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Jennifer Pfeiffer
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Chemistry)
GRADE / DEGREE

Department of Chemistry
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

The Synthesis of 2-*epi*-Pumiliotoxin C Via Intramolecular Alkene Cope-Type Hydroamination and New Routes Toward Ketonitrones

TITRE DE LA THÈSE / TITLE OF THESIS

A. Beauchemin
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

R. Ben

C. Boddy

Gary W. Slater
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

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and
New Routes Toward Ketonitrones

By

Jennifer Y. Pfeiffer

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University of Ottawa

Candidate

Jennifer Y. Pfeiffer

Supervisor

Dr. André M. Beauchemin

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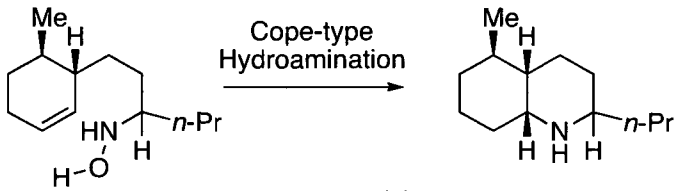
Abstract

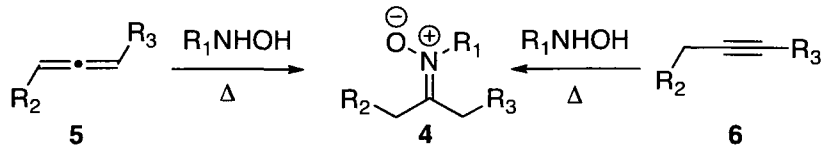
Despite recent advances in the field, the hydroamination methodology has not yet reached its full potential. This thesis focuses on new investigations in Cope-type hydroamination by first examining six-membered ring formation in order to explore and expand the scope of intramolecular Cope-type hydroamination of disubstituted olefins. This objective was achieved by synthesizing pumiliotoxin C (±)-**3** and its epimer (±)-**2** through the cyclization of a hydroxylamine precursor (±)-**1** under transition metal-free reaction conditions.



(±)-**1**

(±)-*epi*- and pumiliotoxin C
(±)-**2** and (±)-**3**

In the second chapter we discuss the scarcity of methods to make ketonitrones **4** in the current literature and our approach to overcome this constraint using Cope-type hydroamination which involved heating allenes **5** and alkynes **6** with hydroxylamines under metal-free reaction conditions. Improved reaction conditions for the Schiff-base reactions of ketones will also be presented.



5 **4** **6**

Scientific progress goes 'boink'.
-Hobbes

Acknowledgements

There are so many people who were instrumental in helping me reach this significant milestone. First and foremost, none of this would be possible without the help, guidance, and encouragement of Prof. André Beauchemin. His constant positive outlook nicely counteracted my usual cynicism and his outstanding memory still amazes me. Thank you for accepting me into the group, for providing an excellent learning opportunity, and for being even happier after a few drinks!

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Nothing can encompass what I would like to express towards Dr. Daniel Black- for all your help, support, advice, encouragement and understanding over grad school and since we met. I cherish all the laughs and memories we share and those we will continue to create. I could never have done this without you and who knows, I could have ended up at U of T (gasp)! Thanks for putting up with all my nonsense. I love you. A lot.

Finally, I would never have gotten anywhere without my family. Thank you for pretending to understand what I do, for tolerating chemistry scribbles on the mirrors, and for getting excited for my publications even though Naomi then throws them out (or recycles them). I love you all.

Table of Contents

List of Abbreviations

AM	anti-Markovnikov
Ac	acetyl
AcOH	acetic acid
approx.	approximately
aq.	aqueous
Ar	argon
BHT	2,6-di-*tert*-butyl-*para*-cresol *or* butylated hydroxytoluene
BL3YP	Beck-3-Lee-Yang-Parr
Bn	benzyl
Bu	butyl
^{o}C	degree Celsius
calcd	calculated
cat.	catalytic
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
conv.	conversion
Cy	cyclohexyl
$\Delta G^{\ddagger}$	energy of activation
δ	chemical shift in parts per million
DFT	density functional theory
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
E_a	energy of activation
ee	enantiomeric excess
equiv.	equivalent
Et_2O	diethyl ether
EtOAc	ethyl acetate
G	free energy
g	gram

h	hour(s)
HA	hydroamination
HRMS	high-resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
$KMnO_4$	potassium permanganate
L	litre; ligand
LAH	lithium aluminum hydride
M	Markovnikov; molar
MeCN	acetonitrile
MeOH	methanol
mg	milligram
min	minutes
mL	millilitre
mmol	millimol
Ms	methanesulfonyl
MS	molecular sieves
N_2	nitrogen
NMR	nuclear magnetic resonance
o	ortho
p.t.	proton transfer
PhH	Benzene
PhMe	Toluene
r	reaction
RC	reactants complex
Rf	reterntion factor
rt.	room temperature
S	entropy
t	time

T	temperature
TLC	thin-later chromatography
THF	tetrahydrofurane
TMS	trimethylsilyl
UV	ultra-violet

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1 Introduction

1.1 Background of hydroamination as a useful synthetic tool

As a high proportion of drug candidates and biologically active molecules contain at least one nitrogen atom in their core structure, heterocyclic chemistry is gaining importance and there are many methodologies available to form such an important class of structures. Many of the processes currently invoked to form carbon-nitrogen bonds involve Ritter amination, reductive amination of ketones, *N*-alkylation of amines, or reduction of amides, nitriles,[1] nitrogroups, or azides (Figure 1.1).

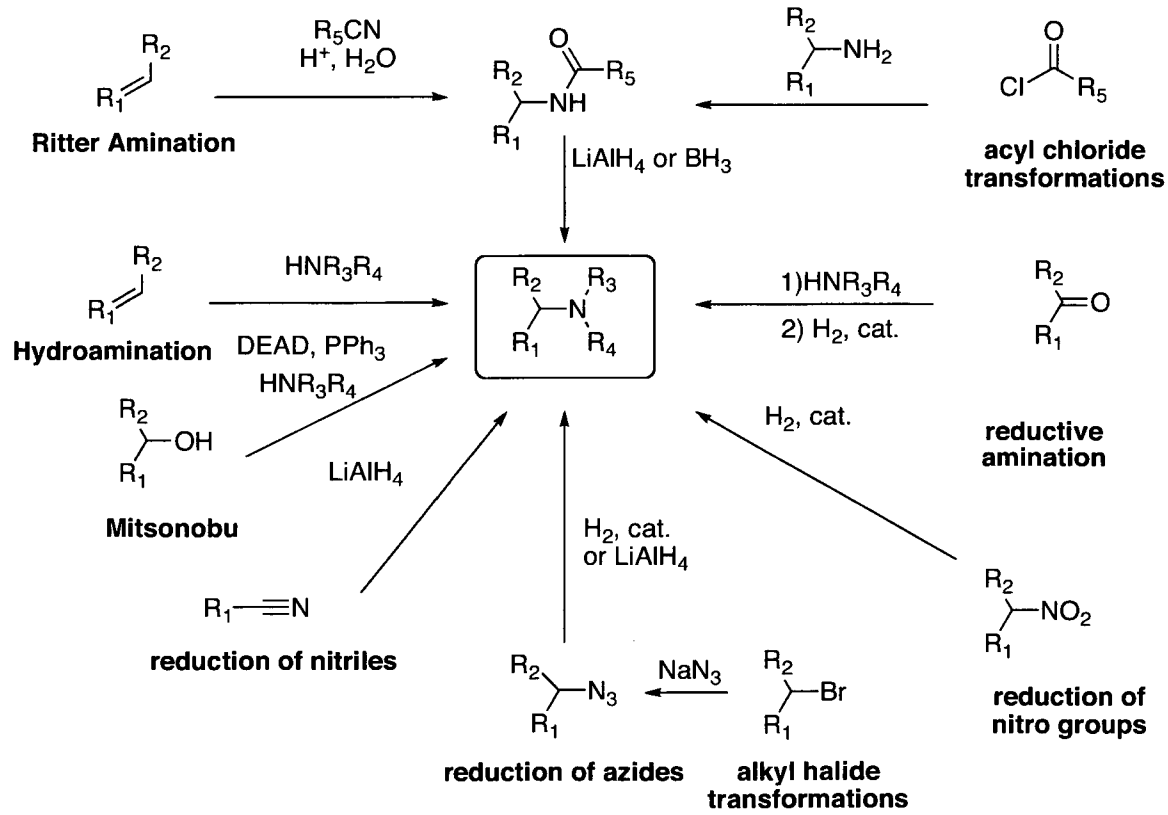


Figure 1.1: Different Routes to Amine Functional Group

[1] Patra, P.K; Nishide, K.; Fuji, K.; Node, M. *Synthesis* **2004**, 1003

Recent investigations in hydroamination chemistry have demonstrated its potential in expanding this field as it rapidly introduces a nitrogen and hydrogen across an unactivated carbon-carbon multiple bond.[2] By using this method one can generate amines and imines from alkenes and alkynes respectively, as well as imines and allylic amines from allenes (Figure 1.2). Furthermore, saturated and unsaturated heterocycles can be obtained if the reaction is performed intramolecularly.

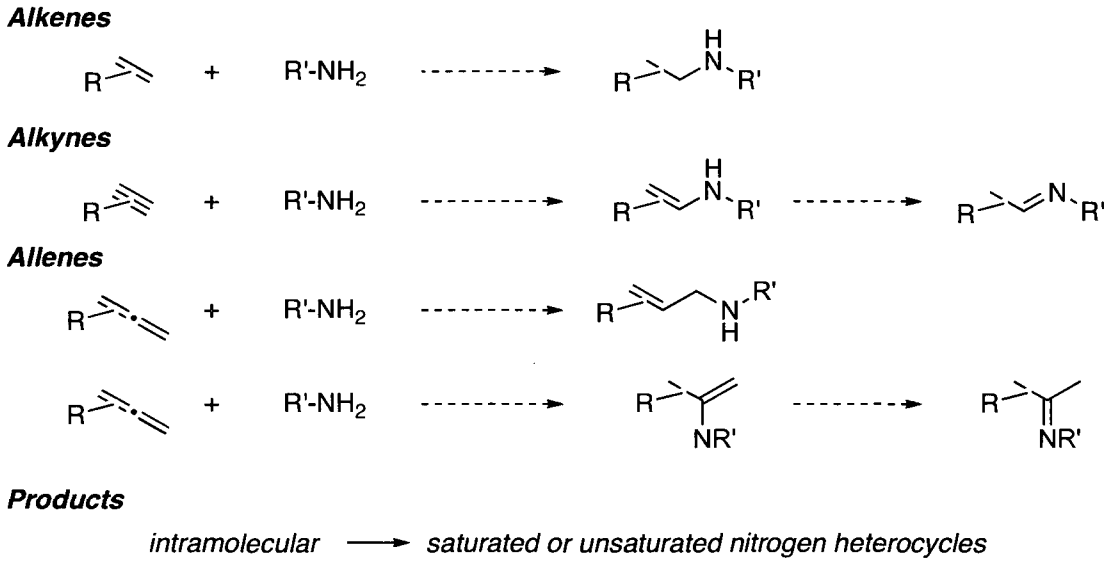


Figure 1.2: Synthetic Potential of a Difficult Transformation

The hydroamination technique has not achieved its full potential despite recent progress in the field as it has encountered a few obstacles that have limited its applicability, scope,

---

[2] For recent reviews see: General: (a) Müller, T. E.; Hultzsch, K.C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795 (b) Müller, T. E.; Beller, M., *Chem. Rev.* **1998**, *98*, 675 Alkynes: (c) Alonso, F.; Beletskaya, I.P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079 (d) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104 (e) Nobis, M.; Drießen-Hölscher, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3983 Asymmetric: (f) Hultzsch, K.C. *Adv. Synth. Catal.* **2005**, *347*, 367 Markovnikov and anti-Markovnikov functionalization: (g) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 9306 For futher information and details see: (h) Moran, M. Ph.D. Thesis, University of Ottawa, Ottawa, Ontario, 2009 (i) Lebrun, M.-E. M.Sc. Thesis, University of Ottawa, Ottawa, Ontario, 2008

and results. The main issue to overcome in hydroamination is that the electrostatic repulsion between the nitrogen lone pair and the electron rich π-system raises the energy of activation of the reaction. Furthermore, in the case of the intermolecular hydroamination of olefins, the reaction is near thermoneutrality or mildly exothermic at best with less stable alkenes such as ethylene and norbornene (Figure 1.3).[3] Increasing reaction temperatures to overcome the energy barrier further disfavours product formation due to the negative entropic term resulting from bringing two molecules together into one.

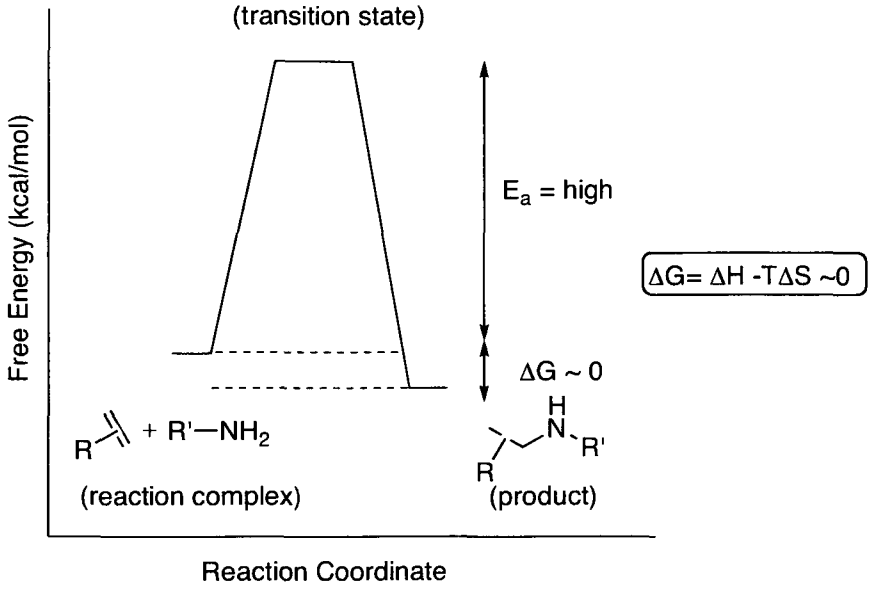


Figure 1.3: Thermodynamic Problem with Intermolecular Hydroamination of Alkenes

As such, different methods have been examined to circumvent these issues. The basicity of the nitrogen has posed constraints in the potential of acid catalysis therefore transition-metal catalysis has been the principal technique used to lower the activation energy. The

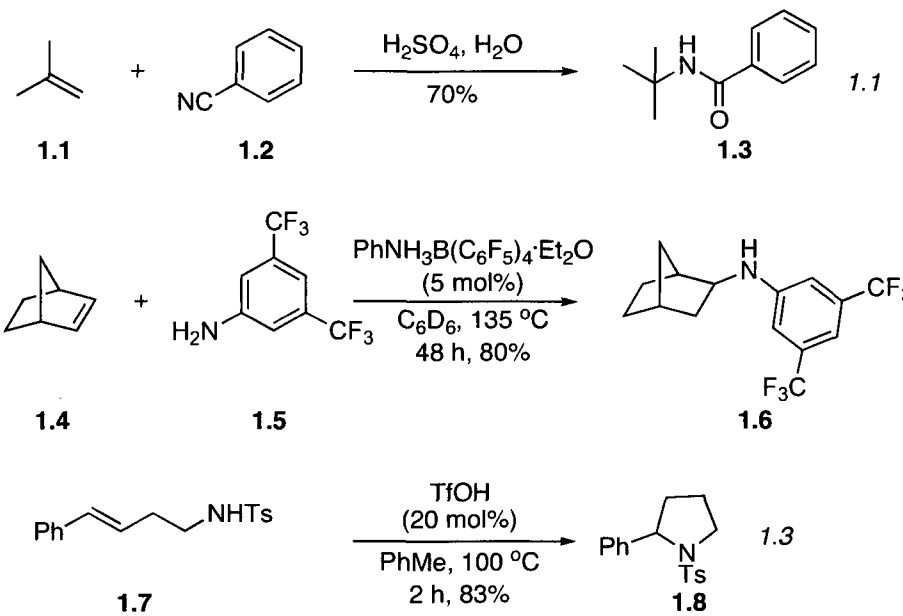
[3] Johns, A.M.; Sakai, N.; Ridder, A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 9306

synthetic applications, however, are rare and important limitations still exist despite large research efforts by the scientific community. The next section (Section 1.2) will survey different areas explored in hydroamination.[2a-b,h-i]

1.2 Literature precedent in hydroamination reactions

1.2.1 Via acid-catalysis

As mentioned briefly earlier, acid-catalyzed hydroamination is dependent on the basicity of the amine selected since the nitrogen acts as the nucleophile and protonation would result in the loss of nucleophilicity. Furthermore, the basic nitrogen atom can act as a buffering agent in the acidic medium thus preventing the protonation of the π-bond. Examples of acid-catalyzed hydroamination are presented below.[4,5,6]



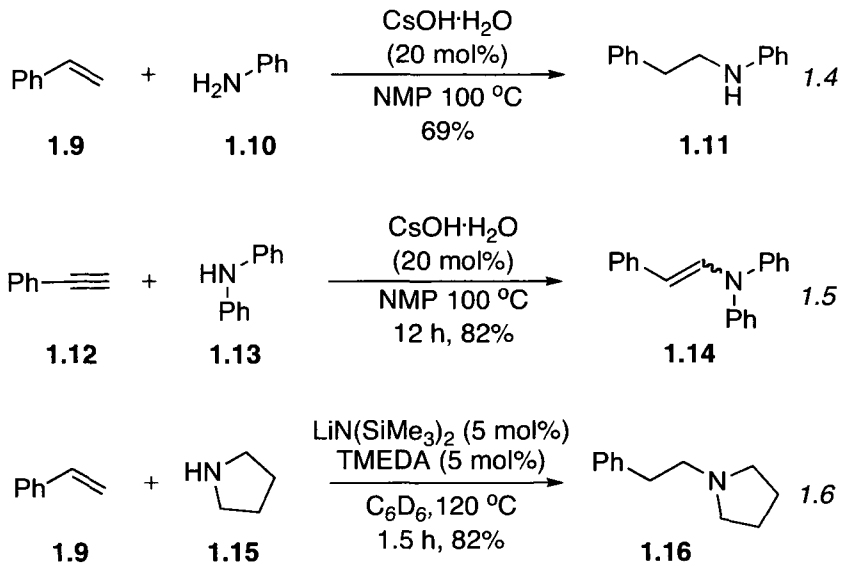
As a result of the limitations delineated above, the acid-catalyzed hydroamination strategy is plagued by poor functional group compatibility and biased substrate scopes. Less basic amines can be utilized like a nitrile group in the Ritter amination (Equation

1.1),[4] as well as highly reactive olefins (Equation 1.2)[5] or substrates that highly favour intramolecular reactivity (Equation 1.3).[6] Generally acid-catalyzed hydroamination reactions yield the Markovnikov product as the more stable carbocation is produced.

In summary, substrates developed for the acid-catalyzed hydroamination are biased towards reactivity and functional group compatibility under the strongly acidic conditions is problematic.

1.2.2 Via base-catalysis

Base-catalyzed hydroamination is also possible but forcing conditions are necessary.[2f,7] Some examples are presented below (Equation 1.4 through Equation 1.6).[8,9]



Recently, Knochel and co-workers developed a cesium hydroxide catalyzed system whereby anilines could be added to styrene and phenylacetylene.[8] In another system,

---

[4] Krimen, L.I.; Cota, D. J. *Org. React.* **1969**, *17*, 213
[5] Anderson, L.L.; Arnold, J.; Bergman, R.G. *J. Am. Chem. Soc.* **2005**, *127*, 14542
[6] Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471
[7] Howk, B.W.; Little, E.L.; Scott, S.L.; Whitman, G.M. *J. Am. Chem. Soc.* **1954**, *76*, 1899
[8] Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193

vinyl aromatics were able to be hydroaminated with secondary amines with $LiN(SiMe_3)_2$/TMEDA as catalyst and could be reacted in solvent-free conditions.[9] Di-amination products were observed with primary amines. This forcing strategy can only be applied on conjugated substrates that can stabilize the partial negative charge forming in the transition-state.

1.2.3 Via metal-catalysis

Various laboratories have explored metal-catalyzed hydroamination and this has been the main line of attack towards hydroamination to date.[2,10] The majority of the progress has been made with respect to hydroamination of non-activated alkynes while intermolecular reactivity with alkenes is still substrate-specific and suffers from the thermodynamic issue previously discussed (Figure 1.3). On the other hand, the intramolecular hydroamination of alkenes has had more success, especially to form five-membered cycles.

1.2.3.1 Alkyne hydroamination

The methodologies developed for alkyne hydroamination[2c] have their individual shortcomings, especially those that employ toxic metals like mercury and thallium.[11] The reaction conditions associated with organolanthanides are milder but require extremely anhydrous and anaerobic environments thereby diminishing their appeal. Group IV

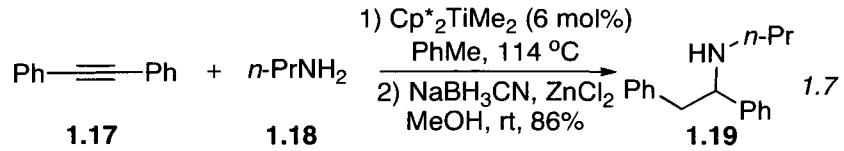
---

[9] Horillo-Martinez, P.; Hultzsch, K.C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311

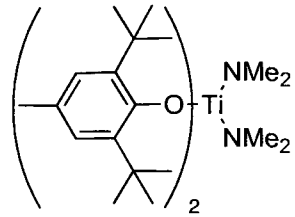
[10] For selected reviews, see : (a) Severin, R.; S. Doye, *Chem. Soc. Rev.* **2007**, *32*, 1407 (b) Matsunaga, S. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 778 (c) Roesky, P. W.; Müller, T. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 2708

[11] Barluenga, J.; Aznar, A.; Liz, R.; Rodes, R. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2732

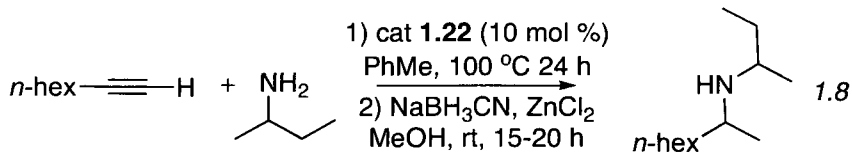
metals like zirconium and titanium have also been examined[12] and the latter has been the focus of a lot of studies due to its cheap availability and high reactivity (Equation 1.7 through Equation 1.9).[12a-d]



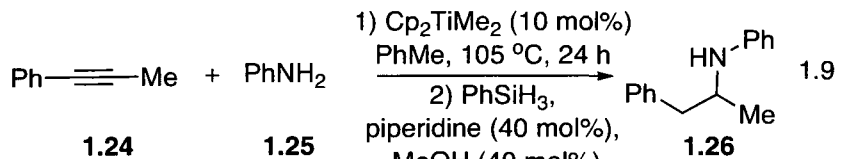
1.17 + 1.18 → 1.19 *1.7*



1.22



1.20 + 1.21 → 1.23 *1.8*



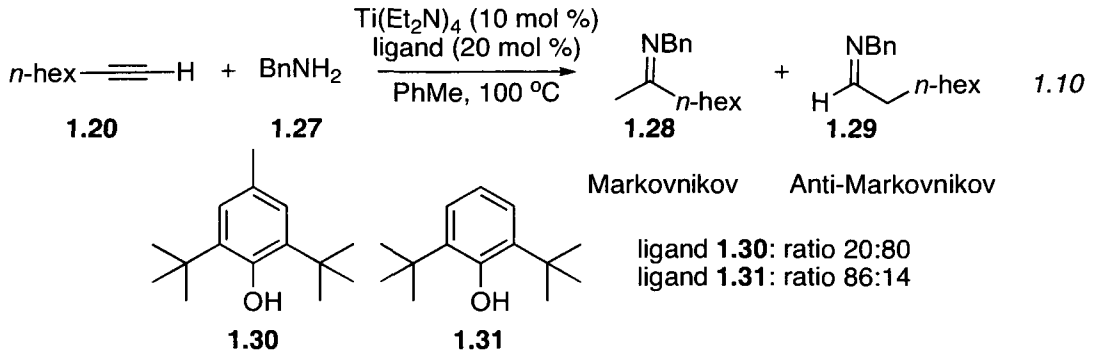
1.24 + 1.25 → 1.26 1.9

Different titanium catalyst systems have been developed for the intermolecular hydroamination of internal and terminal alkynes. The imine intermediates are subsequently reduced to the amines by cyanoborohydride reduction[12c-d] or, more recently, by hydrosilylation as a one-pot reaction with the same titanium catalyst.[12a]

---

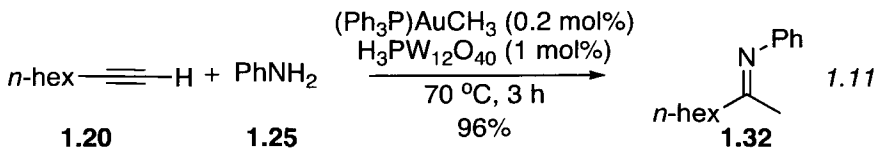
[12] (a) Heutling, A.; Pohlki, F.; Bytschkov, I.; Doye, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2951 (b) Tillack, A.; Khedkar, V.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 8875 (c) Heutling, A.; Doye, S. *J. Org. Chem.* **2002**, *67*, 1961 (d) Khedkar, V.; Tillack, A.; Beller, M *Org. Lett.* **2003**, *5*, 4767 (e) Cao, C.; Shi, Y.; Odom, A.L. *Org. Lett.* **2002**, *4*, 2853 (f) Straub, B.F. Bergman, R.G. *Angew. Chem. Int. Ed.* **2001**, *40,* 4632 (g) Pohlki, F.; Doye, S. *Angew. Chem. Int. Ed.* **2001**, *40,* 2305

Regioselectivity and yield of the reaction depends on the metal, ligand, amine or alkyne used. Beller and co-workers demonstrate this characteristic with an interesting report of titanium-catalyzed hydroamination of terminal alkynes whereby modifying the sterics of the phenol ligands controlled the regioselectivity of the reaction (Equation 1.10).[12b]



1.10

Late-transition metals have also been used for intermolecular alkyne hydroamination. Using a variety of anilines with a gold catalyst and acid promoter under solvent-free conditions, aliphatic and aromatic terminal alkynes produced the corresponding ketimine while internal alkynes required longer reaction times but still reacted successfully (Equation 1.11).[13]

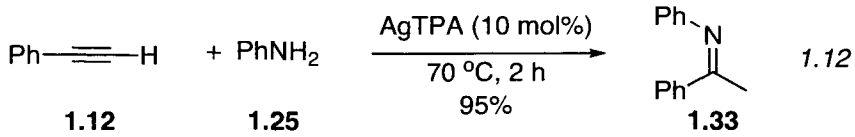


1.11

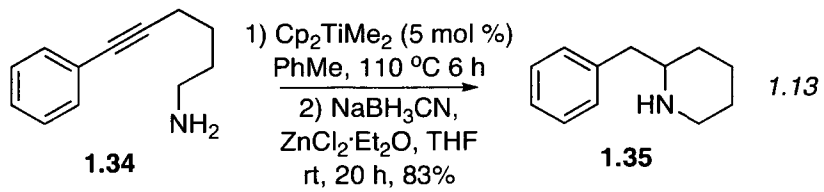
Another solvent-free reaction system used a silver tungstophosphoric acid (TPA) catalyst for the hydroamination of both aliphatic and aromatic alkynes with aniline derivatives.[14] Only the Markovnikov ketimine products were observed for terminal alkyne reactions

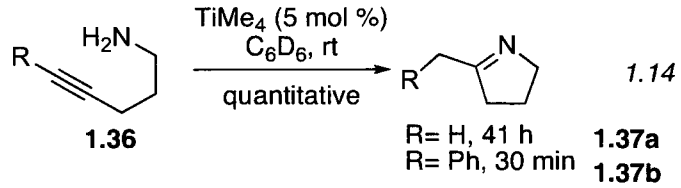
[13] Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349
[14] Lingaiah, N.; Seshu Babu, N.; Mohan Reddy, K.; Sai Prasad, P.S.; Suryanarayana, I. *Chem. Commun.* **2007**, 278

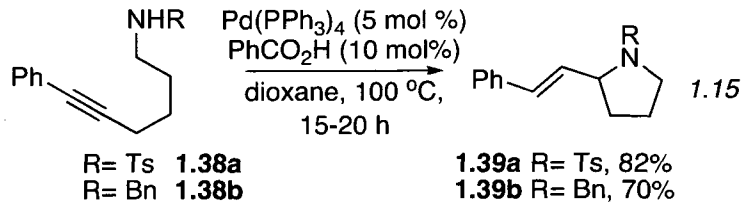
(Equation 1.12). The hydroamination of internal alkynes afforded lower yields of the corresponding imine.



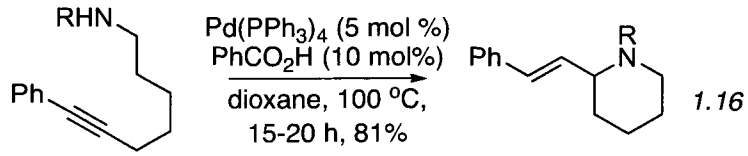
Intramolecular hydroamination of alkynes via metal catalysis has generated both five- and six-membered heterocycles in excellent yields. Both titanium[15,16] and late transition-metals[17,18] can be employed (Equation 1.13 through Equation 1.17) to obtain both five- and six-membered rings.





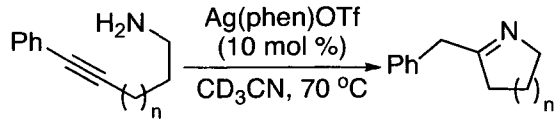


[15] Bytschkov, I.; Doye, S. *Tetrahedron Lett.* **2002**, *43*, 3715
[16] Ackermann, L.; Bergman, R.G. *Org. Lett.* **2002**, *4*, 1475
[17] Kadota, I.; Shibuya, A.; Lutete, L.M.; Yamamoto. Y. *J. Org. Chem.* **1999**, *64*, 4570
[18] Carney, J.M; Donoghue, P.J.; Wuest, W.M.; Wiest, O.; Helquist, P. *Org. Lett.* **2008**, *10*, 3903



1.16

R= Ts **1.40a** **1.41a** R= Ts, 0%
R= Bn **1.40b** **1.41b** R= Bn, 81%

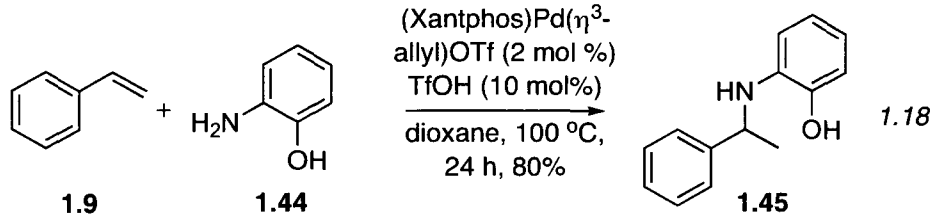


1.17

n= 1 **1.42a** **1.43a** n= 1, 95%
n= 2 **1.42b** **1.43b** n= 2, 77%

1.2.3.2 Alkene Hydroamination

The intermolecular hydroamination of alkenes is still restricted to activated or biased substrates including styrenes,[19] dienes,[20] norbornenes, and methylenecyclopropane (Equation 1.18 and Equation 1.19);[21] only a few examples exist with unactivated alkenes like cyclooctene (Equation 1.20).[22,23]



1.9 **1.44** **1.45**

1.18

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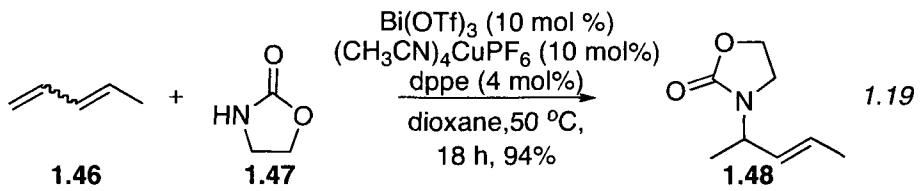
[19] Johns, A.M.; Utsunomiya, M.; Incarvito, C.D.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 1828

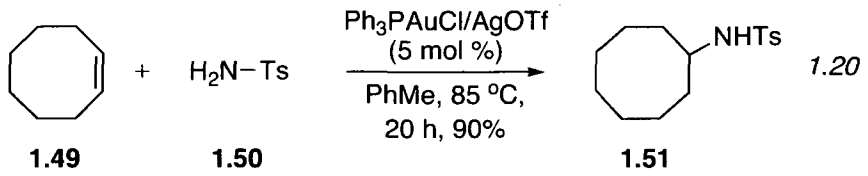
[20] Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611

[21] Smolensky, E.; Kapon, M.; Eisen, M.S. *Organometallics* **2007**, *26*, 4510

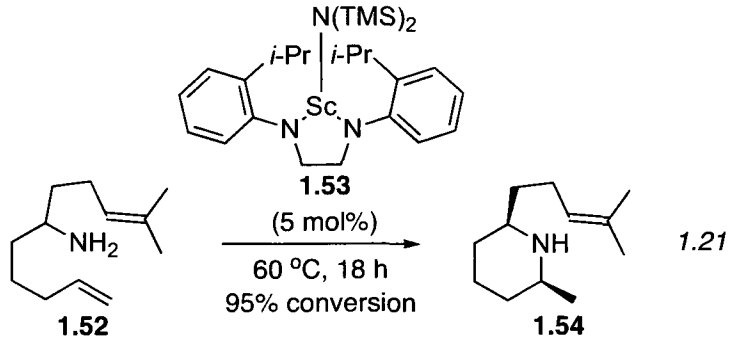
[22] Zhang, J.; Yang, C-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798

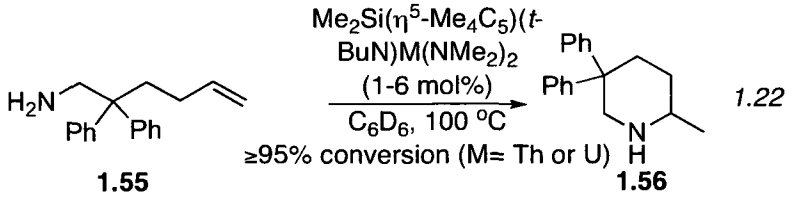
[23] (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C-G.; Reich, N.W.; He. C. *Org. Lett.* **2006**, *8*, 4175 (b) Schlummer, B.; Hartwig, J.F. *Org. Lett.* **2002**, *4*, 1471





There are numerous cases of intramolecular hydroamination of alkenes to form five- but not six- membered rings.[24] The following examples (Equation 1.21 through Equation 1.24) illustrate examples of intramolecular alkene hydroamination to form piperidines via metal catalysis.[25,26,27,28]





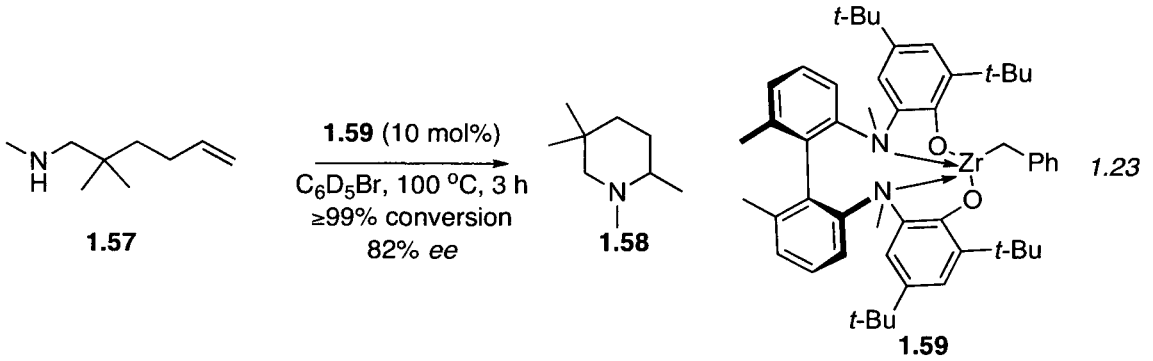
[24] Lebrun, M.-E.; Pfeiffer, J.Y.; Beauchemin, A.M. *Synlett* **2009**, 1087 and references cited therein

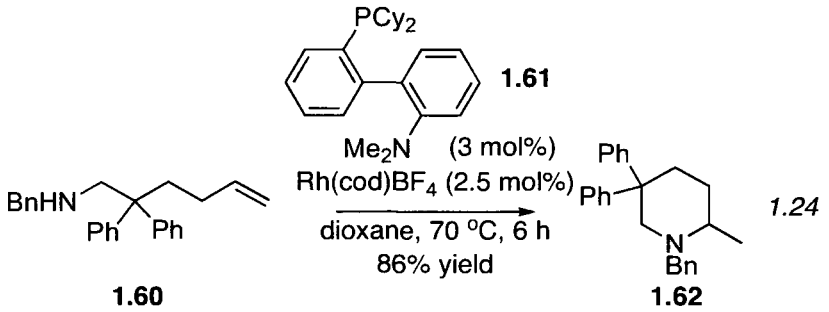
[25] Kim, J.Y.; Livinghouse, T. *Org. Lett*, **2005**, *7*, 4391

[26] Stubbert, B.D.; Marks, T.J. *J. Am. Chem. Soc.* **2007**, *129*, 4253

[27] Knight, P.D.; Munslow, I.; O'Shaughnessy, P.N.; Scott, P. *Chem. Commun.* **2004**, 894

[28] Liu, Z.; Hartwig, J.F. *J. Am. Chem. Soc.* **2008**, *130*, 1570





Interestingly, Equation 1.21 demonstrates the selective hydroamination of a terminal olefin instead a trisubstituted one, forming a piperidine over a pyrrolidine.[25] Additionally, terminal and disubstituted olefins can be cyclized with thallium or uranium catalysis to produce the six-membered ring (Equation 1.22).[26] Conditions for this transformation must be stringently free of water or oxygen. Rhodium was also used to catalyze the intramolecular hydroamination of internal and un-activated terminal olefins (Equation 1.24).[28]

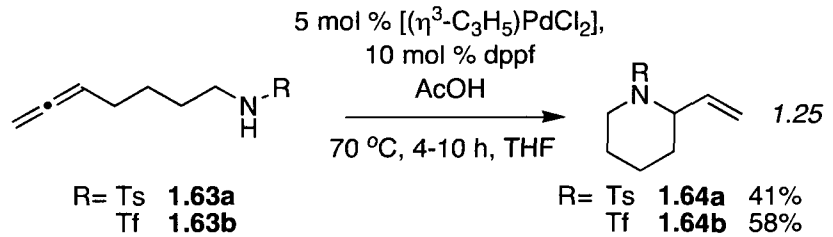
Such recent developments, especially with late transition metals, highlight that the scope of intramolecular alkene hydroamination is gradually expanding to encompass reactions forming larger ring systems, to allow the use of various nitrogen precursors (primary and secondary amines, protected derivatives), and to allow reactions with more substituted alkenes. None of the methods, however, reported in the literature is broadly applicable,

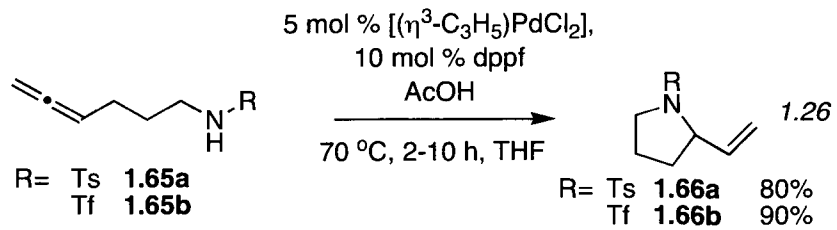
and substrates biased with the Thorpe-Ingold effect are often encountered for difficult reactions.

1.2.3.3 Allene Hydroamination

The intramolecular hydroamination of allenes has been widely explored in the literature[29, 30] and we will discuss a select few of those examples in this section.

Yamamoto's group[31] described a facile intramolecular hydroamination of allenes containing an amine or sulfonyl amine at the end of the carbon chain via a palladium catalysis. Both piperidine (Equation 1.25) and pyrrolidine (Equation 1.26) products were formed in high yields but only limited substrates could be used in the reaction.





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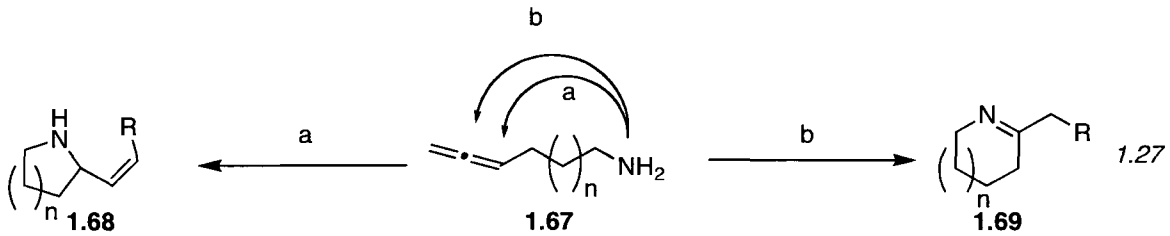
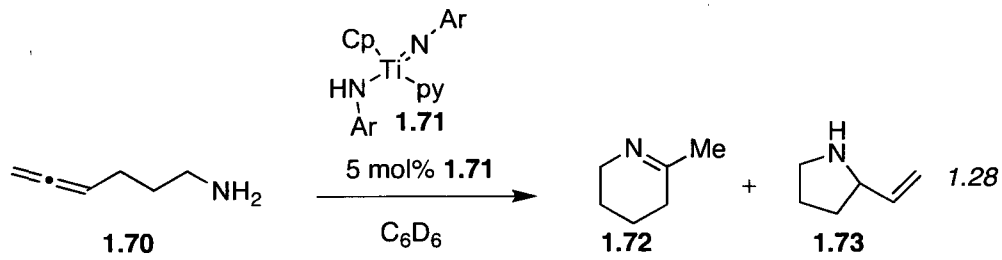
[29] For some recent examples see: (a) Voltz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519 (b) Zhang, Z.; Bender, C.F. Widenhoefer, R.A. *Org. Lett.* **2007**, *9*, 2887 (c) LaLonde, R.L., Sherry, B.D.; Kang, E.J.; Toste, F.D. *J. Am. Chem. Soc.* **2007**, *129*, 2452 (d) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, 4634 (e) Patil, N.; Lutete, L.M.; Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 4749 (f) Lee, P.H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H.; Seomoon, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 1840 (g) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121 (h) Hong, S.; Kawaoka, A.M.; Marks, T.J. *J. Am. Chem. Soc.* **2003**, *125*, 15878

[30] Use in natural product synthesis (a) Ha, J.D.; Lee, D.; Cha. J.K. *J. Org. Chem.* **1997**, *62*, 4550 (b) Ha, J.D.; Cha, J.K. *J. Am. Chem. Soc.* **1999**, *121*, 10012

[31] Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421

The Bergman group examined group 4 catalysts in the intramolecular hydroamination of alkynes and allenes.[32] By varying the metal and ligand set, the regioselectivity and reactivity of the cyclizations could be affected. This is different from silver, mercury, and palladium-based catalysts which produce allylamines via path a,[31,33] and lanthanide catalysts which give mixtures of the two regioisomers via both pathways (Equation 1.27).[34] Titanium and zirconium bis(sulfamido) complexes were examined by Bergman to catalyze the intramolecular hydroamination of allenes (Equation 1.28).



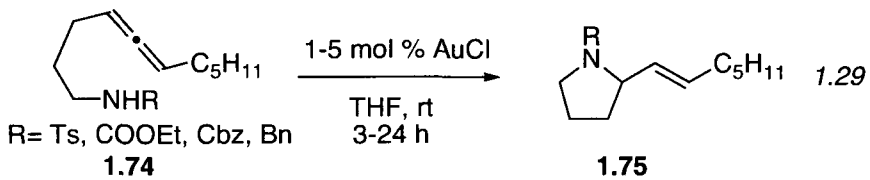


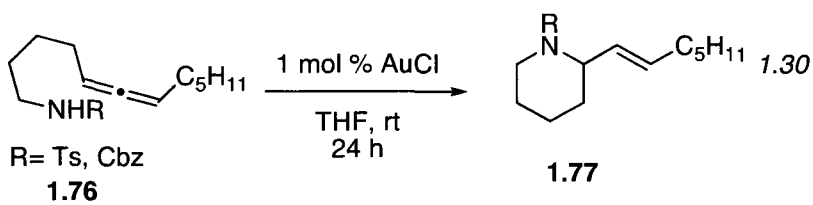
[32] Ackermann, L.; Bergman, R.G.; Loy, R.N. *J. Am. Chem. Soc.* **2003**, *125*, 11956

[33] (a) Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071 (b) Fox, D.N.A.; Gallagher, T. *Tetrahedron Lett.* **1990**, *46*, 4697 (c) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc, Chem. Commun.* **1987**, 243 (d) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997

[34] (a) Arredondo, V.M.; McDonald, F.E.; Marks, T.J. *J. Am. Chem. Soc.* **1998**, *120*, 4871 (b) Arredondo, V.M.; Tian, S.; McDonald, F.E.; Marks, T.J. *J. Am. Chem. Soc.* **1999**, *121*, 3633 (c) Arredondo, V.M.; McDonald, F.E.; Marks, T.J. *Organometallics* **1999**, *18*, 1949.

In an attempt to deviate from palladium-catalysis and the high reaction temperatures needed, the Yamamoto group explored the intramolecular cyclization of aminoallenes via gold catalysis.[29e] Reaction optimization lead to the selection of AuCl as the catalyst due to its air stability compared to $AuCl_3$ and $AuBr_3$ which gave similar results. The amines were protected with tosyl, benzyl, benzyloxycarbonyl, and ethoxylcarbonyl groups but the free amine, nor strong electron withdrawing groups were not tolerated. This was explained by the effect of the amine on the Lewis acidity of the catalyst. Both pyrrolidines and piperidines could be formed but required protection of the amine, as previously stated (Equation 1.29 and Equation 1.30).

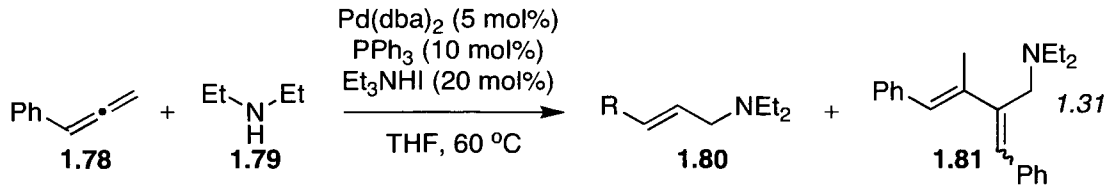




The intermolecular hydroamination of allenes, which can procure both allylic amines and imines, has been much less explored in comparison to alkenes and alkynes so we will study a few of the examples in the literature in more detail. Cazes originally presented work in which amines were added to allenes via palladium catalysis in the presence of triethylammonium iodide.[35] A mixture of allylic amines and bisallylic amines were

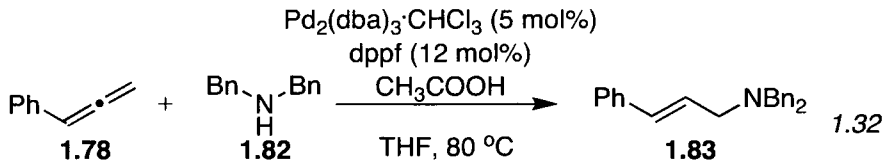
[35] Besson, L.; Gore, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857

obtained with certain substrates and 1,3-disubstituted allenes showed no reactivity (Equation 1.31).



1.78 + 1.79 → 1.80 + 1.81 (1.31)

Yamamoto and co-workers expanded on Cazes' conditions and described an intermolecular hydroamination system of mono-substituted allenes with protected amines via palladium catalysis (Equation 1.32).[33a] Higher reactivity was observed for benzyl allenes regardless of the electronics at the para position of the phenyl ring. Some diamination was observed when the tosylamine group was used but by employing different protected amines, this method can be used to access various allyl amines.

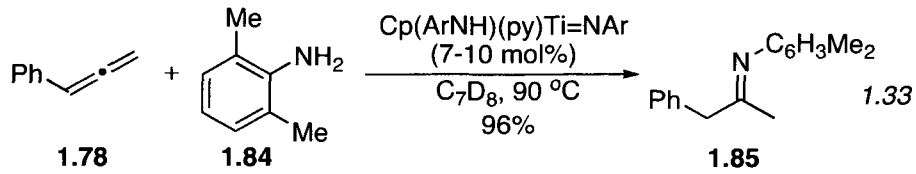


1.78 + 1.82 → 1.83 (1.32)

The Bergman group demonstrated the catalytic activity of group 4 metals towards the hydroamination of alkynes and allenes.[36] The group expanded their chemistry from bis(cyclopentadienyl)zirconium catalysts to titanium-based imido complexes.[37] Cp_2TiMe_2 catalyzed the hydroamination of 1,2-propadiene in good yields, where aryl and alkylamines, in addition to hydrazines were tolerated. Another titanium complex was able to catalyze allene hydroamination at lower temperature and was capable of performing reactions with substituted allenes including 1-phenyl-1,2-propadiene, 1,2-nonadiene, and

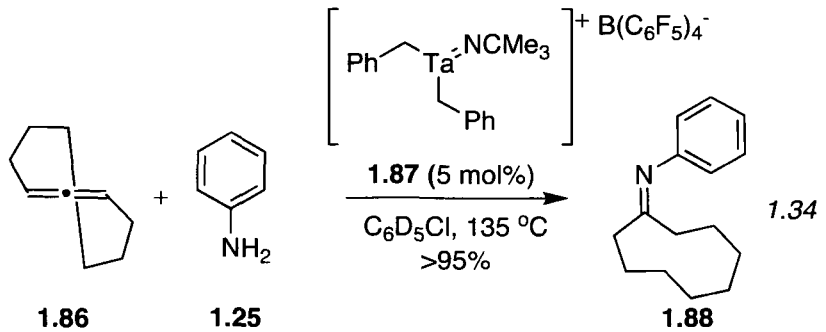
[36] Walsh, P.J.; Baranger, A.M.; Bergman, R.G. *J. Am. Chem. Soc.* **1992**, *114*, 1708
[37] Johnson, J.S.; Bergman, R.G. *J. Am. Chem. Soc.* **2001**, *123*, 2923

1,2-cyclononadiene. The only amine reported for this reactivity was 2,6-dimethylaniline (Equation 1.33).



1.78 1.84 1.85 *1.33*

In an effort to explore analogues of group 4 metal hydroamination catalysts,[36,38] Bergman and co-workers also examined cationic group 5 imido compounds.[39] These complexes are isoelectronic to the group 4 catalysts and the greater polarity in the metal-nitrogen bond was proposed to increase the catalytic activity. The bulk of the research focused on the synthesis of neutral and cationic imidotantalum complexes and their relevance towards the hydroamination of alkynes but the researchers extended their scope to the addition of aniline to allenes and olefins. While one catalyst did not show any activity, a second catalyst examined did indeed catalyze the hydroamination of two allenes. The reactivity of 2,6-dimethylaniline with 1,2-propadiene, as well as that of aniline with 1,2-cyclononadiene, was observed (Equation 1.34).

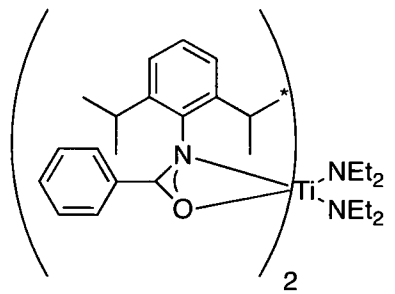


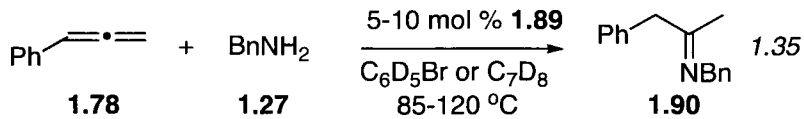
1.86 1.25 1.88 *1.34*

[38] Sweeney, Z.K.; Salsman, J.L.; Andersen, R.A.; Bergman, R.G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2339

[39] Anderson, L.L.; Arnold, J.; Bergman, R.G. *Org. Lett.* **2004**, *6*, 2519

The Schafer group employed a titanium catalyst in the hydroamination of alkynes[40] and noticed its ability to catalyze the intramolecular hydroamination of aminoallenes. In order to demonstrate the utility of their complex they revealed the use of a bis(amidate)-bis(amido) titanium complex as a precatalyst for the intermolecular hydroamination of allenes (Equation 1.35).[41] Arylamines underwent the hydroamination reaction at a lower temperature than alkylamines and also required lower precatalyst loading. Unfortunately, 1,1-disubstituted allenes were not reactive under the reaction conditions.





1.78 **1.27** **1.90**

Hydroamination of allenes via gold catalysis has been previously reported[29c-e,42] in the literature and a few of the synthetic techniques will be discussed. Yamamoto and co-workers reported a gold(III)-catalyzed intermolecular hydroamination of allenes with arylamines to give the allylic amines.[42d] The diversity of the arylamine scope was

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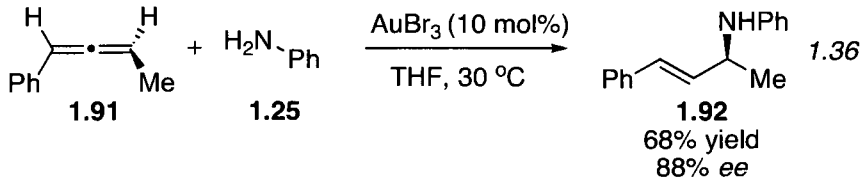
[40] Zhang, Z.; Schafer, L.L. *Org. Lett.* **2003**, *5*, 4733

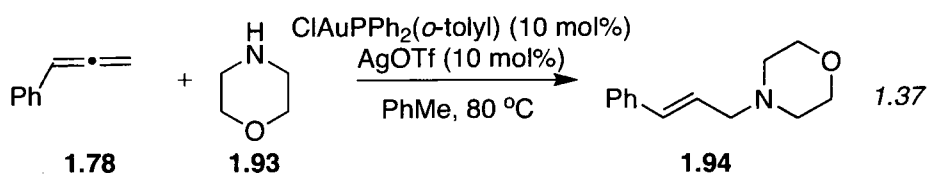
[41] Ayinla, R.O.; Schafer, L.L. *Inorg. Chim. Acta* **2006**, *359*, 3097

[42] For recent examples see: (a) Kinder, R.E.; Zhang, Z.; Widenhoefer, R.A. *Org. Lett.* **2008**, *10*, 3157 (b) Zhang, Z.; Bender, C.F.; Widenhoefer, R.A. *Org. Lett.* **2007**, *9*, 2887 (c) Zhang, Z.; Liu, C.; Kinder, R.E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066 (d) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314 (e) Krause, N.; Morita, N.; *Org. Lett.* **2004**, *6*, 4121

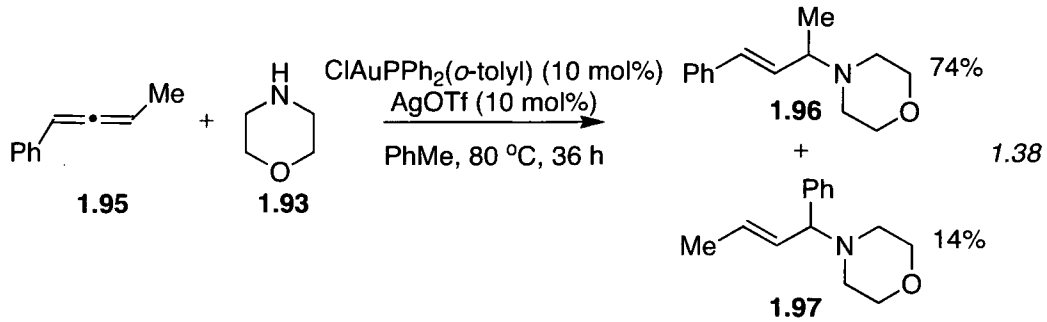
severely limited. They also demonstrated that the axial chirality of the allenes could be transferred to the products with high *ee* values (Equation 1.36). Monosubstituted aryl- and alkyl allenes reacted well under the reaction conditions but sterically bulky allenes did not prove to be suitable substrates. 1,3-disubstituted allenes gave good yields but not 1,1-disubstituted substrates. Allenes containing an olefin moiety further down the carbon chain also reacted well which can possibly be explained by the π-bond coordinating to the gold species, bringing the two reactants in closer proximity.



Yamamoto and Nishina also reported a gold-catalyzed intermolecular hydroamination of allenes with the aliphatic amine morpholine.[43] Control of the steric environment around the gold centre with appropriate phosphine ligands appeared necessary for the aliphatic hydroamination to occur but the desired reactivity was achieved with $ClAuPPh_2$(*o*-tolyl) (Equation 1.37). Aryl allenes gave good yields, followed by aliphatic allenes with moderate ones. Sterically bulky allenes were not good substrates but 1,3-disubstituted allenes showed comparable reactivity to monosubstituted allenes, along with decent regioselectivity (Equation 1.38). 1,1-Disubstituted allenes gave inseparable stereoisomeric mixtures of product in low yield.

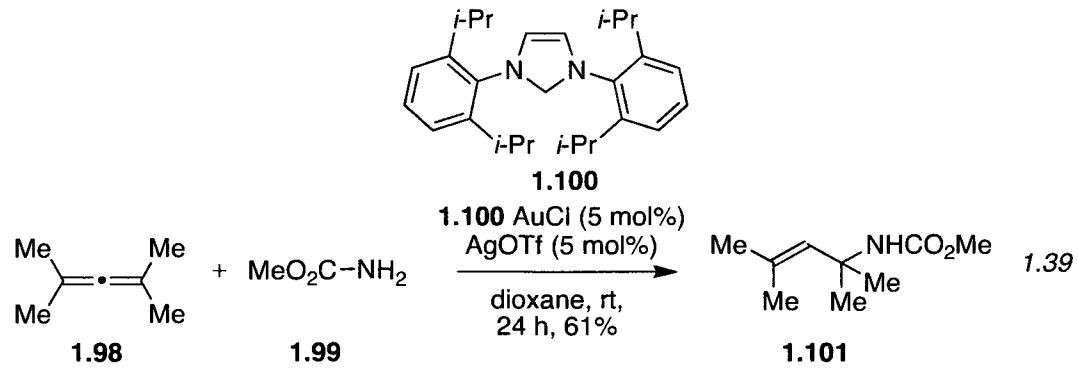


[43] Nishina, N.; Yamamoto, Y. *Synlett* **2007**, 1767



1.95 1.93

Most recently, the Widenhoefer group described a regio- and stereoselective gold-catalyzed procedure for the intermolecular hydroamination of allenes with *N*-substituted carbamates (Equation 1.39).[44] Examples of a 1,1-disubstituted allene, a trisubstituted substrate, and a tetrasubstituted allene reacted under the conditions to afford the tertiary allylic *N*-carbamate in modest yield.



1.98 1.99 1.101

In summary, general shortcomings of metal-catalyzed hydroamination of alkynes, alkenes and allenes are limited substrate scope, air sensitivity, costs associated with metal and ligands, toxicity, functional group tolerance, required conjugation, or altering the electronics of the nitrogen. Recent progress has been made on expanding the scope, regioselectivity, and even enantioselectivity of the hydroamination reactions yet despite this growth, more has to be achieved to make this a broadly applicable method. The inter- and intra- molecular hydroamination of alkynes has been significantly more developed

[44] Kinder, R.E.; Zhang, A.; Widenhoefer, R.A. *Org. Lett.* **2008**, *10*, 3157

than similar reactivity in alkenes where the relative difficulty of forming six-membered rings over five needs to be addressed. Additionally, more work has to be done to develop this technique into a more economically, environmentally, and atom friendly route.

1.3 A different strategy: Cope-type hydroamination

The three hydroamination projects reported in this thesis (Chapters 2 and 3) use a simple, metal-free method. This strategy that has shown increasing potential is the reverse Cope elimination, from hereon in referred to as Cope-type hydroamination. The reactivity and limitations of this method will be discussed later in the chapter but first its general features will be considered.

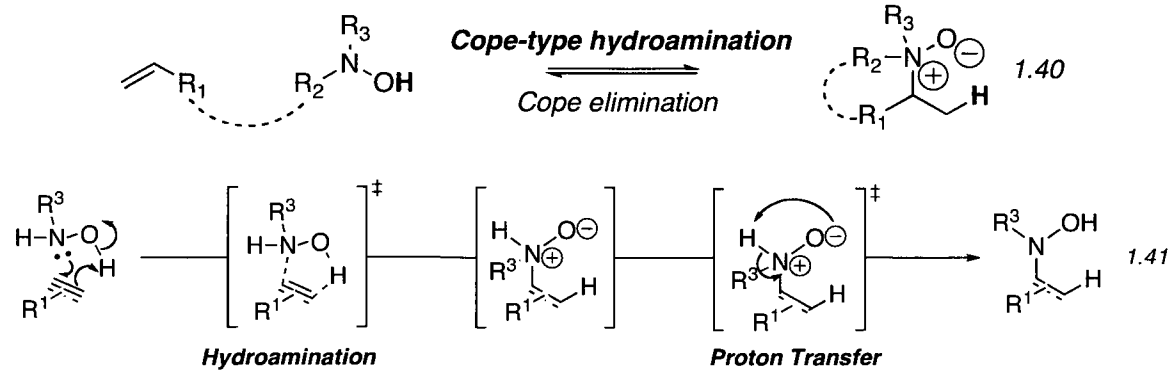
1.3.1 Cope-type hydroamination: Mechanism and general features

Cope-type hydroamination forms a new carbon-nitrogen and carbon-hydrogen bond across a carbon-carbon multiple bond using a bi-functional reagent, such as hydroxylamine or hydrazine (Equation 1.40). This conceptually different and general approach can be applied to alkenes and alkynes.[45,46] The concerted mechanism characteristic of the reaction allows for a high degree of predictability and renders it conceptually different from the other methods in the literature (Equation 1.41). The concerted addition between the hydroxylamine and the π-bond produces an *N*-oxide intermediate. A proton transfer, if possible, follows this step yielding a neutral hydroamination product.

---

[45] (a) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803 (b) Ciganek, E.; Read, Jr., J. M.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795 (c) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139 (d) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007 (e) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863 (f) House, H. O.; Manning, D. T. ; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855

[46] For a review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243



The reversible nature of this reaction has been known for over twenty five years[47] but its exact mechanistic pathway has been debated. In 1976, House and co-workers initially proposed a radical mechanism[45e-f] but the concerted process has now been proven and accepted.[45d,48]

The synthetic utility of Cope-type hydroamination is currently limited to intramolecular reactivity. Specifically, Figure 1.4 can summarize its general features in the hydroamination of un-activated alkenes.[46] Firstly, it is more effective at forming five-membered rings and the instances of six-membered ring formation in the literature are scarce. Additionally, hydroamination of primary hydroxylamines require elevated temperatures but the more stable secondary hydroxylamines are more reactive (Equation 1.42). Thus secondary hydroxylamines are preferred for increased substrate reactivity but nitrogen substitution limits the substrate scope as less stable *N*-oxide products are produced (Equation 1.43). Furthermore, intramolecular Cope-type hydroamination is significantly activated by steric compression, otherwise known as the Thorpe-Ingold

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[47] (a) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, *20*, 4391 (b) Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295

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

effect. The main restriction of Cope-type intramolecular hydroamination, arguably, is the exclusion of any substituent on the terminal alkene,[6,26,49] eliminating a site for further synthesis. There are no examples, to our knowledge, of piperidine formation by cyclization onto a distally substituted alkene, but there are a few examples where pyrrolidines or morpholine *N*-oxides are formed (Equation 1.44 and Equation 1.45).[24,45b,50]

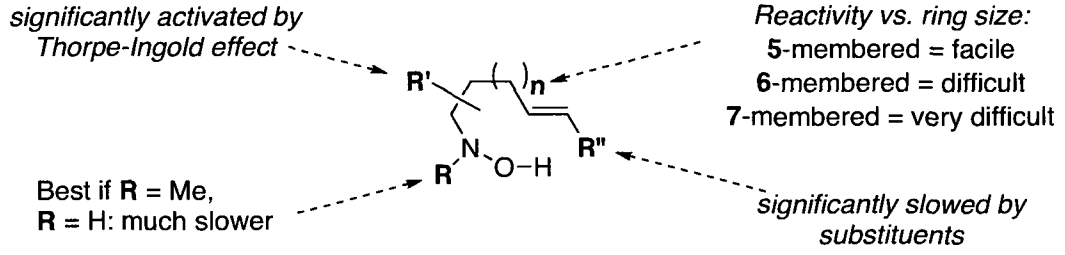
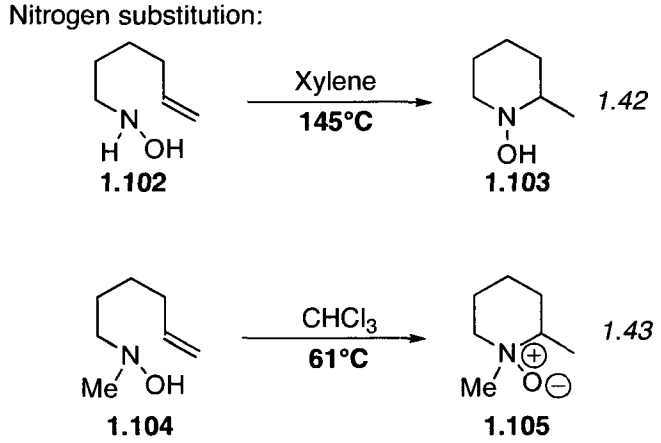


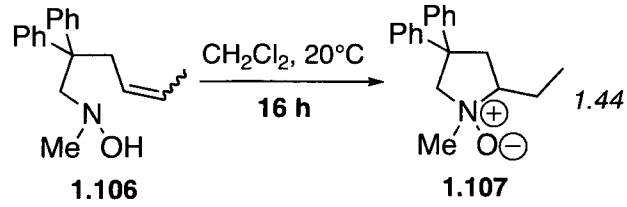
Figure 1.4: General Trends of Intramolecular Alkene Cope-Type Hydroaminations



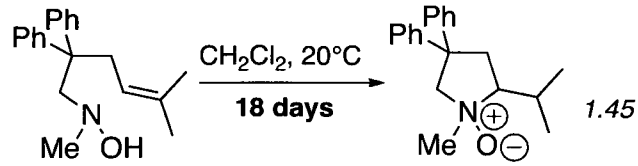
[49] Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2938

[50] (a) Henry, N.; O'Neil, I.A. *Tetrahedron Lett.* **2007**, *48*, 1691 (b) O'Neil, I.A.; Cleator, E.; Ramos, V.E.; Chorlton, A.P.; Tapolczay, D.J. *Tetrahedron Lett.* **2004**, *45*, 3655

Distal alkene substituents:

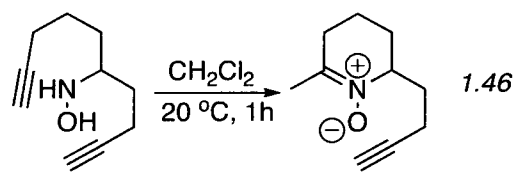


1.106 1.107 *1.44*



1.108 1.109 *1.45*

The intramolecular Cope-type hydroamination of alkynes, on the other hand, strongly favours the six-membered ring formation over that of the five-membered ring (Equation 1.46). Similarly to the olefin cyclization, the reactivity of a terminal alkyne is much greater than that of a disubstituted one. Consequently, a theoretically useful way to access piperidines could be via the hydroamination of an alkyne followed by reduction of the double bond to give the saturated six-membered ring.

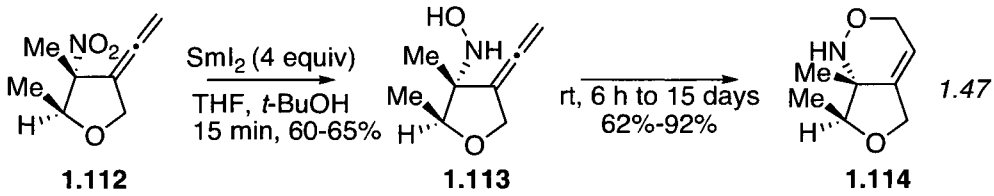


1.110 1.111 *1.46*

The few examples of Cope-type hydroamination with allene substrates in the litereature all react with an internal hydroxylamine and form 3,6-dihydro-1,2-oxazine products.[51]

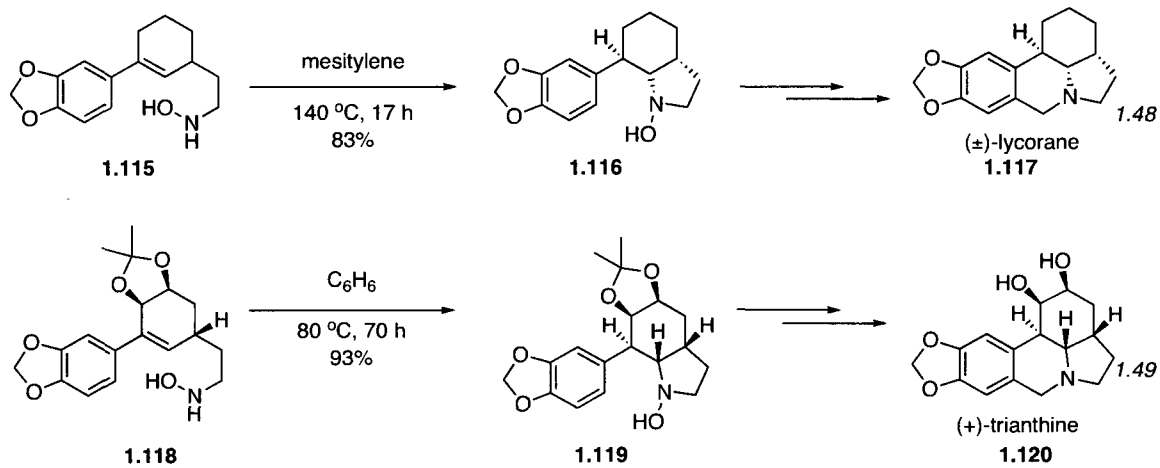
[51] (a) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632 (b) Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur. J. Org. Chem.* **2001**, 2577 (c) Dumez, E.; Dulcère, J.-P. *Chem. Commun.* **1998**, 479

Dumez and Dulcère reported the reduction of nitrocompound **1.112** to its hydroxylamine equivalent and then its cyclization upon standing at room temperature (Equation 1.47).[51c]

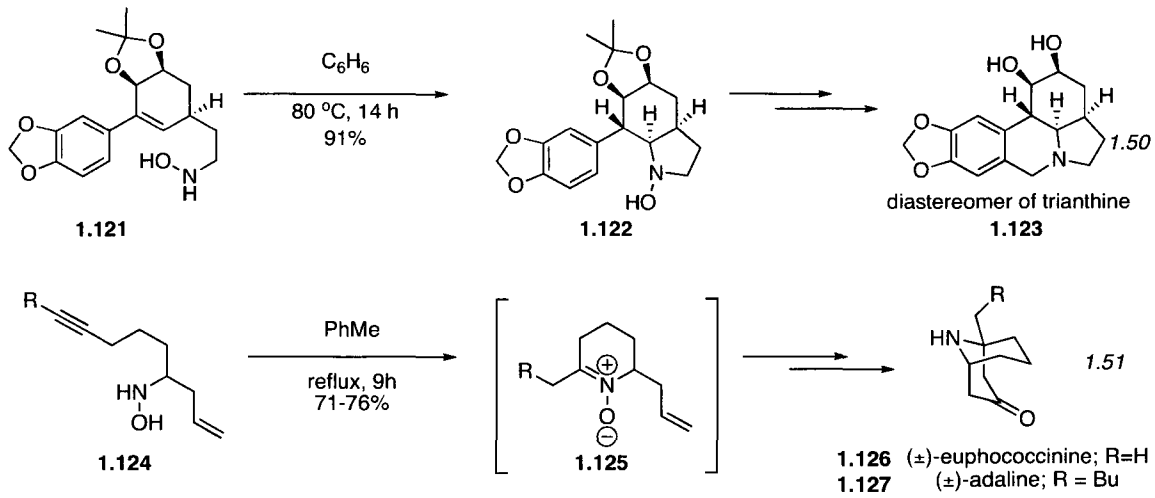


1.3.2 Cope-type hydroamination in total synthesis

Due to the restrictions listed above, the published methods for intramolecular Cope-type hydroamination of six-membered rings form mainly α-methyl piperidine *N*-oxides and other amine oxides that cripple its applicability in the pharmaceutical industry. The potential of this method, however, has been demonstrated in the few alkaloid syntheses that do indeed use intramolecular Cope-type hydroamination as a key step (Equation 1.48 through Equation 1.51).[45c,46,52]



[52] Davison, E.C.; Holmes, A.B.; Forbes, I.T. *Tetrahedron Lett.* **1995**, *36*, 9047

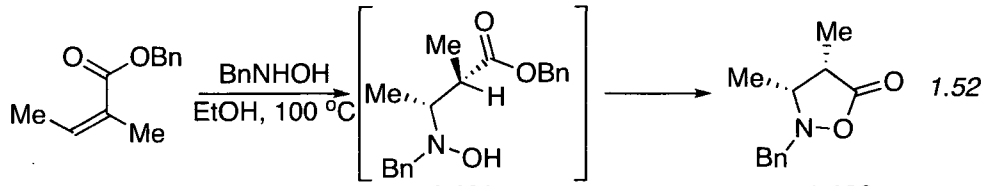


Oppolzer and co-workers accomplished the total synthesis of (±)-α-lycorane and (+)-trianthine and its diastereomer through intramolecular hydroamination of trisubstituted olefins forming the required pyrollidine rings.[45] Holmes and co-workers synthesized (±)-euphococcinine and (±)-adaline via the intermolecular hydroamination of terminal and disubstituted alkynes. The resulting nitrones were reacted *in situ* with the internal olefin.[52] These examples demonstrate the synthetic potential of Cope-type hydroamination to make alkaloids along with the possibility of inducing stereoselectivity with alkenes.

1.3.3 Known reactivity in intermolecular Cope-type hydroamination

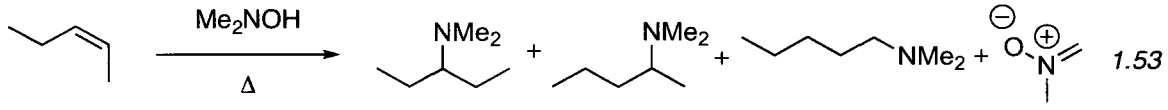
In contrast to intramolecular Cope-type hydroamination, instances of intermolecular reactions are scarce. Niu and Zhao reported the 1,4-addition of *N*-methyl- and *N*-benzylhydroxylamine to α,β–unsaturated esters via a concerted mechanism (Equation 1.52),[53] but the literature is void of synthetically useful intermolecular examples using unbiased olefins.

[53] Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456



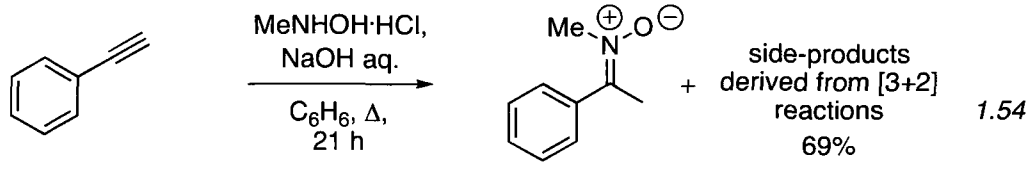
1.128 1.129 1.130

In a 1973 report by Laughlin, Cope-type hydroamination may have transpired, although multiple complex side-reactions occurred as well (Equation 1.53). [47b] The side-products stemming from secondary reactions with the nitrone, and the attainment of all the possible hydroamination products render this transformation inefficient.



1.131 1.132 1.133 1.134 1.135

Nitrones can also be obtained from the intermolecular hydroamination of alkynes but only aryl acetylenes were tolerated under conditions developed by Padwa and Wong (Equation 1.54).[54] The products without pendant dipolarophiles were isolated in low yields due to their instability but others could be trapped with an intramolecular [3+2] cycloaddition.

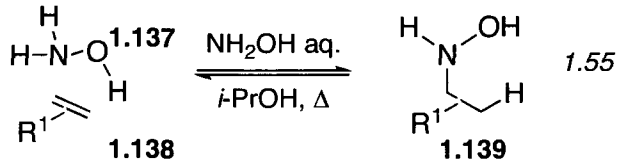


1.12 1.136

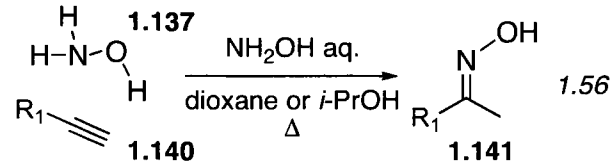
1.3.4 Progress by the Beauchemin group

[54] Padwa, A.; Wong, S. K. *J. Org. Chem.* **1986**, *51*, 3125

In order to fill the large gaps in the literature, the Beauchemin group started investigating ways to improve intermolecular Cope-type hydroaminations. Upon experimentation we discovered mild, metal-free conditions whereupon heating aqueous hydroxylamine with alkenes (Equation 1.55) and alkynes (Equation 1.56) afforded the intermolecular hydroamination products.[55]



1.55



1.56

Preliminary reactions with alkenes used norbonene as the exploratory substrate since the molecular strain could offer extra reactivity. The release of strain could also provide more favourable thermodynamics as intermolecular alkene hydroaminations are typically nearly thermoneutral.[3] After considerable optimization, the quantitative conversion of norbornene was observed and the conditions were applied successfully to other strained alkenes as well as styrene.

The intermolecular hydroamination of alkynes predominantly yielded the Markovnikov ketoxime products under the optimized reaction conditions. Steric and electronic variations on the aromatic ring of the acetylene substituent were tolerated as well as internal alkyne substrates and those with alkyl chains.

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[55] Beauchemin, A.M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Zhang, L.; Gorelsky, S.I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410

To account for the experimental results and the improved reactivity observed using alcoholic solvents, density functional theory (DFT) computations were performed for two proton transfer pathways in both systems. The calculations suggested the relative ease of a bimolecular transfer step over a unimolecular transformation (Figure 1.5) and this explains the successful results obtained when propanol was used as solvent. A protic species like water or alcohol can mediate the proton transfer step, pushing the reaction is a forward direction towards the more stable hydroxylamine or oxime products and prevent the Cope-elimination from occurring on the amine oxide intermediate.

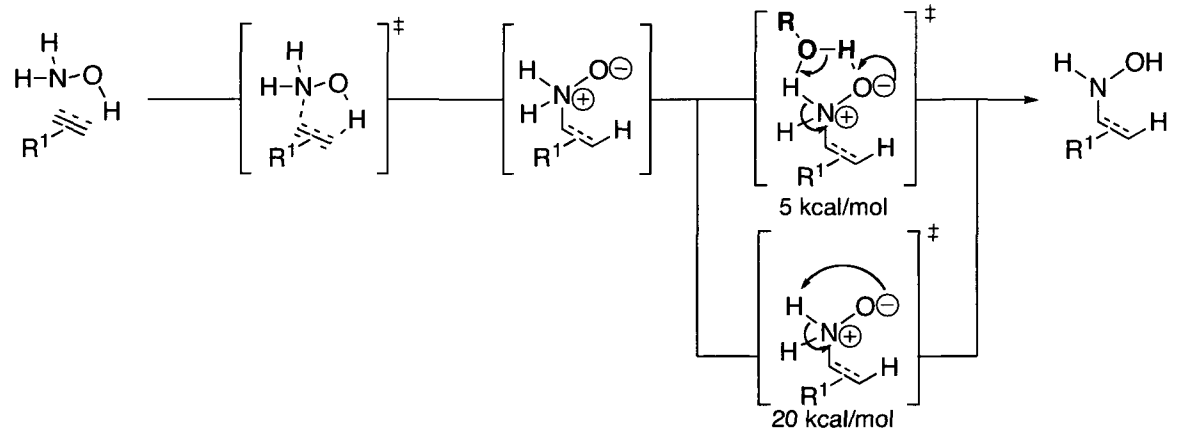


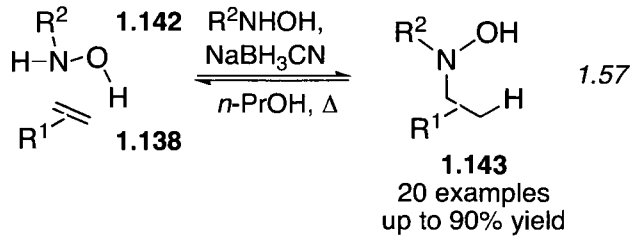
Figure 1.5: Bimolecular versus unimolecular proton transfer step

Further studies in the intermolecular hydroamination of alkenes with *N*-alkylhydroxylamines further validated the suggestion that alcoholic solvents enabled the desirable reaction (Equation 1.57).[56] As assorted side reactions were observed,[57] various additives were investigated and sodium cyanoborohydride was revealed to partially inhibit the decomposition pathways. Using the optimized reaction conditions a variety of

[56] Moran, J.; Gorelsky, S.I.; Dimitrijevic, M.-E.; Bédard, A.-C; Séguin, C.; Beauchemin, A.M. *J. Am. Chem. Soc.* **2008**, *130*, 17893

[57] Horiyama, S.; Suwa, K.; Yamaki, M.; Kataoka, H.; Katagi, T.; Takayama, M. Takeuchi, T. *Chem. Pharm. Bull.* **2002**, *50*, 996

N-alkylhydroxylamines were reacted successfully with norbornene to prepare the hydroxylamine products. Vinylarenes also reacted well with *N*-benzylhydroxylamine.



The work of this thesis continued to build on the research previously done in the Beauchemin lab. In view of the fact that the group had expanded the scope of intermolecular Cope-type hydroamination of alkenes, sights were set on developing useful challenging intramolecular variations, specifically to form six-membered rings. Thus the synthesis (±)-pumiliotoxin C was selected as one of the targets pursued using the aforementioned strategy as its key step. This work will be discussed in Chapter 2.

