uOttawa

L'Université canadienne
Canada's university

FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES

uOttawa

L'Université canadienne
Canada's university

FACULTY OF GRADUATE AND POSDOCTORAL STUDIES

Joseph Moran
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

Ph.D. (Chemistry)
GRADE / DEGREE

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

Intermolecular Hydroamination of Alkenes. Strain-Release Hydroamination and Cope-Type Hydroamination

TITRE DE LA THÈSE / TITLE OF THESIS

André Beauchemin
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

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

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Keith Fagnou

James Gleason (McGill University)

Jeffrey Manthorpe

William Ogilvie

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

Intermolecular Hydroamination of Alkenes.

Strain-Release Hydroamination & Cope-Type Hydroamination

by

Joseph Moran

Thesis submitted to the
Faculty of Graduate & Postdoctoral Studies
University of Ottawa
in partial fulfillment of the requirements for the
Ph.D. degree in the

Ottawa-Carleton Chemistry Institute
University of Ottawa

Candidate	Supervisor
Joseph Moran	Dr. André M. Beauchemin

© Joseph Moran, Ottawa, Canada, 2009

Library and Archives Canada

Published Heritage Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et Archives Canada

Direction du Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence
ISBN: 978-0-494-61369-6
Our file Notre référence
ISBN: 978-0-494-61369-6

NOTICE:

The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

Abstract

The development of efficient routes to nitrogen-containing molecules from olefin feedstocks is of paramount importance to the life science, bulk chemical and fine chemical sectors. The hydroamination reaction, the addition of an N-H bond across an unsaturated C-C bond, is therefore one of the simplest and most desirable transformation for which no general solution exists. This thesis describes the development of conceptually new metal-free intermolecular hydroamination methods designed to address key limitations in this field.

The first part of the thesis describes the use of photoinduced strain-release activation to enable 1,4-additions and hydroamination reactions of azoles with cyclolkenones and cycloalkenes, respectively. This is the first time that nitrogen nucleophiles more basic than aniline have undergone an efficient acid-catalyzed hydroamination reaction with unactivated alkenes.

The second part of this work describes the development of thermal intermolecular hydroamination reactions of hydroxylamines with strained alkenes, terminal vinylarenes, alkynes and allenes. These transformations give cheap one-step access to nitrogen-containing compounds such as *N*-alkylhydroxylamines, *N,N*-dialkylhydroxylamines, oximes and ketonitrones. Analogous reactivity of hydrazines with alkynes gives hydrazones with complementary regioselectivity. Density functional theory studies shed light on the importance of the proton transfer step during the reaction. Taken together, these reactions are among the most operationally and conceptually simple hydroamination methods.

The last section describes early work aimed at the development of an organocatalytic directed Cope-type hydroamination reaction, as well as a hydroamination/Cope-elimination tandem sequence designed to enable endergonic hydroamination reactions.

Acknowledgements

Being the first student in a research group, especially for a PhD student, has the potential for disaster. The risk of spending years before getting that first hit or the uncertainty of your new supervisor's abilities as a mentor or as a researcher can be enough of a reason to steer clear. After spending about 15 minutes on the phone with him while he was still a postdoc with David Evans at Harvard, I decided to join André Beauchemin's group. After meeting over beers at the Royal Oak and helping him move into his Ottawa residence, we began to tackle setting up the lab. Four and a half years and seven publications together (so far) later, the "risk" was one of the best decisions I've ever made. Since day one, André has been exactly the supervisor I needed: inspiring me with his breadth of knowledge, giving me his honest opinion when I wanted it and when I needed it, sensing when it was time to tighten the reins and when to give me slack, challenging me to exceed my limits, encouraging me when things didn't turn out like I'd planned, but above all for sharing his *unparalleled* enthusiasm for research. It has been a privilege to partake in his journey from benching with me in 431 to running three labs above capacity. If I can transmit only half of his enthusiasm for chemistry to my own endeavours, they will surely be a success.

I am grateful to several faculty and staff members who graciously took me into their group as a member, honourary member, group meeting attendant or collaborator, particularly Bill Ogilvie, Keith Fagnou, Louis Barriault, Tito Scaiano, John Pezacki, Serge Gorelsky and Susannah Scott. A big thanks to NSERC for the USRA (×3), CGS-M and PGS-D scholarships.

Being the only grad student in the Beauchemin group for the first year would have been incredibly lonely were it not for sharing a bay with Mathieu Lemay of the Ogilvie group. Nothing is better or surprisingly more productive than working alongside one of your best

friends. I will never forget running reactions while watching the Matrix trilogy over Christmas, the Aldrich blow dart gun, *il y a du sang sur le plancher*, Mess Around, the ether bottle incident, the couch-cutting party and late night jazz. I hope we can work together again some day! The second Beauchemin grad student to appear on the scene was Marie-Eve Lebrun. Although I did manage to convince her to stand upside down to let the argon out of her lungs, Marie-Eve was a shy yet meticulous chemist and baymate *avec un coeur d'or* who surprised me with her courage in her work and personal life. Next along were Pamela "Saurus" Cebrowski and Joffré Bourgeois. Pam has always been there to lend an open ear, but still needs to teach me to skate backwards after I helped her move twice in one summer. Joffré was an excellent baymate, beer drinker, running partner, pronouncer of "world" and was always in to go *aux danseuses* (our code words for buffet). *J'ai hâte d'assister à plusieurs saisons gagnantes de nos Canadiens ensembles!* The addition of Isabelle Dion to our group from L'Université de Sherbrooke marked the first of a number of students to join from outside Ottawa and the last of the self-proclaimed Beauchemin Originals. Isa will be the senior PhD student once I leave and I know she will be up to the task. The next years saw many new faces: Hao Peng (Concordia), Jean Roveda (Ottawa), Francis Loiseau (McGill), Toni "DJ" Rizk (Ottawa), Yael "Jennifer" Pfeiffer (McGill), Ashley Hunt (Western) and Peter Ng (Toronto). They are a fun and dedicated bunch. I can tell from our conversations and parties that the group is in good hands. Jenn was my fifth and final baymate. Together we were nearly a "24 hour grad student" but any time we did overlap was lots of fun. Francis, Jenn and Isa have helped me enormously by proofing this thesis, so if you find any mistakes, it's their fault! Thanks to all of you for making my time here so great.

I have had the privilege to supervise and often learn from a number of brilliant and hardworking undergraduate students: Tanya Suen, Peter Dornan, Pam Cebrowski, Lili Zhang,

Catherine Séguin, Elena Dimitrijevic and Marija Antonic. The prank wars that occurred between Catherine and myself in the summer of 2006 were truly the stuff of legend! I have also enjoyed sharing the lab with Maria Zlotorzynska, Eric Beaulieu, Chris Whipp, Anna Chkrebtii, Anne-Catherine Bédard, Emily Manthorpe, Lei Zhang and Christian Clavette.

I am eternally grateful to the chemists at Ottawa who are unafraid to share their talents outside of chemistry. In particular, those involved with playing open mics and with rock bands UOCGSAOJME and the Accommodators (Mathieu Lemay, Mathieu Frenette, Hasan Khan, Jessie Blake, Roger Tam, Matt Yorke, Patrick Ang, Charles Russell and David Bryce). The music and friendship we have shared together has made my life richer.

I would also like to thank my fellow executives on the Chemistry Graduate Student Association, particularly Mathieu Frenette, Jessie Blake, Nathalie Lavoie, Kathy McGilivry and Joffré Bourgeois. Together we renovated the reading room, made record-breaking BBQ profits, initiated the Chemistry Olympics and Semi-Formal and sailed across the canal dressed as pirates!

There are also a number of other friends who have made my time here enjoyable, both in the department (Eve Heafey, Natalie Nguyen, Jennifer Scott, Marc Lafrance, LC Campeau, Sophie Rousseaux, Katarina Vulic, Alex Bush, Patrick Crewdson) and outside (Claire Foottit, Steph Prise, Dave Blair, Allan Miskell, Nic Campione, Yamile Wasslen and my friends at Orpheus Musical Theatre Society). Special thanks to Jane Evans for her support and encouragement from abroad during the writing of this thesis.

Lastly and most importantly, thanks to John, Joan, Sheilah, George, Dorothy, Jane, Jack and the rest of my family for your love and support throughout my life. Without you this accomplishment would not be possible. I love you.

"Simplicity is the ultimate sophistication." – Leonardo da Vinci

Intermolecular Hydroamination of Alkenes.

Strain-Release Hydroamination & Cope-Type Hydroamination

Table of Contents

List of Abbreviations

$[\alpha]^{25}_{D}$	specific rotation at 25 °C and 589 nm
Å	angstrom (10^{-10} meters)
Ac	acetyl
AcOH	acetic acid
anti	against, opposite
aq	aqueous
Ar	aryl
B3LYP	Becke-3-Lee-Yang-Parr
BHT	2,6-di-*tert*-butyl-*para*-cresol (butylated hydroxytoluene)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
cat.	catalytic
°C	degree Celsius
cal	calorie
cis	*L.*, on the same side
conv.	conversion
Cy	cyclohexyl
δ	chemical shift in parts per million
d	deuterium (in NMR solvents); doublet

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	*Ger.*, entgegen
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
FT	Fourier transform
g	gram
h	hour
h	Planck constant (6.626×10^{-34} J s)
$h\upsilon$	light; electromagnetic radiation
H-bond(ing)	hydrogen bond(ing)
HRMS	high-resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
k	rate constant
K	equilibrium constant

λ	wavelength
L	liter; ligand
m	meta
M	molar; metal
Me	methyl
mg	milligram
min	minute
mL	milliliter
mmol	millimol
Ms	methanesulfonyl
MS	molecular sieves
Nu	nucleophile
NMR	nuclear magnetic resonance
o	ortho
p	para
p	−log()
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
Pr	propyl
R ($R^{\#}$)	radical group (carbon-based substituent)
rt	room temperature
s	second

sat.	saturated
S_N1 or S_N2	nucleophilic substitution first order; or second order
syn	together, same side
t	tertiary
temp.	temperature
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
UV	ultra-violet
X	heteroatom or pseudohalide
Z	*Ger.*, zusammen

List of Figures

List of Schemes

List of Tables

Chapter 1. The Intermolecular Hydroamination of Alkenes

1.1. Introduction

Nitrogen-containing molecules are ubiquitous in nature and in society. Over 90% of drugs possess at least one nitrogen atom in their structure and approximately one in six reactions performed in the pharmaceutical industry involve the formation of a carbon-nitrogen bond.[1] The development of efficient routes to nitrogen-containing molecules is therefore of paramount importance to the life science, bulk chemical and fine chemical sectors. However, unlike nature, chemists must ultimately create their value-added products primarily from petroleum feedstocks. Given the ready availability of inexpensive olefins, the hydroamination reaction, the addition of an N-H bond across an unsaturated carbon-carbon bond, stands out as one of the simplest and most desirable transformations for which no general solution currently exists. Intramolecular hydroamination reactions produce valuable saturated heterocycles, while intermolecular hydroamination reactions can rapidly increase the complexity of simple amines in a single atom-economic step (Figure 1.1).

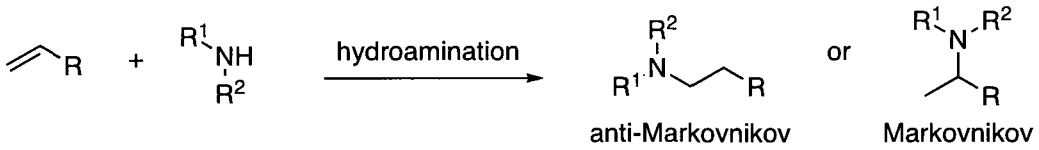


Figure 1.1. Intermolecular Hydroamination of Alkenes.

In the last two decades, the hydroamination of alkenes and alkynes has become the subject of intense research. Fifty-five *review articles* have been published on the hydroamination reaction since 1989, yet none has specifically focused on the intermolecular reactivity of

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

alkenes.[2] Although in recent years the hydroamination of alkynes has been achieved with fairly general scope via several different catalytic approaches,[3] a correspondingly general intermolecular reactivity of alkenes has been much more elusive.[4]

This chapter aims to give an overview of the state of the art for the various reported methods for achieving intermolecular hydroamination reactions of alkenes up to April 2009, organized by reaction mechanism and catalyst class. Organized in this way, it becomes obvious that despite excellent progress, the lack of cheap, mild and practical methods for the intermolecular hydroamination of basic amines, particularly for thermodynamically unfavourable cases, still constitutes an important void in the chemical literature.

1.2. Acid-Catalyzed Hydroamination

1.2.1. Brønsted-Acid Catalysis

Brønsted-acid catalysis is a conceptually simple and potentially highly practical approach to the hydroamination of alkenes. Akin to the related Ritter reaction,[5] the alkene is protonated to

---

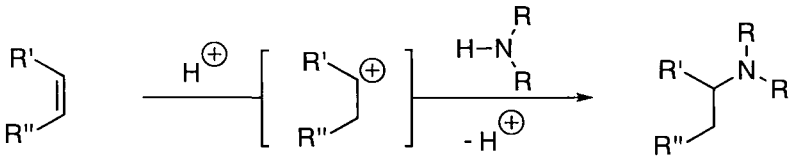
(2) For the most recent comprehensive review on the hydroamination reaction as of April 2009, see: Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. See also ref 3j.

(3) For reviews on the catalytic hydroamination of alkynes, see: (a) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *32*, 1407. (b) Bruneau, C.; Dixneuf, P. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 2176. (c) Odom, A. L.; *Dalton Trans.* **2005**, 225. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368. (f) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (g) Molander, G. A.; Romero, J. A. C. *Chem. Rev.* **2002**, *102*, 2161. (h) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579. (i) Brunet, J.-J.; Neibecker, D. in *Catalytic Heterofunctionalization*; Togni, A.; Grützmacher, H. Eds.; Wiley-VCH, Weinheim, 2001; pp 91-141. (j) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(4) Even in intramolecular cases, reactivity is only general for 5-membered cyclizations, and is diminished by alkene substitution. For selected recent examples of intramolecular catalytic hydroamination of alkenes, see: (a) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570. (b) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2008**, 2741. (c) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Chem. Commun.* **2008**, 1422. (d) Zhang, W.; Werness, J. B.; Tang, W. *Org. Lett.* **2008**, *10*, 2023. (e) Bauer, E. B.; Andavan, G. T. S.; Hollis, T. K.; Rubio, R. J.; Cho, J.; Kuchenbeiser, G. R.; Helgert, T. R.; Letko, C. S.; Tham, F. S. *Org. Lett.* **2008**, *10*, 1175. (f) Dochnahl, M.; Löhnwitz, K.; Pissarek, J.-W.; Roesky, P. W.; Blechert, S. *Dalton Trans.* **2008**, 2844. (g) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (h) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (i) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (j) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 354.

give a carbocation intermediate, which then combines with a nitrogen nucleophile to give the hydroamination adduct and regenerate an acidic proton (Scheme 1.1).

Scheme 1.1. Mechanism of acid-catalyzed hydroamination.

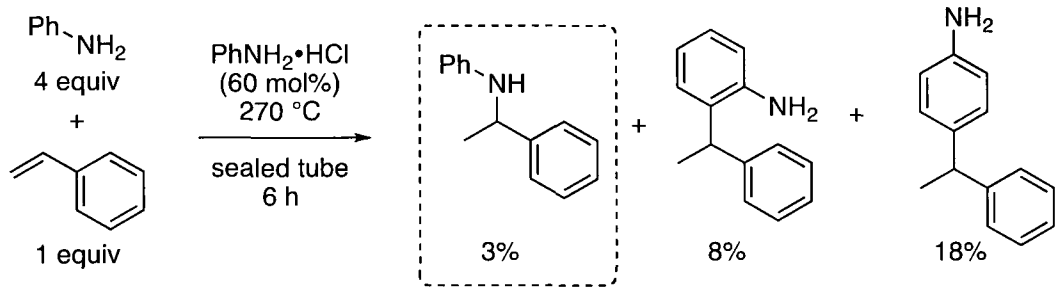


Unfortunately, basic nitrogen nucleophiles do not lead to hydroamination products but instead perform an acid-base reaction with the acid catalyst. This buffering effect results in both inefficient alkene protonation and in the deactivation of the nucleophile by the formation of the conjugate acid. As a consequence, reports of acid-catalyzed hydroamination reactions generally feature nitrogen atoms whose basicity has been attenuated by the presence of electron-withdrawing groups (anilines, amides, sulfonamides, etc.).

Hickinbottom first reported an intermolecular acid-catalyzed hydroamination of an amine to an alkene in 1932. The reaction required high temperatures (250-300 °C) and gave very low yields.[6] Styrene was heated in the presence of an excess of aniline (4 equiv) and anilinium chloride (60 mol%) to give hydroarylation adducts and the branched hydroamination adduct as a minor product in 3% yield (Equation 1.1).

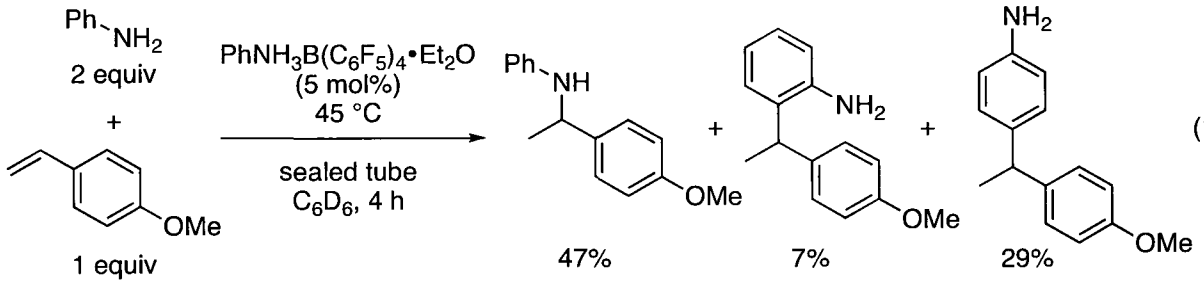
(5) (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. For a review of the Ritter reaction, see: (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

(6) (a) Hickinbottom, W. J. *J. Chem. Soc.* **1932**, 2644. (b) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 319. (c) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 1981.



(1.1)

In 2005, 73 years later, Bergman and coworkers reported an improved version of Hickinbottom's result by realizing that non-coordinating anions are essential to achieving acceptable yields at lower reactions temperatures (Equation 1.2).[7] Despite the optimization, hydroarylation was still a competitive side reaction.



(1.2)

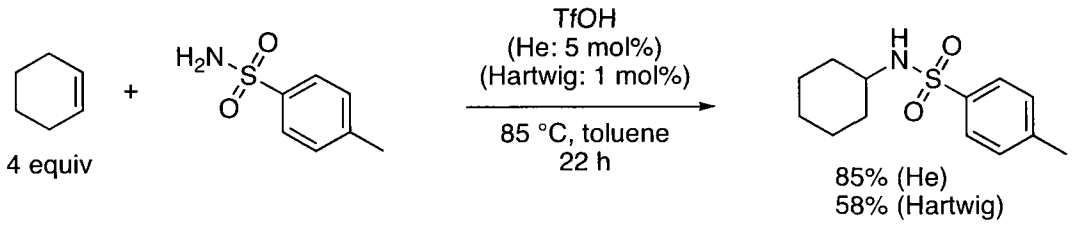
Soon after, other weakly basic nitrogen nucleophiles were reported to undergo acid-catalyzed addition to simple olefins. The groups of He and Hartwig nearly simultaneously reported the use of commercially available triflic acid to effect additions of sulfonamides and amides and both examined whether triflic acid might in fact be the active species in related metal triflate-catalyzed hydroamination processes (Equation 1.3).[8] Kaneda and coworkers showed that recyclable proton-exchanged montmorillonite clay was as effective as triflic acid.[9]

---

(7) (a) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542 (b) Lapis, A. A. M.; DaSilveira Neto, B. A.; Scholten, J. D.; Nachtigall, F. M.; Eberlinb, M. N.; Duponta, J. *Tetrahedron Lett.* **2006**, *47*, 6775.

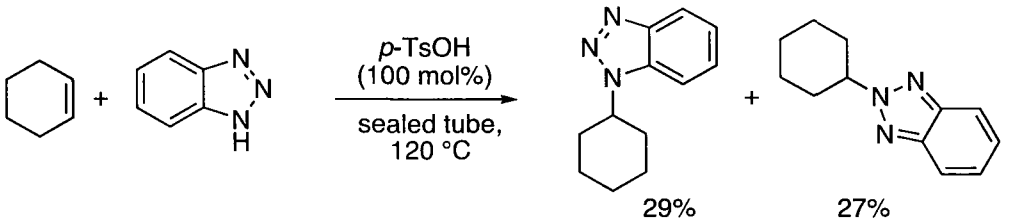
(8) (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.

(9) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617.

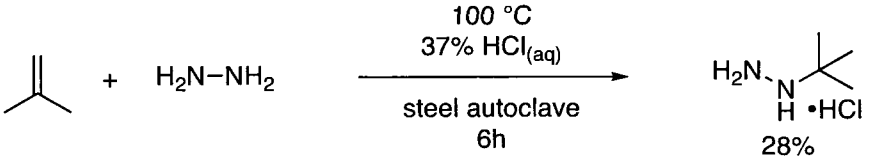


(1.3)

Additions of moderately basic nitrogen nucleophiles such as azoles and hydrazine are rare, require harsh conditions and are of narrow scope with respect to the nucleophile. Katritzky and coworkers reported the addition of benzotriazole to olefins in modest yields, but this specific reactivity could not be extended to other nitrogen heterocycles and often required a stoichiometric amount of *p*-toluenesulfonic acid (Equation 1.4).[10]



(1.4)



(1.5)

Chemists at Bayer patented a procedure for the addition of hydrazine to isobutylene, which required heating the reagents in concentrated hydrochloric acid in a steel autoclave at 100 °C to give *tert*-butylhydrazine in 28% yield (Equation 1.5).[11] Until the work described in Chapter 2, this harsh and low-yielding example represented the only basic nitrogen nucleophile with $pKa_H>5$ in H_2O to undergo acid-catalyzed hydroamination.

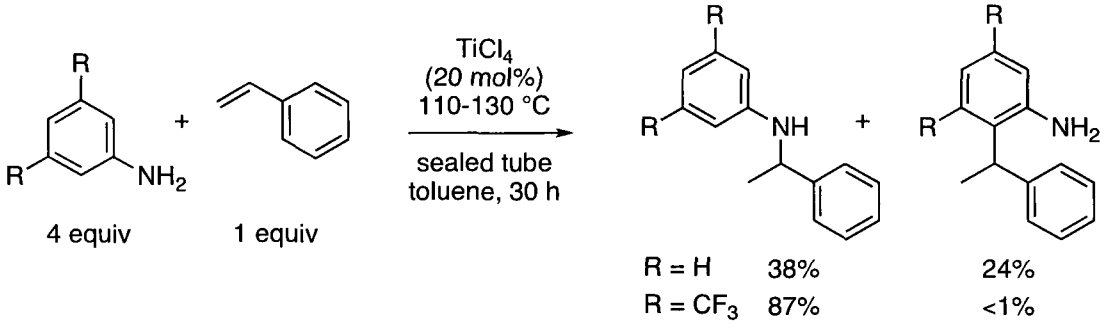
---

(10) (a) Katritzky, A. R.; Puschmann, I. B.; Stevens, C. V.; Wells, A. P. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1645. (b) Katritzky, A. R.; Qi, M.; Wells, A. P. *Geterotsikl. Soedin.* **1996**, 1520. (c) Ostrovskii, V. A.; Koren, A. O. *Heterocycles* **2000**, *53*, 1421 (and references cited therein). (d) Gaponik, P. N.; Voitekhovich, S. V.; Klyaus, B. G. *Zh. Org. Khim.* **2004**, *40*, 624.

(11) (a) Kelly, M. J. Preparation of alkylhydrazines. U.S. Patent 4,954,655, September 4, 1990. (b) Eichinger, W.; Fiege, H. Process for the preparation of alkylhydrazine salts. U.S. Patent 5,585,521, December 17, 1996.

1.2.2. Lewis Acid-Generated Brønsted Acid Catalysis

Several common Lewis acids such as $BiCl_3$, $AlCl_3$, $FeCl_3$ and $SnCl_4$ catalyze intermolecular hydroamination reactions of alkenes by reacting with aniline to form a strong Brønsted acid.[12] Reactions catalyzed by $TiCl_4$,[13] Au(I),[14] $Bi(OTf)_3$,[15] and Pt(II)[16] triflates also appear to be operating by such a mechanism, although the authors did not originally propose such a mechanism. As with Brønsted acid-catalyzed reports, competitive hydroarylation can be stopped only by the presence of blocking or deactivating groups on the aniline ring (Equation 1.6). Furthermore, these reactions are catalyzed with equal or greater efficiency by Brønsted acids and the metal-catalyzed reactions display carbocationic isomerization products consistent with acid catalysis (Figure 1.2).[8]



(1.6)

(12) Wei, H.; Qian, G.; Xia, Y.; Li, K.; Li, Y.; Li, W. *Eur. J. Org. Chem.* **2007**, 4471.

(13) (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, *6*, 2515. (b) Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, 44, 5972.

(14) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

(15) (a) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611. (b) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 150.

(16) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640.

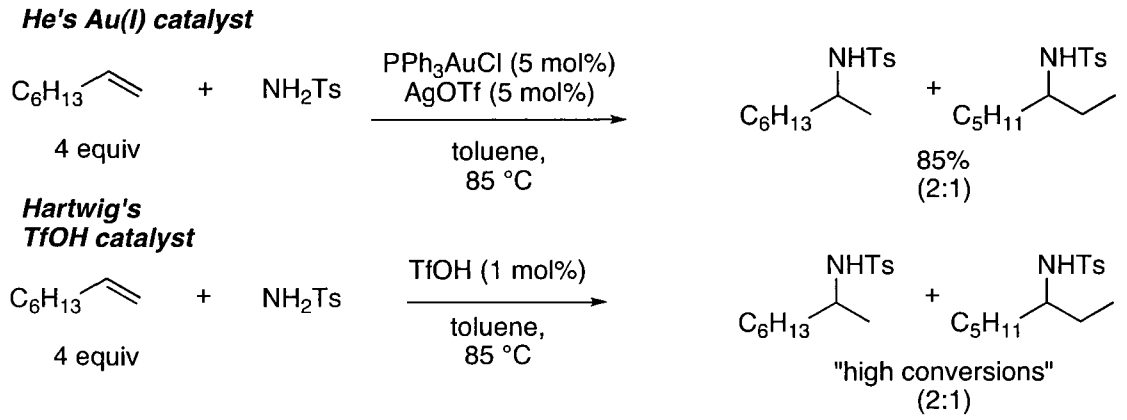


Figure 1.2. Comparison of Gold and Brønsted acid catalysts for hydroamination of 1-octene.

A recent mechanistic study by Tilley and coworkers supports a Brønsted acid catalyzed pathway for the Pt(II)-catalyzed hydroamination of alkenes with sulfonamides (Figure 1.3).[17]

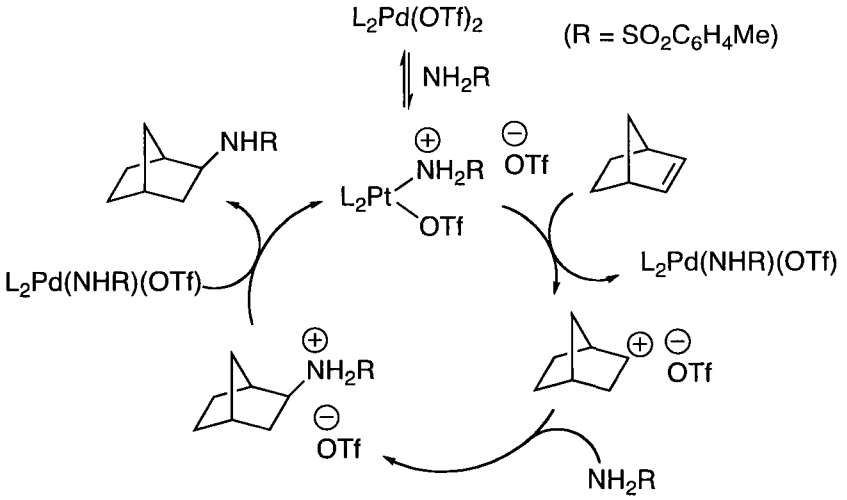


Figure 1.3. Mechanism of $Pt(OTf)_2$-catalyzed intermolecular hydroamination of alkenes.

(17) McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562.

1.3. Amine Activation

1.3.1. Base-Catalyzed Hydroamination[18]

Deprotonation of an amine renders it significantly more nucleophilic and allows for anti-Markovnikov hydroamination reactions involving basic amines (Figure 1.4).[19] However, this approach does not allow for the presence of weak electrophiles or any functional groups more acidic than an amine and is limited to mildly electron-poor alkenes such as ethylene, 1,3-dienes and vinylarenes.

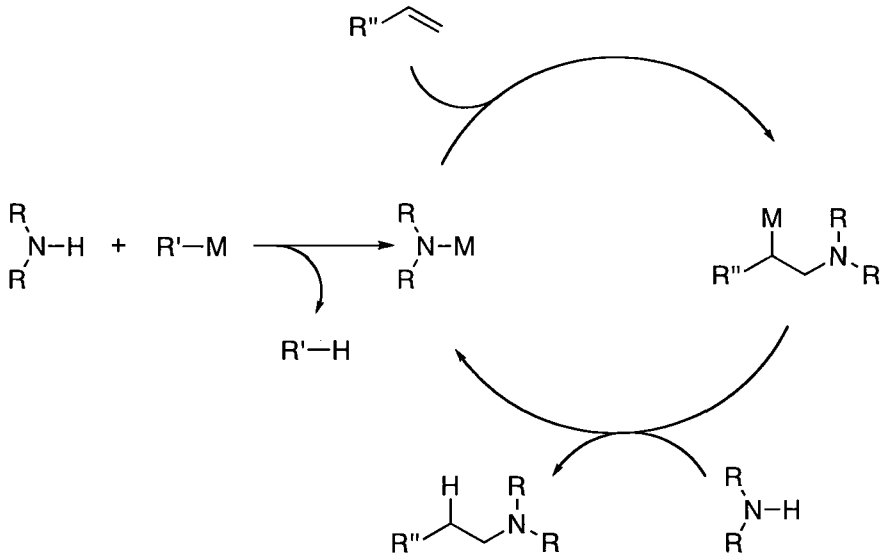


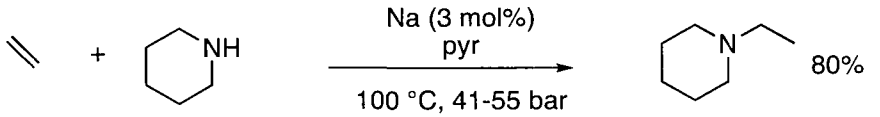
Figure 1.4. Catalytic cycle for base catalyzed intermolecular hydroaminations of alkenes.

The extremely reactive basic catalysts are simple and commercially available, but conditions are inherently harsh. High temperatures and pressures are often necessary (Equation

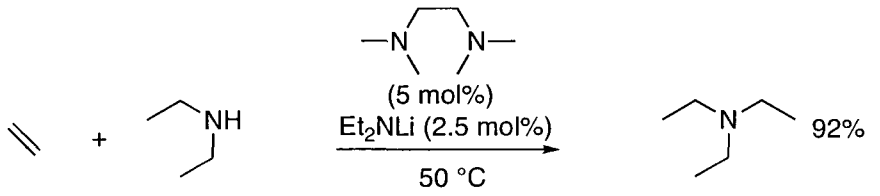
(18) For a recent review of base-catalyzed hydroamination, see: Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.

(19) For selected examples of intermolecular strong base-catalyzed hydroamination, see: (a) Horrillo-Martinez, P.; Hultzsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311. (b) Pez, G. P.; Galle, J. E. *Pure Appl. Chem.* **1985**, *57*, 1917. (c) Lehmkuhl, H.; Reinehr, D. *J. Organomet. Chem.* **1973**, *55*, 215. (d) Takabe, K.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 222. (e) Closson, R. D.; Napolitano, J. P.; Ecke, G. G.; Kolka, A. *J. Org. Chem.* **1957**, *22*, 646.

1.7).[19e] Bidentate chelating ligands such as EDTA were found to enhance reactivity (Equation 1.8).[20]



(1.7)



(1.8)

Base-catalyzed telomerization of 1,3-dienes, pioneered by Takabe and colleagues,[21] has notably been employed in the Takasago process for the asymmetric synthesis of (–)-menthol (Figure 1.5).[22]

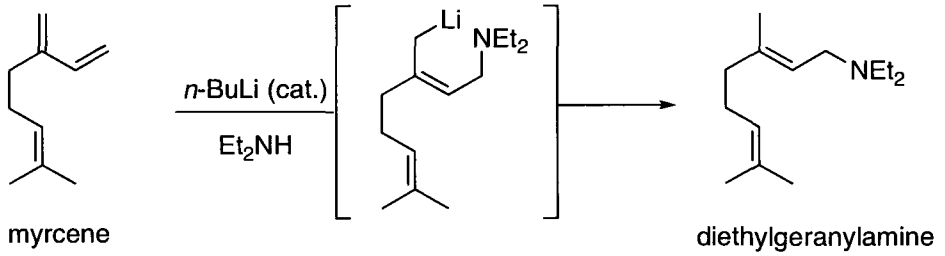


Figure 1.5. Telomerization of myrcene in the Takasago synthesis of (–)-menthol.

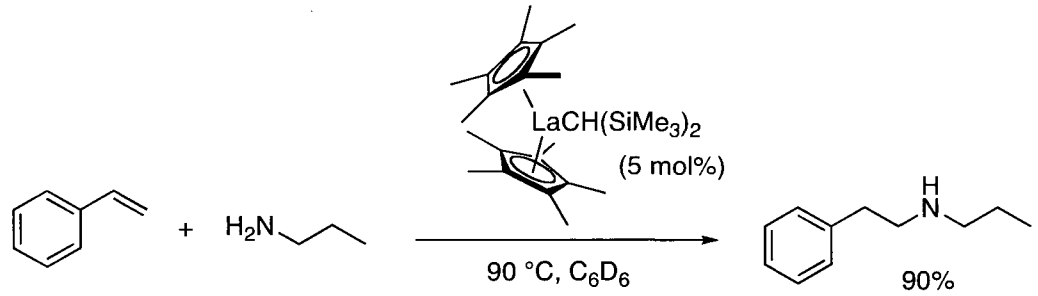
(20) Khedkar, V.; Tillack, A.; Benisch, C.; Melder, J.-P.; Beller, M. *J. Mol. Catal. A: Chem.* **2005**, *241*, 175.

(21) (a) Takabe, K.; Katagiri, T.; Tanaka, J. *Tetrahedron Lett.* **1972**, 4009. (b) Takabe, K.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 222. (c) Fujita, T.; Suga, K.; Watanabe, S. *Chem. Ind. (London)* **1973**, 231. (d) Takabe, K.; Katagirir, T.; Tanaka, J.; Fujita, T.; Watanabe, S.; Suga, K. *Org. Synth.* **1989**, *67*, 44.

(22) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otuska, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208.

1.3.2. Lanthanide-Catalyzed Hydroamination

Lanthanide complexes effectively catalyze intramolecular hydroamination reactions of alkenes and basic amines[23] but efficient intermolecular examples are limited to vinylarenes (Equation 1.9).[24]



(1.9)

Lanthanide catalysts are thought to function by olefin insertion into a Ln-N bond. The anti-Markovnikov regioselectivity observed with vinylarenes is attributed to aryl-directing interactions of the weakly coordinating arene π system and the electrophilic lanthanide centre (Figure 1.6). Substrates lacking an aryl activating group, such as 1-pentene, are slow, require a large excess of alkene (71 equiv) and give the Markovnikov regioisomer (Equation 1.10). These catalysts also suffer from high sensitivity to air and moisture as well as low functional group compatibility.

(23) For a review of lanthanide-catalyzed hydroamination, see: Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.

(24) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

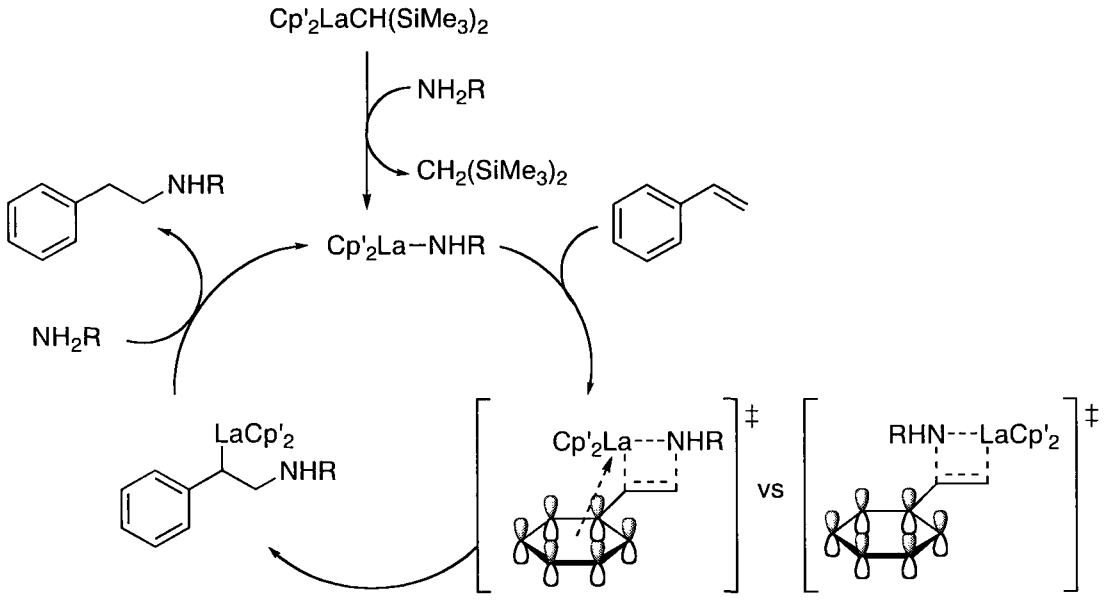
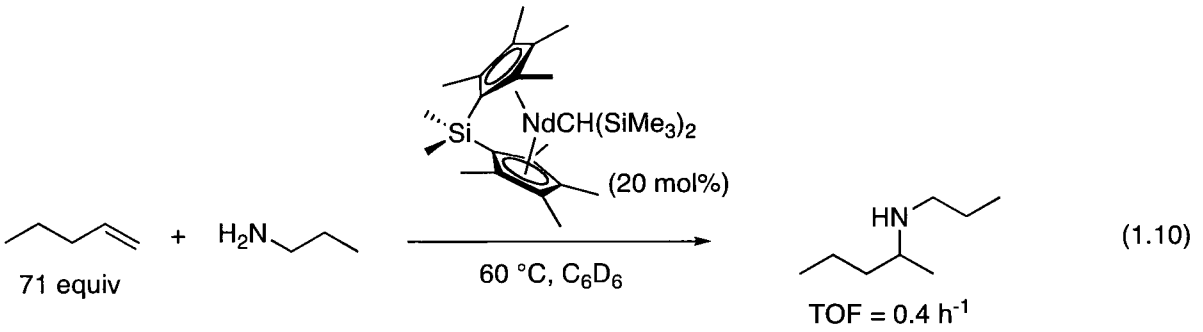


Figure 1.6. Proposed catalytic cycle for organolanthanide-catalyzed intermolecular vinylarene hydroamination.

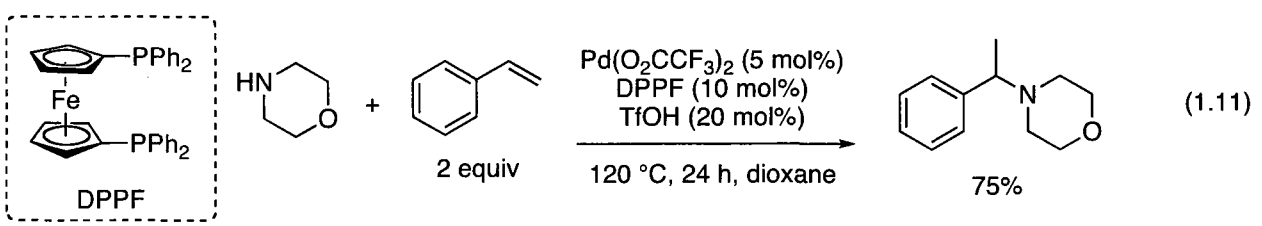


(1.10)

1.4. Late Transition Metal Catalysis

1.4.1. Pd and Ni: Nucleophilic Attack on π-Allyl or π-Benzyl Complexes

The ability to access metal-stabilized π-allyl or π-benzyl complexes from 1,3-dienes or vinylarenes led to the development of the first asymmetric methods for intermolecular hydroamination for such substrates.



(1.11)

Beginning in 2000, Hartwig and coworkers disclosed a series of Pd- and Ni-catalyzed Markovnikov-selective hydroamination reactions of vinylarenes and 1,3-dienes with anilines and alkylamines (Equation 1.11), including some promising enantioselective results (Figure 1.7).[25]

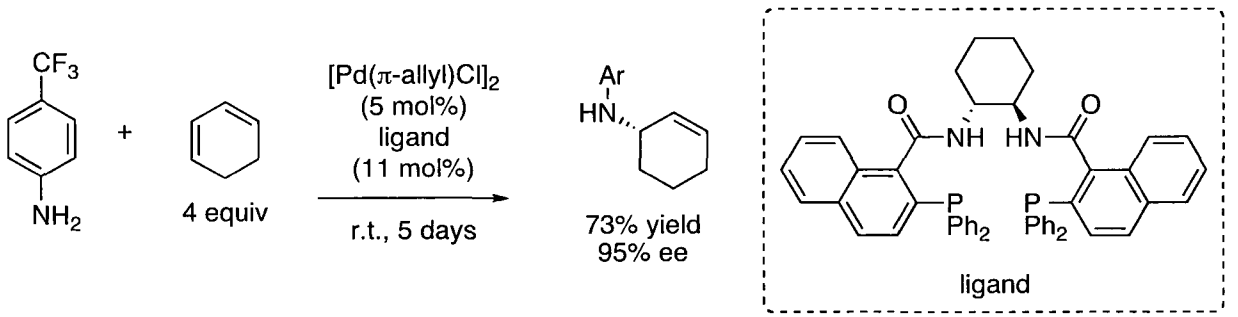


Figure 1.7. Hartwig's Pd-catalyzed asymmetric hydroamination of 1,3-dienes.

With dienes, the mechanistic model involves addition of the palladium species and acid to the diene to give a π-allyl complex (Figure 1.8). Turnover-limiting nucleophilic attack of the amine on the carbon at the 1- or 3- position provides an ammonia alkenyl complex. Deprotonation of the ammonium followed by displacement of the allylic amine by another diene completes the cycle. For vinylarenes, a similar mechanistic model was proposed involving an η^3-benzyl complex.[25e]

(25) Pd: (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. (b) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (c) Nettevoken, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166. (d) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286. (e) Johns, A. M.; Utsunomiya, M.; Incarrito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828. (f) Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 8134. Ni: (g) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669.

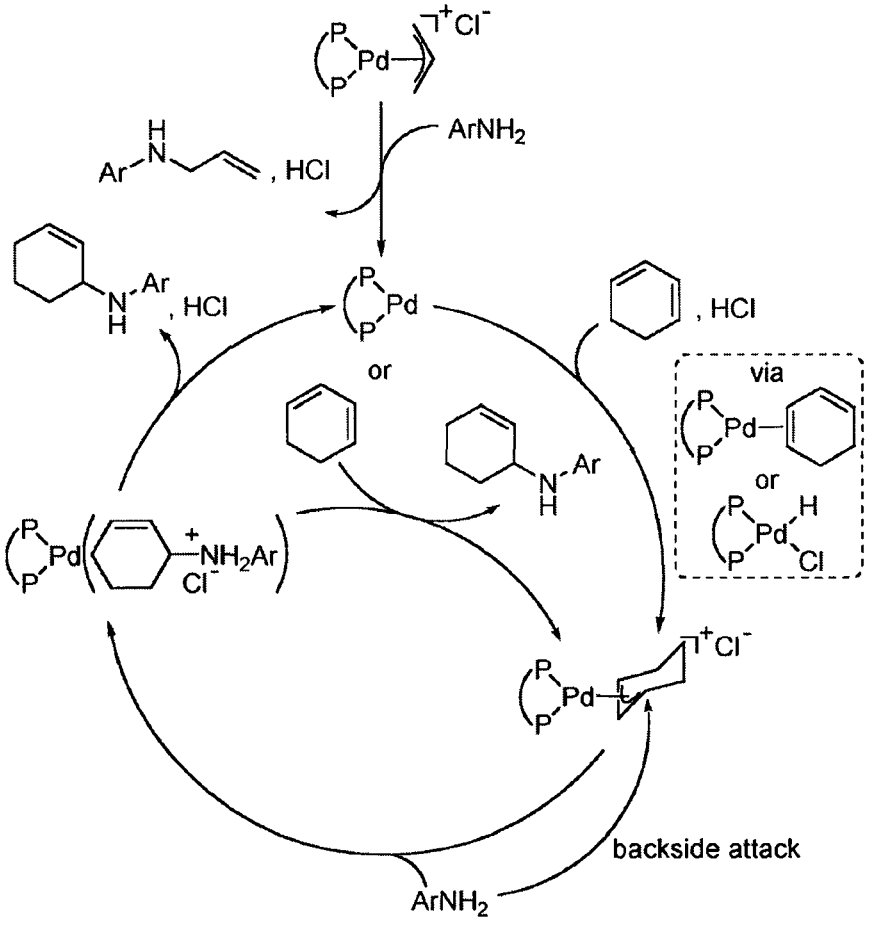
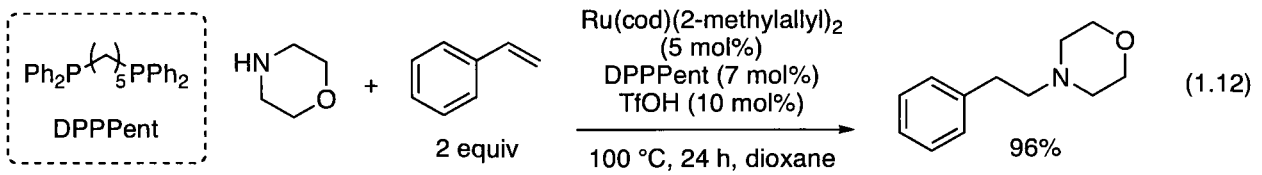


Figure 1.8. Mechanism of palladium-catalyzed hydroamination of 1,3-dienes.

1.4.2. Ru: Activation of Vinylarenes via π-Arene Complexes

Ru-catalyzed reactions with cyclic basic amines give anti-Markovnikov regiochemistry with vinylarenes. (Equation 1.12).

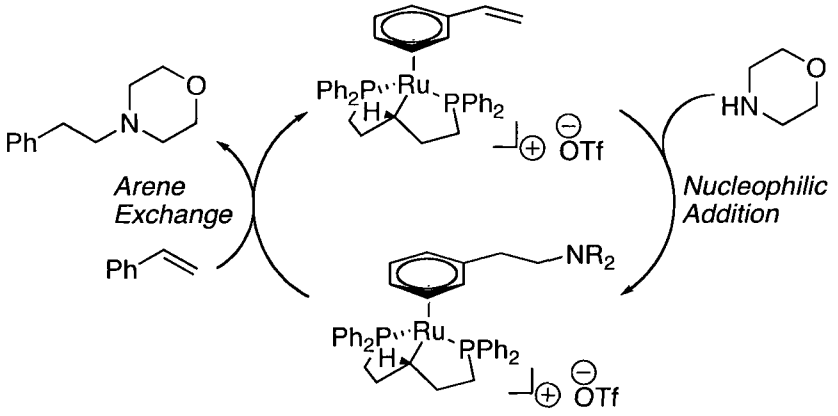


(1.12)

Hartwig and coworkers reported that ruthenium-catalyzed reactions occur by a mechanism involving a rare example of catalytic chemistry through a π-arene complex (Scheme

1.2).[26] Michael-type addition of the amine to an η^6-alkenylarene complex results in the anti-Markovnikov hydroamination product, which then undergoes arene exchange with a new vinylarene to complete the catalytic cycle. The mechanism was confirmed by the isolation and investigation of the π-arene complex.[26c]

Scheme 1.2. Proposed mechanism for ruthenium-catalyzed intermolecular hydroamination of vinylarenes.



At this juncture, it should be noted that while the development of Pd, Ni and Ru catalysis has led to the development of several asymmetric intermolecular hydroamination reactions, the alkene scope is still limited to vinylarenes and 1,3-dienes. Highly enantioselective transformations only exist for the latter. In all three cases, the alkene scope limitations are fundamental to the mechanism.

1.4.3. Rh: Oxidative Hydroamination vs. Hydroamination

In 1971, chemists at DuPont reported that Rh salts catalyzed the hydroamination of secondary amines with ethylene.[27a] Several other catalytic systems based on Rh and Ir have also been shown to catalyze the transformation with ethylene, norbornene and styrene.[27,] Interestingly,

---

(26) For Ru, see: (a) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702. (b) Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756.

(27) For Rh, see: (a) Coulson, D. R. *Tetrahedron Lett.* **1971**, *5*, 429 (b) Diamond, S. E.; Szalkiewicz, A.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 490. (c) Diamond, S. E.; Mares, F.; Szalkiewicz, A. *Fundam. Res. Homogeneous. Catal.* **1979**, *3*, 345. (d) Brunet, J. J.; Neibecker, D.; Philipot, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1215. (e)

both Markovnikov and anti-Markovnikov selectivity has been observed for styrene. [27e,g] In the anti-Markovnikov hydroamination of bidentate amines such as morpholine with styrene reported by Beller in 1997, the desired amine was only a minor product while the major products were an enamine and an equimolar amount of ethylarene, which result from a competitive oxidative hydroamination process (Figure 1.9).[27g] The only substrate where the amine was the major product was 2-vinylpyridine.[27h] Beller proposed that all three products arose from a common intermediate. Reductive elimination or β-hydride elimination from an alkylrhodium species would lead to the amine or enamine, respectively.

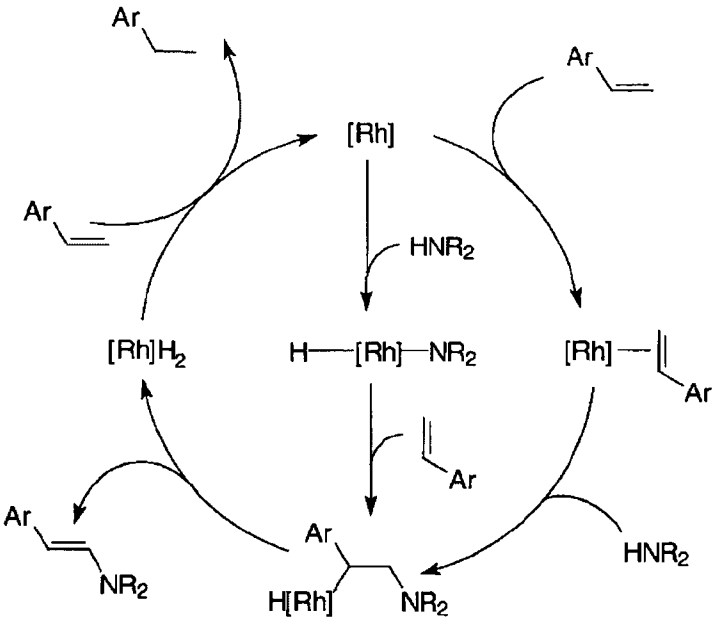
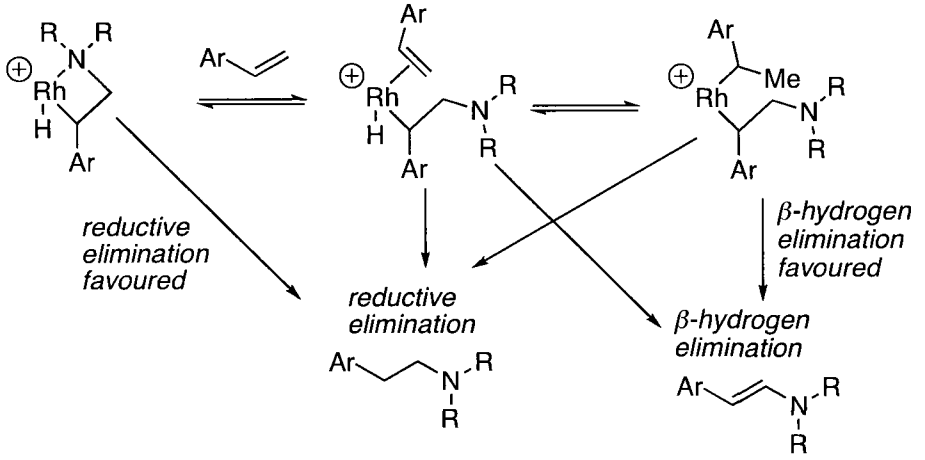


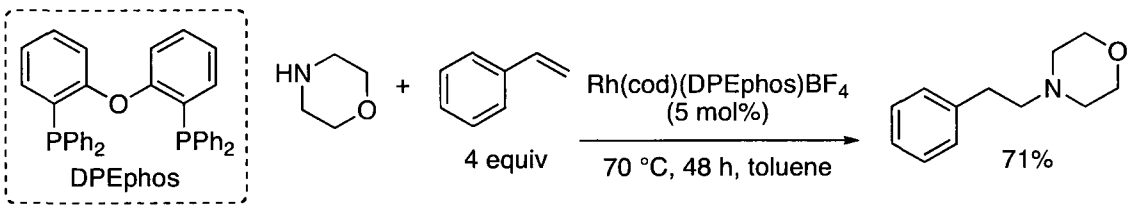
Figure 1.9. Beller's proposed mechanism for the oxidative hydroamination of vinylarenes.

Brunet, J.-J.; Neibecker, D.; Philippot, K. *Tetrahedron Lett.* **1993**, *34*, 3877. (f) Brunet, J. J.; Commenges, G.; Neibecker, D.; Philippot, K. *J. Organomet. Chem.* **1994**, *469*, 221. (g) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem. Int. Ed.* **1997**, *36*, 2225. (h) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E. *Eur. J. Inorg. Chem.* **1999**, *7*, 1121. (i) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306. (j) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608.

Scheme 1.3. Influence of alkene concentration on amine:enamine product ratio.



In 2003, Hartwig and coworkers reported that a larger excess of vinylarene decreases the amine:enamine product ratio, and proposed that a second alkene prevents reductive elimination to the amine by insertion into the Rh-H bond (Scheme 1.3). Reduction of alkene concentration to 4 equiv and further ligand optimization gave improved selectivity for the amine product (Equation 1.13).[27j]



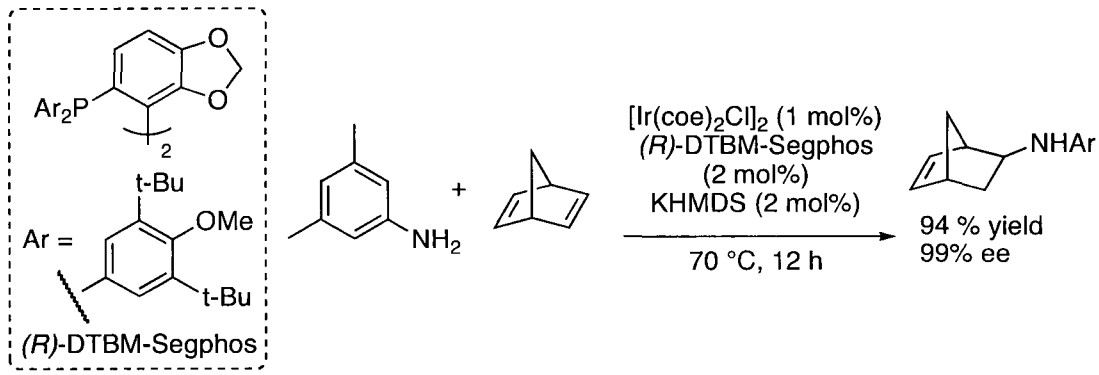
(1.13)

1.4.4. Ir: Highly Enantioselective Hydroaminations of Strained Alkenes.

Nearly a decade after the initial report of Ir-catalyzed hydroamination of norbornene with aniline by Milstein in 1988,[28a] Togni and coworkers reported a low yielding enantioselective variant in which addition of fluoride was found to be beneficial, although the origin of the effect was not conclusively elucidated.[28b] In 2008, Hartwig and coworkers showed that fluoride was in fact acting as a base to deprotonate aniline and formed a catalytic quantity of reactive amide.

(28) For Ir, see: (a) Casanuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. (b) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. (c) Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

Optimization of the base and the use of bidentate phosphine ligands bearing a small backbone dihedral angle led to reactions of strained alkenes with excellent yield and enantioselectivity (Equation 1.14).[28c]



(1.14)

1.4.5. Pt(II) and Au(I): Catalytic Hydroamination of Unactivated Alkenes

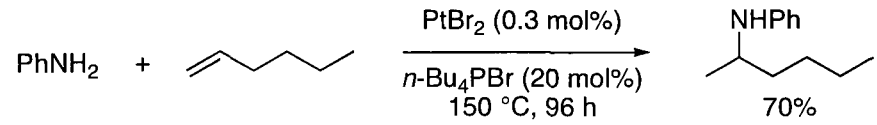
While some Pt(II) and Au(I) catalysts function by generating a strong Brønsted acid,[29] others possess significantly different substrate scope and more strongly coordinating counterions and appear to function by electrophilic activation of the alkene.

Beginning in 2004, several Pt(II) complexes capable of mediating intermolecular hydroamination reactions of alkenes were disclosed.[30] Brunet and coworkers showed that simple $PtBr_2$ was an active catalyst for the hydroamination of ethylene and simple alkenes with aniline, displaying high Markovnikov regioselectivity in ionic liquids (Equation 1.15).[30a,d] Brønsted acid catalysts are notoriously unable to catalyze reactions of ethylene, indicating that this was not the operative mechanism. Widenhoefer and coworkers reported similar reactivity with amides.[30b,c]

---

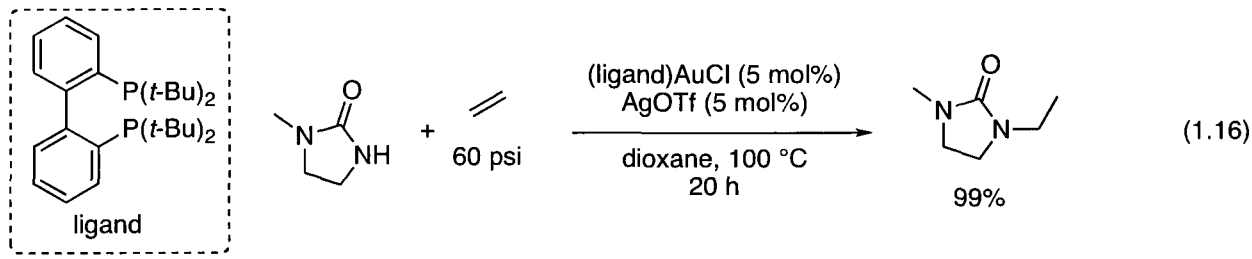
(29) See Section 1.2.2.

(30) (a) Brunet, J.-J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothers, E. *Organometallics* **2004**, *23*, 1264. (b) Widenhoefer, R. A.; Wang, X. *Organometallics* **2004**, *23*, 1649. (c) Widenhoefer, R. A.; Qian, H. *Org. Lett.* **2005**, *7*, 2635. (d) Brunet, J.-J.; Chu, N. C.; Diallo, O. *Organometallics* **2005**, *24*, 3104. For a review, see: (e) Brunet, J.-J.; Chu, N. C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, 4711.

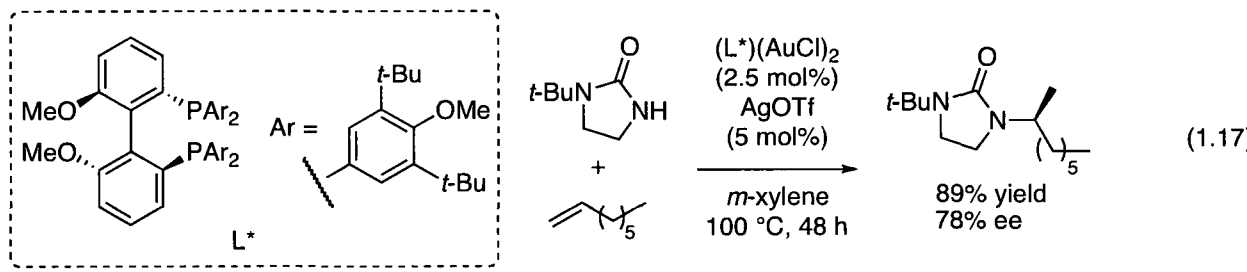


(1.15)

Very recently, the Widenhoefer group disclosed that Au(I) complexes containing bidentate phosphine ligands are capable of catalyzing the hydroamination of a wide variety of alkenes with cyclic ureas (Equation 1.16). The catalyst can tolerate the presence of free hydroxyl and carboxylic acid groups. The use of chiral diphosphine ligands results in the only examples of asymmetric intermolecular hydroamination of unactivated alkenes, giving moderate enantioselective excess (Equation 1.17).[31a] The group has also recently furthered the hypothesis that the reaction proceeds by direct coordination of the olefin to the metal centre by obtaining the crystal structure of a cationic Au(I) π-alkene complex with isobutylene.[31b]



(1.16)



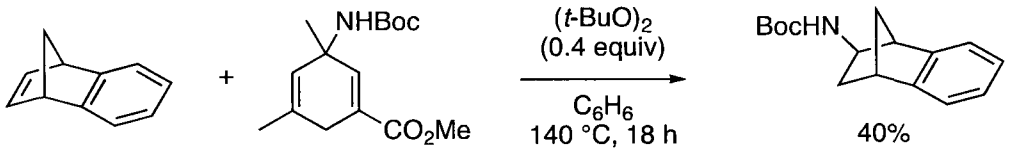
(1.17)

(31) (a) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372. (b) Brown, T. J.; Dickens, M. G.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 6350.

1.5. Radical-Mediated Hydroamination

1.5.1. Chemical Precursors to Radical Hydroamination

Nitrogen-centered radicals have long been known to add to alkenes in an intermolecular fashion, but their use in hydroamination has been limited due to the difficulty associated with hydrogen transfer from nitrogen to a carbon-centered radical.[32] In 2005, Studer and Kemper demonstrated that heating 3-amidyl-1,4-cyclohexadienes in the presence of an alkene and di-*tert*-butylperoxide as initiator results in a radical hydroamination reaction with anti-Markovnikov selectivity in modest yields (Equation 1.18).[33a]



(1.18)

Studer and coworkers later reported that the difficult H-atom transfer from nitrogen to carbon can be accelerated by the addition of thiols, which are superior hydrogen donors and can be regenerated by hydrogen abstraction from a 1,4-cyclohexadiene (Figure 1.10).[33b]

(32) For recent examples of intermolecular addition of *N*-centered radicals to olefins, see: (a) Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 3865. (b) Kitagawa, O.; Miyaji, S.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2003**, *68*, 3184. (c) Tsuritani, Y.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 3246.

(33) (a) Kemper, J.; Studer, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 4914. (b) Guin, J.; Mück -Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498. (c) Guin, J.; Fröhlich, R.; Studer, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 779.

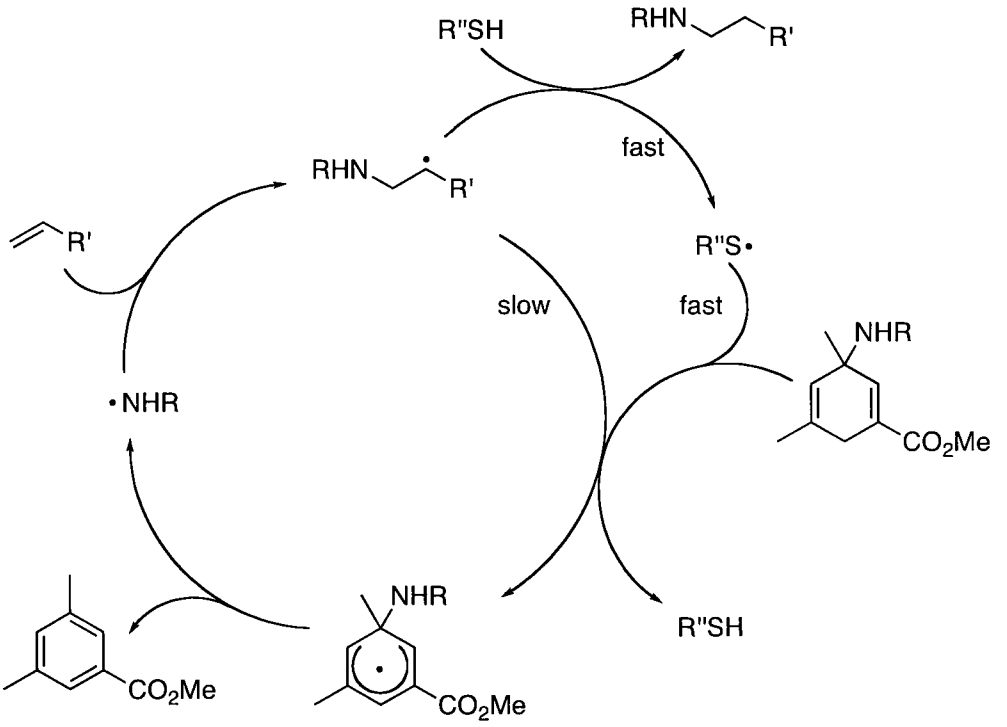
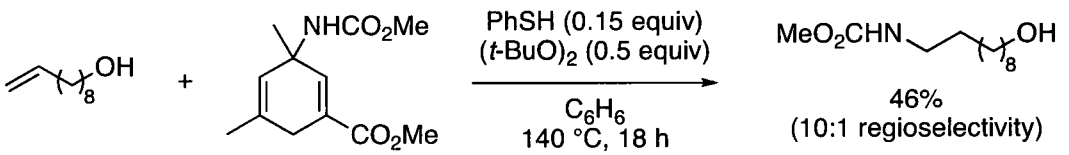


Figure 1.10. Studer's radical transfer hydroamination.

The Studer method boasts good generality with respect to alkene substitution and exhibits notable functional group compatibility with free alcohols, malonates, esters, amides and common *O*-protecting groups (Equation 1.19).



(1.19)

The energetically coupled nature of the radical reaction allows for its broad scope with stable, substituted alkenes. The free energy lost from a contrathermodynamic hydroamination is offset by the energy gained during the aromatization of the cyclohexadiene moiety. On the other hand, the need for the multistep preparation of the radical precursor, which is lost as it aromatizes during the reaction, contradicts the atom-economical aspects of the hydroamination reaction.

1.5.2. Photochemical Routes to Radical Hydroamination

The photochemical generation of transient radical cations from alkenes under redox-photosensitization offers an opportunity to perform anti-Markovnikov hydroamination reactions under very mild conditions (Figure 1.11).[34,35] However very specific criteria must be fulfilled for such a process to be efficient. No other chromophore must absorb in the desired wavelength. Furthermore, the redox chemistry between the excited photosensitizer (a reducing agent) and the electron acceptor must not be disturbed by any species in the reaction mixture.

Despite these challenges, Yasuda and coworkers reported the 1,2,4-triphenylbenzene (TPB)-sensitized hydroamination of indene or 1,2-dihydronaphthalene with ammonia in the presence of 1,3-dicyanobenzene (DCB), which serves to facilitate electron transfer between the sensitizer and the intermediates (Equation 1.20).[35e]

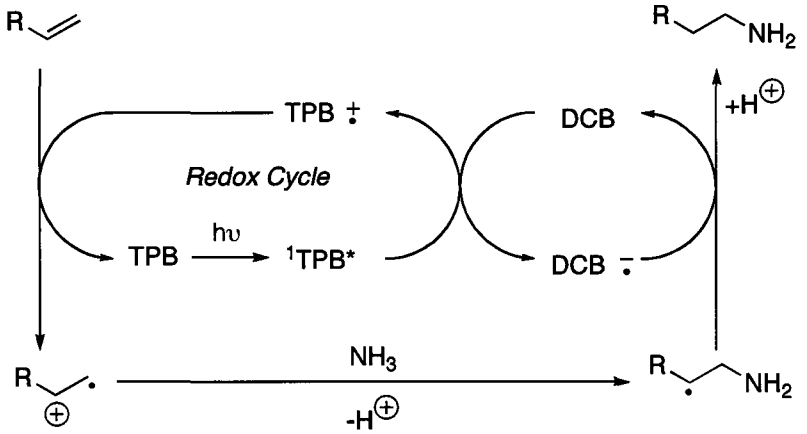
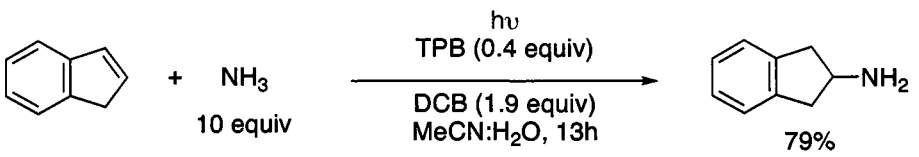


Figure 1.11. Mechanism for redox-photosensitized hydroamination.

(34) For more on photosensitization, see Section 2.1.1.3, pg. 33.

(35) (a) Yasuda, M.; Isami, T.; Kubo, J.; Mizutami, M.; Yamashita, T.; Shima, K. *J. Org. Chem.* **1992**, *57*, 1351. (b) Yamashita, T.; Yasuda, M.; Isami, T.; Tanabe, K.; Shima, K. *Tetrahedron* **1994**, *50*, 9275. (c) Yasuda, M.; Wakisaka, T.; Kojima, R.; Tanabe, K.; Shima, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3169. (d) Kojima, R.; Yamashita, T.; Tanabe, K.; Shiragami, T.; Yasuda, M.; Shima, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 217. (e) Yasuda, M.; Kojima, R.; Tsutsui, H.; Utsunomiya, D.; Ishii, K.; Jinnouchi, K.; Shiragami, T. *J. Org. Chem.* **2003**, *68*, 7618.



(1.20)

Although the simplicity of this transformation is attractive, its utility is limited by its narrow scope with respect to both reaction partners.

1.6. Thermodynamic Considerations

Several reviews have stated that the hydroamination of alkenes is thermodynamically favoured, but until recently, no quantitative thermodynamic results could confirm such a statement for intermolecular systems.[3h,j] Estimates concerning the enthalpy have been made using bond dissociation energies of ammonia and ethylene, while the entropy of addition had been estimated using values in the gas phase.[36] Finally in 2006, Hartwig and coworkers reported experimental values by directly measuring the equilibrium constants of reactions in solution in both the forward and reverse direction.[37] As expected, analysis of the addition of *N*-methylaniline to styrene confirmed that the reaction was exothermic but nearly ergoneutral due to the negative entropy associated with an intermolecular addition reaction. The measurement of equilibrium constants for the addition of styrene to anilines of various substitution patterns demonstrated that steric changes on the aniline have a much larger impact on the equilibrium constants than do electronic changes. Small changes in alkene structure can also result in large thermodynamic variations. For example, the free energy of reaction of the addition of *m*-anisidine to 1,2-dihydronaphthalene (1.31±0.18 kcal/mol) is less favourable than that for indene (0.26±0.05 kcal/mol) and significantly less so than for styrene (-3.54±0.01

(36) (a) Steinborn, D.; Taube, R. *Z. Chem.* **1986**, *26*, 349. (b) R. Taube in Applied Homogeneous Catalysis, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Vol. 1, p 513.

(37) Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306.

kcal/mol). These results clearly illustrate that small changes in the substitution patterns of either reaction partner can result in significantly different thermodynamic outcomes and these considerations must be taken into account when high yielding reactions are desired or in the design of stereoselective transformations.

1.7. Summary and Outlook

Significant progress towards intermolecular hydroamination of alkenes has been made via several distinct mechanistic approaches. Acid-catalyzed reactions are simple, cheap, and Markovnikov-selective but require deactivated amines and exhibit low functional group compatibility. Several Lewis acids also appear to be functioning through a Brønsted acid-catalyzed pathway. Base-catalyzed reactions are simple, cheap and anti-Markovnikov selective, but require electron-rich amines and also exhibit narrow scope and low functional group compatibility. Lanthanide-catalyzed reactions give anti-Markovnikov selectivity for vinylarenes but are too slow for other substrates and are air and moisture sensitive. Late transition metal catalysts (specifically Pd and Au) exhibit better functional group tolerance and are less sensitive. Racemic anti-Markovnikov selective reactions of vinylarenes have been reported with Ru and Rh-based catalysts, while Markovnikov selective racemic reactions of unactivated terminal alkenes have been achieved with Pt and Au. Asymmetric transition metal catalyzed reactions have been achieved with Markovnikov selectivity with varying degrees of enantioselectivity for 1,3-dienes (Pd – good), vinylarenes (Pd – modest), norbornene (Ir – excellent) and unactivated terminal alkenes (Au – modest). Thermal and photochemical radical-based methods have also been developed, the former of which displays excellent alkene scope and functional group tolerance, but requires a multistep synthesis of the radical precursor and gives modest yields.

Despite this excellent progress, the lack of broad substrate generality with respect to both amine and alkene reaction partners remains the primary limitation in the field. The lack of cheap and highly practical methods has also hindered the reaction from becoming a commonly used tool in organic synthesis. While the vast majority of the efforts directed at intermolecular hydroamination of alkenes have been focused at overcoming difficult kinetic barriers, the near thermoneutral nature of the reaction poses special challenges to the development of general atom economical transformations. Catalysts modify only the kinetics of a reaction, but cannot promote a thermodynamically unfavourable process in an efficient manner unless the energetic cost is offset in some way. Therefore, the continued development of processes involving energy input, such as photochemical hydroamination reactions, wasteful thermal hydroamination reactions or thermal *amination* reactions containing removable functionality[38] is ultimately necessary for the intermolecular hydroamination reaction of alkenes to achieve its long-sought generality.

(38) (a) Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676. (b) Waser, J.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4099. (c) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

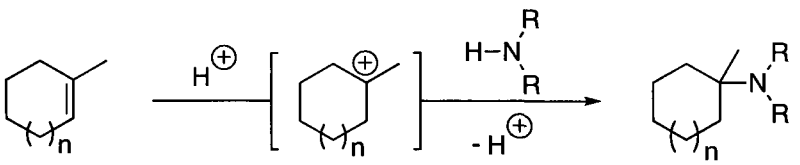
Chapter 2. Photoinduced Intermolecular Strain-Release Hydroamination of Cycloalkenes and Cycloalkenones[1]

(1) Portions of this chapter have been published: (a) Moran, J.; Dornan, P.; Beauchemin, A. M. *Org. Lett.* **2007**, *9*, 3893. (b) Moran, J.; Cebrowski, P. H.; Beauchemin, A. M. *J. Org. Chem.* **2008**, *73*, 1004.

2.1. Introduction

As we have seen in Chapter 1, considerable efforts have been directed at hydroamination of electron-rich alkenes, both in intra- and intermolecular systems. Despite the encouraging progress, the hydroamination of alkenes stands out as one of the simplest and most desirable synthetic transformations for which no general solution exists and remains a largely unused tool in the synthesis of complex organic molecules.[2] In fact, hydroamination methods are rarely employed to prepare even relatively simple amine starting materials, aside from in their original publication. This can partly be attributed to their relatively recent appearance in the literature, but is realistically largely due to the lack of practicality of the available methods, most of which require reagents or catalysts that are difficult to handle, expensive, moisture sensitive or that cannot be purchased or made from commercially available starting materials in a single step.

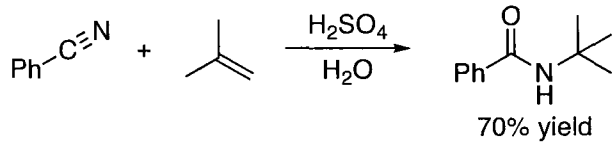
Scheme 2.1. Acid-catalyzed hydroamination of alkenes.



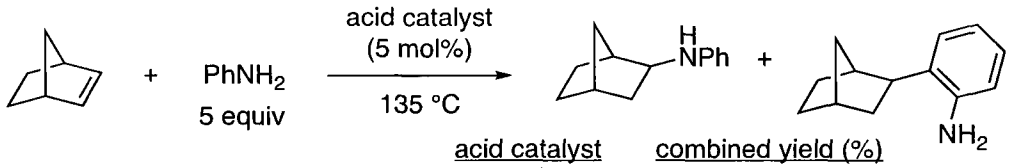
Acid-catalyzed hydroamination is a conceptually simple approach and has the potential to be the most cost-effective and practical method, yet suffers from drawbacks of its own (Scheme 2.1). Various functionalities are not compatible with the strength of the Brønsted acids required to protonate a typical unactivated alkene. On the other hand, most nitrogen nucleophiles do not lead to hydroamination products due to an acid-base reaction with the Brønsted acid. This

(2) For selected examples of alkene hydroamination in total synthesis, see: (a) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2003**, *125*, 8744. (b) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878. (c) Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344.

buffering effect results in both inefficient alkene protonation and in the deactivation of the nucleophile by the formation of the conjugate acid. As such, most Brønsted acid hydroaminations are related to the Ritter reaction,[3] in which nitriles are used as the nitrogen nucleophiles (Equation 2.1).



(2.1)



(2.2)

acid catalyst	combined yield (%)
$PhNH_3B(C_6F_5)_4$	60 (1:1 ratio)
HOTf	13 (1:1 ratio)

Other weakly basic reagents such as anilines,[4] azoles,[5] hydrazines,[6] sulfonamides[7] and amides,[7c] can also add efficiently under strongly acidic conditions. The nature of the counterion has a profound impact on the efficiency of these reactions (Equation 2.2).[4a] Lastly, as with most other hydroamination methods, acid-catalyzed hydroamination is under thermodynamic control and its synthetic utility is limited by the poor thermodynamic driving force of the reaction.[8]

---

(3) (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. For a review of the Ritter reaction, see: (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

(4) (a) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542. (b) Lapis, A. A. M.; DaSilveira Neto, B. A.; Scholten, J. D.; Nachtigall, F. M.; Eberlinb, M. N.; Duponta, J. *Tetrahedron Lett.* **2006**, *47*, 6775.

(5) (a) Katritzky, A. R.; Puschmann, I. B.; Stevens, C. V.; Wells, A. P. *J. Chem. Soc. Perkin Trans. 2* **1995**, 1645. (b) Katritzky, A. R.; Qi, M.; Wells, A. P. *Geterotsikl. Soedin.* **1996**, 1520.(c) Ostrovskii, V. A.; Koren, A. O. *Heterocycles* **2000**, *53*, 1421 (and references cited therein). (d) Gaponik, P. N.; Voitekhovich, S. V.; Klyaus, B. G. *Zh. Org. Khim.* **2004**, *40*, 624.

(6) (a) Kelly US Patent 4,954,655, filed 03/1989. (b) Eichinger; Fiege US Patent 5,585,521, filed 09/1995.

(7) (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179. (c) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617.

(8) Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306. See Section 1.6, pg. 23.

As highlighted in the example shown in Equation 2.2, strained organic molecules often display high reactivity, consistent with high ground state energy and low activation energy for a variety of transformations (Figure 2.1).[9] As such, strain provides unique opportunities for organic chemists to develop reactions and methodologies that would otherwise not be possible. Strained alkenes could potentially permit acid-catalyzed hydroamination reactions with basic nitrogen nucleophiles due to the increased ability of the olefin to undergo protonation.

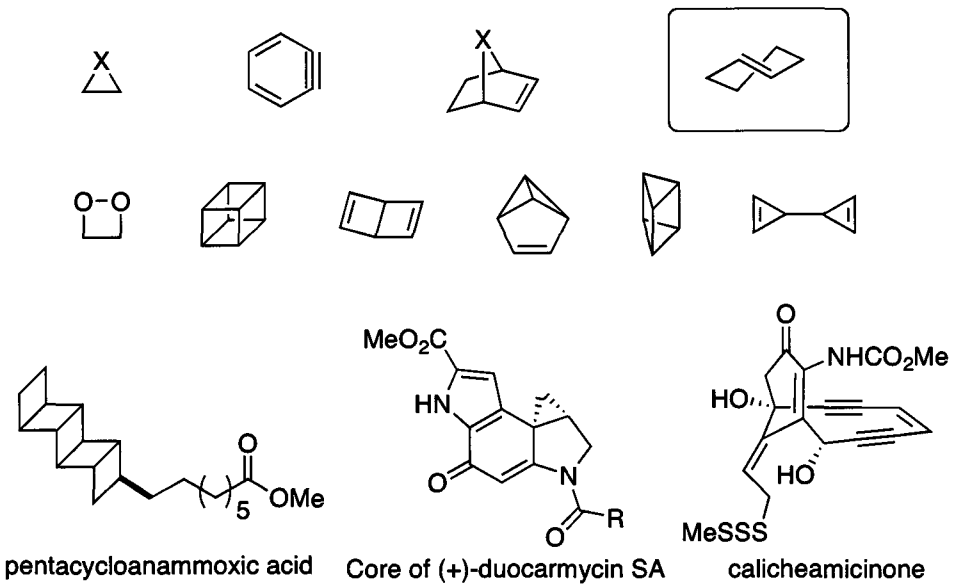


Figure 2.1. Selected strained synthetic molecules and natural products.

Fortunately, a well-studied class of strained alkenes can be generated photochemically. Six- to eight-membered E-cycloalkenes and E-cycloalkenones are highly strained intermediates that can be rapidly generated via photoisomerization of the corresponding Z-isomer without any further chemical steps. Their high ground state energy results in greatly increased reactivity

(9) (a) Liebman, J. F.; Greenberg, A., A *Chem. Rev.* **1976**, *76*, 311. (b) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.

under mild conditions (Figure 2.2). Additionally, products arising from stereospecific reactions of these species possess valuable *trans* relationships that can be otherwise difficult to synthesize.

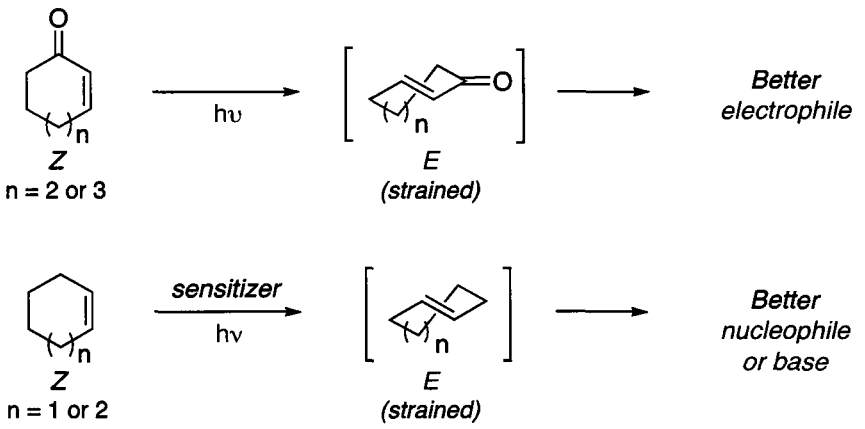


Figure 2.2. Strain-induced reactivity trends of E-cycloalkenones and E-cycloalkenes.

The strong basicity of E-cycloalkenes therefore represents an opportunity to develop mild acid-catalyzed hydroamination reactions that function regardless of the acid-buffering properties of the amine and that are not under thermodynamic control. Given the relatively more complex photochemistry of E-cycloalkenes, we first decided to apply this concept to E-cycloalkenones, which can be generated without the need for special glassware or sensitization.

This chapter documents the development of the first stoichiometric strain-release 1,4-additions of amines to E-cycloalkenones and the subsequent application of that knowledge to the more complex problem of mild hydroaminations of E-cycloalkenes. Photochemical cis-trans isomerization of cyclic alkenes and enones is employed throughout this chapter in order to generate strain. In order to appreciate how these reactions occur, a brief review of the relevant photochemistry is first described, followed by a summary of the known reactivity of these remarkable species.

2.1.1. Brief Review of Relevant Photochemistry

2.1.1.1. Summary of Photochemical Processes[10]

The ability of an electron to transition from one electronic state to another is governed by the change in multiplicity between those states (Figure 2.3). In the Jablonski diagram, electronic states are represented by anharmonic energy wells (S_0, S_1 and T_1), while the horizontal lines within each well represent vibrational states. For a two-electron system, the electrons can either have the opposite spin (called singlet multiplicity) or have the same spin (called triplet multiplicity). Electronic transitions between states of the same multiplicity (vertical transitions) are said to be spin-allowed and occur rapidly without the necessity for atomic motion (illustrated by the vertical arrow from S_0 to S_1).

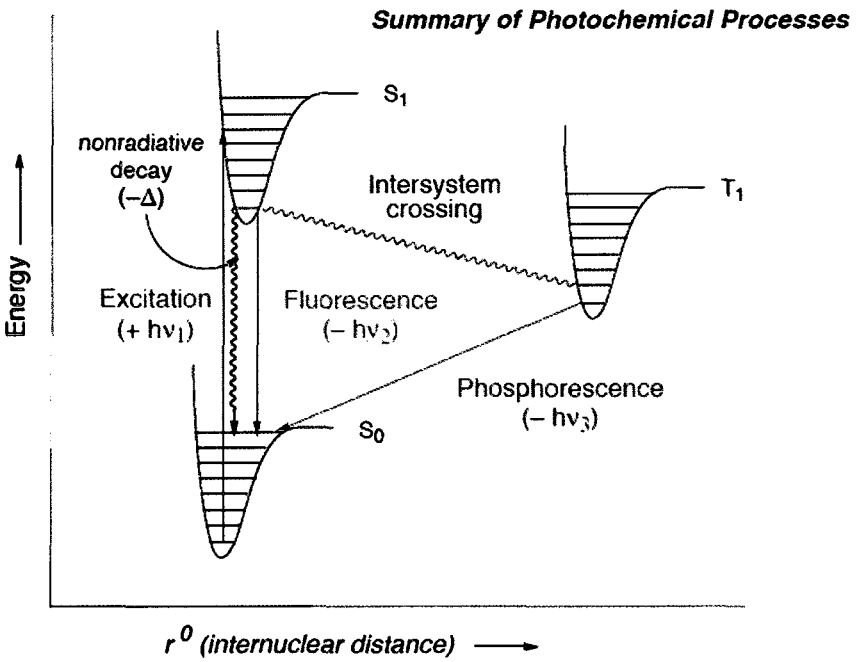


Figure 2.3. Jablonski diagram summarizing photochemical processes.[11]

(10) For a more detailed discussion, see: Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry*, 4th ed., Kluwer Academic/Plenum Publishers, New York, 2000, pp. 743-747.

(11) Figure adapted from Evans, D. A. *Chem 206 Notes,* Harvard University, 2003.

Transitions occurring between electronic states of differing multiplicity (horizontal transitions) are called intersystem crossings and are said to be spin-forbidden. These transitions occur relatively slowly due to their necessity to be coupled with the vibrational relaxation of atoms (illustrated by the wavy lines connecting S_1 and T_1). When a molecule in its ground electronic state (S_0) absorbs a photon, it is promoted initially to an excited singlet state (typically S_1) and can either slowly return to its ground state by vibrational relaxation, rapidly return to its ground state by release of a photon (fluorescence) or slowly undergo a spin-forbidden intersystem crossing to a lower energy triplet state (T_1). If in T_1, the molecule may return to the ground state with release of a photon via a slow process called phosphorescence. While in an excited electronic state, a molecule possesses increased energy, often resulting in different geometry and orbital symmetry, and therefore is capable of drastically different reactivity compared to its ground state.

2.1.1.2. Photochemical Cis-Trans Isomerization of Alkenes.

One of the most common applications of photochemistry in organic synthesis is the interconversion of cis and trans alkene isomers, which is particularly useful when the contra-thermodynamic isomer is desired. Isomerization occurs when an alkene is electronically excited, promoting an electron from the π to the π^* orbital (Figure 2.4). The resulting species quickly undergoes rotation to give an excited state in which the two sp^2 carbons are twisted 90° with respect to one another.[12] This perpendicular arrangement is thought to be the minimum-energy geometry for both the singlet and triplet excited states, and continued rotation permits for the possibility to return to either the cis or trans ground states.

(12) (a) Mulliken, R. S.; Roothann, C. C. J. *Chem. Rev.* **1947**, *47*, 219. (b) Merer, A. J.; Mulliken, R. S. *Chem. Rev.* **1969**, *69*, 639.

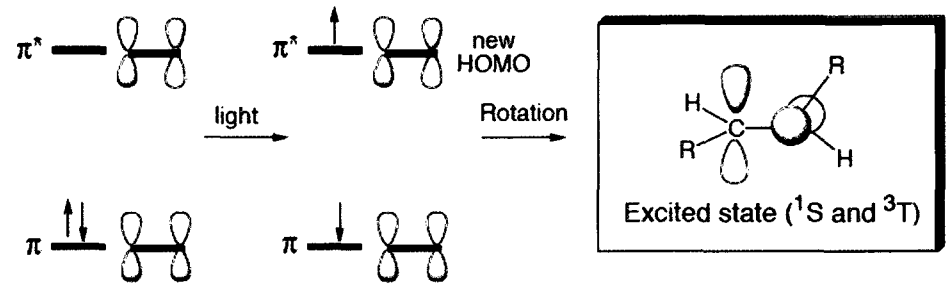


Figure 2.4. Mechanism for the photochemical isomerization of alkenes.[11]

Cis and trans isomers usually exhibit slightly different absorption maxima. Therefore, the relative amount of light absorbed by the cis and trans isomers at a given wavelength will not be identical, and is proportional to their extinction coefficients, ε_c and ε_t, at that wavelength. In consequence, the isomerization of one isomer will occur faster than the other and its concentration will diminish until a photostationary state is reached where the rate of trans-cis isomerization is equal to the rate of cis-trans isomerization. For monochromatic light, the relationship can be expressed as:

$$\frac{[t]_s}{[c]_s} = \left(\frac{\varepsilon_c}{\varepsilon_t}\right)\left(\frac{\phi_{c\to t}}{\phi_{t\to t}}\right)$$

where Φ is the quantum yield (the number of times the isomerization occurs per absorbed photon).

2.1.1.3. Photosensitization

The photoexcited states of a particular substrate can also be accessed indirectly by energy transfer from an excited molecule, called a *photosensitizer* (or *sensitizer*), to the substrate. In a *sensitized* reaction, light is not absorbed by the reactive substrate, but by the sensitizer, which does not undergo an overall chemical change, but simply transfers electronic energy to the substrate. Sensitization is governed by the same rules as other energy transfer processes.

Conservation of energy requires that the excitation energy of the sensitizer be equal or greater than that of the substrate, while conservation of angular momentum requires that multiplicity of the system be conserved. Therefore, sensitizers with a long triplet lifetime give substrates in a triplet state (e.g. *p*-xylene, acetophenone), while sensitizers with a long singlet lifetime give substrates in a singlet state (e.g. methyl benzoate).

Sensitization is often more advantageous than direct irradiation as it offers access to the chemistry of the triplet state for substrates that cannot achieve that multiplicity via direct irradiation due to inefficient intersystem crossing from S_1 to T_1. Sensitization is also useful when dealing with substrates that absorb at a wavelength too short to be accessed with common light sources. For example, simple alkenes possess $\pi \rightarrow \pi^*$ absorption maxima in the range of 190-200 nm (corresponding to a $S_0 \rightarrow S_1$ transition), but the most common sources are mercury vapor lamps, which emit mainly at 254, 313 and 366 nm.[13] Therefore, most photochemical reactions of simple alkenes are carried out using benzene or *p*-xylene, triplet sensitizers whose triplet energy is higher than the triplet energy of the alkene. A comparison of direct and benzene-sensitized pathways for the excitation of ethylene is shown in Figure 2.5.

Photochemical reactions have also been reported to occur with singlet sensitizers even when the singlet energy of the sensitizer is lower than that of the substrate.[14] This seeming

---

(13) For the emission characteristics of various light sources and the transmission properties of glasses and filter solutions, see: (a) A. J. Gordon and R. A. Ford, *The Chemist's Companion*, Wiley-Interscience, New York, 1972, pp. 348-368. (b) S. L. Murov, I. Carmichael, G. L. Hug, *Handbook of Photochemistry*, 2nd ed., Marcel Dekker, New York, 1993.

(14) (a) Inoue, Y.; Kunitomi, Y.; Takamuku, S.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 1024. (b) Inoue, Y.; Takamuku, S.; Kunitomi, Y.; Sakurai, H. *J. Chem. Soc. Perkin Trans. 2* **1980**, 1672. (c) Takamuku, S.; Sakurai, H.; Inoue, Y.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1678. (d) Inoue, Y.; Yokoyama, T.; Yamasaki, N.; Tai, A. *J. Am. Chem. Soc.* **1989**, 111, 6480. (e) Inoue, Y.; Shimoyama, H.; Yamasaki, N.; Yokoyama, T.; Tai, A. *Chem. Lett.* **1991**, 593. (f) Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* **1992**, *57*, 1332. (g) Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* **1993**, *58*, 1011. (h) Inoue, Y.; Yamasaki, N.; Shimoyama, H.; Tai, A. *J. Org. Chem.* **1993**, *58*, 1785. (i) Tsuneishi, H.; Hakushi, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1601. (j) Inoue, Y.; Tsuneishi, H.; Hakushi, T.; Tai, A. *J. Am. Chem. Soc.* **1997**, *119*, 472. (k) Inoue, Y.; Matsushima, E.; Wada, T. *J. Am. Chem. Soc.* **1998**, *120*, 10687. (l) Hoffmann, R.; Inoue, Y. *J. Am. Chem. Soc.*

violation of conservation of energy has been shown to occur via an *exciplex* (excited complex) pathway, where an exciplex formed between substrate and sensitizer possesses an excitation energy lower than the energy of the absorbed photon. The exciplex mechanism resolves the apparent violation of conservation of energy and allows for singlet sensitizers to be used, sometimes with different photochemical reactivity or side reactions.

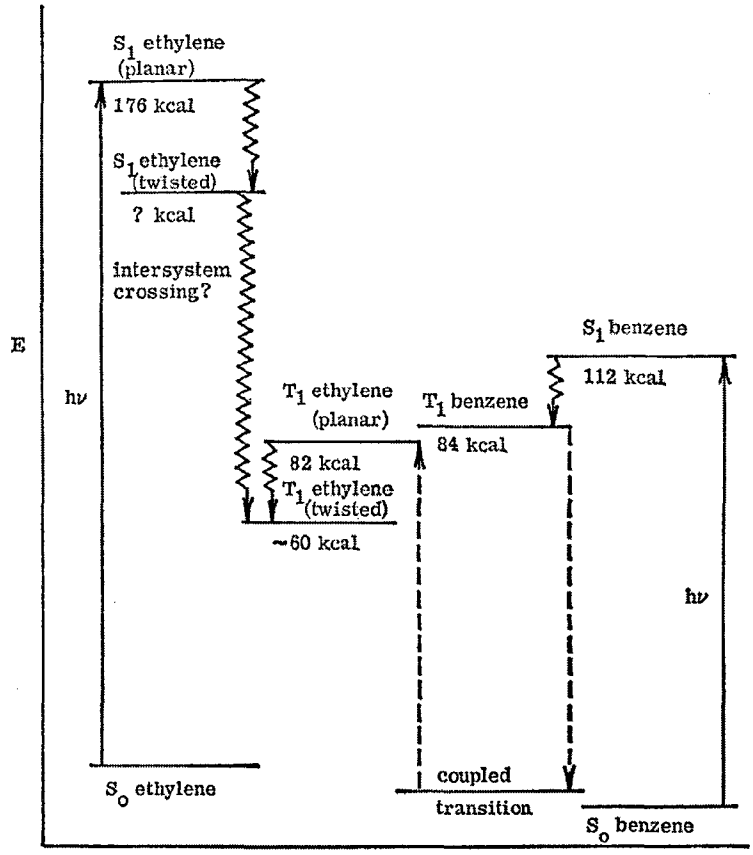


Figure 2.5. Excitation of ethylene by direct irradiation and by a benzene-sensitized pathway.[15]

1999, *121*, 10702. (m) Inoue, Y.; Ikeda, H.; Kaneda, M.; Sumimura, T.; Everitts, S. R. L.; Wada, T. *J. Am. Chem. Soc.* **2000**, *122*, 406.

(15) Figure adapted from: Marshall, J. A. *Science* **1970**, *170*, 137.

Although sensitization was originally developed for use in mechanistic investigations, it has also been used for synthetic purposes.[16] However, stringent requirements are required to obtain results of synthetic value. A sensitizer must be the major light absorber, must only transfer its energy to the substrate and must not react under the reaction conditions.

2.1.2. Generation and Reactivity of Strained (E)-Cycloalkenones

2.1.2.1. Trapping of E-Cycloalkenones via Cycloaddition Reactions

In 1964, Eaton and Lin reported the synthesis of E-cyclooctenone via photoisomerization of the Z isomer.[17] When irradiated at wavelengths greater than 300 nm in a solution of cyclohexane, the resulting photoequilibrium gives a 4:1 (E:Z) mixture of isomers.[18] Although a pure sample could not be isolated, the NMR spectrum displayed peaks at 4.3 and 3.5 ppm with coupling constants of 18 Hz. Such values are consistent with a coupling of trans vinyl hydrogens in an octene ring.[19] The addition of even a small trace of mineral acid led to the nearly instantaneous regeneration of Z-2-cyclooctenone. Unlike its Z-counterpart, the Diels-Alder reaction of E-2-cyclooctenone with an electron poor diene occurred vigorously at room temperature, yielding products with a trans ring junction (Equation 2.3).

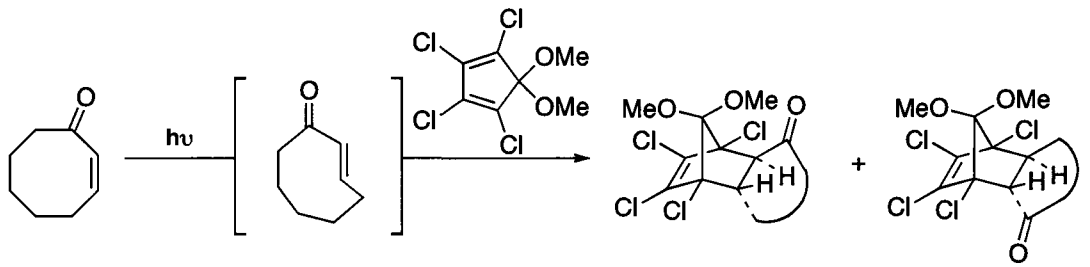
---

(16) For a review on Photosensitization in Organic Synthesis, see: Albini, A. *Synthesis* **1981**, 249.

(17) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1964**, *86*, 2087.

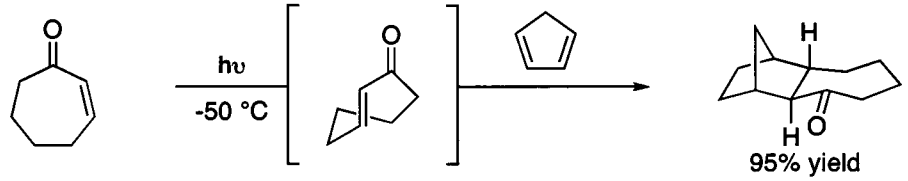
(18) The light source was a 450W Hanovia mercury lamp surrounded by water-cooled Pyrex filters.

(19) Chapman, O. L. *J. Am. Chem. Soc.* **1963**, *85*, 2014.



(2.3)

Soon after, Corey and Eaton simultaneously reported the generation of E-cycloheptenone.[20] This compound was much more reactive than its higher homologue. Irradiation of a mixture of Z-2-cycloheptenone and cyclopentadiene (excess) at –50 °C afforded the trans-fused Diels-Alder adduct in 95% yield (Equation 2.4).



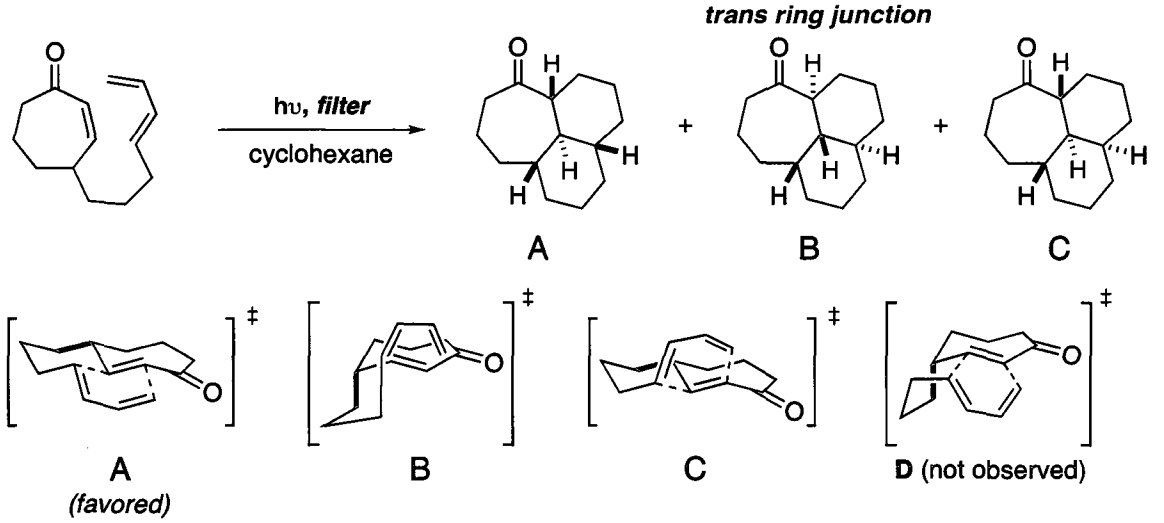
(2.4)

As the E-isomer was too reactive to isolate directly, experiments were conducted by the Corey group to determine whether the reactive intermediate was in fact the strained ground state isomer or a short-lived photoexcited state. 2-Cycloheptenone was irradiated in methylcyclohexane at –195 °C for 6 h and was then left to stand in the dark for 5 min. Addition of a cold solution of cyclopentadiene in pentane, followed by slow warming gave observable product. The observation of reactivity after standing in the dark demonstrates that the product arises not from an electronically excited state, but from ground state E-cycloheptenone. Furthermore, low temperature IR experiments by the Eaton group show a shift in the carbonyl absorption frequency from 1663 cm^{-1} (α,β-unsaturated carbonyl) to 1715 cm^{-1} (unconjugated carbonyl) as would be expected with a strained E-ground state intermediate. Subsequent laser

(20) (a) Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051. (b) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1965**, *87*, 2052.

flash photolysis experiments by Bonneau and coworkers further support that the reactive intermediate is E-2-cycloheptenone.[21]

Intramolecular Diels-Alder reactions of E-cycloheptenones, reported by Dorr and Rawal, produce complex polycyclic structures possessing trans-fused ring junctions (Figure 2.6).[22] Good diastereoselectivity and yields could be achieved when the reaction was conducted at –75 °C using a uranium filter (cutting off $\lambda < 340$ nm) to avoid Norrish-type photochemistry.



	cut off ~285 nm	cut off ~340 nm	
rxn temp	**pyrex yield**	**uranium filter yield**	**A:B:C**
rt	69%	88%	3:2:1
–75 °C	39%	77%	10:–:1

Figure 2.6. Intramolecular Diels-Alder reactions of E-cycloheptenones.

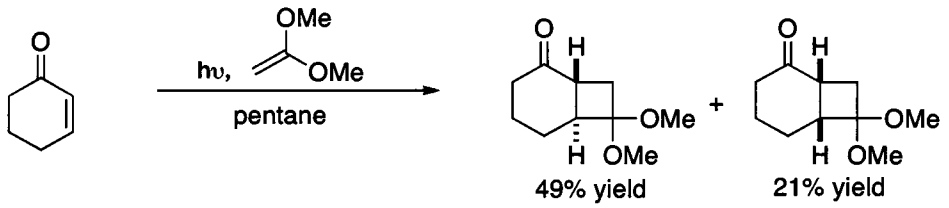
The Corey group has reported photochemical [2+2] cycloadditions of 2-cyclohexenone giving trans products (Equation 2.5).[23] The unusual regiochemistry can be rationalized by an

(21) Bonneau, R.; Fornier de Violet, P.; Joussot-Dubien, J. *Nouv. J. Chim.* **1977**, *1*, 31.

(22) Dorr, H.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 10229.

(23) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

E-2-cyclohexenone intermediate whose alkene and ketone are not conjugated. In that case, the alkene carbon proximal to the carbonyl would be the more electrophilic due to the inductive withdrawing effect of the oxygen. E-2-Cyclohexenone would presumably be extremely reactive and short-lived, making mechanistic experiments designed to differentiate its reactivity from that of an electronically excited state of 2-cyclohexenone quite difficult.



(2.5)

2.1.2.2. Photodeconjugation via E-Cycloalkenones

In 1970, Noyori and coworkers reported that cycloalkenones undergo photodeconjugation via an electronically excited state arising from an E-cycloalkenone intermediate (Figure 2.7).[24]

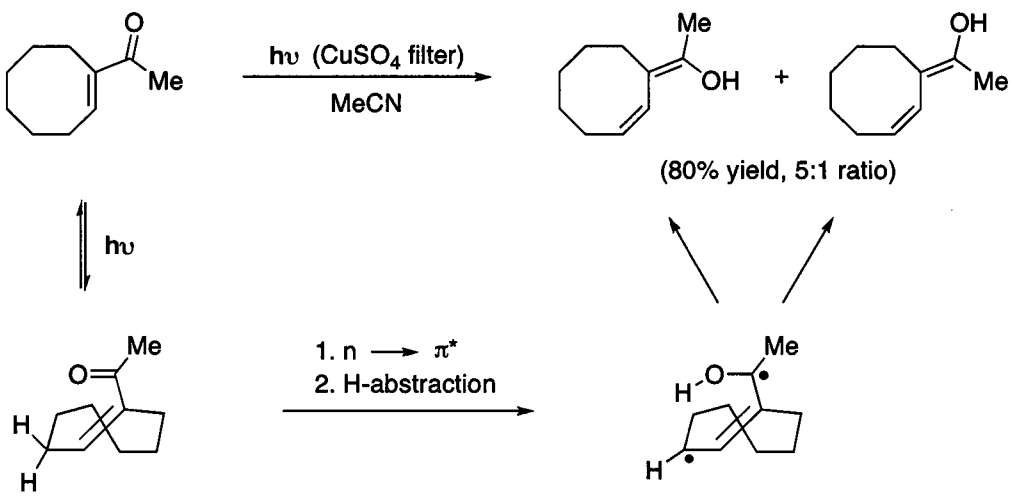
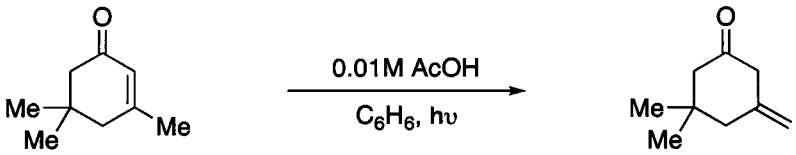


Figure 2.7. Noyori's report of photodeconjugation of cycloalkenones.

Weedon and coworkers then demonstrated the reaction also occurs with 2-cyclohexenones and showed that a trace amount of mineral acid is necessary to induce

(24) Noyori, R.; Inoue, H.; Kato, M. *J. Am. Chem. Soc.* **1970**, *92*, 6699.

deconjugation, thus providing a way to avoid this potentially destructive side-reaction (Equation 2.6).[25] The reaction was proposed to occur via an E-cyclohexenone intermediate and provides further indirect evidence for the existence of this species.



(2.6)

2.1.3. Overview of 1,4-Additions of Nitrogen Nucleophiles to α,β-Unsaturated Systems

The conditions under which 1,4-additions of nitrogen nucleophiles to α,β-unsaturated systems may be accomplished vary depending on the strength of the nucleophile.[26] Simply stirring lithium amides and some aliphatic amines in the presence of a Michael acceptor will typically produce a reaction at room temperature or with mild heating, while weaker nitrogen nucleophiles such as anilines, azoles and carbamates require either acid[27] or base[28] catalysis (Figure 2.8).

---

(25) Rudolph, A.; Weedon, A. C. *J. Am. Chem. Soc.* **1989**, *111*, 8756.

(26) Jung, M. E. in Comprehensive Organic Synthesis, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 30-41 and references therein.

(27) (a) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141. (b) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109. (c) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319. (d) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052. (e) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Perciaccante, P.; Tolomelli, A. *J. Org. Chem.* **2001**, *42*, 6719. (f) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960. (g) Loh, T.-P.; Wei, L.-L. *Synlett* **1998**, 975. (h) Pérez, M.; Pleixats, R. *Tetrahedron* **1995**, *51*, 8355. (i) Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827. (j) Rosenthal, D.; Braundrup, G.; Davis, K. H.; Wall, M. E. *J. Org. Chem.* **1965**, *30*, 3689.

(28) (a) Han, X. *Tetrahedron Lett.* **2007**, *48*, 2845. (b) Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett* **2000**, 1257. (c) de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkov, S. I.; Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, 3105. (d) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700. (e) Es-Sayed, M.; Graftkowski, C.; Krass, N.; Meyers, A. I.; de Meijere, A. *Synlett* **1992**, 962.

Han reported that additions of pyrazoles to enoates occur at room temperature in the presence of an equivalent of DBU.[28a] Conversely, Kobayashi reported the addition of carbamates to enones with transition metal salts or Lewis acids.[27b]

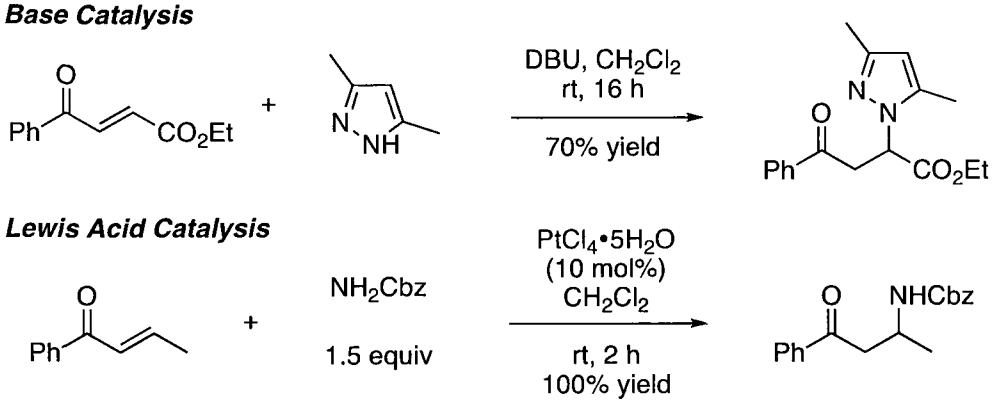


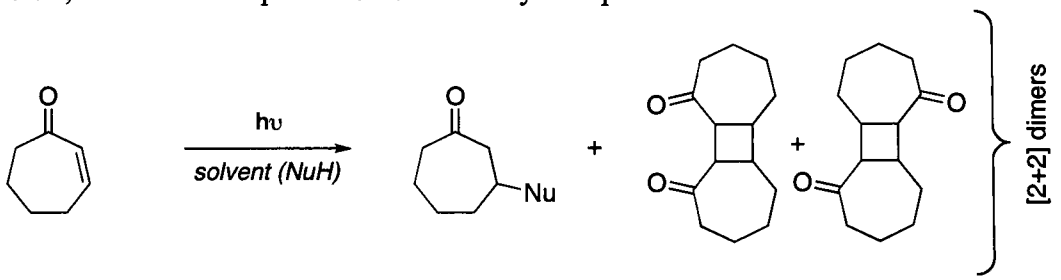
Figure 2.8. Representative methods for the aza-Michael reactions.

2.1.3.1. 1,4-Additions to E-Cycloalkenones

Despite exhibiting UV and IR spectral properties indicating that E-cycloalkenones do not possess a fully conjugated double bond, these species nonetheless exhibit increased reactivity with respect to 1,4-additions for simple nucleophiles used as solvents. Noyori and coworkers reported that 2-cycloheptenone undergoes conjugate additions with alcohols and diethylamine in modest yields when these nucleophiles are used as *solvents*.[29] Yields are often low due to competing [2+2] dimerization reactions (Table 2.1).

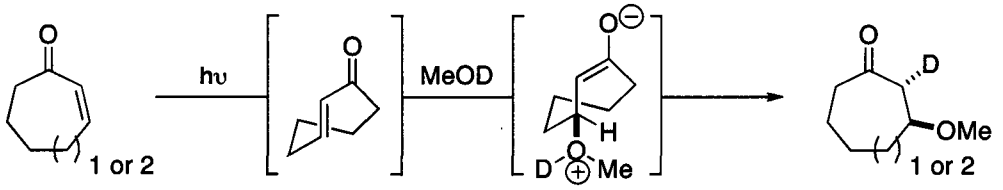
(29) (a) Nozaki, H.; Kurita, M.; Noyori, R. *Tetrahedron Lett.* **1968**, 2025. (b) Noyori, R.; Katô, M. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1460.

Table 2.1. 1,4-Additions of protic solvents to 2-cycloheptenone.



entry	solvent	addition product, %	dimer, %
1	cyclohexane	-	88
2	MeOH	86	0
3	EtOH	73	0
4	*i*-PrOH	50	18
5	*t*-BuOH	3	56
6	AcOH	23	31
7	H_2O:MeCN (1:5)	27	18
8	$HNEt_2$	66	n.d.

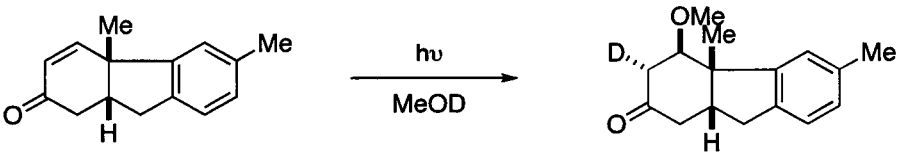
Hart and Dunkelblum observed that these 1,4-additions are stereospecific. Irradiation of 2-cycloheptenone in MeOD was proposed to occur via nucleophilic addition followed by deuteration from the exposed face, producing an adduct where the methoxy group and deuterium atom exhibit a trans relationship (Equation 2.7).[30]



(2.7)

(30) Hart, H.; Dunkelblum, E. *J. Am. Chem. Soc.* **1978**, *100*, 5141.

A similar reactivity and stereochemical relationship was observed with the six-membered Pummerer's ketone, although no mention was made as to whether such reactivity could be extended to a simple 2-cyclohexenone (Equation 2.8).[31]



(2.8)

2.1.4. Generation and Reactivity of Strained (E)-Cycloalkenes

Like their E-cycloalkenone cousins, the high ground state energy of six and seven-membered E-cycloalkenes allows for a variety of transformations under atypically mild reaction conditions. Non-photochemical approaches towards their synthesis only give useful yields for E-cyclooctene, and to date six-membered E-cycloalkenes, perhaps the most desirable and reactive of ring sizes, have not been accessed without photochemistry.[32] On the other hand, photochemical isomerization offers a rapid and efficient way to access six-membered and higher E-cycloalkenes in situ directly from cheap commercially available starting materials. However, unlike enones, simple alkenes (absorption maxima 190-200 nm) do not absorb in a practical region for typical laboratory equipment. Thus sensitized isomerization, rather than direct irradiation, is necessary.

In this section, an overview of the reactivity of E-cycloalkenes is described to highlight their potential usefulness in the development of mild acid-catalyzed hydroamination reactions.

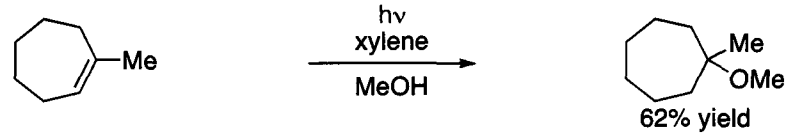
---

(31) Dunkelblum, E.; Hart, H.; Jeffares, M. *J. Org. Chem.* **1978**, *43*, 3409.

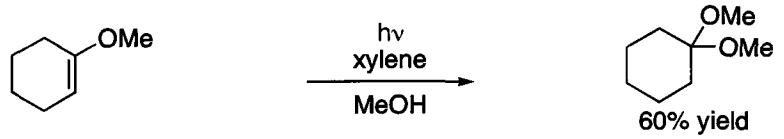
(32) (a) Corey, E. J.; Carey, F. A.; Winter, R. A. E. *J. Am. Chem. Soc.* **1965**, *87*, 934. (b) Jendralla, H.; Spur, B. *J. Chem. Soc., Chem. Commun.* **1984**, 887. (c) Coates, R. M.; Last, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 7322. (d) Dervan, P. B.; Jones, C. R. *J. Am. Chem. Soc.* **1979**, *44*, 2116. (e) Jendralla, H.; Laumen, K. *Chem. Ber.* **1983**, *116*, 2136.

2.1.4.1. Photoinduced Additions of Alcohols[33]

In 1966, the groups of Kropp and Marshall simultaneously reported that xylene-sensitized photoisomerization of six- or seven-membered cycloalkenes in the presence of methanol led to a Markovnikov hydroetherification product.[34] Kropp, in particular, showed that these photochemical reactions could be carried out on gram scales with synthetically useful yields where both alkyl and alkoxy groups were tolerated on the alkene (Equation 2.9 and Equation 2.10).[35]



(2.9)



(2.10)

2.1.4.2. Mechanism of Photoinduced Alchol Additions: Photoprotonation.

Several of Kropp and Marshall's observations need to be considered in order to postulate a mechanism.

1) Subsequent studies showed that water, other alcohols, and carboxylic acids undergo the addition reaction with Markovnikov selectivity, but only with cyclohexenes and cycloheptenes.[35]

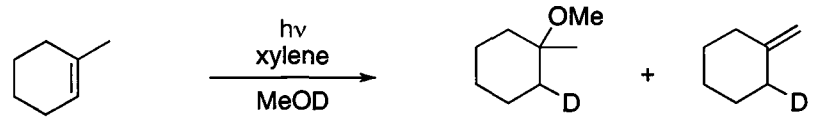
---

(33) For reviews, see: (a) Marshall, J. A. *Science* **1970**, *170*, 137. (b) Kropp, P. J. *Mol. Photochem.* **1978**, *9*, 39.

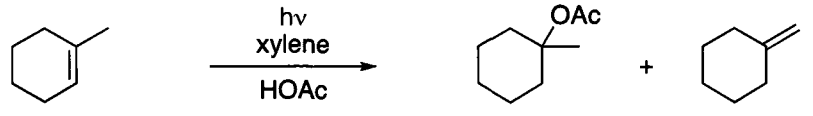
(34) (a) Kropp, P. J. *J. Am. Chem. Soc.* **1966**, *88*, 4091. (b) Marshall, J. A.; Carroll, R. D. *J. Am. Chem. Soc.* **1966**, *88*, 4092.

(35) (a) Kropp, P. J.; Krauss, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 5199. (b) Tise, F. P.; Kropp, P. J. *Org. Synth.* **1983**, *61*, 112.

2) These additions are typically accompanied by positional isomerization of the double bond to give the exocyclic product (Equation 2.11 and Equation 2.12).[36]



(2.11)



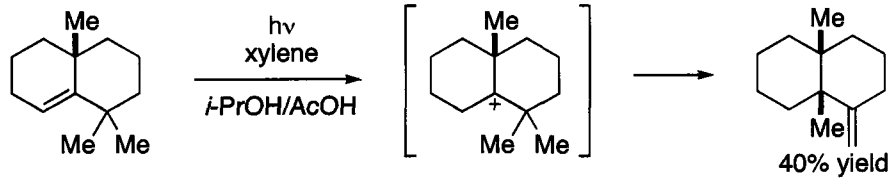
(2.12)

3) Interestingly, acyclic, exocyclic, larger and smaller ring alkenes failed to give Markovnikov addition products or positional alkene isomerization.

4) The reactions are faster at lower pH.

5) Kinetic isotope effects indicate a proton, not a hydrogen atom, is transferred to the olefin.[37]

6) Methyl migration occurs in highly substituted cyclohexenes (Equation 2.13).[38]



(2.13)

7) Rate inhibition is observed when triplet quenchers are added.[34b]

Taken together, the evidence suggests the reactions proceed by a common carbocationic pathway derived from the triplet state of the alkene. However, simple protonation of the triplet alkene does not rationalize the ring-size dependence. Cyclopentenes give free radical products,[39]

---

(36) For an example of application in total synthesis, see: Marshall, J. A.; Pike, M. T. *J. Org. Chem.* **1968**, *33*, 435.

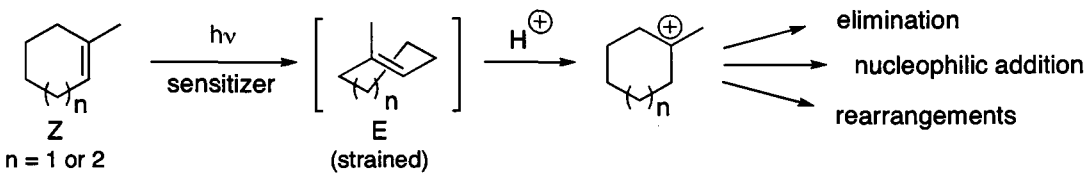
(37) Marshall, J. A.; Wurth, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 6788.

(38) Marshall, J. A.; Hochstetler, A. R. *Chem. Commun.* **1967**, 732.

(39) Kropp, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 3650.

while cyclooctenes undergo observable cis-trans isomerization or polymerization.[40] Kropp and Krauss postulated that the reaction proceeds via the triplet excited state of the cyclohexene or cycloheptene, which can isomerize to the E isomer or return to the Z (Scheme 2.2). The latter case would produce no reactivity, while the former case would result in a highly strained ground state E-cycloalkene intermediate. The severe torsional strain present in such a system would reasonably allow for alkene protonation to occur in solvents of relatively high pKa. The resulting carbocation would produce the observed ionic additions, isomerization and alkyl migrations.

Scheme 2.2. Kropp's proposed mechanism for reactivity of cyclohexenes and cycloheptenes.



This also would explain the reactivity (or lack thereof) of other alkenes. E-Cyclopentene would be far too strained to exist. Photochemical reactions of cyclopentene would therefore likely occur through the triplet state, giving reaction products consistent with a free radical mechanism. On the other hand, production of E-cyclooctene would not result in ionic reactivity, as that isomer does not possess enough strain to undergo protonation in alcohols. Similarly, no significant strain would be produced by cis-trans isomerization of acyclic alkenes, and therefore only geometric isomerization of the starting material would be observed.

Despite the large amount of indirect chemical evidence supporting this mechanism, the possibility that the intermediate could potentially be either an orthogonal triplet or an orthogonal zwitterion could not be conclusively ruled out. Direct irradiation laser flash studies of 1-

(40) Crandall, J. K.; Mayer, C. F. *J. Am. Chem. Soc.* **1967**, *89*, 4374.

phenylcyclohexene by Bonneau and coworkers identified a transient species with a lifetime of 9 μs[41] (too long to be a orthogonal triplet) that is insensitive to the presence of dissolved oxygen (a triplet quencher) and to the polar nature of the solvent (therefore unlikely to be a zwitterion).[42] The intermediate is quenched by hydrogen ion with a rate constant of $k = 7.6 \times 10^6\ M^{-1}s^{-1}$, consistent with the rapid reactivity expected of an E-cycloalkene. Finally, in 1993, Cozens and coworkers identified cationic intermediates during the laser flash photolysis of 1-phenylcyclohexene in hexafluoroisopropanol, conclusively verifying Kropp's proposed mechanism.[43]

2.1.4.3. Diastereoselectivity and the Nature of the Sensitizer

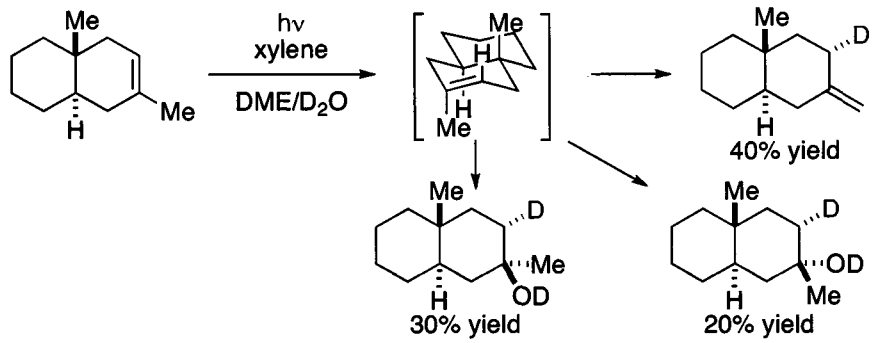
Diastereoselective protonation of unactivated alkenes possessing a chiral centre is notoriously difficult due to the high temperatures usually associated with the reaction. E-Cycloalkenes therefore are in a unique position to achieve higher diastereoselectivity, as they can be protonated by weaker acids at or below room temperature. Marshall and Wurth reported that addition of deuterium oxide to 2,10-dimethyl-trans-2-octalin under the triplet-sensitized conditions described earlier leads to deuteroetherification products with deuteration exclusively occurring from one face (Equation 2.14).[37] The subsequent ionic addition is much less selective, leading to a 3:2 mixture of diastereomers as well as 40% of the exocyclic olefin isomer.

---

(41) An orthogonal alkene triplet state is expected to have a very short lifetime. For example, the triplet-state lifetime of substituted stilbenes is around 100 ns. See: Bent, D. V.; Schulte-Frohlinde, D. *J. Phys. Chem.* **1974**, *78*, 446.

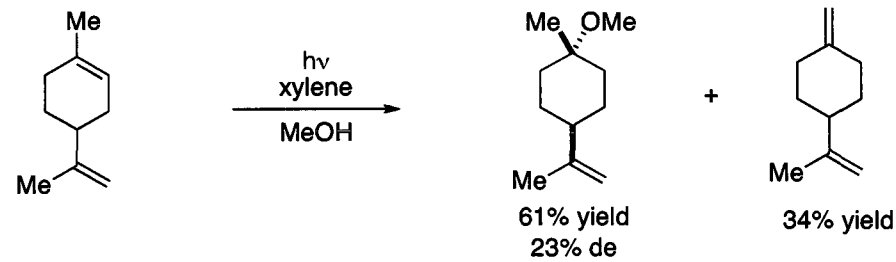
(42) Bonneau, R.; Joussot-Dubien, J.; Salem, L.; Yarwood, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 4329.

(43) Cozens, F. L.; McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.* **1993**, *115*, 5050.



(2.14)

In their original communication, Marshall and Wurth also reported on the diastereoselectivity of the hydroetherification of limonene, although they did not report experiments concerning the selectivity of the protonation step (Equation 2.15).[34b] The diastereoselectivity was similarly low, giving the adducts in 23% de and 61% yield, along with 34% exocyclic isomer and 6% starting materials.

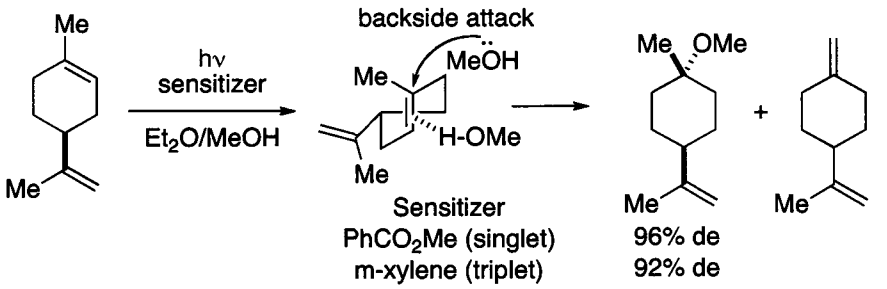


(2.15)

The Inoue group set out to develop conditions for highly diastereoselective photochemical additions by fine-tuning reaction conditions such as solvent polarity, concentration, reaction temperature and the structure and spin-multiplicity of the sensitizer. In 2002, they reported that the addition of methanol to limonene occurred in >96% de when carried out upon singlet sensitization with methyl benzoate at –75 °C in a 0.5 M methanol/diethyl ether solution (Equation 2.16).[44] Similar conditions employed with triplet sensitizer *m*-xylene give

(44) Shim, S. C.; Kim, D. S.; Yoo, D. J.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2002**, *67*, 5718.

92% de. It should be noted that reactions giving high diastereoselectivity also gave very low yield (typically <10%).

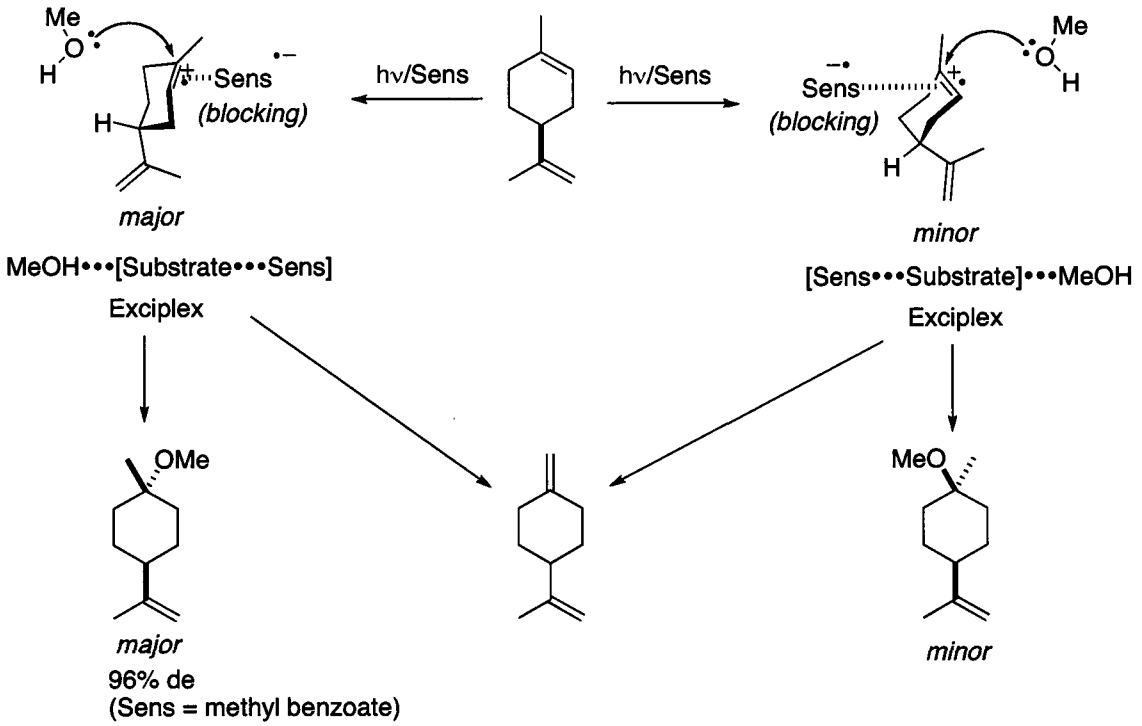


(2.16)

Besides the low temperature, the selection of solvent and sensitizer influence the mechanism and warrant further discussion. First, the use of less polar solvents was proposed to change the addition to the E-cycloalkene from a stepwise S_N1 process to one that resembles the microscopic reverse of an E2 elimination (concerted addition/protonation), thus increasing diastereodifferentiation in the transition state (Equation 2.16). Secondly, the use of the singlet sensitizer methyl benzoate was proposed to fundamentally change the mechanism, and is hence responsible for the generally higher de values observed when singlet sensitization was employed. Methyl benzoate has a smaller $S_0 \rightarrow S_1$ energy gap than an alkene and thus excitation of the alkene is only energetically possible if the two species form an exciplex.[45] In such an exciplex, Inoue and coworkers proposed the alkene possesses radical cationic character, while the sensitizer possesses radical anionic character (Scheme 2.3). Nucleophilic additon of methanol to this crowded intermediate followed by electron transfer would give the products. The necessity for strain is unclear in such a proposal, yet no mention was made as to whether acyclic alkenes were viable when singlet sensitization was employed. The increased diastereoselectivity observed with less polar solvents was attributed to the increased bulk of a tight ion pair between sensitizer and substrate.

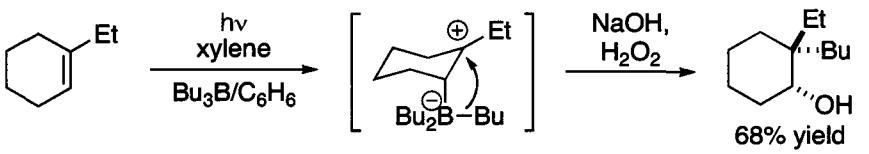
(45) For more background on sensitization, see section 2.1.1.2, pg 32.

Scheme 2.3. Inoue's proposed exciplex intermediate for singlet sensitization.



2.1.4.4. Carbometallation Reactions of E-Cycloalkenes

E-Cycloalkenes also display increased reactivity towards carbometallation reactions. In 1971, Miyamoto and coworkers disclosed that trialkylboranes undergo *syn* addition to 1-ethylcyclohexene under triplet sensitization (Equation 2.17).[46] Successive oxidation of the photolysate gives the *syn*-alcohol.



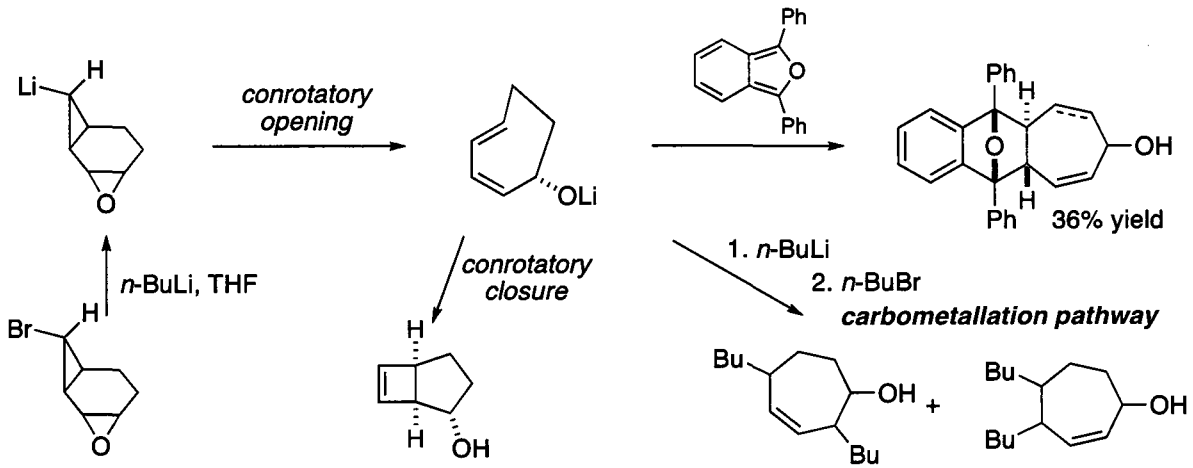
(2.17)

Coates and Last later reported that alkyllithium reagents also add to E-cycloalkenes.[32c] Their E,Z-cycloheptadiene, generated by a lithium-halogen exchange/electrocyclization

(46) (a) Miyamoto, N.; Isiyama, S.; Ultimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1971**, 4597. (b) Miyamoto, N.; Isiyama, S.; Ultimoto, K.; Nozaki, H. *Tetrahedron* **1973**, *29*, 2365.

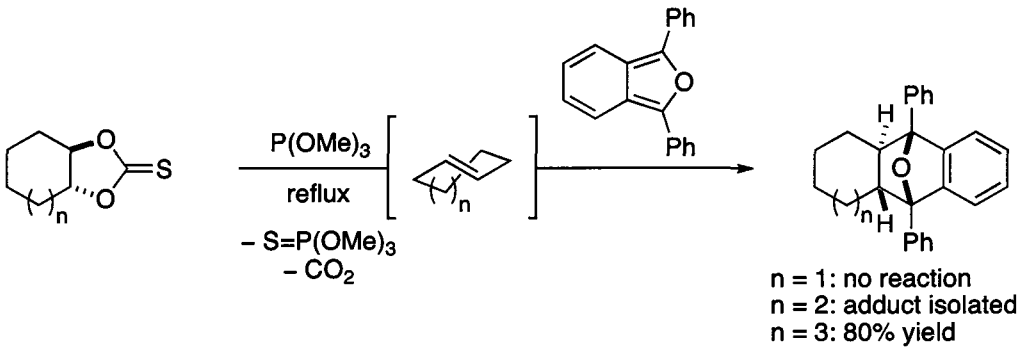
sequence, gives a regioisomeric mixture of dialkylation products upon addition of *n*-BuLi and subsequent quenching with *n*-BuBr (Scheme 2.4).

Scheme 2.4. Carbometallation of E,Z-cycloheptadienes with *n*-butyllithium.



2.1.4.5. Diels-Alder Reactions Involving E-Cycloalkenes

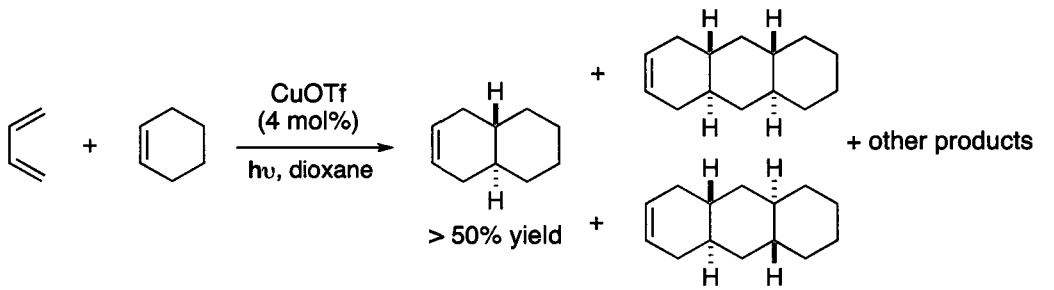
Diels-Alder reactions of E-cycloalkenes provide an extraordinarily efficient route to the synthesis of trans-bicyclic compounds. In an early attempt to find a non-photochemical route to E-cycloalkenes, Corey and coworkers generated E-cyclooctene from the corresponding *trans*-1,2-diol via a Corey-Winter olefination, and trapped it with an isobenzofuran to give the trans-fused cycloadduct in good yield (Equation 2.18).[32a]



(2.18)

Similar adducts arising from E-cycloheptene could be isolated in trace quantities, but all attempts to generate E-cyclohexene were unsuccessful. E-Cycloalkenes can also be trapped with simple dienes.[47]

Evers and Mackor reported that even Diels-Alder adducts arising from E-cyclohexene can be made under photochemical conditions in the presence of 4 mol% copper (I) triflate (Equation 2.19).[48] The metal is likely acting both as a sensitizer and a stabilizing agent for the highly reactive E-cyclohexene intermediate.



(2.19)

2.1.4.6. Enantioselective Generation of E-Cycloalkenes

Even though they do not possess an asymmetric carbon, E-cycloalkenes possess helical chirality by virtue of their internal helical twist. Much effort has been invested into the enantioselective generation of E-cycloalkenes through the use of chiral photosensitizers. The Inoue group developed the use of chiral aromatic esters as enantioselective singlet sensitizers for both E-cyclooctene and E-cycloheptene (Equation 2.20).[49,50]

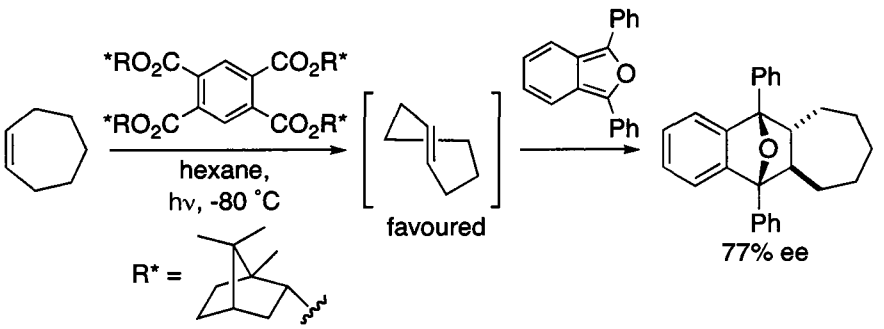
---

(47) (a) Jendralla, H. *Angew. Chem. Int. Ed.* **1980**, *19*, 1032. (b) Jendralla, H.; Spur, B. *J. Chem. Soc., Chem. Commun.* **1984**, 887.

