2016

Unprecedented Ractivity Of 1-Aza-2-Azoniaallene Salts: New Methodologies And Mechanistic Studies For The Formation Of Diazenium Salts And Tetrahydropyridazines

Nezar Al-Bataineh
University of Vermont

UNPRECEDENTED REACTIVITY OF 1-AZA-2-AZONIAALLENE SALTS: NEW METHODOLOGIES AND MECHANISTIC STUDIES FOR THE FORMATION OF DIAZENIUM SALTS AND TETRAHYDROPYRIDAZINES

A Dissertation Presented

By

Nezar Al-Bataineh

To

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Chemistry
May, 2016

Defense Date: January 01, 2016
Dissertation Examination Committee:
Matthias Brewer, Ph.D., Advisor
Stephen Everse, Ph.D., Chairperson
Jose Madalengoitia, Ph.D.
Rory Waterman, Ph.D.
Cynthia J. Forehand, Ph.D., Dean of the Graduate College

ABSTRACT

This thesis describes the research conducted towards the overall goal of developing new synthetic organic methods to facilitate the synthesis of structurally complex nitrogen-containing polycyclic compounds. More specifically, I will describe the diverse reactivity of 1-aza-2-azoniaallene systems to make polycyclic diazenium salts and tetrahydropyridazine rings. I will also describe mechanistic studies undertaken to better understand this reactivity.

The Brewer research group has discovered that hydrazones undergo an oxidation reaction with chlorodimethylsulfonium chloride to afford α-chloroazo compounds, which react intramolecularly with pendent alkene units to give bicyclic ring fused and bridged diazenium salts. My work includes a mechanistic study to understand how the reaction proceeds and what factors affect its outcome. I will also describe the development of a new method to make diazenium salts in a shorter and more efficient route using a hypervalent Iodine (III) reagent.

More recently, our group discovered new and different modes of reactivity of 1-aza-2-azoniaallene salts that included C-H amination reactions, polar [4 + 2] cycloadditions, electrophilic aromatic substitutions, and a chloroamination reaction. Our group was able to utilize these newly discovered reactivities in the preparation of pyrazolines, pyrazoles, tetrahydrocinnolines, and pyridazines, which are all complex compounds of great synthetic utilities that were made in short chemical transformations. Herein I describe my work to understand the scope and limitations of using these heteroallenes in the synthesis of pyridazines.

CITATIONS

Material from this dissertation has been published in the following form:

Wyman, J.; Javed, M. I.; Al-Bataineh, N.; Brewer M.. (2010) Synthetic Approaches to Bicyclic Diazenium Salts, The Journal of Organic Chemistry, 75 (23), pp 8078–8087.

Al-Bataineh, N.; Brewer M.. (2012) Iodine(III)-mediated bicyclic diazenium salt formation, Tetrahedron Letters, 53 (40), pp 5411-5413.

Hong, X; Bercovici, D. A.; Yang, Z; Al-Bataineh, N.; Srinivasan, R.; Dhakal, R. C.; Houk, K. N.; Brewer, M.. (2015) Mechanism and Dynamics of Intramolecular C–H Insertion Reactions of 1-Aza-2-azoniaallene Salts, Journal of the American Chemical Society, 137 (28), pp 9100–9107.

DEDICATION

To my only love, my wonderful wife, and my best friend, Duha;
to my precious children, Juri, Mariam, and Kareem;
it was their unconditional love, support, patience,
and inspiration that made this possible...

ACKNOWLEDGMENTS

It cannot express enough in words how thankful I am to Professor Matthias Brewer who has not only been a great advisor, but also a wonderful person. Matthias has always been giving me unlimited guidance and support over all the years. I learned a lot from him about approaching research problems, conducting scientific research, techniques that expanded my skills, and I learned how to be a better teacher. Matthias by all means has been the best example of an advisor, a person, a teacher, and a friend.

I would like to thank my committee members, Professor Jose S. Madalengoitia and Professor Rory Waterman for their direct and indirect help and advice through my graduate studies. I would like to thank Professor Stephen Everse for being the chair of my dissertation committee.

I thank Professor Stephen Waters for teaching organic chemistry and for helping in many research problems. I thank Dr. Muhammad Irfan Javed for helping me in my life and in research. Thanks to Professor Paul Krapcho for his advice and friendship. I very much appreciate all of the faculty at UVM Chemistry Department; especially, Professor Christopher Landry for his help, advise, and support, and Professor Giuseppe A. Petrucci. I thank the staff at the department of chemistry: Christine Cardillo, Kevin Kolinich, Andrea Lucey, Bruce O'Rourke, Travis Verret, Angela Gatesy, Hollis Robinson, and Edward Curtiss. Special thanks to Jodi Ogilvie and Ali Bayir, for their advice and help in research. I thank all previous and current Brewer group members: Christian Dragicci, Daniel Bercovicci, Quefang Huang, Nikolay Tsvetkov, Spencer Scholz, Nitin Jabre, Sarah Cleary, Ram Dhakal, Ramya Srinivasan, and Geoff Giampa.

Many thanks to Dr. Nathir Al-Rawashdeh, Dr. Ahamad Al-Ajlouni, Dr. Khaled Shawakfeh, for providing help and advice both during my M.Sc. program and while applying to schools in the U.S. I am specially thankful for my dear friends in Vermont Fuad Musanovic, Wahid Lahmadi, Mostafa Dawodi, Mostafa El-Kasabi, and their families for the love and support to me and my family. I also thank my friends Kathy Weekes and Donna Aviano. I thank very much my wonderful friends and brothers Vadim Bors and Vadim Stirbate.

I would like to thank my family in the U.S., specially Abdullah Bataineh and Read Bataineh for their continuous help to me and my family. I can't thank enough my wife's family members, Um Ali, Ali, Tareq, Omar, Muhammad, Saji, Batoul, Sausan, and all the other family members for the love and help they provided me and my family.

I am sincerely grateful to my sister, Norma, and her family who have been providing me and my family all the love and support; my brothers Ma'in, Ahmad, Muhammad, and Omar who all have been the best family and friends and who have been providing endless love and support even though being in a different part of the world.

I would like to express my deepest love and appreciation for being the son of the most loving parents in the world, Aisha Al-Bataineh and Qaseem Al-Bataineh. I wouldn't have been the person who I am without them and all the words will never fulfill how I feel about them, I love you.

And finally, I thank the people who were my inspiration, who I would have never done this without, who made this and made my life more meaningful, who always loved and supported me, and who I love the most: my love Duha, and my angels Juri, Mariam, and Kareem.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. CHAPTER 1:

Introduction

1.1. Preface

This dissertation will include the work that I have done towards the overall goal of developing new synthetic organic methods to facilitate the synthesis of structurally complex nitrogen-containing polycyclic compounds. More specifically, I will be describing the research I have conducted on using the reactivity of 1-aza-2-azoniaallene salts to make polycyclic diazenium salts and tetrahydropyridazine ring systems.

I will start by presenting the work discovered by our research group and show why we became interested in evaluating the reactivity of 1-aza-2-azoniaallene salts. This will include our discovery that hydrazones undergo an oxidation reaction with chlorodimethylsulfonium chloride to afford α-chloroazo compounds. I will then describe our discovery that α-chloroazo compounds can be sued to produce bicyclic ring fused and bridged diazenium salts by treating them with a halophilic Lewis Acid. This latter reactivity is based on an intramolecular cycloaddition reaction that is governed by the structure of the α-chloroazo compound and the alkene tether. I will also include in the first chapter the second method the group has developed which directly enabled us to convert hydrazones with pendent alkenes to bicyclic diazenium salts.

In the second chapter, I will describe a study that I undertook to better understand the mechanism of the cycloaddition reaction. This was accomplished by studying what

effect the N'-aryl substituent has on the ratio of the ring fused and bridged diazenium salts. The results of this study were consistent with our proposed mechanism for the cycloaddition reaction.

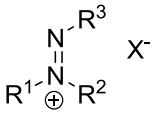
The third chapter will document a new and efficient method that I discovered for the synthesis of diazenium salts directly from hydrazones. This discovery was based on using a hypervalent iodine reagent as an oxidant.

In the last chapter, I will discuss a new and unprecedented reactivity of 1-aza-2 azoniaallene salts. The reactivity of the 1-aza-2-azoniaallene intermediate is dependent on the structure of the precursor and is determined by the structural constrains between the 1-aza-2-azoniaallene center and the pendent alkene. The most recent discovery was a chloroamination reaction that occurred to give tetrahydropyradizine. Our hypothesis is that this heterocyclic ring system is formed by ring opening of aziridinium ion intermediate. The scope of the tetrahydropyradizine formation was assessed in more detail by making a diverse library of heteroallenes. The reactivity of the heteroallenes was observed to give a variety of products based on their structure.

1.2. Diazenium Salts: Introduction

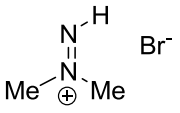
Diazenium salts, also referred to as pyrazolium salts, are compounds that have two adjacent nitrogen atoms with a double bond between them and with one of them having a positive charge and a coordination number of four.[1] Some of the examples are illustrated in figure **1.1**.

Figure 1.1. Examples of diazenium salts



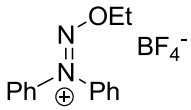
1

R^1 = H, alkyl, aryl
R^2 = H, alkyl, aryl
R^3 = H, alkyl, aryl, O-alkyl, OAc
X^- = halogen, ClO_4, BF_4, $SbCl_6$, etc.



2

1,1-dimethyldiazenium bromide

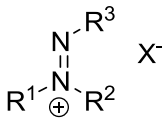


3

1,1-dibenzyl-2-ethoxydiazenium tetrafluoroborate

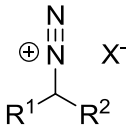
Diazenium salts (**4**, figure **1.2**) are close in their structures to diazonium salts (**5**) and immonium salts (**6**). These diazenium salts analogs have also similar reactivities and react in a similar way like diazenium salts.[1]

Figure 1.2. Diazenium salts analogs



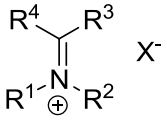
4

diazenium salts



5

diazonium salts



6

immonium salts

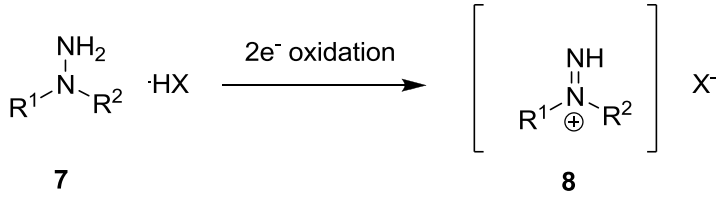
As shown above, 1,1-disubstituted diazenium salts are known and have been widely explored and studied. However, trisubstituted diazenium salts have not received much attention and have not been as widely investigated. An example, among only a few limited other examples, is the alkoxy diazenium salt (e.g. **4**, R^3 = O-alkyl, figure **1.1**). Unsubstituted and monosubstituted diazenium salts are unstable compounds and have not been widely studied for that reason.[1]

1.3. Methods for the preparation of diazenium Salts

1.3.1 Oxidation of Hydrazines

McBride discovered in 1957 a new compound that was the product of a two-electron oxidation process of 1,1-dialkyl hydrazine in an acid. This diazo-like compound (**8**, scheme **1.3**) had both similar chemical and spectroscopic properties to the already known diazo compounds and was given the name 1,1-diazenium salt. It was the conjugate acid of a 1,1-diazine or aminonitrene (scheme **1.1**).[2,3]

Scheme 1.1



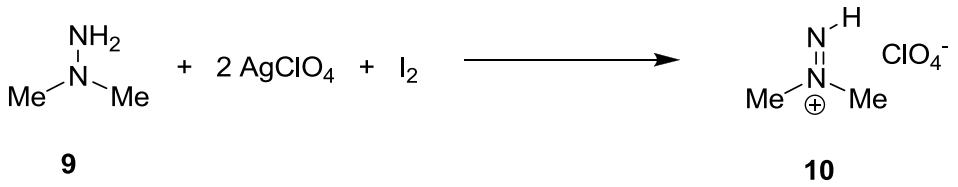
7 **8**

Oxidants: halogens, alkali metal halogenates (KIO_3, $KBrO_3$).. etc; HX= HCl..etc

Since this discovery, the oxidation of 1,1-disubstituted hydrazines in acidic medium became the most widely used route for the preparation of these diazenium salts.

McBride also reported the synthesis of 1,1-dimethyl diazenium perchlorate (**10**) from 1,1-dimethyl hydrazine (**9**) using iodine and silver perchlorate as an oxidant (scheme **1.2**).[3]

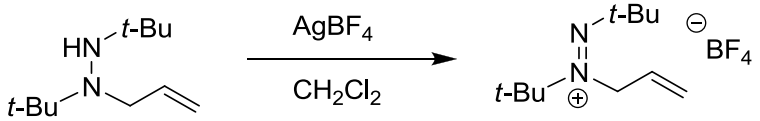
Scheme 1.2



9 **10**

In a similar manner, trisubstituted diazenium salts (e.g. **12**, scheme **1.3**) can be made by the oxidation of the trialkyl hydrazine precursor (e.g. **11**) in the presence of silver tetrafluoroborate.[4,5] The electrochemical methods mentioned earlier can also be used for the preparation of trisubstituted diazenium salts.[6]

Scheme 1.3



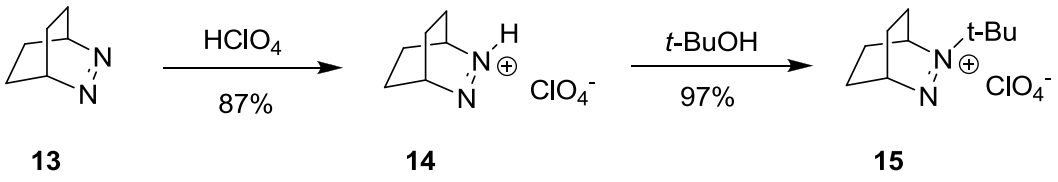
11 **12**

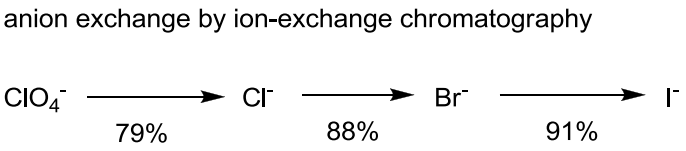
1.3.2. Alkylation of Azo Compounds

In 1975, Snyder reported an additional method for the preparation of trisubstituted diazenium salts,[7] the alkylation of bicyclic-azo compounds with strong electrophiles. One example is treating 2,3-diazobicyclo[2.2.2]oct-2-ene (**13**, scheme **1.4**) with perchloric acid which provided the stable cation (**14**), which upon treatment with refluxing *tert*-

butanol was smoothly converted into trisubstituted diazenium salt **15** (Scheme **1.6**). In this method, it is possible to obtain the trisubstituted diazenium salt product with an alternative counter anion through ion-exchange chromatography.

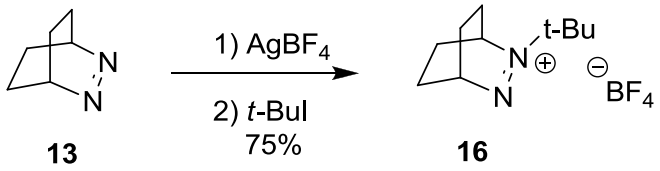
Scheme 1.4





Trisubstituted diazenium salts can also be prepared directly from the azo-compound by treatment with strong alkylating agents. An example of this effective method is the preparation of 3-*tert*-butyl-2,3-diazanorborn-2-ene tetraflouroborate (**16**) by the treatment of 2,3-diazanorborn-2-ene (**13**) with silver flourborate and *tert*-butyl iodide (scheme **1.5**).[5,8]

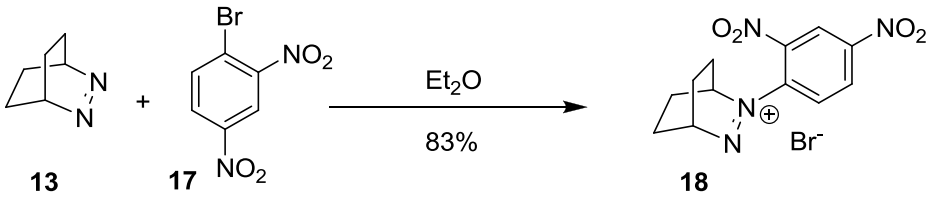
Scheme 1.5



Another related method is the alkylation of aryl groups. For example, treatment of 2,3-diazobicyclo[2.2.2]oct-2-ene (**13**) with 2,4-dinitrobromobenzene (**17**) under milder

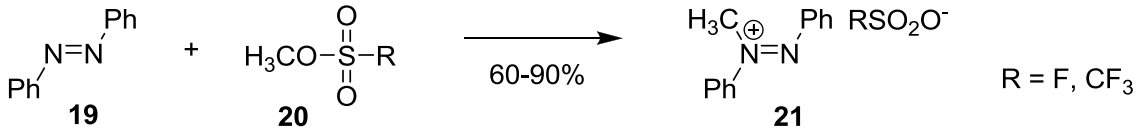
reaction conditions in ether provided the corresponding aryl diazenium slat derivative **18** in very good yield (scheme **1.6**).[7]

Scheme 1.6



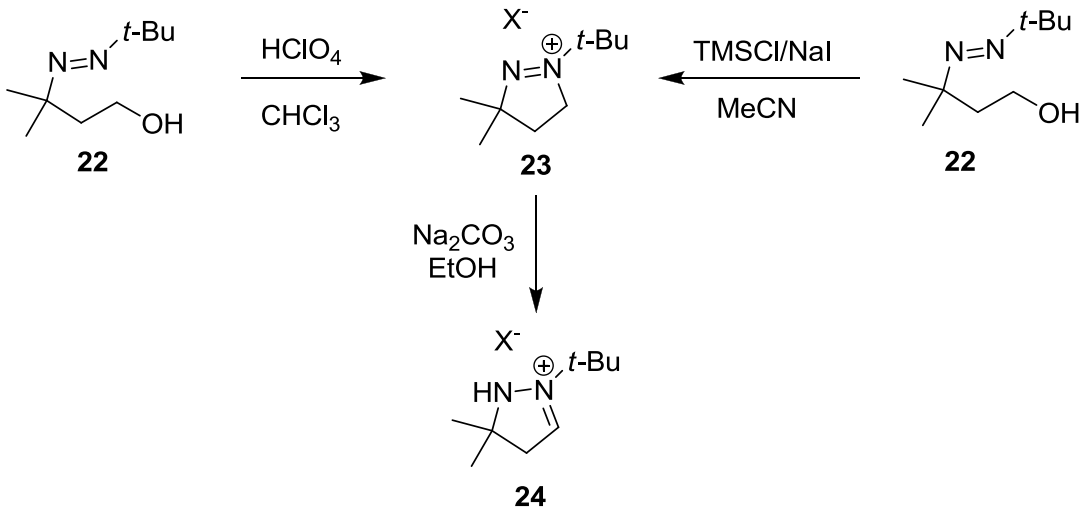
An additional example is the alkylation of aromatic azo compounds, such as **19** (scheme **1.7**), with triflouromethansulfonate (**20**, R = CF_3) or methylflourosulfonate (**20**, R = F) which provided trisubstituted diazenium salt (**21**).[9]

Scheme 1.7



Intramolecular cyclization and formation of diazenium salts has also been reported but only few examples exist. One example of intramolecular diazenium salt formation is the synthesis of 1-pyrazolium salt **23** (scheme **1.8**). This was achieved by treating azoalcohol **22** with perchloric acid. The same 1-pyrazolium salt **23** was also obtained by treating the same azoalcohol **22** with trimethylsilyl chloride/ sodium iodide in acetonitrile. When the resultant 1-pyrazolium salt was treated with a weak base, the tautomerized diazenium salt (**24**) was obtained.[10]

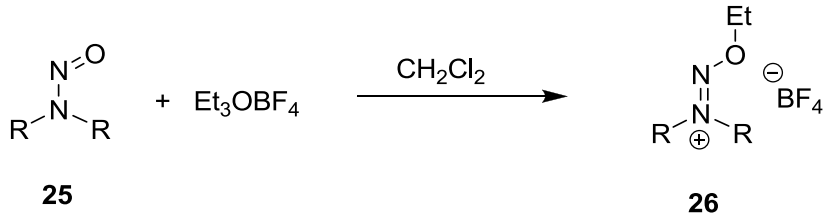
Scheme 1.8



1.3.3 Alkylation of *N*-Nitrosamines

The Alkylation of *N*-nitrosamines (**25**, scheme **1.9**) is another method that has been used for the preparation of diazenium salts. It actually produces quantitative amounts of alkoxydiazenium salts (**26**).[11] *N*-nitrosamines can be alkylated using trialkyloxonium tetraflouroborates. In this method, both purely aliphatic and alkyl aryl substituted *N*-nitrosamines can be used.

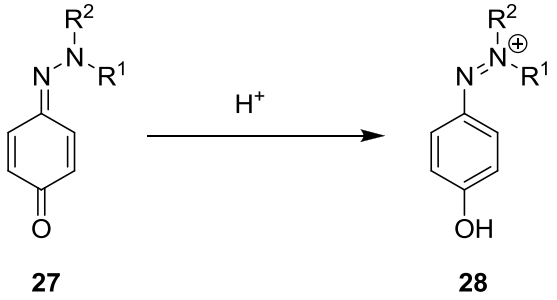
Scheme 1.9



1.3.4 Diazenium Salts From Other Methods

Other less reliable methods have been reported for the formation of diazenium salts. These methods are not general and are limited to certain type of substrates and reaction conditions. An example of these chemical transformations that lead to diazenium salts is the synthesis of trisubstituted diazenium salt **28** (scheme **1.10**) which is formed upon dissolving 4-(2,2-dialkylhydrazono)benzoquinone (**27**) in a 50%:50% solution of 2,2,2-trifluoroacetic acid and 2,2,3,3,4,4,4-heptafluorobutanoic acid.[12]

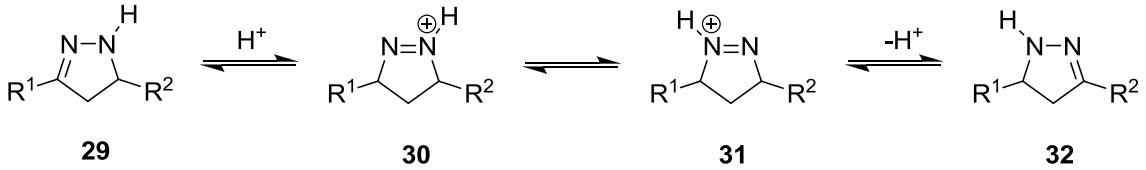
Scheme 1.10



27 **28**

Diazenium salts are also believed to be involved as intermediates in the acid-mediated inter conversion of 2-pyrazolidines (**30**) as shown in scheme **1.11**.[13]

Scheme 1.11



29 **30** **31** **32**

1.3.5 Limitation of the previous methods

The previous methods mentioned above have several limitations, which leaves room to explore new and more efficient methods. One of these limitations is the fact that the substrate scope is quite small; only precursors that have a high degree of symmetry in their structure can be used or a regioisomeric mixture of diazenium salts will form. Another limitation is that most of these methods work with the requirement of harsh reaction conditions including the use of strong acids or strong alkylating reagents. The last important limitation is directly related: few methods are known for the synthesis of trisubstituted diazenium salts. With these limitations in mind, we decided to explore a new, general, and efficient method to form trisubstituted diazenium salts.

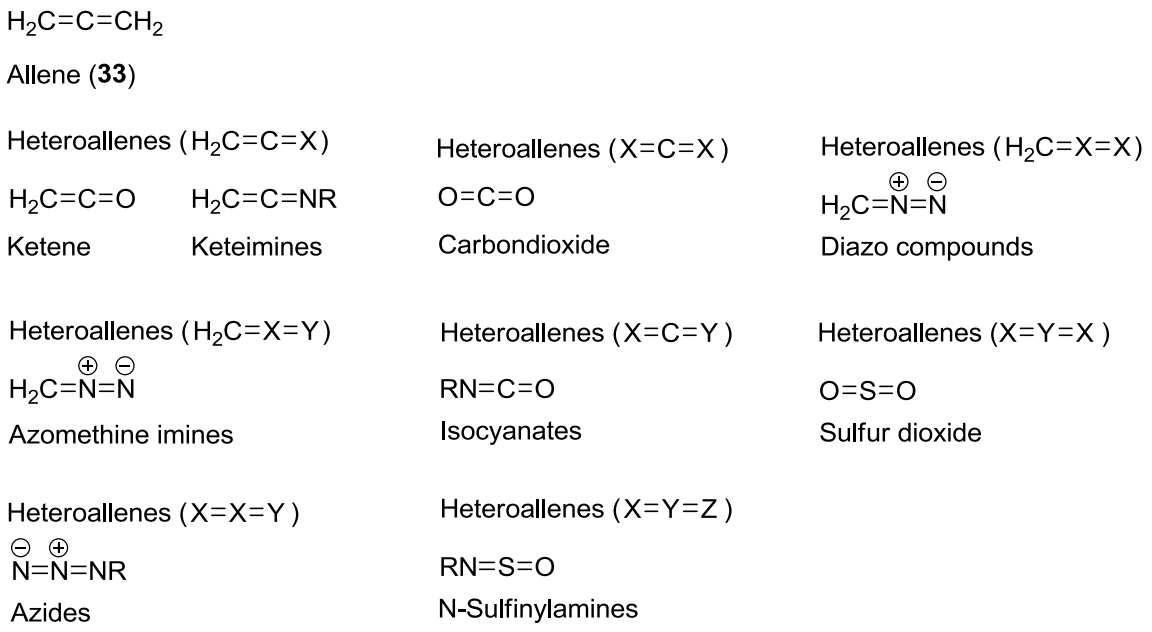
The next few sections provide the background of how our group was able to develop new more general and more efficient methods for the preparation of diazenium salts.

1.4 Heterocumulenes and Heteroallenes

Cumulenes are hydrocarbons with cumulative or consecutive doublebonds. Allenes are hydrocarbons having two double bonds from one carbon atom to two others ($R_2C=C=CR_2$). Heterocumulenes are derivatives of cumulenes where one or more of the carbon atoms of the molecule is substituted by a heteroatom such as oxygen, nitrogen or sulfur. In the same way, heteroallenes are the derivatives of allenes where one or more of the carbon atoms is being substituted by a heroatom.[14] Allene **33** is an example of an all-carbon allene. Examples of heteroallenes are shown in figure **1.3** which include ketenes,

keteimines, carbon dioxide, diazo compounds, nitrones, nitrile imines, azomethine imines, and isocyanates.

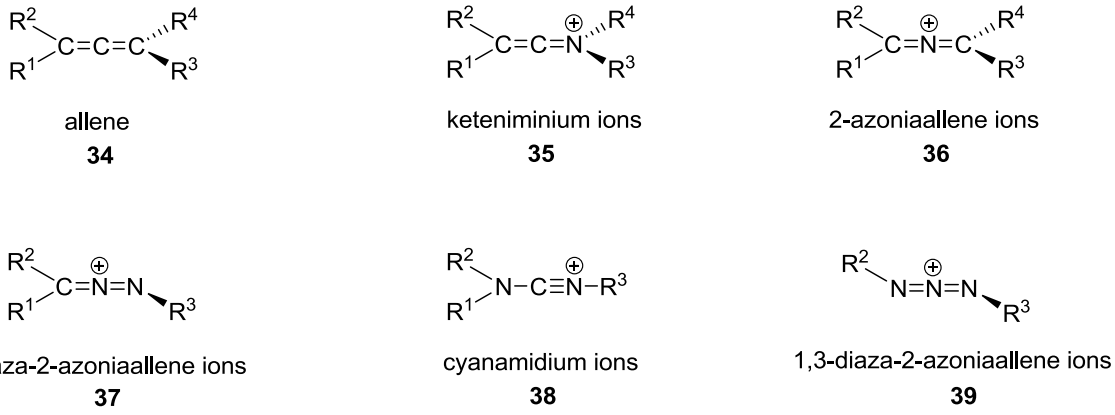
Figure 1.3. Examples of heteroallenes



1.4.1. A New Type of Heteroallene: 1-Aza-2-azoniaallene

In addition to the neutral heteroallenes mentioned in the previous section, charged heteroallenes are also known in the literature. Cationic heteroallenes, which are the ones related to our work, will be discussed and more specifically N-containing heteroallenes will be discussed in more details. Looking at allene structure **34**, by substituting one or more carbon atoms with nitrogen atom(s), five classes of cataionic heteroallenes are generated as shown in figure **1.4**.

Figure 1.4. Classes of cataionic heteroallenes



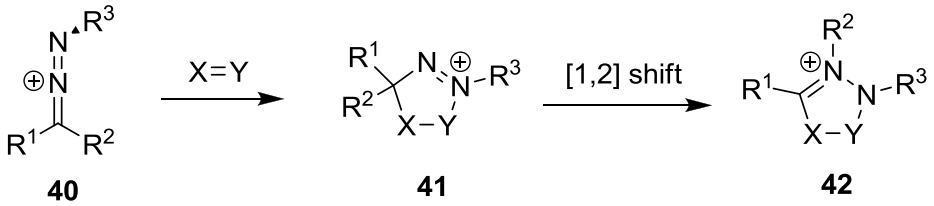
In addition to the fact that all of these monocations are known in the literature and have been prepared, they also undergo different chemical reactions. For example, keteniminium salts **35**, 2-azoniaallene salts **36**, and 1,3-diaza-2-azoniaallene salts **39** each undergo [3+2]-cycloaddition reactions with alkenes, alkynes, and other allenes and heteroallenes. Other reactions has also been reported involving aminonitrilium ions such as cyanamidium cations **38**.[15]

1.4.2. Synthesis of 1-Aza-2-Azoniaallene Salts

A more recent advance in the preparation of heteroallenes was reported by Jochims and coworkers that involved the preparation of 1-aza-2-azoniaallene salts **40** (scheme **1.12**).[16-18] These heteroallene salts are unstable compounds; they are only stable in solution at low temperatures. All attempts so far to isolate these salts have failed.[17,19] It was also found that 1-aza-2-azoniaallene salts were very reactive intermediates and undergo a [3+2] cycloaddition reactions with alkenes, alkynes, nitriles, isocyanates,

carbodiimides, and other multiple bond systems to provide 3*H*-pyrazolium salts **41**. After being formed, the 3*H*-pyrazolium salt undergoes a spontaneous [1,2] shift in most cases to provide the more stable 1*H*-pyrazolium salt **42**. The cycloadducts resulting from the [3+2] cycloaddition reactions of alkenes with 2-azoniaallenes however did not undergo that spontaneous rearrangement.

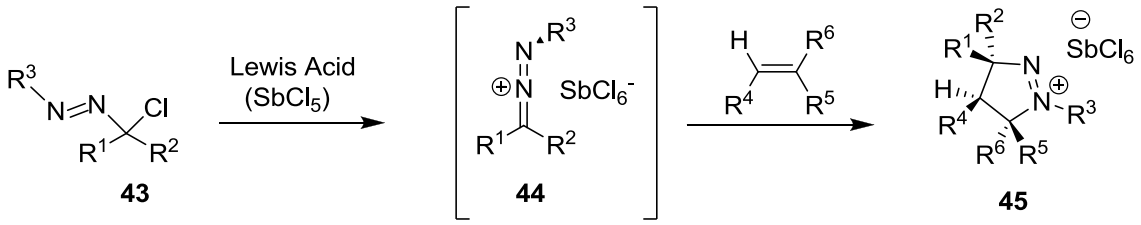
Scheme 1.12



X=Y = alkenes, alkynes, nitriles, carbodiimides, isocyanates, isothiocyanates

An example that illustrates this reactivity is the recent synthesis of diazenium salts by Jochims (scheme **1.13**).[16,17,20,21] This example is based on the ability of 1-aza-2-azoniaallene salts to undergo [3+2] cycloaddition reactions with alkenes. This discovery was considered as a new method for the synthesis of five-membered ring heterocycles. In addition, it was also a new way of making a 1-aza-2-azoniaallene (**44**) from the corresponding α-chloroazo precursor (**43**). This was achieved by treating the α-chloroazo with a halophilic Lewis acid, such as $SbCl_5$ or $AlCl_3$, to obtain the desired heteroallene salt. Once formed, the heteroallene salt can then react with an alkene to provide the trisubstituted diazenium salt **45**.

Scheme 1.13



In addition to their importance as precursors in the formation of diazenium salts, aryl α-chloroazo compounds are useful synthetic precursors to azoalkenes,[22] tetrahydropyridazines,[22] 1,2,4-triazolium salts,[23,24] *N*-(azoalkyl)iminium salts,[25] 1,2,4,5-tetrazinium salts,[25] *1H*-pyrazolium salts,[26] and pyrazoles.[26] Aryl-a-chloroazoalkanes were also found to be useful as foaming agents in polymer synthesis and are also known to react with a variety of nucleophiles such as OR^-, N_3^-, RCO_2^-, and CN^- by the displacement of the halogen to provide substituted azo products.[27,28]

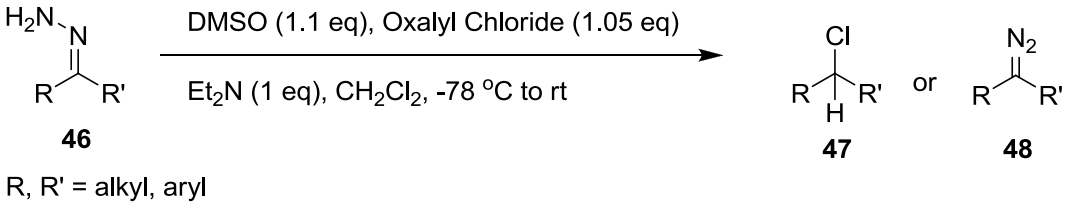
The methods exist for the preparation of α-chloroazo compounds are very limited. Moon *et. al.* have developed procedures in which hydrazones are treated with either chlorine gas or tert-butyl hypochlorite.[29,30] However, these methods are not ideal and use chlorinating reagents that are highly reactive and can be incompatible with a variety of functional groups. Only structurally simple hydrazones can react successfully under these conditions. For example, when aryl hydrazones that do not bear an electron-withdrawing groups on the aromatic ring are used as substrates, the aromatic ring is chlorinated prior to the carbon–nitrogen double bond, which results in complex product mixtures.[27,30] Another important fact related to the synthesis is that there has been no examples

reported of phenylhydrazones undergoing clean conversion to phenyl-α-chloroazo-alkanes.

1.4.3. Brewer Group Preparation of Phenyl and Aryl-α-chloroazoalkanes

The Brewer group has recently observed that N-unsubstituted hydrazones (e.g. **46**, scheme **1.14**) react cleanly with chlorodimethylsulfonium chloride to provide alkyl chlorides (**47**) or diazo compounds (**48**), depending on the conditions used, in high yields.[31,32]

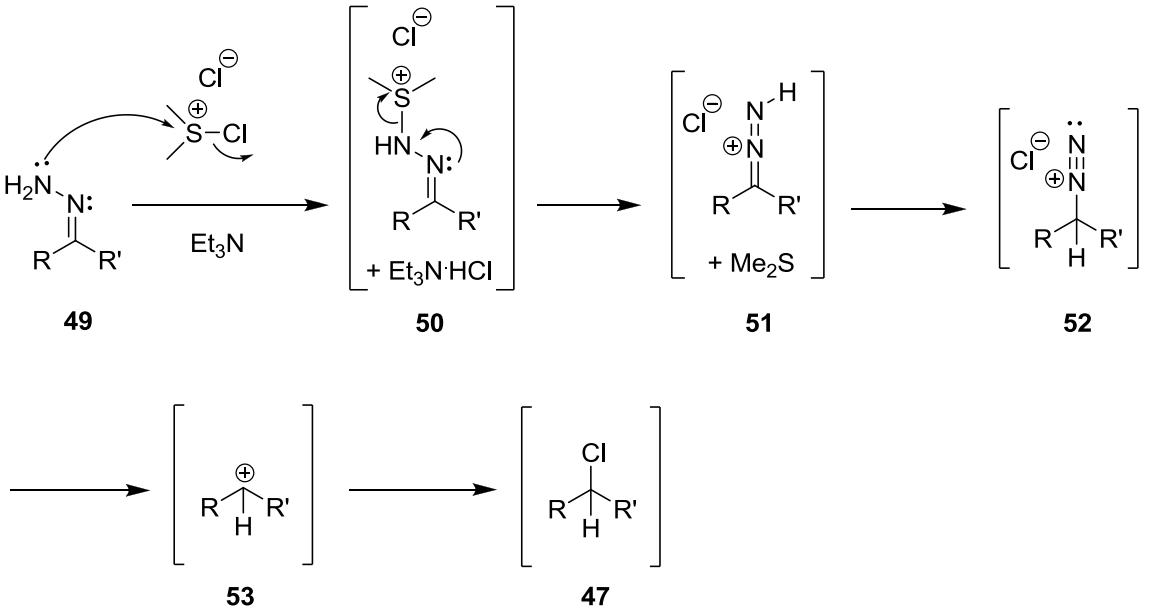
Scheme 1.14



A hypothized mechanism for the formation of the product is presented in Scheme **1.15**. Hydrazone **49** reacts with the dimethylchlorosulphonium ion, which is generated by the reaction of oxalyl chloride with DMSO, to provide azosulphonium ion **50** upon deprotonation with Et_3N. A lone pair donation by the α-nitrogen results in the elimination of dimethyl sulfide to provide N-protonated diazonium ion **51**. Migration of a proton from nitrogen to carbon provides diazonium ion **52**, which then provides alkyl chloride **47** either directly via S_N2 substitution of nitrogen by chloride, or through an S_N1 mechanism in which loss of nitrogen provides carbenium ion **53** as an intermediate.

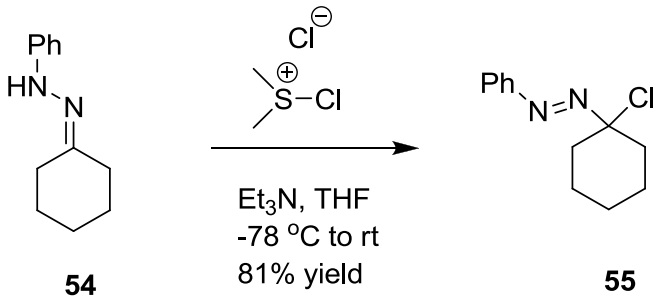
Based on that discovery, the group became interested in studying the reactivity of hydrazones bearing a substituent on the terminal nitrogen with sulfonium salts. The result was that phenylhydrazones derived from ketones were smoothly converted into the corresponding phenyl-α-chloroazoalkane in good to excellent yields upon treatment with

Scheme 1.15



chlorodimethylsulfonium chloride.[33] Using this method, phenylhydrazones that were derived from simple aliphatic ketones provided good yields of the phenyl-α-chloroazoalkane products without chlorination of the phenyl ring, which was not possible by previous synthetic methods. For example, cyclohexanone phenyl hydrazone (**54**) reacted with chlorodimethylsulfonium chloride in the presence of triethylamine at low temperature to provide phenyl-α-chloroazo compound **55** in 81% yield (scheme **1.16**).

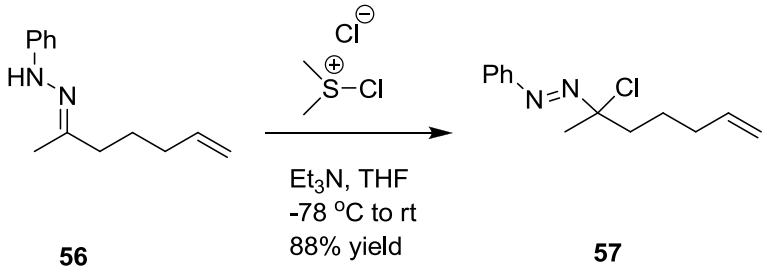
Scheme 1.16



54 **55**

A result of particular importance in relation to the synthesis of diazenium salts, the group found that hydrazones that contain pendent alkenes, such as **56** (scheme **1.17**), can also be smoothly converted into phenyl-α-chloroazoalkene compound (**57**) with no modification of the olefin.[33] Our group was successfuly able to prepare a wide range of a-chloroazo compounds with different steric and electronic properties in excellent yileds (table **1.1**). This work was in preparation for the following related study which will be discussed below.

Scheme 1.17

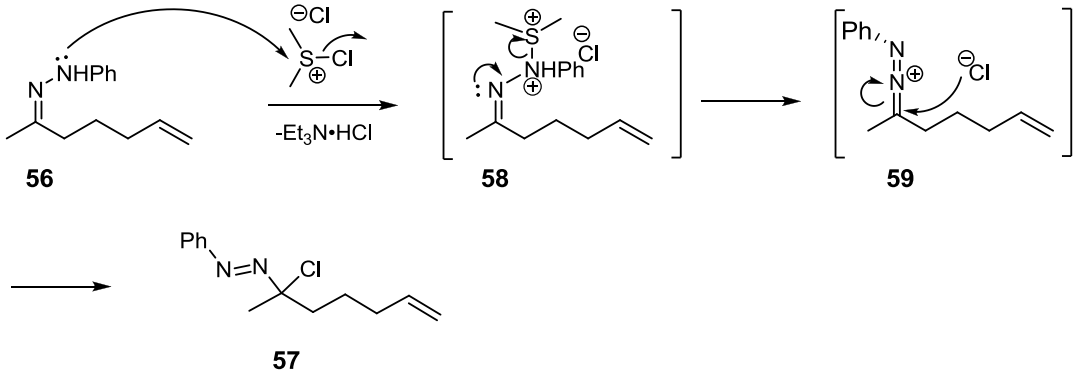


56 **57**

The proposed mechanism (scheme **1.18**) for the formation of the product is very similar to that proposed in scheme **1.17**. Hydrazone **56** reacts with the dimethylchlorosulphonium chloride to provide diazosulphonium ion **58** upon

deprotonation with Et_3N. A lone pair donation by the α-nitrogen results in the elimination of dimethyl sulfide to provide the 1-aza-2-azoniaallene salt **59**. Then a chloride attack on the carbon center of the 1-aza-2-azoniaallene intermediate provides the final α-chloroazo product **57**.

Scheme 1.18



1.4.4. Brewer Group Preparation of Bicyclic Diazenium Salts

The formation of the α-chloroazo compounds was not the only goal of this work. In fact, because of the functional group combination present, the α-chloroazo and pendent alkene tether, the group was interested in examining the reactivity of these compounds in intramolecular [3+2] cycoaddition reactions. It was proposed by the group that since 1-aza-2-azoniallene salts react with alkenes to provide diazenium salts, then a more efficient intramolecular cycloaddition with the teathered alkene should afford the bicyclic diazenium salt. In fact, our group found that treating α-chloroazo **57** (scheme **1.19**) with antimony pentachloride resulted in an intramolecular cycloaddition forming a

mixture of 5,5-fused diazenium salt **60** and 6,5-bridged diazenium salt **61** both in which a new carbocyclic and a new heterocyclic ring were formed.

Scheme 1.19

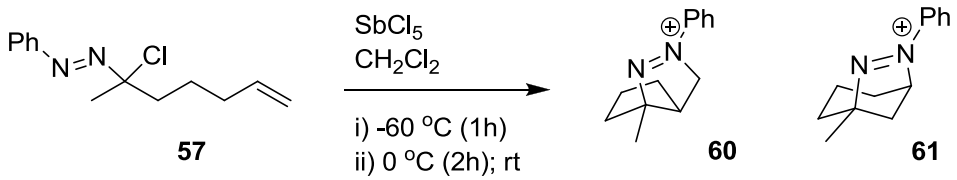
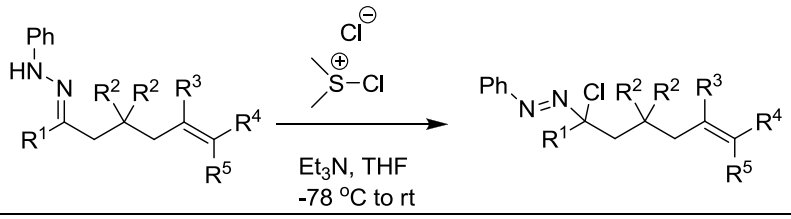
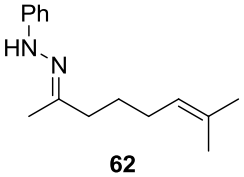
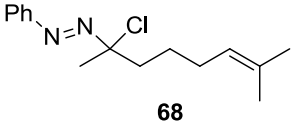
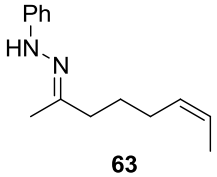
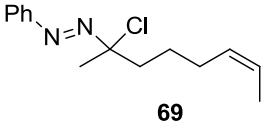
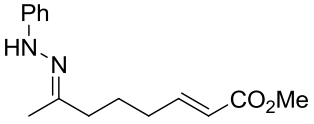
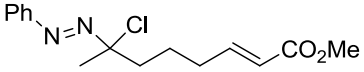
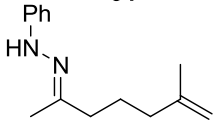
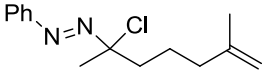
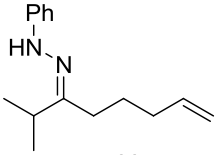
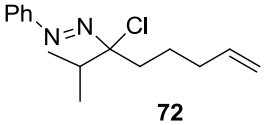
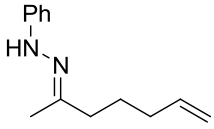
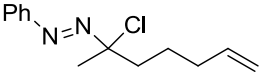
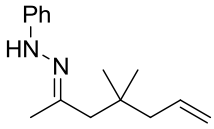
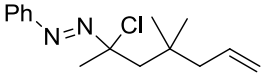


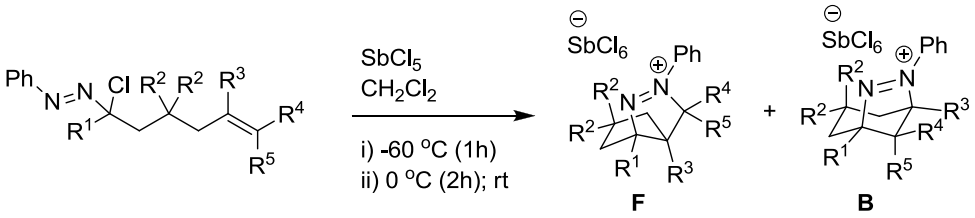
Table 1.1. Yields of phenyl substituted α-chloroazo compounds with pendent alkenes

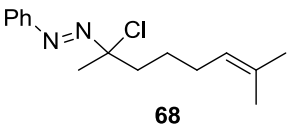
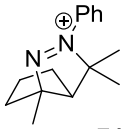
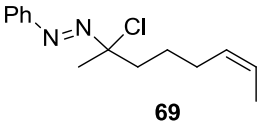
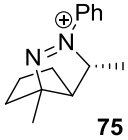
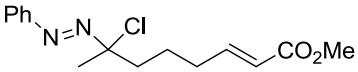
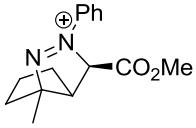
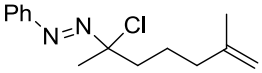
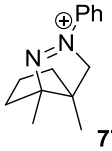
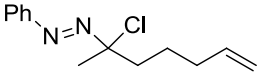
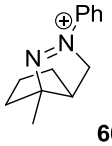
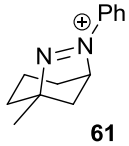
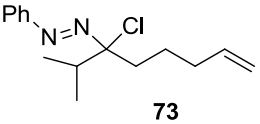
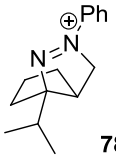
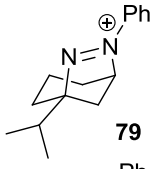
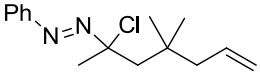
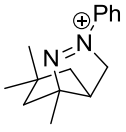
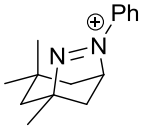


Entry	hydrazone	α-chloroazo product	yield
1	 **62**	 **68**	94%
2	 **63**	 **69**	89%
3	 **64**	 **70**	75%
4	 **65**	 **71**	87%
5	 **66**	 **72**	83%
6	 **56**	 **57**	88%
7	 **67**	 **73**	80%

To study the scope of this intramolecular cycloaddition reaction, our group reacted α-chloroazo compounds with different steric and electronic properties with antimony pentachloride and the results obtained are shown in table **1.2**. For example, α-chloroazo compound **68** provided fused bicyclic diazenium salt **74** as a single diastereomer in 71% isolated yield (entry 1, table **1.2**). Also, *cis*-disubstituted alkene **69** (entry 2, table **1.2**) produced diazenium salt **75** as a single diastereomer in 88% yield. Interestingly, electron-deficient alkene **70** also reacted to provide diazenium salt **76** in 83% yield (entry 3, table **1.2**). This was an important finding since electron-deficient alkenes did not participate in intermolecular cycloadditions of this type and thus our methodology broadens the substrate range of this transformation. When disubstituted terminal alkene **71** was treated with $SbCl_5$ (entry 4, table **1.2**), a complex mixture of products was observed by ^{1}H-NMR which did not contain the expected diazenium salts. This was most probably due to steric hindrance that would exist in the transition state from two adjacent quaternary centers and in turns inhibited cyclization. Other compounds that contained terminal pendent alkene units provided a mixture of diazenium salts. For example, treating isopropyl derivative **73** with the Lewis acid provided a 1:0.05 ratio of fused (**78**) to bridged (**79**) products (entry 6, table **1.2**). Similarly, α-chloroazo compound **73** with a gem-dimethyl group within the chain provided the fused (**80**) and bridged (**81**) products in a 1:0.09 ratio.