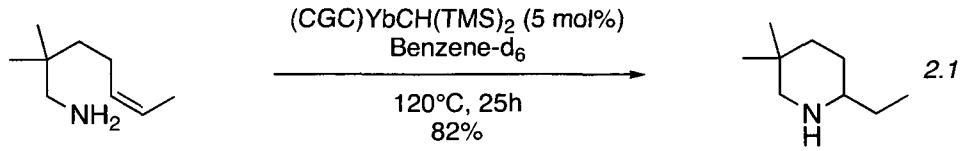
Additionally, investigations were also made into the intermolecular Cope-type hydroamination of allenes and alkynes to form ketonitrones. This research initiated improvements in Schiff base chemistry generating the same class of compounds. This work will be presented in Chapter 3.

2 The Synthesis of 2-*epi*-Pumiliotoxin C Via a Key Intramolecular Cope-Type Hydroamination of an Alkene[58]

2.1 *Pumiliotoxin C as a useful target to develop intramolecular hydroamination reactivity*

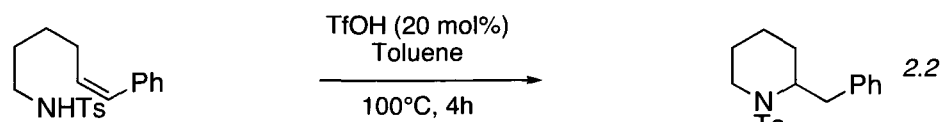
To date, the use of hydroamination in the total synthesis of molecules containing saturated six-membered rings is uncommon, within which only terminal alkenes have been utilized as substrates. This void, which limits product formation to piperidine rings with an α-methyl substituent, can be attributed to one of the major drawbacks of the hydroamination methodology: the diminished reactivity of substituted alkenes. There are only a few examples in hydroamination literature where non-terminal olefins are used (Equation 2.1 through Equation 2.4).[23b,49,59]

Lanthanides catalysis:



2.1 **2.2** *2.1*

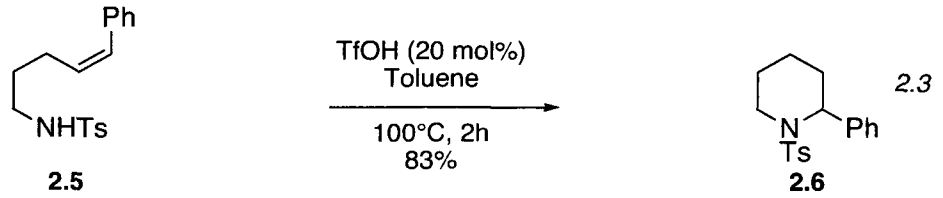
Acid catalysis:



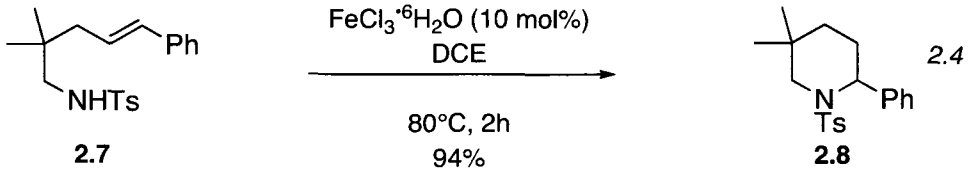
2.3 **2.4** *2.2*

[58] Portions of this chapter have been published, see ref 24

[59] Ryu, J.; Marks, T.J..; McDonald F.E.. *Org. Lett.* **2001**, *3*, 3091

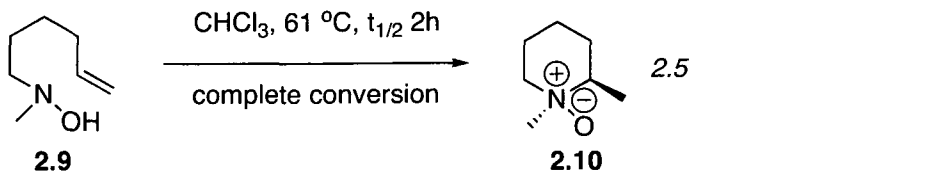


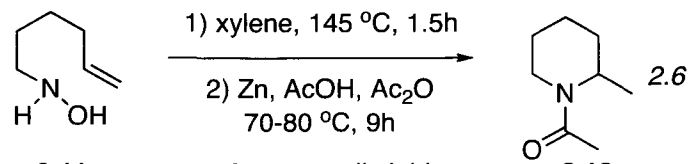
Iron/acid catalysis:



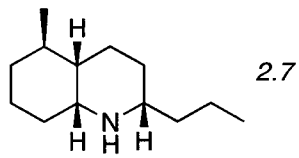
Within the context of Cope-type hydroamination, the use of mono-substituted alkenes restricts products to α-methyl piperidine *N*-oxides thereby limiting the applicability of the methodology in the synthesis of more complex molecules. Furthermore, the increased reactivity of *N*-methylhydroxylamines (Equation 2.5 and Equation 2.6) reduces the instances of products with free nitrogen positions. This potentially general strategy of heterocycle formation is currently suffering from extreme limitations that must be overcome.

Generally, *N*-methylhydroxylamines (Equation 2.5) are the substrate of choice in Cope-type hydroamination since aliphatic nitrogen substitution has been shown to increase the rate of reactions. Refluxing solvent conditions are commonly exercised, such as in chloroform, methanol or hydrocarbons. The reaction reported by House and Lee[45e] (Equation 2.6) is one of the few examples whereby a primary hydroxylamine is cyclized to form a six-membered ring.





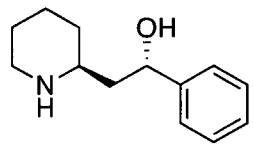
The abovementioned restrictions nullify hydroamination's potential to form a vast array of natural or biologically active molecules, specifically those containing an aza-bicyclic ring system or a substituent other than a methyl group at the α-position. In order to fill the void in the literature, the Beauchemin group decided to investigate the reactivity of Cope-type hydroamination by studying the total synthesis of pumiliotoxin C **2.13** (Equation 2.7).



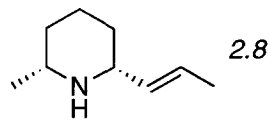
2.13
(–)-pumiliotoxin C

Pumiliotoxin C was selected as a substrate due to the relative simplicity of its framework and the comparative ease of accessing the key intermediate necessary to test the intramolecular Cope-type hydroamination. Pumiliotoxin C, with its six-membered aza-bicyclic ring system and lack of a fully-substituted nitrogen, has the characteristic traits of a difficult Cope-type hydroamination. The cyclization performed can be used as a testing ground for novel developments in the field of saturated heterocycle synthesis. If this cyclization is achieved with a primary hydroxylamine it would set a strong precedent in the field and the methodology can then be applied to the synthesis of other natural products containing piperidine frameworks, such as sedamine **2.14** and pinidine **2.15** (Equation 2.8). These compounds would be excellent targets to which the intramolecular

hydroamination technique could be applied as they contain two different substituents adjacent to the nitrogen atomand would present exceptional opportunities to develop more stereoselective hydroamination methods. Before delving into our retrosynthetic strategy, an overview of previously reported syntheses of pumiliotoxin C will be briefly discussed in Section 2.2. Of significance is the fact that none of these procedures took advantage of a hydroamination step in its assembly.



sedamine
2.14



pinidine
2.15

2.2 Previous synthetic reports on pumiliotoxin C

Pumiliotoxin C is a physiologically active alkaloid found in Dendrobatidae neotropical frog skin secretions,[60] which reversibly blocks nicotinic acetylcholine receptors and ion channels in the nervous system. Once in the blood stream, intense convulsions, suffocation, fierce palpitations and, finally, cardiac arrest can follow. The frogs, more commonly known as poison dart frogs, amass the alkaloid from ants in their diet and approximately 250 frogs are required to isolate 15 mg of the toxin. Pumiliotoxin C has been the target of synthetic efforts, both asymmetric and racemic, due to the difficulty of its isolation from natural sources, its *cis*-fused decahydroquinoline skeleton, four stereogenic centres, and interesting neurological properties.

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[60] Daly, J.W.; Spande, T.F. in *Alkaloids: Chemical and Biological Perspectives,* ed. S.W. Pelletier, Wiley, New York, **1986**; vol. 4, ch 1, pp. 1-274.

Pumiliotoxin C was the first of more than thirty alkaloids in the 2,5-disubstituted decahydroquinoline class to be identified by mass spectrometry in 1969,[61] while Oppolzer and Flaskamp revised the absolute configuration of the natural product in 1977.[62] Syntheses between 1969 and 1976 have been previously reviewed[63] and in the quarter century following that mark there were approximately fifty publications synthesizing pumiliotoxin C, eleven of which used asymmetric routes.[64] There are many reported syntheses of pumiliotoxin C[62,64,65] and its stereoisomers using a variety of approaches including electrochemical,[65e] Haller-Bauer cleavage,[65i] aminocyclization reactions,[65f,g] cycloaddition reactions,[65h,l,n,o] [3-3]-sigmatropic rearrangements,[65j] Grignard reagent additions, [65k] biomimetic approaches,[65m] and Beckmann rearrangements.[65d] The syntheses by means of Diels-Alder cycloadditions or Beckmann rearrangements have been previously discussed in an earlier thesis in the Beauchemin

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[61] Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L. *Liebigs Ann. Chem.* **1969**, *729*, 198

[62] Oppolzer, W.; Flaskamp, E. *Helv. Chem. Acta* **1977**, *60*, 204

[63] Inubushi, Y.; Ibuka, T. *Heterocycles*, **1977**, *8*, 633

[64] Oppolzer, W.; Flaskamp, E.; Bieber, L.W. *Helv. Chem. Acta* **2001**, *84*, 141

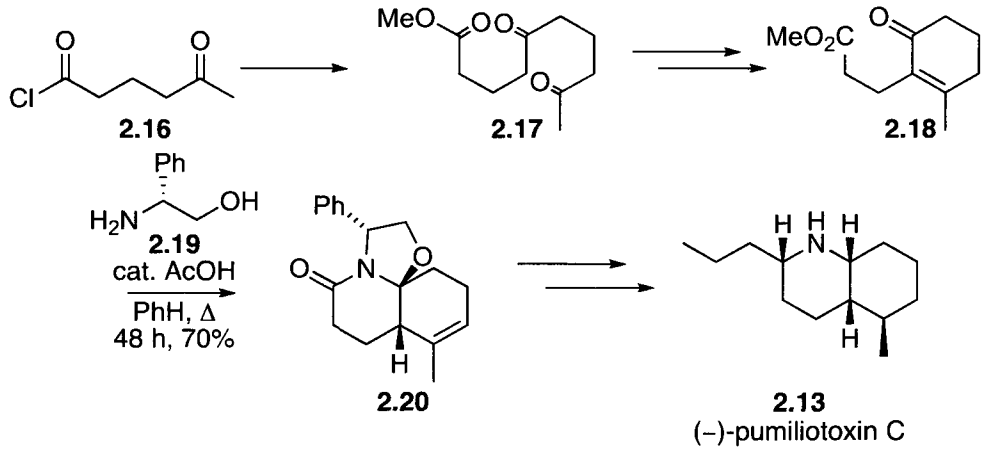
[65] Pumiliotoxin C has been synthesized numerous times using a variety of routes. For selected syntheses, see: (a) Mori, M. *Heterocycles* **2009**, *78*, 281 (b) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3348 (c) Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSeve, H. Spino, C. *J. Org. Chem.* **2008**, *73*, 6239 (d) Garrido, N.M.; Diez, D.; Dominguez, S.H.; Garcia, M.; Sanchez, M.R.; Davies, S.G. *Tetrahedron: Assymetry.* **2006**, *17*, 2183 (e) Girard, N.; Hurvois, J-P.; Moinet, C.; Toupet, L. *Eur. J. Org. Chem.* **2005**, 2269 (f) Akashi, M.; Sato, Y.; Mori, M. *J. Org. Chem.* **2001**, *66*, 7873 (g) Riechers, T.; Krebs, H. C.; Wartchow, R.; Habermehl, G. *Eur. J. Org. Chem.* **1998**, 2641 (h) Back, T. G.; Nakajima, K., *Tetrahedron Lett.* **1997**, *38*, 989 (i) Mehta, G.; Praveen, M. *J. Org. Chem.* **1995**, *60*, 279 (j) Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57*, 4103 (k) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697 (l) LeBel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363 (m) Bonin, M.; Besselièvre, R.; Grierson, D. S.; Husson, H. P. *Tetrahedron Lett.* **1983**, *24*, 1493 (n) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179 (o) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48

group[2i] and therefore will not be expanded upon here. The synthetic pathways using a biomimetic strategy (Section 2.2.1) or tandem process (Section 2.2.2) will be presented. Of notable interest is the fact that although pumiliotoxin C has been synthesized numerous times using a variety of creative methods, none have examined hydroamination as a key step. As such, the Beauchemin group is the first to investigate this methodology in the synthesis of the toxic alkaloid. The rest of the second chapter will discuss the new reactivity encountered.

2.2.1 Synthesis via a Biomimetic Approach

Although little is known about the biosynthetic pathway of pumiliotoxin C and other 2,5-disubstituted decahydroquinolines, some have hypothesized that they're derived from the polyketide route by the aminocyclization of polycarbonyl intermediates. In line with this speculation, Amat, Bosch and co-workers approached the synthesis of (–)-pumiliotoxin C **2.13** in an enantioselective bio-mimetic fashion.[65b] The researchers used 1,5-polycarbonyls, as corresponding synthetic equivalents to the proposed biogenetic polyketide intermediates, and *(R)*-phenylglycinol **2.19** as a chiral source of ammonia in their enantioselective aminocyclization (Scheme 2.1).

Scheme 2.1: Biomimetic synthetic pathway towards (–)-pumiliotoxin C

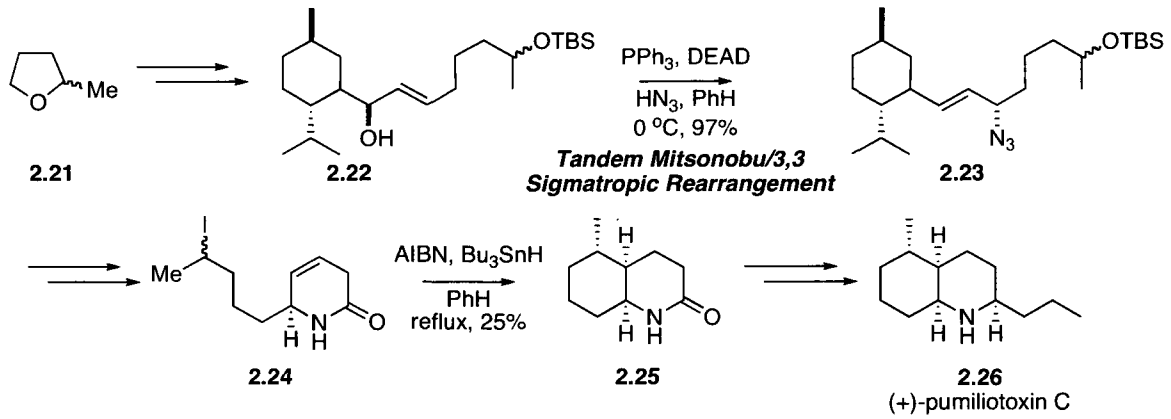


The polycarbonyl was prepared from 5-oxohexanoyl chloride **2.16**, converted to the tricyclic hydroquinolone lactam **2.20** via an intramolecular aldol condensation followed by the cyclocondensation with *(R)*-phenylglycinol **2.19**. The lactam carbonyl makes substitution at the 2-position available with relative ease. The tricyclic hydroquinolone lactam **2.20** was manipulated over numerous steps into the desired natural product. The lactams, however, are easily accessed and can be employed in the assembly of complex hydroquinoline ring systems.

2.2.2 Synthesis via a Tandem Mitsonobu/3,3-Sigmatropic Rearrangement

Recently, Spino and co-workers[65c] demonstrated the application of their tandem Mitsonobu/3,3-sigmatropic rearrangement of chiral allylic azides on a variety of alkaloids, including a synthesis of the enantiomer of (+)-pumiliotoxin C **2.26** (Scheme 2.2). The chiral auxiliary used can be obtained over two steps from either enantiomer of menthone and can be regenerated at the end of the synthetic sequence.

Scheme 2.2: Synthesis of (+)-pumiliotoxin C via a Tandem Mitsonobu/3,3-sigmatropic rearrangement pathway



Racemic 2-methylfuran **2.21** was converted into alcohol **2.22** over seven steps and then finally into azide **2.23** using the tandem procedure. Ring-closing metathesis was used to form the heterocycle **2.24** and cleave the auxiliary. The second cyclization, by radical methods, gave poor yield but extensive variations of the system did not improve results. These reactivity supports previous findings that 6-*exo*-trig cyclizations of decaline-type systems are quite difficult.[66] The synthesis was completed over fifteen steps with an overall yield of 4% despite the low yield of the radical cyclization.

2.3 Pumiliotoxin C : A retrosynthetic analysis

The first retrosynthetic analysis for pumiliotoxin C via Cope-type hydroamination prepared by Dr. A. Beauchemin and M.E. Lebrun allows three possible pathways demonstrating its versatility.[2i] The key intramolecular step can be easily tested from three different precursors: the oxime **2.28**, the hydroxylamine **2.29**, and the hydrazine **2.30**, all of which can be readily prepared from the same ketone intermediate **2.31**. This possibility

[66] Zard, S.Z. In *Radical Reactions in Organic Synthesis*; Oxford University Press: New York, 2003; p 224.

can be exploited later on by comparing the relative reactivities of the different hydroamination precursors.

The common ketone precursor itself can be procured via an umpolung alkylation between an alkyl iodide **2.33** and a dithiane **2.32** used as a masked acyl anion. The conversion of an ester group to the halogen functional group would yield the alkyl iodide. A Johnson-Claisen rearrangement from the allylic alcohol **2.36** can produce this ester **2.35**. A similar alcohol was used in this type of rearrangement by Toyota and co-workers[67] in the synthesis of (+)-pumiliotoxin C to give the ester in 78% yield thus suggesting the likelihood of the reaction working with our ethyl 2-(6-methylcyclohex-2-enyl)acetate **2.35**. The anti (±)-4-methylcyclohex-2-enol **2.36** is prepared by an S_N2' opening of the epoxide of 1,3-cyclohexadiene **2.37** according to previous literature precedent.[68] This retrosynthetic pathway seemed promising as a rapid route to explore intramolecular Cope-type hydroamination, especially since multiple intermediates can be synthesized for investigation.

[67] Toyota, M.; Asoh, T.; Matsuura, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 8687
[68] Marino, J. P.; Jaén, J.C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.

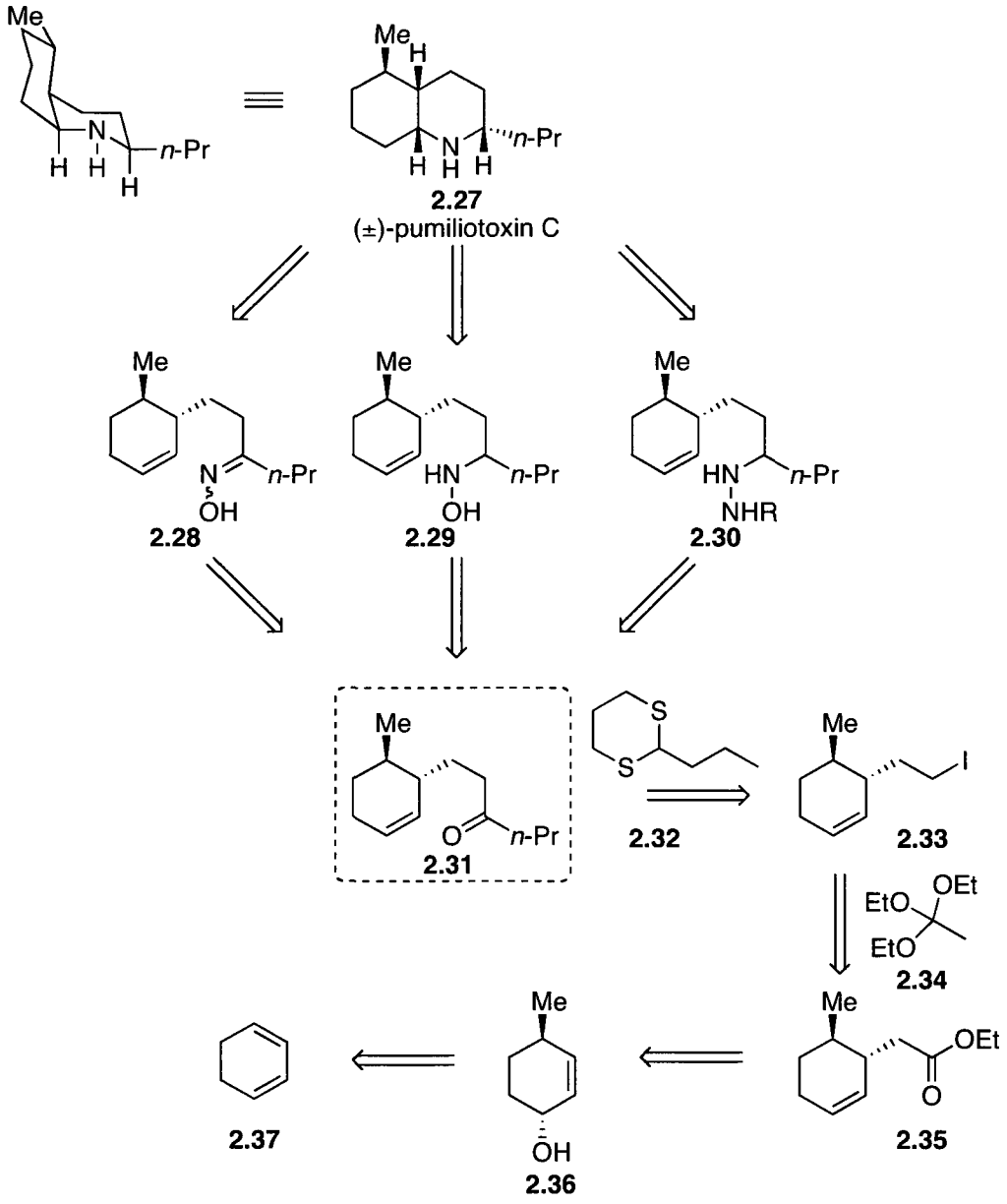


Figure 2.1: Retrosynthetic Analysis of pumiliotoxin C

Intramolecular hydroamination to form the desired product will be examined shortly, however first the stereochemistry expected from this intramolecular Cope-type hydroamination from a mixture of hydroxylamines will be discussed.

2.4 Predicted Stereochemistry of the Intramolecular Cope-Type Hydroamination

Upon closer examination of the Cope-type hydroamination of the hydroxylamine it was evident that complications could arise. Although the desired product of the hydroamination reaction being explored was the *N*-hydroxy-pumiliotoxin C, this was by no means the only product possible. Due to the non-selective reduction of the oxime with sodium cyanoborohydride there were two diastereomers (and their enantiomers) of hydroxylamines **2.40** and **2.41** present in the reaction system. Each of the diastereomers would be able to cyclize via two pathways forming a *cis* and *trans* decahydroquinoline respectively (Figure 2.2). In the best case scenario, the *cis* pathway would be more favoured than that of the trans thereby giving a possible 1:1 ratio of (±)-*N*-hydroxy-pumiliotoxin C **2.42** and (±)-*N*-hydroxy-2-*epi*-pumiliotoxin C **2.43**.

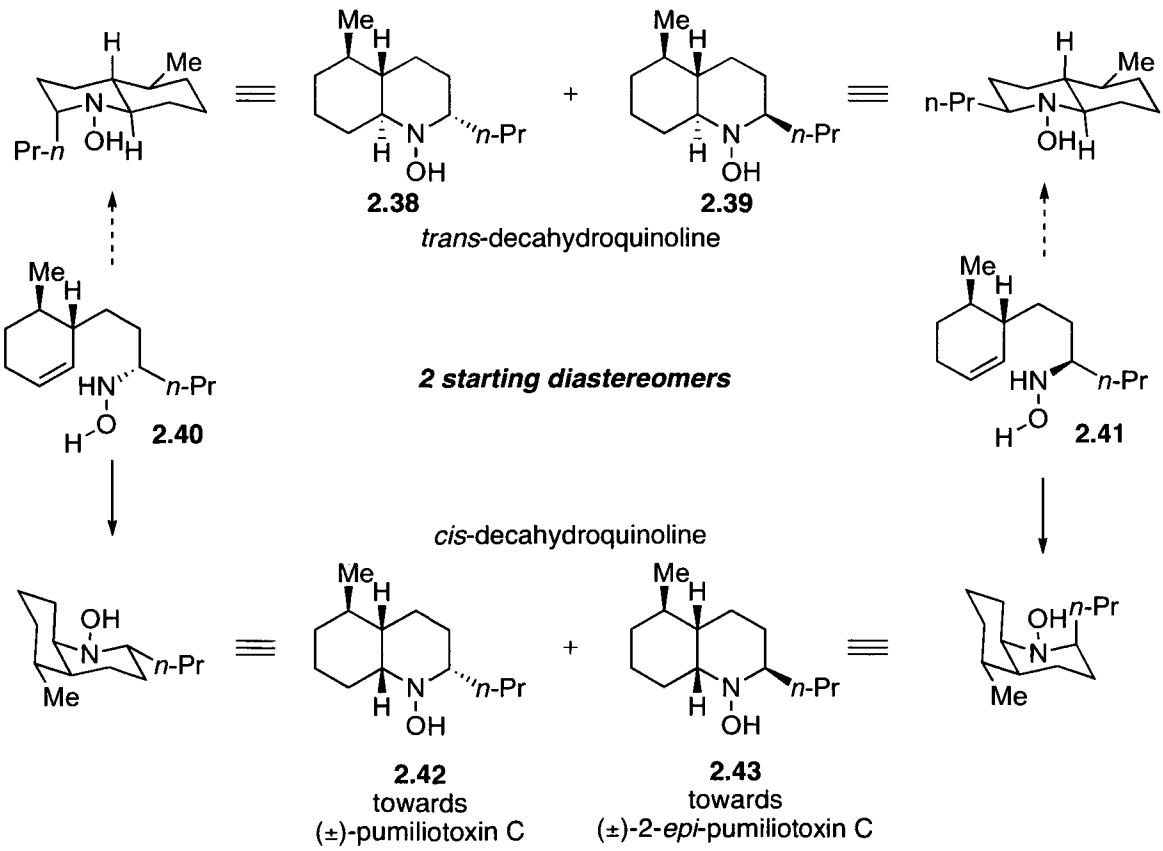


Figure 2.2: Possible cyclizations via trans or cis pathways from either diastereomer

According to molecular models built (Figure 2.3), the tricyclic transition state forming a *cis*-decahydroquinoline junction seemed more favourable than that of the *trans* due to the chair conformation of the six-membered ring forming and the more organized transition state. In the instance of the *trans* decahydroquinoline formation, the hydroxylamine did not seem properly arranged to establish the necessary co-planar orientation required for the transformation to occur, and the six-membered ring developing seemed more strained. Therefore the construction of the aza-bicycle via a *cis* pathway was proposed to be the more plausible channel.[2i]

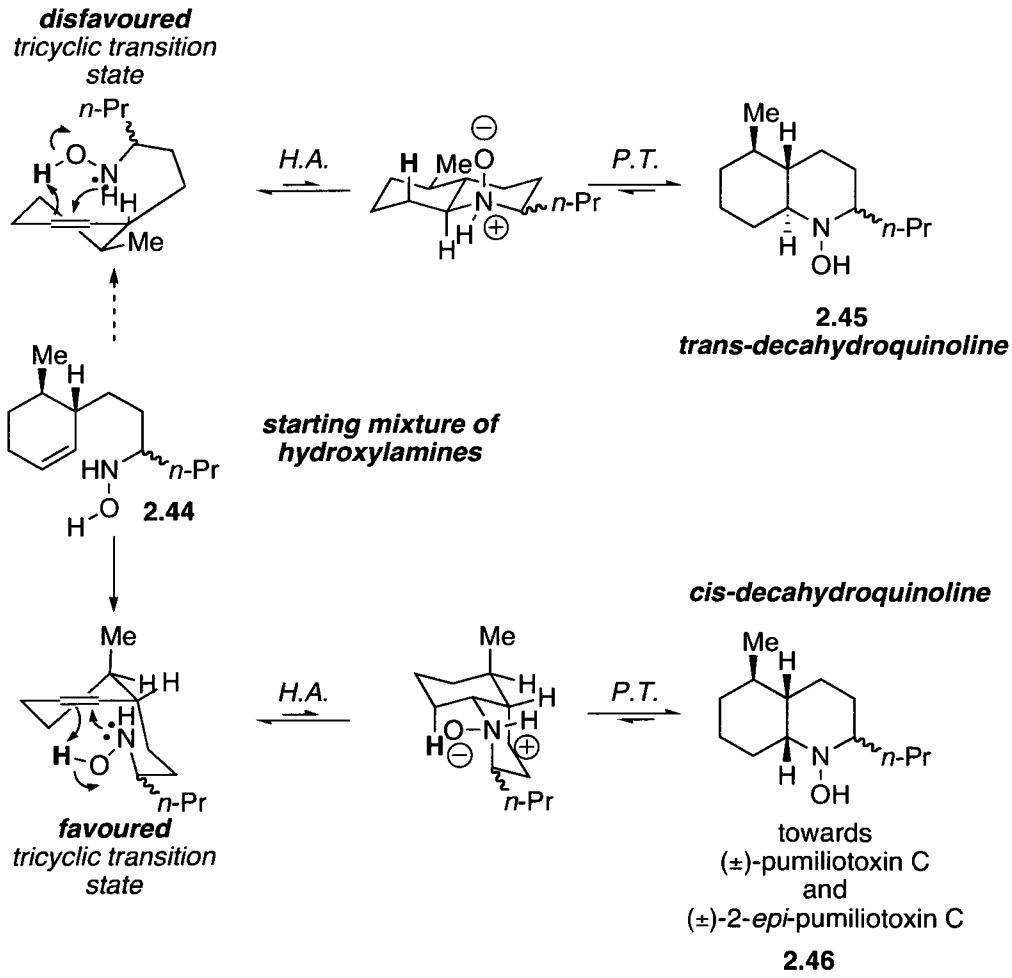


Figure 2.3: Plausible tricyclic transition state of hydroamination

The probable ratio of *N*-hydroxy-pumiliotoxin C **2.42** and *N*-hydroxy-2-*epi*-pumiliotoxin C **2.43** was more difficult to predict although it was expected that the *N*-hydroxy-pumiliotoxin C **2.42** would form faster than the epimer **2.43** (Figure 2.4). This was based on the more stable conformation of the two alkyl substituents being located in equatorial positions in the product. The epimer would have the methyl group in an equatorial position but the propyl group in the less favoured axial position, generating additional 1,3-diaxial interactions therefore making it the less likely of the two to cyclize.

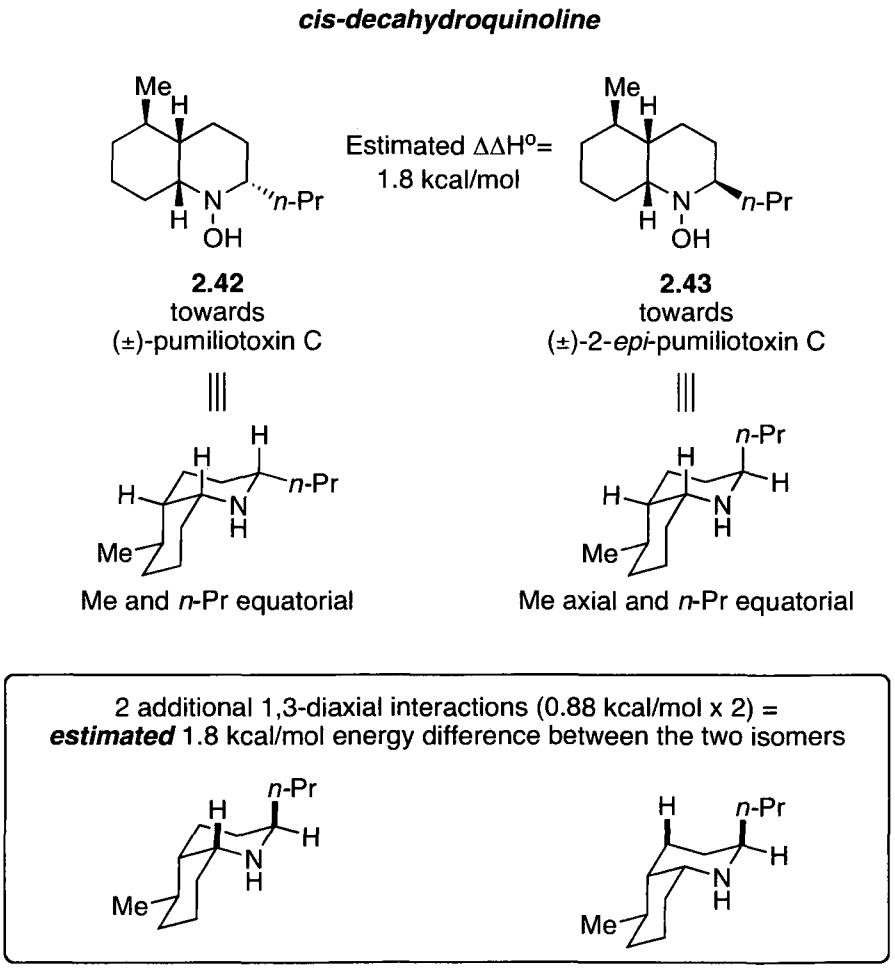


Figure 2.4: Difference in alkyl substituent location between hydroxylamine diastereomers

2.5 Pumiliotoxin C : Progress towards the hydroamination precursor

The hydroxylamine precursor **2.29**, as can be seen from the retrosynthetic strategy, can be obtained in nine steps from 1,3-cyclohexadiene **2.37**, a commercially available material. As a consequence of its new cost being prohibitive, it was initially synthesized from cyclohexene **2.47** over two steps with an overall yield of 36% (Scheme 2.3). The purification after step 1 was a time-consuming distillation that often required repetition but produced a good yield of 88%.[69] The second step of the process used the highly toxic and carcinogenic HMPA as solvent, generates a vile residue, and supplied a low yield of 41%.[70] Using literature procedure[71] the epoxide **2.49** was obtained in 28% yield, in a 1.12:1 mixture of desired and undesired epoxide products. Care was exercised during the addition of the peracid to the diene to ensure the reaction temperature did not exceed 0 °C. The products, until this step in the synthesis inclusively, were purified via distillation. 4-Methylcyclohex-2-en-1-ol **2.36** was formed via literature procedure in 29% yield.[68] This step required several attempts and was determined to be extremely sensitive to salt content and impurities in the methyl lithium reagent. As with most copper-lithium chemistry, the ratio of the reagents was tremendously vital for the success of the reaction. A mixture of two isomers was obtained in a 4.44:1 ratio and separated to the best of capability. The tribulations of this reaction sequence were resolved upon purchase of 1,3-

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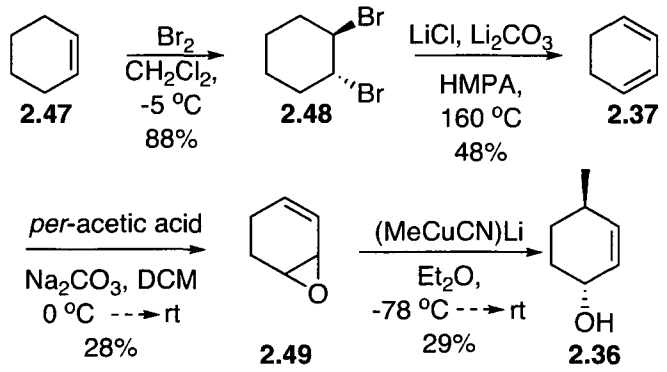
[69] (a) Johnson, J. R.; McEwen, W.L. *Org. Synth.* **1941,** *Coll Vol 1*, 521 (b) Snyder, H.R.; Brooks, L.A. *Org. Synth.* **1943**, *Coll Vol 2*, 171

[70] Gluchowski, C.; Tiner-Harding, T.; Smith, J.K.; Bergbreiter, D.E.; Newcomb, M., *J. Org. Chem.* **1984,** *49*, 2650

[71] Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423

cyclohexadiene from a cheaper supplier. The inseparable impurities from the prior reactions were affecting the outcome of the reactions and the synthesis proceeded smoothly after this acquisition.

Scheme 2.3: Synthesis of pumiliotoxin C precursors

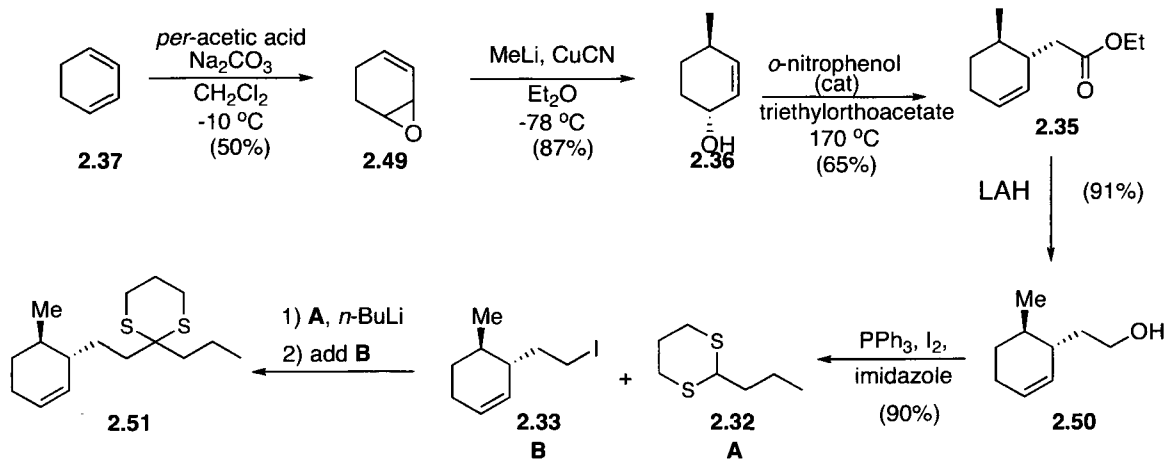


Using the commercially available 1,3-cyclohexadiene **2.37**, the synthesis was continued (Scheme 2.4) and the same epoxidation[71] was performed with a yield of 50% (previously 28%). The organocuprate addition occurred in 87% yield giving a 10:1 ratio of stereoisomers according the procedure of Marino and Jaen.[68] The *trans* relationship between the methyl and alcohol groups was verified by comparing ^{13}C NMR of the synthesized sample to those of the *trans* and *cis* products reported in the literature.[72] The Johnson-Claisen rearrangement was executed on the *trans*-4-methylcyclohex-2-enol **2.36** via acid catalysis[67] yielding the ester in 65% yield. The ester **2.35** was reduced to the alcohol **2.50** with standard lithium aluminum hydride conditions followed by a Fieser quench in 91% yield. The alcohol was then converted to the alkyl halide **2.33** in 96% yield using iodine and triphenylphosphine. All products were purified by column chromatography but care was taken during concentration *in vacuo* due to their volatility. The alkyl halide was subjected to an umpolung reaction with thioacetal-protected

[72] Young, D.; Kitching, W.; Wickham, G. *Aust. J. Chem.* **1984**, *37*, 1841

butyraldehyde **2.32** and butyl lithium[73] but an attempt at this reaction failed. The dithiane protected aldehyde was synthesized by the reaction of 1,3-propanedithiol and butyraldehyde in the presence of boron trifluoride-diethyl etherate in 99% yield.[74] Both the alkyl halide and thioacetal-protected butyraldehyde required multiple azeotropes with benzene (three times) prior to addition to the reaction conditions and considering the volatility of the alkyl halide it is possible that the starting material was lost in the process. The fastidious nature of this reaction tempted us to re-evaluate the synthetic pathway developed by M.-E. Lebrun, perhaps decreasing the number of steps towards the hydroamination precursor, as well as improving the robustness of the synthesis and its applicability to other natural products.

Scheme 2.4: Initial pathway and results

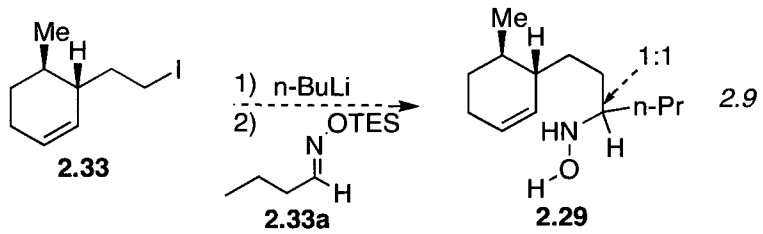


2.6 Re-visiting the synthetic pathway to pumiliotoxin C

2.6.1 First attempt to condense the synthesis of pumiliotoxin C

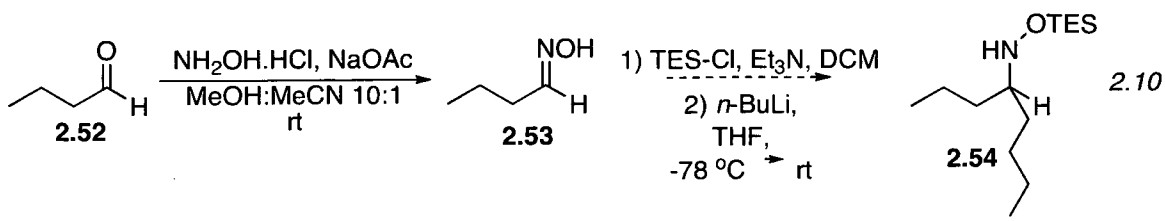
[73] Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231
[74] Abad, J.; Fabrias, G.; Camps, F. *J. Org. Chem.* **2000**, *65*, 8582

A preliminary idea to shorten the synthesis of the hydroxylamine was by performing a lithium-halogen exchange on the alkyl iodide **2.33**, followed by a nucleophilic addition of the lithium intermediate onto a protected oxime to afford the hydroamination substrate **2.29** (Equation 2.9). This modification had the possibility to eliminate four steps in the total synthesis, remove the finicky masked acyl anion step, yet still use material previously synthesized.

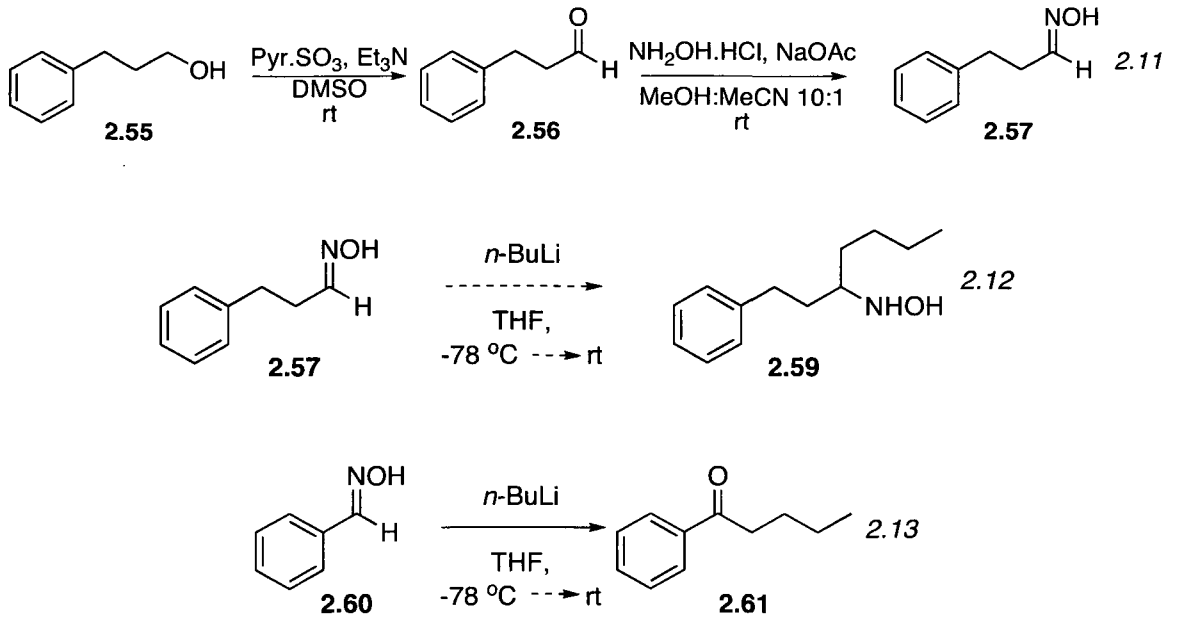


2.9

To test this theory, the oxime **2.53** was synthesized from butyraldehyde **2.52** in 85% yield. Protection was first attempted with chloro-trimethylsilane and while the reaction was successful, the product was extremely volatile and unstable. Further reactions on the oxime were inconclusive as the products were difficult to find by thin-layer chromatography (Equation 2.10). The benzaldehyde oxime **2.60** was therefore examined as it contains a UV-active phenyl ring. Attempts at nucleophilic addition of *n*-butyllithium to the synthesized unprotected or protected (triethylsilane) oximes (Equation 2.11) were either unsuccessful (Equation 2.12) or yielded valerophenone **2.61** (Equation 2.13), therefore another angle was examined.

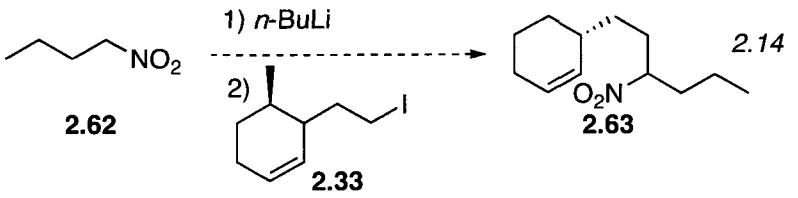


2.10

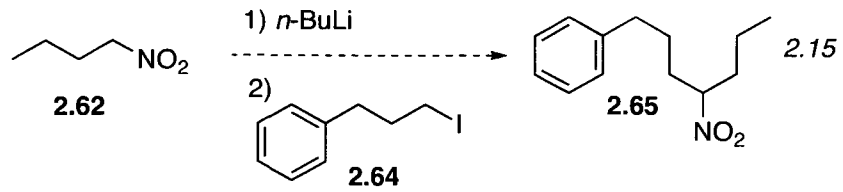


2.6.2 Second attempt to condense the synthesis of pumiliotoxin C

Upon the disappointing results of the first attempt to shorten the synthesis, we also tried to modify a procedure developed by Seebach[75] in which nitrobutane **2.62** is doubly deprotonated by butyl lithium and reacted with the iodocompound **2.33** (Equation 2.14). The test substrate 1-iodo-3-phenyl-propane **2.64** was used due to its UV-activity and nitrobutane was synthesized from iodobutane with either sodium or silver nitrite (Equation 2.15). The three reactions tried varied the equivalents of butyl lithium used but all produced starting material.

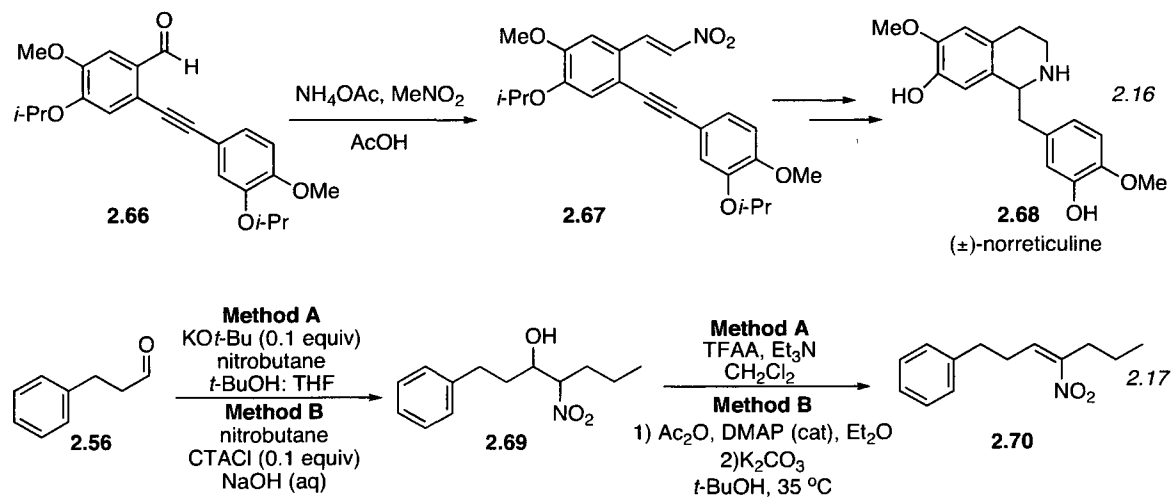


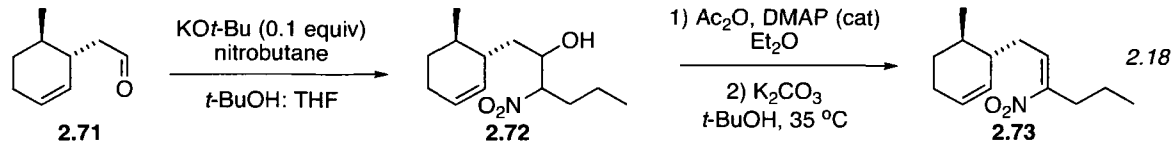
[75] Seebach, D.; Lehr, F. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 505



2.6.3 Third attempt to condense the synthesis of pumiliotoxin C

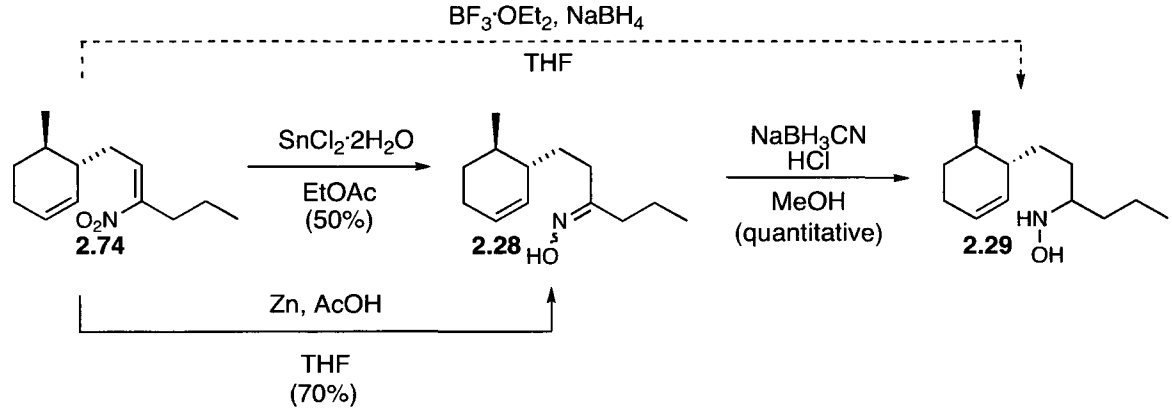
Due to the previous results, other methods were explored to abbreviate the synthesis of the hydroamination precursor. Another graduate student, Pamela Cebrowski, used a Henry reaction to obtain a nitroalkene as an intermediate in the total synthesis of norreticuline **2.68** (Equation 2.16). With this idea in mind, the aldehyde of 3-phenyl-1-propanal **2.56** was synthesized again and a nitroaldol reaction was performed using two different processes to yield the nitroalcohol (Equation 2.17). This substrate was then dehydrated using two other methods. Since the reactions worked on the test substrate, the strategy was performed on the desired materials (Equation 2.18). The original ester **2.35** was reduced using diisobutyl aluminum hydride and then attacked with an α-deprotonated nitrobutane. The alcohol **2.72** was acetylated and then eliminated with potassium carbonate yielding the desired nitroolefin **2.73**.





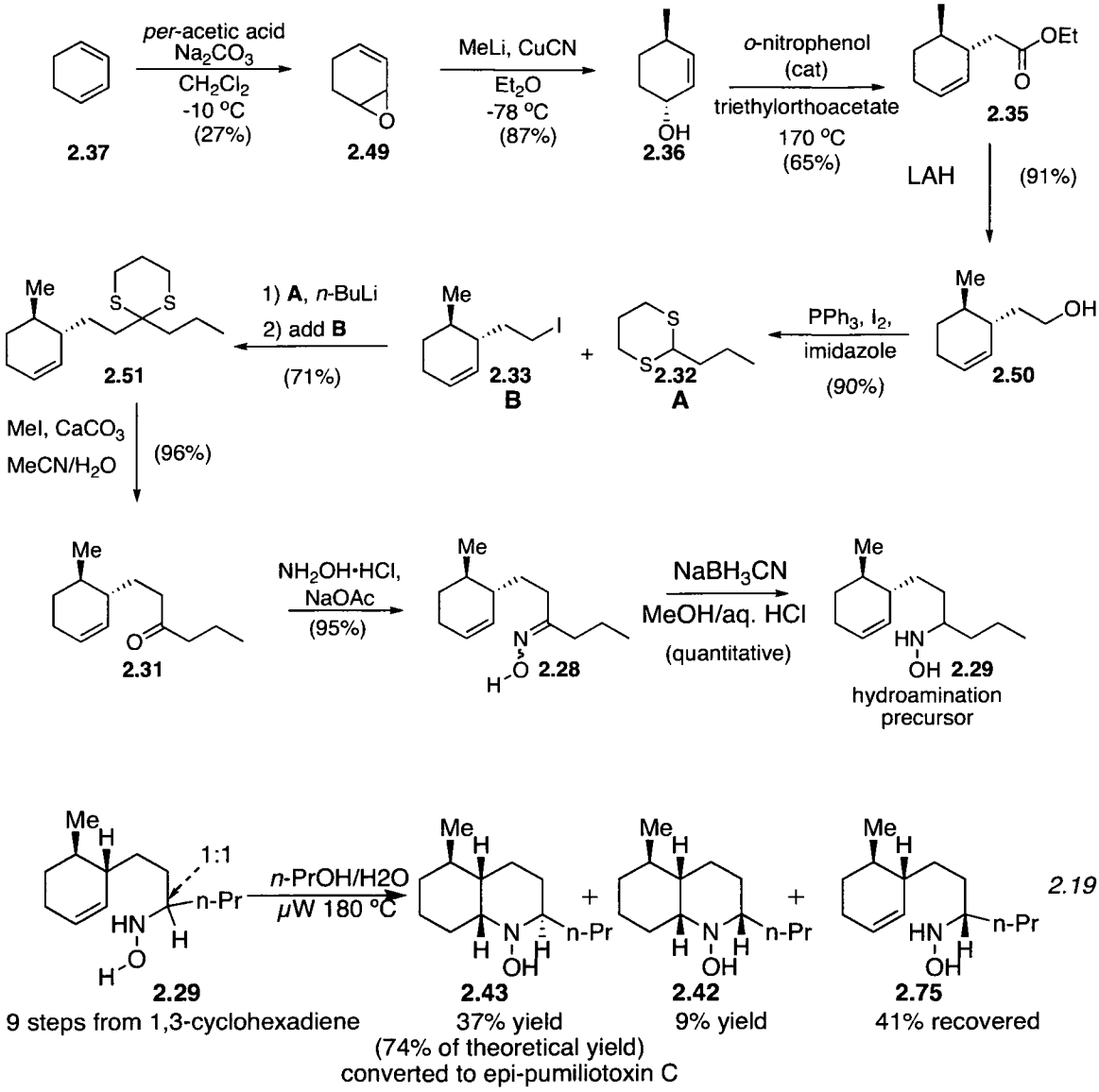
Multiple methods were employed to reduce the nitroolefin to the hydroxylamine (Scheme 2.5). After attempts at a direct reduction to the hydroxylamine failed, the nitroalkene **2.73** was reduced sequentially, first to the oxime **2.28** and then to the hydroxylamine **2.29**.

Scheme 2.5: Reduction of nitroolefin to hydroxylamine

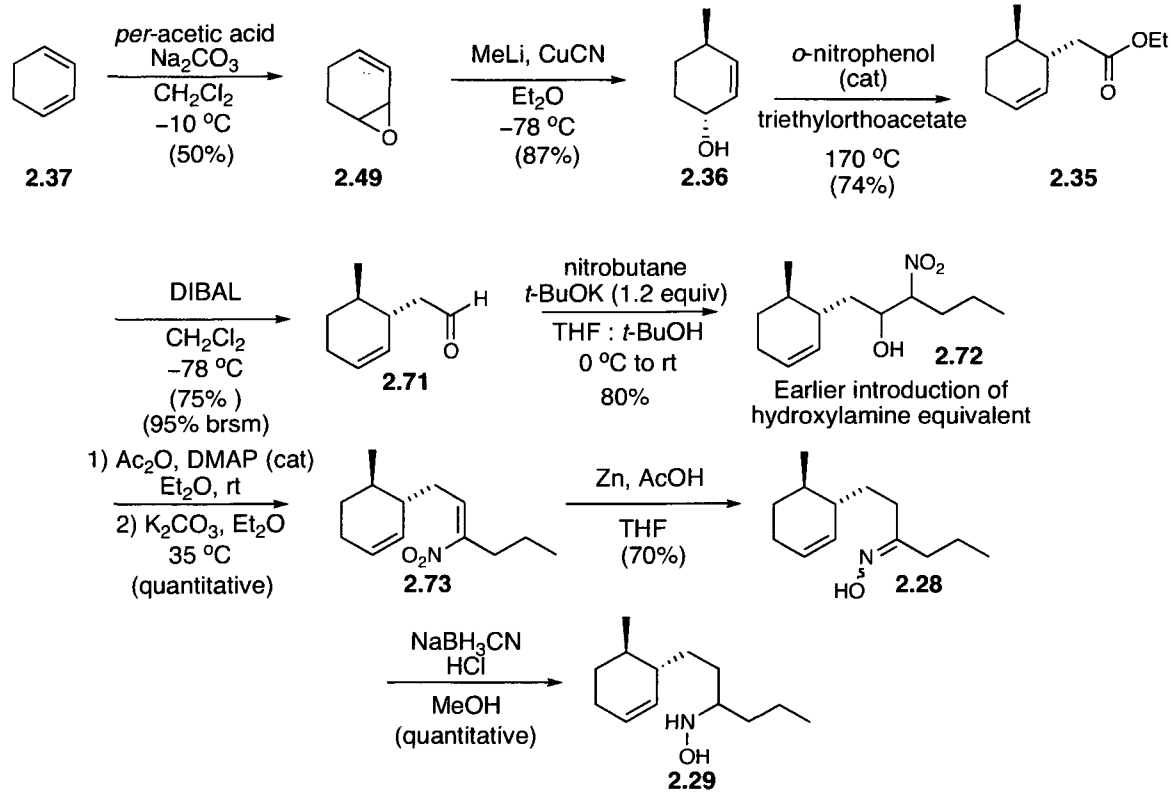


Previous research in the Beauchemin lab, conducted by graduate Marie-Eve Lebrun, completed the synthesis of the hydroxylamine **2.29** via the first synthetic pathway (Scheme 2.6) as a mixture of two diastereomers (Equation 2.19). The intramolecular hydroamination key step was achieved but the results afforded *N*-hydroxy-*epi*-pumiliotoxin C **2.43** precursor in a 37% yield (74% of the theoretical yield). The modified procedure (Scheme 2.7) reduced the synthesis of the hydroxylamine by one step, increased the overall yield of the desired compound, eliminated sensitive reaction conditions, and introduced the hydroxylamine equivalent, the nitro group, earlier in the synthesis. The two methods to pumiliotoxin C can be compared and have the same origins until the ester.

Scheme 2.6: Original synthesis of hydroxylamine 2.29



Scheme 2.7: Second generation synthesis of the hydroxylamine 2.29



Progress was made towards the synthesis of the hydroxylamine precursor to pumiliotoxin C and we were now able to apply our intramolecular Cope-type hydroamination interests. The goal of the project then became to conduct further attempts on the cyclization precursor and to optimize the intramolecular hydroamination conditions to complete the conversion of the less reactive product. This would yield the pumiliotoxin C precursor and finish the synthesis of the desired stereoisomer.

2.7 Intramolecular Intramolecular Cope-Type Hydroamination Cyclization Trial

2.7.1 Prior Attempts at Cope-Type Hydroamination Forming pumiliotoxin C

Previous work by M.-E. Lebrun in the Beauchemin group explored different cyclization approaches to form pumiliotoxin C. Methods that were examined include Grigg-type chemistry from the oxime **2.28**,[76] Cope-type hydroamination from the hydroxylamine **2.29**, as well as strategies substituting the hydroxylamine with sacrificial chains.[2i] The cyclization from the hydroxylamine **2.29** was investigated more thoroughly in order to learn more about challenging cyclizations. The reaction would be forming a six-membered ring via an intramolecular Cope-type hydroamination using a distally substituted alkene all tipping the scale towards a difficult transformation.

The initial attempts at Cope-type hydroamination performed by M.-E. Lebrun are summarized (Table 2.1). The first solvents tested, chloroform, xylene and toluene, were those frequently used in Cope-type hydroamination literature.[46] The desired product was not obtained, rather the starting material was recovered in its original state as the hydroxylamine or in its oxidized for as the oxime. It was observed, through the difference between entries 2 and 3 that the lack of oxygen in the reaction medium diminished the rate of hydroxylamine oxidation. Even in the absence of oxygen, however, it is possible for certain solvents to induce hydroxylamine oxidation.[77] This explains the formation of oxime even after the reaction was bubbled through with argon. The discovery of the importance of the proton transfer step, and how protic solvents facilitate this transformation (Figure 2.5),[55,56] led to trials with alcoholic solvents. DFT calculation in the gas state revealed that protic solvents favour the proton transfer step by 15 kcal/mol

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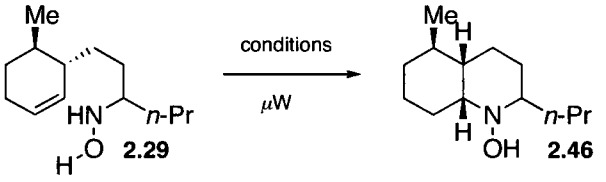
[76] (a) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W.J. *Tetrahedron* **1992**, *48*, 6929 (b) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M. Warnock, W.J. *Tetrahedron* **1992**, *48*, 10399

[77] Horiyama, S.; Suwa, K.; Yamaki, M.; Kataoka, H.; Katagi, T.; Takayama, M.; Takeuchi, T. *Chem. Pharm. Bull.* **2002**, *50*, 996

in comparison to an intramolecular proton transfer step. At last, a product without an alkene moiety was formed under microwave conditions in an alcoholic solvent but was unable to be isolated and characterized.

Table 2.1: Previous cyclization attempts performed by M.-E. Lebrun[2i]



Entry	Solvent [a]	Temperature (°C)	Time (h)	Results
1	$CDCl_3$, air	80	20	hydroxylamine **2.29**
2	*p*-xylene, air	120	3.5	oxime **2.28**
3	*p-xylene, Ar*	115	18	hydroxylamine **2.29**
	" "	+150	4	oxime **2.28** + side-product
4	PhMe, Ar	135	14	hydroxylamine **2.29** < oxime **2.28**
5	*i*-PrOH, Ar [b]	140	17	hydroxylamine **2.29** > oxime **2.28**
6	*n*-PrOH, Ar	160	13	hydroxylamine **2.29** > oxime **2.28**
7	dioxane (aq) (4:1), Ar	160	12.5	hydroxylamine **2.29** + oxime **2.28** + side-product
8	*n*-PrOH, Ar	200[c]	3	alkene-free product + side-product

[a] *Air indicates atmospheric oxygen; Ar signifies that argon was bubbled through the sample for 10 minutes*

[b] Argon bubbled through for 30 minutes

[c] reaction performed in the microwave

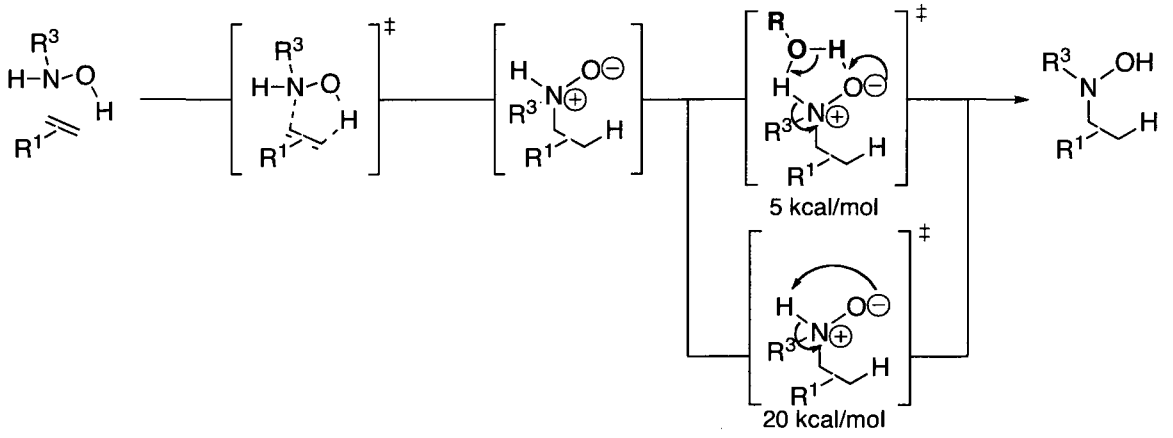
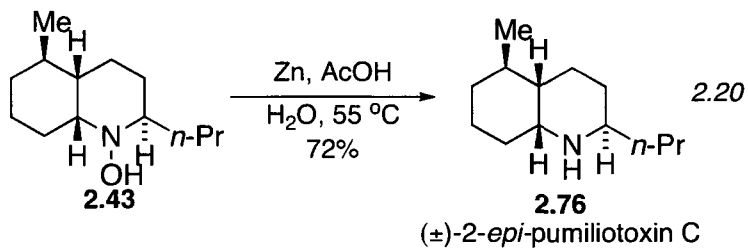
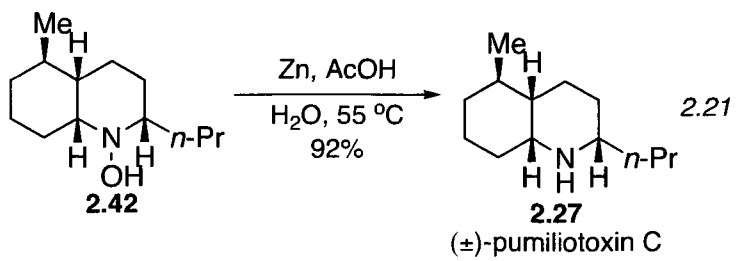


Figure 2.5: Cope-type hydroamination followed by intra- and bimolecular proton transfer step

After these initial results, the reaction was attempted again in alcoholic solvents bubbled through with argon to remove traces of oxygen and subjected to microwave conditions, however, this time performed on a 100 mg scale. This would demostrate if the reaction performed better on a larger scale and would also allow us to obtain enough of the resulting products to perform proper structure identification. Gratifyingly, a cyclization product was observed after heating to 180 °C for five hours in the microwave reactor in the presence of *n*-propanol and water (Equation 2.19). The linear propanol solvent was selected over the branched *i*-propanol due to the greater accessibility of the proton in a crowded environment. Water was included along the same line of reasoning. Two cyclized products were observed with different R_f values by thin layer chromatography and lack of olefinic protons by ^1H NMR. Once the two products were isolated, the nitrogen-oxygen bonds were cleaved to afford the corresponding free amines, (±)-pumiliotoxin C **2.27** and its diastereomer (±)-2-*epi*-pumiliotoxin C **2.76** (Equation 2.20 and Equation 2.21).



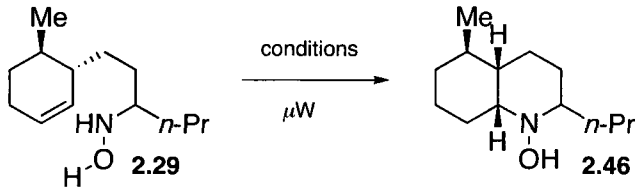


Unfortunately, major product was not the *N*-hydroxy-pumiliotoxin C **2.42** and the recuperated hydroxylamine **2.75** was of a single diastereomer. This suggested that the epimeric hydroxylamine cyclized more readily and oxidation was not the problem in this circumstance. The stereochemical assignment of the products and recovered hydroxylamine are discussed in detail in the thesis of M.-E. Lebrun.[2i]

2.7.2 Further Attempts at Cope-Type Hydroamination Forming *pumiliotoxin C*

Subsequent examination of the difficult cyclization revisited common solvent systems in order to demonstrate the importance of alcoholic solvents in the proton transfer step. Moreover, different conditions using *n*-propanol as solvent were investigated (Table 2.2).

Table 2.2: Further attempts at cyclization



Entry	Solvent	Temperature (°C)	Time (h)	Results
1	$CHCl_3$	125	10	oxime **2.28**
2	Benzene (s.t.)*	180	18	dimerization
3	*n*-PrOH	180	10	trace products
4	*n*-PrOH/$NaBH_3CN$	180	5	dimerization
5	*n*-PrOH/H_2O	180	5	37% **2.43**, 9% **2.42**
6	*n*-PrOH/H_2O	180	10	29% **2.43**, 26% **2.42** and **2.43**-dimer
7	*n*-PrOH/H_2O	190	10	no product

• Reactions were bubbled with argon prior to heating

* Oppolzer conditions

As anticipated, no improvements were made using standard literature procedures. The pressure associated with heating chloroform to the required temperature in the microwave exceeded the maximum tolerated by the equipment thus the reaction was heated to the limit (19 bar) (Entry 1). Even though the reaction had been bubbled through with argon prior, oxidized product was still observed, further supporting previous literature.[77] Using "Oppolzer conditions" [48d] (Entry 2) afforded a dimer as the main product. Reverting to using *n*-propanol as the sole solvent without any additives (Entry 3) but for double the reaction time procured trace amounts of product. This insinuated the importance of water in the reaction system. Since sodium cyanoborohydride had benefited other systems investigated in the Beauchemin lab,[55,56] it was added to the intramolecular alkene cyclization to investigate its utility in these systems (Entry 4). Regrettably, dimerized product was attained yet again. The initial conditions discovered by M.-E. Lebrun were

attempted once more (Entry 5) to ensure their reproducibility and identical results were obtained. In order to persuade the less reactive hydroxylamine to cyclize, the reaction was left for double the initial reaction length (Entry 6). This resulted in improved yield in the desired cyclization yet at the expense of the epimer formation. These findings, coupled with the failure of the reaction at a higher temperature (Entry 7) suggested that the reaction conditions are at the threshold of hydroxylamine stability and decomposition occurred. These attempts at cyclization, however, may have had a different outcome had the reactions been run on enantiomerically pure starting material. Due to the conflicting nature of these results with our earlier predictions, we evaluated possible explanations for our observed reactivity.

2.8 Hypotheses explaining the difference in diastereomer cyclization reactivity

The results delineated in Sections 2.7.1 and 2.7.2 illustrate the ease of one diastereomer undergoing the desired cyclization over the other. Below, two possible scenarios that can explain these results are elucidated.

2.8.1 Critical role of the proton transfer step

The importance of the proton transfer step in Cope-type hydroamination has already been discussed (Figure 2.5)[55,56] and it is possible that this step is playing a decisive role in the pumiliotoxin C system (Figure 2.6).

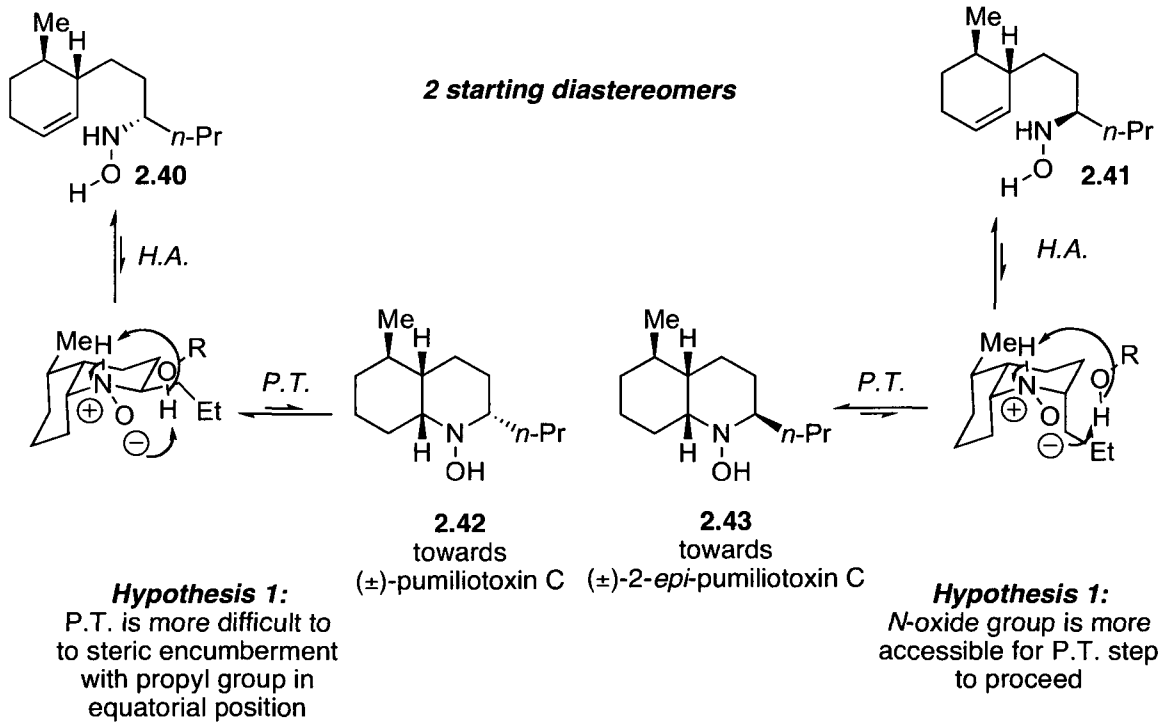


Figure 2.6: Difference in proton transfer step between the two diastereomers cyclizations

Due to the unfavourable 1,3-diaxial interactions in bicyclic systems, the *N*-oxide intermediates in each cyclization are less stable than both the starting material and product. As previously discussed (Figure 2.4), the Cope-type hydroamination step forming the *N*-oxide corresponding to (±)-pumiliotoxin C should be favoured due to the positioning of both alkyl substiuents equatorial. Conversely, it can be suggested that the next step, the proton transfer, can have a large influence on the reactivity and can explain the results encountered. In the instance of the *N*-oxide corresponding to (±)-pumiliotoxin C, the propyl group can have a steric interaction with the alcohol solvent and prevent it from coming in close proximity to aid in the bimolecular sequence. This would not occur in the other diastereomer due to the different location of the propyl group. This can explain why the reaction performed in *n*-propanol and not *i*-propanol due to the

restrictive sterics of the latter, preventing it from reaching the *N*-oxide and the reaction undergo Cope elimination, reforming the starting material. This hypothesis can also explain the improved results upon the addition of water to the reaction medium. The smaller sized molecule would have less interaction with the alkyl group than the alocohol but is still able to perform bimolecular proton transfer agent role.

2.8.2 An additional tricyclic transition state to be considered

The stereochemical outcome of the Cope-type hydroamination was initially predicted based on a tricyclic, chair-like transition state (Section 2.4). This would align the hydroxylamine in a co-planar orientation with the alkene, as necessary by microscopic reversibility. Furthermore this conformation would release strain on the piperidine ring developing and afford the more stable product with both alkyl group equatorial. The results of the cyclization attempts produced the less stable product thereby suggesting kinetic control and a different pathway must be at play. Upon further examination of possible models, a tricyclic, boat-like transition state can also be achieved.[78] This representation would favour the formation of the *N*-oxide corresponding to (±)-2-*epi*-pumiliotoxin C over the desired transformation (Figure 2.7).

[78] This reasoning is based on DFT calculations in simpler systems conducted by Dr. Serge I. Gorelsky

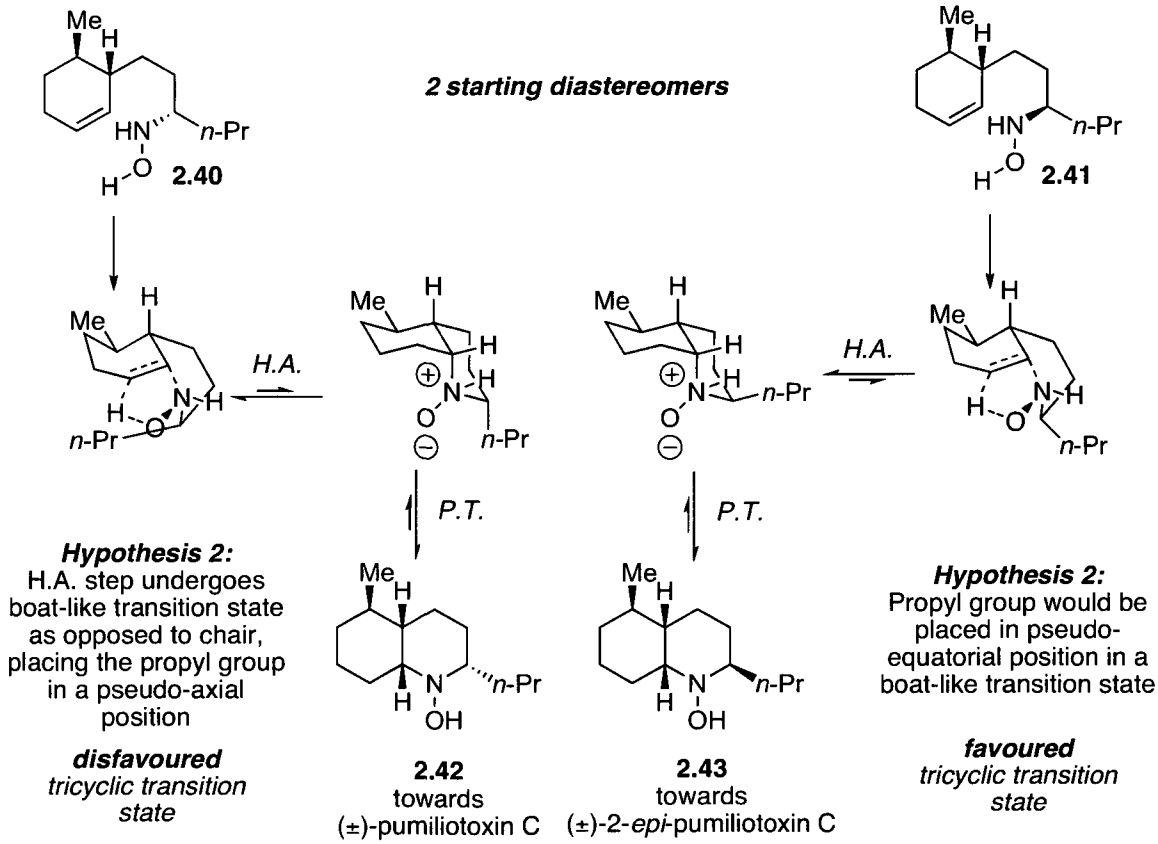


Figure 2.7: Proposed stereochemical outcome of tri-cyclic boat-like transition state

If the cyclization did indeed undergo a boat-like transition state, propyl group in the diastereomer corresponding to (±)-2-*epi*-pumiliotoxin C would be in a pseudo-equatorial position as opposed to a disfavoured pseudo-axial position in the other isomer. This transition-state would explain the results obtained from the cyclization trials and why the non-predicted product from the initial stereochemical calculations was the major one isolated.