(48) Evers, J. T. M.; Mackor, A. *Tetrahedron Lett.* **1978**, 2317.

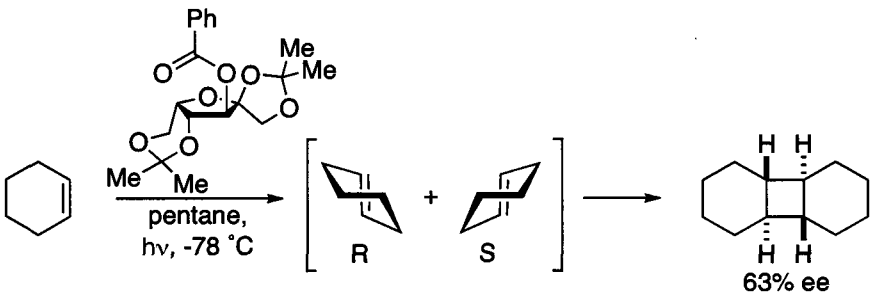
(49) Cyclooctene: (a) Inoue, Y.; Matsushima, E.; Wada, T. *J. Am. Chem. Soc.* **1998**, *120*, 10687. Cycloheptene: (b) Hoffmann, R.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10702.

(50) For a discussion of the entropic dependence of singlet sensitization, see: Inoue, Y.; Sugahara, N.; Wada, T. *Pure Appl. Chem.* **2001**, *73*, 475.



(2.20)

Reaction products arising from dimerization of E-cyclohexene could also be generated using a chiral photosensitizer approach, but in modest ee with low conversions (Equation 2.21).[51]



(2.21)

Another strategy for the enantioselective discrimination of E-cycloalkenes is via kinetic resolution with chiral metal complexes. Nishiyama and coworkers reported that E-cyclooctene binds to chiral ruthenium pybox complexes, giving exclusively one diastereomer as product (Figure 2.9).[52] The structure was confirmed by X-ray crystallography. Complexes could also be obtained with E-cycloheptene upon in situ irradiation of the Z-isomer, but as a 1:1 mixture of diastereomers. The authors attribute the lack of diastereoselectivity in this case to the smaller dihedral angle of E-cycloheptene. Another possibility is that the significantly increased strain energy of E-cycloheptene makes binding, with its accompanying partial strain release, irreversible.

(51) Asaoka, S.; Horiguchi, H.; Wada, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, *4*, 737.

(52) Nishiyama, H.; Naitoh, T.; Motoyama, Y.; Aoki, K. *Chem. Eur. J.* **1999**, *5*, 3509.

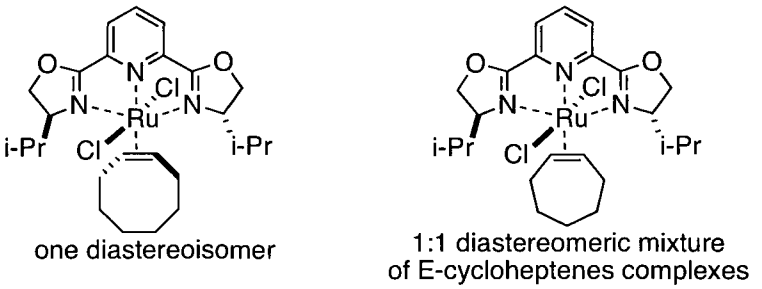


Figure 2.9. Nishiyama's E-cycloalkene metal complexes.

2.1.4.7. Thermal Trans-Cis Isomerization of E-Cycloalkenes

Despite their strain, E-cycloalkenes still possess significant thermal barriers to rotation about the π-bond. With the calculated trans-cis rotational barrier of ethylene being 65 kcal/mol and the strain energy of E-cycloheptene being 23-29 kcal/mol, the thermal trans-cis isomerization of E-cycloheptene should have a barrier of at least 35 kcal/mol.[53] In other words, E-cycloheptene should be stable and resist thermal isomerization to the Z-isomer at temperatures well above room temperature! However, experimentally, the barrier has been observed to be only 17 kcal/mol and the upper limit for thermal stability has been observed to be only -30 °C.[54] In 2005, Squillacote and coworkers rationalized the incompatibility between calculation and observation by demonstrating that E-cycloheptene undergoes a *bimolecular* decay arising from an "interrupted" dimerization, where an initially formed 1,4-biradical rapidly changes its geometry and cleaves back to produce two Z-cycloheptene molecules (Figure 2.10).[55]

(53) (a) Saltiel, J.; Charlton, J. L. In *Rearrangements in the Ground and Excited States*; DeMayo, P., Ed.; Academic Press: New York, 1980; p 25. (b) Wallaff, G. M.; Boyd, R. H.; Michl, J. *J. Am. Chem. Soc.* **1983**, *105*, 4550.

(54) (a) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Chem. Commun.* **1981**, 1031. (b) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 983. (c) Squillacote, M.; Bergman.; DeFelippis, J. *Tetrahedron Lett.* **1989**, *30*, 6805.

(55) Squillacote, M. E.; DeFellipis, J.; Shu, Q. *J. Am. Chem. Soc.* **2005**, *127*, 15983.

Presumably, such a mechanism might also be possible for E-cyclohexene. This non-productive pathway should be taken into account when designing new reactions of E-cycloalkenes.

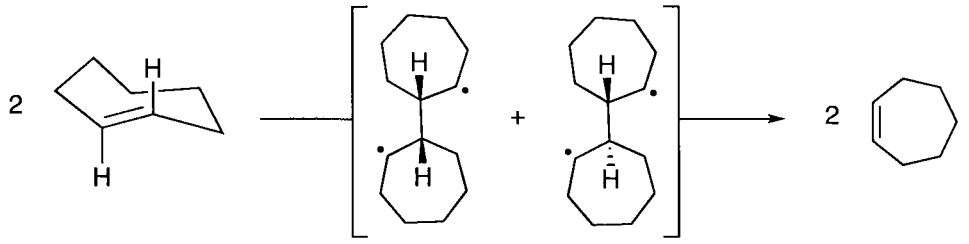


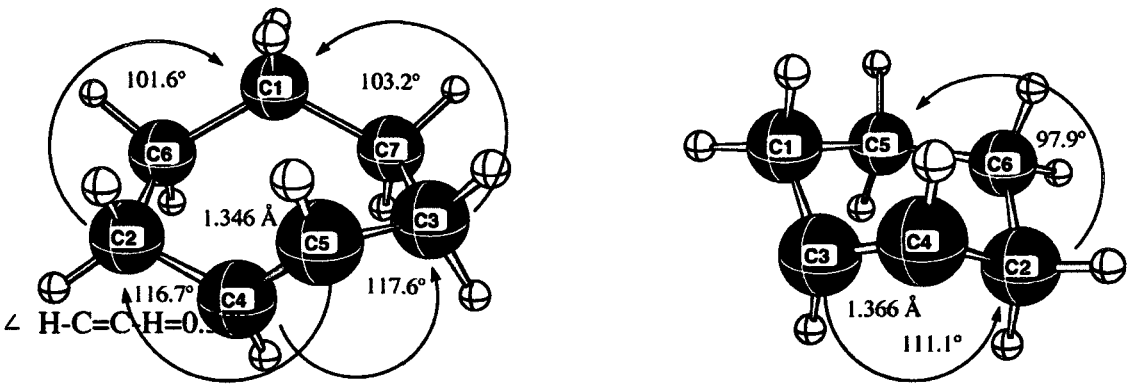
Figure 2.10. Bimolecular mechanism for trans-cis isomerization of E-cycloheptene.

2.1.4.8. Calculated Ring Strain Energies and Geometries

The high lability of E-cyclohexenes and E-cycloheptenes pose challenges to the detailed analysis of their kinetics and of their structure by spectroscopy or crystallography. Theoretical calculations are therefore especially valuable for obtaining information about these reactive intermediates. Recently, Bach disclosed ring strain energies and enthalpies of hydrogenation for both species, calculated using DFT at the highly accurate G3 level of theory.[56] The strain energies for E-cyclohexene and E-cycloheptene are calculated to be 49.3 and 25.2 kcal/mol, respectively.

Optimized geometries are shown in Figure 2.11. The geometry of the E-cyclohexene alkene is very distorted. Although the H-C=C-H dihedral angle is close to the idealized 180°, the C^1-C^3-C^4-C^2 dihedral angle is only 88.5°. The C=C-C and C^2-C^6-C^5 angles are also contracted (111.1° and 97.9°).

(56) Bach, R. D. *J. Am. Chem. Soc.* **2009**, *131*, 5233.



∠H-C=C-H=175.3°
∠C2-C4-C5-C3=117.4°
G3-E-cycloheptene

∠H-C=C-H=174.9°
∠C1-C3-C4-C2=88.5°
G3-E-cyclohexene

Figure 2.11. E-cycloheptene and E-cyclohexene optimized at the G3 level of theory.[57]

2.1.4.9. Overview of Lessons from the E-Cycloalkenone and E-Cycloalkene Literature

Several key points from this literature survey are useful in the development of mild hydroamination reactions. Six and seven-membered E-cycloalkenes are much more reactive than the Z-isomer and can undergo protonation with compounds as weakly acidic as alcohols. Therefore, acid-catalyzed additions of nitrogen nucleophiles should be possible despite a significant buffering effect. However, the photochemistry of these systems is complex due to the requirement for sensitization and the possibility of bimolecular thermal trans-cis isomerization. Other possible side-reactions include alkene isomerization and cationic skeletal rearrangements.

Given these complexities, the development of model systems involving 1,4-additions of amines to E-cycloalkenones might be useful. Seven- and eight-membered E-cycloalkenones are also highly reactive, can be excited conveniently by direct irradiation and still display electrophilic reactivity despite the lack of conjugation of their π-bonds. 1,4-Additions of

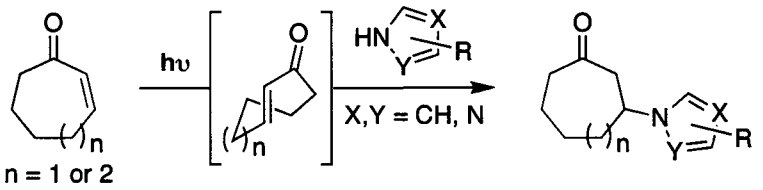
(57) Figure adapted from ref 56.

alcohols to these species are known, but only when the alcohols are used as solvents. Possible side-reactions include dimerization and photodeconjugation.

2.2. Results and Discussion

2.2.1. Photoinduced 1,4-Additions of Azoles to Cycloalkenones

As a stepping-stone towards our goal of achieving strain-release hydroamination of *unactivated* cycloalkenes, we proposed that a strain-release approach could enable the 1,4-addition of nitrogen nucleophiles to cycloalkenones (a formal yet less challenging hydroamination reaction) under very mild conditions. Herein we report results demonstrating that efficient strain-release activation via E-cycloalkenones is possible, and leads to near stoichiometric 1,4-addition of various nitrogen heterocycles to cyclohept-2-enones and cyclooct-2-enone upon photoisomerization at room temperature in a variety of solvents (Equation 2.22).



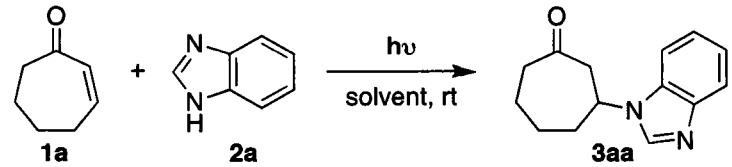
(2.22)

Initial experiments showed that benzimidazole (**2a**) reacts efficiently with cyclohept-2-enone (**1a**) upon irradiation with UVA lamps (ca. 350 nm) in a CH_2Cl_2/MeCN (8:1) mixture, affording the 1,4-adduct in 94% isolated yield. To our delight, the reactivity proved general in a variety of solvents (Table 2.2), with little or no thermal reaction observed in samples not exposed to UV light. The use of a 8:1 mixture of CH_2Cl_2/MeCN was selected for substrate scope determination as these conditions allow solubilization of most heterocycles while minimizing the likelihood of a thermal reaction involving the cis form of the cycloalkenone.

The substrate scope with respect to various nitrogen heterocycles is shown in Table 2.3.[58]

(58) In control experiments, no 1,4-addition was observed with **2a-c**, **2e-h** under identical conditions but in the absence of UV light. In contrast, **2d** led to 53% conversion (vs. >99% conversion upon UV irradiation).

Table 2.2. Solvent and concentration effects in the reaction of **1a** with **2a**.[a,b]



1a **2a** **3aa**

entry	solvent	[**1a**], mol/L	conversion (%)[c]
1	$PhCF_3$	0.05	37
2	Et_2O	0.05	58
3	THF	0.05	86
4	EtOAc	0.05	91
5	CH_2Cl_2/MeCN (8:1)		
6	"	0.05	94
7	"		
8	MeCN	0.05	94
9	*i*-PrOH	0.05	71
10	DMSO	0.05	55

[a] Reaction conditions: Enone (1 equiv), benzimidazole (3 equiv), UVA bulbs (ca. 350 nm), 16 h. [b] Samples not subjected to UVA irradiation showed no conversion, except in *i*-PrOH (11%) and THF (<5%). [c] Determined by ^{1}H NMR relative to unreacted starting material.

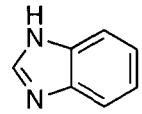
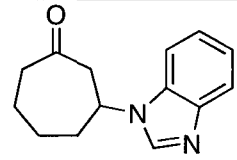
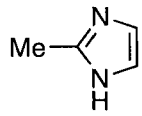
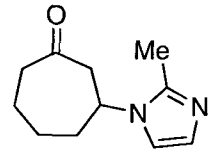
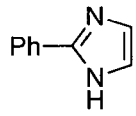
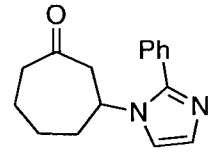
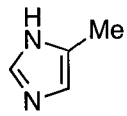
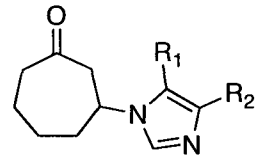
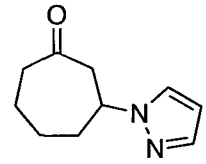
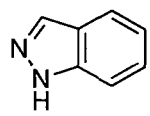
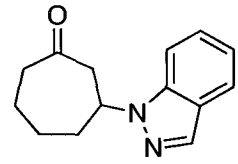
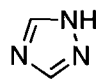
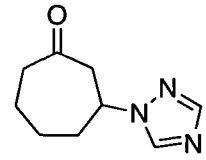
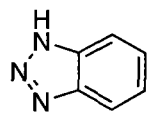
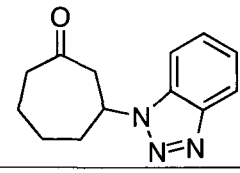
Various imidazoles reacted to afford the 1,4-adducts in good yield (entries 1-4).[59] Substitution at the 2 and 4 positions was tolerated (entries 2-4), and 7:1 selectivity was observed for 4-methylimidazole, favouring attack from the least hindered nitrogen atom (entry 4).[60] The reaction was also efficient with pyrazoles, with pyrazole and benzopyrazole affording the desired product in 99 and 92% yield, respectively (entries 5-6). Triazoles also added efficiently under the reaction conditions (entries 7-8). The observed selectivity for the reaction of benzotriazole (entry 8) was in agreement with that typically observed for related reactions.[61]

(59) In contrast with the nucleophiles shown in table 2, imidazole underwent a high yielding thermal addition with Z-cycloheptenone.

(60) Mr. Peter Dornan is thanked for his assistance with these substrates.

(61) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

Table 2.3. Nucleophile scope for the reaction of azoles with **1a**.[a]

entry	nucleophile		product(s)		yield(%)[b]
1		**2a**		**3aa**	94
2		**2b**		**3ab**	70
3		**2c**		**3ac**	44
4		**2d**		**3ad**	73[c]
5		**2e**		**3ae**	99
6		**2f**		**3af**	92
7		**2g**		**3ag**	66
8		**2h**		**3ah**	53[d]

[a] Reaction conditions: 2-Cycloheptenone (1 equiv), azole (3 equiv), UVA bulbs (ca. 350 nm), CH_2Cl_2/MeCN (8:1), 16 h. [b] Isolated yield after column chromatography. [c] 7 (R_1= H, R_2 = Me): 1 (R_1 = Me, R_2 = H) inseparable mixture of isomers. [d] 11% of the parent N2 isomer was also isolated.

As shown in Table 2.4, the enone substrate scope was consistent with that of other reactions involving E-cycloalkenones.[17,20] For entries 1-6, benzimidazole was selected as

nucleophile as only a very slow thermal reaction, if any, was observed at room temperature in a CH_2Cl_2/MeCN mixture with these substrates. However, upon irradiation, a very clean conversion to the 1,4-adducts was observed. Cyclohept-2-enone and cyclooct-2-enone afforded these products in 94% and 90% yield, respectively (entries 1-2). Substituted cyclohept-2-enones also reacted efficiently (entries 3-4) and cycloheptadienone afforded the monoadduct in 51% yield (entry 5), despite the possibility of double addition or Nazarov cyclization.[62] In addition, substitution at the 4-position was also tolerated, and afforded the 1,4-adducts as mixtures of diastereoisomers (entries 6-7). Notably, irradiation of a cyclohex-2-enone and benzimidazole mixture under identical reaction conditions did not lead to any photoinduced reactivity, in agreement with the expected propensity of the highly strained E-cyclohex-2-enone to isomerize back to Z-cyclohex-2-enone (if formed).[63] Similarly, no photoinduced reactivity was observed upon irradiation of a mixture of several other cyclic and acyclic enones with benzimidazole (Figure 2.12).

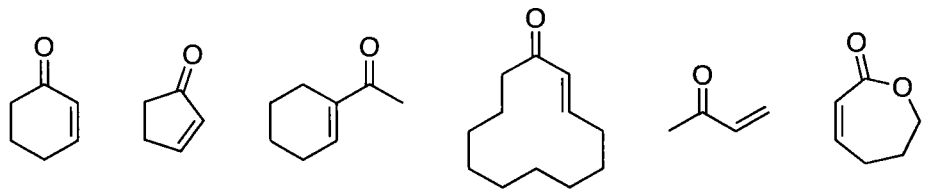
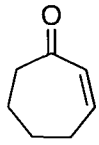
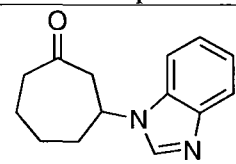
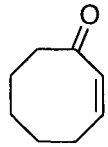
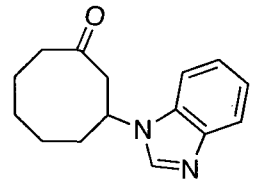
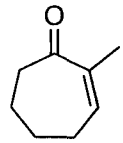
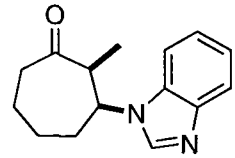
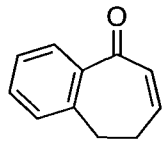
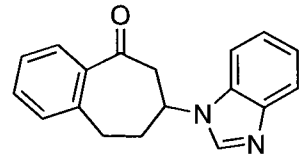
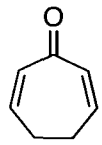
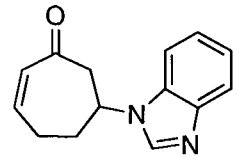
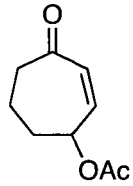
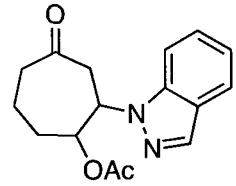
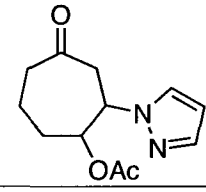


Figure 2.12. Unsuccessful substrates for photoinduced reactivity with benzimidazole.

(62) Nozaki, H.; Kurita, M.; Noyori, R. *Tetrahedron Lett.* **1968**, 3635.

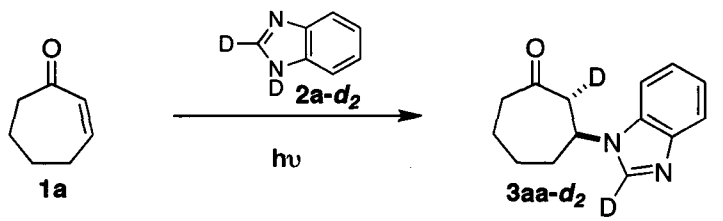
(63) E-Cyclohex-2-enones have been invoked as intermediates in a number of reactions. However, they have not been observed directly by low temperature laser flash photolysis and are expected to be very short lived, if formed. For a discussion, see: Schuster, D. I. in *CRC Handbook of Organic Photochemistry and Photobiology*, Horspool, W. M., Song, P.-S., Eds, CRC Press, 1995, chapter 48.

Table 2.4. Electrophile scope for the reaction of cycloalkenones with azoles.[a]

entry	electrophile		product		yield(%)[b]
1		**1a**		**3aa**	94
2		**1b**		**3ba**	90
3		**1c**		**3ca**	66[c]
4		**1d**		**3da**	92
5		**1e**		**3ea**	51
6		**1f**		**3ff**	79[d]
7	**1f**			**3fe**	87[e]

[a] Reaction conditions: 2-Cycloalkenone (1 equiv), azole (3 equiv), UVA bulbs (ca. 350 nm), 16 h. [b] Isolated yield after column chromatography. [c] 12:1 dr (cis:trans). [d] 1.3:1 dr (cis:trans). [e] 1.1:1 dr (cis:trans).

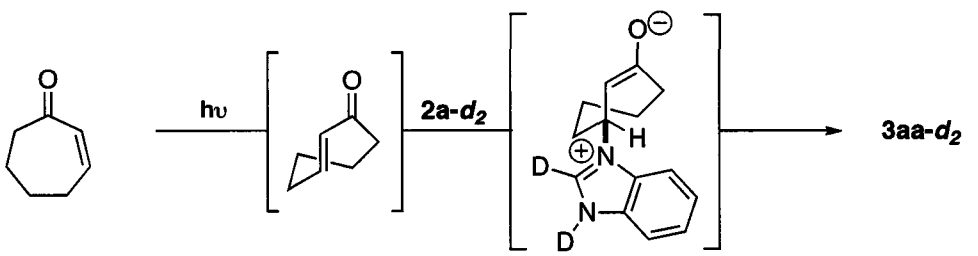
Interestingly, the addition of deuterated benzimidazole **2a-d_2** to cyclohept-2-enone is stereospecific (Equation 2.23). This result is in good agreement with the stereochemical outcome of solvolysis reactions outlined in Equation 2.7.



(2.23)

A plausible mechanism for the formation of **3aa-d_2** involves the 1,4-addition to E-cycloheptenone, forming a zwitterionic intermediate (Scheme 2.5). After conformational relaxation, deuteron transfer (likely involving **2a-d_2**) and subsequent proton transfer would provide adduct **3aa-d_2** selectively. A similar rationale has been proposed by Hart and Dunkelblum (Equation 2.7).[30]

Scheme 2.5. Proposed mechanism for 1,4-addition of azoles to 2-cycloheptenone.

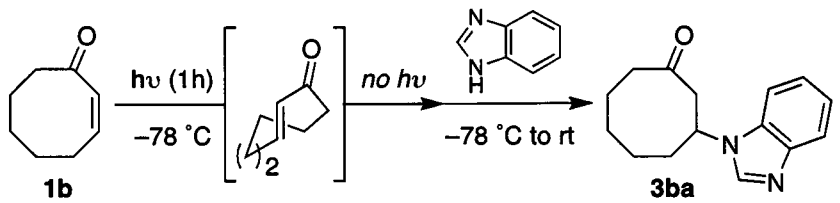


Despite a substrate scope consistent with the reactivity of a E-cycloalkenone intermediate, more conclusive evidence was needed.[64] Therefore, we performed low temperature generation/trapping experiments,[65] which involved generation of the strained ground state intermediate upon UV irradiation of a cyclooct-2-enone solution in CH_2Cl_2 at –78 °C. After one hour, the irradiation was stopped, the flask was covered with aluminium foil, benzimidazole was added and the mixture was allowed to warm to room temperature. A modest 18% conversion to

(64) E-Cyclohept-2-enone has been observed by laser flash photolysis: Bonneau, R.; Fornier de Violet, P.; Joussot-Dubien, J. *Nouv. J. Chim.* **1977**, *1*, 31.

(65) For other low temperature generation/trapping experiments, see references 20a and 29. Such experiments are based on the longer lifetimes of ground state intermediates compared to excited states, which are known to rapidly decay to the ground state (typically << 1 s).

the 1,4-adduct **3ba** was observed; suggesting that a long-lived strained E-cycloalkenone ground state intermediate is involved in this transformation (Equation 2.24). In the absence of irradiation, no conversion to the 1,4-adduct was observed under similar conditions.



(2.24)

Seeking a more definitive proof for the likely ground state intermediate, we repeated the reaction shown in Equation 2.24 in CD_2Cl_2/CD_3CN and monitored the reaction by low temperature NMR. Following enone irradiation at –75 °C in an NMR tube, benzimidazole was added and the sample was inserted in the NMR probe (pre-cooled to –20 °C). An initial spectra (ii, Figure 2.13) confirmed that photoisomerization had occurred, leading to the appearance of E-cyclooctenone (**(E)-1b** , **B**, diagnostic $J_{CH=CH}$ = 18.0 Hz)[17] and only traces of 1,4-adduct **3ba** were observed at that temperature. A comparison of the relative chemical shifts of the two vinylic protons for **(Z)-1b** and **(E)-1b** indicate that the ketone of E-cyclooctenone is no longer conjugated with the alkene. For **(Z)-1b**, the doublet at 5.9 ppm and the doublet of triplets at 6.3 ppm are consistent with the anisotropy of a conjugated system. However, for **(E)-1b**, the doublet is observed at 6.4 ppm and the doublet of triplets has shifted upfield to 5.7 ppm, consistent with the inductive effects expected in an unconjugated system. Upon warming to 10 °C (over ca. 10 minutes), **(E)-1b** reacted efficiently to afford **3ba**, as judged by the similar ratios relative to **(Z)-1b** [**B/A** = 0.29 in spectra ii *vs* **C/A** = 0.28 in spectra iii]. This finding suggests that only little unproductive E to Z thermal isomerization occurred under the reaction conditions. Overall, these results support the involvement of highly strained E-cycloalkenone ground state intermediates under the reaction conditions.

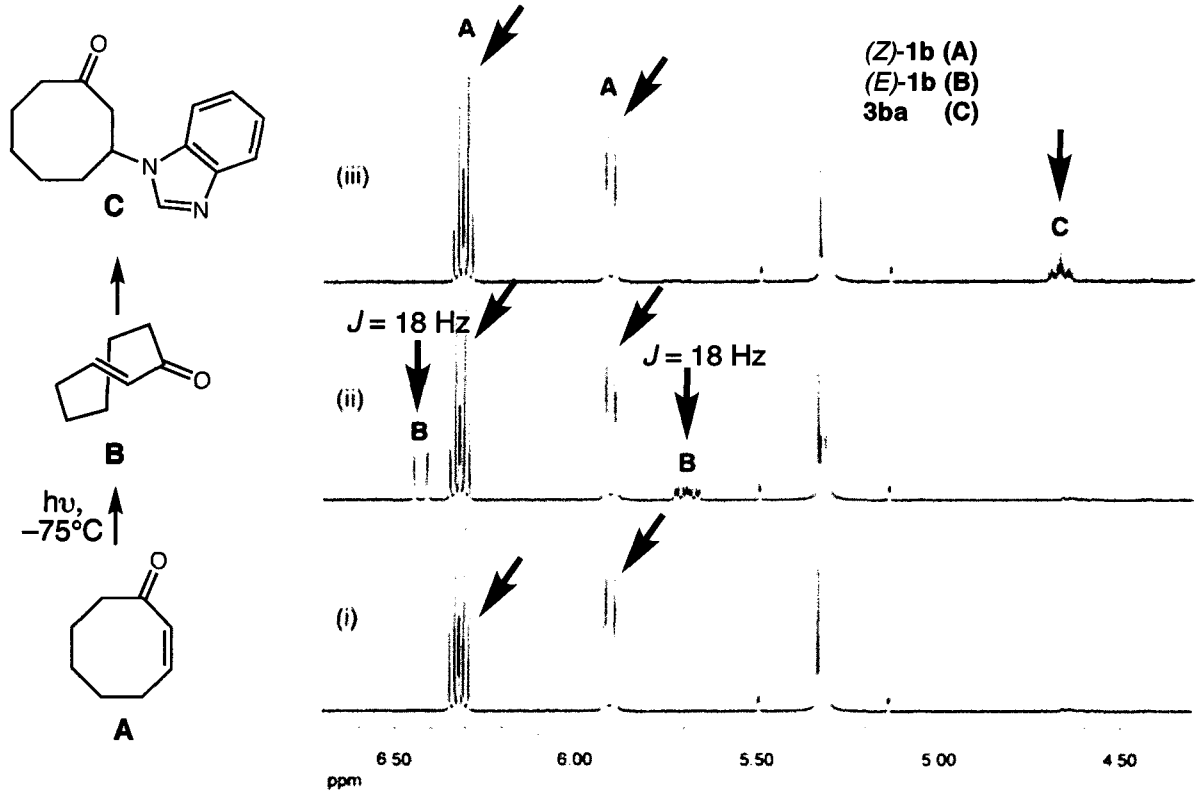


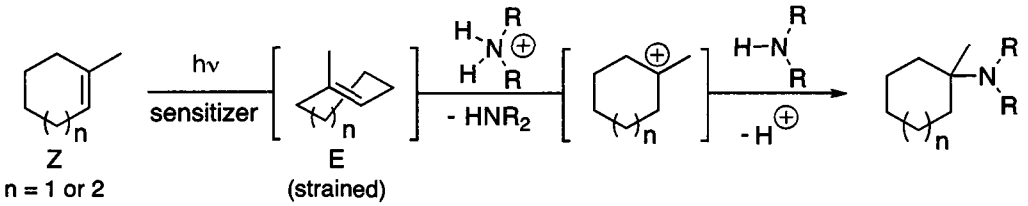
Figure 2.13. ^{1}H NMR monitoring of low temperature generation / trapping experiments (Equation 2.24). (i) Spectrum before photoisomerization (350 nm) at –78 °C; (ii) spectrum after photoisomerization, but before addition of benzimidazole (**2a**); (iii) spectrum after addition of excess **2a** and warming to 10 °C.

In summary, we have demonstrated that significant electrophilic activation can be achieved via E-cycloalkenones, leading to near stoichiometric 1,4-addition of imidazoles, pyrazoles and triazoles upon UV irradiation of 7- and 8-membered cycloalkenones. With this knowledge in hand, we then turned our efforts towards the considerably more difficult challenge of achieving strain-release intermolecular hydroamination of unactivated alkenes.

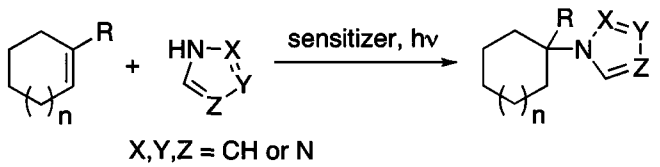
2.2.2. Photoinduced Hydroamination of Azoles with Unactivated Cycloalkenes

Inspired by the work of Kropp, Marshall and Inoue on the intermolecular hydroetherification of strained E-cycloalkenes (section 2.1.4.1), we set out to develop mild hydroamination reactions of unactivated cycloalkenes (Scheme 2.6).[34-39, 44]

Scheme 2.6. Mechanistic hypothesis for acid-catalyzed hydroamination of E-cycloalkenes.



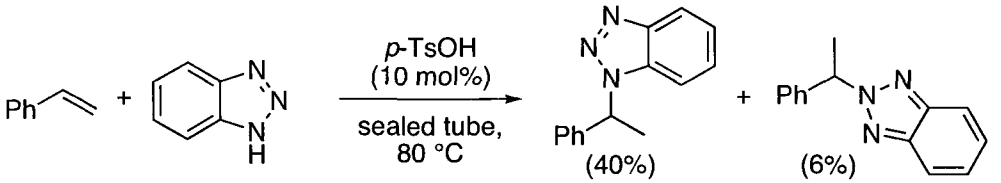
Several key challenges to their discovery exist. First, the practical necessity for *sensitization* greatly increases the photochemical complexity of the system compared to the chemistry of cycloalkenones. The sensitizer must carry out its energy transfer without interference from the alkene, amine, solvent or other additives. Secondly, ionic additions to E-cycloalkenes have been described only when the nucleophiles are employed as *solvents*. For an efficient reaction, conditions must be found where only a near-stoichiometric quantity of amine is required. Herein, we report that this strain-release approach can be used to perform intermolecular hydroaminations using azole nucleophiles (Equation 2.25).



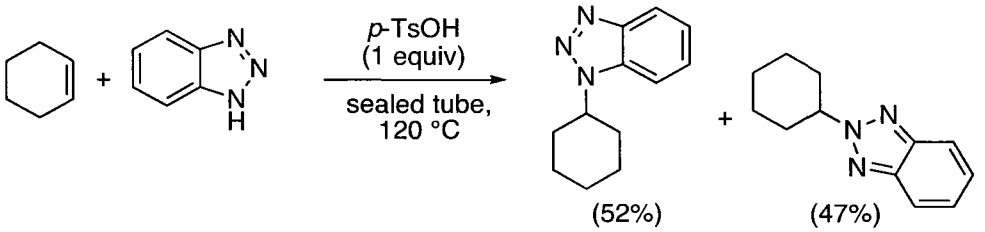
(2.25)

Reported additions of azoles to electron-rich alkenes are scarce.[5] A representative, well-studied system involves the acid-catalyzed addition of benzotriazole to various alkenes. Katritzky and co-workers have shown that benzotriazole will form a mixture of hydroamination

products in the presence of a strong acid additive and excess alkene.[5a] While styrene affords the desired hydroamination products in the presence of catalytic amounts of *p*-TsOH at 80 °C (Equation 2.26), cyclohexene requires the use of a stoichiometric amount of *p*-TsOH at 120 °C (Equation 2.27). Typically, alkene isomerization (if possible) also occurs under the latter conditions.



(2.26)

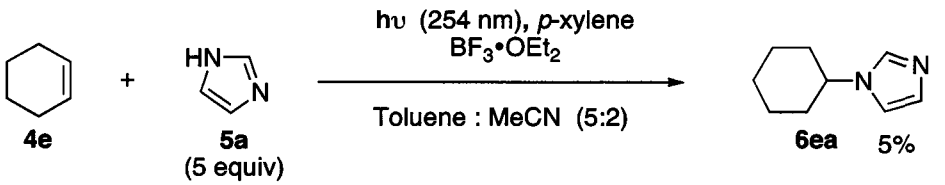


(2.27)

We embarked on our search for conditions by drawing precedence from the work of Kropp and Marshall, in which xylenes (or *p*-xylene) are used as a triplet sensitizer and the nucleophile, MeOH, is used as a solvent (see section 2.1.4.1). Our initial goal was to identify conditions in which the nucleophile could be used in near stoichiometric quantities.

Cyclohexene was initially chosen for preliminary investigation and screened against a variety of representative nitrogen nucleophiles (alkyl amines, anilines, indoles, amides and azoles) using triplet sensitizers such as toluene and *p*-xylene as solvents. The reactions were carried out in quartz tubes and irradiated with UVC bulbs (254 nm) while stirring. Acetonitrile was sometimes employed as co-solvent for less soluble nitrogen nucleophiles. Although complex mixtures of compounds and polymerization were observed upon irradiation for several hours, no

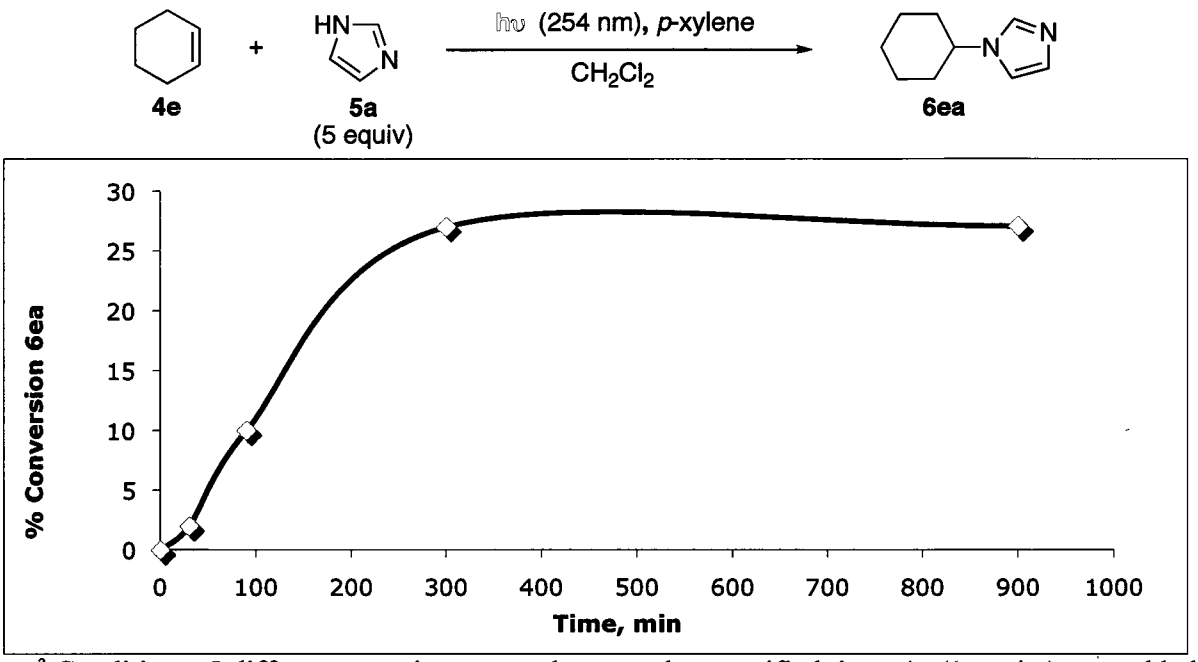
hydroamination products could be detected.[66] We then investigated the effect of Lewis acid additives in a variety of solvents. The lead hit revealed that cyclohexene undergoes hydroamination to give **6ea** in a modest 5% yield upon irradiation in the presence of *p*-xylene, excess imidazole and a stoichiometric amount of boron trifluoride etherate (Equation 2.28). The product was isolated from a complex mixture of compounds after several attempts. Control experiments showed that the Lewis acid was not necessary, and an identical yield was obtained when the reaction was performed without boron trifluoride.



4e + **5a** (5 equiv) → **6ea** 5% (2.28)

A solvent scan revealed an unusually severe solvent dependence. The reaction gave no more than 5% (typically no reactivity observed) in all solvents tested under these conditions *except* in CH_2Cl_2, where at an alkene concentration of 0.05 M, the yield increased to 27%. All other attempts to probe the reaction were unsuccessful. Acidic additives showed no improved reactivity while basic additives slowed or completely stopped the reaction. Varying the sensitizer concentration had no effect within the range tested (0.01-5.0 equiv). Time trial experiments showed a reaction plateau after 5 hours (Figure 2.14).

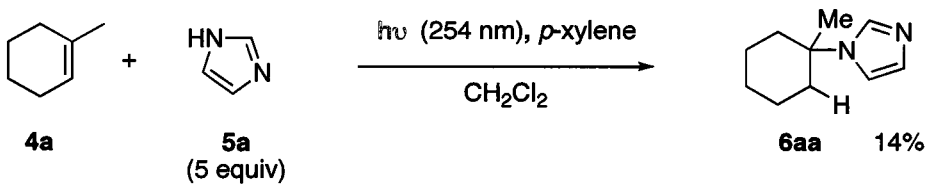
(66) Traces of *N*-cyclohexylacetamide arising from a Ritter amination of cyclohexene were deteced by GC-MS.



[a] Conditions: 5 different experiments, each stopped at specified time. **4a** (1 equiv.) was added to a solution of **5a** (5 equiv.), sensitizer (7% v/v for *p*-xylene or 1.8 equiv. of $PhCO_2Me$), and solvent (0.05 M) in a quartz tube under N_2, then irradiated with UVC lamps (254 nm) at rt. [b] Conversions were determined by ^1H NMR based on imidazole resonances

Figure 2.14. Plot of Conversion of **6ea** vs Time.

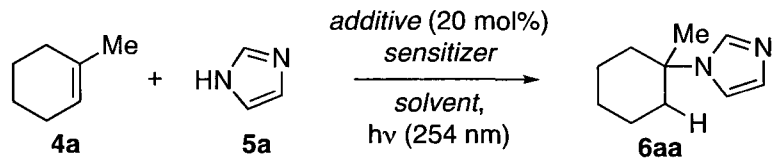
Reasoning that perhaps the secondary carbocation that might be initially formed upon protonation was too unstable to survive in a non-polar solvent at room temperature, we turned to 1-methyl-1-cyclohexene (**4a**), as this substrate could form a more stable tertiary carbocationic intermediate and hence offered a better chance for success. Unfortunately, exposure of **4a** to the best conditions gave the hydroamination product **6aa** in only 14% yield (Equation 2.29).



(2.29)

At this point, ongoing experimentation in another area displayed a similar puzzling solvent dependence on dichloromethane and inhibition by basic additives.[67] Taken together, these results led us to believe that the observed solvent effects were not due to unique dielectric properties of the solvent, but due to photogeneration of an acidic species (presumably HCl) from CH_2Cl_2. The groups of Inoue and Galvez have also made such a proposal.[44,68] If true, CH_2Cl_2 was likely not the optimal solvent, nor was the photogenerated species the optimal acidic additive. Thus, concurrent reinvestigation of solvent and acidic additives was undertaken. Highlights from the initial screening (38 experiments) with 1-methyl-1-cyclohexene are presented in Table 2.5.

Table 2.5. Selected Optimization Data Highlighting the Importance of Sensitizer and Additives to Achieve Intermolecular Hydroamination[a]



4a **5a** **6aa**

entry	additive	sensitizer	solvent	conversion (%)[b]
1	—	*p*-xylene	dioxane	0
2	AcOH	*p*-xylene	dioxane	4
3	TfOH	*p*-xylene	dioxane	13
4	TfOH	*p*-xylene	EtOAc	5
5	TfOH	$PhCO_2Me$	dioxane	14
6	TfOH	$PhCO_2Me$	dioxane	26[c]
7 (**no hv**)	TfOH	$PhCO_2Me$	dioxane	0

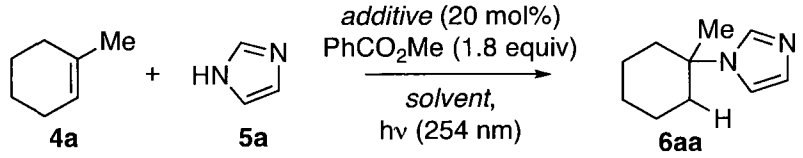
[a] Conditions: **4a** (1 equiv.) was added to a solution of **5a** (7.6 equiv.), additive (20 mol%), sensitizer (7% v/v for *p*-xylene or 1.8 equiv. of $PhCO_2Me$), and solvent (0.05 M) in a quartz tube under N_2, then irradiated with UVC lamps (254 nm) for 18 hours at rt. [b] Conversions were determined by ^1H NMR based on imidazole resonances [c] Only 1.0 equiv. of imidazole was used.

(67) Over the course of these studies, we discovered that indoles react with enones, likely via a photoinduced electron transfer mechanism: Moran, J.; Suen, T.; Beauchemin, A. M. *J. Org. Chem.* **2006**, *71*, 676. See Appendix I.

(68) Claret, J.; Fernandez, I.; Galvez, C.; Lapouyade, R. *J. Photochem. Photobiol. A: Chem.* **1991**, *55*, 347.

Again, attempts to perform photoinduced, direct hydroamination in a variety of solvents failed, as illustrated in entry 1. The addition of 20 mol% of an acid additive (leading to the *in situ* formation of the imidazolium conjugate acid) to facilitate protonation of the putative E-cycloalkene intermediate provided our initial leads (entries 2-3) and our results are consistent with the counterion effects documented by Anderson, Arnold and Bergman (entry 3).[4a] While encouraging reactivity was observed in various solvents (entries 3-4 are representative examples), multiple products could be seen in the unpurified reaction mixture. Inspired by the elegant work of Inoue using benzoates as singlet sensitizers,[14,44] methyl benzoate-sensitized photoisomerization was explored and led to a similar conversion (entry 5) but minimized the side-reactions associated with the use of *p*-xylene as triplet sensitizer. Importantly, irradiation of an equimolar mixture of 1-methylcyclohexene and imidazole using $PhCO_2Me$ as sensitizer led to a 26% conversion to the desired product (entry 6) and served as the starting point for the reaction optimization presented in Table 2.6. Control experiments were routinely performed during this investigation and *in all cases no hydroamination could be observed in the absence of UV irradiation*, which is consistent with the buffering effect of azoles (illustrated by Table 2.5, entry 7).

Table 2.6. Optimization Using Methyl Benzoate as Sensitizer[a]



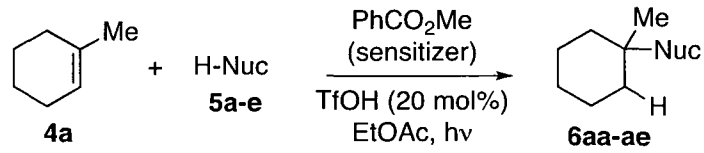
4a 5a 6aa

entry	solvent	additive	alkene/azole ratio	conversion (%)[b]
1	Dioxane	TfOH	1:1	26
2	EtOAc	TfOH	1:1	22
3	EtOAc	AcOH	1:1	0
4	EtOAc	CF_3CO_2H	1:1	7
5	EtOAc	TfOH	1:2	18
6	EtOAc	TfOH	5:1	23
7	EtOAc	TfOH	5:1[d]	72

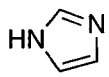
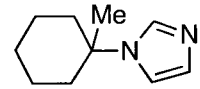
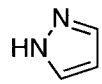
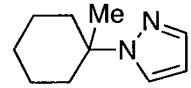
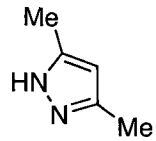
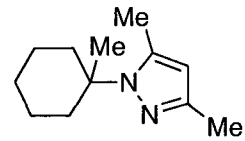
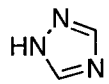
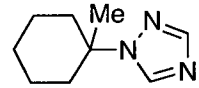
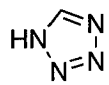
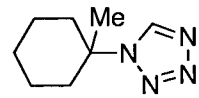
[a] Conditions: **4a** was added to a solution of **5a** (molar ratio shown), additive (20 mol%), $PhCO_2Me$ (1.8 equiv.), and solvent (0.05 M) in a quartz tube under N_2, then irradiated with UVC lamps (254 nm) for 18 hours at rt. [b] Conversions were determined by ^1H NMR based on imidazole resonances. [d] 1 equiv of **4a** was added every 6-12 h.

Solvent and counterion effects were briefly reinvestigated using methyl benzoate as sensitizer and both the use of imidazolium *trifluoromethanesulfonate* as a conjugate acid and EtOAc as solvent were found to be optimal (Table 2.6, entry 2). Surprisingly, increasing the ratio in favour of one of the reactants had only a minimal impact on the reaction outcome (entries 5-6). Stimulated by the work of Squillacote and co-workers suggesting that E-cycloalkenes undergo a thermal bimolecular E-Z isomerization,[55] we performed the reaction by adding the excess alkene in five portions over the course of approximately 30 hours, rather than at once. This new procedure led to a significant improvement: 72% conversion to the desired hydroamination product was observed (entry 7 vs. entry 6). With optimized conditions in hand, we could examine the reaction scope with respect to the azole reacting partner. These studies were performed using 1-methyl-1-cyclohexene as substrate and are presented in Table 2.7.

Table 2.7. Photoinduced Additions of Azoles to 1-Methyl-1-cyclohexene[a]



4a 6aa-ae

entry	azole		product		yield(%)[b]
1		**5a**		**6aa**	72
2		**5b**		**6ab**	72
3		**5c**		**6ac**	47
4		**5d**		**6ad**	68
5		**5e**		**6ae**	74

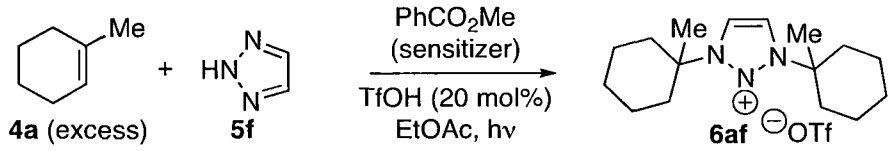
[a] Conditions: **1a** (0.41 mmol) was added to a solution of nitrogen heterocycle (0.41 mmol), TfOH (20 mol%), $PhCO_2Me$ (1.8 equiv.) and EtOAc (8 mL) in a quartz tube under N_2, then irradiated with UVC lamps (254 nm) at rt. Additional 1-methyl-1-cyclohexene was added portion-wise over time (1 equiv / 6-12 hours to a total of 5 equiv) with continued irradiation. [b] Isolated yield.

The hydroamination reactivity discovered with imidazole (Table 2.7, entry 1) extended well to other azole nucleophiles. For example, pyrazoles (entries 2 and 3) led to the formation of the desired adducts, albeit in lower yield with the hindered 2,5-dimethylpyrazole (**5c**, entry 3). 1,2,4-Triazole (entry 4) and tetrazole[69] (entry 5) also afforded the desired products in good yield. An unexpected result was obtained with 1,2,3-triazole, which afforded the nitrenium salt **6af** in an unoptimized 20% yield (Equation 2.30). Such nitrenium salts have been shown by Boche to have remarkable properties,[70] as expected based on their isoelectronic nature with the related

(69) Ms. Pamela H. Cebrowski is thanked for her assistance with this entry.

(70) Boche, G.; Andrews, P.; Harms, K.; Marsch, M.; Rangappa, K. S.; Schimeczek, M.; Willeke, C. *J. Am. Chem.*

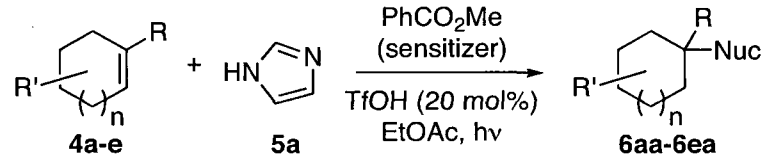
Arduango carbenes.[71] Therefore, the method provides simple access to hindered nitrenium derivatives such as **6af**. Azoles possessing phenyl chromophores (e.g. bezimidazole and purine) were not successful.



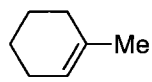
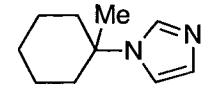
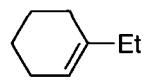
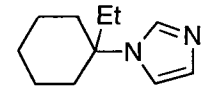
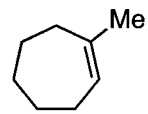
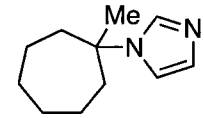
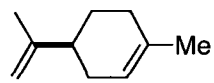
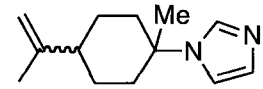
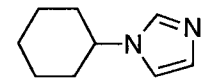
4a (excess) **5f** **6af** (2.30)

With the azole scope explored, we turned our attention to the reaction of other cyclic alkenes with imidazole. These results are presented in Table 2.8.

Table 2.8. Photoinduced Additions of Imidazole to Cyclic Alkenes[a]



4a-e **5a** **6aa-6ea**

entry	alkene		product		yield(%)[b]
1		**4a**		**6aa**	72
2		**4b**		**6ba**	40
3		**4c**		**6ca**	45
4		**4d**		**6da**	81[c]
5		**4e**		**6ea**	26

[a] Conditions: Cycloalkene (0.41 mmol) was added to a solution of imidazole (0.41 mmol), TfOH (20 mol%), $PhCO_2Me$ (1.8 equiv.) and EtOAc (8 mL) in a quartz tube under N_2, then irradiated with UVC lamps (254 nm) at rt. Additional cycloalkene was added portion-wise over

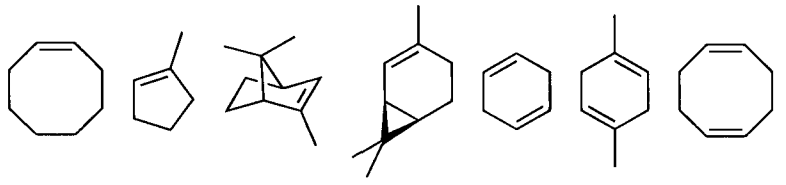
Soc. **1996**, *118*, 4925.

(71) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

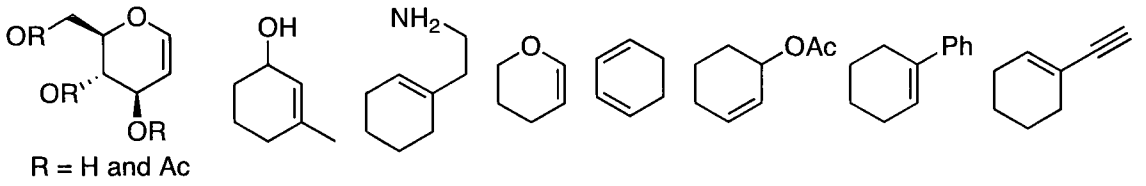
time (1 equiv / 6-12 hours to a total of 5 equiv) with continued irradiation. [b] Isolated yield. [c] 1.3:1 mixture of diastereoisomers.

The hydroamination reactivity observed with 1-methyl-1-cyclohexene and imidazole (Table 2.8, entry 1) could also be extended to other alkenes. Variation of the alkene substituent or of the ring size led to somewhat lower yields, as shown by the reaction of 1-ethyl-1-cyclohexene[69] (entry 2) and 1-methyl-1-cycloheptene (entry 3). Encouragingly, (–)-limonene (**4d**) led to selective hydroamination of the cyclic alkene,[72] with a mixture of diastereoisomers isolated in good yield (entry 4). The use of cyclohexene (**4e**) led to the hydroamination product in modest yield (entry 5).

Too much (or not enough) ring strain



Photochemical interference from functional groups or by conjugation



Successful but low yielding (<10% conversion)

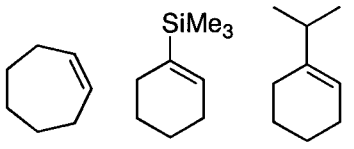
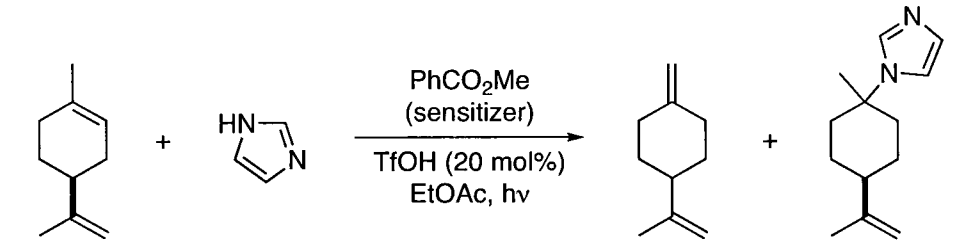


Figure 2.15. Unsuccessful or low-yielding cycloalkenes substrates.

(72) This selectivity for the cyclic alkene in limonene, as well as the lack of reactivity observed with 1-methylcyclopentene, cyclooctene and in control experiments performed with other cyclic alkenes (α-pinene and 2-carene, for example) strongly suggest the intermediacy of highly strained E-cycloalkene intermediates. We also prefer this rationale over other possibilities, including reactivity arising from azole excited states being more acidic, for example.

Unsuccessful cycloalkene substrates can generally be divided into three categories (Figure 2.15). The first category involves alkenes that either do not form enough strain upon isomerization (e.g. cyclooctene) or that are too strained to form (e.g. 1-methylpentene and 1,4-cyclohexadiene). The second category includes substrates that possess functional groups or conjugation that appears to interfere with the necessary photochemical processes involved in photoisomerization (e.g. 1-phenylcyclohexene). The third includes alkenes that were successful but low yielding, usually due to steric bulk (e.g. 1-isopropylcyclohexene).



4d (1 equiv) **5a** (1 equiv) **7** (55%) **6ea** (30%) (+ 15% starting material) (2.31)

The variability observed with respect to the alkene structure for the successful substrates can be explained by looking at the efficiency of the hydroamination step. The reaction conditions require the presence of an excess of alkene to obtain high yields of the hydroamination product. This excess is necessary due to an unproductive isomerization step, which leads to the formation of the exocyclic alkene. For example, if the reaction with (–)-limonene (**4d**) is performed using equimolar amounts of alkene and imidazole, the product distribution favours the isomerization product **7** over the hydroamination product **6ea** (Equation 2.31). This control experiment suggests the formation of highly strained E-cycloalkenes under our reaction conditions is efficient as shown by the total conversion to **6ea** and **7**. However, the tertiary carbocation formed upon alkene protonation can either react with imidazole to provide the desired hydroamination product or undergo deprotonation, which either leads back to the starting material (with erosion

of ee)[73] or leads to the formation of an exocyclic alkene. The latter irreversible reactivity of E-cycloalkenes is well documented and cannot lead to the formation of hydroamination products.[74]

2.3. Conclusion and Outlook

In summary, a photoinduced procedure for intermolecular hydroamination of cyclic alkenes using azoles has been developed. The presence of a mild acid additive and sequential addition of the alkene over time were found to be crucial to obtain good yields of the complex *N*-alkyl azole products. Highly strained E-cycloalkenes, formed in situ via sensitized photoisomerization using methyl benzoate at 254 nm, are likely reaction intermediates. The examples documented herein are to date the most basic nitrogen nucleophiles known to undergo efficient acid-catalyzed hydroamination with unactivated alkenes.

In one sense, the development of the methodologies described within this chapter can certainly be considered a success. Numerous complex photochemical and chemical hurdles were overcome to develop an operationally simple hydroamination reaction that does not require a fragile or expensive catalyst or a glovebox and that can work directly on cheap commercially available alkenes. These examples also represent the first protonation/addition reactions of E-cycloalkenes where the nucleophiles are not used in large excess as solvents.

On the other hand, several fundamental limitations present in these methodologies preclude their use as a general solution to hydroamination. Obviously, the alkene substrate must be cyclic and either 6- or 7-membered (or at least in principle capable of generating significant strain upon photoisomerization). Secondly, substrates bearing phenyl groups or other strong chromophores are not amenable to this chemistry as they interfere with the photochemical

(73) In agreement with this rationale, the limonene recovered from the reaction shown in eq 2.32 was found to be racemic. Please see the experimental section for details.

(74) See section 2.1.4.2 for a discussion.

processes required to generate sufficient concentrations of the reactive intermediates. Finally, the unavoidable competition between elimination and hydroamination reactions led us to conclude that hydroamination pathways involving a carbocationic intermediate are fundamentally inefficient when basic amines are employed. It is with these considerations in mind that we abandoned the photochemical strain-release approach towards hydroamination described in this chapter in search of more simple and general alternatives.

2.4. Experimental Section

2.4.1. Photoinduced 1,4-Additions of Azoles to Cycloalkenones

General Information. All reactions were performed in air-dried or oven-dried borosilicate tubes. Reactions were either carried out in a Rayonet photoreactor or between two Luzchem exposure panels equipped with four ultraviolet lamps each. UV-A bulbs (~350 nm)[75,76] and exposure panels were purchased from Luzchem Research, Inc. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 μm). Analytical thin layer chromatography was performed on aluminum sheets pre-coated with silica gel 60 F254, cut to size. Visualization was accomplished with UV light and an aqueous vanillin solution followed by heating.

Infrared spectra were recorded on a Bruker Equinox 55 spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance300 (300 MHz) or Avance400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.15 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 solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm or C_6D_6 at 128.02 ppm). High-resolution mass spectra were recorded on a Kratos-Concept IIH instrument operated by the Ottawa-Carleton Mass Spectrometry Centre.

Materials. Dichloromethane and acetonitrile were dried by distillation over calcium

(75) For specifications, see http://www.luzchem.com/handbook/LESUVA011.pdf

(76) Alternatively, this apparatus could be substituted for a medium pressure Hg lamp fitted with a uranium glass filter.

hydride. Tetrahydrofuran was dried by distillation over sodium/benzophenone ketyl. Diethyl ether was purified by passage through a column of activated alumina under a nitrogen atmosphere.[77] Unless otherwise noted, all commercial materials were used without further purification. Reagents were purchased from Sigma-Aldrich. Cyclohept-2-enone,[78] cyclooct-2-enone,[79] 2,6-cycloheptadienone,[80] 2,3-benzo-2,6-cycloheptadienone[81] and 4-acetylcyclohept-2-enone[82] were prepared according to literature procedures.

General Procedure for Solvent Scan (Table 2.2). Into each of 10 borosilicate tubes equipped with stir bars were added cyclohept-2-enone (0.025 g, 0.23 mmol) and benzimidazole (80 mg, 0.68 mmol). To each tube was added 4 mL of solvent (Table 2.2). The tube was capped with a rubber septum and purged with a nitrogen balloon and an outlet for 10 minutes with stirring. The tubes were then placed on a Luzchem rotating carousel in a Rayonet photoreactor equipped with eight 8W UV-A bulbs for 16 hours. The reactions were monitored by TLC (5% $MeOH/CH_2Cl_2$). The contents of each tube were then transferred to round-bottom flasks, and the solvent was removed under reduced pressure. The contents of the flask were then completely dissolved in 1.00 mL of d_6-DMSO. ^1H NMR spectra of these solutions were recorded, and the conversion calculated based on the relative integration of the resonance corresponding to one of the product's protons (1H) at 8.32 ppm compared to the integration of the resonance

(77) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(78) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.

(79) Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048.

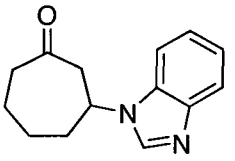
(80) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

(81) Hart, H.; Dunkelblum, E. *J. Am. Chem. Soc.* **1978**, *100*, 5141.

(82) Fujimoto, Y.; Xie, R.; Tully, S. E.; Berova, N.; Nakanishi, K. *Chirality* **2002**, *14*, 340.

corresponding to a benzimidazole peak at 8.24 ppm (1H).[83] This method is estimated to have an error of approximately ±5%.

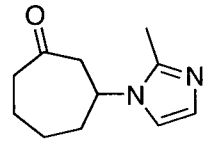
General Procedure for Photoinduced 1,4-Addition of Nitrogen Heterocycles (Table 2.3 and Table 2.4). A borosilicate tube was charged with a stir bar, cycloalkenone (0.45 mmol) and nitrogen heterocycle (1.38 mmol). A volume of 8.0 mL dichloromethane and 1.0 mL acetonitrile was added to the mixture. The tube was capped with a septum and was purged with a nitrogen balloon and an outlet for 5 minutes while stirring. The tube was then placed between two Luzchem exposure panels each equipped with four ultraviolet lamps for 18 hours. The reaction was monitored by thin layer chromatography. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the 1,4-addition product.



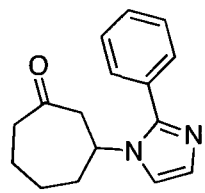
3-Benzoimidazol-1-yl-cycloheptanone (3aa)(Table 2.3, entry 1). Isolated 97 mg (94%) as a clear, colourless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.56 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.96 (s, 1H), 7.80-7.74 (m, 1H), 7.42-7.34 (m, 1H), 7.30-7.22 (m, 2H), 4.51 (tt, 1H, J = 11.5 and 2.9 Hz), 3.27 (dd, 1H, J = 13.8 and 11.8 Hz), 2.86 (dt, 1H, J = 13.8 and 2.4 Hz), 2.70-2.61 (m, 1H), 2.54 (ddd, 1H, J = 16.0, 11.7 and 4.1 Hz), 2.36-2.02 (m, 4H), 1.86-1.46 (m, 2H); ^{13}C NMR (75 MHz) 209.8 (C), 144.1 (C), 140.6 (CH), 133.0 (CH), 123.5 (CH), 122.9 (CH), 120.9 (CH), 110.4 (CH), 53.9 (CH), 50.3 (CH_2), 44.3 (CH_2), 37.8 (CH_2), 27.3 (CH_2), 24.1 (CH_2); IR (film): 3383, 3086, 3054, 2935, 2862, 1700, 1613, 1489, 1458,

(83) Benzimidazole was used as the internal standard for this calculation rather than 2-cycloheptenone, which is known to undergo photochemical dimerization.

1406, 1348, 1279, 1219, 1009, 935, 889, 744, 700, 633 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{16}N_2O$ $[M]^+$: 228.1263. Found: 228.1261.

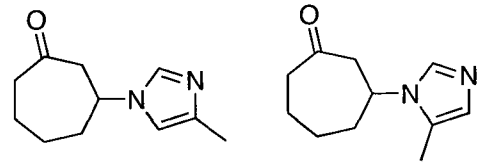


3-(2-Methyl-imidazol-1-yl)-cycloheptanone (3ab)(Table 2.3, entry 2). Isolated 61 mg (70%) as a clear, colourless oil after column chromatography (6% $MeOH/CH_2Cl_2$). TLC R_f 0.25 (5% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.89 (ap s, 1H), 6.82 (d, 1H, J = 1.1 Hz), 4.16 (tt, 1H, J = 11.6 and 2.8 Hz), 3.07 (dd, 1H, J = 13.8 and 11.7 Hz), 2.67 (dt, 1H, J = 2.4 and 13.7 Hz), 2.62-2.42 (m, 2H), 2.37 (s, 3H), 2.19-1.96 (m, 3H), 1.90 (q, 1H, J = 11.2 Hz), 1.72 (ddd, 1H, J = 16.1, 12.5 and 4.4 Hz), 1.56-1.38 (m, 1H); ^{13}C NMR (75 MHz) 209.9 (C), 143.8 (C), 128.0 (CH), 115.4 (CH), 53.6 (CH), 51.1 (CH_2), 44.2 (CH_2), 38.8 (CH_2), 27.1 (CH_2), 24.0 (CH_2), 13.6 (CH_3); IR (film): 3376, 3110, 2934, 2862, 1698, 1447, 1419, 1279, 749, 678 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{16}N_2O$ $[M]^+$: 192.1263. Found: 192.1276.



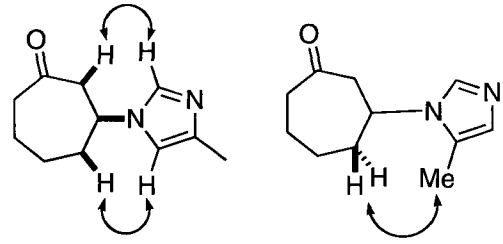
3-(2-Phenyl-imidazol-1-yl)-cycloheptanone (3ac)(Table 2.3, entry 3). Isolated 51 mg (44%) as a white crystalline solid after column chromatography (5% $MeOH/CH_2Cl_2$). TLC R_f 0.53 (10% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) 7.54-7.38 (m, 5H), 7.14 (d, 1H, J = 0.9 Hz), 7.05 (d, 1H, J = 1.3 Hz), 4.48 (tt, 1H, J = 11.3 and 2.8 Hz), 3.16 (dd, 1H, J = 14.3 and 11.6 Hz), 2.78 (dt, 1H, J = 14.3 and 2.5 Hz), 2.63-2.54 (m, 1H), 2.39 (ddd, 1H, J = 16.0, 12.1 and 3.8Hz), 2.24-2.13 (m, 1H), 2.08-1.91 (m, 3H), 1.79-1.61 (m, 1H), 1.47-1.29 (m, 1H); ^{13}C NMR (75 MHz) 209.8 (C), 147.3 (C), 130.8 (C), 129.7 (CH), 129.5 (CH), 129.4 (CH), 129.2 (CH), 116.7 (CH),

53.8 (CH), 51.7 (CH_2), 44.1 (CH_2), 39.5 (CH_2), 27.2 (CH_2), 24.1 (CH_2); IR (film): 3380, 2934, 2862, 1700, 1466, 1445, 1416, 1275, 1260, 765, 749, 714, 701 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{18}N_2O$ $[M]^+$: 254.1419. Found: 254.1443.



7 : 1

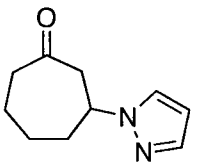
3-(4-Methyl-imidazol-1-yl)-cycloheptanone (major) and 3-(5-methyl-imidazol-1-yl)-cycloheptanone (minor) (3ad)(Table 2.3, entry 4).[84] Isolated 64 mg (73%) as a yellow oil after column chromatography (1.5% MeOH/CH_2Cl_2). This mixture of isomers co-eluted in a variety of solvent systems. TLC R_f 0.25 (5% MeOH/CH_2Cl_2); IR (film, mixture): 3374, 3111, 2935, 2863, 1699, 1496, 1448, 1275, 1260, 1233, 1164, 764, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{16}N_2O$ $[M]^+$: 192.1263. Found: 192.1268.



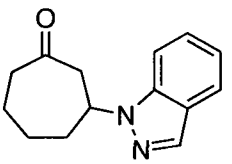
major product: ^1H NMR ($CDCl_3$, 300 MHz) 7.39 (s, 1H), 6.61 (s, 1H), 4.19 (tt, 1H, J = 11.3 and 2.9 Hz), 3.08 (dd, 1H, J = 14.0 and 11.6 Hz), 2.76 (dt, 1H, J = 4.8 and 2.6 Hz), 2.59 (dt, 1H, J = 9.5 and 4.4 Hz), 2.47 (ddd, 1H, J = 15.7, 11.5 and 3.9 Hz), 2.17 (s, 3H), 2.09-1.86 (m, 4H), 1.79-1.61 (m, 1H), 1.57-1.39 (m, 1H); ^{13}C NMR (75 MHz) 210.0 (C), 139.0 (C), 134.7 (CH), 113.5 (CH), 54.9 (CH), 51.5 (CH_2), 44.3 (CH_2), 39.1 (CH_2), 27.0 (CH_2), 24.0 (CH_2), 14.1 (CH_3).

(84) The regioisomers were differentiated by NOE measurements and were consistent with the expected reactivity.

minor product: ^{1}H NMR ($CDCl_3$, 300 MHz, diagnostic peaks only) 7.45 (s, 1H), 6.73 (s, 1H), 4.08 (tt, 1H, J = 11.7 and 2.6 Hz), 2.18 (s, 3H); ^{13}C NMR (75 MHz) 209.9 (C), 134.0 (C), 127.2 (CH), 126.7 (CH), 52.9 (CH), 51.3 (CH_2), 38.9 (CH_2), 27.3 (CH_2), 23.9 (CH_2), 9.9 (CH_3).

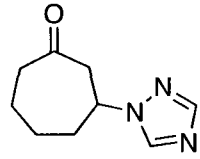


3-Pyrazol-1-yl-cycloheptanone (3ae)(Table 2.3, entry 5). Isolated 81 mg (99%) as a clear, colourless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.64 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.48 (d, 1H, J = 1.5 Hz), 7.37 (d, 1H, J = 2.3 Hz), 6.21 (t, 1H, J = 2.1 Hz), 4.46 (tt, 1H, J = 11.1 and 3.2 Hz), 3.25 (dd, 1H, J = 14.4 and 11.2 Hz), 2.82 (ddd, 1H, J = 14.4, 2.9 and 1.8 Hz), 2.61 (dddd, 1H, J = 16.0, 5.3, 4.0 and 1.3 Hz), 2.48 (ddd, 1H, J = 15.9, 11.2 and 3.9 Hz), 2.25-1.90 (m, 4H), 1.82-1.67 (m, 1H), 1.59-1.45 (m, 1H); ^{13}C NMR (75 MHz) 210.4 (C), 139.1 (CH), 127.0 (CH), 105.3 (CH), 58.7 (CH), 50.1 (CH_2), 44.0 (CH_2), 37.7 (CH_2), 26.5 (CH_2), 23.6 (CH_2); IR (film): 2935, 2861, 1702, 1511, 1445, 1397, 1284, 1225, 1090, 1048, 967, 913, 747, 623 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{14}N_2O$ $[M]^+$: 178.1106. Found: 178.1094.

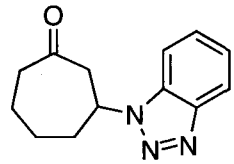


3-Indazol-1-yl-cycloheptanone (3af)(Table 2.3, entry 6). Isolated 95 mg (92%) as a clear, colourless oil after column chromatography (40% EtOAc/hexanes). TLC R_f 0.37 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.06 (d, 1H, J = 5.7 Hz), 6.81 (ap ddd, 2H, J = 13.6, 10.2 and 7.0 Hz), 6.43 (dd, 1H, J = 14.0 and 6.8 Hz), 6.22 (dd, 1H, J = 13.8 and 6.9 Hz), 3.89-3.86 (m, 1H), 2.66-2.55 (m, 1H), 2.09 (br d, J = 14.4 Hz), 1.87-1.62 (m, 2H), 1.49-1.41 (m,

2H), 1.24-1.13 (m, 2H), 1.04-0.89 (m, 1H), 0.80-0.65 (m, 1H); ^{13}C NMR (75 MHz) 209.8 (C), 148.5 (C), 125.9 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.1 (CH), 117.3 (CH), 60.4 (CH), 50.3 (CH_2), 43.9 (CH_2), 38.1 (CH_2), 26.5 (CH_2), 23.5 (CH_2); IR (film): 3118, 3059, 2934, 2861, 1701, 1628, 1513, 1447, 1379, 1348, 1291, 1135, 912, 757, 655 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{16}N_2O$ $[M]^+$: 228.1263. Found: 228.1267.

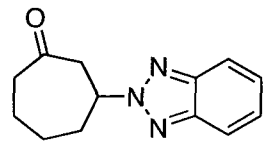


3-[1,2,4] Triazol-1-yl-cycloheptanone (3ag)(Table 2.3, entry 7). Isolated 54 mg (66 %) as a clear, colourless oil after column chromatography (3% MeOH/CH_2Cl_2). TLC R_f 0.46 (10% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 8.09 (s, 1H), 7.93 (s, 1H), 4.55 (tt, 1H, J = 11.3 and 3.3 Hz), 3.30 (dd, 1H, J = 14.2 and 11.2 Hz), 2.85 (ddd, 1H, J = 14.2, 2.8 and 1.7 Hz), 2.71-2.62 (m, 1H), 2.51 (ddd, 1H, J = 16.1, 11.2 and 4.0 Hz), 2.29-1.94 (m, 4H), 1.87-1.72 (m, 1H), 1.63-1.50 (m, 1H); ^{13}C NMR (75 MHz) 209.8 (C), 152.3 (CH), 141.7 (CH), 57.5 (CH), 50.0 (CH_2), 44.4 (CH_2), 37.9 (CH_2), 26.6 (CH_2), 23.8 (CH_2); IR (film): 3165, 2936, 2878, 1702, 1503, 1445, 1347, 1275, 1140, 1013, 913, 744, 681, 663 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{13}N_3O$ $[M]^+$: 179.1059. Found: 179.1062.

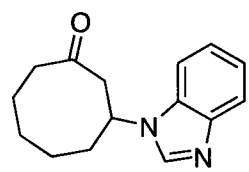


3-Benzotriazol-1-yl-cycloheptanone (3ah)(Table 2.3, entry 8). Isolated 56 mg (53%) as a white crystalline solid after column chromatography (1.5% MeOH/CH_2Cl_2). TLC R_f 0.55 (10% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 8.05 (dt, 1H, J = 8.3 and 1.0 Hz), 7.53 (ddd, 1H, J = 8.4, 1.3 and 0.9 Hz), 7.45 (ddd, 1H, J = 8.2, 6.6 and 1.0 Hz), 7.34 (ddd, 1H, J = 8.3, 6.6 and

1.4 Hz), 4.97 (tt, 1H, J = 10.7 and 3.2 Hz), 3.59 (dd, 1H, J = 14.2 and 11.4 Hz), 2.92 (ddd, 1H, J = 14.2, 3.0 and 1.9 Hz), 2.73 (dddd, 1H, J = 16.2, 5.5, 4.2 and 1.4 Hz), 2.58 (ddd, 1H, J = 16.1, 11.2 and 4.1 Hz), 2.50-2.35, (m, 1H), 2.35-2.25 (m, 1H), 2.15–1.77 (m, 4H), 1.67-1.51 (m, 1H); ^{13}C NMR (75 MHz) 210.1 (C), 146.4 (C), 132.2 (C), 127.8 (CH), 124.5 (CH), 120.6 (CH), 109.7 (CH), 56.7 (CH), 49.7 (CH_2), 44.4 (CH_2), 37.4 (CH_2), 26.9 (CH_2), 24.0 (CH_2); IR (film): 3063, 2934, 2861, 1702, 1453, 1299, 1269, 1237, 1162, 1069, 766, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O$ $[M]^+$: 229.1215. Found: 229.1210.

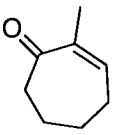


3-Benzotriazol-2-yl-cycloheptanone (3ah)(Table 2.3, entry 8). Isolated 12 mg (11%) as a white crystalline solid after column chromatography (1.5% MeOH/CH_2Cl_2). TLC R_f 0.55 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.85 (dd, 2H, J = 6.6 and 3.0 Hz), 7.38 (dd, 2H, J = 6.6 and 3.1 Hz), 5.24-5.13 (m, 1H), 3.54 (dd, 1H, J = 15.1 and 10.8 Hz), 3.10 (dd, 1H, J = 15.2 and 2.5 Hz), 2.76-2.65 (m, 1H), 2.59 (ddd, 1H, J = 15.9, 10.4 and 3.6 Hz), 2.47 -2.38 (m, 2H), 2.09-1.93 (m, 2H), 1.92-1.6 (m, 2H); ^{13}C NMR (75 MHz) 209.9 (C), 144.4 (C), 126.9 (CH), 118.5 (CH), 63.7 (CH), 49.7 (CH_2), 44.6 (CH_2), 37.9 (CH_2), 27.0 (CH_2), 24.1 (CH_2); IR (film): 3502, 3388, 3065, 2933, 2861, 1701, 1447, 1346, 1319, 1295, 1272, 1241, 1212, 1199, 1142, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O$ $[M]^+$: 229.1215. Found: 229.1198.



3-Benzoimidazol-1-yl-cyclooctanone (3ba)(Table 2.4, entry 2). Isolated 58 mg (90%) as a clear, colourless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.69 (10%

MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.03 (s, 1H), 7.82-7.79 (m, 1H), 7.52-7.49 (m, 1H), 7.35-7.26 (m, 2H), 4.67 (tt, 1H, J = 11.9 and 3.7 Hz), 3.35 (t, 1H, J = 11.9 Hz), 2.71 (ddd, 1H, J = 11.8, 3.4 and 1.6 Hz), 2.53 (ap ddd, 2H, J = 5.6, 5.4 and 2.8 Hz), 2.27-1.22 (m, 8H); ^{13}C NMR (75 MHz) 212.1 (C), 143.7 (C), 140.7 (CH), 133.1 (C), 123.6 (CH), 123.0 (CH), 120.8 (CH), 110.4 (CH), 56.2 (CH), 46.6 (CH_2), 44.3 (CH_2), 33.3 (CH_2), 28.1 (CH_2), 23.5 (CH_2), 22.7 (CH_2); IR (film): 2936, 2872, 1699, 1489, 1458, 1283, 1221, 1206, 1082, 744 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{18}N_2O$ $[M]^+$: 242.1419. Found: 242.1428.

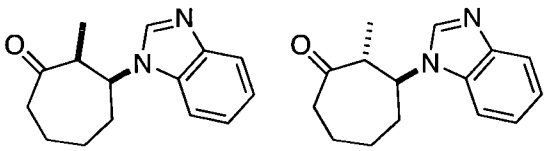


2-Methyl-cyclohept-2-enone (1c)(Table 2.4, entry 3). Prepared according to a modification of the procedure of Paquette.[85] To a stirred solution of triethylamine (4.86 g, 48 mmol) in 8 mL dry dimethylformamide (both components freshly distilled from calcium hydride) were added chlorotrimethylsilane (2.61 g, 24 mmol) and cyclohexanone (1.96 g, 20 mmol). This mixture was heated at the reflux temperature for 6 h, cooled to room temperature, and diluted with 30 mL pentane. The precipitated triethylamine hydrochloride was separated by filtration and washed well with pentane (3 × 15 mL). The combined filtrates were washed with ice-cold saturated sodium bicarbonate solution (3 × 30 mL) and brine (10 mL) prior to drying over Na_2SO_4. Solvent evaporation left 3.04 g (89%) of the silyl enol ether that was used directly without further purification.

n-Butyllithium in hexane (46 mL of 1.10 M, 51 mmol) was slowly added under nitrogen during 6 h to a cold (–40 °C), magnetically stirred solution of the preceding product (3.04 g, 17.8 mmol) and 1,1-dichloroethane (5.64 g, 57.0 mmol) in anhydrous ether (7.0 mL). The mixture was

(85) Paquette, L. A.; Hun Ham, W. *J. Am. Chem. Soc.* **1987**, *109*, 3025.

allowed to warm to 0 °C over 1 h, at which point it was diluted with ether (15 mL), washed with water (4 × 10 mL), dried, and concentrated. The residual oil (4.0 g) was dissolved in a mixture of toluene (80 mL) and ethylene glycol (7.5 mL) and heated at the reflux temperature under nitrogen for 24 h. The crude reaction mixture was concentrated under reduced pressure. The oil was taken up in hexanes and washed with water (3 × 30 mL) to remove ethylene glycol, followed by drying over Na_2SO_4. The mixture was then submitted twice to column chromatography (8% EtOAc/Hexanes, then CH_2Cl_2) to give the product (0.483 g, 20%) as a clear, colourless oil. TLC R_f 0.32 (8% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 6.49 (tq, 1H, J = 6.4 and 1.4 Hz), 2.50 (ap dd, 2H, J = 7.4 and 5.6 Hz), 2.32-2.26 (m, 2H), 1.75 (ap q, 3H, J = 1.4 Hz), 1.71-1.63 (m, 4H); ^{13}C NMR (75 MHz) 205.2 (C), 142.9 (CH), 139.6 (C), 42.7 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 21.7 (CH_2), 19.7 (CH_3); IR (film): 2938, 2866, 1667, 1453, 1375 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{12}O$ $[M]^+$: 124.0888. Found: 124.0886.

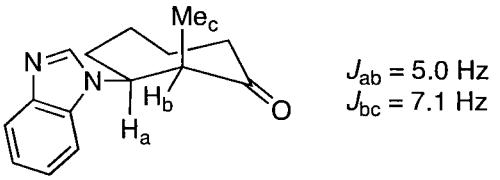


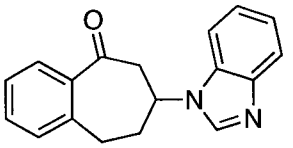
12 : 1

***syn* 3-Benzoimidazol-1-yl-2-methyl-cycloheptanone (3ca)(Table 2.4, entry 3).**[86] Isolated 71 mg (66%) as a clear, colourless oil after column chromatography (3% MeOH/CH_2Cl_2). TLC R_f 0.32 (3% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.03 (s, 1H), 7.82 (ddd, 1H, J = 3.5, 2.2 and 0.6 Hz), 7.42-7.39 (m, 1H), 7.35-7.27 (m, 2H), 4.91 (ddd, 1H, J = 9.0, 6.7 and 5.0 Hz), 3.18 (qd, 1H, J = 7.1 and 5.0 Hz), 2.81-2.62 (m, 2H), 2.34-2.27 (m, 2H), 2.13-2.03 (m, 2H), 1.86-1.71 (m, 2H), 0.93 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz) 211.9 (C), 142.9 (C), 140.6 (CH), 133.1

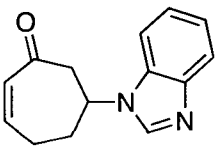
(86) The relative stereochemistry of the methyl and benzoimidazol-1-yl substituents was ascertained by analysis of the ^{1}H NMR spectroscopy vicinal coupling constants. Typical pseudo *trans*-diaxial coupling constants for H_a (≈11.5 Hz) were not observed. For examples of these coupling constants, see compounds **3aa**, **3ab**, **3ad**, **3ae**, **3ag**, **3ah**, **3da.** Rather, they are consistent with a *cis* relationship (J_{ab} = 5.0 Hz).

(C), 123.0 (CH), 122.4 (CH), 120.3 (CH), 109.5 (CH), 56.2 (CH), 50.0 (CH), 42.5 (CH_2), 31.2 (CH_2), 26.8 (CH_2), 24.1 (CH_2), 10.2 (CH_3); IR (film): 3084, 3059, 2936, 2864, 1700, 1488, 1458, 1284, 1218, 744 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{18}N_2O$ $[M]^+$: 242.1419. Found: 242.1405.

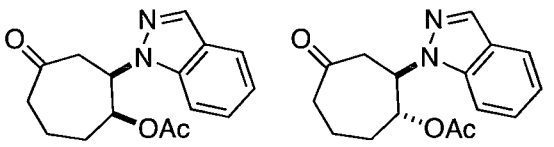




7-Benzoimidazol-1-yl-6,7,8,9-tetrahydro-benzocyclohepten-5-one (3da)(Table 2.4, entry 4). Isolated 115 mg (92%) as a clear, colourless oil after column chromatography (3% MeOH/CH_2Cl_2). TLC R_f 0.41 (3% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 8.02 (s, 1H), 7.83-7.79 (m, 2H), 7.52 (td, 1H, J = 7.5 and 1.5 Hz), 7.41 (dd, 1H, J = 7.7 and 1.2 Hz), 7.37 (dd, 1H, J = 3.7 and 2.1 Hz), 7.32-7.28 (m, 3H), 4.83 (tdd, 1H, J = 10.1, 6.8 and 3.8 Hz), 3.52 (dd, 1H, J = 15.2 and 10.0 Hz), 3.33-3.23 (m, 2H), 3.07 (ddd, 1H, J = 15.7, 5.7 and 4.0 Hz), 2.58-2.34 (m, 2H); ^{13}C NMR (75 MHz) 200.0 (C), 143.7 (C), 140.5 (CH), 140.1 (C), 137.7 (C), 132.9 (CH), 132.8 (C), 130.0 (CH), 128.9 (CH), 127.3 (CH), 122.9 (CH), 122.4 (CH), 120.5 (CH), 109.8 (CH), 51.0 (CH), 47.0 (CH_2), 32.4 (CH_2), 30.7 (CH_2); IR (film): 3346, 3117, 3057, 2946, 2872, 1680, 1613, 1599, 1489, 1457, 1404, 1285, 1260, 1025, 745 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{18}H_{16}N_2O$ $[M]^+$: 276.1263. Found: 276.1283.



6-Benzoimidazol-1-yl-cyclohept-2-enone (3ea)(Table 2.4, entry 5). Isolated 35 mg (51%) as a clear, colourless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.67 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.01 (s, 1H), 7.84-7.79 (m, 1H), 7.41-7.27 (m, 3H), 6.75 (dt, 1H, J = 12.0 and 5.4 Hz), 6.19 (br d, 1H, J = 12.2 Hz), 4.86 (tt, 1H, J = 8.4 and 5.2 Hz), 3.30 (dd, 1H, J = 15.3 and 8.4 Hz), 3.21 (dd, 1H, J = 15.3 and 5.4 Hz), 2.68-2.61 (m, 2H), 2.51-2.33 (m, 2H); ^{13}C NMR (75 MHz) 198.9 (C), 146.8 (CH), 144.2 (C), 140.7 (CH), 133.31 (C), 133.27 (CH), 123.6 (CH), 123.0 (CH), 121.1 (CH), 110.2 (CH), 51.6 (CH), 49.6 (CH_2), 34.0 (CH_2), 27.9 (CH_2); IR (film): 2936, 1708, 1658, 1650, 1611, 1491, 1459, 1407, 1285, 1217, 745 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_2O$ $[M]^+$: 226.1106. Found: 226.1095.

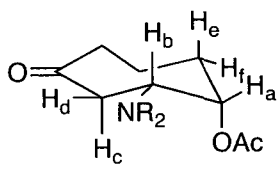


1.3 : 1

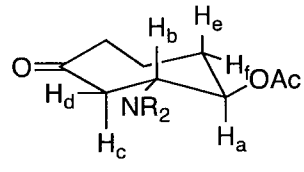
***syn* Acetic acid 2-indazol-1-yl-4-oxo-cycloheptyl ester (3ff)(Table 2.4, entry 6).**[87] Isolated 40 mg (45%) as a clear, colourless oil after column chromatography (50% EtOAc/Hex). TLC R_f 0.17 (50% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.91 (s, 1H), 7.69 (d, 1H, J = 9.1 Hz), 7.66-7.63 (m, 1H), 7.33-7.28 (m, 1H), 7.13-7.08 (m, 1H), 5.43 (dt, 1H, J = 7.1 and 1.8 Hz), 5.16-5.11 (m, 1H), 3.63 (dd, 1H, J = 15.8 and 10.6 Hz), 2.99 (dd, 1H, J = 15.9 and 2.9 Hz), 2.92-2.83 (m, 1H), 2.68-2.58 (m, 1H), 2.30-2.17 (m, 1H), 2.08 (s, 3H), 2.01-1.77 (m, 3H); ^{13}C NMR (100

(87) The relative stereochemistry of the O-acetoxy and indazol-1-yl substituents was ascertained by analysis of the ^{1}H NMR spectroscopy vicinal coupling constants. The *syn* isomer is indicated by H_a, which is a dt (J = 7.1 and 1.8 Hz) at 5.43 ppm. Conversely, the *anti* isomer is indicated by H_a, which is a td (J = 9.8 and 3.7 Hz) at 5.53 ppm.

MHz) 203.3 (C), 169.4 (C), 126.6 (C), 122.3 (CH), 121.7 (CH), 120.3 (CH), 117.29 (CH), 117.26 (C), 74.8 (CH), 61.6 (CH), 43.4 (CH_2), 31.1 (CH_2), 21.0 (CH_3), 18.4 (CH_2); IR (film): 2940, 1738, 1702, 1376, 1233, 1028, 859 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{18}N_2O_3$ $[M]^+$: 286.1317. Found: 286.1325.

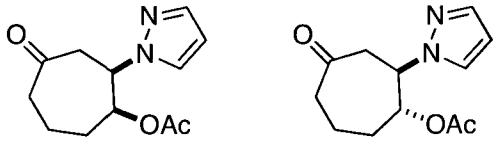


J_{ab} = 7.1 Hz
J_{ae} = 1.8 Hz
J_{af} = 1.8 Hz
J_{bc} = 10.6 Hz
J_{bd} = 2.9 Hz
J_{cd} = 15.8 Hz



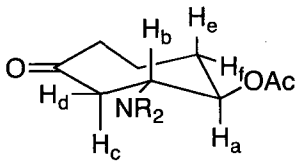
J_{ab} = 9.8 Hz
J_{ae} = 9.8 Hz
J_{af} = 3.7 Hz
J_{bc} = 11.5 Hz
J_{bd} = 2.4 Hz
J_{cd} = 13.1 Hz

***anti* Acetic acid 2-indazol-1-yl-4-oxo-cycloheptyl ester (3ff)(Table 2.4, entry 6).**[13] Isolated 30 mg (34%) as a clear, colourless oil after column chromatography (50% EtOAc/Hex). TLC R_f 0.23 (50% EtOAc/Hexanes); ^1H NMR ($CDCl_3$, 300 MHz) 7.94 (s, 1H), 7.70 (d, 1H, J = 8.8 Hz), 7.63 (dt, 1H, J = 8.4 and 1.0 Hz), 7.32-7.26 (m, 1H), 7.08 (ddd, 1H, J = 8.2, 6.7 and 0.6 Hz), 5.53 (td, 1H, J = 9.8 and 3.7 Hz), 4.61 (ddd, 1H, J = 11.5, 9,2 and 2.4 Hz), 3.68 (dd, 1H, J = 13.1 and 11.7 Hz), 2.87 (dd, 1H, J = 13.2 and 2.5 Hz), 2.75 (dtd, 1H, J = 17.3, 4.7 and 0.7 Hz), 2.58-2.47 (m, 1H), 2.33-2.24 (m, 1H), 2.11-1.98 (m, 2H), 1.77 (s, 3H), 1.69-1.55 (m, 1H); ^{13}C NMR (100 MHz) 211.8 (C), 169.3 (C), 126.5 (CH), 122.9 (CH), 122.1 (C), 121.2 (C), 117.6 (CH), 76.4 (CH), 63.0 (CH), 45.4 (CH_2), 43.4 (CH_2), 31.2 (CH_2), 20.7 (CH_3), 18.5 (CH_2); IR (film): 2943, 1736, 1704, 1376, 1233, 1032 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{18}N_2O_3$ $[M]^+$: 286.1317. Found: 286.1330.



1.1 : 1

***syn* Acetic acid 4-oxo-2-pyrazol-1-yl-cycloheptyl ester (3fe)(Table 2.4, entry 7).**[88] Isolated 46 mg (46%) as a clear, colourless oil after column chromatography (2% MeOH/CH_2Cl_2, then 50% EtOAc/Hexanes). TLC R_f 0.28 (50% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49 (br s, 1H), 7.37 (br s, 1H), 6.26 (br s, 1H), 5.31 (br d, 1H, J = 7.1 Hz), 4.82-4.79 (m, 1H), 3.47 (dd, 1H, J = 15.7 and 10.4 Hz), 2.86 (dd, 1H, J = 15.8 and 2.6 Hz), 2.80 (ddd, 1H, J = 11.3, 8.6 and 3.4 Hz), 2.57 (ddd, 1H, J = 16.4, 10.0 and 3.0 Hz), 2.20-2.12 (m, 1H), 2.06 (s, 3H), 1.96-1.75 (m, 3H); ^{13}C NMR (100 MHz) 208.9 (C), 169.5 (C), 139.2 (CH), 128.1 (CH), 106.1 (CH), 74.8 (CH), 59.8 (CH), 43.7 (CH_2), 43.6 (CH_2), 31.1 (CH_2), 21.0 (CH_3), 18.4 (CH_2); IR (film): 3119, 3060, 2943, 2870, 1736, 1704, 1628, 1376, 1233, 1032 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O_3$ $[M]^+$: 236.1161. Found: 236.1141.

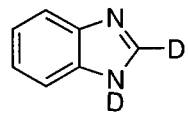


J_{ab} = 9.2 Hz
J_{ae} = 9.9 Hz
J_{af} = 3.7 Hz
J_{bc} = 11.4 Hz
J_{bd} = 2.5 Hz
J_{cd} = 13.3 Hz

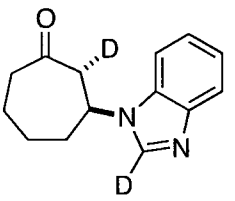
***anti* Acetic acid 4-oxo-2-pyrazol-1-yl-cycloheptyl ester (3fe)(Table 2.4, entry 7).**[14] Isolated 41 mg (41%) as a clear, colourless oil after column chromatography (2% MeOH/CH_2Cl_2, then 50% EtOAc/Hex). TLC R_f 0.25 (50% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.51 (br d, 1H, J = 1.5 Hz), 7.37 (br d, 1H, 1.5 Hz), 6.20 (t, 1H, J = 2.1 Hz), 5.33 (ddd, 1H, J = 9.9, 9.2 and 3.7

(88) The relative stereochemistry of the *O*-acetoxy pyrazol-1-yl substituents was ascertained by analysis of the ^{1}H NMR spectroscopy vicinal coupling constants for the *anti* isomer. Due to broad signals, the relevant coupling constants could not be extracted for the remaining isomer. It was thus assigned as the *syn* isomer by process of elimination as well as by analogy with compound **3ff**.

Hz), 4.31 (ddd, 1H, J = 11.4, 9.0, 2.5 Hz), 3.47 (dd, 1H, J = 13.3 and 11.4 Hz), 2.82 (dd, 1H, J = 13.4 and 2.5 Hz), 2.69 (dtd, 1H, J = 17.4, 4.9 and 0.9 Hz), 2.48 (ddd, 1H, J = 17.4, 10.6, 5.3 Hz), 2.23-2.17 (m, 1H), 2.07-1.90 (m, 2H), 1.85 (s, 3H), 1.60 (dddd, 1H, J = 14.3, 10.2, 10.1 and 2.1 Hz); ^{13}C NMR (100 MHz) 209.6 (C), 169.2 (C), 139.9 (CH), 129.2 (CH), 105.3 (CH), 76.1 (CH), 61.3 (CH), 45.1 (CH_2), 43.3 (CH_2), 31.3 (CH_2), 20.7 (CH_3), 18.5 (CH_2); IR (film): 3121, 3061, 2940, 1738, 1702, 1376, 1233, 1028 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O_3$ $[M]^+$: 236.1161. Found: 236.1183.

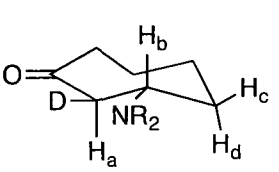


***1,2*-Dideuterobenzimidazole (2a-d_2)(equation 4).** Oxalyl chloride (0.048 g, 0.38 mmol) was added slowly to a 25 mL round bottom flask containing 8 mL D_2O under magnetic stirring. The solution was refluxed for 1h and then cooled to room temperature. Benzimidazole (0.443 g, 3.75 mmol) was then added to the solution, and the heterogenous mixture was then refluxed for two hours to give a clear homogeneous solution. Upon cooling to room temperature over 20 minutes, precipitation of white crystals was observed. The mixture was filtered in a glass frit and the crystals were washed with diethyl ether, followed by drying under reduced pressure to give the product as white needles (0.430 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.69 (dd, 2H, J = 6.1 and 3.2 Hz), 7.31 (dd, 2H, J = 6.1 and 3.2 Hz); ^{13}C NMR (100 MHz) 137.3 (C), 123.1 (CH), 115.5 (CH); IR (film): 3136, 3073, 3045, 3026, 2981, 2960, 2824, 2786, 2725, 2678, 2606, 1590, 1565, 1553, 1439, 913 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_4D_2N_2$ $[M]^+$: 120.0657. Found: 120.0677.



Procedure for Deuterium Labelling Experiment for Determination of Stereochemistry (3aa-d_2)(equation 2.23). [89] A borosilicate tube was charged with a stir bar, cyclohept-2-enone (0.025 g, 0.23 mmol) and 1,2-dideuterobenzimidazole (**2a-d_2**) (0.080 g, 0.68 mmol). A volume of 4.0 mL dichloromethane and 0.5 mL of CD_3CN was added to the mixture. The tube was capped with a septum and was purged with a nitrogen balloon and an outlet for 5 minutes while stirring. The tube was then placed between two Luzchem exposure panels each equipped with four 8W UV-A bulbs for 16 hours while stirring. The reaction was monitored by TLC and was found to have R_f 0.56 on silica gel (10% MeO/CH_2Cl_2). The crude mixture was then transferred to a round bottom flask and the solvent was evaporated under reduced pressure. The resulting oil was purified by column chromatography using 4% MeOH/CH_2Cl_2. The product was a clear, colourless oil (39 mg, 75%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83-7.79 (m, 1H), 7.44-7.40 (m, 1H), 7.34-7.26 (m, 2H), 4.53 (ddd, J = 11.5, 11.5 and 3.0 Hz, 1H), 3.27 (d, J = 11.5 Hz, 1H), 2.74-2.32 (m, 3H), 2.25-2.02 (m, 3H), 1.86-1.73 (m, 1H), 1.63-1.50 (m, 1H); ^{13}C NMR (100 MHz) 209.8 (C), 123.6 (CH), 123.0 (CH), 121.1 (CH), 110.4 (CH), 54.0 (CH), 50.4 (CH_2), 44.4 (CH_2), 38.0 (CH_2), 27.4 (CH_2), 24.2 (CH_2); IR (film): 2936, 2872, 1699, 1489, 1458, 1283, 1221, 1206, 1082, 744 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{14}D_2N_2O$ $[M]^+$: 230.1388. Found: 230.1401.

(89) Despite multiple attempts, it was not possible to obtain completely isotopically pure **3aa-D** at the C-2 position. This is attributed to imperfect deuteration of **2a-D** and a potential kinetic isotope effect during the reaction.



J_{ab} = 11.5 Hz
J_{bc} = 3.0 Hz
J_{bd} = 11.5 Hz

Procedure for Low Temperature Generation/Trapping of (*E*)-Cyclooct-2-enone.[90,91] A borosilicate tube was charged with a stir bar, (*Z*)-cyclooct-2-enone (0.025 g, 0.20 mmol) and 3.0 mL of a 8:1 CH_2Cl_2/MeCN. The volume was marked on the tube and an excess of 1-2 mL of CH_2Cl_2 was then added. The tube was capped with a septum and was purged with stirring using a nitrogen balloon and an outlet for at least 5 min or until the solvent evaporated to the volume marked. The solution was cooled to –75 °C and was allowed to sit between two exposure panels each equipped with four 8W UV-A bulbs for 1 hr, maintaining cooling.[92] Irradiation was stopped, and a heterogeneous mixture of benzimidazole (0.095 g, 0.80 mmol) in 1.5 mL 8:1 CH_2Cl_2/MeCN, pre-cooled to –75 °C, was then added by syringe to the borosilicate tube.[93] The reaction mixture was allowed to gradually warm to room temperature while stirring under N_2 for 45 minutes. The formation of a new product was observed by TLC (R_f 0.69 in 10% MeOH/CH_2Cl_2). The solvent was evaporated under reduced pressure and the crude reaction mixture was completely dissolved in d_6-DMSO. ^{1}H NMR of the crude reaction mixture indicated the conversion of 18% of the starting material to 3-benzoimidazol-1-yl-cyclooctanone, based on

(90) For examples of low temperature generation/trapping experiments with (*E*)-cycloalkenones, see: (a) Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051. (b) Noyori, R.; Watanabe, A.; Katô, M. *Tetrahedron Lett.* **1968**, *52*, 5443. (c) Katô, M.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1460.

(91) For examples of low temperature generation/trapping experiments with (*E*)-cycloalkenes, see: (a) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Chem. Commun.* **1981**, 1031. (b) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 983. (c) Steinmetz, M. G.; Seguin, K. J.; Udayakumar, B. S.; Behnke, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 6601.

(92) The sample was immersed in a 95% ethanol bath contained in a 5L quartz Dewar and cooled to –75 °C by an FTS Systems FC100 immersion cooler.

(93) Benzimidazole was pre-ground with a mortar and pestle to maximize its surface area.

the integration of the resonance corresponding to the product's C3 methine proton at 4.83 ppm relative to the resonance corresponding to the enone's C3 sp^2 methine proton at 6.36 ppm.

Procedure for Low Temperature NMR experiments with (*E*)-Cyclooct-2-enone. To an NMR tube was added (*Z*)-Cyclooct-2-enone (**(*Z*)-1b**) (6 mg, 0.05 mmol), followed by 1.0 mL of an 8:1 CD_2Cl_2/CD_3CN solution. The tube was capped with a septum and exposed to three quick freeze/pump/thaw cycles to remove molecular oxygen and was backfilled with nitrogen. The solution was cooled to –75 °C and was allowed to sit between two exposure panels each equipped with four 8W UV-A bulbs for 45 min, maintaining cooling.[17] The NMR tube was then stored in a bath of dry ice in acetone (–78 °C) for approx. 5 min until it could be transferred to a Bruker Avance500 NMR spectrometer, pre-cooled to –20 °C. An initial spectrum was taken, indicating a newly formed compound with alkene resonances at 6.46 (d, J = 18.0 Hz, 1H) and 5.69 (ddd, J = 18.0, 10.9 and 4.1 Hz, 1H) ppm. The tube was then ejected, and benzimidazole (18 mg, 0.15 mmol) was added. The tube was quickly inverted to allow mixing and was reintroduced into the NMR. Another spectrum was taken at –20 °C which indicated that no reaction occurred at this temperature. The NMR was allowed to warm to 10 °C, and spectra were taken every 5 minutes. After 20 minutes, the **(*E*)-1b** had reacted efficiently to afford **3ba**, as judged by the relative ratios of integration of the relevant peaks, while the **(*Z*)-1b** remained unreacted.

2.4.2. Photoinduced Hydroamination of Azoles with Unactivated Cycloalkenes

General Information. All reactions were performed in air-dried or oven-dried quartz tubes. Reactions were either carried out between two Luzchem exposure panels equipped with

four ultraviolet lamps each. UV-C bulbs (~254 nm)[94,95] and exposure panels were purchased from Luzchem Research, Inc. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 μm). Analytical thin layer chromatography was performed on aluminum sheets pre-coated with silica gel 60 F254, cut to size. Visualization was accomplished with an aqueous potassium permanganate solution followed by heating.

Infrared spectra were recorded on a Bruker Equinox 55 spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance300 (300 MHz) or Avance400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.15 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 solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm or C_6D_6 at 128.02 ppm). High-resolution mass spectra were recorded on a Kratos-Concept IIH instrument operated by the Ottawa-Carleton Mass Spectrometry Centre.

Materials. Dichloromethane and acetonitrile were dried by distillation over calcium hydride. Tetrahydrofuran was dried by distillation over sodium/benzophenone ketyl. Diethyl ether was purified by passage through a column of activated alumina under a nitrogen atmosphere.[96] Unless otherwise noted, all commercial materials were used without further

(94) For specifications, see http://www.luzchem.com/handbook/LESUVC011.pdf

(95) Alternatively, this apparatus could be substituted for a low pressure Hanovia Hg lamp.

(96) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

purification. Reagents were purchased from Sigma-Aldrich. 1-Methylcycloheptene[97] and 1-ethylcyclohexene[98] were prepared according to literature procedures.

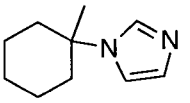
General Procedure for Optimization Trials (Table 2.5 and Table 2.6). A 10 mL quartz tube was charged with a stir bar, methyl benzoate (0.10 g, 0.73 mmol), imidazole (0.41 mmol), 8.0 mL of solvent, followed by trifluoromethanesulfonic acid (0.012 g, 0.081 mmol). The mixture was stirred for 10s. 1-Methylcyclohexene (0.41 mmol) was added, the tube was capped with a rubber septum and purged with a nitrogen balloon and an outlet for 10 minutes while stirring. The tubes were then placed on a Luzchem rotating carousel between two Luzchem exposure panels each equipped with four 8W UV-C bulbs lamps for 18 hours while stirring. The reactions were monitored by TLC (10% MeOH/CH_2Cl_2). The contents of each tube were then transferred to a round-bottom flask, and the solvent was removed under reduced pressure. To each flask was added 1.5mL of deuterochloroform. ^{1}H NMR spectra of these solutions were recorded, and the % conversion calculated based on the ratio of the unreacted imidazole (1H) resonance at 7.89 ppm to the resonance corresponding to the product's aromatic proton resonance (1H) at 8.00 ppm. The method is estimated to have an error of approximately ±5%.

General Procedure for Photoinduced Hydroamination of Cycloalkenes (Table 2.7 and Table 2.8). A 10 mL quartz tube was charged with a stir bar, methyl benzoate (0.10 g, 0.73 mmol), nitrogen heterocycle (0.41 mmol), 8.0mL EtOAc, followed by trifluoromethanesulfonic acid (0.012 g, 0.081 mmol). The mixture was stirred for 10s. Cycloalkene (0.41 mmol) was added, the tube was capped with a rubber septum and purged with a nitrogen balloon and an outlet for 5 minutes while stirring. The tube was then placed between two Luzchem exposure panels each equipped with four ultraviolet lamps for 6-12 hours while stirring. Irradiation was

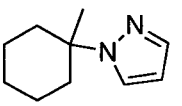
(97) Barbier, M.; Hugel, M. F. *Bull. Soc. Chem. Fr.* **1961**, 951.

(98) Barluenga, J.; Yus, M.; Bernad, P. *J. Chem. Soc., Chem. Comm.* **1978**, 847.

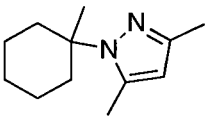
then stopped, and a further equivalent of cycloalkene (0.41 mmol) was added, the tube was again purged with nitrogen, and subjected to irradiation. This was continued until 5 equivalents of the cycloalkene had been added. The reaction was monitored by thin layer chromatography. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the *N*-substituted heterocycle.



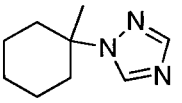
1-(1-Methylcyclohexyl)-1*H*-imidazole (6aa, Table 2.7 and Table 2.8, entry 1). Isolated 47 mg (70%) as a clear, colourless oil after column chromatography (4% MeOH/CH_2Cl_2). TLC R_f 0.56 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.63 (s, 1H), 7.06 (s, 1H), 7.02 (s, 1H), 2.07 (ddd, 2H, J = 12.7, 7.7 and 4.5 Hz), 1.84-1.78 (m, 2H), 1.63-1.43 (m, 6H), 1.42 (s, 3H); ^{13}C NMR (75 MHz) 134.5 (CH), 128.9 (CH), 116.0 (CH), 57.3 (C), 37.9 (CH_2), 29.5 (CH_2), 25.2 (CH_2), 22.0 (CH_3); IR (film): 2935, 2859, 1488, 1215, 1080, 911, 742 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{16}N_2$ $[M]^+$: 164.1313. Found: 164.1323.



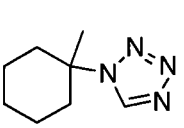
1-(1-Methylcyclohexyl)-1*H*-pyrazole (6ab, Table 2.7, entry 2). Isolated 49 mg (72%) as a clear, colourless oil after column chromatography (2.5% MeOH/CH_2Cl_2). Unable to visualize by chemical stains; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.54 (d, 1H, J = 1.6 Hz, 1H), 7.53 (dd, J = 2.4, 0.6 Hz, 1H), 6.41-6.04 (m, 1H), 2.33-2.28 (m, 2H), 1.82-1.76 (m 2H), 1.56-1.44 (m, 6 H), 1.43 (s, 3H); ^{13}C NMR (75 MHz) 138.2 (CH), 125.6 (CH), 104.4 (CH), 60.4 (C), 37.0 (CH_2), 29.5 (CH_2), 25.2 (CH_2), 22.1 (CH_3); IR (film): 2932, 2861, 1727, 1243, 913, 745 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{16}N_2$ $[M]^+$: 164.1313. Found: 164.1315.



3,5-Dimethyl-1-(1-methylcyclohexyl)-1*H*-pyrazole (6ac, Table 2.7, entry 3). Isolated 37 mg (47%) as a clear, colourless oil after column chromatography (5% MeOH/CH_2Cl_2). TLC R_f 0.35 (5% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) 5.78 (s, 1H), 2.46-2.40 (m, 2H), 2.36 (s, 3H), 2.20 (s, 3H), 1.76 (td, J = 12.9, 4.3 and 4.3 Hz, 2H), 1.59-1.53 (m, 4H), 1.46 (dd, J = 11.3 and 5.7 Hz, 2H), 1.40 (s, 3H); ^{13}C NMR (75 MHz) 145.1 (C), 138.4 (C), 107.7 (CH), 61.8 (C), 37.4 (CH_2), 26.9 (CH_3), 25.5 (CH_2), 22.4 (CH_2), 14.8 (CH_3), 13.4 (CH_3); IR (film): 2928, 2858, 1726, 1551, 1444, 775 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{20}N_2$ $[M]^+$: 196.1626. Found: 196.1629.

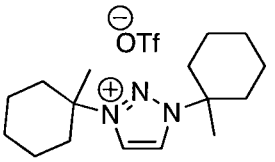


1-(1-Methylcyclohexyl)-1*H*-1,2,4-triazole (6ad, Table 2.7, entry 4). Isolated 45 mg (68%) as a clear, colourless oil after column chromatography (50% EtOAc/Hexanes). TLC R_f 0.33 (50% EtOAc/Hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.16 (s, 1H), 7.95 (s, 1H), 2.27-2.24 (m, 1H), 1.87-1.81 (m, 2H), 1.65-1.56 (m, 2H), 1.50-1.44 (m, 7H); ^{13}C NMR (75 MHz) 151.2 (CH), 140.4 (CH), 60.9 (C), 37.0 (CH_2), 28.2 (CH_2), 25.1 (CH_2), 22.0 (CH_3); IR (film): 3421, 3124, 2939, 2861, 1502, 1447, 1349, 1278, 1004, 957, 671 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{15}N_3$ $[M]^+$: 165.1266. Found: 165.1245.



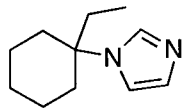
1-(1-Methylcyclohexyl)-1*H*-tetrazole (6ae, Table 2.7, entry 5). Isolated 49 mg (74%) as a clear, colourless oil after column chromatography (CH_2Cl_2 → 2.5% MeOH/CH_2Cl_2). TLC R_f is

unknown as compound does not stain in all attempted stains. Compound was isolated after column chromatography via evaporation of fractions followed by ^{1}H NMR of the residues; ^{1}H NMR (C_6D_6, 400 MHz) 8.54 (s, 1H), 2.06-2.00 (m, 2H), 1.55-1.49 (m, 2H), 1.30-1.25 (m, 2H), 1.21-1.50 (m, 7H); ^{13}C NMR (100 MHz) 140.7 (CH), 61.5 (C), 36.7 (CH_2), 27.9 (CH_2), 24.7 (CH_2), 21.7 (CH_3); IR (film): 3128, 2938, 2854, 1719, 1460, 1390, 1174, 1095, 967, 866 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{14}N_4$ $[M]^+$: 166.1218, C_7H_{13} [M – tetrazole] $^+$: 97.1017. Found: 97.1016.

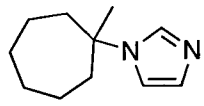


1,3-Di(1-methylcyclohexyl)triazolium triflate (6af, Equation 7). A 100 mL quartz flask was charged with a stir bar, methyl benzoate (0.497 g, 3.63 mmol), 1,2,3-triazole (0.140 g, 2.03 mmol), 40 mL EtOAc, followed by trifluoromethanesulfonic acid (0.061 g, 0.041 mmol). The mixture was stirred for 1 min. 1-Methylcyclohexene (0.195 g, 2.03 mmol) was added, the flask was capped with a rubber septum and purged with a nitrogen balloon and an outlet for 10 minutes while stirring. The flask was then placed between two Luzchem exposure panels each equipped with four UVC lamps for 6-12 hours while stirring. Irradiation was then stopped, and a further equivalent of 1-methylcycloalkene (0.195 g, 2.03 mmol) was added, the flask was again purged with nitrogen, and subjected to irradiation. This was continued until 5 equivalents of the cycloalkene had been added. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography to give 0.17 g (20% relative to triazole, >99% relative to trifluoromethanesulfonic acid) of the titled compound as a clear, colourless oil after column chromatography (3% MeOH/ CH_2Cl_2). TLC R_f 0.34 (3% MeOH/ CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) 8.84 (s, 2H), 2.31 (ddd, J = 12.1, 8.6 and 3.1 Hz, 4H), 2.03 (ddd, J = 12.1, 7.5

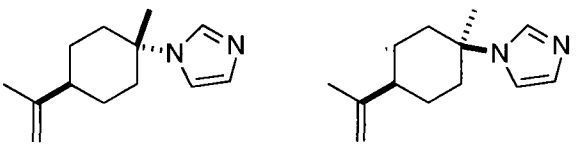
and 3.5 Hz, 4H), 1.71-1.62 (m, 4H), 1.68 (s, 6H), 1.61-1.43 (m, 8H); ^{13}C NMR (75 MHz) 129.1 (CH), 120.7 (q, J_{CF} = 320 Hz) (C), 69.1 (C), 36.7 (CH_2), 27.6 (CH_2), 24.4 (CH_2), 21.9 (CH_3); IR (film): 2940, 2865, 1451, 1258, 1223, 1154, 1031, 637 cm^{-1}.



1-(1-Ethylcyclohexyl)-1*H*-imidazole (6ba, Table 2.8, entry 2). Isolated 29 mg (40%) as a clear, colourless oil after column chromatography (gradient 15% Acetone/CH_2Cl_2 → 5% MeOH/CH_2Cl_2). TLC R_f 0.35 (3.5% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) 7.58 (s, 1H), 7.07 (s, 1H), 6.96 (t, J = 1.3 Hz, 1H), 2.11 (dd, J = 13.3 and 5.8 Hz, 2H), 1.80-1.71 (m, 2H), 1.67 (q, J = 7.5 Hz, 2H), 1.62-1.37 (m, 6H), 0.60 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz) 135.3 (CH), 128.8 (CH), 116.4 (CH), 59.8 (C), 35.5 (CH_2), 35.4 (CH_2), 25.4 (CH_2), 21.6 (CH_2), 7.1 (CH_3); IR (film): 3391 (br), 3107, 2937, 2861, 1667, 1488, 1450, 1214, 1082, 668 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{18}N_2$ $[M]^+$: 178.1470. Found: 178.1469.

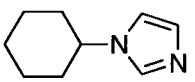


1-(1-Methylcycloheptyl)-1*H*-imidazole (6ca, Table 2.8, entry 3). Isolated 33 mg (45%) as a clear, colourless oil after column chromatography (15% Acetone/CH_2Cl_2 → 5% MeOH/CH_2Cl_2). TLC R_f 0.56 (10% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 7.68 (br s, 1H), 7.10 (br s, 1H), 2.128-2.12 (m, 2H), 1.89 (ap dd, J = 15.3 and 6.6 Hz, 2H), 1.82 (s, 2H), 1.62-1.51 (m, 8H), 1.46 (s, 3H); ^{13}C NMR (75 MHz) 134.6 (CH), 128.7 (CH), 116.5 (CH), 61.2 (C), 41.2 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 22.7 (CH_3); IR (film): 2927, 2858, 1489, 1223, 1087, 914 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{16}N_2$ $[M]^+$: 178.1470. Found: 178.1473.



1.3 : 1

***anti* 1-(4-Isopropenyl-1-methyl-cyclohexyl)-1H-imidazole and *syn* 1-(4-isopropenyl-1-methyl-cyclohexyl)-1H-imidazole (6da, Table 2.8, entry 4).**[99] Isolated 68 mg (81%) of a mixture of diastereomers as a clear, colourless oil after column chromatography (4% $MeOH/CH_2Cl_2$). TLC R_f 0.56 (10% $MeOH/CH_2Cl_2$); IR (film): 3083, 2936, 2864, 1728, 1704, 1644, 1491, 1453, 1224, 1205, 1156, 1129, 1082, 1031, 887 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{20}N_2$ $[M]^+$: 204.1626. Found: 204.1637. **major**: ^1H NMR ($CDCl_3$, 300 MHz) 7.70-7.65 (m, 1H), 7.13-7.04 (m, 2H), 4.76-4.74 (m, 2H), 2.13-2.09 (m, 2H), 2.03-1.82 (m, 3H), 1.76 (s, 3H), 1.74-1.66 (m, 2H), 1.52 (s, 3H), 1.32-1.22 (m, 2H); ^{13}C NMR (75 MHz) 134.5 (CH), 128.9 (CH), 116.0 (CH), 57.3 (C), 44.3 (CH), 38.3 (CH_2), 33.2 (CH_2), 27.7 (CH_2), 25.2 (CH_3), 21.0 (CH_3); **minor**: ^1H NMR ($CDCl_3$, 300 MHz) 7.65-7.61 (m, 1H), 7.13-7.04 (m, 1H), 7.02-6.98 (m, 1H), 4.65-4.64 (m, 1H), 4.59-4.58 (m, 1H), 2.49-2.39 (m, 2H), 2.13-2.09 (m, 2H), 2.03-1.82 (m, 3H), 1.62 (s, 3H), 1.36 (s, 3H), 1.32-1.22 (m, 2H); ^{13}C NMR (75 MHz) 134.5 (CH), 128.9 (CH), 116.0 (CH), 56.7 (C), 44.0 (CH), 37.2 (CH_2), 33.2 (CH_2), 26.5 (CH_2), 25.2 (CH_3), 20.8 (CH_3).



1-Cyclohexyl-1*H*-imidazole (6ea, Table 2.8, entry 5). Isolated 16 mg (26%) as a clear, colourless oil after column chromatography (5% $MeOH/CH_2Cl_2$). TLC R_f 0.37. (10% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) 7.57 (s, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 3.90 (tt, J = 11.7 and 3.8 Hz, 1H), 2.17-2.03 (m, 2H), 1.94-1.84 (m, 2H), 1.80-1.52 (m, 3H), 1.47-1.15 (m,

(99) Relative stereochemistry was assigned by analogy with the ethers described by Inoue in ref. 44, pg. 48.

3H); ^{13}C NMR (75 MHz) 135.6 (CH), 128.9 (CH), 117.4 (CH), 57.2 (CH), 34.7 (CH_2), 25.7 (CH_2), 25.5 (CH_2); IR (film): 3107, 2938, 2858, 1715, 1497, 1449, 1276, 1232, 1079, 660 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{14}N_2$ $[M]^+$: 150.1157. Found: 150.1161. Spectral data were found to be in good agreement with those in the literature.[100]

Procedure for Equation 2.32. A 100 mL quartz flask was charged with a stir bar, methyl benzoate (0.198 g, 1.46 mmol), imidazole (0.276 g, 4.06 mmol), 80 mL EtOAc, followed by trifluoromethanesulfonic acid (0.122 g, 0.810 mmol). The mixture was stirred for 10s. (*R*)-(+)-Limonene, **4d,** (0.553 g, 4.06 mmol) was added, the flask was capped with a rubber septum and purged with a nitrogen balloon and an outlet for 20 minutes while stirring. The septum was then covered with black electrical tape to create a better airtight seal. The tube was then placed between two Luzchem exposure panels each equipped with four ultraviolet lamps for 72 hours while stirring. The crude reaction mixture was concentrated under reduced pressure and analyzed by ^1H NMR. The mixture was determined to contain 30% of a 1.3:1 mixture of *anti* and *syn* 1-(4-Isopropenyl-1-methyl-cyclohexyl)-1H-imidazole, respectively, as well as 55% 1-Isopropenyl-4-methylenecyclohexane[101] and 15% Limonene, calculated with respect to unreacted Limonene. The crude reaction mixture was then purified by column chromatography (hexanes) to give a 3.7:1 mixture of **7** and **4d**, respectively. A solution of the mixture in pentane (3.77g/100mL with respect to Limonene) was prepared, and found to have an $[\alpha]^{25}_D = 0°$, indicating the Limonene had racemized under the reaction conditions. In comparison, a solution of fresh (*R*)-(+)-Limonene in pentane (3.77g/100mL) was also prepared and found to have an

(100) Perry, M. C.; Powell, M. T.; Cui, X.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.

(101) Shim, S. C.; Kim, D. S.; Yoo, D. J.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2002**, *67*, 5718.

$[\alpha]^{25}_{D}$ = 114°, consistent with results reported in the literature.[102] The optical rotations were recorded on a Perkin-Elmer 241 Polarimeter equipped with a sodium lamp operating at 589 nm.

(102) Sakane, S.; Fujwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 6154.

Chapter 3. Intermolecular Cope-Type Hydroamination of Unsaturated Substrates [1]

(1) Portions of this chapter have been published: (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410. (b) Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492. (c) Moran, J.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893. (d) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895.

3.1. Introduction

Acid-catalysis is a conceptually simple and potentially highly practical approach to the hydroamination of alkenes, yet it suffers from key limitations. Chapter 2 described a photochemical method to overcome the buffering effect of basic amines, the classical hurdle to achieving acid-catalyzed hydroamination. This progress revealed yet another potentially insurmountable obstacle for the acid-catalyzed approach: once a carbocation is formed, elimination is competitive with nucleophilic addition of the basic amine. The fundamental limitations of a mechanism involving *stepwise* protonation followed by amination led us to consider if *concerted* addition pathways could serve as alternatives. Concerted reactions of alkenes are among the most reliable and widely used in organic synthesis (Figure 3.1).

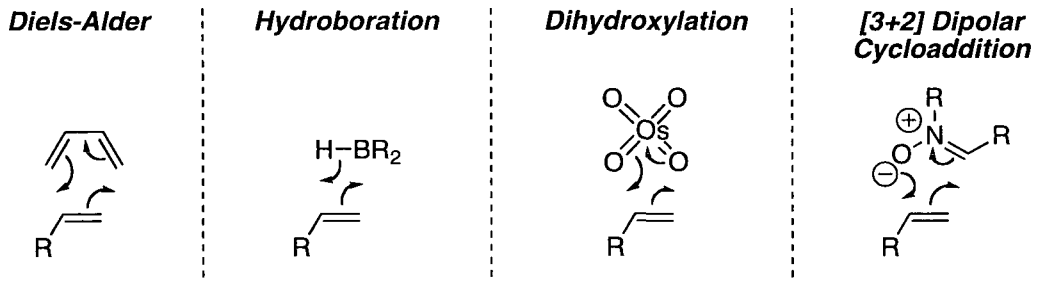


Figure 3.1. Examples of widely used concerted reactions of alkenes.

We hypothesized that bifunctional amines of the type RNHXH could undergo concerted amination/protonation of the alkene, resulting in a simple, low-energy hydroamination pathway that completely bypasses the buffering problems associated with acid catalysis. One such potential concerted approach to hydroamination is the microscopic reverse of the Cope elimination reaction, where the hydrogen and nitrogen of a hydroxylamine add to give an amine *N*-oxide (Figure 3.2).

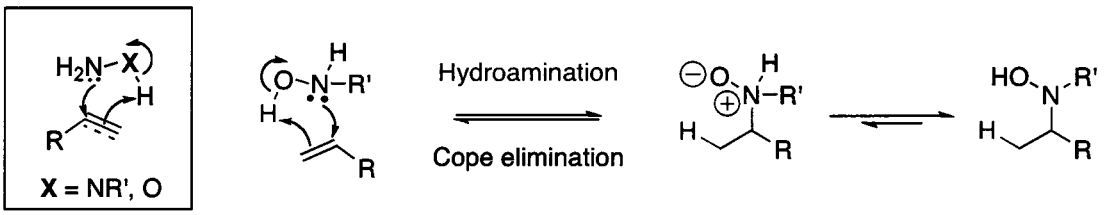


Figure 3.2. The microscopic reverse of the Cope elimination is hydroamination.

This chapter documents the development of intermolecular hydroamination reactions that are mechanistically related to the Cope elimination. To help appreciate this reactivity, the Cope elimination, the reverse Cope cyclization and the Beauchemin group's lead results in this area are reviewed.

3.1.1. The Cope Elimination[2]

Although described by Wolffenstein as early as 1898,[3] a systematic series of reports by Cope and coworkers beginning in 1949 showed that heating trialkylamine-*N*-oxides possessing a β-hydrogen leads to the formation of an olefin and a *N,N*-dialkylhydroxylamine.[4] The reaction, commonly referred to as the Cope elimination, is well established as an intramolecular *syn*-elimination as determined by stereochemical[4b-g,5] and labeling studies[6] as well as kinetic isotope effects[7] (Figure 3.3).

---

(2) For a reviews, see: (a) DePuy, C. H.; King, R. W. *Chem Rev.* **1960**, *60*, 431. (b) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.

(3) (a) Wernick, W.; Wolffenstein, R. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1553. (b) Mamlock, L.; Wolffenstein, R. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 159.

(4) (a) Cope, A. C.; Foster, T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929. (b) Cope, A. C.; Pike, R. A.; Spencer, C. *J. Am. Chem. Soc.* **1953**, *75*, 3212. (c) Cope, A. C.; McLean, D. C.; Nelson, N. A. *J. Am. Chem. Soc.* **1955**, *77*, 1628. (d) Cope, A. C.; Bumgardner C. L. *J. Am. Chem. Soc.* **1957**, *79*, 960. (e) Cope, A. C.; Bumgardner, C. L.; Schweizer, E. E. *J. Am. Chem. Soc.* **1957**, *79*, 4729. (f) Cope, A. C.; Acton, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 355. (g) Cope, A. C.; Ciganek, E.; Howell, C. F.; Schweizer, E. E. **1960**, *82*, 4663. (h) Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656.

(5) Cram, D. J.; McCarty, J. E. *J. Am. Chem. Soc.* **1954**, *76*, 5740.

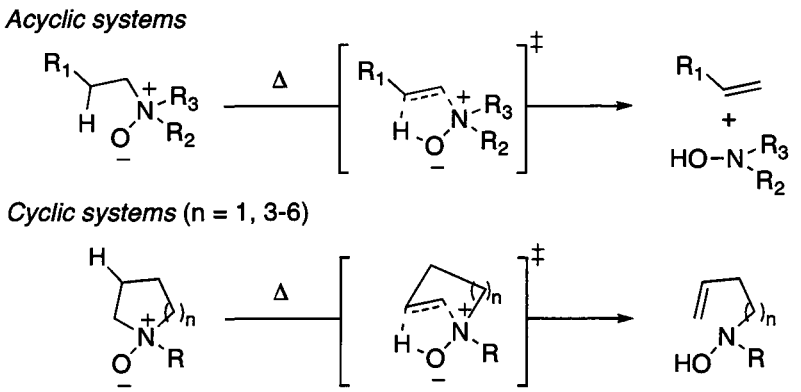
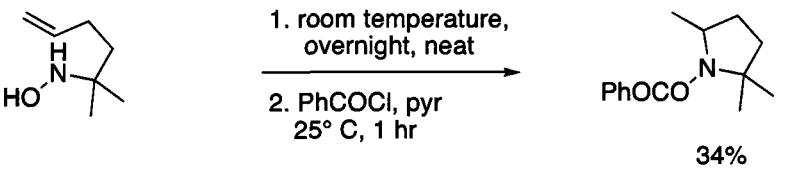


Figure 3.3. The Cope elimination is a *syn*-elimination.

Cyclic amine-*N*-oxides (5 and 7-10 membered rings) ring-open to produce an alkenylhydroxylamine, but with 6-membered rings the reaction is difficult.[4h]

3.1.2. The Reverse Cope Cyclization[8]

The microscopic reverse of the Cope elimination in a cyclic system is called the "reverse Cope cyclization." The reaction was first reported by House and coworkers in 1976 to form pyrrolidines from alkenylhydroxylamines simply upon standing at room temperature via a proposed free radical mechanism (Equation 3.1).[9]



(3.1)

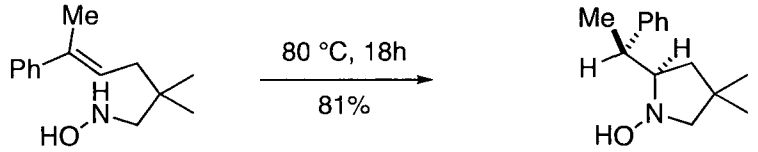
(6) Bach, R. D.; Andrzejewski, D.; Dusold, L. R. *J. Org. Chem.* **1973**, *38*, 1742.

(7) (a) Chiao, W.-B.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2802. (b) Kwart, H.; George, T. J.; Louw, R.; Ultee, W. *J. Am. Chem. Soc.* **1978**, *100*, 3927. (c) Kwart, H.; Brechbiel, M. *J. Am. Chem. Soc.* **1978**, *100*, 2802.

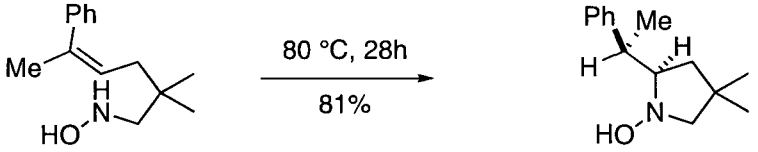
(8) For an excellent review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

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

Seminal studies by Ciganek revealed the scope and limitations of this hydroamination reaction, however several observations, as well as those of Black and Doyle, seemed to be more consistent with a concerted mechanism.[10] Finally in 1994, Oppolzer and coworkers provided compelling stereochemical evidence for such a mechanism, which proceeds through a suprafacial five-membered transition state (Equation 3.2 and Equation 3.3).[11]



(3.2)



(3.3)

These reports revived interest in the reverse Cope cyclization and subsequent contributions from Holmes, Knight, Jäger and others expanded the scope to include alkynes,[12] investigated its use in saturated heterocycle synthesis[13] and introduced creative ways to access

(10) (a) Black, D. St. C.; Doyle, J. E.; *Aust. J. Chem.* **1978**, *31*, 2317. (b) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. (c) Ciganek, E.; Read, J. M. Jr.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795. (d) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803.

(11) (a) Oppolzer, W; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139. See also: (b) Oppolzer, W. *Gazz. Chim. Ital.* **1995**, *125*, 207.

(12) (a) Pradhan, S. K.; Akamanchi, K. G.; Divakaran, P. P.; Pradhan, P. M. *Heterocycles* **1989**, *28*, 813. (b) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393. (c) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *Tetrahedron Lett.* **1992**, *33*, 7421. (d) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M.; Ziller, J. W. *Tetrahedron Lett.* **1992**, *33*, 7425. (e) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3379. (f) Davison, E. C.; Holmes, A. B.; Forbes, I. T. *Tetrahedron Lett.* **1995**, *36*, 9047. (g) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (h) Smith, C. J.; Holmes, A. B.; Press, N. J. *Chem. Commun.* **2002**, 1214.

(13) (a) Bagley, M. C.; Tovey, J. *Tetrahedron Lett.* **2001**, *42*, 351. (b) Knight, D. W.; Leese, M. P.; De Kimpe, N. *Tetrahedron Lett.* **2001**, *42*, 2597. (c) Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593. (d) Yamada, F.; Hasewaga, T.; Wakita, M.; Sugiyama, M.; Somei, M. *Heterocycles* **1986**, *24*, 1223. (e) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *J. Org. Chem.* **1997**, *62*, 8251. (f) Coogan, M. P.; Knight, D. W. *Tetrahedron Lett.* **1996**, 37, 6417.

the cyclization precursors from nitrones.[14] The overall reactivity trends of the reverse Cope cyclization are summarized in Figure 3.4.

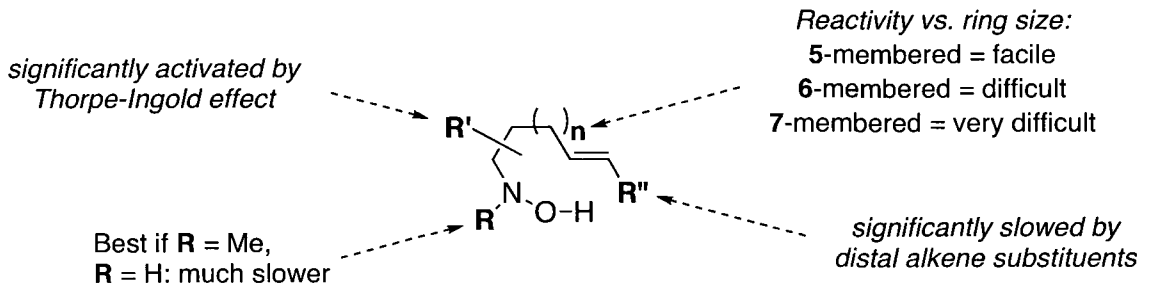
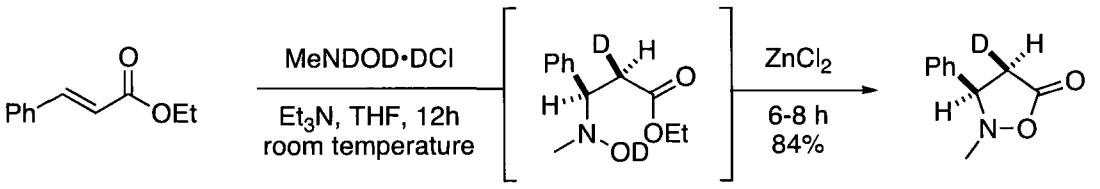


Figure 3.4. Summary of reactivity tends for the reverse Cope cyclization.

3.1.3. Precedent for Intermolecular Cope-Type Hydroamination

In stark contrast to the body of work on the reverse Cope cyclization, reports of intermolecular Cope-type hydroamination reactions are scarce. Niu and Zhao reported that *N*-methylhydroxylamine undergoes a stereospecific 1,4-addition to α,β-unsaturated esters via a concerted mechanism (Equation 3.4), but synthetically useful intermolecular variants that do not involve a biased electrophilic olefin have yet to appear in the literature.[15]

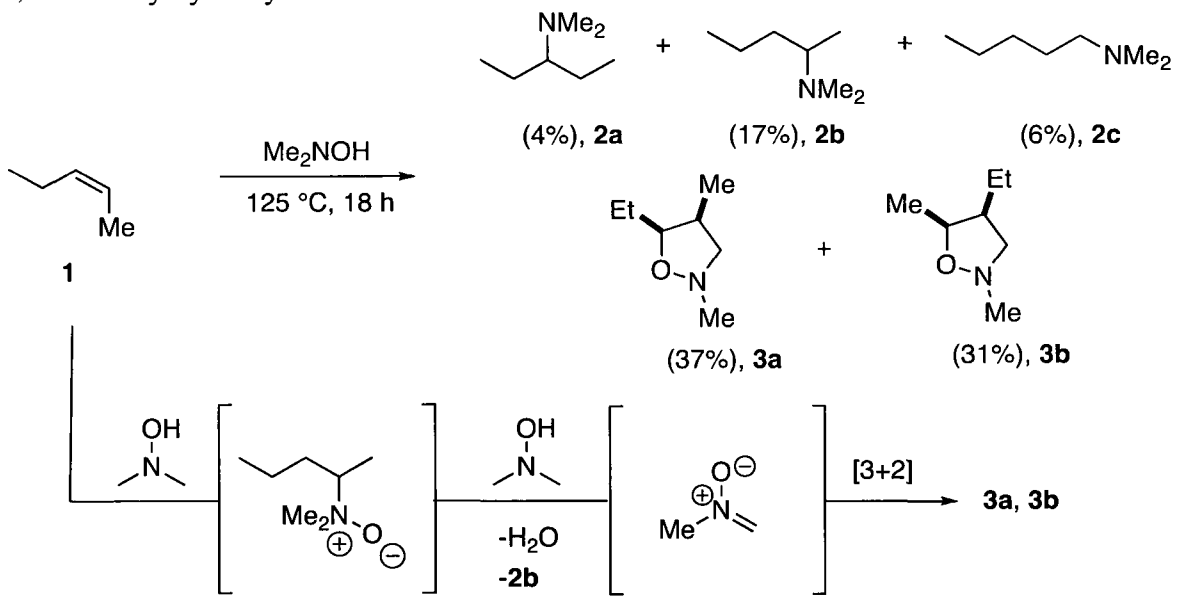


(14) For access to reverse Cope cyclization precursors via nucleophilic additions to nitrones, see: (a) Takahashi, S.; Kusumi, T.; Sato, Y.; Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1777. (b) Gravestock, M. B.; Knight, D. W.; Malik, K. M. A.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3292. (c) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169. (d) Bell, K. E.; Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8545. (e) Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8549. (f) Wheildon, A. R.; Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **1997**, *38*, 8553. (g) Hanrahan, J. R.; Knight, D. W.; Salter, R. *Synlett* **2001**, 1587. (h) Palmer, A. M.; Jäger, V. *Eur. J. Org. Chem.* **2001**, *1293*, 2547. (i) Jäger, V.; Bierer, L.; Dong, H.-R.; Palmer, A. M.; Shaw, D.; Frey, W. *J. Heterocycl. Chem.* **2000**, *37*, 455. (j) Hanrahan, J. R.; Knight, D. W. *Chem. Commun.* **1998**, 2231.

(15) (a) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456. See also: (b) Moglioni, A. G.; Muray, E.; Castillo, J. A.; Álvarez-Larena, Á.; Moltrasio, G. Y.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2002**, *67*, 2402.

