_6	100	–
5	C_6D_6	150	26
6	C_6D_6	150	42 [b]

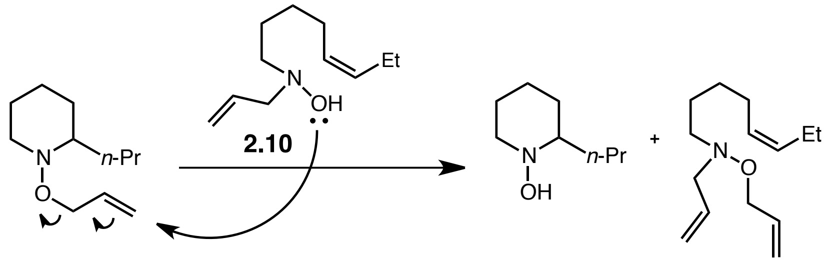
[a] isolated yields [b] degassed



2.9 **2.13** **2.8**

Figure 2.2 – Common side products of reaction sequence

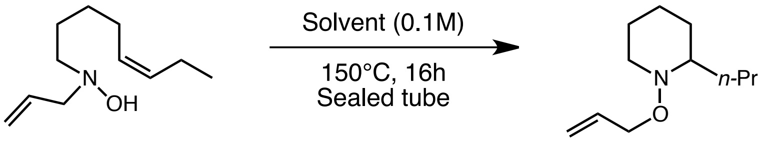
The formation of side products **2.13** and **2.8** could be explained by the S_N2' attack of the starting material onto the cyclized product (Eq. 2.2). Formation of proposed dimer **2.9** could be coming from a hydroxylamine disproportionation process followed by addition reaction of the newly formed reagents. Similar side products have been reported in previous publications on intramolecular Cope-type hydroamination.[20b] More diluted conditions were chosen in subsequent optimization to minimize their formation.



2.12 **2.8** **2.13** (2.2)

A solvent scan was performed in order to improve the hit obtained in benzene (Table 2.5). Alcoholic solvents were tried, as they had proven efficient with the intermolecular variant of the sequence (see section 2.4.5.1). Surprisingly, they only provided moderate yields and best results were still obtained when the reaction was performed in benzene. The addition of ten equivalents of water did not significantly increase the yield, but provided a cleaner reaction where the starting material could be recuperated.

Table 2.5 – CHMR sequence solvent scan



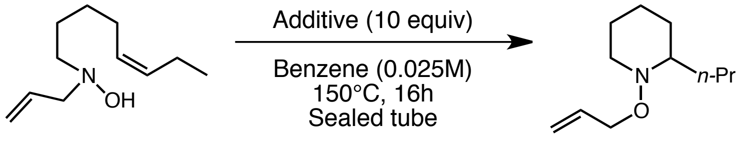
2.10 **2.12**

Entry	Solvent	Yield [a] %
1	MeOH	degradation
2	*i*-PrOH	14
3	*i*-PrOH + H_2O	16
4	*n*-PrOH + H_2O	12
5	Toluene	degradation
6	(trifluoromethyl)benzene	12
7	$CHCl_3$	4
8	Benzene	33
9	Benzene + H_2O	34

[a] isolated yields

In order to study the effect of scale, the CHMR sequence was performed multiple times on 50 or 100 mg of starting material. It revealed that reactions performed on scales smaller than 100 mg were unreliable. The yields were lower and higher quantities of side products were observed. Consequently, further optimization was performed on a 100 mg scale. In order to clarify the effect of water onto the reaction, other additives were tried. It was hypothesized that water helped to stabilize the charged intermediate in the aprotic solvent and as such, alcohols, thiols and amines were tested (Table 2.6).

Table 2.6 – Effect of additives onto the CHMR sequence



2.10 **2.12**

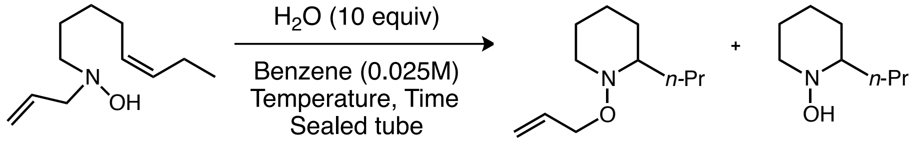
Entry	Additive	Yield [a] %
1	-	33
2	H_2O	34
3	*t*-BuOH	2
4	n-PrOH	29
5	H_2O + PhSH	22
6	*i*-Pr_2EtN	41
7	Et_3N	36
8	Et_2NH	20
9	$NaCNBH_3$ [b]	32 [c]
10	H_2O + $NaCNBH_3$ [b]	30

[a] isolated yields [b] one equiv [c] 120°C

The addition of *t*-butanol provided the lowest yield (Table 2.6, entry 3), which could be attributed to its bulkiness. A possible hydrogen bonding interaction with the hydroxylamine starting material prior to cyclization would interfere with the alkene approach, preventing the hydroamination to occur. Supporting this theory, the smaller alcohol *n*-propanol showed better results, similar to those of water. The addition of thiophenol proved to be detrimental to the reaction (Table 2.6, entry 5). This could be attributed to the acidity of the thio group (pka = 7) could partially protonate the hydroxylamine (pka = 5.96). Both side reactions would prevent the Cope-type hydroamination reaction from occurring. The increase in yields observed when adding Hunig's base or triethylamine led to the hypothesis that the charged intermediate was stabilized by the additive's lone pairs rather than via hydrogen bonding (Table 2.6, entries 7 & 8). Addition of sodium cyanoborohydride to the reaction, both in the presence and absence of water, did not afford the expected yield increase, despite the reducing agent's presumed stabilizing effect with the intramolecular Cope-type hydroamination starting material (see section 2.4.4, Table 2.3). The reaction conditions using benzene with water were kept, as they provided the most reliable results.

A temperature scan was then performed in order to see its effect on the CHMR sequence (Table 2.7). As it was already known that a reaction ran at 100°C would not provide the desired product (see Table 2.4), the experiments were performed within a range in between 120 and 170°C. In addition to the temperature scan, the reactions were performed over shorter or longer period than the 16 hours used in current optimization.

Table 2.7 – CHMR sequence temperature scan



2.10 **2.12** **2.8**

Entry	Temperature °C	Time h	Yield %^{a} **2.12**(**2.8**)
1	120	16	36^b
2	120	48	28^b
3	140	16	34
4	150	6	29 (< 2)
5	150	16	34 (< 2)
6	150	64	39 (< 2)
7	170	16	37 (19)
8	150^c	5	17^b

[a] isolated yields [b] starting material recovered [c] μW

The formation of the de-allylated side product **2.8** was seen to increase at higher temperatures (Table 2.7, entries 4-7). However, reactions performed at lower temperatures, even for long periods of time, would not go to completion. Heating via microwave irradiation did not provide a good conversion and was plagued with solvent volume limitations. The optimal temperature was set to 140°C, since it provided the mildest, cleanest reaction, if not the highest overall yield (product + side product). A more convenient 16 hours reaction time was kept for further optimization, as it did not lead to a significant yield loss. Despite optimization, the best isolated yield was 39% (Table 2.7, entry 6). To determine if degradation of the final product was occurring under reaction conditions, cyclized product **2.12** was isolated and resubmitted to experimental conditions (Table 2.7, entry 5), with and without the addition of 10 equivalents of water. No significant traces of degradation were observed by NMR.

Having seen intermolecular reactivity and dimerization as side reactions under the best CHMR sequence conditions, a concentration scan was undertaken (Table 2.8). A significant increase in cyclization yield was observed when diluting the reaction to a 0.01M dilution. Greater dilution did not provide higher yields, with error margin becoming more important due to the smaller samples used and volume constraints. The concentration affording the highest yield (0.01M) was kept constant and a quick temperature and time of reaction optimization were performed (Table 2.8, entries 4-7). Reaction sequences ran for longer periods and at lower temperatures did not improve the reaction yield. The best conditions (Table 2.8, entries 2 & 5) being reproducible, they were therefore kept. Finally, the CHMR sequence was attempted on the *E*-isomer of the starting material, which provided similar results, albeit in a slightly lower yield (Eq. 2.3). This could be explained by the boat transition state associated with intramolecular Cope-type hydroamination, during which an *E*-alkene could be creating more important steric hindrance than a *Z*-alkene (Figure 2.3).[76]

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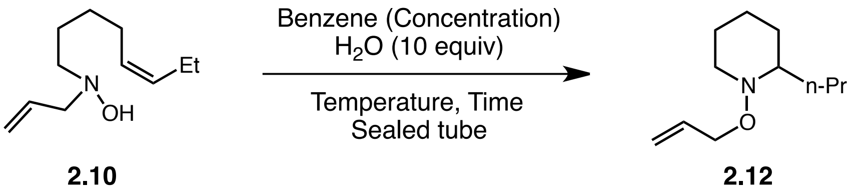
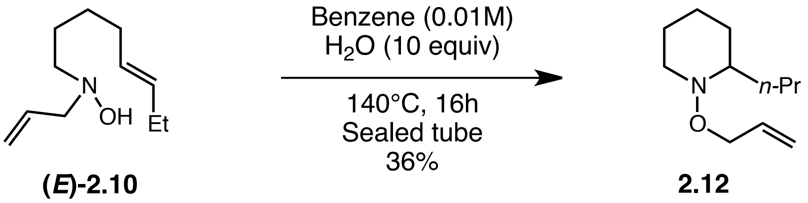
[76] Lebrun, M-E.; Pfeiffer, J. Y.; Beauchemin, A. M. *Synlett* **2009***,* 1087.

Table 2.8 – CHMR sequence concentration scan

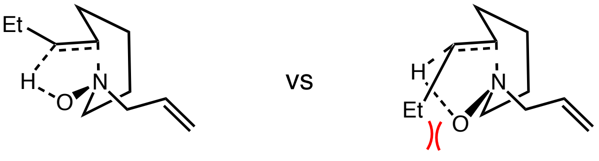


Entry	Concentration	Temperature °C	Time h	Yield [a] %	% of SM recovered [a]
1	0.025M	140	16	34	–
2	0.01M	140	16	46	–
3	0.0025M	140	16	40	–
4	0.01M	140	10	42	50
5	0.01M	140	16	47	15
6	0.01M	120	16	33	51
7	0.01M	120	32	44	22

[a] isolated yields



(2.3)

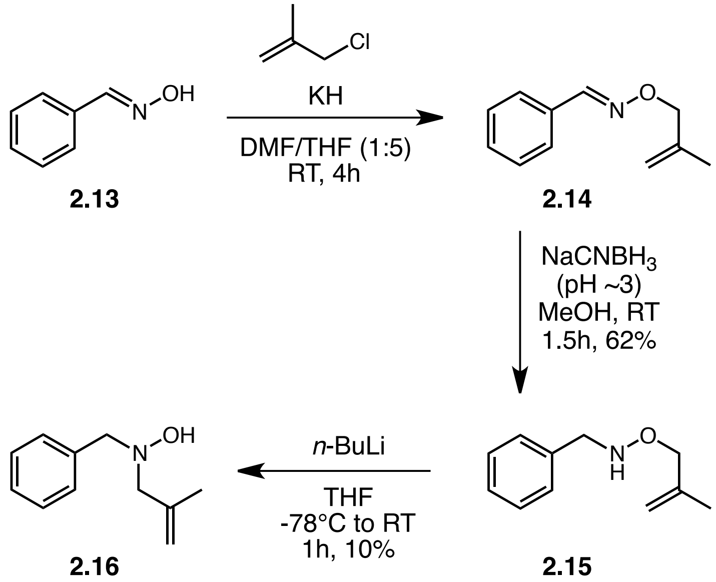


(*Z*)-2.10 **(*E*)-2.10**

Figure 2.3 – Difference in transition state between alkene isomers

2.4.5.5 CHMR Sequence Optimization with Methylallyl Substitution

In an attempt to further optimize the CHMR sequence, the allyl substituent was replaced by a more hindered 2-methylallyl (methallyl) based on the fact that the S_N2' de-allylation had been identified as a major side reaction (see Eq. 2.2). Poor conversions were obtained when allylating with 3-chloro-2-methyl-1-propene under the conditions optimized for allylbromide (6%). The methallylation reaction was therefore optimized on commercially available model (*E*)-benzaldehyde oxime. Literature precedents provided a possible route to *N*-allylation via a reverse Meisenheimer rearrangement, which could circumvent the direct methallylation problems (Scheme 2.25).[77] Allylation[78] and reduction[74,20b] of benzaldehyde oxime were successfully executed, but the reverse Meisenheimer rearrangement provided mostly degradation of the substrate. This lengthy path was therefore abandoned.



Scheme 2.25 – Reverse Meisenheimer rearrangement for *N*-methallylation

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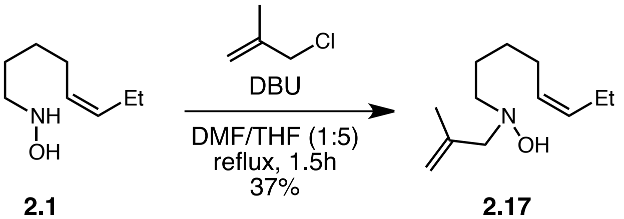
[77] Davies, S. G.; Fox, J. F.; Jones, S.; Price, A. J.; Sanz, M. A.; Sellers, T. G. R.; Smith, A. D.; Teixeira, F. C.; *J. Chem. Soc., Perkin Trans. 1* **2002**, 1757.

[78] Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892.

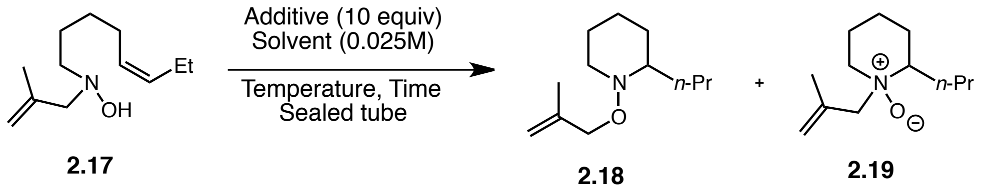
Another graduate student, Francis Loiseau, also worked on the optimization of the hydroxylamine's nitrogen methallylation.[75] From this joint effort, the use of an organic base, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), under reflux, came through as a more efficient way to obtain the desired methallylated cyclization precursor (Eq. 2.4). The same conditions were subsequently used for the intermolecular variant of the CHMR sequence (see section 2.4.5.1).



2.1 **2.17** (2.4)

Cyclization trials were then attempted for the CHMR sequence with the methallyl substituent. The best conditions developped with the allyl-substituted cyclization precursor **2.10** (benzene and water), were applied at different temperatures for standard and various time periods (Table 2.9). From these experiments, it was determined that the reaction was not going to completion, even when submitted for longer periods of time. Interestingly, a possible *N*-oxide intermediate was observed by ^{1}H NMR under the reaction conditions. The more hindered methallyl substituent was hypothesized to be preventing the Meisenheimer rearangement from taking place. Isolation and characterization of the *N*-oxide intermediate was not possible due to the reversibility of the hydroamination step at room temperature. Polar aprotic and protic solvents were tried in order to attempt stabilization of the intermediate, however no improvement was noted (Table 2.9, entries 4 & 5). The methallyl substituent was therefore considered unsuitable for the optimization of the CHMR sequence.

Table 2.9 – Cyclization conditions for the methallyl substituted cyclization precursor

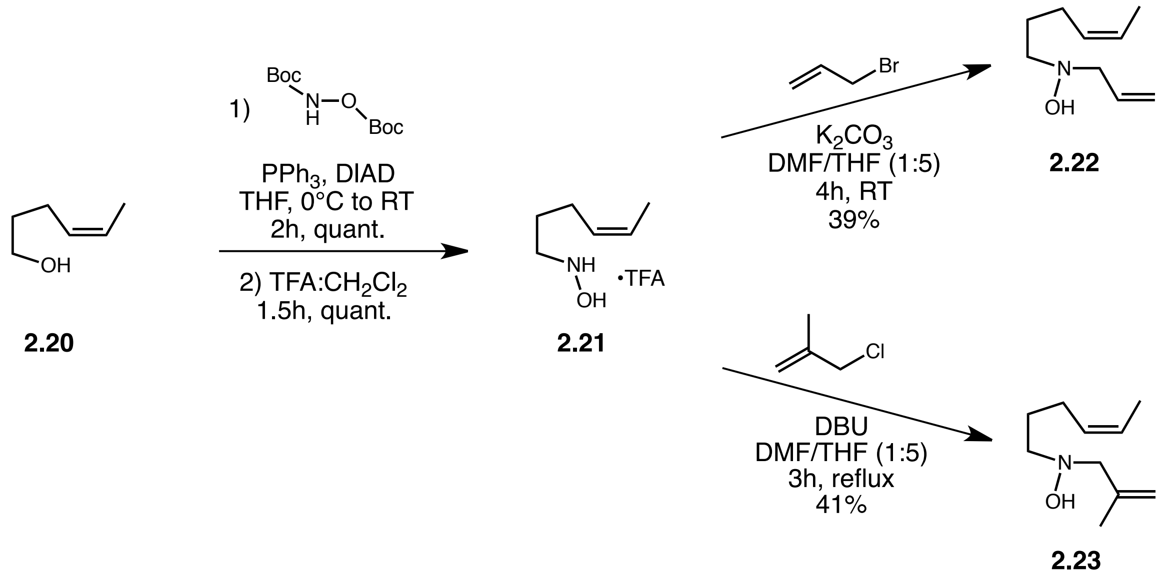


Entry	Solvent	Additive	Temperature °C	Time h	Yield %[a] **2.18**(**2.19**)[b]	% of SM recovered [a]
1	Benzene	H_2O	150	16	31 (18)	–
2	Benzene	H_2O	120	16	13 (8)	51
3	Benzene	H_2O	120	48	5 (29)	–
4	$PhCF_3$	–	120	16	16 (2)	35
5	*n*-PrOH	–	120	16	1 (12)	46

[a] isolated yields [b] ^1H NMR ratio with product

2.4.5.6 CHMR Sequence applied to the Cyclization of Five-Membered Rings

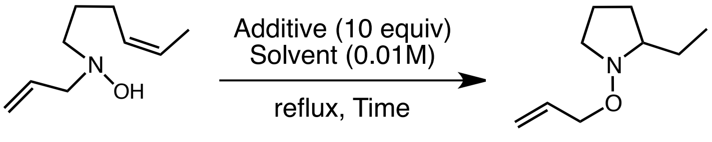
Known to cyclize more easily via Cope-type hydroamination, substrates leading to five-membered rings were then chosen in order to see if an increased reactivity could also be gained from the application of the reaction sequence. The previously developed pathway (see Scheme 2.24) was applied to the commercially available (*Z*)-4-hexen-1-ol. The Mitsunobu reaction,[72a] followed by deprotection of the Boc groups with trifluoroacetic acid afforded the hydroxylamine **2.21** quantitatively. It was then allylated or methallylated with previously developed methods (see Eq. 2.1 and 2.4) to afford the allyl and methallyl reaction sequence precursors in 39% and 41% yield, respectively (Scheme 2.26).



Scheme 2.26 – Synthesis of five membered rings cyclization precursors

Cyclization trials were first attempted on the allylated substrate (Table 2.10). It was quickly determined that, as with six-membered rings cyclization, a more dilute solution was needed to obtain cleaner reactions and prevent intermolecular side reactions. The first attempt at cyclization in a sealed tube yielded little of the desired product. Hence, a more traditionnal set of conditions, involving reflux, was chosen (Table 2.10, entries 1 & 2). As expected for facile five-membered rings cyclizations, CHMR sequence products were obtained at lower temperature. However, the observed yields were surprisingly low for what was expected to be an easier cyclization. Supposed volatility of the product under the reaction condidtions could explain these results, despite attempts at traping the five-membered ring as an HCl salt during workup. Longer reaction time only led to degradation of the starting material (Table 2.10, entry 3). Perhaps the most representative result came from the reaction ran in chloroform at reflux. Under these milder reaction conditions, the cyclization took place, while the lower temperature prevented the supposed loss of the volatile product through evaporation.

Table 2.10 – Cyclization trials of the five-membered allylated substrate



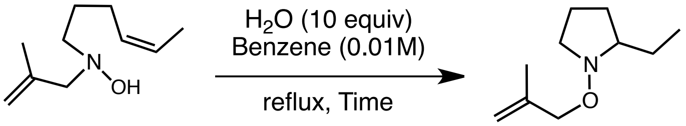
2.22 **2.24**

Entry	Solvent	Additive	Time h	Yield [a] %
1	Benzene	H_2O	16	1[b]
2	Benzene	H_2O	2	10
3	Benzene	H_2O	6	18[c]
4	$CDCl_3$	–	24	34

[a] isolated yields [b] 0.025M, 110°C, in a sealed tube [c] degradation observed

Cyclization of the methallylated substrate was concurrently attempted. The reaction conditions developed for the cyclization of allylated five-membered rings allowed the formation of a greater quantity of the desired product when applied to the methallylated variant (Table 2.11). The reaction sequence could be run for longer time periods on methallylated substrates before degradation was observed (Table 2.11, entry 2 vs. Table 2.10, entry 3). No *N*-oxide intermediate was observed in the cyclization of the methallyl substrates leading to five-membered rings as opposed to their homologated counterparts (see section 2.4.5.5, Table 2.9).

Table 2.11 – Cyclization trials of the five-membered methallylated substrate



2.23 **2.25**

Entry	Time h	Yield [a] %
1	9	24
2	17	45
3	16	34[b]

[a] isolated yields [b] 51% conversion

Application of the reaction sequence to the cyclization of five-membered rings has proven that substrates forming five-membered rings would cyclize at lower temperature, but would not provide higher yields than their six-membered counterparts. Hypothesized volatility of the products, combined with isolation issues (see Table 2.11, entry 3), prevented the full optimization of the five-membered rings reaction sequence.

2.4.6 Final Steps in the Synthesis of (±)-Coniine

With the cyclized product **2.12** obtained from the optimized reaction sequence, the synthesis of coniine was one step away from completion. The N-O bond of **2.12** was cleaved using zinc dust in a solution of acetic acid.[79] The crude coniine obtained was then quickly reacted with acetic anhydride in pyridine to successfully afford the protected *N*-acetyl-(±)-coniine **2.26** in 10% yield over two steps (Scheme 2.27). The known toxicity of coniine imposed an inherent limitation on the total quantity that could be safely synthesized. Therefore, the final steps were run on scales smaller than 5 milligrams.[80]

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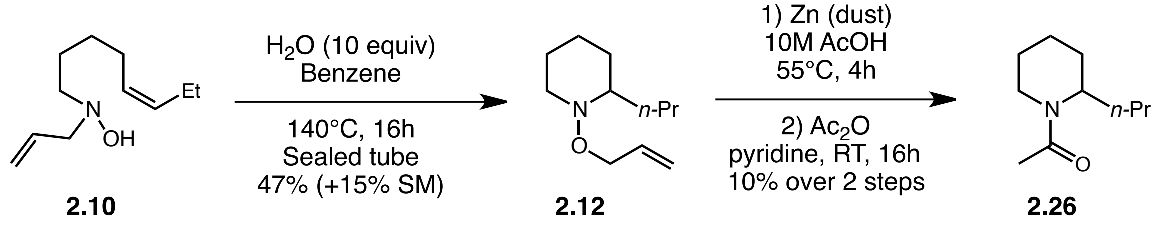
[79] Roush W. R.; Walts, A. E. *Tetrahedron* **1985**, *41*, 3463.

[80] Clinical toxicology of commercial products, Gosselin, R. E.; Smith, R. P.; Hodge, H. C. Williams & Wilkins, 5th ed. 1984.



Scheme 2.27 – Final steps in the synthesis of (±)–*N*-acetyl coniine

2.4.6.1 Optimization of N-O Bond Cleavage

Optimization of the N-O bond cleavage was not possible on the desired substrate as it provided the pure, toxic coniine. A model substrate was therefore synthesized from benzaldehyde in order to develop a higher yielding bond cleavage reaction (Scheme 2.28).[81,20b,78] A cleavage method developed by the Dolle group afforded benzylacetamides **2.32** and **2.33** in good yields from mono- and bis- substituted hydroxylamine (Scheme 2.29).[82]

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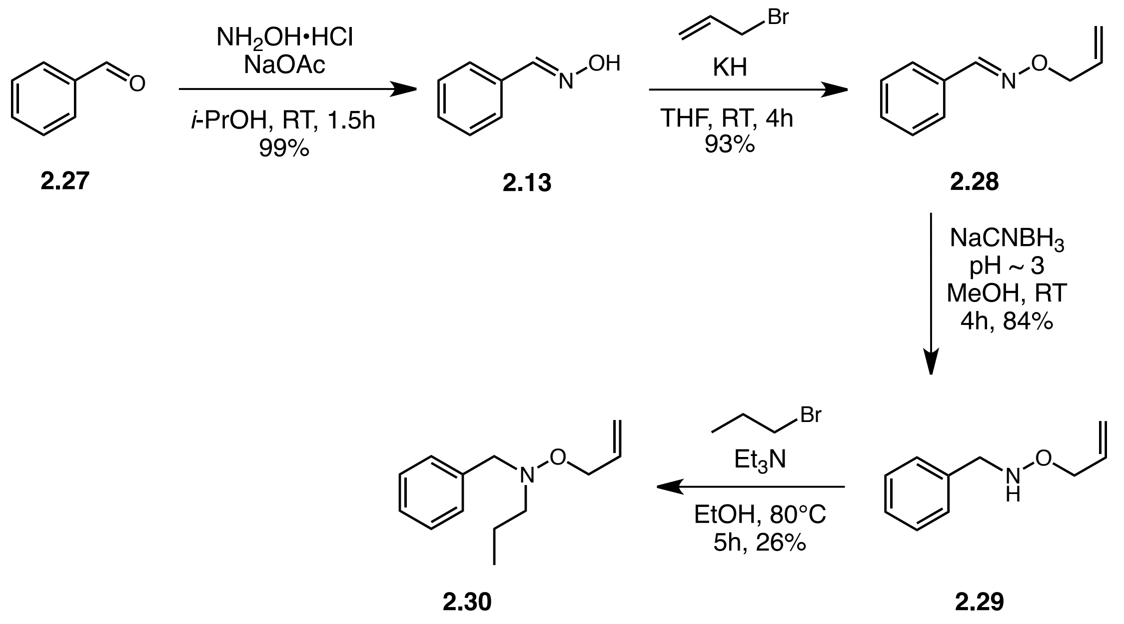
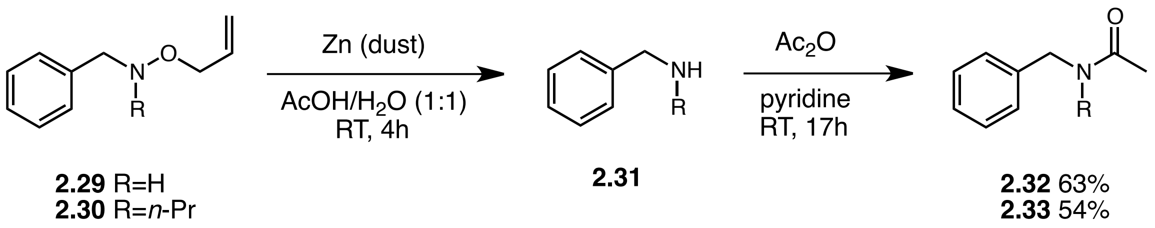
[81] a) Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M.-L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656. b) Strasser, M.; Cooper, P.; Dewald B.; Payne, T. *Helv. Chim. Acta* **1988**, *71,* 1156.

[82] a) Le Bourdonnec, B.; Goodman, A. J.; Michaut, M.; Ye, H.-F.; Graczyk, T. M.; Belanger, S.; Herbertz, T.; Yap, G. P. A.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006***, 49*, 7278. b) Freudenreich, C.; Samama, J. P.; Biellmann, J. F. *J. Am. Chem. Soc.* **1984***, 106*, 3344.



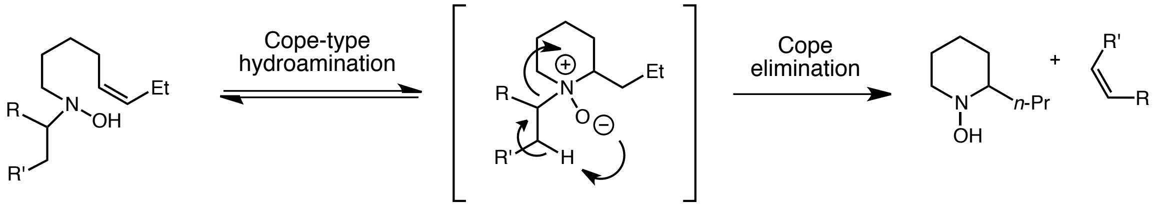
Scheme 2.28 – Synthesis of the model substrate for N-O bond cleavage optimization



Scheme 2.29 – N-O bond cleavage and protection of model substrate

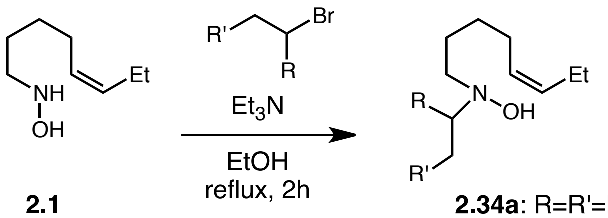
2.5 Cope-Type Hydroamination-Cope Elimination Sequence

Building on the encouraging results obtained from the optimization of the Cope-type hydroamination-Meisenheimer rearrangement sequence in the synthesis of coniine, a new reaction sequence was elaborated. Taking advantage of the increased stability of bis-substituted hydroxylamine nitrogens, the Cope-type hydroamination-Cope elimination sequence would make use of an elimination reaction in order to neutralize the charges of the *N*-oxide intermediate. Furthermore, forming two products from one molecule of starting material, an increase in entropy could help drive the reaction equilibrium towards the hydroamination products (Scheme 2.30).



Scheme 2.30 – Cope-type hydroamination-Cope elimination sequence

Starting from common hydroxylamine **2.1**, the reaction sequence was attempted with *n*-propyl, ethyl and *i*-propyl substituents in order to provide alkene by-products with various degrees of substitution. The *N*-alkylation reactions were performed based on a procedure developed by the Payne group and afforded the desired cyclization precursors in modest yields (Eq. 2.5).[81d]



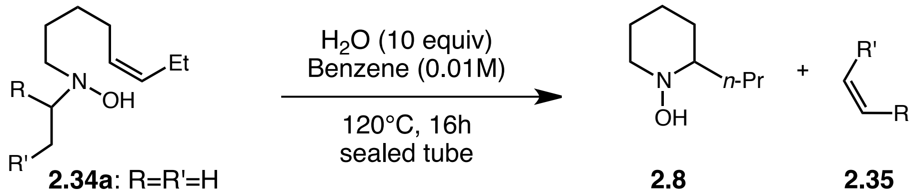
2.1

2.34a: R=R'=H, 12%
2.34b: R=H, R'=Me, 46%
2.34c: R=Me, R'=H, 28%

(2.5)

Such molecules were prone to degradation and had to be quickly submitted to cyclization reaction conditions. Two different sets of conditions based on the optimization done for the Cope-type hydroamination-Meisenheimer rearrangement, were employed, but no desired product was observed (Table 2.12).

Table 2.12 – Attempts at the Cope-type hydroamination-Cope elimination sequence



2.34a: R=R'=H
2.34b: R=H, R'=Me
2.34c: R=Me, R'=H

2.8

2.35

Entry	Substrate	R	R'	Yield [a] %
1	**2.34a**	H	H	0
2	**2.34a**	H	H	0^b
3	**2.34b**	H	Me	0^c
4	**2.34c**	Me	H	0

[a] isolated yields [b] reflux, 48h [c] ran at 0.05M

In view of the difficulties encountered with both the synthesis of the precursors and the sequence itself, the Cope-type hydroamination-Cope elimination sequence was quickly abandoned and efforts were focused on the application of the Cope-type hydroamination-Meisenheimer rearrangement sequence in total synthesis of complex molecules.

2.6 Total Synthesis of (±)–N-Norreticuline via Cope-Type Hydroamination

2.6.1 Previous Work by Ms. Pamela Cebrowski

The synthesis of *N*-norreticuline via Cope-type hydroamination was executed by Pamela Cebrowski as one of her graduate studies' projects.[83] It was hypothesized that the molecule could be synthesized via a key CHMR sequence (Scheme 2.31). As such, it would support the newly optimized sequence as way to apply Cope-type hydroamination in total synthesis. The synthesis was elaborated and effected by Ms. Cebrowski during her graduate studies.

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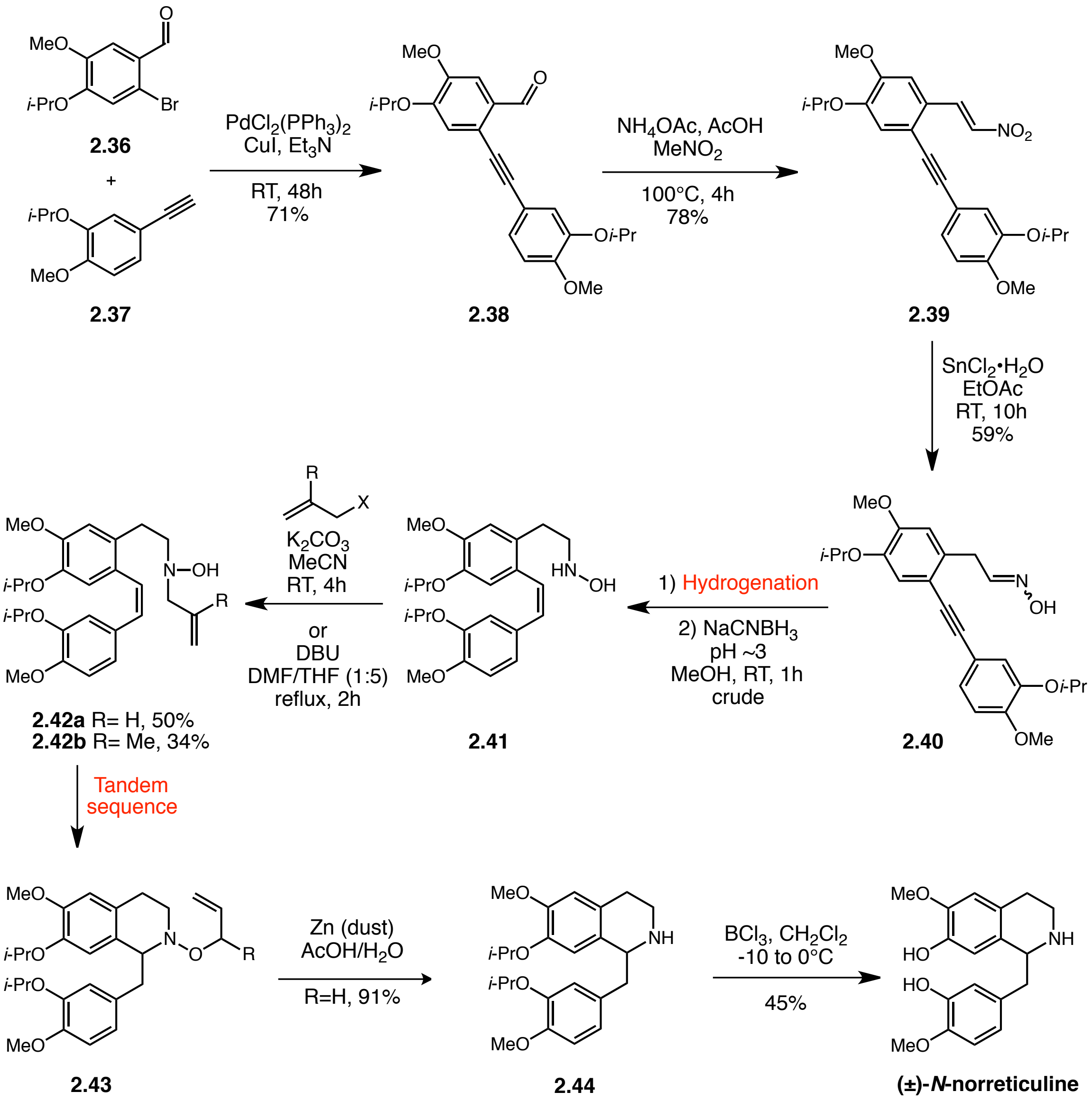
[83] Cebrowski, P. H. Application of Cope-Type Hydroamination in the Synthesis of Hydrazones and the Total Synthesis of the Benzyltetrahydroisoquinoline Norreticuline. M.Sc. Thesis, University of Ottawa, ON, 2009.

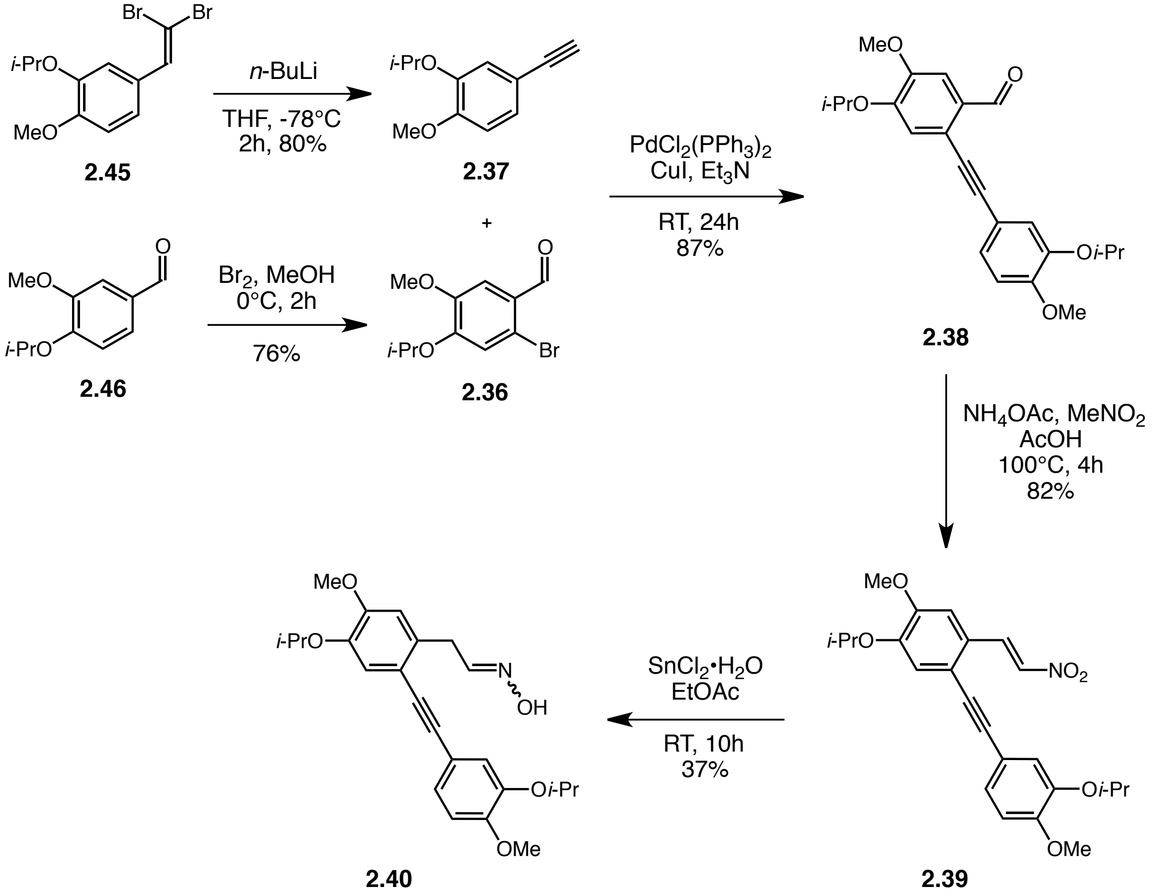
Bis-substituted alkyne **2.38** came from the coupling of modified iso-vanillin and brominated vanillin via a Sonogashira reaction. The oxime moiety **2.40** was generated by means of a modified Henry reaction on substituted benzaldehyde **2.38**, followed by reduction. The cyclization precursor **2.41** was obtained by hydrogenation of alkyne **2.40** to the cis-alkene and reduction to the hydroxylamine. After cyclization via the CHMR sequence, cleavage of the N-O bond and selective deprotection afforded *N*-norreticuline in an overall 3.8% yield. Due to time constrains, optimization of the hydrogenation step and CHMR key sequence could not be completed by Ms. Cebrowski.



Scheme 2.31 – Synthesis of (±)-*N*-norreticuline by Pamela Cebrowski[83]

2.6.2 Optimization of the Alkyne Hydrogenation

In order to solve the problematic hydrogenation reaction and to optimize the key step of the synthesis, larger quantities of the hydrogenation precursor **2.40** were synthesized according to the synthetic pathway elaborated by Ms. Cebrowski. Bromination of protected vanillin afforded the Sonogashira precursor in good yield.[84] Having the dibromoalkene derived from iso-vanillin already in hands, the second step of the Corey-Fuchs reaction afforded alkyne **2.37** in 80% yield.[85] The Sonogashira reaction reacted more quickly than initially assumed and provided the bis-substituted alkyne within 24h.[86] Subsequently, the modified Henry reaction proceeded smoothly and, despite efforts, the previous results for the tin-mediated reduction of the nitro-alkene were not reproducible (Scheme 2.32).[87]



Scheme 2.32 – Synthesis of the hydrogenation precursor for optimization

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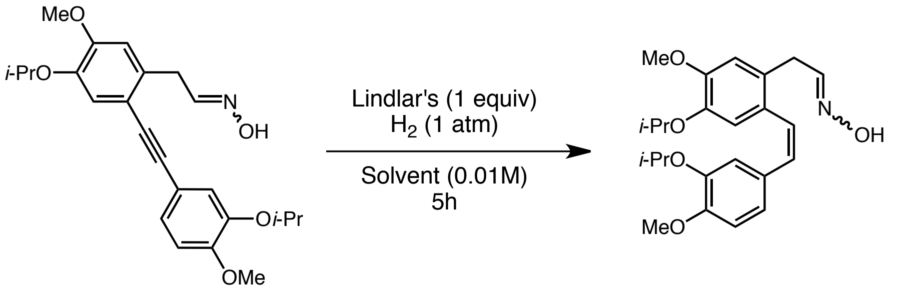
[84] Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Chem. Eur. J.* **2007**, *13*, 6452.
[85] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3772.
[86] Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3595.
[87] a) Coté, A.; Lindsay, V. N. G.; Charette, A. B. *Org. Lett.* **2007**, *9*, 85. b) Kabalka, G. W.; Guindi, L. H. M.; Varma, R. S. *Tetrahedron* **1990**, *46*, 7443.

With the desired substrate in hand, hydrogenation of the alkyne to the cis-alkene was attempted using two different sets of conditions in order to prevent the over-reduction observed by Ms. Cebrowski. The use of Lindlar's catalyst in presence of a sacrificial alkene provided optimal conditions for the desired cis-alkene (Table 2.13, entries 2 & 3).

Table 2.13 – Optimization of the alkyne hydrogenation



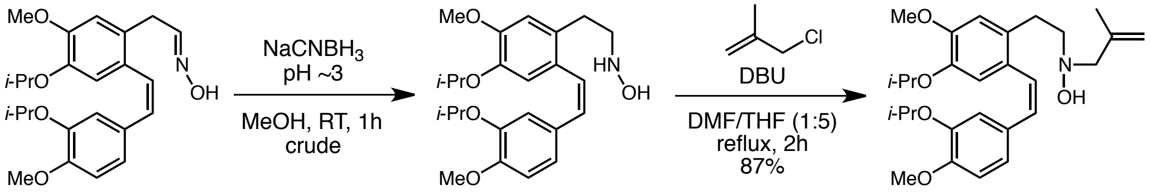
2.40 **2.47**

Entry	Solvent	Yield [a] %
1	pyridine	75[b]
2	EtOAc/1-hexene (1:1)	87
3	EtOAc/1-hexene (1:1)	81[c]

[a] isolated yields [b] over-reduction observed [c] 1g scale

2.6.3 Optimization of the CHMR Sequence

Following this, the oxime was reduced with sodium cyanoborohydride to the unstable hydroxylamine,[74] which was quickly methallylated with the set of conditions previously developed for the synthesis of coniine (see Section 2.4.5.5).

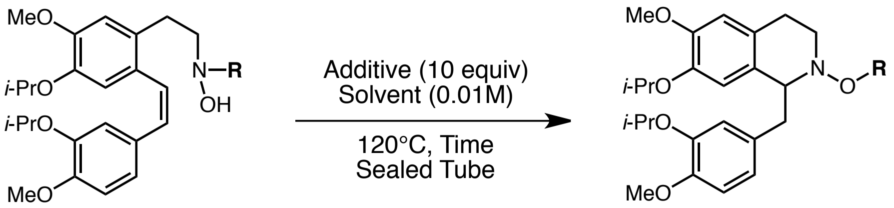


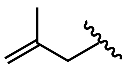
2.47 **2.41** **2.42b**

Scheme 2.33 – Synthesis of the CHMR sequence precursor

Optimization of the CHMR sequence was performed on the methallylated substrate, as Ms. Cebrowski had already undertaken the reaction sequence on the allylated variant. Cyclization on the free hydroxylamine was also attempted for comparison (Table 2.14, entries 1-3). All reactions were run at lower temperatures than those used for the synthesis of coniine (120 vs. 140°C), as the fused phenyl group offered beneficial conformational effect incorporating favorable Thorpe-Ingold effect. The CHMR sequence afforded *N*-norreticuline precursor **2.43** in yields similar to those obtained by Ms. Cebrowski with the allylated substrates (55% vs. 45% average) and to those observed in the synthesis of coniine (47%). The slight increase in yield can be attributed to the use of the hindered methallyl substituent, which is less prone to degradation and side reactions. The Cope-type hydroamination ran on the free hydroxylamine substrates provided lower yields than those obtained from the CHMR sequence, which is consistent with the trends observed with coniine (see Table 2.8 vs Table 2.3). Finally, the (*E*)-isomer of the starting material was isolated after the reaction, confirming that the intramolecular Cope-type hydroamination was reversible under the reaction conditions (Table 2.14, entry 2). The (*E)*-isomer was resubmitted to the reaction conditions and successfully provided the desired product.

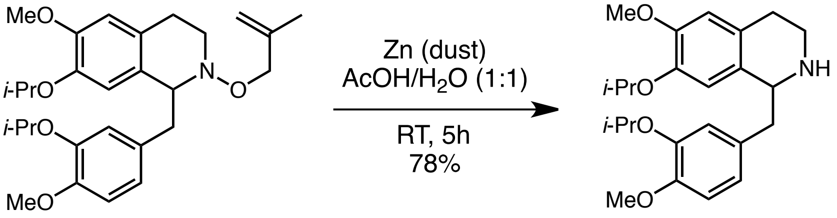
Table 2.14 – Optimization of CHMR sequence toward the synthesis of *N*-norreticuline



Entry	Substrate	R	Additive	Solvent	Time h	Product	Yield [a] %
1	**2.42b**		H_2O	Benzene	16	**2.43b**	57
2	**2.42b**		H_2O	Benzene	24	**2.43b**	54[b]
3	**2.41**	H	–	Benzene	16	**2.48**	<7
4	**2.41**	H	–	*n*-PrOH	16	**2.48**	27
5	**2.41**	H	$NaCNBH_3$[c]	*n*-PrOH	16	**2.48**	51

[a] isolated yields [b] +32% starting material (*E*)-isomer [c] 1 equiv

To finalize the optimization of the *N*-norreticuline synthetic pathway, the methallylated product of the CHMR sequence was submitted to the previously established N-O bond cleavage conditions (see section 2.4.6.1). Protected *N*-norreticuline was thus obtained in 78% yield (Eq. 2.6).

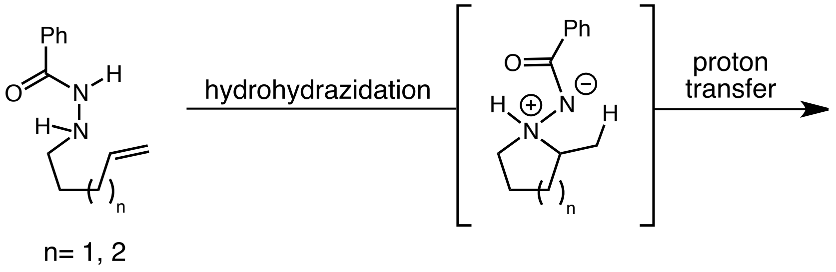


2.43b **2.44** (2.6)

2.7 Total Synthesis of (±)–10-Desbromoarborescidine A via Hydroamination

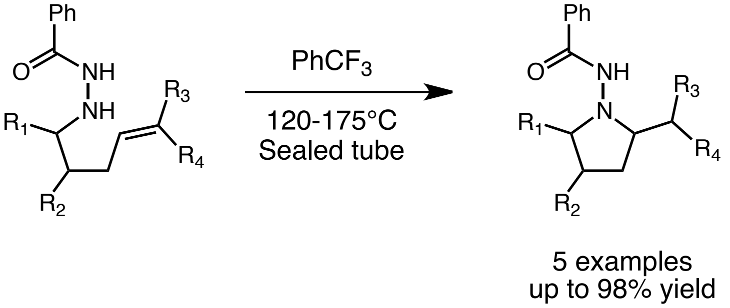
2.7.1 Previous Results in the Beauchemin Group

While the work on CHMR sequence was taking place, other members of the Beauchemin group were working on the optimization of hydrazide-mediated hydroamination, also known as hydrohydrazidation, as a mean to circumvent the known side reactions and thermal instability of hydroxylamines.[88] Being "bench-stable" and resistant to temperatures as high as 230°C, hydrazides, like hydroxylamines, offer a bi-functional moiety necessary for the Cope-type hydroamination reaction to proceed. They also provide an intramolecular pathway for the proton transfer step, given the presence of the carbonyl group (Eq. 2.7).

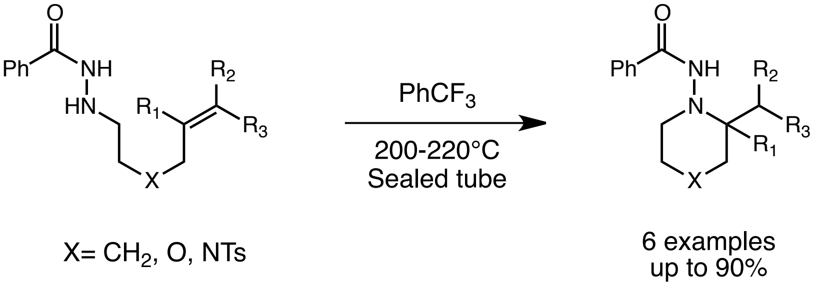


(2.7)

Optimization of this reactivity showed that benzoic hydrazides provided hydroamination products in high yields over a wide substrate scope (Eq. 2.8 and 2.9).



(2.8)



(2.9)

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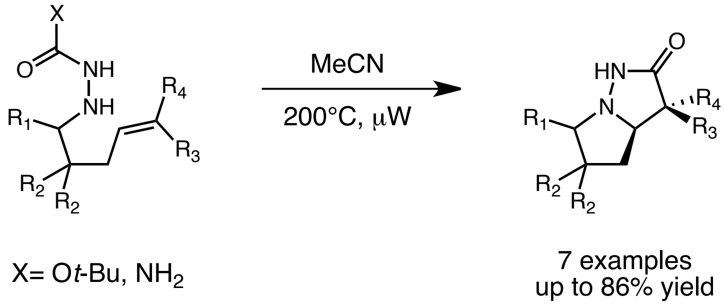
[88] a) Roveda, J-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740. b) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, *47*, 562.

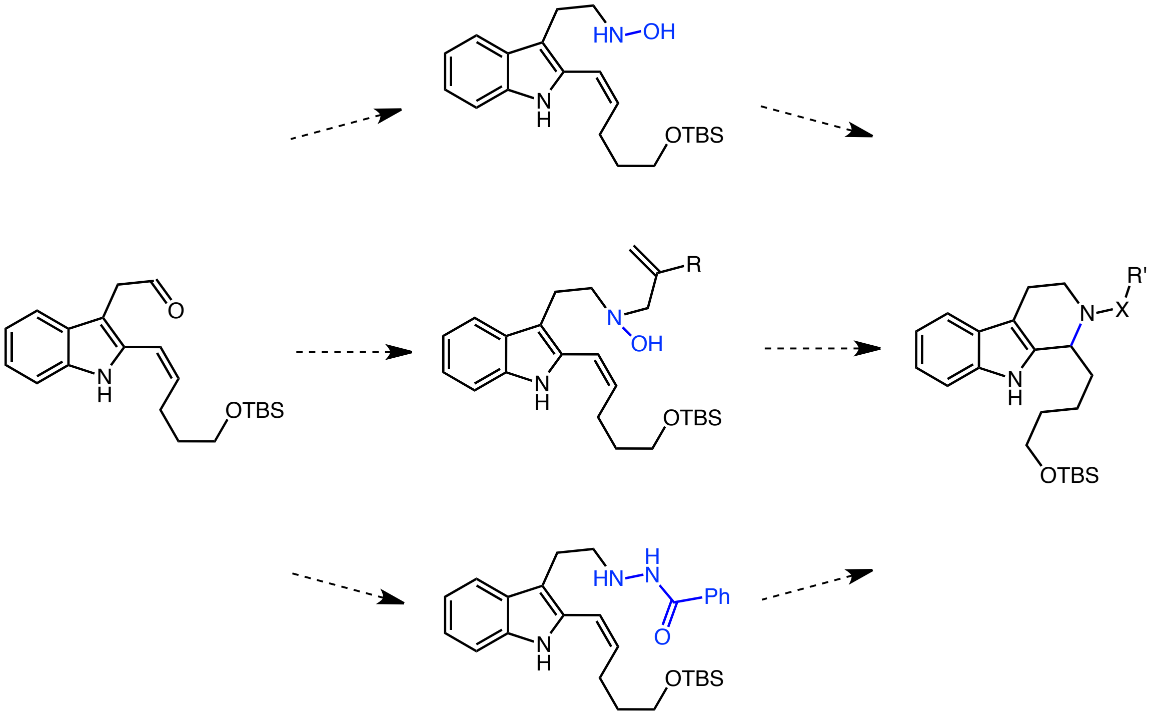
Substituting the phenyl group in favor of other alkyl groups provided similar results, while heteroatoms afforded preferentially the generation of aminocarbonylation products (Eq. 2.10).



(2.10)

2.7.2 Project Objectives

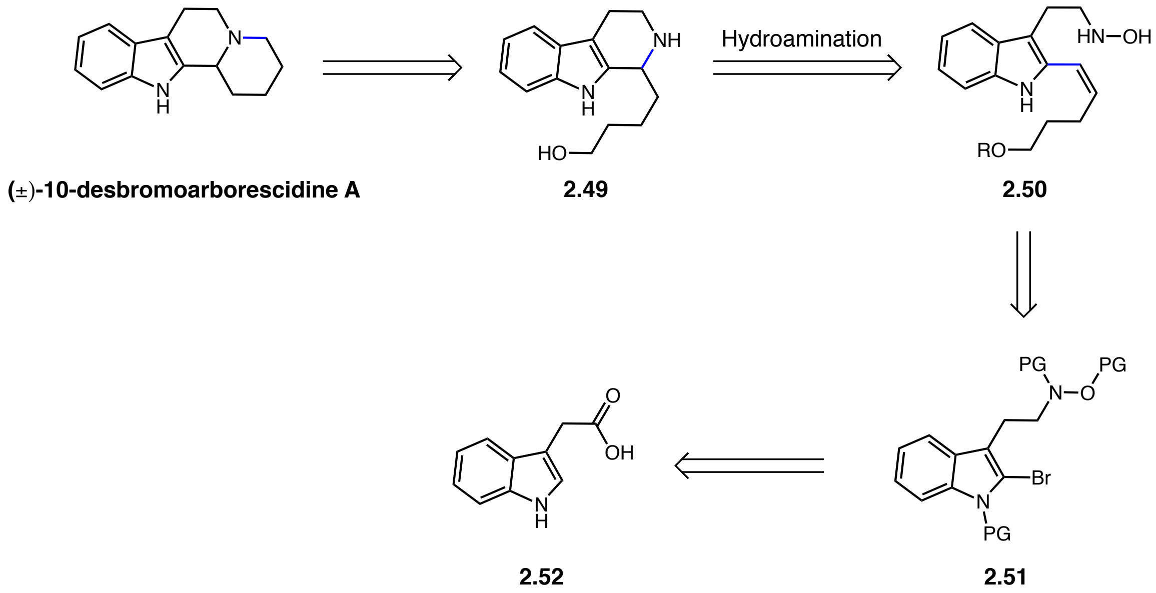
The synthesis of 10-desbromoarborescidine A was designed to compare the optimized CHMR sequence and the newly developed hydrohydrazidation method. The synthetic pathway was designed in order to easily install the various moieties at a late stage in the synthesis, allowing for quick comparison of the key steps (Scheme 2.34).



Scheme 2.34 – Key step of (±)–10-desbromoarborescidine synthesis for comparison of hydroamination methods

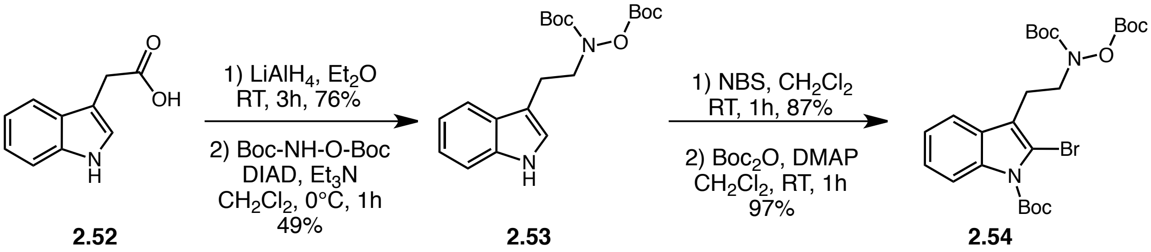
2.7.3 Toward the Synthesis of (±)–10-Desbromoarborescidine A (Lei Zhang Honour's Project)

Honor student Lei Zhang started working on the project in 2008-2009. It was planned that the final cyclization of 10-desbromoarborescidine A would be coming from the reductive amination of alcohol **2.49**. The key intramolecular hydroamination step would provide the first six-membered ring from hydroxylamine **2.50**. The alkene necessary for this reaction would be installed via a palladium-catalyzed cross-coupling, on a brominated indole (Scheme 2.35).



Scheme 2.35 – First retrosynthetic pathway to (±)–10-desbromoarborescidine

The 3-indoleacetic acid was reduced with lithium aluminum hydride and the resulting alcohol was reacted with hydroxylamine bis-Boc under Mitsunobu conditions.[89,72] The resulting hydroxylamine-substituted indole was then brominated at the 2-position and *N*-protected, providing the Sonogashira precursor **2.54**, in four steps from indole-3-acetic acid, with an overall yield of 31% (Scheme 2.36).[90]



Scheme 2.36 – Synthesis of Sonogashira precursor by Lei Zhang

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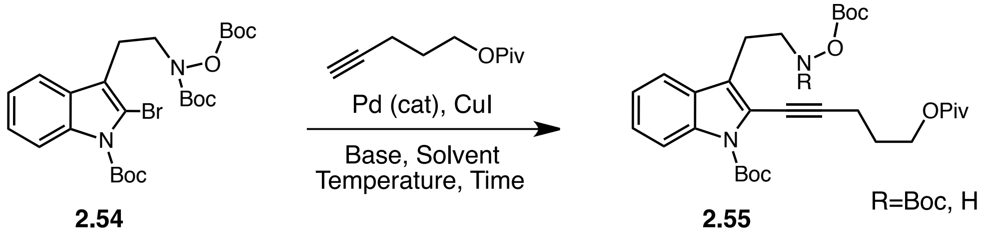
[89] Snyder, H. R.; Pilgrim, F. J. *J. Am. Chem. Soc.* **1948**, *70*, 3770.
[90] Feldman, K. S.; Karatja A. G. *Org. Lett.* **2006**, *8*, 4137.

A Suzuki cross-coupling was first envisioned, but a difficult boronic ester precursor synthesis, combined with the presence in the literature of more consistent Sonogashira procedures on similar substrates, favored the later.[91] Despite multiple attempts, only traces of the Sonogashira product were observed (Table 2.15). In all cases, the hydroxylamine moiety was deprotected. It was therefore hypothesized that, due to the bulky bis-Boc hydroxylamine, the brominated indole was too hindered for the reaction to proceed.

Table 2.15 – Optimization of the Sonogashira reaction by Lei Zhang



2.54 **2.55**

Entry	Pd (cat)	Base	Solvent	Temperature °C	Time h	Yield [a] %
1	$Pd(PPh_3)_4$	*i*-$PrNH_2$	DME	70	0.5	–
2	$(PPh_3)_2PdCl_2$	*t*-$BuNH_2$	–	100	16	10[b]
3	$(PPh_3)_2PdCl_2$	*t*-$BuNH_2$	–	60	12	20[b]

[a] isolated yields [b] deprotected product: R=H

In order to circumvent this problem, the synthesis plan of 10-desbromoarborescidine A was redesigned with inverted Mitsunobu and Sonogashira steps (Scheme 2.37). This way, the palladium-mediated coupling would be performed in the presence of a smaller ester group.

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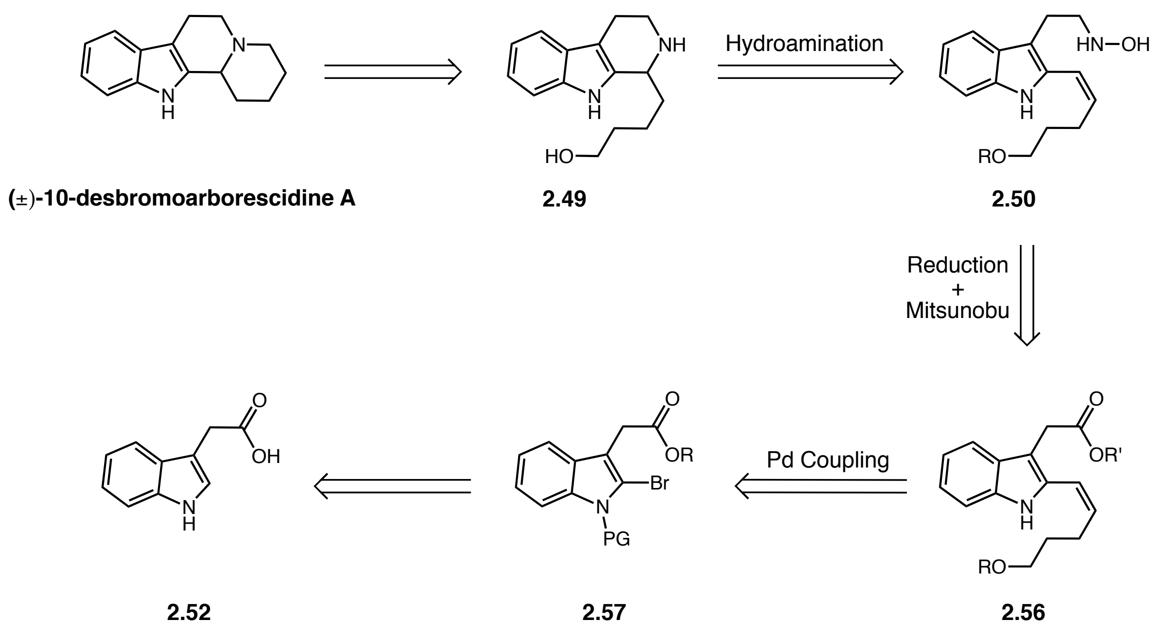
[91] Zhang, L. Toward a Total Synthesis of (±)-10-Desbromoarborescidine A via an Intramolecular Cope-Type Hydroamination Key Step. Honour Thesis, University of Ottawa, ON, 2009.



Scheme 2.37 – Second retrosynthetic pathway to (±)–10-desbromoarborescidine

Both the carboxylic moiety and the nitrogen of the indole needed to be protected before the Mitsunobu reaction. The acid was esterified in acidified *n*-propanol and the indole was Boc-protected after bromination of the 2-position (Scheme 2.38).[92,90] After optimization, the Sonogashira was performed.[93,91] Hydrogenation with palladium on carbon in the presence of a sacrificial alkene afforded the cis-alkene needed for the key step (see section 2.6.2). Due to time constraints, Lei Zhang was forced to leave the synthesis of 10-desbromoarborescidine A after the first attempt at the DIBAL-mediated reduction.[89b]

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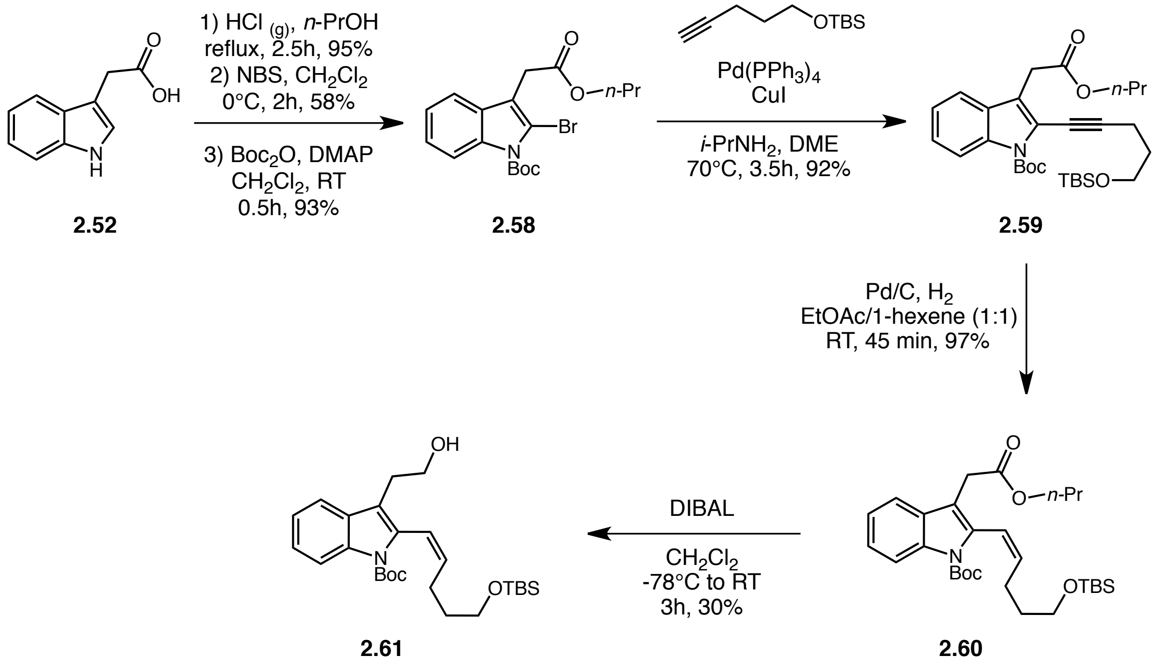
[92] Jackson, R. W. *J. Biol. Chem*. **1930**, *88*, 659.
[93] Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem. Int. Ed*. **2005**, *44*, 3714.



Scheme 2.38 – Efforts toward the synthesis of (±)–10-desbromoarborescidine A by Lei Zhang

2.7.4 Total Synthesis of (±)–10-Desbromoarborescidine A (Jean-François Vincent-Rocan Honour's Project)

2.7.4.1 Synthesis of the Key Step Precursor

Jean-François Vincent-Rocan continued the project a year and a half later. The advanced intermediate **2.59** was quickly synthesized according to the pathway previously designed (Scheme 2.39). The hydrogenation step proved to be scale sensitive, with little product formation on a scale bigger than 500 mg.[94] Alkyne hydrogenation with Lindlar's catalyst was therefore replaced by Rosenmund catalyst (Pd on $BaSO_4$) hydrogenation and the desired alkene was obtained in 96% yield.[95] The ester reduction was performed with $LiAlH_4$ instead

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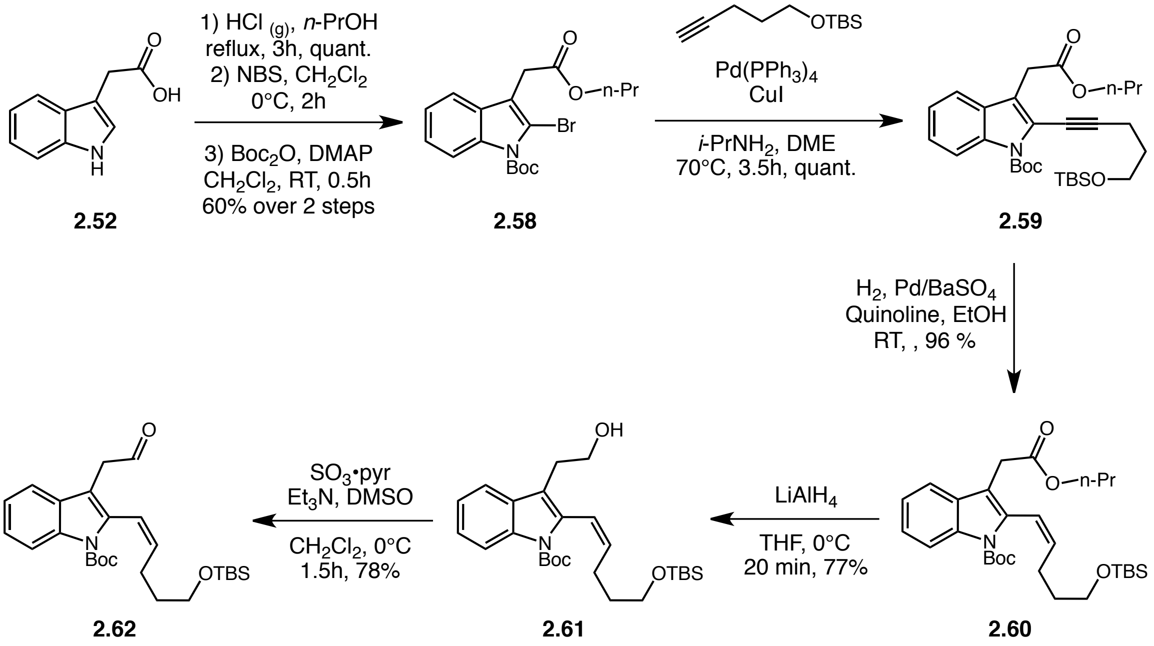
[94] Vincent-Rocan, J-F. Comparison of Different Hydroamination Methods During Synthetic Efforts Towards (±)-10-Desbromoarborescidine A. Honour Thesis, University of Ottawa, ON, 2011.

[95] Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505.

of DIBAL and provided alcohol **2.61** in 77% yield.[96] Oxidation under Parikh-Doering conditions afforded aldehyde **2.62**, which is the common precursor to all bi-functional reagents.[73]



Scheme 2.39 – Synthesis of common aldehyde intermediate by Jean-François Vincent-Rocan

The hydroxylamine moiety was incorporated via reductive amination, instead of using the Mitsunobu reaction (see section 2.4.2), thanks to a newly optimized reduction method in the Beauchemin group. As such, the desired bi-functional reagent was afforded in 61% yield over two steps (Eq. 2.11). An unexpected deprotection of the alcohol was also observed under the reducing conditions. This shortened the synthesis by one step. Following a simple procedure, the hydrazide-substituted precursor was synthesized in two steps from common aldehyde **2.62** (Eq. 2.12). In addition, the bis-trifluoromethylbenzoyl hydrazide chosen for the key step comparison came from recent discoveries in the Beauchemin group.[88b] It has

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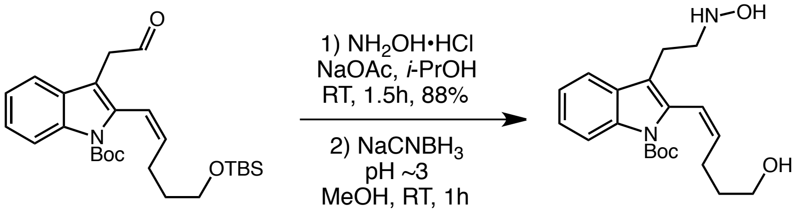
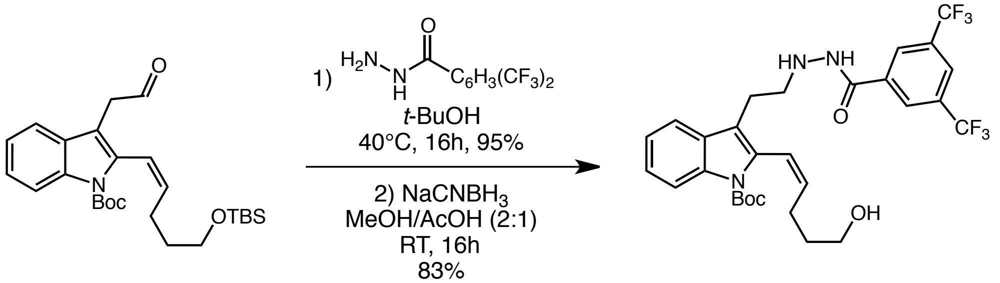
[96] Sato, S.;Shibuya, M.; Kanoh, N.; Iwabuchi Y. *Chem. Commun.* **2009**, *45*, 6264.

shown increased reactivity in both intra and intermolecular hydrohydrazidation over the unsubstituted benzoic hydrazide.



2.62 **2.63**

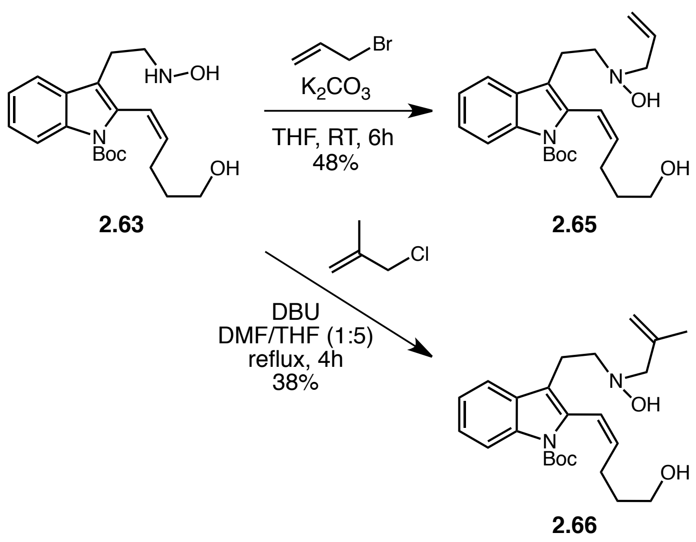
(2.11)



2.62 **2.64**

(2.12)

Synthesis of the CHMR sequence precursors was performed as previously reported (see Sections 2.4.5.3 and 2.4.5.5) and afforded the allylated and methallylated substrates in 48% and 38% yield, respectively.



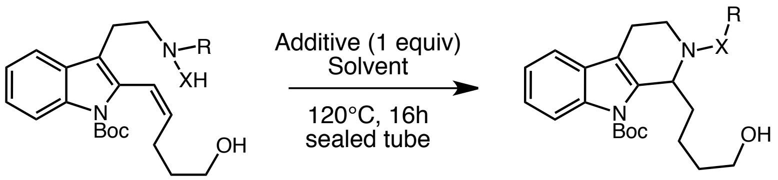
Scheme 2.40 – Formation of CHMR sequence precursors in the synthesis of (±)-10-desbromoarborescidine A by Jean-François Vincent-Rocan

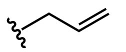
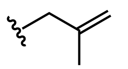
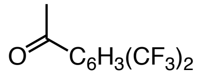
2.7.4.2 Key Step Comparison Studies

Comparative experiments of the key step were attempted for hydroxylamine moieties with the free amine and the allylated and methallylated variants (Table 2.16). Results obtained were consistent with the observations made in the synthesis of coniine and *N*-norreticuline. The reaction sequence facilitated the hydroamination reaction and provided higher yields of the desired product (Table 2.16, entries 2 vs. 9, 10). As noted in the synthesis of coniine, the methallylated substituent provided a smaller yield of cyclized product than its allylated counterpart, which could be due to steric hindrance preventing the Meisenheimer rearrangement from occurring easily (see Section 2.4.5.5). This result is in contrast to what was observed in the synthesis of *N*-norreticuline, where the methallylated substrate provided the best results. The instability of the allylated precursor in the synthesis of *N*-norreticuline, both at room temperature and under the reaction conditions, could explain these discrepancies (see section 2.6.3).

Microwave irradiation of the free hydroxylamines provided increased yields of the Cope-type hydroamination product over the sealed tube conditions, both in the presence and absence of the $NaCNBH_3$ additive (Table 2.16, entries 3, 4 vs. 5, 6). As previously demonstrated in the Beauchemin group, the use of *t*-BuOH as solvent minimized degradation and provided the desired product in yields as high as 87%.[25] The use of structurally similar *t*-amyl alcohol provided equivalent results under microwave irradiation (Table 2.16, entries 6 vs. 8). Despite the use of optimized conditions for hydrohydrazidation, the bis-trifluorobenzoyl hydrazide substrate failed to provide the cyclization product *en route* to 10-desbromoarborescidine. Only partial recovery of the starting material was possible (Table 2.16, entry 11).

Table 2.16 – Key hydroamination optimization by Jean-François Vincent-Rocan



Entry	Substrate	X	R	Solvent	Additive	Product	Yield [a] %
1	**2.63**	O	H	*n*-PrOH	–	**2.67**	0
2	**2.63**		H	*n*-PrOH	$NaCNBH_3$	**2.67**	40
3	**2.63**		H	*t*-BuOH	–	**2.67**	48
4	**2.63**		H	*t*-BuOH	$NaCNBH_3$	**2.67**	77
5	**2.63**		H	*t*-BuOH[b]	–	**2.67**	70
6	**2.63**		H	*t*-BuOH[c]	$NaCNBH_3$	**2.67**	87
7	**2.63**		H	*t*-AmOH	–	**2.67**	44
8	**2.63**		H	*t*-AmOH[b]	$NaCNBH_3$	**2.67**	80
9	**2.65**	O		benzene	H_2O[d]	**2.68**	64
10	**2.66**			benzene	H_2O[d]	**2.69**	53
11	**2.64**	N 	H	trifluorotoluene[e]	–	**2.70**	–[f]

[a] isolated yields [b] μW irradiation, 4h [c] μW irradiation, 16h [d] 10 equiv [e] 160°C [f] 66% recovered s. mat.

2.7.4.3 Finals Steps in the Synthesis of (±)–10-Desbromoarborescidine A

The indole of the cyclized hydroxylamine **2.67** was deprotected under acidic conditions. The N-O bond was then cleaved using zinc dust to afford the crude amine **2.49** in 73% yield for the one-pot procedure. The primary alcohol was then replaced by a chloride leaving group and the cyclization was effected under basic conditions, providing (±)–10-desbromoarborescidine A in a total of 13 steps and 8% overall yield (Scheme 2.41).[97]

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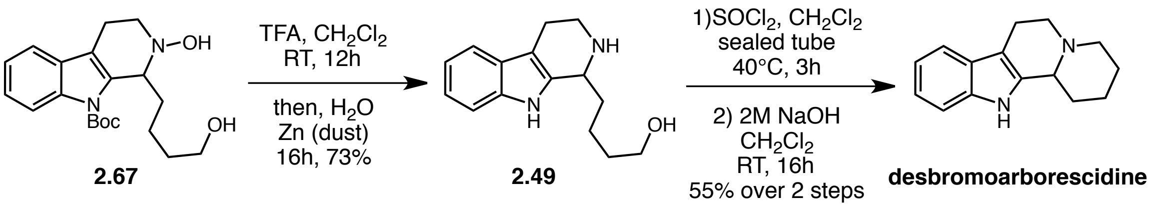
[97] Louafi, F.; Moreau, J.; Shahane, S.; Golhen, S.; Roisnel, T.; Sinbandhit, S.; Hurvois, J-P. *J. Org. Chem.* **2011**, *76*, 9720.



Scheme 2.41 – Final steps in the synthesis of (±)–10- desbromoarborescidine A by Jean-François Vincent-Rocan

2.8 Conclusion

The elaboration of the novel Cope-type hydroamination-Meisenheimer rearrangement (CHMR) sequence has allowed for the cyclization of five-membered as well as difficult six-membered systems (see Sections 2.4.5.6 & 2.4.5.4). Moreover, the optimization of this new method with both allyl or methallyl substituent has increased the efficiency of such cyclizations when compared to the Cope-type hydroamination reaction alone and helped overcome the main limitations associated with it, such as unfavorable thermodynamics and thermal instability of the products and starting materials (see section 2.4.5.5).

Furthermore, the successful application of the CHMR sequence in the synthesis of the coniine, *N*-norreticuline and 10-desbromoarborescidine A alkaloids has proven the efficiency and applicability of the method in the synthesis of elaborate piperidine-containing natural products (see Sections 2.4.6, 2.6 & 2.7). At the same time, these total syntheses have allowed for systematic comparison of various hydroamination methods, defining the limits of the methodology (see Section 2.7.4.2).

3 Efforts Towards the Total Synthesis of Manzamine A Using Aminodienes Containing a bi-Functional Moiety

3.1 Isolation and Biological Activity of Manzamine A

Manzamine A was the first of a novel alkaloid family, which was isolated by Higa and coworkers in 1986 from the marine sponge *Ircina* found off the coast of Okinawa.[98] They successfully elucidated its structure and absolute configuration by X-ray crystallography. Shortly after, the Makamura group isolated manzamine A from the *Pellina* marine sponge and, unaware of the Higa group discovery, named it Keramamine A.[99] Manzamine A is considered to be part of the greater β-carboline family as its skeleton contains an indole fused pyridine moiety. At the time of its discovery, the structure of manzamine A sparked chemists' interest with its five chiral centers and a core made of five fused rings (Figure 3.1). Synthetically challenging, the molecule also contains a tertiary alcohol and two macrocycles. Manzamine A shows important biological activity as exemplified by its potent antimalarial and cytotoxic properties. It shows antileukemial activity against P388 mouse cells with an IC_{50} of 0.07 ug/mL.[98] As an antimalarial agent, it prolongs the life of infected mice 15-fold, leading to recovery. As such, it proved more efficient than the current leading human antimalarial drugs, while showing lower levels of toxicity.[100]

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[98] Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986***, 108,* 6404.

[99] Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y. *Tetrahedron Lett.* **1987**, *28,* 621.

[100] Ang, K. K. H.; Holmes, M. J.; Higa, T.; Hamann, M. T.; Kara, U. A. K. *Antimicrob Agents Chemother.* **2000**, *44*, 1645.

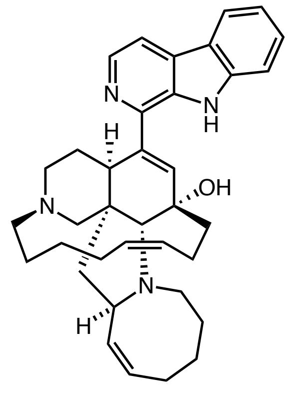

Figure 3.1 – Manzamine A

3.2 Biosynthesis of Manzamine A

It was suggested by Baldwin and Whitehead that manzamine B originates from two C_{10} symmetrical dialdehydes, two acrolein molecules and ammonia. After condensation of these building blocks, an intramolecular Diels-Alder reaction would occur to form the core of the molecule. Condensation with tryptophan, followed by aromatization, would afford manzamine B (Scheme 3.1).[101]

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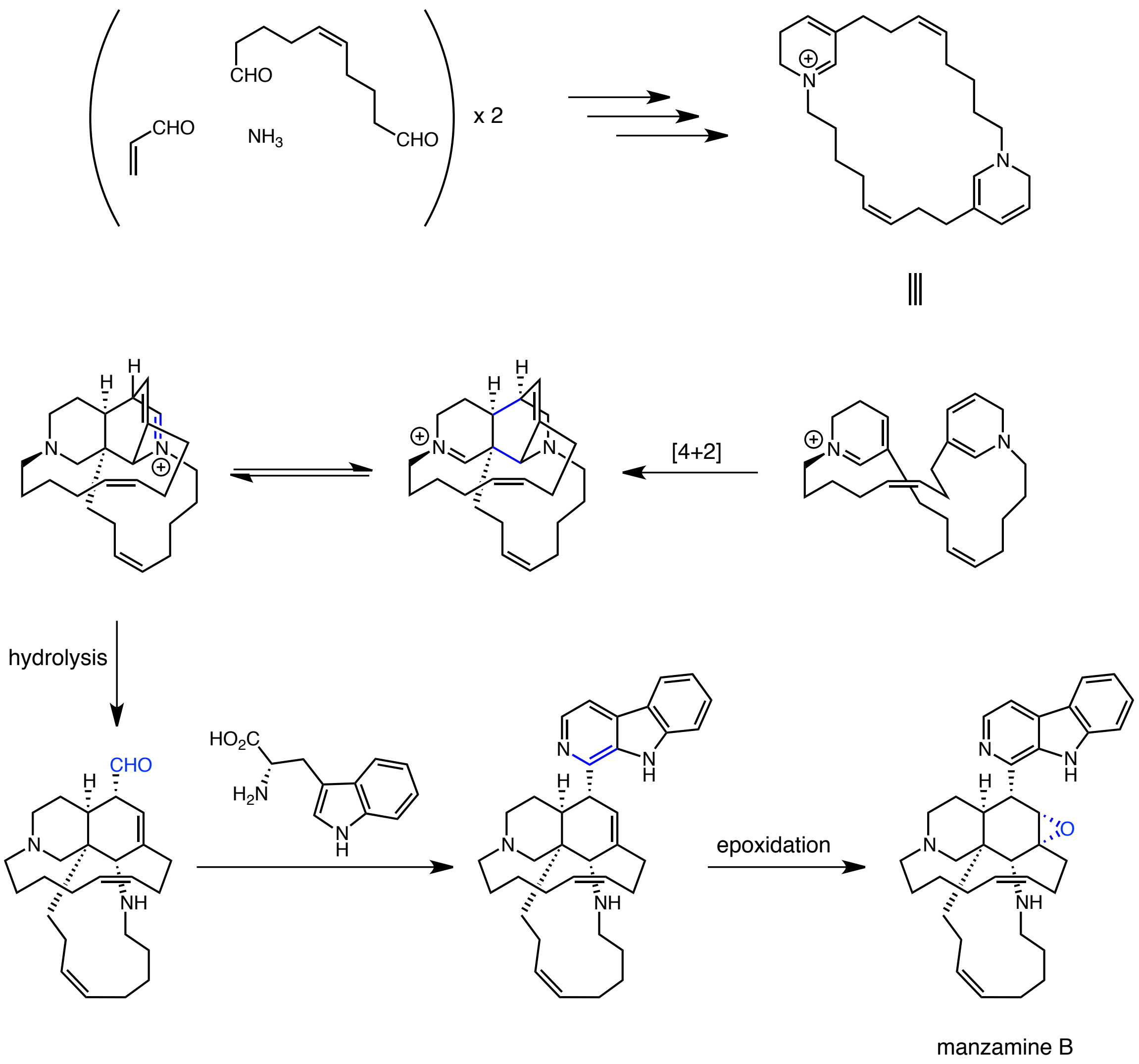
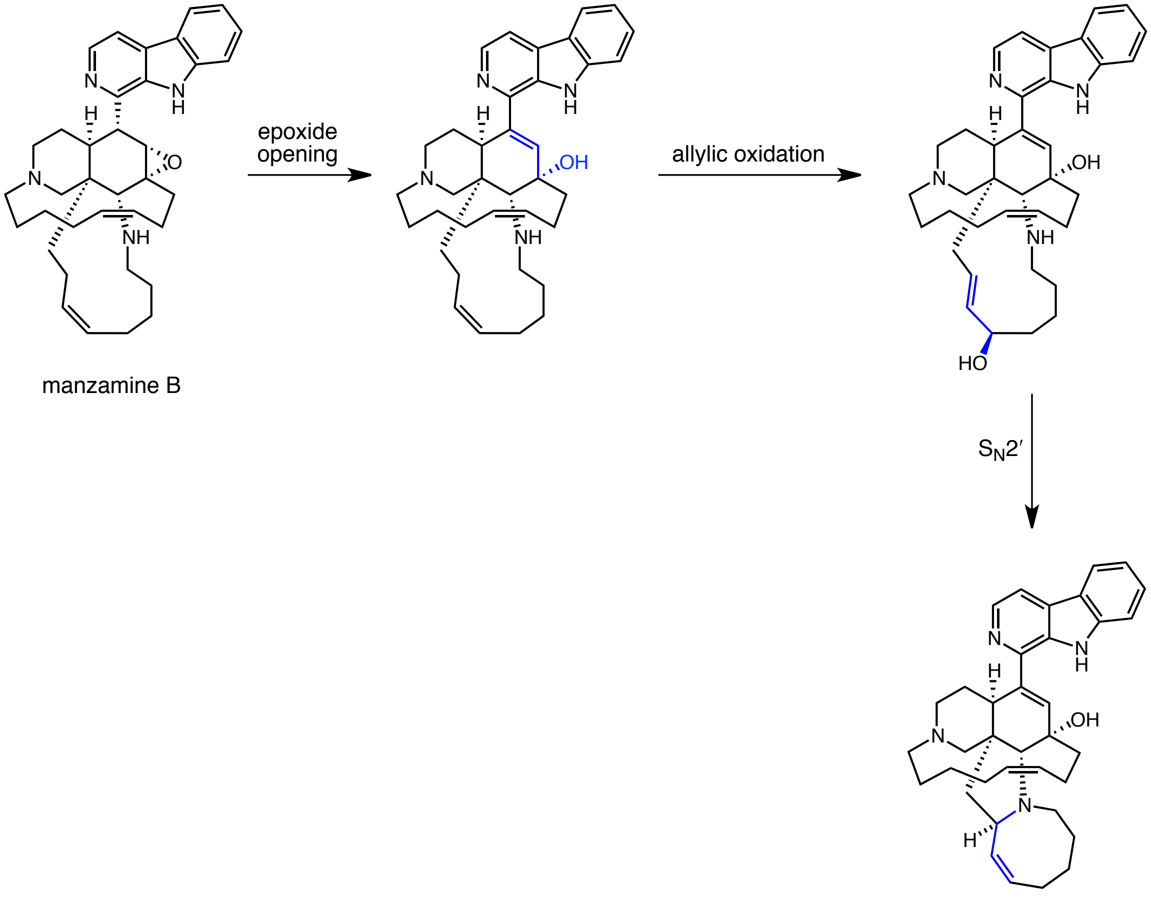
[101] Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059.



Scheme 3.1 – Proposed biosynthetic pathway of manzamine B

Manzamine A is thought to be obtained from manzamine B via an eliminative epoxide opening, followed by an allylic oxidation and rearrangement. Final trans-annular ring closure forms the [5,8] fused rings (Scheme 3.2).



Scheme 3.2 – Proposed biosynthetic pathway of manzamine A from manzamine B

3.3 *Previous Total Syntheses and Efforts Towards Manzamine A*

3.3.1 Total Synthesis of Manzamine A by the Winkler and Axten Group

Winkler and Axten presented the first total synthesis of manzamine A twelve years after its discovery. Their key step consisted of a [2+2] intramolecular photocycloaddition, followed by a retro-Mannich fragmentation and Mannich closure forming one of the two six-membered rings portion of the molecule (Scheme 3.3).[102]

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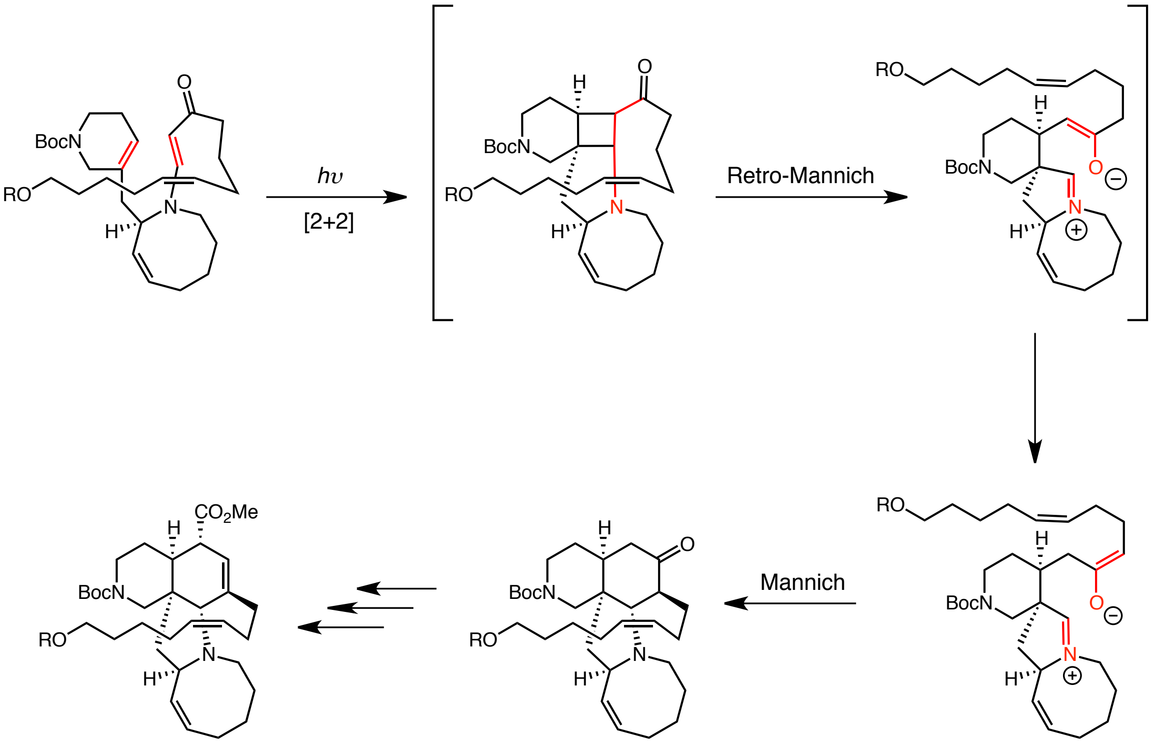
[102] Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998***, 120,* 6425.



Scheme 3.3 – Key steps of the synthesis of manzamine A by the Winkler and Axten group

The tertiary hydroxy group was introduced with a selenide oxidation-elimination sequence or via an epoxidation followed by opening in basic media (Scheme 3.4). The thirteen-membered ring was then closed via nucleophilic substitution. Conversion of the methyl ester to an aldehyde led to ircinal A, which synthesis was also a premiere. Ircinal A was then converted to manzamine A via a Pictet-Spengler reaction, followed by DDQ oxidation, as previously reported by Kobayashi and coworkers, which afforded the desired natural product in a total of 31 steps.[103]

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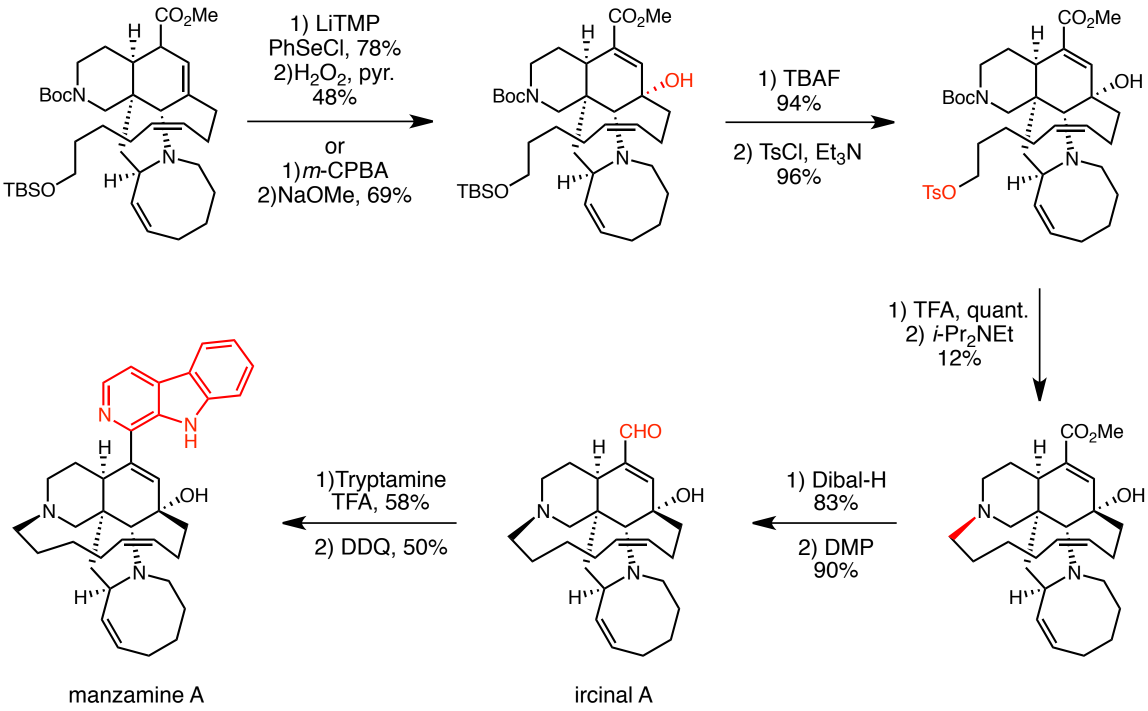
[103] Kobayashi, J.; Sasaki, T.; Ishibashi, M.; Kikuchi, Y.; Shigemori, H.; Kondo, K. *J. Org. Chem.* **1992**, *57*, 2480.



Scheme 3.4 – Final steps leading to manzamine A by the Winkler and Axten group

3.3.2 Total Synthesis of Manzamine A by the Martin Group

The Martin group published the second total synthesis of manzamine A in 1999.[104] The core of the alkaloid was achieved using an intramolecular Diels-Alder reaction building the central six membered ring in one step with correct stereochemistry. The eight and thirteen-membered rings were then sequentially closed via RCM and ircinal A was also obtained as a common intermediate. The final steps leading to manzamine A were executed according to the procedure developed by the Kobayashi group, affording the alkaloid in 21 steps (Scheme 3.5).[103]

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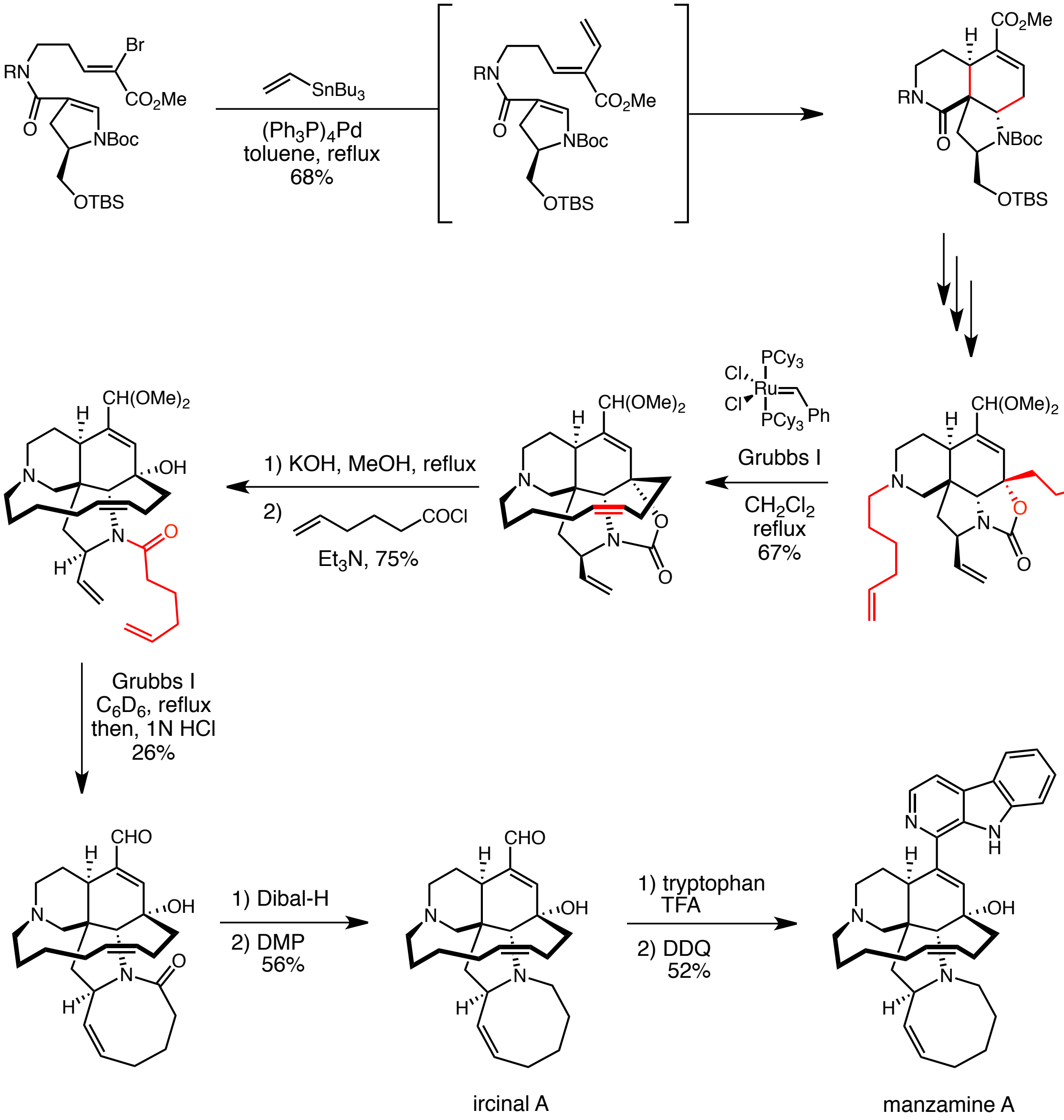
[104] a) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. b) Humphrey, J. M.; Liao, Y. ; Ali, A.; Rein, T.; Wong, Y-L.; Chen, H-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002***, 124,* 8584.



Scheme 3.5 – Key steps of the synthesis of manzamine A by the Martin group

3.3.3 Total Synthesis of Manzamine A by the Fukuyama Group

The Fukuyama group is the most recent group to have completed the total synthesis of manzamine A.[105] The pathway they chose involved a diastereoselective intermolecular Diels-Alder reaction, followed by functional groups interconversion in order to build a strained fifteen-membered ring. Alpha-allylation of the enone was followed by epoxidation. A [3,3]-

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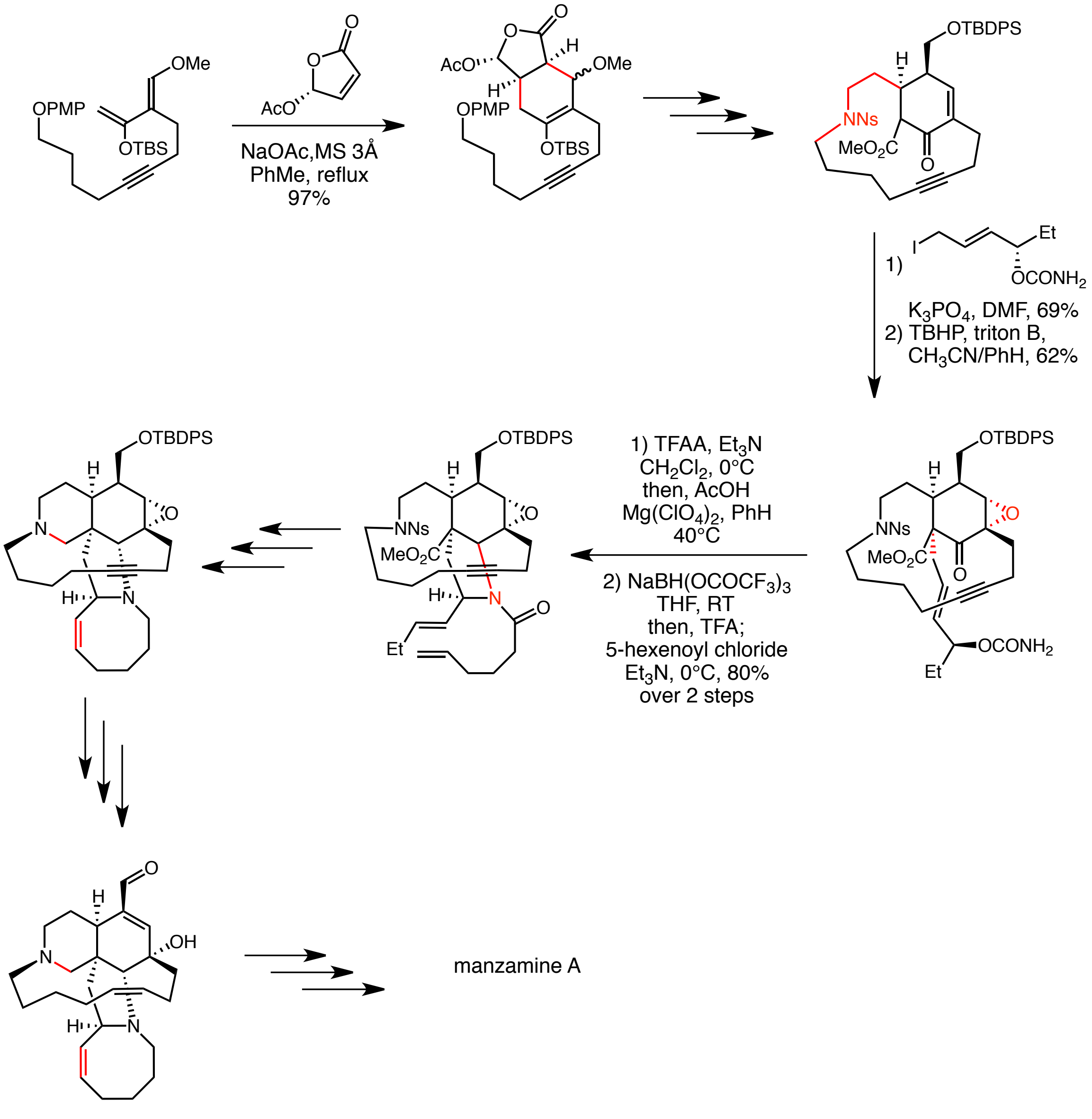
[105] Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132,* 10233.

rearrangement under dehydrating conditions allowed for closure of the five-membered ring. Reductive amination formed the remaining six-membered ring, while a RCM neatly closed the eight-membered ring in the presence of an alkyne. Selective cis-hydrogenation of this alkyne was followed by primary alcohol deprotection and oxidation, under which conditions a desired epoxide opening was observed, affording ircinal A (Scheme 3.6). The advanced intermediate was then converted into manzamine A under conditions previously reported for a total of 38 steps (see section 3.3.2).



ircinal A

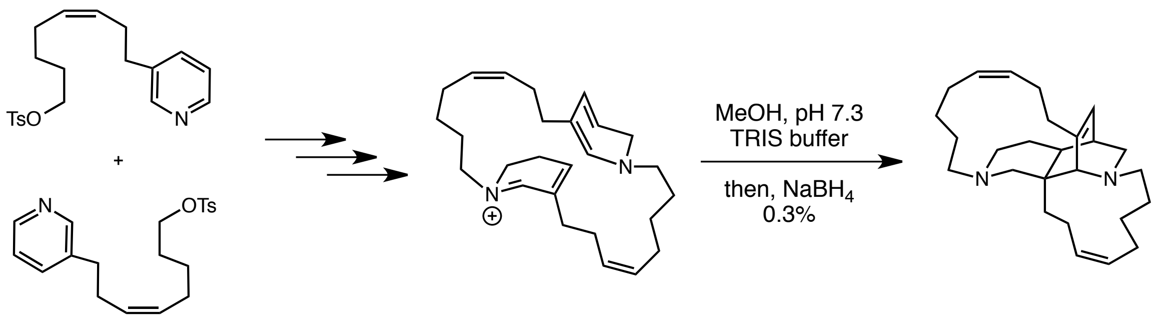
Scheme 3.6 – Key steps of the synthesis of manzamine A by the Fukuyama group

3.3.4 Previous Efforts Towards the Synthesis of Manzamine A

Even though few total syntheses of manzamine A have been reported to date, many groups have attempted the journey and published efforts towards the tricyclic core of the alkaloid. Adding to the methods mentioned above, biomimetic approaches, intra- and intermolecular Diels-Alder, radical reactions, ionic cyclizations, [2+3] cycloadditions, Pauson-Khand and enyne methatheses have been used.[106] Of all these methods, the Diels-Alder reaction is the most encountered.

3.3.4.1 Biomimetic Methods

Biomimetic approaches have been developed by both the Baldwin[107] and Marazano[108] groups. These routes involve a Diels-Alder reaction between a dihydropyridine (DHP) and the alkene of an α,β-unsaturated iminium (Scheme 3.7). Both approaches have been applied to the synthesis of keramaphidin B, which is considered to be formed via the same biological pathway as manzamine A (see section 3.2).



keramaphidin B

Scheme 3.7 – Example of a biomimetic synthesis of keramaphidin B by the Baldwin group

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[106] For reviews on the subject: a) Nishida, A.; Nagata, T.; Nakagawa, M. *Top Heterocycl. Chem.* **2006***, 5,* 255. b) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201.

[107] a) Baldwin, J. E.; Claridge, T. D. W.; Heupel, F. A.; Whitehead, R. C. *Tetrahedron Lett.* **1994***, 35,* 7829. b) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Smrckova, S.; Whitehead, R. C. *Tetrahedron Lett.* **1996***, 37,* 6919. c) Baldwin, J. E.; Bischoff, L.; Claridge,T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. C. *Tetrahedron* **1997***, 53,* 2271. d) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661.

[108] a) Gil, L.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36, 707.* b) Gil, L.; Baucherel, X.; Martin, M-T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995***, 36*, 6231.

3.3.4.2 Other Diels-Alder Approaches

The inter- and intramolecular Diels-Alder reactions have been extensively used in the synthesis of the manzamine A core. Examples of Diels-Alder disconnections used by the Simpkins,[109] Nalagawa,[110] Marko,[111] Pandit,[112] Langlois[113] and Marazano[114] groups are shown below (Scheme 3.8).

---

[109] a) de Oliviera Imbroisi, D.; Simpkins, N. S. *Tetrahedron Let.* **1989**, *30*, 4309. b) de Oliviera Imbroisi, D.; Simpkins, N. S. *J. Chem. Soc. Perkin Trans 1* **1991**, 1815.

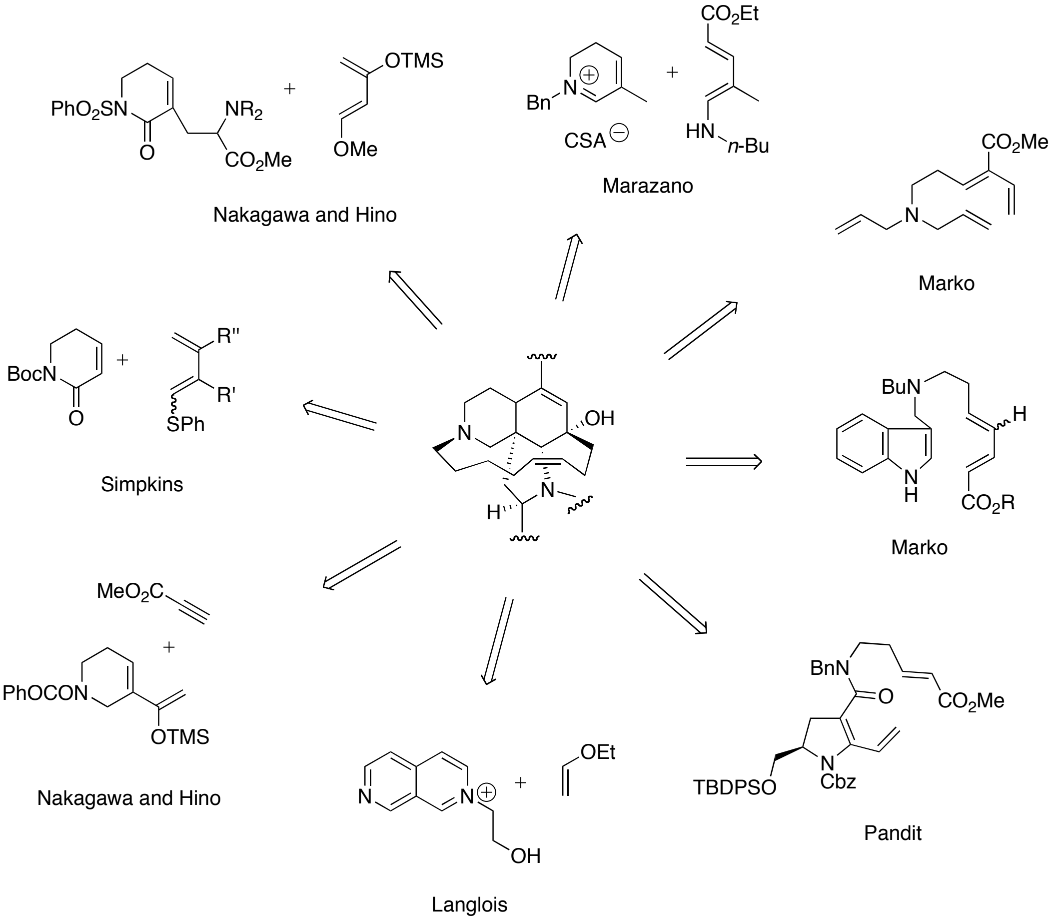
[110] a) Nakagawa, M. *J. Heterocyclic Chem.* **2000**, *37*, 567. b) Nakagawa, M.; Torisawa, Y.; Hino, T. *Heterocycles* **1994**, *38*, 1609.

[111] a) Chesney, A.; Marko, I. E. *Synth. Commun.* **1990**, *20*, 3167. b) Chesney, A.; Marko, I. E. *Synlett* **1992**, 275. c) Marko, I. E.; Southern, J. M.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 4657.

[112] a) Brands, K. M. J.; Pandit, U. K. *Tetrahedron Lett.* **1989**, *30*, 1423. b) Brands, K. M. J.; Pandit, U. K., *Heterocycles* **1990**, *30*, 257. c) Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 2005. d) Borer, B.C.; Deerenberg, S.; Bierlugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35,* 3191. e) Pandit, U. K.; Borer, B. C.; Bierlugel, H. *Pure & Appl. Chem.* **1996**, *68,* 659. f) Pandit, U. K. *J. Heterocyclic Chem.* **1994**, *31*, 615. g) Pandit, U. K. Borer, B. C.; Bierlugel, H.; Deerenberg, S. *Pure & Appl. Chem.* **1994**, *66,* 2131.

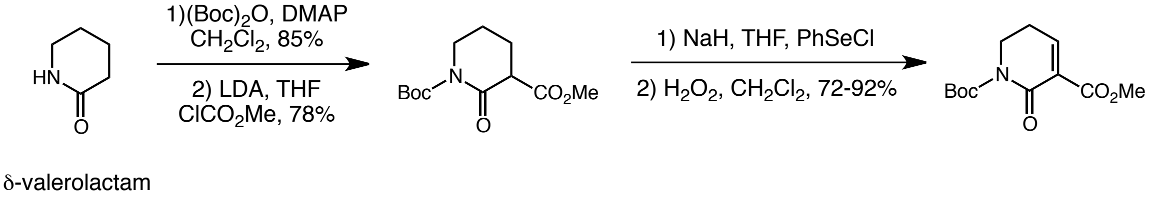
[113] a) Magnier, E.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 9475. b) Magnier, E.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39,* 837. c) Sageot, O.; Monteux, D.; Langlois, Y.; Riche, C.; Chiaroni, A. *Tetrahedron Lett*. **1996**, *37*, 7019.

[114] Herderman, M.; Al-Mourabit, A.; Martin, M-T.; Marazano, C. *J. Org. Chem.* **2002**, *67,* 1890.

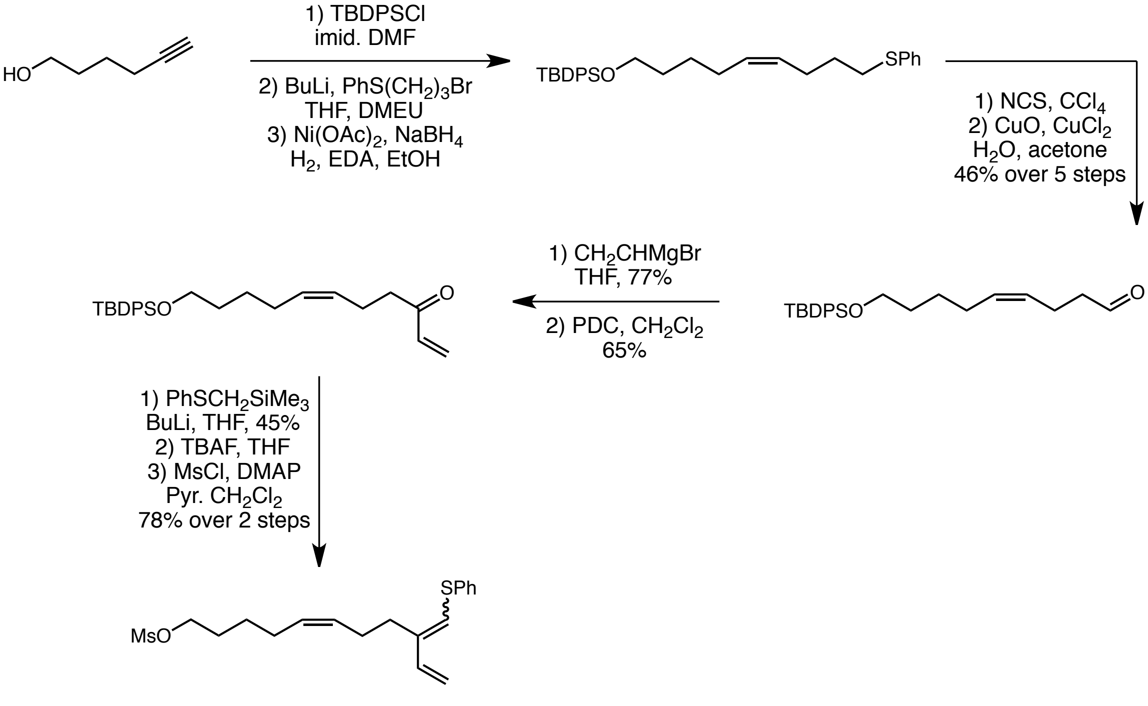


Scheme 3.8 – Other Diels-Alder approaches to the manzamine A core

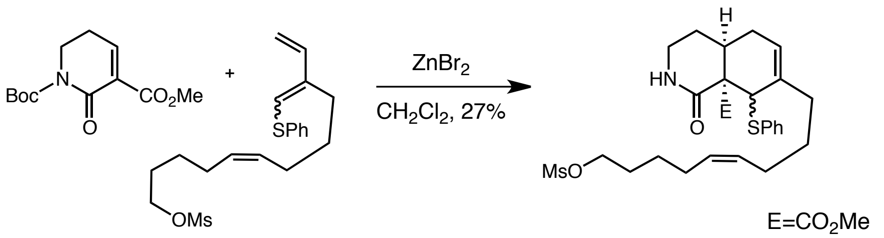
Three groups approached the core of manzamine A with a disconnection similar to the one presented in this thesis (see Section 3.4). The Simpkins group approached the core of manzamine A via an intermolecular Diels-Alder using an α,β-unsaturated lactam and 2-alkenyl-1-thiophenyl butadiene.[109] δ-valerolactam was first protected with a *tert*-butyl carbamate (Boc) group, then acylated at the α position. The dienophile was obtained via selenium-oxide elimination (Scheme 3.9). The diene was obtained by alkylation of a terminal alkyne followed by hydrogenation in presence of nickel boride to afford the cis-alkene. Transformation of the thiophenyl to an aldehyde was performed by reaction with NCS followed by oxidation. Addition of vinylmagnesium bromide and oxidation of the resulting alcohol provided the desired ketone. A Peterson-type olefination, followed by protecting group interconversion afforded the thiophenyldiene in 16% overall yield (Scheme 3.10). The Diels-Alder reaction was performed in the presence of $ZnBr_2$ and provided the desired product in 27% yield (Eq. 3.1).



Scheme 3.9 – Simpkins group dienophile synthesis

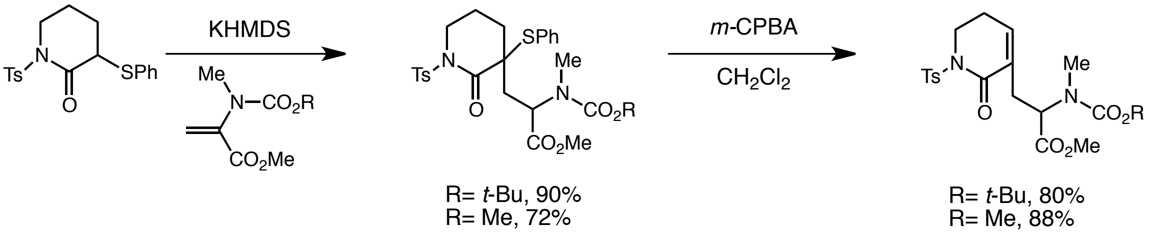


Scheme 3.10 – Simpkins group diene synthesis



(3.1)

The Nakagawa and Hino's Diels-Alder strategy for the synthesis of the core of manzamine A also involved the use of an α,β-unsaturated lactam.[115] The dienophile was obtained from a thiophenyl α–substituted lactam, which was alkylated with a Michael acceptor. Oxidation of the thiophenyl, followed by elimination, afforded the desired dienophile in 63%-72% yield, depending of the nitrogen substitution of the Michael acceptor (Scheme 3.11). The dienophile was then reacted with known Danishefsky's diene and, after protecting groups interconvertions, afforded the core of manzamine A in 60% yield over four steps (Scheme 3.12). The research group later developed an enantioselective version of their Diels-Alder strategy using L-serine-derived Garner aldehyde as a chiral nitrogen source.[116]



Scheme 3.11 – Nakagawa group dienophile synthesis

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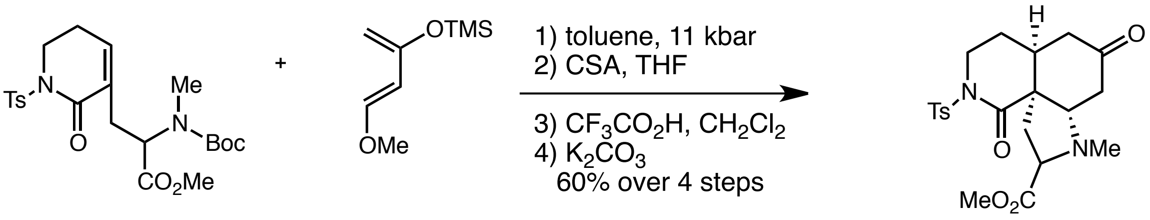
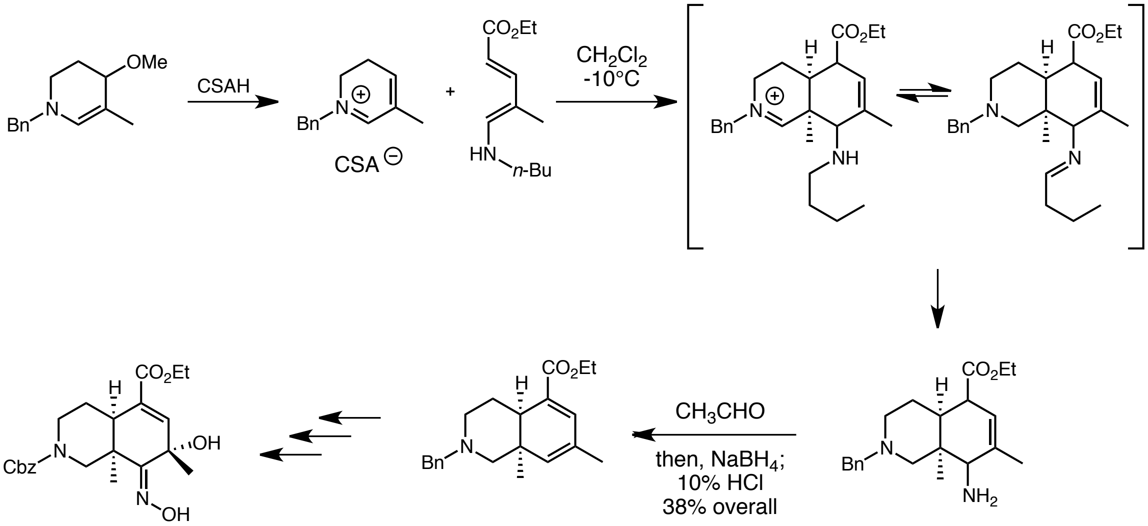
[115] Torisawa, Y.; Nakagawa, M.; Arai, H.; Lai, Z.; Hino, T.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1990**, *31*, 3195.

[116] Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 113.



Scheme 3.12 – Approach of the Nakagawa group to the core of manzamine A

The Marazano group has developed a route involving the cycloaddition of a 1-amino-1,3-diene with a cyclic iminium dienophile. The Diels-Alder product then underwent a redox process (1,5-hydride shift), affording a primary amine upon hydrolysis. Condensation with acetaldehyde, followed by reduction and acidic treatment, installed a diene alpha to the ester. Further modifications provided an advanced intermediate to the core of manzamine A (Scheme 3.13).[114,117]



Scheme 3.13 – Efforts towards the core of manzamine A by the Marazano group

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[117] Jakubowicz, K.; Abdeljelil, B.; Herdemann, M.; Martin, M-T.; Gateau-Olesker, A.; Mourabit, A. A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381.

3.4 Project Objectives

With a Cope-type hydroamination-Meisenheimer rearrangement (CHMR) sequence optimized and successfully employed in the synthesis of various small alkaloids (see Chapter 2), the application of the hydroamination reaction to the synthesis of a more complex molecule was envisioned.[118] Manzamine A was chosen as its structure offered the perfect level of complexity and, to that date, only two total syntheses had been reported. It was envisioned that manzamine A could be obtained from ircinal A via previously reported conditions (see Section 3.3.1). Ircinal A could come from the opening of an epoxide by alpha-elimination of oxidized intermediate **3.1** (Scheme 3.14). The thirteen and eight-membered rings could be formed via RCM of alkenyl substituents and the chiral epoxide could be installed via a nitrogen-directed epoxidation reaction. The core of manzamine A could come from a key one-pot intermolecular Diels-Alder reaction followed by an intramolecular allene hydroamination reaction between an α,β-unsaturated lactam and a novel bi-functional moiety-containing aminodiene. Effecting the hydroamination reaction onto an allene substrate should produce the desired five-membered ring of manzamine A, while still providing the unsaturation necessary for the following RCM step (Scheme 3.14, intermediate **3.3**).[25] Such disconnections could reduce the total number of steps from the shortest total synthesis of manzamine A by up to five steps.[102] The elaboration of the novel key step involves the elaboration of a new type of bi-functional moiety-containing aminodienes (see Section 3.7) and future application of the newly developed method to the synthesis of a variety of [5,6] and [6,6] bicyclic systems.

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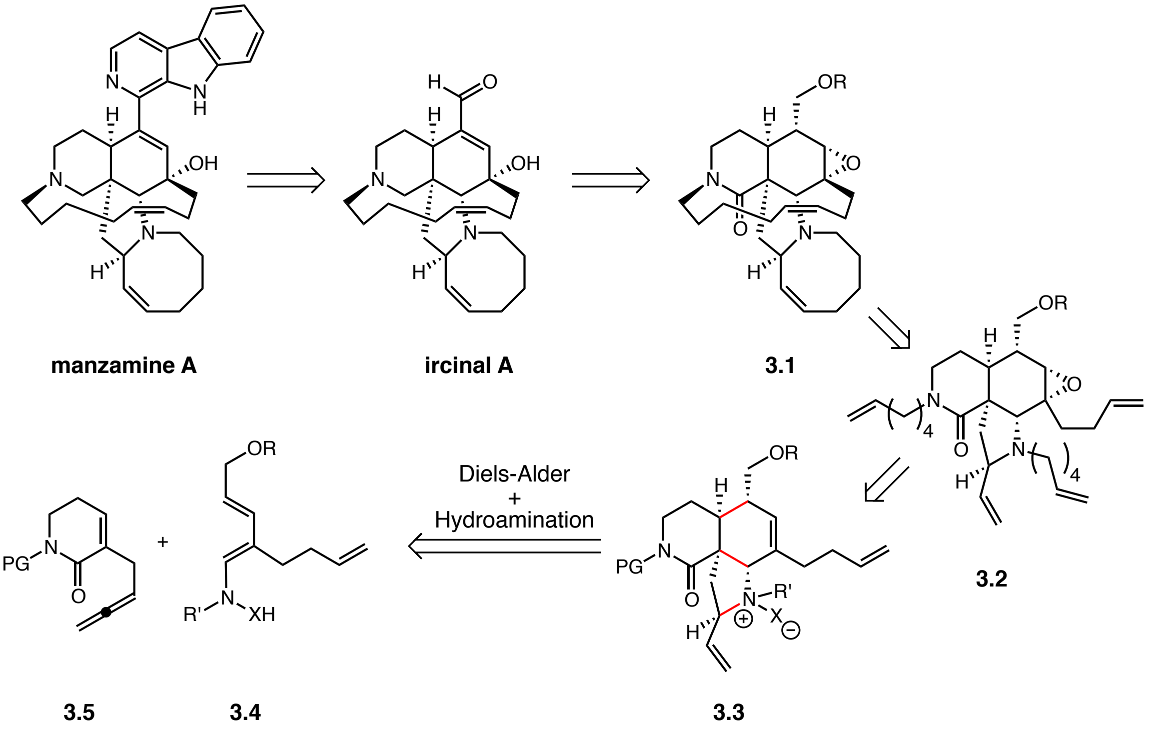
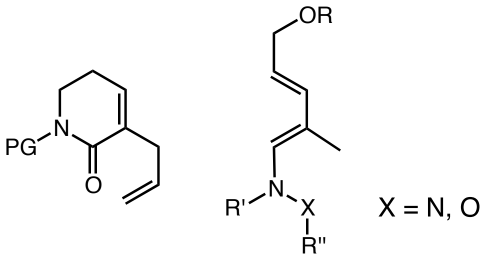
[118] The term hydroamination is used in this section as a simplification for the possible use of either Cope-type hydroamination or hydrohydrazidation.



Scheme 3.14 – Proposed retrosynthesis of manzamine A

3.4.1 Model Substrates

In order to explore the selectivity of the Diels-Alder and hydroamination reactions before embarking on the total synthesis, a model system was designed. An allyl group replaced the allene substituent of the dienophile as it allowed for an easier synthesis. It would also keep the unsaturation necessary for the subsequent hydroamination reaction. An electron-withdrawing protecting group on the nitrogen of lactam **3.6** would minimize electron donation into the carbonyl of the dienophile, which should maintain a high reactivity for the normal-electron-demand Diels-Alder reaction (Figure 3.2). The model 1-amino-1,3-diene would keep simplified alpha and gamma substitutions in order to take into account any possible steric interactions. Furthermore, the use of an aminodiene that contain a bi-functional reagent, such as a hydroxylamine or hydrazide, is planned to allow the hydroamination reaction of the key step (Figure 3.2).

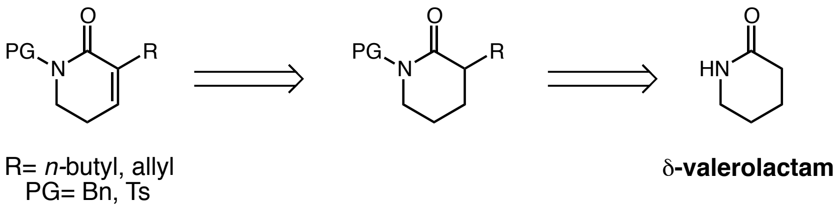


3.6 **3.7**

Figure 3.2 – Model substrates

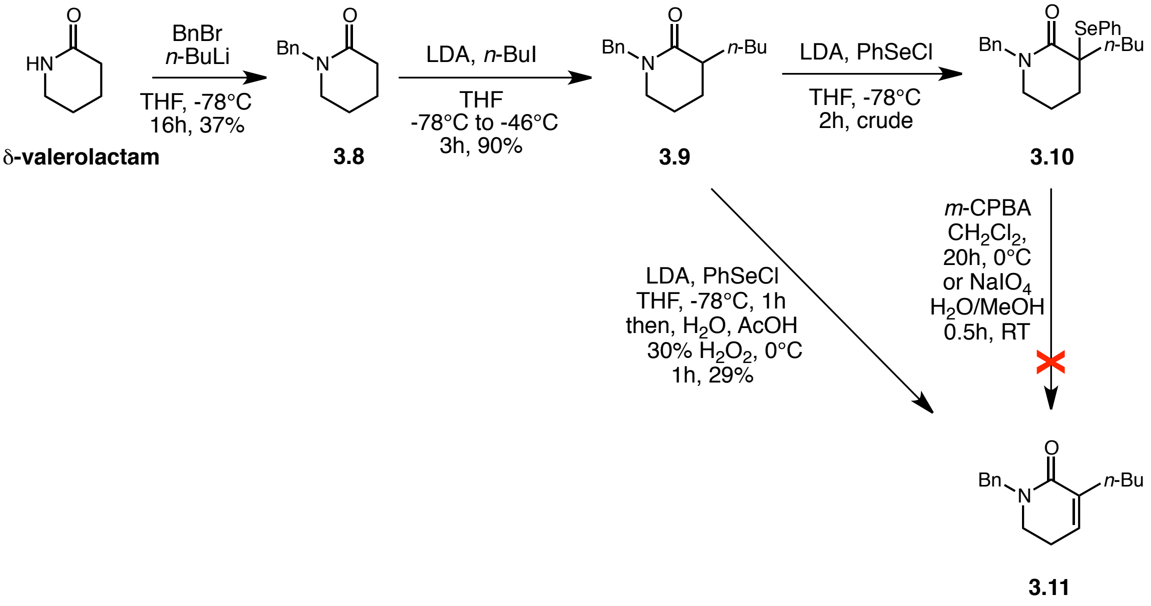
3.5 Synthesis of the Dienophile

It was thought that the unsaturation providing the α,β-unsaturated lactam could be introduced via selenoxide elimination of an alpha-alkylated delta-valerolactam (Scheme 3.15). In the initial planning of the model dienophile, simple alkyl substituents were chosen as protecting group and replacement for the allene substituent. They would later be replaced respectively by an electron-withdrawing protecting group and by an allyl substituent with the goal of attempting the key sequential Diels-Alder-hydroamination reaction as a one-pot procedure (see Section 3.4.1).



Scheme 3.15 – Proposed dienophile synthesis

δ-Valerolactam was first protected with a benzyl group,[119] then a *n*-butyl group was installed alpha to the carbonyl (Scheme 3.16).[120] The *n*-butyl substituent was chosen as it contained the same number of carbons as the desired allene substituent of the dienophile for the full synthesis. Intermediate **3.9** was then treated with phenylselenyl chloride under basic conditions to obtain selenated product **3.10**.[121] Treatment of the crude reaction mixture with oxidizing reagents *m*-CPBA or $NaIO_4$ failed to provide the desired α,β-unsaturated lactam as only degradation was observed.[121c,122] A one-pot procedure was therefore attempted and afforded the desired product in a modest 29% yield.[121b]



Scheme 3.16 – Synthesis of dienophile via phenylselenoxide elimination

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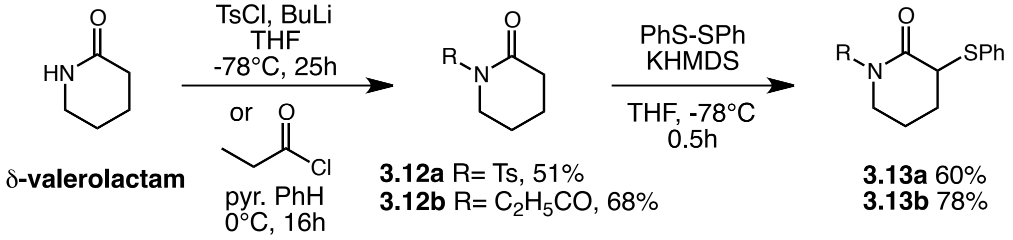
[119] Cossy, J.; de Filippis, A.; Pardo, D. G. *Org. Lett.* **2003**, *5*, 3037.

[120] Dieter, K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180.

[121] a) Zoretic, P. A.; Soja, P. *J. Org. Chem.* **1976**, *41*, 3587. b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. c) Ficini, J.; Guingant, A.; D'Angelo, J. *J. Am. Chem. Soc.* **1979**, *101*, 1318.

[122] a) Diez, A.; Castells, J.; Forns, P.; Rubiralta, M.; Grierson, D. S.; Husson, H-P.; Solans, X.; Font-Bardía, M. *Tetrahedron* **1994**, *50*, 6585. b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

In concordance with the low yields observed for the selenation/elimination reaction, a publication by the Nakagawa group confirmed that α-alkylated lactams did not easily undergo such reactions due to the steric hindrance associated with the selenium atom. Furthermore, a tertiary alkylselenium could easily cleave to form a stabilized tertiary radical alpha to the carbonyl, leading to degradation of the molecule. Sulfur was considered a more effective and less labile reagent for hindered substrates.[123,110a] In an attempt to facilitate the eventual Diels-Alder reaction (see Section 3.4.1), the *N*-benzyl protecting group was replaced at that moment by a *para*-toluenesulfonyl group or a propionyl group. The tosyl protecting group was chosen based on literature precedents,[123,110] while the propionyl chloride was chosen based on its capacity to complex bidentate Lewis acids, in the eventuality that catalysis would be necessary for the Diels-Alder reaction.[124] After protection with either protecting group, diphenyl disulfide was successfully installed on the lactam in basic conditions (Scheme 3.17).



Scheme 3.17 – Preparation of sulfur derivative

The alkylation with *n*-butyl iodide did not yield the desired product **3.14** (Scheme 3.18). To circumvent this difficulty, substrate **3.13** was alkylated with more reactive allyl bromide. The

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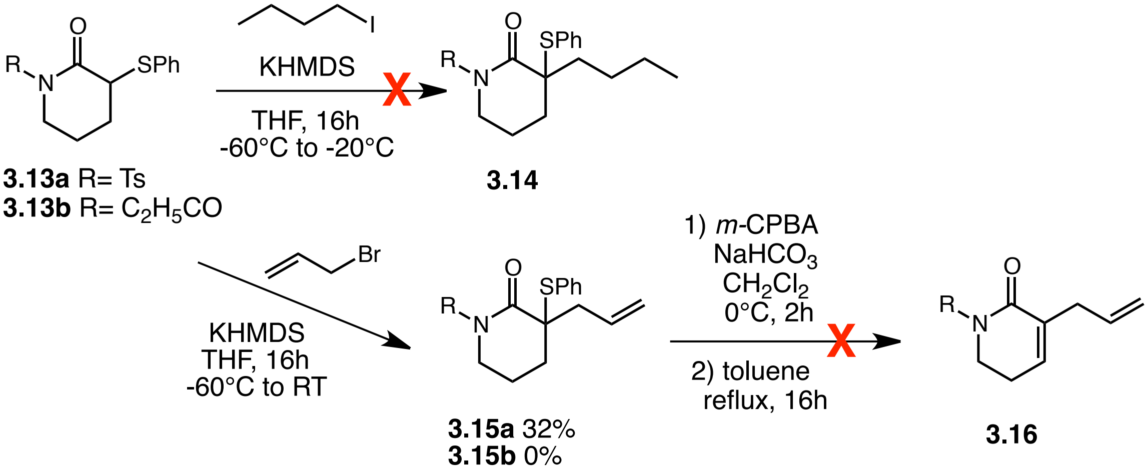
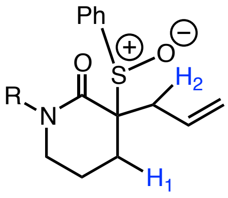
[123] Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T.; Hino, T. *J. Org. Chem.* **1992**, *57*, 5741.

[124] Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982***,* *38*, 1949.

reaction afforded intermediate **3.15a** in 32% yield. No product was obtained when the allylation was performed on the propionyl-protected substrate. Oxidation of the sulfur was then executed on substrate **3.15a** using *m*-CPBA, but the elimination reaction yielded a complex mixture of products from which the desired unsaturated lactam **3.16** could not be isolated. The competitive elimination between hydrogen H_1 leading to the endocyclic unsaturation, and hydrogen H_2 providing the external diene, was presumably troublesome in this case (Figure 3.3).