In summary, the experimental results of this cyclization can be explained via the two hypotheses presented above and summarized below (Figure 2.8 and Figure 2.9)

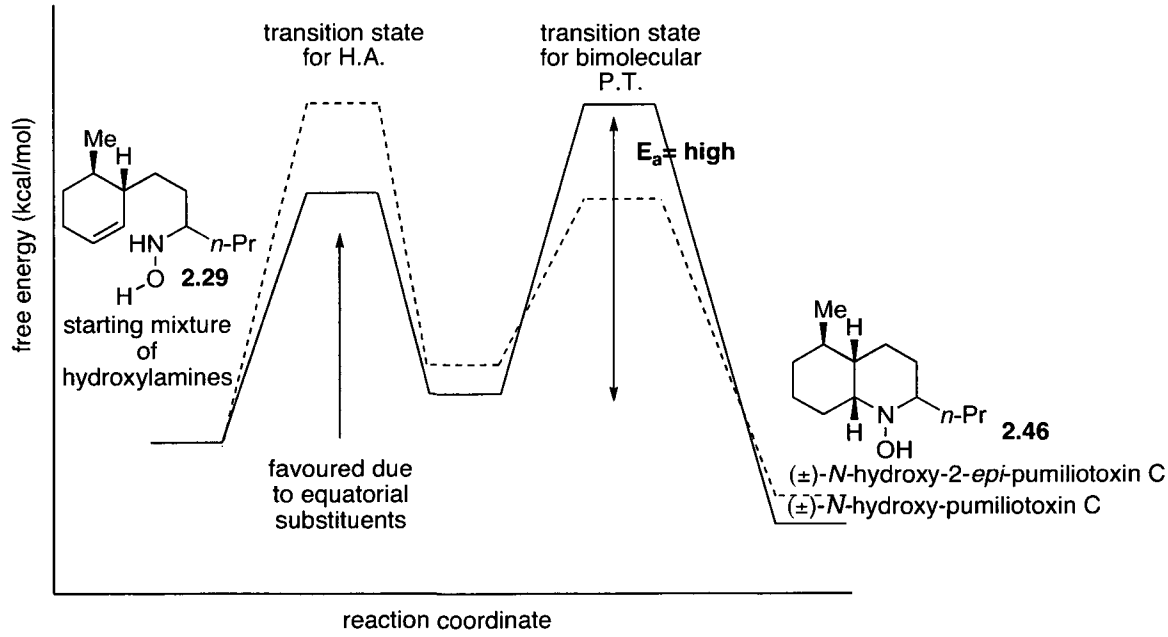


Figure 2.8: First hypothesis with the proton transfer step being rate limiting

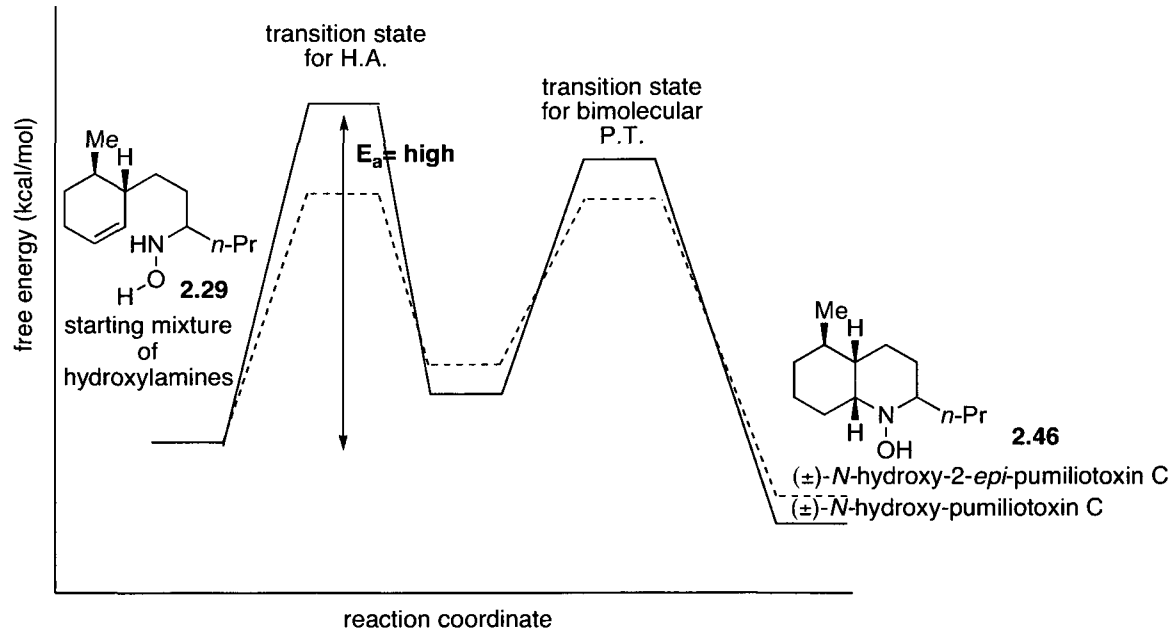


Figure 2.9: Second hypothesis with the hydroamination step being rate limiting

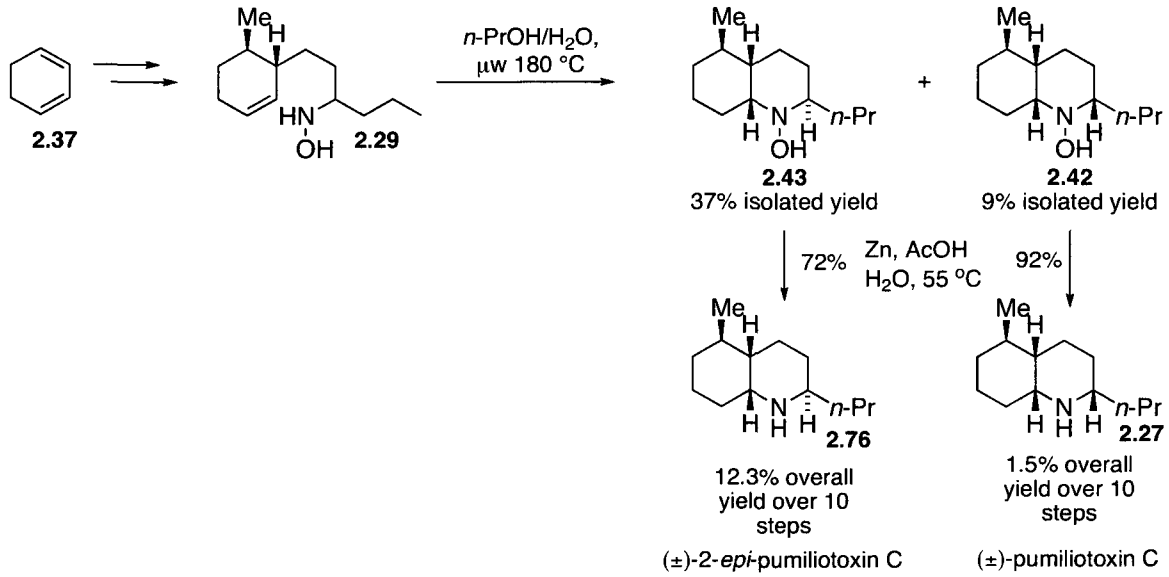
Even though pumiliotoxin C was initially predicted as more stable by 1.8 kcal/mol than its epimer, it was not the favoured product. According to the first hypothesis, the activation energy of the proton transfer step would be more difficult in the case of the natural product due to steric interactions between the alcohol and the propyl group in the equatorial position. This relationship would not be present in the epimer. In the second hypothesis, the hydroamination step could undergo a tricyclic boat-like transition state whereby the propyl group in the natural product would be in a disfavoured pseudo-axial position in contrast to a pseudo-equatorial position in the case of the epimer. It is the author's opinion that the second hypothesis seems more logical since there is also water present in the reaction medium. As a much smaller molecule than the alcohol, the water should be able to mediate the proton transfer step even if the propyl group is in the

equatorial position. The boat-like transition state predicted by the DFT calculations accounts for the large ratio difference between the two products obtained.

2.9 Conclusion

The synthesis of 2-*epi*-pumiliotoxin C **2.76** was completed by a difficult intramolecular Cope-type hydroamination key step (Scheme 2.8).

Scheme 2.8: Our racemic synthesis of pumiliotoxin C and its epimer via a Cope-type hydroamination key step



The hydroamination precursor with a hydroxylamine moiety **2.29** was heated in the microwave at 180 °C in a mixture of water and deoxygenated propanol for five hours. This solvent system was selected after extensive experimentation in intermolecular reactivity in the Beauchemin lab demonstrated the superiority of alcoholic solvents in enabling the proton transfer step. Two cyclized products were isolated and the precursor of (±)-2-*epi*-pumiliotoxin C **2.43** was the major cyclized product in 37% yield (74% of the theoretical yield) and the precursor of (±)-pumiliotoxin C **2.42** was the minor product with a 9% yield (18% of the theoretical yield). The recovered hydroxylamine (41% yield)

was of a single diastereomer suggesting the hydroxylamine precursor of pumiliotoxin C was less reactive to the cyclization conditions. The synthesis of pumiliotoxin C and its epimer was completed over ten steps with an overall yield of 1.5% for the natural product (3% of theoretical yield) and 12.3% for its epimer (24.6% of theoretical yield) from 1,3-cyclohexadiene **2.37** as starting material. These yields are a dramatic improvement over those obtained via the first synthetic pathway by M.-E. Lebrun where pumiliotoxin C and its epimer were obtained in 0.8% (1.6% of theoretical) and 1.4% (2.8% of theoretical) yields respectively. DFT calculations suggest the reaction is under kinetic control whereby the Cope-type hydroamination is the rate-determining step via a boat-like transition state.

It has thus been proven that the Cope-type hydroamination methodology could be used to form aza-bicyclic ring systems with non-α-methyl substituents as discussed in Section 2.1. Six-membered rings were formed with this strategy using the most difficult characteristics of an intramolecular Cope-type hydroamination on the substrate. Our comprehension of the importance of the proton transfer step enabled us to accomplish this cyclization. Our synthesis demonstrated the potential of Cope-type hydroamination in building larger, biologically useful molecules and our newfound knowledge of the transition state can enable us to better predict future syntheses undertaken in the lab.

3 New Routes Towards Ketonitrone Synthesis via Hydroamination of Allenes, Alkynes, and Improved Schiff base Chemistry with Ketones[79]

3.1 Introduction

Nitrones are a highly useful and versatile class of organic compounds which can be used both as synthetic intermediates and as end products.[80] They have been used as spin trap reagents in the identification of transient radicals,[81] and as biologically active compounds as therapeutic agents.[82] From the viewpoint of a synthetic chemist, nitrones can be used as 1,3-dipoles in cycloaddition reactions[83] and as electrophiles for organometallic reagents.[84] Nitrones, therefore, have been frequently used in the construction of natural products. The application of ketonitrones, however, has been rare toward said construction when compared to the synthetic uses described for aldonitrones, despite their

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[79] Portions of this chapter have been published (a) Moran, J.; Pfeiffer, J.Y.; Gorelsky, S.I.; Beauchemin, A.M. *Org. Lett.* **2009**, *11*, 1895 (b) Pfeiffer, J.Y.; Beauchemin, A.M. *J. Org. Chem. accepted*

[80] (a) Tufariello, J.J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed; John Wiley & Sons: New York, 1984; Vol. 2, Chapter 9 (b) Torssell, K.B.G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; Feuer, H. Ed.; VCH: Weinheim, Germany, 1988 (c) Jones, R.C.F.; Martin, J.N. In *Synthetic Applications of 1,3-Dipolar Cycloadditions. Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W.H. Eds; John Wiley & Sons: Hoboken, NJ, 2003; Chapter 1 (d) Bokach, N.A.; Kukushkin, V.Y. *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 1869 (e) Ruck-Braun, K.; Freysoldt, T.H.E.; Wierchem, F. *Chem. Soc. Rev.* **2005**, *34*, 507 (f) Cardona, F.; Goti, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7832 (g) Grigor'ev. I.A. In *Nitrile Oxides, Nitrones, and Nitroates in Organic Synthesis*; Feuer, H., Ed.; John Wiley & Sons: Hoboken, 2008; Chapter 2

[81] Villamena, F.A.; Xia, S.; Merle, J.K.; Lauricella, R.; Tuccio, B.; Hadad, C.M.; Zweier, J.L. *J. Am. Chem. Soc.* **2007**, *129*, 8177

[82] (a) Fevig, T.L.; Bowen, S.M.; Janowick, D.A.; Jones, B.K. Munson, H.R.; Ohlweiler, D.F.; Thomas, C.E. *J. Med. Chem.* **1996**, *39*, 4988 (b) Frejaville, C.; Karoui, H.; Le Moigne, F.; Culcasi, M.; Pietri, S.; Lauricella, R.; Tordo, P. *J. Med. Chem.* **1995**, *38*, 258

[83] Gothelf, K.V.; Jorgensen, K.A. *Chem. Rev.* **1998**, *98*, 863

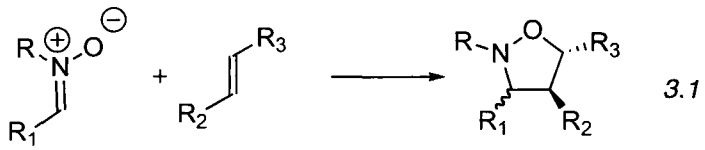
[84] Bloch, R. *Chem. Rev.* **1998**, *98*, 1407

synthetic potential to build nitrogenated quaternary centres. This void in the literature can be partially attributed to the scarcity of effective methods developed for ketonitrone formation.

3.2 Synthetic applications of nitrones

3.2.1 In cycloaddition chemistry

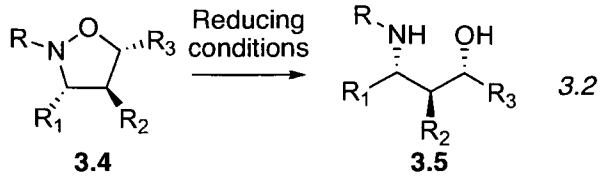
The 1,3-dipolar cycloaddition of nitrones and olefins towards the synthesis of five-membered isoxazolidines can now be considered a fundamental reaction in organic chemistry (Equation 3.1).



3.1 **3.2** **3.3** *3.1*

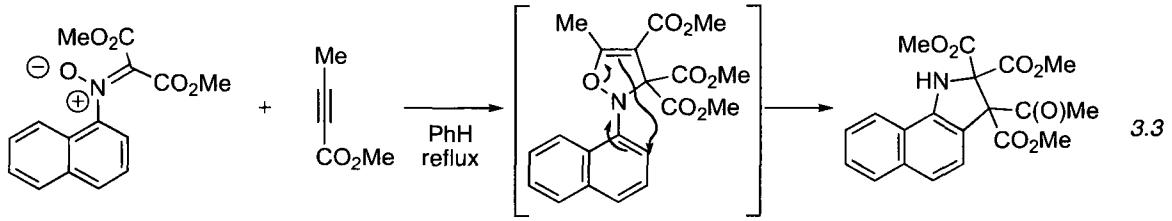
Much has been written on this subject,[80a-d,f,g,85] including reviews on stereoselective variants,[83] and it continues to be used in synthetic strategies due to the significant breadth of functionalities that can be prepared from isoxazolidines. The five-membered ring can be opened through reduction methods to prepare β-amino alcohols with retention of configuration at the chiral centres formed through the cycloaddition (Equation 3.2). These reductions have been performed using palladium or Raney nickel catalysts, or with zinc in acid. Depending on the nature of the amino group desired, the nitrogen substituent (e.g. benzyl) could be removed in the reducing conditions.

[85] Koumbis, A.E.; Gallos, J.K. *Curr. Org. Chem.* **2003**, *7*, 585



3.4 3.5 3.2

Far more limited accounts have described the 1,3-dipolar cycloaddition of nitrones and alkynes yielding isoxazolines.[86] The 2,3-dihydroisoxazole products though are unstable and undergo a variety of decomposition and rearrangement pathways. This method has, however, been described as a route to access indolines (Equation 3.3).[87]



3.6 3.7 3.8 3.9 3.3

Recently, 1,3-dipolar cycloaddition has been discovered in the reaction of nitrones and cyclopropanes to generate tetrahydro-1,2-oxazines (Equation 3.4).[88] Due to strain in the ring system, the bonds in cyclopropanes are deemed to have considerable π-character[89] and Lewis acids can significantly weaken this bond via polarization. This methodology can access one-carbon homologues of the reaction with olefins. Furthermore an account of an application towards the synthesis of the tricyclic core of FR-900482 via this methodology was described (Equation 3.5).

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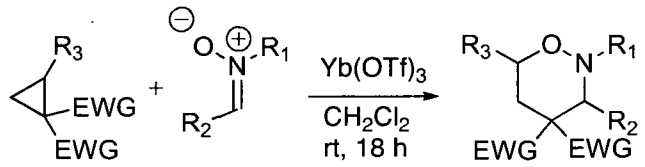
[86] Freeman, J.P. *Chem. Rev.* **1983**, *83*, 241

[87] Tomioka, Y.; Nagahiro, C.; Nomura, Y.; Maruoka, H. *J. Heterocyclic Chem.* **2003**, *40*, 121

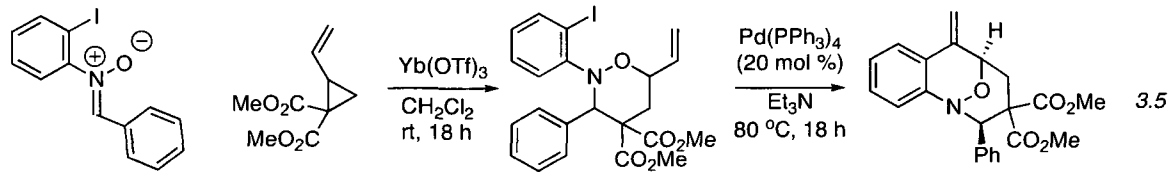
[88] Young, I.S.; Kerr, M.A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023

[89] Tidwell, T.T. In *The Chemistry of the Cyclopropyl Group, part I*; Rappoport, Z. Ed; John Wiley & Sons: New York, 1987



3.4

3.10 **3.11** **3.12**

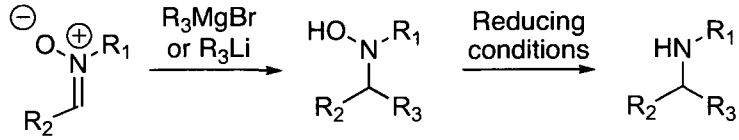


3.5

3.13 **3.14** **3.15** **3.16**

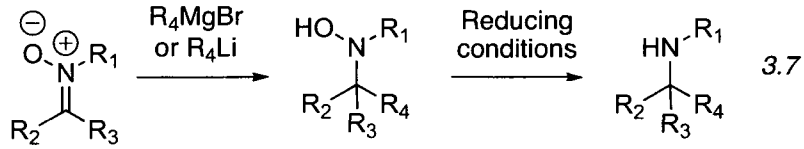
3.2.2 In organometallic chemistry

The addition of nucleophiles to the carbon-nitrogen double bond in imines, hydrazones, and oximes is a valuable method to form primary and secondary amines. Unfortunately, progress of this field was hindered by the poor electrophilicity of the Schiff bases thus multiple strategies were developed to improve the scope of organometallic addition. Nitrones, however, have a significantly polarized carbon-nitrogen double bond and thereby have great electrophilic character. As such, nitrones have been a significant interest in nucleophilic 1,2-addition work (Equation 3.6 and Equation 3.7). Furthermore, the reactive oxygen of the nitrone group can provide rigid chelates which can be exploited to control the stereoselectivity of additions.[84]



3.6

3.17 **3.18** **3.19**



3.20 **3.21** **3.22**

The addition of a Grignard reagent or organolithium species to nitrones can afford secondary and tertiary hydroxylamines that can then be transformed into the corresponding amines by cleavage of the nitrogen-oxygen bond.[90] Moreover, secondary allylamines have been generated by the addition of vinyl Grignard reagents to aldonitrones.[91] Unfortunately, addition to ketonitrones has generally been limited to cyclic nitrones[92] but some examples with acyclic substrates have been demonstrated.[93]

3.2.3 In total synthesis

As can be anticipated from the above-described reactivity, nitrones are highly useful intermediates in the assembly of complex molecules. Manipulations of the moiety are prevalent in total syntheses and a few recent examples will be discussed below.

The syntheses of both (−)-histrionicotoxin 285A **3.31** and (−)-perhydrohistrionicotoxin **3.32** performed by Holmes and co-workers started from the same tricycle intermediate **3.30** and diverged afterwards (Scheme 3.1).[94] The nitrone **3.29** was procured via the intramolecular *N*-alkylation of the oxime and was immediately protected with styrene in a cycloaddition fashion, generating the isoxazolidine **3.28**. This intermediate was later

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[90] Volkmann, R.A. In *Comprehensive Organic Synthesis: Additions to C-X π -Bonds, Part I*; Schreiber, S.L. Ed.; Pergamon: Oxford, 1991; Vol. I, p. 355-396

[91] Dondoni, A.; Merchan, F.L.; Merino, P.; Tejero, T. *Synth. Commun* **1994**, *24*, 2551

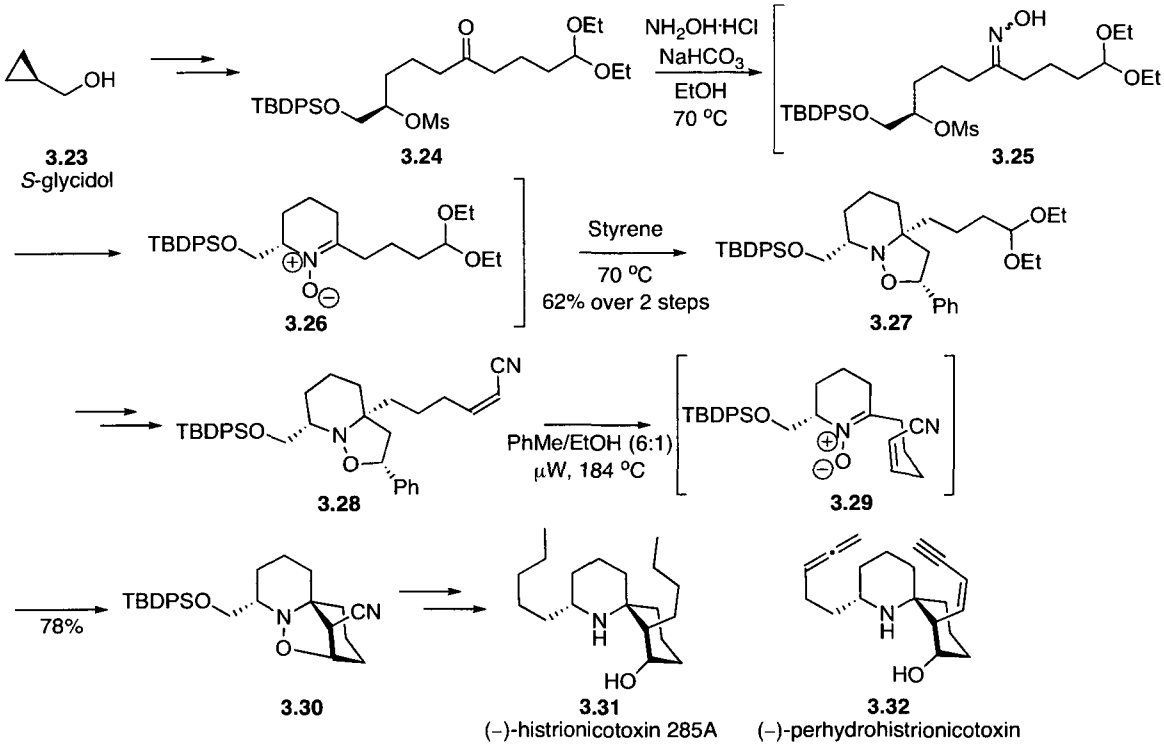
[92] Murahashi, S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watnabe, S. *J. Org. Chem.* **1990**, *55*, 1736

[93] Schwartz, M.; Hu, X. *Tetrahedron Lett.* **1992**, *33*, 1689

[94] Macdonald, J.M.; Horsley, H.T.; Ryan, J.H.; Saubern, S.; Holmes, A.B. *Org. Lett.* **2008**, *10*, 4227

subjected to microwave irradiation whereby styrene was extruded through a 1,3-dipolar cycloreversion and the liberated nitrone performed another 1,3-dipolar cycloaddition with the internal olefin to produce the desired tricycle **3.30**. In this synthesis we observe the formation of the nitrone through the oxime alkylation and its reactivity in 1,3-dipolar cycloaddition.

Scheme 3.1: Total synthesis of (−)-histrionicotoxin 285A and (−)-perhydrohistrionicotoxin

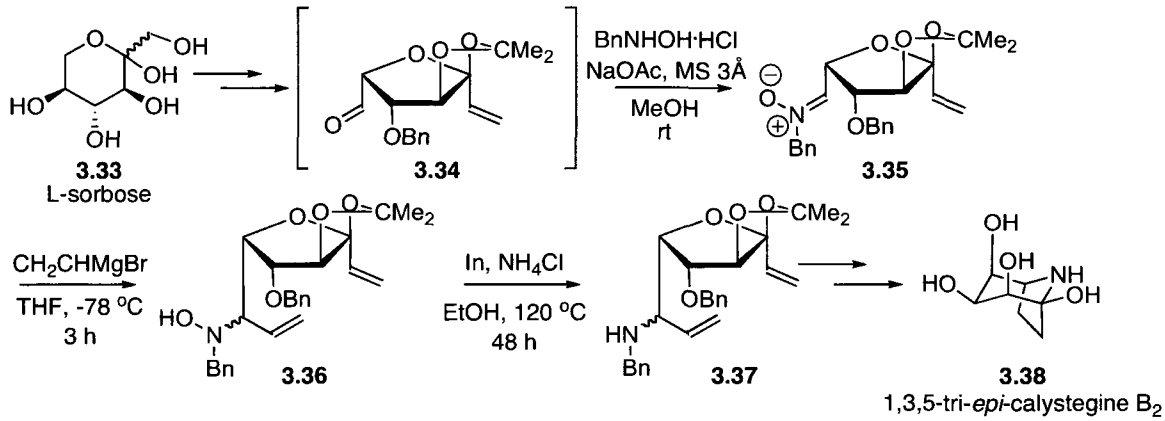


In an attempt to deviate from common intramolecular nitrone-alkene cycloaddition and ring-closing metathesis strategies to construct amino polyhydroxycycloheptane derivatives, Tamayo and co-workers described their approach to the assembly of *nor*-tropane alkaloids (Scheme 3.2).[95] Starting with L-sorbose **3.33**, nitrone intermediate **3.35**

[95] Lo Re, D.; Franco, F.; Sanchez-Cantalejo, F.; Tamayo, J.A. *Eur. J. Org. Chem.* **2009**, 1984

was obtained by the condensation of aldehyde **3.34** with benzylhydroxylamine hydrochloride. The electrophilic nitrone was then attacked with vinylmagnesium bromide to yield the hydroxylamine **3.36**. The hydroxyl group was removed under mild reducing conditions to generate the amine **3.37**. In this synthetic strategy we see the construction of the oxime via simple aldehyde-hydroxylamine condensation followed by nucleophilic addition onto the carbonyl carbon with an organometallic reagent.

Scheme 3.2: Synthesis of polyhydroxycycloheptane derivative via a nitrone intermediate

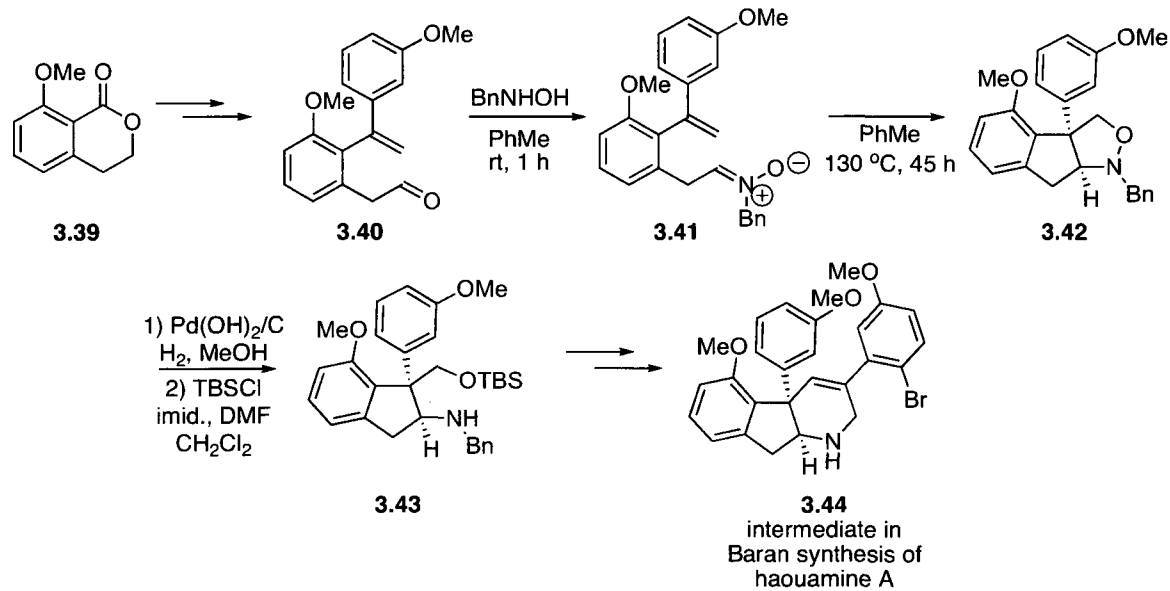


Haouamine A, a polycyclic marine alkaloid, was first isolated in 2003[96] - Baran and co-workers published its first total synthesis in 2006.[97] In that same year, Weinreb and Jeong illustrated a different approach to Baran's pentacyclic intermediate **3.44**, thus completing a formal synthesis of the natural product (Scheme 3.3).[98] The nitrone was obtained through a condensation reaction between benzylhydroxylamine and aldehyde **3.40** generating nitrone **3.41** which underwent an intramolecular cycloaddition reaction creating the isoxazolidine intermediate **3.42**. Continuing with their strategy to construct

[96] Garrido, L.; Zubia, E.; Ortega, M. *J. Org. Chem.* **2003**, *68*, 293
[97] Baran, P.; Burns, N.Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908
[98] Jeong, J.H.; Weinreb, S.M. *Org. Lett.* **2006**, *8*, 2309

the required tetrahydropyridine ring, the isoxazolidine was reduced to the corresponding amino alcohol and subsequently protected as the silyl ether **3.43**. Thus, over this synthesis we yet again observe the formation of the nitrone intermediate through a condensation reaction. The nitrone obtained was used in a cycloaddition reaction and then reduced to afford the amino alcohol which was further manipulated.

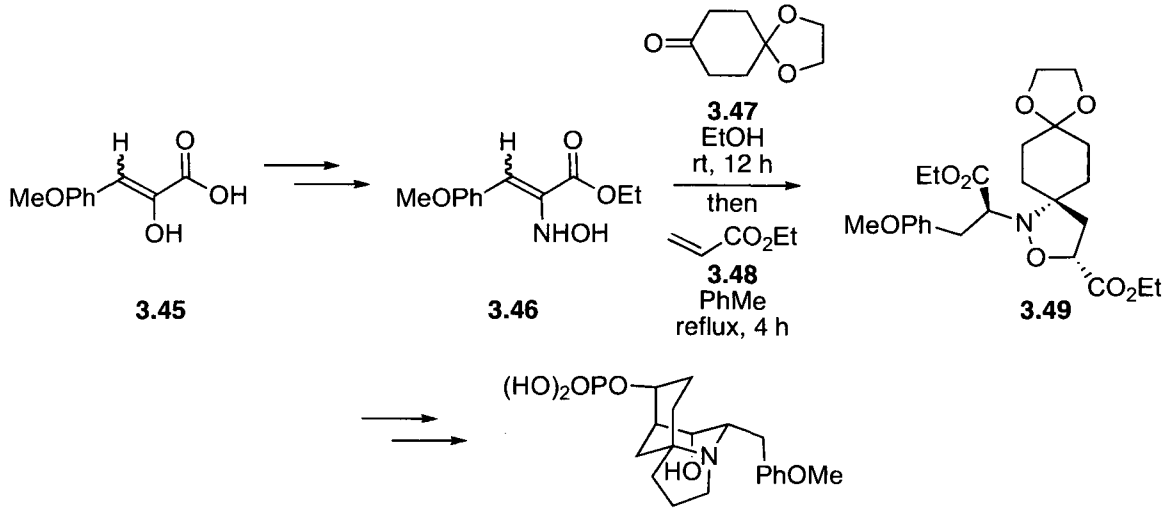
Scheme 3.3: Weinreb's formal synthesis of marine alkaloid haouamine A



There are few illustrations in total synthesis whereby a ketonitrone is used as an intermediate. Snider and co-workers presented one such example in the assembly of FR901483 (Scheme 3.4).[99] Treatment of hydroxylamine **3.46** with ketone **3.47** afforded a nitrone intermediate, which was treated with ethyl acrylate to give the resultant isoxazolidine **3.49**. This method illustrates the potential of nitrones to construct spiro centres.

[99] Snider, B.B.; Lin, H.; Foxman, B.M. *J. Org. Chem.* **1998**, *63*, 6442

Scheme 3.4: Snider synthesis of FR901483 through a ketonitrone intermediate



In summary, we have seen the synthetic utility of nitrones in cycloaddition reactions and as substrates for organometallic reagents and how these reactivities have been applied in total synthesis. Aldonitrones are more easily accessed and have been more widely used as substrates than ketonitrones. Nitrones themselves, however, are not always simple to assemble and strategies for their formation will be discussed.

3.3 Preparation of nitrones in the literature

As elucidated above, nitrones are highly useful intermediates in organic synthesis particularly due to their reactivity in 1,3-dipolar cycloadditions and towards nucleophiles. Their formation, however, is not so straightforward and there are limited, often restricted, preparative techniques to attain some of these compounds. A vast array of methods can be employed to form nitrones[80] but only a selection of the more common strategies will be discussed.[80g] Although a variety of methods have been employed to form nitrones,

none use hydroamination techniques. Furthermore, it is noteworthy that routes to form ketonitrones are more scarce and less well developed.

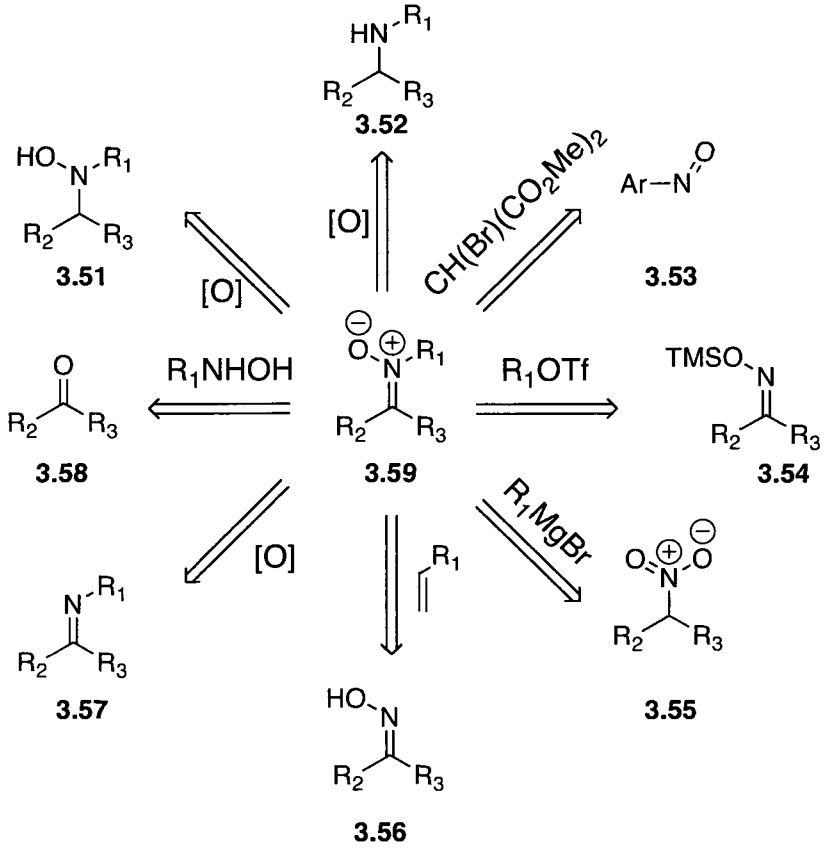


Figure 3.1: Nitrone forming reactions

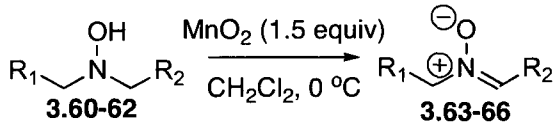
3.3.1 Formation of nitrones via oxidation of hydroxylamines, amines and imines

There are several reagents used to oxidize *N,N*-dialkylhydroxylamines to the corresponding nitrones. Prior to 2001, the most commonly utilized oxidant for this transformation was yellow mercury oxide. The toxicity, and required excess of the reagent under the reaction conditions, led the Goti group to explore other alternatives. Besides for the environmentally friendly method of simply using bleach as the oxidant,[100]

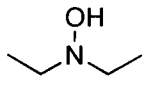
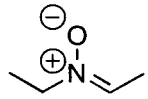
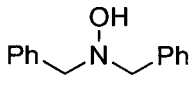
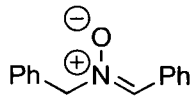
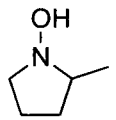
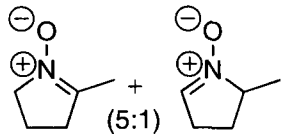
[100] Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, *64*, 7243

the group also explored manganese dioxide as a useful replacement.[101] The substrate scope of the reaction was narrow and formed only aldonitrones, except in one example where a mixture of aldo- and ketonitrones was obtained (Table 3.1).

Table 3.1: Oxidation of *N,N*-dialklylhydroxylamines with MnO_2



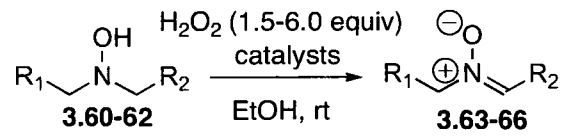
3.60-62 → 3.63-66

Substrate	Product	Yield (%)
 **3.60**	 **3.63**	90 (1)
 **3.61**	 **3.64**	93 (2)
 **3.62**	 (5:1) **3.65** **3.66**	92 (3)

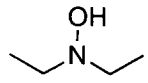
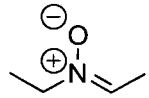
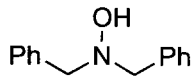
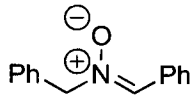
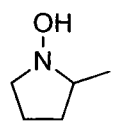
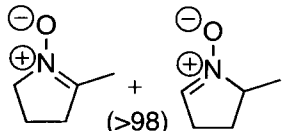
Using a more complex oxidant, Goti and co-workers explored different methylrhenium trioxide (MTO) catalyst systems.[102] Poly(4-vinylpyridine)/MTO (PVP/MTO) and microencapsulated polystyrene/MTO (PS/MTO) compounds efficiently oxidized *N,N*-dialkylhydroxylamines to the resultant nitrones with hydrogen peroxide (Table 3.2). Multiple conditions are presented for each substrate. Identical substrates as in an earlier publication[101] are attempted and the selectivity of ketonitrone formation of 2-methyl-*N*-hydroxypyrrolidine is vastly improved. Each susbtrate was tried in six catalytic systems with different yields obtained in each.

[101] Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503
[102] Saladino, R.; Neri, V.; Cardona, F.; Goti, A. *Adv. Synth. Catal.* **2004**, *346*, 639

Table 3.2: Oxidation of *N,N*-dialkylhydroxylamines with PVP/MTO and PS/MTO systems



3.60-62 **3.63-66**

Substrate	Product	
 **3.60**	 **3.63**	(1)
 **3.61**	 **3.64**	(2)
 **3.62**	 **3.65** + (>98) **3.66**	(3)

The broader range of commercially available secondary amines causes their oxidation to nitrones to be more direct and favoured. Generally, hydrogen peroxide (2-7 equiv) is used as the primary oxidant in the presence of catalytic selenium dioxide,[103] MTO,[104] sodium molybdate, or sodium tungstate.[103b,105] Licini and co-workers studied titanium (IV) catalysts to transform secondary amines into the subsequent nitrones.[106] Among the substrates explored, two yielded ketonitrones while the five produced aldonitrones (Table 3.3).

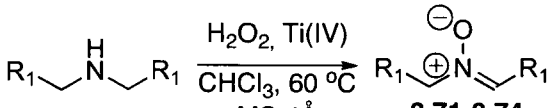
[103] (a) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316 (b) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett.* **1995**, *36*, 3561

[104] (a) Murray, R.W.; Iyanar, K. *J. Org. Chem.* 1996, 61, 8099 (b) Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025

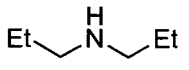
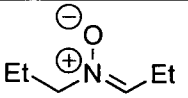
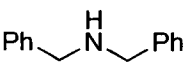
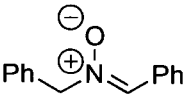
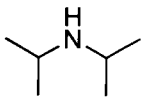
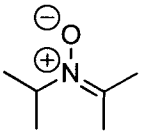
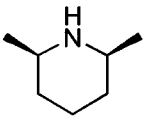
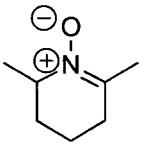
[105] Murahashi, S.-I. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443

[106] (a) Forcato, M.; Nugent, W.A.; Licini, G. *Tetrahedron Lett.* **2003**, *44*, 49 (b) Zonta, C.; Cazzola, E.; Mba, M.; Licini, G. *Adv. Synth. Catal.* **2008**, *350*, 2503

Table 3.3: Oxidation of secondary amines with titanium(IV) catalysts



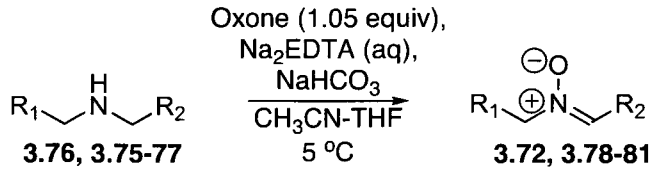
3.67-3.70 **3.71-3.74**

Substrate	Product	Yield (%)	
		70	(1)
3.67	**3.71**		
		91	(2)
3.68	**3.72**		
		98	(3)
3.69	**3.73**		
		39	(4)
3.70	**3.74**		

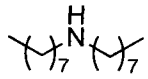
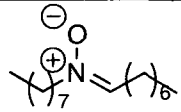
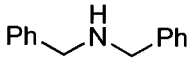
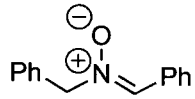
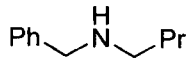
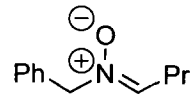
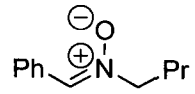
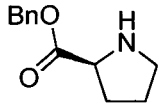
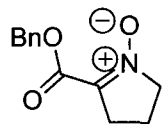
Recently, a new transition-metal free method has been developed to oxidize secondary amines utilizing Oxone in a biphasic basic medium (Table 3.4).[107] An asymmetric amine substrate gave regioisomeric nitrones, which could be separated upon purification. Although the benzyl ester yielded the sole ketonitrone product, the free acid gave a decarboxylated aldonitrone while the free alcohol did not react at all. Imines subjected to the reaction did not react as desired.

[107] Gella, C.; Ferrer, E.; Alibes, R.; Busque, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, DOI: 10.1021/jo901108u

Table 3.4: Oxidation of secondary amines with Oxone



3.76, 3.75-77 → **3.72, 3.78-81**

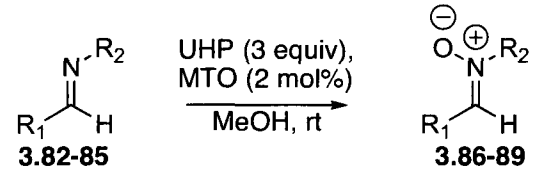
Substrate	Product	Yield %	
 **3.75**	 **3.78**	72	(1)
 **3.68**	 **3.72**	86	(2)
 **3.76**	 **3.79**	84	(3)
	 **3.80**	1:1	
 **3.77**	 **3.81**	82	(4)

The abovementioned methods suffer from regioselectivity issues when unsymmetrical secondary amines or hydroxylamines are employed, however the use of imines as substrates has been demonstrated to circumvent this problem. Goti and co-workers reported the first chemoselective catalytic oxidation of imines to nitrones, which also offered a solution to the regiochemical problems encountered in other nitrone forming methods.[108] Upon exposure of the imines to MTO as catalyst with urea hydrogen peroxide (UHP) as the stoichiometric oxidant, the respective nitrones were prepared

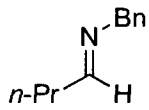
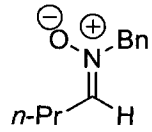
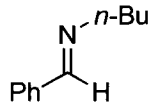
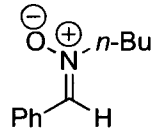
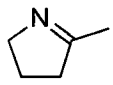
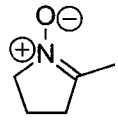
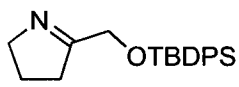
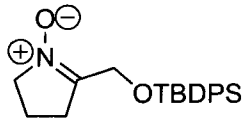
[108] Soldaini, G.; Cardona, F. Goti, A. *Org. Lett.* **2007**, *9*, 473

(Table 3.5). Aldimines consisted the majority of the substrates but two ketimines were also present.

Table 3.5: Oxidation of imines to prepare nitrones

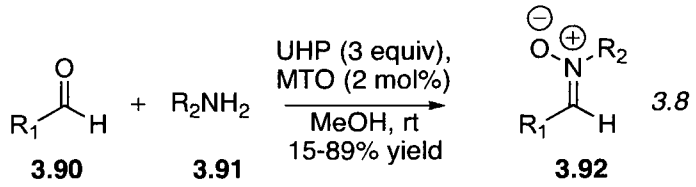


3.82-85 **3.86-89**

Substrate	Product	Yield %	
 **3.82**	 **3.86**	50	(1)
 **3.83**	 **3.87**	85	(2)
 **3.84**	 **3.88**	98	(3)
 **3.85**	 **3.89**	95	(4)

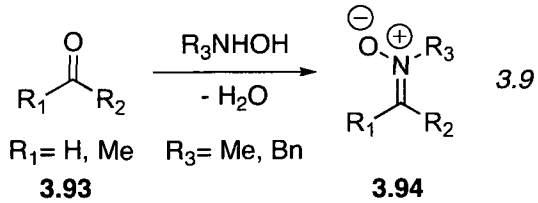
The authors then demonstrated the possibility of their reaction to be performed as a one-pot oxidative direct conversion of primary amines and aldehydes into nitrones using the same conditions (Equation 3.8).[109] Since the reaction does not go through an oxaziridine intermediate, by-products are minimal and purification is simpler than in other methods.

[109] Cardona, F.; Bonanni, M.; Soldaini, G.; Goti, A. *ChemSusChem,* **2008**, *1*, 327



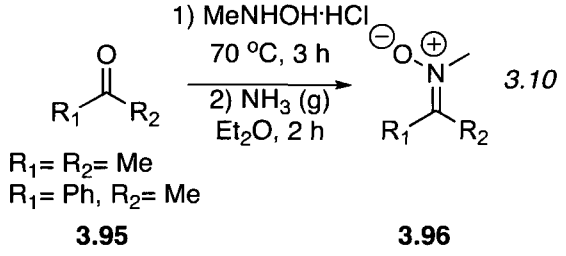
3.3.2 Formation of nitrones via the condensation of hydroxylamines and carbonyl compounds

Aldonitrones can be constructed simply through a condensation reaction between hydroxylamines and aldehydes. This method was clearly illustrated in the total syntheses (Scheme 3.2 and Scheme 3.3) presented since it can be carried out under mild conditions.[80a] The assembly of ketonitrones through the same technique is not as efficient since the less reactive ketones consistently require heating or longer reaction time, and can be accompanied by hydroxylamine decomposition,[77] thus hindering their usefulness in synthetic procedures.[110] The vast majority of these reactions, though, only employ methylhydroxylamine or benzylhydroxylamine and there are few examples without these limitations (Equation 3.9). Furthermore, of the reactions that employ ketones, the substrates are most often narrow in scope, limited to methyl ketones, and rare for linear ketones.

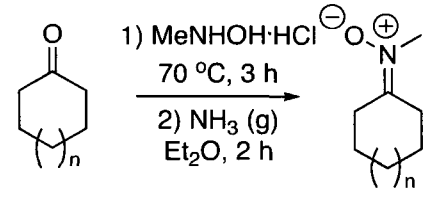


[110] Osborn, H.M.I.; Gemmell, N.; Harwood, L.M. *J. Chem. Soc. Perkin Trans. 1*, **2002**, 2419

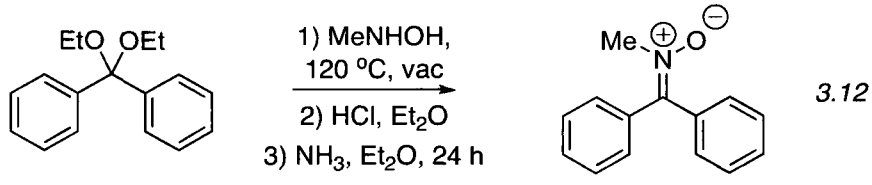
The main procedure used to date to form ketonitrones from their respective ketones follows the method described by Exner in 1951.[111] The ketone is condensed with the *N*-methylhydroxylamine hydrochloride, the nitrone salt then purified and neutralized with ammonia to liberate the ketonitrone (Equation 3.10 and Equation 3.11). For more challenging substrates, reactions were driven by entropically favourable conditions utilizing the dialkylketal equivalents instead (Equation 3.12).



3.95 **3.96** *3.10*



3.97 **3.98** *3.11*

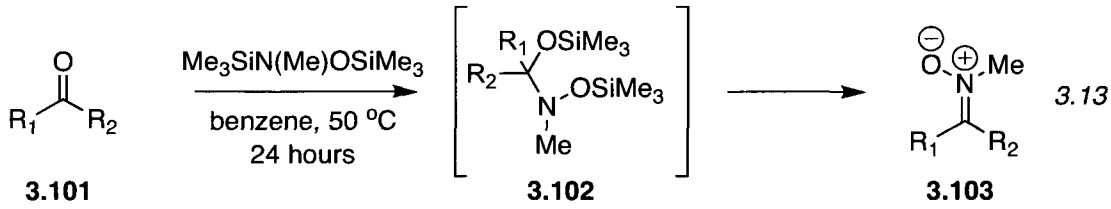


3.99 **3.100** *3.12*

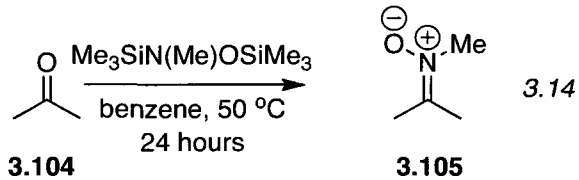
Hwu and co-workers described another report used to condense carbonyl compounds with hydroxylamines that included ketone substrates (Equation 3.13).[112] This method employed excess aldehydes and ketones with *N*-methyl-*N,O*-bis(trimethylsilyl)hydroxylamine to form *N*-methylnitrones which could be isolated or

[111] Exner, O. *Coll. Czechoslov. Chem. Commun.* **1951**, *16*, 258
[112] Robl, J.A.; Hwu, J.R. *J. Org. Chem.* **1985**, *50*, 5913

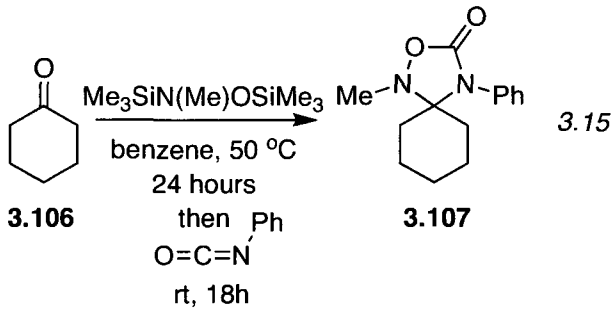
reacted with alkenes in situ. The ketones described in the substrate scope of this reaction system were acetone (Equation 3.14) and cyclohexanone (Equation 3.15) and only methyl aldo- or ketonitrones can be accessed via this strategy. The atom efficiency and synthetic utility of this method could be questioned as well.



3.101 **3.102** **3.103**



3.104 **3.105**

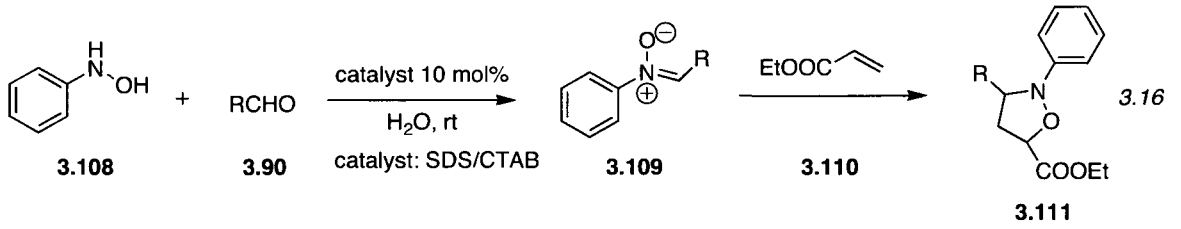


3.106 **3.107**

The Bhattacharya group explored the formation of nitrones from a green chemistry standpoint using surfactants to help solubilize the compounds in an aqueous environment.[113] The emulsion droplets observed upon the addition of the surfactant catalyst had a hydrophobic interior in which the reaction could occur. Upon product formation the molecule of water would be expelled from the micelle. The nitrones in this case were not isolated since upon product formation, a dipolarophile (ethyl acrylate) was

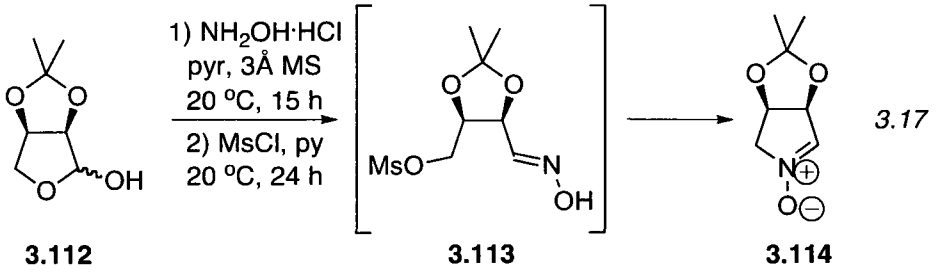
[113] Chatterjee, A.; Maiti, D.K.; Bhattacharya, P.K. *Org. Lett.* **2003**, *5*, 3967

added to induce a cycloaddition reaction and the isoxazolidine was isolated (Equation 3.16).



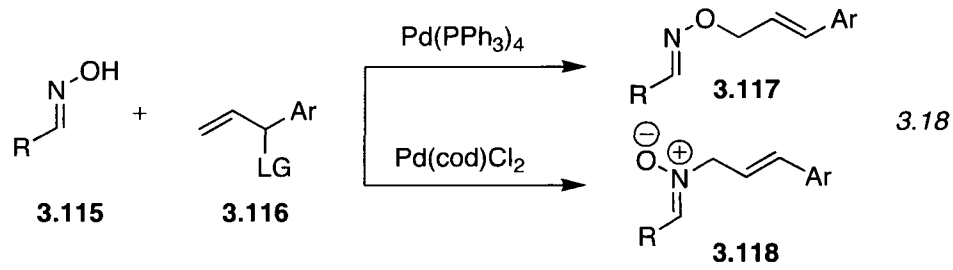
3.3.3 Nitrone formation via oximes

Oximes can also be used to prepare nitrones, most commonly through *N*-alkylation via the lone pair on the nitrogen. This method, as observed in the total syntheses presented (Scheme 3.1), has been found to be an effective process to synthesize nitrones but mixtures of the *N*-alkylated and *O*-alkylated products still poses a hindrance to this technique and at times temporary protection of the oxygen is required.[114] This approach was illustrated by Goti and co-workers via the one-pot procedure whereby the oxime was generated from the lactol and then the nitrogen displaced the mesyl leaving group (Equation 3.17).[115]



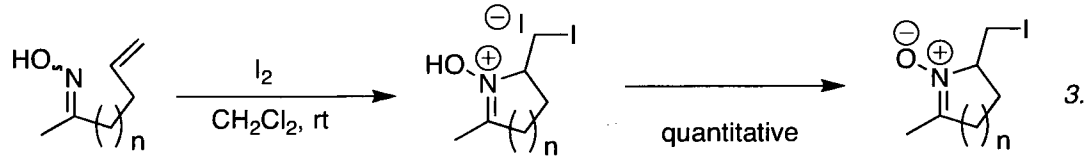
[114] LeBel, N. A.; Balasubramanian, N. *Tetrahedron Lett.* **1985**, *26*, 4331 (and references cited therein)
[115] Cicchi, S.; Marradi, M.; Vogel, P. Goti, A. *J. Org. Chem.* **2006**, *71*, 1614

Takemoto and co-workers also described a selective synthesis of both oxime ethers and nitrones by simply changing the catalyst in their reaction (Equation 3.18).[116] Utilizing a palladium (II) catalyst with Lewis acid properties in solvent-free conditions the formation of *N*-allylated nitrones was observed.



3.18

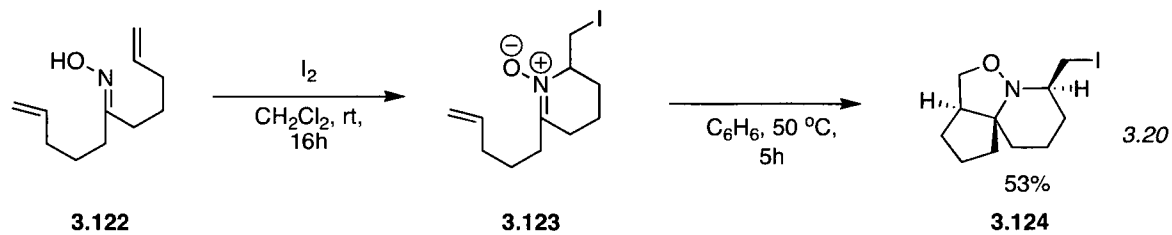
Another reported method using oximes in a different manner, proposed a general inter- and intra-molecular electrophile induced addition of oximes to alkenes that can also further react in a cycloaddition manner.[117] Upon the addition of NBS, NIS, ICl or iodine in dichloromethane at room temperature, the oxime attacks the alkene and can form either nitrones or their corresponding salts depending on whether the proton is removed via base (Equation 3.19). If an additional olefin is present in the reaction medium, a cycloaddition cascade can continue (Equation 3.20).



3.19

[116] Miyabe, H.; Kazumasa, Y.; Reddy, V.K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630

[117] (a) Dondas, H.A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Kennewell, P. Thornton-Pett, M. *Tetrahedron* **2001**, *57*, 1119 (b) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc. Chem. Commun.* **1993**, 1340



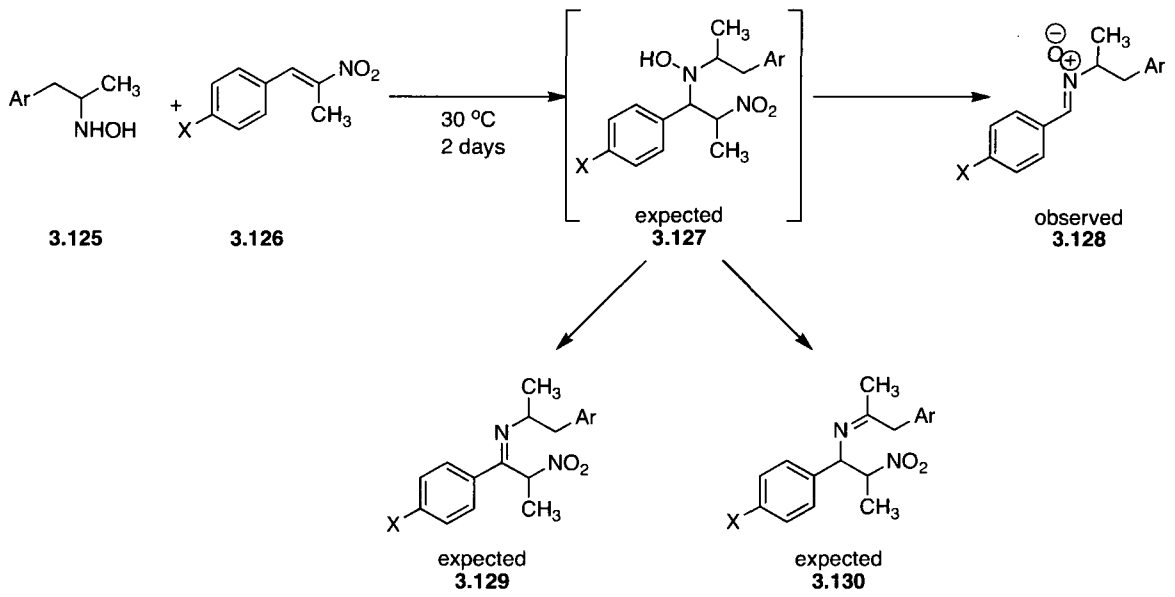
3.122 **3.123** **3.124**

3.3.4 Nitrone formation via other routes

In an investigative attempt to study the nucleophilic properties of 1-methyl-2-arylethylhydroxylamine, an equimolar amount of a hydroxylamine substrate and nitrostyrene were ground together at room temperature. The expected products, a secondary hydroxylamine or one of its dehydrated imines, were not encountered but rather the nitrone formation was observed (Scheme 3.5).[118] This was explained through a tandem addition-elimination sequence with a nitroethane anion leaving group stabilized by the nitro electon-withdrawing capacity. Though the same products can be formed in similar yields in shorter time with the respective aldehydes, this study demonstrated the nucleophilicity of hydroxylamines in solvent-free conditions.

[118] Amutha, C.; Muthusubramanian, S. *Synthesis* **2008**, 328

Scheme 3.5: Unexpected nitrone product upon combining hydroxylamine and styrene



In summary, we have discussed the utility of nitrones in synthesis and described common techniques to form them. Unfortunately, current literature significantly lacks applications of ketonitrones and this void can likely be attributed to the scarcity of processes to produce them efficiently. If ketonitrone-forming methods can be improved, perhaps we will see an increase in their application to more complex molecules. It is with this interest that the Beauchemin lab began to examine the intermolecular Cope-type hydroamination strategy as a means to construct ketonitrones.

3.4 Ketonitrone formation via Cope-type hydroamination of allenes with N-alkylhydroxylamines[119]

As previously discussed (Section 1.2.3.3), the addition of amines to allenes has been a subject of interest and can produce either imines or allylamines depending on the regioselectivity of the reaction. None of the previous work, however, generated

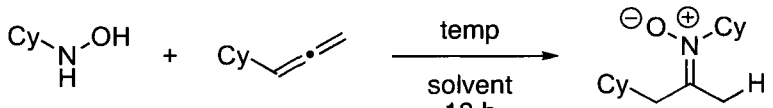
[119] Dr. Joseph Moran conducted portions of the work presented in this section and this is noted where possible.

ketonitrone products. Furthermore, most of the work on nitrones focused on aldonitrones due to their relative ease of formation from the condensation of aldehydes with hydroxylamines. Herein we report an atom-efficient preparation of ketonitrones through the intermolecular Cope-type hydroamination of *N*-alkylhydroxylamines with allenes.[79a]

3.4.1 Results and discussion

Upon exposure of cyclohexylallene to cyclohexylhydroxylamine under reaction conditions previously used to add *N*-alkylhydroxylamines to strained alkenes,[55,56] an acceptable level of product was observed by ^{1}H NMR conversion (Table 3.6, Entry 3). After observing positive results, optimization of the reaction ensued (Table 3.6). As in the synthesis of (±)-pumiliotoxin C, the solvent systems frequently used in Cope-type cyclizations, benzene and chloroform, were tried (Entries 1 and 2). These solvents did not give improved results thus other protic solvents were examined (Entries 4 and 5). Although there was no significant improvement with regards to conversion, the decomposition of the starting hydroxylamine appeared to be minimized in *tert*-butanol. Selecting *tert*-butanol as solvent, other reaction conditions were manipulated (Entries 6, 7 and 9), culminating in increased temperature and 0.5 M concentration. With only one equivalent of allene used (Entry 8) the reaction gave good conversion but less than in the optimized conditions.

Table 3.6: Optimization of allene hydroamination with *N*-alkylhydroxylamines



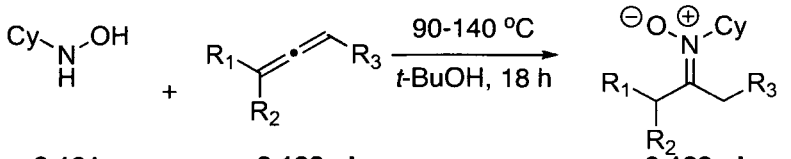
3.131a **3.132a** **3.133a**

Entry	Solvent	Temp (°C)	Concentration (M)	NMR yield (%)[b]
1	C_6H_6	110	0.50	62
2	$CHCl_3$	110	0.50	63
3	*n*-PrOH	110	0.50	62
4	*i*-PrOH	110	0.50	~65
5	*t*-BuOH	110	0.50	61
6	*t*-BuOH	140	0.25	65
7	*t*-BuOH	140	0.50	91
8	*t*-BuOH	140	0.50	67[c]
9	*t*-BuOH	140	1.0	75

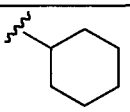
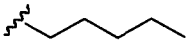
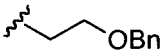
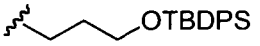
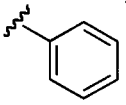
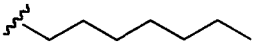
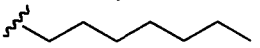
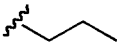
[a] Conditions: 2 equiv allene, 1 equiv hydroxylamine, sealed tube, 18 h
[b] NMR yields determined using 1,4-dimethoxybenzene as an internal standard
[c] Only 1 equivalent allene used

Once the optimized reaction conditions were identified, the applicability of the reaction of a variety of allenes was explored (Table 3.7). The reaction worked well with an assortment of alkyl-substituted allenes including those containing benzyl- and silyl-protected alcohols. Aryl-allenes proved to be more reactive and thus more challenging to control. The reaction provided one regioisomer, with the nitrogen exclusively attacking the central carbon, and the products were easily purified by silica gel chromatography. Regrettably, neither 1,3- nor geminally-disubstituted allenes provide sufficient reactivity although this is a common shortcoming in allene literature.

Table 3.7: Reaction scope of cyclohexylhydroxylamine and allenes



3.131a **3.132a-h** **3.133a-h**

Entry	R_1	R_2	R_3	Conversion[b] (%)	Yield[c] (%)
1	 **3.132a, 3.133a**	H	H	91	91
2	 **3.132b, 3.133b**	H	H	85	81
3	 **3.132c, 3.133c**	H	H	81	75
4	 **3.132d, 3.133d**	H	H	85	73
5	 **3.132e, 3.133e**	H	H	52	40[d]
6	 **3.132f, 3.133f**	*i*-Pr	H	n.r.	-
7	 **3.132g, 3.133g**	*n*-Pr	H	n.r.	-
8	 **3.132h, 3.133h**	H	*n*-Pr	n.r.	-

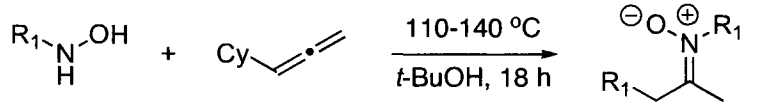
[a] Conditions: 2 equiv allene, 1 equiv hydroxylamine, *t*-BuOH (0.5 M), 140 °C, sealed tube, 18 h
[b] NMR yields determined using 1,4-dimethoxybenzene as an internal standard
[c] Isolated yield after column chromatography
[d] Heated to 90 °C

Finally, the scope of hydroxylamine substitution was investigated and a variety of *N*-alkylhydroxylamines worked reasonably well in the reaction system (Table 3.8). Linear alkyl groups were tolerated whereas they had previously decomposed under the

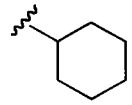
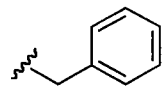
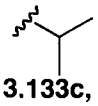
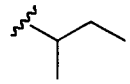
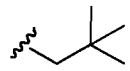
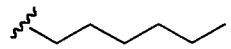
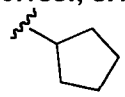
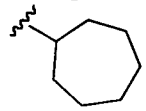
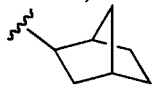
conditions developed for alkene hydroamination.[120] Branched and bulky alkyl substituents, such as neopentyl and *sec*-butyl, also performed well affording the respective ketonitrones. Additionally, cyclic and bicyclic *N*-alkylhydroxylamines afforded moderate to good yields.

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

Table 3.8: Scope of *N*-alkylhydroxylamine hydroamination with cyclohexylallene[121]



3.131a-i **3.132a** **3.133a, 3.134b-i**

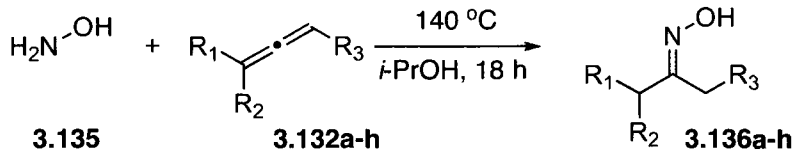
Entry	R_1	Conversion[b] (%)	Yield[c] (%)
1	 **3.133a, 3.133a**	91	91
2	 **3.133b, 3.134b**	80	81
3	 **3.133c, 3.134c**	n.d.[d]	63[e]
4	 **3.133d, 3.134d**	51	49
5	 **3.133e, 3.134e**	n.d.[c]	47
6	 **3.133f, 3.134f**	54	51
7	 **3.133g, 3.134g**	62	58
8	 **3.133h, 3.134h**	n.d.[c]	71
9	 **3.133i, 3.134i**	40	38

[a] Conditions: 2 equiv allene, 1 equiv hydroxylamine, *t*-BuOH (0.5 M), 140 °C, sealed tube, 18 h
[b] NMR yields determined using 1,4-dimethoxybenzene as an internal standard
[c] Isolated yield after column chromatography
[d] Not determined due to overlapping peak in ^{1}H NMR
[e] Heated to 110 °C

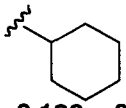
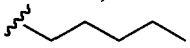
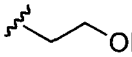
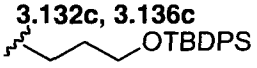
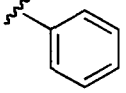
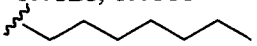
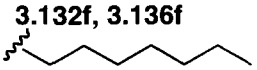
[121] The majority of the work for this table was performed by Dr. Joseph Moran

The reaction of allenes with aqueous hydroxylamine (NH_2OH) was then attempted using conditions optimized for the addition of NH_2OH on alkenes. The reaction time, temperature, and reaction scope was similar to that observed with *N*-alkylhydroxylamines, however 1,3- and geminally-disubstituted allenes reacted, albeit poorly. The augmented yields were probably due to the better thermal stability of aqueous hydroxylamine.

Table 3.9: Reactivity of allenes with aqueous hydroxylamine[a]



3.135 **3.132a-h** **3.136a-h**

Entry	R_1	R_2	R_3	Yield[b] (%)
1	 **3.132a, 3.136a**	H	H	75
2	 **3.132b, 3.136b**	H	H	93
3	 **3.132c, 3.136c**	H	H	99
4	 **3.132d, 3.136d**	H	H	88
5	 **3.132e, 3.136e**	H	H	71
6	 **3.132f, 3.136f**	*i*-Pr	H	n.r.
7	 **3.132g, 3.136g**	*n*-Pr	H	21[c]
8	 **3.132h, 3.136h**	H	*n*-Pr	13

[a] Conditions: 1 equiv allene (2.5 M), 2 equiv aq. NH_2OH, *i*-PrOH (0.5 M), 140 °C
[b] Isolated yield after column chromatography
[c] Heated in the microwave

3.4.2 Density functional theory analysis of Cope-type hydroamination of allenes

In order to obtain further details on our intermolecular hydroamination of allenes, density functional theory (DFT) calculations were performed by Dr. Serge I. Gorelsky on its transition states structures and energies (Figure 3.2).

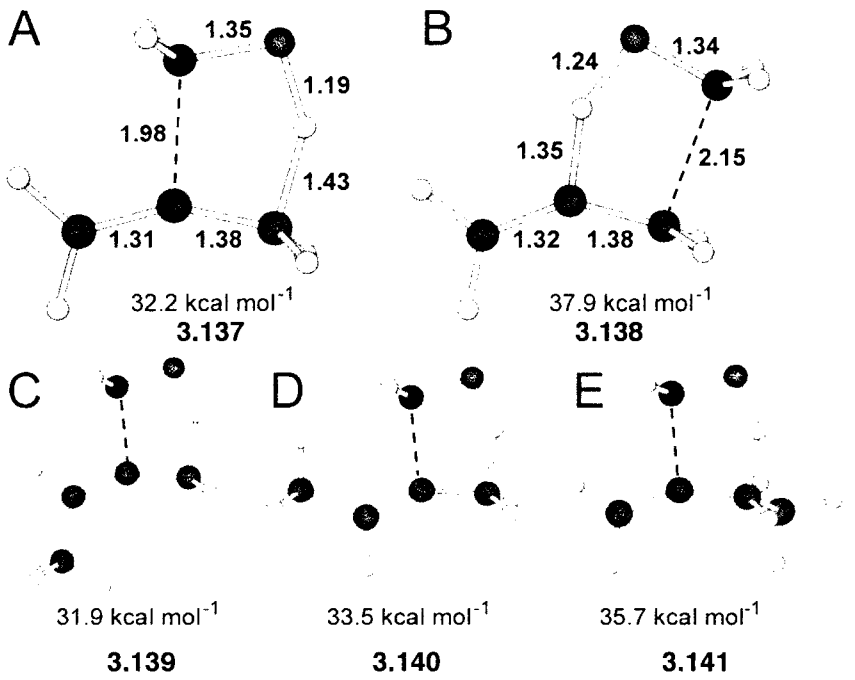
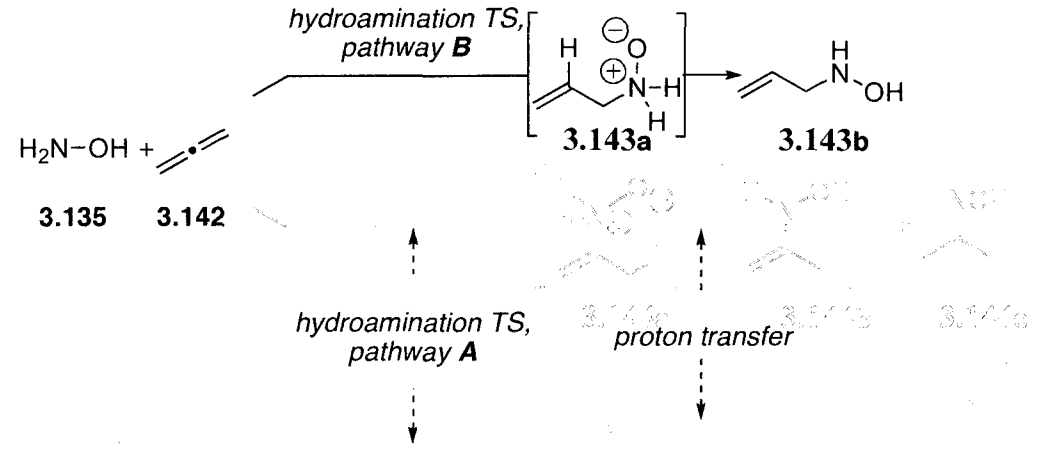


Figure 3.2: Transition state structures for the Cope-type hydroamination of hydroxylamine with allene (A, B) and methylallene (C, D, E). The internuclear distances (Å) are only shown for relevant chemical bonds

According to the B3LYP/TZVP level of theory, the concerted hydroamination reaction undergoes a five-membered coplanar transition state whereby the amination is favoured on the central carbon of the allene by 5.7 kcal/mol (A versus B). The addition of the hydroxylamine to the terminal π-bond in either isomeric form of methylallene (31.9 kcal/mol for C and 33.5 kcal/mol for D) was more favoured than the addition to the internal π-bond (35.7 kcal/mol for E). These calculations explain the lack of reactivity

observed with geminally disubstituted allenes. Due to A(1,3) interactions developing in the terminal transition state between the alkyl groups on the allene and hydroxylamine, the reaction is less favoured to occur. Calculations of the potential energy surface are consistent with the product distribution being controlled kinetically (Figure 3.3).



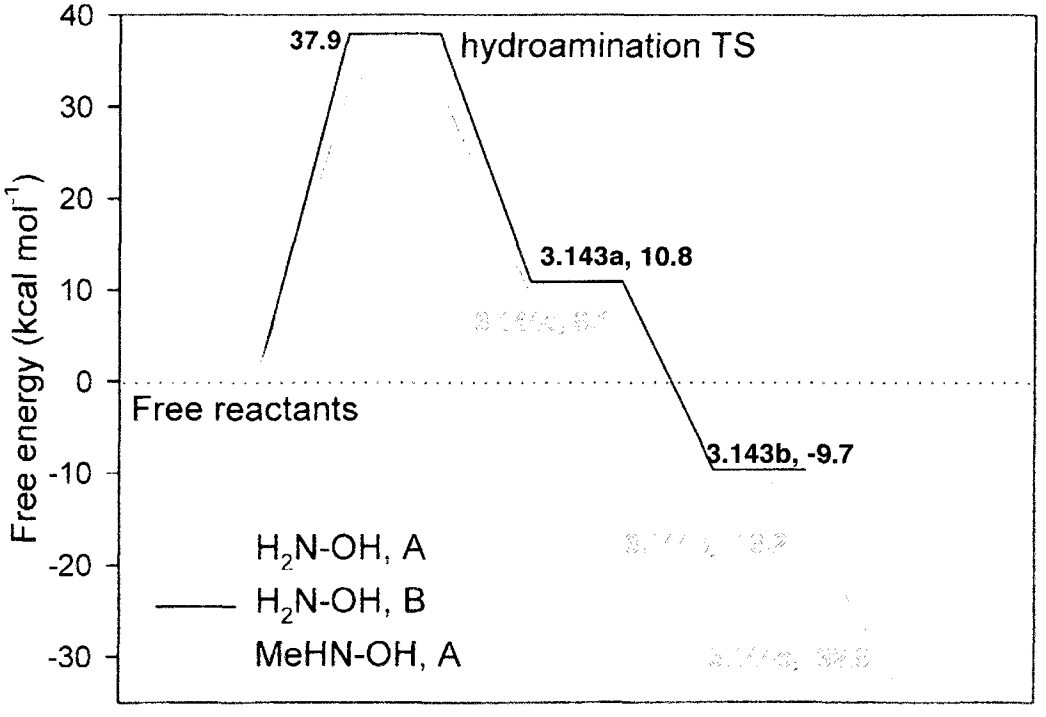


Figure 3.3: Gibbs free energy (in kcal/mol, 298 K, 1 atm) profiles for the Cope-type hydroamination of allenes using NH2OH (A and B) and MeNHOH (A). Pathways A

and B correspond to amination of the central and terminal carbons of allene respectively

3.5 Cope-type hydroamination of alkynes with N-alkylhydroxylamines

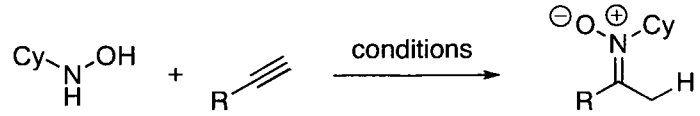
Previous research in the Beauchemin lab investigated the reactivity of alkynes and aqueous hydroxylamine to form oximes.[55,56] Based on the success of this transformation, the prospect of forming ketonitrones via the Cope-type hydroamination of alkynes with *N*-alkylhydroxylamines was explored.[122]

3.5.1 Results and discussion

Some of the prior optimization work performed by Marija Antonic is summarized below (Table 3.10). Using similar conditions developed for the alkene hydroamination as a starting point, usual reaction manipulations were performed but with little improvement. Upon examination of the ^{1}H NMR conversions, *tert*-butanol again seemed to minimize hydroxylamine decomposition and was selected for further reactions.

[122] In addition to the work presented in this thesis, Ms. Marija Antonic and Ms. Catherine Séguin both spent four months trying to optimize this reaction, as well as efforts by Dr. Joseph Moran.

Table 3.10: Prior optimization performed in the Beauchemin lab[123]



3.131a **3.147** **3.148**

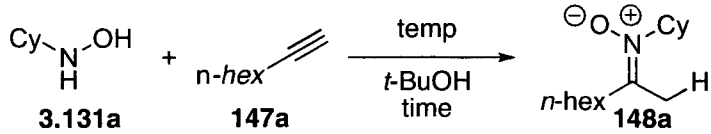
Entry	Solvent	Temp (°C)	Equiv. Alkyne	Concentration (M)	Time (hr)	NMR yield (%)[a]
1	THF	110	5	0.12	16	28
2	Benzene	110	5	0.12	16	44
3	*i*-PrOH	110	5	0.12	16	53
4	*t*-BuOH	110	5	0.12	16	56
5	*n*-PrOH	110	5	0.12	16	43
6	*n*-PrOH	110	15	0.4	16	50
7	*n*-PrOH	110	2	0.4	16	36
8	*n*-PrOH	110	1	0.4	16	28
9	*n*-PrOH	110	5	0.4	16	46
10	*n*-PrOH	110	5	2.0	16	33
11	*n*-PrOH	110	5	1.0	16	35
12	*n*-PrOH	110	5	0.4	72	46
13	*n*-PrOH	95	1	0.4	16	20
14	*n*-PrOH	125	1	0.4	16	29

[a] NMR yields determined using 1,4-dimethoxybenzene as an internal standard

After selecting *tert*-butanol as a solvent, the reaction was further investigated with regards to ratio of alkyne to hydroxylamine, temperature, time, the addition of sodium cyanoborohydride, and microwave reactivity (Table 3.11). The reactions were performed on a 0.867 mmol scale but were then observed to be scale-dependent. The conditions were all repeated on a 1.3 mmol scale. More concentrated conditions decreased the observed yield. The best condition gave a modest 48% conversion to the Markovnikov product (Entry 16) and was selected for the substrate scope.

[123] The work in this table was performed by Ms. Marija Antonic

Table 3.11: Optimization performed on alkyne hydroamination reactivity



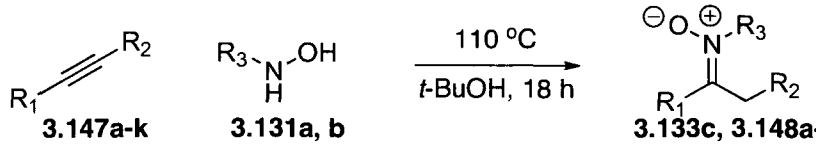
3.131a 147a 148a

Entry	Scale	Temp (°C)	Equiv. Alkyne	Concentration (M)	Time (hr)	Note	NMR yield (%)[a]
1	0.867	110	5	0.5	4	μW	16% Mark
2	0.867	140	5	0.5	1		22% Mark
3	0.867	110	2.5	0.5	18	$NaBH_3CN$	32% Mark
4	0.867	110	2.5	0.5	18		35% Mark
5	0.867	110	5	0.5	18		32% Mark
6	0.867	110	5	0.5	24		22% Mark
7	0.867	140	5	0.5	3		7% Mark
8	0.867	140	5	0.5	6		12% Mark
9	1.734	110	5	0.5	18		43% Mark
10	1.3	110	2.5	0.5	18	$NaBH_3CN$	38% Mark
11	1.3	110	2.5	0.5	18		41% Mark
12	1.3	140	5	0.5	1		<43% Mark
13	1.3	140	5	0.5	3		30% Mark
14	1.3	140	5	0.5	6		35% Mark
15	1.3	110	5	0.5	4	μW	21% Mark
16	1.3	110	5	0.5	18		48% Mark
17	1.3	110	5	0.5	24		20% Mark
18	1.3	110	5	0.5	42		33% Mark
19	1.3	110	5	1.0	18		6% Mark

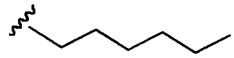
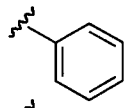
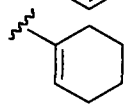
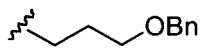
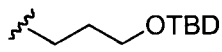
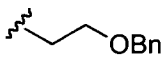
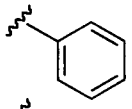
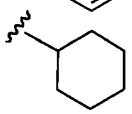
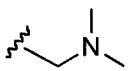
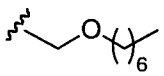
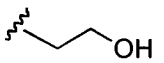
[a] NMR yields determined using 1,4-dimethoxybenzene as an internal standard

The optimized reaction conditions were employed and a variety of acetylene substrates were explored. A mixture of Markovnikov and anti-Markovnikov addition was observed, giving a combination of keto- and aldonitrone products. Unfortunately, aldonitrones are known to be more reactive and less stable on silica gel than ketonitrones and therefore was only characterized for one substrate. Both benzyl and silyl protecting groups were tolerated under the reaction conditions. A 1,2- and 1,1-disubstituted alkyne, diphenylacetylene and cyclohexylacetylene, showed limited reactivity. Unfortunately, substrates with a β–heteroatom or free alcohol did not react as desired.