A report by Laughlin in 1973 hinted that intermolecular Cope-type hydroamination might have occurred, although the reaction pathway was obscured by subsequent complex side reactions (Scheme 3.1).[16] The formation of amines may be rationalized by an intermolecular Cope-type hydroamination reaction to give regioisomeric amine *N*-oxides, followed by reduction with another molecule of *N,N*-dimethylhydroxylamine to give a nitrone and amines **2a-c**. The resulting nitrone could then undergo subsequent [3 + 2] cycloaddition reactions to give the observed isoxazolidines **3a** and **3b**.

Scheme 3.1. Laughlin's report of amination reactivity between alkenes and *N,N*-dimethylhydroxylamine.

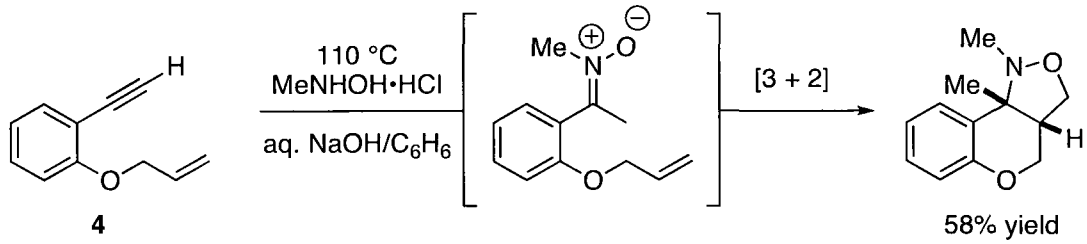


Padwa and Wong reported three examples in which an aryl acetylene (eg. **4**) reacts with an *N*-alkylhydroxylamine to form a nitrone intermediate which is then efficiently trapped by an intramolecular [3+2] cycloaddition (Equation 3.5).[17] However, the reaction could not be

(16) Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

(17) Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125.

extended to simpler substrates lacking a pendant dipolarophile such as phenyl acetylene, for example.

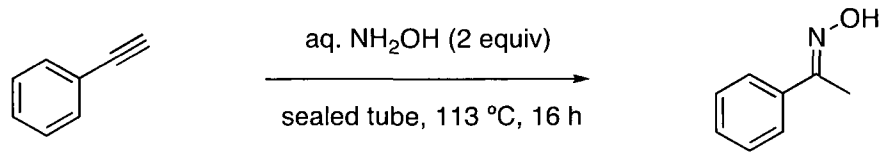


(3.5)

3.1.4. Preliminary Investigations into the Reactivity of Hydroxylamine with Alkynes

In light of the excellent progress in intramolecular systems over the past three decades, our group set out to develop efficient intermolecular Cope-type hydroaminations where the reactivity of the products is controlled. In an attempt to avoid the side products associated with oxidation of *N,N*-dialkylhydroxylamines observed by Laughlin, we began the investigation with the reaction of phenylacetylene with hydroxylamine itself, as a cheap commercially available 50 wt% aqueous solution. We reasoned that the weaker π bond of an alkyne, combined with the stability of the oxime products would allow for the greatest chance of achieving the desired reactivity. Gratifyingly, Ms. Catherine Séguin and Ms. Marie-Eve Lebrun observed encouraging conversions to acetophenone oxime upon heating phenylacetylene and hydroxylamine in a sealed tube in a variety of organic solvents (dioxane, *i*-PrOH, DMSO, etc.). Further optimization by Séguin and Lebrun revealed that using dioxane as solvent is most efficient at higher concentrations, giving near quantitative conversion to the desired oxime (Table 3.1, entry 7).

Table 3.1. Optimization of the addition of aqueous hydroxylamine to phenylacetylene.[a]



5a **6a**

entry	solvent	[alkyne] (mol/L)	conversion (%)[b]
1	PhMe	0.25	10
2	$CHCl_3$	0.25	3
3	DME	0.25	33
4	THF	0.25	52
5	Dioxane	0.25	63
6	"	0.050	24
7	"	1.0	99
8	EtOH	0.25	49
9	*i*-PrOH	0.25	42
10	*n*-PrOH	0.25	48
11	DMSO	0.25	61
12	H_2O	0.25	1

[a] Standard conditions: alkyne (1 equiv), aq. NH_2OH (2 equiv.), 113 °C, 16 h. [b] Conversion determined by ^1H NMR using styrene as an internal standard

Heating the reaction mixture under similar aqueous conditions without the presence of hydroxylamine did not lead to any ketone product, leading us to believe that hydration followed by oxime formation was not the mechanistic pathway.

Preliminary substrate scope investigations showed that terminal aryl alkynes react well under these reaction conditions, with both steric and electronic variations on the arene ring being well tolerated. However, alkylacetylenes and internal alkynes gave low yields under these conditions.[18] More work was necessary to expand the generality of this reaction.

(18) For full details concerning the scope of this reaction, please see section 3.2.2.

3.2. Results and Discussion

3.2.1. Reactions of Aqueous Hydroxylamine with Alkenes

Stimulated by the success with alkynes, investigations were initiated towards the intermolecular Cope-type hydroamination of alkenes. Success in this venture would allow for the rapid synthesis of *N*-alkyl- and *N,N*-dialkylhydroxylamines, which can be easily reduced to the parent amines, but also have applications as monoamine oxidase inhibitors,[19] lipid antioxidants,[20] and as photographic developers.[21] Initial reactions were performed with norbornene, whose strain energy renders it significantly more reactive and provides a thermodynamic driving force, although it was not known if the produced *N*-alkylhydroxylamines would survive the reaction conditions.[22,23] After extensive experimentation, the reaction was found to be very sensitive to solvent and concentration effects. Surprisingly, initial trials in dioxane under the conditions used for aromatic alkynes showed almost no reaction. Starting materials were consumed when DMSO-d_6 was employed as solvent, but despite considerable effort, a complex reaction mixture containing little desired product was produced. For alkenes,

---

(19) Benington, F.; Morin, R. D.; Clark, L. C., Jr. *J. Med. Chem.* **1965**, *8*, 100.

(20) Van Der Veen, J. Weil, J. T.; Kennedy, T. E.; Olscott, H. S. *Lipids* **1970**, *5*, 509.

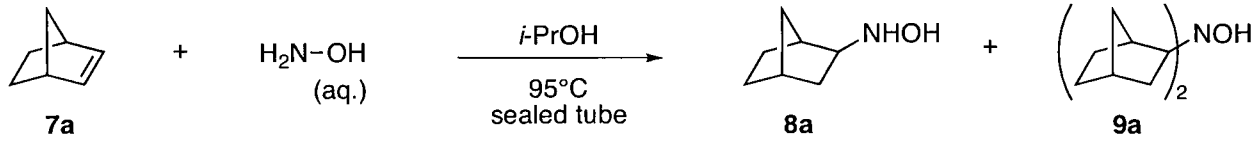
(21) Green, M.; Adnan, S. A.; Ulrich, H. Aminoalkyl hydroxylamines as photographic developers. U.S. Patent 3,287,125, November 22, 1966.

(22) For selected examples of norbornene in catalytic hydroamination reactions, see: (a) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *126*, 1798. (c) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179. (d) Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561. (e) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640. (f) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542. (g) Kemper, J.; Studer, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 4914. (h) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, *6*, 2515. (i) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519. (j) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857.

(23) For an example of an alternate route to *exo*-norbornylamines, see: Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedron Lett.* **2005**, *46*, 7831.

unlike alkynes, alcoholic solvents proved uniquely effective to obtain hydroamination products and minimize side reactions (Table 3.2).

Table 3.2. Optimization of hydroamination of norbornene in aqueous NH_2OH.[a,b]



7a **8a** **9a**

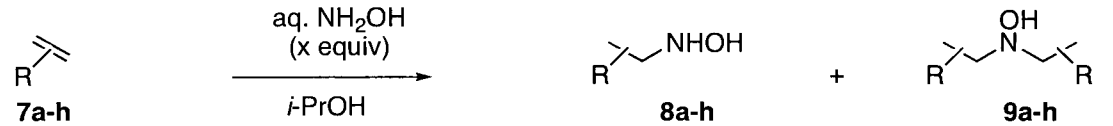
entry	solvent	[NH_2OH] (mol/L)[c]	equiv NH_2OH	time (h)	conversion (%)	ratio (**8a**:**9a**)
1	C_6D_6	10	10	14	<1	_
2	THF	10	10	14	<1	_
3	Dioxane	10	10	14	3	>20:1
4	$CDCl_3$	10	10	14	5	>20:1
5	MeOH	10	10	14	29	8.7:1
6	EtOH	10	10	14	14	>20:1
7	*i*-PrOH	10	10	14	53	9.6:1
8	"	1.0	5.0	14	<1	_
9	"	5.0	2.0	14	65	1:1.5
10	"	5.0	2.0	24	99[d]	1:2.2
11	"	10	2.0	14	54	7.0:1
12	*n*-PrOH	10	10	14	21	6.0:1
13	CF_3CH_2OH	10	10	14	10	>20:1
14	DMSO-d_6	10	10	14	2	>20:1
15	none[e]	N/A	10	14	<1	_

[a] Conditions: alkene (1 equiv), aq. NH_2OH, sealed tube (+ blast shield), 14-24h. [b] Conversions determined by ^1H NMR using styrene as an internal standard. [c] Relative to *i*-PrOH. [d] Isolated yield after column chromatography. [e] No *i*-PrOH added. Heterogeneous mixture.

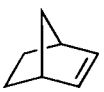
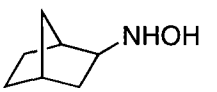
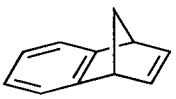
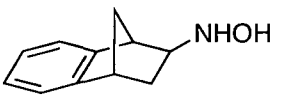
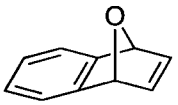
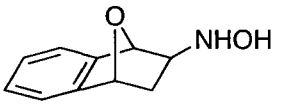
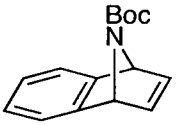
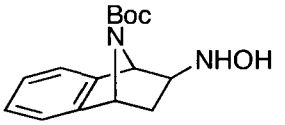
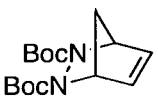
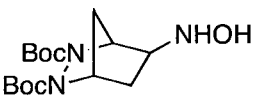
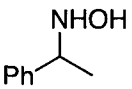
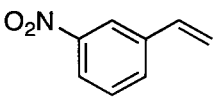
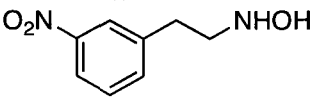
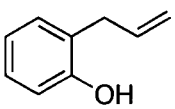
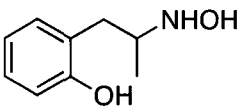
Isopropanol was found to be the most effective alcohol for this reaction, most likely due to its ability to solubilize both aqueous hydroxylamine and norbornene. Compounds **8a** and **9a** were formed in 53% combined conversion (**8a**:**9a** = 9.6:1) simply upon heating to 95 °C in *i*-PrOH for 14 h. As the reaction appeared to be very sensitive to changes in the water to *i*-PrOH ratio, both concentration and equivalents of aqueous hydroxylamine had to be studied independently in order to maximize conversion. At the optimum concentration (5.0 M in *i*-PrOH), selectivity for either the mono- or bis-hydroamination product can be achieved by varying the equivalents of NH_2OH. A tenfold excess of hydroxylamine gave

monohydroamination product **8a** with good selectivity (entry 7), while a twofold excess resulted in a slight preference for bishydroamination product **9a** in 99% combined yield (entry 10).

Table 3.3. Reaction of aqueous NH_2OH with alkenes.[a]



7a-h **8a-h** **9a-h**

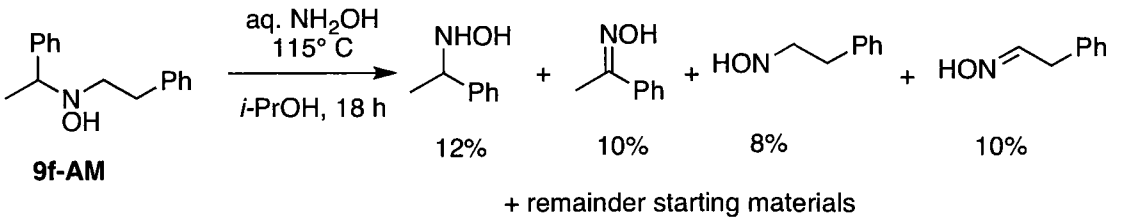
entry	alkene		monoaddition product		x	T (°C)	yield **8+9** (%)	ratio (**8**:**9**)
1		**7a**		**8a**	2	95	99	1:2.2
					10	95	65	7.1:1
2		**7b**		**8b**	2	95	98	1:1.5
					10	95	49	14:1
3		**7c**		**8c**	2	95	95	1.9:1
4		**7d**		**8d**	2	95	48	> 20:1
5		**7e**		**8e**	2	95	55	> 20:1
6		**7f**		**8f**	2	140	39	2.2:1[b]
7		**7g**		**8g**	2	95	30	> 20:1
8		**7h**		**8h**	2	115	13	> 20:1

[a] Conditions: alkene (1 equiv), aq. NH_2OH (x equiv, 5M in *i*-PrOH), sealed tube (+ blast shield), 24-48h. [b] 12:1 mixture of regioisomers (branched:linear).

A variety of strained alkenes displayed excellent reactivity under these optimized reaction conditions (Table 3.3). Predictably, mixtures of mono- and bis-hydroamination products were observed. While the bis-hydroamination product **9** is typically favoured in the presence of 2

equivalents of NH_2OH (entries 1 and 3), the mono-hydroamination product **8** is favoured in the presence of excess NH_2OH (entries 2 and 4). More hindered strained alkenes also led to selective formation of the mono-hydroamination product **8** (entries 4-5). Given their lack of strain release energy and a report by Hartwig that hydroamination of vinylarenes are approximately thermoneutral,[8] such substrates were expected to be more challenging. Gratifyingly, simply heating styrene and other vinylarenes under similar conditions gave hydroamination products (entries 6-7). Even the unconjugated 2-allylphenol was found to be reactive, albeit in very low yield (entry 8). Both the regioselectivity and preference for forming either the mono- or bis-hydroamination product was found to be substrate specific, as was the yield. Nonetheless, these results offered promise that greater alkene generality was possible.

Control experiments were conducted to determine if the reactions with vinylarenes were reversible. Heating secondary hydroxylamine **9f-AM** under similar reaction conditions led to the detection of several primary hydroxylamine compounds as well as oximes that appear to arise from their oxidation (Equation 3.6). These initial results indicated that reactions of vinylarenes were under thermodynamic control.



(3.6)

3.2.2. Reinvestigation of the Reaction of Aqueous Hydroxylamine with Alkynes[24]

The discovery that alcohols mediate difficult Cope-type hydroamination reactions prompted reinvestigation of the substrate scope with respect to alkynes. Table 3.4 summarizes all

(24) The work in section 3.2.2 was performed by Ms. Marie-Eve Lebrun, Ms. Catherin Séguin and Ms. Anne-Catherine Bédard. Full experimental data and characterization for this section are not contained in this thesis but can be found in refs. 1a and 1c.

findings after reinvestigation of conditions by Ms. Marie-Eve Lebrun and Ms. Anne-Catherine Bédard. In general, terminal aryl alkynes react well under these reaction conditions, with both steric and electronic variations on the arene ring being well tolerated (entries 1-7). Enynes and alkylacetylenes are also reactive, requiring higher temperatures to achieve good yields (entries 8-10). Notably, the reaction is compatible with alkynes bearing a basic pyridine group, free hydroxyl groups,[25] and common protecting groups (entries 7, 11-15, 17-19). However, a tetrahydropyran-protected substrate led to the isolation of the deprotected product in 65% yield (entry 16). In general, heating to 140 °C in *i*-PrOH under microwave irradiation was found to give improved yields for less reactive terminal (entries 8-19) and internal alkynes (entries 20-22). In most cases, the unreacted starting material could be recovered and the products were conveniently isolated by chromatography or recrystallization. The transformation has been carried out easily on scales of over 4 g, and can also be performed without the use of a sealed tube under typical reflux conditions by employing a higher boiling solvent such as 1-butanol (entry 1, condition B).

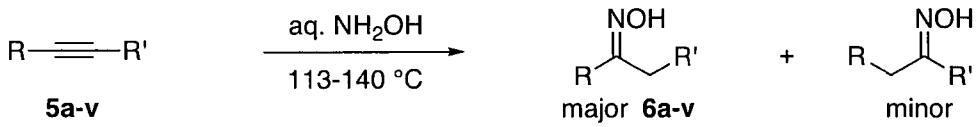
To rule out hydration of the alkyne to the ketone and subsequent oxime formation as a mechanistic pathway, phenylacetylene, 1-octyne and 1,1-diphenylpropargyl alcohol were heated to 140 °C in aqueous *i*-PrOH under microwave irradiation and no ketone products were detected in all cases.[26] Furthermore, heating the reaction products under the reaction conditions showed little reversibility, indicating the reactions of alkynes are under kinetic control.

---

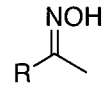
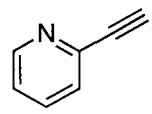
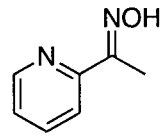
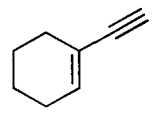
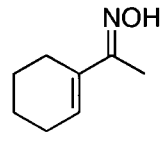
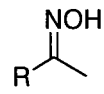
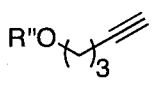
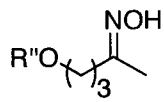
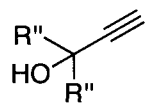
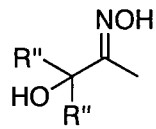
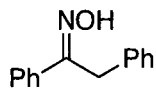
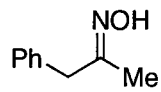
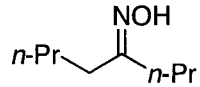
(25) For applications of α-hydroxy oximes as ligands in ferromagnetically coupled complexes see: Pathmalingam, T.; Gorelsky, S. I.; Burchell, T. J.; Bédard, A.-C.; Beauchemin, A. M.; Clérac, R.; Murugesu, M. *Chem. Commun.* **2008**, 2782.

(26) For selected reviews on the hydration of alkynes, see: (a) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121. (b) Oestrich, M. In *Science of Synthesis*, Vol. 25; Brüchner, R., Ed.; Thieme: Stuttgart, 2006; p 199. (c) Figadière, B.; Franck, X. In *Science of Synthesis*, Vol. 26; Cossy, J., Ed.; Thieme: Stuttgart, 2004; p 401. (d) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

Table 3.4. Reaction of alkynes with aqueous NH_2OH.



5a-v major **6a-v** minor

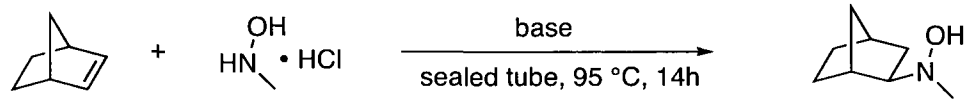
entry	substrate	conditions[a]	major product		yield(%)[b]
1	R= Ph, R' = H	A B		**6a**	87(5) 90(8)
2	R= 4-$OMeC_6H_4$, R' = H	A		**6b**	83(3)
3	R= 4-FC_6H_4, R' = H	A[c]		**6c**	71(8)
4	R= 2-MeC_6H_4, R' = H	A		**6d**	45(11)
5	R= 3-MeC_6H_4, R' = H	A		**6e**	75(2)
6	R= 4-MeC_6H_4, R' = H	A		**6f**	65(3)
7		A[c]		**6g**	73(15)
8		C D		**6h**	55(1) 72(3)
9	R= *n*-C_6H_{13}, R' = H	C D		**6i**	62 86(2)
10	R= *c*-C_6H_{11}, R' = H	D		**6j**	72
11	 R"= H	D		**6k**	91
12	R"= TBS	D		**6l**	86
13	R"= Bn	D		**6m**	98
14	R"= Piv	D		**6n**	90
15	R"= PMB	D		**6o**	98
16	R"= THP	D		**6p**	0[d]
17	 R"= H	E		**6q**	89(<1)
18	R"= Me	D		**6r**	75(<1)
19	R"= Ph	D		**6s**	63(1)
20	Ph—≡—Ph	C		**6t**	71
21	Ph—≡—Me	C D		**6u**	31(3) 53(5)
22	*n*-Pr—≡—*n*-Pr	C D		**6v**	7 12

[a] Reaction conditions: A: alkyne (1 equiv), aq. NH_2OH (2.5 equiv), dioxane (1 M), sealed tube (behind a blast shield), 113 °C, 16-18 h; B: reflux condenser, 1-butanol (1 M), 16 h; C: 140 °C, dioxane (2 M), 38-40 h; D: *i*-PrOH (1 M), 140°C (microwave), 5-10 h; E: 110 °C, *i*-PrOH (2 M), 70 h, sealed tube. [b] Yield of isolated products. Yield of minor regioisomer shown in parentheses. [c] 2 M in dioxane. [d] Led to isolation of unprotected oxime in 65% yield.

3.2.3. Reactions of *N*-Alkylhydroxylamines with Alkenes

The ability to use *N*-alkylhydroxylamines as starting materials in the Cope-type hydroamination promises to greatly expand the synthetic scope of the reaction and to simplify its outcome by eliminating the possibility of bis-hydroamination.

Table 3.5. Base and solvent effects on reactivity of *N*-methylhydroxylamine hydrochloride salt.[a]



7a **10h•HCl** **11h**

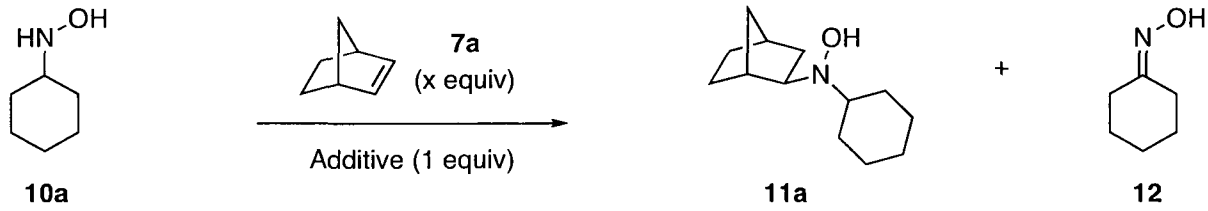
entry	solvent	base	**11h** (%)[b]
1	*i*-PrOH: H_2O (3:1)	NaOH	19
2	*i*-PrOH: H_2O (2:1)	Et_3N	13
3	*i*-PrOH	Et_3N	10
4	*i*-PrOH	imidazole	2
5	*i*-PrOH	NaO*i*-Pr	8
6	*i*-PrOH	K_2CO_3	4
7	*i*-PrOH	NaOH	12
8	THF	Et_3N	4

[a] Conditions: alkene (1 equiv), hydroxylamine (2 equiv), base (2 equiv), 95 °C, 14h, sealed tube. [b] NMR yield determined by ^1H NMR using styrene as internal standard.

As *N*-alkylhydroxylamines are typically commercially available as hydrochloride salts, we began our investigation with the addition of *N*-methylhydroxylamine hydrochloride

(**10h**•HCl) to norbornene. Reactions were screened using different *i*-PrOH:H_2O ratios and bases, however efficient conditions were not identified (Table 3.5).[27]

Table 3.6. Optimization of hydroamination of *N*-cyclohexylhydroxylamine with norbornene.[a]



10a **11a** **12**

entry	solvent	T (°C)	x	additive	**11a** (%)[b]	**12** (%)[b]
1	*i*-PrOH	95	1	none	13	29
2	MeOH	95	1	none	4	28
3	*n*-BuOH	95	1	none	9	35
4	*t*-BuOH	95	1	none	22	17
5	*n*-PrOH	95	1	none	30	31
6	*n*-PrOH	95	1	$NaCNBH_3$	46	10
7	*n*-PrOH	95	1	BHT[c]	31	31
8	*n*-PrOH	110	2	none	67	16
9	*n*-PrOH	110	2	$NaCNBH_3$	91[d]	<1
10	*n*-PrOH	110	2	$NaCNBH_3$	87[e]	<1
11	*n*-PrOH	110	5	$NaCNBH_3$	87	<1

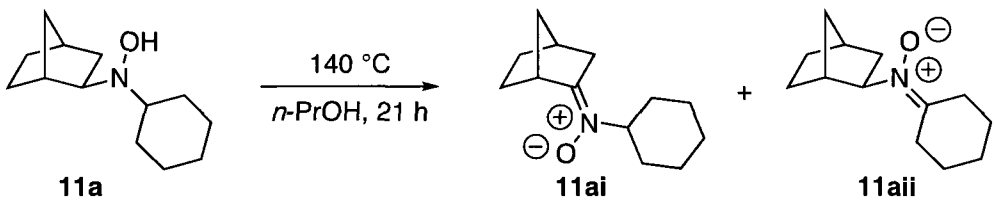
[a] Conditions: alkene (x equiv), hydroxylamine (1 equiv), additive (1 equiv), solvent (0.6 M in hydroxylamine), sealed tube, 18h. [b] NMR yield determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [c] BHT = 2,6-di-*tert*-butyl-4-methylphenol. [d] Isolated 83% yield after column chromatography. [e] Performed without Ar atmosphere.

The documented propensity of *N*-methylhydroxylamines to undergo oxidation chemistry[16] combined with the added complications of working with salts led us to investigate alternative *N*-alkylhydroxylamine sources. However, initial attempts to effect the addition of *N*-cyclohexylhydroxylamine (**10a**) to norbornene using our previously developed conditions did

(27) Ms. Elena Dimitrijevic is thanked for her honours project work, which resulted in Table 3.5 and significant parts of Table 3.6 and Table 3.7.

not prove fruitful as the major product was found to be the oxidation byproduct cyclohexanone oxime **12** and the bulk of the mass balance was unreacted starting material (Table 3.6, entry 1). *N*-Alkylhydroxylamines are known to undergo such oxidation chemistry simply upon dissolution in degassed polar solvents.[28]

Investigation of other alcohols revealed *n*-PrOH as a superior solvent (entries 2-5). The screening of a large number of additives (salts and reducing agents) revealed that one equivalent of sodium cyanoborohydride partially inhibited this oxidative pathway and gave a 46% yield of the desired hydroxylamine with only 10% loss to the oxime (entry 6). Examination of common anti-oxidant additives such as BHT did not decrease unwanted oxidation in the same manner (entry 7). Increasing the temperature to 110 °C and employing a twofold excess of alkene allowed for a more efficient reaction even without additive (entry 8). Finally, combining these improved conditions with the beneficial effects of $NaCNBH_3$ led to a 91% conversion (83% isolated yield) with no observable oxime byproduct (entry 9). Surprisingly, performing the reaction without an argon atmosphere did not significantly lead to increased oxidation (entry 10). Further increases in the amount of excess alkene were not beneficial (entry 11).



(3.7)

Expectedly, no reaction was observed when cyclohexanone oxime was re-exposed to the reaction conditions, confirming that the sodium cyanoborohydride was not simply reducing the

(28) (a) Horiyama, S.; Suwa, K.; Yamaki, M.; Kataoka, H.; Katagi, T.; Takayama, M.; Takeuchi, T. *Chem. Pharm. Bull.* **2002**, *50*, 996. (b) Beckett, A. H.; Rashid Purkaystha, A.; Morgan, P. H. *J. Pharm. Pharmacol.* **1977**, *29*, 15. (c) Lindeke, B.; Anderson, E. *Acta Pharm. Sueu.* **1975**, *12*, 183. (d) Posner, T. *Ann. Chim.* **1912**, *389*, 1. (e) Fischer, E.; Scheibler, H.; Groh, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2020. (f) Posner, T. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2316.

oxime back to the hydroxylamine under the reaction conditions. Acid is typically required to activate the oxime for such a transformation.[29] The additive therefore inhibits the thermal decomposition of the products at the required reaction temperatures. When **11a** was exposed to typical reaction conditions, significant decomposition to a mixture of compounds believed to be nitrones **11ai** and **11aii** was observed (Equation 3.7).[30] The same experiment, but with the addition of sodium cyanoborohydride, resulted in nearly quantitative recovery of starting materials. Only traces of the ^{1}H NMR resonances corresponding to the decomposition products could be observed under these conditions.

With new conditions compatible with *N*-alkylhydroxylamines in hand, we investigated the scope of the reaction with respect to the alkyl substituent on the hydroxylamine. A variety of *N*-alkylhydroxylamines successfully perform Cope-type hydroamination in good yields when heated to 110 °C with norbornene in the presence of sodium cyanoborohydride in *n*-PrOH (Table 3.7). Products possessing accessible β-hydrogens did not appear to undergo degradation via Cope elimination (entries 1 and 3-4). Unfortunately, *sec*-butylhydroxylamine did not provide any diastereoselectivity in our hands (entry 4). Hydroxylamines possessing bulky alkyl substituents such as neopentyl and norbornyl groups performed well under these conditions (entries 5-6). *N*-Phenylhydroxylamine underwent hydroamination albeit in low conversions, despite its propensity to disproportionate[31] and its predicted nucleophilic deactivation due to the adjacent

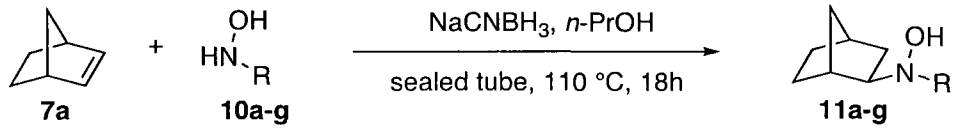
(29) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(30) The oxidation of unsymmetrical secondary hydroxylamines to nitrones has been studied. See: (a) Ali, S. A.; Hashmi, S. M. A.; Siddiqui, M. N.; Wazeer, M. I. M. *Tetrahedron* **1996**, *52*, 14917. (b) Hassan, A.; Wazeer, M. I. M.; Ali, S. A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 393. (c) Hassan, A.; Wazeer, M. I. M.; Saeed, M. T.; Siddiqui, M. N.; Ali, S. A. *J. Phys. Org. Chem.* **2000**, *13*, 443.

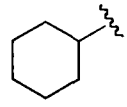
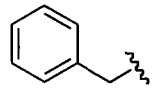
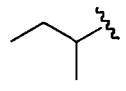
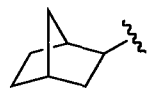
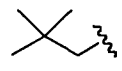
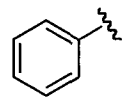
(31) The thermal disproportionation of PhNHOH to form aniline, nitrosobenzene and water is well documented. (a) Waters, W. A. *J. Chem. Soc. Perkin Trans. 2* **1976**, 732. (b) Becker, A. R.; Sternson, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2003.

phenyl ring (entry 7).[32] *N*-Alkylhydroxylamine hydrochloride salts can also be directly employed provided an equimolar quantity of NaOH is also added (entry 8).

Table 3.7. Reaction of *N*-alkylhydroxylamines with norbornene.[a]



7a + **10a-g** → **11a-g**

entry	R	product	conversion (%)[b]	yield (%)[c]
1		**11a**	91 (67[d])	83
2		**11b**	98	90
3		**11c**	99 (18[d])	73
4		**11d**	75 (8[d])	63[e]
5		**11e**	86	78
6		**11f**	72	68
7		**11g**	23	7
8[f]		**11h**	n.d.[g]	48

Conditions: [a] alkene (2 equiv), hydroxylamine (1 equiv), additive: $NaCNBH_3$ (1 equiv), *n*-PrOH (0.6 M), sealed tube, 110 °C, 18h. [b] Conversion determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard. [c] Isolated yield after column chromatography. [d] No $NaCNBH_3$. [e] dr = 1:1. [f] *N*-methylhydroxylamine hydrochloride (**10h**•HCl) and 1 equiv NaOH were employed. [g] Not determined due to broad peaks in ^1H NMR.

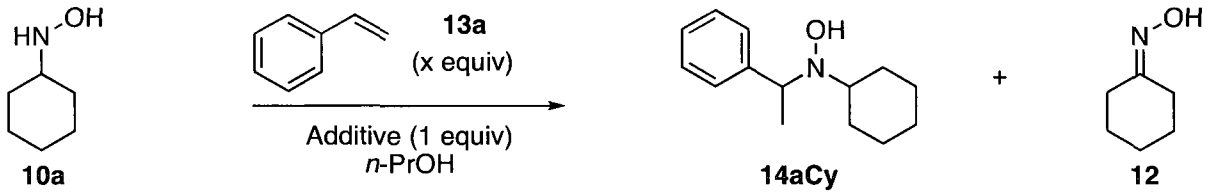
The extent of the beneficial effect of sodium cyanoborohydride varies drastically with the alkyl substitution of the hydroxylamine. For example, the conversion drops from 91% to 67% if

(32) The difficult product isolation in this case was likely due to the propensity of *N*-phenyl, *N*-alkylhydroxylamines to form stable nitroxyl radicals.

sodium cyanoborohydride is not employed with *N*-cyclohexylhydroxylamine (entry 1), but drops from 99% to 18% if it is not present when *N*-isopropylhydroxylamine undergoes addition (entry 3).

The reaction of **10a** with styrene to give the Markovnikov regioisomer **14aCy** was then optimized (Table 3.8). Similar trends were observed as with norbornene. Smaller quantities of oxidation byproducts were observed when $NaCNBH_3$ was employed (entry 2), although higher temperatures were required to achieve acceptable yields with styrene compared to strained alkenes (entries 3-5). Significant decomposition of the product occurred at temperatures above 140 °C.

Table 3.8. Optimization of hydroamination of *N*-cyclohexylhydroxylamine with styrene.[a]



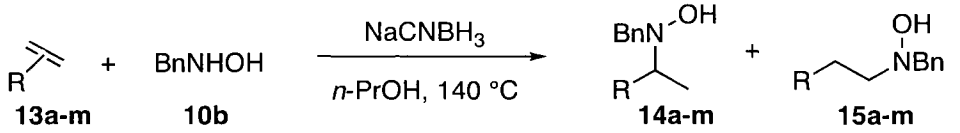
entry	T (°C)	t (h)	x	additive	**14aCy** (%)[b]	**12** (%)[b]
1	120	9	2	none	9	12
2	120	9	2	$NaCNBH_3$	18	5
3	100	16	5	$NaCNBH_3$	15	3
4	130	16	5	$NaCNBH_3$	43	5
5	140	16	5	$NaCNBH_3$	50	13

[a] Conditions: alkene (x equiv), hydroxylamine (1 equiv), additive (1 equiv), *n*-PrOH (0.6 M in hydroxylamine), sealed tube, 9-16h. [b] NMR yield determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard.

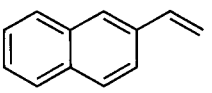
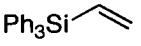
Reinvestigation of alkene scope with *N*-benzylhydroxylamine (**10b**), which possesses similar thermal stability to **10a**, revealed more efficient reactivity with vinylarenes than was previously observed with aqueous hydroxylamine. A variety of vinylarenes reacted with **10b** in

modest to good yields, consistent with precedent that hydroamination with such alkenes displays near thermoneutral reaction thermodynamics (Table 3.9).[8]

Table 3.9. Reaction of *N*-benzylhydroxylamine with vinylarenes and trimethylvinylsilane.[a]



13a-m **10b** **14a-m** **15a-m**

entry	reactant	major product	ratio (**14**:**15**)	yield (%)[b]
1	R = H	**14a**	>20:1	58
2	R = 4-F	**14b**	4.6:1	49
3	R = 4-Ph	**14c**	2.1:1	49
4	R = 3-Me	**14d**	>20:1	54
5	R = 4-Me	**14e**	>20:1	51
6	R = 2,4-Me	**14f**	>20:1	33
7	R = 4-OMe	**14g**	>20:1	49
8	R = 4-NH_2	**14h**	>20:1	36
9	R = perfluoro	**15i**	<1:20	66
10	R = CF_3	**15j**	1:2.7	59
11	R = 2-Br	**15k**	1:1.1	79
12		**14l**	>20:1	36
13		**15m**	<1:20	71

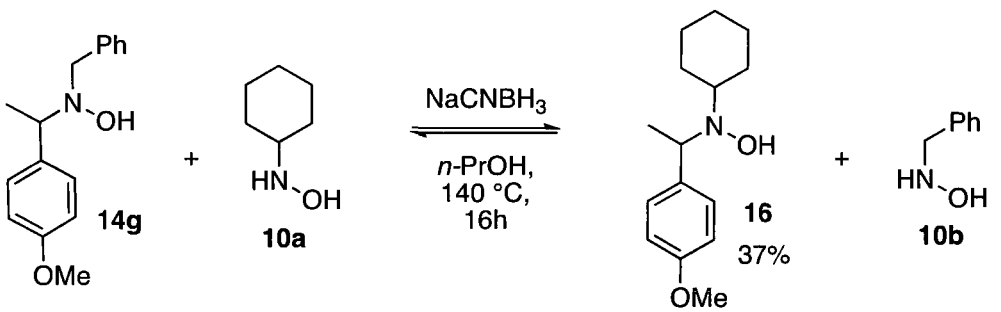
[a] Conditions: alkene (2 equiv), *N*-alkylhydroxylamine (1 equiv), $NaCNBH_3$ (1 equiv), *n*-PrOH (0.6 M), sealed tube, 140 °C, 14-18h. [b] Isolated yield after column chromatography.

In most cases, the mass balance was unreacted starting material and the products could be conveniently isolated by column chromatography. Steric variations near the alkene are well tolerated (entries 6-11), while electronic variations on the arene ring give slightly better yields while influencing regioselectivity. The more electron poor arenes favoured the anti-Markovnikov (**15**) products, offering a simple route to bioactive phenethylamines.[33] Styrene

(33) Parker, E. M.; Cubeddon, L. X. *J. Pharmacol. Exper. Ther.* **1988**, *245*, 199.

itself and other relatively less electron poor arenes favoured the formation of the Markovnikov (**14**) adducts. The complementary nature of this procedure versus metal-catalyzed methodologies is perhaps best illustrated by the successful reaction of alkenes possessing an aniline (entry 8) or aryl bromide moiety (entry 11). Triphenylvinylsilane was also reactive under these conditions, giving exclusively **15m** in 71% yield (entry 13).

Crossover experiments were designed to test the assertion that the addition to vinylarenes is indeed under thermodynamic control. Hydroamination product **14g** was heated to 140 °C in a sealed tube in the presence of one equivalent of *N*-cyclohexylhydroxylamine **10a** and $NaCNBH_3$. After 16 h, 37% of crossover product **16** was detected in the unpurified reaction mixture by ^1H NMR spectroscopy according to its characteristic triplet of triplets resonance at 2.53 ppm upon comparison with an independently synthesized sample (Equation 3.8). To ensure a direct comparison, hydroxylamine **16** was synthesized independently using 4-methoxystyrene and *N*-cyclohexylhydroxylamine (**10a**) under the conditions described in Table 3.9.

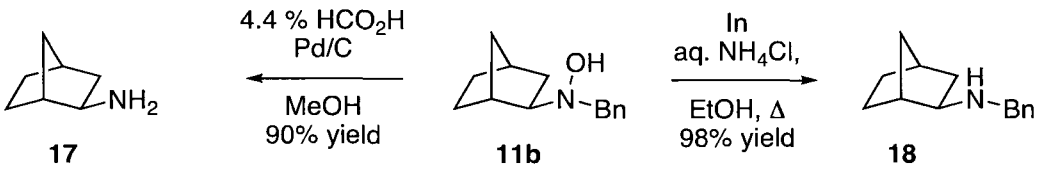


(3.8)

It should be noted that *N*-benzylhydroxylamine might be viewed as either an ammonia or a benzylamine equivalent in the context of the Cope-type hydroamination, as products can be selectively and efficiently deprotected to give either the primary amine[34] or the *N*-benzylamine[35] in one step (Scheme 3.2).[36]

(34) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442.

Scheme 3.2. Access to reduced derivatives of *N*-norbornyl-*N*-benzylhydroxylamine (**11b**).



Limitations were identified with respect to alkene substitution pattern and with certain functional groups (Figure 3.5). 1,3-Dienes, trisubstituted strained alkenes, 1,1- and 1,2-disubstituted styrenes and several unactivated alkenes showed no reaction under the conditions developed for both aqueous hydroxylamine and *N*-alkylhydroxylamines. Alkenes possessing moderately acidic groups such as carboxylic acids or boronic acids were not soluble in *n*-PrOH even upon addition of an external base and showed no reactivity. Alkenes possessing nitro groups were not compatible with the conditions developed for *N*-alkylhydroxylamines, although they survived in the presence of aqueous hydroxylamine (see Table 3.3).

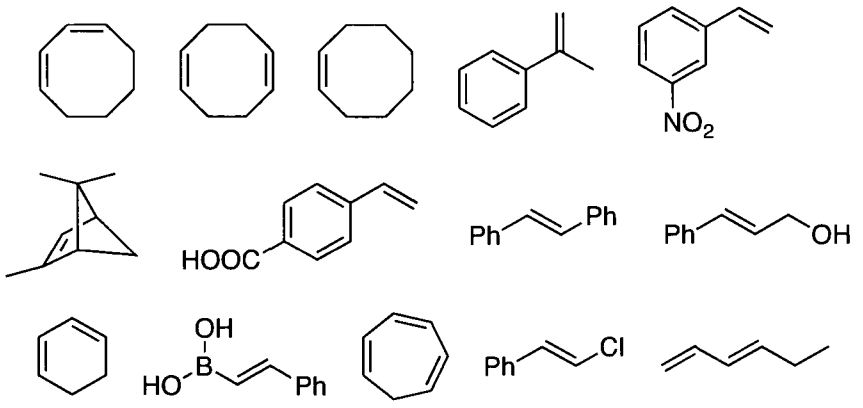


Figure 3.5. Unreactive or incompatible alkenes.

(35) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.

(36) For other representative methods for the reduction of *N,N*-disubstituted hydroxylamines, see: (a) Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973. (b) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 6469. (c) Murahashi, S.-I.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645. (d) Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett.* **1985**, *26*, 4633. (e) Kodera, Y.; Watanabe, S.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2542. (f) Merino, P.; Anoro, S.; Franco, S., Gascon, J. M.; Martin, V.; Merchan, F. L.; Revuelta, J.; Tejero, T.; Tunon, V. *Synth. Commun.* **2000**, *30*, 2989. (g) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159.

3.2.3.1. Reactions of *N*-Alkylhydroxylamines with Allenes: Access to Ketonitrones[37]

Nitrones are highly useful intermediates in organic synthesis and their reactivity has been studied extensively, particularly in the context of 1,3-dipolar cycloaddition chemistry.[38,39] The large bulk of this work focuses on aldonitrones, largely due to their ease of preparation via the condensation of an *N*-alkyhydroxylamine with an aldehyde. In contrast, the preparation of ketonitrones may not always be accomplished by simple condensation with a ketone and occasional reports of synthetic routes to these compounds are typically of narrow scope and are rare for linear ketonitrones.[40] As such, the applications of ketonitrones as 1,3-dipoles and radical traps have been much less extensive than for their aldonitrone cousins.[39-41] Herein, we report a direct preparation of ketonitrones via an *intermolecular* Cope-type hydroamination reaction of *N*-alkylhydroxyalmines with allenes.[42]

---

(37) Ms. Yael "Jennifer" Pfeiffer is thanked for the synthesis of non-commercially available allenes and well as selected hydroamination reactions presented in this section.

(38) (a) Grigor'ev, I. A. in *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Feuer, H., Ed.; Wiley: Hoboken, 2008; Chapter 2. (b) Tufaniello, J. J. in *1,3-Dipolar Cycloaddition Chemistry, Vol. 2*; Padwa, A., Ed.; VCH: New York, 1988; pp. 83-168.

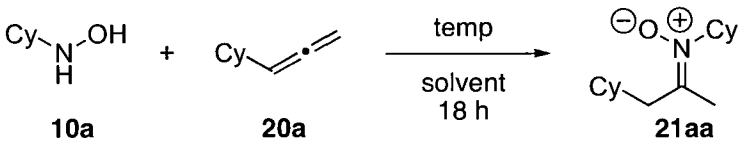
(39) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.

(40) (a) Fischer, R.; Hyrgova, E.; Fisera, L.; Hametner, C.; Cyranski, M. *Chemical Papers* **2005**, *59*, 275. (b) Tomioka, Y.; Nagahiro, C.; Nomura, Y.; Maruoka, H. *J. Heterocyclic Chem.* **2003**, *40*, 121. (c) Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *68*, 4772. (d) Hulsbos, E.; Marcus, J.; Brussee, J.; van der Gen, A. *Tetrahedron Asymmetry* **1997**, *8*, 1061. (e) Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1995**, *25*, 2275. (f) Black, D. St. C.; Johnson, L. M. *Aust. J. Chem.* **1984**, *37*, 117. (g) Exner, O. *Coll. Czechoslov. Chem. Commun.* **1951**, *16*, 258.

(41) (a) Hassan, I. E.; Charles, L.; Lauricella, R.; Tuccio, B. *New. J. Chem.* **2008**, *32*, 680. (b) Hassan, I. E.; Lauricella, R.; Tuccio, B. *Cent. Eur. J. Chem.* **2006**, *4*, 338.

(42) For intramolecular hydroaminations of *N*-allenylhydroxylamines, see: (a) Dumez, E.; Dulcère, J.-P. *Chem. Commun.* **1998**, 479. (b) Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur J. Org. Chem.* **2001**, 2577. (c) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632.

Table 3.10. Optimization of Reaction of **10a** with **20a**.



10a **20a** **21aa**

entry	solvent	temp (° C)	concentration (M)	conversion[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	87
8	*t*-BuOH	140	0.50	67[c]
9	*t*-BuOH	140	1.0	75

[a] Conditions: 2 equiv allene, 1 equiv **10a**, sealed tube, 18h. [b] Conversion determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [c] Only 1 equiv allene.

The addition of amines to allenes has been particularly well studied due to the activated nature of their double bonds and their ability to give either imines or allylamines depending on the regiochemistry of the reaction. [43,44,45] Gratifyingly, exposure of cyclohexylallene (**10a**) to the conditions known to effect additions of *N*-alkylhydroxylamines to strained alkenes resulted in the formation of ketonitrone **20aa** in acceptable yield (Table 3.10, entry 3). Optimization was undertaken to maximize the rate of addition while minimizing the amount of unwanted thermal

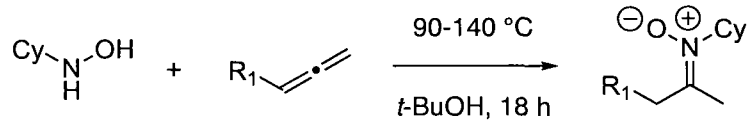
(43) For selected reviews including allene substrates, see: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (c) Hunt, P. A. *Dalton Trans.* **2007**, 1743. (d) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367-391. (e) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(44) For recent examples of intramolecular hydroaminations of allenes, see: (a) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (b) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (c) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (d) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2008**, 2741.

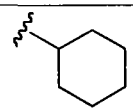
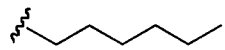
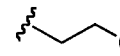
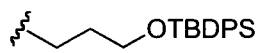
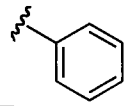
(45) For recent example of intermolecular hydroamination of allenes, see: (a) Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 5224. (b) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314. (c) Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157.

decomposition of hydroxylamine **10a**.[46] The reaction was found to occur in various protic and aprotic solvents. Although little change in the rate of the reaction was observed between the various solvents, *tert*-butanol was found to be most effective at minimizing this decomposition. Increasing the temperature and performing the reaction at 0.50 M in **10a** resulted in an efficient and clean reaction in 87% conversion (entry 8). The reaction still proceeded in 67% conversion if only 1 equivalent of allene was employed (entry 9).

Table 3.11. Reaction of **10a** with Allenes



10a **20a-e** **21aa-ae**

entry	R_1	product	conversion[a] (%)	yield[b] (%)
1		**21aa**	87	91
2		**21ab**	85	81
3		**21ac**	81	75
4		**21ad**	85	73
5		**21ae**	52	40[c]

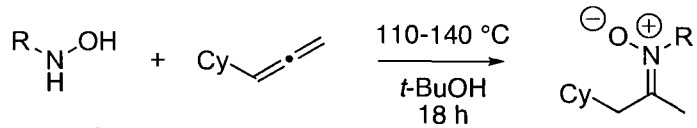
[a] Conversion determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [b] Isolated yield after column chromatography. [c] Heated to 90 °C.

The scope of the reaction with respect to the allene partner was then investigated. The reaction was found to be compatible with a variety of alkyl-substituted allenes, while aryl-substituted allenes were more challenging (Table 3.11). The ketonitrone products were easily purified by silica gel chromatography and in all cases no regioisomeric products were observed

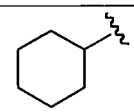
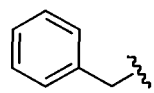
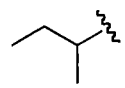
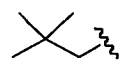
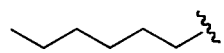
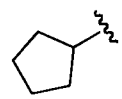
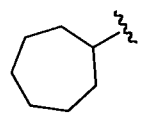
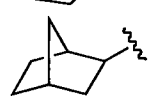
(46) For more on the thermal oxidation of hydroxylamines, see section 3.2.3, pg. 121.

by ^{1}H NMR. Unfortunately, reactions with disubstituted terminal and non-terminal allenes did not result in synthetically useful yields.

Table 3.12. Reaction of *N*-alkylhydroxylamines with cyclohexylallene



10a-i **20a** **21aa-ia**

entry	R	product	temperature (° C)	conversion[a] (%)	yield[b] (%)
1		**21aa**	140	87	91
2		**21ba**	140	80	81
3		**21ca**	110	n.d.[c]	63
4		**21da**	140	51	49
5		**21ea**	140	n.d.[c]	47
6		**21fa**	140	54	51
7		**21ga**	140	62	58
8		**21ha**	140	n.d.[c]	71
9		**21ia**	140	40	38

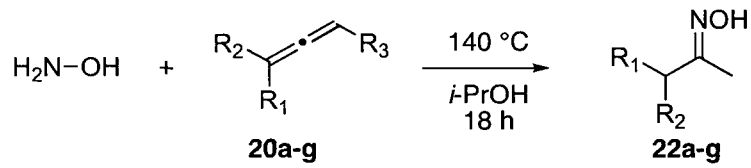
[a] Conversion determined by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. [b] Isolated yield after column chromatography. [c] Not determined due to overlapping peak in ^{1}H NMR.

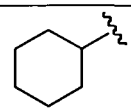
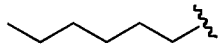
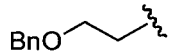
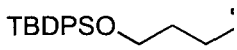
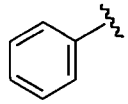
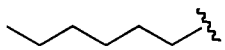
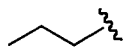
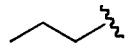
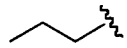
Investigation of the reaction scope with respect to hydroxylamine substitution revealed that a variety of *N*-alkylhydroxylamines afford Cope-type hydroamination products in good yields (Table 3.12). Hydroxylamines possessing bulky alkyl substituents such as neopentyl and

norbornyl groups performed well under the reaction conditions. Although hydroxylamines possessing linear alkyl groups decomposed under our conditions optimized for alkenes, *n*-hexylhydroxylamine gave the ketonitrone **21fa** in good yield under these reaction conditions.

Additions of aqueous hydroxylamine to allenes to give oximes were then carried out in excellent yields under the optimal conditions for addition of NH_2OH to alkenes (Table 3.13). The reaction times, temperature and reaction scope were similar to those observed with *N*-alkylhydroxylamines, while the higher yields were likely due to the superior thermal stability of aqueous hydroxylamine.

Table 3.13. Reaction of aqueous hydroxylamine with allenes[a]

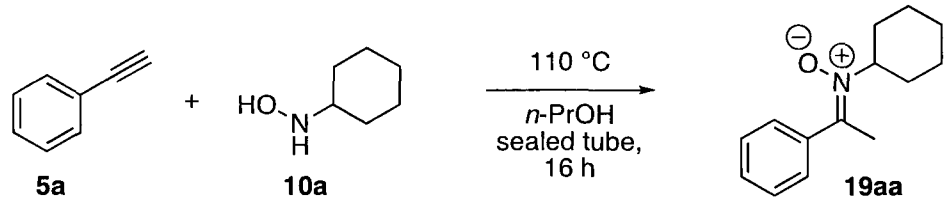


entry	R_1	R_2	R_3	product	yield[b] (%)
1		H	H	**22a**	75
2		H	H	**22b**	93
3		H	H	**22c**	99
4		H	H	**22d**	88
5		H	H	**22e**	71
6			H	**22f**	21[c]
7		H		**22g**	13

[a] Conditions: 1 equiv allene (2.5 M), 2 equiv aq. NH_2OH, *i*-PrOH, sealed tube, 140 °C, 18 h. [b] Isolated yield after column chromatography. [c] Heated in a microwave reactor.

3.2.4. Reactions of *N*-Alkylhydroxylamines with Alkynes

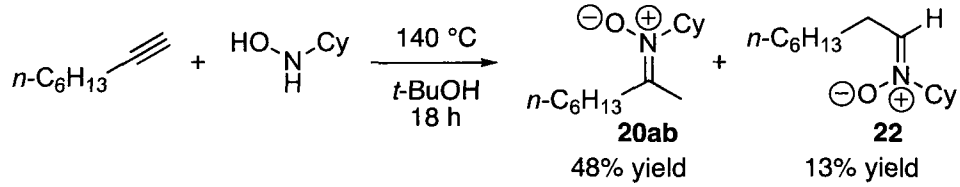
Ketonitrones could also potentially be accessed by Cope-type hydroamination of alkynes with hydroxylamines. Employing similar conditions to those used for alkenes, *N*-cyclohexylhydroxylamine was heated in the presence of phenylacetylene with *n*-PrOH as solvent to give the corresponding ketonitrone **19aa** in 52% yield (Equation 3.9).



5a **10a** **19aa**
52% yield

(3.9)

Although efforts are still ongoing, numerous attempts to optimize the reaction did not result in higher yields.[47] Variation of typical reaction parameters including time, temperature, concentration, relative equivalence, solvent, reaction scale and hydroxylamine did not show significantly improved reactivity and in nearly all cases was worse. The diminished reactivity of *N*-alkylhydroxylamines toward alkynes (relative to allenes) may be rationalized by the calculated hydroamination transition state structures shown in Figure 3.14. For example, the fact that 1-octyne affords the branched Markovnikov nitrone **21ab** in lower yield and regioselectivity (Equation 3.10) than allene **20b** under similar conditions is likely due to destabilizing interactions between the n-C_6H_{13} and Cy substituents of the reacting partners in the Markovnikov hydroamination transition state.



20ab 48% yield **22** 13% yield

(3.10)

(47) Aside from the author's efforts, Ms. Marija Antonic and Ms. Catherine Séguin each spent 4 months attempting to optimize this lead result or variants thereof during their Honours work.

At this juncture, alkynes possess great potential as precursors for rapid access to ketonitrones, but further work is necessary to achieve efficient reactivity.

3.2.5. DFT Analysis of the Intermolecular Cope-Type Hydroamination

To further investigate the mechanism as well as the subtle differences in reactivity between alkenes, alkynes and allenes, density functional theory (DFT) calculations were performed in collaboration with Dr. Serge I. Gorelsky to map the potential energy surface of the reaction and to study the nature of both the hydroamination and proton transfer transition state structures. The groups of Tronchet[48] and Jorgensen[49] have reported related calculations, but these only provided information regarding the microscopic reverse of the intermolecular hydroamination of *N,N-dialkyhydroxylamines* with *alkenes* (i.e. the Cope elimination).

3.2.5.1. Alkynes

Initial calculations were directed at determining the relative energies of the reactants complex, intermediates, products and transition states (TSs) for both the hydroamination and proton transfer steps. The potential energy surfaces for the reactions of hydroxylamine with acetylene (C_2H_2) and phenylacetylene (C_8H_6) were calculated in the gas phase at the B3LYP/TZVP level of theory (298K and 1 atm) and are shown in Figure 3.6. The zero energy is defined as the sum of the energies of the free reactants at an infinite distance, while the non-zero energy of the reactant complex (RC) arises from the entropic cost of bringing two free species together into one complex.

(48) Komaromi, I.; Tronchet, J. M. J. *J. Phys. Chem. A* **1997**, *101*, 3554.

(49) Acevedo, O.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2006**, *128*, 6141.

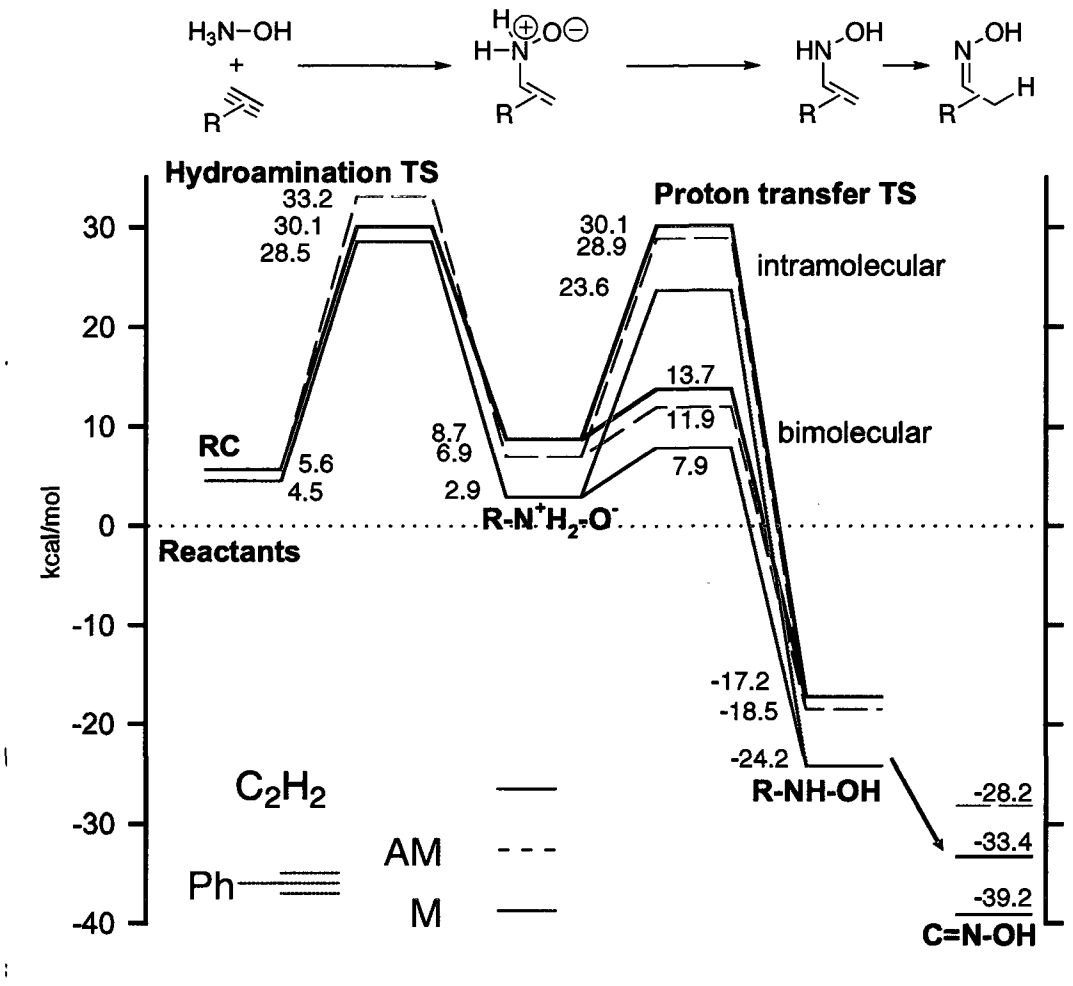


Figure 3.6. Free energies of reaction species and transition states for hydroamination of acetylene, C_2H_2 (black lines) and phenylacetylene, C_8H_6 (red lines) at the B3LYP/TZVP level of theory.

Transition state structures leading to both the Markovnikov (M) and Anti-Markovnikov (AM) products are shown in Figure 3.7. Consistent with our mechanistic rationale, the hydroamination process occurs via a 5-membered coplanar transition state. Amination at the internal position (M) of phenylacetylene is favoured by 3.2 kcal/mol. As expected, an intramolecular proton transfer has a large activation barrier (21.4-22.0 kcal/mol for phenylacetylene) but is not rate-limiting, while a bimolecular proton transfer with *i*-PrOH is

relatively facile (5 kcal/mol in vacuum and 7.5 kcal/mol in methanol). The thermodynamic driving force (ΔG_r) for the hydroamination products is very favourable due to the relative weakness of the alkyne π bond and due to the ability of the resulting *N*-hydroxyenamine intermediates to form more stable oxime products. For example, formation of the *N*-hydroxyenamines is favourable (–24.2 kcal/mol for C_2H_2 and –17.2 kcal/mol for $PhCCH_{(M)}$), but formation of the related oximes is even more so (ΔG_r = –39.2 kcal/mol and –33.4 kcal/mol, respectively).

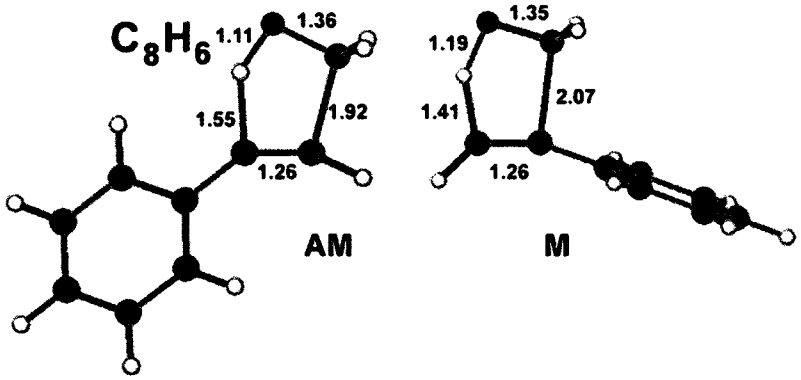


Figure 3.7. Transition state structures for the Cope-type hydroamination of NH_2OH with phenylacetylene at the B3LYP/TZVP level of theory; M= Markovnikov, AM=anti-Markovnikov product. The internuclear distances (Å) are shown only for relevant chemical bonds.

Bond formation between acetylene and NH_2OH involves only two donor-acceptor frontier orbital interactions: $HOMO_{NH2OH} \rightarrow LUMO_{CC}$ and $HOMO_{CC} \rightarrow LUMO_{NH2OH}$ (Figure 3.8). The reaction of phenylacetylene with NH_2OH involves additional occupied and unoccupied molecular orbitals, due to conjugation of the triple C-C bonds with the phenyl ring.

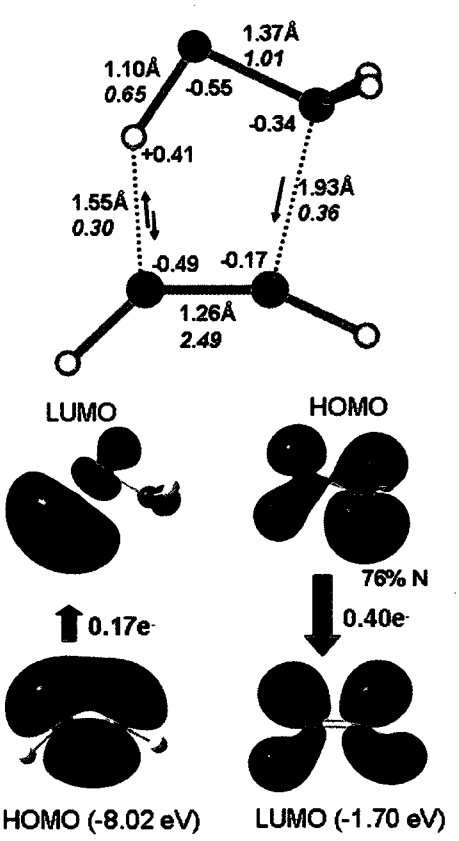


Figure 3.8. (Top) The transition states for hydroamination of C_2H_2 showing the internuclear distances and bond orders (Italics) and NPA charges (blue). (Bottom) Major donor-acceptor interactions that contribute to bond formation between NH_2OH and C_2H_2. The charge transfer Q for each interaction is shown in green and red.

3.2.5.2. Alkenes

3.2.5.2.1. Potential Energy Surface and Transition State Structure

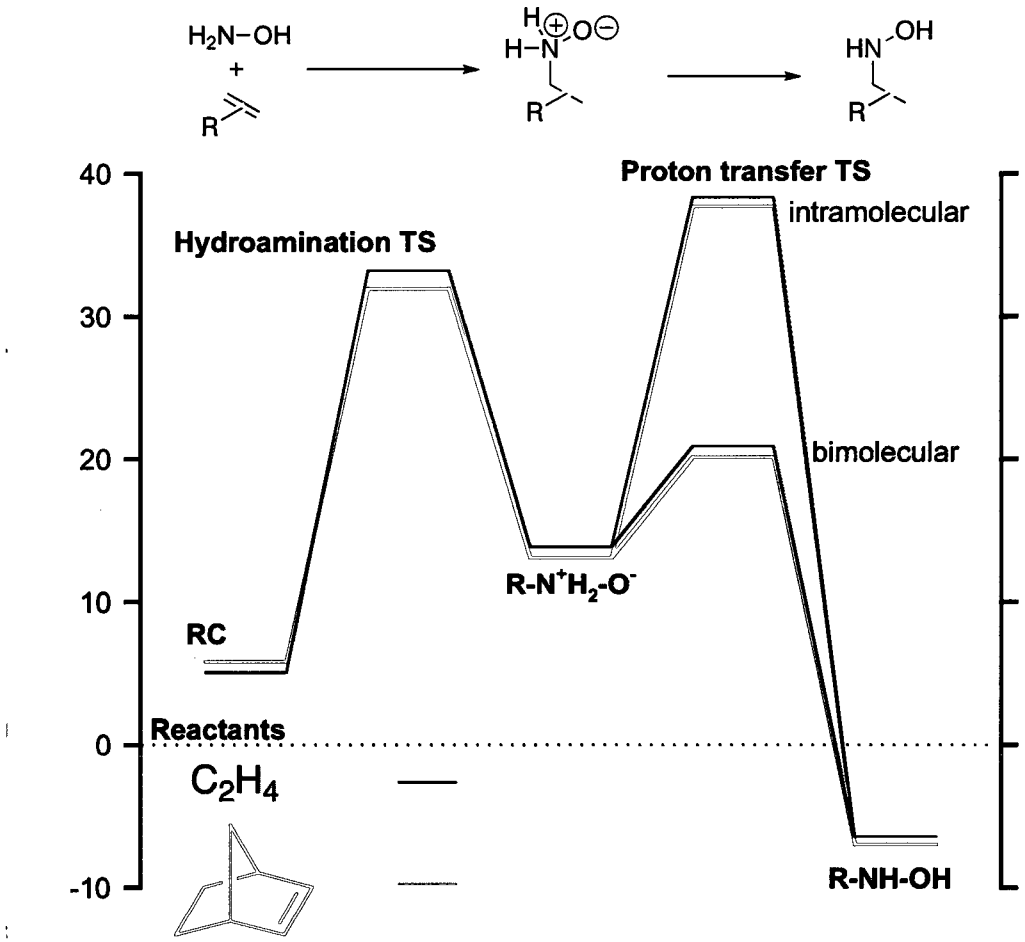


Figure 3.9. Free energies of reaction species and transition states for hydroamination of ethylene, C_2H_4 (black lines) and norbornene, C_7H_{10} (red lines) at the B3LYP/TZVP level of theory.

The potential energy surfaces for the reactions of hydroxylamine with ethylene, norbornene (Figure 3.9) and styrene (not shown) were calculated in the gas phase at the B3LYP/TZVP level of theory (298K and 1 atm).

In all cases the 5-membered, co-planar transition states involve a concerted hydroamination process.

Transition state structures leading to both the *exo* and *endo* norbornene adducts as well as those leading to the Markovnikov (M) and Anti-Markovnikov (AM) styrene hydroamination products are shown in Figure 3.10.

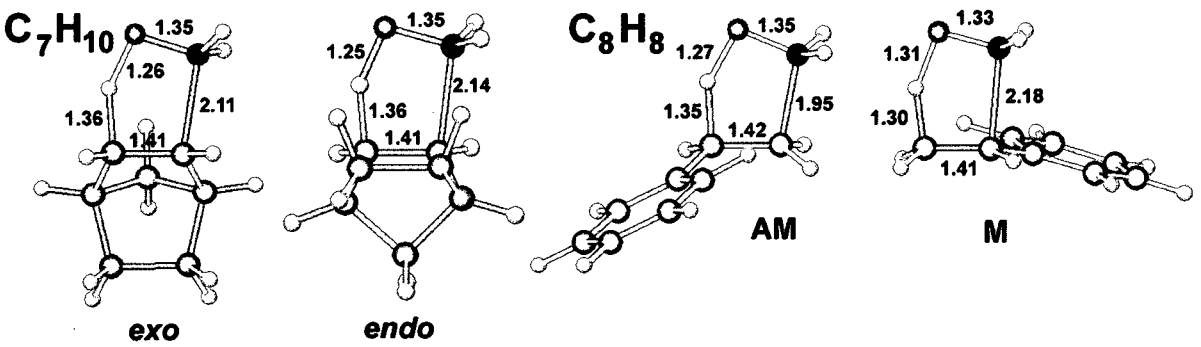


Figure 3.10. Transition state structures for the Cope-type hydroamination of NH_2OH with norbornene and styrene at the B3LYP/TZVP level of theory; M= Markovnikov, AM=anti-Markovnikov product. The internuclear distances (Å) are shown only for relevant chemical bonds.

3.2.5.3. The Hydroamination Step: Alkenes vs. Alkynes

A comparison of the energies of the regioisomeric transition states for the hydroamination of styrene vs. phenylacetylene is given in Table 3.14. In general, the similar activation energies calculated for the Cope-type hydroamination transition states of alkynes and alkenes ($\Delta G^{\ddagger}_{HA}$, 30.1 vs. 32.0 kcal/mol for $PhCCH_{(M)}$ and C_7H_{10}, respectively) correlate well with the ability of these substrates to undergo hydroamination at similar temperatures (ca. 100 °C).[50] For the hydroamination of norbornene (C_7H_{10}, Figure 3.10), the high *exo* selectivity observed experimentally (Table 3.3) was also found to be consistent with the calculated activation energies for the hydroamination step (39.1 vs. 32.0 kcal/mol for *endo* and *exo* additions, respectively.

(50) For DFT analysis of the hydroamination of alkynes, see section 3.2.5.1, pg. 136.

Table 3.14. Free energies (kcal/mol) of the reaction species for hydroamination reactions (NH_2OH) with alkenes and alkynes (evaluated at 298K and 1 atm). The energies are relative to the free reactants.

	Alkenes			Alkynes		
Species	**CH_2CH_2**	**$PhCHCH_{2\ AM}$**	**$PhCHCH_{2\ M}$**	**HCCH**	**$PhCCH_{AM}$**	**$PhCCH_M$**
RC [a]	5.1	5.9	5.9	4.5	5.6	5.6
Hydroamination TS	33.2	38.4	33.4	28.5	33.2	30.1
R-$NH_2^+O^-$	13.9	19.5	18.7	2.9	6.9	8.7
Intramolecular H^+ transfer TS	38.3	44.0	44.2	23.6	28.9	30.1
bimolecular H^+ transfer TS [b]	20.9	26.5 [c]	25.7 [c]	7.9	11.9 [c]	13.7 [c]
R-NHOH	–6.4	0.3	–0.5	–24.2	–18.5	–17.2
C=N-OH	—	—	—	–39.2	–28.2	–33.4

[a] Reactants complex. [b] the transition state for proton transfer between R-$NH_2^+O^-$ and *i*-PrOH. [c] The energy of the transition state was evaluated using the calculated activation free energy for the proton transfer for the C_2H_5-NH_2O...*i*-PrOH complex (to form C_2H_5-NHOH...*i*-PrOH) for alkenes and the C_2H_3-NH_2O...*i*-PrOH complex (to form C_2H_3-NHOH...*i*-PrOH) for alkynes (7.0 kcal/mol and 5.0 kcal/mol in vacuum, respectively and 9.7 kcal/mol and 7.5 kcal/mol in methanol). See reference [51].

However, the calculated energies of the *N*-oxide intermediates, of the transition states of the proton transfer step and of the reaction products are very different for the reactions of alkynes and alkenes. These differences likely result from the weaker π bond of alkynes relative to alkenes (ca. 15 kcal/mol difference), which translates into increased stability of alkenyl *N*-oxide

(51) These activation energies show little variability to the nature of the proton shuttle. For example, the activation free energy for the proton transfer for the C_2H_5-NH_2O...HOH and C_2H_3-NH_2O...HOH complexes in vacuum are 7.3 kcal/mol and 5.3 kcal/mol, respectively. The energies of the other hydroamination reaction species (minima and TSs) were also evaluated in the presence of H-bound *i*-PrOH. However, this produced only a minor energy change for the hydroamination reaction steps in Figure 3.9 (except in the proton transfer step).

intermediates relative to the alkyl *N*-oxide intermediates (ΔG_{NO}, 2.9 vs. 13.9 kcal/mol for the C_2H_2 and C_2H_4 adducts, respectively; 8.7, 13.1 and 18.7 kcal/mol for the $PhCCH_{(M)}$, C_7H_{10} and $PhCHCH_2$ adducts, respectively). The relative stability of these *N*-oxide intermediates is important as it determines the likelihood of the reverse reaction (the Cope elimination) relative to the subsequent proton transfer step, which leads to the hydroamination products.

3.2.5.4. Frontier Molecular Orbital Interactions in the Hydroamination Step

Bond formation in the reaction of hydroxylamine with ethylene is dominated by two important donor-acceptor interactions, whose charge transfer (Q) values were calculated by fragment orbital (FO) analysis (Figure 3.11). The major interaction (Q = 0.45e$^-$) arises mostly from donation of the nitrogen non-bonding electrons into the π^* orbital of the alkene ($nb_N \rightarrow \pi^*_{C\text{-}C}$), while the minor interaction (Q = 0.30e$^-$) arises mostly from the donation of electron density from the alkene π orbital into the hydroxylamine O-H σ^* orbital ($\pi_{C\text{-}C} \rightarrow \sigma^*_{O\text{-}H}$).[52] The relatively small difference in charge transfer between these two interactions might constitute a potential kinetic explanation for the observed regioselectivity in the hydroamination of vinylarenes. Relatively electron-rich alkenes such as **13g** have dominant $\pi_{C\text{-}C} \rightarrow \sigma^*_{O\text{-}H}$ interactions and display Markovnikov selectivity, while electron poor alkenes such as **13i** have dominant $nb_N \rightarrow \pi^*_{C\text{-}C}$ interactions and display anti-Markovnikov selectivity. However, a thermodynamic explanation for the regioselectivity is more likely (see section 3.2.5.6).

(52) The reaction of styrene with NH_2OH also involves other occupied and unoccupied FOs of alkenes, due to conjugation of the π and π^* orbitals of the double C-C bond with the π and π^* orbitals of the phenyl ring.

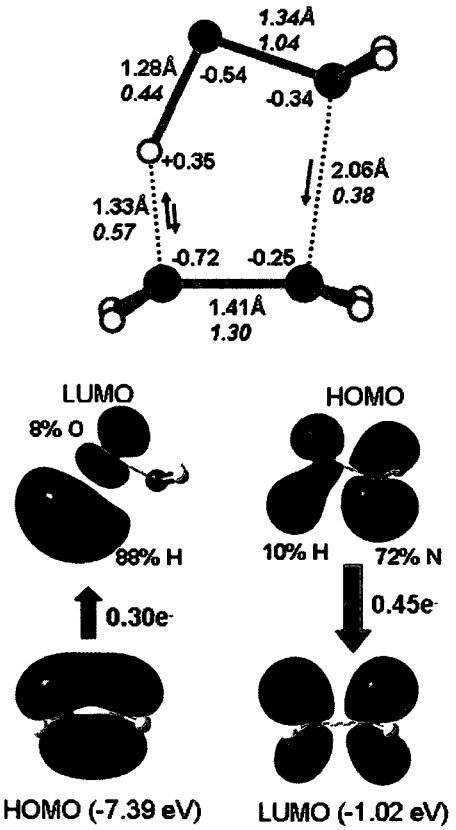


Figure 3.11. (Top) The transition states for hydroamination of C_2H_4 showing the internuclear distances and bond orders (italics) and NPA charges (blue). (Bottom) Major donor-acceptor interactions that contribute to bond formation between NH_2OH and C_2H_2. The charge transfer Q for each interaction is shown in green and red.

3.2.5.5. The Proton Transfer Step: Alkenes vs. Alkynes

In the absence of a proton shuttle, the activation energy required to access the transition state of the intramolecular proton transfer step ($\Delta G^{\ddagger}_{PT}$) is high and kinetically relevant. While for alkynes the energy barrier for the proton transfer is close in magnitude to the barrier for the hydroamination step, the *intramolecular* proton transfer step is rate limiting for reactions of alkenes. These results are consistent with the observed reactivity difference in alcoholic solvents: while the hydroamination of phenylacetylene can be performed in various solvents (Table 3.1),

the hydroamination of norbornene could not be performed satisfyingly in aprotic solvents (Table 3.2).[53]

The calculated transition state energies of the intramolecular proton transfer process are high, due to its three-membered nature (Figure 3.12, **A**). In accord with the experimental data, the lowest energy transition state (Figure 3.12, **B**) was found for a bimolecular proton transfer step involving the amine oxide intermediate and a protic species such as *i*-PrOH and H_2O. Activation free energies for this proton transfer ($E_{act,PT} = \Delta G^{\ddagger}_{BPT} - \Delta G_{NO}$) for alkynes ($C_2H_2$) and alkenes ($C_2H_4$) are ca. 5 and 7 kcal/mol, respectively, in the gas phase and ca. 8 and 10 kcal/mol, respectively, in methanol and are relatively independent of the nature of the proton shuttle (ROH). This pathway involving a bimolecular proton transfer is favoured over an intramolecular alternative by ca. 15 kcal/mol. Alternatively, an *N*-oxide dimer such as **C** (Figure 3.12) would collapse to the reaction products.[54] However, the formation of such a dimer is kinetically unlikely and does not account for the beneficial solvent effect observed with alcohols (conditions D, Table 3.4). Optimized transitions state structures are shown in Figure 3.13.

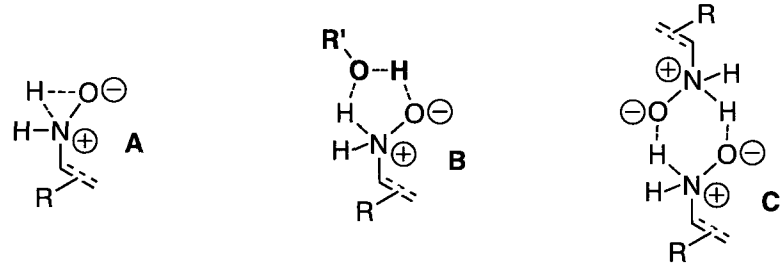


Figure 3.12. *N*-Oxide proton transfer pathways investigated computationally.

(53) For example, only low conversions were observed in dioxane and DMSO-d_6 at 95 °C and attempts at higher temperatures were not successful due to side reactions.

(54) Due to the remarkable efficiency of the bimolecular proton transfer pathway **B** (Figure 3.12), investigations into alternative bimolecular pathways were not pursued using DFT calculations. Experimentally, various attempts using either mildly basic (Et_3N) or acidic (AcOH) additives did not result in significant rate accelerations.

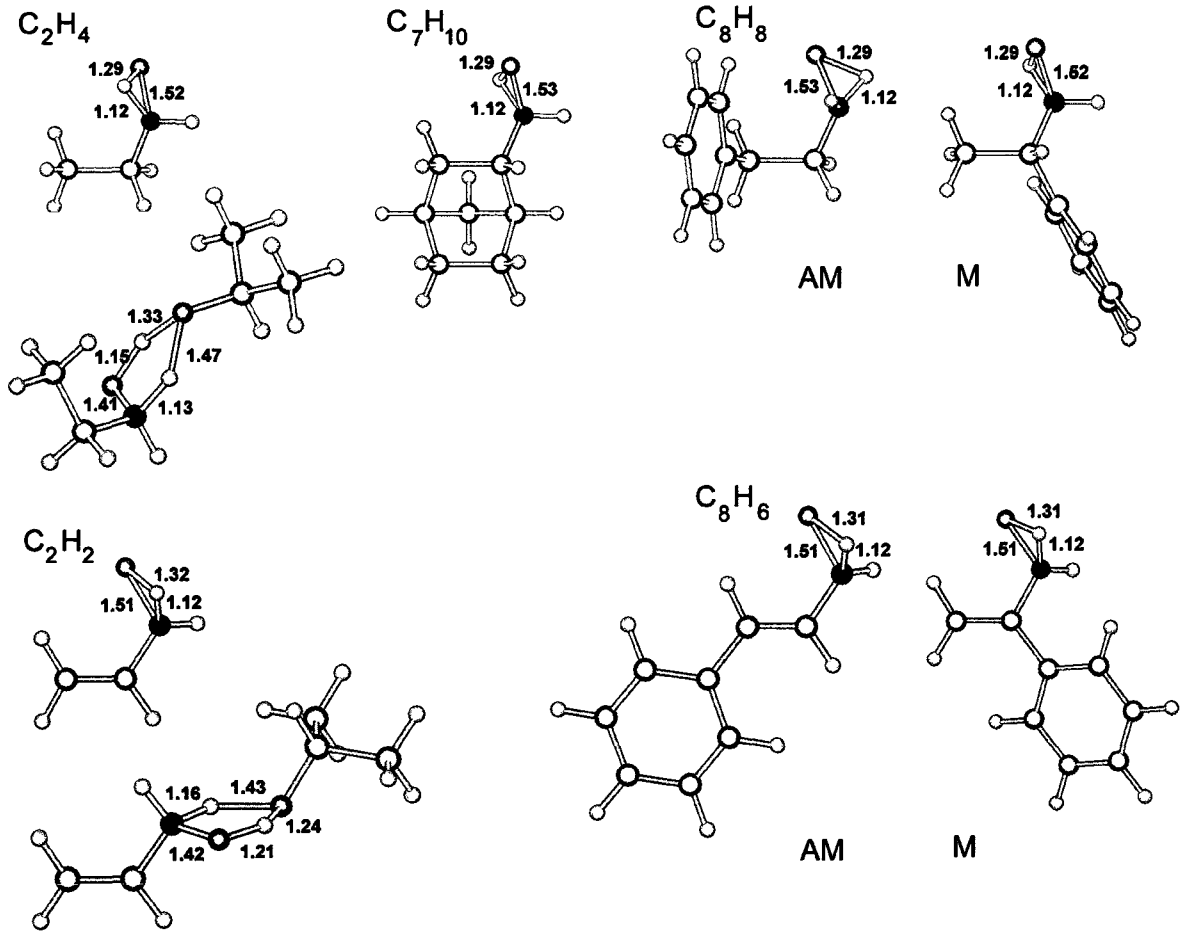


Figure 3.13. Transition state structures for intramolecular and bimolecular proton transfer in the hydroamination reactions of hydroxylamine with ethylene, acetylene, norbornene, styrene and phenylacetylene at the B3LYP/TZVP level of theory. M= Markovnikov product, AM=anti-Markovnikov product. The internuclear distances (Å) are shown only for relevant chemical bonds. The TS structures for bimolecular proton transfer are shown for reactions of R-$NH_2^+O^-$ with *i*-PrOH.

Alcoholic solvents are likely also beneficial through increased stabilization of the *N*-oxide intermediate in polar solvents. To evaluate the effect of various solvents on the potential energy surface of the reaction, DFT calculations were performed for the hydroamination of C_7H_{10} in C_6H_6, $CHCl_3$, DMSO and MeOH (Table 3.15). Two important trends are observed: A) The *N*-oxide intermediate is best stabilized in polar solvents due to their polar nature (Table 3.15), for example the calculated free energies for the C_7H_{10}-derived *N*-oxide intermediate is 13.1 kcal/mol

in the gas phase and 8.3 kcal/mol in methanol (for C_2H_4: 13.9 and 4.9 kcal/mol in gas phase and methanol, respectively). Ciganek has also observed experimentally the increased stabilization of *N*-oxides in polar ($CHCl_3$) and protic (MeOH) solvents.[10b-c] B) Polar solvents also appear to reduce the calculated thermodynamic driving force (ΔG_r). For the reactions for C_7H_{10} and NH_2OH, ΔG_r is –7.0 and –3.1 kcal/mol in the gas phase and in MeOH, respectively, due to increased stabilization of NH_2OH relative to the hydroamination product in polar solvents.

Table 3.15. Gas-phase dipole moments (Debye) and free energies (kcal/mol) of the reaction species for hydroamination reactions (NH_2OH) with C_7H_{10} in C_6H_6, $CHCl_3$, DMSO and MeOH (evaluated at 298K). The energies are relative to the free reactants in solvent.

Species	D (Debye)	ΔG_{298K} (kcal/mol) in				
		vacuum	C_6H_6	$CHCl_3$	DMSO	MeOH
Reactant Complex	0.84	5.8	8.0	8.6	9.4	11.0
Hydroamination TS	3.03	32.0	31.9	32.4	32.4	34.3
R-$NH_2^+O^-$	5.44	13.1	11.0	10.5	9.2	8.3
Intramolecular H^+ transfer TS	4.02	38.3	37.4	38.0	37.8	38.8
bimolecular H^+ transfer TS	—	—	—	—	—	18.1
R-NHOH	0.88	–7.0	–6.1	–5.1	–4.6	–3.1

3.2.5.6. Thermodynamic Driving Force

The thermodynamic driving force (ΔG_r) for the reactions of alkynes and alkenes are also markedly different. Unlike the hydroamination of alkynes, whose products are heavily favoured, the formation of the *alkene* hydroamination products is very dependent on the nature of the alkene. For example, formation of the products is moderately favoured for C_2H_4 (ΔG_r = –6.6 kcal/mol) and C_7H_{10} (ΔG_r = –7.0 kcal/mol). However, both substrates are biased: ethylene is less

stable than most alkenes since it is unsubstituted and the reaction of norbornene benefits from partial release of strain energy. For the more stable vinylarenes, our calculations suggest that the reaction is thermoneutral (ΔG_r = –0.5 and 0.3 kcal/mol, respectively, for the Markovnikov and anti-Markovnikov styrene adducts), in agreement with the moderate yields reported in Table 3.9. Furthermore, these results are in agreement with Hartwig's observation that the reaction of vinylarenes and anilines is thermoneutral.[55]

3.2.5.7. The Impact of Nitrogen and π-Bond Substitution

The impact of nitrogen and alkene or alkyne substitution in *intramolecular* Cope-type hydroaminations has been delineated experimentally and discussed in a recent review by Cooper and Knight.[8] In general, π-bond substitution translates into a more difficult hydroamination step, with substitution at the distal position of the unsaturation having a significant impact on rates of cyclization (up to ~25 times slower). In contrast, nitrogen substitution is found to be beneficial in intramolecular systems: *N*-methyl-*N*-alkenylhydroxylamine substrates cyclize significantly faster than the parent (N-H) *N*-alkenylhydroxylamines. The latter trend is in contrast with our experimental results presented in Table 3.3 and Table 3.4, as hydroaminations with NH_2OH and *N*-alkylhydroxylamines proceed under similar reaction conditions. Therefore, a comprehensive set of calculations was performed to provide insight into the substitution effects with respect to both reacting partners.

(55) Johns, A. M. Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306.

Table 3.16. Nitrogen substitution: free energies (kcal/mol) of the reactions and activation free energies for hydroamination reactions of various hydroxylamines with C_7H_{10} and C_8H_6 in the gas phase (evaluated at 298K and 1 atm.). The energies are relative to the free reactants.

Alkene/Alkyne	Hydroxylamine	Regioselectivity	$\Delta G^{\ddagger}_{HA}$ kcal/mol	ΔG_r kcal/mol
C_7H_{10}	NH_2OH	—	32.0	–7.0
C_7H_{10}	NH(Me)OH	—	30.7	–3.7
C_7H_{10}	$N(Me)_2OH$	—	32.5	+14.9
PhCCH	NH_2OH	AM	33.2	–28.2
		M	30.1	–33.4
PhCCH	NH(Me)OH	AM	32.1	–18.3
		M	29.7	–14.8
PhCCH	$N(Me)_2OH$	AM	31.3	+5.4
		M	30.3	+12.0

Table 3.17 Free energies (kcal/mol) of the reaction species for hydroamination reactions (NH_2OH) with CH_3- and CF_3- substituted ethylene and acetylenes (evaluated at 298K and 1 atm). The energies are relative to the free reactants.

	Alkenes				Alkynes			
	CH_3CHCH_2		CF_3CHCH_2		CH_3CCH		CF_3CCH	
Species	**AM**	**M**	**AM**	**M**	**AM**	**M**	**AM**	**M**
RC [a]	5.3	5.3	6.5	6.5	5.7	5.7	7.7	7.7
Hydroamination TS	38.3 [b]	34.5 [b]	31.2	33.1	34.4 [c]	31.2 [c]	24.9	25.0
R-$NH_2^+O^-$	18.9	15.8	15.3	17.8	8.1	6.9	0.7	2.1
Intramolecular H^+ transfer TS	43.2	40.8	40.5	42.1	29.5	28.5	20.4	23.2
R-NHOH	–1.6	–3.9	–4.8	–3.7	–16.9	–19.0	–30.2	–25.1
C=N-OH	—	—	—	—	–29.7	–35.0	–41.3	–39.8

a) Reactants complex; b) 38.2 kcal/mol for the hydroamination of *cis*-CH_3-CH=CH-CH_3; c) 35.5 kcal/mol for the hydroamination of CH_3-CC-CH_3

Several trends emerge from the data presented in Table 3.16 and Table 3.17. First, the activation energy for the hydroamination step does not vary significantly with increased substitution on the hydroxylamine used (NH_2OH vs. MeNHOH vs. Me_2NOH). This theoretical data also suggests that the increased reactivity of *N*-methyl-*N*-alkenylhydroxylamine with respect to the parent (N-H) *N*-alkenylhydroxylamines substrates in intramolecular systems cannot be attributed to a more facile Cope-type cyclization step. A possible rationale for this trend could be that the proton transfer step from the *N*-oxide intermediate to the hydroxylamine product is kinetically relevant for Cope-type cyclizations of (N-H) *N*-alkenylhydroxylamines, and that such cyclizations would also benefit from the presence of a proton shuttle.

DFT studies on π-bond substitution (Table 3.17) correlate well with the experimental data with respect to the required reaction temperatures and with the trends documented for intramolecular Cope-type hydroaminations.[8] Importantly and likely due to the increased stability inherently linked to π bond substitution, activation free energies for the hydroamination step increase with π bond substitution. Increased stability of the alkene or alkyne starting material thus translates into reduced relative stability of the *N*-oxide intermediates and hydroamination products. Conversely, electron-withdrawing substituents reduce the activation energy required for anti-Markovnikov Cope-Type hydroaminations of alkenes and alkynes, in accord with a more important $HOMO_{NH2OH} \rightarrow LUMO_{CC}$ interaction. Finally, for intermolecular reactions of alkenes, substitution can have a direct impact on reaction efficiency since for styrene the reaction is nearly thermoneutral.[55] Therefore, *at 298 K*, hydroaminations of ethylene, strained and terminal alkenes are slightly more thermodynamically favourable than reactions of vinylarenes. Disubstituted alkenes are also predicted to be more challenging substrates, both kinetically and thermodynamically. Due to the negative entropy of intermolecular reactions, the position of the

equilibrium depends on the reaction temperature and the formation of hydroamination products is obviously more favourable at lower temperatures. The data regarding the thermodynamic driving force of the reactions (ΔG_r) should be used from this perspective, keeping in mind that more challenging hydroamination substrates often require higher reaction temperatures, which translate into less favourable reaction thermodynamics.

3.2.5.8. Allenes

In light of our results for intermolecular reactions of alkenes and alkynes, a concerted process also appears consistent with the experimental regioselectivity and scope observed with allenes. Seeking to obtain more information, DFT calculations were performed to obtain transition state structures and energies for the reaction of NH_2OH with allene and methylallene (Figure 3.14).

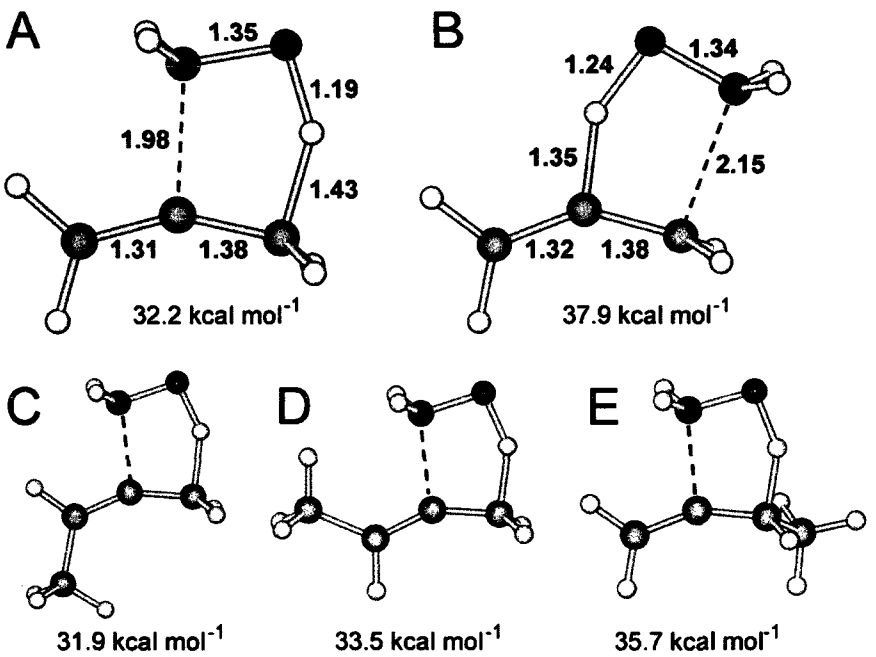


Figure 3.14. Transition state structures for the Cope-type hydroamination of NH_2OH with allene (A, B) and methylallene (C, D, E) at the B3LYP/TZVP level of theory. The internuclear distances (Å) are shown only for relevant chemical bonds.

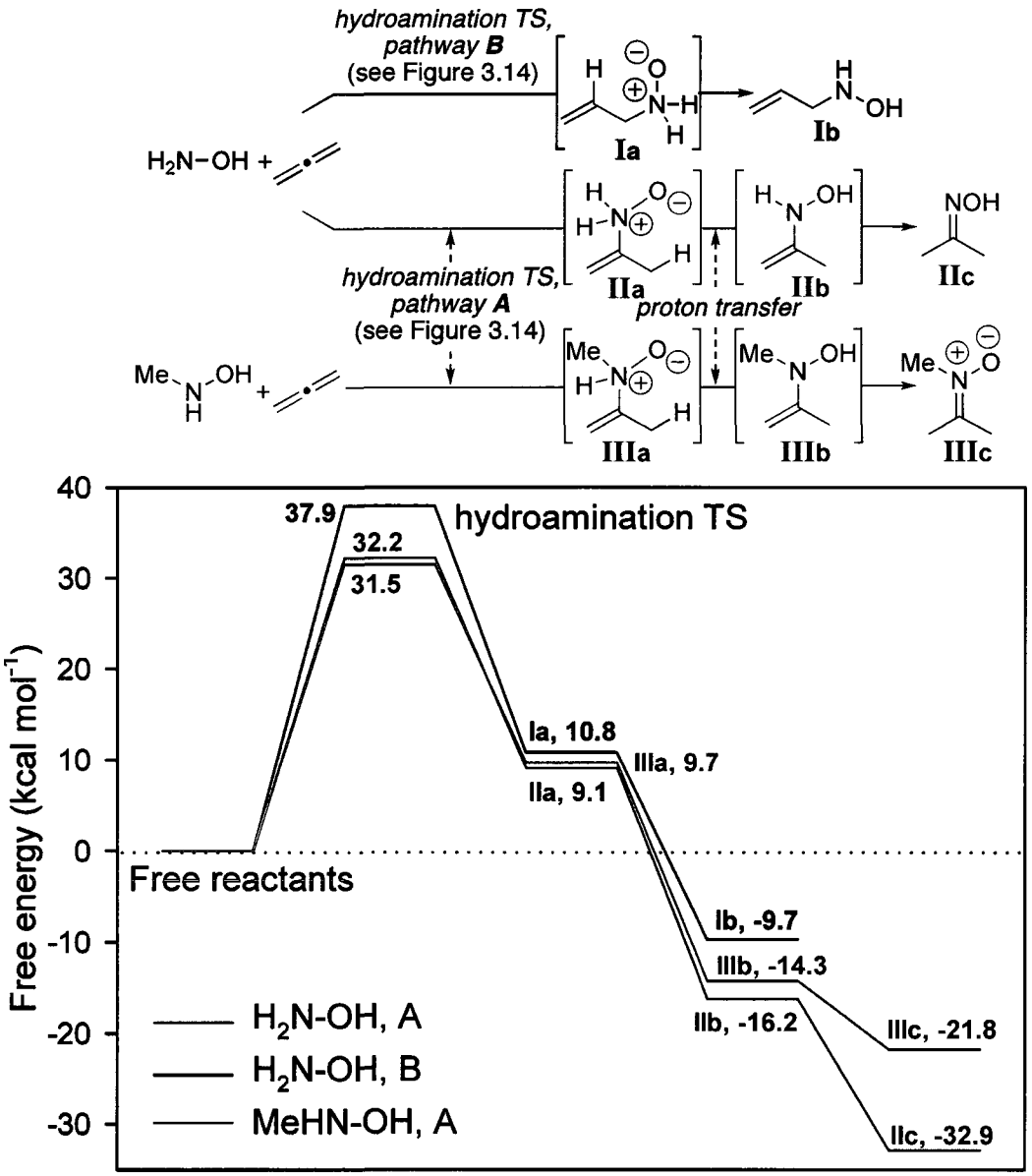


Figure 3.15. Gibbs free energy (in kcal/mol, 298K, 1 atm) profiles for the Cope-type hydroamination of allenes using H_2NOH (A and B) and MeHNOH (A). Pathways A and B correspond to amination of the central and terminal carbons of allene, respectively.

The concerted hydroamination process occurs via a 5-membered coplanar transition state, and amination on the central carbon of allene is favoured by 5.7 kcal/mol (**A** vs. **B**). For methylallene, the isomeric transition states for the addition to the terminal π bond (31.9 kcal/mol for **C** and 33.5 kcal/mol for **D**) were both found to be lower energy than for addition to the

internal π bond (35.7 kcal/mol for **E**). The experimental observation that the reactions of *N*-alkylhydroxylamines with geminally disubstituted allenes are more difficult is thus explained by the developing A(1,3) interactions that arise in the terminal transition states between the alkyl groups on the hydroxylamine and on the allene. Overall, the potential energy surface is consistent with product distribution being under kinetic control (Figure 3.15).

3.2.6. Controlling Regiochemistry: Anti-Markovnikov Reactivity of Hydrazines[56]

The anti-Markovnikov hydroamination of olefins has been named one of the "Ten Challenges for Catalysis".[57] Although not requiring a catalyst, the discovery that the regioselectivity of the Cope-type hydroamination reaction can be tuned by small changes in the electronics of the unsaturated substrate led us to consider if anti-Markovnikov regiocontrol could be achieved by wise selection of the bifunctional amine (NH_2XH). As we have seen in Section 3.2.5.4, the regioselectivity of the Cope-type hydroamination might be kinetically controlled by the competition between the $\pi_{C\text{-}C} \rightarrow \sigma^*_{X\text{-}H}$ and $nb_N \rightarrow \pi^*_{C\text{-}C}$ interactions in the transition state. When the former dominates, Markovnikov products are formed, while anti-Markovnikov products are observed when the latter dominates.

Unactivated hydrazines possess a slightly stronger X-H bond (higher pKa) than hydroxylamines, and thus a relatively weaker $\pi_{C\text{-}C} \rightarrow \sigma^*_{X\text{-}H}$ interaction (Figure 3.16). We thus began to investigate the reactivity of unactivated hydrazines with the long-term goal of developing intermolecular anti-Markovnikov Cope-type hydroamination reactions of alkenes.

---

(56) Most of the work in section 3.2.6 was performed by Ms. Pam Cebrowski and Mr. Jean-Gregoire Roveda and is included for completeness. The author's contributions involve early discovery work and the determination of the conditions used for the lead results. Full experimental data and characterization for this section are not contained in this thesis but can be found in ref. 1b.

(57) Higgins, J. *Chem. Eng. News* **1993**, *71*, 23.

Herein, we report that hydrazines also undergo an intermolecular Cope-type hydroamination process with alkynes and that the use of a substituted hydrazine, $MeNHNH_2$, favours the formation of anti-Markovnikov hydrazones.[58,59]

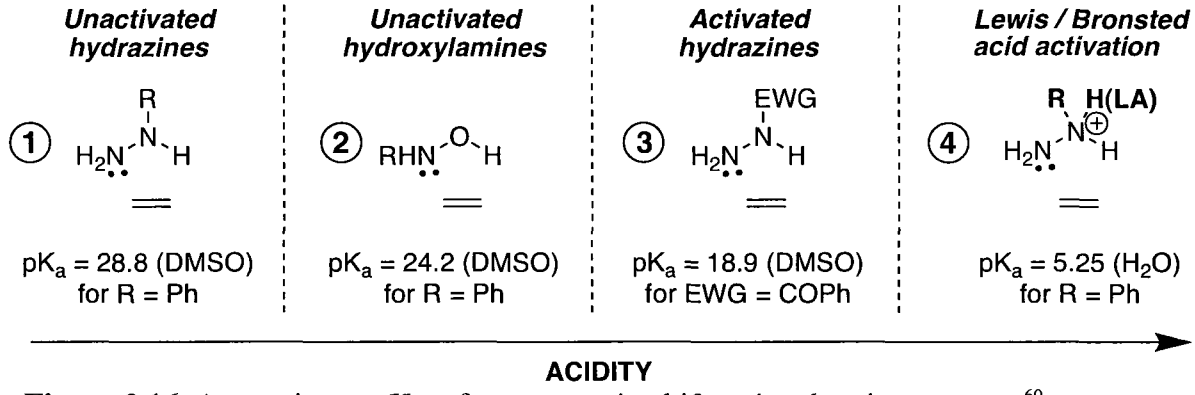


Figure 3.16. Approximate pK_as of representative bifunctional amine systems.[60]

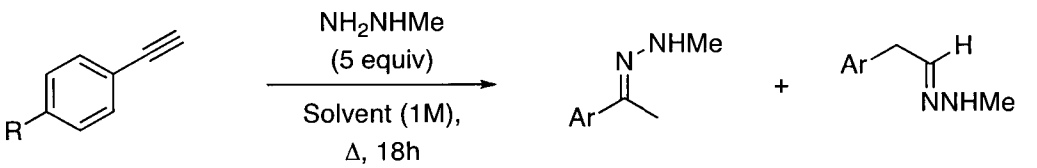
Initial trials to extend the Cope-type hydroamination to hydrazines were performed using aqueous hydrazine and phenylacetylene. Early attempts to perform the reaction in non-polar solvents were ineffective. Following the realization that protic solvents mediate the reactions of hydroxylamines by speeding up the proton transfer step, alcohols were explored with hydrazines. Encouragingly, 53% conversion to a 2.5/1 mixture of regioisomers favouring the anti-Markovnikov hydrazone was obtained in *i*-PrOH at 113 °C.

(58) For a review article on the reactivity of hydrazines and alkynes, see: Sucrow, W. *Org. Prep. Proc. Intl.* **1982**, *14*, 91.

(59) For metal-catalyzed reactions of alkynes and hydrazines, see: (a) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *Chem. Commun.* **1988**, 121. (b) Cao, C.; Shi, Y.; Odom, A. L. *Org. Lett.* **2002**, *4*, 2853. (c) Li, Y.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 1794.

(60) Phenylhydrazine: (a) Zhao, Y.; Bordwell, F. G.; Cheng, J.-P.; Wang, D. *J. Am. Chem. Soc.* **1997**, *119*, 9125. Phenylhydroxylamine: (b) Bordwell, F. G., private communication to Hans J. Reich. Benzhydrazide: (c) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. Phenylhydrazinium: (d) do Amaral, L.; Sandstrom, W. A.; Cordes, E. H. *J. Am. Chem. Soc.* **1966**, *88*, 2225.

Table 3.18. Optimization of the hydroamination using $MeNHNH_2$



23a R = H, **23b** R = Me **24a-b** **25a-b**

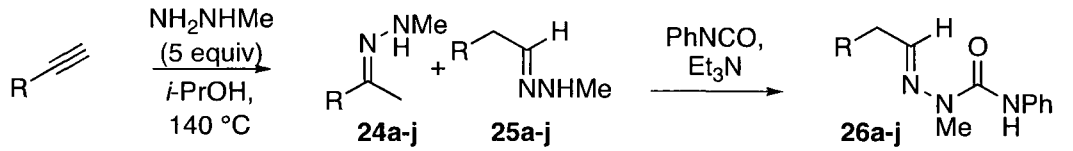
entry	R	solvent	temp (°C)	conversion (%) (**25**:**24**)[a,b]
1	H	dioxane	113	22 (10:1)
2	H	DMSO-d_6	113	41 (5:1)
3	H	*i*-PrOH	113	87 (17:1)
4	H	*i*-PrOH	140	88 (14:1)
5	H	PhMe	140	26 (9:1)
6	Me	*i*-PrOH	113	34 (11:1)
7	Me	dioxane	140	29 (4:1)
8	Me	DMSO-d_6	140	53 (6:1)
9	Me	*i*-PrOH	140	73 (8:1)
10[c]	Me	*i*-PrOH	140	24 (8:1)

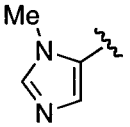
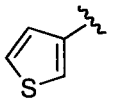
[a] Conversions were determined by ^{1}H NMR of the unpurified reaction mixture using styrene as an internal standard. [b] Regioselectivity was determined by ^{1}H NMR. [c] 2 equiv. of $MeNHNH_2$ were used.

Ms. Pamela Cebrowski optimized the lead result by using $MeNHNH_2$, which led to both increased conversions and regioselectivities (Table 3.18). Initial screening of reaction conditions using phenylacetylene (**23a**) as substrate showed encouraging reactivity in various solvents (Table 3.18, entries 1-3), with protic solvents such as *i*-PrOH providing optimal conversion and regiocontrol for the formation of linear hydrazone **25a**. In general, the reaction is more efficient at high concentrations (1M) and the use of distilled $MeNHNH_2$ under an inert atmosphere is beneficial. Due to its reduced reactivity compared to **23a**, optimization was continued using *p*-tolylacetylene (**23b**, entries 6-10). Gratifyingly, upon heating at 140 °C in *i*-PrOH for 18 hours, good conversion and regioselectivity for the linear hydrazone **25b** was obtained (entry 9). With optimized conditions in hand, Ms. Pamela Cebrowski and Mr. Jean-Gregoire Roveda evaluated

the substrate scope with respect to the alkyne (Table 3.19). Derivatization of the linear hydrazone regioisomer allowed for product isolation by column chromatography.

Table 3.19. Determination of substrate scope with different alkynes



entry	R	NMR yield (%, **24+25**)[a]	regioselectivity (**25**:**24**)[b]	yield (**26**)[c] (%)
1	C_6H_5	87	14:1	58
2	2-Me(C_6H_4)	76	5:1	50
3	3-Me(C_6H_4)	77	15:1	49
4	4-Me(C_6H_4)	73	8:1	37
5	4-F(C_6H_4)	72	9:1	44
6	2-MeO(C_6H_4)	66	32:1	40
7	4-MeO(C_6H_4)	30	5:1	—
8	3,5-$(CF_3)_2C_6H_3$	77	10:1	31
9		76	25:1	55
10		81	6:1	45

[a] Determined by ^{1}H NMR of the unpurified reaction mixture using styrene as an internal standard. [b] Ratio determined by ^{1}H NMR. [c] Isolated yield after column chromatography.

Hydroamination of aromatic acetylenes using $MeNHNH_2$ proceeds in good conversions and good to excellent regioselectivity for the linear hydrazone products (**25a-j**). Substitution on the arene ring is generally well tolerated (entries 2-6 and 8), with the exception of 4-methoxyphenylacetylene, which shows only modest reactivity (entry 7). In addition, heterocyclic acetylenes also react efficiently under these reaction conditions (entries 9-10).[61] In all cases, the

(61) To date, trials with aliphatic (1-octyne), vinylic (1-ethynylcyclohexene) and internal (diphenylacetylene) alkynes have only showed minimal reactivity.

semicarbazone derivative of the major regioisomer (**26a-j**) could be isolated after derivatization, in modest to acceptable yields over 2 steps. Unfortunately, attempts to extend this reactivity to alkenes were not successful, even at temperatures up to 160 °C.

3.2.6.1. DFT Analysis of the Reaction of Hydrazines with Alkynes

DFT calculations[62] were also performed to gain insight regarding a possible concerted mechanism[63,64] related to the Cope-type hydroamination reactivity of hydroxylamines. The activation free energies ($\Delta G^{\ddagger}$) associated with the four possible concerted 5-membered planar transition states for phenylacetylene are shown in Figure 3.17.

Figure 3.17. Calculated activation energies associated with the four possible hydroamination transition states.[62]

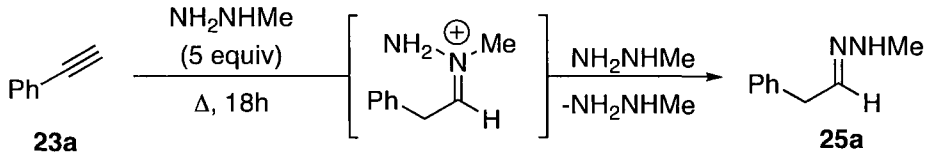
As $MeNHNH_2$ is unsymmetrical, both nitrogen atoms can be involved in the C-N bond-forming event, which can occur also on both carbons of the alkyne. The transition state with minimal steric interactions between the alkyne and hydrazine substituents is favoured by 1.4 kcal/mol and leads to the formation of the linear hydrazone **25a** via a

(62) Calculated free energies of TS in gas-phase at 298K and 1 atm, relative to the free reactants, B3LYP/TZVP level of theory.

(63) For related examples of aza-Cope eliminations likely occurring through a similar transition state, see: (a) Morris, D. G.; Smith, B. W.; Wood, R. J. *Chem. Commun.* **1968**, 1134. (b) Posvic, H.; Rogers, D. *J. Org. Chem.* **1974**, 39, 1588.

(64) Control experiments performed with **22a**, $MeNHNH_2$ (5 equiv) in *i*-PrOH (1M) at 140 °C in the presence of AcOH (1 equiv) or *i*-Pr_2NEt led to only slight decrease in conversions (56% and 35%, respectively), suggesting alternative acid or base-catalyzed mechanisms are not operating under the reaction conditions.

hydroamination/nucleophilic displacement pathway (Equation 3.11). These calculations are thus in good agreement with the observed regioselectivity (14:1).



23a 25a (3.11)

3.3. Conclusion and Outlook

In summary, an intermolecular Cope-type hydroamination reaction has been developed for unsaturated substrates including terminal and internal alkynes, strained alkenes, terminalvinylarenes and allenes (Figure 3.18).

The use of alcoholic solvents is generally necessary for reactions of alkenes to proceed. The solvent assists product formation by mediation of a *bimolecular* proton transfer with the *N*-oxide intermediate. Protic solvents also facilitate the reactions of alkynes and allenes. In addition, a beneficial additive effect observed with sodium cyanoborohydride has allowed for the reactivity of alkenes to be extended from aqueous hydroxylamine to *N*-alkylhydroxylamines. Selective reduction conditions allow *N*-benzylhydroxylamine to act as a "hydroamination equivalent" for either ammonia or benzylamine. All reactions can be carried out in concentrated alcoholic solvents, do not require rigorous exclusion of water and are easily scalable. The practicality and functional group tolerance (towards common protecting groups, free OH and NH bonds, aryl bromides, etc.) of this procedure highlight its complimentary role among existing intermolecular hydroamination methods. Hydrazines display more modest reactivity than hydroxylamines with alkynes, but lead to complimentary *anti*-Markovnikov hydrazones. DFT calculations provided insight into this reactivity, including information on the potential energy surfaces of the reactions and on the nature of the hydroamination and proton transfer transition states. A detailed molecular orbital description for the concerted hydroamination transition states

is provided, and highlights the high electronic tunability of this process with respect to the alkene, alkyne and bifunctional amine reaction partners. Control experiments and calculations indicate the reactions of vinylarenes are under thermodynamic control, while the reactions of strained alkenes, alkynes and allenes are under kinetic control. Extensions and applications of this reactivity, including intramolecular variants, have recently been reported and continue to be developed in the Beauchemin laboratories.[65]

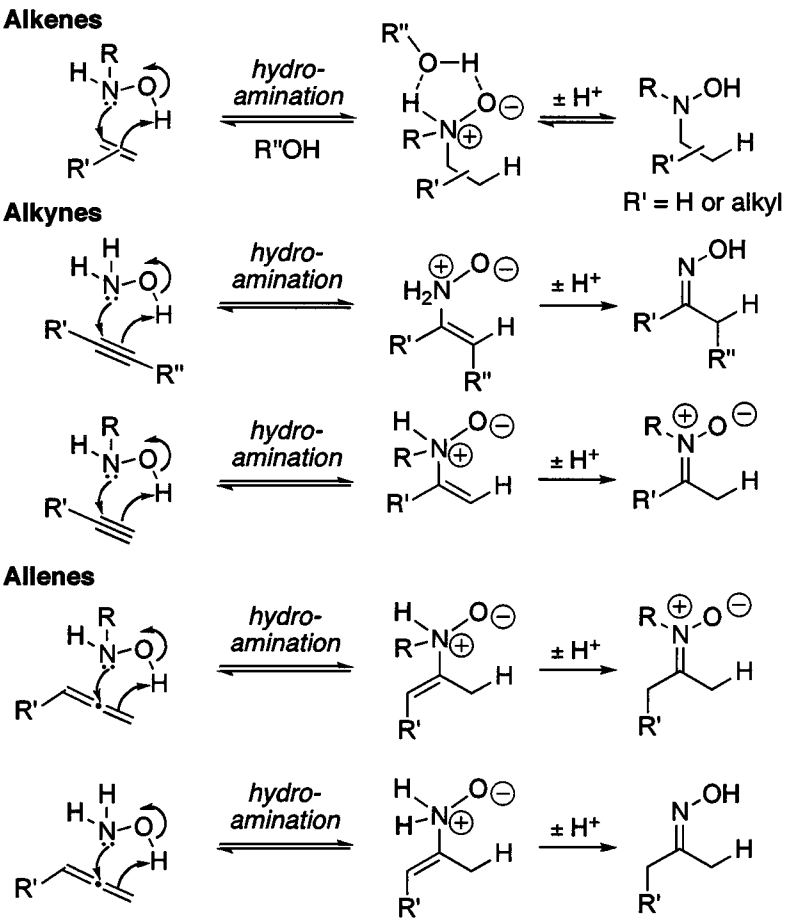


Figure 3.18. Summary of Cope-type hydroamination reactivity of hydroxylamines.

(65) (a) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874. (b) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740. (c) Rizk, T.; Bilodeau, E. J.-F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *accepted*. (d) Pfeiffer, J. Y.; Beauchemin, A. M. *J. Org. Chem.* **2009**, *accepted*.

3.4. Experimental Section

CAUTION: Hydroxylamine free base (HAFB) – 50% wt aqueous solution. Hydroxylamine free base does not cause any problems if handled with care. For example, it is currently produced by BASF (>7000 ton/year) and used for a variety of industrial applications. However, HAFB can decompose spontaneously with the liberation of large volumes of gas if not handled properly. Violent decomposition of hydroxylamine can be caused by metal (especially iron) and metal ion impurities, oxidizing and reducing agents, bases, high temperatures above 75 °C, or high concentrations of hydroxylamine, for example due to evaporation. The use of more dilute solutions is inherently safer.[66] *Therefore, under standard reaction conditions, the hydroxylamine (HAFB) content of the solution being heated is in the 5-10% wt range.* Hydroxylamine concentration should not be increased. The use of a blast shield to perform the experiments in sealed tubes or in flask equipped with a reflux condensor should be a standard operating procedure. Alternatively, commercially available microwave synthesizers are designed for safe operation at elevated temperatures and pressure, and were used regularly for reactions with aqueous NH_2OH. During the course of our studies (>500 experiments using NH_2OH, using the experimental setups described above), we have performed reactions up to a 5-gram scale and have observed only minimal gas evolution (ie. a bit of pressure was released upon opening the sealed tubes to air, at room temperature, at the end of the reaction). No incidents occurred.

General Information. All reactions were performed in air-dried 3, 8, 12 or 48 mL sealed tubes under an argon atmosphere unless otherwise noted. Microwave reactions were run in a CEM Discover LabMate microwave. Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm). Analytical thin layer

(66) For an evaluation of the safety profile of 20 to 85% wt NH_2OH aqueous solutions, see: Iwata, Y.; Koseki, H. *Process Safety Progress* **2002**, *21*, 136.

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.

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 or CD_3OD at 3.31). 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 or CD_3OD at 49.05). 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. Melting points were determined with a Thomas-Hoover Unit or a Gallenkamp P1106G melting point apparatus.

Materials. Unless otherwise noted, all commercial materials were purchased from Sigma-Aldrich and used without further purification. *N*-Alkylhydroxylamines (**10a-d** and **10f**) were synthesized by reduction of the corresponding oxime according to the procedure of House.[67] *N*-phenylhydroxylamine (**10g**) was prepared from nitrobenzene according to the

(67) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

procedure of Nakayama.[68]

3.4.1. Reactions of Aqueous Hydroxylamine with Alkenes

Optimization of hydroamination of norbornene in aqueous hydroxylamine (Table 3.2).

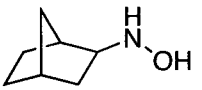
Solvent Scan (entries 1-7 and 12-15). A 3 mL sealed tube was charged with a stir bar, an aqueous solution of hydroxylamine (50 wt% in water, 0.99 g, 15 mmol), solvent (1.5 mL), and norbornene (0.14 g, 1.5 mmol). The tube was then sealed with a screw cap and heated while stirring in an oil bath at 95°C for 14 hrs. The tube was cooled to ambient temperature and concentrated under reduced pressure. Styrene (0.16 g, 1.5 mmol) was then added as an internal standard. The biphasic mixture was taken up in $CDCl_3$, and the organic phase was transferred to an NMR tube. ^{1}H NMR spectra of these solutions were recorded, and the conversion calculated based on the relative integration of the resonance corresponding to one of the product's protons (1H) at 2.96 ppm compared to the integration of the resonance corresponding to a styrene proton at 6.69 ppm (1H).

Concentration, Time and Equivalence Scan (entries 8-11). A 15 mL sealed tube was charged with a stir bar, a 50 wt% aqueous solution of hydroxylamine (2.0-5.0 equiv, 1.0-10 M in *i*-PrOH), *i*-PrOH, and norbornene (0.14 g, 1.5 mmol). The tube was capped with a septum and purged with argon and outlet for 5 minutes while stirring. The septum was removed and the tube was then quickly sealed with a Teflon screw cap and heated while stirring in an oil bath at 95°C for 14-24 hrs. The tube was cooled to ambient temperature and concentrated under reduced pressure. Styrene (0.16 g, 1.5 mmol) was then added as an internal standard. The biphasic mixture was taken up in $CDCl_3$, and the organic phase was transferred to an NMR tube. ^{1}H NMR spectra of these solutions were recorded, and the conversion calculated based on the relative

(68) Nakayama, K.; Endo, M.; Majima, T. *Bioconjugate Chem.* **2005**, *16*, 1360.

integration of the resonance corresponding to one of the product's protons (1H) at 2.96 ppm compared to the integration of the resonance corresponding to a styrene proton at 6.69 ppm (1H).

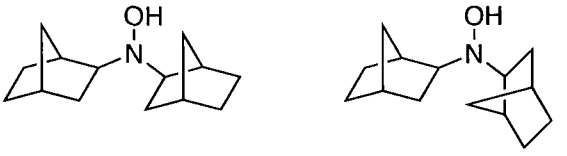
General Procedure for the reaction of aqueous hydroxylamine with alkenes (Table 3.3). A 48 mL sealed tube was charged with a stir bar, an aqueous solution of hydroxylamine (50 wt% in water, 1.32 g, 20.0 mmol), isopropanol (4.0 mL), and alkene (10.0 mmol). The tube was capped with a septum and purged with argon and outlet for 10 minutes while stirring. The septum was removed and the tube was then quickly sealed with a Teflon screw cap and heated while stirring in an oil bath at 95-140°C for 12-72 hrs. The tube was cooled to ambient temperature, and the reactions were then monitored by thin layer chromatography (40% EtOAc/hexanes). For substrates where additional reaction time was deemed necessary, the tube was again purged with argon before exposure to heat. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (typically 10% EtOAc/hexanes → 50% EtOAc/hexanes) to give the corresponding *N*-alkyl- and *N,N*-dialkylhydroxylamines.



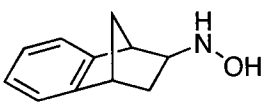
***exo-N*-Hydroxybicyclo[2.2.1]heptan-2-amine (Table 3.3, entry 1).** Synthesized according to general procedure A (95°C, 24 hrs). Isolated 0.39 g (31%) as square white crystals after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). The stereochemistry was assigned by cleavage of the N-O bond under reductive conditions (H_2, Pd/C in MeOH) and comparison with the ^{1}H NMR of the corresponding known *exo*-amine.[69] TLC R_f 0.26 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 6.41 (br s, 2H), 2.96 (dd, J = 7.7 and 3.7 Hz, 1H), 2.32 (d, J = 3.7 Hz, 1H), 2.17 (t, J = 4.1 Hz, 1H), 1.54-1.37 (m, 3H), 1.36-1.30 (m, 1H), 1.16-

(69) Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *J. Org. Chem.*. **1981**, *46*, 4296.

1.02 (m, 3H), 1.01-0.92 (m, 1H); ^{13}C NMR (100 MHz) 65.1 (CH), 38.9 (CH), 35.36 (CH), 35.34 (CH_2), 34.5 (CH_2), 28.5 (CH_2), 26.5 (CH_2); IR (film): 3252, 3160, 2961, 2869, 1495, 1449, 1350, 1087, 996, 860 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{13}NO$ $[M]^+$: 127.0997. Found: 127.1001.



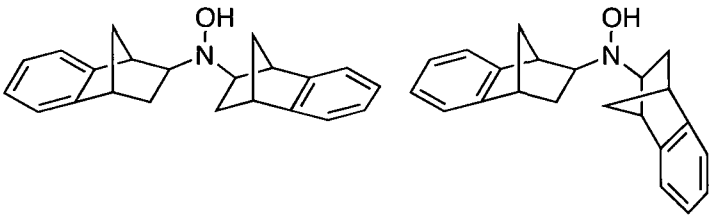
***N*-(Bicyclo[2.2.1]heptan-2-yl)-*N*-hydroxybicyclo[2.2.1]heptan-2-amine (Table 3.3, entry 1).** Synthesized according to general procedure A (95°C, 24 hrs). Isolated 0.76 g (69%) as a clear, colourless oil (mixture of diastereoisomers) after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). TLC R_f 0.57 (25% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) **major**: 5.21 (br s, 1H), 2.71 (dd, J = 6.6 and 5.3 Hz, 2H), 2.38 (s, 2H), 2.23 (s, 2H), 1.83-1.22 (m, 10H), 1.20-0.97 (m, 6H) **minor**: 5.21 (br s, 1H), 2.78 (dd, J = 7.3 and 5.5 Hz, 2H), 2.38 (s, 2H), 2.23 (s, 2H), 1.83-1.22 (m, 10H), 1.20-0.97 (m, 6H); ^{13}C NMR (DMSO-*d*6, 300 MHz, 100°C)[70] **major**: 66.0 (CH), 38.6 (CH), 34.89 (CH), 34.7 (CH_2), 34.1 (CH_2), 27.69 (CH_2), 27.18 (CH_2) **minor**: 66.0 (CH), 37.8 (CH), 34.93 (CH), 34.85 (CH_2), 34.1 (CH_2), 27.64 (CH_2), 27.24 (CH_2) ; IR (film): 3382, 2950, 2869, 1452, 1313, 998, 733 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{23}NO$ $[M]^+$: 221.1780. Found: 221.1757.



***exo*-*N*-Hydroxy-*N*-(1,3,4-trihydro-1,4-methano-2-naphthalenyl)amine (Table 3.3, entry 2).** Synthesized according to general procedure A (95°C, 24 hrs) starting with 7.0 mmol (0.18 g) of corresponding alkene. All other reagents and solvents scaled down accordingly. Isolated 0.48 g

(70) Broad peaks were observed in the ^{13}C NMR spectrum if recorded at 22 °C in $CDCl_3$. The compound was therefore dissolved in DMSO-*d6*, and spectra were recorded at 100°C, producing sharp singlets.

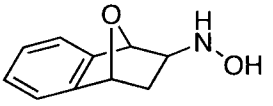
(39%) as white crystals after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). The stereochemistry was assigned by cleavage of the N-O bond under reductive conditions (H_2, Pd/C in MeOH) and comparison with the ^{13}C NMR of the known *exo*-amine.[71] TLC R_f 0.26 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) 7.31-7.22 (m, 1H), 7.18 (td, J = 7.7 and 3.8 Hz, 1H), 7.15-7.07 (m, 2H), 6.38 (br s, 2H), 3.54 (s, 1H), 3.34 (d, J = 2.2 Hz, 1H), 3.21 (dd, J = 7.7 and 3.6 Hz, 1H), 1.95-1.84 (m, 2H), 1.64 (ddd, J = 12.2, 7.7 and 1.8 Hz, 1H), 1.41 (td, J = 12.3 and 3.8 Hz, 1H); ^{13}C NMR (75 MHz) 148.9 (C), 145.6 (C), 125.9 (CH), 125.7 (CH), 121.6 (CH), 120.7 (CH), 64.0 (CH), 46.5 (CH), 45.5 (CH_2), 42.7 (CH), 33.3 (CH_2); IR (film): 3257, 3144, 2979, 2933, 2870, 2328, 1465, 1046, 879, 743 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_1O_1$ $[M]^+$: 175.0997. Found: 175.1003.



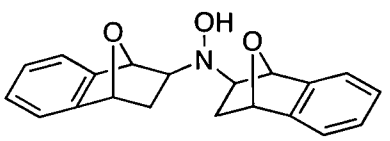
***N*-Hydroxy-*N*,*N*-di(1,3,4-trihydro-1,4-methano-2-naphthalenyl)amine (Table 3.3, entry 2).** Synthesized according to general procedure A (95°C, 24 hrs) starting with 7.0 mmol (0.18 g) of corresponding alkene. Isolated 0.66 g (59%) as a white gum (mixture of diastereoisomers) after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). TLC R_f 0.76 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) **major**: 7.45-7.15 (m, 8H), 5.46 (br s, 1H), 3.68 (s, 2H), 3.48 (s, 2H), 3.11 (dd, J = 6.8 and 4.2 Hz, 2H), 2.39 (t, J = 8.9 Hz, 4H), 1.93-1.85 (m, 4H), 1.51 (ddd, J = 11.3, 7.7 and 1.8 Hz, 2H) **minor**: 7.45-7.15 (m, 8H), 5.46 (br s, 1H), 3.68 (s, 2H), 3.48 (s, 2H), 3.23 (dd, J = 7.2 and 4.6 Hz, 2H), 2.39 (t, J = 8.9 Hz, 4H), 2.15-1.97 (m, 2H), 1.74

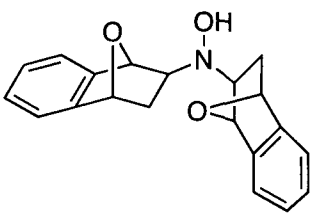
(71) Burn, P. K.; Crooks, P. A. *Org. Magn. Resonance* **1978**, *11*, 370.

(ddd, J = 10.6, 7.9 and 1.6 Hz, 2H); ^{13}C NMR (100 MHz)[72] **major**: 149.09 (C), 147.2 (C), 125.7 (CH), 125.4 (CH), 121.0 (CH), 120.7 (CH), 66.8, (CH) 47.7 (br) (CH), 46.6 (CH_2), 43.33 (CH), 33.1 (CH_2) **minor**: 149.1 (C), 147.3 (C), 125.6 (CH), 125.4 (CH), 120.9 (CH), 120.7 (CH), 66.8 (CH), 47.7 (br) (CH), 46.8 (CH_2), 43.28 (CH), 33.1 (CH_2); IR (film): 3218, 2971, 2943, 2871, 2244, 1627, 1468, 1459, 909, 755, 731, 647 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{22}H_{23}NO$ $[M]^+$: 317.1780. Found: 317.1790.



***N*-Hydroxy-*N*-(1,3,4-trihydro-1,4-oxide-2-naphthalenyl)amine (Table 3.3, entry 3).** Synthesized according to general procedure A (95°C, 24 hrs) starting with 2.5 mmol (0.36 g) of corresponding alkene. All other reagents and solvents scaled down accordingly. Isolated 0.276 g (62%) after column chromatography (20% EtOAc/hexanes → 100% EtOAc). TLC R_f 0.21 (60% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.33-7.27 (m, 1H), 7.23-7.12 (m, 3H), 6.03 (br s, 1H), 5.52 (s, 1H), 5.34 (d, J = 4.8 Hz, 1H), 3.32 (dd, J = 7.5 and 2.7 Hz, 1H), 1.73 (dd, J = 12.4 and 7.5 Hz, 1H), 1.49 (ddd, J = 12.4, 4.8, and 2.7 Hz, 1H); ^{13}C NMR (75 MHz) 146.3 (CH), 142.6 (CH), 127.0 (CH), 126.8 (CH), 120.2 (CH), 118.8 (CH), 80.2 (CH), 78.2 (CH), 63.6 (CH), 32.7 (CH_2); IR (film): 3261, 2999, 2929, 2850, 1453, 843 cm^{-1}; HRMS (EI): $C_{10}H_{11}N_1O_2$ $[M]^+$ not found, exact mass calcd for $C_{10}H_{10}NO$ $[M\text{-}OH]^+$: 160.0762. Found: 160.0780.

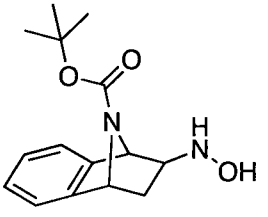




(72) Broad peaks were observed in the ^{13}C NMR spectrum when recorded at 22 °C in $CDCl_3$. The compound was therefore dissolved in DMSO-*d6*, and spectra were recorded at 100 °C, however rapid decomposition occurred under these conditions.

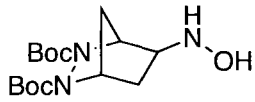
***N*-Hydroxy-*N*,*N*-di(1,3,4-trihydro-1,4-oxide-2-naphthalenyl)amine (Table 3.3, entry 3).**

Major. Isolated 0.086 g (21%) after column chromatography (20% EtOAc/hexanes → 100% EtOAc). TLC R_f 0.57 (60% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.36-7.28 (m, 2H), 7.24-7.11 (m, 6H), 5.89 (br s, 1H), 5.61 (s, 2H), 5.43 (d, J = 4.7 Hz, 2H), 3.08 (dd, J = 6.6 and 3.0 Hz, 2H), 2.21-2.06 (m, 2H), 1.44 (dd, J = 11.5 and 7.6 Hz, 2H); ^{13}C NMR (75 MHz) 146.2 (CH), 143.9 (CH), 126.9, (CH) 126.7 (CH), 119.7 (CH), 119.1 (CH), 82.5 (CH), 79.1 (CH), 66.0 (CH), 31.1 (br) (CH_2); IR (film): 3387, 3050, 3003, 2956, 1766, 1453 cm^{-1}; **minor.** Isolated 0.049 g (12%) after column chromatography (20% EtOAc/hexanes → 100% EtOAc). TLC R_f 0.43 (60% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.31-7.14 (m, 8H), 5.61 (s, 2H), 5.47 (d, J = 3.9 Hz, 2H), 3.34-3.25 (m, 2H), 2.24-2.10 (m, 2H), 1.78 (dd, J = 10.9 and 7.8 Hz, 2H); ^{13}C NMR (75 MHz) 146.4 (C), 143.8 (C), 127.0 (CH), 126.8 (CH), 119.5 (CH), 119.2 (CH), 80.5 (CH), 79.0 (CH), 66.7 (CH), 32.3 (CH_2); IR (film): 3382, 3051, 3003, 2952, 1764, 1460 cm^{-1}; HRMS (EI): $C_{20}H_{19}NO_3$ $[M]^+$ not found, exact mass calcd for $C_{10}H_{10}N_1O$ $[M\text{-}OH]^+$: 304.1338. Found: 304.1326.

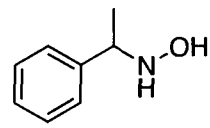


***N*-Hydroxy-*N*-(1,3,4-trihydro-1,4-(*tert*-butylcarbamato)-2-naphthalenyl)amine (Table 3.3, entry 4).** Synthesized according to general procedure A (95°C, 18 hrs) starting with 0.72 mmol (0.18 g) of corresponding alkene. All other reagents and solvents scaled down accordingly. Isolated 0.095 g (48%) after column chromatography ($CHCl_3$ → 5% MeOH/$CHCl_3$). TLC R_f 0.28 (5% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32-7.28 (m, 1H), 7.22-7.19 (m, 1H), 7.14-7.11 (m, 2H), 5.30 (s, 1H), 5.05 (d, J = 3.6 Hz, 1H), 3.26 (dd, J = 7.5 and 3.2 Hz, 1H), 1.62 (dd,

J = 12.3 and 7.5 Hz, 1H), 1.52 (ddd, J = 12.4, 4.4, 3.5 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz) 155.6 (C), 146.4 (C), 142.7 (C), 142.7 (C), 127.0 (CH), 126.8 (CH), 121.1 (CH), 119.8 (CH), 80.6 (C), 64.3 (CH), 63.5 (CH), 60.7 (CH), 33.1 (CH_2), 28.4 (CH_3); IR (film): 3354, 2978, 2932, 2187, 1694, 1681, 1392 cm^{-1}; HRMS (EI): $C_{15}H_{20}N_2O_3$ $[M]^+$ not found, exact mass calcd for $C_{10}H_{11}N_2O$ $[M\text{-Boc}]^+$: 175.0871. Found: 175.0872.

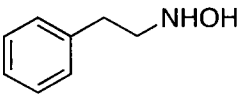


Di-*tert*-butyl 5-(hydroxyamino)-2,3-diaza-bicyclo[2.2.1]heptane-2,3-dicarboxylate (Table 3.3, entry 5). Synthesized according to general procedure A (95°C, 48 hrs) starting with 2.3 mmol (0.67 g) of corresponding alkene. All other reagents and solvents scaled down accordingly. Isolated 0.41 g (55%) after column chromatography (40% EtOAc/hexanes). TLC R_f 0.34 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 6.03 (br s, 2H), 4.63-4.21 (m, 2H), 3.46-3.26 (m, 1H), 2.08-1.64 (m, 2H), 1.58-1.47 (m, 1H), 1.37 (s, 18 H), 1.18-1.05 (m, 1H); ^{13}C NMR (100 MHz) 158.6 (C), 81.5 (C), 61.9 (CH), 61.3 (CH), 59.1 (CH), 33.9 (CH_2), 32.0 (CH_2), 28.0 (CH_3); IR (film): 3402 (s), 2980, 2934, 2250, 1694, 1455 cm^{-1}; HRMS (EI): exact mass calcd for $C_{15}H_{27}N_3O_5$ $[M]^+$: 329.1951. Found: 329.1962.

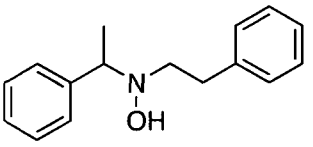


***N*-Hydroxy-1-phenylethanamine (Table 3.3, entry 6).** Synthesized according to general procedure A (140°C, 72 hrs). Isolated 0.16 g (12%) as a white powder after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). TLC R_f 0.52 (5% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37-7.23 (m, 5H), 4.08 (q, J = 6.7 Hz, 1H), 1.37

(d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz) 142.2 (C), 128.5 (CH), 127.6 (CH), 127.2 (CH), 61.7 (CH), 19.3 (CH_3). Spectral data were found to be in good agreement with those in the literature.[73]



***N*-Hydroxy-2-phenylethanamine (Table 3.3, entry 6).** Synthesized according to general procedure A (140°C, 72 hrs). Isolated 0.014 g (1.0%) as thin white crystals after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). TLC R_f 0.42 (5% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35-7.18 (m, 5H), 4.62 (br s, 2H), 3.20 (t, J = 7.0 Hz, 2H), 2.89 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz) 139.0 (C), 128.8 (CH), 128.6 (CH), 126.3 (CH), 54.7 (CH_2), 33.0 (CH_2); Spectral data were found to be in good agreement with those in the literature.[74]

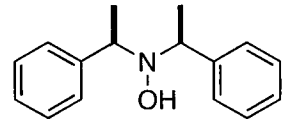


***N*-Hydroxy-*N*-phenethyl-1-phenylethanamine (Table 3.3, entry 6).** Synthesized according to general procedure A (140°C, 72 hrs). Isolated 0.19 g (16%) as a clear, colourless oil after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). TLC R_f 0.53 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32-7.29 (m, 4H), 7.27-7.21 (m, 3H), 7.19-7.10 (m, 3H), 3.82 (q, J = 6.6 Hz, 1H), 3.00-2.77 (m, 4H), 1.46 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz) 142.4 (C), 140.1 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.9 (CH), 127.4 (CH), 126.0 (CH), 67.7 (CH), 58.6 (CH_2), 33.8 (CH_2), 19.7 (CH_3); IR (film): 3262, 3027, 2973, 2933, 2866,

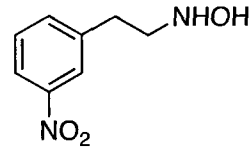
(73) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464.

(74) R. J. Rahalm Jr. ; Maleczka, Jr, R. E. *Org. Lett.* **2005**, *7*, 5087.

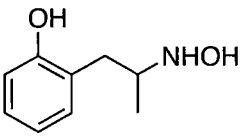
1744, 1602, 1494, 1453, 1369, 1073, 1029, 752, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO$ $[M]^+$: 241.1467. Found: 241.1445.



***meso* *N*-Hydroxy-1-phenyl-*N*-(1-phenylethyl)ethanamine (Table 3.3, entry 6).** Synthesized according to general procedure A (140°C, 72 hrs). Isolated 0.12 g (10%) as a clear, colourless oil after column chromatography (10% EtOAc/hexanes → 50% EtOAc/hexanes). TLC R_f 0.61 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) 7.43-7.24 (m, 10H), 3.93 (q, J = 6.6 Hz, 2H), 1.45 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) 143.3 (C), 128.3 (CH), 127.9 (CH), 127.1 (CH), 62.1 (CH), 17.3 (CH_3); Spectral data were found to be in good agreement with those in the literature.[73]

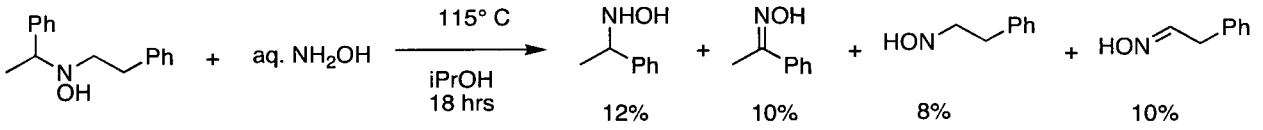


***N*-Hydroxy-2-(3-nitrophenyl)ethanamine, 8g (Table 3.3, entry 7).** Synthesized according to the general procedure (95°C, 24 hrs) on 5.0 mmol of alkene (all reagents and solvents scaled down accordingly). Isolated 0.27 g (30%) as thin white crystals after column chromatography ($CHCl_3$ → 5% MeOH/$CHCl_3$). TLC R_f 0.35 (5% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) 8.09-8.02 (m, 2H), 7.55-7.51 (m, 1H), 7.44 (t, J = 7.8 Hz, 1H), 6.00 (br s, 2H), 3.19 (t, J = 7.1 Hz, 2H), 2.98 (t, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz) 148.3 (C), 141.3 (C), 135.1 (CH), 129.4 (CH), 123.6 (CH), 121.5 (CH), 54.1 (CH_2), 32.8 (CH_2); IR (film): 3301, 3191, 2843, 1580, 1537, 1359, 1314, 1123, 1052, 865, 737 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{10}N_2O_3$ $[M]^+$: 182.0691. Found: 182.0680.