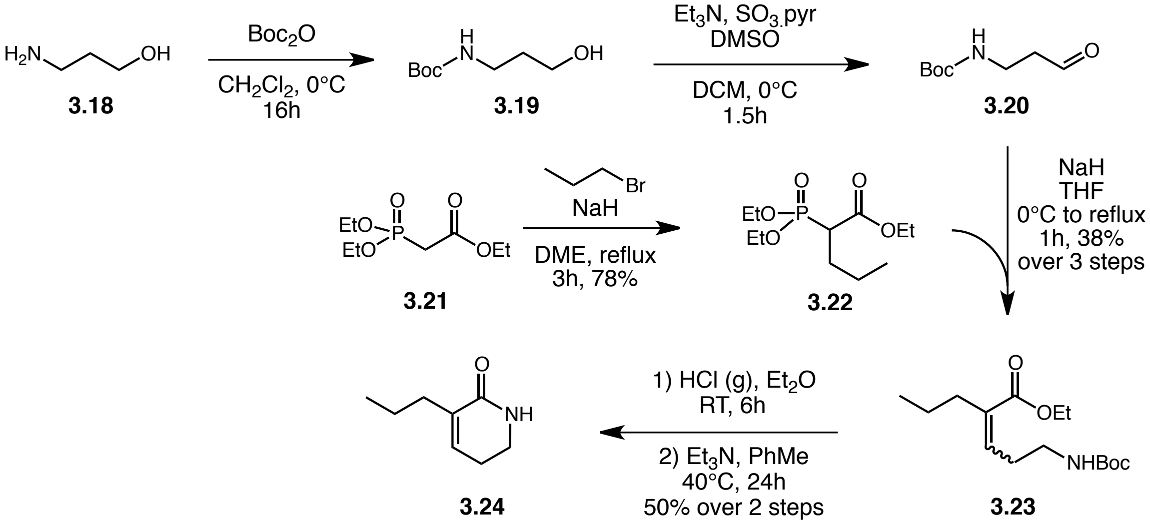
Scheme 3.18 – Attempts at synthesis of dienophile via thio-oxide elimination



3.17

Figure 3.3 – Competitive elimination

Efforts were therefore directed towards new means of forming the desired unsaturated lactam. Based on a procedure by the Coutrot group,[125] 3-amino-1-propanol was protected[126] and oxidized to the aldehyde.[127] The aldehyde was then condensed in a Horner-Wadsworth-Emmons reaction with ethyl-substituted triethylphosphonoacetate,[128] providing unsaturated ester **3.23** in a modest 38% yield, but good selectivity towards the *Z*-isomer (7:3 to >99:1). The nitrogen was deprotected under acidic conditions and subsequently treated with triethylamine in toluene to allow cyclization (Scheme 3.19).[125] The possibility to protect the nitrogen at the very end of the synthesis, allowed to easily introduce different protecting groups.



Scheme 3.19 – Synthesis of the *n*-butyl-substituted dienophile

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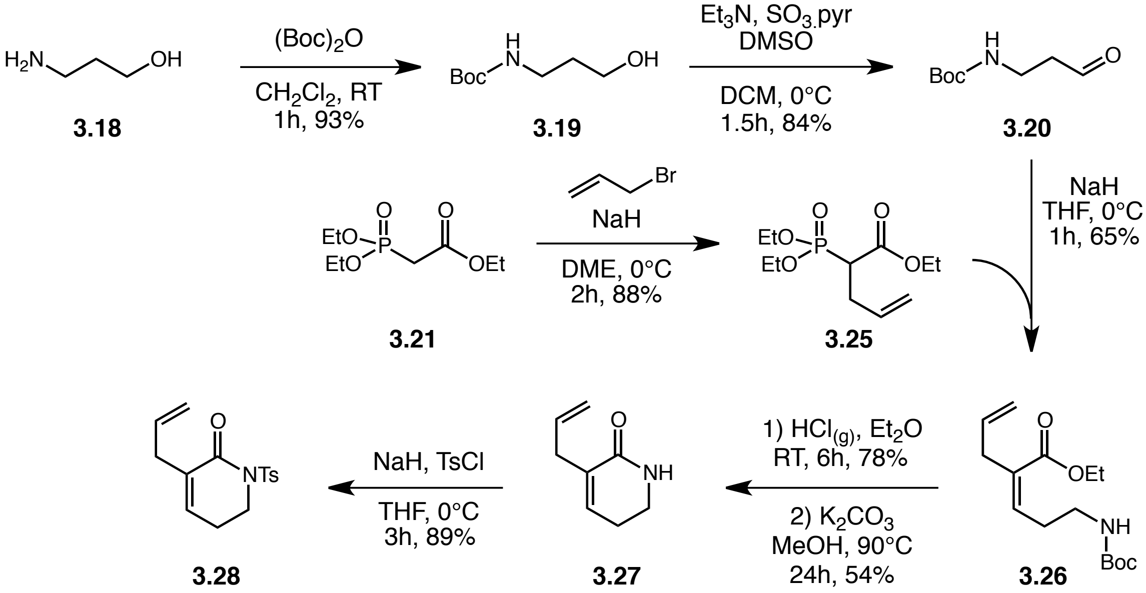
[125] Grison, C.; Genève, S.; Coutrot, P. *Tetrahedron Lett.* **2001**, *42*, 3831.
[126] Mattingly, P. G. *Synthesis*, **1990***,* 366.
[127] Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383.
[128] Nakazato, A.; Kumagai, T.; Ohta, K.; Chaki, S.; Okuyama, S.; Tomisawa, K. *J. Med. Chem.* **1999**, *42*, 3965.

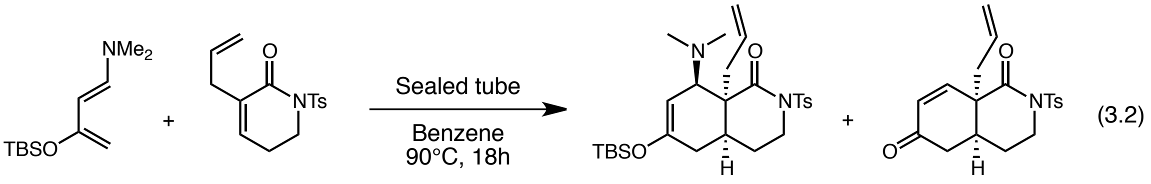
3.5.1.1 Nicholas Wong Honours Project

The synthesis of the model dienophile with an alpha-allyl substituent was then passed along to Nicholas Wong, an honours student, for optimization and scaling up. Under slightly modified conditions, the new dienophile was afforded in 6 steps with an overall yield of 19% (Scheme 3.20).



Scheme 3.20 – Synthesis of the allyl-substituted dienophile by Nicholas Wong

Mr. Wong then proceeded to evaluate the reactivity of the newly formed dienophile by reacting it with the known Rawal diene (see Section 3.6.2). When dienophile **3.28** was submitted to react with the diene overnight at 90°C in a sealed tube, the desired Diels-Alder adduct was obtained in 43% yield along with 7% of elimination product **3.31** (Eq. 3.2). In comparison, reaction at -78°C of the Rawal diene with *N*-phenylmaleimide is known to provide the Diels-Alder adduct in 96% yield.[136] From these experiments, it was concluded that dienophile **3.28** was weakly reactive and that thermal activation or Lewis acid catalysis would be necessary for the Diels-Alder key step to proceed efficiently.



3.29 **3.28** **3.30** 43% **3.31** 7% (3.2)

3.6 Aminodienes in Diels-Alder Reactions

3.6.1 Synthesis of 1-Amino-1,3-Dienes

As shown in Section 3.3.4, the Diels-Alder reaction allows for the quick formation of highly complex molecules. Depending on the substrate and/or Lewis acid catalyst used, stereocontrol can be achieved.[129] Oxygen-substituted dienes have often been employed as means of inserting a heteroatom within a molecule.[130] On the other end, nitrogen-substituted dienes have not been as widely used in synthesis.

Aminodienes can be separated in two main categories, the 1-amino-1,3-dienes and the 2-amino-1,3-dienes. Only 1-amino-1,3-dienes will be covered, as they are the most encountered aminodienes in syntheses of alkaloids similar to manzamine A. These Diels-Alder precursors can be formed via condensation of a mono or disubstituted amine with an α,β-unsaturated aldehyde. The desired diene is then produced by isomerization. In the case of monosubstituted amines, protection of the imine with an acyl or alkyl group is often

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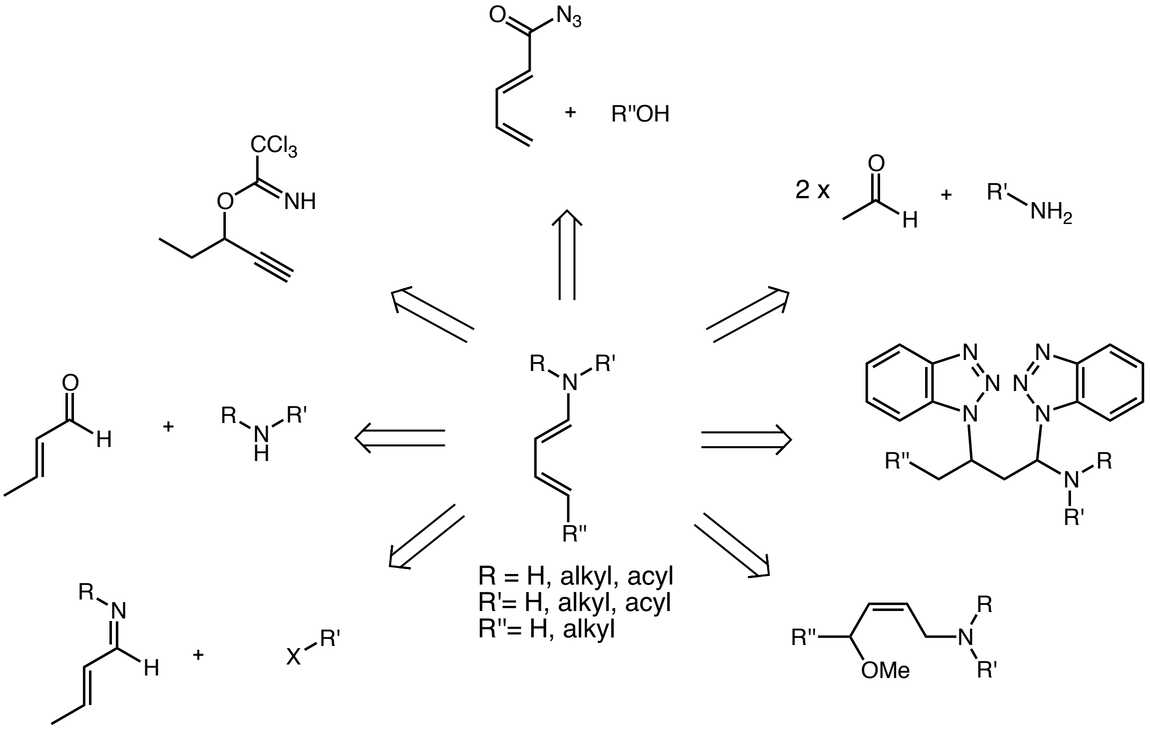
[129] Nicolaou, K. C. ; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. E. *Angew. Chem. Int. Ed.* **2002***, 41*, 1668.
[130] Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

required to force the isomerization.[131] Other methods for the formation of this category of aminodienes include Claisen or Curtius rearangements,[132] multi-components condensation,[133] double elimination[134] or 1,4-elimination (Scheme 3.21).[135] The formation of specific types of aminodienes will be discussed below.



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[131] For examples, see a) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570. b) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 981. c) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 4537. d) Wu, T-C.; Mareda, J.; Gupta, Y. N.; Houk, K. N. *J. Am. Chem. Soc.* **1983**, *105*, 6996. e) Blau, K.; Kapst, U.; Voerckel, V. *J. Prakt. Chem.* **1989**, *331*, 671. Sammis, G. M.; f) Flamme, E. M.; Xie, H.; Ho, D. M.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8612. g) Aznar, F.; Fañanás-Mastral, M.; Alonso, J.; Fañanás, F. J. *Chem. Eur. J.* **2008**, *14*, 325.

[132] a) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98,* 2352. b) Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 2807. c) Overman, L. E; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, 3089. d) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.

[133] Gördes, D.; von Wangelin, A. J.; Klaus, S.; Neumann, H.; Strübing, D.; Hübner, S.; Jiao, H.; Baumann, W.; Beller, M. *Org. Biomol. Chem.* **2004***, 2,* 845.

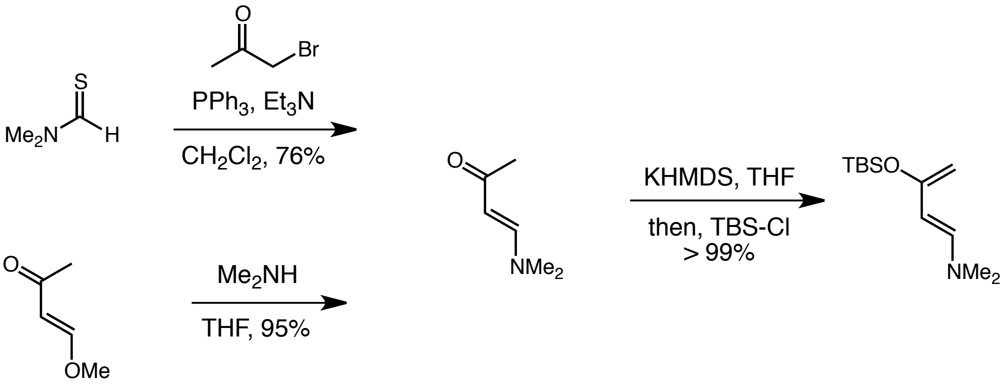
[134] Katritzky, A. R.; Long, Q-H.; Lue, P. *Tetrahedron Lett.* **1991**, *32*, 3597.

[135] Tayama, E.; Sugai, S. *Tetrahedron Lett.* **2007**, *48*, 6163.

Scheme 3.21 – Formation of 1-amino-1,3-dienes

3.6.2 The Rawal Diene

One of the most used 1-amino-1,3-diene is the Rawal diene or 1-amino-3-siloxy-1,3-butadiene. It is formed via an addition-elimination reaction of dimethylamine on a vinylogous ester, or via a one pot Eschenmoser contraction, followed by formation of a TBS enol ether (Scheme 3.22). The presence of the electron-rich nitrogen atom makes it more reactive under standard Diels-Alder conditions than its parent 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene, known as Danishefsky's diene.[136]



Scheme 3.22 – Formation of the Rawal diene

The Rawal diene has been used in syntheses of molecules such as platencin (Scheme 3.23),[137] the ergoline skeleton,[138] or for asymmetric Diels-Alder reactions.[139] In all cases, the

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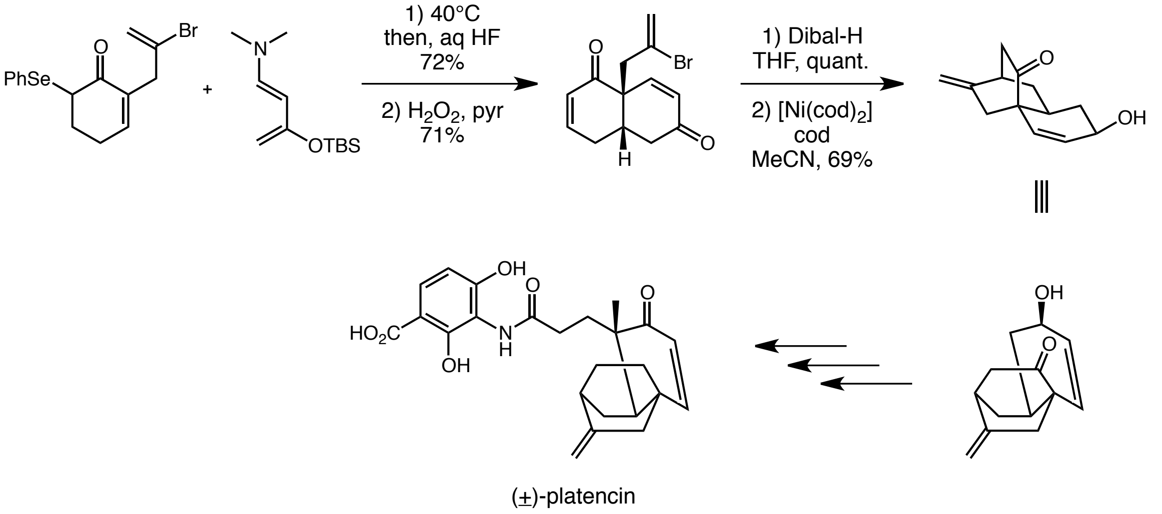
[136] Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62,* 5252.

[137] Hayashida, J.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2008***, 47*, 4373.

[138] a) Bur, S. K.; Padwa, A. *Org. Lett.* **2002***, 4*, 4135. b) Padwa, A.; Bur, S. K.; Zhang, H. *J. Org. Chem.* **2005***, 70*, 6833.

[139] a) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2005***, 7,* 5473. b) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336. c) Friberg, A.; Olsson, C.; Ek, F.; Berg, U.; Frejd, T. *Tetrahedron: Asymmetry* **2007**, *18*, 885.

dimethylamine is removed under acylating or desilylating conditions to provide the synthetically useful enone.



Scheme 3.23 – Use of Rawal diene in the synthesis of (±)-platencin by the Rawal group

An interesting example of the use of the Rawal diene by the Danishefsky group is in the efforts towards the synthesis of a manzamine A-related molecule, xestocyclamine A. Their plan involved a diastereoselective Diels-Alder, followed by de-silylation to obtain the enone. A new silylated diene was formed and used in a Mannich reaction, followed by a double Michael addition. Further modifications produced an advanced intermediate towards the synthesis of xestocyclamine A (Scheme 3.24).[140]

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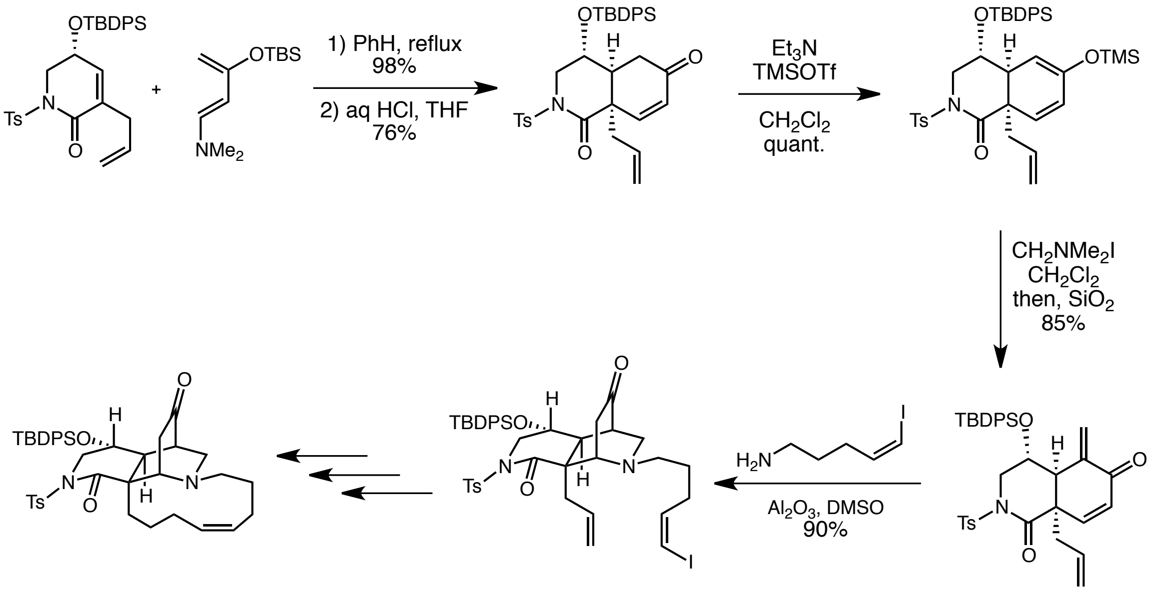
[140] Gagnon, A.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2002**, *41,* 1581.



Scheme 3.24 – Use of Rawal diene towards xestocyclamine A by the Danishefsky group

The Smith group used a modified version of the Rawal diene in the stereoselective total synthesis of (–)-okilactomycin. The diastereoselective Diels-Alder reaction, followed by elimination of the pyrolidine-derived chiral auxiliary, were the first step in the synthesis of okilactomycin, which involved a key Petasis-Ferrier rearrangement (Scheme 3.25). [141]

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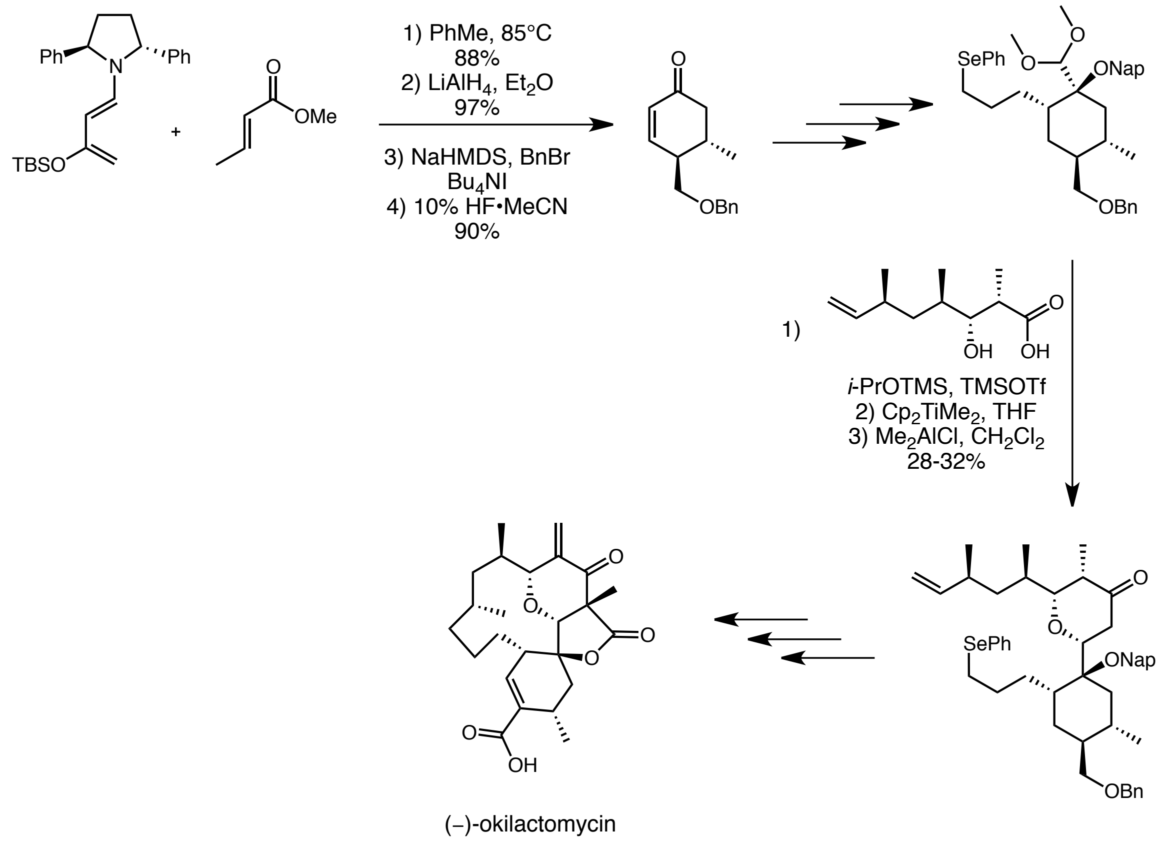
[141] a) Smith III, A. B.; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872. b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165.



Scheme 3.25 - Use of Rawal diene in the synthesis of okilactomycin by the Smith group

Modified substituents on the nitrogen of the aminodiene can help in the incorporation of said nitrogen into the molecule being synthesized. In 2002, the Rawal group used this strategy in the synthesis of tabersonine (Scheme 3.26).[142] The *N*-allyl substituent was subsequently used in a ring closing metathesis, while the ester-substituent was kept as a protecting group until the near end of the synthesis.

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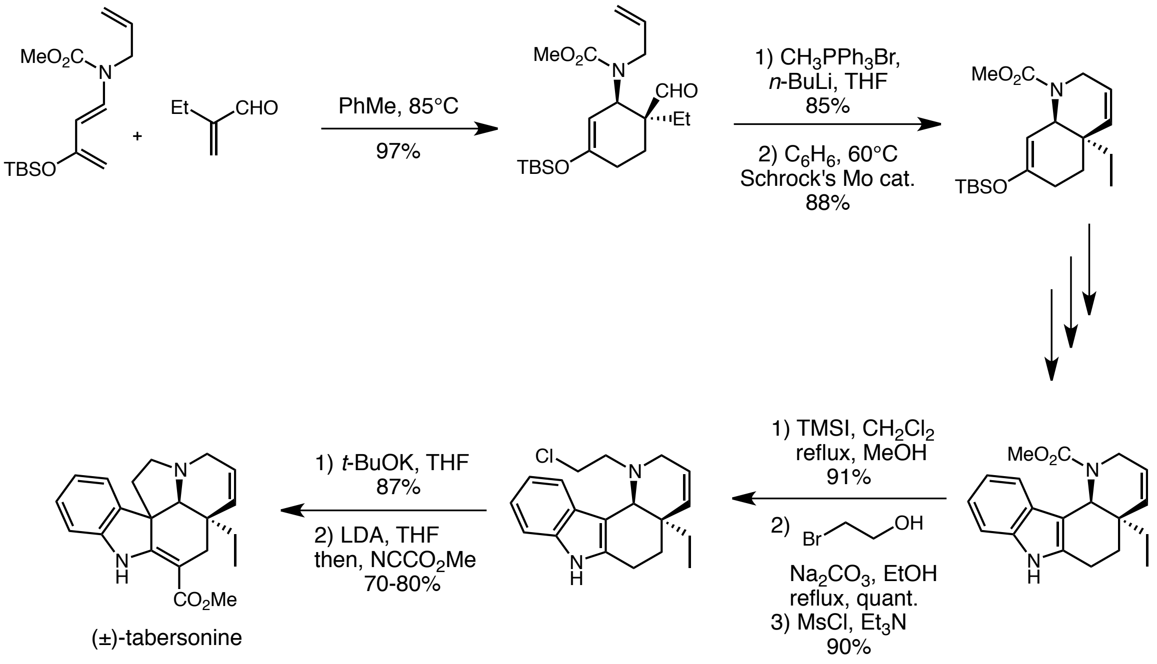
[142] a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998,** *120,* 13523. b) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.



Scheme 3.26 – Use of a modified Rawal diene in the synthesis of tabersonine by the Rawal group

The group of Nishida, in collaboration with Nakagawa, has used a similar Rawal diene derivative in the synthesis of the core of manzamine B.[143] Their approach employed a *N*-2-chloroacetyl-*N*-allyl-1-amino-1,3-diene in order to afford the Diels-Alder product in high yield and enantiomeric excess using a (*R,R*)-Cr-salen complex as chiral catalyst. Both protecting groups were lost in the subsequent steps leading to an advanced intermediate on the way to manzamine B (Scheme 3.27).

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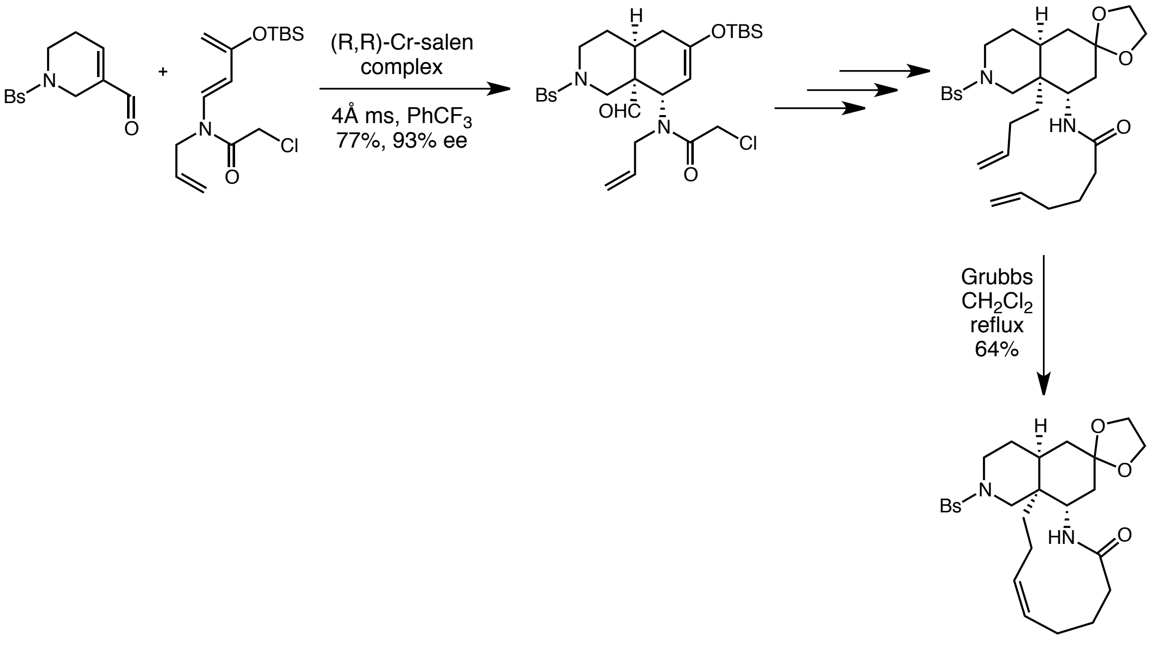
[143] Matsumura, T.; Akiba, M.; Arai, S.; Nakagawa, M.; Nishida, A. *Tetrahedron Lett.* **2007**, *48,* 1265.



Scheme 3.27 – Use of a modified Rawal diene in the efforts towards manzamine B by the Nishida and Nakagawa groups

3.6.3 *N*-Acyl-1-amino-1,3-dienes

Modifications of the amine protecting groups of the Rawal diene lead to the second type of 1-amino-1,3-dienes: the *N*-acylaminodienes. These acyl-protected aminodienes are slightly less reactive than their alkyl substituted counterpart in normal electron demand Diels-Alder reactions. They are formed by condensation of a primary amine onto a ketone or an aldehyde, followed by acylation of the imine formed. Otherwise, they can be formed via a Curtius rearrangement. They were first generated and used in Diels-Alder reactions by the Oppolzer[144,131bc] and Overman groups.[132abd,145] They have since been used in syntheses of various natural products such as pumiliotoxin-C,[146] gephyrotoxin[147] and dendrobine.[148]

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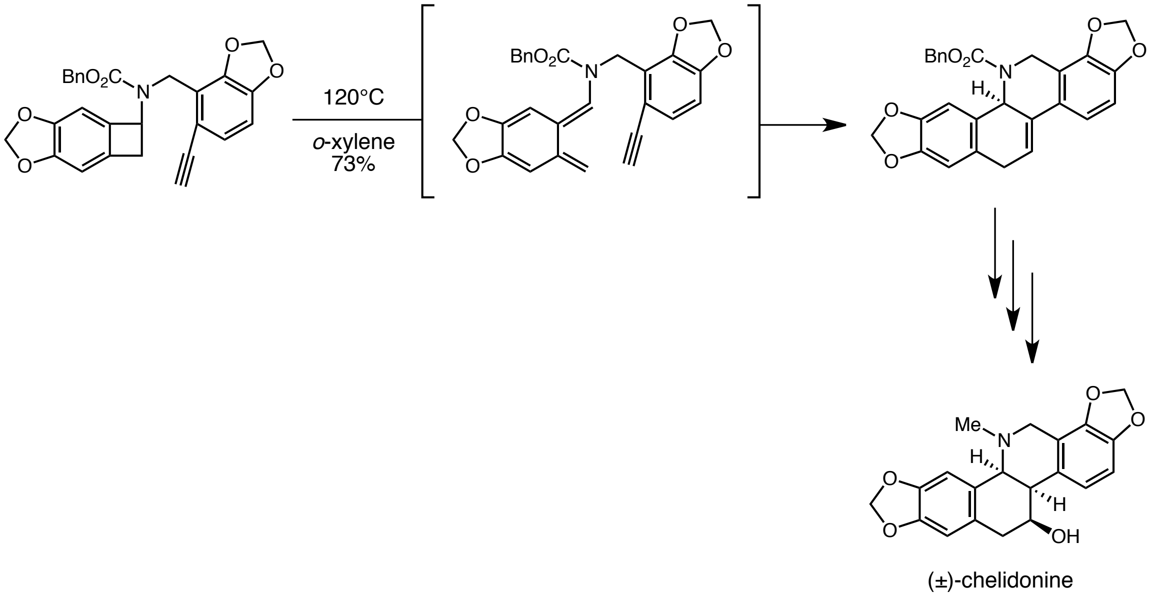
[144] Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93,* 3836. For more on the synthesis of acylaminodienes and their use by Oppolzer: a) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590. b) Oppolzer, W. *Angew. Chem. Int. Ed.* **1977**, *16,* 10. c) Oppolzer, W. *Synthesis* **1978**, 793.

The Oppolzer group first made use of an acylaminodiene in 1971 in the synthesis of *dl*-chelidonine.[144] The aminodiene was formed *in situ* via an electrocyclization and was immediately trapped by the dienophile in an intramolecular Diels-Alder reaction. Functional groups manipulations and deprotection of the amine afforded (±)-chelidonine (Scheme 3.28).



Scheme 3.28 – The Oppolzer group synthesis of (±)-chelidonine

The Oppolzer group reported in 1975 the first synthesis of pumiliotoxin C using an aminodiene component in a Diels-Alder reaction.[146a] This aminodiene was obtained via reduction of an oxime, followed by condensation of the newly formed amine onto crotonaldehyde. Acylation of the imine formed forced isomerization, which afforded the

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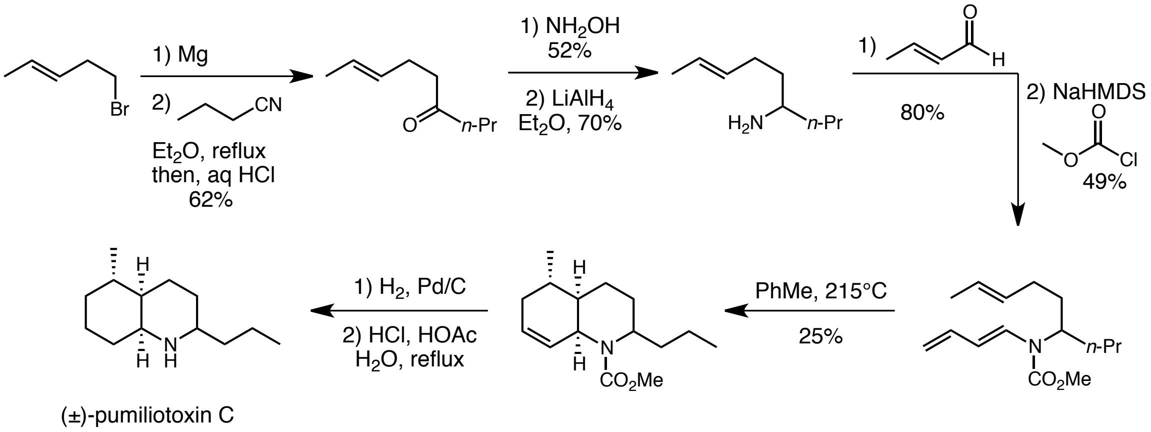
[145] For more on the synthesis of acylaminodienes and their use by Overman: a) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. b) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816. c) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.

[146] a) Oppolzer, W.; Fröstl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593. b) Overman, L. E.; Jessup, P. J. *Tetrahedron Lett.* **1977**, 1253. c) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141.

[147] Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105,* 5373.

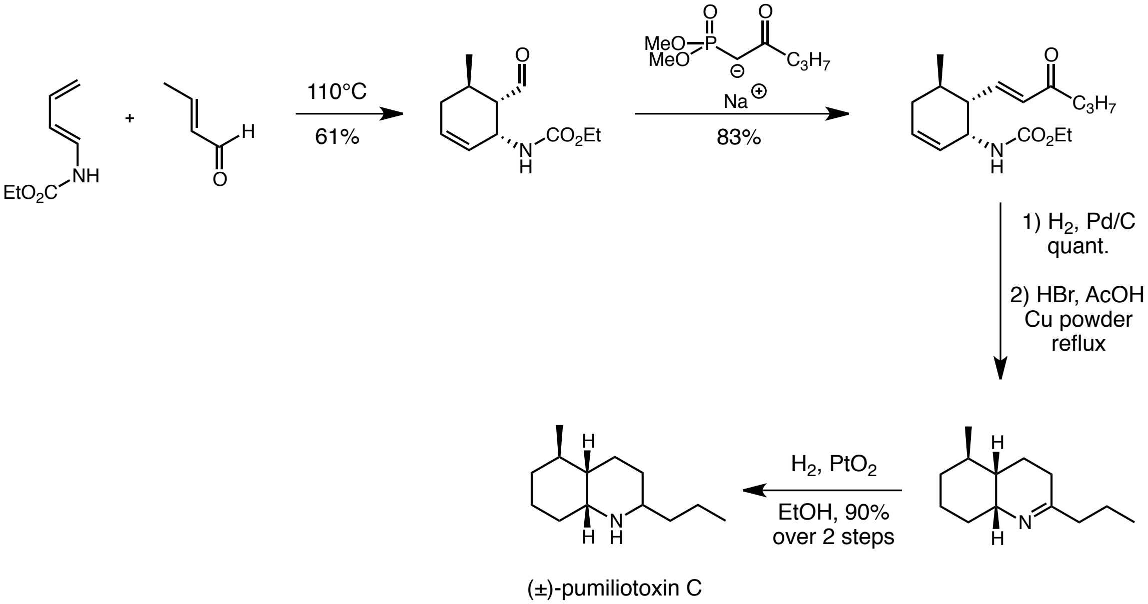
[148] Martin, S. F.; Li, W. *J. Org. Chem*. **1989**, *54*, 265.

Diels-Alder precursor (Scheme 3.29). An intramolecular Diels-Alder reaction, followed by alkene hydrogenation and acid hydrolysis of the carbamate provided the (±)-pumiliotoxin C in a total of nine steps.



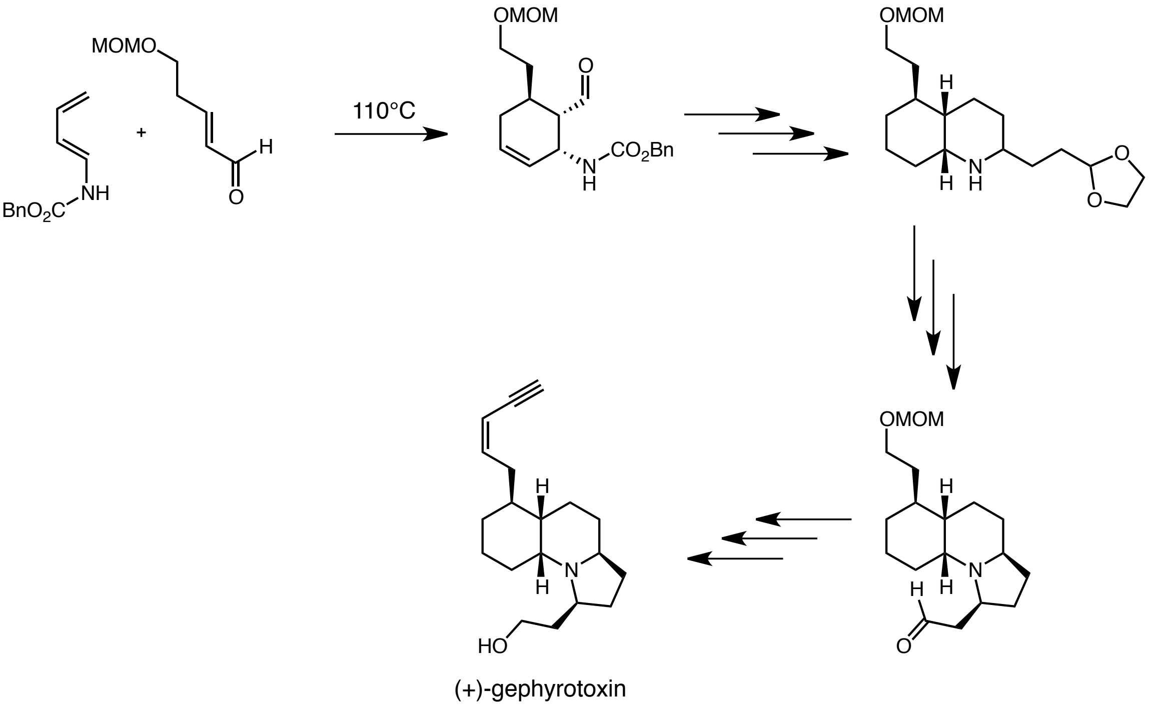
Scheme 3.29 – The Oppolzer group synthesis of (±)-pumiliotoxin C

A short synthesis of pumiliotoxin C by the Overman group made use of an acylated aminodiene in an intermolecular Diels-Alder (Scheme 3.30).[146b] A Horner-Wadsworth-Emmons reaction provided the chain necessary for the *n*-propyl-substituted piperidine ring. This reaction also incorporated a carbonyl, which allowed for condensation on the amine after deprotection and closure of the second six-membered ring. A final hydrogenation afforded pumiliotoxin C in an overall yield of 45%, excluding the Curtius rearrangement used in the formation of the acylaminodiene.



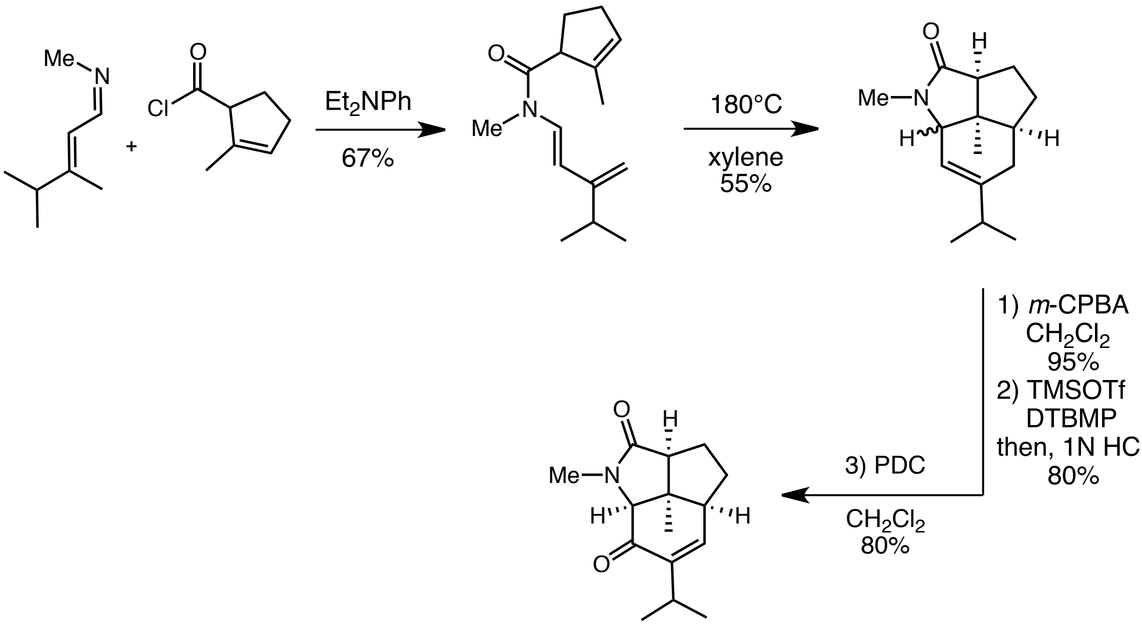
Scheme 3.30 – The Overman group synthesis of (±)-pumiliotoxin C

The Overman group used a similar strategy in the total synthesis of gephyrotoxin.[147] The intermolecular Diels-Alder reaction of an acylaminodiene with a γ-sustituted crotonaldehyde provided an intermediate with three new stereocenters. A Horner-Watsworth-Emmons was then applied to the aldehyde and provided the side chain that allowed ring closure via condensation. An intramolecular Michael addition closed the third ring. Final modifications afforded the ene-yne side chain and gephyrotoxin was synthesized in fifteen steps with an overall yield of 6.5% (Scheme 3.31).



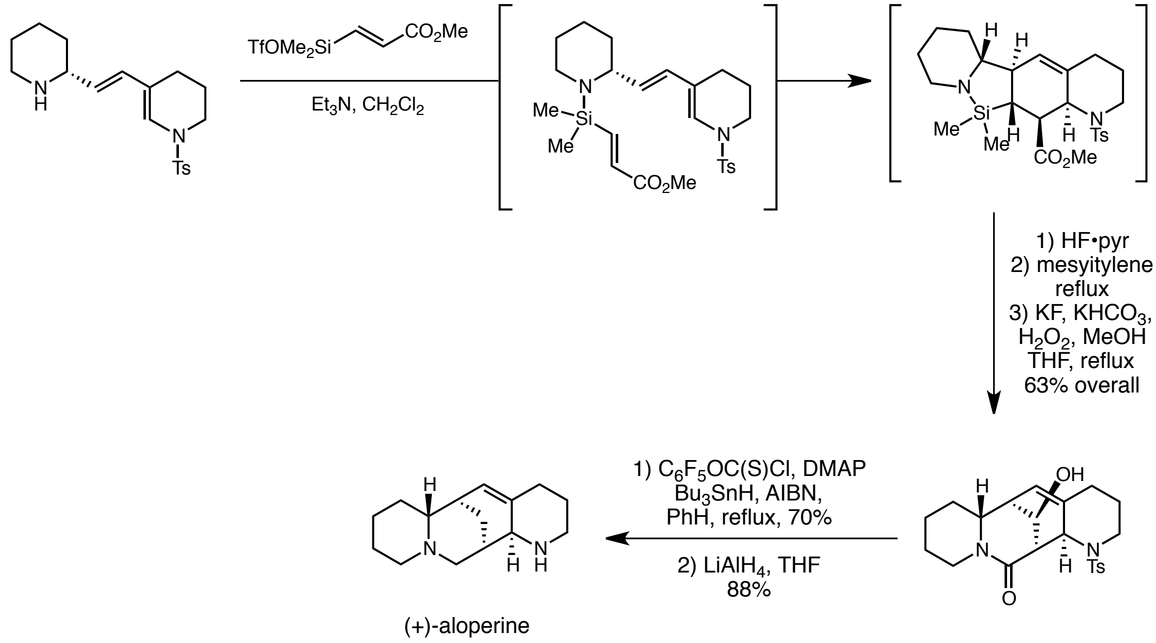
Scheme 3.31 – The Overman group synthesis of (±)-gephyrotoxin via a Diels-Alder reaction

In 1989, the Martin group used an acylated aminodiene in an intramolecular Diels-Alder reaction for the formal synthesis of (+)-dendribine.[148] Acylation of the primary imine formed the Diels-Alder precursor, with tethered dienophile and aminodiene. Upon heating, it afforded the cycloadduct in 55% yield. Epoxidation of the alkene followed by an eliminative opening of the epoxide and alcohol oxidation provided an advanced intermediate (Scheme 3.32).



Scheme 3.32 – Efforts towards (±)-dendrobine by the Martin group

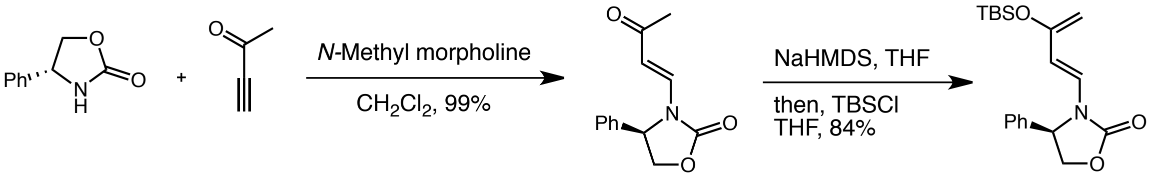
More recently, the Overman group completed the total synthesis of (+)-aloperine via a silica-tethered intramolecular Diels-Alder.[145c] The *N*-tosyl aminodiene was formed in seven steps from 3-hydroxypiperidine. The free nitrogen of the diene was then tethered to the dienophile with a sylil group and, upon standing at room temperature, the desired Diels-Alder cycloadduct was obtained. The crude product was then submitted to a HF treatment, which allowed deprotection of the sylilated amine. The free amine then underwent a nucleophilic attack on the neighboring ester, closing the remaining six-membered ring. Reaction under Tamao-Fleming conditions afforded the oxygenated lactam intermediate. Barton deoxygenation, followed by reduction of the amide, provided (+)-aloperine in 24% overall yield (Scheme 3.33).



Scheme 3.33 – The Overman group synthesis of (+)-aloperine

3.6.4 Evans' Oxazolidinone in 1-Amino-1,3-Dienes

Aminodienes using the Evans' oxazolidinone chiral auxiliary can be synthesized by 1,4-addition of the oxazolidinone or its pre-cyclized form onto ynones or enones (Scheme 3.34 and Scheme 3.35).[149]



Scheme 3.34 – Synthesis of an oxazolidinone-containing aminodiene by the Rawal group

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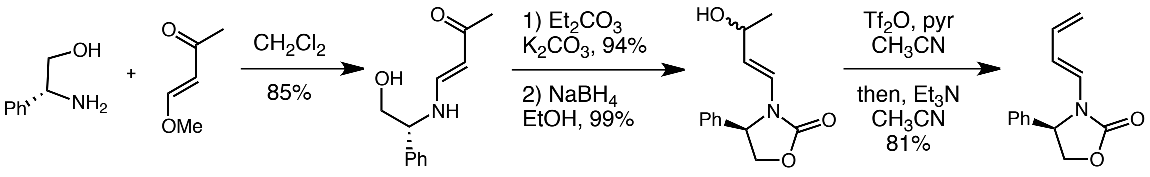
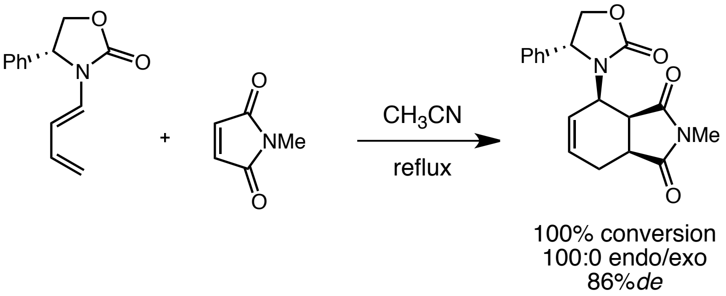
[149] a) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059. b) McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69.



Scheme 3.35 – Synthesis of an oxazolidinone-containing aminodiene by the Stevenson group

The Stevenson and Marchand-Brynaert groups have developed and applied these aminodienes in simple Diels-Alder reactions with good diastereo and endo selectivity (Eq. 3.3).[149b,150]

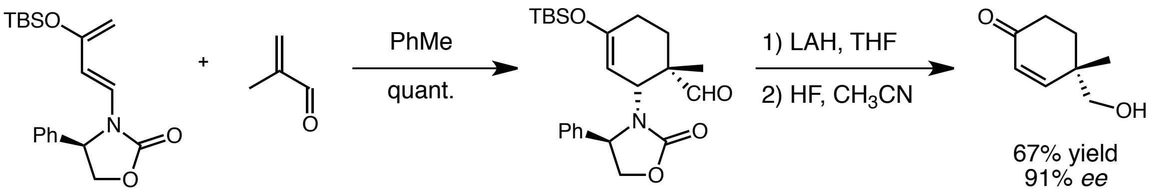


(3.3)

The use of a chiral amine being an efficient yet simple way to perform a diastereoselective Diels-Alder, the Rawal group also introduced Evans' oxazolidinones as a modified version of their diene.[149a] They demonstrated that, after cycloaddition and subsequent elimination of the auxiliary, cyclohexanones could be obtained in good yield and enantiomeric excesses (Scheme 3.36).

---

[150] a) Defacqz, N.; Touillaux, R.; Marchand-Brynaert, J. *J. Chem. Research* **1998**, 512. b) Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* **2003**, *68*, 9809.



Scheme 3.36 – Use of an oxazolidinone-containing aminodiene by the Rawal group

A good example of this chiral diene's applicability in synthesis was demonstrated in the previous efforts towards the synthesis of manzamine A by the Fukuyama group (for their total synthesis via a different path, see section 3.3.3).[151] Reaction of the optically active diene with an advanced intermediate provided a cis-decalin, which was modified and opened via an Eschenmoser-Tanabe fragmentation. Further functional group modifications allowed the formation of the core of manzamine A (Scheme 3.37).

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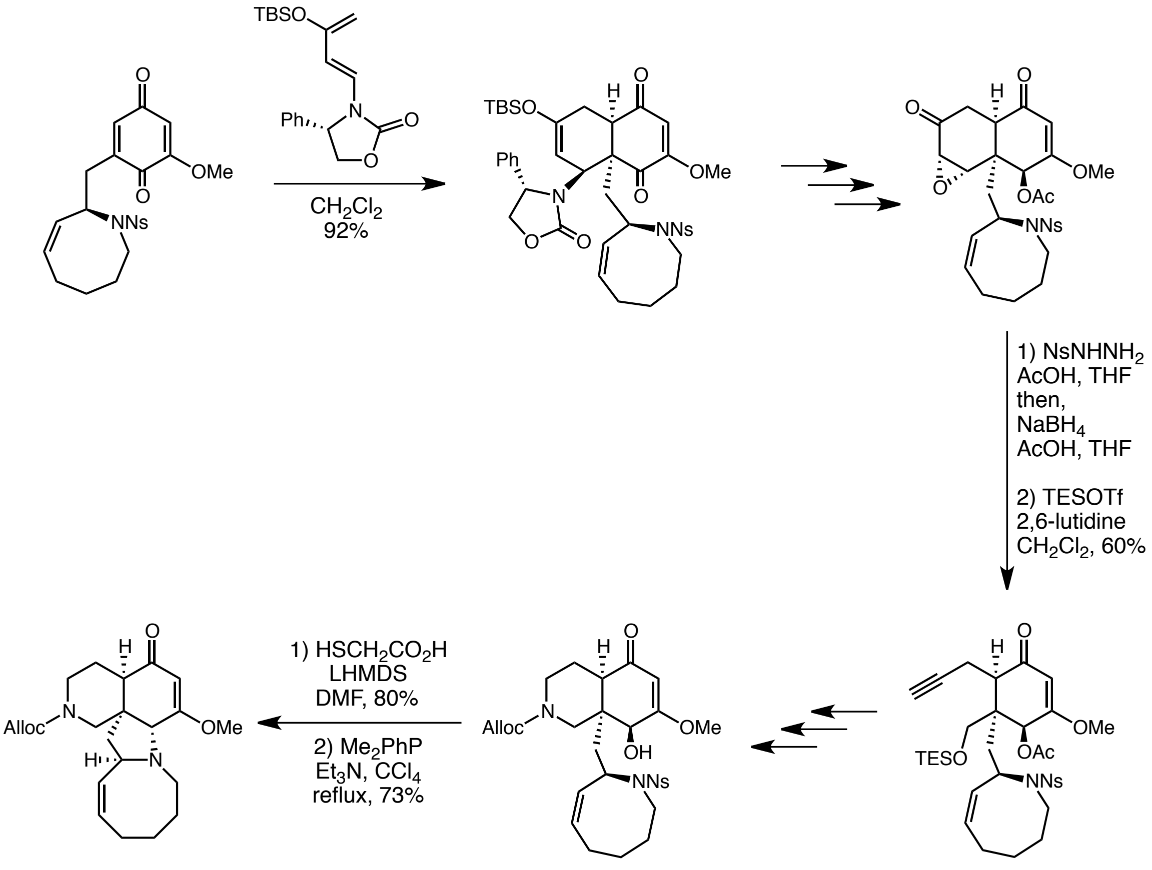
[151] Kita, Y.; Toma, T.; Kan, T.; Fukuyama, T. *Org. Lett.* **2008***, 10,* 3251.



Scheme 3.37 – Efforts towards the synthesis of manzamine A by the Fukuyama group

3.6.5 Push-Pull 1-Amino-1,3-Dienes

Another sub-category of 1-amino-1,3-dienes is the push-pull diene family. Those consist of a butadiene in between an electron-donating amine substituent and an electron-withdrawing group (EWG); usually an ester, an aldehyde or a nitrile (Figure 3.4).

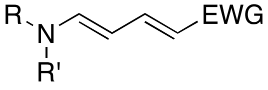
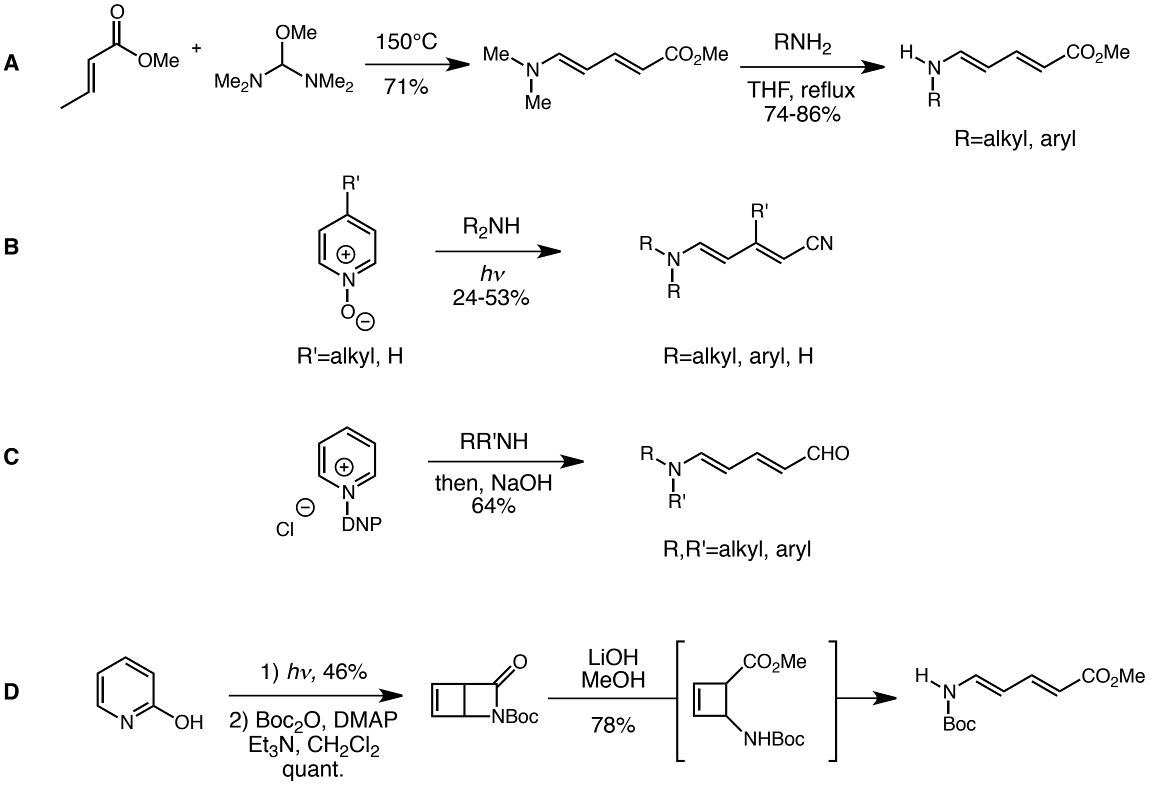


Figure 3.4 – Push-pull diene

They can be prepared by a variety of methods, depending on the electron-withdrawing group desired. Methyl crotonate can be condensed with tetramethylmethylenediamine to obtain the dimethylamino methylester diene (Scheme 3.38, A). This aminodiene can then be transformed into an *N,N*-heterodisubstituted aminodiene via an addition-elimination reaction.[152] Push-pull aminodienes can also be obtained via the opening of activated pyridines (Scheme 3.38, B, C) or by photoelectrocyclization of 2-hydroxypyridine, followed by opening of the formed cyclobutene under basic conditions (Scheme 3.38, D).[153]



Scheme 3.38 – Formation of push-pull aminodienes

Push-pull dienes are known to undergo formal cycloadditions, but their intrinsic polarity allows them to react in a non-concerted way. For example, two consecutive additions, instead of a [4+2] cycloaddition, were seen in the synthesis of norfluorocurarine by the

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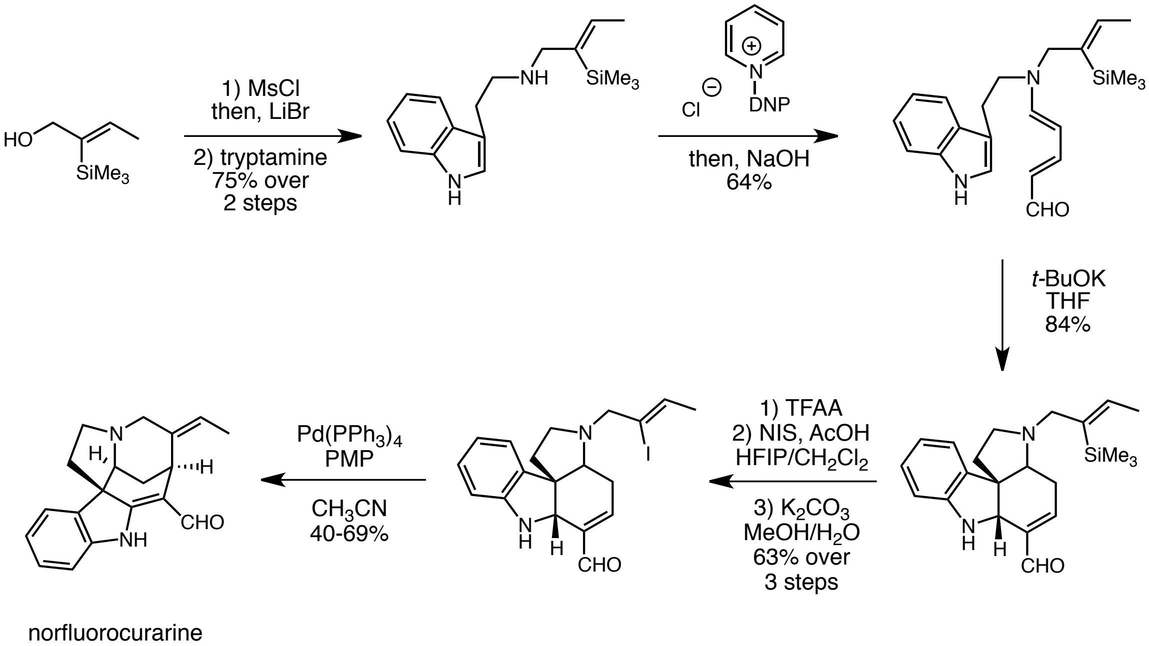
[152] a) Koike, T.; Tanabe, M.; Takeuchi, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1997***, 45*, 243. b) Koike, T.; Tanabe, M.; Takeuchi, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1997**, *45*, 27.

[153] a) Becher, J.; Finsen, L.; Winckelmann, I. *Tetrahedron,* **1981**, *37*, 789. b) Kearney, A. M.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2006**, *45,* 7803. c) J. Becher, *Synthesis* **1980**, 589. d) Gauvry, N.; Huet, F. *J. Org. Chem.* **2001**, *66*, 583.

Vanderwal group (Scheme 3.39).[154] Conjugation of the alkene with the aldehyde was observed under the reaction conditions. After iodination, an intramolecular Heck reaction afforded the desired natural product in a total of nine steps with an overall yield of 18%.



Scheme 3.39 – Synthesis of norfluorocurarine using a push-pull diene by the Vanderwal group

3.6.6 Cyclic 1-Amino-1,3-dienes

An overlooked family of aminodienes is the cyclic aminodiene dihydropyridine (DHP). Unsubstituted DHPs can be easily obtained from reduction of a pyridinium salt by a metal hydride, while nucleophilic addition of a Grignard-type reagent will provide 2-substituted

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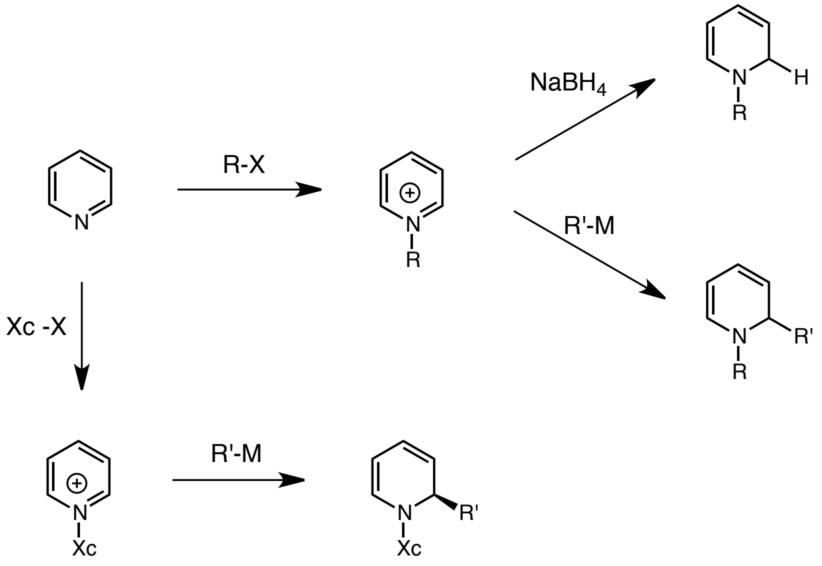
[154] Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472. For a similar synthesis of strychnine: Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77,* 17.

DHPs.[155,156] Chiral auxiliaries (Xc) can be used to ensure diastereoselectivity of the reaction (Scheme 3.40).[157]



Scheme 3.40 – Formation of unsubstituted or 2-substituted DHP's

5-Substituted DHPs can be difficult to obtain selectively from the 3-substituted DHPs due the low selectivity of the reduction reaction on a 3-alkylpyridinium salt (Eq. 3.4). Other means have been developed to circumvent this problem. 5-Substituted DHPs can be

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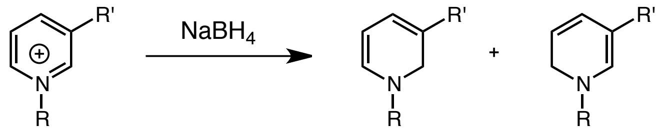
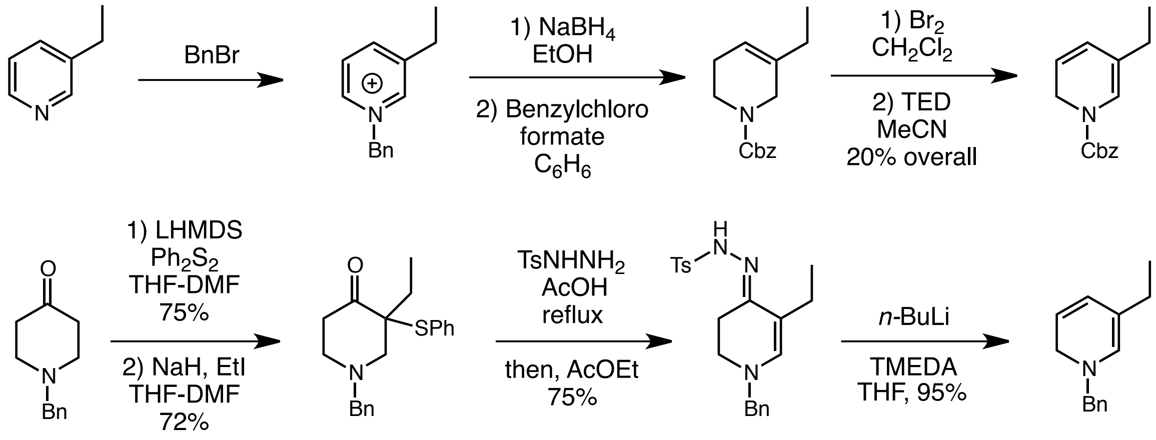
[155] For reviews: a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72,* 1. b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, 82, 223. c) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.
[156] a) Krow, G.; Michener, E.; Ramey, K. C. *Tetrahedron Lett.* **1971**, 3653. b) Krow, G. R.; Carey, J. T.; Zacharias, D. E.; Knaus, E. E. *J. Org. Chem.* **1982**, *47*, 1989. c) Krow, G. R.; Cannon, K. C.; Carey, J. T.; Ramjit, H. G. *J. Het. Chem.* **1985***, 22,* 131. d) Krow, G. R.; Lee, Y. B.; Raghvachari, R.; Alston, P. V.; Baker, A. D. *Tetrahedron Lett.* **1988***, 29*, 3187. e) Krow, G. R.; Alston, P. V.; Szczepanski, S. W.; Raghavachari, R.; Cannon, K. C.; Carey, J. T. *Synth. Comm.* **1990***, 20,* 1949. f) Krow, G. R.; Lee, Y. B.; Raghavachari, R.; Szczepanski, S. W.; Alston, P. V. *Tetrahedron* **1991***, 47*, 8299. g) Krow, G. R.; Huang, Q.; Szczepanski, S. W.; Hausheer, F. H.; Carroll, P. J. *J. Org. Chem.* **2007**, *72*, 3458. h) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098. i) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.
[157] Sales, M.; Charette, A. B. *Org. Lett.* **2005***, 7,* 5773.

selectively obtained via bis-elimination of a dibromo intermediate,[158] or via Shapiro elimination of a cyclic enone (Scheme 3.41).[159]



(3.4)

3-R'-DHP 5-R'-DHP



Scheme 3.41 – Formation of 5-substituted DHP's

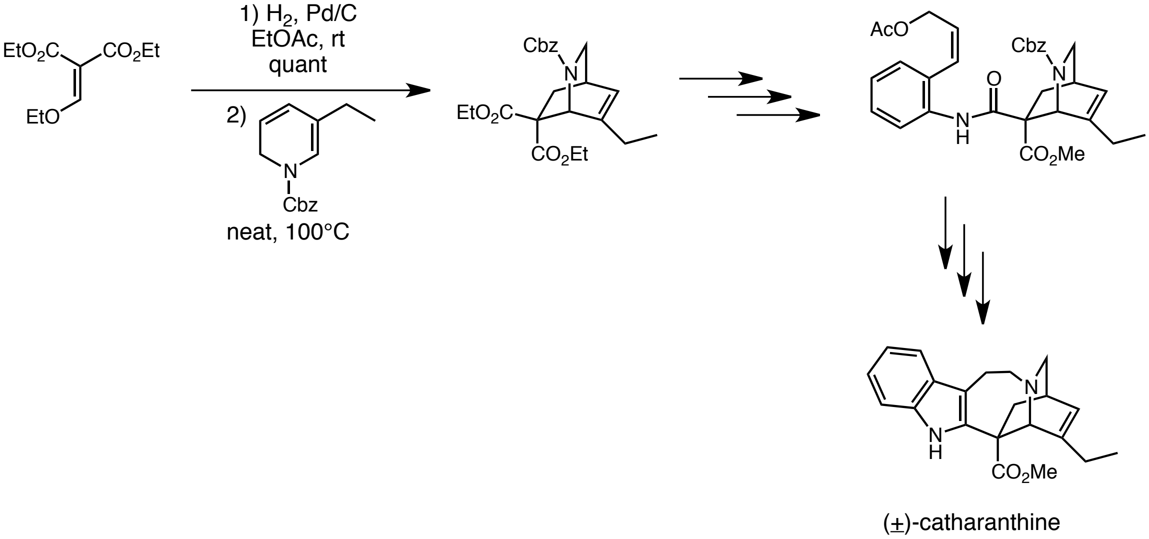
DHPs usually have a carboxy-protected amine, making them less electron rich and therefore less reactive. On the other hand, their stability under thermal conditions has allowed their use in a variety of Diels-Alder reactions. Many have applied the particular structure of the DHPs

---

[158] a) Szantay, C.; Bolcskei, H.; Gacs-Baitz, E.; Keve, T. *Tetrahedron*, **1990**, *46*, 1687. b) Szantay, C.; Bolcskei, H.; Gacs-Baitz, E. *Tetrahedron*, **1990**, *46*, 1711. c) Raucher, S.; Lawrence, R. F. *Tetrahedron Lett.* **1983***, 24*, 2927. d) Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999***, 1,* 973.

[159] a) Menmandoust, M.; Marazano, C.; Singh, R.; Gillet, B.; Cesario, M.; Fourrey, J-L.; Das, B. C. *Tetrahedron Lett.* **1988***, 29*, 4423. b) Marazano, C.; Le Goff, M-T.; Fourrey, J-L.; Bhupesh, C. D. *J. Chem. Soc. Chem. Comm.* **1981**, 389.

in the synthesis of Iboga alkaloids such as (±)-catharanthine (Scheme 3.42).[160,158bc,158b] Others have used these cyclic aminodienes in the synthesis of molecules such as reserpine,[161] luciduline,[162] oseltamivir,[163] or lepadin B.[164]



Scheme 3.42 – The Fukuyama group synthesis of (±)-catharanthine using DHP's

3.7 Synthesis of the Aminodiene

As previously described (see Section 3.4), the proposed synthesis of manzamine A involved a key step combining a Diels-Alder reaction followed by an intramolecular hydroamination.[118] In order for this key step to succeed, a novel bi-functionnal moiety-containing aminodiene, necessary for the hydroamination step, had to be designed.

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[160] a) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3237. b) Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442.
With chiral catalysts: a) Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299. b) Nakano, H.; Tsugawa, N.; Takahashi, K.; Okuyama, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 10879.

[161] Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157.

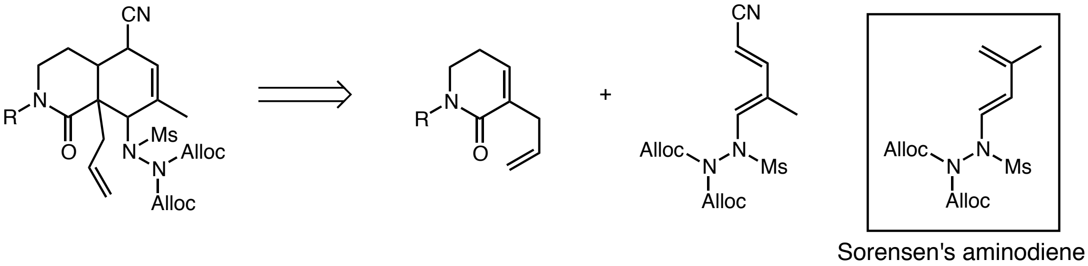
[162] Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1,* 229.

[163] Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734.

[164] Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 13873.

3.7.1 1st Generation: Push-Pull Hydrazide-Aminodiene

The design of the model aminodiene was elaborated with substitution at the 2-position in order to consider all sterics involved in the key step. The use of an electron-withdrawing nitrile substituent at position 4 made the new aminodiene part of the push-pull dienes family. The nitrile substituent was chosen as it could be converted to an aldehyde later in the synthesis and, as such, allow the formation of ircinal A (see Scheme 3.14). The hydrazide moiety was based on Sorensen's hydrazide-containing diene, as it was known to undergo the desired [4+2] cycloaddition reaction (Eq. 3.5).[131f]



(3.5)

The aminodiene could be obtained from condensation of an α,β-unsaturated aldehyde with the protected carbazate, followed by substitution of the chloride to the nitrile (Scheme 3.43). The isomerization of the diene could be instigated by further hydrazone *N*-protection. Finally, the aldehyde intermediate could come from isoprene via chloride S_N2' addition onto an epoxide, followed by oxidation of the formed alcohol.[165]

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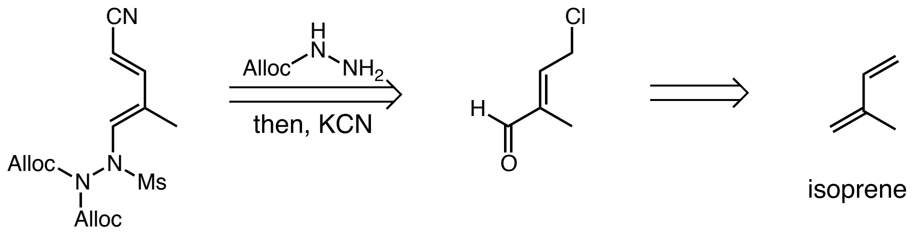
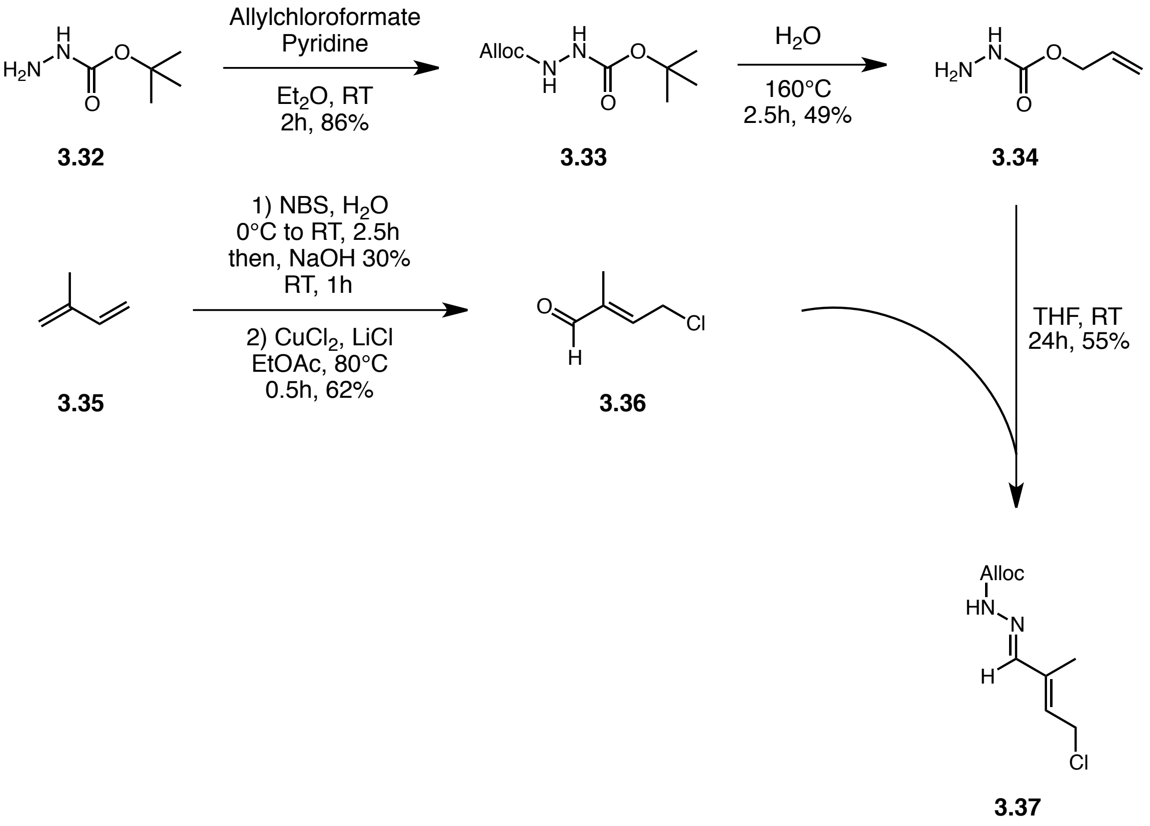
[165] a) Choi, H.; Ji, M.; Park, M.; Yun, I-K.; Oh, S-S.; Baik, W.; Koo, S. *J. Org. Chem.* **1999**, *64*, 8051. b) Johnston, B. D.; Oehlschlager, A. C. *Can. J. Chem.* **1984**, *62*, 2148.



Scheme 3.43 – Aminodiene retrosynthesis

The *t*-butylcarbazate was first protected with an alloc group, after which the Boc protecting group was removed under thermal conditions.[131f] This new carbazate was condensed with an α,β-unsaturated aldehyde,[131f] which was prepared from isoprene via a bromohydrin intermediate (Scheme 3.44).[165]



Scheme 3.44 – Synthesis of chlorohydrazone 3.37

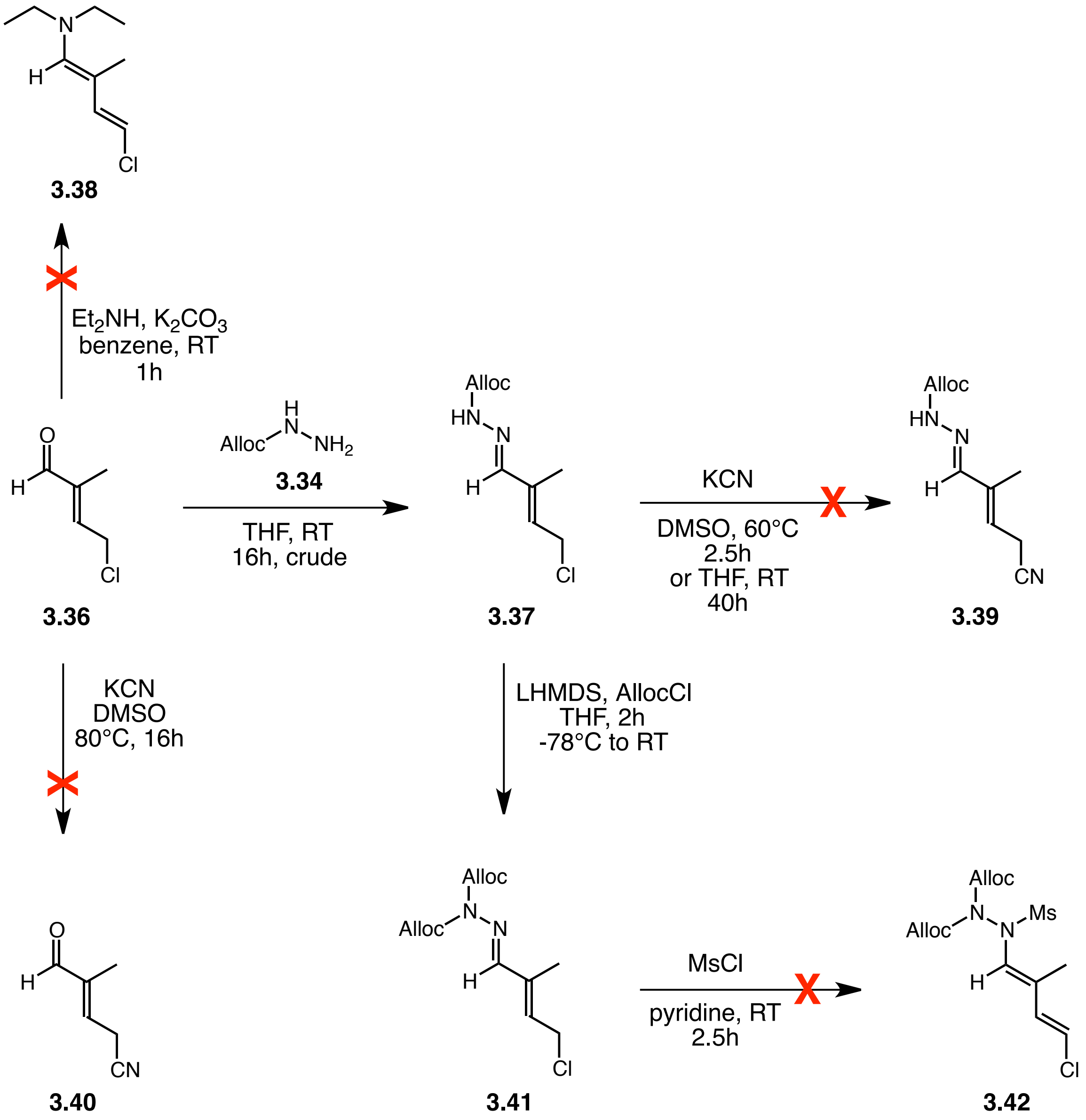
The chloroaldehyde 3.36 and subsequent chlorohydrazone **3.37** were highly unstable and all attempts to obtain the nitrile-substituted hydrazone **3.39**, or 4-chloroaminodiene **3.38** led to degradation (Scheme 3.45).[166] Stabilization of chlorohydrazone **3.37** via *N*-protection followed by reaction with mesyle chloride was attempted, but none of the desired product **3.42** was isolated.[131f] Replacing the chloride substituent of chloroaldehyde **3.36** or chlorohydrazone **3.37** by a nitrile group did not provide further results.[167] Forced isomerization of the substrate by condensation of the chloroaldehyde **3.36** with a disubstituted amine was also unsuccessful.[168]

---

[166] Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 3734.

[167] Miller, J. F.; Furfine, E. S.; Hanlon, M. H.; Hazen, R. J.; Ray, J. A.; Robinson, L.; Samano, V.; Spaltenstein, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 959.

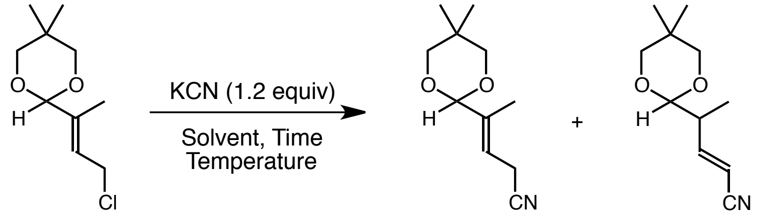
[168] Hunig, S.; Kahanek, H. *Chem. Ber.* **1957**, *90*, 238.



Scheme 3.45 – First attempts at the synthesis of aminodiene 3.42

The chloroaldehyde was therefore protected as an acetal, allowing substitution of the chloride by the nitrile.[166] This afforded a mixture of isomers as the unsaturation underwent partial conjugation with the new substituent. Optimization of the nitrile substitution reaction did not provide reproducible results or increased yields. The original procedure was therefore kept (Table 3.1, entry 2).

Table 3.1 – Optimization of nitrile substitution

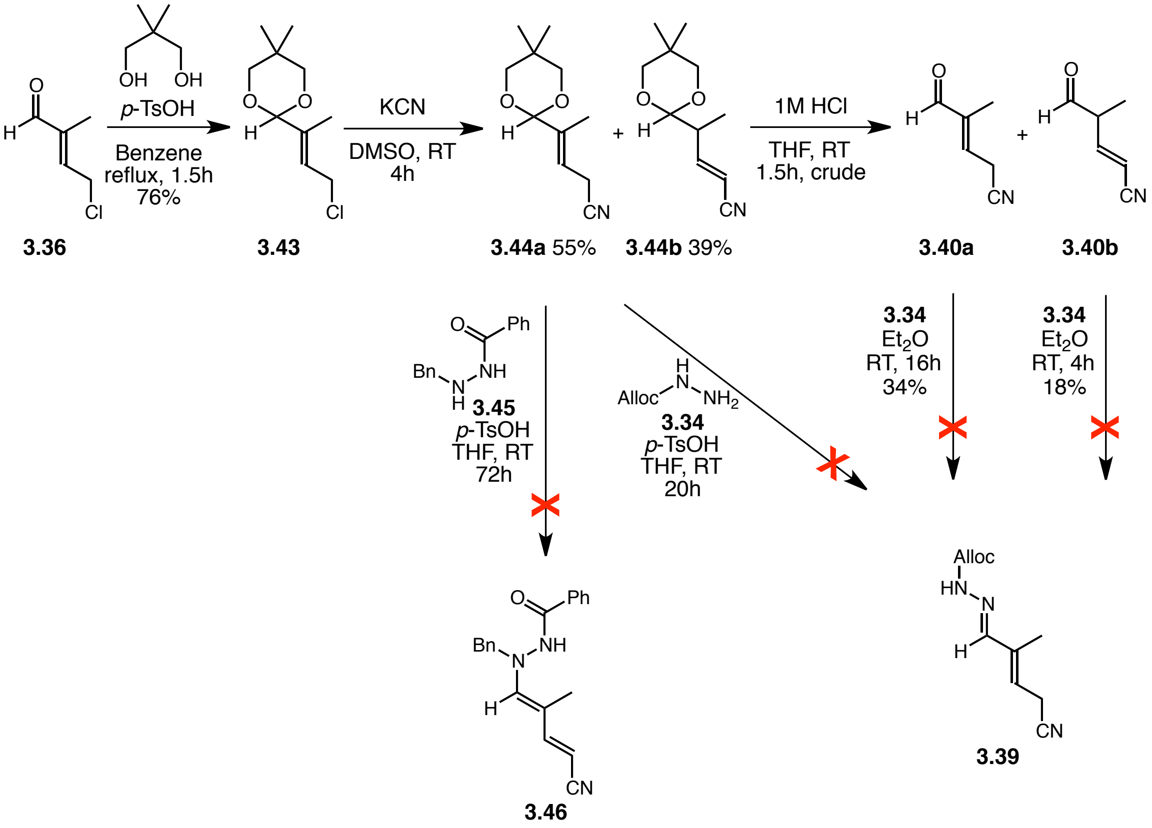


3.43 **3.44a** **3.44b**

Entry	Solvent [0.1M]	Time h	Temperature °C	Yield **3.44a**[a] %	Yield **3.44b**[a] %
1	DMSO	2.5	60	33	26
2	DMSO	4	RT	55	39
3	DMSO[b]	3	RT	0	0
4	THF/DMF	18	RT	11	n/a
5	DMF	1.5	RT	17	31
6	DMF[c]	1.5	RT	13	15
7	DMF	4	RT	20	34
8	DMF	16	RT	0	0

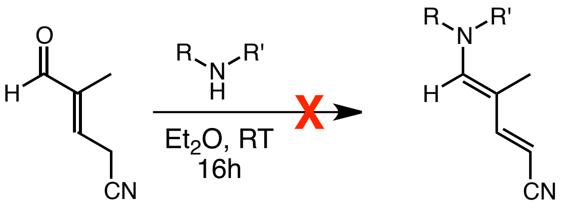
[a] isolated yields [b] 2.0 equiv. of KCN [c] ran at [1M]

The two nitrile isomers **3.44a** and **3.44b** were then separated and deprotected under acidic conditions (Scheme 3.46).[167] An inseparable mixture of products was obtained after condensation of each of the two aldehyde isomers with hydrazide **3.34**. The products isolated are presumably a mixture of hydrazone rotamers at equilibrium. Supporting this theory, both aldehyde isomers **3.40a** and **3.40b** independently gave a similar ^{1}H NMR ratio of product **3.39** isomers. Characterization or further reaction was not possible as the products were unstable at room temperature. A one-pot procedure was attempted from protected aldehyde **3.44a**, using *para*-toluenesulfonic acid as catalyst. Two different hydrazides were employed (3.45 and 3.34, Scheme 3.46) and traces of the desired product were observed by ^{1}H NMR after two days with hydrazide **3.34**. No further progression was noted and no product could be isolated. As the use of hydrazide **3.45** did not lead either to the desired product, the one-pot procedure was abandoned.



Scheme 3.46 – Second approach towards dienes 3.39 and 3.46

Condensation of aldehyde **3.40a** with different disubstituted amine derivatives (hydroxylamine, hydrazide and amine) was attempted in order to force isomerization to the aminodiene, to no avail (Eq. 3.6).[131f]



(3.6)

3.40a

3.46: R=Bn, R'=NHCOPh
3.47: R=Bn, R'=OH
3.48: R=R'=Bn

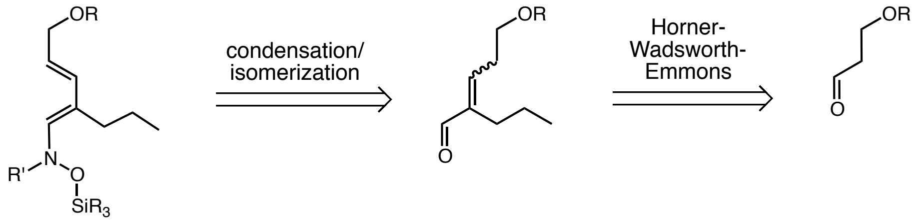
In light of the difficulties encountered in the synthesis of the 1st generation, the relevance of this family of aminodienes in the synthsesis of manzamine A was re-evaluted. The lack of reactivity of a push-pull diene due to the electron withdrawing group at position 4 could render a cycloaddition with the desired dienophile difficult. The aminodiene envisionned could be too electron poor for a Diels-Alder reaction with weakly reactive dienophile **3.28** (see section 3.5.1.1). A new aminodiene was therefore envisioned.

3.7.2 2nd Generation: 1-Silyloxylamino-1,3-diene

3.7.2.1 Synthesis of the Common Aldehyde

The nitrile was replaced by a protected alcohol, as it could also be converted to an aldehyde in the eventuality of the full synthesis. This way, the presence of two electron donating groups on the diene, thought not in synergy with respect to electron density, would improve the reactivity of the diene by raising the energy of its HOMO.

A new aminodiene synthesis involving a key Horner-Wadsworth-Emmons reaction was elaborated. Condensation of the newly formed α,β-unsaturated aldehyde with an amine derivative could then provide the desired aminodiene (Scheme 3.47).



Scheme 3.47 – Retrosynthetic pathway for the preparation of a silyloxylaminodiene

Starting with 1,3-propane diol, the *tert*-butyldiphenyl silyl (TBDPS) group was chosen as a protecting group due to its ease of removal.[169] After oxidation under Parikh-Doering conditions,[127] aldehyde **3.51** was reacted with Horner-Wadsworth-Emmons reagent **3.22**, formed by alkylation of triethylphosphonoacetate.[128,170] A major product was isolated, but could not be fully characterized. The presence of extra alkene peaks in the ^{1}H NMR spectrum suggested elimination of the protecting group, while none of the desired product was observed under the reaction conditions. (Scheme 3.48).

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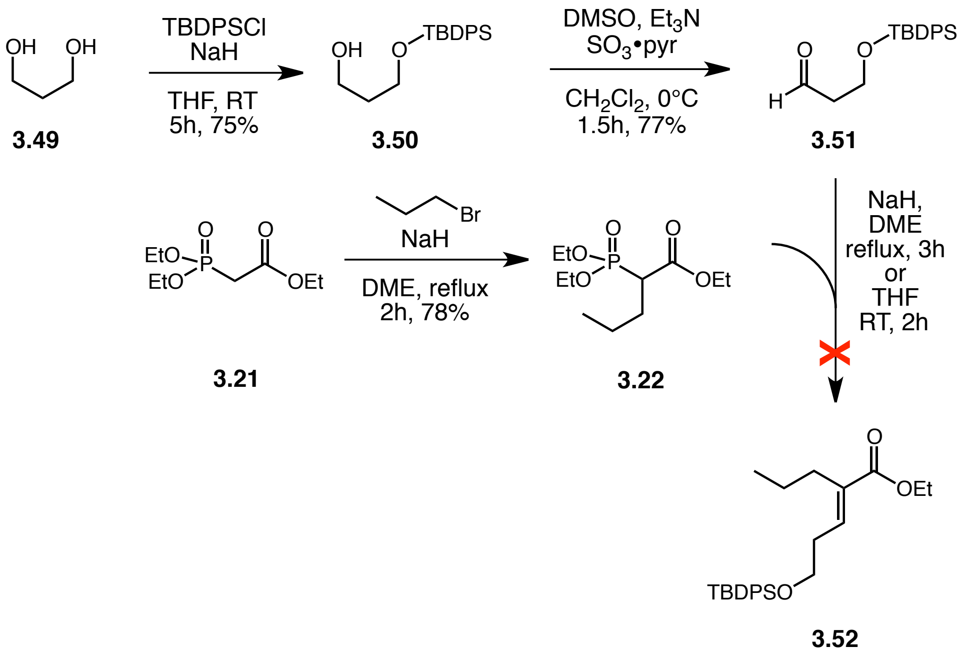
[169] Ferrié, L.; Boulard, L.; Pradaux, F.; Bouzbouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864.

[170] Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005***, 127*, 15704.



Scheme 3.48 – First attempt at the synthesis of the aminodiene precursor

Based on literature precedents, the silyl protecting group was replaced by a benzyl group.[171] The change in protection allowed for the Horner-Wadsworth-Emmons to reach completion (Scheme 3.49). The resulting product was an inseparable 50:50 mixture of Z/E alkene isomers, which degraded when submitted to reducing conditions.

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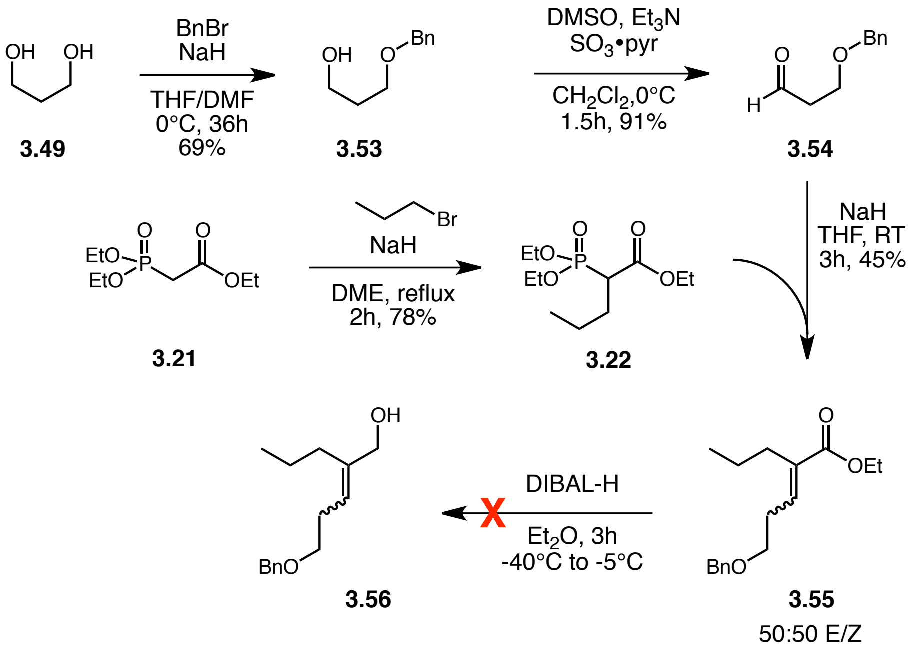
[171] Li, L-S.; Yikang, W.; Hu, Y-J.; Xia, L-J.; Wu, Y-L. *Tetrahedron: Asymmetry* **1998**, *9*, 2271.

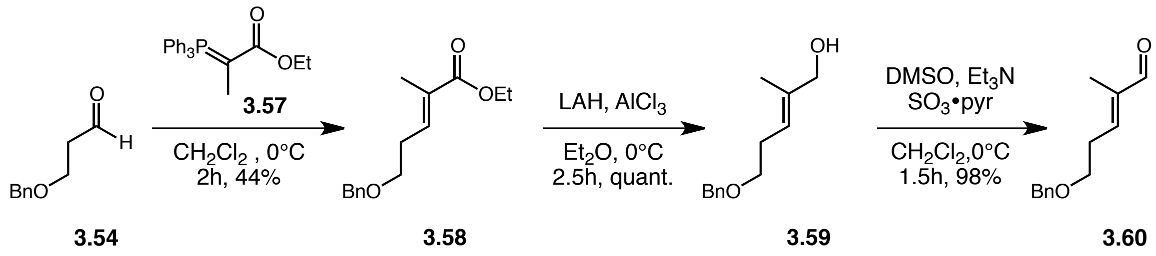


Scheme 3.49 – Second attempt at the synthesis of the aminodiene precursor

For simplicity, efforts were directed towards the use of commercially available stabilized Witig reagent **3.57**, which is commonly known to provide exclusively the *E*-isomer.[172] Under mild conditions, the reagent successfully afforded ester **3.58** in 44% yield as a single isomer (Scheme 3.50). Using reagent **3.57**, the propyl substituent was replaced by a methyl group, which would still display the important steric interactions. The ester was then reduced to the alcohol following a procedure by Inoue[173] and reoxidized to the aldehyde.[127]

---

[172] a) Chakraborty, T. K.; Tapadar, S. *Tetrahedron Lett.* **2003***, 44,* 2541. b) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett.* **2007**, *48*, 5177.
[173] Honda, K; Tabuchi, M.; Kurokawa, H.; Asami, M.; Inoue, S. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1387.



Scheme 3.50 – Synthesis of the aminodiene precursor

3.7.2.2 First Attempts at an Electronically Neutral 1,3-aminodiene

The aldehyde **3.60** was condensed with different bis-substituted amines in order to provide an aminodiene via iminium formation and isomerization, as it is one of the most common ways of synthesizing 1-amino-1,3-dienes (see Section 3.6.1). The first attempts at the synthesis of a morpholine-substituted diene led to degradation of the starting material. The aldehyde was then tentatively condensed with pyrrolidine using a Dean-Stark apparatus or K_2CO_3 as a base and drying agent, but both procedures failed to provide the aminodiene (Table 3.2).[174,131a] It was hypothesized that the allylic $A^{1,3}$ interaction between the methyl and the amine substituents was too important to allow condensation under the reaction conditions.

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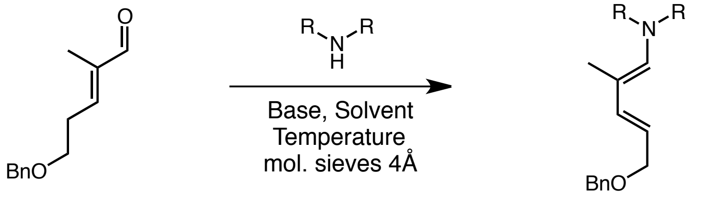
[174] Herr, M. E.; Heyl, F. W. *J. Am. Chem. Soc.* **1952**, *74*, 3627.

Table 3.2 – Attempts at the formation of the aminodiene by condensation

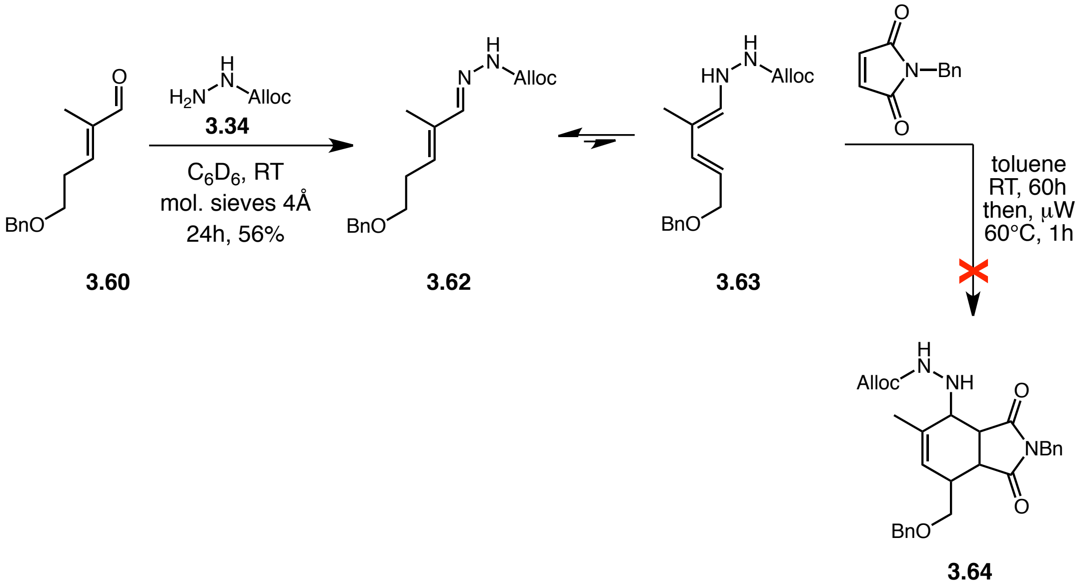


3.60 **3.61a-b**

Entry	Amine source	Solvent	Temperature °C	Base	Yield [a] %
1	morpholine	C_6D_6	100	–	0
2	morpholine	C_6D_6	100	K_2CO_3	0
3	pyrrolidine	benzene[b]	100	–	0
4	pyrrolidine	–	50	K_2CO_3	0[c]
5	pyrrolidine	–	110	K_2CO_3	0

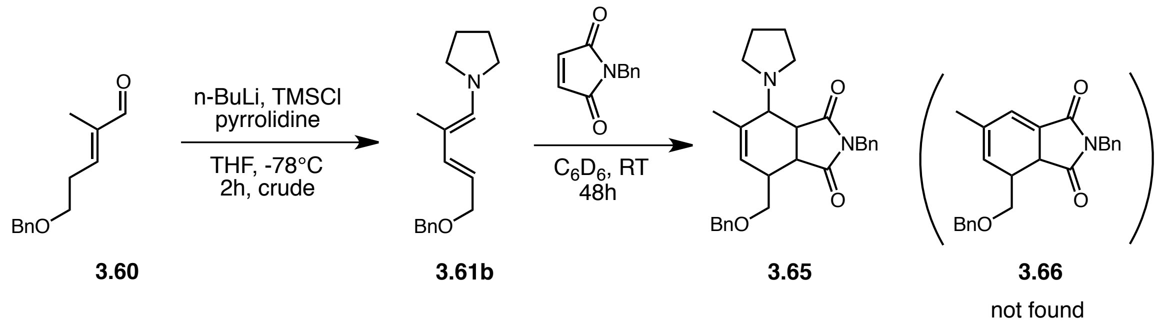
[a] isolated yields [b] Dean-Stark [c] s. mat. recovered

Aldehyde **3.60** was then combined to allylcarbamate **3.62** (see Section 3.7.1). The resulting hydrazone was heated in the presence of the highly reactive dienophile *N*-benzylmaleimide in the hopes of the molecule undergoing an *in-situ* isomerization and [4+2] cycloaddition. None of the desired Diels-Alder product nor hetero-Diels-Alder product were observed.



Scheme 3.51 – Attempts at *in-situ* trapping of isomerized hydrazone 3.63.

A breakthrough came from a procedure by Fañanás and coworkers, which was originally designed for condensation of diisopropylamine onto an aldehyde. It made use of *n*-BuLi to deprotonate the amine, hence forming a better nucleophile and TMSCl to provide a better leaving group.[131g] Aminodiene **3.61b** was obtained as a crude oil and trapped immediately with *N*-benzylmaleimide for structure confirmation (Scheme 3.52). Unfortunately, despite a newly formed alkene peak in the ^{1}H NMR spectrum, no pure Diels-Alder product could be isolated by column chromatography. The possibility of amine elimination and formation of diene **3.66** was envisioned, but it could not be observed by ^{1}H NMR or GC-MS.



Scheme 3.52 – Formation and Diels-Alder reaction of aminodiene 3.61b

3.7.2.3 Formation of the *N*-Silyloxyl-1,3-aminodiene

The observation of cycloaddition product **3.65** by ^{1}H NMR confirmed that the newly designed aminodiene could successfully undergo Diels-Alder reactions. Efforts were therefore directed towards the incorporation of a bi-functional moiety onto the aminodiene frame. The hydroxylamine functionality was chosen based on its minimized bulk and previous synthetic applications (see Chapter 2). Nitrone **3.67** was obtained in 71% yield using a procedure developed in the Beauchemin group.[175] It proved stable and the incorporation of a silyl group was used in order to induce isomerization (Scheme 3.53).[176] Aminodienes **3.68a** and **3.68b** were synthesized in two steps from common aldehyde **3.60** in 25% and 31% overall yield, respectively.

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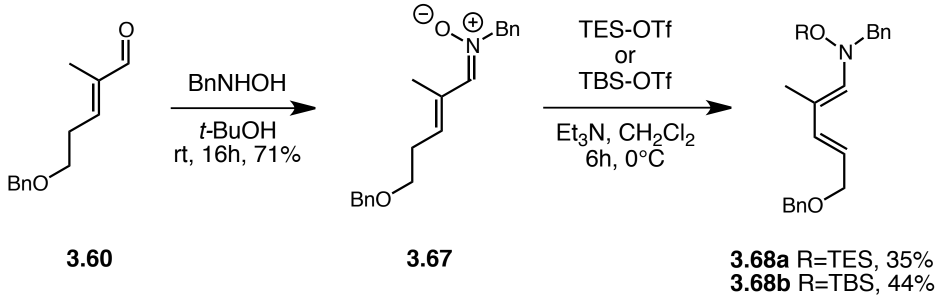
[175] Pfeiffer, J. Y.; Beauchemin, A. M. *Org. Lett.* **2009**,*74,* 8381.

[176] Evans, D. A.; Kværnø, L.; Dunn, T. B.; Beauchemin, A. M.; Raymer, B.; Mulder, J. A.; Olhava, E. J.; Juhl, M.; Kagechika, K.; Favor, D. A. *J. Am. Chem. Soc.* **2008**, *130,* 16295.



Scheme 3.53 – Formation of aminodiene 3.68

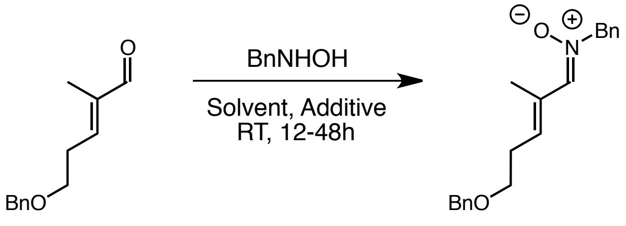
After the first attempts at the formation of nitrone **3.67**, it became obvious that the procedure developed for ketonitrones was not reproducible when applied to the synthesis of aldonitrone **3.67**. Competing dimerization of the product was observed and its formation was difficult to prevent. Various procedures were attempted[177] and conditions developed by the Merino group allowed for the formation of the desired nitrone in a reproducible 76% yield (Table 3.3).[178]

---

[177] a) Heinenberg, M.; Ritter, H. *Macromol. Chem. Phys.* **1999**, *200*, 1792. b) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999. c) Nakano, Y.; Kato, Y.; Imai, K.; Ochiai, E.; Namekawa, J-I.; Ishizuka, S.; Takenouchi, K.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *J. Med. Chem.* **2006**, *49*, 2398.

[178] Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1995**, *25*, 2275.

Table 3.3 – Optimization for the formation of nitrone 3.67



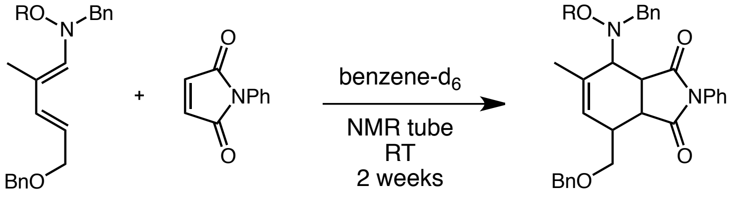
3.60 **3.67**

Entry	Solvent	Additives	Yield^a %
1	*t*-BuOH	–	9-75^b
2	EtOH	–	0^b
3	Et_2O	K_2CO_3	0^b
4	CH_2Cl_2	Et_3N	0^b
5	CH_2Cl_2	$MgSO_4$, $ZnCl_2$	76

^{a} isolated yields ^{b} dimerization observed

3.7.2.4 Key Step Attempts

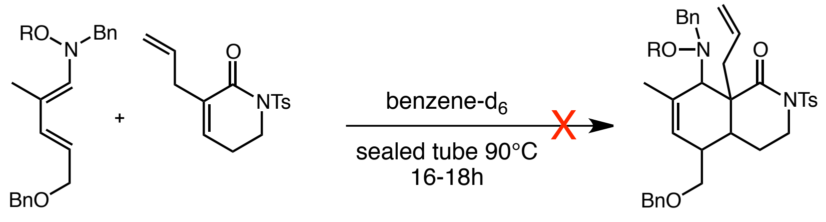
With a reliable method for the formation of nitrone **3.67** in hand (see Scheme 3.53), a Diels-Alder cycloadditon was ran with aminodienes **3.68** and *N*-phenyl maleimide. Aminodiene **3.68a** was left to react at room temperature over fourteen days, providing Diels-Alder adduct **3.70a** in 60% yield (Eq. 3.7). The reaction of aminodiene **3.68b** with *N*-benzyl maleimide (not shown) provided a similar conversion as with *N*-phenyl maleimide (90% vs. 95%). However, the Diels-Alder reaction took an extra seven days to reach completion, as the *N*-benzyl group lacked the favorable electron-withdrawing sp^2 character of the phenyl.



(3.7)

3.68a, R=TES **3.69** **3.70a** 60% isolated yield
3.68b, R=TBS **3.70b** >95% ^{1}H NMR yield

Aminodienes **3.68** were then reacted with the key lactam dienophile (see Section 3.5). While no reaction occured at room temperature, complete degradation of the aminodienes was observed upon heating in the presence of dienophile **3.28** (Eq. 3.8).



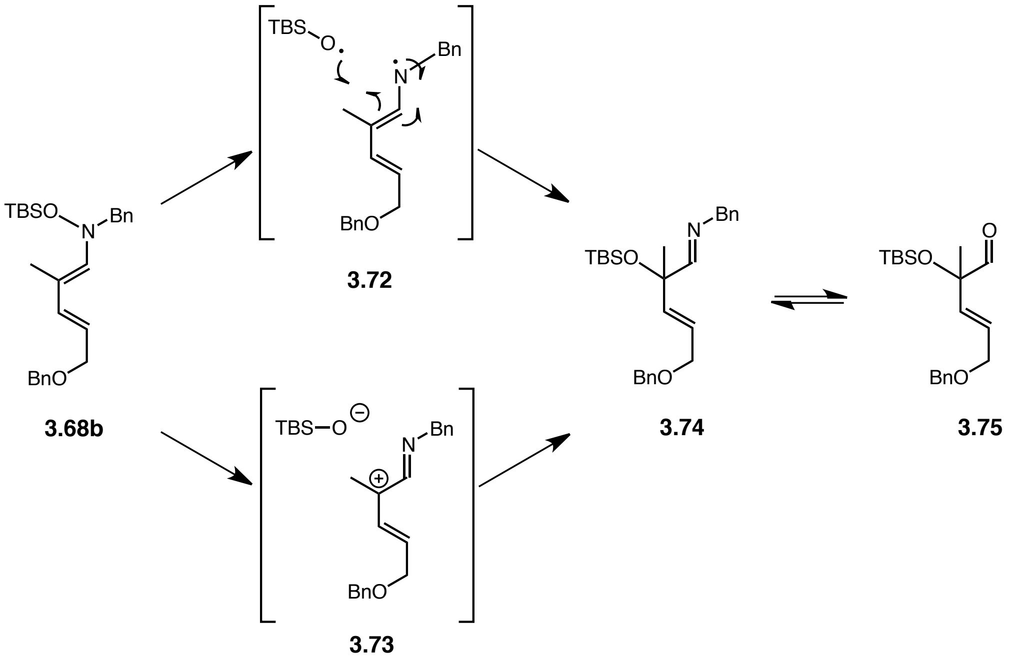
(3.8)

3.68a, R=TES
3.68b, R=TBS
3.68c, R=TIPS

3.28

3.71

Heating aminodienes **3.68a** and **3.68b** in the absence of any dienophile showed that degradation occured under the reaction conditions. Major side product **3.75** was isolated in 8% yield, which suggested that cleavage of the N-O bond, followed by reorganization and hydrolysis, was the major pathway of degradation. This novel rearrangement could be taking place either via homolytic cleavage of the N-O bond, followed by recombination, or by ejection of the silyloxide and recombination with a tertiary carbocation (Scheme 3.52). The rearrangement was not further investigated, but could become an interesting way to install an oxygen moiety alpha to an aldehyde.



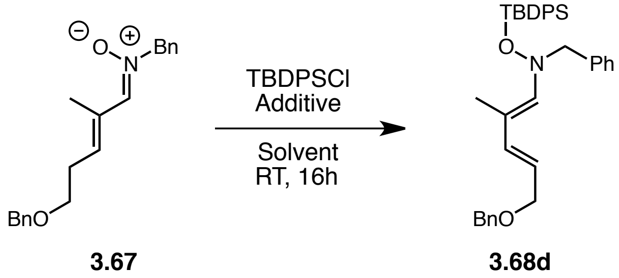
Scheme 3.54 – Proposed formation of major degradation product

In order to minimize rearrangement of the aminodiene, protection of the nitrone was attempted with the more robust *t*-butyldiphenylsilyl group. Despite multiple attempts, it was not possible to install this protecting group (Table 3.4).[176,179] It was hypothesized that the two phenyl substituents were too hindering, therefore preventing the attack of the weakly nucleophilic oxygen of the nitrone.

---

[179] a) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4786. b) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2007**, *129*, 14556. c) Lim, S. M.; Hill, N.; Myers, A. G.; *J. Am. Chem. Soc.* **2009**, *131*, 5763. d) Ventura, D. L.; Li, Z.; Coleman, M. G.; Davies, H. M. L. *Tetrahedron* **2009**, *65*, 3052.

Table 3.4 – Attempts at protecting nitrone 3.67 with a TBDPS protecting group



Entry	Additive	Solvent	Yield[a] %
1	Et_3N	CH_2Cl_2[b]	0[c]
2	Et_3N	CH_2Cl_2	0[c]
3	Et_3N, NaI	CH_3CN	0
4	KHMDS[d]	CH_2Cl_2	0
5	imidazole	CH_2Cl_2	0
6	imidazole	DMF	0

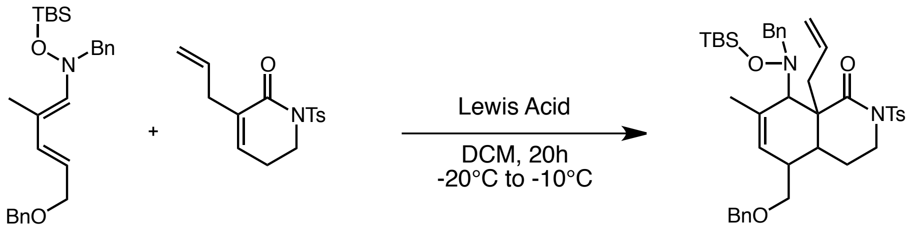
[a] isolated yields [b] TBDPSOTf [c] degradation
[d] -78°C to RT, 2h

Since aminodienes **3.68** are thermally unstable, catalysis with Lewis acids was investigated as a way to help run the Diels-Alder reaction with the desired dienophile **3.28**. Based on similarities to Oppolzer's sultam,[180] dialkylaluminum chlorides and zinc bromide were chosen as Lewis acid catalysts (Table 3.5). Traces of the possible product were observed by crude ^1H NMR after reaction with diethylaluminum chloride, but no isolation was possible (Table 3.5, entry 2).

---

[180] Oppolzer, W.; Seletsky, B. M.; Bernardinelli, G. *Tetrahedron Lett.* **1994**, *35*, 3509.

Table 3.5 – Catalysis of Diels-Alder reaction with Lewis acids

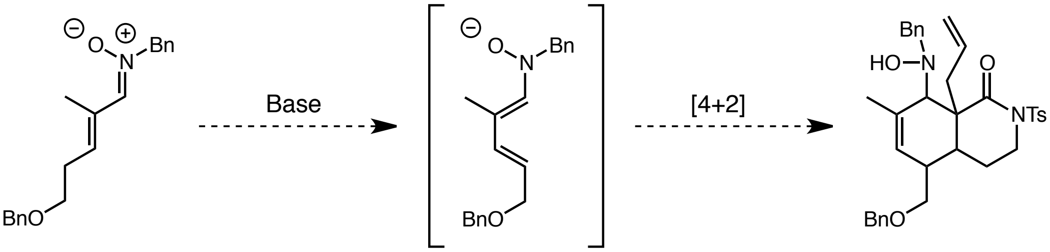


3.68b **3.28** **3.71b**

Entry	Lewis acid	Yield^a %
1	Me_2AlCl	0^b
2	Et_2AlCl	0^c
3	$ZnBr_2$	0

^{a} isolated yields ^{b} warmed to RT
^{c} traces

It was then speculated that the diene could be formed *in situ* under basic conditions, allowing the trapping of the anionic diene **3.76** by a dienophile via a formal [4+2] cycloaddition (Scheme 3.55).

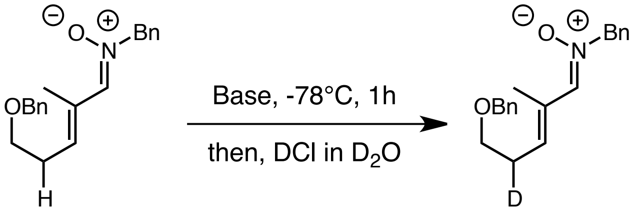


3.67 **3.76** **3.71e**

Scheme 3.55 – *In* situ formation of the aminodiene and possible use

In order to verify if deprotonation at the gamma position was possible, deuteration was attempted under strong basic conditions. When the reaction was performed in the presence of an amine-based base such as LDA, LHMDS or KHMDS, degradation of the starting material was observed (Table 3.6, entries 1-4). On the other hand, the starting material was recovered when the reaction was run in the presence of 0.1N KOH in D_2O. This is consistent with the assumed acidity of the γ-proton (pKa ~30). In the case of hydride bases, the use of KH afforded degradation, while NaH allowed partial recovery of the starting material. In all cases, no deuteration was observed at the γ-position according to the ^{1}H NMR spectra.

Table 3.6 – Deuteration of nitrone under basic conditions



3.67 **3.77**

Entry	Solvent	Base	Yield^a %
1	THF	LDA	0^b
2	THF	KHMDS	0^b
3	THF	LHMDS	0^b
4	THF	NaH^c	0^{bd}
5	THF	KH^c	0^b
6	D_2O^e	KOH	0^d

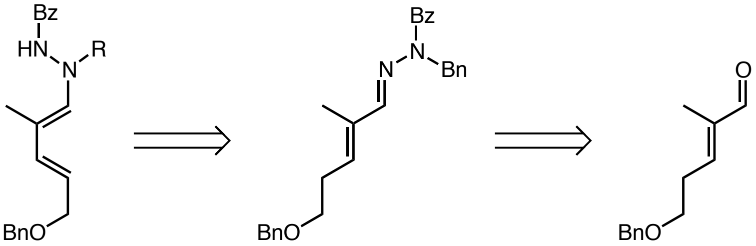
^{a} isolated yields ^{b} degradation ^{c} 0°C
^{d} s. mat. recovered ^{e} 60°C, 3h

Aminodienes **3.68a** and **3.68b** were the first of the newly designed aminodienes to undergo a Diels-Alder reaction with a reactive dineophile (see Eq. 3.7). However, despite thermal activation, Lewis acid or base catalysis, aminodienes **3.68a-c** did not undergo a Diels-Alder cycloaddition with the lactam-based dienophile **3.28** necessary in the synthesis of manzamine A. No reaction could be observed at room temperature and the weakness of the N-O bond led to rearrangements under thermal activation. While interesting for the synthesis of alpha-oxygenated aldehydes, these rearrangements were not desired in the course of this work and could not be prevented by interchaging the oxygen protecting group. As such, it was decided that the hydroxylamine bi-functional moiety of aminodiene **3.68** would be replaced by a more stable hydrazide.

3.7.3 3rd Generation: Hydrazide-Aminodiene

3.7.3.1 Hydrazide-Aminodienes via Condensation

As a mean to circumvent the stability issues encountered with silyloxylaminodiene 3.68 (see Scheme 3.54), a new hydrazide-aminodiene was designed. The thermo-stable bi-functional reagent was designed based on previous results in the Beauchemin group (see Section 2.7.1). As such, optimal benzoyl substitution on the distal nitrogen was envisioned. *N*-Alkyl substitution would force isomerization of the mono-protected hydrazone, affording the desired aminodiene (Scheme 3.56).



Scheme 3.56 – Proposed retrosynthesis for novel hydrazide-aminodiene

Common aldehyde **3.60** (see Section 3.7.2.1) was condensed with benzoic hydrazide, but the following benzyl-protection of hydrazone **3.79** did not provide the desired product (Scheme 3.57).[181] It is thought that hydrolysis of the hydrazone is occurring under the protection

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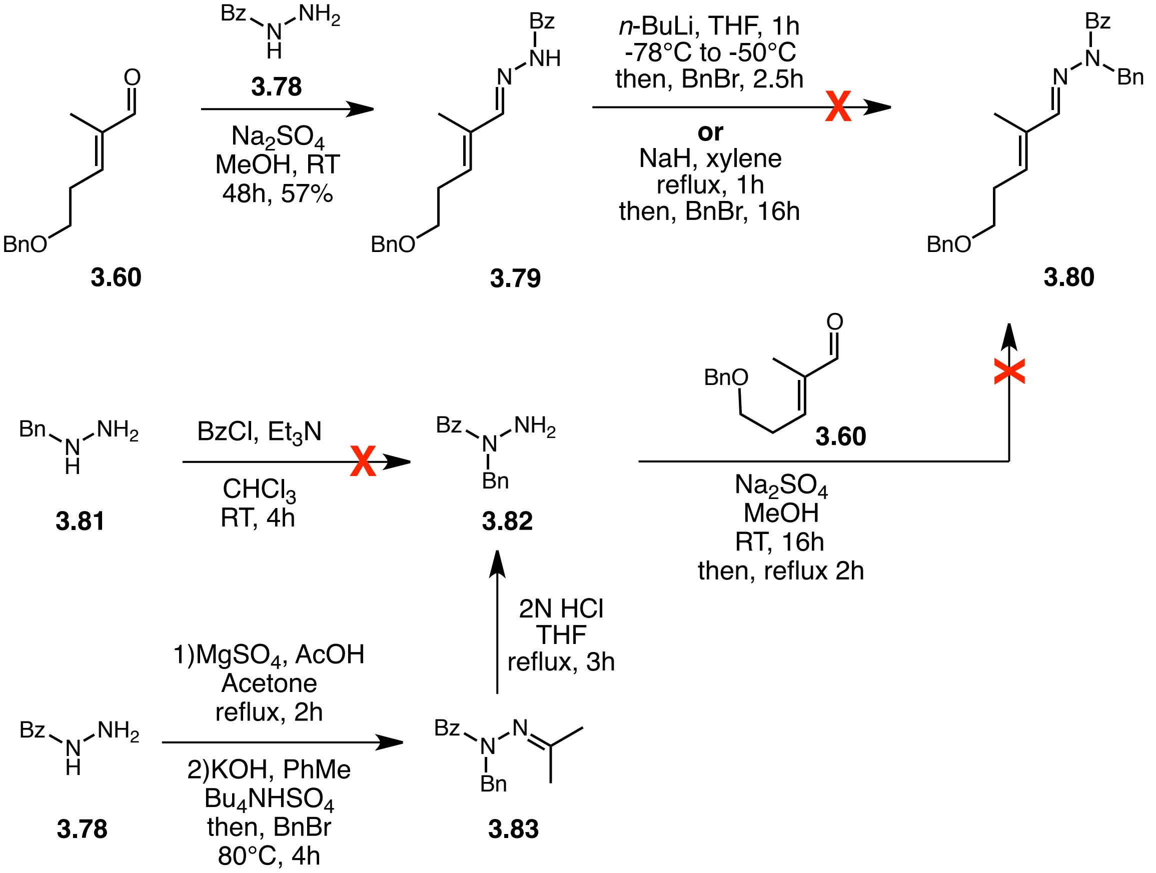
[181] a) Bredihhin, A.; Mäeorg, U. *Org. Lett.* **2007**, *9*, 4975. b) Pérez, J. M.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1995**, *51*, 6573.

conditions as aldehyde **3.60** was recovered. Further attempts, including benzoylation of benzylhydrazine[182] or benzylation of the hydrazide before condensation with aldehyde **3.60**[183] did not lead to the desired product.



Scheme 3.57 – Efforts towards the hydrazide-containing aminodiene

Following the conditions allowing the formation of nitrone **3.67** (see Section 3.7.2.3), the condensation of *N*-benzyl-*N'*-Boc hydrazide with aldehyde **3.60** was attempted, but none of the desired charged intermediate **3.85**, or its isomerized counterpart **3.86**, was observed (Eq. 3.9).[178]

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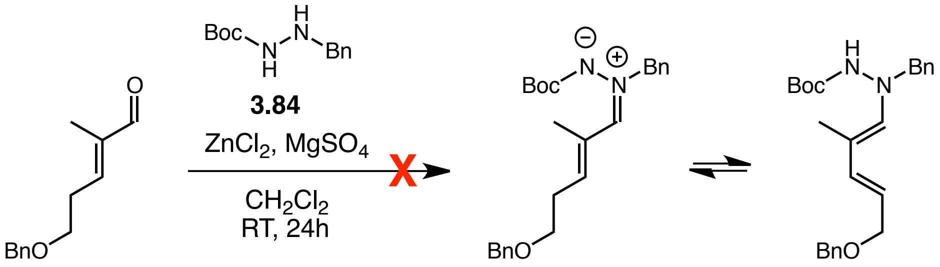
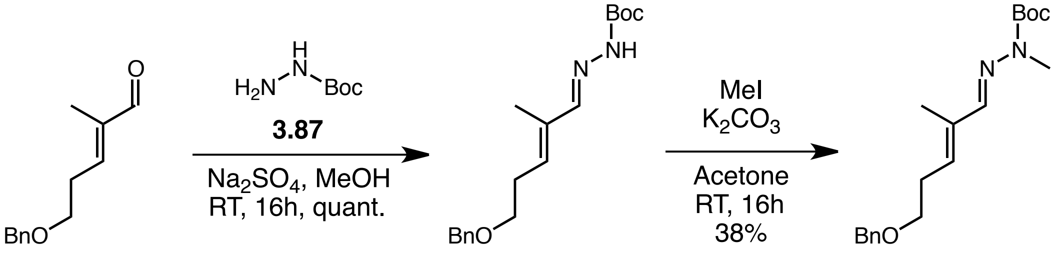
[182] Rooney, C. S.; Cragoe, E. J.; Porter, C. C.; Sprague, J. M. *J. Med.Chem.* **1962**, *5*, 155.
[183] Meyer, K. G. *Synlett* **2004**, 2355.



3.60 **3.85** **3.86**

(3.9)

A new hydrazone was therefore elaborated, where the removable benzyl protecting group was replaced by a permanent methyl group in order to minimize possible steric interactions. Such a hydrazide still contained an EWG, but lacked the N-H bond necessary for the hydrohydrazidation reaction to occur after the Diels-Alder cycloaddition (see Section 3.4). As such, this type of hydrazide-aminodiene was elaborated specifically to determine if it could react in a Diels-Alder reaction despite presenting more important steric interactions than the silyloxylaminodiene **3.68** (see Section 3.7.2). Hydrazone **3.89** was therefore synthesized by condensation of *t*-butyl carbazate with common aldehyde **3.60**, followed by methylation (Scheme 3.58).[184]



3.60 **3.88** **3.89**

Scheme 3.58 – Formation of hydrazide-aminodiene precursor

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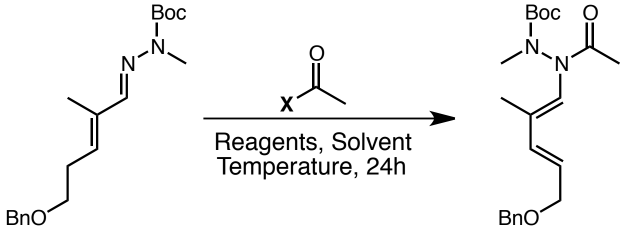
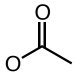
[184] Lawton, G.; Moody, C. J.; Pearson, C. J.; Williams, D. J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 885.

With protected hydrazone **3.89** in hands, a variety of acetylation methods were tried in order to form aminodiene **3.90** by isomerization. Acetic anhydride[185] or acetyl chloride[186] were employed in the presence of catalytic DMAP, but the substituted hydrazide could not be formed (Table 3.7, entries 1 and 2). Furthermore, only degradation was observed when forceful conditions, involving aluminium trichloride and formation of an acylium intermediate, were attempted (Table 3.7, entry 3).[187] Finally, γ-deprotonation with LDA and *in-situ* traping with acetic anhydride or *N*-phenylmaleimide was attempted, but neither of the desired products were observed (Scheme 3.59).

Table 3.7 – Efforts towards acetylation of hydrazone 3.89



3.89 **3.90**

Entry	X	Reagents	Solvent	Temperature °C	Yield[a] %
1		pyridine DMAP	$CDCl_3$	reflux	0[b]
2	Cl	pyridine DMAP	CH_2Cl_2	RT	0[b]
3	Cl	$AlCl_3$	EDC	RT[c]	0[d]

[a] isolated yields [b] s. mat. recovered [c] 1h [d] degradation

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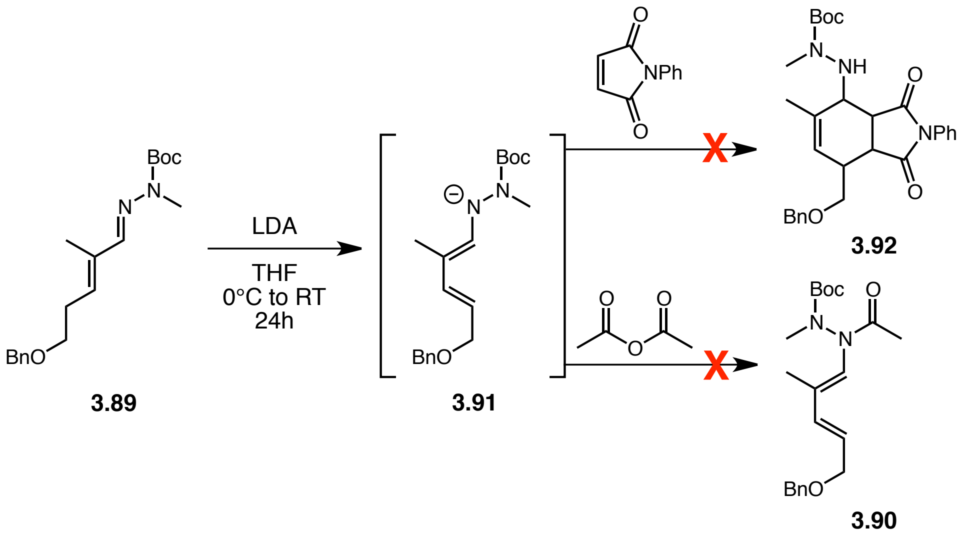
[185] Kamitori, Y.; Hojo, M.; Msuda, R.; Yoshida, T.; Ohara, S.; Yamada, K.; Yoshikawa, N. *J. Org. Chem.* **1988**, *53*, 519.

[186] Miyata, O.; Takeda, N.; Kimura, Y.; Takemoto, Y.; Tohnai, N.; Miyata, M.; Naito, T. *Tetrahedron* **2006**, *62*, 3629.

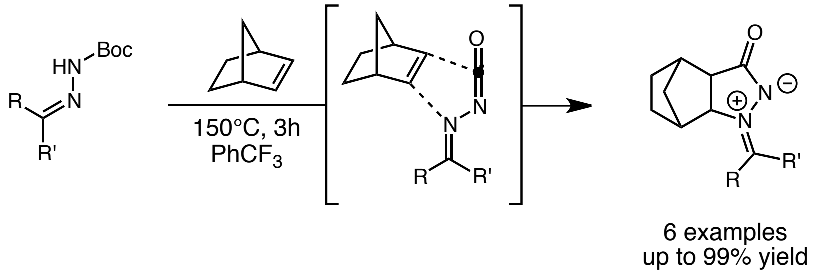
[187] Elwood, T.A.; Flack, W.R.; Inman, K.J.; Rabideau, P.W. *Tetrahedron* **1974**, *30*, 535.



Scheme 3.59 – Attempts at *in-situ* trapping of isomerized hydrazone 3.85

3.7.3.2 Hydrazide-Aminodienes via Other Methods

Further attempts at the formation of a hydrazide-containing aminodiene involved the use of intermolecular aminocarbonylation with iminoisocyanate and coupling reactions. The aminocarbonylation reactions were planned based on previous results in the Beauchemin group. It had been demonstrated that intermolecular aminocarbonylation could be obtained when reacting a ketone-derived *t*-butyl carbamate hydrazone with an activated or terminal alkene (Eq. 3.10 and 3.11).[188]



(3.10)

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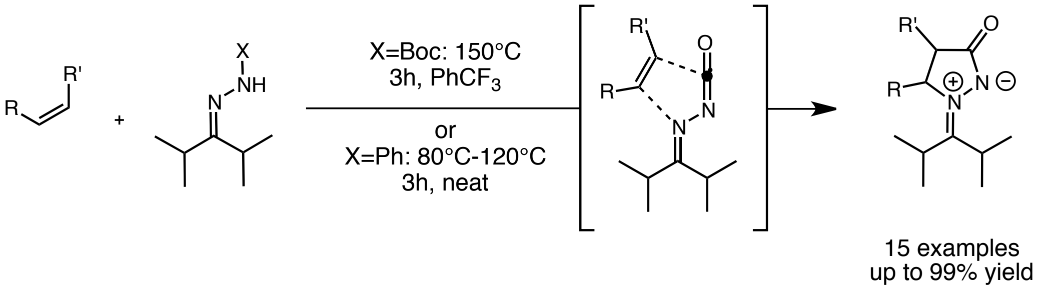
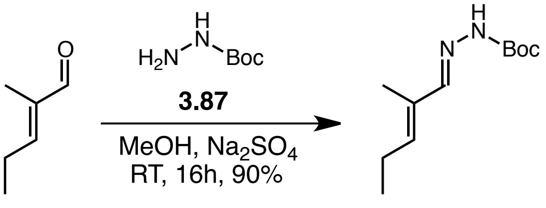
[188] Clavette, C.; Gan, W.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. unpublished results.



(3.11)

Working with commercially available 2-methyl-2-pentenal, hydrazone **3.94** was formed by condensation with *t*-butyl carbazate (Eq. 3.12).

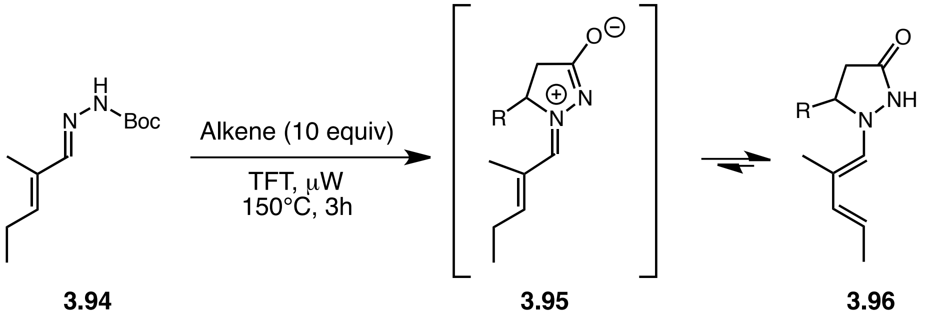


3.93 **3.94**

(3.12)

Two different alkenes were employed, based on results by Ph.D. student Christian Clavette. It was thought that after formation of the azomethine imine intermediate, an isomerization would allow neutralization of the charged intermediate and formation of the desired aminodiene. The use of an excess of 1-hexene did not lead to the desired product and these results were independent of the scale used (Table 3.8, entries 1 & 2). Intermolecular aminocarbonylation reactions performed with aldehyde-derived hydrazones are known to undergo further cycloaddition reactions from the azomethine imine intermediate.[188] This could explain why no desired product was observed when performing the reaction with aldehyde **3.93**.

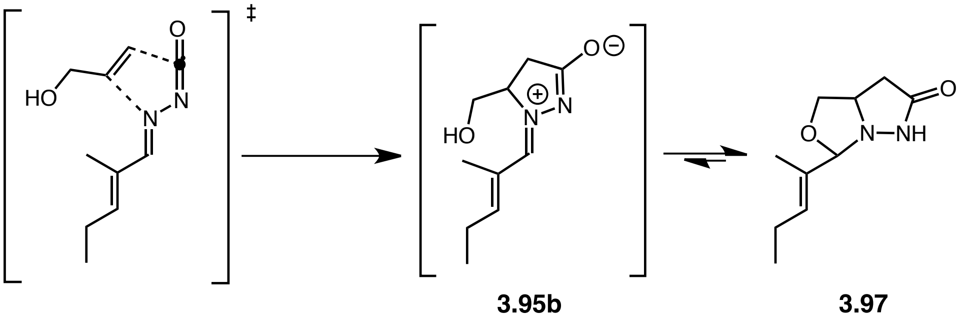
Table 3.8 – Attempts at the formation of an aminodiene via iminocarbonylation



Entry	Alkene	Yield^a %
1	1-hexene	0
2	1-hexene^b	0
3	allyl alcohol^c	0

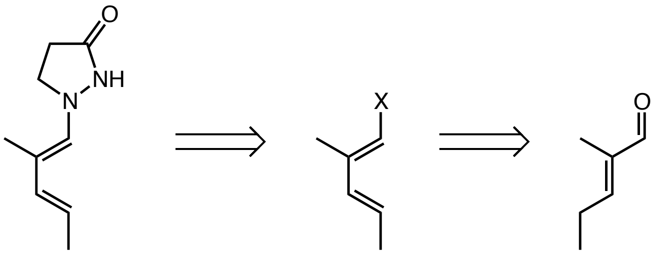
^{a} isolated yields ^{b} alkene as cosolvent
^{c} 200°C

It had been hypothesized that allyl alcohol could trap the charged intermediate formed after aminocarbonylation by means of 1,2-addition of the oxygen onto the iminium, but no traces of the desired product or the neutralized intermediate **3.97** were observed (Scheme 3.60, Table 3.8, entry 4).