Table 3.12: Substrate scope for Cope-type hydroamination of alkynes with *N*-alkylhydroxylamine

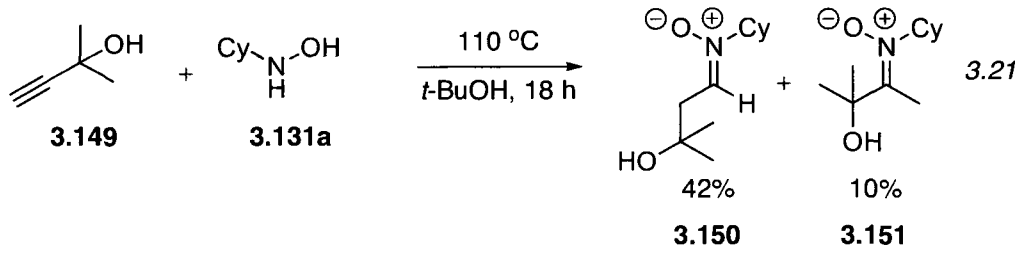


3.147a-k **3.131a, b** **3.133c, 3.148a-l**

Entry	R_1	R_2	R_3	Conversion[b] (%)	Yield[c] (%)
1	 **3.147a**	H	Cy **3.148a**	47% Mark 13% Anti-Mark	47% Mark 13% Anti-Mark
2		H	Bn **3.148b**	22% Mark	5% Mark[c]
3	 **3.147b**	H	Cy **3.148c**	44% Mark	44% Mark
4	 **3.147c**	H	Cy **3.148d**	35% Mark 10% Anti-Mark	18% Mark
5	 **3.147d**	H	Cy **3.133c**	60% Mark 5% Anti-Mark	50% Mark
6		H	Bn **3.148e**	46% Mark	6% Mark[d]
7	 **3.147e**	H	Cy **3.148f**	65% Mark 6% Anti-Mark	57% Mark
8	 **3.147f**	H	Cy **3.148g**	44% Mark	44% Mark
9	 **3.147g**	Ph	Cy **3.148h**	17%	15%
10	 **3.147h**	H	Cy **3.148i**	< 25%	n.d.
11	 **3.147i**	H	Cy **3.148j**	14%	n.d.
12	 **3.147j**	H	Cy **3.148k**	0%	-
13	 **3.147k**	H	Cy **3.148l**	0%	-

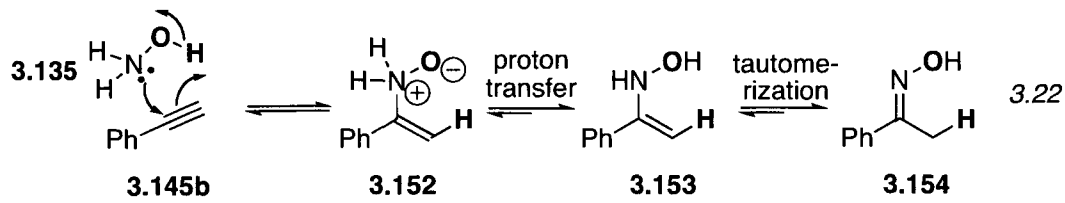
[a] Conditions: 5 equiv alkyne, 1 equiv hydroxylamine, *t*-BuOH (0.5 M), 110 °C, sealed tube, 18 h
[b] NMR yields determined using 1,4-dimethoxybenzene as an internal standard
[c] Isolated yield after column chromatography
[d] Substrates decomposed into starting material upon exposure to silica gel
n.d. = not determined

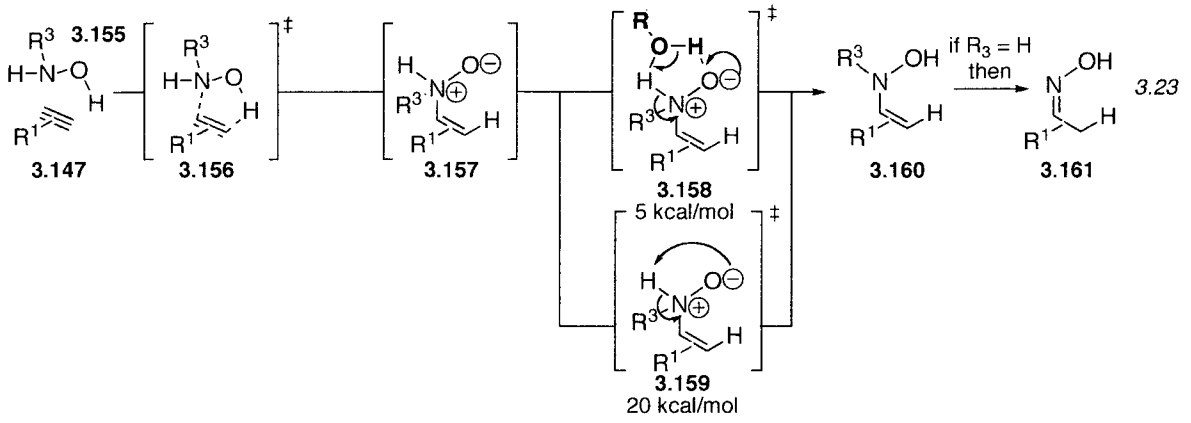
Sterically-bulky acetylenes reversed the regioselectivity of the transformation by producing aldonitrones as opposed to ketonitrones. This reactivity was specifically observed with 2-methylbut-3-yne-2-ol where the Anti-Markovnikov product was isolated in 7% yield although by ^{1}H NMR, the regioisomer was present in 42% conversion (Equation 3.21).



3.5.2 Density functional theory analysis of Cope-type hydroamination of alkynes

In order to better understand the reactivity of alkynes and the mixture of regioisomers obtained, density functional theory (DFT) calculations were examined for the reaction of phenylacetylene and hydroxylamine (NH_2OH) (Equation 3.22). The relative energies of the starting materials, transition states, intermediates, and products for both the Markovnikov and Anti-Markovnikov addition were calculated in the gas phase according to the B3LYP/TZVP level of theory (298K and 1 atm). Additional calculations were performed for both the inter- and intramolecular proton transfer step (Equation 3.23). The potential energy diagram for the reaction of phenylacetylene with hydroxylamine is shown in Figure 3.4.





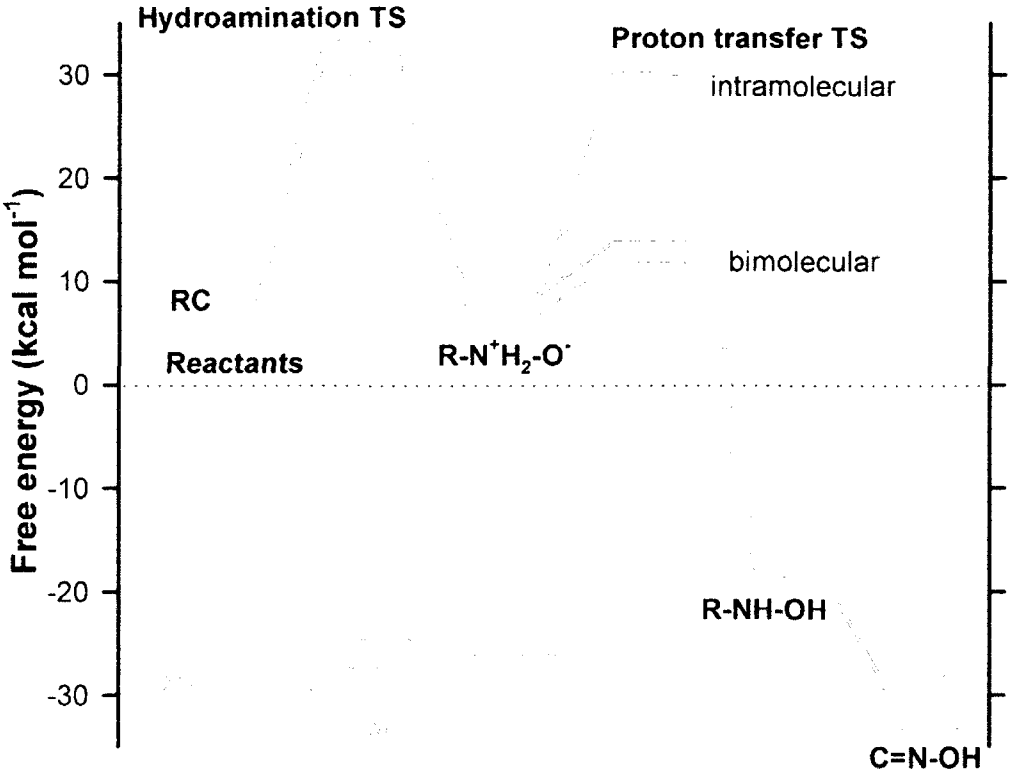


Figure 3.4: Free energy for hydroamination of phenylacetylene at the B3LYP/TZVP level of theory

As can be seen, the Markovnikov oxime is the kinetic product, though it was the only one observed in the specified reaction. This indicates that the reaction of phenylacetylene and aqueous hydroxylamine is under kinetic control.

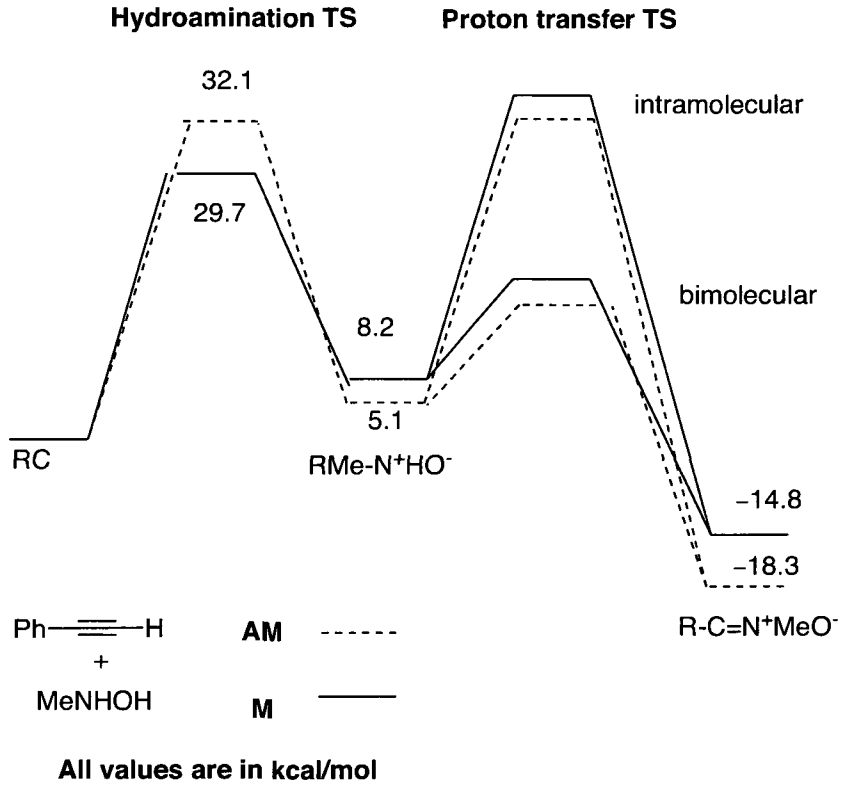
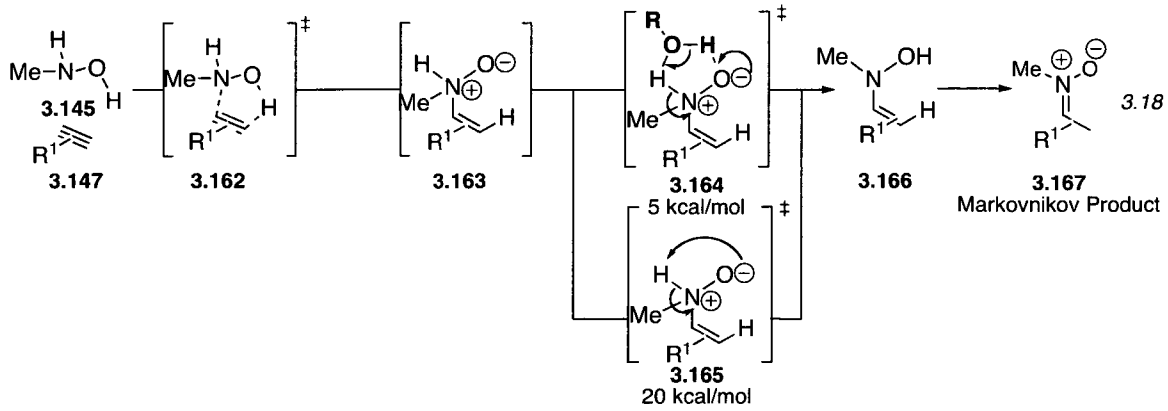
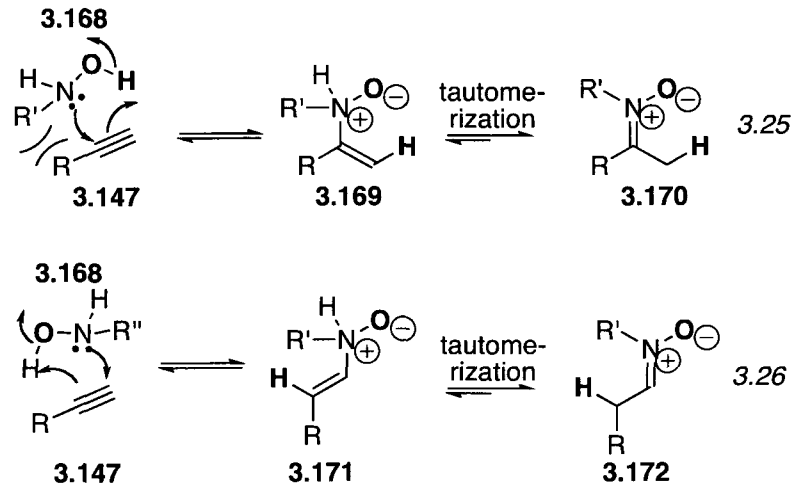


Figure 3.5: Free energy for hydroamination of phenylacetylene and methylhydroxylamine at the B3LYP/TZVP level of theory



Upon use of an *N*-alkylhydroxylamine, on the other hand, a mixture of both Markovnikov and anti-Markovnikov products were observed in most cases (Table 3.12). As can be seen from Figure 3.5, the addition of methylhydroxylamine to phenylacetylene in a Markovnikov manner is still the kinetic product (Equation 3.24). This figure assumes the

same difference between the inter- and intramolecular proton transfer step calculated in previous systems. Upon experimentation with bulkier hydroxylamines and alkynes, the isomer ratio became mixed between the keto- and aldonitrones. This suggests that the bulky substituents could raise the energy of the Markovnikov hydroamination step, bringing it closer to that of the anti-Markovnikov addition and induce competition (Equation 3.25, Equation 3.26). The results from the hydroamination of alkyne **3.147d** (Table 3.12, Entry 5) and those from alkyne **3.149** (Equation 3.21) can be compared to illustrate this phenomenon. The less bulky substrate, **3.147d**, provided 60% of the Markovnikov ketonitrone and only 5% of the anti-Markovnikov product whereas the bulky **3.149** substrate provided the anti-Markovnikov aldonitrone as the major product. The increased steric bulk around the reaction site of this substrate could cause the Markovnikov pathway's energy barrier to be elevated and become less favourable than that of the anti-Markovnikov. The decreased efficiency of the reaction is testament to the difficulty of the reaction and the possibility of side reactions. Importantly, as with the reaction of alkynes with hydroxylamine, the absence of a proton shuttle causes the activation energy of the proton transfer step to be high and kinetically relevant.



3.6 *Ketonitrone formation via the condensation of ketones and N-alkylhydroxylamines*

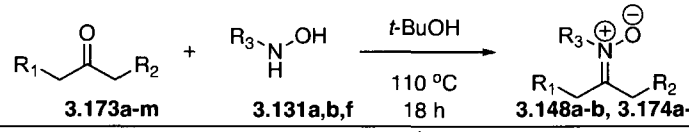
As detailed in Section 3.3.2, the preparation of ketonitrones via the simple condensation of ketones and *N*-alkylhydroxylamines is far more limited than their aldonitrone cousins due to the scarcity of reports in the literature. This paucity can be attributed to the less reactive properties of ketones with respect to aldehydes, thus requiring heat in the transformations. The nature of hydroxylamines, though, does not lend itself to these reaction requirements because of their tendency to decompose upon heating in common organic solvents.[77] Under the condition used in our recent work on Cope-type hydroamination of allenes (Section 3.4) and alkynes (Section 3.5), we observed an increased thermal stability of the hydroxylamines. If these reaction conditions could be applied to the condensation of ketones and *N*-alkylhydroxylamines, and the thermal stability of the hydroxylamines continue, we could explore the increased scope of this direct and convenient approach to ketonitrone formation.

3.6.1 Results and discussion

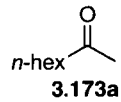
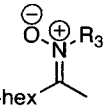
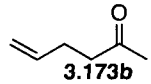
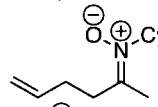
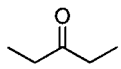
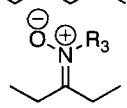
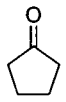
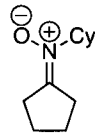
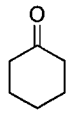
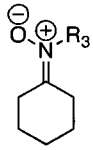
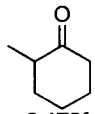
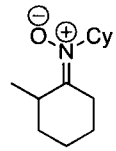
Gratifyingly, exposure of 2-octanone to cyclohexylhydroxylamine under the previously optimized reaction conditions afforded the corresponding nitrone in 81% yield. Reactions were performed using the more sensitive *n*-hexylhydroxylamine and benzylhydroxylamine to determine the applicability of the reaction. Fortunately, both hydroxylamines provided the nitrones in good yield. As Table 3.13 illustrates, the condition were amenable to a variety of ketones with both acyclic, and cyclic hydroxylamines. The reaction did show some incompletion with acyclic non-methyl ketones (Entries 5 and 6). Interestingly, α,β-unsaturated ketones reacted exclusively in a

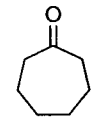
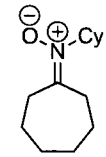
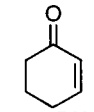
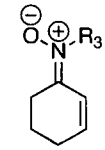
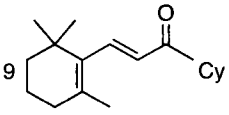
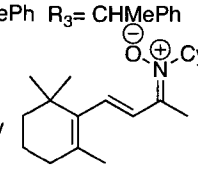
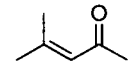
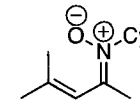
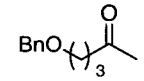
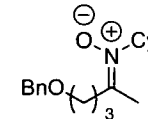
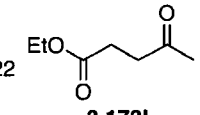
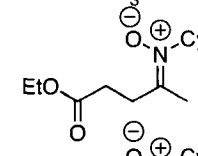
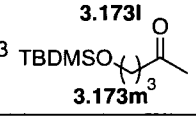
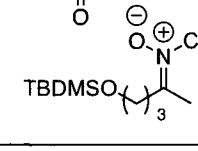
1,2-manner (Entries 15 through 20) which is complementary to previous work done by Zhao where 1,4-addition is observed.[53] Unfortunately, esters, benzyl- and silyl-ethers (Entries 21 through 23) did not perform as well as anticipated but still showed some stability in the reaction medium.

Table 3.13: Scope of ketone condensation with *N*-alkylhydroxylamines



3.173a-m + 3.131a,b,f → 3.148a-b, 3.174a-u

Entry	Ketone	R_3	Product	NMR[a]/Yield[b] (%)
	 3.173a			
1	"	Cy	R_3= Cy	**3.148a** 85/89
2	"	Bn	R_3= Bn	**3.148b** 90/82
3	"	*n*-hex	R_3= *n*-hex	**3.174a** 79/70
4	 3.173b	Cy		**3.174b** 65/60
				
5[d]	"	Cy	R_3= Cy	**3.174c** 59/41
6[d]	" 3.173c	Bn	R_3= Bn	**3.174d** 71/71
7	 3.173d	Cy		**3.174e** 99/83
	 3.173e			
8	"	Cy	R_3= Cy	**3.174f** 99/94
9	"	Bn	R_3= Bn	**3.174g** 81/61
10	"	*n*-hex	R_3= *n*-hex	**3.174h** 78/78
11	"	*c*-C_5H_9	R_3= *c*-C_5H_9	**3.174i** 91/82
12	"	*c*-C_7H_{13}	R_3= *c*-C_7H_{13}	**3.174j** 88/88
13	 3.173f	Cy		**3.174k** 36/26

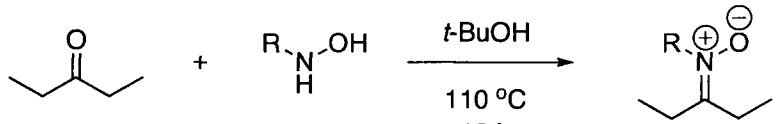
Entry	Ketone	R_3	Product	NMR[b]/Yield[c] (%)
14	 3.173g	Cy		**3.174l** 95/83
	 3.173h			
15	"	Cy	R_3= Cy	**3.174m** 99/91
16	"	Bn	R_3= Bn	**3.174n** 71/71
17	"	*n*-hex	R_3= *n*-hex	**3.174o** 70/63
18	"	CHMePh	R_3= CHMePh	**3.174p** 84/63
19	 3.173i	Cy		**3.174q** 89/80
20	 3.173j			**3.174r** 53/44
21	 3.173k			**3.174s** n.d./37
22	 3.173l			**3.174t** ~41/25
23	 3.173m			**3.174u** 40/37

[a] Conditions: 2 equiv ketone, 1 equiv hydroxylamine, *t*-BuOH (0.5 M), 110 °C, sealed tube, 18 h
[b] NMR yields determined using 1,4-dimethoxybenzene as an internal standard
[c] Isolated yield after column chromatography
[d] Use of 5 equiv of ketone instead of 2
n.d. = not determined

Conditions for reaction of 3-pentanone, a non-methyl ketone, were manipulated to improve reaction outcome (Table 3.14). The addition of five equivalents of either benzyl- or cyclohexylhydroxylamine improved the yield of the corresponding ketonitrone. Of

interest was the intuitive heating of the reaction, to temperatures required in the allene chemistry, provided decomposition or a decreased yield of product. Leaving the reaction for extended periods of time improved the reaction to the same extent as a large excess ketone.

Table 3.14: Optimization of reaction with 3-pentanone



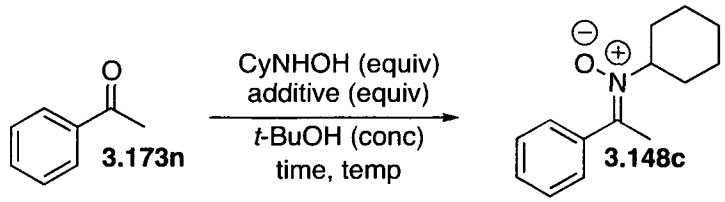
3.173c **3.131a-b** **3.174c-d**

Entry	Equiv Ketone	Temp (°C)	Time	R	NMR yield (%)[a]
1	2	110	18	Cy	46
2	5	110	18	Cy	59
3	2	110	38	Cy	58
4	2	140	18	Cy	-
5	5	140	18	Cy	44
6	2	110	18	Bn	60
7	5	110	18	Bn	71

[a] NMR yields determined using 1,4-dimethoxybenzene as an internal standard

Although various cyclic and acyclic alkyl ketones reacted well under the reaction conditions, acetophenone did not yield any product under the reaction conditions. Due to the water by-product, a variety of dessicants and conditions were explored to induce favourable thermodynamics (Table 3.15). Indeed, the use of magnesium sulfate in more concentrated reaction conditions allowed the *N*-benzyl ketonitrone to be attained. The stark contrast between the results obtained with magnesium sulfate versus other dessicants suggests that the salt is playing a dual role, perhaps both as a dessicant and as a Lewis acid.

Table 3.15: Effect of additives on the condensation of *N*-cyclohexylhydroxylamine with acetophenone

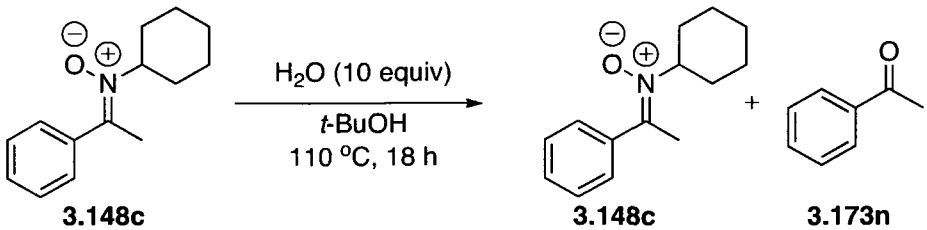


Entry	Equiv ketone	Equiv CyNHOH	Temp (°C)	Concentration (M)	Time (h)	Additive	Equiv	NMR yield (%)[a]
1	2	1	110	0.50	18	-	-	0
2	2	1	110	0.50	18	MS 4Å	150 mg	0
3	2	1	110	0.50	18	$MgSO_4$	1	15
4	2	1	140	0.50	18	$MgSO_4$	1	26
5	1	2	110	0.50	18	$MgSO_4$	1	19
6	2	1	110	1.0	18	$MgSO_4$	1	33
7	2	1	75	1.0	18	$MgSO_4$	1	10
8	2	1	110	1.0	18	BaO	1	14
9	2	1	110	1.0	18	$CaCl_2$	1	6
10	2	1	110	1.0	18	K_2CO_3	1	3
11	2	1	110	1.0	18	Na_2SO_4	1	9
12	2	1	110	2.0	18	$MgSO_4$	1	41
13	2	1	110	2.0	18	$MgSO_4$	0.5	29
14	2	1	110	2.0	18	$MgSO_4$	2	42
15	2	1	110	0.5	18	$MgSO_4$	5	30
16	2	1	110	1.0	54	$MgSO_4$	1	33
17	2	1	110	2.0	54	$MgSO_4$	1	34

[a] NMR yields determined using 1,4-dimethoxybenzene as an internal standard

These results led us to investigate the position of the equilibrium in this reaction. We had previously noted the improvement in yield obtained by adding excess ketone, driving the reaction towards the product according to LeChatelier's principle. The hydrolysis of ketonitrone **3.148c** in the presence of water under similar reaction procedures indicated that the condensation of ketonitrones was close to thermoneutrality (Equation 3.27). The position of the equilibrium could depend on the stability of the ketone and steric interactions within the product. In the seminal work on the condensation of ketones and hydroxylamines, dialkylketals can be used instead of ketones to drive the reaction

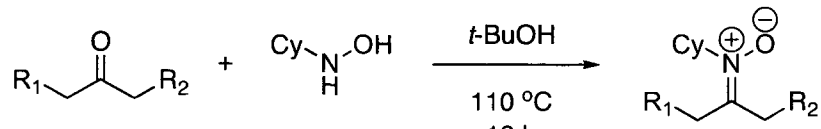
forward.[111] The favourable entropy in using these replacements can move the equilibrium toward product formation.



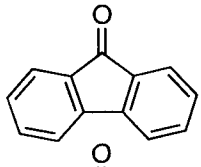
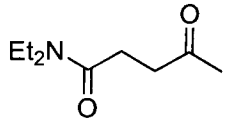
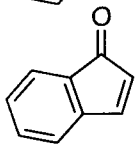
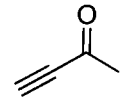
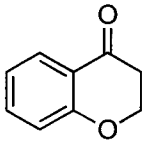
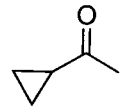
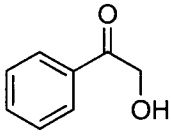
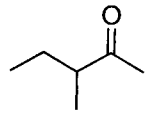
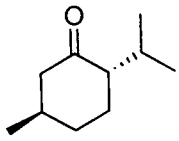
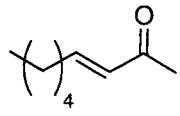
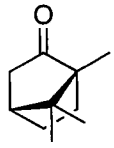
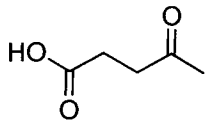
3.148c → **3.148c** (65%) + **3.173n** (31%)

Unfortunately, not all substrates were successful in the reaction conditions (Table 3.16). Indanone gave acceptable results but fluorenone, chromanone, (−)-menthone, and camphor did not work. Free carboxylic acid groups and amides were not tolerated. Sterically bulky ketones did react but with meager results.

Table 3.16: Substrates with limited or no success



3.173o 3.175

Entry	Ketone	Conversion[a] /Yield[b] (%)	Entry	Ketone	Conversion[b] /Yield[c] (%)
1	 **3.173o** -		8	 **3.173v**	-
2	 **3.173p** 45/43 **3.175a**		9	 **3.173w**	-
3	 **3.173q** -		10	 **3.173x**	18/n.d.
4	 **3.173r** -		11	 **3.173y**	39/n.d.
5	 **3.173s** -		12	 **3.173z**	36/n.d.
6	 **3.173t** -				
7	 **3.173u** -				

[a] Conditions: 2 equiv ketone, 1 equiv hydroxylamine, *t*-BuOH (0.5 M), 110 °C, sealed tube, 18 h
[b] NMR yields determined using 1,4-dimethoxybenzene as an internal standard
[c] Isolated yield after column chromatography
n.d. not determined

3.7 Conclusion

Over the course of this chapter we have seen multiple strategies to prepare nitrones and our investigations have developed two new methods to form ketonitrones via the intermolecular Cope-type hydroamination of allenes and alkynes respectively. By performing the developed methodology on allenes we were able to synthesize thirteen products from the intermolecular Cope-type hydroamination of allenes with yields ranging from 38 to 91%. We also explored the intermolecular Cope-type hydroamination of alkynes with *N*-alkylhydroxylamines in an attempt to discover more accessible methods to prepare ketonitrones. Regrettably, reactivity was not as we anticipated and the scope of the transformation was more limited. Nevertheless we were able to synthesize nine different ketonitrones and one aldonitrone with yields ranging from 5% to 57%.

Finally, the examination of ketonitrone formation via condensation strategies led to improved conditions for Schiff base chemistry to be elucidated. The application of our conditions to this condensation was successful and we were able to synthesize a wide array of ketonitrones using commercially available, or easily prepared, material. We were able to synthesize twenty-five different ketonitrones via the simple condensation of ketones with *N*-alkylhydroxylamines in yields ranging from 25% to 94%. This reactivity clearly demonstrates the increased thermal stability of the alkylhydroxylamines in these conditions.

Thus we have demonstrated the viability of Cope-type hydroamination in synthetically useful transformations in addition to using our knowledge of hydroxylamines and nitrones to enrich the literature with a simple, direct method to form ketonitrones.

4 General Conclusions

4.1 General conclusions

Pumiliotoxin C attracted our interest as a natural product to which the Cope-type hydroamination techniques could be applied due to its six-membered nitrogen-containing ring. A previous graduate student in the laboratory, Marie-Eve Lebrun, had completed its synthesis by means of this methodology and the second chapter of this thesis described the modifications performed to shorten her synthesis where possible. This led to a revised, more reliable synthetic strategy towards the natural product. Attempts to obtain the natural product in higher yields did not prove to be successful and DFT calculations demonstrated that the system undergoes a boat-like transition state whereby the *epi*-product is the more favoured product.

New synthetic methodology projects were also investigated and atom-economical techniques to form ketonitrones were explored in the third chapter. The hydroamination of allenes with both aqueous and alkyl hydroxylamines was investigated. We achieved oxime formation in yields ranging from 13 to 99% and ketonitrones from 38 to 91%. We also explored the intermolecular Cope-type hydroamination of alkynes with *N*-alkylhydroxylamines in an attempt to discover more accessible methods to prepare ketonitrones. This reactivity would also be complementary to previous research performed in the lab on the hydroamination of alkynes with aqueous hydroxylamine.[55] Regrettably, the scope of the transformation was more limited. Finally, we also examined a convenient and direct approach to ketonitrone formation through the condensation of

ketones with *N*-alkylhydroxylamines. The application of our conditions to this condensation was successful and we were able to synthesize a wide array of ketonitrones using commercially available, or easily prepared, starting materials.

4.2 Contributions to research

1) Application of hydroamination methodology to the synthesis of (±)-2-*epi*-pumiliotoxin C via a key intramolecular Cope-type hydroamination step of an alkene, consisting the first intramolecular example on a non-terminal alkene forming a piperidine.

2) Methodology studies to optimize the intermolecular Cope-type hydroamination of allenes with *N*-alkylhydydroxylamines to form ketonitrones and with aqueous hydroxylamine to form oximes. A preliminary substrate scope for this reactivity was established.

3) Methodology studies to optimize a general reactivity between alkynes and *N*-alkylhydroxylamines forming ketonitrones. A limited substrate scope was performed.

4) Examination of the reactivity between ketones and *N*-alkylhydroxylamines to make ketonitrones via simple Schiff-base chemistry and investigation of scope.

4.3 Publications

3) Pfeiffer, J.Y.; Beauchemin, A.M. "Improved Reaction Conditions for the Formation of Ketonitrones from Ketones and Hydroxylamines" *J. Org. Chem.* **2009**, *Manuscript Accepted*

2) Moran, J,; Pfeiffer, J.Y.; Gorelsky, S.I.; Beauchemin, A.M. "Ketonitrones via Cope-Type Hydroamination of Allenes" *Org. Lett.* **2009**, *11*, 1895

1) Lebrun, M.E.; Pfeiffer, J.Y.; Beauchemin, A.M. "Synthesis of 2-epi-Pumiliotoxin C

Via A Challenging Intramolecular Hydroamination Key Step" *Synlett* **2009**, 1087

4.4 Presentations

4) "New Routes for the Synthesis of Ketonitrones" Pfeiffer, J.Y.; Moran, J.; Gorelsky, S.I. Beauchemin, A.M. Ottawa-Carleton Chemistry Institute (OCCI) Day (Ottawa), May 2009 (oral).

3) "Synthesis of 2-epi Pumiliotoxin C via an intramolecular alkene hydroamination key step" Lebrun, M.E.; Pfeiffer, J.Y.; Gorelsky, S.I.; Beauchemin, A.M. QOMSBOC 2008 (Toronto), November 2008 (poster). **Winner of Poster Award**.

2) "Synthesis of Pumiliotoxin C via an intramolecular alkene hydroamination key step" Lebrun, M.E.; Pfeiffer, J.Y.; Gorelsky, S.I.; Beauchemin, A.M. Synthesis Day (Ottawa), June 2008 (poster).

1) "Synthesis of Pumiliotoxin C via an intramolecular alkene hydroamination key step" Lebrun, M.E.; Pfeiffer, J.Y.; Gorelsky, S.I.; Beauchemin, A.M. Ottawa-Carleton Chemistry Institute (OCCI) Day (Ottawa), May 2008 (poster).

5 Experimental Section

5.1. General Information

All reactions were performed in flame-dried round-bottomed flasks. Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm). Caution must be taken when evaporating solvents under reduced pressure since most of the intermediates in the synthesis are volatile. 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 unless otherwise noted. Microwave reactions were run in Biotage microwave.

Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). ^{1}H NMR spectra were recorded on a Bruker Avance300 (300 MHz) or Avance400 (400 MHz) spectrometer at ambient temperature unless otherwise noted and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm, $(CD_3)_2CO$ at 2.05 ppm or CD_3OD at 3.31 ppm). 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. ^{13}C NMR spectra were recorded on a Bruker Avance300 (75 MHz) or Avance400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, C_6D_6 at 128.02 ppm, $(CD_3)_2CO$ at 30.83 ppm or CD_3OD at 49.05 ppm). 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.

Materials. Unless otherwise noted, all solvents and commercial materials were purchased from Sigma-Aldrich and used without further purification. Dichloromethane, acetonitrile and triethylamine were dried by distillation over calcium hydride. Tetrahydrofuran and diethyl ether were dried by distillation over sodium/benzophenone ketyl. Distillations for purification of reagents were done under an inert atmosphere of argon. Sodium cyanoborohydride and cyclohexylallene (**3.132a**) were purchased from Sigma-Aldrich and used without further purification. Methyllithium and *n*-butyllithium were titrated prior to use with BHT.[124] Drops of ether were added to boron trifluoride diethyl etherate before distilling it over calcium hydride. *N*-alkylhydroxylamines **3.131a-c**, **3.131e** and **3.131f** were prepared by reductive amination of the corresponding oximes according to the method of House and Lee.[45e] *N*-Alkylhydroxylamine **3.131i** was prepared according to the procedure in our earlier communication.[55] Allenes **3.132c-d** were prepared according to previous literature procedure.[125] Allene **3.132e** was prepared according to a known method.[126] Alkynes **3.147d-f** were prepared according to literature procedure and NMR data corresponded with characterization previously reported. [127,128,129] Ketones **3.173l-m** were synthesized according literature procedure[130,131]and the NMR data corresponded with characterization previously reported.[132,133]

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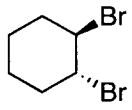
[124] Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755
[125] Yoshida, Y.; Matsuda, K.; Shoji, Y.; Gotou, T.; Ihara, M.; Shishido, K. *Org. Lett.* **2008**, *10*, 5183
[126] Chen, T.R; Anderson, M.R.; Grossman, S.; Peters, D.G. *J. Org. Chem.* **1987**, *52*, 1232
[127] Marshal, J.A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863
[128] Hall, D.G.; Deslongchamps, P. *J. Org. Chem.* **1995**, *60*, 7796
[129] Schmidt, J.; Eschgfaller, B.; Benner, S.A. *Helv. Chim. Acta* **2003**, *86*, 2937

5.2. *Experimental for Chapter 2*

5.2.1. Procedures and Characterization



(±)-(1*R,2*R**)-1,2-Dibromocyclohexane 2.48** was prepared according to literature procedure[69] except that dichloromethane was used as the solvent instead of carbon tetrachloride and that bromine was added as a 10.0 M solution in dichloromethane instead of being added neat. The purification was done following the procedure of Snyder and Brooks[69b] and the extraction suggested in the same paper in note 7 should be followed for a potentially higher yield in the next step. In a round-bottomed flask, equipped with a stirrer and fitted with an addition funnel, was added cyclohexene (12.8 g, 15.0 mL, 148 mmol) in dichloromethane (6.0 M, 25 mL). The mixture was cooled to -5 °C. A solution of bromine (24.6 g, 7.91 mL, 154 mmol, 1.03 equiv) in dichloromethane (15 mL, 10 M) was then allowed to drop in slowly from the addition funnel at such a rate that the temperature of the reaction did not rise above 0 °C. The addition required about 3 hours after which distillation yielded a light yellow liquid as the product (32.6 g, 135 mmol,

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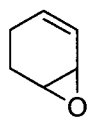
[130] Klostergaard, H. *J. Org. Chem.* **1958**, *23*, 108
[131] Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc. Perkin Trans. 1 Chem.* **1996**, *8*, 793
[132] Yasuda, M.; Nishio, M.; Shibata, I.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1994**, *59*, 486
[133] Liu, H.; Wan, S.; Floreancig, P.E. *J. Org. Chem.* **2005**, *70*, 3814

91.2% yield). Spectral ^{1}H NMR data were found to be in good agreement with those in the literature.[134]

1,3-Cyclohexadiene 2.37 which is commercially available was prepared according to literature procedure. [70,135] In a two-necked round-bottomed flask, equipped with a stirrer and fitted with an addition funnel as well as a short condenser set for distillation, was placed a mixture of lithium carbonate (5.6 g, 75 mmol, 0.56 equiv) and lithium chloride (3.5 g, 84 mmol, 0.6 equiv) in hexamethylphosphoric triamide (8.1 M, 17 mL). The mixture was heated at 160 °C under inert atmosphere for 30 min after which 1,2-dibromocyclohexane (32.6 g, 135 mmol, 1.00 equiv) was added dropwise from the addition funnel. An immediate distillation of 1,3-cyclohexadiene resulted. After the complete addition of 1,2-dibromocyclohexane, a gentle stream of argon was passed through the system which resulted in an additional small amount of distillate. The product was obtained as 6.4 g of a light yellow liquid as a 1.4 : 1 ratio of 1,3-cyclohexadiene : cyclohexene (3.7 g, 47 mmol, 35% yield).



3,4-Epoxycyclohexene 2.49 was prepared according to literature procedure.[71] To a stirring mixture of 1,3-cyclohexadiene (12.7 g, 15.1 mL, 159 mmol) and anhydrous sodium carbonate (86 g, 635 mmol, 4.0 equiv) in dichloromethane (0.900 M, 174 mL) at

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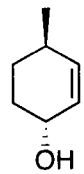
[134] Allen, G. D.; Buzzeo, M. C.; Davies, I. G.; Villagran, C.; Hardacre, C.; Compton, R. G. *J. Phys. Chem. B* **2004**, *108*, 16322

[135] Weisz, A.; Mandelbaum, A. *J. Org. Chem.* **1984**, *49*, 2648

−1 °C was added dropwise a commercially available 32% peracetic acid (12.6 g, 35.1 mL, 167 mmol, 1.05 equiv) solution in dilute acetic acid which had been pretreated with a small amount of sodium acetate. The mixture was stirred at room temperature until a negative peroxide test was obtained with starch-iodide paper. By TLC, the reaction looked done after 3 hours. The solid salts were removed by filtration and were washed well with additional solvent. Distillation through a Vigreux column permitted the separation of the solvent from the subsequent collection of the product in an ice-cold collecting flask as a light yellow liquid (7.7 g, 80 mmol, 50%). TLC R_f 0.57 (20% EtOAc:hexanes). Spectral ^{1}H NMR data was found to be in good agreement with those in the literature.[136]

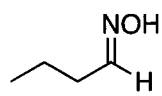


(±)-(1*S,4*S**)-4-Methylcyclohex-2-enol 2.36** was prepared according to literature procedure[68] but the copper cyanide was azeotroped with dry toluene 2mL toluene for each 100 mg copper cyanide before use in the reaction.[137] *The salt content of the starting methyllithium ether solution was said to be very important. A common ion effect seems to cause the cyanocuprate to be quite insoluble, to the extent that the reaction may not take place at all in some instances when the solutions are not salt free. The organocuprate could be lowered down to 2 equivalents without affecting the yields.* Copper cyanide (3.8 g, 42 mmol, 3.0 equiv) was gently flame dried under vacuum in the reaction flask. It was

[136] Ramesh, K.; Wolfe, M. S.; Lee, Y.; Velde, D. V.; Borchardt, R. T. *J. Org. Chem.* **1992**, *57*, 5861

[137] Taylor, R.J.K.; Casy, G. In *Organocopper Reagents: A Practical Approach*; Taylor, R.J.K., Ed; Oxford University Press: New York, 1994; Chapter 2

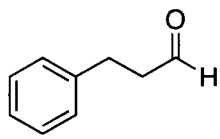
then suspended in dried ether (0.070 M, 210 mL) under inert atmosphere before being cooled to -40 °C. An equimolar amount of freshly titrated methyllithium solution (28 mL, 42 mmol, 3.0 equiv, 1.5 M in diethyl ether) was slowly added. The suspension was then stirred at the same temperature until no copper cyanide remained visible at the bottom of the light beige solution which took about 1 hour. The solution was cooled to -78 °C and an ether solution (0.40 M, 40 mL) of the 3,4-epoxycyclohexene (1.4 g, 14 mmol) was cannulated. The bright yellow mixture was allowed to slowly warm up to room temperature over 5 hours and then was quenched with 130 mL of a saturated NH_4Cl solution. After filtration through a Celite pad and washing of the ether layer with a brine solution, the organic phase was dried over sodium sulfate and carefully concentrated in vacuo because of its volatility. Isolated the product as a colorless liquid (1.38 g, 12.3 mmol, 87.8% yield) after column chromatography (30%-40% Et_2O/hexanes). The product was sometimes even used as the crude directly in the next step. TLC R_f 0.14 (20% EtOAc:hexanes). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with those in the literature[138] except that an extra peak at 2.72 ppm (s, 1H) was found in the ^1H NMR spectra. The *trans* stereochemistry was confirmed by comparing the obtained ^{13}C NMR data with both the ones for the *trans* and the *cis* stereoisomers reported in the literature.[72]



Butyraldehyde oxime 2.53 was prepared by adding hydroxylamine hydrochloride (5.3 g, 76 mmol, 1.1 equiv), and sodium acetate (17.1 g, 208 mmol, 3.00 equiv) to a round-

[138] Bertozzi, F.; Crotti, P.; Feringa, B. L.; Macchia, F.; Pineschi, M. *Synthesis* **2001**, 483

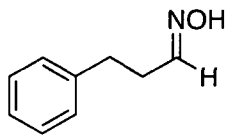
bottomed flask containing butyraldehyde (5.0 g, 6.2 mL, 69 mmol) in methanol:acetonitrile (138 mL : 13.8 mL). The reaction was stirred at room temperature overnight under an atmosphere of argon. The crude reaction was quenched with a saturated sodium carbonate solution and extracted with ether. The combined organic layers were washed with brine, dried over sodium sulfater and concentrated *in vacuo*. The crude was purified by flash chromatography (10-20% Ethyl acetate: Hexanes) to afford a light yellow oil (5.1 g, 59 mmol, 85% yield). TLC R_f 0.28 (20% Ethyl acetate: Hexanes). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with those in the literature.[139]



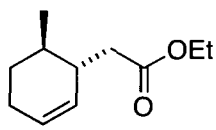
3-Phenyl-1-propanaldehyde 2.56 was prepared according to literature procedure.[140] To 3-phenyl-1-propanal (3.0 g, 3.0 mL, 22 mmol) in dry DMSO (0.4 M, 55 mL) at room temperature was added triethylamine (22 g, 31 mL, 220 mmol, 10 equiv) under an atmosphere of argon. A solution of pyridine-sulfurtrioxide complex (11.6 g, 72.7 mmol, 3.30 equiv) in DMSO (1.3 M, 55 mL) was added via syringe and the reaction was stirred at room temperature for forty minutes. The reaction was acidified to a pH of 4.5 by a dropwise addition of 10% v/v solution of HCl. Water was added to the reaction mixture. The crude reaction was extracted with ethyl acetate. The combined organic layers were washed with water three times, a saturated solution of sodium carbonate, and brine, dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The crude was purified by

[139] Crandall, J.K.; Riex, T. *J. Org. Chem.* **1992**, *57*, 6759
[140] Parikh, J.R.; Doering, W.v.E. *J. Am. Chem. Soc.* **1967**, *89*, 5505

flash chromatography (5-11% Ethyl acetate: Hexanes) to afford a yellow oil. TLC R_f 0.27 (11% Ethyl acetate: Hexanes) Spectral ^1H and ^{13}C NMR data were found to be in good agreement with those in the literature.[141]



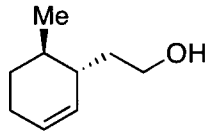
3-Phenyl-1-propanaldehyde oxime 2.57. To 3-phenyl-1-propanaldehyde (0.5 g, 3.7 mmol) in a 10:1 ratio of methanol:acetonitrile (0.45 M, 7.5 mL : 0.75 mL) in a round bottom flask was added hydroxylamine hydrochloride (0.29 g, 4.1 mmol, 1.1 equiv), and sodium acetate (0.92 g, 11 mmol, 3.0 equiv). The reaction was stirred at room temperature overnight under an atmosphere of argon. The crude reaction was quenched with a saturated sodium carbonate solution and extracted ether. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The crude was purified by flash chromatography (10-20% Ethyl acetate: Hexanes) to afford white crystals (0.49 g, 3.3 mmol, 89% yield). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with those in the literature.[142]



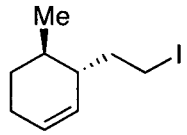
(±)-Ethyl 2-((1*R,6*S**)-6-methylcyclohex-2-enyl)acetate 2.35** was prepared according to the literature procedure[67] except that a higher temperature than 160 °C was employed. A mixture of the allylic alcohol (4.8 g, 42 mmol, 1.0 equiv), 2-nitrophenol (0.55 g, 3.9 mmol, 0.090 equiv) and triethyl orthoacetate (0.100 M, 434 mL) was heated at 170 °C for

[141] Jiang, N.; Ragauskas., A.J. *J. Org. Chem.* **2006**, *71*, 7087
[142] Odfield, M.F.; Botting, N.P. *J. Labelled Cpd. Radiopharm.* **1998**, *XLI*, 29

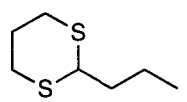
a period of 6 hours with a Dean-Stark apparatus. The Dean Stark trap was emptied every hour. After completion of reaction, the triethyl orthoacetate was then distilled through a Vigreux column under vacuum at 65 °C. The distillate was purified by column chromatography (3% ether/hexanes) to give a colorless liquid with a flowery smell (5.7 g, 31 mmol, 74% yield). TLC R_f 0.71 (20% EtOAc/hexanes). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]



(±)-2-((1*R,6*S**)-6-Methylcyclohex-2-enyl)ethanol 2.50** was prepared according to literature procedure.[67] To a suspension of LAH (0.72 g, 19 mmol, 1.8 equiv) in dried THF (0.12 M, 86 mL) was added dropwise a solution of the ester (1.9 g, 10 mmol) in dried THF (1.2 M, 8.6 mL) at 0 °C under inert atmosphere. The solution was stirred at room temperature for 2 hours even though the reaction was done by TLC after 20 min. A Fieser quench was performed. The solution was cooled to 0 °C and H_2O (0.72 mL) was cautiously added followed by 15% aqueous NaOH (0.72 mL) and H_2O (2.2 mL). After stirring overnight, even though they waited only 20 min in the procedure, hexane and $MgSO_4$ were added. The mixture was filtered through Celite and the filtered solids were rinsed with Et_2O several times. The crude was then carefully concentrated in vacuo followed by purification by column chromatography (50% Et_2O/hexanes) to give a colorless liquid (1.3 g, 9.4 mmol, 91% yield). TLC R_f 0.47 (20% EtOAc/hexanes). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]

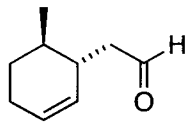


(±)-(3*R,4*S**)-3-(2-Iodoethyl)-4-methylcyclohex-1-ene 2.33**. The alcohol (0.074 g, 0.53 mmol) was dissolved in a mixture of Et_2O (0.13 M, 4.1 mL) and MeCN (0.39 M, 1.4 mL) at 0 °C. Imidazole (0.072 g, 1.1 mmol, 2.0 equiv), triphenylphosphine (0.28 mg, 1.1 mmol, 2.0 equiv) and iodine (0.27 mg, 1.1 mmol, 2.0 equiv) were then added in that order. After 45 min, the reaction mixture was diluted with a $Na_2S_2O_3$ solution and extracted with hexanes. The combined organic extracts were washed with brine, dried over sodium sulfater and carefully concentrated in vacuo to give a residue. The crude was then purified by flash chromatography (100% Hexanes) to give a colorless oil (0.13 g, 0.51 mmol, 96% yield). TLC R_f 0.96 (20% EtOAc/hexanes). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]



2-Propyl-1,3-dithiane 2.32 was prepared according to literature procedure.[74] *All the glassware and equipment were subsequently soaked in Javex to neutralize odors.* In a two-necked round-bottomed flask equipped with a condenser was refluxed freshly distilled boron trifluoride diethyl etherate (11.8 g, 10.5 mL, 83.0 mmol, 2.40 equiv) and acetic acid (20.8 mL, 363 mmol, 10.5 equiv) in dried chloroform (1.0 M, 20 mL) at 74 °C under inert atmosphere. A solution of chloroform (87 mL, 0.40 M) containing butyraldehyde (3.0 mL, 2.4 g, 35 mmol) and 1,3-propanedithiol (5.6 g, 5.2 mL, 52 mmol, 1.5 equiv) was then added dropwise by cannula over a period of 30 min. The reaction was left refluxing overnight after which it was cooled to room temperature. The reaction

mixture was washed with a 10% aqueous KOH solution followed by brine. The organic layer was dried over Sodium sulfate, filtered and evaporated. Purification by column chromatography (5% Et_2O/hexanes) gave protected aldehyde as a light yellow liquid (11.6 g, 71.4 mmol, 99.0% yield) which was later distilled to obtain purer product. TLC R_f 0.75 (20% EtOAc/hexanes) or *R_f 0.39 (30% DCM/hexanes)*. Spectral data were found to be in good agreement with those in the literature.[2i]



(±)-2-((1*S,6*R**)-6-Methylcyclohex-2-enyl)acetaldehyde 2.71** was prepared according to literature procedure.[143] To a flame dried flask under an atmosphere of argon was added ester **2.35** (0.26 g, 1.4 mmol) in dichloromethane (0.15M, 9.3 mL). The reaction was cooled with an ether/dry ice bath to below –78 °C. After a few minutes of stirring, diisobutyl aluminun hydride (1.0M in toluene, 1.4 mL, 1.0 equiv) was added along the side of the flask. The reaction was stirred for one hour and then quenched with dry MeOH (1.4 mL) and a saturated solution of Rochelle salt (5.6 mL). The reaction was diluted with ether, removed from the ice bath and stirred for 20 minutes. The solution was filtered over Celite which was further washed with ether. The organic layer was dried with sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography (16% ether/hexanes) gave the aldehyde as a light yellow oil (0.15 g, 1.1 mmol, 77% yield, 95% brsm). TLC R_f 0.38 (8% ether:hexanes). The aldehyde was then used for the following reaction.

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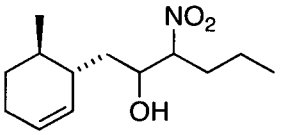
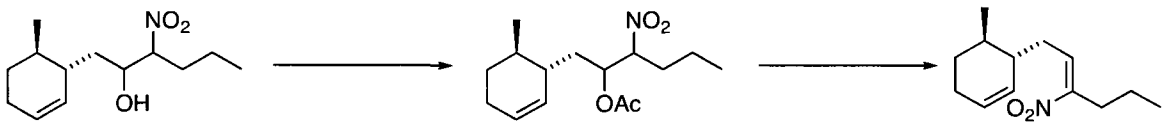
[143] Kalvin, D.M.; Woodard, R.W. *Tetrahedron* **1984**, *40*, 3387



(±)-1-((1*S,6*R**)-6-Methylcyclohex-2-enyl)-3-nitrohexan-2-ol 2.72** and its diasteriomer were prepared according to a modified literature procedure[144] but can also be prepared in aqueous medium.[145] To a flame dried flask was added the aldehyde (0.40 g, 2.9 mmol), nitrobutane (0.36 g, 3.5 mmol, 1.5 equiv) in a 1:1 mixture of THF (1.9 M, 1.5 mL) and *t*-butanol (1.9 M, 1.5 mL). The reaction was cooled to 0 °C and potassium *t*-butoxide (0.32 g, 2.9 mmol, 1.0 equiv) was added. The ice bath was removed after 15 minutes and the reaction was stirred at room temperature for 2 hours. The reaction was quenched with a saturated solution of ammonium chloride and then extracted with ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography (16% ether/hexanes) gave the product as a light yellow oil (0.546 g, 2.26 mmol, 77.9% yield). TLC R_f 0.11 (8% ether/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 5.78-5.66 (m, 1H), 5.66-5.48 (m, 1H), 4.44 (ddd, J = 14.9, 7.9, 3.6 Hz, 1H), 4.23-4.10 (m, 1H), 2.42 (dd, J = 18.4, 4.3 Hz, 1H), 2.21-2.04 (m, 1H), 2.04-1.92 (m, 2H), 1.83-1.59 (m, 3H), 1.54 (t, J = 6.2 Hz, 1H), 1.48-1.23 (m, 4H), 1.03-0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 129.7 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 92.6 (CH), 92.1 (CH), 71.0 (CH), 69.8 (CH), 39.4 (CH), 38.3 (CH), 37.6 (CH_2), 37.4 (CH_2), 33.0 (CH), 31.8 (CH_2), 30.3 (CH), 29.5 (CH_2), 29.4 (CH_2), 28.2 (CH_2), 24.2 (CH_2), 23.4 (CH_3), 19.8 (CH_2), 19.7 (CH_2), 19.3 (CH_2), 13.5 (CH_3), 13.5 (CH_3); IR (film): 3447, 2964, 2922, 2877, 1546, 1455, 1375, 1356 cm $^{-1}$; MS m/z

[144] (a) Cote, A; Lindsay, V.N.G.; Charette, A.B. *Org. Lett.* **2007**, *9*, 85 (b) Gomez, L.; Denmark, S.E. *Org. Lett.* **2001**, *3*, 2907
[145] Ballini. *J. Org Chem.* **1997**, 62, 425

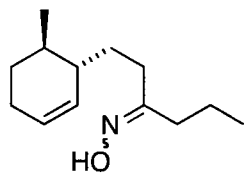
(relative intensity): 237.9917 (11.8%), 236.9803 (62.2%), 218.9570 (23.6%), 215.0195 (35.5%), 214.9851 (34.8%), 158.9971 (28.6%), 138.1005 (21.1%), 137.0224 (93.1%), 109. 0996 (47.3%), 95.0855 (75.6%).



(±)-(3*S,4*R**)-4-Methyl-3-((*Z*)-3-nitrohex-2-enyl)cyclohex-1-ene 2.73** and enantiomer were prepared according to literature procedure.[144b] A solution of the nitroalcohol **2.72** (0.16 g, 0.67 mmol), and acetic acid anhydride (0.075 g, 0.069 mL, 0.73 mmol, 1.1 equiv) in ether (0.15 M, 4.4 mL) was cooled to 0 °C. The reaction was stirred for a few minutes and DMAP (0.016 g, 0.13 mmol, 0.20 equiv) was added and the reaction was allowed to stir at room temperature for 2 hours. The reaction was then diluted with ether, and quenched with water. The organic layer was washed sequentially with a saturated solution of sodium bicarbonate and then ammonium chloride. The aqueous layers were back extracted with ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated *in vacuo*.. The crude was used directly for the next reaction.

To the crude nitroacetate was added *t*-BuOH (0.14 M, 4.8 mL) at room temperature followed by potassium carbonate (0.11 g, 0.80 mmol, 1.2 equiv). The reaction was warmed to 35 °C, and stirred at that temperature overnight under an argon atmosphere. The reaction was quenched with water and extracted with ether. The combined organic layers were dried with sodium sulfate, filtered and concentrated *in vacuo*. The crude was purified with flash chromatography (4% ether/hexanes) to afford the yellow oil (0.15 g, 0.67 mmol, >99% yield). TLC R_f 0.26 (4% ether/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 7.12 (dd, J = 8.8, 6.7 Hz, 1H), 5.76 (ap dq, J = 10.1, 2.3 Hz, 1H), 5.45 (ap dq, J = 10.0, 2.1 Hz, 1H), 2.66-2.50 (m, 2H), 2.48-2.32 (m, 1H), 2.31-2.18 (m, 1H), 2.09-1.90

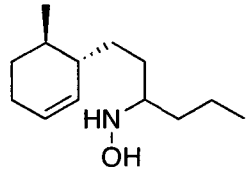
(m, 3H), 1.76-1.62 (m, 1H), 1.61-1.46 (m, 1H), 1.45-1.21 (m, 1H), 1.00 (d, J = 6.3 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 152.3 (C), 135.1 (CH), 128.9 (CH), 128.6 (CH), 42.1 (CH), 32.8 (CH), 32.2 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 24.4 (CH_2), 21.2 (CH_2), 20.0 (CH_3), 13.7 (CH_3). IR (film): 3021, 2964, 2926, 2842, 1664, 1520, 1459, 1432, 1379, 1337, 1105, 847, 729 cm $^{-1}$; HRMS (EI): Exact mass calculated for $C_{13}H_{21}NO_2$ $[M]^+$: 223.1572. Found: 223.1581.



(±)-1-((1*R*,6*S*)-6-Methylcyclohex-2-enyl)hexan-3-one oxime 2.28 was prepared according to literature procedure.[146] A round-bottomed flask was charged with a stir bar and zinc dust (1.04 g, 15.9 mmol, 9.90 equiv) was added. The flask was flame-dried under argon. 1,2-Dibromoethane (0.035 mL) was added in THF (0.5 mL) and the solution was flamed to boil three times. Chlorotrimethylsilane (0.032 mL) was added and the reaction was stirred for approximately 5 minutes at room temperature. Once the zinc was successfully activated half of the THF (0.95 M, 17 mL) was added and the reaction was cooled to 0 °C. A 4M solution of acetic acid (8.0 mL, 31.9 mmol, 19.8 equiv) was added and the reaction was stirred for a few more minutes. The nitroalkene (0.359 g, 1.61 mmol) was diluted with the rest of the THF and then cannulated into the reaction and the reaction was stirred for 5 minutes. The reaction was quenched slowly with a saturated solution of sodium bicarbonate, filtered over Celite and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate, dried and concentrated in vacuo. The crude was purified by flash chromatrography (20%

[146] Ghosh, A.K.; Gong, G. *Org. Lett.* **2007**, *9*, 1437

ether/hexanes) to afford a clear oil (0.237 g, 1.13 mmol, 70.3% yield). TLC R_f 0.37 and 0.31 (20% EtOAc/hexanes). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]



(±)-*N*-Hydroxy-1-((1*S,6*R**)-6-methylcyclohex-2-enyl)hexan-3-amine 2.29** was prepared according to literature procedure[45d] and worked-up using the a known method.[147] To a solution of the oxime (0.053 g, 0.26 mmol) in MeOH (0.078 M, 3.3 mL) was added a crystal of methyl orange (just enough to render a yellow color to the solution). Sodium cyanoborohydride (0.018 mg, 0.28 mmol, 1.1 equiv) was then added under inert atmosphere. The yellow solution was stirred at room temperature and a HCl / MeOH (1 : 5) solution was added dropwise so as to keep the solution pink. This kept the pH just below 4.4, above which the solution turned back to yellow. After the solution had stayed pink for 30 min the reaction was also done by TLC. The mixture was neutralized with a 25% aqueous NaOH solution and then poured into brine. The suspension was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (60% ether/hexanes) gave a colorless oil (0.051 g, 0.24 mmol, 95% yield). TLC R_f 0.08 (20% EtOAc/hexanes). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]

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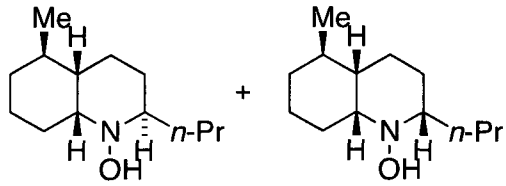
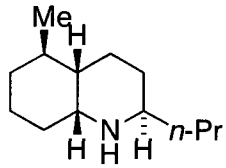
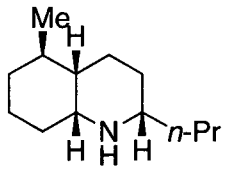
[147] Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601



(±)-*N*-Hydroxy-(2*R,4a*S**,5*R**,8a*R**)-decahydro-5-methyl-2-propylquinoline** (or **(±)-*N*-Hydroxy-*epi*-pumiliotoxin C**) **2.43** and **(±)-*N*-Hydroxy-(2*S**,4a*S**,5*R**,8a*R**)-decahydro-5-methyl-2-propylquinoline** (or **(±)-*N*-Hydroxy-pumiliotoxin C**) **2.42** were cyclized using conditions developed during our intramolecular Cope-type hydroamination project (Chapter 2). *Due to facile oxidation of the hydroxylamine, great care was taken to eliminate traces of oxygen from the reaction mixture. n-PrOH and H_2O were distilled under argon prior to use.* In a pressure vessel equipped with a magnetic stirbar was added the hydroxylamine (0.955 mg, 0.452 mmol). It was then dissolved in a mixture of *n*-PrOH (0.15 M, 3.0 mL) and H_2O (0.081 mL, 4.5 mmol, 10 equiv) under argon. The solution was degassed at 0 °C by bubbling argon for 10 min. The pressure vessel was capped and it was heated in the microwave at 180 °C for 5 hours. After cooling to room temperature, more H_2O was added and it was extracted with EtOAc. The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography (10-60% Ether/hexanes) gave *N*-hydroxy-*epi*-pumiliotoxin C (0.036 g, 0.17 mmol, 37% yield) with 20% Ether/hexanes as eluent and *N*-hydroxy-pumiliotoxin C (0.0089 g, 0.042 mmol, 9.3% yield) with 8% Ether/hexanes as eluent, both as white solids. The unreacted starting hydroxylamine was also found with 60% Ether/hexanes as eluent (0.0389 g, 0.184 mmol, 40.7% yield) as one stereoisomer. Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]



(±)-2-*Epi*-pumiliotoxin C (or **(±)-(2*R**,4a*S**,5*R**,8a*R**)-Decahydro-5-methyl-2-propylquinoline**) **2.76** and enantiomer were prepared according to literature procedure[148] *N*-hydroxy-*epi*-pumiliotoxin C (0.0145 g, 0.0687 mmol) was dissolved in a 10 M AcOH aqueous solution (0.040 M, 1.7 mL). The mixture was heated to 55 °C and then zinc dust (0.045g, 0.69 mmol, 10 equiv) was added with vigorous stirring. After 4 hours, TLC analysis revealed complete consumption of the starting material. The reaction mixture was cooled, diluted with 13 mL of H_2O and basified to pH 14 by addition of 6 M KOH. The solution was extracted with $CHCl_3$. The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography (0-100% EtOAc/$CHCl_3$) gave 2-*epi*-pumiliotoxin C as the free base as a white solid (0.013 g, 0.067 mmol, 72% yield) with 20-100% EtOAc/$CHCl_3$ as eluent. TLC R_f 0.06 (10% MeOH/EtOAc). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]



(±)-Pumiliotoxin C (or **(±)-(2*S**,4a*S**,5*R**,8a*R**)-Decahydro-5-methyl-2-propylquinoline**) **2.27** and enantiomer were prepared according to the same literature procedure as described previously for epi-pumiliotoxin C.[148] Purification by column chromatography (0-50% EtOAc/$CHCl_3$) gave pumiliotoxin C as the free base as a white

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

solid (0.0035 g, 0.018 mmol, 92% yield) with 0-20% EtOAc/$CHCl_3$ as eluent. TLC R_f 0.12 (10% MeOH/EtOAc). Spectral ^1H and ^{13}C NMR data were found to be in good agreement with previous reports.[2i]

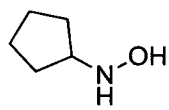
5.3. *Experimental for Chapter 3*

5.3.1. Procedures and Characterization for Allene Reactivity

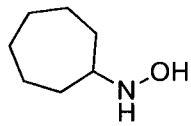
Optimization of reaction of *N*-cyclohexylhydroxylamine with cyclohexylallene (Table 3.6). A 3 mL tapered bottom screwcap vial was charged with a stir bar, *N*-cyclohexylhydroxylamine (0.047 g, 0.41 mmol), solvent (either 0.40 mL (0.25 M), 0.80 mL (0.50 M) or 1.6 mL (1.0 M)), and cyclohexylallene (0.099 g, 0.81 mmol). The vial was capped with a septum and purged with argon and an outlet for 5 minutes while stirring. The septum was removed and the vial was then quickly sealed with a screw cap and Teflon tape and heated while stirring in a wax bath at the specified temperature for 18 h. The vial was cooled to ambient temperature and concentrated under reduced pressure. 1,4-dimethoxybenzene (≈ 0.014 g, 0.10 mmol) was then added as an internal standard. The mixture was taken up in $CDCl_3$ and transferred to an NMR tube. ^1H NMR spectra of these solutions were recorded, and the conversion calculated based on the relative integration of the resonance corresponding to the product's methine protons (1H) (the sum of the peaks at 4.07 ppm (major isomer) and 3.98 ppm (minor isomer)) compared to the integration of the resonance corresponding to a 1,4-dimethoxybenzene proton at 6.83 ppm (1H).

Preparation of *N*-alkylhydroxylamines. *N*-alkylhydroxylamines **3.131g** and **3.131h**

were prepared by reductive amination of the corresponding oximes according to a modification of the method of House and Lee.[45d] To a round-bottomed flask equipped with a magnetic stirring bar was added oxime (1.0 equiv), diluted in methanol so that the concentration of oxime is 1M. A minimum amount of methyl orange indicator was added, followed by sodium cyanoborohydride (1.2 equiv). Contents were capped with a rubber septum and flushed with argon. The reaction was monitored using the indicator such that when a yellow color was observed, a 1:1 solution of methanol and hydrochloric acid was added dropwise to maintain a pink reaction mixture. After approximately half an hour of the reaction remaining pink, and verification using TLC, the reactions were deemed complete. To quench the reaction, a 25% sodium hydroxide solution in water was added dropwise until the solution was basified to pH 8. Dilution with water and extraction three times with dichloromethane, drying over anhydrous sodium sulfate and concentration under reduced pressure furnished the crude product. Purified material was obtained after column chromatography (80% EtOAc/hexanes).

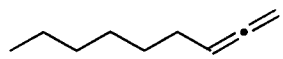


***N*-Cyclopentylhydroxylamine, 3.131g.** Performed on 39.5 mmol oxime. Isolated 0.88 g (22% yield) as a white solid after column chromatography (80% EtOAc/hexanes). TLC R_f 0.28 (100% EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 6.10 (br s, 2H), 3.69-3.20 (m, 1H), 1.82-1.42 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 63.1 (CH), 30.1 (CH_2), 24.4 (CH_2); IR (film): 3265, 3133, 2917, 2840 cm^{-1}; Exact mass calcd for $C_5H_{11}NO[M]^+$: 101.0841. Found: 101.0848.



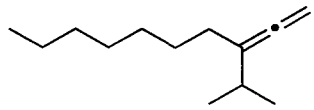
***N*-Cycloheptylhydroxylamine, 3.131h.** Performed on 39.5 mmol of cycloheptanone oxime. Isolated 3.3 g (65% yield) as a white solid after column chromatography (80% EtOAc/hexanes). TLC R_f 0.29 (100% EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 6.36 (br s, 2H), 2.98 (tt, J = 8 Hz, 4 Hz, 1H), 1.94-1.78 (m, 2H), 1.73-1.26 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 62.6 (CH), 31.3 (CH_2), 28.6 (CH_2), 24.3 (CH_2); IR (film): 3255, 3150 cm^{-1}; Exact mass calcd for $C_5H_{11}NO[M]^+$: 129.1154. Found: 129.1155.

Preparation of allenes.



Nona-1,2-diene, 3.132b. Using literature procedure, nona-1,2-diene was prepared.[125] To a stirred solution of 1-octyne (3.0 g, 4.0 mL, 27 mmol,) in dioxane (1.5 M, 18 mL) were added paraformaldehyde (2.0 g, 68 mmol, 2.5 equiv), diisopropylamine (5.5 g, 7.7 mL, 54 mmol, 2.0 equiv) and copper bromide (1.9 g, 14 mmol, 0.5 equiv) at room temperature. The reaction was warmed to reflux and maintained at that temperature for twenty-two hours. The reaction was cooled, filtered over Celite, and concentrated. The residue was acidified to pH 2-3 with 10% HCl solution and extracted with ether. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude was purified by flash chromatography

(Hexanes) to give a clear oil (1.13 g, 33.5% yield). TLC R_f 0.83 (Hexanes); The NMR corresponded with characterization previously reported.[149]



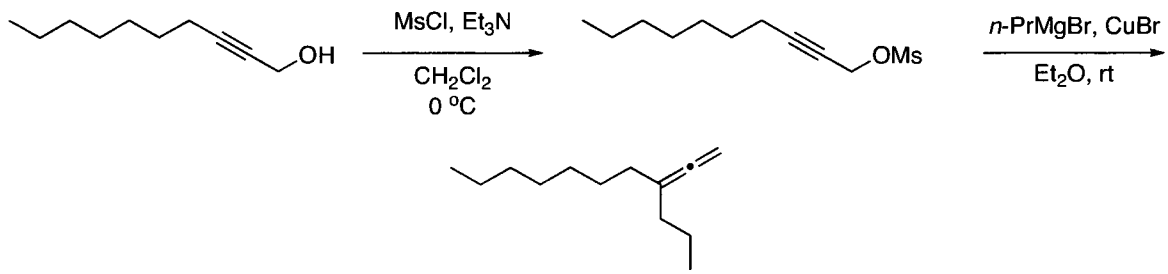
3-isopropyldeca-1,2-diene, 3.132f. The allene was prepared by a modified procedure.[150] To a solution of 2-decyn-1-ol (3.0 g, 3.5 mL, 19 mmol) in dichloromethane (0.100 M, 194 mL) at 0 °C were added triethylamine (3.7 g, 5.2 mL, 37 mmol, 1.9 equiv) and methanesulfonyl chloride (3.8 g, 2.6 mL, 33 mmol, 1.7 equiv). The reaction was stirred at 0 °C for 2 hours after which it was quenched with a pH 7 phosphate buffer and then washed with water twice. The organic layer was dried with anhydrous sodium sulfate and concentrated in a room temperature water bath. The crude was immediately used for the next reaction.

To a flame dried flask was added copper bromide (0.29 g, 2.0 mmol, 0.10 equiv) and ether (1.0 M to alcohol, 20 mL). The solution temperature was maintained at room temperature by placing in a bath of water at room temperature. *i*-propylmagnesium bromide (23.9 mmol, 2.14 M, 11.2 mL, 1.20 equiv) was added followed by a SLOW addition of dec-2-ynyl methanesulfonate in ether (1.0 M, 20 mL) via cannula. The reaction was stirred at room temperature for two hours after which it was quenched with a cold saturated ammonium chloride solution and extracted with ether. The combined organic phases were dried with anhydrous sodium sulfate, filtered, and concentrated.

The crude was purified by flash chromatography (Hexanes) to give a clear oil (0.45 g, 13 % yield). TLC R_f 0.85 (Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 4.68 (dt, J = 3.4, 2.7 Hz,

[149] Endo, T.; Takagi, K.; Tomita, I. *Tetrahedron*, **1997**, *53*, 15194

2H), 2.13-2.03 (m, 1H), 1.93 (tt, J = 7.1, 3.4 Hz, 2H), 1.46-1.36 (m, 2H), 1.34-1.22 (m, 8H), 1.02 (d, J = 6.8, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 204.7 (C), 109.8 (C), 76.5 (CH), 31.9 (CH_2), 30.3 (CH_3), 30.3 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 22.7 (CH_2), 21.6 (CH_3), 14.1 (CH_3); IR (film): 2968, 2930, 2858, 1953, 1466, 1459, 835 cm $^{-1}$.



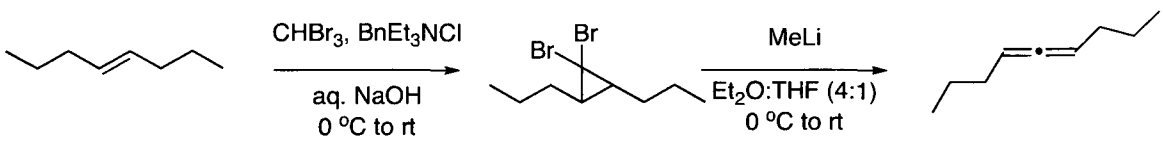
4-Vinylideneundecane, 3.132g. The allene was synthesized using a modified procedure.[150] To a solution of 2-decyn-1-ol (1.5 g, 1.8 mL, 9.9 mmol) in dichloromethane (0.100 M, 100 mL) at 0 °C were added triethylamine (1.9 g, 2.7 mL, 19 mmol, 1.9 equiv) and methanesulfonyl chloride (1.9 g, 1.3 mL, 17 mmol, 1.7 equiv). The reaction was stirred at 0 °C for 2 hours after which it was quenched with a pH 7 phosphate buffer and then washed with water twice. The organic layer was dried with anhydrous sodium sulfate and concentrated in a room temperature water bath. The crude was immediately used for the next reaction.

To a flame dried flask was added copper bromide (0.14 g, 1.0 mmol, 0.10 equiv) and ether (1.0 M to alcohol, 10 mL). The solution temperature was maintained at room temperature by placing in a bath of water at room temperature. n-propylmagnesium bromide (12 mmol, 2.3 M, 5.3 mL, 1.2 equiv) was added followed by a SLOW addition

[150] Moreau, J-L.; Gaudemar, M. *J. Organomet. Chem.* **1976**, *108*, 159

of dec-2-ynyl methanesulfonate in ether (1.0 M, 10 mL) via cannula. The reaction was stirred at room temperature for two hours after which it was quenched with a cold saturated ammonium chloride solution and extracted with ether. The combined organic phases were dried with anhydrous sodium sulfate, filtered, and concentrated.

The crude was purified by flash chromatography (Hexanes) to give a clear oil (0.53 g, 30% yield). TLC R_f 0.78 (Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 4.63 (p, J = 3.2 Hz, 2H), 1.96-1.85 (m, 4H), 1.52-1.35 (m, 4H), 1.36-1.17 (m, 8H), 0.91 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 205.7 (C), 103.1 (C), 75.1 (CH_2), 34.2 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.5 (CH_2), 22.6 (CH_2), 20.7 (CH_2), 14.1 (CH_3), 13.8 (CH_3); IR (film): 2958, 2933, 2873, 2857, 1961, 1466, 1455, 1371, 835 cm $^{-1}$; HRMS (EI): Exact mass calculated for $C_{13}H_{24}$ $[M]^+$: 180.1878. Found: 180.1855.



Nona-4,5-diene, 3.132h. The allene was synthesized using a modified procedure.[151] Trans-4-octene (5.0 g, 7.0 mL, 45 mmol), benzyl-triethylammonium chloride (1.0 g, 4.5 mmol, 0.10 equiv) and bromoform (28.0 g, 9.74 mL, 111 mmol, 2.50 equiv) were added to a 100 mL flask. The reaction was cooled to 0 °C and a 25 M NaOH solution (2.50 M, 17.8 mL) was added dropwise. The reaction was warmed to room temperature and stirred overnight open to air. The reaction was quenched with water and filtered through Celite. The reaction was extracted with dichloromethane and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated.

[151] Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254

The crude was purified by flash chromatography (Hexanes) followed by fractional distillation to give a clear oil (6.39 g, 50.6% yield). TLC R_f 0.78 (Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 1.71-1.29 (m, 9H), 1.08 (ddd, J = 6.0, 4.5, 1.8 Hz, 2H), 0.97 (t, J = 7.07 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 39.4 (C), 36.8 (CH), 34.6 (CH_2), 21.5 (CH_2), 13.8 (CH_3); IR (film): 2960, 2930, 2873, 2360, 1459, 1018, 744 cm^{-1}.

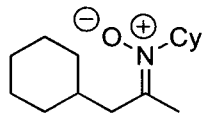
To a stirred solution of 1,1-dibromo-2,3-dipropylcyclopropane (6.39 g, 22.5 mmol) in 4:1 ether:THF (0.200 M, 100 mL) at 0 °C was added methyl lithium (1.3 M, 37 mL, 47 mmol 2.1 equiv). The reaction was stirred at this temperature for thirty minutes, warmed to room temperature and then stirred for another hour at this temperature. The reaction was quenched with a pH 7 phosphate buffer and extracted with ether. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated in a room temperature rotovap bath. The crude material was purified by flash column chromatography (Pentane) to give a clear oil (2.2 g, 79% yield). TLC R_f 0.71 (Hexanes); The NMR corresponded with characterization previously reported.[152]

Reaction of *N*-cyclohexylhydroxylamine with allenes (Table 3.7).

General procedure for the reaction of *N*-cyclohexylhydroxylamine with allenes. A 2 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, *N*-cyclohexylhydroxylamine (0.047g, 0.41 mmol, 1.0 equiv), *t*-butanol (0.80 mL, 1.0 M to allene), and allene (0.81 mmol, 2.0 equiv). The vial was sealed using a cap with a resealable septum and purged through the septum with argon and an outlet for 5 minutes

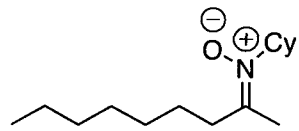
[152] Crandall, J.K.; Batal, D.J.; Sebesta, D.P.; Lin, F. *J. Org. Chem.* **1991,** *56,* 1153

while stirring. The vial was then heated while stirring in a wax bath at 140°C for 18 hrs and analyzed by TLC. The tube was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR ($CDCl_3$) using 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding nitrone.

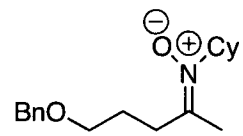


***N*-(1-Cyclohexylpropan-2-ylidene)cyclohexanamine oxide, 3.133a (Table 3.7, entry 1 and Table 3.8, entry 1).** Synthesized from *N*-cyclohexylhydroxylamine[153] according to the general procedure, but using 0.093 g, 0.81 mmol **3.132a** (all reagents and solvents scaled up accordingly). Isolated 0.18 g (91%) of a 1.6:1 mixture of isomers as a clear colorless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.36 and 0.41 (5% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) 4.07 (tt, J = 11.4, 3.8 Hz, 1H) (major), 3.98 (tt, J = 11.4, 3.8 Hz, 1H) (minor), 2.44 (d, J = 7.3 Hz, 1H), 2.28 (d, J = 7.3 Hz, 2H), 2.09 (s, 3H) (major), 2.06 (s, 3H) (minor), 2.14-1.97 (m, 1H), 1.94-1.45 (m, 11H), 1.39-0.86 (m, 8H); ^{13}C NMR (100 MHz) 145.7 (C), 144.3 (C), 65.8 (CH), 65.1 (CH), 41.1 (CH_2), 40.6 (CH_2), 37.1 (CH), 35.0 (CH), 33.4 (CH_2), 33.2 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 26.2 (CH_2), 26.10 (CH_2), 26.07 (CH_2), 26.0 (CH_2), 25.08 (CH_2), 25.06 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 19.5 (CH_3), 19.2 (CH_3); IR (film): 3392, 2925, 2853, 1574, 1450, 1180, 896 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{27}NO$ $[M]^+$: 237.2093. Found: 237.2089.