2-(2-(Hydroxyamino)propyl)phenol, 8h (Table 3.3, entry 8). Synthesized according to the general procedure (115°C, 12 hrs). Isolated 0.22 g (13%) after column chromatography (40% EtOAc/hexanes). TLC R_f 0.13 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39 (br s, 3H), 7.13 (dt, J = 7.9, 7.9, 1.6 Hz, 1H), 7.00 (dd, J = 7.4, 1.6 Hz, 1H), 6.86 (dd, J = 7.9, 1.0 Hz, 1H), 6.81 (dt, J = 7.4, 7.4, 1.0 Hz, 1H), 3.39 (dp, J = 6.7, 6.7, 6.7, 6.7, 2.2 Hz, 1H), 3.07 (dd, J = 15.0, 2.2 Hz, 1H), 2.69 (dd, J = 15.0, 6.7 Hz, 1H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz) 155.5 (C), 132.3 (CH), 128.5 (CH), 124.8 (C), 120.3 (CH), 117.5 (CH), 57.8 (CH), 36.0 (CH_2), 16.9 (CH_3); IR (film): 3349, 3256, 2975, 2934, 1582, 1456, 1248, 753 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{13}NO_2$ $[M]^+$: 167.0946. Found: 167.0944.

Reversibility Experiments



Procedure for Cope Elimination of *N*-hydroxy-*N*-phenethyl-1-phenylethanamine (Equation 3.6). A 2m L sealed tube was charged with a stir bar, an aqueous solution of hydroxylamine (50 wt% in water, 0.11 g, 1.7 mmol), *i*PrOH (0.40mL) and *N*-hydroxy-*N*-phenethyl-1-phenylethanamine (0.040 g, 0.17 mmol). The tube was capped with a septum and purged with argon and outlet for 10 minutes while stirring. The septum was removed and the tube was then quickly sealed with a screw cap. The tube was heated in an oil bath at 115°C for 18 hrs. The tube was cooled to ambient temperature, the solvent was evaporated and the residue taken up in $CDCl_3$. ^{1}H NMR analysis revealed that a fraction of the starting *N*-hydroxy-*N*-phenethyl-1-

phenylethanamine had been converted to Cope elimination products *N*-hydroxy-1-phenylethanamine (12%), *N*-hydroxy-2-phenylethanamine (8%) as well as the oxidation byproducts acetophenone oxime (10%) and 2-phenylacetaldehyde oxime (10%). The remainder was unreacted starting material. The oxidative byproducts were also observed in the forward reaction. Several attempts to remove O_2 from the reaction vessel slowed but did not suppress the oxidative process. Monosubstituted hydroxylamines are known to undergo anaerobic solvent-induced oxidation.[75]

3.4.2. Reactions of *N*-Alkylhydroxylamines with Alkenes

General Procedure for the optimization of hydroamination of *N*-cyclohexylhydroxylamine with norbornene (Table 3.6). A 3 mL tapered bottom screwcap vial was charged with a stir bar, *N*-cyclohexylhydroxylamine (0.050 g, 0.44 mmol), *n*-propanol (0.7 mL), sodium cyanoborohydride (0.028 g, 0.44 mmol) and norbornene (0.16 g, 1.7 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 an oil bath at 110°C for 18 hrs. The vial was cooled to ambient temperature and concentrated under reduced pressure. Styrene (≈ 0.046 g, 0.44 mmol) was then added as an internal standard. The mixture was taken up in $CDCl_3$ and transferred to an NMR tube. ^{1}H NMR spectra of these solutions were recorded, and the conversion calculated based on the relative integration of the resonance corresponding to one of the product's protons (1H) (either at 2.85 or 2.63 ppm) compared to the integration of the resonance corresponding to a styrene proton at 6.69 ppm (1H).

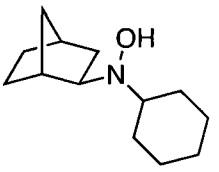
Inhibition of thermal decomposition of 11a (Equation 3.6). *N*-Cyclohexyl-*N*-hydroxy-*exo*-

---

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

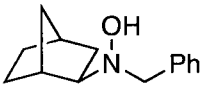
bicyclo[2.2.1]heptan-2-amine (**11a,** 0.10 g, 0.48 mmol) in *n*-propanol (0.8 mL) was stirred in a sealed tube under an argon atmosphere while heating to 140 °C in an oil bath for 21 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and taken up in $CDCl_3$. TLC analysis (5% $MeOH/CH_2Cl_2$) and ^1H NMR spectra of this solution showed significant decomposition to compounds believed to be nitrones **11ai** and **11aii** (isolated as an inseparable mixture by column chromatography; 5% $MeOH/CH_2Cl_2$). The same experiment, but with the addition of sodium cyanoborohydride (0.030 g, 0.48 mmol), resulted in nearly quantitative recovery of starting materials. Only traces of the ^1H NMR resonances thought to correspond to nitrones **11ai** and **11aii** could be observed under these conditions.

General Procedure for the reaction of *N*-alkylhydroxylamines with norbornene (Table 3.7). An 8 mL screwcap vial was charged with a stir bar, *N*-alkylhydroxylamine (0.20 g, 1.0 equiv), *n*-propanol (such that the concentration of *N*-alkylhydroxylamine is 0.60 M), sodium cyanoborohydride (1.0 equiv) and norbornene (2.0 equiv). The tube was capped with a septum and purged with argon and an outlet for 5 minutes while stirring. The septum was removed and the tube was then quickly sealed with a screw cap and Teflon tape and heated while stirring in an oil bath at 110°C for 18 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^1H NMR using styrene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding *N*,*N*-dialkyhydroxylamine.



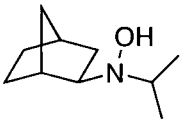
***N*-Cyclohexyl-*N*-hydroxy-*exo*-bicyclo[2.2.1]heptan-2-amine, 11a (Table 3.7, entry 1).** A 15 mL sealed tube was charged with a stir bar, *N*-cyclohexylhydroxylamine[23] (0.10 g, 0.87 mmol),

n-propanol (1.4 mL), sodium cyanoborohydride (0.055 g, 0.87 mmol) and norbornene (0.16 g, 1.7 mmol). The tube was capped with a septum and purged with argon and an outlet for 5 minutes while stirring. The septum was removed and the tube was then quickly sealed with a Teflon screw cap and heated while stirring in an oil bath at 110°C for 21 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography (10% EtOAc/hexanes) to give the titled compound (0.15 g, 83%) as a white gum. When the reaction was performed in the absence of sodium cyanoborohydride the yield was slightly reduced (0.12 g, 67%). TLC R_f 0.35 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 4.54 (br s, 1H), 2.85 (t, J = 5.8, 5.8 Hz, 1H), 2.63 (tt, J = 11.3, 11.3, 3.1, 3.1 Hz, 1H), 2.35 (s, 1H), 2.23 (s, 1H), 1.79 (ap d, J = 9.3 Hz, 4H), 1.69-0.98 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) 65.7 (CH), 61.1 (CH), 39.5 (CH), 36.0 (CH), 35.9 (CH_2), 35.2 (CH_2), 28.3 (CH_2), 27.6 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.6 (CH_2); IR (film): 3432, 2910, 2851, 1451 cm^{-1}; HRMS (EI): exact mass calcd for $C_{13}H_{23}NO$ $[M]^+$: 209.1780. Found: 209.1797.

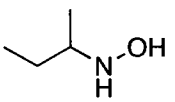


***N*-Benzyl-*N*-*exo*-hydroxybicyclo[2.2.1]heptan-2-amine, 11b (Table 3.7, entry 2).** Synthesized according to the general procedure on 3.25 mmol of norbornene (all reagents and solvents scaled down accordingly). Isolated 317 mg (90% yield) as a clear colourless oil after column chromatography (5% EtOAc/hexanes). TLC R_f 0.24 (5% EtOAc/hexanes). ^{1}H NMR (C_6D_6, 300 MHz) δ ppm 7.44 (d, J = 7 Hz, 2H), 7.33-7.22 (m, 3H), 5.9 (br s, 1H), 3.57-3.77 (m, 2H), 2.67-2.58 (m, 2H), 2.26 (s, 1H), 1.86 (d, J = 9 Hz, 1H), 1.51-1.00 (m, 7H); ^{13}C NMR (C_6D_6, 75 MHz) δ ppm 138.64 (C), 130.35 (CH), 128.34 (CH), 127.29 (CH), 71.00 (CH), 61.45 (CH_2), 40.03 (CH), 36.78 (CH), 35.60 (CH_2), 28.82 (CH_2), 27.58 (CH_2); IR (film): 3422, 2952, 2870, 2361,

2341, 1496, 1453, 1345, 1089, 743, 698, 611 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{14}H_{19}NO$ [M^+]: 217.1467. Found: 217.1477.

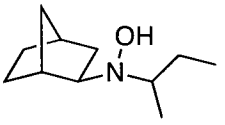


***N-exo*-(Bicyclo[2.2.1]heptan-2-yl)-*N*-isopropylhydroxylamine, 11c (Table 3.7, entry 3).** Synthesized according to the general procedure (110°C, 18 hrs). Isolated 327 mg (73% yield) as a clear oil after column chromatography (3% MeOH/CH_2Cl_2). TLC R_f 0.32 (5% MeOH/ CH_2Cl_2). ^1H NMR (C_6D_6, 300 MHz) δ ppm 8.59 (br s, 1H), 3.00-2.85 (m, 1H), 2.76 (dd, J = 6, 4 Hz, 1H), 2.40 (br s, 1H), 2.13 (br s, 1H), 1.79 (d, J = 9 Hz, 1H), 1.49-0.87 (m, 13H); ^{13}C NMR (C_6D_6, 75 MHz) δ ppm 67.38 (CH), 52.32 (CH), 39.76 (CH), 36.69 (CH), 36.13 (CH_2), 35.50 (CH_2), 28.78 (CH_2), 27.86 (CH_2), 22.63 (CH_3); IR (film): 3362, 2955, 2870, 2360, 2341, 1376, 1344, 1089, 944, 890, 611 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{10}H_{19}N_1O_1$[M^+]: 169.1467. Found: 169.1474.

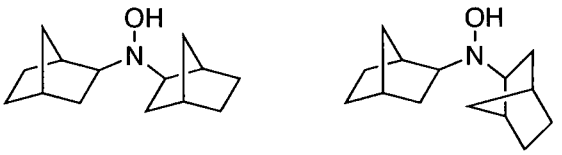


***N*-Secbutyl Hydroxylamine, 10d.** Procedure modified from original, as reported by House.[1] To a round bottomed flask equipped with a magnetic stirring bar was added 1.0 equivalent of oxime, diluted in methanol so that the concentration of oxime is 1M. A minimum amount of methyl orange indicator was added, followed by 1.2 equivalents sodium cyanoborohydride. 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

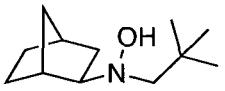
deemed complete. To quench the reaction, a 25% sodium hydroxide solution in water was added dropwise until the solution was basified to pH 8. Dilution with water and extraction three times with dichloromethane, drying over anhydrous sodium sulfate and concentration under reduced pressure furnished the product. Performed on 11.48 mmol oxime. Isolated 0.49 g (48% yield) as a white solid after column chromatography (100% CH_2Cl_2 → 2% MeOH/ CH_2Cl_2). TLC R_f 0.24 (5% MeOH/CH_2Cl_2). ^1H NMR (C_6D_6, 400 MHz) δ ppm 2.74 (qt, *J* = 12, 12, 12, 6, 6 Hz, 1H), 1.43 (dqd, *J* = 13, 8, 8, 8, 6 Hz, 1H), 1.21-1.06 (m, 1H), 0.93 (d, *J* = 6 Hz, 3H), 0.74 (t, *J* = 8, 8Hz, 3H). ^{13}C NMR (C_6D_6, 100 MHz) δ ppm 58.72 (CH), 26.64 (CH_2), 56 17.32 (CH_3), 10.28 (CH_3). IR (film): 3397, 2968, 2910, 2861, 2356, 2337, 1698, 1554, 1451, 1227, 1048, 780 cm^{-1}. HRMS (EI): Exact mass calculated for $C_4H_{11}NO[M^+]$: 89.0841, found: 89.0850.



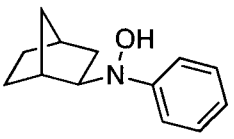
***N-exo*-(Bicyclo[2.2.1]heptan-2-yl)-*N-sec*-butylhydroxylamine, 11d (Table 3.7, entry 4).** Synthesized according to the general procedure (110°C, 18 hrs). Isolated 487 mg (63% yield) of a 1:1 mixture of diastereomers as a clear oil after column chromatography (1% MeOH/CH_2Cl_2). TLC R_f 0.72 (50% EtOAc/hexanes). ^1H NMR (C_6D_6, 300 MHz) δ ppm 2.74 (qt, *J* = 12 and 6 Hz, 1H), 1.43 (dqd, *J* = 13, 7, 6 Hz, 1H), 1.21-1.06 (m, 1H), 0.93 (d, *J* = 6 Hz, 3H), 0.74 (t, *J* = 7 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ ppm 67.8 (CH), 67.6 (CH), 60.9 (CH), 59.1 (CH), 39.1 (CH), 38.9 (CH), 36.2 (CH), 36.1 (CH), 35.5 (CH_2), 35.2 (CH_2), 35.0 (CH_2), 28.0 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 11.3 br (CH_3), 10.7 (CH_3), 10.6 (CH_3); IR (film): 2966, 2877, 2337, 2176, 1459, 1389, 1307, 1089, 611 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{11}H_{21}NO[M^+]$: 183.1623. Found: 183.1623.



***N-exo*-(Bicyclo[2.2.1]heptan-2-yl)-*N-exo*-hydroxybicyclo[2.2.1]heptan-2-amine, 11e (Table 3.7, entry 5).** Synthesized according to the general procedure (110°C, 18 hrs). Isolated 462 mg (78% yield) of a 1:1 mixture of diastereomers as a clear, colourless oil after column chromatography (30% EtOAc/hexanes). TLC R_f 0.55 (40% EtOAc/hexanes). See section 3.4.1 for characterization data.

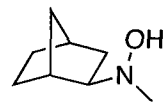


***N-exo*-(Bicyclo[2.2.1]heptan-2-yl)-*N*-neopentylhydroxylamine, 11f (Table 3.7, entry 6).** Synthesized according to the general procedure (110°C, 18 hrs). Isolated 0.24 g (72%) as a white powder after column chromatography (7% EtOAc/hexanes). TLC R_f 0.47 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 4.72 (br s, 1H), 2.52 (dd, J = 7, 4 Hz, 1H), 2.42 (d, J = 14 Hz, 1H), 2.36 (s, 1H), 2.34 (d, J = 14 Hz, 1H), 2.23 (s, 1H), 1.65-1.00 (m, 8H), 0.93 (s, 9H); ^{13}C NMR (75 MHz) 72.3 (CH), 68.9 (CH_2), 40.0 (CH), 37.1 (CH_2), 36.4 (CH), 34.8 (CH_2), 31.6 (C), 28.66 (CH_2), 28.63 (CH_3), 27.0 (CH_2); IR (film): 3426, 2950, 2867, 1473, 1356 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{23}NO$ $[M]^+$: 197.1780. Found: 197.1770.



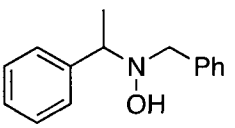
***N-exo*-(Bicyclo[2.2.1]heptan-2-yl)-*N*-phenylhydroxylamine, 11g (Table 3.7, entry 7).** Synthesized according to the general procedure (110°C, 18 hrs). Performed on 2.75 mmol of norbornene. Isolated 19.5 mg (7% yield) as a yellow oil after column chromatography (100% hexanes → 30% EtOAc/hexanes). TLC R_f 0.68 (1% MeOH/ CH_2Cl_2); ^{1}H NMR (C_6D_6, 300 MHz)

δ ppm 7.25-7.10 (m, 2H), 6.77 (tt, J = 7, 1 Hz, 1H), 6.48 (dd, J = 9, 1 Hz, 2H), 3.12 (br s, 1H), 2.99 (dd, J = 7, 3 Hz, 1H), 2.07 (br s, 1H), 2.00 (br s, 1H), 1.47 (ddd, J = 13, 8, 2 Hz, 1H), 1.39-0.85 (m, 7H); ^{13}C NMR (C_6D_6, 75 MHz) δ ppm 148.07 (C), 129.47 (CH), 117.24 (CH), 113.50 (CH), 56.61 (CH), 41.37 (CH), 40.99 (CH_2), 35.86 (CH), 35.41 (CH_2), 28.74 (CH_2), 26.44 (CH_2); IR (film): 3410, 2952, 2869, 2360, 2341, 1601, 1503, 1352, 1241, 1087, 746, 610 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{17}NO$ [M^+]: 203.1310. Not found. Exact mass calculated for $C_{13}H_{16}NO$ [M^+–H]: 202.1232. Found: 202.1225.

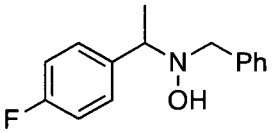


***N-exo*-(Bicyclo[2.2.1]heptan-2-yl)-*N*-methylhydroxylamine, 11h (Table 3.7, entry 8).** A 15 mL sealed tube was charged with a stir bar, *N*-methylhydroxylamine hydrochloride (0.073 g, 0.87 mmol), *n*-propanol (1.4 mL), sodium hydroxide (0.035 g, 0.87 mmol), sodium cyanoborohydride (0.055 g, 0.87 mmol) and norbornene (0.16 g, 1.7 mmol). The tube was capped with a septum and purged with argon and an outlet for 5 minutes while stirring. The septum was removed and the tube was then quickly sealed with a Teflon screw cap and heated while stirring in an oil bath at 110°C for 21 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography (2% MeOH/ CH_2Cl_2) to give the titled compound (0.059 g, 48%) as a clear colourless oil. TLC R_f 0.35 (2% MeOH/ CH_2Cl_2); ^{1}H NMR (C_6D_6, 400 MHz) δ ppm 8.42 (br s, 1H), 2.87 (s, 1H), 2.72-2.37 (m, 5H), 2.32-1.90 (m, 2H), 1.77 (d, J = 10 Hz, 1H), 1.60-1.34 (m, 3H), 1.25-0.86 (m, 5H); ^{13}C NMR (C_6D_6, 100 MHz) δ ppm 73.6 (CH), 45.1 (CH_3), 40.2 (CH_2), 36.7 (CH), 35.3 (CH_2), 28.5 (CH_2), 27.4 (CH_2); IR (film): 3432, 2910, 2851, 1451 cm^{-1}; HRMS (EI): exact mass calcd for $C_8H_{15}NO$ [M]$^+$: 141.1154. Found: 141.1149.

General Procedure of the reaction of *N*-benzylhydroxylamine with vinylarenes and trimethylvinylsilane (Table 3.9). A 15 mL sealed tube was charged with a stir bar, *N*-benzyylhydroxylamine (0.81 mmol, 0.10 g), *n*-propanol (1.4 mL), sodium cyanoborohydride (0.81 mmol, 0.051 g) and vinylarene (1.6 mmol). The tube was capped with a septum and purged with argon and an outlet for 5 minutes while stirring. The septum was removed and the tube was then quickly sealed with a Teflon screw cap and heated while stirring in an oil bath at 140°C for 11-24 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography (10% EtOAc/hexanes) to give the corresponding *N*,*N*-dialkyhydroxylamine.

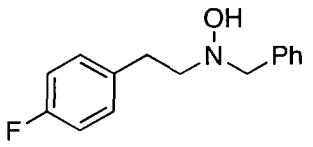


***N*-Benzyl-*N*-hydroxy-1-phenylethanamine, 14a (Table 3.9, entry 1).** Synthesized according to the general procedure (140°C, 17 hrs). Isolated 0.11 g (58%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.57 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.45-7.26 (m, 10 H), 5.90 (s, 1H), 3.82 (q, J = 7 Hz, 1H), 3.74 (d, J = 13 Hz, 1H), 3.60 (d, J = 13 Hz, 1H), 1.49 (d, J = 7 Hz, 3H); ^{13}C NMR (75 MHz) 142.6 (C), 138.1 (C), 129.5 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 66.6 (CH), 61.0 (CH_2), 19.4 (CH_3); IR (film): 3068, 3048, 3021, 2926, 1427, 1111, 734, 700 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{17}NO$ $[M]^+$: 227.1310. Found: 227.1316.

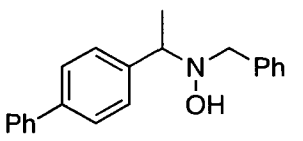


***N*-Benzyl-1-(4-fluorophenyl)-*N*-hydroxyethanamine, 14b (Table 3.9, entry 2).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.092 g (46%) as a white powder

after column chromatography (10% EtOAc/hexanes). TLC R_f 0.24 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36-7.21 (m, 7H), 7.06-6.99 (m, 2H), 5.78 (br s, 1H), 3.76 (q, J = 7, 7, 7 Hz, 1H), 3.66 (d, J = 13 Hz, 1H), 3.54 (d, J = 13 Hz, 1H), 1.41 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz) 162.0 (d, J = 245 Hz) (C), 138.2 (d, J = 2 Hz) (C), 137.9 (C), 129.47 (d, J = 8 Hz) (CH), 129.47 (CH_2), 128.2 (CH), 127.2 (CH), 115.2 (d, J = 21 Hz) (CH), 65.8 (CH), 60.9 (CH_2), 19.3 (CH_3); IR (film): 3528, 3234, 2918, 2245, 1944 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{16}FNO$ $[M]^+$: 245.1216. Found: 245.1242.

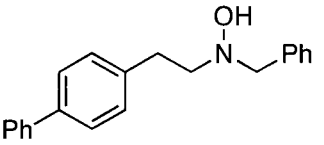


***N*-Benzyl-2-(4-fluorophenyl)-*N*-hydroxyethanamine, 15b (Table 3.9, entry 2).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.020 g (10%) as a white powder after column chromatography (10% EtOAc/hexane). TLC R_f 0.19 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35-7.22 (m, 5H), 7.16-7.11 (m, 2H), 6.98-6.91 (m, 2H), 5.27 (br s, 1H), 3.81 (s, 2H), 2.96-2.85 (m, 4H); ^{13}C NMR (100 MHz) 161.4 (d, J = 244 Hz) (C), 137.2 (C), 135.6 (d, J = 3 Hz) (C), 130.1 (d, J = 8 Hz) (CH), 129.5 (CH), 128.4 (CH), 127.5 (CH), 115.1 (d, J = 21 Hz) (CH), 65.1 (CH_2), 61.3 (CH_2), 33.0 (CH_2); HRMS (EI): Exact mass calcd for $C_{15}H_{16}FNO$ $[M]^+$: 245.1216. Not found. Exact mass calcd for $C_{15}H_{14}FN$ $[M\text{-}H_2O]^+$: 227.1111. Found: 227.1087.

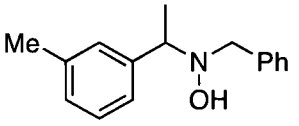


***N*-Benzyl-*N*-(1-(biphenyl-4-yl)ethyl)hydroxylamine, 14c (Table 3.9, entry 3).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.080 g (33%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.40 (20% EtOAc/hexanes); ^{1}H

NMR ($CDCl_3$, 400 MHz) 7.63-7.57 (m, 4H), 7.48-7.42 (m, 4H), 7.38-7.28 (m, 6H), 3.87 (q, J = 7, 7, 7 Hz, 1H), 3.78 (d, J = 13 Hz, 1H), 3.64 (d, J = 13 Hz, 1H), 1.51 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz) 141.6 (C), 140.9 (C), 140.2 (C), 138.1 (C), 129.5 (CH), 128.7 (CH), 128.4 (CH), 128.20 (CH), 127.18 (CH), 127.15 (CH), 127.0 (CH), 66.5 (CH), 61.2 (CH_2), 19.5 (CH_3); IR (film): 3251, 3029, 2898, 1486, 1453 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{21}H_{21}NO$ $[M]^+$: 303.1623. Found: 303.1643.

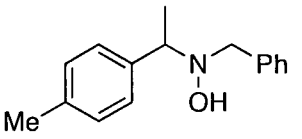


***N*-Benzyl-*N*-(2-(biphenyl-4-yl)ethyl)hydroxylamine, 15c (Table 3.9, entry 3).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.039 g (16%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.29 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) 7.60-7.48 (m, 4H), 7.44-7.39 (m, 2H), 7.37-7.22 (m, 8H), 3.86 (s, 2H), 3.05-2.95 (m, 4H), 1.25 (br s, 1H); ^{13}C NMR (100 MHz) 141.0 (C), 139.1 (C), 139.0 (C), 137.0 (C), 129.6 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 127.5 (CH), 127.13 (CH), 127.06 (CH), 126.99 (CH), 65.0 (CH_2), 61.1 (CH_2), 33.3 (CH_2); IR (film): 3215, 3034, 2937, 2851, 1487 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{21}H_{21}NO$ $[M]^+$: 303.1623. Found: 303.1597.

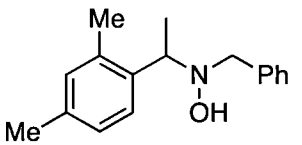


***N*-Benzyl-*N*-(1-*m*-tolylethyl)hydroxylamine, 14d (Table 3.9, entry 4).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.085 g (43%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.33 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) 7.40-7.10 (m, 9H), 5.79 (br s, 1H), 3.78 (q, J = 7 Hz, 1H), 3.75 (d, J = 13 Hz, 1H), 3.60 (d, J = 13 Hz, 1H), 2.41 (s, 3H), 1.48 (d, J = 7 Hz, 3H); ^{13}C NMR (75 MHz) 142.6 (C),

138.2 (C), 137.9 (C), 129.5 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.1 (CH), 124.9 (CH), 66.7 (CH), 61.1 (CH_2), 21.5 (CH_3), 19.5 (CH_3); IR (film): 3528, 3234, 2918, 2245, 1944 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO$ $[M]^+$: 241.1467. Found: 241.1414.

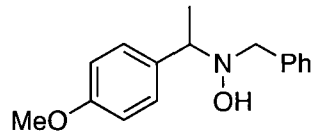


***N*-Benzyl-*N*-(1-*p*-tolylethyl)hydroxylamine, 14e (Table 3.9, entry 5).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.081 g (41%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.37 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) 7.36-7.12 (m, 9H), 5.73 (br s, 1H), 3.75 (q, J = 7 Hz, 1H), 3.70 (d, J = 13 Hz, 1H), 3.55 (d, J = 13 Hz, 1H), 2.35 (s, 3H), 1.43 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz) 139.6 (C), 138.3 (C), 136.9 (C), 129.5 (CH), 129.1 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 66.4 (CH), 61.0 (CH_2), 21.1 (CH_3), 19.6 (CH_3); IR (film): 3528, 3234, 2918, 2245, 1944 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO$ $[M]^+$: 241.1467. Found: 241.1414.

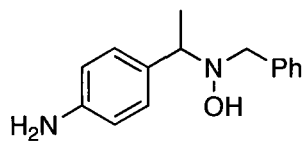


***N*-Benzyl-*N*-(1-(2,4-dimethylphenyl)ethyl)hydroxylamine, 14f (Table 3.9, entry 6).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.068 g (33%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.67 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) major rotamer: 7.48-7.21 (m, 6H), 7.09-6.94 (m, 2H), 5.26 (br s, 1H), 4.08 (q, J = 7 Hz, 1H), 3.78 (d, J = 13, 1H), 3.61 (d, J = 13 Hz, 1H), 2.310 (s, 3H), 2.305 (s, 3H), 1.43 (d, J = 6 Hz, 3H) minor rotamer: 7.48-7.21 (m, 6H), 7.09-6.94 (m, 2H), 5.26 (br s, 1H), 4.08 (q, J = 7 Hz, 1H), 3.79 (d, J = 13, 1H), 3.63 (d, J = 13 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 1.44 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz) major rotamer: 138.6 (C), 138.3

(C), 136.3 (C), 135.4 (C), 131.2 (CH), 129.4 (CH), 128.1 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 62.3 (CH), 61.1 (CH_2), 20.9 (CH_3), 19.5 (CH_3), 19.0 (CH_3) minor rotamer: 141.4 (C), 138.3 (C), 135.5 (C), 132.4 (C), 130.4 (CH), 129.4 (CH), 128.2 (CH), 127.5 (2C) (CH), 127.1 (CH), 62.6 (CH), 61.2 (CH_2), 21.1 (CH_3), 19.1 (CH_3), 18.9 (CH_3); IR (film): 3250, 3031, 2979, 2922, 1497, 1453, 824, 747, 698 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{21}NO$ $[M]^+$: 255.1623. Found: 255.1627.

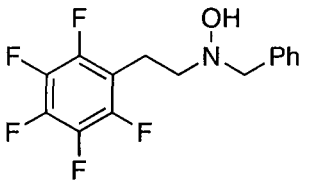


***N*-Benzyl-*N*-(1-(4-methoxyphenyl)ethyl)hydroxylamine, 14g (Table 3.9, entry 7).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.102 g (49%) as a clear, colourless oil after column chromatography (10% EtOAc/hexanes). TLC R_f 0.48 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) 7.51-7.17 (m, 7H), 6.89 (d, J = 8 Hz, 2H), 5.98 (br s, 1H), 3.80 (s, 3H), 3.73 (q, J = 6 Hz, 1H), 3.69 (d, J = 13 Hz, 1H), 3.52 (d, J = 13 Hz, 1H), 1.42 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz) 158.8 (C), 138.1 (C), 134.4 (C), 129.6 (CH), 129.1 (CH), 128.1 (CH), 127.1 (CH), 113.7 (CH), 65.8 (CH), 60.8 (CH_2), 55.2 (CH_3), 19.3 (CH_3); IR (film): 3237, 2836, 1612, 1513, 1248, 1034, 834 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO_2$ $[M]^+$: 257.1416. Found: 257.1435.

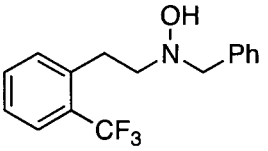


4-(1-(Benzyl(hydroxy)amino)ethyl)aniline, 14h (Table 3.9, entry 8). Synthesized according to the general procedure (140°C, 18 hrs). Isolated 0.070 g (36%) as a clear colourless oil after column chromatography (20% EtOAc/hexanes → 30% EtOAc/hexanes). TLC R_f 0.28 (30% EtOAc/hexanes); ^1H NMR (CD_3OD, 400 MHz) 7.36-7.12 (m, 7H), 6.75-6.70 (m, 2H), 4.87 (br s,

3H), 3.71 (d, J = 13 Hz, 1H), 3.67 (q, J = 6 Hz, 1H), 3.46 (d, J = 13 Hz, 1H), 1.45 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz) 147.7 (C), 140.5 (C), 134.2 (C), 130.3 (CH), 129.8 (CH), 128.9 (CH), 127.7 (CH), 116.7 (CH), 68.7 (CH), 62.5 (CH_2), 21.1 (CH_3); IR (film): 3383, 3332, 3242, 2984, 2839, 1509, 1262, 992, 734, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{18}N_2O$ $[M]^+$: 242.1419. Found: 242.1403.

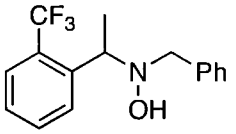


***N*-Benzyl-*N*-hydroxy-2-(perfluorophenyl)ethanamine, 15i (Table 3.9, entry 9).** Synthesized according to the general procedure (140°C, 18 hrs). Isolated 0.17 g (66%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.35 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.41-7.22 (m, 5H), 6.11 (br s, 1H), 3.81 (s, 2H), 3.00 (dd, J = 10, 4 Hz, 1H), 2.89 (dd, J = 10 Hz, 4 Hz, 1H); ^{13}C NMR (100 MHz) 136.7 (C), 129.5 (CH), 128.3 (CH), 127.5 (CH), 64.7 (CH_2), 57.8 (CH_2), 20.3 (CH_2); IR (film): 3297, 2882, 2843, 1505, 1495, 1456, 1309, 963, 734 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{12}F_5NO$ $[M]^+$: 317.0839. Found: 317.0826.

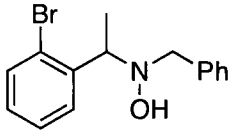


***N*-Benzyl-*N*-hydroxy-2-(2-(trifluoromethyl)phenyl)ethanamine, 15j (Table 3.9, entry 10).** Synthesized according to the general procedure (140°C, 18 hrs). Isolated 0.103 g (43%) as a white powder after column chromatography (10% EtOAc). TLC R_f 0.35 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.60 (d, J = 8 Hz, 1H), 7.44 (t, J = 7, 7 Hz, 1H), 7.35-7.20 (m, 7H), 6.68 (br s, 1H), 3.79 (s, 2H), 3.10 (dd, J = 9, 6 Hz, 2H), 3.10 (dd, J = 9, 6 Hz, 2H), 2.93 (dd, J =

9, 6 Hz, 2H); ^{13}C NMR (100 MHz) 138.6 (q, J = 2 Hz) (C), 136.9 (C), 131.7 (CH), 131.5 (CH), 129.7 (CH), 128.8 (q, J = 30 Hz) (C), 128.3 (CH), 127.5 (CH), 126.1 (CH), 125.9 (q, J = 6 Hz) (CH), 64.9 (CH_2), 60.8 (CH_2), 30.2 (CH_2); IR (film): 3329, 3067, 3035, 2983, 2943, 1608, 1583, 1495, 1457, 1318, 1162, 1122, 1036, 770 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{16}F_3NO$ $[M]^+$: 295.1184. Found: 295.1168.

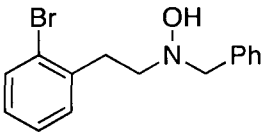


***N*-Benzyl-*N*-hydroxy-1-(2-(trifluoromethyl)phenyl)ethanamine, 14j (Table 3.9, entry 10).** Synthesized according to the general procedure (140°C, 18 hrs). Isolated 0.038 g (16%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.35 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.65 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.6, 7.6 Hz, 1H), 7.39-7.23 (m, 7H), 4.67 (br s, 1H), 4.33 (dq, J = 6, 6, 6, 1.5 Hz, 1H), 3.71 (d, J = 13 Hz, 1H), 3.66 (d, J = 13 Hz, 1H), 1.50 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz) 143.4 (C), 138.6 (C), 132.2 (CH), 129.1 (CH), 128.6 (C), 128.2 (CH), 127.7 (q, J = 30 Hz) (C), 127.1 (CH), 127.0 (CH), 125.6 (q, J = 6 Hz) (CH), 62.7 (CH), 61.8 (CH_2), 21.7 (CH_3); IR (film): 3241, 2846, 2881, 1608, 1583, 1318, 1060, 911, 768, 699, 654 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{16}F_3NO$ $[M]^+$: 295.1184. Found: 295.1194.

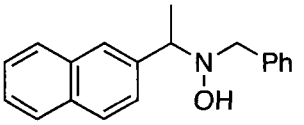


***N*-Benzyl-*N*-(1-(2-bromophenyl)ethyl)hydroxylamine, 14k (Table 3.9, entry 11).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.092 g (37%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.60 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.63 (dd, J = 8, 2 Hz, 1H), 7.55 (dd, J = 8, 1 Hz, 1H), 7.35-7.21 (m,

6H), 7.10 (ddd, J = 8, 8, 2 Hz, 1H), 5.03 (br s, 1H), 4.43 (q, J = 7, 7, 7 Hz, 1H), 3.77 (d, J = 13 Hz, 1H), 3.71 (d, J = 13Hz, 1H), 1.44 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz) 142.4 (C), 138.1 (C), 132.9 (CH), 129.4 (CH), 129.0 (CH), 128.5 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 124.0 (C), 65.1 (CH), 61.4 (CH_2), 19.1 (CH_3); IR (film): 3258, 3066, 3034, 1470, 1437, 1022, 754 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{16}BrNO$ $[M]^+$: 305.0415. Found: 305.0400.

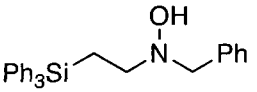


***N*-Benzyl-*N*-(2-bromophenethyl)hydroxylamine, 15k (Table 3.9, entry 11).** Synthesized according to the general procedure (140°C, 16 hrs). Isolated 0.10 g (42%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.49 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.55-7.48 (m, 1H), 7.43-7.16 (m, 7H), 7.05 (ddd, J = 8, 6, 3 Hz, 1H), 3.82 (s, 2H), 3.05 (dd, J = 10, 6 Hz, 2H), 2.94 (dd, J = 10, 6 Hz, 2H); ^{13}C NMR (100 MHz) 139.3 (C), 136.9 (C), 132.8 (CH), 130.8 (CH), 129.7 (CH), 128.3 (CH), 127.8 (CH_2), 127.5 (CH), 127.4 (CH), 124.7 (C), 64.9 (CH_2), 59.1 (CH_2), 33.8 (CH_2); IR (film): 3235, 3070, 3034, 2842, 1471, 1454, 1021, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{16}BrNO$ $[M]^+$: 305.0415. Found: 305.0441.

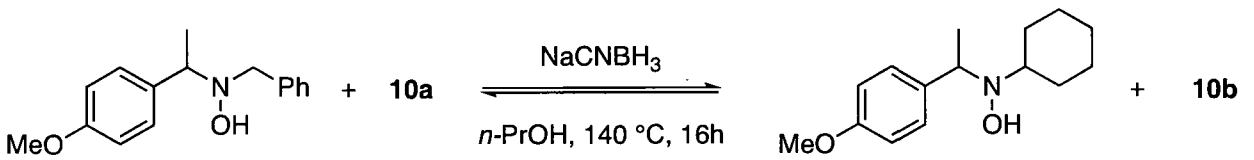


***N*-Benzyl-*N*-hydroxy-1-(naphthalen-2-yl)ethanamine, 14l (Table 3.9, entry 12).** Synthesized according to the general procedure (140°C, 18 hrs). Isolated 0.081 g (36%) as a white powder after column chromatography (10% EtOAc/hexanes). TLC R_f 0.24 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.88-7.79 (m, 4H), 7.64-7.21 (m, 8H), 5.56 (br s, 1H), 4.00 (q, J = 7, 7, 7 Hz, 1H), 3.78 (d, J = 13 Hz, 1H), 3.66 (d, J = 13 Hz, 1H), 1.57 (d, J = 7 Hz, 3H); ^{13}C NMR

(100 MHz) 140.4 (C), 138.1 (C), 133.4 (C), 132.9 (C), 129.5 (CH), 128.2 (2C) (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 126.6 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 67.2 (CH_2), 61.3 (CH_3), 19.8 (CH_2); IR (film): 3532, 3251, 2933, 2246, 1950, 1807, 1601, 1453, 1375, 1297, 1271, 909, 858, 820 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{19}NO$ $[M]^+$: 277.1467. Found: 277.1497.

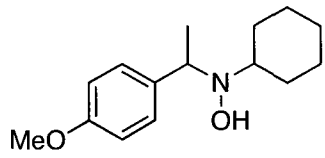


***N*-Benzyl-*N*-hydroxy-2-(triphenylsilyl)ethanamine, 15m (Table 3.9, entry 13).** Synthesized according to the general procedure (140°C, 11 hrs). Isolated 0.291 g (71%) as a white gum after column chromatography (10% EtOAc/hexanes). TLC R_f 0.48 (20% EtOAc/hexanes); ^1H NMR (C_6D_6, 300 MHz) 7.74-7.65 (m, 6H), 7.35-7.11 (m, 14H), 3.68 (s, 2H), 3.11 (t, J = 8, 8 Hz, 2H), 2.00 (br t, J = 8, 8 Hz, 2H); ^{13}C NMR (75 MHz) 138.3 (C), 136.2 (CH), 135.5 (C), 130.2 (CH), 129.9 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 64.5 (CH_2), 55.9 (CH_2), 12.0 (CH_2); IR (film): 3535, 1959, 1888, 1588, 1456, 788 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{27}H_{27}NOSi$ $[M]^+$: 409.1862. Not found. Exact mass calcd for $C_{27}H_{26}NSi$ $[M\text{-}OH]^+$: 392.1835. Found: 392.1735.



Reversibility experiments (Equation 3.8). A 3 mL tapered bottom screwcap vial was charged with hydroamination product **14g** (0.19 mmol, 0.050 g), *N*-cyclohexylhydroxylamine (0.19 mmol, 0.022 g) sodium cyanoborohydride (0.19 mmol, 0.012 g) and *n*-PrOH (0.3 mL). 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

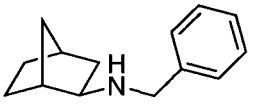
heated while stirring in an oil bath at 140°C for 16 hrs. The vial was cooled to ambient temperature and concentrated under reduced pressure. The mixture was taken up in $CDCl_3$ and transferred to an NMR tube. A small amount of crossover product **16** was detected in the crude reaction mixture by TLC analysis (20% EtOAc/hexanes) and ^{1}H NMR spectroscopy according to its characteristic triplet of triplets resonance at 2.53 ppm upon comparison with an independently synthesized sample (see below).



***N*-Cyclohexyl-*N*-(1-(4-methoxyphenyl)ethyl)hydroxylamine, 16 (Equation 3.8).** The compound was prepared independently for comparison with the product observed in Equation 6. A 15 mL sealed tube was charged with a stir bar, *N*-cyclohexylhydroxylamine (0.81 mmol, 0.094 g), *n*-propanol (1.4 mL), sodium cyanoborohydride (0.81 mmol, 0.051 g) and 4-vinylanisole (1.6 mmol, 0.22 g). The tube was capped with a septum and purged with argon and an outlet for 5 minutes while stirring. The septum was removed and the tube was then quickly sealed with a Teflon screw cap and heated while stirring in an oil bath at 140°C for 18 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography (20% EtOAc/hexanes) to give the corresponding *N*,*N*-dialkyhydroxylamine. Isolated 0.082 g (40%) as a clear colourless oil after column chromatography (20% EtOAc/hexanes). TLC R_f 0.34 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.29 (d, J = 9 Hz, 2H), 6.88 (d, J = 9 Hz, 2H), 4.56 (br s, 1H), 4.07 (q, J = 7, 7, 7 Hz, 1H), 3.82 (s, 1H), 2.53 (tt, J = 11, 11, 3, 3 Hz, 1H), 2.00-1.45 (m, 7H), 1.41 (d, J = 7 Hz, 3H), 1.25-1.05 (m, 3H); ^{13}C NMR (75 MHz) 158.5 (C), 135.4 (C), 128.8 (CH), 113.6 (CH), 60.9 (CH), 60.8 (CH), 55.1 (CH), 26.1 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 19.5 (CH_3); IR (film): 3237, 2836, 1612, 1513, 1248, 1034,

834 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{23}NO_2$ $[M]^+$: 249.1729. Found: 249.1732.

***exo*-Bicyclo[2.2.1]heptan-2-amine, 17 (Scheme 3.2).** Prepared by the method of ElAmin and coworkers.[76] *N*-Benzyl-*N*-*exo*-hydroxybicyclo[2.2.1]heptan-2-amine (**11b**) (0.050 g, 0.23 mmol) was dissolved in 2 ml of 4.4% formic acid/methanol and added to a 25 ml round bottom flask containing palladium on carbon and 10 ml of 4.4% formic acid/methanol. The mixture was stirred under an argon atmosphere for 45 min at ambient temperature, until the reaction was deemed complete by TLC analysis (20% EtOAc/hexanes). The reaction mixture was then poured through a pad of celite, which was washed with methanol. The filtrate and washings were then concentrated under reduced pressure. The residual oil was taken up in EtOAc (20 ml), washed with a saturated solution of sodium bicarbonate, then with H_2O, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give the primary amine (0.023 g, 90%) as a clear, colourless oil whose ^1H NMR spectrum was found to be consistent with that reported in the literature.[77]



***N*-*exo*-Benzylbicyclo[2.2.1]heptan-2-amine, 18 (Scheme 3.2).** Prepared by the method of Cicchi and coworkers.[78] *N*-Benzyl-*N*-*exo*-hydroxybicyclo[2.2.1]heptan-2-amine (**11b**) (0.217 g, 1.00 mmol) is dissolved into a 2:1 solution of EtOH and saturated aqueous NH_4Cl (6 mL) in a 25-mL round-bottomed flask equipped with a Claisen condenser and a magnetic stirring bar.

(76) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442.

(77) Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *J. Org. Chem.* **1981**, *46*, 4296.

(78) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.

Indium powder (0.144 g, 1.25 mmol) is then added, and the mixture is heated under reflux for 5 hours until the reaction was deemed complete when no starting material remained by TLC analysis (20% EtOAc/hexanes). The mixture is cooled to ambient temperature and filtered through a pad of Celite. The Celite is washed with methanol. The washing are combined with the filtrate and concentrated under reduced pressure. A saturated Na_2CO_3 solution (15 mL) is added, and the product is extracted with ethyl acetate (3 ×15 mL). The organic phase is dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the titled amine (0.197 g, 98%). ^{1}H NMR confirmed that no further purification was necessary. ^{1}H NMR (C_6D_6, 400 MHz) 7.40-7.15 (m, 5H), 3.68 (d, J = 13 Hz, 1H), 3.64 (d, J = 13 Hz, 1H), 2.54 (dd, J = 7, 3 Hz, 1H), 2.18 (s, 1H), 2.10 (s, 1H), 1.69-1.63 (m, 1H), 1.50-1.39 (m, 3H), 1.16-0.96 (m, 4H), 0.82 (br s, 1H); ^{13}C NMR (100 MHz) 141.8 (C), 128.5 (CH), 128.4 (CH), 126.9 (CH), 61.8 (CH), 52.3 (CH_2), 41.3 (CH), 40.3 (CH_2), 36.1 (CH), 35.1 (CH_2), 29.2 (CH_2), 27.0 (CH_2); IR (film): 2950, 2868, 1495, 1454, 1124, 730, 698 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{19}N$ $[M]^+$: 201.1517. Found: 201.1517.

3.4.3. Reactions of Hydroxylamines with Allenes

Materials. Unless otherwise noted, all solvents and commercial materials were purchased from Sigma-Aldrich and used without further purification. Sodium cyanoborohydride and cyclohexylallene (**20a**) were purchased from Sigma-Aldrich and used without further purification. *N*-alkylhydroxylamines **10a-c**, **10e** and **10f** were prepared by reductive amination of the corresponding oximes according to the method of House and Lee.[79] Allenes **20c-d** were prepared according to previous literature procedure.[80] Allene **20e** was prepared according to a

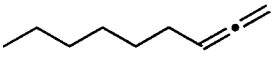
(79) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

(80) Yoshida, Y.; Matsuda, K.; Shoji, Y.; Gotou, T.; Ihara, M.; Shishido, K. *Org. Lett.* **2008**, *10*, 5183.

known method.[81]

Optimization of reaction of *N*-cyclohexylhydroxylamine with cyclohexylallene (Table 3.10). A 3 mL tapered bottom screwcap vial was charged with a stir bar, *N*-cyclohexylhydroxylamine (0.047 g, 0.41 mmol), solvent (either 0.4 mL (0.25 M), 0.8 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).

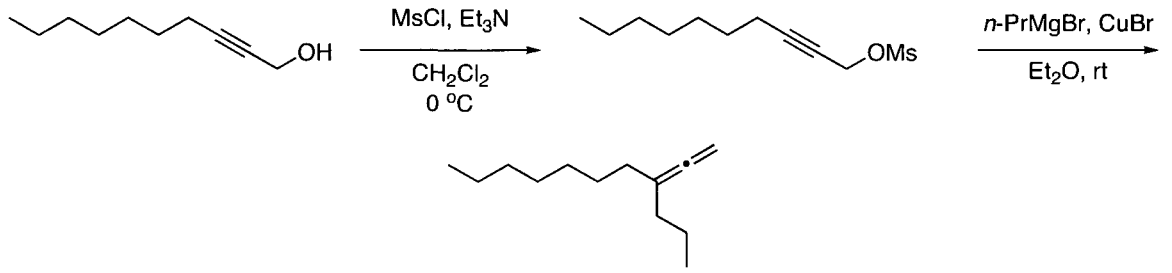
Preparation of allenes.



Nona-1,2-diene, 20b. Using literature procedure, nona-1,2-diene was prepared.[3] To a stirred solution of 1-octyne (3.0 g, 4.0 mL, 27.2 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, 54.4 mmol, 2.0 equiv) and copper bromide (1.9 g, 13.6 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

(81) Chen, T.R; Anderson, M.R.; Grossman, S.; Peters, D.G. *J. Org. Chem.* **1987**, *52*, 1232.

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 oil 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.[82]



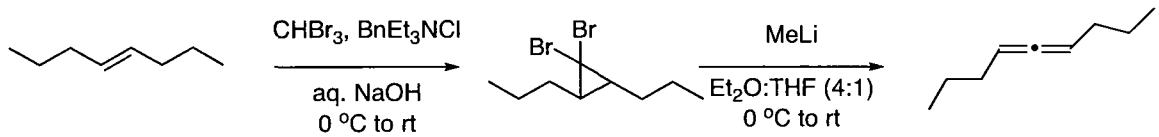
4-Vinylideneundecane, 20f. The allene was synthesized using a modified procedure.[83] To a solution of 2-decyn-1-ol (1.5 g, 1.8 mL, 9.9 mmol) in dichloromethane (0.1 M, 100 mL) at 0 °C were added triethylamine (1.9 g, 2.7 mL, 19.1 mmol, 1.9 equiv) and methanesulfonyl chloride (1.9 g, 1.3 mL, 16.9 mmol, 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, 0.1 equiv) and ether (1 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 (11.9 mmol, 2.3 M, 5.3 mL, 1.2 equiv) was added followed by a SLOW addition of dec-2-ynyl methanesulfonate in ether (1 M, 10 mL) via cannula. The reaction was stirred at room temperature for two hours after which it

(82) Endo, T.; Takagi, K.; Tomita, I. *Tetrahedron*, **1997**, *53*, 15194.

(83) Moreau, J-L.; Gaudemar, M. J. *Organometallic Chem.* **1976**, *108*, 159.

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, 29.5% 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, 20g. The allene was synthesized using a modified procedure.[84] Trans-4-octene (5.0 g, 7.0 mL, 44.5 mmol), benzyl-triethylammonium chloride (1.0 g, 4.5 mmol, 0.1 equiv) and bromoform (28.0 g, 9.7 mL, 111.4 mmol, 2.5 equiv.) were added to a 100 mL flask. The reaction was cooled to 0 °C and a 25 M NaOH solution (2.5 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.

The crude was purified by flash chromatography (Hexanes) followed by fractional distillation to give a clear oil (6.4 g, 50% 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

(84) Iwasawa, Takaya, *J. Am. Chem. Soc.* **2008**, *130*, 15254.

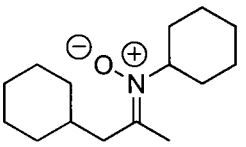
NMR (75 MHz, $CDCl_3$) 39.4 (C), 36.8 (CH), 34.6 (CH_2), 21.5 (CH_2), 13.8 (CH_3); IR (film): 2960, 2930, 2873, 2360, 1459, 1018, 744 cm^{-1}.

To a stirred solution of 1,1-dibromo-2,3-dipropylcyclopropane (6.4 g, 22.5 mmol) in 4:1 ether:THF (0.2 M, 100 mL) at 0 °C was added methyl lithium (1.3 M, 37 mL, 46.4 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, 78.5% yield). TLC R_f 0.71 (Hexanes); The NMR corresponded with characterization previously reported.[85]

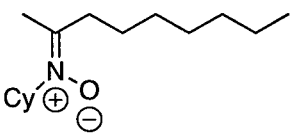
Reaction of *N*-cyclohexylhydroxylamine with allenes (Table 3.11).

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 (0.47g, 0.41 mmol, 1.0 equiv), *t*-butanol (0.80 mL, 1 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 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 ^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.

(85) Crandall, J.K.; Batal, D.J.; Sebesta, D.P.; Lin, F. *J. Org. Chem.* **1991,** *56,* 1153.



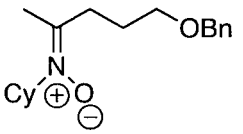
***N*-(1-Cyclohexylpropan-2-ylidene)cyclohexanamine oxide, 21aa (Table 3.11, entry 1 and Table 3.12, entry 1).** Synthesized from *N*cyclohexylhydroxylamine[86] according to the general procedure, but using 0.093 g, 0.81 mmol **10a** (all reagents and solvents scaled up accordingly). Isolated 0.18 g (91%) of a 1.6:1 mixture of isomers as a clear colourless 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, 11.4, 3.8, 3.8 Hz, 1H) (major), 3.98 (tt, *J* = 11.4, 11.4, 3.8, 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.



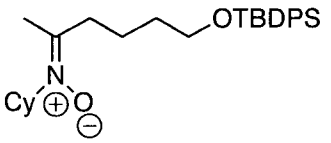
***N*-(Nonan-2-ylidene)cyclohexanamine oxide, 21ab (Table 3.11, entry 2).** Synthesized according to general procedure using 0.10 g (0.81 mmol) of the corresponding allene. Isolated 0.79 g (82% yield) as a yellow oil after column chromatography (0-5% MeOH/CH_2Cl_2). TLC R_f: 0.11, 0.14 (4% MeOH/CH_2Cl_2); ^{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

(86) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

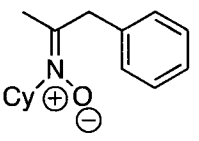
Hz, 2H), 1.66 (d, J = 8.7 Hz, 1H), 1.56-1.43 (m, 2H), 1.41-1.18 (m, 11H), 0.89 (t, J = 6.7 Hz, 3H); ^{13} C NMR (75 MHz, $CDCl_3$) 146.0 (C), 65.1 (CH), 33.4 (CH_2), 31.6 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 27.2 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 22.5 (CH_2), 18.7 (CH_3), 14.0 (CH_3); IR (film) : 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, 21ac (Table 3.11, 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, 21ad (Table 3.11, 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% $MeOH/CH_2Cl_2$); ^1H 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%).



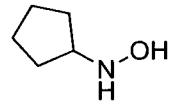
***N*-(1-Phenylpropan-2-ylidene)cyclohexanamine oxide, 21ae (Table 3.11, entry 5).** Synthesized according to the general procedure using 0.94 g (0.81 mmol) of the corresponding allene. Isolated 0.38 g (40% yield) as a 4.63:1 ratio of isomers as a light yellow oil after column chromatography (0-4% $MeOH/CH_2Cl_2$). TLC R_f: 0.13, 0.15 (4% $MeOH/CH_2Cl_2$); ^1H 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.

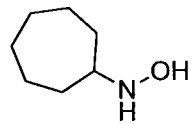
Preparation of *N*-alkylhydroxylamines. *N*-Alkylhydroxylamines **10g** and **10h** were prepared by reductive amination of the corresponding oximes according to a modification of the method of House and Lee.[87] To a round-bottomed flask equipped with a magnetic stirring bar was added oxime (1.0 equiv), 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

(87) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

after column chromatography (80% EtOAc/hexanes).



***N*-Cyclopentylhydroxylamine, 10g.** 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.

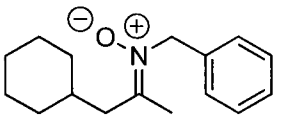


***N*-Cycloheptylhydroxylamine, 10h.** Performed on 39.5 mmol of cycloheptanone oxime. Isolated 3.29 g (65% yield) as a white solid after column chromatography (80% EtOAc/hexanes). TLC R_f 0.29 (100% EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 6.36 (br s, 2H), 2.98 (tt, J = 8 Hz, 4 Hz, 1H), 1.94-1.78 (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.

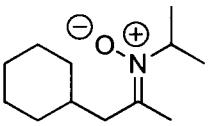
Reaction of *N*-alkylhydroxylamines with cyclohexylallene (Table 3.12).

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.



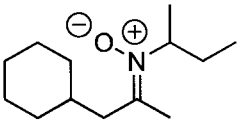
***N*-(1-Cyclohexylpropan-2-ylidene)-1-phenylmethanamine oxide, 21ba (Table 3.12, entry 2).** Synthesized from *N*-benzylhydroxylamine[88] according to the general procedure. Isolated 0.16 g (81%) of a 1.9:1 mixture of isomers as a clear colourless oil after column chromatography (4% MeOH/CH_2Cl_2). 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 (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, 21ca (Table 3.12, entry 3).**

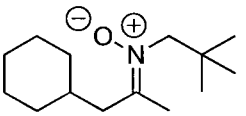
(88) Maskill, H.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 2062.

Synthesized from **10c** according to the general procedure. Isolated 0.10 g (63%) of a 1.5:1 mixture of isomers as a clear colourless oil after column chromatography (5% MeOH/CH_2Cl_2). TLC R_f 0.34 and 0.37 (10% MeOH/CH_2Cl_2); ^{1}H 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.

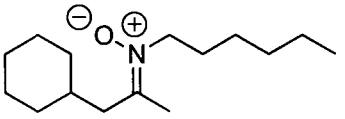


***N*-(1-Cyclohexylpropan-2-ylidene)butan-2-amine oxide, 21da (Table 3.12, entry 4).** Synthesized from *N-sec*-butylhydroxylamine according to the general procedure, but on a 0.41 mmol scale (all reagents and solvents scaled down accordingly). Isolated 0.042 g (49%) of a 1.2:1 mixture of isomers as a clear colourless oil after column chromatography (5% MeOH/ CH_2Cl_2). TLC R_f 0.32 and 0.39 (5% MeOH/ CH_2Cl_2); ^{1}H 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.



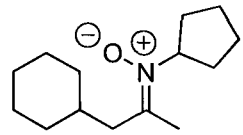
***N*-(1-Cyclohexylpropan-2-ylidene)-2,2-dimethylpropan-1-amine oxide, 21ea (Table 3.12, entry 5).** Synthesized from *N*-neopentylhydroxylamine[89] according to the general procedure, but on a 0.41 mmol scale (all reagents and solvents scaled down accordingly). Isolated 0.043 g (47%) of a 1.1:1 mixture of isomers as a clear colourless 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), 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.



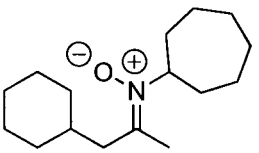
***N*-(1-Cyclohexylpropan-2-ylidene)hexan-1-amine oxide, 21fa (Table 3.12, entry 6).** Synthesized from *N*-hexylhydroxylamine[90] according to the general procedure. Isolated 0.099 g (51%) of a 1.2:1 mixture of isomers as a clear colourless oil after column chromatography (5%

(89) Heydari, A.; Tavakol, H.; Aslanzadeh, S.; Azarnia, J.; Ahmadi, N. *Synthesis* **2005**, 627.
(90) Shiino, M.; Watanabe, Y.; Umezawa, K. *Biiorg. Med. Chem.* **2001**, *9*, 1233.

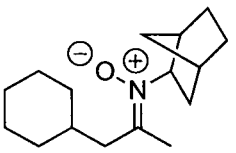
MeOH/CH_2Cl_2). TLC R_f 0.47 (7% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) 3.81 (t, J = 7.2 Hz, 2H) (minor), 3.78 (t, J = 7.2 Hz, 2H) (major), 2.43 (d, J = 7.2 Hz, 1H), 2.24 (d, J = 7.2 Hz, 1H), 2.06 (d, J = 13.3 Hz, 3H), 1.96-0.70 (m, 22H); ^{13}C NMR (75 MHz) 146.9 (C), 145.7 (C), 59.3 (CH_2), 58.5 (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, 21ga (Table 3.12, entry 7).** Synthesized from *N*-cyclopentylhydroxylamine (**20g**) according to the general procedure. Isolated 0.11 g (58%) as a clear colourless 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.



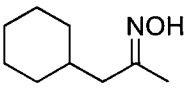
***N*-(1-Cyclohexylpropan-2-ylidene)cycloheptanamine oxide, 21ha (Table 3.12, entry 8).** Synthesized according to the general procedure. Isolated 0.15 g (71%) as a clear colourless oil after column chromatography (5% $MeOH/CH_2Cl_2$). TLC R_f 0.38 (7% $MeOH/CH_2Cl_2$); ^1H NMR ($CDCl_3$, 300 MHz) 4.29 (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.



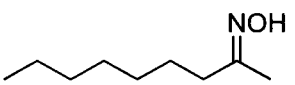
(*Z*)-*exo*-*N*-(1-Cyclohexylpropan-2-ylidene)bicyclo[2.2.1]heptan-2-amine oxide, 21ia (Table 3.12, entry 9). Synthesized from **20i** according to the general procedure. Isolated 0.077 g (38%) as a clear colourless oil after column chromatography (4% $MeOH/CH_2Cl_2$). TLC R_f 0.34 (7% $MeOH/CH_2Cl_2$); ^1H 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 3.13).

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 equiv), HPLC grade *i*-PrOH (0.65 mL μL, 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.

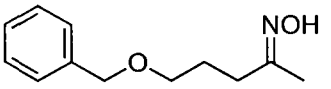


1-Cyclohexylpropan-2-one oxime, 22a (Table 3.13, entry 1). Synthesized according to the general procedure. Isolated 0.19 g (75%) as a clear colourless oil after column chromatography as a 2.8:1 mixture of isomers (10% EtOAc/hexanes → 20% EtOAc/hexanes). TLC R_f 0.50 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 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.

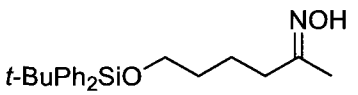


Nonan-2-one oxime, 22b (Table 3.13, entry 2). Synthesized according to the general procedure. Isolated 0.24 g (93%) of a clear colourless oil after column chromatography as a 3:1 mixture of

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.

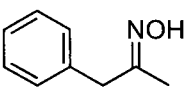


5-(Benzyloxy)pentan-2-one oxime, 22c (Table 3.13, entry 3). Synthesized according to the general procedure. Isolated 0.33 g (99%) as a clear colourless oil after column chromatography (15% EtOAc/hexanes). TLC R_f 0.31 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.37-7.26 (m, 5H), 4.51 (s, 2H) (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.

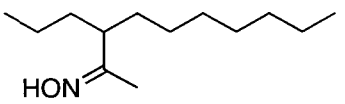


6-(*tert*-Butyldiphenylsilyloxy)hexan-2-one oxime, 22d (Table 3.13, entry 4). Synthesized according to the general procedure using 0.54 g (1.6 mmol) of the corresponding allene. Isolated

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.



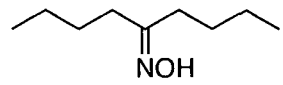
1-Phenylpropan-2-one oxime, 22e (Table 3.13, entry 5). Synthesized from phenylallene according to the general procedure. Isolated 0.17g (71%) as a clear colourless oil after column chromatography (15% EtOAc/hexanes). TLC R_f 0.33 (20% EtOAc/hexanes. Spectral data was found to be in good agreement with the literature.[91]



3-Propyldecan-2-one oxime, 22f (Table 3.13, entry 6). 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,

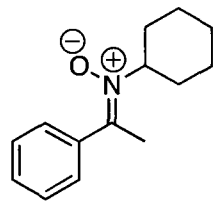
(91) Hwu, J. R.; Tseng, W. N.; Patel, H. V.; Wong, F. F.; Horng, D.; Liaw, B. R.; Lin, L. C. *J. Org. Chem.* **1999**, *64*, 2211.

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): 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, 22g (Table 3.13, entry 7). 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); ^{1}H 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.

3.4.4. Reactions of *N*-Alkylhydroxylamines with Alkynes



(*E*)-*N*-(1-Phenylethylidene)cyclohexanamine-*N*-oxide, 19 (Equation 3.8). A 3 mL screwcap vial was charged with a stir bar, *N*-cyclohexylhydroxylamine (0.050 g, 0.43 mmol), *n*-propanol

(0.5 mL) and phenylacetylene (0.22 g, 2.1 mmol). The vial was capped with a septum and purged with argon and an outlet for 2 minutes while stirring. The septum was removed and the vial was then quickly sealed with a screw cap whose joints were sealed with Teflon tape and heated while stirring in an oil bath at 110°C for 14 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography (2% $MeOH/CH_2Cl_2$) to give the titled compound (0.049 g, 52%) as a clear, colourless oil. TLC R_f 0.33 (5% $MeOH/CH_2Cl_2$); ^1H NMR (C_6D_6, 300 MHz) 7.05-6.87 (m, 5H), 4.11 (tt, J = 11.4, 11.4, 3.7, 3.7 Hz, 1H), 2.39 (s, 3H), 1.75 (ap d, J = 12.1 Hz, 2H), 1.53-1.15 (m, 4H), 1.08-0.66 (m, 4H); ^{13}C NMR (C_6D_6, 75 MHz) 137.7 (C), 129.0 (C), 128.5 (CH), 127.9 (CH), 127.7 (CH), 67.2 (CH), 30.8 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 20.8 (CH_3); IR (film): 3418, 2932, 2855, 1680, 1556, 1210 cm^{-1}; HRMS (EI): exact mass calcd for $C_{14}H_{19}NO$ $[M]^+$: 217.1467. Found: 217.1460.

Chapter 4. Future Directions in Cope-Type Hydroamination

4.1. Introduction

The development of the basic Cope-type hydroamination reactivity described in Chapter 3 opens up several new avenues to solve important problems in the field. This chapter describes early efforts to develop a tandem sequence for irreversible hydroamination as well an approach towards intermolecular organocatalytic hydroamination reactions. The lead results presented herein continue to be explored by other students in the Beauchemin research group.

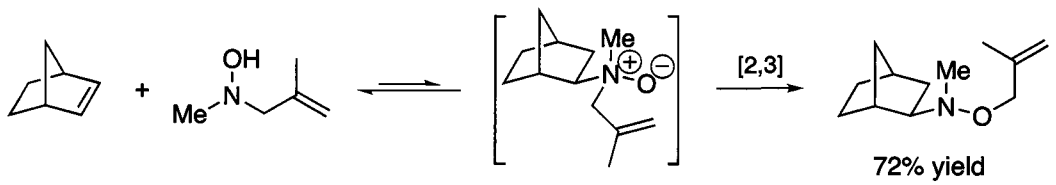
4.2. The Tandem Hydroamination/Cope-Elimination Sequence

As we have seen throughout this thesis, the hydroamination reaction of alkenes is nearly thermoneutral, and small changes in substrate structure can render a transformation thermodynamically unfavourable. Catalysis changes only the kinetics of a reaction, and on its own cannot be a general solution to hydroamination. In order to achieve high efficiency, endergonic reactions must be coupled to a secondary exogonic photochemical or chemical process. Chapter 2 described an irreversible photochemical method to bias difficult hydroamination reactions towards products, but the narrow scope of the transformation limits its usefulness as a general solution. The Cope-type hydroamination developed in Chapter 3 is not limited by photochemical processes or fundamental alkene constraints, but does not provide a secondary thermodynamic driving force to push difficult reactions. We therefore set out to develop tandem sequences where a Cope-type hydroamination is followed by a thermodynamically more favourable reaction.

4.2.1. Precedent: The Tandem Hydroamination/[2,3]-Rearrangement Sequence

The first intermolecular approach, developed in the Beauchemin group by Mr. Joffré Bourgeois and further optimized by Mr. Francis Loiseau, was a Cope-type hydroamination/[2,3]-

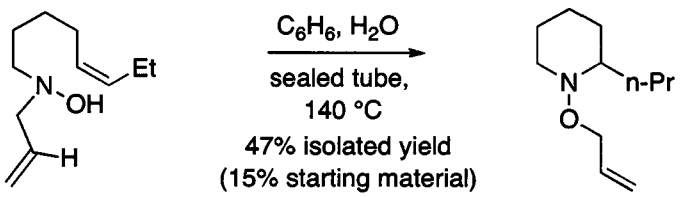
Meisenheimer rearrangement sequence aimed at biasing the thermodynamics primarily via a change in *enthalpy* (Equation 4.1).[1]



(4.1)

Little thermodynamic data exists concerning the [2,3]-Meisenheimer rearrangement, but reactions conducted at temperatures similar to that required for the Cope-type hydroamination (95-140 °C) qualitatively indicate that the reaction is favourable. A very crude estimate of the free energy change for the Meisenheimer rearrangement of about -12.5 kcal/mol can be made using bond dissociation energies and assuming no change in entropy.[2]

Coniine - Key Step



Norreticuline - Key Step

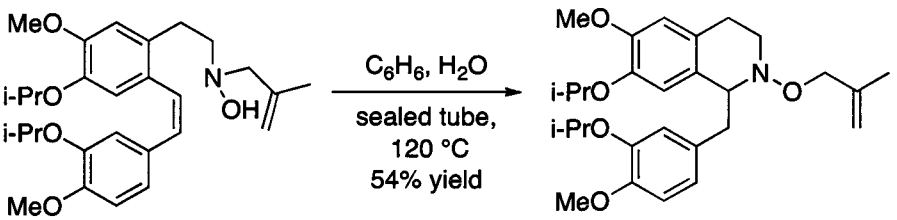


Figure 4.1. Tandem hydroamination/[2,3]-Meisenheimer rearrangement as the key steps in total syntheses of Coniine and Norreticuline.

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

(2) $BDE_{C\text{-}N} - BDE_{O\text{-}C} = 79$ kcal/mol – 91.5 kcal/mol = –12.5 kcal/mol .

Although the tandem sequence possessed similar alkene scope and lower reaction yields in intermolecular reaction sequences compared to the original Cope-type hydroamination methodology presented in Chapter 3, it did provide significantly increased yields in intramolecular reverse-Cope cyclizations, as illustrated by syntheses of two alkaloids, coniine (Ms. Isabelle Dion) and norreticuline (Ms. Pamela Cebrowski) featuring difficult hydroamination key steps (Figure 4.1).[1]

4.2.2. Results and Discussion

Hypothesizing that a tandem sequence that would offset the *entropic* losses of the hydroamination step might be more beneficial for intermolecular reactions, we proposed a tandem hydroamination/Cope-elimination sequence that would release a molecule of a stable alkene in a kinetically irreversible manner.[3] We reasoned that Cope-type hydroamination of the two reaction partners would give an amine *N*-oxide, which could then undergo a Cope-elimination reaction to irreversibly generate ethylene gas (Figure 4.2). We chose the reaction of norbornene with commercially available *N,N*-diethylhydroxylamine (**1**) as a biased model system.

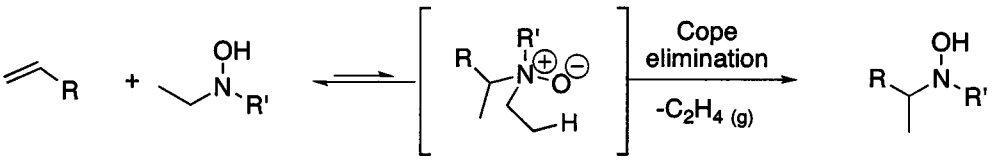
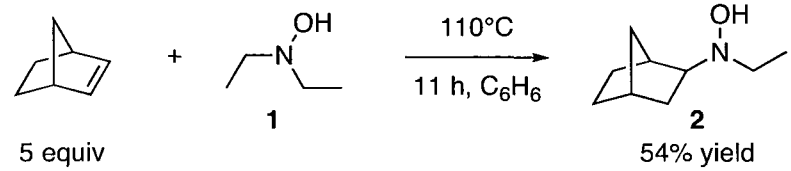


Figure 4.2. Mechanistic rationale for tandem hydroamination/Cope-elimination sequence.

Gratifyingly, 54% isolated yield of *N*-ethyl-*N*-norbornylhydroxylamine (**2**) was obtained upon heating norbornene and **1** in a sealed tube in benzene at 110 °C for 11 h (Equation 4.2).

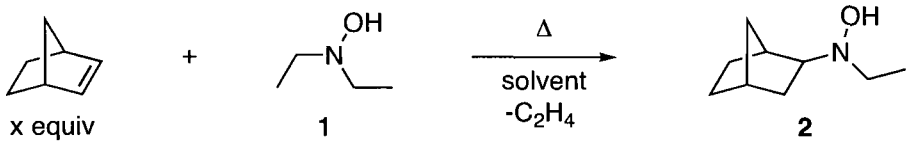
(3) For more on the Cope-elimination, see Section 3.1.1, pg. 108.

Pressure was released upon opening the cooled tube, indicating that ethylene had also been formed during the reaction.



5 equiv 1 2 54% yield (4.2)

Table 4.1. Optimization of tandem hydroamination/Cope-elimination sequence with norbornene.



x equiv 1 2

entry	solvent	x	temp. (°C)	time (h)	additive	yield **2** (%)[b]
1	$CDCl_3$	5	100	42	-	27
2	$PhCF_3$	5	100	42	-	49
3	THF	5	100	42	-	54
4	C_6H_6	5	130	16	-	61
5	"	5	110	11	-	54
6	"	5	100	24	-	62
7	"	5	90	42	-	50
8	"	2.5	100	42	-	55
9	*n*-PrOH	5	125	16	$NaCNBH_3$	66

[a] Conditions: 1 equiv **1** (1M), x equiv norbornene, solvent, sealed tube. [b] Isolated yield after column chromatography.

The reaction was found to occur in a variety of aprotic and protic solvents (Table 4.1).[4] Employing similar conditions to those used in the reactions of *N*-alkylhydroxylamines with sodium cyanoborohydride as additive led to the best results, giving **2** in 66% isolated yield (entry 9). Comparable efficiency was observed with the tandem hydroamination/[2,3]-Meisenheimer sequence for the same substrate. The increased steric bulk surrounding the nitrogen atom of the

(4) Ms. Emily Manthorp (summer student) is thanked for her optimization work that led to Table 4.1.

product compared to the starting material attenuates its reactivity, and no bis-hydroamination product was detected in all cases.

While this new tandem sequence appears to possess similar scope to its predecessor and does not require an inefficient preparation of the amine starting materials,[1] more work is required to ascertain its potential use in difficult hydroamination reactions. Both sequences face the problem of decreased kinetic reactivity of *N*,*N*-dialkylhydroxylamines compared to *N*-alkylhydroxylamines or hydroxylamine itself. Further investigation of several *N*-ethyl-*N*-alkylhydroxylamines is required to determine if this is truly a synthetically useful strategy. Conversely, investigation of several electronically and sterically varied alkene "leaving groups" might also lead to an overall reaction that is favourable with respect to *entropy* and *enthalpy*.

4.3. Progress Towards Directed Organocatalytic Hydroamination

Intramolecular reactions are often more rapid and possess better regio- and stereoselectivity than their intermolecular counterparts. In intermolecular reactions, nonbonding interactions and stereoelectronic effects typically control this selectivity. However, preassociation of the reacting partners either via hydrogen-bonding, covalent bonds or Lewis acid-base interactions can allow an intermolecular reaction to proceed via a pseudo-intramolecular pathway with dramatic rate acceleration and can even direct a reaction to a contrasteric outcome.[5] Several metal-based catalytic directed reactions have been developed (usually for oxygen-based directing groups), but despite intense research into organocatalytic

(5) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

reactions over the past decade,[6] metal-free catalytic directed reactions have not been described. A recent survey by MacMillan found that all 1500 reports on organocatalysis since 1996 can be classified into only 5 generic activation modes: enamine catalysis, hydrogen-bonding catalysis, iminium catalysis, SOMO catalysis, and counterion catalysis (Figure 4.3).[7] These activation modes all require the substrate to contain a functional group or to produce an intermediate that is related to a carbonyl (aldehydes, enamines, oxocarbenium ions etc.), but the extension of the organocatalytic approach to unrelated functional groups has yet to be achieved. The design of a *directed* activation mode that takes advantage of kinetically facile intramolecular processes could lead to dramatic rate acceleration regardless of the nature of the reactive functional group.

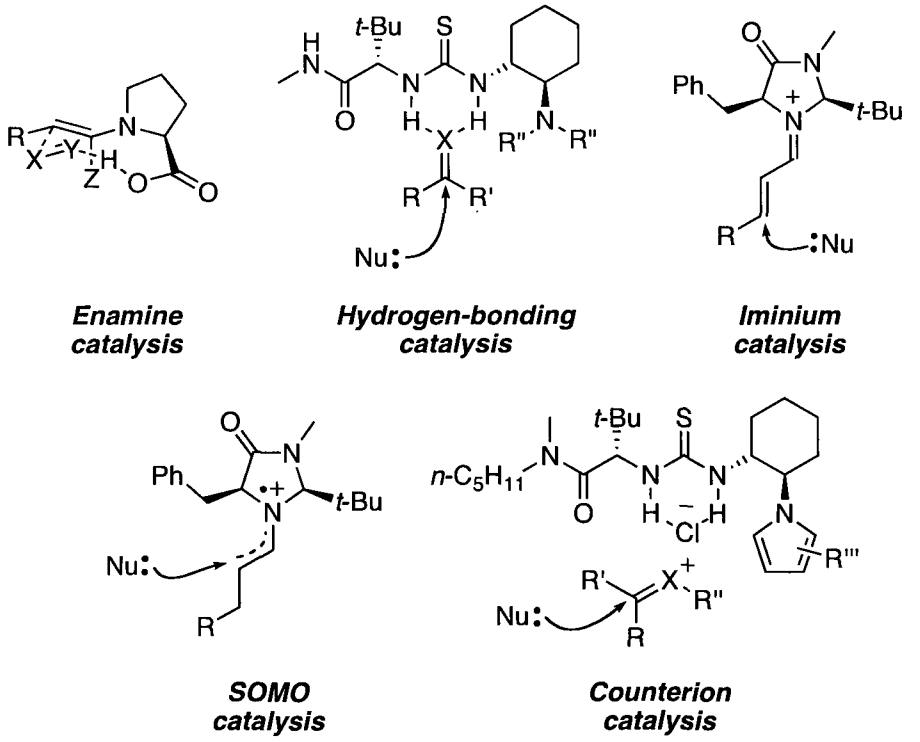


Figure 4.3. Existing generic activation modes in organocatalysis.

(6) (a) Dalko, P. I., ed., Enantioselective Organocatalysis: Reactions and Experimental Procedures (Wiley-VCH, Weinheim, Germany, 2007). (b) Berkessel, A.; Gröger, Eds., Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis (Wiley-VCH, Weinheim, Germany, 2005).

(7) MacMillan, D. W. C. *Nature* **2008**, *455*, 304 and references cited therein.

We therefore envisioned an organocatlytic *tether* activation mode, where preassociation of two substrates to a chiral catalyst results in a diastereoselective intramolecular reaction, followed by catalyst dissociation and regeneration of the active catalytic species (Figure 4.4). Herein, we describe the application of this concept towards the development of a directed organocatalytic intermolecular hydroamination of alkenes.

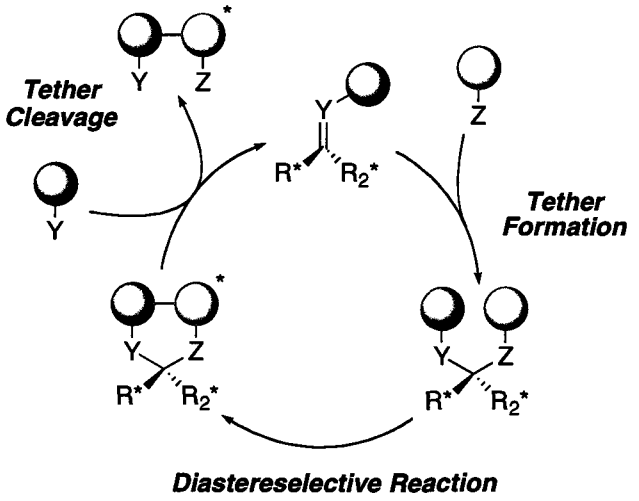
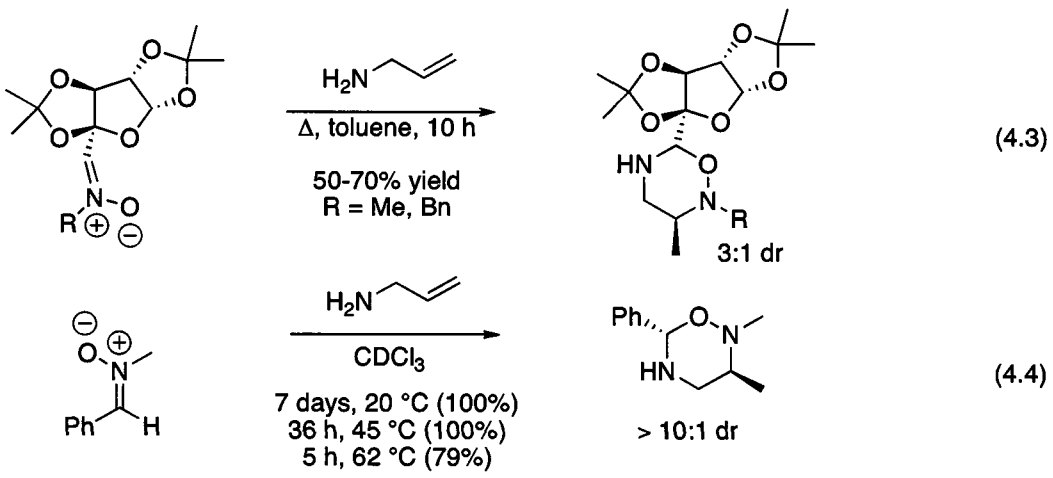


Figure 4.4. Organocatalytic Tether Catalysis.



Inspired by the work of Knight and coworkers (Equation 4.3 and Equation 4.4), who determined that the unexpected products of an attempted [3+2]-dipolar cycloaddition actually arose via a pathway involving a diastereoselective tandem addition/intramolecular

hydroamination/[1,2]-Meisenheimer sequence (Figure 4.5), we wondered if such a stoichiometric temporary chiral tether approach could be made *catalytic* with respect to the nitrone.[8,9]

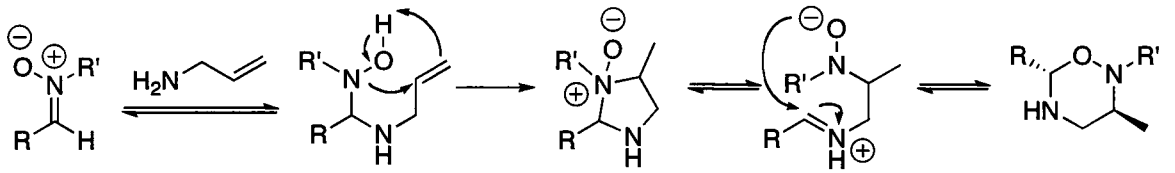


Figure 4.5. Knight's proposed addition/hydroamination/Meisenheimer rearrangement mechanism for observed products.

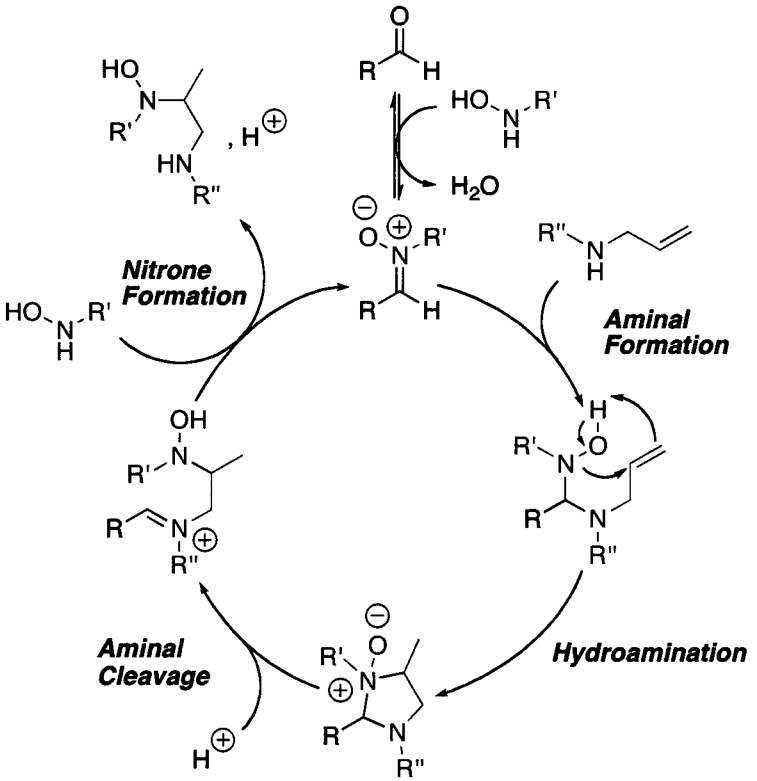


Figure 4.6. Proposed catalytic cycle for the intermolecular hydroamination of allylamines.

(8) (a) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169. (b) Bell, K. E.; Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8545. (c) Gravestock, M. B.; Knight, D. W.; Malik, K. M. A.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3293.

(9) For reviews on stoichiometric reactivity of chiral tethers, see: (a) Gauthier, D. R. Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, 2289. (b) Sugimura, T. *Eur. J. Org. Chem.* **2004**, *6*, 1185.

We therefore envisioned that intermolecular catalysis of the Cope-type hydroamination might be accomplished via *tether* catalysis involving enantiofacial nucleophilic 1,2-addition of an allylamine to a nitrone to generate an aminal tether, followed by diastereoselective intramolecular hydroamination, aminal cleavage and nucleophilic addition of a new hydroxylamine to release the diamine product and regenerate the catalytic nitrone species (Figure 4.6).

Although the benzylic aldonitrone employed by Knight formed a cyclic 1:1:1 hemiaminal adduct following hydroamination rather than undergoing nitrone formation, we proposed that such catalyst poisoning might be overcome by the use of highly electron-poor nitrones to facilitate aminal of hemiaminal cleavage. We therefore began our investigation into the racemic hydroamination of allylamine with hydroxylamines by studying the effect of the addition of catalytic amounts of various achiral electron-poor nitrones, generated in situ via an aldehyde (Figure 4.7).

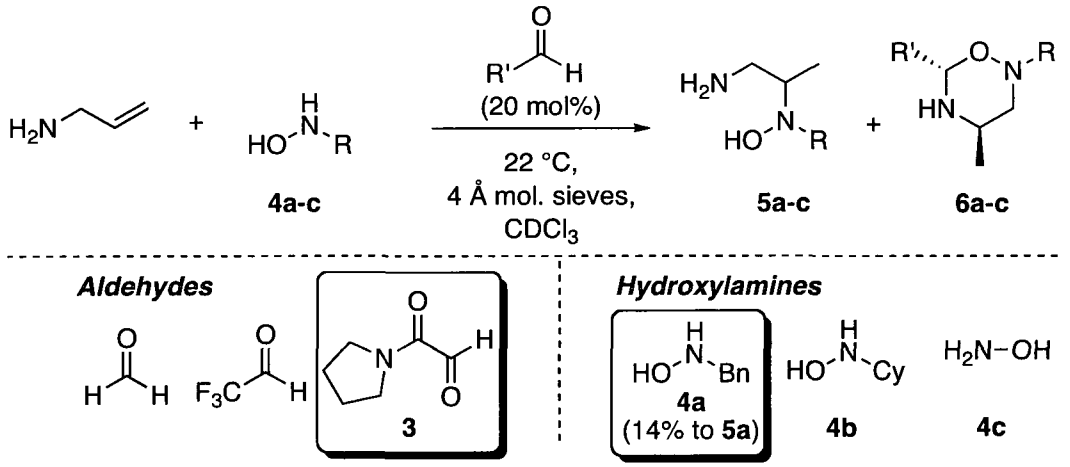
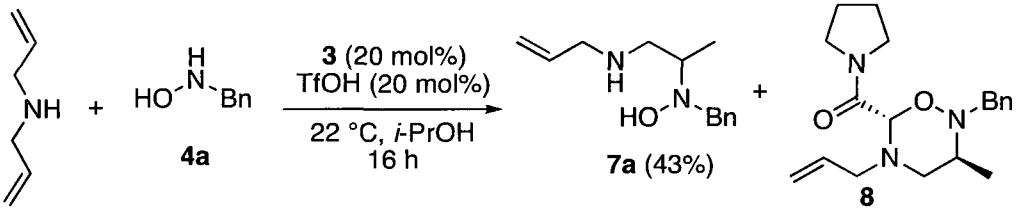


Figure 4.7. Preliminary screen of aldehyde catalysts and hydroxylamines.

Allylamine, a hydroxylamine, an aldehyde (20 mol%) and 4 Å MS were stirred together in $CDCl_3$ at room temperature for 18 h. Of these aldehydes, only glyoxamide **3** displayed signs

of reactivity, which was best when paired with *N*-benzylhydroxylamine (**4a**). Glyoxamide **3** was prepared in two steps from diethyl tartrate by a known procedure and was isolated and used as the hydrate.[10] Analysis of the crude ^{1}H NMR spectra using an internal standard revealed peaks consistent with the formation of vicinal diamine **5a**, as indicated by the newly formed doublet (J = 6 Hz, 3H) at 1.12 ppm thought to correspond to the methyl group in the product. If these were in fact the correct peaks, the reaction occurred with a conversion of 14%. Numerous attempts to isolate the extremely polar product by column chromatography were unsuccessful.

To increase our chances of product isolation without further derivitization as well as to examine the potential allylamine scope of the reaction, we performed a reaction using diallylamine and attempted to isolate the secondary diamine, this time using TfOH as a co-catalyst to speed up proton transfers (Equation 4.5).



(4.5)

Gratifyingly, these conditions appeared more successful, giving 43% conversion by ^{1}H NMR. This exciting result implied that catalytic turnover had been achieved. Again, product isolation by column chromatography under a variety of conditions proved difficult, however enough was obtained in one attempt to obtain relatively clean ^{1}H NMR and MS data which confirmed the identity of **7a** (a full characterization was not carried out). From this spectra, it appears that the diamine **7a**, not the cyclic adduct **8**, is the major product in the crude reaction mixture (even if both have identical chemical shifts for the methyl group). No reaction was

(10) (a) Suzuki, M.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3559. (b) Trova, M. P.; Gauuan, P. J. F.; Pechulis, A. D.; Bubb, S. M.; Bocckino, S. B.; Crapo, J. D.; Day, B. J. *Bioorg. Med. Chem.* **2003**, *11*, 2695.

observed in the absence of **3**. Attempts to perform hydroamination reactions of allyl alcohols were not successful, likely due to their decreased nucleophilic character compared to amines.

At this point it was observed that the glyoxamide catalyst **3** was decomposing simply upon standing in the freezer, as well as in the reaction mixture, even at room temperature. The proper study of such a complex reaction required a robust catalyst that would not decompose under the reaction conditions. Unfortunately, the stability and isolation challenges indicated that the timeframe of this project would far exceed the author's remaining time in the lab, but this exciting result prompted the continuation of this line of investigation as of September 2008 by Mr. Peter Ng.

While significant progress continues to be made and will be reported in due course, these early lead results bring allylamines into the realm of viable alkene substrates for catalytic intermolecular Cope-type hydroamination reactions. Investigation of chiral aldehyde catalysts based on new or existing scaffolds, such as the one proposed in Figure 4.8, might lead to the development of asymmetric organocatalytic Cope-type hydroamination reactions. Finally, we anticipate that this new organocatalytic *tether* activation mode, which takes advantage of the increased facility of intramolecular reactions, will find use in intermolecular directed reactions whose substrates cannot be activated by existing methods.

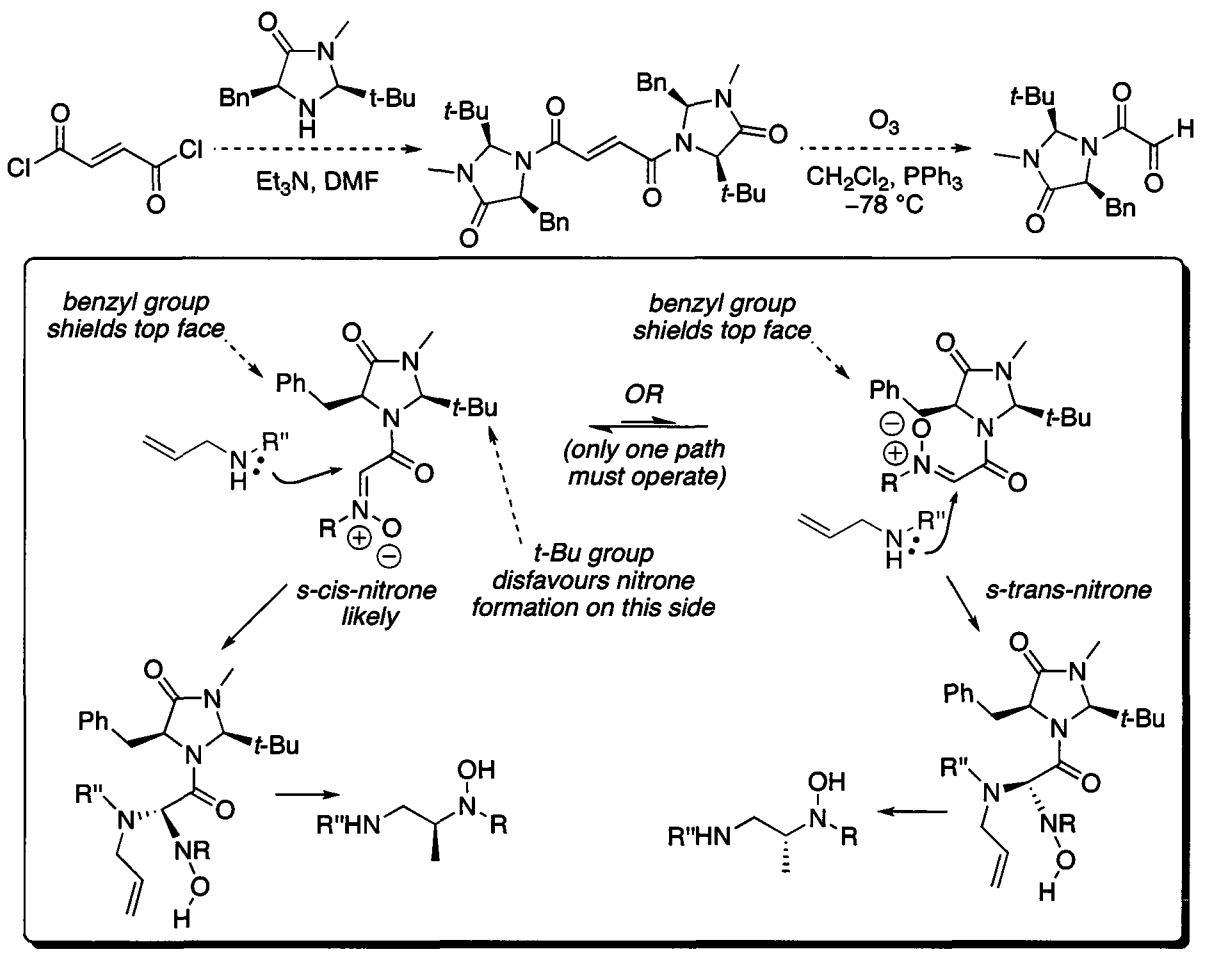
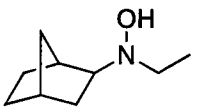


Figure 4.8. Proposed chiral glyoxamide catalysts based on MacMillan's scaffold.[7]

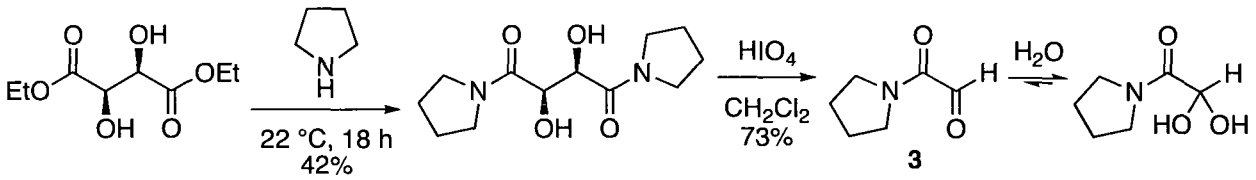
4.4. Experimental Section

Typical Procedure for the Tandem Hydroamination/Cope Elimination Sequence with Norbornene.



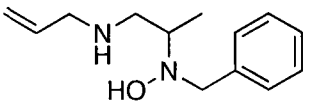
***N-exo*-(Bicyclo[2.2.1]heptan-2-yl)-*N*-ethylhydroxylamine, 2 (Equation 4.2).** *N,N*-Diethylhydroxylamine (0.4 g, 4.5 mmol) and norbornene (2.1 g, 22 mmol) were added to a sealed tube containing a magnetic stirbar and dissolved in benzene (4.5 mmol). The tube was capped with a septum and purged with argon and an outlet for 5 minutes while stirring. The

septum was removed and the tube was quickly sealed with a Teflon screwcap and immersed in an oil bath set at 100 °C for 24 h while stirring. The tube was cooled to ambient temperature, and the reaction was then monitored by thin layer chromatography (40% EtOAc/hexanes). The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (10% EtOAc/hexanes) to give the titled compound (0.43 g, 62%) as a clear colourless oil. TLC R_f 0.32 (5% MeOH/ CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ ppm 7.00 (br s, 1H), 2.76 (br s, 1H), 2.50 (s, 2H), 2.19 (br s, 2H), 1.60-1.26 (m, 4H), 1.15-0.99 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 70.7 (CH), 50.5 (CH_2), 39.5 (CH), 36.4 (CH_2), 36.2 (CH), 35.2 (CH_2), 28.3 (CH_2), 27.5 (CH_2), 11.2 (CH_3); IR (film): 3362, 2955, 2870, 2360, 2341, 1376, 1344, 1089, 944, 890, 611 cm^{-1}; HRMS (EI): Exact mass calculated for $C_9H_{17}NO$ [M^+]: 155.1310. Found: 155.1303.



Synthesis of Glyoxamide 3. Prepared in two steps from diethyl tartrate by the procedure of Suzuki and a modified procedure of Gauuan.[10] A mixture of diethyl tartrate (5.3 g, 26 mmol) and pyrrolidine (5.3 g, 75 mmol) was stirred in a round bottom flask at room temperature for 18 h. After removal of the excess pyrrolidine reduced pressure, the residue was purified by filtration through a short column (EtOAc → EtOAc:MeOH 9:1) to give 2,3-dihydroxy-1,4-di(pyrrolidin-1-yl)butane-1,4-dione as a pale yellow solid (2.77 g, 42%). A solution of the diol (2.77 g, 10.8) in CH_2Cl_2 (68 mL) was magnetically stirred at 0 °C under an argon atmosphere, as periodic acid dihydrate (2.6 g, 14 mmol) was added. The resulting solution was stirred for 15 h, decanted from the solid precipitate, dried over sodium sulfate, filtered and the solvent evaporated under reduced

pressure to provide crude product (1.6 g, 73%) as a clear colourless oil. Column chromatography (CH_2Cl_2 → 10% CH_2Cl_2/MeOH). TLC R_f (5% MeOH/CH_2Cl_2). Spectral data was consistent with that reported by Stetter.[11]



_N_-(2-(Benzyl(hydroxy)amino)propyl)prop-2-en-1-amine (7a, Equation 4.5). _N_-Benzylhydroxylamine (0.050 g, 0.40 mmol), diallylamine (0.040 g, 0.40 mmol) and glyoxamide **3** hydrate (0.012 g, 0.081 mmol) were dissolved in _i_-PrOH (0.5 mL) in a small test tube containing a magnetic stir bar. Trifluoromethanesulfonic acid (0.012 g, 0.081 mmol) was then added. The tube was capped with a septum and the reaction was stirred at room temperature for 16 h. TLC analysis (10% MeOH/CH_2Cl_2; stain with $KMnO_4$) indicated several new products. The mixture was transferred to a round bottom flask and concentrated under reduced pressure. Styrene (≈ 0.049 g, 0.47 mmol) was then added as an internal standard. The mixture was taken up in $CDCl_3$ and transferred to an NMR tube. ^{1}H NMR spectra of the solution was recorded, and the conversion calculated based on the relative integration of the resonance corresponding to one of the proposed product's methyl protons (3H) (at 1.12 ppm) compared to the integration of the resonance corresponding to a styrene proton at 6.69 ppm (1H). This gave a calculated conversion of 43%. Column chromatography (10% MeOH/CH_2Cl_2) of the mixture led to the isolation of a small amount (<5 mg) of **7a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 7.47-7.13 (m, 5H), 5.91-5.75 (m, 1H), 5.37 (d, J = 10 Hz, 1H), 5.27 (d, J = 18 Hz, 1H), 4.08 (d, J = 13 Hz, 1H), 3.80 (d, J = 13 Hz, 1H), 3.39-3.31 (m, 2H), 3.07 (d, J = 6 Hz, 2H), 2.82-2.71 (m, 1H), 1.12 (d, J = 5 Hz, 3H); HRMS (EI): Exact mass calculated for $C_{13}H_{20}N_2O$ [M^+]: 220.1576. Found: 220.1569.

(11) Stetter, H.; Skobel, H. *Chem. Ber.* **1987**, *120*, 643.

Appendix I. Photoinduced 1,4-Additions of Indoles to Enones

JOC Article

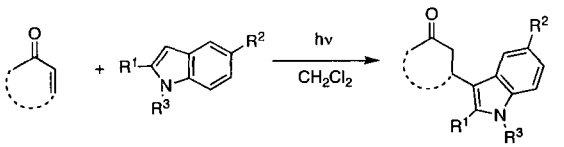
Photoinduced 1,4-Additions of Indoles to Enones

Joseph Moran, Tanya Suen, and André M. Beauchemin*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

andre.beauchemin@uottawa.ca

Received October 7, 2005



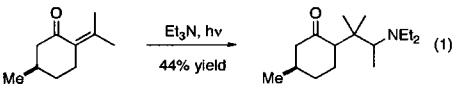
A photoinduced procedure for the 1,4-addition of indoles to enones is described. This reaction occurs with modest to excellent yield for cyclic and some acyclic enones. This reaction is experimentally simple, requiring only irradiation (UVA lamps, ca. 350 nm) of the reagents in a CH_2Cl_2 solution at room temperature, and avoids the necessity to use a Lewis acid. An important solvent effect was noticed, with CH_2Cl_2 and $CHCl_3$ being the optimal solvents. Various substituents are tolerated on the indole moiety and an electronic trend was noticed, as electron-withdrawing groups can suppress this reaction. A mechanism involving single electron transfer between the enone triplet excited state and the indole is proposed and accounts for all experimental observations.

Introduction

The 1,4-addition of carbon nucleophiles is a powerful C−C bond forming strategy. While significant effort has focused on the development of general "thermal" processes, the parent photochemical processes have received less attention from the synthetic community. As part of a general program toward the activation of alkenes, we became interested in using UV irradiation to promote the addition of nucleophiles to α,β-unsaturated systems.

The prevalence of the indole motif in natural and bioactive products continues to be a vector for the development of new synthetic methods. The 1,4-addition of indoles to α,β-unsaturated systems is an efficient approach to indole-containing molecules. The ability of Lewis acids to promote 1,4-addition is well established[1] and recently led to the development of enantioselective versions of this reaction.[2] A related approach involves the use of organocatalysts to activate the α,β-unsaturated system toward nucleophilic attack.[3] In contrast, 1,4-addition of the indole nucleus could also occur via single electron transfer (SET) between the α,β-unsaturated system and the indole ring system,[4] followed by coupling of the resulting radical ions, proton transfer, and tautomerization (Scheme 1). Herein, we disclose that UV light promotes such a process, leading to the 1,4-addition of indoles to enones, and we establish the scope and limitations of this transformation.

The ability of enones to act as electron acceptors in SET reactions is well established.[5] For example, the photolysis of enones and tertiary amines leads to a formal 1,4-addition of α-amino radical to the enone (eq 1).[6] Both intra- and intermo-



(1)

(1) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047 and references therein.

(2) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *105*, 10780. Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309. Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942.

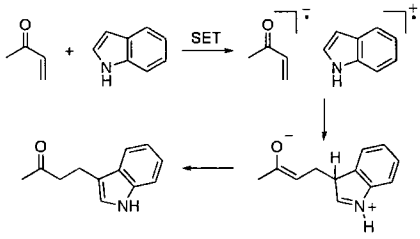
(3) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Ziao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482.

(4) To the best of our knowledge, 1,4-additions of indoles to enones occurring via SET have not been reported in the literature. For related, specific photoinduced additions of indoles, see the following. To 1-methyl-2-pyridone: (a) Ohmiya, S.; Noguchi, M.; Ina, S.; Kubo, H.; Otomasu, H. *Chem. Pharm. Bull.* **1992**, *40*, 854. (b) Sakurai, N.; Ohmiya, S. *J. Chem. Soc., Chem. Commun.* **1993**, 297. To 3-acetyl-6-nitrocoumarin (solid state): (c) Du, D.-M.; Wang, Y.-M.; Meng, J.-B.; Zhou, X.-Z.; Zhang, H.-P. *Gaodeng Xuexiao Huaxue Xuebao* **1996**, *17*, 252 (CAS 124:189184). (d) Wang, Y.-M.; Du, D.-M.; Li, X.-L.; Meng, J.-B.; Zhou, X.-Z. *Youji Huaxue* **1997**, *17*, 433 (CAS 128:28491). To 1,4-naphthoquinone (solid state): (e) Wang, Y.-M.; Wen, Z.; Chen, X.-M.; Du, D.-M.; Matsuura, T.; Meng, J.-B. *J. Heterocycl. Chem.* **1998**, *35*, 313.

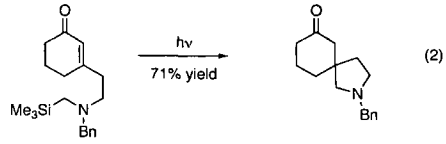
(5) For a review of enone photochemistry, see: Schuster, D. I. in *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons, Ltd.: Chichester, 1989; pp 623−756.

10.1021/jo0521044 CCC: $33.50 © 2006 American Chemical Society
Published on Web 12/17/2005

SCHEME 1. Single Electron Transfer Approach to 1,4-Addition of Indoles to Enones



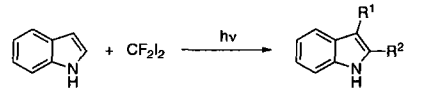
lecular versions of this reaction have been reported. In addition, elegant work by Mariano has demonstrated the synthetic potential of the related reactions of α-silylamine substrates (eq 2).[7] The generally accepted reaction mechanism[8] involves



(2)

photoinduced electron transfer (PET) between the amine and the enone triplet, affording the parent amine radical cation and enone radical anion. Deprotonation (or desilylation, i.e., eq 2) of the amine radical cation affords the α-amino carbon-centered radical, which couples to the enone radical anion to afford the formal 1,4-addition product.

Indoles are generally compounds with rather low oxidation potentials. Therefore, indoles are prone to participate/react through electron-transfer processes. In biological systems, the redox properties of indole moieties (i.e., tryptophan residues) are key to the catalytic activity of certain enzymes.[9] Synthetically, it has also been established that a number of reactions of indoles involve SET and not ionic intermediates, as initially suggested.[10] An example of reactivity derived from PET is the trifluoromethylation of indole derivatives (eq 3).[11,12]



(3)

R^1 = H, R^2 = CF_3: 28% yield
R^1 = CF_3, R^2 = H: 18% yield

(6) (a) Cookson, R. C.; Hudec, J.; Mirza, N. A. *J. Chem. Soc., Chem. Commun.* **1968**, 180. (b) Pienta, N. J.; McKimmey, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 5501.

(7) Xu, W.; Jeon, Y. T.; Hasegawa, E.; Yoon, U. C.; Mariano, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 406. The scope of these reactions has also been extended through the use of sensitizers such as 9,10-dicyanoanthracene. For more examples and a detailed discussion, see: Jeon, Y. T.; Lee, C.-P.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8847. Xu, W.; Zhang, X.-M.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8863.

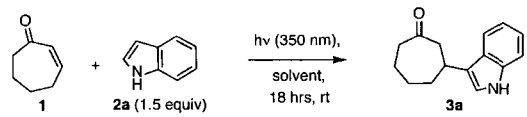
(8) Dunn, D. A.; Schuster, D. I.; Bonneau, R. *J. Am. Chem. Soc.* **1985**, *107*, 2802. Schuster, D. I.; Insogna, A. M. *J. Org. Chem.* **1991**, *56*, 1879.

(9) (a) Sivaraja, M.; Goodin, D. B.; Smith, M.; Hoffman, B. M. *Science* **1989**, *245*, 738. (b) Huyett, J. E.; Doan, P. E.; Gurbiel, R.; Houseman, A. L. P.; Sivaraja, M.; Goodin, D. B.; Hoffman, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9033. (c) Bonagura, C. A.; Sundaramoorthy, M.; Pappa, H. S.; Patterson, W. R.; Poulos, T. L. *Biochemistry* **1996**, *35*, 6107.

(10) Astolfi, P.; Greci, L.; Rizzoli, C.; Sgarabotto, P.; Marrosu, G. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1634.

(11) Chen, Q.-Y.; Li, Z.-T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 645.

TABLE 1. Solvent Effect in Photoinduced 1,4-Addition of Indole to Cyclohept-2-enone



entry	*solvent*	*% conversion*[a]
1	hexanes	23
2	C_6H_6	28
3	$PhCF_3$	23
4	CH_2Cl_2	84
5	$CHCl_3$	90
6	Et_2O	0
7	THF	0
8	MeCN	0
9	*i*-PrOH	0
10	DMSO	6

[a] Determined by ^{1}H NMR.

Results and Discussion

Early experiments focused on the photolysis of cyclohept-2-enone (**1**) and indole (**2a**) in CH_2Cl_2 at ca. 350 nm (UVA lamps). Gratifyingly, we observed quantitative formation of the conjugate addition product **3a** upon irradiation at 0.1 M in CH_2Cl_2 (^{1}H NMR analysis). This reaction is very dependent on the nature of the solvent utilized (Table 1). The use of nonpolar solvents results in modest conversion to the conjugate addition product (entries 1−3). Conversely, little or no reaction is observed with more polar solvents (entries 6−10). In contrast, halogenated solvents such as CH_2Cl_2 or $CHCl_3$ are uniquely effective for this reaction (entries 4 and 5), with CH_2Cl_2 being the solvent of choice. Overall, CH_2Cl_2 and $CHCl_3$ appear to significantly increase the concentration of the enone triplet excited state present in the flask at any given time, thereby allowing a more efficient single electron transfer process. Two possibilities could account for this. The first is the heavy-atom solvent effect,[13] which can promote singlet−triplet crossing (enone). Alternatively, the triplet lifetimes in CH_2Cl_2 and $CHCl_3$ could also be longer than in other solvents.[14] Experimentally, decreasing the concentration to 0.05 M in CH_2Cl_2 also led to quantitative conversion (^{1}H NMR analysis), but the TLC proved somewhat cleaner; these conditions appear to minimize the formation of an indole-derived byproduct. Therefore, these conditions were selected for the study of this transformation.

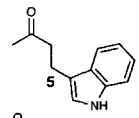
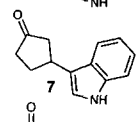
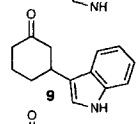
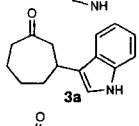
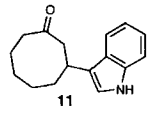
With suitable reaction conditions identified, various electrophiles were surveyed (Table 2). Methyl vinyl ketone (entry 1) and a number of cyclic enones (entries 2−5) are suitable substrates for the 1,4-addition of indole. The substrate scope of this transformation is limited, as a number of processes compete with this rather slow photoinduced reaction. In acyclic systems, the addition to methyl vinyl ketone occurred in a modest 46% yield (entry 1). The reaction could not be extended to other acyclic enones, as in these systems enone photodeconjugation and photoisomerization are known to be efficient processes.[15]

(12) For other examples of SET reactivity of indoles and related systems, see: (a) Yoshida, K. *J. Chem. Soc., Chem. Commun.* **1978**, 1108. (b) Yamasaki, K.; Matsuura, T.; Saito, I. *J. Chem. Soc., Chem. Commun.* **1974**, 944.

(13) Cowan, D. O.; Drisko, R. L. E. *J. Am. Chem. Soc.* **1970**, *92*, 6281.

(14) Natarajan, A.; Kaanumalle, L. S.; Ramamurthy, V. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M., Lanci, F., Eds.; CRC Press: Boca Raton, 2004; Chapter 107.

TABLE 2. Photoinduced 1,4-Addition of Indole to α,β-Unsaturated Systems

Entry	Enone	Product	Yield[a]
1	 4	 5	46
2	 6	 7	19
3	 8	 9	13
4	 1	 3a	98
5	 10	 11	66

[a] Isolated yield after column chromatography.

In cyclic systems, the addition of indole to cyclopent-2-enone (entry 2) and cyclohex-2-enone (entry 3) occurs in low yield due to competing dimerization of the enones.[16] In larger ring systems, the dimerization is slower and the formal 1,4-addition is efficient, resulting in addition to cyclohept-2-enone and cyclooct-2-enone in 98% and 66% yield, respectively (entries 4 and 5). The increased efficiency observed in cyclic systems can be explained by the suppression of known nonproductive pathways, as photodeconjugation is impossible due to geometrical constraints and photoisomerization is disfavored (or impossible) due to strain.

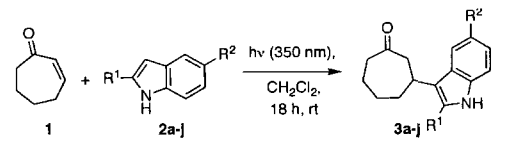
Thus, cyclohept-2-enone was selected as substrate to determine the nucleophile scope (Table 3), as its reaction with indole occurs in 98% yield (entry 1). Substitution at the 2 position is tolerated, affording the desired product in 58% and 50% yield for methyl and phenyl substituents, respectively (entries 2 and 3). Unfortunately, substitution at the 3 position is not tolerated, and only enone dimerization is observed.[17] Substitution at the 5 position is tolerated, affording the desired products in modest to good yields (entries 4–8). From these entries, it is clear that the reaction is more efficient with electron-donating substituents. This reaction is even suppressed with indoles bearing strong electron-withdrawing substituents such as nitro or cyano groups (entries 9 and 10). This trend is consistent with electron-withdrawing substituents retarding the PET process and allowing enone dimerization to occur competitively. In general, even indoles bearing electron-donating substituents (entry 4) lead to a lower isolated yield compared to the reaction with indole itself (entry 1). This observation is consistent with the increased stability (diminished reactivity) of the substituted indole radical cations.

(15) Pete, J. P. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, 1995; pp 593–606.

(16) For a good discussion on the differences in the photochemistry of various cyclic enones, see: Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50.

(17) See Experimental Section for details.

TABLE 3. Photoinduced 1,4-Addition of Indoles to Cyclohept-2-enone

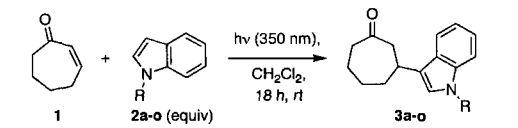


1 2a-j 3a-j

entry	R^1	R^2	2a–j (equiv)	% yield[a]
1	H	H	**2a** (1.1)	98
2	Me	H	**2b** (1.1)	58
3	Ph	H	**2c** (3.0)	50
4	H	OMe	**2d** (3.0)	75
5	H	Me	**2e** (3.0)	49
6	H	Br	**2f** (3.0)	43
7	H	F	**2g** (3.0)	33
8	H	CO_2Me	**2h** (3.0)	22
9	H	CN	**2i** (3.0)	0
10	H	NO_2	**2j** (3.0)	0

[a] Isolated yield after column chromatography.

TABLE 4. Effect of Nitrogen Substitution in Photoinduced 1,4-Addition of Indoles to Cyclohept-2-enone



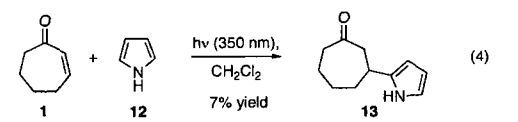
1 2a-o (equiv) 3a-o

entry	R	2a–o (equiv)	% yield[a]
1	H	**2a** (1.1)	98
2	Me	**2k** (1.0)	51
3	Allyl	**2l** (1.0)	53
4	Bn	**2m** (1.0)	33
5	Ac	**2n** (1.2)	0
6	Boc	**2o** (1.2)	0

[a] Isolated yield after column chromatography.

Experiments aimed at determining the scope with respect to nitrogen substitution were then performed (Table 4). N-H substitution is optimal for a clean 1,4-addition to proceed (entry 1). However, methyl, benzyl, and allyl substitution is tolerated, affording the desired adducts in 51%, 33%, and 53% yield, respectively (entries 2–4). In contrast, electron-withdrawing nitrogen protecting groups such as Boc or Ac suppress 1,4-addition (entries 5 and 6), which is consistent with a mechanism involving SET (destabilization of the indole radical cation).

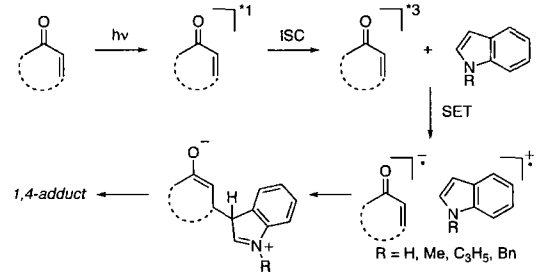
Finally, attempts were made to extend the scope of this transformation to other 1,4-acceptors such as unsaturated esters and lactones, with no success. Other nitrogen heterocycles were also poor substrates for this reaction. For example, photolysis of a mixture of cyclohept-2-enone (**1**) and pyrrole (**12**) led only to a modest 7% yield of adduct **13** (eq 4).



1 12 13 (4)

Proposed Mechanism. A photoinduced electron-transfer mechanism such as shown in Scheme 2 is in good agreement with all of our experimental findings. As discussed in the

SCHEME 2. Proposed Photoinduced Electron Transfer Mechanism for 1,4-Addition of Indoles to Enones



Introduction, there is ample evidence present in the literature for the participation of enones in PET reactions, for example, with tertiary amines.[6-8] It is also well established that indoles can react through pathways involving SET. The strong solvent dependence and restricted substrate scope are consistent with the proposed mechanism. Furthermore, the long reaction times (typically 18 h) suggest a low quantum yield, consistent with forbidden intersystem crossing (ISC) leading to the formation of the triplet enone. Single electron transfer between the triplet enone excited state and indole affords the radical ions, which combine to form the C−C bond. Intramolecular deprotonation at C3 of the indole (*N*-alkyl substitution is tolerated) followed by tautomerization affords the 1,4-adduct. A similar mechanism was proposed for 1,4-additions of indoles to 1-methyl-2-pyridone,[4a-b] and this mechanism is likely operating in reported photoinduced 1,4-additions of indole to 3-acetyl-6-nitrocoumarin and 1,4-naphthoquinone in the solid state.[4c-e] We also noted that reactions exposed to air did not lead to any 1,4-adduct formation, consistent with oxygen quenching of the enone triplet required for the electron-transfer step.[17,18]

Conclusion

We have developed a photoinduced procedure for the 1,4-addition of indoles to enones. This reaction occurs with modest to excellent yield for cyclic and some acyclic enones. This reaction is experimentally simple, requiring only irradiation (UVA lamps) of the reagents in a CH_2Cl_2 solution at room temperature and avoids the necessity to use a Lewis acid. A mechanism involving single electron transfer between the enone triplet excited state and the indole is proposed and accounts for all experimental observations.

(18) A more detailed mechanistic discussion can be found in the Supporting Information.

Experimental Section

General Procedure for Photoinduced 1,4-Addition of Indoles (Tables 2−4). 3-(1*H*-Indol-3-yl)cycloheptanone (Table 2, entry 4). A borosilicate tube was charged with a stir bar, cyclohept-2-enone (0.105 g, 0.949 mmol), and indole (0.117 g, 0.999 mmol). A volume of 18.0 mL of CH_2Cl_2 was added to the mixture and the volume was marked on the tube. An excess of 1−2 mL of solvent was then added to the tube. The tube was capped with a septum and was purged with stirring using a nitrogen balloon and an outlet until the solvent evaporated to the volume marked. The reaction mixture was then placed on a stir-plate and allowed to stir between two exposure panels each equipped with four 8W UV-A bulbs for 18 h to obtain the crude mixture as a dark red liquid.[19] The reaction was monitored by TLC and the product was found to have TLC R_f of 0.51 on silica gel (40% EtOAc/hexanes). The crude mixture was concentrated under reduced pressure to a few milliliters and was purified by flash chromatography using CH_2Cl_2. The purified product was a clear, colorless oil (0.211 g, 98% yield).

Acknowledgment. We thank the NSERC for generous support through discovery grants and research tools and instrumentation programs and the University of Ottawa for startup funds. J.M. also thanks NSERC for a CGS-M postgraduate scholarship and the University of Ottawa for a SAD award.

Supporting Information Available: Typical experimental procedures, experimental details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0521044

(19) The described transformations were typically accompanied by a change in color from a clear to a red or an amber solution.

Photoinduced 1,4-Additions of Indoles to Enones

Joseph Moran, Tanya Suen, and André M. Beauchemin*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada, K1N 6N5

andre.beauchemin@uottawa.ca

Supporting Information

Table of Contents

General Information. All reactions were performed in air-dried or oven-dried borosilicate tubes. Reactions were either carried out in a Rayonet photoreactor equipped with eight 8W ultraviolet lamps or between two Luzchem exposure panels equipped with four 8W ultraviolet lamps each. UV-A bulbs (~350 nm),[1,2] UV-B bulbs (~300 nm), and exposure panels were purchased from Luzchem Research, Inc. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 μm). Analytical thin layer chromatography was performed on aluminum sheets pre-coated with silica gel 60 F254, cut to size. Visualization was accomplished with UV light and an aqueous vanillin solution followed by heating.

^{1}H NMR spectra were recorded on a 300 MHz spectrometer at ambient temperature and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.15 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 at 75 MHz. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm or C_6D_6 at 128.02 ppm). High-resolution mass spectra were obtained from the Ottawa-Carleton Mass Spectrometry Centre.

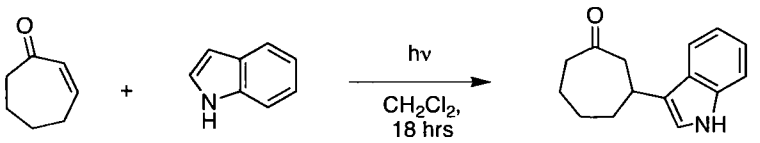
(1) For specifications, see http://www.luzchem.com/handbook/LESUVA011.pdf

(2) Alternatively, this apparatus could be substituted for a medium pressure Hg lamp fitted with a uranium glass filter.

Materials. Dichloromethane was dried by distillation over calcium hydride. Tetrahydrofuran was dried by distillation over sodium/benzophenone ketyl. Diethyl ether was purified by passage through a column of activated alumina under a nitrogen atmosphere.[3] Unless otherwise noted, all commercial materials were used without further purification. Cyclohept-2-enone and cyclooct-2-enone were prepared according to literature procedures.[4,5] 1-Benzylindole and 1-allylindole were prepared according to the procedure of Guida.[6] 1-Acetylindole was prepared according to the procedure of Nickisch.[7] *tert*-Butylindole-1-carboxylate was prepared according to the procedure of Vazquez.[8]

General Procedure for Solvent Scan (Table 1). Into each of 10 borosilicate tubes equipped with stirbars was added cyclohept-2-enone (0.033 g, 0.30 mmol) and indole (0.053 g, 0.45 mmol). To each tube was added 2 mL of solvent (Table 1). In the case of volatile solvents, the volume was marked on the tube, and an excess of solvent was added. The tube was capped with a rubber septum and purged with a nitrogen balloon and an outlet while stirring for a minimum of 5 minutes or until the solvent had evaporated to the marked level. The tubes were then placed on a Luzchem rotating carousel equipped with a stirplate and allowed to stir in a Rayonet photoreactor equipped with eight 8W UV-A bulbs for 18 hours. The reactions were monitored by TLC (40% EtOAc/hexanes). The contents of each tube were then transferred to a round-bottom flask, and the solvent was removed under reduced pressure. To each flask was added 1.00 mL of a standardized solution of 1% tetramethylsilane in deuterochloroform. ^{1}H NMR spectra of these solutions were recorded, and the % conversion calculated based on the ratio of the tetramethysilane (12H) resonance at 0.0 ppm to the resonance corresponding to the product's methine proton (1H) at 3.26 ppm. The method is estimated to have an error of approximately ±5%.

Table 5. Concentration Scan for the Photoinduced 1,4-Addition of Indole to Cyclohept-2-enone



1 : 1.5

Entry	[Enone] (mol/L)	% Conversion[a]
1	0.05	Quantitative
2	0.10	Quantitative
3	0.30	74
4	0.50	49

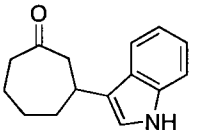
[a] Determined by ^{1}H NMR using TMS as an internal standard

General Procedure for Concentration Scan (Table 5). Into each of 4 borosilicate tubes equipped with stirbars were added cyclohept-2-enone (0.033 g, 0.30 mmol) and indole (0.053 g, 0.45 mmol). To each tube

(3) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
(4) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.
(5) Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048.
(6) Guida, W. C.; Mathre, D. J. *J. Org. Chem.* **1980**, *45*, 3172.
(7) Nickisch, K.; Klose, W.; Bohlmann, F. *Chem. Ber.* **1980**, *113*, 2036.
(8) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551.

was then added either 6.0, 3.0, 1.0, or 0.60 mL of dichloromethane to give concentrations of 0.050, 0.10, 0.30 and 0.50 M, respectively. The volume was marked on the tube, and an excess of solvent was added. The tube was capped with a rubber septum and purged with a nitrogen balloon and an outlet while stirring for a minimum of 5 minutes or until the solvent had evaporated to the marked level. The tubes were then placed on a Luzchem rotating carousel equipped with a stirplate and allowed to stir in a Rayonet photoreactor equipped with eight 8W UV-A bulbs for 18 hours. The contents of each tube were then transferred to a round-bottom flask, and the solvent was removed under reduced pressure. To each flask was added 1.00 mL of a standardized solution of 1% tetramethylsilane in deuterochloroform. ^{1}H NMR spectra of these solutions were recorded, and the % conversion calculated based on the ratio of the tetramethysilane (12H) resonance at 0.0 ppm to the resonance corresponding to the product's methine proton (1H) at 3.26 ppm. The method is estimated to have an error of approximately ±5%.

General Procedure for Photoinduced 1,4-Addition of Indoles (Tables 2, 3 and 4).

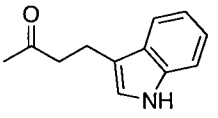


3-(1H-Indol-3-yl)cycloheptanone (3a)(table 2, entry 4). A borosilicate tube was charged with a stir bar, cyclohept-2-enone (0.105 g, 0.949 mmol) and indole (0.117 g, 0.999 mmol). A volume of 18.0 mL dichloromethane was added to the mixture and the volume was marked on the tube. An excess of 1-2 mL of solvent was then added to the tube. The tube was capped with a septum and was purged with stirring using a nitrogen balloon and an outlet until the solvent evaporated to the volume marked. The reaction mixture was then placed on a stir-plate and allowed to stir between two exposure panels each equipped with four 8W UV-A bulbs for 18 hours to obtain the crude mixture as a dark red liquid.[9] The reaction was monitored by TLC and the product was found to have TLC R_f 0.51 on silica gel (40% EtOAc/hexanes). The crude mixture was concentrated under reduced pressure to a few milliliters and was purified by flash chromatography using CH_2Cl_2. The purified product was a clear, colorless oil (0.211 g, 98% yield); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.65-7.62 (m, 1H), 7.26-7.17 (m, 2H), 7.12-7.09 (m, 1H), 6.99 (br s, 1H), 6.38 (d, 1H, J = 2.4 Hz), 3.05 (tt, 1H, J = 10.4 and 2.7 Hz), 2.79 (ddd, 1H, J = 14.4, 3.6 and 1.5 Hz), 2.71 (dd, 1H, J = 14.4 and 10.5 Hz), 2.29 (ap dd, 2H, J = 9.2 and 4.5 Hz), 2.07-2.01 (m, 1H), 1.63-1.43 (m, 3H), 1.36-1.09 (m, 2H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.7, 136.9, 126.5, 122.2, 121.4, 119.6, 119.5, 119.4, 111.5, 50.5, 43.8, 38.2, 34.0, 29.2, 24.4; IR (film): 3411, 3057, 2927, 2856, 1691, 1458, 1339, 1099, 741 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{17}NO$ [M]$^+$: 227.1310. Found: 227.1304.

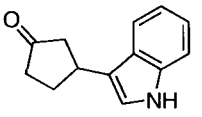
(9) The described transformations were typically accompanied by a change in color from a clear to a red or an amber solution.

Table 2a. Experimental Details for Results in Table 2

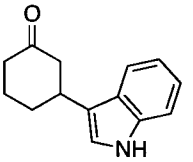
Entry	m_{enone} (g)	n_{enone} (mmol)	m_{indole} (g)	n_{indole} (mmol)	$V_{solvent}$ (mL)
1	0.034	0.49	0.080	0.68	10
2	0.033	0.40	0.071	0.61	8.0
3	0.033	0.34	0.060	0.51	7.0
4	0.105	0.949	0.117	0.999	19
5	0.033	0.27	0.047	0.40	5.5



4-(1H-Indol-3-yl)butan-2-one) (5)(table 2, entry 1). Isolated 42 mg as white crystals after column chromatography (15% EtOAc/hexanes). Spectral data were found to be in good agreement with those in the literature.[10]

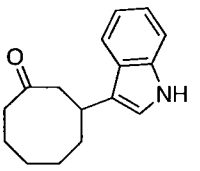


3-(1H-Indol-3-yl)cyclopentanone (7)(table 2, entry 2). Isolated 15 mg as a white powder after column chromatography (25% EtOAc/hexanes). Spectral data were found to be in good agreement with those in the literature.[11]



3-(1H-Indol-3-yl)cyclohexanone (9)(table 2, entry 3). Isolated 10 mg as a clear, colorless oil after column chromatography (30% EtOAc/hexanes). Spectral data were found to be in good agreement with those in the literature.[12]

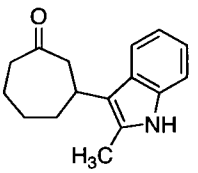
(10) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, *14*, 2165.
(11) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700.
(12) Magnus, P.; Lacour, J.; Evans, P. A.; Rigollier, P.; Tobler, H. *J. Am. Chem. Soc.* **1998**, *120*, 12486.



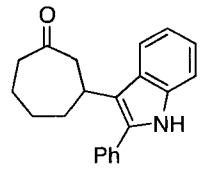
3-(1H-Indol-3-yl)cyclooctanone (11)(table 2, entry 5). Isolated 43 mg as a clear, colorless oil after column chromatography (20% EtOAc/hexanes). TLC R_f 0.53 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (br s, 1H), 7.68 (d, 1H, J = 7.8 Hz), 7.36 (d, 1H, J = 8.1 Hz), 7.19 (td, 1H, J = 7.2 and 1.2 Hz). 7.12 (td, 1H, J = 7.8 and 0.9 Hz), 6.98 (d, 1H, J = 2.4 Hz), 3.57 (tt, 1H, J = 12 and 3.3 Hz), 2.92 (t, 1H, J= 12.6 Hz), 2.66 (ddd, 1H, J = 12.9, 3.2 and 1.2 Hz), 2.58 (dd, 1H, J = 12.3 and 3 Hz), 2.46-2.39 (m, 1H), 2.18–1.42 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.9, 136.9, 126.8, 122.4, 121.6, 119.9, 119.7, 119.6, 111.6, 48.3, 42.8, 35.7, 34.5, 27.9, 25.1, 24.6; IR (film): 3410, 3055, 2929, 2857, 1686, 1458, 1339, 740 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO[M]^+$: 241.1467. Found: 241.1487.

Table 3a. Experimental Details for Results in Table 3

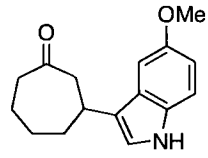
Entry	m_{enone} (g)	n_{enone} (mmol)	m_{indole} (g)	n_{indole} (mmol)	$V_{solvent}$ (mL)
1	0.105	0.949	0.117	0.999	19
2	0.100	0.907	0.131	0.998	18
3	0.050	0.45	0.263	1.36	9.0
4	0.033	0.30	0.132	0.906	6.0
5	0.050	0.45	0.178	1.36	9.0
6	0.050	0.45	0.267	1.36	9.0
7	0.050	0.45	0.184	1.36	9.0
8	0.050	0.45	0.239	1.36	9.0
9	0.050	0.45	0.193	1.36	9.0
10	0.050	0.45	0.221	1.36	9.0



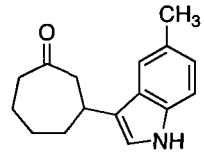
3-(2-Methyl-1H-indol-3-yl)cycloheptanone (3b)(table 3, entry 2). Isolated 128 mg as a clear, colorless oil after column chromatography (CH_2Cl_2). TLC R_f 0.35 (25% EtOAc/hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.60-7.57 (m, 1H), 7.21 (ddd, 2H, J = 13.9, 7.0, and 1.5 Hz), 7.07-7.04 (m, 1H), 6.46 (br s, 1H), 3.14 (dd, 1H, J = 13.4 and 12.1 Hz), 3.05-2.95 (m, 1H), 2.60 (dt, 1H, J = 13.4 and 1.9 Hz), 2.34-2.30 (m, 2H), 1.99-1.86 (m, 2H), 1.83 (s, 3H), 1.69-1.47 (m, 2H), 1.44-1.29 (m, 1H), 1.19-1.05 (m, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.5, 135.9, 128.7, 127.4, 121.1, 119.6, 119.4, 116.8, 110.8, 50.6, 43.9, 38.1, 35.2, 29.8, 24.4, 11.6; IR (film): 3357, 3053, 2928, 2856, 1695, 1461, 1264, 739 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO[M]^+$: 241.1467. Found: 241.1473.



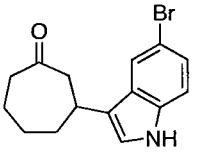
3-(2-Phenyl-1H-indol-3-yl)cycloheptanone (3c)(table 3, entry 3). Isolated 69 mg as a clear, colorless oil after column chromatography (15% EtOAc/hexanes). TLC R_f 0.49 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (br s, 1H), 7.74 (d, 1H, J = 7.8 Hz), 7.47-7.37 (m, 6H), 7.22 (ap q, 1H, J = 7.2 Hz), 7.14 (ap q, 1H, J = 7.4 Hz), 3.50-3.33 (m, 2H), 2.69 (d, 1H, J = 13.2 Hz), 2.61-2.56 (m, 2H), 2.34-1.41 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.6, 136.6, 133.8, 133.5, 129.3, 129.1, 128.4, 127.3, 122.5, 120.9, 119.9, 118.2, 111.6, 60.0, 44.3, 38.4, 34.9, 30.1, 24.9; IR (film): 3344, 2925, 2853, 1689, 1457, 1275, 764, 749, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{21}H_{21}NO[M]^+$: 303.1623. Found: 303.1629.



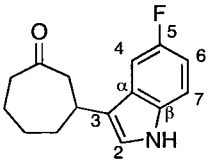
3-(5-Methoxy-1H-indol-3-yl)cycloheptanone (3d)(table 3, entry 4). Isolated 58 mg as a clear, colorless oil after column chromatography (30% EtOAc/hexanes). TLC R_f 0.44 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (br s, 1H), 7.22 (d, 1H, J = 8.8 Hz), 7.03 (d, 1H, J = 2.3 Hz), 6.89 (d, 1H, J = 2.3 Hz), 6.85 (dd, 1H, J = 8.8 and 2.4 Hz), 3.86 (s, 3H), 3.19 (tt, 1H, J = 10.8 and 2.5 Hz), 2.93 (t, 1H, J = 12.4 H), 2.83 (dddd, 1H, J = 14.4 Hz, J = 1.6 Hz, J = 1.5 Hz, J = 1.4 Hz), 2.63 (q, 2H, J = 4.4 Hz), 2.28 (d, 1H, J = 14.0 Hz), 2.09-1.95 (m, 2H), 1.83-1.51 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.9, 154.2, 132.0, 126.8, 121.5, 121.0, 112.5, 112.4, 101.4, 56.4, 50.9, 44.5, 38.4, 34.3, 29.6, 24.8; IR (film): 3366, 2930, 2855, 1691, 1583, 1485, 1441, 1211, 1052, 796, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO_2[M]^+$: 257.1416. Found: 257.1406.



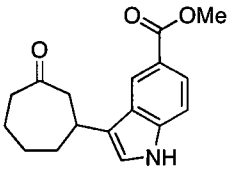
3-(5-Methyl-1H-indol-3-yl)cycloheptanone (3e)(table 3, entry 5). Isolated 53 mg as a clear, colorless oil after column chromatography (CH_2Cl_2). TLC R_f 0.33 (25% EtOAc/hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.51 (d, 1H, J = 0.7 Hz), 7.08 (dd, 1H, J = 8.4 and 1.3 Hz), 7.00 (d, 1H, J = 8.3 Hz), 6.57 (s, 1H), 6.33 (d, 1H, J = 2.1 Hz), 3.08 (tt, 1H, J = 10.4 and 2.5 Hz), 2.83 (ddd, 1H, J = 14.4, 3.3, and 1.6 Hz), 2.74 (dd, 1H, J = 14.4 and 10.9 Hz), 2.44 (s, 3H), 2.31 (dd, 2H, J = 8.5 and 4.6 Hz), 2.11-2.03 (m, 1H), 1.67-1.43 (m, 3H), 1.37-1.11 (m, 2H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.5, 135.5, 128.1, 127.2, 124.2, 121.4, 119.9, 119.4, 111.4, 50.8, 44.1, 38.6, 34.4, 29.5, 24.9, 22.0; IR (film): 3367, 2926, 2856, 1698, 1444, 1347, 795 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO[M]^+$: 241.1467. Found: 241.1460.



3-(5-Bromo-1H-indol-3-yl)cycloheptanone (3f)(table 3, entry 6). Isolated 60 mg as a clear, colorless oil after column chromatography (CH_2Cl_2). TLC R_f 0.31 (30% EtOAc:hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.86 (d, 1H, J = 1.9 Hz), 7.33 (dd, 1H, J = 8.7 and 1.8 Hz), 6.71 (dd, 1H, J = 8.6 and 0.4 Hz), 6.67 (br s, 1H), 6.23 (br d, 1H, J = 2.3 Hz), 2.87-2.78 (m, 1H), 2.62-2.60 (m, 2H), 2.34-2.17 (m, 2H), 1.89-1.83 (m, 1H), 1.53-1.02 (m, 5H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.2, 135.3, 125.2, 122.1, 121.4, 121.0, 113.01, 112.99, 50.2, 43.8, 38.4, 33.7, 29.1, 24.4; IR (film): 3348, 2926, 2855, 1692, 1459, 1275, 1260, 884, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{16}BrNO[M]^+$: 305.0415. Found: 305.0399.