Table 1.2. Phenyl substituted bicyclic diazenium slat formation



Entry	a-chloroazo precursor	Product	Yield (Ratio **F:B**)
1	 **68**	 **74**	71%
2	 **69**	 **75**	88%
3	 **70**	 **76**	83%
4	 **71**	 **77**	0%
5	 **57**	 **60**  **61**	87% 1 : 0.2
6	 **73**	 **78**  **79**	88% 1 : 0.05
7	 **73**	 **80**  **81**	75% 1 : 0.09

References:

(1) Kuznetsov, M. A. *Russ. Chem. Rev.* **1979**, *48*, 563.

(2) Taber, D. F.; Guo, P. *J. Org Chem.* **2008**, *73*, 9479.

(3) McBride, W. R.; Kruse, H. W. *J. Am. Chem. Soc.* **1957**, *79*, 572.

(4) Cauquis, g.; Chabaud, B.; Genies, M. *Tetraherdron Lett.* **1974**, 2389.

(5) Nelson, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 1788.

(6) Cauquis, g.; Genies, M. *Compt Rend.* **1974**, *C279*, 2389.

(7) Heyman, M. L., Snyder, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 4416.

(8) Nelsen, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1973**, *95*, 2719.

(9) Feguson, A. N. *Tetrahedron Lett.* **1973**, *30*, 2999.

(10) Sanders, C., G.; Sharp, T., R; Allres, E., L. *tetrahedron Lett*. **1986**, *27*, 3231.

(11) Buttner, G.; Hunig, S., *Chem. Ber.* **1971**, *104*, 1088.

(12) Mannschreck, A.; Kolb, B. *Chem. Ber.* **1972**, *105*, 696.

(13) Elguero, J.; Jacquier, R.; Marzin, C. *Tetrahedron Lett.* **1970**, 3099.

(14) Ulrich, H. In *Cycloaddition Reactions of Heterocumulenes*; Blomquist, A. T.; Academic Press: New York, **1976**, Vol. 9, p 1.

(15) Wirschun, W. G. *J. Prakt. Chem.* **1998**, *340*, 300.

(16) Wirschun, W. G.; Al-Soud, Y. A.; Nusser, K. A.; Orama, O.; Maier, G. M.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4356.

(17) Wang, Q. R.; Amer, A.; Mohr, S.; Ertel, E.; Jochims, J. C. *Tetrahedron* **1993**, *49*, 9973.

(18) Wang, Q. R.; Jochims, J., C.; Kohldbrandt, S.; Dahlenburg, L.; Altalib, M.; Hamed, A.; Ismail, A. E. H. *Synth.* **1992**, 710.

(19) Wang, Q. R.; Amer, A.; Troll, C.; Fischer, H.; Jochims, J. C. *Chem. Ber.* **1993**, *126*, 2519.

(20) Guo, Y. P.; Wang, Q., R.; Jochims, J. C. *Synth*. **1996**, 274.

(21) Al-Soud, Y. A.; Wirschun, W.; Hassan, N. A.; Maier, G., M.; Jochims, J. C. *Synth.* **1998**, 721.

(22) Gaonkar, S. L.; Rai, K. M. L. *Tetrahedron Lett*. **2005**, *46*, 5969–5970.

(23) Wang, Q. R.; Jochims, J. C.; Kohlbrandt, S.; Dahlenburg, L.; Altalib, M.; Hamed, A.; Ismail, A. E. H. *Synthesis* **1992**, 710–718.

(24) Wang, Q. R.; Liu, X. J.; Li, F.; Ding, Z. B.; Tao, F. G. *Synth. Commun*. **2002**, *32*, 1327–1335.

(25) Al-Soud, Y. A.; Shrestha-Dawadi, P. B.; Winkler, M.; Wirschun, W.; Jochims, J. C. J. Chem. Soc., *Perkin Trans.* **1998**, *1*, 3759–3766.

(26) Wang, Q. R.; Amer, A.; Mohr, S.; Ertel, E.; Jochims, J. C. *Tetrahedron* **1993**, *49*, 9973–9986.

(27) MacLeay, R. E.; Sheppard, C. S. Tertiary-aliphatic amidazo compounds; U.S. Patent 4001207, January 4, 1977.

(28) Kamens, E. R.; Kressing, D. M.; Lange, H. C.; MacLeay, R. R. Polymeric cellular structures; U.S. patent 4029615, June 14, 1977.

(29) Moon, M. W. *J. Org. Chem*. **1972**, *37*, 383–385.

(30) Moon, M. W. *J. Org. Chem*. **1972**, 37, 386–390.

(31) Brewer, M *Tetrahedron Lett.* **2006**, *47*, 7731–7733.

(32) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789–1792.

(33) Wyman, J.; Jochum, S.; Brewer, M. *Synth. Commun.* **2008**, *38*, 3623.

(34) Wyman, J.; Javed, M.; Al-Bataineh, N.; Brewer, M., *J. Org. Chem.* **2010**, 75, 8078.

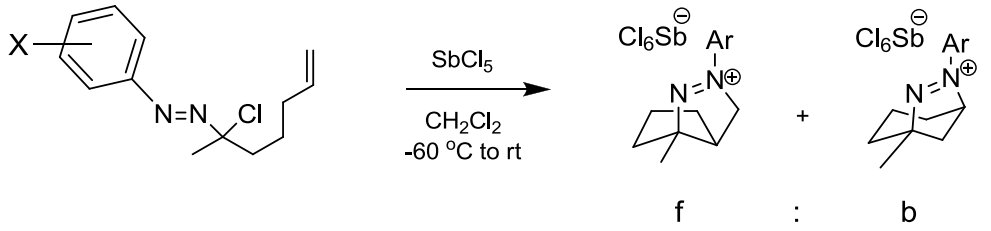
2. CHAPTER 2:

Effect of the N'-Aryl Substituent on the Cycloaddition Reaction and Formation of Diazenium Salts

The data presented in chapter one (table 1.2) clearly shows that the outcome of the cycloaddition reaction leading to diazenium salt formation is determined by the structure of the α-chloroazo precursor. The structure of the α-chloroazo not only determines the yield, but also the ratio of the fused and bridged bicyclic diazenium salt systems. The effect seems to be primarily based on electronic considerations in which the substituents on the α-chloroazo directed the formation of only the ring fused diazenium slat in some examples (entries 1-3, tabel 1.2), a mixture of the ring fused and bridged diazenium salts with different ratios (entries 5-7, table 1.2), or forming none of the desired products (entry 4, table 1.2).

With those preliminary results in hand, we became interested in studying the effect of the electronics of the aryl ring on the outcome of the cycloaddition reaction. We thought this study might help us to better understand the cycloaddition reaction mechanism and allow us to predict the outcome of these reactions. With this in mind we designed a set of experiment in which the structure of the pendent alkene of the α-chloroazo compound was held constant, and the N'-aryl substituent was varied (scheme 2.1). We chose hept-6-en-2-one as the alkene portion of the α-chloroazo (entry 5, table 1.2). I will show its synthesis in the next section, and then describe its use in the preparation of a range of hydrazones.

Scheme 2.1

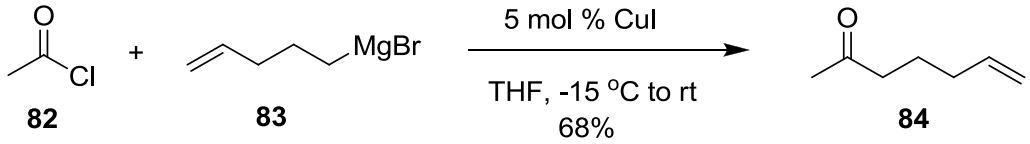


2.1. Synthesis of Ketone Starting Material

Synthesis of Hept-6-en-2-one via Addition to Acetyl Chloride

The first method used to prepare hept-6-en2-one (**84**, scheme 2.2) was the copper cata;yzed addition of pent-4-en-1-ylmagnesium bromide (**83**) to acetyl chloride (**82**) following Gribkov's method.[1] this method provided hept-6-en-2-one in 68% yield after purification by distillation. Since a relatively larger amount of this ketone was required for this study, a less expensive procedure was used for its synthesis which will be presented in the following section.

Scheme 2.2

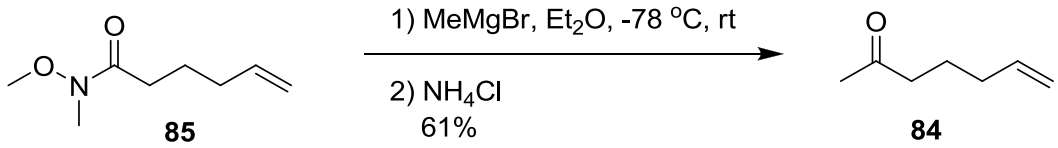


Synthesis of Hept-6-ene-2-one via Addition to Weinreb Amide

An alternative approach to hept-6-ene-2-one involved the addition of methylmagnesium bromide to Weinreb amide **85** (scheme 2.3). This was a less costly

method to prepare the desired ketone because it did not require the use of 5-bromopent-1-ene. The Weinreb amide **85** was made and provided by Matthias Brewer.

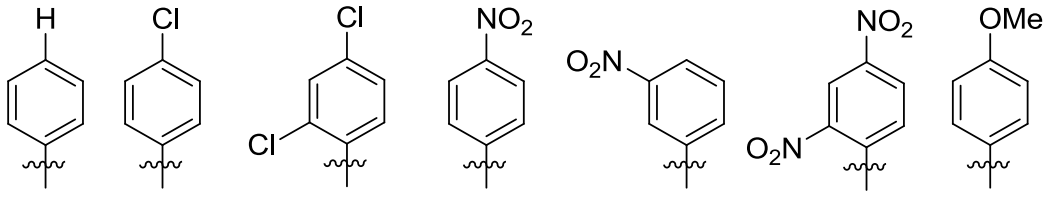
Scheme 2.3



2.2 Synthesis of Hydrazones

To determine how the electronics of the N'-aryl substituent affect the cylcoaddition reaction, we prepared a range of hydrazones from hept-6-en2-one and subjected them to the α-chloroazo formation reaction conditions. As shown in figure 2.1, these included both electron withdrawing substituents, such as -NO_2 and -Cl, as well as electron donating substituents, such as -CH_3 and -OCH_3. Two alternative procedures were used to prepare the hydrazones, and these methods will be described in the following sections.

Figure 2.1. N'-Aryl substituents

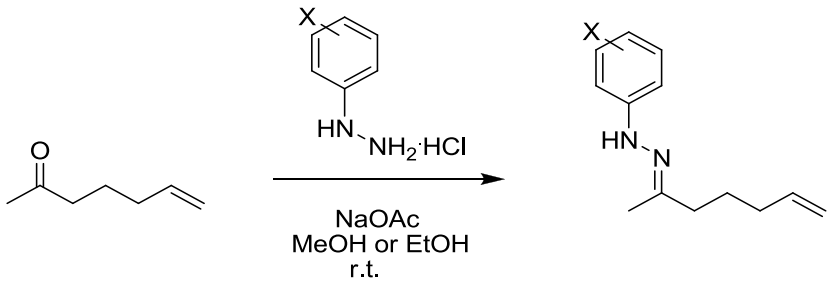


Method A: Used when starting with the hydrochloride salt of the hydrazine

In this method (scheme 2.4), the solvent used was either dry methanol or dry ethanol. The solvent was degassed by sparging with nitrogen gas for about 30 minutes in the presence of molecular sieves to remove any dissolved oxygen. The hydrazine hydrochloride salt and sodium acetate were then added under a nitrogen atmosphere. The mixture was stirred at room temperature for 15 minutes at which point the ketone was added, and the reaction was then stirred at room temperature for about two hours. The solvent was evaporated *in vacuo* at room temperature and the resultant oil was quickly dissolved in dry pentane and filtered through a short plug of basic alumina. the pentane was removed *in vacuo* and the remaining oil was carried on to next step without any further purification.

When the aryl ring contained either a strong electron withdrawing group, such as -NO_2, or when there was a substituent present at the *ortho* position the condensation took place overnight at the refluxing temperature of the solvent used.

Scheme 2.4



Method B: used for free hydrazines

The hydrazine was added to dry oxygen-free dichloromethane containing molecular sieves under a nitrogen atmosphere, and the ketone was then added at room temperature. The reaction was stirred at room temperature for two hours and was then filtered through a short plug of basic alumina and the solvent was evaporated *in vacuo*. The resultant oil was used in the next step without any further purification. When a strong electron withdrawing group was present on the aryl ring, or if a substituent was present at the *ortho* position of the hydrazine, the reaction was heated to reflux overnight.

Both methods above provided pure hydrazones in very good to excellent yields (table 2.1) as mixtures of *E/Z* diastereomers which were not separated.[2] The isolated aryl hydrazones were very sensitive to oxygen in the air and, if not carefully handled, underwent an autoxidation reaction (scheme 2.5). Autoxidation of hydrazones is a generally occurring reaction, leading to the formation of α-azohydroperoxides (**89**, scheme 2.5). All types of hydrazones, having at least one hydrogen atom on nitrogen, are prone to autoxidation. What makes it even more challenging is the fact that hydrazones of aliphatic ketones are about 1-2 orders of magnitude more reactive than analogous derivatives of aromatic ketones. [3]

Scheme 2.5

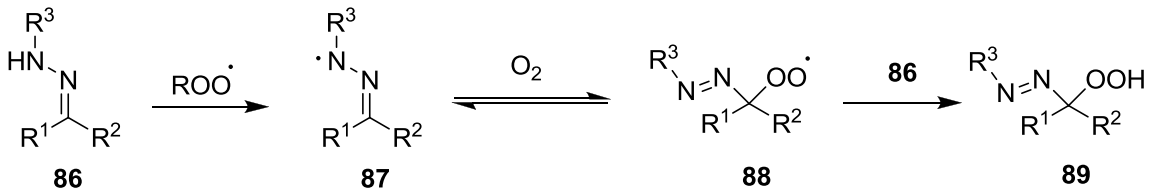
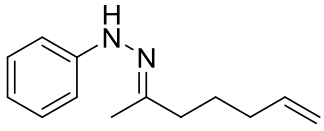
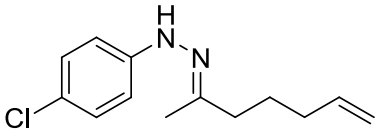
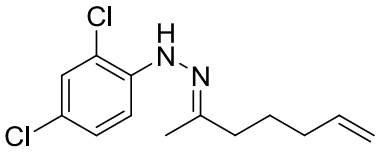
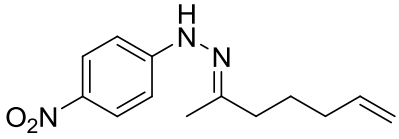
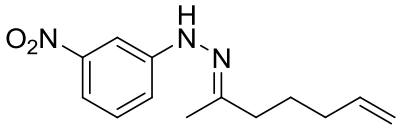
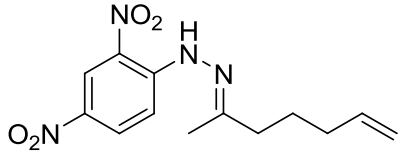
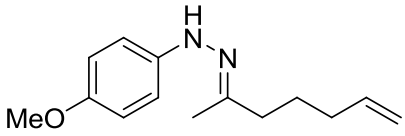


Table 2.1: Isolated Yields of N'-Aryl Substituted Hydrazones

Entry	hydrazone	Yield	Method	*E/Z* ratio
1	 **90**	94	A, r.t	1 : 0.2
2	 **91**	91	A, r.t B, r.t	1 : 0.2
3	 **92**	72	B, reflux	1 : 0.1
4	 **93**	78	B, reflux	1 : 0.2
5	 **94**	90	B, r.t	1 : 0.1
6	 **95**	70	B, reflux	1 : 0.1
7	 **96**	92	B, r.t	1 : 0.2

The step of filtering the reaction mixture through a short plug of basic alumina mentioned in the methods above was done to remove oxidation byproducts formed during the reaction, which was particularly problematic in cases where the condensation reaction took a longer time to go to completion. Also, during and after the isolation of these hydrazones, special care was required when handling these sensitive hydrazones, which were always made fresh and used shortly after being isolated.

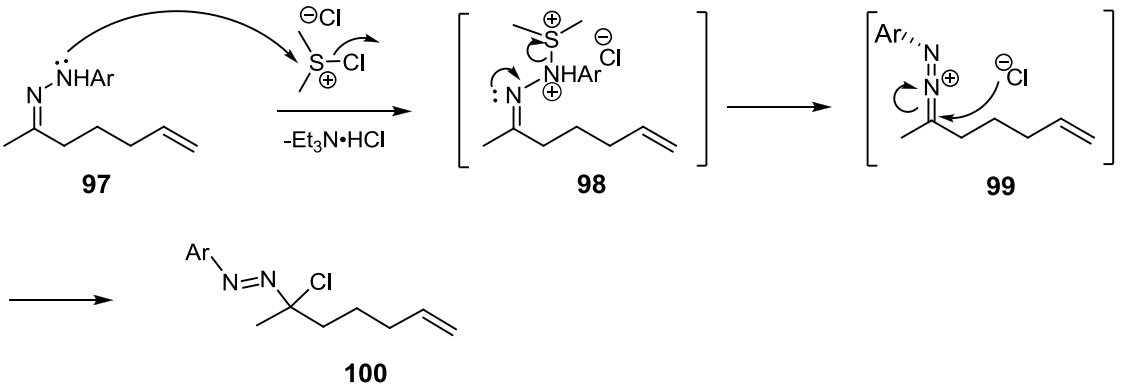
Another fact worth mentioning is that it was not possible to monitor the reaction progress via thin layer chromatography since the hydrazone product is unstable and decomposes upon exposure to silica jell in open air. The only way to find the optimum reaction conditions was through trial and error.

2.3. Synthesis of N'-Aryl Substituted α-Chloroazo Compounds

After optimizing the conditions for the hydrazone formation, the next step was to prepare the cycloaddition reaction precursors: the α-chloroazo compounds. To achieve this, the hydrazones were reacted with chlordimethylsulfonium chloride according to the procedure developed by the group. However, a few modifications were made since the N'-aryl substituents affected the electronic properties of the hydrazones, which had an effect on the reaction progress. The first step of the reaction involves the lone pair donation of the α-nitrogen atom into the sulfur atom of the chlordimethylsulfonium chloride (scheme 2.6). I found out that if the aryl ring had an electron withdrawing group, then the reaction took longer to go to completion, required a larger excess of the oxidant, and resulted in lower reaction yield (table 2.2). For example, when 1-(hept-6-en-2-

ylidene)-2-(4-nitrophenyl) hydrazine **105** (entry 5, table 2.2) was subjected to the reaction conditions, less than 30% yield of product was observed. After the reaction conditions were modified to include 10 equivalents of the oxidant, the reaction yield was still only 50% (entry 5, table 2.2).[2]

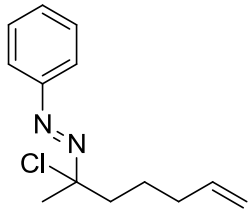
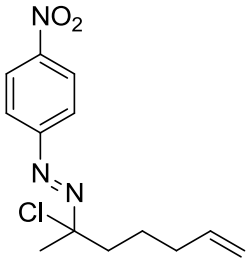
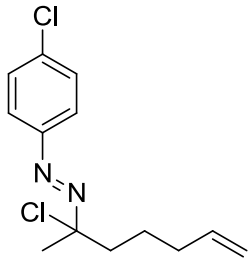
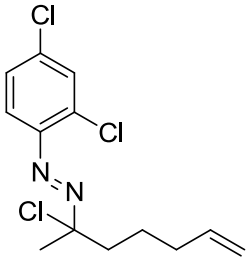
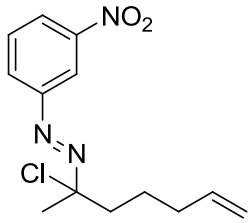
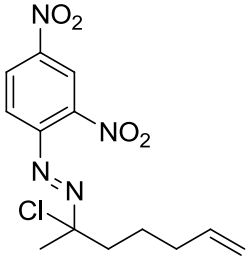
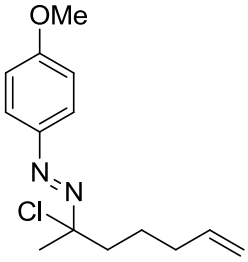
Scheme 2.6



As shown in table Y, in most cases hydrazones were successfully converted to the corresponding α-chloazo compounds in very good yields. The examples include the strong electron donating N'-methoxyphenyl diazine (entry 4), the moderate electron withdrawing N'-chlorophenyl diazine (entry 2), and the strong electron withdrawing N'-nitrophenyl diazine (entry 3). The other important fact is that the pendent alkene, which was required for next step as a reaction partner in the cycloaddition reaction leading to diazenium salts, remained unchanged during the oxidation reaction.[3]

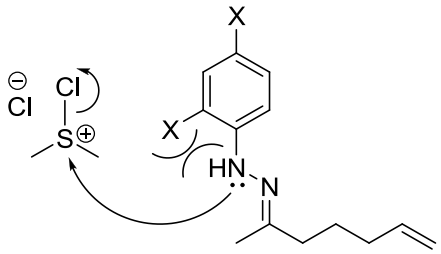
Hydrazones **106** and **107** (entires 6 and 7 respectively, table 2.2) did not produce the desired α-chloroaza compounds after several attempts and using different reaction conditions. We believe that this could be a steric effect or an electronic effect or more

Table 2.2: Isolated Yields of N'-Aryl Substituted α-Chloroazo Compounds

Entry	α-Chloroazo	Yield	Entry	α-Chloroazo	Yield
1	 **101**	80	5	 **105**	~50
2	 **102**	86	6		0
3	 **103**	75	7		0
4	 **104**	82			

likely a combination of both. Having a substituent on the *o*-position at the N'-aryl ring affects the ability of the nitrogen atom to react with the chlordimethylsulfonium chloride which is the first step of the reaction (figure 2.2). The other cause would be that the aryl ring is too electron poor and would withdraw electron density from the nitrogen atom and make it a poor nucleophile.

Figure 2.2. Steric hindrance of *o*-substituted aryl hydrazones



Both ^{1}H-NMR and ^{13}C-NMR clearly showed characteristic signals for the formation of the α-chloroazo compounds. In fact, using ^{1}H NMR was a great tool to monitor the progress of reaction as well. After being converted to the α-chloroazo compound, the N'-aryl protons have a clear and characteristic shift (7.5-9 ppm) and the corresponding peaks of the hydrazone disappear (6.5-7 ppm). Also, in all cases a characteristic α-chloroazo carbon resonance was observed at 96-98 ppm.

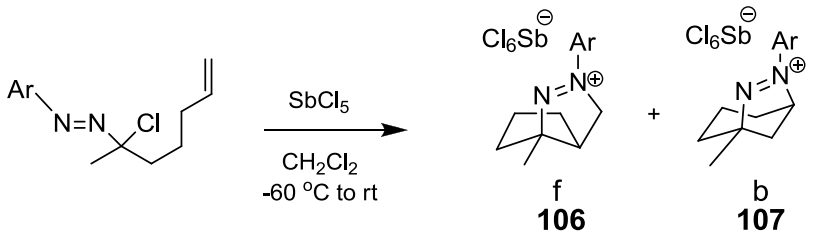
2.4. Synthesis of N'-Aryl Substituted Diazenium Salts

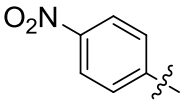
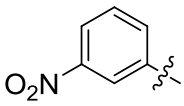
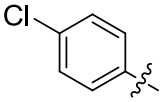
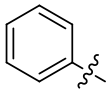
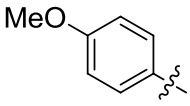
After successfully preparing the N'-aryl substituted a-chloroazo compounds with various electronic properties, I moved on to the next step to evaluate the effect of that variable on the outcome of the cycloaddition reaction. I was interested in exploring what effect that would have on both the yield of the reaction and more importantly the effect

on the regioselectivity. After subjecting the α-chloroazo compounds to the intramolecular cycloaddition reaction conditions developed by the group, a noticeable difference in the ring fused and the bridged dizaenium salt ratio was observed (table 2.3). When the N'-aryl substituent was the unsubstituted phenyl ring, the reaction gave a 1:0.2 ratio of fused to bridged diazenium salts (entry d, table 2.3). The presence of an electron donating substituent on the N'-aryl ring decreased the formation of the bridged diazenium salt and gave a fused to bridged ratio of 1:0.1 (entry e, table 2.3). A higher ratio of 0.2 for the bridged diazenium salt was observed in the case of the unsubstituted phenyl analog. Electron withdrawing groups, however, resulted in the formation of more of the bridged diazenium salt. A ratio of 0.4 was observed when the N'-aryl ring contained a chlorine substituent on the *para* position (table 2.3, entry c). A stronger electron withdrawing group, such -NO_2, resulted in a considerably higher ratio of 1 for the bridged diazenium salt (table 2.3, entry a).[2]

The other fact worth discussing was the difference in the bridged diazenium salt ratio observed when changing the position of the electron withdrawing-NO_2 group from the *para* position to the *meta* position. When the electron withdrawing substituent was at the *meta* position, that resulted in lowering the ratio to 0.9 (table 2.3, entry 2) for the bridged diazenium salt from being a ratio of 1 in the case where the same substituent was at the *para* position.

Table 2.3: Effect of N'-Aryl Substituent on Diazenium Salts Ratio



Entry	α-Chloroazo	Diazenium Salt ratio (106:107)	Yield
a		**1 : 1**	60%
b		**1 : 0.8**	81%
c		**1 : 0.4**	92%
d		**1 : 0.2**	88%
e		**1 : 0.1**	92%

2.5. The Hammett Correlation

In 1937, Louis Plack Hammett published the Hammett equation which describes the effect of substituents of an aromatic ring on reaction progress. This mathematical relationship quantitatively relates the observed changes in equilibrium constants, or rate constants, as a result of changing the aryl ring substituent electronic properties.[4] The Hammett equation measures the ratio of equilibrium constants in relation to a reaction constant ρ, and a substituent constant σ:

$$\log (KX / KH) = \rho \sigma$$

The reaction constant ρ reflects how a reaction is affected upon changing the electronic properties of a substituent. This constant depends on both the type of chemical reaction and the reaction conditions. The nature of charge developed during a reaction progress determines both the sign and magnitude of the reaction constant. For example, reactions with a positive ρ value proceed through a transition state that includes a negative charge build up. These are favored by stabilization of that negative charge and therefore would favor electron withdrawing groups. However, reactions with a negative ρ value proceed through a transition state that includes a positive charge build up. These reactions will favor electron donating groups to stabilize the positive charge. [4,5]

The substituent constant is related to the electronic effects, both inductive and resonance, that a certain substituent provides to a molecule. Electron withdrawing substituents will have a positive σ values whereas electron donating substituents will have a negative σ value. Examples are shown in table 2.4.[6]

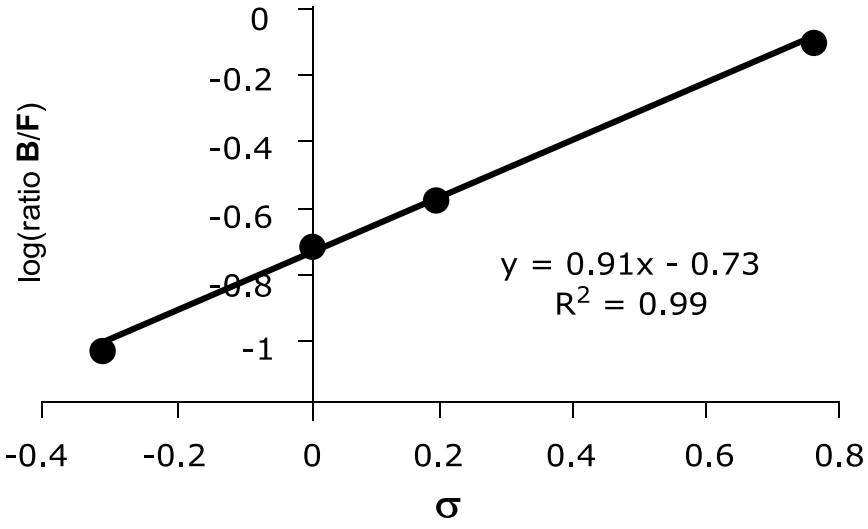
Table 2.4: Substituent constants (σ) for Common Substituents (5)

substituent	σ_{meta}	σ_{para}
-NH_2	-0.04	-0.66
-OH	0.12	-0.37
-CH_3	-0.07	-0.17
-OCH_3	0.12	-0.27
-H	0.00	0.00
-Ph	0.06	-0.01
-Cl	0.37	0.23
-Br	0.39	0.25
-I	0.35	0.18
-CN	0.56	0.68
-NO_2	0.71	0.78

A particular substituent will provide different effects that is dependent on its position with respect to to the reaction centre and also on its ability to contribute in resonance stabilization. The variations between σ_{meta} and σ_{para} values of a particular substituent is due to the different inductive and resonance effects which that substituent can contribute to a molecule. Resonance effects are determined by the ability of a substituent to change the electron distribution through resonance structures. These effects can only occur for ortho and para substituents. However, meta substituents have a negligible resonance contribution and contribute through inductive effects. Inductive effects exist from electronegativity differences and reduce with distance from the reactive centre. For the above reasons, σ_R values are greater for *orto* and *para* substituents and σ_I is greater for *meta* substituents.[7]

A Hammett plot of our results obtained for the ratio of the ring fused and bridged diazenim salts (table 2.3) was established (figure 2.3). Based on our assumption that the reaction is irreversible under the reaction conditions we have used, the log of the ratio of products obtained was used for these plots. This was a valid calculation because these values are directly related to the free energy difference between the two transition states for the two regeoismers. Remarkably, the Hammett plot of those results shows a linear correlation between the ratio of the products formed and the Hammett constants for the aryl ring substituents.[2] This relationship is similar to other cases where Hammett plots were used for results obtained for enantioselective reactions. Our results were consistent and show that the changes in structure produced proportional changes in the transition state energies and the reaction outcome. In addition, the structural modifications we made were very successful and produced additional data that helped us prove the proposed mechanism which will be discussed in the following section.

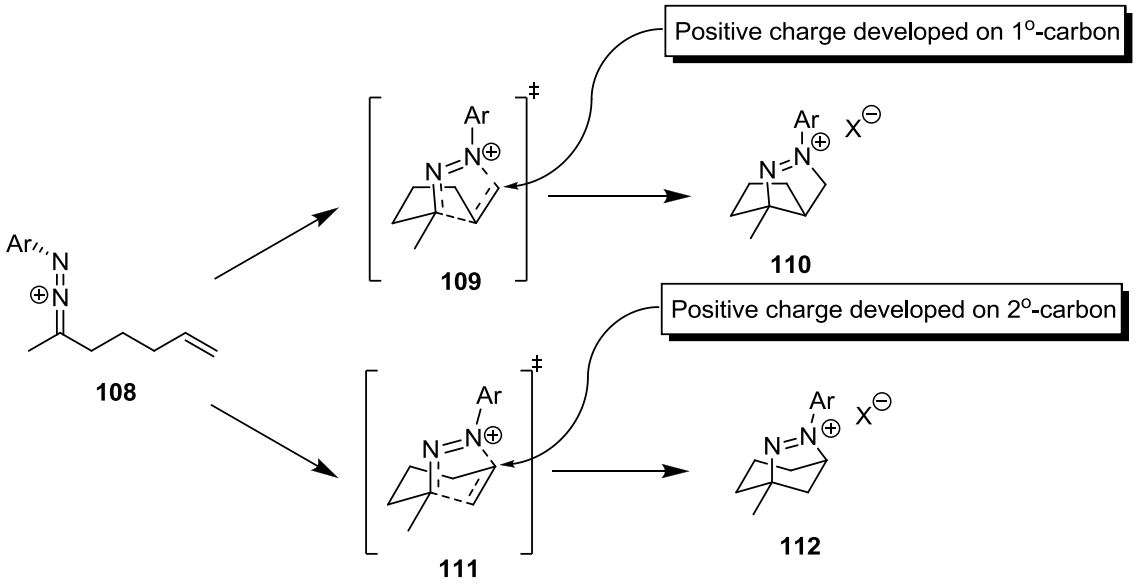
Figure 2.3. Hammett plot of results



2.6. Proposed Mechanism and Explanation of Results

Previous results clearly demonstrated that the electronics of the N'-aryl ring determines the ratio of the 5,5-fused and the 5,6-bridged diazenium salts. From these observations we propose that the cycloaddition reaction proceeds through a concerted but asynchronous reaction mechanism. In this case, the C-C bond formation to the highly electrophilic carbon atom of heteroallene **108** (figure 2.4) is more advanced at the transition state than N-C bond formation to the heteroallene nitrogen.

Figure 2.4. Cycloaddition reaction mechanism

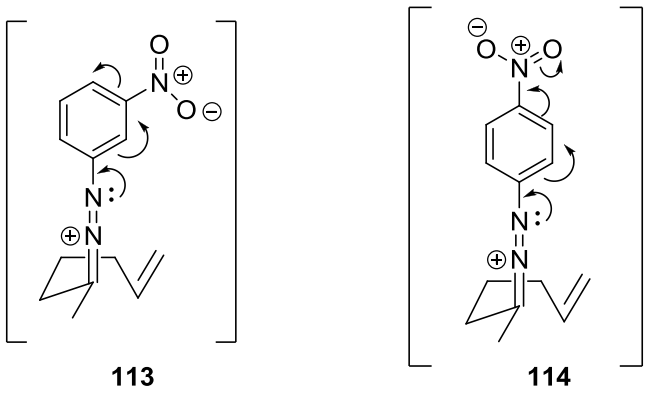


Because the C-N bond formation lags C-C bond formation, the transition state will involve the formation of a partial positive charge on the carbon atom that forms the new bond with nitrogen. Transition state **111** (Figure 2.4), leading to the formation of 6,5-bridged product **112**, would have a partial positive charge developed on a secondary carbon atom. However, transition state **109**, leading to the formation of 5,5-fused product

110, would have a partial positive charge develop on the primary carbon. Even though cationic charge buildup on a primary carbon would make transition state **109** higher in energy, we think that this transition state is entropically more favored, which explains why the 5,5-fused diazenium salt **110** is always the higher percentage regioisomer formed (table 1.2, chap 1). However, when the N'-aryl substituent becomes more electron withdrawing, which will directly affect the electron density of the nitrogen atom, the C-N bond formation should be even further delayed in the transition state and the amount of partial positive charge developed at the transition state would increase. For that reason, a higher proportion of the molecules will go through transition state **111** where the partial positive charge is developed on the secondary carbon. In which case, the percentage of bridged diazenium salt **112** formed would be expected to increase. These results are very consistent with the proposed mechanism (Table 2.3).

The results obtained when the electron-withdrawing $-NO_2$ is located diferent positions on the aryl ring are also consistent with the above explanation. In this case, a higher ratio of the 5,6-bridged diazenium salt (1.0:1.0) was obtained when the electron withdrawing group was at the *para* position whereas a lower ratio of (0.8:1.0) was obtained when the same group was at the *meta* position. This can be explained by the higher ability of the electron withdrawing group in contributing to the resonance of the ring being at the *para* position and in decreasing the electron density on the nitrogen atom in the transition state leading to the formation of product (figure).

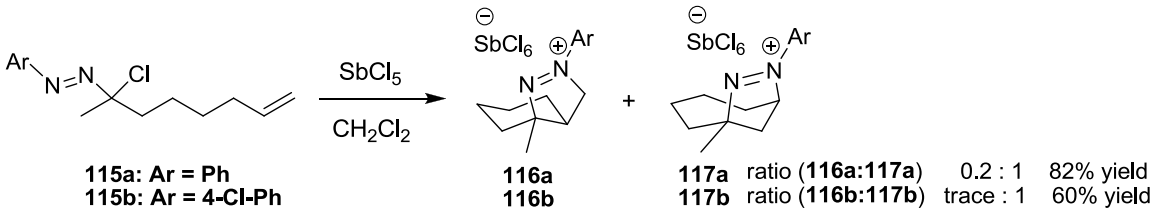
Figure 2.5. *Ortho* Vs. *meta* substituent effect



2.7. Synthetic Application: Formation of Large Size Ring Bicyclic Enones

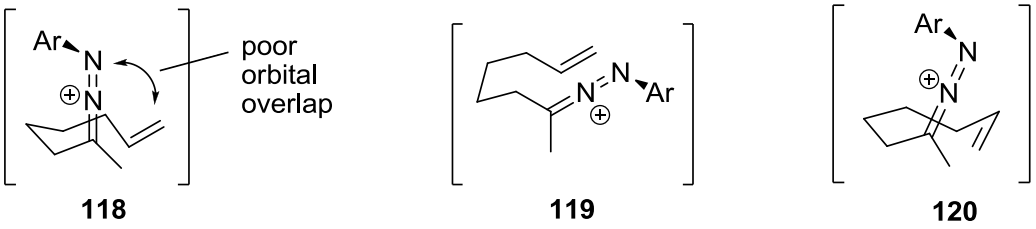
Interestingly, the Brewer group discovered that when the distance between the heteroallene center and the pendent alkene was lengthened by one carbon atom, the 7,5-bridged product **117** (scheme 2.7) was obtained preferentially.[8] This can be explained by the fact that a poor overlap of orbitals occurs when the heteroallene adopts a conformation in which the forming 6-membered ring is in a chair-like conformation (**120**, figure 2.6). To obtain proper orbital overlap, the 1-aza-2-azoniaallene intermediate must

Scheme 2.7



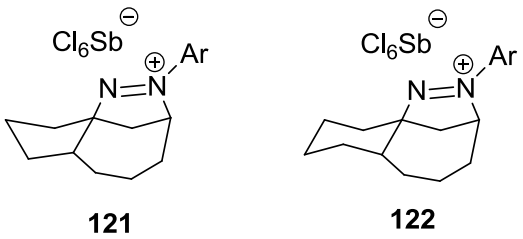
adopt an unfavorable boat-like conformation (**119**). In this case, it seems that the longer tether length provided enough conformational flexibility to the structure to allow the reacting centers, the heteroallene and the alkene, to more easily align in in transition state **120**. This conformation leads to the formation of the bridged seven-membered ring carbocyclic product. The formation of the 7,5-bridged bicyclic product would also have been predicted to be more favorable in an asynchronous concerted reaction mechanism.

Figure 2.6. Formation of the 7,5-bridged bicyclic product



Based on this discovery, we became interested in evaluating the reactivity of cyclic 1-aza-2-azoniaallenes that could lead to tricyclic diazenium salts, such as **121** and **122** (figure 2.7). My initial target was tricyclic diazenium salt **121** (scheme 2.8). Ketone

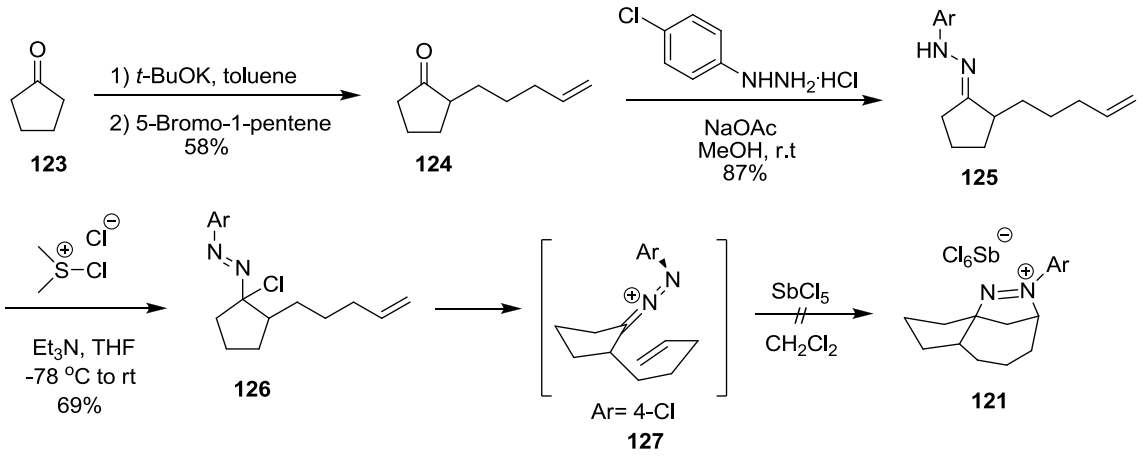
Figure 2.7. Tricyclic diazenium salts



124 was successfully made by the treatment of cyclopentanone with potassium *tert*-butoxide followed by the addition of 5-bromo-1-pentene to give the desired product in

58% yield after purification. Formation of the hydrazone and the α-chloroazo was achieved following the previous procedures developed in the group to give hydrazone **125** and α-chloroazo compound **126** in 84% yield and 69% yield respectively. When the α-chloroazo precursor was subjected to the Lewis acid mediated cycloaddition using $SbCl_5$, none of the desired product was observed after several attempts were made varying the reaction conditions. This could possibly be due to a poor orbital alignment between the heteroallene and the alkene.

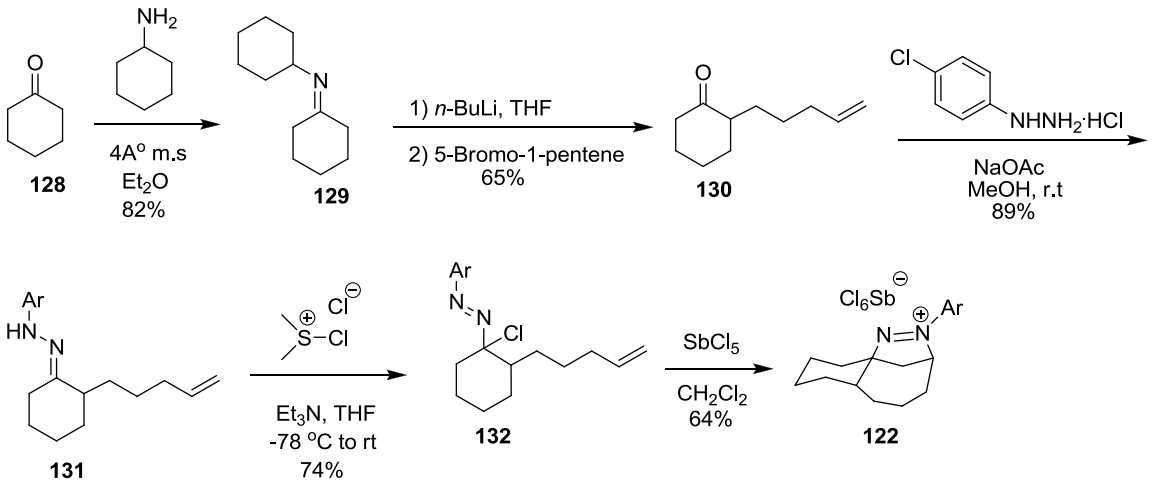
Scheme 2.8



Interestingly, attempts to make dizenium salt **122** (scheme 2.9) were successful. To prepare ketone **130**, cyclohexanone was treated with cyclohexyl amine in the presence of 4Å molecular sieves in diethyl ether to give imine **129** in 82% yield after purification. The imine was then treated with *n*-butyllithium followed by 5-bromo-1-pentene to give the desired ketone in 65% yield. Formation of the corresponding hydrazone **131** and α-chloroazo compound **132** proceeded smoothly in yields of 89% and 74% respectively.

The α-chloroazo precursor **132** was subjected to the Lewis acid mediated cycloaddition conditions and I was glad to see the desired product form in 64% yield.

Scheme 2.9



Diazenium salt **122** was hydrolyzed with aqueous sodium bicarbonate to yield the aryldiazenyl bicyclic heptanone **133** in 93% yield (scheme 2.10). Several attempts were made to eliminate the aryldiazene and form the 6,7-bicyclic fused enone **134** using a variety of reagents and reaction conditions but none gave the desired product (table 2.5).

Scheme 2.10

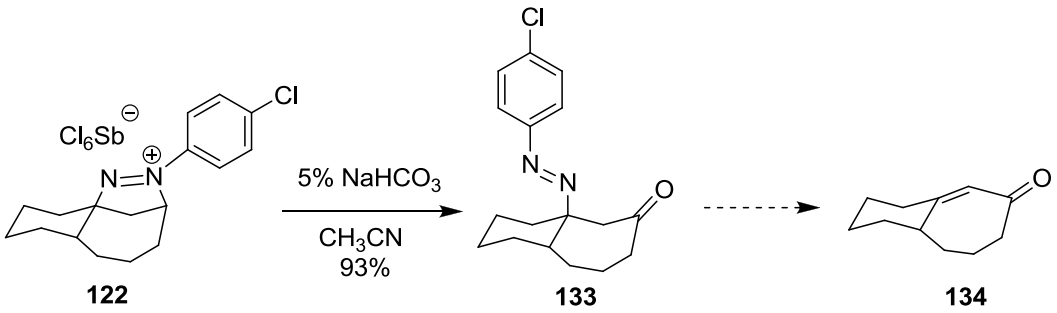
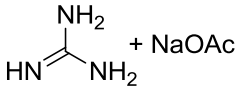


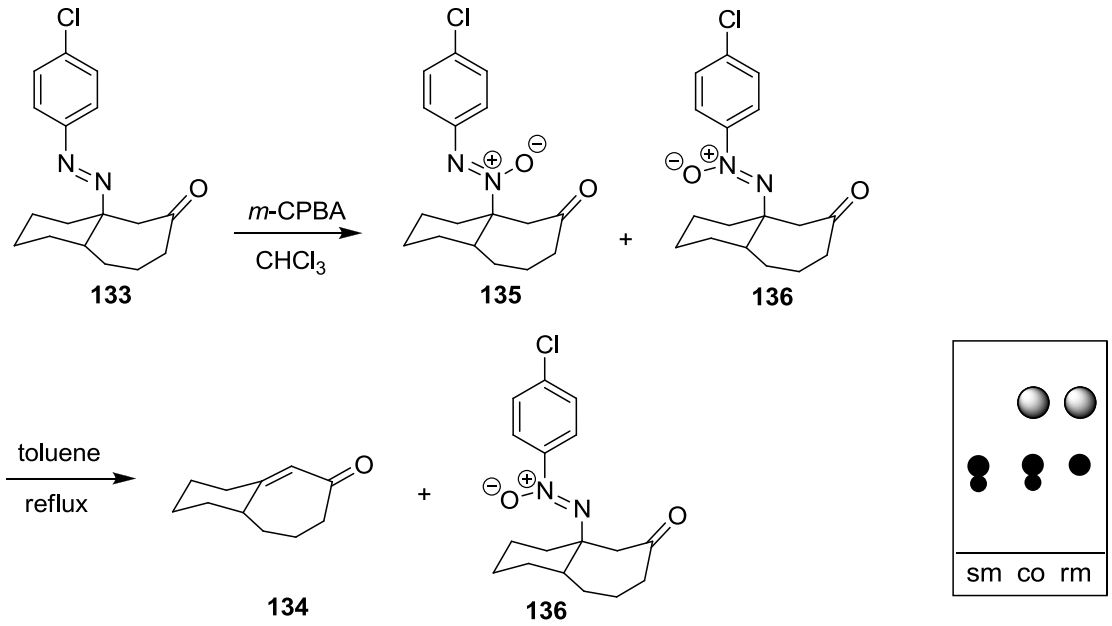
Table 2.5: Conditions used for the elimination of aryldiazene

Entry	Reagent	Solvent	Temp (^oC)	Time (hr)	Result
1	NEt_3	CH_2Cl_2	r.t	8	no reaction
2	*p*-Toluene sulfonic acid	toluene	reflux	overnight	no reaction
3	DBU	CH_2Cl_2	r.t	overnight	no reaction
4	DBU	CH_2Cl_2	reflux	overnight	no reaction
5	DBU	toluene	reflux	overnight	no reaction
6	10% NaOH	CH_2Cl_2	r.t	overnight	no reaction
7		MeOH	r.t, reflux	4, overnight	no reaction
8	*t*-BuOK	DMSO	r.t	6	no reaction
9	*t*-BuOK	*t*-BuOH	r.t, reflux	overnight	no reaction
10	NaOme	EtOH	r.t, reflux	6, overnight	no reaction
11	$LiNH_2$	DMSO	r.t, reflux	2, overnight	no reaction
12	 + NaOAc	MeOH	r.t, reflux	overnight	no reaction
13	LDA	THF	-78 ^oC, rt	overnight	no reaction
14	NaH	DMF	0 ^oC, rt	48	no elimination
15	AIBN, Bu_3SnH	Benzene	reflux	overnight	no elimination
16	Ph-I$(OTf)_2$, TEA	CH_2Cl_2	-40 ^oC, 40 ^oC	0.08	no elimination
17	H_2SO_4	toluene	reflux	5	EAS
18	*t*-BuOK	DMSO	reflux	overnight	no elimination

After doing more research, an interesting procedure for the elimination reaction was found applicable which involved oxidizing the diazene into the corresponding *N*-oxide using *m*-chloroperoxy-benzoic acid (scheme 2.11). The oxidation resulted in the

formation of about 0.7 : 1.0 of both regioisomers, **135** and **136** (scheme 2.11). After allowing the reaction mixture to reflux in toluene overnight, *N*-oxide **135** reacted completely and gave ketone **134**.