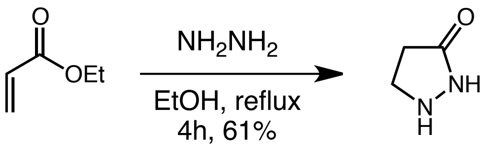
Scheme 3.60 – Intramolecular trapping of charged intermediate with allyl alcohol

It was previously reported by the Buchwald group that a hydrazide could be selectively coupled to either of its nitrogens depending on the conditions used (Scheme 3.61).[189] As such, coupling of a vinyl halide with an unprotected hydrazide was envisioned as the last attempt to form the hydrazide-aminodiene.



Scheme 3.61 – Formation of hydrazide-aminodiene via coupling reaction

The use of cyclic hydrazide **3.99** would minimize allylic $A^{1,3}$ interactions, while providing the EWG and N-H bonds needed for the hydrohydrazidation reaction. It was quickly synthesized following a procedure by the White group (Eq. 3.13).[190]



3.98 **3.99** (3.13)

The pseudo-halide triflate was first envisioned as a coupling agent, since it could easily be derived from an aldehyde. Submitting the 2-methyl-2-pentenal to strong basic conditions in the presence of *N*-phenyl-bis(trifluoromethanesulfonimide) led to degradation of the starting

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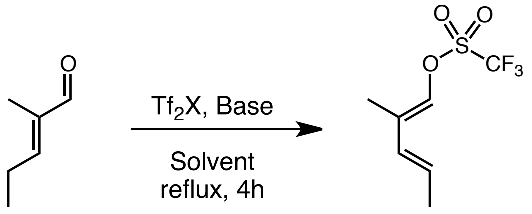
[189] Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

[190] Perri, S. T.; Slater, S. C.; Toske, S. G.; White, J. D. *J. Org. Chem.* **1990**, *55*, 6037.

material (Table 3.9, entry 1).[191] The reaction was therefore performed with weaker base 2,6-di-tert-butyl-4-methylpyridine and triflic anhydride.[192] Small amounts of the desired product were observed by ^{1}H NMR, but isolation by column chromatography or distillation proved difficult (Table 3.9, entries 2 & 3). Furthermore, the product degraded when left in the crude mixture and could not be used directly for coupling without purification.

Table 3.9 – Attempts at the formation of triflate diene 3.96 from 2-methyl-2-pentenal



3.93

3.100

Entry	Triflate source	Base	Solvent	Yield[a] %
1	Tf_2NPh	*t*-BuOK	THF[b]	0[c]
2	Tf_2O	DTBMP	CH_2Cl_2	0[d]
3	Tf_2O	DTBMP	CH_2Cl_2	0[e]
4	Tf_2O	DTBMP	CH_2Cl_2	0[f]

[a] isolated yields [b] 0°C, 2h [c] degradation [d] lost on column
[e] lost via distillation [f] crude degradation

Efforts were then directed towards the formation of a 1-iodo-1,3-diene coupling partner. Diene **3.102** was successfully formed from Shapiro-derived reactivity, but deemed impossible to purifiy as degradation was observed when purification by column chromatography or distillation were attempted.[193] It was therefore directly used in the following coupling reaction, but only degradation was observed (Scheme 3.62).[189]

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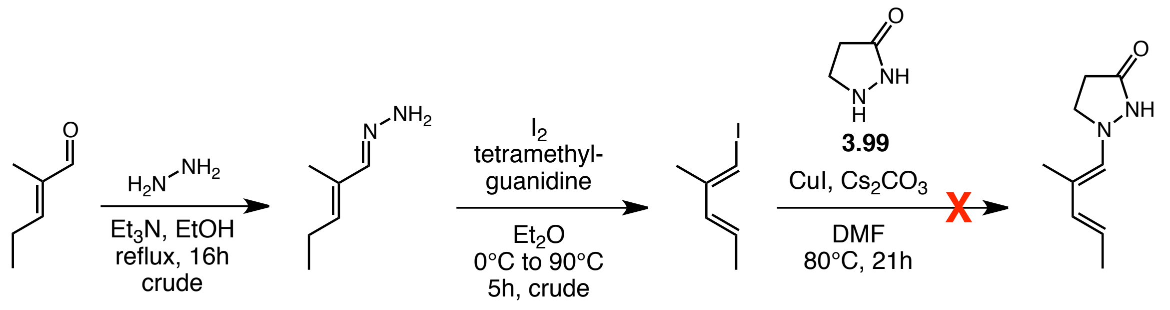
[191] Wada, A.; Nomoto, Y.; Tano, K.; Yamashita, E.; Ito, M. *Chem. Pharm. Bull.* **2000**, *48*, 1391.

[192] Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

[193] Takács, A.; Ács, P.; Farkas, R.; Kokotos, G.; Kollár, L. *Tetrahedron* **2008**, *64*, 9874.



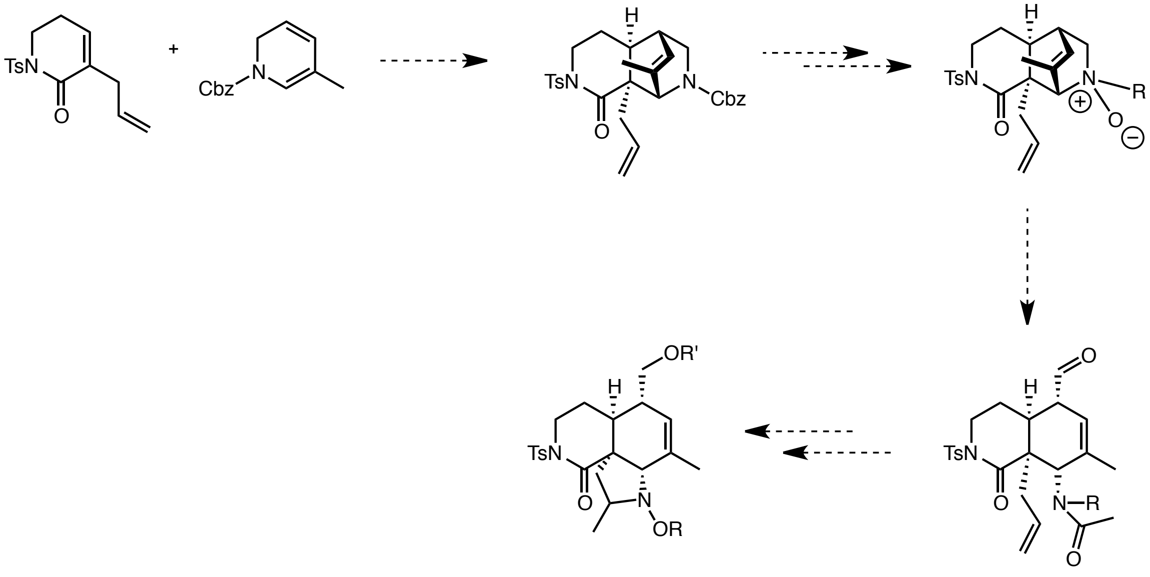
3.93 **3.101** **3.102** **3.103**

Scheme 3.62 – Attempts at aminodiene formation via coupling

From these experiments, it became obvious that the desired hydrazide-aminodiene could not be synthesized from condensation, aminocarbonylation or coupling reactions. When comparing with silyloxylaminodiene **3.68** (see Section 3.7.2.3), it was hypothesized that the increased sterics coming from the extra hydrazide *N*-substituent was the culprit. However, less hindered cyclic hydrazide **3.95** also failed to provide the desired product. In light on these results, the aminodiene needed for the key step of the synthesis was completely redesigned.

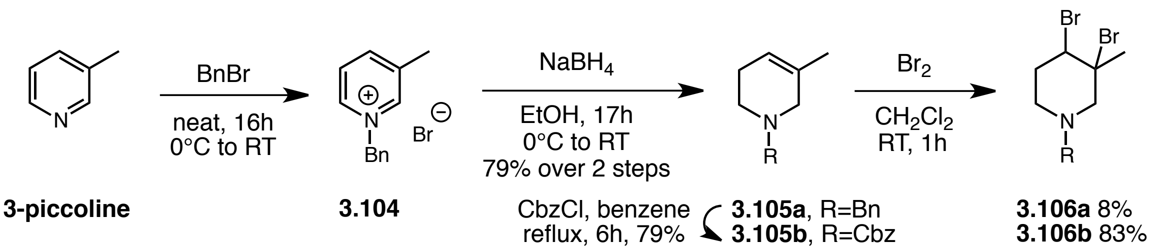
3.7.4 4th Generation: DHP Aminodiene

A cyclic aminodiene was chosen in an attempt to circumvent the degradation problems of silyloxylaminodienes and the synthetic challenges associated with hydrazides-containing aminodienes. The use of a DHP diene would still allow the formation of the desired core of manzamine A via a Diels-Alder reaction. After cycloaddition and oxidation of the tertiary amine, a Polonovski-Potier reaction would open the bicyclic system and afford the desired backbone (Scheme 3.63). The key Cope-type hydroamination reaction could then be performed as previously envisioned for the formation of the core of manzamine A with a slightly higher step count.



Scheme 3.63 – Synthetic plan for manzamine A using a cyclic aminodiene

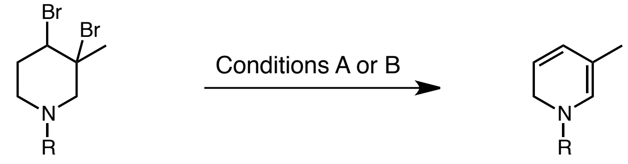
Synthesis of aminodiene **3.107** was executed according to a procedure by Fukuyama and coworkers, which involved reduction of a *N*-alkyl pyridinium salt, followed by the formation of a dibromopiperidine precursor (Scheme 3.64).[158d] In order to minimize protecting group interconversions, formation of the aminodiene with a benzyl protecting group was attempted in parallel to the known carboxybenzyl group.



Scheme 3.64 – Formation of the dibromo piperidine precursor

The formation of DHP diene **3.107a** from the dibromo precursor **3.106a** was irreproducible under basic conditions (Table 3.10, entries 1 & 2).[160c,194] However, it could be obtained using ethylaluminum dichloride in HMPA following a procedure by the Raucher group (Table 3.10, entry 4).[160c] No diene was formed when performing the reaction on the benzyl-protected piperidine **3.106b**. A more electron rich benzylated nitrogen would destabilize the negative charge forming at the 2-position upon deprotonation and prevent the elimination from taking place.

Table 3.10 – Formation of cyclic aminodiene under acidic and basic conditions



3.106a-b **3.107a-b**

Entry	Substrate	R	Conditions	Yield[a] %
1	**3.106a**	Bn	A	0
2	**3.106b**	Cbz	A	4
3	**3.106a**	Bn	B	0
4	**3.106b**	Cbz	B	28

Conditions A: $EtAlCl_2$, HMPA, 0°C to 60°C,1.5h
Conditions B: DABCO, CH_3CN, reflux, 6h
[a] ^1H NMR yields

Aminodiene **3.107b** was reacted with *N*-phenylmaleimide without further purification, as it was prone to rearomatization upon standing at room temperature. Heating the reaction neat provided the desired Diels-Alder adduct in 59% yield (Eq. 3.14). The same reaction conditions did not allow a Diels-Alder cycloadditon to proceed with the less reactive lactam

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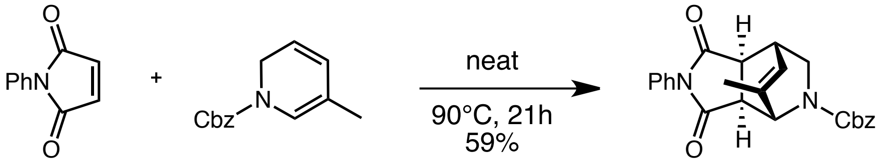
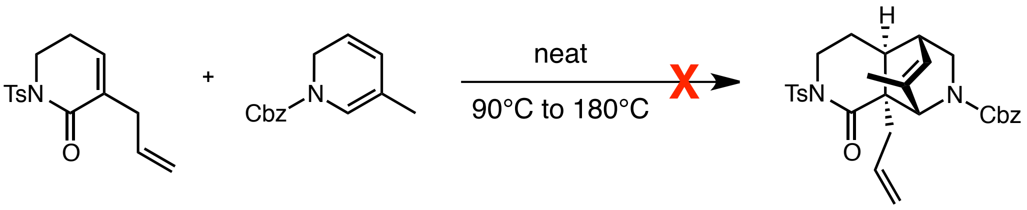
[194] Szántay, C.; Bölcskei, H.; Gács-Baitz, E. *Tetrahedron* **1990**, *46*, 171.

dienophile **3.28**. Heating at higher temperatures only afforded degradation and rearomatization of the aminodiene (Eq. 3.15).



(3.14)

3.69 **3.107b** **3.108**



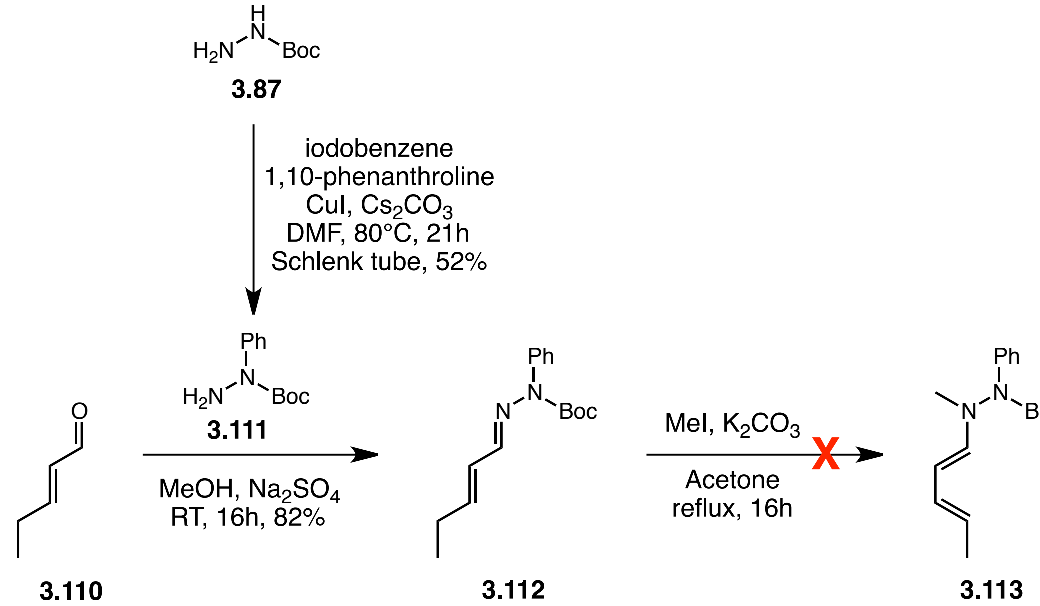
(3.15)

3.28 **3.107b** **3.109**

Based on the low yielding synthesis and isolation difficulties encountered in the preparation of the DHP aminodiene, combined with its lack of reactivity towards the key dienophile **3.28**, this aminodiene family was abandoned. Keeping in mind the successful Diels-Alder reactions obtained previously with silyloxylaminodiene **3.68** (see Section 3.7.2.4, Eq. 3.7), the silyloxylaminodiene and hydrazide-aminodiene families were revisited.

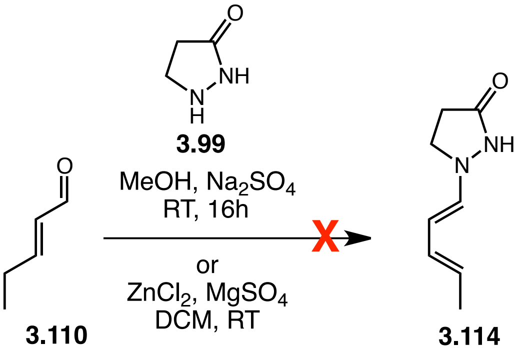
3.7.5 5th Generation: Aminodienes with Minimized Sterics

Steric interactions were thought to be the main reason behind the difficulties encountered with the silyloxylaminodienes reactivity in the Diels-Alder reaction and hydrazide-aminodienes formation (see Sections 3.7.2 and 3.7.3). As such, new substrates that lacked the alpha-substitution responsible for the allylic $A^{1,3}$ interaction were synthesized from *E*-pentenal. The aldehyde was first condensed onto the newly synthesized *N*-phenyl-*N*-Boc hydrazide providing hydrazone **3.113** (Scheme 3.65),[189] but the following methylation failed to provide the desired hydrazide.[184]



Scheme 3.65 – Attempts at formation of a hydrazide-aminodiene via condensation/isomerization

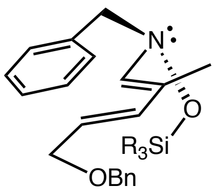
Condensation with di-substituted hydrazide **3.99** was then attempted under two known sets of conditions. However, none of the desired product was observed.[178]



(3.16)

During the same period, 1-silyloxylamino-1,3-dienes were also revisited. They had previously provided a Diels-Alder cycloaddition product with reactive dienophile *N*-

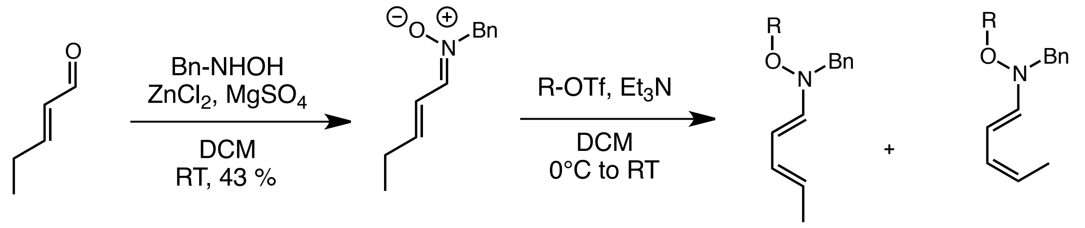
phenylmaleimide, but had failed to provide the desired model core of manzamine A. The instability of silyloxylaminodiene **3.68** upon heating was causing cleavage of the N-O bond and rearrangement (see Section 3.7.2.4). Furthermore, it was noted that even reactions with highly reactive dienophiles had proven lengthy, with reaction times ranging from two to three weeks. The later was thought to be attributable to the substituent moiety at the 2-position forcing the hydroxylamine protecting groups to shield both faces of the aminodiene, efficiently preventing the dienophile approach. Twisted in such a way, the nitrogen was also prevented from being conjugated with the diene, hence minimizing the reactivity of the later (Figure 3.5).



3.68

Figure 3.5 – Proposed conformation of aminodiene 3.68

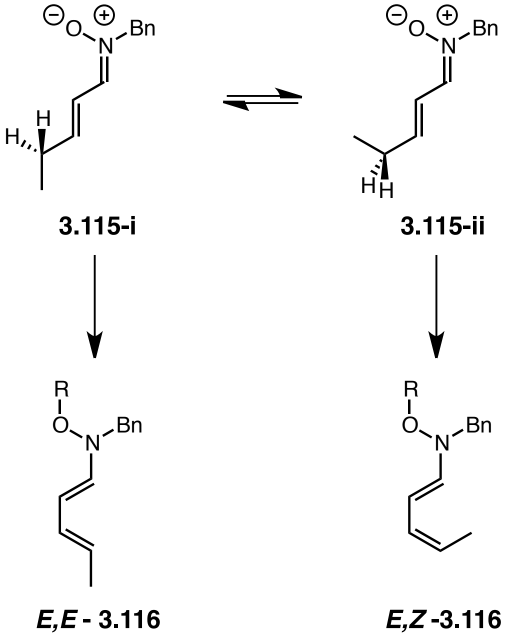
In order to prove this hypothesis, new 1-silyloxylamino-1,3-dienes were synthesized from *E*-pentenal. Protection of the nitrone oxygen with TES or TBS in basic conditions gave an inseparable mixture of the *E,E* and *E,Z* diene isomers (Scheme 3.66). In comparison, only the *E,E*-isomer was obtained upon formation of the alpha-methyl-substituted aminodiene **3.68**. The missing allylic $A^{1,3}$ interaction in the new substrate is thought to allow the presence of conformations **3.115-i** (s-trans) and **3.115-ii** (s-cis) during deprotonation, leading to the two diene isomers. The alpha-methyl substituted silyloxylaminodiene **3.68** only existed in conformation **3.68-i** (s-trans) (Scheme 3.67).



3.110 **3.115**

3.116a, R=TBS: 44% (*E,E*/*E,Z* 0.57:1)
3.116b, R=TES: 23% (*E,E*/*E,Z* 0.43:1)

Scheme 3.66 – Formation of less hindered silyloxylaminodienes

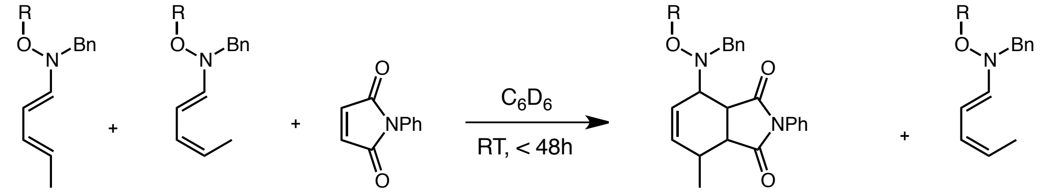


3.115-i **3.115-ii**

***E,E* - 3.116** ***E,Z* -3.116**

Scheme 3.67 – Conformations allowing the formation of *E,E* and *E,Z* isomers of aminodiene 3.113

The isomeric mixture was reacted with *N*-phenylmaleimide and provided cycloadducts **3.117a** and **3.117b** (Eq. 3.17). The *E,Z*-isomers proved unreactive and were recovered. Despite further heating and longer reaction times, major side-product **3.75** was not observed (see Scheme 3.54). This supported the hypothesis that the thermal instability of aminodiene **3.68** was due to steric interactions. Furthermore, the proposed negative effect of the alpha-substituent on the nitrogen conjugation and overall aminodiene reactivity (see Figure 3.5) was supported by the fact that reaction with aminodienes **3.116a** and **3.116b** both provided Diels-Alder adducts within less than 48h. The Diels-Alder products **3.117a** and **3.117b** were characterized as a mixture of endo and exo products (~0.84:1 endo/exo). Previously, only the endo cycloadduct was isolated when the reaction was performed with the alpha-methyl-substituted aminodiene **3.68**. This can be explained by the fact that the reaction was formerly ran at room temperature, while it had been warmed up to 60°C in the presence of dienes **3.116a** and **3.116b**. At this temperature, *N*-phenylmaleimide is known to undergo a reversible Diels-Alder cycloaddition.[195]



(3.17)

3.116a, R=TBS (*E,E*/*E,Z* 0.57:1)
3.116b, R=TES (*E,E*/*E,Z* 0.43:1)

3.69

3.117a 78% (endo/exo, 0.85:1)
3.117b 43% (endoe/exo, 0.83:1)

***E,Z*- 3.116a**
recovered

3.8 Conclusions

A new family of aminodienes was designed in an attempt to obtain the core of manzamine A. As such, an efficient way to synthesize these aminodienes containing a bi-functional moiety was elaborated and successfully executed (see Section 3.7.2.3, Scheme 3.53 and Section 3.7.5, Scheme 3.66). This method efficiently provided highly strained aminodienes **3.71a-b**, as well as less sterically hindered aminodienes **3.117a** and **3.117b**. The successful synthesis of these 1-silyloxylamino-1,3-dienes allowed their application in Diels-Alder reactions, providing cycloaddition products in synthetically useful yields (see Section 3.7.2.4, Eq. 3.7

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[195] Cooley, J. H.; Williams, R. V. *J. Chem. Ed.* **1997**, *74*, 582.

and Section 3.7.5, Eq. 3.17). In addition, a straightforward method for the alpha-oxidation of aldehydes has been brought to our attention. The use of aminodiene **3.116** solved the issues encountered with the initial development of the 1-silyloxylamino-1,3-diene family. As such, this newly elaborated aminodiene family is stable and reactive, which now opens the doors to the key step attempts combining both the Diels-Alder reaction and the Cope-type hydroamination.

Furthermore, it was confirmed that hydroamination reactions using hydrazides are not easily applicable in synthesis. The added steric hindrance prevented the synthesis of the 1-hydrazide-amino-1,3-diene family, while they failed to provide a hydrohydrazidation product in the desbromoarborescidine A synthesis (see Sections 3.7.3 and 2.7.4.2).

The core of manzamine A was not completed via the desired key Diels-Alder reaction-hydroamination sequence despite multiple attempts with different types of aminodienes. Nonetheless, a novel family of 1,3-aminodienes: the 1-silyloxylamino-1,3-dienes, was developed. The application of a cycloaddition-hydroamination sequence for the synthesis of [5,6] and [6,6] bicyclic systems has since been elaborated with this new family and is currently ongoing.

4 Hydrohydrazidation of Alkynes in the Synthesis of Azomethine Imines

4.1 Previous work by Ashley D. Hunt

The use of hydrazide moieties for the hydroamination of alkenes had previously been developed in the Beauchemin group as an alternative to the use of thermally unstable hydroxylamines (see Chapter 2, section 2.7.1).[88] The next step was therefore optimizing this reactivity towards alkynes, for the formation of azomethine imines. These charged substrates can be used in inter- and intra-molecular 1,3-dipolar cycloadditions, allowing the rapid incorporation of nitrogen moieties within a molecule.[196] Over the course of her Master's degree, Ms. Hunt elaborated efficient reaction conditions and developed an intramolecular substrate scope of seven examples, securing both five and six-membered rings (Table 4.1). The reaction tolerates substitutions next to the hydrazide moiety as well as on the terminal position of the alkyne. Furthermore, she established a method allowing the isolation of these charged molecules, which previously could only be characterized as derivatized species.[197] Following up on Ms. Hunt work, it was of interest to further probe the functional group tolerance of this intramolecular reactivity and increase the scope of the reaction.

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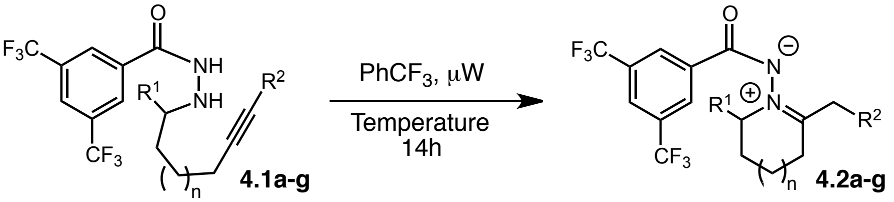
[196] Schantl, J. G. in *Science of Synthesis*; Padwa, A.; Bellus, D., Ed.; Thieme: New York, **2008**, vol. 27, p.731-824.

[197] Hunt, A. D. Intramolecular Cope-type hydroamination of alkenes and alkynes using hydrazides. M.Sc. Thesis, University of Ottawa, ON, 2011.

Table 4.1 – Formation of azomethine imines via hydrohydrazidation of alkynes by Ashley Hunt[197]



Entry	n	Alkynyl hydrazide	Temperature °C	Product	Yield^a %
1	1	R^1=R^2=H	140	**4.2a**	68
2	1	R^1=H, R^2=Ph	140	**4.2b**	72
3	1	R^1=H, R^2=3,5-dimethylphenyl	140	**4.2c**	92
4	1	R^1=Me, R^2=H	110	**4.2d**	91
5	1	R^1=*n*-Bu, R^2=H	120	**4.2e**	93
6	0	R^1=R^2=H	140	**4.2f**	44^b
7	0	R^1=H, R^2=Ph	150	**4.2g**	62

^{a} isolated yields ^{b} isolated as the reduced hydrazide

4.2 Intramolecular Hydrohydrazidation of Alkynes

The synthesis of new hydrohydrazidation precursors started with the Sonogashira cross-coupling of 5-hexyn-1-ol with either 2-iodothiophene or 1-bromo-4-iodobenzene.[198] Oxidation of alcohol **4.4** under Parikh-Doering conditions,[73] followed by condensation with bis-trifluoromethylbenzoyl hydrazide[197] and reduction of the formed hydrazone,[20b,74] afforded precursors **4.1i** and **4.1l** in 42% and 47% yield over three steps (Scheme 4.1).

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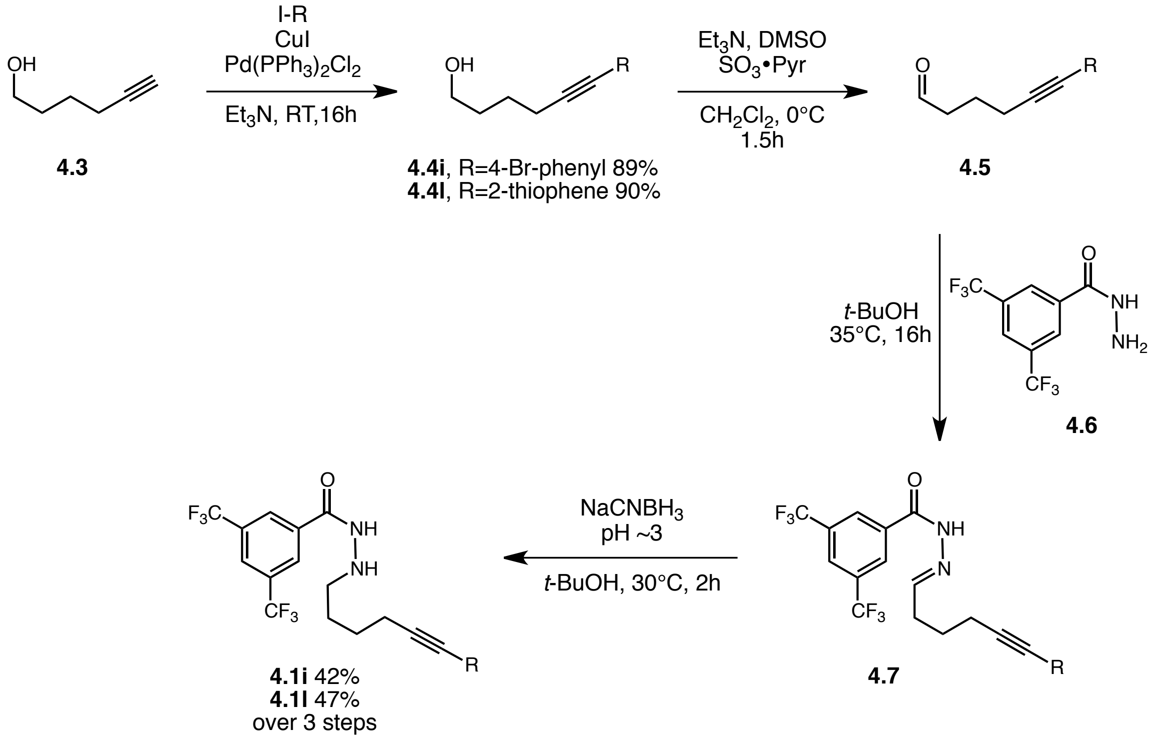
[198] Lin, G-Y.; Yang, C-Y.; Liu, R-S. *J. Org. Chem.* **2007**, *72*, 6753.



Scheme 4.1 – Synthesis of hydrohydrazidation precursors 4.1i and 4.1l

In order to synthesize precursor **4.1n**, 2-aminoethanol was *N*-protected with a Boc group, then *O*-protected with a TBS group.[199] Finally, it was *N*-alkylated with propargyl bromide.[198] The following Sonogashira cross-coupling reaction afforded intermediate **4.12**,[198] which was then *O*-deprotected[199] and oxidized.[73] Aldehyde **4.14** was condensed with bis-trifluoromethylbenzoyl hydrazide and the hydrazone formed was reduced to precursor **4.1n** in an overall 17% yield over 8 steps (Scheme 4.2).[20b,74]

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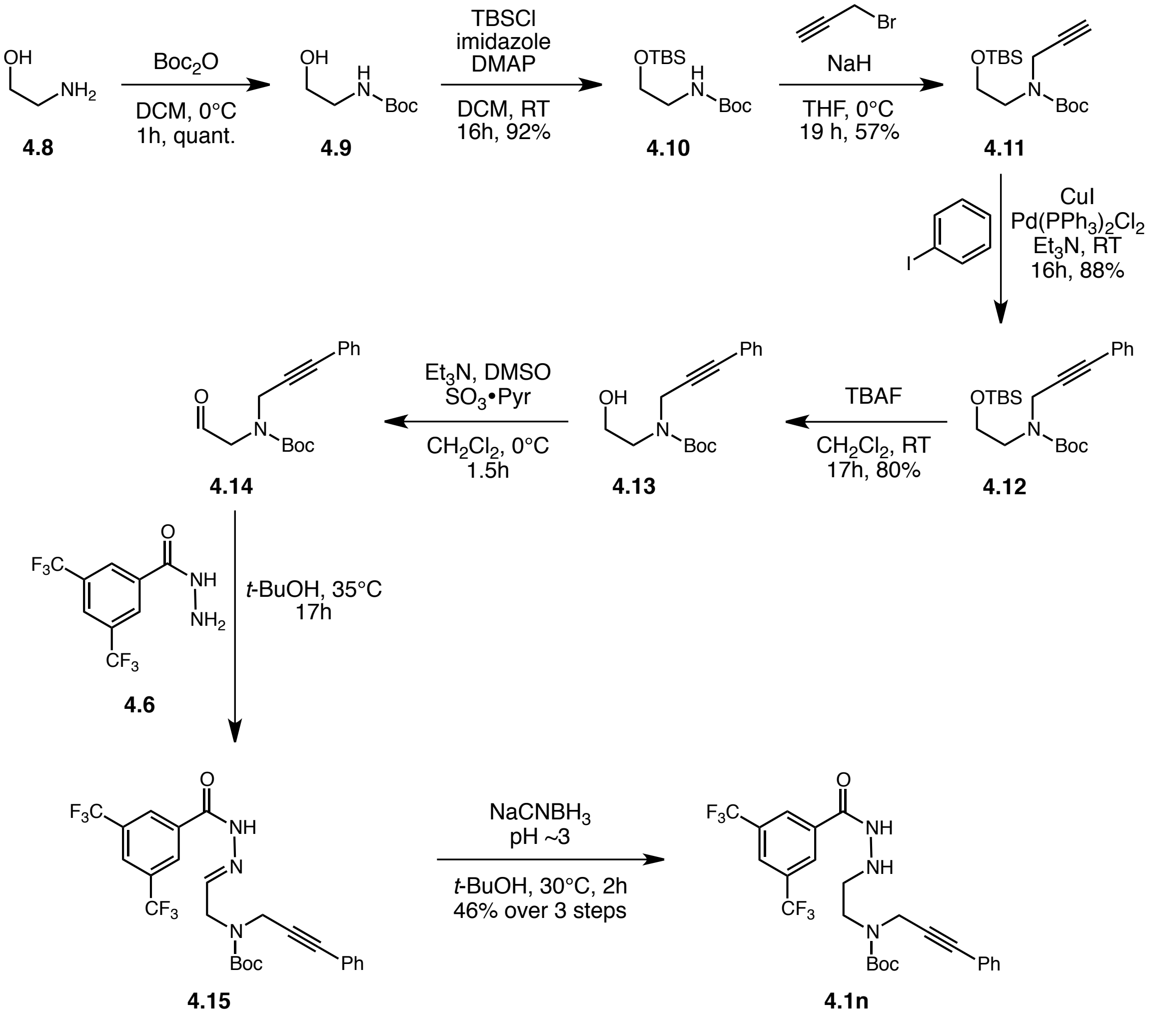
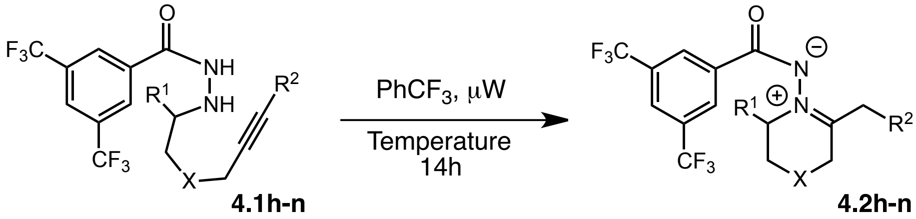
[199] Molander, G. A.; Cormier, E. P. *J. Org. Chem.* **2005**, *70*, 2622.



Scheme 4.2 – Synthesis of hydrohydrazidation precursor 4.1n

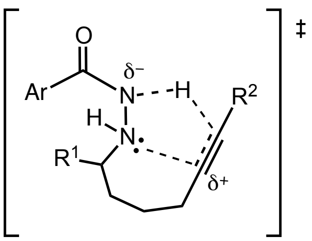
Thanks to work previously performed by Ms. Sandrine Taing, which involved the preparation of hydrazides, substrates **4.1h**, **4.1j** and **4.1m** were already on hand. Substrate **4.1k** was provided by Ms. Ashley Hunt. Alkyl and electron-rich aryl substitutions were well tolerated at the alkyne terminal position (Table 4.2, entries 1-3), as well as at the position alpha to the hydrazide moiety (Table 4.2, entry 6). The presence of a thiophene heterocycle or electron-withdrawing *p*-methylbenzoate on the terminal position of the alkyne caused a lowering of the yield, both affording 53% yield of azomethine imines **4.2k** and **4.2l**. This is consistent with destabilization of the positive charge forming at the 5-position during the transition state[197] by the ester of substrate **4.1k** and the inductive effect of the thiophene in substrate **4.1l** (Figure 4.1).[200] Finally, substrate **4.1n** did not afford the desired hydrohydrazidation product **4.2n**. Despite performing the reaction at lower temperature, no starting material was recuperated and complete degradation was observed (Table 4.2, entries 7 and 8).

Table 4.2 – Formation of azomethine imines via hydrohydrazidation of alkynes



Entry	X	Alkynyl hydrazide	Temperature °C	Product	Yield^{a} %
1	CH_2	R^1=H, R^2=Me	160	**4.2h**	67
2	CH_2	R^1=H, R^2=*p*-bromophenyl	140	**4.2i**	73
3	CH_2	R^1=H, R^2=*p*-methoxyphenyl	140	**4.2j**	86
4	CH_2	R^1=H, R^2=*p*-methylbenzoate	140	**4.2k**	53
5	CH_2	R^1=H, R^2=thiophene	120	**4.2l**	53
6	CH_2	R^1=Ph, R^2=H	120	**4.2m**	91
7	NBoc	R^1=H, R^2=Ph	140	**4.2n**	0^{b}
8	NBoc	R^1=H, R^2=Ph	110	**4.2n**	0^{b}

^{a} isolated yields ^{b} degradation



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[200] Joule, J. A.; Mills, K. *Heterocyclic chemistry* 4th ed.; Blackwell: Malden, **2000**; pp. 5-7.

Figure 4.1 – Proposed transition state for the hydrohydrazidation of alkynes

4.3 Conclusions

This project allowed furthering the knowledge on the novel hydrohydrazidation reaction on alkyne substrates previously elaborated by Ms. Hunt. As such, the formation of multiple azomethine imines was achieved. The method tolerated terminal and internal alkynes, as well as electron-rich and electron-poor substrates. Furthermore, the column chromatography isolation of these azomethine imines developed by Ms. Hunt was a first. It defined the way such charged compounds can now be handled and stored in the laboratory.

5 Supporting Information

5.1 *General Information.*

All reactions were performed in a flame-dried or oven-dried glass round bottom flasks, or 15-48 mL sealed tubes, under argon. Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm). 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 dipping in a potassium permanganate solution and heating.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 MHz or 400 MHz and 75 MHz or 100 MHz spectrometers respectively at ambient temperature. Spectra are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm for ^{1}H NMR and $CDCl_3$ at 77.0 ppm, C_6D_6 at 128.1 ppm for ^{13}C NMR). ^{1}H NMR data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70ev at the Ottawa-Carleton Mass Spectrometry Centre. Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and were recorded on an ABB Bomem, MB Series 100 Fourier Transform Infrared spectrometer (FT-IR). Melting points were determined using a Gallenkamp P1106G melting point apparatus.

Materials. Dichloromethane, isopropanol, DME and toluene were dried by distillation over calcium hydride. Tetrahydrofuran and diethyl ether were dried by distillation over sodium/benzophenone ketyl. DMSO and DMF were dried over activated 3Å molecular sieves. Triethylamine was dried by distillation over calcium hydride, while diisopropylamine and diethylamine were dried by distillation over KOH pellets. Unless otherwise noted, all commercial materials were used without further purification.

5.2 General Procedure for the Synthesis of Protected Hydroxylamines via Mitsunobu

Based on a procedure by the Alemany group.[201] To a 0°C solution of *N*-*tert*-butyl carbamate-*O*-*tert*-butyl carbonate hydroxylamine (2.34 mmol), the alcohol (2.34 mmol) and triphenylphosphine (7.02 mmol) in THF (23 mL) was added di-isopropylazodicarboxylate (7.02 mmol) dropwise. The solution was stirred at 0°C for 25 min. It was then concentrated *in vacuo* and directly purified by flash chromatography on silica gel.

5.3 General Procedure for the Boc-Deprotection of Hydroxylamines

A solution of the protected hydroxylamine (1.46 mmol) in dichloromethane and trifluoroacetic acid (4:1) (15 mL) was stirred at room temperature for 30 min. The solution was concentrated *in vacuo* and purified directly by flash chromatography on silica gel treated with (1%) triethylamine.

5.4 General Procedure for the Synthesis of Aldehydes

Based on a procedure by Greene and coworkers.[202] To a 0°C solution of the alcohol (2.34

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[201] Parry, R. J.; Tao, T.; Alemany, L. B. *Org. Lett.* **2003**, *5*, 1213.
[202] Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383.

mmol) and DMSO (7.68 mmol) in dichloromethane (10 mL) was added triethylamine (7.63 mmol). The solution was stirred for 5 min at 0°C before addition sulfur trioxide pyridine complex (7.04 mmol). The solution was stirred at 0°C for 1.5h before addition of a saturated solution of NH_4Cl. The mixture was then warmed to room temperature and extracted three times with dichloromethane. The organic extracts were combined and washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude was purified by flash chromatography on silica gel.

5.5 General Procedure for the Reduction of Oximes

Based on a procedure by the House and Warner groups.[203] To a solution of oxime (0.35 mmol) in methanol (21.0 ml) at room temperature under argon was added sodium cyanoborohydride (0.42 mmol). A pinch of methyl orange was added as indicator. A solution of HCl in methanol (1:5) was added dropwise to keep the solution pink (pH ~3). When the color of the solution was constant for 45 min, the reaction solution was basicified to pH 8 with a solution of 2.5% NaOH in water and poured in brine. The mixture was extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel.

5.6 General Procedure for the Allylation of Hydroxylamines

To a solution of hydroxylamine (0.54 mmol) and potassium carbonate (1.08 mmol) in THF (0.54 mL) at room temperature under argon was added allyl bromide (2.70 mmol) dropwise.

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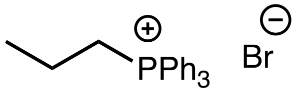
[203] a) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863. b) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601.

The solution was stirred at room temperature for 4h. It was then dissolved in dichloromethane, the remaining K_2CO_3 was filtered off and the filtrate was concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel.

5.7 Preparation of the Cope-type Hydroamination Substrates (Chapter 2)



***n*-Propyl triphenylphosphonium bromide (Scheme 2.18).** Based on a procedure by Young and coworkers.[204] In a sealed tube equipped with a magnetic stirbar was added triphenylphosphine (19.1 g, 73.0 mmol) and bromopropane (6.7 mL, 73.2 mmol). The tube was sealed and heated at 135°C for 24 h. After cooling to room temperature, the crude solid was triturated with Et_2O, filtered and dried *in vacuo*. The crude was then recristalized with MeOH:Et_2O (1:6) to give the desired product as a white solid (26.4 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90-7.88 (m, 3H), 7.83-7.78 (m, 12H), 3.58 (dt, *J*=8.2, 13.4 Hz, 2H), 1.56 (m, 2H), 1.70 (td, *J*=1.7, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 134.8 (d, *J*=2.9 Hz, 1C, CH), 133.5 (d, *J*=10.1 Hz, 2C, CH), 130.1 (d, *J*=12.4 Hz, 2C, CH), 118.5 (d,

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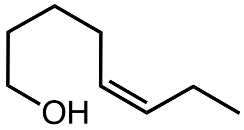
[204] Young, S. T.; Turner, J. R.; Tarbell, D. S. *J. Org. Chem.* **1963**, *28*, 928.

J= 85.6 Hz, 1C, C_4), 21.8 (d, J= 49.8 Hz, 1C, CH_2), 15.8 (d, J= 4.1 Hz, 1C, CH_3), 14.8 (d, J=18.3 Hz, 1C, CH_2); The carbon spectral data corresponds to that reported in literature.[205]



(*Z*)-Oct-5-en-1-ol (Scheme 2.18, 2.3). Based on procedures by the Jaenicke and Keyes groups.[206] To a solution of freshly distilled δ-valerolactone (2.80 mL, 29.9 mmol) in toluene (100 mL) at –60°C was added a 1.0 M solution of Dibal-H in toluene (35.9 mL, 35.9 mmol) dropwise. The reaction solution was stirred at –60°C for 16h at which point MeOH (0.242 mL, 5.98 mmol) was added. In another round bottom flask under argon, equipped with a magnetic stirbar, was dissolved *n*-propyl triphenylphosphonium bromide (16.8 g, 39.4 mmol) in THF (45.0 mL) at 0°C. To this solution was added a solution of *n*-BuLi in hexanes (16.2 mL, 38.4 mmol). This reaction solution was warmed to room temperature and stirred for 45 min before being cooled back to 0°C. The reduced δ–valerolactone solution was then added via cannula. The combined mixtures were refluxed 1 h, cooled to room temperature and transferred to an Erlenmeyer containing brine. The reaction mixture was then extracted three times with ethyl acetate. The organic extracts were combined and washed with HCl 5%, a saturated solution of $NaHCO_3$ and brine. They were then dried over Na_2SO_4 and

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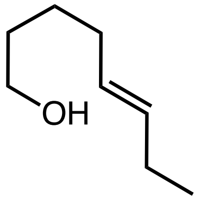
[205] Gray, G.A. *J. Am. Chem. Soc.* **1973**, *14*, 7736.

[206] a) Boland, W.; Ney, P.; Jaenicke, L. *Synthesis* **1980**, 1015. b) Andrus, M.B.; Li, W.; Keyes, R F. *J. Org. Chem.* **1997**, *62*, 5542.

concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with gradients from 0% to 20% of EtOAc in hexanes to yield the desired product as a colorless oil (3.46 g, 90%). The isomers E/Z were separated by flash chromatography with silver nitrate treated silica gel with an eluent of 1% MeOH in dichloromethane to yield the *Z*-isomer as a colorless oil (1.93 g, 50%). TLC R_f 0.62 (70% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.42-5.28 (m, 2H), 3.65 (t, *J*= 6.6 Hz, 2H), 2.10-1.99 (m, 4H), 1.63-1.54 (m, 2H), 1.47-1.38 (m, 2H), 1.25 (s, 1H), 0.96 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 131.9, 128.7, 62.9, 32.3, 26.8, 25.8, 20.5, 14.4; IR (film): 3355, 3005, 2963, 2873, 1652, 1455, 1303, 1067, 719 (cis) cm^{-1}; HRMS (EI): Exact mass calculated for $C_8H_{16}O_1$ $[M]^+$: 128.1201; found: 128.1195.



(*E*)-Oct-5-en-1-ol (Scheme 2.18, not shown): The isomers E/Z were separated by flash chromatography on silver nitrate treated silica gel with an eluent of 1% MeOH in dichloromethane to yield the E isomer as a colorless oil (277 mg, 7%).[207] TLC R_f 0.62 (70% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.50-5.35 (m, 2H), 3.65 (t, *J*= 6.5 Hz, 2H), 2.04-1.97 (m, 4H), 1.61-1.54 (m, 2H), 1.46-1.38 (m, 2H), 1.23 (s, 1H), 0.96 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 132.4, 128.8, 62.9, 32.2 (2C), 25.7, 25.6, 13.9;

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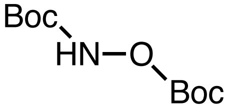
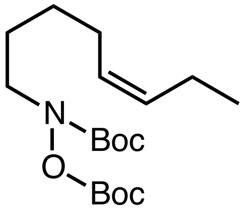
[207] Li, T-S.; Li, J-T.; Li, H-Z. *J. Chromatogr. A* **1995**, *715*, 372.

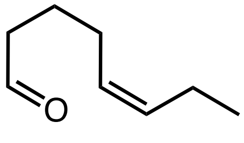
IR (film): 3341, 3032, 2961, 2872 1720, 1457, 1374, 1060, 966 (trans) cm^{-1}; HRMS (EI): Exact mass calculated for $C_8H_{16}O_1$ $[M]^+$: 128.1201; found: 128.1205.



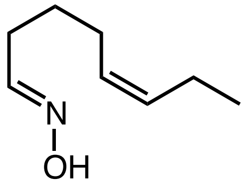
***N-tert*-Butyl carbamate-*O-tert*-butyl carbonate hydroxylamine (Scheme 2.18).** Based on a procedure by the Alemany group.[201] To a solution of hydroxylamine hydrochloride (1.00 g, 14.4 mmol) and triethylamine (4.40 mL, 31.7 mmol) in THF:H_2O (1:1) (60 mL) at 0°C was added Di-*tert*-butyl dicarbonate (8.8 g, 40 mmol). The solution was warmed to room temperature and stirred for 16h. It was then concentrated *in vacuo*. The residue was extracted three times with dichloromethane. The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 2.5% EtOAc in hexanes to yield the desired product as a colorless oil (2.09 g, 62%). TLC R_f 0.50 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.57 (s, 1H), 1.51 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.6, 153.5, 85.4, 83.1, 27.9 (3C), 27.5 (3C) cm^{-1}; The spectral data corresponds to that reported in literature.[201] Commercially available.



(*Z*)-*N*-*tert*-Butyl carbamate-*O*-*tert*-butyl carbonate-*N*-hydroxyoct-5-en-1-amine (Scheme 2.18, not shown). Synthesized according to the general procedure 5.2 using the corresponding alcohol (0.300 g, 2.34 mmol). The crude mixture was concentrated *in vacuo* and directly purified by flash chromatography on silica gel with an eluent of 2.5% EtOAc in hexanes to yield the desired product as a colorless oil (483 mg, 60%). TLC R_f 0.77 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.46-5.19 (m, 2H), 3.62-2.52 (m, 2H), 2.12-1.94 (m, 4H), 1.68-1.29 (m, 4H), 1.53 (s, 9H), 1.47 (s, 9H), 0.94 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 154.80, 152.2, 131.9, 128.5, 84.5, 81.9, 49.9, 28.0 (3C), 27.5 (3C), 26.5, 26.5, 20.4 (2C), 14.3; IR (film): 3004, 2979, 2935, 2873, 1787, 1715, 1457, 1394, 1369, 1247, 1152, 754 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{18}H_{33}NO_5$ $[M-(Boc)_2]^+$: 143.1310; found: 143.1321.



(*Z*)-Oct-5-enal (Scheme 2.19, 2.2). Synthesized according to the general procedure 5.4 using the corresponding alcohol (0.300 mg, 2.34 mmol). The crude mixture was purified by flash chromatography on silica gel with an eluent of 1% EtOAc in hexanes and yielded the desired product as a colorless oil (136 mg, 46%). TLC R_f 0.85 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.77 (s, 1H), 5.50-5.20 (m, 2H), 2.44 (dt, *J*= 7.3, 1.7 Hz, 2H), 2.12-1.97 (m, 4H), 1.73-1.55 (m, 2H), 0.96 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.7, 132.9, 127.6, 43.3, 26.3, 22.0, 20.5, 14.2; IR (film): 3009, 2963, 2925, 2872, 2807, 2709, 1726, 1458, 751 cm^{-1}; The spectral data corresponds to that reported in literature.[208]



(*Z*)-Oct-5-enal oxime (Scheme 2.19, 2.4). In a sealed tube equipped with a magnetic stirbar was dissolved (*Z*)-oct-5-enal (0.050 g, 0.40 mmol) and hydroxylamine (50% in water, 0.073 mL, 1.2 mmol) in isopropanol (4 mL). The tube was sealed and heated at 115˚C for 5h. After cooling to room temperature, the reaction mixture was diluted with a saturated solution of $NaHCO_3$ and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 20% EtOAc in

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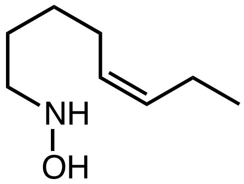
[208] Wálchli, P.C.; Eugster, C.H. *Helv. Chim. Acta.* **1978**, *61*, 885.

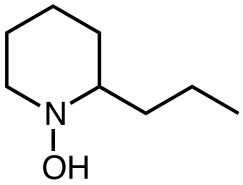
hexanes to yield the oxime product (50 mg, 89%). As a mixture of isomers: TLC *R*f 0.43 and 0.32 (20% EtOAc/hexanes); Isomer #1: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.44 (t, *J*= 6.1 Hz, 1H), 5.48-5.24 (m, 2H), 2.23 (ap q, *J*= 7.4 Hz, 2H), 2.17-1.94 (m, 4H), 1.65-1.50 (m, 2H), 0.95 (t, *J*=7.5 Hz, 3H); Isomer #2: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.88 (m, 1H), 5.48-5.24 (m, 2H), 2.45 (ap q, *J*= 7.6 Hz, 2H), 2.17-1.94 (m, 4H), 1.65-1.50 (m, 2H), 0.95 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm as a mixture of isomers 152.7, 152.1, 132.6, 132.5, 127.9, 127.8, 29.0, 26.7, 26.5, 26.4, 26.0, 24.6, 24.5, 20.5, 14.3 (2C); IR (film): 3341, 3005, 2962, 2933, 2868, 1657, 1455, 1070, 718 cm^{-1}; HRMS (EI): Exact mass calculated for $C_8H_{15}NO$ [M]$^+$: 141.1154; found: 141.1165.



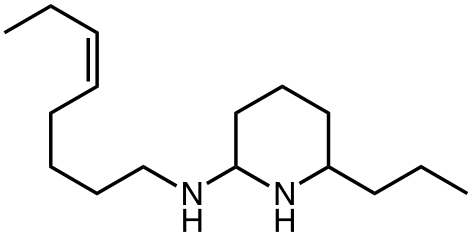
(*Z*)-*N*-Hydroxyoct-5-en-1-amine (Scheme 2.18 and 2.19, 2.1). Synthesized according to the general procedure 5.3 using the corresponding Boc-protected hydroxylamine (0.500 g, 1.46 mmol). The crude mixture was purified directly by flash chromatography on silica gel treated with (1%) triethylamine with an eluent of 20% EtOAc and 1% Et_3N in hexanes to yield the desired compound as a colorless oil (433 mg, 80%).

Alternate synthesis with the corresponding oxime (0.050 g, 0.35 mmol), according to the general procedure 5.5. The crude mixture was purified by flash chromatography on silica gel with an eluent of 100% EtOAc to yield the hydroxylamine 16 as a colorless oil (22 mg, 44%). TLC R_f 0.56 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.73 (s, 2H), 5.43-5.25 (m, 2H), 2.96 (t, *J*= 7.1 Hz, 2H), 2.11-1.97 (m, 4H), 1.63-1.52 (m, 2H), 1.46-1.34 (m, 2H), 0.95 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 132.1, 128.5, 53.4, 27.1, 26.8, 26.1, 20.5, 14.3; IR (film): 3294, 3005, 2961, 2932, 2859, 1652, 1454, 1310, 1066 cm^{-1}; LRMS m/z (relative intensity): 40.9877 (19.8%), 57.0761 (100.0%).

5.7.1 Procedure for the Cope-Type Hydroamination Reaction

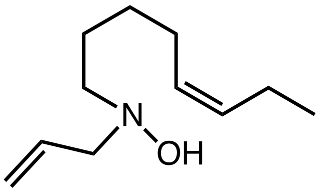


***N*-Hydroxy-coniine (Table 2.1, 2.8).** In a sealed tube equipped with a magnetic stirbar was dissolved (*Z*)-*N*-hydroxyoct-5-en-1-amine (0.10 g, 0.72 mmol) in *n*-Propanol (60 mL) and sodium cyanoborohydride (0.044 g, 0.72 mmol). Argon was bubbled in the solution for 10 min. The tube was sealed and heated at 140°C for 16h. After cooling to room temperature, the reaction mixture was dissolved in EtOAc, then washed with Brine twice. The organic extract was then dried on Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 80% EtOAc in hexanes to yield the desired compound as a colorless oil (23 mg, 23%); TLC R_f 0.26 (80% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.32 (ap d, *J*= 11.3 Hz, 1H), 2.49 (ap t, *J*= 13.0 Hz, 1H), 2.29-2.22 (m, 1H), 1.96-1.82 (m, 2H), 1.74-1.54 (m, 3H), 1.44-1.10 (m, 5H), 0.92 (t, *J*= 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 67.5, 59.7, 35.5, 30.9, 25.8, 23.8, 18.9, 14.4; IR (film): 3203, 2937, 2860, 1447, 1040 cm^{-1}; HRMS (EI): Exact mass calculated for $C_8H_{17}NO$ $[M]^+$: 143.1310; found: 144.1342.

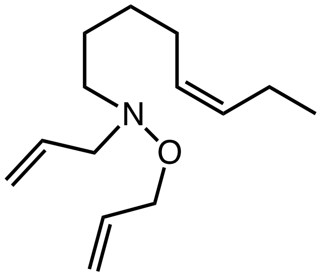


(*Z,Z*)-*N*-(2-Propylpiperidin-6-yl)oct-5-en-1-amine (Table 2.1, 2.9). Proposed structure. Observed as a side product of the cyclization reaction. TLC *R*$_f$ 0.93 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 5.40-5.28 (m, 2H), 3.99 (dd, J= 13.2, 6.4 Hz, 1H), 3.47 (m, 1H), 2.90-2.80 (m, 2H), 2.65-2.56 (m, 1H), 2.08-1.99 (m, 4H), 1.82-1.72 (m, 1H), 1.82-1.35 (m, 13H), 1.25 (s, 1H), 0.96 (t, J= 6.26 Hz, 3H), 0.95 (t, J= 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 131.7, 129.0, 102.8, 79.3, 67.1, 49.8, 49.7, 27.8, 27.6, 27.1, 26.5, 26.2, 21.9, 20.5, 14.4, 11.3; IR (film): 3005, 2960, 2865, 1458, 1371 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{16}H_{34}N_2$ $[M]^+$: 252.2565; found: 252.2281.

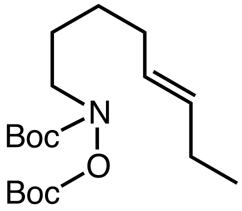
5.8 Preparation of the CHMR Sequence Substrates (Chapter 2)



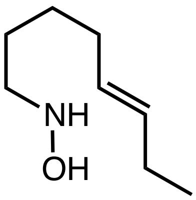
(*Z*)-*N*-Allyl-*N*-hydroxyoct-5-en-1-amine (Equation 2.1, 2.10). Synthesized according to the general procedure 5.6 using the corresponding hydroxylamine (0.20 g, 0.54 mmol). The crude mixture was purified by flash chromatography on silica gel with an eluent of 10% EtOAc in hexanes to yield the desired product as a yellow oil (49 mg, 49%). TLC R_f 0.70 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.11-5.78 (tdd, *J*= 6.6, 10.3, 17.1 Hz, 1H), 5.42-5.26 (m, 2H), 5.22-5.12 (m, 2H), 3.35 (d, *J*= 6.6 Hz, 2H), 2.66 (t, *J*= 7.4 Hz, 2H), 2.09-1.96 (m, 4H), 1.65-1.55 (m, 2H), 1.41-1.31 (m, 2H), 0.94 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 133.8, 131.9, 128.8, 118.6, 63.6, 59.6, 27.4, 26.9, 26.8, 20.5, 14.3; IR (film): 3239, 3005, 2961, 2933, 2858, 1648, 1462, 991, 922, 717 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{21}NO$ $[M]^+$: 183.1623; found: 183.1570.



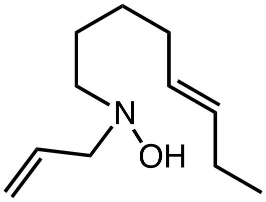
(*Z*)-*N*-Allyl-*N*-(allyloxy)oct-5-en-1-amine (Equation 2.1, 2.13). Observed as a side product of the allylation reaction. TLC R_f 0.96 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.14-5.71 (m, 2H), 5.41-5.29 (m, 2H), 5.28-5.13 (m, 4H), 4.20 (d, *J*= 5.9 Hz, 2H), 3.35 (d, *J*= 6.4 Hz, 2H), 2.65 (t, *J*= 7.4 Hz, 2H), 2.07-1.97 (m, 4H), 1.65-1.52 (m, 2H), 1.39 (td, *J*= 15.0, 7.6 Hz, 2H), 0.96 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 134.2, 134.1, 131.8, 128.9, 118.2, 117.7, 74.9, 62.1, 58.5, 27.5, 26.9, 26.8, 20.5, 14.4; IR (film): 3081, 2959, 2933, 2855, 1732, 1648, 1454, 994, 919, 739 cm^{-1}; LRMS m/z (relative intensity): 41.0386 (90.0%), 70.0661 (35.2%), 86.0595 (100.0%), 112.0770 (24.8%), 166.1613 (22.3%).



***N*-*tert*-Butyl carbamate-*O*-*tert*-butyl carbonate-(*E*)-*N*-hydroxyoct-5-en-1-amine (Equation 2.3, not shown).** Synthesized according to the general procedure 5.2 using the corresponding alcohol (0.50 g, 3.9 mmol). The crude mixture was purified by flash chromatography on silica gel with an eluent of 1% EtOAc in hexanes to yield the desired product as a colorless oil (1.08 g, 81%). TLC R_f 0.47 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.49-5.30 (m, 2H), 3.56 (t, *J*= 5.8 Hz, 2H), 2.03-193 (m, 4H), 1.73-1.26 (m, 4H), 1.52 (s, 9H), 1.47 (s, 9H), 0.95 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 154.8, 152.2, 132.3, 128.5, 84.4, 81.9, 49.9, 31.9, 27.9 (3C), 27.5 (3C), 26.3, 25.4, 13.8. IR (film): 2980, 2834, 1789, 1459, 1370, 1131, 968 cm^{-1}; HRMS (EI): Exact mass calculated for $C_8H_{17}NO$ [M-(Boc)$_2$]$^+$: 143.1310; found: 143.13208.

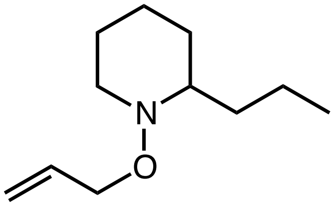


(*E*)-*N*-Hydroxyoct-5-en-1-amine (Equation 2.3, not shown). Synthesized according to the general procedure 5.3 using the corresponding Boc-protected hydroxylamine (1.1 g, 2.9 mmol). The solution was concentrated *in vacuo* and used directly without further purification.



(*E*)-*N*-Allyl-*N*-hydroxyoct-5-en-1-amine (Equation 2.3, 2.10) Synthesized according to the general procedure 5.6 using the corresponding hydroxylamine (crude, 2.9 mmol). The crude mixture was purified by flash chromatography on silica gel with an eluent of 20% EtOAc in hexanes to yield the desired product as a colorless oil (223 mg, 42%). TLC R_f 0.38 (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.94 (ddt, *J*= 6.5, 10.2, 16.8 Hz, 1H), 5.51-5.33 (m, 2H), 5.29-5.16 (m, 2H), 3.33 (d, *J*= 6.5 Hz, 2H), 2.65 (t, *J*= 7.3 Hz, 2H), 2.03-1.94 (m, 4H), 1.64-1.54 (m, 2H), 1.44-1.34 (m, 2H), 0.95 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 133.8, 132.3, 128.8, 118.5, 63.6, 59.5, 32.4, 27.3, 26.6, 25.5, 13.9; IR (film): 3283, 2961, 2932, 2852, 1439, 920 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{21}NO$ $[M]^+$: 183.1623; found: 183.1572.

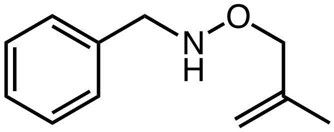
5.8.1 Procedure for the CHMR Sequence



1-(Allyloxy)-2-propylpiperidine (Table 2.4, 2.12). In a sealed tube equipped with a magnetic stirbar was dissolved hydroxylamine 25 (0.050 g, 0.27 mmol) in benzene (2.7 mL). Argon was bubled in the solution for 10 min. The tube was sealed and heated at 150°C for 16 h. After cooling to room temperature, the reaction mixture was directly purified by flash chromatography on silica gel with a gradient of 1% to 10% diethyl ether in hexanes to yield the desired compound as a yellow oil (21 mg, 42%). TLC R_f 0.78 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.97-5.89 (tdd, *J*= 6.1, 10.4, 16.5 Hz, 1H), 5.27 (dd, *J*= 1.5, 15.8 Hz, 1H), 5.16 (ap d, *J*= 10.3 Hz, 1H), 4.25-4.15 (m, 2H), 3.36 (d, *J*= 9.9 Hz, 1H), 2.41

(ap t, *J*= 10.4 Hz, 1H), 2.31 (ap t, *J*= 6.4 Hz, 1H), 1.87-1.78 (m, 2H), 1.71-1.68 (m, 1H), 1.61-153 (m, 2H), 1.42-1.36 (m, 1H), 1.34-1.27 (m, 2H), 1.25-1.14 (m, 2H), 0.91 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 134.6, 117.9, 74.4, 67.3, 57.4, 35.7, 31.2, 26.2, 24.3, 19.1, 14.9; IR (film): 3085, 2936, 2859, 2828, 1648, 1443, 1036, 995, 921 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{21}NO$ [M]$^+$: 183.1623; found: 183.1621.

5.9 Preparation of the Methallylated Substrates (Chapter 2)



***N*-(2-Methylallyloxy)benzylamine (Scheme 2.25, 2.15).** Based on a procedure by the Meyers group.[209] KH (30% in mineral oil, 0.450 g, 3.36 mmol) was washed three times with pentane, dried under argon and resuspended in THF (2.6 mL). A solution of benzaldehyde oxime (0.380 g, 3.14 mmol) in THF (6.3 mL) was added dropwise at room temperature. The mixture was stirred for 1h at which point a solution of 2-methyl-2-propenyl chloride (0.30 mL, 3.1 mmol) in THF (3.4 mL) and DMF (2.6 mL) was added. The reaction was stirred at room temperature for 3 h. H_2O and DCM were added and the phases were separated. The aqueous phase was extracted three times with diethyl ether. The organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The crude oxime (0.506 g, 2.89

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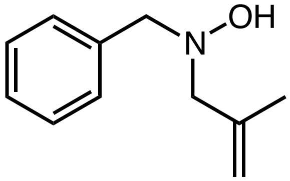
[209] Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892.

mmol) was then reduced according to the general procedure 5.5. The crude mixture was purified by flash chromatography on silica gel with an eluent of 10% EtOAc in hexanes to yield the title compound as a colorless oil (316 mg, 62%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.35-7.26 (m, 5H), 5.69 (br, 1H), 4.93 (d, *J*= 0.9 Hz, 1H), 4.89 (d, *J*= 0.9 Hz, 1H), 4.07 (ap s, 4H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 142.0, 137.5, 128.8, 128.2, 127.3, 112.5, 77.8, 56.3, 19.6; IR (film): 3260, 3030, 2972, 2858, 1656, 1454, 993 cm^{-1}.



***N*-(2-Methylallyl)-*N*-hydroxy-benzylamine (Scheme 2.25, 2.16).** Based on a procedure by Davies and coworkers.[210] To a solution of *N*-(2-methylallyloxy)benzylamine (0.303 mg, 1.71 mmol) in THF (17 mL) at -78°C was added *n*BuLi (1.85 mL, 2.22 mmol). The reaction was stirred for 1h at -78°C, then warmed to room temperature and stirred for an extra 45 minutes. Water was added and the mixture was extracted three times with diethyl ether. The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel with an eluent of 30% EtOAc in hexanes to yield the desired product as a colorless oil (20 mg, 7%) which degraded on column. TLC R_f 0.18 (10% EtOAc/hexanes);

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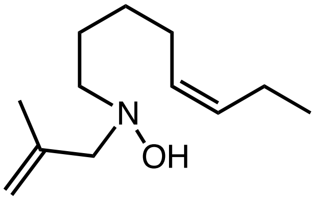
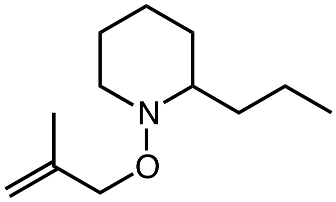
[210] Davies, S. G.; Fox, J. F.; Jones, S.; Price, A. J.; Sanz, M. A.; Sellers, T. G. R.; Smith, A. D.; Teixeira, F. C. *J. Chem. Soc.; Perkin Trans. 1* **2002**, 1757.



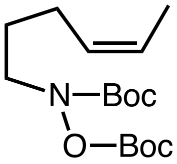
(*Z*)-*N*-Hydroxy-*N*-(2-methylallyl)oct-5-en-1-amine (Equation 2.4, 2.17). To a solution of (*Z*)-*N*-hydroxyoct-5-en-1-amine (0.361 g, 2.52 mmol) and DBU (0.396 mL, 2.65 mmol) in THF (8.4 mL) and DMF (1.7 mL) at room temperature was added 3-Bromo-2-methylpropene (0.740 mL, 7.56 mmol) dropwise. The solution was refluxed for 1.5 h. It was then extracted with EtOAc, washed three times with 50:50 H_2O/brine. The organic phases were combined, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent gradient of 2% to 5% EtOAc in hexanes to yield the desired product as a colorless oil (187 mg, 37%). TLC R_f 0.28 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.34 (ttd, *J*= 6.5, 6.0, 11.1 Hz, 2H), 4.92 (d, *J*= 1.1 Hz, 1H), 4.89 (d, *J*= 1.1 Hz, 1H), 4.86 (br, 1H), 3.23 (s, 2H), 2.64 (t, *J*= 7.1 Hz, 2H), 2.08-1.99 (m, 4H), 1.78 (s, 3H), 1.65-1.55 (m, 2H), 1.45-1.37 (m, 2H), 0.95 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 142.1, 131.8, 128.9, 113.5, 67.4, 59.8, 27.4, 27.0, 26.9, 21.1, 20.5, 14.4; IR (film): 3256, 3005, 2962, 2933, 2857, 1652, 1453, 899 cm^{-1}; LRMS m/z (relative intensity): 41.0386 (90.0%), 55.0548 (18.5%), 70.0661 (35.2%), 86.0595 (100.0%), 112.0770 (24.8%), 166.1613 (22.3%).

5.9.1 Procedure for the Methallylated CHMR Sequence

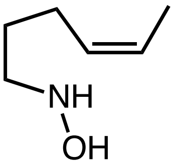


1-(2-Methylallyloxy)-2-propylpiperidine (Table 2.9, 2.18). In a sealed tube equipped with a magnetic stirbar was dissolved hydroxylamine **4** (0.10 g, 0.51 mmol) in benzene (20 mL). Argon was bubled in the solution for 10 min. The tube was sealed and heated at 150°C for 16 h. After cooling to room temperature, the reaction mixture was directly purified by flash chromatography on silica gel with a gradient of 5% to 20% EtOAc in hexanes to yield the desired compound as a colorless oil (31 mg, 31%). TLC R_f 0.78 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.97 (d, *J*= 1.0 Hz, 1H), 4.87 (d, *J*= 1.0 Hz, 1H), 4.15-4.09 (m, 2H), 3.37 (d, *J*= 10.0 Hz, 1H), 2.43 (ap t, *J*= 10.6 Hz, 1H), 2.34 (ap t, *J*= 8.3 Hz, 1H), 1.87-1.78 (m, 2H), 1.77 (s, 3H), 1.71-1.68 (m, 1H), 1.61-153 (m, 2H), 1.42-1.36 (m, 1H), 1.34-1.27 (m, 2H), 1.25-1.14 (m, 2H), 0.91 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.8, 113.0, 77.1, 66.9, 56.7, 35.2, 30.9, 25.8, 23.9, 20.2, 18.7, 14.5; IR (film): 3077, 2937, 2859, 2828, 1655, 1453, 1022, 898 cm^{-1}; LRMS m/z (relative intensity): 55.0561 (13.2%), 100.0763 (100.0%), 140.1046 (42.6%), 142.1220 (47.2%).

5.10 Preparation of the five-Membered CHMR Sequence Substrates

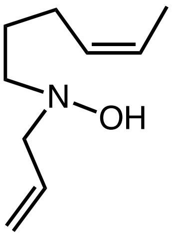


***N-tert*-Butyl carbamate-*O-tert*-butyl carbonate-(*Z*)-*N*-hydroxyhex-4-en-1-amine (Scheme 2.26, not shown).** Synthesized according to the general procedure 5.2 using the corresponding alcohol (1.2 g, 9.6 mmol). The crude mixture was purified by flash chromatography on silica gel with an eluent of 5% EtOAc in hexanes to yield the desired product as a yellow oil (2.84 g, 86%). TLC R_f 0.72 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.55-5.21 (m, 2H), 3.55 (t, *J*= 5.5 Hz, 2H), 2.07 (dt, *J*= 7.2, 7.2 Hz, 2H), 1.63 (tt, *J*= 7.3, 14.6 Hz, 2H), 1.57 (d, *J*= 6.0 Hz, 3H), 1.50 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.8, 152.2, 129.1, 124.6, 84.4, 81.9, 49.5, 27.9 (3C), 27.5 (3C), 26.7, 23.7, 12.6; IR (film): 3009, 2933, 1781, 1713, 1394, 1245 850 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{21}NO_3$ [M-Boc]$^+$: 215.1521; found: 215.1529.

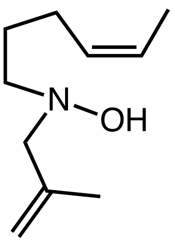


(*Z*)-*N*-Hydroxyhex-4-en-1-amine (Scheme 2.26, 2.21). Synthesized according to the general procedure 5.3 using the corresponding Boc-protected hydroxylamine (1.0 g, 3.2

mmol). The crude was directly used in the next step without further purification. TLC R_f 0.25 (100% EtOAc).

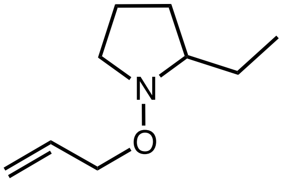


(*Z*)-*N*-Allyl-*N*-hydroxyhex-4-en-1-amine (Scheme 2.26, 2.22). Synthesized according to the general procedure 5.6 using the corresponding hydroxylamine (0.23 g, 2.0 mmol). The crude mixture was purified by flash chromatography on silica gel with an eluent of 20% EtOAc in hexanes to yield the desired product as a yellow oil (103 mg, 34%). TLC R_f 0.27 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.94 (ddt, *J*=16.9, 10.2, 6.5 Hz, 1H), 5.49-5.24 (m, 2H), 5.22 (dd, *J*= 1.5, 17.2 Hz, 1H), 5.18 (dd, *J*= 0.8, 10.4 Hz, 1H), 3.34 (d, *J*= 6.6 Hz, 2H), 2.66 (t, *J*= 7.3 Hz, 2H), 2.08 (dt, *J*= 7.3, 7.3 Hz, 2H), 1.66 (tt, *J*= 7.5, 15.0 Hz, 2H), 1.60 (d, *J*= 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 133.9, 129.9, 124.3, 118.5, 63.7, 59.2, 27.0, 24.5, 12.7; IR (film): 3235, 3013, 2935, 2844, 1439, 992, 922 cm^{-1}; HRMS (EI): Exact mass calculated for $C_9H_{17}NO$ $[M]^+$: 155.1310; found: 155.1305.

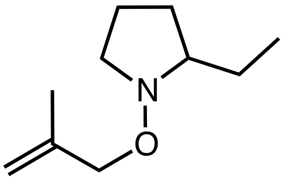


(*Z*)-*N*-Hydroxy-*N*-(2-methylallyl)hex-4-en-1-amine (Scheme 2.26, 2.23). To a solution of (*Z*)-*N*-hydroxyhex-4-en-1-amine (2.0 g, 4.8 mmol) and DBU (0.760 mL, 5.13 mmol) in THF (19 mL) at room temperature was added 3-Chloro-2-methylpropene (1.40 mL, 14.6 mmol) dropwise. The solution was refluxed under argon for 2 h. It was then dissolved in hexanes, filtered and the filtrate was concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 7% Et_2O in hexanes to yield the desired product as a colorless oil (333 mg, 41%). TLC R_f 0.73 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.52-5.34 (m, 2H), 5.20 (br, 1H), 4.9 (ap d, *J*= 10.6 Hz, 2H), 3.23 (s, 2H), 2.64 (t, *J*= 7.1 Hz, 2H), 2.10 (dt, *J*= 7.0, 6.9 Hz, 2H), 1.78 (s, 3H), 1.66 (tt, *J*= 7.5, 14.7 Hz, 2H), 1.61 (d, *J*= 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.7, 130.1, 124.2, 114.1, 67.5, 59.1, 27.0, 24.5, 21.2, 12.7; IR (film): 3291, 2926, 2861, 1652, 1447, 1375, 892 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{10}H_{19}NO$ $[M]^+$: 169.1467; found: 169.1455.

5.10.1 Procedure for the five-membered CHMR Sequence

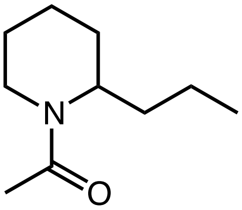


1-(Allyloxy)-2-ethylpyrrolidine (Table 2.10, 2.24). (*Z*)-*N*-allyl-*N*-hydroxyhex-4-en-1-amine (0.177 g, 1.14 mmol) was dissolved in benzene (114 mL) and distilled water (0.206 mL, 11.4 mmol). The reaction solution was refluxed for 6 h. After cooling to room temperature, the reaction mixture was directly purified by flash chromatography on silica gel with an eluent of 10% Et_2O in hexanes. HCl gas was bubbled in the combined unconcentrated fractions to form the HCl salt. Evaporation of the solvent yielded the desired compound as a colorless oil (67 mg, 45%). The HCl salt was quenched with Et_3N and extracted with EtOAc for characterization purpose. TLC R_f 0.61 (15% EtOAc/hexanes); Isolated with the $Et_3N{\cdot}HCl$ salt present: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.94, (ddt, *J*= 17.3, 12.0, 6.0 Hz, 1H), 5.25 (ap dq, *J*= 17.3, 1.7 Hz, 1H), 5.15 (dm, *J*= 10.3 Hz, 1H), 4.21 (d, *J*= 6.0 Hz, 2H), 3.30-3.23 (m, 1H), 2.81-2.71 (m, 2H), 2.67 (q, *J*= 7.14 Hz, Et_3N), 1.95-1.84 (m, 1H), 1.81-1.67 (m, 3H), 1.38-1.24 (m, 2H), 1.12 (t, *J*= 7.2 Hz, Et_3N), 0.91 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 134.8, 117.2, 74.4, 74.3, 69.3, 55.7, 45.7 (Et_3N), 26.8, 26.2, 20.2, 11.0 (Et_3N), 8.6; IR (film): 3078, 2962, 2743, 2497, 1475, 1444, 1037, 921 cm^{-1}; LRMS m/z (relative intensity): 41.0375 (15.3%), 43.0168 (22.1%), 55.0557 (15.7%), 86.0639 (100.0%), 114.0923 (89.2%),140.1059 (14.7%).



1-(2-Methylallyloxy)-2-ethylpyrrolidine (Table 2.11, 2.25). (*Z*)-*N*-hydroxy-*N*-(2-methylallyl)hex-4-en-1-amine (0.50 mg, 0.32 mmol) was dissolved in benzene (32 mL) and distilled water (0.058 mL, 3.2 mmol). The reaction solution was refluxed under argon for 17 h. After cooling to room temperature, the reaction mixture was directly purified by flash chromatography on silica gel with an eluent of 10% Et_2O in hexanes to yield the desired compound as a colorless oil (67 mg, 45%). TLC R_f 0.67 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, DMSO-d_6, 78°C) δ ppm 4.88 (s, 1H), 4.81 (s, 1H), 4.05 (s, 2H), 3.16-3.11 (m, 1H), 2.80-2.71 (m, 2H), 1.88-1.81 (m, 1H), 1.75-1.67 (m, 1H), 1.69 (s, 3H), 1.64-1.54 (m, 2H), 1.36-1.23 (m, 2H), 0.88 (t, *J*= 7.5 Hz, 3H). Full resolution could not be obtained upon heating; ^{13}C NMR (125 MHz, DMSO-d_6, 78°C) δ ppm 141.9, 111.4, 76.1, 68.3, 54.6, 26.3, 25.2, 19.9, 19.1, 10.3; IR (film): 2971, 2937, 2880, 1455, 1021, 896 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{10}H_{19}NO$ $[M]^+$: 169.1467; found: 169.1437.

5.11 Procedure for the Synthesis of N-Protected (±)-Coniine



(±)-*N*-Acetyl coniine (Scheme 2.27, 2.26). Based on a procedure by the Dole group.[211] To a solution of 1-(Allyloxy)-2-propylpiperidine (0.11 g, 0.062 mmol) in 10 M acetic acid (1.5 mL) at 55°C was added zinc powder (0.078 g, 1.2 mmol). The reaction mixture was stirred at 55°C for 4 h, after which time it was quenched by addition of distilled water, then basicified to a pH of 14 with a solution of KOH 6 M. The mixture was then extracted three times with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude colorless oil was dissolved in pyridine (0.6 mL) at room temperature. Acetic anhydride (0.034 mL, 0.36 mmol) was added. The reaction was stirred at room temperature for 3 h after which water was added. The mixture was acidified to pH 3 with a solution of 10% HCl and extracted three times with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 20% EtOAc in hexanes to yield the *N*-acetyl coniine as a colorless oil (1 mg, 10% over 2 steps). TLC R_f 0.12 (23% EtOAc/hexanes); As a mixture of diastereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.78 (dd, *J*= 8.3, 12.9 Hz, 1H), 4.52 (dd, *J*= 4.5, 13.5 Hz, 1H), 3.84 (ap t, *J*= 6.2 Hz, 1H), 3.56 (dd, *J*= 2.6, 12.8 Hz, 1H), 3.10 (ddd, *J*= 13.3, 13.3, 2.4 Hz, 1H), 2.57 (ddd, *J*= 13.0, 13.0, 1.5 Hz, 1H) 2.08 (s, 3H), 2.07 (s, 3H), 1.74-1.19 (m, 20H), 0.94 (t, *J*=

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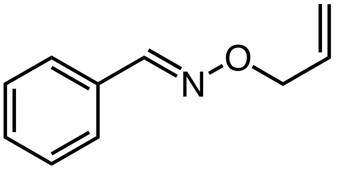
[211] Le Bourdonnec, B.; Goodman, A. J.; Michaut, M.; Ye, H-F.; Graczyk, T. M.; Belanger, S.; Herbertz, T.; Yap, G. P. A.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006***, 49*, 7278.

7.3 Hz, 3H), 0.91 (t, *J*= 7.3 Hz, 3H); HRMS (EI): Exact mass calculated for $C_{10}H_{19}NO$ $[M]^+$: 169.1467; found: 169.1462. The spectral data corresponds to that reported in literature.[212]

5.12 Procedures for the Optimization of the N-O Bond Cleavage



***O*-Allyl benzaldehyde oxime (Scheme 2.28, 2.28).** Based on a procedure by the Meyers group.[209] KH (pentane washed, 0.357 mg, 8.92 mmol) was suspended in THF (7 mL) in a flamed dry round bottom flask under argon. A solution of benzaldehyde oxime (1.0 g, 8.3 mmol) in THF (17 mL) was added dropwise to the KH suspension. The reaction mixture was stirred at room temperature for 1h at which time a solution of allylbromide (0.781 mL, 8.13 mmol) in THF (10 mL) was added. The reaction was stirred at room temperature under argon for 3.5 hours. Water was added to the mixture, after which the THF was evaporated. The crude was then dissolved and extracted twice with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 1% EtOAc in hexanes to yield the desired product as a yellow oil (454 mg, 34%). TLC R_f 0.76 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (s, 1H), 7.62-7.60 (m, 2H), 7.40-7.37 (m, 3H), 6.09 (ddt, *J*= 11.5, 10.7, 5.8 Hz, 1H), 5.39 (dd, *J*= 1.5, 17.3 Hz, 1H), 5.28 (dd,

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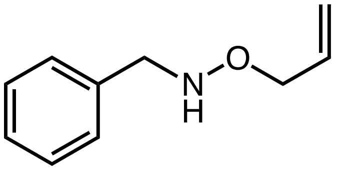
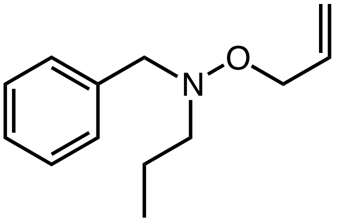
[212] Hassner, A.; Kumareswaran, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2269.

J= 1.0, 10.5 Hz, 1H), 4.71 (d, *J*= 5.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 148.8, 134.0, 132.2, 129.7, 128.6, 127.0, 117.8, 75.1; IR (film): 3062, 3032, 2990, 2869, 1447, 1039, 931 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{10}H_{11}NO$ [M]$^+$: 161.0841; found: 161.0849.



***O*-Allyl benzylhydroxylamine (Scheme 2.28, 2.29).** Synthesized according to the general procedure 5.5 using the corresponding oxime (0.454 mg, 2.83 mmol). The crude mixture was purified by flash chromatography on silica gel with an eluent of 15% EtOAc in hexanes to yield the desired product as a colorless oil (386 mg, 84%). TLC *R*$_f$ 0.53 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm 7.39-7.34 (m, 4H), 7.32-7.29 (m, 1H), 5.93 (ddt, *J*= 21.8, 17.3, 5.9 Hz, 1H), 5.74 (br, 1H), 5.28 (ap dq, *J*= 17.3, 1.5 Hz, 1H), 5.19 (dm, *J*= 10.4 Hz, 1H), 4.18 (d, *J*= 5.9 Hz, 2H), 4.08 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ ppm 137.4, 134.4, 128.9, 128.3, 127.3, 117.5, 75.0, 56.5; IR (film): 3260, 3089, 2910, 1496, 1454, 992, 926 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{10}H_{13}NO$ [M]$^+$: 163.0997; found: 163, 1015.



***O*-Allyl-*N*-propyl benzylhydroxylamine (Scheme 2.19, 2.30).** Based on a procedure by Payne and coworkers.[213] To a solution of *O*-Allyl benzylhydroxylamine (0.300 g, 1.84 mmol) in ethanol (4.1 mL) at room temperature were added triethylamine (0.644 mL, 4.62 mmol) and 1-bromopropane (0.670 mL, 7.36 mmol). The reaction was heated at 50°C for 16 h, then refluxed for 24 h. Ethanol was evaporated, then the crude mixture was directly purified by flash chromatography on silica gel with an eluent of 1% Et_2O in hexanes to yield the desired product as a pale yellow solid (73 mg, 19%). TLC R_f 0.62 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.37-7.23 (m, 5H), 5.77 (ddt, *J*=16.6, 10.4, 6.2 Hz, 1H), 5.13 (dd, *J*=17.5, 1.4 Hz, 1H), 5.08 (dd, *J*=10.3, 0.9 Hz, 1H), 3.98 (d, *J*=6.2 Hz, 2H), 3.82 (s, 2H), 2.67 (t, *J*=7.2 Hz, 2H), 1.61 (ap s, *J*=7.4 Hz, 2H), 0.91 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 137.7, 134.0, 129.7 (2C), 128.0 (2C), 127.1, 117.5, 74.9, 63.4, 60.7, 20.4, 11.8; IR (film): 2964, 2831, 1455, 1029 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{19}NO$ $[M]^+$: 205.1467; found: 205.14622.

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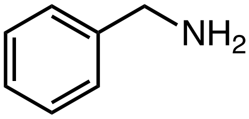
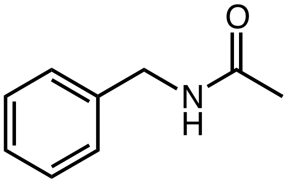
[213] Strasser, M.; Cooper, P.; Dewald B.; Payne, T. *Helv. Chim. Acta* **1988**, *71,* 1156.

5.12.1 Procedure for the *N-O* Bond Cleavage



Benzylamine (Scheme 2.29, 2.31, R=H). Based on a procedure by the Dole group.[211] To a solution of *O*-Allyl benzylhydroxylamine (0.300 g, 1.84 mmol) in acetic acid and water (1:1, 6.4 mL) at room temperature was added zinc powder (0.600 g, 9.19 mmol). The reaction mixture was stirred at room temperature for 1 h, after which it was filtered over celite with warm MeOH, then added to basicified brine (pH 14) The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine (pH 7), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. Used directly without further purification.



***N*-Benzylacetamide (Scheme 2.29, 2.32).** Based on a procedure by the Biellmann group.[214] Benzylamine (0.20 g, 1.8 mmol) was added to glacial acetic acid (0.60 mL, 6.3 mmol). The reaction was stirred for 16 h at room temperature. Excess acetic acid was evaporated *in*

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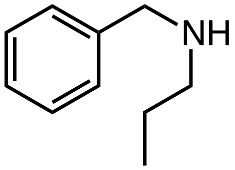
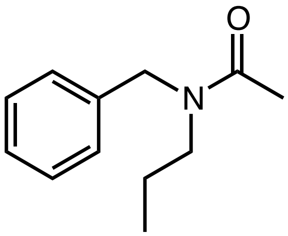
[214] Freudenreich, C.; Samama, J. P.; Biellmann, J. F. *J. Am. Chem. Soc.* **1984***, 106*, 3344.

vacuo to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 2% MeOH in dichloromethane to yield the desired product as a pale yellow solid (174 mg, 63%). TLC R_f 0.54 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34-7.24 (m, 5H), 6.95 (br, 1H), 4.34 (s, 2H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.3, 138.2, 128.3, 127.4, 127.1, 43.3, 22.7; IR (film): 3294, 3063, 1637, 1558, 1454, 695 cm^{-1}; HRMS (EI): Exact mass calculated for $C_9H_{11}NO$ $[M]^+$: 149.0841; found: 149.0868.



***N*-Propylbenzylamine (Scheme 2.29, 2.31, R=*n*-Pr).** Based on a procedure by the Dole group.[211] To a solution of *O*-Allyl-*N*-propyl benzylhydroxylamine (0.073 g, 0.36 mmol) in acetic acid and water (1:1, 1.2 mL) at room temperature was added zinc powder (0.116 g, 1.78 mmol). The reaction mixture was stirred at room temperature for 1 h, after which it was filtered over celite with warm MeOH, then added to basicified brine (pH 14). The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine (pH 7), dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid. Used directly without further purification.

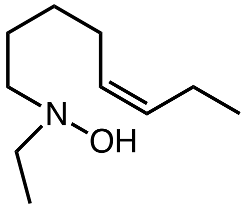


***N*-Propyl-*N*-benzyl acetamide (Scheme 2.29, 2.33).** Based on a procedure by the Biellmann group.[214] *N*-propyl benzylamine (crude, 1.85 mmol) was added to glacial acetic acid (0.612 mL, 6.48 mmol) and triethylamine (12.9 mL, 92.5 mmol). The reaction was stirred for 16 h at room temperature. Excess acetic acid was evaporated *in vacuo* to give a residue. The crude mixture was purified by flash chromatography on silica gel with an eluent of 2% MeOH in dichloromethane to yield the desired product as a colorless oil (190 mg, 54%). TLC R_f 0.39 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39-7.11 (m, 5H), 4.60 (ap dd, *J*=3.2, 3.0 Hz, 1H), 4.51 (ap dd, *J*=3.5, 3.2 Hz, 1H), 3.38-3.27 (m, 1H), 3.18-3.08 (m, 1H), 2.18-2.15 (m, 1H), 2.10-2.07 (m, 1H), 1.60-1.48 (m, 2H), 0.94 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm as a mixture of isomers: 170.5, 170.1, 137.4, 136.6, 128.5, 128.1, 127.5, 127.1, 126.8, 125.8, 51.5, 49.1, 47.6, 47.3, 21.4, 21.2, 21.0, 20.4, 11.0, 10.8; IR (film): 3485, 2965, 1636, 1420 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{12}H_{17}NO$ $[M]^+$: 191.1310; found: 191.12879.

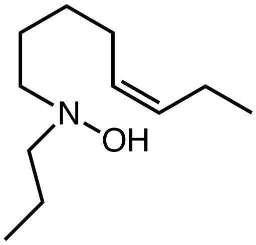
5.13 General procedure for the synthesis of Cope-Type Hydroamination-Cope Elimination Sequence Substrates

Based on a procedure by Payne and coworkers.[213] To a solution of the hydroxylamine (0.54 mmol) in ethanol (1.3 mL) at room temperature were added triethylamine (3.19 mmol) and

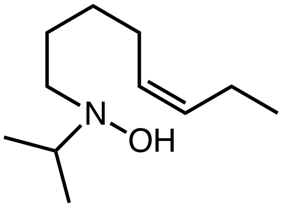
1-bromopropane (2.32 mmol). The reaction was heated at reflux for 2 h. Ethanol was evaporated, then the crude residue was directly purified by flash chromatography on silica gel.



(*Z*)-*N*-Ethyl-*N*-hydroxyoct-5-en-1-amine (Equation 2.5, 2.34a). Synthesized according to the general procedure 5.13 using the corresponding hydroxylamine (0.15 g, 0.58 mmol) and bromoalkyl (0.173 mL, 2.32 mmol). The crude residue was purified by flash chromatography on silica gel with an eluent of 10% EtOAc in hexanes to yield the desired product as a colorless oil which quickly degraded upon standing at room temperature (13 mg, 12%). TLC R_f 0.30 (20% EtOAc/hexanes).

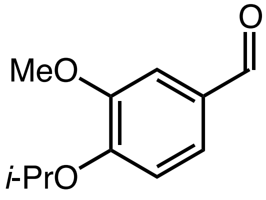


(*Z*)-*N*-Propyl-*N*-hydroxyoct-5-en-1-amine (Equation 2.5, 2.34b). Synthesized according to the general procedure 5.13 using the corresponding hydroxylamine (0.15 g, 0.58 mmol) and bromoalkyl (0.211 mL, 2.32 mmol). The crude residue was purified by flash chromatography on silica gel with an eluent of 10% EtOAc in hexanes to yield the desired product as a colorless oil which quickly degraded upon standing at room temperature (50 mg, 46%). TLC R_f 0.42 (20% EtOAc/hexanes).

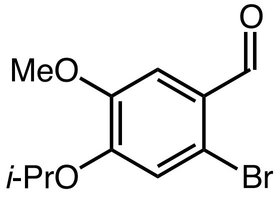


(*Z*)-*N*-(2-Methylethyl)-*N*-hydroxyoct-5-en-1-amine (Equation 2.5, 2.34c). Synthesized according to the general procedure 5.13 using the corresponding hydroxylamine (0.360 g, 1.94 mmol) and bromoalkyl (0.526 mL, 4.27 mmol). The crude residue was purified by flash chromatography on silica gel with an eluent of 10% EtOAc in hexanes to yield the desired product as a colorless oil which quickly degraded upon standing at room temperature (73 mg, 28%). TLC R_f 0.65 (100% EtOAc).

5.14 Preparation of the Cope-Type Hydroamination Precursors for the Synthesis of N-Norreticuline



4-Isopropoxy-3-methoxybenzaldehyde (Scheme 2.32, 2.46). The title compound was prepared according to the procedure by Ridley and coworkers.[215] In a flame-dried round-bottomed flask equipped with a magnetic stir bar, vanillin (20.0 g, 132 mmol) was suspended in DMF (100 mL). Isopropyl bromide (19.0 mL, 203 mmol) and K_2CO_3 (29.2 g, 211 mmol) were subsequently added. The reaction mixture was flushed with argon and stirred at room temperature for 48 h. The resulting crude mixture was poured into water and extracted with diethyl ether. The organics were washed with 5% aq. NaOH, dried over $MgSO_4$, filtered, and concentrated by *in vacuo*. The resulting crude oil was purified by silica column chromatography with an eluent of 20% EtOAc in hexanes and yielded a clear, light yellow oil (25.5 g, quant.). TLC R_f 0.34 (20% EtOAc/hexanes); The spectral data corresponds to that reported in literature.[215]



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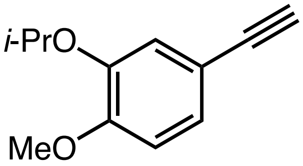
[215] Ridley, C. P; Reddy, M. V. R.; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285.

4-Hydroxy-2-bromo-5-methoxybenzaldehyde (Scheme 2.32, 2.36). The title compound was synthesized based on the procedure by Appukkuttan and coworkers.[216] 4-Isopropoxy-3-methoxybenzaldehyde (0.600 g, 3.09 mmol) was dissolved in MeOH (15 mL) in a flame-dried round-bottomed flask equipped with a magnetic stir bar. The reaction mixture was cooled to 0°C and bromine (0.162 mL, 3.24 mmol) was added. The reaction was then allowed to warm to room temperature and was stirred for 6 h until completion. Dichloromethane was added, the organic phase was washed twice with an aqueous saturated solution of $Na_2S_2O_3$, then with brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude orange oil was purified by silica column chromatography with an eluent of 5-10% EtOAc in hexanes to yield light yellow crystals (0.589 g, 76%). mp 116-117°C (recrystallized from 4:1 hexanes/ethyl acetate. TLC R_f 0.53 (20% EtOAc/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 10.13 (s, 1H), 7.37 (s, 1H), 7.01 (s, 1H), 4.63 (sept, J = 6.0 Hz, 1H), 3.86 (s, 3H), 1.40 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ ppm 189.7, 153.5, 150.4, 126.8, 119.9, 117.7, 111.3, 71.4, 55.1, 21.5; IR (film): 2975, 2929, 2846, 1675, 1594, 1499, 1393, 1273, 1105, 988, 865 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{13}BrO_3$ $[M]^+$: 272.0048. Found: 272.0072.



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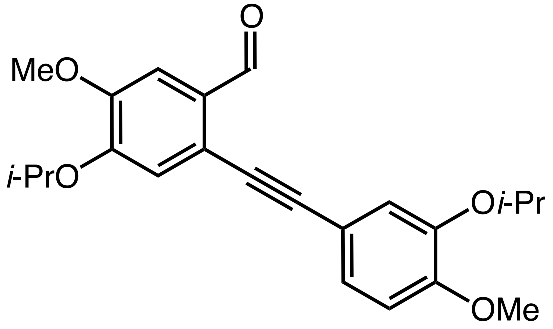
[216] Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Chem. Eur. J.* **2007**, *13*, 6452.

4-Ethynyl-2-isopropoxy-1-methoxybenzene (Scheme 2.32, 2.37). Based on a procedure by the Ridley group.[215] 4-(2,2-Dibromovinyl)-2-isopropoxy-1-methoxybenzene (6.00 g, 17.1 mmol) was added to a flame-dried round-bottomed flask equipped with a magnetic stir bar, purged with argon for 10 minutes, and dissolved in THF (17 mL). The reaction was cooled to –78˚C with a dry ice/acetone bath and stirred for 5 minutes. A solution of *n*-BuLi in hexanes (101 mL, 171 mmol) was added dropwise and the reaction was stirred at –78˚C for 30 minutes. The reaction was allowed to warm to room temperature and was stirred for an additional 60 minutes. The crude was quenched with a saturated solution of ammonium chloride and the aqueous phase was extracted three times with ether. The combined organic phases were dried with $MgSO_4$, filtered and concentrated. The crude alkyne was purified by silica column chromatography with an eluent of 10% Et_2O in hexanes and a pale yellow powder was obtained (2.61 g, 80%). The spectral data corresponds to that reported in literature.[215]



4-Isopropoxy-2-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-5-methoxybenzaldehyde (Scheme 2.32, 2.38). The title compound was prepared according to the literature procedure by Itami and coworkers.[217] To a flame-dried round bottomed flask equipped with a magnetic stir bar was added 4-Hydroxy-2-bromo-5-methoxybenzaldehyde (2.87 g, 11.1 mmol), $Pd(PPh_3)_2Cl_2$ (0.23 g, 0.33 mmol), CuI (0.063 g, 0.33 mmol), Et_3N (56 mL) and 4-Ethynyl-2-isopropoxy-1-methoxybenzene (3.17 g, 16.7 mmol). The reaction mixture was purged with argon for 15 minutes and was stirred at room temperature in the dark for 18 h. To the reaction mixture was added an aqueous saturated solution of ammonium chloride and diethyl ether and the resulting phases were separated. The aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated. The resulting brown crude oil was purified by silica column chromatography with an eluent of 2% acetone in toluene and resulted in a yellow solid (3.69 g, 87%). TLC R_f 0.35 (20% EtOAc/hexanes); ^1H NMR (400 MHz, C_6D_6) δ ppm 11.0 (s, 1H), 7.55 (s, 1H), 7.24 (d, *J*= 1.9 Hz, 1H), 7.21 (dd, *J*= 8.2, 2.0 Hz, 1H), 7.05 (s, 1H), 6.45 (d, *J*= 8.3 Hz, 1H), 4.20 (sept, *J*= 6.1 Hz, 1H), 4.07 (sept, *J*= 5.7 Hz, 1H), 3.28 (s, 3H), 3.21 (s, 3H), 1.12 (d, *J*= 6.0 Hz, 6H), 1.01 (d, *J*= 6.0 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ ppm 189.5, 152.7, 152.3, 151.3, 148.0, 130.6, 125.6, 121.7, 119.1, 116.9, 115.3, 112.5, 109.3, 95.6, 84.5, 71.3, 71.0, 55.3, 55.1, 22.1, 21.7; IR (film): 2978, 2941, 2842, 1770, 1682, 1593, 1270, 1110, 775, 733 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{23}H_{26}O_5$ $[M]^+$: 382.1780. Found: 382.1768.

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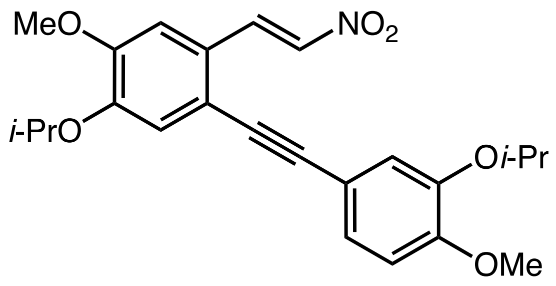
[217] Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3595.



1-Isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E*)-2-nitrovinyl]benzene (Scheme 2.32, 2.39). The title compound was prepared according to the procedure by Charette and coworkers.[218] A round bottomed flask equipped with a magnetic stir bar and a condenser was flame-dried and placed under an argon atmosphere. Ammonium acetate (0.484 g, 6.28 mmol) was dissolved in acetic acid (3.7 mL), and nitromethane (0.97 mL, 18 mmol) and 4-Isopropoxy-2-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-5-methoxybenzaldehyde (1.0 g, 2.6 mmol) were subsequently added. The reaction was stirred at room temperature for 30 minutes and was then heated to 100°C for 4 h. The reaction was allowed to cool to room temperature, then was poured into water and neutralized to pH 7 with a 3 M aqueous solution of NaOH. The resulting aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. A crude brown solid resulted which was purified by silica gel chromatography with an eluent of 100% CH_2Cl_2. The title compound was isolated as an orange solid (0.91 g, 82%). mp 144-145°C (recrystallized from 4:1 hexanes:ethyl acetate). TLC R_f 0.34 (20% EtOAc/hexanes); ^1H NMR (400 MHz, C_6D_6) δ ppm 8.80 (d, *J*= 13.7 Hz, 1H), 7.52 (d, *J*= 13.7 Hz, 1H), 7.39 (d, *J*= 1.9 Hz, 1H), 7.37 (dd, *J*= 8.1, 2.0 Hz, 1H), 7.03

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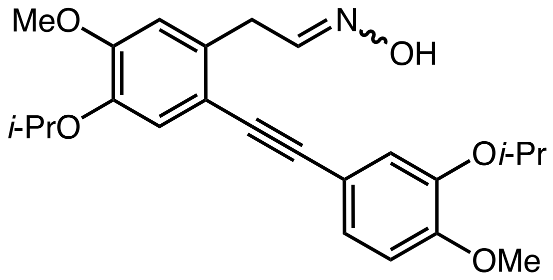
[218] Cote, A.; Lindsay, V. N. G.; Charette, A. B. *Org. Lett.* **2007**, *9*, 85.

(s, 1H), 6.42 (d, *J*= 8.2 Hz, 1H), 6.37 (s, 1H), 4.36 (sept, *J*= 6.1 Hz, 1H), 4.04 (sept, *J*= 6.2 Hz, 1H), 3.27 (s, 3H), 3.19 (s, 3H), 1.20 (d, *J*= 6.0 Hz, 6H), 1.02 (d, *J*= 6.0 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ ppm 152.1, 151.0, 150.6, 148.0, 136.8, 136.4, 125.1, 124.2, 119.8, 118.3, 116.7, 114.8, 112.4, 110.2, 96.9, 85.9, 71.0, 70.8, 55.1, 55.1, 21.9, 21.6; IR (film): 2975, 2930, 2839, 1596, 1512, 1329, 1265, 1246, 1136, 1105, 946 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{24}H_{27}NO_6$ [M]$^+$: 425.1838. Found: 425.1817.



1-Isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E/Z*)-acetaldehyde oxime]benzene (Scheme 2.32, 2.40). The title compound was prepared according to the procedure by Kabalka and coworkers.[219] 1-Isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E*)-2-nitrovinyl]benzene (0.460 g, 1.08 mmol) was dissolved in ethyl acetate (5.4 mL), and tin(II)chloride dihydrate (0.488 g, 2.16 mmol) was added. The reaction was stirred at room temperature open to air and was complete after 1.5 h. The reaction was poured into ice water and the resulting solution was made slightly basic (pH 7-8) upon the addition of 5% aq. $NaHCO_3$. Diethyl ether was added, and the layers separated. The aqueous layer was extracted with diethyl ether three times and the

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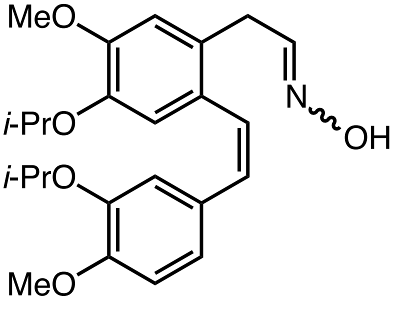
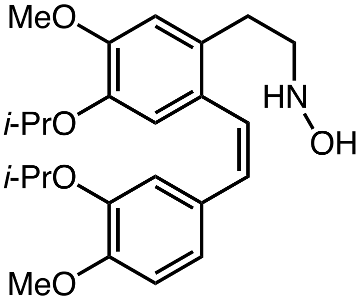
[219] Kabalka, G. W.; Guindi, L. H. M.; Varma, R. S. *Tetrahedron* **1990**, *46*, 7443.

combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated to yield a dark orange oil. The crude was purified by silica column chromatography with an eluent of 40% EtOAc in hexanes to yield the desired compound as a yellow oil (0.16 g, 37%). TLC R_f 0.40 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, isolated as a 52:48 mixture of *E* and *Z* oximes); Oxime 1: δ ppm 8.04 (br, 1 H), 7.62 (t, *J*=6.2, 6.2 Hz, 1 H), 7.09 (dd, *J*=1.9, 4.8 Hz, 1 H), 7.05 (s, 1 H), 7.04 (d, *J*=2.1 Hz, 1 H), 6.84 (d, *J*=5.0 Hz, 1 H), 6.72 (s, 1 H), 4.48-4.61 (m, 1 H), 3.90 (d, *J*=5.1 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 1.39 (d, *J*=5.2 Hz, 6 H), 1.37 (d, *J*=5.2 Hz, 6 H); Oxime 2: δ ppm 7.54 (br, 1 H), 7.11 (dd, *J*=1.9, 4.8 Hz, 1 H), 7.04 (d, *J*=2.0 Hz, 1 H), 7.04 (s, 1H), 6.93 (t, *J*=5.1 Hz, 1 H), 6.82 (d, *J*=5.0 Hz, 1 H), 6.76 (s, 1 H), 4.48-4.61 (m, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.72 (d, *J*=6.2 Hz, 2 H), 1.38 (d, *J*=6.1 Hz, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$, isolated as a mixture of *E* and *Z* oximes) δ ppm 151.1, 150.9, 150.9, 150.8, 150.8, 147.0, 146.0, 145.9, 132.1, 131.5, 125.0, 125.0, 118.9, 118.8, 118.5, 118.5, 115.5, 115.5, 115.2, 115.1, 112.9, 112.7, 111.8, 92.6, 92.4, 86.1, 86.0, 71.7, 71.6, 71.6, 56.0, 56.0, 34.4, 30.5, 22.1, 22.1; IR (film): 3473, 2976, 2930, 2846, 1514, 1242, 1135, 1112, 1025, 976, 866, 813 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{24}H_{29}NO_5$ $[M]^+$: 411.2046. Found: 411.2022.

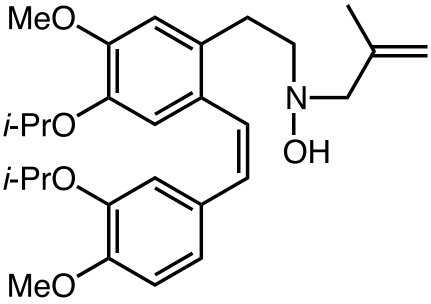
5.14.1 Procedure for the cis-Hydrogenation of Alkynes



2-(2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl)ethoxime (Table 2.13, 2.47). To a solution of the alkyne precursor (0.10 g, 0.24 mmol) in EtOAc (12 mL) and 1-hexene (12 mL) (used as sacrificial alkene) was added Lindlard's catalyst (0.030 g, 30% by weight). The suspension was put under hydrogen atmosphere and stirred at room temperature for 3.5 h. Filtered over celite and rinsed with Et_2O. Concentrated. Purified by column chrotamography with 12% EtOAc in dichloromethane. Gave 87 mg of the desired product (87%) as an orange oil. As a mixture of isomers: TLC R_f 0.38+0.34 (15% $EtOAc/CH_2Cl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.38 (t, *J*= 6.2 Hz, 0.5H, isomer 1), 6.73-6.69 (m, 4H), 6.71 (m, 0.5H, isomer 2), 6.61 (d, *J*= 4.1 Hz, 1H), 6.51-6.49 (m, 2H), 4.33-4.25 (m, 1H), 4.17-4.08 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.63 (d, *J*= 3.4 Hz, 1H), 3.43 (d, *J*= 6.2 Hz), 1.22-1.16 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 150.3, 149.4, 149.3, 146.6, 146.2, 146.1, 130.8, 129.8, 129.7, 129.6, 127.1, 126.6, 126.4, 122.3, 116.4, 116,4, 115.4, 114.0, 113.2, 111.4, 71.1, 70.9, 56.0, 55.8, 33.3, 21.8; IR (film): 3460, 2976, 2930, 2837, 1602, 1510, 1267, 1112 813 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{24}H_{31}NO_5$ $[M]^+$: 413.2202; found: 413.21876.

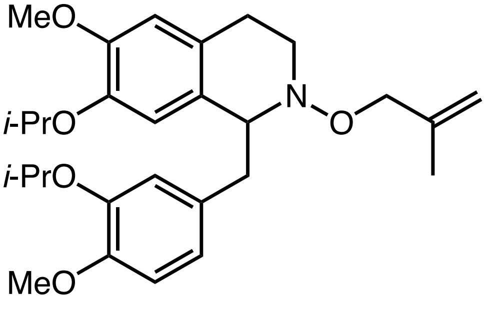


(Z)-2-[2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl]-N-hydroxyethanamine (Scheme 2.33, 2.41). Synthesized according to the general procedure 5.5 using the corresponding oxime (0.197 g, 0.477 mmol). The crude oil was used directly without further purification due to instability.

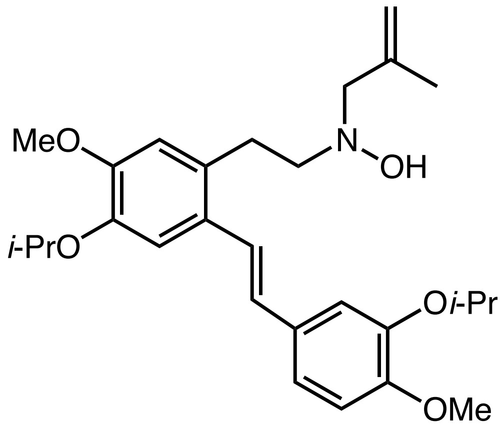


(Z)-*N*-(2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxy-2-methylprop-2-en-1-amine (Scheme 2.33, 2.42b). In a flame-dried round bottomed flask equipped with a magnetic stir bar was added the hydroxylamine (crude, 0.48 mmol) which was dissolved in a 5:1 mixture of THF:DMF (2.4 mL). DBU (0.081 mL, 0.52 mmol) and 3-chloro-2-methylpropane (0.140 mL, 1.43 mmol) were subsequently added and the solution was purged with argon. The reaction was heated and stirred under reflux for 1 hour. The reaction was allowed to cool to room temperature and diluted with ethyl acetate. The mixture was washed 5 times with a 50:50 mixture of water and brine. The organics were dried with Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica gel chromatography with an eluent of 10% EtOAc in hexanes and yielded a pale yellow oil (0.195 g, 87% over 2 steps). TLC R_f 0.85 (50% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.75 (s, 1H), 6.73 (dd, *J*= 1.8, 8.2 Hz, 1H), 6.69 (d, *J*= 6.5 Hz, 1H), 6.68 (s, 1H), 6.65 (d, *J*= 1.5 Hz, 1H), 6.57 (d, *J*= 11.9 Hz, 1H), 6.49 (d, *J*= 12.0 Hz, 1H), 4.83 (s, 1H), 4.80 (s, 1H), 4.25-4.21 (m, 1H), 4.13-4.09 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.26 (s, 2H), 2.91-2.79 (m, 4H), 1.72 (s, 3H), 1.20-1.15 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.3, 149.1, 146.5, 145.5, 141.2, 130.5, 130.1, 129.7, 129.4, 127.1, 122.2, 116.5, 115.4, 114.3, 113.3, 111.3, 71.0, 70.8, 67.2, 60.0, 56.0, 55.8, 31.1, 21.8, 21.8, 21.8, 21.8, 21.1; IR (film): 3493, 3245, 2975, 2934, 2836, 1602, 1511, 1267, 1091, 1029, 731 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{28}H_{39}NO_5$ $[M]^+$: 469.2828; found: 469.28322.

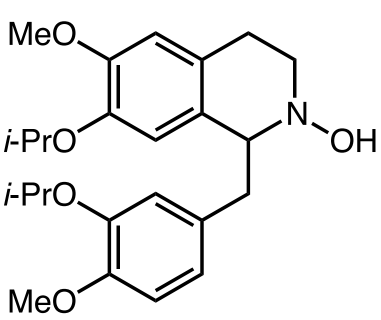
5.14.2 Procedure for the CHMR Sequence for the Synthesis of *N*-Norreticuline



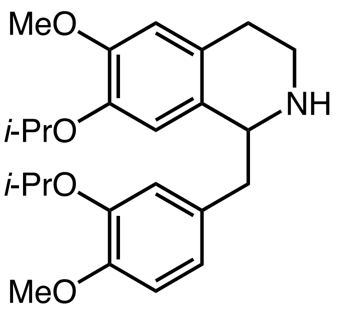
1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline-*N*-(2-methylallyloxide) (Table 2.14, 2.43b). In an oven-dried sealed tube equipped with a magnetic stir bar was dissolved the methallylated hydroxylamine (0.040 g, 0.085 mmol) in benzene (8.5 mL). Distilled water (0.015 mL, 0.85 mmol) was added and the reaction mixture was purged with argon for 15 minutes through a septum. The septum was quickly replaced by a Teflon screw cap and the reaction vessel was sealed. The reaction was heated at 120°C for 16 h. The reaction was then cooled, transferred to a separate round-bottomed flask, rinsed three times with additional benzene, and the solvent was evaporated. The crude residue was purified by silica column chromatography with an eluent of 1% EtOAc in hexanes and resulted in a clear, colourless oil (0.023 g, 57%). TLC R_f 0.27 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ ppm 6.97 (d, *J*=1.9 Hz, 1 H), 6.83 (dd, *J*=2.0, 8.1 Hz, 1 H), 6.61 (d, *J*=8.2 Hz, 1 H), 6.59 (s, 1 H), 6.41 (s, 1 H), 5.09 (d, *J*=1.0 Hz, 1 H), 4.87 (d, *J*=0.6 Hz, 1 H), 4.52 (t, *J*=6.0 Hz, 1 H), 4.35 (sept, *J*=6.0 Hz, 1 H), 4.22 (q, *J*=11.9 Hz, 2 H), 4.21 (sept, *J*=6.0 Hz, 1 H), 3.39 (s, 6 H), 3.28-3.35 (m, 2H), 3.18-3.24 (m, 1H), 3.07 (dd, *J*=6.7, 14.1 Hz, 1 H), 2.91 (ddd, *J*=5.3, 8.2, 15.6 Hz, 1 H), 2.56 (ddd, *J*=5.2, 5.2, 16.0 Hz, 1 H), 1.72 (s, 1 H), 1.21 (d, *J*=6.0 Hz, 1 H), 1.20 (d, *J*=6.1 Hz, 1 H), 1.19 (d, *J*=6.2 Hz, 1 H), 1.16 (d, *J*=6.1 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ ppm 150.1, 149.9, 147.9, 146.3, 142.6, 133.0, 129.7, 126.9, 122.8, 118.9, 116.5, 112.8, 112.6, 76.7, 71.4, 71.2, 66.8, 55.6, 55.5, 48.5, 40.9, 26.4, 22.4, 22.3, 20.2; IR (film): 3428, 2975, 2934, 2835, 1607, 1508, 1261, 1223, 1109, 1033, 892, 854, 801, 775 cm^{-1}; MS (Electrospray): Exact mass calculated for $C_{28}H_{39}NO_5$ [M+1H]: 469.2828. Found: 470.6.



(E)-*N*-(2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxy-2-methylprop-2-en-1-amine (Table 2.14, not shown). Isolated as a side product of the cyclization reaction of (Z)-*N*-(2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxy-2-methylprop-2-en-1-amine. TLC R_f 0.05 (5% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.64 (d, *J*= 16.0 Hz, 1H), 7.48 (s, 1H), 7.37 (d, *J*= 1.9 Hz, 1H), 7.15 (1H), 7.11 (d, *J*= 16.0 Hz, 1H), 6.65 (s, 1H), 6.62 (d, *J*= 8.3 Hz, 1H), 4.89 (s, 1H), 4.81 (s, 1H), 4.55-4.47 (m, 1H), 4.46-4.40 (m, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.38-3.12 (m, 2H), 3.13 (s, 2H), 2.92-2.89 (m, 2H), 1.70 (s, 3H), 1.28 (d, *J*= 6.0 Hz, 6H), 1.25 (d, *J*= 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.2, 131.0, 128.7, 128.0, 124.0, 120.0, 113.9, 113.8, 113.6, 112.1, 100.0, 71.5, 70.9, 67.3, 60.1, 56.0, 56.0, 31.1, 22.2, 22.1, 21.9, 21.1; HRMS (EI): Exact mass calculated for $C_{28}H_{39}NO_5$ $[M]^+$: 469.2828; found: 469.28565.

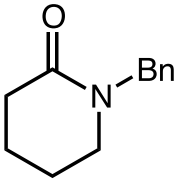


1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline-*N*-hydroxide (Table 2.14, 2.48). In an oven-dried sealed tube equipped with a magnetic stir bar was dissolved the primary hydroxylamine (crude, 0.14 mmol) and $NaCNBH_3$ (0.0085 g, 0.14 mmol) in *n*-PrOH (14 mL). The reaction mixture was purged with argon for 15 minutes through a septum. The septum was quickly replaced by a Teflon screw cap and the reaction vessel was sealed. The reaction was heated at 120°C for 16 h. The reaction was then cooled, transferred to a separate round-bottomed flask, rinsed three times with additional *n*-PrOH, and the solvent was evaporated. The crude residue was purified by silica column chromatography with an eluent of 50% EtOAc in hexanes and resulted in a yellow oil (29 mg, 51%). TLC R_f 0.72 (70% EtOAc/hexanes); ^{1}H NMR (400 MHz, C_6D_6) δ ppm 6.94 (d, *J*=2.0 Hz, 1H), 6.81 (dd, *J*=1.9, 8.1 Hz, 1H), 6.63 (s, 1H), 6.61 (d, *J*=8.2 Hz, 1H), 6.38 (s, 1H), 4.31-4.37 (m, 2H), 4.20-4.27 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.28-3.34 (m, 2H), 3.06-3.15 (m, 2H), 2.78 (ddd, *J*=5.6, 5.6, 12.2 Hz, 1H), 2.67 (ddd, *J*=6.1, 6.1, 16.4 Hz, 1H), 1.20 (d, *J*=6.0 Hz, 3H), 1.20 (d, *J*=6.0 Hz, 3H), 1.19 (d, *J*=6.0 Hz, 3H), 1.17 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ ppm 150.1, 150.0, 148.0, 146.3, 132.8, 129.5, 122.81, 118.9, 116.4, 113.0, 112.6, 71.5, 71.3, 68.7, 55.7, 55.5, 51.9, 26.6, 22.4, 22.4, 22.3, 22.1; IR (film): 2979, 2934, 2842, 1607, 1512, 1445, 1261, 1235, 1109, 1033, 934, 858, 813, 771 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{18}NO_3$ [M – 3-isopropoxy-4-methoxybenzyl]$^+$: 236.1287. Found: 236.1268.



1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline (Equation 2.6, 2.44). Based on a procedure by the Dolle group.[211] The *N*-(2-methylallyloxide)tetrahydroisoquinoline (0.01 g, 0.02 mmol) was dissolved in a 1:1 (v/v) of AcOH and water (0.068 mL) and zinc dust (0.039 g, 0.60 mmol) was added. The reaction flask was capped with a rubber septum with an outlet needle and the reaction was stirred vigorously at room temperature for 5 h. The crude mixture was poured onto basicified brine (pH 14). The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine (pH 7), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The resulting crude yellow oil was purified by silica column chromatography with an eluent of 5% MeOH in dichloromethane and resulted in a colorless oil (6.3 mg, 78%). TLC R_f 0.05 (5% MeOH/CH_2Cl_2); Previously characterized by Ms. Pamela Cebrowski.[220]

5.15 Synthesis of the Dienophile (Chapter 3)



1-Benzylpiperidin-2-one (Scheme 3.16, 3.8). Based on a procedure by Pardo and coworkers.[221] *n*-BuLi in hexanes (19.2 mL, 46.7 mmol), was dissolved in THF (130 mL) at -78°C. To this was added a solution of δ-valerolactam (4.10 g, 41.4 mmol) in THF (40 mL). This reaction solution was stirred at -78°C for 20 min at which time freshly distilled benzylbromide (4.91 mL, 41.4 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 16 h at which point a saturated solution of NH_4Cl was added The mixture was extracted three times with EtOAc. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 100% EtOAc and resulted in a colorless oil (2.93 g, 37%). TLC R_f 0.73 (100% EtOAc); ^{1}H NMR (300 MHz,

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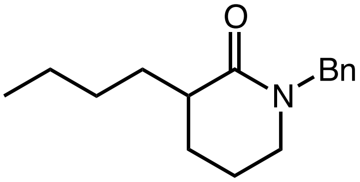
[220] Cebrowski, P. H. Application of Cope-Type Hydroamination in the Synthesis of Hydrazones and the Total Synthesis of the Benzyltetrahydroisoquinoline Norreticuline. M.Sc. Thesis, University of Ottawa, ON, 2009.
[221] Cossy, J.; de Filippis, A.; Pardo, D. G. *Org. Lett.* **2003**, *5*, 3037.

$CDCl_3$) δ ppm 7.34-7.24 (m, 5H), 4.60 (s, 2H), 3.19 (t, *J*= 6.2 Hz, 2H), 2.47 (t, *J*= 6.2 Hz, 2H), 1.81-1.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.0, 137.2, 128.4, 127.9, 127.1, 49.9, 47.1, 32.3, 23.0, 21.2; IR (film): 2946, 2868, 1634, 1466, 1352, 1176, 698 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{12}H_{15}N_1O_1$ $[M]^+$: 189.1154; found: 189.11452.



1-Benzyl-3-butylpiperidin-2-one (Scheme 3.16, 3.9). Based on a procedure by the Dieter group.[222] To a solution of freshly distilled diisopropylamine (0.411 mL, 2.91 mmol) in THF (5.28 mL) at 0°C was added *n*-BuLi in hexanes (1.19 mL, 2.91 mmol). The solution was stirred for 20 min, then cooled to -78°C, at which time a solution of 1-benzylpiperidin-2-one (0.500 g, 2.64 mmol) in THF (5.28 mL) was added. The solution was warmed to -48°C at which time iodobutane (0.441 mL, 3.96 mmol) was added. The reaction solution was stirred at -48°C for 1h. A saturated solution of NH_4Cl was added. The mixture was extracted three times with Et_2O. The combined organic phases were washed twice with a saturated solution of NH_4Cl, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 20% EtOAc in hexanes and resulted in a colorless oil (0.58 g, 90%). TLC R_f 0.73 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34-7.23 (m, 5H), 4.58 (dd, *J*= 14.7, 22.1 Hz, 2H), 3.18 (dd, *J*= 5.0, 7.0 Hz, 2H), 2.40-2.31

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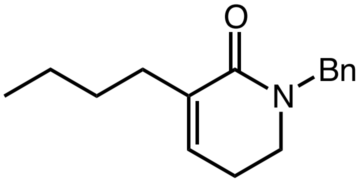
[222] Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180.

(m, 1H), 2.10-1.81 (m, 2H), 1.81-1.76 (m, 1H), 1.74-1.65 (m, 1H), 1.63-1.47 (m, 2H), 1.43-1.27 (m, 4H), 0.93 (t, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.8, 137.5, 128.4, 127.9, 127.1, 50.2, 47.3, 41.5, 29.3, 26.3, 22.7, 21.54, 14.0; IR (film): 2929, 2861, 1645, 1489, 1436, 1192, 701 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{16}H_{23}N_1O_1$ $[M]^+$: 245.1780; found: 245.17952.



1-Benzyl-3-butyl-5,6-dihydropyridin-2(1*H*)-one (Scheme 3.16, 3.11). Based on a procedure by the Reich group.[223] To a solution of diisopropylamine (0.103 mL, 0.727 mmol) in THF (2.42 mL) at -78°C was added a solution of *n*-BuLi in hexanes (0.251 mL, 0.727 mmol) dropwise. It was followed by addition of the protected lactam (0.100 g, 0.404 mmol) in THF (0.2 mL). The solution was stirred for 10 min at which time a solution of PhSeCl (0.139 g, 0.727 mmol) in THF (0.242 mL) was added. The reaction was warmed to 0°C and stirred for 30 min. Water (0.364 mL) and acetic acid (0.069 mL, 1.2 mmol) were added followed by 30% hydrogen peroxide (0.34 g, 3.0 mmol) while always keeping the mixture temperature below 25°C. The reaction was stirred at room temperature for 45 min, was dissolved in diethyl ether and a saturated solution of $NaHCO_3$. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic phases were

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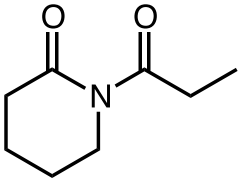
[223] Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography (5% Et_2O/Hexanes) and resulted in a yellow oil (42 mg, 29%). TLC R_f 0.67 (50% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.26-7.33 (m, 5H), 6.25 (t, *J*= 4.3 Hz, 1H), 4.64 (s, 2H), 8.28 (t, *J*= 7.0 Hz, 2H), 2.23-2.34 (m, 4H), 1.29-1.51 (m, 4H), 0,92 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.5, 137.8, 135.9, 132.7, 128.5, 128.0, 127.2, 50.0, 44.8, 30.9, 30.5, 23.9, 22.4, 13.9; IR (film): 2956, 2926, 2857, 1666, 1622, 1207, 699 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{16}H_{21}NO$ $[M]^+$: 243.1623. Found: 243.1617.



1-Propionylpiperidin-2-one (Scheme 3.17, 3.12b). Based on a procedure by Fales and coworkers.[224] To a solution of δ-valerolactam (2.00 g, 20.2 mmol) in benzene (53 mL) and pyridine (3.18 mL, 40.2 mmol) at 0°C was added dropwise a solution of propionyl chloride (1.66 mL, 19.0 mmol) in THF (7 mL). The reaction was warmed to room temperature and stirred for 16 h. The reaction was diluted in benzene (150 mL) and washed three times with 10% HCl and once with 10% NaOH. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an

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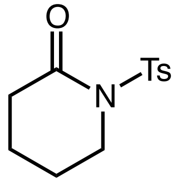
[224] Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982***, 38*, 1949. with modified workup: Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569.

eluent of 30% EtOAc in hexanes and resulted in a colorless oil (1.99 g, 68%). TLC R_f 0.69 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.70 (ap s, 2H), 2.88 (q, *J*= 7.3 Hz, 2H), 2.51 (ap q, *J*= 1.7 Hz, 2H), 1.80 (m, 4H), 1.10 (t, *J*= 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.8, 173.2, 43.8, 34.8, 33.0, 22.4, 20.2, 9.1; IR (film): 2941, 2879, 1702, 1357, 1203 cm^{-1}; HRMS (EI): Exact mass calculated for $C_8H_{13}NO_2$ $[M]^+$: 155.0946. Found: 155.0966.



1-Tosylpiperidin-2-one (Scheme 3.17, 3.12a). Based on a procedure by Pardo and coworkers.[225] To a solution of *n*-BuLi in hexanes (1.82 mL, 5.70 mmol) in THF (8.6 mL) at -78°C was added dropwise a solution of δ-valerolactam (0.500 g, 5.04 mmol) in THF (5.7 mL). The reaction was stirred for 20 min at -78°C at which time a solution of *para*-toluenesulfonyl chloride (0.961 g, 5.04 mmol) in THF (5.7 mL) was added dropwise. The reaction was warmed slowly to room temperature via an ice bath and stirred for 16 h at room temperature. A saturated solution of NH_4Cl was added and the reaction mixture was extracted three times with diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 20% to 30% EtOAc in hexanes and resulted in a light

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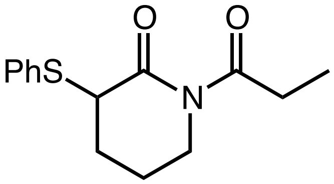
[225] de Filippis, A.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2004***, 60*, 9757.

yellow oil (297 mg, 23%). TLC R_f 0.49 (50% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (d, *J*= 8.3 Hz, 2H), 7.30 (d, *J*= 8.2 Hz, 2H), 3.90 (t, *J*= 5.9 Hz, 2H), 2.41 (s, 3H), 2.40 (t, *J*= 6.7 Hz, 2H), 1.86-1.92 (m, 2H), 1.73-1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.1, 144.6, 136.0, 129.2, 128.6, 46.8, 34.0, 23.3, 21.6, 20.3; The spectral data corresponds to that reported in literature.[226]



3-(Phenylthio)-1-propionylpiperidin-2-one (Scheme 3.17. 3.13b). Based on a procedure by Nakagawa and coworkers.[227] To a solution of the protected lactam (0.176 g, 1.13 mmol) and 1,2-diphenyldisulfane (0.279 g, 1.28 mmol) in THF (13 mL) at -60°C was added a KHMDS (0.5 M in THF, 4.5 mL) dropwise. Stirred at -60°C for 20 min at which time a saturated aqueous solution of NH_4Cl and mix of Et_2O and EtOAc (1:1) were added. The phases were separated and extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 10% EtOAc in hexanes and resulted in a colorless oil (662 mg, 78%). TLC R_f 0.81 (50% EtOAc/Hexanes); ^{1}H NMR

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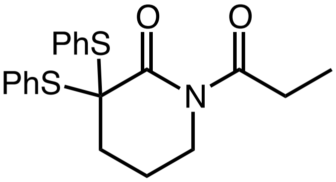
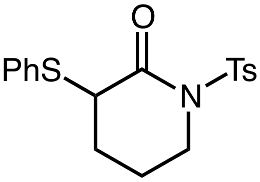
[226] Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.* **2004***, 69*, 5668.

[227] Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T.; Hino, T. *J. Org. Chem*. **1992**, *57*, 5741.

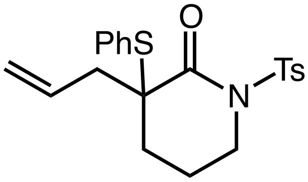
(300 MHz, $CDCl_3$) δ ppm as a mix of 2 diastereomers: 7.50-7.54 (m, 2H), 7.30-7.36 (m, 3H), 3.86-3.96 (m, 2H), 3.71 (dd, *J*= 4.5, 8.2 Hz, 1H, isomer A), 3.68 (dd, *J*= 4.2, 8.2 Hz, 1H, isomer B), 2.89 (dq, *J*= 17.6, 7.3 Hz, 1H), 2.75 (dq, *J*= 17.6, 7.3 Hz, 1H), 2.22-2.31 (m, 1H), 1.97-2.08 (m, 2H), 1.75-1.84 (m, 1H), 1.13 (t, *J*= 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 177.6, 171.6, 133.3, 132.8, 129.0, 128.1, 51.0, 43.2, 32.3, 27.8, 20.3, 9.1; IR (film): 3378, 2940, 1710, 1481, 1201 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{14}H_{17}NO_2S[M]^+$: 263.0980. Found: 263.0979.



3,3-Bis(phenylthio)-1-propionylpiperidin-2-one (Scheme 3.17, not shown). Obtained as a side product in the formation of 3-(phenylthio)-1-propionylpiperidin-2-one. TLC *R*f 0.94 (50% EtOAc/Hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.66-7.69 (m, 4H), 7.34-7.42 (m, 6H), 3.74 (t, *J*= 6.0 Hz, 2H), 2.60 (q, *J*= 7.3 Hz, 2H), 2.09 (m, 2H), 1.93 (m, 2H), 1.08 (t, *J*= 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 178.1, 169.7, 136.5, 130.9, 129.8, 128.9, 68.8, 44.1, 35.0, 32.3, 20.0, 9.2; IR (film): 3063, 2938, 1696, 1439, 1155 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{20}H_{21}N_1O_2S_2$ $[M]^+$: 371.1014. Found: 371.1027.

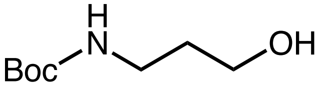


3-(Phenylthio)-1-tosylpiperidin-2-one (Scheme 3.17, 3.13a). Based on a procedure by Nakagawa and coworkers.[227] To a solution of the protected lactam (0.327 g, 1.29 mmol) and 1,2-diphenyldisulfane (0.319 g, 1.46 mmol) in THF (14 mL) at -60°C was added KHMDS (0.5 M in THF, 8 mL) dropwise. Stirred at -60°C for 20 min at which time a saturated aqueous solution of NH_4Cl and mix of Et_2O and EtOAc (1:1) were added. The phases were separated and extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 20% EtOAc in hexanes and resulted in a colorless oil (277 mg, 60%). TLC R_f 0.70 (50% EtOAc/Hexanes); The spectral data corresponds to that reported in literature.[227]



3-(Phenylthio)-3-allyl-1-tosylpiperidin-2-one (Scheme 3.18, 3.15a). Based on a procedure by the Nakagawa group.[227] To a solution of the protected lactam (0.050 g, 0.14 mmol) in

THF (1.38 mL) at -60°C was added solid KHMDS (0.050 g, 0.25 mmol). The reaction was stirred at -60°C until the solid dissolved, at which time a solution of freshly distilled allyl bromide (0.026 mL, 0.30 mmol) in THF (0.6 mL) was added dropwise. The reaction mixture was warmed to -30°C over 1 h, then extra KHMDS (0.0044 g, 0.022 mmol) was added. Warmed to room temperature over 2 h and stirred for an extra 3 h. A saturated solution of NH_4Cl and EtOAc were added and the phases were separated. The organic phase was washed twice with brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was ran through a silica pad with an eluent of 10% EtOAc in hexanes and resulted in a colorless oil (17 mg, 32%). The compound was used directly without further purification.



***tert*-Butyl 3-hydroxypropylcarbamate (Scheme 3.19, 3.19).** According to a modified protocol by Mattingly and coworkers,[228] a solution of di-tert-butyldicarbonate (0. 626 g, 2.87 mmol) in dichloromethane (1.56 mL) at room temperature was added dropwise to a solution of 3-amino-1-propanol (0.200 g, 2.66 mmol) in dichloromethane (1.56 mL). After one hour, the reaction was diluted in diethyl ether and washed once with saturated NH_4Cl, twice with saturated $NaHCO_3$ and once with brine. The organic phase was then dried over $MgSO_4$,

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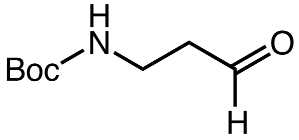
[228] Mattingly, P. G. *Synthesis* **1990**, 366.

filtered and concentrated. Used without further purification. The spectral data corresponds to that reported in literature.[229]



***tert*-Butyl 2-formylethylcarbamate (Scheme 3.19, 3.20).** Based on a procedure by the Greene group,[202] the alcohol (0.200 g, 2.66 mmol), triethylamine (1.21 mL, 8.71 mmol) and dimethylsufoxide (0.607 mL, 8.55 mmol) were dissolved in dichloromethane (12.2 mL) at 0°C. To this solution was added sulfur trioxide pyridine complex (1.27 g, 8.01 mmol). Stirred at 0°C for 1.5 h at which time a saturated solution NH_4Cl was added. The mixture was extracted three times with dichloromethane. The organic phases were combined, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was directly used for the next reaction without further purification. TLC R_f 0.35 (10% $MeOH/CH_2Cl_2$).

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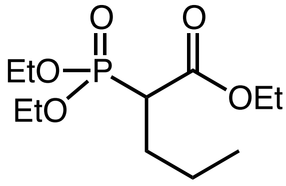
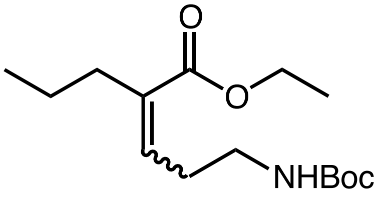
[229] ^1H NMR: Lee, B. H.; Miller, M. J. *J. Org. Chem*. **1983**, *48*, 24. ^{13}C NMR: Heinonen, P.; Virta, P.; Lönnberg, H. *Tetrahedron* **1999**, *55*, 7613. IR: Yokoyama, H.; Ejiri, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. Tetrahedron: *Asymmetry* **2007**, *18*, 852.



Ethyl 2-(diethoxyphosphoryl)pentanoate (Scheme 3.19, 3.22). Based on a procedure by Tomisaya and coworkers.[230] To a suspension of NaH (0.540 g, 13.5 mmol), in 1,2-dimethoxyethane (16 mL) at room temperature was added triethylphosphonoacetate (2.68 mL, 13.5 mmol) dropwise. Stirred at room temperature for 1 h, at which time 1-bromopropane (15.0 mL, 165 mmol) was added. The reaction was then refluxed for 2h. Water was added and the reaction mixture was extracted three times with diethyl ether. The organic phases were combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by distillation under reduced pressure (bp: 113°C at 0.1 mmHg) and resulted in a colorless oil (2.79 g, 78%). TLC R_f 0.48 (100% EtOAc); Commercially available.



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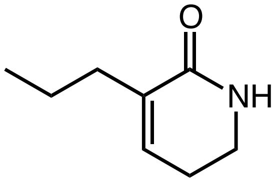
[230] Nakazato, A.; Kumagai, T.; Ohta, K.; Chaki, S.; Okuyama, S.; Tomisawa, K. *J. Med. Chem.* **1999**, *42*, 3965.