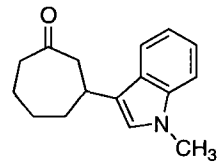
3-(5-Fluoro-1*H*-indol-3-yl)cycloheptanone (3g)(table 3, entry 7). Isolated 36 mg as a clear, colorless oil after column chromatography (30% EtOAc/hexanes) followed by column chromatography with 1% MeOH/dichloromethane. TLC R_f 0.31 (30% EtOAc:hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.33 (dd, 1H, J = 9.7 and 2.3 Hz), 6.97 (td, 1H, J = 8.9 and 2.4 Hz), 6.80 (ap dd, 2H, J = 8.8 and 4.4 Hz), 6.33 (d, 1H, J = 2.2 Hz), 2.91-2.83 (m, 1H), 2.65 (ap d, 2H, J = 7.6 Hz), 2.30-2.24 (m, 2H), 1.91 (ap d, 1H, J = 14.9 Hz), 1.56-1.29 (m, 5H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.5, 158.2 (d, J = 234.1 Hz, C(5)-F), 133.3, 126.8 (d, J = 9.4 Hz, C(α)-F), 121.7 (d, J = 4.8 Hz, C(3)-F), 121.6, 112.2 (d, J = 9.6 Hz, C(7)-F), 110.6 (d, J = 26.2 Hz, C(6)-F), 104.5 (d, J = 23.3 Hz, C(4)-F), 50.2, 43.8, 38.2, 33.9, 29.1, 24.4; IR (film): 3349, 2928, 2856, 1689, 1581, 1486, 1456, 1347, 1259, 1161, 1100, 938, 850, 796, 763, 749 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{16}FNO[M]^+$: 245.1216. Found: 245.1201.



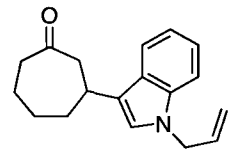
Methyl 3-(3-oxocycloheptyl)-1H-indole-5-carboxylate (3h)(table 3, entry 8). Isolated 28 mg as a clear, colorless oil after column chromatography (40% EtOAc/hexanes). TLC R_f 0.20 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (br s, 2H), 7.88 (d, 1H, J = 8.4 Hz), 7.34 (d, 1H, J = 8.6 Hz), 7.00 (s, 1H), 3.92 (s, 3H), 3.30 (br ap t, 1H, J = 13.1 Hz), 2.95 (dd, 1H, J = 14.7 and 11.4 Hz), 2.82 (d, 1H, J = 14.5 Hz), 2.63 (ap dt, 2H, J = 7.8 and 3.8 Hz), 2.26 (br d, 1H, J = 13.4 Hz), 2.08-1.95 (m, 2H), 1.85-1.58 (m, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.5, 168.0, 139.4, 126.3, 123.9, 123.1, 122.5, 122.1, 121.3, 111.4, 51.5, 50.4, 43.8, 38.6, 33.8, 29.1, 24.4; IR (film): 3339, 2926, 2855, 1697, 1437, 1275, 1260, 1109, 764, 750 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{19}NO_3[M]^+$: 285.1365. Found: 285.1369.

Table 4a. Experimental Details for Results in Table 4

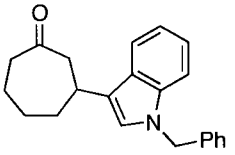
Entry	m_{enone} (g)	n_{enone} (mmol)	m_{indole} (g)	n_{indole} (mmol)	$V_{solvent}$ (mL)
1	0.105	0.949	0.117	0.999	19
2	0.050	0.45	0.060	0.45	9.0
3	0.050	0.45	0.071	0.45	9.0
4	0.050	0.45	0.094	0.45	9.0
5	0.050	0.45	0.087	0.55	9.0
6	0.050	0.45	0.118	0.55	9.0



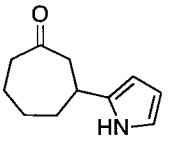
3-(1-Methyl-3-indolyl)-cycloheptanone (3k)(table 4, entry 2). Isolated 56 mg as a clear, colorless oil after column chromatography (20% EtOAc/hexanes). TLC R_f 0.29 (20% EtOAc/hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.67 (d, 1H, J = 7.9 Hz), 7.29-7.17 (m, 2H), 7.03 (d, 1H, J = 7.6 Hz), 6.27 (s, 1H), 3.10 (apt t, 1H, J = 10.7 and 2.9 Hz), 2.94 (s, 3H), 2.82-2.72 (m, 2H), 2.33 (dd, 2H, J = 9.7 and 4.7 Hz), 2.11-2.05 (m, 1H), 1.68-1.47 (m, 3H), 1.40-1.14 (m, 2H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.4, 137.9, 127.4, 124.5, 122.2, 120.7, 119.9, 119.4, 109.8, 51.0, 44.1, 38.8, 34.3, 32.0, 29.5, 24.8; IR (film): 3052, 2927, 2855, 1697, 1472, 1326, 1262, 1154, 740 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO[M]^+$: 241.1467. Found: 241.1479.



3-(1-Allyl-3-indolyl)-cycloheptanone (3l)(table 4, entry 3). Isolated 64 mg as a clear, colorless oil after column chromatography (20% hexanes/CH_2Cl_2). TLC R_f 0.58 (CH_2Cl_2); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.78 (dd, 1H, J = 6.8 and 1.1 Hz), 7.38-7.29 (m, 4H), 6.56 (s, 1H), 5.65 (ddt, 1H, J = 17.0, 10.4 and 5.3 Hz), 4.95 (ddd, 1H, J = 10.2, 2.9 and 1.4 Hz), 4.85 (ddd, 1H, J = 17.1, 3.1 and 1.6 Hz), 4.16 (dt, 2H, J = 5.3 and 1.6 Hz), 3.21 (tt, 1H, J = 10.6, 2.7 Hz), 2.94 (ddd, 1H, J = 14.4, 3.3, 1.6 Hz), 2.86 (dd, 1H, J = 14.4 and 10.9 Hz), 2.44 (dd, 1H, J = 9.3 and 4.4 Hz), 2.22-2.16 (m, 1H), 1.79-1.24 (m, 5H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.2, 137.2, 134.0, 127.3, 123.4, 122.1, 121.0, 119.8, 119.4, 116.6, 110.1, 50.7, 48.4, 43.9, 38.5, 34.5, 29.4, 24.5; IR (film): 3052, 2926, 2856, 1697, 1644, 1613, 1466, 1331, 1266, 992, 740 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{18}H_{21}NO[M]^+$: 267.1623. Found: 267.1601.



3-(1-Benzyl-3-indolyl)-cycloheptanone (3m)(table 4, entry 4). Isolated 47 mg as a clear, colorless oil after column chromatography (30% hexanes/CH_2Cl_2). TLC R_f 0.58 (CH_2Cl_2); ^{1}H NMR (C_6D_6, 300 MHz) δ7.81-7.77 (m, 1H), 7.31-7.29 (m, 4H), 7.21-7.16 (m, 1H), 7.12-7.08 (m, 3H), 6.93-6.90 (m, 2H), 6.57 (s, 1H), 4.79 (s, 2H), 3.21 (ap tt, 1H, J = 13.7 and 2.7 Hz), 2.97-2.91 (m, 1H), 2.83 (dd, 1H, J = 14.3 and 11.1 Hz), 2.43 (ap dd, 2H, J = 9.8 and 4.7 Hz), 2.18 (br d, 1H, J = 13.9 Hz), 1.77-1.54 (m, 3H), 1.49-1.22 (m, 2H); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.0, 138.1, 137.3, 128.7, 127.3, 126.7, 123.7, 122.2, 121.2, 119.7, 119.5, 110.0, 50.6, 49.5, 43.8, 38.3, 34.1, 29.3, 24.4; IR (film): 3055, 3029, 2926, 2856, 1696, 1466, 1453, 1347, 1331, 1264, 1178, 1015, 741 703 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{22}H_{23}NO[M]^+$: 317.1780. Found: 317.1783.



3-(1H-Pyrrol-2-yl)cycloheptanone (13)(eq 4). A borosilicate tube was charged with a stir bar, cyclohept-2-enone (0.100 g, 0.907 mmol) and pyrrole (0.182 g, 2.72 mmol). A volume of 6.0 mL dichloromethane was added to the mixture and the volume was marked on the tube. An excess of 1-2 mL of solvent was then added to the tube. The tube was capped with a septum and was purged with a nitrogen balloon and an outlet to the volume marked. The reaction mixture was then placed on a stir-plate and allowed to stir between two exposure panels each equipped with four 8W UV-A bulbs for 48 hours to obtain the crude mixture as a dark red liquid. The crude mixture was concentrated under reduced pressure to a few milliliters and was purified by flash chromatography using 25% ethyl acetate in hexanes. The purified product was a clear, colorless oil (0.011 g, 7% yield). TLC R_f 0.39 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (br s, 1H), 6.68 (dd, 1H, J = 3.8 and 2.3 Hz), 6.10 (dd, 1H, J = 5.8 and 2.9 Hz), 5.92 (s, 1H), 3.00 (ap t, 1H, J = 10.4 and 3.3 Hz), 2.89-2.73 (m, 2H), 2.53 (d, 1H, J = 4.9 Hz), 2.50 (d, 1H, J = 4.4 Hz), 2.17 (ap br d, 1H, J = 13.3 Hz), 2.03-1.87 (m, 2H), 1.82-1.44 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.0, 117.1, 108.6, 104.3, 53.83, 50.18, 44.4, 37.6, 35.6, 28.6, 24.4; IR (film): 3374, 2928, 2856, 1692, 1275, 764, 750, 718 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{15}NO$: 177.1154. Found: 177.1156.

Procedure for Attempted Low Temperature Generation/Trapping of (*E*)-cyclooct-2-enone.[13,14] A borosilicate tube was charged with a stir bar and (*Z*)-cyclooct-2-enone (0.033 g, 0.27 mmol). A volume of 5.4 mL dichloromethane was added and the volume was marked on the tube. An excess of 1-2 mL of solvent was then added to the tube. The tube was capped with a septum and was purged with stirring using a nitrogen

(13) For examples of low temperature generation/trapping experiments with (*E*)-cycloalkenones, see: (a) Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051. (b) Noyori, R.; Watanabe, A.; Katô, M. *Tetrahedron Lett.* **1968**, *52*, 5443. (c) Katô, M.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1460.

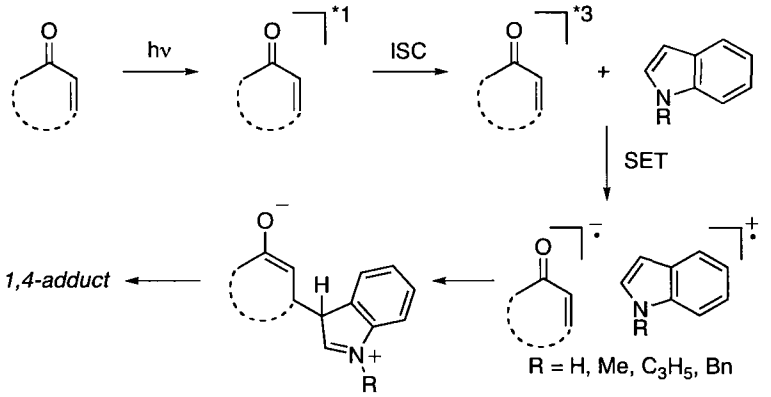
(14) For examples of low temperature generation/trapping experiments with (*E*)-cycloalkenes, see: (a) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Chem. Commun.* **1981**, 1031. (b) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 983. (c) Steinmetz, M. G.; Seguin, K. J.; Udayakumar, B. S.; Behnke, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 6601.

balloon and an outlet until the solvent evaporated to the volume marked. The solution was cooled to –75 °C and was then placed on a stir-plate and allowed to stir between two exposure panels each equipped with four 8W UV-A bulbs for 20 minutes, maintaining cooling.[15] Irradiation was then stopped, and a heterogeneous mixture of indole (0.034 g, 0.242 mmol) in 1.0 mL dichloromethane, pre-cooled to –75 °C, was then added to the borosilicate tube. The reaction mixture was then allowed to gradually warm to room temperature while stirring for 45 minutes. No reaction was observed by TLC. The solvent was evaporated under reduced pressure. ^{1}H NMR of the crude reaction mixture indicated only a mixture of starting materials.

Procedure for Oxygen-Induced Quenching of Enone Triplet. A borosilicate tube was charged with a stir bar, cyclohept-2-enone (0.025 g, 0.23 mmol) and indole (0.029 g, 0.25 mmol). A volume of 4.5 mL dichloromethane was added to the tube and stirred open to the atmosphere for 1 minute. The tube was capped with a septum and was then placed on a stir-plate and allowed to stir between two exposure panels each equipped with four 8W UV-A bulbs for 18 hours. No indole adduct was observed by TLC. The solvent was evaporated under reduced pressure. ^{1}H NMR of the crude reaction mixture indicated a mixture of starting materials as well as a modest amount of dimers of cyclohept-2-enone.[13a]

Discussion of Mechanistic Alternatives

Scheme 2. Proposed photoinduced electron transfer mechanism for the 1,4-addition of indoles to enones



We favor the PET mechanism presented in Scheme 2 over a [2+2] cycloaddition/cyclobutane ring opening sequence that could afford the same products. Such a mechanistic scenario is not consistent with the observed electronic effects on the indole moiety. In addition, the regiochemistry observed in enone [2+2] cycloadditions usually favors formation of the cycloadduct in which the carbonyl and the electron rich group are in a head to

(15) The sample was immersed in a 95% ethanol bath contained in a 5L quartz Dewar and cooled to –75 °C by an FTS Systems cold finger apparatus.

tail configuration, which could not form the formal 1,4-adduct upon cyclobutane ring opening. During the course of these studies, we have not observed formation of [2+2] cycloadducts between indoles and enones.[16]

In specific cases, other mechanisms could also be operating. For example, cyclohept-2-enone and cyclooct-2-enone could also afford the observed 1,4-addition product through an *E*-cycloalkenone intermediate.[13] However, low temperature generation/trapping experiments have been performed with *E*-cyclooct-2-enone and have resulted in recovery of the starting materials,[13] suggesting *E*-cycloalkenones are not likely intermediates for these substrates. We also speculate that reaction of methyl vinyl ketone (MVK) via a Bauld-Steckhan type cycloaddition mechanism,[17] namely a formal hetero-Diels-Alder reaction of MVK with the indole radical cation (affording the 1,4-adduct upon hydrolysis), is unlikely and not consistent with the substrate scope of the reaction.

(16) For examples of [2+2] cycloadditions between *N*-acylindoles and alkenes, see: Weedon, A. C.; Zhang, B. *Synthesis* **1992**, 95 and references cited therein.

(17) (a) Bauld, N. L; Bellville, D. J.; Harirchian, B.; Lorenz, K. T.; Pabon, R. A. Jr.; Reynolds, D. W.; Wirth, D. D.; Chiou, H.-S.; Marsh, B. K. *Acc. Chem. Res.* **1987**, *20*, 371. (b) Mlcoch, J.; Steckhan, E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 412.

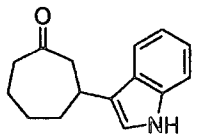
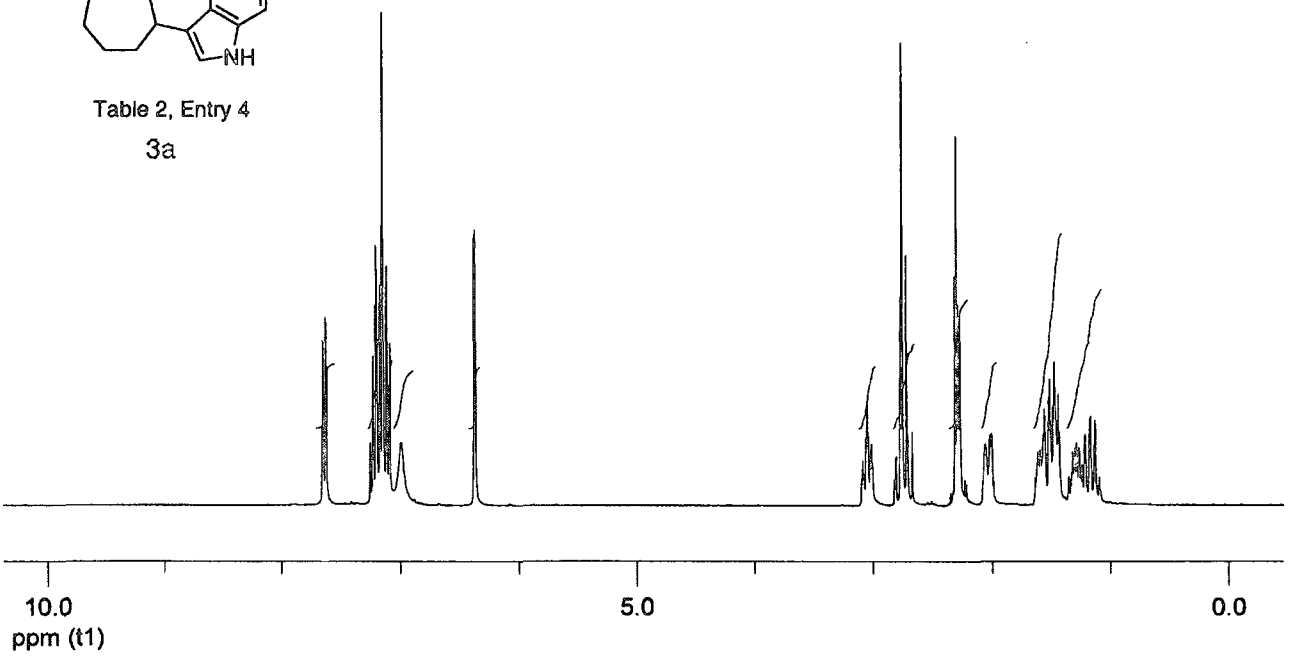
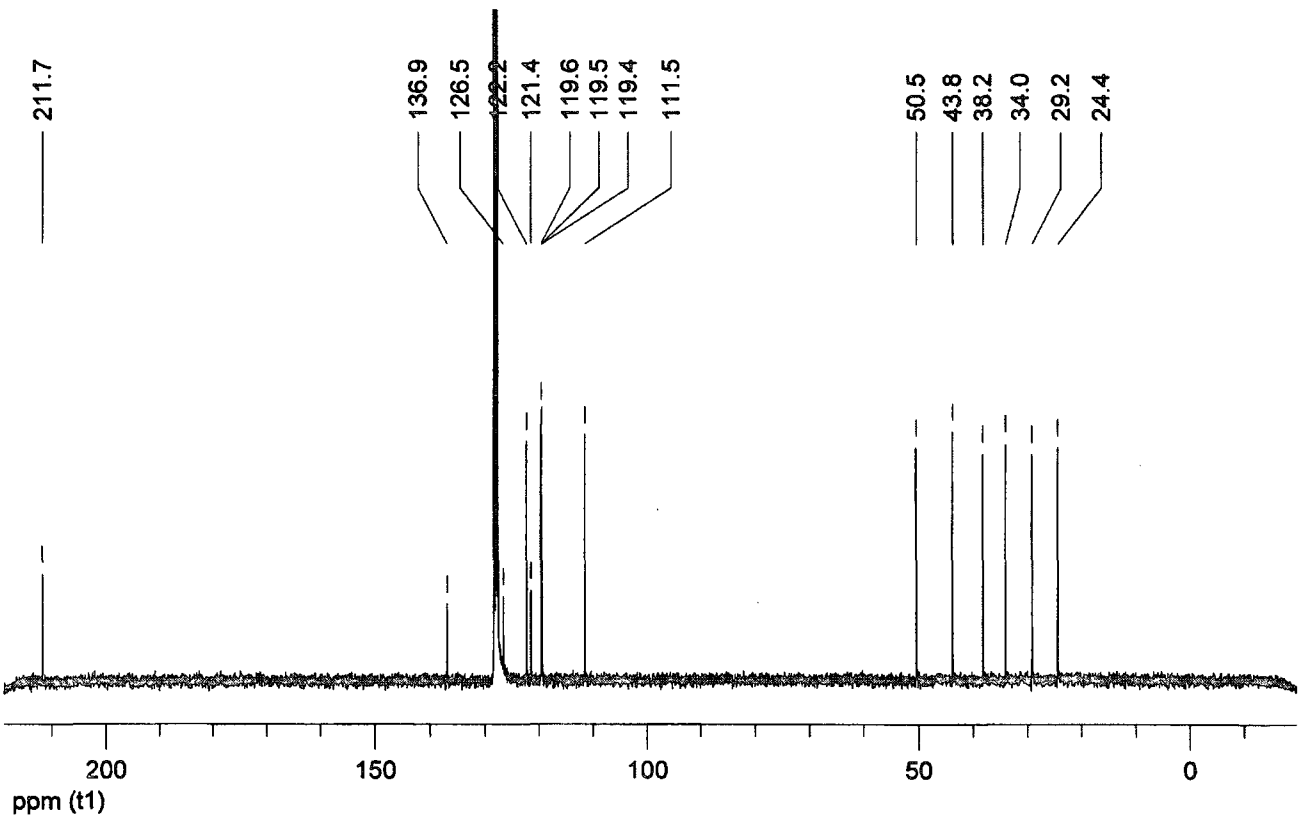


Table 2, Entry 4

3a





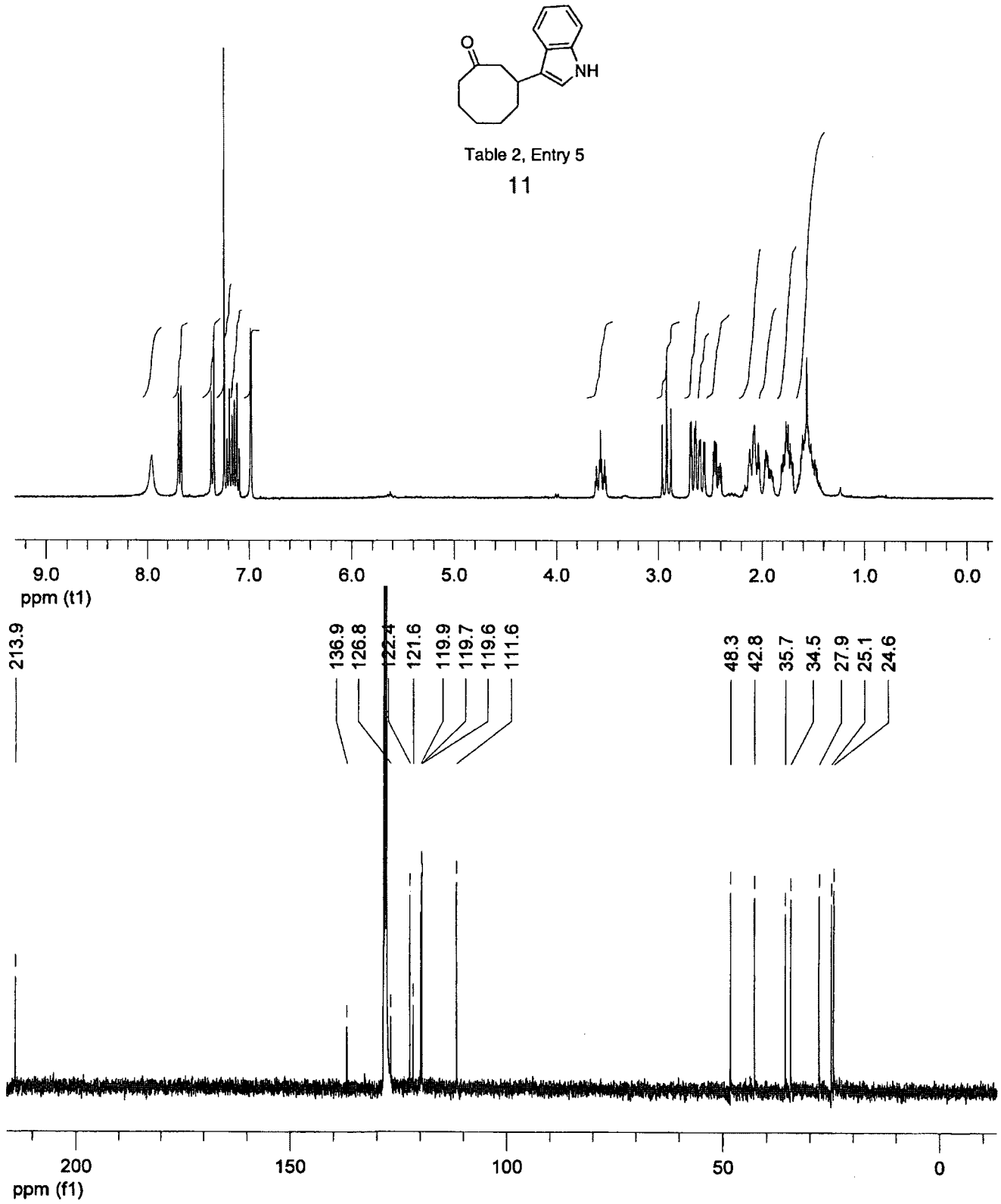
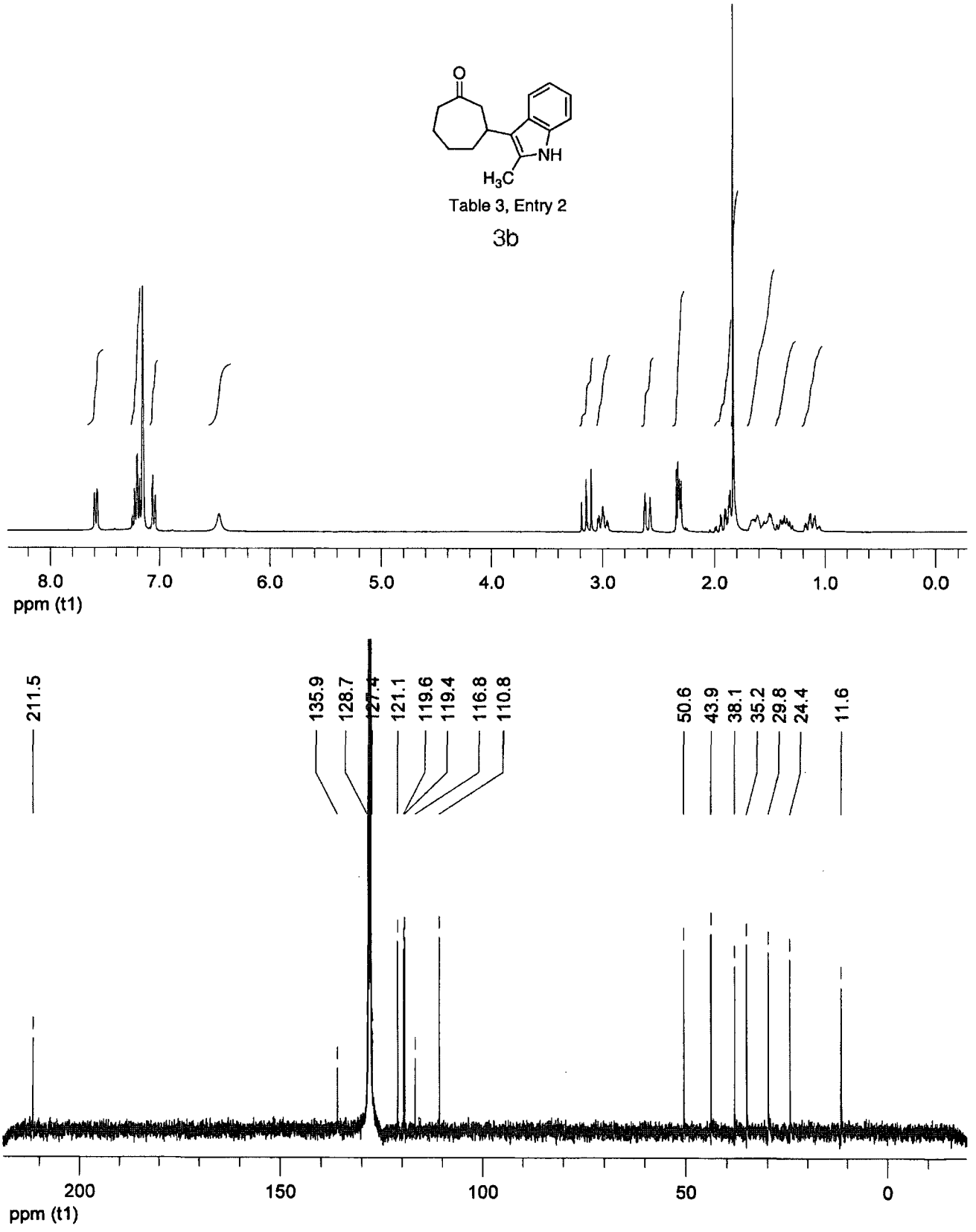
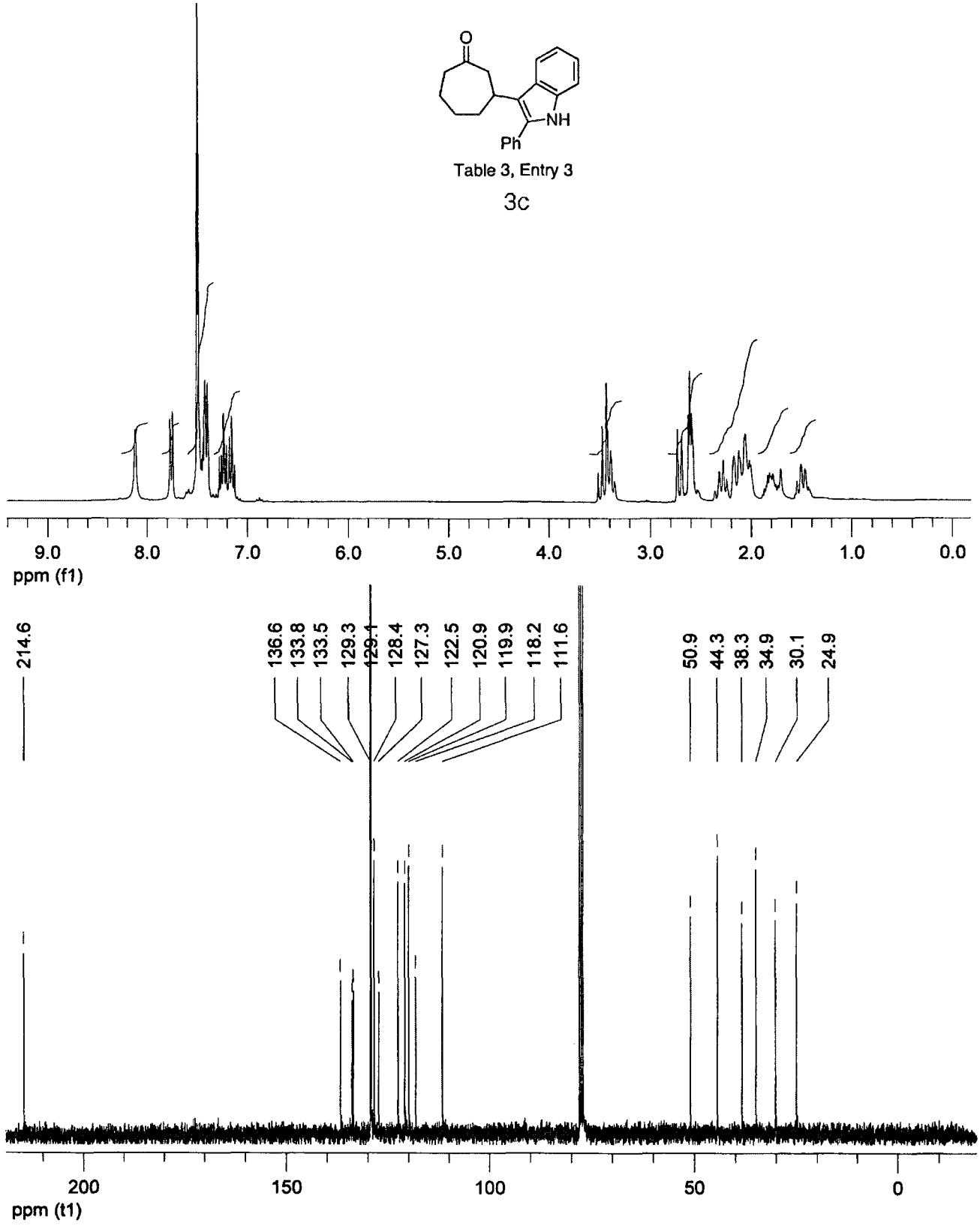


Table 2, Entry 5

11


O
NH
H_3C
Table 3, Entry 2
3b
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
211.5
135.9
128.7
127.4
121.1
119.6
119.4
116.8
110.8
50.6
43.9
38.1
35.2
29.8
24.4
11.6
200
150
100
50
0
ppm (t1)


O
NH
Ph
Table 3, Entry 3
3c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)
214.6
136.6
133.8
133.5
129.3
129.1
128.4
127.3
122.5
120.9
119.9
118.2
111.6
50.9
44.3
38.3
34.9
30.1
24.9
200
150
100
50
0
ppm (t1)

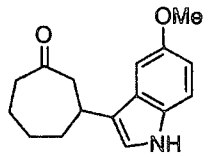
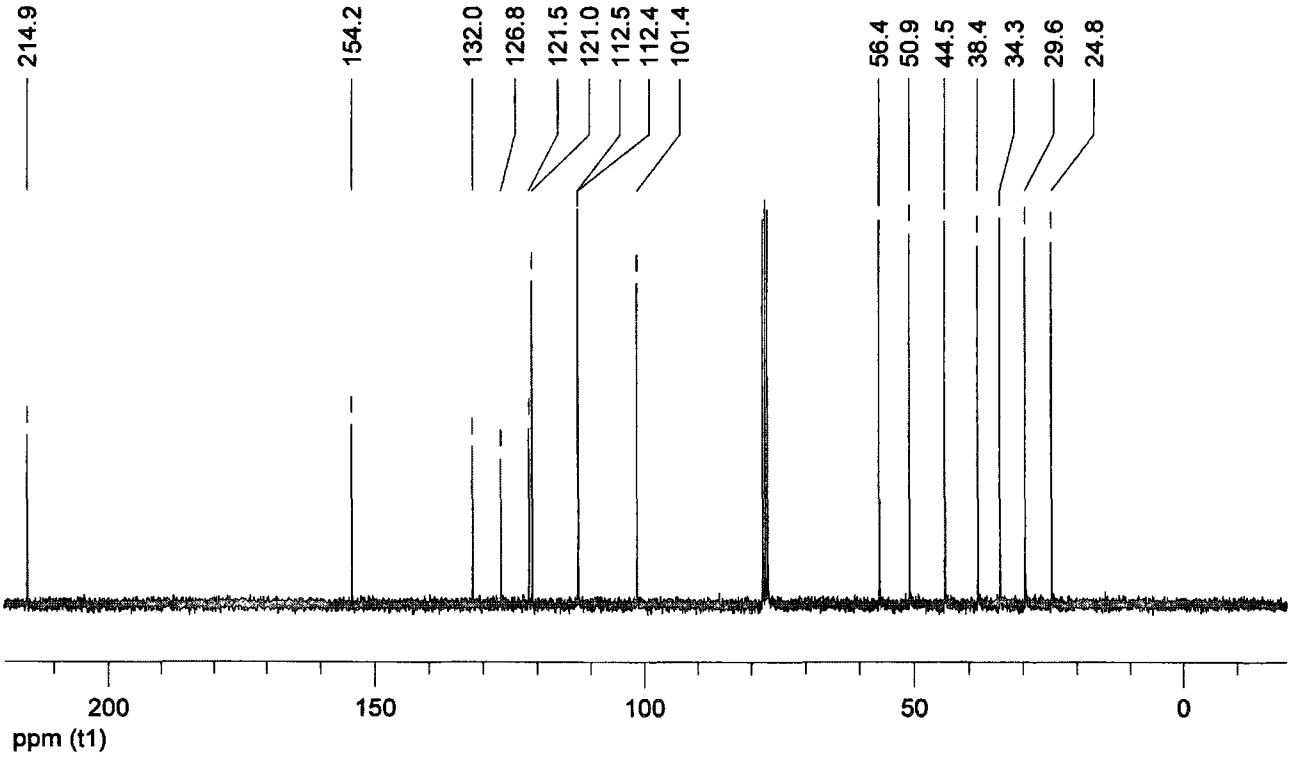


Table 3, Entry 4

3d



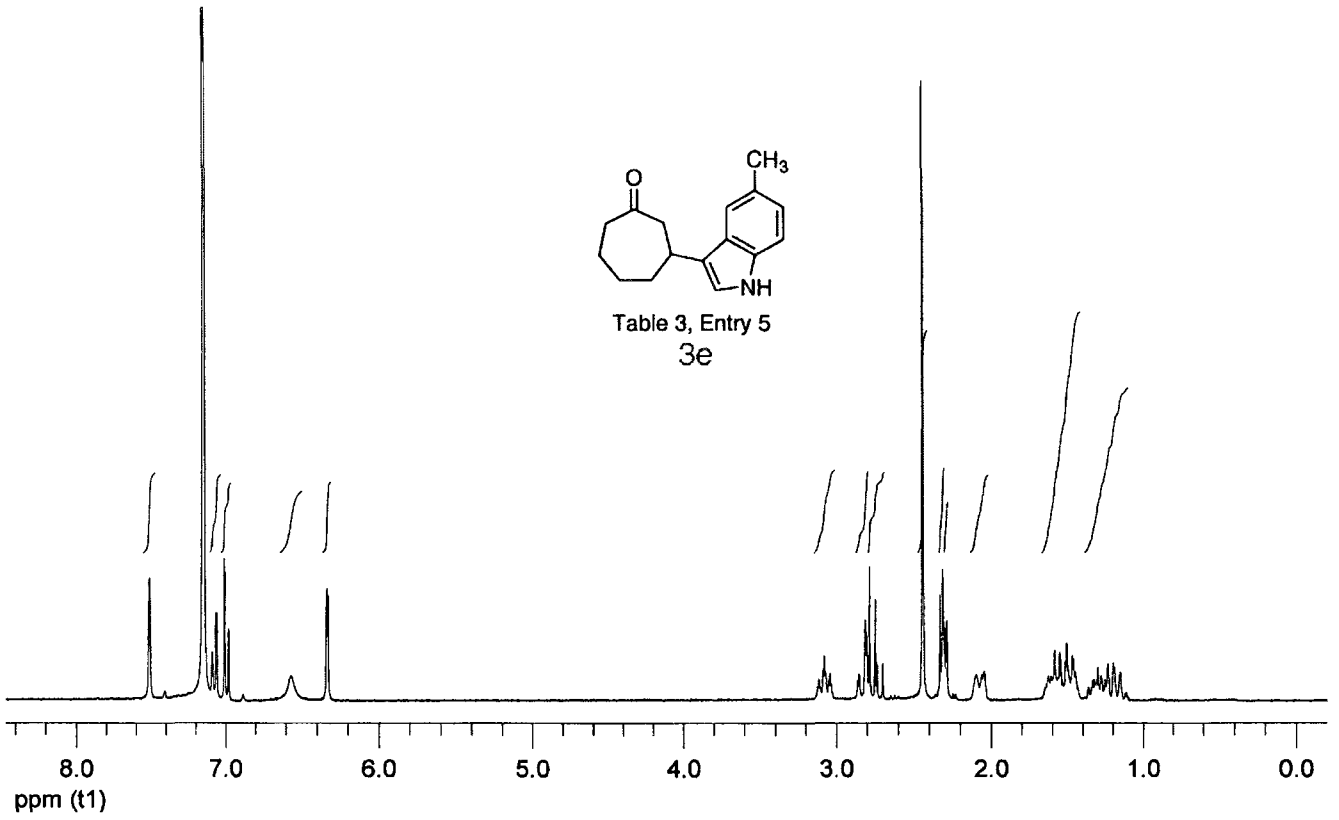
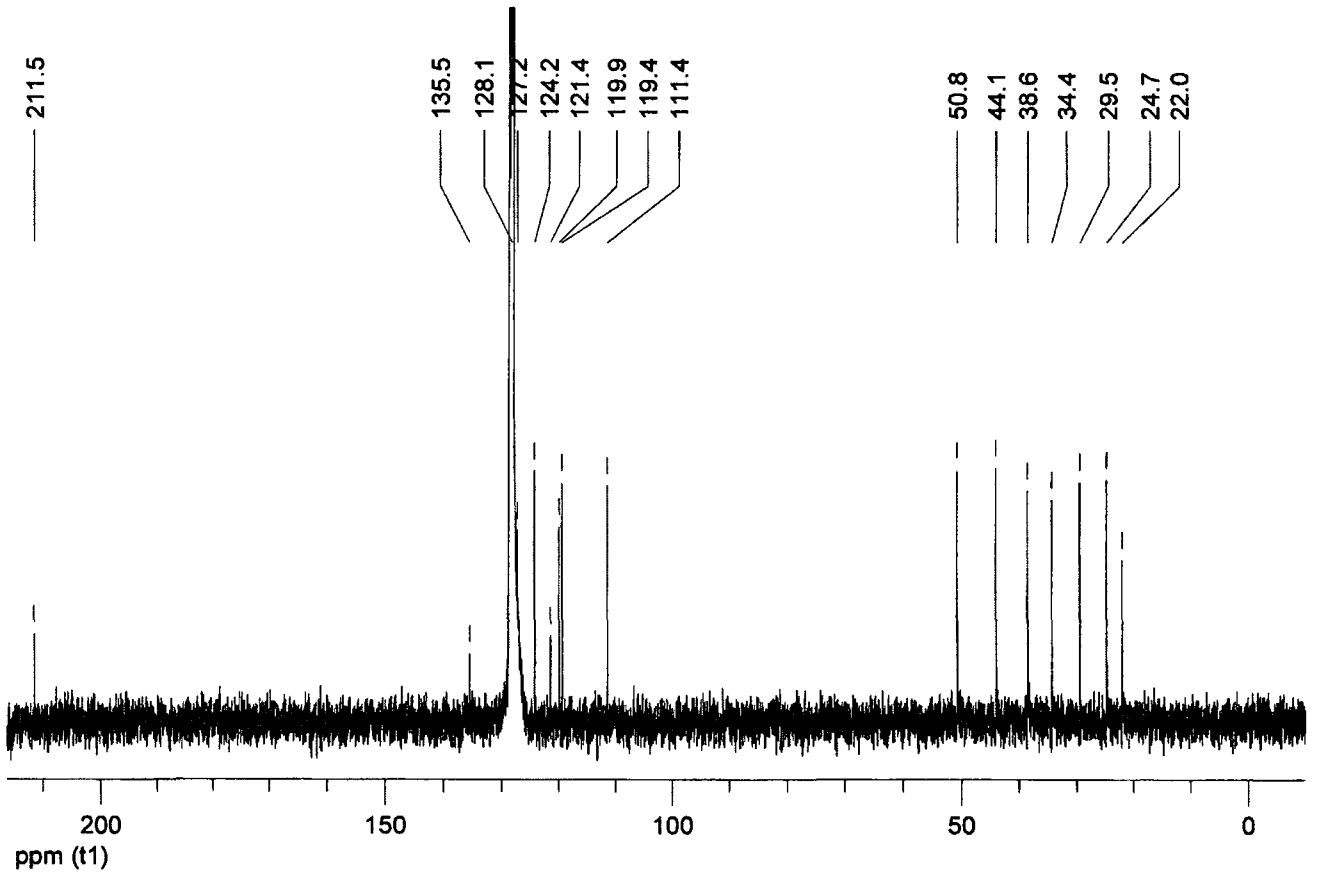


Table 3, Entry 5

3e



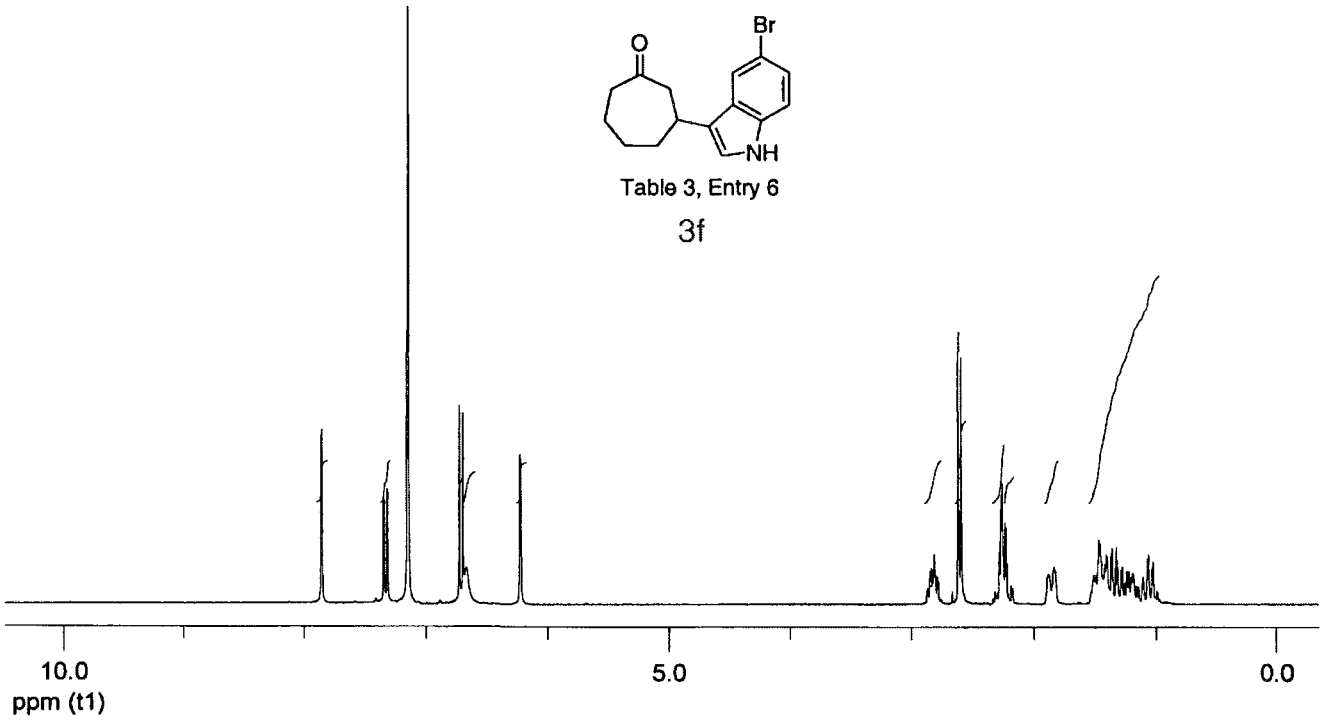
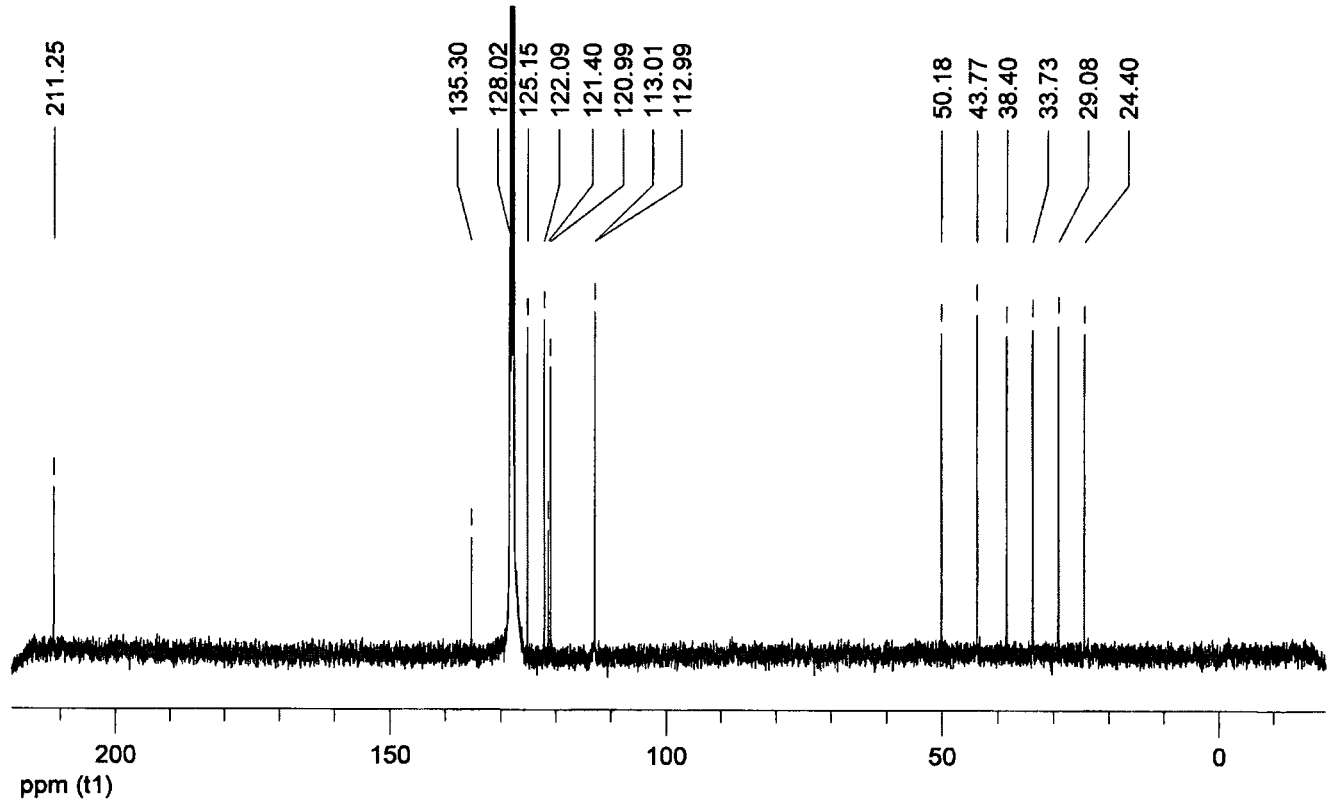


Table 3, Entry 6

3f



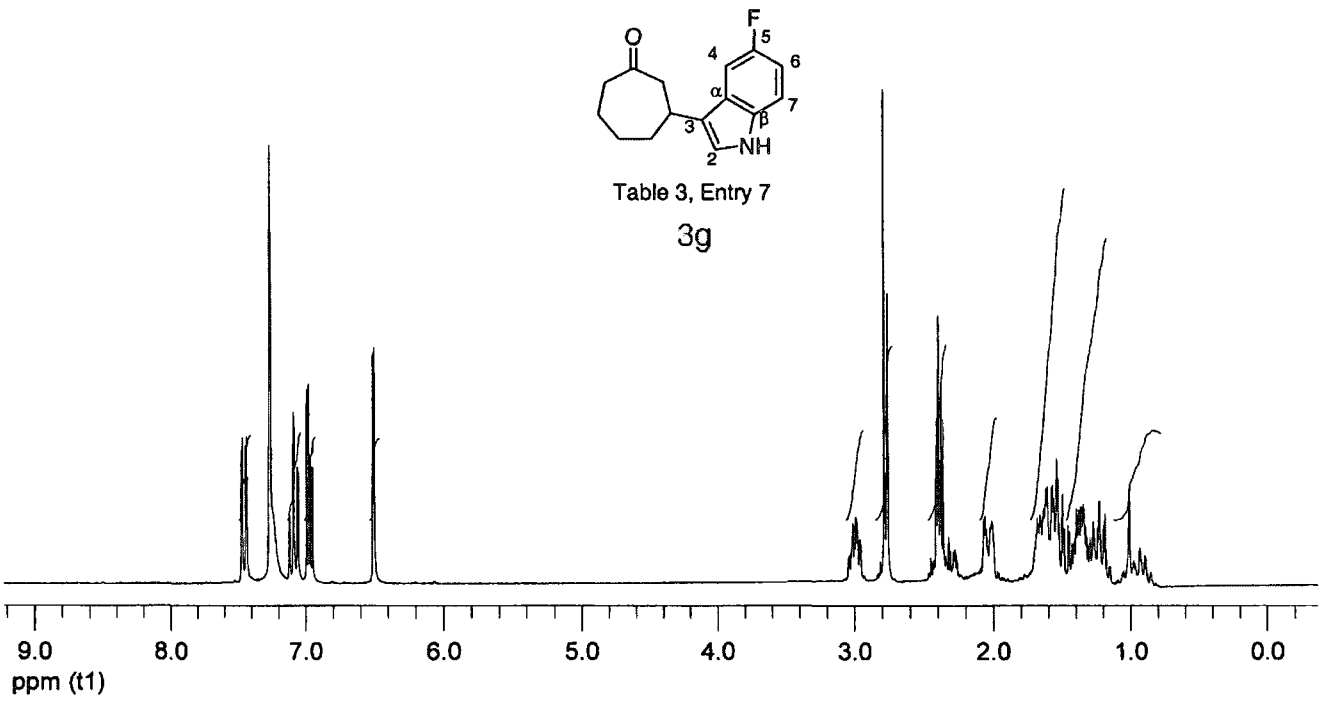
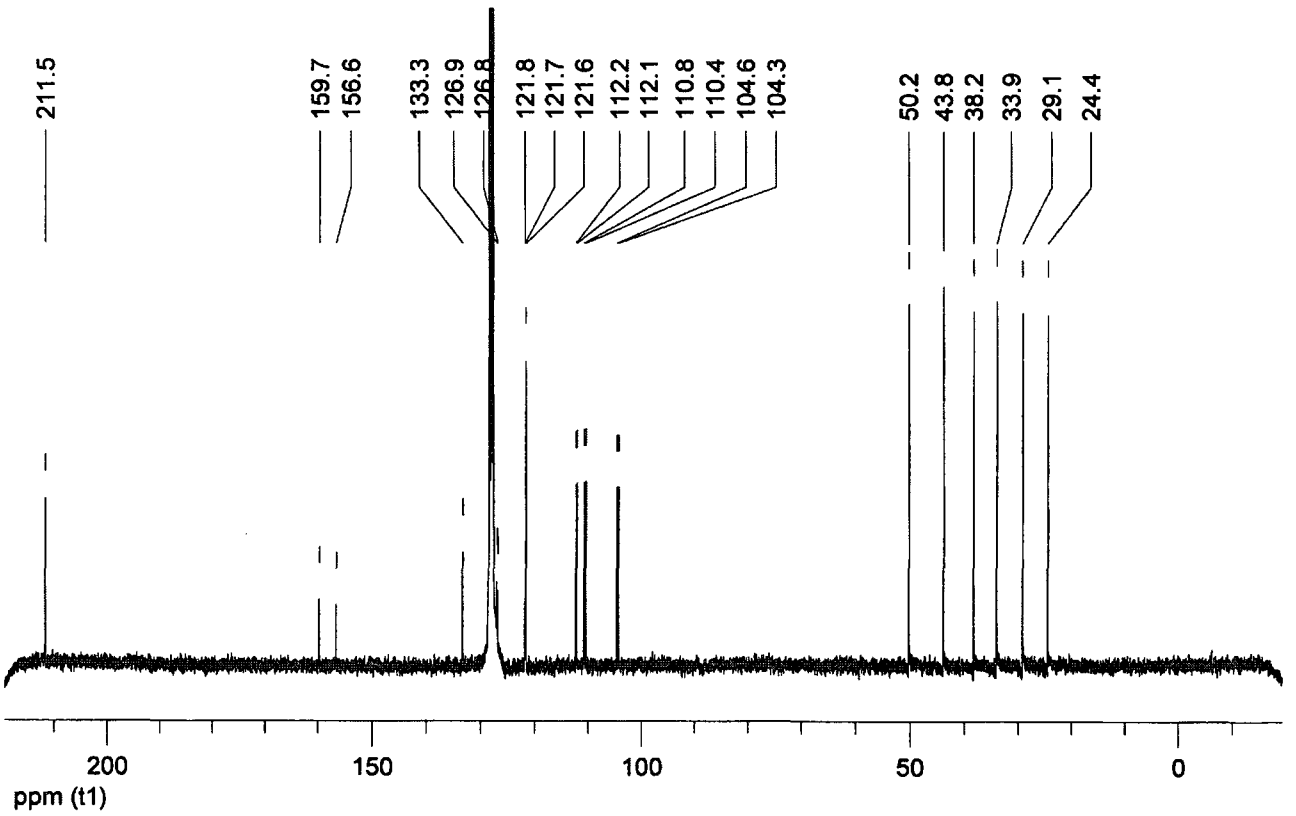


Table 3, Entry 7

3g



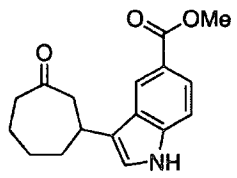
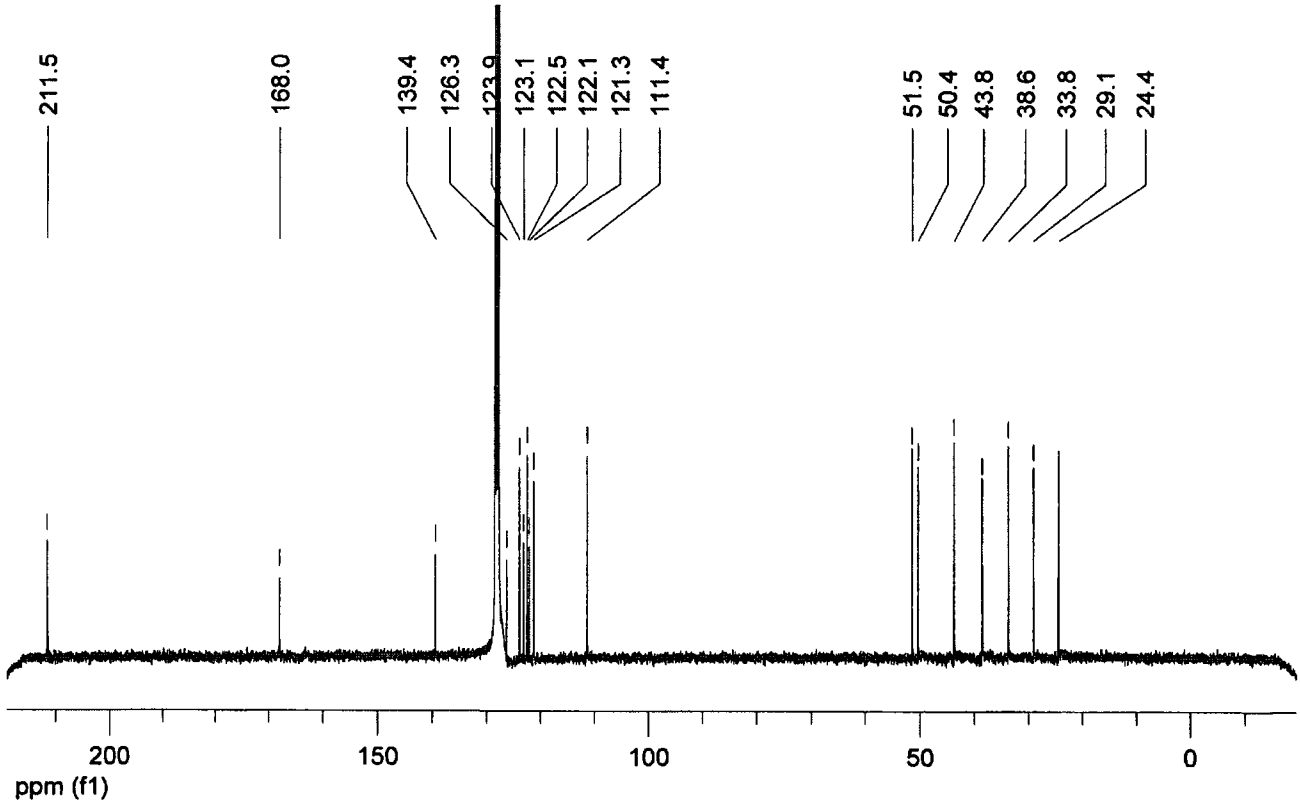


Table 3, Entry 8

3h



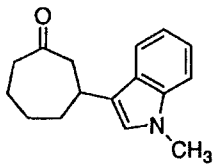
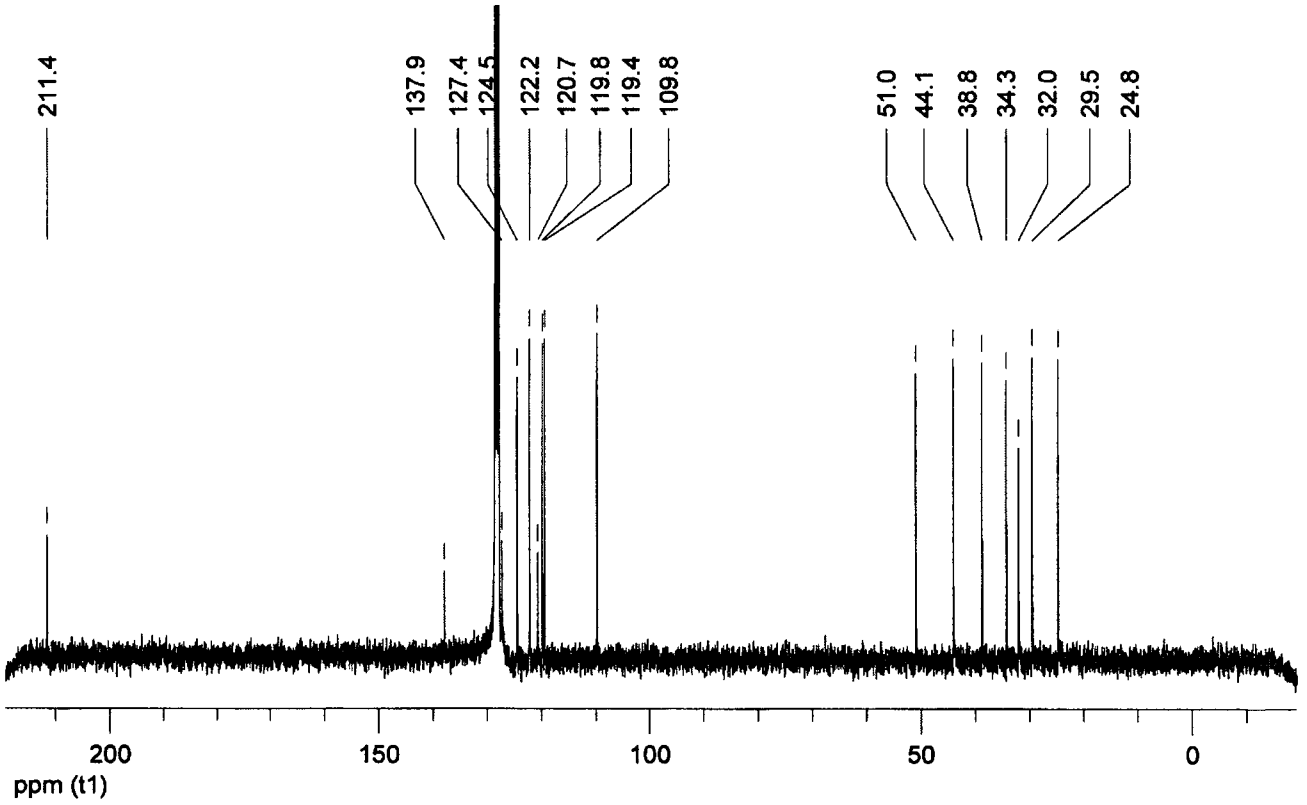


Table 4, Entry 2

3k



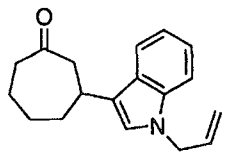
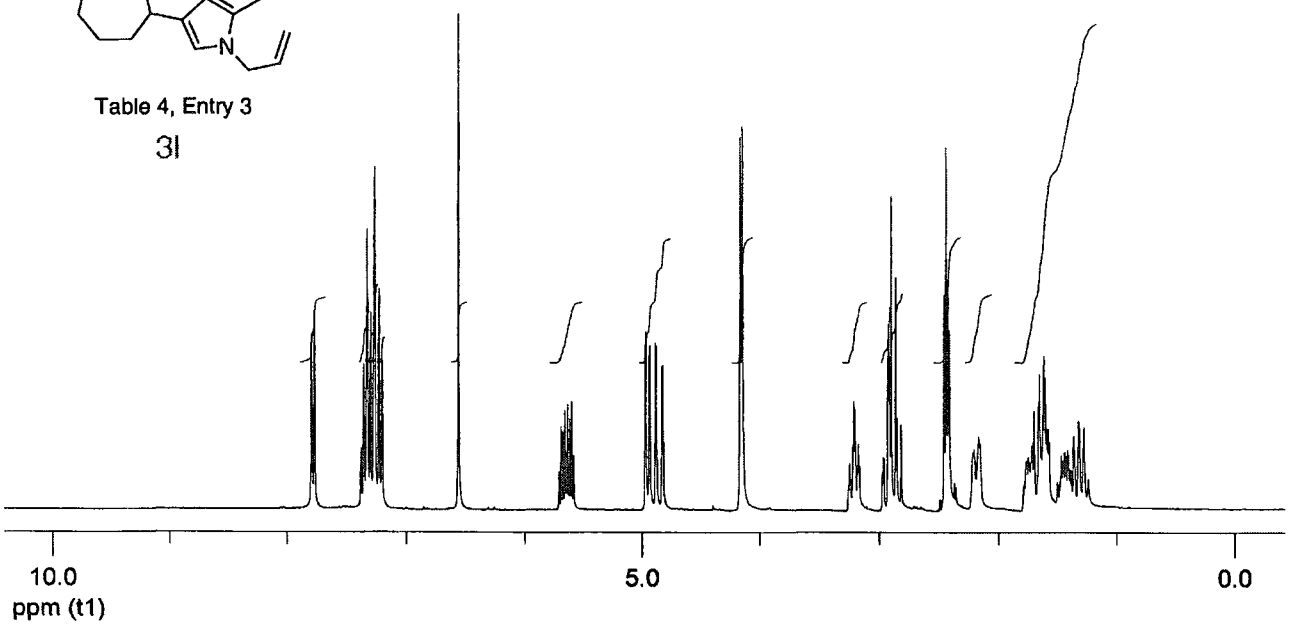
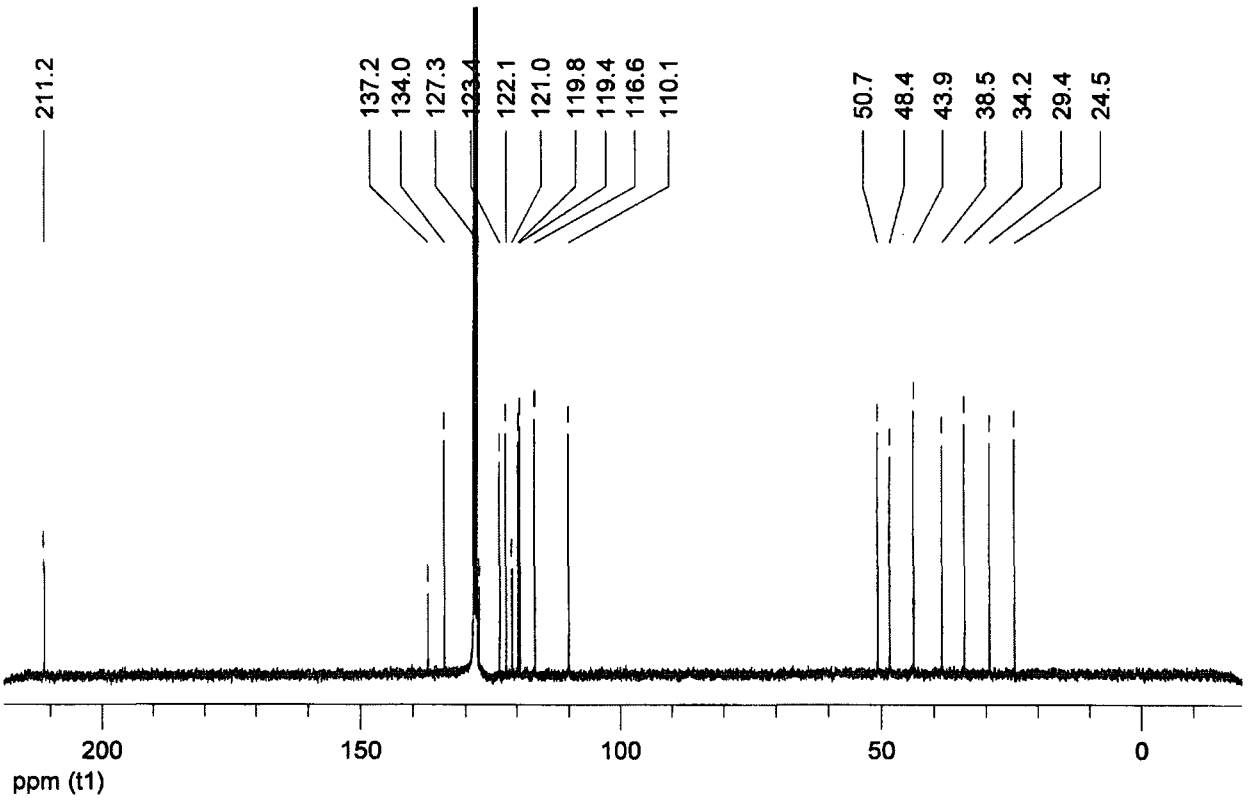


Table 4, Entry 3

3l





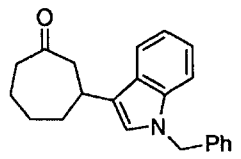
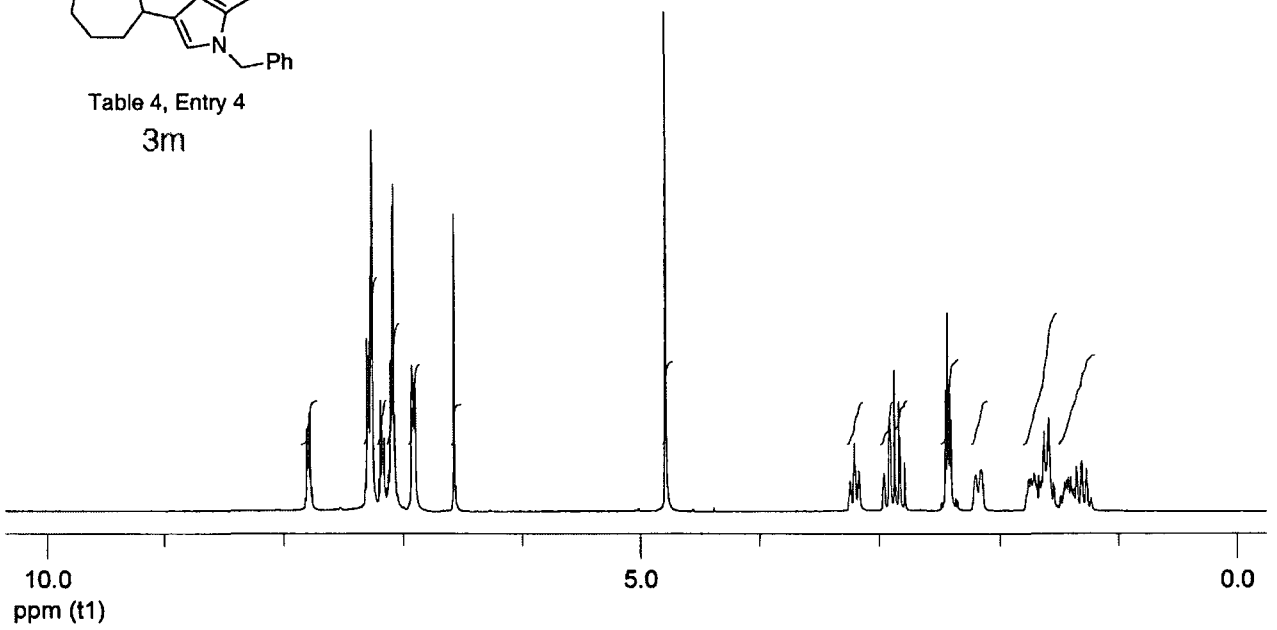
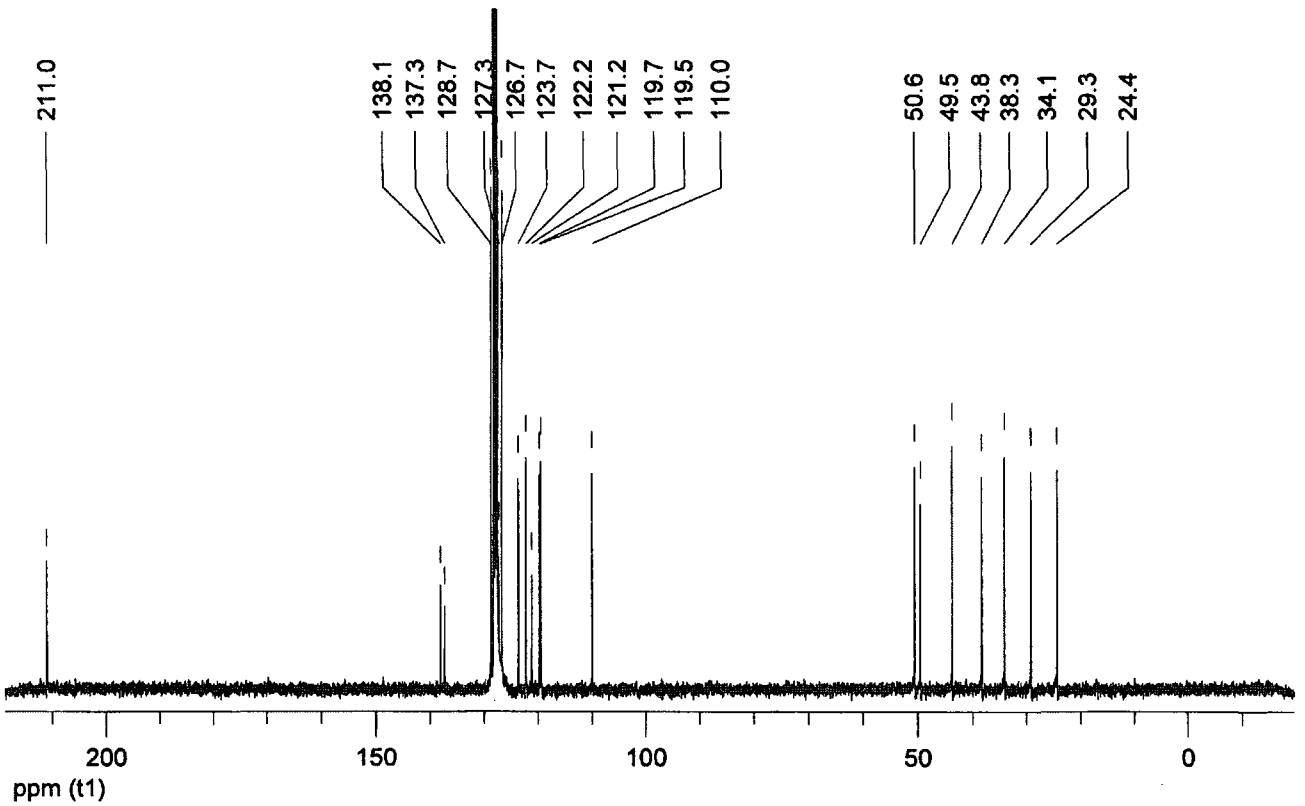
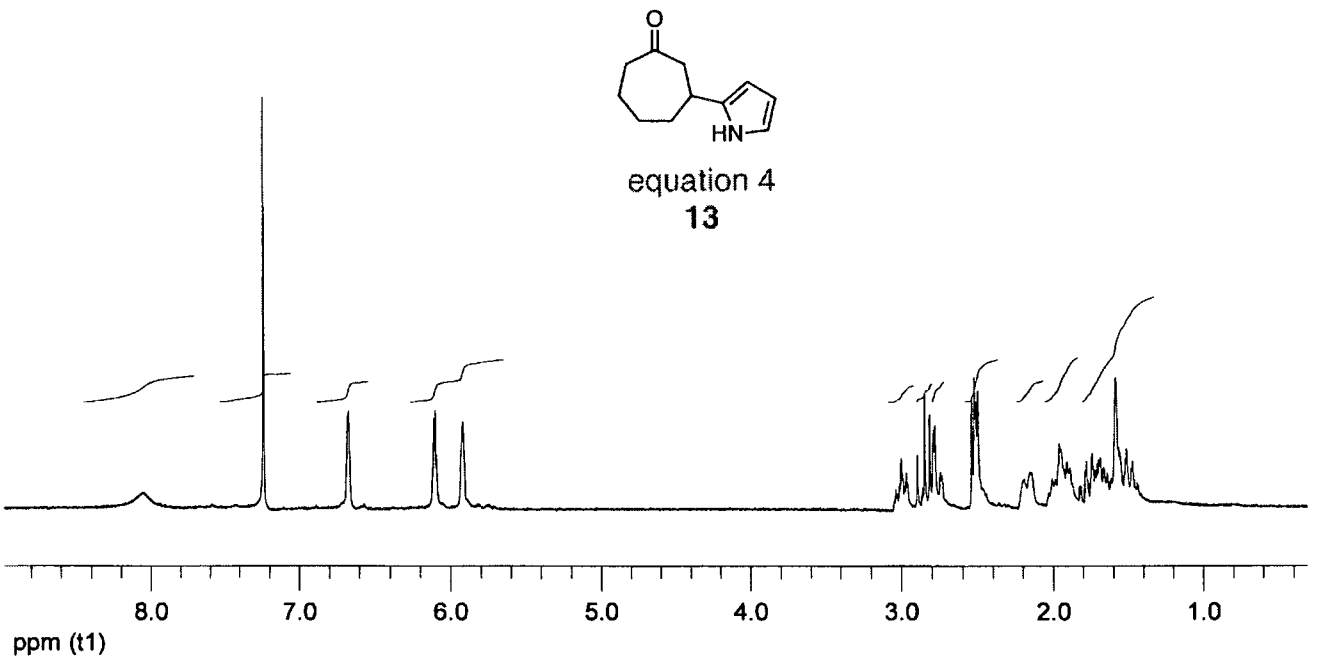


Table 4, Entry 4

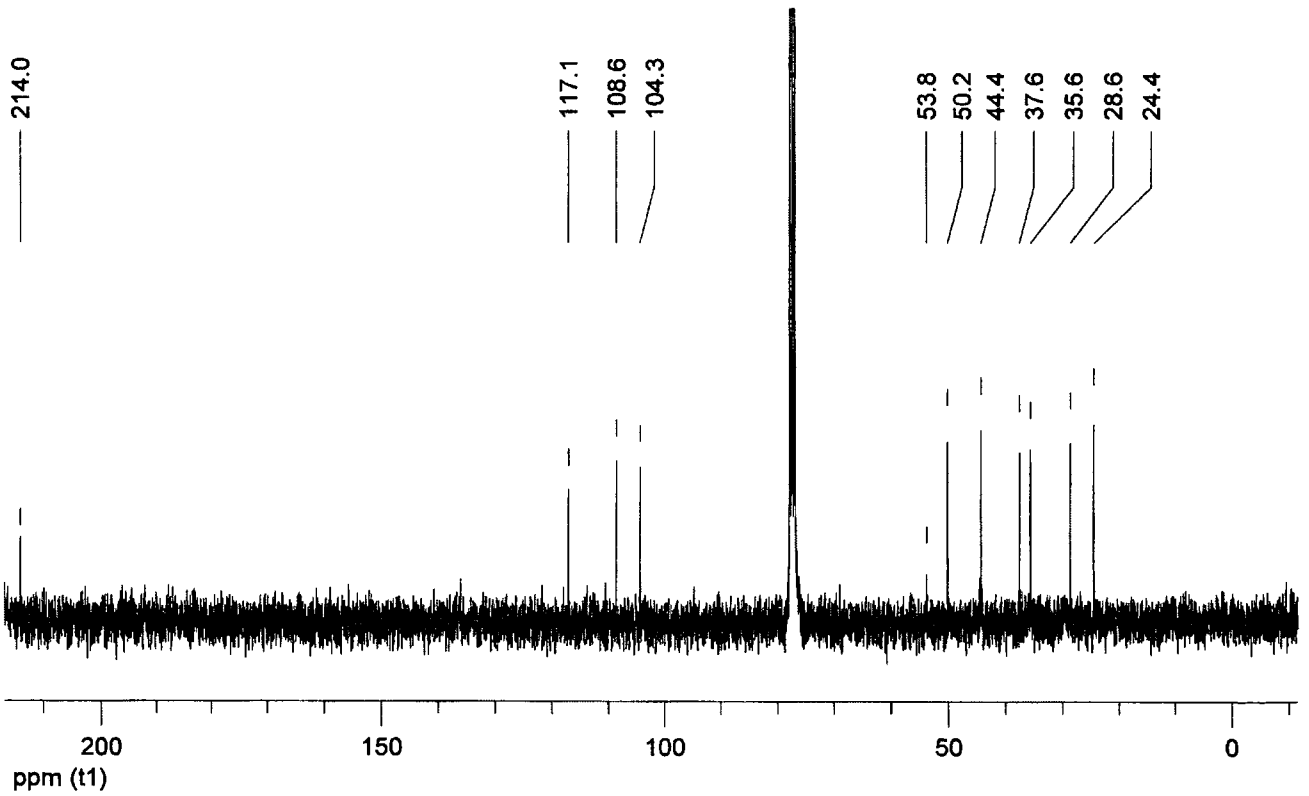
3m



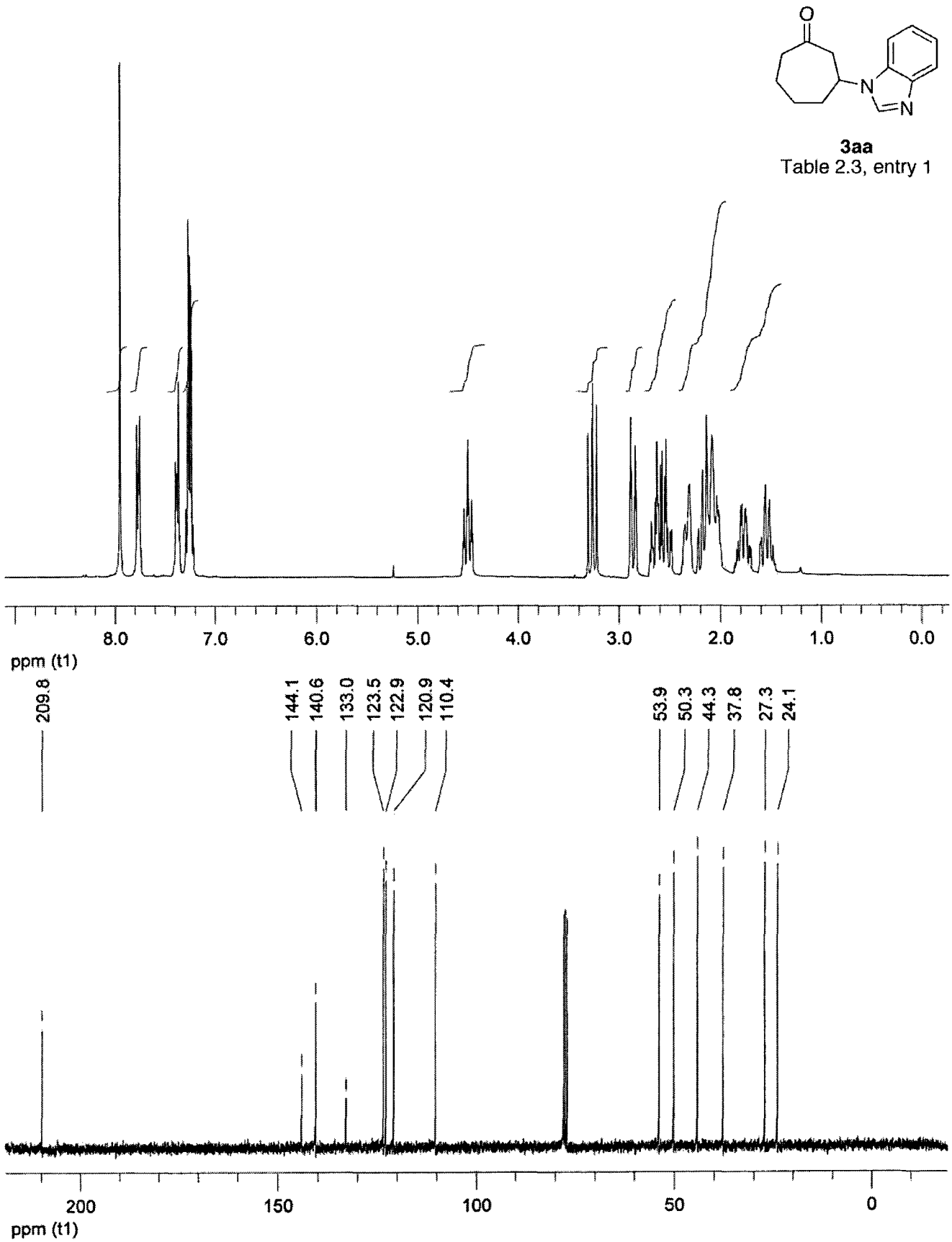




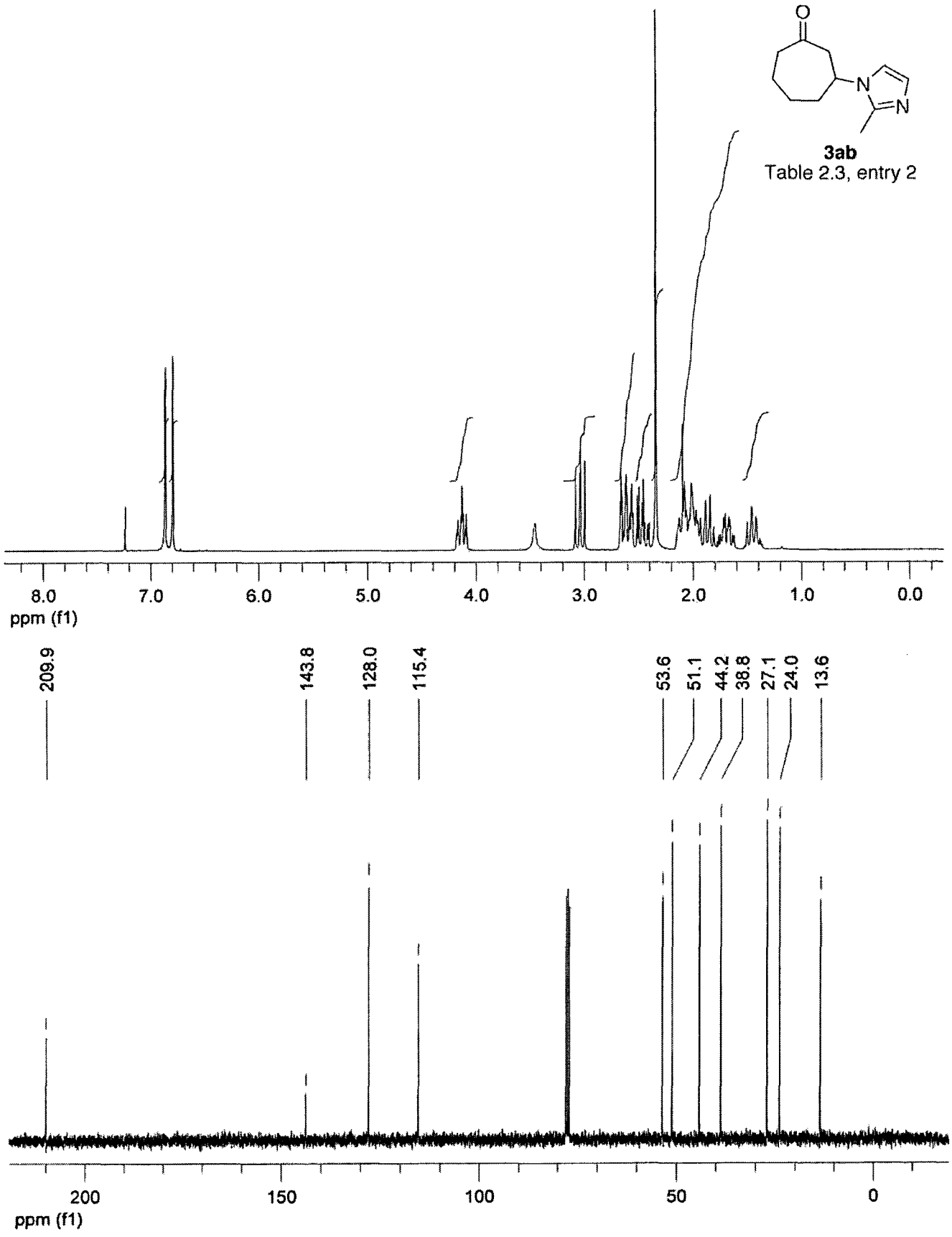
equation 4
13

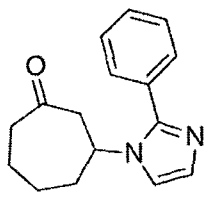


Appendix II. Supporting Information for Chapter 2.

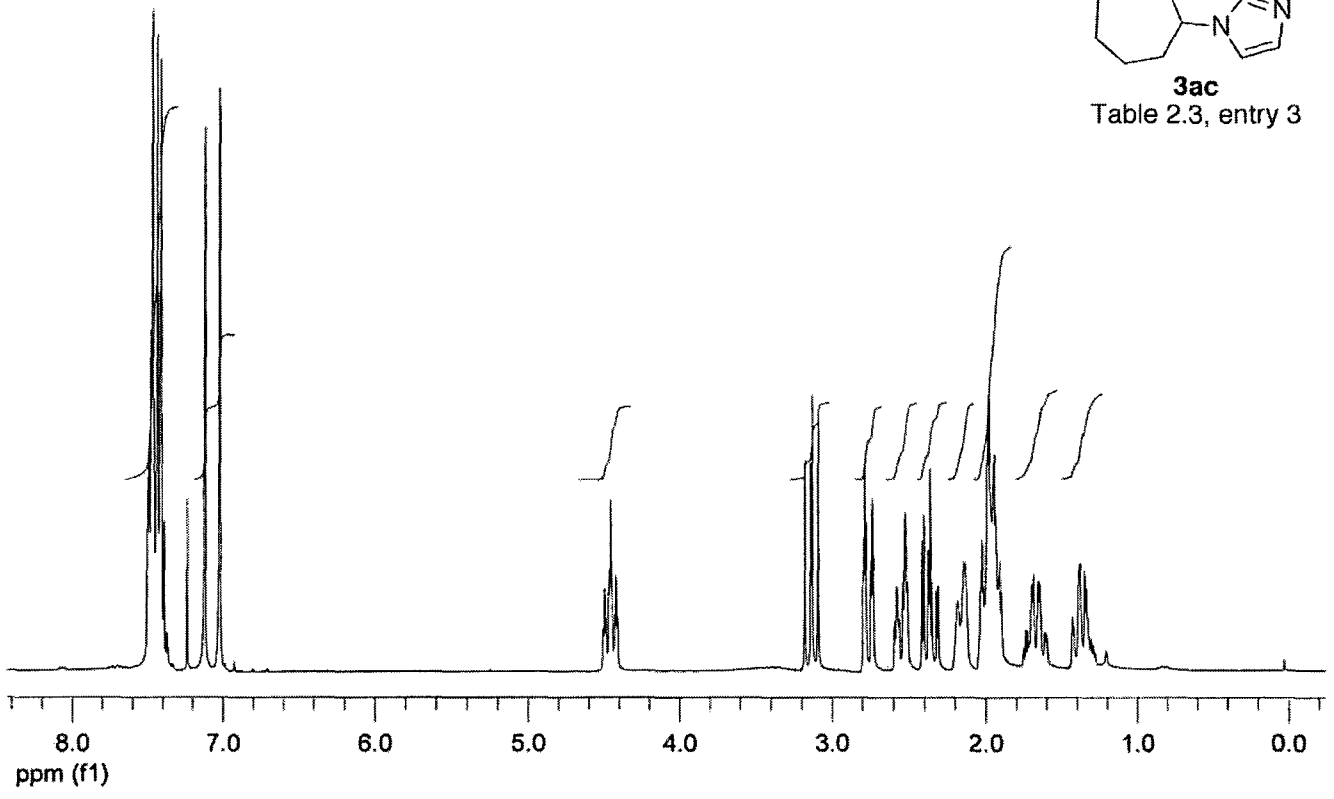


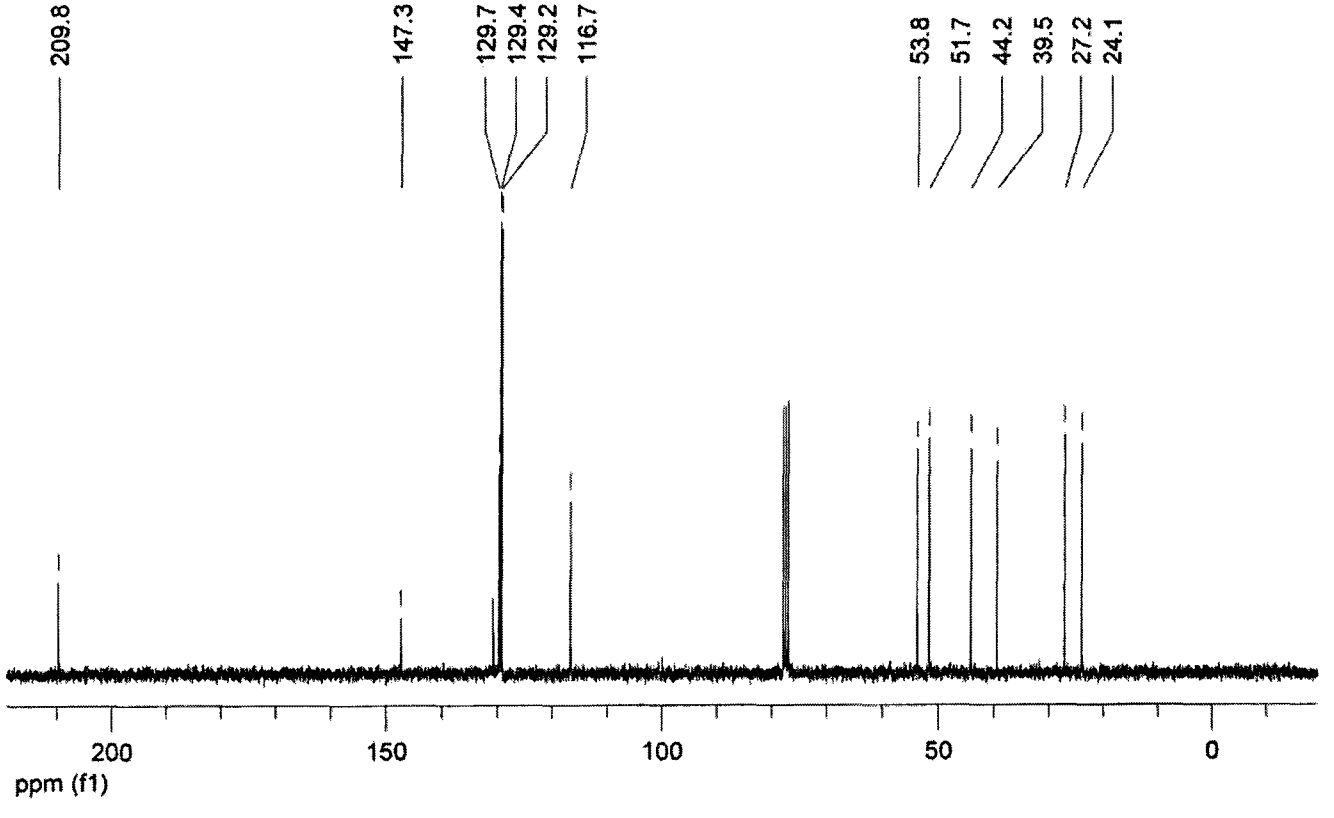
3aa
Table 2.3, entry 1

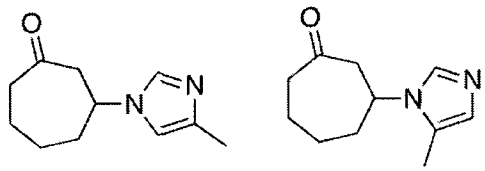

O
N
N
3ab
Table 2.3, entry 2
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)
209.9
143.8
128.0
115.4
53.6
51.1
44.2
38.8
27.1
24.0
13.6
200
150
100
50
0
ppm (f1)



3ac
Table 2.3, entry 3



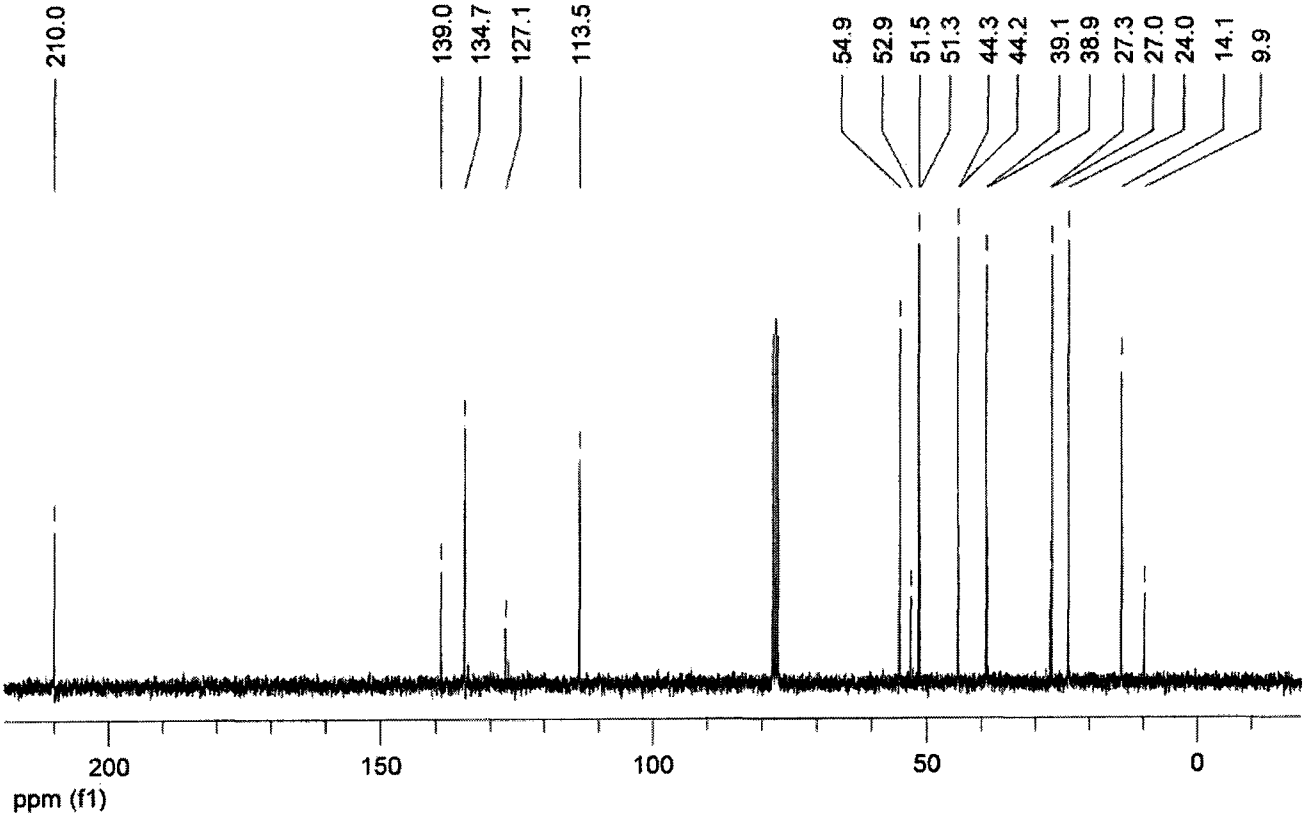


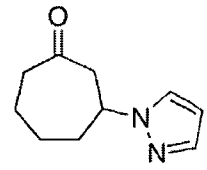


7 : 1

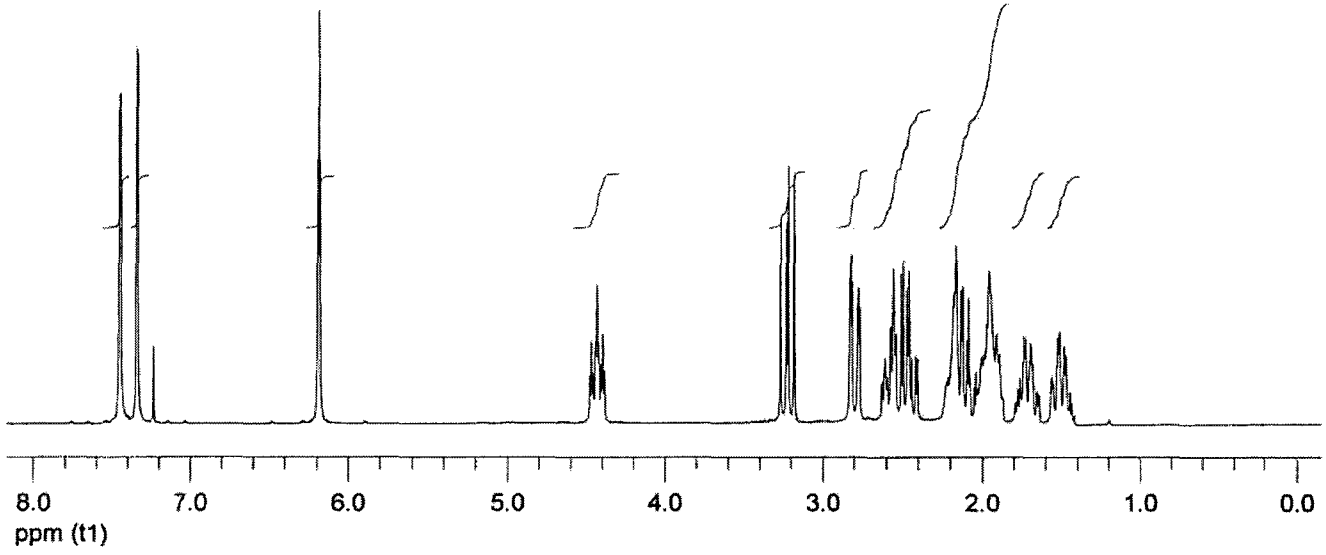
3ad

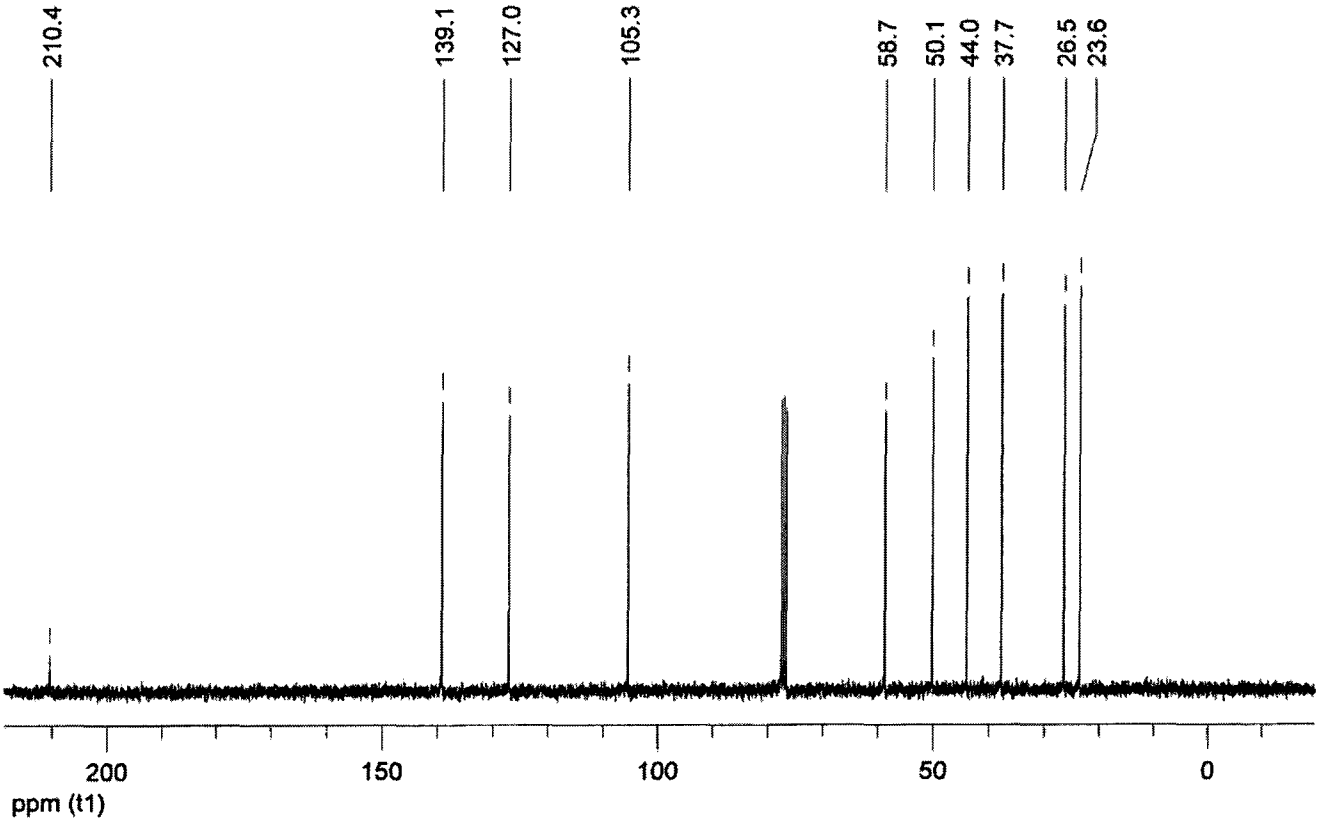
Table 2.3, entry 4

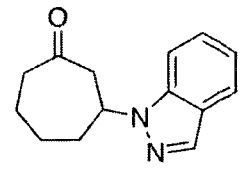




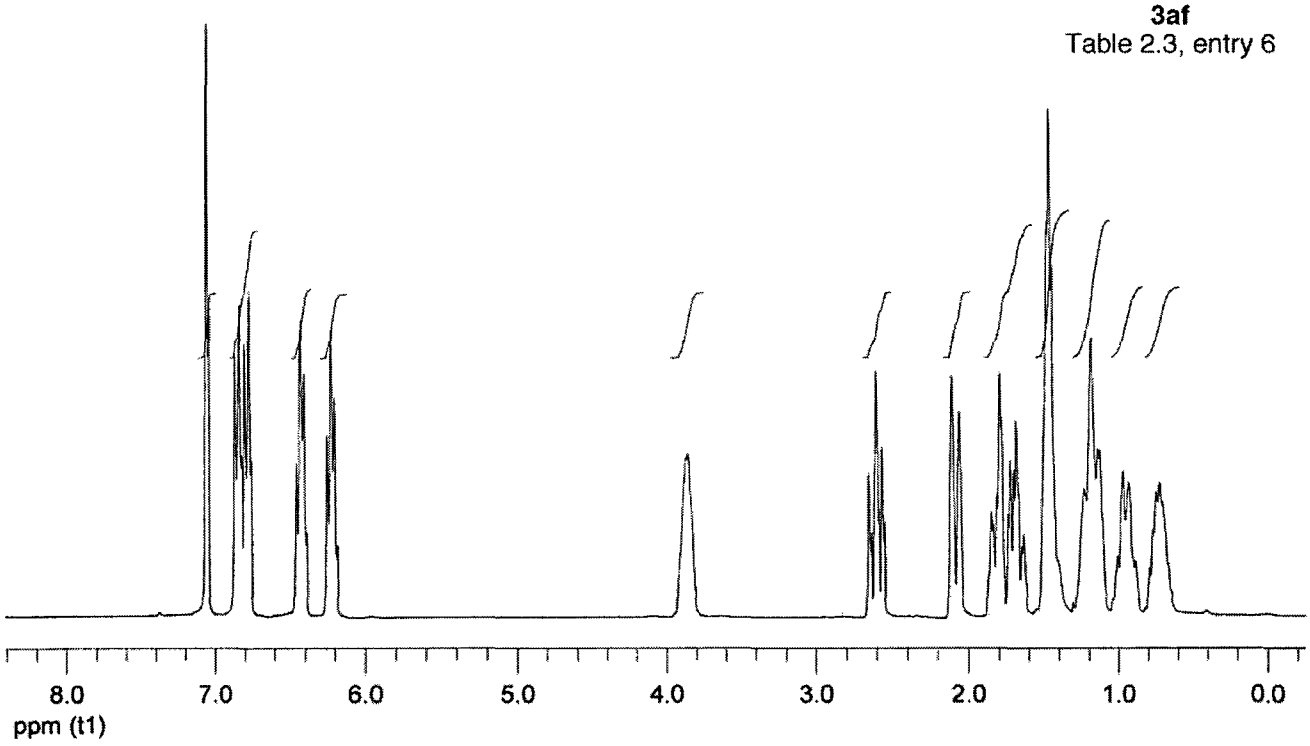
3ae
Table 2.3, entry 5

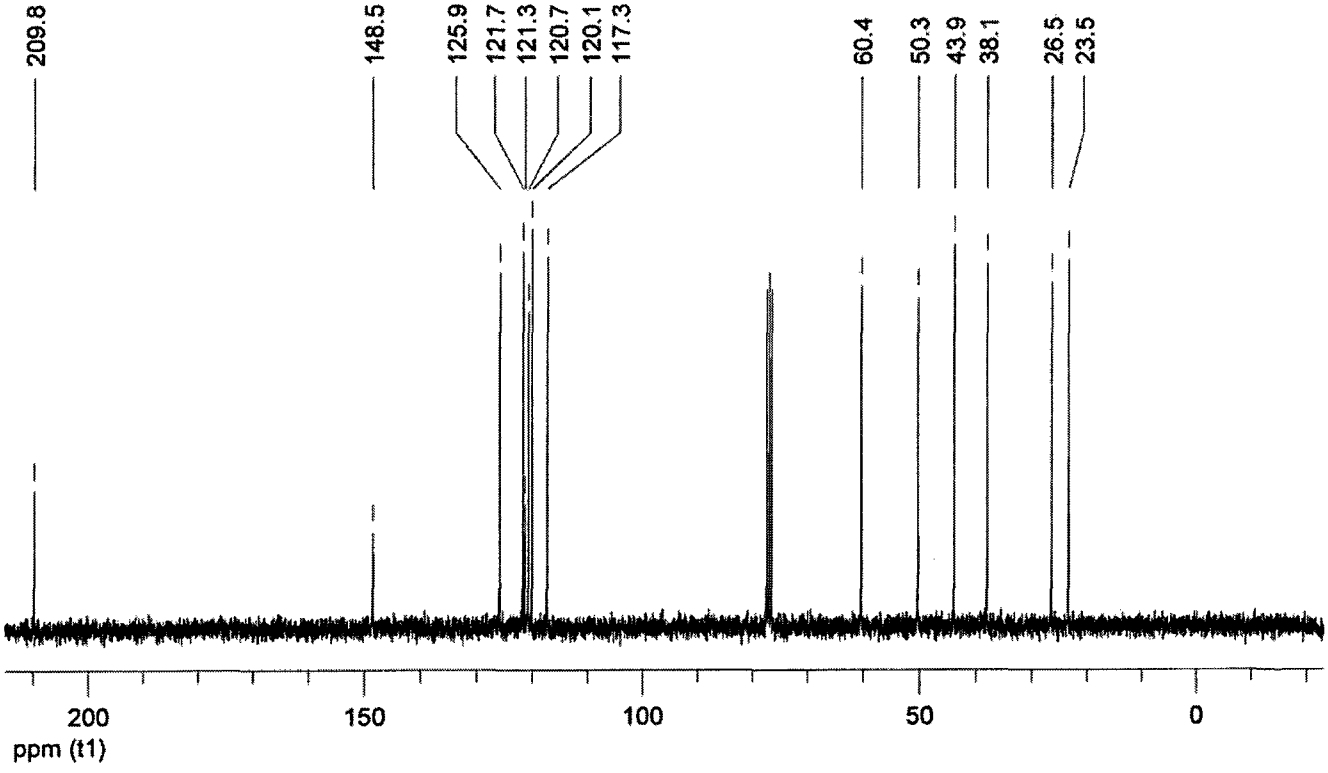


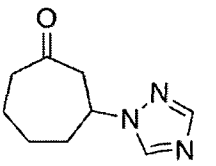




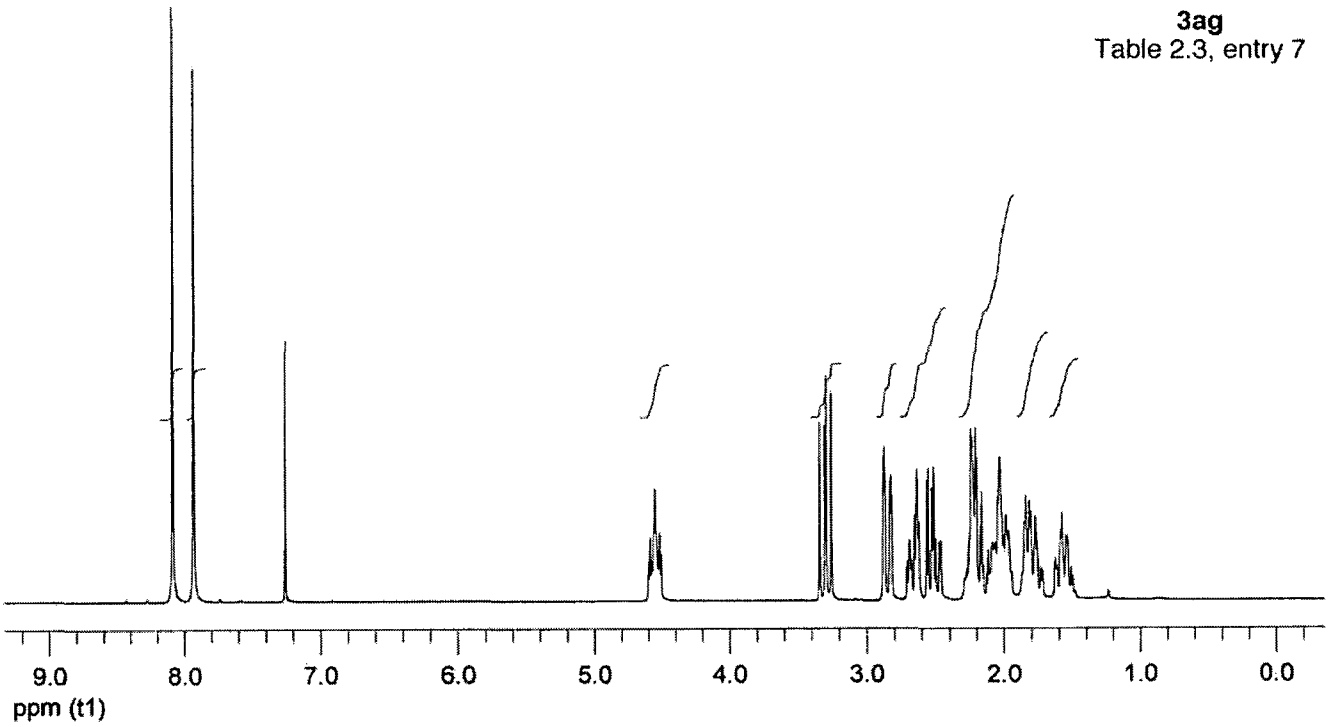
3af
Table 2.3, entry 6

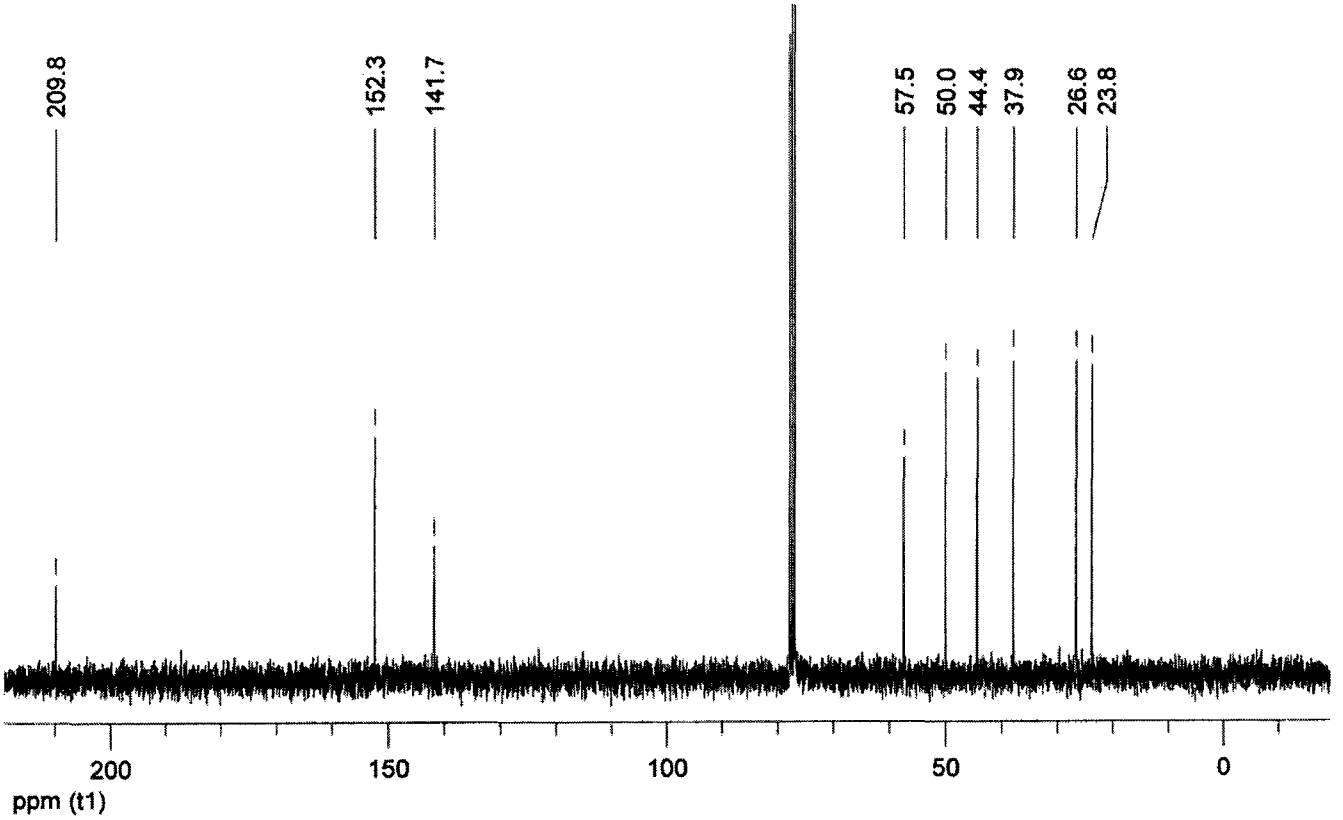


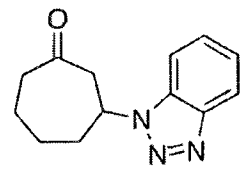




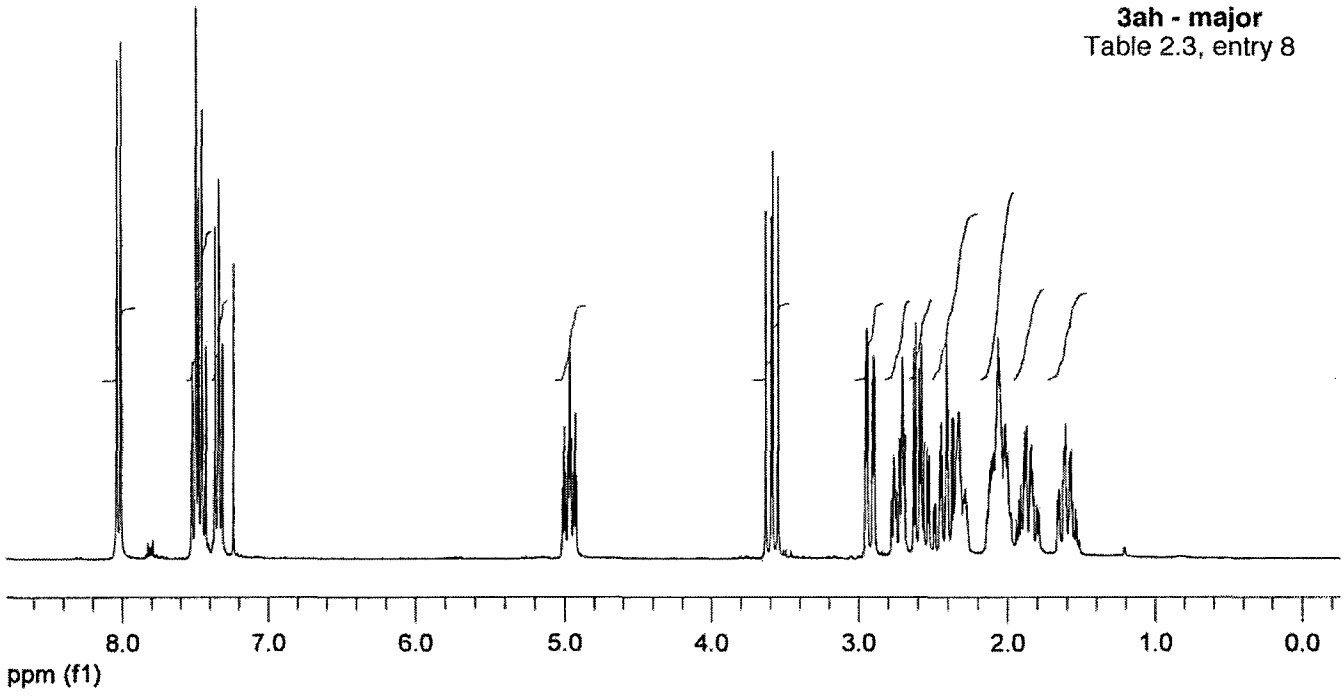
3ag
Table 2.3, entry 7

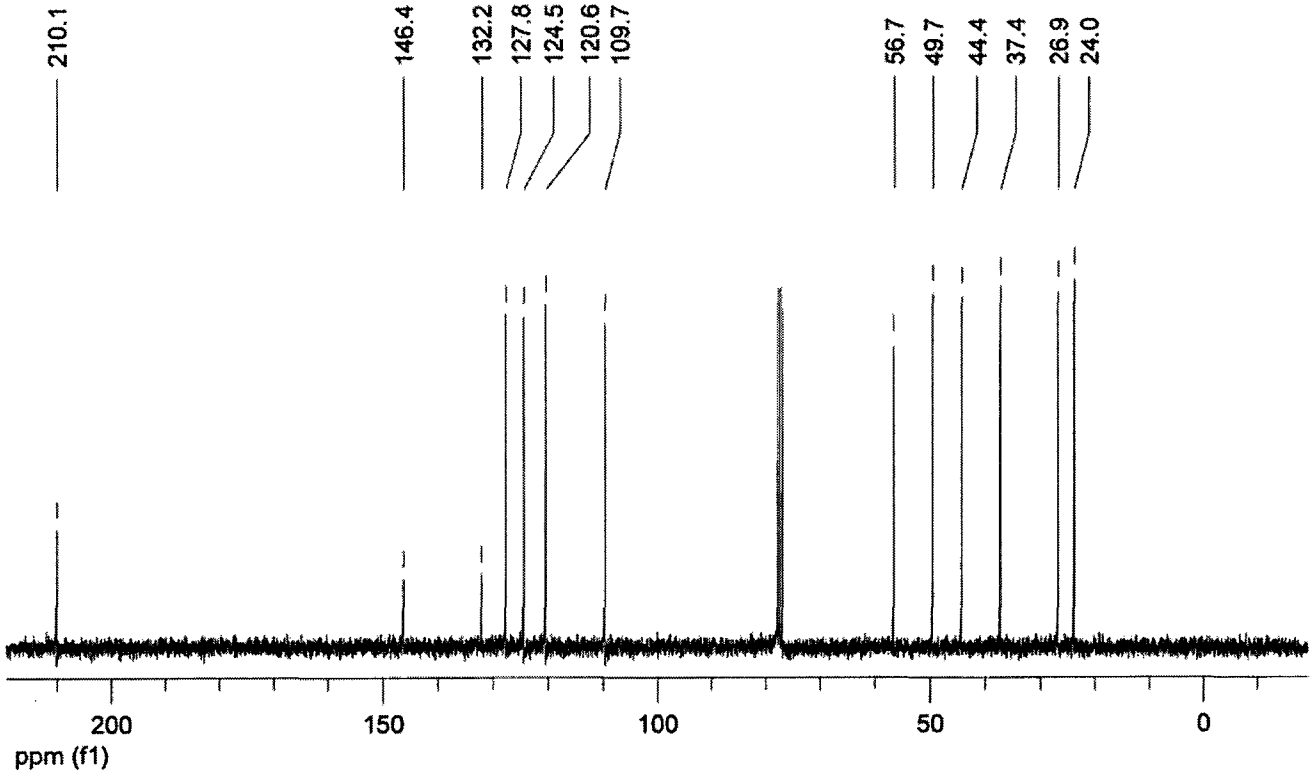


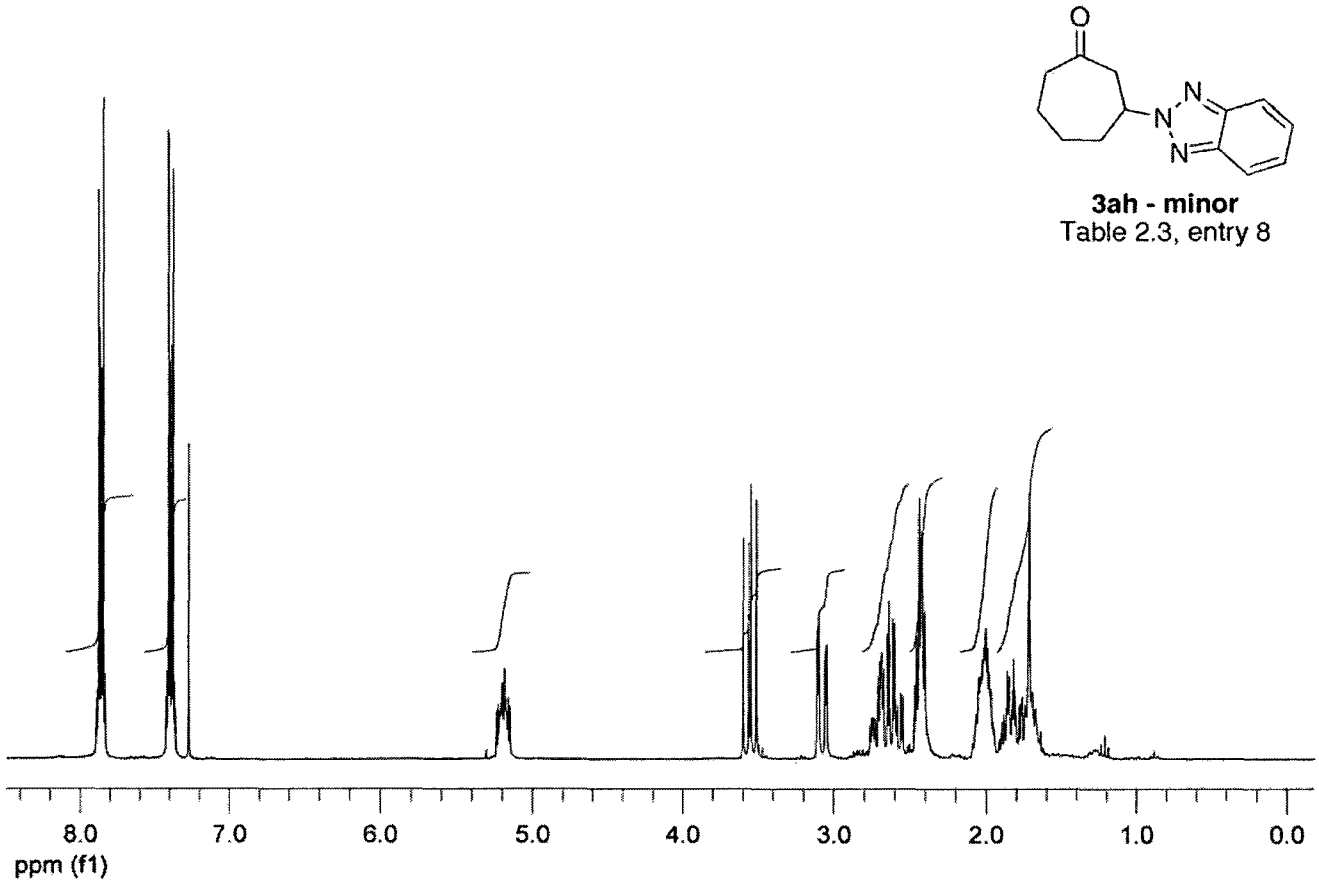




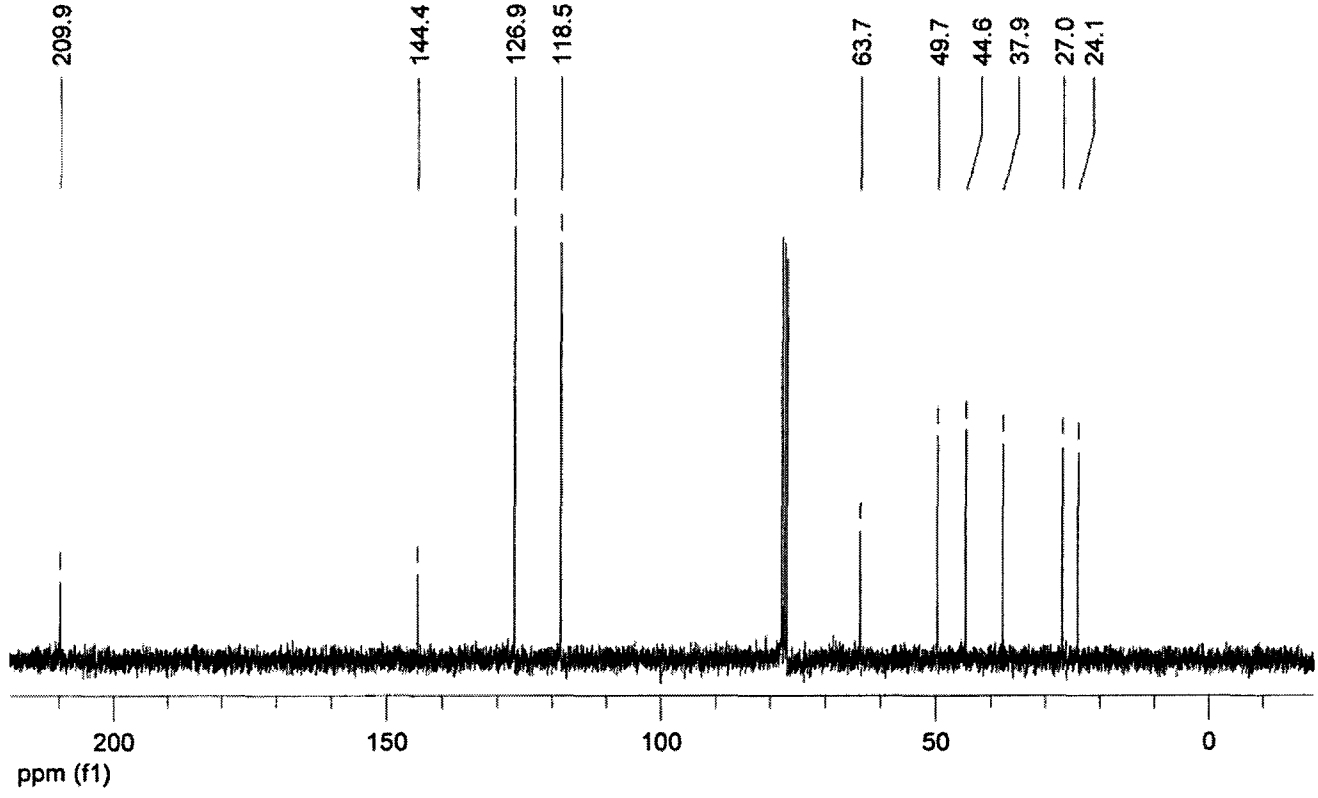
3ah - major
Table 2.3, entry 8

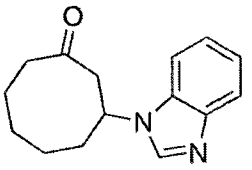




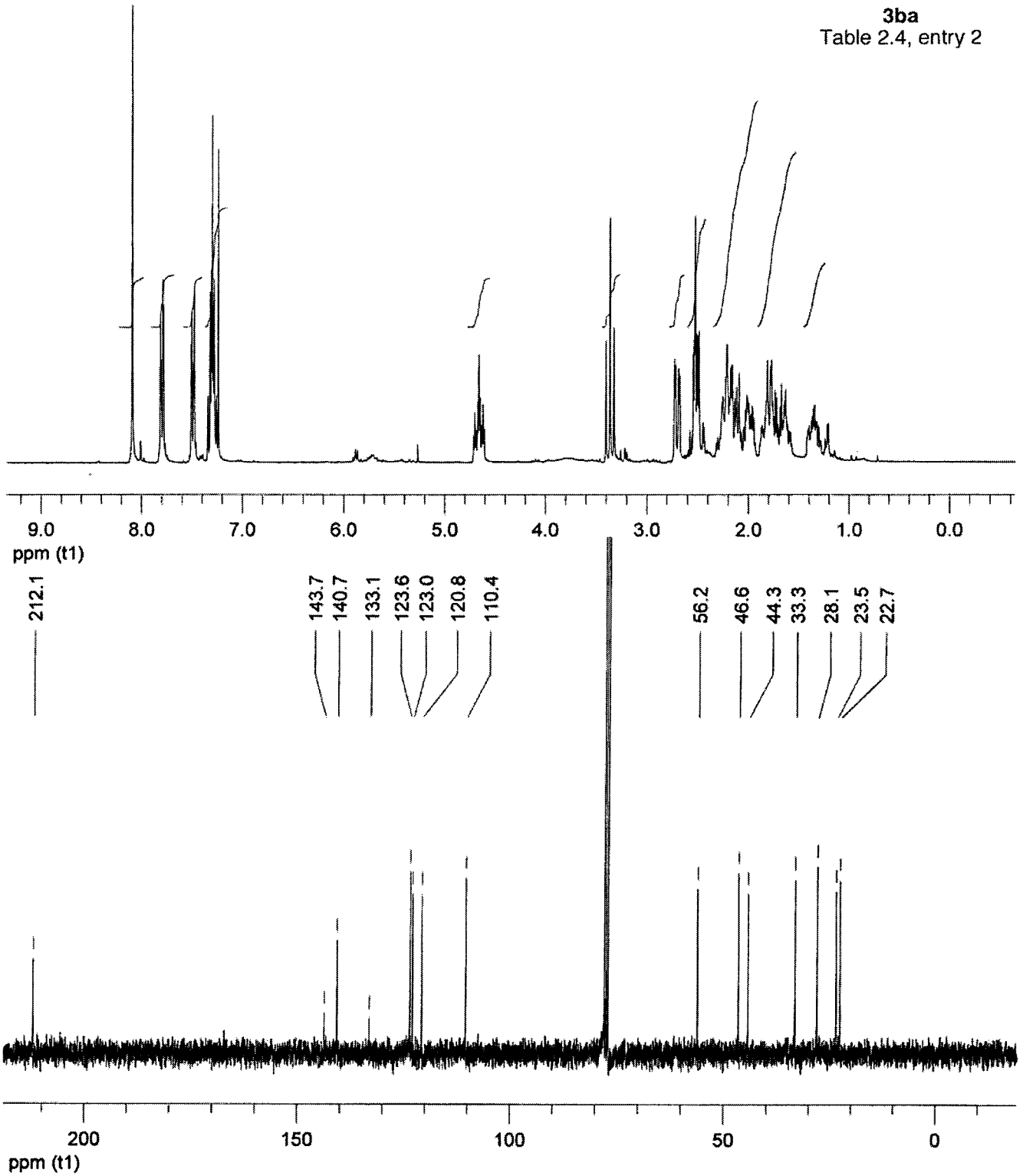


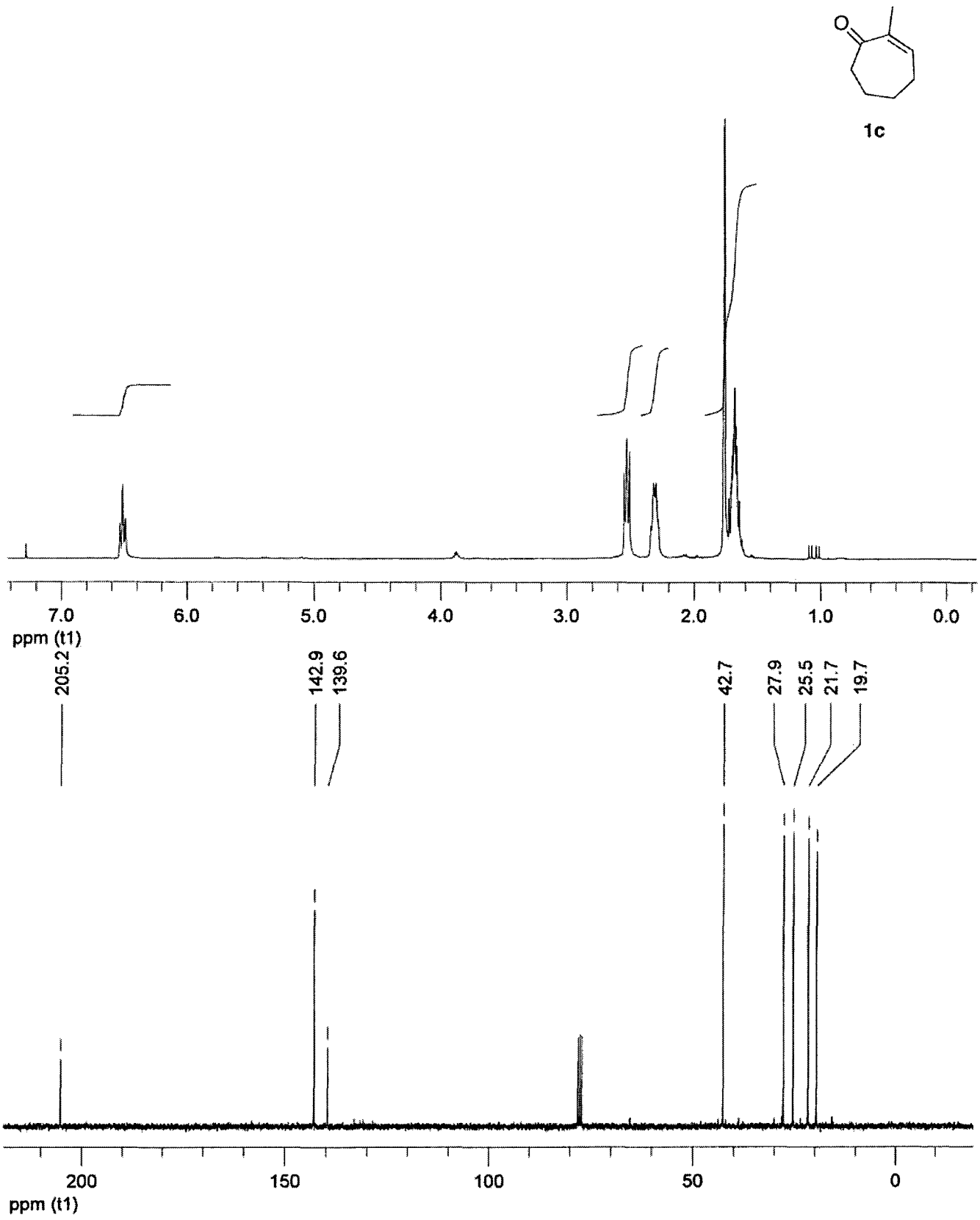
3ah - minor
Table 2.3, entry 8

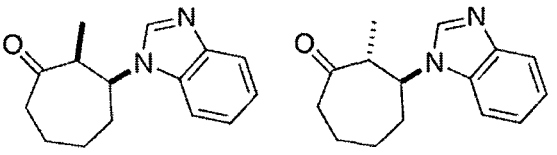




3ba
Table 2.4, entry 2



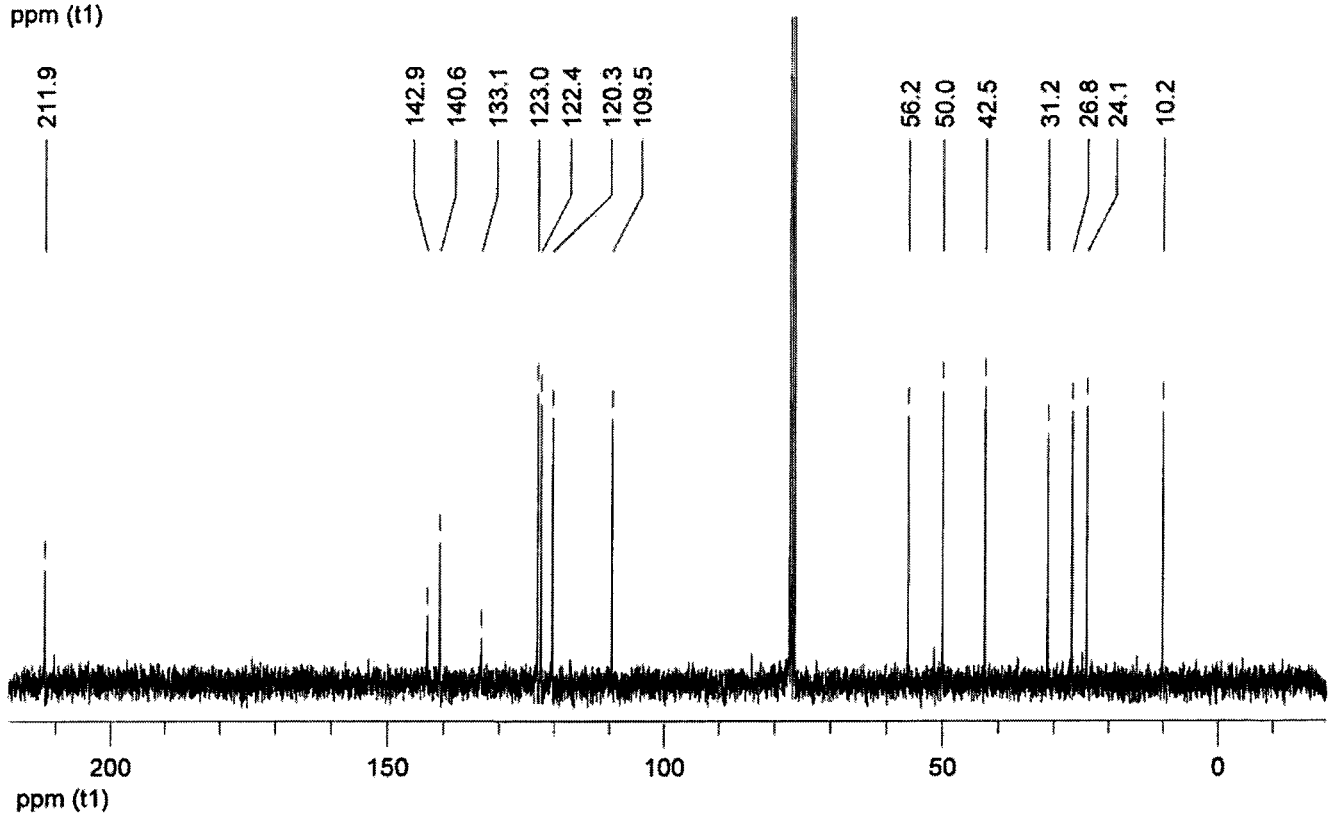

1c
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
205.2
142.9
139.6
42.7
27.9
25.5
21.7
19.7
200
150
100
50
0
ppm (t1)