Scheme 2.11



2.8. Summary

I described a study that enabled us to better understand the mechanism of the cycloaddition reaction. This was accomplished by studying what effect the N'-aryl substituent had on the ratio of the ring fused and bridged diazenium salts. The results of this study were consistent with our proposed mechanism for the cycloaddition reaction.

References:

(1) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

(2) Wyman, J.; Javed, M.; Al-Bataineh, N.; Brewer, M., *J. Org. Chem.* **2010**, 75, 8078.

(3) Harej, M; Dolene, D. *J. Org. Chem.*, **2007**, *72*, 7214.

(4) Hammett, L. P. *J. Am. Chem. Soc.* **1937,** *59*, 96.

(5) *Hansch, C.; Leo, A.; Taft, R. W. Chem. Rev.* **1991**, 91, *165.*

(6) *Keenan, S. L.; Peterson, K. P.; Peterson, K.; Jacobson, K. J. Chem. Educ.* ***2008****, 85, 558.*

(7) Um, I. H.; Lee, J. Y.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2004**, *69*, 2436.

(8) Javed, M. I.; Wyman, J. M.; Brewer, M. *Org. Lett.* **2009**, *11*, 2189

3. CHAPTER 3:

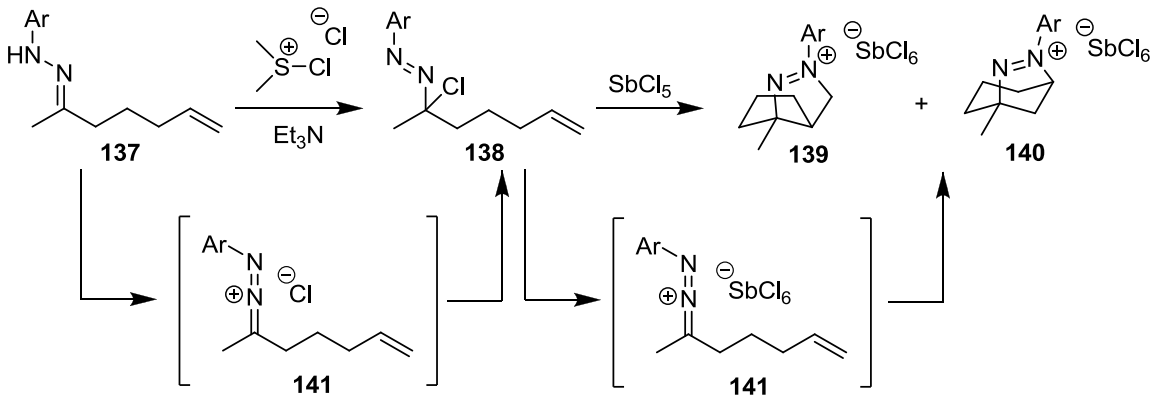
Iodine(III)-Mediated Bicyclic Diazenium Salt Formation

3.1. Introduction

In chapter one I described Brewer group's development of the intramolecular cycloaddition reaction to form bicyclic diazenium salts. That Lewis acid-mediated cycloaddition reaction used α-chloroazo compounds as precursors for the cycloaddition reaction. The α-chloroazo compounds were prepared using a procedure developed by the Brewer group that involved oxidizing hydrazones with chlorodimethylsulfonium chloride in the presence of a base (scheme 3.1).

The proposed mechanism for the formation of the α-chloroazo compounds, as shown in scheme 3.1, involves the formation of 1-aza-2-azoniallene salt intermediate **141**, which is subsequently captured by the chloride counterion. Using a Lewis acid, the α-chloroazo compound is then transformed into the diazenium salt via the same 1-aza-2-azoniaallene salt intermediate. With this in mind, the group hypothesized that a sulfonium salt bearing a counterion that is significantly less nucleophilic than chloride might react with aryl hydrazones to directly provide diazenium salts without forming an intermediate via nucleophilic capture. In other words, the heteroallene salt intermediates generated from hydrazones could undergo the intramolecular cycloaddition without getting trapped by the nucleophilic counterion of the oxidant used.

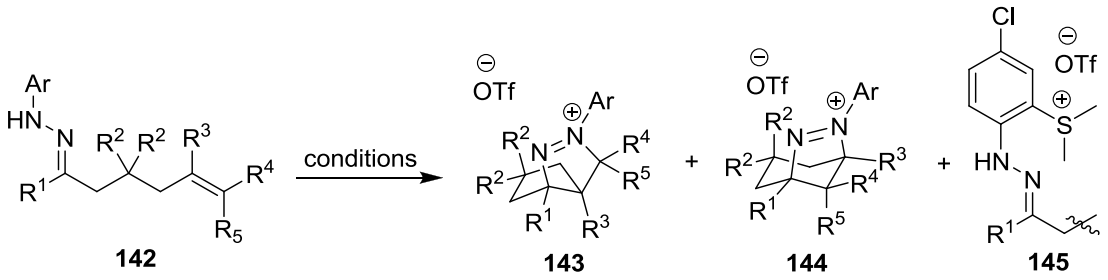
Scheme 3.1



3.2. Sulfonium Salt-Mediated Conversion of Hydrazones to Diazenium Salts

The Brewer group recently confirmed that this is possible; hydrazones react effectively with dimethyl sulfide ditriflate (DMSD) at low temperature to directly form diazenium triflate salts (scheme 3.2).[1] This is considered the second procedure developed by the group for the synthesis of diazenium salts. It is a milder methodology that does not require the use of a toxic Lewis acid for the cycloaddition reaction and avoids the formation and isolation of the α-chloroazo intermediate.

Scheme 3.2



Conditions: DMSD (1.1 equiv), DTBMP (1.2 equiv), CH_2Cl_2 (0.02M); -78 ^oC (20 min); -78 ^oC to rt (35-40 min); added dibenzyl ether (0.5 equiv); quick conc.

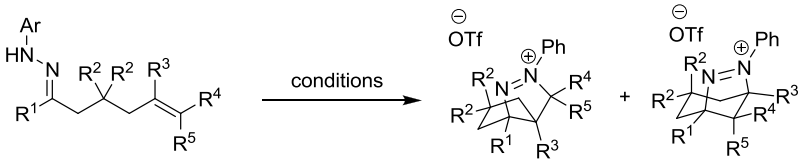
The Brewer group was also able to expand the substrate scope to include a variety of structures as shown in table 3.1. Overall, the yields for the cycloaddition reaction were slightly lower than what was observed previously when the diazenium salts were obtained from α-chloroazo precursors. As shown in scheme 3.2, the aryl sulfonium salt **145**, which was the result of an electrophilic aromatic substitution reaction, was identified as a side product and was a major cause for lowering the overall yield. This more recently developed method also gave slightly different ratios of the 5,5-fused and 6,5-bridged diazenium salts. Table 3.2 shows a relative comparison of the yields and regioisomeric ratios for the triflate diazenium salts and hexachloroantimonate diazenium salts.

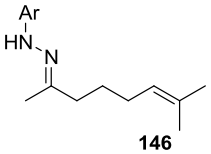
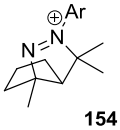
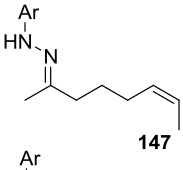
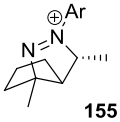
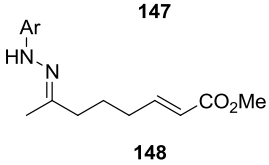
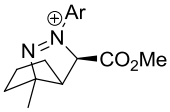
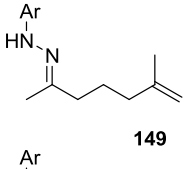
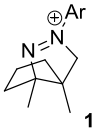
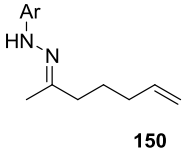
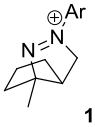
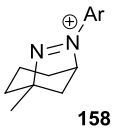
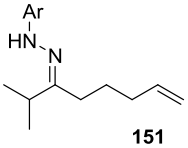
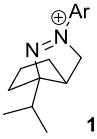
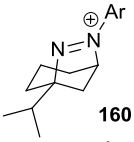
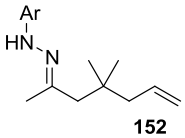
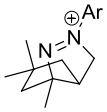
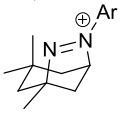
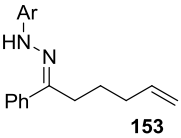
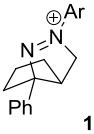
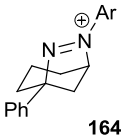
From an experimental point of view, the second method using dimethyl sulfide ditriflate to form diazenium salts from hydrazones, has some practical limitations. Among these, the fact that Tf_2O, which was the reagent used to generate the active oxidant dimethyl sulfide ditriflate, is very sensitive to moisture and has a very short shelf

life. Distillation of the reagent was done continuously under strictly inert atmosphere conditions.

After obtaining these results, we became interested in doing more research on the direct conversion of hydrazones to diazenium salts. More specifically, we started to research a newer method that could combine both cleaner results with higher yields similar to the ones obtained by the first method but be a one-step conversion similar to the second method. In the next section, I will be describing my work to develop a third and most efficient method for the formation of diazenium salts using a hypervalent iodine(III) oxidant.

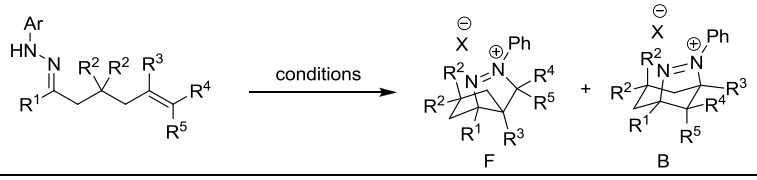
Table 3.1. Substrate Scope and Yields for Diazenium Triflate Salts

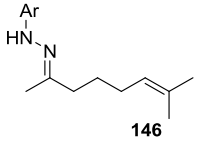
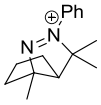
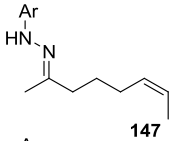
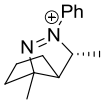
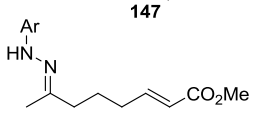
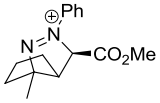
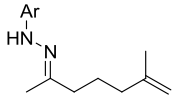
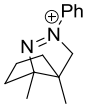
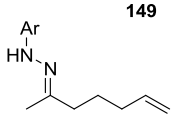
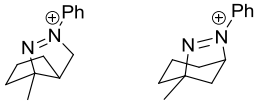
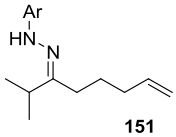
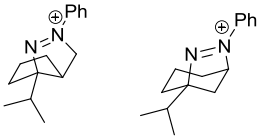
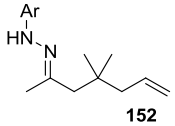
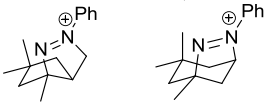
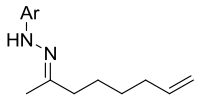
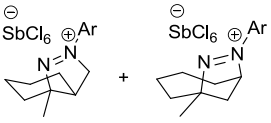
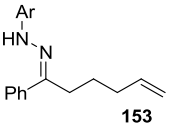
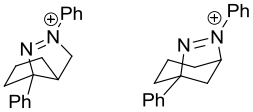


Entry	Hydrazone	Product	Yield (Ratio **Z**:**Z**)
1	 **146**	 **154**	29%
2	 **147**	 **155**	63%
3	 **148**	 **156**	41%
4	 **149**	 **156**	0%
5	 **150**	 **157**  **158**	67% 1 : 0.45
6	 **151**	 **159**  **160**	70% 1 : 0.15
7	 **152**	 **161**  **162**	54% 1 : 0.12
8	 **153**	 **163**  **164**	63% 1 : 0.4

Conditions: DMSD (1.1 equiv), DTBMP (1.2 equiv), CH_2Cl_2 (0.02M); -78 °C (20 min); -78 °C to rt (35-40 min); added dibenzyl ether (0.5 equiv); quick conc.

Table 3.2. Comparison Between Dizenium Hexachlororoantimonates and Triflates



Entry	Hydrazone	Product	Ar = 4-Cl-Ph X = OTf Yield Ratio (**F**:**B**)	Ar = Ph X = $SbCl_6$ Yield Ratio (**F**:**B**)	Ar = 4-Cl-Ph X = OTf Yield Ratio (**Z=F**:**B**)
1	 **146**		29%	71%	80%
2	 **147**		63%	88%	–
3	 **148**		41%	83%	–
4	 **149**		0%	0%	–
5	 **150**		67% 1 : 0.45	87% 1 : 0.2	92% 1 : 0.3
6	 **151**		70% 1 : 0.15	88% 1 : 0.05	80% 1 : 0.07
7	 **152**		54% 1 : 0.12	75% 1 : 0.09	89% 1 : 0.08
8	 **165**		48% 0.16 : 1	80% 0.2 : 1	–
9	 **153**		63% 1 : 0.4	–	–

3.3. Hypervalent Iodine Chemistry

3.3.1. General Properties and Structural Features

Iodine is most commonly found in monovalent compounds with an oxidation state of -1. However, due to its ability to exist in extended octet forms, iodine also forms other stable polycoordinate multivalent compounds which are known as hypervalent or polyvalent iodine compounds. Formally, iodine belongs to the main group p-block elements. However, because of its large atomic size, the bonding in iodine compounds is described differently from the light main-group elements. The structural features and reactivity behavior of hypervalent iodine compounds in many ways are similar to the derivatives of transition metals; reactions of hypervalent iodine reagents are commonly oxidative addition, ligand exchange, reductive elimination, and ligand coupling, which are typical reactions of transition metals.[2]

The first polyvalent organic iodine complex, dichloroiodo benzene ($PhICl_2$), was prepared was by German chemist Conrad H.C. Willgerodt in 1886. Shortly after that, in 1893 this compound was recognized as a powerful oxidant. Interestingly, it was not until very recently that the organic chemistry of hypervalent iodine compounds as oxidants has seen a much development. The most recent achievements in the area of organohypervalent iodine chemistry include the development of several new hypervalent iodine oxidants, the development of enantioselective reactions involving chiral hypervalent iodine reagents, and the discovery of catalytic applications of organoiodine compounds.[3]

The new found interest in the chemistry of hypervalent iodine compounds stems from the fact that the chemical properties and reactivity of these compounds are similar to heavy metal reagents such as Hg(III), Tl(III), Pb(IV). However, this reactivity comes without the toxicity and environmental issues of heavy metals and offer mild reaction conditions, easy handling, and commercial availability of key precursors.

3.3.2. Nomenclature and Classes of Hypervalent Iodine Compounds

The term hypervalent was established in 1969 for molecules with elements of groups 15-18 bearing more electrons than octet in their valence shell. The IUPAC rules designate λ as non-standard bonding. For example, H_3I is a λ^3-iodane and H_5I is a λ^5-iodane. Iodine itself contains seven valence electrons and in a λ^3-iodane three more are donated by the ligands making it a decet structure. λ^5-iodanes are dodecet molecules. The common decet structure is λ^3-iodane $ArIL_2$ (L = heteroatom) and for dodecet structure is λ^5-iodane $ArIL_4$.[4]

The traditional classification of hypervalent iodine compounds is based on the number of carbon ligands on the central iodine. Iodinanes can be 1C-bond which are called iodosyl or iodoso compounds (RIO) and their derivatives (RIX_2, where X = non-carbon ligands and R = aryl or CF_3), 2C-bonds which are called iodonium salts ($R_2I^+ X^-$), or 3C-bonds which are not synthetically useful since compounds with 3C-I bonds are thermally unstable. Periodinanes can be 1C-bond which are called iodyl or iodoxy compounds (RIO_2) and their derivatives (RIX_4 or RIX_2O), or 2C-bonds which are called iodyl salts ($R_2IO^+ X^-$). Compounds with more than one formal carbon bond to iodine can

be alkenyliodonium ($PhI^{+}C{=}CHR\ X^{-}$), alkynyliodonium ($PhI^{+}C{\equiv}CR\ X^{-}$) salts, and iodonium ylides (PhI=CXY, where X, Y = electron acceptors).[5]

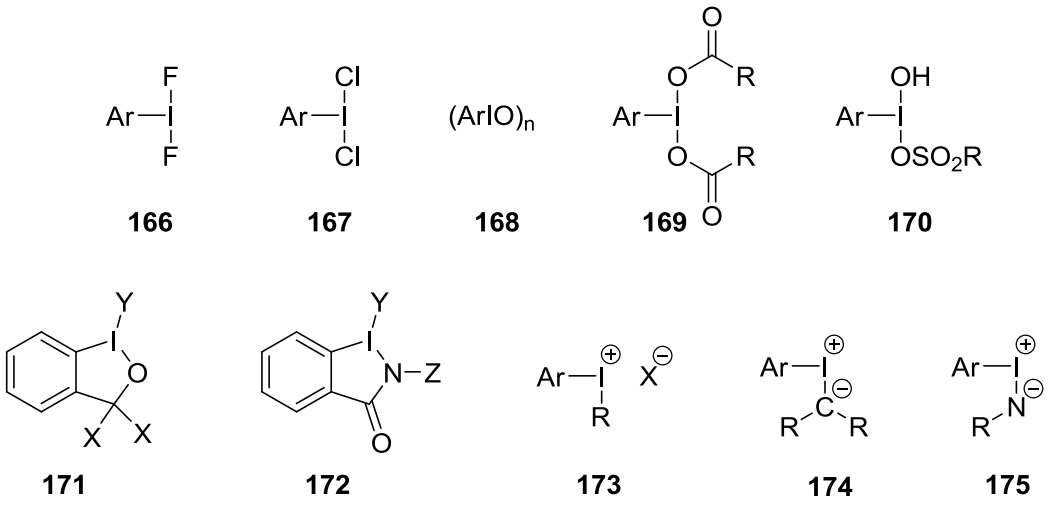
3.3.3. Classification and General Structural Features of Organic Iodine (III) Compounds

Organic iodine (III) compounds are normally classified by the type of ligands attached to the iodine atom.[3,4] The following general classes of iodine (III) compounds have been mad and have also found broad applications in organic synthesis. Among these (figure 3.1) are (difluoroiodo) arenes **166**, (dichloroiodo) arenes **167**, iodosylarenes **168**, [bis(acyloxy)iodo]arenes **169**, aryliodine (III) organosulfonates **170**, five-membered iodine heterocycles (benziodoxoles **171** and benziodazoles **172**), iodonium salts **173**, iodonium ylides **174**, and iodonium imides **175**. In terms of synthetic applications, (Difluoroiodo) arenes **166** and (dichloroiodo) arenes **167** are effective fluorinating and chlorinating reagents, respectively. Iodosylarenes **168**, aryliodine (III) carboxylates **169**, and organosulfonates **170** in general are strong oxidizing agents. There has been several reports for their applications as reagents for oxygenation and oxidative functionalization of organic substrates.[4,5] The most important and commercially available versions of aryliodine (III) carboxylates are (diacetoxyiodo) benzene $PhI(OAc)_2$, which has several common abbreviations, such as DIB, PID, PIDA (phenyliodine diacetate), IBD, or IBDA (iodosobenzene diacetate), and [bis(trifluoroacetoxy)iodo] benzene $PhI(OCOCF_3)_2$, which is abbreviated as BTIB or PIFA [(phenyliodine bis(trifluoroacetate)]. The most important version of aryliodine (III) organosulfonates is the commercially available

[hydroxy(tosyloxy)iodo]benzene PhI(OH)OTs which is abbreviated as HTIB and is also known as Koser's reagent.

In the next few sections, I will be focusing more on the properties and synthetic applications of organic iodine (III) as an oxidant, which will be more directly related to the research I will be describing in this chapter.

Figure 3.1. Common classes of polyvalent iodine(III) compounds.



3.3.4 Hypervalent Iodine (III) Compounds as Efficient Oxidants

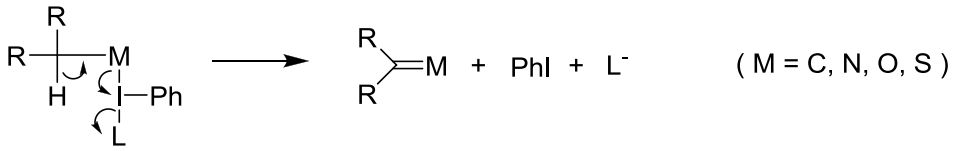
Oxidation reactions are among the most important transformations in organic synthesis. However, in spite of their utility in both research laboratory and industrial scale production, oxidation reactions are among the most problematic processes. This is due to safety concerns, environmental hazards, and operational issues. The use of severe

reaction conditions, thermal instability, and the highly reactive nature of many of the known oxidants are factors that restrict their applicability on a large scale.

As mentioned earlier in this chapter, the use of hypervalent iodine reagents as oxidants has recently been receiving a lot of attention due to their low toxicity, mild reactivity, availability, high stability, and ease of handling. They have become useful alternatives to highly toxic heavy metal oxidizers such as lead(IV), mercury(II) and thallium(III) reagents.

The reactivity of hypervalent iodine (III) is basically determined by the strongly electrophilic nature of the iodine, which makes it highly susceptible to nucleophilic attack. In addition, the arylliodonio group (-IArX) has excellent leaving group ability; for comparison, it is about 10^6 times greater than triflate. The key to the reactivity of hypervalent iodine (III) compounds as oxidants is their favorable reduction to normal valency by reductive elimination of iodobenzene (scheme 3.3).

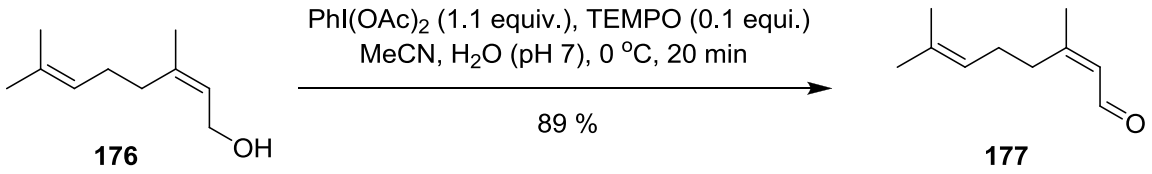
Scheme 3.3



An important example that illustrates the reactivity of iodine (III) reagents as oxidants is the oxidation of alcohols to the corresponding carbonyl compounds.[9-16] For example, an efficient procedure for the oxidation of alcohols with DIB in the presence of

catalytic amounts of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) has been developed and is frequently used (Scheme 3.4).

Scheme 3.4

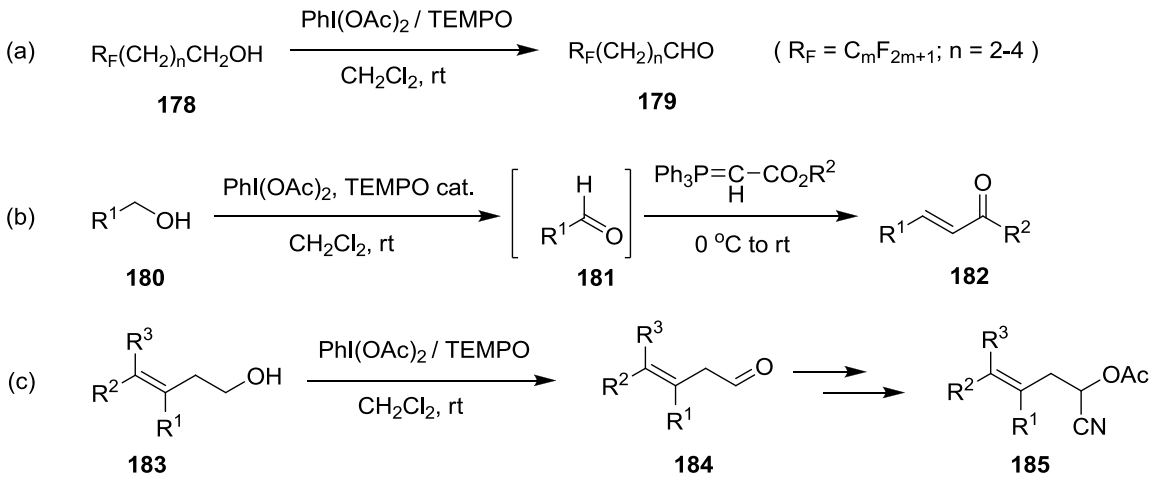


176 **177**

This method demonstrates very high selectivity for the oxidation of primary alcohols to aldehydes without any overoxidation to carboxylic acids. This oxidation was successful with high chemoselectivity in the presence of either secondary alcohols, or in the presence of other oxidizable functional groups. This method has been used for the oxidation of (fluoroalkyl) alkanols ($R_F(CH_2)_nCH_2OH$) to aldehydes (scheme 3.5-a),[11] the one-pot selective oxidation/olefination of primary alcohols using stabilized phosphorus ylides (scheme 3.5-b),[12] and in the chemo-enzymatic oxidation/hydrocyanation of γ,δ-unsaturated alcohols (scheme 3.5-c).[13] The yields reported for these reactions range from good to excellent and were quantitative in some examples.[11-13]

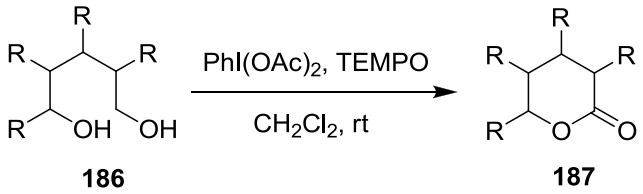
Based on the ability of the DIB-TEMPO system to selectively oxidize primary alcohols to the corresponding aldehydes in the presence of secondary alcohols, Forsyth and coauthors have developed a selective oxidative conversion procedure for a wide

Scheme 3.5



range of highly functionalized 1,5-diols into the corresponding δ-lactones in excellent yields (scheme 3.6).[14,15]

Scheme 3.6

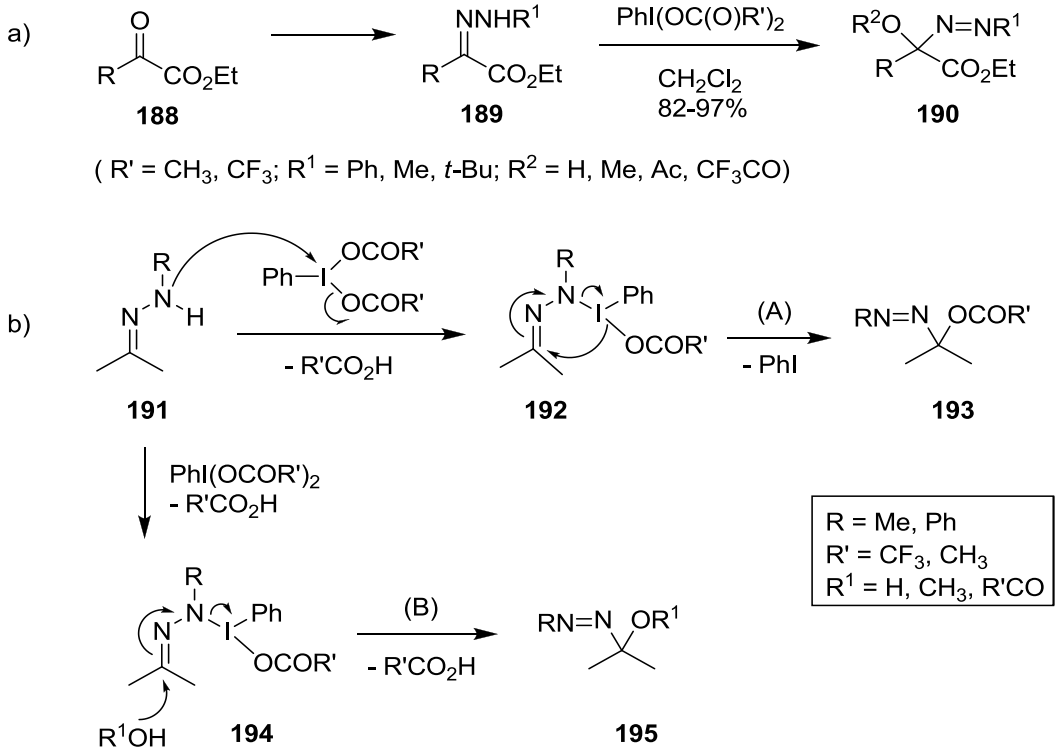


3.3.5. Hypervalent Iodine (III) Oxidation of Hydrazones

Derek Barton and coworkers described the oxidation of hydrazones by hypervalent iodine (III) reagents, such as BTIB and IBDA.[17] This work was reported as an approach to the synthesis of 3-deoxy-D-mamlo-2-octulosonic acid (KDO). Phenylhydrazine was chosen to protect the α-keto ester group to avoid the undesired *β*-

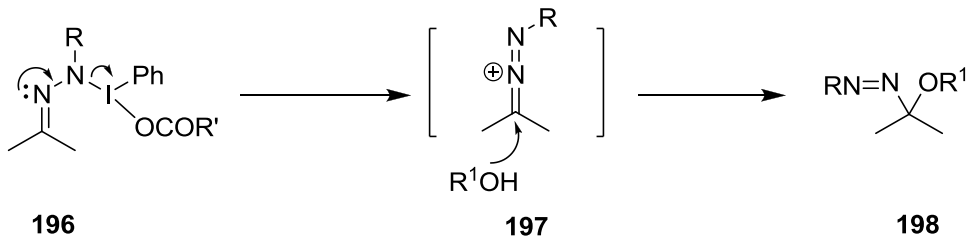
elimination of the acetoxy group and facilitated the successful isolation of the KDO phenylhydrazone derivative (scheme 3.7-a).[18] After forming the α-phenylhydrazone esters and screening several organic and inorganic oxidants, they discovered that using IBDA would control the oxidation of phenyl hydrazones to form the α-acetoxy phenylazo compounds under anhydrous conditions. The report also contained mechanistic considerations they proposed for these oxidations (scheme 3.7-b).[19] In both paths, A and B, the first step which initiates the oxidation reaction involves a ligand exchange between the hydrazone and organo-iodine (III) to form **192** (path A) or **194** (path B). In path A, the formation of the phenylazo compound **193** could occur by the intramolecular rearrangement of intermediate **192** with reductive elimination to iodobenzene. In path B, an alternative way to get to phenylazo **195** is achieved when a nucleophilic solvent, such as methanol, was used.

Scheme 3.7



The results obtained in this study clearly show that using a nucleophilic ligand or nucleophilic solvent results in the formation of the α-alkoxyazo or α-acetoxyazo compounds. These products are similar to the α-chloroazo compounds that were formed by our group when hydrazones were reacted with chlorodimethylsulfonium chloride as an oxidant. It can be hypothesized that upon reduction of the organoiodine, a 1-aza-2-azoniallene intermediate is being formed which can then react with the nucleophilic ligand/solvent to give the phenylazo derivatives (scheme 3.8).

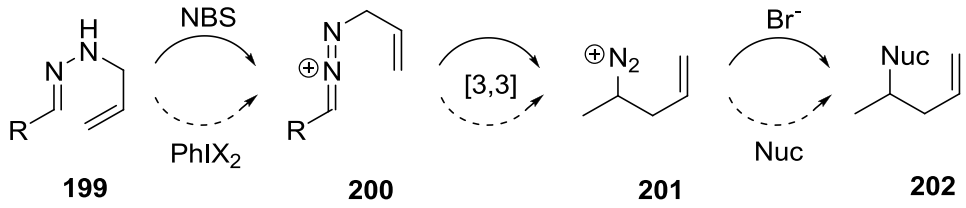
Scheme 3.8



196 **197** **198**

More recently, Thomson and coworkers reported a fragment coupling cascade reaction of *N*-allyl hydrazones initiated by hypervalent iodine (III).[20] This recent research aimed to widen the scope of a reaction they previously developed that used *N*-bromosuccinimide (NBS) to initiate the rearrangement shown in scheme 3.9 .[21,22]

Scheme 3.9

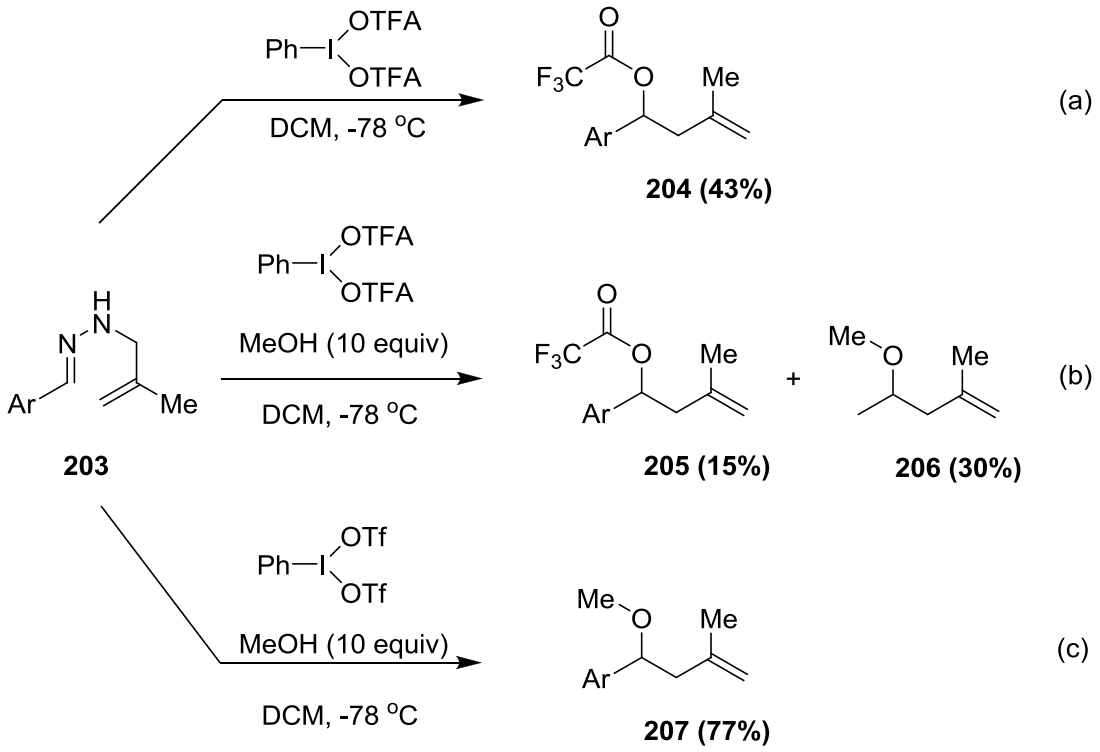


199 **200** **201** **202**

As shown in scheme 3.9, the cascade reaction sequence is initiated through the formation of 1-aza-2-azoniallene **200** followed by [3,3] sigmatropic rearrangement to give diazonium ion **201** which reacts with a nucleophile, such as bromide, to give the final product **202**. The group then started investigating the possibility of initiating the hydrazone oxidation with hypervalent iodine reagents such as $PhI(OAc)_2$ (PIDA), $PhI(OTFA)_2$ (PIFA), and $PhI(OTf)_2$. In their work, the Thomson group did not limit the use of the nucleophile to the ligand coordinated to the iodine atom of hypervalent iodine

reagent (scheme 3.10). Initially, they investigated the use of commercially available hypervalent iodine reagents, such as PIDA and PIFA, and the hydrazone derived from the condensation of 2-naphthaldehyde and methylallyl hydrazine.

Scheme 3.10



When they used PIDA as the oxidant, no desired product was observed under the reaction conditions they previously developed. However, PIFA did provide trifluoroacetate **204** in 43% yield (scheme 2.10-a). They did not succeed in getting a higher yield after several attempts to optimize the reaction conditions. Although this reaction was low-yielding, it gave an initial indication that hypervalent iodine (III) was a promising reagent to perform the rearrangement of *N*-allylhydrazones. An additional

result reported by the Thomson group, which was found during the scan for various exogeneous nucleophiles, was the outcome of the reaction of hydrazone **203** with PIFA in the presence of methanol (10 equiv). In this latter experiment, they observed the formation of ester **205** along with the competitive formation of ether **206** (scheme 2.10-b). The formation of ether **206** could have been possibly favored if methanol was used as a solvent but that would limit this method to be used only for readily available alcohols that are liquid. Taking these results into consideration, they concluded that the next step was to use a hypervalent iodine reagent with a much less nucleophilic ligand that would not compete as a nucleophile and they chose $PhI(OTf)_2$.[23] This reagent was generated in situ by the reaction of iodosobenzene with TMSOTf. One equivalent smoothly converted hydrazone **203** to the desired ether **207** in 77% yield (scheme 2.10-c) in the presence of methanol (10 equiv) without the formation of any of the undesired triflate product.

3.4. Brewer Group Development of Iodine(III)-Mediated Diazenium Salt Formation

From the examples presented in the previous sections, it can be clearly seen that hypervalent iodine (III) is a powerful oxidant that is also mild, readily available, stable ,easy to handle, and of low toxicity. In addition, at the beginning of this chapter I presented the results obtained by our group for the formation of both diazenium salt hexachlorostibates and triflates and explained why we became interested in doing more research on the direct conversion of hydrazones to diazenium salts.

With the above in mind, we became interested in studying the use of hypervalent iodine (III) as oxidants for the direct conversion of phenyl hydrazones to diazenium salts. The following sections will introduce the successful development of this methodology.

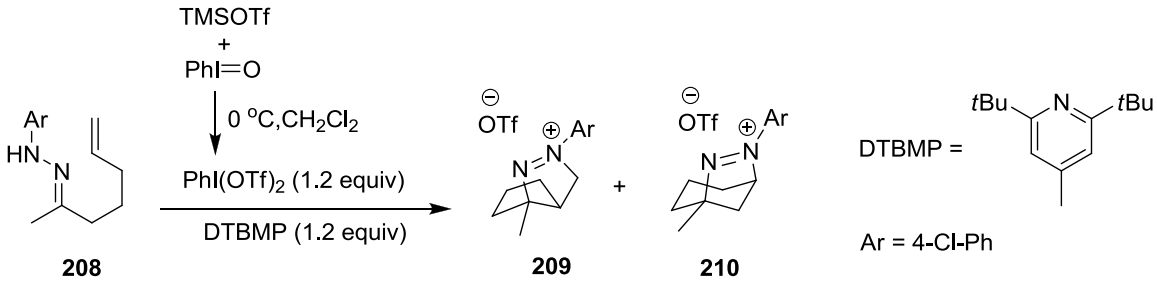
3.4.1. Initial Reaction Development

At the initial stages of developing the methodology of using iodine (III) as an oxidant to facilitate the cycloaddition reaction to form diazenium salts from hydrazones, iodosobenzene diacetate, $PhI(OAc)_2$ was our first choice of oxidant due to its stability and commercial availability. However, in view of Barton's results,[17] it is not surprising that treating hydrazone **208** (scheme 3.11) with $PhI(OAc)_2$ in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) did not provide any of the desired diazenium salt products. We decided to change the oxidant to $PhI(OTFA)_2$. Unfortunately, this latter reagent gave a complex mixture of products that did not contain any of the expected fused diazenium salt **209** (scheme 3.11), but did contain a small amount of bridged diazenium salt **210** that was observed in the NMR spectrum of the crude reaction mixture. We think it is possible that the fused diazenium salt did form, but since it is a more labile product, then degraded under the reaction conditions.

After obtaining these results we thought about taking into consideration the results obtained previously by the group when dimethyl sulfide ditriflate was used as oxidant for the intramolecular cycloaddition. It became clear to us then that the nucleophilicity of the counterion was a key factor for the success of the reaction. Because of these results we switched to use $PhI(OTf)_2$ as the oxidant and we were happy to

observe the formation of the desired diazenium salt mixture when treating hydrazone **208** with $PhI(OTf)_2$ (scheme 3.11).[23]

Scheme 3.11



The first step of developing this methodology was to master the preparation and handling of the reagent, $PhI(OTf)_2$. The preparation was a straight forward procedure starting from commercially available $PhI(OAc)_2$ which was treated with an aqueous solution of sodium hydroxide to obtain iodosobenzene, PhIO, as a nice fluffy yellow powder after aqueous workup and drying. Iodosobezene was stored on the shelf and no changes in its physical properties or reactivity were observed over time. As reported in the literature,[24] $PhI(OTf)_2$ was generated in situ by the addition of two equivalents of TMSOTf to a 0 ^oC solution of iodosobenzene at in dichloromethane (scheme 3.11). Once $PhI(OTf)_2$ was generated, a premixed solution of the hydrazone and a 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in CH_2Cl_2 was added to the reaction mixture at 0 ^oC and it was stirred for 30 minutes. We were pleased to see that ^{1}H-NMR data of the crude reaction mixture showed the formation of the desired product mixture of both diazenium salts in about 30% and the remaining 70% was the starting hydrazone.

3.4.2. Optimizing Reaction Conditions

With the previous result in hand that showed the partial conversion of a hydrazone to the desired diazenium salts, we decided to optimize the reaction conditions. Our first approach was increasing the equivalents of the $PhI(OTf)_2$ and DTBMP used. That did not result in much success and in fact in some cases, especially when the reaction was allowed to run for longer times, resulted in a decrease in the overall yield and the formation of an unidentified side product. The same can be said when triethyl amine was used as a base instead of DTBMP.

We next turned our attention on varying and optimizing the reaction temperature. We chose to do this because the outcome of dimethyl sulfide ditriflate mediated diazenium salt formation was highly dependent on the reaction temperature. Table 3.1 summarizes the results I obtained in a study that was aimed at optimizing the reaction temperature/time. It can be clearly seen from the data below that carrying out the reaction for longer periods of time did not have a positive improvement to the yield. In fact, a slight decrease in the yield was observed and the formation of an unidentified product was seen when the reaction was performed for longer times. A notable change in results was seen upon changing the procedure to adding the hydrazone/base mixture to $PhI(OTf)_2$ at -78 ^{o}C and then immediately concentrating the reaction mixture at room temperature. In this case the crude reaction mixture showed an increase in yield to 73% (experiment 6, table 3.1). A better conversion and yield was observed when the addition was done at -78 ^{o}C and reaction was immediately concentrated in a warm (40 ^{o}C) water bath (experiment 11, table 3.1). After few more experiments were performed, we found

that the best results were obtained upon applying the addition at -40 ^{o}C, immediately warm up the reaction mixture to 40 ^{o}C, and then concentrating the mixture (experiment 12, table 3.1). 1H-NMR analysis of this later experiment revealed that no starting material existed and a yield of 78% was recorded.

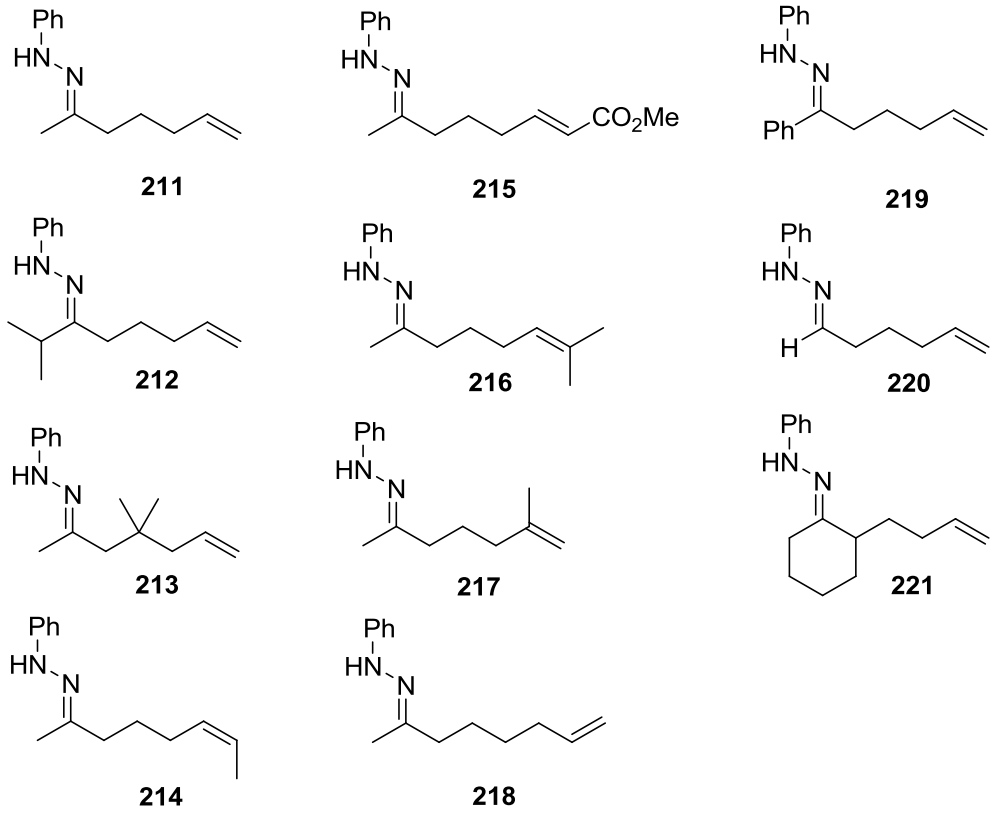
Table 3.3. Optimizing Reaction Temperature/Time

Experiment	Temperature (^{o}C)	Time (min)	Ratio of major d.s : s.m	Combined % Yeild
1	0	30	0.3 : 1	31
2	0	60	0.6 : 1	40
3	0	120	0.7 : 1	48
----------	----------	----------	----------	----------
4	-25	30	0.6 : 1	47
5	-25	60	0.5 : 1	43
----------	----------	----------	----------	----------
6	**-78**	**0**	**10 : 1**	**73**
7	-78	15	0.8 : 1	54
8	-78	30	0.7 : 1	51
9	-78	120	0.5 : 1	48
----------	----------	----------	----------	----------
11	-78 then 40	0	1 : < 0.05	75
12	**-40 then 40**	**0**	**1 : 0**	**78**

3.4.3. Assessing the Reaction Scope

It was important to us to uncover the applicability of the new methodology over different hydrazones and test the consistency of the optimized reaction conditions. For that purpose, we selected a group of hydrazones of different structural features as shown in figure 3.2. The choice of such hydrazones was based on our need to test the different steric and electronic effects on the outcome of the cycloaddition reaction. None of the ketone precursors for these hydrazones was commercially available, and in the next section I will describe the methods I used to prepare these starting materials.

Figure 3.2. Selected hydrazones for the study



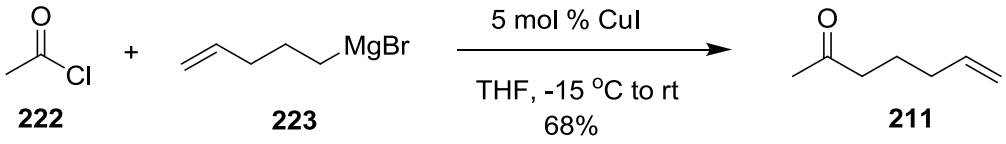
3.4.3.1 Synthesis of Ketone Starting Materials

Most of the ketone precursors were prepared and purified according to known literature procedures for similar compounds. However, our ketone targets generally had lower boiling points, which made it harder to purify them in good yields and methods of purification followed were selected carefully. These included either careful distillation of the crude reaction mixture at atmospheric pressure, or by silica gel chromatography using low boiling solvents as eluents.

*Synthesis of hept-6-ene-2-one (**211**)*

Hept-6-ene-2-one (**211**) was prepared following Gribkov's method via the copper catalyzed addition of pent-4-en-1-ylmagenesium bromide (**223**) to acetyl chloride (**222**) (scheme 3.12).[25] This method provided hept-6-ene-2-one in 68% yield after aqueous workup and distillation at atmospheric pressure.

Scheme 3.12

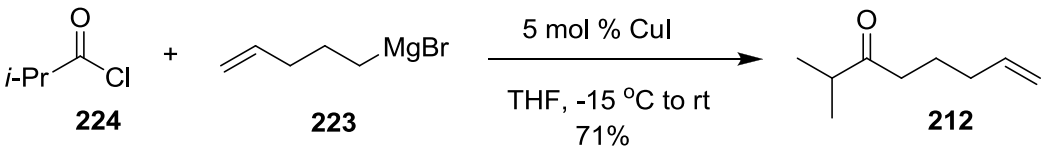


222 **223** **211**

*Synthesis of 2-methyl-oct-7-ene-3-one (**212**)*

Gribkov's method method was also used to prepare 2-methyl-oct-7-ene-3-one (**212**, scheme 3.13).