[153] Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897

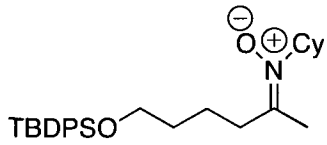


***N*-(Nonan-2-ylidene)cyclohexanamine oxide, 3.133b (Table 3.7, entry 2).** Synthesized according to general procedure using 0.10 g (0.81 mmol) of the corresponding allene. Isolated 0.79 g (82% yield) as a yellow oil after column chromatography (0-5% MeOH/CH_2Cl_2). TLC R_f: 0.11, 0.14 (4% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 4.05 (tt, J = 11.3, 3.7 Hz, 1H), 2.43-2.34 (m, 2H), 2.21-1.96 (m, 2H), 2.11 (s, 3H), 1.88 (d, J = 12.0 Hz, 2H), 1.74 (d, J = 13.2 Hz, 2H), 1.66 (d, J = 8.7 Hz, 1H), 1.56-1.43 (m, 2H), 1.41-1.18 (m, 11H), 0.89 (t, J = 6.7 Hz, 3H); ^{13} C NMR (75 MHz, $CDCl_3$) 146.0 (C), 65.1 (CH), 33.4 (CH_2), 31.6 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 27.2 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 22.5 (CH_2), 18.7 (CH_3), 14.0 (CH_3); IR (film) : 3416, 2918, 2857, 1717, 1652, 748 (cm $^{-1}$) ; HRMS (EI): Exact mass calculated for $C_{15}H_{29}NO$ $[M]^+$: 239.2249. Found: 239.2235.



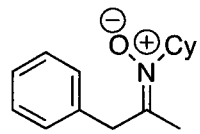
***N*-(5-(Benzyloxy)pentan-2-ylidene)cyclohexanamine oxide, 3.133c (Table 3.7, entry 3).** Synthesized according to the general procedure using 0.20 g (1.2 mmol) of the corresponding allene. Isolated 0.13 g (75% yield) as a mixture of isomers (1.3:1) as a light yellow oil after column chromatography (0-5% MeOH/CH_2Cl_2). TLC R_f 0.37, 0.46 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 7.39-7.27 (m, 5H), 4.51 (s, minor isomer), 4.50 (s, major isomer), 4.14 (tt, J = 11.4, 3.9 Hz, minor isomer), 3.98 (tt, J = 11.4, 3.9 Hz, major isomer), 3.52 (t, J = 6.4 Hz, major isomer), 3.48 (t, J = 5.9 Hz, minor isomer), 2.68-2.62 (m, 2H), 2.12 (s, minor isomer), 2.07 (s, major isomer), 2.17-1.95 (m,

2H), 1.95-1.77 (m, 4H), 1.78-1.58 (m, 4H), 1.37-1.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 145.2 (C), 144.3 (C), 138.5 (C), 138.1 (C), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.5 (CH), 73.0 (CH_2), 72.9 (CH_2), 70.0 (CH_2), 68.5 (CH_2), 65.7 (CH), 65.1 (CH), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 27.4 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 18.6 (CH_3), 18.2 (CH_3); IR (film) : 3089, 3066, 3032, 2929, 2854, 2797, 1713, 1573, 1497, 1451, 1368, 1311, 1288, 1246, 1200, 1170, 1113, 1098, 1079, 1025, 896, 733, 698 cm $^{-1}$; HRMS (EI): Exact mass calculated for $C_{18}H_{27}NO_2$ $[M]^+$: 289.2042. Not found. Exact mass calculated for $C_{11}H_{20}NO_2$ 1[M – Bn]$^+$: 198.1494. Found : 198.1462.



***N*-(6-(*tert*-Butyldiphenylsilyloxy)hexan-2-ylidene)cyclohexanamine oxide, 3.133d (Table 3.7, entry 4).** Synthesized according to the general procedure using 0.27 g (0.81 mmol) of the corresponding allene. Isolated 0.13 g (73% yield) as a mixture of isomers in a 3:1 ratio as a light yellow oil after column chromatography (0-5% MeOH/CH_2Cl_2). TLC R_f: 0.30, 0.41 (5% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.65 (td, J = 7.9, 1.9 Hz, 4H), 7.48-7.32 (m, 6H), 4.04 (tt, J = 12.0, 4.0 Hz, major isomer), 3.68 (t, J = 5.5 Hz, 2H), 2.82 (tt, J = 10.4, 3.5 Hz, minor isomer), 2.57 (t, J = 6.6 Hz, minor isomer), 2.40 (t, J = 7.4 Hz, 2H), 2.11 (s, 3H), 2.21-1.98 (m, 2H), 1.97-1.50 (m, 10H) , 1.39-1.09 (m, 4H), 1.05 (s, 9H); ^{13} C NMR (75 MHz, $CDCl_3$) 145.9 (C), 144.6 (C), 135.4 (CH), 133.9 (C), 133.6 (C), 129.6 (CH), 129.5 (CH), 127.6 (CH), 127.5 (CH), 65.7 (CH), 65.1 (CH), 63.5 (CH_2), 63.1 (CH_2), 33.3 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 26.8 (CH_3), 26.8 (CH_3), 25.0 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 23.8 (CH_2), 21.3

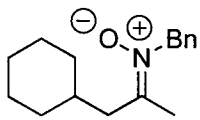
(CH_2), 19.2 (C), 19.1 (C), 18.7 (CH_3), 17.7 (CH_3); IR (film) : 3442, 2933, 2853, 2105, 1698, 1652, 1109, 1094, 820, 744, 702 cm $^{-1}$; MS m/z (relative intensity): 298.1334 (15.7%), 297.1300 (54.4%), 200.0597 (21.7%), 199.0546 (100%), 139.0212 (12.9%), 113.0838 (18.6%).



***N*-(1-Phenylpropan-2-ylidene)cyclohexanamine oxide, 3.133e (Table 3.7, entry 5).** Synthesized according to the general procedure using 0.94 g (0.81 mmol) of the corresponding allene. Isolated 0.38 g (40% yield) as a 4.6:1 ratio of isomers as a light yellow oil after column chromatography (0-4% MeOH/CH_2Cl_2). TLC R_f: 0.13, 0.15 (4% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 7.37-7.21 (m, 3H), 7.16-7.06 (m, 2H), 4.18 (tt, J = 11.4, 3.8 Hz, major isomer), 4.05, (tt, J = 11.1, 3.8 Hz, minor isomer), 3.96 (s, minor isomer), 3.81 (s, major isomer), 2.16 (s, major isomer), 2.20-2.02 (m, 2H), 1.98 (s, minor isomer), 1.95-1.56 (m, 5H), 1.38-1.15 (m, 3H); ^{13} C NMR (100 MHz, $CDCl_3$) 143.6 (C), 135.9 (C), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.1 (CH), 126.6 (CH), 66.0 (CH), 65.8 (CH), 39.0 (CH_2), 38.4 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 19.5 (CH_3), 17.6 (CH_3); IR (film) : 3062, 3028, 2937, 2853, 1717, 1702, 1648, 1576, 1497, 1447, 1364, 1166, 1135, 1033, 9995, 896, 740, 694 cm $^{-1}$; HRMS (EI): Exact mass calculated for $C_{15}H_{21}NO[M]^+$: 231.1623. Found: 231.1623.

Reaction of *N*-alkylhydroxylamines with cyclohexylallene (Table 3.8).

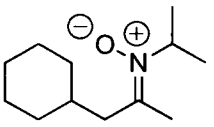
General procedure for reaction of *N*-alkylhydroxylamines with cyclohexylallene. A 5 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, *N*-alkylhydroxylamine (0.81 mmol, 1.0 equiv), *t*-butanol (1.6 mL, 0.50 M in *N*-alkylhydroxylamine), and cyclohexylallene (0.20 g, 1.6 mmol, 2.0 equiv). The vial was sealed using a cap with a resealable septum and purged through the septum with argon and an outlet for 5 minutes while stirring. The vial was then heated while stirring in a wax bath at 140°C for 18 hrs and analyzed by TLC (7% MeOH/CH_2Cl_2). The tube was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^1H NMR ($CDCl_3$) using 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography (typically 4% MeOH/CH_2Cl_2) to give the corresponding nitrone.



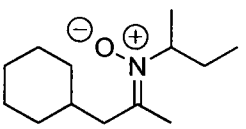
***N*-(1-Cyclohexylpropan-2-ylidene)-1-phenylmethanamine oxide, 3.134b (Table 3.8, entry 2).** Synthesized from *N*-benzylhydroxylamine[154] according to the general procedure. Isolated 0.16 g (81%) of a 1.9:1 mixture of isomers as a clear colorless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.34 (5% MeOH/ CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) 7.41-7.24 (m, 5H), 5.08 (s, 2H) (major), 5.04 (s, 2H) (minor), 2.47 (d, J = 7 Hz, 2H) (minor), 2.29 (d, J = 7 Hz, 2H) (major), 2.14 (s, 3 H) (major), 2.05 (s, 3H) (minor), 1.72-1.49 (m, 6H), 1.28-0.81 (m, 5H); ^{13}C NMR (100 MHz) 147.9 (C), 146.7 (C), 134.2 (C), 134.0 (C), 128.80 (CH), 128.76 (CH), 128.09 (CH), 127.65 (CH), 64.5 (CH_2), 63.4 (CH_2), 41.7 (CH_2), 40.4 (CH_2), 37.0 (CH), 34.9

[154] Maskill, H.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 2062

(CH), 33.5 (CH_2), 33.2 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 20.0 (CH_3), 19.0 (CH_3); IR (film): 2923, 2851, 1583, 1449, 1162, 732, 699; HRMS (EI): Exact mass calcd for $C_{16}H_{23}NO$ $[M]^+$: 245.1780. Found: 245.1766.

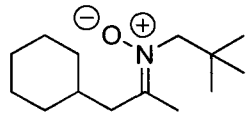


***N*-(1-Cyclohexylpropan-2-ylidene)propan-2-amine oxide, 3.134c (Table 3.8, entry 3).** Synthesized from **1c** according to the general procedure. Isolated 0.10 g (63%) of a 1.5:1 mixture of isomers as a clear colorless oil after column chromatography (5% $MeOH/CH_2Cl_2$). TLC R_f 0.34 and 0.37 (10% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 400 MHz) 4.48 (sept, J = 6 Hz, 1H) (major), 4.38 (sept, J = 6 Hz, 1H) (minor), 2.41 (d, J = 7 Hz, 2H) (minor), 2.26 (d, J = 7 Hz, 2H) (major), 2.06 (s, 3H) (major), 2.05 (s, 3H) (minor), 1.84-1.43 (m, 6H), 1.32 (d, J = 6 Hz, 6H) (major), 1.31 (d, J = 6 Hz, 6H) (minor), 1.25-0.86 (m, 5H); ^{13}C NMR (100 MHz) 145.4 (C), 143.9 (C), 57.2 (CH), 56.5 (CH), 41.1 (CH_2), 40.5 (CH_2), 37.0 (CH), 34.9 (CH), 33.3 (CH_2), 33.1 (CH_2), 26.1 (CH_2), 26.03 (CH_2), 26.00 (CH_2), 25.96 (CH_2), 20.1 (CH_3), 19.7 (CH_3), 19.5 (CH_3), 19.2 (CH_3); IR (film): 2974, 2924, 2851, 1579, 1449, 1363, 1185, 1075 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{23}NO$ $[M]^+$: 197.1780. Found: 197.1761.



***N*-(1-Cyclohexylpropan-2-ylidene)butan-2-amine oxide, 3.134d (Table 3.8, entry 4).** Synthesized from *N-sec*-butylhydroxylamine[56] according to the general procedure, but on a 0.41 mmol scale (all reagents and solvents scaled down accordingly). Isolated 0.042 g (49%) of a 1.2:1 mixture of isomers as a clear colorless oil after column chromatography

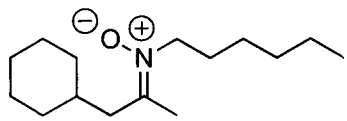
(5% MeOH/ CH_2Cl_2). TLC R_f 0.32 and 0.39 (5% MeOH/ CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) 4.26-4.17 (m, 1H) (major), 4.17-4.08 (m, 1H) (minor), 2.55 (dd, J = 14, 7 Hz, 1H) (minor), 2.33 (dd, J = 14, 7 Hz, 1H), 2.22 (dd, J = 14, 7 Hz, 1H) (major), 2.09 (s, 3H) (major), 2.05 (s, 3H) (minor), 2.03-1.90 (m, 1H), 1.88-1.43 (m, 7H), 1.31 (t, J = 7 Hz, 3H), 1.27-0.87 (m, 5H), 0.816 (t, J = 7 Hz, 3H) (major), 0.824 (t, J = 7 Hz, 3H) (minor); ^{13}C NMR (100 MHz) 146.5 (C), 145.2 (C), 63.3 (CH), 62.6 (CH), 41.2 (CH_2), 40.8 (CH_2), 37.1 (CH), 34.8 (CH), 33.5 (CH_2), 33.4 (CH_2), 33.3 (CH_2), 33.0 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 26.07 (CH_2), 26.05 (CH_2), 26.01 (CH_2), 19.6 (CH_3), 19.5 (CH_3), 18.6 (CH_3), 18.4 (CH_3), 10.8 (CH_3), 10.7 (CH_3); IR (film): 2967, 2931, 2924, 2852, 1573, 1449, 1370, 1184, 1086 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{25}NO$ $[M]^+$: 211.1936. Found: 211.1919.



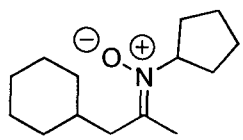
***N*-(1-Cyclohexylpropan-2-ylidene)-2,2-dimethylpropan-1-amine oxide, 3.134e (Table 3.8, entry 5).** Synthesized from *N*-neopentylhydroxylamine[155] according to the general procedure, but on a 0.41 mmol scale (all reagents and solvents scaled down accordingly). Isolated 0.043 g (47%) of a 1.1:1 mixture of isomers as a clear colorless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.38 (5% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 3.71 (s, 2H) (minor), 3.69 (s, 2H) (major), 2.47 (d, J = 7 Hz, 2H) (minor), 2.27 (d, J = 7 Hz, 2H) (major), 2.11 (s, 3H) (minor), 2.07 (s, 3H) (major), 1.76-1.49 (m, 6H), 1.34-0.81 (m, 5H), 1.08 (s, 9H) (major), 1.07 (s, 9H) (minor); ^{13}C NMR (75 MHz) 148.3 (C), 147.3 (C), 68.6 (CH_2), 67.9 (CH_2), 42.4 (CH_2), 40.7 (CH_2), 37.0 (CH),

[155] Heydari, A.; Tavakol, H.; Aslanzadeh, S.; Azarnia, J.; Ahmadi, N. *Synthesis* **2005**, 627

34.8 (CH), 33.5 (CH_2), 33.2 (CH_2), 28.7 (CH_3), 28.6 (CH_3), 28.03 (C), 27.5 (C), 26.22 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 21.1 (CH_3), 18.9 (CH_3); IR (film): 2976, 2924, 2851, 1579, 1473, 1356 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{27}NO$ $[M]^+$: 225.2093. Found: 225.2057.



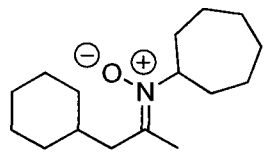
***N*-(1-Cyclohexylpropan-2-ylidene)hexan-1-amine oxide, 3.134f (Table 3.8, entry 6).** Synthesized from *N*-hexylhydroxylamine[156] according to the general procedure. Isolated 0.099 g (51%) of a 1.2:1 mixture of isomers as a clear colorless oil after column chromatography (5% MeOH/CH_2Cl_2). TLC R_f 0.47 (7% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 3.81 (t, J = 7.2 Hz, 2H) (minor), 3.78 (t, J = 7.2 Hz, 2H) (major), 2.43 (d, J = 7.2 Hz, 1H), 2.24 (d, J = 7.2 Hz, 1H), 2.06 (d, J = 13.3 Hz, 3H), 1.96-0.70 (m, 22H); ^{13}C NMR (75 MHz) 146.9 (C), 145.7 (C), 59.3 (CH_2), 58.5 (CH_2), 41.5 (CH_2), 40.2 (CH_2), 36.9 (CH), 34.8 (CH), 33.3 (CH_2), 33.1 (CH_2), 31.34 (CH_2), 31.30 (CH_2), 27.7 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 22.4 (CH_2), 19.7 (CH_3), 18.9 (CH_3), 13.84 (CH_3), 13.83 (CH_3); IR (film): 3416, 2918, 2857, 1717, 1652, 748 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{29}NO$ $[M]^+$: 239.2249. Found: 239.2202.



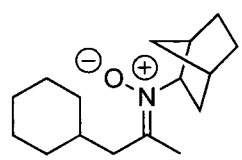
***N*-(1-Cyclohexylpropan-2-ylidene)cyclopentanamine oxide, 3.134g (Table 3.8, entry 7).** Synthesized from *N*-cyclopentylhydroxylamine (**3.131g**) according to the general

[156] Shiino, M.; Watanabe, Y.; Umezawa, K. *Biiorg. Med. Chem.* **2001**, *9*, 1233

procedure. Isolated 0.11 g (58%) as a clear colorless oil after column chromatography (5% MeOH/CH_2Cl_2). TLC R_f 0.42 (7% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) 4.65 (tt, J = 8 Hz, 6Hz, 1H) (major), 4.54 (tt, J = 8 Hz, 6 Hz, 1H) (minor), 2.40 (d, J = 7 Hz, 2H) (minor), 2.29 (d, J = 7 Hz, 2H) (major), 2.24-2.07 (m, 2H), 2.06 (s, 3H), 1.95-1.44 (m, 12H), 1.26-0.85 (m, 5H); ^{13}C NMR (100 MHz) 146.4 (C), 144.7 (C), 66.3 (CH), 65.5 (CH), 41.5 (CH_2), 40.7 (CH_2), 37.0 (CH), 34.8 (CH), 33.3 (CH_2), 33.1 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 26.1 (CH_2), 26.01 (CH_2), 25.97 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 19.7 (CH_3), 19.6 (CH_3); IR (film): 2929, 2853, 1574, 1450, 897 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{25}NO$ $[M]^+$: 223.1936. Found: 223.1932.



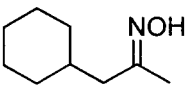
***N*-(1-Cyclohexylpropan-2-ylidene)cycloheptanamine oxide, 3.134h (Table 3.8, entry 8).** Synthesized according to the general procedure. Isolated 0.15 g (71%) as a clear colorless oil after column chromatography (5% MeOH/CH_2Cl_2). TLC R_f 0.38 (7% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 4.29 (tt, J = 9, 9, 4, 4 Hz, 1H), 2.28 (d, J = 7 Hz, 2H), 2.07 (s, 3H), 1.92-1.34 (m, 18 H), 1.33-0.85 (m, 5H); ^{13}C NMR (75 MHz) 144.7 (C), 66.5 (CH), 41.4 (CH_2), 37.2 (CH), 33.2 (CH_2), 32.5 (CH_2), 28.4 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.0 (CH_2), 19.4 (CH_3); IR (film): 2924, 2853, 1571, 1450, 1180, 1144, 896 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{29}NO$ $[M]^+$: 251.2249. Found: 251.2238.



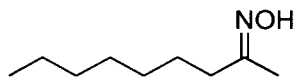
(*Z*)-*exo*-*N*-(1-Cyclohexylpropan-2-ylidene)bicyclo[2.2.1]heptan-2-amine oxide, 3.134i (Table 3.8, entry 9). Synthesized from **3.131i**[55] according to the general procedure. Isolated 0.077 g (38%) as a clear colorless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.34 (7% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 4.11 (dd, J = 8, 5 Hz, 1H), 2.48-2.18 (m, 5H), 2.10 (s, 3H), 1.83-0.89 (m, 18 H); ^{13}C NMR (75 MHz) 146.1 (C), 67.4 (CH), 42.9 (CH), 41.5 (CH_2), 37.1 (CH), 36.9 (CH_2), 36.5 (CH_2), 35.6 (CH), 33.3 (CH), 33.2 (CH), 28.1 (CH_2), 28.0 (CH_2), 26.13 (CH_2), 26.10 (CH_2), 26.05 (CH_2), 19.7 (CH); IR (film): 2967, 2931, 2924, 2852, 1573, 1449, 1370, 1184, 1086 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{27}NO$ $[M]^+$: 249.2093. Found: 249.2101.

Reaction of aqueous hydroxylamine with allenes (Table 3.9).

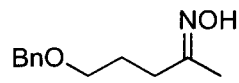
General Procedure for the formation of oximes: A non-flame-dried 2 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, 50% aqueous hydroxylamine (3.2 mmol, 2.0 equiv), HPLC grade *i*-PrOH (0.65 mL, 2.5 M to allene), and allene (1.6 mmol, 1.0 equiv). The vial was sealed using a cap with a resealable septum and purged through the septum with argon and an outlet for 5 minutes while stirring. The vial was then heated while stirring in a wax bath at 110°C for 18 hrs and analyzed by TLC. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding oxime.



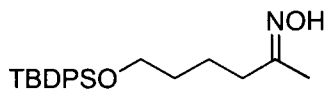
1-Cyclohexylpropan-2-one oxime, 3.136a (Table 3.9, entry 1). Synthesized according to the general procedure. Isolated 0.19 g (75%) as a clear colorless oil after column chromatography as a 2.8:1 mixture of isomers (10% EtOAc/hexanes → 20% EtOAc/hexanes). TLC R_f 0.50 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 9.44 (br s, 1H), 2.27 (d, J = 7 Hz, 2H) (minor), 2.05 (d, J = 7 Hz, 2H) (major), 1.86 (s, 3H) (major), 1.85 (s, 3H) (minor), 1.76-1.44 (m, 6H), 1.33-0.75 (m, 5H); ^{13}C NMR (75 MHz) 158.0 (C), 157.6 (C), 43.3 (CH_2), 36.2 (CH_2), 35.10 (CH), 35.05 (CH), 33.3 (CH_2), 33.0 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.17 (CH_2), 26.10 (CH_2), 20.7 (CH_3), 13.6 (CH_3); IR (film): 3275, 3226, 3123, 2922, 2861, 2835, 1432, 1008; HRMS (EI): Exact mass calcd for $C_9H_{17}NO$ $[M]^+$: 155.1310. Found: 155.1291.



Nonan-2-one oxime, 3.136b (Table 3.9, entry 2). Synthesized according to the general procedure. Isolated 0.24 g (93%) of a clear colorless oil after column chromatography as a 3:1 mixture of isomers (15% EtOAc/hexanes → 20% EtOAc/hexanes). TLC R_f 0.50 and 0.62 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 9.57 (br s, 1H), 2.34 (t, J = 8 Hz, 2H) (minor), 2.16 (t, J = 8 Hz, 2 H) (major), 1.87 (s, 3H) (major), 1.85 (s, 3H) (minor), 1.57-1.40 (m, 2H), 1.37-1.16 (m, 8H), 0.86 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz) 158.9 (C), 158.6 (C), 35.7 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 29.03 (CH_2), 28.98 (CH_2), 28.6 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 19.8 (CH_3), 14.0 (CH_3), 13.3 (CH_3); IR (film): 3256, 2956, 2929, 2861, 1667, 1462, 1363, 1108, 945 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{19}NO$ $[M]^+$: 157.1467. Found: 157.1468.

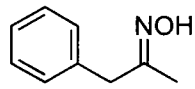


5-(Benzyloxy)pentan-2-one oxime, 3.136c (Table 3.9, entry 3). Synthesized according to the general procedure. Isolated 0.33 g (99%) as a clear colorless oil after column chromatography (15% EtOAc/hexanes). TLC R_f 0.31 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.37-7.26 (m, 5H), 4.51 (s, 2H) (minor), 4.50 (s, 2H) (major), 3.50 (t, J = 6 Hz, 2H), 2.47 (t, J = 8 Hz, 2H) (minor), 2.31 (t, J = 8 Hz, 2H) (major), 1.89 (s, 3H) (major), 1.88 (s, 3H) (minor), 1.88-1.81 (m, 2H); ^{13}C NMR (75 MHz) 158.3 (C), 158.0 (C), 138.3 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 72.8 (CH_2), 69.8 (CH_2), 69.4 (CH_2), 32.6 (CH_2), 26.3 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 19.9 (CH_3), 13.5 (CH_3); IR (film): 3334, 2922, 2859, 1663, 1453, 1366, 1104, 737, 698 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{12}H_{17}NO_2[M]^+$: 207.1259. Not found. Exact mass calculated for $C_5H_{10}NO_2[M\text{-}Bn]^+$: 116.0712. Found: 116.0711.

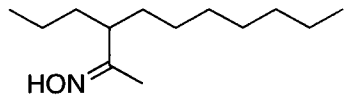


6-(*tert*-Butyldiphenylsilyloxy)hexan-2-one oxime, 3.136d (Table 3.9, entry 4). Synthesized according to the general procedure using 0.54 g (1.6 mmol) of the corresponding allene. Isolated 0.52 g (87% yield) as a 2.8:1 ratio of isomers as a clear, colourless oil after column chromatography (30% ether/pentane). TLC R_f: 0.325, 0.2 (30% ether/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) 7.80 (br, 1H), 7.69-7.64 (m, 4H), 7.45-7.34 (m, 6H), 3.68 (q, J = 6.0 Hz, 2H), 2.37 (t, J = 7.4 Hz, minor isomer), 2.17 (t, J = 7.3 Hz, major isomer), 1.86 (s, major isomer), 1.85 (s, minor isomer), 1.66-1.52 (m, 4H), 1.05 (s, 9H); ^{13} C NMR (100 MHz, $CDCl_3$) 159.1 (C), 158.7 (C), 135.5 (CH), 133.9 (C), 129.5 (CH), 127.6 (CH), 63.4 (CH_2), 63.4 (CH_2), 35.5 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 28.0 (CH_2), 26.8 (CH_3), 22.5 (CH_2), 21.8 (CH_2), 19.7 (CH_3), 19.2 (C), 13.1 (CH_3); IR (film) : 3431, 2952, 2929, 2857, 2108, 1652, 1641, 1113, 1094, 938, 820, 744, 698 (cm

[1]) ; HRMS (EI): Exact mass calculated for $C_{22}H_{31}NO_2Si[M]^+$: 369.2124. Not found. Exact mass calculated for $C_{18}H_{22}NO_2Si[M - \textit{tert}\text{-butyl}]^+$: 312.1420 Found: 312.1359.



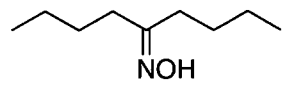
1-Phenylpropan-2-one oxime, 3.136e (Table 3.9, entry 5). Synthesized from phenylallene according to the general procedure. Isolated 0.17g (71%) as a clear colorless oil after column chromatography (15% EtOAc/hexanes). TLC R_f 0.33 (20% EtOAc/hexanes. Spectral data was found to be in good agreement with the literature.[157]



3-Propyldecan-2-one oxime, 3.136g (Table 3.9, entry 7). A non-flame-dried 2 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, the corresponding allene (0.20 g, 1.1 mmol), 50% aqueous hydroxylamine (0.18 g, 2.8 mmol, 2.5 equiv) and HPLC grade *i*-PrOH (0.25 M, 4.4 mL). The reaction was purged with argon for 5 minutes and the tube was sealed. The reaction was heated to 160 °C in the microwave for 4 hours. Isolated 0.037 g as a clear, colourless oil after column chromatography (30% ether/hexanes). TLC R_f: 0.253, 0.338 (30% ether/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.37 (br, 1H), 2.29-2.18 (m, 1H), 1.75 (s, 3H), 1.43-1.33 (4, 1H), 1.33-1.14 (m, 12H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H); ^{13} C NMR (75 MHz, $CDCl_3$) 161.5 (C), 44.7 (CH), 34.7 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.2 (CH_2), 27.4 (CH_2), 22.6 (CH_2), 20.6 (CH_2), 14.1 (CH_3), 14.1 (CH_3), 9.5 (CH_3); IR (film) :

[157] Hwu, J. R.; Tseng, W. N.; Patel, H. V.; Wong, F. F.; Horng, D.; Liaw, B. R.; Lin, L. C. *J. Org. Chem.* **1999**, *64*, 2211

3424, 2078, 1649, 1637 (cm^{-1}) ; HRMS (EI): Exact mass calculated for $C_{13}H_{27}NO[M]^+$: 213.2093. Found: 203.2095.



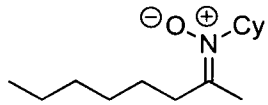
Nonan-5-one oxime, 3.136h (Table 3.9, entry 8). Synthesized according to the general procedure using 0.20 g (1.6 mmol) of the corresponding allene. Isolated 0.032 g (13% yield) as a clear, colourless oil after column chromatography (20% ether/hexanes). TLC R_f: 0.27 (20% ether/hexanes); ^1H NMR (300 MHz, $CDCl_3$) 7.20 (br, 1H), 2.35 (dd, J = 8.7, 6.9 Hz, 2H), 2.18 (dd, J = 8.6, 6.6 Hz, 2H), 1.50 (tt, J = 7.4, 5.9 Hz, 4H), 1.36 (qd, J = 15.3, 7.3 Hz, 4H), 0.95 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13} C NMR (75 MHz, $CDCl_3$) 162.5 (C), 33.7 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 27.1 (CH_2), 23.0 (CH_2), 22.4 (CH_2), 13.8 (CH_3); IR (film): 3419, 211, 1652, 1630, 782 (cm^{-1}) ; HRMS (EI): Exact mass calculated for $C_9H_{19}NO[M]^+$: 157.1467. Found: 157.1460.

5.3.2. Procedures and Characterization of Alkyne Reactivity

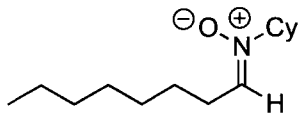
Reaction of *N*-alkylhydroxylamines with alkynes (Table 3.12).

General procedure for the reaction of *N*-alkylhydroxylamines with alkynes. A 2 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, *N*-cyclohexylhydroxylamine (0.15 g, 1.3 mmol, 1.0 equiv), *t*-butanol (2.6 mL, 0.5 M to hydroxylamine), and 1-octyne (6.5 mmol, 5.0 equiv). The vial was sealed using a cap with a resealable septum and purged through the septum with argon and an outlet for 5 minutes while stirring. The vial was then heated while stirring in an oil bath at 110°C for 18 hrs and analyzed by TLC. The tube was cooled to ambient temperature, concentrated

under reduced pressure and analyzed by ^{1}H NMR ($CDCl_3$) using 1,4-dimethoxybenzene as an internal standard.

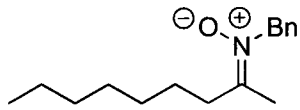


***N*-(Octan-2-ylidene)cyclohexanamine oxide, 3.148a (Table 3.12, entry 1a).** Synthesized according to the general procedure using *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 1-octyne (0.72 g, 6.5 mmol). Isolated 0.15 g (47% yield) as a light yellow oil after column chromatography (2-4% MeOH/ CH_2Cl_2) TLC R_f: 0.23 and 0.29 (4% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.98 (ttd, J = 19.1, 11.4, 3.8 Hz, 1H), 2.55-2.45 (m, 2H) (major), 2.37-2.30 (m, 2H) (minor), 2.06 (s, 3H) (minor), 2.01 (s, 3H) (major), 2.16-1.90 (m, 2H), 1.90-1.53 (m, 5H), 1.53-1.36 (m, 2H), 1.37-1.11 (m, 9H), 0.82 (q, J = 6.7, Hz, 3H); ^{13} C NMR (75 MHz, $CDCl_3$) 145.9 (C), 144.7 (C), 65.5 (CH), 65.0 (CH), 33.3 (CH_2), 32.6 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 27.1 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 18.6 (CH_3), 17.8 (CH_3), 13.9 (CH_3), 13.8 (CH_3); IR (film): 3423, 2933, 2861, 1660, 1451, 1150, 1113 (cm $^{-1}$) ; HRMS (EI): Exact mass calculated for $C_{14}H_{27}NO[M]^+$: 225.2093. Found: 225.2072.

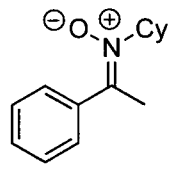


***N*-Octylidenecyclohexanamine oxide, 3.148aa (Table 3.12, entry 1aa).** TLC R_f: 0.43 (3% MeOH/CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$ δ ppm 6.66 (t, J = 5.7 Hz, 1H), 3.62 (tt, J = 11.5, 3.6 Hz, 1H), 2.46 (dt, J = 7.6, 5.8 Hz, 2H), 1.97 (d, J = 11.0 Hz, 2H), 1.88-1.77 (m, 4H), 1.65 (d, J = 12.4 Hz, 2H), 1.48 (td, J = 15.5, 7.67 Hz, 2H), 1.37-1.12 (m, 10H),

0.85 (t, J = 7.0 Hz, 3H); ^{13} C NMR (125 MHz) 136.9 (CH), 73.7 (CH), 31.6 (CH_2), 31.1 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 26.5 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (film): 3412, 2933, 2861, 1652, 1584, 1455, 1367, 1170, 1139, 1052, 911, 892, 744 (cm $^{-1}$) ; HRMS (EI): Exact mass calculated for $C_{14}H_{27}NO[M]^+$: 225.2093. Found: 225.2037.

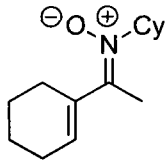


***N*-(Nonan-2-ylidene)-1-phenylmethanamine oxide, 3.148b, (Table 3.12, entry 1b).** Synthesized according to the general procedure using *N*-benzylylhydroxylamine[154] (0.16 g, 1.3 mmol) and 1-octyne (0.72 g, 6.5 mmol). Isolated 0.016 g (4.9% yield) as a light yellow oil after column chromatography (3% MeOH/CH_2Cl_2). TLC R_f 0.23 and 0.28 (3% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 7.44-7.27 (m, 5H), 5.09 (s, 2H, major isomer), 5.06 (s, minor isomer), 2.43-2.34 (m, 2H, major isomer), 2.63-2.55 (m, minor isomer), 2.14 (s, 3H, major isomer), 2.06 (s, minor isomer), 1.63-1.15 (m, 8H), 0.86 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.5 (CH), 134.1 (CH_2), 133.9 (CH_2), 129.0 (CH_2), 128.8 (CH_2), 128.8 (CH_2), 128.4 (CH_2), 128.1 (CH_2), 128.0 (CH_2), 127.6 (CH_2), 127.5 (CH_2), 127.5 (CH_2), 64.3 (CH_2), 63.5 (CH_2), 34.2 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 26.7 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 18.7 (CH_3), 18.1 (CH_3), 14.0 (CH_3), 13.9 (CH_3); IR (film): 2956, 2934, 2857, 1451, 1151 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{23}NO$ $[M]^+$: 233.1780. Found: 233.17706.

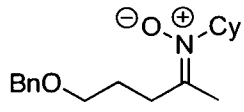


***N*-(1-Phenylethylidene)cyclohexanamine oxide, 3.148c (Table 3.12, entry 3)**

Synthesized according to the general procedure using *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and phenylacetylene (0.66 g, 6.5 mmol). Isolated 0.124 g (44% yield) as a clear, colourless oil after column chromatography (2% $MeOH/CH_2Cl_2$). TLC R_f 0.33 (5% $MeOH/CH_2Cl_2$). The NMR data corresponded with characterization previously reported.[55]

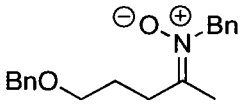


***N*-(1-Cyclohexenylethylidene)cyclohexanamine oxide, 3.148d (Table 3.12, entry 4).** Synthesized according to the general procedure using *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 1-ethynylcyclohex-1-ene (0.69 g, 6.5 mmol). Isolated 0.52 g (18% yield) as a yellow oil after column chromatography (2-5% $MeOH/CH_2Cl_2$). TLC R_f: 0.25, 0.31 (4% $MeOH/CH_2Cl_2$);^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.68-5.61 (m, 1H), 4.17 (tt, J = 11.4, 3.8 Hz, 1H), 2.17-1.96 (m, 4H), 2.12 (s, 3H), 1.89-1.76 (m, 2H), 1.75-1.54 (m, 8H), 1.33-1.09 (m, 4H); ^{13}C NMR δ ppm 147.3 (C), 134.6 (C), 127.9 (CH), 66.6 (CH), 30.3 (CH_2), 26.8 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 22.3 (CH_2), 21.5 (CH_2), 18.2 (CH_3); IR (film): 3424, 2933, 2857, 1652, 1561, 1451, 1193, 1143, 1063, 911, 744 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{23}NO$ $[M]^+$: 221.1780. Found: 233.17717.

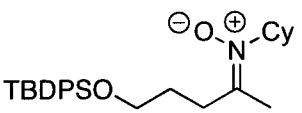


***N*-(5-(Benzyloxy)pentan-2-ylidene)cyclohexanamine oxide, 3.133c (Table 3.12, entry 5).** Synthesized according to the general procedure using *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and the corresponding alkyne **3.147d** (1.1 g, 6.5 mmol). Isolated 0.19

g (50% yield) as a light yellow oil after column chromatography (3-4% MeOH/CH_2Cl_2). TLC R_f 0.37, 0.46 (5% MeOH/CH_2Cl_2); For characterization data see allene section.

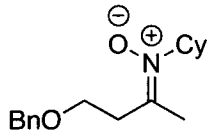


***N*-(5-(Benzyloxy)pentan-2-ylidene)-1-phenylmethanamine oxide, 3.148e, (Table 3.12, entry 6).** Synthesized according to the general procedure using *N*-benzylhydroxylamine[154] (0.16 g, 1.3 mmol) and and the corresponding alkyne **3.147d** (1.1 g, 6.5 mmol). Isolated 0.023 g (5.9% yield) as a 1.1:1 ratio of isomers as a yellow oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f: 0.26, 0.31 (4% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.47-7.27 (m, 10H), 5.10 (s, 2H), 5.04 (s, minor isomer H), 4.48 (s, 2H), 3.52 (t, J = 6.3 Hz, 2H, major isomer), 3.44 (t, J = 5.8 Hz, minor isomer), 2.69 (dd, J = 8.5, 7.0 Hz, 2H, major isomer), 2.53 (m, minor isomer), 2.14 (s, 3H), 2.07 (s, minor isomer), 1.99-1.84 (m, 2H, major isomer), 1.83-1.71 (m, minor isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 147.6 (C), 147.0 (C), 138.3 (C), 138.0 (C), 134.2 (C), 133.8 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 73.0 (CH_2), 72.9 (CH_2), 69.9 (CH_2), 68.4 (CH_2), 64.3 (CH_2), 63.6 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 26.9 (CH_2), 24.8 (CH_2), 19.1 (CH_3), 17.9 (CH_3). IR (film): 3463, 2937, 2857, 2108, 1647, 1455, 1098, 1087 cm^{-1}; MS m/z (relative intensity): 164.0829 (10%), 107.0490 (32.6%), 106.0651 (25.0%), 101.0599 (17.1%), 91.0531 (100.0%).



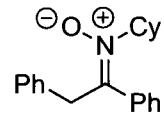
***N*-(5-(*tert*-Butyldiphenylsilyloxy)pentan-2-ylidene)cyclohexanamine oxide, 3.148f**

(Table 3.12, entry 7). Synthesized according to the general procedure using *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and the corresponding alkyne **3.147e** (2.1 g, 6.5 mmol). Isolated 0.33 g (57% yield) as a yellow oil after column chromatography (3-4% MeOH/CH_2Cl_2). TLC R_f: 0.30 (4% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.71-7.56 (m, 4H), 7.48-7.34 (m, 6H), 4.12 (tt, *J* = 11.23, 11.23, 3.75, 3.75 Hz, 1H), 3.69 (t, *J* = 5.70, 5.70 Hz, 2H), 2.61-2.47 (m, 2H), 2.11 (s, 3H), 2.19-2.00 (m, 2H), 1.94-1.79 (m, 2H), 1.80-1.60 (m, 5H), 1.37-1.18 (m, 3H), 1.08 (s, 9H), 1.04 (s, minor isomer);); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 145.5 (C), 135.5 (CH), 135.5 (CH), 133.4 (C), 129.8 (CH), 127.7 (CH), 127.6 (CH), 65.1 (CH), 62.6 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 26.9 (CH_3), 25.0 (CH_2), 24.9 (CH_2), 19.2 (C), 18.7 (CH_3); IR (film): 3509, 2934, 2857, 2086, 1653, 1451 cm^{-1}; MS m/z (relative intensity): 380.2058 (7.8%), 365.2195 (11.7%), 364.2178 (37.8%), 282.1312 (22.1%), 266.0997 (6.9%), 199.0574 (100.0%), 181.0622 (11.0%), 155.1306 (20.5%).

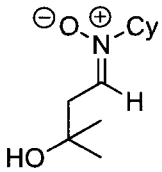


***N*-(4-(Benzyloxy)butan-2-ylidene)-1-cyclohexanamine oxide, 3.148g (Table 3.12, entry 8).** Synthesized according to the general procedure using *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and the corresponding alkyne **3.147f** (1.04 g, 6.5 mmol). Isolated 0.158 g (44% yield) as a 1.4:1 ratio of isomers as a yellow oil after column chromatography (2.5-4% MeOH/CH_2Cl_2). TLC R_f: 0.24, 0.27 (4% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.46-7.07 (m, 5H), 4.47 (s, minor isomer), 4.46 (s, 2H, major isomer), 4.16 (tt, *J* = 11.3, 3.6 Hz, 1H, major isomer), 4.01 (tt, *J* = 11.5, 3.9 Hz, minor isomer), 3.74 (t, *J* = 6.0 Hz, minor isomer), 3.58 (t, *J* = 6.3

Hz, 2H, major isomer), 2.85 (t, J = 6.0 Hz, minor isomer), 2.69 (t, J = 6.3 Hz, 2H, major isomer), 2.12 (s, minor isomer), 2.10 (s, 3H, major isomer), 2.07-1.52 (m, 5H), 1.36-1.12 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 143.1 (C), 142.9 (C), 138.2 (C), 137.5 (C), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 73.2 (CH_2), 72.7 (CH_2), 66.6 (CH), 65.9 (CH), 65.6 (CH_2), 65.3 (CH_2), 34.0 (CH_2), 33.6 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 18.8 (CH_3), 18.6 (CH_3); IR (film): 3585, 2937, 2860, 2108, 1652, 1447, 1360, 1101 cm^{-1}; MS m/z (relative intensity): 247.9862 (1.8%), 168.1367 (18.2%), 161.9906 (23.7%), 142.9926 (20.5%), 120.0572 (21.5%), 107.0485 (80.6%), 91.0560 (100.0%).



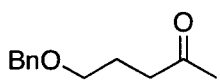
***N*-(1,2-diphenylethylidene)cyclohexanamine oxide, 3.148h (Table 3.12, entry 9).** Synthesized according to the general procedure using *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and diphenylacetylene (1.2 g, 6.5 mmol). Isolated 0.057 g (15% yield) as a colourless oil after column chromatography (3-4% MeOH/CH_2Cl_2). TLC R_f: 0.28 (4% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35-7.28 (m, 3H), 7.21-7.12 (m, 5H), 7.03-6.98 (m, 2H), 4.16 (s, 2H), 4.14 (s, minor isomer), 3.92 (tt, J = 11.4, 3.5 Hz, 1H), 2.50-2.45 (m, minor isomer), 2.25-2.00 (m, 2H), 1.81-1.46 (m, 6H), 1.26-0.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 147.2 (C), 136.4 (C), 135.4 (C), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 127.7 (CH), 126.4 (CH), 67.8 (CH), 39.0 (CH_2), 30.2 (CH_2), 24.8 (CH_2), 24.7 (CH_2); IR (film): 3443, 2930, 2856, 1455, 1217 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{20}H_{23}NO$ $[M]^+$: 293.1780. Found: 293.17634.



***N*-(3-hydroxy-3-methylbutylidene)cyclohexanamine oxide, 3.150 (Equation 3.21).** Synthesized according to the general procedure using N-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 2-methylbut-3-yne-2-ol (0.55 g, 6.5 mmol). Isolated 0.018 g (7% yield) as a yellow oil after column chromatography (2-4% MeOH/CH_2Cl_2). TLC R_f: 0.21, 0.29 (4% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 1H NMR (300 MHz, $CDCl_3$) δ ppm 6.92 (t, J = 6.2 Hz, 1H), 4.93 (br, 1H), 3.71 (tdd, J = 11.2, 7.3, 3.7 Hz, 1H), 2.67 (d, J = 6.2 Hz, 2H), 2.08-1.95 (m, 2H), 1.93-1.75 (m, 4H), 1.72-1.61 (m, 2H), 1.50-1.12 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz)) δ ppm 134.6 (CH), 73.8 (CH), 72.2 (C), 40.4 (CH_2), 31.1 (CH_2), 30.2 (CH_3), 25.0 (CH_2), 24.9 (CH_2); IR (film) 3344, 2971, 2933, 2861, 1664, 1451, 1367, 1128, 892 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{21}NO_2$ $[M]^+$: 199.1572. Not found. Exact mass calculated for $C_{11}H_{19}NO$ 1[M – $H_2O]^+$: 181.1467. Found : 181.1528.

5.3.3. Procedures and Characterization of Ketone Reactivity

Preparation of ketones

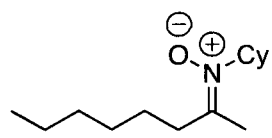


5-(Benzyloxy)pentan-2-one, 3.173k. Sodium hydride (0.26 g, 11 mmol, 1.1 equiv) and THF (0.50 M, 20 mL) were added to a flame-dried round-bottomed flask. The solution was cooled to 0 °C and 3-acetyl-1-propanol (1.0 g, 1.0 mL, 10.0 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 45 minutes after

which benzyl bromide (1.9 g, 1.3 mL, 11 mmol, 1.1 equiv) was added and then stirred overnight. The reaction was quenched with a saturated solution of ammonium chloride and extracted with ether. The combined organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Isolated 0.37 g (20%) as a clear oil after column chromatography (25% Et_2O/Pet.Ether). The ^1H NMR corresponded with characterization previously reported.[158]

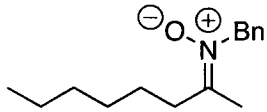
Condensation of *N*-alkylhydroxylamines with ketones (Table 3.13).

General procedure for the condensation of *N*-alkylhydroxylamines with ketones. A flame-dried 2 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, *N*-alkyllhydroxylamine (1.3 mmol, 1.0 equiv), *t*-butanol (2.6 mL, 0.5 M to hydroxylamine), and ketone (2.6 mmol, 2.0 equiv). The vial was sealed with a septum and purged with argon and outlet for 5 minutes while stirring. The vial was sealed using a cap with a resealable septum and was then heated while stirring in an oil bath at 110 °C for 18 hrs and analyzed by TLC. The tube was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^1H NMR ($CDCl_3$) using 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding nitrone.

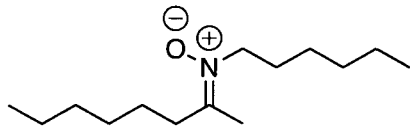


[158] Jiang, J.B.; Urbanski, M.J.; Hajos, Z.G. *J. Org. Chem.* **1983**, *48*, 2001

***N*-(Octan-2-ylidene)cyclohexanamine oxide, 3.148a (Table 3.13, entry 1).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 2-octanone (0.33 g, 0.41 mL, 2.6 mmol) according to the general procedure. Isolated 0.25 g (81%) of a 1.8:1 mixture of isomers as a light yellow oil after column chromatography (2-4% MeOH/CH_2Cl_2). TLC R_f: 0.23 and 0.29 (4% MeOH/CH_2Cl_2). The NMR corresponded with characterization previously reported. [79a]

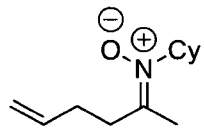


***N*-(Octan-2-ylidene)-1-phenylmethanamine oxide, 3.148b (Table 3.13, entry 2).** Synthesized from *N*-benzylhydroxylamine[154] (0.16 g, 1.3 mmol) and 2-octanone (0.33 g, 0.41 mL, 2.6 mmol) according to the general procedure. Isolated 0.27 g (82%) as a 1.1:1 ratio of isomers as a light yellow oil after column chromatography (3% MeOH/CH_2Cl_2). TLC R_f 0.23 and 0.28 (3% MeOH/CH_2Cl_2). For characterization see alkyne section.

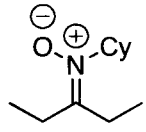


***N*-(Octan-2-ylidene)hexan-1-amine oxide, 3.174a (Table 3.13, entry 3).** Synthesized from *N*-hexylhydroxylamine[156] (0.15 g, 1.3 mmol) and 2-octanone (0.33 g, 0.41 mL, 2.6 mmol) according to the general procedure. Isolated 0.22 g (70%) as a 1.67:1 ratio of isomers of a clear oil after column chromatography (1-3% MeOH/CH_2Cl_2). TLC R_f 0.27 and 0.32 (4% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz)) δ ppm 3.81 (dd, J = 15.5, 8.0 Hz, 2H), 2.58-2.51 (m, minor isomer), 2.38-2.30 (m, 2H), 2.10 (s, 3H), 2.04 (s, minor isomer), 1.93-1.82 (m, 2H), 1.59-1.43 (m, 2H), 1.37-1.23 (m, 12H), 0.91-0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 147.7 (C), 59.3 (CH_2), 58.6 (CH_2), 34.0 (CH_2), 32.5 (CH_2),

31.7 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 27.9 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 24.8 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 18.4 (CH_2), 18.2 (CH_2), 14.0 (CH_3), 13.9 (CH_3); IR (film): 3405, 2957, 2928, 2858, 1717, 1589, 1467, 1379, 1209, 1170, 1109, 729 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{30}NO$ $[M+H]^+$:228.2322. Found: 228.23314.

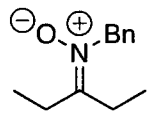


***(Z)-N*-(Hex-5-en-2-ylidene)cyclohexanamine oxide, 3.174b (Table 3.13, entry 4).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 5-hexen-2-one (0.27 mL, 0.26 g, 2.6 mmol) according to the general procedure. Isolated 0.17 g (60%) as white crystals after column chromatography (4-5% $MeOH/CH_2Cl_2$). TLC R_f 0.39 (5% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 5.78 (tdd, *J* = 16.78, 13.33, 4.88, 4.88 Hz, 1H), 5.13-4.93 (m, 2H), 4.04 (tt, *J* = 11.7 3.8 Hz, 1H), 2.80 (tt, *J* = 10.4 3.8 Hz, 1H), 2.66 (t, *J* = 7.4 Hz, 1H), 2.50 (t, *J* = 7.6 Hz, 1H), 2.26 (dd, *J* = 14.6, 7.4 Hz, 2H), 2.11 (s, 1H), 2.06 (s, 1H), 1.95-1.80 (m, 1H), 1.80-1.56 (m, 1H), 1.41-0.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 145.1 (C), 135.9 (CH), 116.7 (CH_2), 65.3 (CH), 33.0 (CH_2), 31.3 (CH_2), 30.2 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 18.8 (CH_3); IR 3427, 2934, 2860, 1647, 1162, 1139 (film): cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{21}NO$ $[M]^+$: 195.1623. Found: 195.16526.

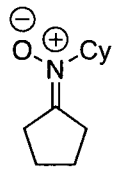


***N*-(Pentan-3-ylidene)cyclohexanamine oxide, 3.174c (Table 3.13, entry 5).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 3-pentanone

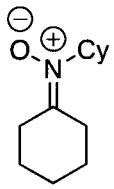
(0.69 mL, 0.56 g, 6.5 mmol, 5.0 equiv) according to the general procedure except with 5 equiv of ketone. Isolated 0.11 g (41%) as a white crystal after column chromatography (2-3% $MeOH/CH_2Cl_2$). TLC R_f 0.25 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 3.97 (tt, J = 11.3, 3.7 Hz, 1H), 2.55 (q, J = 7.5 Hz, 2H), 2.37 (q, J = 7.6 Hz, 2H), 2.08 (dq, J = 12.1, 3.2 Hz, 2H), 1.93-1.57 (m, 5H), 1.40-1.17 (m, 3H), 1.09 (dt, J = 7.6, 2.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 150.9 (C), 65.3 (CH), 30.2 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 24.4 (CH_2), 11.8 (CH_3), 9.1 (CH_3); IR (film): 3412, 2933, 2856, 1576, 1454, 1378, 1172, 1143, 1007, 945, 896, 886, 808 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{21}NO$ $[M]^+$: 183.1623. Found: 183.16204.



***N*-(Pentan-3-ylidene)-1-phenylmethanamine oxide, 3.174d (Table 3.13, entry 6).** Synthesized from *N*-benzylhydroxylamine[154] (0.16 g, 1.3 mmol) and 3-pentanone (0.69 mL, 0.56 g, 6.5 mmol, 5.0 equiv) according to the general procedure except with 5 equiv of ketone. Isolated 0.19 g (71%) as a clear oil after column chromatography (0-4% $MeOH/CH_2Cl_2$). TLC R_f 0.27 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz)) δ ppm 7.41-7.28 (m, 5H), 5.07 (s, 2H), 2.60 (q, J = 7.5 Hz, 2H), 2.40 (q, J = 7.5 Hz, 2H), 1.16 (t, J = 7.5 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 153.4 (C), 134.3 (C), 128.8 (CH), 128.0 (CH), 127.3 (CH), 63.7 (CH), 25.3 (CH_2), 24.0 (CH_2), 11.1 (CH_3), 9.0 (CH_3); IR (film): 3409, 2972, 2937, 2876, 1588, 1497, 1454, 1287, 1153, 1075, 1033, 948, 907, 719, 696 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{17}NO$ $[M]^+$:191.1310. Found: 191.12961.

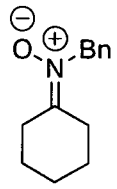


***N*-Cyclopentylidenecyclohexanamine oxide, 3.174e (Table 3.13, entry 7).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and cyclopentanone (0.23 mL, 0.22 g, 2.6 mmol) according to the general procedure. Isolated 0.22 g (83%) as white crystals after column chromatography (5% $MeOH/CH_2Cl_2$). TLC R_f 0.29 (5% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 3.74 (tt, J = 11.5, 3.9 Hz, 1H), 2.61-2.53 (m, 2H), 2.47-2.40 (m, 2H), 2.05-1.88 (m, 2H), 1.84-1.64 (m, 8H), 1.62-1.48 (m, 1H), 1.33-1.06 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 153.1 (C), 67.8 (CH), 30.9 (CH_2), 30.2 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.2 (CH_2); IR (film): 3371, 2922, 2854, 2363, 2185, 1174, 1143, 1090 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{19}NO$ $[M]^+$:181.1467. Found: 181.14610.

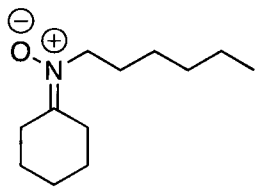


***N*-Cyclohexylidenecyclohexanamine oxide, 3.174f (Table 3.13, entry 8).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and cyclohexanone (0.26 g, 0.27 mL, 2.6 mmol) according to the general procedure. Isolated 0.25 g (91%) as a clear oil after column chromatography (0-5% $MeOH/CH_2Cl_2$). TLC R_f 0.23 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz)) δ ppm 4.10 (tt, J = 11.5, 3.9 Hz, 1H), 2.76 (t, J = 6.4 Hz, 2H), 2.51 (t, J = 6.2 Hz, 2H), 2.07 (dq, J = 12.4, 4.1 Hz, 2H), 1.91-1.51 (m, 11H), 1.28 (dq, J = 13.9, 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 147.8 (C), 65.0 (CH), 30.0 (CH_2), 29.1 (CH_2), 27.1 (CH_2), 25.9 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 24.8 (CH_2), 24.6

(CH_2); IR (film): 3373, 3242, 2931, 2856, 1564, 1450, 1288, 1170, 1143, 988, 896, 756 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{21}NO$ $[M]^+$: 195.1623. Found: 195.16168.

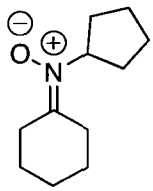


***N*-Cyclohexylidene-1-phenylmethanamine oxide, 3.174g (Table 3.13, entry 9).** Synthesized from *N*-benzylhydroxylamine[154] (0.16 g, 1.3 mmol) and cyclohexanone (0.26 g, 0.27 mL, 2.6 mmol) according to the general procedure. Isolated 0.18 g (61%) as a clear oil after column chromatography (0-5% $MeOH/CH_2Cl_2$). TLC R_f 0.23 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz)) δ ppm 7.43-7.25 (m, 5H), 5.09 (s, 2H), 2.76 (t, J = 6.5 Hz, 2H), 2.50-2.44 (m, 2H), 1.67 (td, J = 12.1, 6.7 Hz, 2H), 1.60-1.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 150.1 (C), 134.1 (C), 128.8 (CH), 128.1 (CH), 127.5 (CH), 63.8 (CH_2), 30.1 (CH_2), 27.0 (CH_2), 25.6 (CH_2), 24.6 (CH_2), 24.6 (CH_2); IR (film): 3393, 3036, 2935, 2858, 1706, 1592, 1497, 1454, 1360, 1152, 1029, 931, 724, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{17}NO$ $[M]^+$: 203.1310. Found: 203.13170.

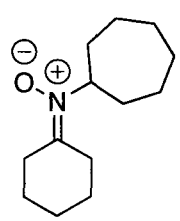


***N*-Cyclohexylidenehexan-1-amine oxide, 3.174h (Table 3.13, entry 10).** Synthesized from *N*-hexylhydroxylamine[156] (0.15 g, 1.3 mmol) and cyclohexanone (0.26 g, 0.27 mL, 2.6 mmol) according to the general procedure. Isolated 0.22 g (78%) as a light yellow oil after column chromatography (2-4% $MeOH/CH_2Cl_2$). TLC R_f 0.35 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz)) δ ppm 3.77 (t, J = 7.5 Hz, 2H), 2.65 (t, J = 6.3, 2H), 2.36

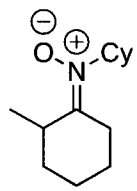
(t, J = 6.1 Hz, 2H), 1.82-1.70 (m, 2H), 1.64-1.38 (m, 6H), 1.30-1.08 (m, 6H), 0.77 (t, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 148.8 (C), 58.9 (CH), 31.2 (CH_2), 29.6 (CH_2), 27.6 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 24.5 (CH_2), 24.4 (CH_2), 22.2 (CH_2), 13.7 (CH_3); IR (film): 3452, 2930, 2857, 2196, 1713, 1672, 1588, 1466, 1455, 1162, 1128, 991, 908, 737 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{23}NO$ $[M]^+$:197.1780. Found: 197.17837.



***N*-Cyclohexylidenecyclopentanamine oxide, 3.174i (Table 3.13, entry 11).** Synthesized from *N*-cyclopentylhydroxylamine[79a] (0.13 g, 1.3 mmol) and cylclohexanone (0.26 g, 0.27 mL, 2.6 mmol) according to the general procedure. Isolated 0.21 g (82%) as a yellow oil after column chromatography (2-4% MeOH/CH_2Cl_2). TLC R_f 0.32 (4% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 4.65 (qd, J = 7.7, 6.2, 6.1 Hz, 1H), 2.74 (t, J = 6.5 Hz, 2H), 2.56-2.50 (m, 2H), 2.18 (ddd, J = 8.5, 7.6, 3.6 Hz, 2H), 1.97-1.74 (m, 4H), 1.71-1.60 (m, 4H), 1.60-1.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 148.2 (C), 65.6 (CH), 30.6 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 24.5 (CH_2); IR (film): 3238, 3108, 2943, 2868, 1707, 1672, 1450, 1185, 1124, 941 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{23}NO$ $[M]^+$:181.1467. Found: 181.14666.

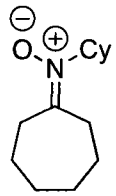


***N*-Cyclohexylidenecycloheptanamine oxide, 3.174j (Table 3.13, entry 12).** Synthesized from *N*-cycloheptylhydroxylamine[79a] (0.17 g, 1.3 mmol) and cyclohexanone (0.26 g, 0.27 mL, 2.6 mmol) according to the general procedure. Isolated 0.26 g (88%) as a clear oil after column chromatography (1-2% $MeOH/CH_2Cl_2$). TLC R_f 0.27 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz)) δ ppm 4.35-4.24 (m, 1H), 2.72 (t, J = 6.4 Hz, 2H), 2.54-2.46 (m, 2H), 2.23-2.10 (m, 2H), 1.88-1.75 (m, 4H), 1.65 (td, J = 12.6, 6.3 Hz, 4H), 1.60-1.50 (m, 6H), 1.50-1.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 147.0 (C), 66.5 (CH), 32.3 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 26.9 (CH_2), 25.9 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 24.6 (CH_2); IR (film): 3397, 2921, 2857, 2690, 2181, 1707, 1584, 1449, 1349, 1280, 1148, 1129, 996, 967, 944, 911, 843, 743 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{23}NO$ $[M]^+$:209.1780. Found: 209.17576.

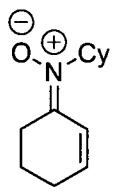


***N*-(2-Methylcyclohexylidene)cyclohexanamine oxide, 3.174k (Table 3.13, entry 13).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and heptanone (0.32 mL, 0.29 g, 2.6 mmol) according to the general procedure. Isolated 0.77 g (26%) as a mixture of isomers of a yellow solid after column chromatography (3% $MeOH/CH_2Cl_2$). TLC R_f 0.27 (5% $MeOH/CH_2Cl_2$); mp 64 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 4.09 (tdd, J = 15.7, 11.9, 4.1 Hz), 2.76 (t, J = 6.5 Hz), 2.54-2.49 (m), 2.36-1.93 (m, 1.93-1.81 (m), 1.80-1.52 (m), 1.36-1.19 (m), 1.16 (d, J = 7.2 Hz), 1.09 (d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 148.0 (C), 65.2 (CH), 65.1 (CH), 64.8 (CH), 42.0 (CH_2), 32.3 (CH_2), 31.6 (CH), 30.9 (CH_2), 30.5 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.1

(CH_2), 29.0 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 23.2 (CH_2), 19.9 (CH_2), 19.5 (CH_2), 18.1 (CH_3), 15.4 (CH_3); IR (film): 3487, 2930, 2857, 2192, 1710, 1649, 1174, 1138, 995 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{23}NO$ $[M]^+$:209.1780. Found: 209.17905.

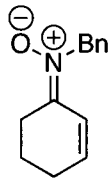


***N*-Cycloheptylidenecyclohexanamine oxide, 3.174l (Table 3.13, entry 14).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and cycloheptanone (0.32 mL, 0.29 g, 2.6 mmol) according to the general procedure. Isolated 0.24 g (83%) as yellow crystals after column chromatography (5% $MeOH/CH_2Cl_2$). TLC R_f 0.29 (5% $MeOH/CH_2Cl_2$); mp 64 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 4.04 (tt, J = 11.5, 3.8 Hz, 1H), 2.75-2.69 (m, 2H), 2.55-2.47 (m, 2H), 2.11-1.95 (m, 2H), 1.87-1.76 (m, 2H), 1.74-1.44 (m, 11H), 1.35-1.08 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 150.7 (C), 64.9 (CH), 31.2 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 26.5 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.3 (CH_2); IR (film): 3367, 2925, 2858, 2363, 2310, 1140, 1090 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{23}NO$ $[M]^+$:209.1780. Found: 209.17905.



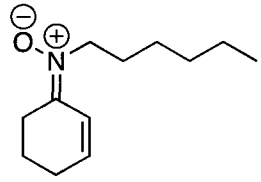
***N*-(Cyclohex-2-enylidene)cyclohexanamine oxide, 3.174m (Table 3.13, entry 15).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 2-cyclohexen-1-

one (0.25 mL, 0.25 g, 2.6 mmol) according to the general procedure. Isolated 0.25 g (91%) as a 3.3:1 ratio of isomers of light yellow oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.29 and 0.36 (4% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 7.09 (td, *J* = 10.4, 2.0 Hz, minor isomer), 6.47 (td, *J* = 10.37, 1.8 Hz, 1H, major isomer), 6.31 (td, *J* = 10.0, 4.4 Hz, minor isomer), 6.07 (dt, J = 10.4, 4.5 Hz, 1H major isomer), 4.18 (tt, *J* = 11.3, 3.8 Hz, 1H, major isomer), 4.00 (tt, *J* = 11.1, 3.6 Hz, minor isomer), 2.74 (t, *J* = 6.6 Hz, 2H, major isomer), 2.58 (t, *J* = 6.6 Hz, minor isomer), 2.15 (ddd, *J* = 10.7, 6.2, 1.9 Hz, 2H), 2.07-1.92 (m 2H), 1.91-1.54 (m, 7H), 1.43-1.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 143.7 (C), 135.0 (CH), 118.8 (CH), 64.7 (CH), 30.0 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 20.8 (CH_2); IR (film): 3409, 2972, 2937, 2876, 1588, 1497, 1454, 1287, 1153, 1075, 1033, 948, 907, 719, 696 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{19}NO$ $[M]^+$:193.1467. Found: 193.14468.

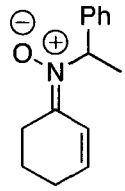


***N*-(Cyclohex-2-enylidene)-1-phenylmethanamine oxide, 3.174n (Table 3.13, entry 16).** Synthesized from *N*-benzylhydroxylamine[154] (0.16 g, 1.3 mmol) and 2-cyclohexen-1-one (0.25 mL, 0.25 g, 2.6 mmol) according to the general procedure. Isolated 0.20 g (71%) as a 20:1 ratio of isomers of yellow oil after column chromatography (2-4% MeOH/CH_2Cl_2). TLC R_f 0.28 and 0.34 (3% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 7.38-7.19 (m, 5H), 6.43 (td, *J* = 10.3, 1.9 Hz, 1H), 6.07 (dt, *J* = 10.3, 4.5 Hz, 1H), 5.07 (s, 2H), 5.01 (s, minor isomer), 2.76 (t, *J* = 6.6 Hz, 2H), 2.51 (t, *J* = 6.8 Hz, minor isomer), 2.16-2.06 (m, 2H), 1.74 (p, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz)

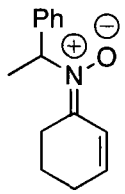
145.2 (C), 136.1 (CH), 134.0 (C), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 119.2 (CH), 62.6 (CH_2), 24.7 (CH_2), 24.6 (CH_2), 20.4 (CH_2); IR (film): 3412, 3059, 3029, 2941, 2872, 2831, 1541, 1496, 1451, 1431, 1370, 1247, 1175, 962, 858, 704 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{15}NO$ $[M]^+$:201.1154. Found: 201.11482.



***N*-(Cyclohex-2-enylidene)hexan-1-amine oxide, 3.174o (Table 3.13, entry 17).** Synthesized from *N*-hexylhydroxylamine[156] (0.15 g, 1.3 mmol) and 2-cyclohexen-1-one (0.25 mL, 0.25 g, 2.6 mmol) according to the general procedure. Isolated 0.18 g (63%) as a 5.5:1 ratio of isomers of a brown oil after column chromatography (1-3% $MeOH/CH_2Cl_2$). TLC R_f 0.20 and 0.24 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz)) δ ppm 7.11 (td, *J* = 10.4, 2.0 Hz, 1H), 6.43-6.34 (m, 1H), 6.22-6.05 (m, minor isomer), 3.92 (t, *J*=7.8 Hz, minor isomer), 3.84 (t, *J*=7.5 Hz, 2H), 2.78 (t, *J* = 6.8 Hz, minor isomer), 2.57 (t, *J*=6.8 Hz, 2H), 2.30-2.13 (m, 2H), 1.99-1.71 (m, 4H), 1.42-1.23 (m, 6H), 0.88 (t, *J* = 6.87, 6.87 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 144.9 (C), 139.0 (CH), 135.7 (CH), 120.7 (CH), 119.3 (CH), 58.6 (CH_2), 31.4 (CH_2), 27.9 (CH_2), 26.4 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 20.7 (CH_2), 13.9 (CH_3); IR (film): 3401, 2928, 2859, 1541, 1467, 1436, 1407, 1372, 1295, 1213, 1180, 1051, 991, 968, 914, 857, 728 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{21}NO$ $[M]^+$:195.1623. Found: 195.16312.



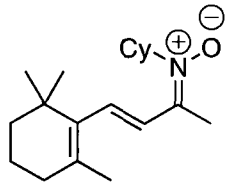
***(E)*-*N*-(Cyclohex-2-enylidene)-1-phenylethanamine oxide, 3.174p (Table 3.13, entry 18).** Synthesized from *N*-hydroxy-1-phenylethanamine[55,159] (0.18 g, 1.3 mmol) and 2-cyclohexen-1-one (0.25 mL, 0.25 g, 2.6 mmol) according to the general procedure. Isolated 0.15 g (49%) as a white solid after column chromatography (2% $MeOH/CH_2Cl_2$). TLC R_f 0.27 (2% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 400 MHz) δ ppm7.49-7.39 (m, 2H), 7.37-7.23 (m, 3H), 6.60 (td, J = 10.4, 1.9 Hz, 1H), 6.12-6.06 (m, 1H), 5.58 (q, J = 6.7 Hz, 1H), 2.92-2.64 (m, 2H), 2.19-2.12 (m, 2H), 1.81-1.73 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.6 (C), 139.6 (C), 135.7 (CH), 128.6 (CH), 128.0 (CH), 126.8 (CH), 118.9 (CH), 64.2 (CH), 25.0 (CH_2), 25.0 ($^{160}CH_2$), 20.7 (CH_2), 19.4 (CH_3); IR (film): 3471, 2097, 1645, 1178 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{17}NO$ $[M]^+$:215.1310. Found: 215.13102.



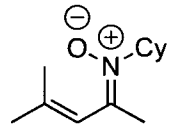
***(Z)*-*N*-(Cyclohex-2-enylidene)-1-phenylethanamine oxide, 3.174p (Table 3.13, entry 18).** Synthesized from *N*-hydroxy-1-phenylethanamine[55,159] (0.18 g, 1.3 mmol) and 2-cyclohexen-1-one (0.25 mL, 0.25 g, 2.6 mmol) according to the general procedure. Isolated 0.039 g (14%) as a light brown oil after column chromatography (2% $MeOH/CH_2Cl_2$). TLC R_f 0.24 (2% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 400 MHz) δ ppm

[159] Change, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464

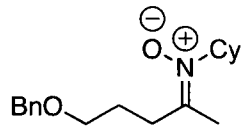
7.47-7.42 (m, 2H), 7.38-7.27 (m, 3H), 7.15 (td, J = 10.3, 2.0 Hz, 1H), 6.37 (td, J = 10.2, 4.4 Hz, 1H), 5.39 (q, J = 6.7 Hz, 1H), 2.71 (ddd, J = 16.1, 8.6, 4.8 Hz, 1H), 2.57 (ddd, J = 16.1, 7.9, 4.7 Hz, 1H), 2.22-2.14 (m, 2H), 1.94-1.59 (m, 3H), 1.76 (d, J = 6.71 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 142.0 (C), 139.5 (C), 139.0 (CH), 128.7 (CH), 128.0 (CH), 126.8 (CH), 121.1 (CH), 65.2 (CH), 26.3 (CH_2), 25.2 (CH_2), 21.8 (CH_2), 19.7 (CH_3); IR (film): 3433, 1652, 1170 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{17}NO$ $[M]^+$:215.1310. Found: 215.13166.



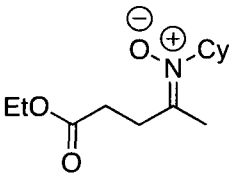
***(E)*-*N*-((*E*)-4-(2,6,6-Trimethylcyclohex-1-enyl)but-3-en-2-ylidene)cyclohexanamine oxide, 3.174q (Table 3.13, entry 19).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and β-ionone (0.53 mL, 0.50 g, 2.6 mmol) according to the general procedure. Isolated 0.32 g (80%) as a yellow oil after column chromatography (1-3% $MeOH/CH_2Cl_2$). TLC R_f 0.33 (4% $MeOH/CH_2Cl_2$); ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 6.40 (d, J = 2.4 Hz, 2H), 4.23 (tt, J = 11.3, 3.7 Hz, 1H), 2.22 (s, 3H), 2.11-1.92 (m, 4H), 1.91-1.74 (m, 4H), 1.71 (s, 3H), 1.68-1.54 (m, 3H), 1.50-1.42 (m, 2H), 1.40-1.16 (m, 3H), 1.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz143.8 (C), 137.5 (C), 132.5 (CH), 131.5 (C), 123.8 (CH), 65.6 (CH), 39.4 (CH_2), 34.1 (C), 33.1 (CH_2), 30.2 (CH_2), 28.9 (CH_3), 25.1 (CH_2), 25.0 (CH_2), 21.7 (CH_3), 18.9 (CH_2), 13.9 (CH_3); IR (film): 3435, 2930, 2862, 2826, 2208, 1514, 1454, 1360, 1310, 1278, 1261, 1201, 1147, 1060, 947, 896, 791, 731, 653 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{31}NO$ $[M]^+$:289.2406. Found: 289.24004.



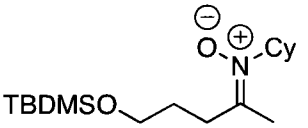
***N*-(4-Methylpent-3-en-2-ylidene)cyclohexanamine oxide, 3.174r (Table 3.13, entry 20).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and mesityl oxide (0.30 mL, 0.26 g, 2.6 mmol) according to the general procedure. Isolated 0.12 g (44%) as yellow crystals after column chromatography (3-4% MeOH/CH_2Cl_2). TLC R_f 0.34 (5% MeOH/CH_2Cl_2); mp 70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 5.80 (d, J = 1.2 Hz, 1H), 4.07 (tt, J = 11.4, 3.9 Hz, 1H), 2.14 (d, J = 1.0 Hz, 3H), 1.97 (dq, J = 12.4, 3.2 Hz, 2H), 1.85-1.76 (m, 2H), 1.82 (d, J = 1.3 Hz, 3H), 1.66 (d, J = 0.91 Hz, 3H), 1.75-1.55 (m, 3H), 1.35-1.11 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz)) δ ppm 142.4 (C), 140.7 (C), 119.0 (CH), 66.3 (CH), 29.6 (CH_2), 25.6 (CH), 25.0 (CH_2), 24.9 (CH_2), 20.2 (CH_3), 19.3 (CH_3); IR (film): 3405, 2925, 2858, 2363, 2341, 2208, 1447, 1375, 1208, 1185, 1083 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{21}NO$ $[M]^+$:195.1623. Found: 195.16180.



***N*-(5-(Benzyloxy)pentan-2-ylidene)cyclohexanamine oxide, 3.133c (Table 3.13, entry 21).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.98 g, 0.84 mmol) and 5-(benzyloxy)pentan-2-one[158] (0.33 g, 1.7 mmol) according to the general procedure. Isolated 0.96 g (37%) mixture of isomers (1.3:1) as a light yellow oil after column chromatography (0-5% MeOH/CH_2Cl_2). TLC R_f 0.37, 0.46 (5% MeOH/CH_2Cl_2). The NMR corresponded with characterization previously reported.[79a]

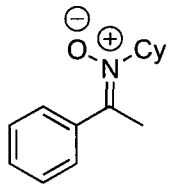


***N*-(5-Ethoxy-5-oxopentan-2-ylidene)cyclohexanamine oxide, 3.174s (Table 3.13, entry 22).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and ethyl 4-oxopentanoate[130] (0.38 g, 2.6 mmol) according to the general procedure. Isolated 0.078 g (25%) as a clear oil after column chromatography (3.5-4.5% $MeOH/CH_2Cl_2$). TLC R_f 0.18 and 0.23 (3.5% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 4.07 (q, J = 7.1 Hz, 1H), 3.97 (ddd, J = 15.3, 7.7, 3.9 Hz, 1H), 2.77-2.63 (m, 2H), 2.11 (s, 2H), 2.07-1.54 (m, 5H), 1.35-1.15 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.0 (C), 143.0 (C), 65.8 (CH), 60.4 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 19.0 (CH_3), 14.1 (CH_3); IR (film): 3419, 2933, 1729, 1641, 1166, 764, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{23}NO_3$ $[M]^+$: 241.1678. Found: 241.16712.



***N*-(5-(*tert*-Butyldimethylsilyloxy)pentan-2-ylidene)cyclohexanamine oxide, 3.174t (Table 3.13, entry 23).** Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 5-(*tert*-butyldimethylsilyloxy)pentan-2-one[133] (0.56 g, 2.6 mmol) according to the general procedure. Isolated 0.16 g (37%) as a 1.5:1 ratio of isomers as a clear oil after column chromatography (4% $MeOH/CH_2Cl_2$). TLC R_f 0.28 and 0.32 (4% $MeOH/CH_2Cl_2$);^1H NMR ($CDCl_3$, 400 MHz) δ ppm 4.11 (tt, 11.3, 3.8 Hz, minor isomer), 3.98 (tt, 11.4, 3.8 Hz, 1H), 2.61-2.56 (m, 2H), 2.53-2.44 (m, minor isomer), 2.10 (s, minor isomer), 2.08 (s, 3H), 2.08-1.95 (m, 2H), 1.90-1.58 (m, 7H), 1.36-1.15 (m, 3H), 0.89 (s, minor isomer), 0.87 (s, 9H), 0.04 (s, minor isomer), 0.02 (s, 6H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ ppm 144.7 (C), 65.7 (CH), 62.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 25.9 (CH_3), 25.0 (CH_2) 25.0, 18.3 (CH_3), -5.7 (CH_3); IR (film): 3439, 2926, 2856, 1647, 1592, 1471, 1460, 1256, 1115, 837 cm^{-1}; MS m/z (relative intensity): 437.2674 (1.0%), 420.2724 (3.0%), 365.2195 (11.7%), 282.1312 (22.1%), 204.0830 (10.0%), 199.0574 (100.0%), 183.0622 (11.0%), 168.1381 (21.2%).



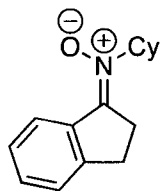
_N_-(1-Phenylethylidene)cyclohexanamine oxide, 3.148c (Table 3.15, entry 12)

Synthesized by a modification of the general procedure. A flame-dried 2 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, _N_-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol), _t_-butanol (0.65 mL, 2.0 M to hydroxylamine), acetophenone (0.30 mL, 0.31 g, 2.6 mmol, 2.0 equiv). Anhydrous $MgSO_4$ (0.15 g, 1.3 mmol, 1.0 equiv) was also added and the reaction was run as usual. Isolated 0.084 g (30%) of a clear oil after column chromatography (2% MeOH/CH_2Cl_2). TLC R_f 0.33 (5% MeOH/CH_2Cl_2). The NMR data corresponded with characterization previously reported.[55]

Hydrolysis of _N_-(1-phenylethylidene)cyclohexanamine oxide (3.148c)

To flame-dried 2 mL sealed vial (Biotage microwave vial 0.5-2 mL) was charged with a stir bar, _N_-(1-phenylethylidene)cyclohexanamine oxide (0.25 g, 1.1 mmol) in _t_-BuOH (1.0 mL, 1.0 M to nitrone) was added water (0.19 mL, 0.19 g, 11 mmol, 10 equiv) was added, and the reaction was run as usual. The vial was cooled to ambient temperature and concentrated under reduced pressure. 1,4-Dimethoxybenzene (0.037 g, 0.27 mmol) was

then added as an internal standard. The mixture was taken up in $CDCl_3$ and transferred to an NMR tube. ^1H NMR spectra of these solutions were recorded, and the conversion calculated based on the relative integration of the resonance corresponding to the product's methine protons (1H) (4.11 ppm) compared to the integration of the resonance corresponding to a 1,4-dimethoxybenzene proton at 6.83 ppm (1H). According to theses calculations, only 65% of the nitrone remained intact. The methine proton (1H) (2.85 ppm) of cyclohexylhydroxylamine was partially obscured by an additional broad peak and therefore could not be accurately recorded. The aromatic peak of acetophenone at 8.88 (2H) was also integrated and corresponded to 31% ketone formation. The difference in calculation can likely be attributed to the volatility of acetophenone, which could have been partially lost during reaction concentration. TLC analysis of the crude reaction also indicated that acetophenone was formed under the reaction conditions [TLC R_f 0.63 (100% CH_2Cl_2)].



***N*-(2,3-Dihydro-1*H*-inden-1-ylidene)cyclohexanamine oxide, 3.175a (Table 3.16, entry 2).**[161] Synthesized from *N*-cyclohexylhydroxylamine[153] (0.15 g, 1.3 mmol) and 1-indanone (0.34 g, 2.6 mmol) according to the general procedure. Isolated 0.14 g (43%) as 1.9:1 ratio of isomers of a white crystal after column chromatography (1-2% $MeOH/CH_2Cl_2$). TLC R_f 0.27 and 0.36 (4% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300

[161] A related reaction was run with $MgSO_4$ under the reaction conditions reported for the formation of ketonitrone **3.148c**. The NMR yield for this transformation was 47%.

MHz) δ ppm 8.93 (d, J = 7.16 Hz, 1H major isomer), 7.41-7.26 (m, 4H), 3.92 (tt, J = 11.3, 3.7 Hz, 1H), 3.42-3.30 (m, minor isomer), 3.22-2.99 (m, 5H), 2.78 (dd, J = 8.2, 5.0 Hz, 1H), 2.14 (dq, J = 12.4, 2.7 Hz, 1H), 2.02-1.79 (m, 6H), 1.79-1.53 (m, 4H), 1.45-1.19 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 147.5 (C), 135.1 (C), 130.1 (CH), 127.2 (CH), 127.1 (CH), 125.4 (C), 124.4 (CH), 68.9 (CH), 33.4 (CH_2), 29.6 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 25.1 (CH_2), 25.1 (CH_2), 25.0 (CH_2); IR (film): 3401, 2930, 2854, 1712, 1653, 1599, 1568, 1464, 1450, 1348, 1324, 1284, 1185, 1099, 895, 761 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{19}NO$ $[M]^+$:229.1467. Found: 229.14422.

5.3.4. DFT calculations[162]

Computational Details

Density functional theory (DFT) calculations have been performed using the *Gaussian 03* program.[163] Optimized molecular geometries were calculated using the B3LYP[164] exchange-correlation functional.

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[162] DFT calculations were performed by Dr. S.I. Gorelsky

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

The triple-zeta TZVP[165] basis set and tight SCF convergence criteria were used for calculations. Wave function stability calculations were performed to confirm that the calculated wave functions corresponded to the ground state. Harmonic frequency calculations were performed to ensure that the stationary points were true energy minima or transition states (TSs) and to calculate vibrational zero point energy and thermal corrections. The unscaled frequencies were used for calculating Gibbs free energies of the species (at 298K and 1 atm). Intrinsic reaction coordinate (IRC)[166,167] calculations were used to confirm the reaction pathways through the CMD transition states (TSs) for all reactants.