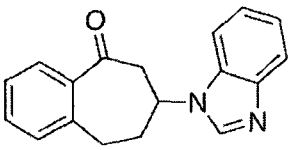


12 : 1

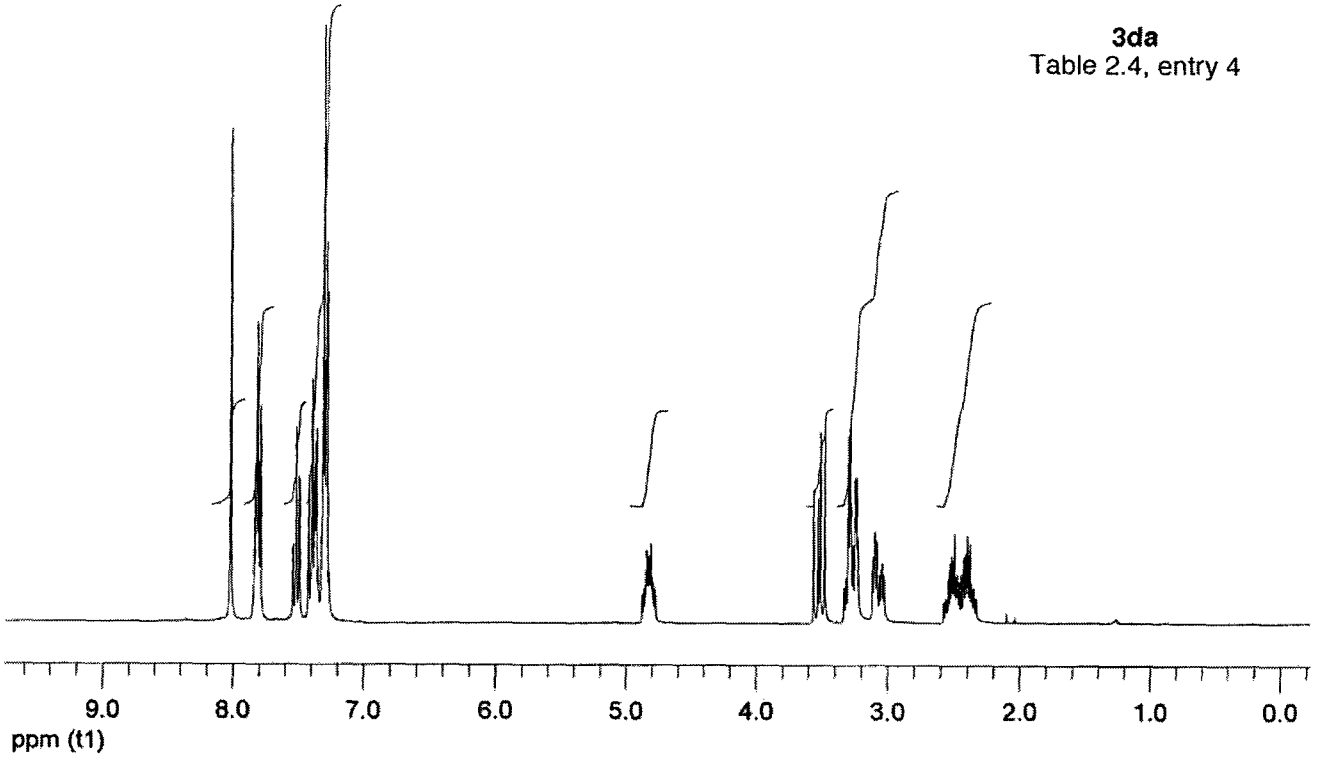
3ca

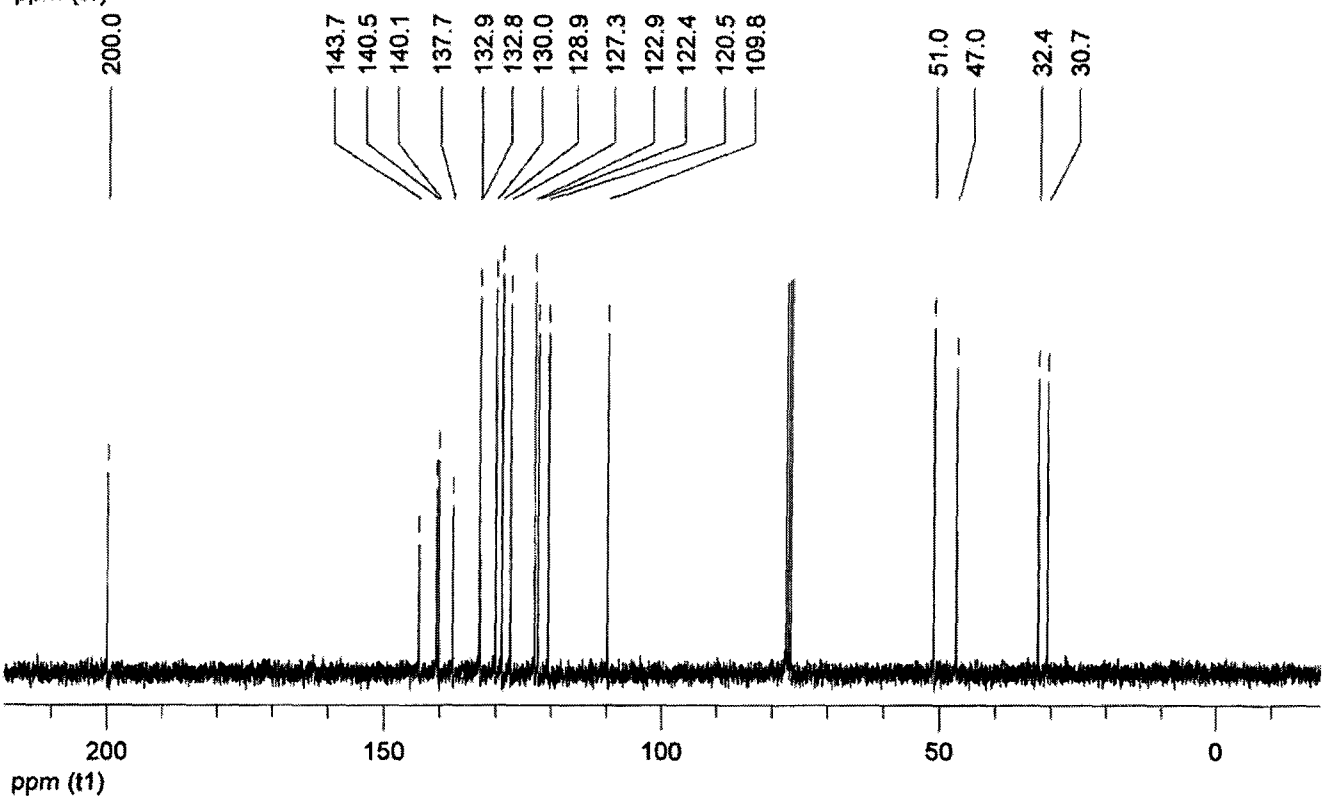
Table 2.4, entry 3

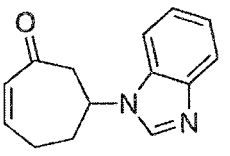




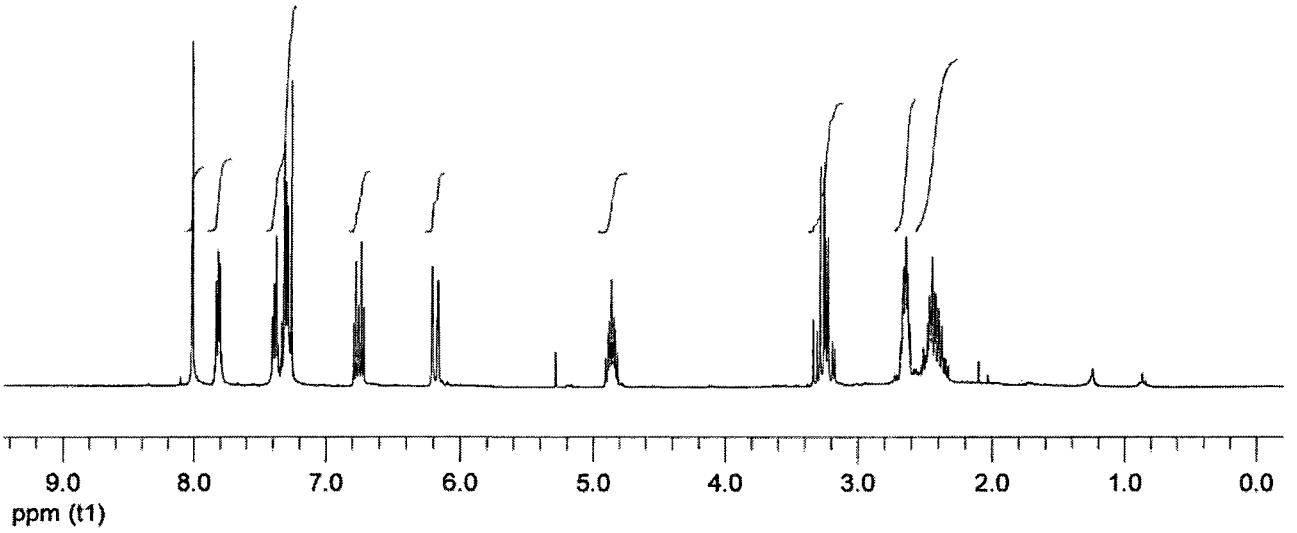
3da
Table 2.4, entry 4

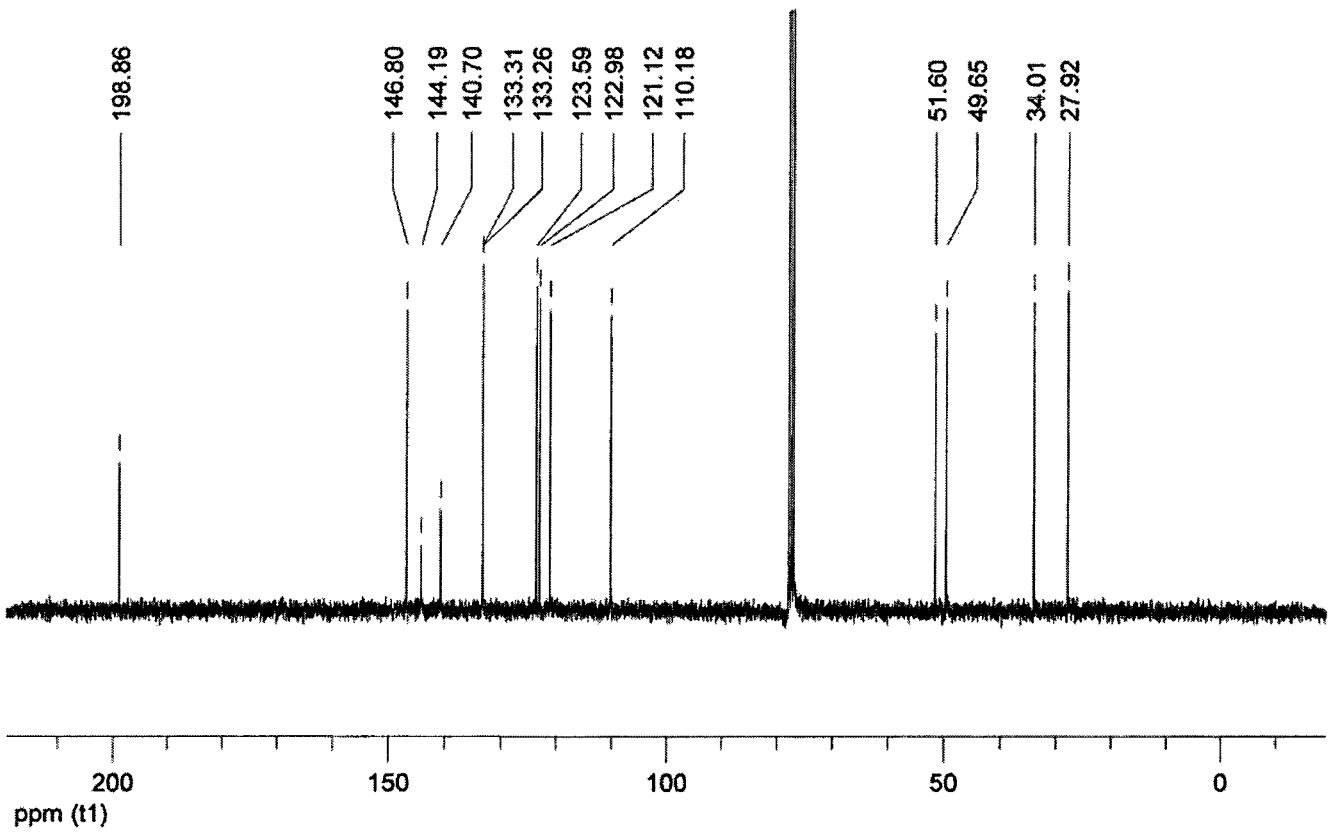


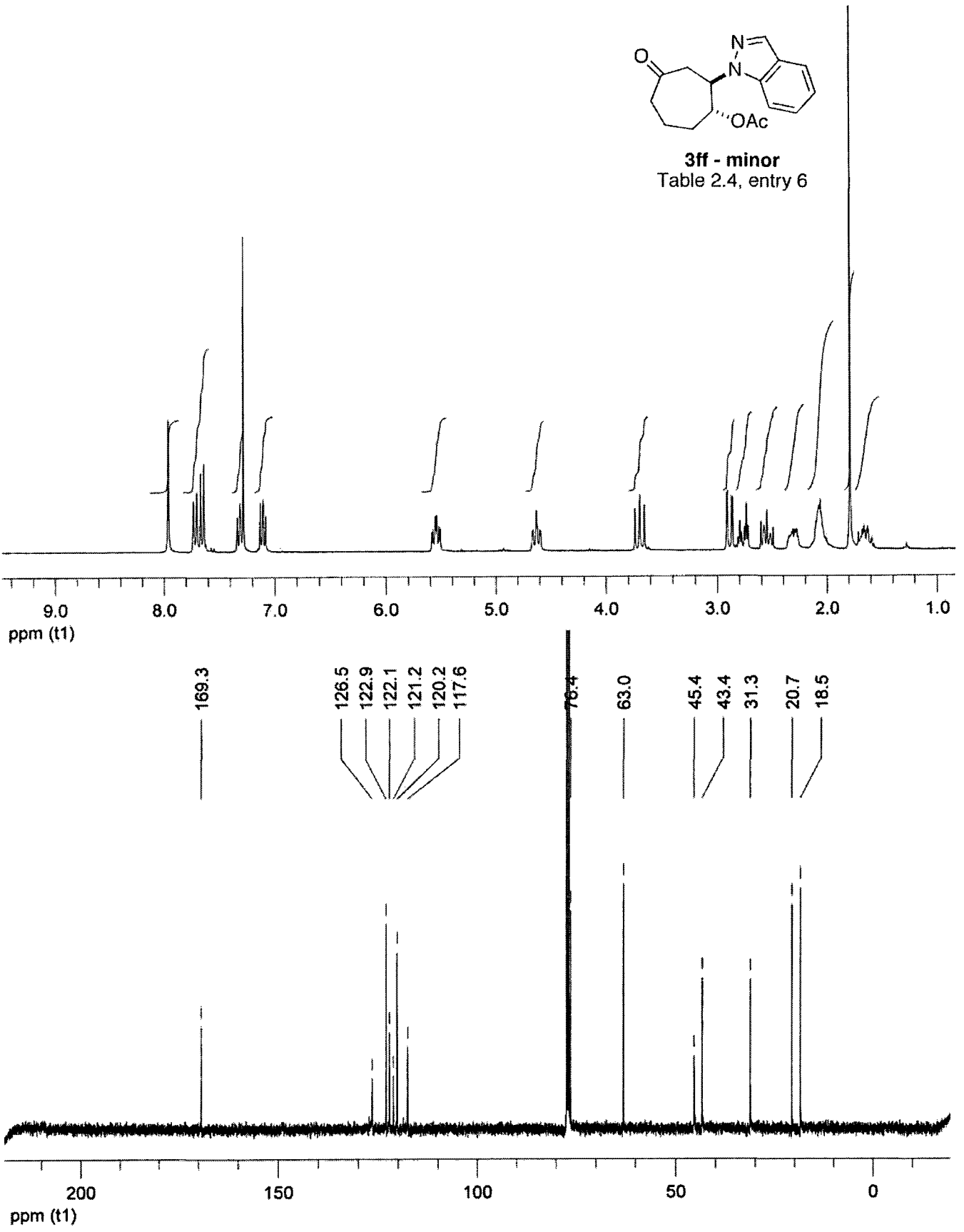


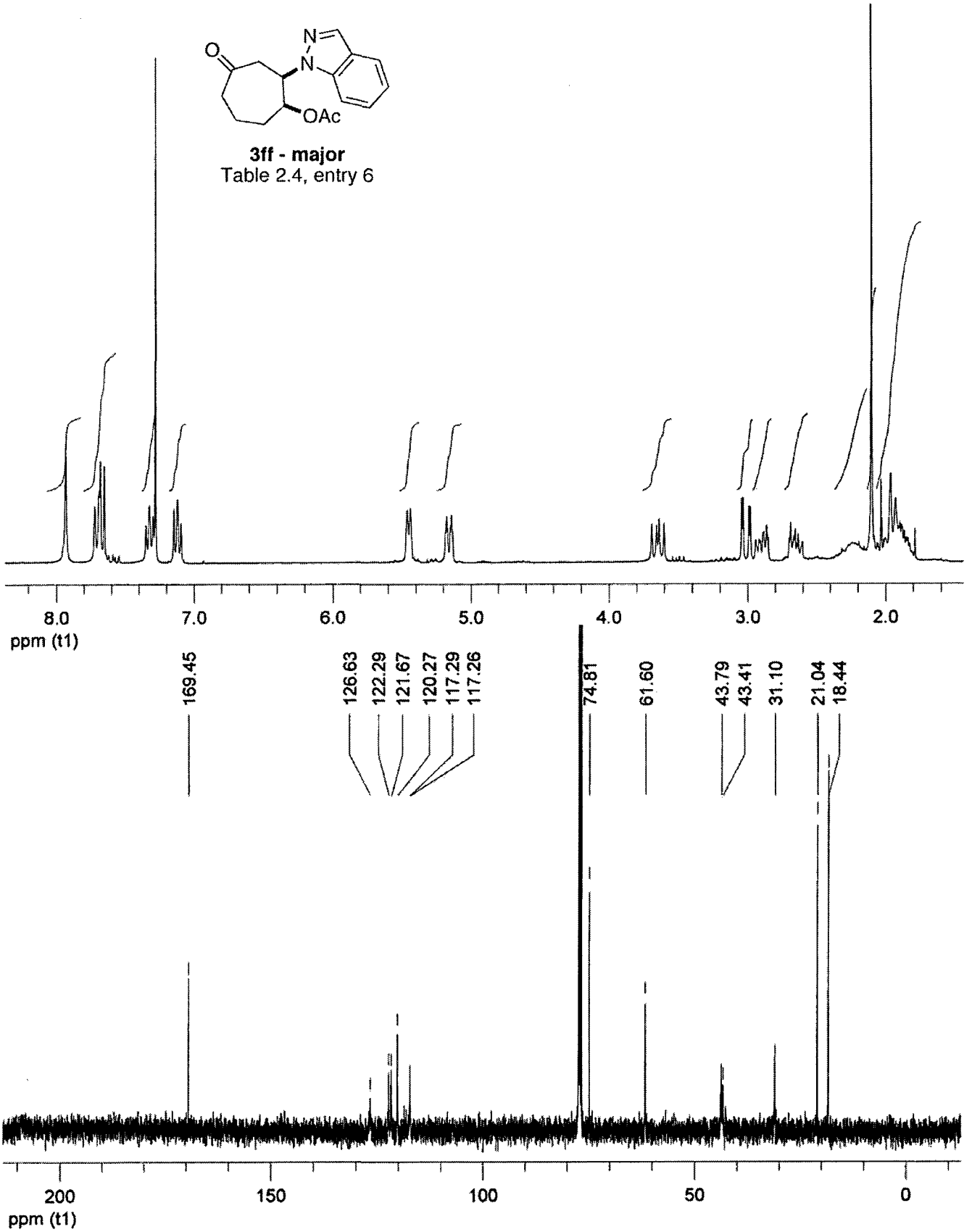


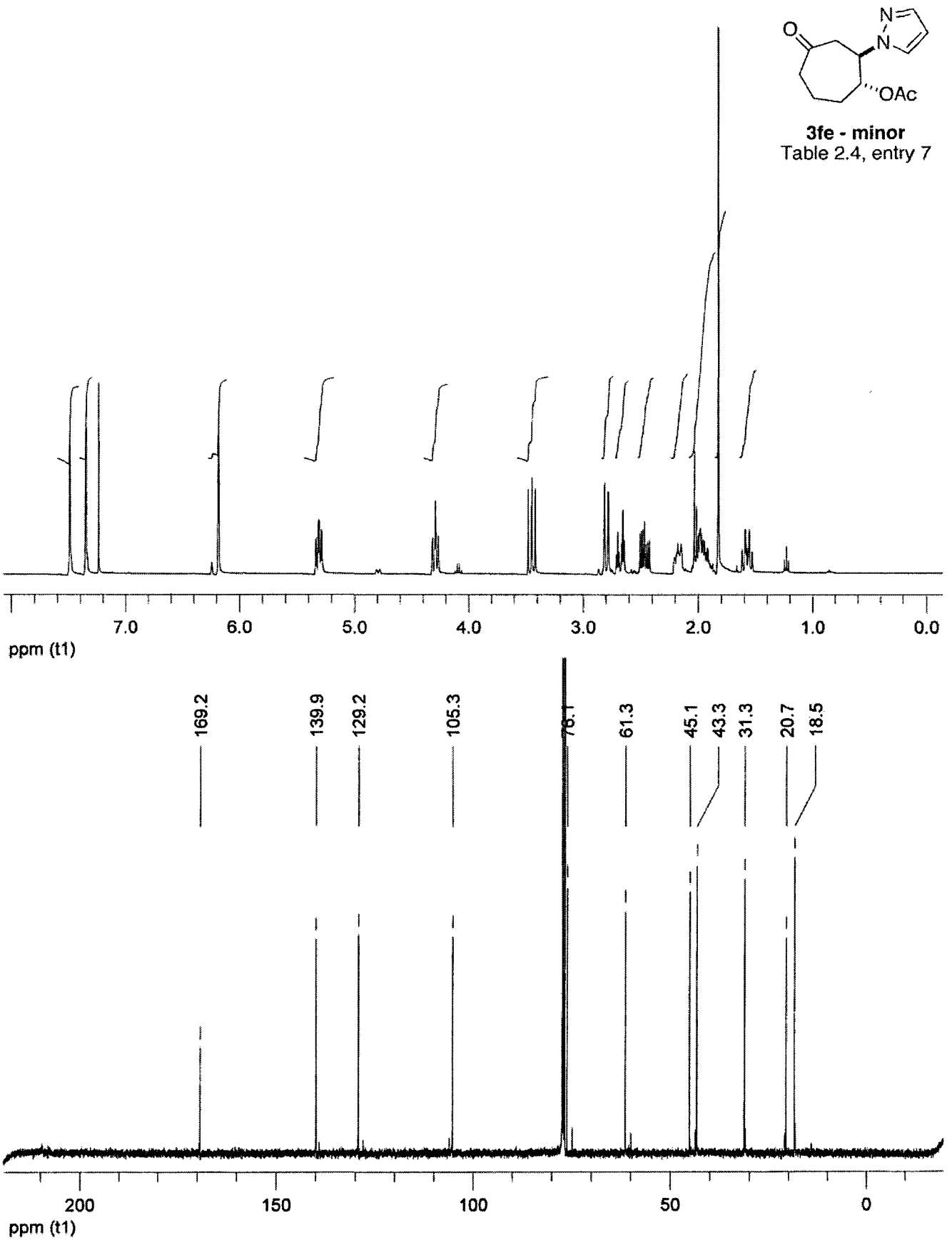
3ea
Table 2.4, entry 5

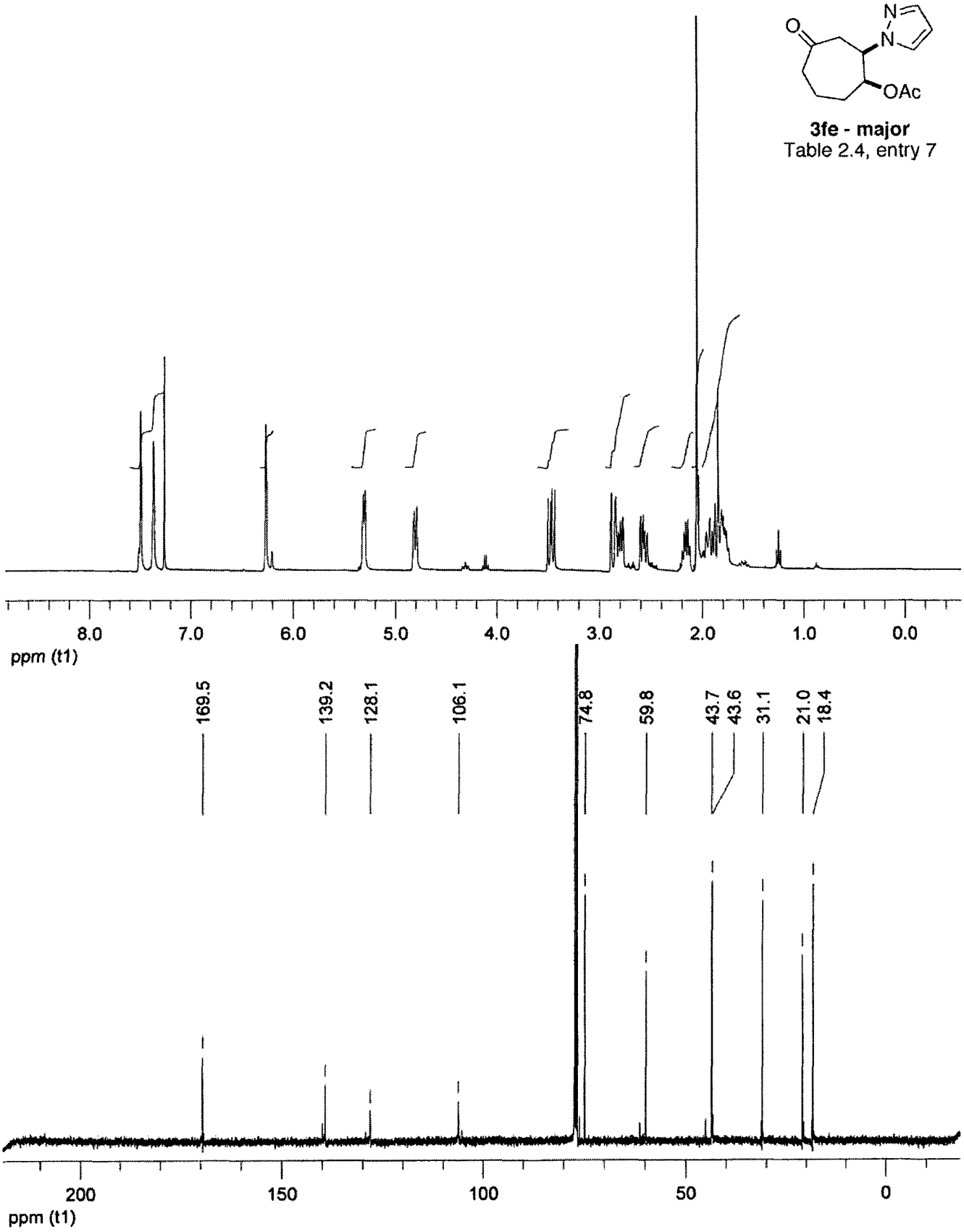


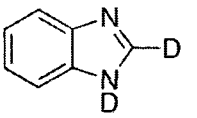



O
N
N
OAc
3ff - minor
Table 2.4, entry 6
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)
169.3
126.5
122.9
122.1
121.2
120.2
117.6
78.4
63.0
45.4
43.4
31.3
20.7
18.5
200
150
100
50
0
ppm (t1)

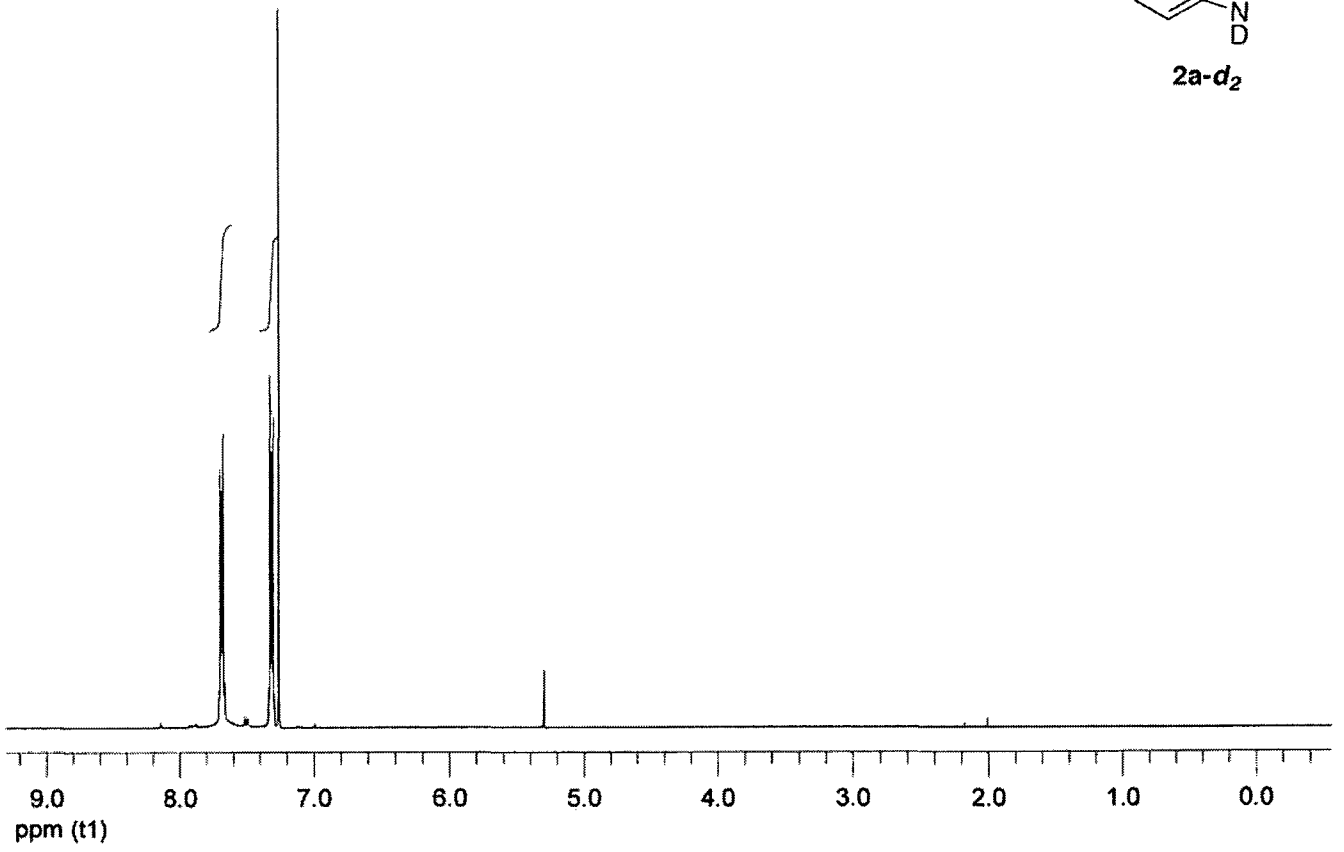

O
N
N
OAc
3ff - major
Table 2.4, entry 6
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)
169.45
126.63
122.29
121.67
120.27
117.29
117.26
74.81
61.60
43.79
43.41
31.10
21.04
18.44
200
150
100
50
0
ppm (t1)

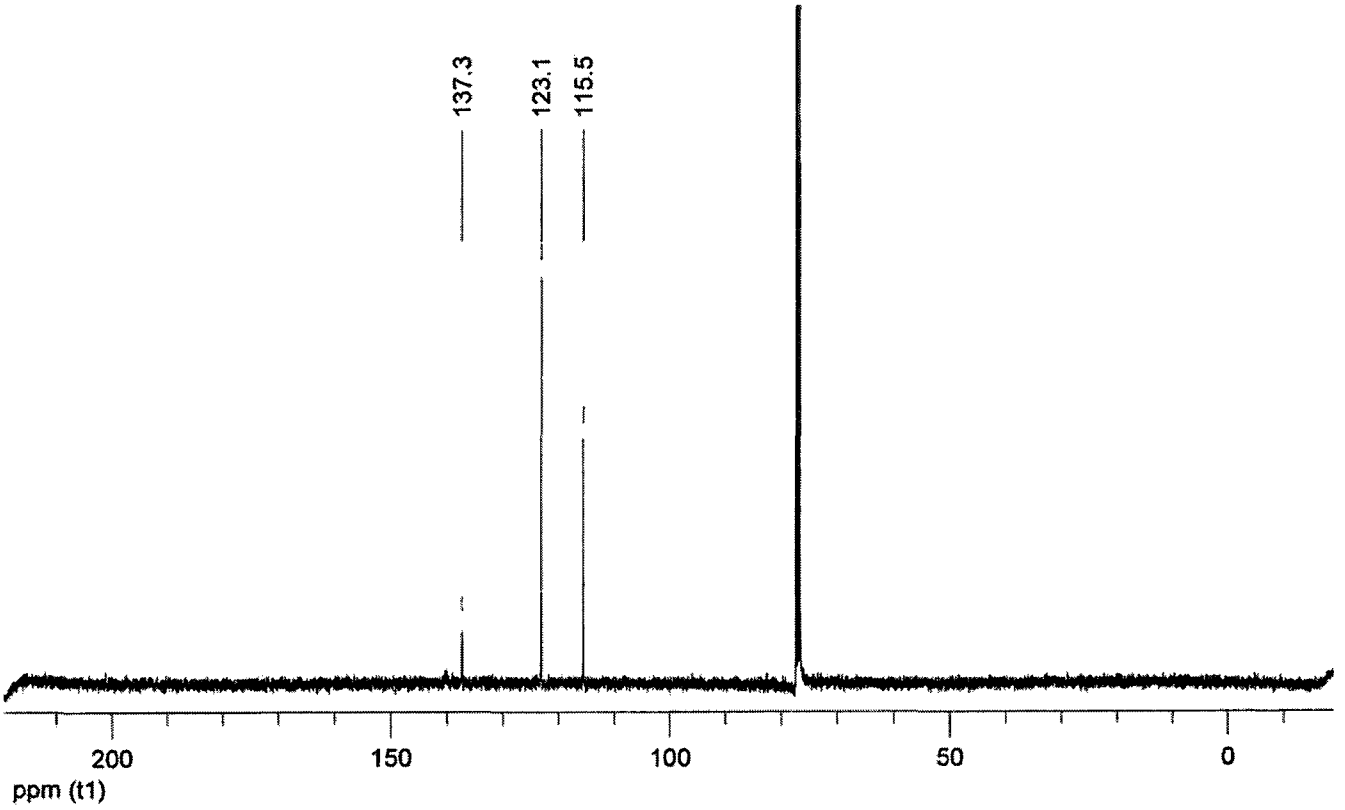

O
N
N
OAc
3fe - minor
Table 2.4, entry 7
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
169.2
139.9
129.2
105.3
76.1
61.3
45.1
43.3
31.3
20.7
18.5
200
150
100
50
0
ppm (t1)

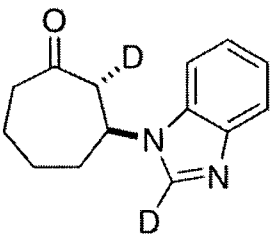

O
N
N
OAc
3fe - major
Table 2.4, entry 7
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
169.5
139.2
128.1
106.1
74.8
59.8
43.7
43.6
31.1
21.0
18.4
200
150
100
50
0
ppm (t1)


N
D
N
D

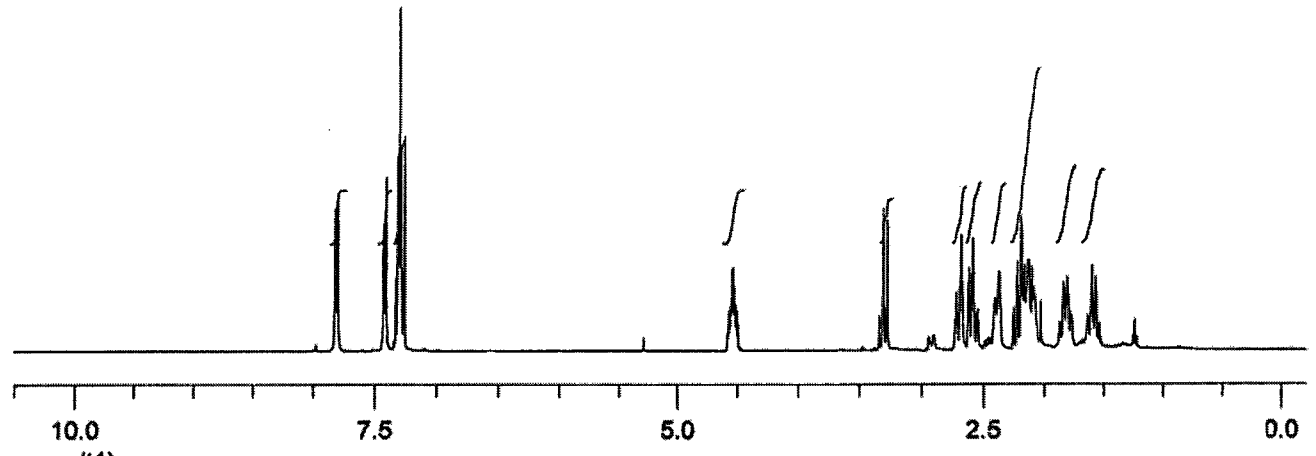
2a-d_2

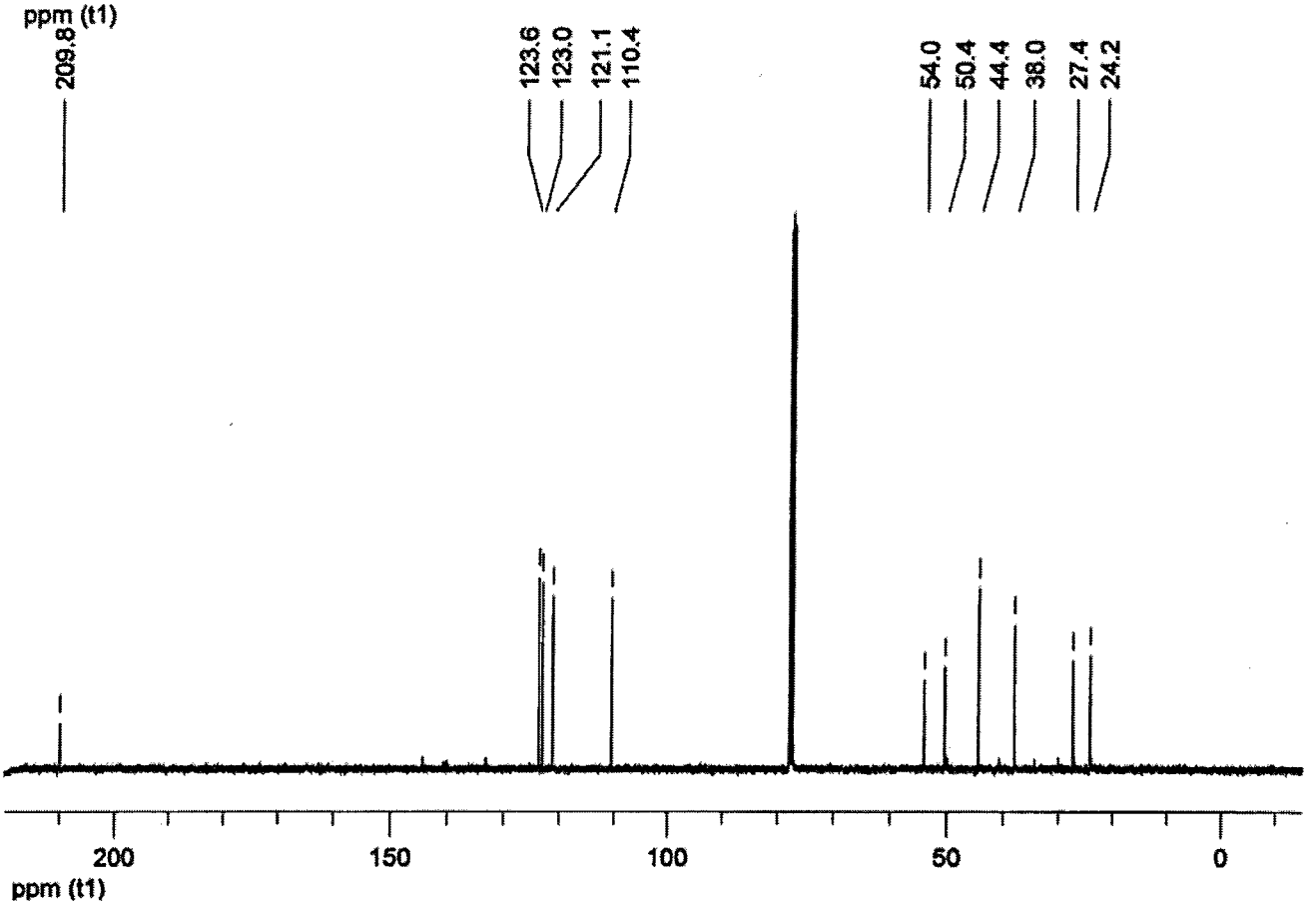

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

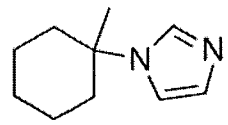

137.3
123.1
115.5
200
150
100
50
0
ppm (t1)


O
D
N
N
D

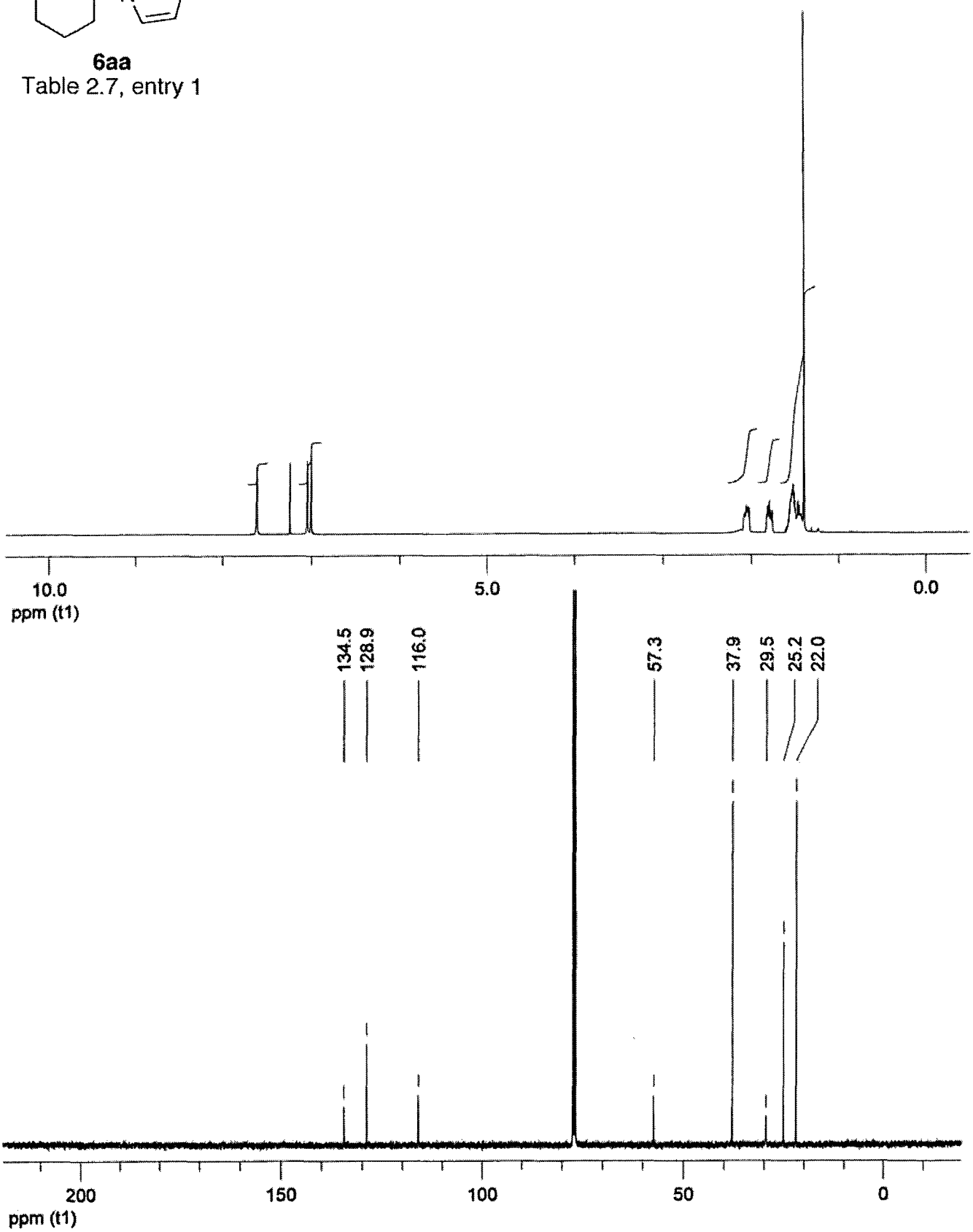
3aa-d_2

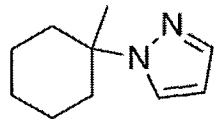

10.0
7.5
5.0
2.5
0.0
ppm (t1)


209.8
123.6
123.0
121.1
110.4
54.0
50.4
44.4
38.0
27.4
24.2
200
150
100
50
0
ppm (t1)

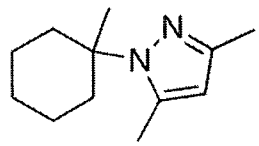


6aa
Table 2.7, entry 1

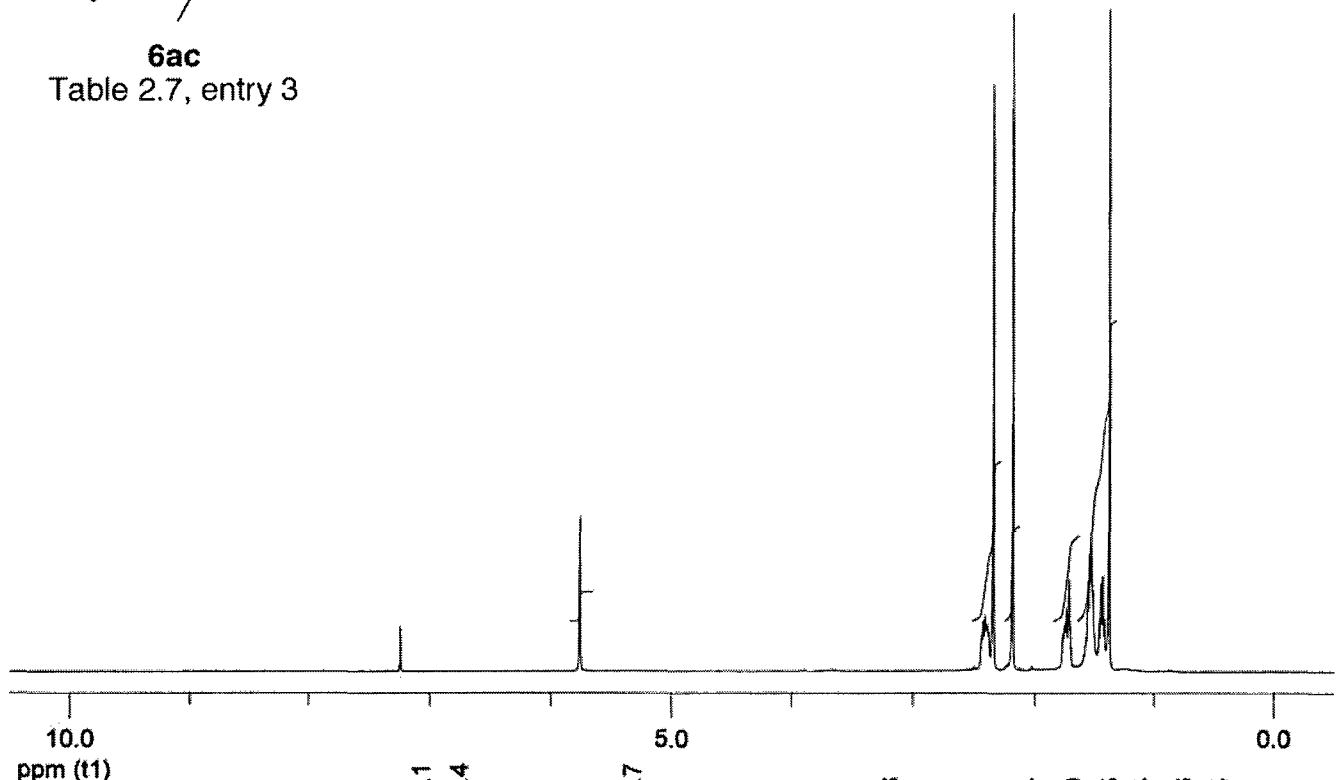


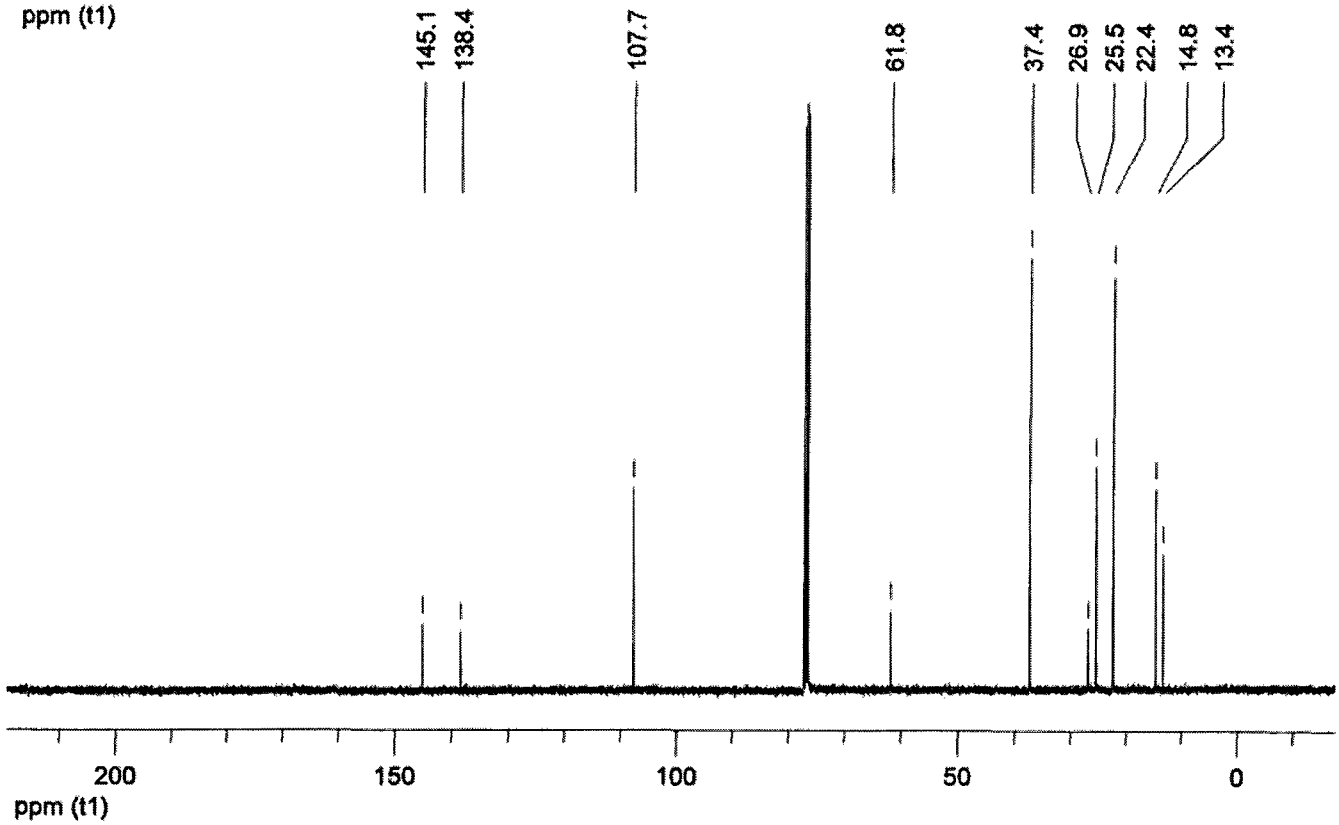


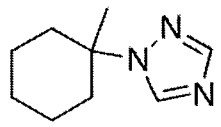
6ab
Table 2.7, entry 2



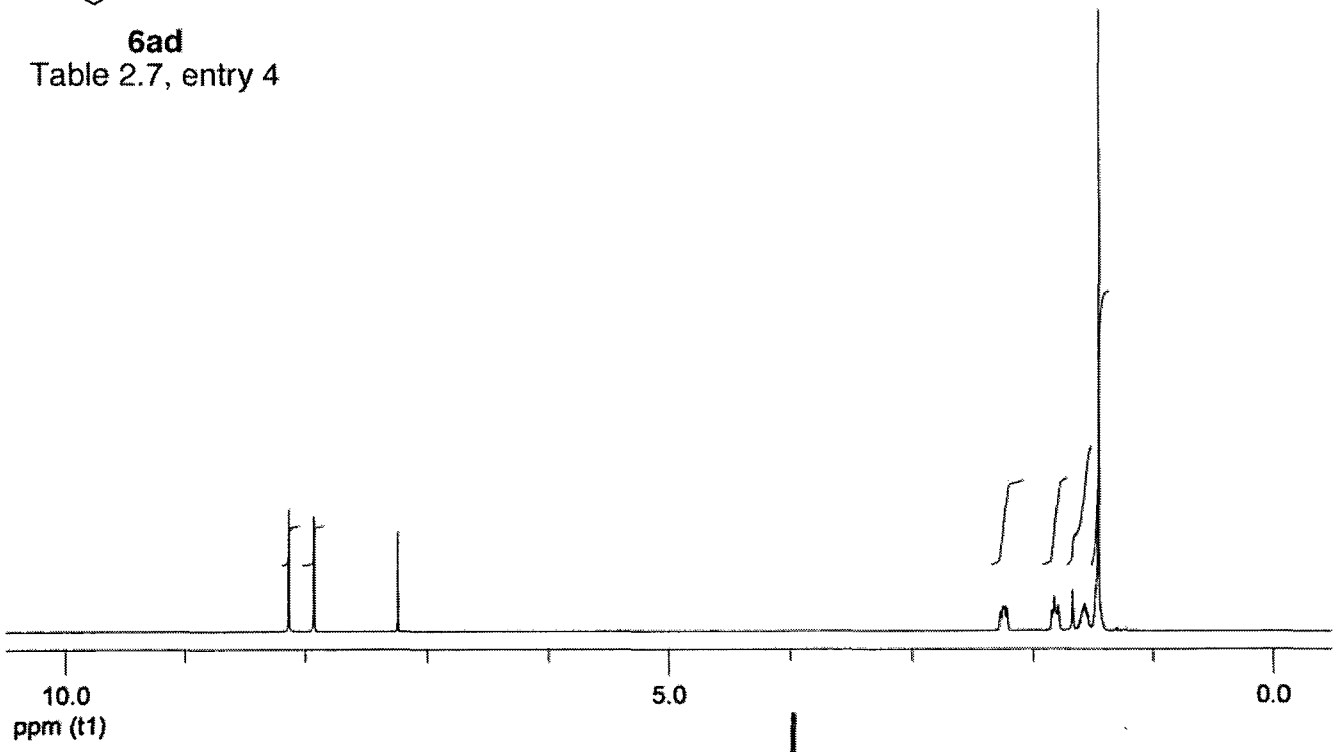
6ac
Table 2.7, entry 3

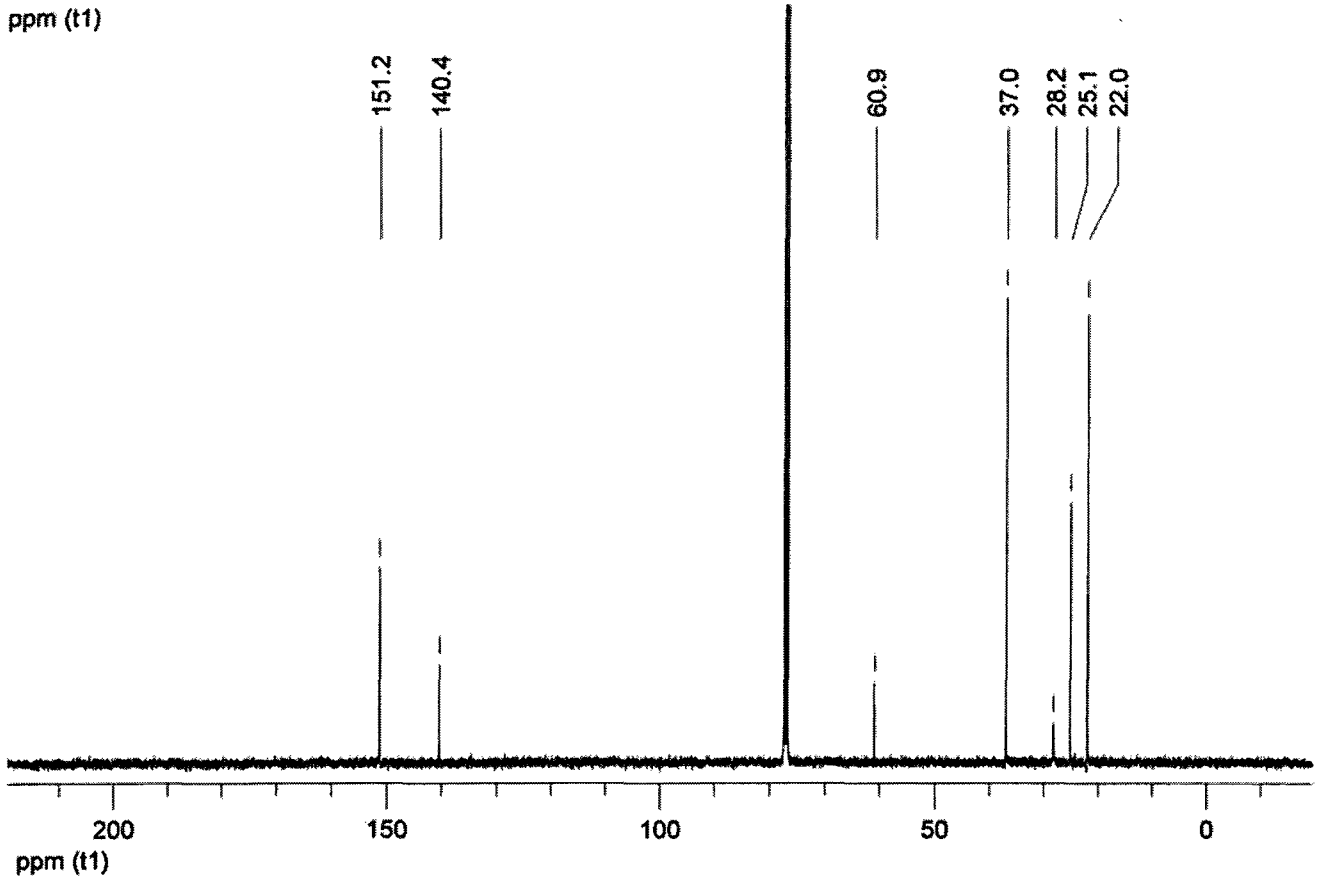


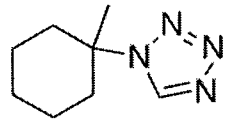




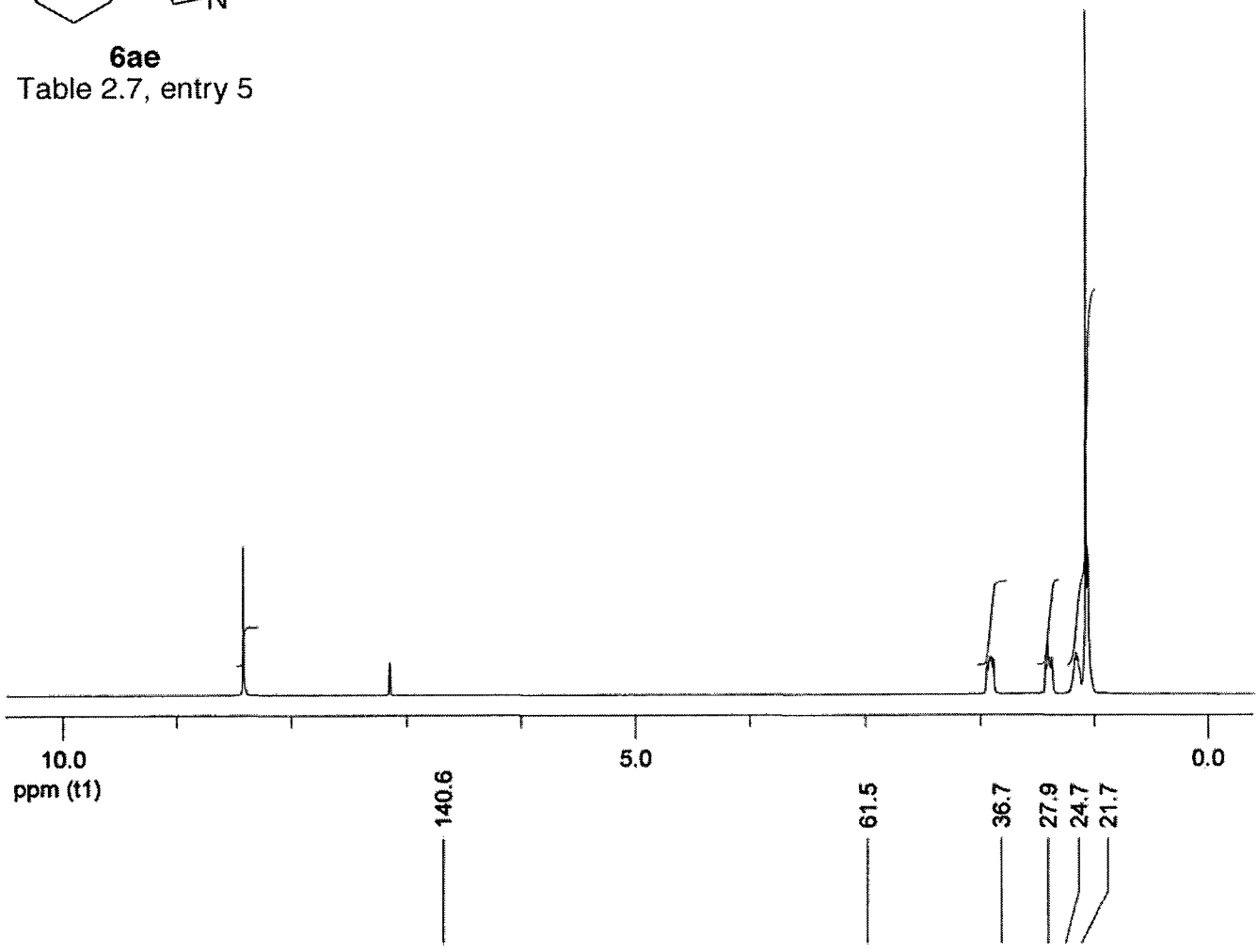
6ad
Table 2.7, entry 4

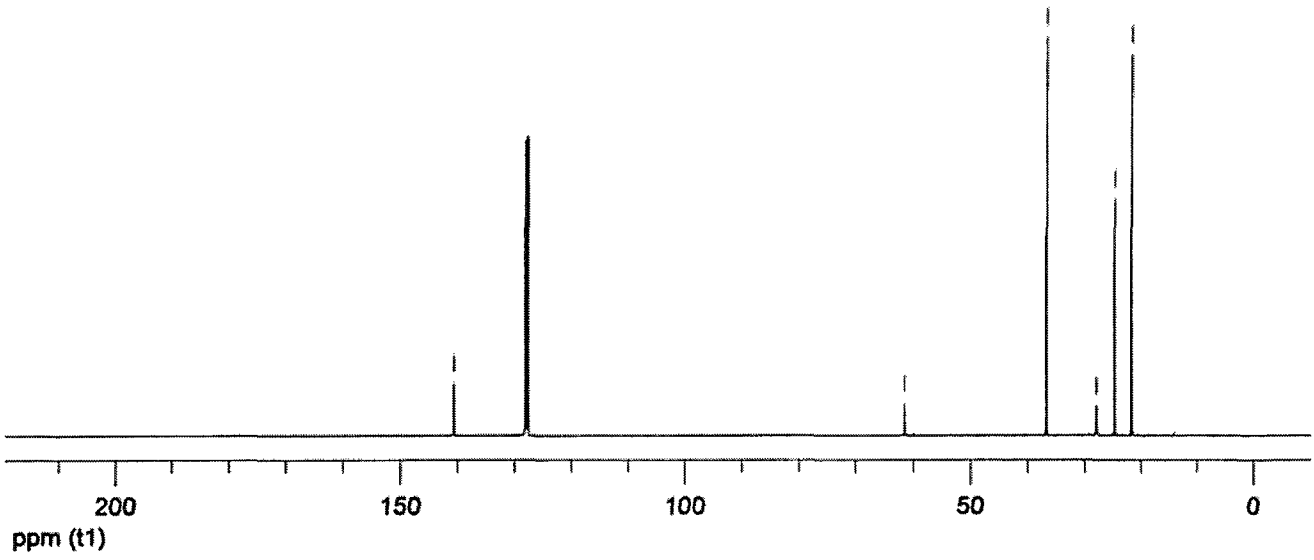


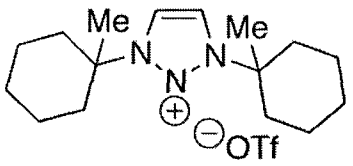




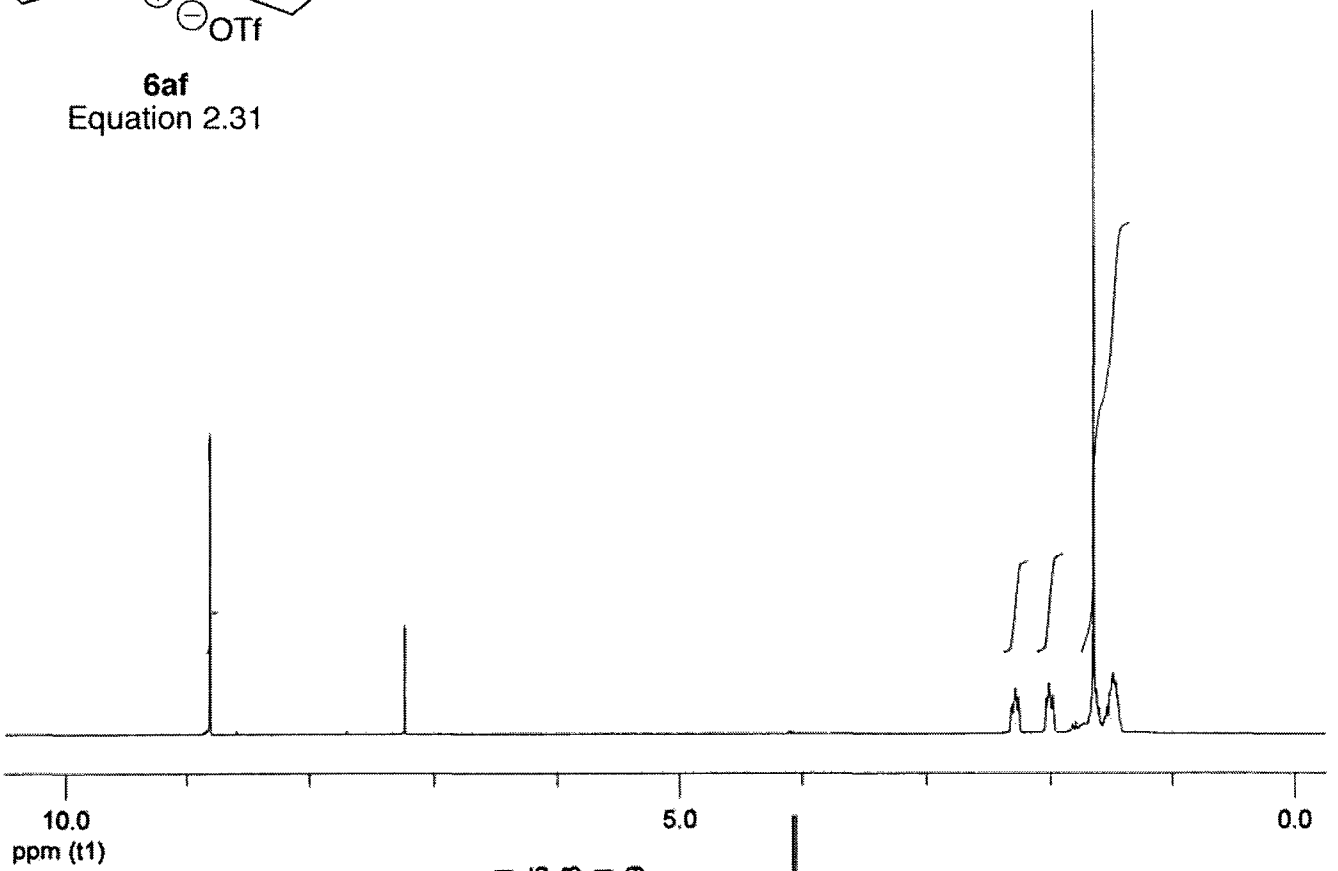
6ae
Table 2.7, entry 5

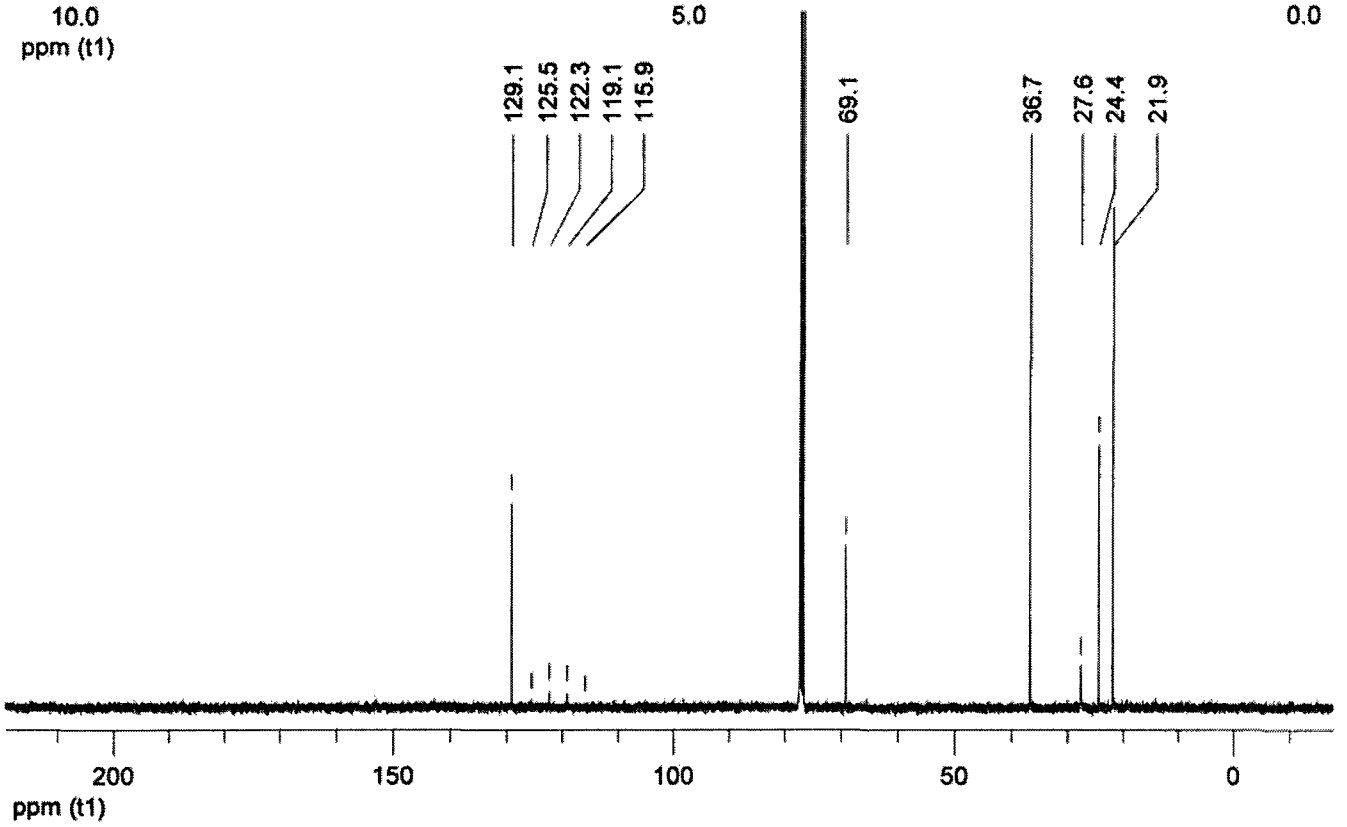


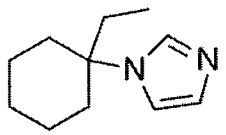




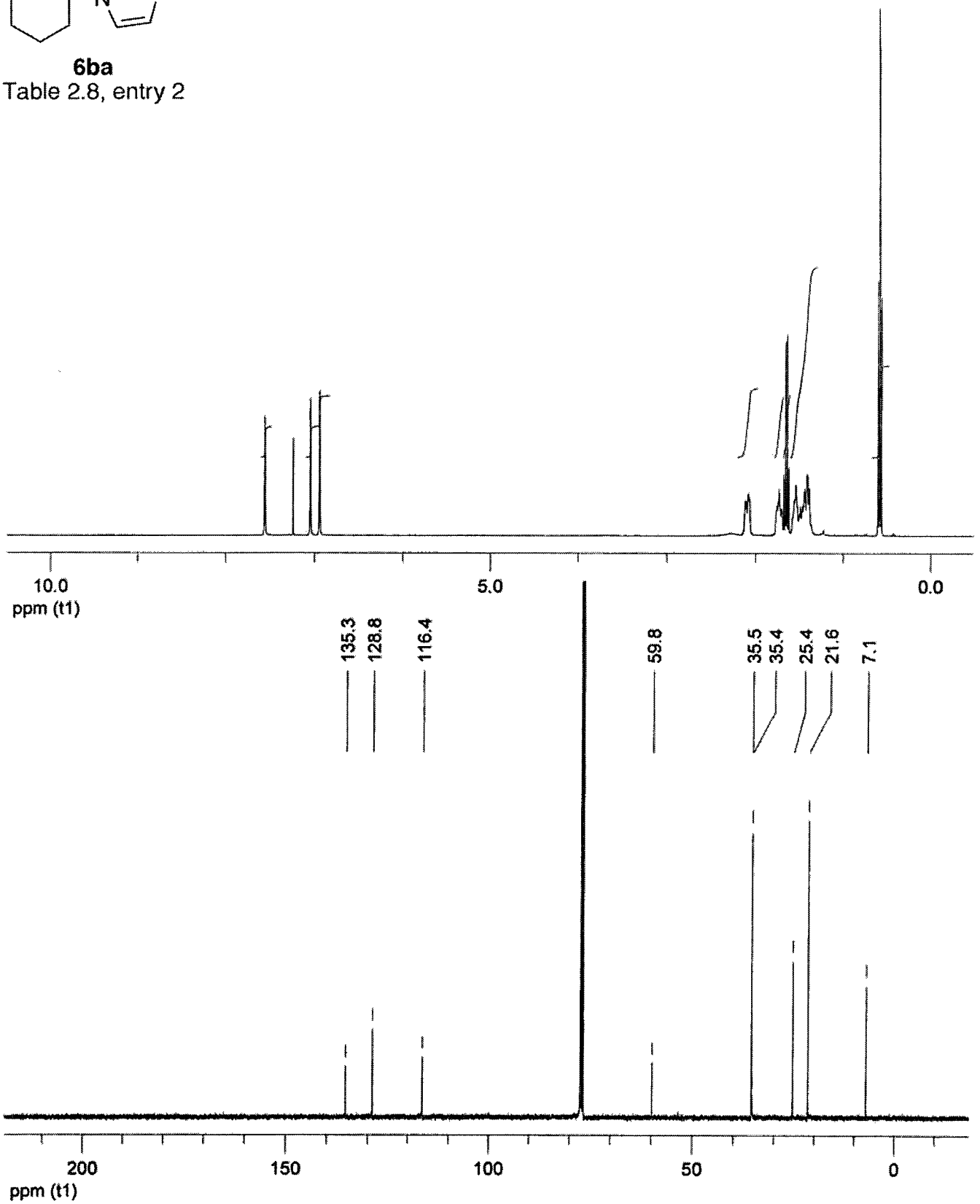
6af
Equation 2.31

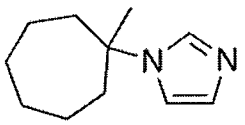




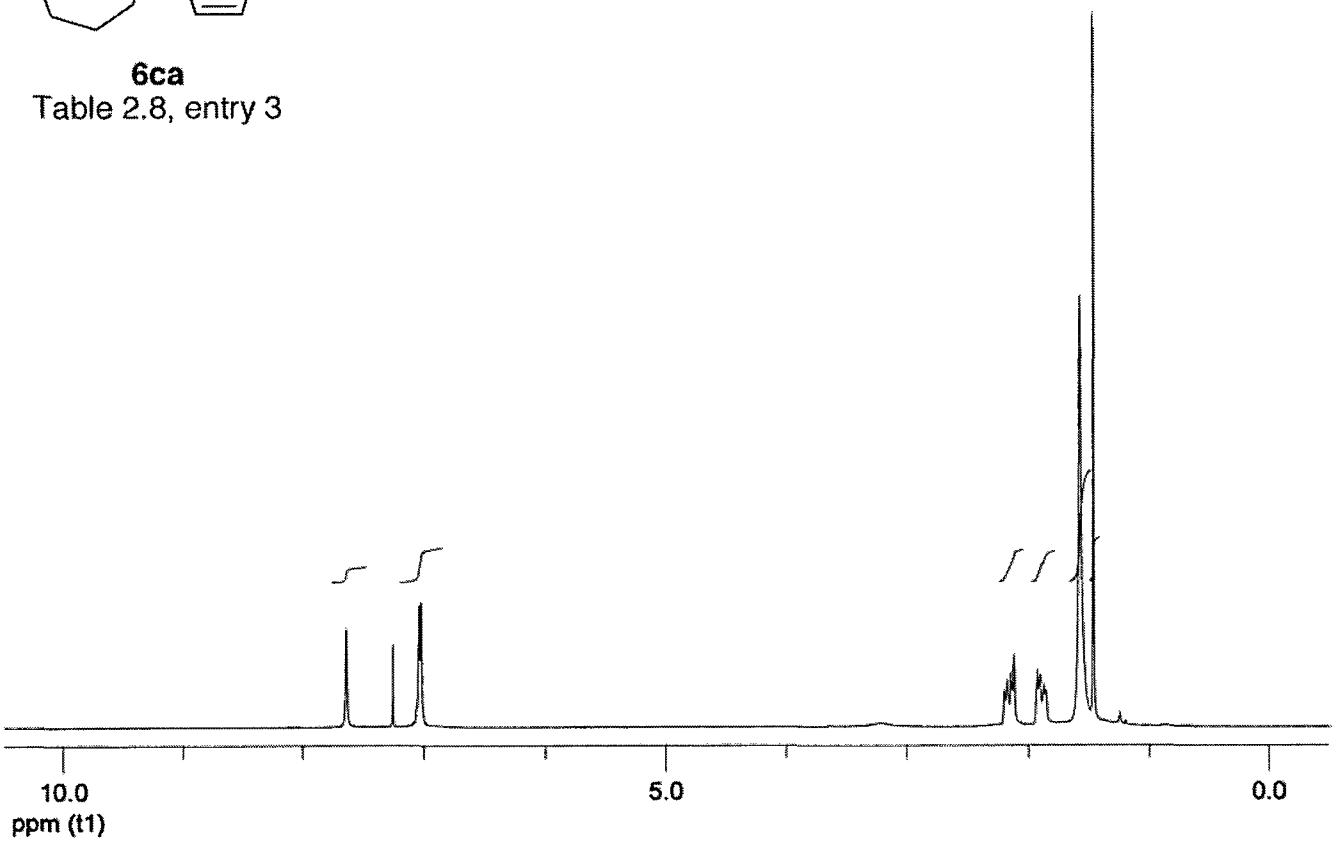


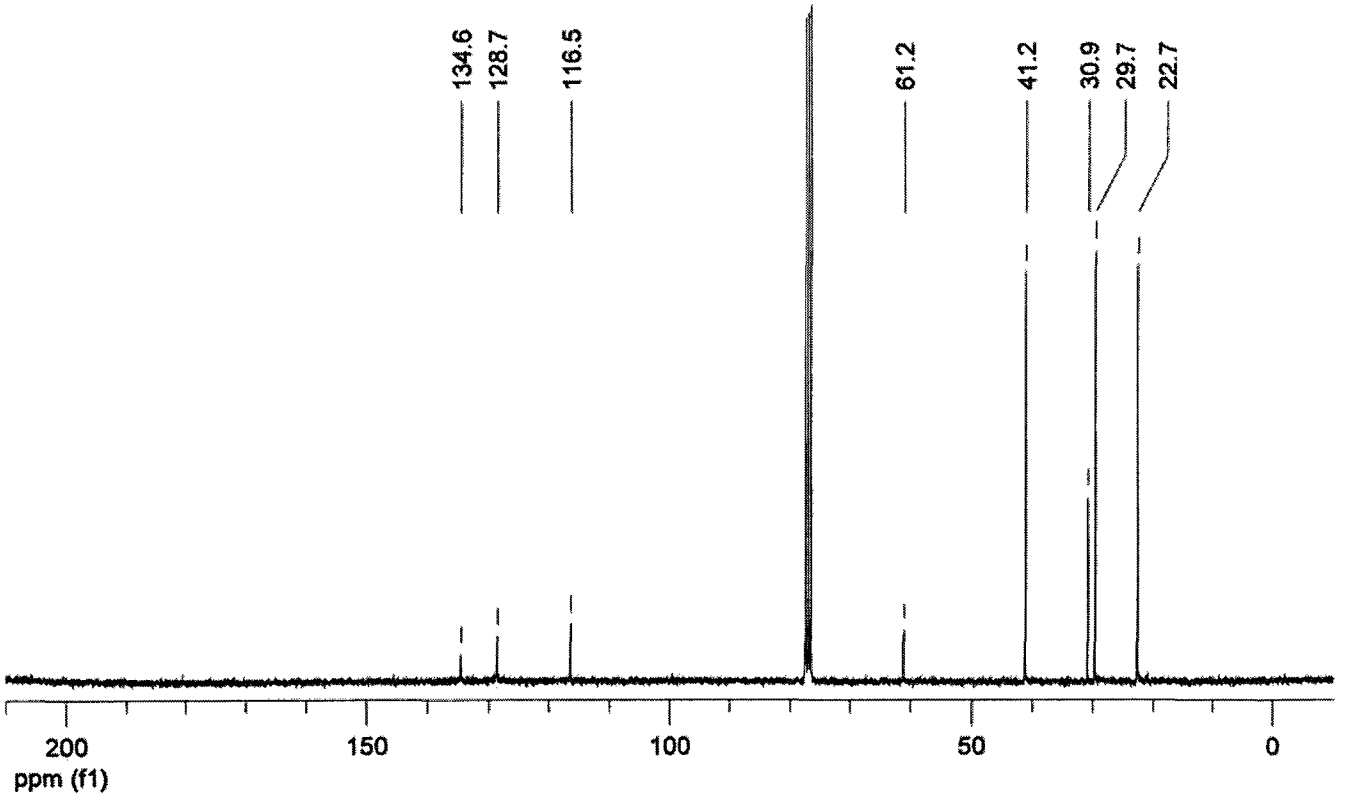
6ba
Table 2.8, entry 2

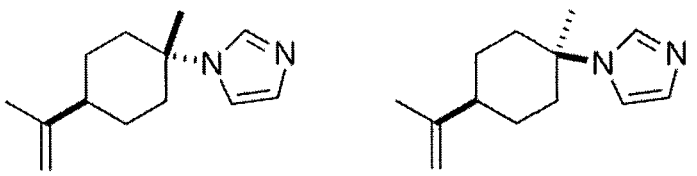




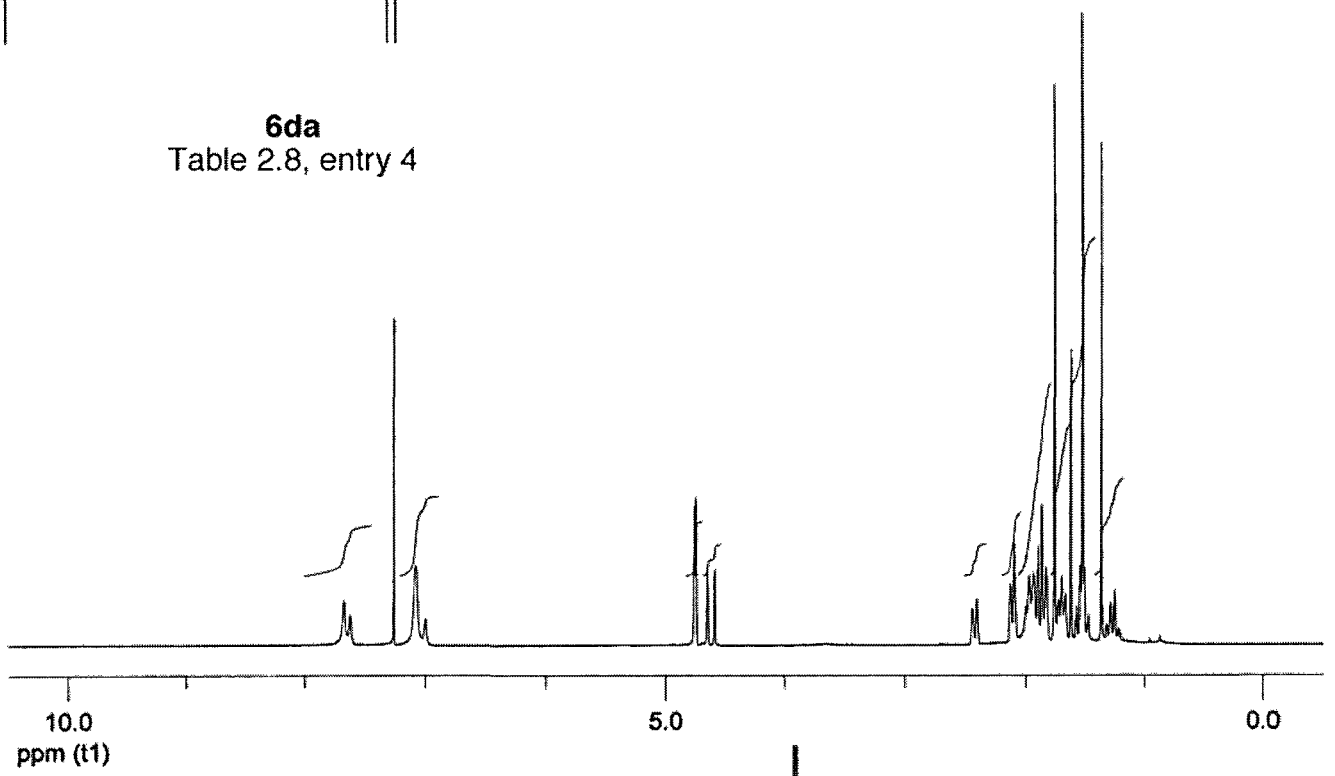
6ca
Table 2.8, entry 3

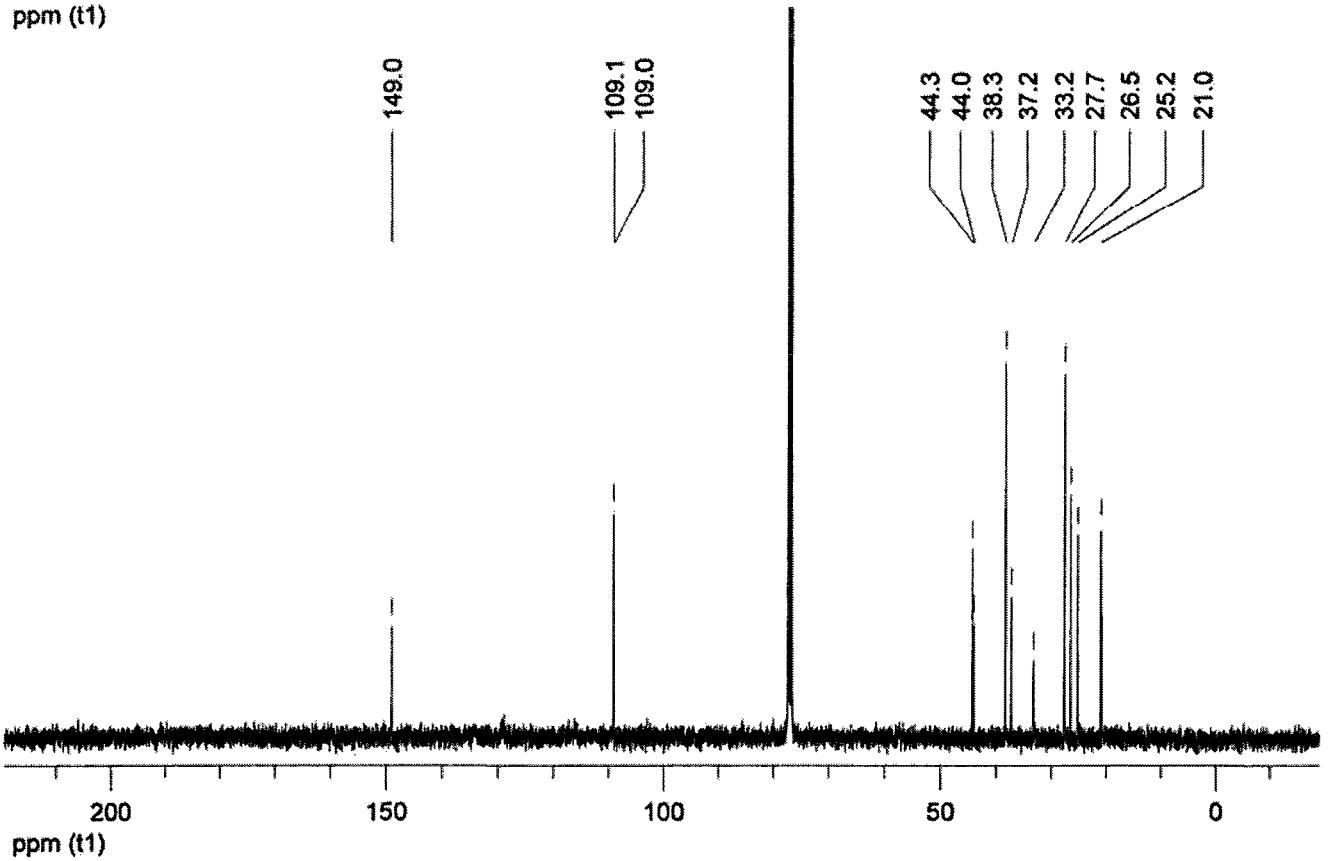


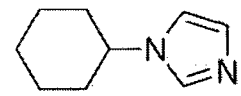




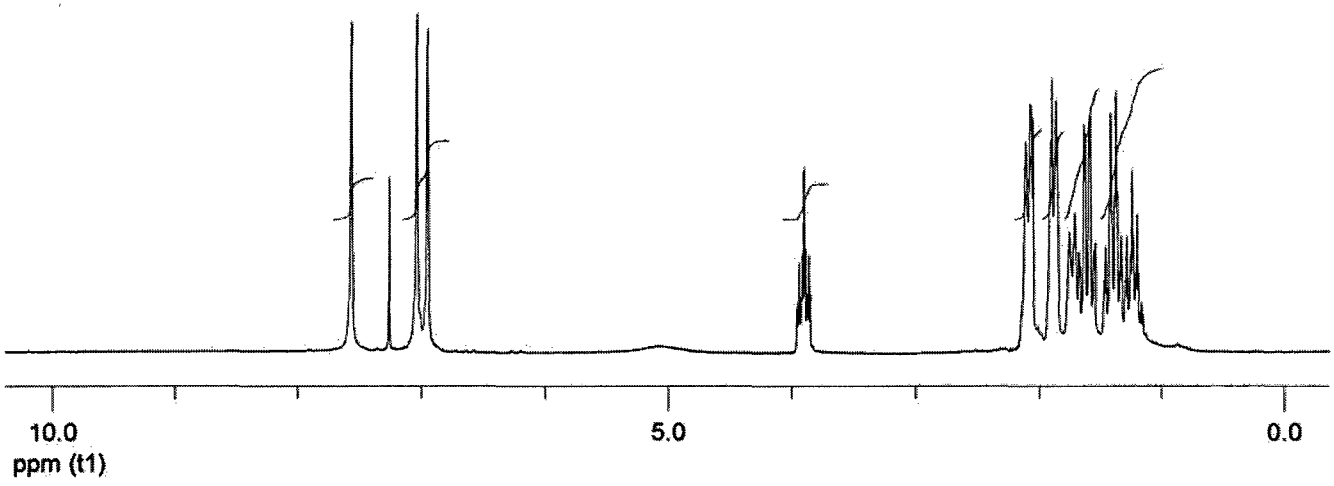
6da
Table 2.8, entry 4



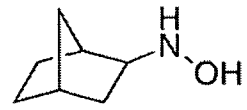




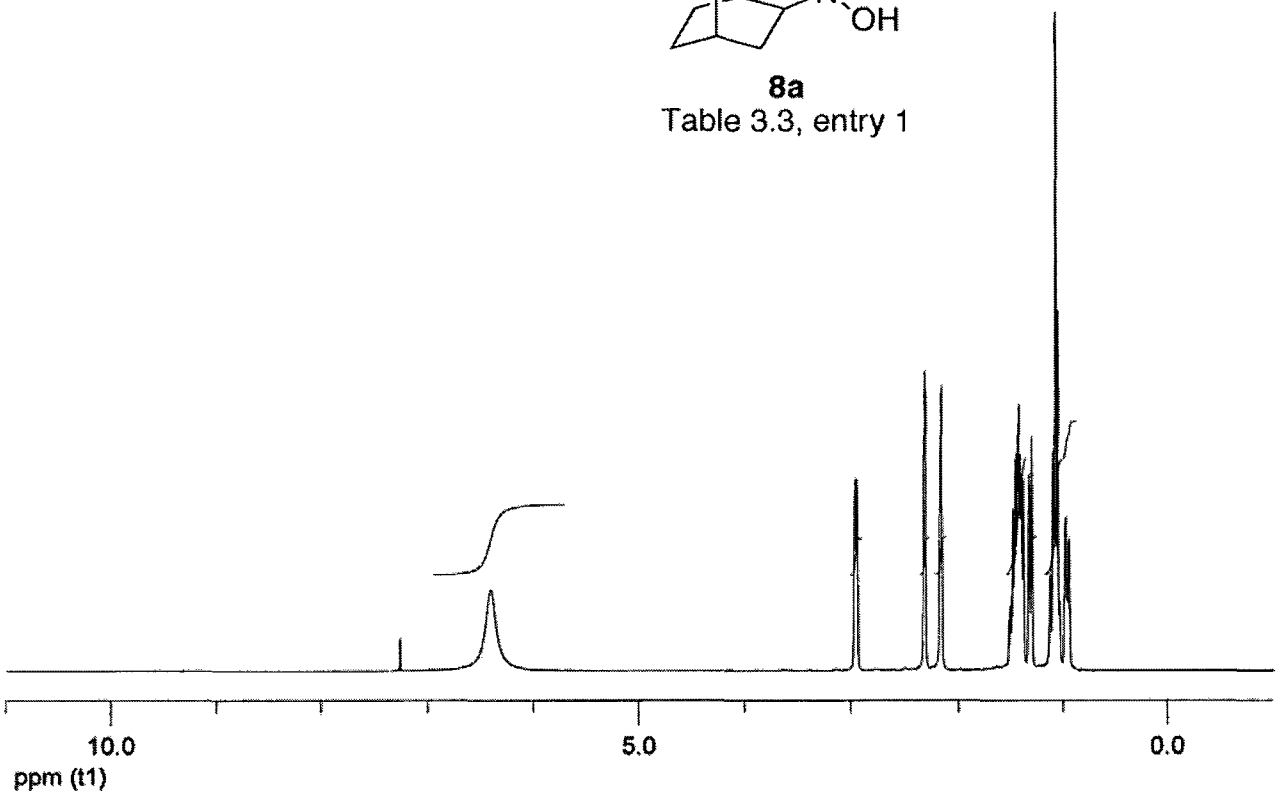
6ea
Table 2.8, entry 5

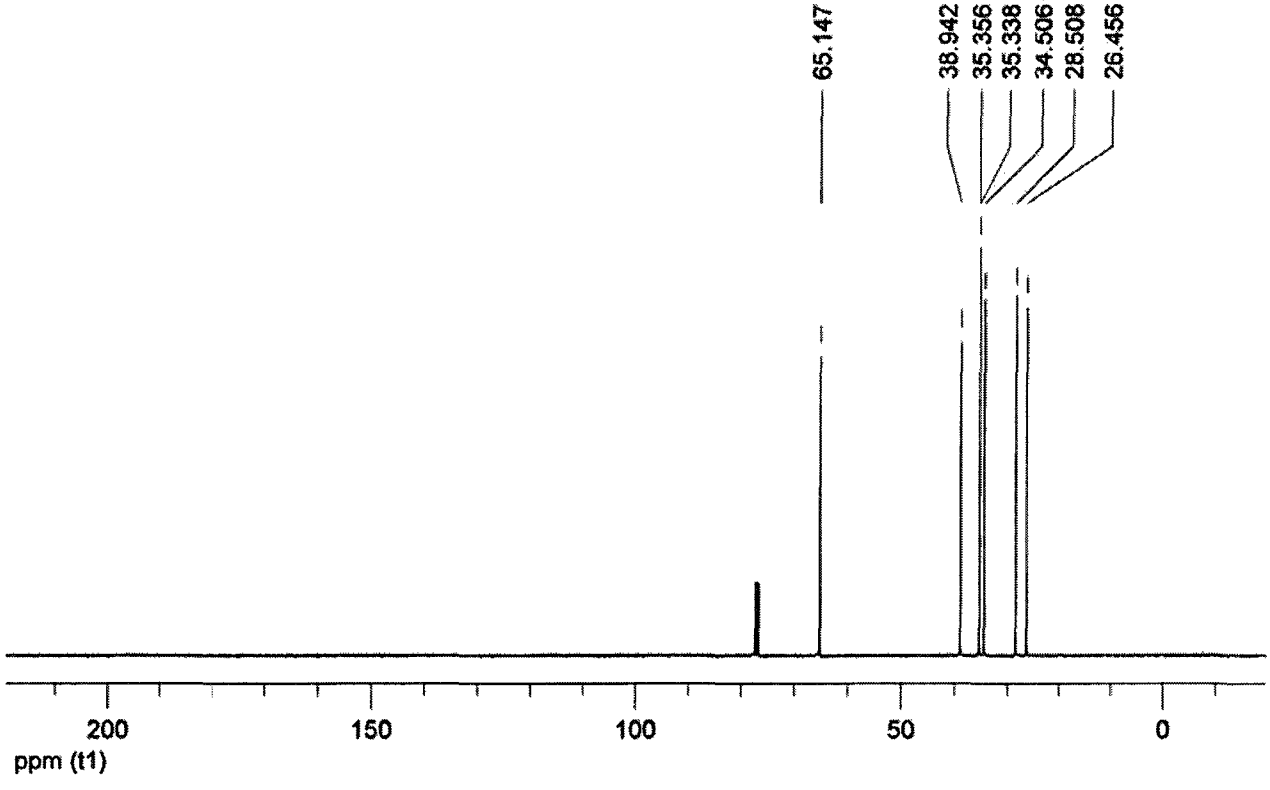


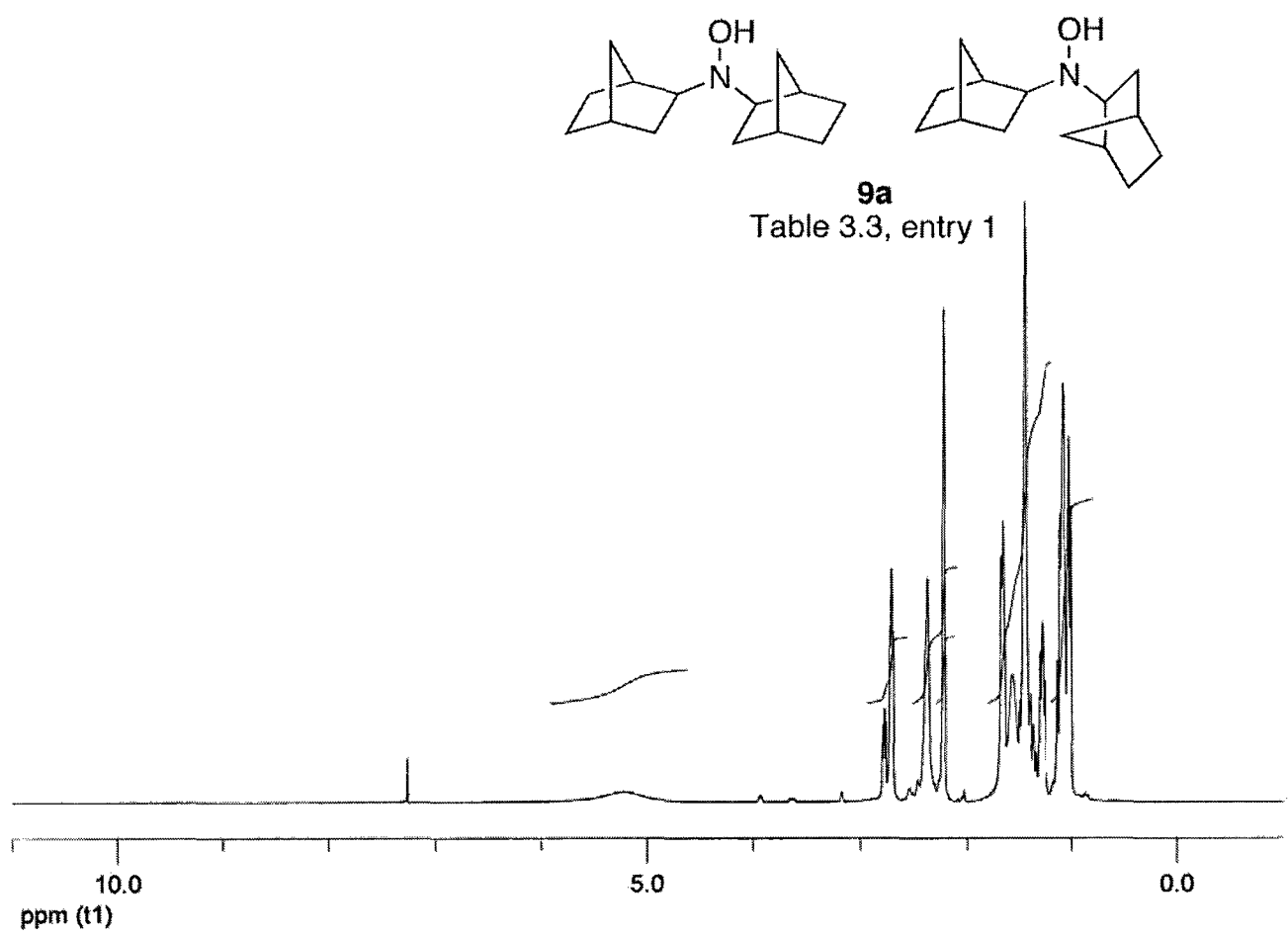
Appendix III. Supporting Information for Chapter 3.

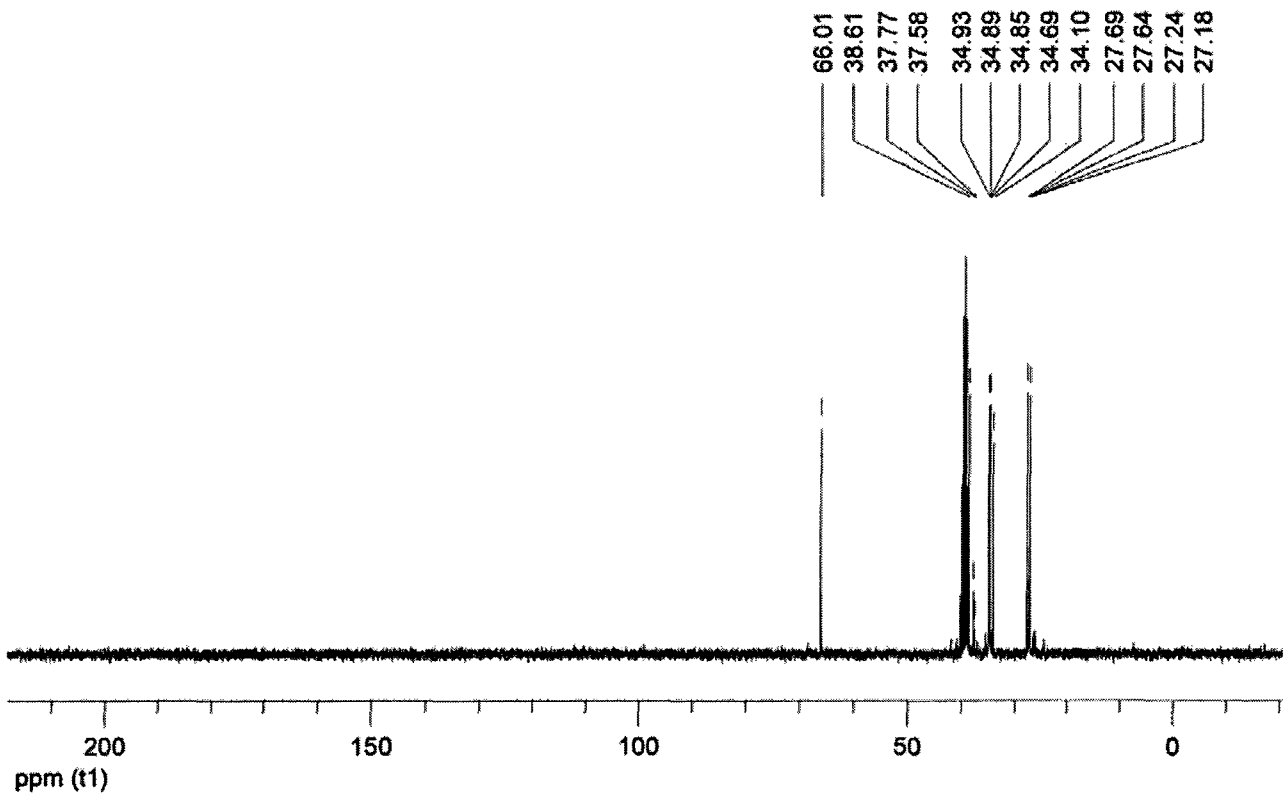


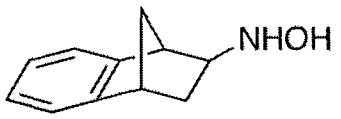
8a
Table 3.3, entry 1





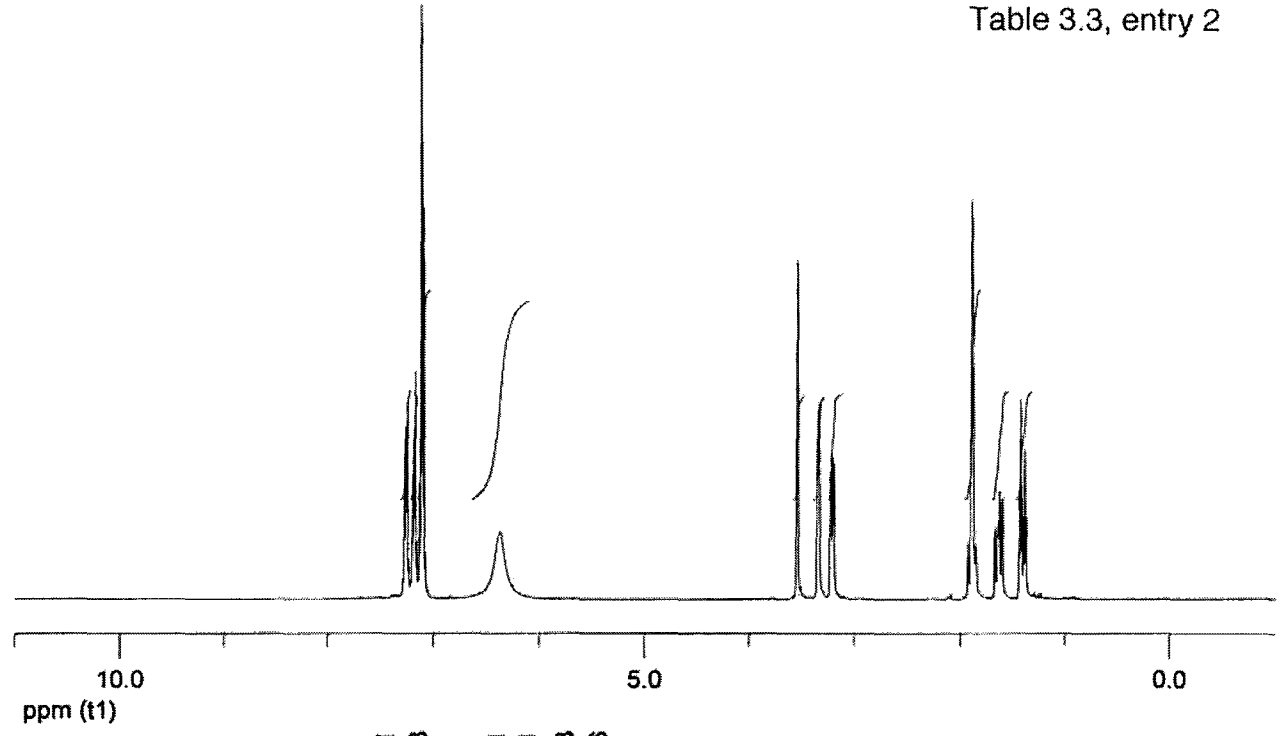

OH
N
OH
N
9a
Table 3.3, entry 1
10.0
5.0
0.0
ppm (t1)

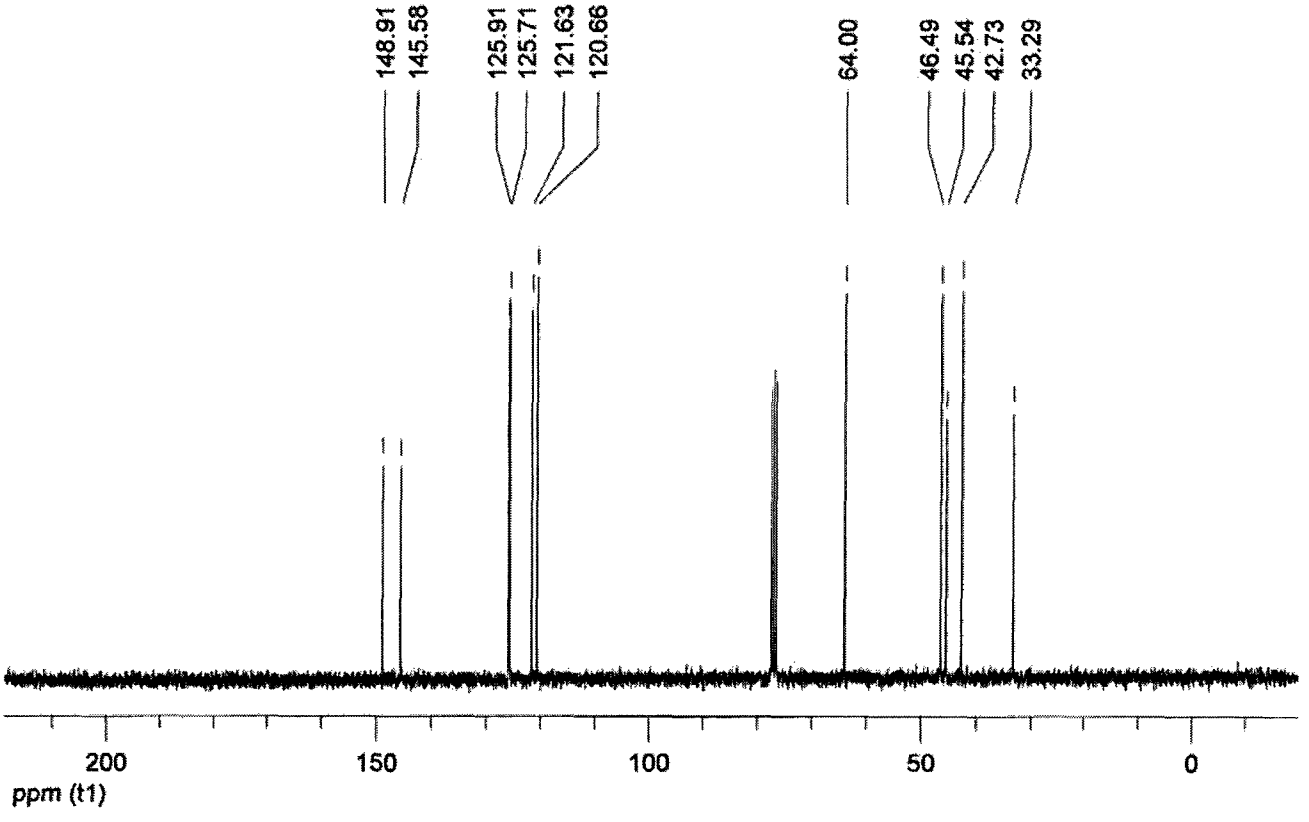

66.01
38.61
37.77
37.58
34.93
34.89
34.85
34.69
34.10
27.69
27.64
27.24
27.18
200
150
100
50
0
ppm (t1)