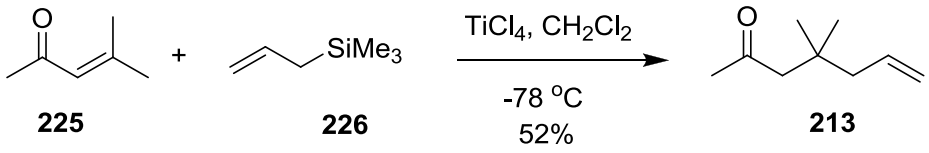
Scheme 3.13



*Synthesis of 4,4-gemdimethyl-hept-6-ene-2-one (**213**)*

4,4-gemdimethyl-hept-6-ene-2-one (**213**) was prepared and purified by another group member, Muhammad Irfan Javed, via the Sakurai reaction of mesityl oxide (**225**) and allyltrimethylsilane (**226**), which gave the desired ketone in 52% yield (scheme 3.14).[26]

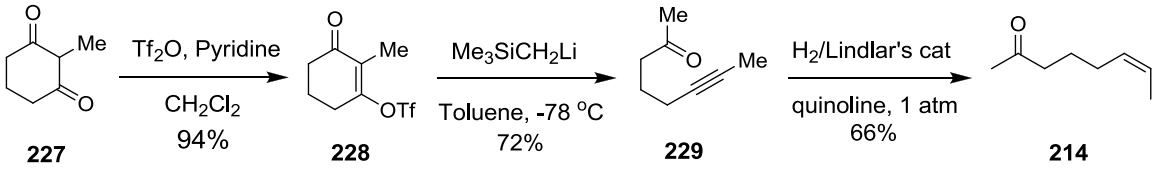
Scheme 3.14



*Synthesis of (Z)-oct-6-en-2-one (**214**)*

Ketone **214** was prepared using an efficient method (scheme 3.15) developed by Gregory B. Dudley.[27,28] Following the Dudley fragmentation, timethylsilylmethyl lithium was added to vinylogous triflate **228**, which was generated by the reaction of dimedone **227** with trifluoromethanesulfonic anhydride (triflic anhydride), forming oct-6-yn-2-one **229** in 72% yield. The alkyne product was then subjected to hydrogenation using Lindlar's catalyst to provide (*Z*)-oct-6-en-2-one (**214**) in 66% yield after distillation.

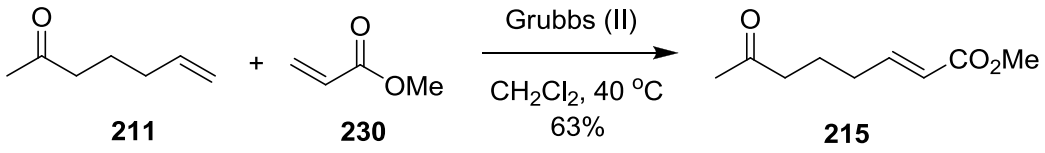
Scheme 3.15



*Synthesis of methyl(E)-7-oxo-2-octenoate (**215**)*

To make ketone **215**, I followed the Grubbs cross metathesis reaction procedure (scheme 3.16) between hept-6-ene-2-one (**211**) and ethyl acrylate (**230**) using Grubbs 2nd generation catalyst.[29] The reaction yielded ketone **215** in 63% yield after purification by silica gel chromatography.

Scheme 3.16

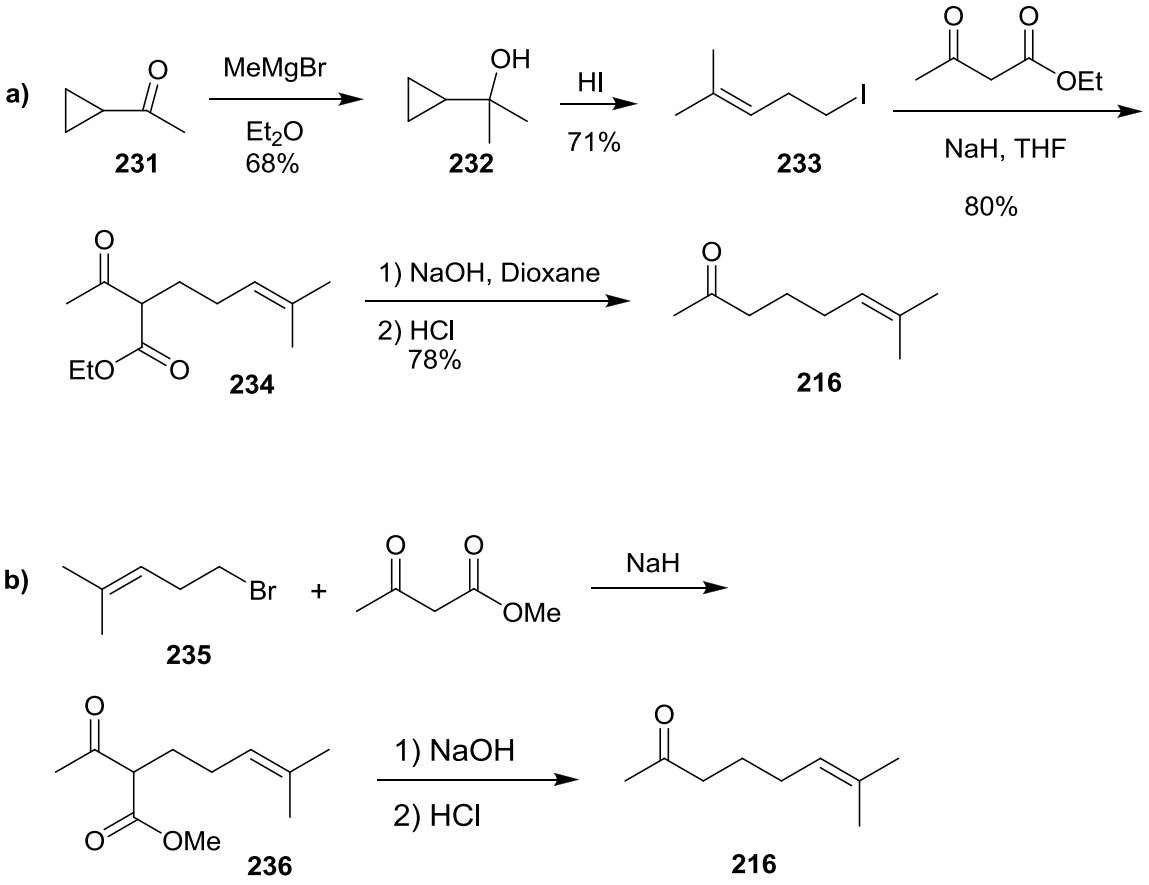


*Synthesis of 7-methyl-oct-6-ene-2-one (**216**)*

My first attempt to make ketone **216** is shown in scheme 3.17-a.[30,31] The first step involved adding methylmagnesium bromide to 1-cyclopropylethanone (**231**) to give 2-cyclopropylpropan-2-ol (**232**) in 68% yield. Treating alcohol **232** with aqueous hydroiodic acid produced iodide **233**, upon dehydration and subsequent rearrangement, in 71% yield. Iodide **233** was then used to alkylate ethylacetoacetate (80%) and the product (**234**) was then subjected to decarboxylation to give the final ketone **216** (78%). Although

this method provided the product, the route was lengthy, and gave low overall yield. I switched to using a shorter synthesis (scheme 3.17-b) starting from commercially available bromide **235**, which upon alkylation with methylacetoacetate and subsequent decarboxylation provided the desired ketone **216** in an overall yield of 59%.

Scheme 3.17

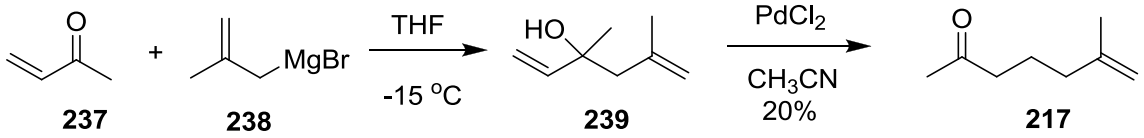


*Synthesis of 6-methyl-hept-6-ene-2-one (**217**)*

Ketone **217** was made and purified by Matthias Brewer using the method shown in scheme 3.18. In this method, methallylmagnesium bromide (**238**) was added to methyl

vinyl ketone (**237**) to give allylic alcohol (**239**), which then gave the desired ketone (**217**) in about 20% yield upon undergoing palladium catalyzed oxy-Cope rearrangement.[32]

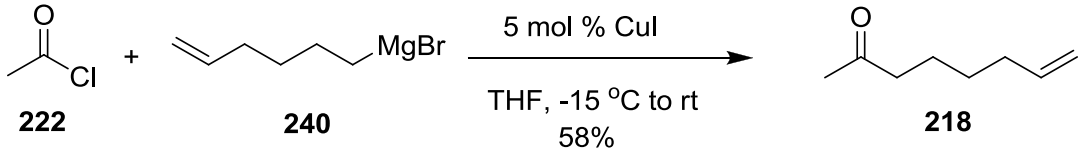
Scheme 3.18



*Synthesis of oct-7-ene-2-one (**218**)*

Oct-7-ene-2-one was prepared via the copper catalyzed addition of hex-5-en-1-ylmagenesium bromide (**240**) to freshly distilled acetyl chloride following Gribkov's method (scheme 3.19).[2] The desired ketone (**218**) was obtained in 58% yield after aqueous workup and distillation at atmospheric pressure.

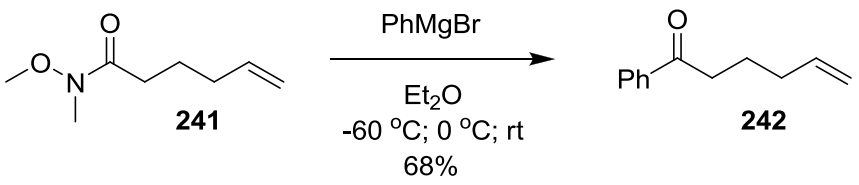
Scheme 3.19



*Synthesis of 1-phenyl-hex-5-ene-1-one (**219**)*

1-phenyl-hex-5-ene-1-one (**219**) was previously made by Muhammad Irfan Javed through the addition of phenylmagnesium bromide to Weinreb amide **241** (scheme 3.20) to give the product in 68% yield.

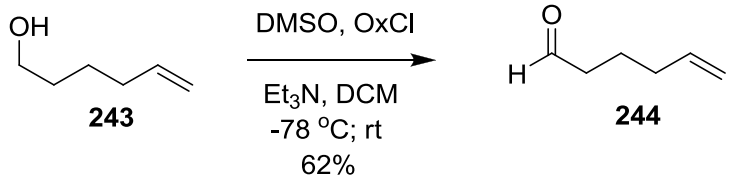
Scheme 3.20



*Synthesis of hex-5-enal (**220**)*

We were interested in examining the reactivity of the hydrazone resulting from aldehyde **244** (scheme 3.21) to undergo the cycloaddition reaction. This specific substrate has failed to from the α-chloroazo derivative in previous experiments performed by our group. For that purpose, aldehyde **244** was made by the Swern oxidation of hex-5-en-1-ol (**243**) to give the product in 62% yield after purification by silica gel chromatography.

Scheme 3.21

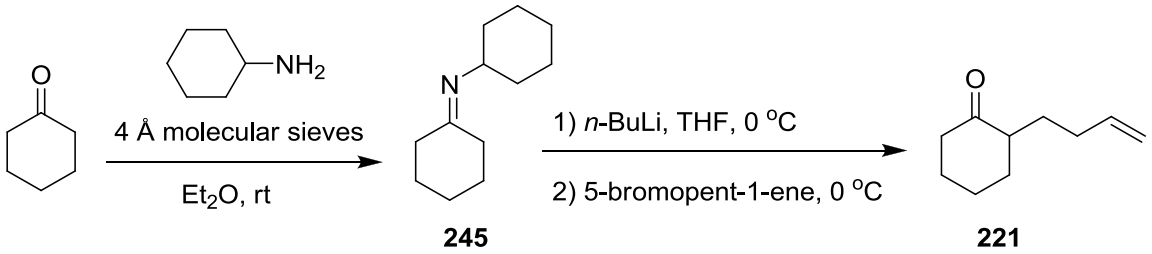


*Synthesis of 2-(but-3-enyl)cyclohexanone (**221**)*

Cyclic ketone **221** (scheme 3.22) was prepared to examine possible formation of tricyclic diazenium salts directly from cyclic hydrazones with a pendent alkene unit. This ketone was prepared by converting cyclohexanone to imine **246** which was then reacted

with *n*-butyllithium followed by the addition of freshly distilled 5-bromopent-1-ene.[34,35] Ketone **221** was isolated in 77% yield after purification by silica gel chromatography.

Scheme 3.22



3.4.3.2 Synthesis of Hydrazones

The cycloaddition reaction of hydrazones to diazenium triflate salts via $PhI(OTf)_2$ was performed using phenyl hydrazones. Before being used, phenyl hydrazine was filtered through a short plug of basic alumina then added to dry, oxygen-free, dichloromethane in a flame-dried flask containing molecular sieves under a nitrogen atmosphere. The desired ketone was then added at room temperature. The reaction was allowed to reflux for two hours. After completion, the reaction mixture was filtered through a short plug of basic alumina and the solvent was evaporated *in vacuo*. The resultant oil was used in the next step without any further purification.

3.4.4. Applying the New Methodology

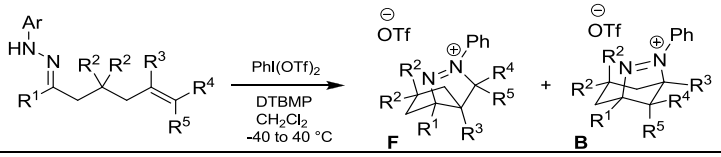
Before conducting a substrate scope study using the newly developed reaction conditions, there was one factor that was still unresolved: an accurate method to

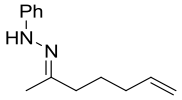
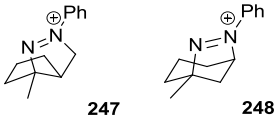
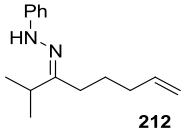
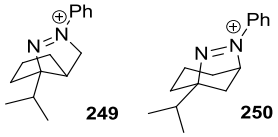
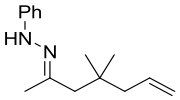
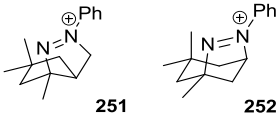
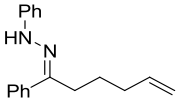
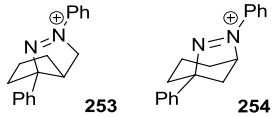
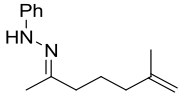
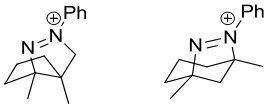
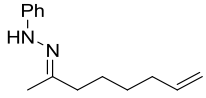
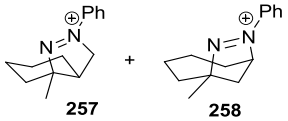
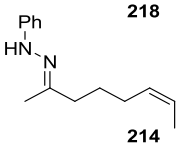
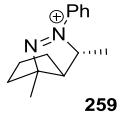
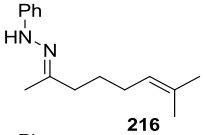
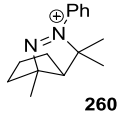
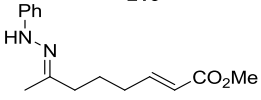
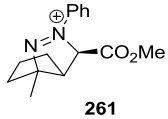
determine the reaction yield. The most accurate method we found was determining the yield by NMR versus an internal standard. After screening several standards, we chose 3,5-dinitrobenzonitrile, which provided distinct peaks far enough downfield that they did not overlap with characteristic peaks of the diazenium salts products. Other factors affecting our choice were the boiling point of the standard and its inertness. A summary of the results obtained by treating phenyl hydrazones with $PhI(OTf)_2$ is presented in table 3.2.[36]

From table 3.2, it can be seen that mono-substituted terminal olefins (entries 1-4) reacted smoothly and provided good yields of the product as a mixtures of fused and bridged bicyclic diazenium salts. In addition, diazenium salt **219** (entry 4), which was not accessible using any of the previous methods, was formed in 68% yield. It was not surprising to us that none of the expected diazenium salt products were formed when hydrazone **217** (entry 5) was reacted with $PhI(OTf)_2$. In previous work done in our group, we have seen that disubstituted terminal olefin **217** failed to produce any of the expected diazenium salts which is consistent with our observation in this work. When the tether length was increased by one carbon, we observed a significant decrease in the product yield (entry 6), where hydrazone **218** provided predominantly the bridged diazenium salt **258** in 22% yield. On the other hand, the case where a 1,2-disubstituted olefin was present, hydrazone **214** (entry 7) reacted easily to provide 5,5-fused diazenium salt **259** as a single diastereomer in 68% yield. Hydrazone **218** (entry 8), which contains a trisubstituted olefin, provided a low yield of 26% for the expected diazenium salt **260**. The effectiveness of the new methodology was also examined on a substrate that had an

electron deficient olefin (entry 9). The formation of none of the expected product can be attributed to the incompatibility of the hydrazone, containing an electron-withdrawing group on the olefin, with the reaction conditions. Previous work done by our group using dimethyl sulfide ditriflate as an oxidant showed a noticeable decrease in the yield when the same hydrazone was reacted.

Table 3.4. Yields for $PhI(OTf)_2$ mediated bicyclic diazenium salt formation

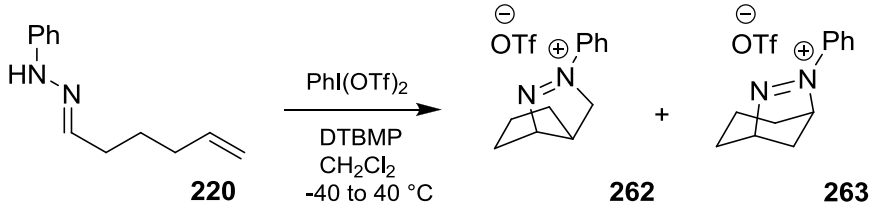


Entry	Hydrazone	Product	Yield (Ratio **F:B**)
1	 **211**	 **247** **248**	78% 1 : 0.4
2	 **212**	 **249** **250**	70% 1 : 0.1
3	 **213**	 **251** **252**	79% 1 : 0.1
4	 **219**	 **253** **254**	69% 1 : 0.4
5	 **217**	 **255** **256**	0%
6	 **218**	 **257** **258**	22% trace : 1
7	 **214**	 **259**	68%
8	 **216**	 **260**	26%
9	 **215**	 **261**	0%

Yield determined by NMR vs. an internal standard

An interesting result was observed when hydrazone **Y** (scheme 3.23), derived from hex-5-enal, gave a small amount (less than 20%) of the expected diazenium salt. This was not possible by previous methods; several attempts to form the α-chloroazo derivative and diazenium salt by our original methods were unsuccessful.

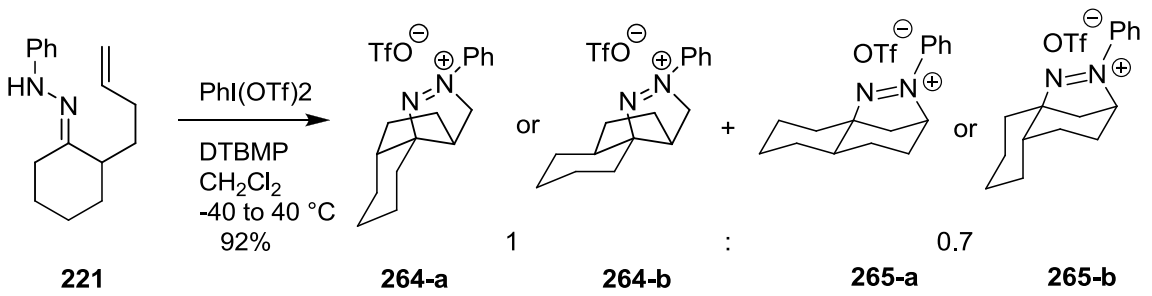
Scheme 3.23



220 **262** **263**

To discover more about this iodine mediated reaction, and about the chemistry of making diazenium salts in general, we decided to examine the formation of 6,5,5- and 6,6,5-tricyclic diazenium salts. An excellent result in terms of yield was obtained when hydrazone **221** (scheme 3.24) was reacted with $PhI(OTf)_2$ under the developed reaction conditions to give a mixture of both fused (**264-a** or **264-b**) and bridged (**265-a** or **265-b**) diazenium salts in 92% yield. The only piece of that reaction outcome that remained unresolved was figuring out which diastereomer of each regioisomer was present. Although, theoretically, one diastereomer of each pair would be entropically more favored, however there was no easy and convenient way to determine which.

Scheme 3.24



3.5. Summary

The goal of research conducted and explained in this chapter was to develop a new and more efficient method to synthesize diazenium salts. We successfully discovered a new method that involved a hypervalent iodine(III) reagent, $PhI(OTf)_2$, for the direct conversion of hydrazones to diazenium salts. $PhI(OTf)_2$ was a powerful oxidant for that purpose that was also mild. Compared to previous methods developed by the group, this method generally provided diazenium salts in higher yields than those provided by the use of dimethyl sulfide ditriflate.

References:

(1) Wyman, J.; Javed, M. I.; Al-Bataineh, N.; Brewer, M. *J. Org.Chem.* **2010**, *75*, 8078–8087.

(2) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1991**, *3*, 431-447.

(3) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*, VCH, New York, **1992**.

(4) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008,** *108*, 5299-5358.

(5) Wirth, T.; Ochiai, M.; Varvgolis, A.; Zhdankin, V. V.; Koser,G. F.; Tohma, H.; Kita Y.; *Topics in Current Chemistry: Hypervalent Iodine Chemistry/Modern Developments in Organic Synthesis*, pp. 1-248, 224. Springer-Verlag, Berlin, **2002**.

(6) Varvoglis, A., *Hypervalent Iodine in Organic Synthesis*, pp. 1-223, Academic Press, London, **1997**.

(7) Stang, P.; Zhdankin, V. V.; *Chem. Rev.* **1996**, *96*, 1123-1178.

(8) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427.

(9) Piancatelli, G.; Leonelli, F.; Do, N.; Ragan, *J. Org. Synth.* **2006**, *83*, 18.

(10) Moroda, A.; Togo, H. *Tetrahedron* **2006**, *62*, 12408.

(11) Pozzi, G.; Quici, S.; Shepperson, I. *Tetrahedron Lett.* **2002**, *43*, 6141.

(12) Vatele, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715.

(13) Vugts, D. J.; Veum, L.; al-Mafraji, K.; Lemmens, R.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Hanefeld, U.; Orru, R. V. A. *Eur. J. Org. Chem*. **2006**, 1672.

(14) Zhao, X.-F.; Zhang, C. *Synthesis* **2007**, 551.

(15) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Letters* **2002**, *44*, 57.

(16) Li, Y.; Hale, K. J. Org. Lett. **2007**, *9*, 1267.

(17) Barton, D. H. R.; Jaszberenyi, J. Cs.; Lui, W.; Shinada, T. *Tetrahedron*, **1996**, *52*, 14673.

(18) Barton, D. H.; Jaszberenyi, J. Cs.; Liu, W.; Shinada, T. *Tetrahedron*, **1996**, *52*, 2717.

(19) Barton, D. H. R.; Jaszberenyi, J. Cs.; Lebmann, K.; Timar, T. *Tetrahedron*, **1992**, *48*, 8881.

(20) Lutz, K. E.; Thomson, R. J. *Angew. Chem. Int. Ed.* **2011,** *50*, 4437-4440.

(21) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *Org. Lett.* **2009**, *11*, 465-468.

(22) Mundal, D. A.; Aventta, C. A. Jr.; Thomson, R. J. *Nat. Chem.* **2010**, *2*, 294-297.

(23) Al-Bataineh, N. Q.; Brewer, M *Tetrahedron Letters*, **2012**, *53*, 5411–5413.

(24) Zefirov, N. S.; Safravov, S. O.; Kaznacheev, A. A.; Zhdankin, V.V.; *Zh. Org. Khim.* **1989**, *25*, 1807-1808.

(25) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

(26) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

(27) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028.

(28) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499.

(29) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3171.

(30) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094.

(31) Hiranuma, S.; Shibata, M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 5321.

(32) Waser, J.; Gaspar, B; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

(33) Omura, K.; Swern, D. *Tetrahedron* **1978**, 11, 1651.

(34) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem*. **1983**, *48*, 2607.

(35) Carre, M. C.; Ndebeka, G.; Riondel, A.; Bourgasser, P.; Caubere, P. *Tetrahedron Letters* 1984, *25*, 1551.

(36) Al-Bataineh, N. Q.; M. Brewer *Tetrahedron Letters*, **2012**, *53*, 5411.

4. CHAPTER 4:

Unprecedented Reactivity of 1-Aza-2-azoniaallene Salts: Formation of Tetrahydropyridazine

4.1. Introduction

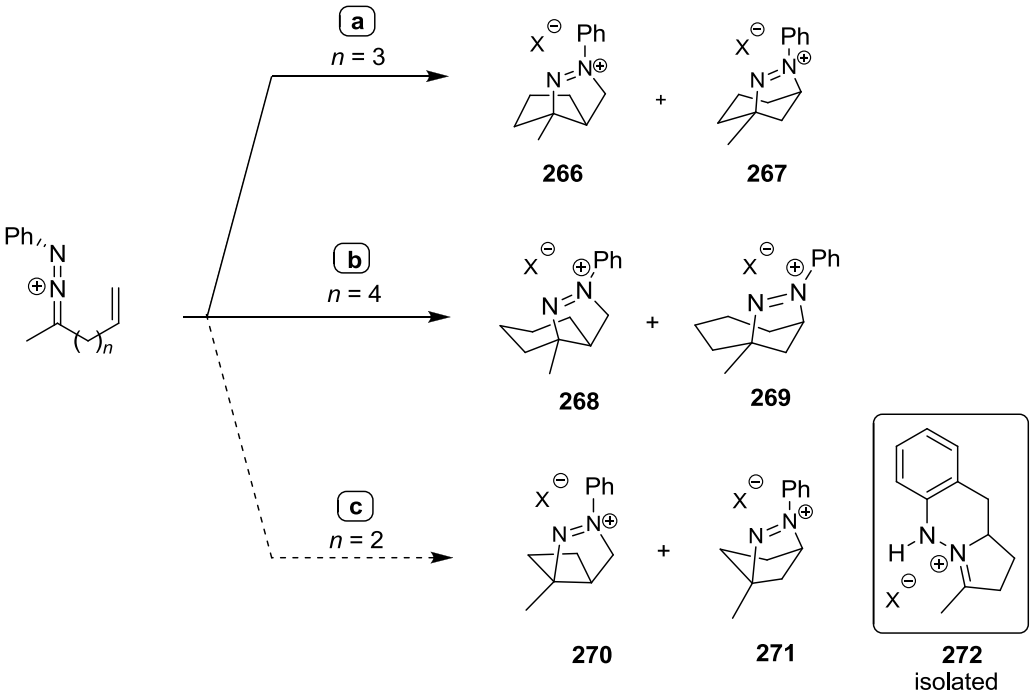
Previous chapters described extensive work done by our group towards the development of new synthetic methods for the preparation of bicyclic diazenium salts. The mechanism for this reaction is a [3+2] cycloaddition between a 1-aza-2-azoniaallene salt intermediate and a pendent alkene. We became interested in probing the reactivity of 1-aza-2-azoniaallene salts when the system is modified so that the heteroallene and alkene can not react by cycloaddition due to structural constrains. The following sections will introduce two main findings in our group that stems from recent research. These results include an unprecedented intramolecular polar [4$^{\oplus}$+2] cycloaddition of aryl-1-aza-2-azoniaallene salts leading to protonated azomethine imines, and an intramolecular C−H amination reaction of 1-aza-2- azoniaallene salts that provides pyrazoline products.

4.1.1. Intramolecular polar [4$^{\oplus}$+2] cycloaddition of aryl-1-aza-2-azoniaallene salts

Results obtained by previous work in our group showed that 5,5-fused diazenium salts formed as the major products when a 1-aza-2-azoniaallene center was connected to a pendent akene by a three carbon atom linker (scheme 4.1-a). When the number of carbon atoms was incresed to four, 5,7-bridged diazemium salts were the major products (scheme 4.1-b). However, when the number of carbon atoms was increased to five, no productive reaction occured. This latter observation is likely due to the increase in

degrees of freedom for the system which would prevent the reaction partners from aligning properly in the transition state to produce a productive overlap leading to the expected large ring diazenium salt. Based on these results, we became interested in examining how the system would behave when the tether was shortened to two carbon atoms. Theoretically, the expected products of the [3+2] cycloaddition would be the 5,4-fused diazenium salt (**270**) and/or the 5,5-bridged diazenium salt (**271**). Each one of these expected products would have a Baldwin-disfavored ring closure since the cycloaddition mechanism is asynchronous concerted and we were not surprised when none of the expected diazenium salts products were formed. Instead, a very interesting result was observed; a new compound was isolated and characterized as the protonated azomethine imine (**272**, scheme 4.1-c).

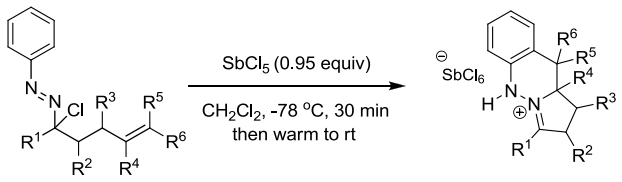
Scheme 4.1

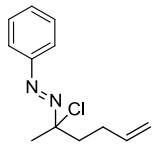
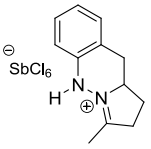
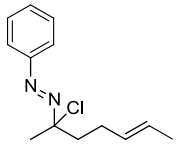
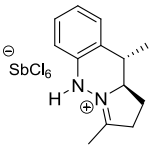
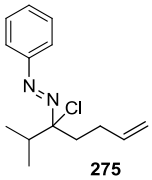
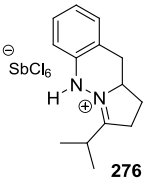
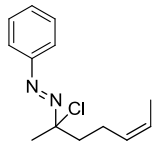
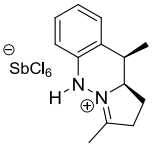
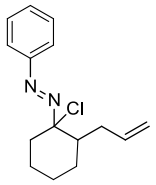
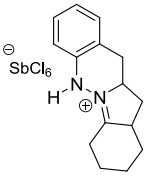
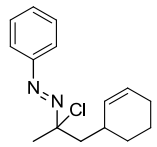
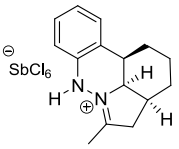
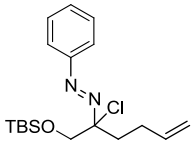
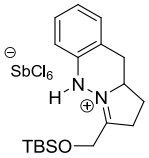
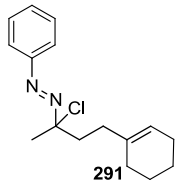
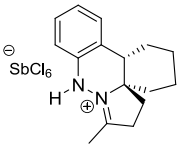
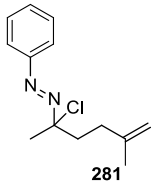
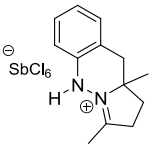
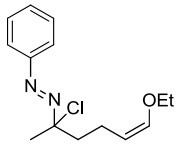
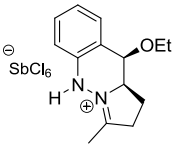
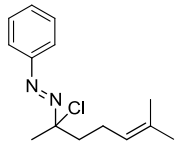
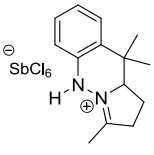
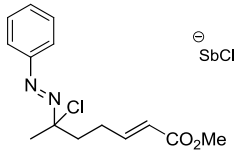
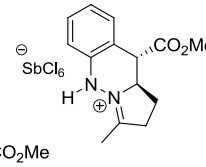


This unprecedented reactivity of a 1-aza-2-azoniaallene salt involves an intramolecular [4$^{\oplus}$+2] cycloaddition reaction and provided tricyclic azomethine imine (**272**) which contains a 1,2,3,4-tetrahydrocinnoline scaffold. Our group was able to build a wide library of compounds to both assess the scope of reaction and to gain better understanding of the reaction mechanism. Table 4.1 below shows examples of the protonated azomethine imine products which were formed mainly in very good to excellent yields. The stereospecificity retained (entries 7 and 8, table 4.1) in the cycloaddition reaction strongly suggests that it is a concerted process involving the 1-aza-2-azoniaallene center, the alkene, and the aryl ring.

Considering these results with the previous [3+2] cycloaddition results, we concluded that the intramolecular [3+2] cycloaddition leading to the formation of diazenium salts is probably more favorable than the corresponding [4$^{\oplus}$+2] cycloaddition leading to protonated azomethine imines. When the precursors of each reaction pathway are compared, the only difference is the tether length which determines how the orbitals will align in the transition state. However, longer tether length did not form any of the [4$^{\oplus}$+2] products which is why we concluded it was the less favorable pathway.

Table 4.1: Substrate scope of the [4⊕+2] cycloaddition reaction

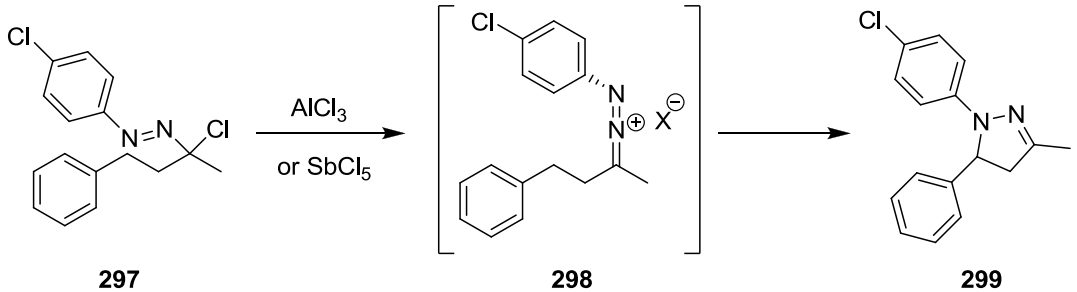


Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1	 **273**	 **274**	86	7	 **285**	 **286**	81
2	 **275**	 **276**	88	8	 **287**	 **288**	82
3	 **277**	 **278**	83	9	 **289**	 **290**	89
4	 **279**	 **280**	71	10	 **291**	 **292**	85
5	 **281**	 **282**	97	11	 **293**	 **294**	33
6	 **283**	 **284**	98	12	 **295**	 **296**	93

4.1.2. Intramolecular C−H Amination of 1-Aza-2- azoniaallene Salts

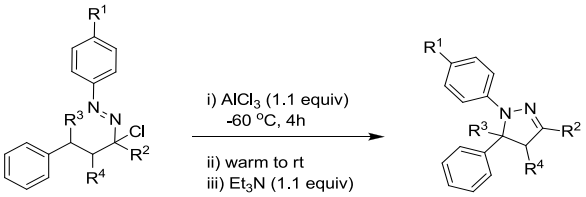
While the [4⊕+2] methodology described in the previous section was being developed, our group was also working on another interesting and unprecedented reactivity of 1-aza-2-azoniaallene salts. This work, undertaken by Daniel Bercovici, stemmed from our interest in examining the reactivity of 1-aza-2-azoniaallene salts in systems that lack a pendant alkene and therefore cannot participate in either of the cycloaddition reactions already known to us. For that purpose, a different heteroallene system, such as **298** (scheme 4.2) was considered. When α-chloroazo compound **297** was prepared and treated with $AlCl_3$ or $SbCl_5$, we were surprised to observe the formation of pyrazoline **299** in good yield. The substrate scope of this reaction was widely studied by Daniel and consistently good yields were observed as shown in table 4.2.[2] After performing mechanistic studies, Daniel's results were in support that the amination reaction proceeded through a concerted C−H insertion reaction of a singlet-state nitrenium ion intermediate. This finding by our group is considered as the first example in which a heteroallene reacts as a nitrene-like species to provide the product of an intramolecular C−H amination reaction.

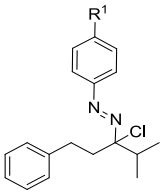
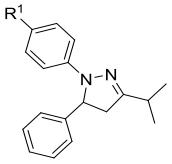
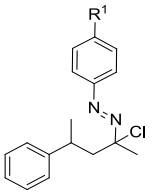
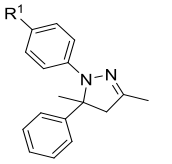
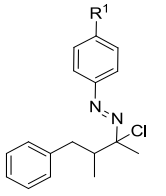
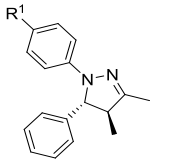
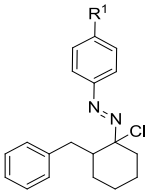
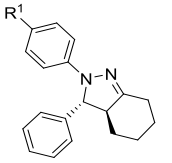
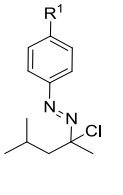
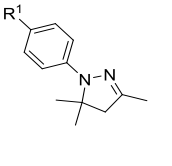
Scheme 4.2



297 **298** **299**

Table 4.2: Examples of substrate scope for C-H amination



entry	a-chloroazo	product	yield
1			
	300	**301;** R^1 = Cl	64
	302	**303;** R^1 = Me	79
2			
	304	**305;** R^1 = Cl	~6
	306	**307;** R^1 = Me	66
3			
	308	**309;** R^1 = Cl	12
	310	**311;** R^1 = Me	35
4			
	312	**313;** R^1 = Cl	44
	314	**315;** R^1 = Me	67
5			
	316	**317;** R^1 = Cl	59
	318	**319;** R^1 = Me	62

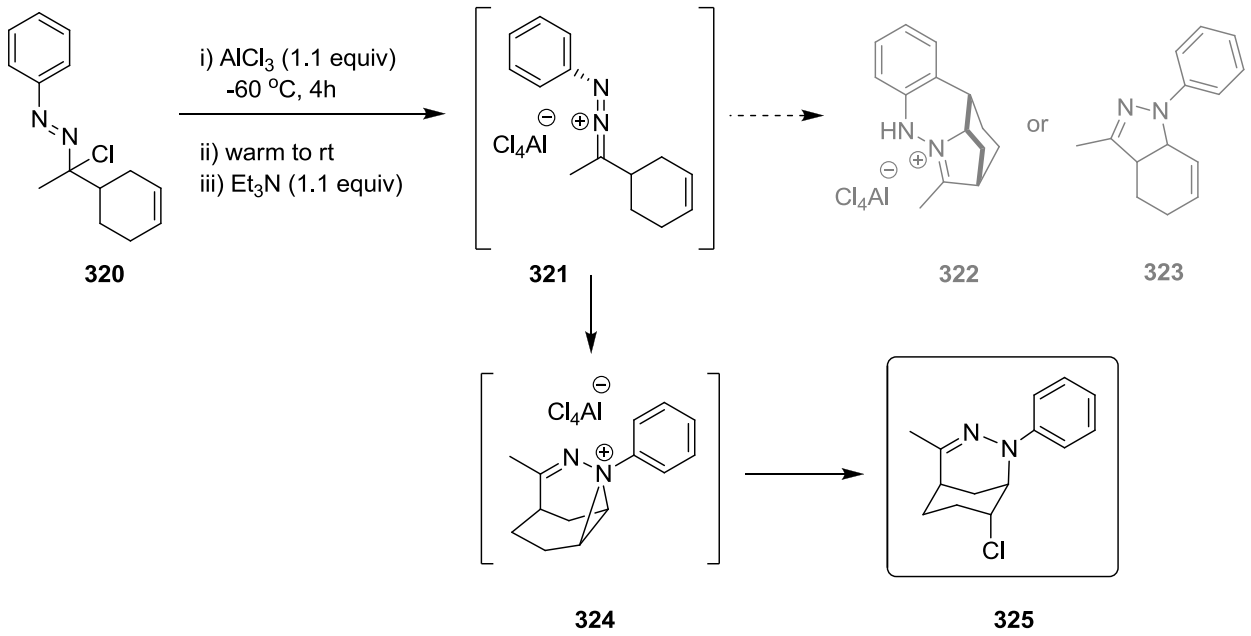
4.1.3 Discovery of New Reactivity: Chloro-amination Reaction

The results explained in the previous section inspired us to explore other systems to evaluate the reactivity of 1-aza-2-azoniaallene intermediate. At that point, our understanding was that C-H amination is a reaction that occurs in systems that cannot undergo either [3+2] cycloaddition or [4$^{\oplus}$+2] cycloaddition due to the absence of the tethered alkene. One experiment Daniel was interested in performing was to include an alkene tether in a ring while maintaining the same tether length required for the [4$^{\oplus}$+2] cycloaddition (i.e. two carbon atoms between the 1-aza-2-azoniaallene center and the alkene). In this case, the system would not undergo [4$^{\oplus}$+2] cycloaddition because it would be too strained to align properly, and we thought it might instead undergo C-H amination at the allylic center to form a pyrazoline product. For that purpose, Daniel prepared α-chloroazo compound **320** (scheme 4.3) and reacted it with $AlCl_3$. After aqueous workup, none of the expected products **322** or **323** were formed, but a very clean transformation was observed to have occurred based on the ^{1}H-NMR spectra of the crude reaction mixture. After purification and full characterization of the product, we confirmed the formation of tetrahydropyridazine **325** as the product of an unprecedented chloroamination reaction. We believe that the product was formed by the formation and subsequent opening of aziridinium intermediate **324**.

After obtaining these results, we planned on studying this latter reactivity in more detail to assess the scope of this transformation and to gain more data to confirm the proposed mechanism involving the formation of the aziridinium intermediate. Table 4.3

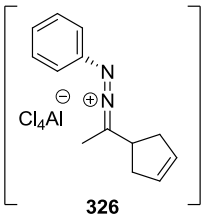
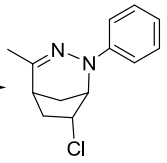
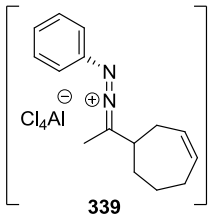
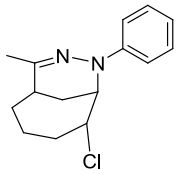
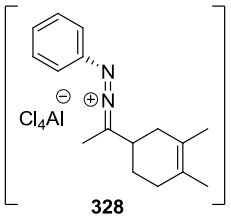
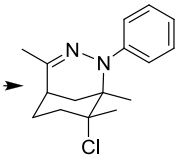
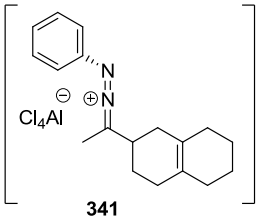
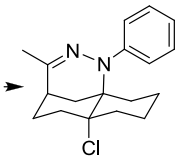
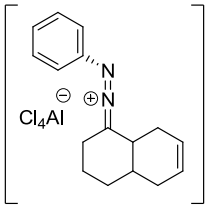
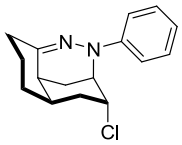
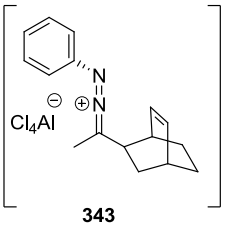
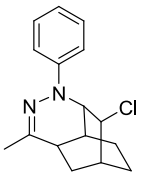
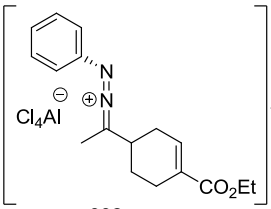
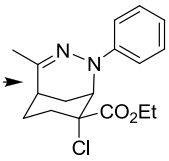
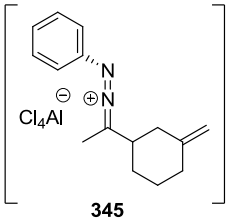
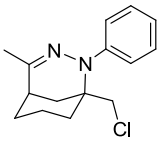
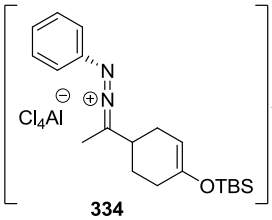
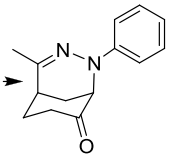
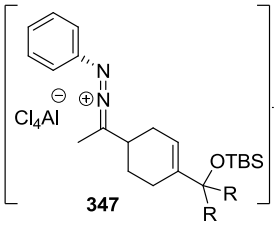
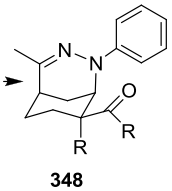
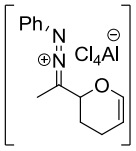
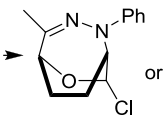
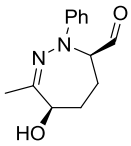
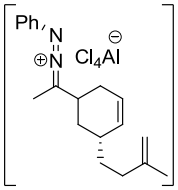
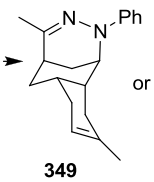
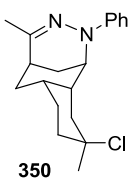
shows examples of heteroallenes we planned on generating and the corresponding hypothesized tetrahydropyridazine products that would form as a result.

Scheme 4.3



The heteroallenes proposed in table 4.3 could be generated from the reaction of α-chloroazo precursors with a halophilic Lewis acid, and $AlCl_3$ was our choice for this study as a less toxic reagent that gave better results. The ketone starting materials were prepared through different procedures depending on the structural complexity. In the following sections, I will first present the synthesis of the ketone starting materials, followed by the preparation of the corresponding phenyl hydrazones.

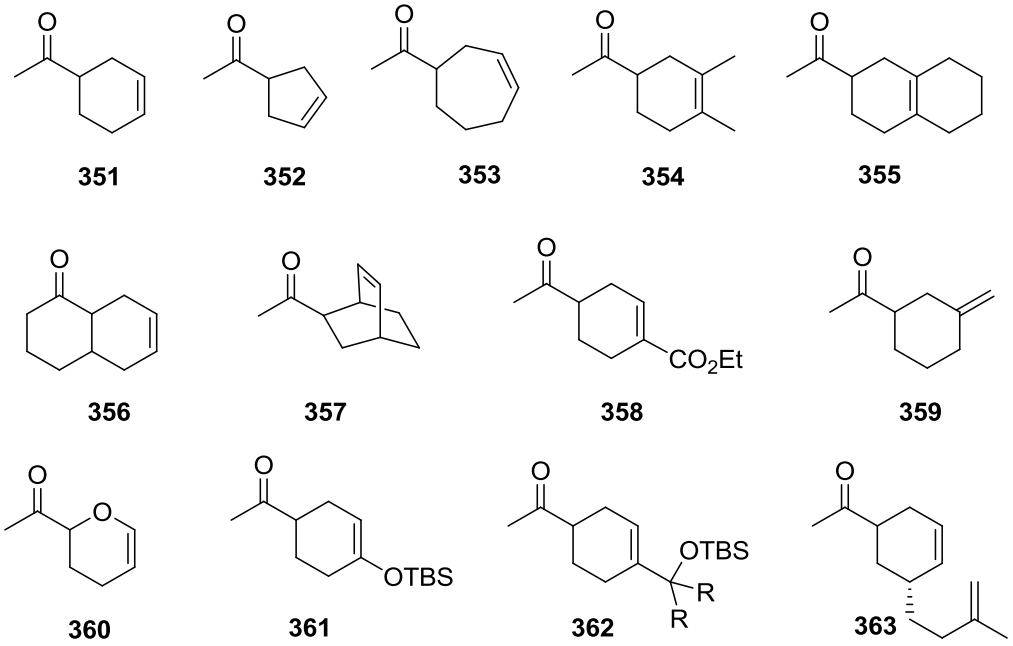
Table 4.3: Proposed heteroallene systems and expected products

Heteroalene	Expected product	Heteroalene	Expected product
 **326**	 **327**	 **339**	 **340**
 **328**	 **329**	 **341**	 **342**
 **330**	 **331**	 **343**	 **344**
 **332**	 **333**	 **345**	 **346**
 **334**	 **335**	 **347**	 **348**
  or  **336** **337** **338**		  or  **349** **350**	

4.2. Synthesis of Ketone Starting Materials

Our criteria for selecting substrates was to assess the scope of reaction in terms of alkene structure. Figure 4.1 below shows the targeted ketone starting materials which were not commercially available and I will show how they were synthesized and purified.

Figure 4.1

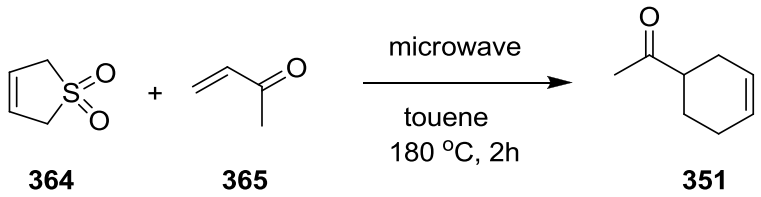


*Synthesis of 1-(cyclohex-3-enyl)ethanone (**351**)*

1-(cyclohex-3-enyl)ethanone (**352**) was initially prepared by an undergraduate student in our group, Andrew Spaulding, following a Diels-Alder reaction procedure described in scheme 4.4 below.[3] The reaction between sulfolene (**364**), or butadiene sulfone, with methyl vinyl ketone, or MVK, (**365**) was carried out in the microwave and

I followed the same procedure to synthesize ketone **351** on larger scale. Ketone (**351**) was isolated in 71% yield after purification using silica gel chromatography.

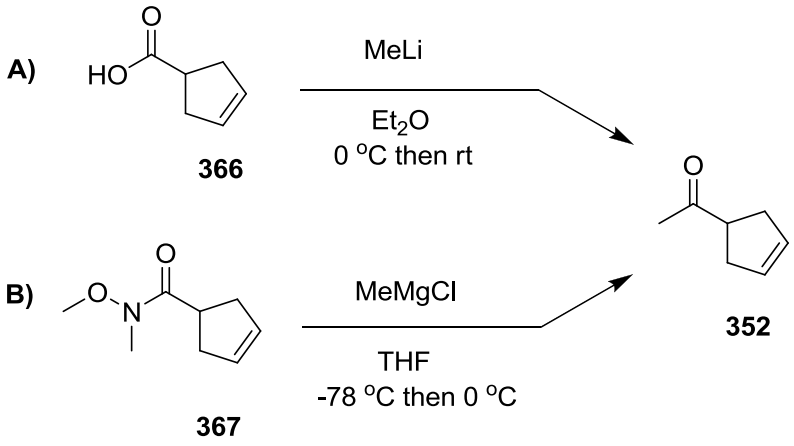
Scheme 4.4



*Synthesis of 1-(cyclopent-3-enyl)ethanone (**352**)*

1-(cyclopent-3-enyl)ethanone (**352**) was prepared by two methods as shown in scheme 4.5. Method **A** involved treatment of commercially available acid **366** with methyllithium and gave ketone **352** only in 32% yield after purification using silica gel chromatography.[4] An alternative method (**B**) gave the desired ketone in 68% yield by reacting Weinreb amide **367** with methylmagnesiumchloride.