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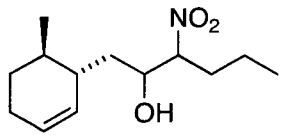
[164] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
[165] Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.
[166] Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
[167] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

Appendix : NMR Spectra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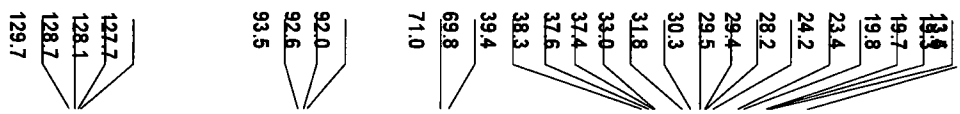
OH

2.72

10.0
5.0
0.0
ppm (t1)


129.7
128.7
128.1
127.7
93.5
92.6
92.0
71.0
69.8
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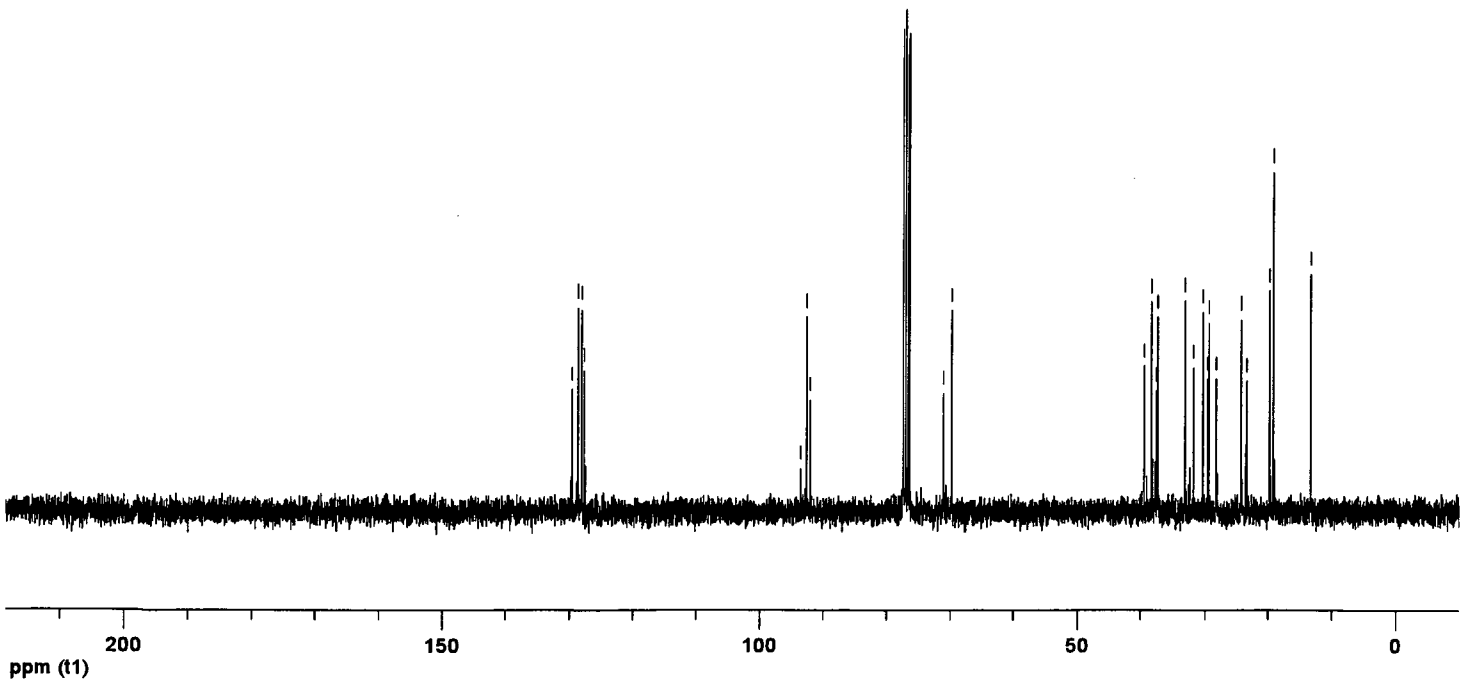
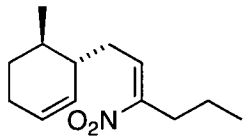
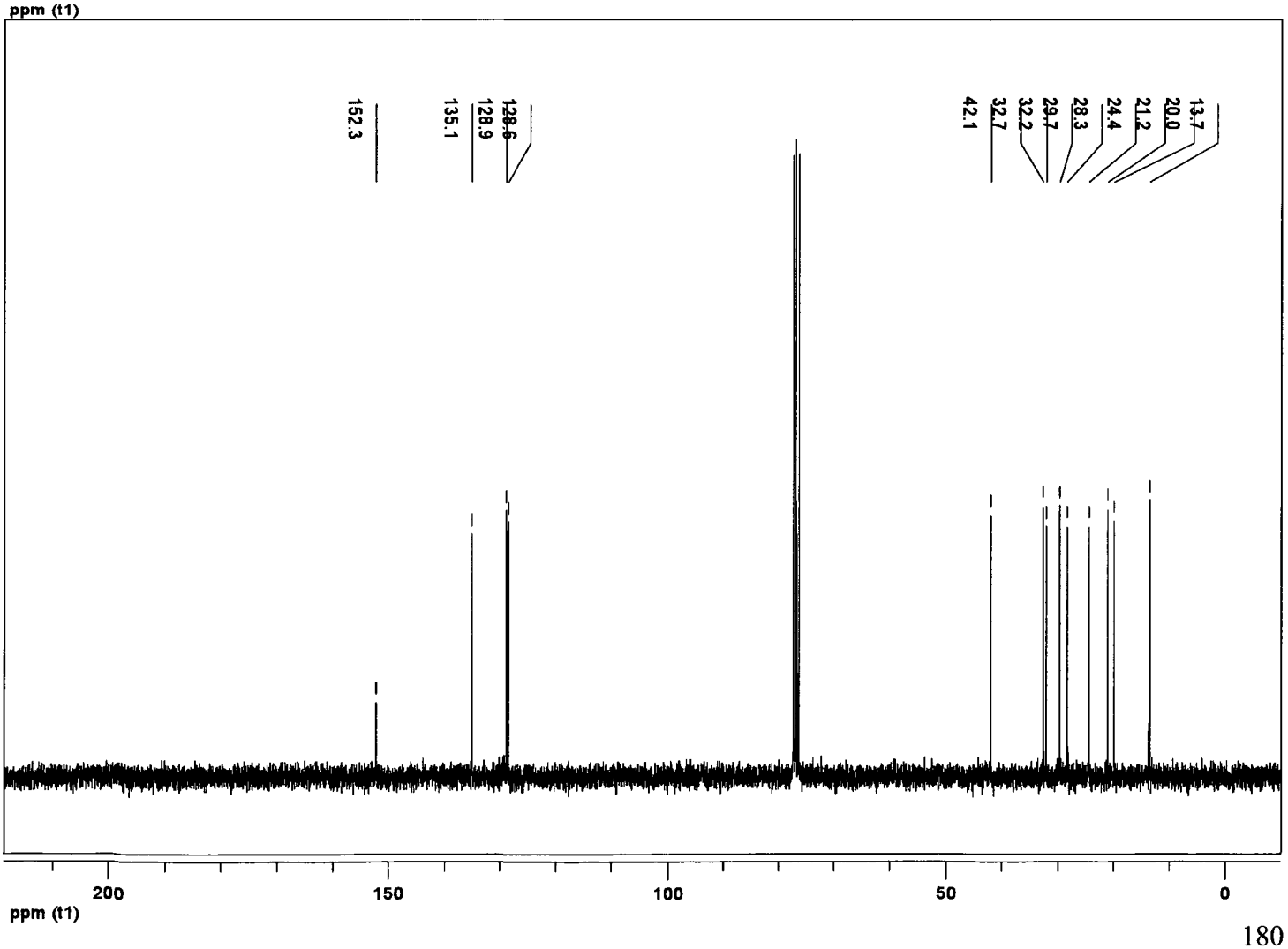
37.6
37.4
33.0
31.8
30.3
29.5
29.4
28.2
24.2
23.4
19.8
19.7

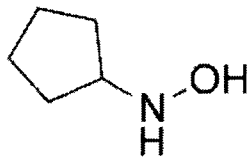

200
150
100
50
0
ppm (t1)


O2N

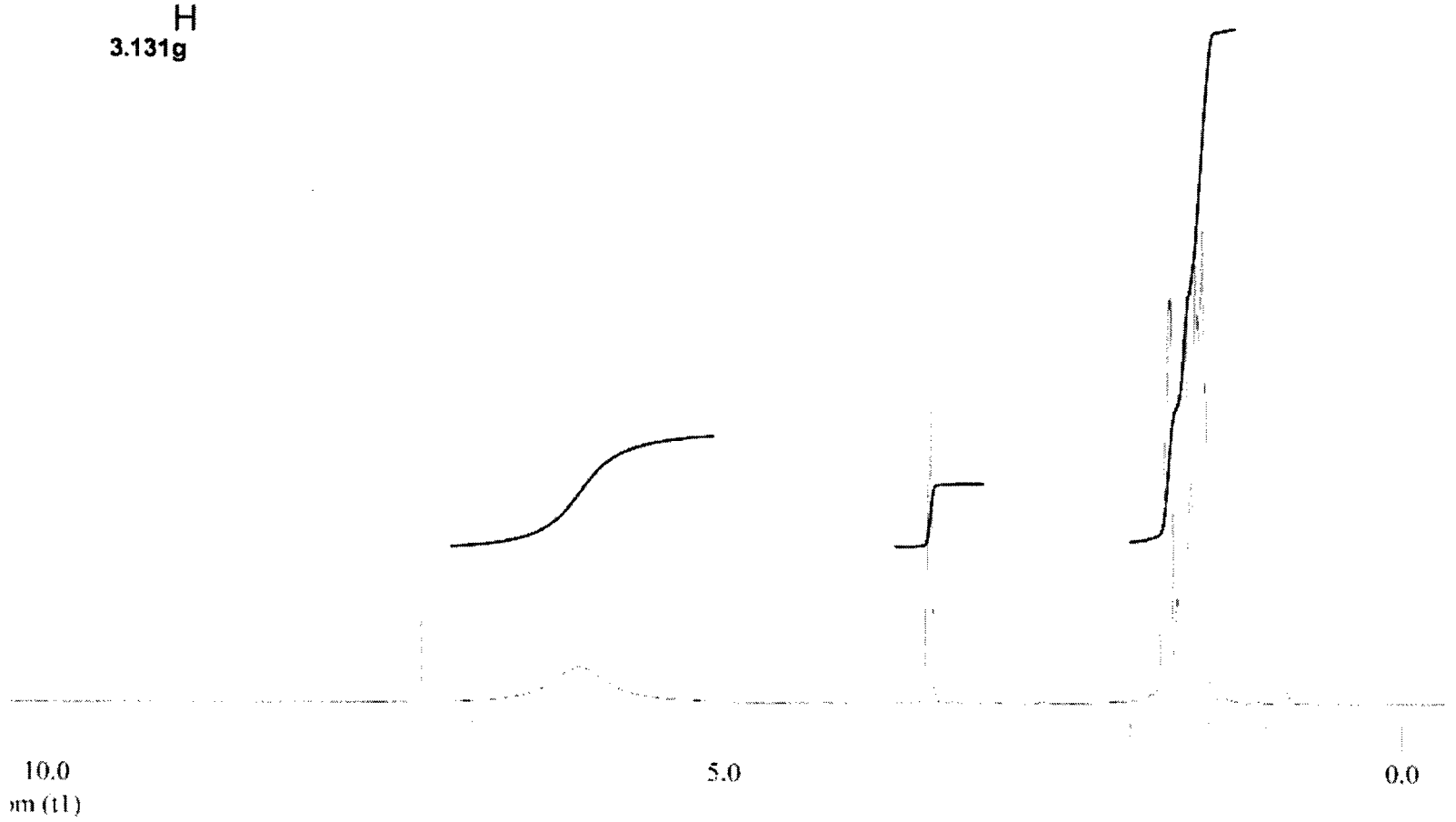
2.73

10.0
5.0
0.0
ppm (t1)


152.3
135.1
128.9
128.6
42.1
32.7
32.2
29.7
28.3
24.4
21.2
20.0
13.7
200
150
100
50
0
ppm (t1)



3.131g



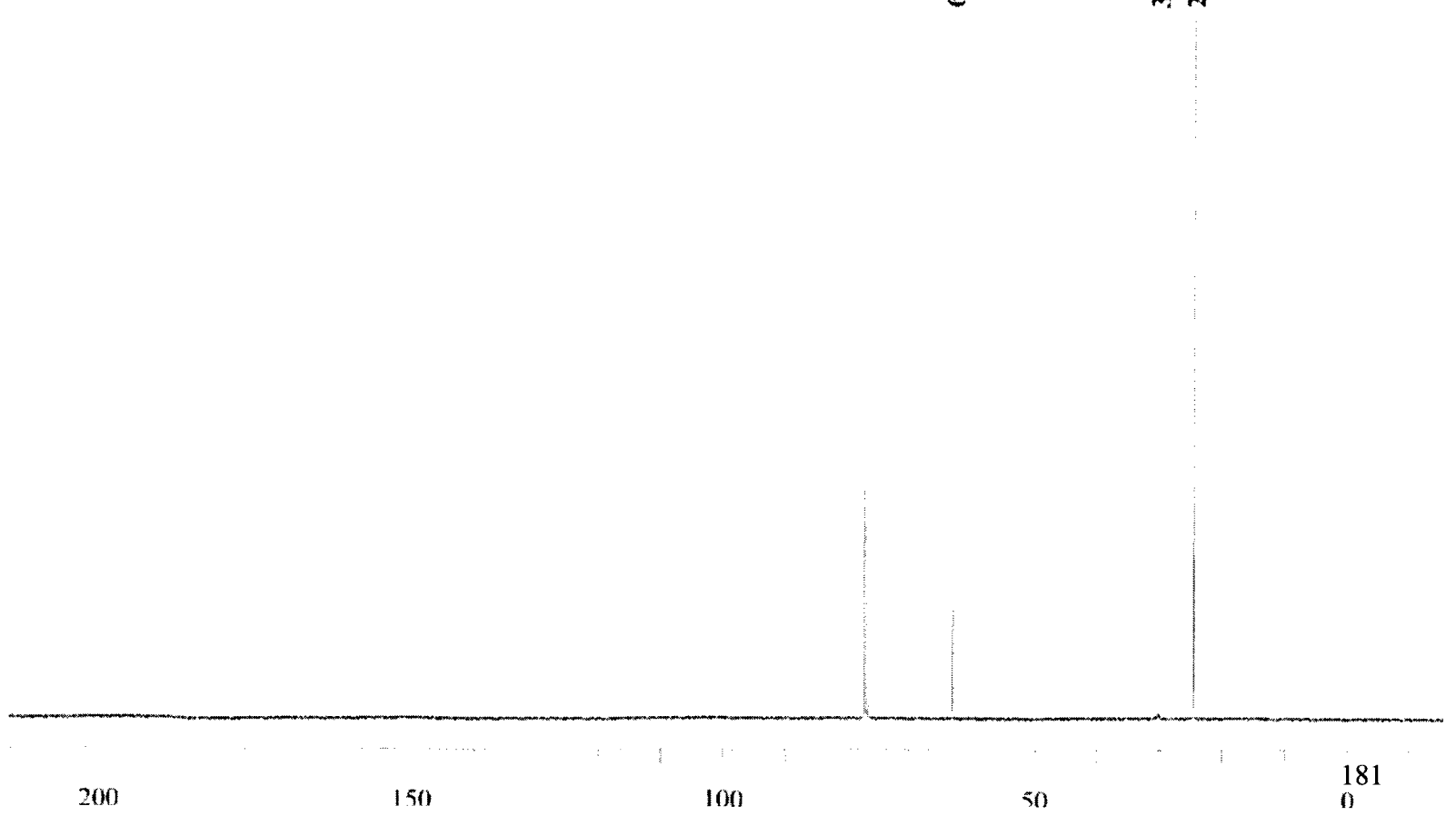
10.0 5.0 0.0

)m (t1)

63.1

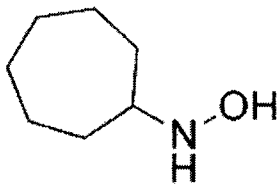
30.1

24.4

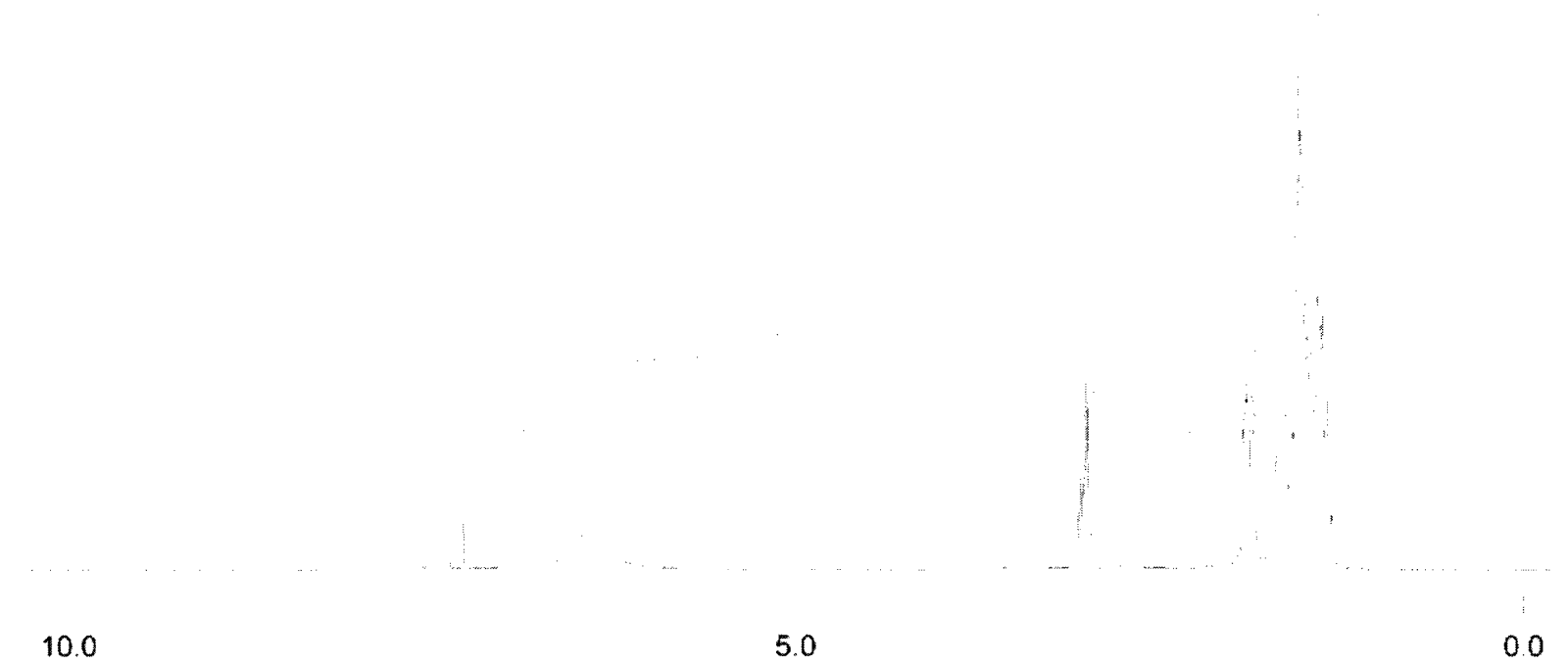


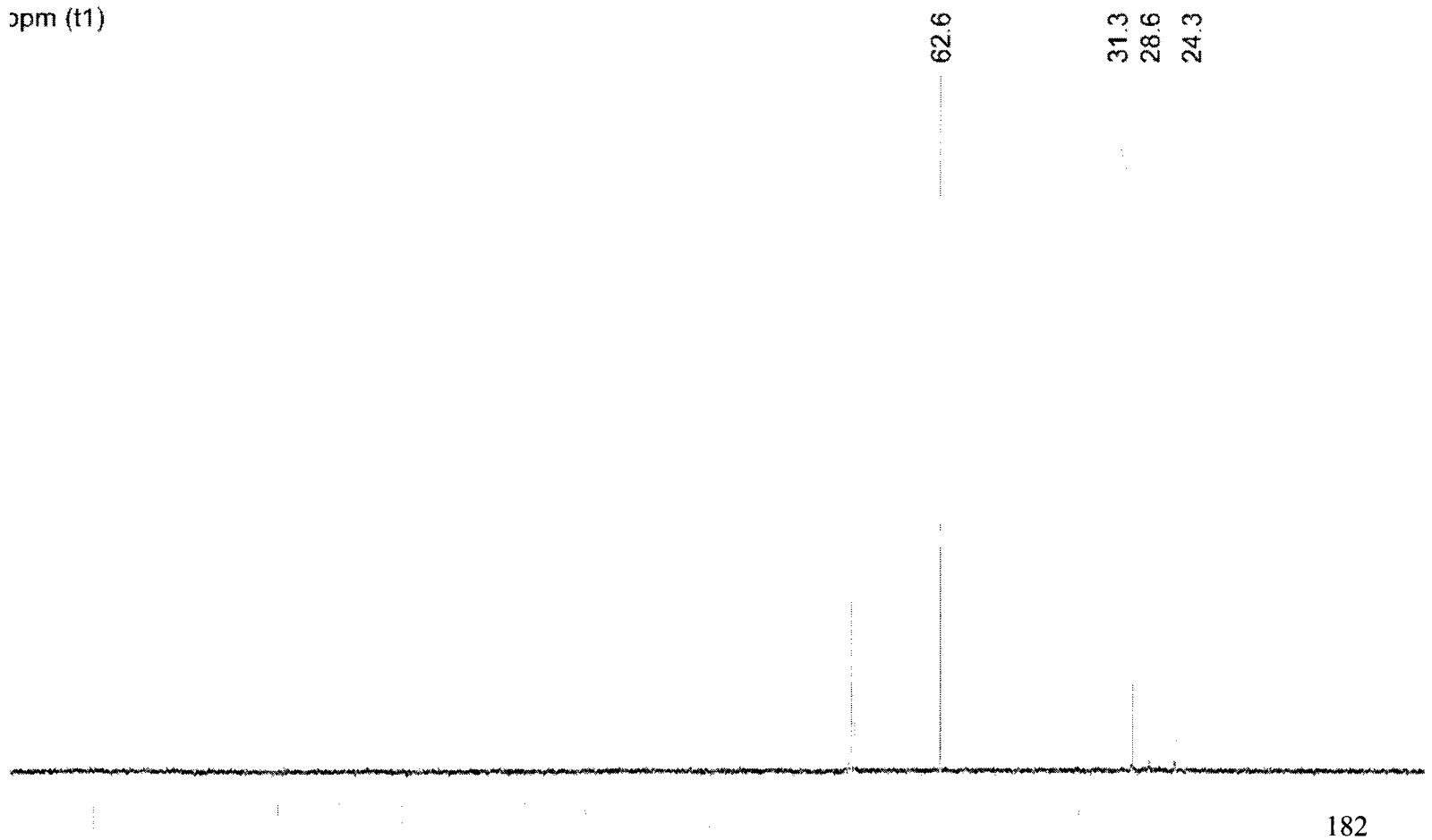
200 150 100 50 0

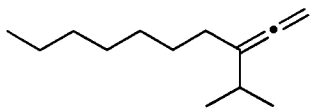
181



3.131h

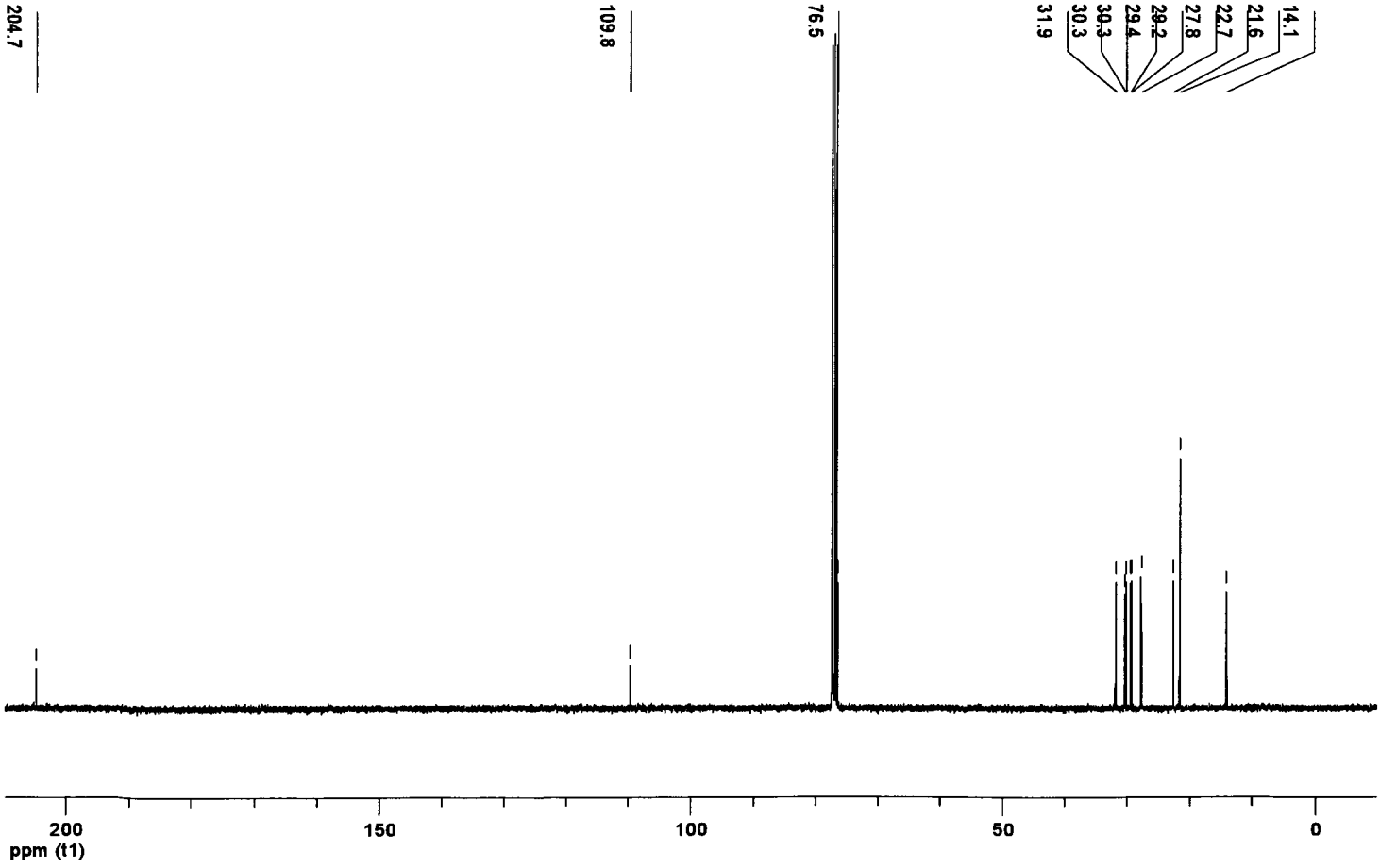


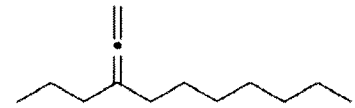




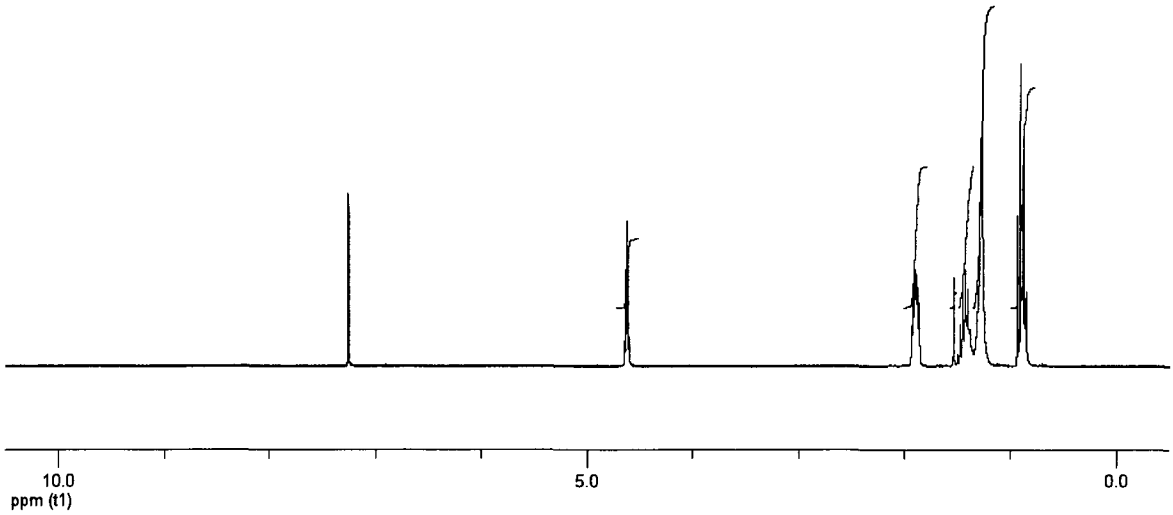
3.132f

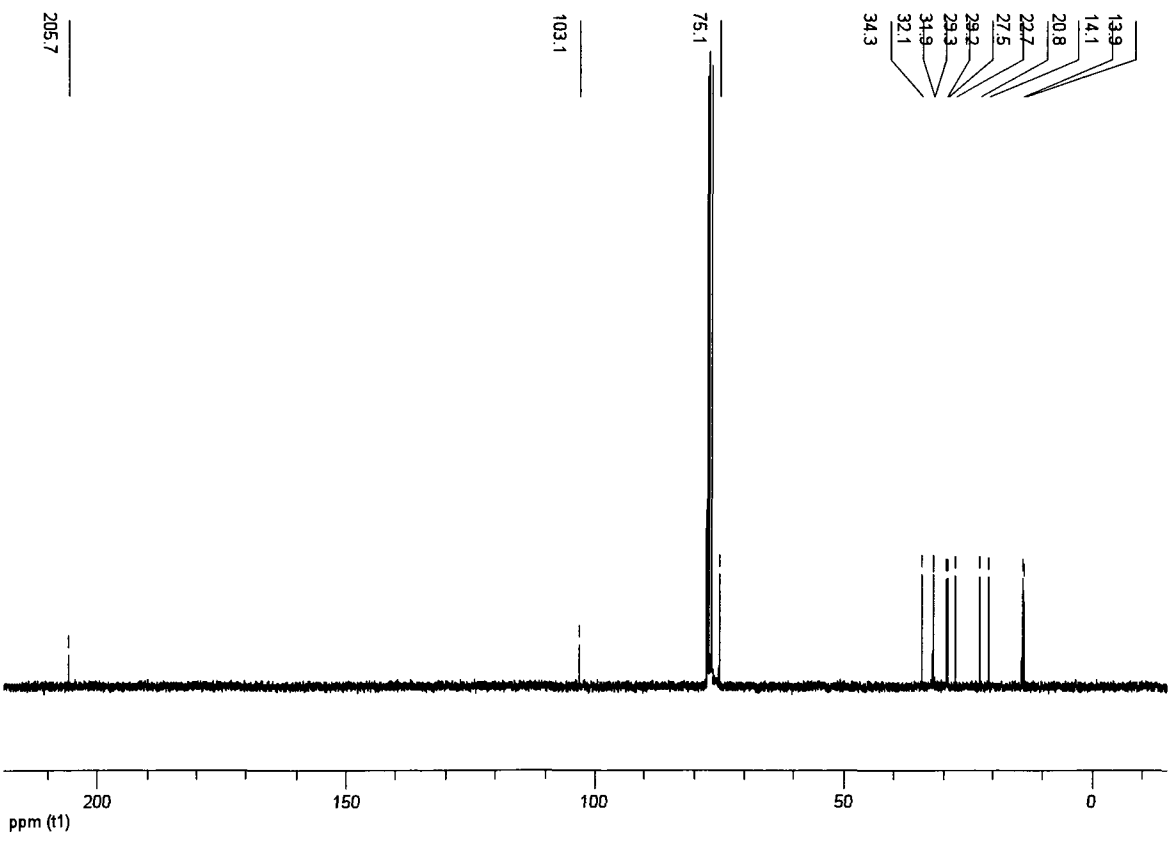
10.0
ppm (t1)
5.0
0.0

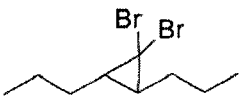

204.7
109.8
76.5
31.9
30.3
30.3
29.4
29.2
27.8
22.7
21.6
14.1
200
ppm (t1)
150
100
50
0



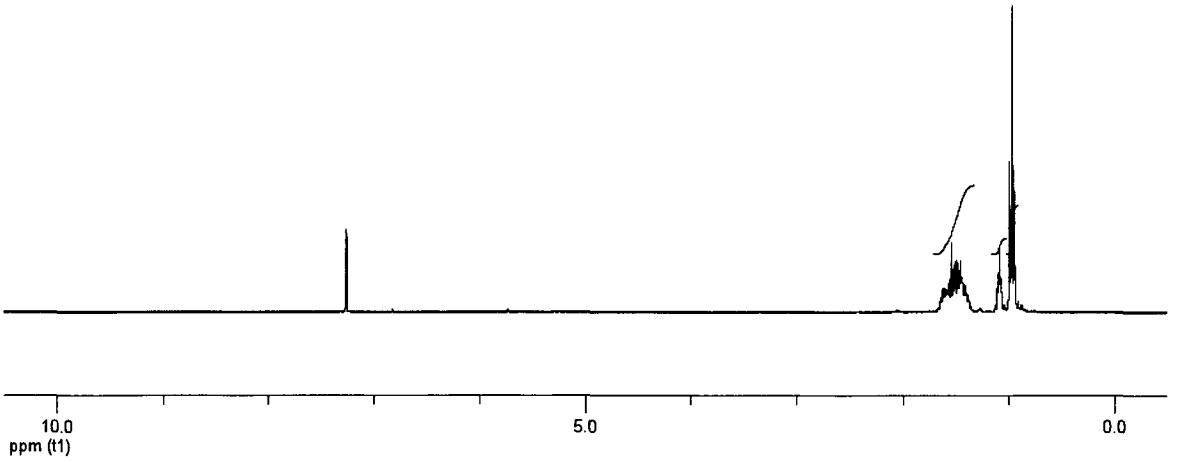
3.132g

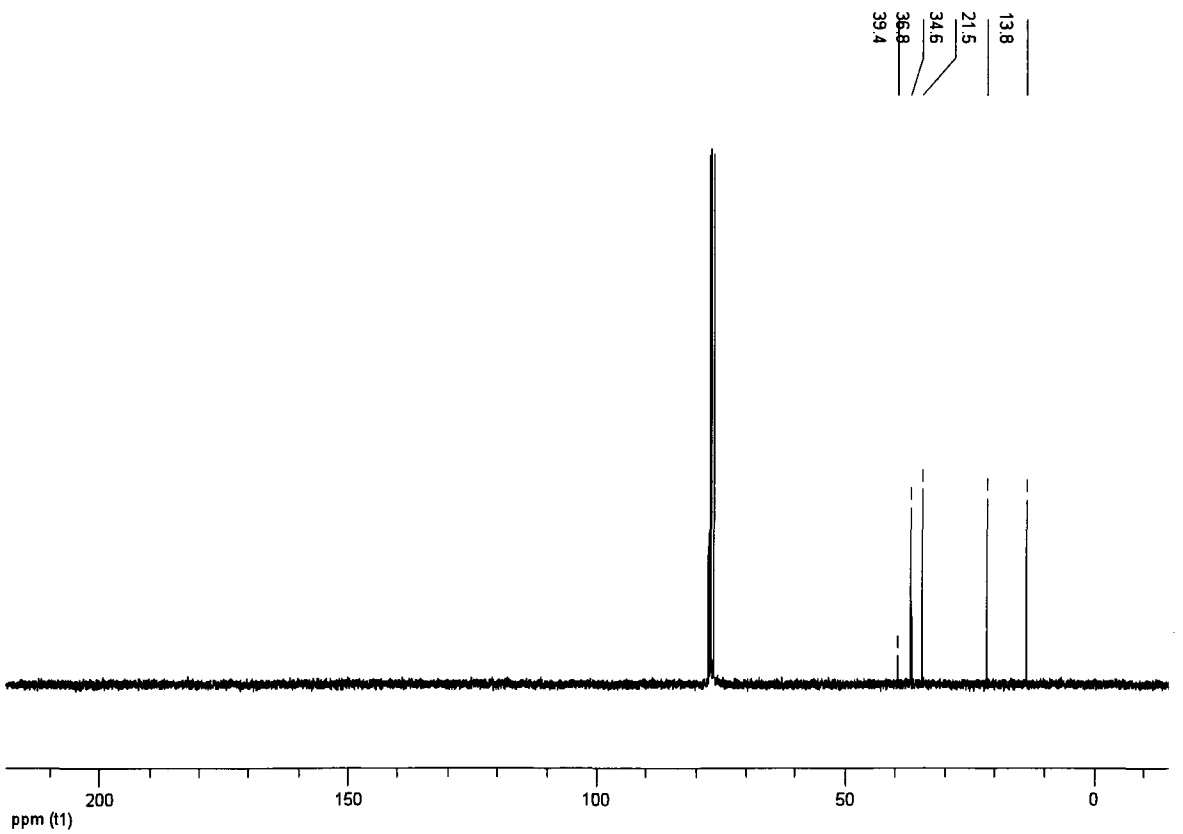

10.0
ppm (t1)
5.0
0.0

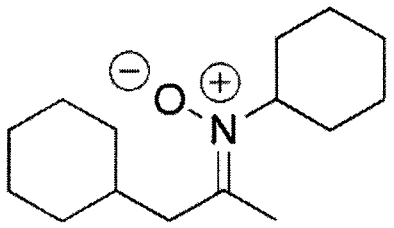

205.7
103.1
75.1
34.3
32.1
31.9
29.3
29.2
27.5
22.7
20.8
14.1
13.9
200
150
100
50
0
ppm (t1)



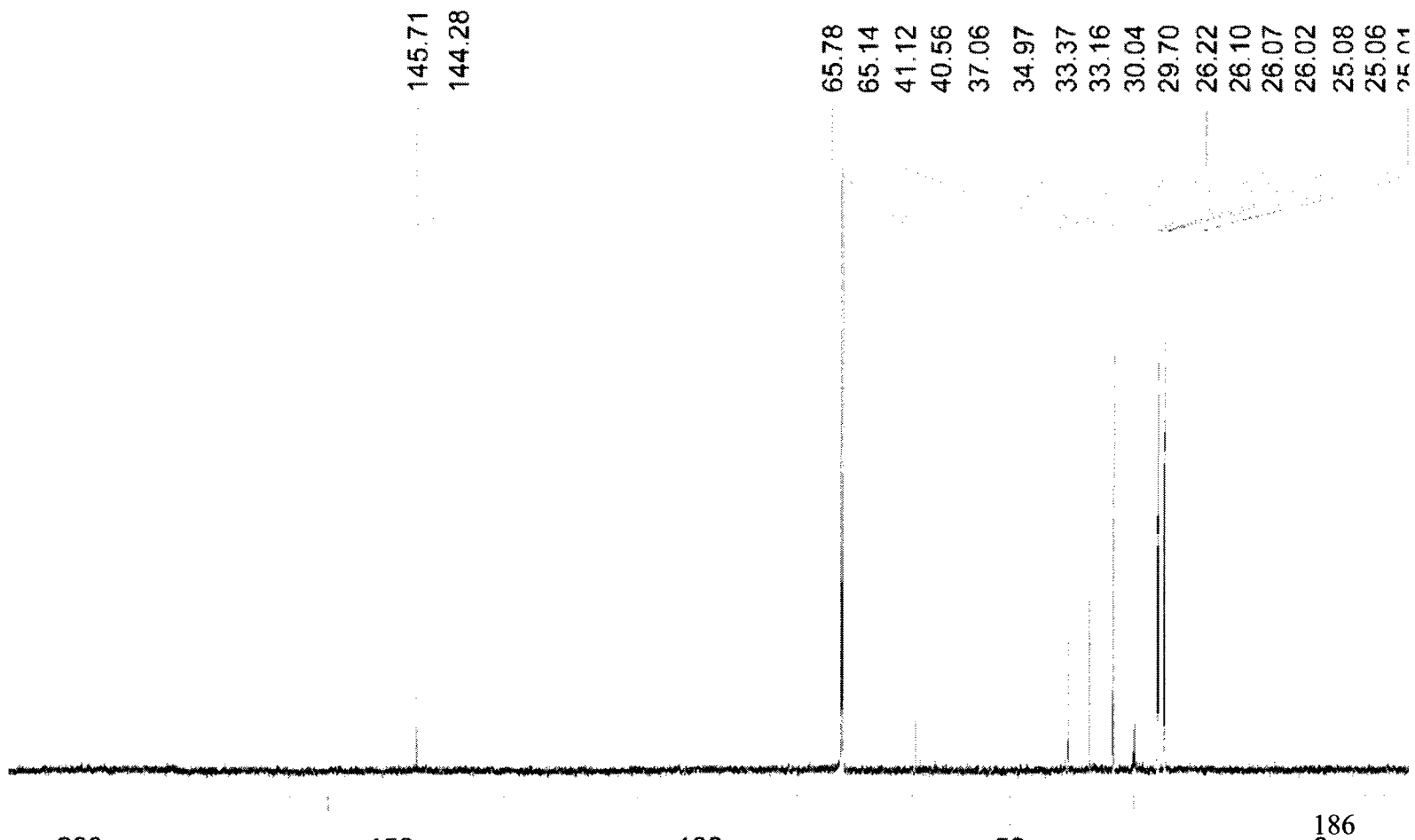
3.132h1

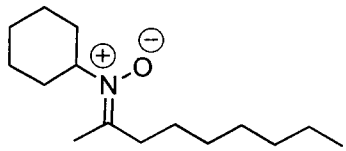




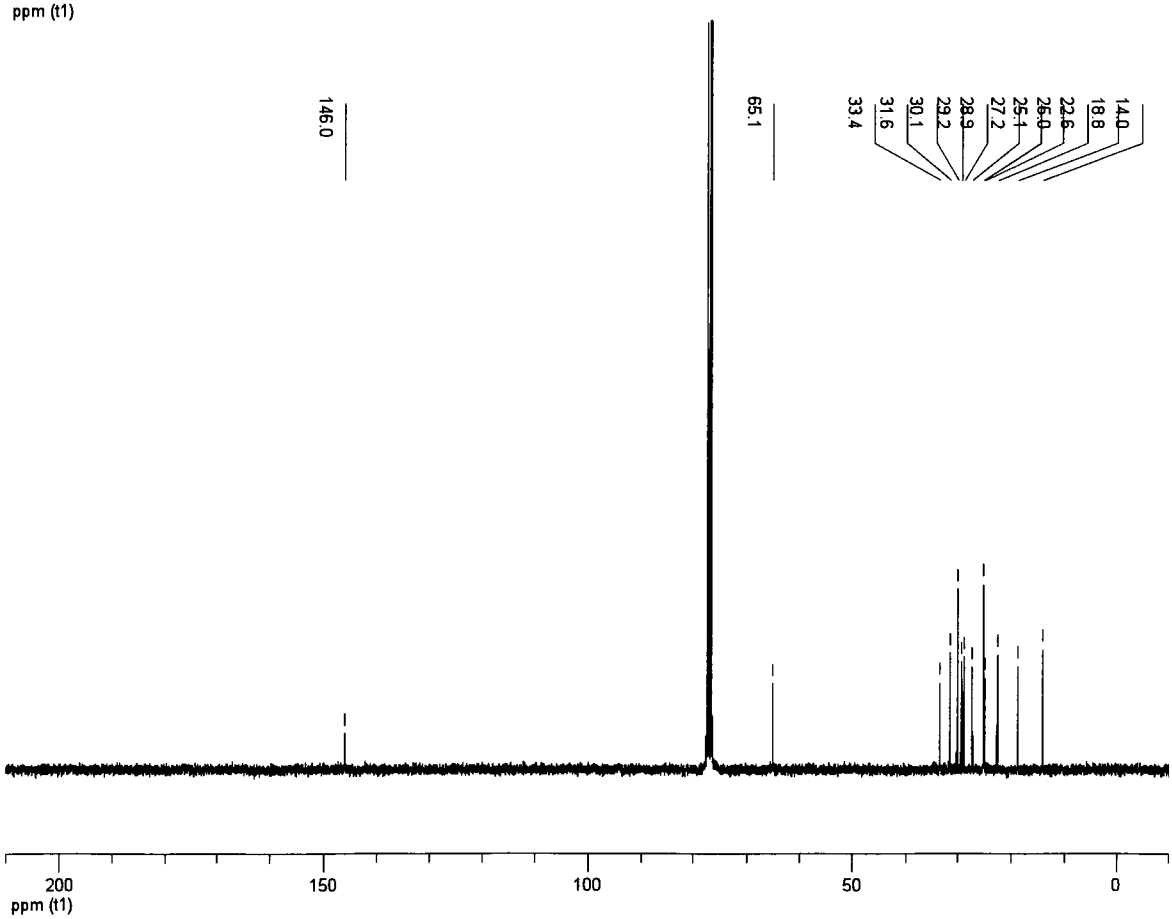


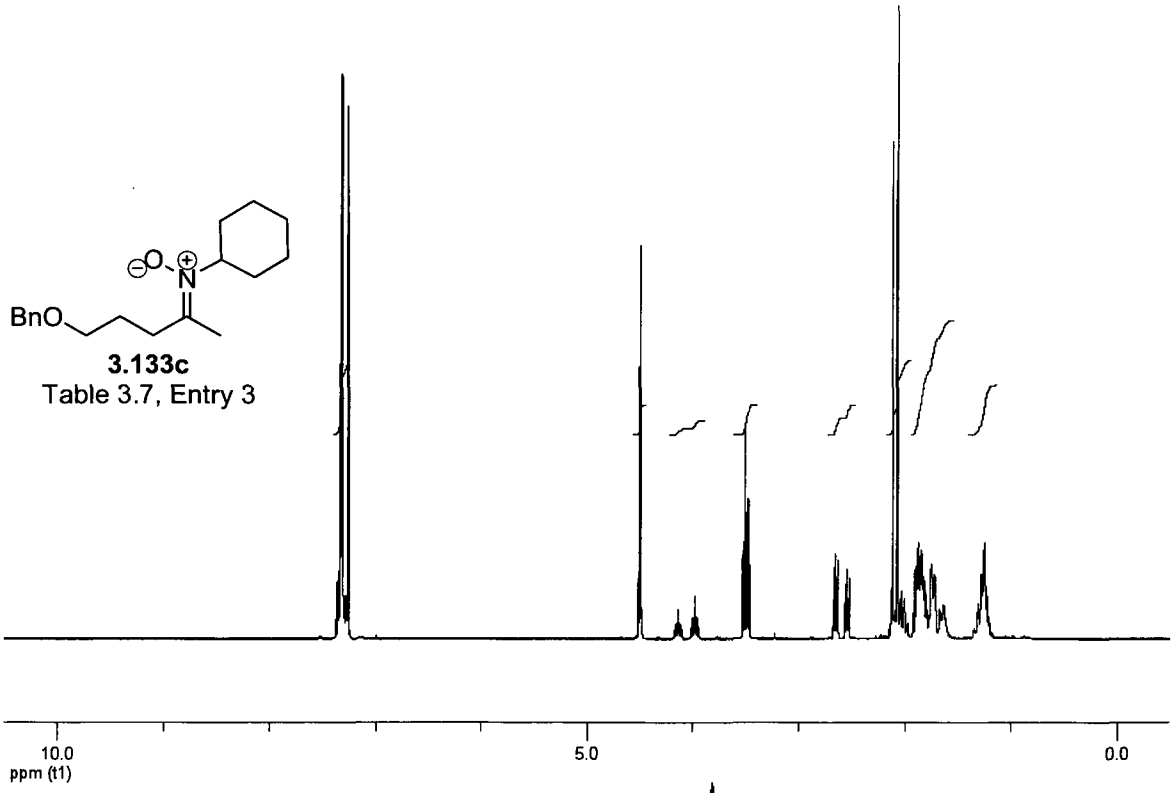
3.133a
Table 3.7, Entry 1





3.133b
Table 3.7, Entry 2





3.133c
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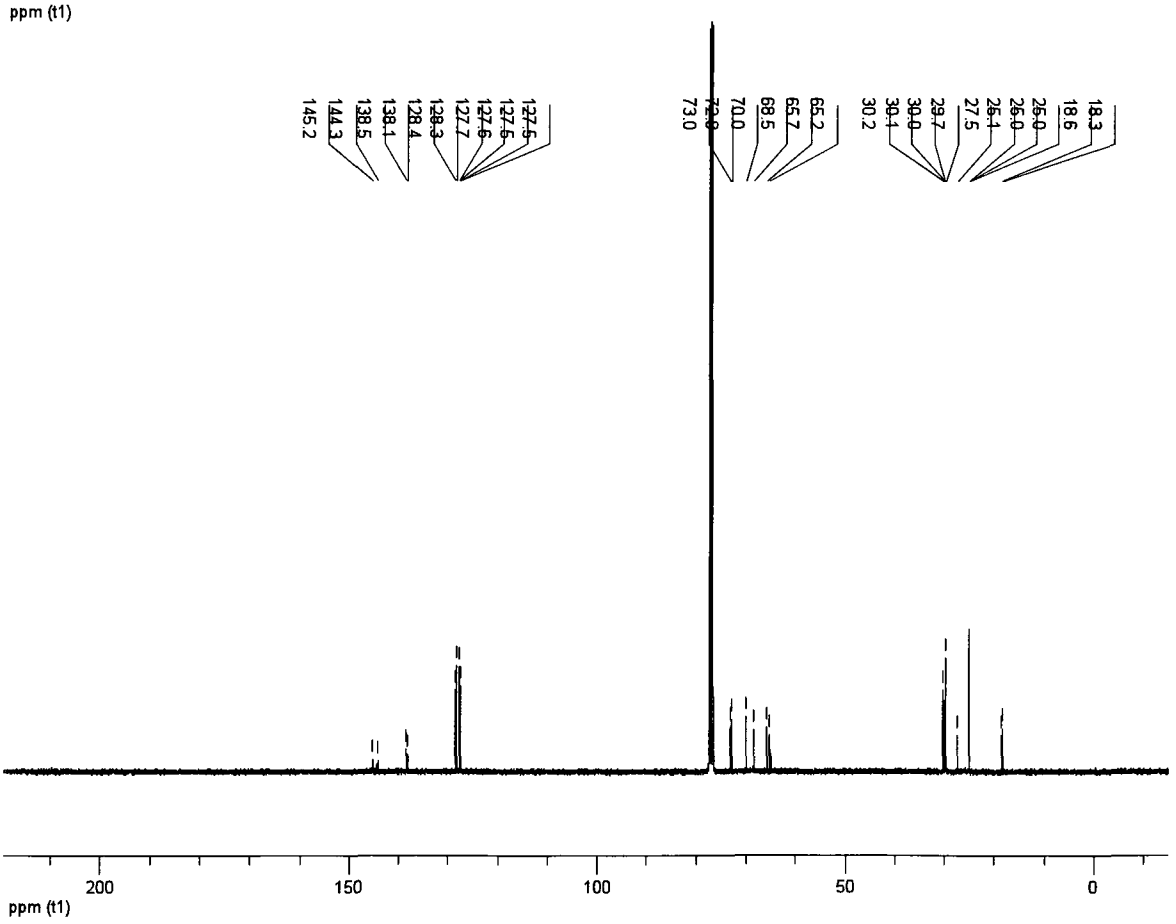
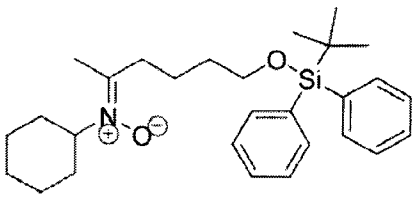
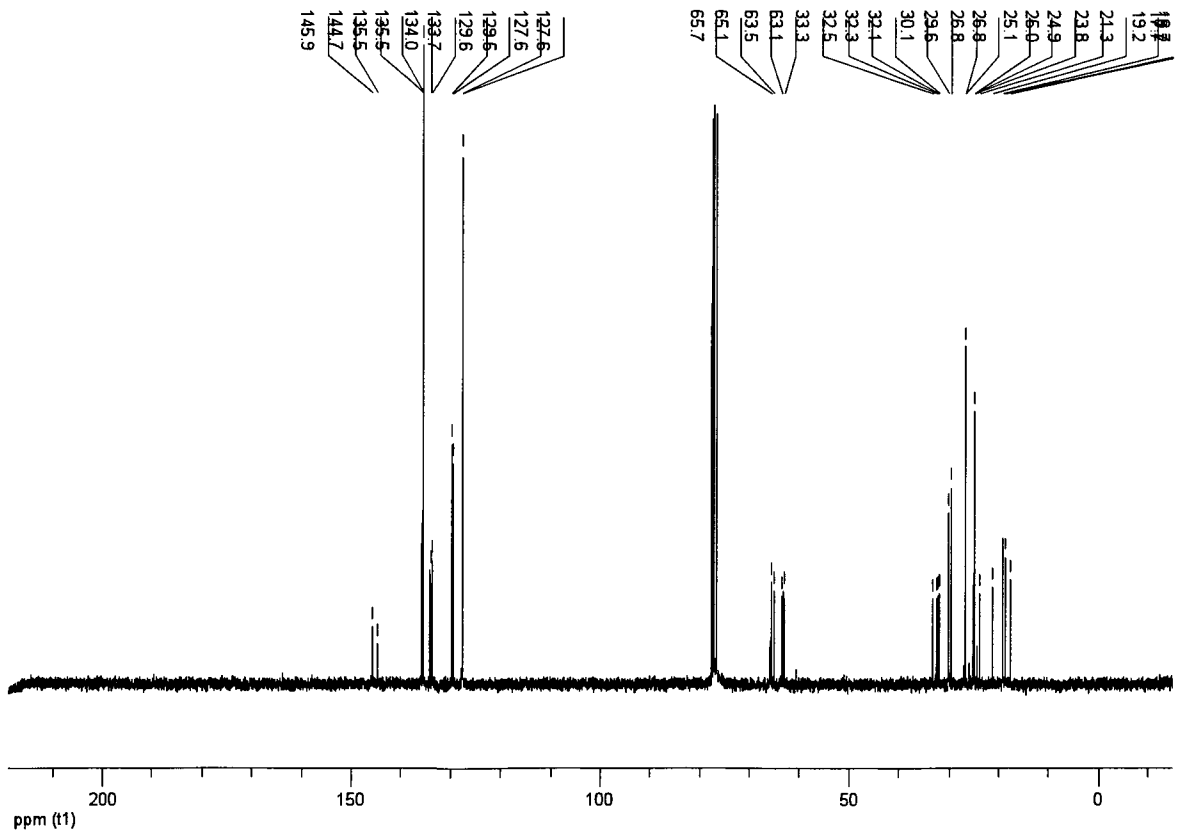
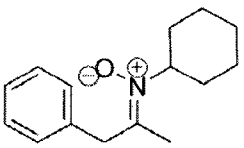


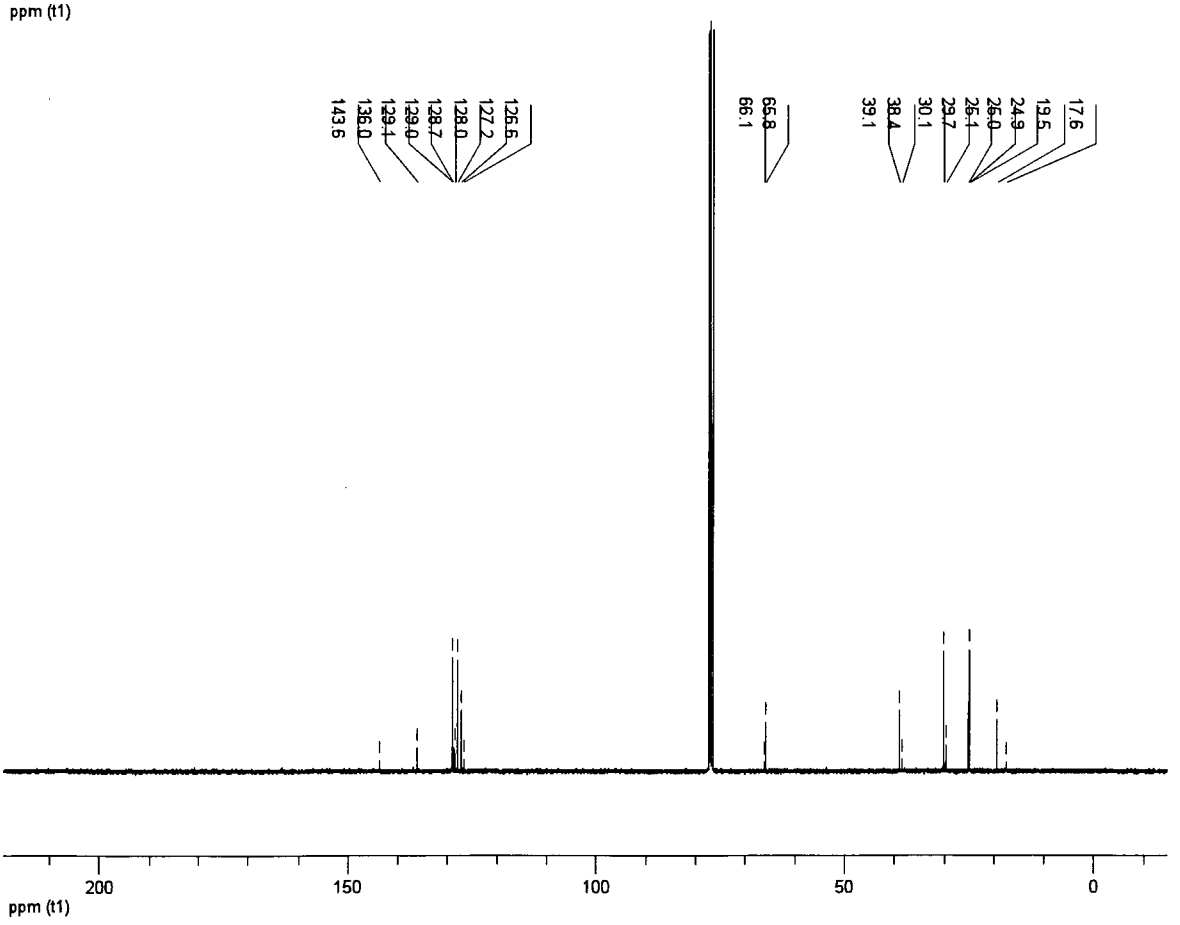


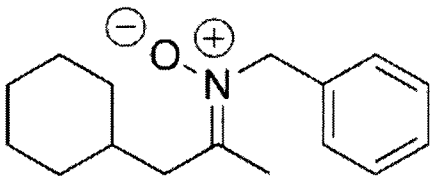
3.133d
Table 3.7 Entry 4



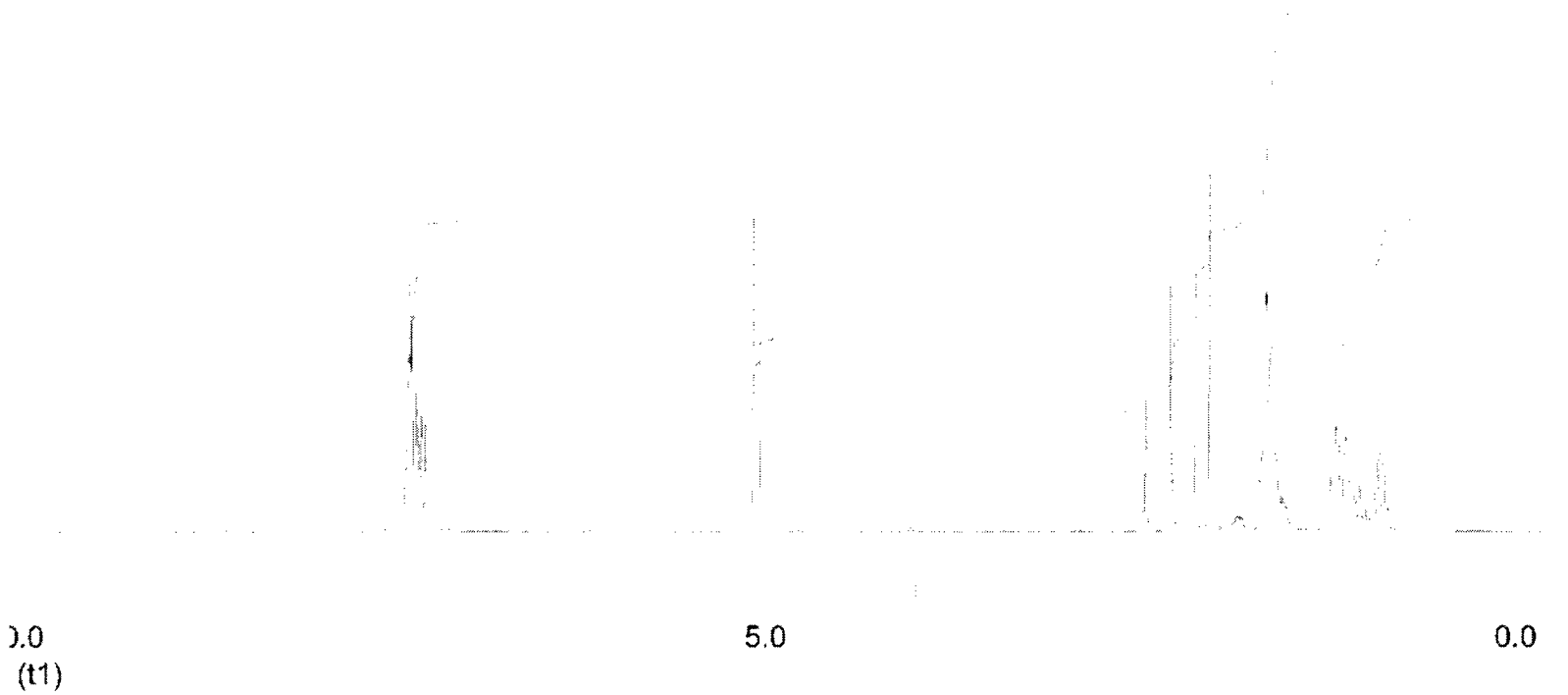


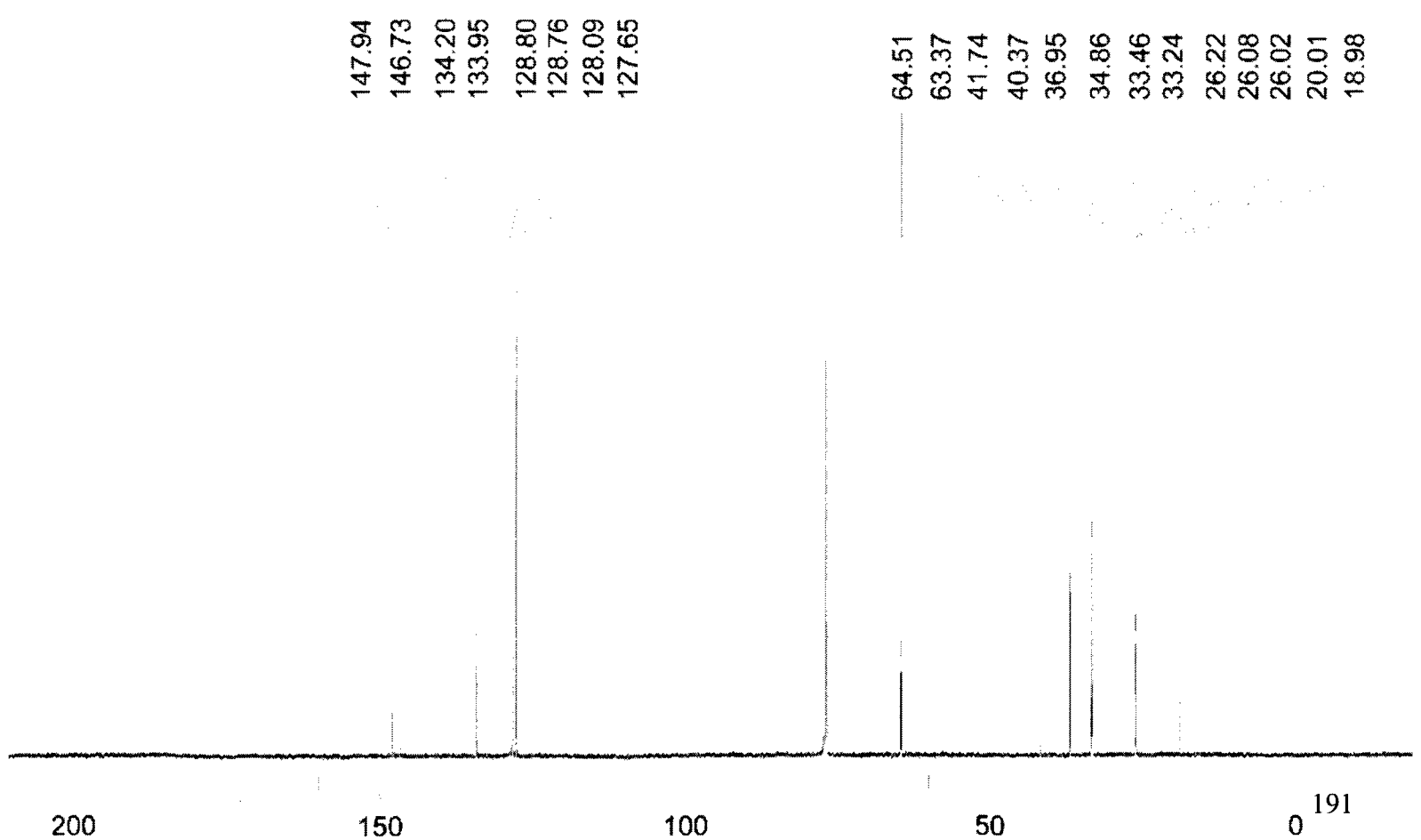
3.133e
Table 3.7, Entry 5

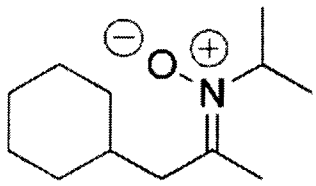




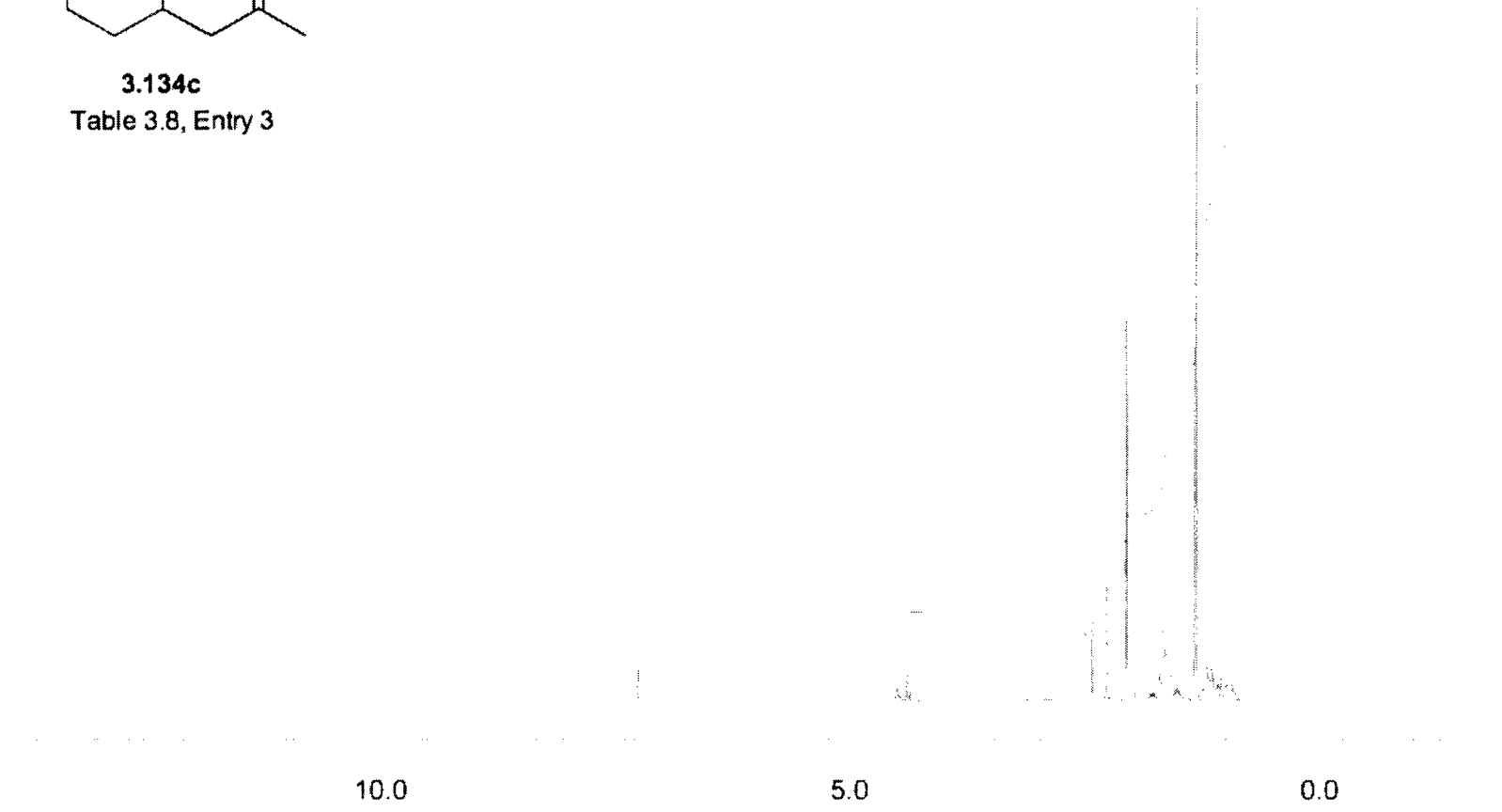
3.134b
Table 3.8, Entry 2

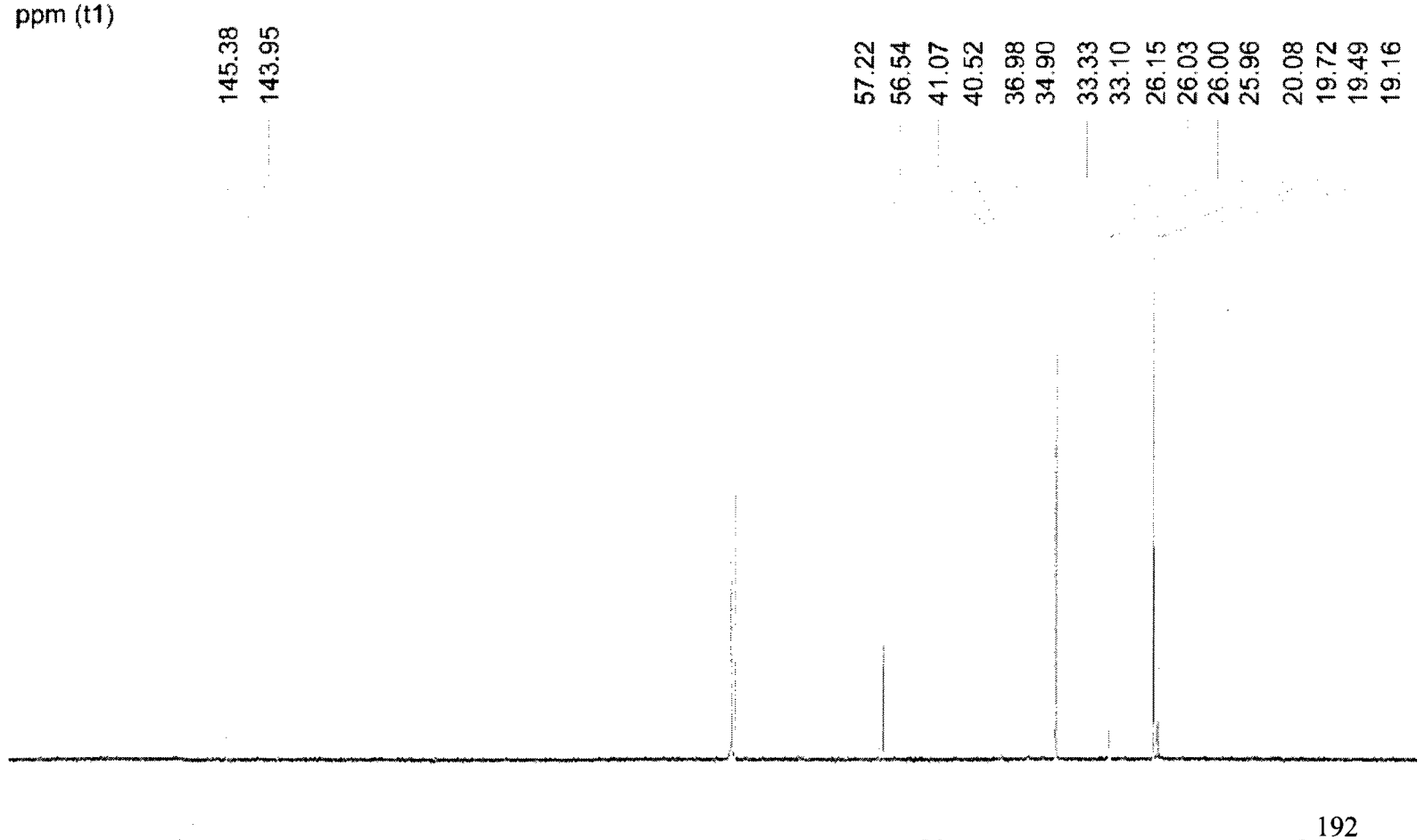


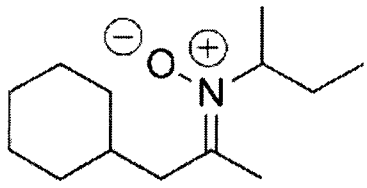




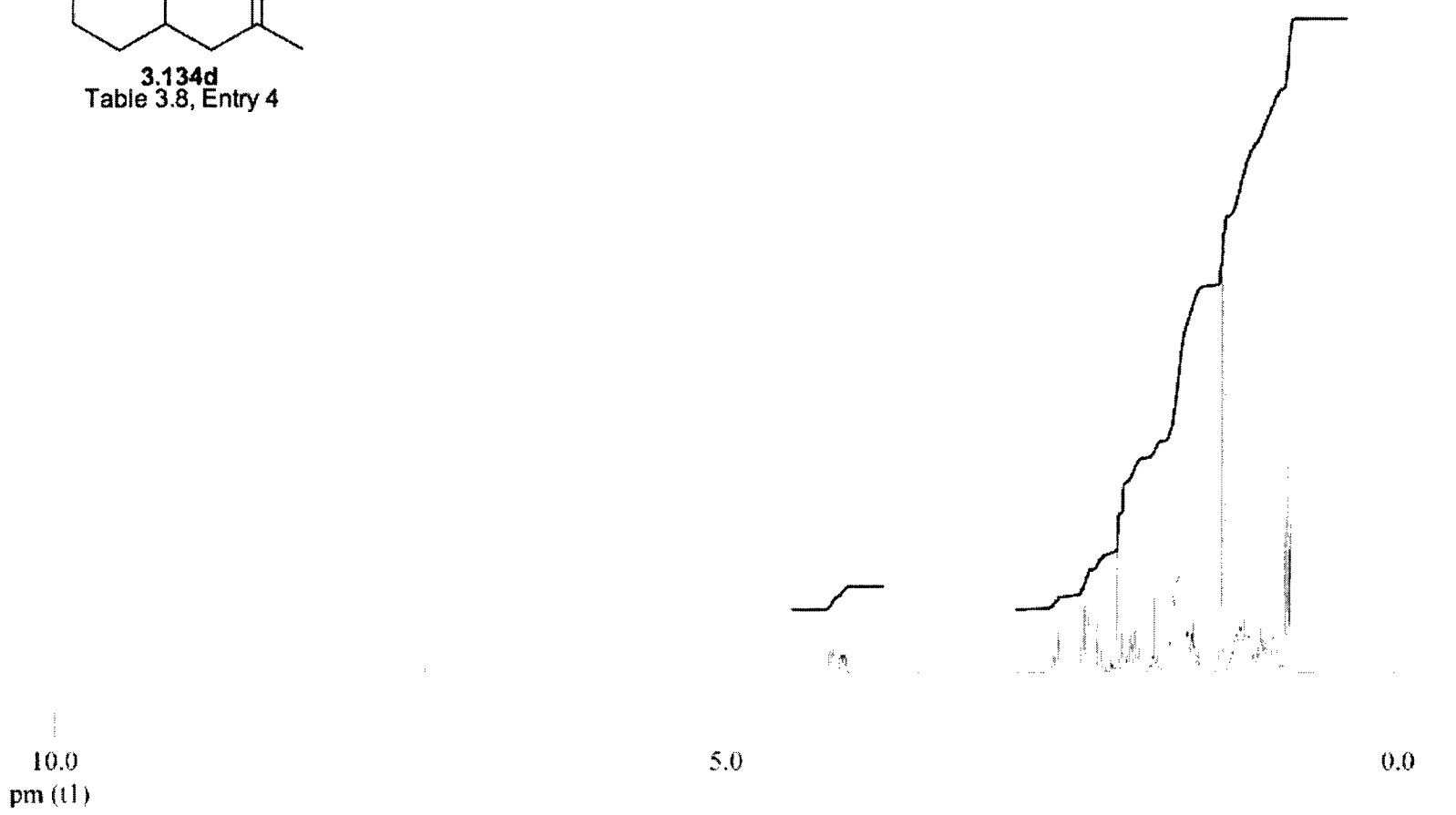
3.134c
Table 3.8, Entry 3

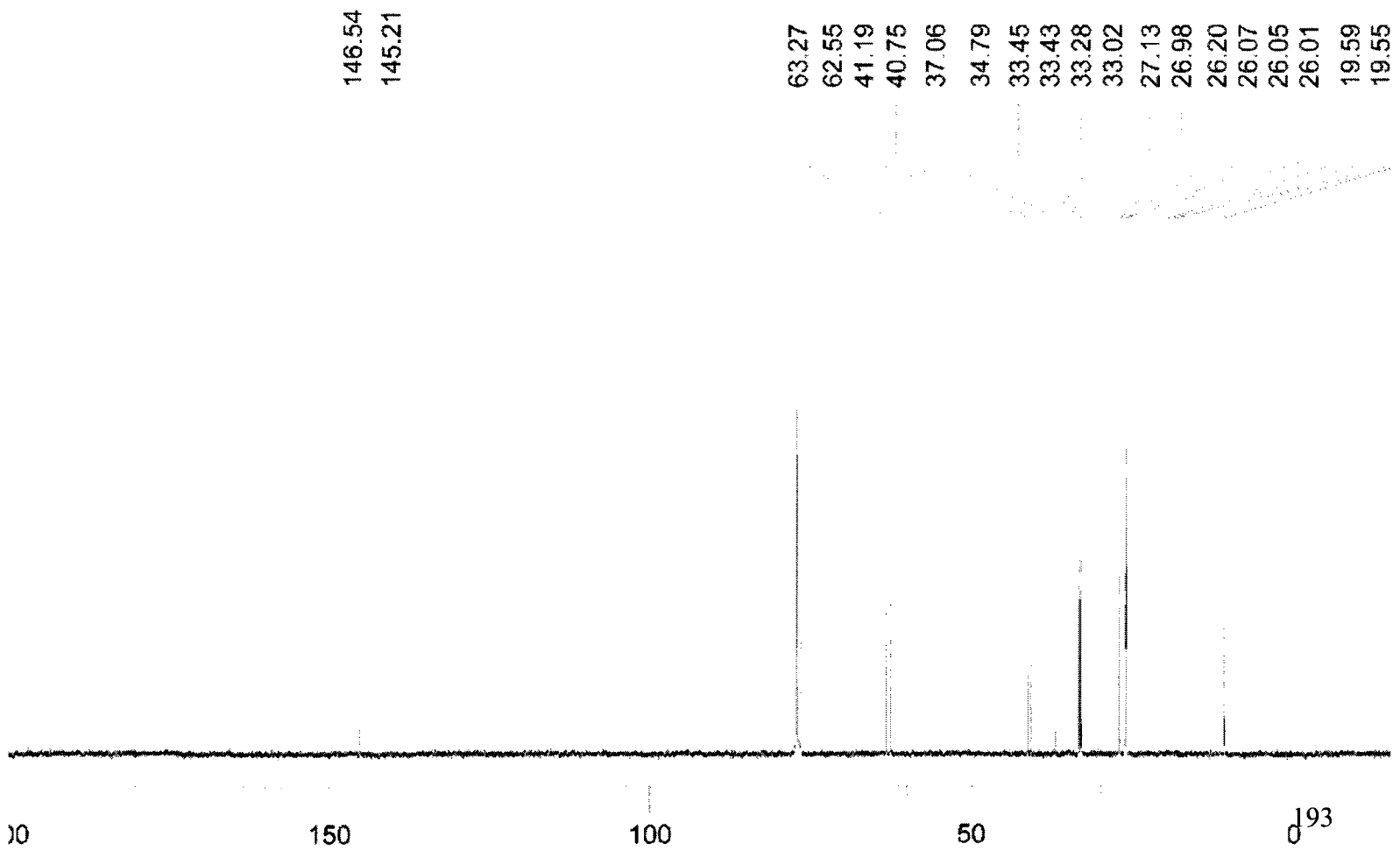


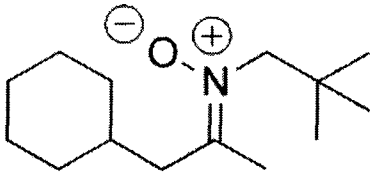




3.134d
Table 3.8, Entry 4





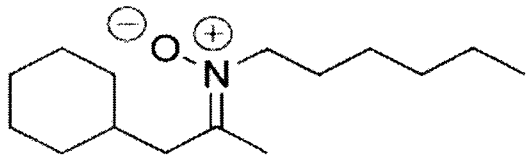


3.134e
Table 3.8, Entry 5

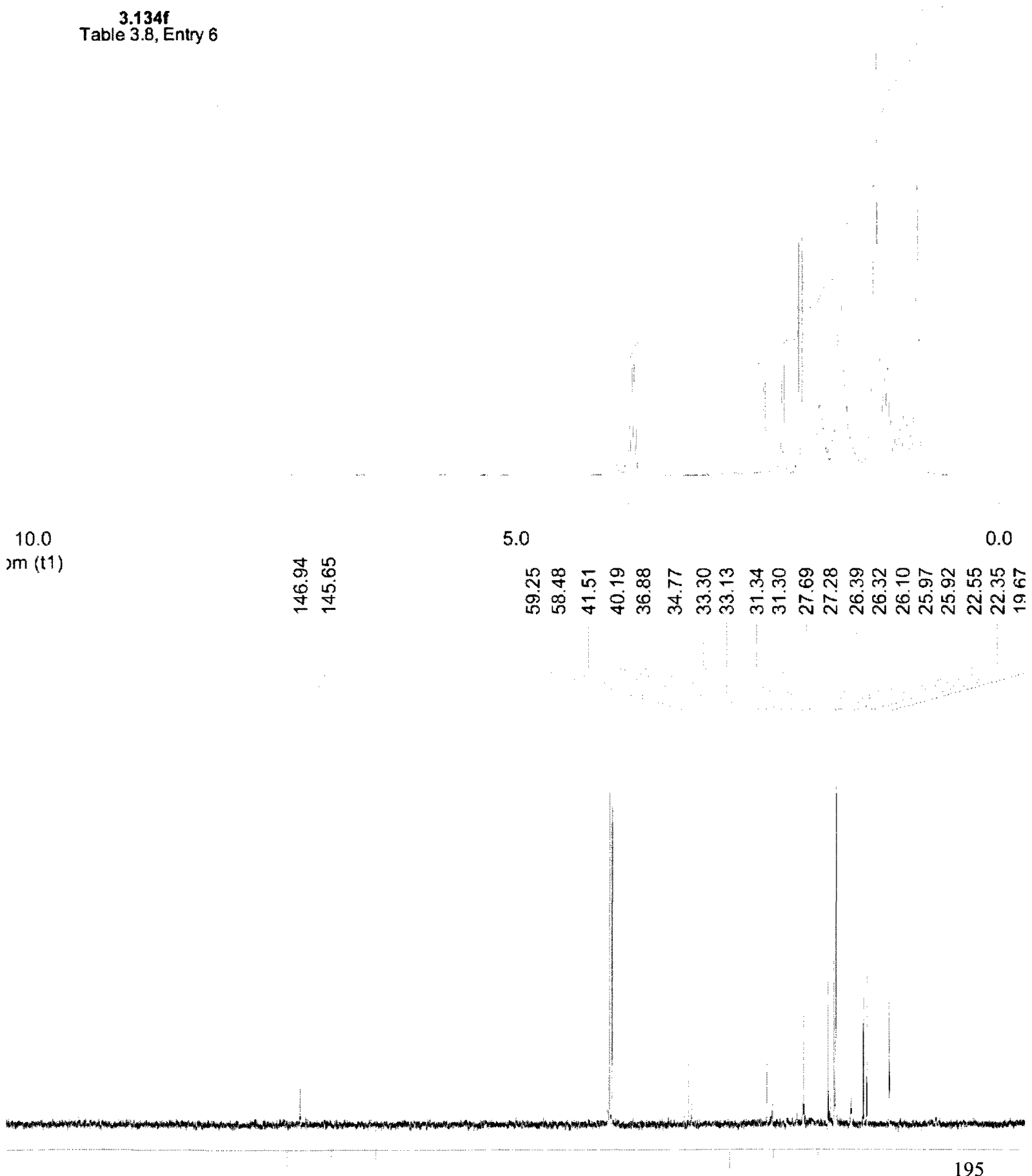
10.0 5.0 0.0
ɔm (t1)