***tert*-Butyl 4-(ethoxycarbonyl)hept-3-enylcarbamate (Scheme 3.19, 3.23).** Based on a procedure by Boger and coworkers.[231] The phosphorane (0.404 g, 1.46 mmol) was added dropwise to a suspension of NaH (0.077 g, 1.9 mmol) in THF (12 mL) at 0°C. The mixture was stirred for 10 min at which time a solution of the aldehyde (0.230 g, 1.33 mmol) in THF (3.2 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 30 min. Water was added and the phases were separated. The aqueous phase was extracted three times with diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 10% EtOAc in hexanes and resulted in a colorless oil (145 mg, 38% over 3 steps). TLC R_f 0.83 (50% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm as a mix of 2 isomers: 6.62 (t, *J*= 7.5 Hz, 0.5H, isomer A), 5.74 (t, *J*= 7.5 Hz, 0.5H, isomer B), 4.87 (br, 0.5H, isomer A), 4.76 (br, 0.5H, isomer B), 4.12 (ap q, *J*= 6.6 Hz, 2H, 2 isomers), 3.16 (m, 2H), 2.50 (ap q, *J*= 6.9 Hz, 1H), 2.32 (ap q, *J*= 7.0 Hz, 1H), 2.18 (ap q, *J*= 7.4 Hz, 2H), 1.36 (m, 2H), 1.36 (s, 9H), 1.22 (m, 3H), 0.82 (q, *J*= 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.0, 167.5, 155.9, 155.7, 138.3, 136.8, 134.5, 79.0, 78.7, 60.3, 60.1, 39.9, 39.5, 36.4, 29.7, 29.2, 28.6, 28.2, 22.3, 21.6, 14.1, 13.8, 13.4; IR (film): 3370, 2964, 1716, 1683, 1520, 1277 cm^{-1}; LRMS m/z (relative intensity): 30.0341 (48.3%), 41.0394 (23.2%), 57.0708 (89.0%), 140.1053 (18.6%), 156.1145 (100.0%), 229.1324 (13.4%).



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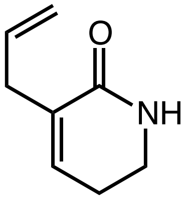
[231] Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704.

3-Propyl-5,6-dihydro-1H-pyridin-2-one (Scheme 3.19, 3.24). Based on a procedure procedure by Lampe and Hughes.[232] To a solution of *tert*-Butyl 4-(ethoxycarbonyl)hept-3-enylcarbamate (0.075 g, 0.26 mmol) in Et_2O (3 mL) was bubbled anhydrous HCl gas for 3.5 h. Upon completion, the reaction mixture was concentrated *in vacuo* resulting in a yellow oil. The crude oil was redissolved in toluene (5.3 mL). Et_3N (0.092 mL, 0.66 mmol) was added and the reaction was heated to 40°C for 2 h. The reaction was then allowed to react for 24 hours at room temperature. Upon completion, EtOAc and a saturated solution of $NaHCO_3$ were added and the phases were separated. The aqueous phase was extracted twice with EtOAc. The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 70% EtOAc in hexanes and resulted in a colorless oil (13 mg, 50%). The spectral data corresponds by comparison to that reported by Nicholas Wong (*vide infra*).[233]



3-Allyl-5,6-dihydro-1H-pyridin-2-one (Scheme 3.20, 3.28). Synthesized by Nicholas Wong as part of his honors thesis.[233]

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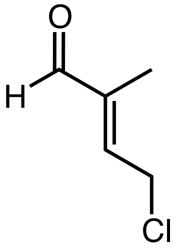
[232] Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *54*, 5148

[233] Wong, N. Studies Towards the Synthesis of Manzamine A. Honors Thesis, University of Ottawa, ON, 2009.

TLC R_f 0.68 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 6.35 (t, *J* = 8.4 Hz, 1H), 6.25 (br s, 1H), 5.84 (m, 1H), 5.08 (d, *J* = 7.2 Hz 1H), 5.05 (s, 1H), 3.38 (t, *J* = 14.4 Hz, 2H), 3.02 (d, *J* =6.8 Hz, 2H), 2.33 (q, *J* = 18.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 167.0, 135.7, 133.6, 116.4 (2C), 39.8, 34.1, 24.1; IR (film): 3191, 3070, 2933, 2902, 1671, 1621, 1477, 1424, 1302, 1150, 994, 926, 850, 690 cm^{-1}; HRMS (EI): Exact mass calculated for $C_8H_{11}NO$ [M^+]: 137.0841 found 137.08269.

5.16 Preparation of the 1st Generation of Aminodienes (Chapter 3)



(*E*)-4-Chloro-2-methylbut-2-enal (Scheme 3.44, 3.36). Based on procedures by the Koo and Oehlschlager groups.[234] To a suspension of isoprene (11.0 g, 115 mmol) in H_2O (43 mL) at 0°C was added NBS (20.0 g, 112 mmol). The reaction was warmed to room temperature and stirred until a negative starch paper test was obtained. A solution of 30% NaOH (35 mL) was then added and the reaction solution was stirred for 1h. The solution was extracted three times with 15 mL of EtOAc. The combined organic phases were combined, dried with

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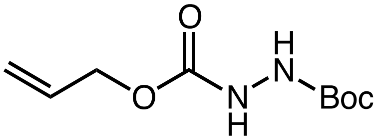
[234] a) Choi, H.; Ji, M.; Park, M.; Yun, I-K.; Oh, S-S.; Baik, W.; Koo, S. *J. Org. Chem*. **1999**, *64*, 8051. b) Johnston, B. D.; Oehlschlager, A. C. *Can. J. Chem.* **1984**, *62*, 2148.

K_2CO_3, and filtered. To this solution was added $CuCl_2$ (15.0 g, 112 mmol) and LiCl (4.70 g, 112 mmol). The reaction mixture was stirred at 80°C for 30 min, then cooled down to room temperature and filtered off. The filtrate phases were separated and the aqueous phase was extracted three times with hexanes. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 1-10% EtOAc in hexanes and resulted in a yellow oil (8.25 g, 62%). TLC R_f 0.78 (50% EtOAc/hexanes); The spectral data corresponds to that reported in literature.[234]



2-Allylcarbamate-1-*t*-butylcarbazate (Scheme 3.44, 3.33). Based on a procedure by Sorensen and coworkers.[235] *t*-Butylcarbazate (5.00 g, 37.8 mmol) and pyridine (3.35 mL, 41.6 mmol) were dissolved in diethyl ether (151 mL) at 0°C. Allylchloroformate (4.01 mL, 37.8 mmol) was added dropwise. The reaction solution was stirred at 0°C for 45 min then warmed to room temperature and stirred for an additional hour. The reaction mixture was washed with H_2O, 5% HCl and 5% $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil cristalized at room temperature to provide a pale yellow solid (7.06 g, 86%). TLC R_f 0.67 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.42 (s, 1H), 6.27 (2, 1H), 5.96-5.86 (m, 1H), 5.34 (dd, *J*= 1.2, 17.3 Hz, 1H), 5.24 (dd,

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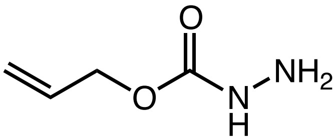
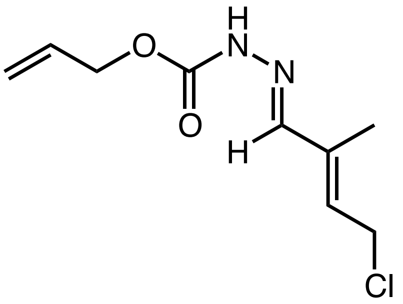
[235] Flamme, E. M.; Xie, H.; Ho, D. M.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8612.

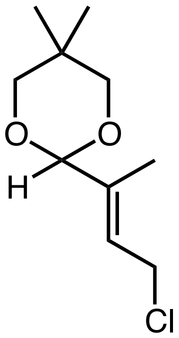
J= 0.7, 10.4 Hz, 1H), 4.64 (d, *J*= 5.7 Hz, 2H), 1.47 (s, 9H); The spectral data corresponds to that reported in literature.[235]



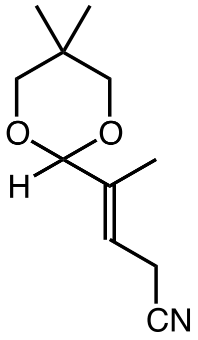
Allylcarbazate (Scheme 3.44, 3.34). Based on a procedure by Sorensen and coworkers.[235] Protected *t*-butylcarbazate (7.06 g, 32.6 mmol) was suspended in water (45.7 mL) and heated at 160°C for 2.5 h. The reaction mixture was cooled to room temperature extracted three times with diethyl ether. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 6% MeOH in CH_2Cl_2 and resulted in a yellow oil (1.87 g, 49%). TLC R_f 0.39 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.01 (s, 1 H), 5.98-5.85 (m, 1 H), 5.32 (dd, *J*= 1.3, 17.2 Hz, 1H), 5.24 (dd, *J*= 0.9, 10.4 Hz, 1H), 4.61 (d, *J*= 5.6 Hz, 2H), 3.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.5, 132.4, 118.1, 66.0; The spectral data corresponds to that reported in literature.[235]



(4-(Chloro)2-methylbut-2-enylidene)-carbamic acid allyl ester (Scheme 3.44, 3.37). Based on a procedure by Sorensen and coworkers.[235] Allylcarbazate (0.088 g, 0.76 mmol) and (*E*)-4-chloro-2-methylbut-2-enal (0.10 g, 0.84 mmol) were dissolved in THF (3.1 mL) and stirred for 16 h at room temperature. The reaction mixture was concentrated *in vacuo* and purified by silica column chromatography with an eluent of 5% EtOAc in dichloromethane and resulted in a yellow oil which quickly degraded upon standing at room temperature (0.090 g, 55%).



2-((*E*)-4-Chlorobut-2-en-2-yl)-5,5-dimethyl-1,3-dioxane (Scheme 3.46, 3.43). Based on a procedure by the Koo group.[234a] To a solution of (*E*)-4-chloro-2-methylbut-2-enal (3.53 g, 29.8 mmol) in benzene (23 mL) were added neopentyl glycol (3.73 g, 35.8 mmol) and para-toluenesulfonic acid monohydrate (0.057 g, 0.29 mmol). The reaction was refluxed for 1.5 h at which time the reaction was cooled to room temperature, dissolved in diethyl ether and washed with water. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 5% EtOAc in hexanes and resulted in a colorless oil (4.61 g, 76%). TLC R_f 0.56 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.86 (t, *J*= 8.5 Hz, 1H), 4.73 (s, 1H), 4.11 (d, *J*= 7.8 Hz, 2H), 3.66 (d, *J*= 11.1 Hz, 2H), 3.50 (d, *J*= 10.7 Hz, 2H), 1.81 (s, 3H), 1.21 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 138.2, 124.3, 103.5, 77.2, 39.5, 30.2, 22.9, 21.8, 11.4; The spectral data corresponds to that reported in literature.[234a]



(*E*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)pent-3-enenitrile (Scheme 3.46, 3.44a). Based on a procedure by Miller and coworkers.[236] To a solution of 2-((*E*)-4-chlorobut-2-en-2-yl)-5,5-dimethyl-1,3-dioxane (0.250 g, 1.22 mmol) in DMSO (12 mL) at room temperature was

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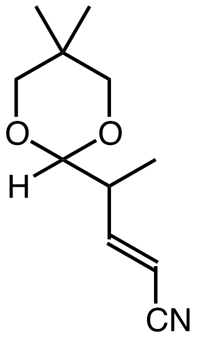
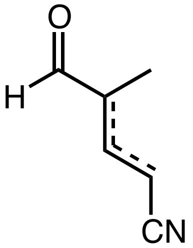
[236] Miller, J. F.; Furfine, E. S.; Hanlon, M. H.; Hazen, R. J.; Ray, J. A.; Robinson, L.; Samano, V.; Spaltenstein, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 959.

added KCN (0.087 g, 1.3 mmol). The reaction was stirred at room temperature for 4 h. The mixture was dissolved in ethyl acetate and washed three times with a basicified (pH 14) solution of 50:50 water/brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography (7% EtOAc/Hexanes) and resulted in a colorless oil (132 mg, 55%). TLC R_f 0.23 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.68 (t, *J*= 6.3 Hz, 1H), 4.73 (s, 1H), 3.66 (d, *J*= 11.1 Hz, 2H), 3.50 (d, *J*= 10.7 Hz, 2H), 3.11 (d, *J*= 6.9 Hz, 2H), 1.77 (s, 3H), 1.21 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 139.1, 117.6, 116.3, 103.0, 77.2, 30.2, 22.9, 21.8, 15.8, 11.8; IR (film): 2956, 2853, 2253, 1470, 1398, 1109, 1018, 980 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{17}NO_2$ $[M]^+$: 195.1259. Found: 195.1198.

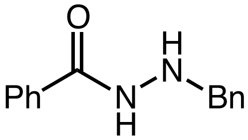


(*E*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)pent-2-enenitrile (Scheme 3.46, 3.44b). Obtained as a side product due to isomerization of the alkene in the reaction forming (*E*)-4-(5,5-dimethyl-1,3-dioxan-2-yl)pent-3-enenitrile. TLC R_f 0.35 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.82 (dd, *J*= 16.6, 7.3 Hz, 1H), 5.37 (dd, *J*= 16.6, 1.4 Hz, 1H), 4.33 (d, *J*= 4.0 Hz, 1H), 3.61 (d, *J*= 11.2 Hz, 2H), 3.40 (dd, *J*= 10.8, 3.3 Hz, 2H), 2.52–2.64 (m, 1H), 1.15

(s, 3H), 1.11 (d, *J*= 7.0 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 155.7, 117.5, 102.6, 100.3, 77.2, 41.9, 30.2, 22.9, 21.7, 13.5; IR (film): 2955, 2846, 2223, 1634, 1467, 1389, 1101, 960 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{17}NO_2$ $[M]^+$: 195.1259. Found: 195.12523.

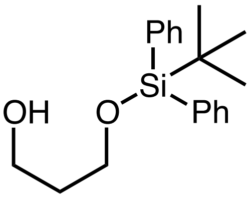


4-Cyano-2-methylpent-2-enal (Scheme 3.46, 3.40). Based on a procedure by Koo and coworkers.[234a] To a solution of (*E*)- or (*Z*)- 4-(5,5-Dimethyl-1,3-dioxan-2-yl)pent-2-enenitrile (0.027 g, 0.14 mmol) in THF (2 mL) at room temperature was added 1M HCl (2.5 mL). The reaction mixture was stirred at room temperature for 1 h. It was then extracted three times with diethyl ether. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. Used directly without further purification.



***N'*-Benzyl-*N*-benzohydrazide (Scheme 3.46, 3.45).** A solution of benzaldehyde (1.00 g, 9.42 mmol) and benzoic hydrazide (1.17 g, 8.57 mmol) in methanol (43 mL) was stirred at room temperature for 2 h. The crude solid was filtered off and redissolved in methanol (17 mL). Methyl orange was added as an indicator, followed by sodium cyanoborohydride (1.42 g, 20.5 mmol). The solution was kept under pH 3 (methyl orange turning point, pink) with a solution of 1:5 HCl in methanol. After 4 h, the reaction mixture was basicified to pH 8 with 3M NaOH. Poured onto brine and extracted three times with dichloromethane. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. Resulted in a beige solid (1.35 g, 70% over 2 steps). TLC R_f 0.27 (45% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.94 (s, 1H), 7.68-7.70 (m, 2H), 7.48-7.52 (m, 1H), 7.26-7.42 (m, 7H), 4.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.4, 137.4, 132.7, 131.8, 129.1, 128.6, 128.5, 127.6, 126.8, 55.9; IR (film): 3283, 3028, 1645, 1314 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{14}H_{14}N_2O$ $[M]^+$: 226.1106. Found: 226.1101.

5.17 Preparation of the 2nd Generation of Aminodienes (Chapter 3)



***O-t*-Butyldiphenylsilylpropane-1,3-diol (Scheme 3.48, 3.50).** Based on a procedure by Cossy and coworkers.[237] To a suspension of NaH (1.05 g, 26.3 mmol) in THF (38 mL) at

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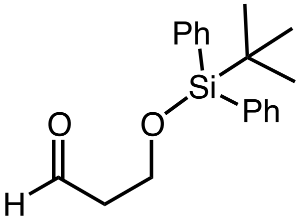
[237] Ferrié, L.; Boulard, L.; Pradaux, F.; Bouzbouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864.

0°C was added 1,3-propanediol (2.00 g, 26.3 mmol). The reaction mixture was stirred for 5 min at 0°C at which time *tert*-butylchlorodiphenylsilane (6.73 mL, 26.3 mmol) was added. The reaction was warmed to room temperature and stirred for 8 h. Water was added and the reaction was extracted three times with ethyl acetate. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude oil was purified by silica column chromatography with an eluent of 20% EtOAc in hexanes and resulted in a colorless oil (6.20 g, 75%). TLC R_f 0.64 (50% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.66-7.70 (m, 4H), 7.37-7.45 (m, 6H), 3.82-3.88 (m, 4H), 2.35 (t, *J*= 5.5 Hz, 1H), 1.81 (q, *J*= 5.7 Hz, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 135.5, 133.2, 129.8, 127.8, 63.3, 62.0, 34.2, 26.8, 19.1; The spectral data corresponds to that reported in literature.[238]



***O-t*-Butyldiphenylsilyl-3-hydroxypropanal (Scheme 3.48, 3.51).** Synthesized according to the general procedure 5.4 using the corresponding alcohol (1.50 g, 4.77 mmol). The resulting crude oil was purified by silica column chromatography with an eluent of 10% EtOAc in hexanes and resulted in a colorless oil (761 mg, 51%). TLC R_f 0.55 (20% EtOAc/Hexanes);

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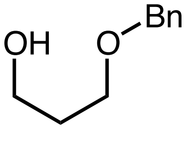
[238] Xu, Y-C.; Roughton, A. L.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993***, 71*, 1169.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.82 (t, *J*= 2.2 Hz, 1H), 7.64-7.67 (m, 4H), 7.37-7.44 (m, 6H), 4.02 (t, *J*= 6.0 Hz, 2H), 2.61 (td, *J*= 6.0, 2.2 Hz, 2H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 201.9, 135.5, 133.2, 129.8, 127.8, 58.3, 46.4, 26.7, 19.1; The spectral data corresponds to that reported in literature.[237]



3-(Benzyloxy)propan-1-ol (Scheme 3.49, 3.53). Based on a procedure by Wu and coworkers.[239] To a suspension of NaH (5.89 g, 147 mmol) in THF/DMF (10:7, 100 mL) at 0°C was added dropwise a solution of 1,3-propanediol (10.0 g, 131 mmol) in THF (30 mL). The reaction was warmed to room temperature and stirred for 3 h. Benzyl bromide (15.6 mL, 131 mmol) was added dropwise (exothermic!) and the reaction was stirred at room temperature for 48 h. Water was added and the reaction mixture was extracted three times with diethyl ether. The organic phases were combined, washed three times with a solution of 50:50 water/brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 20% EtOAc in hexanes and resulted in a light yellow oil (10.57 g, 69%). TLC R_f 0.10 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18-7.29 (m, 5H), 4.44 (s, 2H), 3.68 (t, *J*= 5.6 Hz, 2H), 3.57 (t, *J*= 5.8 Hz, 2H), 2.83 (br, 1H), 1.78 (ap q, *J*= 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm

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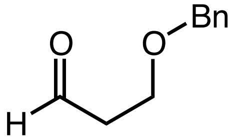
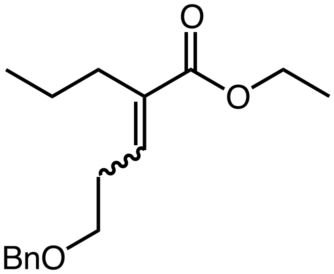
[239] Li, L-S.; Yikang, W.; Hu, Y-J.; Xia, L-J.; Wu, Y-L. *Tetrahedron: Asymmetry* **1998**, *9*, 2271.

138.0, 128.3, 127.6, 127.5, 73.1, 69.0, 61.4, 32.0; IR (film): 3390, 2937, 2861, 1451, 1083, 732 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{10}H_{14}O_2$ $[M]^+$: 166.0994. Found: 166.1000.

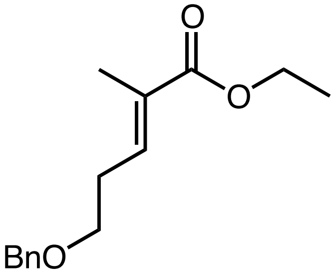


3-(Benzyloxy)propanal (Scheme 3.49, 3.54). Synthesized according to the general procedure 5.4 using the corresponding alcohol (4.00 g, 34.4 mmol). The resulting crude oil was used for the next reaction without further purification. TLC R_f 0.79 (100% EtOAc).



Ethyl 5-(benzyloxy)-2-propylpent-2-enoate (Scheme 3.49, 3.55). Based on a procedure by by Boger and coworkers.[231] The phosphorane (crude, 8.6 mmol) was added dropwise to a suspension of NaH (0.545 g, 13.6 mmol) in THF (83 mL) at 0°C. The mixture was stirred for 10 min at which time a solution of 3-(benzyloxy)propanal (2.15 g, 8.11 mmol) in THF (21 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 3 h.

Water was added and the phases were separated. The aqueous phase was extracted three times with diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 8% EtOAc in hexanes and resulted in a colorless oil (1.0 g, 45% over 2 steps). TLC R_f 0.43 (10% EtOAc/hexanes). Could not be obtained pure. Used directly without further purification.



(*E*)-Ethyl 5-(benzyloxy)-2-methylpent-2-enoate (Scheme 3.50, 3.58). Based on the procedures by the Jennings and Tapadar groups.[240] To a solution of the ylid (5.73 g, 15.8 mmol), in dichloromethane (17 mL) at 0°C was added dropwise a solution of the aldehyde (1.50 g, 13.2 mmol) in dichloromethane (9 mL). The reaction was warmed to room temperature and stirred for one hour at which time water was added and the phases were separated. The aqueous layer was extracted twice with diethyl ether. The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 10%

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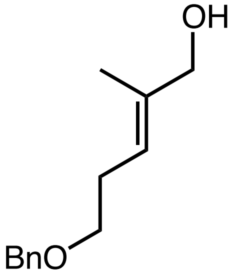
[240] a) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett*. **2007**, *48*, 5177. b) Chakraborty, T. K.; Tapadar, S. *Tetrahedron Lett*. **2003**, *44*, 2541.

EtOAc in hexanes and resulted in a colorless oil (1.37 g, 42%). TLC R_f 0.76 (50% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37-7.28 (m, 5H), 6.79 (tq, *J*=7.2, 1.5 Hz, 1H), 4.53 (s, 2H), 4.19 (q, *J*=7.1 Hz, 2H), 3.57 (t, *J*=6.8 Hz, 2H), 2.49 (dt, *J*=7.1, 6.7 Hz, 2H), 1.83 (d, *J*=1.3 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.1, 137.9, 128.8, 127.8 (2C), 127.0 (3C), 72.3, 68.1, 59.8, 28.9, 13.7, 12.0; IR (film): 2987, 2860, 1700, 1276, 1096 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{15}H_{20}O_3$ $[M]^+$: 248.1412. Found: 248.1342.



(*E*)-5-(Benzyloxy)-2-methylpent-2-en-1-ol (Scheme 3.50, 3.59). Based on a procedure by Inoue and coworkers.[241] To a suspension of lithium aluminum hydride (0.033 g, 0.88 mmol) in diethyl ether (0.40 mL) at 0°C was added dropwise a solution of aluminum trichloride (0.046 g, 0.34 mmol) in dichloromethane (0.57 mL). Stirred at 0°C for 1 hour after which a solution of the ester (0.063 g, 0.20 mmol) in dichloromethane (287 mL) was added dropwise. The reaction was stirred at 0°C for 1.5 hours. The reaction was diluted in diethyl ether and washed with 10% HCl. The aqueous layer was extracted with diethyl ether. The organic

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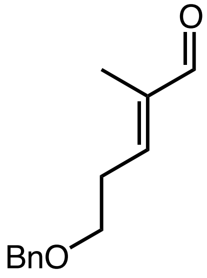
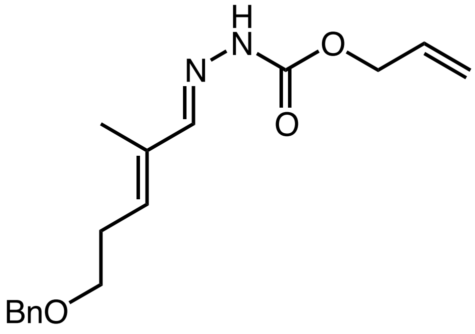
[241] Honda, K.; Tabuchi, M; Kurokawa, H.; Asami, M.; Inoue, S. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1387.

phases were combined, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 40% EtOAc in hexanes and resulted in a colorless oil (28 mg, 68%). TLC R_f 0.23 (30% EtOAc/Hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.28-7.35 (m, 5H), 5.45 (ap tdd, *J*= 7.0, 2.5, 1.2 Hz, 1H), 4.52 (s, 2H), 4.00 (d, *J*= 5.0 Hz, 2H), 3.50 (t, *J*= 6.9 Hz, 2H), 2.37 (ap qd, *J*= 6.9, 0.8 Hz, 2H), 1.68 (s, 3H), 1.35 (t, *J*= 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.1, 136.6, 128.1, 127.4, 121.3, 72.6, 69.5, 68.0, 28.0, 13.5; IR (film): 3397, 2914, 2858, 1095, 1010 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{18}O_2[M]^+$: 206.1307. Found: 206.1281.



(*E*)-5-(benzyloxy)-2-methylpent-2-enal (Scheme 3.50, 3.60). Synthesized according to the general procedure 5.4 using the corresponding alcohol (0.122 g, 0.591 mmol). The resulting crude oil was used directly for the next reaction without further purification. TLC R_f 0.73 (30% EtOAc/Hexanes).



(5-(Benzyloxy)-2-methylpent-2-enylidene)-carbamic acid allyl ester (Scheme 3.51, 3.62). Based on a procedure by Westheimer and coworkers,[242] allylcarbazate (0.039 mL, 0.33 mmol) was added to a solution of the aldehyde (0.060 g, 0.29 mmol) in benzene-d_6 (0.12 mL) with molecular sieves 4Å (0.12 g). After 3 h, the reaction was filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 30% EtOAc in hexanes + 1% Et_3N and resulted in a colorless oil (50 mg, 56%). TLC R_f 0.30 (30% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.00 (s, 1H), 7.44 (s, 1H), 7.28-7.36 (m, 5H), 5.96 (m, 1H), 5.79 (t, J= 7.1 Hz, 1H), 5.28 (d, J= 17.1 Hz, 1H), 5.24 (d, J= 10.4 Hz, 1H), 4.62 (ap s, 2H), 4.52 (s, 2H), 3.54 (t, J= 6.6 Hz, 2H), 2.53 (q, J= 6.7 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.2, 135.6, 134.6, 132.2, 128.7, 127.6, 118.3, 69.0, 66.2, 29.0, 11.6; IR (film): 3238, 3066, 2865, 1721, 1546, 1246 cm^{-1}; LRMS m/z (relative intensity): 41.0394 (52.3%), 91.0550 (100.0%), 111.0912 (16.9%), 196.1199 (26.7%).

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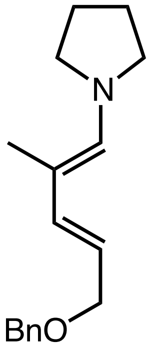
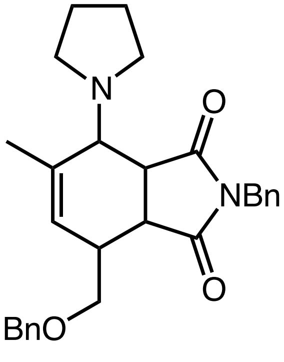
[242] Westheimer, F. H.; Taguchi, K. *J. Org. Chem.* **1971**, *36*, 1570.



(1*E*,3*E*)-5-(Benzyloxy)-2-methylpenta-1,3-dien-1-pyrrolidine (Scheme 3.52, 3.61b). Based on a procedure by the Fañanás group.[243] To a solution of pyrrolidine (0.025 mL, 0.31 mmol) in THF (0.25 mL) at 0°C was added *n*-Buli in hexanes (0.062 mL, 0.31 mmol) dropwise, followed by (*E*)-5-(benzyloxy)-2-methylpent-2-enal (0.050 g, 0.25 mmol) and chlorotrimethylsilane (0.047 mL, 0.37 mmol). The reaction was warmed to room temperature and stirred for 16 h. The crude mixture was concentrated *in vacuo* and used directly without further purification. TLC R_f 0.75 (35% EtOAc/Hexanes).



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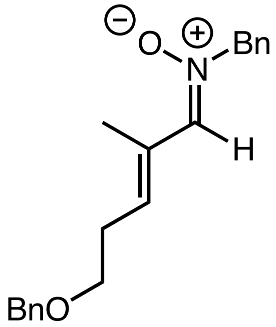
[243] Aznar, F.; Fañanás-Mastral, M.; Alonso, J.; Fañanás, F. J. *Chem. Eur. J.* **2008**, *14*, 325.

Diels-Alder adduct (Scheme 3.52, 3.65). To a solution of the aminodiene (crude, 0.25 mmol) in benzene-d_6 (1.2 mL) at room temperature was added *N*-benzylmaleimide (0.060 g, 0.32 mmol). Stirred for 48 h. Directly purified by silica column chromatography with an eluent of 15% EtOAc in hexanes and resulted in a colorless oil (15 mg, 14%). TLC R_f 0.14 (30% EtOAc/Hexanes). Could not be obtained pure.

5.17.1 Procedures for the Synthesis of the Hydroxylaminodiene



(*E*)-5-(Benzyloxy)-2-methylpent-2-enaldehyde nitrone (Scheme 3.53, 3.67). Based on a modified procedure by the Beauchemin group.[244] Benzylhydroxylamine (0.015 g, 0.12 mmol) was added to a solution of the aldehyde (0.050 g, 0.25 mmol) in *tert*-butanol (0.25 mL). Stirred for 16 h. The reaction was concentrated to produce the crude oil, which was purified by silica column chromatography with an eluent of 1.5% MeOH in dichloromethane and resulted in a yellow oil (27 mg, 71%).

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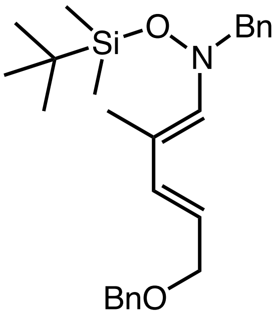
[244] Pfeiffer, J. Y.; Beauchemin, A. M. *J. Org. Chem.* **2009**, *74,* 8381.

Alternate synthesis based on a modified procedure by the Merino group.[245] To a solution of the aldehyde (0.500 g, 2.45 mmol) in dichloromethane (17 mL) at room temperature were added anhydrous $ZnCl_2$ (0.334 g, 2.45 mmol), benzylhydroxylamine (0.301 g, 2.45 mmol) and $MgSO_4$ (0.295 g, 2.45 mmol) in order. The reaction was stirred at room temperature for 12 h. The mixture was then diluted in dichloromethane, washed with 10% HCl and a saturated solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 2% MeOH in dichloromethane and resulted in a yellow oil (574 mg, 76%). TLC R_f 0.45 (5% MeOH/dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.28-7.44 (m, 10H), 7.19 (t, J= 6.8 Hz, 1H), 6.80 (s, 1H), 4.88 (s, 2H), 4.51 (s, 2H), 3.54 (t, J= 7.0 Hz, 2H), 2.50 (ap q, J= 7.0 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.2, 136.3, 134.4, 133.3, 129.0, 128.7, 128.7, 128.2, 127.5, 127.4, 72.9, 70.7, 68.9, 53.3, 29.3, 15.7; IR (film): 3423, 3062, 2858, 1454, 1099 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{20}H_{23}NO_2[M]^+$: 309.1729. Found: 309.1705.



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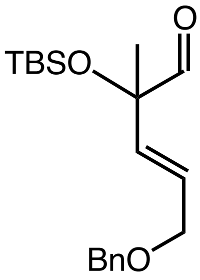
[245] Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1995**, *25*, 2275.

(1*E*,3*E*)-*N*-Benzyl-5-(benzyloxy)-*N*-*tert*-butyldimethylsilyloxy-2-methylpenta-1,3-dien-1-amine (Scheme 3.53, 3.68b). Based on a procedure by the Evans group.[246] To a solution of the nitrone (0.276 g, 0.892 mmol) in dichloromethane (1.8 mL) at 0°C was added triethylamine (0.373 mL, 2.68 mmol). Stirred for 10 min at which time freshly distilled *tert*-butylchlorodimethylsilane (0.201 mL, 1.34 mmol) was added over 20 min. The reaction was sealed, then warmed to room temperature and stirred for an additional 20 h. Pentane was added and the organic phase was washed with pH 7 phosphate buffer and 0.5M $CuSO_4$ aqueous solution. The organic phase was then dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was used directly without further purification.



(*E*)-5-(Benzyloxy)-2-*tert*-butyldimethylsilyloxy-2-methylpent-3-enal (Scheme 3.54, 3.75). Obtained as the major degradation product upon heating of the hydroxylaminodiene. Colorless oil (3 mg, 8%). ^{1}H NMR (400 MHz, C_6D_6) δ ppm 9.37 (s, 1H), 7.34-7.32 (m, 3H), 7.25- 7.14 (m, 2H), 5.99 (dt, *J*= 15.6, 5.1 Hz, 1H), 5.69 (dt, *J*= 15.6, 1.7 Hz, 1H), 4.36 (s, 2H), 3.82 (dd, *J*= 5.5, 1.6 Hz, 2H), 1.33 (s, 3H), 1.02 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C

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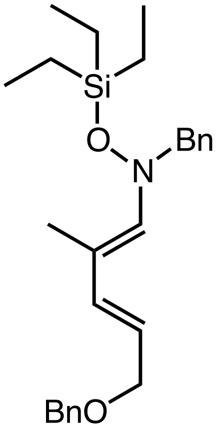
[246] Evans, D. A.; Kværnø, L.; Dunn, T. B.; Beauchemin, A. M.; Raymer, B.; Mulder, J. A.; Olhava, E. J.; Juhl, M.; Kagechika, K.; Favor, D. A. *J. Am. Chem. Soc.* **2008**, *130,* 16295.

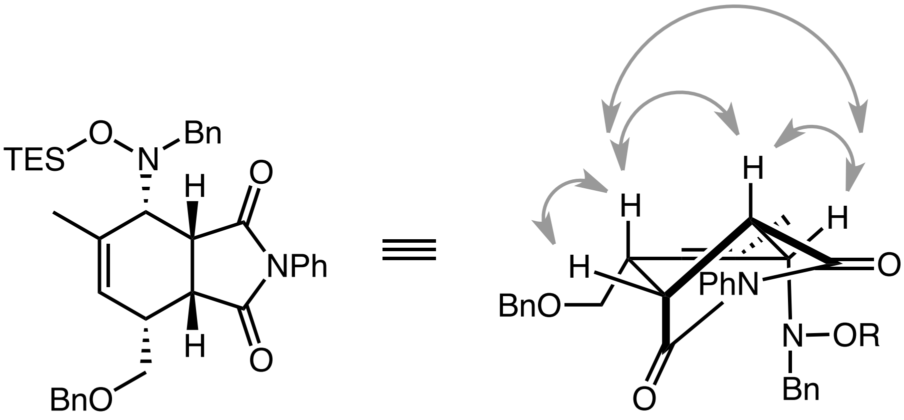
NMR (75 MHz, C_6D_6) δ ppm 199.7, 132.2, 130.2, 81.2, 72.9, 70.1, 26.4 (3C), 23.4, 18.8, 1.8, 2.0 (4 signals under the C_6D_6 peak); IR (film): 2930, 2854, 1736, 1254, 1113 cm^{-1}; LRMS m/z (relative intensity): 73.0467 (14.2%), 77.0385 (12.3%), 91.0545 (100.0%), 161.9919 (7.7%).



(1*E*,3*E*)-*N*-Benzyl-5-(benzyloxy)-*N*-(triethylsilylhydroxy)-2-methylpenta-1,3-dien-1-amine (Scheme 3.53, 3.68a). Based on a procedure by the Evans group.[246] To a solution of (*E*)-5-(Benzyloxy)-2-methylpent-2-enaldehyde nitrone (0.600 g, 1.94 mmol) in dichloromethane (4 mL) at 0°C, was added triethylamine (0.324 mL, 2.33 mmol). Stirred for 5 minutes after which freshly distilled triethylsilyl trifluoromethanesulfonate (0.439 mL, 1.94 mmol) was added dropwise. Warmed to room temperature and stirred for 20 hours. The reaction mixture was then diluted in pentane, washed with phosphate buffer pH 7 and a saturated copper sulfate solution. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography (10% EtOAc in Hexanes) and resulted in a yellow oil (290 mg, 35%). TLC R_f 0.85 (20%

EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.35-7.24 (m, 10H), 6.20 (d, *J*= 15.6 Hz, 1H), 5.94 (s, 1H), 5.69 (dt, *J*= 6.2, 15.4 Hz, 1H), 4.52 (s, 2H), 4.07 (dd, *J*= 1.0, 6.3 Hz, 2H), 3.91 (s, 2H), 1.62 (d, *J*= 1.1 Hz, 3H), 0.86 (t, *J*= 7.9 Hz, 9H), 0.49 (q, *J*= 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 142.9, 138.2, 136.0, 134.2, 130,7, 128.3, 127.8 (2C), 127.8 (2C), 127.5 (2C), 127.4 (2C), 125.5, 124.2, 72.2, 70.9, 65.3, 11.8, 6.72 (3C), 4.02 (3C); IR (film): 2876, 1630, 1496, 1454, 1109 cm^{-1}; LRMS m/z (relative intensity): 91.0561 (100%), 163.0942 (17.9%), 193.1006 (86.5%), 194.1031 (18.3%), 319.1970 (20.0%).

5.17.2 Procedure for the Diels-Alder Reaction of the Hydroxylaminodiene



Diels-Alder adduct (endo adduct) [247] **(Equation 3.7, 3.70a).** A solution of the aminodiene (0.290 g, 0.685 mmol) and *N*-phenylmaleimide (0.154 g, 0.890 mmol) in benzene-d_6 (2.3 mL) was stirred at room temperature for two weeks. Concentrated *in vacuo*, then purified by silica column chromatography with a eluent of 20% EtOAc in hexanes which resulted in a yellow oil (244 mg, 60%). TLC R_f 0.62 (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$)

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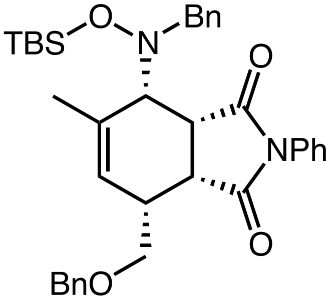
[247] The regioisomer was differentiated by NOE measurements and was consistent with the expected reactivity.

δ ppm 7.38-7.31 (m, 6H), 7.20-7.16 (m, 4H), 7.14-7.06 (m, 4H), 7.02-6.95 (m, 1H), 5.52 (s, 1H), 4.45 (d, *J*=16.1 Hz, 1H), 4.40 (d, *J*=16.1 Hz, 1H), 4.15 (d, *J*=13.8 Hz, 1H), 3.97 (dd, *J*=6.4, 9.1 Hz, 1H), 3.85 (br, 1H), 3.70 (dd, *J*=7.6, 9.0 Hz, 1H), 3.58 (br, 1H), 3.40 (dd, *J*=4.7, 8.5 Hz, 1H), 2.67 (t, *J*=8.3 Hz, 1H), 2.46 (br, 1H), 1.94 (s, 3H), 0.97 (t, *J*=7.9 Hz, 9H), 0.76-0.49 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 175.9, 139.1, 138.2, 132.0, 130.2, 129.0, 128.4, 128.0, 127.9, 127.7, 127.5, 126.5, 73.4, 70.1, 67.4, 43.5, 42.8, 38.6, 36.9, 19.9, 7.1 (3C), 4.7 (3C); IR (film): 2952, 2874, 1713, 1379 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{36}H_{44}N_2O_4Si[M]^+$: 596.3070. Found: 596.30559.



Diels-Alder adduct (endo adduct)[248] (Equation 3.7, 3.70b). A solution of the aminodiene (crude, 0.16 mmol) and *N*-phenylmaleimide (0.039 g, 0.21 mmol) in benzene-d$_6$ (0.54 mL) was stirred at room temperature for two weeks. >95% ^{1}H NMR yield measured by integration of the added internal standard 0.5 equiv. of 1,4-dimethoxybenzene. Not isolated.

5.18 Preparation of the 3rd Generation of Aminodienes (Chapter 3)

5.18.1 General Procedure for the Synthesis of Hydrazones

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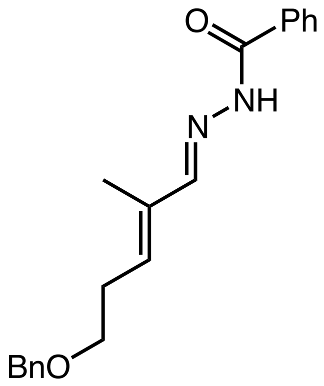
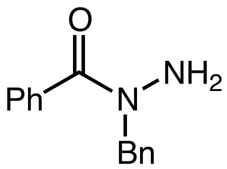
[248] The regioisomer was differentiated by comparison with Diels-Alder adduct 3.70a.

The aldehyde (5.52 mmol) and a carbazate (5.52 mmol) were dissolved in methanol (28 mL) at room temperature. Solid sodium sulfate (7 mmol) was added after 30 minutes. The reaction was stirred for 16 h, filtered over cotton, rinsed with dichloromethane and concentrated. The resulting crude oil was purified by silica column chromatography.



(2*E*)-*N*'-((*E*)-5-(Benzyloxy)-2-methylpent-2-enylidene)benzohydrazide (Scheme 3.57, 3.79). Synthesized according to the general procedure 5.18.1 using the corresponding aldehyde (0.20 g, 0.98 mmol) and hydrazide (0.13 mg, 0.98 mmol). The resulting crude oil was purified by silica column chromatography with an eluent of 30% EtOAc in hexanes and resulted in a yellow oil which degraded upon futher purification attempts (179 mg, 57%). TLC R_f 0.43 (50% EtOAc/Hexanes).



Isopropylidene benzocarbazate (Scheme 3.57, 3.82). Based on a procedure by Meyer.[249] To a solution of benzoic hydrazide (4.00 g, 29.4 mmol) in acetone (29 mL) was added acetic acid (0.2 mL) and $MgSO_4$ (0.77 g). The reaction mixture was refluxed for 2h then cooled to room temperature. The $MgSO_4$ was filtered off and rinsed with acetone. The solution was concentrated *in vacuo.* The hydrazone (crude, 11.3 mmol) was redissolved in toluene (38 mL) and powdered KOH (0.830 g, 14.8 mmol) and Bu_4NHSO_4 (0.384 g, 1.13 mmol) were added. The reaction was warmed to 50°C at which time BnBr (1.62 mL, 13.6 mmol) was added. Warmed to 80°C and stirred for 4 h. The reaction was cooled to room temperature and washed with water until the aqueous extract had a neutral pH (five times). The benzylated hydrazone solidified in solution and was filtered and dried *in vacuo*. It was then redissolved in THF (23 mL) and a 2N HCl solution (5.65 mL, 11.3 mmol) was added. The reaction was stirred at reflux for 3 h, then cooled to room temperature and concentrated. The oil was suspended in EtOH 99% where it crashed and was filtered off. The solid crude hydrazide was used directly without further purification.

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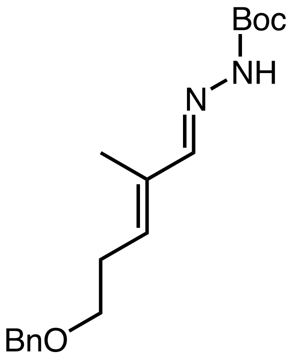
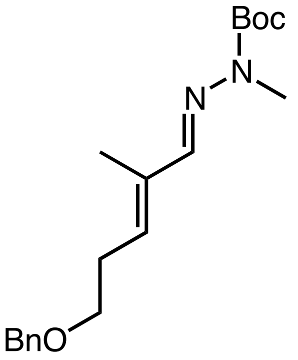
[249] Meyer, K. G. *Synlett* **2004**, 2355.



***N*-*t*-Butylcarbamate-(1*E*)-1-((*E*)-5-(benzyloxy)-2-methylpent-2-enylidene)hydrazine (Scheme 3.58, 3.88).** Synthesized according to the general procedure 5.18.1 using the corresponding aldehyde (0.630 g, 5.52 mmol) and hydrazide (0.729 g, 5.52 mmol). The resulting crude oil was purified by silica column chromatography with an eluent of 15% EtOAc in hexanes and resulted in a yellow oil (720 mg, 41%). TLC R_f 0.75 (50% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.42 (s, 1H), 7.45 (s, 1H), 7.33 (s, 5H), 5.72 (t, *J*=6.6 Hz, 1H), 4.52 (s, 2H), 3.54 (t, *J*= 6.6 Hz, 2H), 2.53 (dt, *J*= 6.5, 6.7 Hz, 2H), 1.89 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 152.6, 148.5, 137.9, 134.7, 134.2, 128.1 (2C), 127.4, 127.3 (2C), 80.4, 72.6, 68.8, 28.7, 28.0 (3C), 11.2; IR (film): 3255, 2858, 2243, 1747, 1539 cm^{-1}; LRMS m/z (relative intensity): 57.0756 (32.4%), 69.0063 (100%), 91.0554 (43.3%), 156.0894 (33.1%).



***N-t*-Butylcarbamate-*N*-methyl-(1*E*)-1-((*E*)-5-(benzyloxy)-2-methylpent-2-enylidene)hydrazine (Scheme 3.58, 3.89).** Based on a procedure by Moody and coworkers.[250] A mixture of the hydrazone (0.30 g, 0.94 mmol), iodomethane (0.073 mL, 1.2 mmol) and potassium carbonate (0.30 g, 1:1 by weight) in acetone (8.6 mL) was refluxed for 16 h. The reaction was cooled to room temperature, filtered and concentrated *in vacuo*. The resulting crude oil was purified by silica column chromatography with an eluent of 15% EtOAc in hexanes and resulted in a yellow oil (118 mg, 38%). TLC R_f 0.40 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.38 (s, 5H), 7.23 (s, 1H), 5.79 (t, J= 7.1 Hz, 1H), 4.53 (s, 2H), 3.54 (t, J= 6.7 Hz, 2H), 3.23 (s, 3H), 2.55 (dt, J= 6.6, 6.7 Hz, 2H), 1.93 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 153.4, 144.4, 138.2, 135.6, 133.9, 128.3 (2C), 127.6 (2C), 127.5, 81.3, 72.9, 69.2, 30.6, 29.0, 28.2 (3C), 11.5; IR (film): 2977, 2859, 1701, 1146 cm^{-1}; LRMS m/z (relative intensity): 41.0385 (28.6%), 57.0543 (100%), 91.0545 (71.1%), 97.0770 (22.2%), 111.0918 (18.0%), 126.1164 (16.1%), 170.1056 (11.5%).

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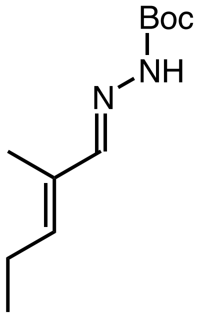
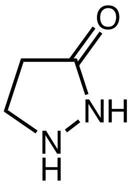
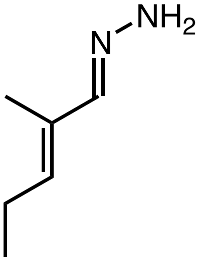
[250] Lawton, G.; Moody, C. J.; Pearson, C. J.; Williams, D. J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 885.



***N-t*-Butylcarbamate-(1*E*)-1-((*E*)-2-methylpent-2-enylidene)hydrazine (Equation 3.12, 3.94).** Synthesized according to the general procedure 5.18.1 using the corresponding aldehyde (1.00 g, 10.2 mmol) and hydrazide (2.02 g, 15.3 mmol). The resulting crude oil was purified by silica column chromatography with an eluent of 100% dichloromethane and resulted in a colorless oil (1.94 g, 90%). TLC R_f 0.32 (15% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.98 (s, 1H), 7.41 (s, 1H), 5.64 (t, *J*= 7.2 Hz, 1H), 2.17 (ap q, *J*= 7.4 Hz, 2H), 1.83 (s, 3H), 1.46 (s, 9H), 0.97 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 152.7, 149.1, 140.6, 132.7, 80.8, 28.2 (3C), 21.5, 13.4, 11.1; IR (film): 3231, 2970, 1699, 1541, 1167 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{20}N_2O_2[M]^+$: 212.1525. Found: 212.15360.



Pyrazolidin-3-one (Equation 13, 3.99). Following a procedure by White.[251] To a solution of hydrazine hydrate (55% in water, 7.90 mL, 139 mmol) in EtOH (75 mL) was added dropwise with an addition funnel a solution of ethyl acrylate (13.5 mL, 125 mmol) in EtOH (50 mL). The reaction was stirred at room temperature for 1 h, then refluxed for 4 h. The reaction was then cooled to room teperature and concentrated *in vacuo*. The resulting crude oil was purified by silica column chromatography with an eluent of 10% MeOH in chloroform and resulted in a yellow oil (6.61 g, 61%). TLC R_f 0.20 (15% MeOH/$CHCl_3$); Spectral data in agreement with that reported in the literature.[251]



1-((*E*)-2-Methylpent-2-enylidene)hydrazine (Scheme 3.62, 3.101). Based on a procedure by Kollár and coworkers.[252] A solution of the aldehyde (1.00 g, 10.2 mmol), hydrazine hydrate (55% in water, 2.94 mL, 52.0 mmol) and triethylamine (14.2 mL, 102 mmol) in EtOH (20 mL) was refluxed for 16h. It was then concentrated *in vacuo* and redissolved in

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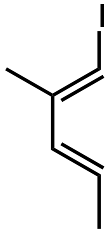
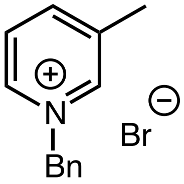
[251] Perri, S. T.; Slater, S. C.; Toske, S. G.; White, J. D. *J. Org. Chem.* **1990**, *55*, 6037.
[252] Takács, A.; Ács, P.; Farkas, R.; Kokotos, G.; Kollár, L. *Tetrahedron* **2008**, *64*, 9874.

chloroform. The organic phase was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was used directly without further purification.

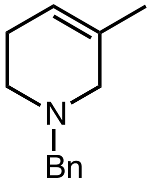


(*E,E*)-1-iodo-2-Methylpenta-1,3-diene (Scheme 3.62, 3.102). Based on a procedure by Kollár and coworkers.[252] To a solution of iodine (5.36 g, 21.1 mmol) in diethyl ether (34 mL) at 0°C was added 1,1,3,3-tetramethyl guanidine (11.5 mL, 91.7 mmol) dropwise. The reaction was warmed to room temperature, at which time the hydrazone (crude, 10.2 mmol) was added over three hours. The reaction was stirred for 1 h at room temperature, then concentrated *in vacuo*. The residue was heated at 90°C for 2 h, then cooled back to room temperature. Water was added and the mixture was extracted with ditethyl ether. The organic phases were combined and washed in order with 1N HCl, water, sat. $NaHCO_3$, water, sat. $Na_2S_2O_3$ and water. They were then dried over Na_2SO_4, filtered and concentrated. Column chromatography on silica gel was attempted with 100% pentane, but the tittle compound could not be obtained pure. Used directly without further purification.

5.19 Preparation of the 4th Generation of Aminodienes (Chapter 3)



***N*-Benzyl-3-methylpyridinium bromide (Scheme 3.64, 3.104).** Based on a procedure by Fukuyama and coworkers.[253] 3-Picoline (15.0 mL, 154 mmol) was cooled to 0°C at which time benzyl bromide (18.0 mL, 154 mmol) was added dropwise. Warmed to room temperature and stirred for 16 h. Transferred to a mortar and grounded. Washed four times with diethyl ether, then dried under vacuum. Gave 34.2 g (84%) of the crude salt as a yellow solid. Directly used without further purification.



***N*-Benzyl-1,2,3,6-tetrahydro-5-methylpyridine (Scheme 3.64, 3.105a).** Based on a procedure by Fukuyama and coworkers.[253] To a suspension of $NaBH_4$ (5.75 g, 152 mmol) in ethanol (108 mL) at 0°C was added a solution of *N*-benzyl-3-methylpyridinium bromide (10 g, 38 mmol) in ethanol (64 mL) dropwise. The reaction was warmed to room temperature

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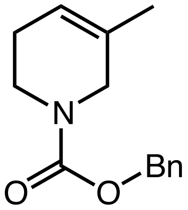
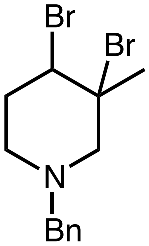
[253] Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973.

and stirred for 16 h. The ethanol was removed *in vacuo* and the residue was redissolved in dichloromethane. Washed with water. The aqueous phase was then extracted three times with dichloromethane. The organic phases were combined and washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 10% EtOAc in hexanes and resulted in a yellow oil (5.66 g, 79% over 2 steps). TLC R_f 0.39 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.42-7.19 (m, 5H), 5.45 (ddq, *J*= 3.1, 1.4, 1.6 Hz, 2H), 3.61 (s, 2H), 2.86 (s, 2H), 2.52 (t, *J*= 5.8, 2H), 2.20-2.06 (m, 2H), 1.62 (d, *J*= 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 138.3, 132.2, 129.1, 128.1, 126.9, 119.4, 62.8, 56.9, 49.4, 25.9, 20.9; IR (film): 3423, 2911, 1454, 1057 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{17}N[M]^{+\cdot}$: 187.1361. Found: 187.13289.

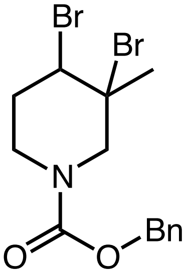


1,2,3,6-Tetrahydro-5-methylpyridine-*N*-benzylcarbamate (Scheme 3.64, 3.105b). Based on a procedure by Fukuyama and coworkers,[253] benzylchloroformate (5.35 mL, 38.0 mmol) was added to a solution of 1-benzyl-1,2,3,6-tetrahydro-5-methylpyridine (3.56 g, 19.0 mmol) in benzene (95 mL). The reaction was heated at 95°C for 6 h, then returned to room temperature and stirred for 16h. The solvent was removed *in vacuo* and the residue was purified by silica column chromatography with an eluent of 10% EtOAc in hexanes and resulted in a colorless oil (3.45 g, 79%). TLC R_f 0.31 (10% EtOAc/Hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.43-7.28 (m, 5H), 5.52 (ap s, 1H), 5.15 (s, 2H), 3.82 (s, 2H), 3.51 (t, *J*= 5.7 Hz, 2H), 2.10 (br, 2H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm as a mixture of isomers 154.8, 154.7, 136.4, 130.9, 130.3, 127.9, 127.4, 127.3, 127.3, 119.4, 119.0, 66.4, 46.6, 46.4, 40.0, 39.6, 24.5, 24.2, 20.0; IR (film): 2915, 1704, 1451, 1238, 1109 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{14}H_{17}NO_2[M]^+$: 231.1259. Found: 231.12400.

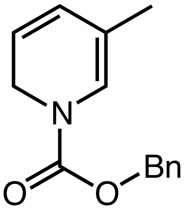


1-Benzyl-3,4-dibromo-3-methylpiperidine (Scheme 3.64, 3.106a). Based on a procedure by Fukuyama and coworkers.[253] Bromine (0.600 mL, 10.7 mmol) was added to a solution of 1-benzyl-1,2,3,6-tetrahydro-5-methylpyridine (2.00 g, 10.7 mmol) in dichloromethane (40 mL) until the red color persisted. The solution was then decolorized by addition of a saturated aqueous solution of $Na_2S_2O_3$. Brine was added and the aqueous phase was extracted with dichloromethane. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 2% EtOAc in hexanes and resulted in a colorless oil (0.28 g, 8%). TLC R_f 0.56 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.40- 7.26 (m, 5H), 4.48 (ap s, 1H), 3.58 (s, 2H), 3.07- 2.88 (m, 1H), 2.87- 2.76 (m, 1H), 2.71 (d, *J*=

12.1 Hz, 1H), 2.61- 2.28 (m, 2H), 2.23- 2.09 (m, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 137.8, 128.6, 128.2, 127.2, 66.0, 61.7, 60.7, 34.0, 31.5, 22.6, 14.1; IR (film): 2946, 2806, 1494, 1453, 730 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{17}NBr_2[M]^+$: 344.9728. Found: 344.96943.



3,4-Dibromo-3-methylpiperidine-*N*-benzylcarbamate (Scheme 3.64, 3.106b). Based on a procedure by Fukuyama and coworkers.[253] Bromine (0.220 mL, 4.32 mmol) was added to a solution of 1,2,3,6-tetrahydro-5-methylpyridine-*N*-benzylcarbamate (1.00 g, 4.32 mmol) in dichloromethane (16 mL) until the red color persisted. The solution was then decolorized by addition of a saturated aqueous solution of $Na_2S_2O_3$. Brine was added and the aqueous phase was exracted with dichloromethane. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The desired product was used directly without further purification. The resulting crude oil was purified by silica column chromatography with an eluent of 5% EtOAc in hexanes. TLC R_f 0.32 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42- 7.27 (m, 5H), 5.16 (s, 2H), 4.58 (t, *J*= 4.0 Hz), 4.23-3.96 (m, 1H), 3.95-3.80 (m, 1H), 3.68-3.57 (m, 1H), 3.55-3.42 (m, 1H), 2.74-2.59 (m, 1H), 1.96 (ap s, 1H), 1.89 (ap d, *J*= 14.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm as a mixture of isomers 154.8, 136.2, 128.3, 127.9, 127.8, 127.7, 127.5, 67.2, 64.4, 58.5, 52.2, 52.0, 39.6, 39.5, 31.9, 31.6, 29.1; IR (film): 3390, 2932, 1716, 1471, 1230 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{14}H_{17}NO_2Br_2[M]^+$: 388.9626. Found: 388.96913.



1,2-Dihydro-5-methylpyridine-*N*-benzylcarbamate (Table 3.10, 3.107b). Based on a procedure by Fukuyama and coworkers.[253] 3,4-Dibromo-3-methylpiperidine-*N*-benzylcarbamate (0.500 g, 1.28 mmol) and freshly purified (recrystalization by sublimation) DABCO (0.503 g, 4.48 mmol) were dissolved in dry acetonitrile (9.8 mL) and heated at reflux for 6 h. The reaction was cooled to room temperature, decanted and the white solid was washed with dichlotomethane. The filtrate was washed with H_2O, which was then extracted twice with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. Used directly without further purification.

Can also be synthesized following a procedure by Raucher.[254] To a solution of 3,4-dibromo-3-methylpiperidine-*N*-benzylcarbamate (0.050 g, 0.13 mmol) in HMPA (0.37 mL) at 0°C was added ethylaluminum dichloride (solution in hexanes, 0.40 mL, 0.40 mmol) dropwise. The reaction was warmed to room temperature, then heated at 60°C for 1.5 h. The reaction

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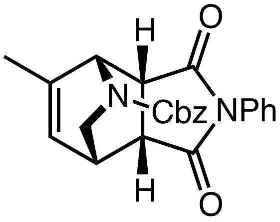
[254] Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442.

was then cooled to 0°C and water was added dropwise. Extracted three times with diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. Used directly without further purification.



Diels-Alder adduct[255] (Equation 3.14, 3.108). Based on a procedure by Fukuyama and coworkers.[253] The diene (crude, 0.26 mmol) and *N*-phenylmaleimide (0.044 g, 0.26 mmol) were heated neat at 90°C in a sealed tube purged with argon for 21 h. Diluted in dichloromethane, then loaded directly on a silica column and eluted with 5% EtOAc in hexanes. Gave 60 mg of a colorless oil (59%). TLC R_f 0.38 (3% EtOAc/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm as a mixture of isomers 7.47-7.37 (m, 8H), 7.14-7.12 (ap d, *J*=7.4 Hz, 2H), 5.99 (s, 1H), 5.23-5.09 (m, 3H), 3.47 (ddd, *J*=18.9, 4.2, 7.8 Hz, 1H), 3.43-3.33 (m, 2H), 3.13-3.09 (m, 2H), 1.91 (s, 1.5H), 1.85 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm as a mixture of isomers 176.8, 176.7, 174.7, 174.5, 155.1, 154.7, 141.9, 141.2, 136.3, 131.6, 129.2, 128.8, 128.5, 128.2, 128.1, 128.0, 126.3, 124.1, 123.8, 67.3, 67.2, 51.1, 50.6, 46.5, 46.2, 45.0, 41.6, 33.7, 33.5, 20.3, 20.1; IR (film): 3481, 3066, 2968, 1713, 1699, 1385 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{25}H_{24}N_2O_4$ $[M]^+$: 402.1580. Found: 402.1577.

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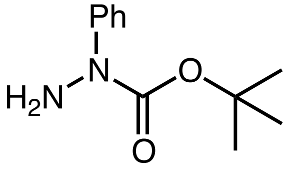
[255] The regioisomer was not differentiated by NOE measurements. It is drawn with the expected endo reactivity.

5.20 Preparation of the 5th Generation of Aminodienes (Chapter 3)



***N*-Phenyl-*N*-*t*-butylcarbazate (Scheme 3.65, 3.111).** Based on a procedure by the Buchwald group.[256] To a flamed dry Schlenk tube was added CuI (0.0038 g, 0.020 mmol), 1,10-phenanthroline (0.040 g, 0.20 mmol) and Cs_2CO_3 (0.922 g, 2.83 mmol). To the mixture was added dropwise a solution of *tert*-butyl carbazate (0.320 g, 2.42 mmol) in DMF (1 mL), followed by iodobenzene (0.226 mL, 2.02 mmol) and extra DMF (1 mL). The tube was then flushed with argon, sealed and heated to 80°C for 21 h, then cooled to room temperature. The reaction mixture was filtered over a silica pad with 100% EtOAc and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 20% EtOAC in hexanes and resulted in a yellow oil (220 mg, 52%). TLC R_f 0.36 (25% EtOAc/hexanes); Spectral data in agreement with that reported in the literature.[256]

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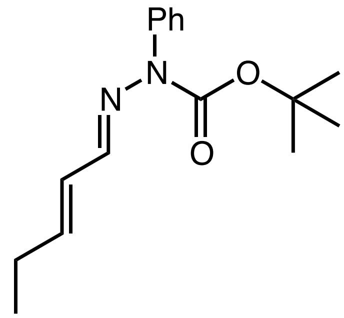
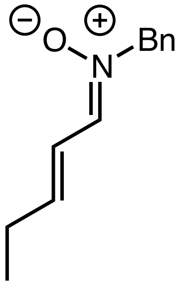
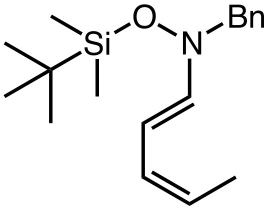
[256] Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.



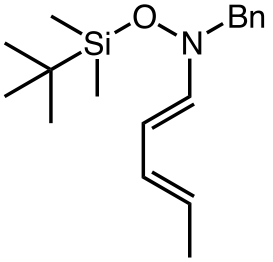
***N-t*-Butylcarbamate-(1*E*)-1-((*E*)-pent-2-enylidene)-2-phenylhydrazine (Scheme 3.65, 3.112).** Synthesized according to the general procedure 5.18.1 using the corresponding aldehyde (0.089 g, 1.1 mmol) and hydrazide (0.220 g, 1.06 mmol). The resulting crude oil was purified by silica column chromatography with an eluent of 10% EtOAc in hexanes and resulted in a colorless oil (238 mg, 82%). TLC R_f 0.62 (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.39-7.33 (m, 2H), 7.30-7.25 (m, 1H), 7.03-7.01 (m, 2H), 6.81 (d, *J*= 9.1 Hz, 1H), 6.25 (ddt, *J*= 15.6, 9.1, 1.6 Hz, 1H), 5.75 (dt, *J*=15.6, 6.4 Hz, 1H), 2.02 (dq, *J*= 6.2, 7.5 Hz, 2H), 1.34 (s, 9H), 0.88 (t, *J*= 7.4Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 152.4, 145.1, 143.2, 137.0, 129.4 (2C), 129.0 (2C), 128.3, 126.6, 81.3, 27.8 (3C), 25.3, 12.5; IR (film): 2974, 1734, 1393, 1160 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{16}H_{22}N_2O_2[M]^+$: 274.1681. Found: 274.16661.



(*E*)-Pent-2-enaldehyde benzonitrone (Scheme 3.66, 3.115). Based on a modified procedure by Merino.[245] To a solution of (*E*)-2-pentenal (0.700 g, 8.32 mmol) in dichloromethane (60 mL) was added consecutively anhydrous zinc dichloride (1.13 g, 8.32 mmol), *N*-benzylhydroxylamine (1.02 g, 8.32 mmol) and $MgSO_4$ (1.00 g, 8.32 mmol). After stirring for 16 h at room temperature, the reaction was diluted in dichloromethane and washed with aqueous solutions of 10% HCl and saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 0.5% MeOH in CH_2Cl_2 and resulted in a yellow oil (228 mg, 14%). TLC R_f 0.41 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43-7.37 (m, 5H), 6.99 (d, *J*= 9.5Hz, 1H), 6.76 (ddt, *J*= 15.9, 9.4, 1.7Hz, 1H), 6.25 (dt, *J*= 15.8, 6.6Hz, 1H), 4.89 (s, 2H), 2.22 (dq, *J*= 6.5, 7.5 Hz, 2H), 1.04 (t, *J*= 7.4 Hz, 3H);[257] ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 144.8, 136.4, 132.9, 128.6 (2C), 128.5 (2C), 128.4, 119.8, 68.5, 26.1, 12.4; IR (film): 3500, 2960, 2220, 1455, 1124 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{12}H_{15}NO[M]^+$: 189.1154. Found: 189.11483.



A



B

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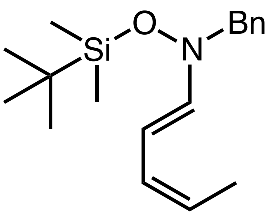
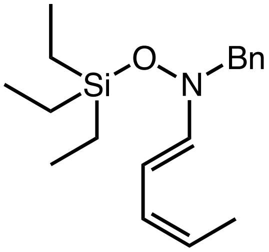
[257] The traces of dichloromethane present in the spectrum were left due to the instability of the product formed.

(1*E*)-*N*-Benzyl-*N*-(*t*-butyldimethylsilylhydroxy)penta-1,3-dien-1-amine (Scheme 3.66, 3.116a). Based on a procedure by the Evans group.[246] To a solution of the nitrone (0.240 g, 1.27 mmol) in dichloromethane (2.5 mL) at 0°C, was added triethylamine (0.212 mL, 1.52 mmol). Stirred for 5 minutes, after which freshly distilled *tert*-butyldimethylylsilyl trifluoromethanesulfonate (0.292 mL, 1.27 mmol) was added dropwise. Warmed to room temperature and stirred for 20 h. The reaction mixture was then diluted in pentane, washed with phosphate buffer pH 7 and a saturated copper sulfate solution. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with an eluent of 20% EtOAc in hexanes and resulted in a yellow oil (171 mg, 44%). TLC R_f 0.84 (20% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm as a mixture of isomers (A:B = 1: 0.57), isomer A: 7.33-7.28 (m, 5H), 6.13 (d, *J*=12.6 Hz, 1H), 5.92 (dd, *J*=12.2, 12.1 Hz, 1H), 5.92-5.84 (m, 1H), 5.20 (dq, *J*=10.2, 7.0 Hz, 1H), 4.09 (s, 2H), 1.67 (dd, *J*=7.0, 1.6 Hz, 3H), 0.97 (s, 9H), 0.05 (s, 6H), isomer B: 7.33-7.28 (m, 5H), 6.03 (d, *J*=13.2 Hz, 1H), 5.92-5.84 (m, 1H), 5.64 (dd, J=13.2, 10.8 Hz, 1H), 5.42 (dq, *J*=13.4, 6.7 Hz, 1H), 4.06 (s, 2H), 1.70 (dd, *J*=6.7, 1.5 Hz, 3H), 0.95 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm as a mixture of isomers: 140.6, 139.1, 135.9, 135.8, 129.8, 129.7, 129.3, 128.2, 128.2, 127.7, 127.6, 127.3, 123.3, 120.4, 110.2, 105.5, 63.2, 63.1, 26.0, 26.0, 25.6, 17.9, 13.0, -5.3; IR (film): 2929, 2857, 1649, 1256 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{18}H_{29}NOSi[M]^+$: 303.2018. Found: 303.20317.



A

(1*E*,3*Z*)-*N*-Benzyl-*N*-(*t*-butyldimethylsilylhydroxy)penta-1,3-dien-1-amine (Equation 3.17, 3.116a). Isolated as the non-reactive hydroxylaminodiene isomer under the Diels-Alder reaction conditions. TLC R_f 0.80 (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.36-7.29 (m, 5H), 6.14 (d, *J*=12.5 Hz, 1H), 5.92 (dd, *J*=11.4, 11.9 Hz, 1H), 5.92-5.83 (m, 1H), 5.19 (dq, *J*=7.0, 9.5 Hz, 1H), 4.10 (s, 2H), 1.68 (d, *J*= 7.1 Hz, 3H), 0.99 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 140.7, 135.9, 129.8 (2C), 128.3 (2C), 127.7, 127.3, 120.5, 105.5, 63.2, 26.0 (3C), 18.0, 13.0, -5.3 (2C); IR (film): 2929, 2857, 1649, 1256 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{18}H_{29}NOSi[M]^+$: 303.2018. Found: 303.20423.



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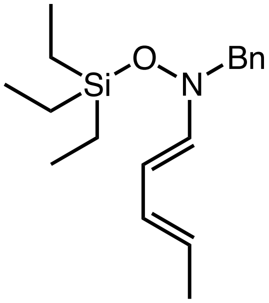
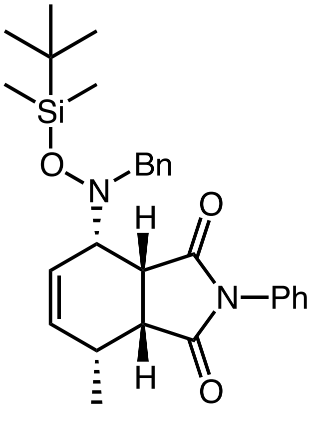


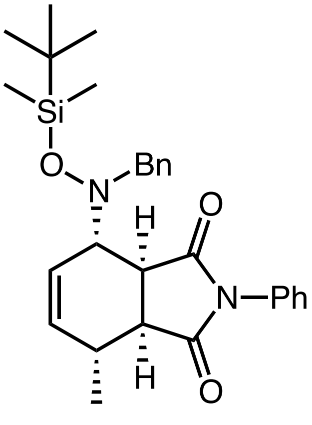
B

(1*E*)-*N*-Benzyl-*N*-(triethylsilylhydroxy)penta-1,3-dien-1-amine (Scheme 3.66, 3.116b). Based on a procedure by the Evans group.[246] To a solution of the nitrone (0.228 mg, 1.20 mmol) in dichloromethane (2.4 mL) at 0°C, was added triethylamine (0.201 mL, 1.44 mmol). Stirred for 5 minutes after which freshly distilled triethylsilyl trifluoromethanesulfonate (0.271 mL, 1.20 mmol) was added dropwise. Warmed to room temperature and stirred for 20 h. The reaction mixture was then diluted in pentane, washed with phosphate buffer pH 7 and a saturated copper sulfate solution. The organic phase was dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified by silica column chromatography with 20% EtOAc in hexanes and resulted in a yellow oil (85 mg, 23%). TLC R_f 0.89 (20% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm as a mixture of isomers (A:B = 1:0.43), isomer A: 7.35-7.27 (m, 5H), 6.13 (d, *J*=12.8 Hz, 1H), 5.90 (dd, *J*=11.4, 12.5 Hz, 1H), 5.89-5.83 (m, 1H), 5.19 (dq, *J*=10.4, 7.0 Hz, 1H), 4.11 (s, 2H), 1.67 (dd, *J*=6.9, 1.6 Hz, 3H), 0.99 (t, *J*=8.0 Hz, 6H), 0.93 (t, *J*=8.0 Hz, 3H), 0.68(q, *J*= 8.0 Hz, 4H), 0.51(q, *J*= 8.0 Hz, 2H), isomer B: 7.35-7.27 (m, 5H), 6.03 (d, *J*=13.2 Hz, 1H), 5.89-5.83 (m, 1H), 5.67 (dd, *J*=13.0, 10.9 Hz, 1H), 5.43 (dq, *J*=13.4, 6.6 Hz, 1H), 4.06 (s, 2H), 1.68 (dd, *J*=6.7, 1.5 Hz, 3H), 0.98 (t, *J*=8.0 Hz, 6H), 0.93 (t, *J*=8.0 Hz, 3H), 0.65(q, *J*= 8.0 Hz, 4H), 0.52(q, *J*= 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm as a mixture of isomers: 140.7, 139.0, 135.9, 135.8, 129.5, 129.3, 128.3, 128.2, 127.7, 127.6, 127.3, 123.4, 120.4, 110.0, 105.1, 63.4, 63.3, 18.1, 13.1, 6.9, 6.8, 6.4, 4.1, 4.0; IR (film): 2955, 2976, 1649, 1238, 741 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{18}H_{29}NOSi[M]^+$: 303.2018. Found: 303.20051.

5.20.1 Procedure for the Diels-Alder Reaction with a Less-Hindered Hydroxylaminodiene



A



B

Diels-Alder adducts (Equation 3.17, 3.117a).[258] A solution of the aminodiene (0.17 g, 0.56 mmol) and *N*-phenylmaleimide (0.13 g, 0.73 mmol) in benzene-d$_6$ (1.9 mL) was stirred at room temperature for 48 h. Concentrated and purified by silica column chromatography with an eluent of 12% EtOAc in hexanes and resulted in a yellow oil (140 mg, 52%, corrected for *E*-isomer only: 78%). TLC R_f 0.60 (30% EtOAc/Hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm as a mixture of diastereoisomers (endo/exo, 0.85:1 dr): **Isomer A (endo adduct):** 7.54-7.24 (m, 10H), 6.18 (d, *J*=9.2 Hz, 1H), 5.75 (ddd, *J*=3.0, 2.7, 9.5 Hz, 1H), 3.95 (br, 1H), 3.72 (br, 1H), 3.55 (br, 2H), 3.10 (dd, *J*=6.5, 7.3 Hz, 1H), 2.37-2.34 (br, 1H), 1.47 (d, *J*=7.4 Hz, 3H), 0.93 (9H), 0.16 (6H); **Isomer B (exo adduct):** 7.54-7.24 (m, 10H), 6.14 (ddd, *J*=1.9, 4.8, 10.3 Hz, 1H), 6.06 (dd, *J*=2.9, 10.2 Hz, 1H), 4.40 (br, 2H), 4.37 (br, 1H), 4.20 (br, 1H), 3.51 (dd, *J*=8.6, 8.5 Hz, 1H), 2.98 (ap dd, *J*=4.7, 10.1 Hz, 0.5H), 2.92 (br, 0.5 H), 1.30 (d, *J*=6.7 Hz, 3H), 0.85 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ ppm as a mixture of isomers: 178.2, 175.9, 175.1, 137.0, 132.8, 132.0, 130.5, 130.2, 128.9, 128.8, 128.3, 128.2, 128.2, 128.1, 127.8, 127.4, 127.3, 126.5, 126.2, 61.7, 59.2, 46.6, 45.6, 43.2, 41.5,

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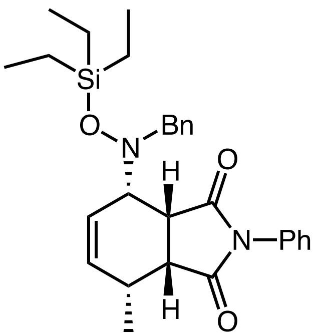
[258] The regioisomers were differentiated by comparison with Diels-Alder adducts 3.117b.

30.5, 28.6, 26.1, 26.0, 18.0, 17.8, 16.7, -4.3, -4.5, -4.8; IR (film): 3480, 2956, 2856, 1713, 1496, 1383, 1177 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{28}H_{36}N_2O_3Si[M]^+$: 476.2495. Found: 476.24805.



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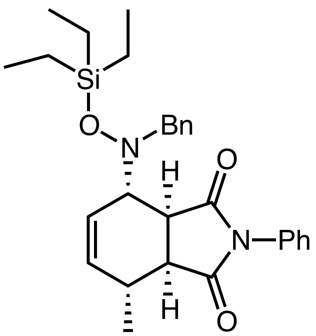

B

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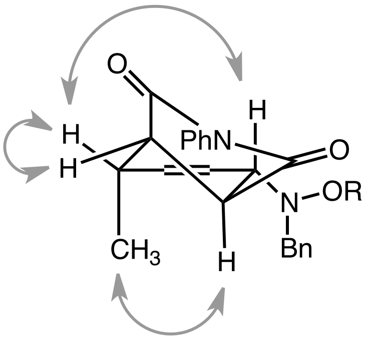

B

Diels-Alder adducts (Equation 3.17, 3.117b).[247] A solution of the aminodiene (0.085 g, 0.28 mmol) and *N*-phenylmaleimide (0.063 g, 0.36 mmol) in benzene-d_6 (0.9 mL) was stirred at room temperature for 48 h. Concentrated and purified twice by silica column chromatography with an eluent of 12% EtOAc in hexanes and resulted in a yellow oil (33 mg, 25%, corrected for *E*-isomer only: 43%). TLC R_f 0.63 (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm as a mixture of diastereoisomers (endo/exo, 0.83:1 dr): **Isomer A (endo adduct):** 7.56-7.19 (m, 10H), 6.16 (ddd, *J*=2.7, 2.7, 9.2 Hz, 1H), 5.77 (ddd, *J*=3.1, 3.1, 9.5 Hz, 1H), 4.46 (d, *J*=14.5 Hz, 1H), 4.27 (d, *J*=14.3 Hz, 1H), 3.56 (ap dd, *J*=7.0, 8.0 Hz, 1H), 3.53-3.48 (m, 1H), 3.12 (dd, *J*=6.0, 8.3 Hz, 1H), 2.47-2.29 (m, 1H), 1.48 (d, *J*=7.4 Hz, 3H), 0.93 (t, *J*=8.0 Hz, 9H), 0.57 (q, *J*=7.9 Hz, 6H); **Isomer B (exo adduct):** 7.56-7.19 (m, 10H), 5.98 (ap s, 2H), 4.21 (br, 1H), 4.08 (ap s, 1H), 4.03 (dd, *J*=3.0, 8.1 Hz, 1H), 3.86 (br, 1H), 3.45 (dd, *J*=8.0, 9.6 Hz, 1H), 2.99-2.90 (m, 1H), 1.25 (d, *J*=7.1 Hz, 3H), 0.87 (t, *J*=7.9 Hz, 9H), 0.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm as a mixture of isomers: 178.2, 176.0, 137.3, 136.7, 133.2, 132.1, 130.2, 130.0, 129.9, 129.0, 128.9, 128.4, 128.3, 128.2, 127.5, 127.4, 126.5, 126.5, 126.3, 63.5, 62.0, 61.1, 47.3, 45.9, 43.3, 41.8, 30.6, 28.6, 21.4, 16.8, 7.1, 7.0, 4.8, 4.6; IR (film): 3476, 2956, 2876, 1717, 1380, 1179 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{28}H_{36}N_2O_3Si[M]^+$: 476.2495. Found: 476.24855.

5.21 General Procedure for the Formation of the Substituted Alkynylalcohols (Chapter 4)

Based on a procedure by Liu and coworkers.[259] To a solution of hex-5-yn-1-ol (13.7 mmol) in Et_3N (40 mL) was added the iodoalkyl or iodoaryl (16.5 mmol), CuI (0.27 mmol) and $PdCl_2(PPh_3)_2$ (0.14 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction solution was washed with $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica column chromatography.

5.22 General Procedure for the Formation of the Hydrohydrazidation Substrates (Chapter 4)

Synthesized according to the general procedure 5.4 using the corresponding alcohol (7.72 mmol). The resulting crude aldehyde (3.95 mmol) was then dissolved in *t*-BuOH (20 mL)

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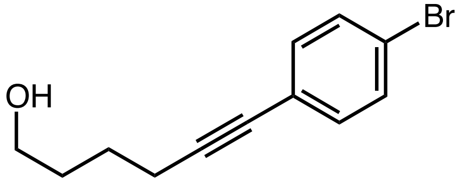
[259] Lin, G-Y.; Yang, C-Y.; Liu, R-S. *J. Org. Chem.* **2007**, *72*, 6753.

and bis-trifluoromethylbenzoyl hydrazide (2.63 mmol) was added. The reaction mixture was warmed to 35°C and stirred for 16 h at which point it was reduced according to general procedure 5.5. The resulting crude oil was purified by silica column chromatography.



6-(4-Bromophenyl)hex-5-yn-1-ol (Scheme 4.1, 4.4i). Synthesized according to the general procedure 5.21 using hex-5-yn-1-ol (1.51 g, 13.7 mmol) and 1-bromo-4-iodobenzene (4.66 g, 16.5 mmol). The crude product was purified by silica column chromatography with an eluent of 30% Et_2O in pentane. The title compound was obtained as a brown oil (3.1 g, 89% yield). TLC R_f 0.24 (60% Et_2O/pentane). ^1H NMR (300 MHz, $CDCl_3$) 7.41 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 3.71 (t, *J*= 6.2 Hz, 2H), 2.44 (t, *J* = 6.7 Hz, 2H), 1.64-1.84 (m, 4H), 1.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 132.9 (2C), 131.4 (2C), 122.8, 121.6, 91,1, 79.9, 62.4, 31.9, 24.9, 19.2; IR (film) 3370, 2941, 1486, 1072, 824 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{12}H_{13}BrO$ $[M]^+$ = 252.0150. Found: 252.01651.[260]

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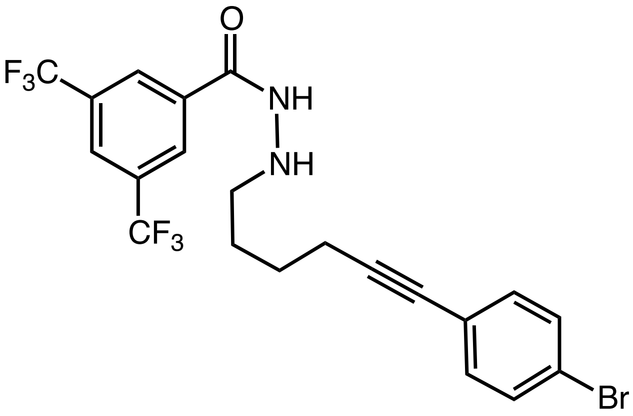
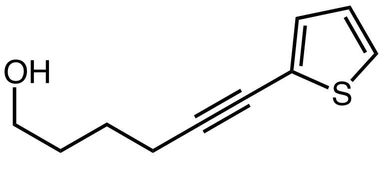
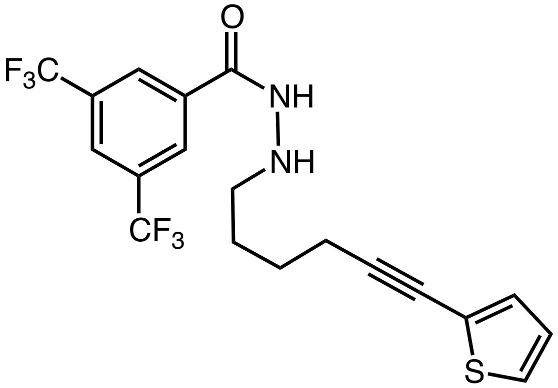
[260] ^1H and ^{13}C NMR spectra from Ms. Taing: Taing, S. Intramolecular Cope-Type Hydroamination of Alkynes Using Hydrazides. Internship Report, University of Ottawa, ON, 2010.



***N'*-(6-(4-Bromophenyl)hex-5-ynyl)-3,5-bis(trifluoromethyl)benzohydrazide (Scheme 4.1, Table 4.2, 4.1i).** Synthesized according to the general procedure 5.22 using 6-(4-bromophenyl)hex-5-yn-1-ol (2.00 g, 7.90 mmol). The crude oil was purified by silica column chromatography on silica gel with an eluent of 20% Et_2O in pentane. The title compound was obtained as a beige solid (0.84 g, 42% yield). TLC R_f = 0.22 (30% Et_2O/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, 134.8, 132.9 (2C), 132.4 (q, *J*= 33.9 Hz, 2C, $\underline{C}$-CF_3), 131.4 (2C), 127.3 (2C), 125.4, 121.8 (q, *J*= 131.0 Hz, 2C, $\underline{C}F_3$), 121.7, 90.8, 80.1, 51.7, 27.0, 25.9, 19.2; IR (film) 3308, 2941, 1654, 1279, 1137 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{21}H_{17}BrF_6N_2O$ $[M]^+$ = 506.0428. Found: 506.03320.[260]



6-(Thiophen-2-yl)hex-5-yn-1-ol (Scheme 4.1, 4.4l). Synthesized according to the general procedure 5.21 using hex-5-yn-1-ol (2.00 mL, 18.4 mmol) and 2-iodothiophene (2.22 mL, 21.8 mmol). The crude product was purified by silica column chromatography with an eluent of 25% EtOAc in hexanes. The title compound was obtained as a red oil (3.0 g, 90% yield). TLC R_f 0.54 (50% EtOAc/hexanes). The spectral data was in agreement with that previously reported in the literature.[261]



3,5-Bis(trifluoromethyl)-*N'*-(6-(thiophen-2-yl)hex-5-ynyl)benzohydrazide (Scheme 4.1, Table 4.2, 4.1l). Synthesized according to the general procedure 5.22 using 6-(thiophen-2-yl)hex-5-yn-1-ol (1.0 g, 5.6 mmol). The crude product was purified by silica column chromatography with an eluent of 0.5% MeOH in CH_2Cl_2. The title compound was obtained as a white solid (1.14 g, 47% yield). TLC R_f = 0.32 (2% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.20 (s, 2H), 8.02 (s, 1H), 7.77 (s, 1H), 7.16 (dd, *J*= 1.1, 5.2 Hz, 1H),

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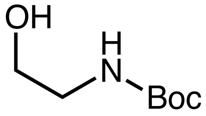
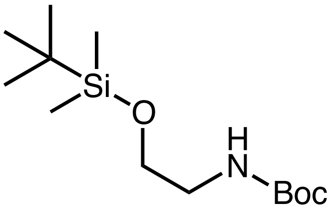
[261] Pereira, R.; Iglesias, B.; de Lera A. R. *Tetrahedron* **2001**, *57*, 7871.

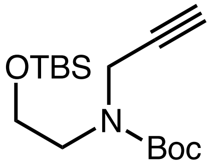
7.10 (dd, *J*= 1.0, 3.6 Hz, 1H), 6.92 (dd, *J*= 3.6, 5.2 Hz, 1H), 4.89 (s, 1H), 3.03 (t, *J*= 5.8 Hz, 2H), 2.53-2.46 (m, 2H), 1.77-1.68 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 164.5, 134.7, 132.1 (q, *J*= 34.0 Hz, 2C, $\underline{C}$-CF$_3$), 130.9, 127.3 (2C), 126.7, 125.9, 125.2, 123.7, 122.8 (q, *J*= 273.1 Hz, 2C, $\underline{C}$F$_3$), 93.6, 74.1, 51.5, 27.0, 25.8, 19.4; IR (film) 3219, 2938, 1653, 1380, 1128, 906 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{19}H_{16}SF_6N_2O$ [M]$^+$ = 434.0888. Found 434.08915.



***tert*-Butyl 2-(hydroxy)ethylcarbamate (Scheme 4.2, 4.9).** According to a modified protocol by Mattingly and coworkers,[228] a solution of di-tert-butyldicarbonate (23.9 g, 110 mmol) in dichloromethane (40 mL) was added dropwise to a solution of 2-amino-1-ethanol (6.00 g, 99.7 mmol) in dichloromethane (25 mL). After one hour, the reaction was concentrated *in vacuo*. Used directly without further purification.



***tert*-Butyl 2-(tert-butyldimethylsilyloxy)ethyl(*N*-prop-2-ynyl)carbamate (Scheme 4.2, 4.10).** Done according to a procedure by the Beauchemin group.[262] To a solution of *tert*-Butyl 2-(*tert*-butyldimethylsilyloxy)ethylcarbamate (10 g, 62 mmol) in dichloromethane (124 mL) was added TBSCl (10.3 g, 68.2 mmol), imidazole (6.3 g, 93 mmol) and DMAP (1.14 g, 9.30 mmol). The reaction mixture was stirred at room temperature for 16 h at which time it was washed with water, a saturated solution of NH_4Cl and brine. The organic phase was then dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by silica column chromatography with an eluent of 15% EtOAc in hexanes and resulted in a yellow oil (15.7 g, 92% yield). The spectral data is in agreement with that previously reported in the literature.[262]



***tert*-Butyl 2-(tert-butyldimethylsilyloxy)ethyl-prop-2-ynylcarbamate (Scheme 4.2, 4.11).** Done according to a procedure by the Beauchemin group.[262] To a suspension of NaH (1.63 g, 40.8 mmol) in THF (30 mL) at 0°C was added a solution of the carbamate (7.50 g, 27.2 mmol) in THF (10 mL). The reaction was warmed to room temperature and stirred for 1 h before being cooled back to 0°C. Propargyl bromide (12 mL, 68 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 17 h. Water was

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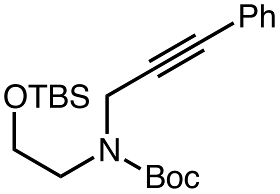
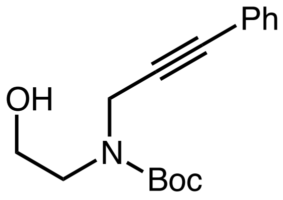
[262] Rizk, T.; Bilodeau, E.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8325.

added and the mixture was extracted three times with EtOAc. The Organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by silica column chromatography with an eluent of 5% EtOAc in hexanes and resulted in a yellow oil (4.87 g, 57% yield). The spectral data is in agreement with that previously reported in the literature.[262]



***tert*-Butyl 2-(tert-butyldimethylsilyloxy)ethyl-3-phenylprop-2-ynylcarbamate (Scheme 4.2, 4.12).** Synthesized according to the general procedure 5.21 using *tert*-Butyl 2-(tert-butyldimethylsilyloxy)ethyl(*N*-prop-2-ynyl)carbamate (3.00 g, 9.57 mmol) and iodobenzene (1.28 mL, 11.5 mmol). The crude residue was purified by silica column chromatography with an eluent of 5% EtOAc in hexanes. The title compound was obtained as a yellow oil (3.3 g, 88% yield). TLC R_f 0.24 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (* denotes conformer) 7.45-7.36 (m, 2H), 7.33-7.24 (m, 3H), *4.40 (s, 1H), *4.31 (s, 1H), 3.79 (t, *J*= 5.8 Hz, 2H), 3.48 (t, *J*= 5.9 Hz, 2H), 1.48 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) (as a mixture of conformers, * denotes minor conformer) δ ppm 154.9, 131.6, 128.1, 128.0, 123.0, *85.3, 85.2, *83.2, 82.7, 79.9, *61.8, 61.6, *48.6, 48.3, *38.9, 37.6, 28.4 (3C), 25.8 (3C), 18.1, 5.4 (2C); IR (film) 2930, 2854, 1702, 1413, 1247 cm$^-$

[1]; HRMS (EI): Exact mass calculated for $C_{22}H_{35}SiNO_3$ $[M\text{-}Boc]^+$ = 289.1862. Found: 289.1822.



***tert*-Butyl 2-hydroxyethyl-3-phenylprop-2-ynylcarbamate (Scheme 4.2, 4.13).** Based on a modified procedure by Molander.[263] To a solution of *tert*-butyl 2-(tert-butyldimethylsilyloxy)ethyl3-phenylprop-2-ynylcarbamate (2.21 g, 5.67 mmol) in dichloromethane (28 mL) at room temperature was added tetrabutylammonium fluoride (in THF, 6.81 mL, 6.81 mmol). Stirred at room temperature for 16 h at which time a saturated solution of NH_4Cl was added. The reaction mixture was extracted with ethyl acetate. The organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was used directly without further purification.

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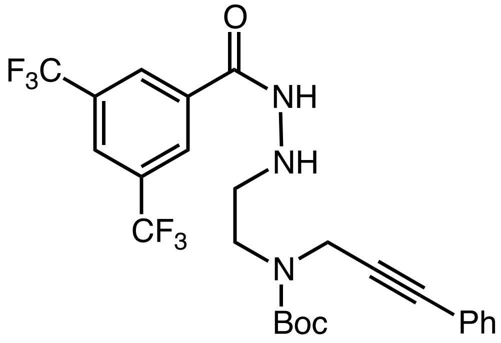
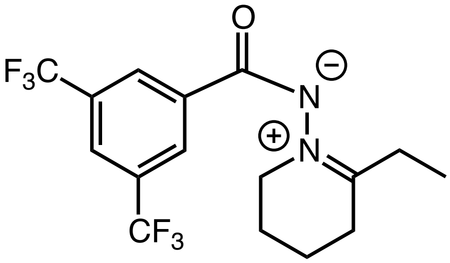
[263] Molander, G. A.; Cormier, E. P. *J. Org. Chem.* **2005**, *70,* 2622.



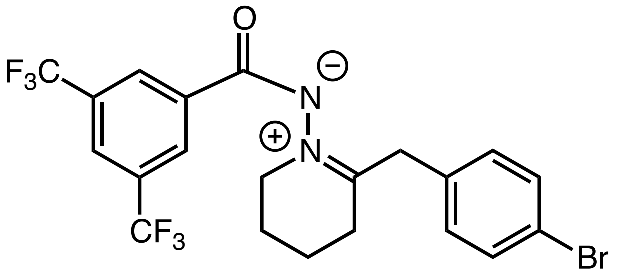
***N'*-(2-(3-Phenylprop-2-ynyl-*N*-Boc-amino)ethyl)-3,5-bis(trifluoromethyl)benzohydrazide (Scheme 4.2, Table 4.2, 4.1n).** Synthesized according to the general procedure 5.22 using *tert*-Butyl 2-hydroxyethyl3-phenylprop-2-ynylcarbamate (1.25 g, 4.54 mmol). The crude residue was purified by silica column chromatography with an eluent of 1% MeOH in CH_2Cl_2. The title compound was obtained as a white solid (1.10 g, 46% yield). TLC R_f = 0.48 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.85 (br, 1H), 8.39 (s, 2H), 8.00 (s, 1H), 7.42-7.39 (m, 2H), 7.35-7.28 (m, 3H), 4.29 (s, 2H), 3.66 (t, *J*= 5.4 Hz, 2H), 3.16 (t, *J*= 5.6 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 162.7, 156.7, 135.2, 132.0 (q, *J*= 33.7 Hz, 2C, $\underline{C}$-CF_3), 131.5 (2C), 128.4, 128.3 (2C), 127.4, 124.8, 122.9 (q, *J*= 273.1 Hz, 2C, $\underline{C}F_3$), 122.4, 84.2, 83.7, 81.6, 47.9, 43.7, 37.4, 28.2 (3C); IR (film) 3295, 3093, 2979, 1694, 1131 cm^{-1}; LRMS m/z (relative intensity): 473.1279 (35.6%), 285.0463 (34.8%), 241.0063 (64.1%), 144.0810 (51.6%), 115.0549 (100%).

5.23 General Procedure for Alkynes Hydrohydrazidation

In a microwave flask equipped with a stir bar, the hydrazide (0.397 mmol) was dissolved in trifluorotoluene (9 mL). The flask was flushed with argon, then sealed and warmed to 120°C in increments of 20°C per minute from 80°C, then heated by microwave irradiation at 120°C for 12 h. The resulting crude mixture was then concentrated and purified by silica column chromatography.



(3,5-Bis(trifluoromethyl)benzoyl(6-ethyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (Table 4.2, 4.2h). Synthesized according to the general procedure 5.23, heating for 14 hours at 160 °C using hydrazide 4.1h (0.050 g, 0.14 mmol). The crude residue was isolated by column chromatography with an eluent of 4% MeOH in CH_2Cl_2. The title compound was obtained as a yellow oil (0.030 g, 67% yield). TLC R_f 0.30 (6% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.50 (s, 2H), 7.87 (s, 1H), 3.94 (ap s, 2H), 2.73 (ap s, 2H), 2.65 (ap s, 2H), 2.04 (ap s, 2H), 1.94-1.85 (m, 2H), 1.17 (t, *J*= 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 176.1, 165.7, 139.6, 131.0 (q, *J*= 33.3 Hz, 2C, $\underline{C}$-CF_3), 128.0 (2C), 123.5 (q, *J*= 272.7 Hz, 2C, $\underline{C}F_3$), 123.1, 54.3, 29.6, 27.7, 21.8, 17.9, 9.2; IR (film) 3405, 2360, 1653, 1278, 1132 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{16}H_{16}F_6N_2O$ $[M]^+$ = 366.1167. Found 366.12117.



(3,5-Bis(trifluoromethyl)benzoyl(6-(4-bromobenzyl)-2,3,4,5-tetrahydropyridinium-1-yl)amide (Table 4.2, 4.2i). Synthesized according to the general procedure 5.23, heating for 14 hours at 140 °C using hydrazide 4.1i (0.250 g, 0.493 mmol). The crude residue was isolated by column chromatography with an eluent of 2% MeOH in CH_2Cl_2. The title compound was obtained as a light red oil (0.18 g, 73% yield). TLC R_f 0.34 (2% MeOH/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 (ap s, 2H), 3.88 (s, 2H), 2.45 (ap s, 2H), 1.98 (ap s, 2H), 1.82-1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 132.5, 132.1 (2C), 131.4 (2C), 131.0 (q, *J*= 33.2 Hz, 2C, $\underline{C}$-CF_3), 127.9, 123.5 (q, *J*= 272.7 Hz, 2C, $\underline{C}F_3$), 123.2, 121.8, 54.5, 39.6, 30.0, 21.7, 17.8 traces of chloroform present;[264] missing two quaternary carbon;[265] IR

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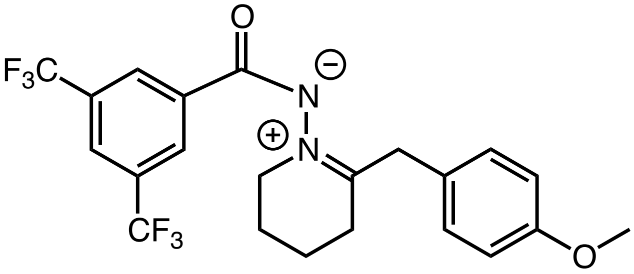
[264] The traces of chloroform present in the spectrum were left due to the instability of the product formed.

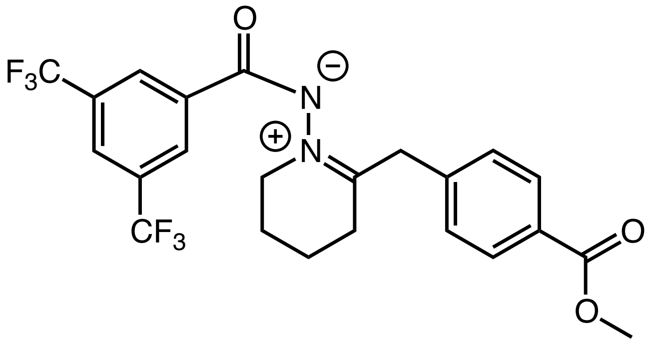
[265] Characterization complete for simpler compound such as 4.2h shows broad peaks at 176.1, 165.7 and 139.6 ppm corresponding to the molecule's quaternary carbons. The spectrum was acquired for 11h with 30 mg at room temperature with the university's most sensitive NMR equipment. Heating the sample was not possible due to degradation issues.

(film) 3378, 2943, 1728, 1568, 1276 1132 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{21}H_{17}BrF_6N_2O$ $[M]^+$: 506.0428. Found: 506.04220.[260]

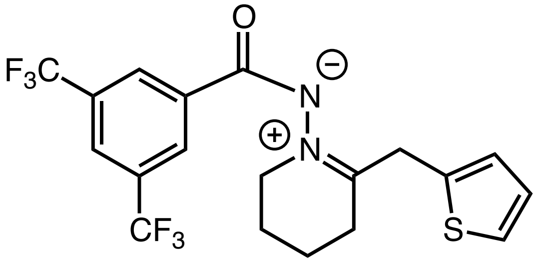


(3,5-Bis(trifluoromethyl)benzoyl(6-(4-methoxybenzyl)-2,3,4,5-tetrahydropyridinium-1-yl)amide (Table 4.2, 4.2j). Synthesized according to the general procedure 5.23, heating for 14 hours at 140 °C using hydrazide 4.1j (0.250 g, 0.545 mmol). The crude residue was isolated by column chromatography with an eluent of 1-2% MeOH in CH_2Cl_2. The title compound was obtained as a yellow oil (0.215 g, 86% yield). TLC R_f 0.11 (1% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.54 (s, 2H), 7.88 (s, 1H), 7.17 (d, *J*= 8.5 Hz, 2H), 6.86 (d, *J*= 8.6 Hz, 2H), 3.99 (ap s, 2H), 3.91 (s, 2H), 3.79 (s 3H), 2.51 (ap s, 2H), 2.04-1.99 (m, 2H), 1.85-1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.1, 139.4, 130.9 (q, *J*= 33.3 Hz, 2C, $\underline{C}$-CF_3), 130.8 (2C), 128.0 (2C), 124.8, 123.6 (q, *J*= 272.6 Hz, 2C, $\underline{C}F_3$), 123.1, 114.4 (2C), 55.1, 54.5, 39.3, 30.0, 21.7, 17.7 missing two quaternary carbons;[265] IR (film) 2956, 1569, 1514, 1316, 1279, 1132 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{22}H_{20}F_6N_2O_2$ $[M]^+ = 458.1429$. Found: 458.14221.

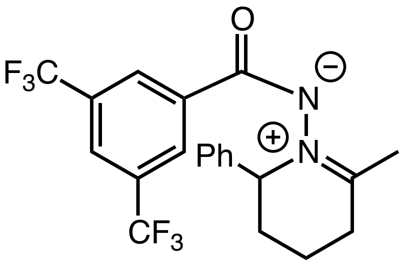
Unfortunately, compounds 4.2i, 4.2j, 4.2k, 4.2l are missing some of these broad resonances despite acquisition of the spectra under similar conditions with up to 6 times the sample quantity. However, all other data is compatible with assigned structure.



(3,5-Bis(trifluoromethyl)benzoyl(6-(4-methyl benzoate)-2,3,4,5-tetrahydropyridinium-1-yl)amide (Table 4.2, 4.2k). Synthesized according to the general procedure 5.23, heating for 14 hours at 140 °C using hydrazide 4.1k (0.25 g, 0.51 mmol). The crude residue was isolated by column chromatography with an eluent of 2% MeOH in CH_2Cl_2. The title compound was obtained as a yellow solid (0.132 g, 53% yield). TLC R_f 0.43 (5% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.50 (s, 2H), 8.01 (ap d, *J*= 8.4 Hz, 2H), 7.88 (s, 1H), 7.34 (ap d, *J*= 8.4 Hz, 2H), 4.00 (ap s, 4H), 3.90 (s, 3H), 2.47 (ap s, 2H), 2.07-1.96 (m, 2H), 1.85-1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.6, 138.7, 131.1 (q, *J*= 33.3 Hz, 2C, $\underline{C}$-CF_3), 130.3 (2C), 129.8 (2C), 129.7, 128.0 (2C), 123.4 (q, *J*= 272.7 Hz, 2C, $\underline{C}F_3$), 123.3, 54.6, 52.2, 40.2, 30.2, 21.8, 17.9 missing three quaternary carbons;[265] IR (film) 3287, 2954, 2235, 1725, 1679, 1573, 1279, 1133, 904 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{23}H_{20}F_6N_2O_3$ $[M]^+$ = 486.1378. Found: 486.13870.



(3,5-Bis(trifluoromethyl)benzoyl(6-(2-thiophene)-2,3,4,5-tetrahydropyridinium-1-yl)amide (Table 4.2, 4.2l). Synthesized according to the general procedure 5.23, heating for 14 hours at 120 °C using hydrazide 4.11 (0.500 g, 1.14 mmol). The crude residue was isolated by column chromatography with an eluent of 1.5% MeOH in CH_2Cl_2. The title compound was obtained as a yellow oil (0.263 g, 53% yield). TLC R_f 0.38 (5% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.52 (s, 2H), 7.88 (s, 1H), 7.25 (dd, *J*= 1.3, 4.8 Hz, 1H), 7.02-6.94 (m, 2H), 4.10 (s, 2H), 3.95 (ap s, 2H), 2.57 (ap s, 2H), 1.99 (ap s, 2H), 1.88-1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm (as a mixture of conformers, * denotes minor conformer) 169.6, 163.1, 134.1, 131.1 (q, *J*= 33.2 Hz, 2C, $\underline{C}$-CF_3), 128.2, 127.8 (2C), 127.2, 126.0, 123.4 (q, *J*= 272.7 Hz, 2C, $\underline{C}F_3$), 54.2, *51.3, 34.4, *32.5, 29.5, *23.2, 21.7, *20.7, 17.9 missing one quaternary carbon;[265] IR (film) 3237, 2944, 1671, 1626, 1565, 1279, 1133 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{19}H_{16}SF_6N_2O$ $[M]^+$ = 434.0888. Found: 434.09519.



(3,5-Bis(trifluoromethyl)benzoyl(2-phneyl-6-methyl-2,3,4,5-tetrahydropyridinium-1-yl)amide (Table 4.2, 4.2m). Synthesized according to the general procedure 5.23, heating for 12 hours at 120 °C using hydrazide 4.1m (0.170 g, 0.397 mmol). The crude residue was isolated by column chromatography with an eluent of 2% MeOH in CH_2Cl_2. The title compound was obtained as a yellow solid (0.156 g, 91% yield). TLC R_f 0.16 (1% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.31 (s, 2H), 7.79 (s, 1H), 7.37-7.28 (m, 3H), 7.24-7.22 (m, 2H), 5.40 (ap s, 1H), 2.89 (t, *J*= 6.4 Hz, 2H), 2.49-241 (m, 1H), 2.37 (s, 3H), 2.21-214 (m, 1H), 1.87-1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.1, 139.4, 137.8, 130.7 (q, *J*= 33.0 Hz, 2C, $\underline{C}$-CF_3), 128.6 (2C), 127.9 (2C), 127.1, 126.5 (2C), 123.3 (q, *J*= 272.7 Hz, 2C, $\underline{C}F_3$), 122.9, 67.7, 32.7, 30.0, 22.2, 18.8, 14.1 missing one quaternary carbon;[265] IR (film) 3279, 2945, 1660, 1569, 1278, 1133, 907 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{21}H_{18}F_6N_2O$ $[M]^+$ = 428.1323. Found: 428.13142.

Appendix I

The Tandem Cope-Type Hydroamination/[2,3]-Rearrangement Sequence: A Strategy to Favor the Formation of Intermolecular Hydroamination Products and Enable Difficult Cyclizations

J|A|C|S
COMMUNICATIONS

The Tandem Cope-Type Hydroamination/[2,3]-Rearrangement Sequence: A Strategy to Favor the Formation of Intermolecular Hydroamination Products and Enable Difficult Cyclizations

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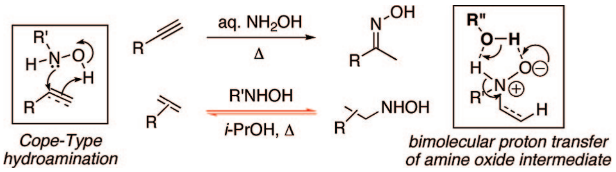
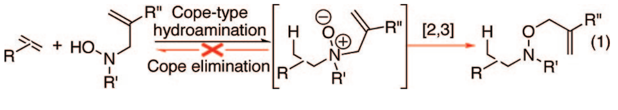
Given the prevalence and diversity of nitrogen-containing motifs in bioactive molecules, the development of efficient C−N bond-forming reactions is of paramount importance. The addition of a N−H bond across electron-rich, unsaturated C−C bonds stands out as one of the simplest and most desirable synthetic transformations for which no general solution currently exists. While significant progress has been achieved (primarily through transition metal catalysis),[1] issues such as limited reaction scope, functional group compatibility, and challenges linked to unfavorable thermodynamics for reactions of alkenes[2] continue to stimulate research directed at hydroamination reactivity. In recent efforts directed toward the development of metal-free alternatives, we reported that intermolecular reactions of hydroxylamine (aq. NH_2OH) and *N*-alkylhydroxylamines with alkenes and alkynes can be performed simply upon heating at 95−140 °C.[3] Under our conditions, alcoholic solvents mediate a facile bimolecular proton transfer of the *N*-oxide intermediate and *enable* the efficient formation of the alkene hydroamination products.

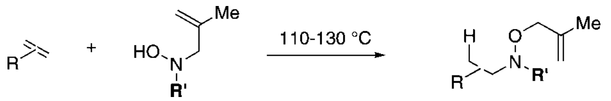


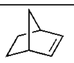
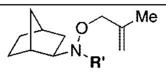
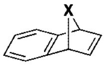
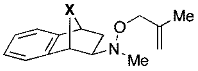
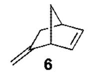
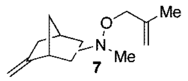
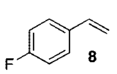
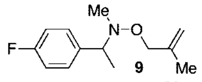
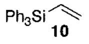
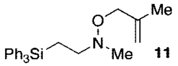
During these studies, modest yields were obtained for unstrained alkenes such as vinylarenes. Our observations are in line with Hartwig's recent report that intermolecular hydroaminations of vinylarenes are nearly thermoneutral.[2] Since substitution of both reagents can have a negative impact on ΔG^r, and since the high temperatures required for unactivated alkenes to react disfavor the reaction entropically, the current synthetic reach of intermolecular hydroaminations is limited. To address this fundamental issue, we were drawn to tandem processes in which hydroamination is followed by a second irreversible reaction, thus providing access to more stable products for the hydroamination sequence. Herein, we report on a proof of concept, a tandem Cope-type hydroamination[4]/Meisenheimer rearrangement[5] sequence (eq 1) that allows intermolecular reactions of *N*,*N*-dialkylhydroxylamines to be more energetically favorable due to the formation of a neutral product, and illustrate the potential for related cyclizations in syntheses of coniine and norreticuline featuring difficult intramolecular hydroamination key steps.



Initial efforts were directed toward performing the intermolecular sequence with norbornene and *N*-allyl-*N*-methylhydroxylamine. While encouraging but variable conversions (∼20−70%) were obtained in various solvents at high concentrations (ca. 1 M) upon heating (1−3 days) at 110−130 °C, the use of forcing conditions led to multiple decomposition products. Careful isolation and analysis of some of these products revealed that an intermolecular hydroamination side reaction with the allyl side chain present in the reagent and product was occurring.[6] Fortunately, the use of the parent *N*-methallyl reagent suppressed most side reactions and allowed efficient reactivity with various alkenes, as shown below.

Table 1. Scope of the Intermolecular Hydroamination Sequence[a]



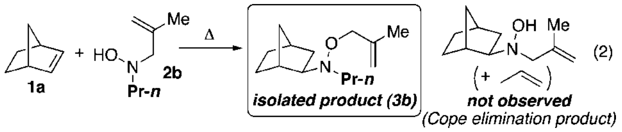
Entry	Alkene	R'C_4H_7NOH	Product	Yield[b]
				
1	**1a**	Me (**2a**)	**3a**	72%
2	**1a**	*n*-Pr (**2b**)	**3b**	48%
3[c]	**1a**	-$(CH_2)_3$OBn (**2c**)	**3c**	52%
4[c]	**1a**	Bn (**2d**)	**3d**	44%
5	**1a**	*i*-Pr (**2e**)	**3e**	21%
				
6	**X** = CH_2 (**4a**)	Me (**2a**)	**5a**	73%
7	**X** = O (**4b**)	Me (**2a**)	**5b**	81%
8	**X**=NBoc (**4c**)	Me (**2a**)	**5c**	86%
9		Me (**2a**)		65% (1:1)
10		Me (**2a**)		28%
11		Me (**2a**)		52%

[a] Conditions: Alkene (5−10 equiv) and R'(C_4H_7)NOH (1 equiv) in C_6H_6 (1.0 M), sealed tube, 110−130 °C (unless indicated otherwise). [b] Isolated yields. [c] In *n*-PrOH (1.0 M) with $NaBH_3CN$ (1 equiv) as additive.

Strained alkenes react efficiently upon heating at ca. 110 °C (entries 1 to 9). 4-Fluorostyrene and vinyltriphenylsilane also react under similar conditions, illustrating that the scope is not limited to strained alkenes (entries 10−11). This reaction sequence is also applicable for various *N*-alkyl-*N*-methallyl hydroxylamines, as shown in entries 1 to 5. Remarkably, primary hydroxylamines **2b** and **2c** only afford the rearranged products (entries 2−3), which

10.1021/ja8077895 CCC: $40.75

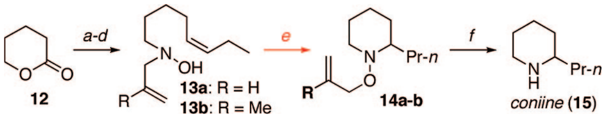
highlights that the Meisenheimer rearrangement is faster than a possible Cope elimination of the alkyl side chain (eq 2). This result is in contrast to the direct reaction of n-PrNHOH and norbornene, which does not lead to any hydroamination product under our previously reported reaction conditions,[3] likely due to the poor thermal stability associated with primary N-alkylhydroxylamines.[7]



The increased stability of such N-methallyl derivatives of primary hydroxylamines suggested that intramolecular variants of this tandem sequence could enable the synthesis of 2-alkylpiperidines. Such products are very difficult to form via hydroamination: examples of 6-membered ring formation are scarce, and most methodologies appear limited to terminal alkenes, suggesting that only 2-methylpiperidines can be accessed reliably with current methods.[8] These considerations, combined with the potential applicability of related hydroaminations in alkaloid synthesis (which requires the use of internal alkenes), led us to select coniine as the target for the study of intramolecular variants of this tandem sequence.[9]

The N-allyl and N-methallyl hydroamination substrates were readily prepared from δ-valerolactone (Scheme 1). After extensive optimization of the key hydroamination sequence, N-allyl derivative **13a** emerged as a slightly superior cyclization precursor for coniine, likely due to a more facile Meisenheimer rearrangement step (Scheme 1). With both substrates, the use of rigorously deoxygenated, dilute solutions (0.01 M) drastically minimized side reactions.[10] To put the 47% isolated yield (55% brsm) in context, all attempts to cyclize the simpler primary hydroxylamine precursor failed to provide more than 23% of the desired hydroamination product.[11]

Scheme 1. Synthesis of Coniine via a Tandem Intramolecular Hydroamination/Meisenheimer Rearrangement Sequence[a]

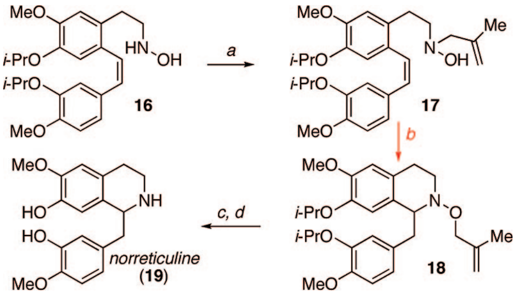


[a] Conditions: (a) DIBAL-H, PhMe, −60 °C; EtCH=PPh$_3$, THF, 0 °C to reflux (74%, Z/E = 7:1). (b) BocNHOBoc, DIAD, PPh$_3$, THF, 0 °C to rt (86%). (c) TFA, CH$_2$Cl$_2$ (91%). (d) **13a**: K$_2$CO$_3$, C$_3$H$_5$Br, THF (68%). **13b**: DBU, C$_4$H$_7$Cl, THF/DMF, reflux (37%). (e) C$_6$H$_6$ (0.01M), H$_2$O (10 equiv), sealed tube, 140 °C (**14a**: 47% + 15% **13a**; **14b**: 31%). (f) Zn/AcOH.

With optimized conditions developed in this unbiased system, we turned our attention to a related cyclization to access the alkaloid norreticuline (Scheme 2). Thus, cyclization precursors **16** and **17** were prepared from isovanillin and vanillin.[11] In this system, methallyl derivative **17** proved a superior cyclization precursor, affording the desired product **18** in 54% yield (32% of the trans isomer derived from **17**, likely formed via hydroamination/Cope elimination, was also isolated). Subsequent N−O bond cleavage was accomplished using standard conditions, and BCl$_3$-mediated cleavage of the i-Pr groups furnished norreticuline (**19**). Again, the use of simpler primary hydroxylamine precursor **16** failed to provide more than 27% of the desired hydroamination product.[11]

In summary, the tandem hydroamination/Meisenheimer rearrangement sequence was developed to address the issue of unfavorable reaction thermodynamics for intermolecular reactions of alkenes and to improve the scope of Cope-type hydroaminations.

Scheme 2. Synthesis of Norreticuline via a Tandem Intramolecular Hydroamination/Meisenheimer Rearrangement Sequence[a]



[a] Conditions: (a) DBU, C$_4$H$_7$Cl, THF/DMF, reflux (50%). (b) C$_6$H$_6$ (0.01M), H$_2$O (10 equiv), sealed tube, 120 °C (54% + 32% of E-**17**). (c) Zn, AcOH (78%). (d) BCl$_3$, CH$_2$Cl$_2$ (>99%).

This tandem sequence allows intermolecular reactions of N-alkyl-N-methallylhydroxylamines to be energetically more favorable and leads to increased efficiency in intramolecular systems as illustrated by syntheses of two alkaloids featuring difficult hydroamination key steps. Efforts directed at the development of other tandem sequences are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic characterization for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected reviews, see:(a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795 (and reviews cited therein). (b) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *32*, 1407. (c) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (d) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (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) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(2) Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306.

(3) (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**, *130*, 17893−17906.

(4) Such reactions are also referred to as "reverse Cope cyclizations" or reverse Cope eliminations in the literature. For an excellent review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

(5) See: Cope, A. C.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3423, and references cited therein.

(6) Oligomers formed from an "anti-Markovnikov" hydroamination pathway have been isolated. See Supporting Information.

(7) In contrast to c-C$_6$H$_{11}$NHOH,[3] which yields the HA product, gas evolution was observed with n-PrNHOH under identical reaction conditions.

(8) Reports of 6-membered piperidine ring formation via hydroamination onto an *internal* alkene are rare. For examples, see: (a) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (b) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938. (c) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

(9) For an intramolecular diene hydroamination approach to coniine: (a) Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *122*, 7886. (b) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *123*, 15878.

(10) Avoiding small-scale cyclization attempts (<50 mg) also proved critical for reproducibility. For the use of similar conditions in a challenging 5-membered system, see: (a) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139. Hydroxylamines can be sensitive to oxygen and prone to bimolecular decomposition: (b) Horiyama, S.; Suwa, K.; Yamaki, M.; Kataoka, H.; Katagi, T.; Takayama, M.; Takeuchi, T. *Chem. Pharm. Bull.* **2002**, *50*, 996.

(11) See Supporting Information for details.

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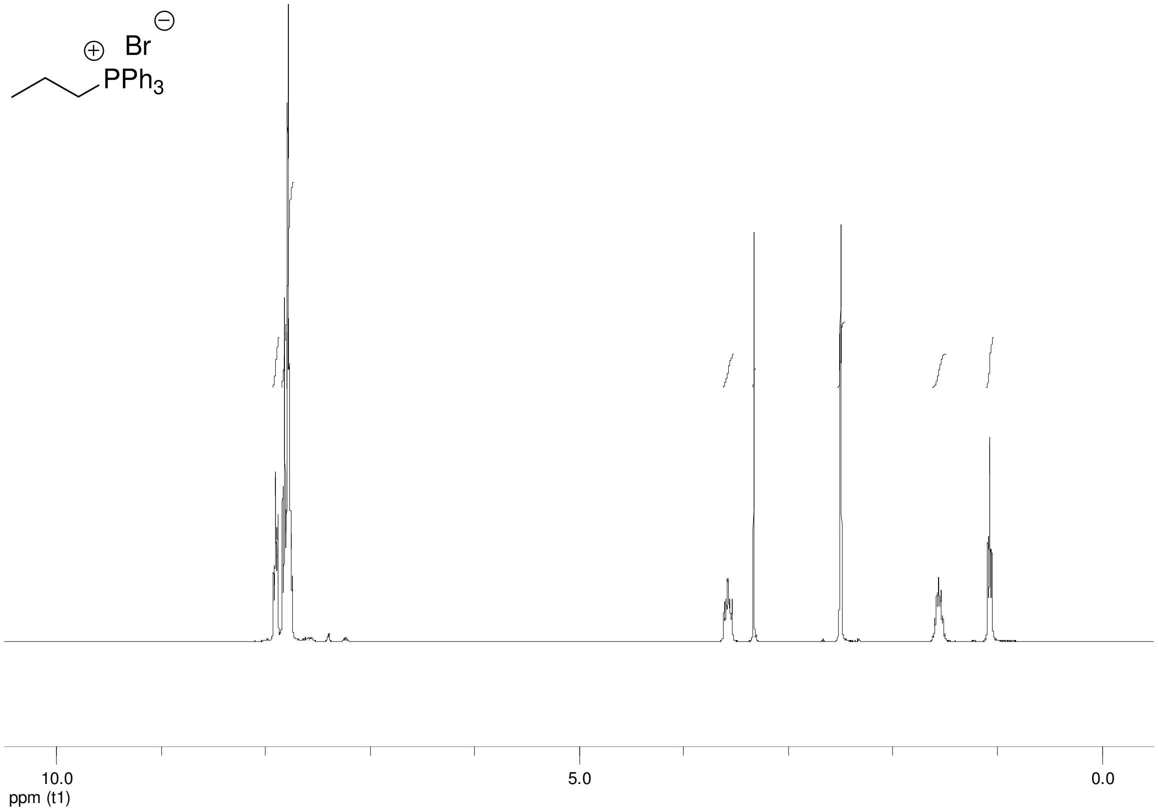
Appendix II

Supporting Information - Chapter 2



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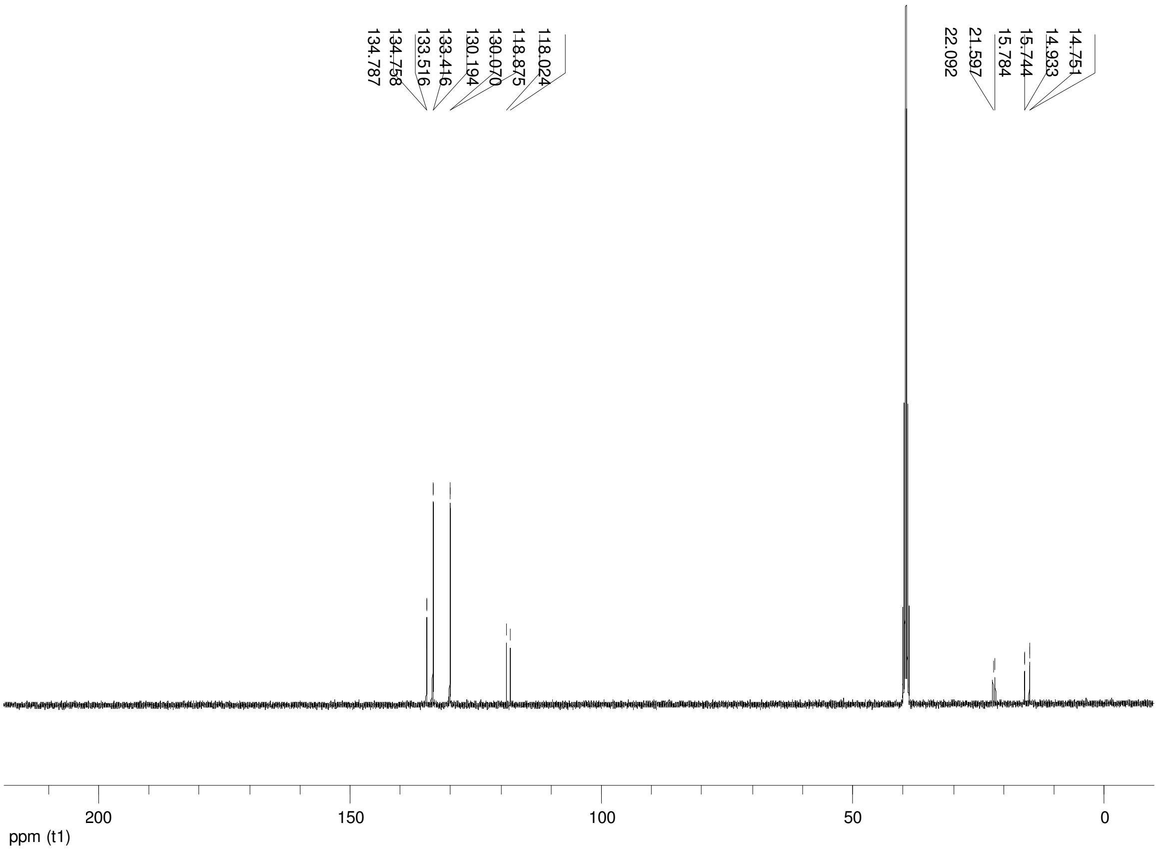