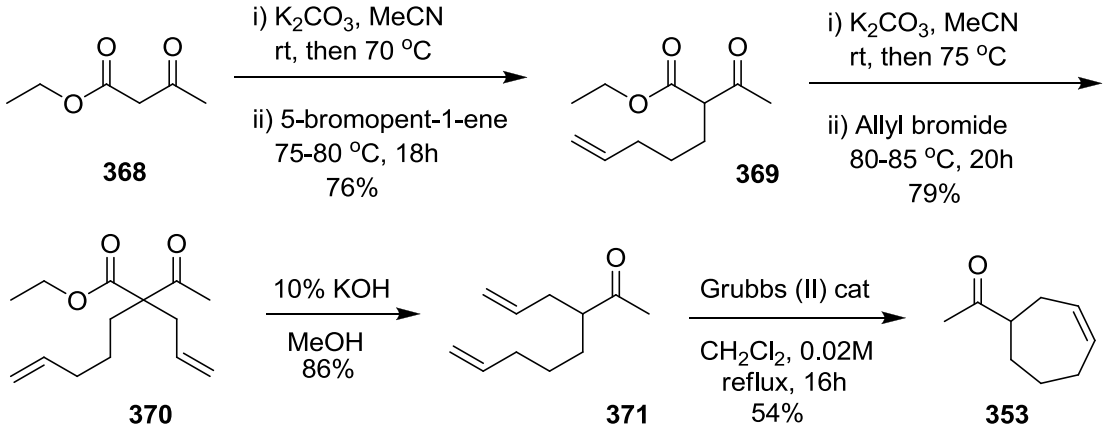
Scheme 4.5



*Synthesis of 1-(cyclohept-3-enyl)ethanone (**353**)*

1-(cyclohept-3-enyl)ethanone (**353**) was prepared according to the sequence of reactions shown in scheme 4.6. The first two steps involved the sequential alkylation of keto ester **368** to generate compound **370**.[5,6] The order of these two steps was an important factor for the success of the second alkylation. After several attempts of starting with addition of allyl bromide as the cheaper material, I switched to adding 5-bromopent-1-ene first and got considerably higher yields for the second alkylation with allyl bromide. Subsequent decarboxylation and ring closing metathesis provided the desired ketone **353** in 54% yield after purification using silica gel chromatography. It is worth noting that maintaining a concentration of 0.02M was important for the success of ring closing metathesis reaction.

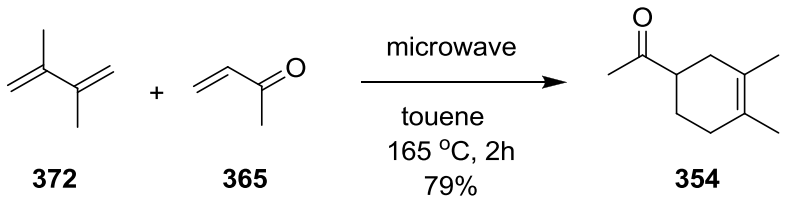
Scheme 4.6



*Synthesis of 1-(3,4-dimethylcyclohex-3-enyl)ethanone (**354**)*

1-(3,4-dimethylcyclohex-3-enyl)ethanone (**354**) was prepared by a simple Diels-Alder reaction (scheme 4.7) between commercially available 2,3-dimethly-1,3-butadiene (**372**) and MVK. The reaction proceeded in a microwave reactor and gave ketone (**354**) in 79% yield after purification by silica gel chromatography.

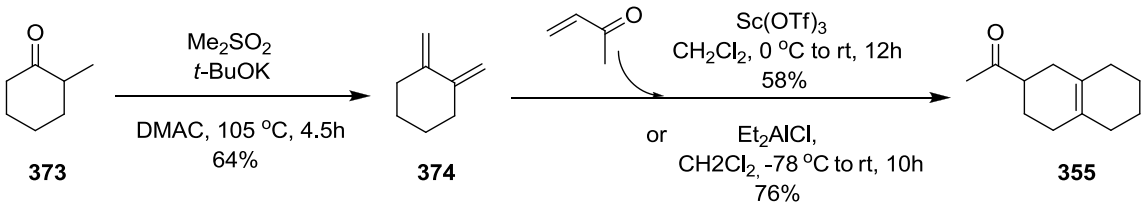
Scheme 4.7



*Synthesis of 1-(1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethanone (**355**)*

Ketone **355** was prepared through the reaction sequence shown in scheme 4.8.[7,8] Diene **374** was prepared by treating 2-methylcyclohexanone with methylsulfonylmethane and potassium tert-butoxide in dimethylacetamide (DMAC). Distillation of the product gave low yields, but more success was achieved when the purification was done using silica gel chromatography with straight hexanes as the eluent which gave the diene product in 64% yield. The desired ketone product (**355**) was obtained by the Diels-Alder reaction of diene **374** with methyl vinyl ketone in the presence of catalytic amount of scandium triflate, which gave the product in 58% yield after purification using silica gel chromatography.[9] In another procedure, diethyl aluminum chloride was used as a catalyst which was a cleaner transformation and gave a higher yield (76%).

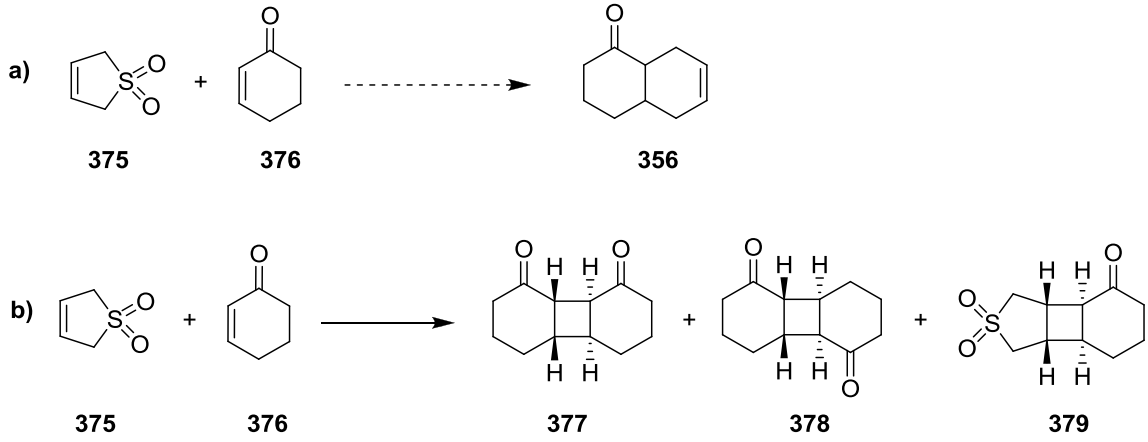
Scheme 4.8



*Synthesis of 3,4,4a,5,8,8a-hexahydronaphthalen-1(2H)-one (**356**)*

We unsuccessfully attempted the synthesis of ketone (**356**) several times following the same reaction procedure (scheme 4.9-a) used for the synthesis of 1-(cyclohex-3-enyl)ethanone (**351**) above. All efforts failed and after doing more literature research, I discovered that this combination of reagents would result in the formation of other products as shown in scheme 4.9-b.[9] We decided not to invest more time on making this ketone since its synthesis would require more steps and it was not a high priority.

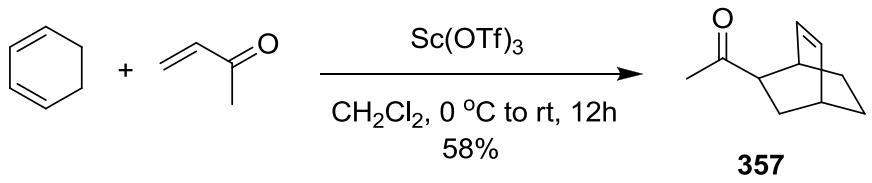
Scheme 4.9



*Synthesis of 1-((1R,4R)-bicyclo[2.2.2]oct-5-en-2-yl)ethanone (**357**)*

Ketone **357** was successfully prepared in a smooth Diels-Alder reaction between commercially available 1,3-cyclohexadiene and methyl vinyl ketone in the presence of a catalytic amount of scandium triflate (scheme 4.10**)** to afford the desired product in 88% yield after purification using silica gel chromatography.[10]

Scheme 4.10

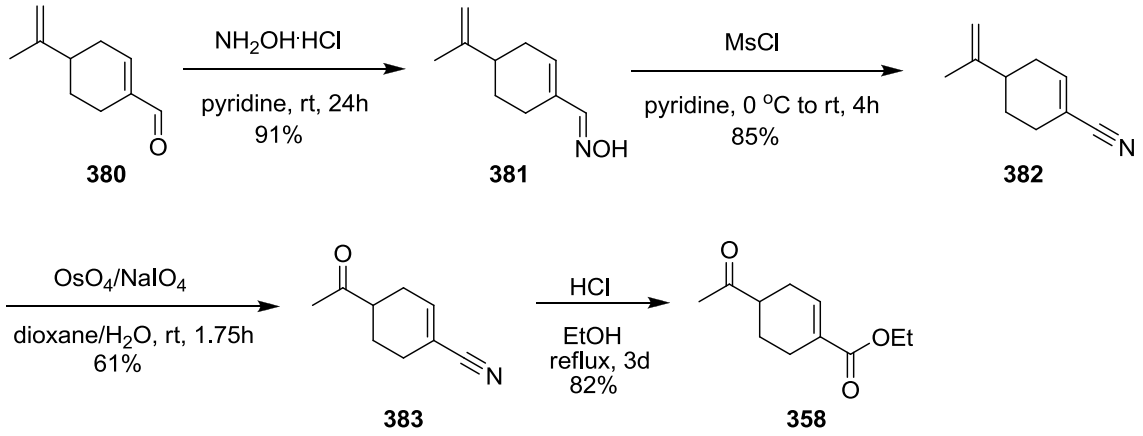


357

*Synthesis of ethyl 4-acetylcyclohex-1-enecarboxylate (**358**)*

Ethyl 4-acetylcyclohex-1-enecarboxylate (**358**) was prepared via the reaction sequence shown in scheme 4.11. Commercially available aldehyde **380** gave oxime **381** in 91% yield. Subsequent conversion to nitrile **382** occured in 85% yield, and selective Lemieux–Johnson oxidation of alkene **382** to ketone **383** was successfully done in 61% yield by using OsO4/NaIO4 as the oxidant.[11] The reaction was monitored by TLC and ^{1}H-NMR until the desired alkene was fully oxidized. The last step involved the Pinner reaction to convert nitrile **383** to ester **358** in 82% yield.

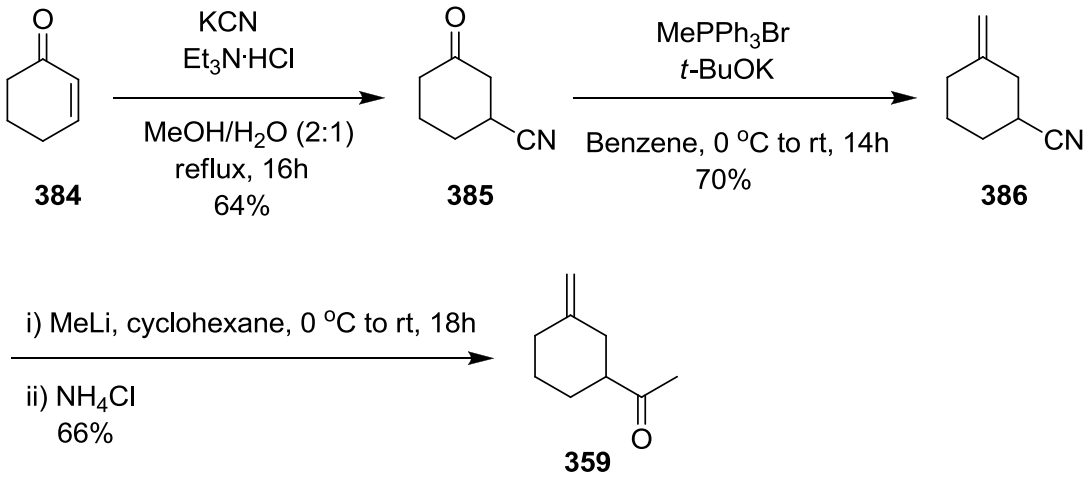
Scheme 4.11



*Synthesis of 1-(3-methylenecyclohexyl)ethanone (**359**)*

The method used for the synthesis of 1-(3-methylenecyclohexyl)ethanone (**359**) is shown in scheme 4.12. Cyclohexanone was converted to nitrile (**385**) in 64% yield via 1,4-additon using potassium cyanide,[12] and a Wittig reaction converted ketone **385** to alkene **386** in 70% yield.[13] In the last step of this synthesis, nitrile **386** was reacted with MeLi which gave ketone **359** in 66% yield after aqueous workup and purification using silica gel chromatography.[14]

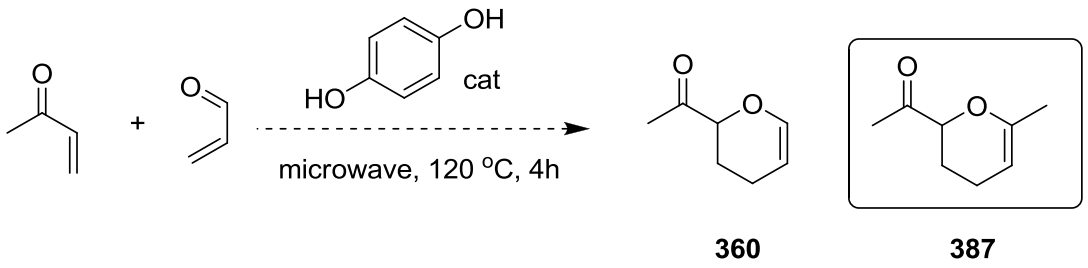
Scheme 4.12



*Synthesis of 1-(3,4-dihydro-2H-pyran-2-yl)ethanone (**360**)*

For the synthesis of ketone **360**, I tried to react methyl vinyl ketone and acrylaldehyde (acrolein) in a Diels-Alder reaction in the presence of a catalytic amount of *p*-hydroquinone (scheme 4.13). The isolated major product was 1-(6-methyl-3,4-dihydro-2H-pyran-2-yl)ethanone (**387**, 36% yield) which resulted from self hetero-Diels-Alder reaction of methyl vinyl ketone. Since this ketone is very similar to **360**, I decided to use it instead for my studies.

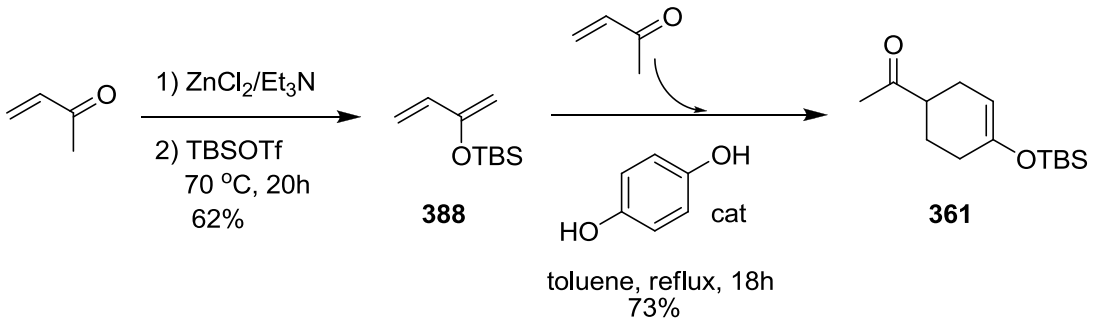
Scheme 4.13



*Synthesis of 1-(4-(tert-butyldimethylsilyloxy)cyclohex-3-enyl)ethanone (**361**)*

Ketone **361** was prepared through a Diels-Alder reaction between diene **388** and methyl vinyl ketone (scheme 4.14). Diene **388** was synthesized by reacting methyl vinyl ketone with zinc chloride/triethylamine co-catalyst followed by the addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) which gave the desired product in 62% yield after distillation at reduced pressure.[15] Diene **388** was then reacted with methyl vinyl ketone in the presence of catalytic amount of *p*-hydroquinone to provide the desired ketone **361** in 73% yield after purification by silica gel chromatography.[16]

Scheme 4.14



4.3. Applying the Methodology

4.3.1 Formation of Hydrazones and α-Chloroazo Compounds

The ketone starting materials described in section 4.2 were converted to the corresponding hydrazones and α-chloroazo compounds following the same standard procedures described in Chapter 2. The majority of these ketones underwent smooth conversion to the corresponding hydrazones and α-chloroazo compounds with a few exceptions that will be mentioned in the following sections. Table 4.4 summarizes the successful formation of hydrazones and α-chloroazo compounds and their corresponding yields.

4.3.2. Reaction of α-Chloroazo compounds with $AlCl_3$

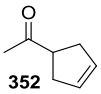
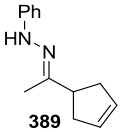
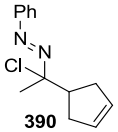
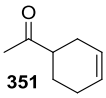
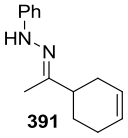
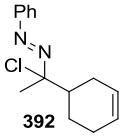
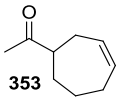
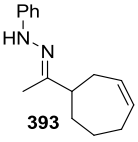
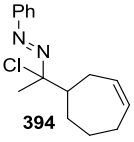
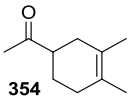
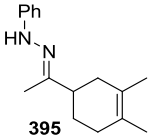
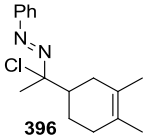
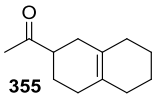
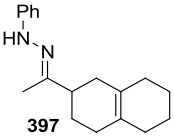
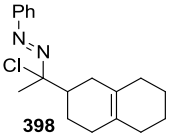
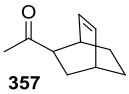
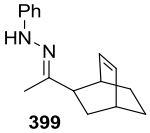
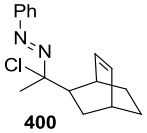
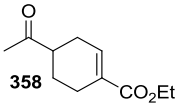
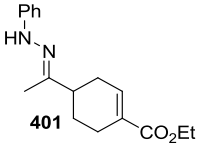
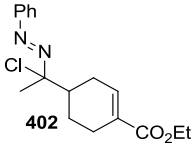
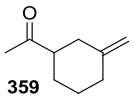
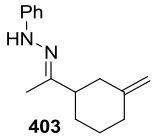
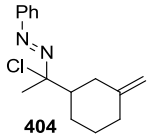
The α-chloroazo compounds were reacted with $AlCl_3$. The procedure was to simply cool a suspension of $AlCl_3$ in CH_2Cl_2 to -78 ^oC followed by a drop wise addition of the α-chloroazo precursor and then allow the reaction to warm to room temperature. Aqueous workup followed by purification using silica gel chromatography was performed in all cases except for one that will be noted in a later discussion.

4.3.2.1 Chloroamination and Formation of Tetrahydropyridazine

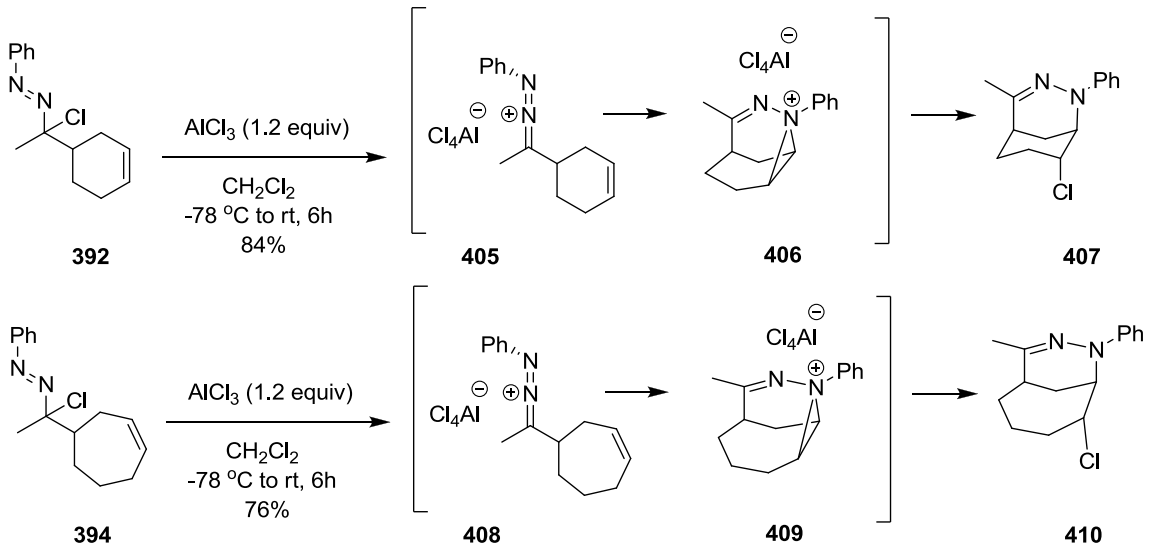
The first preliminary result obtained by our group was a chloroamination reaction of heteroallene **405** to form tetrahydropyridazine product **407** (scheme 4.15). We decided to first examine the effect of the size of the ring containing the alkene. The seven-

membered ring heteroallene **408** successfully formed tetrahydropyridazine product **410** in 76% yield after purification (scheme 4.15).

Table 4.4: Formation of hydrazones and α-chloroazo compounds

entry	ketone	hydrazone	% yield	α-chloroazo	% yield
1	 **352**	 **389**	80	 **390**	72
2	 **351**	 **391**	84	 **392**	80
3	 **353**	 **393**	98	 **394**	92
4	 **354**	 **395**	81	 **396**	72
5	 **355**	 **397**	82	 **398**	67
6	 **357**	 **399**	91	 **400**	68
7	 **358** CO_2Et	 **401** CO_2Et	73	 **402** CO_2Et	62
8	 **359**	 **403**	78	 **404**	87

Scheme 4.15

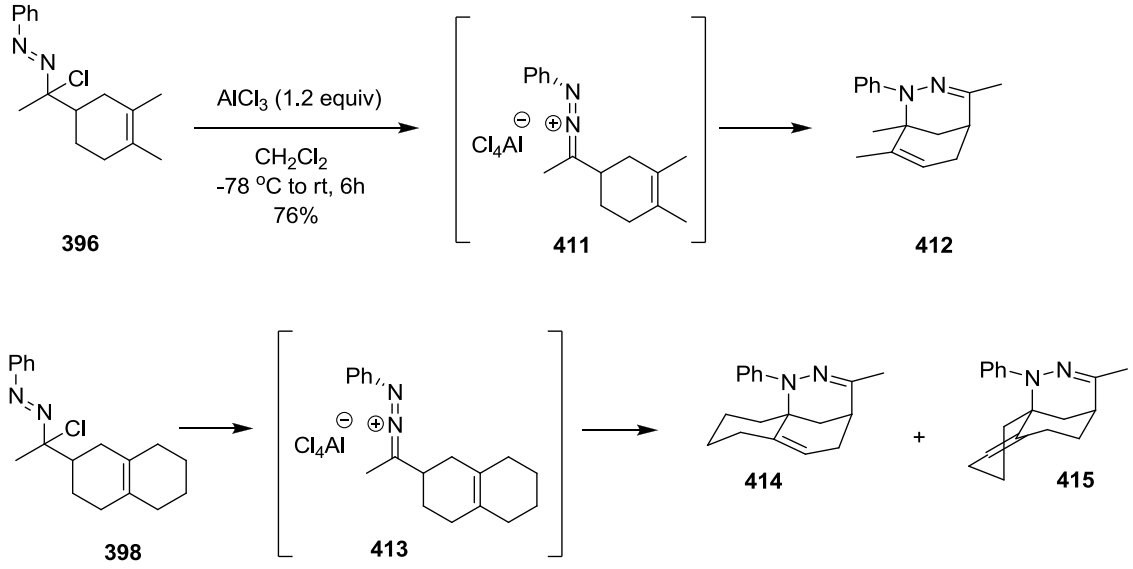


4.3.2.2. Elimination and Formation of Tetrahydropyridazine

Heteroallenes, such as **411** (scheme 4.16), which contain tetrasubstituted alkenes also formed tetrahydropyridazine products, but without chlorine addition. Instead a new alkene formed as a result of elimination. This is probably due to steric hindrance preventing the chloride anion from opening the aziridinium ring intermediate via S_N2-like displacement. Instead deprotonation occurs at the adjacent carbon forming a new alkene. The possibility of forming the chloro- tetrahydropyridazine product that could then undergo elimination upon aqueous workup was overruled since. Previous examples containing unsubstituted alkenes resulted in chloro- tetrahydropyridazine products and no elimination was observed. However, when heteroallene **413** reacted under the same conditions, I was able to see characteristic peaks in the ^{1}H-NMR of the crude reaction

mixture that correspond to chloro-tetrahydropyridazine which disappeared upon purification using silica gel chromatography.

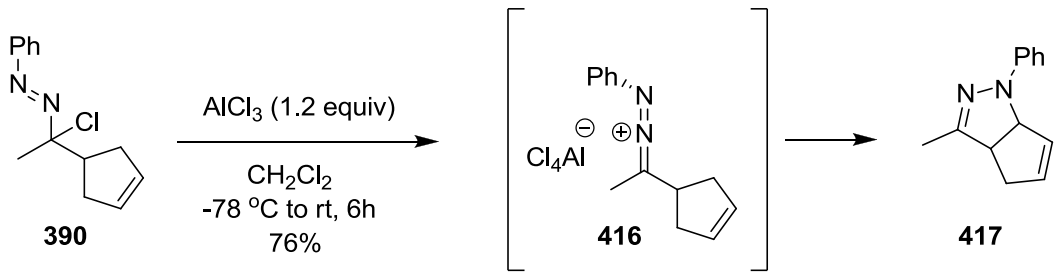
Scheme 4.16



4.3.2.3. Formation of Pyrazoline

The examples illustrated so far show the formation of tetrahydropyridazine products. In all previous examples, the alkene is in a six or seven-membered ring system. We became interested in examining the reactivity when the alkene is contained in a five-membered ring. When heteroallene **416** (scheme 4.17) reacted, a clean transformation occurred but no tetrahydropyridazine was observed by ^{1}H-NMR of the crude reaction mixture. After purification, the product was fully characterized and determined to be pyrazoline **417** that was formed in 69% yield. In this case, insertion at the allylic position occured.

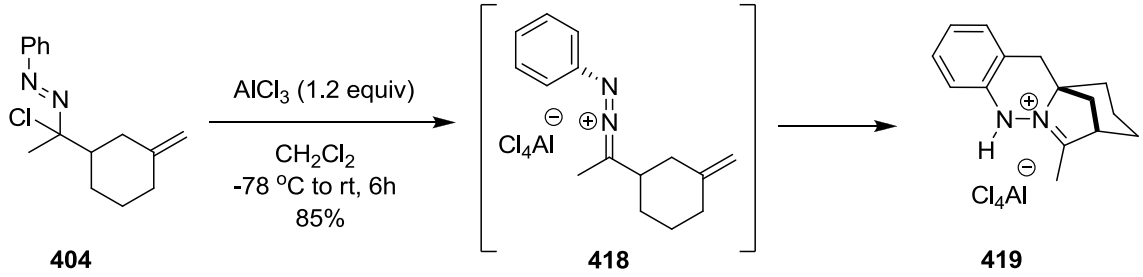
Scheme 4.17



4.3.2.4. Formation of Protonated Azomethine Imine

Heteroallene **418** (scheme 4.18), which contains an alkene as an exo-cyclic methylene group did not give the expected tetrahydropyridazine product on workup. ^{1}H-NMR of the crude reaction taken without performing aqueous workup showed only four aromatic protons present instead of five and we decided to triturate the product mixture with diethyl ether. The product was characterized as the protonated azomethine imine **419**, which was formed in 85% yield.

Scheme 4.18



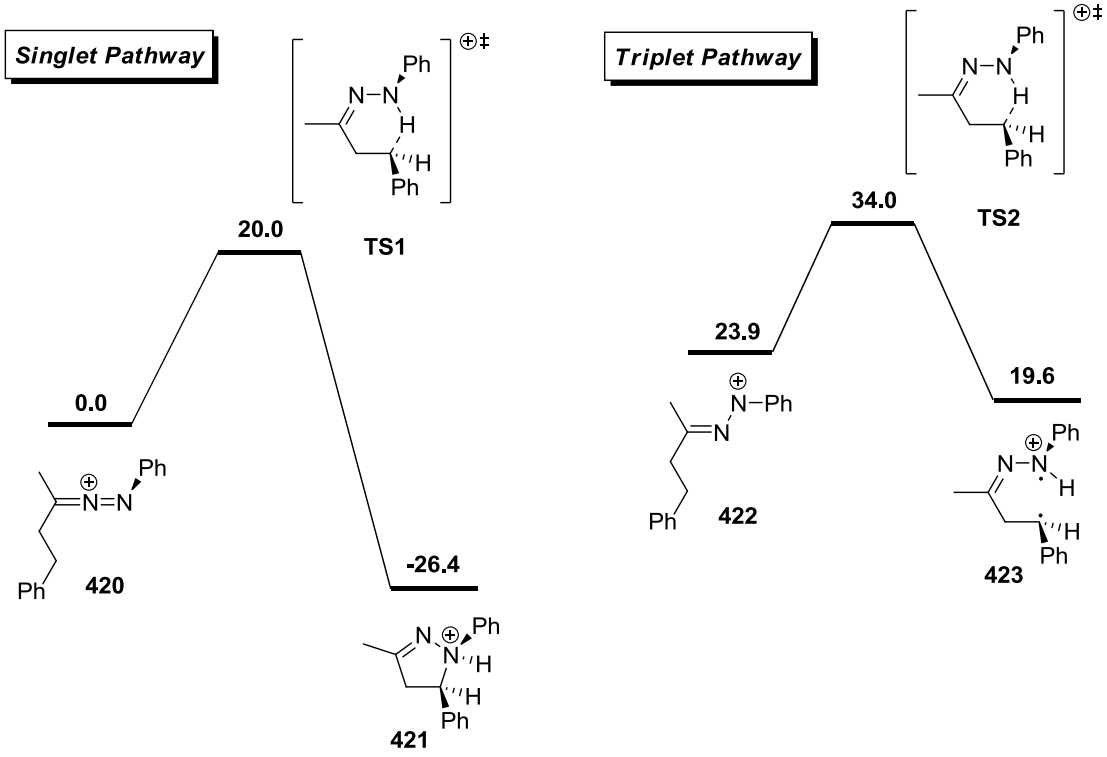
4.3.2.5. Computational Studies

To better understand why 1-aza-2-azoniaallene intermediate undergo different reactions that are controlled by the tether length and the overall structure of the heteroallene, we needed a better understanding of the underlying mechanisms. For that purpose, our group collaborated with professor Kendall Houk's group at UCLA to perform computational studies to explain these results.

Our experimental results for the C-H amination reaction supported a hypothesis that the reaction occurs through a concerted C−H insertion of a singlet-state nitrenium ion intermediate rather than a radical reaction of a triplet-state nitrenium ion-type intermediate. To confirm this hypothesis, Dr Xin Hong and Matthias Brewer numerically determined the transition state energies of each reaction pathway. Figure **4.2** shows the 1-aza-2-azoniaallene cation (**420**) they used to model the insertion reaction mechanism. Both the transition states and the free energy changes for the singlet and triplet pathways were determined. Starting with singlet cation **420**, the C−H amination can proceed through transition state **TS1** that has a free energy barrier of 20.0 kcal/mol to give **421**. In this pathway, the requirement is orbital overlap between the LUMO of the heteroallene and the HOMO of the benzylic C−H bond. If this is the case then a hydride abstraction by the heteroallene occurs first to form the N−H bond and benzyl carbocation. The benzyl carbocation can then form a C−N bond by electron-pair donation from nitrogen to give the insertion product. In an alternative pathway, heteroallene **420** can undergo a spin transition and form triplet diradical **422** that can undergo a C-H amination reaction

through a triplet pathway. Since triplet **422** was found to be less stable than singlet **420** by 23.9 kcal/mol, the singlet pathway would be much more favorable.[17]

Figure 4.2



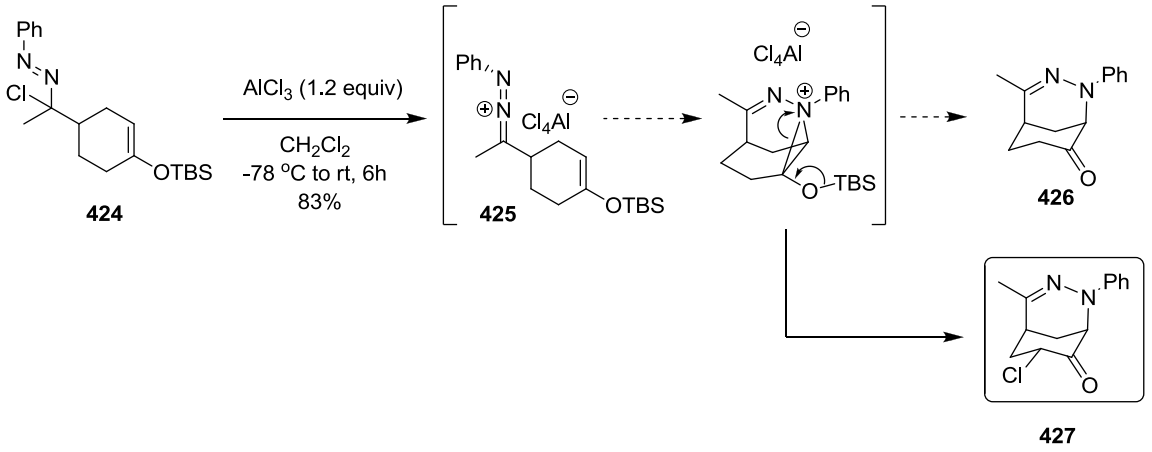
In addition, initial computational data were consistent with our proposed mechanism that tetrahydropyridazine are formed from 1-aza-2-azoniallene through the formation and subsequent opening of aziridnium ring intermediate.

4.3.2.6. Systems Containing Enol Ethers and Allylic Ethers

An interesting result was observed when, what we thought was, α-chloroazo compound **424** (scheme 4.19) reacted with $AlCl_3$ under the optimized reaction

conditions. The expected product of the reaction was ketone **426** which would form based on the reaction mechanism shown in scheme 4.19. However, the ^{1}H-NMR contained an unexpected signal at 4.4 ppm. The compound was fully characterized and all data was in support of structure **427**. It was not easy to determine whether or not the additional chlorine atom was present in the starting α-chloroazo because the ^{1}H-NMR spectrum of **424** was complicated because the sample was a mixture of diastereomers. However, under the Lewis acid mediated cyclization reaction conditions, it did not seem possible to form product **427** starting form α-chloroazo compound **424**.

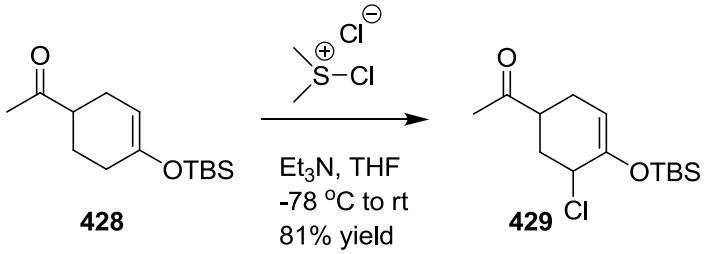
Scheme 4.19



Since this was our first time trying to form an α-chloroazo from a hydrazone that contained a protected enol ether, we decided to run a control experiment to evaluate the compatibility of such systems with chlorodimethylsulfonium chloride (scheme 4.20), and we subjected the ketone starting material to the same oxidation conditions. This control experiment confirmed the addition of chlorine under the reaction conditions; chlorinated

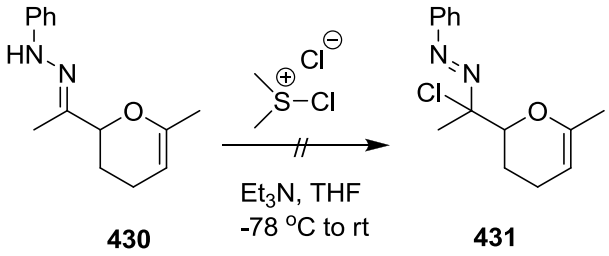
product **429** was formed. This was consistent with other examples reported in the literature where ketones, particularly ones with a high proportion of the enol form, can undergo α-chlorination using a stoichiometric amount of activated DMSO.[18-20]

Scheme 4.20



A similar result was observed when hydrazone **430** (scheme 4.21) was reacted with chlorodimethlysulfonium chloride. Trying this reaction several times did not form the desired product and from ^{1}H-NMR data we concluded that the enol functional group had reacted instead.

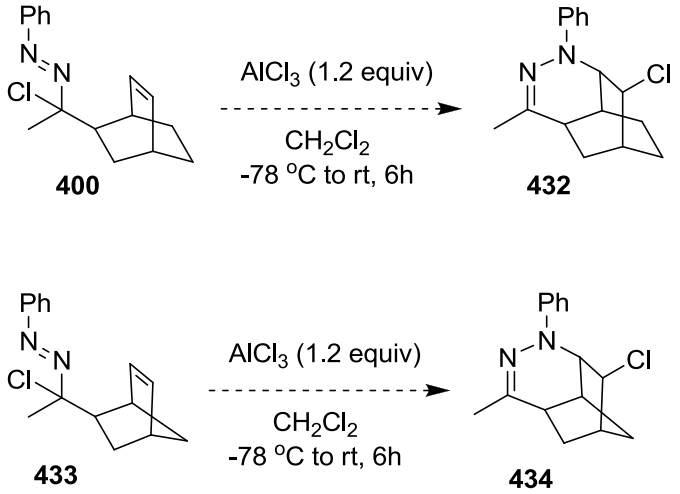
Scheme 4.21



4.3.2.7 Heteroallene Systems that Failed to React Productively

We were interested in testing the ability of other heteroallene systems that have different electronic and structural properties to undergo the chloroamination reaction. For example, we prepared α-chloroazo compounds **400** and **433** (scheme 4.22) and subjected them to the chloroamination conditions. None of these resulted in a clean transformation giving instead a complex mixture that did not contain the expected products.

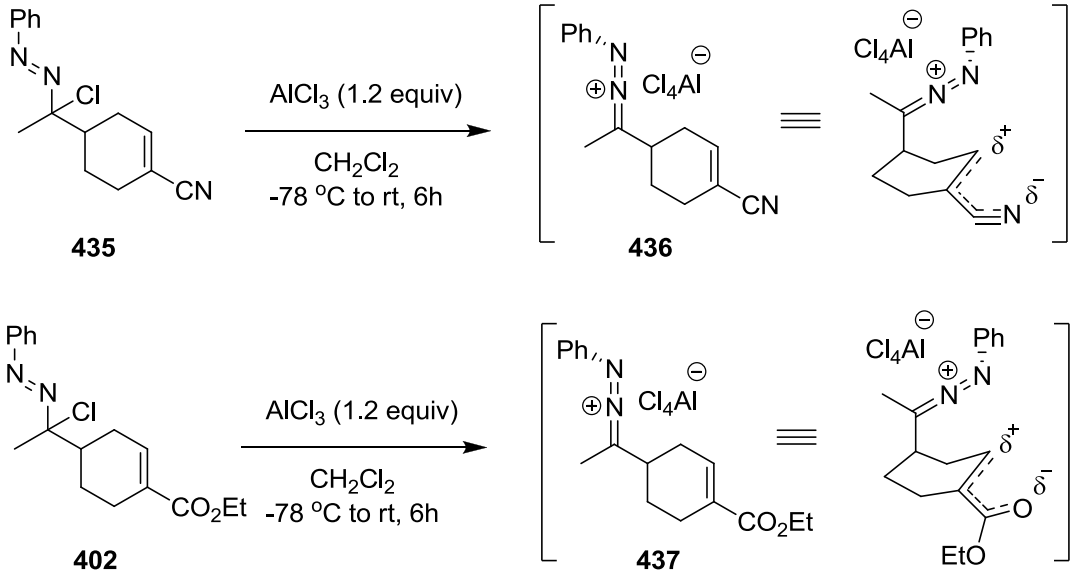
Scheme 4.22



We were also interested in determining what effect an electron-withdrawing group on the pendent alkene would have on the course of the reaction. For that purpose, α-chloroazo compound **435** (scheme 4.23) was prepared and subjected to reaction with $AlCl_3$ under the optimized reaction conditions. In this case, only the ketone starting material was recovered after aqueous workup. We concluded that α-chloroazo compound **435** did not react and upon aqueous workup was hydrolyzed to give the ketone starting

material. Since the Lewis-basic nitrogen of the nitrile group could possibly interact with $AlCl_3$, we tried doubling the equivalents of the Lewis acid but that did not change the outcome. We then decided to prepare α-chloroazo compound **402** that contains a different electron-withdrawing group on the alkene but the same result was observed upon reaction with $AlCl_3$. We concluded that in the presence of an electron-withdrawing group, the alkene may be too electron poor to participate in forming the aziridinium ring intermediate, which would not in turn form the expected product.

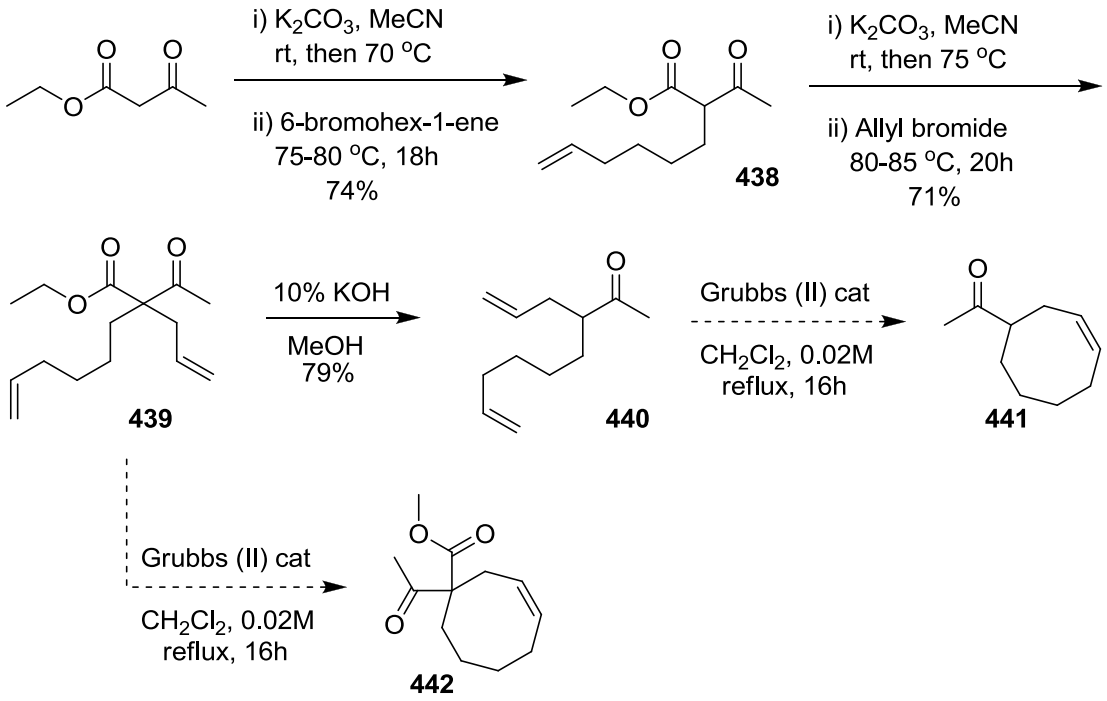
Scheme 4.23



The standard unsubstituted ring systems studied so far reacted by insertion for the case five-membered ring heteroallene, and chloroamination for six-membered ring and seven-membered ring heteroallenes. We became interested in studying the reactivity of eight-membered ring heteroallene. For that purpose, a procedure to prepare the eight-membered ring ketone starting material was followed similar to one used before to

prepare the seven-membered ring (scheme 4.24). However, the ring-closing metathesis step never worked as planned and either formed the dimeric product at low dilution or no reaction at high dilution. We tried doing the metathesis step before decarboxylation to take advantage of the Thorpe-Ingold effect to enhance the chances for productive cyclization, but that also did not work.[21,22]

Scheme 4.24

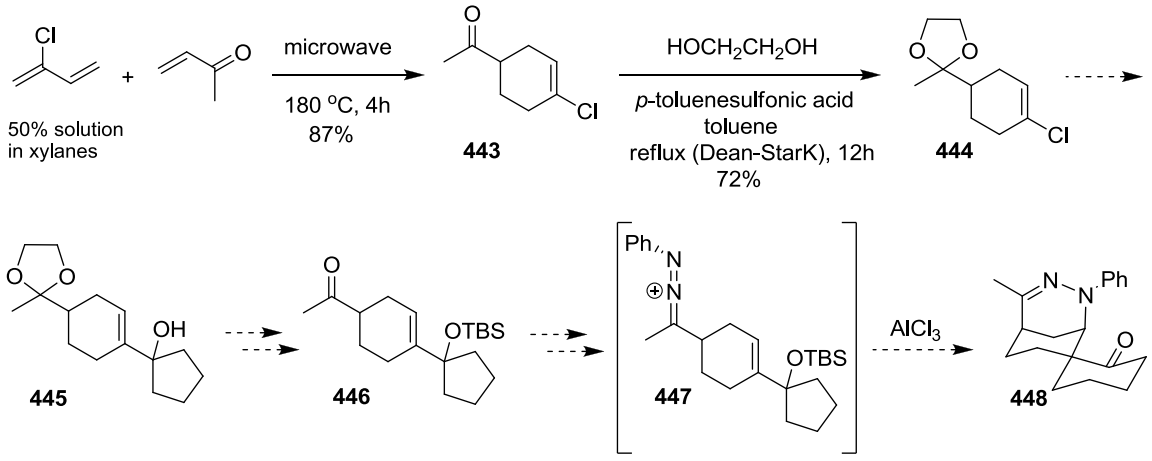


After looking more closely at the literature, we found that this specific problem had been observed for the first time in 1995 by Grubbs and co-workers,[23] and was found not to be trivial at all. The initial study established that the direct cyclization of simple acyclic dienes to give eight-membered rings did not take place, even at high dilution, and afforded only dimeric products resulting from intermolecular metathesis reactions.

Further studies confirmed that similar systems did not result in a ring-closing metathesis reaction that led to the expected eight-membered rings.[24-26]

Heteroallene **447** (scheme 4.25) was another system we were interested in studying. This could potentially undergo an alkyl shift leading to ketone **448**. For that purpose, we decided to synthesis heteroallene **447** starting from ketone **443**. Our proposed approach to synthesize ketone **446** is shown in scheme 4.25. At this point, the synthesis of ketone **446** has not been completed and will probably require an alternative plan because attempts to form an organometallic reagent from chloride **443** have failed.

Scheme 4.25

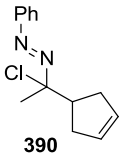
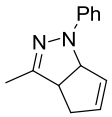
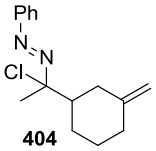
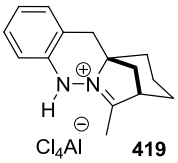
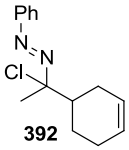
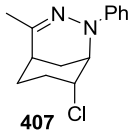
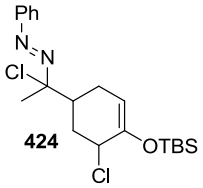
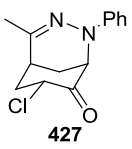
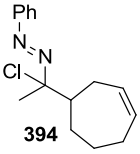
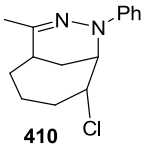
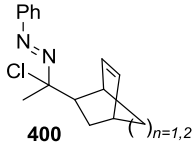
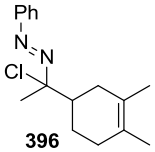
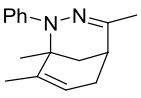
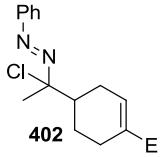
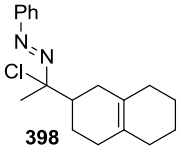
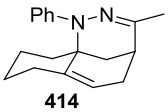
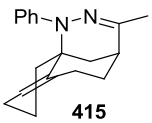
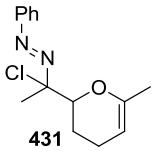


4.4. Summary

We discovered a new reactivity for 1-aza-2-azoniaallene intermediates to form tetrahydropyridazines. This reaction likely occurs through the formation and subsequent opening of an aziridinium ring intermediate. With the aid of Dr. Xin Hong and professor

Kendall Houk we have began to understand the different modes of reactivity for 1-aza-2-azoniaallene intermediates. The results so far demonstrate that the observed reactivity is determined by structural constrains and electronic properties of the pendent alkene as well as the transition state energy changes during the formation of the products. Table 4.5 summarizes the results for different heteroallene systems studied and product yields.