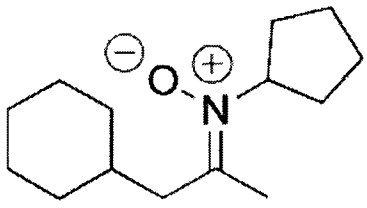
148.27
147.33
68.56
67.91
42.42
40.67
37.03
34.78
33.54
33.23
28.65
28.63
28.03
27.51
26.22
26.09
26.04
21.13

200 150 100 50 0



3.134f
Table 3.8, Entry 6





3.134g
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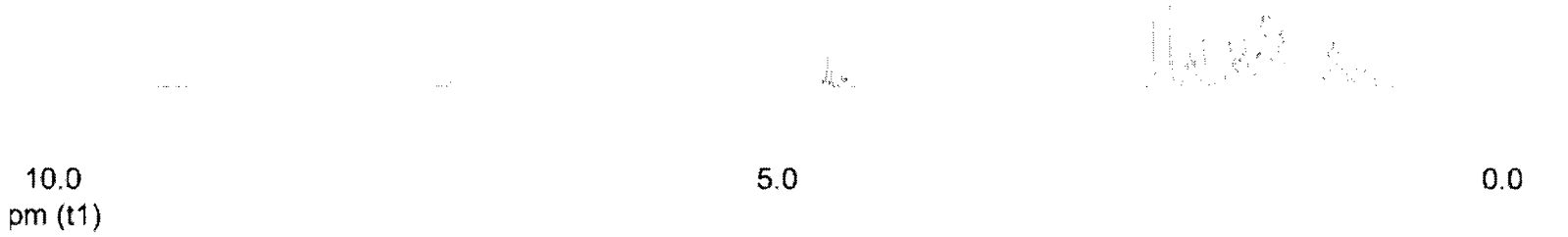
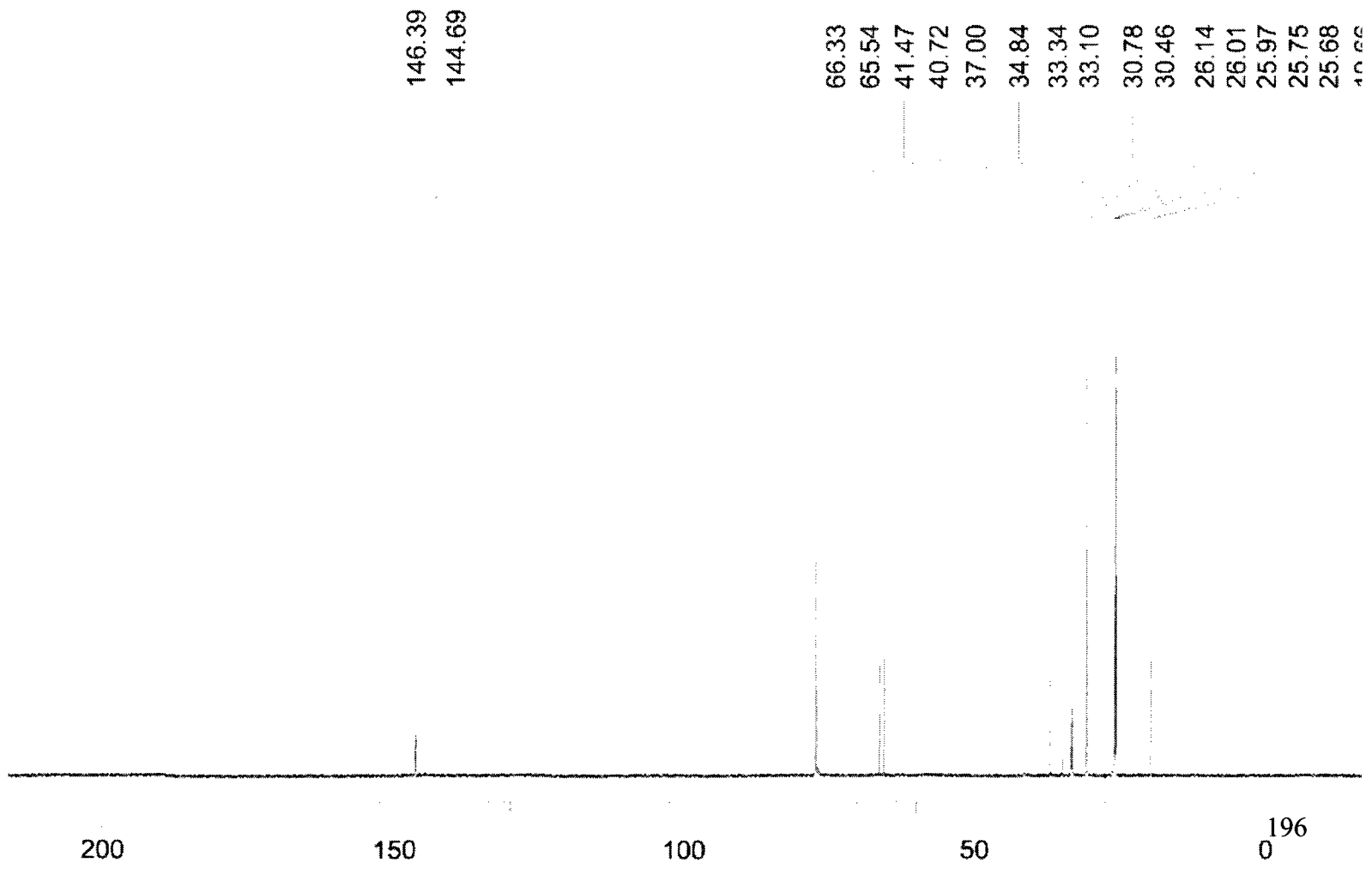
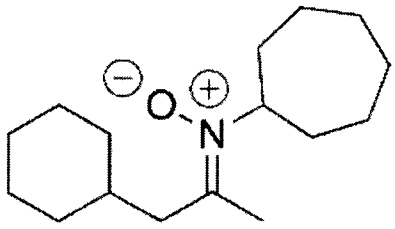
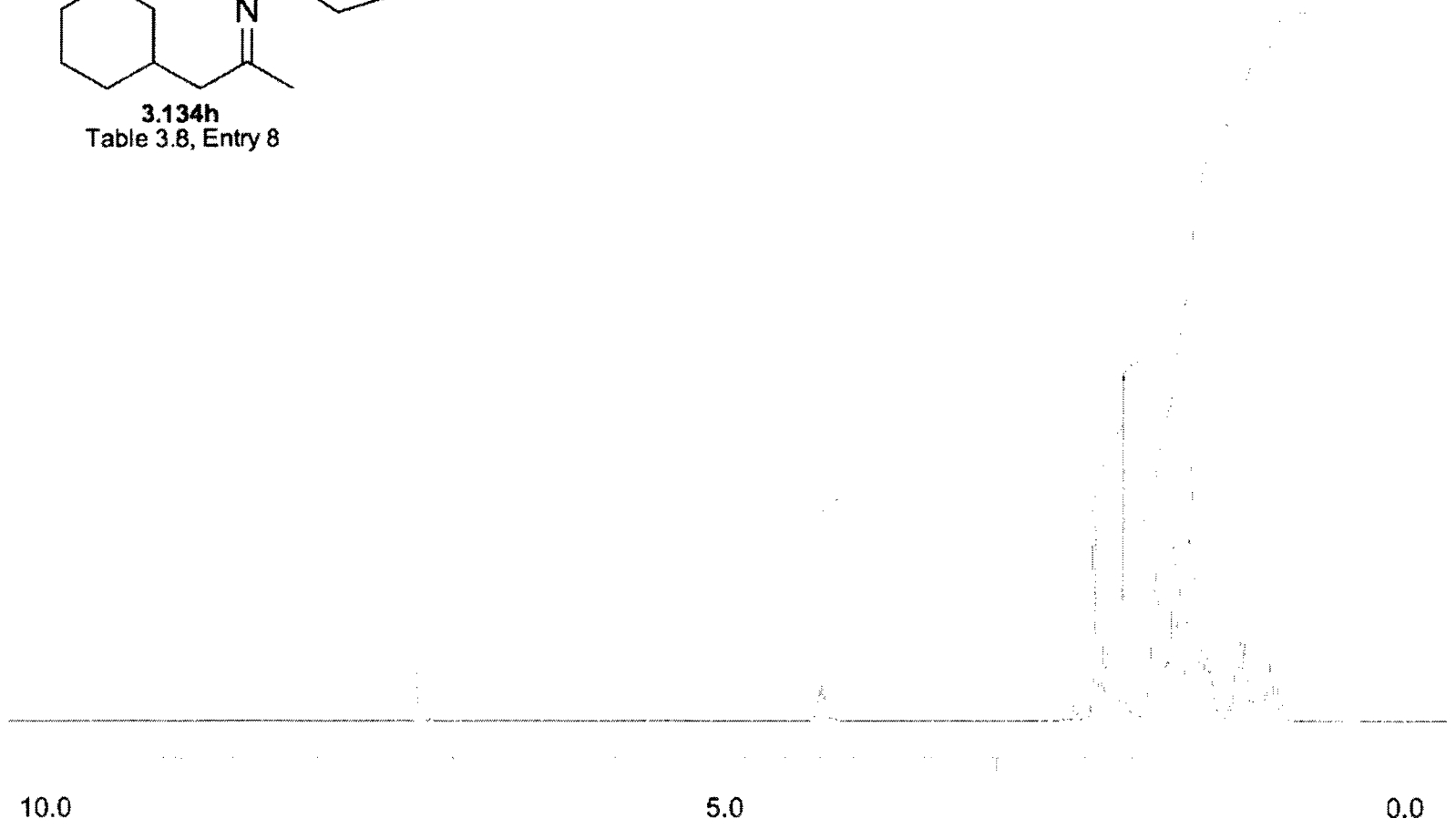
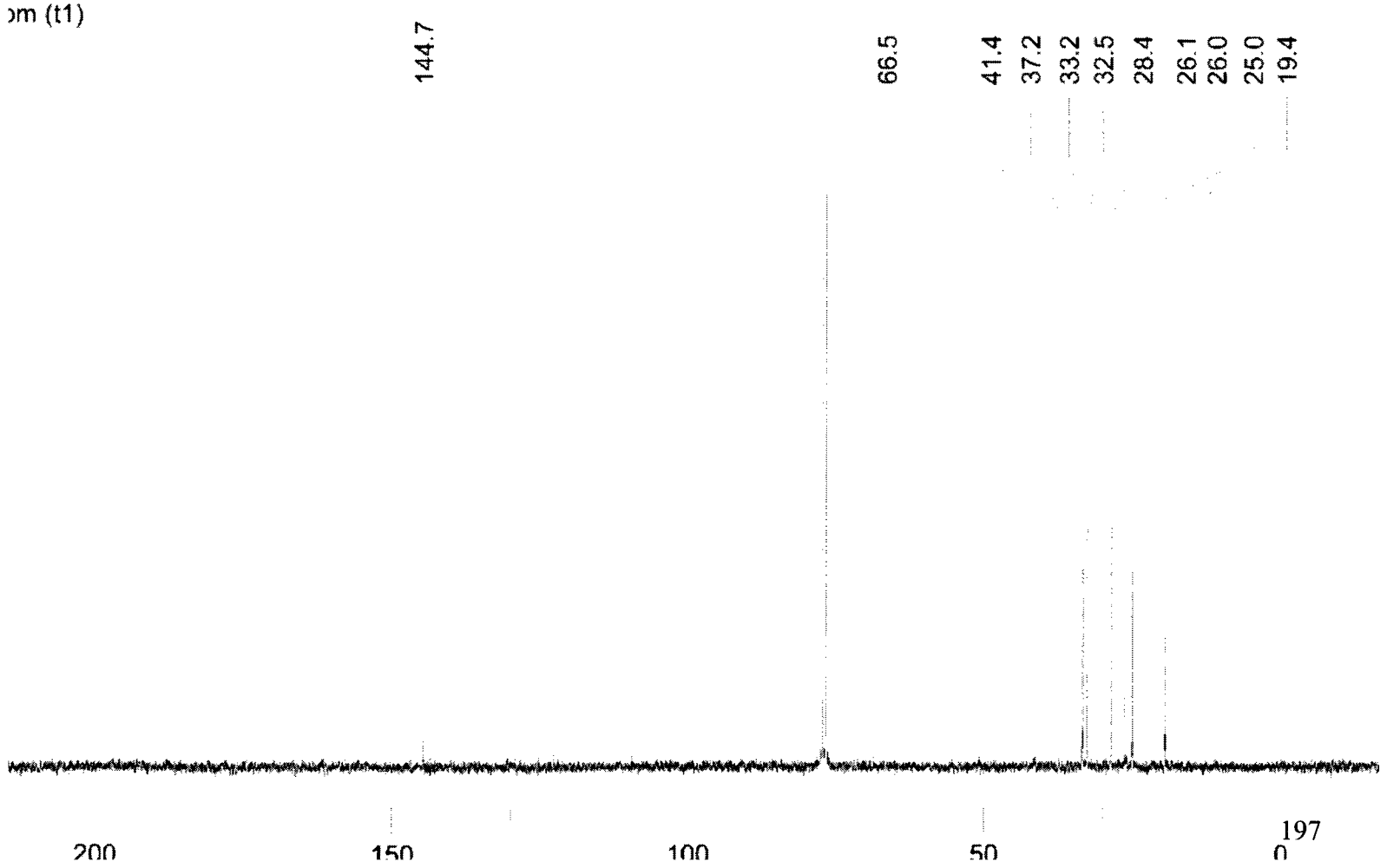


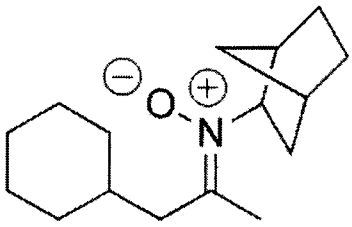




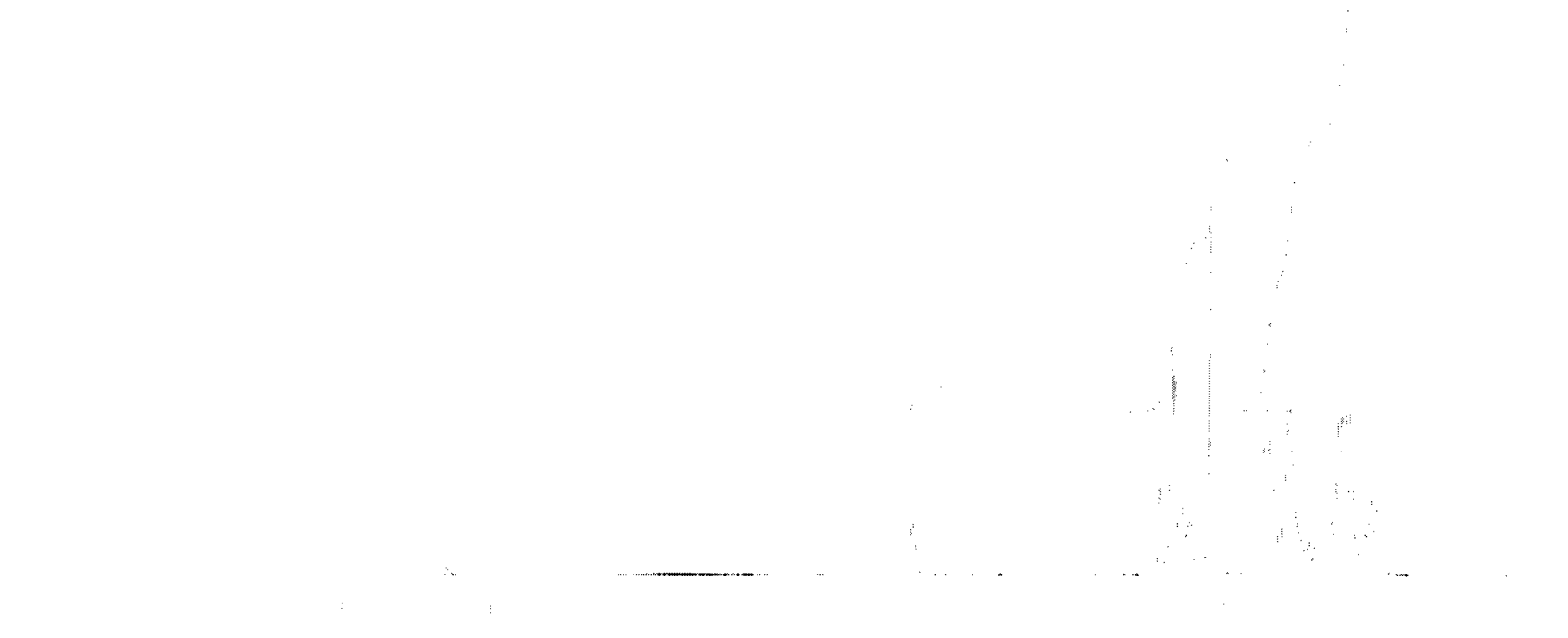
3.134h
Table 3.8, Entry 8

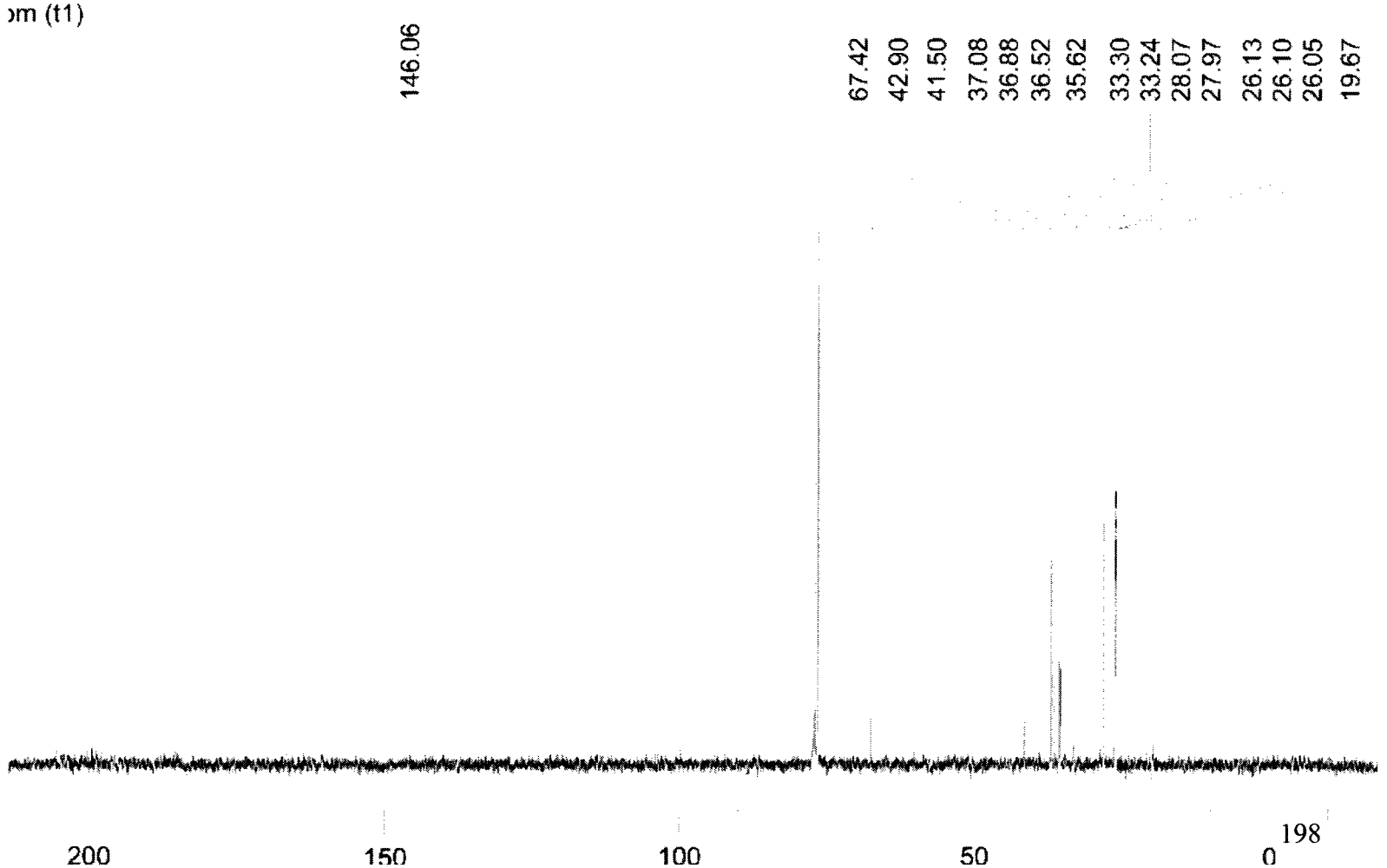


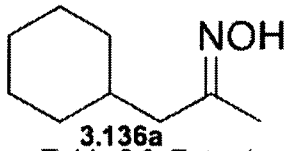




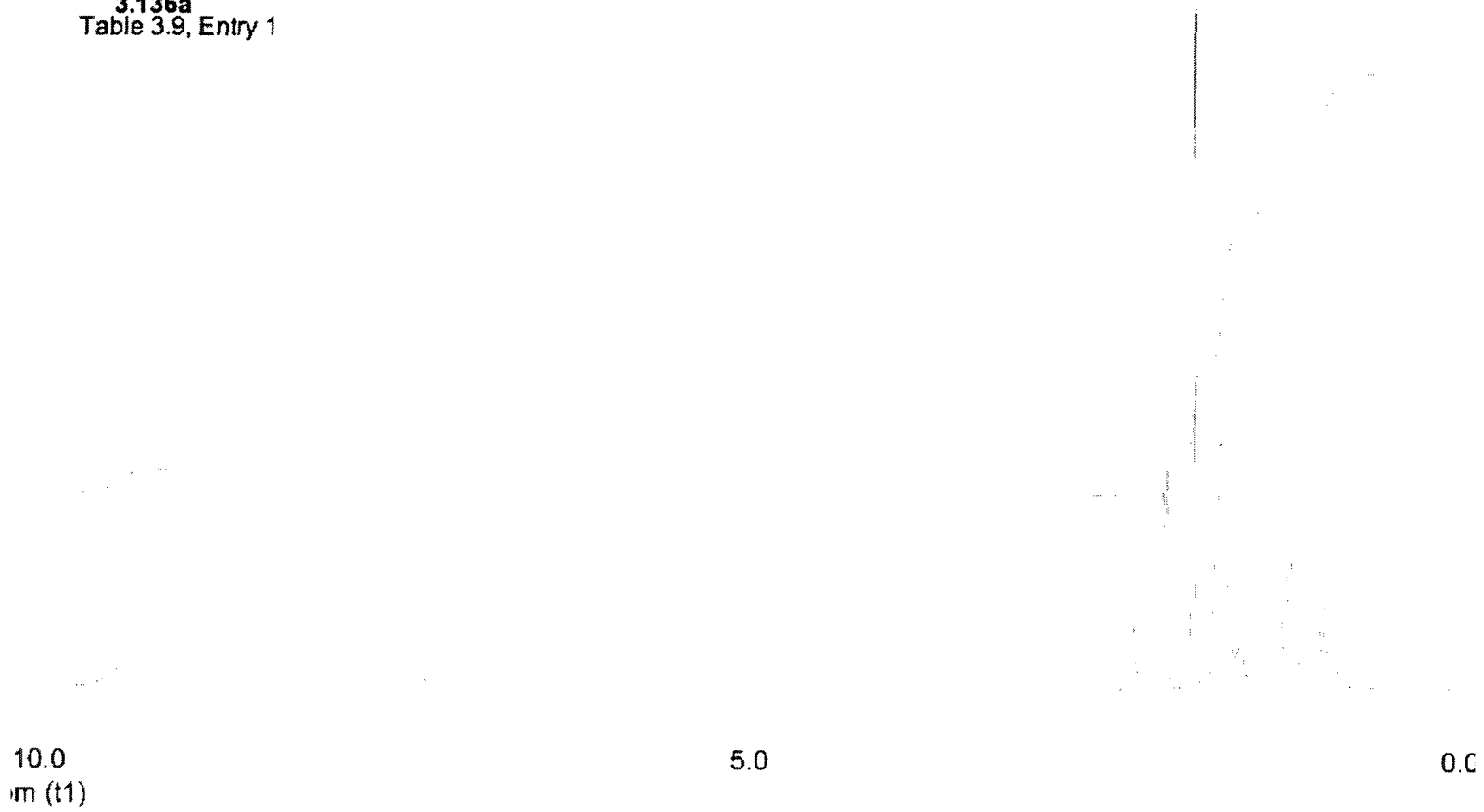
3.134i
Table 3.8, Entry 9

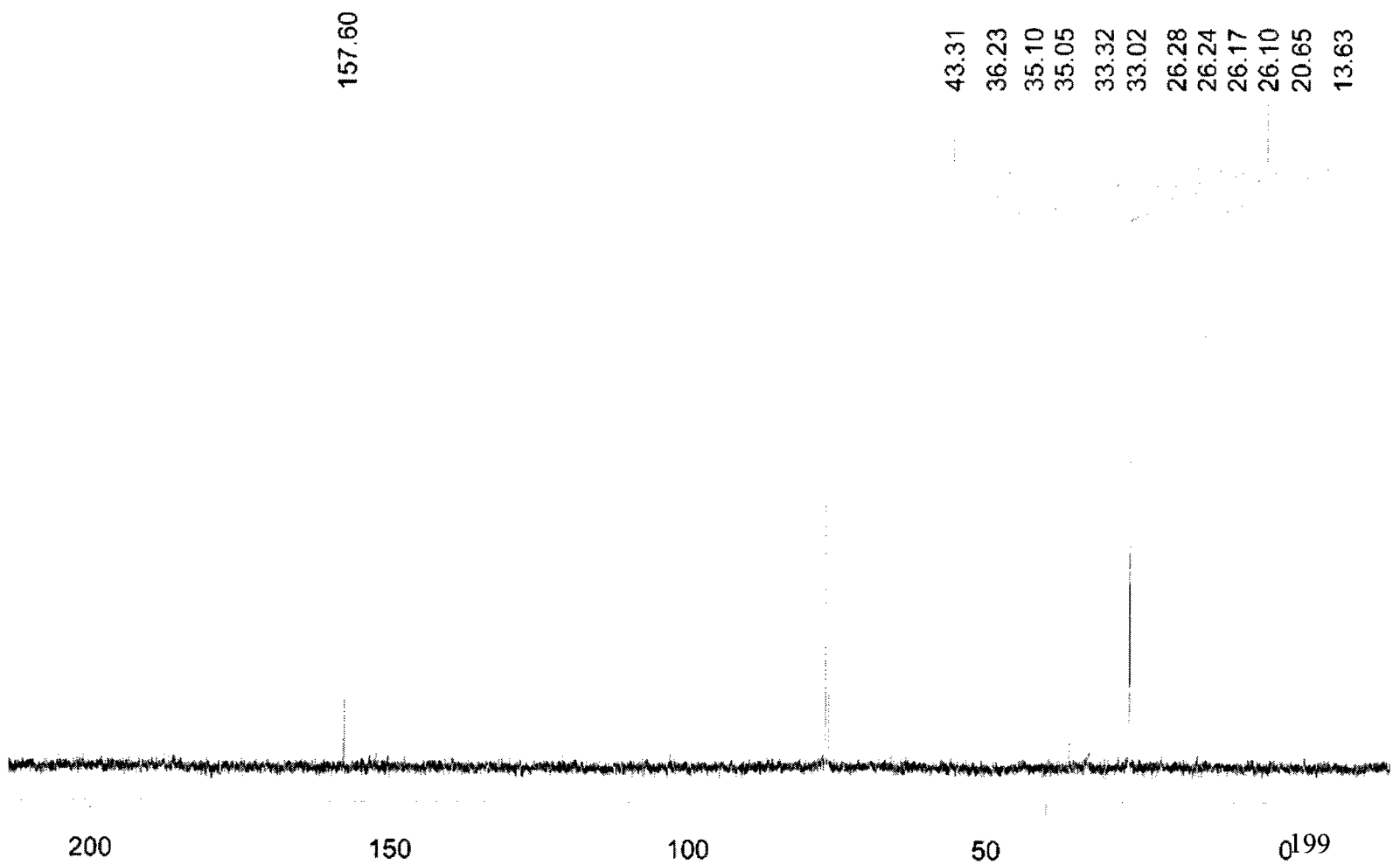


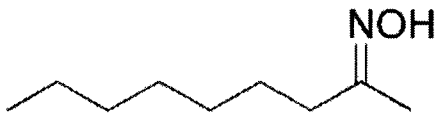




3.136a
Table 3.9, Entry 1

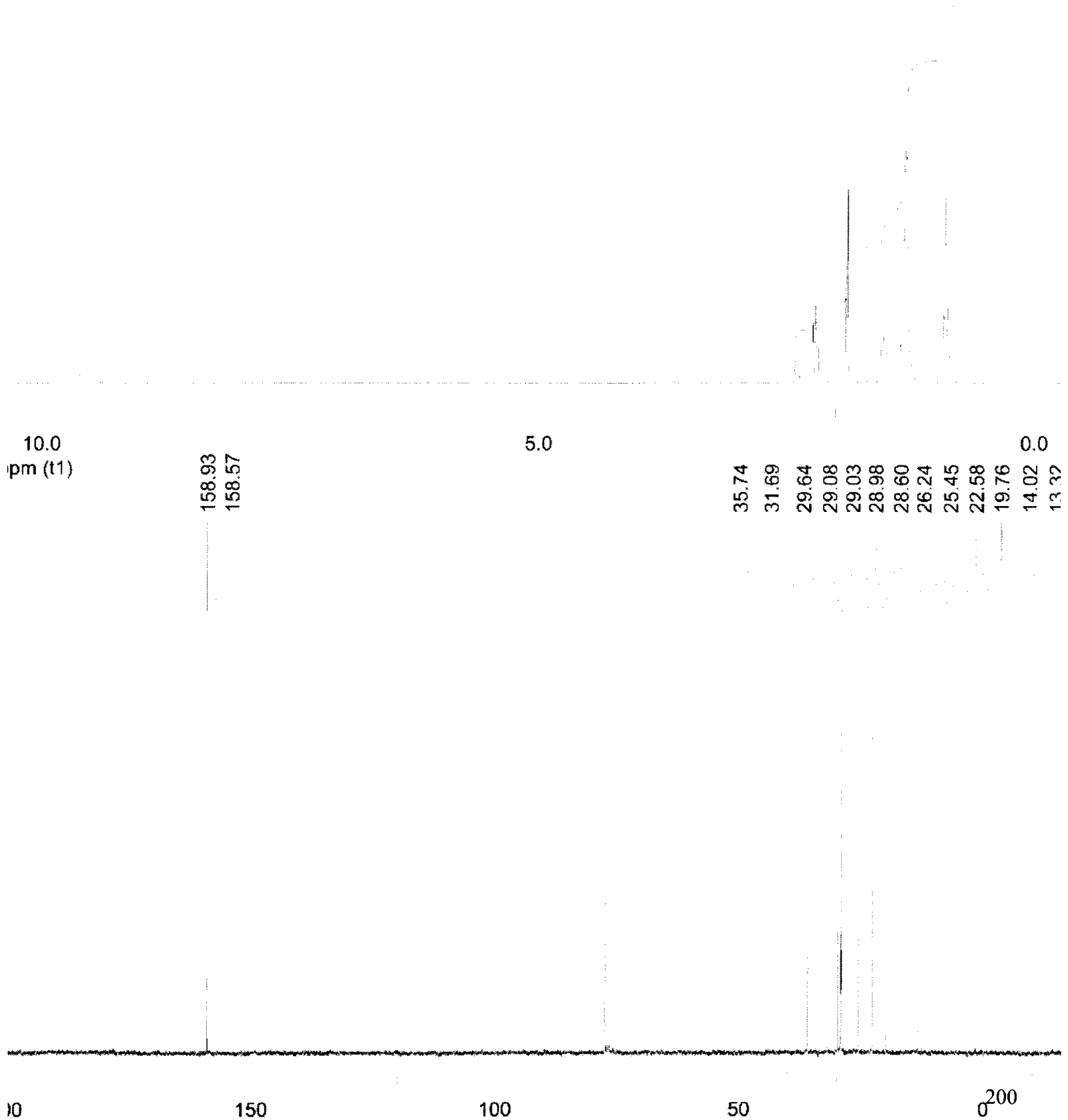


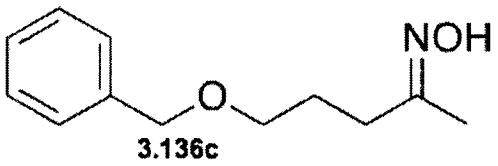




3.136b

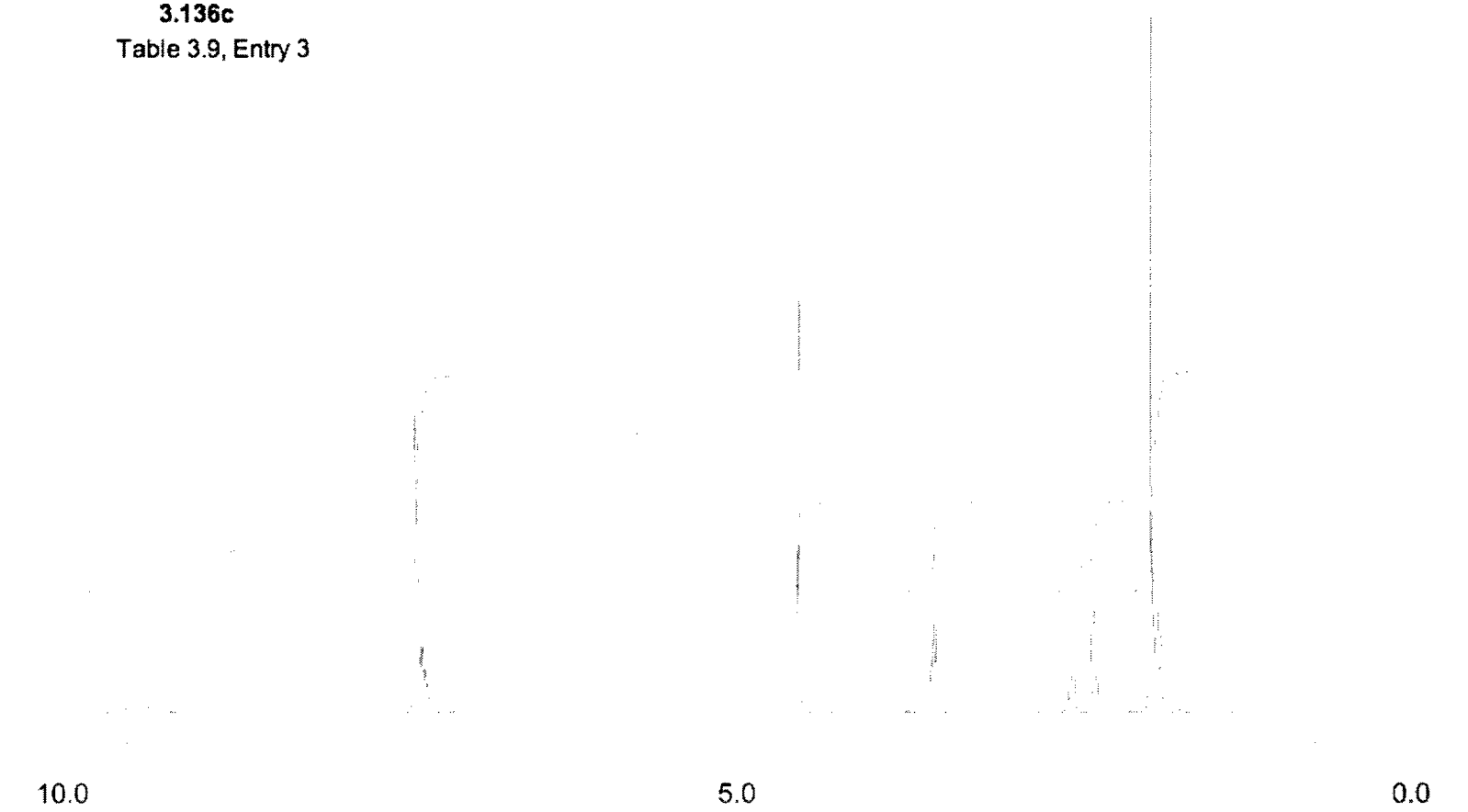
Table 3.9, Entry 2





3.136c

Table 3.9, Entry 3



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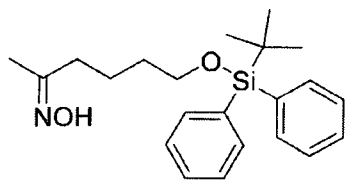
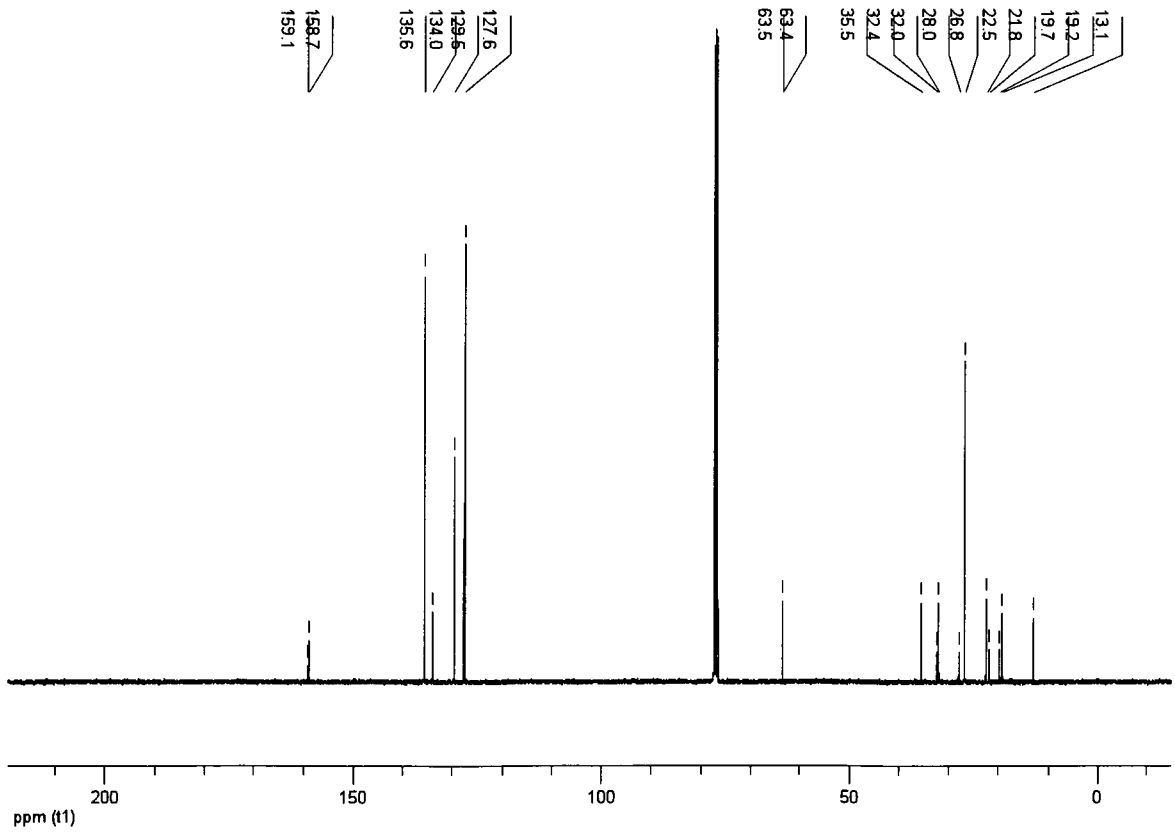
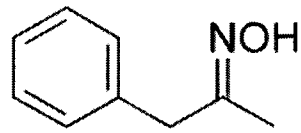
158.0
138.3
128.3
127.6
127.5
72.8
69.8
69.4
32.6
26.3
25.6
25.5
19.9
13.5



3.136d
Table 3.9, Entry 4





3.136e
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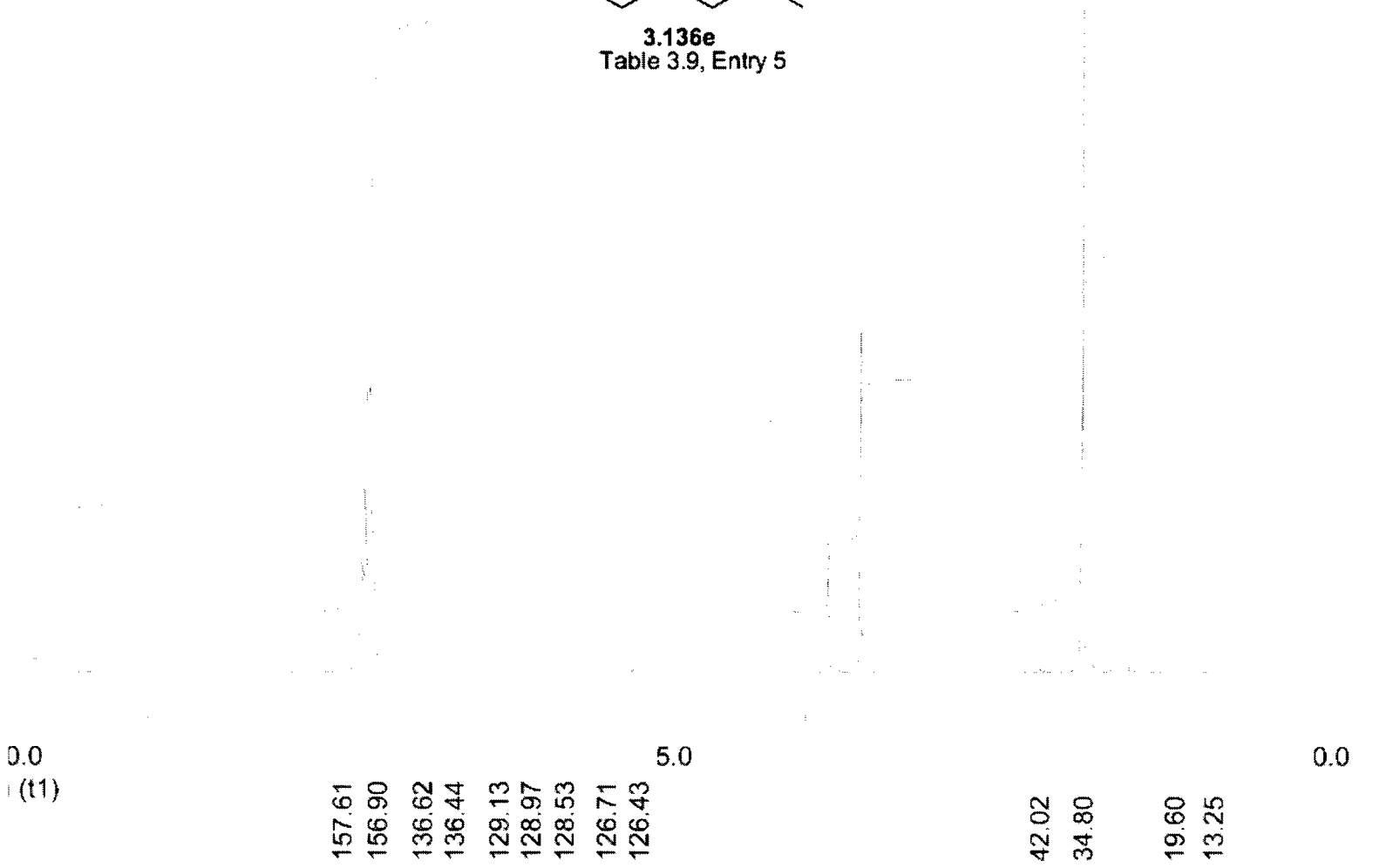
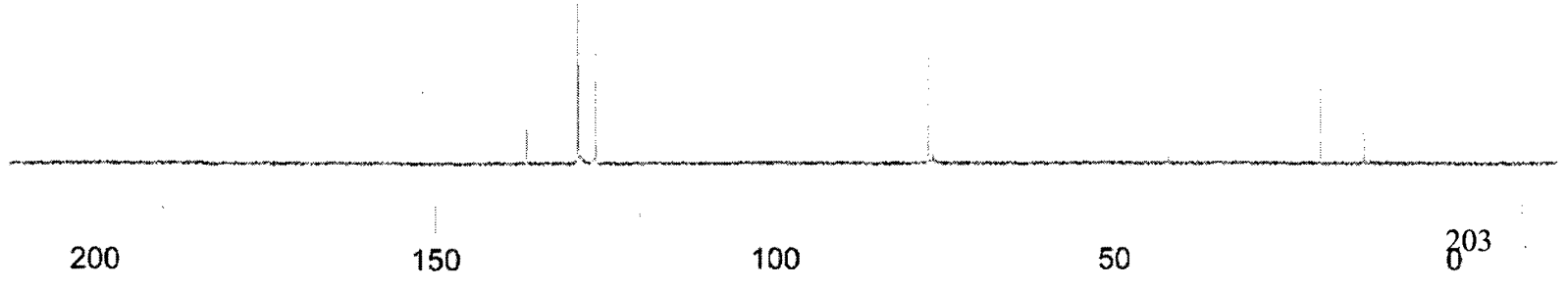
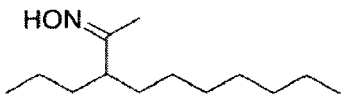
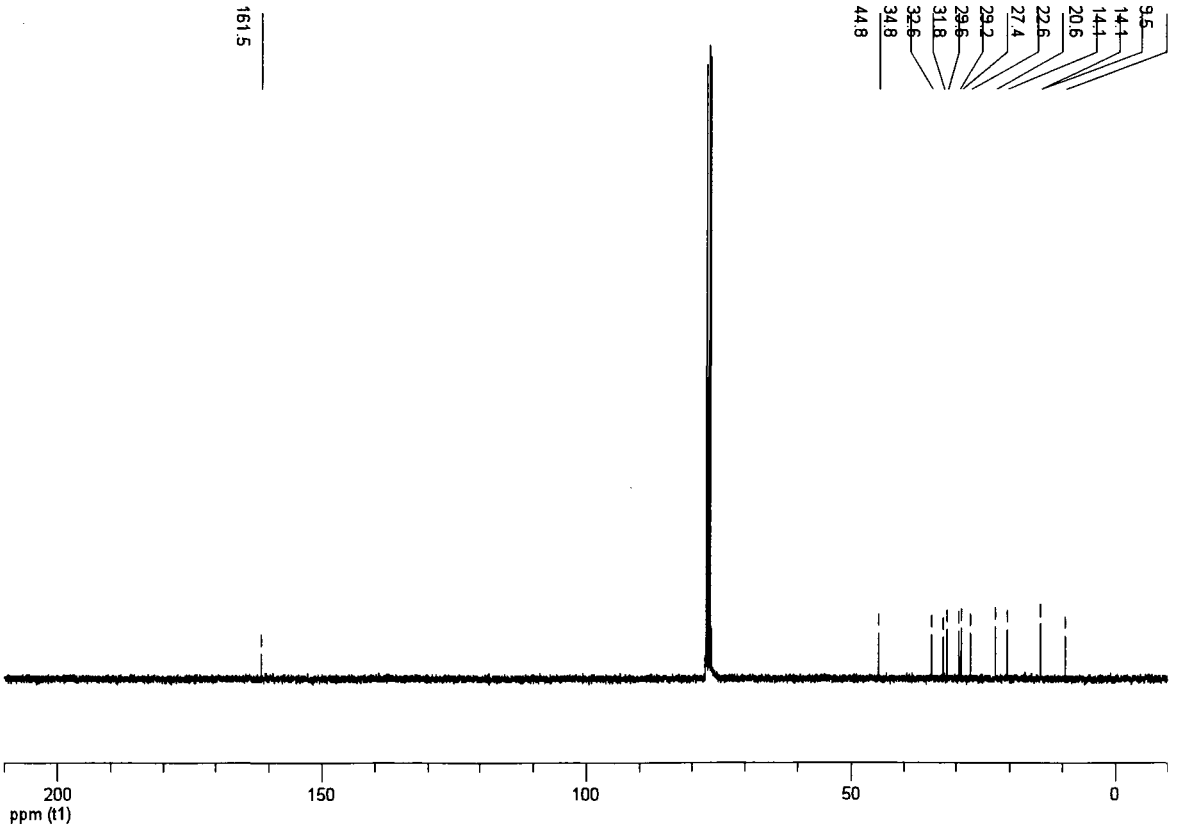
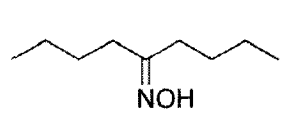




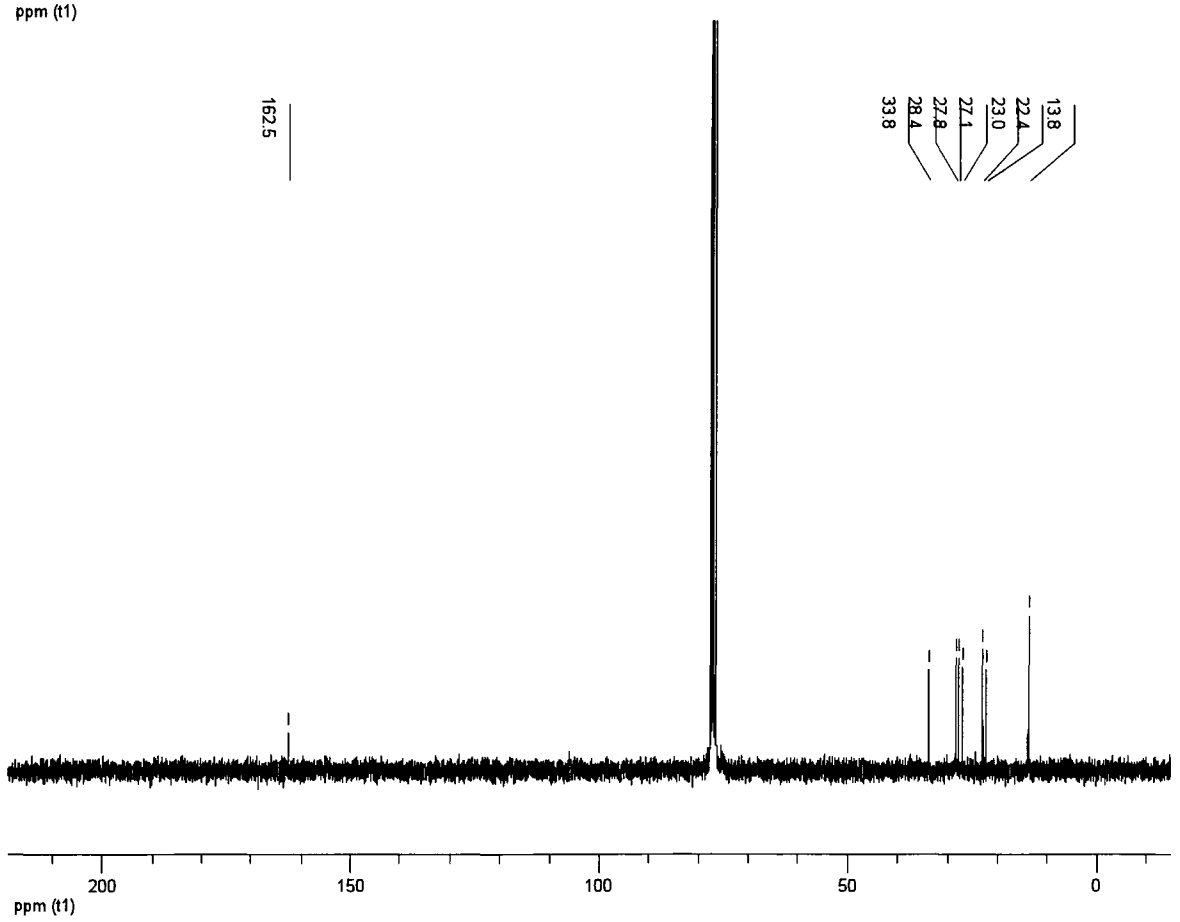


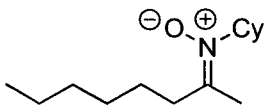
3.136g
Table 3.9, Entry 7





3.136h
Table 3.9, Entry 8





3.148a
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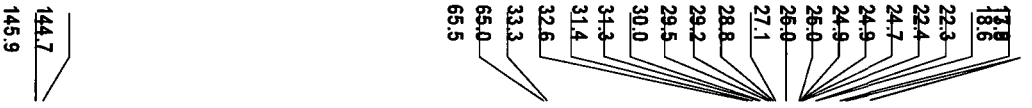
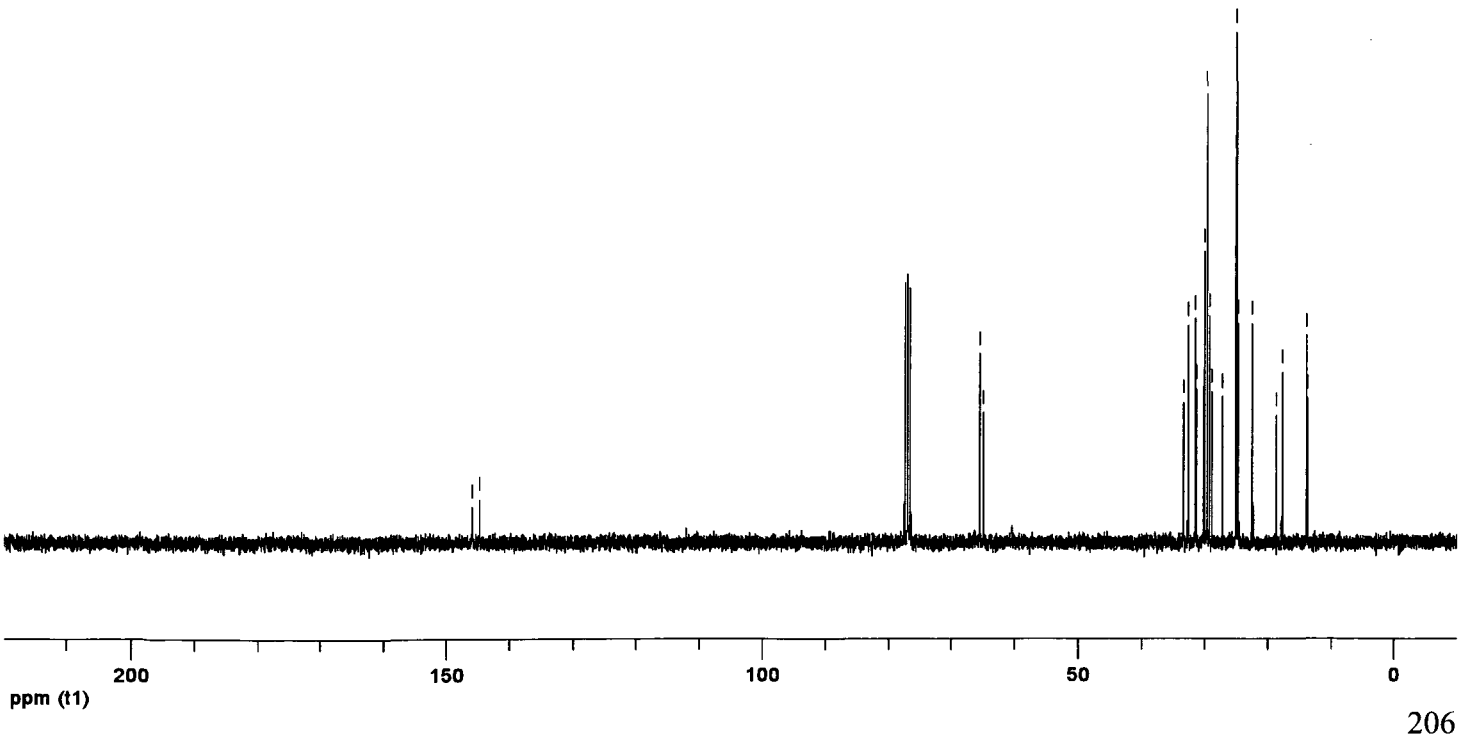
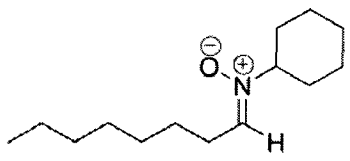
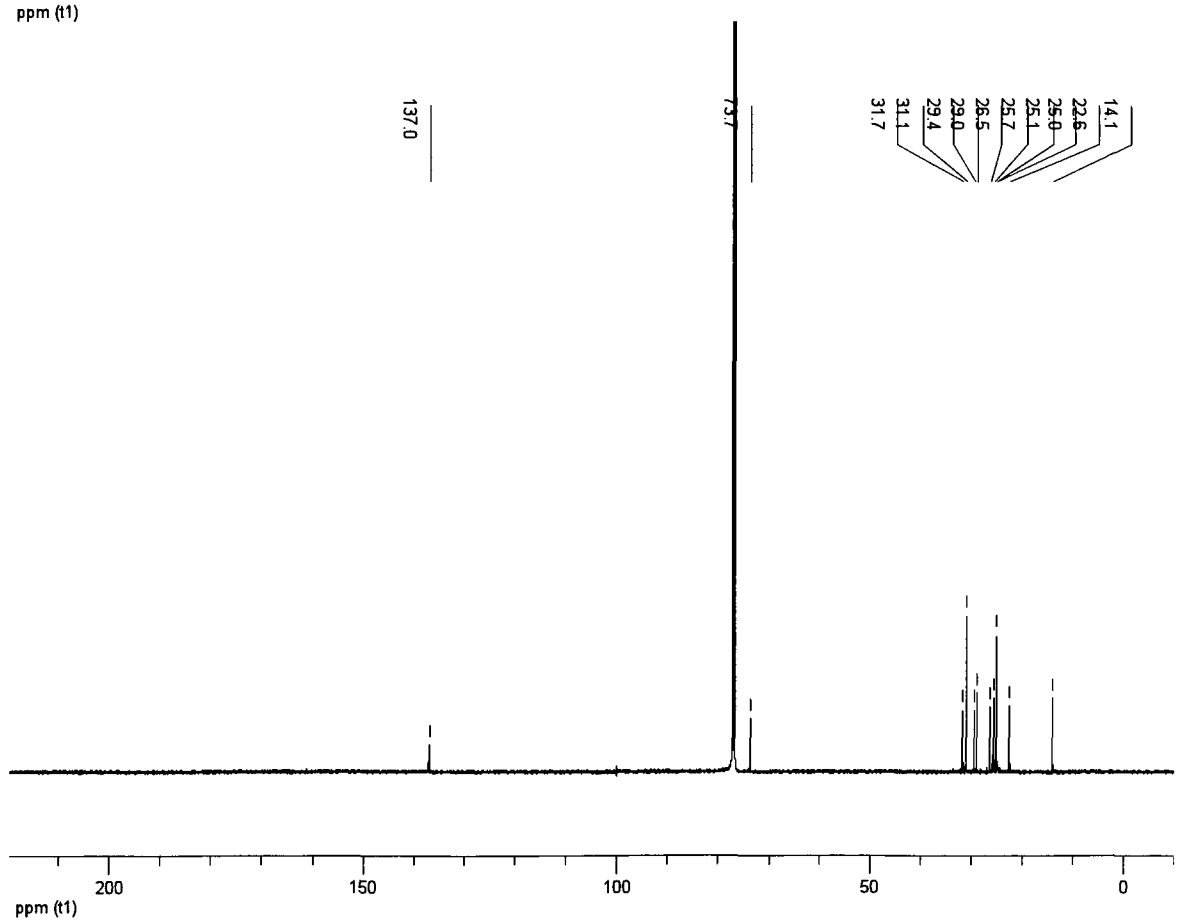
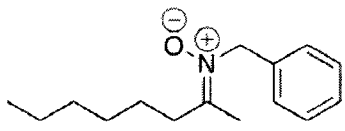






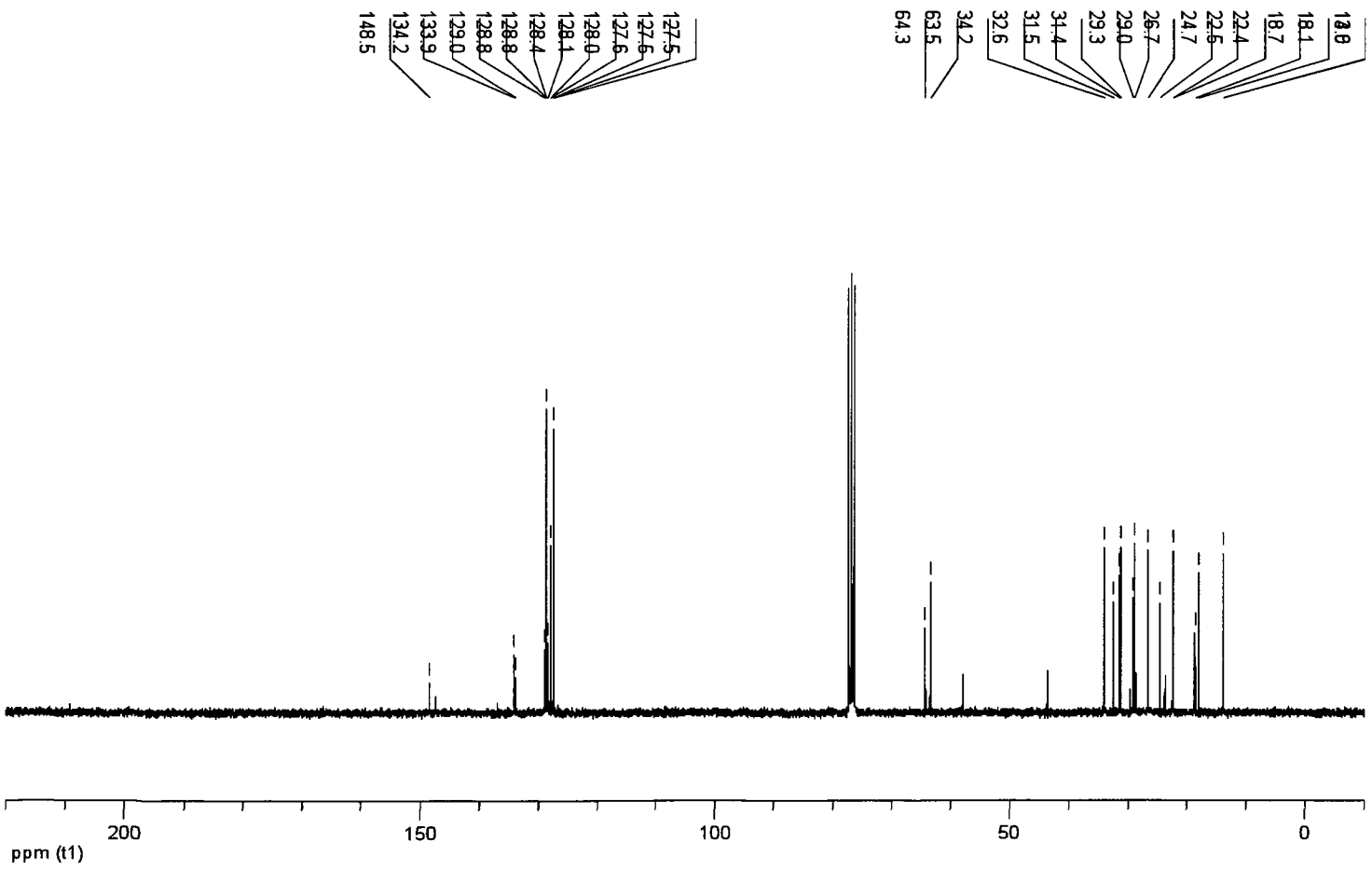
3.148aa
Table 3.12, Entry 1aa

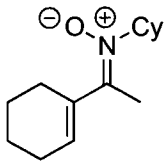




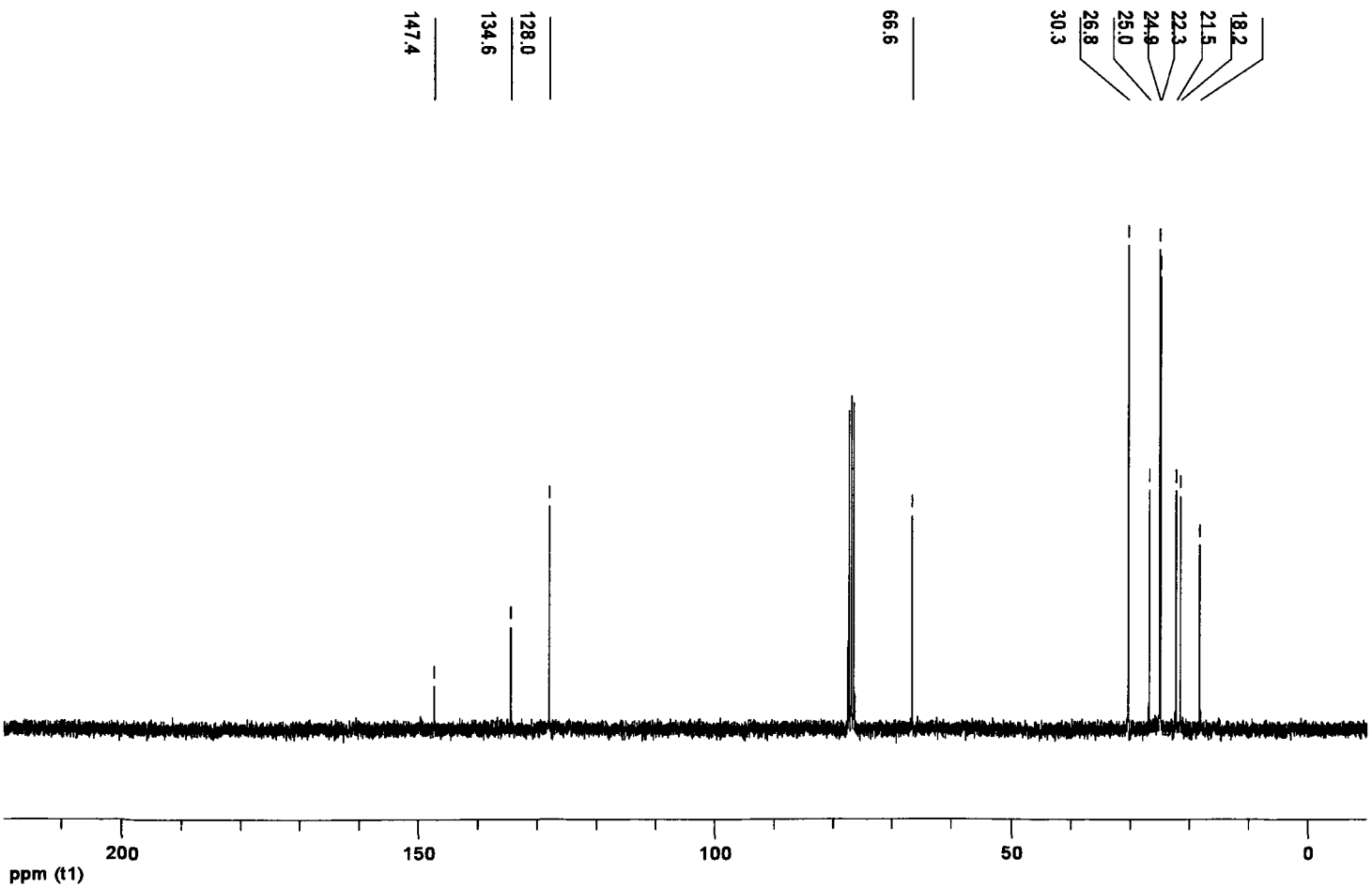
3.148b

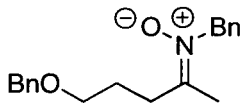
Table 3.12, Entry 1b



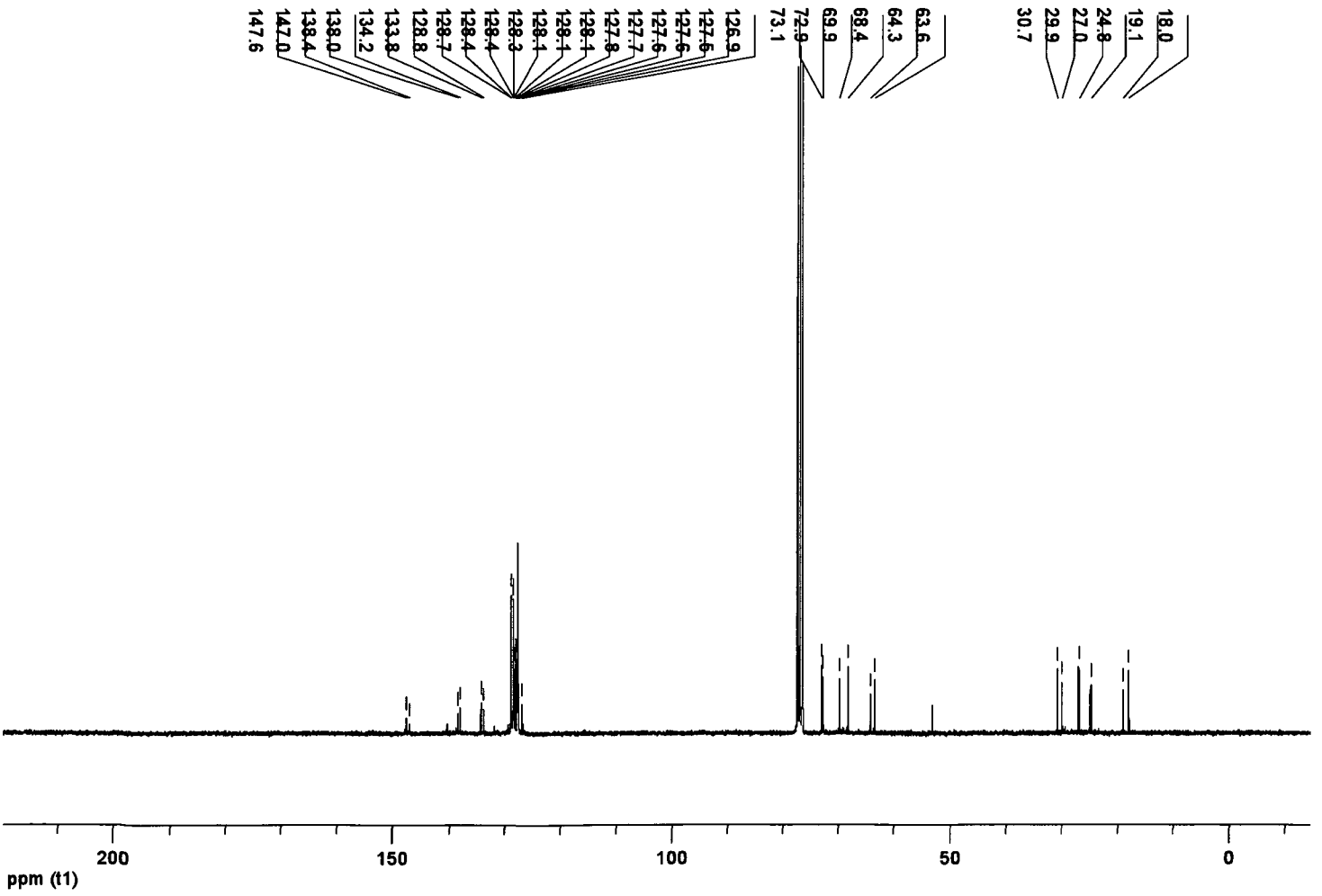


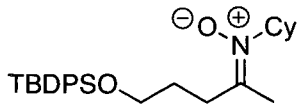
3.148d
Table 3.12, Entry 4





3.148e
Table 3.12, Entry 6





3.148f
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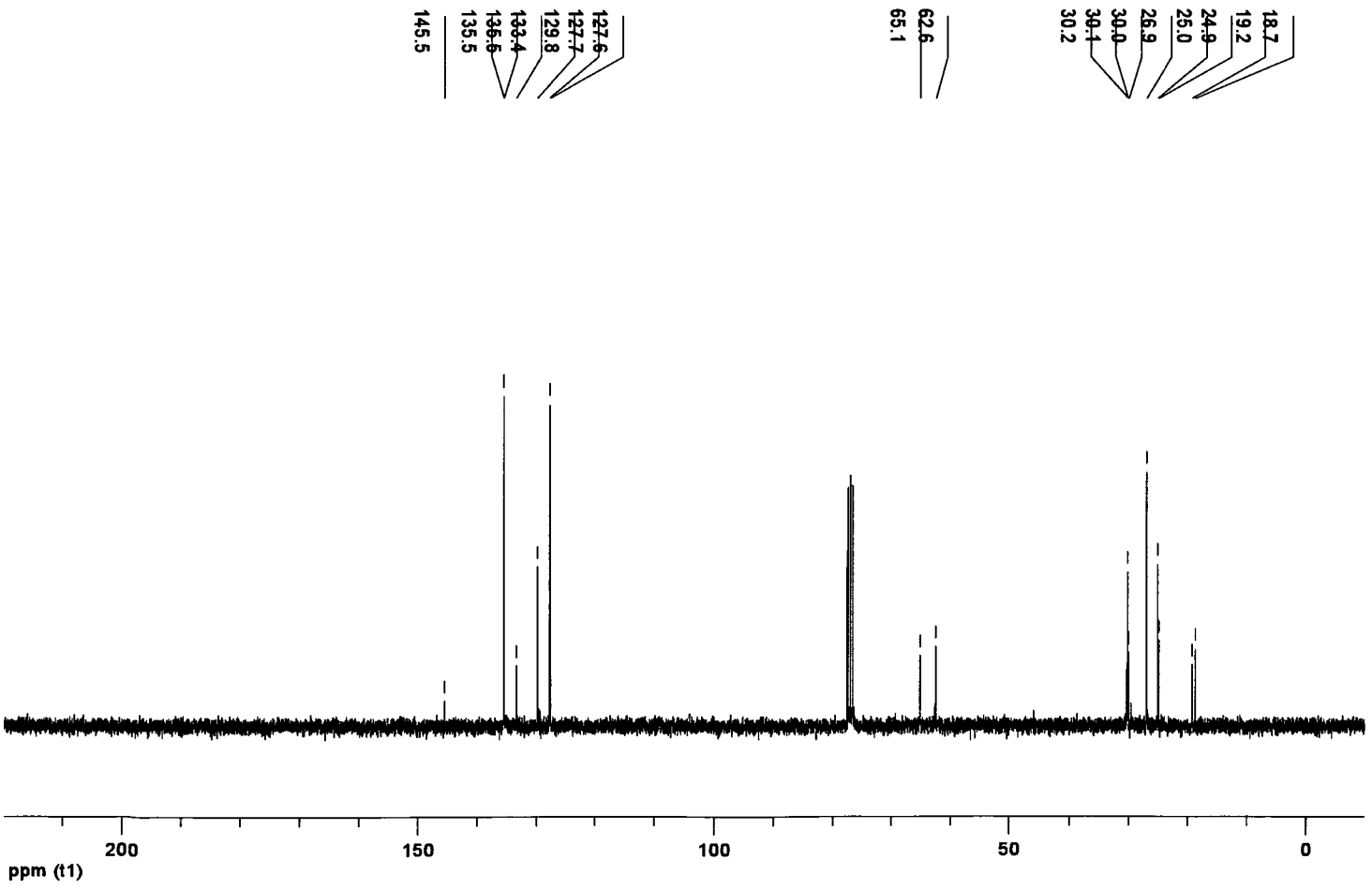

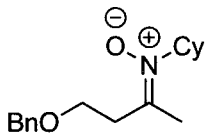

3.148g
Table 3.12, Entry 8

143.1
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138.2
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128.2
127.7
127.7
127.6
127.4
73.2
72.7
66.6
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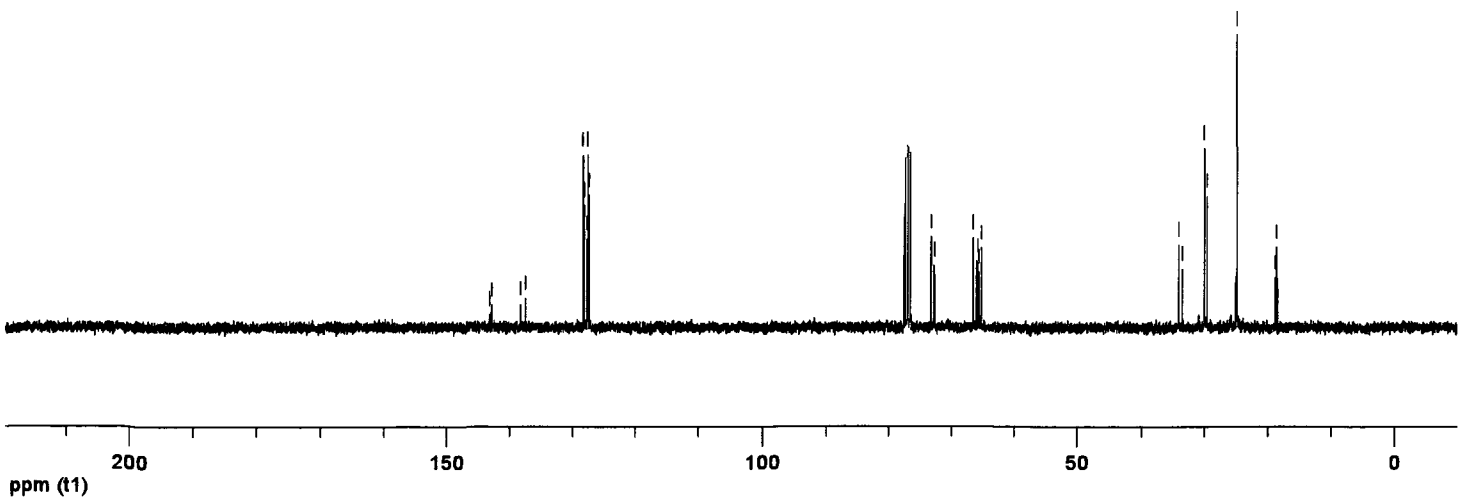
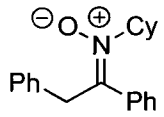
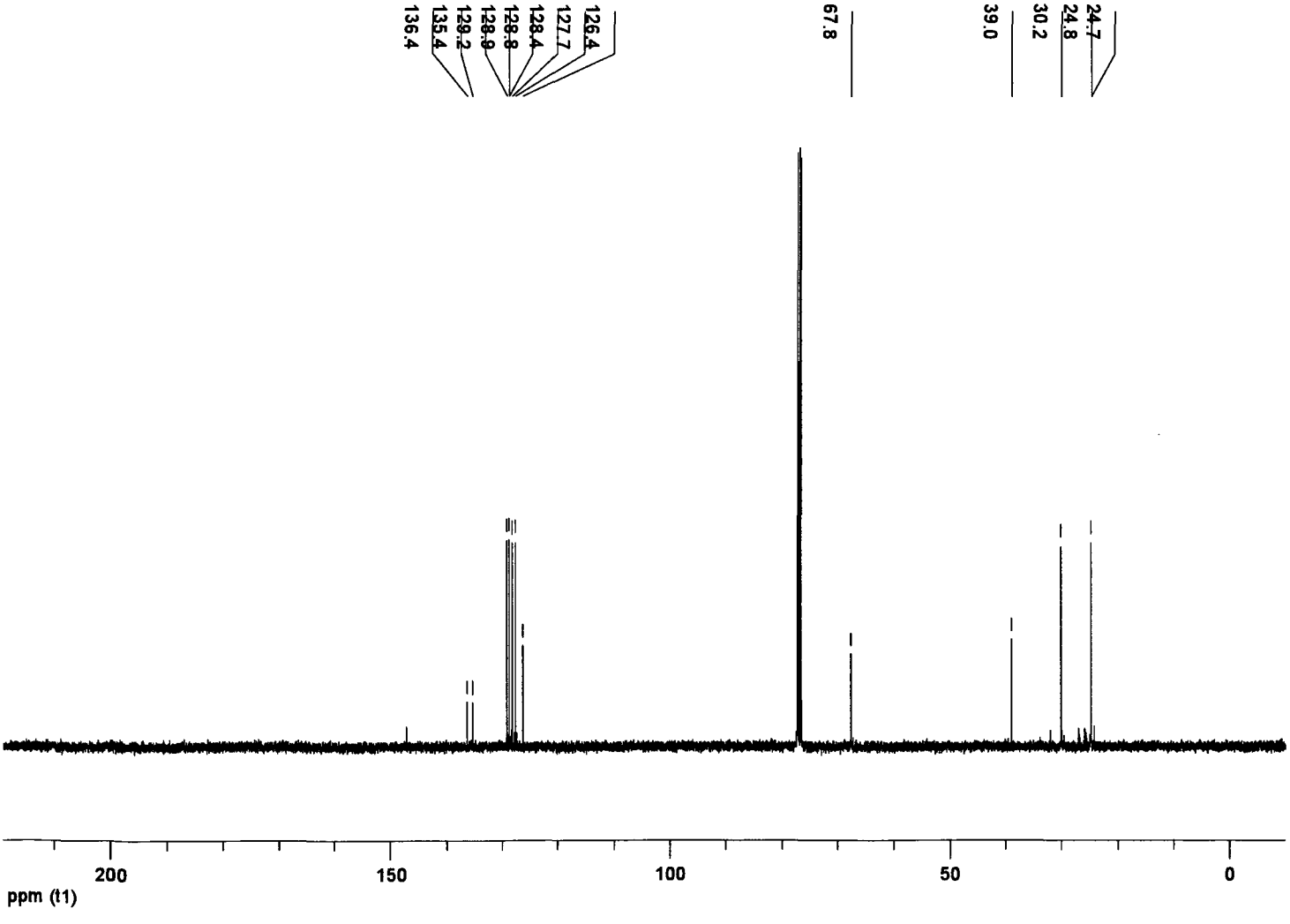
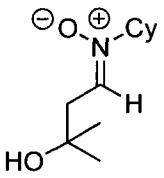
29.9
29.6
24.9
24.9
18.8
18.6