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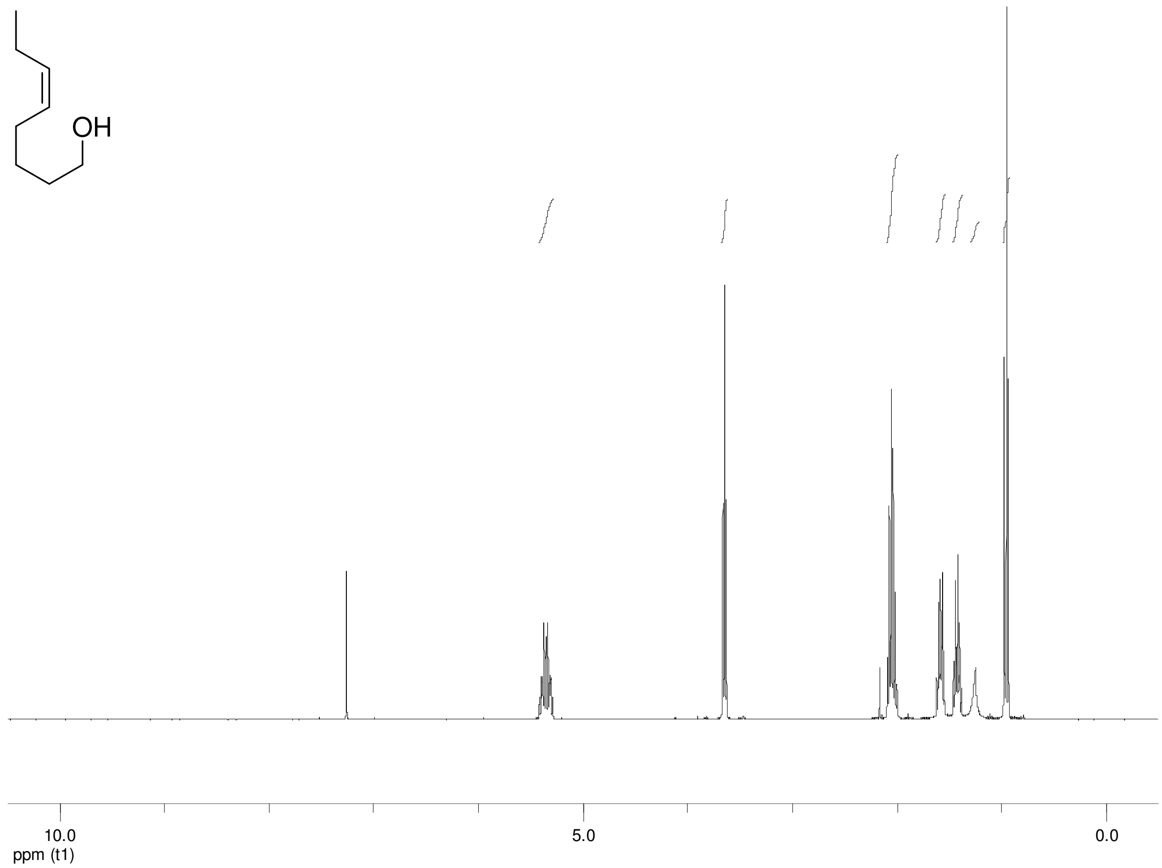
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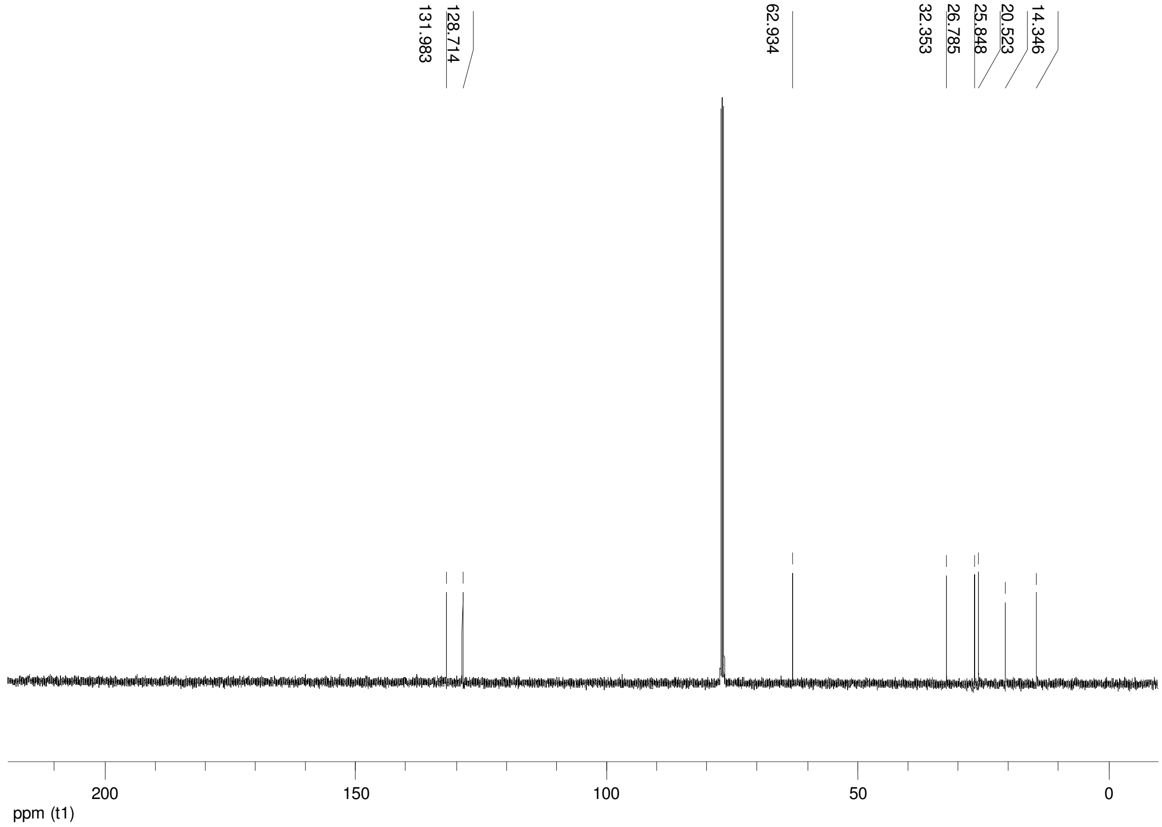
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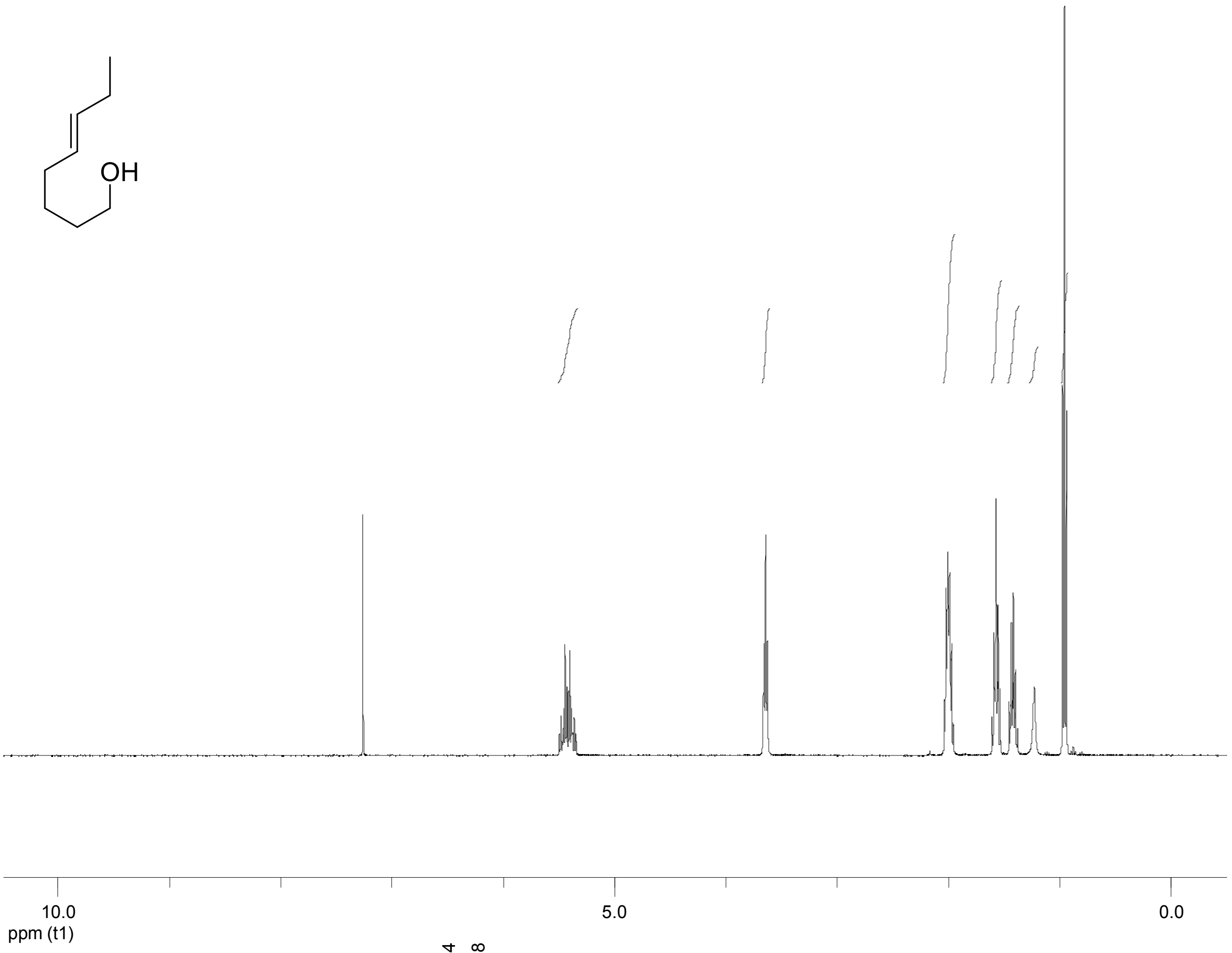
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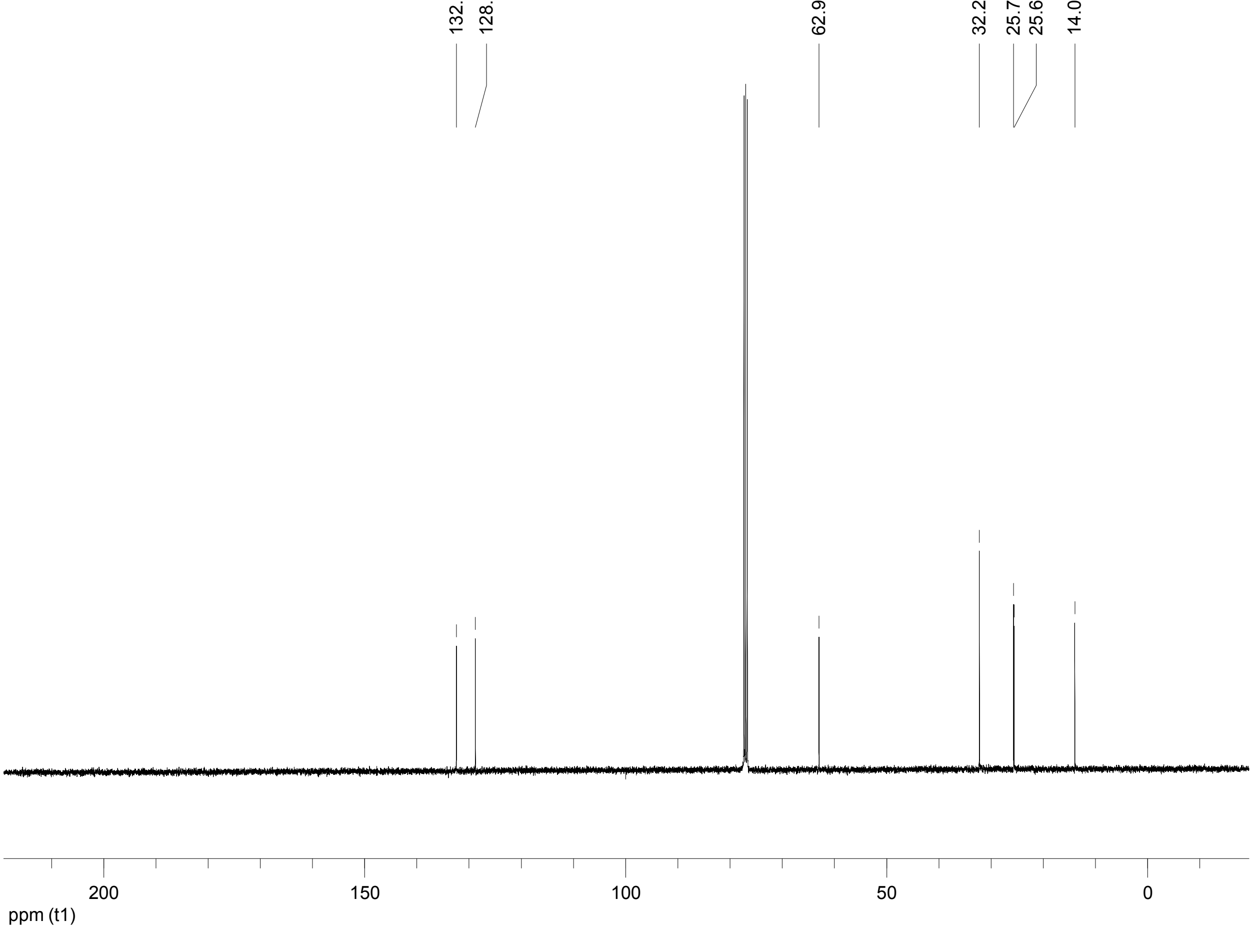
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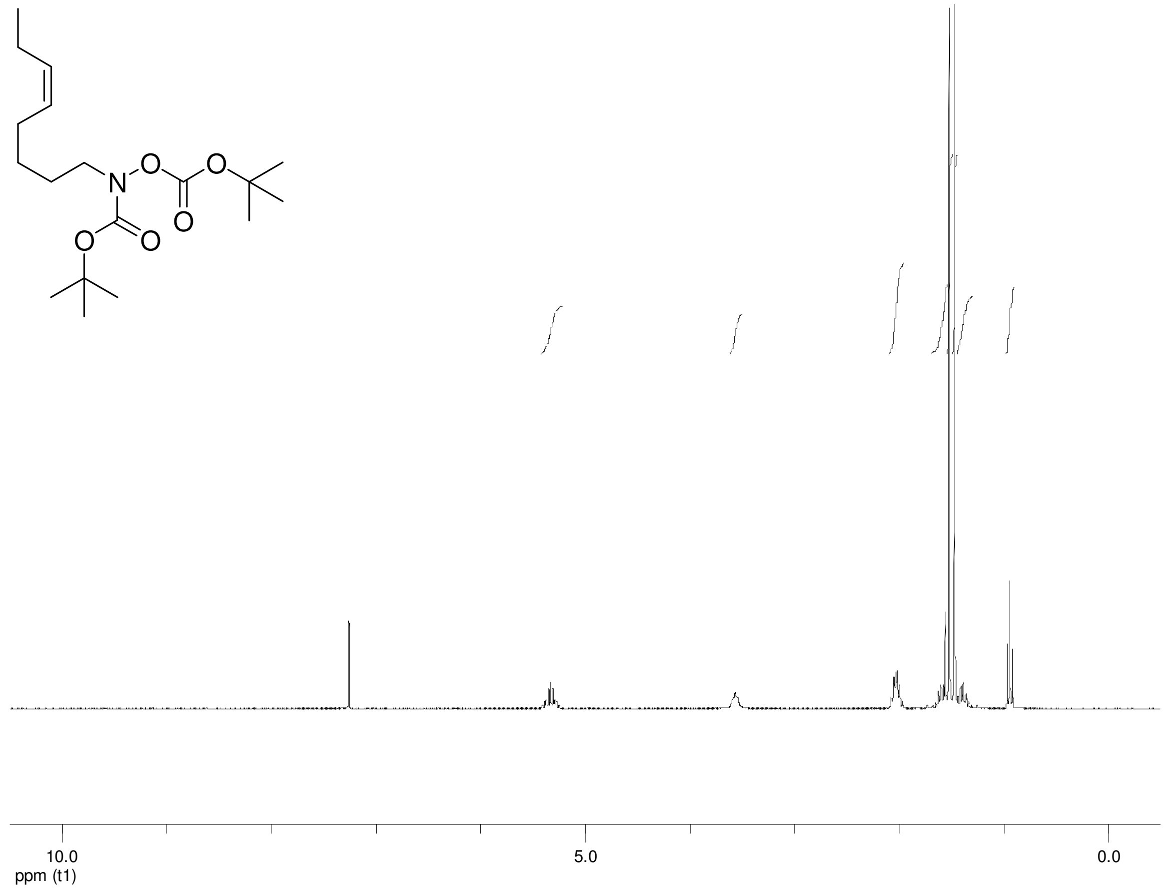
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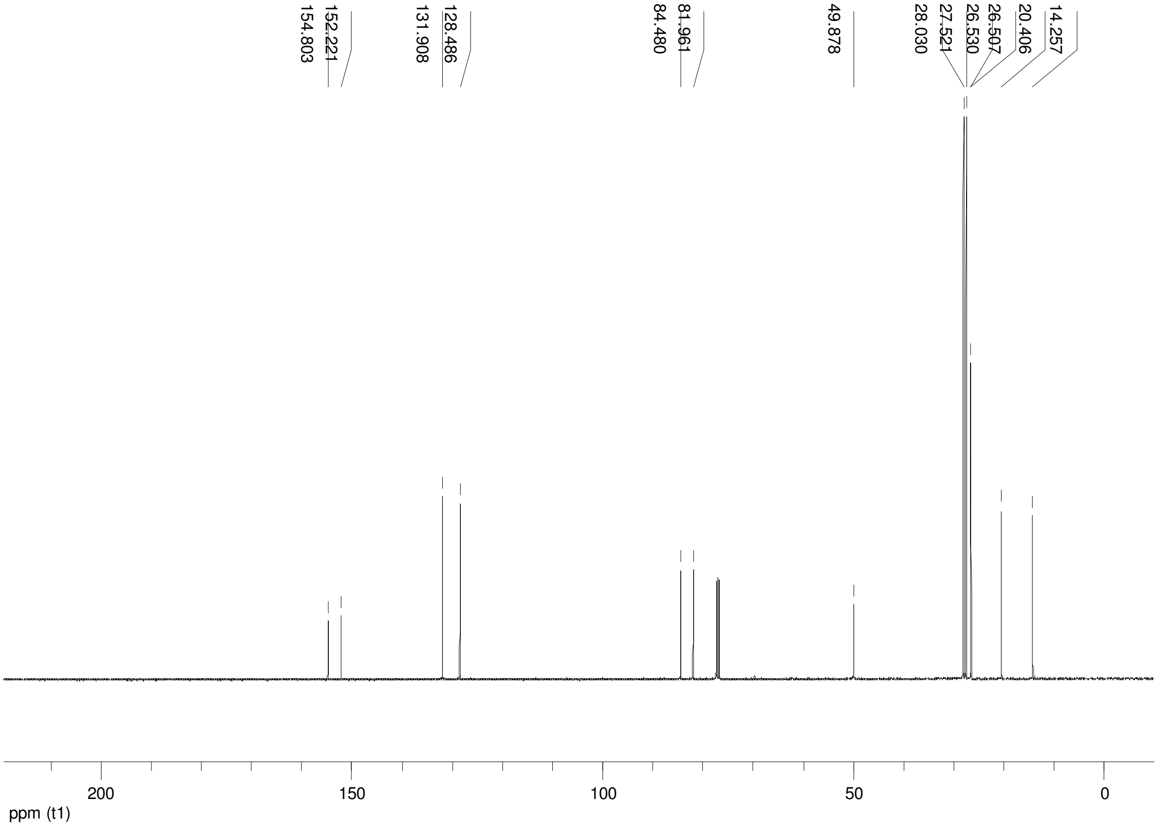
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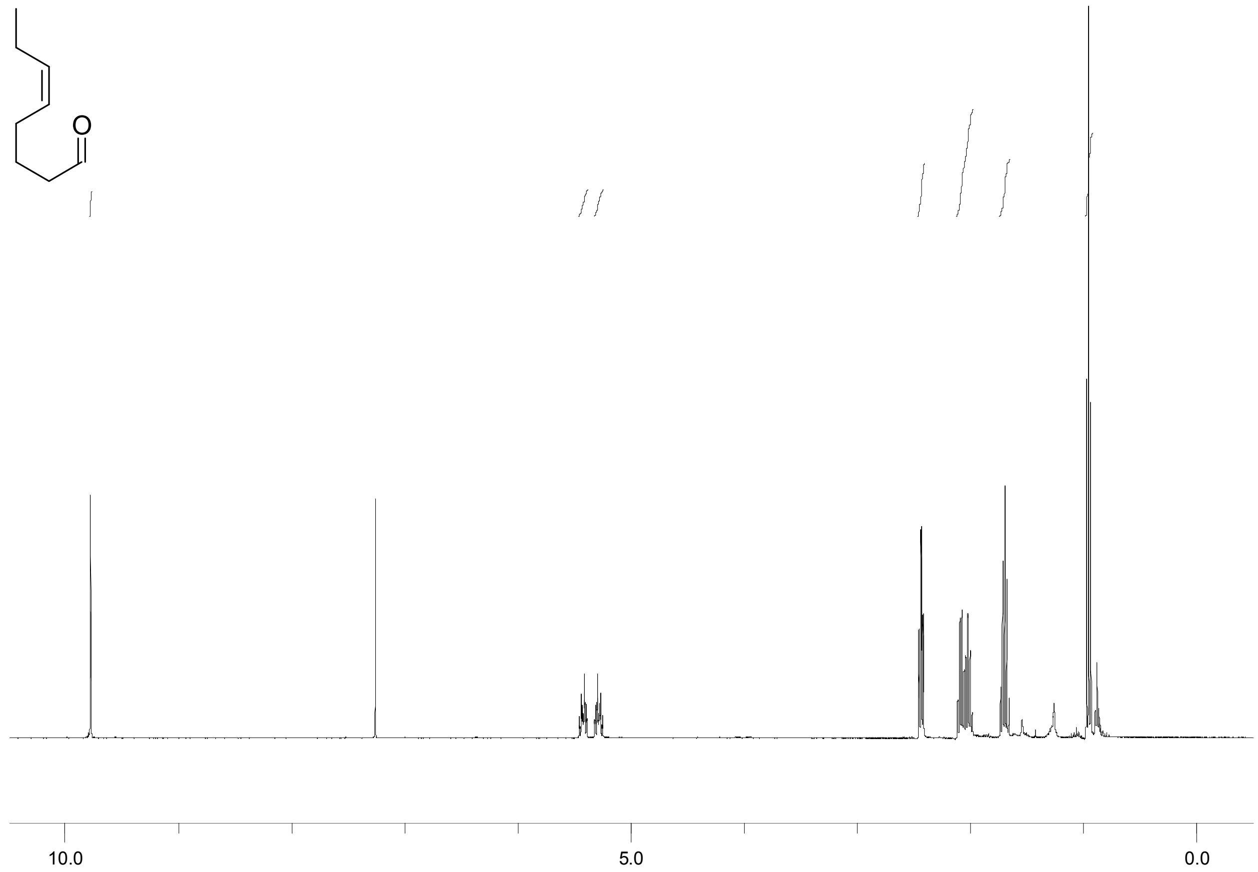
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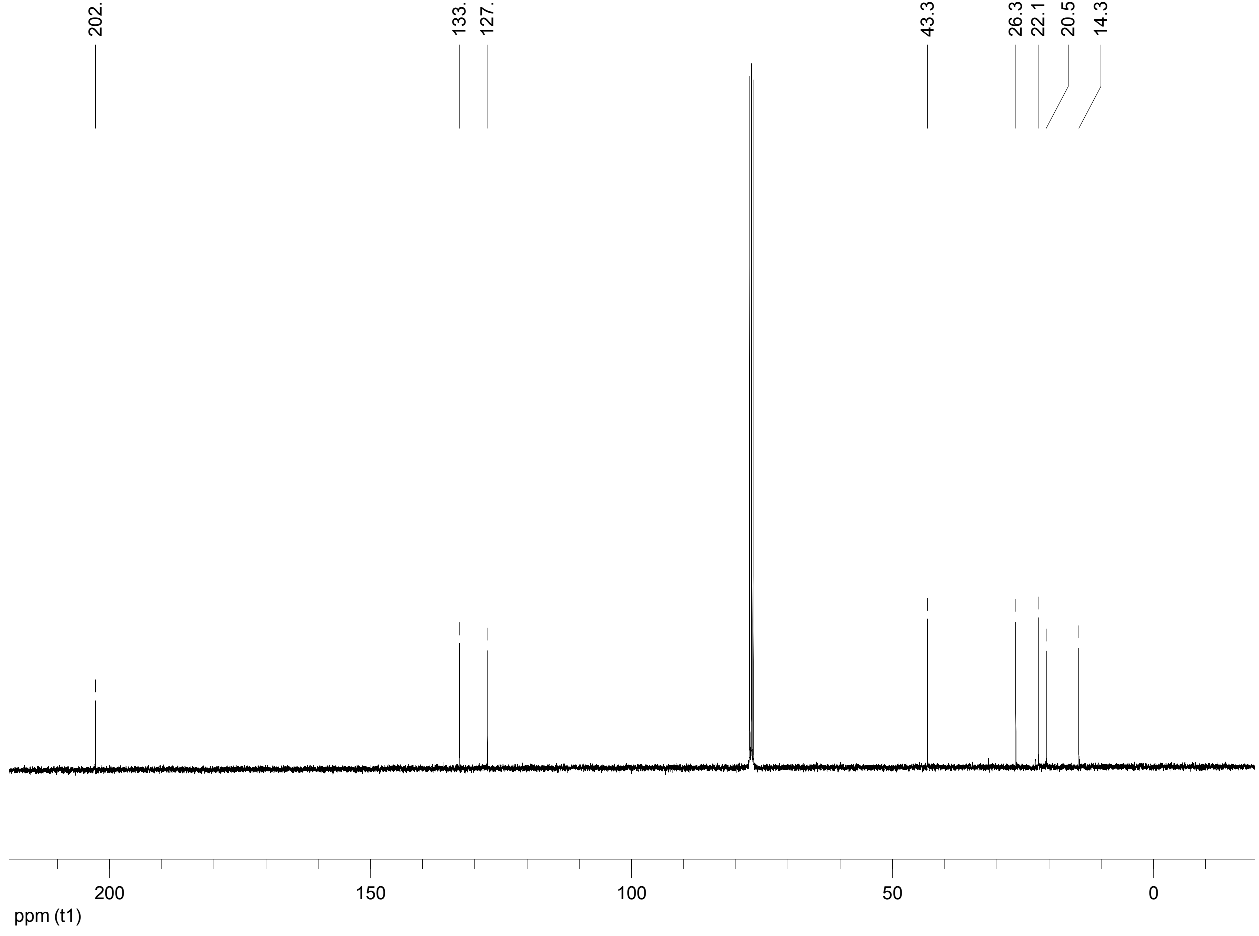
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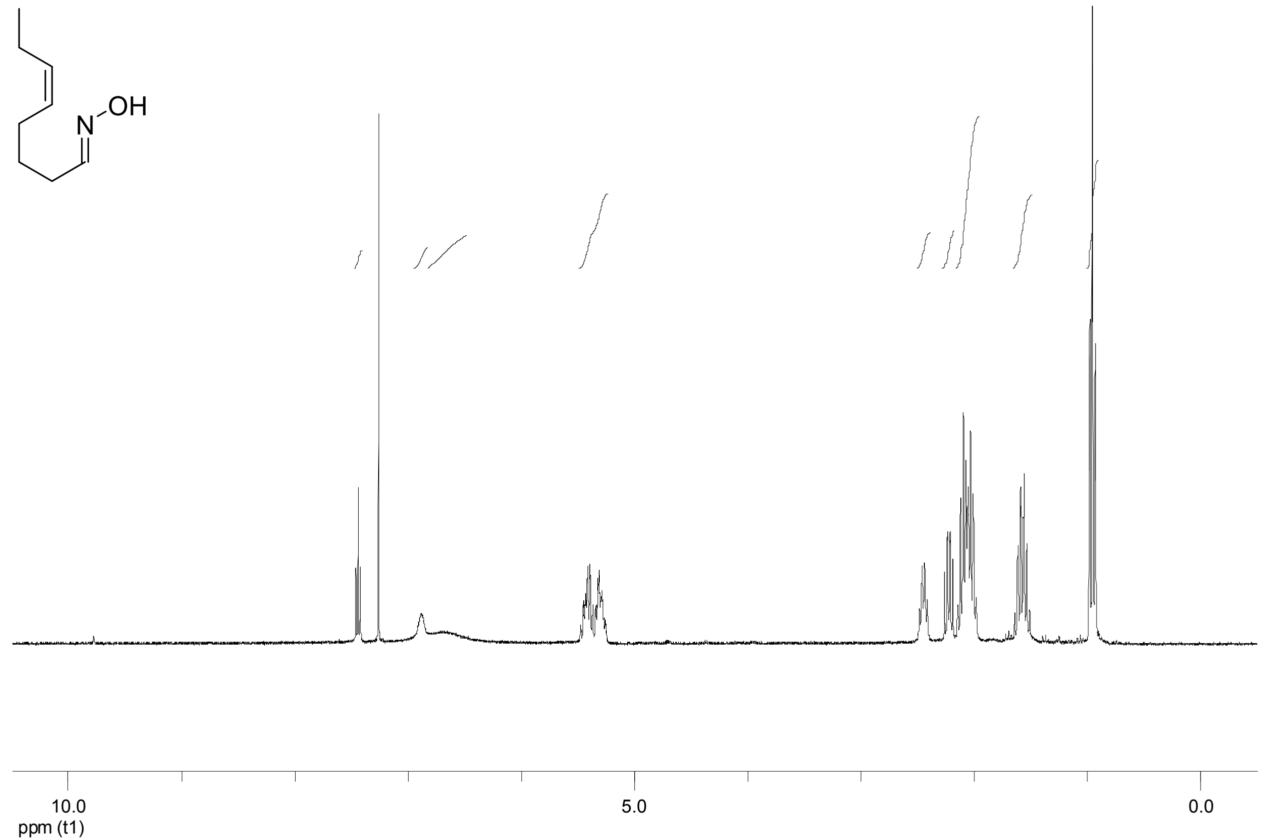
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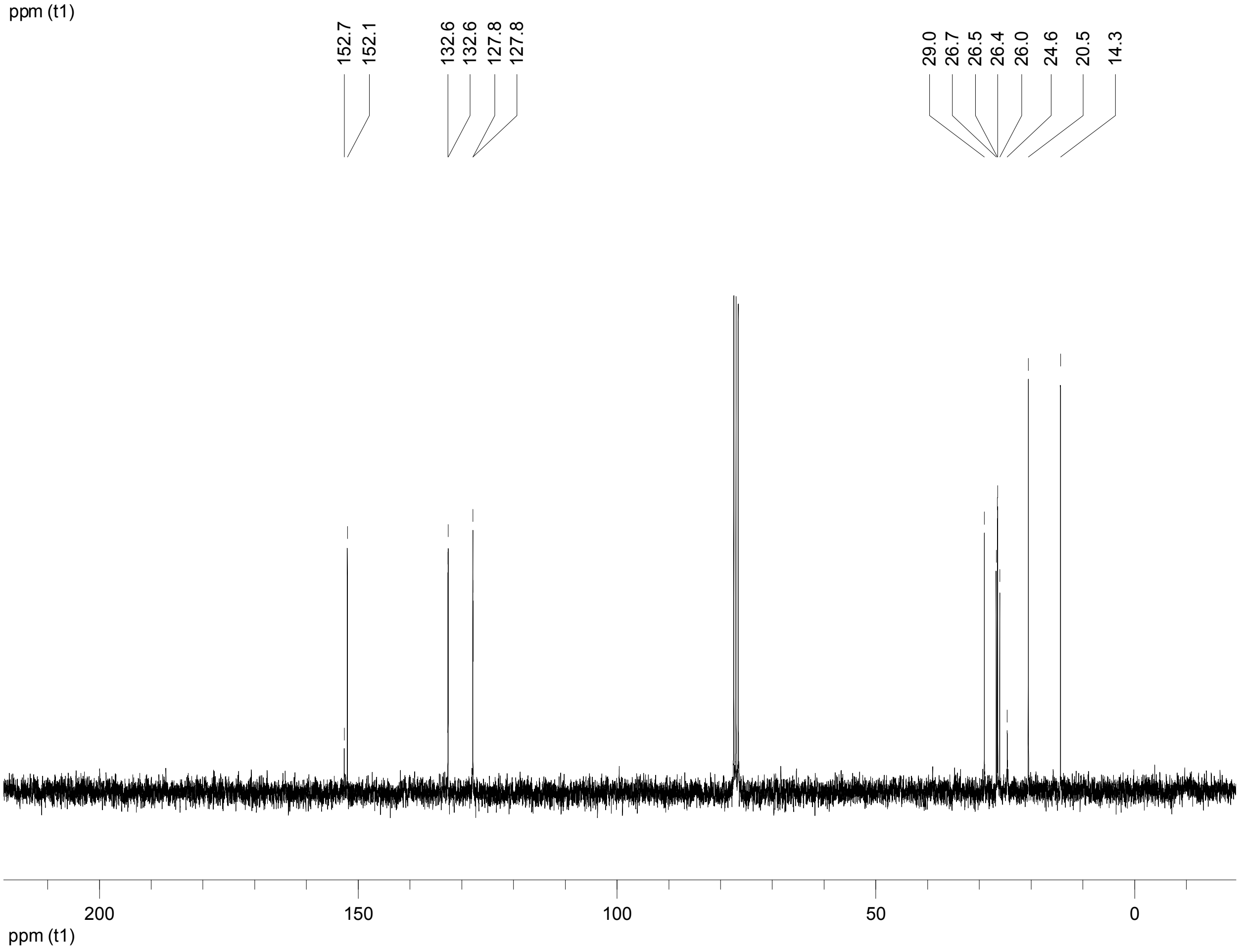
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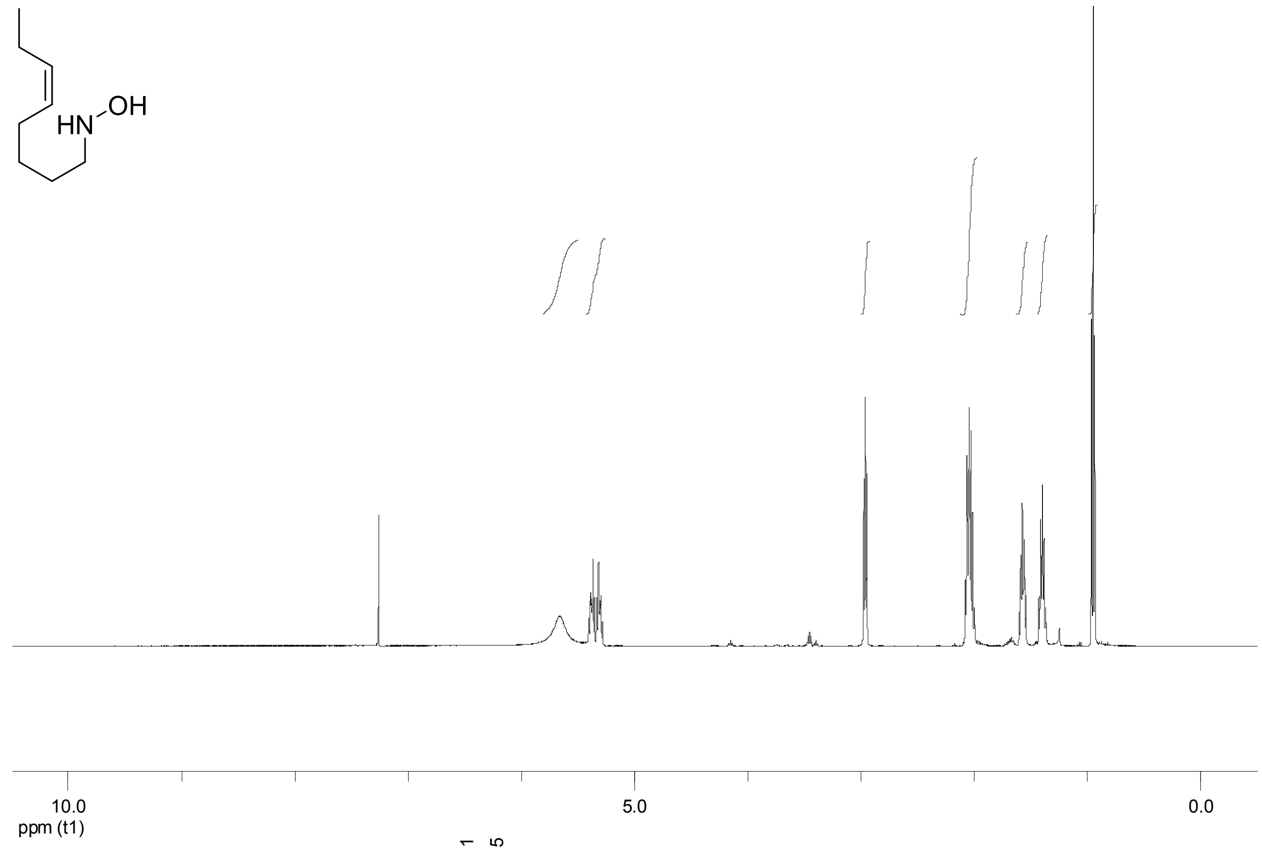
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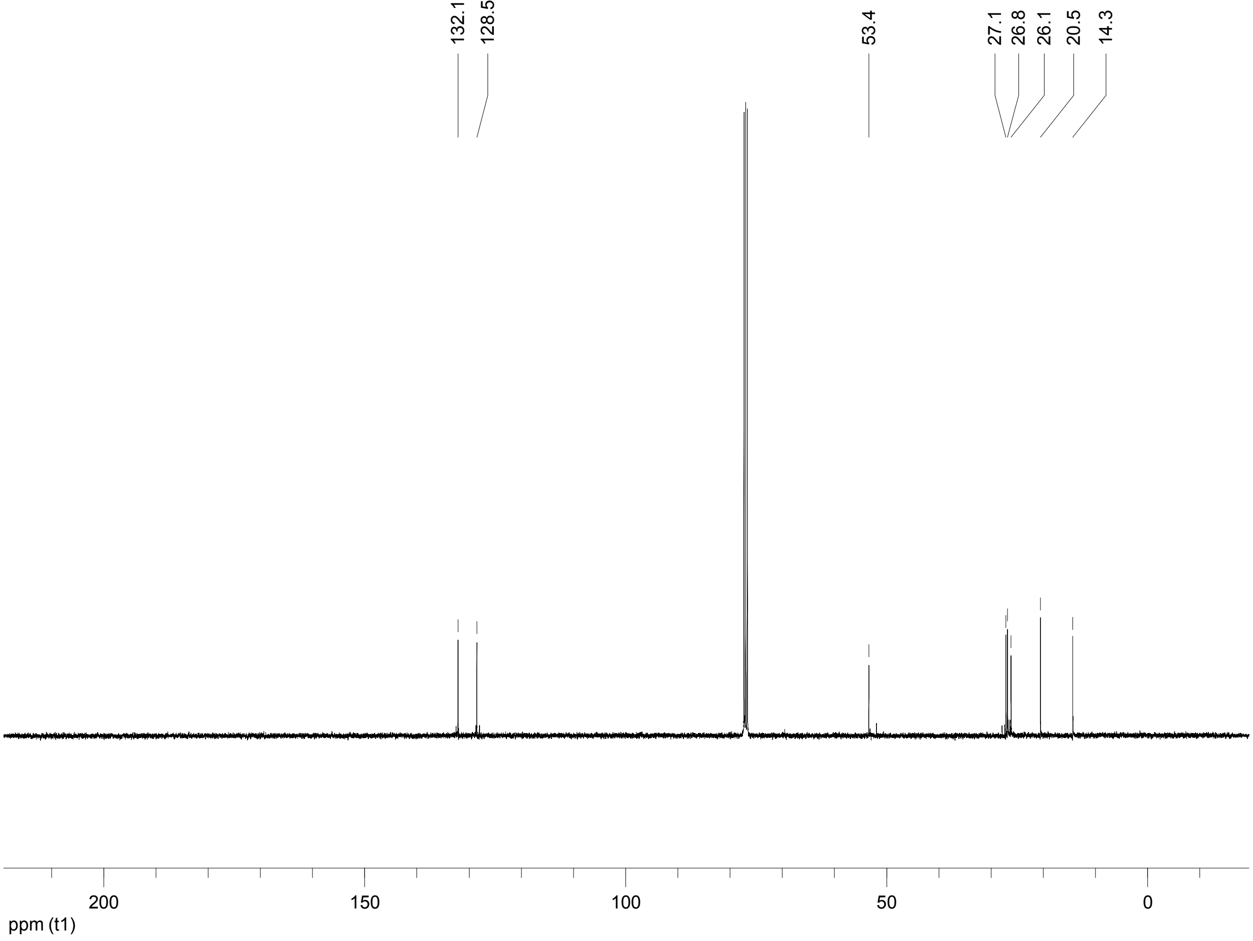
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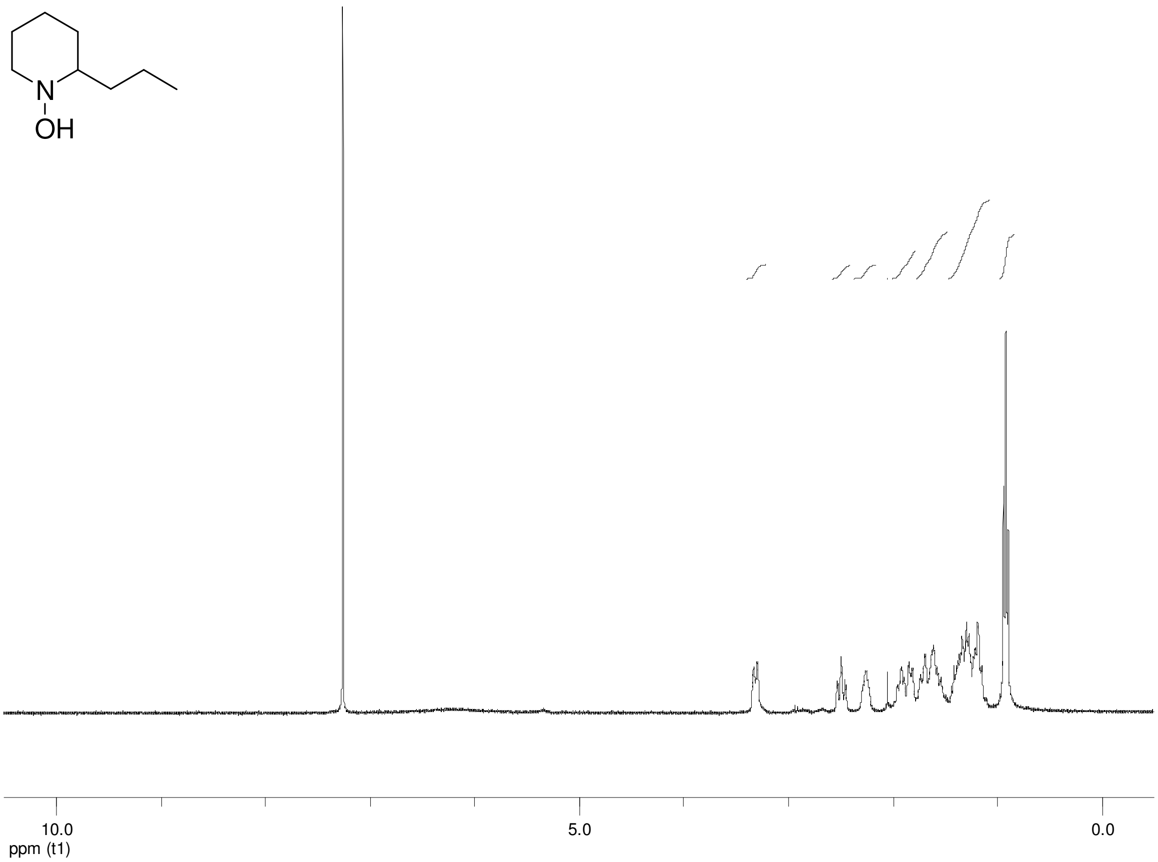
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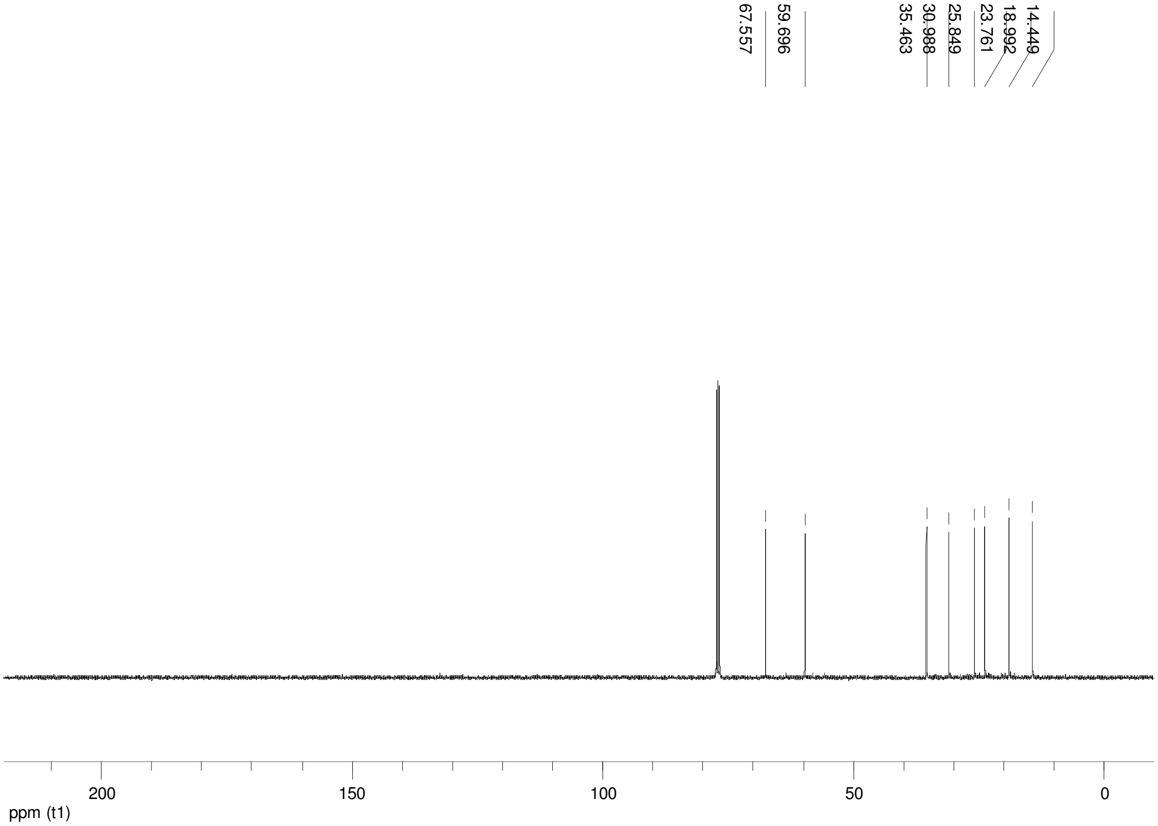
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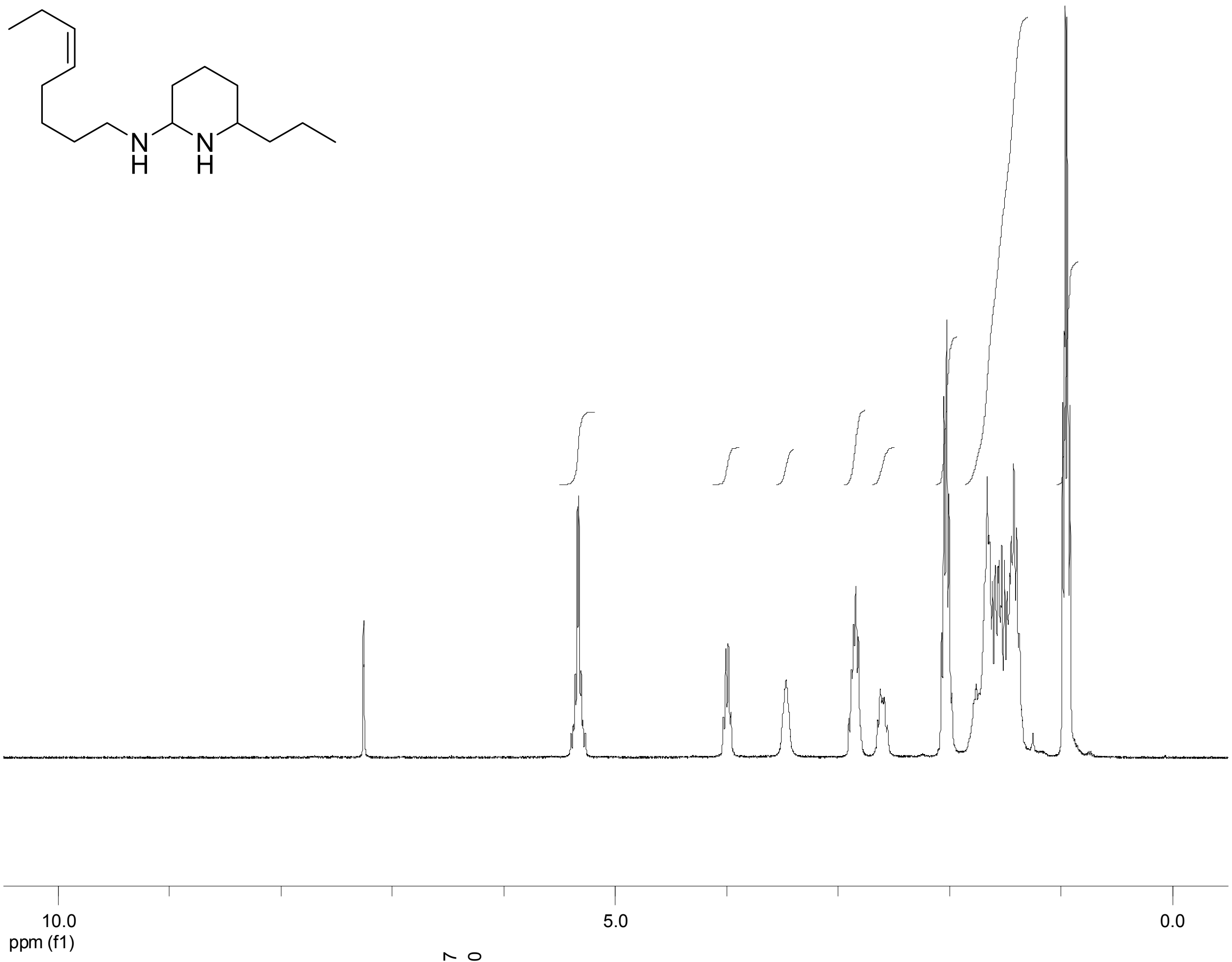
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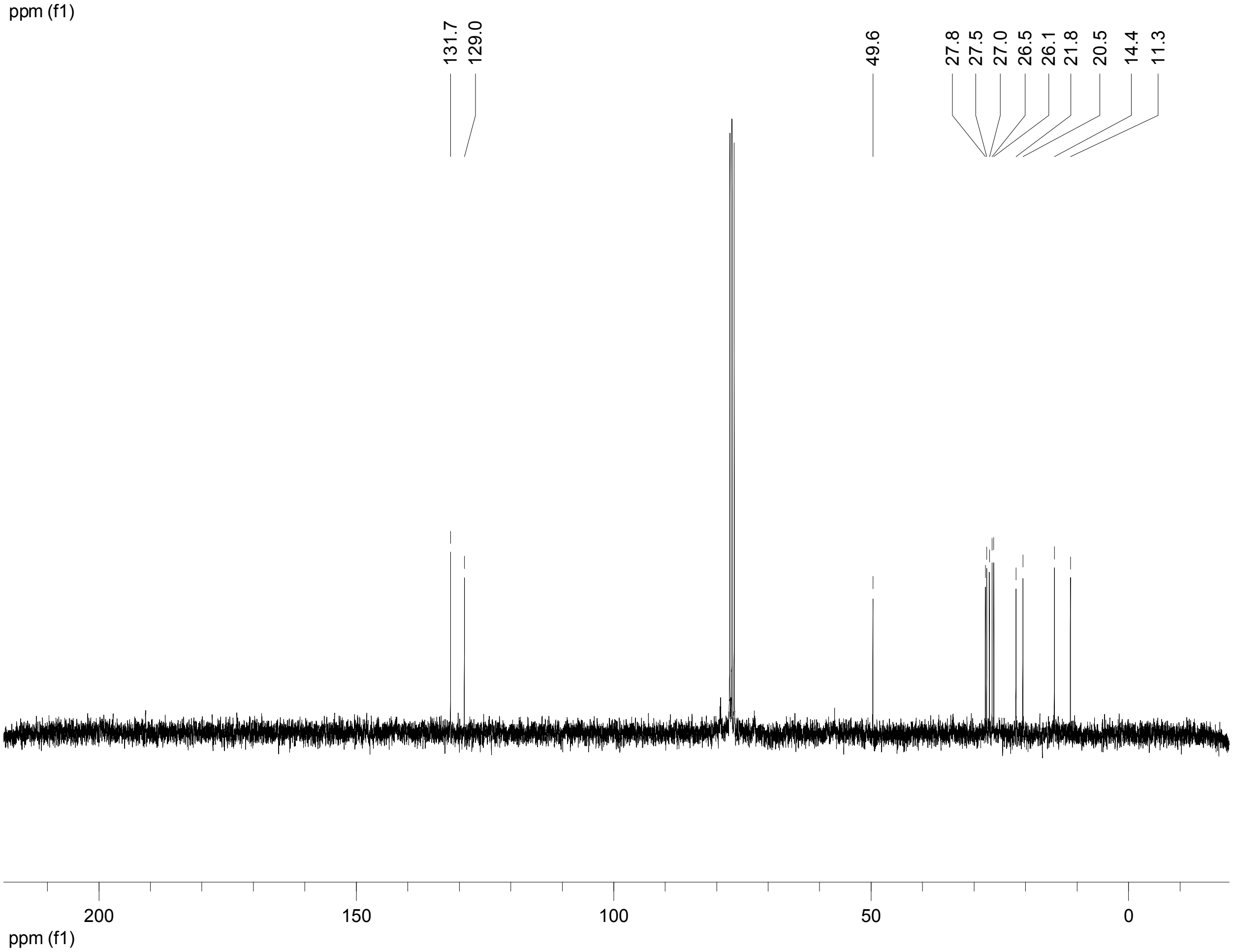
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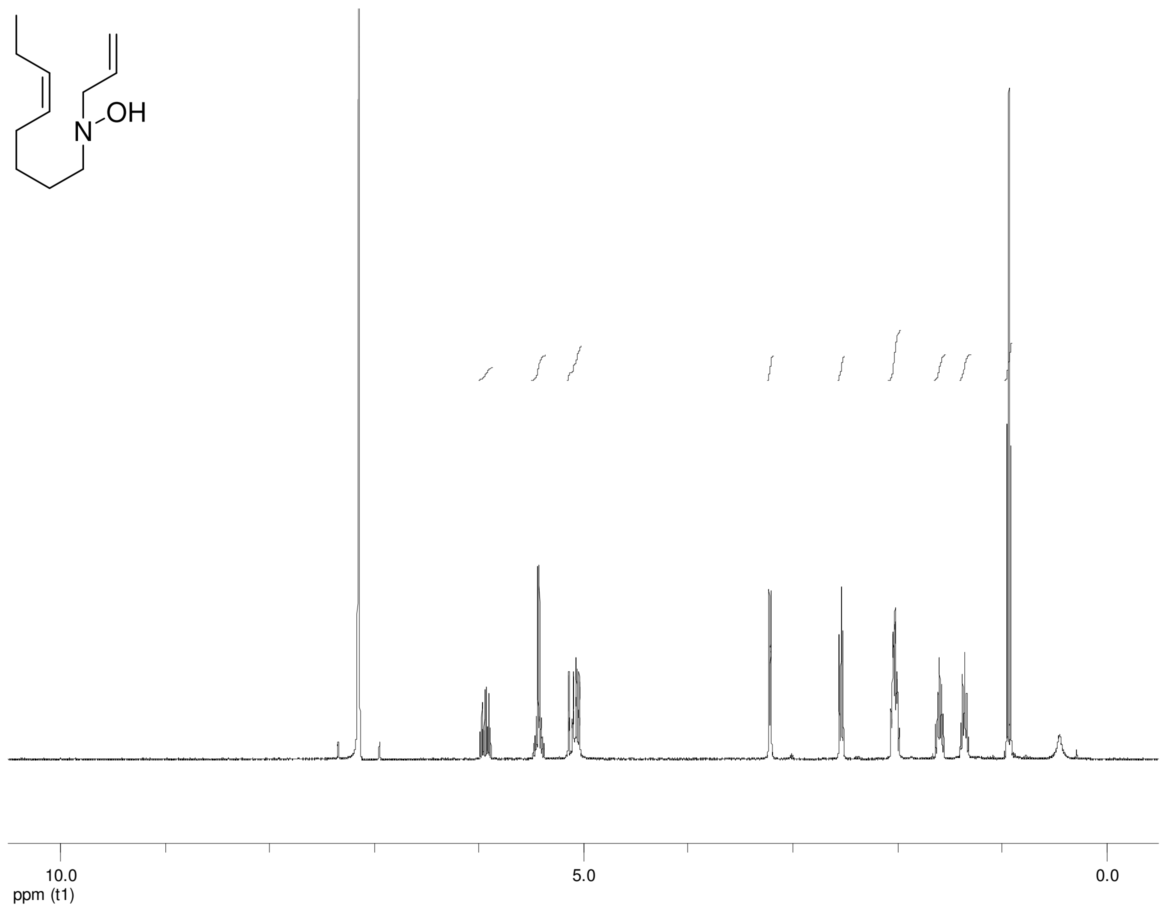
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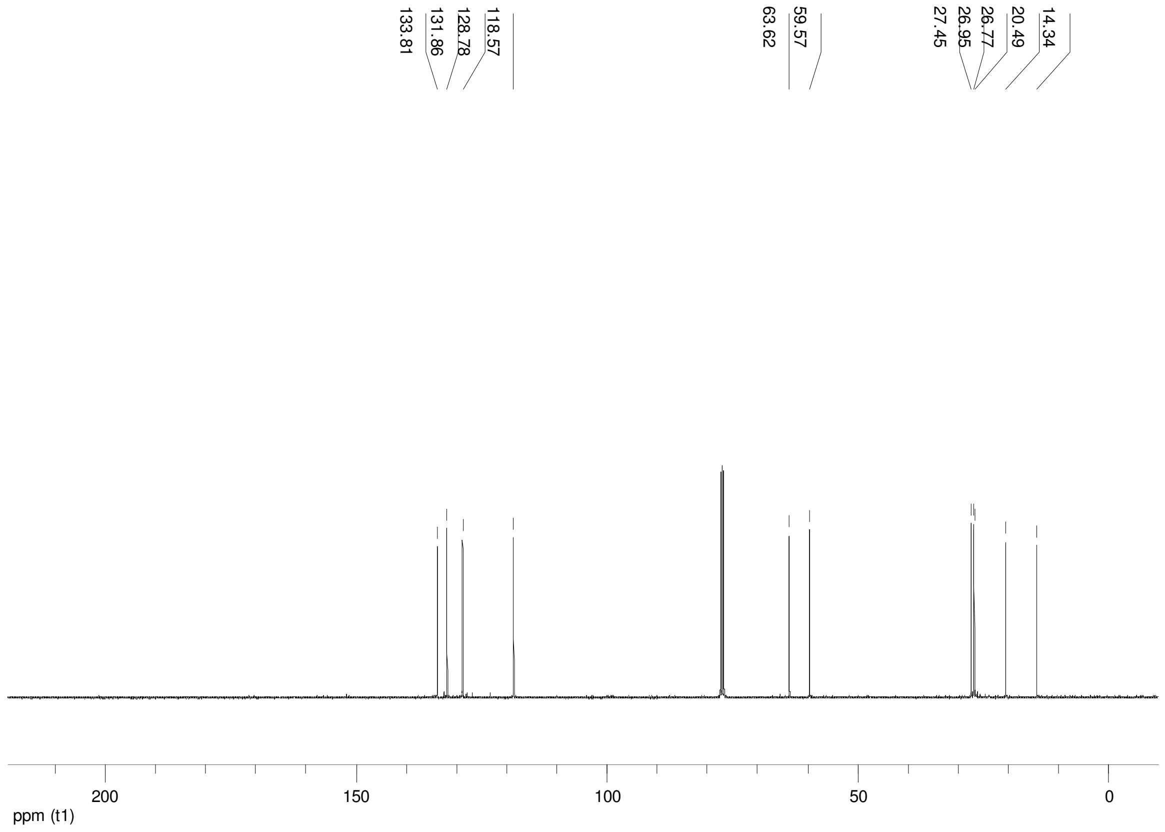
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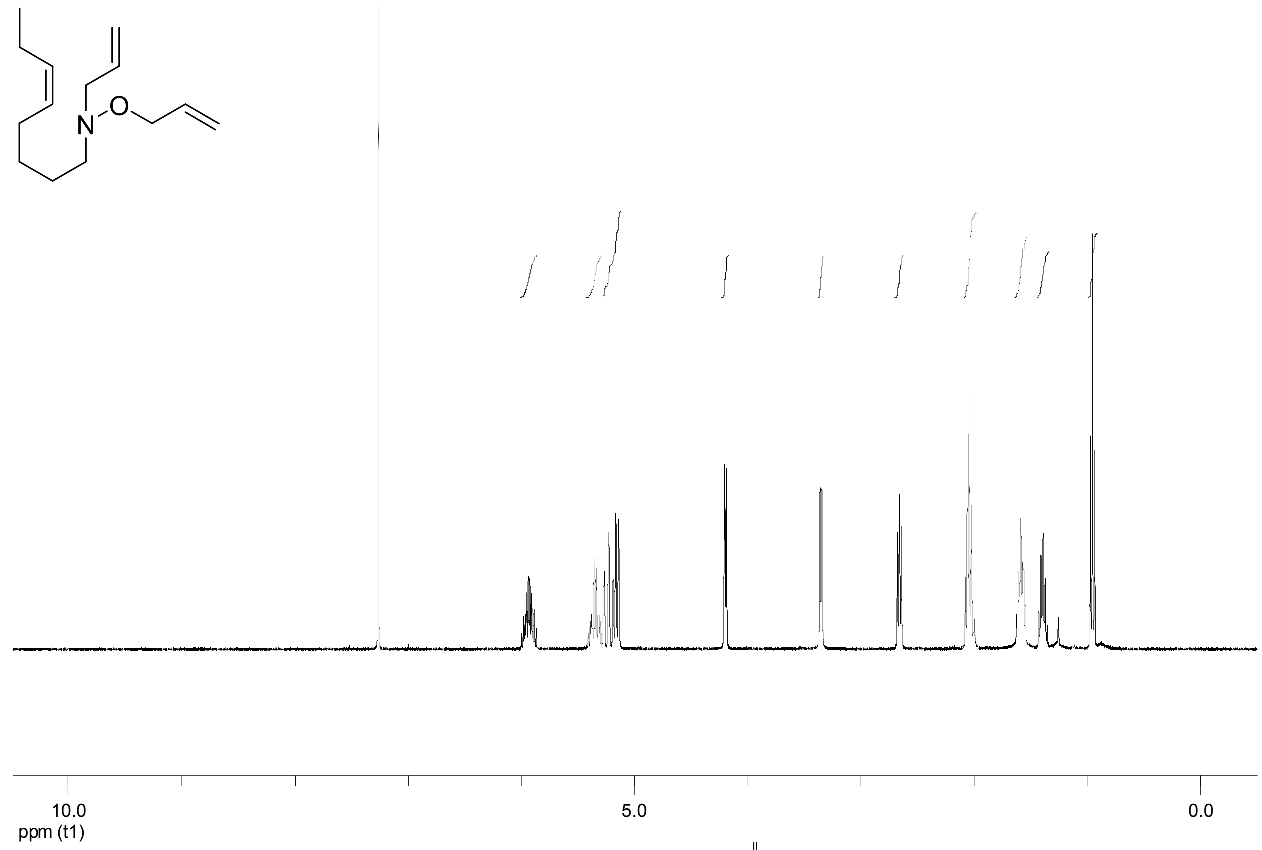
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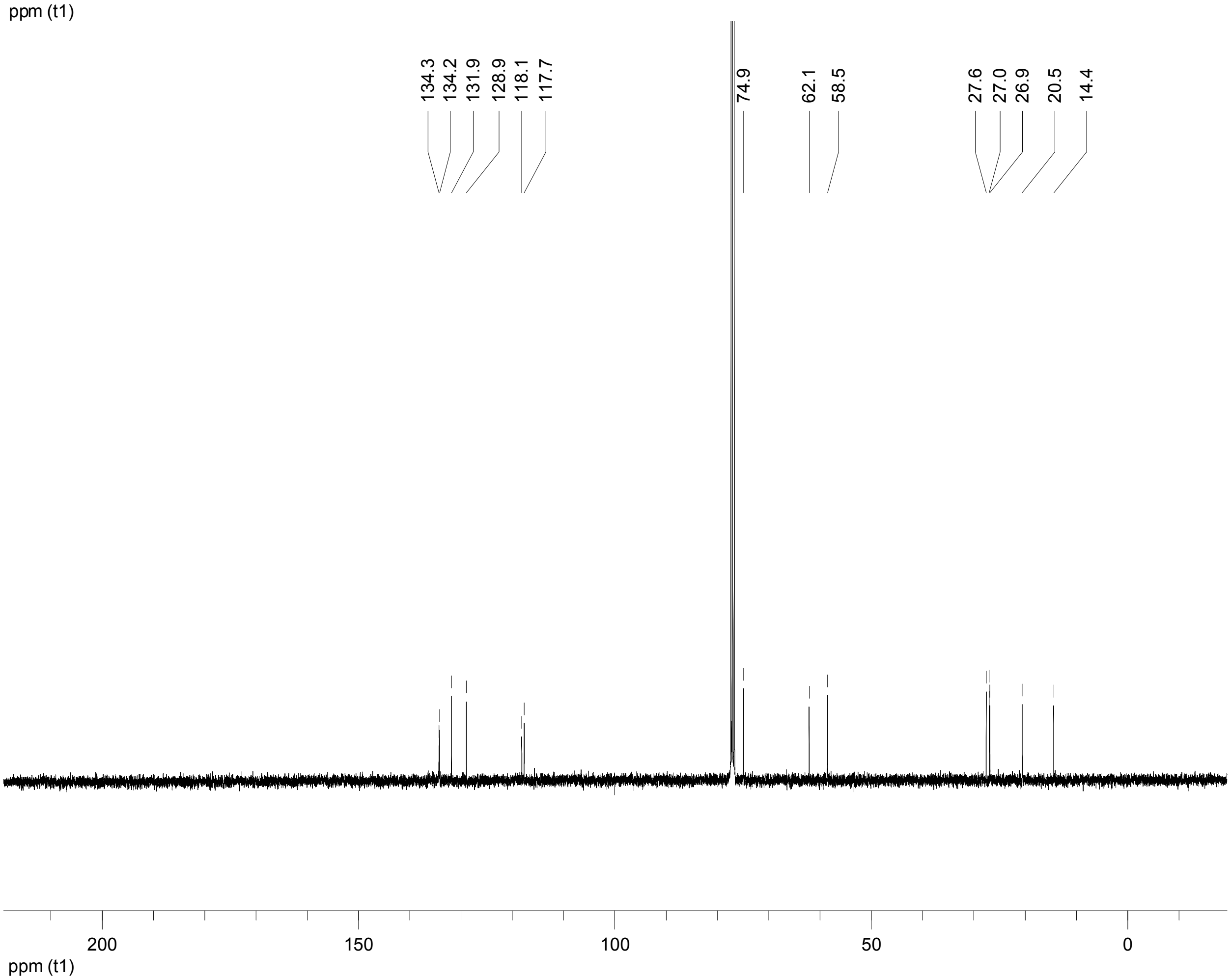
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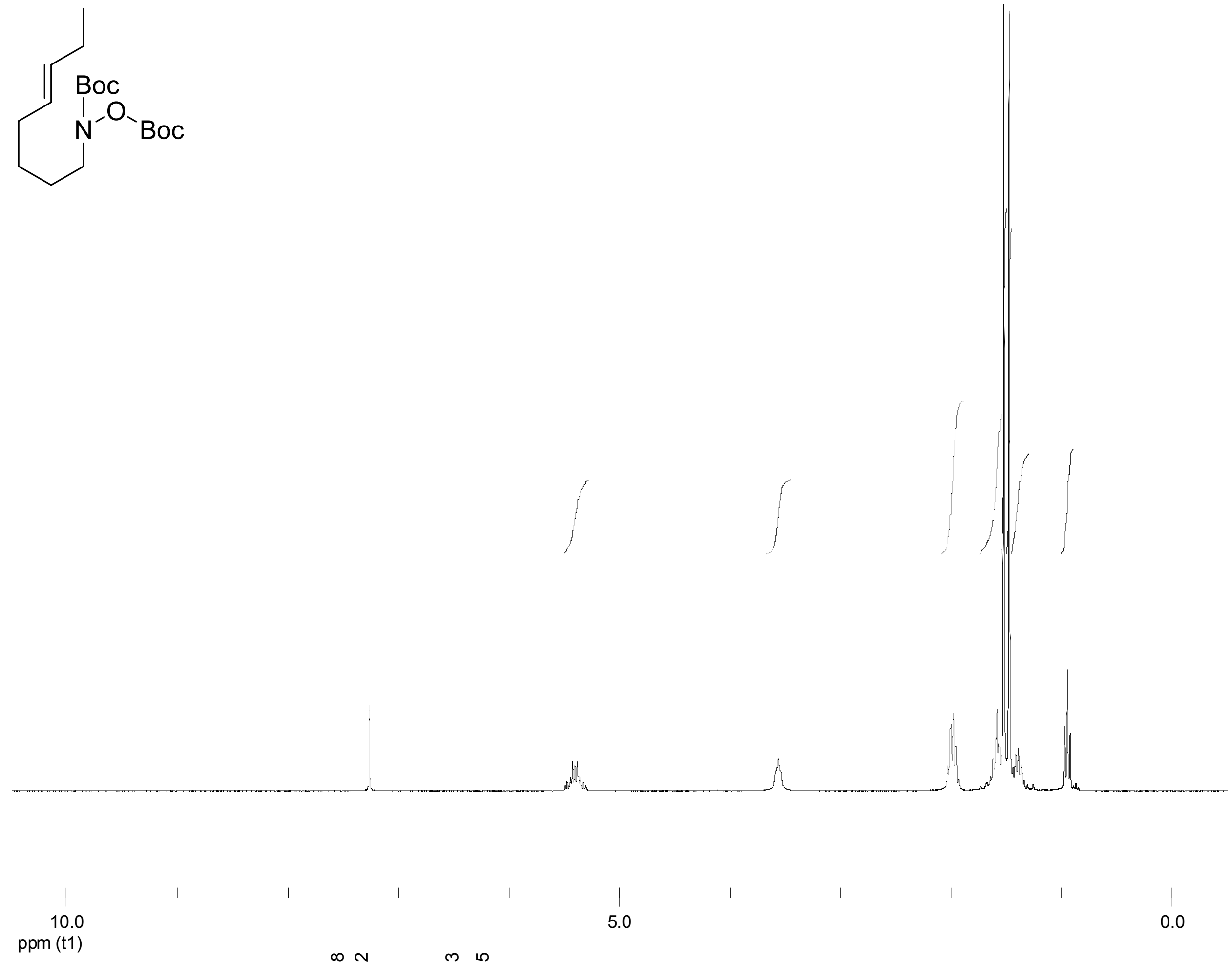
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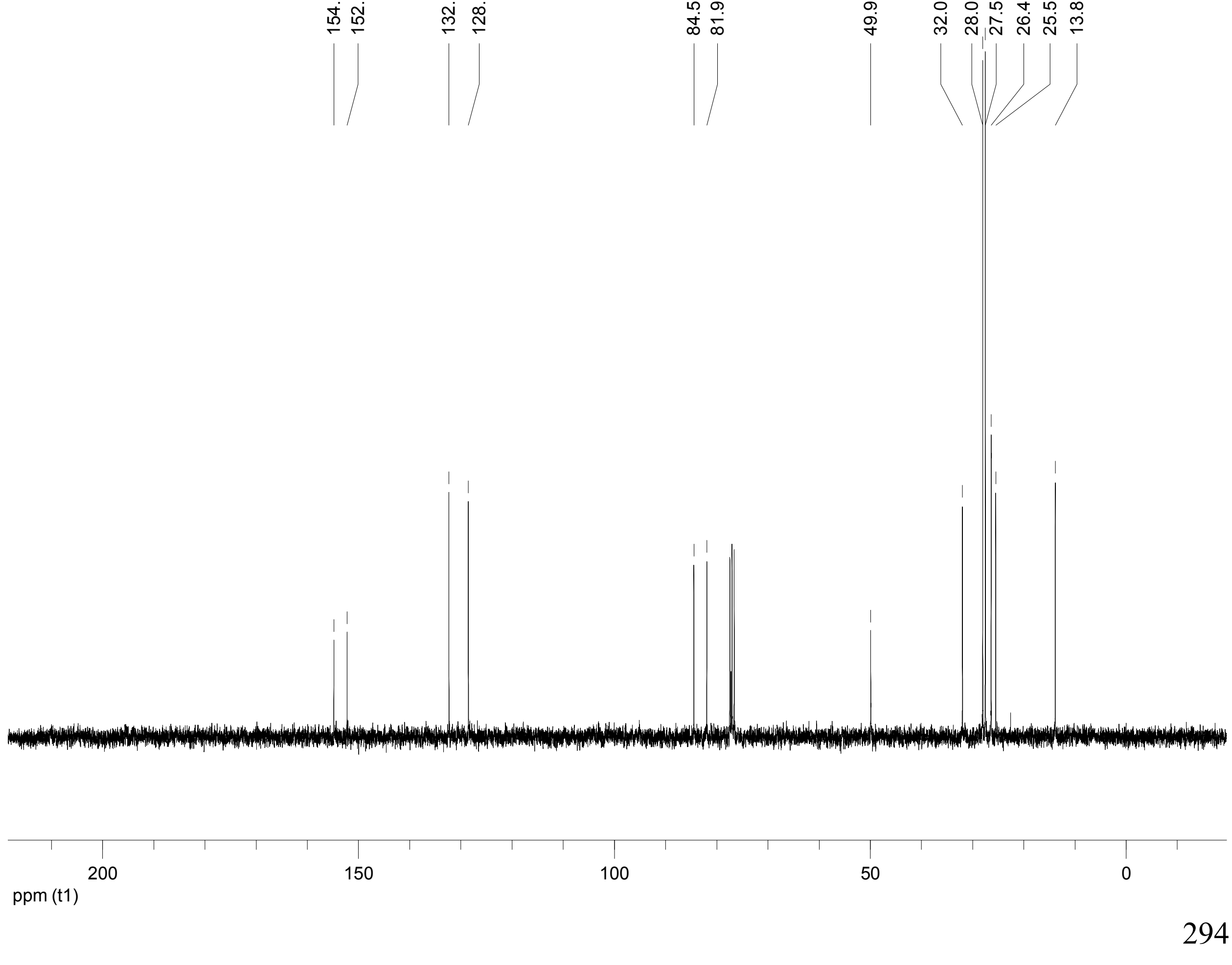
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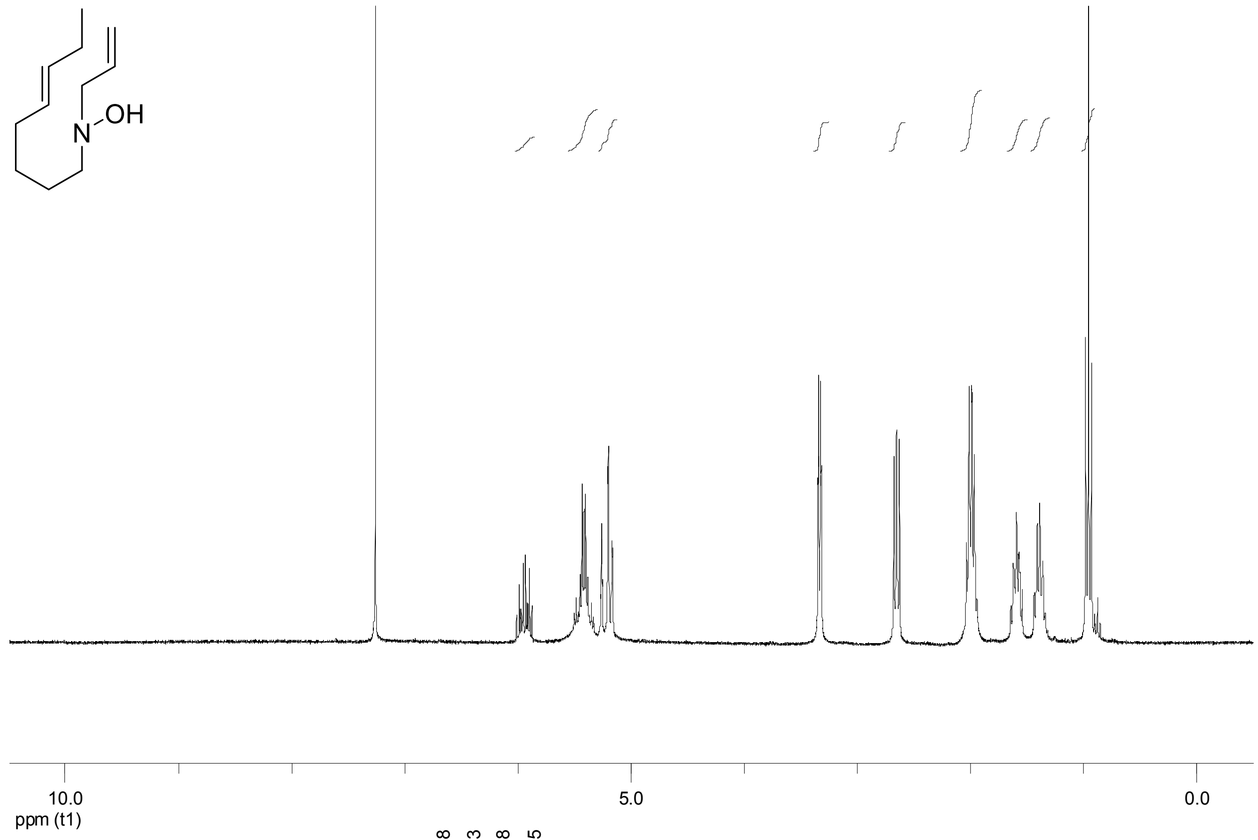
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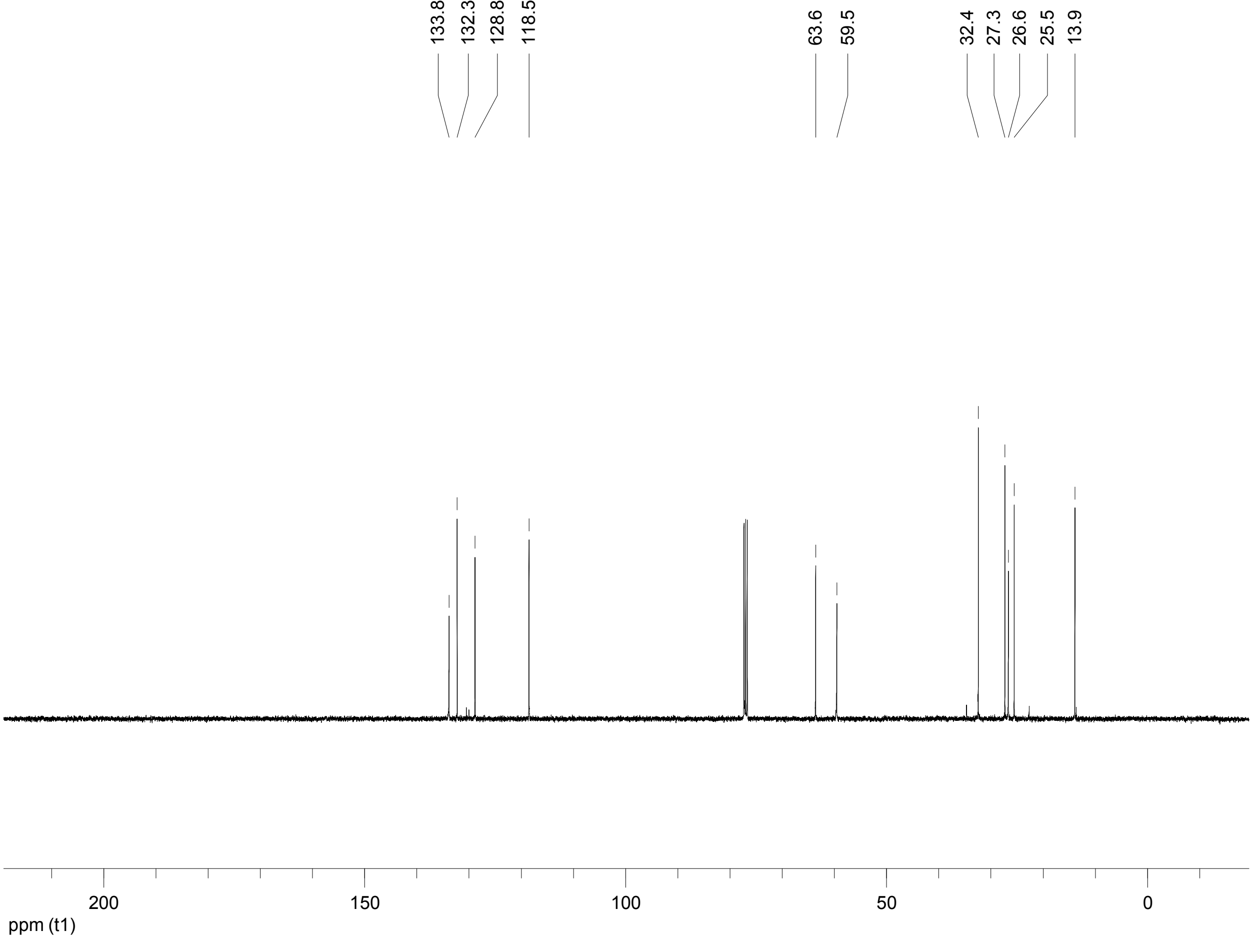
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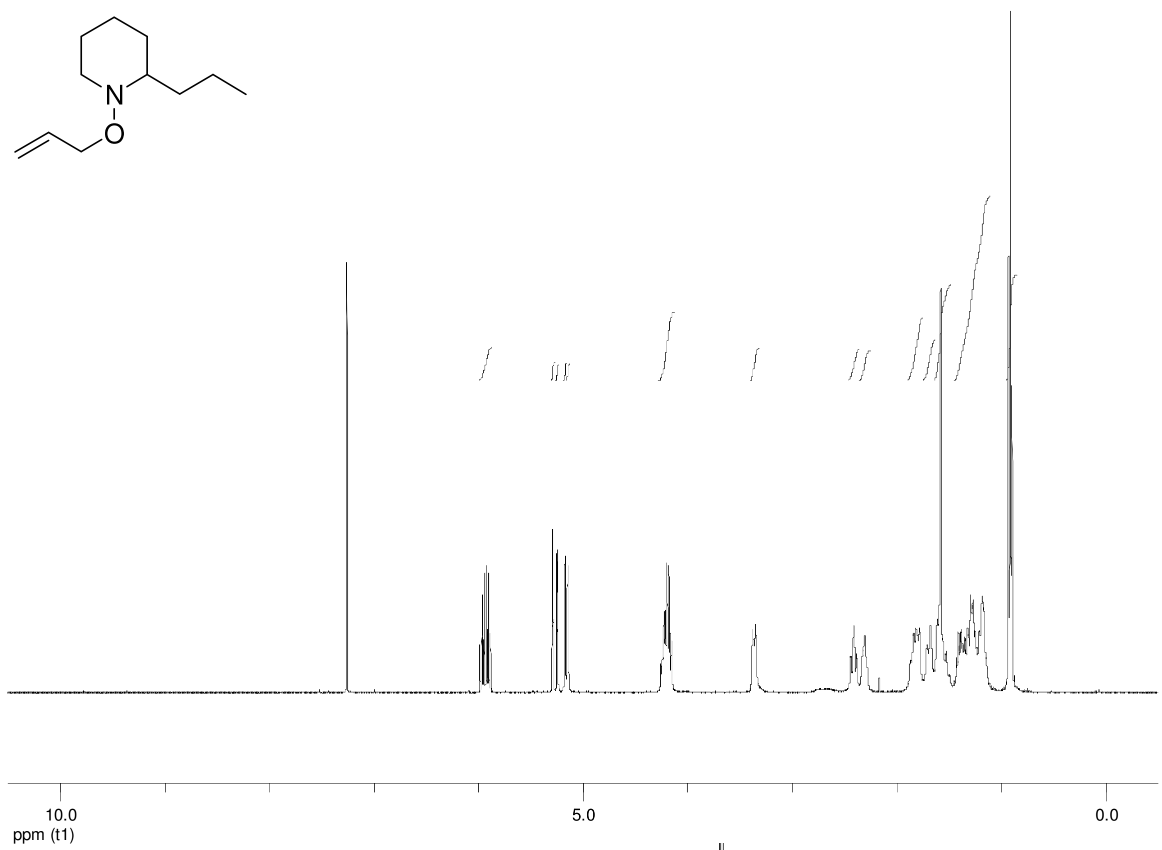

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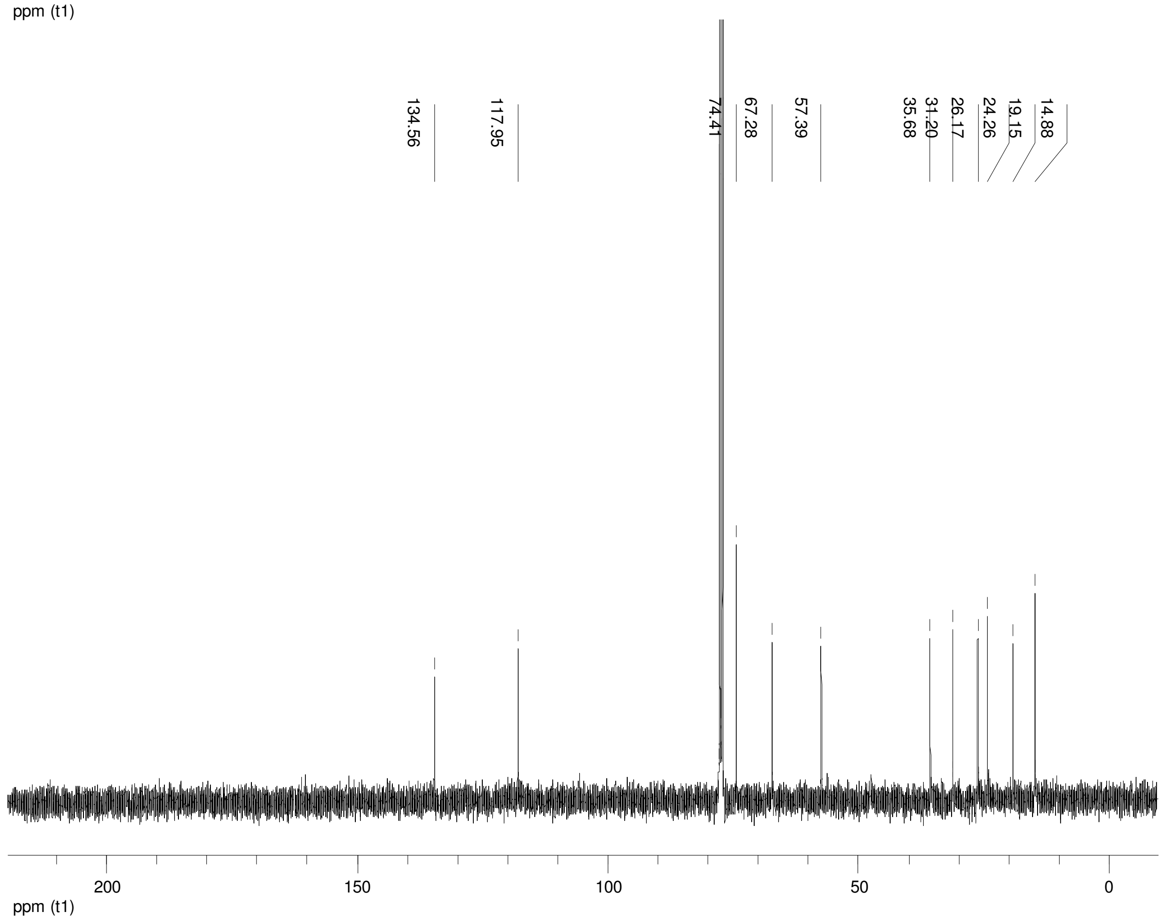

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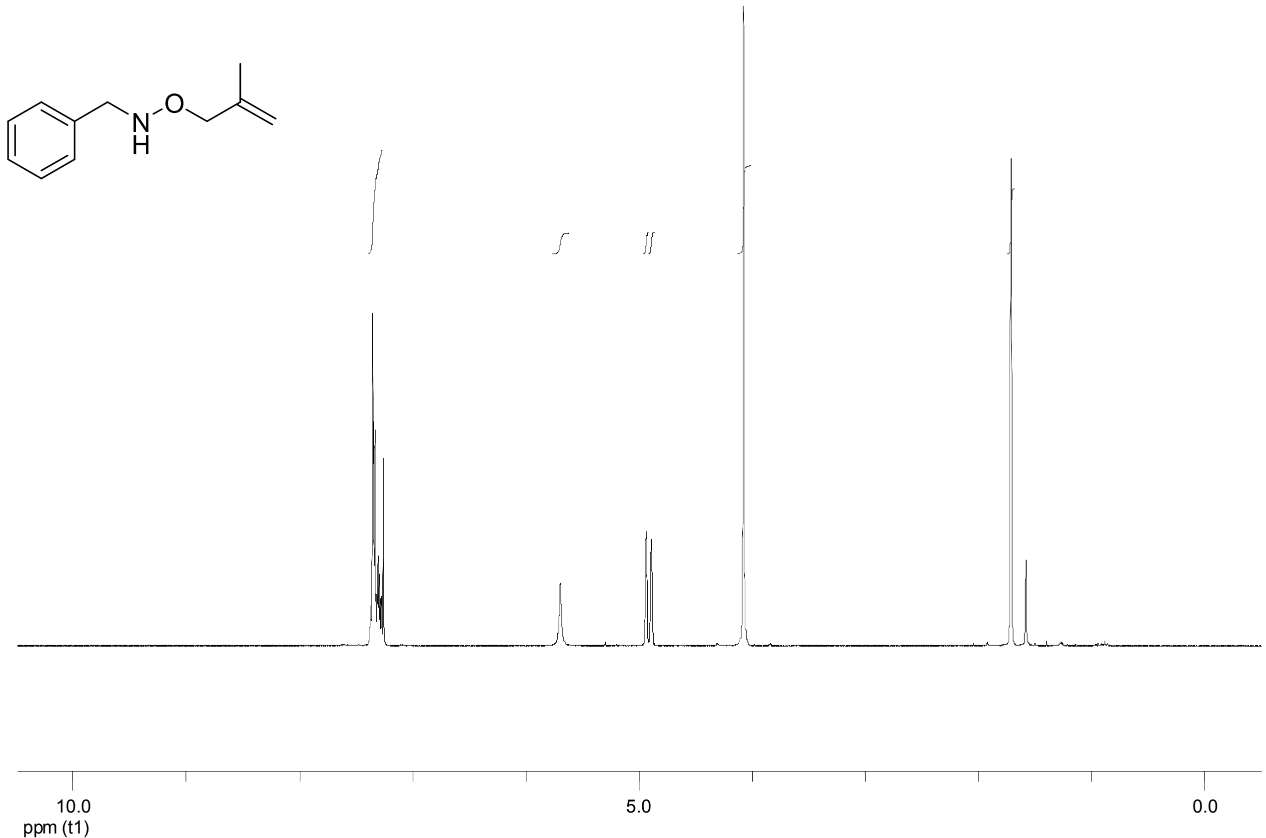
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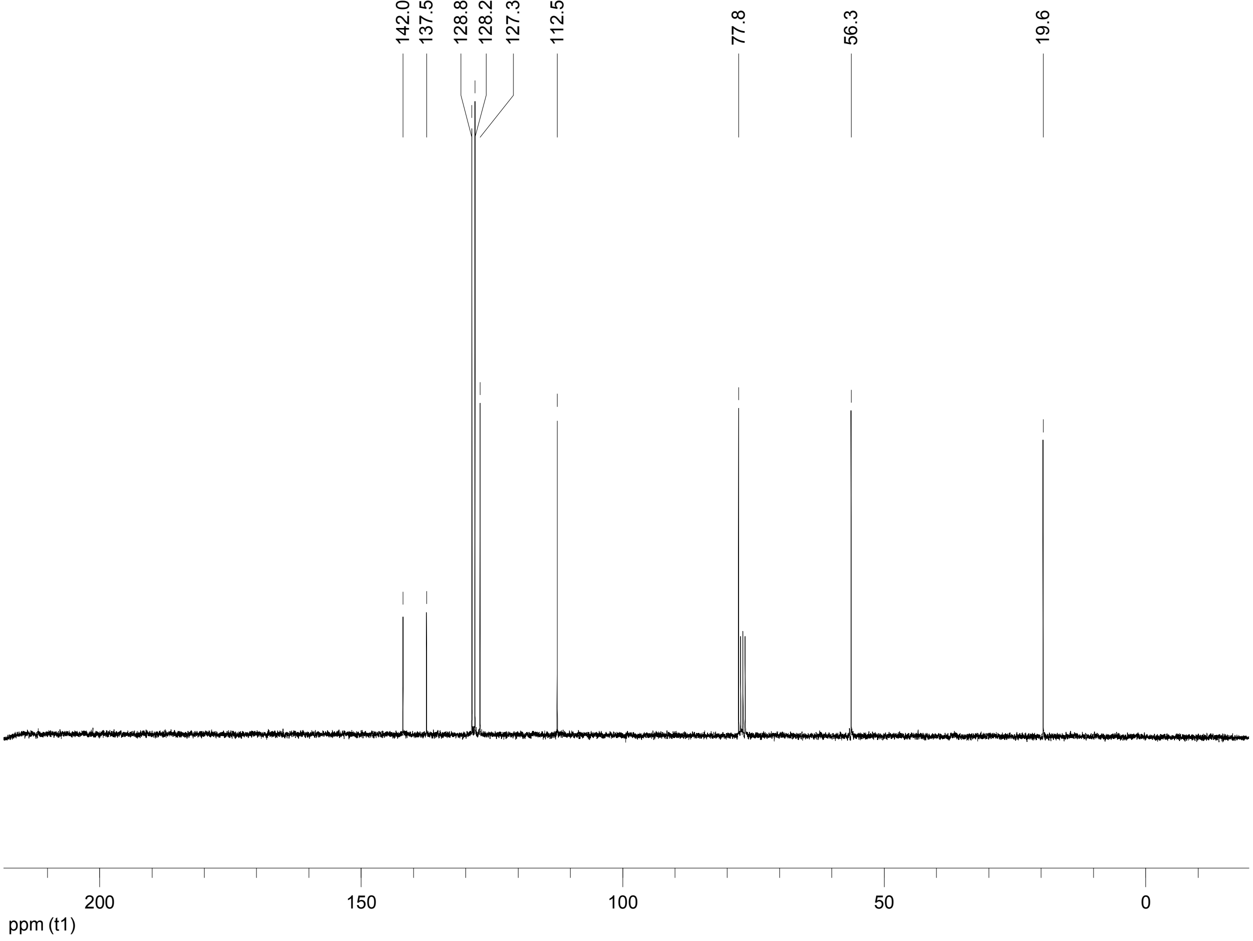
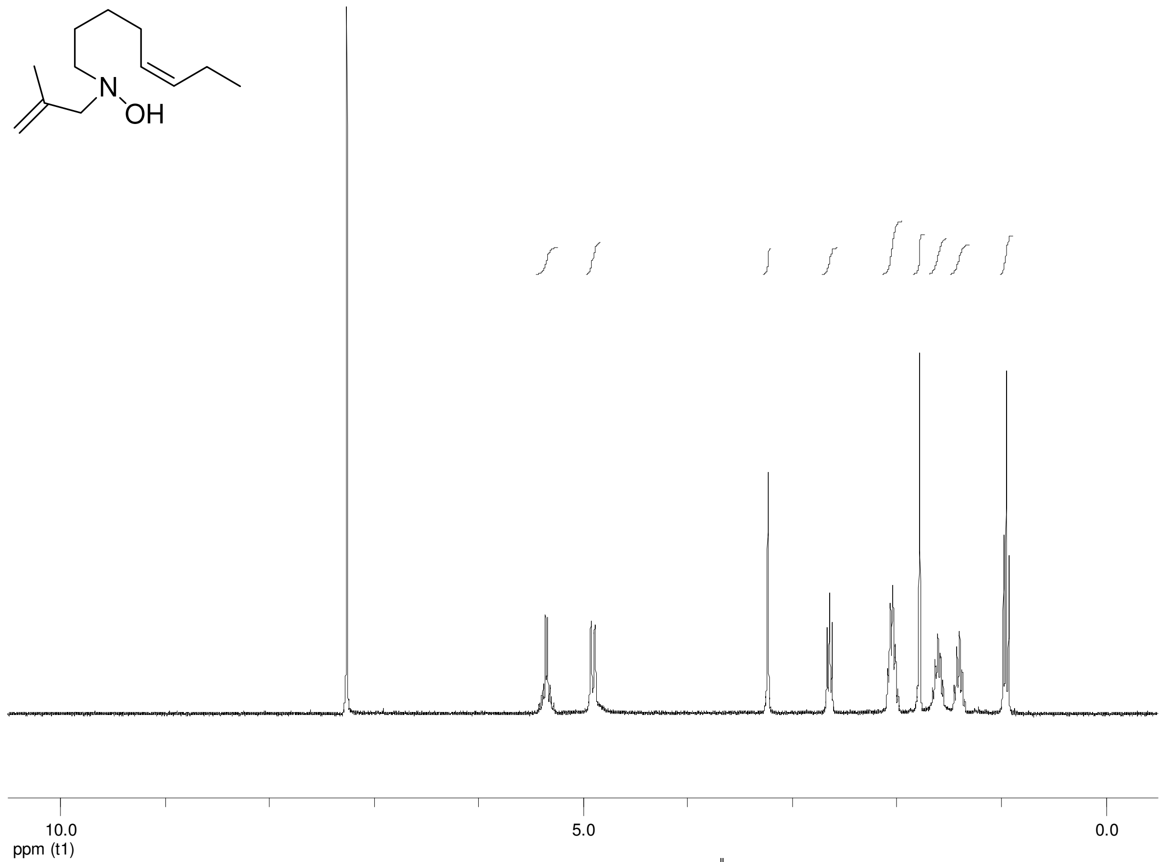
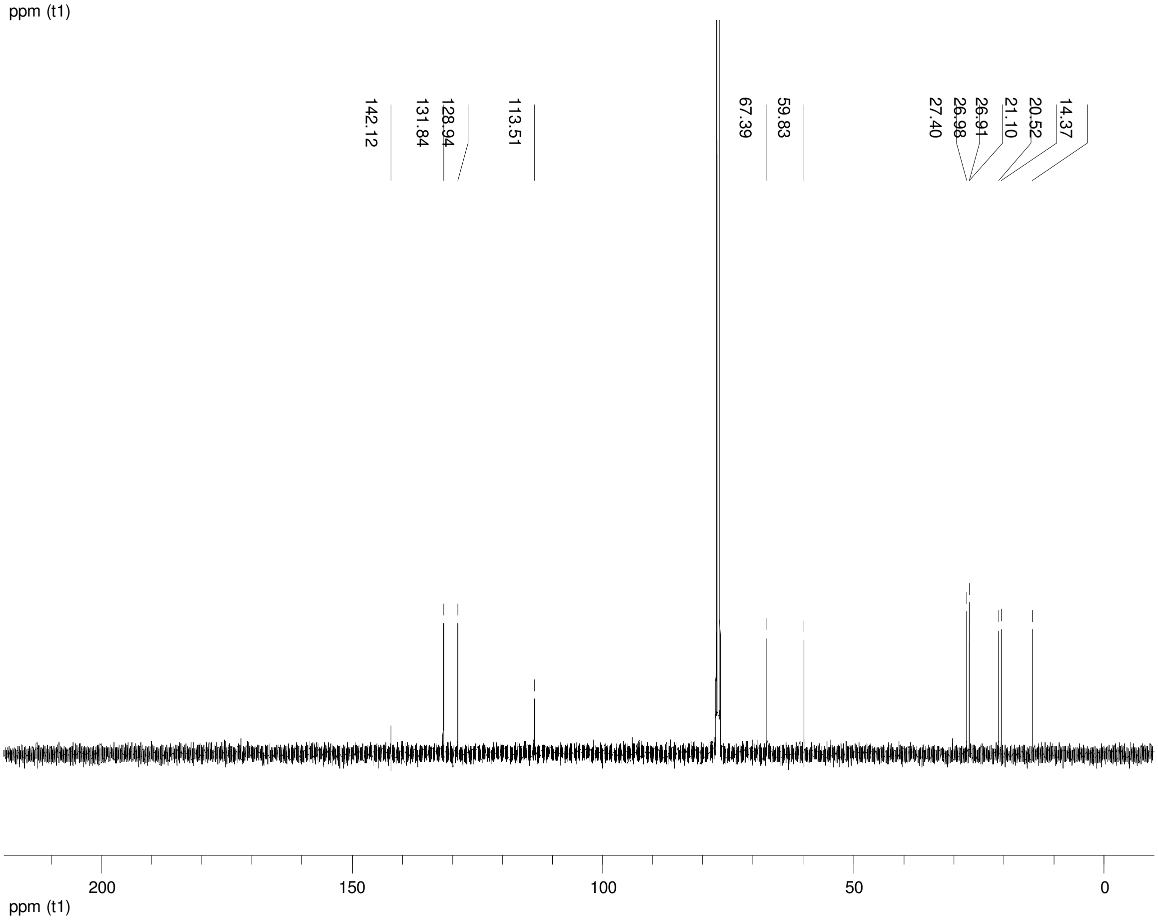
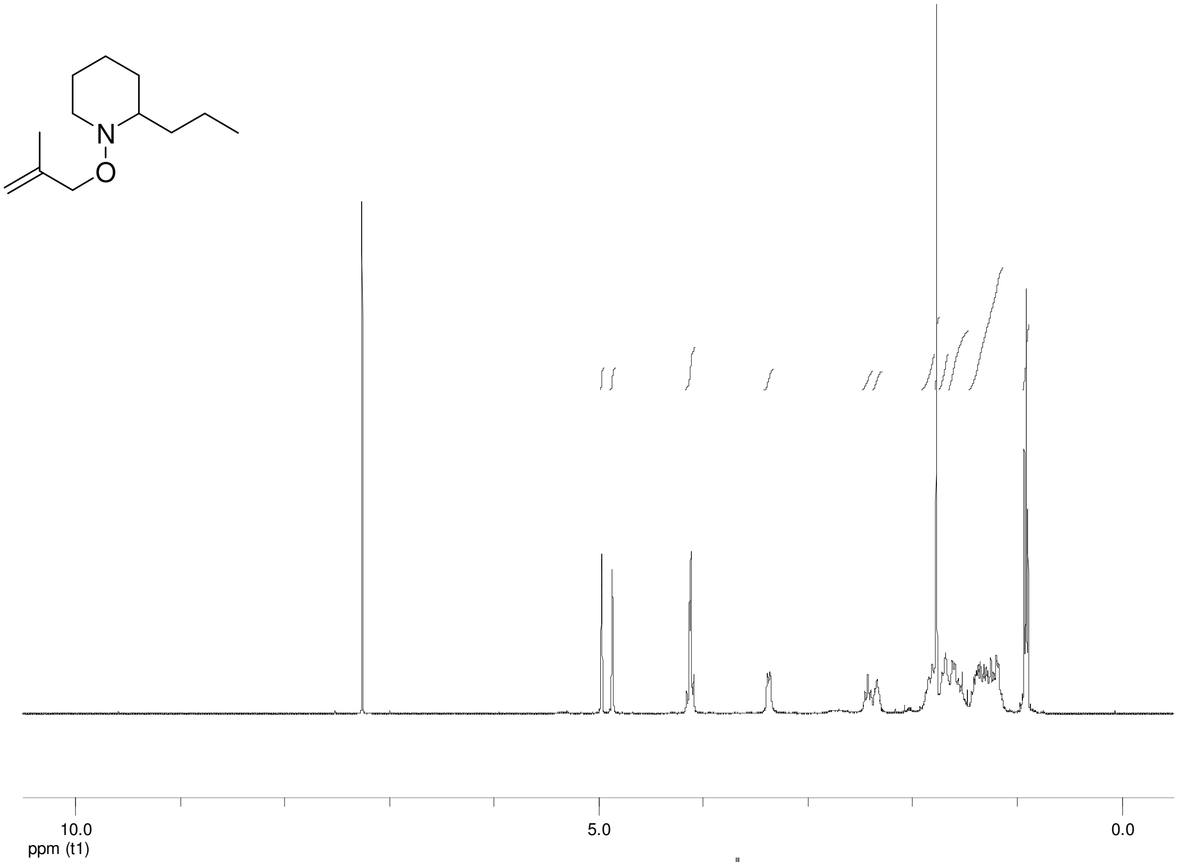
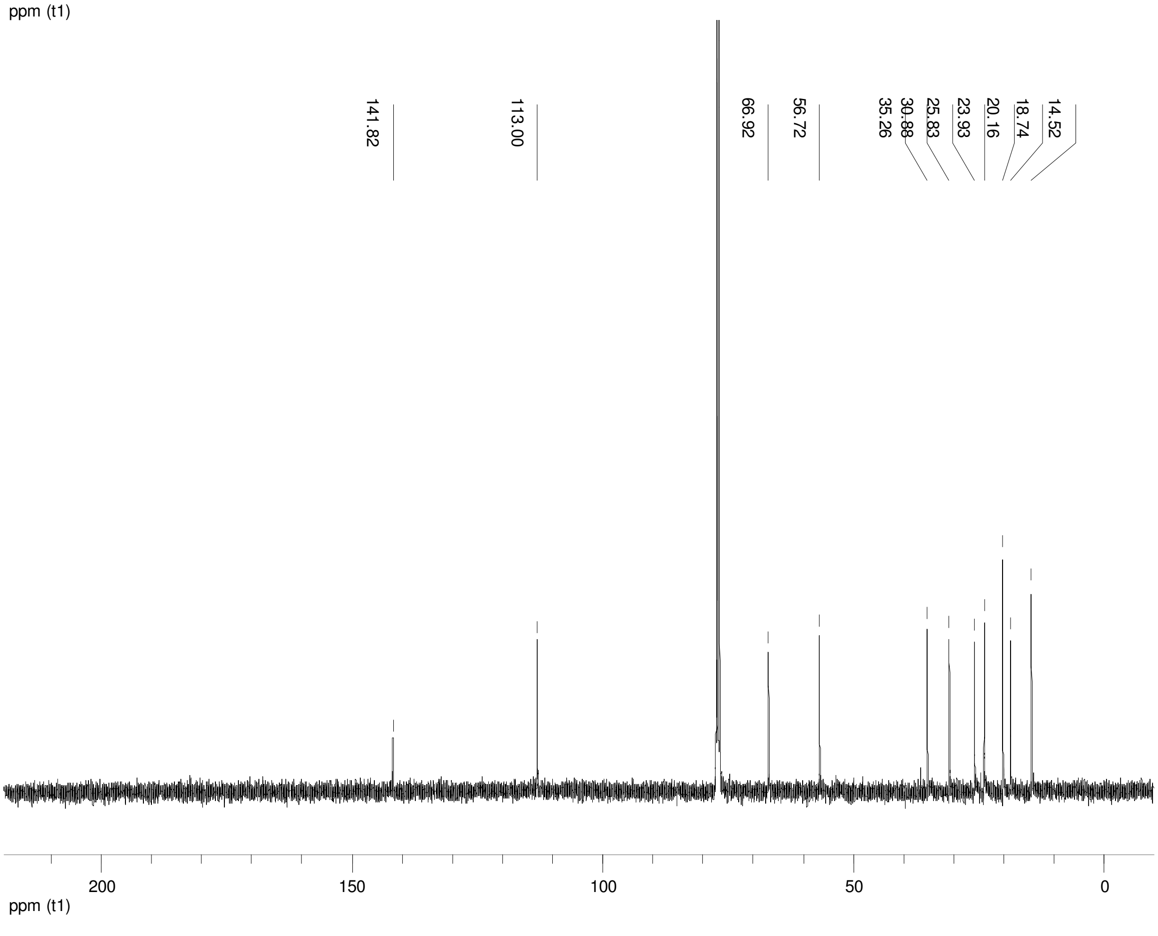
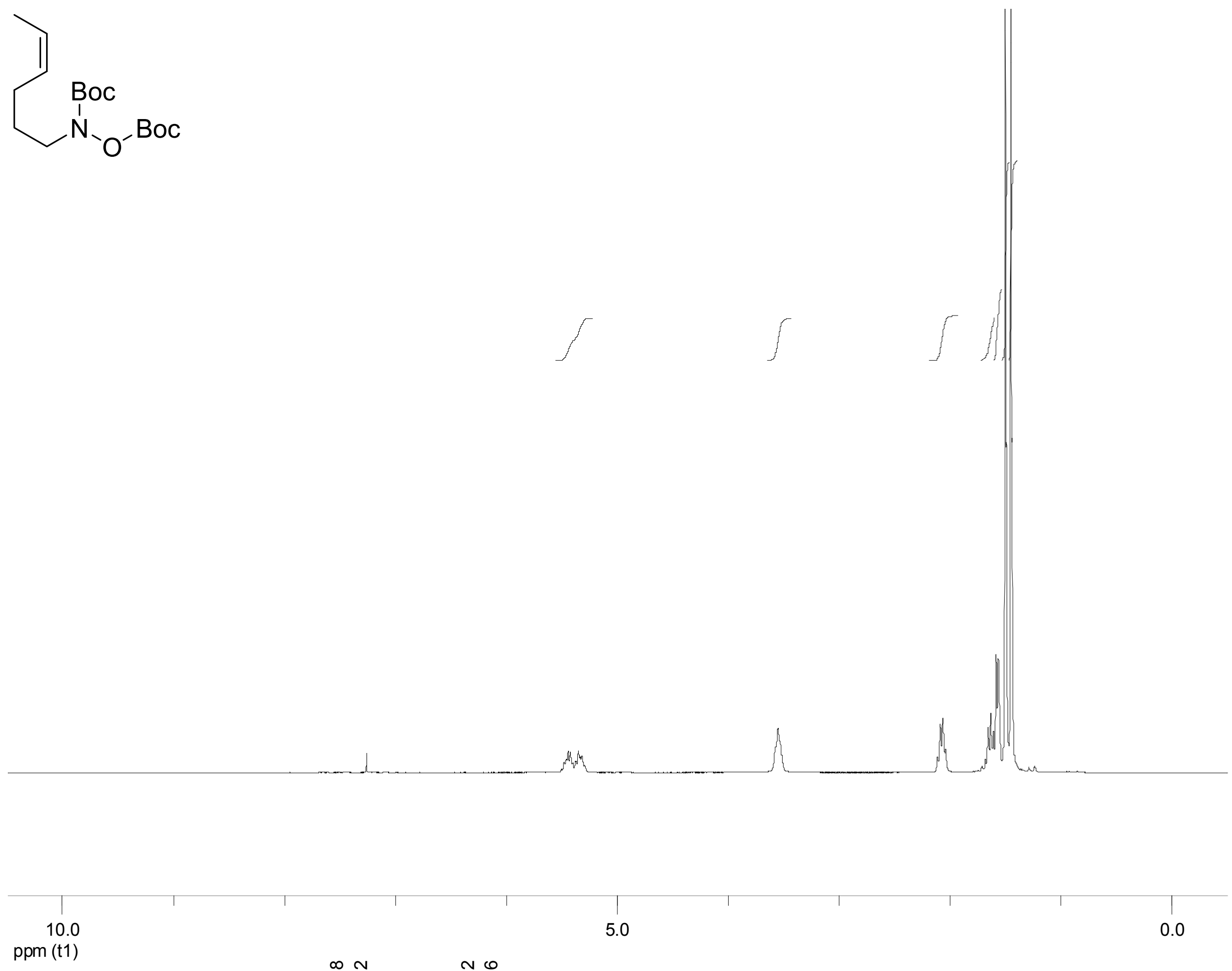

142.0
137.5
128.8
128.2
127.3
112.5
77.8
56.3
19.6
200
150
100
50
0
ppm (t1)

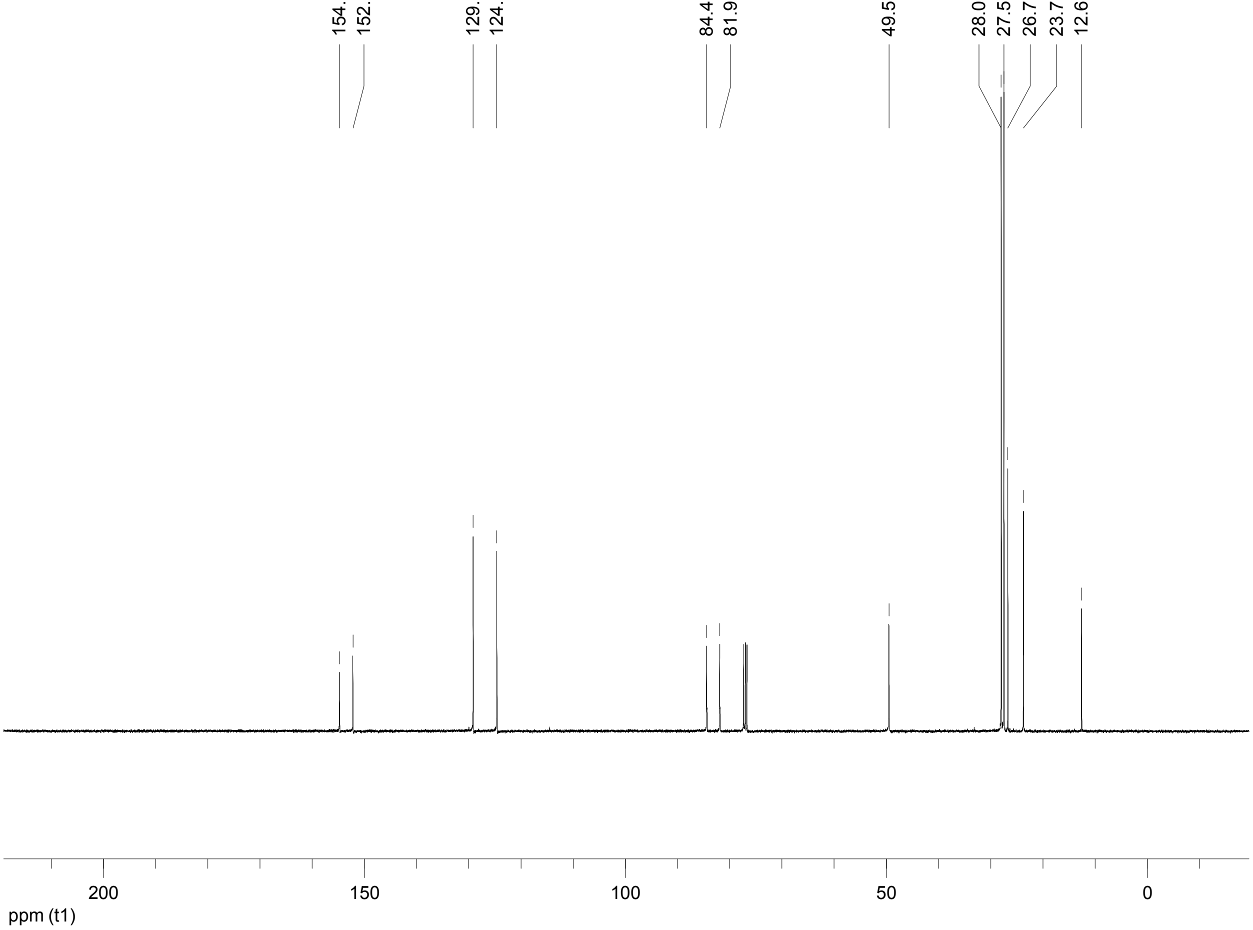

N
OH
10.0
5.0
0.0
ppm (t1)

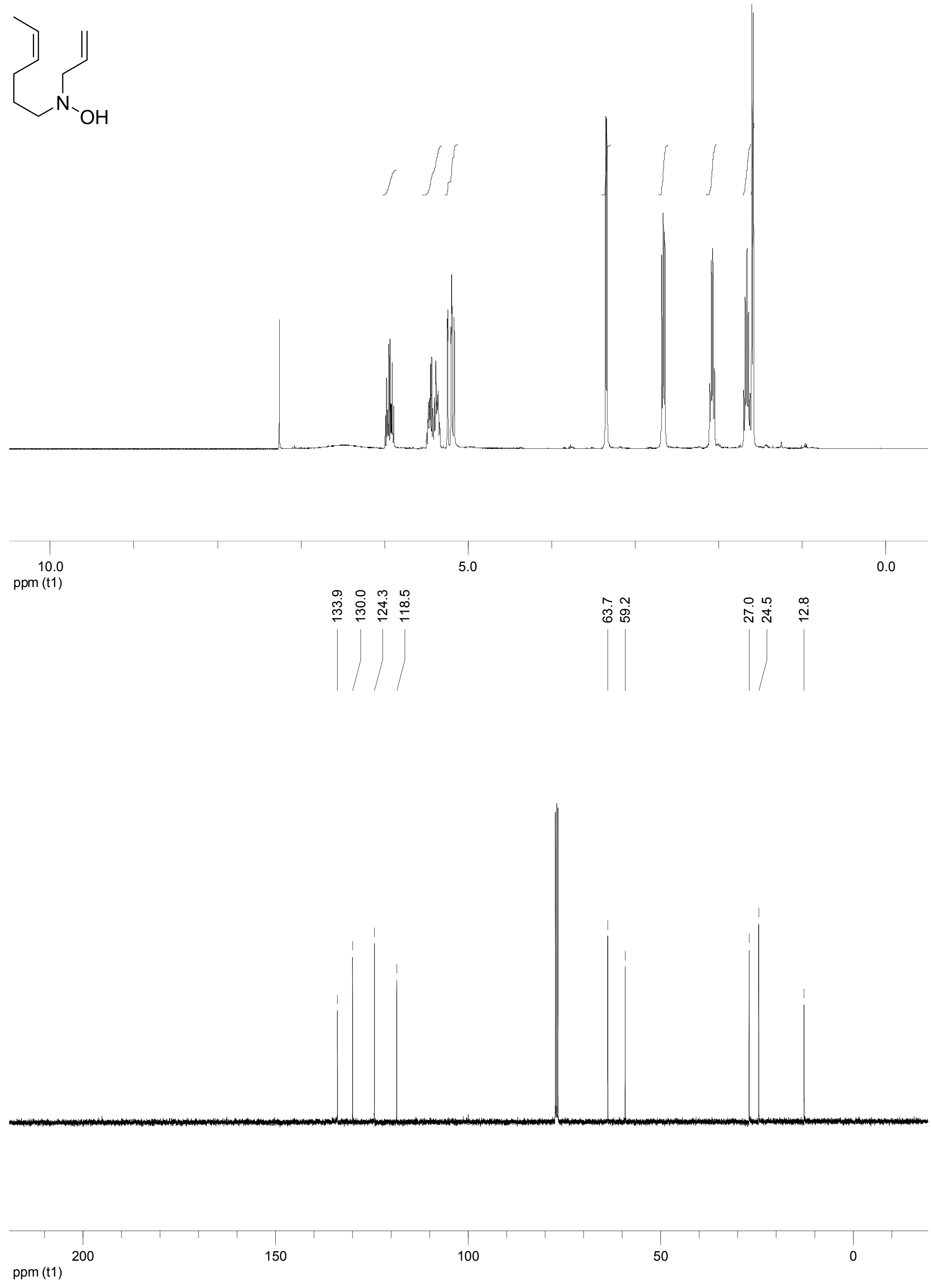

142.12
131.84
128.94
113.51
67.39
59.83
27.40
26.98
26.91
21.10
20.52
14.37
200
150
100
50
0
ppm (t1)

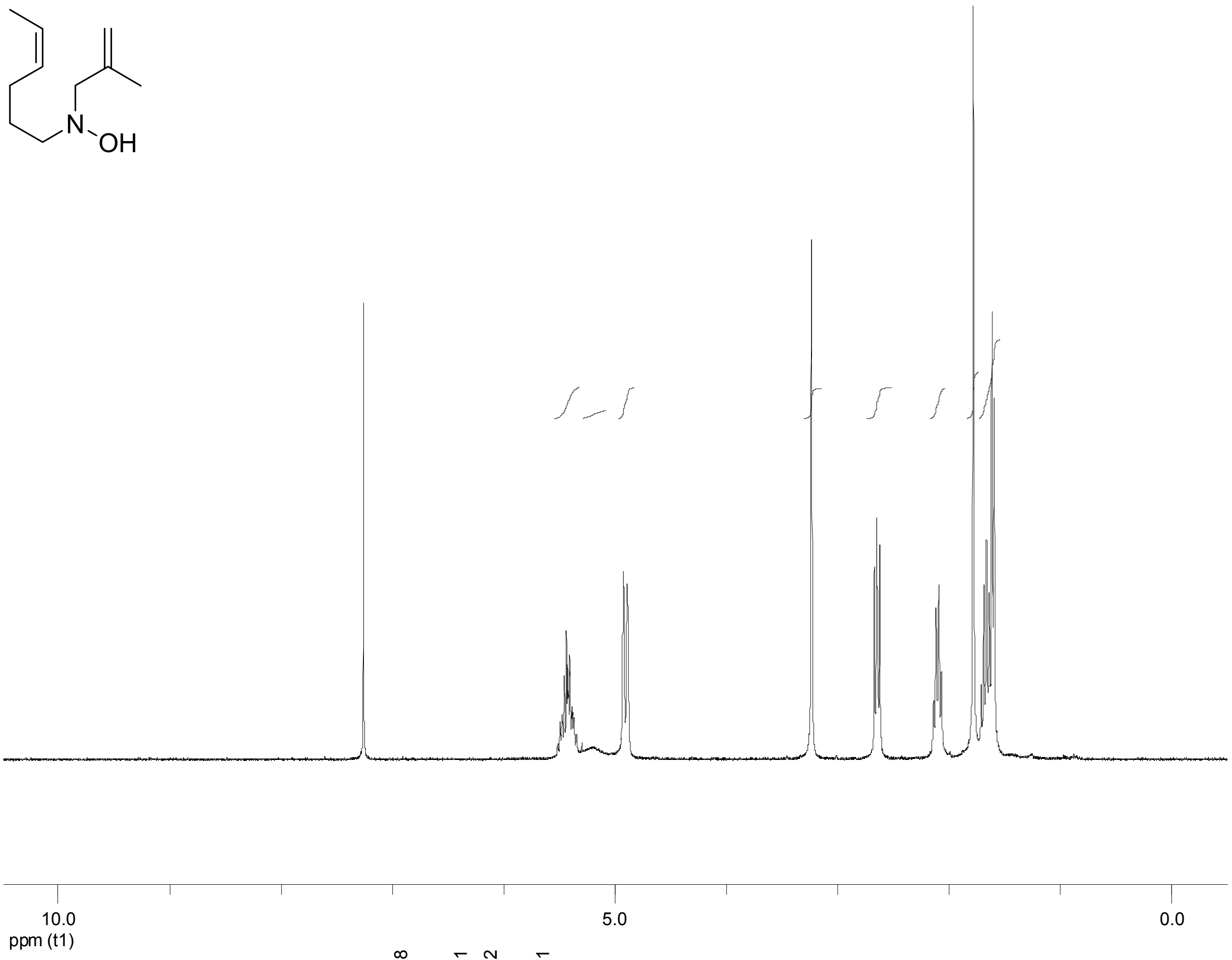

N
O
10.0
5.0
0.0
ppm (t1)

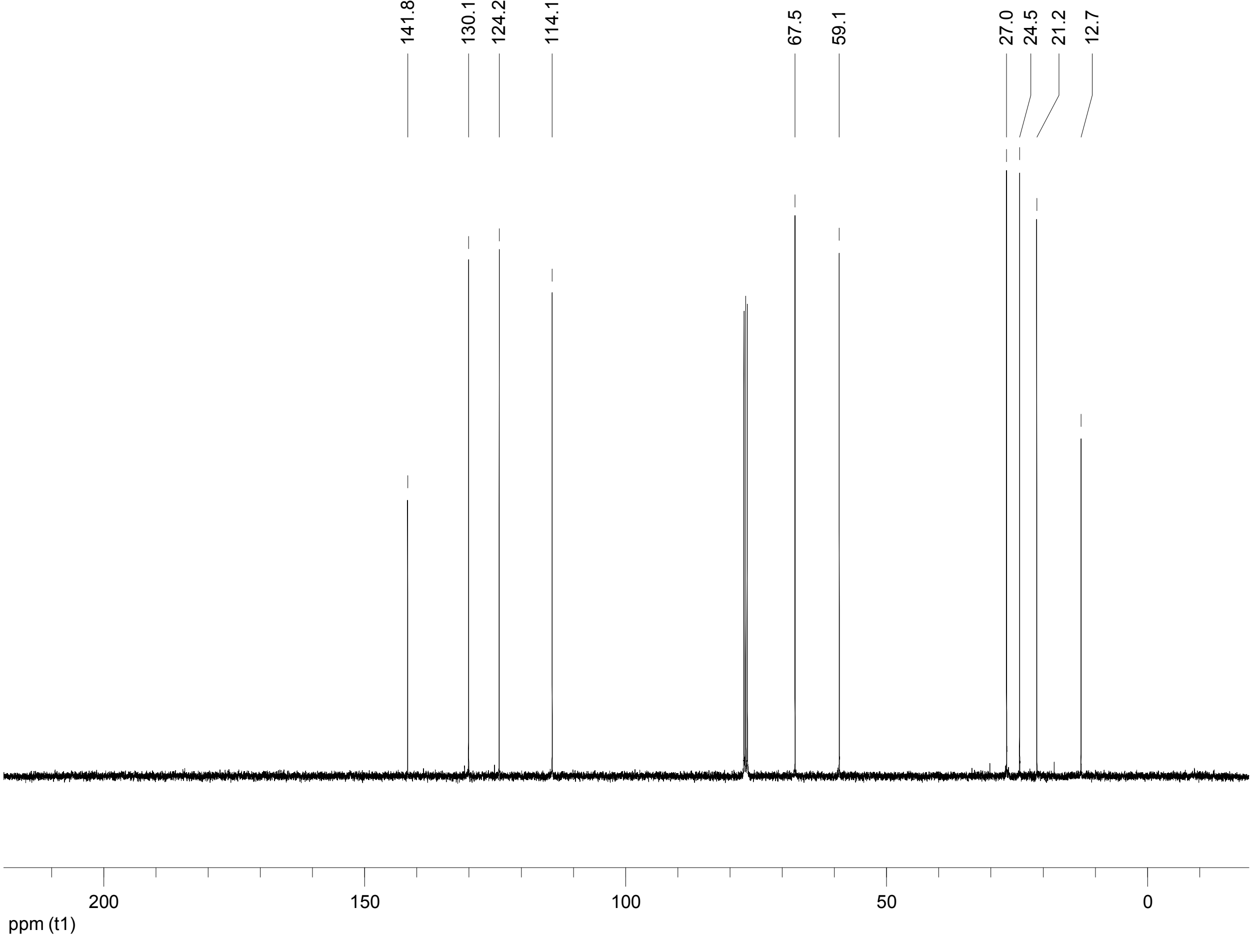

141.82
113.00
66.92
56.72
35.26
30.88
25.83
23.93
20.16
18.74
14.52
200
150
100
50
0
ppm (t1)

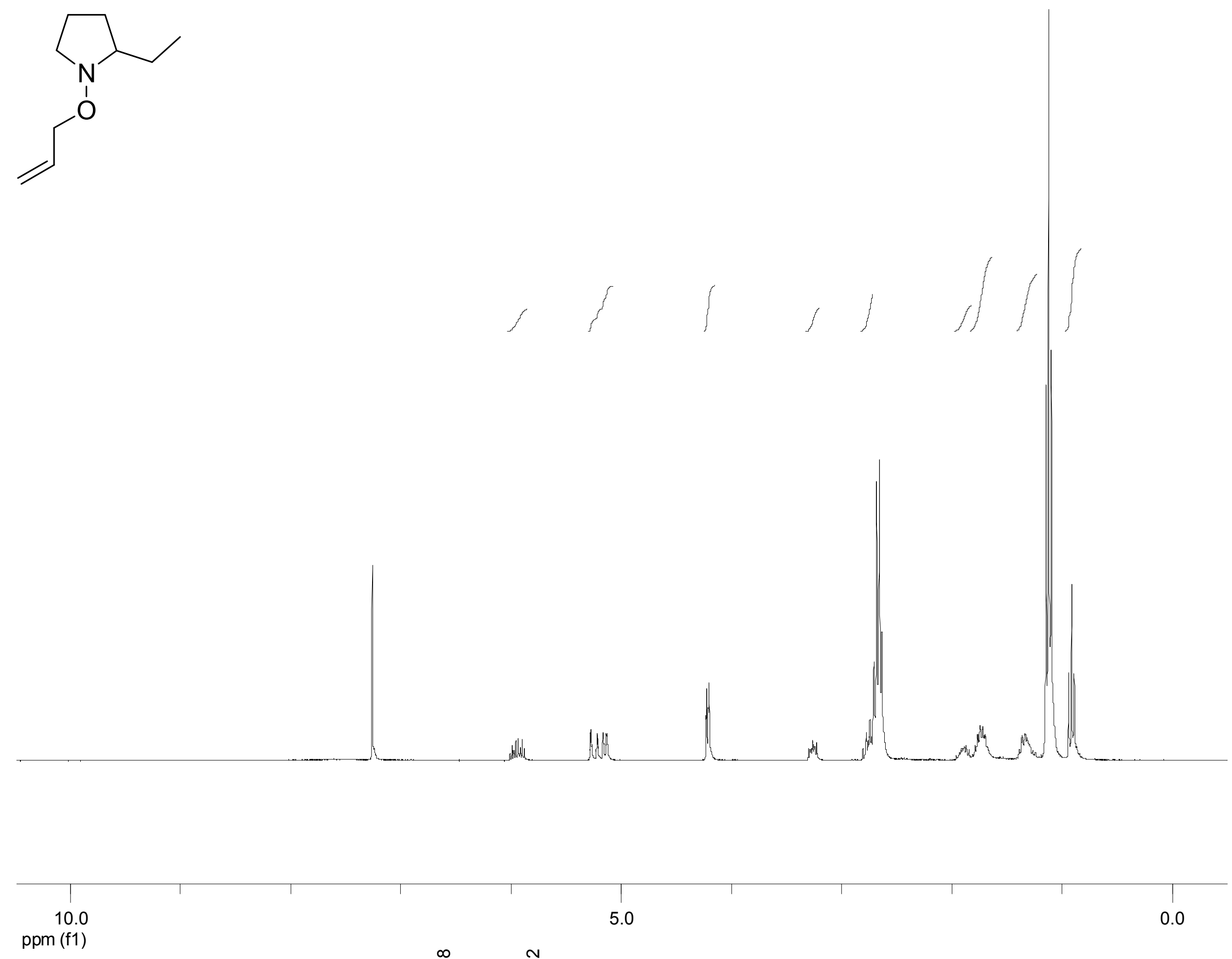

Boc
N
O
Boc
10.0
5.0
0.0
ppm (t1)

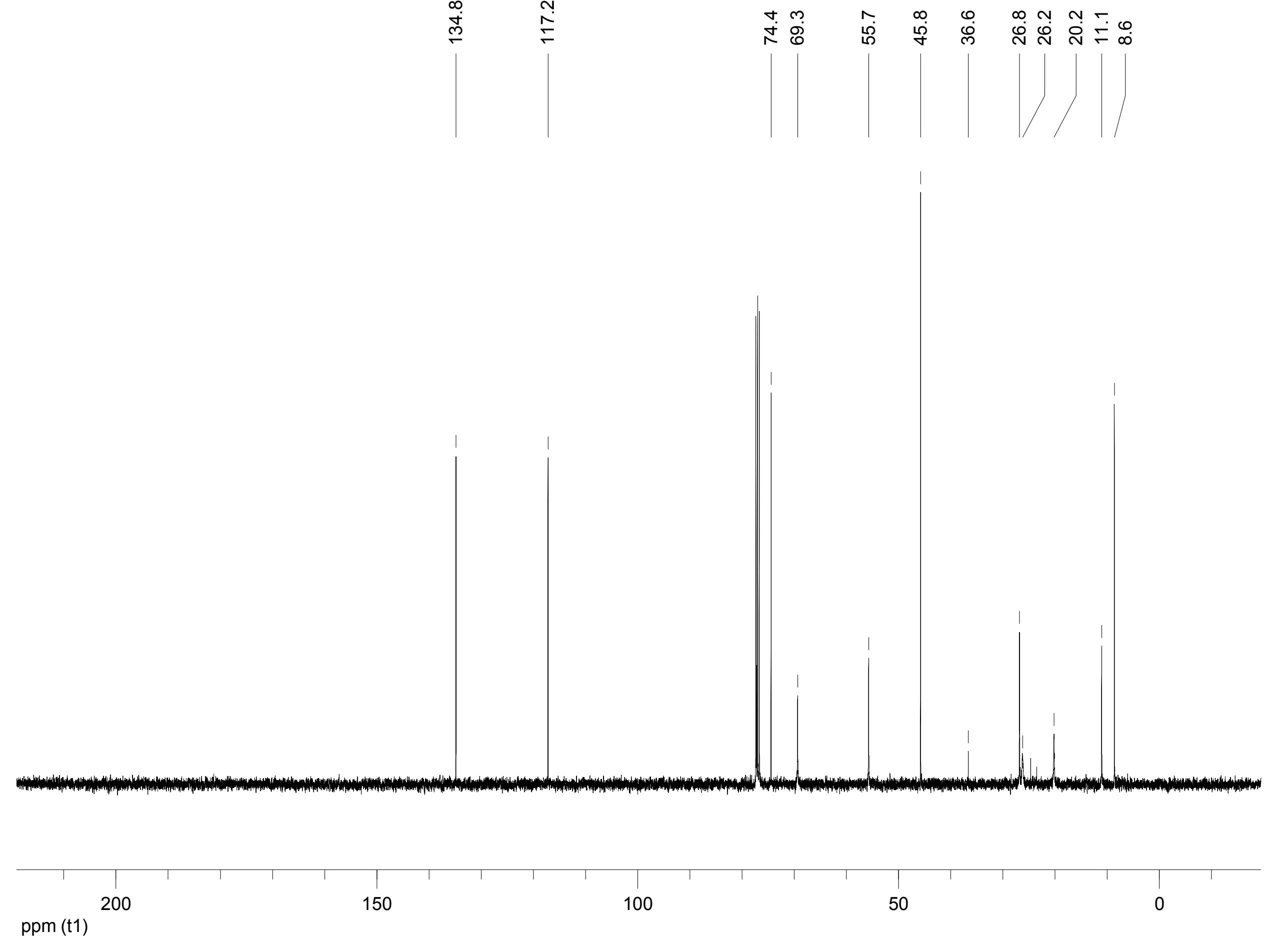

154.8
152.2
129.2
124.6
84.4
81.9
49.5
28.0
27.5
26.7
23.7
12.6
200
150
100
50
0
ppm (t1)

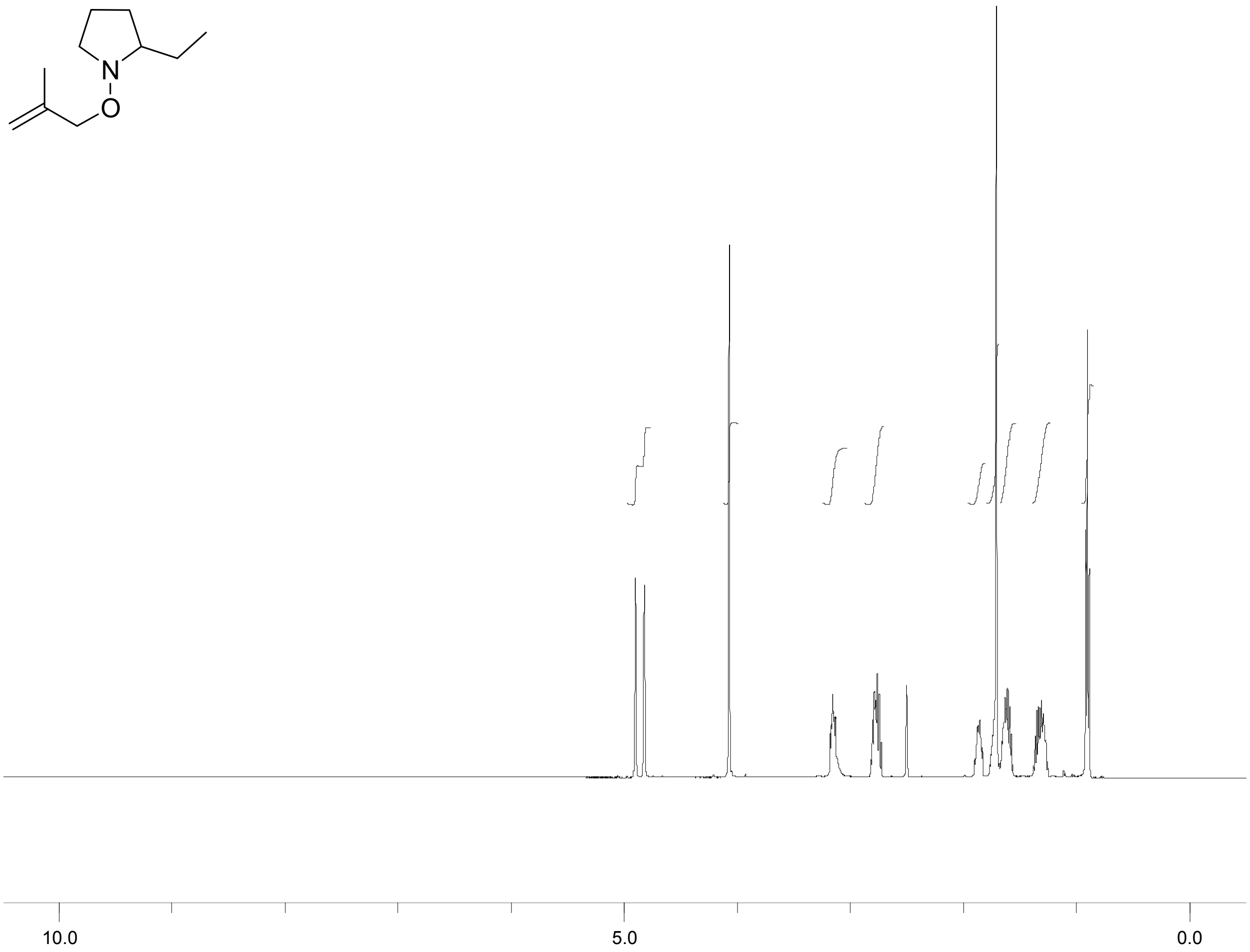

N
OH
10.0
5.0
0.0
ppm (t1)
133.9
130.0
124.3
118.5
63.7
59.2
27.0
24.5
12.8
200
150
100
50
0
ppm (t1)

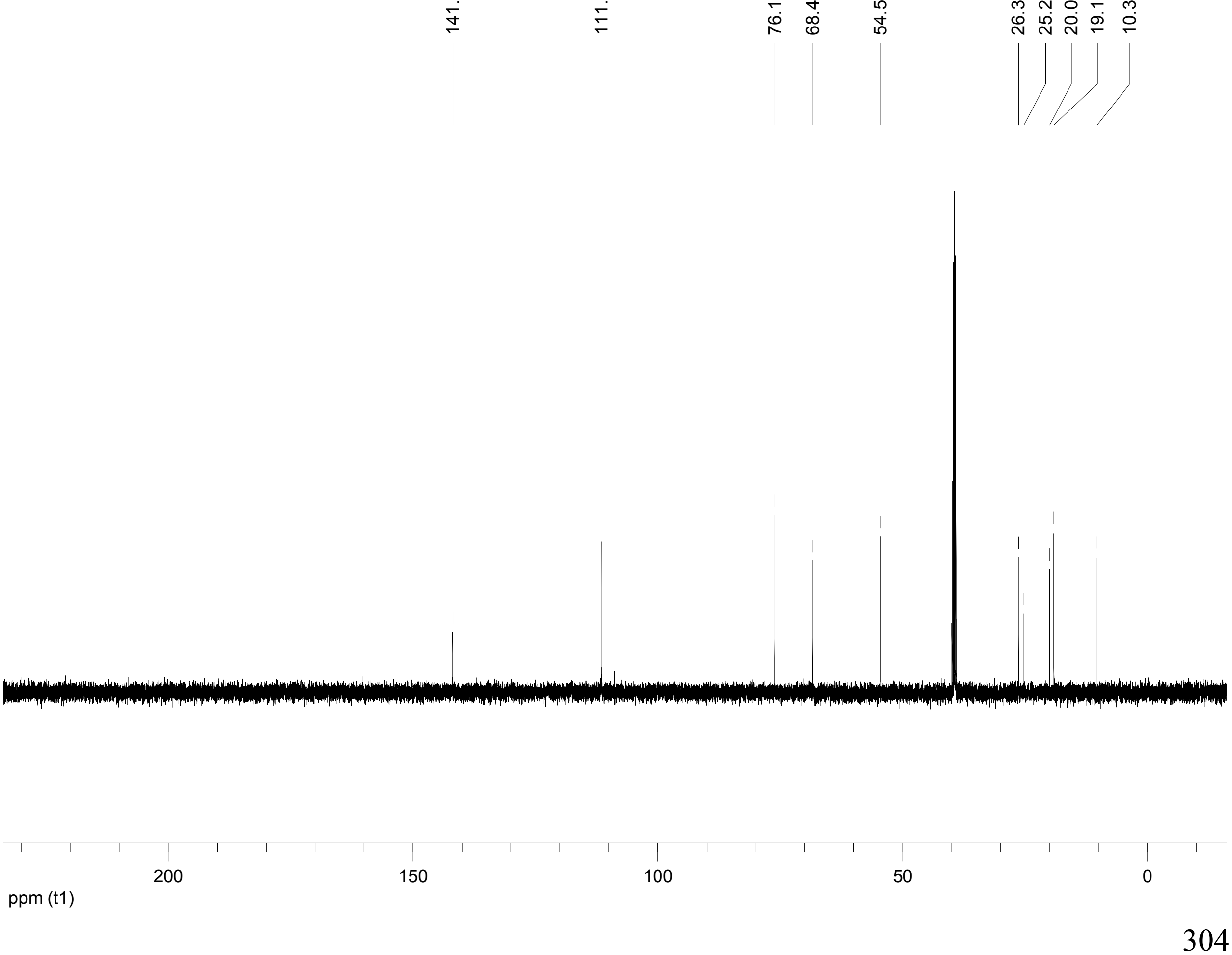

N
OH
10.0
5.0
0.0
ppm (t1)

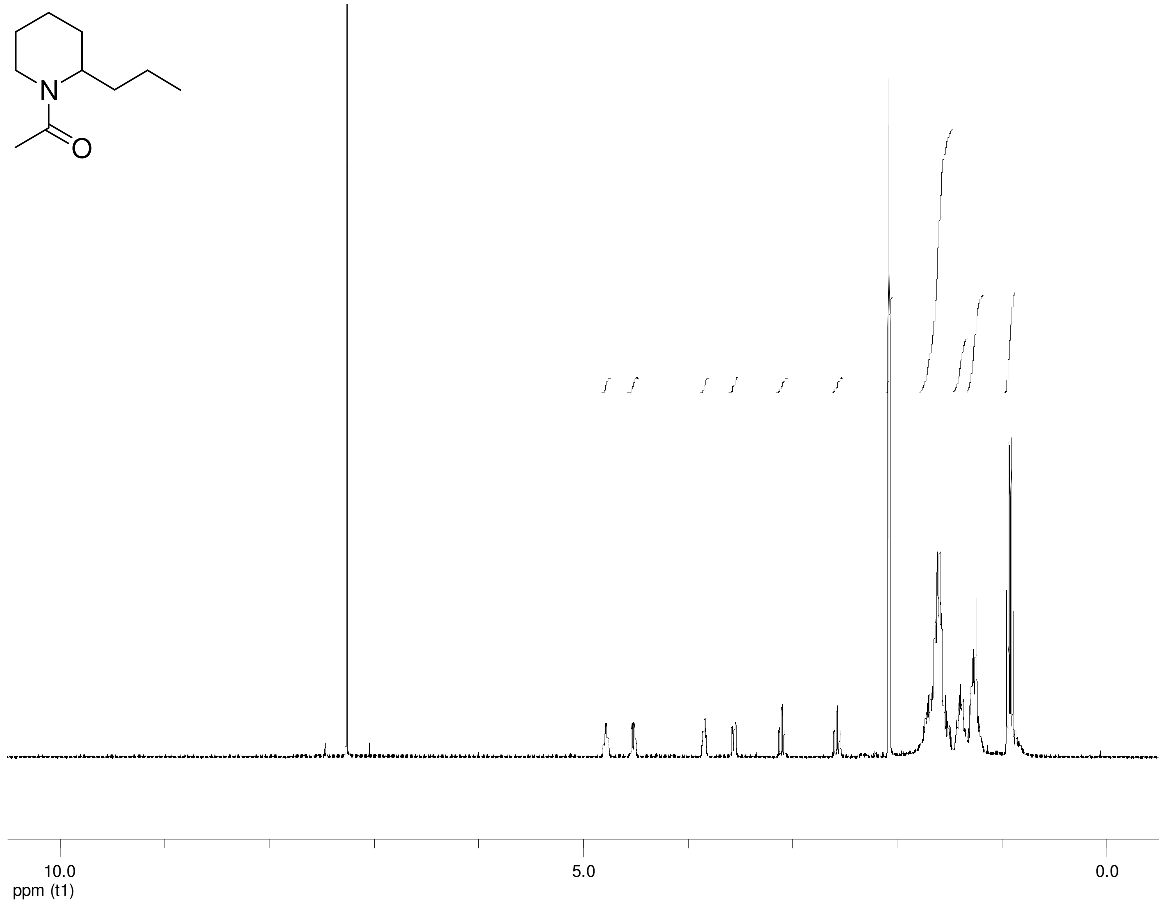

141.8
130.1
124.2
114.1
67.5
59.1
27.0
24.5
21.2
12.7
200
150
100
50
0
ppm (t1)

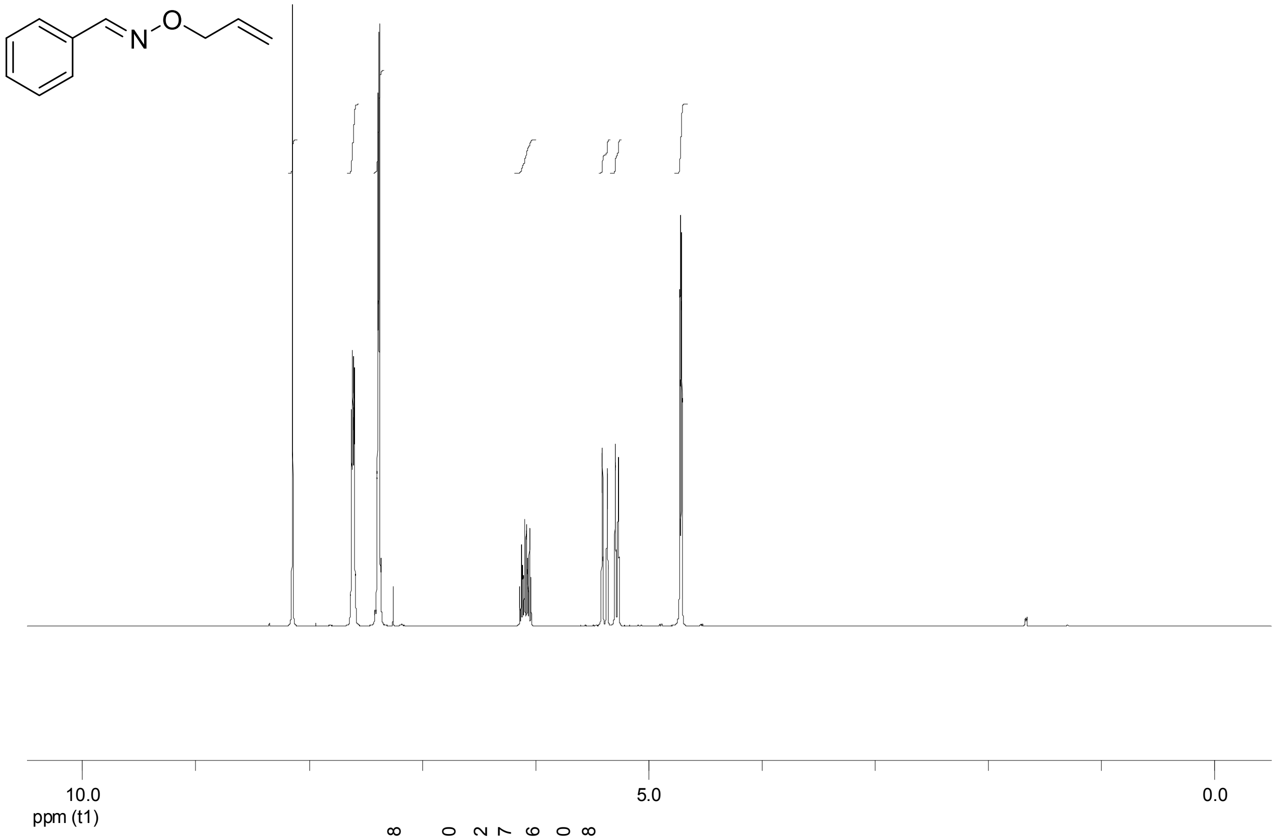

N
O
10.0
5.0
0.0
ppm (f1)

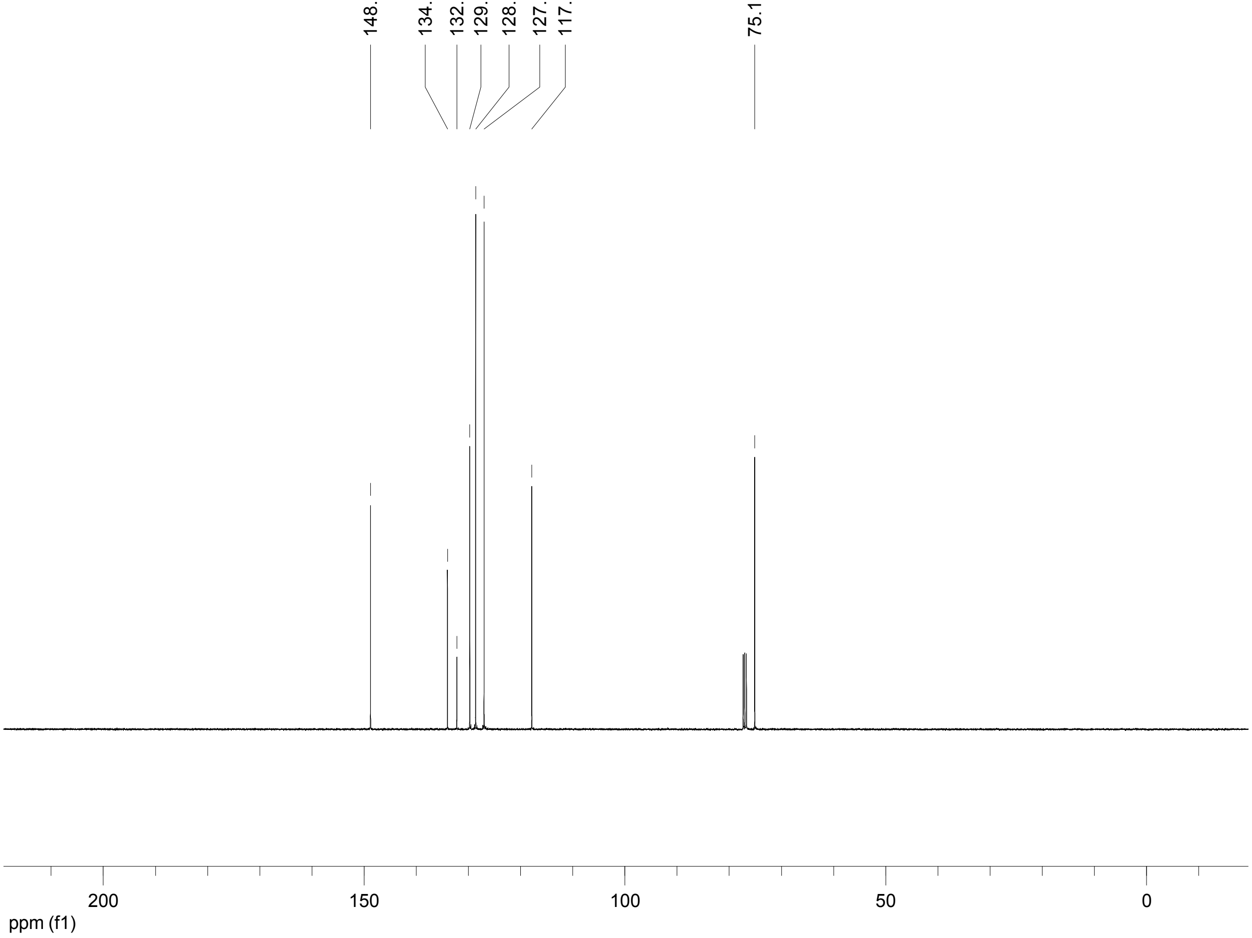

134.8
117.2
74.4
69.3
55.7
45.8
36.6
26.8
26.2
20.2
11.1
8.6
200
150
100
50
0
ppm (t1)