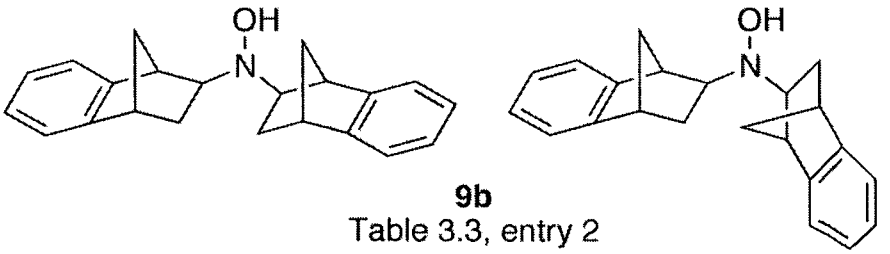


8b

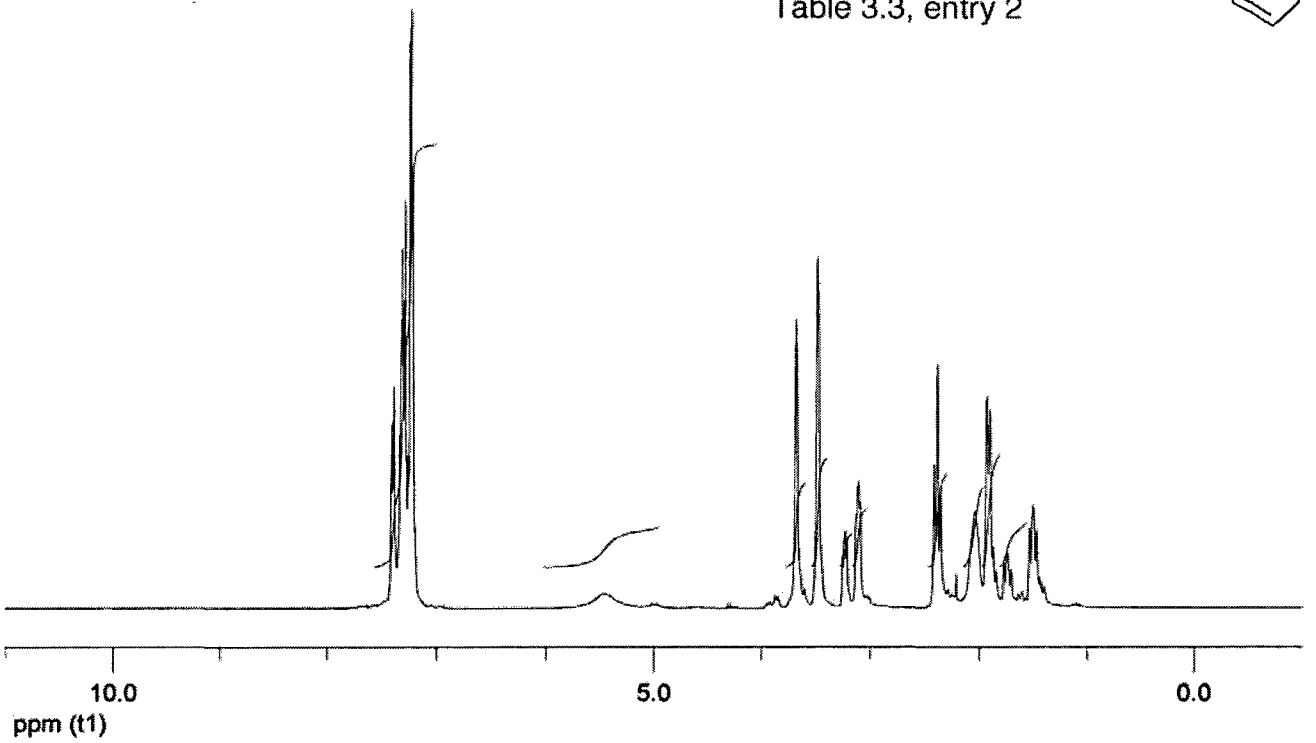
Table 3.3, entry 2

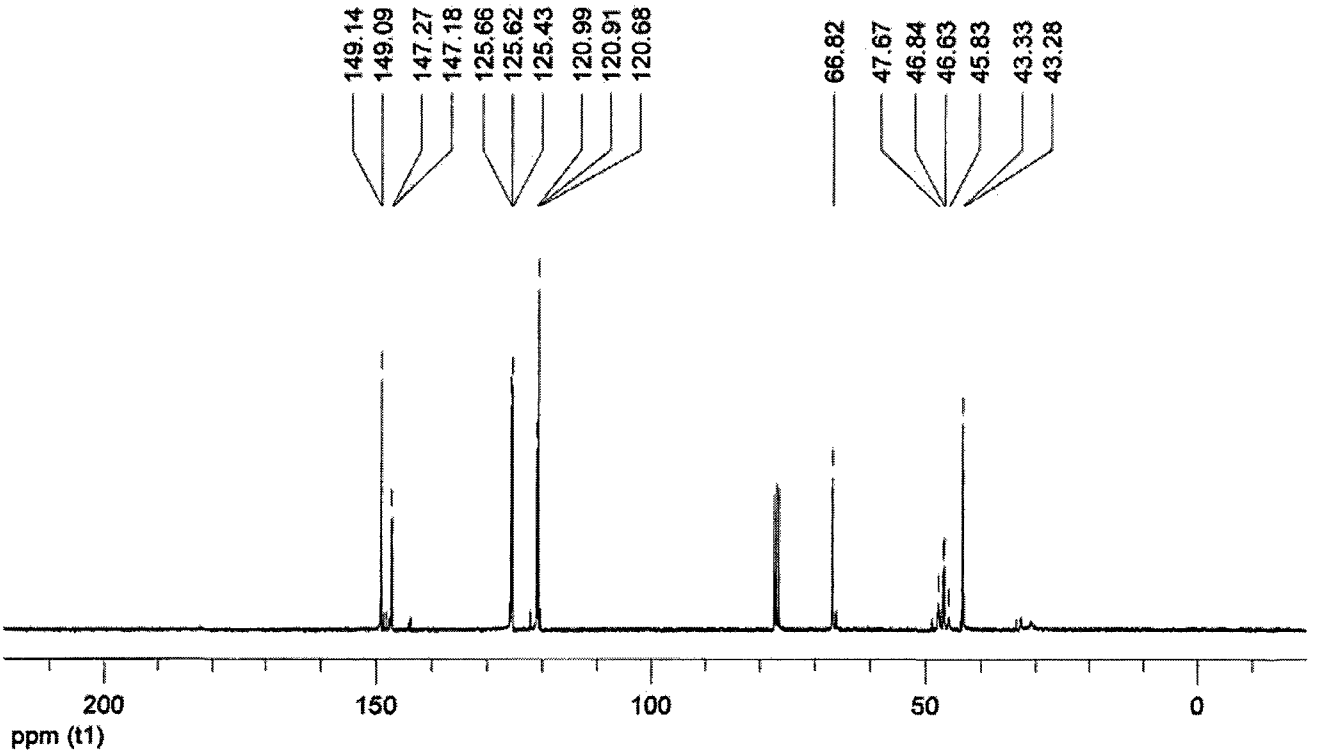


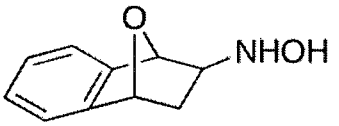




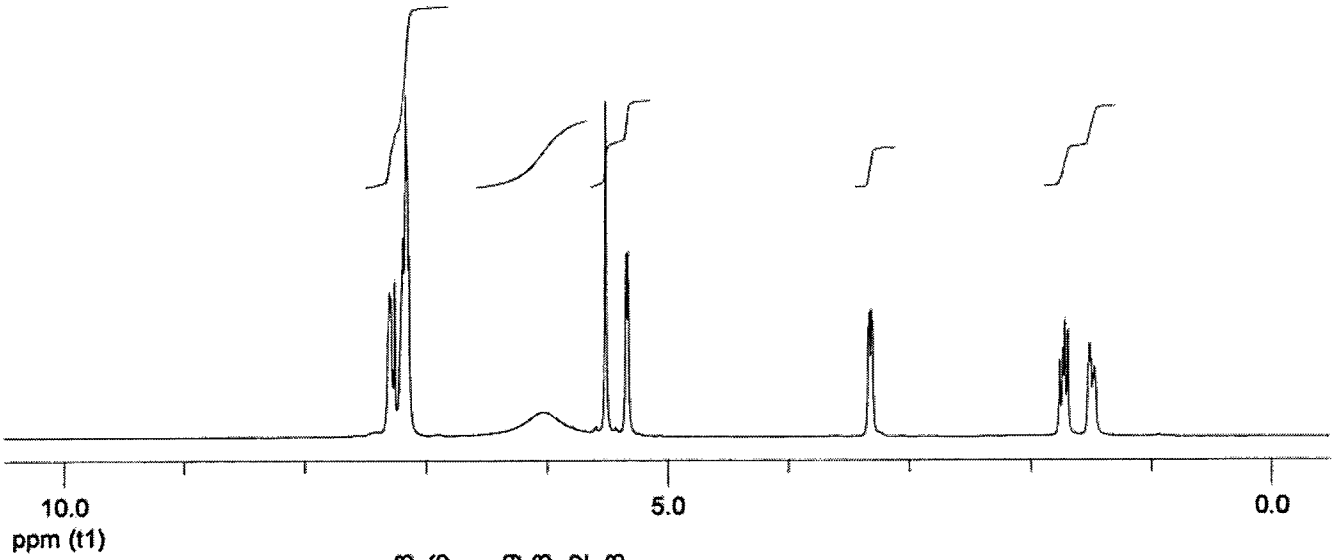
9b
Table 3.3, entry 2

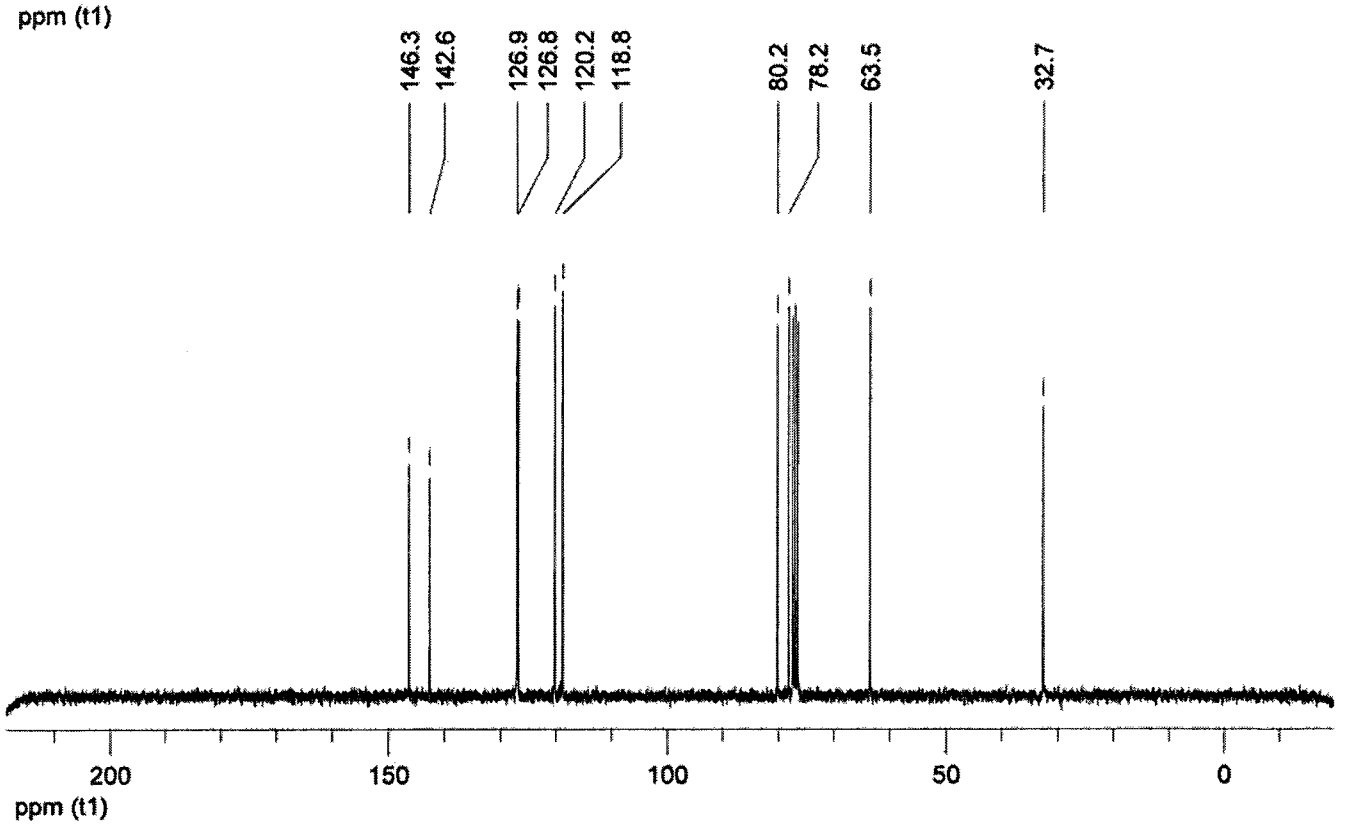


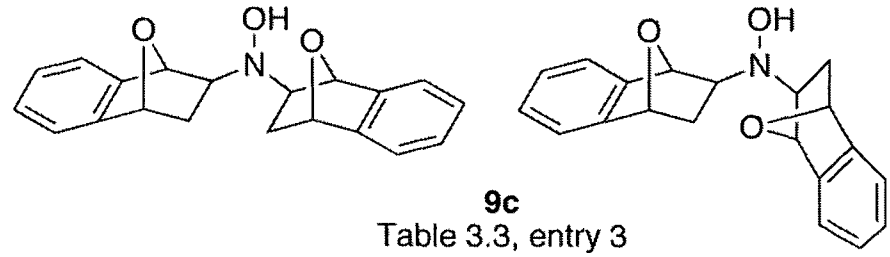




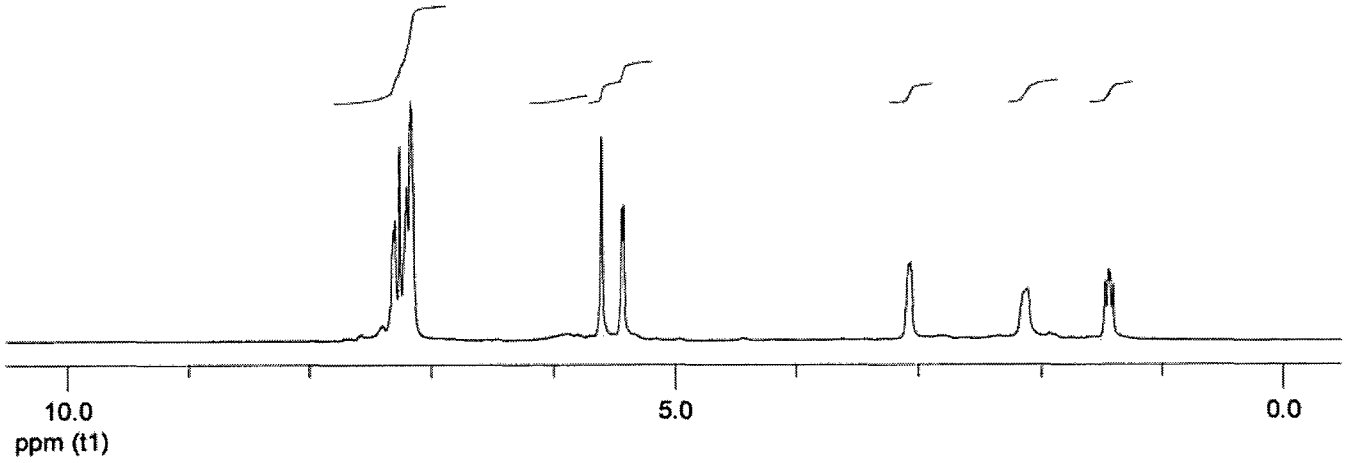
8c
Table 3.3, entry 3

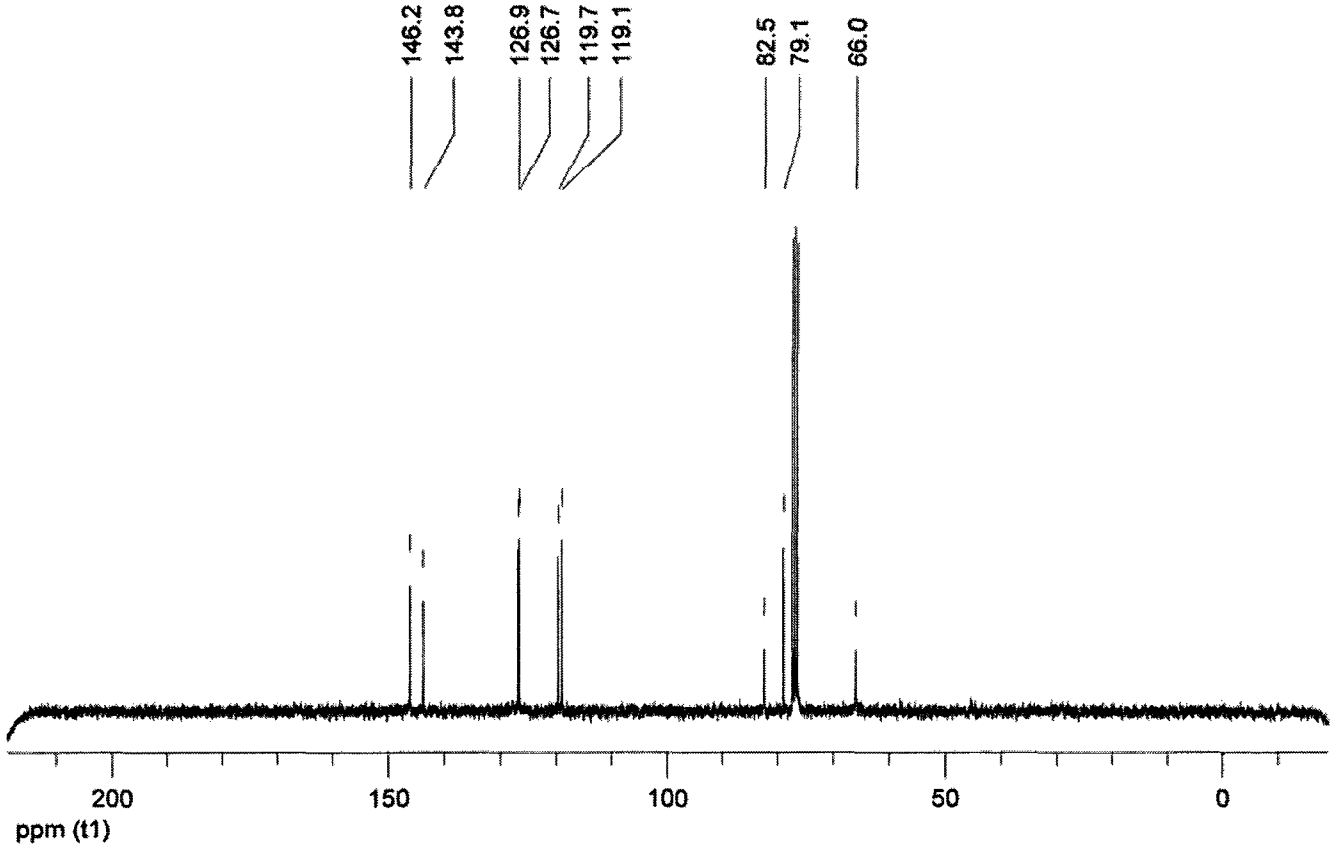


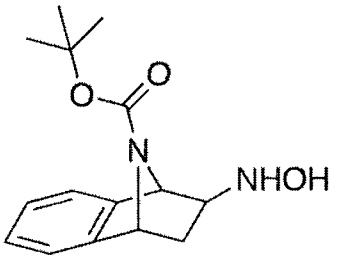




9c
Table 3.3, entry 3

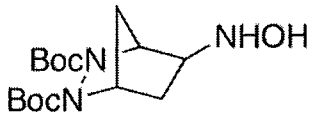






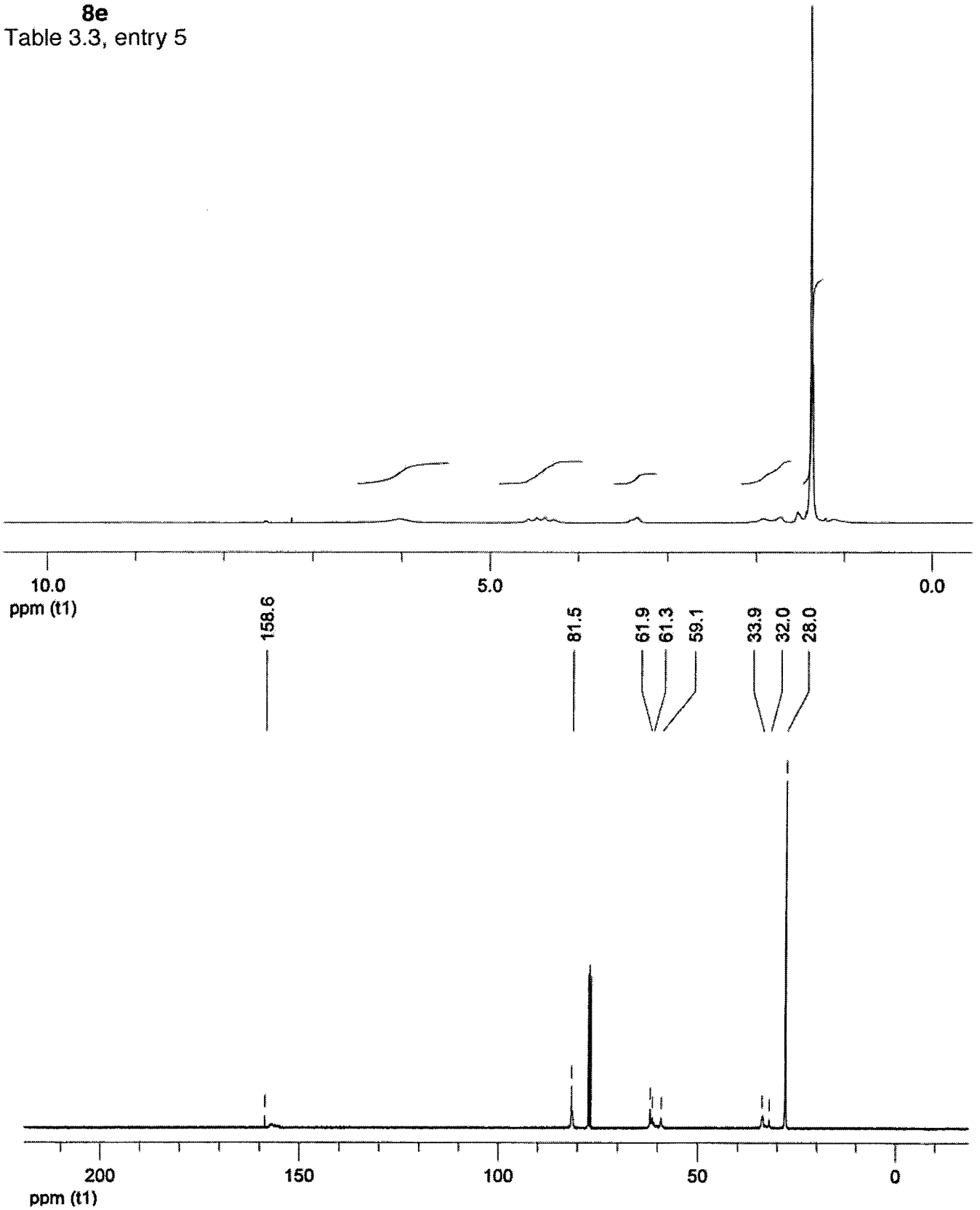
8d

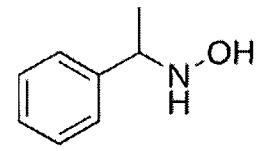
Table 3.3, entry 4



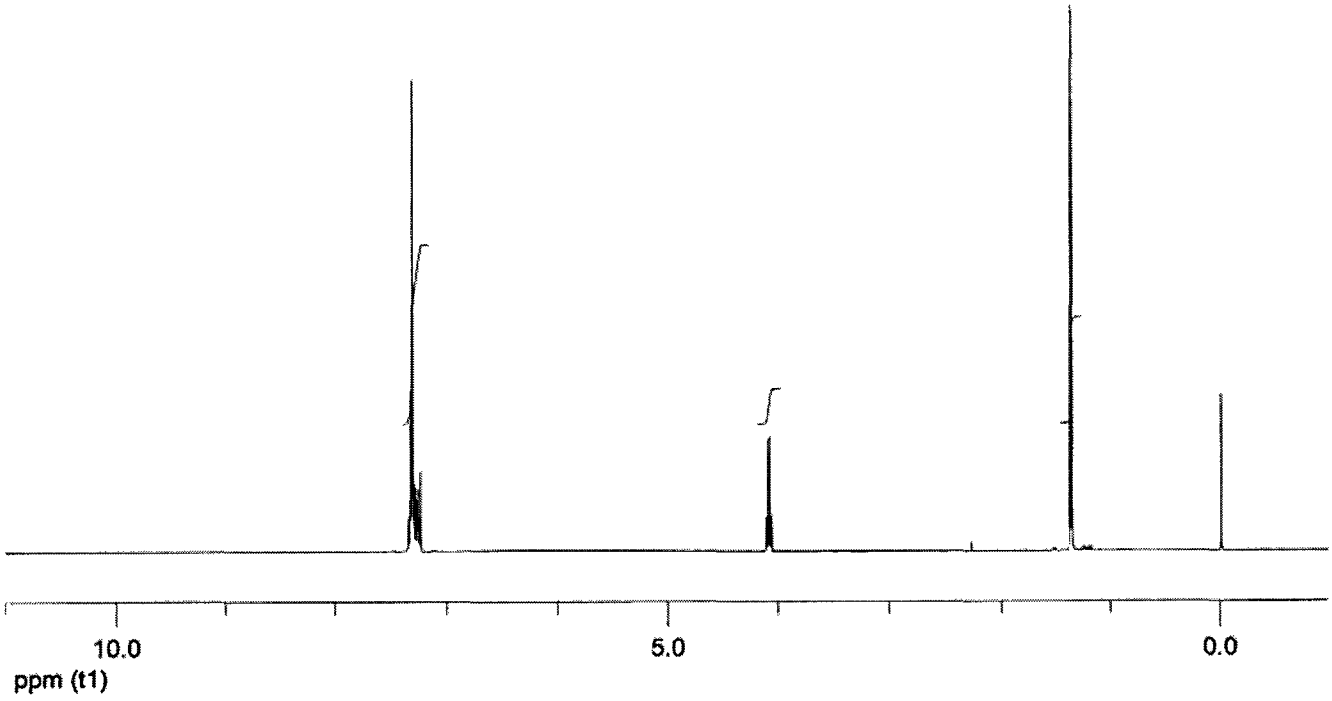
8e

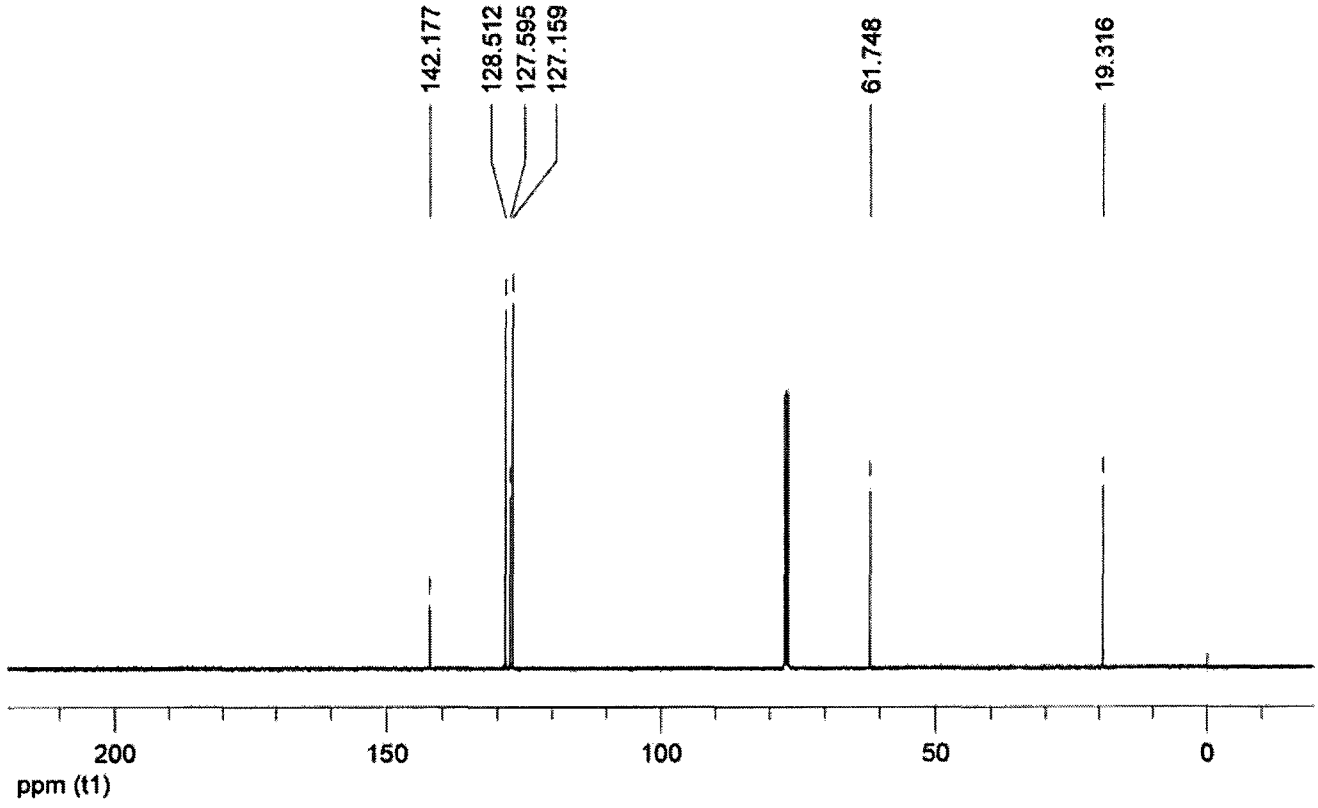
Table 3.3, entry 5

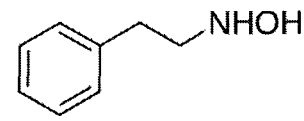




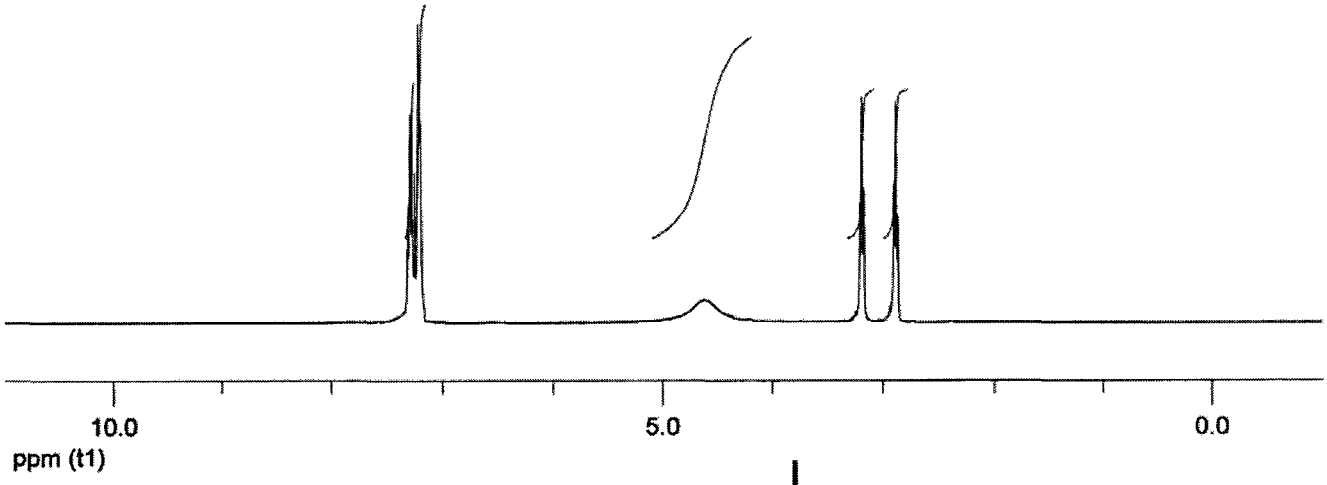
8f-1
Table 3.3, entry 6

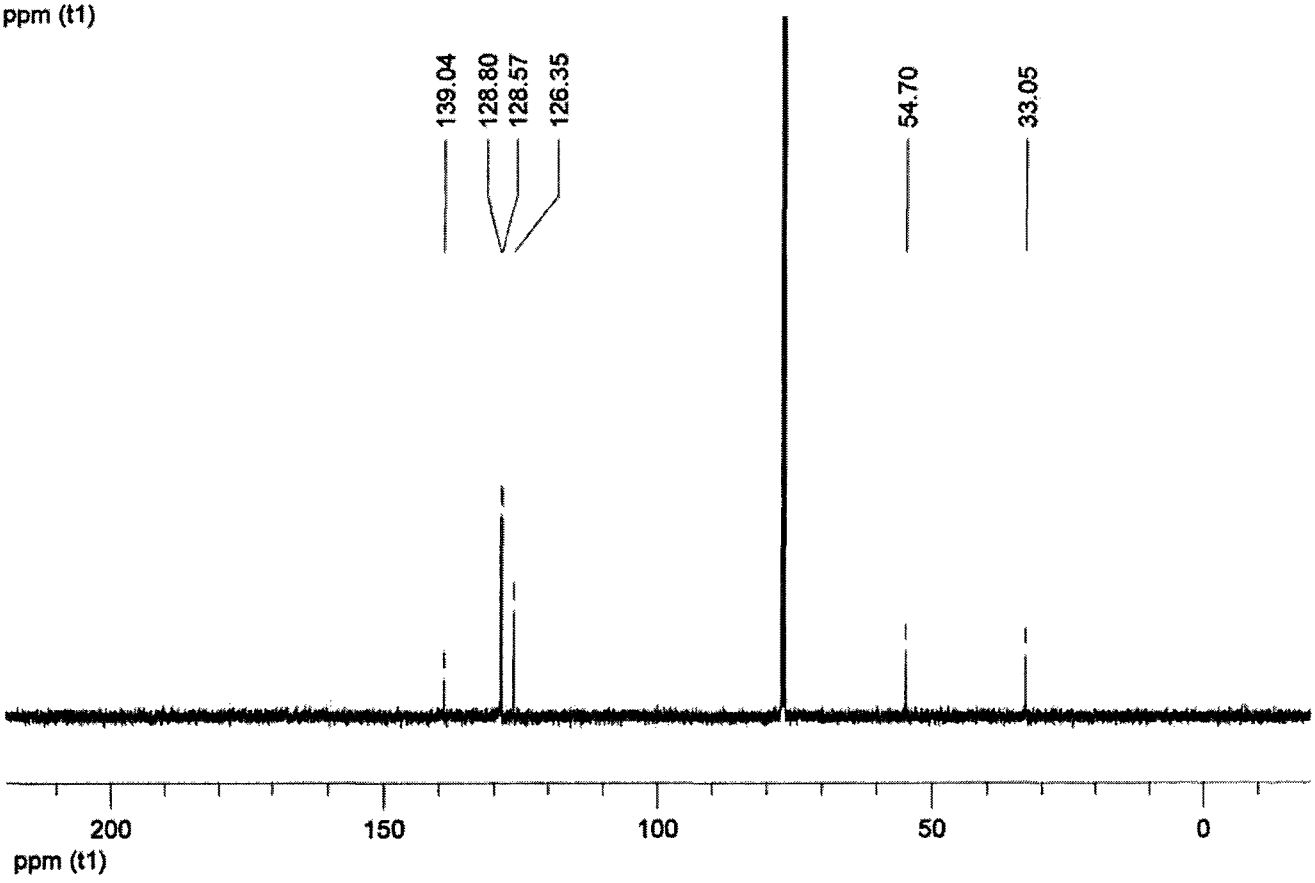


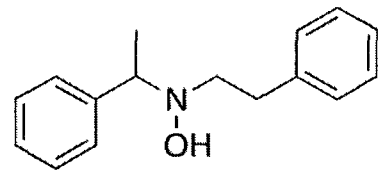




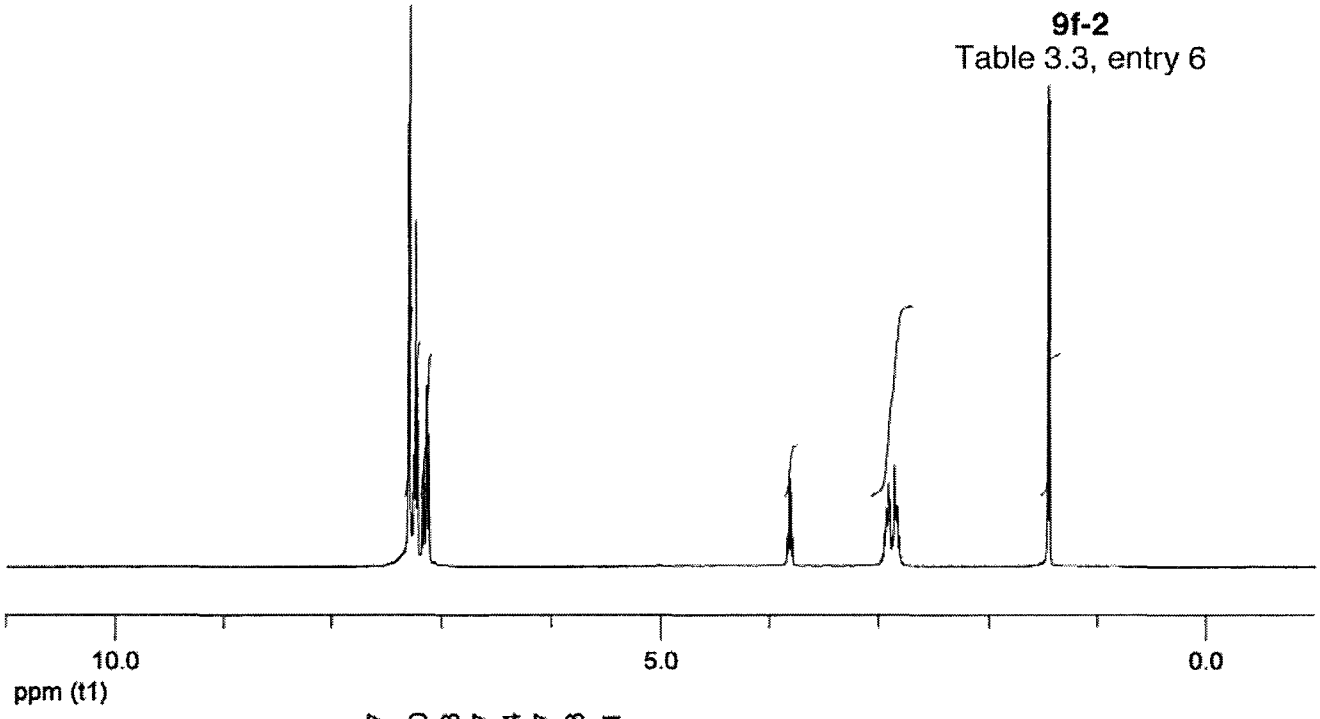
8f-2
Table 3.3, entry 6

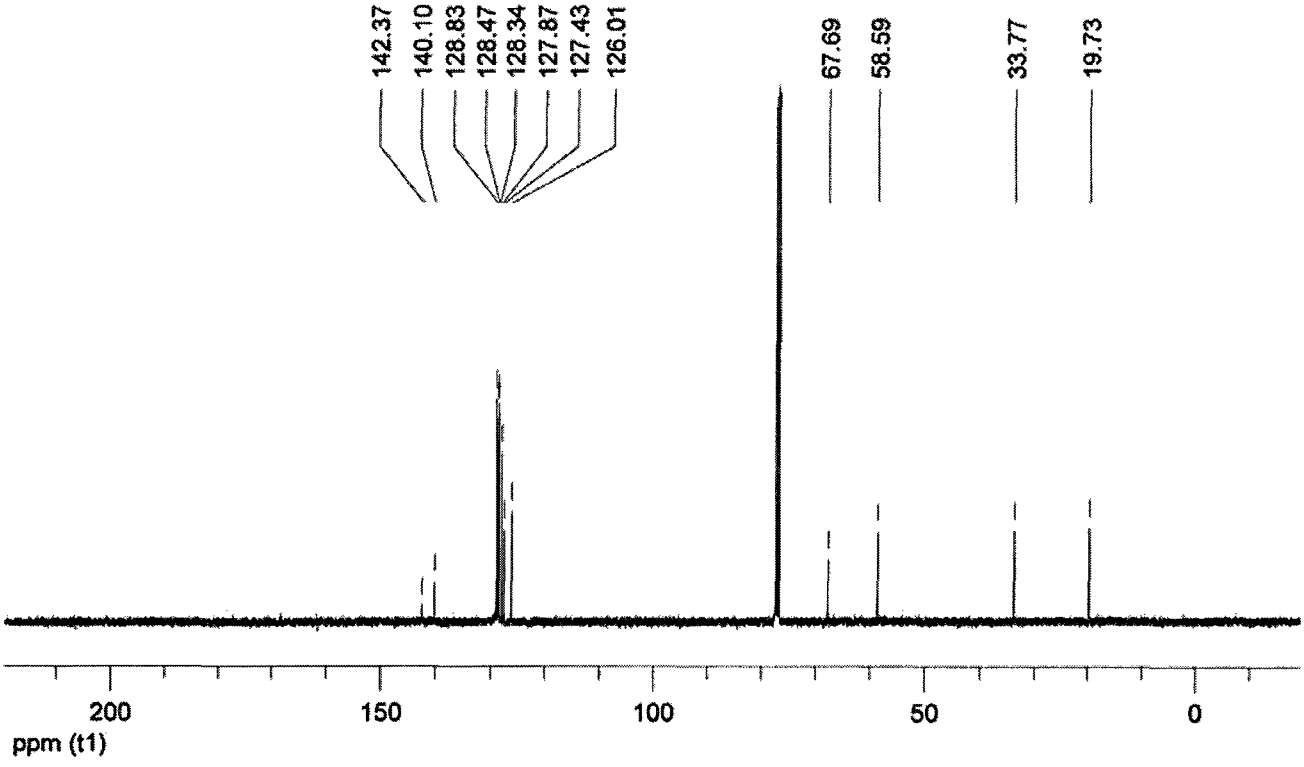


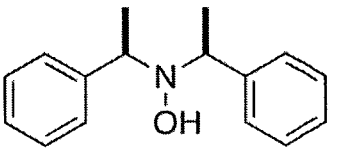




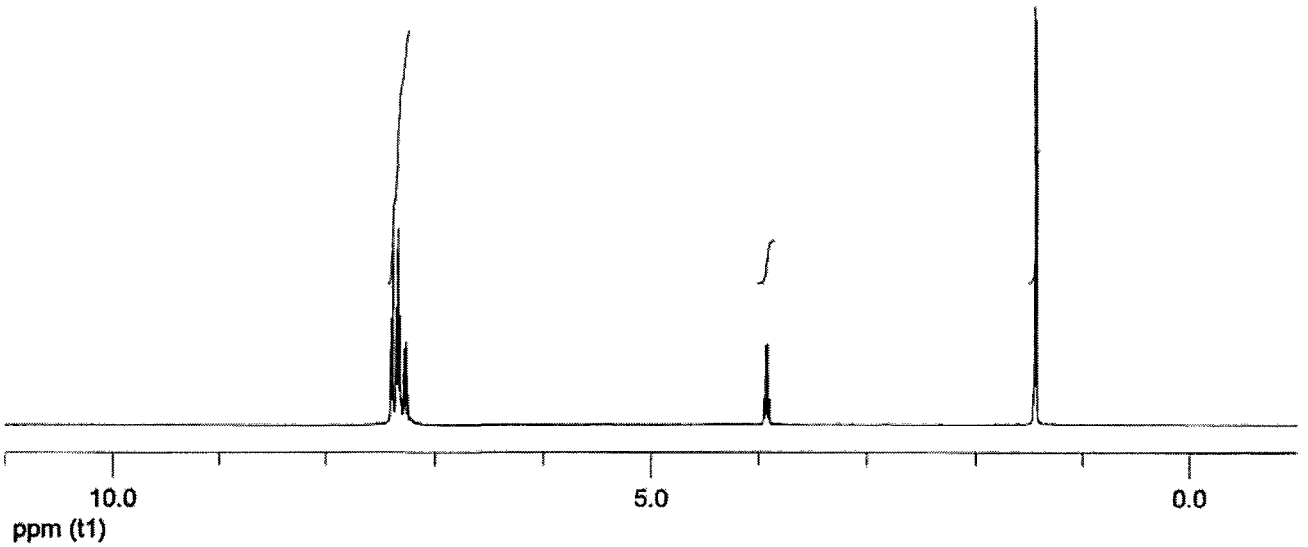
9f-2
Table 3.3, entry 6

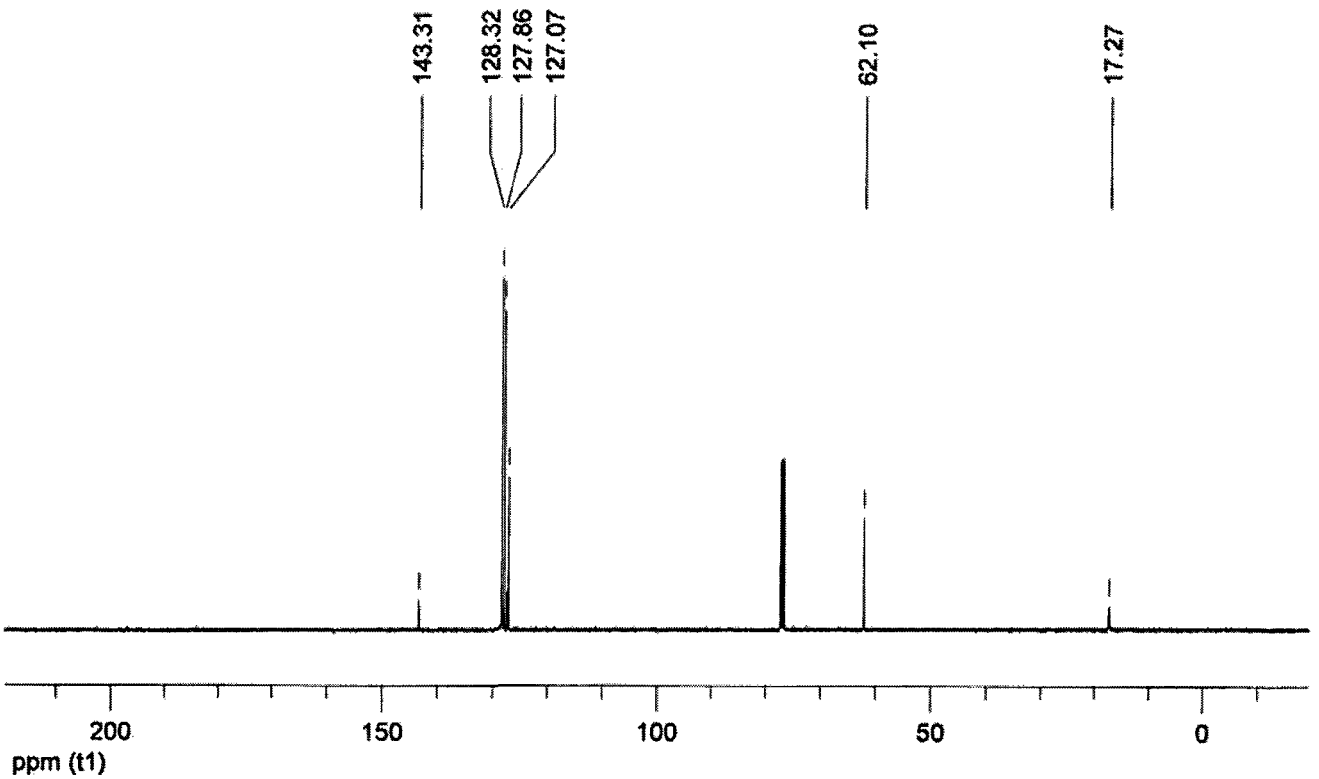


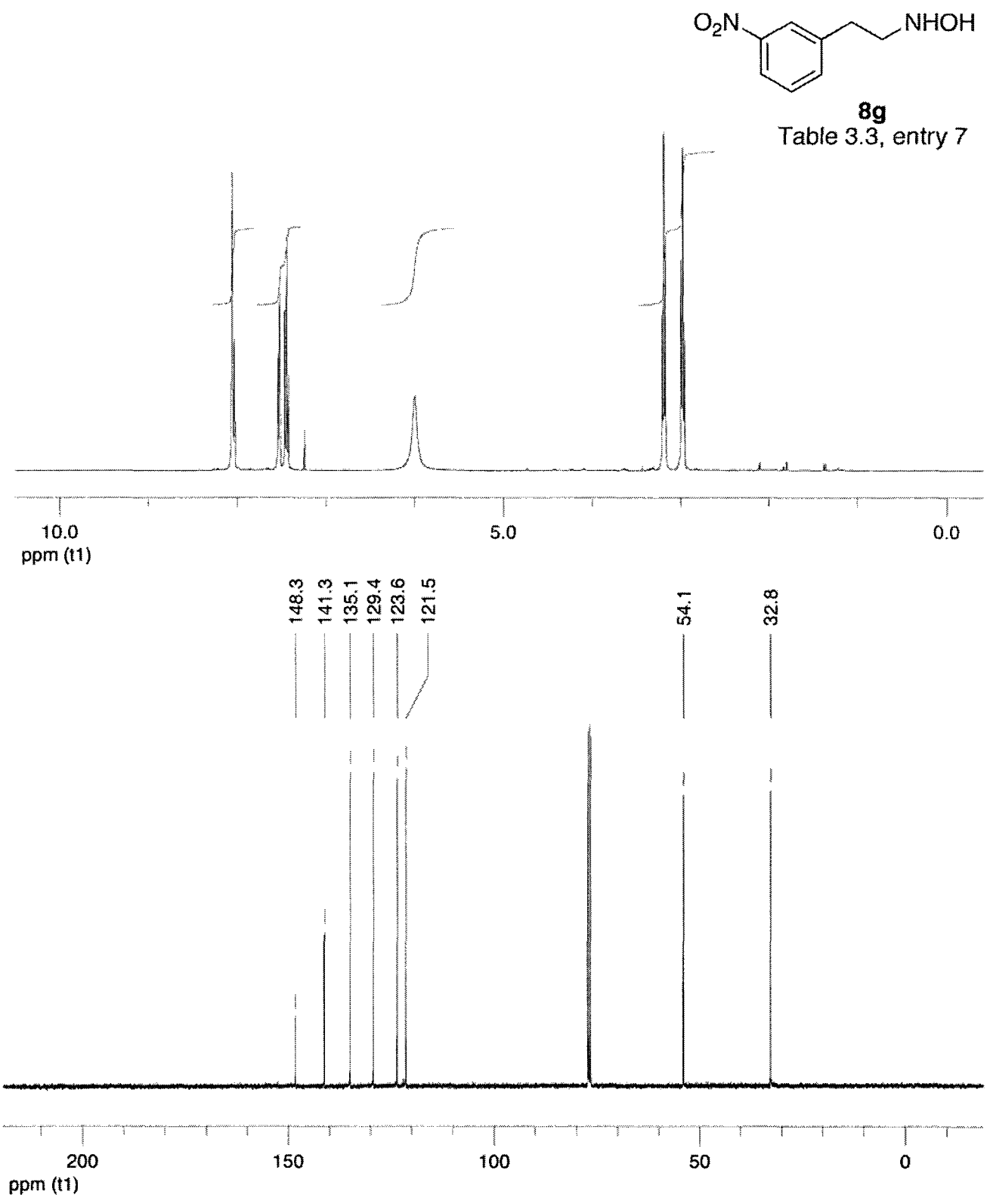


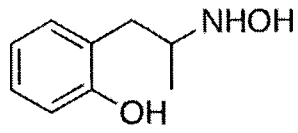


9f-1
Table 3.3, entry 6

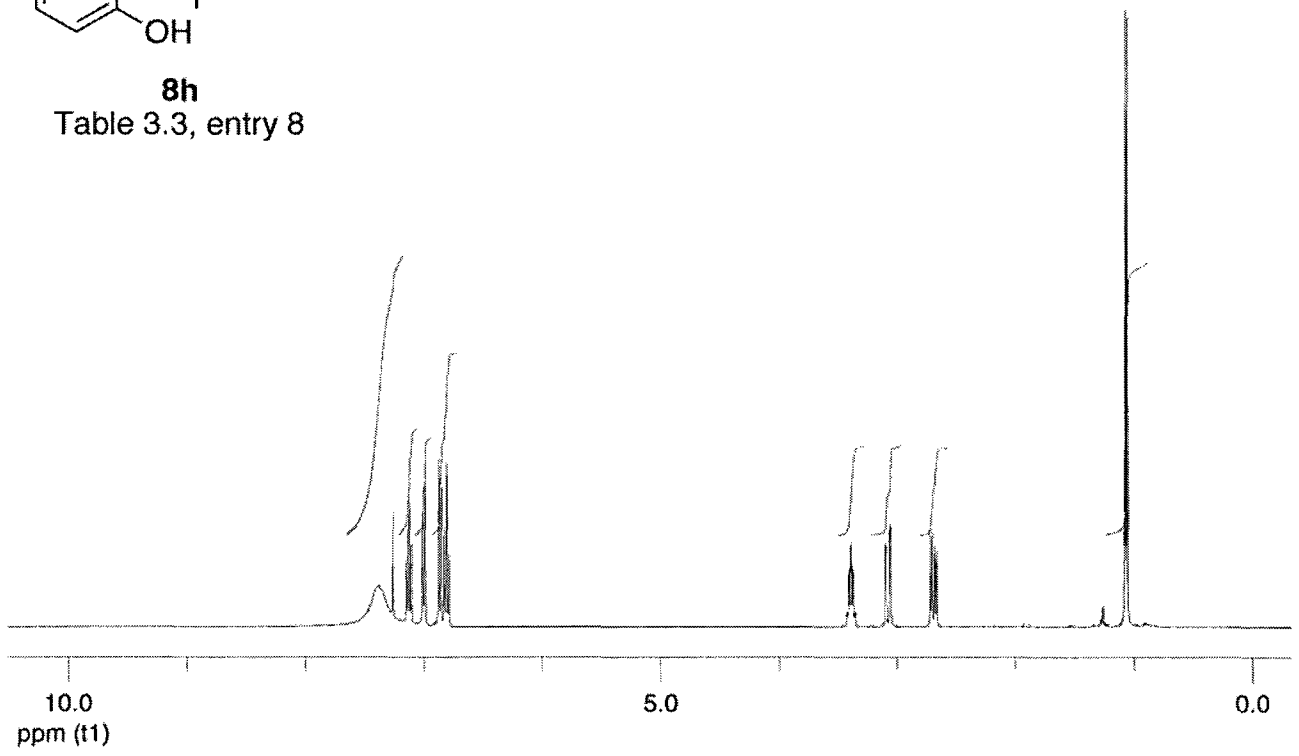


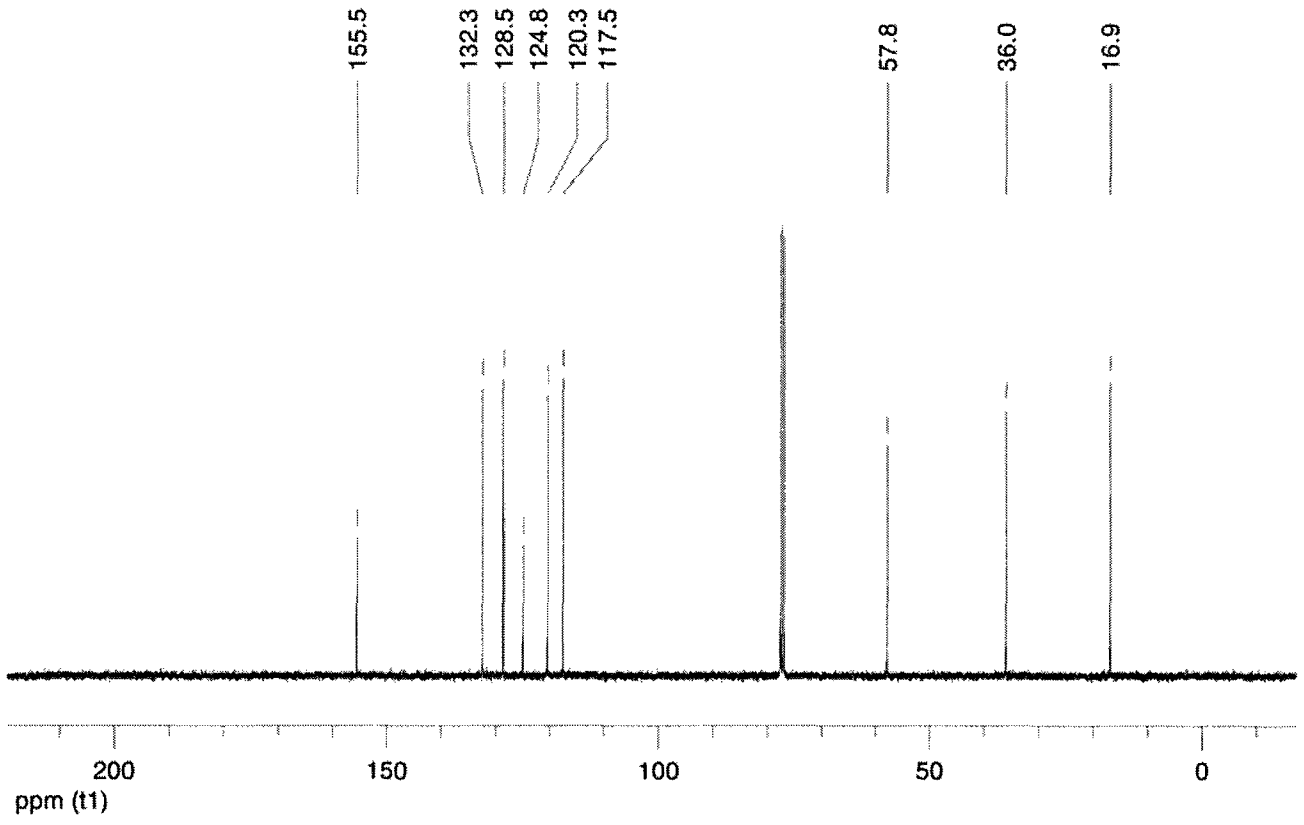


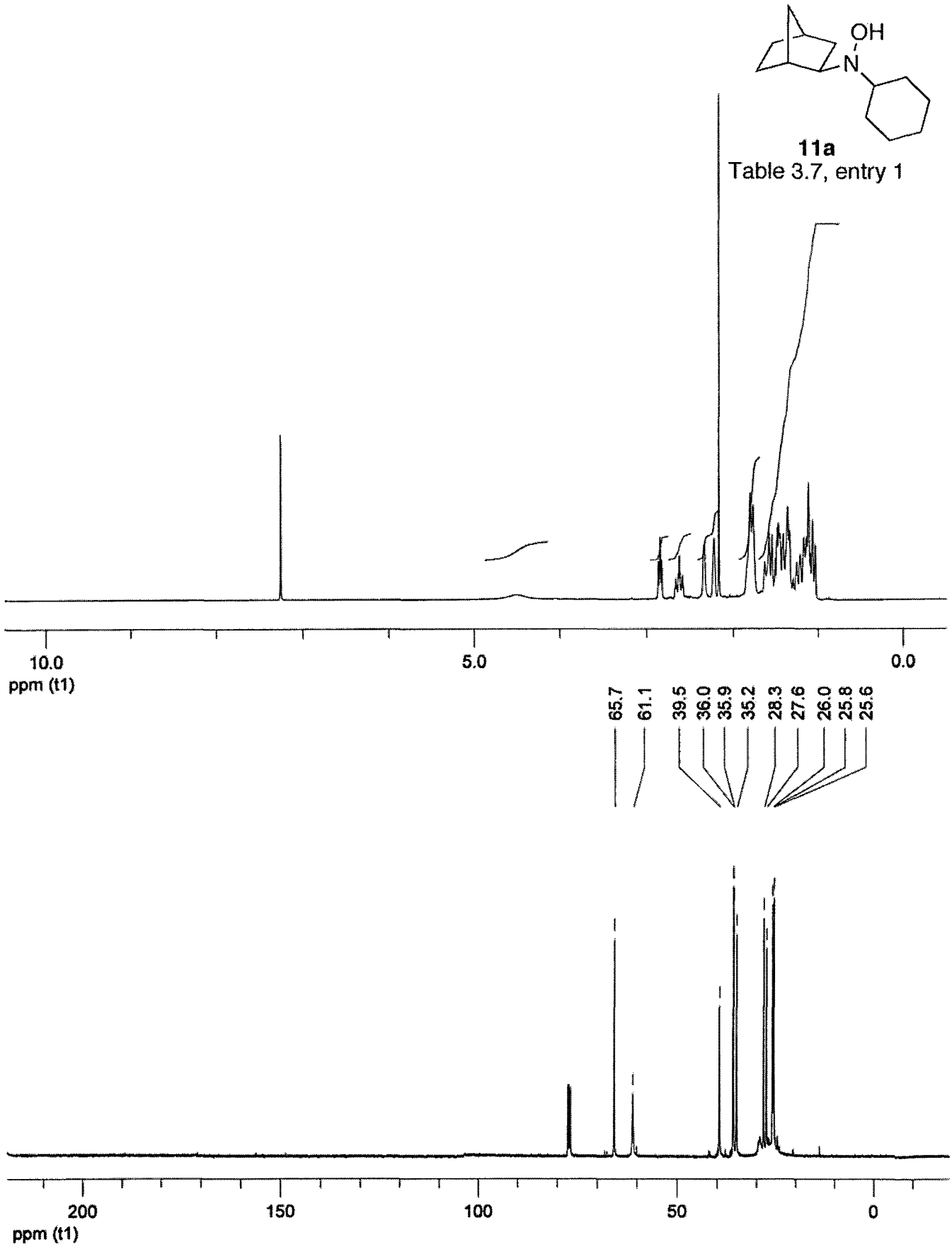

O2N
NHOH
8g
Table 3.3, entry 7
10.0
5.0
0.0
ppm (t1)
148.3
141.3
135.1
129.4
123.6
121.5
54.1
32.8
200
150
100
50
0
ppm (t1)

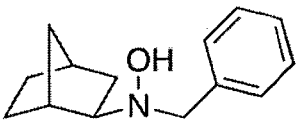


8h
Table 3.3, entry 8

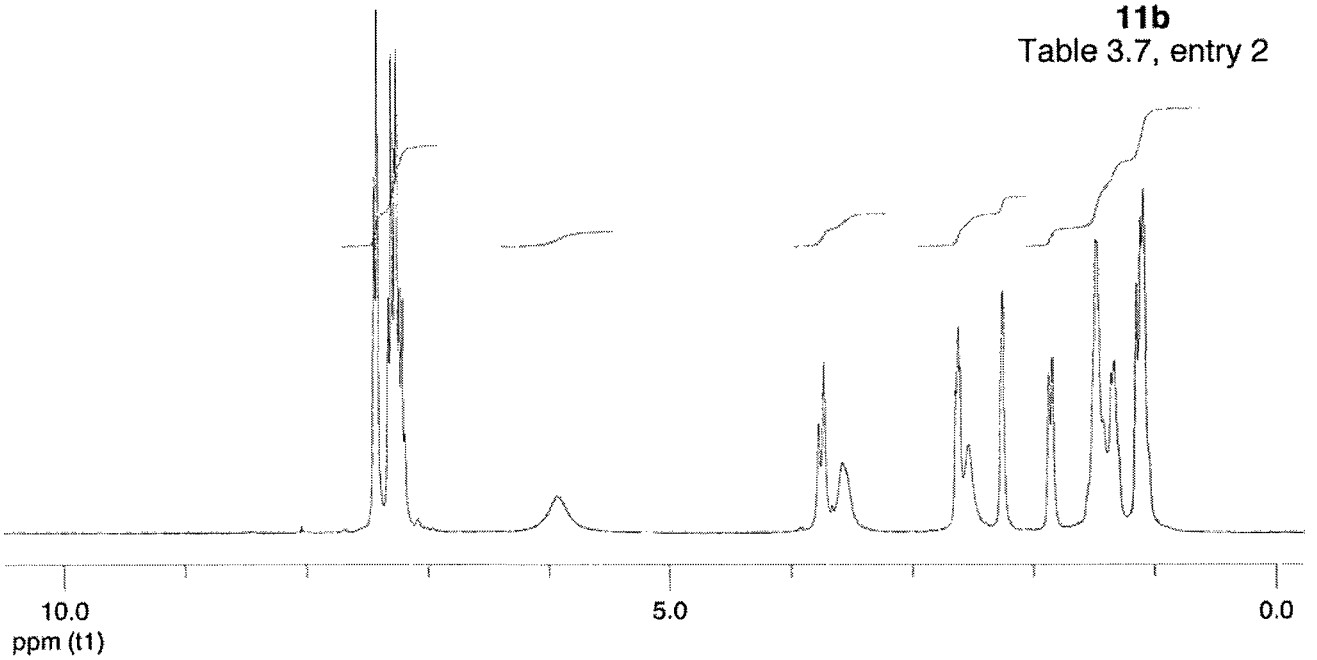


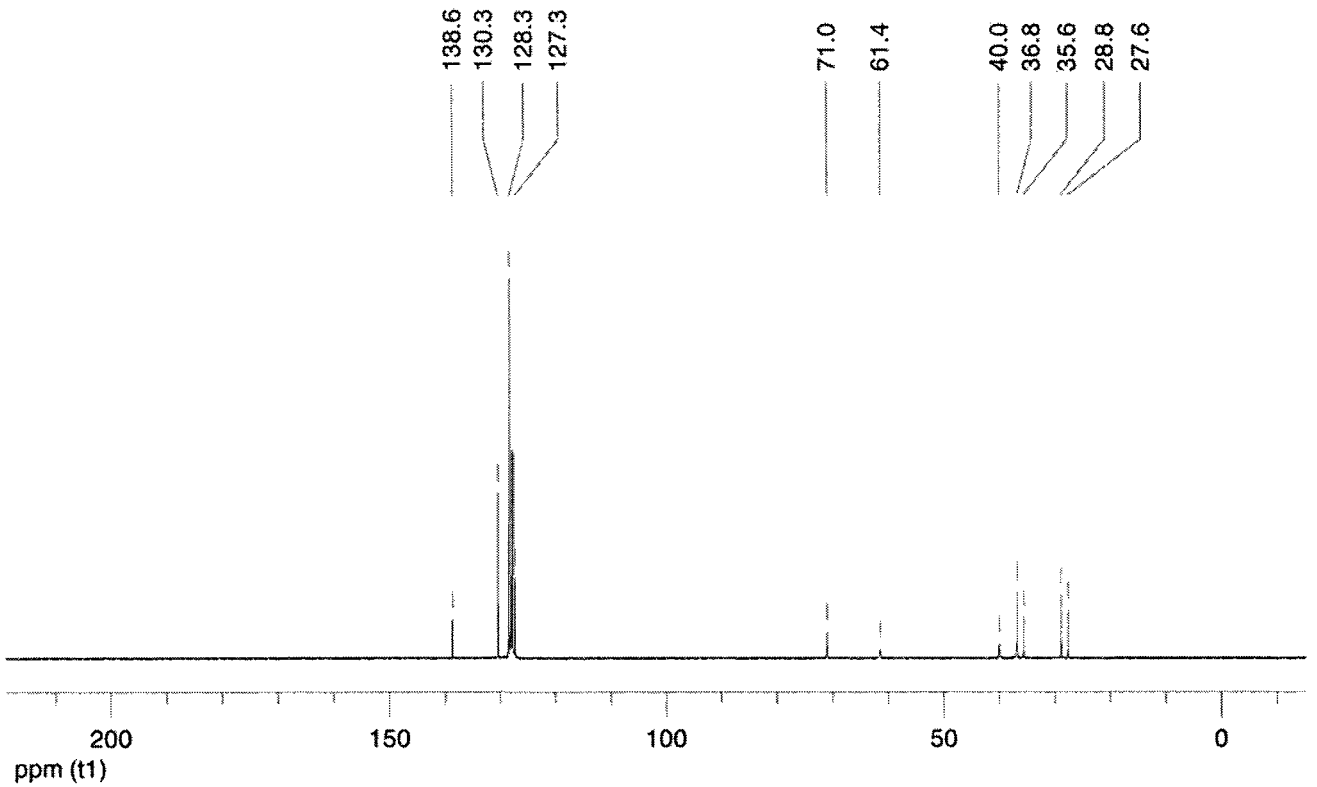


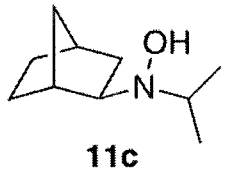

OH
N
11a
Table 3.7, entry 1
10.0
5.0
0.0
ppm (t1)
65.7
61.1
39.5
36.0
35.9
35.2
28.3
27.6
26.0
25.8
25.6
200
150
100
50
0
ppm (t1)



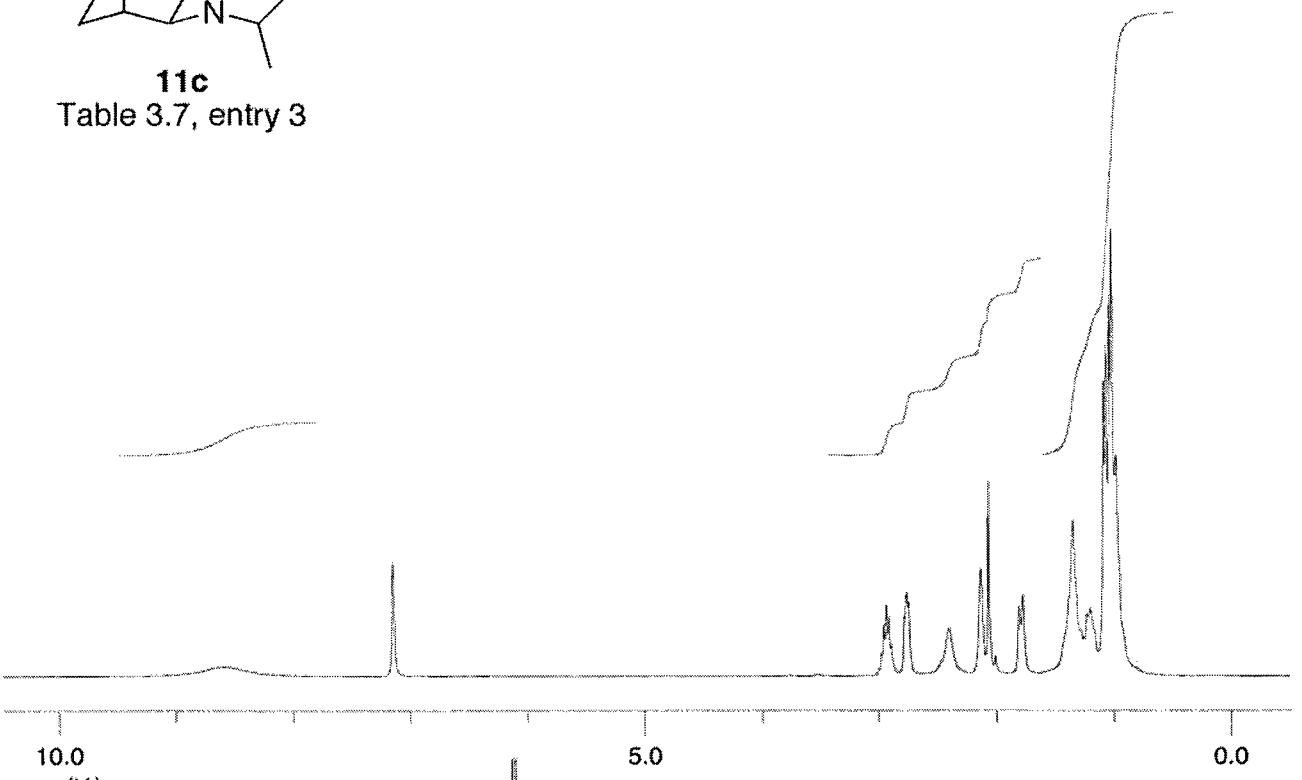
11b
Table 3.7, entry 2

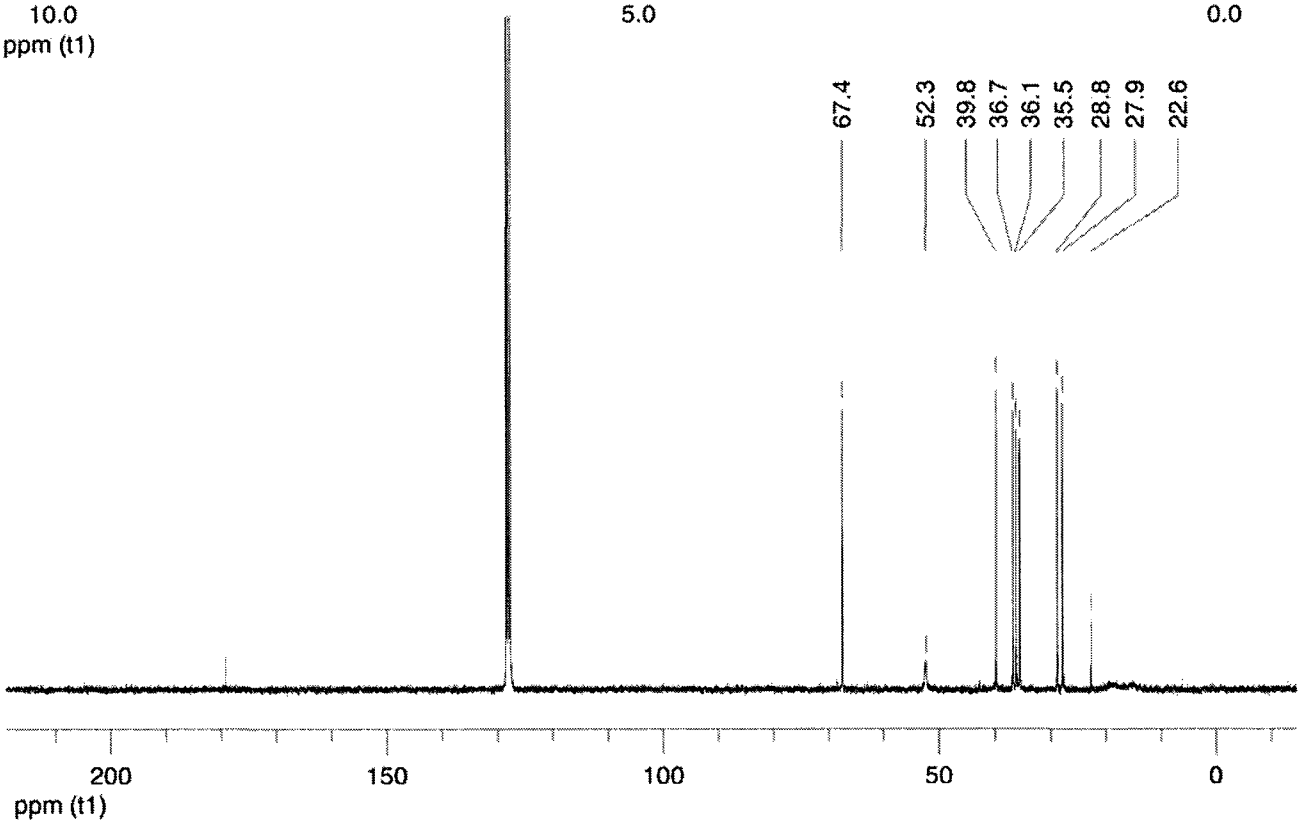


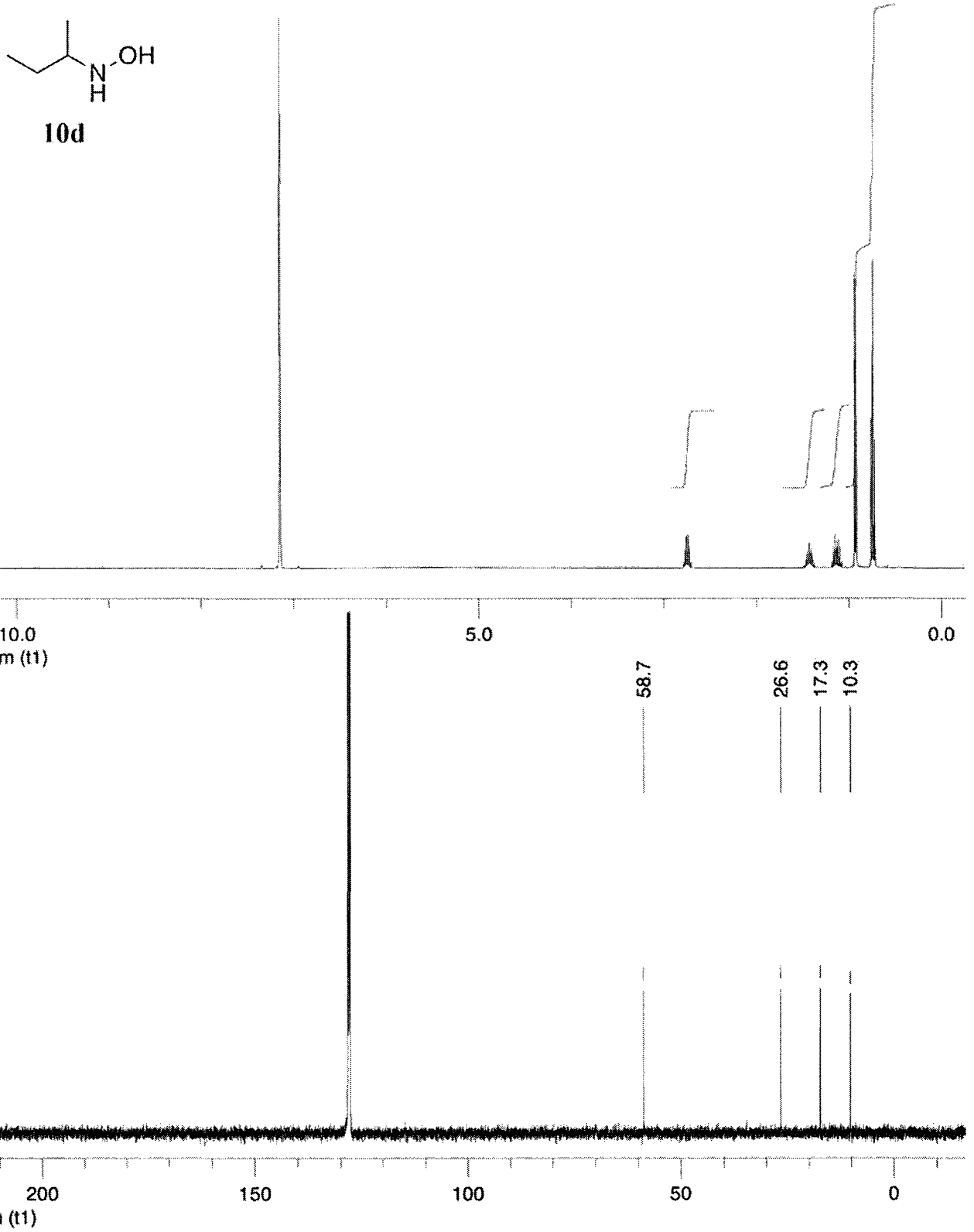


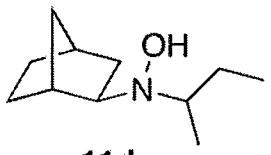


11c
Table 3.7, entry 3

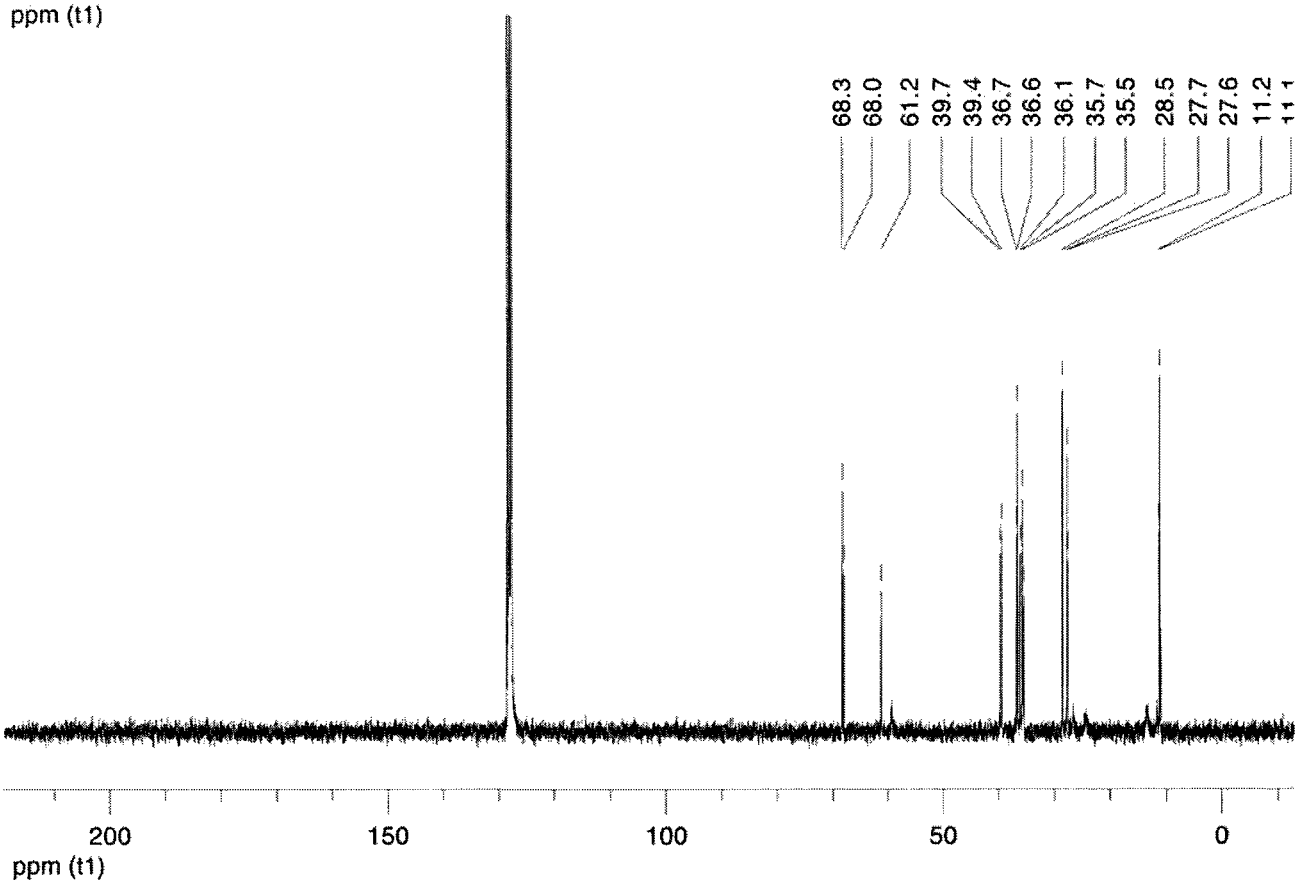


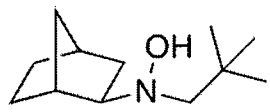



OH
N
H
10d
10.0
ppm (t1)
5.0
0.0
58.7
26.6
17.3
10.3
200
150
100
50
0
ppm (t1)

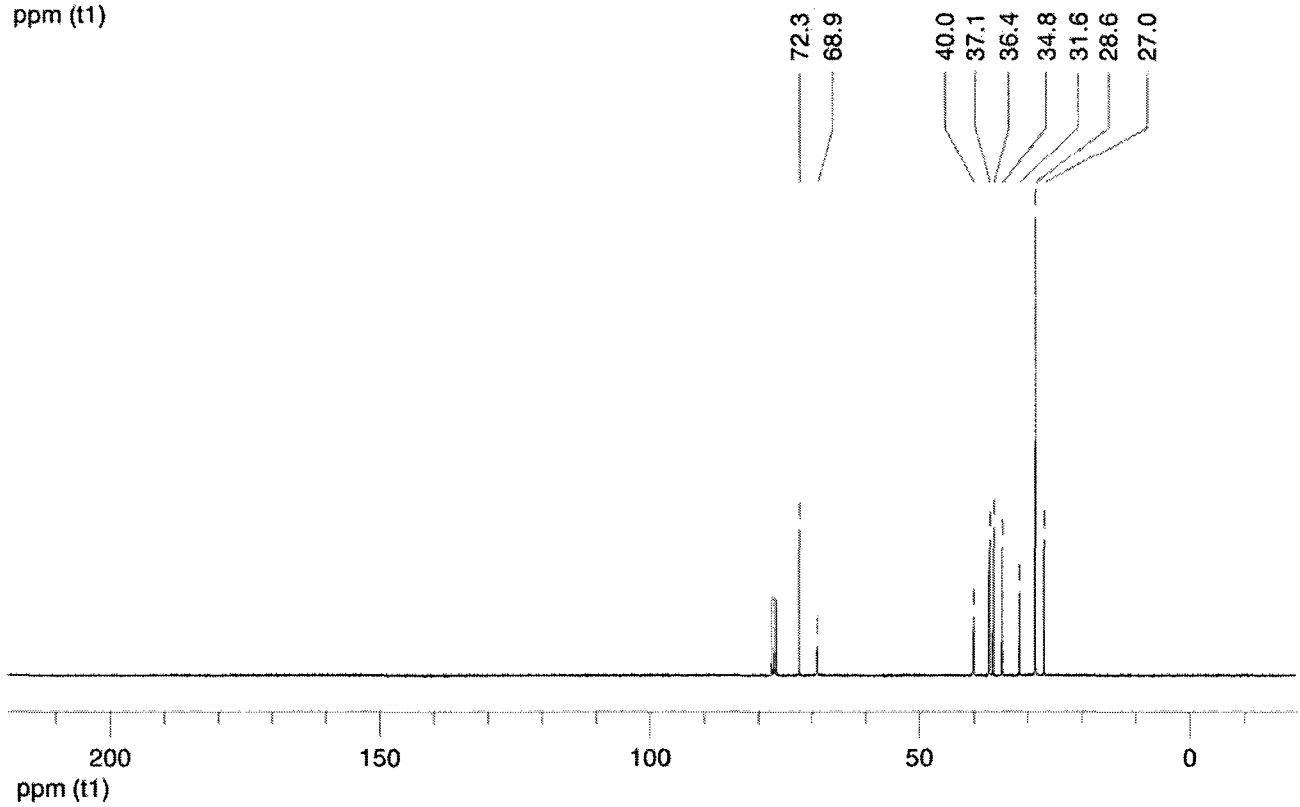


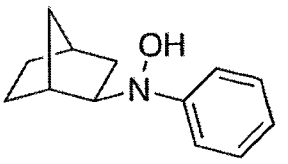
11d
Table 3.7, entry 4



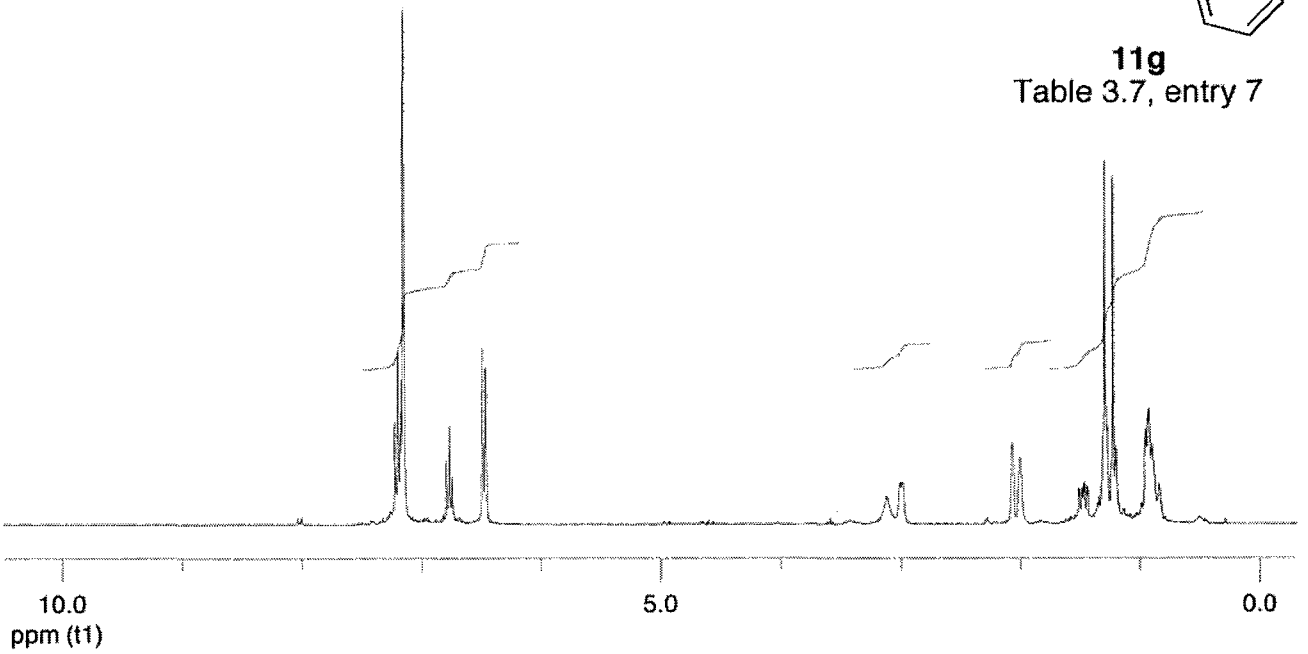


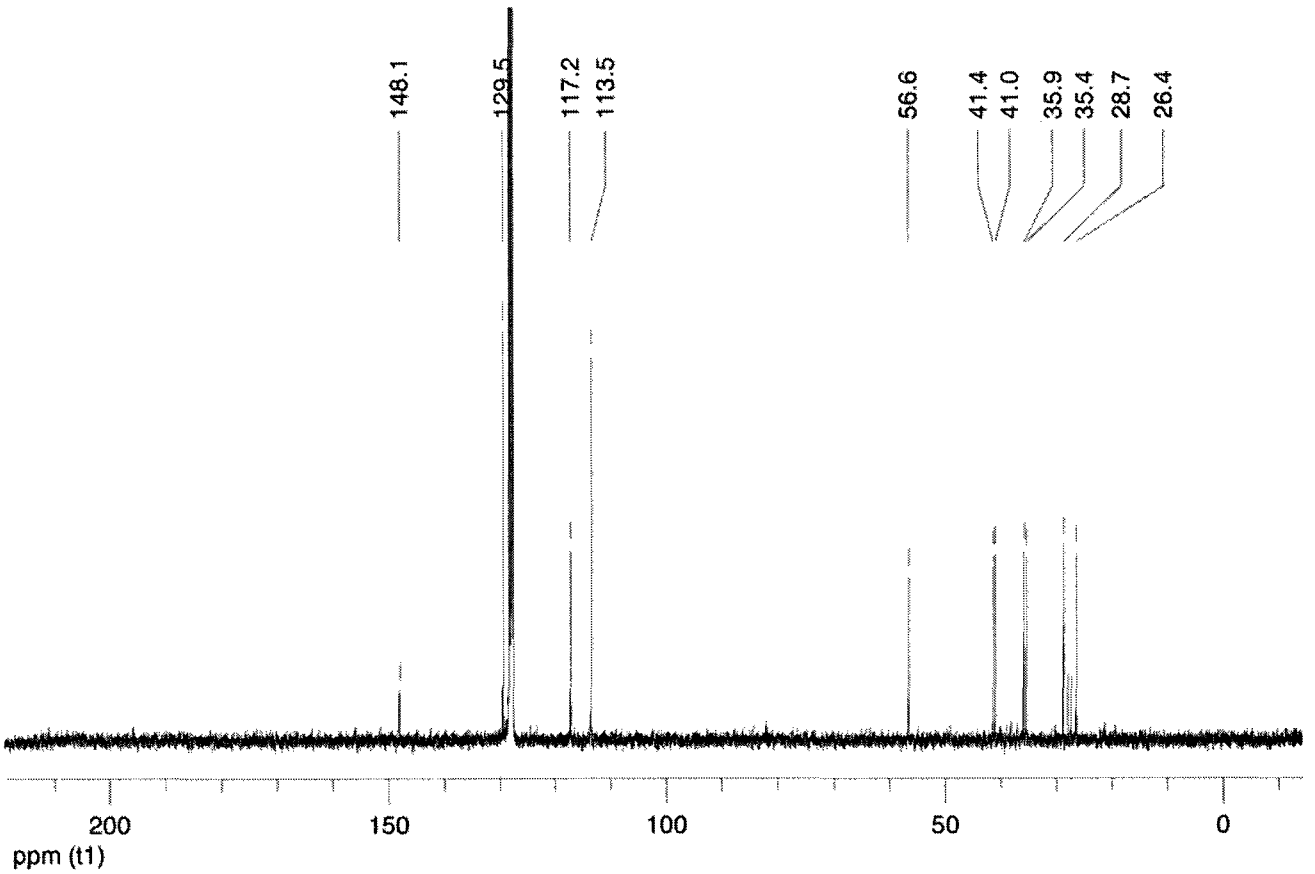
11f
Table 3.7, entry 6

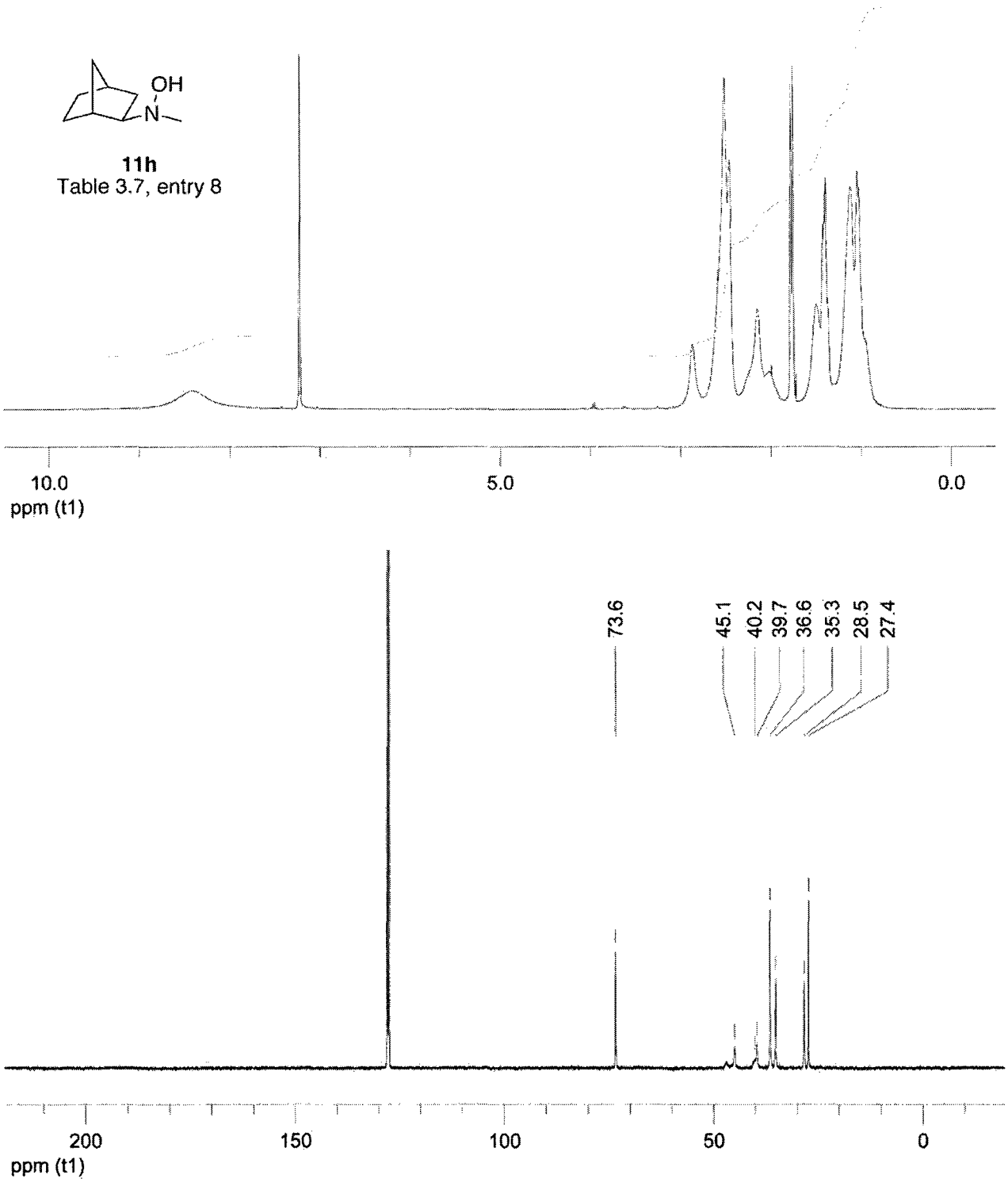


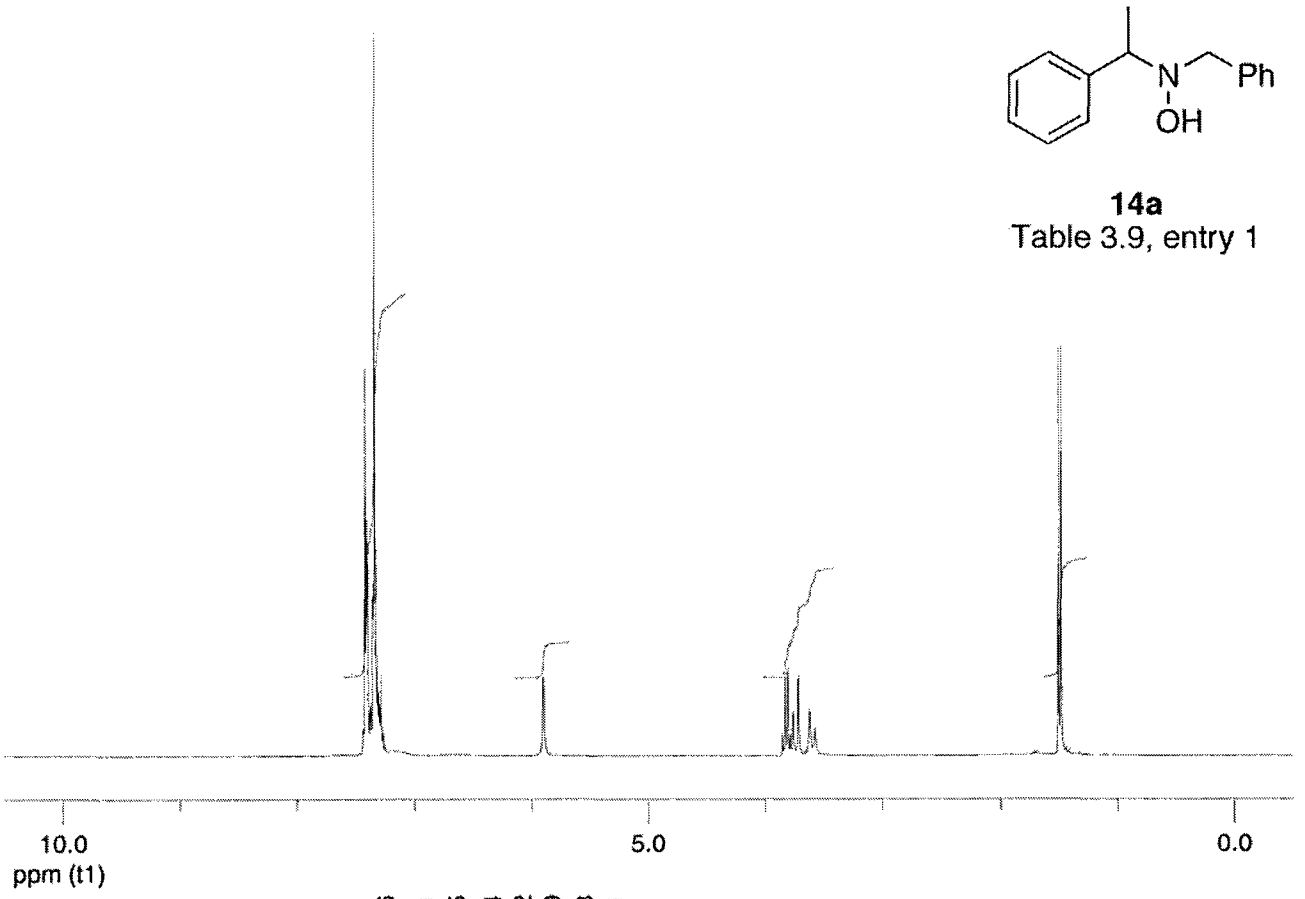


11g
Table 3.7, entry 7

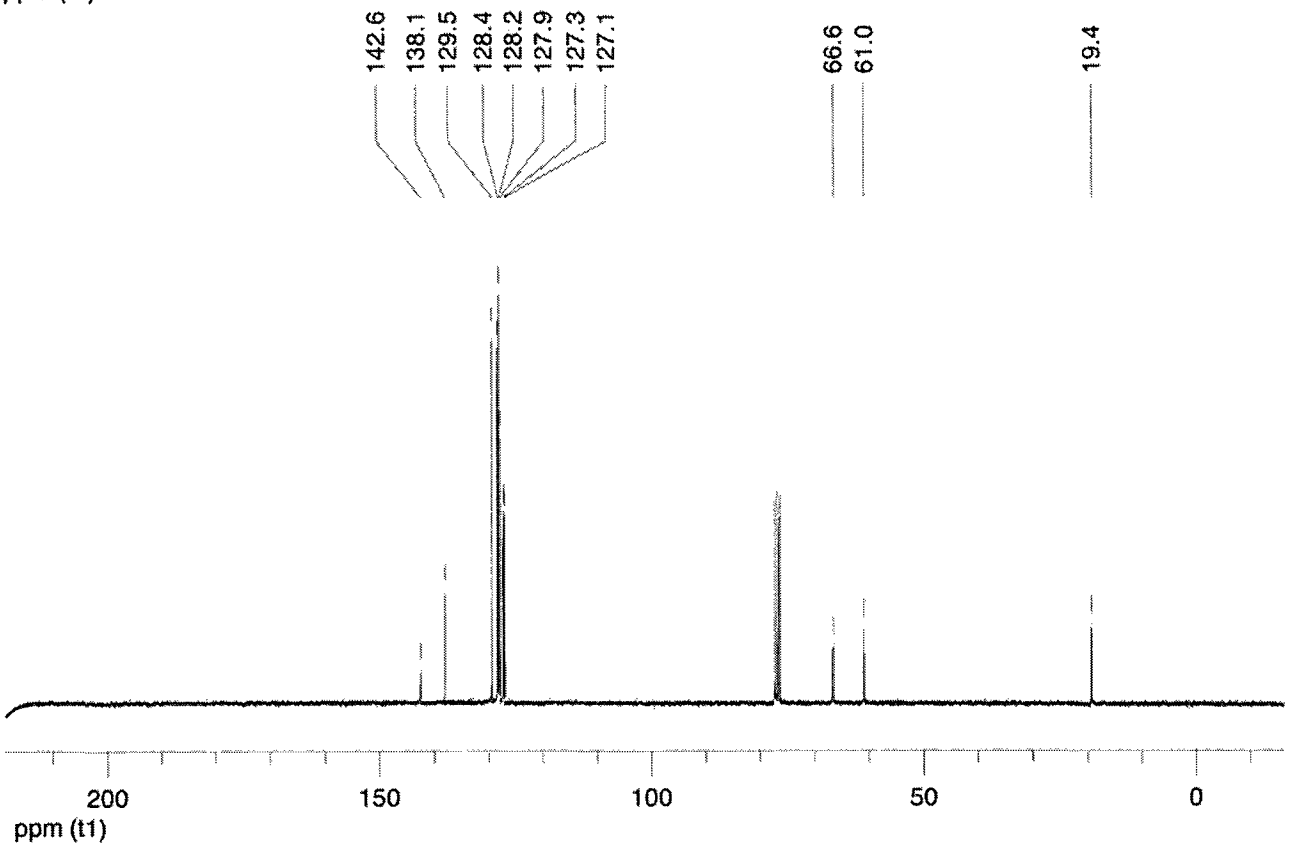


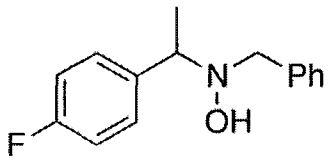



OH
N
11h
Table 3.7, entry 8
10.0
5.0
0.0
ppm (t1)
73.6
45.1
40.2
39.7
36.6
35.3
28.5
27.4
200
150
100
50
0
ppm (t1)

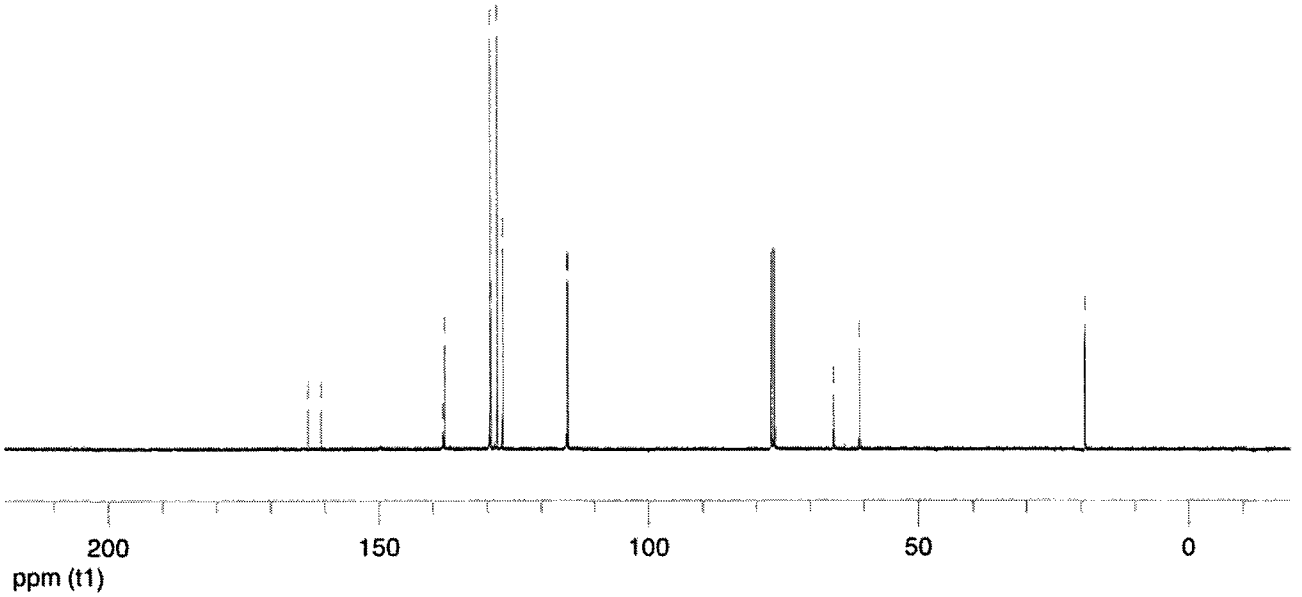


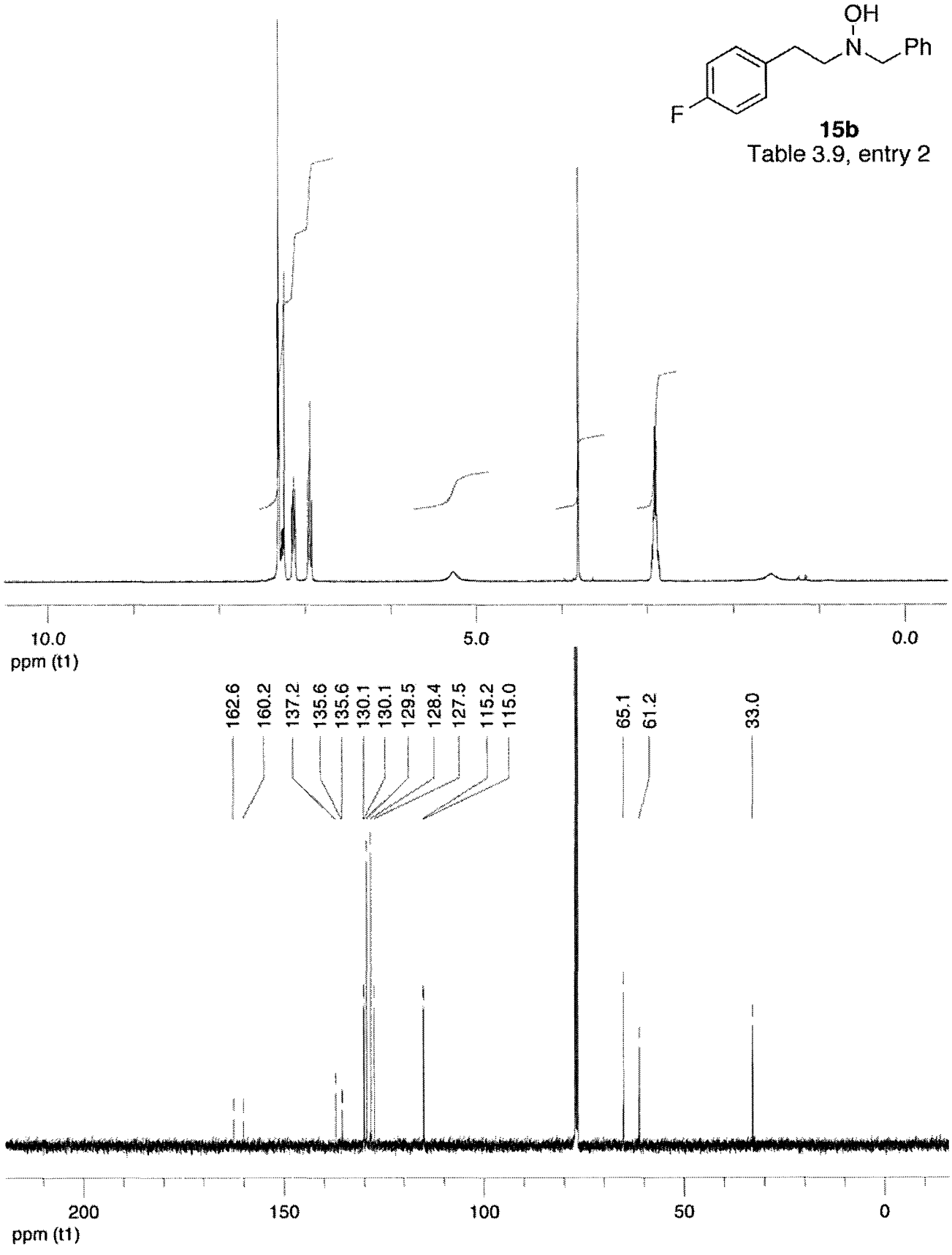
14a
Table 3.9, entry 1

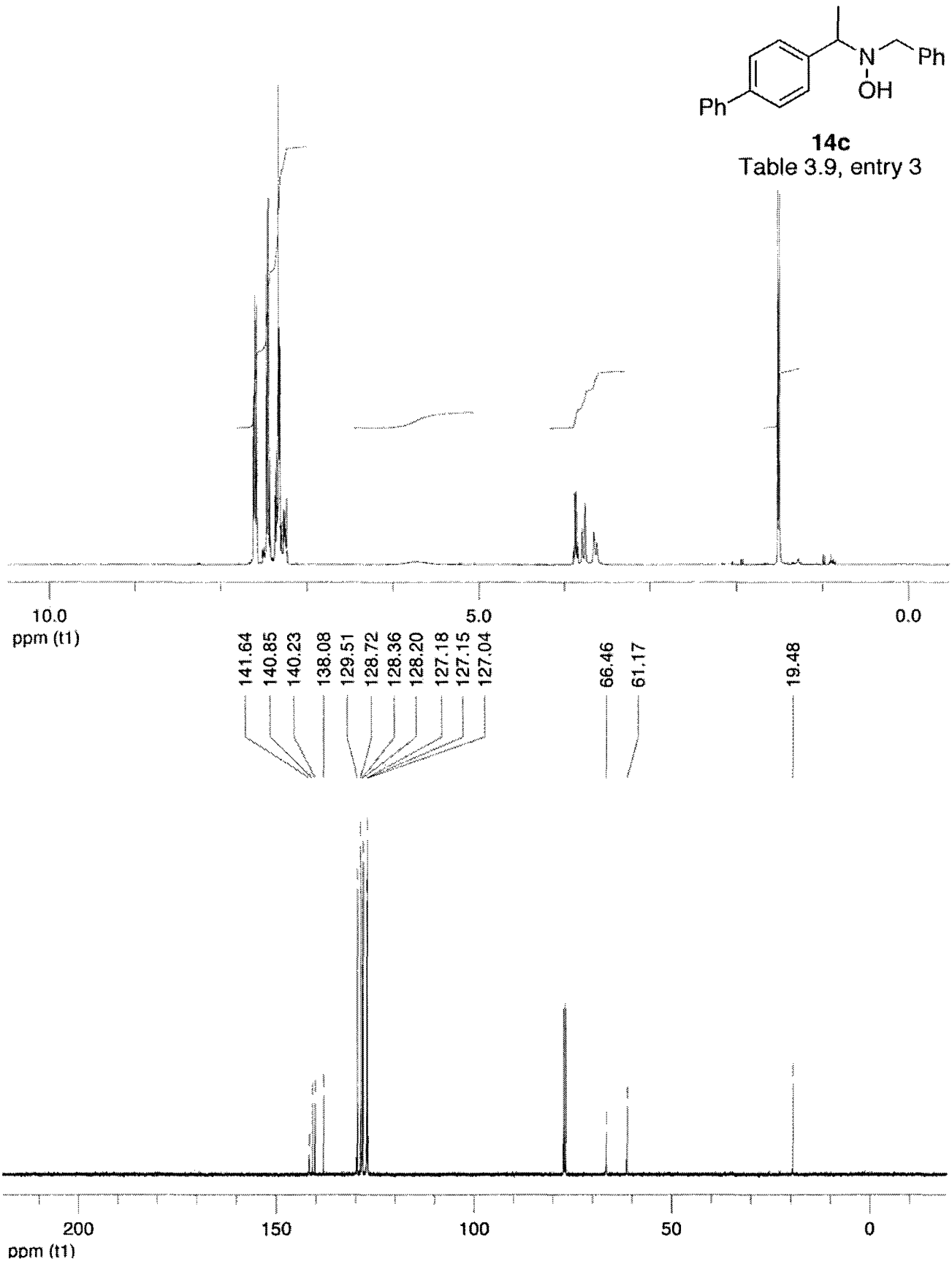


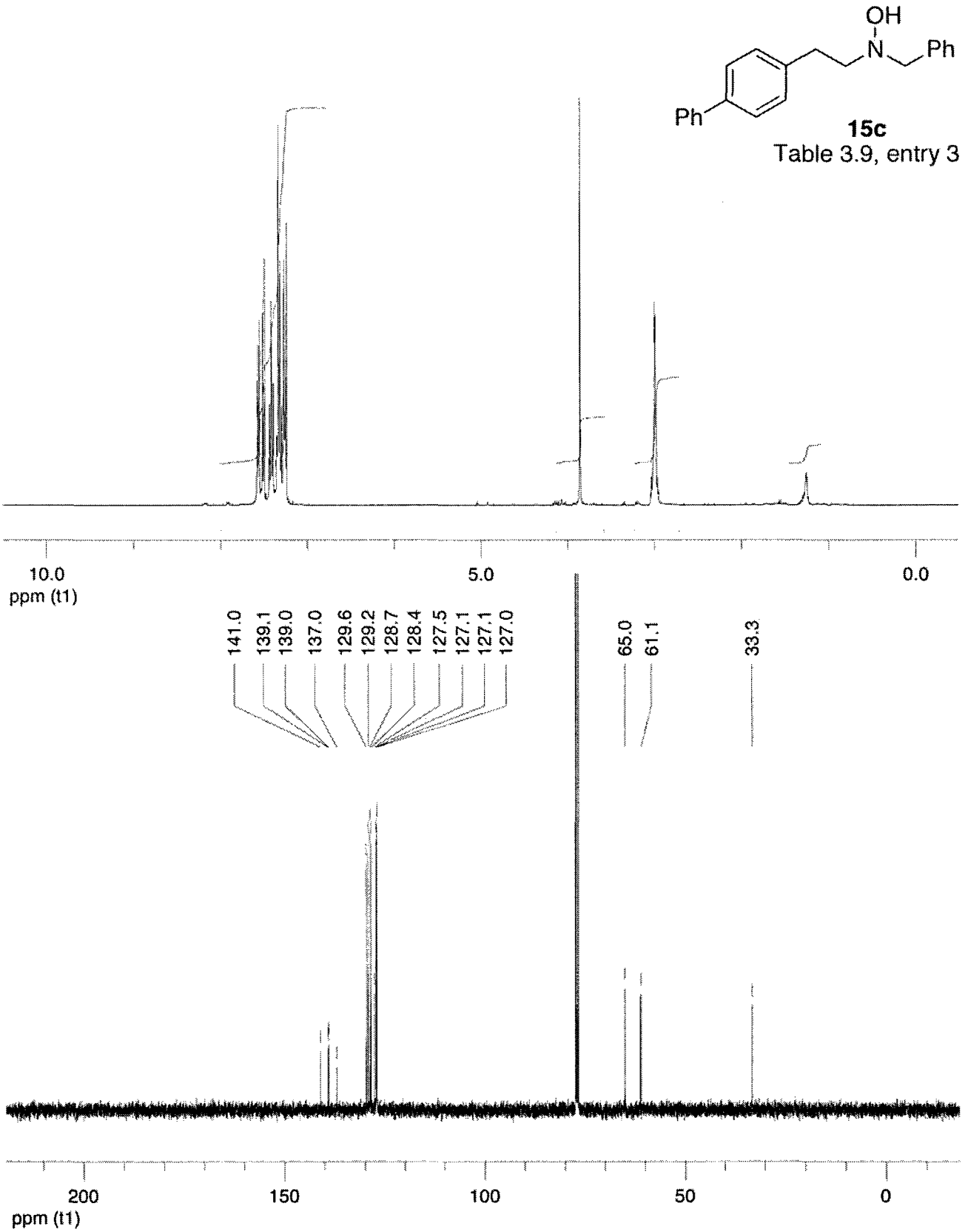


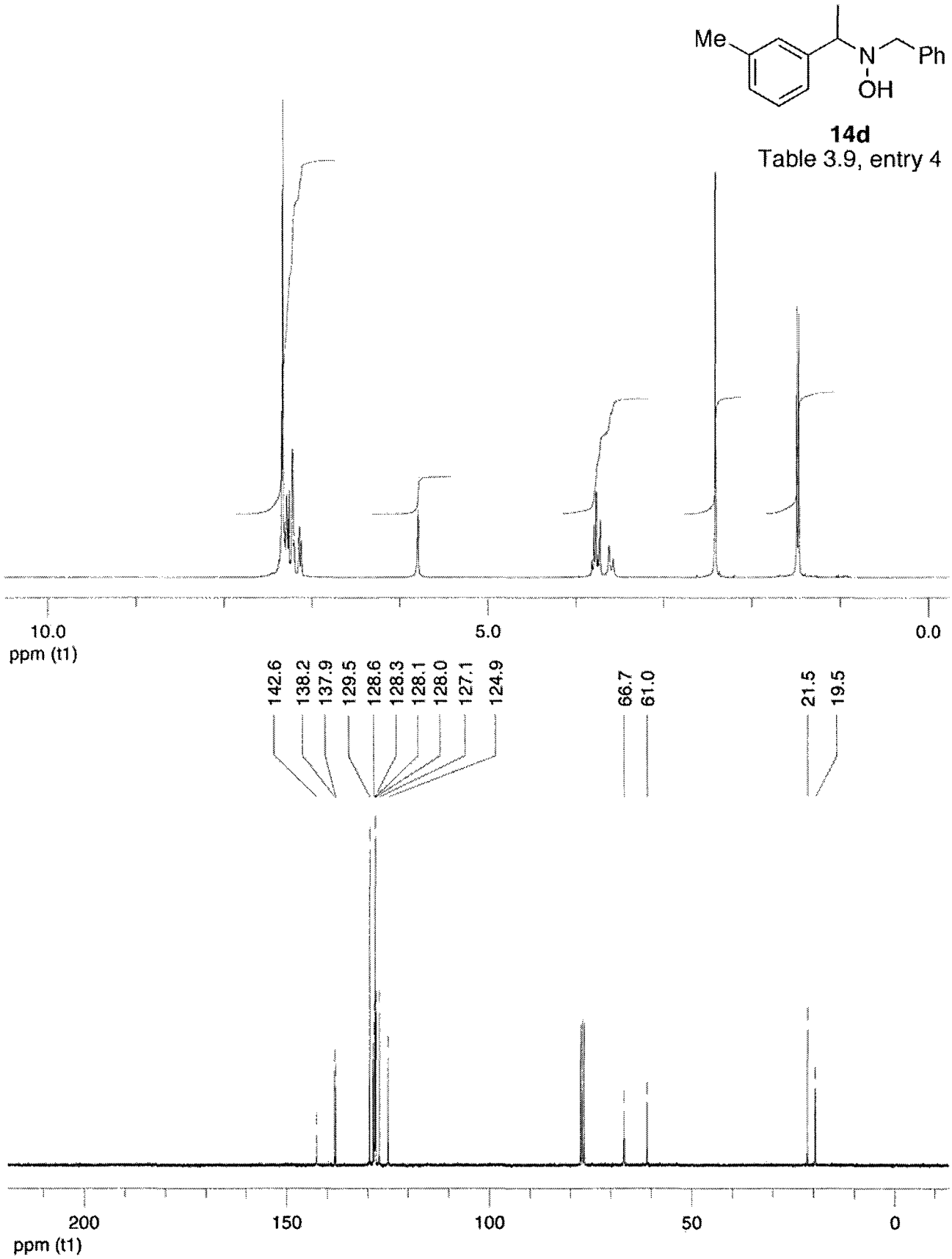
14b
Table 3.9, entry 2

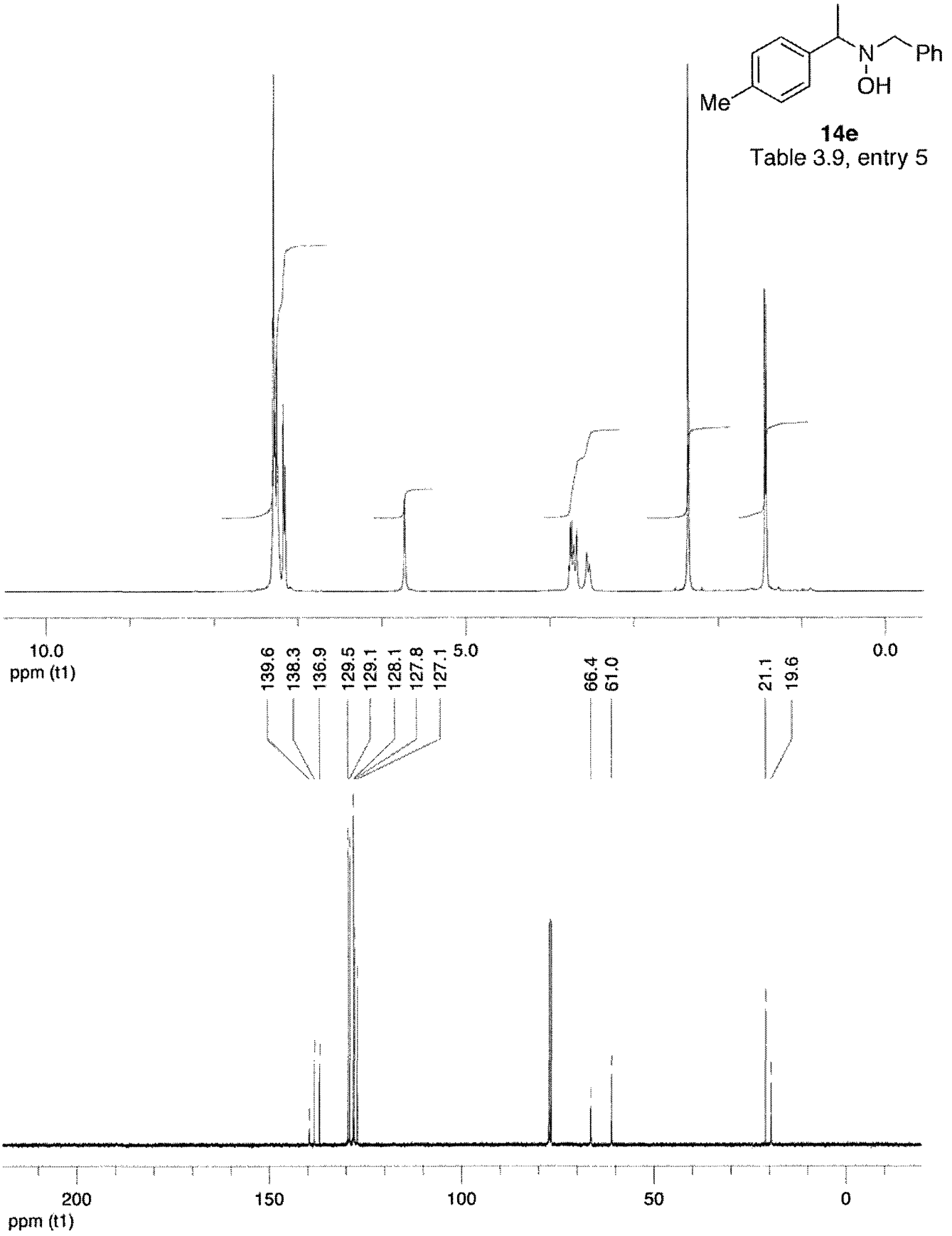


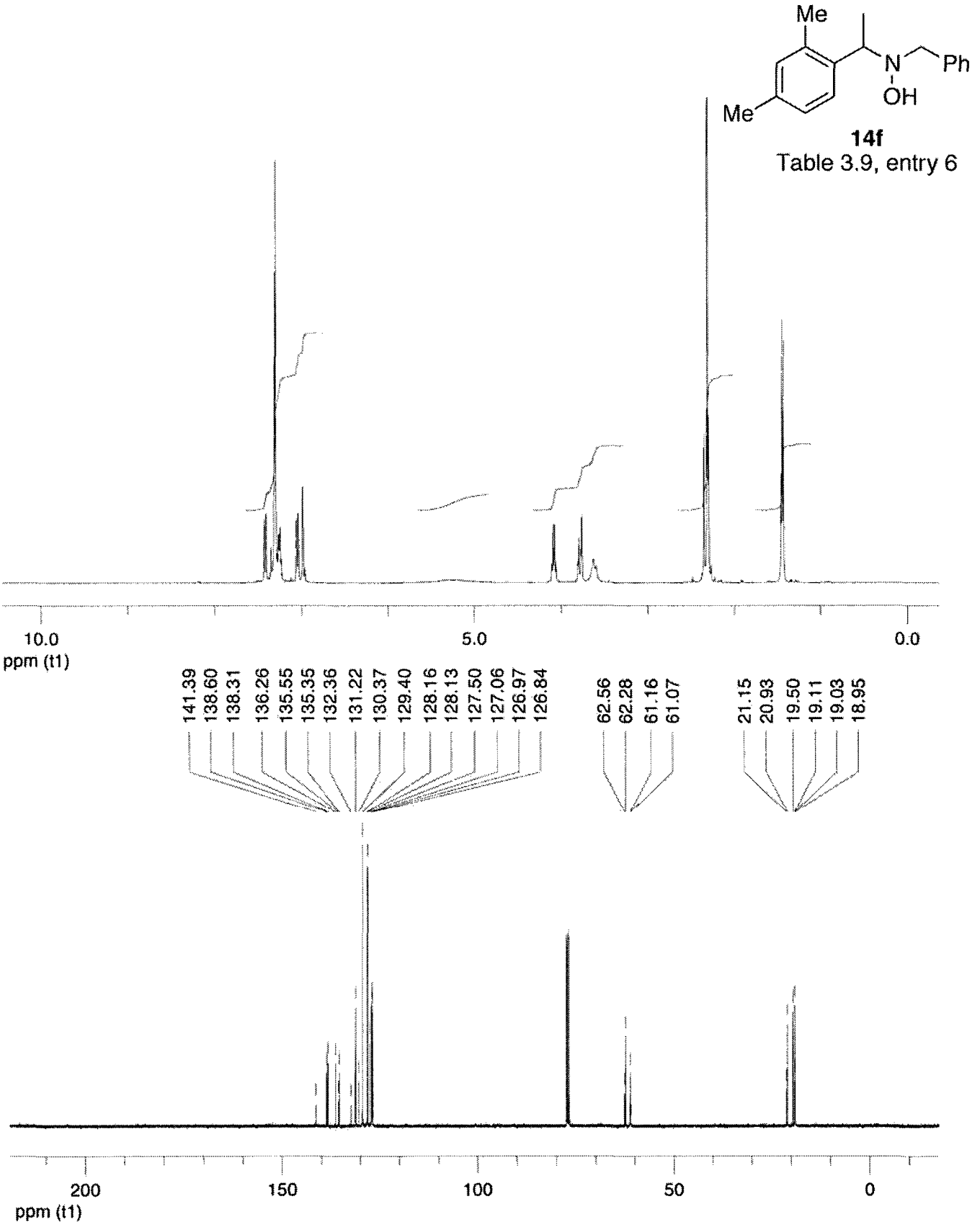

OH
N
Ph
F
15b
Table 3.9, entry 2
10.0
5.0
0.0
ppm (t1)
162.6
160.2
137.2
135.6
135.6
130.1
130.1
129.5
128.4
127.5
115.2
115.0
65.1
61.2
33.0
200
150
100
50
0
ppm (t1)

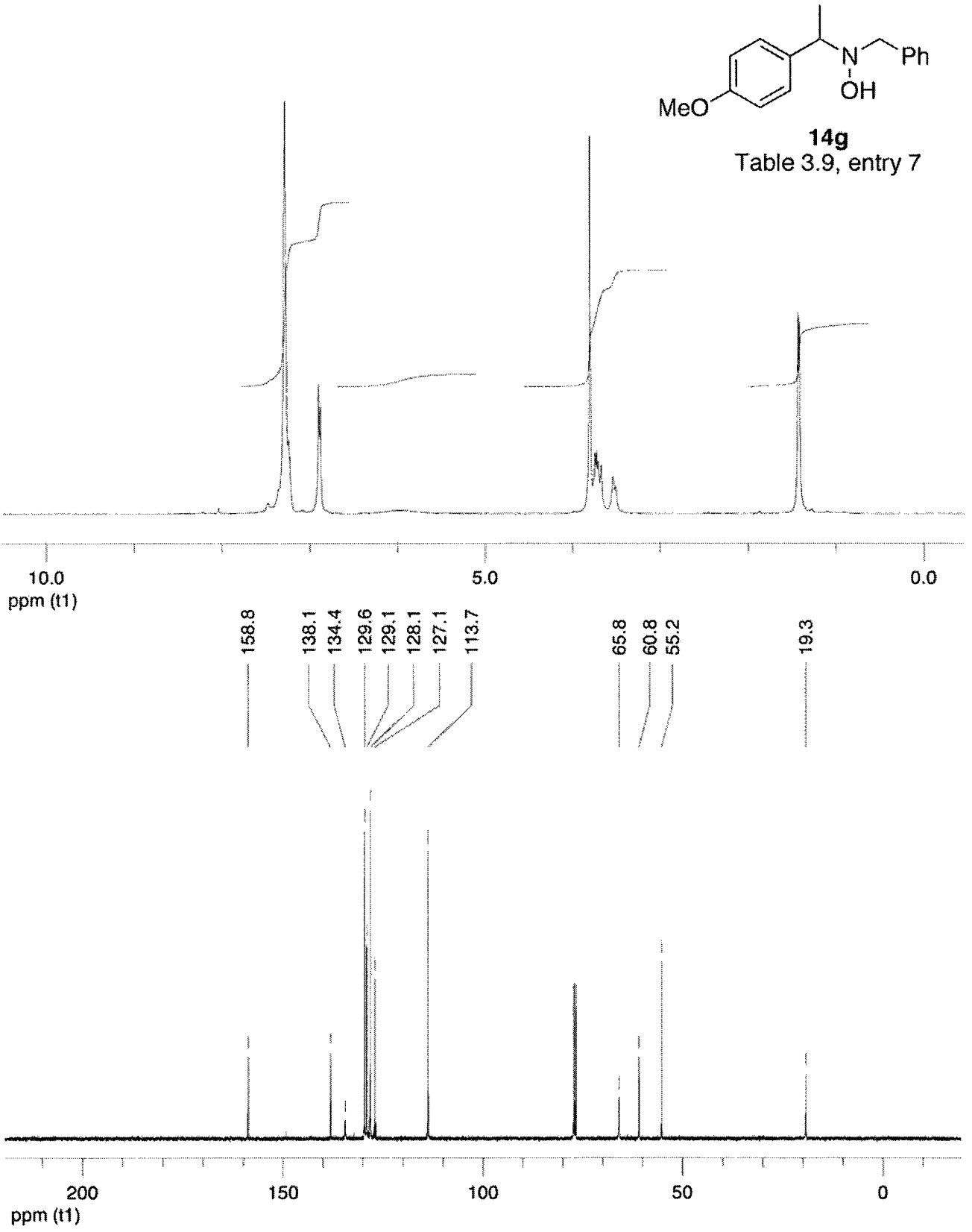

Ph
N
Ph
OH
14c
Table 3.9, entry 3
10.0
5.0
0.0
ppm (t1)
141.64
140.85
140.23
138.08
129.51
128.72
128.36
128.20
127.18
127.15
127.04
66.46
61.17
19.48
200
150
100
50
0
ppm (t1)

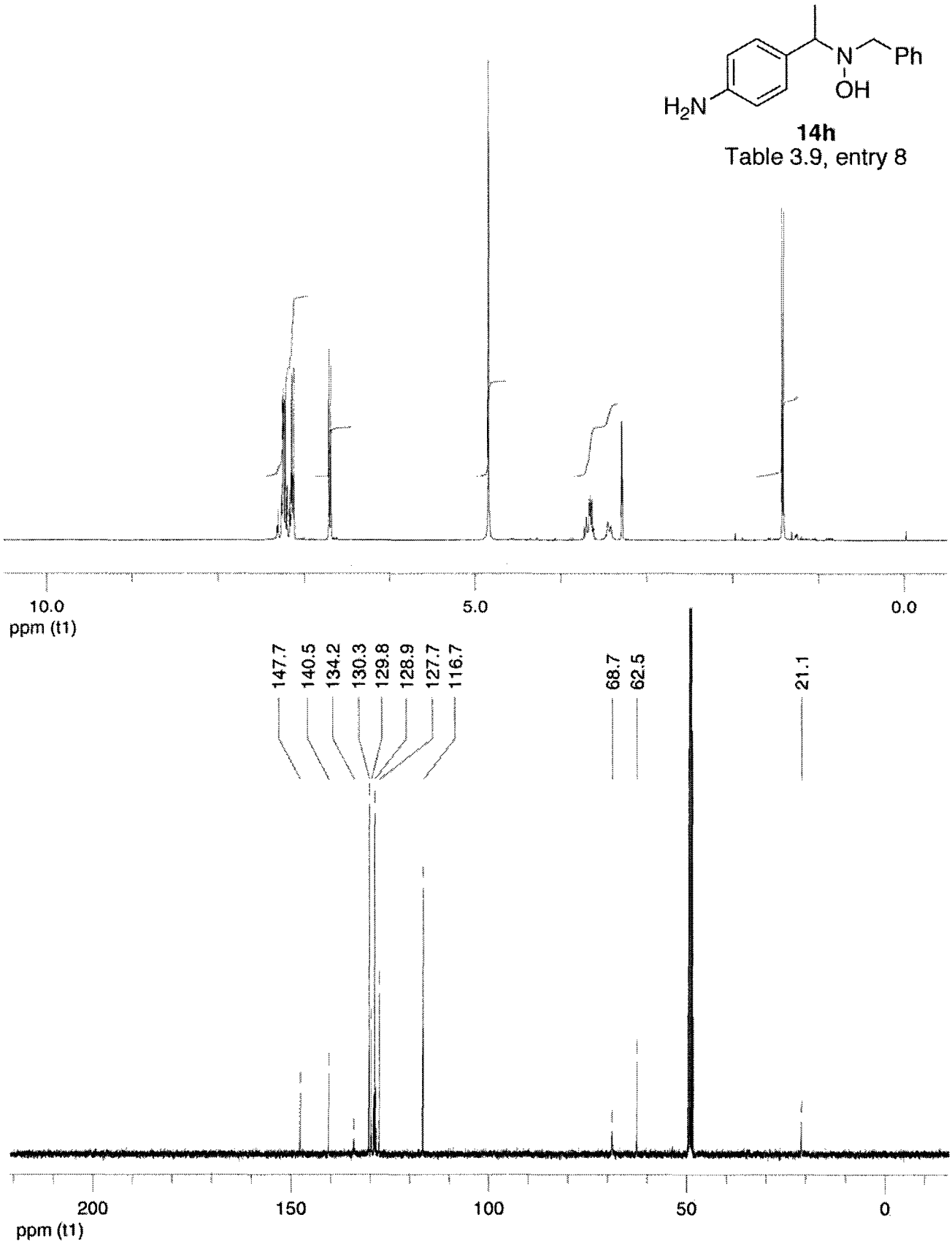

OH
N
Ph
Ph
15c
Table 3.9, entry 3
10.0
ppm (t1)
5.0
0.0
141.0
139.1
139.0
137.0
129.6
129.2
128.7
128.4
127.5
127.1
127.1
127.0
65.0
61.1
33.3
200
150
100
50
0
ppm (t1)

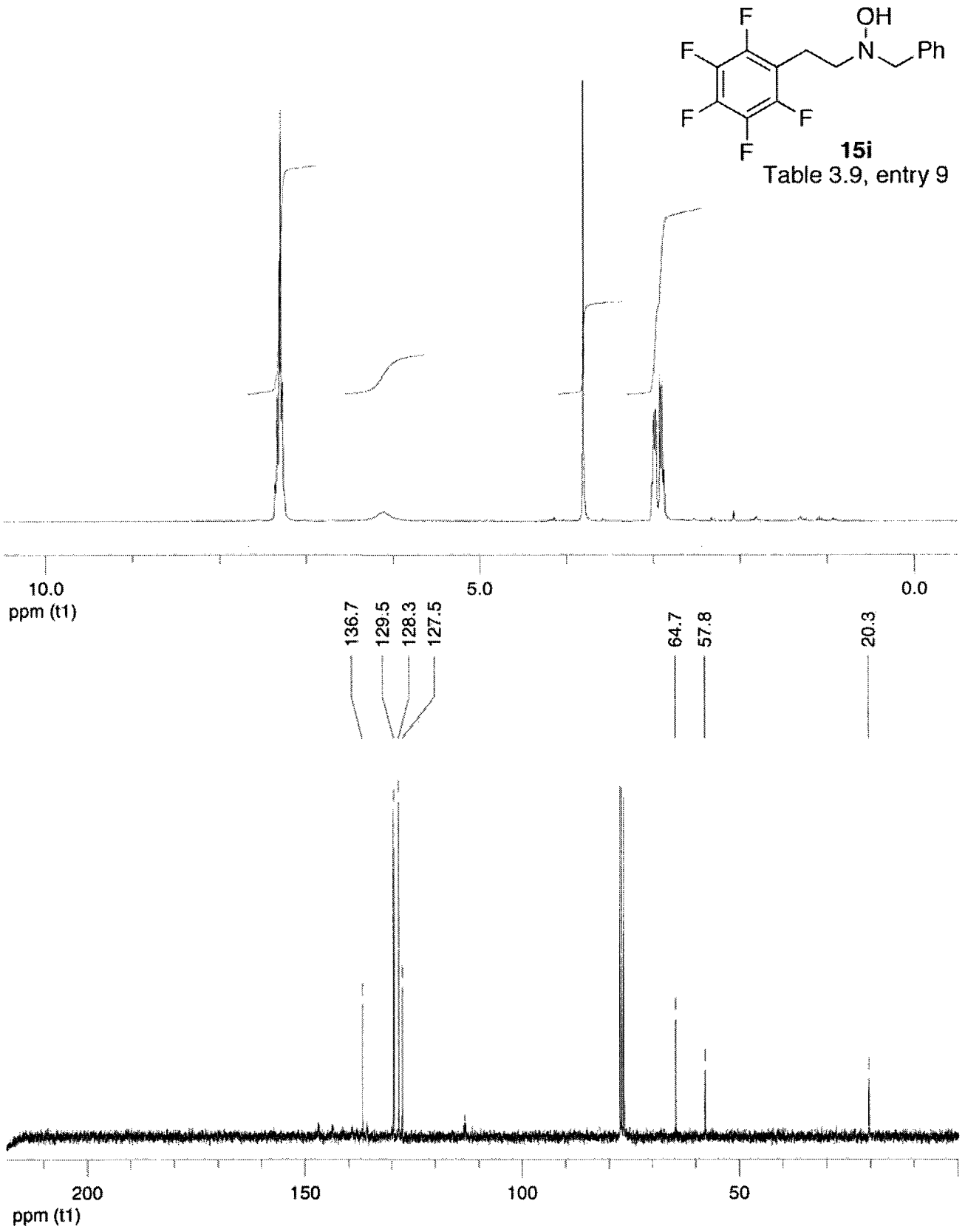

Me
N
Ph
OH
14d
Table 3.9, entry 4
10.0
5.0
0.0
ppm (t1)
142.6
138.2
137.9
129.5
128.6
128.3
128.1
128.0
127.1
124.9
66.7
61.0
21.5
19.5
200
150
100
50
0
ppm (t1)

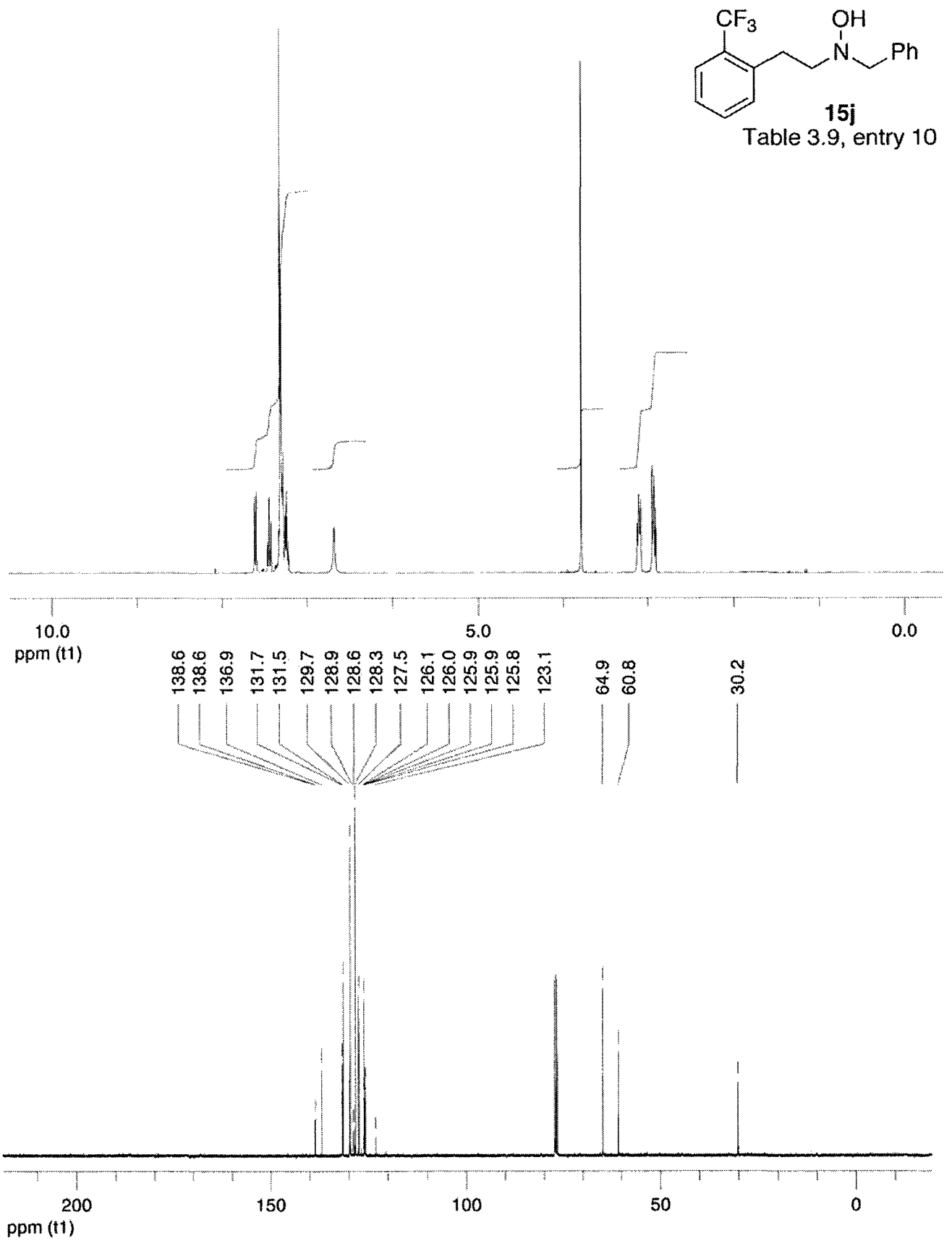

Me
N
OH
Ph
14e
Table 3.9, entry 5
10.0
ppm (t1)
5.0
0.0
139.6
138.3
136.9
129.5
129.1
128.1
127.8
127.1
66.4
61.0
21.1
19.6
200
150
100
50
0
ppm (t1)

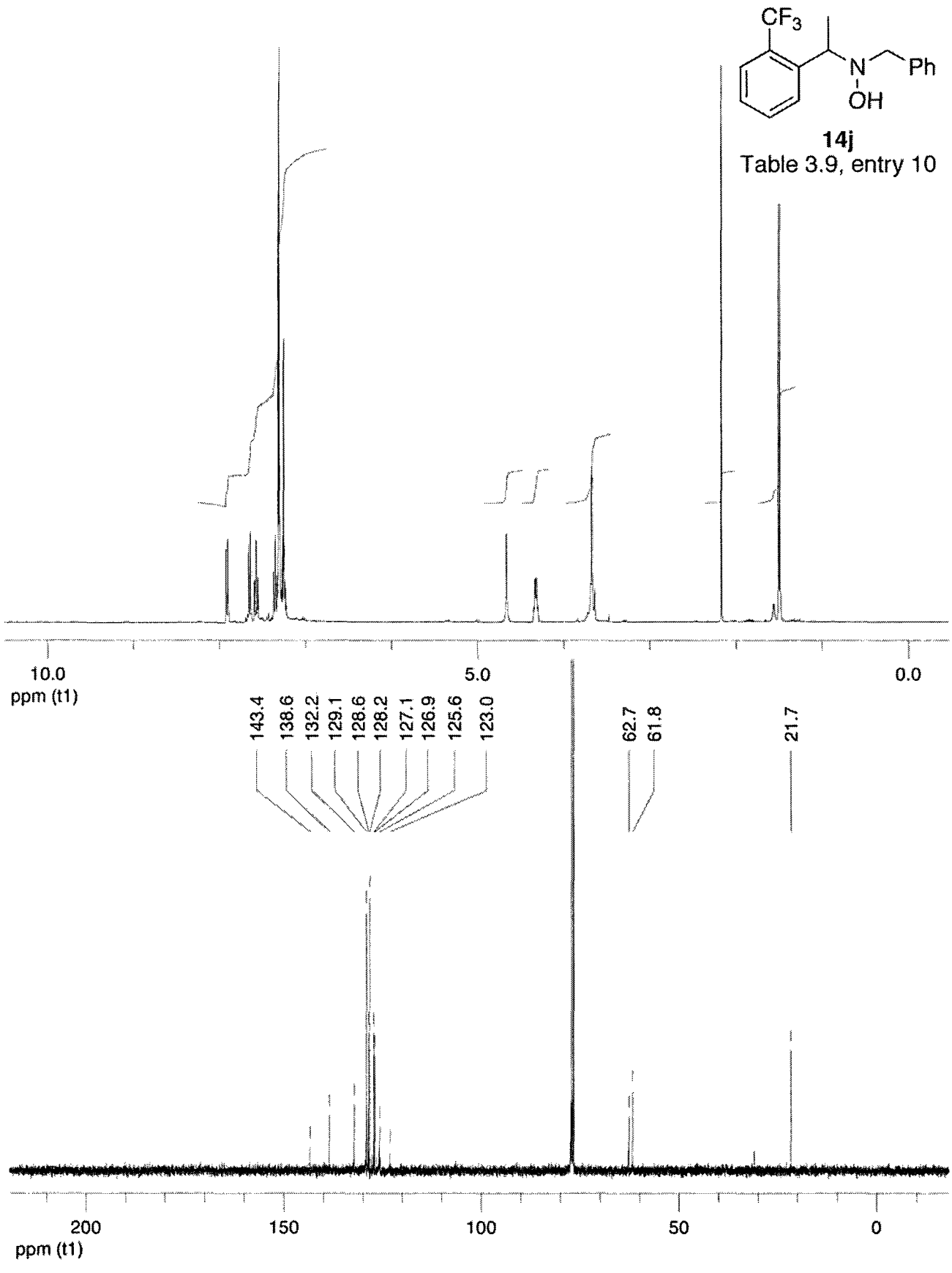

Me
N
Ph
OH
Me
14f
Table 3.9, entry 6
10.0
5.0
0.0
ppm (t1)
141.39
138.60
138.31
136.26
135.55
135.35
132.36
131.22
130.37
129.40
128.16
128.13
127.50
127.06
126.97
126.84
62.56
62.28
61.16
61.07
21.15
20.93
19.50
19.11
19.03
18.95
200
150
100
50
0
ppm (t1)

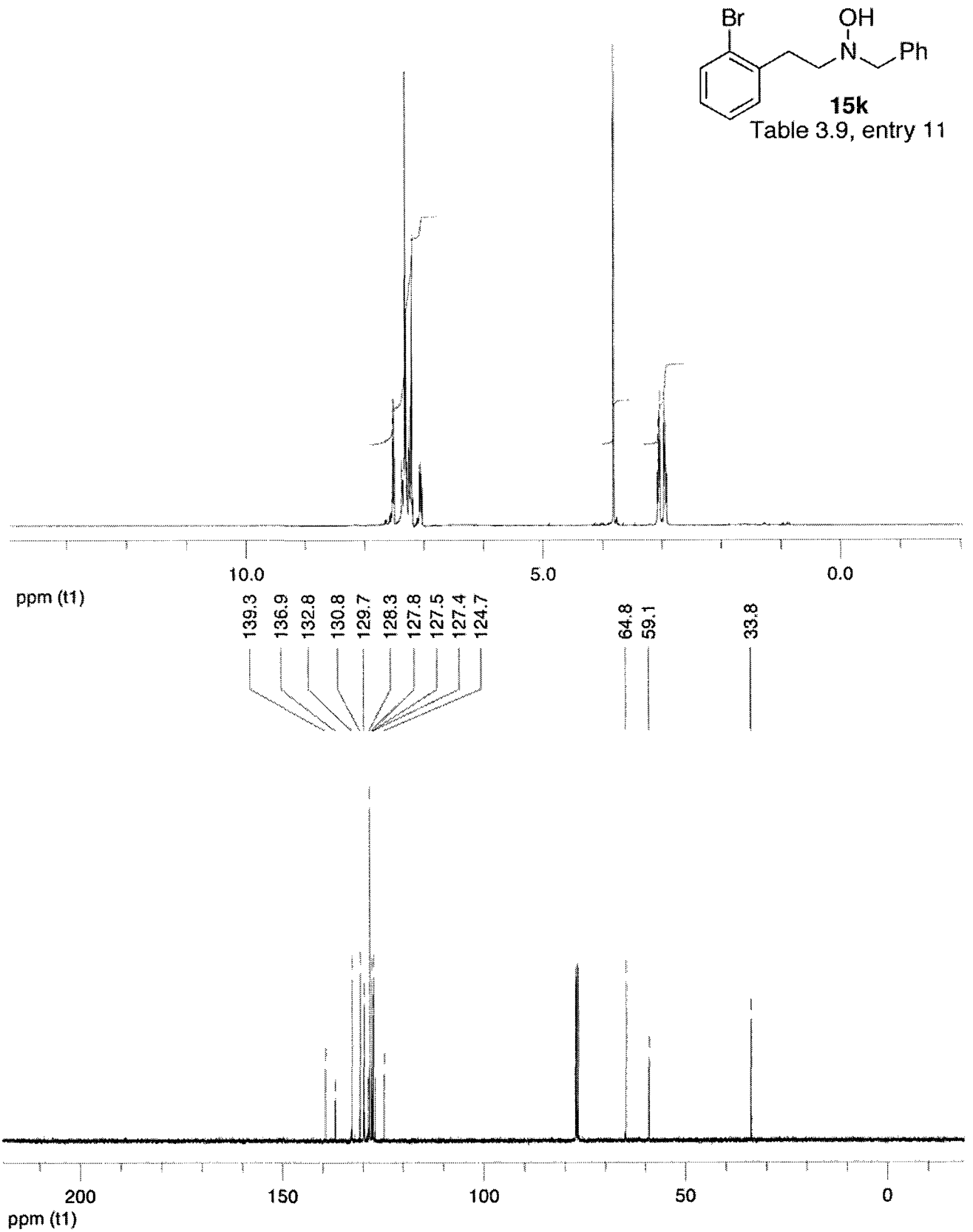

MeO
N
Ph
OH
14g
Table 3.9, entry 7
10.0
ppm (t1)
5.0
0.0
158.8
138.1
134.4
129.6
129.1
128.1
127.1
113.7
65.8
60.8
55.2
19.3
200
150
100
50
0
ppm (t1)

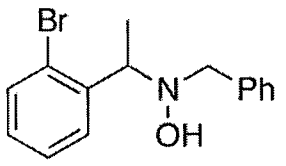

N
Ph
OH
H_2N
14h
Table 3.9, entry 8
10.0
5.0
0.0
ppm (t1)
147.7
140.5
134.2
130.3
129.8
128.9
127.7
116.7
68.7
62.5
21.1
200
150
100
50
0
ppm (t1)


F
OH
F
N
Ph
F
F
F
15i
Table 3.9, entry 9
10.0
ppm (t1)
5.0
0.0
136.7
129.5
128.3
127.5
64.7
57.8
20.3
200
150
100
50
ppm (t1)

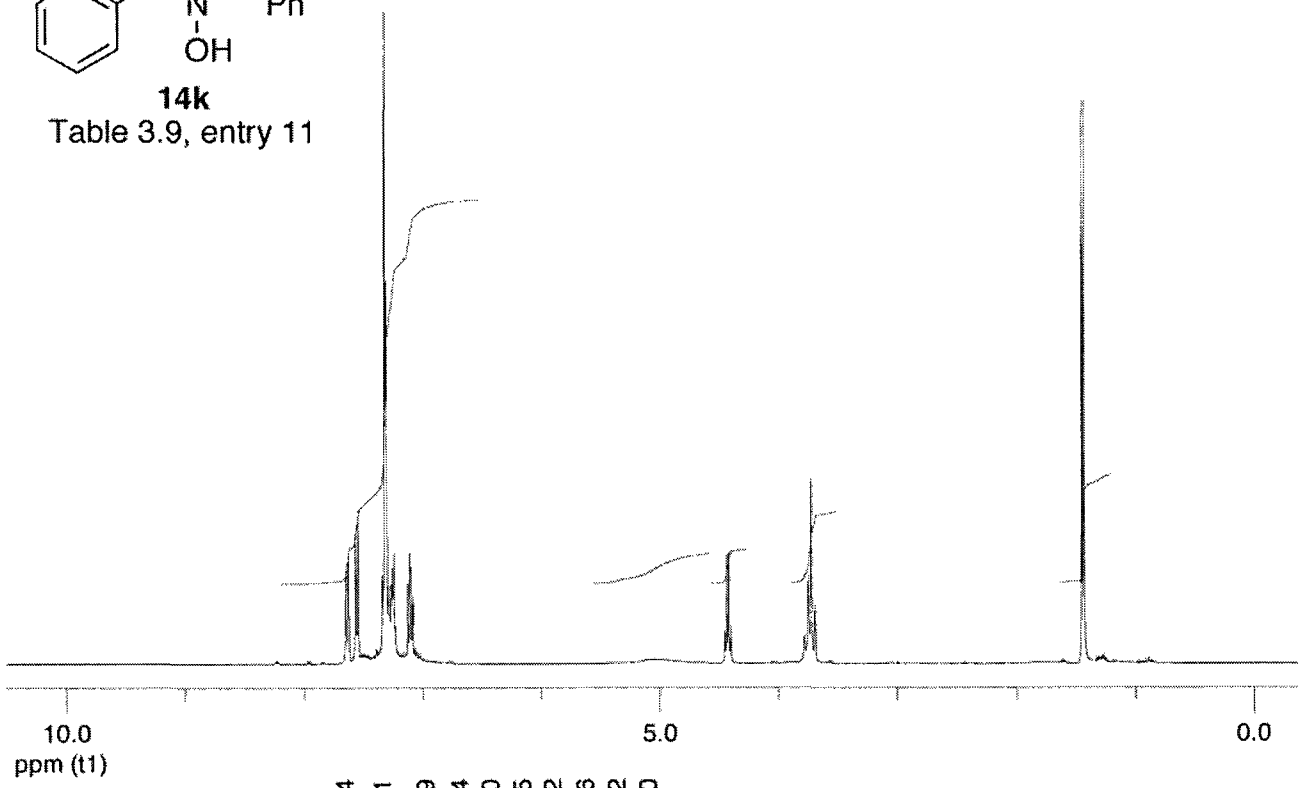

CF3
OH
N
Ph
15j
Table 3.9, entry 10
10.0
5.0
0.0
ppm (t1)
138.6
138.6
136.9
131.7
131.5
129.7
128.9
128.6
128.3
127.5
126.1
126.0
125.9
125.9
125.8
123.1
64.9
60.8
30.2
200
150
100
50
0
ppm (t1)

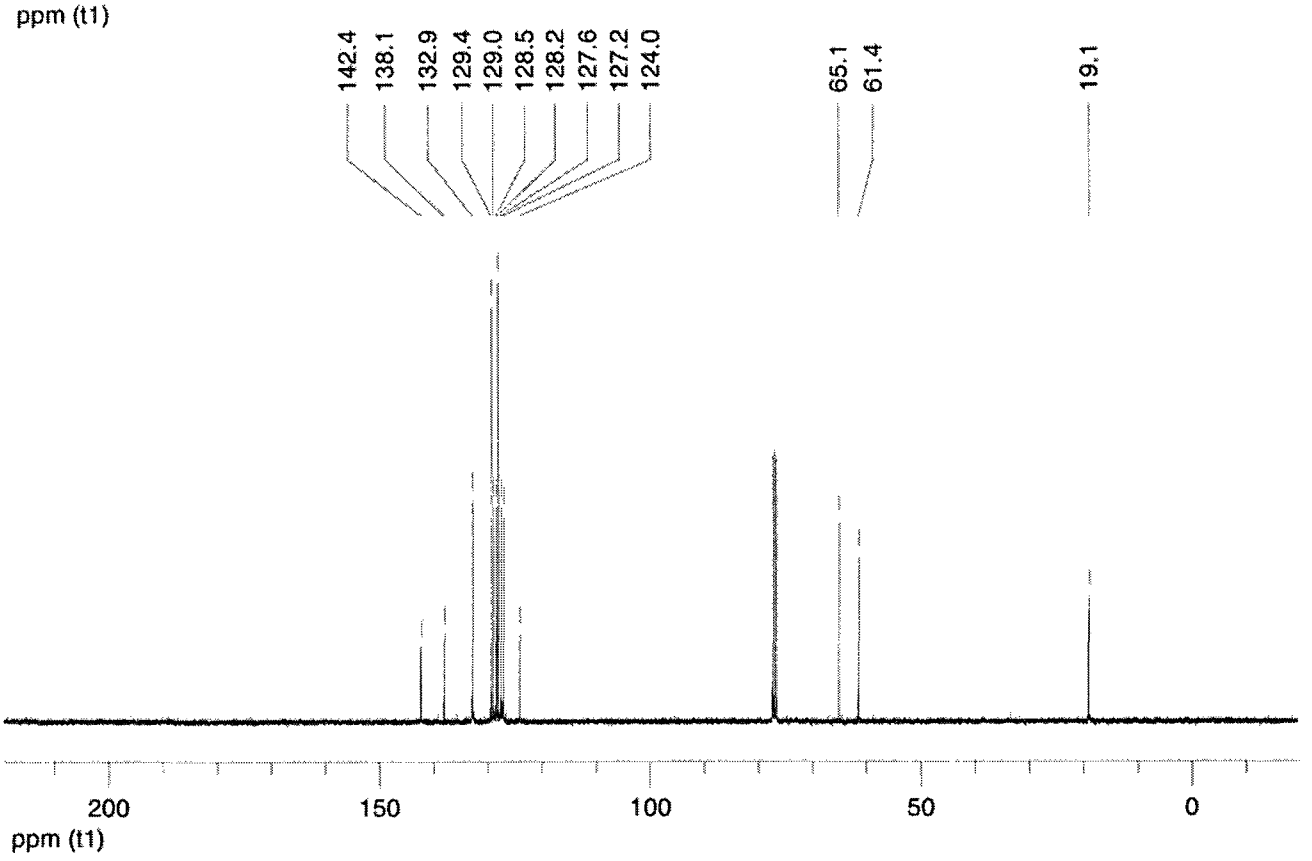

CF3
N
Ph
OH
14j
Table 3.9, entry 10
10.0
ppm (t1)
5.0
0.0
143.4
138.6
132.2
129.1
128.6
128.2
127.1
126.9
125.6
123.0
62.7
61.8
21.7
200
150
100
50
0
ppm (t1)