Table 4.5: Summary of results

entry	α-chloroazo	product	yield	entry	α-chloroazo	product	yield
1	 **390**	 **417**	69	7	 **404**	 **419**	85
2	 **392**	 **407**	84	8	 **424**	 **427**	83
3	 **394**	 **410**	76	9	 **400**	--	--
4	 **396**	 **412**	72	10	 **402** E= CN, CO_2Et	--	--
5	 **398**	 **414**  **415**	78	11	 **431**	--	--

References

(1) Bercovici, D. A; Ogilvie, J. M.; Tsvetkov, N.; Brewer, M. *Angew. Chem.* **2013**, *125*, 13580.

(2) Bercovici, D. A. and Brewer M, *J. Am. Chem Soc.* **2012**, *134*, 9890.

(3) DiFrancesco, D; Pinhas, A. R., *J. Org. Chem*, **1986**, *51*, 2098.

(4) Hodgson, D. M; Gibbs, A. R.; Drew, M. G. B. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 3579.

(5) Sambasivarao, K.; Shirbhate, M. E. *Synlett*, **2012**,*23*, 2183.

(6) Aburel, P. A.; Rømming, C.; Ma, K; Undheim, K.; J. *Chem. Soc., Perkin Trans. 1*, **2001**,
1458.

(7) Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Okrent, R. A.; Avey, A. A. *J. Org. Chem.* ***2006***, *71*, 553.

(8) Cheung, L. L. W.; K. Yudin, A. K. *Chemistry A European Journal* **2010**, *16*, 4100.

(9) Williams, J. R.; Lin, C.; Chodosh, D. F. *J. Org. Chem*, **1985** , *50*, 5815.

(10) Song, C. E; Shim, W. H.; Roh, E. J; Lee, S.; Choi, J. H. *Chemical Communications*, **2001,** *12*, 1122.

(11) Benjamin, R. T.; Radha, S. N.; Babak, B.; *J. Am. Chem. Soc.* **2002**, *124*, 3824.

(12) Sekiyama, Y.; Palaniappan, N.; Reynoldsb, K. A.; Osadaa, H. *Tetrahedron* **2003**, *59*, 7465.

(13) Lambert, J. B.; Taba, K. M. *J. Org. Chem*, **1980**, *45*, 452.

(14) Bazzini, P.; Ouali, M. I.; Pellissier, H.; Santelli, M. *Steroids*, **2006**, *71*, 459.

(15) Beifuss, U.; Gehm, H.; Noltemeyer, M.; Schmidt, H. G. *Angew. Chemie*, **1995** , *107*, 705.

(16) Rigby, J. H.; Kotnis, A.; James Kramer, J. *J. Org. Chem.*, **1990**, *55*, 5078.

Summary of Thesis

I have described the research conducted towards the overall goal of developing new synthetic organic methods to facilitate the synthesis of structurally complex nitrogen-containing polycyclic compounds. The study included diverse reactivities and mechanistic studies of 1-aza-2-azoniaallene systems to make polycyclic diazenium salts and tetrahydropyridazine rings.

I have developed a mechanistic study to understand the intramolecular [3+2] cycloaddition reaction of α-chloroazo compounds with a pendent alkene to give bicyclic and tricyclic fused and bridged diazenium salts. This study included the electronic effects of the N'-aryl substituent on the ratio of bridged and fused diazenium products.

I have also described my development of a new method to make diazenium salts in a shorter and more efficient route. This method included the direct conversion of hydrazones to diazenium salts using a hypervalent Iodine (III) reagent without forming intermaediates. This method also gave access to diazenium salts that were not accessible by previously reported methods.

I have also shown my discovery of a new and unprecedented reactivity of 1-aza-2-azoniaallene intermediates to form tetrahydropyridazines. This reactivity of the 1-aza-2-azoniaallene intermediates was dependent on the structure of the precursor and was determined by the structural constrains between the 1-aza-2-azoniaallene center and the pendent alkene. We have initiated mechanistic studies to understand this latter reactivity and the results are in support of our hypothesis that this heterocyclic ring system is formed by the formation and subsequent ring opening of aziridinium ion intermediate. The scope of the tetrahydropyradizine formation was assessed in more detail by making a diverse library of heteroallenes. The reactivity of the heteroallenes was observed to give a variety of products based on the structure of the reacting heteroallene.

Comprehensive Bibliography:

(1) Aburel, P. A.; Rømming, C.; Ma, K; Undheim, K.; J. *Chem. Soc., Perkin Trans. 1*, **2001**,
1458.

(2) Al-Bataineh, N. Q.; Brewer, M *Tetrahedron Letters*, **2012**, *53*, 5411–5413.

(3) Al-Soud, Y. A.; Shrestha-Dawadi, P. B.; Winkler, M.; Wirschun, W.; Jochims, J. C. J. Chem. Soc., *Perkin Trans.* **1998**, *1*, 3759–3766.

(4) Barton, D. H. R.; Jaszberenyi, J. Cs.; Lebmann, K.; Timar, T. *Tetrahedron*, **1992**, *48*, 8881.

(5) Barton, D. H. R.; Jaszberenyi, J. Cs.; Liu, W.; Shinada, T. *Tetrahedron*, **1996**, *52*, 2717.

(6) Barton, D. H. R.; Jaszberenyi, J. Cs.; Lui, W.; Shinada, T. *Tetrahedron*, **1996**, *52*, 14673.

(7) Bazzini, P.; Ouali, M. I.; Pellissier, H.; Santelli, M. *Steroids*, **2006**, *71*, 459.

(8) Beifuss, U.; Gehm, H.; Noltemeyer, M.; Schmidt, H. G. *Angew. Chemie*, **1995** , *107*, 705.

(9) Benjamin, R. T.; Radha, S. N.; Babak, B.; *J. Am. Chem. Soc.* **2002**, *124*, 3824.

(10) Bercovici, D. A. and Brewer M, *J. Am. Chem Soc.* **2012**, *134*, 9890.

(11) Bercovici, D. A; Ogilvie, J. M.; Tsvetkov, N.; Brewer, M. *Angew. Chem.* **2013**, *125*, 13580.

(12) Brewer, M *Tetrahedron Lett.* **2006**, *47*, 7731–7733.

(13) Carre, M. C.; Ndebeka, G.; Riondel, A.; Bourgasser, P.; Caubere, P. *Tetrahedron Letters* 1984, *25*, 1551.

(14) Cauquis, g.; Genies, M. *Compt Rend.* **1974**, *C279*, 2389.

(15) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3171.

(16) Cheung, L. L. W.; K. Yudin, A. K. *Chemistry A European Journal* **2010**, *16*, 4100.

(17) DiFrancesco, D; Pinhas, A. R., *J. Org. Chem*, **1986**, *51*, 2098.

(18) Elguero, J.; Jacquier, R.; Marzin, C. *Tetrahedron Lett.* **1970**, 3099.

(19) Feguson, A. N. *Tetrahedron Lett.* **1973**, *30*, 2999.

(20) Gaonkar, S. L.; Rai, K. M. L. *Tetrahedron Lett*. **2005**, *46*, 5969–5970.

(21) Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Okrent, R. A.; Avey, A. A. *J. Org. Chem.* ***2006***, *71*, 553.

(22) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem*. **1983**, *48*, 2607.

(23) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

(24) Guo, Y. P.; Wang, Q., R.; Jochims, J. C. *Synth*. **1996**, 274.

(25) Hammett, L. P. *J. Am. Chem. Soc.* **1937,** *59*, 96.

(26) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Letters* **2002**, *44*, 57.

(27*)* Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(28) Harej, M; Dolene, D. *J. Org. Chem.*, **2007**, *72*, 7214.

(29) Heyman, M. L., Snyder, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 4416.

(30) Hodgson, D. M; Gibbs, A. R.; Drew, M. G. B. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 3579.

(31) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

(32) Hranuma, S.; Shibata, M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 5321.

(33) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789–1792.

(34) Javed, M. I.; Wyman, J. M.; Brewer, M. *Org. Lett.* **2009**, *11*, 2189

(35) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094.

(36) Kamens, E. R.; Kressing, D. M.; Lange, H. C.; MacLeay, R. R. Polymeric cellular structures; U.S. patent 4029615, June 14, 1977.

(37) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028.

(38) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499.

(39) Keenan, S. L.; Peterson, K. P.; Peterson, K.; Jacobson, K. *J. Chem. Educ.* **2008**, *85*, 558.

(40) Kuznetsov, M. A. *Russ. Chem. Rev.* **1979**, *48*, 563.

(41) Lambert, J. B.; Taba, K. M. *J. Org. Chem*, **1980**, *45*, 452.

(42) Li, Y.; Hale, K. J. Org. Lett. **2007**, *9*, 1267.

(43) Lutz, K. E.; Thomson, R. J. *Angew. Chem. Int. Ed.* **2011,** *50*, 4437-4440.

(44) MacLeay, R. E.; Sheppard, C. S. Tertiary-aliphatic amidazo compounds; U.S. Patent 4001207, January 4, 1977.

(45) Mannschreck, A.; Kolb, B. *Chem. Ber.* **1972**, *105*, 696.

(46) McBride, W. R.; Kruse, H. W. *J. Am. Chem. Soc.* **1957**, *79*, 572.

(47) Moon, M. W. *J. Org. Chem.* **1972**, *37*, 383–385.

(48) Moon, M. W. *J. Org. Chem.* **1972**, 37, 386–390.

(49) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1991**, *3*, 431-447.

(50) Moroda, A.; Togo, H. *Tetrahedron* **2006**, *62*, 12408.

(51) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *Org. Lett.* **2009**, *11*, 465-468.

(52) Mundal, D. A.; Aventta, C. A. Jr.; Thomson, R. J. *Nat. Chem.* **2010**, *2*, 294-297.

(53) Nelsen, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1973**, *95*, 2719.

(54) Nelson, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 1788.

(55) Omura, K.; Swern, D. *Tetrahedron* **1978**, 11, 1651.

(56) Piancatelli, G.; Leonelli, F.; Do, N.; Ragan, *J. Org. Synth.* **2006**, *83*, 18.

(57) Pozzi, G.; Quici, S.; Shepperson, I. *Tetrahedron Lett*. **2002**, *43*, 6141.

(58) Rigby, J. H.; Kotnis, A.; James Kramer, J. *J. Org. Chem.*, **1990**, *55*, 5078.

(59) Sambasivarao, K.; Shirbhate, M. E. *Synlett*, **2012**,*23*, 2183.

(60) Sanders, C., G.; Sharp, T., R; Allres, E., L. *tetrahedron Lett*. **1986**, *27*, 3231.

(61) Sekiyama, Y.; Palaniappan, N.; Reynoldsb, K. A.; Osadaa, H. *Tetrahedron* **2003**, *59*, 7465.

(62) Song, C. E; Shim, W. H.; Roh, E. J; Lee, S.; Choi, J. H. *Chemical Communications*, **2001,** *12*, 1122.

(63) Stang, P.; Zhdankin, V. V.; *Chem. Rev.* **1996**, *96*, 1123-1178.

(64) Ulrich, H. In *Cycloaddition Reactions of Heterocumulenes*; Blomquist, A. T.; Academic Press: New York, **1976**, Vol. 9, p 1.

(65) Um, I. H.; Lee, J. Y.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2004**, *69*, 2436.

(66) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*, VCH, New York, **1992**.

(67) Varvoglis, A., *Hypervalent Iodine in Organic Synthesis*, pp. 1-223, Academic Press, London, **1997**.

(68) Vatele, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715.

(69) Vugts, D. J.; Veum, L.; al-Mafraji, K.; Lemmens, R.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Hanefeld, U.; Orru, R. V. A. *Eur. J. Org. Chem*. **2006**, 1672.

(70) Wang, Q. R.; Amer, A.; Troll, C.; Fischer, H.; Jochims, J. C. *Chem. Ber.* **1993**, *126*, 2519.

(71) Wang, Q. R.; Amer, A.; Mohr, S.; Ertel, E.; Jochims, J. C. *Tetrahedron* **1993**, *49*, 9973–9986.

(72) Wang, Q. R.; Jochims, J. C.; Kohlbrandt, S.; Dahlenburg, L.; Altalib, M.; Hamed, A.; Ismail, A. E. H. *Synthesis* **1992**, 710–718.

(73) Wang, Q. R.; Liu, X. J.; Li, F.; Ding, Z. B.; Tao, F. G. *Synth. Commun*. **2002**, *32*, 1327–1335.

(74) Waser, J.; Gaspar, B; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

(75) Williams, J. R.; Lin, C.; Chodosh, D. F. *J. Org. Chem*, **1985** , *50*, 5815.

(76) Wirschun, W. G.; Al-Soud, Y. A.; Nusser, K. A.; Orama, O.; Maier, G. M.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4356.

(77) Wirschun, W. G. *J. Prakt. Chem.* **1998**, *340*, 300.

(78) Wirth, T.; Ochiai, M.; Varvgolis, A.; Zhdankin, V. V.; Koser,G. F.; Tohma, H.; Kita Y.; *Topics in Current Chemistry: Hypervalent Iodine Chemistry/Modern Developments in Organic Synthesis*, pp. 1-248, 224. Springer-Verlag, Berlin, **2002**.

(79) Wyman, J.; Javed, M. I.; Al-Bataineh, N.; Brewer, M. *J. Org.Chem.* **2010**, *75*, 8078–8087.

(80) Wyman, J.; Jochum, S.; Brewer, M. *Synth. Commun.* **2008**, *38*, 3623.

(81) Zefirov, N. S.; Safravov, S. O.; Kaznacheev, A. A.; Zhdankin, V.V.; *Zh. Org. Khim.* **1989**, *25*, 1807-1808.

(82) Zhao, X.-F.; Zhang, C. *Synthesis* **2007**, 551.

(83) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008,** *108*, 5299-5358.

5. CHAPTER 5:

Experimental Information

5.1. General Experimental Information

All reactions were done under an atmosphere of nitrogen using flame-dried glassware. Solvents were removed in vacuo using a rotary evaporator equipped with a water condenser and attached to a self-cleaning dry vacuum pump, and samples were further dried under reduced pressure on a high vacuum line. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were dried via a solvent dispensing system, unless otherwise noted. Triethylamine was freshly distilled from CaH_2 before use. Oxalyl chloride (98%) and antimony(V)chloride (99%), purchased from Acros Organics, were freshly distilled before use. Extra dry DMSO stored over molecular sieves was purchased from Acros Organics and used as received. Anhydrous aluminum(III)chloride (98.5%), purchased from Acros Organics, was used as received and stored in a dry glovebox under an atmosphere of nitrogen. All hydrazones were freshly prepared before use since they could not be stored and underwent an auto oxidation reaction on standing in air. Molecular sieves (4 Å) were activated by heating overnight at 120 ^{o}C in a vacuum oven before use. Reactions were cooled to –78 °C by using dry-ice/acetone baths. Flash silica gel column chromatography was carried out using silica gel (230-400 mesh); TLC analysis was carried out using silica on glass plates. Visualization of TLC plates was done by using ultraviolet light, polyphosphomolybdic acid and cerium sulfate in EtOH with H_2SO_4, ceric ammonium molybdate, or iodine. ^{1}H-

NMR and ^{13}C-NMR data were collected at room temperature on a 500 MHz spectrometer in $CDCl_3$ and CD_3CN. ^{1}H-NMR chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane. Solvent peaks were used as internal references for all ^{13}C-NMR. Mass data was accurately acquired in ESI mode using an Orbitrap mass analyzer, or on a LCT Premier (Waters) operated in positive-ion mode. A general sequence for reactions involved 1-aza-2-azoniaallene intermediates generated from a-chloroazo compounds were followed. First, phenyl or aryl hydrazones were prepared from the condensation reaction of the desired hydrazine with a ketone substrate. Most ketones were not commercially available and needed to be prepared. Hydrazones were then reacted with chlorodimethylsulfonium chloride, to prepare α-chloroazo compounds. These α-chloroazo substrates were subsequently reacted with Lewis acids ($SbCl_5$ or $AlCl_3$) to generate the 1-aza-2-azoniaallene intermediates, which then proceeded to react with the pendant alkene system.

5.2. Experimental Information for the Synthesis of N'-Aryl Substituted Diazenium Salts

5.2.1. Synthesis of Hydrazones:

Method A: Used when starting with the hydrochloride salt of the hydrazine

In this method, the solvent used was either dry methanol or dry ethanol. The solvent was degassed by sparging with nitrogen gas for about 30 minutes in the presence of molecular sieves to remove any dissolved oxygen. The hydrazine hydrochloride salt (1 equiv) and sodium acetate (1 equiv) were then added under a nitrogen atmosphere. The

mixture was stirred at room temperature for 15 minutes at which point the ketone (1 equiv) was added, and the reaction was then stirred at room temperature for about two hours. The solvent was evaporated *in vacuo* at room temperature and the resultant oil was quickly dissolved in dry pentane and filtered through a short plug of basic alumina. the pentane was removed *in vacuo* and the remaining oil was carried on to next step without any further purification.

When the aryl ring contained either a strong electron withdrawing group, such as -NO_2, or when there was a substituent present at the *ortho* position the condensation took place overnight at the refluxing temperature of the solvent used.

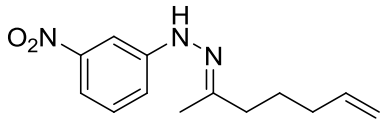
Method B: used for free hydrazines

The hydrazine (1 equiv) was added to dry oxygen-free dichloromethane containing molecular sieves under a nitrogen atmosphere, and the ketone (1 equiv) was then added at room temperature. The reaction was stirred at room temperature for two hours and was then filtered through a short plug of basic alumina and the solvent was evaporated *in vacuo*. The resultant oil was used in the next step without any further purification. When a strong electron withdrawing group was present on the aryl ring, or if a substituent was present at the *ortho* position of the hydrazine, the reaction was heated to reflux overnight.

Both methods above provided pure hydrazones in very good to excellent yields as mixtures of *E/Z* diastereomers which were not separated. The isolated aryl hydrazones

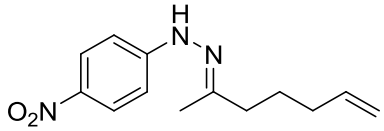
were very sensitive to oxygen in the air and, if not carefully handled, underwent an autoxidation reaction.

5.2.2. Characterization Data of Hydrazones:



94

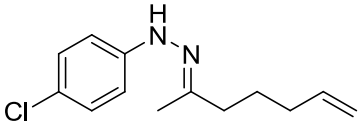
(*E*)-1-(Hept-6-en-2-ylidene)-2-(3-nitrophenyl)hydrazine (**94**): Yield 90%; *E/Z* 1:0.3; ^{1}H NMR (500 MHz, CDCl3) δ 7.88 (s, 1H), 7.60-7.65 (m, 1H), 7.28-7.37 (m, 2H), 7.14 (br s, 1H), 5.84 (ddt, J = 16.9, 10.3, 6.9 Hz, 1H), 5.02-5.07 (m, 1H), 5.00 (br d, J= 10.1 Hz, 1H), 2.34 (t, J= 7.4 Hz, 2H), 2.13 (q, J= 7.0 Hz, 2H), 1.89 (s, 3H), 1.70 (p, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 149.2, 148.9, 146.8, 138.3, 129.7, 118.5, 114.9, 113.9, 107.4, 38.2, 33.3, 25.7, 14.6; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, CDCl3) δ 7.10 (s, 1H), 2.27 (t, J = 7.7 Hz, 2H), 2.04 (s, 3H). MS (ESI) calcd for $[C_{13}H_{17}N_3O_2H]^+$ 248.1399, found 248.1402.



93

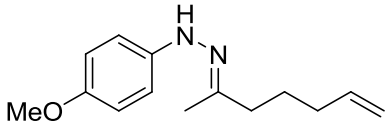
(E)-1-(hept-6-en-2-ylidene)-2-(4-nitrophenyl)hydrazine (**93**): Yield 78%; *E/Z* 1:0.2; ^{1}H NMR (500 MHz, CDCl3) δ 8.14 (dd, J = 9.3 Hz, 2H), 7.44 (s, 1H), 7.04 (dd, J = 9.3 Hz, 2H), 5.95-5.76 (m, 1H), 5.16-4.95 (m, 2H), 2.36 (t, J = 7.6 Hz, 2H), 2.19-2.09 (m, 2H),

1.91 (s, 3H), 1.71 (p, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 150.4, 138.2, 126.1, 115.1, 113.4, 111.6, 111.5, 38.3, 33.2, 25.6, 14.7.



91

(*E*)-1-(4-chlorophenyl)-2-(hept-6-en-2-ylidene)hydrazine (**91**): Yield = 91%; *E/Z*: 1:0.17; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (dm, J = 8.9, 2.1 Hz, 2H), 6.97 (dm, J = 8.9, 2.1 Hz, 2H), 5.84 (ddt, J = 16.9, 10.4, 7.1 Hz, 1H), 5.03 (apt dq, J = 17.3, 1.6 Hz, 1H), 4.96-4.99 (m, 1H), 2.31 (t, J = 7.7 Hz, 2H), 2.08-218 (m, 2H), 1.85 (s, 3H), 1.68 (p, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 147.4, 144.6, 130.1, 129.0, 124.3, 123.9, 114.1, 38.4, 26.4, 14.4; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, CDCl3) δ 6.94 (d, J = 8.8 Hz, 2H), 5.53-5.62 (m, 2H), 2.24 (app t, J = 7.5, 2H); 13C NMR (125 MHz, CDCl3) δ 129.4, 125.6, 123.9, 113.9, 28.6, 26.5, 24.9, 23.1. MS (ESI) calculated for $[C_{13}H_{17}ClN_2H]^+$ 237.1158, found 237.1158.



96

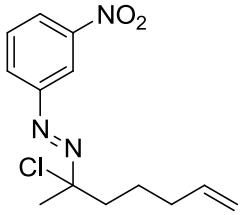
(E)-1-(Hept-6-en-2-ylidene)-2-(4-methoxyphenyl)hydrazine (**96**). Yield 92%; E/Z 1:0.2; ^{1}H NMR (500 MHz, CDCl3) δ 7.00 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9, 2H), 6.69 (br s, 1H), 5.84 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 4.93-5.06 (m, 2H), 3.76 (s, 3H), 2.30 (t, J = 7.3 Hz, 2H), 2.08-2.16 (m, 2H), 1.84 (s, 3H), 1.68 (p, J = 7.6, 2H); ^{13}C NMR (125 MHz, CDCl3) δ 153.5, 146.4, 140.3, 138.6, 114.7, 114.7, 114.3, 77.3, 77.0,

76.8, 55.7, 38.3, 33.3, 25.9, 14.4; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, CDCl3) δ 5.05-5.11 (m, 2H), 2.24 (t, J = 8.0 Hz, 2H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 115.7, 114.2, 28.5, 24.2, 23.1. MS (ESI) calculated for $[C_{14}H_{20}N_2OH]^+$ 233.1654, found 233.1652.

5.2.3. Experimental Procedure for the Synthesis of N'-Aryl Substituted α-Chloroazo Compounds

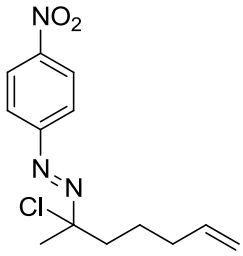
Oxalyl chloride (1.26 mmol, 1.2 equiv) was added in a drop wise manner to a stirred solution of DMSO (1.57 mmol, 1.5 equiv) in THF (10 mL) at -55 °C under a nitrogen atmosphere. The reaction was maintained at -55 ^{o}C until gas evolution ceased (~20 min) at which point the reaction was cooled further to -78 ^{o}C. A mixture of Et_3N (1.26 mmol, 1.2 equiv) and hydrazone (1.05 mmol, 1 equiv) in THF (3 mL) was added in a drop wise manner via cannula. An immediate color change and a concomitant formation of a white precipitate were noted. The reaction mixture was maintained at -78 °C for 30 min and was then removed from the cold bath and warmed to room temperature at which point the solids were removed by filtration through a medium porosity sintered-glass funnel. The filtrate was concentrated by rotary evaporation, the residue was dissolved in pentane (~20 mL) and decanted away from an insoluble red-oil. The pentane was removed in vacuo to provide the desired product. Traces of DMSO could be removed by washing the pentane solution with water before concentrating, but this step was not necessary for the subsequent transformation.

5.2.4 Characterization Data of N'-Aryl Substituted α-Chloroazo Compounds:



103

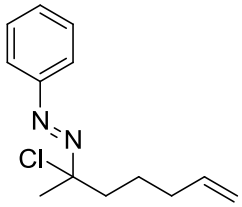
1-(2-Chlorohept-6-en-2-yl)-2-(3-nitrophenyl)diazene (**103**): Yield 75%; ^{1}H NMR (500 MHz, CDCl3) δ 8.57 (s, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.70 (t, J = 8.2 HZ, 1H), 5.80 (ddt, J = 17.0, 10.2, 6.9 Hz, 1H), 4.95-5.06 m (2H), 2.31 (ddd, J = 14.1, 11.8, 4.7 Hz, 1H), 2.21 (ddd, J = 14.4, 11.9, 4.6 Hz, 1H), 2.09 (q, J = 6.9 Hz, 2H), 1.93 (s, 3H), 1.59-1.71 (m, 1H), 1.44-1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 148.9, 137.8, 130.1, 129.4, 125.4, 117.0, 115.2, 96.5, 42.0, 33.3, 28.7, 23.4.



105

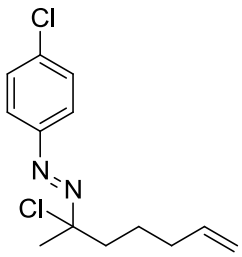
(E)-1-(2-chlorohept-6-en-2-yl)-2-(4-nitrophenyl)diazene (**105**): Yield about 50%; Characterized as mixtures of diasteriomers, ^{1}H NMR (500 MHz, CDCl3) δ 8.37 (dd, J = 8.9 Hz, 2H), 8.15 (dd, J = 9.2 Hz, 2H), 7.89 (dd, J = 8.8 Hz, 2H), 7.05 (dd, J = 9.2 Hz, 2H), 5.91-5.73 (m, 2H), 4.18-4.93 (m, 4H), 2.42-2.10 (m, 10H), 1.95 (s, 3H), 1.94 (s,

3H), 1.75-1.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 148.9, 137.8, 130.1, 129.4, 125.45, 117.0, 115.2, 96.5, 42.0, 33.3, 28.6, 23.4.



101

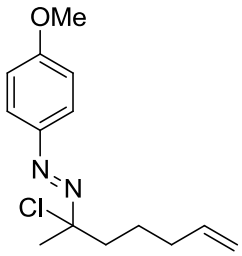
1-(2-Chlorohept-6-en-2-yl)-2-phenyldiazene (**101**): Yield = 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.80 (m, 2H), 7.42-7.53 (m, 3H) 5.78 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.02 (apt dq, J = 17.1, 1.6 Hz, 1H), 4.95-4.98 (m, 1H), 2.30 (ddd, J = 14.0, 11.9, 4.7 Hz, 1H), 2.18 (ddd, J = 14.1, 11.9, 4.6 Hz, 1H), 2.09 (q, J = 7.3 Hz, 2H), 1.90 (s, 3H), 1.60-1.70 (m, 1H), 1.45-1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 138.4, 131.6, 129.4, 123.2, 115.4, 96.9, 42.7, 33.8, 29.1, 23.8.



102

1-(2-Chlorohept-6-en-2-yl)-2-(4-chlorophenyl)diazene (**102**): Yield = 76%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dm, J = 8.6, 1.9 Hz, 2H), 7.48 (dm, J = 8.6, 1.9 Hz, 2H), 5.78 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (apt dq, J = 17.0, 1.6 Hz, 1H), 4.95-4.98 (m, 1H), 2.28 (ddd, J = 14.0, 12.0, 4.7 Hz, 1H), 2.17 (ddd, J = 14.0, 12.0, 4.6 Hz, 1H), 2.09 (q, J =

7.3 Hz, 2H), 1.89 (s, 3H), 1.60-1.70 (m, 1H), 1.44-1.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 138.0, 137.3, 129.3, 124.2, 115.1, 96.5, 42.2, 33.4, 28.7, 23.4.



104

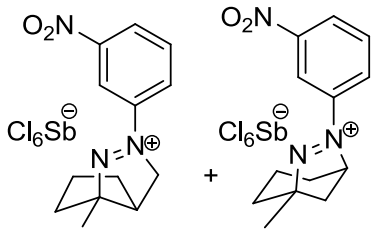
1-(2-Chlorohept-6-en-2-yl)-2-(4-methoxyphenyl)diazene (**104**). Yield 82%; 1 H NMR (500 MHz, CDCl3) δ 7.77 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 5.78 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H), 5.01 (app d, J = 17.2 Hz, 1H), 4.93-4.98 (app d, J = 10.4 Hz, 1H), 3.87 (s, 3H), 2.27 (ddd, J= 14.2, 12.0, 4.7 Hz, 1H), 2.16 (ddd, J = 14.1, 11.9, 4.7 Hz, 1H), 2.09 (q, J = 7.0 Hz, 2H), 1.88 (s, 3H), 1.58-1.70 (m, 1H), 1.46-1.57 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 162.2, 145.1, 138.2, 124.9, 115.0, 114.1, 96.5, 55.6, 42.4, 33.5, 28.8, 23.5.

5.2.5. Experimental Procedures for the Preparation of N'-Aryl Substituted Diazenium Hexachloroantimonates

Antimony pentachloride (0.53 mmol, 1 eq) was added drop wise to a stirred solution of the phenyl- or 4-chlrophenyl α-chloroazoalkane (0.53 mol, 1 eq) in CH_2Cl_2 (10 mL) at -60 °C under a nitrogen atmosphere. The cooling bath was allowed to warm slowly to 0 °C (~45 min) and the reaction was then maintained at that temperature for 1h. The mixture was allowed to stir at room temperature for 10 minutes at which point the

solvent was removed in vacuo to provide a dark oil or foam. This crude material was analyzed by ^{1}H NMR (CD_3CN) to determine the ratio of fused to bridged diazenium salt products. The NMR sample was recombined with the crude reaction mixture, the solvent was removed in vacuo and the residue was triturated with Et_2O to provide the desired diazenium salt as a powder.

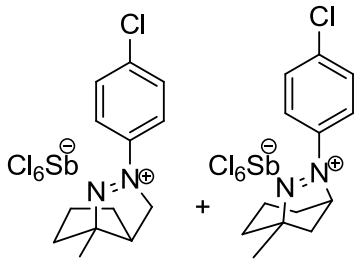
5.2.6. Characterization Data of N'-Aryl Substituted Diazenium Hexachloroantimonates



106b **107b**

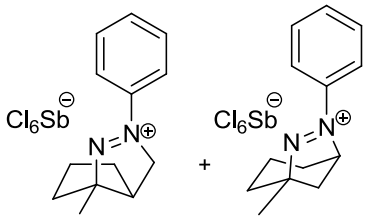
6a-Methyl-2-(3-nitrophenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-2-ium Hexachlorostibate(V) (**106b**). Yield 81%; proton NMR resonances assignable to **106b** : ^{1}H NMR (500 MHz, CD_3CN) δ 8.87 (t, J = 2.1 Hz, 1H), 8.68 (dd, J = 8.3, 1.7 Hz, 1H), 8.46 (dd, J = 8.3, 2.2 Hz, 1H), 8.01 (t, J = 8.3 Hz, 1H), 5.61 (dd, J = 17.3, 9.7 Hz, 1H), 5.23 (dd, J = 17.3, 4.2 Hz, 1H), 2.97-3.05 (m, 1H), 1.86 (s, 3H); proton NMR resonances assignable to 1-methyl-6-(3-nitrophenyl)- 6,7-diazabicyclo[3.2.1]oct-6-en-6-ium hexachlorostibate- (V) (**107b**): ^{1}H NMR (500 MHz, CD_3CN) δ 8.93 (t, J = 2.1 Hz, 1H), 8.71 (dd, J = 8.3, 1.7 Hz, 1H), 8.54 (dd, J = 8.3, 2.4 Hz, 1H), 8.04 (t, J= 8.4 Hz, 1H), 6.17 (t, J= 5.2 Hz, 1H), 2.38 (d, J = 11.8 Hz, 1H), 1.93 (s, 3H), 0.92-1.04 (m, 1H); proton NMR resonances assignable to **106b** and **107b** : 2.52-2.62 (m, 2H), 1.74-2.22 (m, 10 H); carbon NMR resonances assignable to **106b** and **107b** : ^{13}C NMR (125MHz, CD_3CN) δ

150.1, 149.6, 140.6, 139.2, 133.3, 132.8, 131.8, 131.2, 130.5, 130.4, 120.2, 120.1, 101.7, 88.5, 84.5, 78.5, 43.1, 43.0, 39.7, 33.4, 29.1, 24.7, 23.6, 22.6, 22.0, 18.0. MS (ESI) calculated for $[C_{13}H_{16}N_3O_2]^+$ 246.1243, found 246.1248.



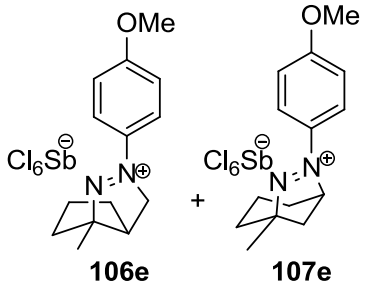
106c **107c**

6a-Methyl-2-(4-chlorophenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-2-ium Hexachlorostibate(V) (**106c**): 92% yield: ^{1}H NMR (500MHz, CD_3CN) δ 8.09 (d, J= 9.1 Hz, 2H), 7.76 (d, J = 9.3 Hz, 2H), 5.54 (dd, J = 17.2, 9.2 Hz, 1H), 5.13 (dd, J = 17.2, 4.5 Hz, 1H), 2.92-2.97 (m, 1H), 2.45-2.54 (m, 1H), 2.03-2.17 (m, 2H), 1.80 (s, 3H), 1.72-1.82 (m, 2H), 1.45-1.56 (m, 1H); ^{13}C NMR (125MHz, CD_3CN) δ143.8, 139.1, 131.7, 126.7, 101.2, 78.0, 43.2, 39.8, 33.7, 25.1, 23.8; observable resonances for minor isomer: 6-(4-chlorophenyl)-1-methyl-6,7-diazabicyclo[3.2.1]oct-6-en-6-ium hexachlorostibate(V) (14e0): ^{1}H NMR (500 MHz, CD_3CN) δ 8.09 (d, J = 6.6 Hz, 2H), 7.79 (d, J = 6.1 Hz, 2H), 6.05 (app t, J = 5.1 Hz, 1 H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 144.6, 132.3, 87.5, 83.7, 29.4, 22.9, 22.6, 18.4; IR (ATR, cm-1) 1586, 1529, 1413, 1095, 83. MS (ESI) calculated for $[C_{13}H_{16}ClN_2]^+$ 235.1002, found 235.0998.



106d **107d**

6a-methyl-2-phenyl-3,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-2-iumhexachlorostibate(V) (**106d**): Yield = 87%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.09-8.14 (m, 2H), 7.89-7.93 (t, J = 7.6 Hz,1H), 7.72-7.77 (m, 2H), 5.55 (dd, J = 17.3, 9.8 Hz, 1H), 5.15 (dd, J = 17.3, 4.2 Hz, 1H), 2.90-2.98 (m, 1H), 2.45-2.52 (m, 1H), 2.02-2.16 (m, 2H), 1.81 (s, 3H), 1.72-1.82 (m, 2H), 1.45-1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 138.2, 132.0, 125.5, 101.3, 78.3, 43.5, 40.2, 34.1, 25.4, 24.2; IR (cm^{-1}): 2967 (br), 1588, 1457, 1238; MS (ESI): Calculated for $[C_{13}H_{17}N_2]^+$: 201.1392 Found: 201.1385.Observable peaks for minor regioisomer (**107d**): ^{1}H NMR (500 MHz, CD_3CN) δ 8.17-8.21 (m, 0.4H), 7.96 (t, J = 7.76 Hz, 0.2H), 7.77-7.81 (m, 0.4H), 6.07 (t, J = 5.7 Hz, 0.2H); ^{13}C NMR (125 MHz, CD_3CN) δ 138.9, 132.5, 83.8, 29.8, 23.3, 23.1, 18.9.



106e **107e**

6a-Methyl-2-(4-methoxyphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-2-ium Hexachlorostibate(V) (**106e**): yield 92%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.09 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 5.47 (dd, J = 16.7, 9.7 Hz, 1H), 5.07 (dd, J = 16.7,

4.1 Hz, 1H), 3.97 (s, 3H), 2.86-2.93 (m, 1H), 2.41-2.47 (m, 1H), 2.03-2.08 (m, 2H), 1.76 (s, 3H), 1.98-2.03 (m, 1H), 1.41-1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 132.2, 126.6 (br), 115.5, 98.1, 75.8, 56.1, 41.8, 38.4, 32.4, 23.7, 22.5. MS (ESI) calculated for $[C_{14}H_{19}N_2O]^+$ 231.1497, found 231.1498.

5.3. Experimental Information for Iodine(III)-Mediated Bicyclic Diazenium Salt Formation

5.3.1. Synthesis of Hydrazones:

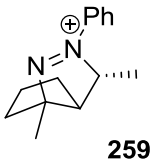
Hydrazones were synthesized according to the detailed procedures described in section 5.2.1 of this chapter.

5.3.2. General Experimental Procedure for the Synthesis of Iodine(III)-Mediated Bicyclic Diazenium Salts

To a suspension of iodoso benzene (1.07 mmol) in 2-ml dry CH_2Cl_2 at 0 ^oC was added 2.14 mmol of TMSOTf dropwise and the reaction mixture was allowed to stir for 5 mins at that temperature then was cooled down to -40 ^oC. A solution of phenyl hydrazone and 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP) in 1-ml CH_2Cl_2 was then added to the $PhI(OTf)_2$. Immediately after the addition, a 0.714 mmol of 1,3-dinitrobenzo nitrile (internal standard) was added and the mixture was transferred to a pre-warmed water bath and concentrated in vacuo. A sample of the crude reaction mixture was then dissolved in deuterated acetonitrile and analyzed by ^{1}H-NMR in. The ratios of diazenium salt products

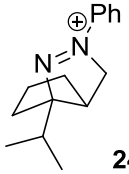
and the reaction yield were determined by calculating the relative integrations to the known amount of the 1,3-dinitronenzo nitrile added.

5.3.4. Characterization Data of Iodine(III)-Mediated Bicyclic Diazenium Salts

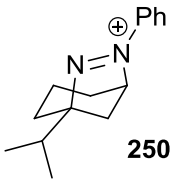


259

2-Phenyl-3,6a-dimethyl-3,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-2-ium triflate (**259**): Yield 68%; ^{1}H NMR (500 mHz, CD_3CN) δ 7.95 (d, J= 9.1 Hz, 2H), 7.76 (d, J= 9.1 Hz, 2H), 5.94 (dq, J = 9.3, 7.2 Hz, 1H), 2.96-3.00 (m, 1H), 2.45-2.53 (m, 1H), 2.18-2.25 (m, 1H), 1.76-1.92 (m, 3H), 1.79 (s, 3H), 1.58 (d, J = 7.2 Hz, 3H), 1.42-1.53 (m, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 142.8, 138.1, 131.5, 127.3, 99.8, 84.6, 46.9, 39.7, 28.6, 25.6, 24.1, 15.7.



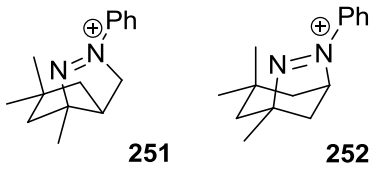
249



250

6a-Isopropyl-2-phenyl-3,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-2-ium triflate (**249**): Yield 70%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.12 (d, J = 9.2 Hz, 2H), 7.76 (d, J = 9.2 Hz, 2H), 5.53 (dd, J = 17.5, 9.8 Hz, 1H), 5.14 (dd, J = 17.5, 4.4 Hz, 1H), 3.11-3.16 (m, 1H), 2.43 (septet, J = 6.5 Hz, 1H), 2.37-2.40 (m, 1H), 2.23-2.29 (m, 1H), 1.90- 1.98 (m, 1H), 1.74-1.81 (m, 2H), 1.41-1.50 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 1.12 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CD3CN) δ 144.0, 139.0, 131.8 (t), 127.0 (m), 108.7, 78.0, 40.1, 37.2, 35.4, 33.8, 24.6, 18.6, 18.3; observable resonances for minor isomer: 6-

phenyl-1-isopropyl-6,7-diazabicyclo[3.2.1]oct-6-en-6-ium triflate (**250**): ^{1}H NMR (500 MHz, CD_3CN) δ 8.19 (d, J = 9.3 Hz, 2H), 7.79 (d, J = 9.3 Hz, 2H), 6.04-6.10 (m, 1H); ^{13}C NMR (125 MHz, CD3CN) δ 38.8, 34.5, 25.4, 22.9, 18.4, 17.9.



251 **252**

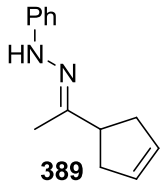
5,5,6a-Trimethyl-2-phenyl-3,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-2-ium triflate (**251**): Yield 79%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.11 (d, J = 9.1 Hz, 2H), 7.76 (d, J=9.3 Hz, 2H), 5.41 (dd, J=16.2, 7.9 Hz, 1H), 5.23 (dd, J =16.2, 2.3 Hz, 1H), 3.12 (qd, J = 8.0, 2.3 Hz, 1H), 2.26 (d, J=13.9 Hz, 1H), 2.20 (dd, J=14.3, 1.7 Hz, 1H), 2.05 (ddd, J= 13.1, 8.3, 1.6 Hz, 1H), 1.75 (s, 3H), 1.47 (ddd, J= 13.1, 9.3, 1.6 Hz, 1H), 1.13 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, CD3CN) δ 143.9, 139.2, 131.8, 127.0, 101.0, 77.0, 51.2, 47.6, 43.2, 39.8, 28.5, 28.3, 25.0; observable resonances for minor isomer: 6-phenyl)-1,3,3-trimethyl-6,7-diazabicyclo[3.2.1]- oct-6-en-6-ium triflate (**252**): ^{1}H NMR (500 MHz, CD3CN) δ 8.18 (d, J = 9.1 Hz, 2H), 7.82 (d, J = 9.3 Hz, 2H), 5.94-5.96 (m, 1H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 132.7, 126.7, 87.6, 81.7, 43.0, 36.4, 31.7, 23.2.

5.4. Experimental Information for the new reactivity of α-chloroazo compounds with $AlCl_3$; Formation of tetrahydropyridazines, pyrazoline, and protonated azomethine imine.

5.4.1. Synthesis of Hydrazones:

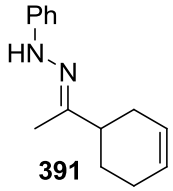
Hydrazones were synthesized according to the detailed procedures described in section 5.2.1.

5.4.2. Characterization Data of Hydrazones:



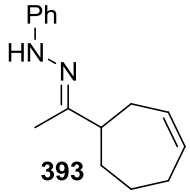
389

1-(cyclopent-3-en-1-yl)ethanone phenyl hydrazone (**389**): 1-(Cyclopent-3-en-1-yl)ethanone (200 mg, 1.81 mmol) was added to a room temperature mixture of phenyl hydrazine (196 mg, 1.81 mmol) and 4Å molecular sieves in CH_2Cl_2 (5 mL) under an atmosphere of nitrogen and the mixture was heated to reflux for 3.5 hours. The reaction was cooled to room temperature, filtered through a short plug of basic alumina, and the volatiles were removed in vacuo to give 172 mg (72% yield) of the title compound as a mixture of diastereomers in the form of a yellow oil: ^{1}H NMR (500 MHz, CDCl3) δ 7.25-7.18 (m, 2H), 7.08-7.02 (m, 2H), 6.86 (s, 1H), 6.81 (tt, J = 7.4, 1.1 Hz, 1H), 5.71 (m, 2H), 3.24 (tt, J = 9.3, 9.1 Hz, 1H), 2.66-2.56 (m, 2H), 2.54-2.46 (m, 2H), 1.85 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 148.8, 146.0, 129.7, 129.2, 119.6, 113.0, 45.4, 36.5, 12.4. MS (ESI): Calculated for $[C_{13}H_{17}N_2]^+$: 201.1392. Found: 201.1396



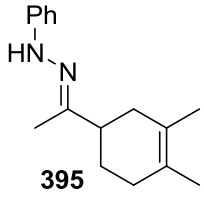
391

(E)-1-(1-(cyclohex-3-enyl)ethylidene)-2-phenylhydrazine (391): Yield 84%; dark orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2 (t, J = 8.4 Hz, 2H), 7.05 (d, J = 7.7 Hz, 2H), 6.90 (s, 1H), 6.81 (t, J = 7.3 Hz, 1H), 5.81-5.64 (m, 2H), 2.52-2.43 (m, 1H), 2.23-2.17 (m, 2H), 2.16-2.10 (m, 2H), 1.96-1.91 (m, 1H), 1.85 (s, 3H), 1.61-1.54 (m, 1H);); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 146.0, 129.1, 126.7, 126.2, 119.5, 113.0, 42.7, 28.8, 26.5, 25.4, 12.8. MS (ESI): Calculated for $[C_{14}H_{19}N_2]^+$: 215.1548. Found: 215.1551.



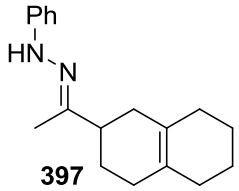
393

(E)-1-(1-(cyclohept-3-enyl)ethylidene)-2-phenylhydrazine (393): Yield 98%; dark orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.19 (m, 2H), 7.08-7.00 (m, 2H), 6.86-6.78 (m, 2H), 5.82-574 (m, 2H), 2.41-2.35 (m, 1H), 2.34-2.28 (m, 2H), 2.22 (ddd, J = 14.1, 7.3, 2.3 Hz, 1H), 2.16-2.04 (m, 2H), 1.84 (s, 3H), 1.86-1.79 (m, 1H), 1.70 (dddd, J = 13.5, 10.5, 6.7, 3.4, 1H), 1.43 (ddt, J = 10.7, 5.8, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 146.0, 132.8, 130.3, 129.1, 119.5, 113.0, 46.8, 35.7, 32.3, 28.6, 26.2, 12.91. MS (ESI): Calculated for $[C_{15}H_{20}N_2]^+$: 229.1705. Found: 229.1714.



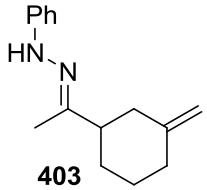
395

(E)-1-(1-(3,4-dimethylcyclohex-3-enyl)ethylidene)-2-phenylhydrazine (**395**): Yield 81%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-720 (m, 2H), 7.08-7.03 (m, 2H), 6.88 (s, 1H), 6.81 (tt, J = 7.4, 1.1 Hz, 1H), 2.49-2.40 (m, 1H), 2.21-2.07 (m, 2H), 2.06-1.99 (m, 2H), 1.94-1.89 (m, 1H), 1.84 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.59-1.49 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 146.1, 129.1, 125.2, 124.7, 119.5, 113.0, 112.8, 43.6, 35.3, 31.9, 27.2, 19.2, 18.9, 12.7. MS (ESI): Calculated for $[C_{16}H_{23}N_2]^+$: 243.1861. Found: 243.1866.



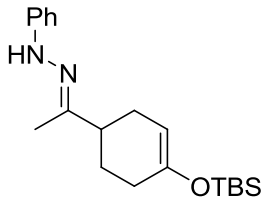
397

(E)-1-(1-(1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethylidene)-2-phenylhydrazine (**397**): Yield 82%; dark yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.19 (m, 2H), 7.08-7.00 (m, 2H), 6.88 (s, 1H), 6.81 (tt, J = 7.3, 1.0 Hz, 1H), 2.52-2.43 (m, 1H), 2.15-2.06 (m, 1H), 2.02-1.86 (m, 7H), 1.84 (s, 3H), 1.72-1.64 (m, 2H), 1.63-1.45 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 146.1, 129.1, 127.6, 127.1, 119.4, 113.0, 43.4, 34.1, 30.6, 30.3, 30.1, 26.9, 23.2, 23.2, 12.7. MS (ESI): Calculated for $[C_{18}H_{25}N_2]^+$: 269.2018. Found: 269.2022.



403

(E)-1-(1-(3-methylenecyclohexyl)ethylidene)-2-phenylhydrazine (**403**): Yield 78%; light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.22 (m, 2H), 7.10-7.05 (m, 2H), 6.91 (s, 1H), 6.84 (tt, J = 7.3, 1.1 Hz, 1H), 4.7 (t, J = 1.6 Hz, 2H), 2.54-2.46 (m, 1H), 2.38-2.32 (m, 1H), 2.30 (dt, J = 11.5, 3.3 Hz, 1H), 2.24-2.16 (m, 1H), 2.06-2.00 (m, 1H), 1.99-1.90 (m, 2H), 1.88 (s, 3H), 1.54-1.35 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ . (ESI): Calculated for $[C_{15}H_{21}N_2]^+$: 229.1705. Found: 229.1710.