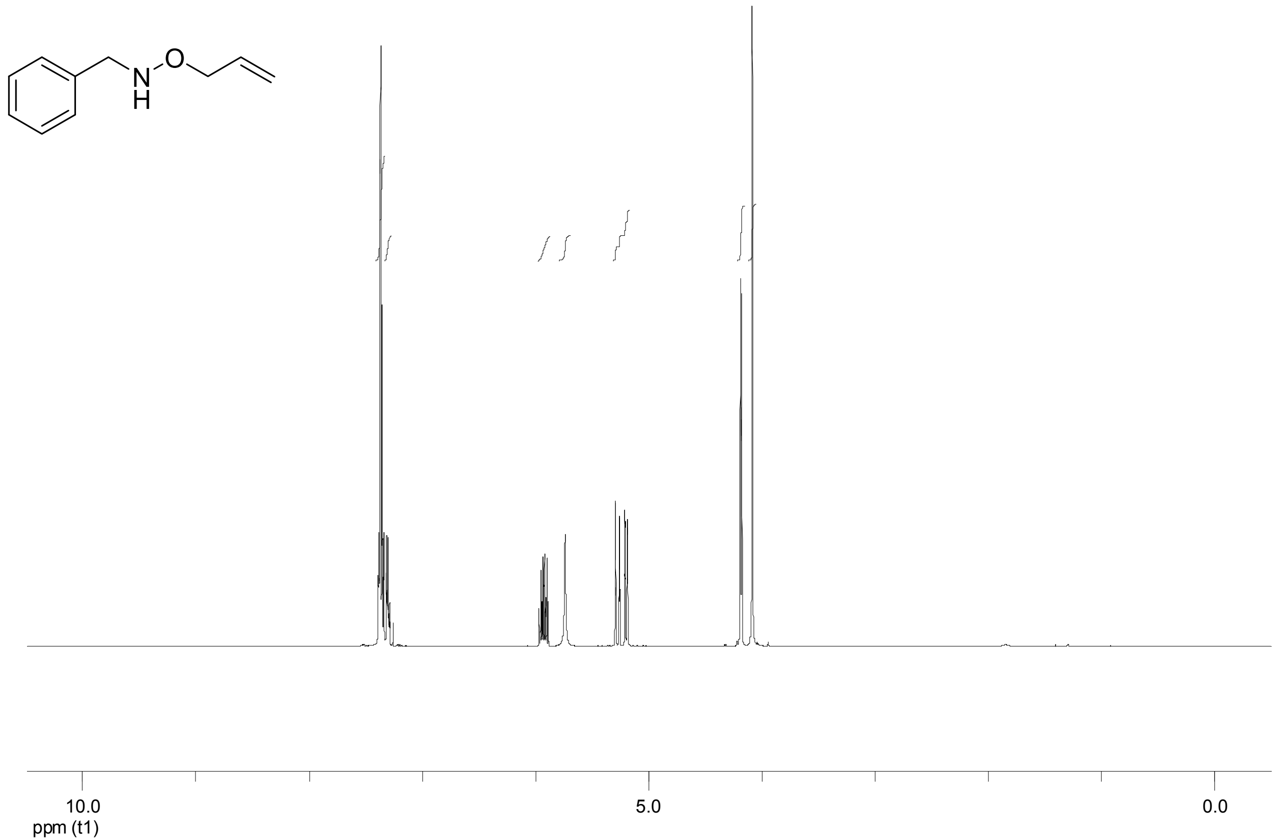

N
O
10.0
5.0
0.0
ppm (f1)

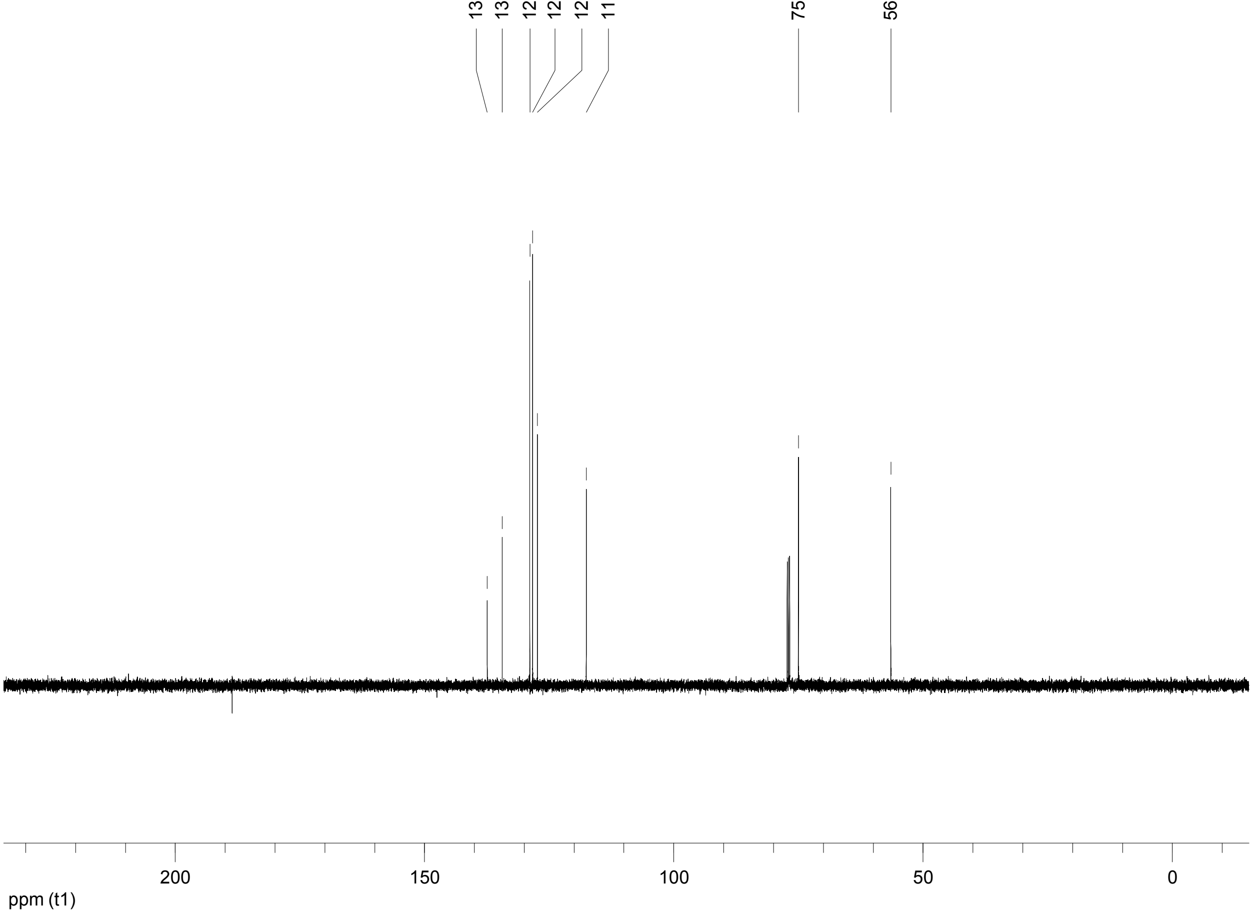

141.9
111.4
76.1
68.4
54.5
26.3
25.2
20.0
19.1
10.3
200
150
100
50
0
ppm (t1)

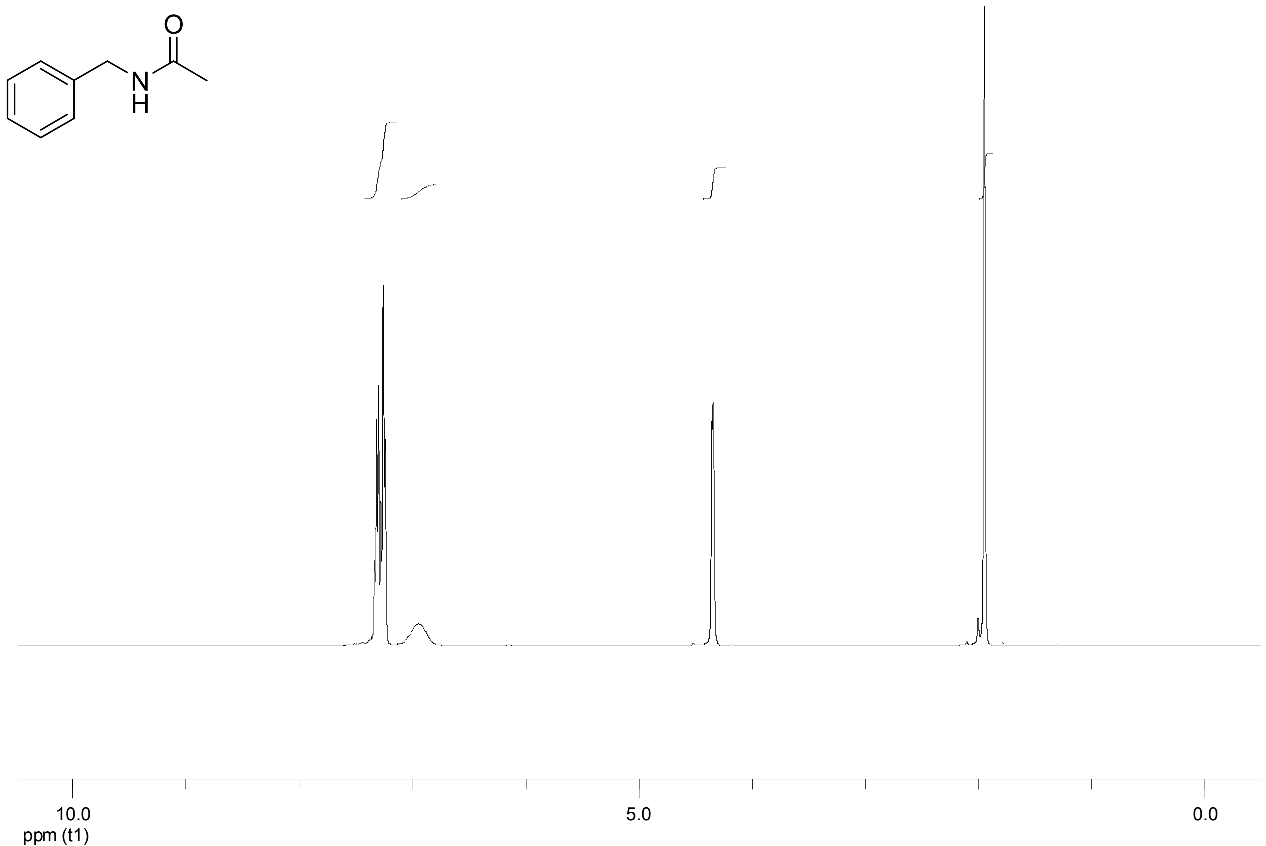

N
O
10.0
5.0
0.0
ppm (t1)

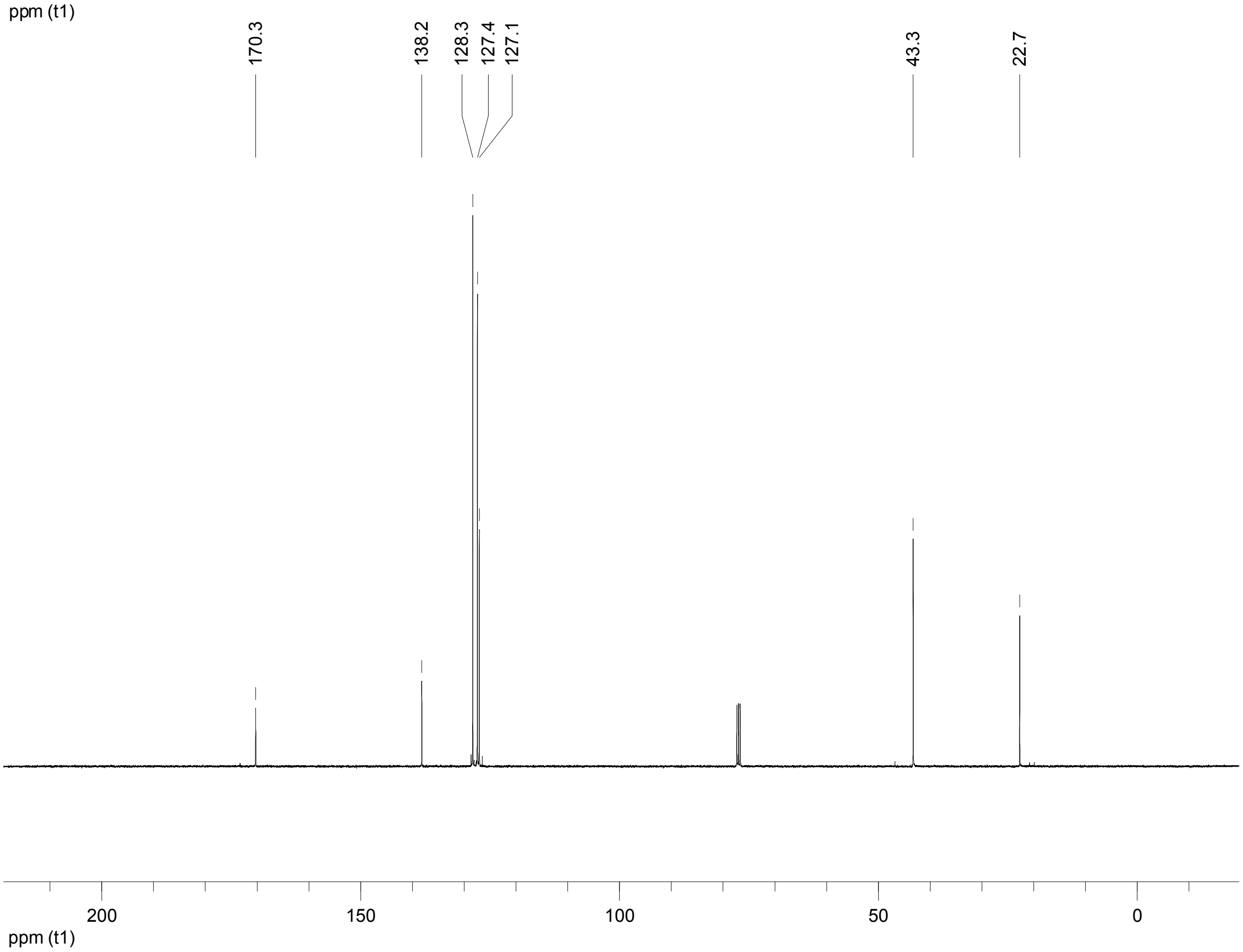

N
O
10.0
5.0
0.0
ppm (t1)

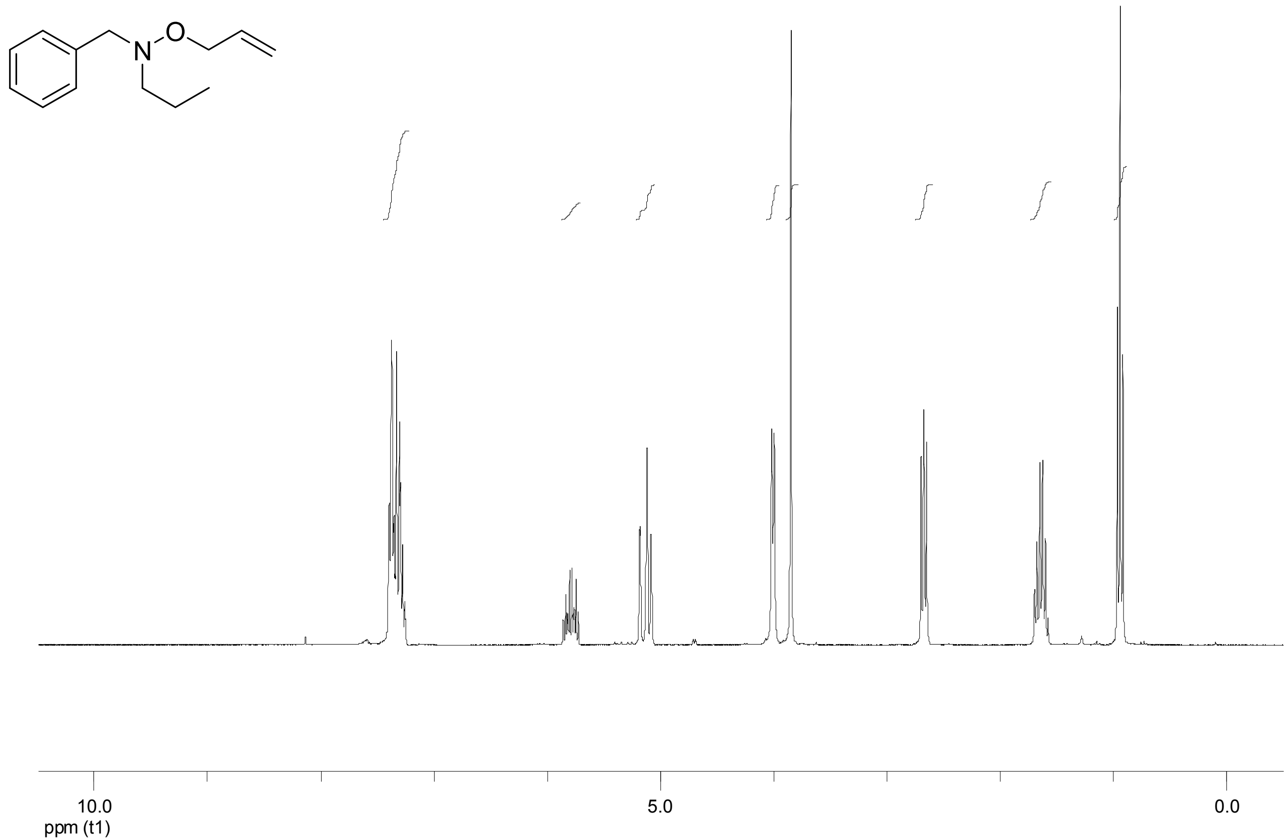

148.8
134.0
132.2
129.7
128.6
127.0
117.8
75.1
200
150
100
50
0
ppm (f1)

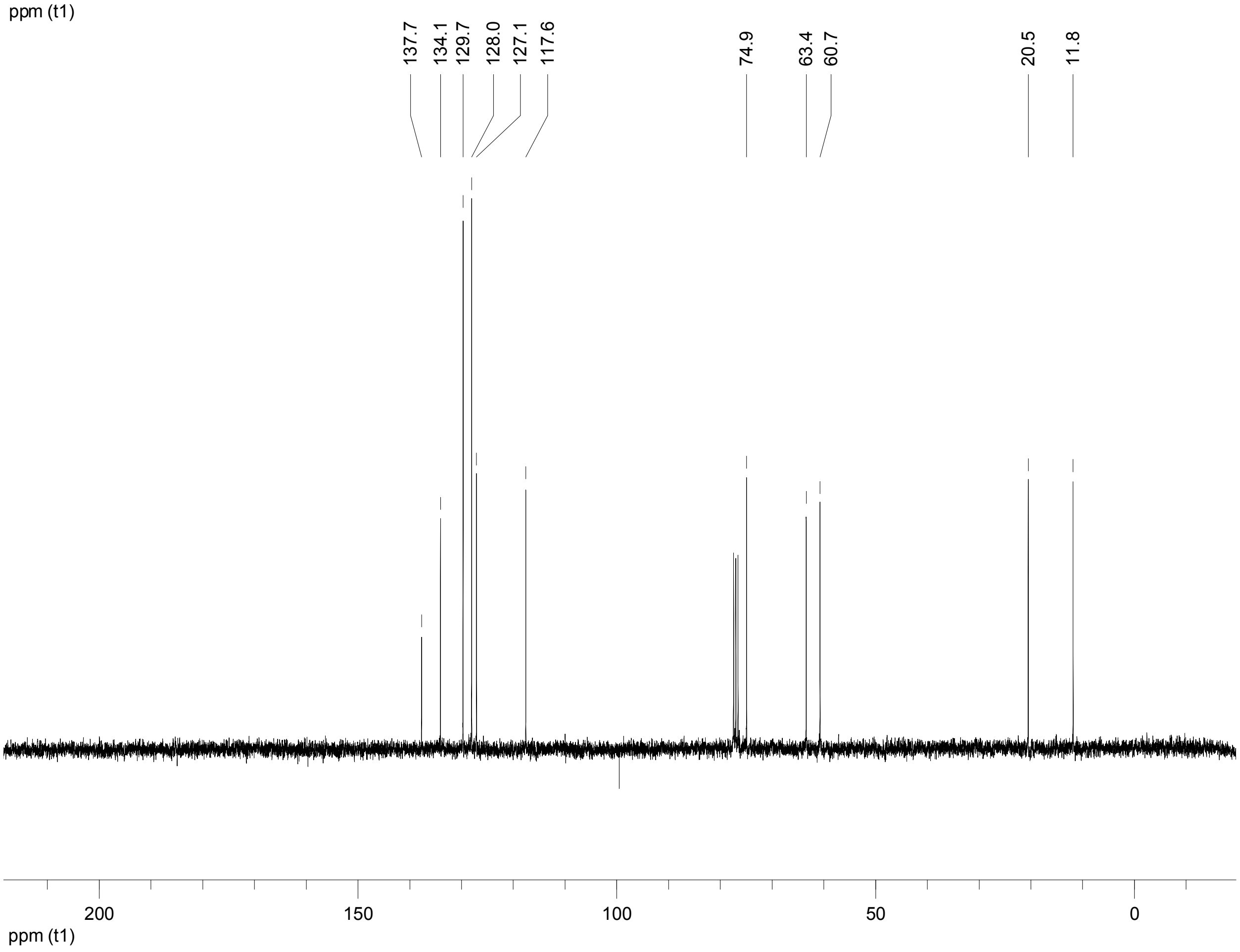

N
H
O
10.0
5.0
0.0
ppm (t1)

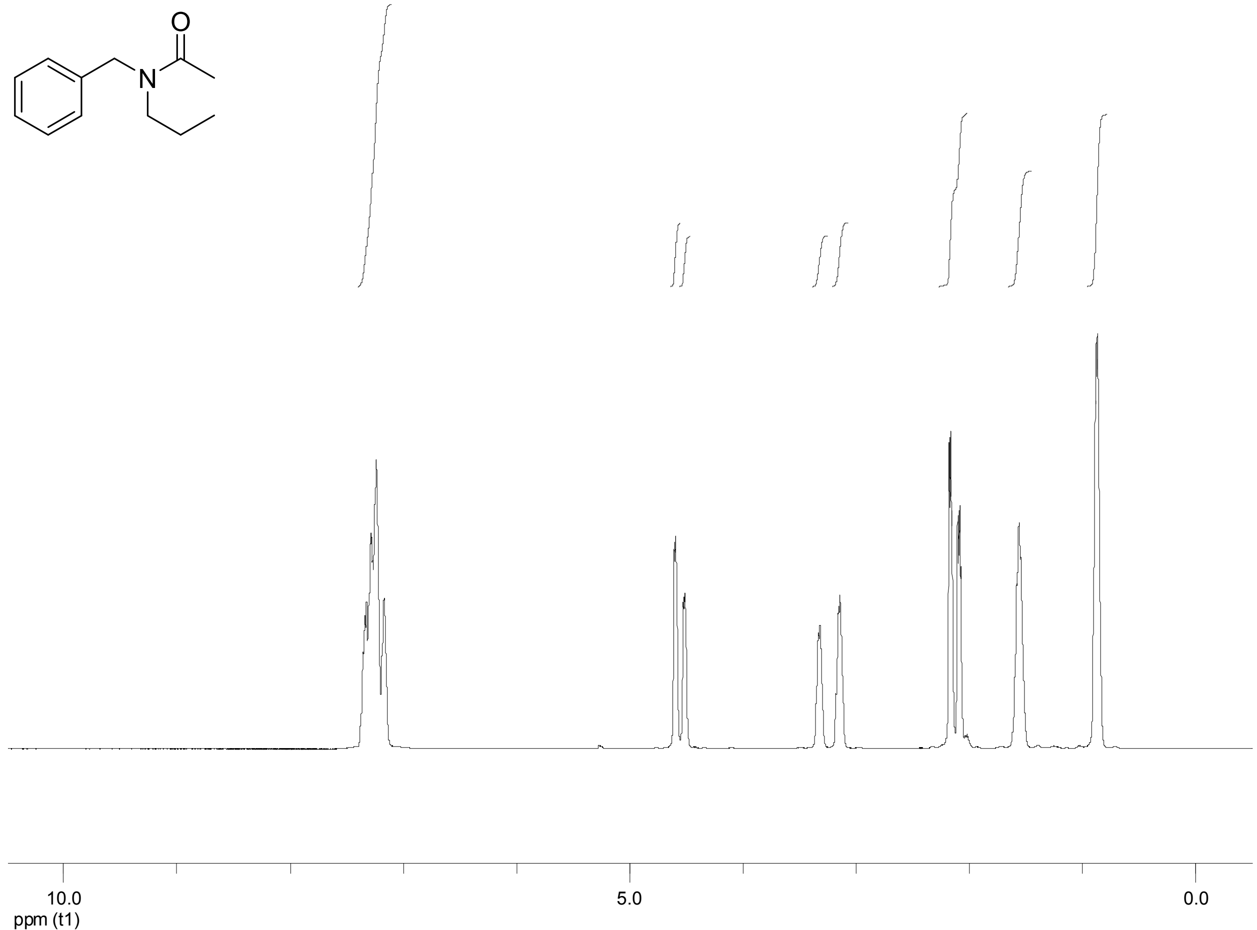

137.4
134.4
128.9
128.3
127.3
117.5
75.0
56.5
200
150
100
50
0
ppm (t1)

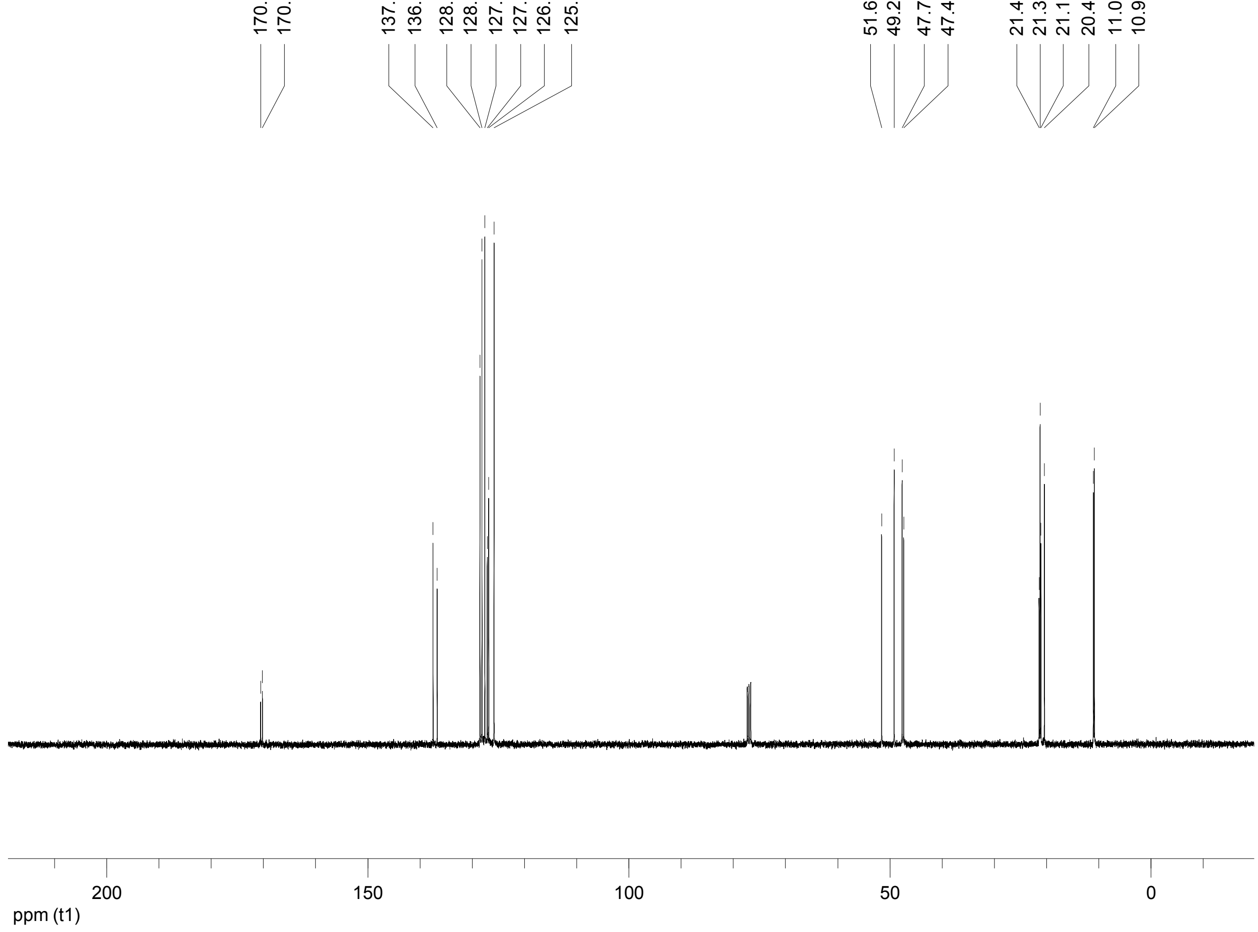

O
N
H
10.0
5.0
0.0
ppm (t1)

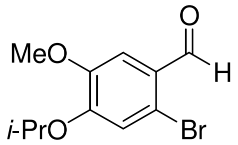

170.3
138.2
128.3
127.4
127.1
43.3
22.7
200
150
100
50
0
ppm (t1)

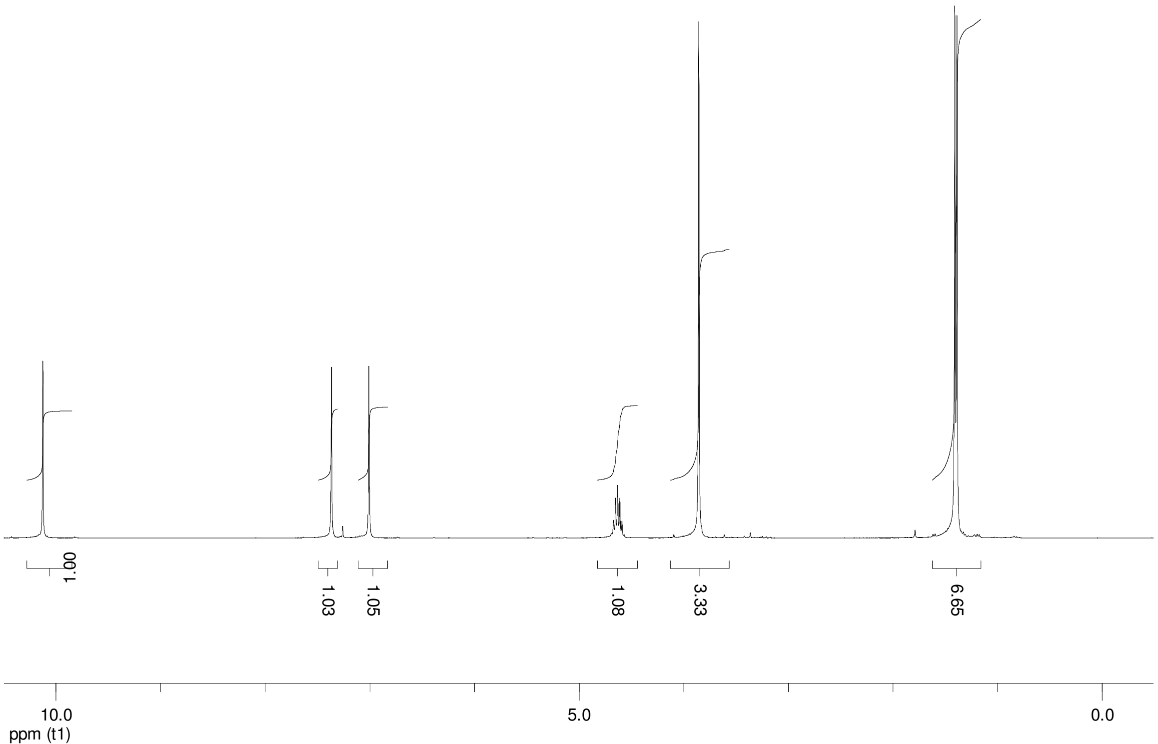

10.0
5.0
0.0
ppm (t1)

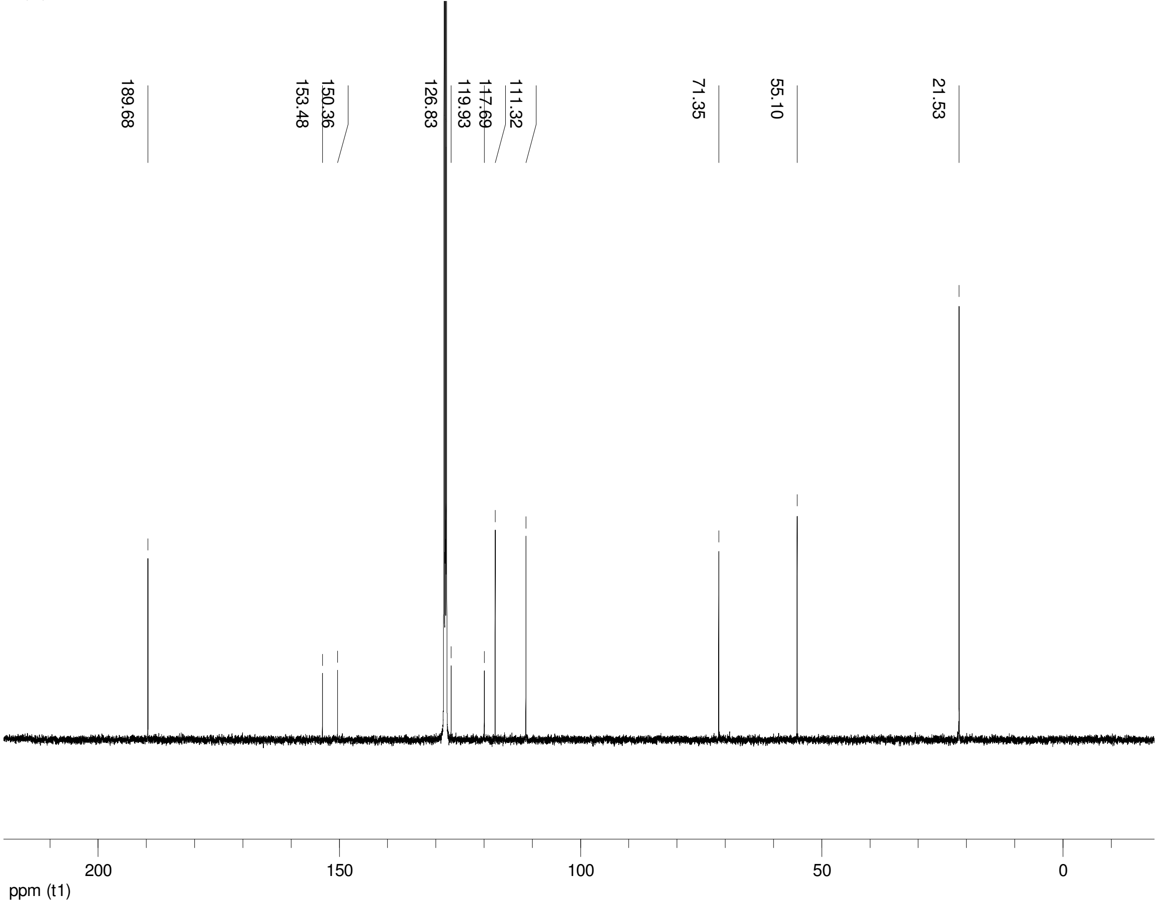

137.7
134.1
129.7
128.0
127.1
117.6
74.9
63.4
60.7
20.5
11.8
200
150
100
50
0
ppm (t1)

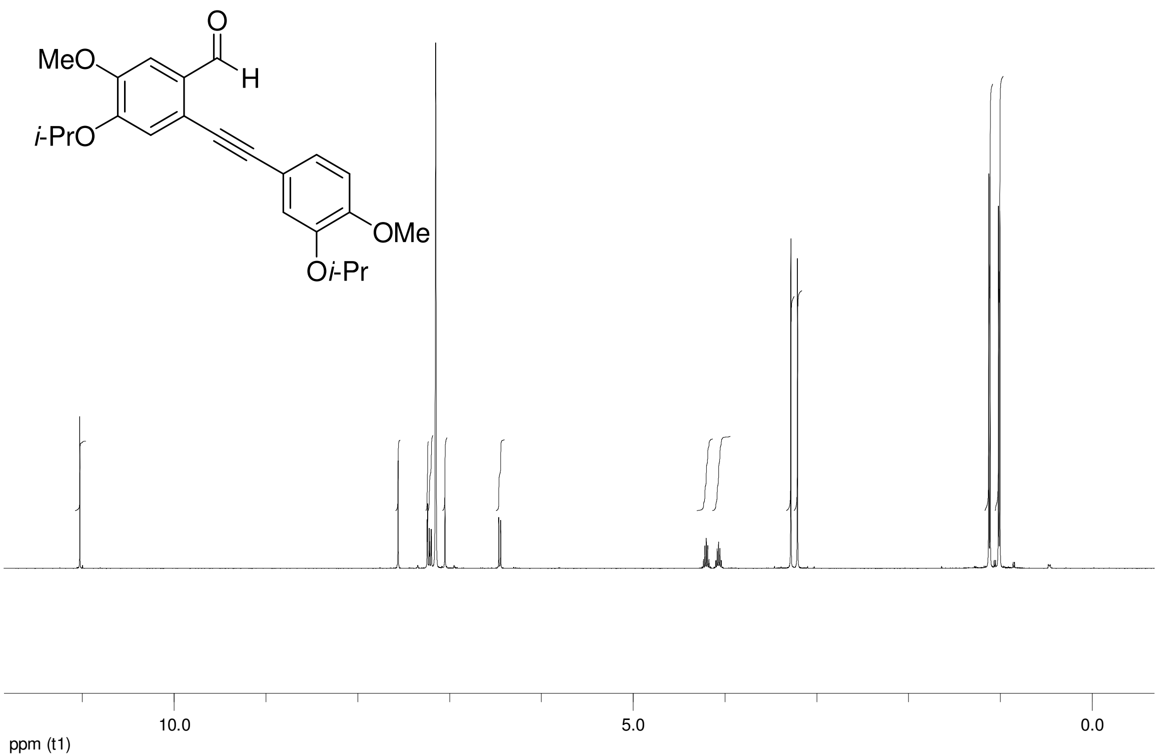

O
N
10.0
5.0
0.0
ppm (t1)

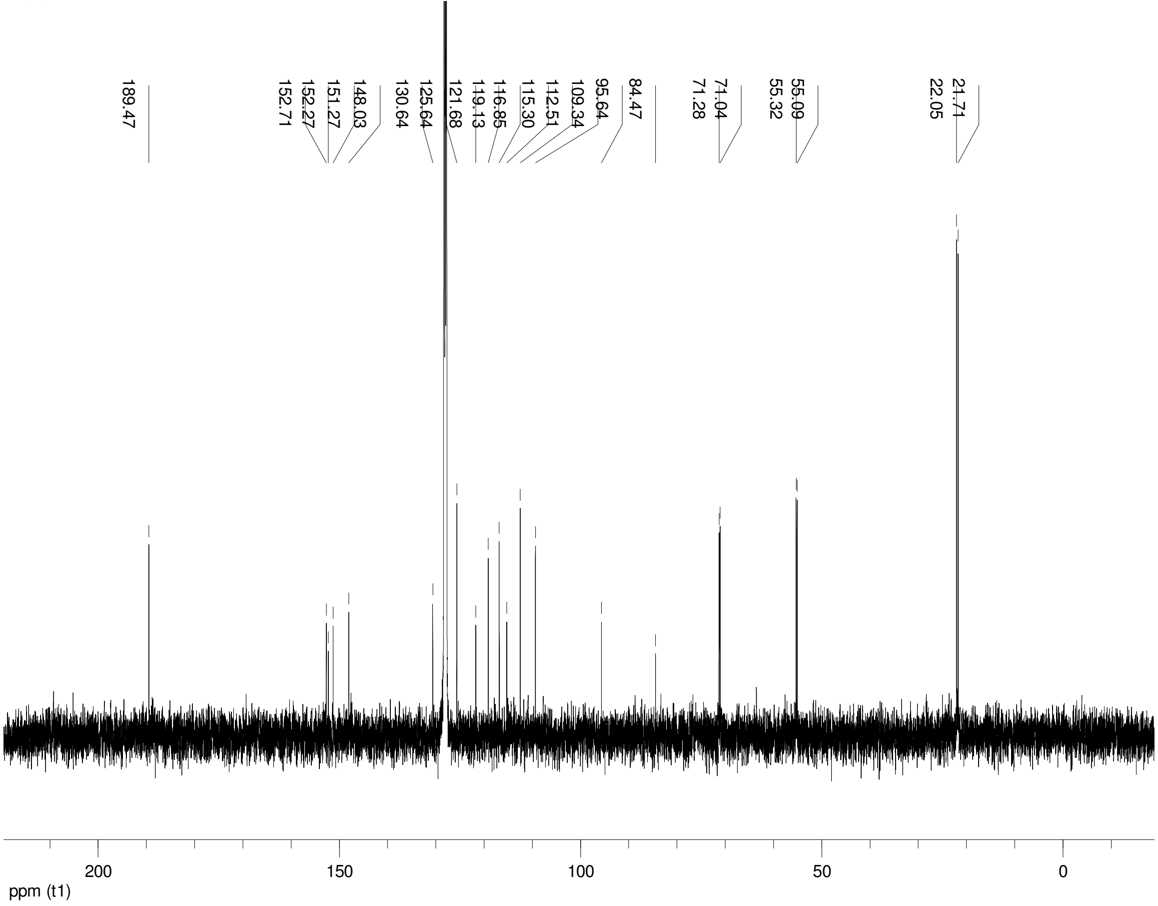

170.5
170.2
137.5
136.7
128.5
128.1
127.6
127.1
126.8
125.8
51.6
49.2
47.7
47.4
21.4
21.3
21.1
20.4
11.0
10.9
200
150
100
50
0
ppm (t1)

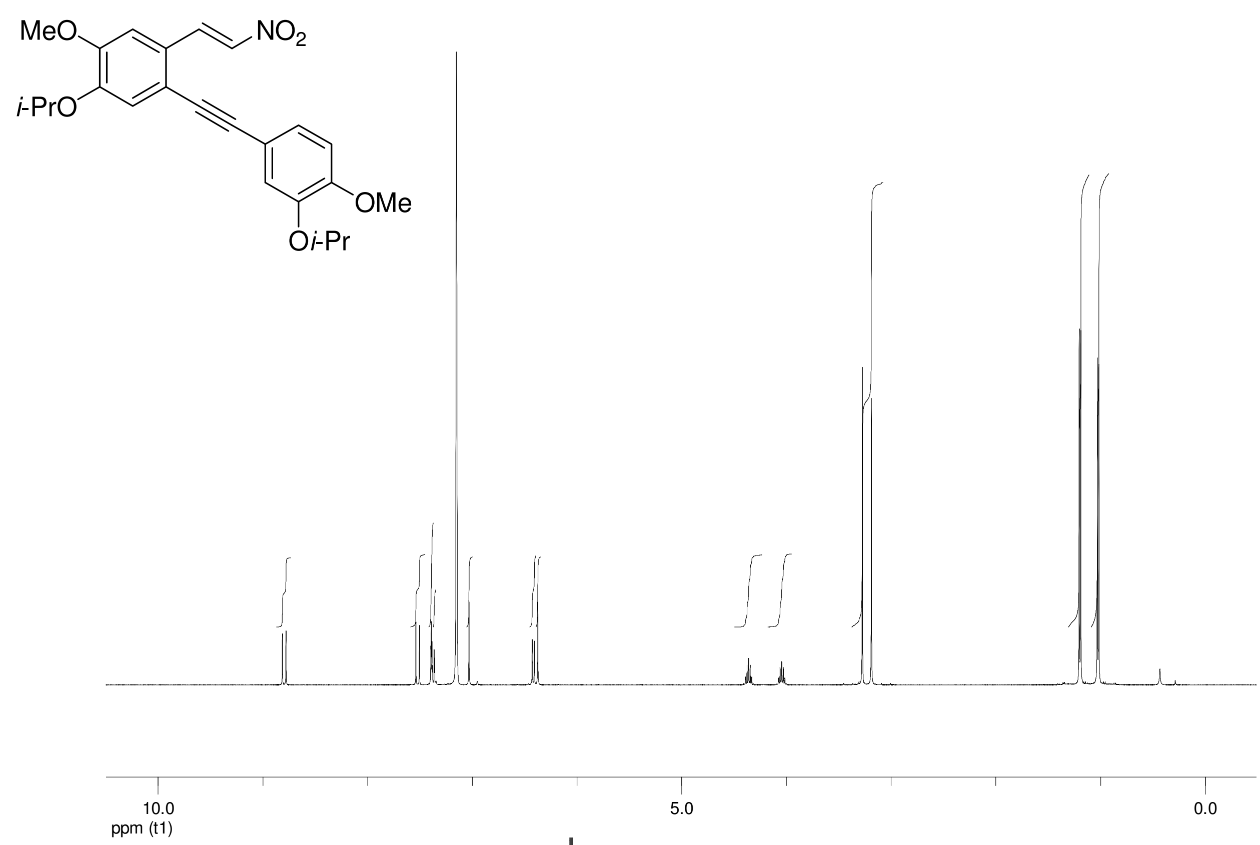

MeO
O
H
i-PrO
Br

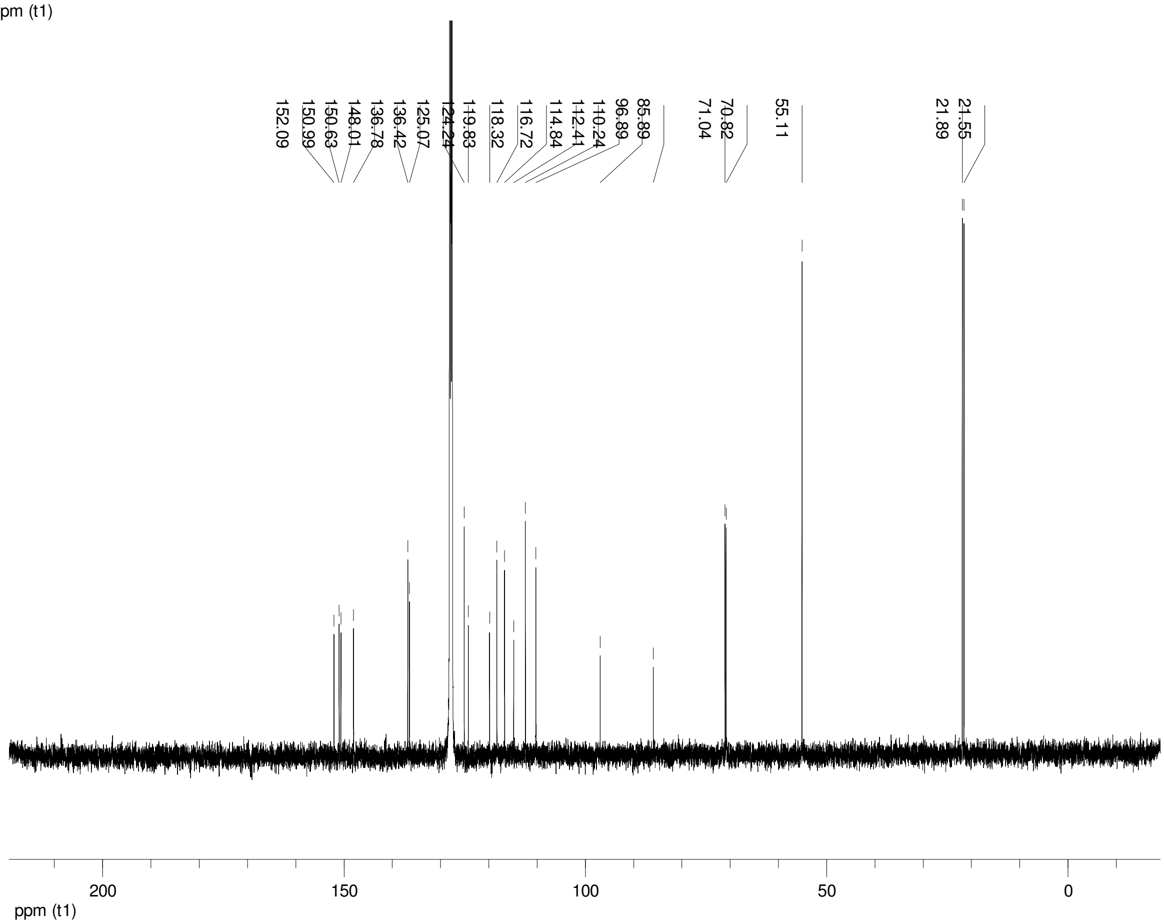

1.00
1.03
1.05
1.08
3.33
6.65
10.0
5.0
0.0
ppm (t1)

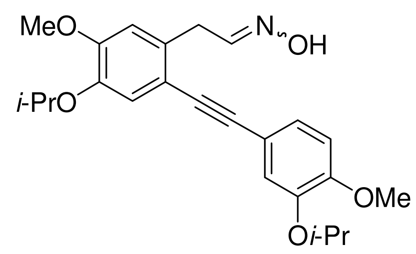

189.68
153.48
150.36
126.83
119.93
117.69
111.32
71.35
55.10
21.53
200
150
100
50
0
ppm (t1)

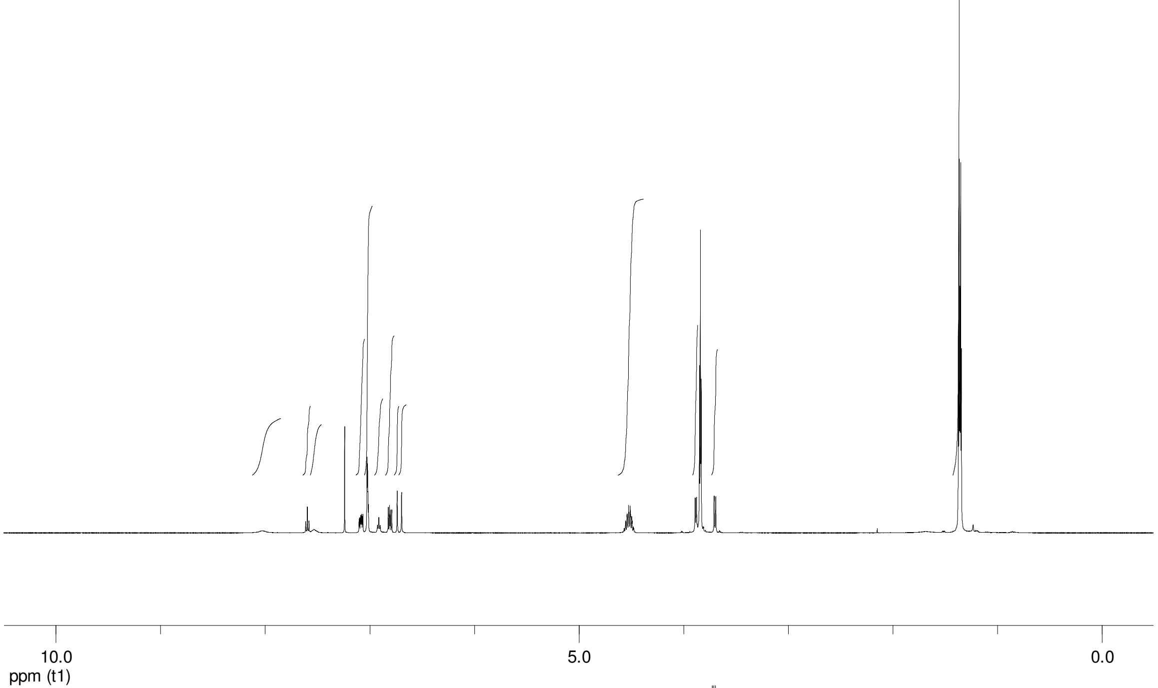

MeO
i-PrO
O
H
OMe
Oi-Pr
10.0
5.0
0.0
ppm (t1)

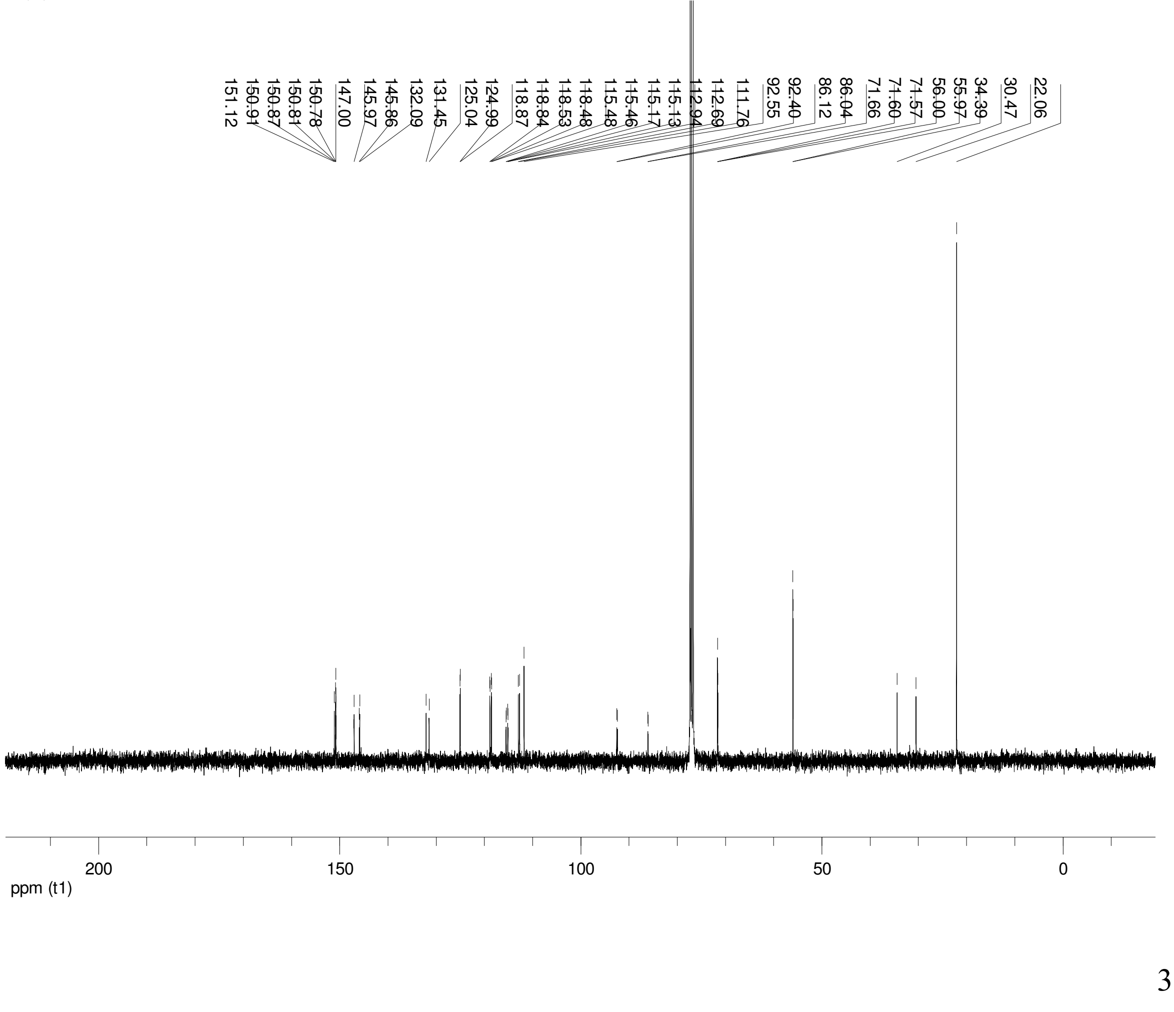

189.47
152.71
152.27
151.27
148.03
130.64
125.64
121.68
119.13
116.85
115.30
112.51
109.34
95.64
84.47
71.28
71.04
55.32
55.09
22.05
21.71
200
150
100
50
0
ppm (t1)

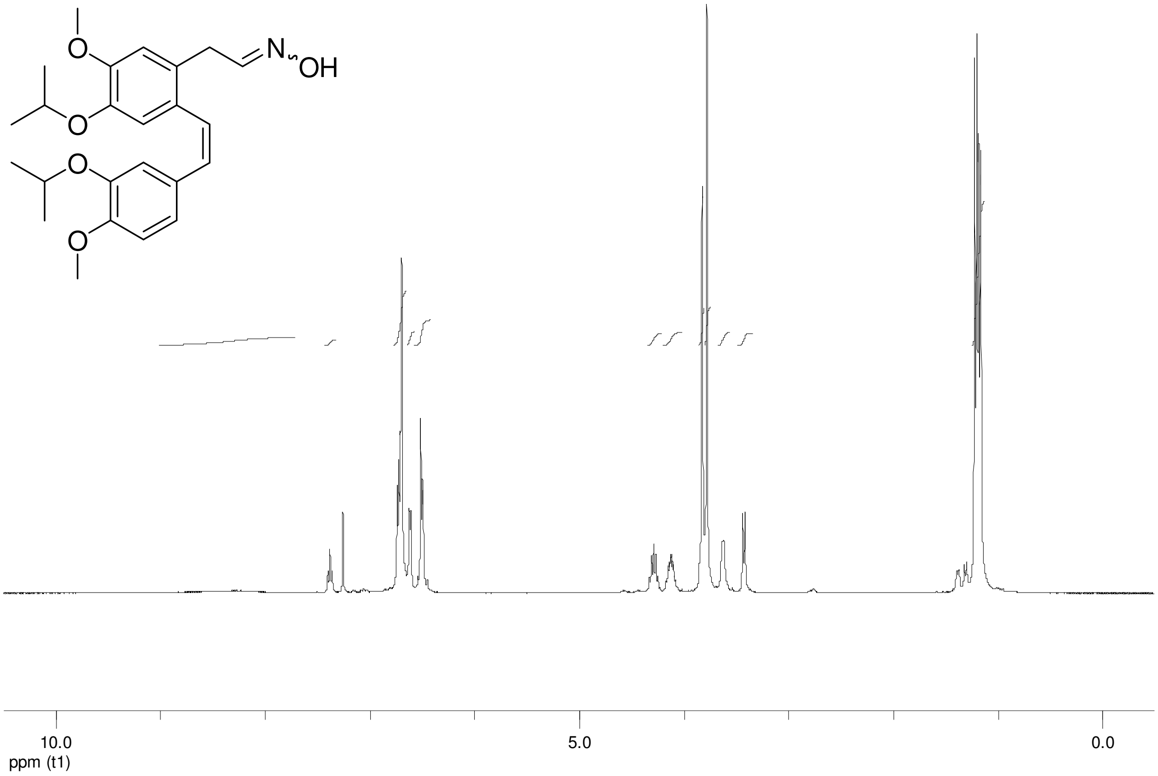

MeO
NO2
i-PrO
OMe
Oi-Pr
10.0
5.0
0.0
ppm (t1)

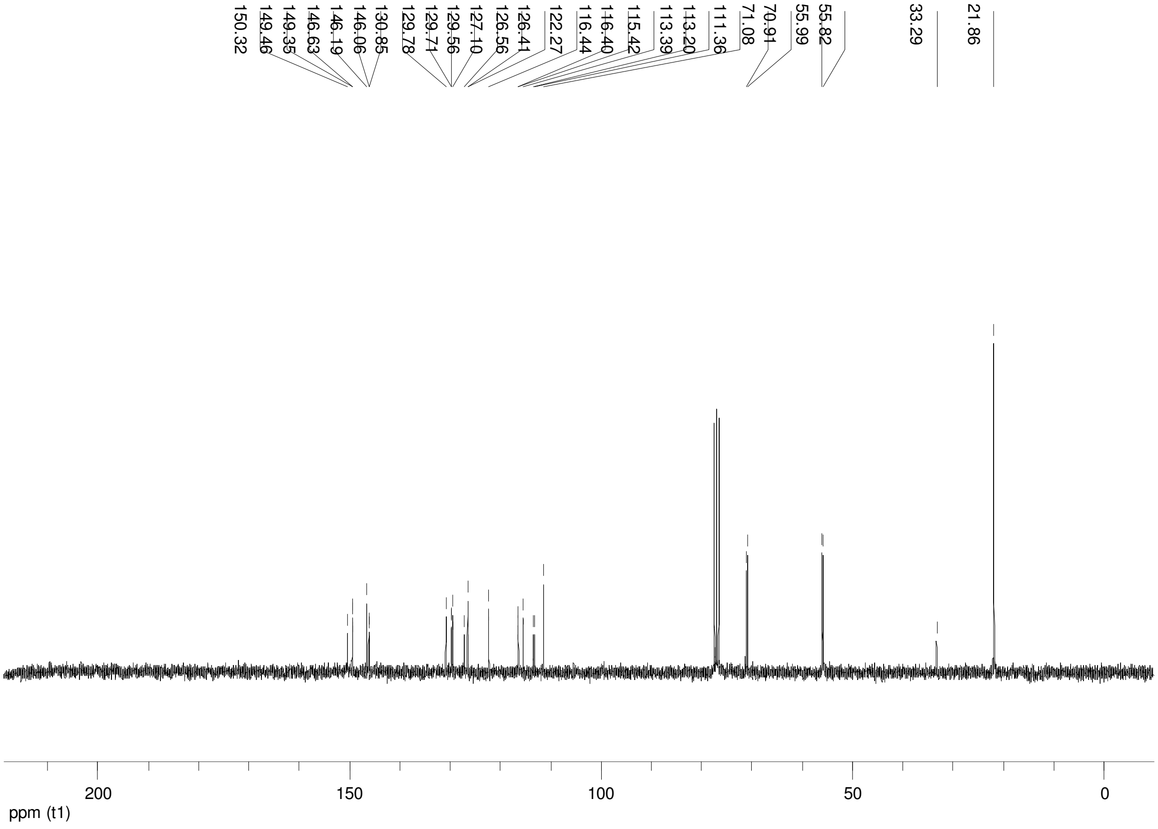

152.09
150.99
150.63
148.01
136.78
136.42
125.07
124.24
119.83
118.32
116.72
114.84
112.41
110.24
96.89
85.89
71.04
70.82
55.11
21.89
21.55
200
150
100
50
0
ppm (t1)

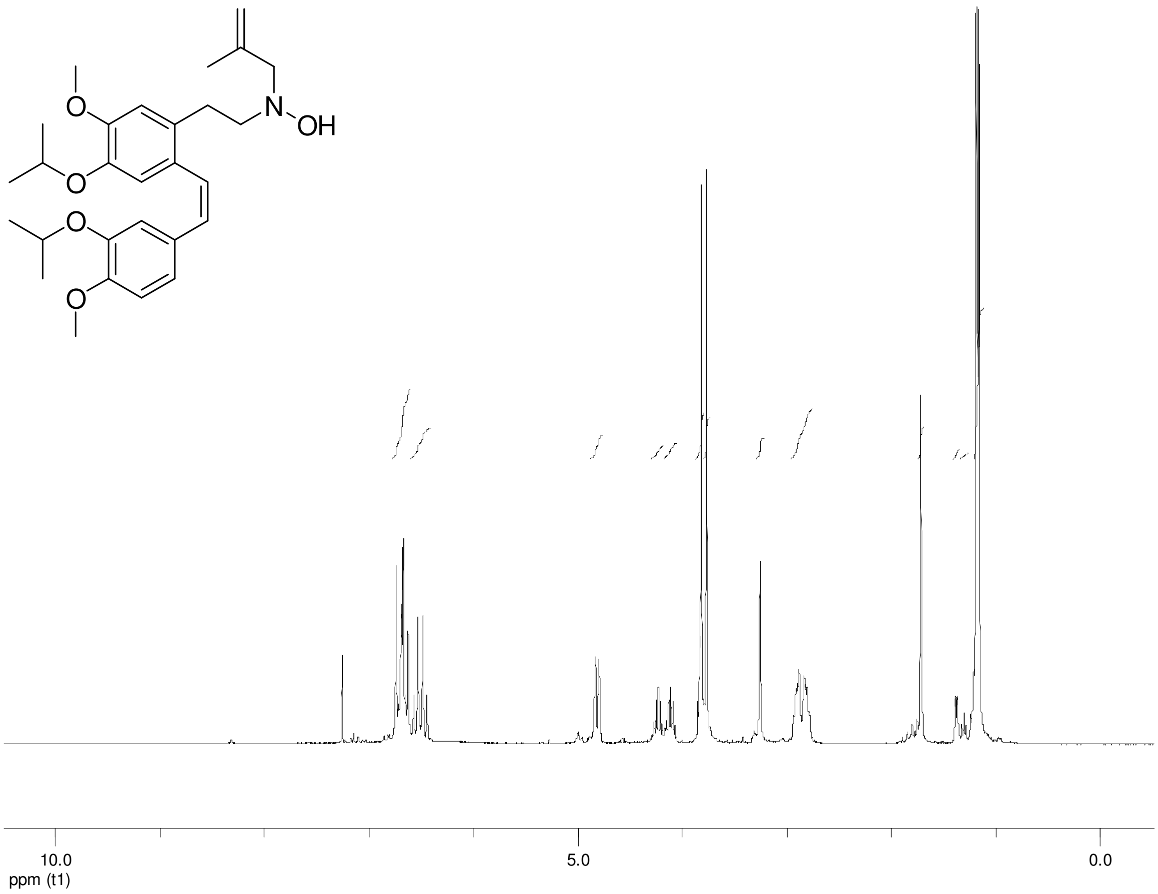

MeO
N
OH
i-PrO
OMe
Oi-Pr


10.0
5.0
0.0
ppm (t1)

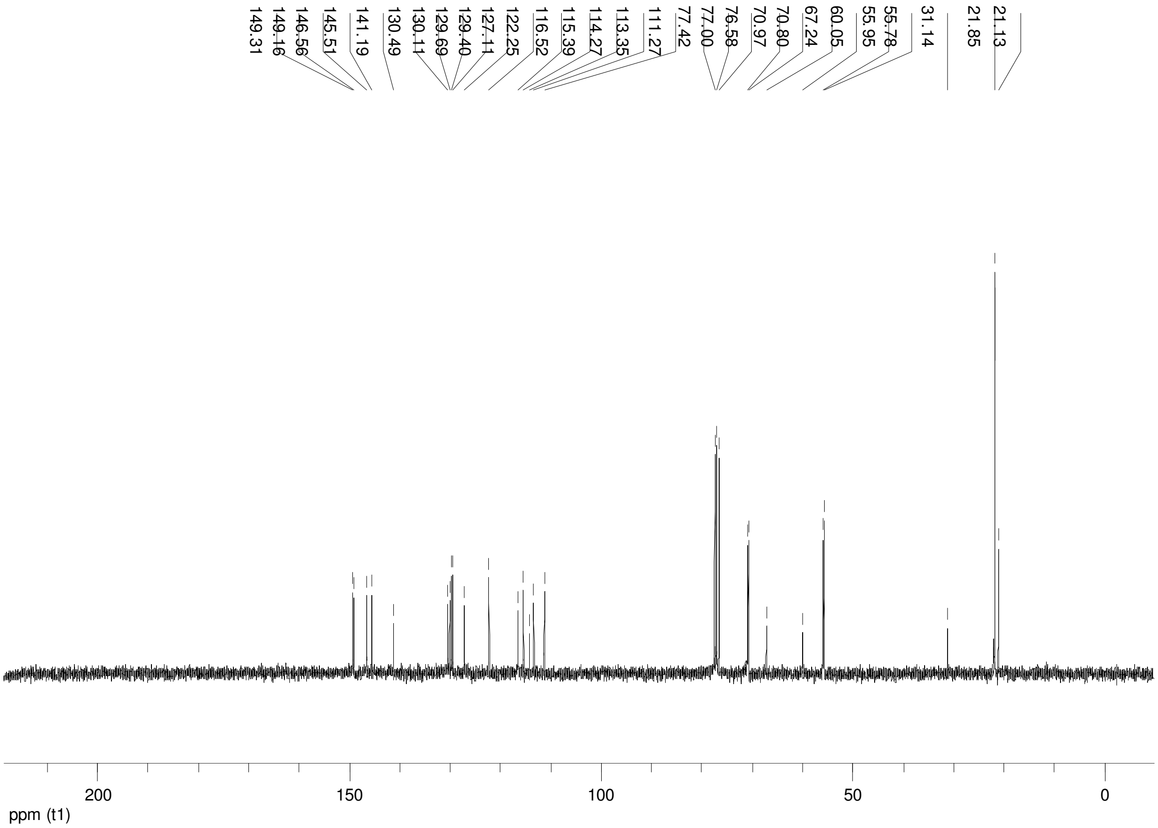

151.12
150.91
150.87
150.81
150.78
147.00
145.97
145.86
132.09
131.45
125.04
124.99
118.87
118.84
118.53
118.48
115.48
115.46
115.17
115.13
112.94
112.69
111.76
92.55
92.40
86.12
86.04
71.66
71.60
71.57
56.00
55.97
34.39
30.47
22.06
200
150
100
50
0
ppm (t1)


O
O
O
O
N
OH
10.0
5.0
0.0
ppm (t1)

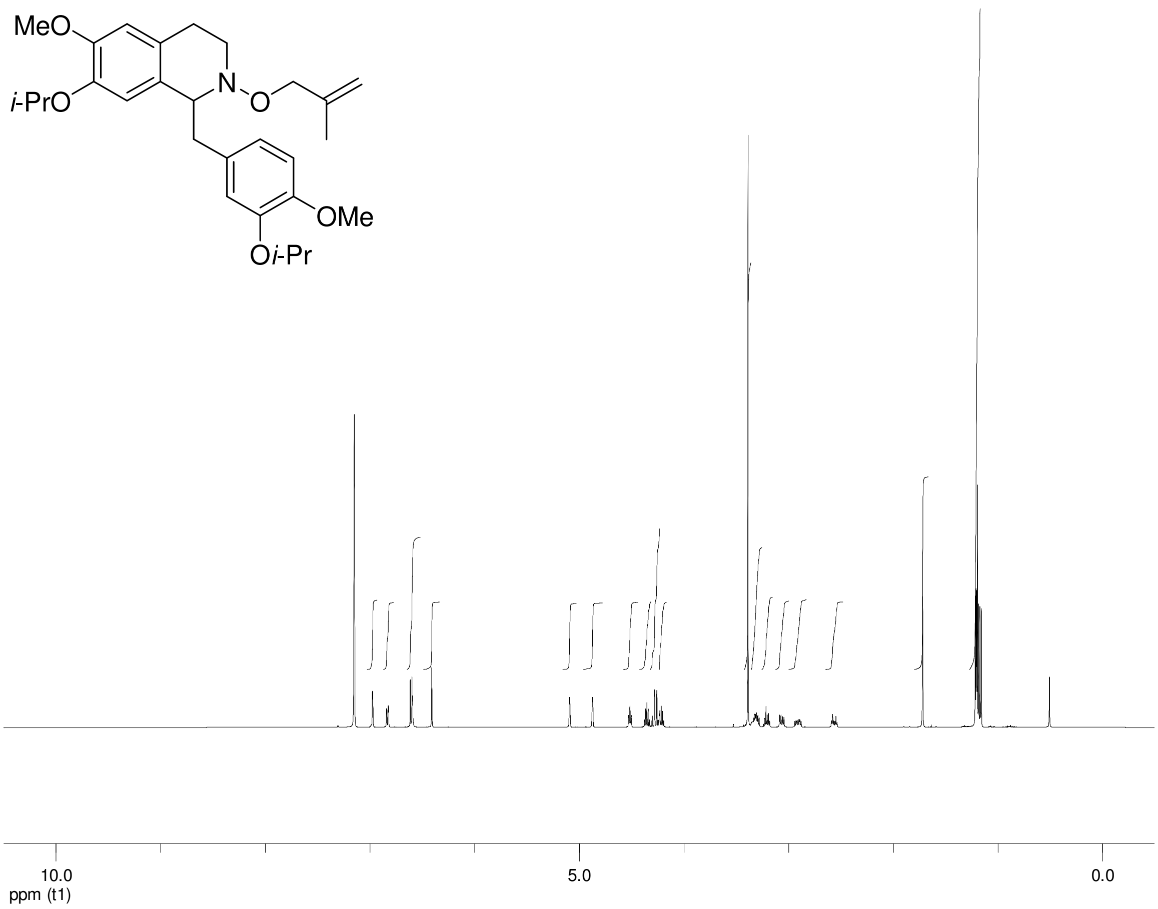

150.32
149.46
149.35
146.63
146.19
146.06
130.85
129.78
129.71
129.56
127.10
126.56
126.41
122.27
116.44
116.40
115.42
113.39
113.20
111.36
71.08
70.91
55.99
55.82
33.29
21.86
200
150
100
50
0
ppm (t1)

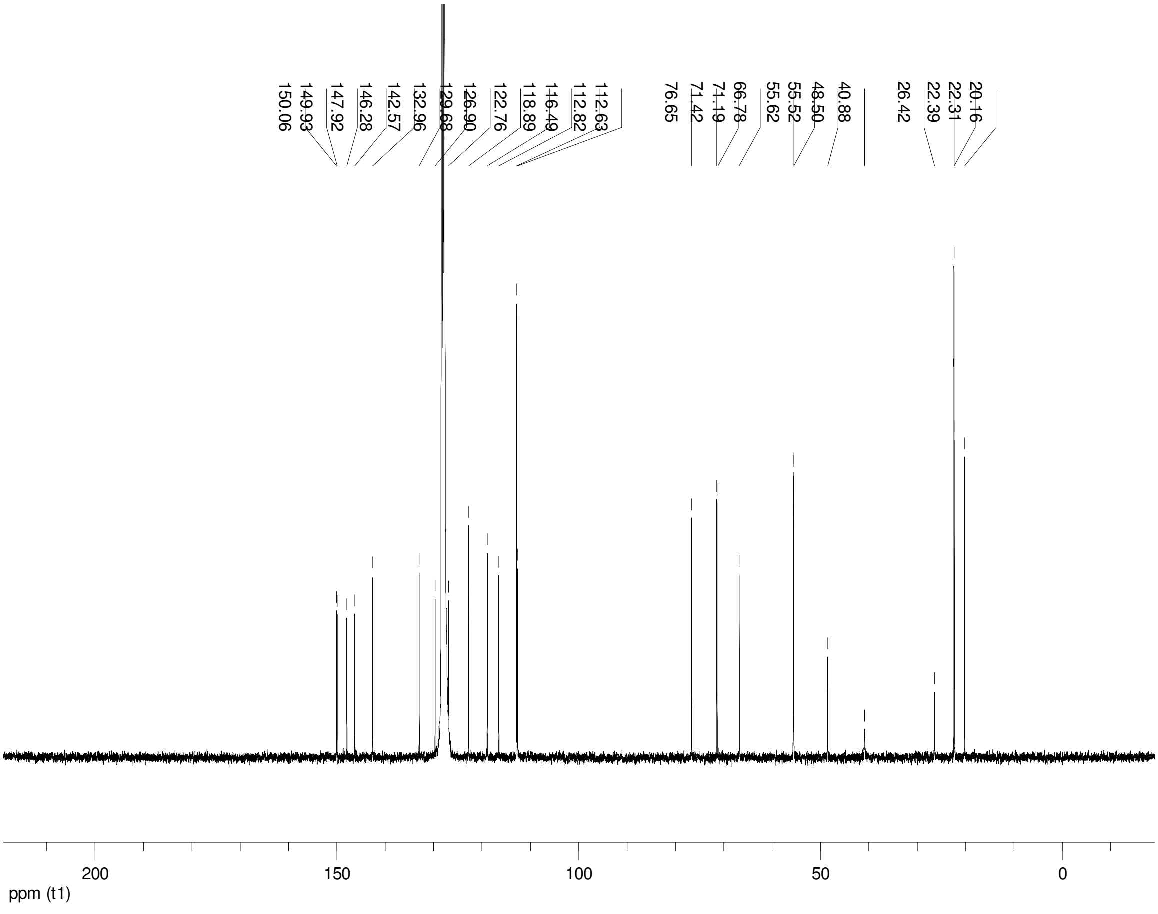


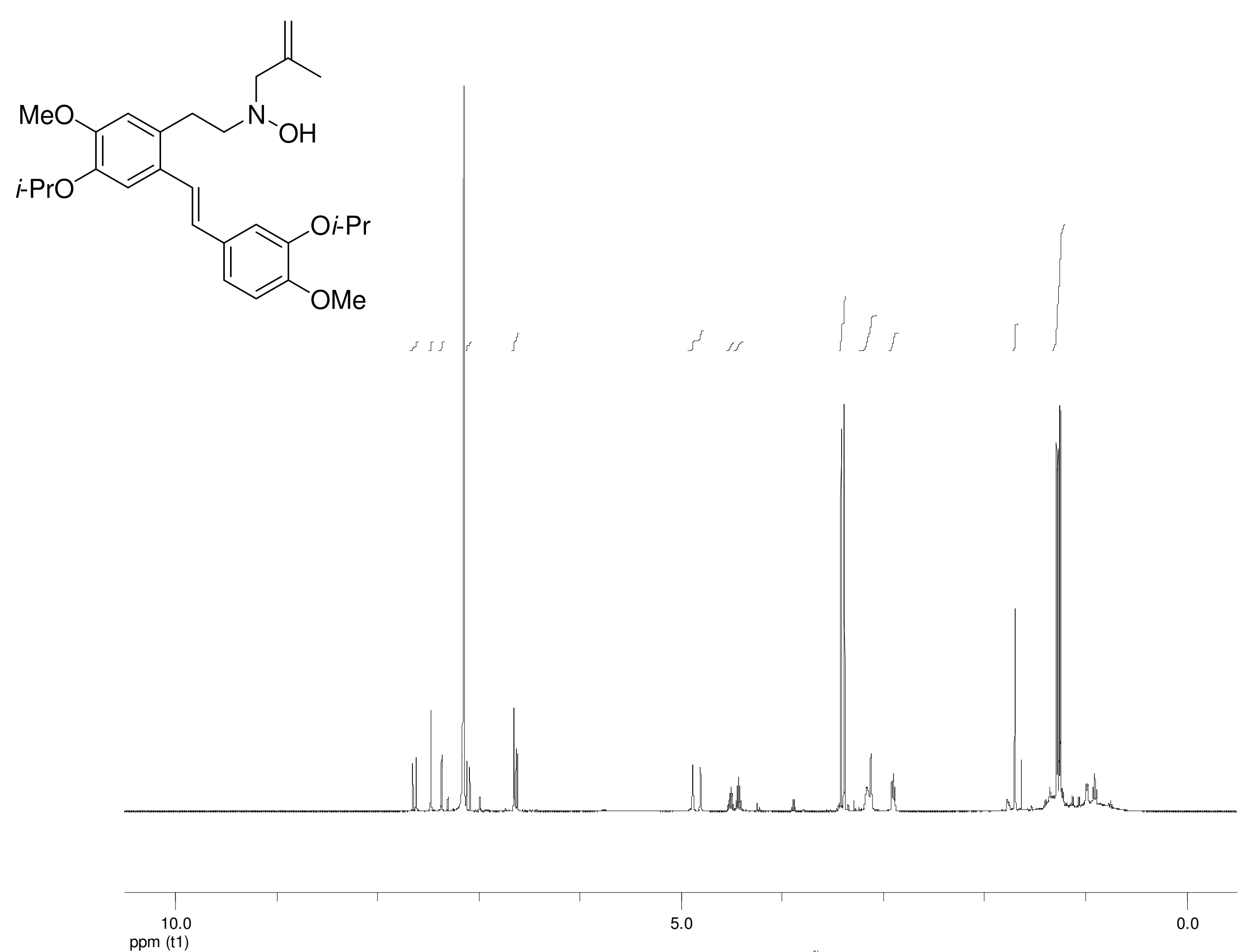
N
OH
O
O
O
O
10.0
5.0
0.0
ppm (t1)

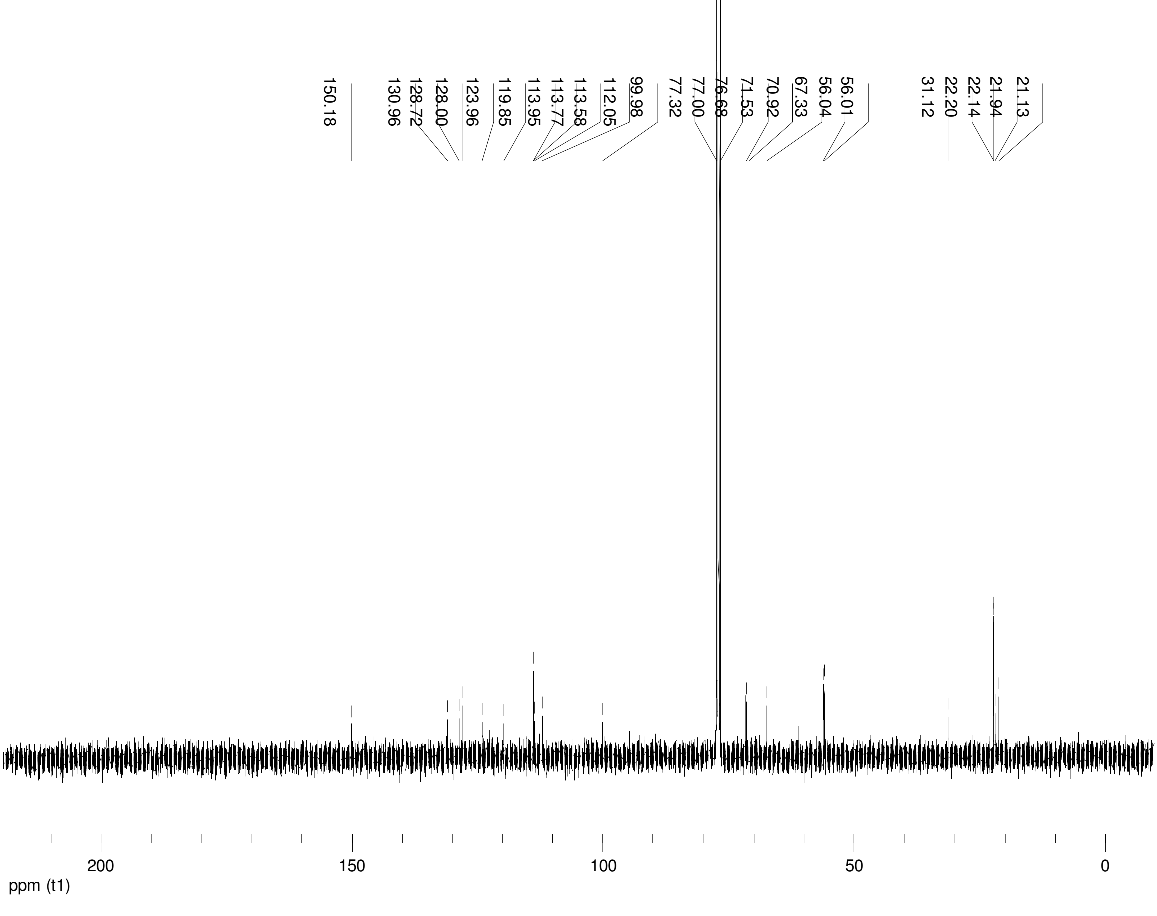


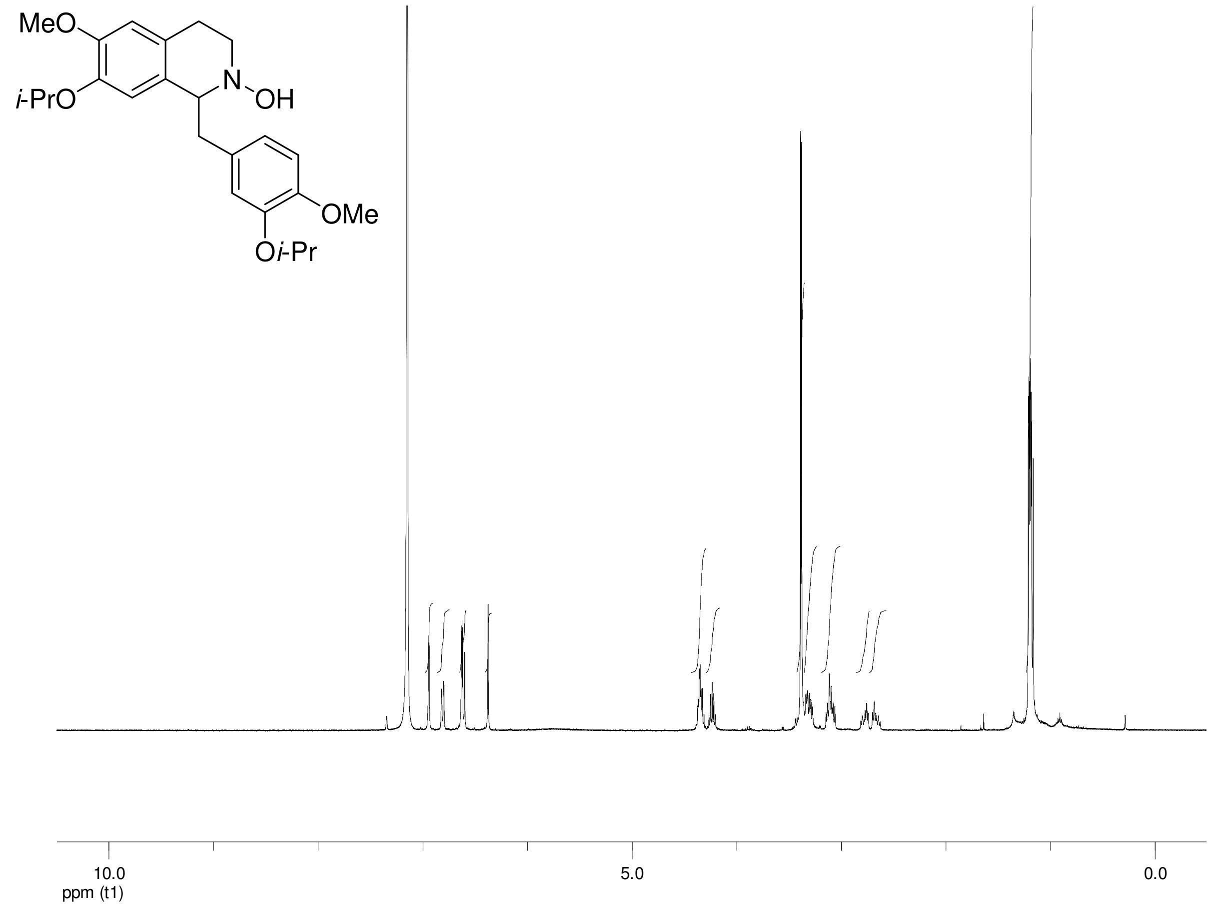
149.31
149.16
146.56
145.51
141.19
130.49
130.11
129.69
129.40
127.11
122.25
116.52
115.39
114.27
113.35
111.27
77.42
77.00
76.58
70.97
70.80
67.24
60.05
55.95
55.78
31.14
21.85
21.13
200
150
100
50
0
ppm (t1)

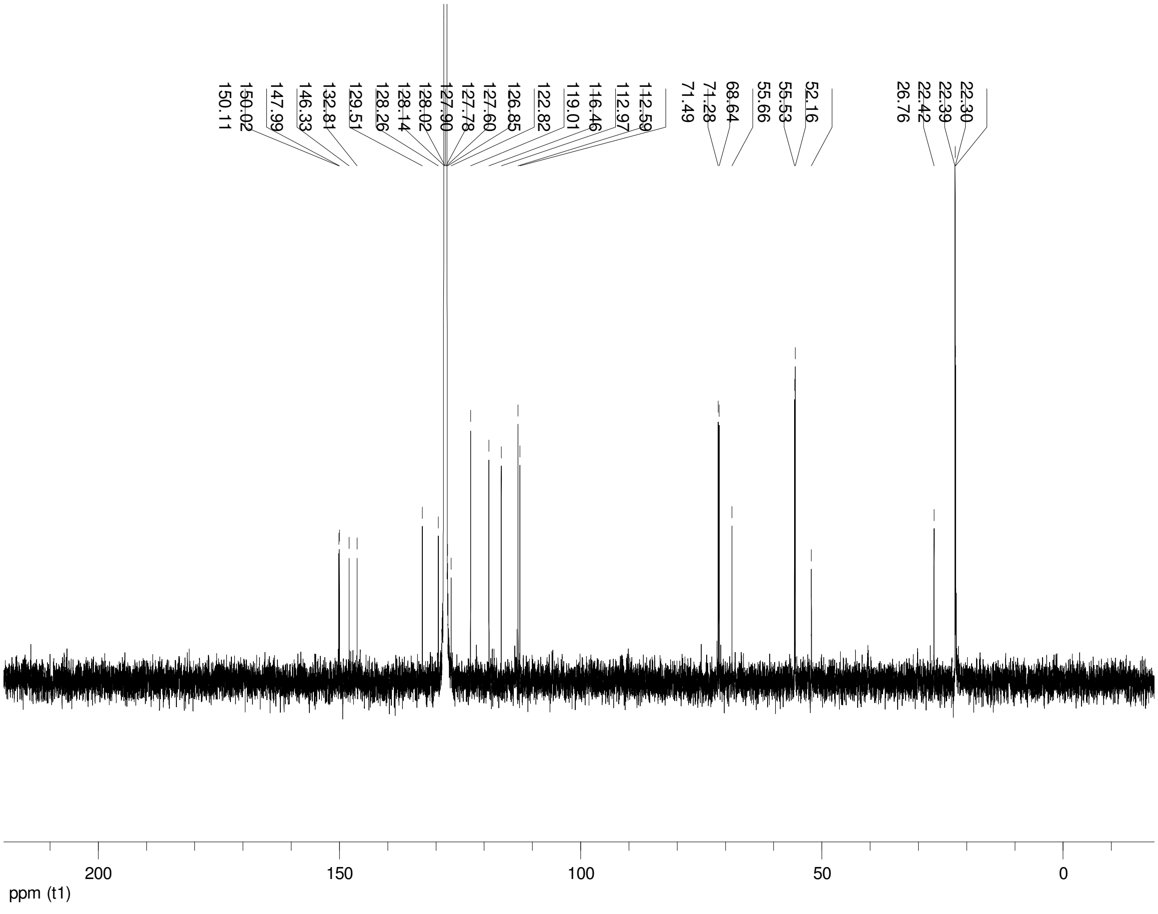

MeO
i-PrO
N
O
OMe
Oi-Pr
10.0
5.0
0.0
ppm (t1)


150.06
149.93
147.92
146.28
142.57
132.96
129.68
126.90
122.76
118.89
116.49
112.82
112.63
76.65
71.42
71.19
66.78
55.62
55.52
48.50
40.88
26.42
22.39
22.31
20.16
200
150
100
50
0
ppm (t1)


MeO
i-PrO
N
OH
Oi-Pr
OMe
10.0
5.0
0.0
ppm (t1)

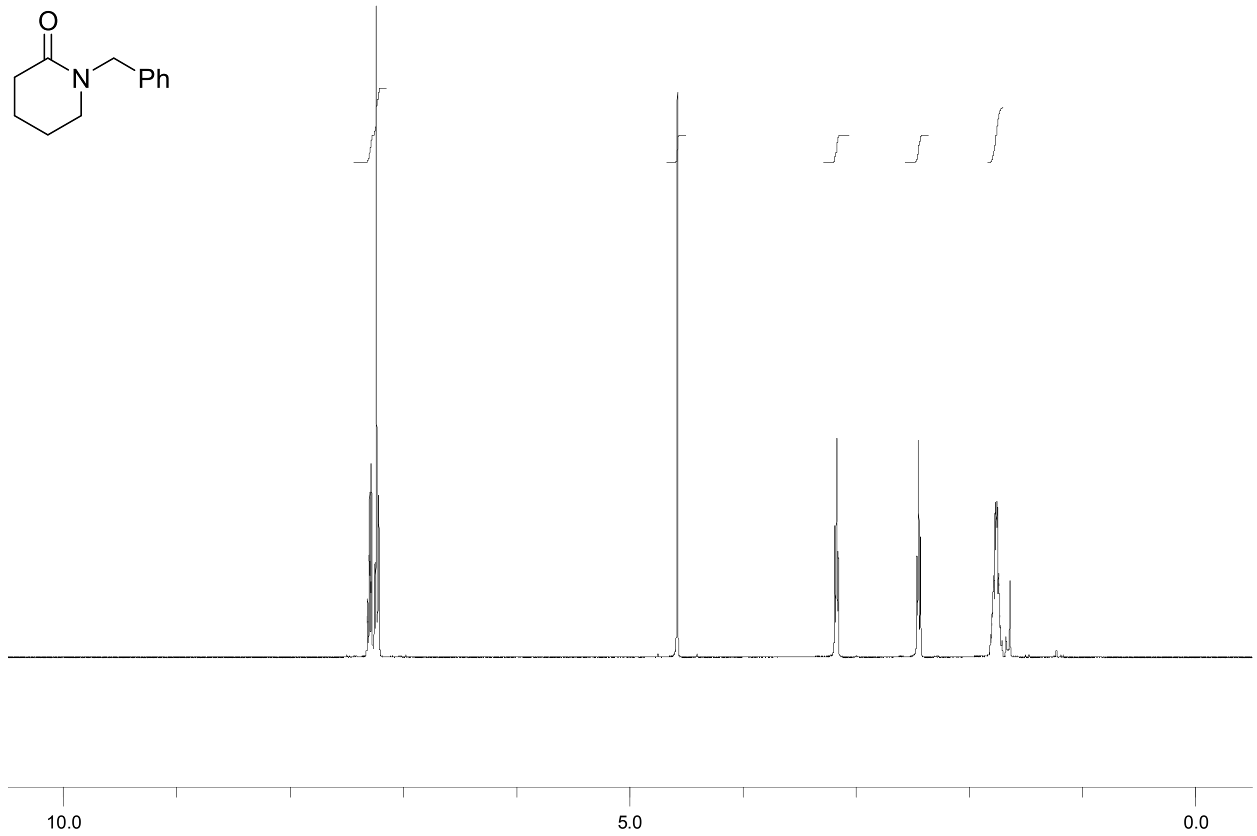

150.18
130.96
128.72
128.00
123.96
119.85
113.95
113.77
113.58
112.05
99.98
77.32
77.00
76.68
71.53
70.92
67.33
56.04
56.01
31.12
22.20
22.14
21.94
21.13
200
150
100
50
0
ppm (t1)

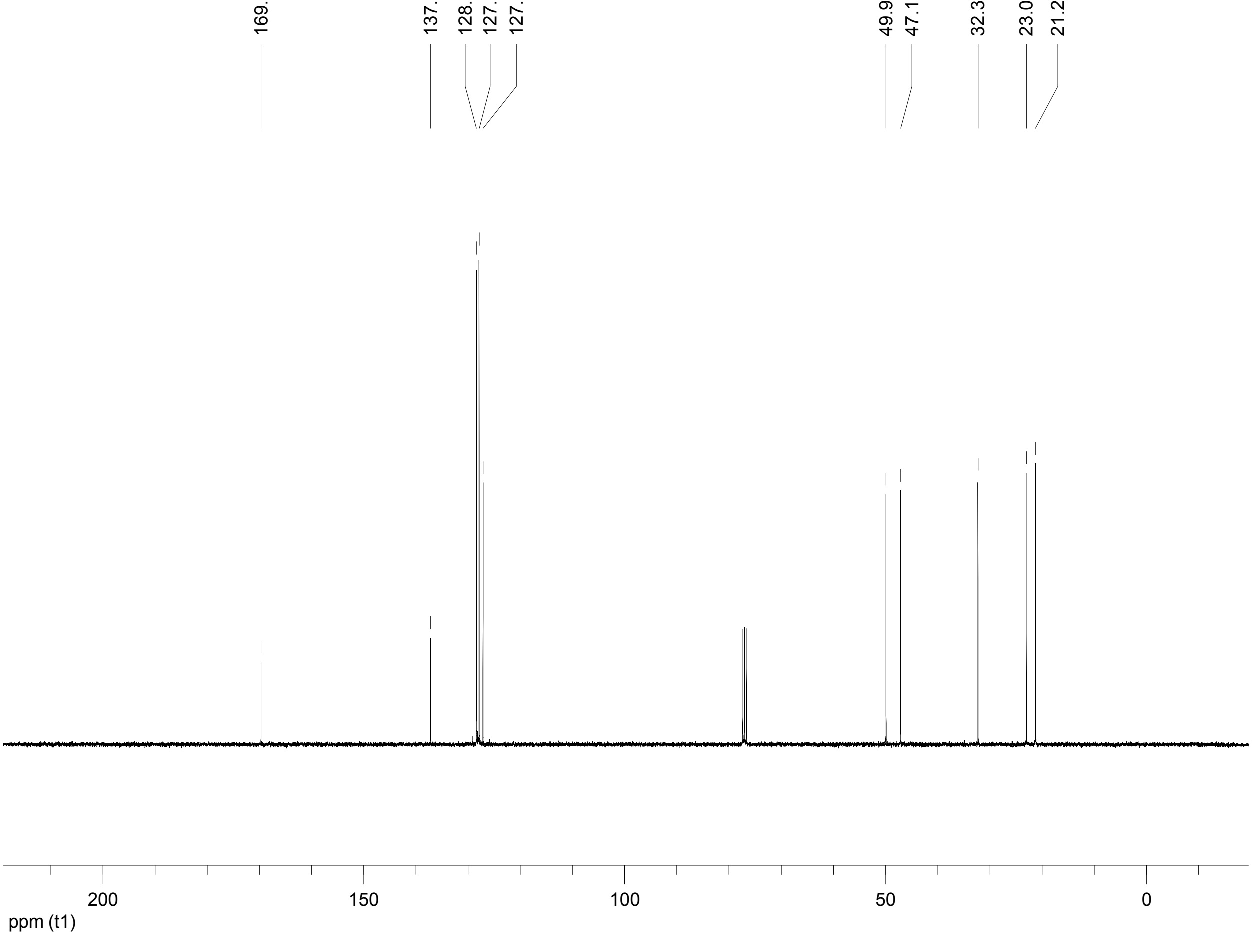

MeO
i-PrO
N
OH
OMe
Oi-Pr
10.0
5.0
0.0
ppm (t1)

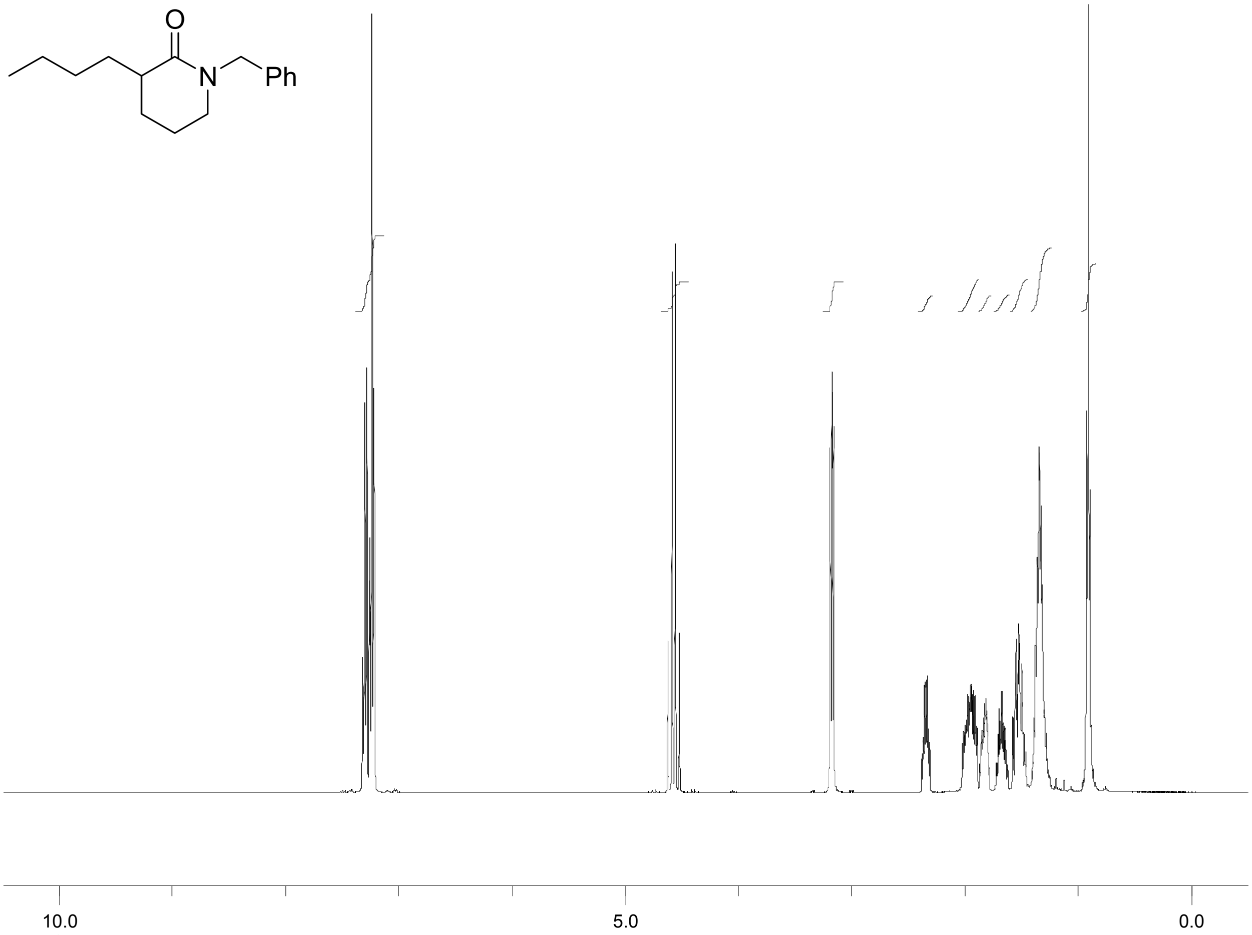

150.11
150.02
147.99
146.33
132.81
129.51
128.26
128.14
128.02
127.90
127.78
127.60
126.85
122.82
119.01
116.46
112.97
112.59
71.49
71.28
68.64
55.66
55.53
52.16
26.76
22.42
22.39
22.30
200
150
100
50
0
ppm (t1)

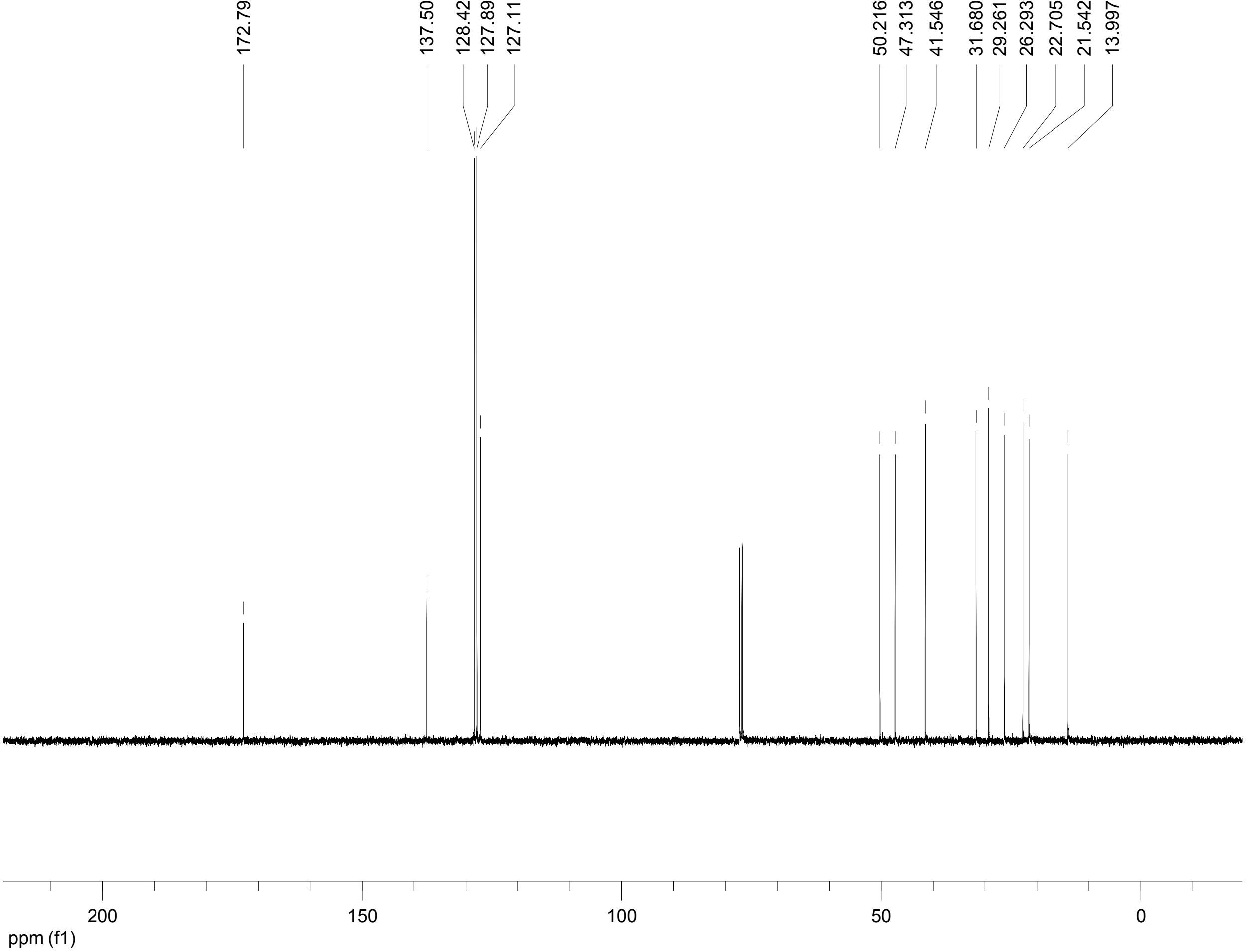
Appendix III

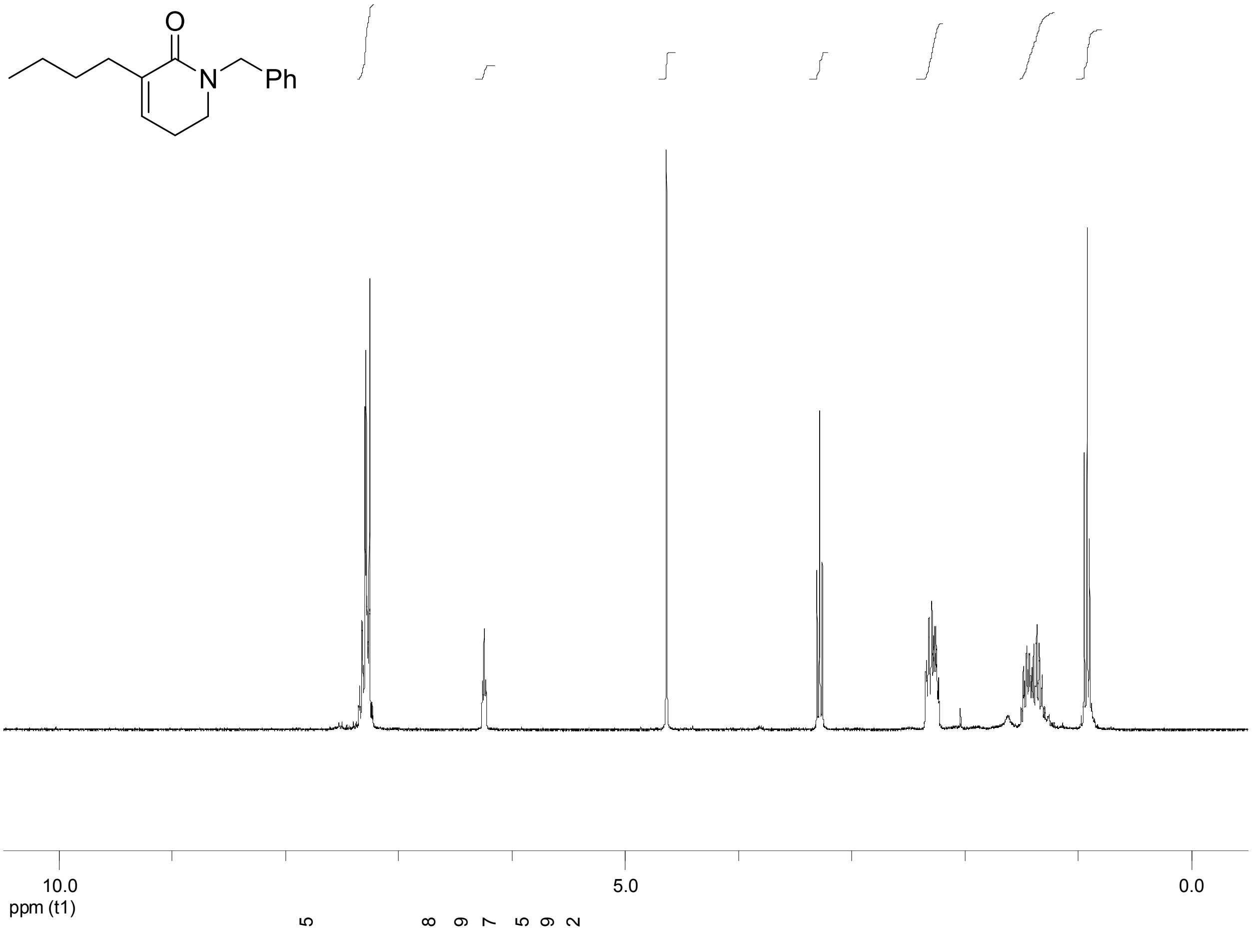
Supporting Information - Chapter 3

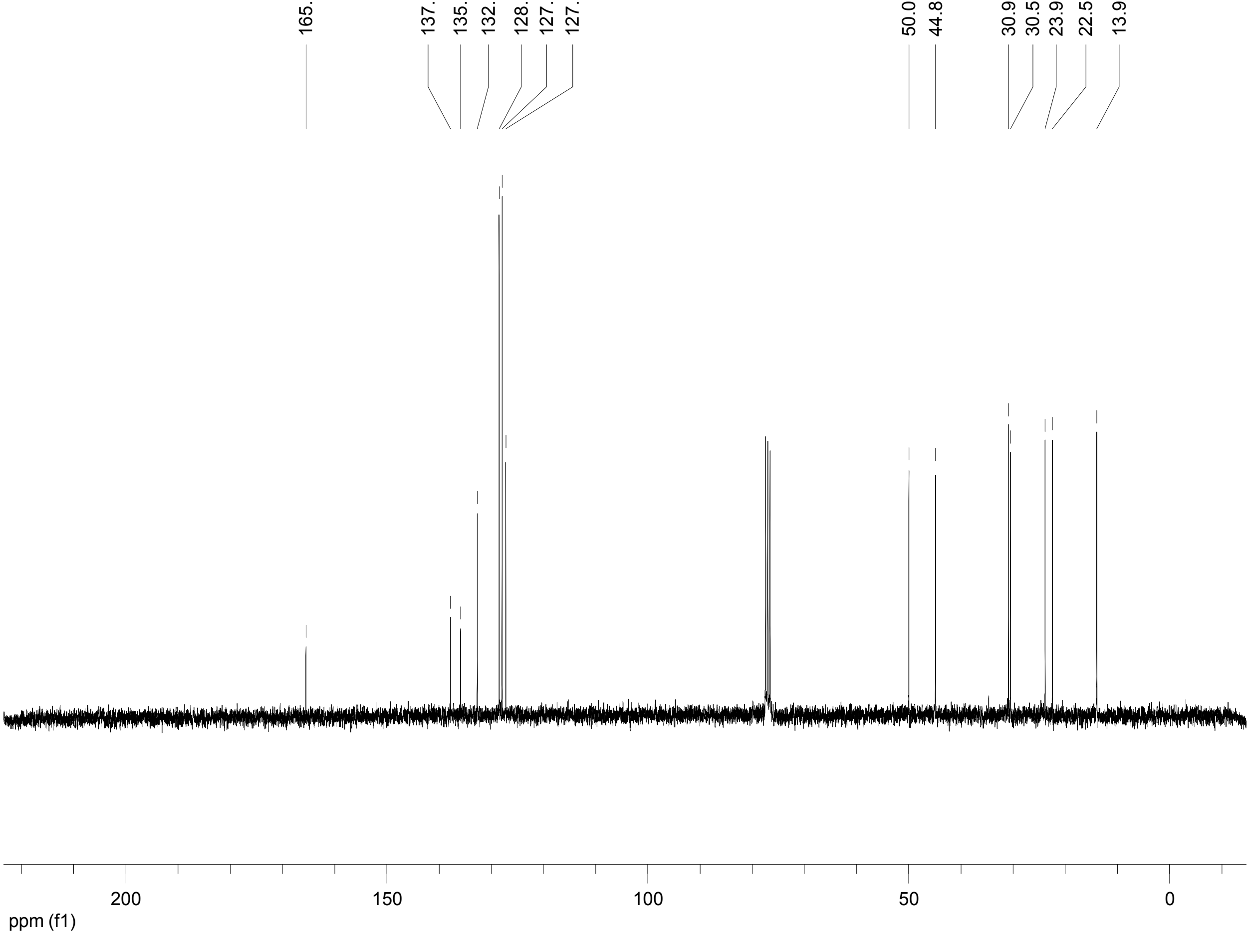

O
N
Ph
10.0
5.0
0.0
ppm (t1)

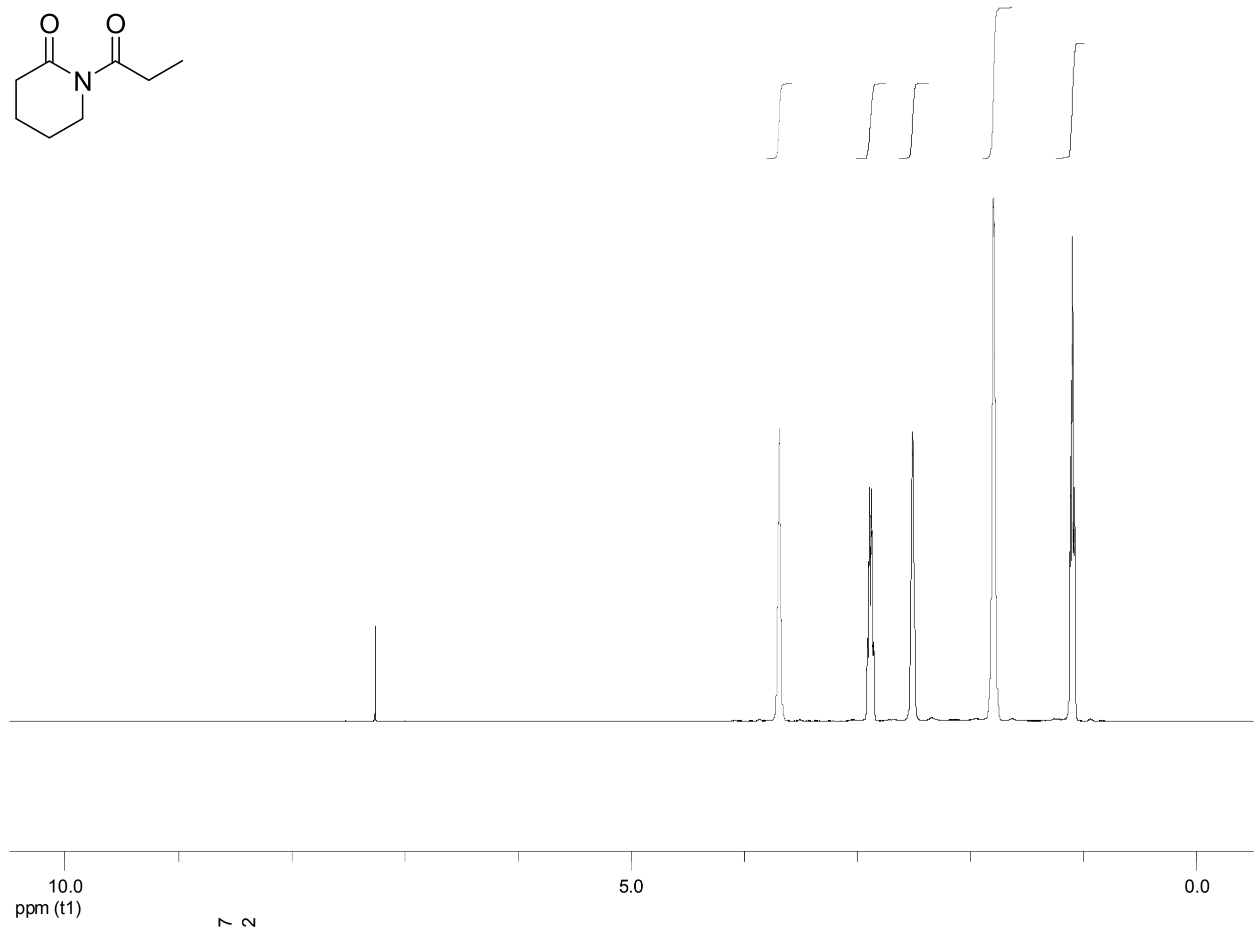

169.7
137.2
128.4
127.9
127.1
49.9
47.1
32.3
23.0
21.2
200
150
100
50
0
ppm (t1)

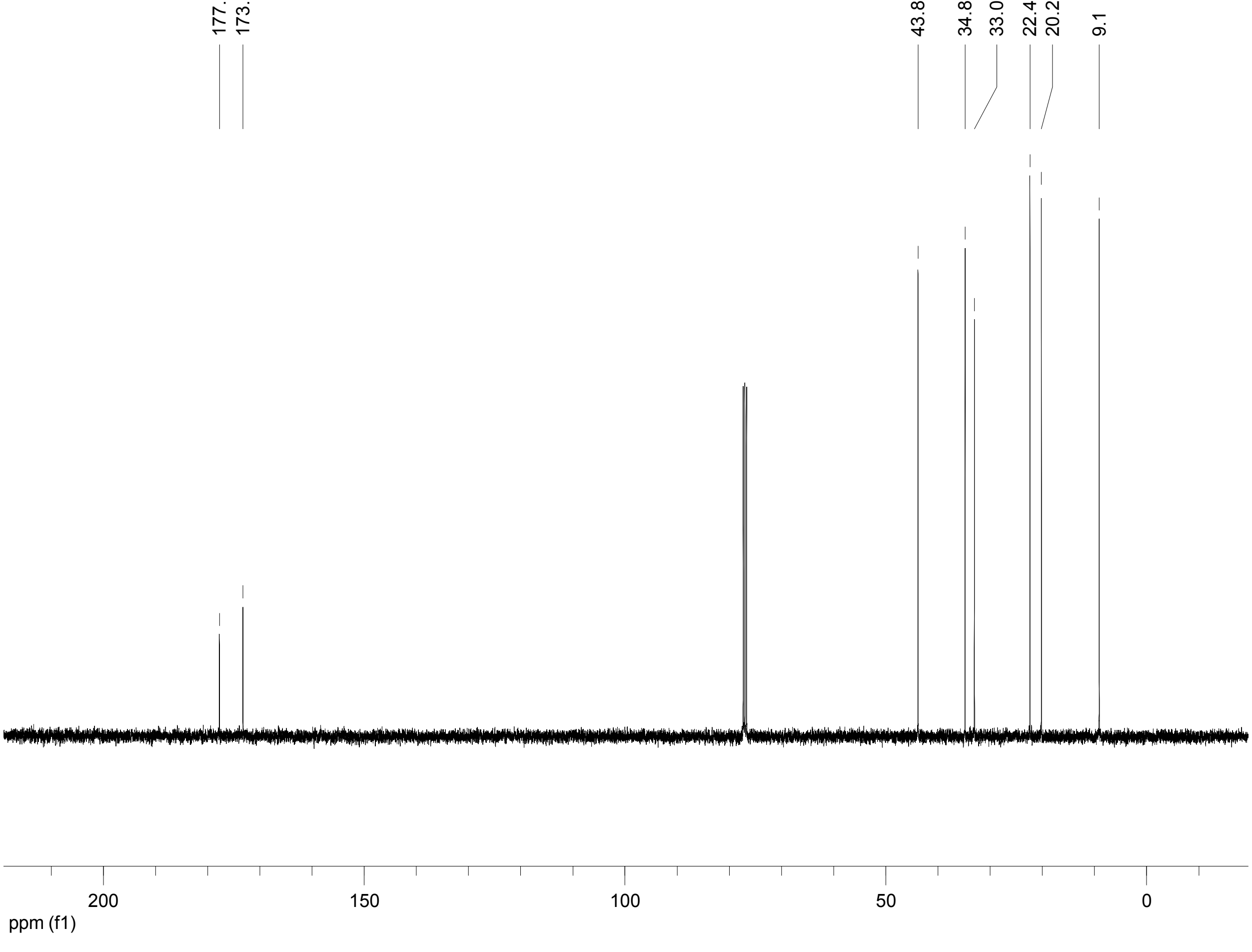

O
N
Ph
10.0
5.0
0.0
ppm (f1)

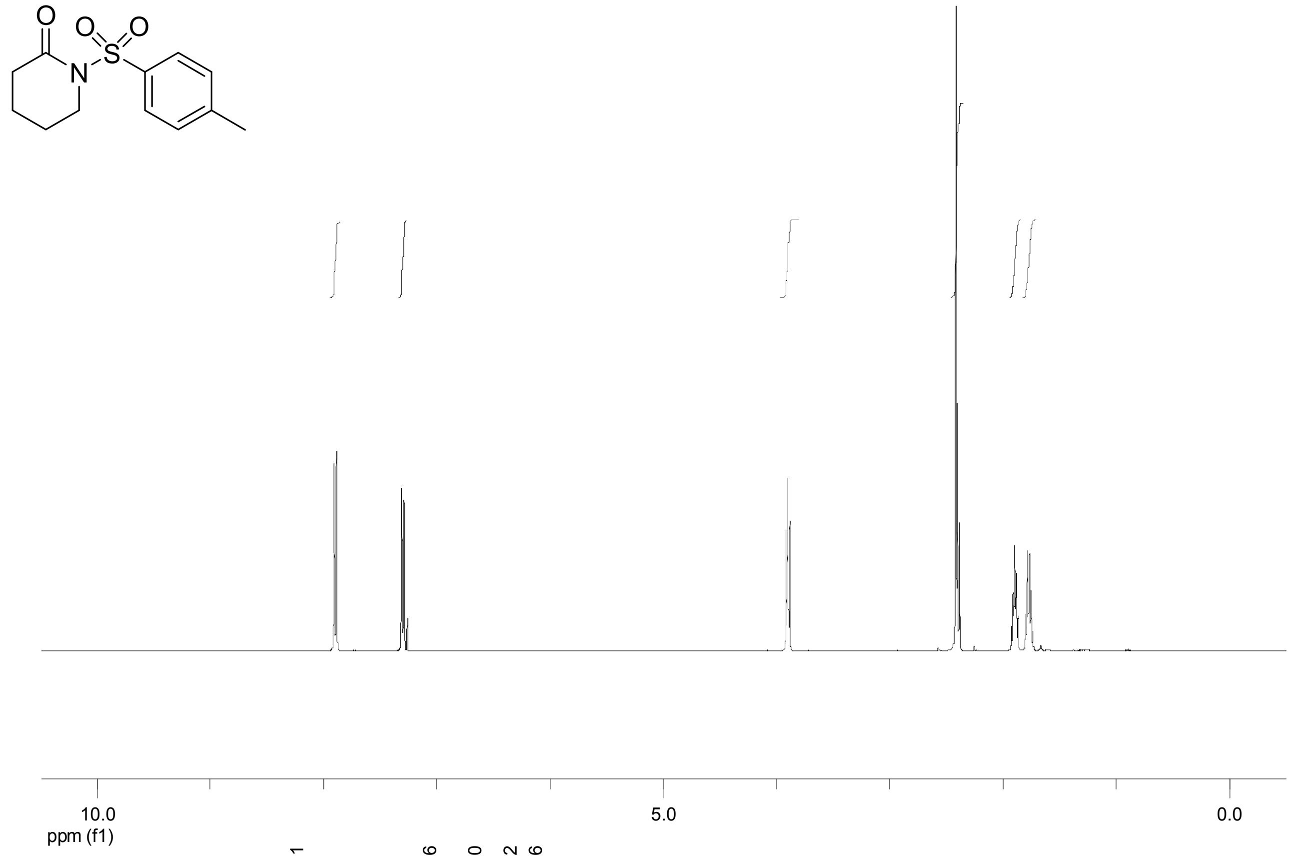

172.795
137.504
128.426
127.897
127.111
50.216
47.313
41.546
31.680
29.261
26.293
22.705
21.542
13.997
200
150
100
50
0
ppm (f1)

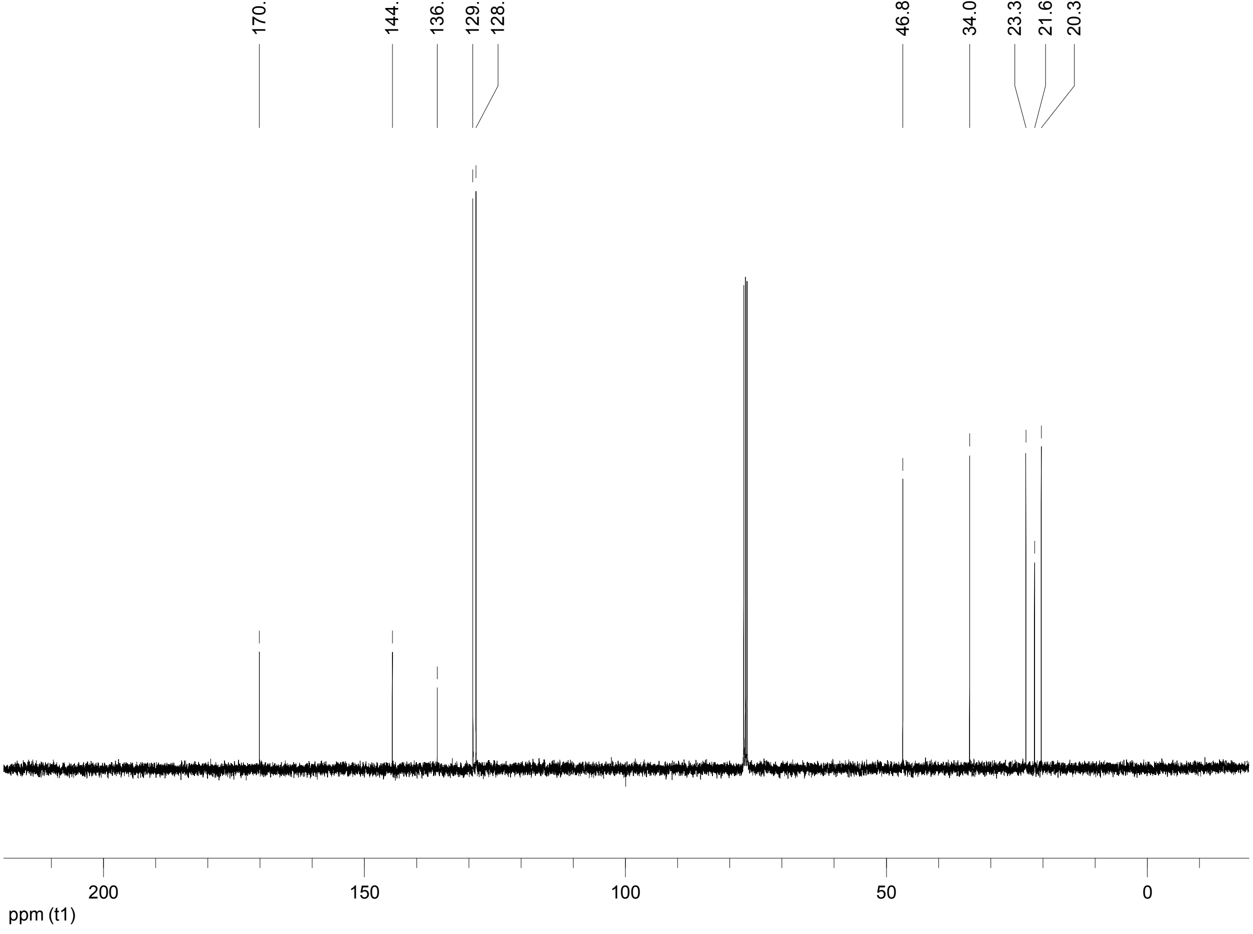

O
N
Ph
10.0
5.0
0.0
ppm (t1)


165.5
137.8
135.9
132.7
128.5
127.9
127.2
50.0
44.8
30.9
30.5
23.9
22.5
13.9
200
150
100
50
0
ppm (f1)


O
O
N
10.0
5.0
0.0
ppm (t1)


177.7
173.2
43.8
34.8
33.0
22.4
20.2
9.1
200
150
100
50
0
ppm (f1)


O
O
S
O
N
10.0
5.0
0.0
ppm (f1)


170.1
144.6
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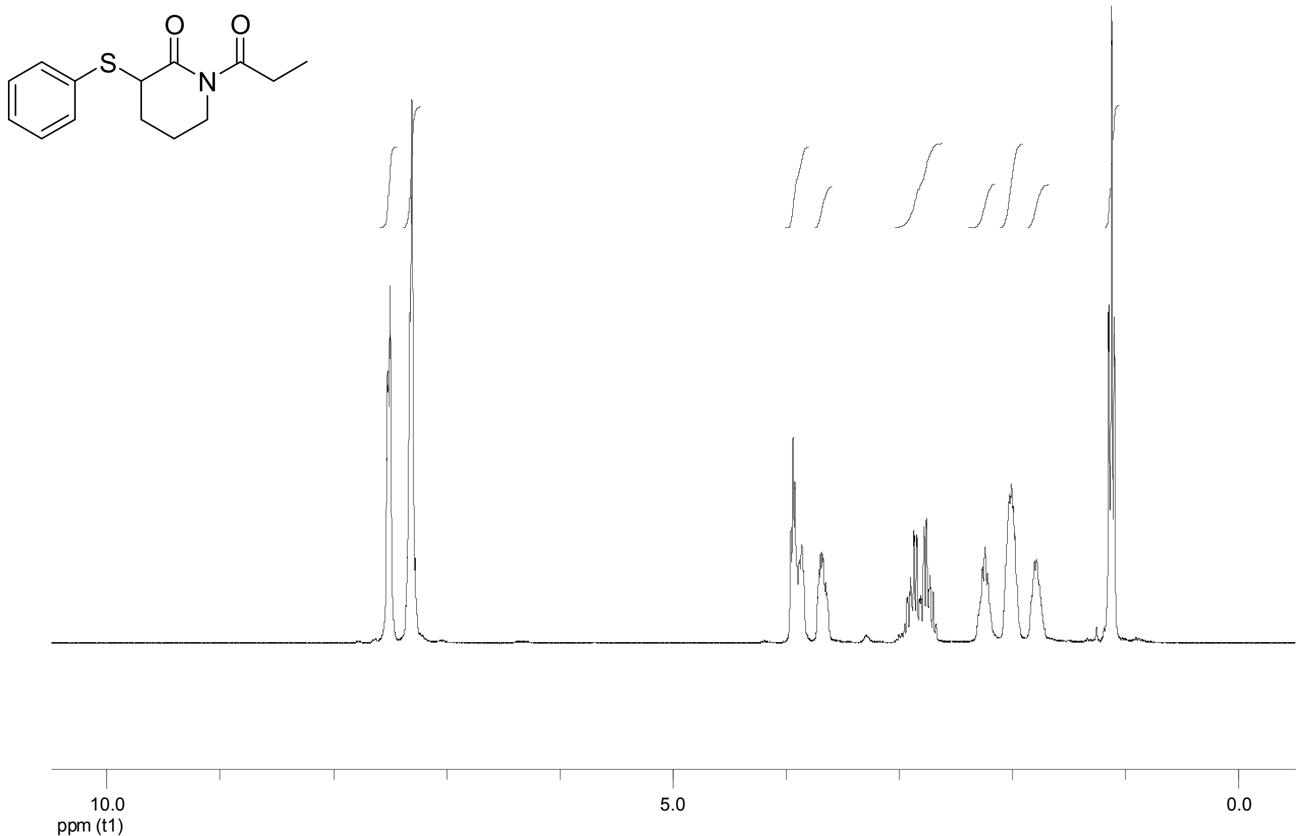
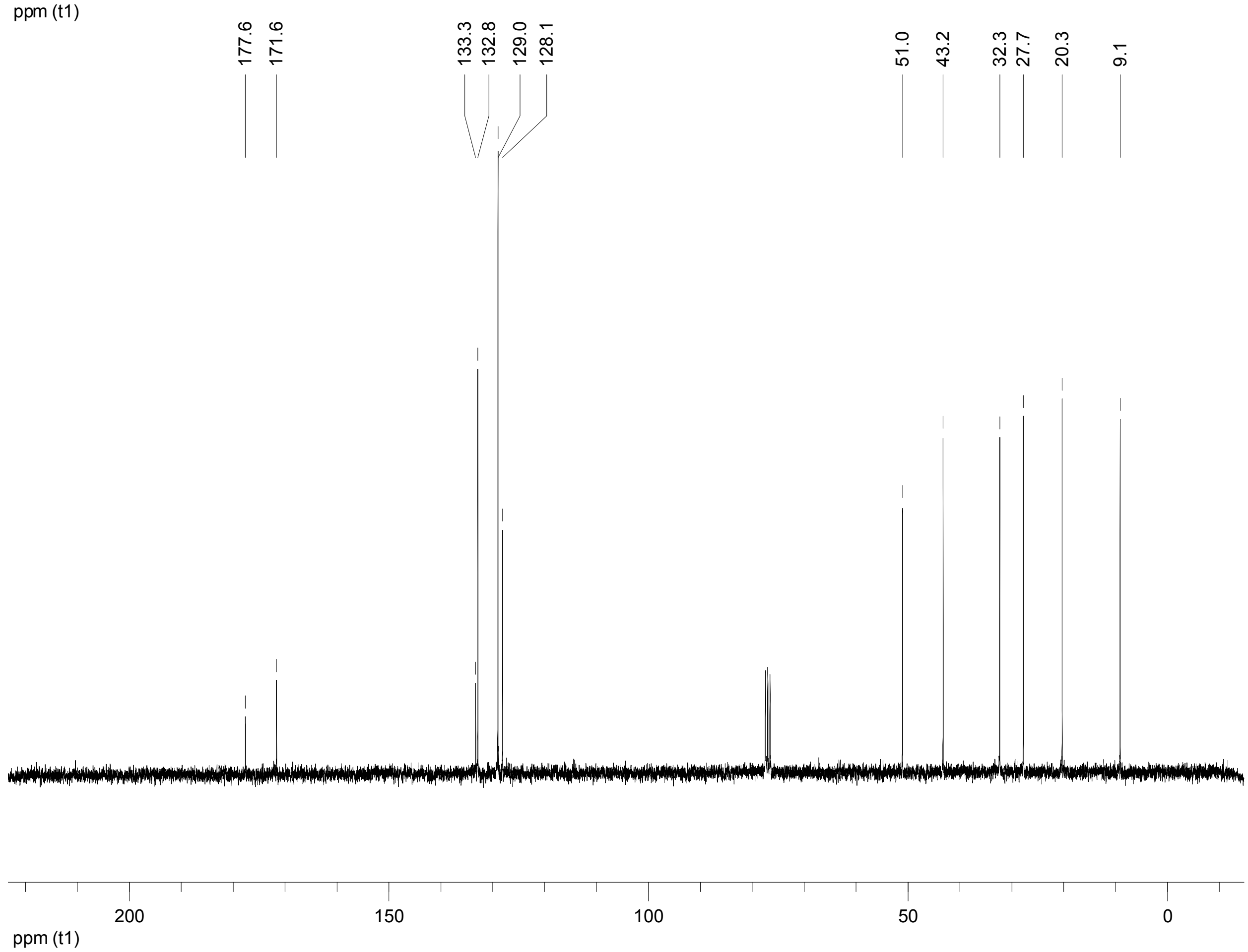
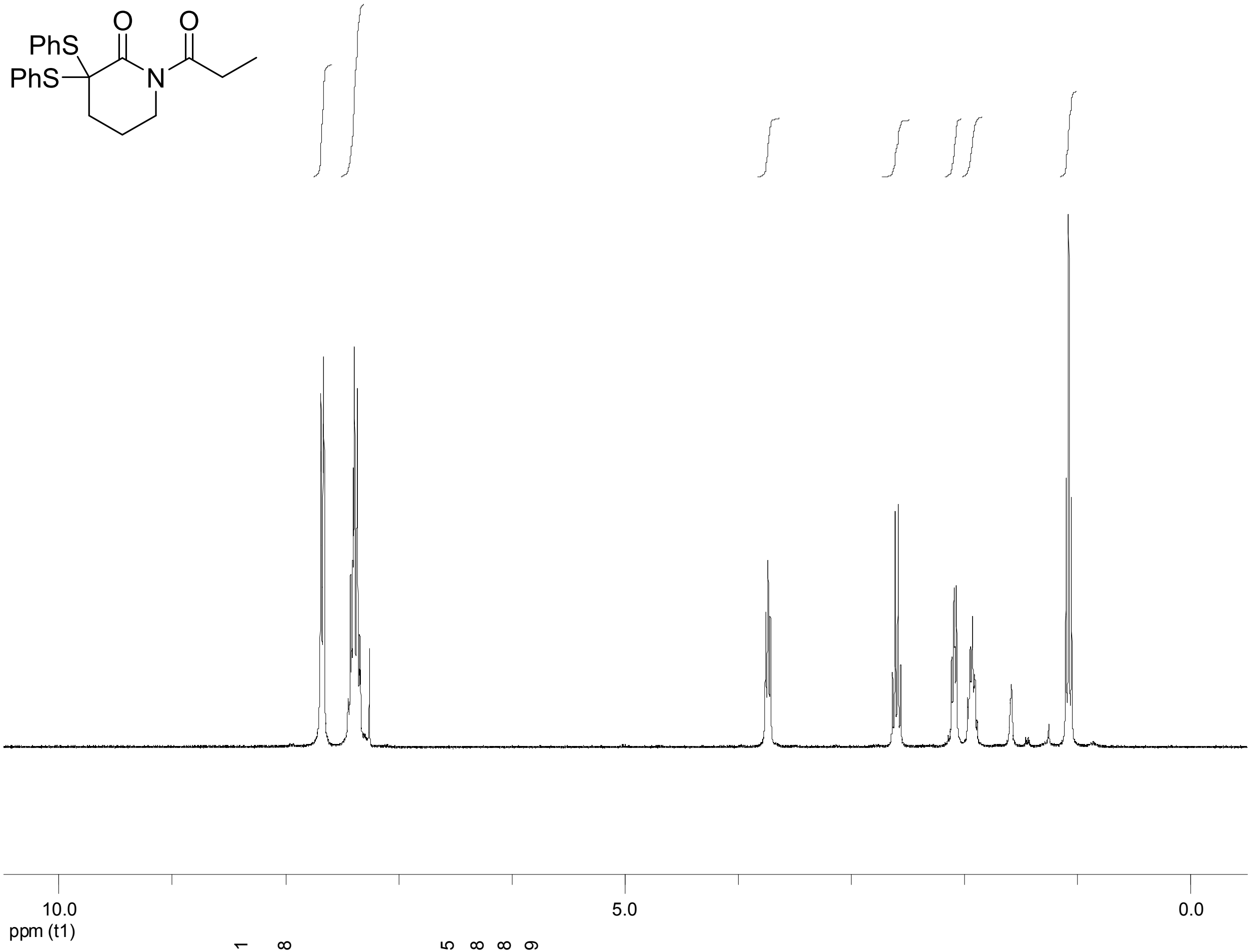
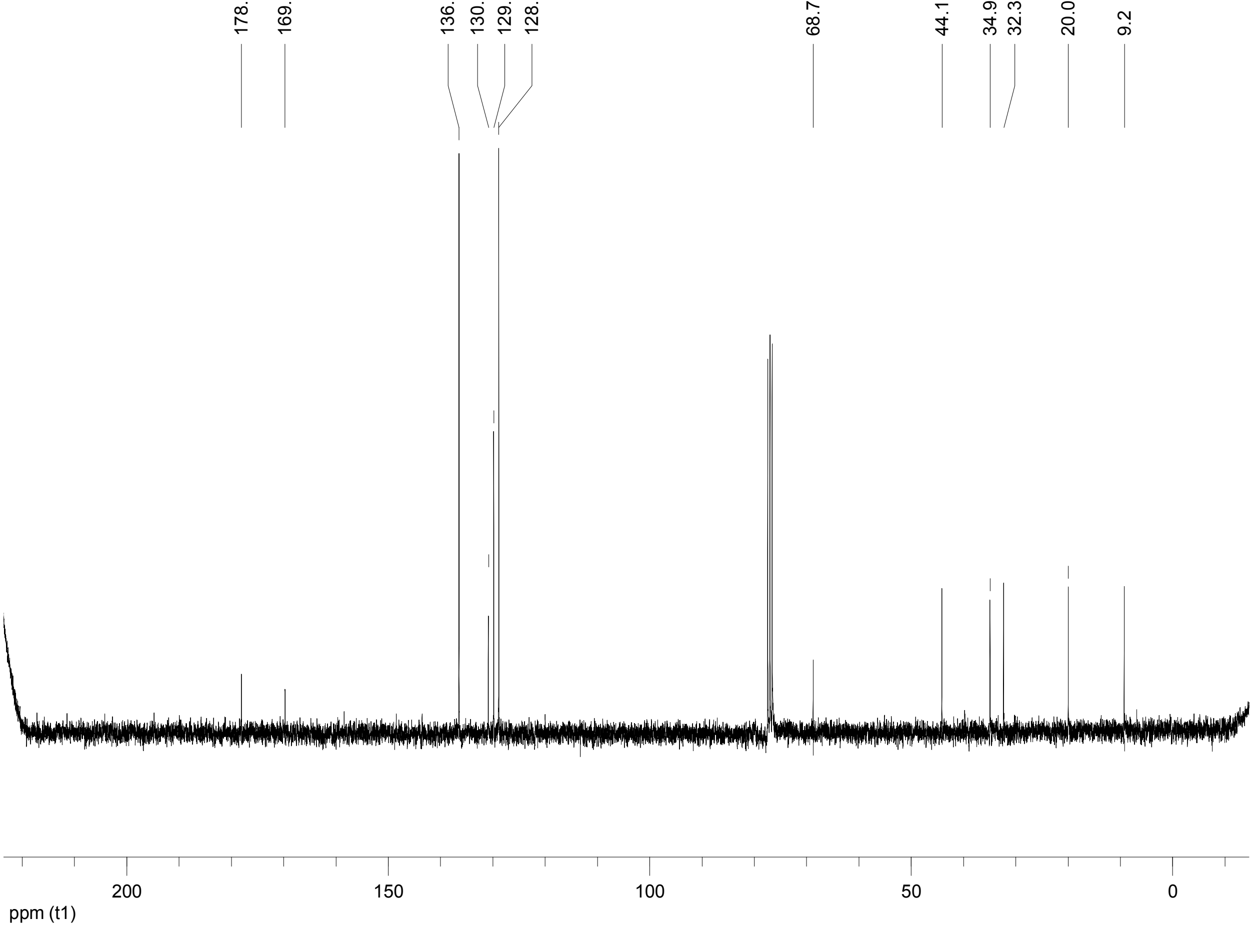
129.2
128.6
46.8
34.0
23.3
21.6
20.3
200
150
100
50
0
ppm (t1)