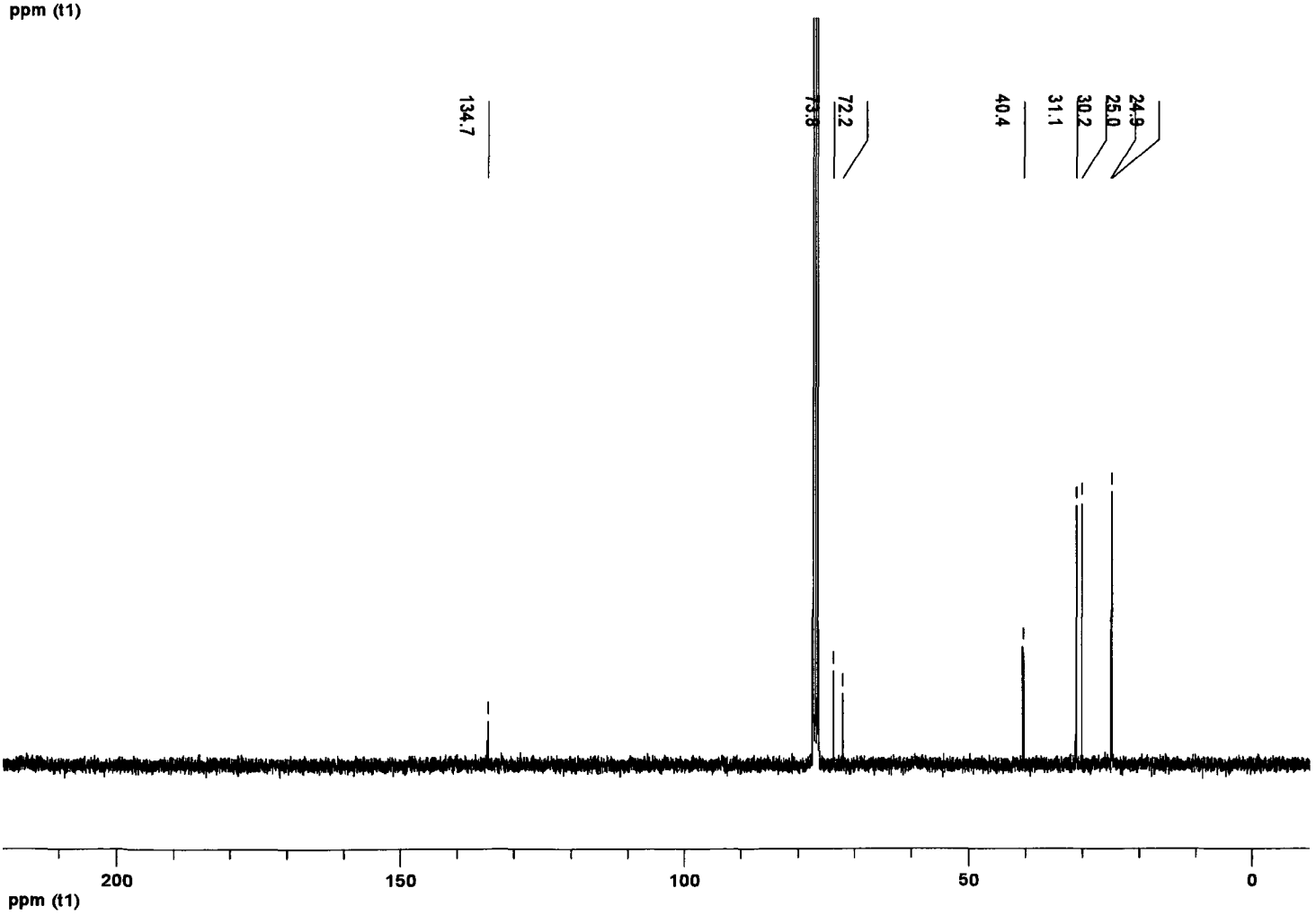


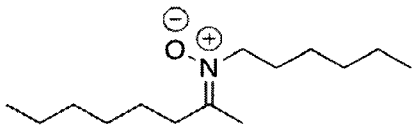
3.148h
Table 3.12, Entry 9





3.150
Equation 3.21





3.174a

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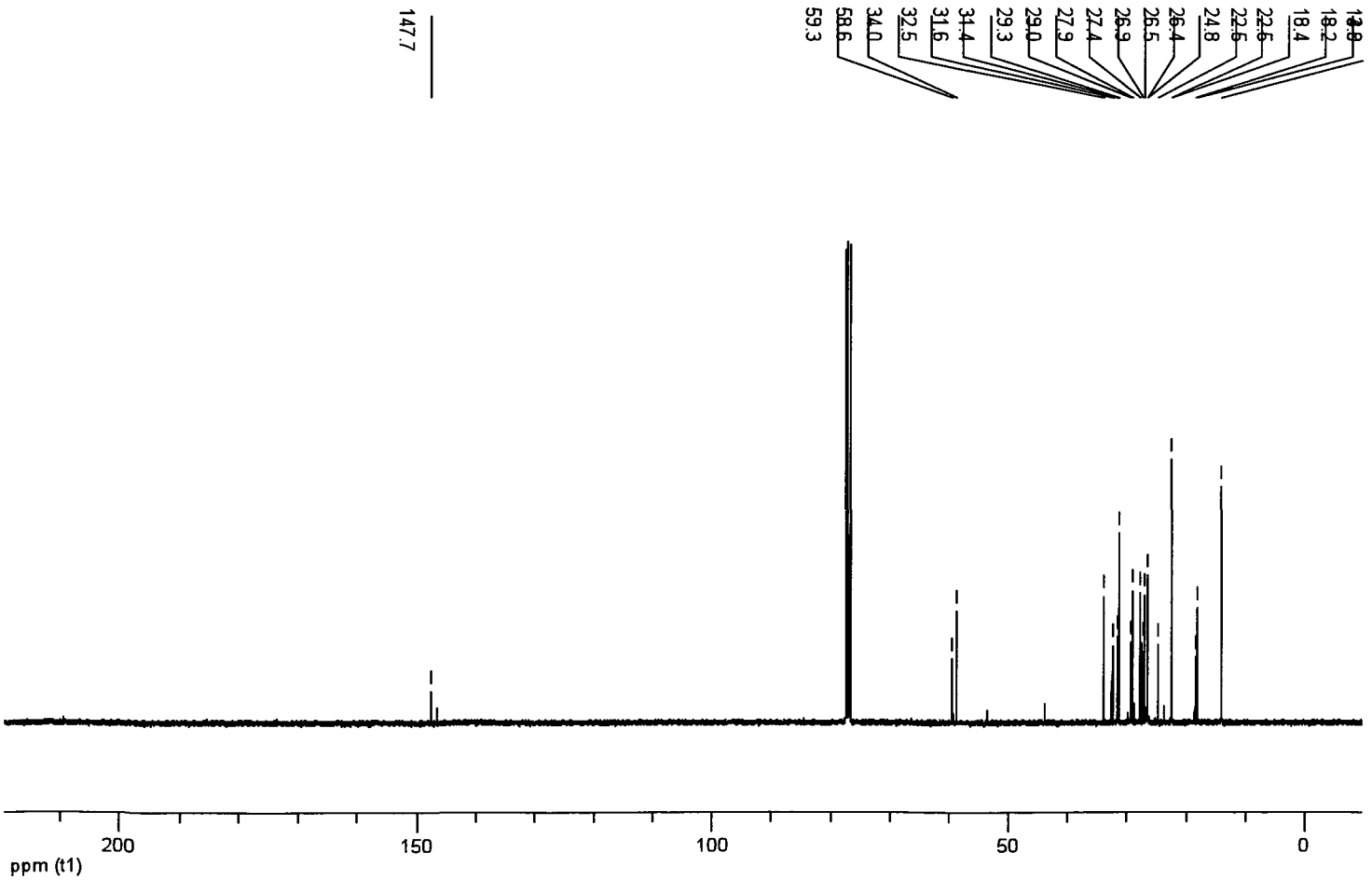

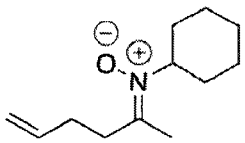

3.174b
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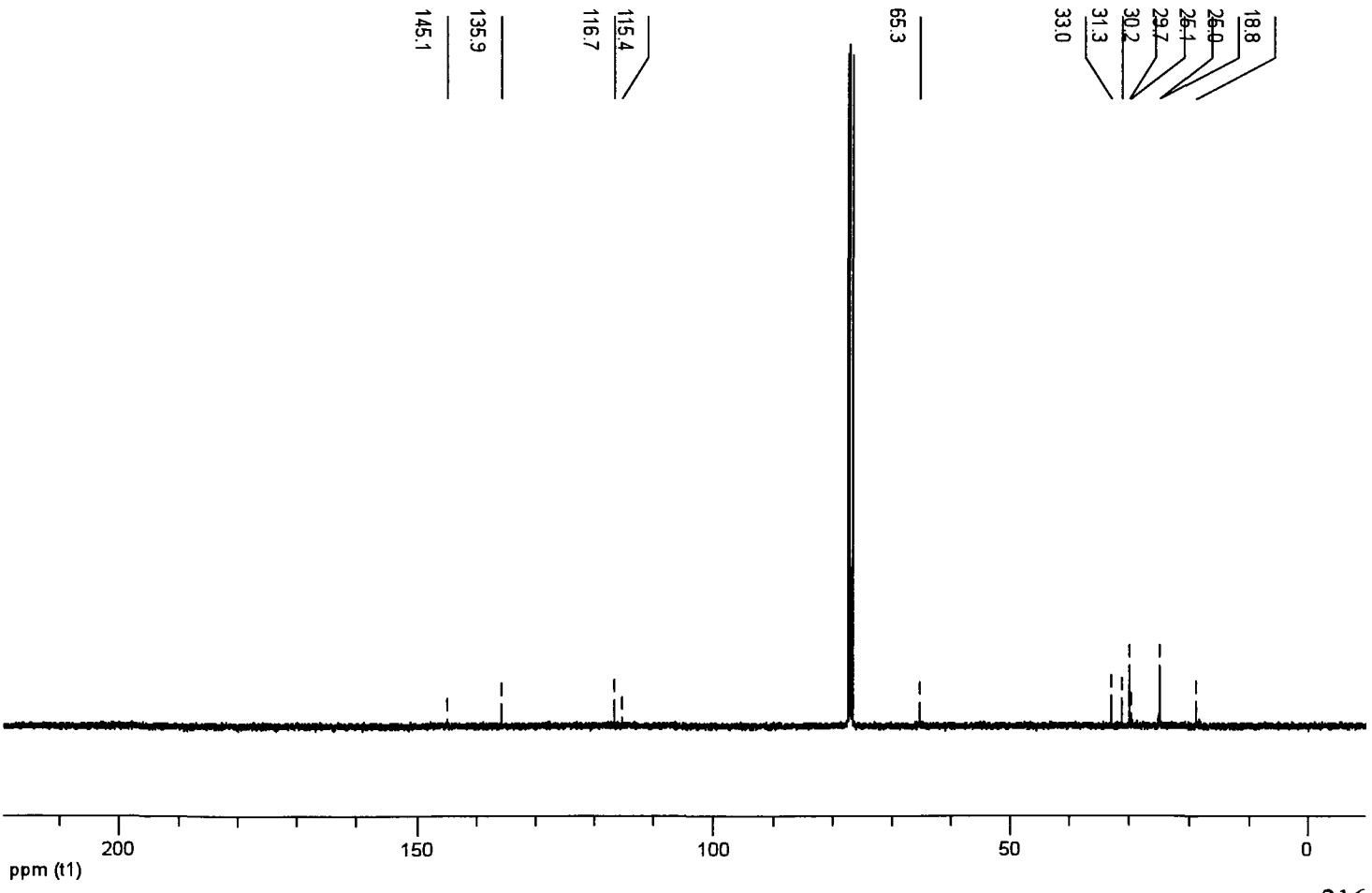

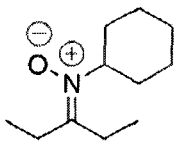

3.174c
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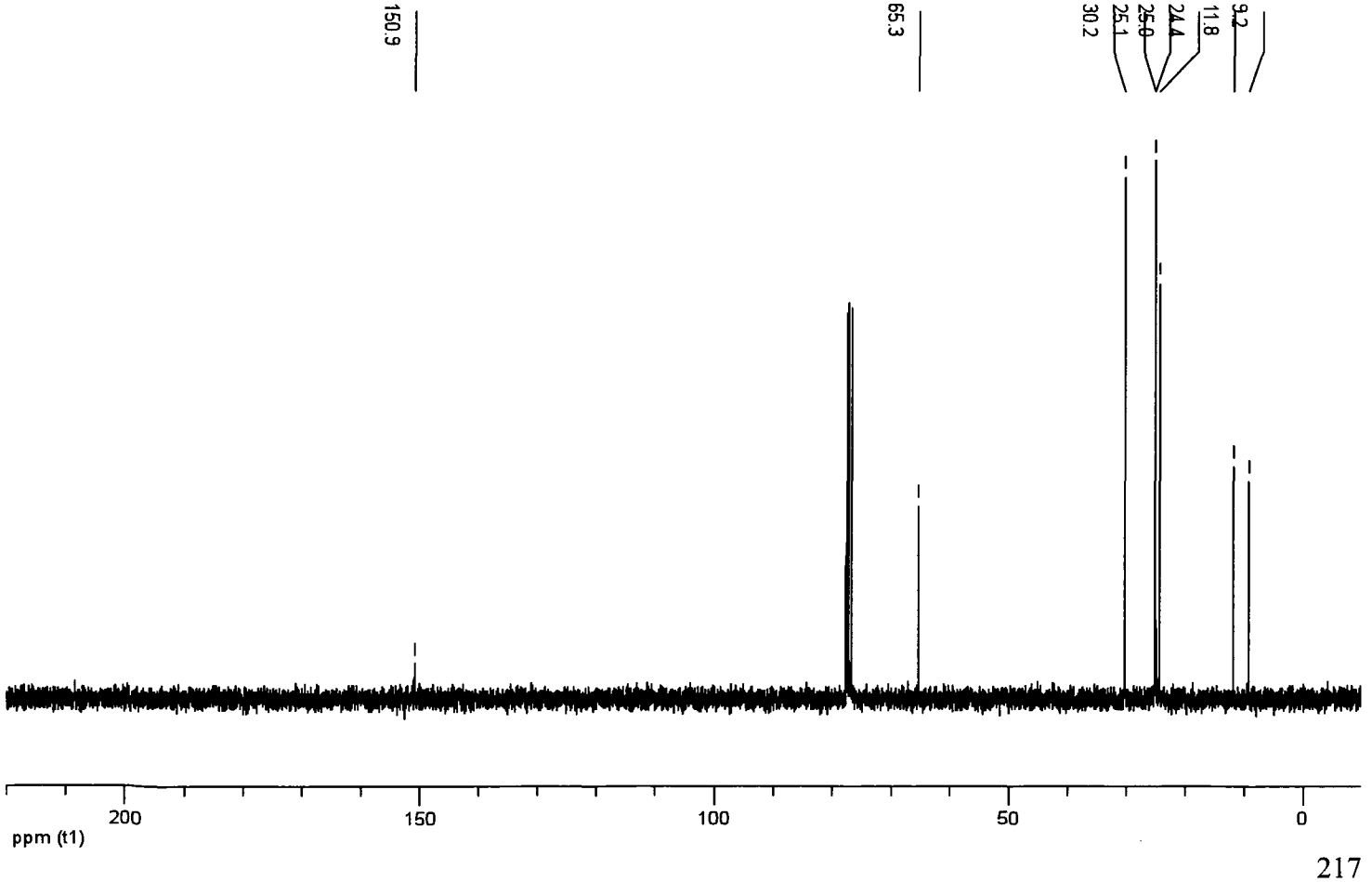
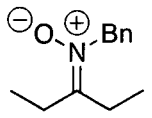
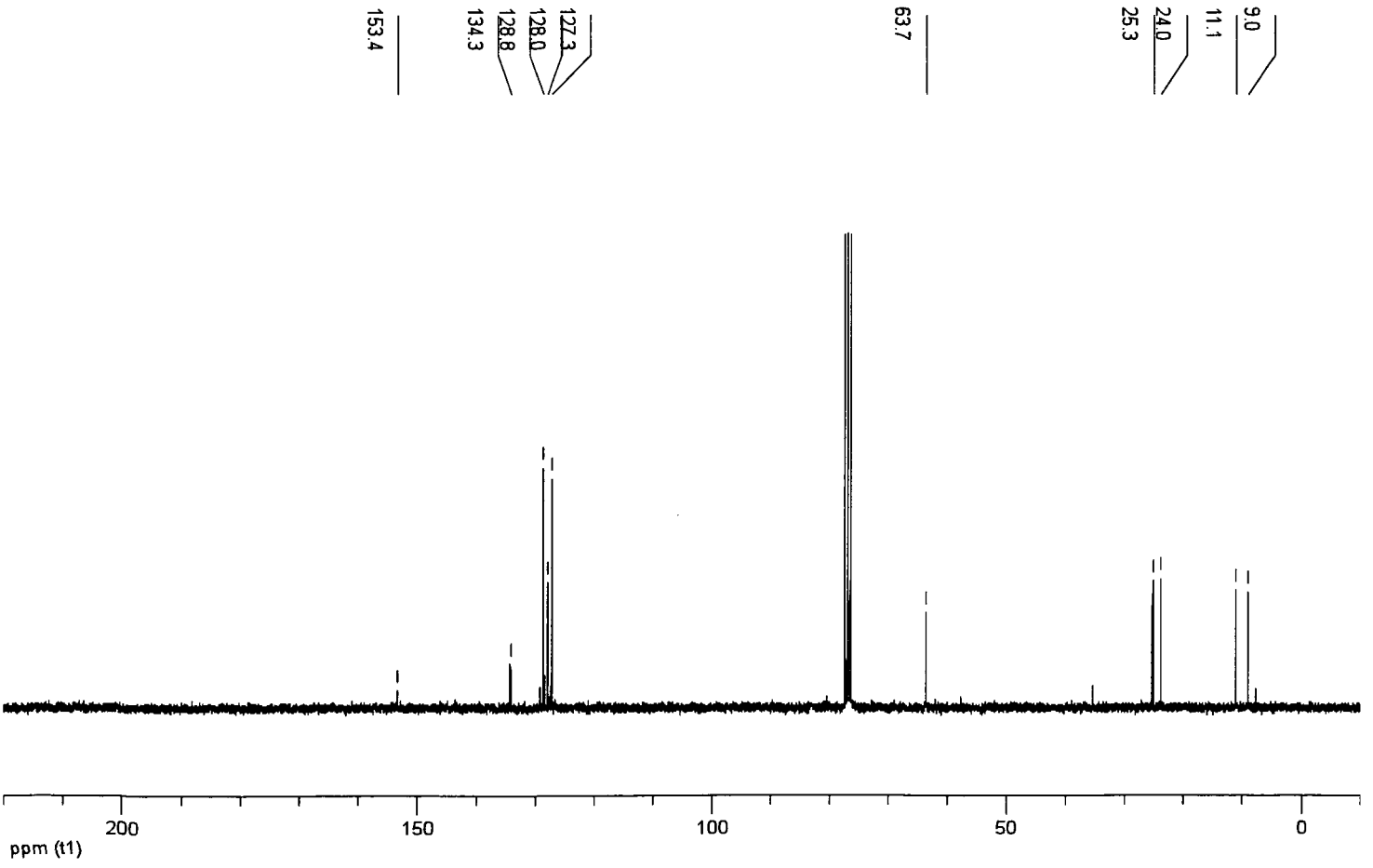
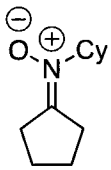


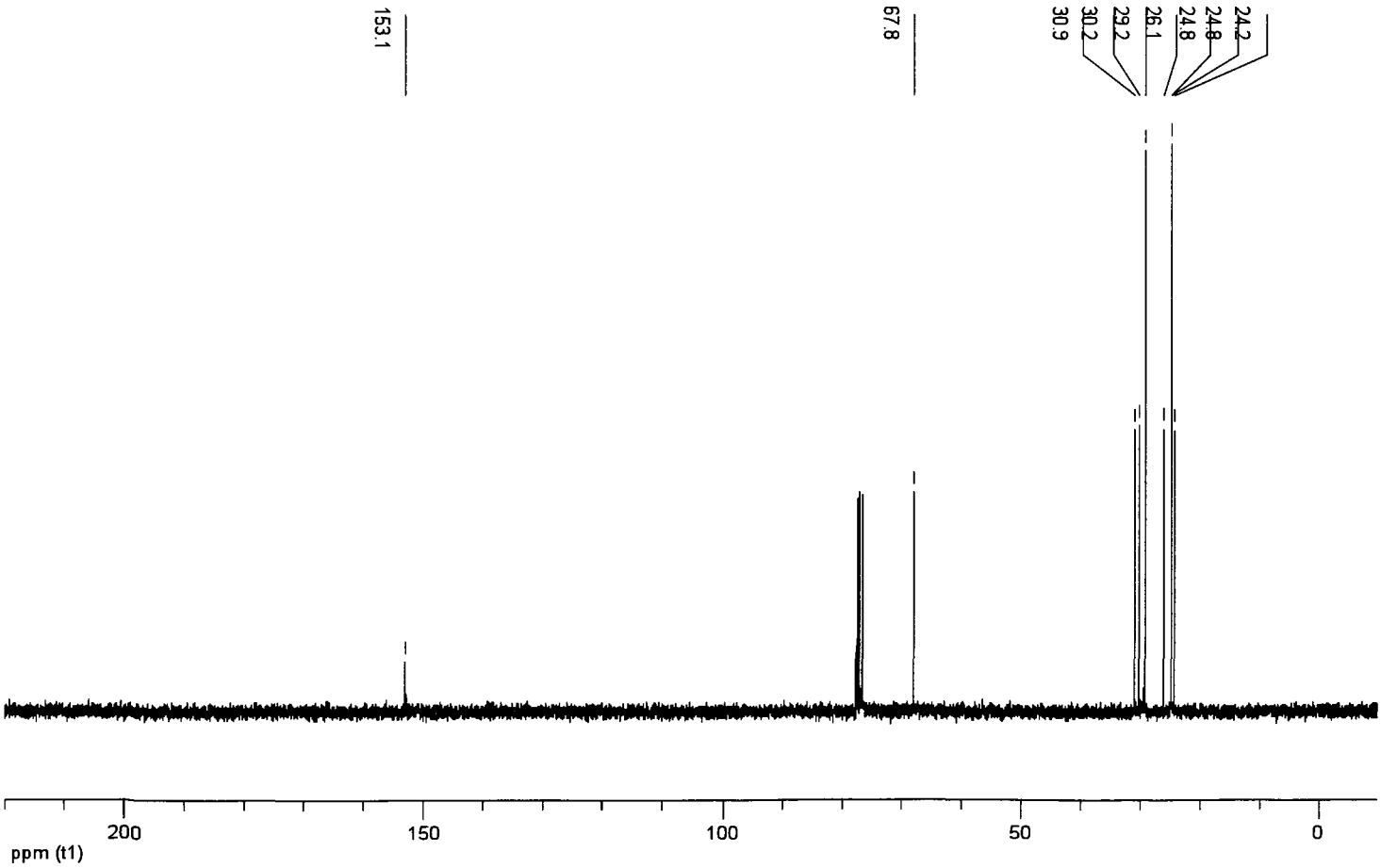


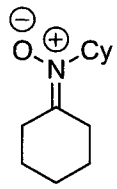
3.174d
Table 3.13, Entry 6



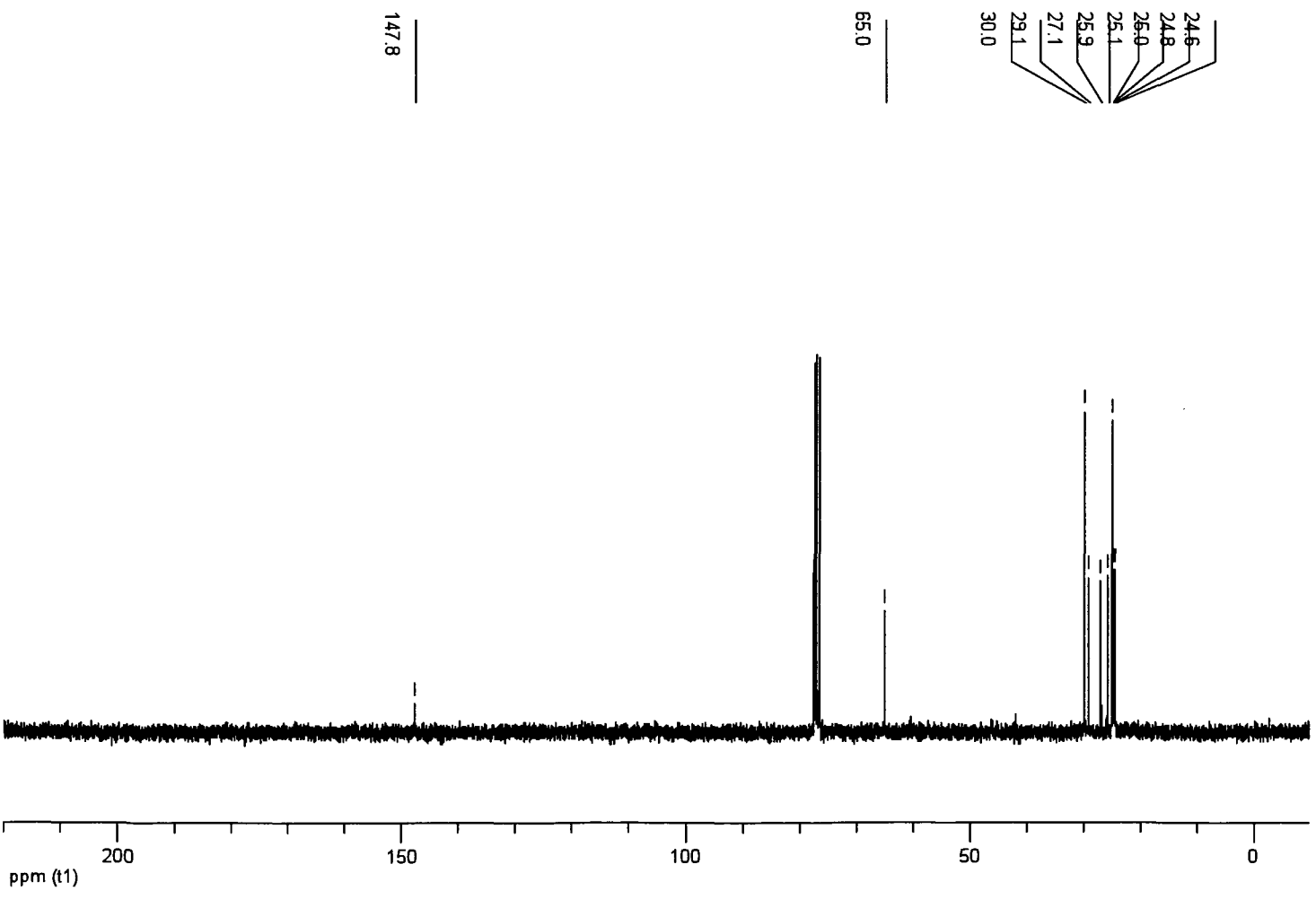


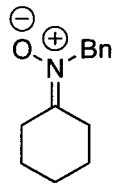
3.174e
Table 3.13, Entry 7



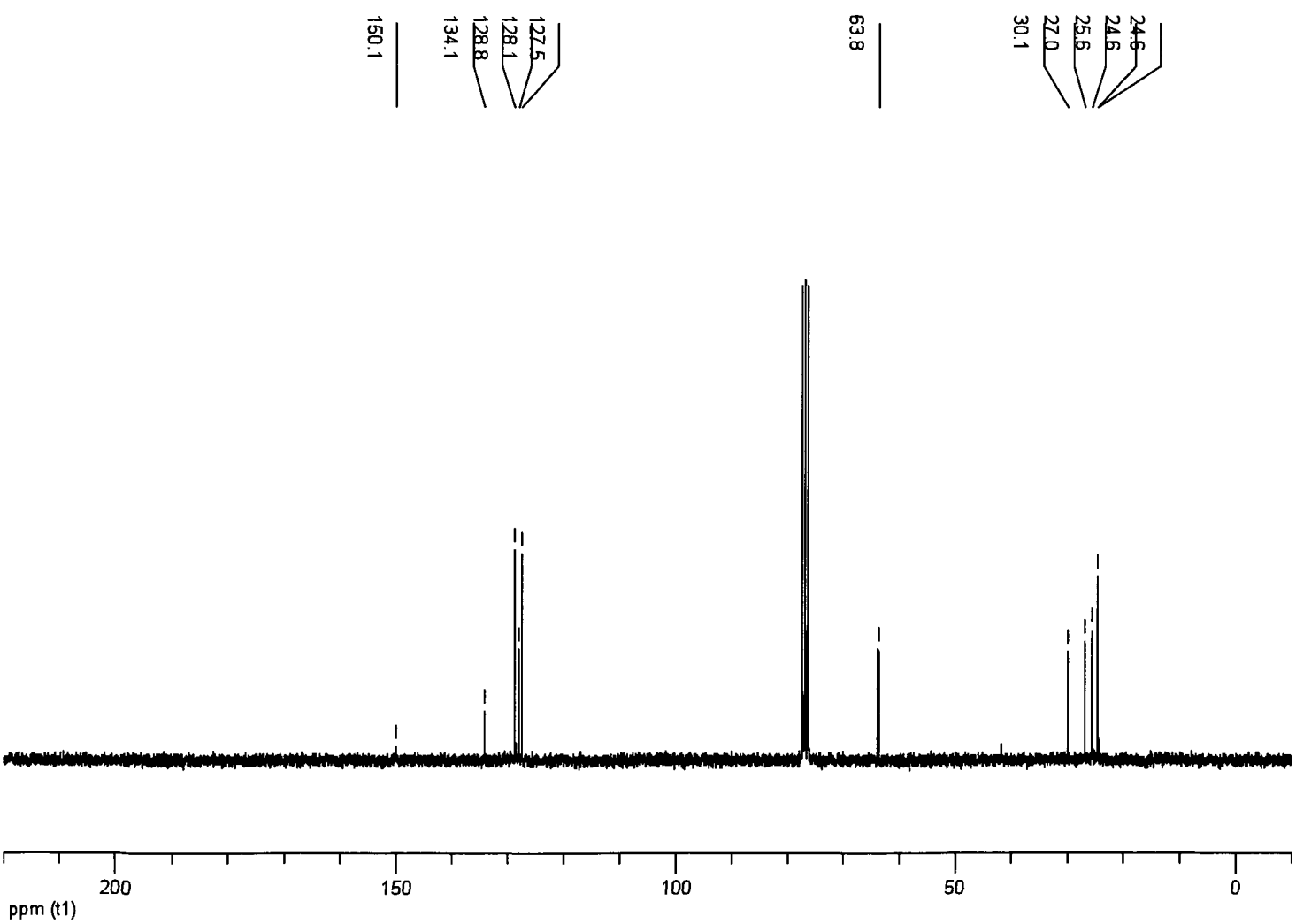


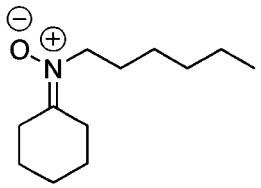
3.174f
Table 3.13, Entry 8





3.174g
Table 3.13, Entry 9





3.174h
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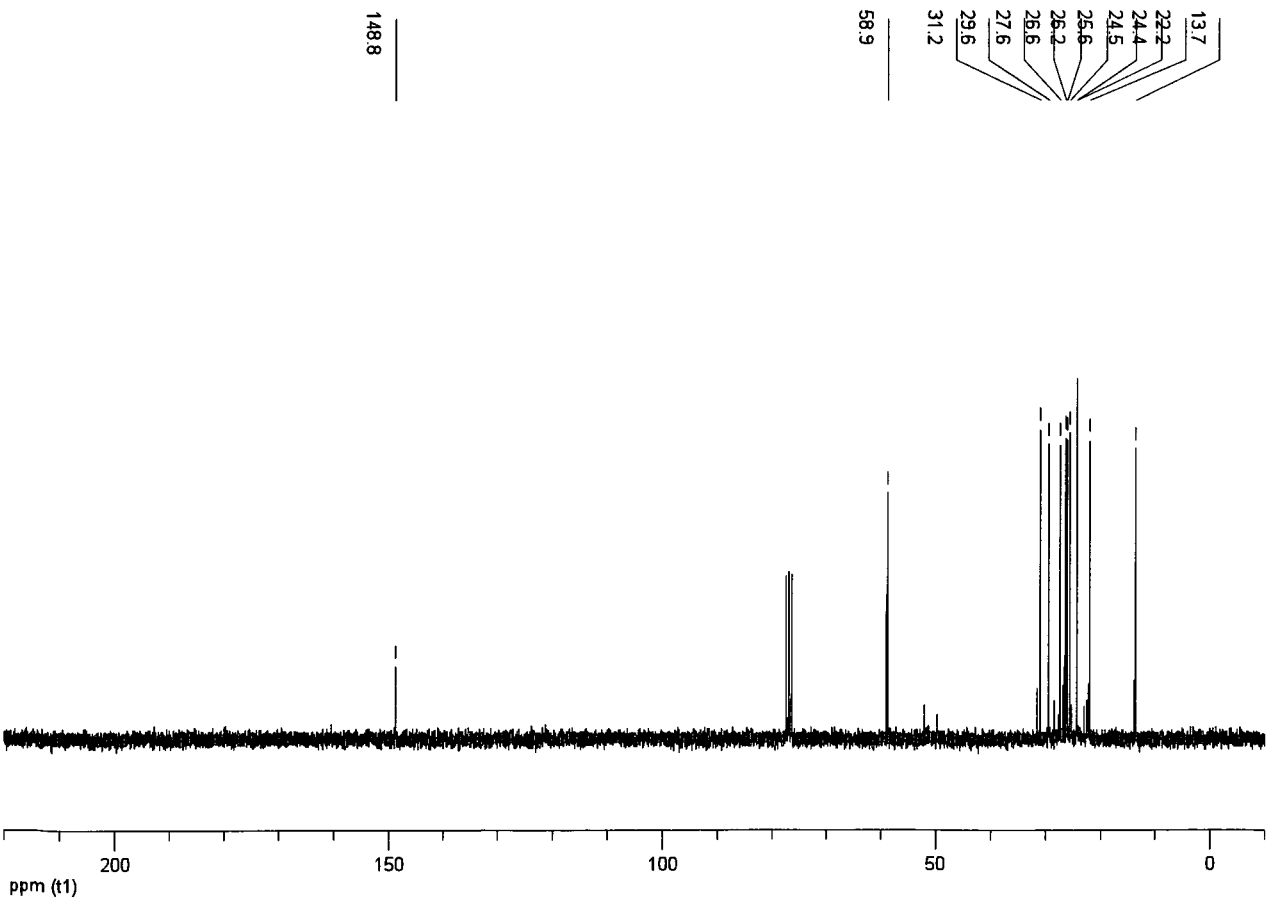

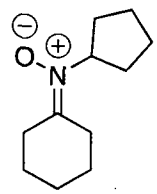

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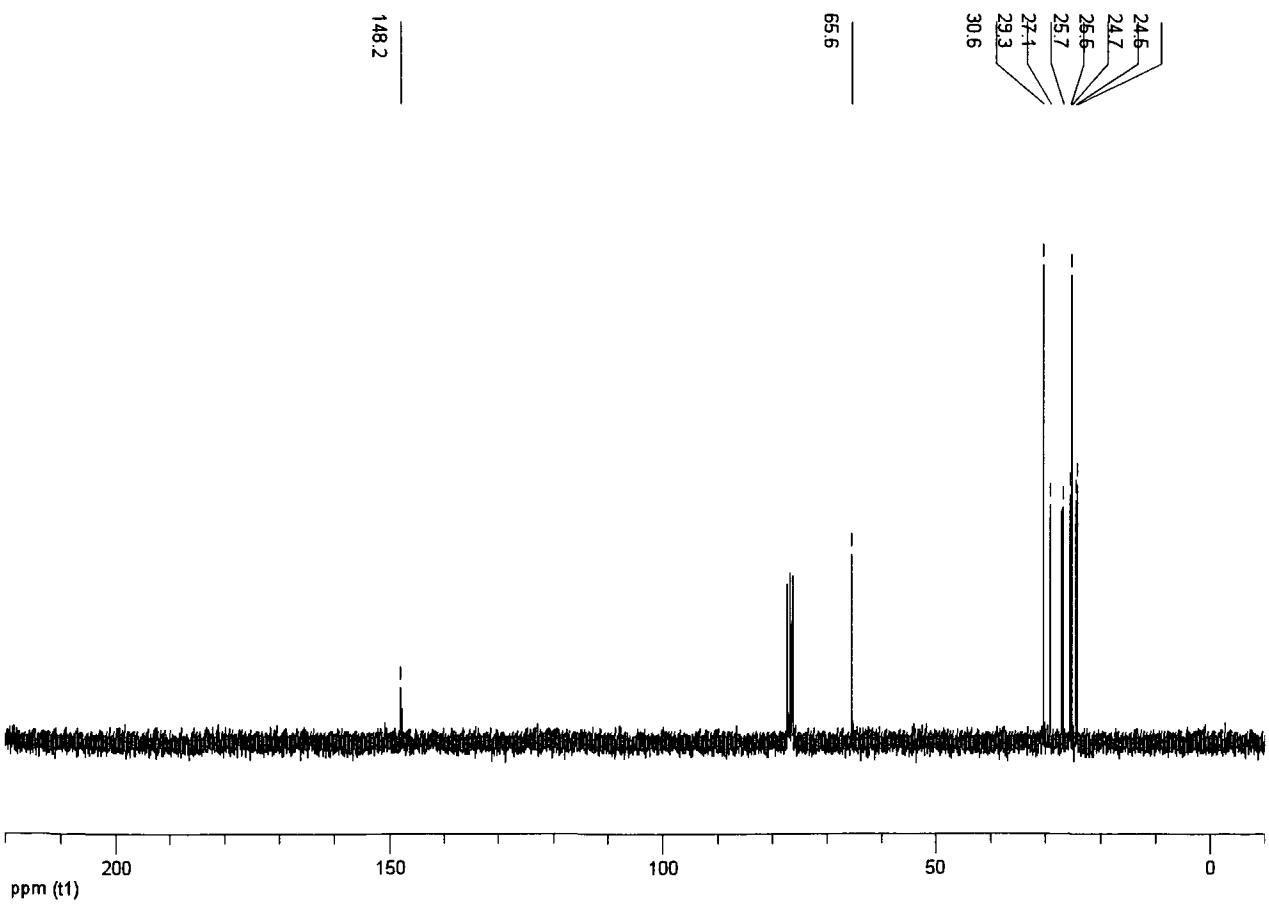

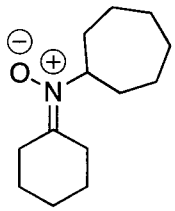

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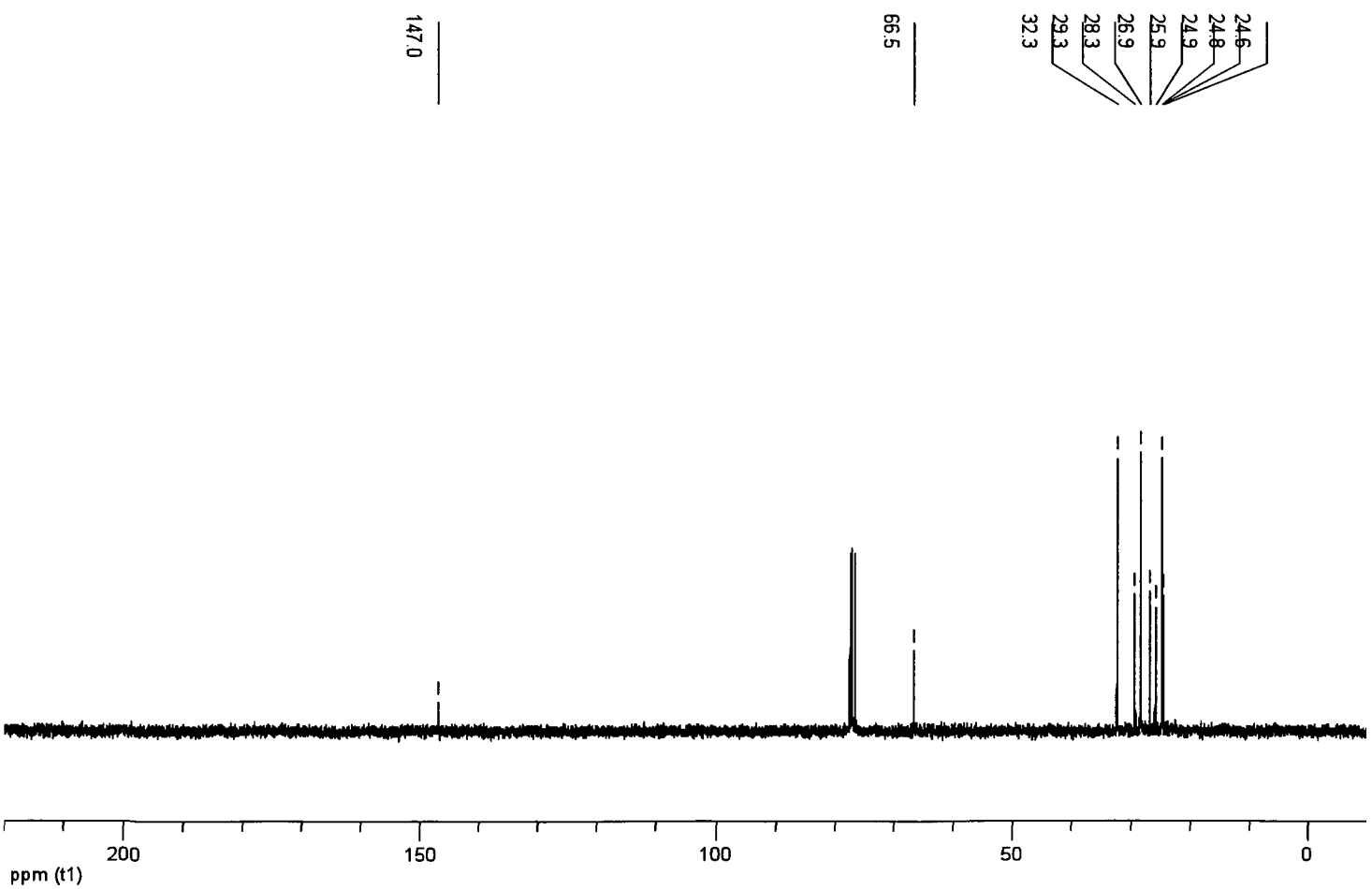

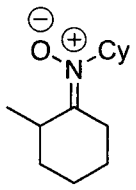

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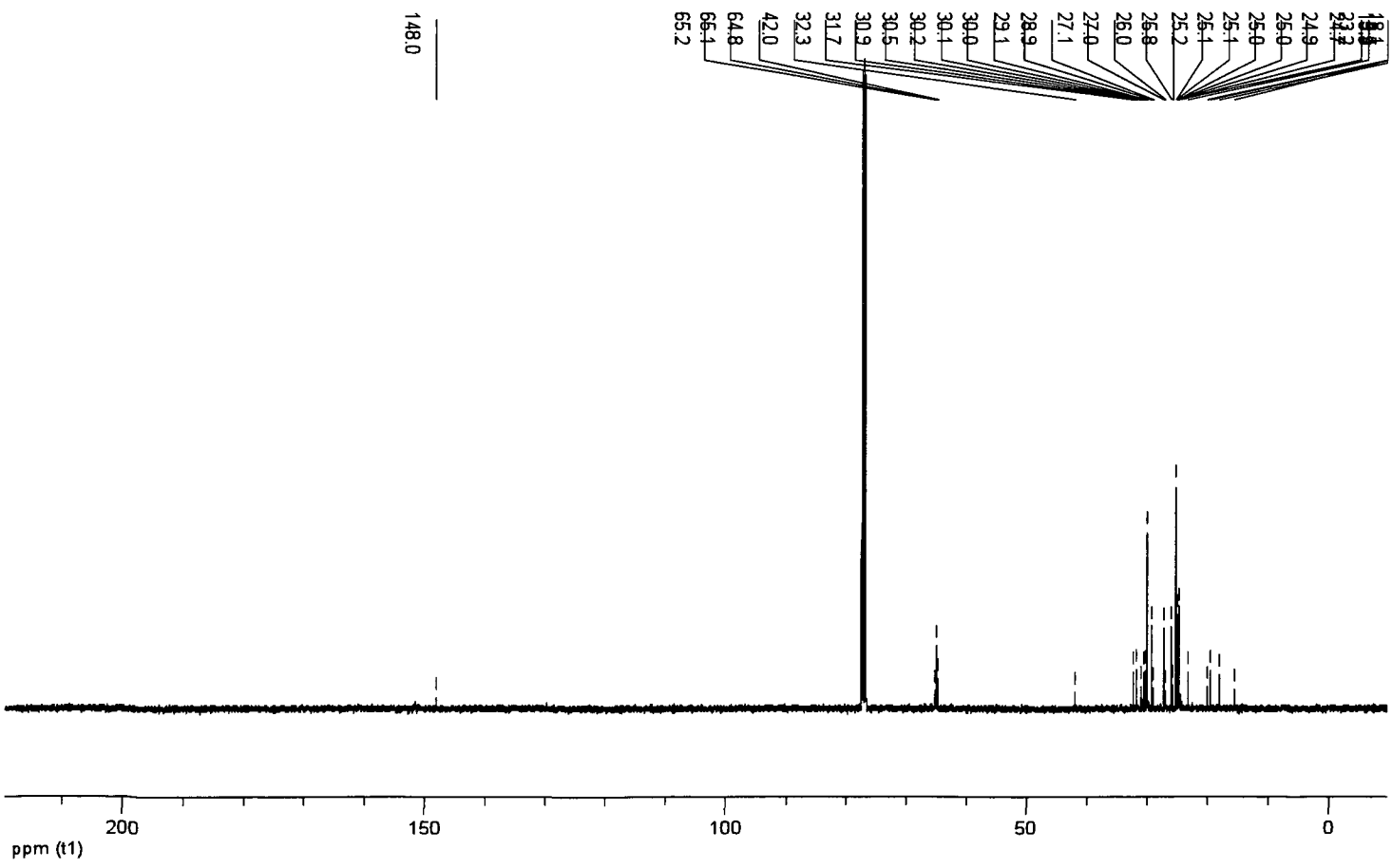

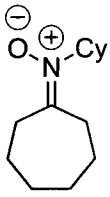

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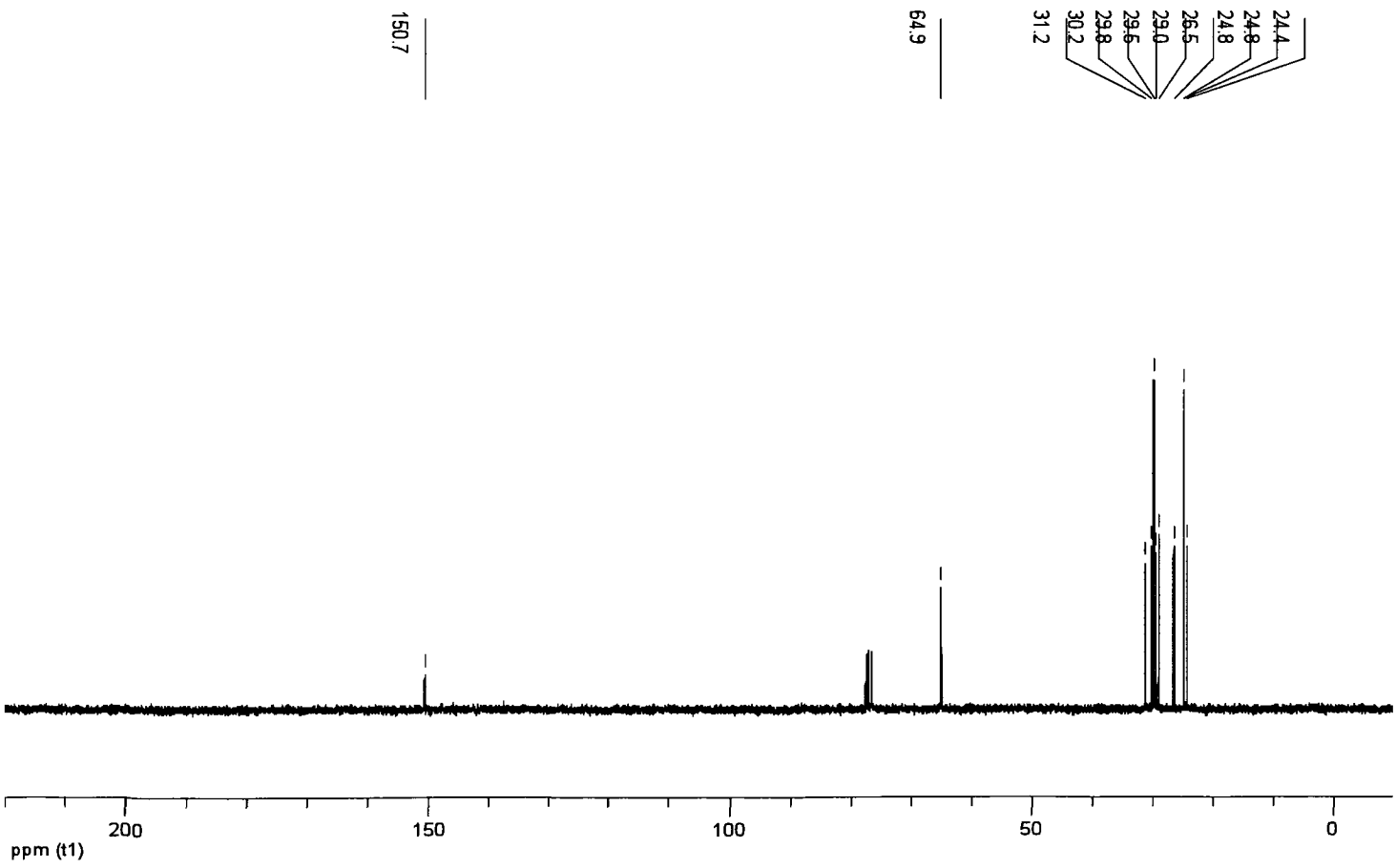

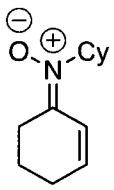

3.174m
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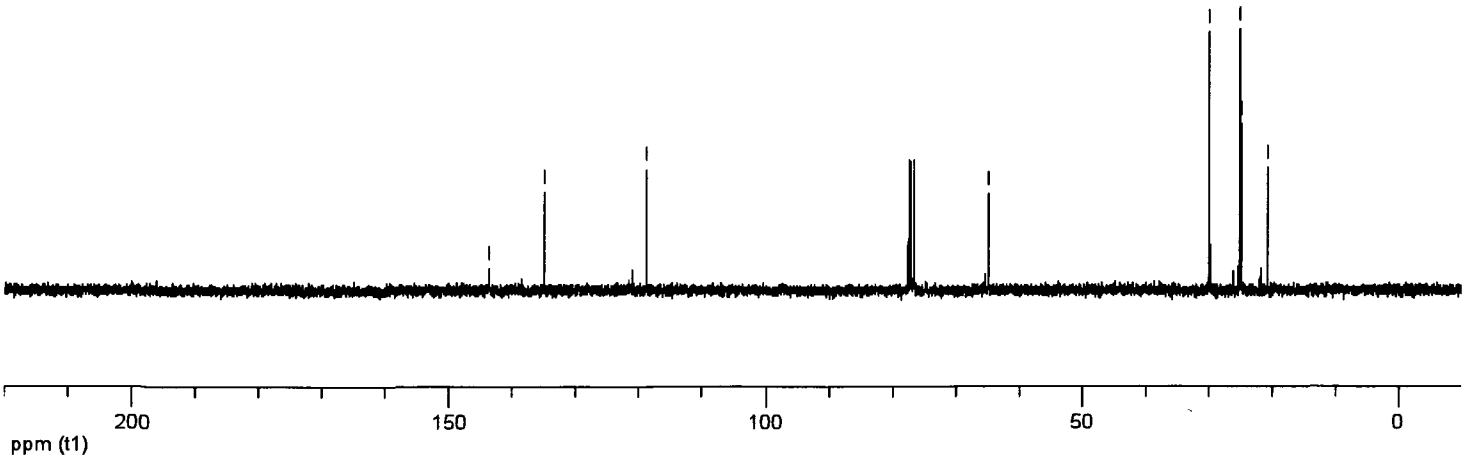

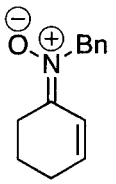

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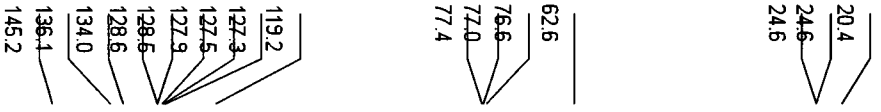
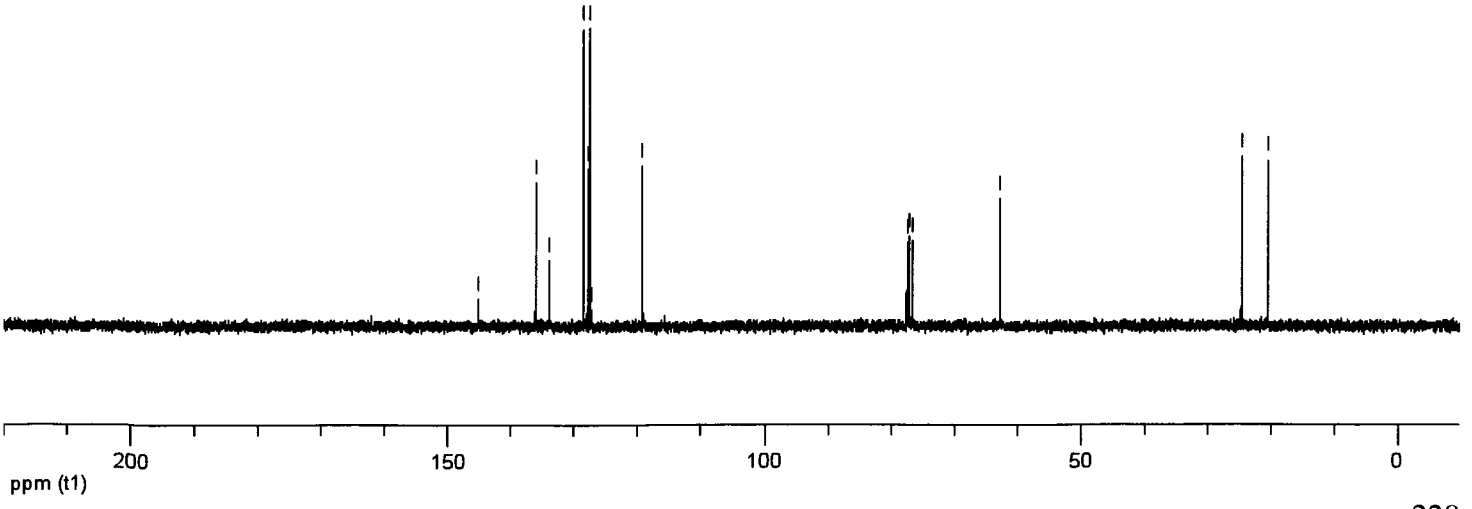
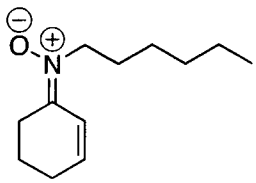
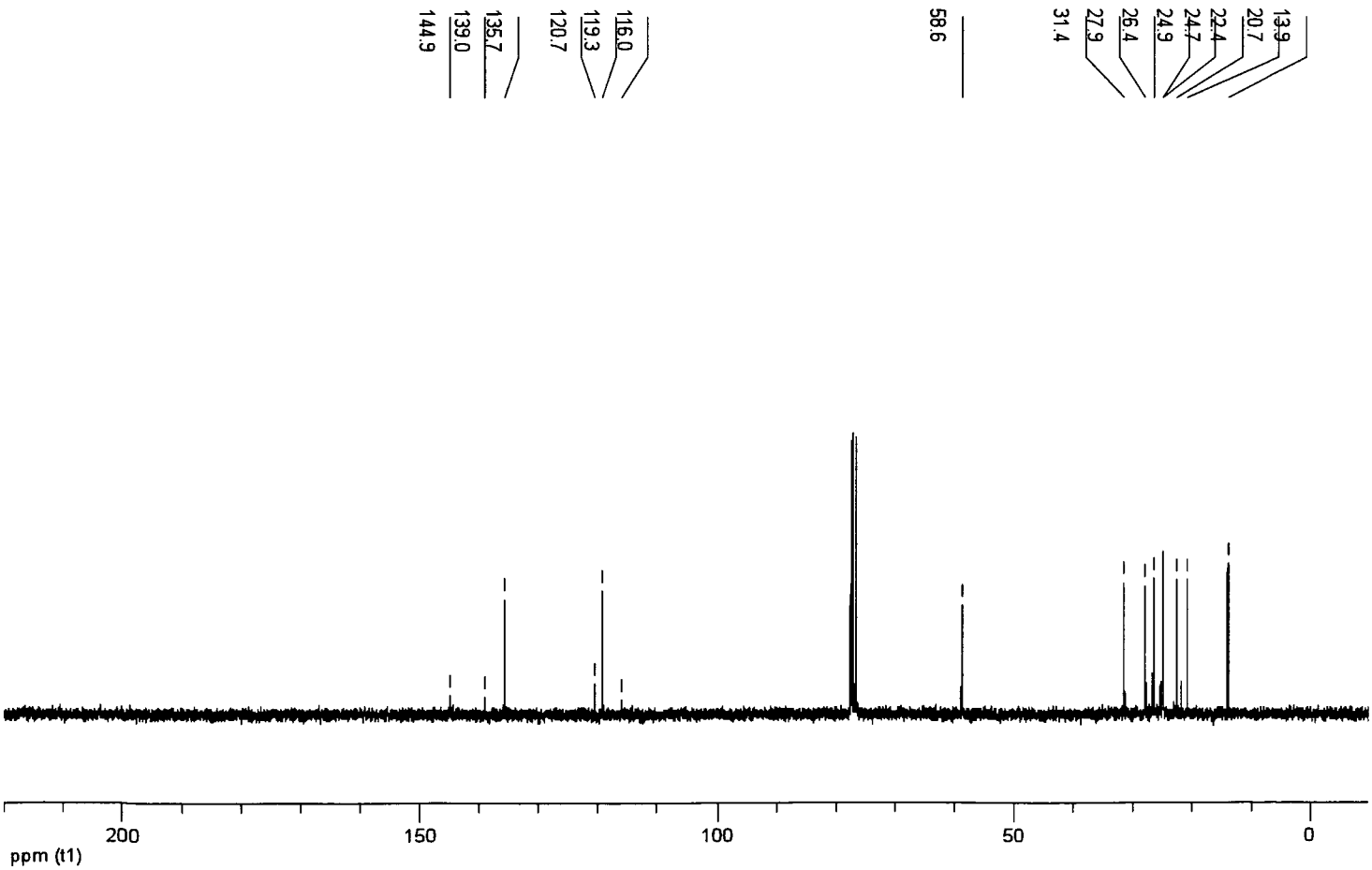
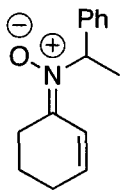




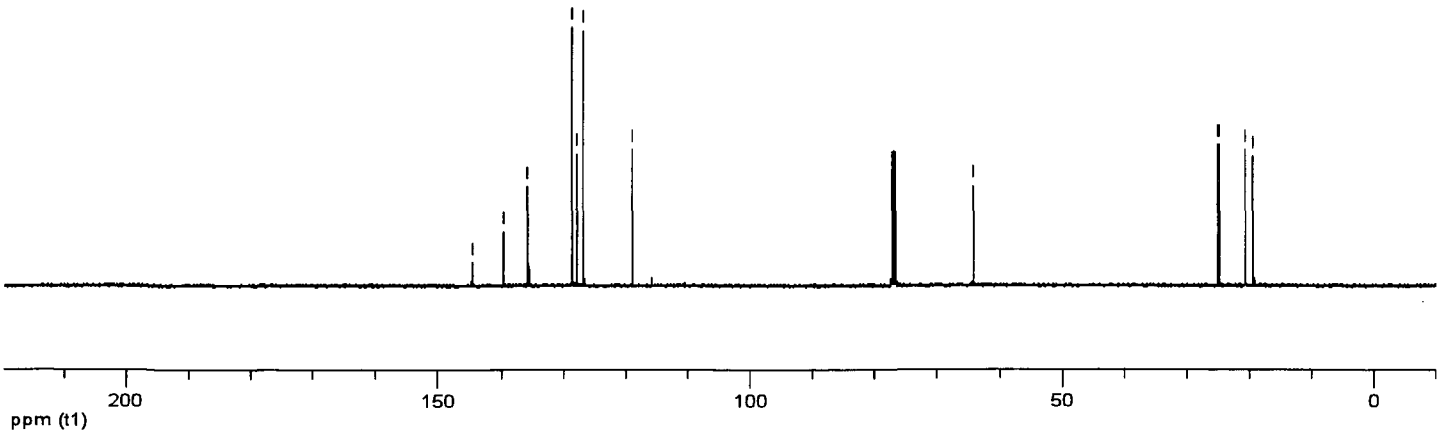


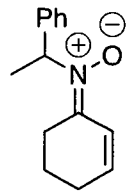
3.174o
Table 3.13, Entry 17



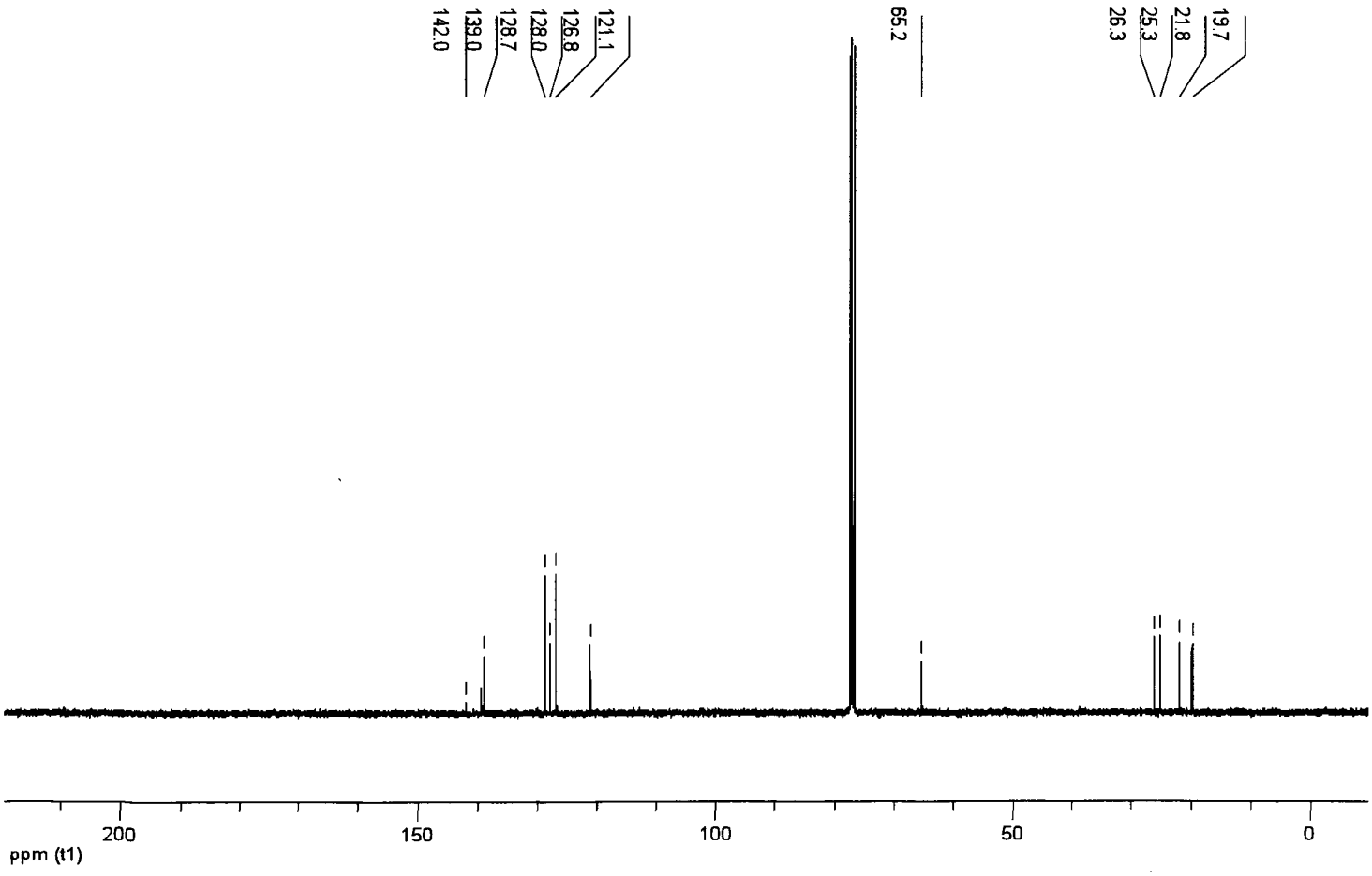


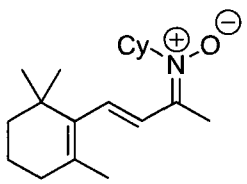
3.174p
Table 3.13, Entry 18



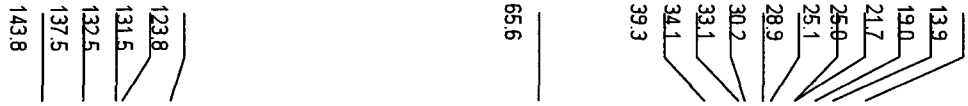


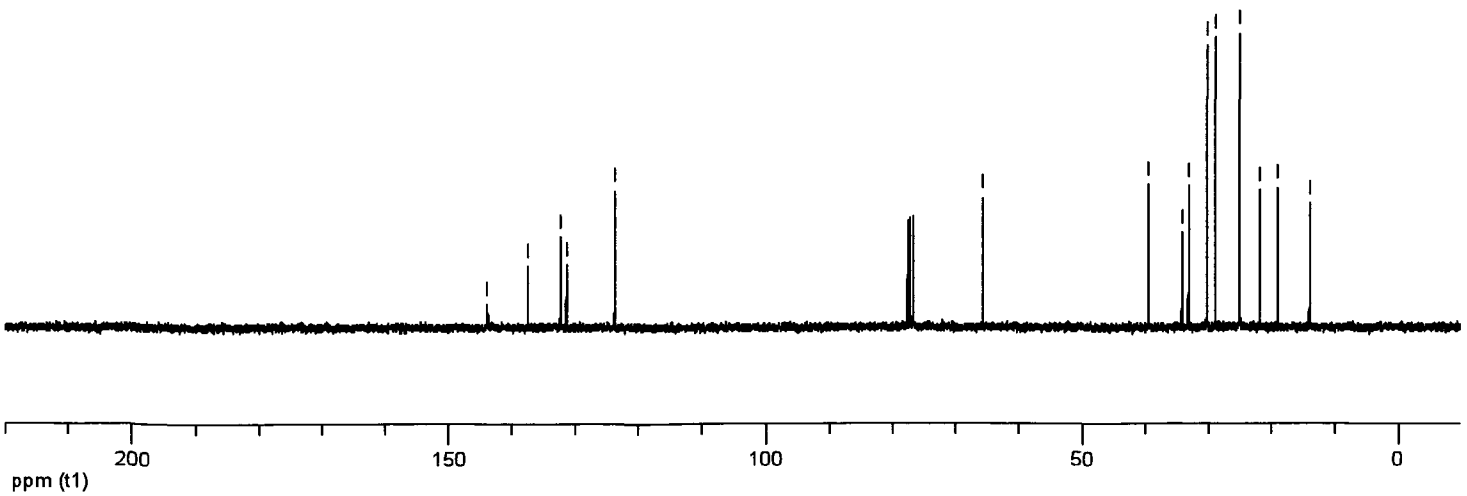
3.174p
Table 3.13, Entry 18

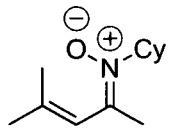




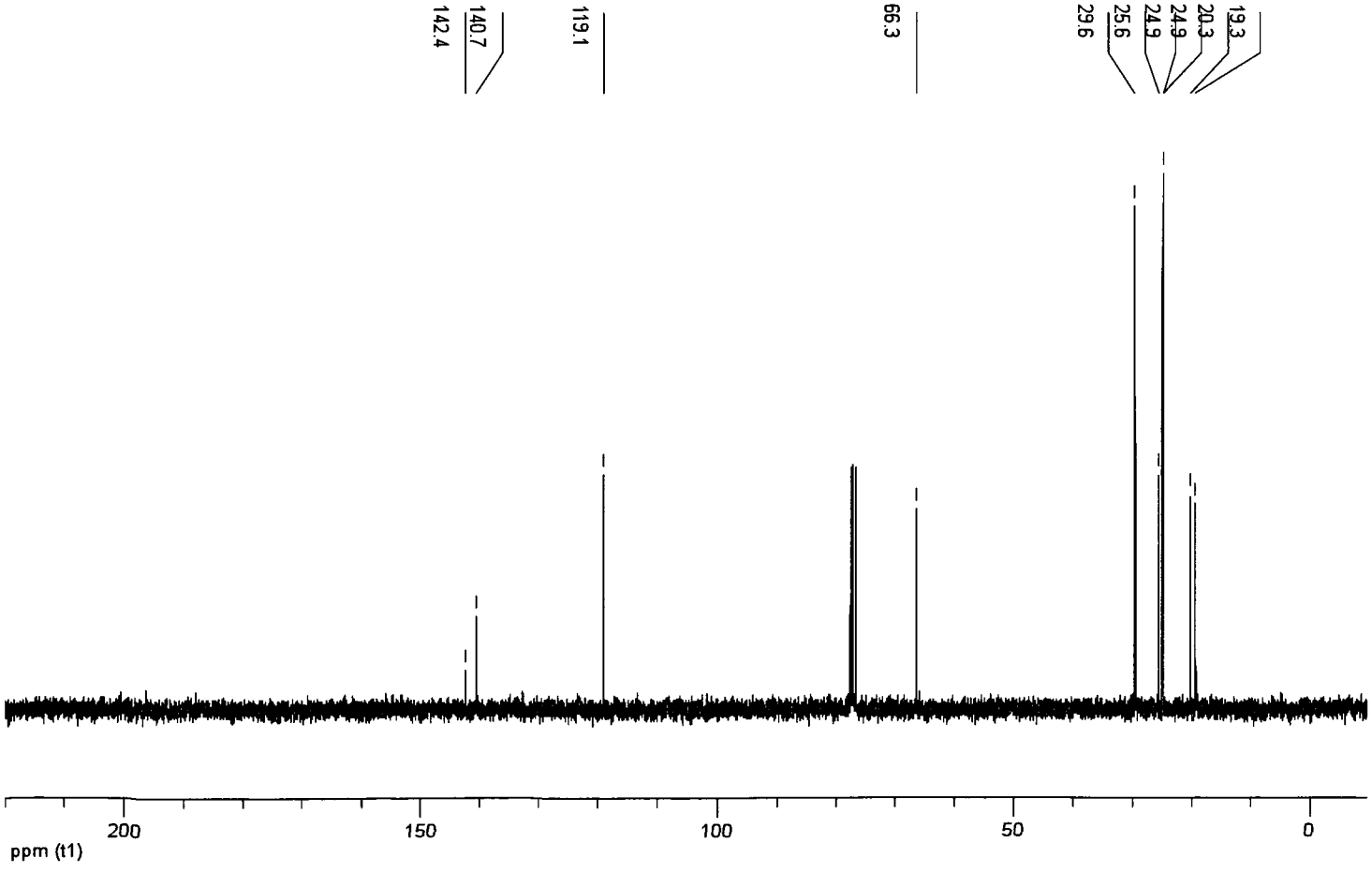
3.174q
Table 3.13, Entry 19

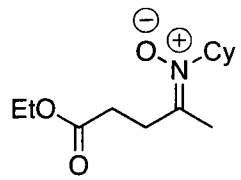




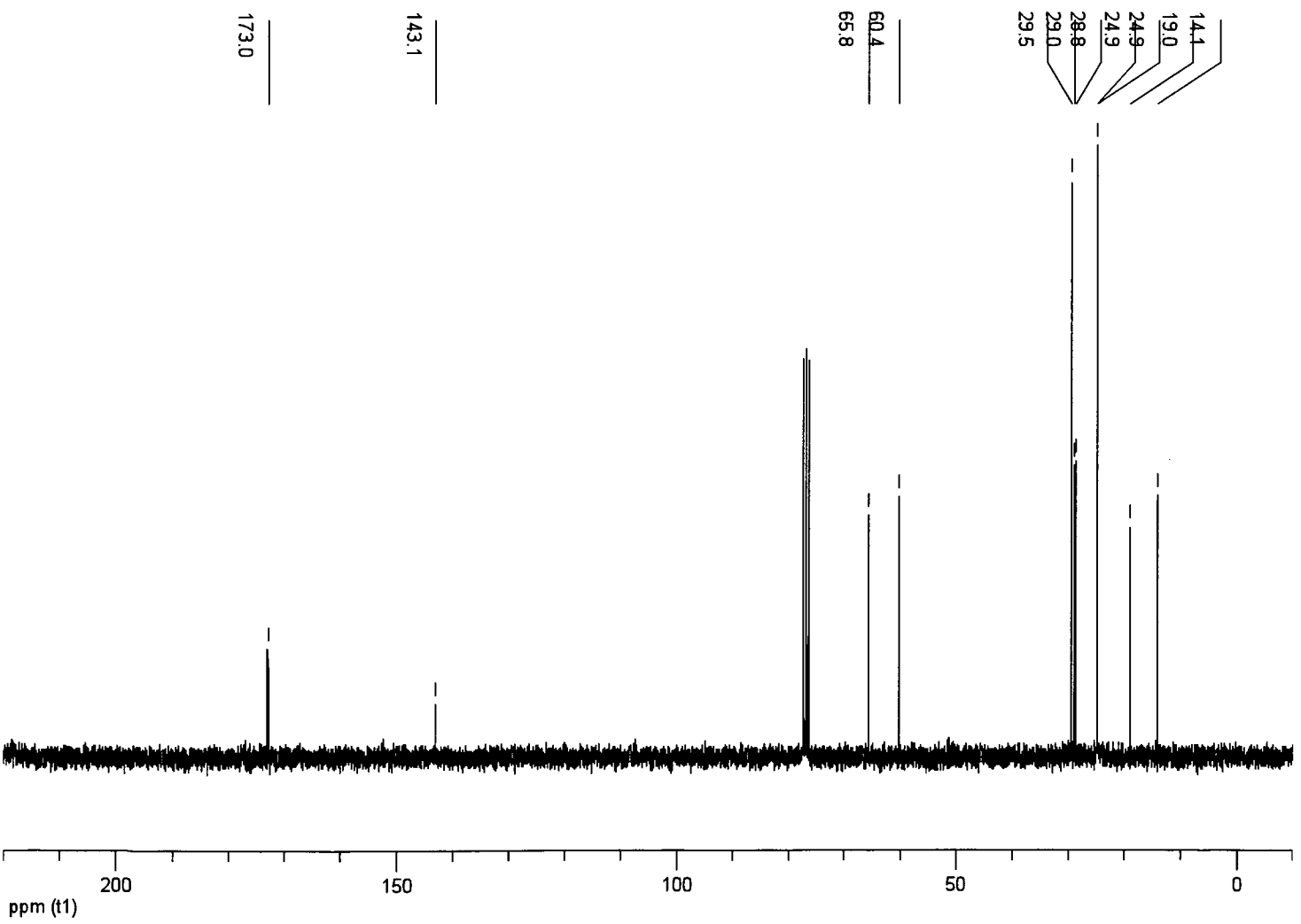


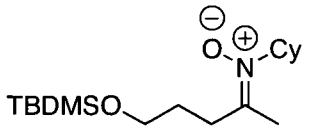
3.174r
Table 3.13, Entry 20





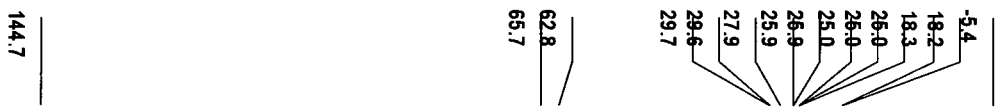
3.174s
Table 3.13, Entry 22

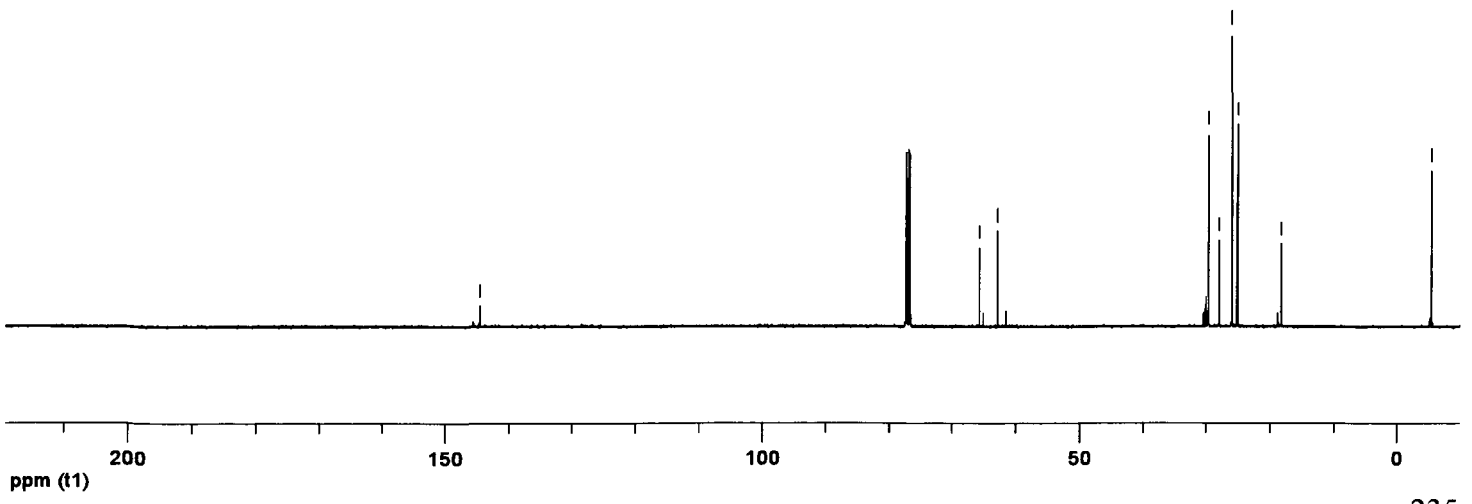


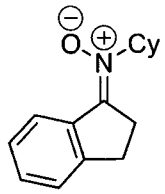


3.174t

Table 3.13, Entry 23







3.175a
Table 3.16, Entry 2