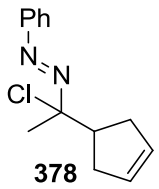


(E)-1-(1-(4-(tert-butyldimethylsilyloxy)cyclohex-3-enyl)ethylidene)-2-phenylhydrazine: Yield 83%; dark brown oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.18 (m, 2H), 7.08-7.01 (m, 2H), 6.88 (s, 1H), 6.84-6.77 (m, 1H), 4.94-4.83 (m, 1H), 2.55-2.38 (m, 1H), 2.25-2.18 (m, 2H), 2.14-2.01 (m, 2H), 1.85 (s, 3H), 1.80-1.62 (m, 2H); 0.94-0.91 (m, 9H), 0.17-0.09 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 148.9, 146.0, 129.1, 119.6, 113.0, 112.9, 103.2, 102.3, 47.1, 42.6, 33.4, 29.8, 27.6, 26.8, 25.7, 25.7, 19.7, 18.0, 12.8.

5.4.3. Experimental Procedure for the Synthesis of α-Chloroazo Compounds:

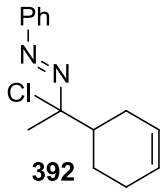
The procedure used was the same mentioned in section 5.2.3 with only one exception for compound **424** that will be explained later.

5.4.4 Characterization Data of α-Chloroazo Compounds:



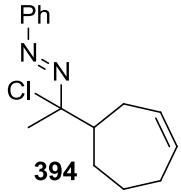
378

1-(1-chloro-1-(cyclopent-3-enyl)ethyl)-2-phenyldiazene (**378**): (230 mg, 80% yield) was prepared as a dark orange oil according to the following procedure: Oxalyl chloride (0.38 ml, 2.21 mmol) was added dropwise to a solution of DMSO (0.39 ml, 3.69 mmol) in THF (4 mL) that was maintained between – 55 °C to –65 °C and the resulting solution was stirred until the formation of bubbles ceased (typically 30 min). The reaction mixture was cooled to –78 °C and a solution of the phenyl hydrazone of 1-(cyclopent-3-en-1-yl)ethanone (261 mg, 1.23 mmol) and Et_3N (0.45 ml, 1.48 mmol) in THF (2 mL) was added. After 30 min the cold bath was removed. Upon reaching room temperature the mixture was filtered and the filtrate was concentrated. The oily residue was dissolved in pentane to give an orange solution that was filtered to remove a dark red insoluble residue. The pentane was removed in vacuo give 230 mg (80% yield) of α-chloroazo **378** as an orange-red liquid; ^{1}H NMR (500 MHz, CDCl3) δ 7.79-7.71 (m, 2H), 7.51-7.44 (m, 3H), 5.68 (m, 2H), 3.29-3.20 (tt, 8.7, 8.3 Hz, 1H), 2.62-2.55 (m, 2H), 2.54-2.38 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 151.3, 131.2, 129.6, 129.2, 129.1, 122.9, 99.9, 48.5, 34.9, 34.7, 27.3.



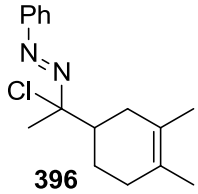
392

(E)-1-(1-chloro-1-(cyclohex-3-enyl)ethyl)-2-phenyldiazene (**392**): Yield 80%; dark orange oil; characterized as mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.82 (m, 4H), 7.53-7.43 (m, 6H), 5.77-5.70 (m, 2H), 5.77-5.60 (m, 4H), 2.33-2.27 (m, 1H), 2.24-2.06 (m, 8H), 1.91 (s, 3H), 1.87 (s, 3H), 1.84-1.79 (m, 1H), 1.58-1.46 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 131.2, 131.2, 129.1, 126.9, 126.7, 125.9, 125.8, 122.9, 99.9, 45.4, 44.8, 27.0, 26.8, 26.5, 26.5, 25.7, 25.6, 23.9, 23.8.



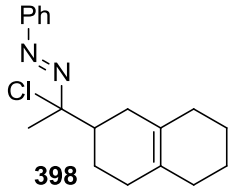
394

(E)-1-(1-chloro-1-(cyclohept-3-enyl)ethyl)-2-phenyldiazene (**394**): Yield 92%; dark orange oil; characterized as mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.72 (m, 4H), 7.53 – 7.44 (m, 6H), 5.86 – 5.73 (m, 3H), 5.72-5.65 (m, 1H), 2.57 – 2.46 (m, 2H), 2.46 – 2.38 (m, 1H), 2.25-2.09 (m, 8H), 2.04-1.98 (m, 1H), 1.92-1.88 (m, 1H), 1.87 (s, 3H), 1.86-1.84 (m, 1H), 1.83 (s, 3H), 1.75-1.61 (m, 2H), 1.57-1.43 (m, 2H); ^{13}C NMR (126 MHz, CDCl3) δ 151.1, 132.8, 132.5, 131.2, 131.2, 129.5, 129.4, 129.1, 122.1, 100.4, 100.4, 48.7, 48.1, 32.1, 31.7, 29.3, 29.2, 28.4, 26.7, 26.5, 26.5, 25.7, 25.7.



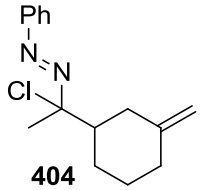
396

(E)-1-(1-chloro-1-(3,4-dimethylcyclohex-3-enyl)ethyl)-2-phenyldiazene (**396**): Yield 72%; orange oil; characterized as mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.69 (m, 4H), 7.58-7.41 (m, 6H), 2.53-2.43 (m, 2H), 2.15-2.10 (m, 4H), 2.07-2.00 (m, 4H), 1.99-1.96 (m, 1H), 1.95-1.93 (m, 1H), 1.91 (s, 3H), 1.88 (s, 3H), 1.81-1.74 (m, 2H), 1.63 (s, 6H), 1.61 (s, 6H), 1.52-1.43 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.2, 129.1, 125.6, 125.4, 124.4, 122.9, 100.0, 48.3, 46.1, 45.6, 33.2, 32.9, 32.0, 32.0, 26.6, 24.5, 24.4, 19.2, 19.1, 18.8.



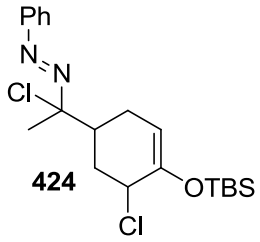
398

(E)-1-(1-chloro-1-(1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethyl)-2-phenyldiazene (**398**): Yield 67%; brown oil; characterized as mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.74 (m, 4H), 7.51-7.43 (m, 6H), 2.58-2.45 (m, 2H), 2.13-2.05 (m, 4H), 2.04-2.02 (m, 1H), 1.97-1.94 (m, 1H), 1.91 (s, 3H), 1.88 (s, 3H), 1.87-1.76 (m, 10H), 1.70-1.65 (m, 4H), 1.57-1.41 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 151.1, 131.1, 131.1, 129.0, 128.0, 127.8, 126.8, 126.6, 122.9, 122.9, 100.1, 100.0, 46.0, 45.5, 32.0, 31.7, 30.7, 30.7, 30.3, 30.3, 29.9, 29.9, 26.6, 26.6, 24.3, 24.2, 23.1, 23.1, 23.0.



404

(E)-1-(1-chloro-1-(3-methylenecyclohexyl)ethyl)-2-phenyldiazene (**404**): Yield 87%; light brown oil; characterized as mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.72 (m, 4H), 7.52-7.44 (m, 6H), 4.71-4.68 (m, 2H), 4.67-4.61 (m, 2H), 2.64-2.57 (m, 1H), 2.38-2.35 (m, 1H), 2.35-2.28 (m, 4H), 2.13-2.04 (m, 3H), 2.01-1.90 (m, 4H), 1.88 (s, 3H), 1.87 (s, 3H), 1.46-1.24 (m, 5H); NMR (126 MHz, $CDCl_3$) δ 151.1, 148.0, 131.2, 129.1, 129.1, 122.9, 108.4, 108.3, 99.7, 49.9, 49.8, 36.4, 36.2, 34.7, 27.1, 26.9, 26.8.



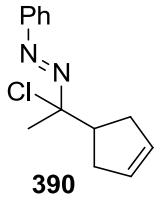
424

(E)-1-(1-(4-(tert-butyldimethylsilyloxy)-5-chlorocyclohex-3-enyl)-1-chloroethyl)-2-phenyldiazene (**424**): Yield 71%; dark brown oil; characterized as mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.73 (m, 4H), 7.51-7.43 (m, 6H), 5.05-4.86 (m, 2H), 4.58-4.32 (m, 2H), 3..04-2.95 (m, 1H), 2.46-2.40 (m, 2H), 2.39-2.32 (m, 2H), 2.24-2.21 (m, 1H), 2.11-2.09 (m, 1H), 2.05-2.02 (m, 1H), 1.93 (s, 1H), 1.89 (s, 2H), 1.87-1.83 (m, 2H), 0.97-0.92 (m, 18H), 0.20-0.14 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 148.8, 131.4, 129.2, 129.1, 123.0, 106.1, 106.0, 105.4, 98.8, 58.1, 58.0, 57.3, 41.0, 39.6, 39.2, 34.1, 27.1, 27.1, 25.7, 25.6, 25.3, 25.2, 25.2, 18.3.

5.4.5. General Experimental Procedure for the Reaction of α-Chloroazo Compounds with $AlCl_3$:

A solution of α-chloroazo (1 equiv) in CH_2Cl_2 (0.25M) was added dropwise to a –78 °C suspension of $AlCl_3$ (1.2 equiv) in CH_2Cl_2 (0.1M). The reaction was allowed to slowly warm to room temperature in the dry-ice/acetone bath (typically 2 h) at which point a saturated aq. solution of $NaHCO_3$ (2 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The organic layers were combined, dried (MgSO4) and concentrated and then was purified by silica gel flash column chromatography.

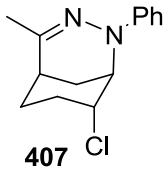
5.4.6. Characterization Data of Final Products:



390

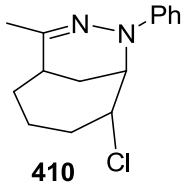
3-methyl-1-phenyl-1,3a,4,6a-tetrahydrocyclopenta[c]pyrazole (**390**). A solution of α-chloroazo (90 mg, 0.38 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a –78 °C suspension of $AlCl_3$ (61 mg, 0.04 mmol) in CH_2Cl_2 (4 mL). The reaction was allowed to slowly warm to room temperature in the dry-ice/acetone bath (typically 2 h) at which point a saturated aq. solution of $NaHCO_3$ (2 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 ml). The organic layers were combined, dried (MgSO4) and concentrated to a dark yellow oil that was purified by silica gel flash column chromatography (9/1; hexanes/ethyl acetate) to give 52 mg (69% yield) of S-4 pyrazole **390** as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.21

(m, 2H), 7.07-7.02 (dd, J = 8.8, 1.1 Hz, 2H), 6.76 (tt, J = 7.3, 1.1 Hz, 1H), 5.95-5.87 (m, 2H), 5.24-5.19 (d, J = 9.8 Hz, 1H), 3.72 (m, 1H), 2.79-2.71 (m, 1H), 2.62-2.55 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 145.3, 132.7, 129.3, 127.7, 118.1, 112.5, 70.4, 51.1, 36.3, 14.5.



407

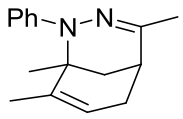
Rel-(1R,5R,8R)-8-chloro-4-methyl-2-phenyl-2,3-diazabicyclo[3.3.1]non-3-ene (**407**): Yield 84%; dark broin oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 8.9, 2H), 7.21 (d, J = 7.8, 2H), 6.84 (t, J = 7.2, 1H), 4.41-4.36 (m, 1H), 4.28-4.23 (m, 1H), 2.51 (dt, J = 13.0, 2.3, 1H), 2.42-2.37 (m, 1H), 2.06-2.01 (m, 1H), 2.03 (s, 3H), 1.88-1.81 (m, 1H), 1.73-1.67 (m, 2H), 1.63-1.56 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.8, 145.7, 129.2, 119.2, 112.5, 57.5, 52.3, 31.5, 27.8, 24.5, 22.6, 20.1. MS (ESI): Calculated for $[C_{14}H_{18}ClN_2]^+$: 249.1159. Found: 249.1163.



410

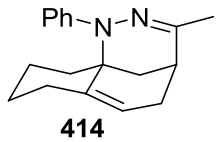
5-chloro-9-methyl-7-phenyl-7,8-diazabicyclo[4.3.1]dec-8-ene (**410**): Yield 76%; Dark yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.28-7.26 (m, 2H), 6.88-6.83 (tt, J = 13.8, 7.0, 1.5), 4.38-4.34 (m, 1H), 4.26-4.30 (m, 1H), 2.41 (t, J = 6.9, 1H), 2.35 (d, J = 14.4, 1H), 2.03 (s, 3H), 2.00-1.83 (m, 5H), 1.72-1.66 (m, 1H), 1.39-1.31 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.8, 145.0, 129.2, 119.1, 112.7, 62.1, 55.0, 33.7,

31.3, 30.1, 22.5, 20.8, 19.9. MS (ESI): Calculated for $[C_{15}H_{20}ClN_2]^+$: 263.1315. Found: 263.1321.

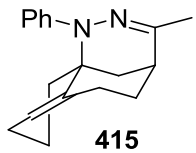


412

1,4,8-trimethyl-2-phenyl-2,3-diazabicyclo[3.3.1]nona-3,7-diene (**412**): Yield 72 %; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.14 (m, 2H), 7.16-7.12 (m, 2H), 7.12-7.08 (m, 1H), 5.63-5.56 (m, 1H), 2.45-2.38 (m, 1H), 2.29-2.21 (m, 2H), 2.03 (dd, J = 12.2, 4.3, 1H), 1.96 (s, 3H), 1.64 (dd, J = 12.1, 1.7, 1H), 1.41, (s, 3H), 1.26-1.20 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 147.5, 134.2, 127.8, 127.0, 124.8, 123.6, 54.3, 35.9, 32.2, 31.6, 25.9, 22.3, 20.4. MS (ESI): Calculated for $[C_{16}H_{21}N_2]^+$: 241.1705. Found: 241.1712.



414



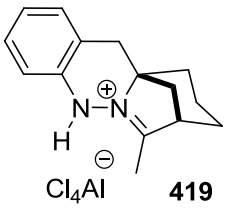
415

Two Regioisomers:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.26-7.22 (m, 2H), 7.17 (tt, J = 7.2, 1.3, 1H), 5.66-5.61 (m, 1H), 2.45-2.41 (m, 1H), 2.41-2.36 (m, 1H), 2.29-2.23 (m, 2H), 2.07 (dd, J = 11.9, 4.5, 1H), 1.96 (s, 3H), 1.89-1.79 (m, 2H), 1.64-1.60 (m, 2H), 1.55-1.53

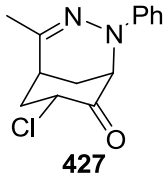
(m, 1H), 1.53-1.51 (m, 1H), 1.14 (dt, J = 13.3, 4.1, 1H), 0.84 (dt, J = 12.8, 4.0, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 130.4, 128.7, 128.3, 126.3, 125.7, 122.2, 54.2, 37.8, 35.9, 33.5, 32.6, 31.6, 26.8, 22.1, 22.1. MS (ESI): Calculated for $[C_{18}H_{23}N_2]^+$: 267.1861. Found: 267.1869.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.24-7.19 (m, 2H), 6.94 (tt, J = 7.2, 1.3 Hz), 5.55-5.50 (m, 1H), 2.47-2.43 (m, 1H), 2.42-2.33 (m, 1H), 2.27-2.18 (m, 1H), 2.11-2.05 (m, 2H), 2.00-1.98 (m, 1H), 1.96 (s, 3H), 1.91-1.86 (m, 1H), 1.78 (dt, J = 12.1 Hz, 2.6), 1.63-1.57 (m, 2H), 1.56-1.51 (m, 2H), 1.37 (dt, J = 13.9, 4.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 144.1, 144.1, 128.2, 122.8, 122.8, 121.9, 120.7, 56.2, 37.8, 33.8, 33.3, 31.5, 30.8, 24.8, 22.3, 21.3. MS (ESI): Calculated for $[C_{18}H_{23}N_2]^+$: 267.1861. Found: 267.1862.



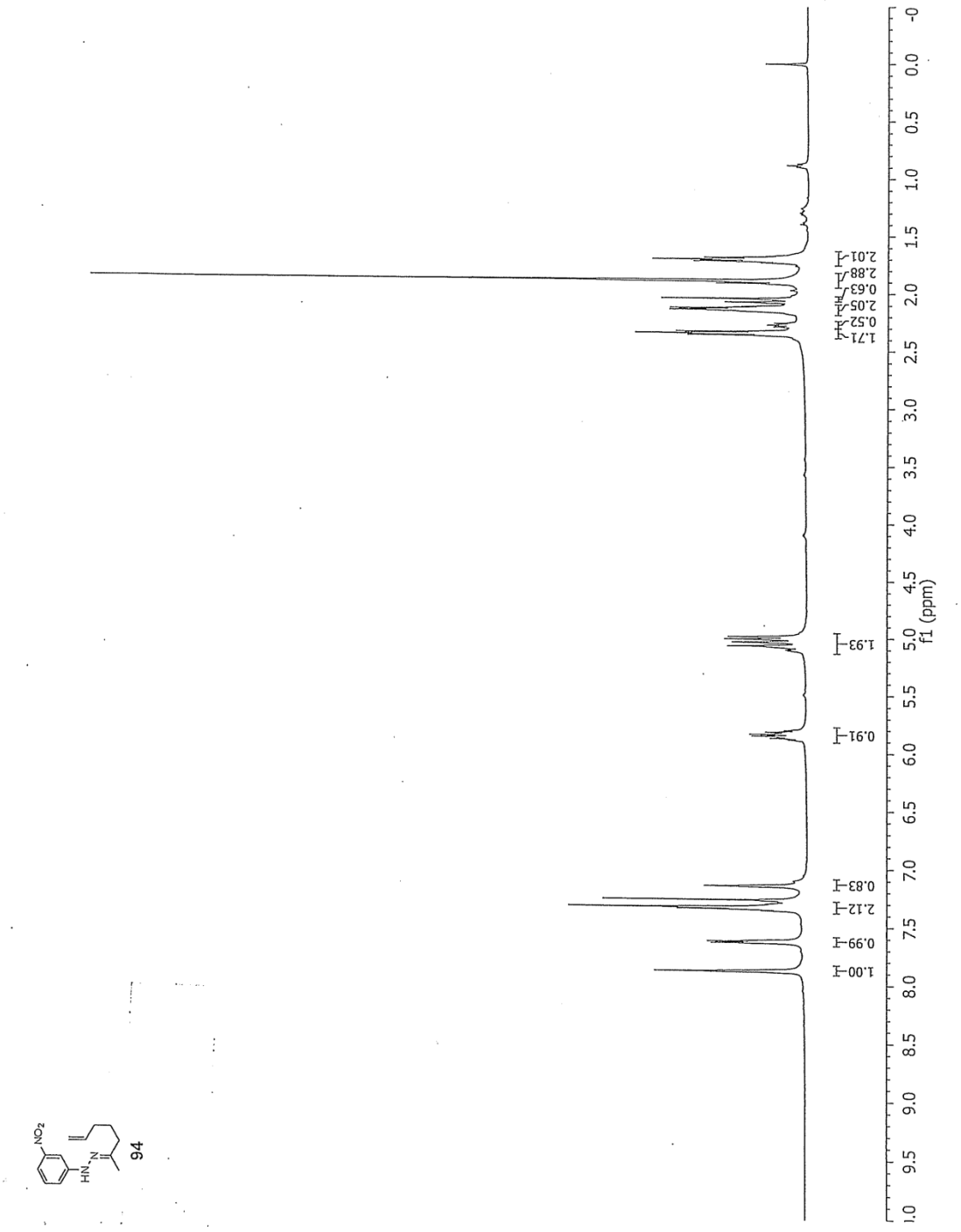
419

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.2, 0.7 Hz, 1H), 7.27-7.22 (m, 1H), 7.2 (d, J = 7.6 Hz, 1H), 7.01 (td, J = 7.5, 1.0 Hz, 1H), 3.31-3.26 (m, 1H), 3.22 (d, J = 16.5 Hz, 1H), 3.09 (d, J = 16.4 Hz, 1H), 2.76 (s, 3H), 2.33-2.25 (m, 1H), 2.18 (d, J = 11.4 Hz, 1H), 1.91-1.84 (m, 1H), 1.84-1.71 (m, 3H), 1.65-1.46 (m, 3H).

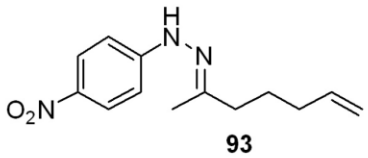


427

Rel- (1R,5S,7R)-7-chloro-4-methyl-2-phenyl-2,3-diazabicyclo[3.3.1]non-3-en-8-one (**427**): Yield 83%; dark gray solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.21 (m, 4H), 6.90 (tt, J = 6.7, 1.8, 1H), 4.80-4.66 (m, 1H), 4.34 (dd, J = 12.9, 7.1 Hz, 1H), 2.77 (dtd, J = 10.0, 6.7, 3.1 Hz, 1H), 2.64-2.53 (m, 1H), 2.17 (s, 3H), 2.15 (d, J = 3.9, 1H), 2.14-2.11 (m, 1H), 2.07 (dt, J = 13.4, 2.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl3) δ 198.9, 145.9, 143.2, 129.2, 120.6, 113.3, 60.6, 60.1, 42.7, 31.7, 26.6, 22.6. MS (ESI): Calculated for $[C_{14}H_{16}ClN_2O]^+$: 263.0951. Found: 263.0957.

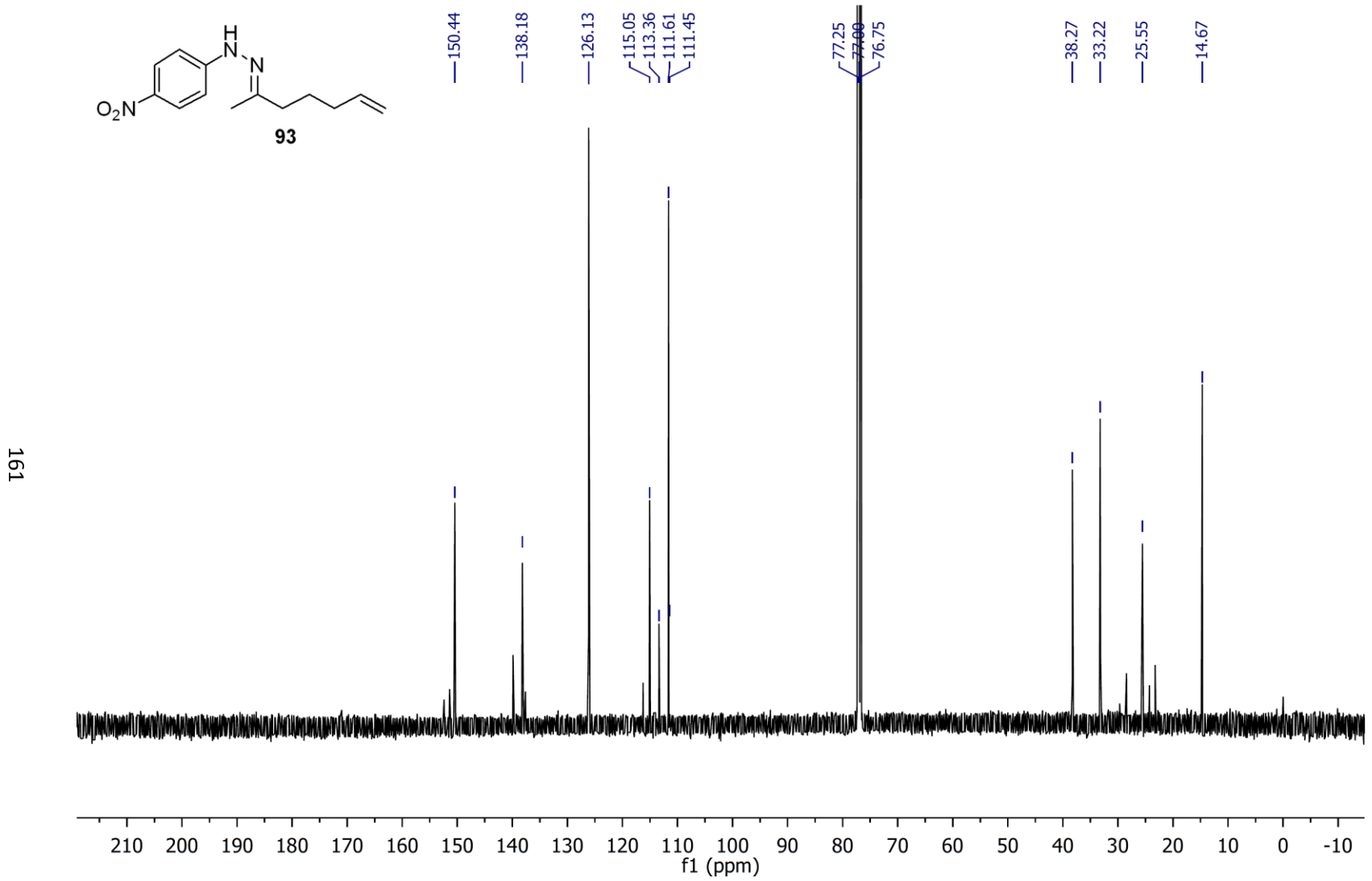

94
1.00
0.99
2.12
0.83
0.91
1.93
1.71
0.52
2.05
0.63
2.88
2.01
f1 (ppm)

94
149.23
148.86
146.82
138.30
129.70
118.52
114.94
113.89
107.39
77.25
77.00
76.75
38.20
33.26
25.70
14.58
f1 (ppm)


H
N
N
O_2N

93

2.26
0.34
0.98
2.03
0.33
1.00
2.07
1.92
0.34
2.10
0.54
2.74
2.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

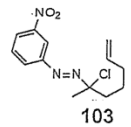

150.44
138.18
126.13
115.05
113.36
111.61
111.45
77.25
77.00
76.75
38.27
33.22
25.55
14.67
93
f1 (ppm)

91
2.10
2.20
0.94
1.00
2.18
1.95
0.37
2.26
0.50
2.85
2.35
f1 (ppm)

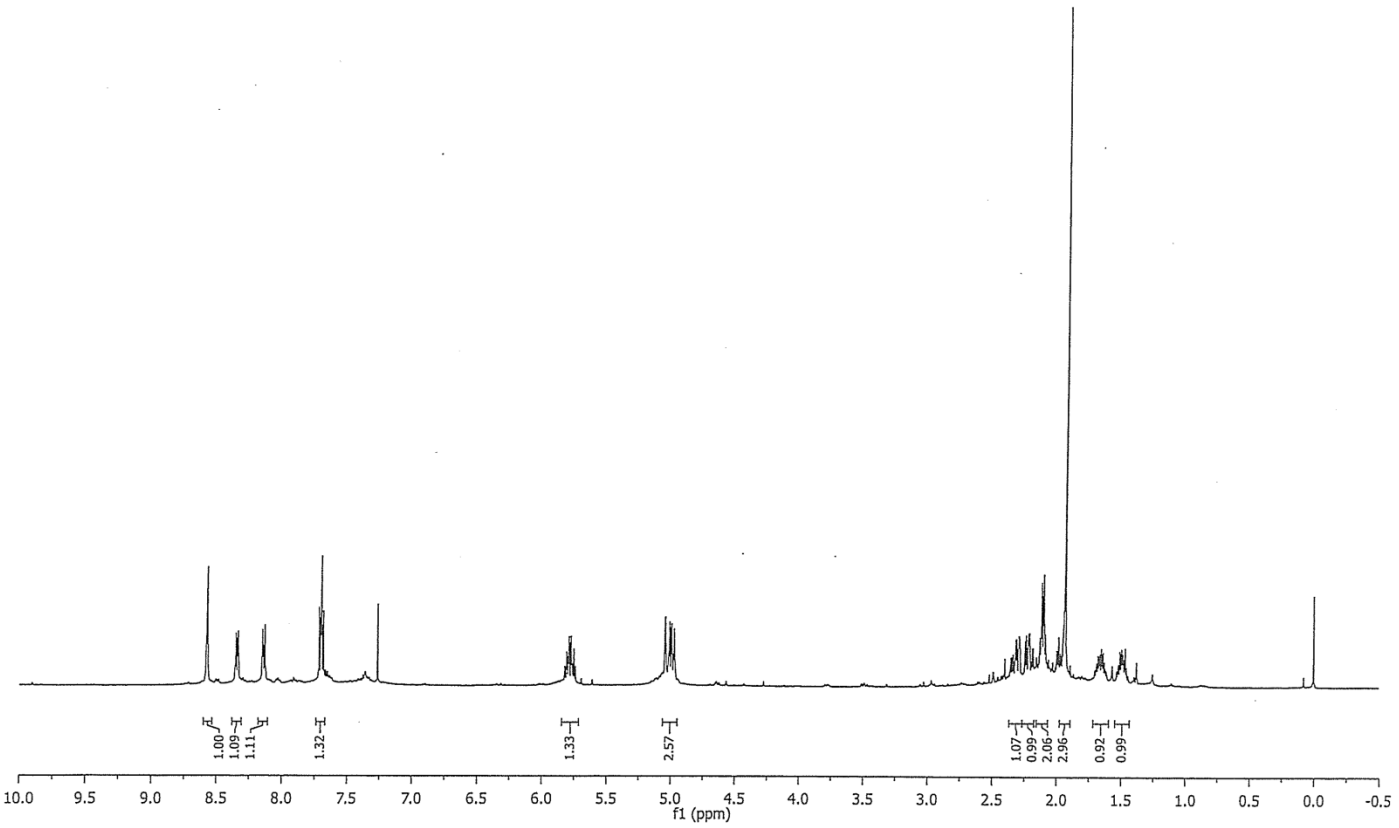
148.12
147.22
144.53
144.43
138.39
137.73
128.92
123.85
115.81
114.77
114.01
113.88
77.25
77.00
76.75
38.17
33.25
28.39
25.71
24.15
23.06
14.37
91
f1 (ppm)

96
OMe
HN
N
1.99
2.00
0.78
0.84
1.85
2.93
1.70
0.37
2.06
0.46
2.48
2.03
f1 (ppm)

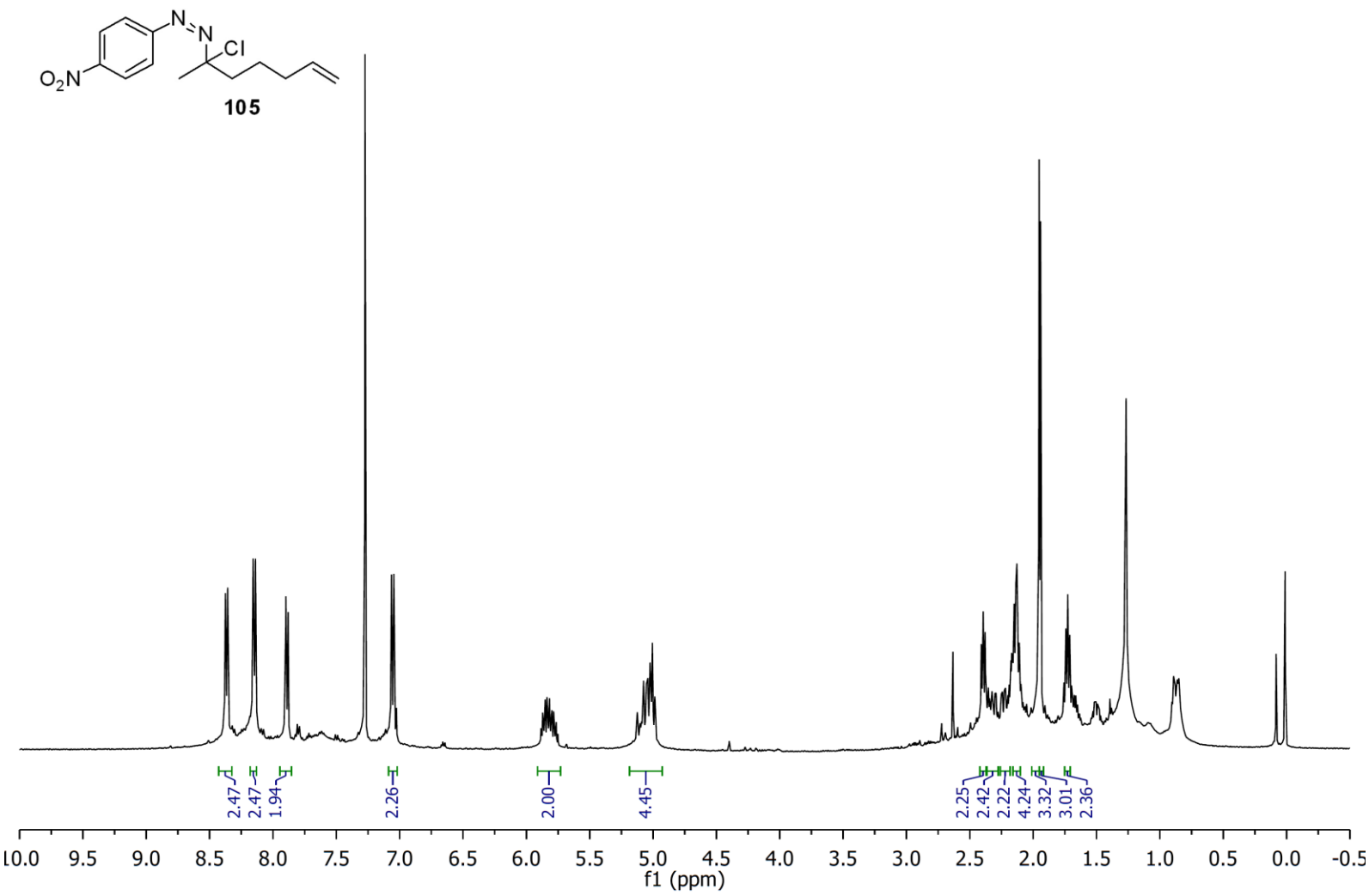
96
153.49
146.42
140.32
138.56
115.71
114.71
114.65
114.30
114.21
77.25
77.00
76.75
55.70
38.26
33.33
28.52
25.90
24.21
23.11
14.39
f1 (ppm)

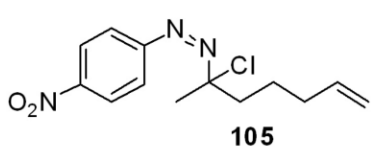

NO2
N=N
Cl

103


1.00
1.09
1.11
1.32
1.33
2.57
1.07
0.99
2.06
2.96
0.92
0.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

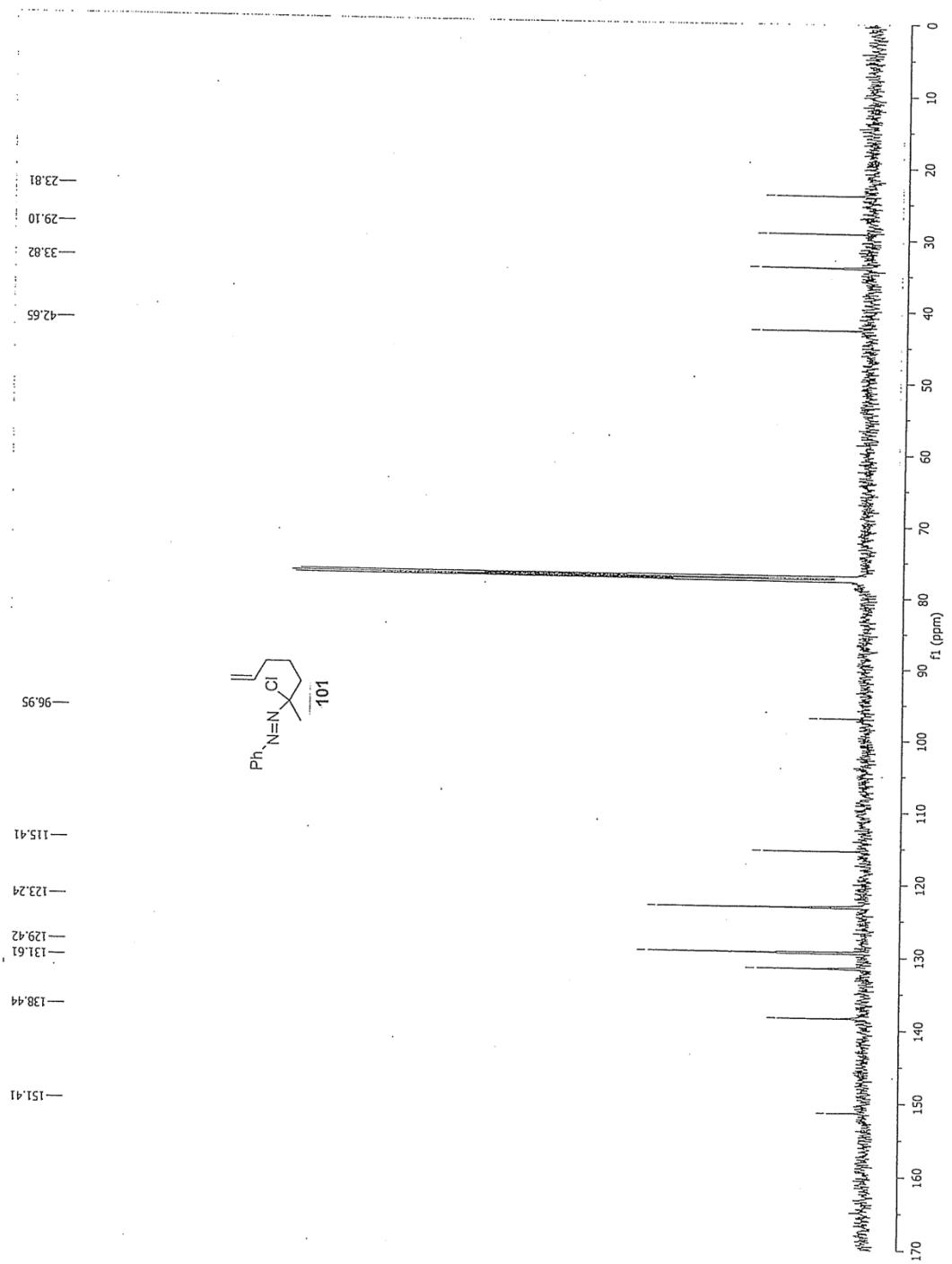
103
151.30
148.85
137.79
130.06
129.42
125.38
117.03
115.19
96.51
77.25
77.00
76.75
42.02
33.30
28.63
23.35
f1 (ppm)

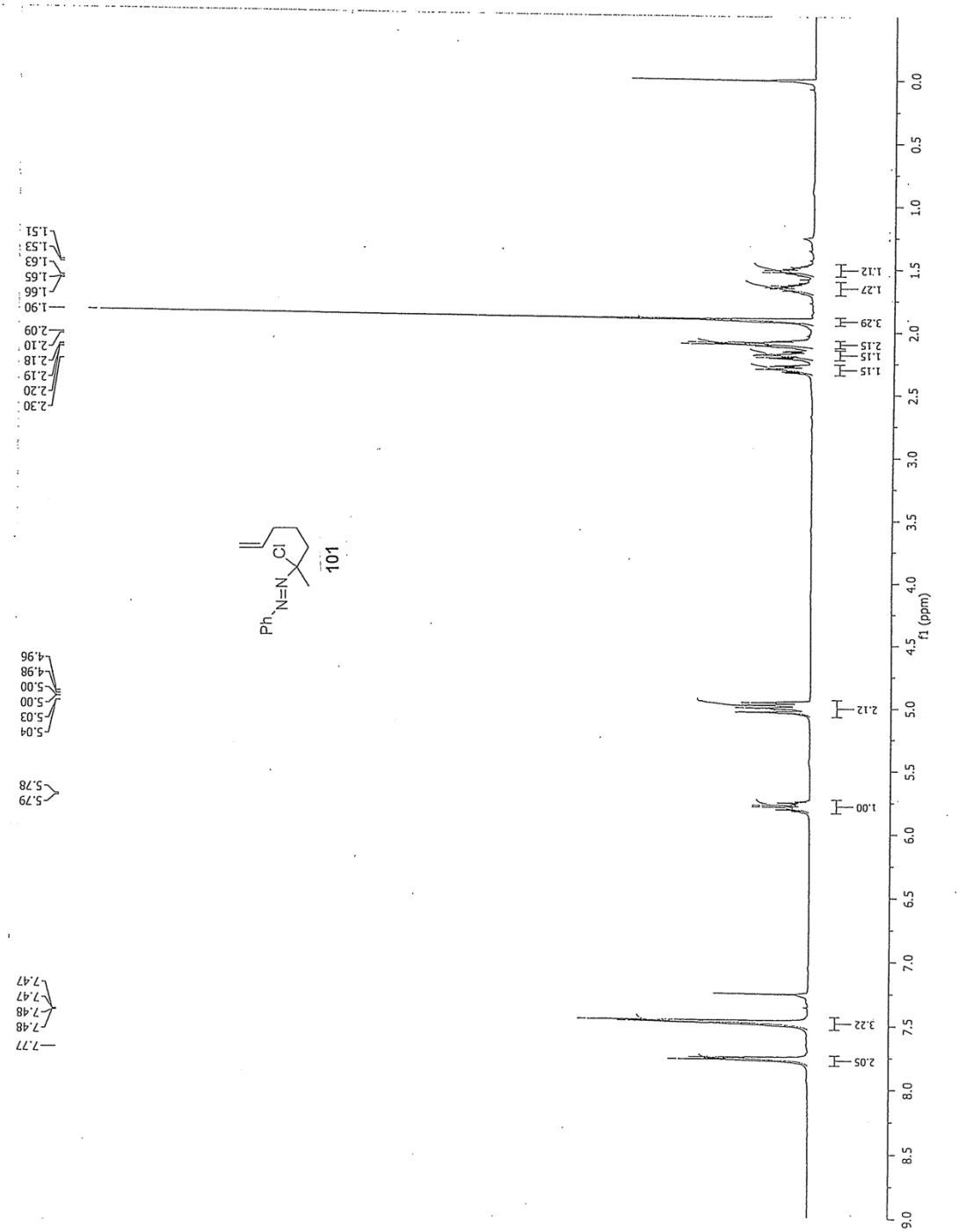

O2N
N
N
Cl
105
2.47
2.47
1.94
2.26
2.00
4.45
2.25
2.42
2.22
4.24
3.32
3.01
2.36
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


O_2N
N
N
Cl

105

151.30
148.85
137.79
130.06
129.42
125.38
117.03
115.19
96.51
77.25
77.00
76.75
42.02
33.30
28.63
23.35
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

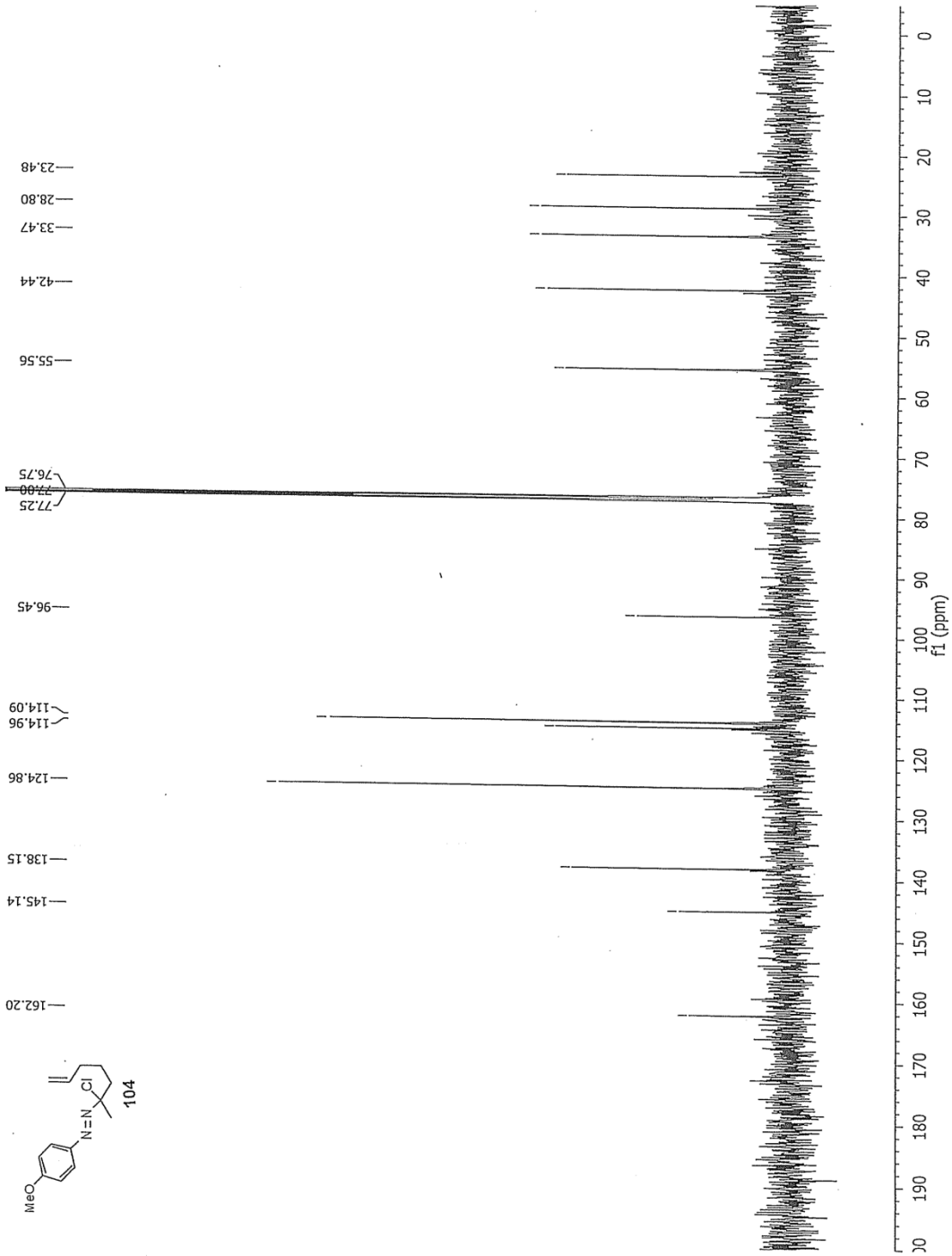

23.81
29.10
33.82
42.65
96.95
115.41
123.24
129.42
131.61
138.44
151.41
Ph
N=N
Cl
101
f1 (ppm)


Ph
N=N
Cl
101
7.77
7.48
7.48
7.47
7.47
5.79
5.78
5.04
5.03
5.00
5.00
4.98
4.96
2.30
2.20
2.19
2.18
2.10
2.09
1.90
1.66
1.65
1.63
1.53
1.51
2.05
3.22
1.00
2.12
1.15
1.15
2.15
3.29
1.27
1.12
f1 (ppm)

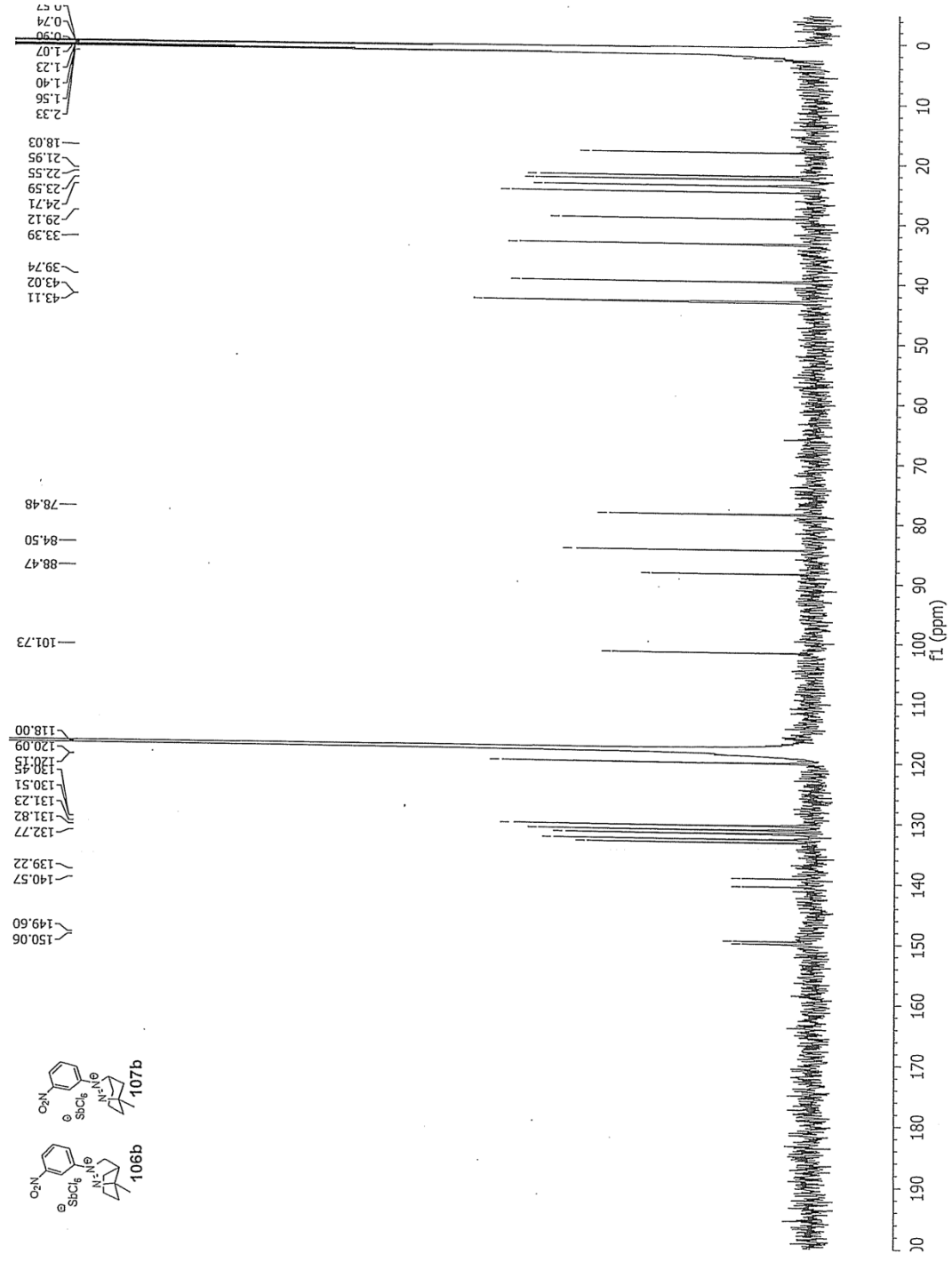
Cl
N=N
Cl
102
1.88
1.99
1.00
2.06
1.09
1.19
2.24
3.10
1.21
1.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