S
O
O
N
10.0
5.0
0.0
ppm (t1)


177.6
171.6
133.3
132.8
129.0
128.1
51.0
43.2
32.3
27.7
20.3
9.1
200
150
100
50
0
ppm (t1)


PhS
PhS
O
O
N
10.0
5.0
0.0
ppm (t1)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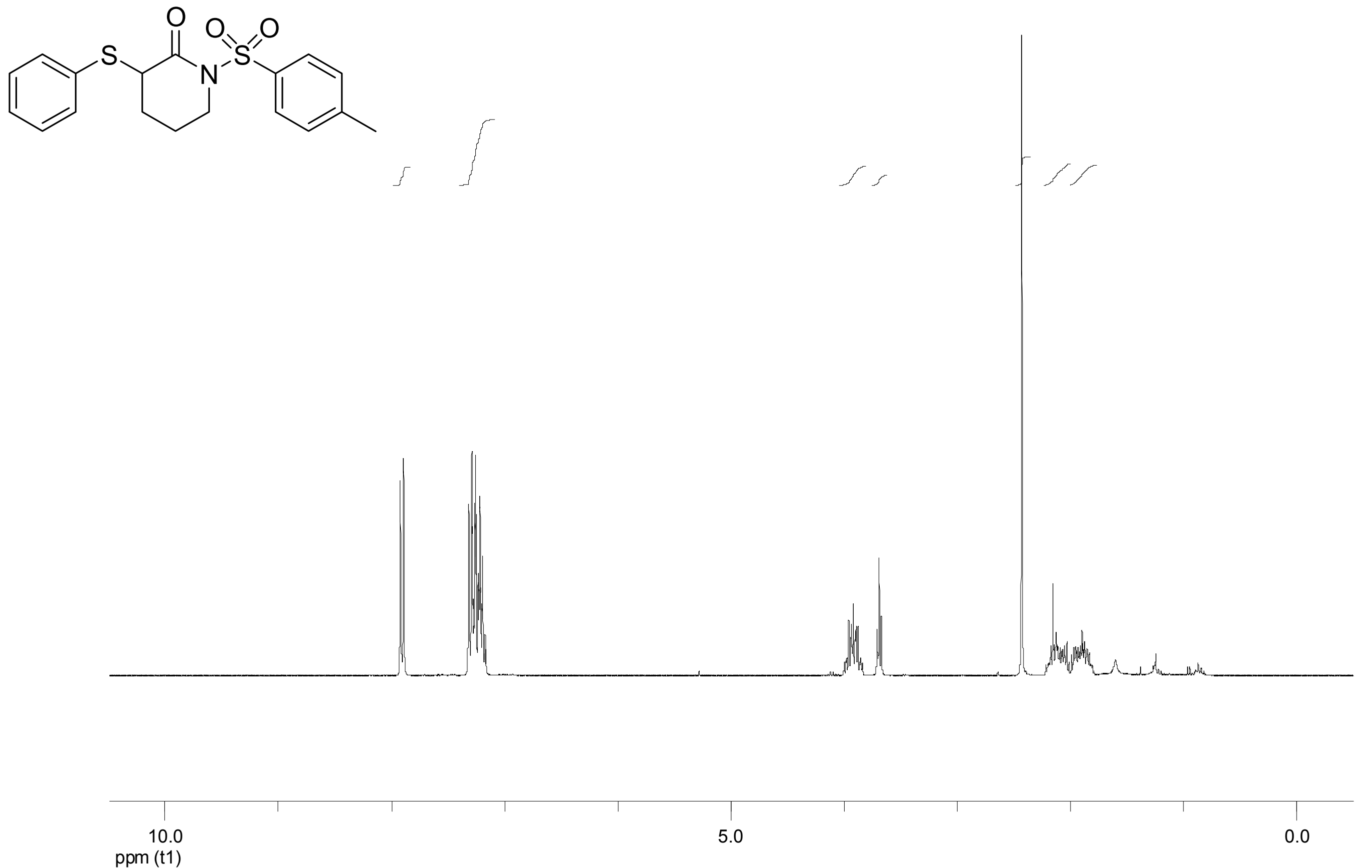
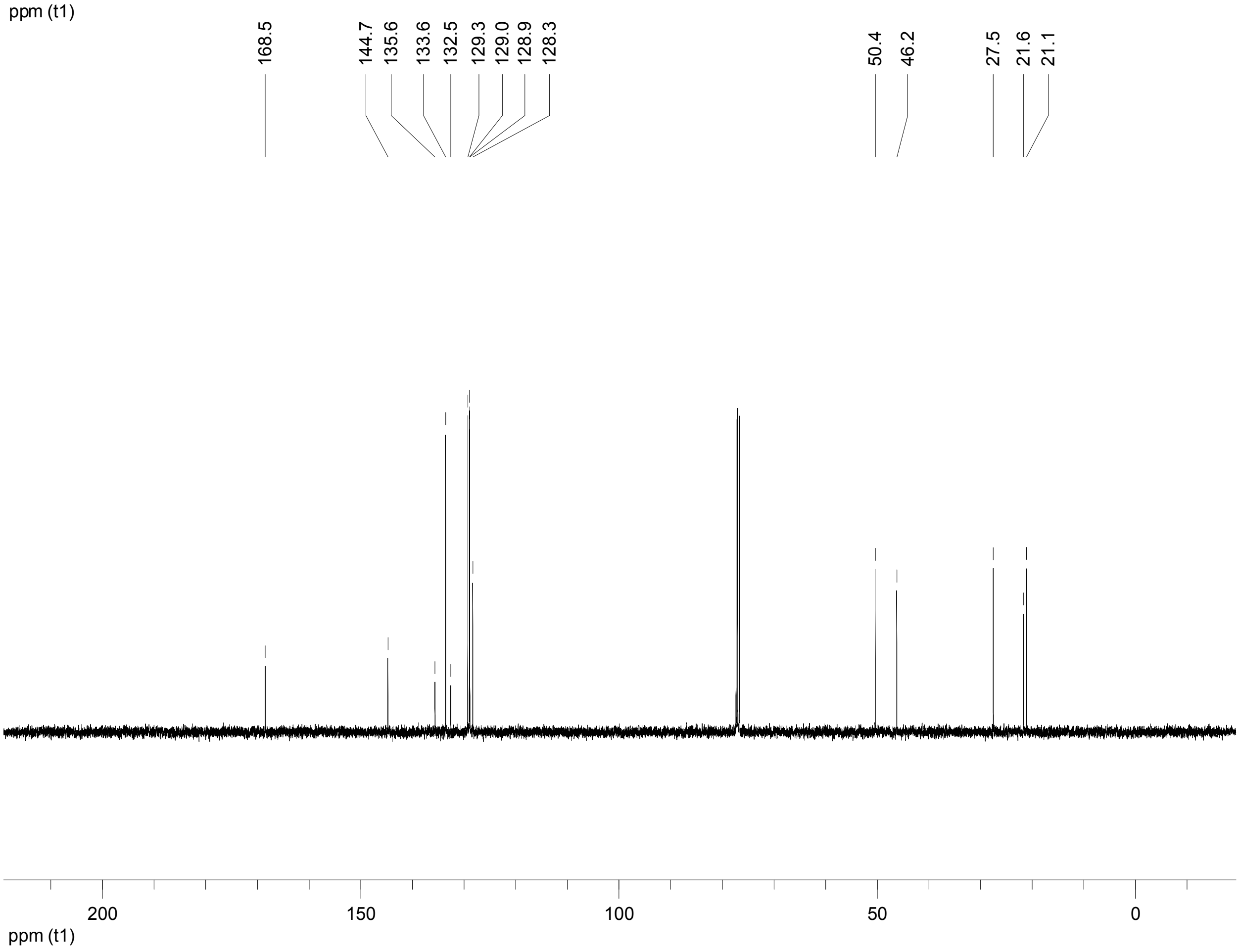
169.8
136.5
130.8
129.8
128.9
68.7
44.1
34.9
32.3
20.0
9.2
200
150
100
50
0
ppm (t1)


S
O
O
S
O
N
10.0
ppm (t1)
5.0
0.0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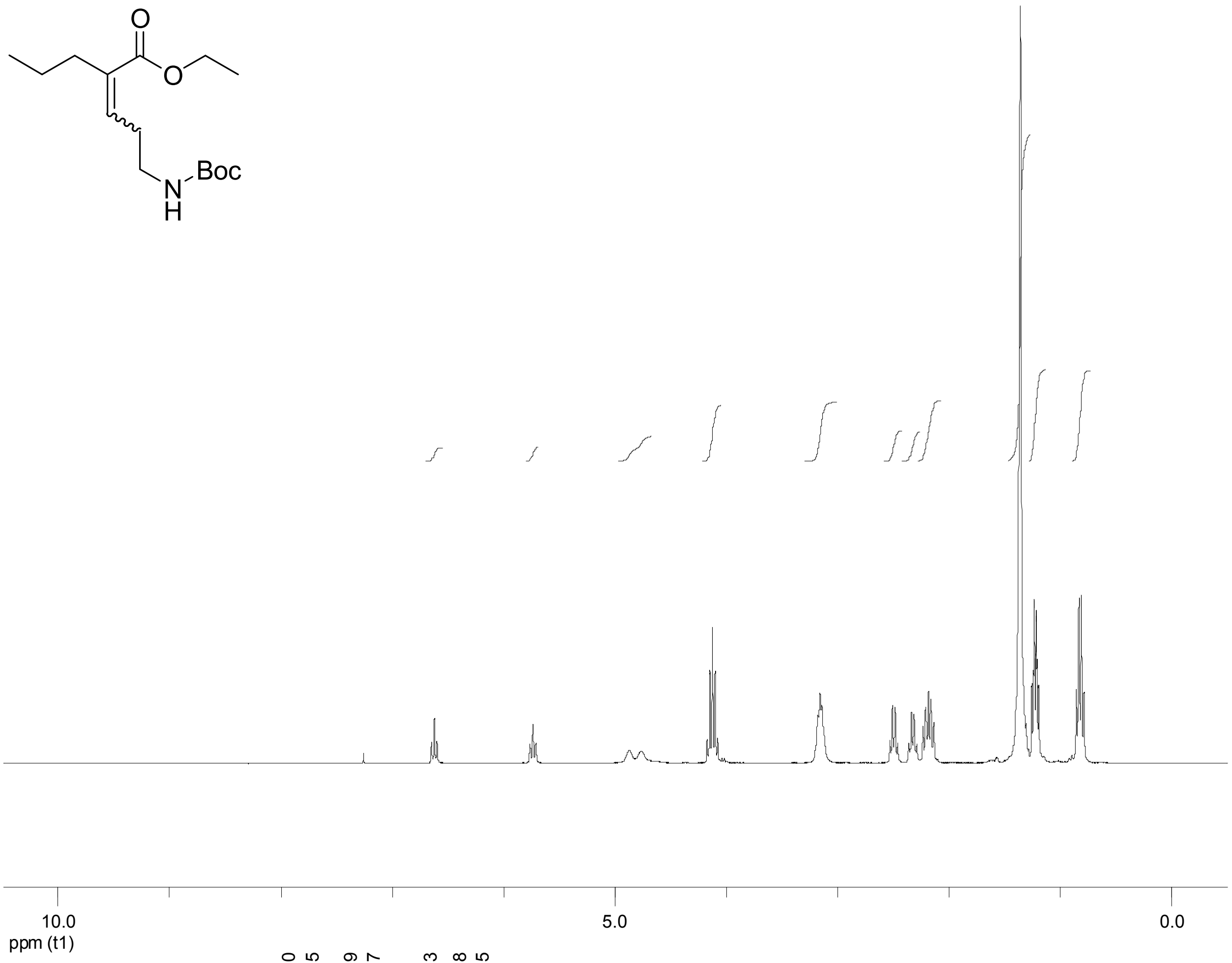
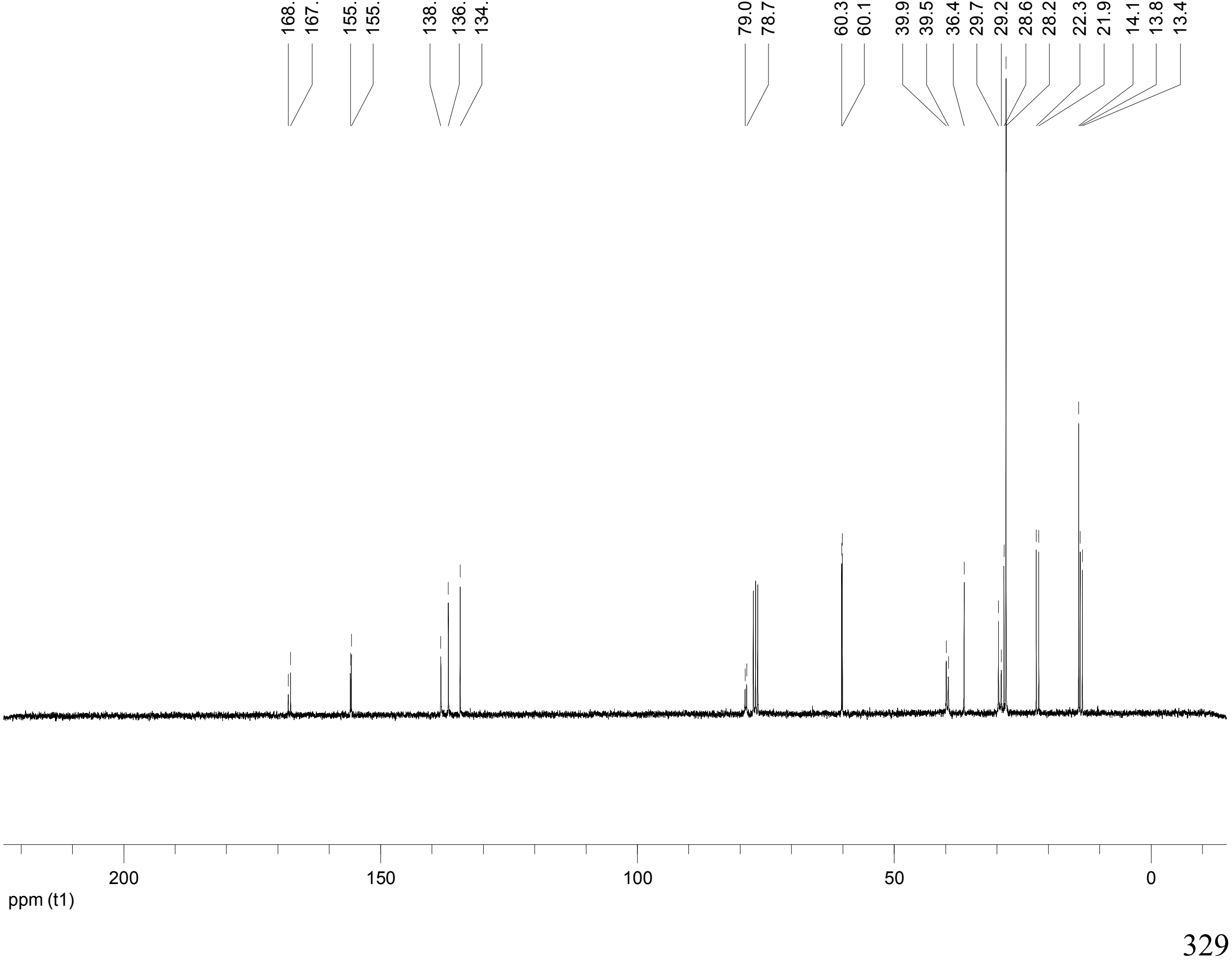
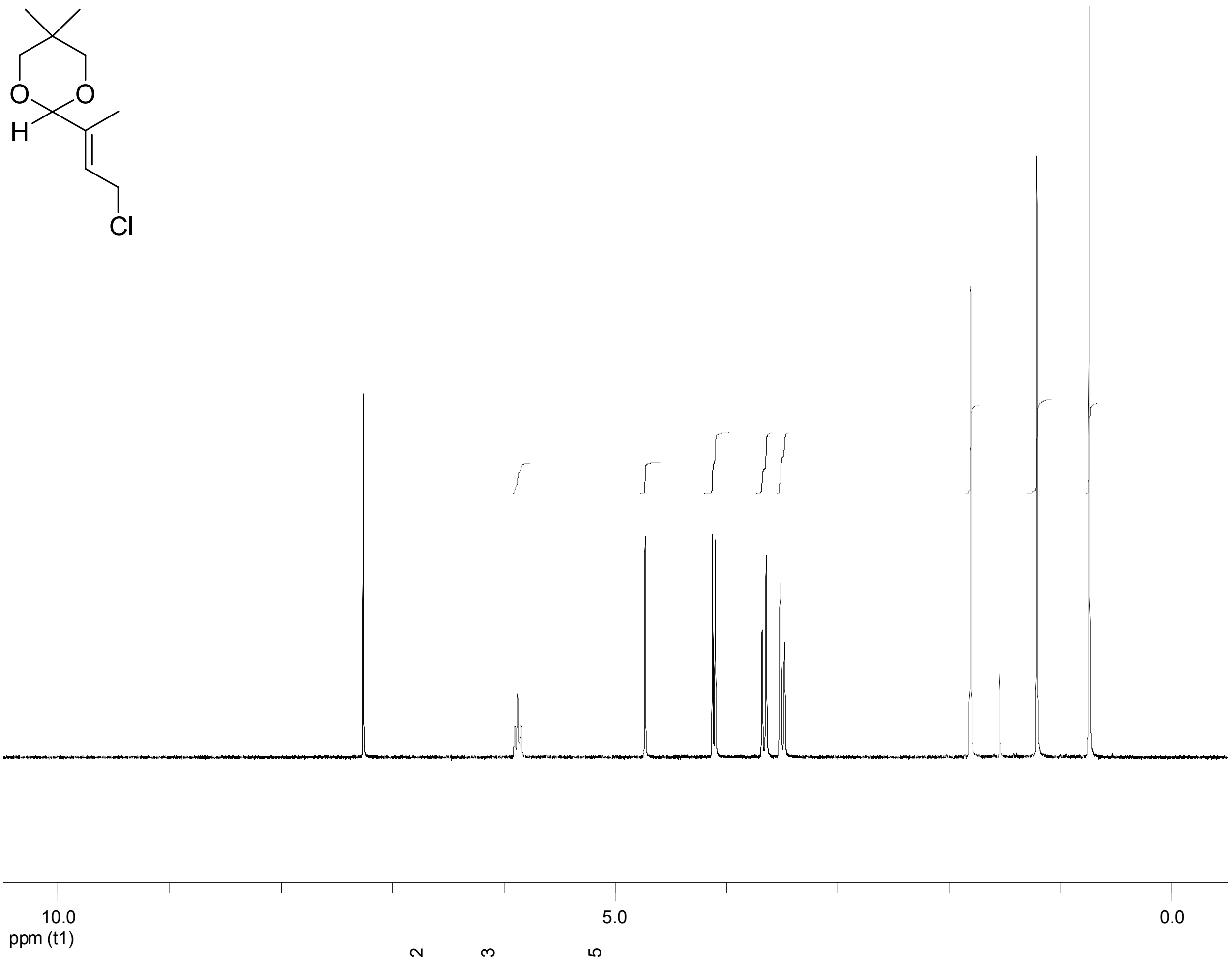
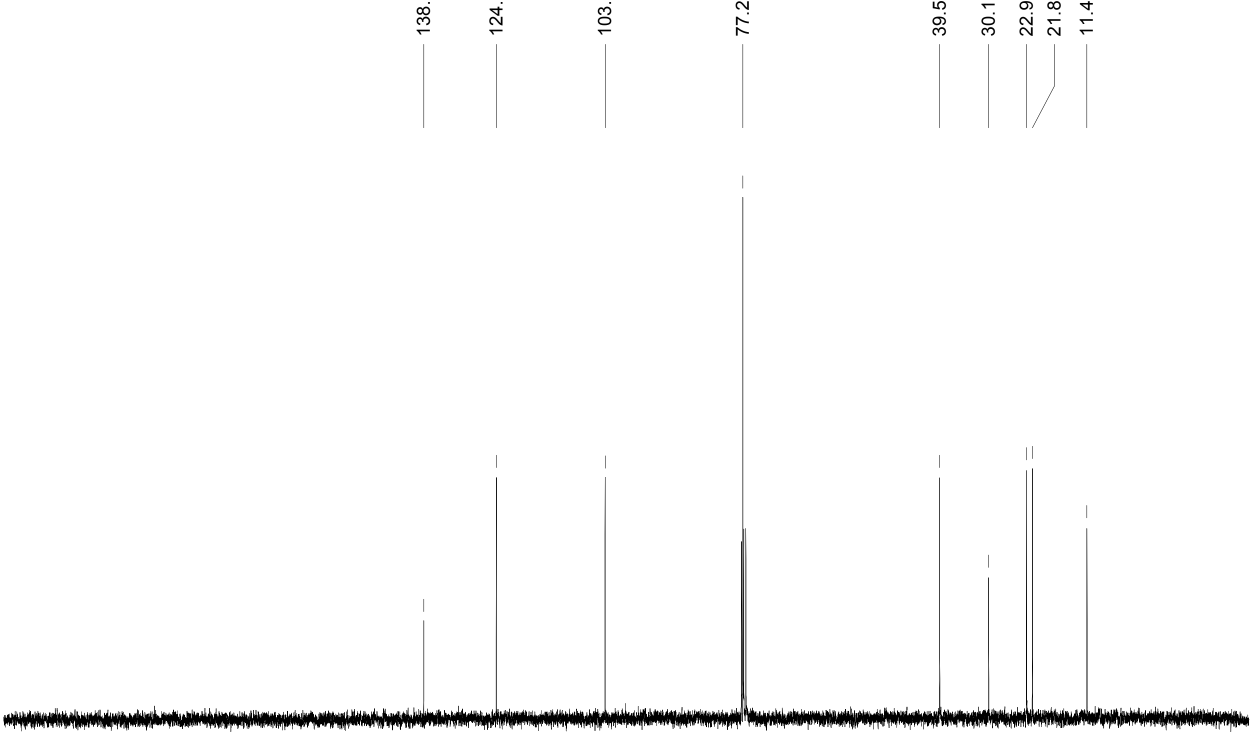
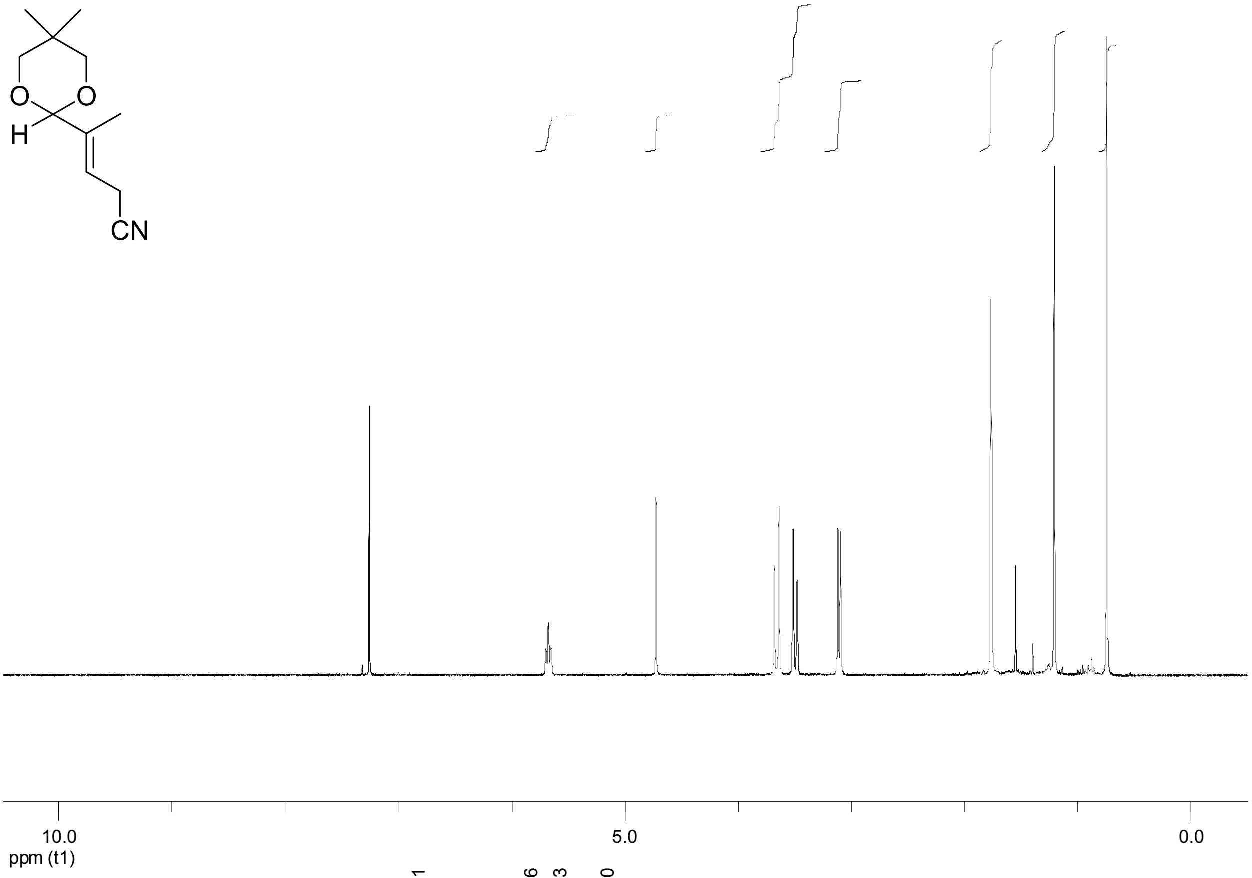
144.7
135.6
133.6
132.5
129.3
129.0
128.9
128.3
50.4
46.2
27.5
21.6
21.1
200
150
100
50
0
ppm (t1)

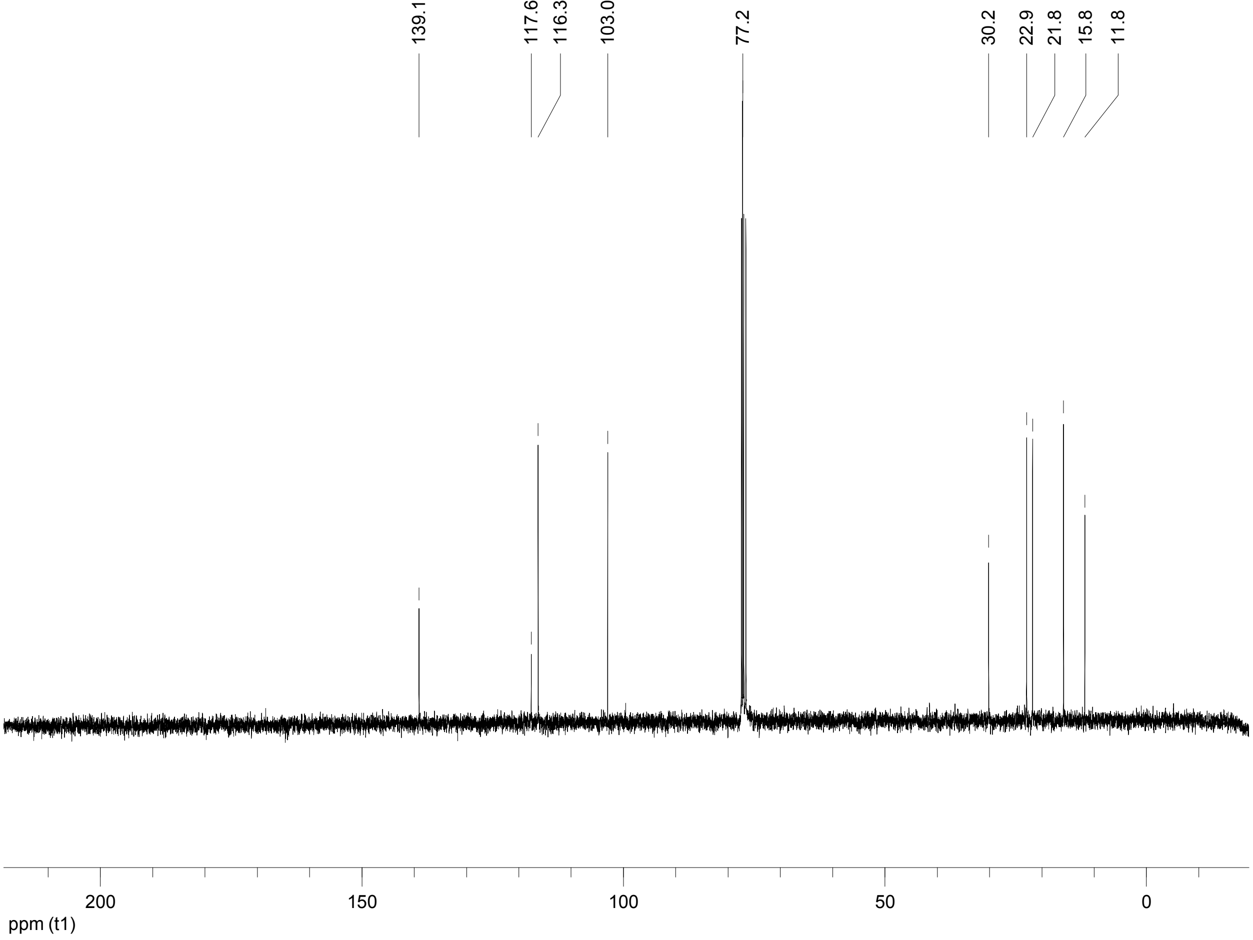

O
O
N
H
Boc
10.0
5.0
0.0
ppm (t1)

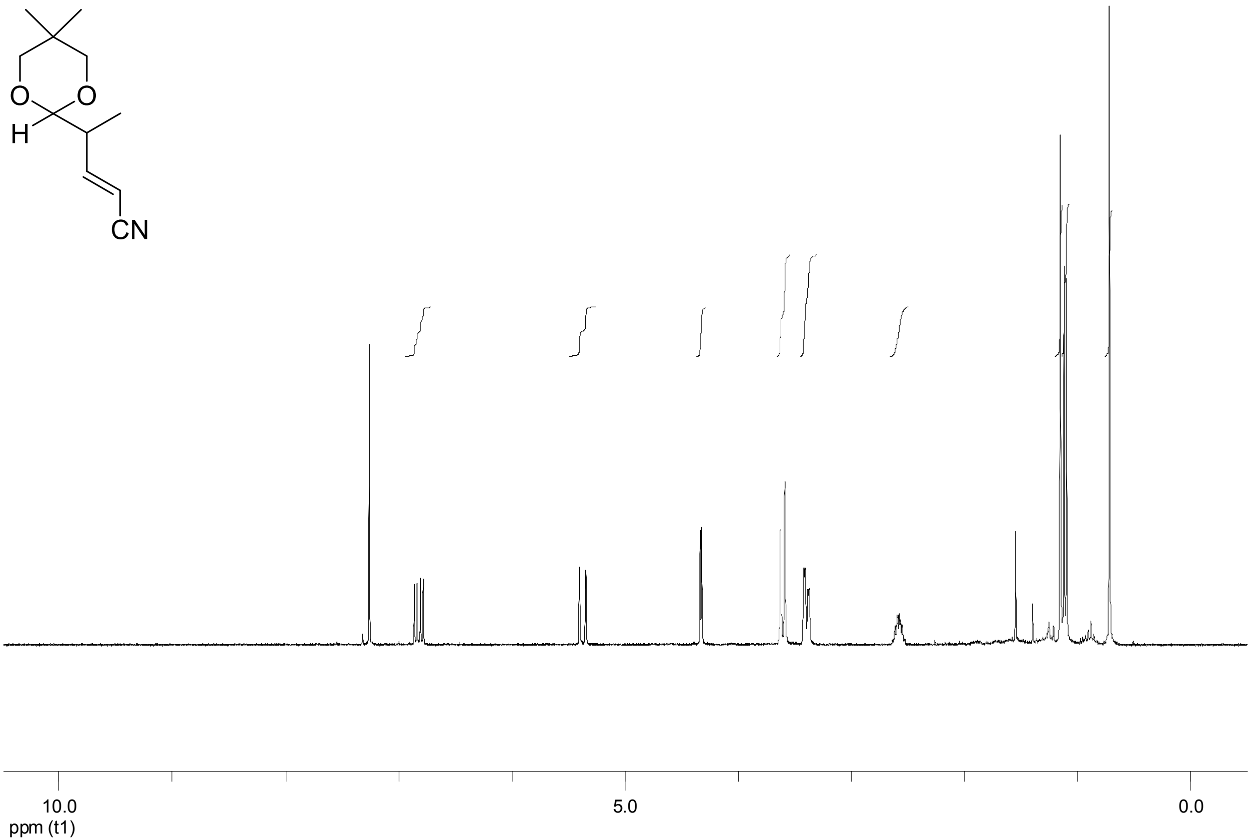

168.0
167.5
155.9
155.7
138.3
136.8
134.5
79.0
78.7
60.3
60.1
39.9
39.5
36.4
29.7
29.2
28.6
28.2
22.3
21.9
14.1
13.8
13.4
200
150
100
50
0
ppm (t1)

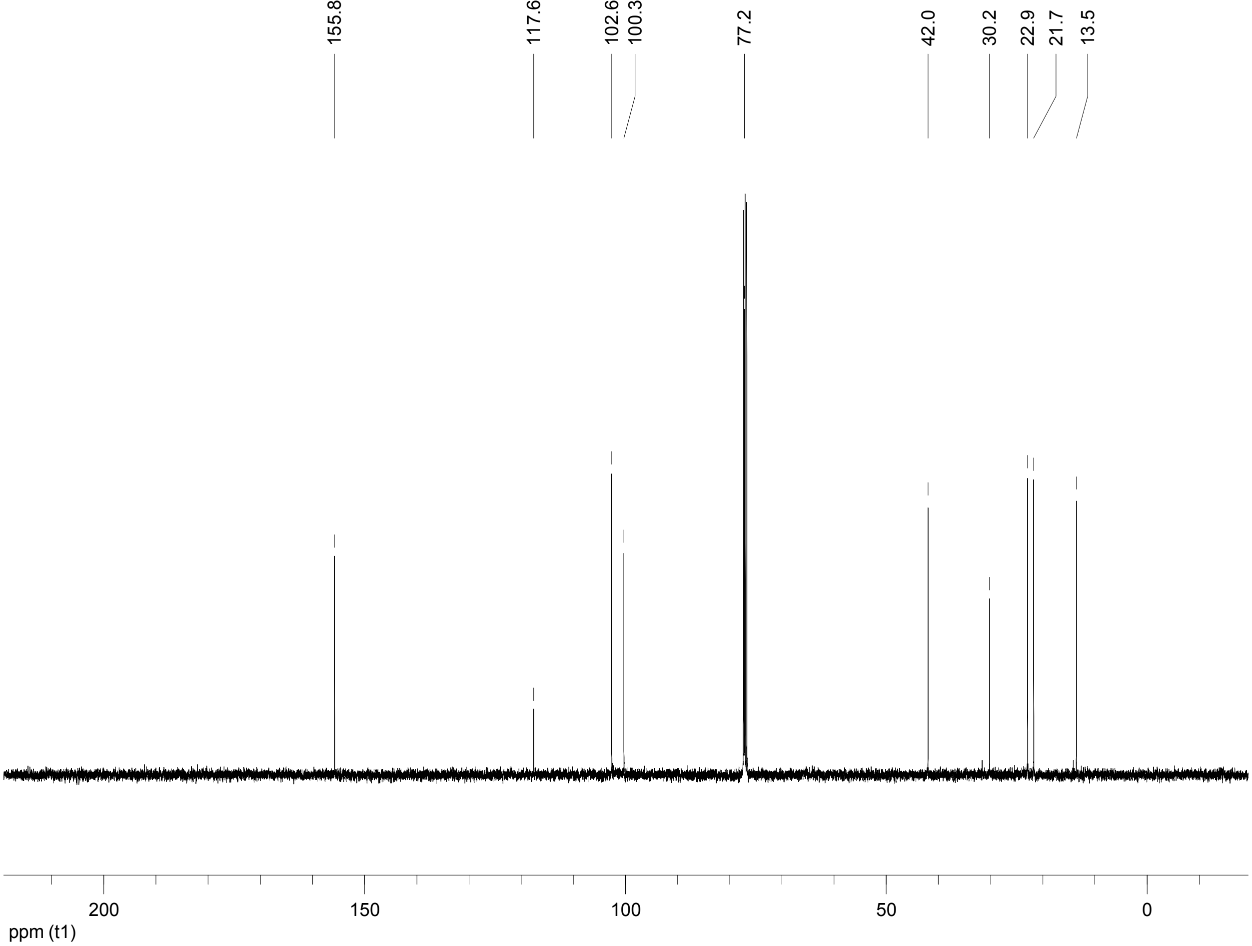

O
O
H
Cl
10.0
5.0
0.0
ppm (t1)

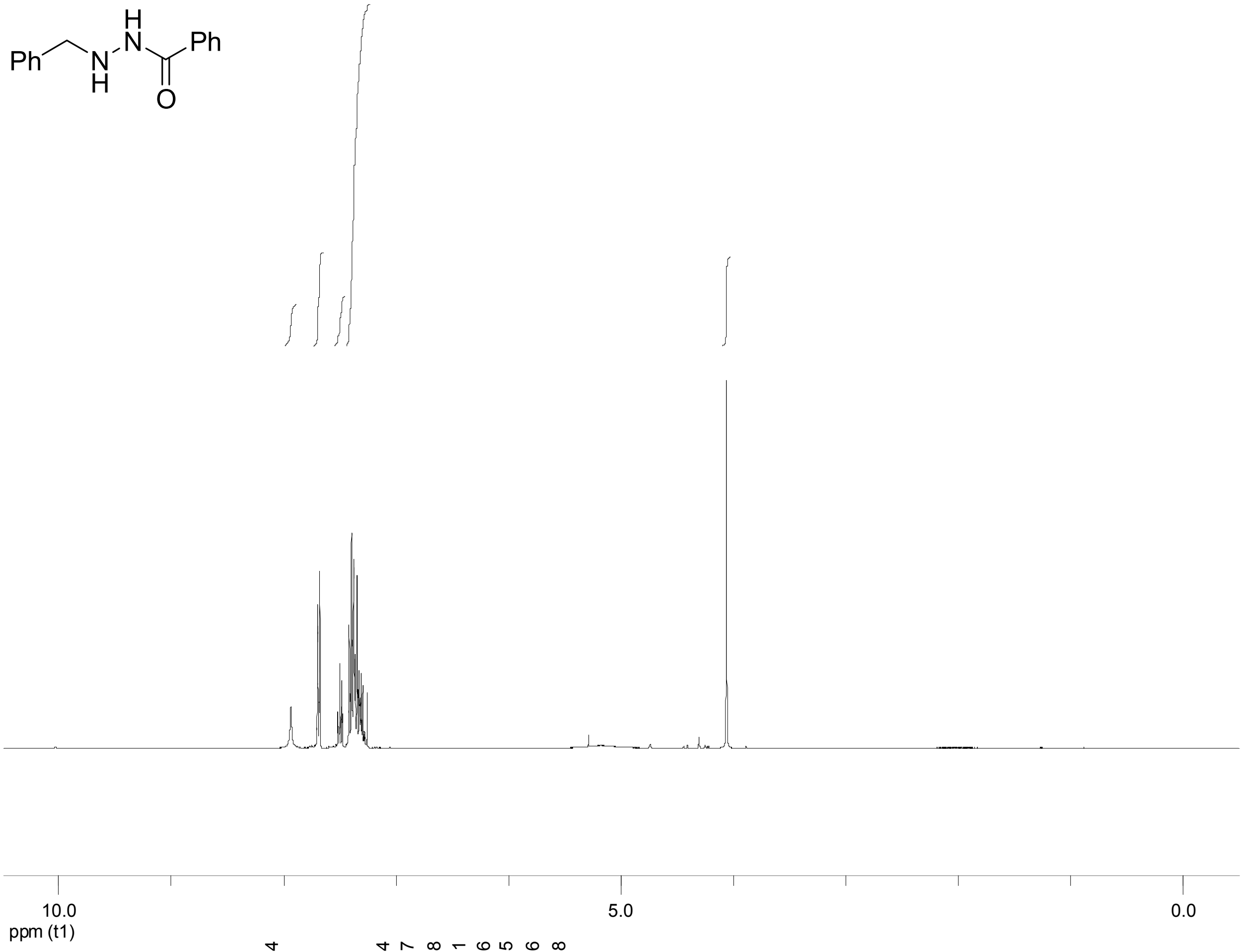

138.2
124.3
103.5
77.2
39.5
30.1
22.9
21.8
11.4
200
150
100
50
0
ppm (t1)


O
O
H
CN
10.0
5.0
0.0
ppm (t1)

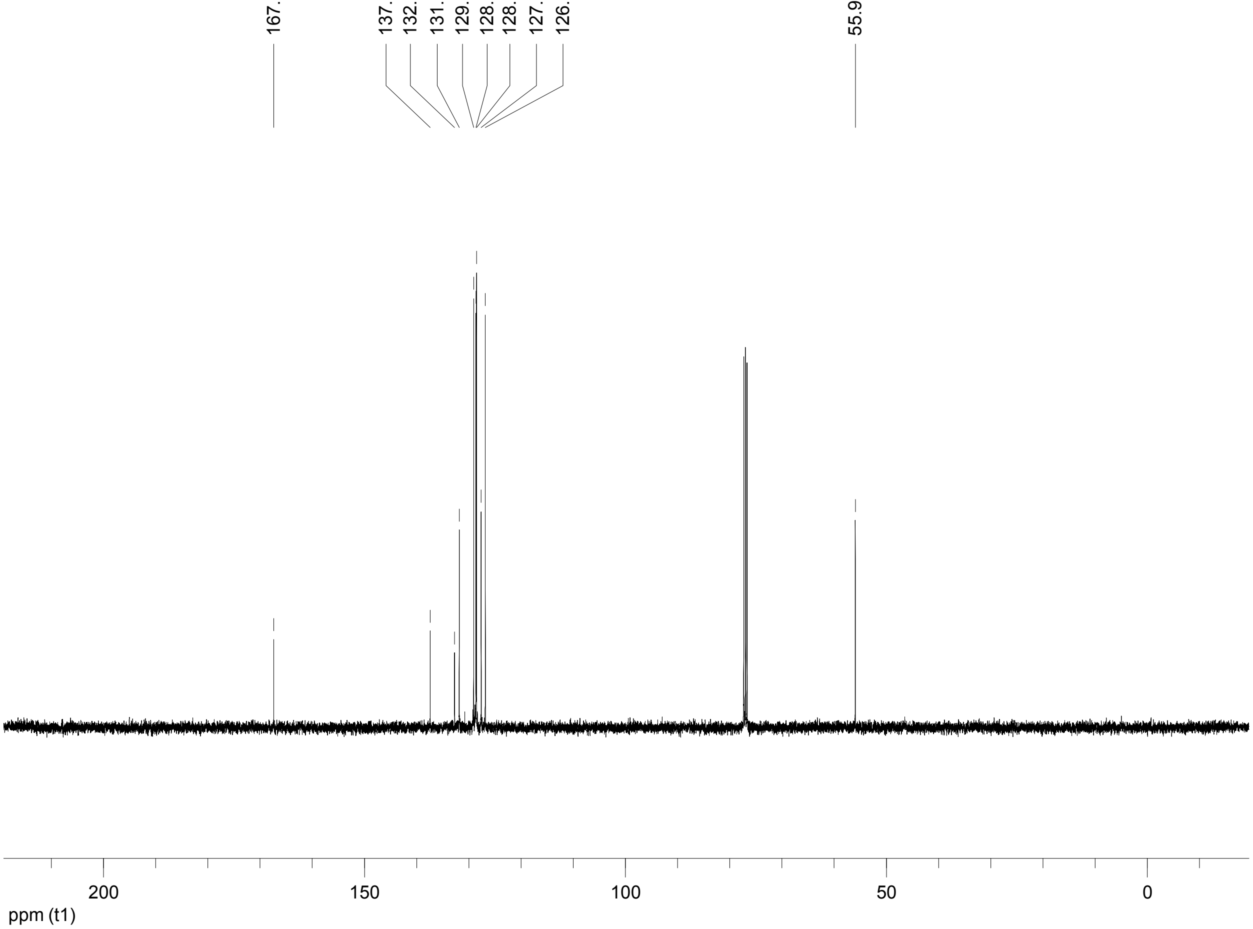

139.1
117.6
116.3
103.0
77.2
30.2
22.9
21.8
15.8
11.8
200
150
100
50
0
ppm (t1)

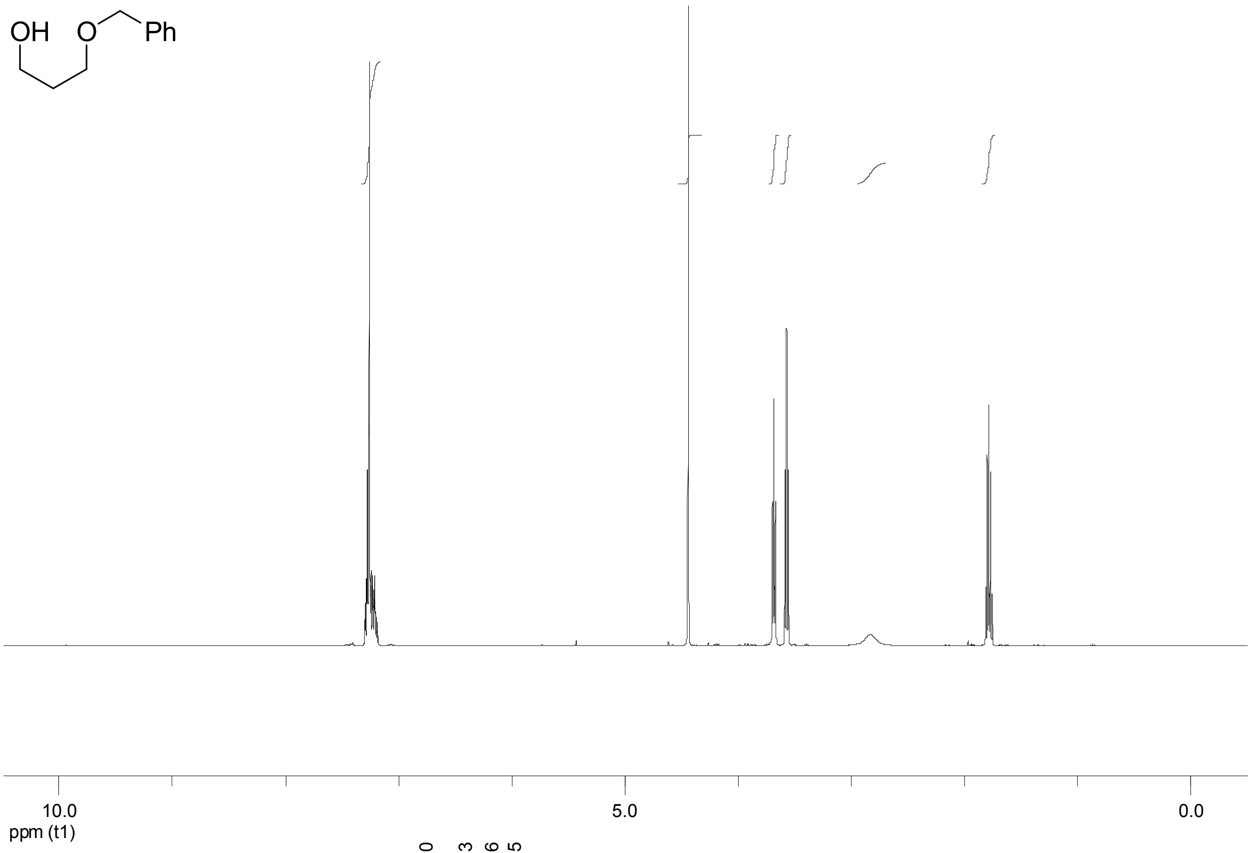

O
O
H
CN
10.0
5.0
0.0
ppm (t1)


155.8
117.6
102.6
100.3
77.2
42.0
30.2
22.9
21.7
13.5
200
150
100
50
0
ppm (t1)


Ph
H
N
N
H
Ph
O

10.0
5.0
0.0
ppm (t1)


167.4
137.4
132.7
131.8
129.1
128.6
128.5
127.6
126.8
55.9
200
150
100
50
0
ppm (t1)


OH
O
Ph
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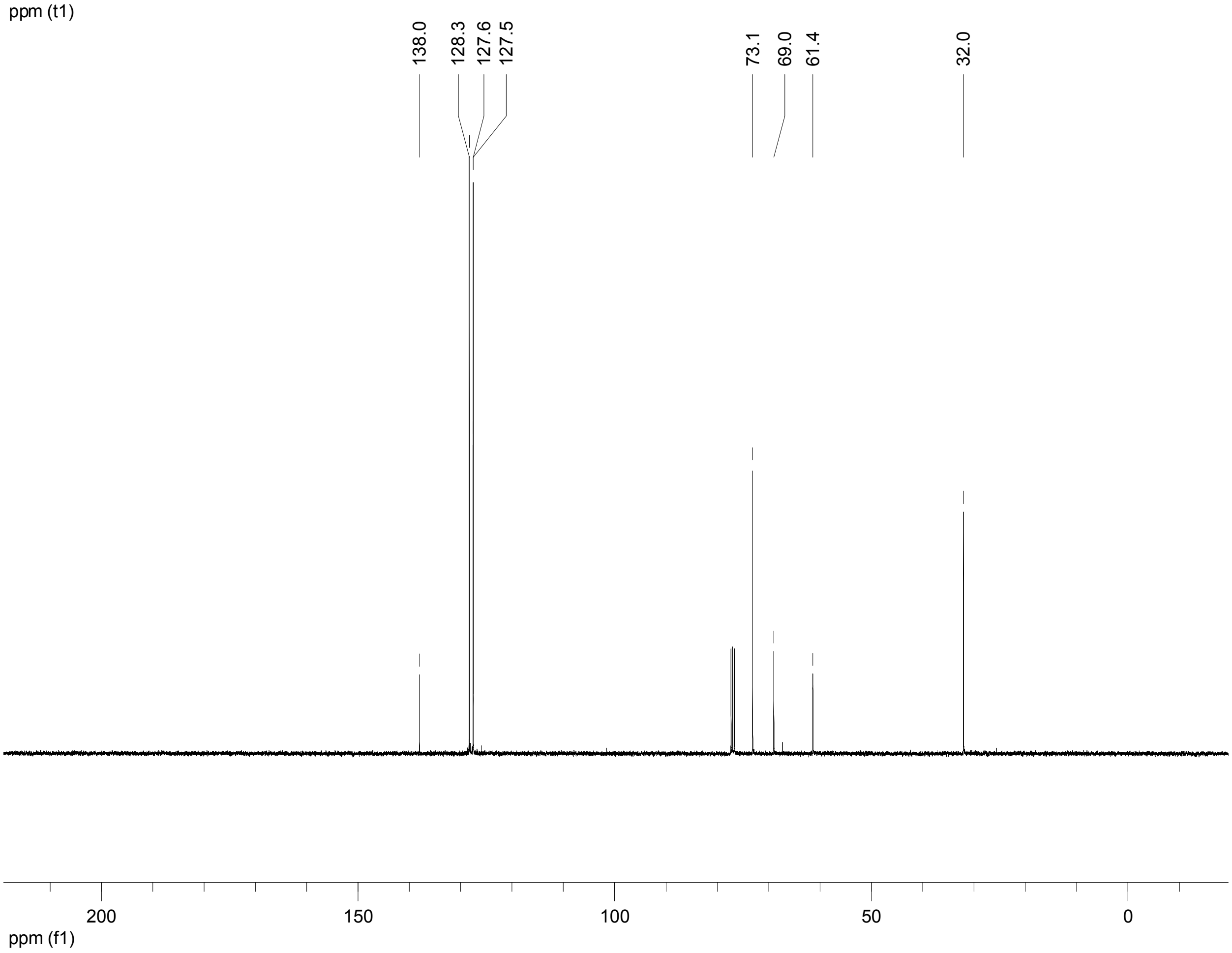
5.0
0.0
ppm (t1)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128.3
127.6
127.5
73.1
69.0
61.4
32.0
200
150
100
50
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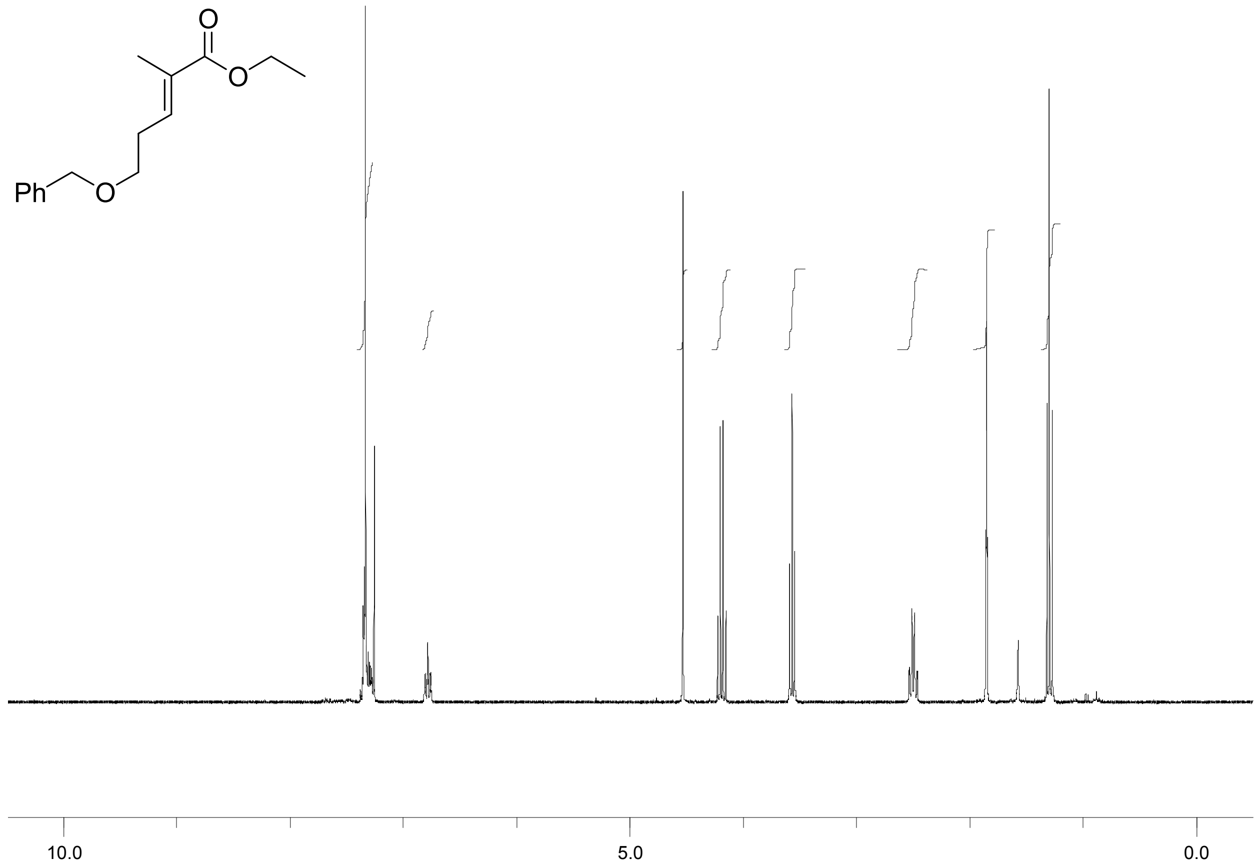
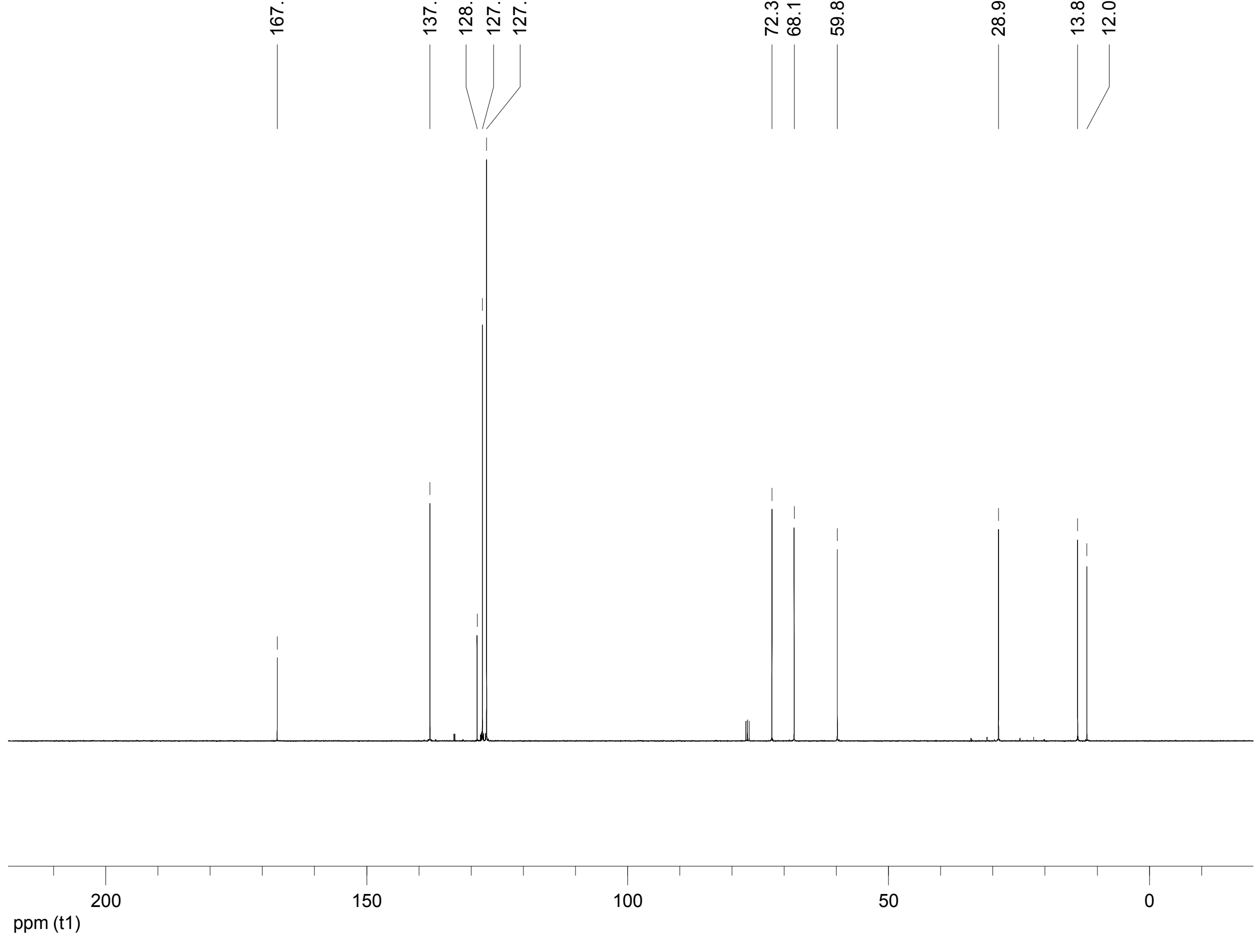
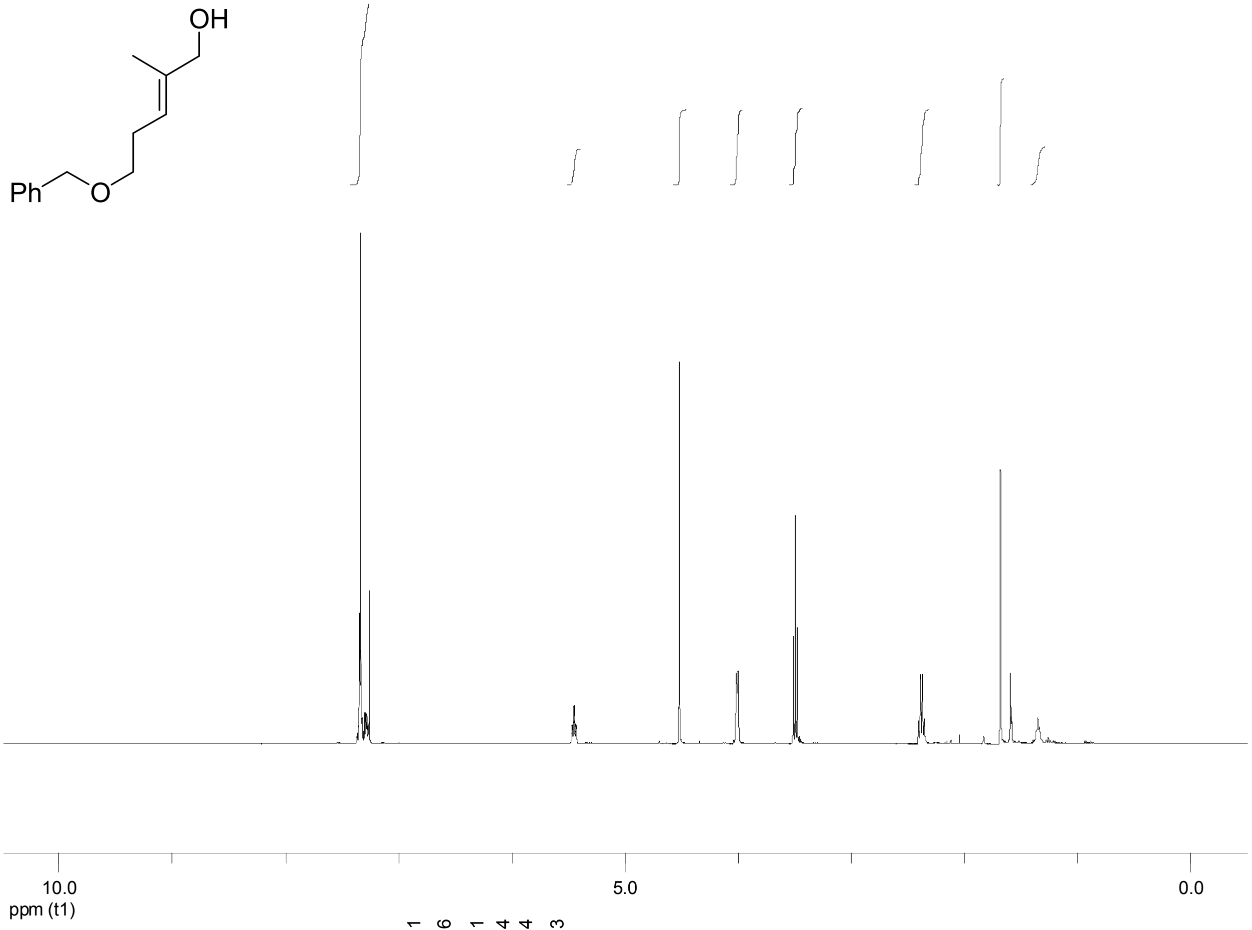
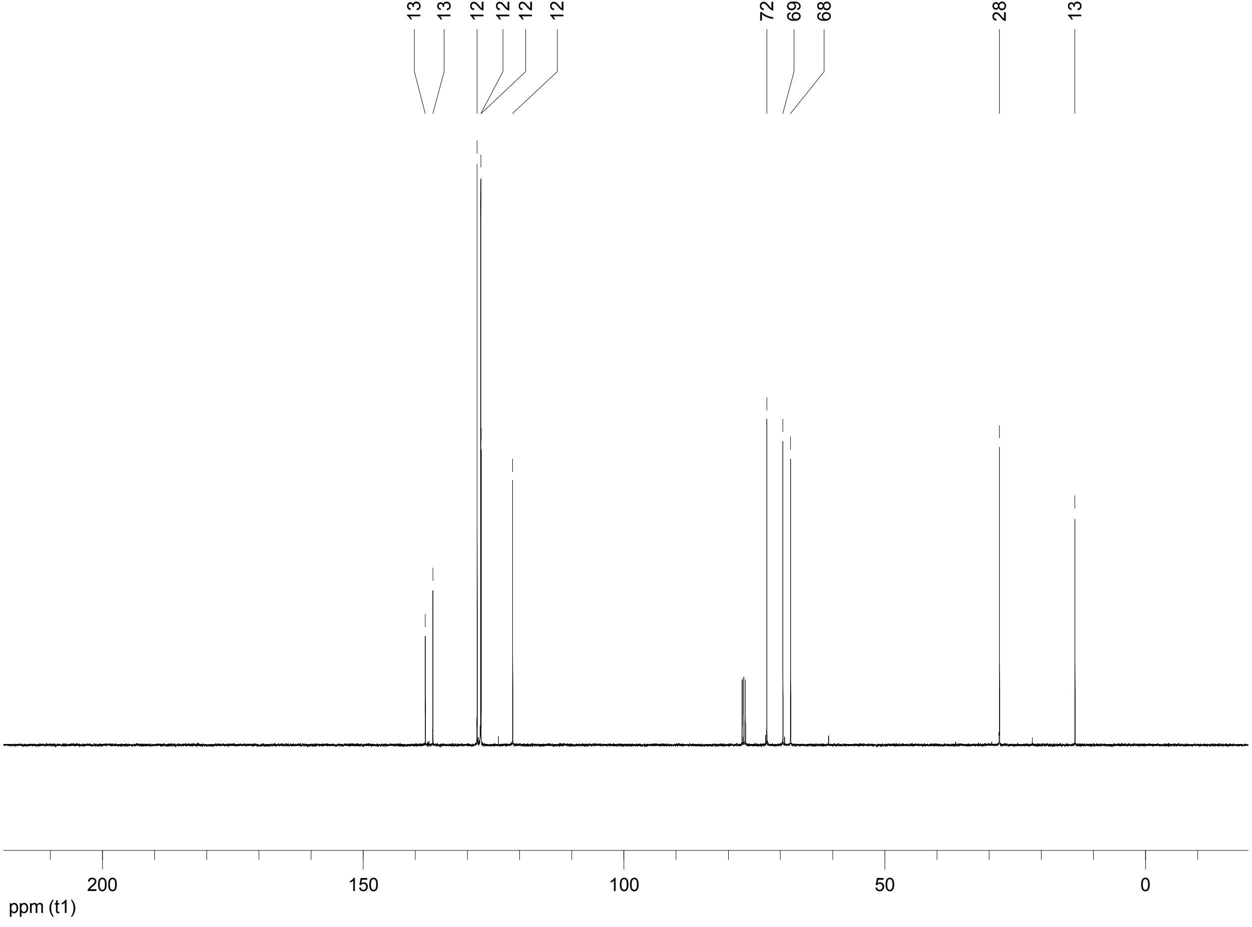
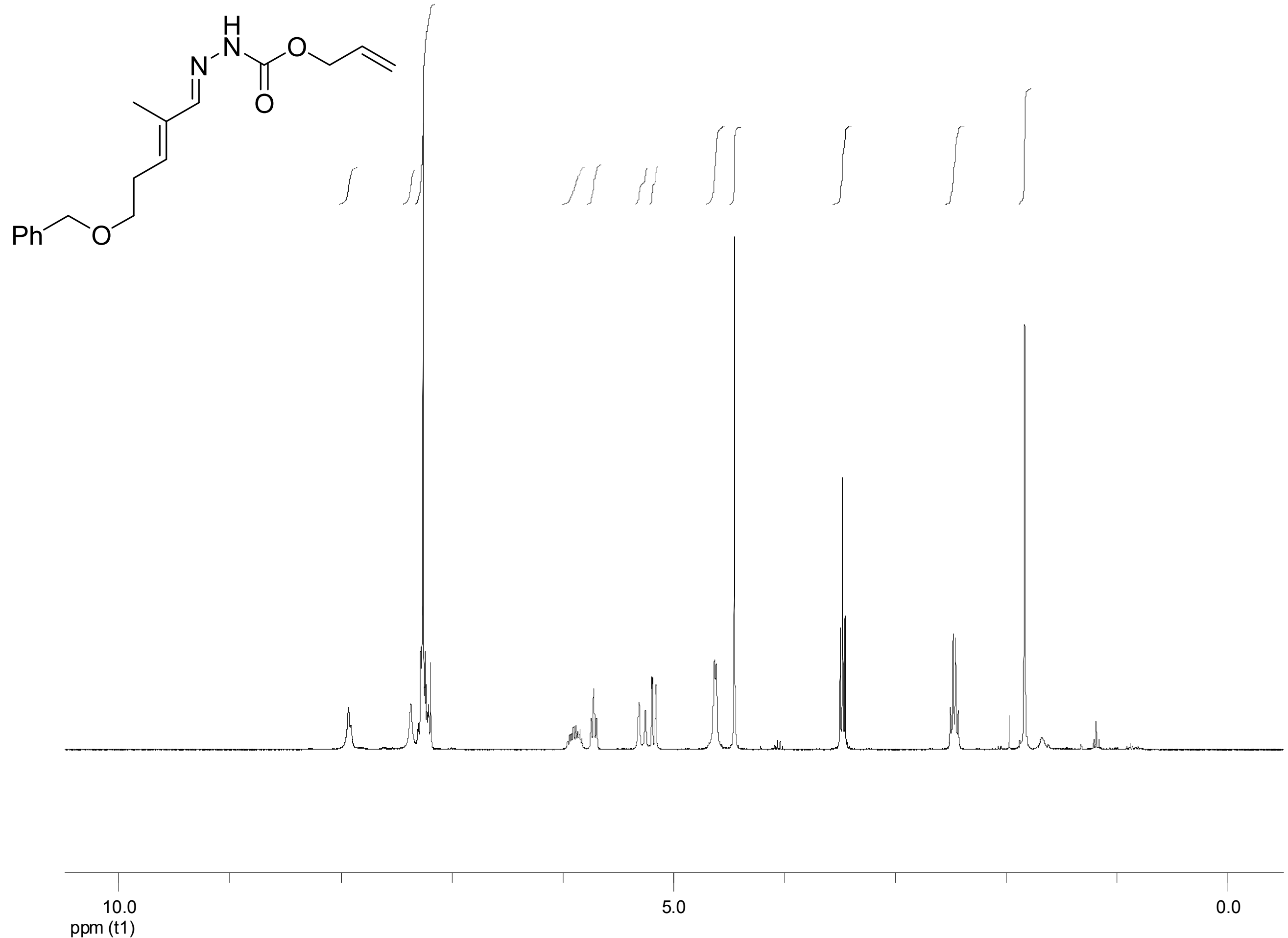
ppm (f1)

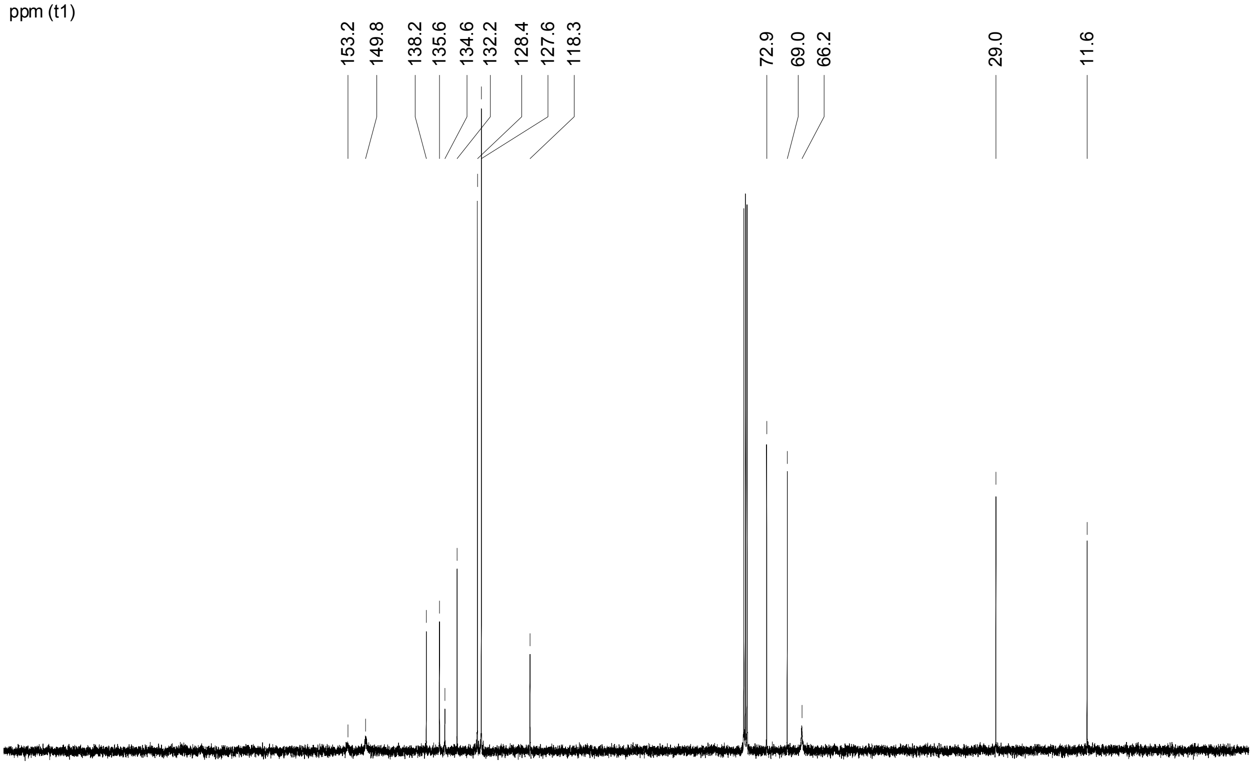

O
O
Ph
O
10.0
5.0
0.0
ppm (t1)

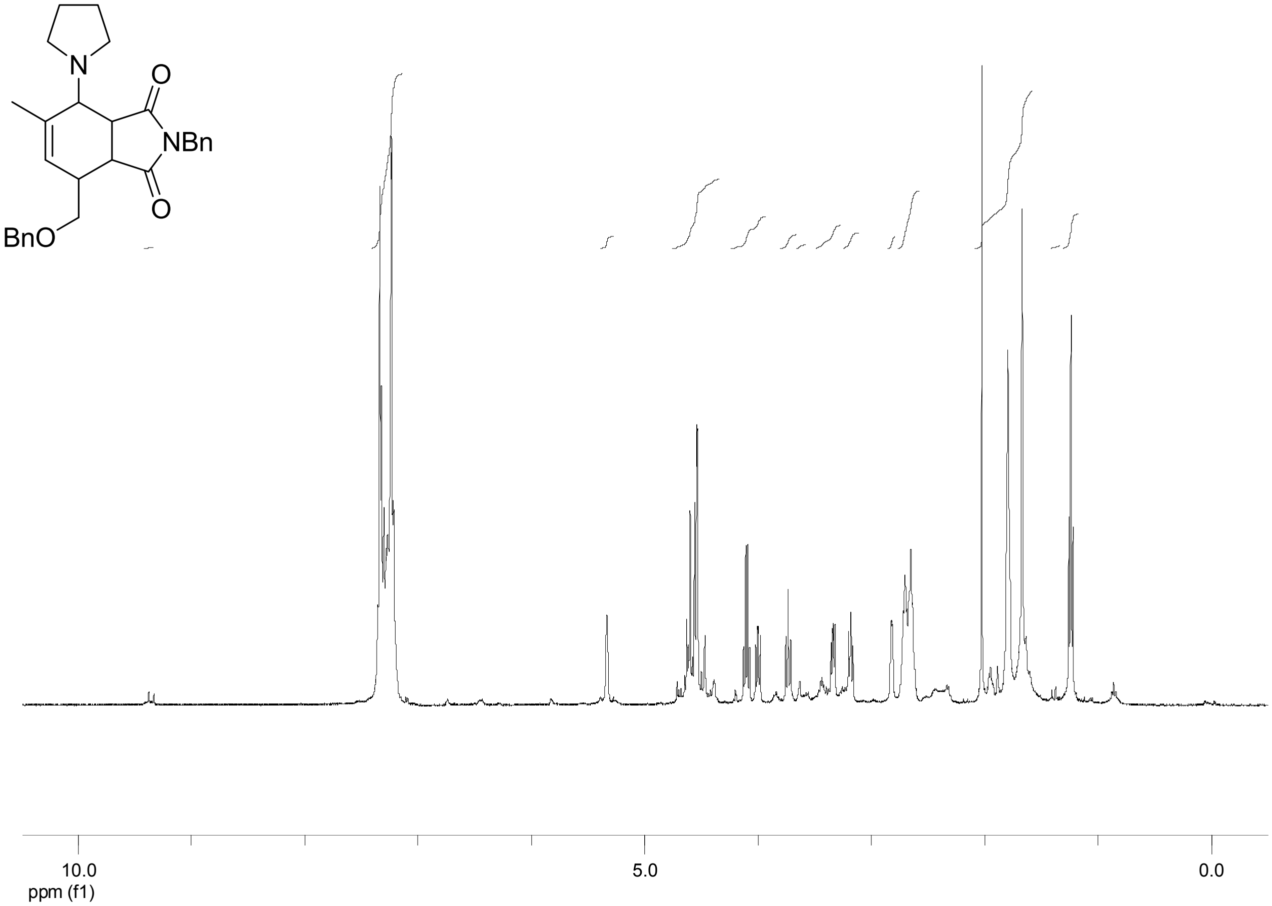

167.1
137.9
128.8
127.8
127.0
72.3
68.1
59.8
28.9
13.8
12.0
200
150
100
50
0
ppm (t1)


OH
Ph
O
10.0
5.0
0.0
ppm (t1)


138.1
136.6
128.1
127.4
127.4
121.3
72.6
69.5
68.0
28.0
13.5
200
150
100
50
0
ppm (t1)


H
N
N
O
O
Ph
O
10.0
5.0
0.0
ppm (t1)


153.2
149.8
138.2
135.6
134.6
132.2
128.4
127.6
118.3
72.9
69.0
66.2
29.0
11.6
200
150
100
50
0
ppm (t1)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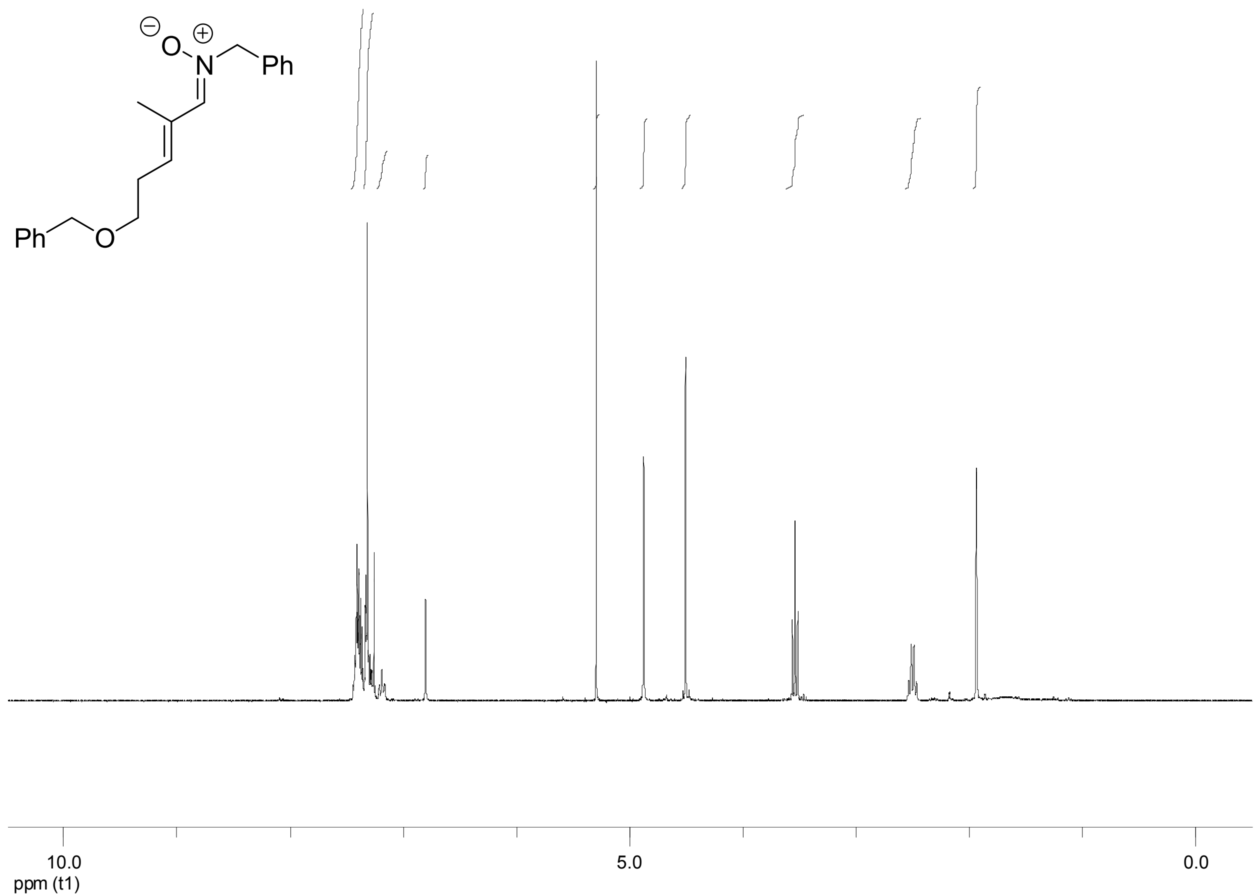
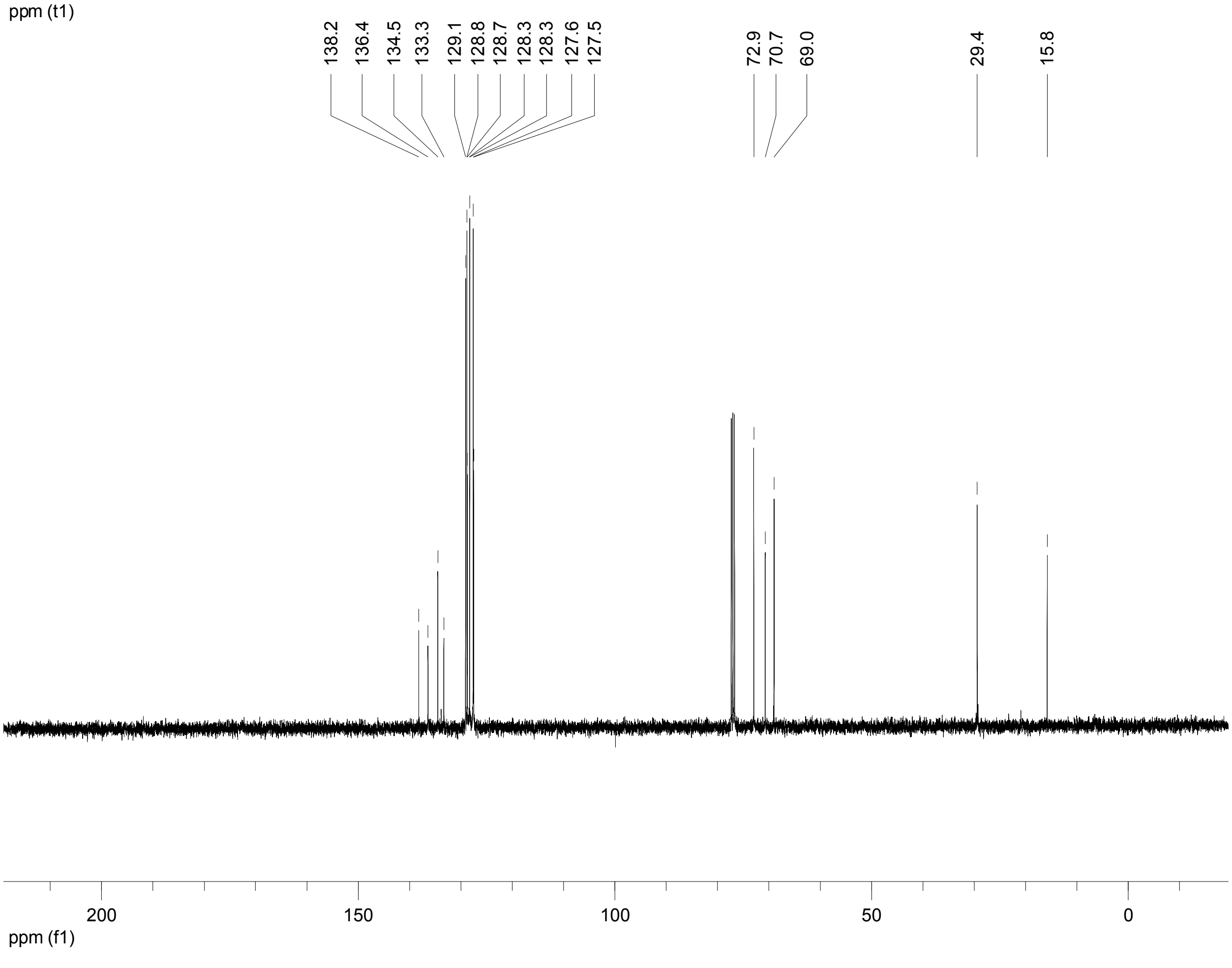
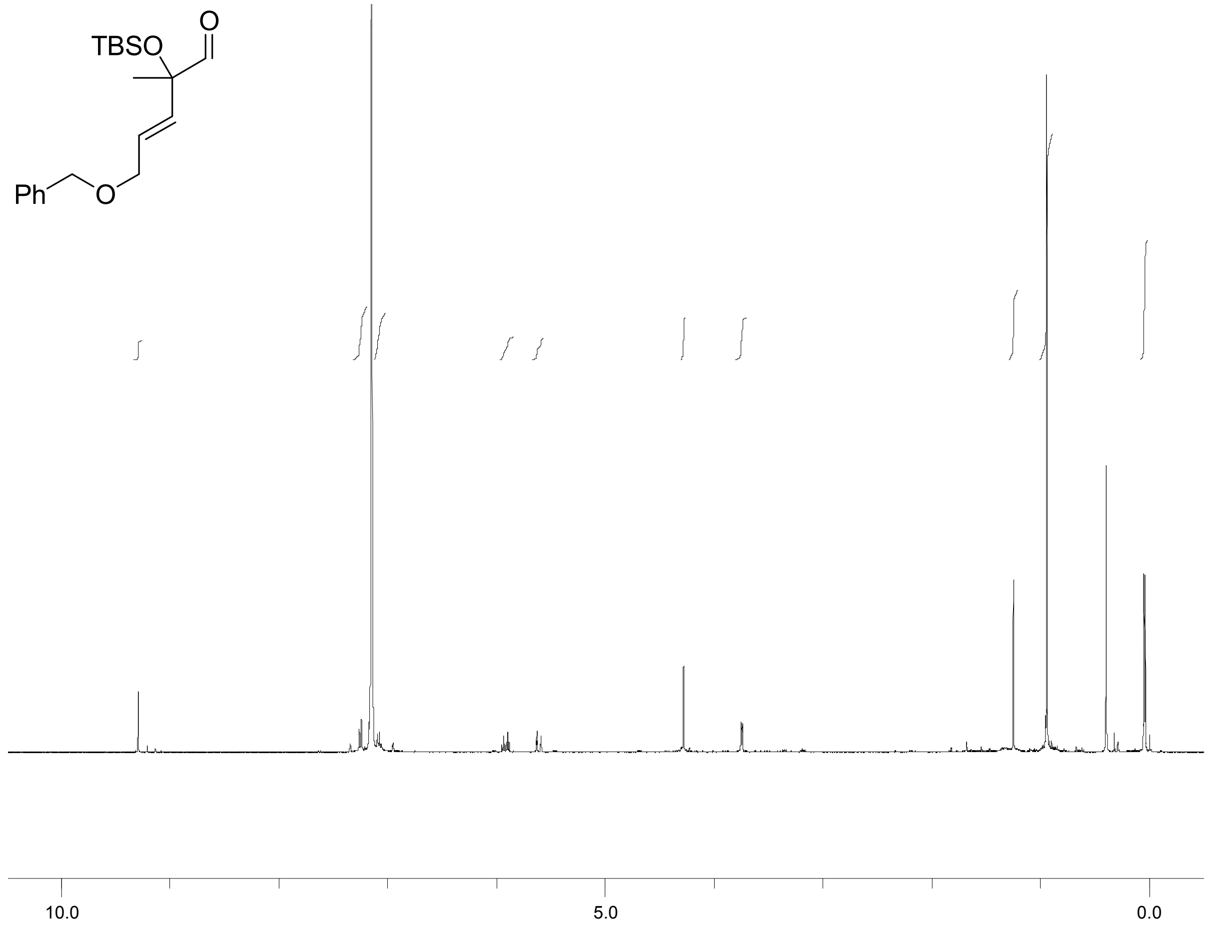
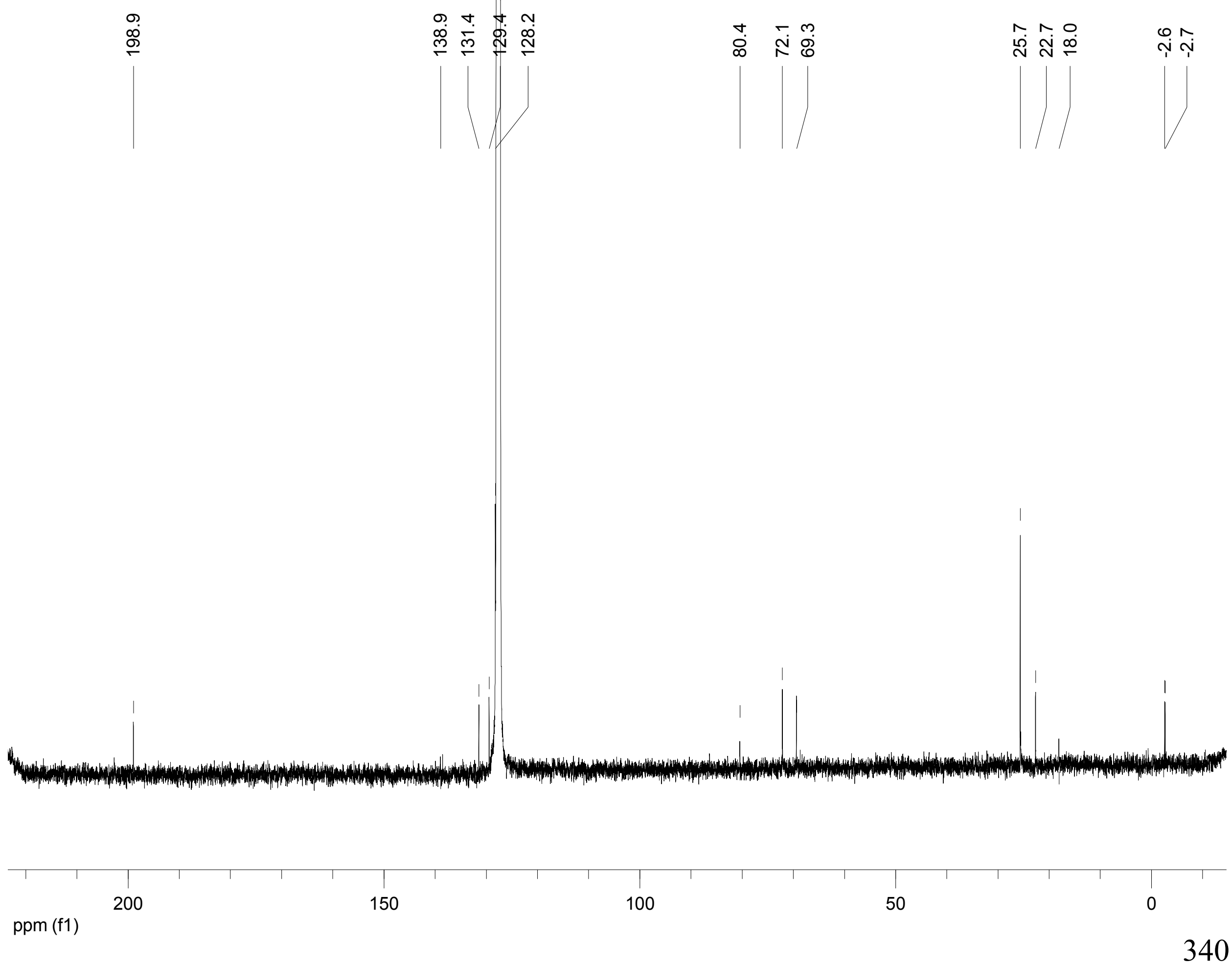
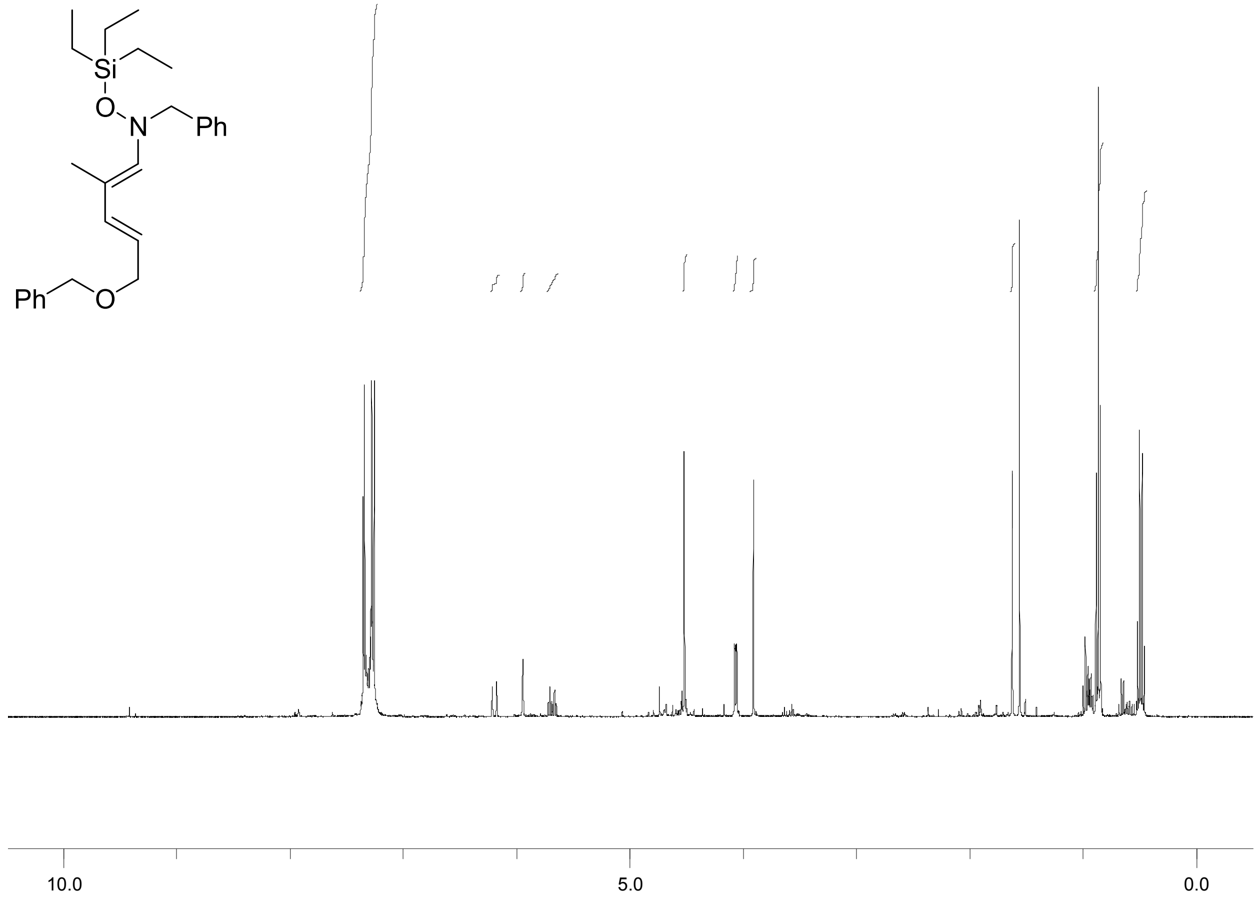
O
NBn
O
BnO
10.0
5.0
0.0
ppm (f1)

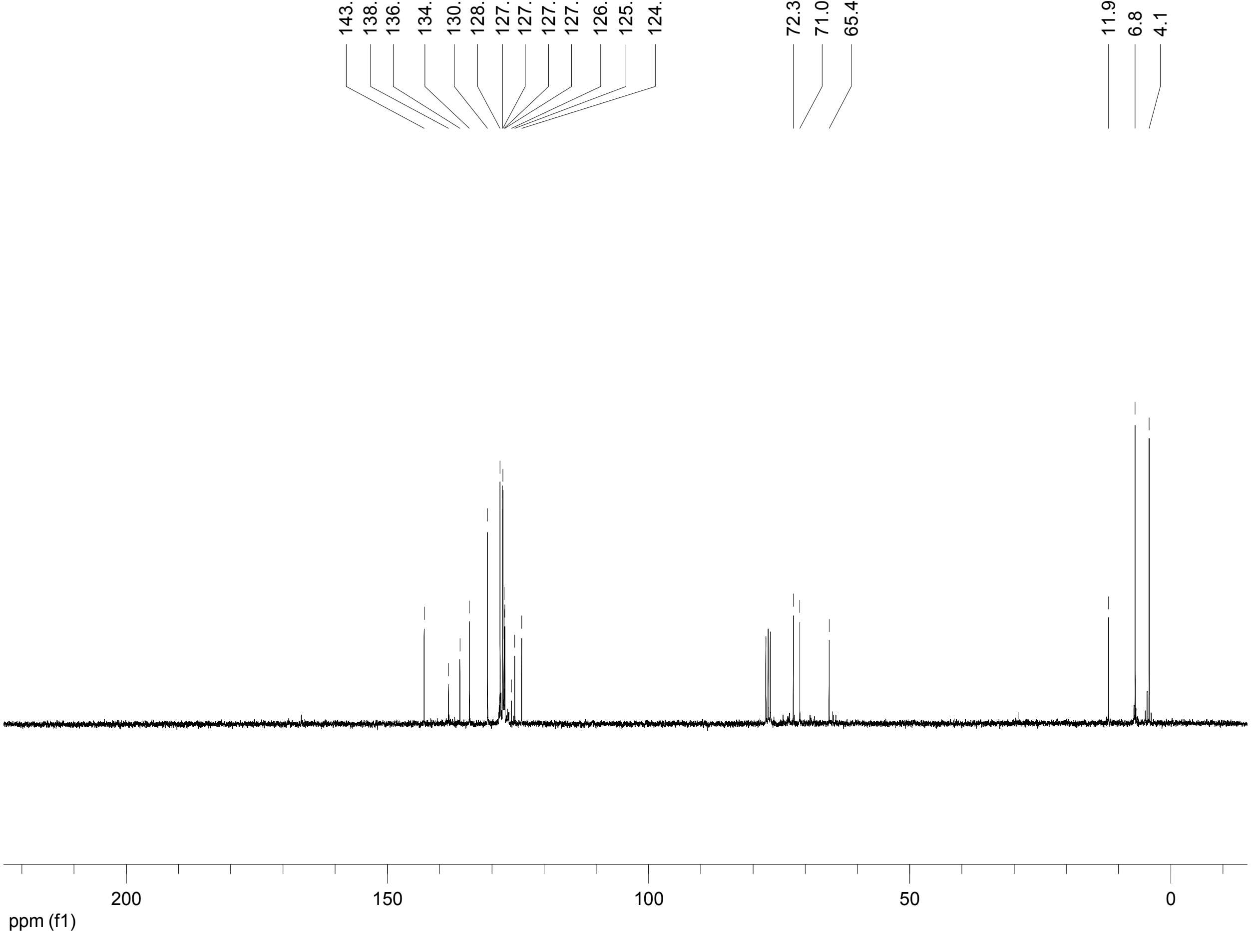

O
N
Ph
Ph
O
10.0
5.0
0.0
ppm (t1)


138.2
136.4
134.5
133.3
129.1
128.8
128.7
128.3
128.3
127.6
127.5
72.9
70.7
69.0
29.4
15.8
200
150
100
50
0
ppm (f1)


TBSO
O
Ph
O
10.0
5.0
0.0
ppm (f1)


198.9
138.9
131.4
129.4
128.2
80.4
72.1
69.3
25.7
22.7
18.0
-2.6
-2.7
200
150
100
50
0
ppm (f1)


Si
O
N
Ph
Ph
O
10.0
5.0
0.0
ppm (f1)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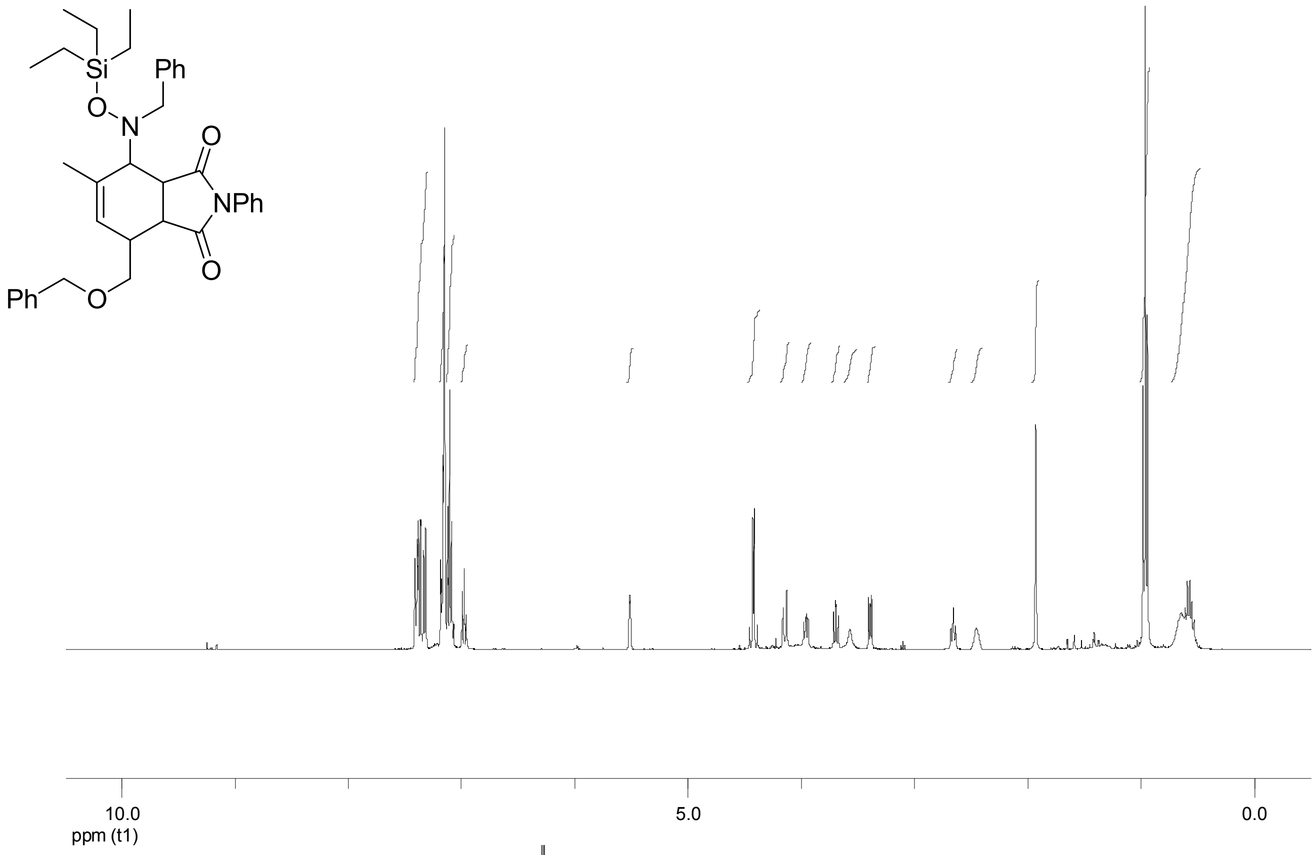
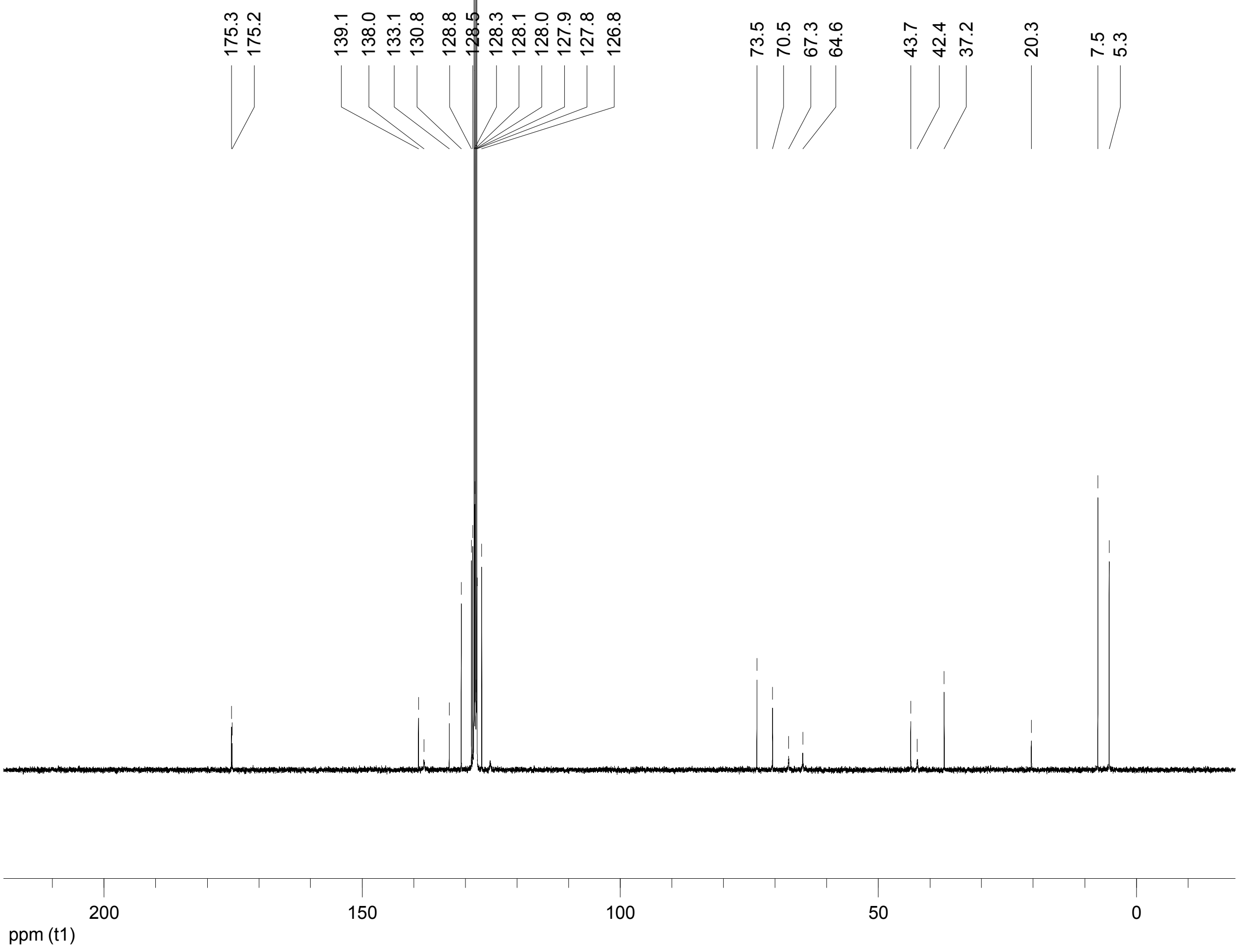
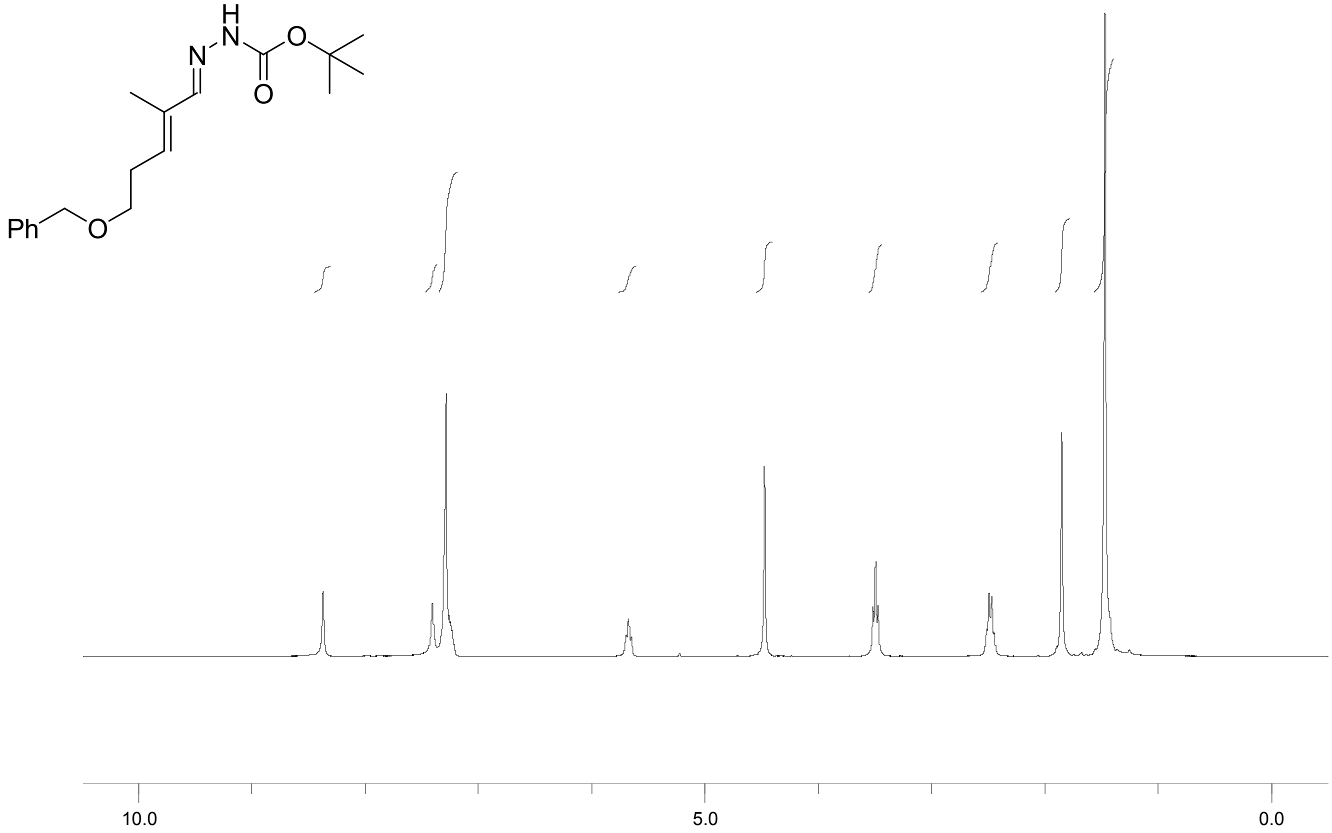
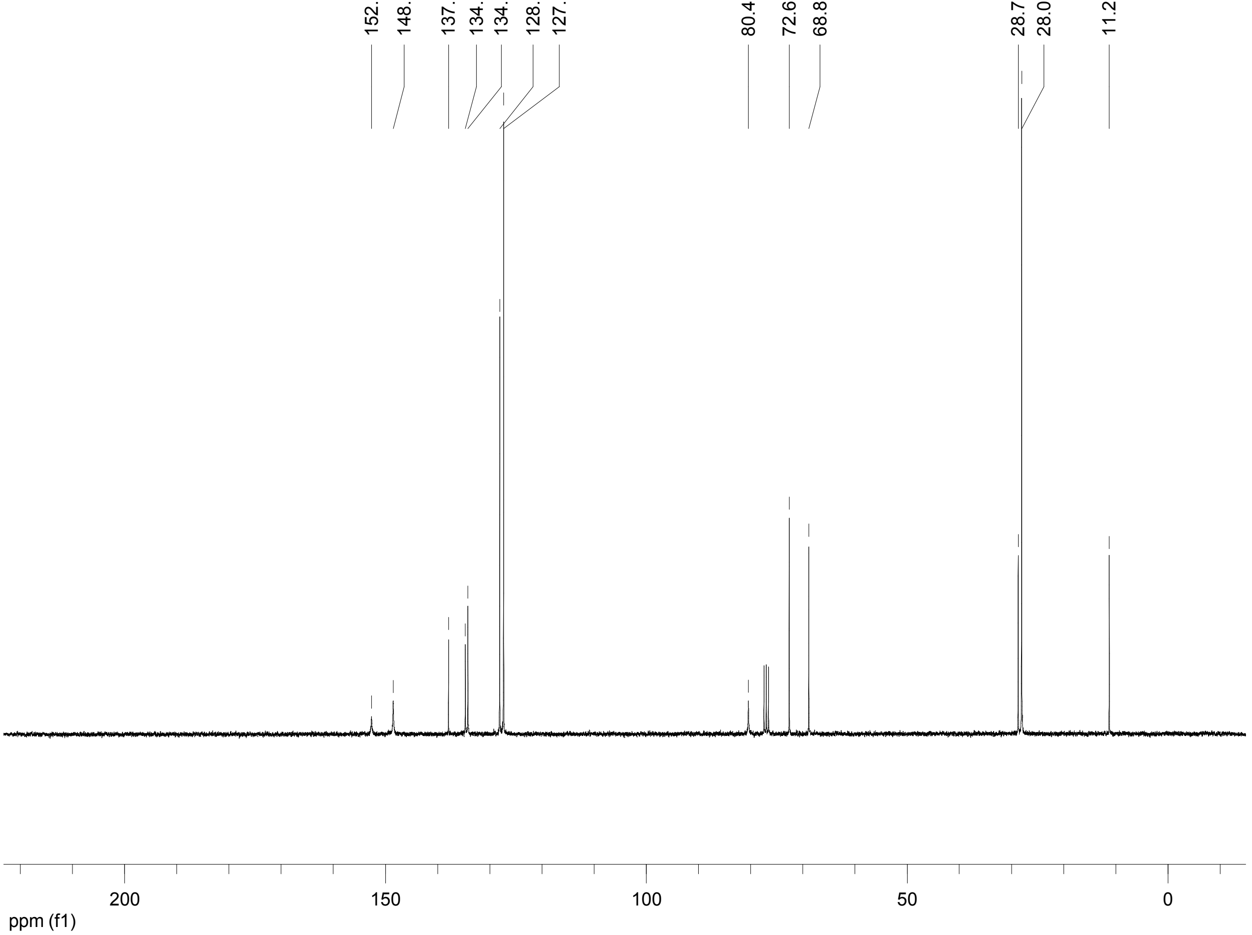
138.3
136.1
134.3
130.8
128.4
127.9
127.9
127.6
127.5
126.2
125.6
124.3
72.3
71.0
65.4
11.9
6.8
4.1
200
150
100
50
0
ppm (f1)


Si
O
N
Ph
O
NPh
O
Ph
O
10.0
5.0
0.0
ppm (t1)

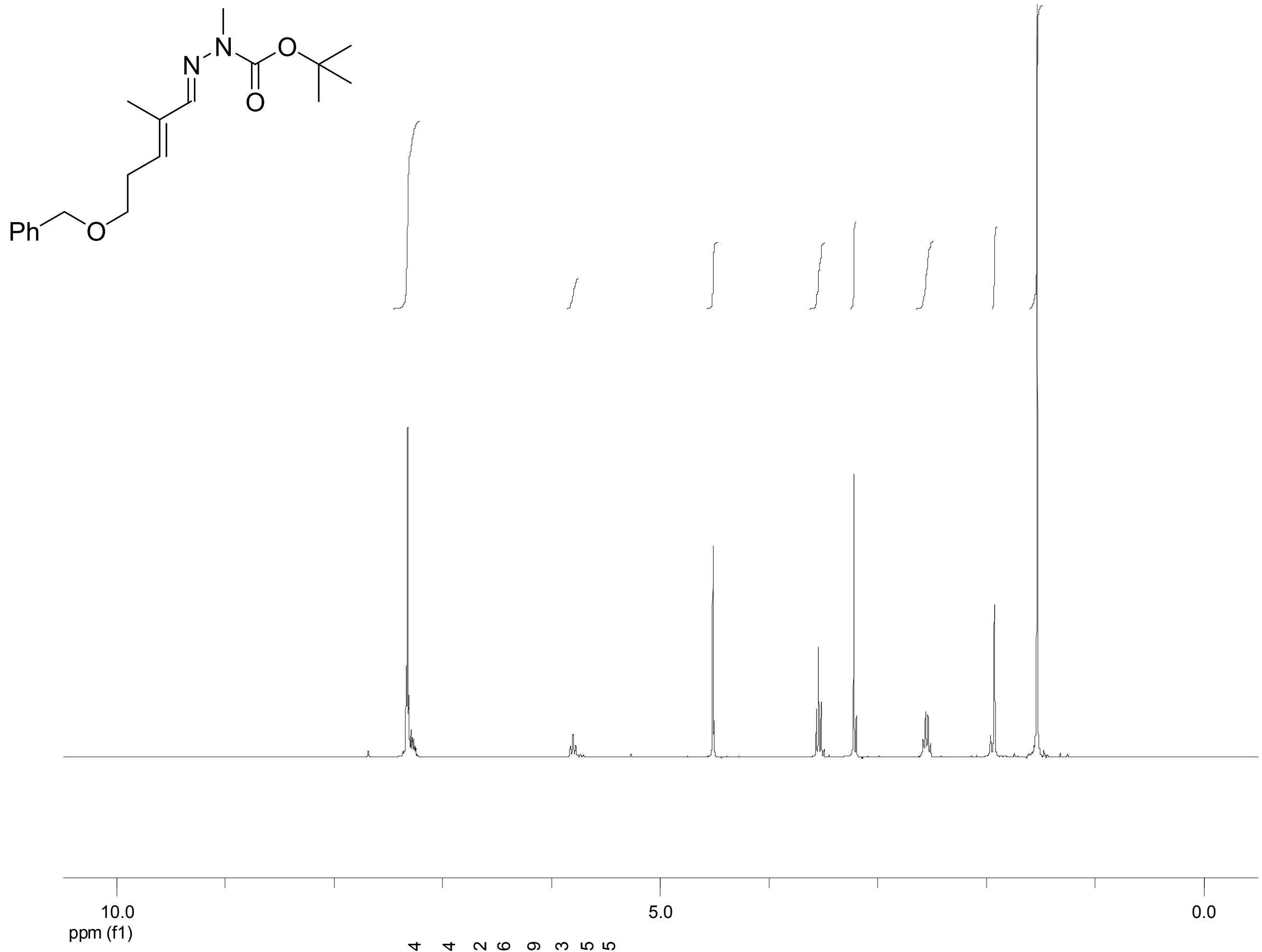

175.3
175.2
139.1
138.0
133.1
130.8
128.8
128.5
128.3
128.1
128.0
127.9
127.8
126.8
73.5
70.5
67.3
64.6
43.7
42.4
37.2
20.3
7.5
5.3
200
150
100
50
0
ppm (t1)

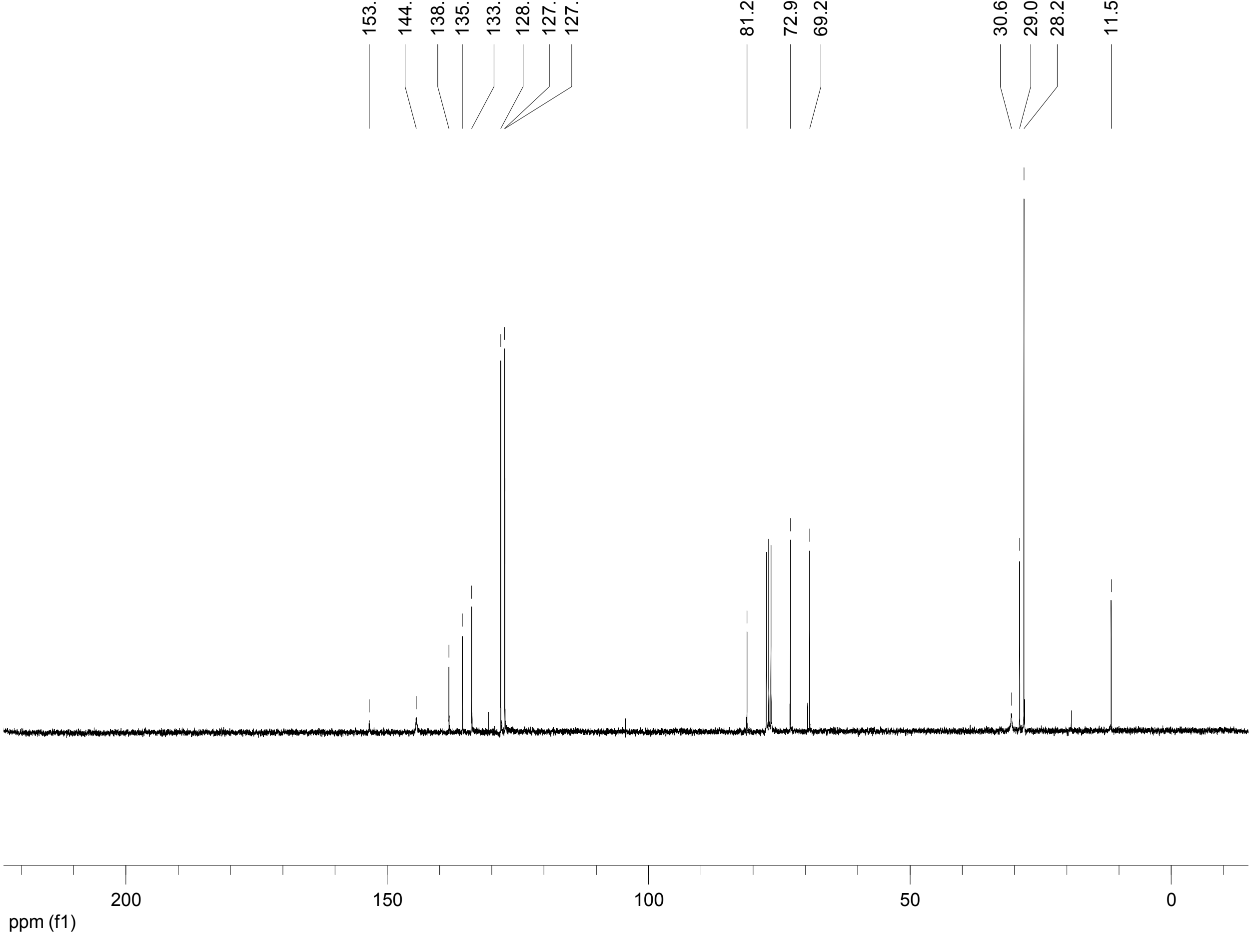


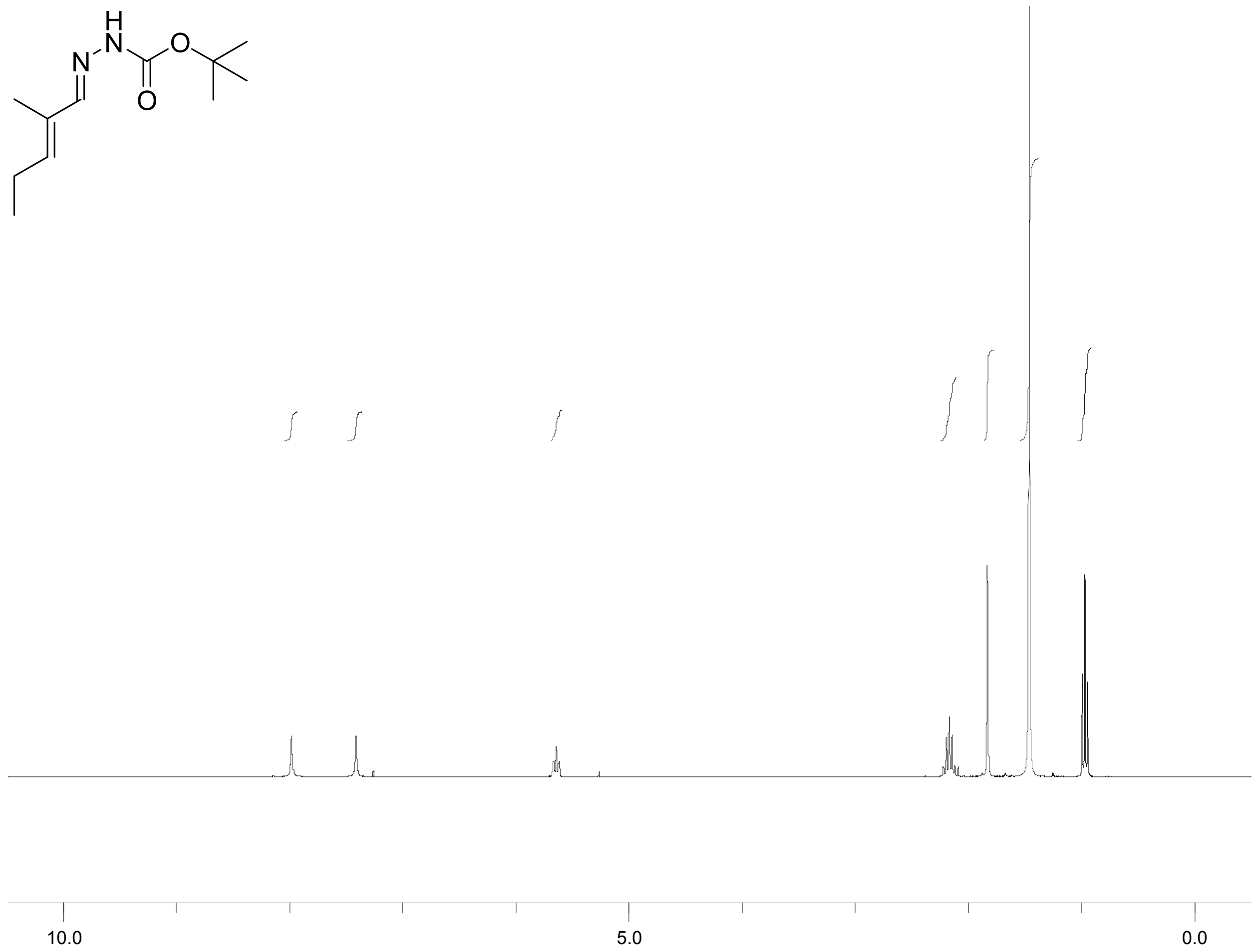
H
N
N
O
O
Ph
O
10.0
5.0
0.0
ppm (f1)

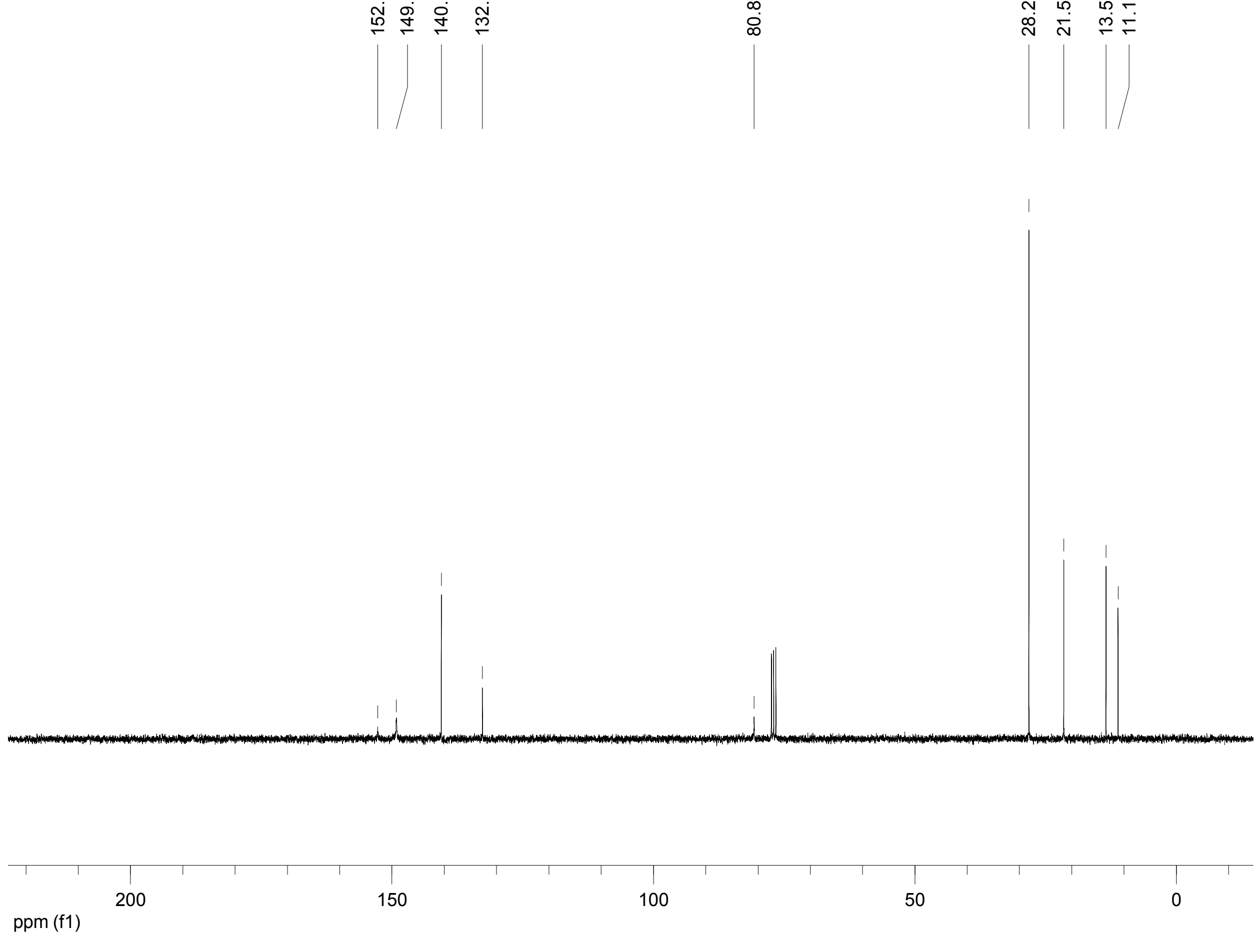


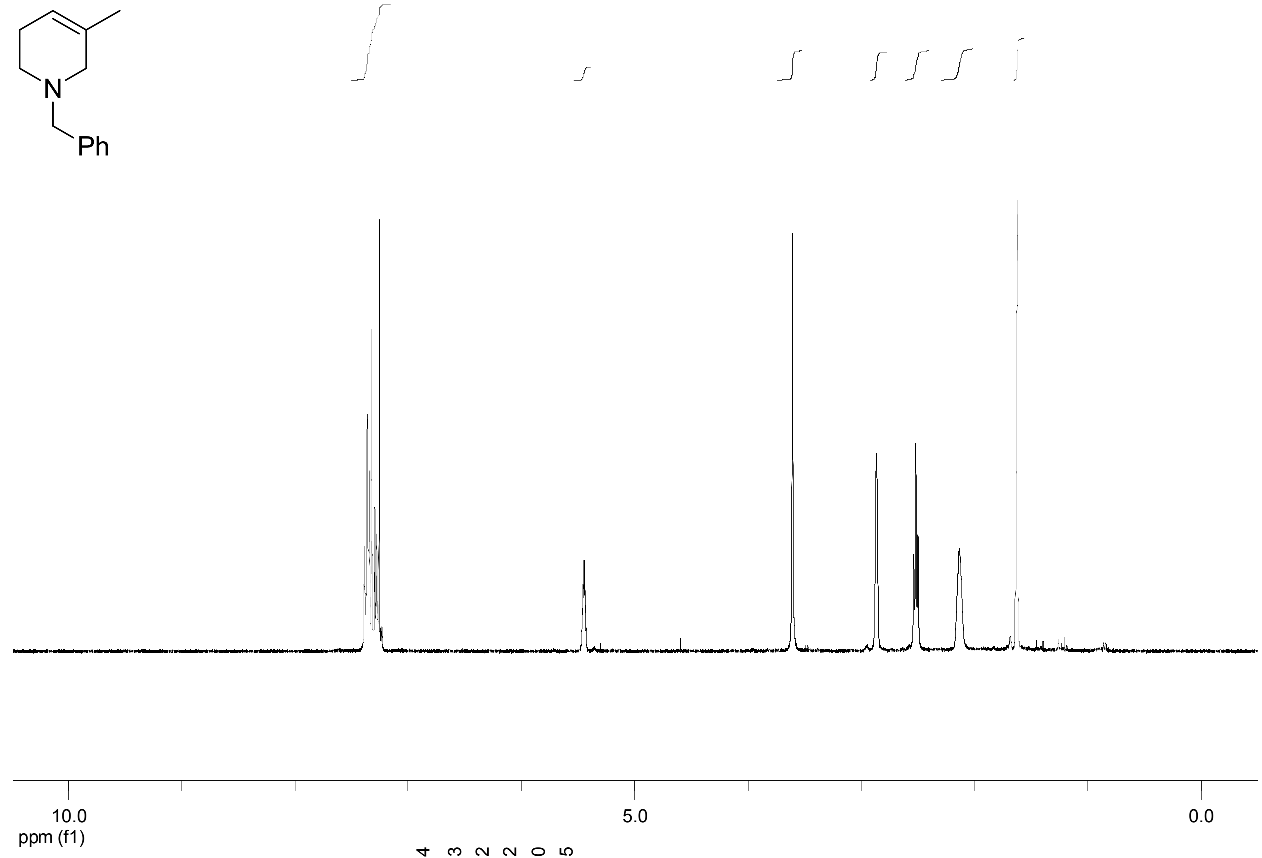
152.6
148.5
137.9
134.7
134.2
128.1
127.3
80.4
72.6
68.8
28.7
28.0
11.2
200
150
100
50
0
ppm (f1)

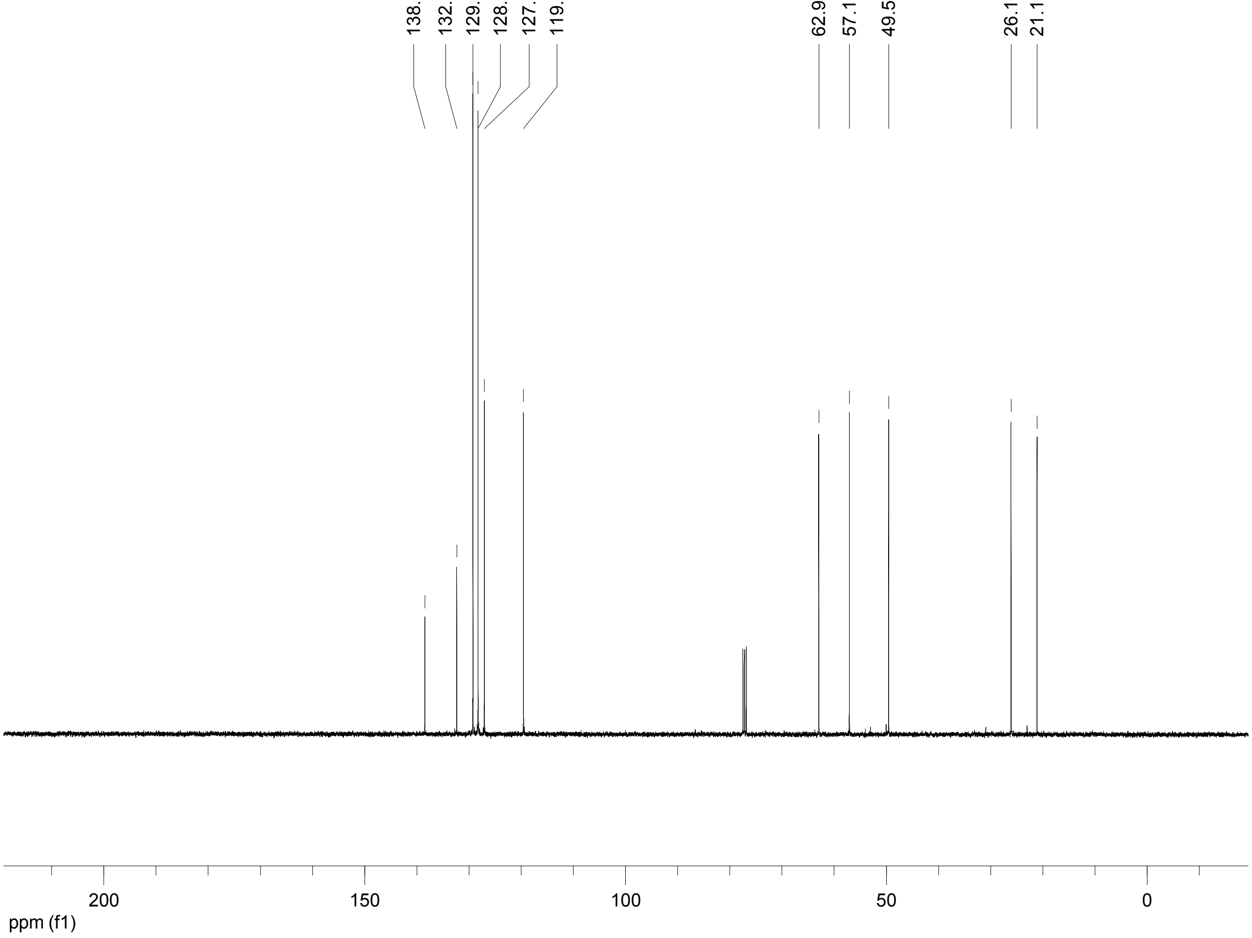

N
N
O
O
Ph
O
10.0
5.0
0.0
ppm (f1)