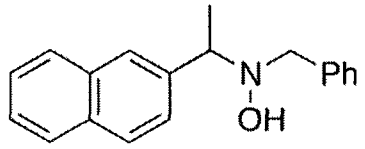

Br
OH
N
Ph
15k
Table 3.9, entry 11
10.0
5.0
0.0
ppm (t1)
139.3
136.9
132.8
130.8
129.7
128.3
127.8
127.5
127.4
124.7
64.8
59.1
33.8
200
150
100
50
0
ppm (t1)



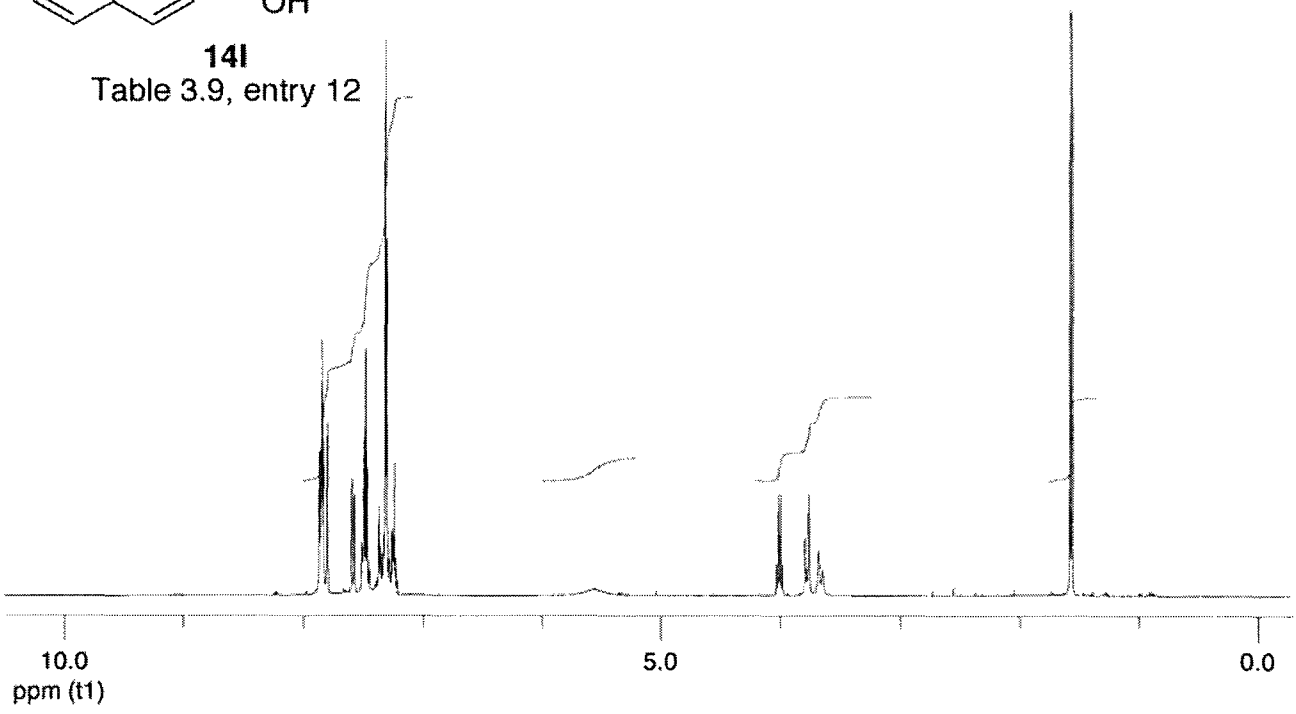
14k
Table 3.9, entry 11

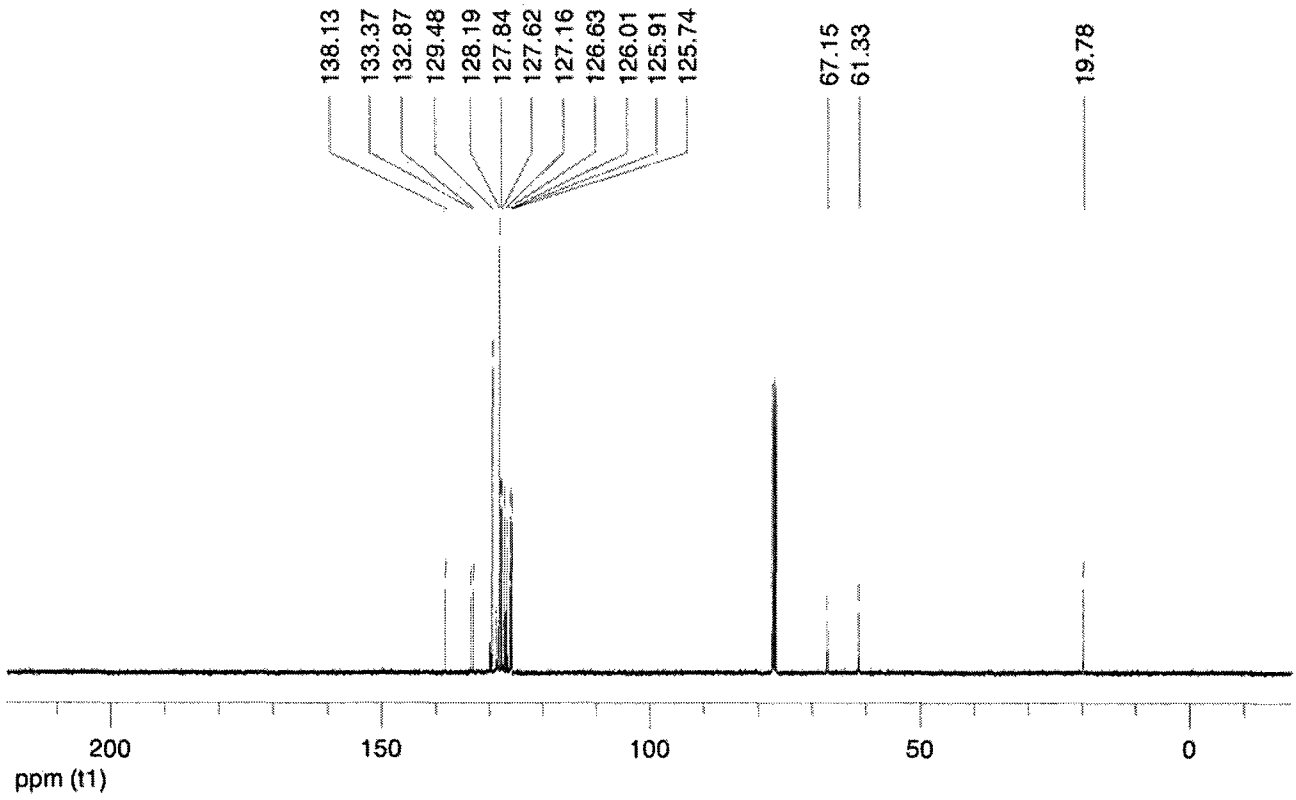


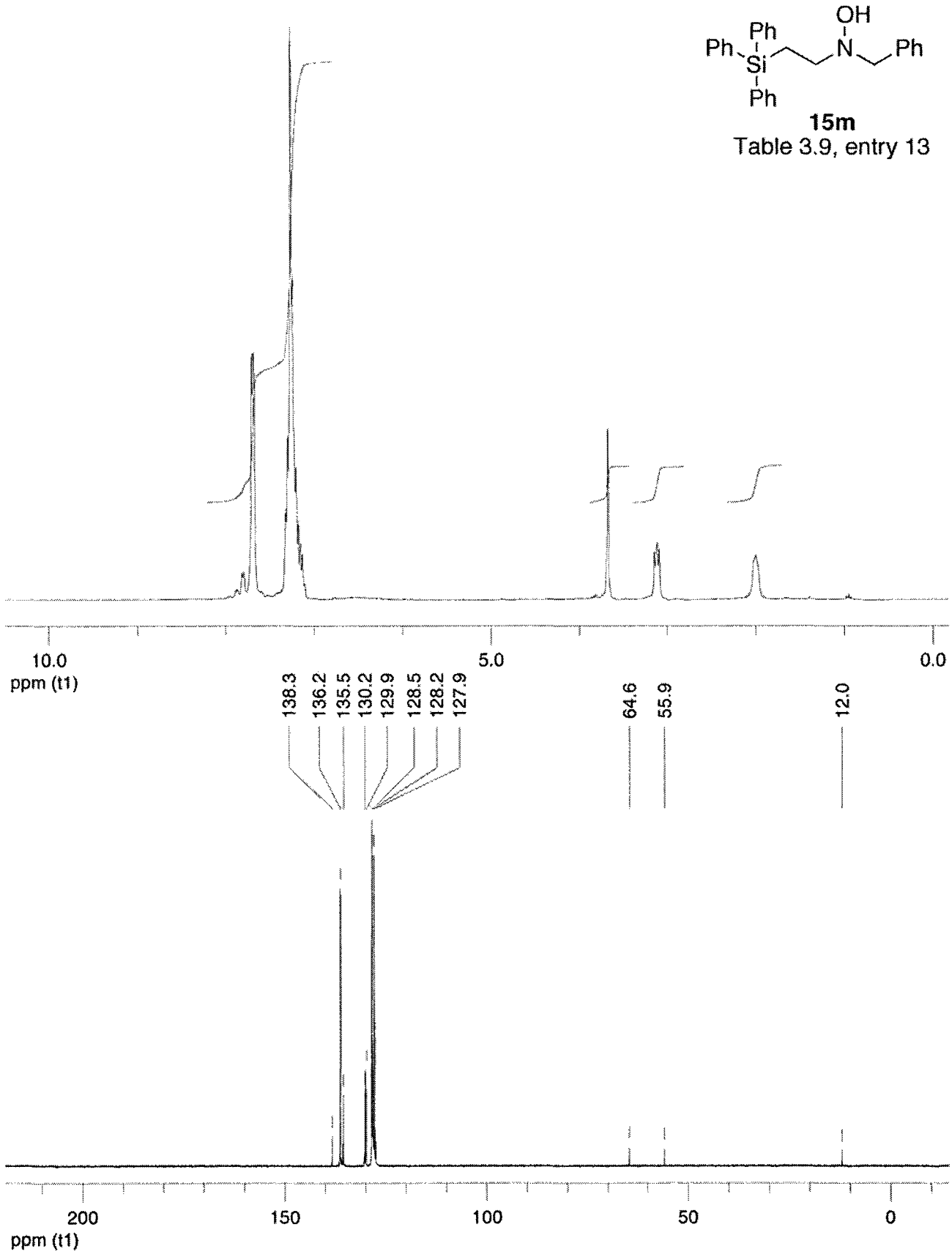


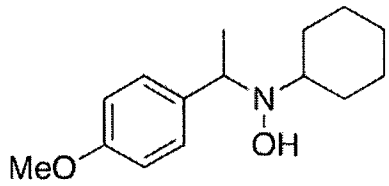


14l
Table 3.9, entry 12

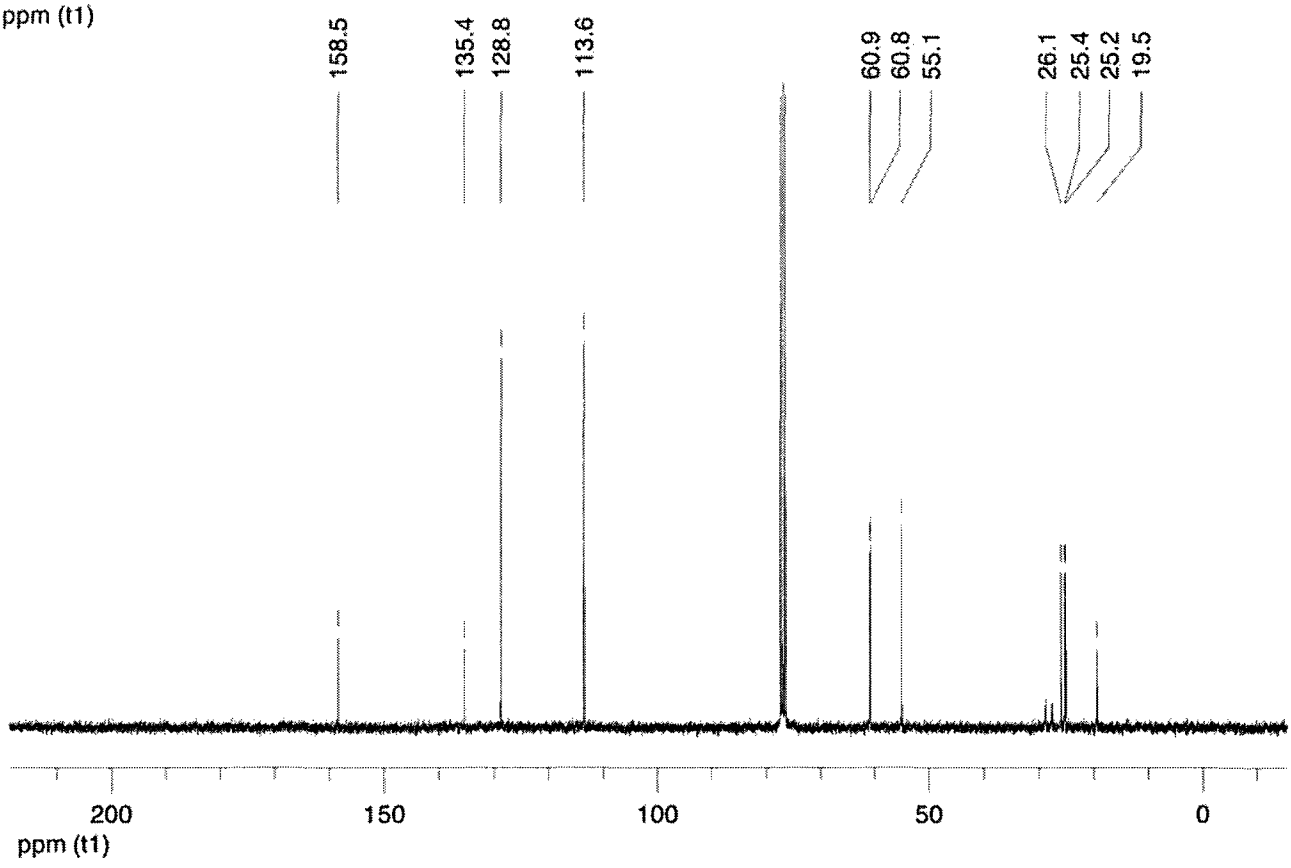


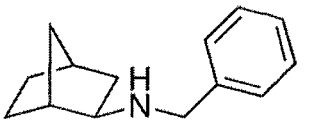



OH
Ph
Ph
Si
N
Ph
Ph
15m
Table 3.9, entry 13
10.0
ppm (t1)
5.0
0.0
138.3
136.2
135.5
130.2
129.9
128.5
128.2
127.9
64.6
55.9
12.0
200
150
100
50
0
ppm (t1)



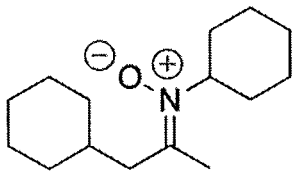
16
Equation 3.8



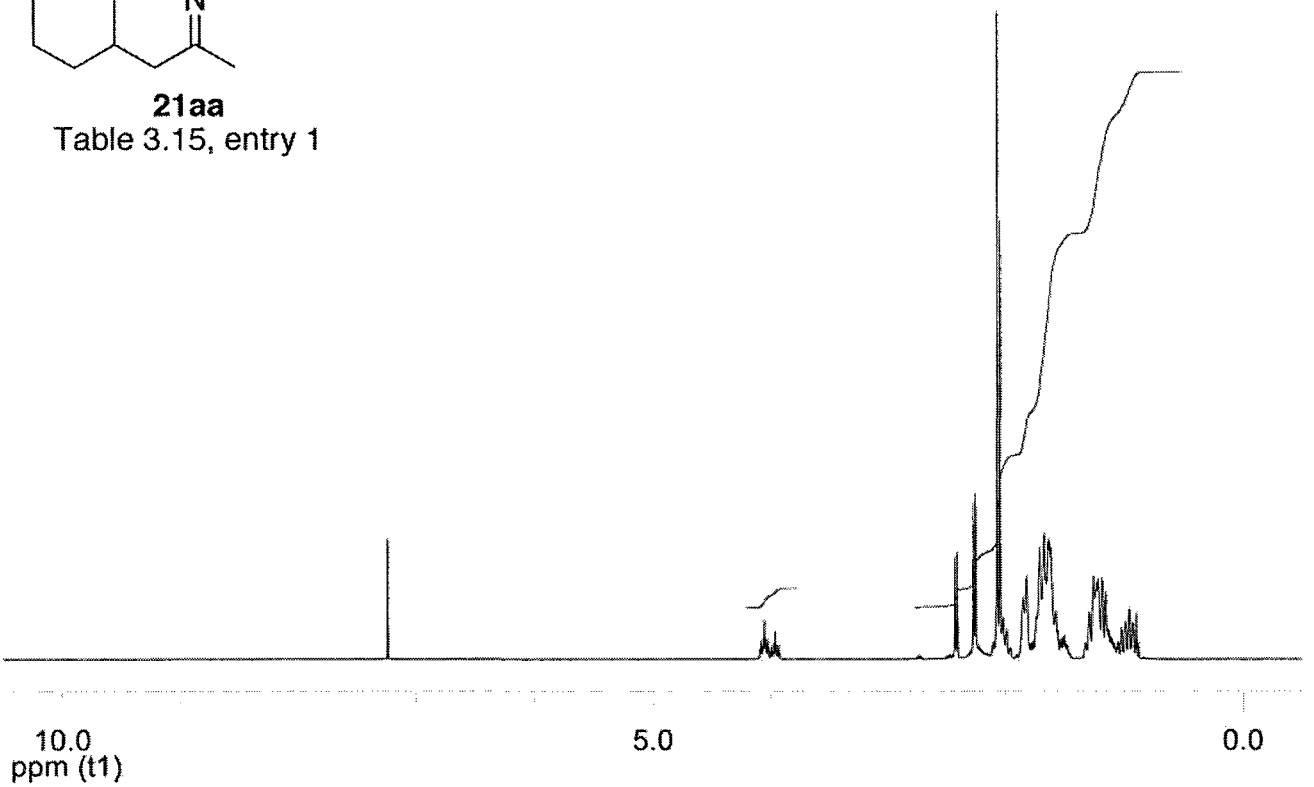


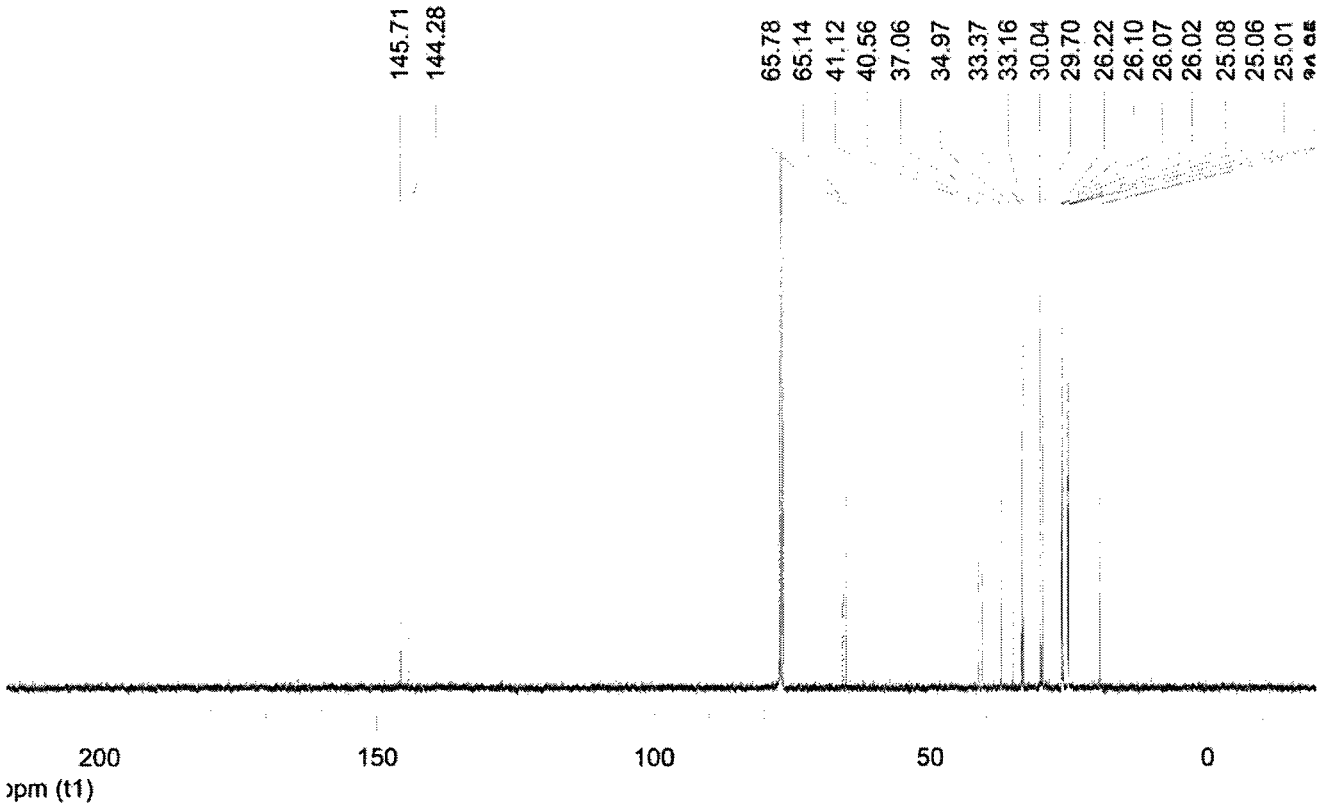
18
Scheme 3.2

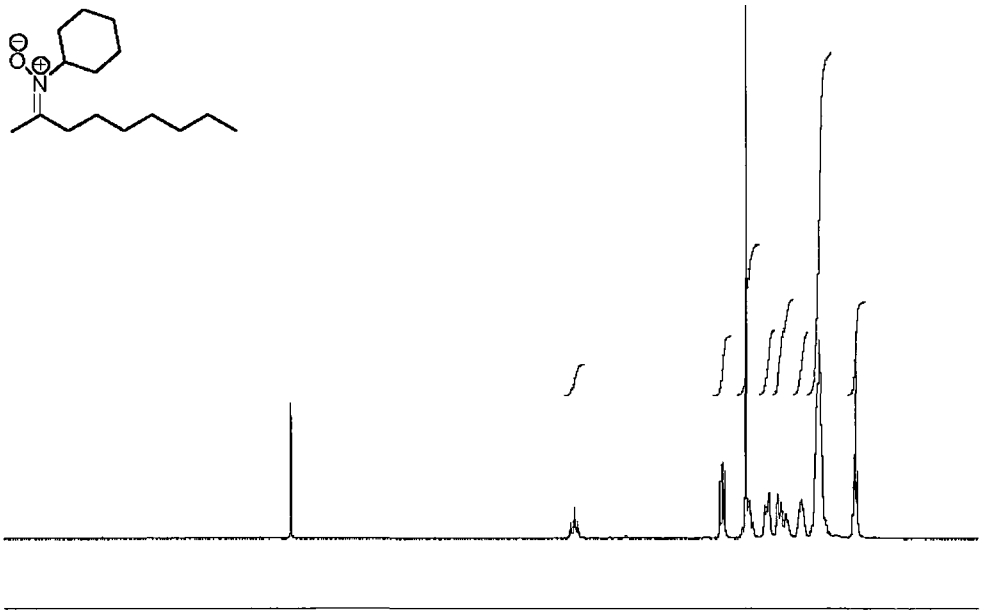
10.0
ppm (t1)
5.0
0.0
141.8
128.5
128.4
126.9
61.8
52.3
41.3
40.3
36.1
35.1
29.2
27.0
200
150
100
50
0
ppm (t1)



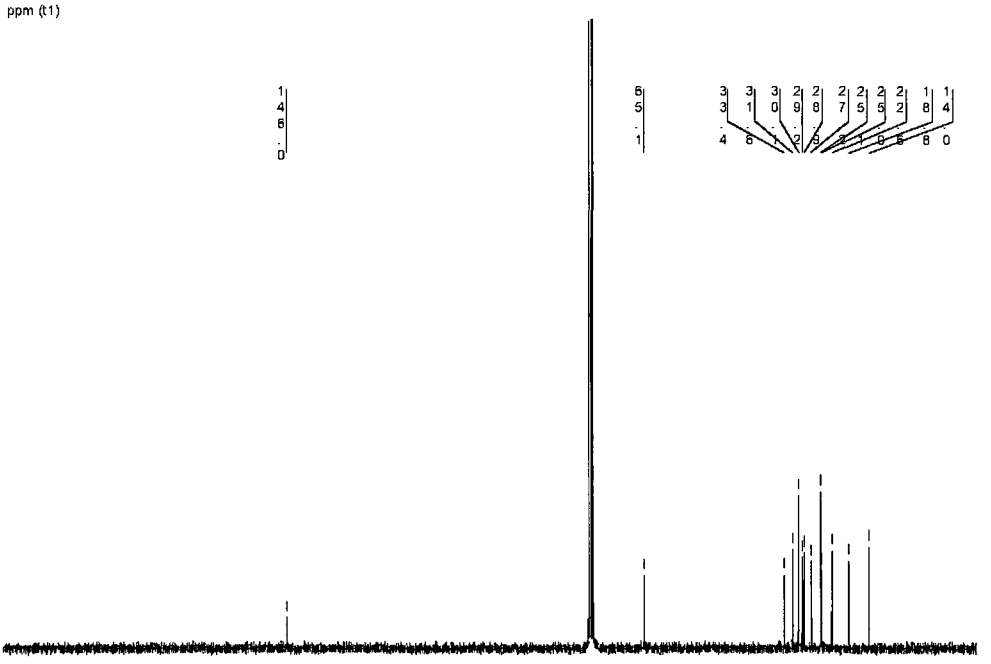
21aa
Table 3.15, entry 1



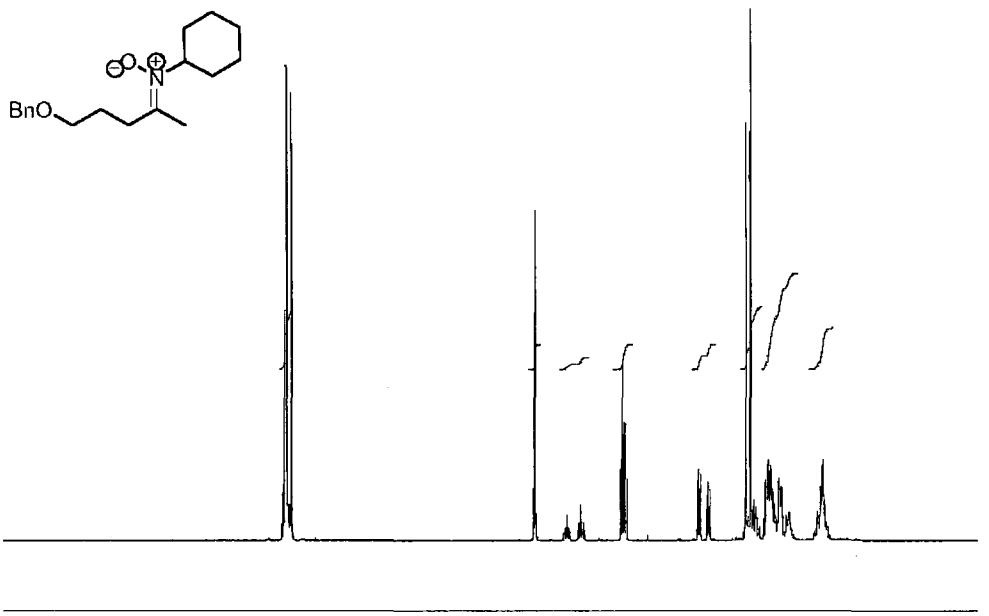




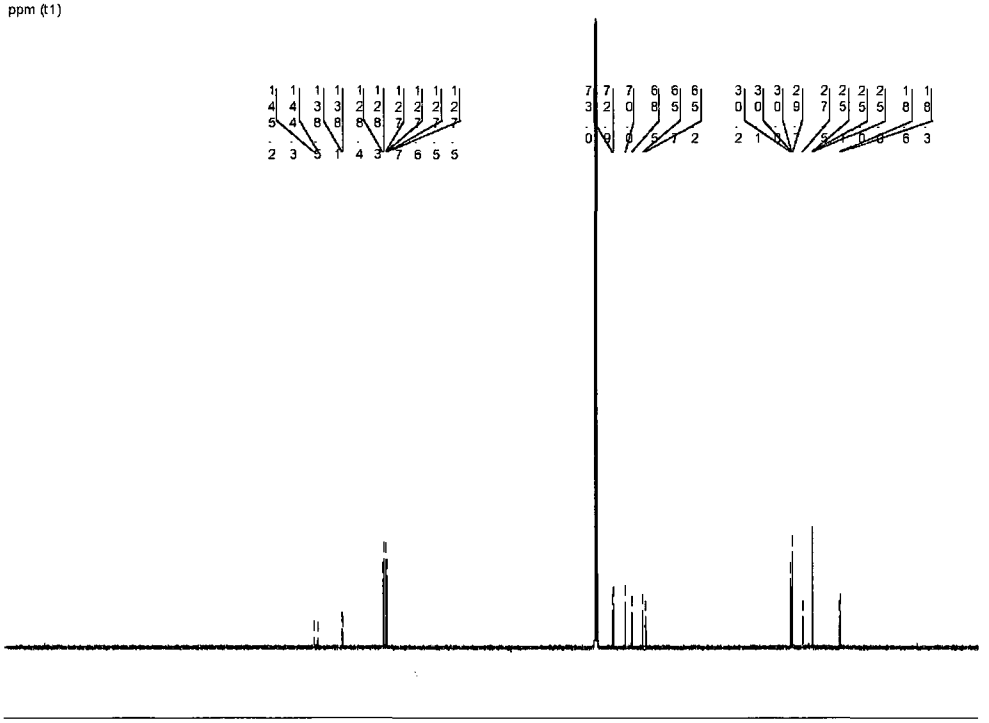
ppm (t1)



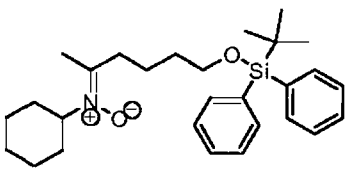
ppm (t1)



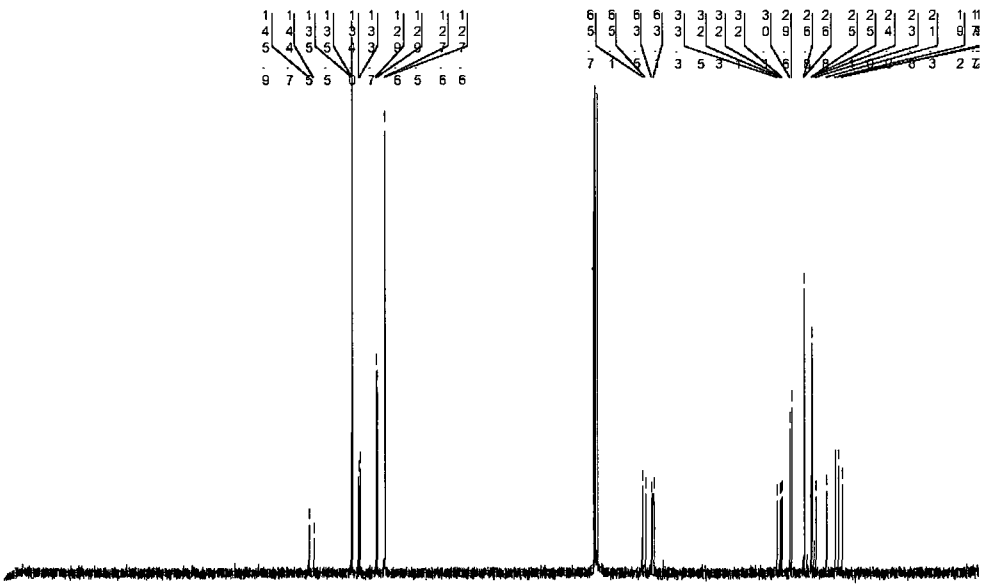
ppm (t1)



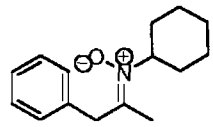
ppm (t1)



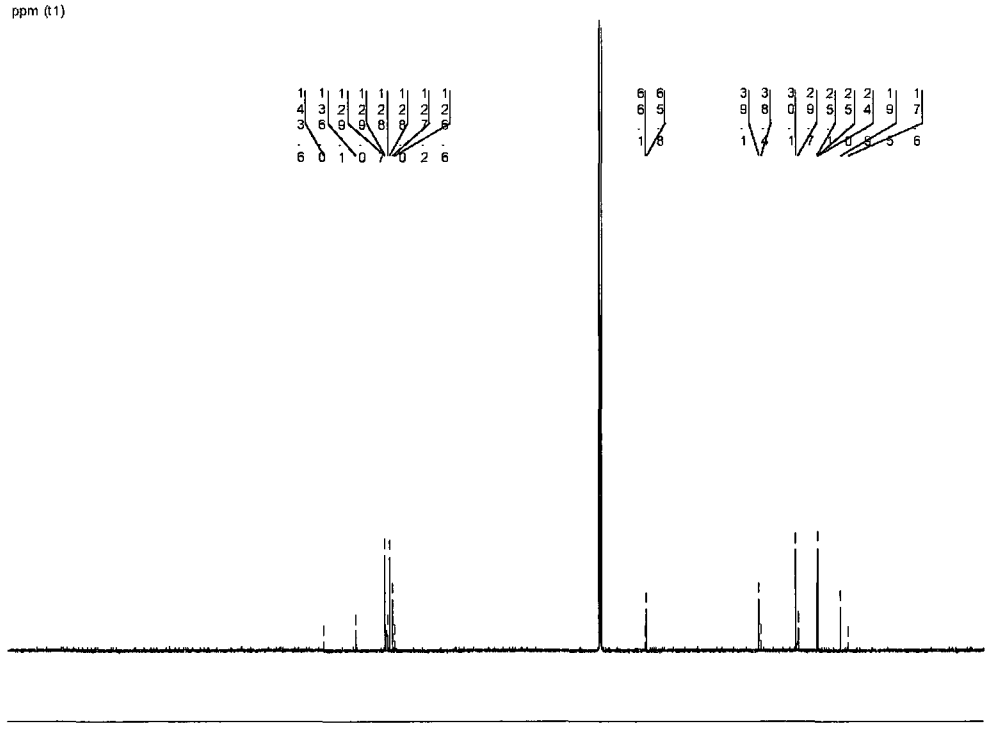
ppm (t1)



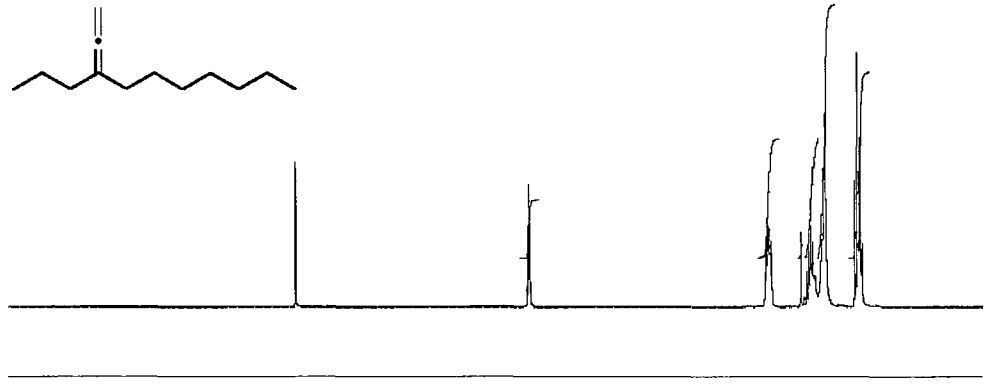
ppm (t1)



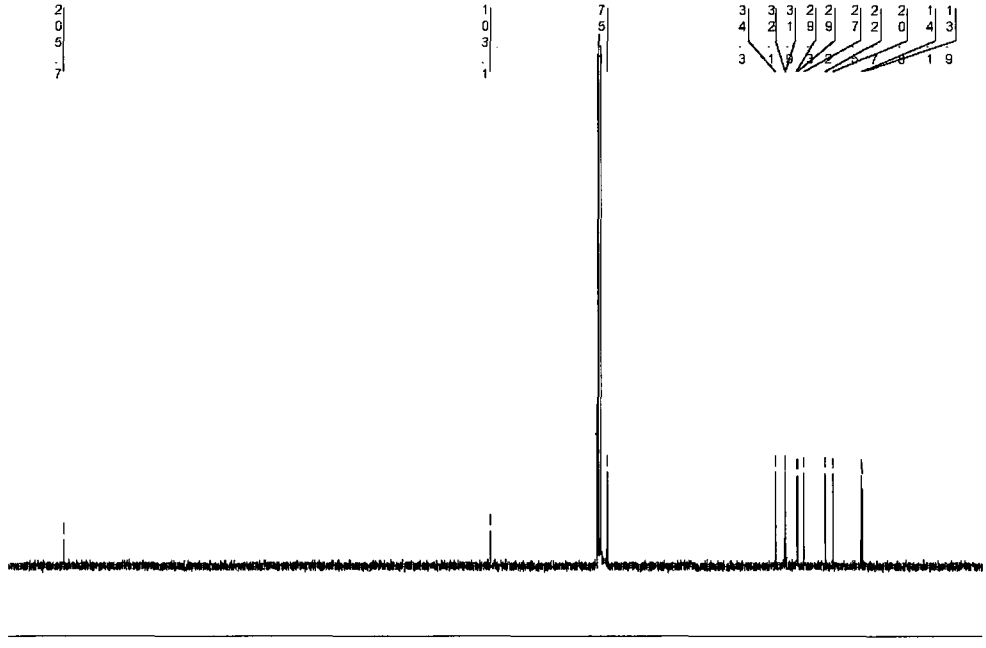
ppm (t1)



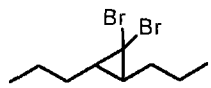
ppm (t1)



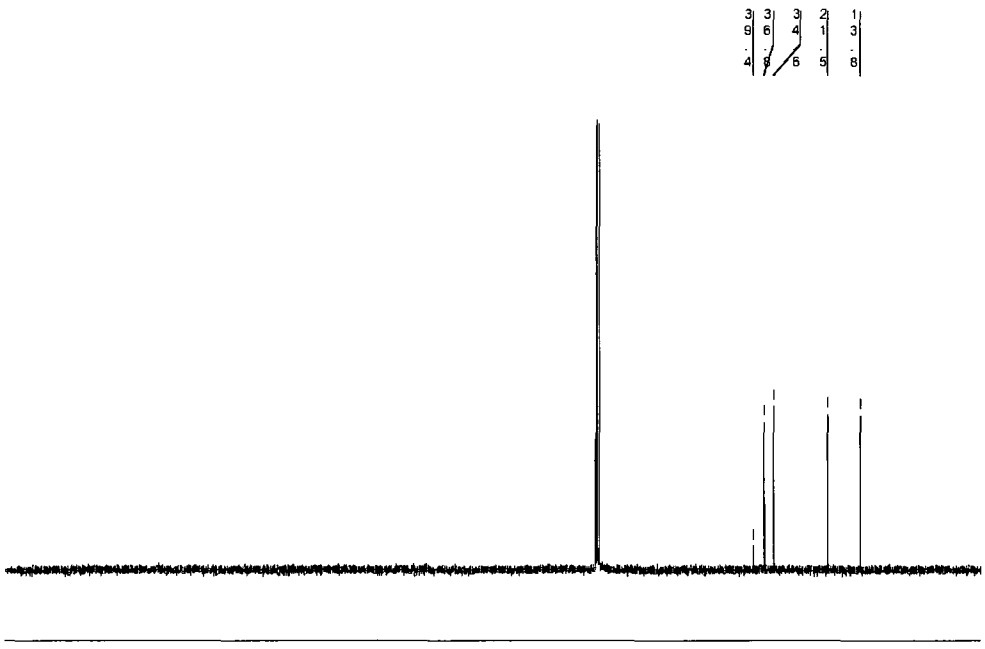
ppm (t1)



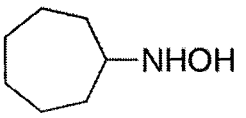
ppm (t1)



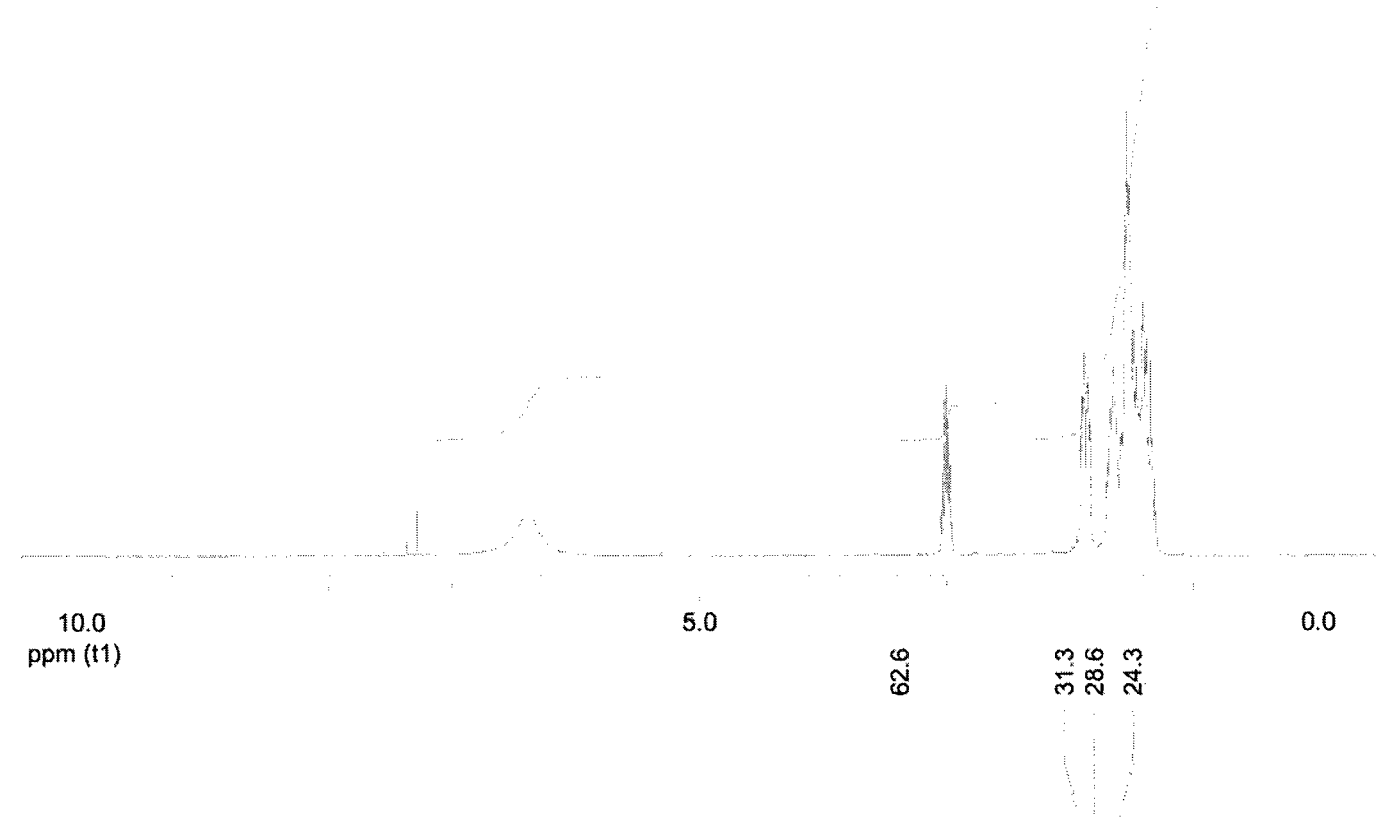
ppm (t1)

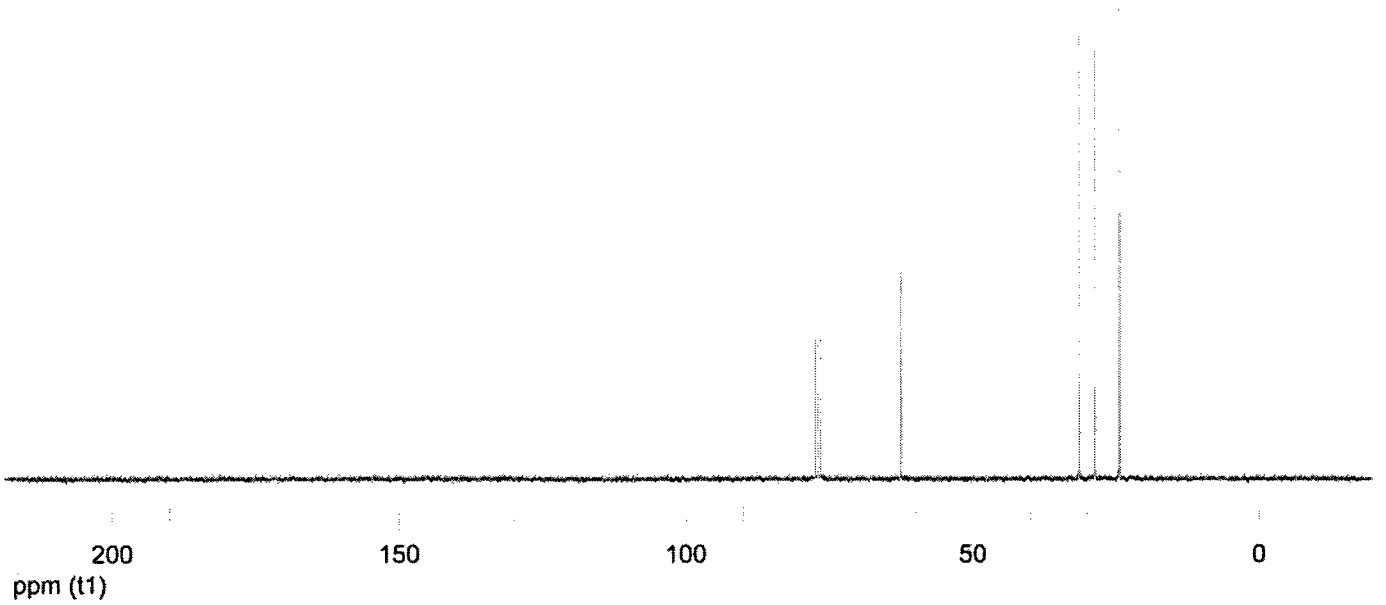


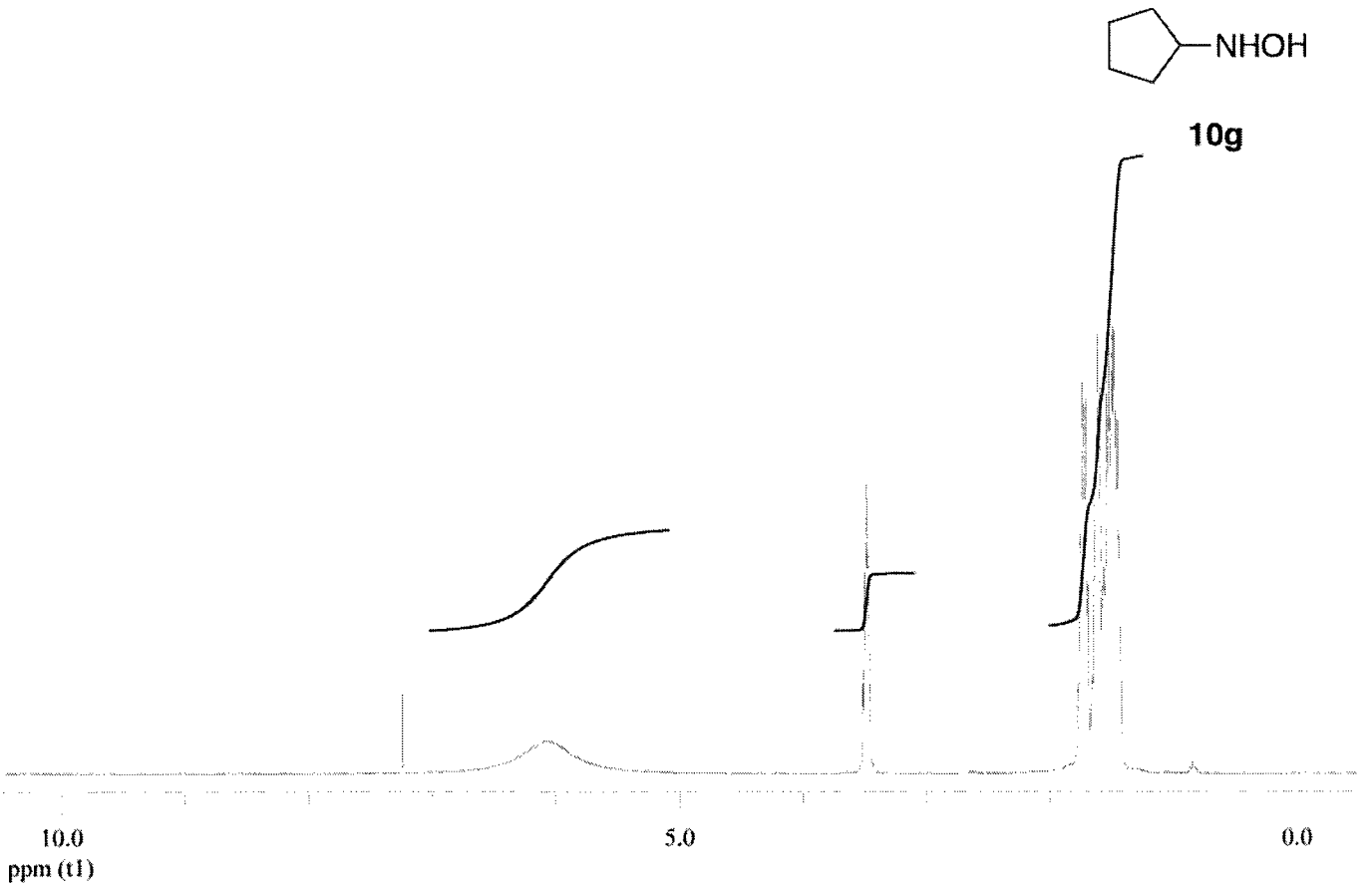
ppm (t1)

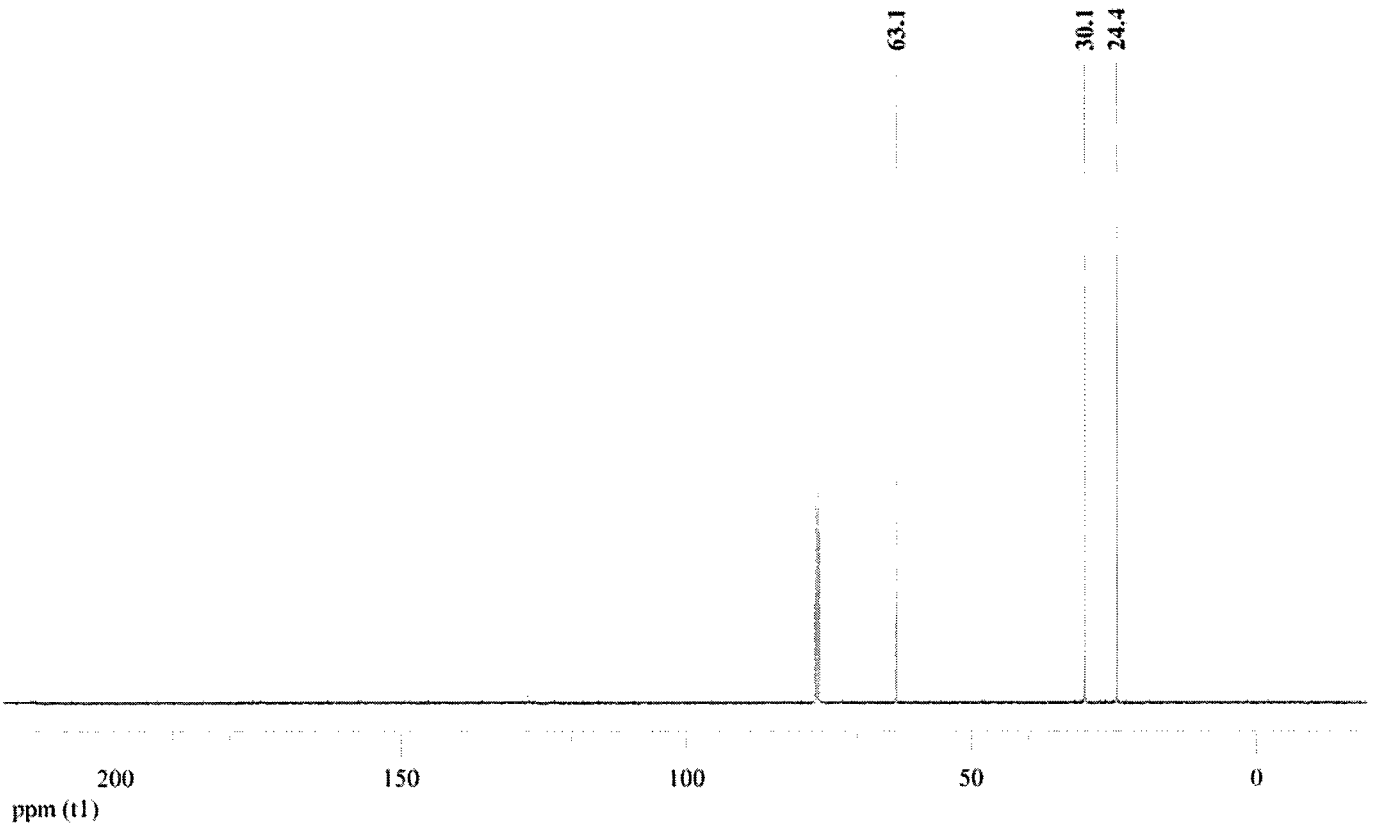


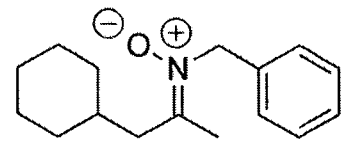
10h



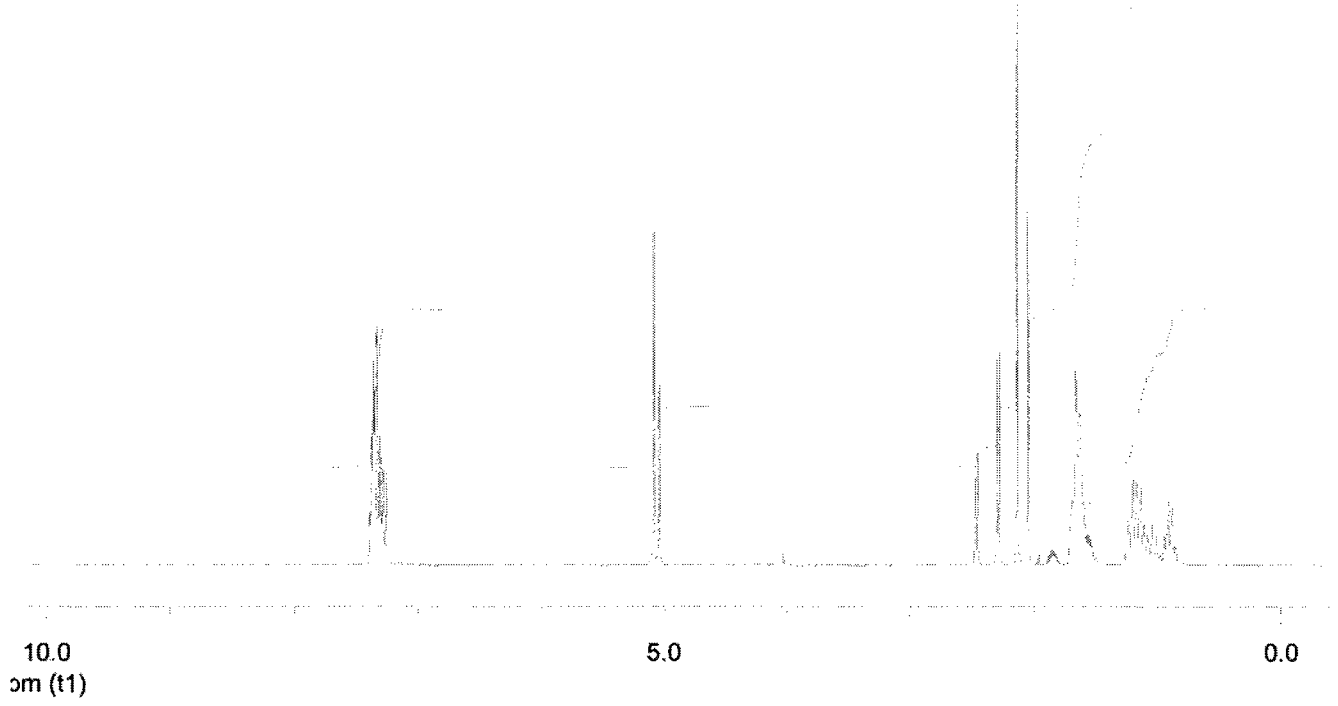


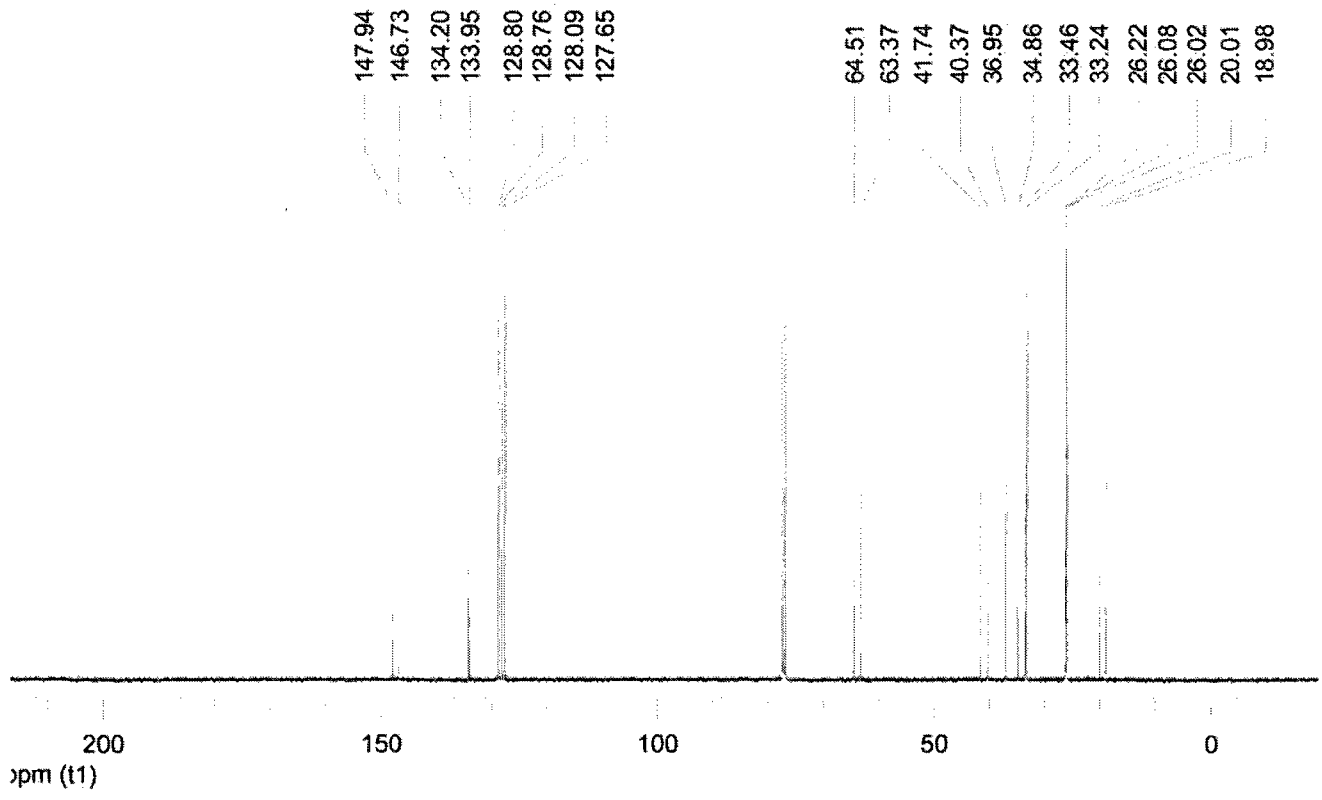

NHOH
10g
10.0
5.0
0.0
ppm (t1)

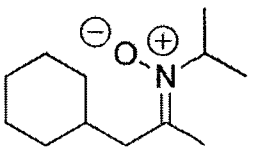

63.1
30.1
24.4
200
150
100
50
0
ppm (t1)



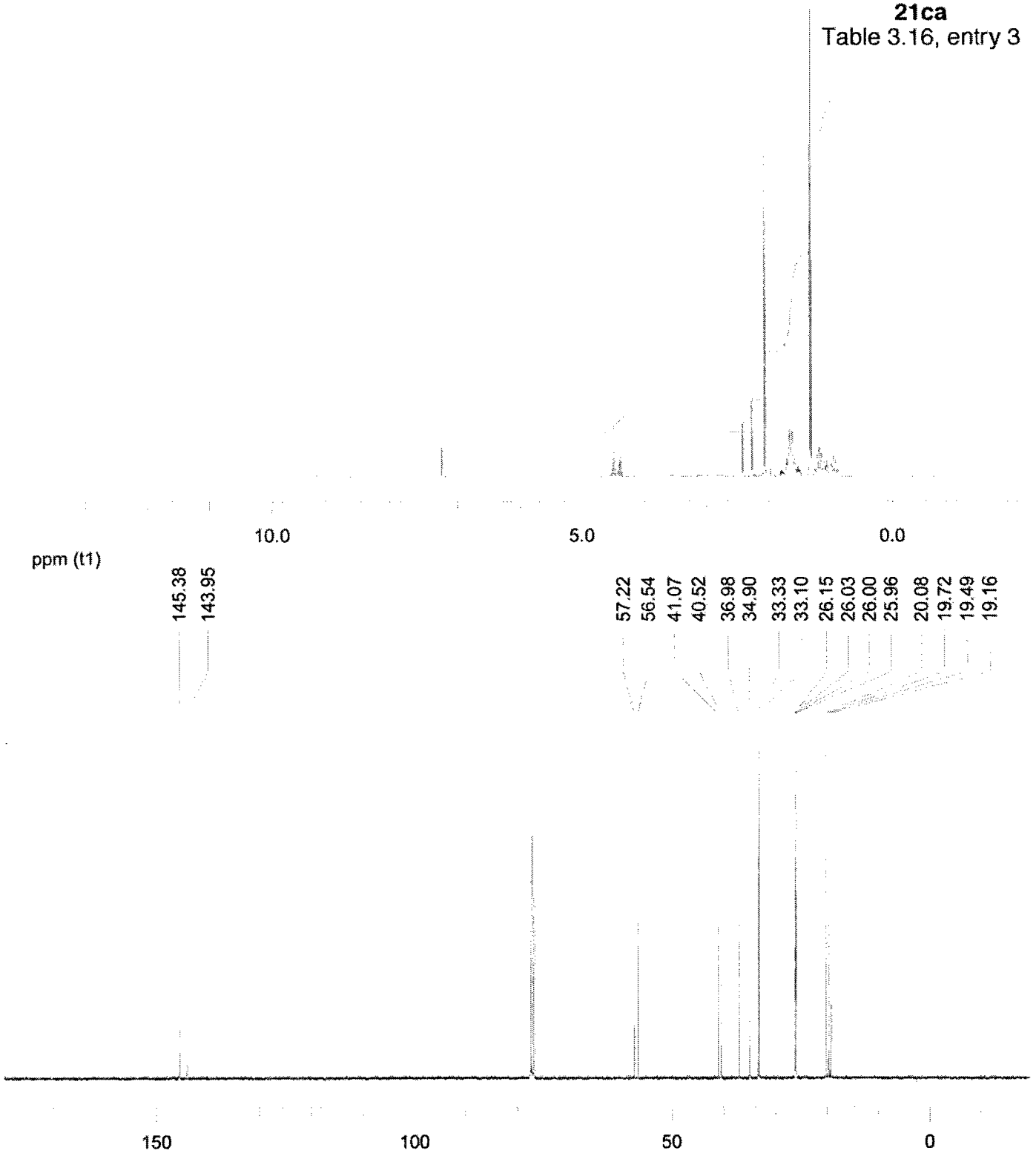
21ba
Table 3.16, entry 2

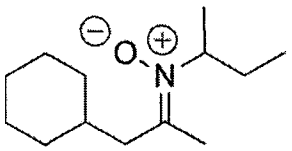




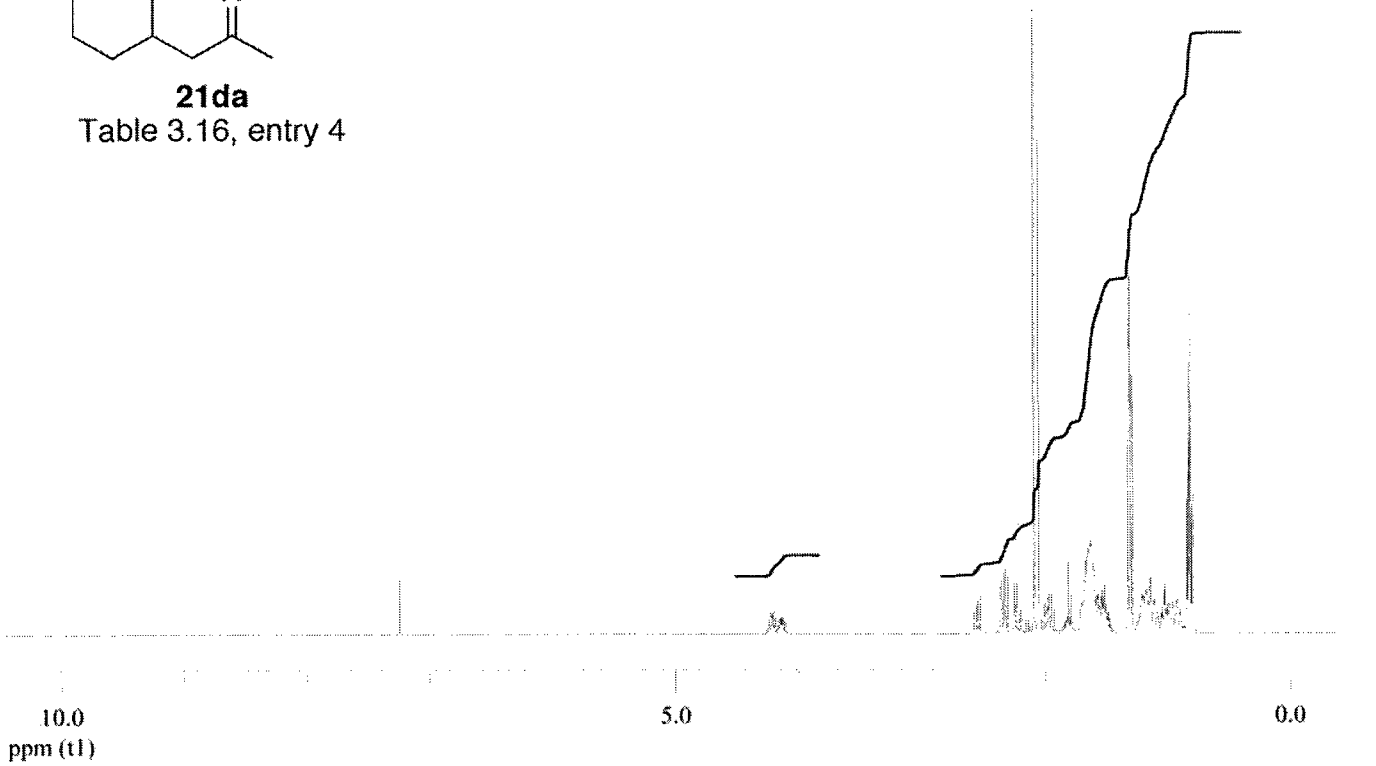


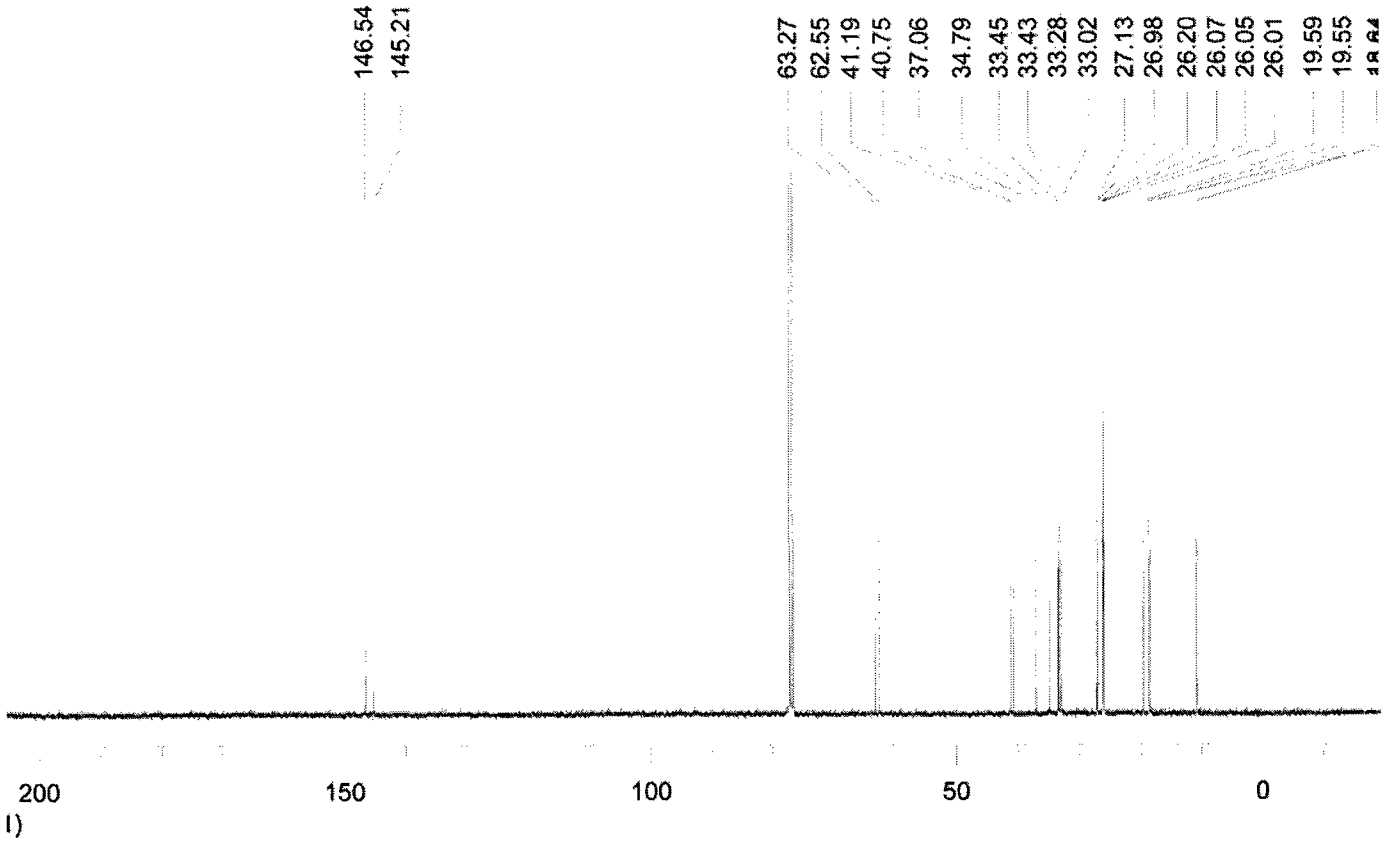
21ca
Table 3.16, entry 3

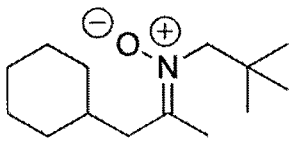




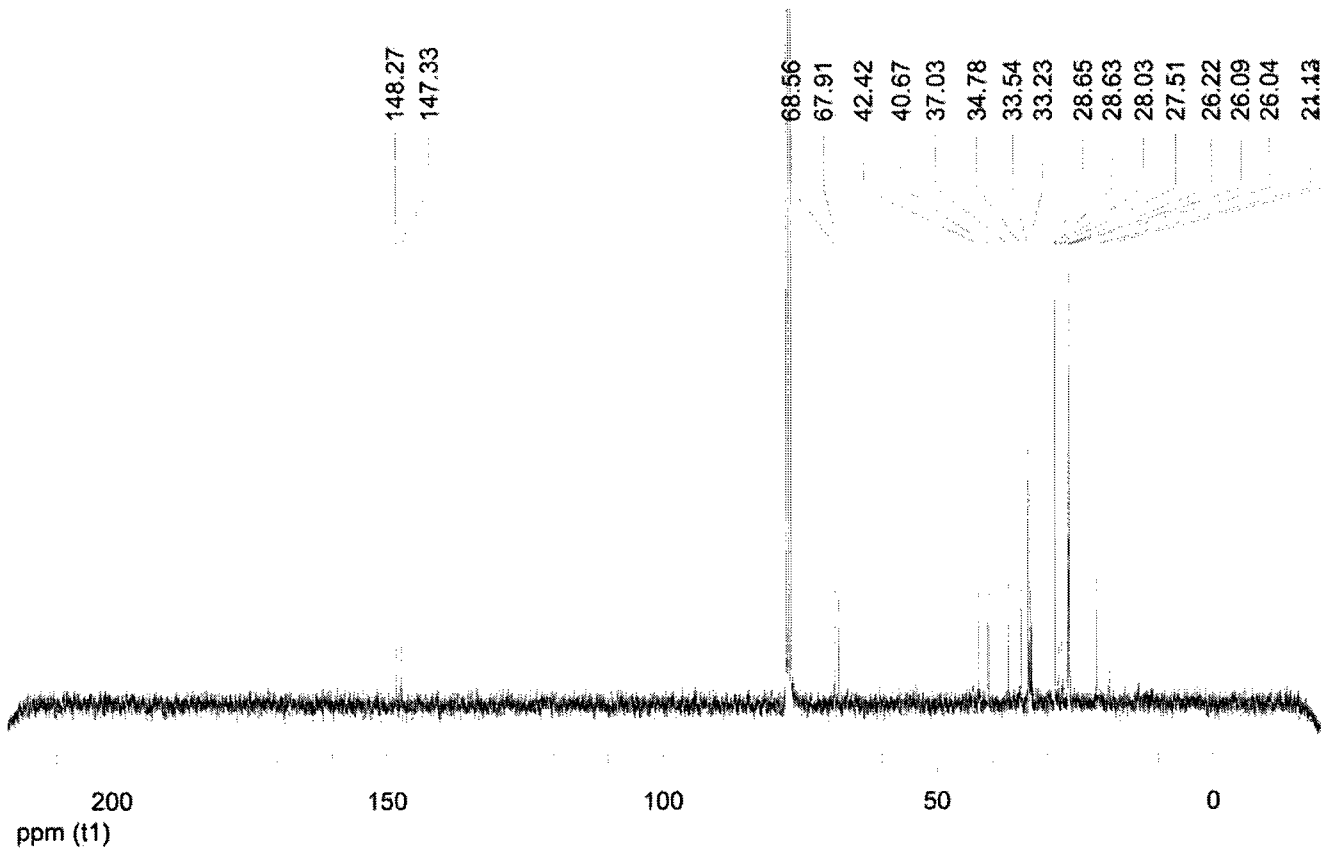
21da
Table 3.16, entry 4

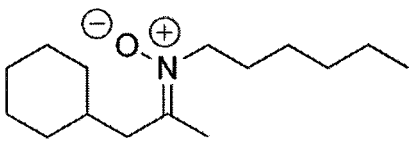




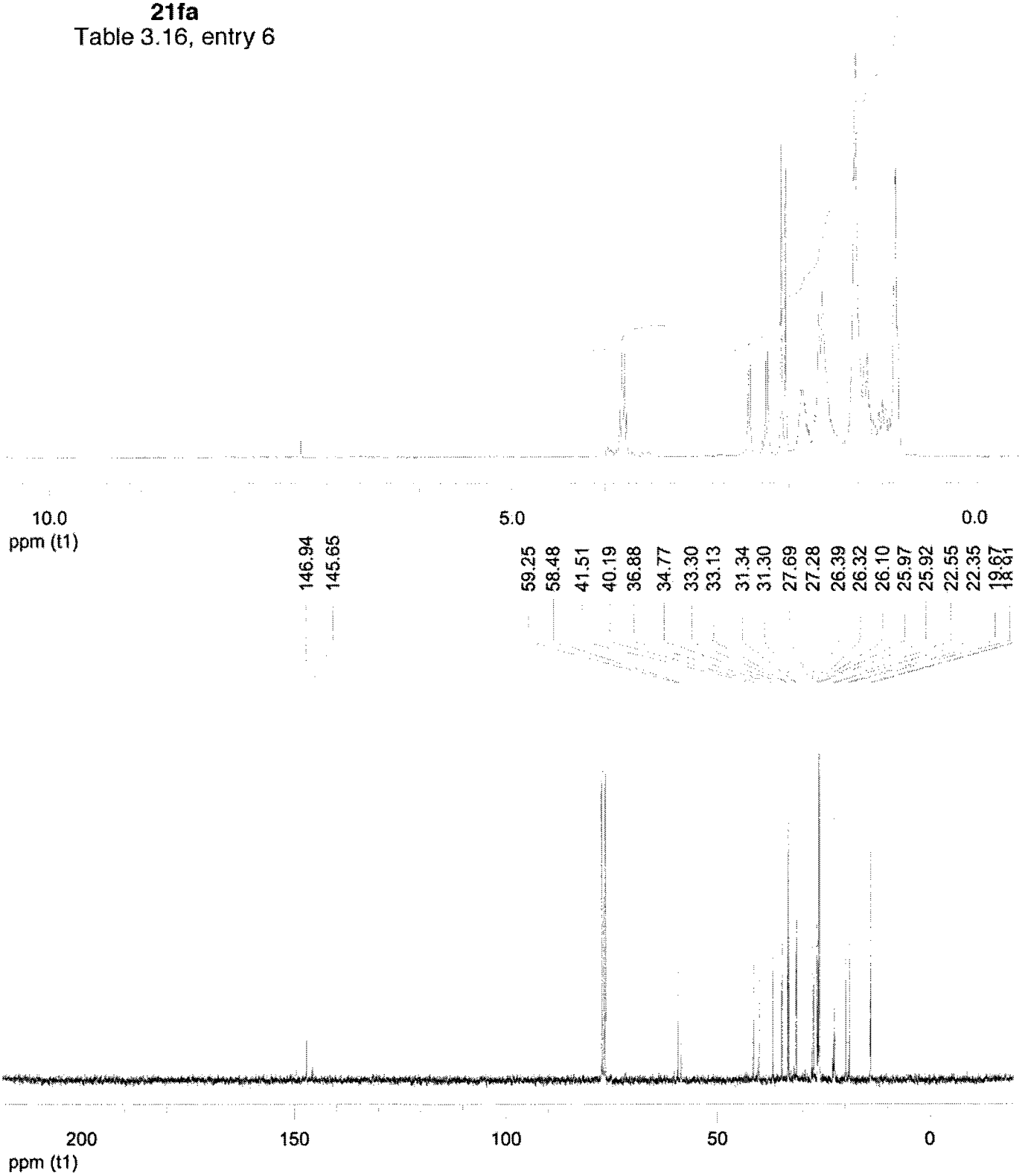


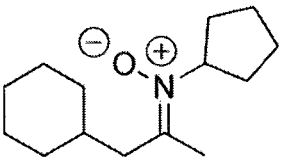
21ea
Table 3.16, entry 5



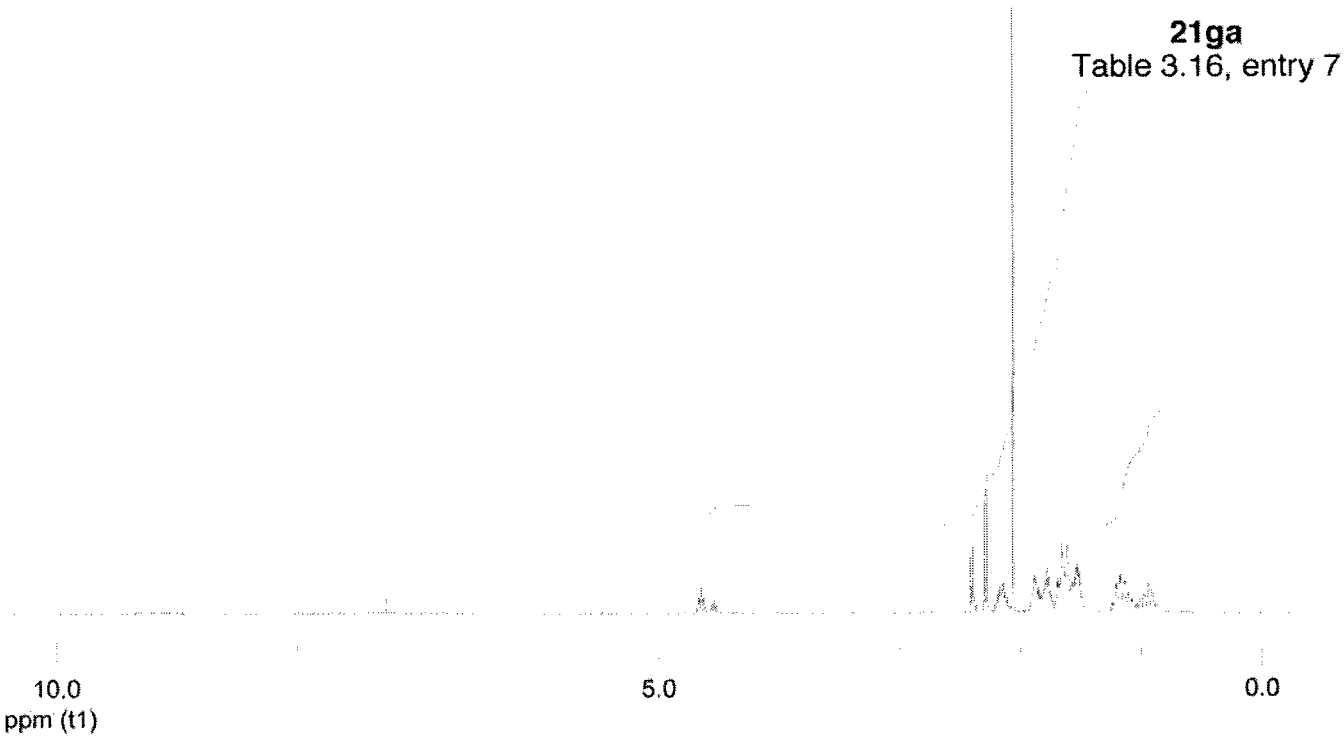


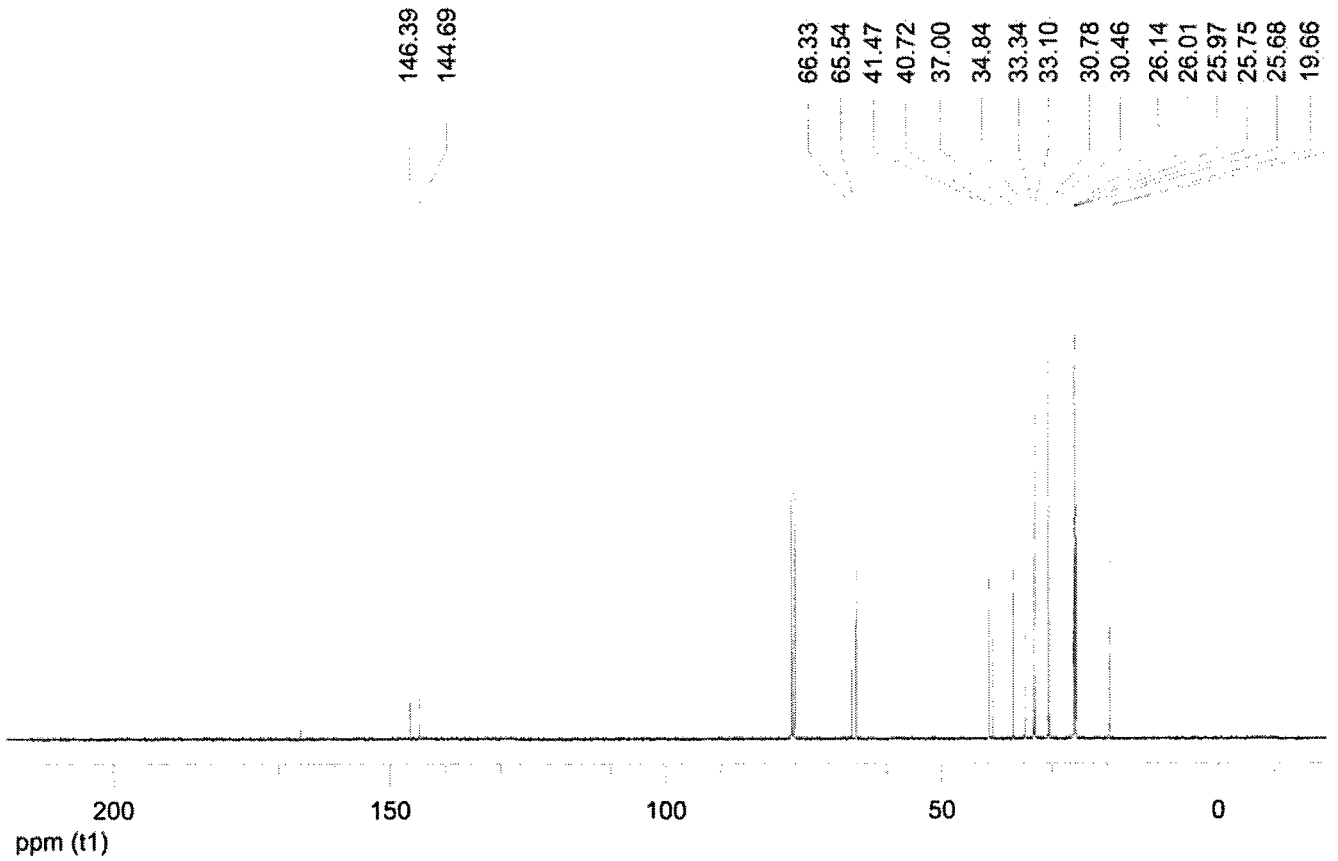
21fa
Table 3.16, entry 6

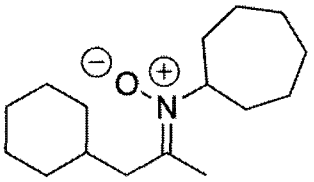




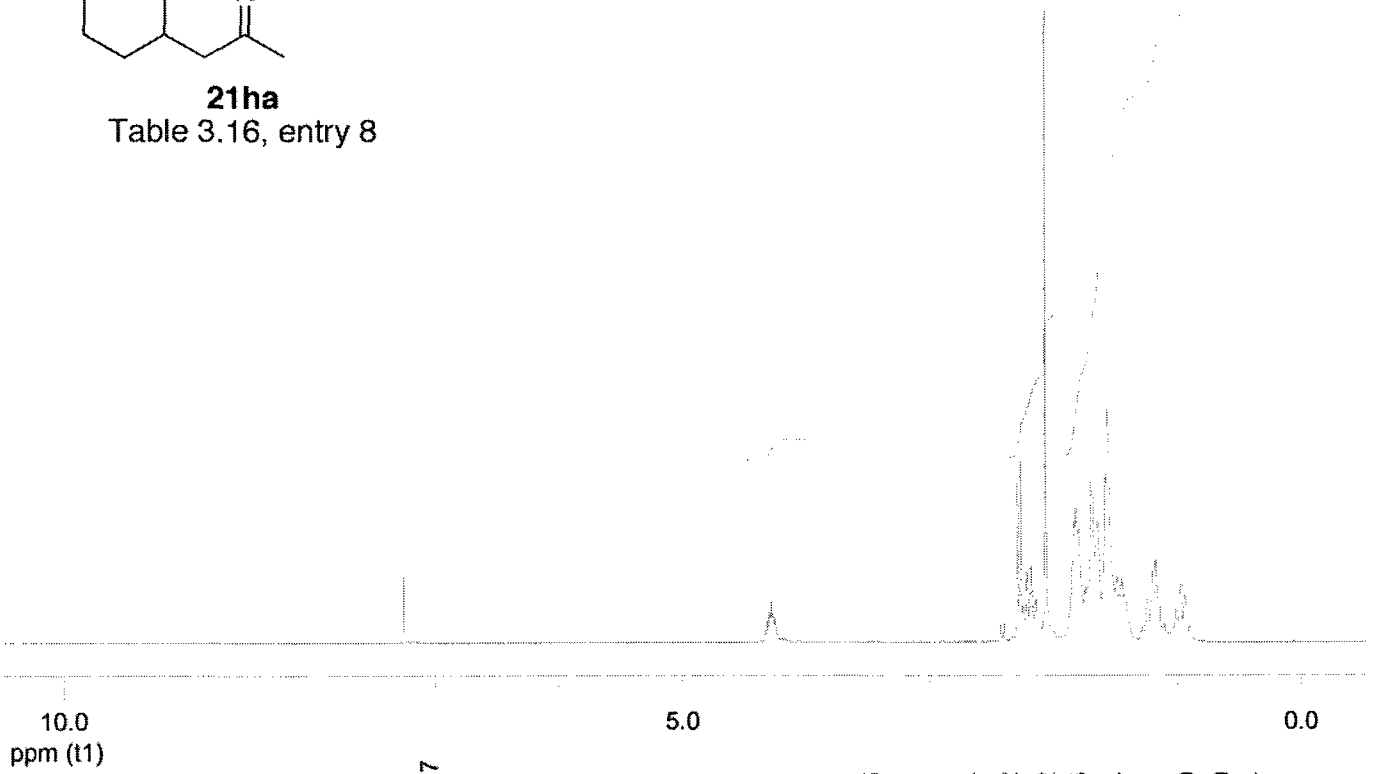
21ga
Table 3.16, entry 7

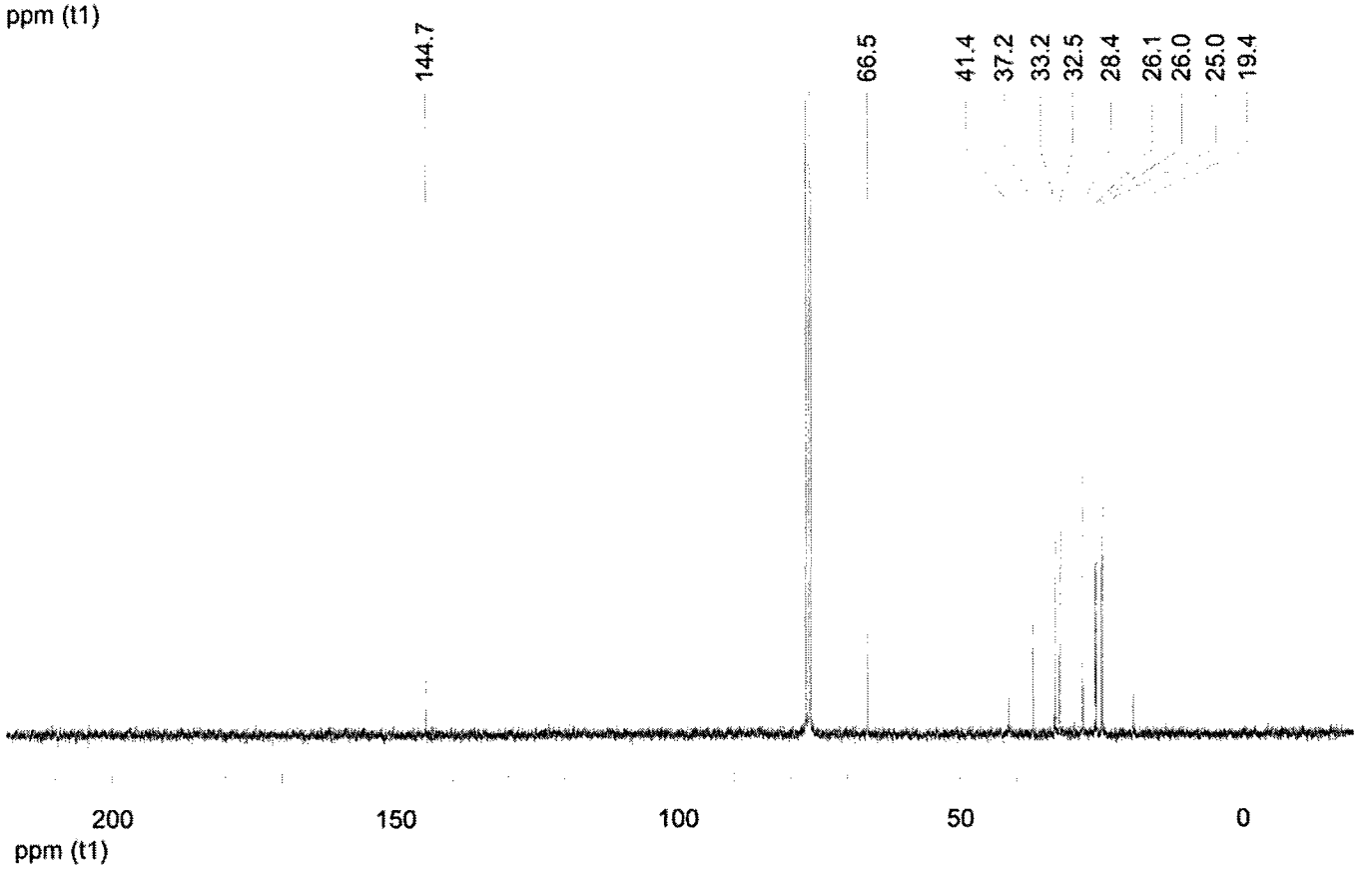


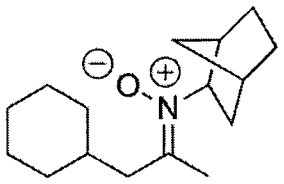




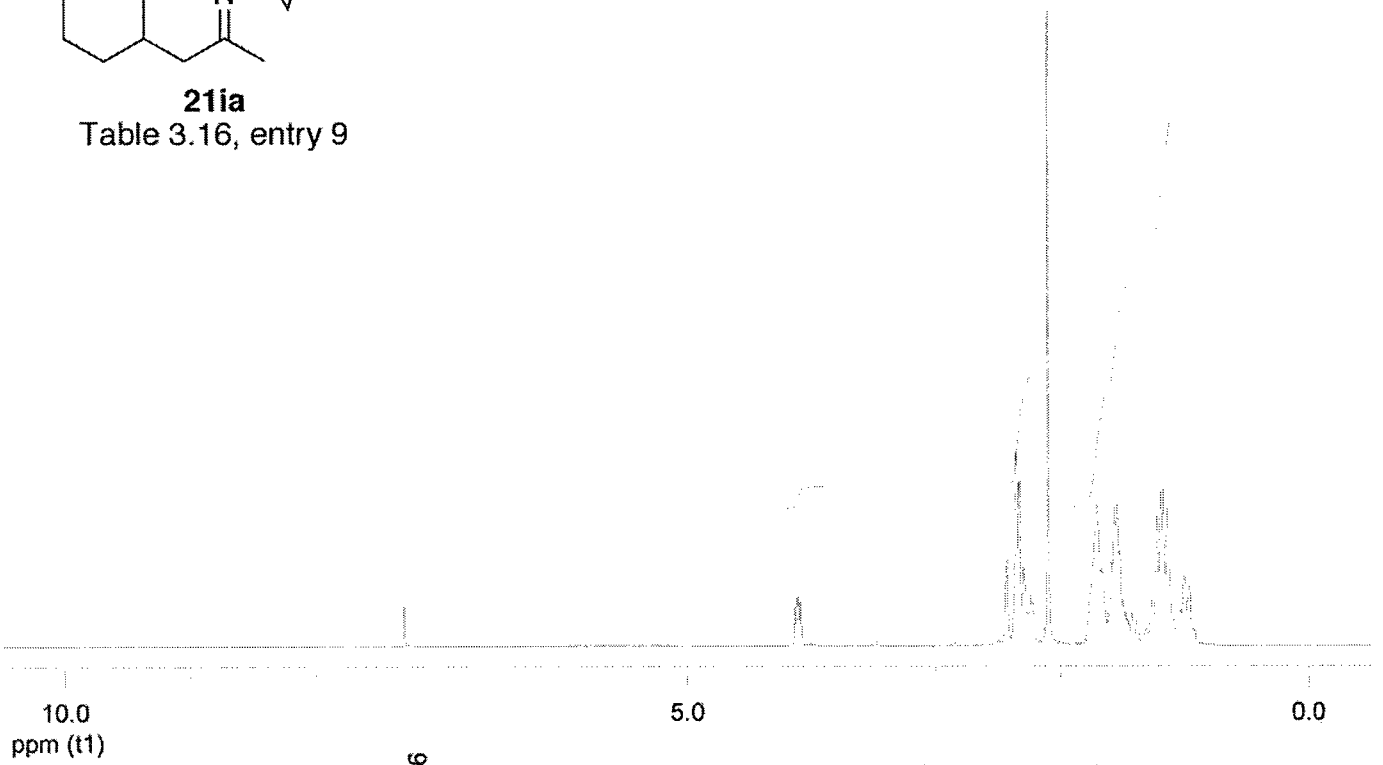
21ha
Table 3.16, entry 8

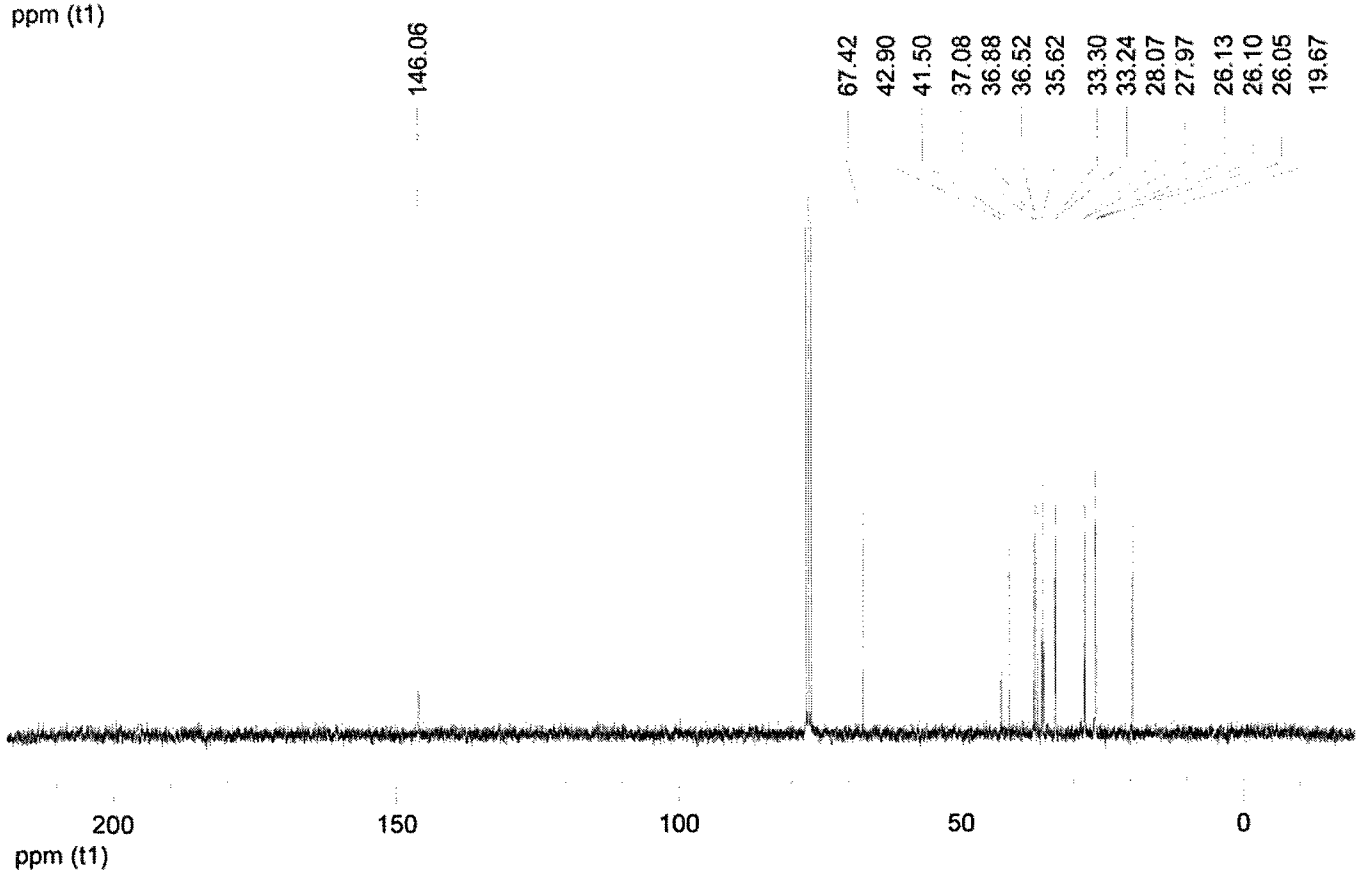


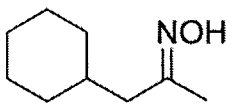




21ia
Table 3.16, entry 9

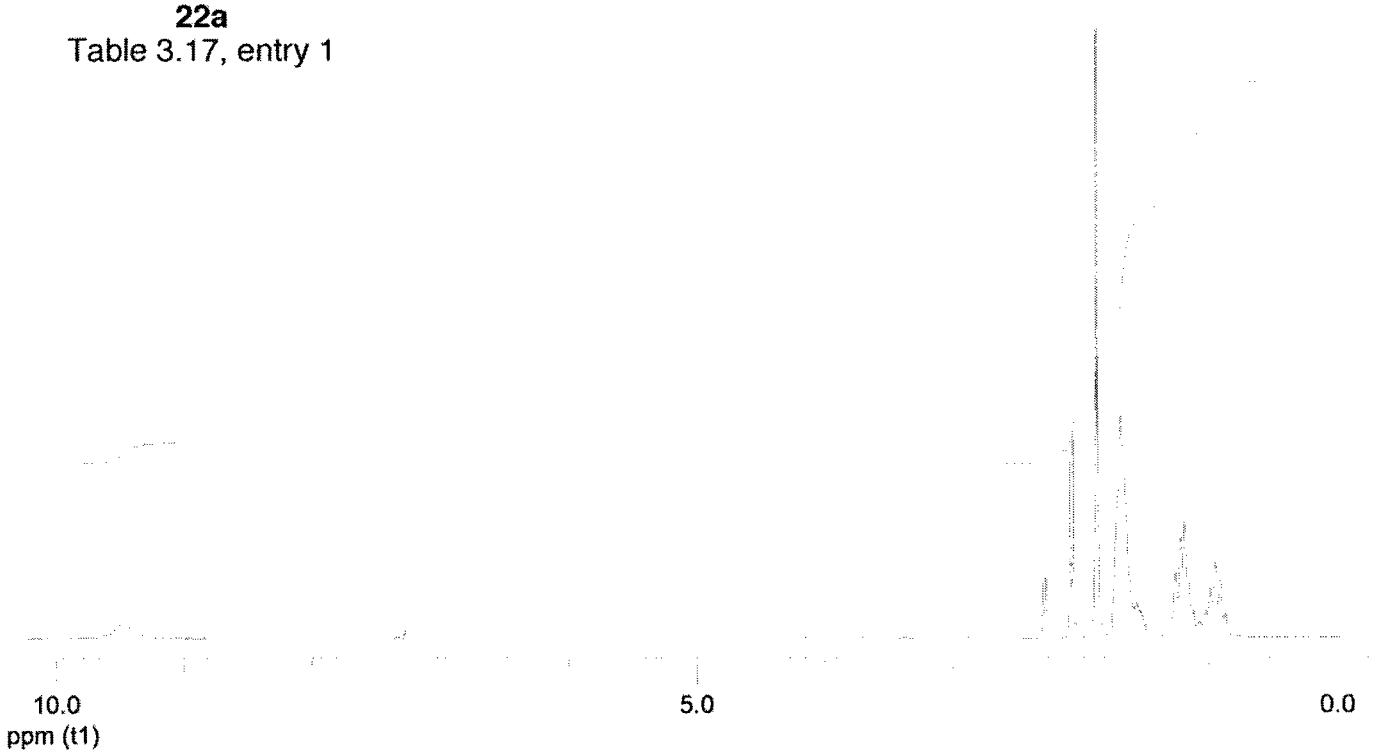


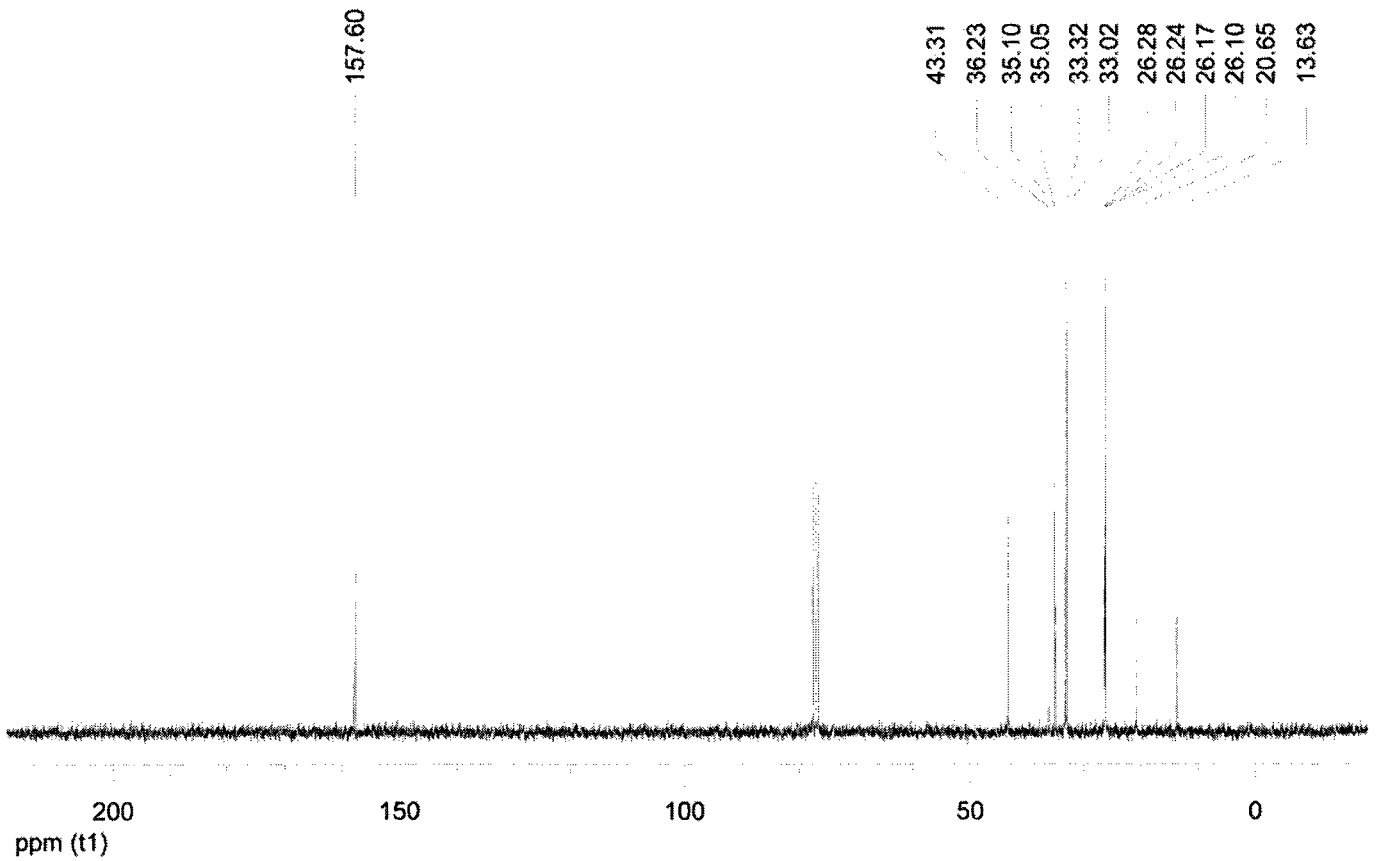


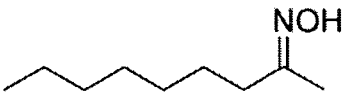


22a

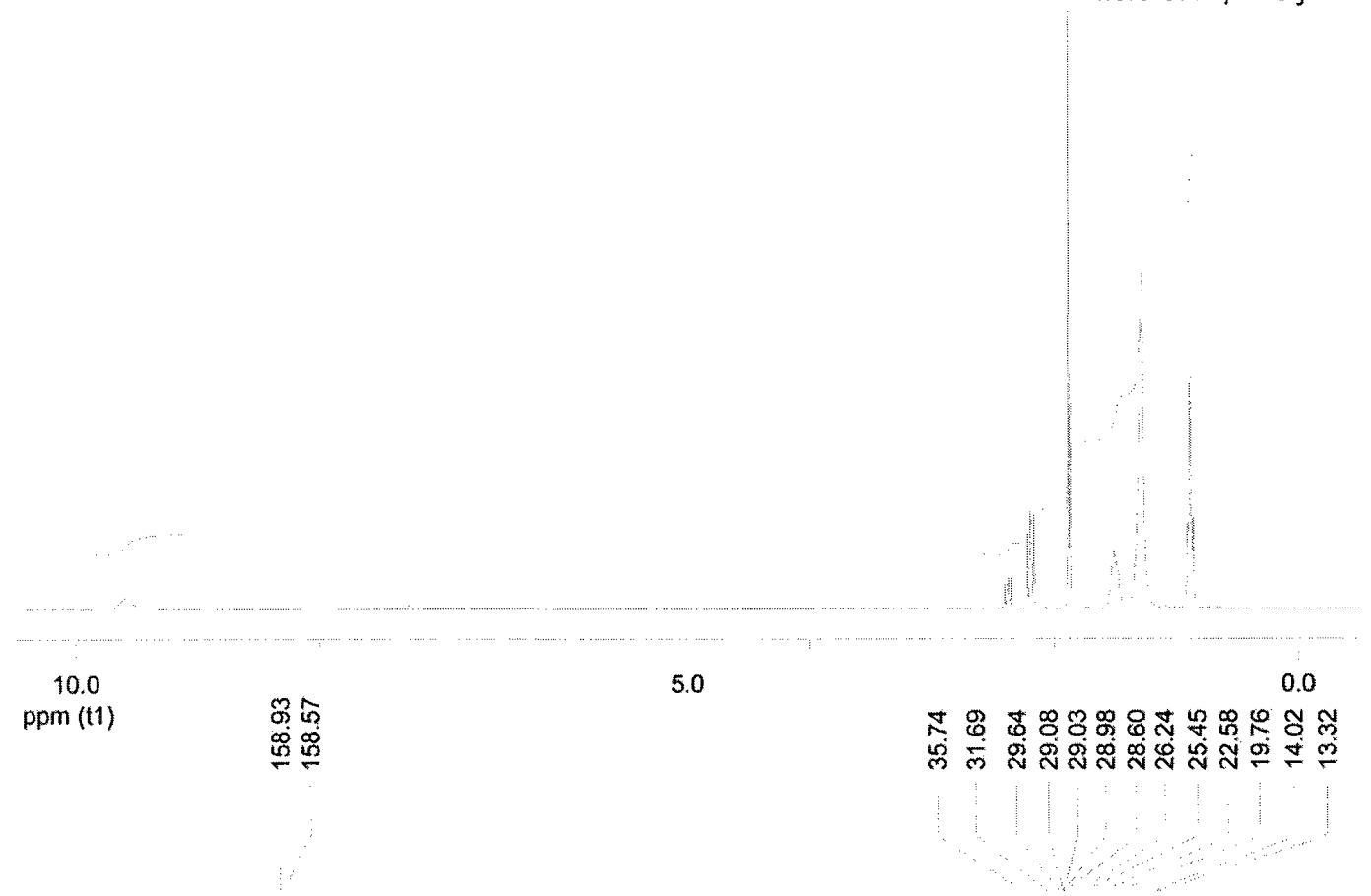
Table 3.17, entry 1

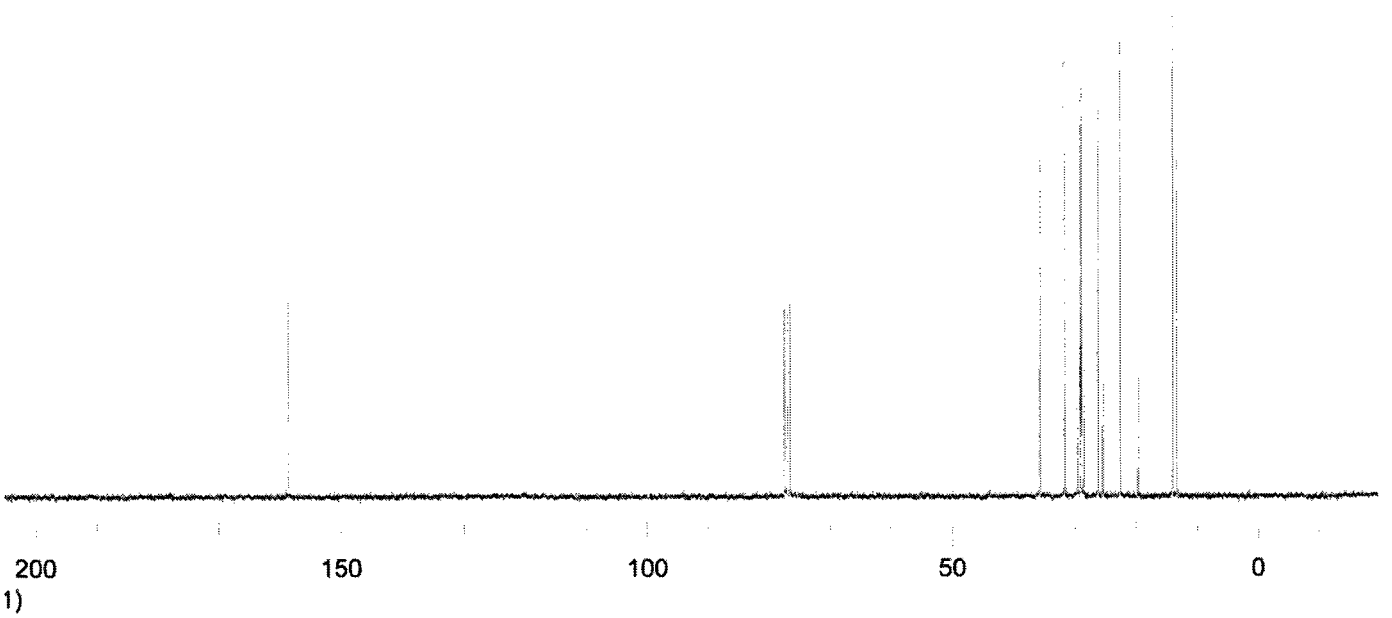


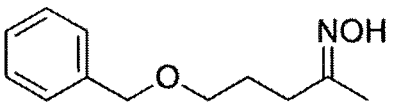




22b
Table 3.17, entry 2

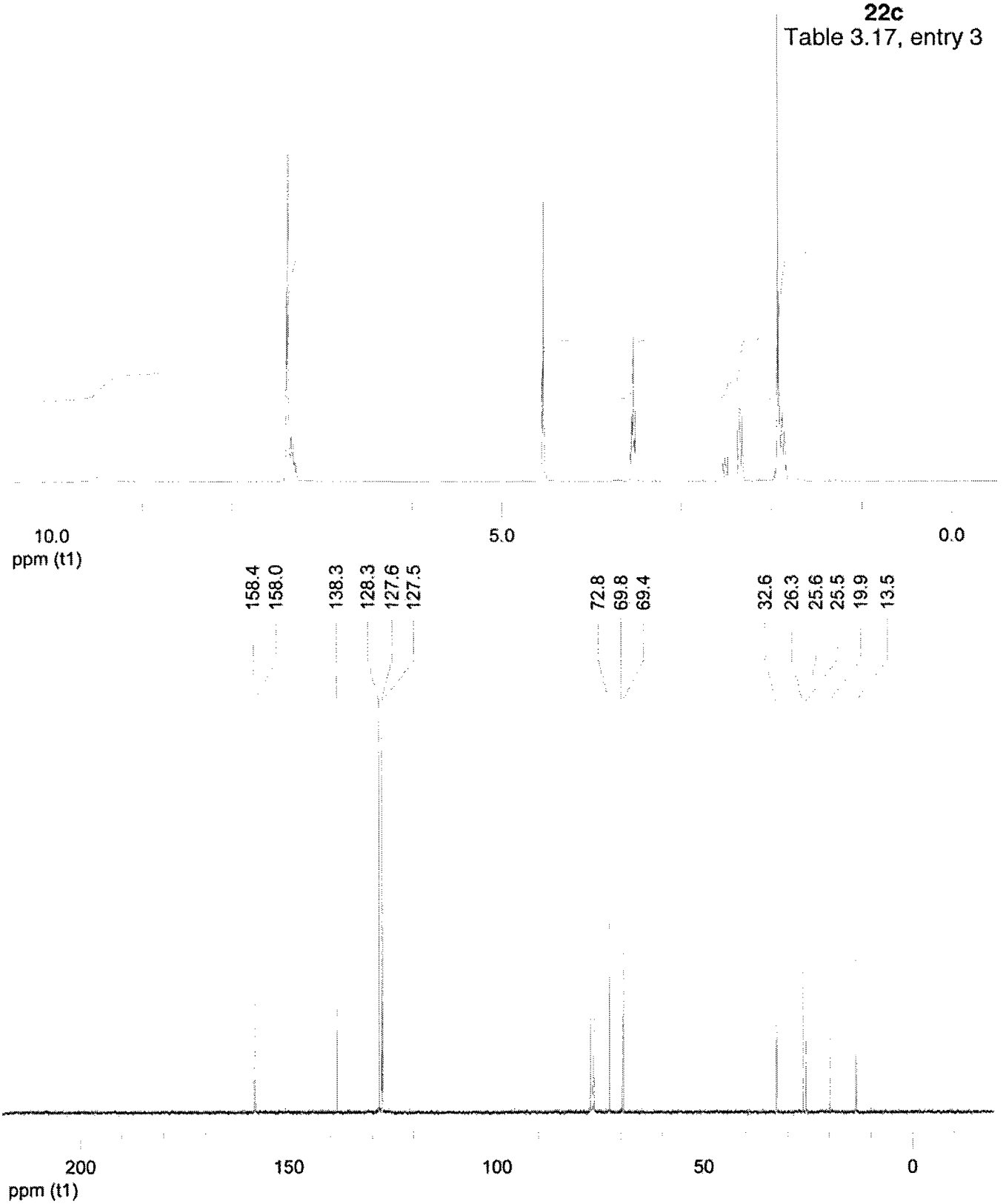


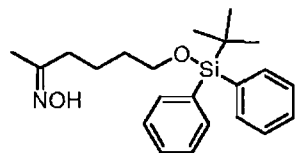




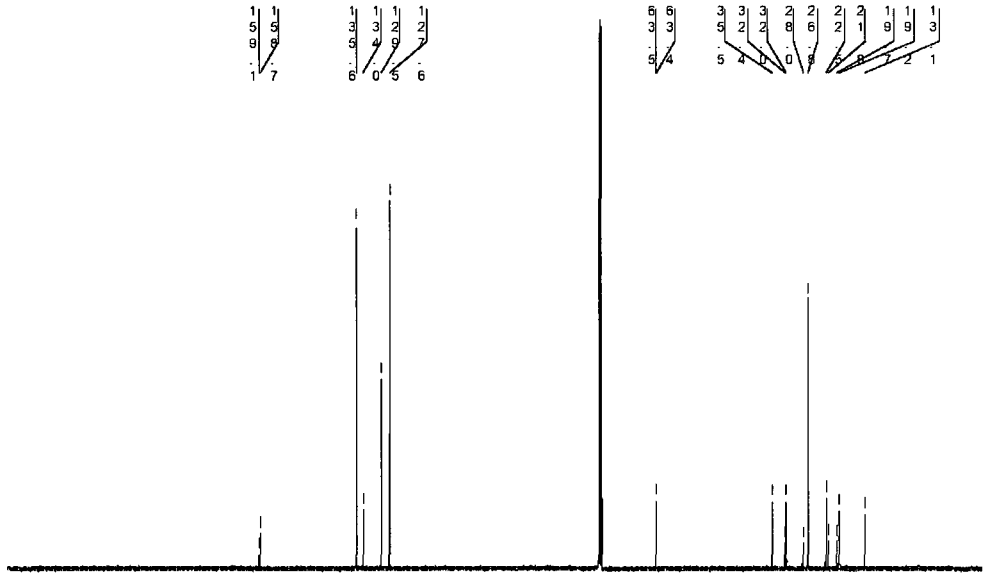
22c

Table 3.17, entry 3

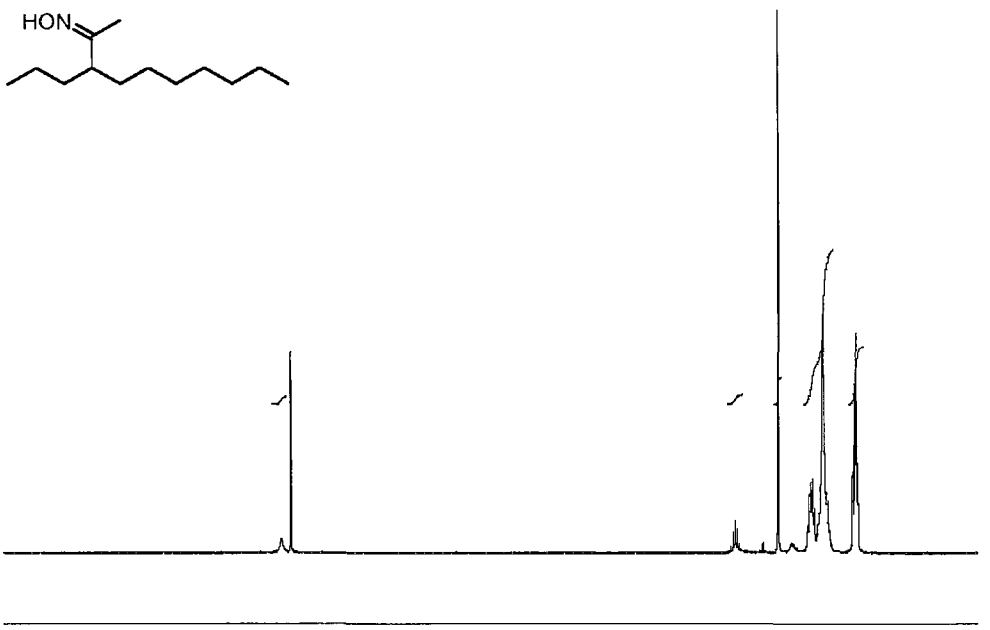




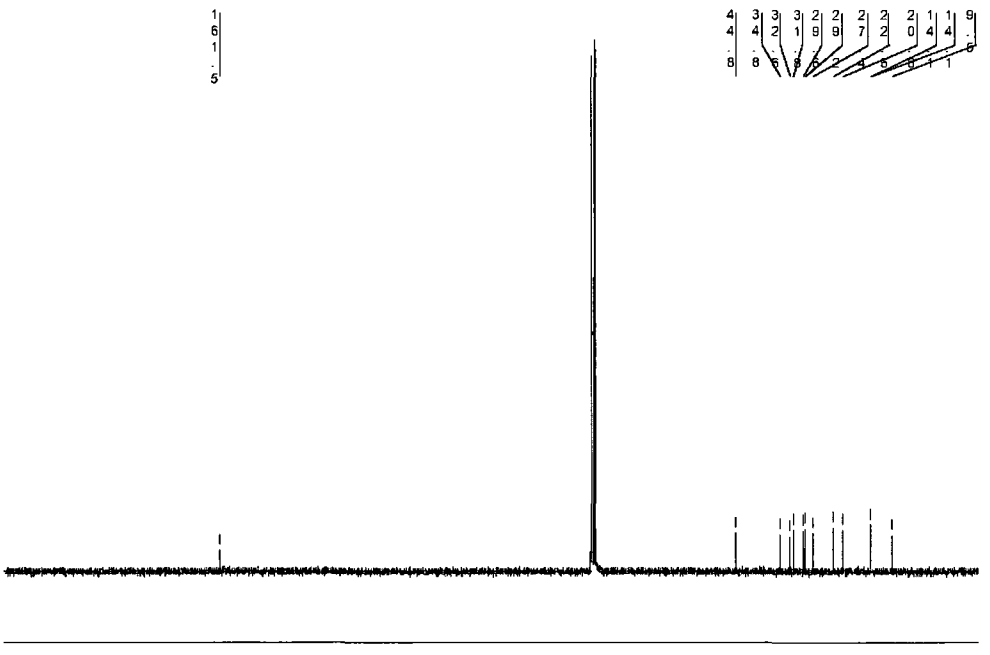
ppm (t1)



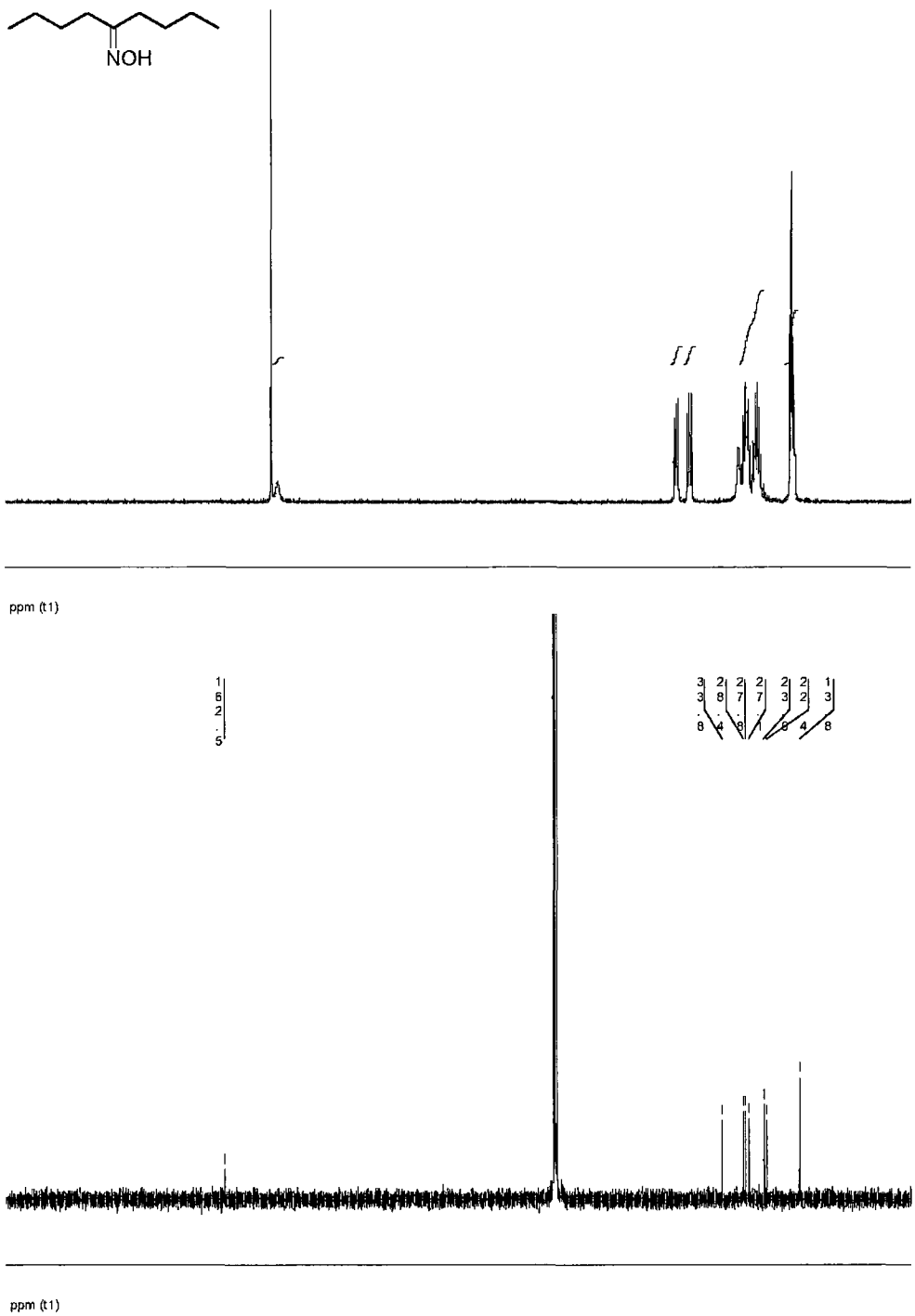
ppm (t1)

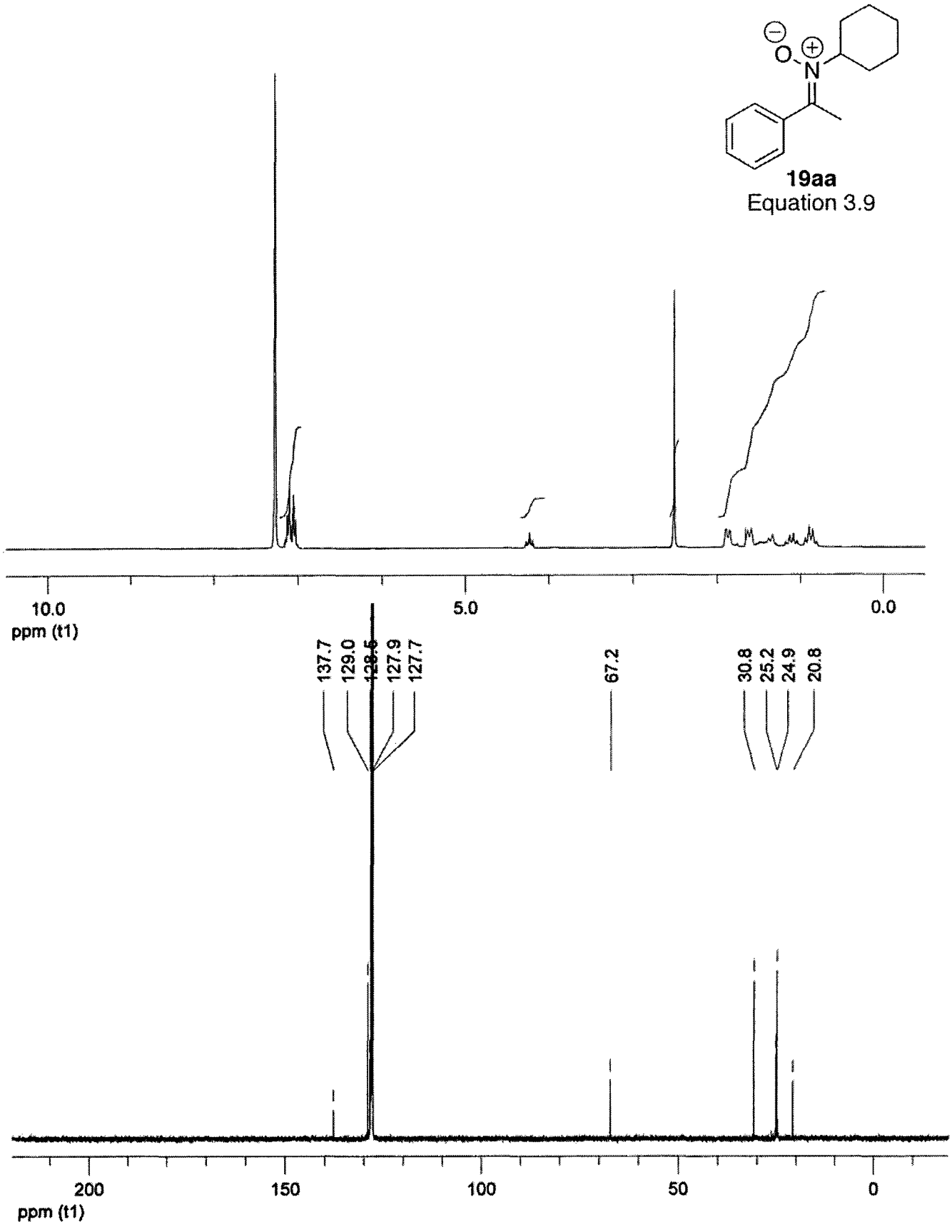


ppm (t1)

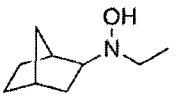


ppm (t1)

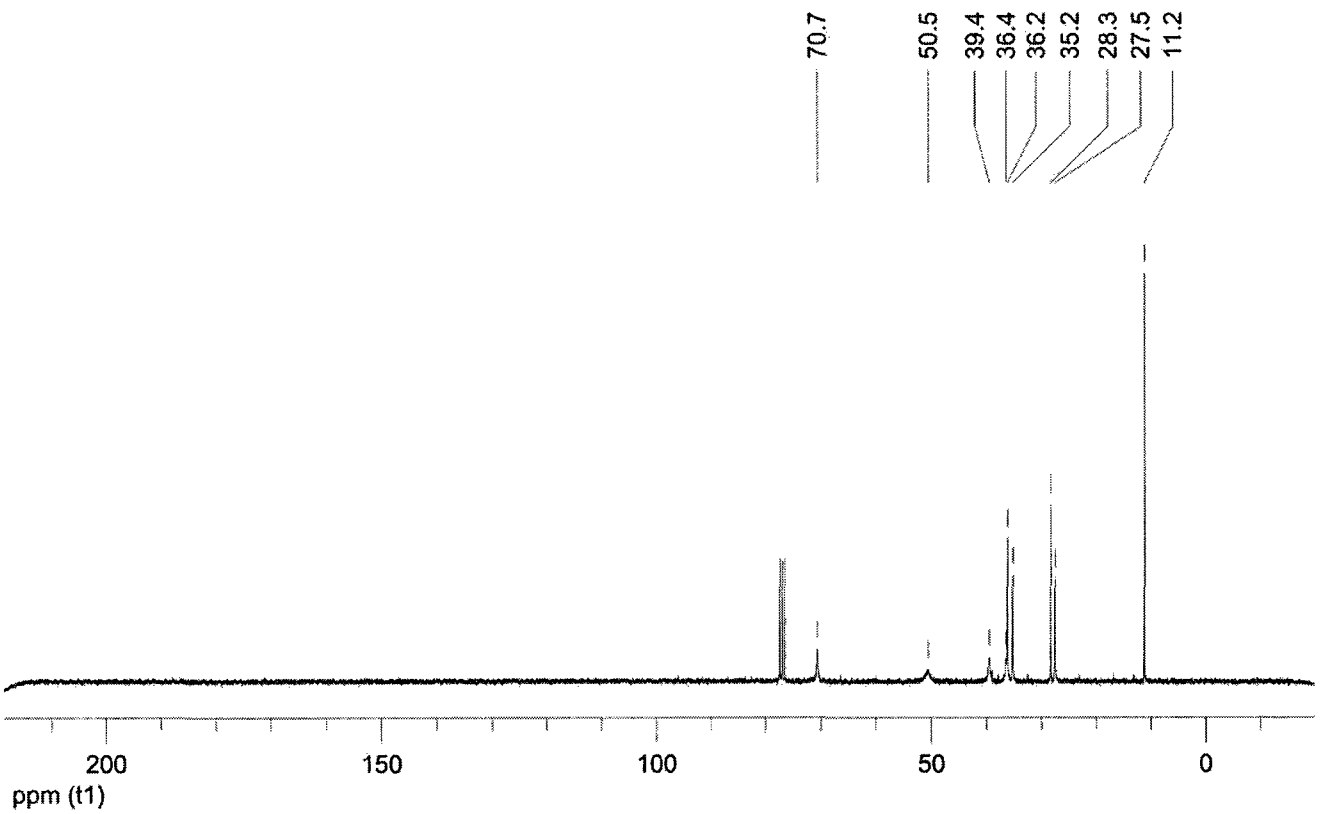

NOH
ppm (t1)
ppm (t1)

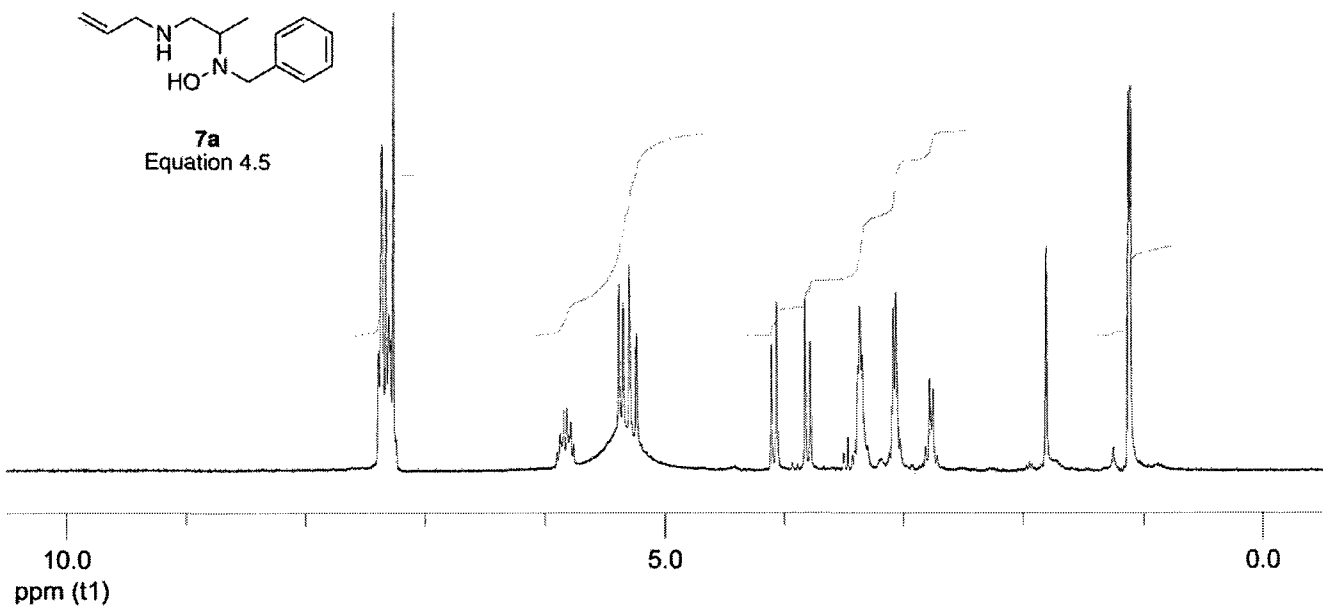

19aa
Equation 3.9
10.0
ppm (t1)
5.0
0.0
137.7
129.0
128.5
127.9
127.7
67.2
30.8
25.2
24.9
20.8
200
150
100
50
0
ppm (t1)

Appendix IV. Supporting Information for Chapter 4.



2
Equation 4.2




HO
N
H
N
7a
Equation 4.5
10.0
ppm (t1)
5.0
0.0