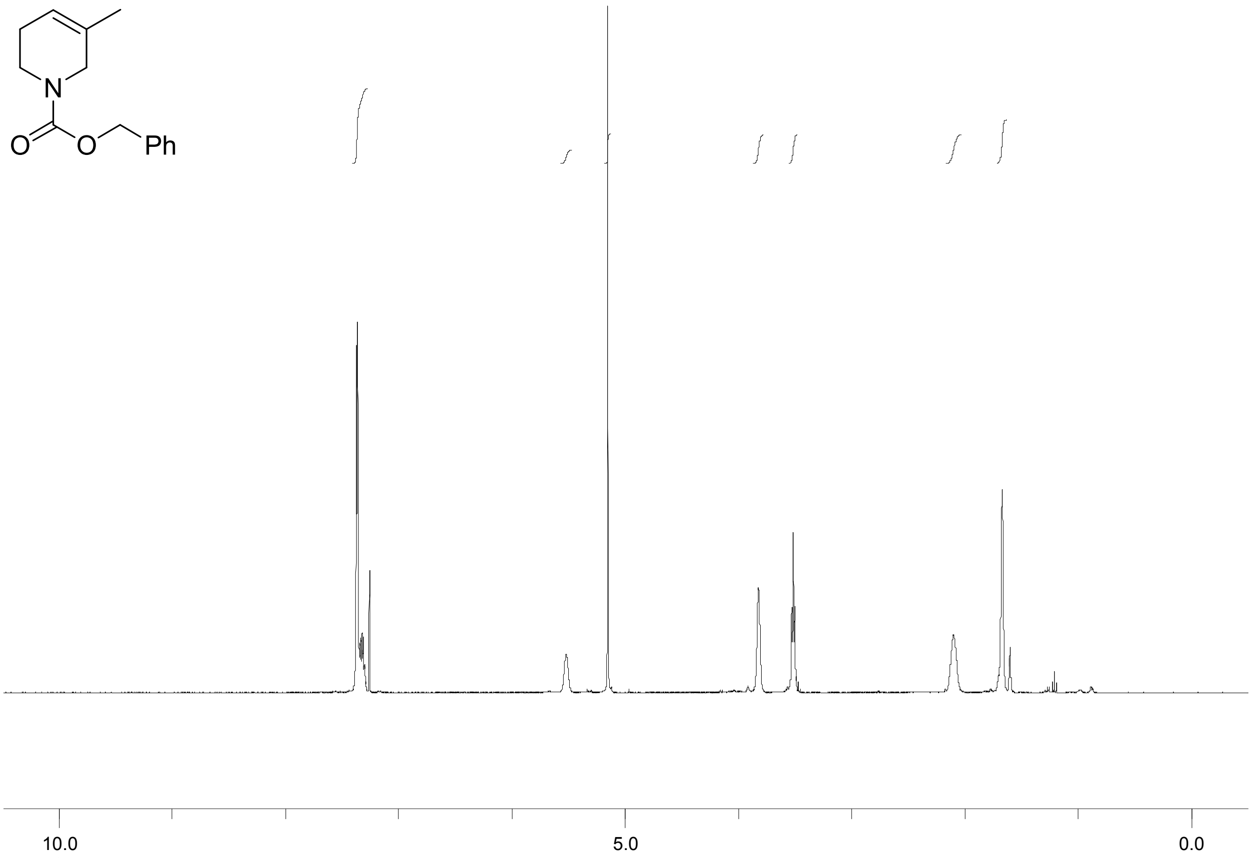

153.4
144.4
138.2
135.6
133.9
128.3
127.5
127.5
81.2
72.9
69.2
30.6
29.0
28.2
11.5
200
150
100
50
0
ppm (f1)

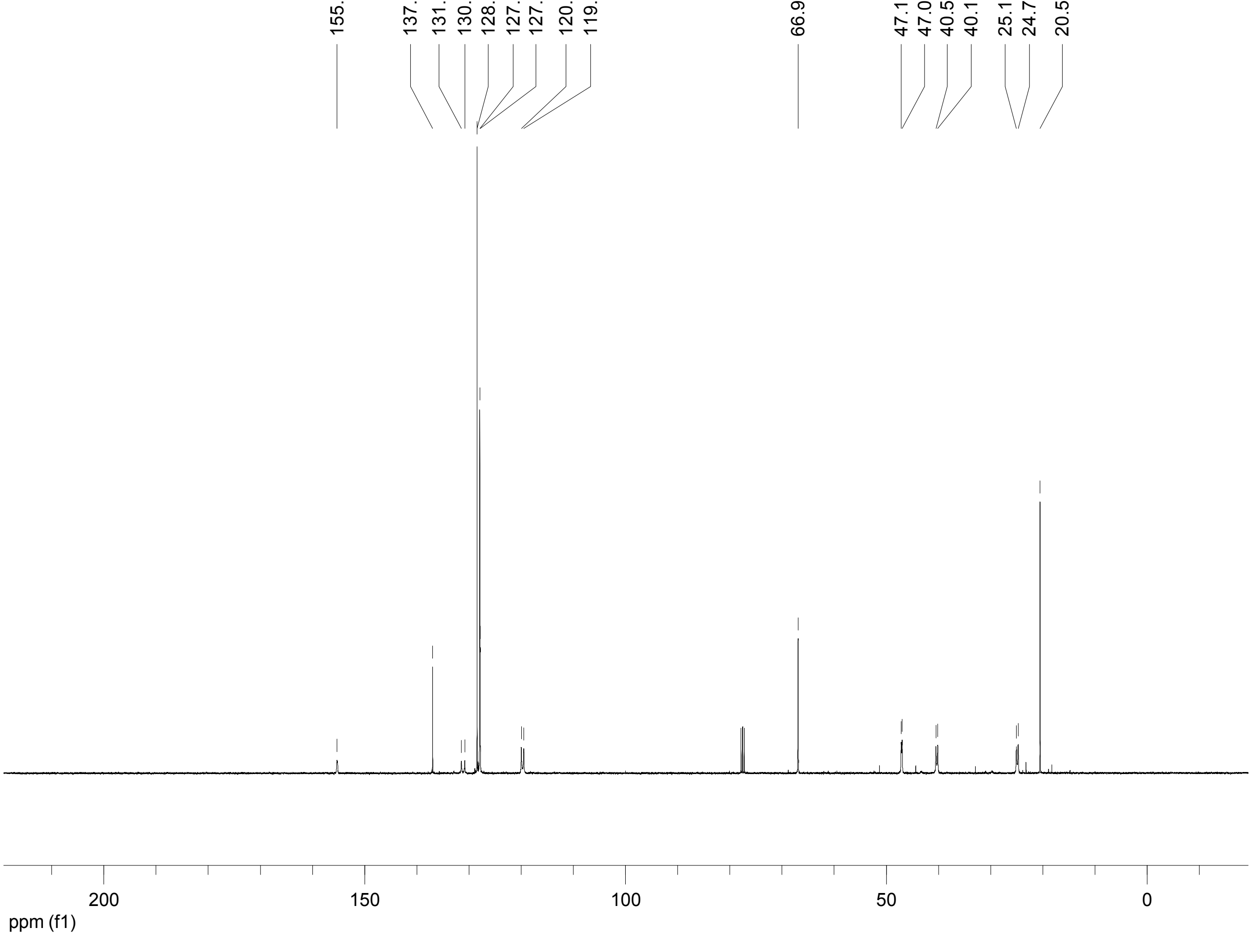

H
N
N
O
O
10.0
5.0
0.0
ppm (f1)

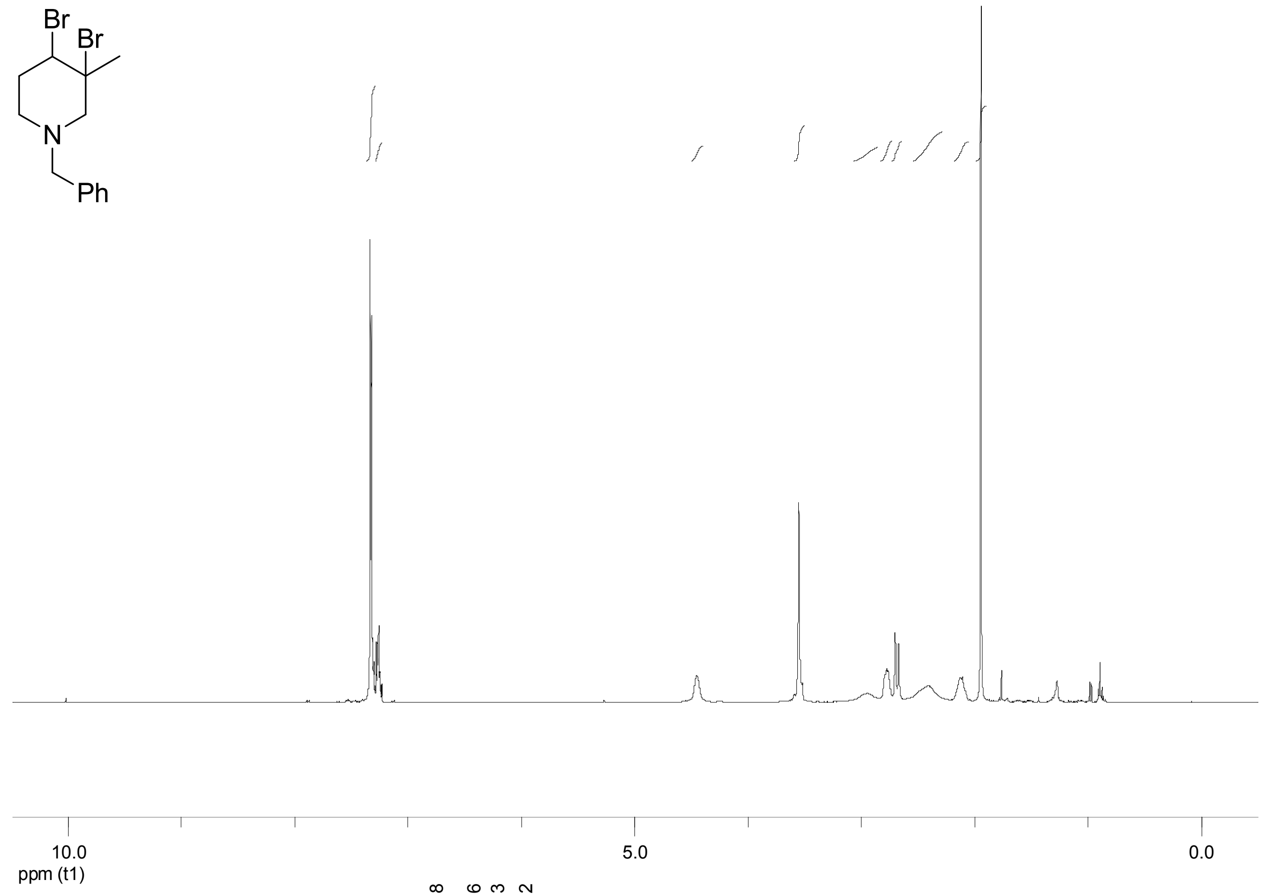

152.7
149.2
140.6
132.7
80.8
28.2
21.5
13.5
11.1
200
150
100
50
0
ppm (f1)

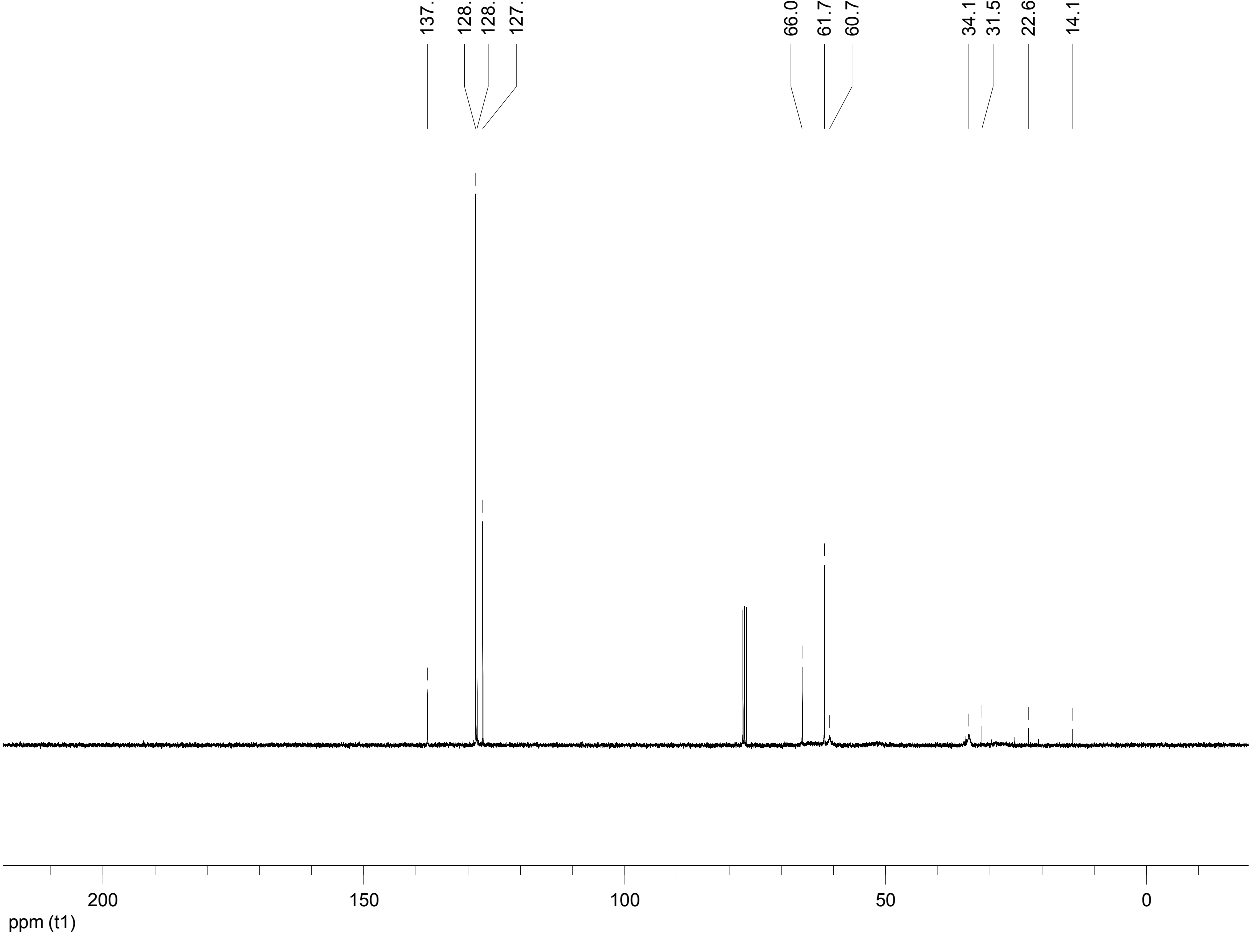

N
Ph
10.0
5.0
0.0
ppm (f1)

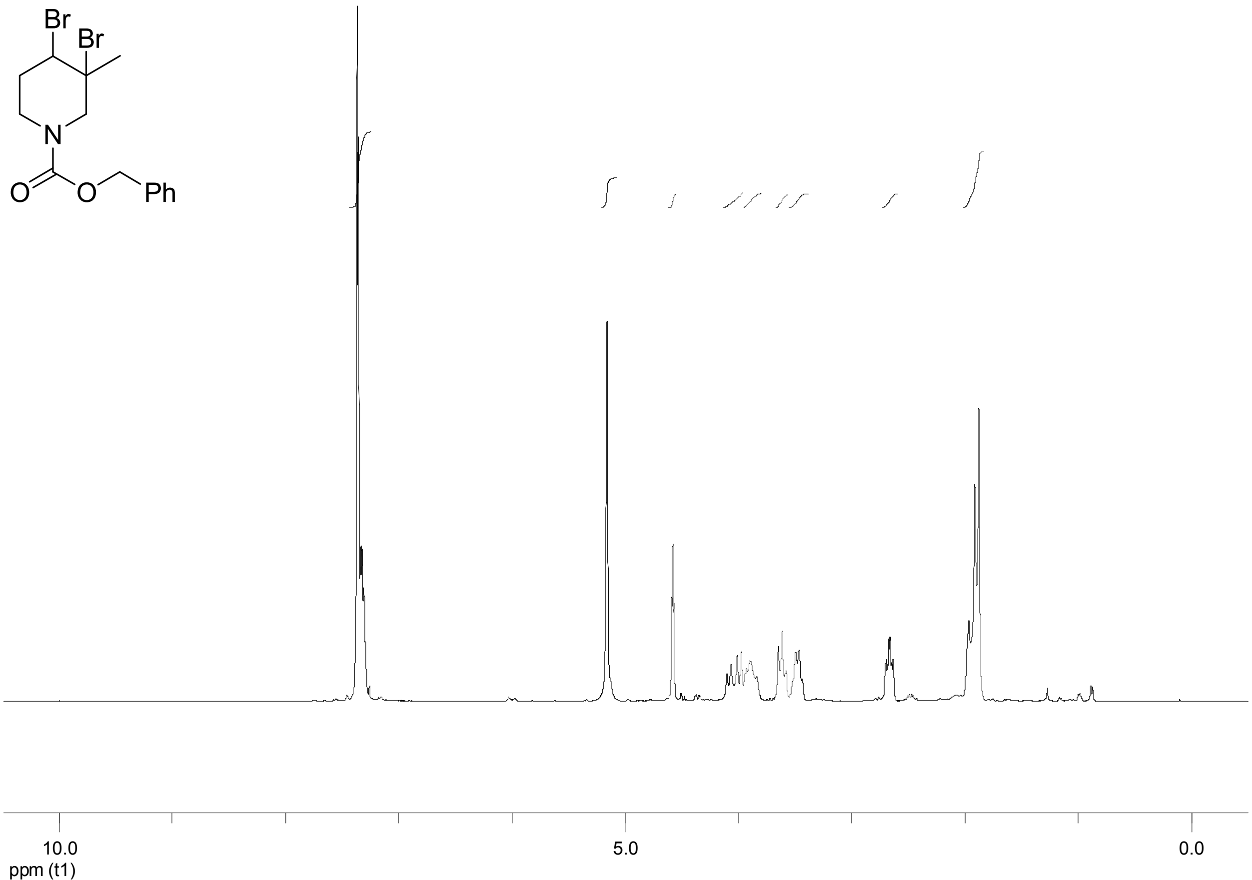

138.4
132.3
129.2
128.2
127.0
119.5
62.9
57.1
49.5
26.1
21.1
200
150
100
50
0
ppm (f1)

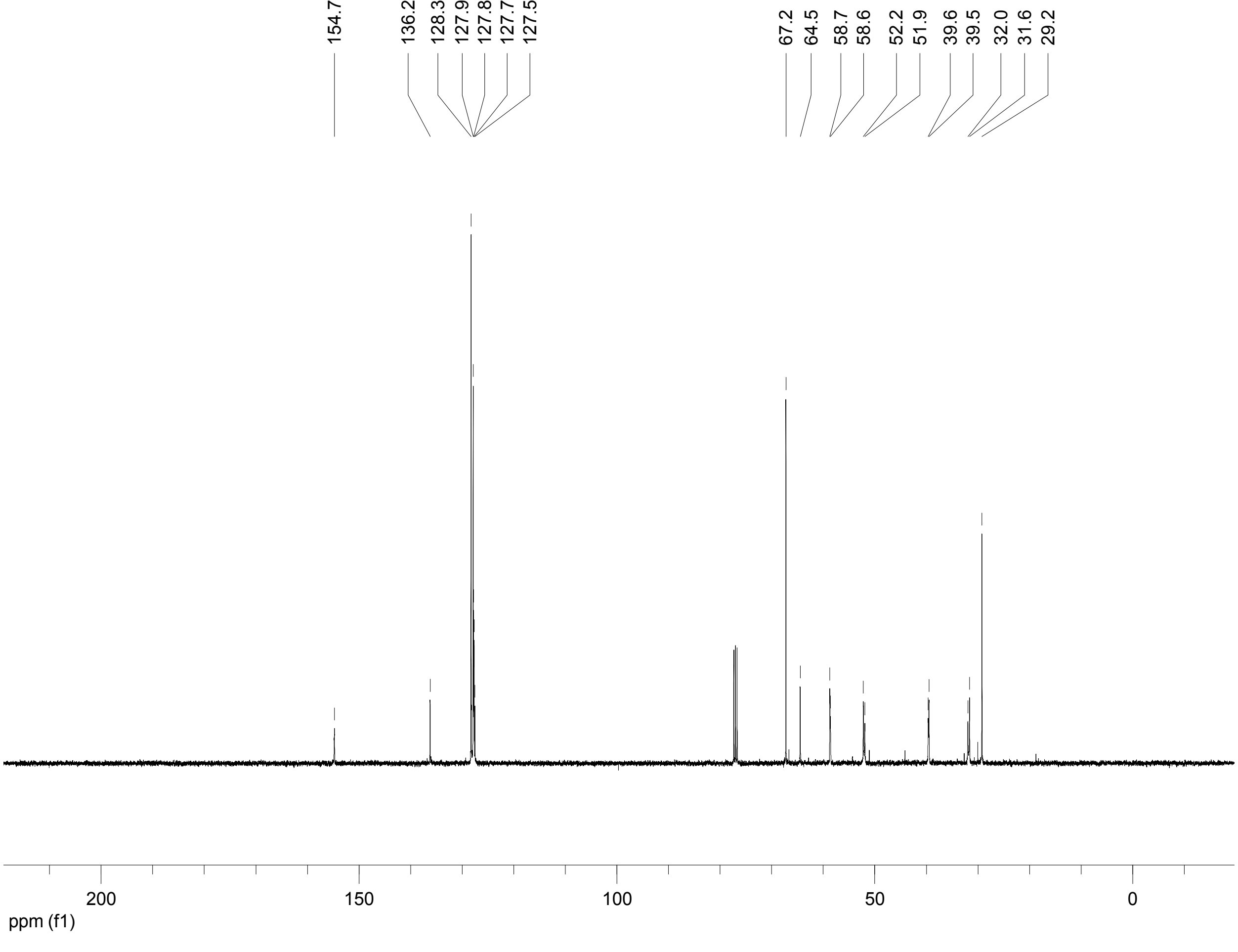

N
O
O
Ph
10.0
5.0
0.0
ppm (f1)

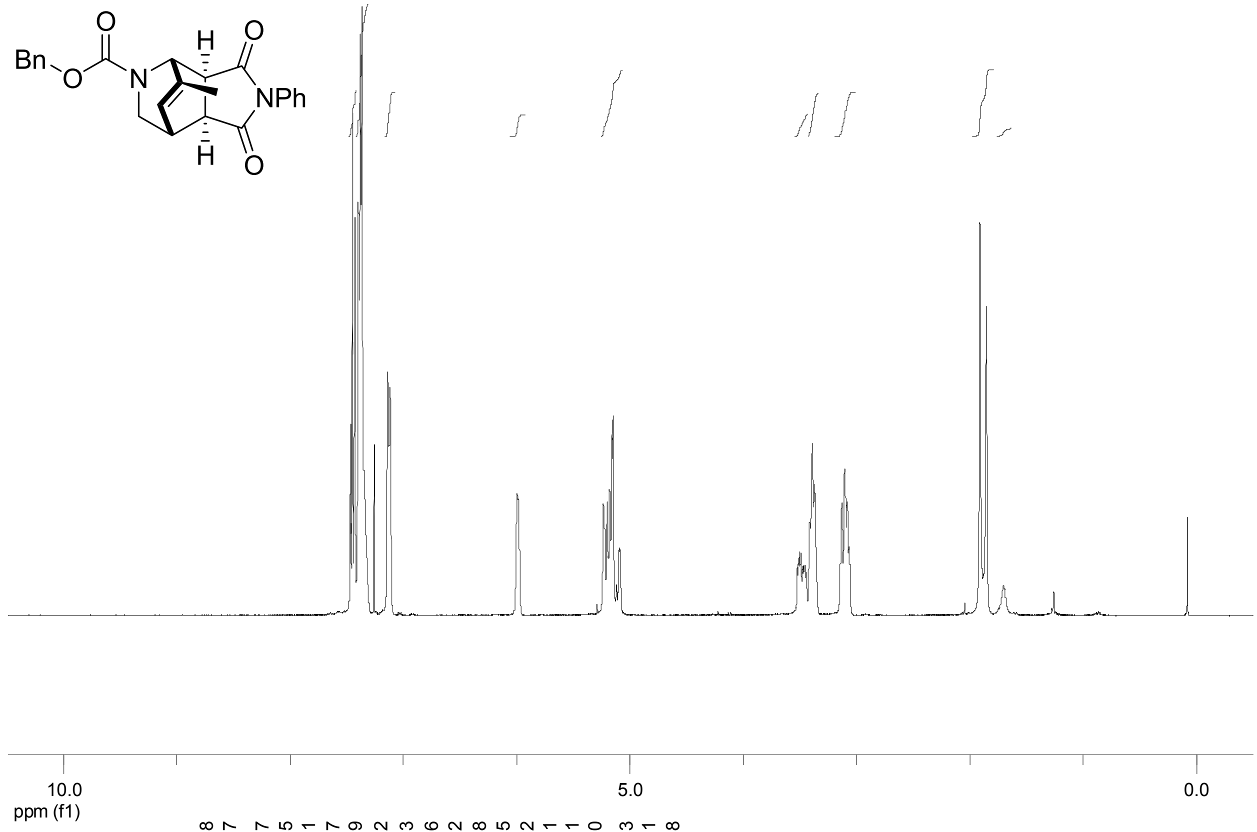

155.3
137.0
131.5
130.8
128.4
127.9
127.9
120.0
119.5
66.9
47.1
47.0
40.5
40.1
25.1
24.7
20.5
200
150
100
50
0
ppm (f1)

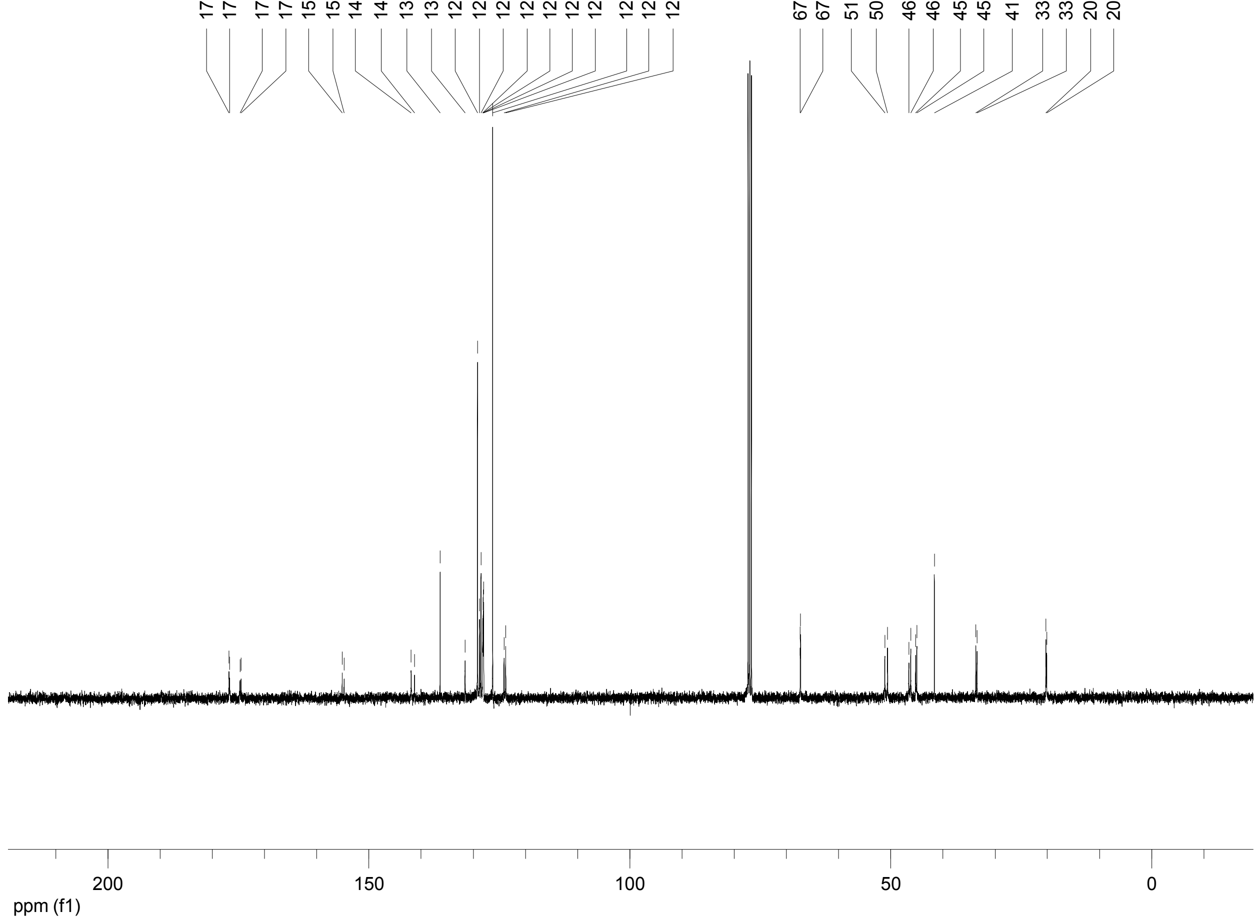

Br
Br
N
Ph
10.0
5.0
0.0
ppm (t1)

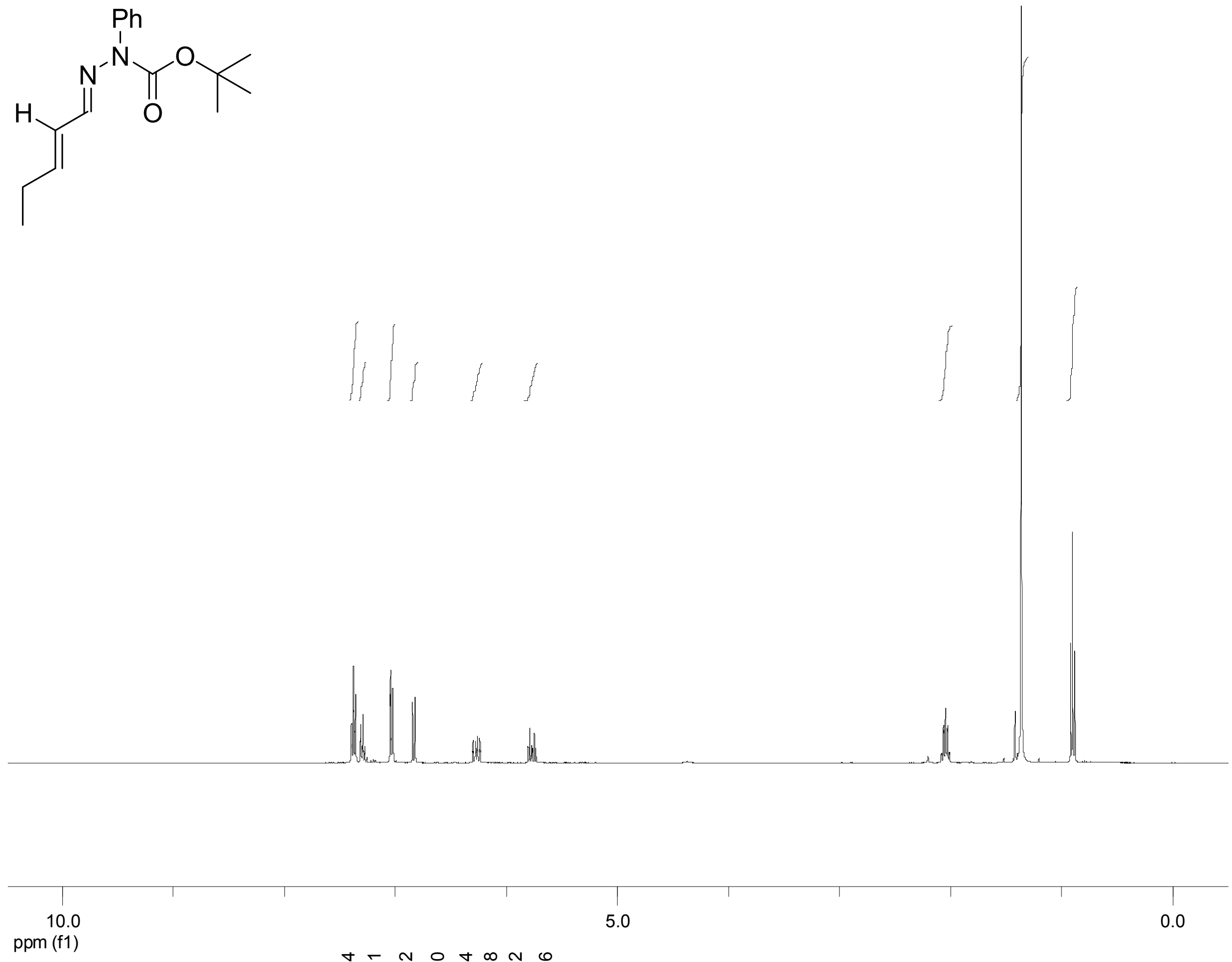

137.8
128.6
128.3
127.2
66.0
61.7
60.7
34.1
31.5
22.6
14.1
200
150
100
50
0
ppm (t1)

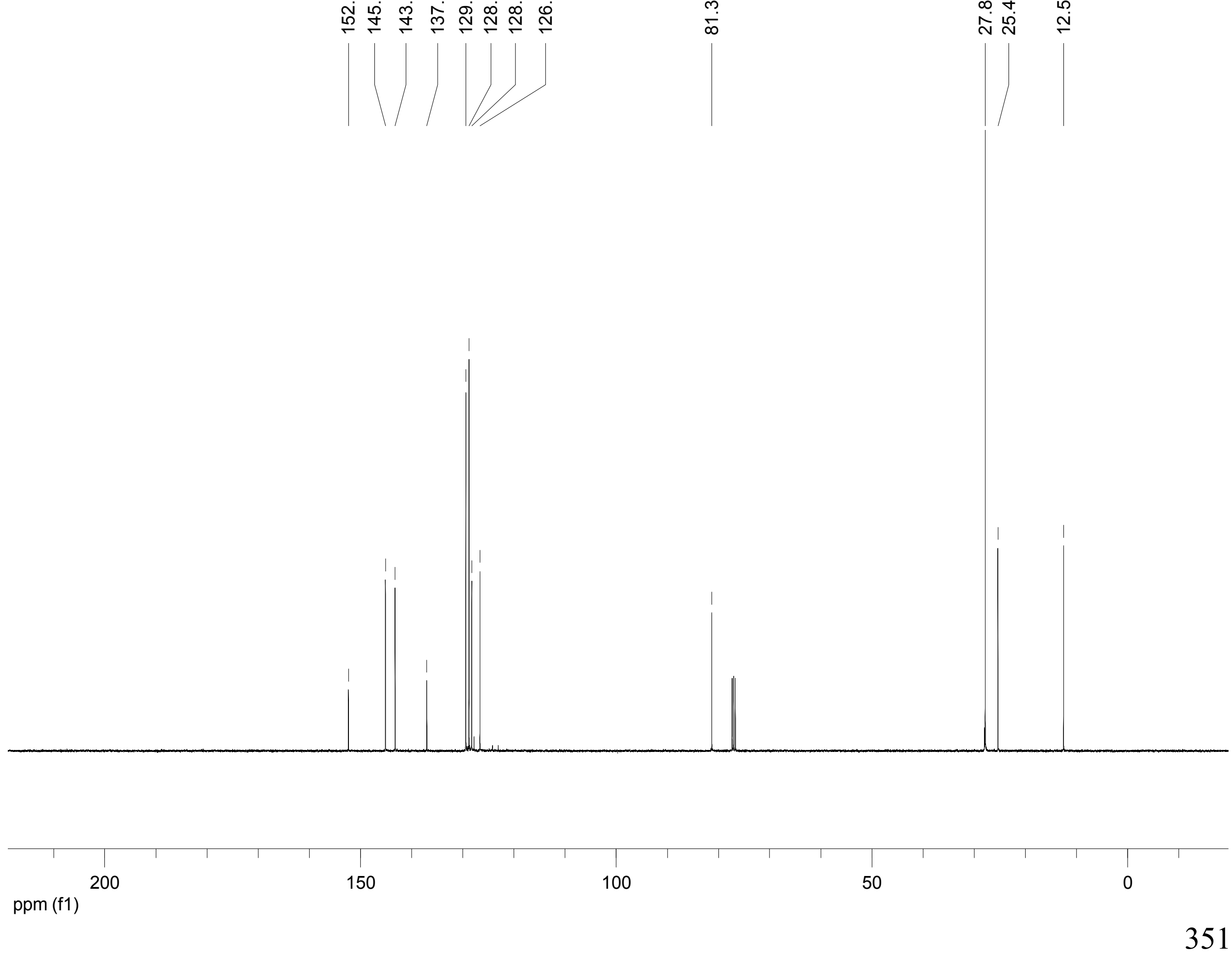

Br
Br
N
O
O
Ph
10.0
5.0
0.0
ppm (t1)

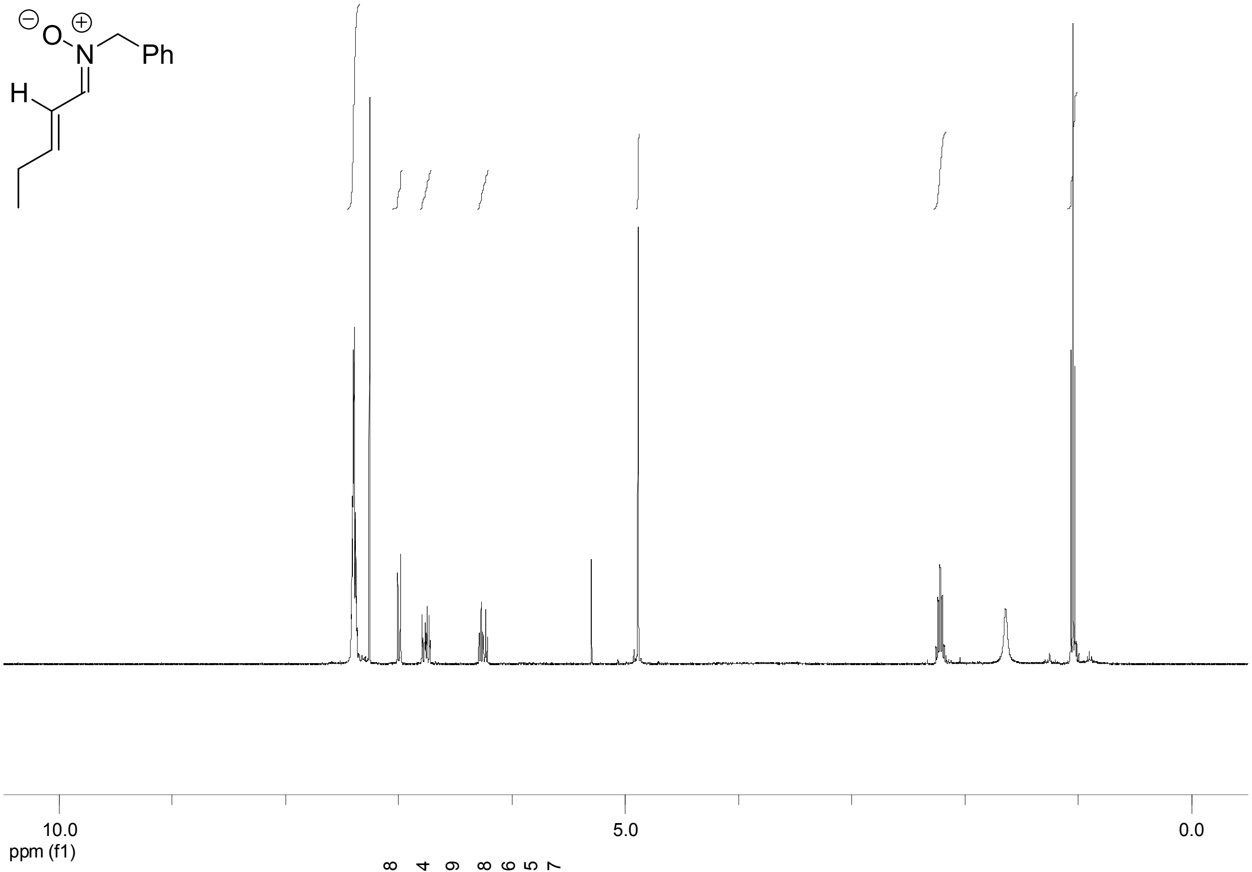

154.7
136.2
128.3
127.9
127.8
127.7
127.5
67.2
64.5
58.7
58.6
52.2
51.9
39.6
39.5
32.0
31.6
29.2
200
150
100
50
0
ppm (f1)

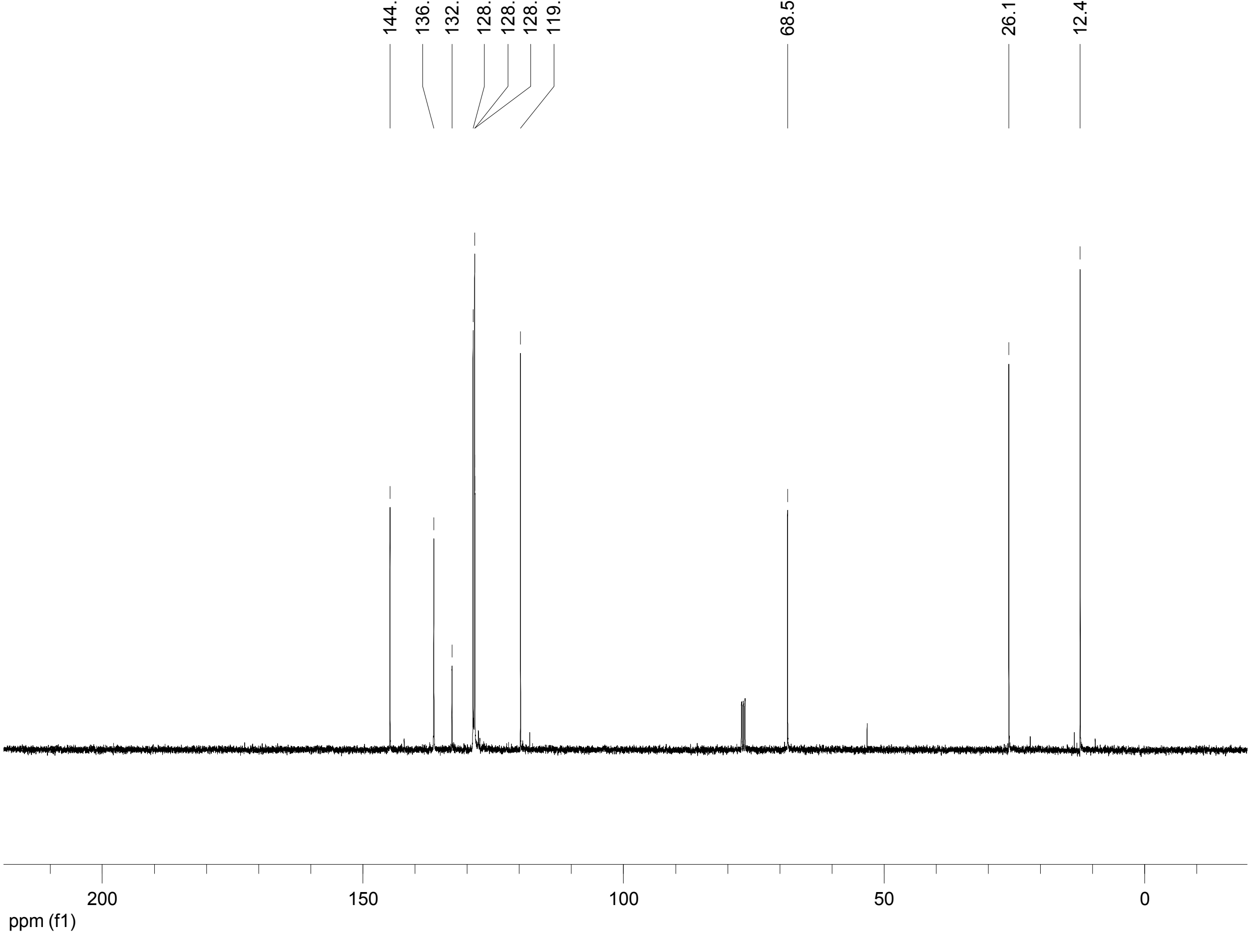

Bn
O
O
N
H
H
O
NPh
O
10.0
5.0
0.0
ppm (f1)

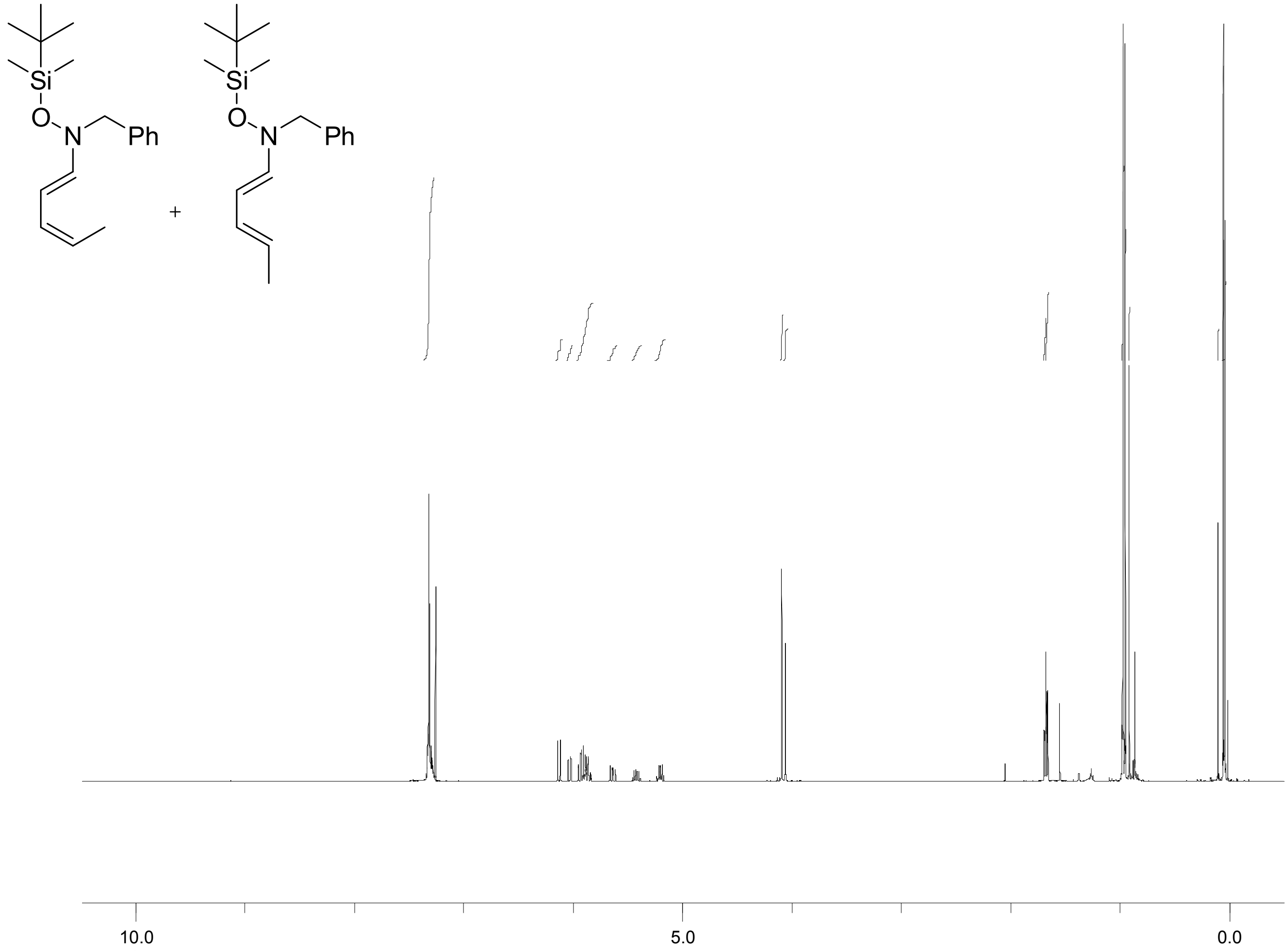

176.8
176.7
174.7
174.5
155.1
154.7
141.9
141.2
136.3
131.6
129.2
128.8
128.5
128.2
128.1
128.1
128.0
126.3
124.1
123.8
67.3
67.3
51.1
50.6
46.5
46.2
45.2
45.0
41.6
33.7
33.5
20.3
20.1
200
150
100
50
0
ppm (f1)


Ph
N
N
O
O
H
10.0
5.0
0.0
ppm (f1)

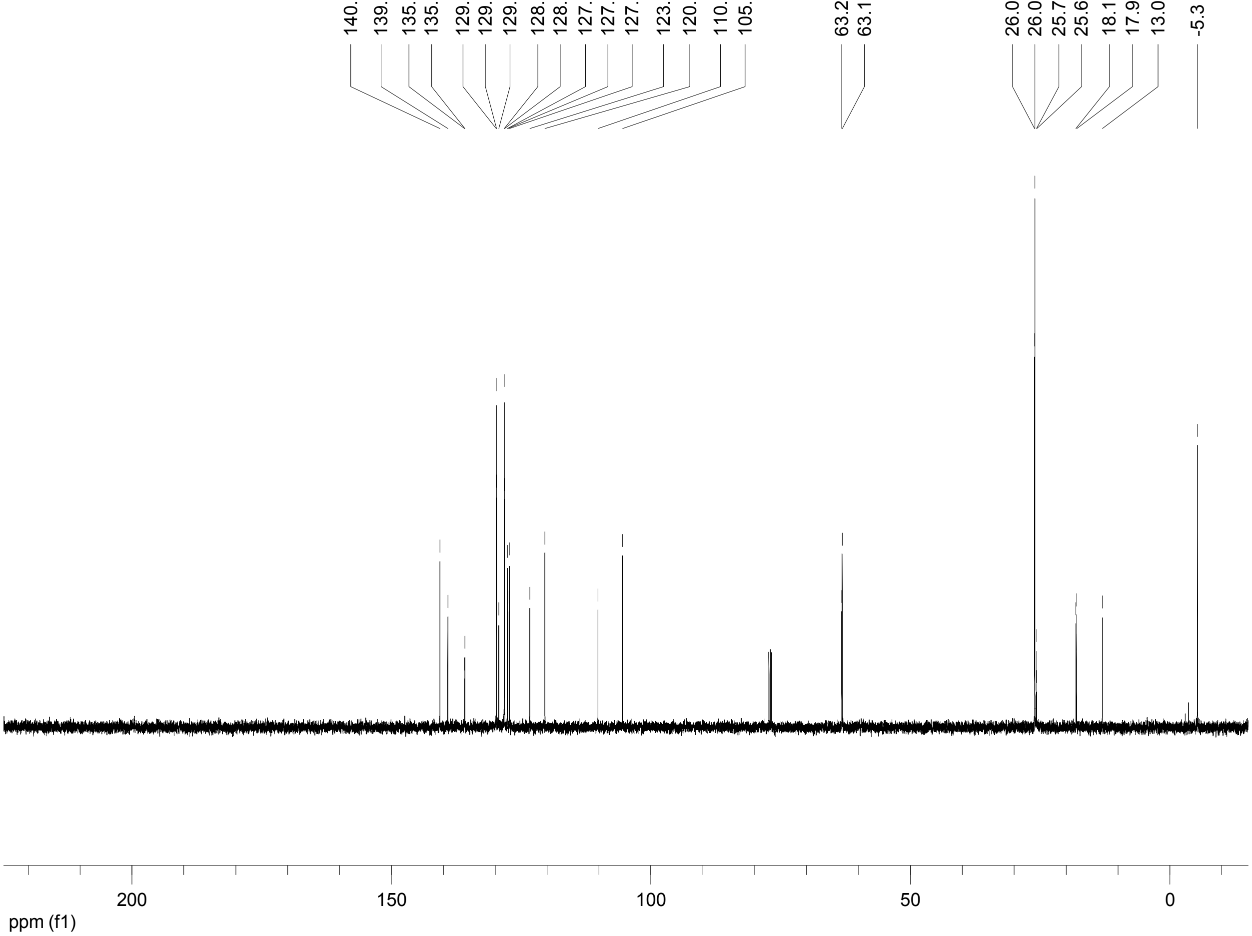

152.4
145.1
143.2
137.0
129.4
128.8
128.2
126.6
81.3
27.8
25.4
12.5
200
150
100
50
0
ppm (f1)

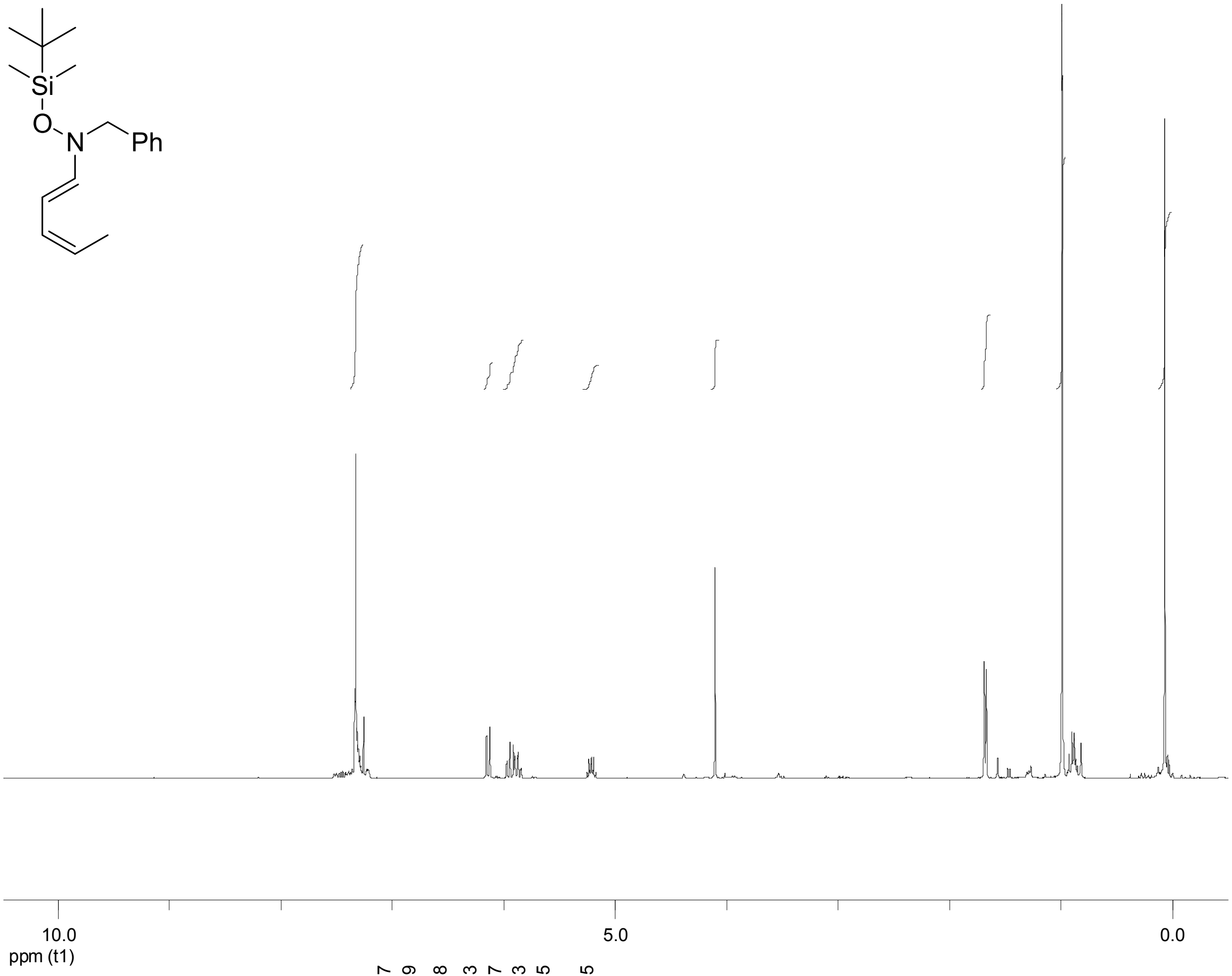

O
N
Ph
H
10.0
5.0
0.0
ppm (f1)

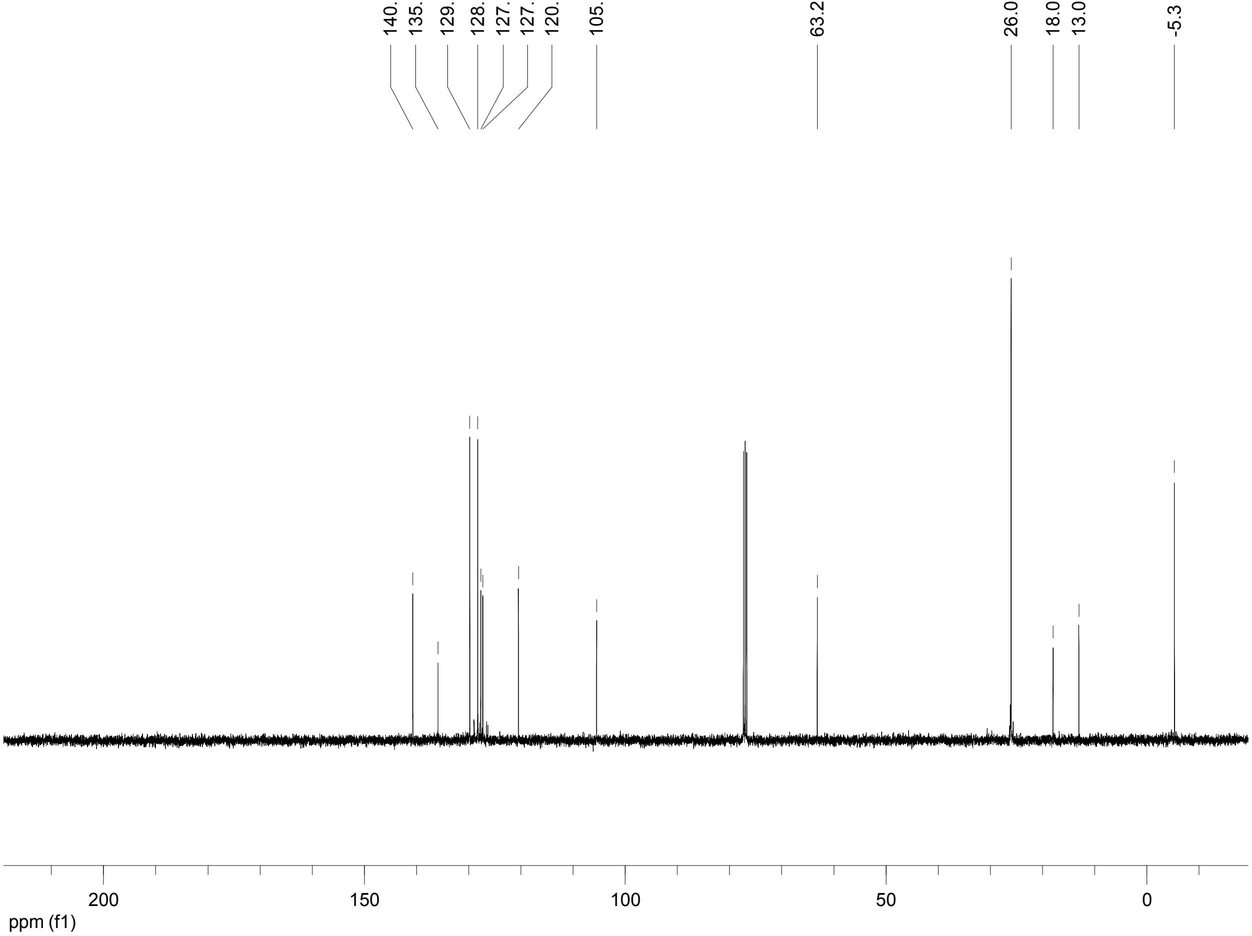

144.8
136.4
132.9
128.8
128.6
128.5
119.7
68.5
26.1
12.4
200
150
100
50
0
ppm (f1)

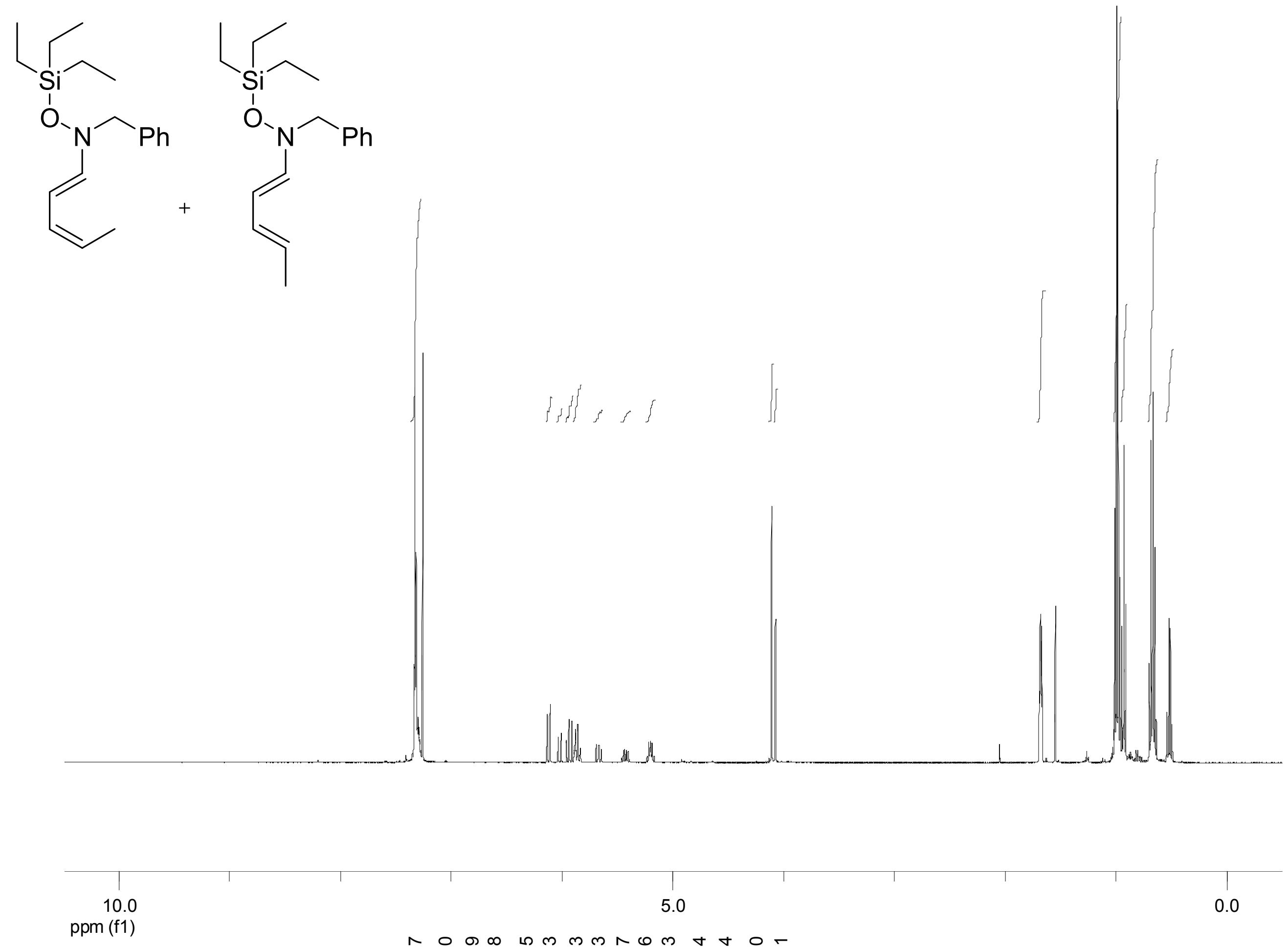

Si
O
N
Ph
+
Si
O
N
Ph

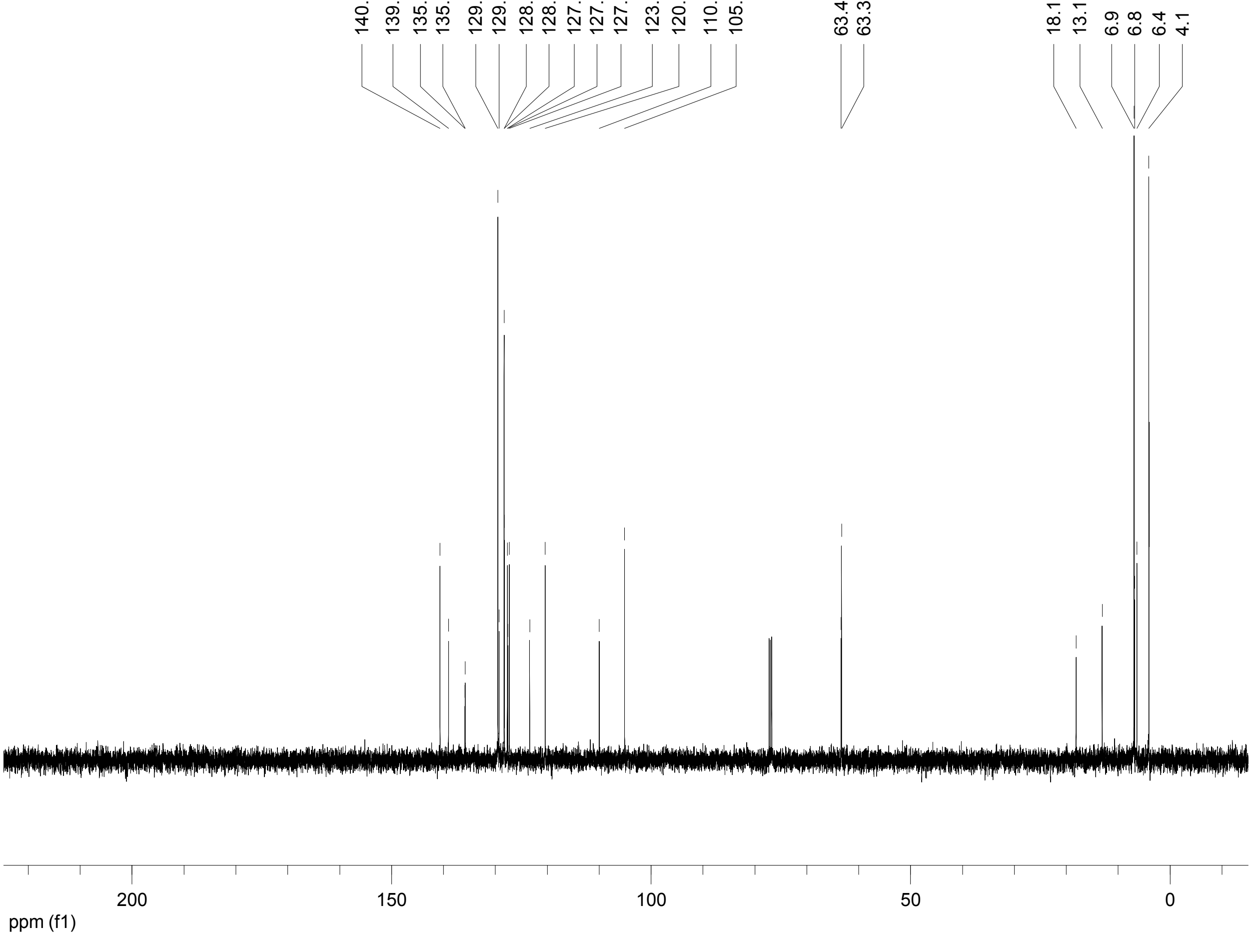
10.0
5.0
0.0
ppm (f1)

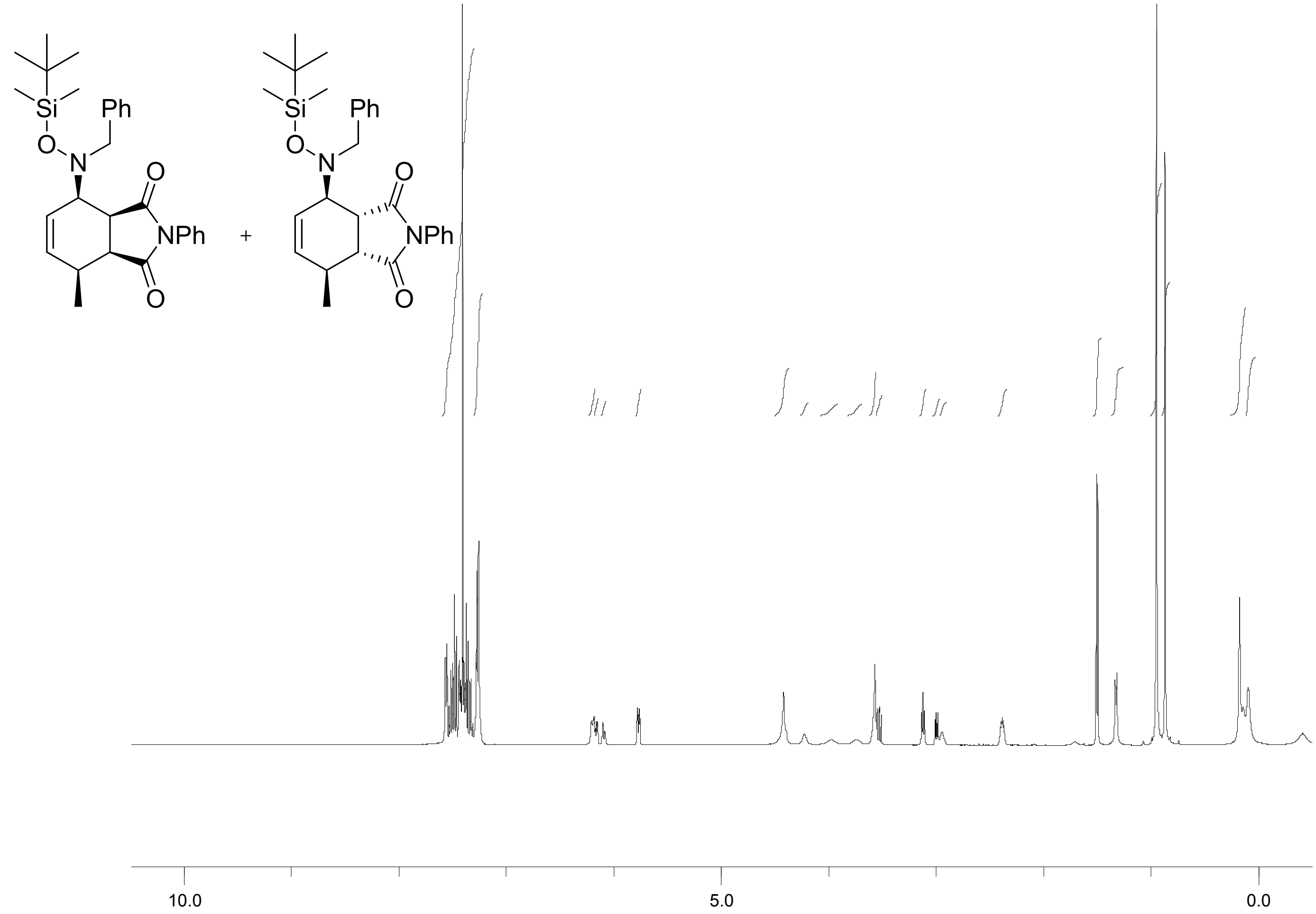

140.6
139.1
135.9
135.8
129.8
129.7
129.3
128.2
128.2
127.7
127.6
127.2
123.3
120.4
110.2
105.5
63.2
63.1
26.0
26.0
25.7
25.6
18.1
17.9
13.0
-5.3
200
150
100
50
0
ppm (f1)


Si
O
N
Ph
10.0
5.0
0.0
ppm (t1)


140.7
135.9
129.8
128.3
127.7
127.3
120.5
105.5
63.2
26.0
18.0
13.0
-5.3
200
150
100
50
0
ppm (f1)

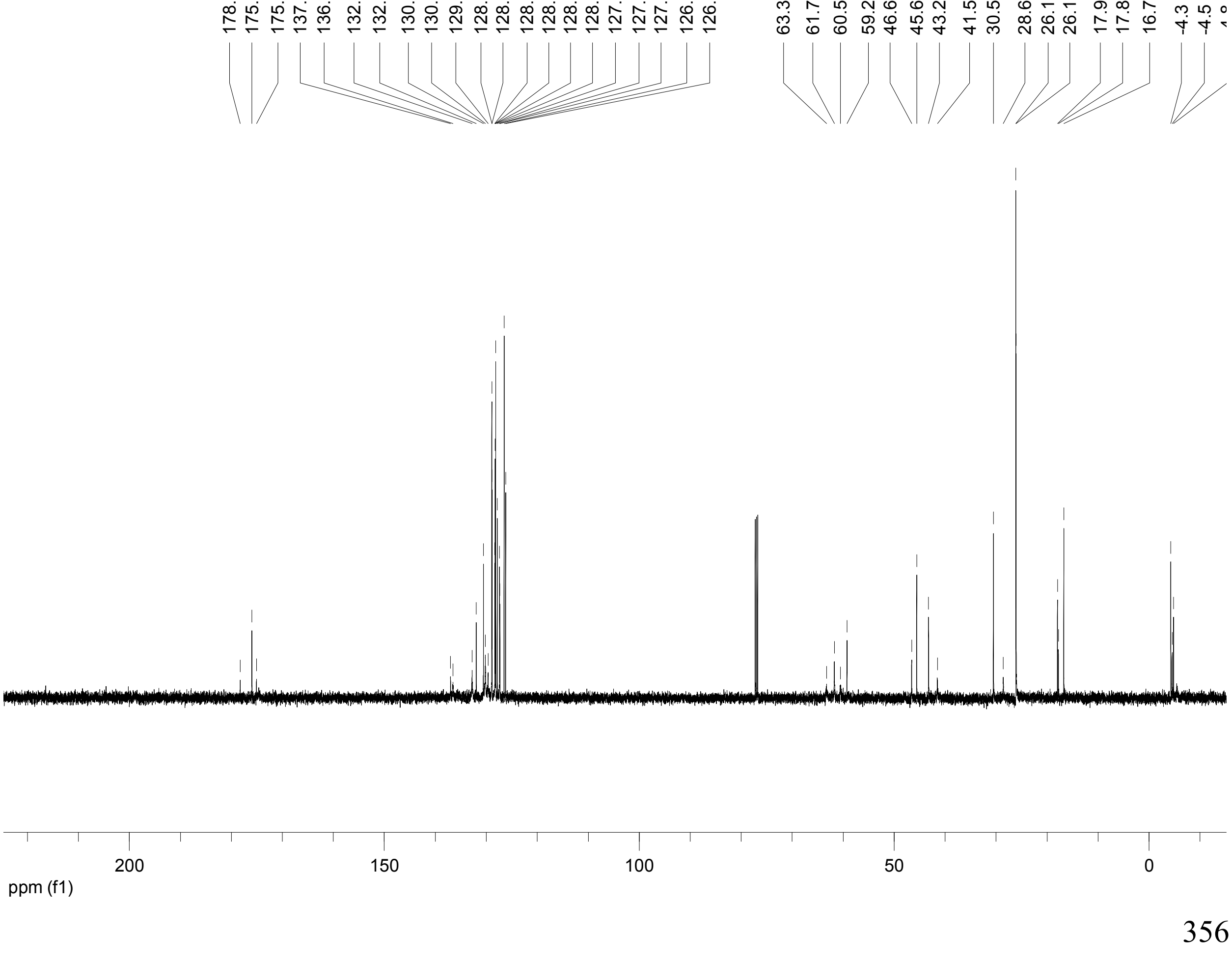

Si
O
N
Ph
+
Si
O
N
Ph
10.0
5.0
0.0
ppm (f1)


140.7
139.0
135.9
135.8
129.5
129.3
128.3
128.3
127.7
127.6
127.3
123.4
120.4
110.0
105.1
63.4
63.3
18.1
13.1
6.9
6.8
6.4
4.1
200
150
100
50
0
ppm (f1)

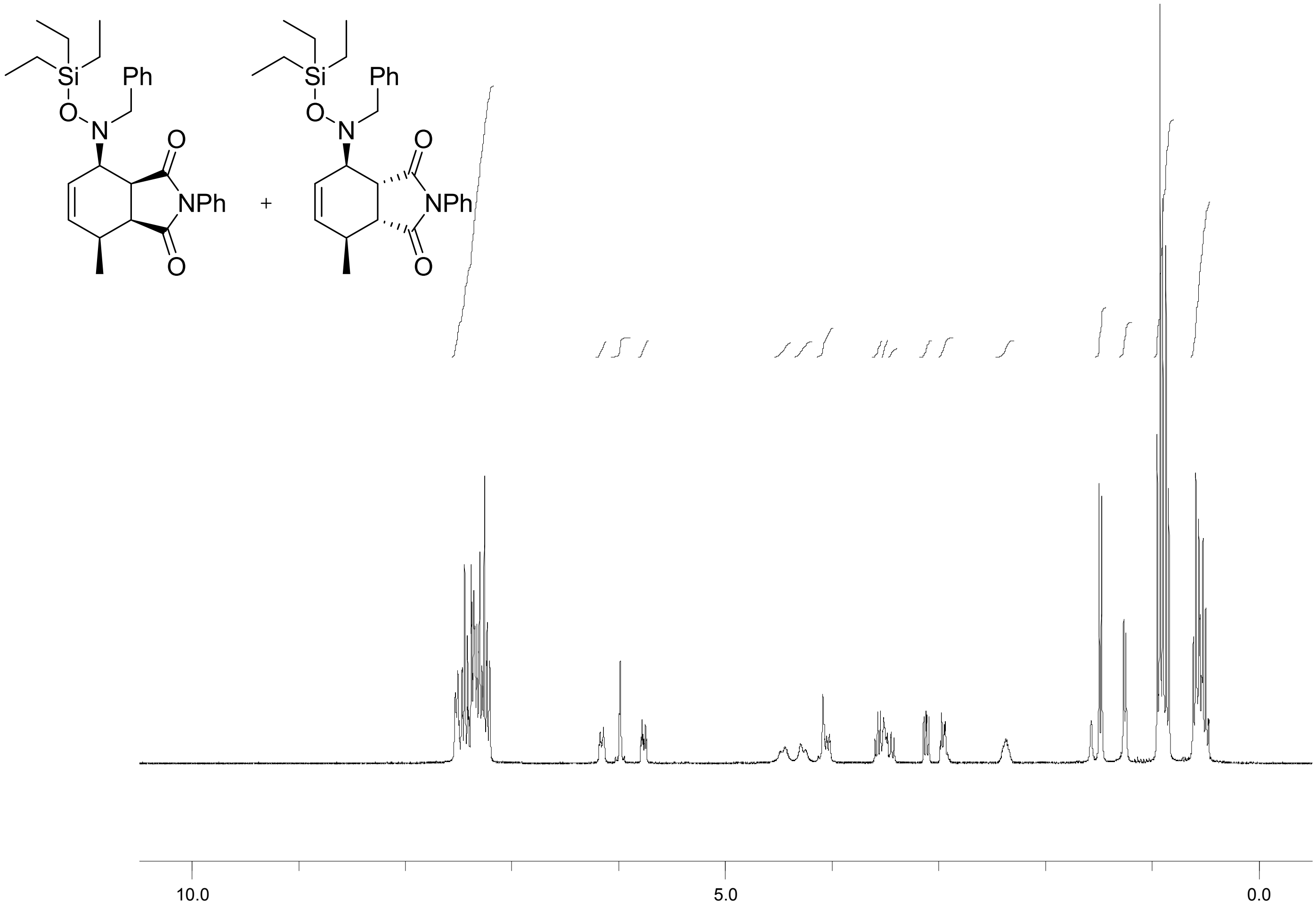


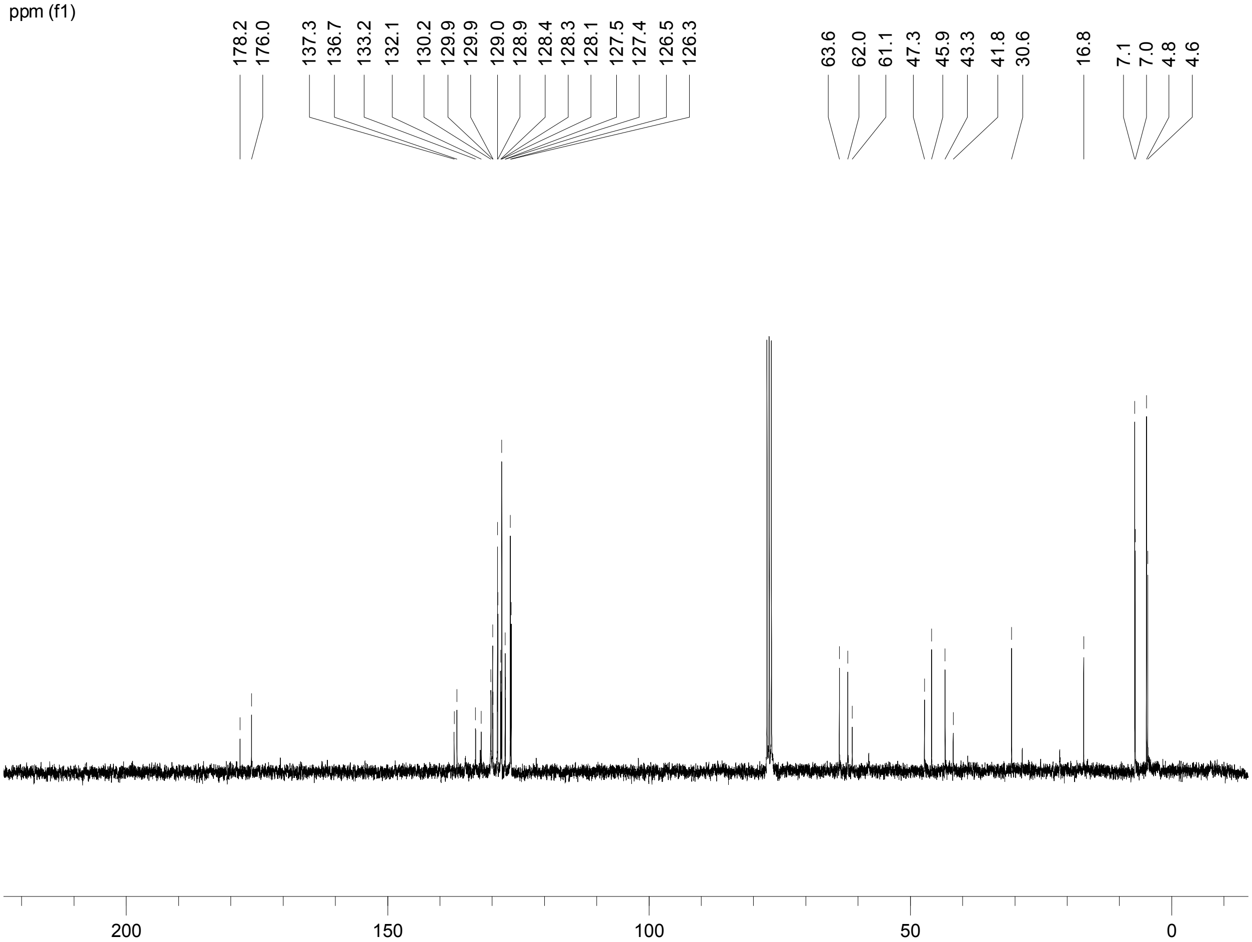
Ph
Si
O
N
O
NPh
O
+
Ph
Si
O
N
O
NPh
O

10.0
5.0
0.0
ppm (t1)



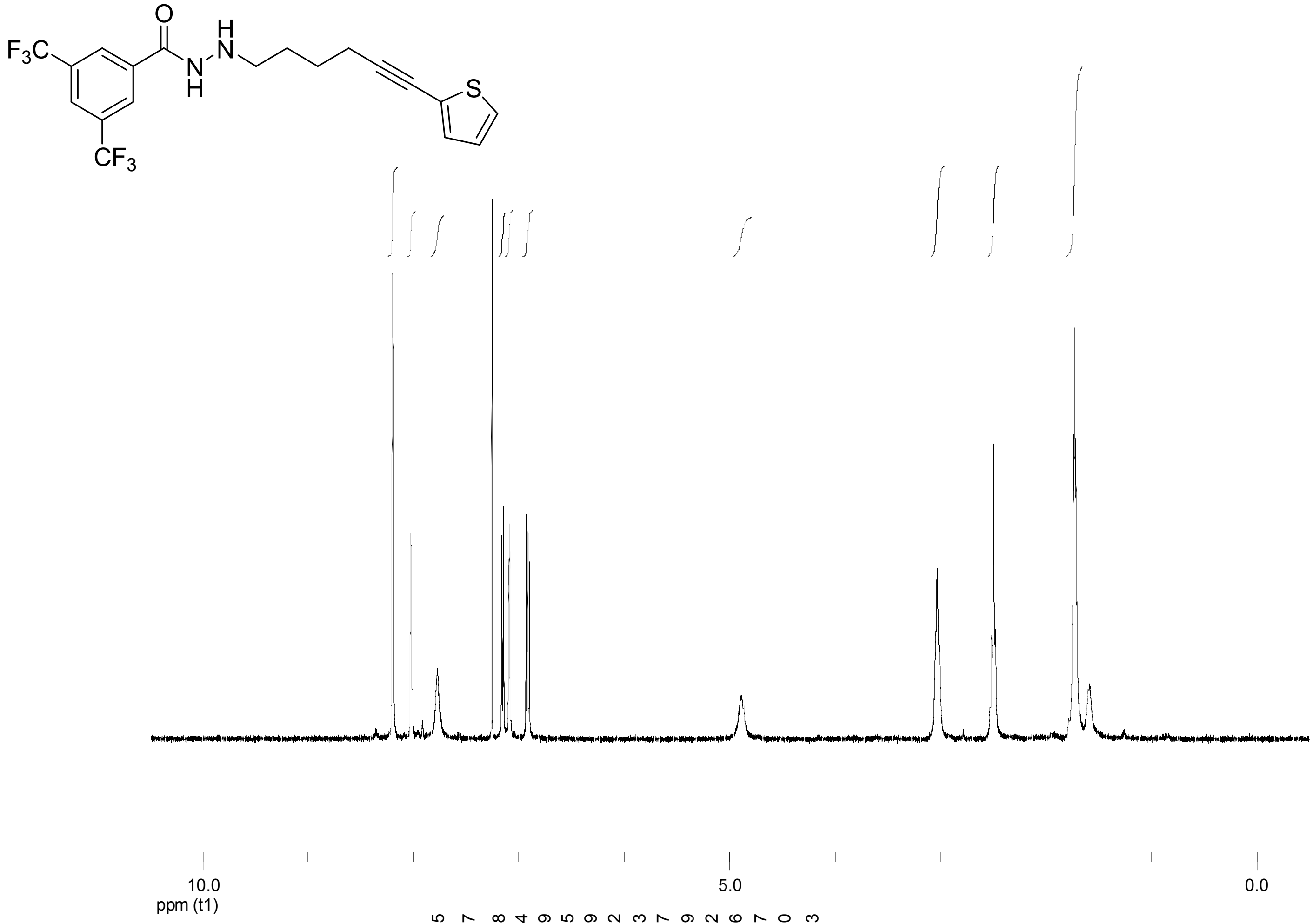
178.3
175.9
175.1
137.0
136.5
132.8
132.0
130.5
130.2
129.6
128.9
128.9
128.3
128.2
128.2
128.1
127.8
127.4
127.3
126.5
126.2
63.3
61.7
60.5
59.2
46.6
45.6
43.2
41.5
30.5
28.6
26.1
26.1
17.9
17.8
16.7
-4.3
-4.5
200
150
100
50
0
ppm (f1)

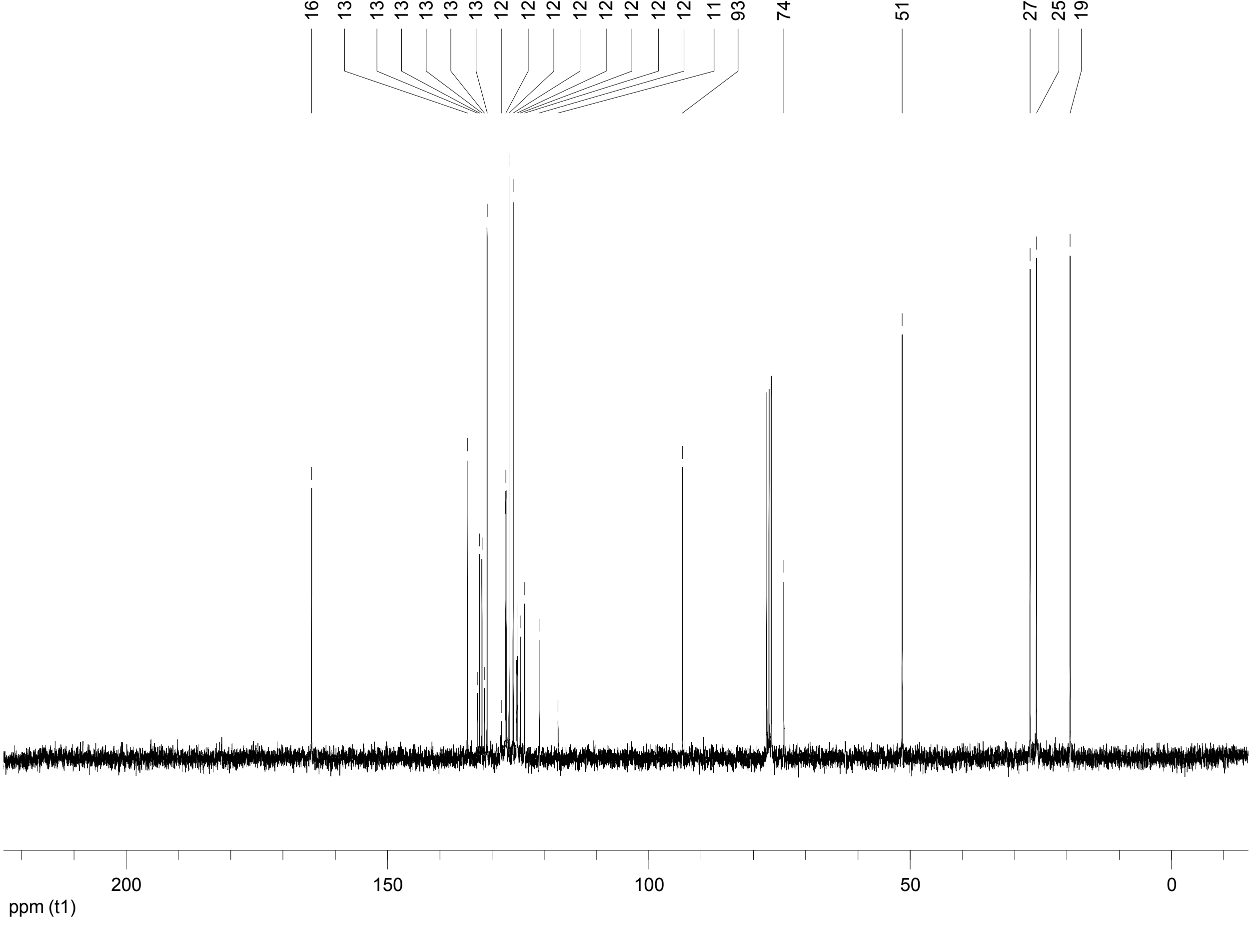

Si
O
N
Ph
O
NPh
O
+
Si
O
N
Ph
O
NPh
O
10.0
5.0
0.0
ppm (f1)

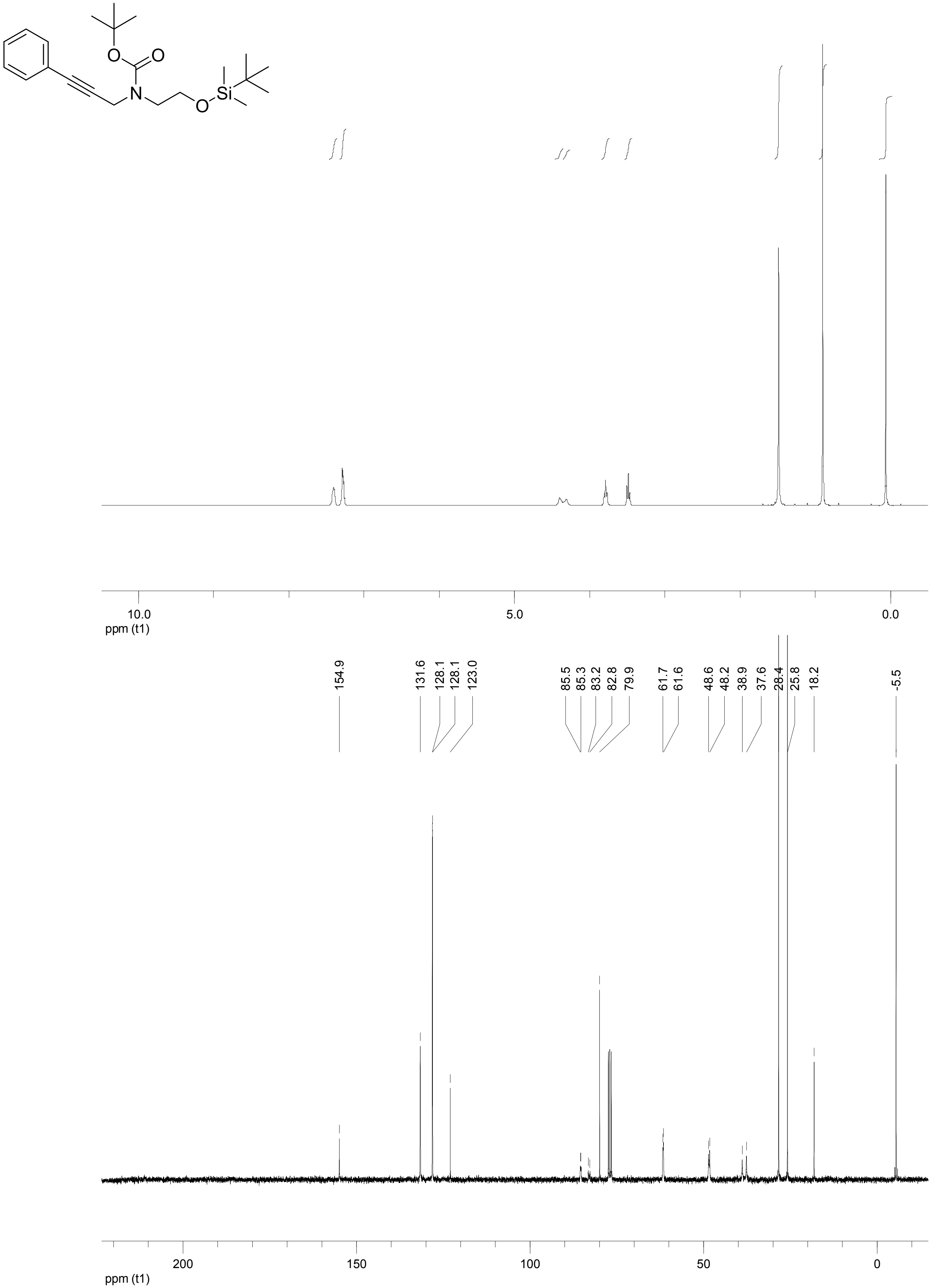

178.2
176.0
137.3
136.7
133.2
132.1
130.2
129.9
129.9
129.0
128.9
128.4
128.3
128.1
127.5
127.4
126.5
126.3
63.6
62.0
61.1
47.3
45.9
43.3
41.8
30.6
16.8
7.1
7.0
4.8
4.6
200
150
100
50
0
ppm (f1)

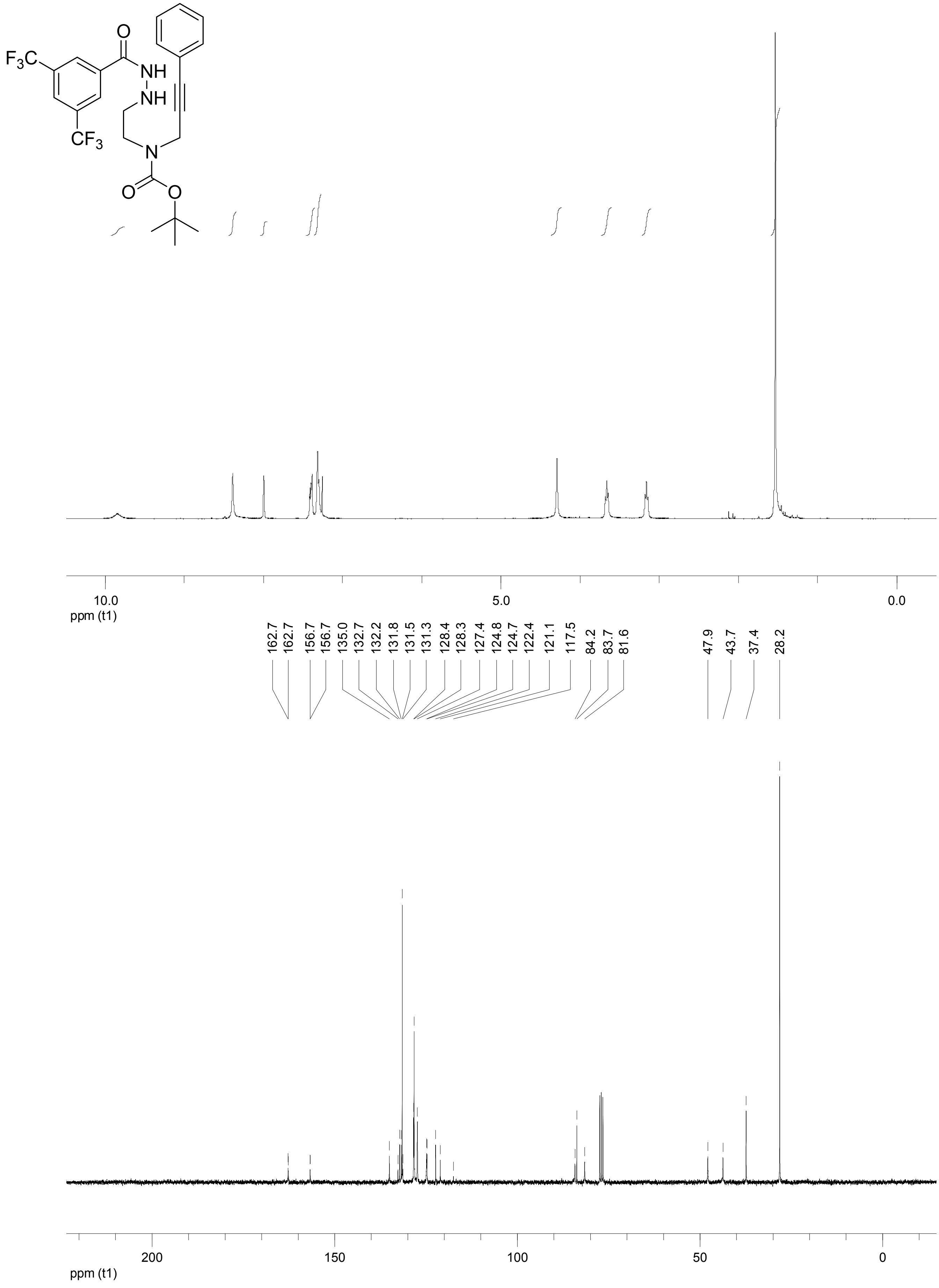
Appendix IV

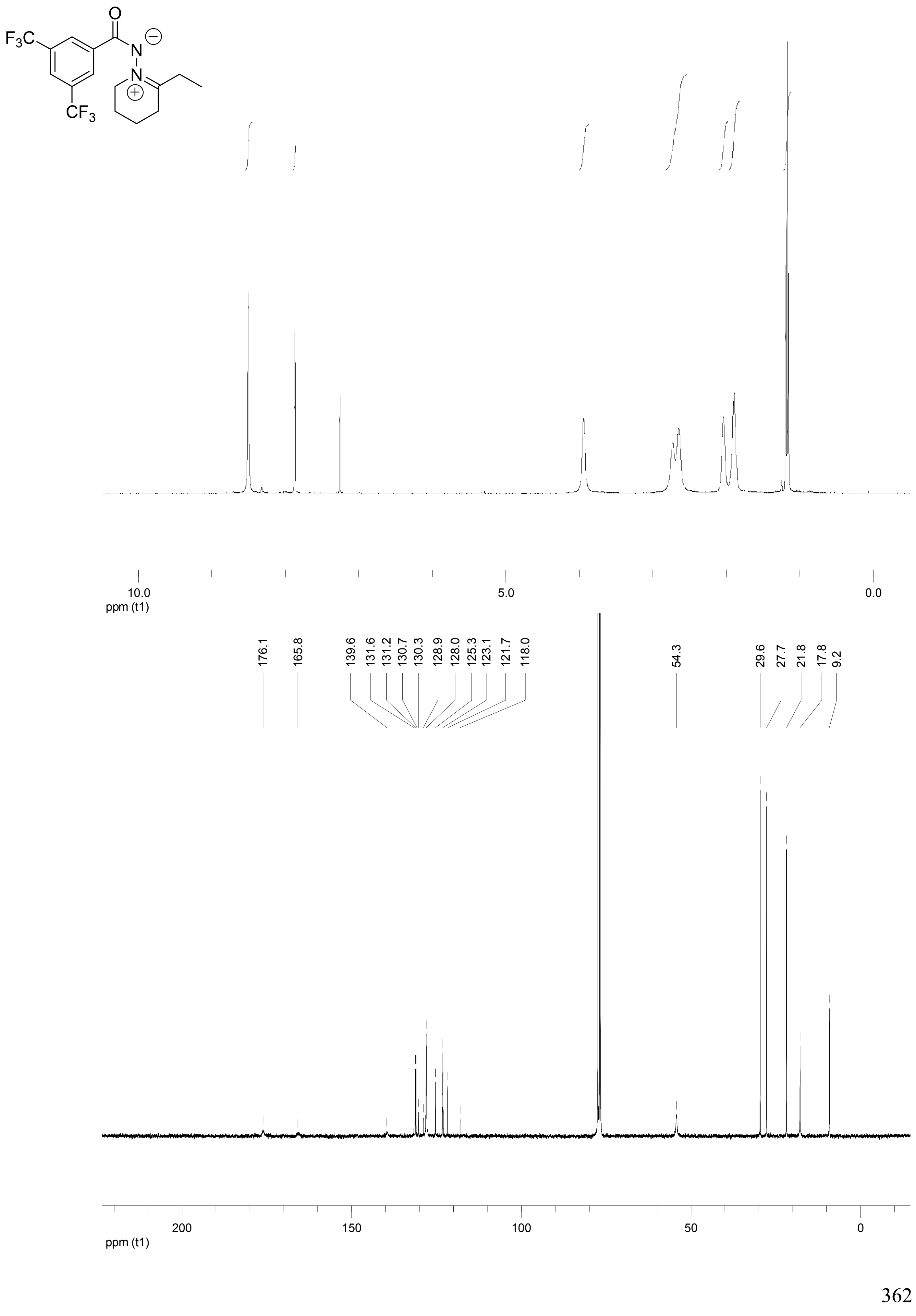
Supporting Information - Chapter 4

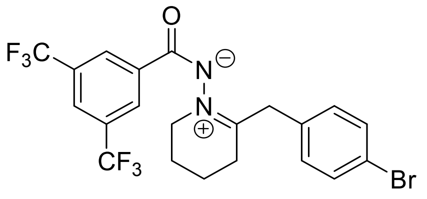

F3C
O
H
N
N
H
S
CF3
10.0
5.0
0.0
ppm (t1)

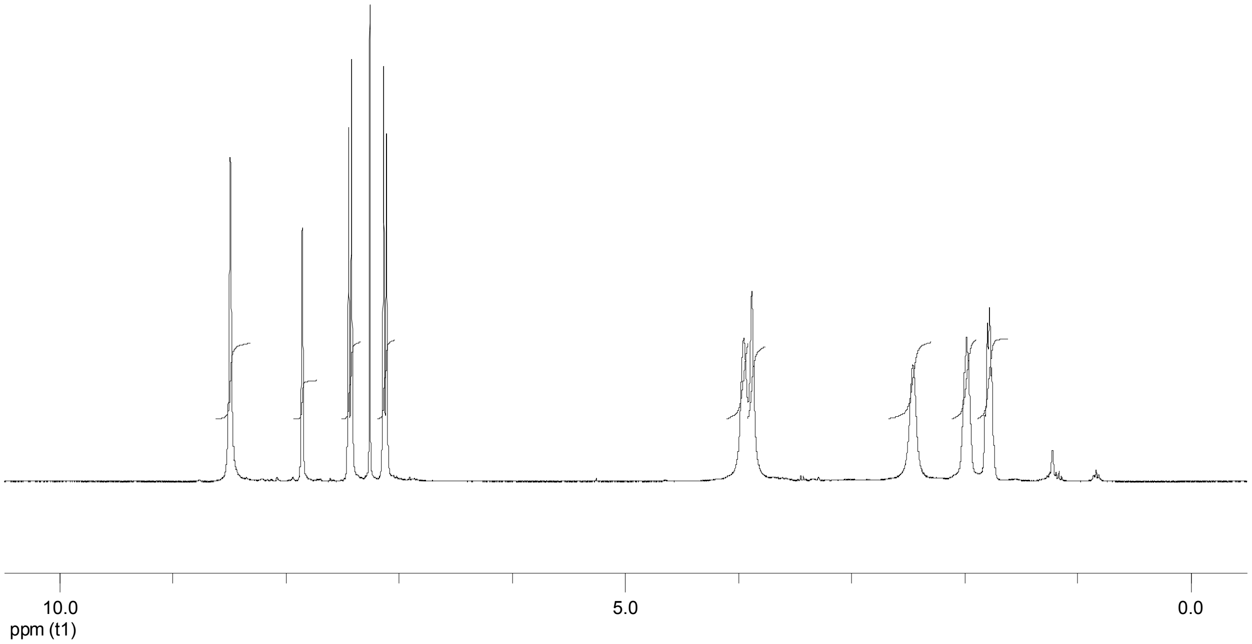

164.5
134.7
132.8
132.4
131.9
131.5
130.9
128.2
127.3
126.7
125.9
125.2
124.6
123.7
121.0
117.3
93.6
74.1
51.5
27.0
25.8
19.4
200
150
100
50
0
ppm (t1)

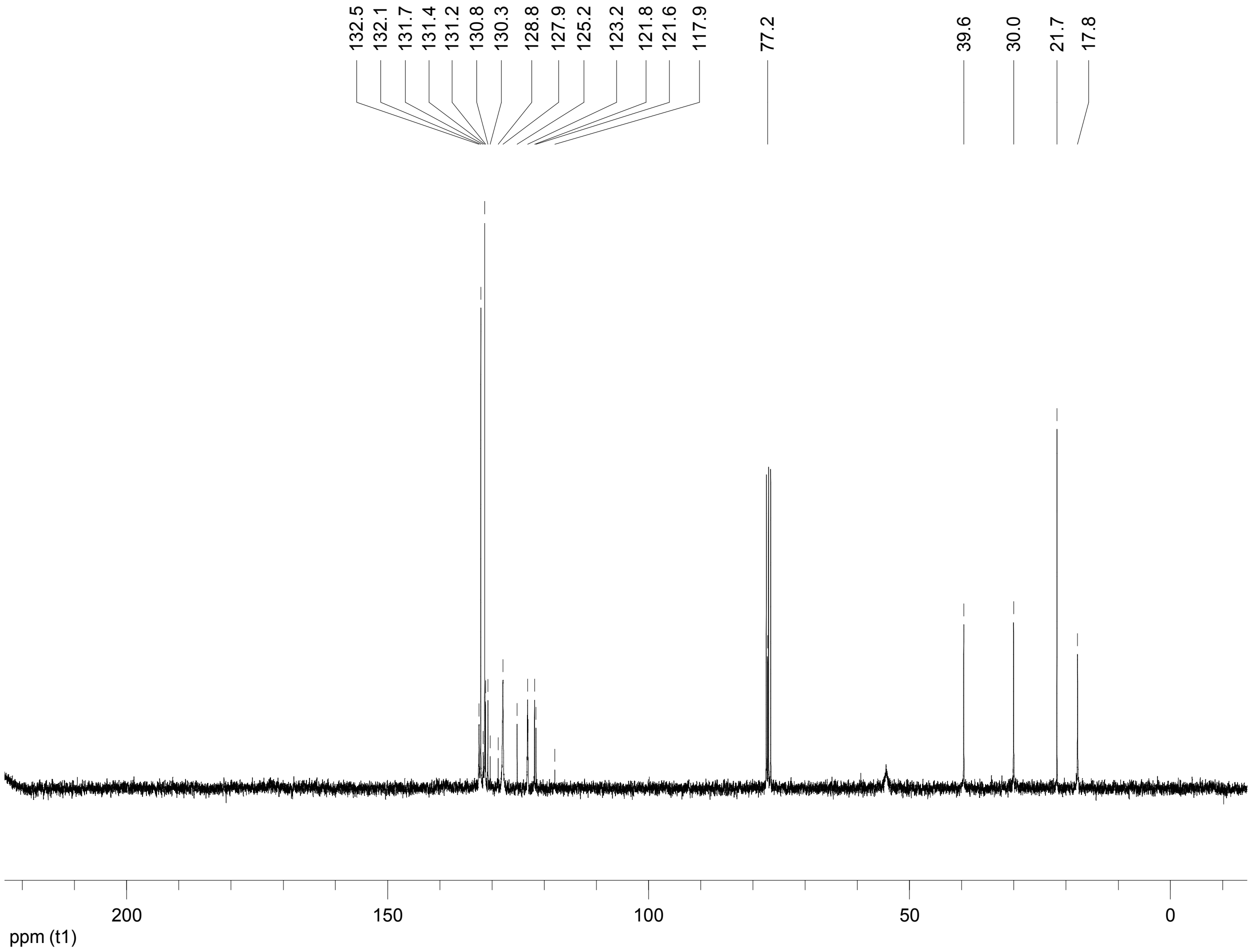

O
O
N
O
Si
10.0
5.0
0.0
ppm (t1)
154.9
131.6
128.1
128.1
123.0
85.5
85.3
83.2
82.8
79.9
61.7
61.6
48.6
48.2
38.9
37.6
28.4
25.8
18.2
-5.5
200
150
100
50
0
ppm (t1)

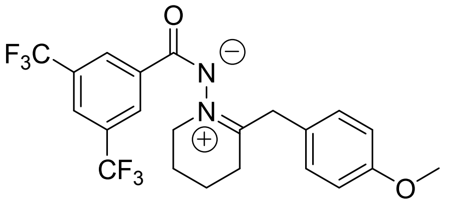

F$_3$C
O
NH
NH
CF$_3$
N
O
O
10.0
5.0
0.0
ppm (t1)
162.7
162.7
156.7
156.7
135.0
132.7
132.2
131.8
131.5
131.3
128.4
128.3
127.4
124.8
124.7
122.4
121.1
117.5
84.2
83.7
81.6
47.9
43.7
37.4
28.2
200
150
100
50
0
ppm (t1)

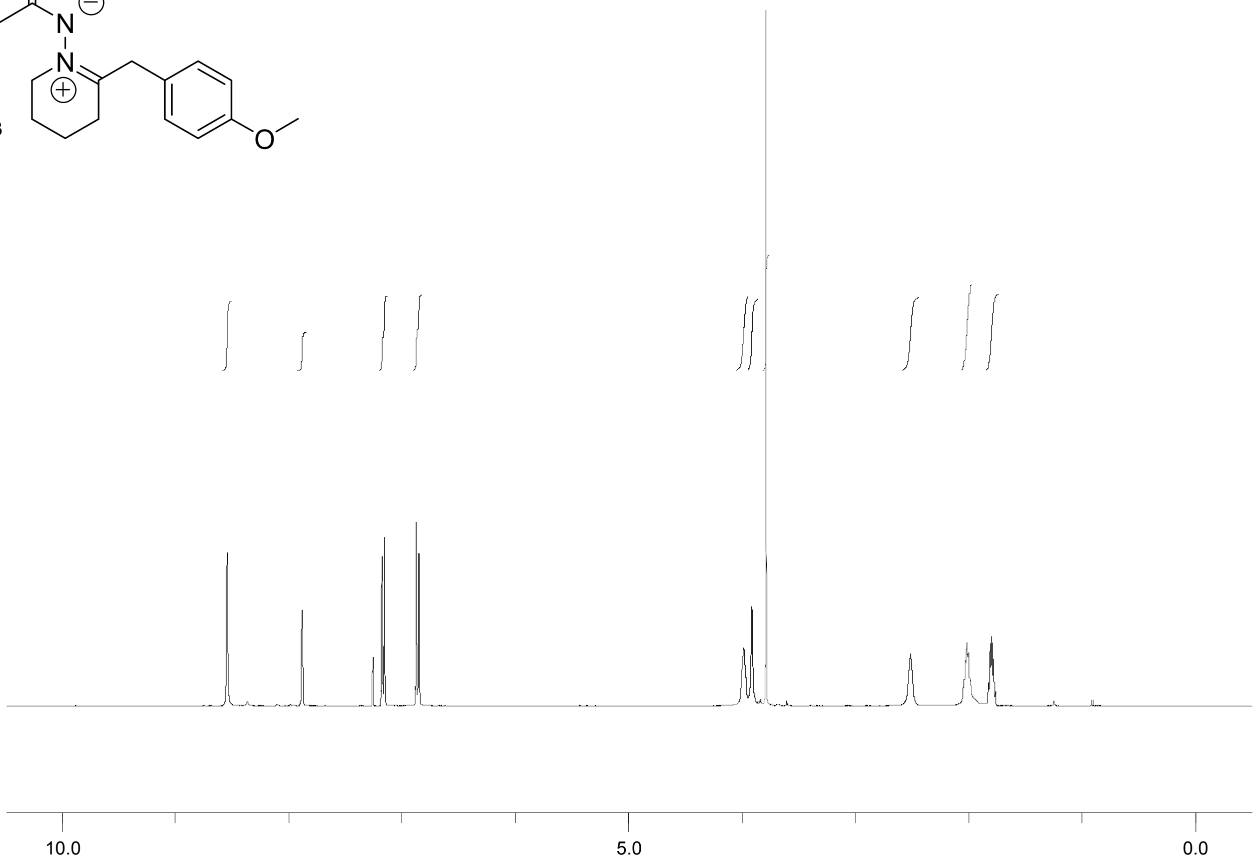

F3C
O
N
N
CF3
10.0
5.0
0.0
ppm (t1)
176.1
165.8
139.6
131.6
131.2
130.7
130.3
128.9
128.0
125.3
123.1
121.7
118.0
54.3
29.6
27.7
21.8
17.8
9.2
200
150
100
50
0
ppm (t1)

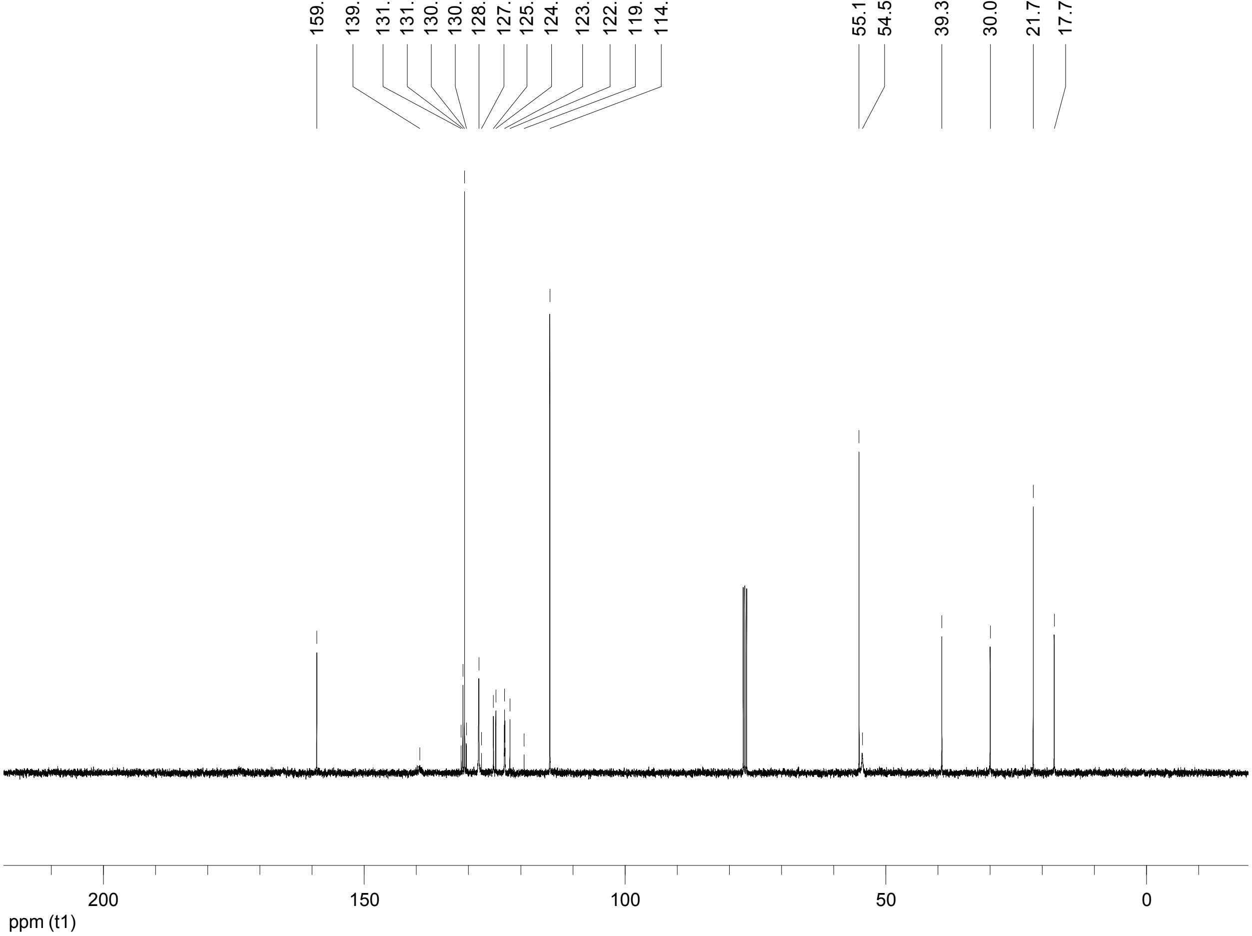

F3C
O
N⊖
N
⊕
CF3
Br

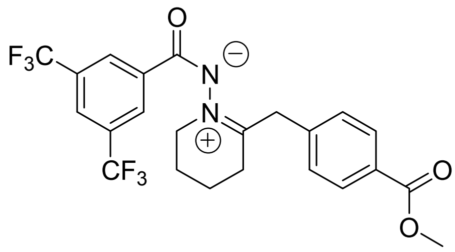

10.0
5.0
0.0
ppm (t1)

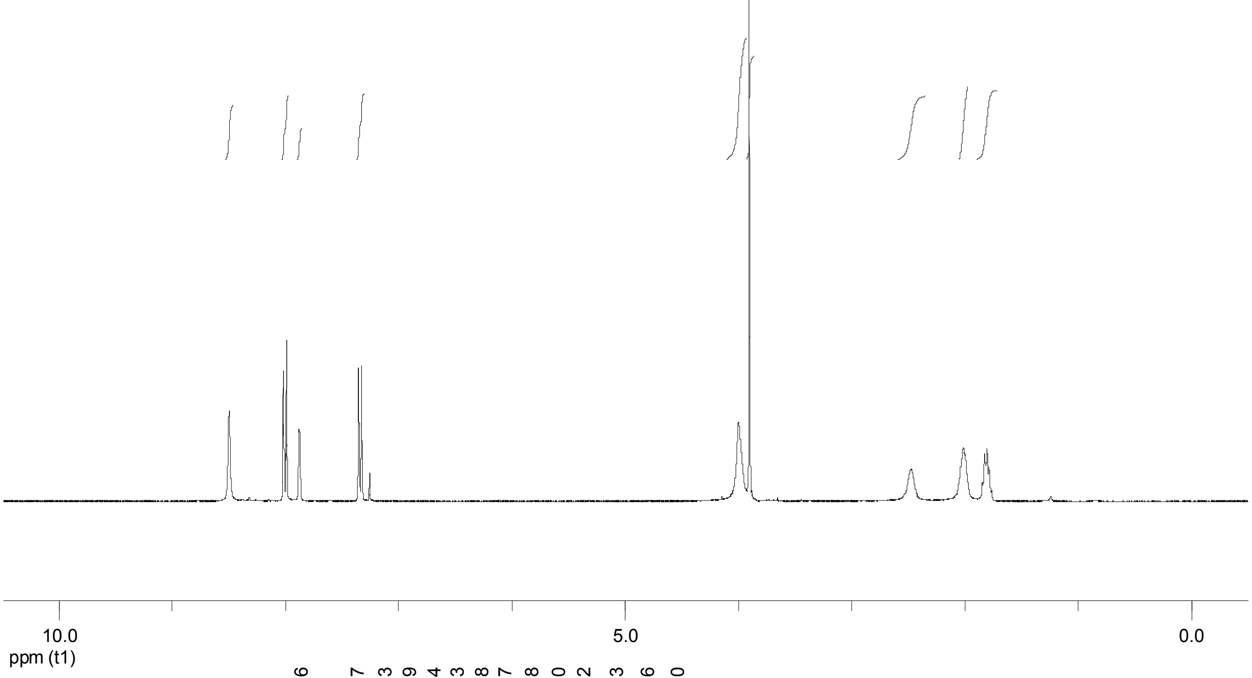

132.5
132.1
131.7
131.4
131.2
130.8
130.3
128.8
127.9
125.2
123.2
121.8
121.6
117.9
77.2
39.6
30.0
21.7
17.8
200
150
100
50
0
ppm (t1)

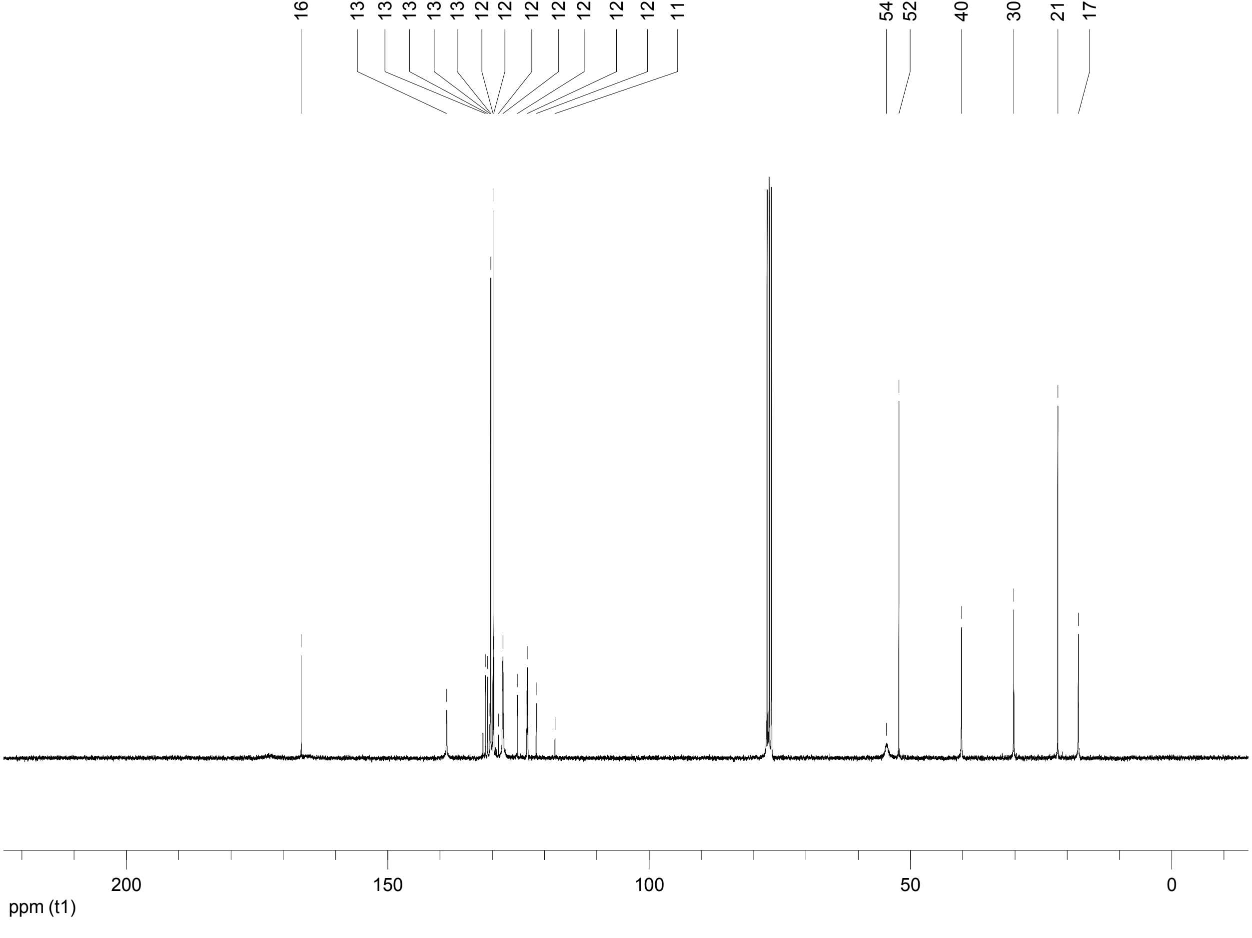

F3C
O
N
N
CF3
O

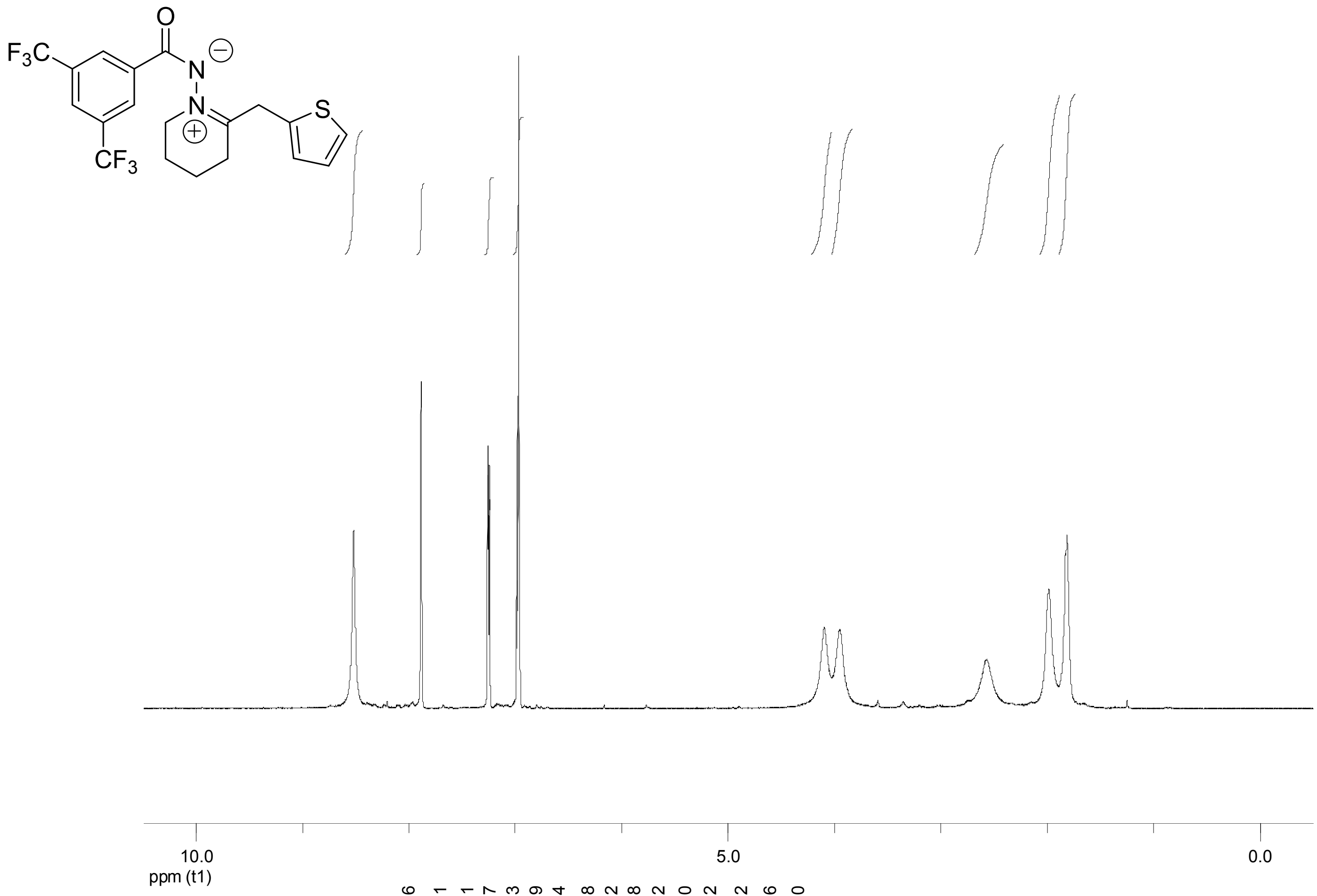

10.0
5.0
0.0
ppm (t1)

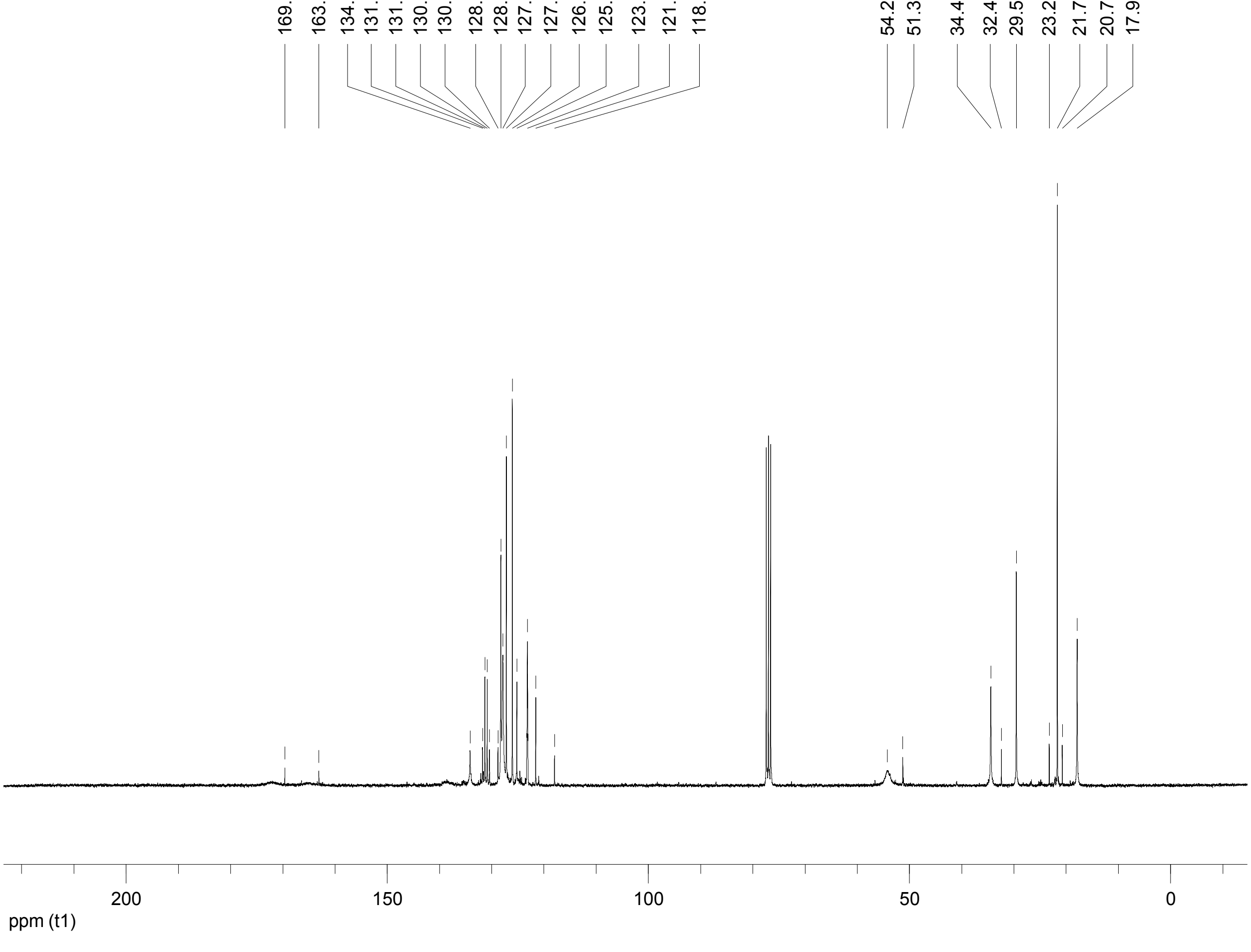

159.1
139.4
131.4
131.1
130.8
130.4
128.0
127.5
125.2
124.8
123.1
122.1
119.4
114.4
55.1
54.5
39.3
30.0
21.7
17.7
200
150
100
50
0
ppm (t1)

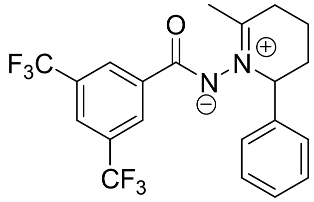

F3C
O
N
N
CF3
O
O


10.0
5.0
0.0
ppm (t1)

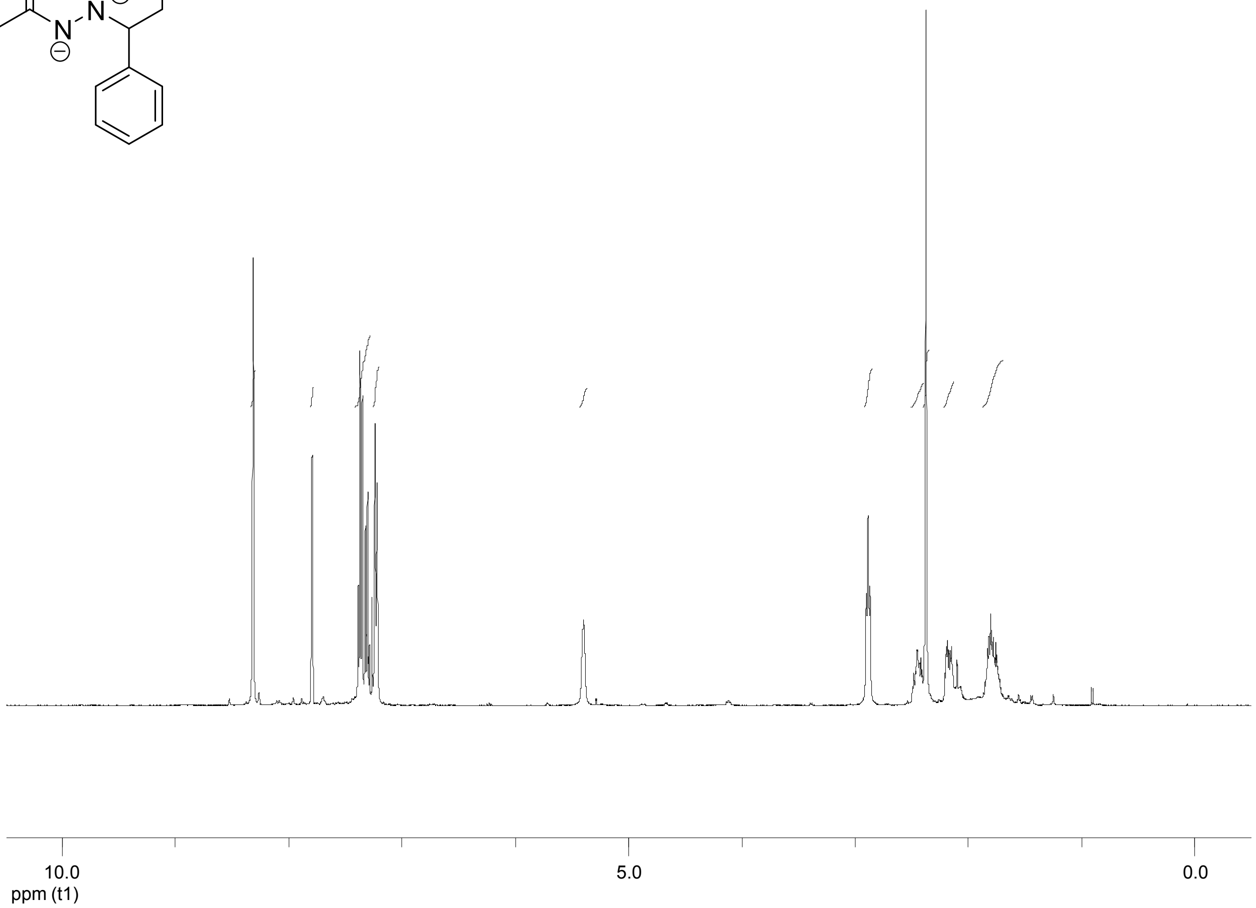

166.6
138.7
131.3
130.9
130.4
130.3
129.8
129.7
128.8
128.0
125.2
123.3
121.6
118.0
54.6
52.2
40.2
30.2
21.8
17.9
200
150
100
50
0
ppm (t1)


O
F3C
N
N
S
CF3
10.0
5.0
0.0
ppm (t1)

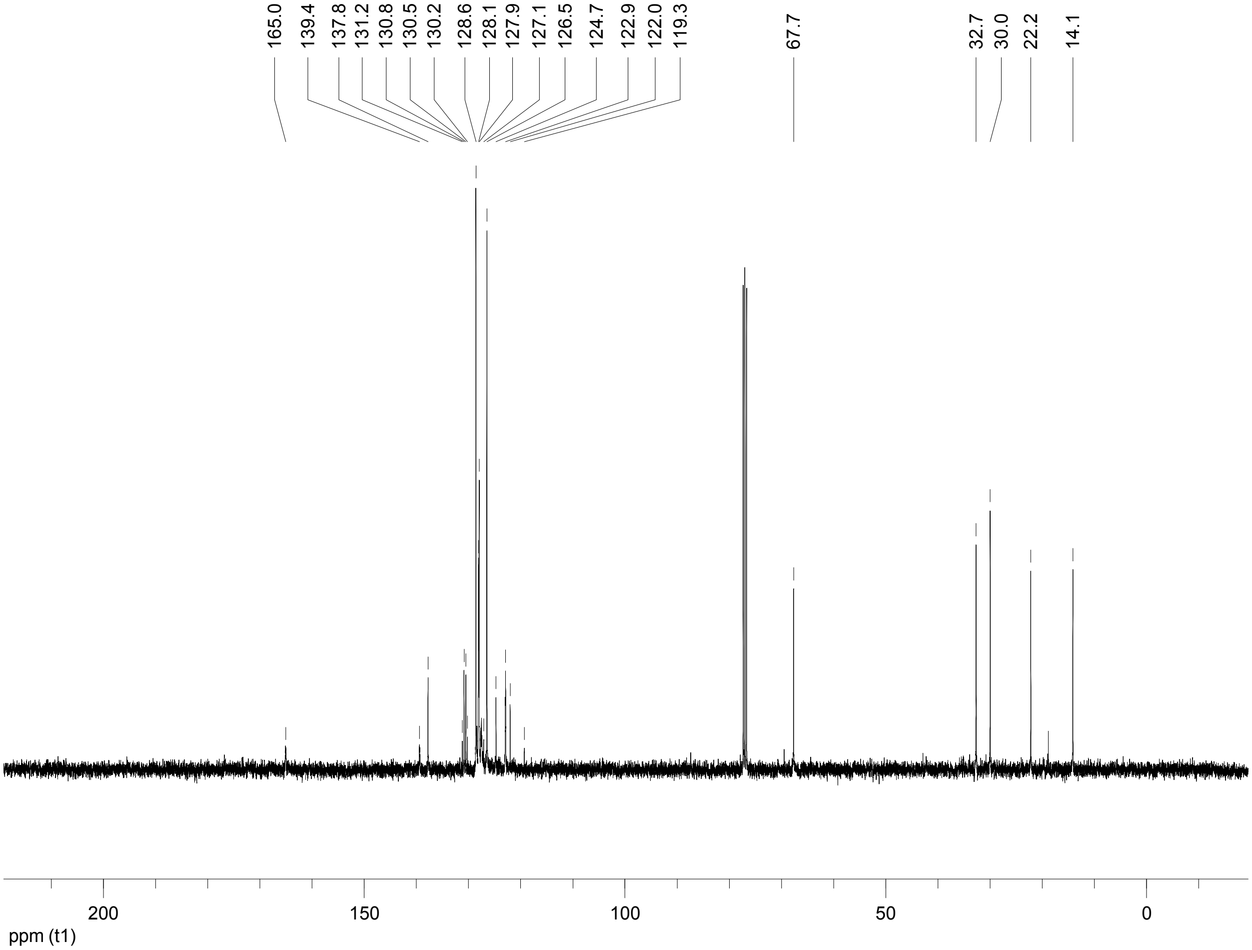

169.6
163.1
134.1
131.7
131.3
130.9
130.4
128.8
128.2
127.8
127.2
126.0
125.2
123.2
121.6
118.0
54.2
51.3
34.4
32.4
29.5
23.2
21.7
20.7
17.9
200
150
100
50
0
ppm (t1)



O
F3C
N
N
CF3



10.0
5.0
0.0
ppm (t1)



165.0
139.4
137.8
131.2
130.8
130.5
130.2
128.6
128.1
127.9
127.1
126.5
124.7
122.9
122.0
119.3
67.7
32.7
30.0
22.2
14.1
200
150
100
50
0
ppm (t1)