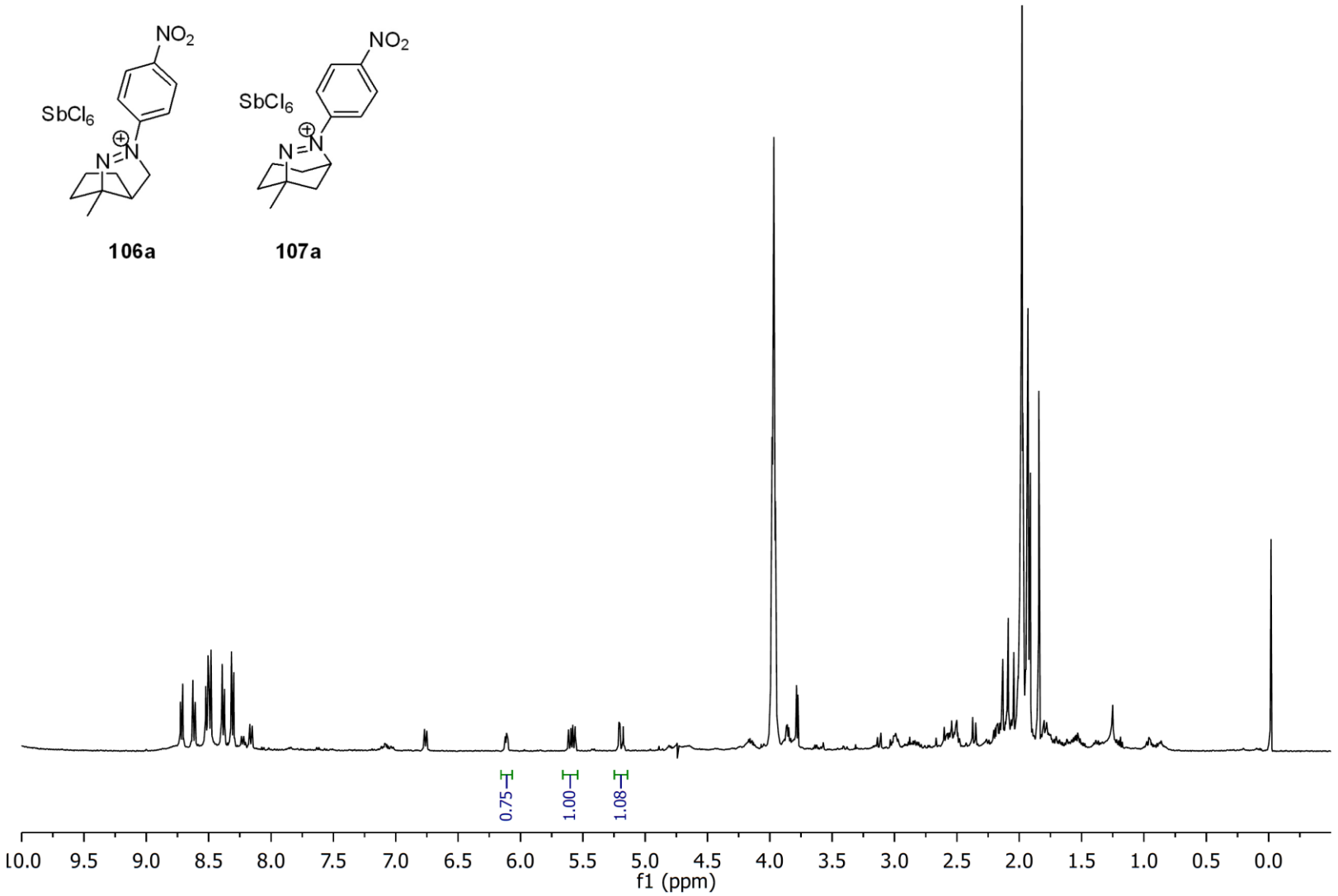
102
149.31
137.98
137.34
129.32
124.22
115.10
96.49
77.25
77.00
76.75
42.22
33.41
28.69
23.42
f1 (ppm)

MeO
N=N
Cl
104
1.91
2.04
1.00
2.07
3.04
1.22
1.34
2.21
3.05
1.18
0.98
f1 (ppm)

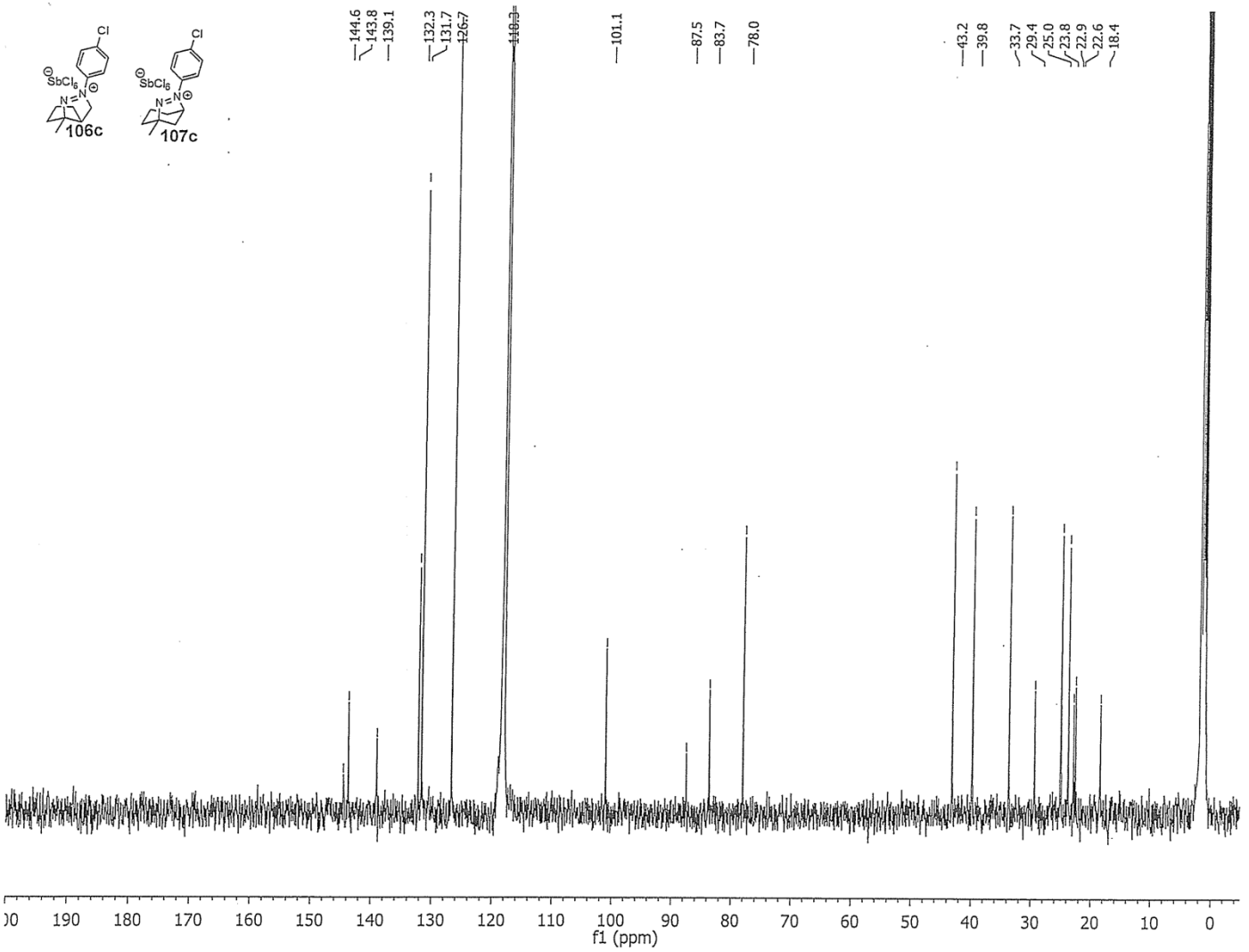

MeO
N=N
Cl
104
162.20
145.14
138.15
124.86
114.96
114.09
96.45
77.25
77.00
76.75
55.56
42.44
33.47
28.80
23.48
f1 (ppm)

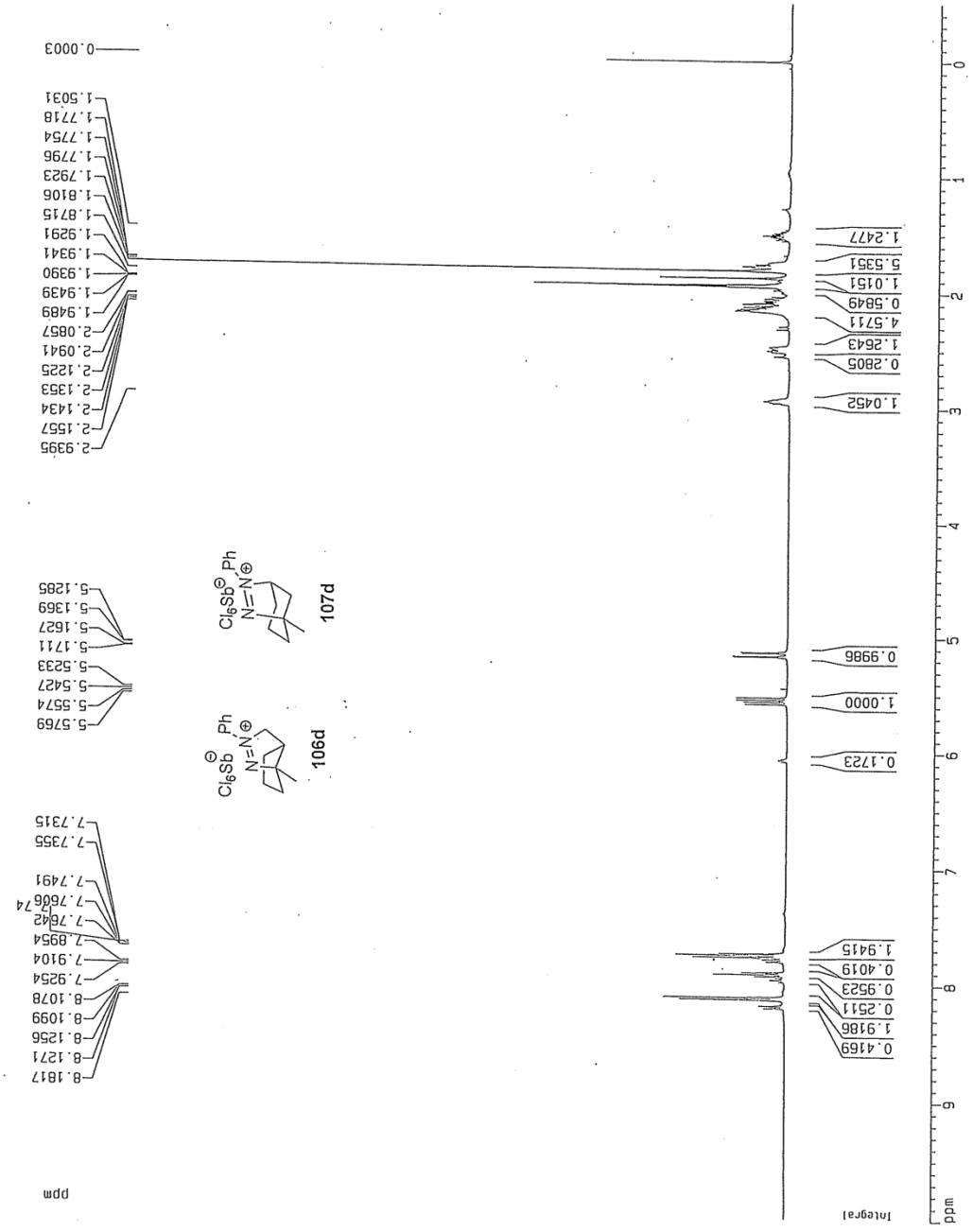
O2N
SbCl6
N2
106b
107b
0.92
1.07
1.06
1.12
1.12
1.22
1.12
1.21
0.92
1.04
1.00
1.13
2.22
1.13
1.04
1.47
f1 (ppm)

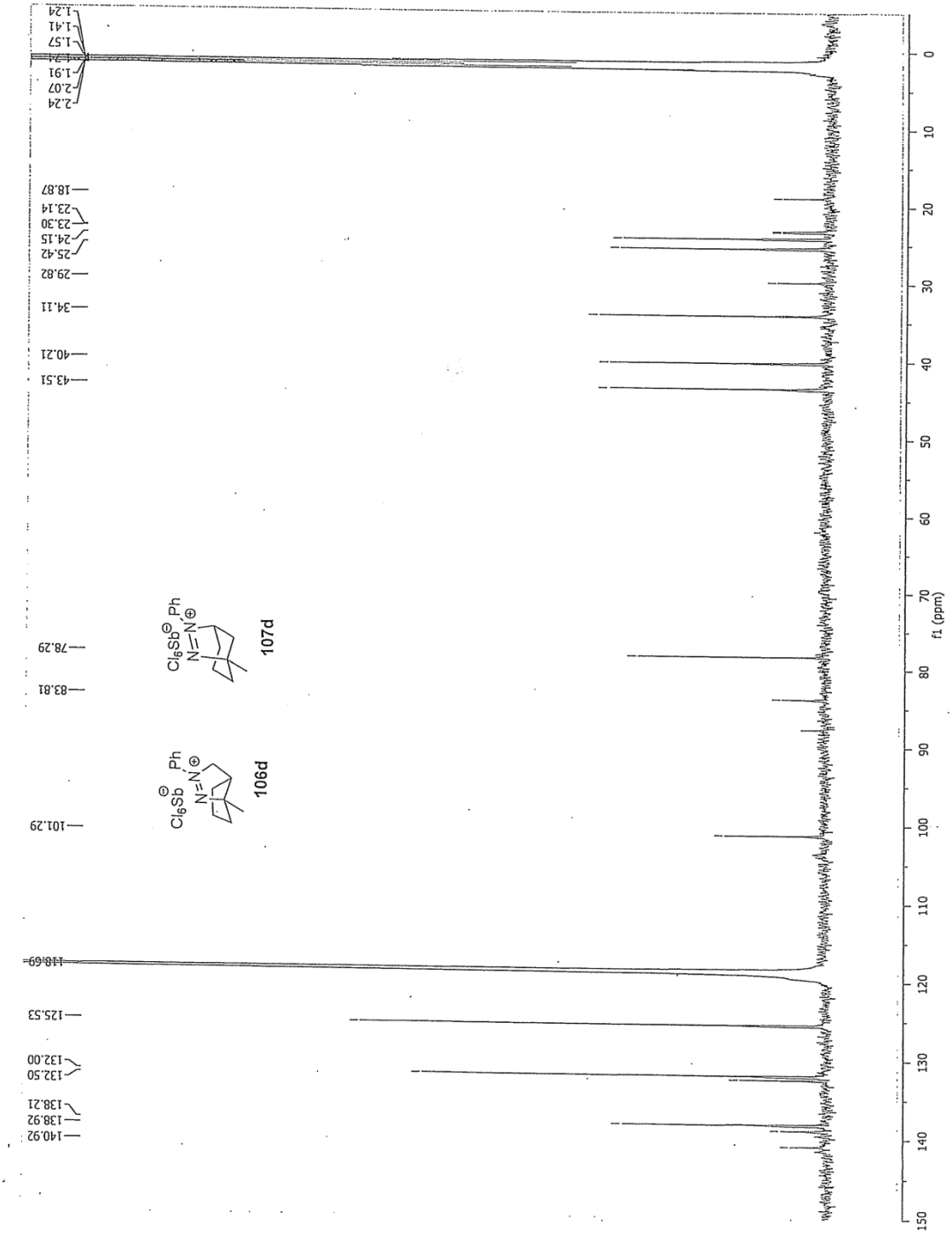

106b
107b
f1 (ppm)

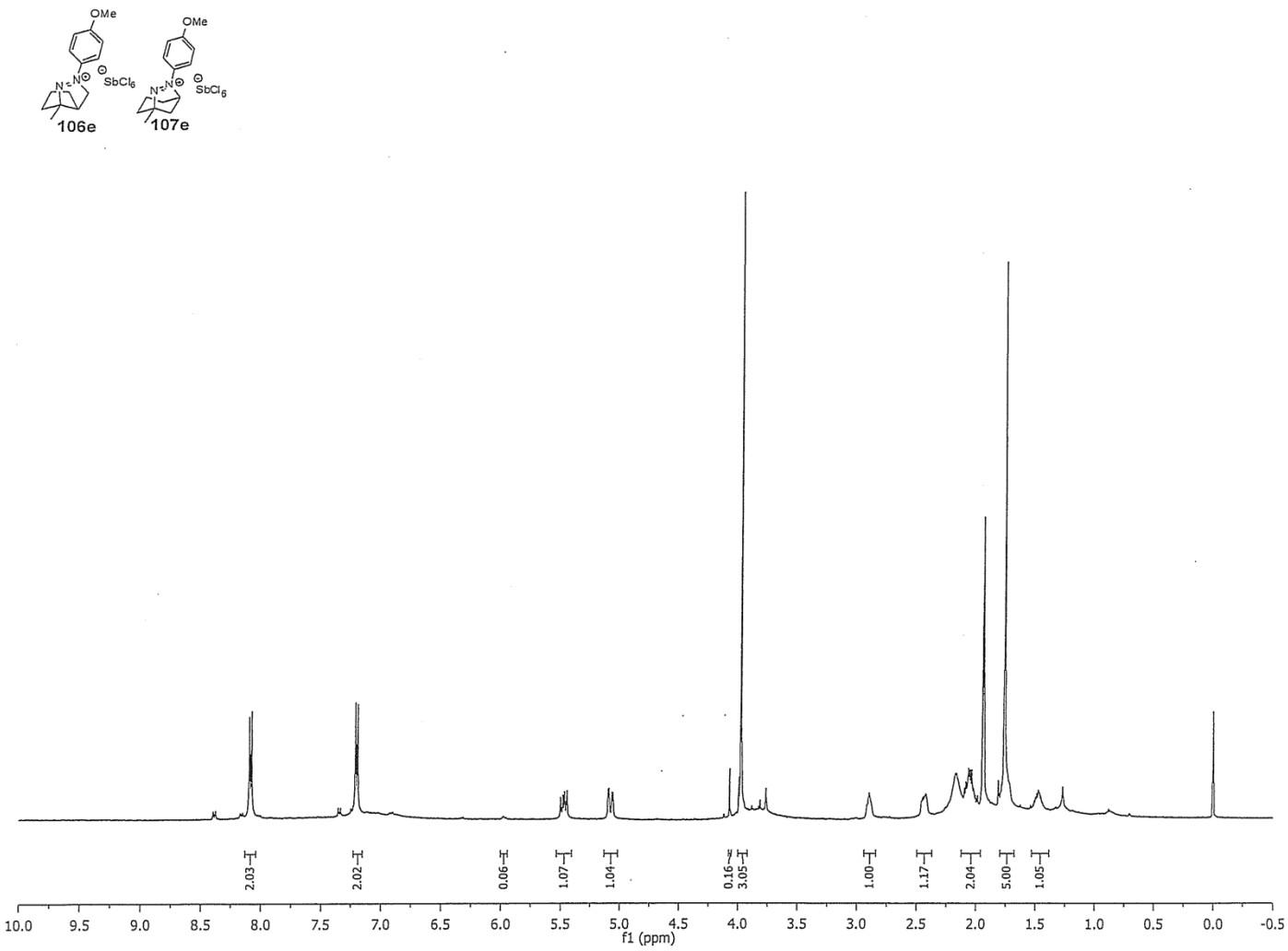

NO2
SbCl6
N
N
106a
NO2
SbCl6
N
N
107a
0.75
1.00
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

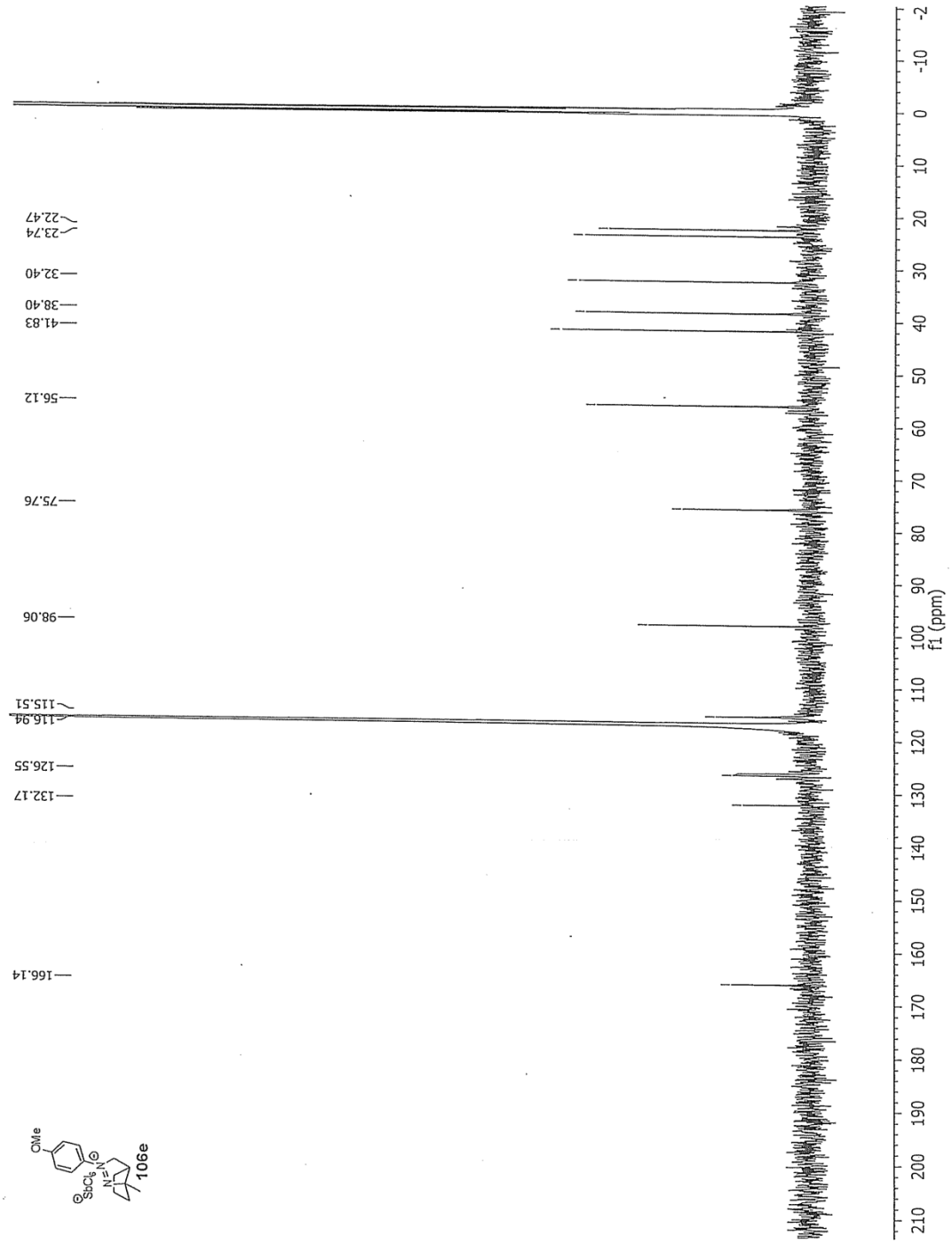
Cl
SbCl6
N=N
107c
106c
0.78
2.00
0.80
2.00
0.38
1.07
1.06
1.15
1.74
2.42
1.28
3.69
2.20
1.28
f1 (ppm)

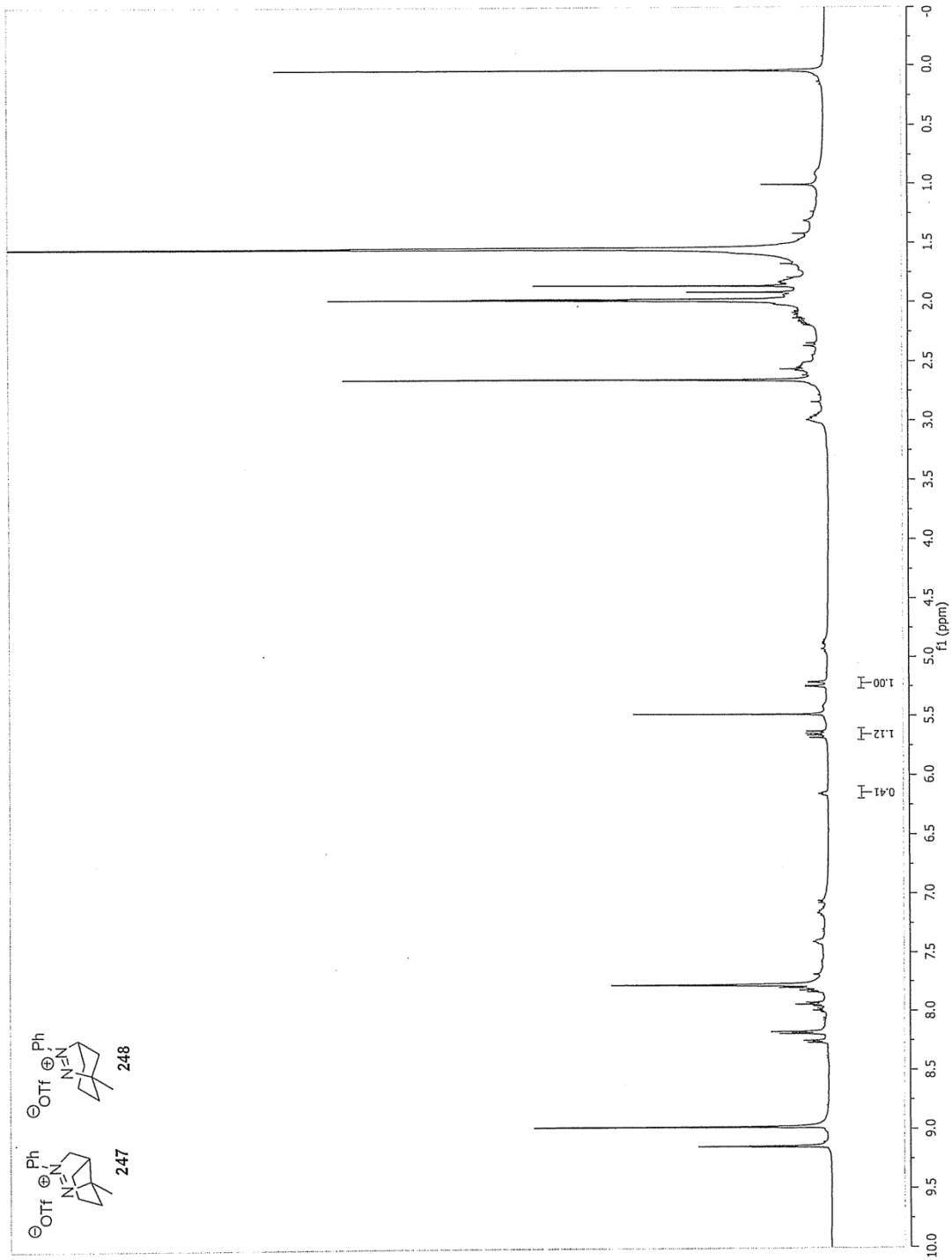

106c
107c
144.6
143.8
139.1
132.3
131.7
126.7
110.3
101.1
87.5
83.7
78.0
43.2
39.8
33.7
29.4
25.0
23.8
22.9
22.6
18.4
f1 (ppm)

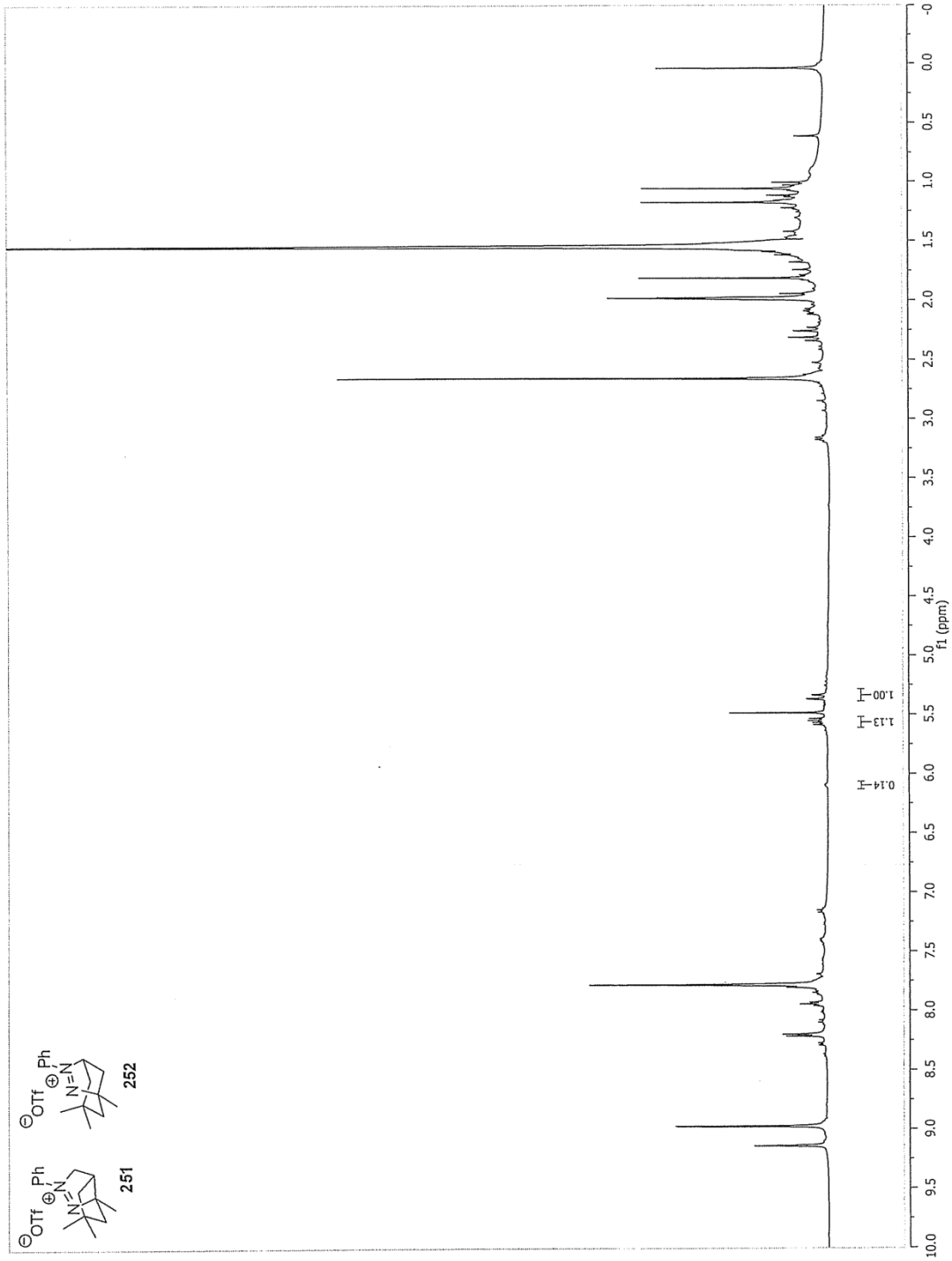

0.0003
1.5031
1.7718
1.7754
1.7796
1.7923
1.8106
1.8715
1.9291
1.9341
1.9390
1.9439
1.9489
2.0857
2.0941
2.1225
2.1353
2.1434
2.1557
2.9395
1.2477
5.5351
1.0151
0.5849
4.5711
1.2643
0.2805
1.0452
0.9986
1.0000
0.1723
1.9415
0.4019
0.9523
0.2511
1.9186
0.4169
5.1285
5.1369
5.1627
5.1711
5.5233
5.5427
5.5574
5.5769
7.3315
7.3555
7.4991
7.7606
7.7642
7.8954
7.9104
7.9254
8.1078
8.1099
8.1256
8.1271
8.1817
106d
107d
ppm
Integral

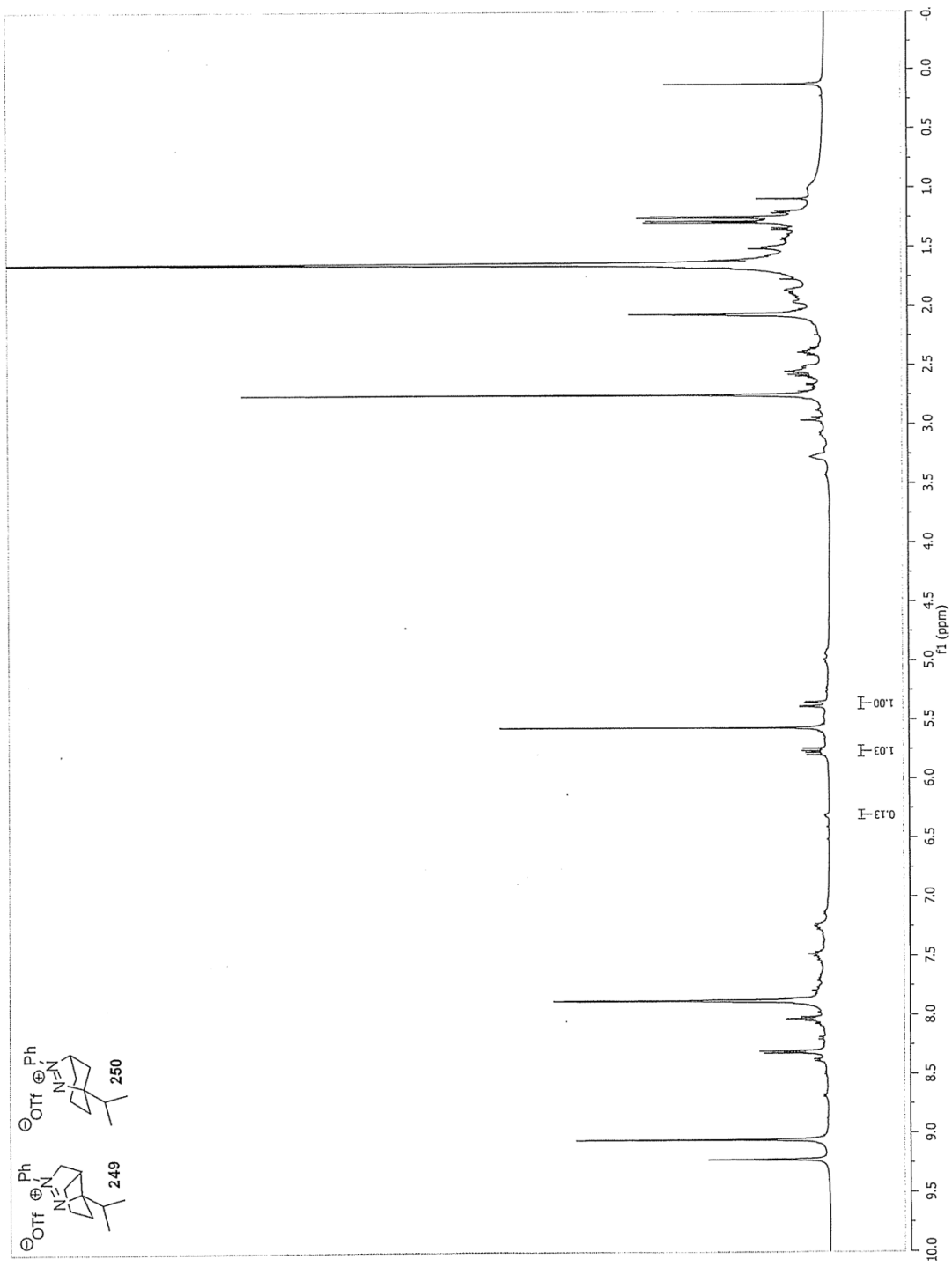

2.24
2.07
1.91
1.57
1.41
1.24
18.87
23.14
23.30
24.15
25.42
29.82
34.11
40.21
43.51
78.29
83.81
101.29
118.69
125.53
132.50
132.00
138.21
138.92
140.92
Cl6Sb⊖
Ph
N=N⊕
106d
Cl6Sb⊖
Ph
N=N⊕
107d
f1 (ppm)

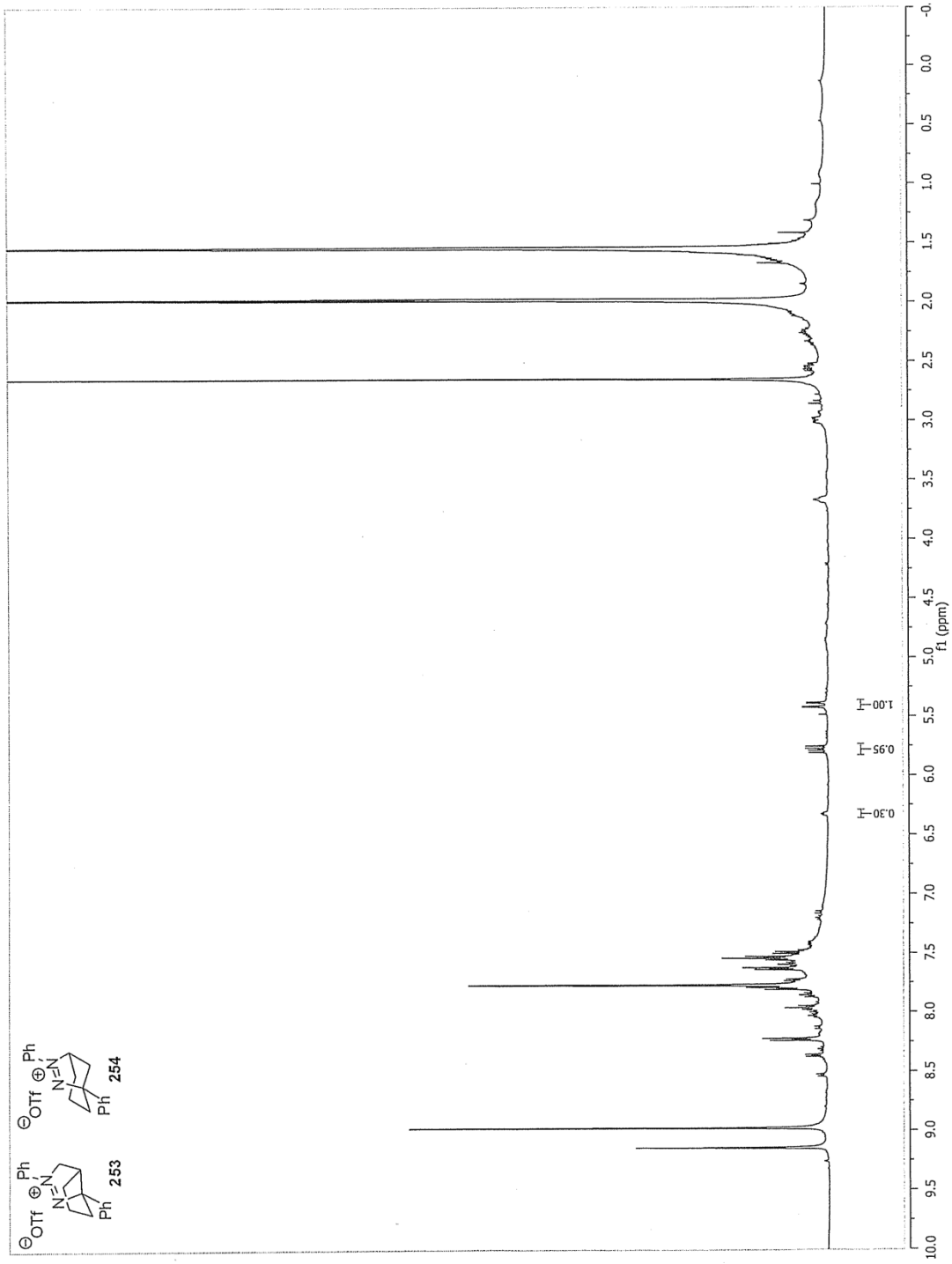

OMe
SbCl6
106e
OMe
SbCl6
107e
2.03
2.02
0.06
1.07
1.04
0.16
3.05
1.00
1.17
2.04
5.00
1.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

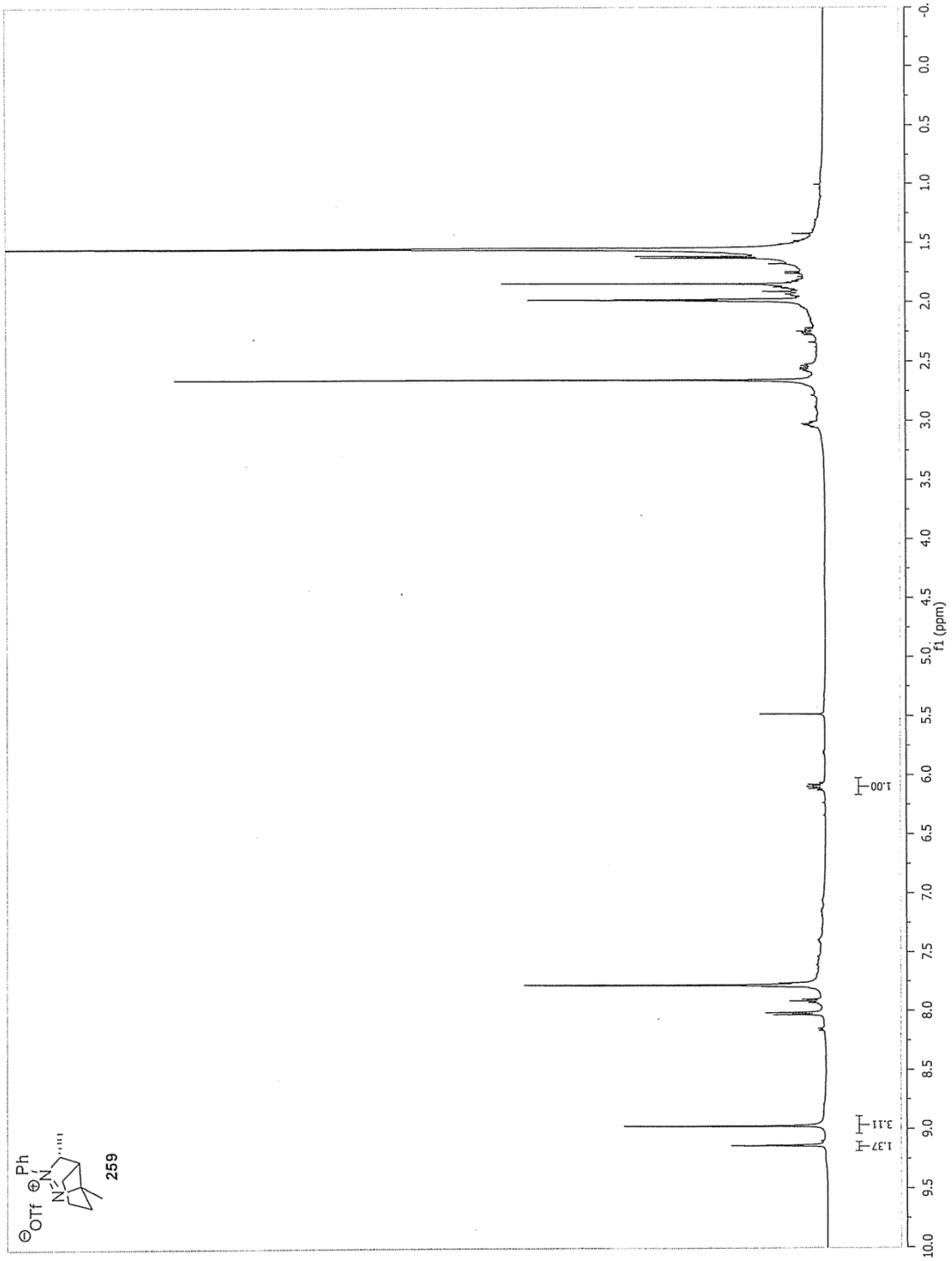

166.14
132.17
126.55
116.94
115.51
98.06
75.76
56.12
41.83
38.40
32.40
23.74
22.47
OMe
SbCl5
106e
f1 (ppm)

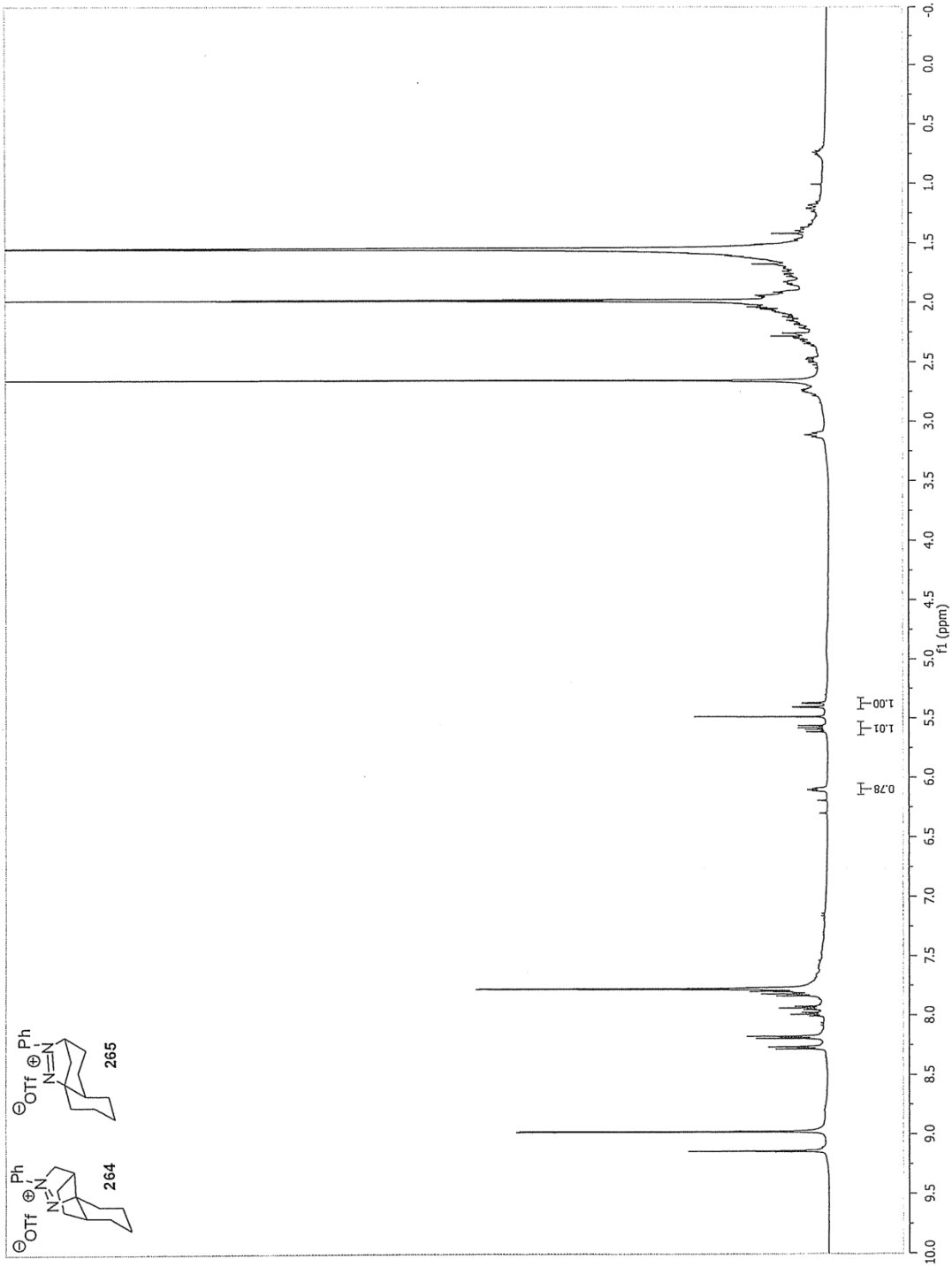

Ph
N=N
⊖OTf ⊕
247
Ph
N=N
⊖OTf ⊕
248
0.41
1.12
1.00
f1 (ppm)

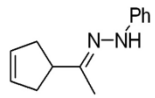

OTf
Ph
N=N
251
252
1.00
1.13
0.14
f1 (ppm)


249
250
0.13
1.03
1.00
f1 (ppm)

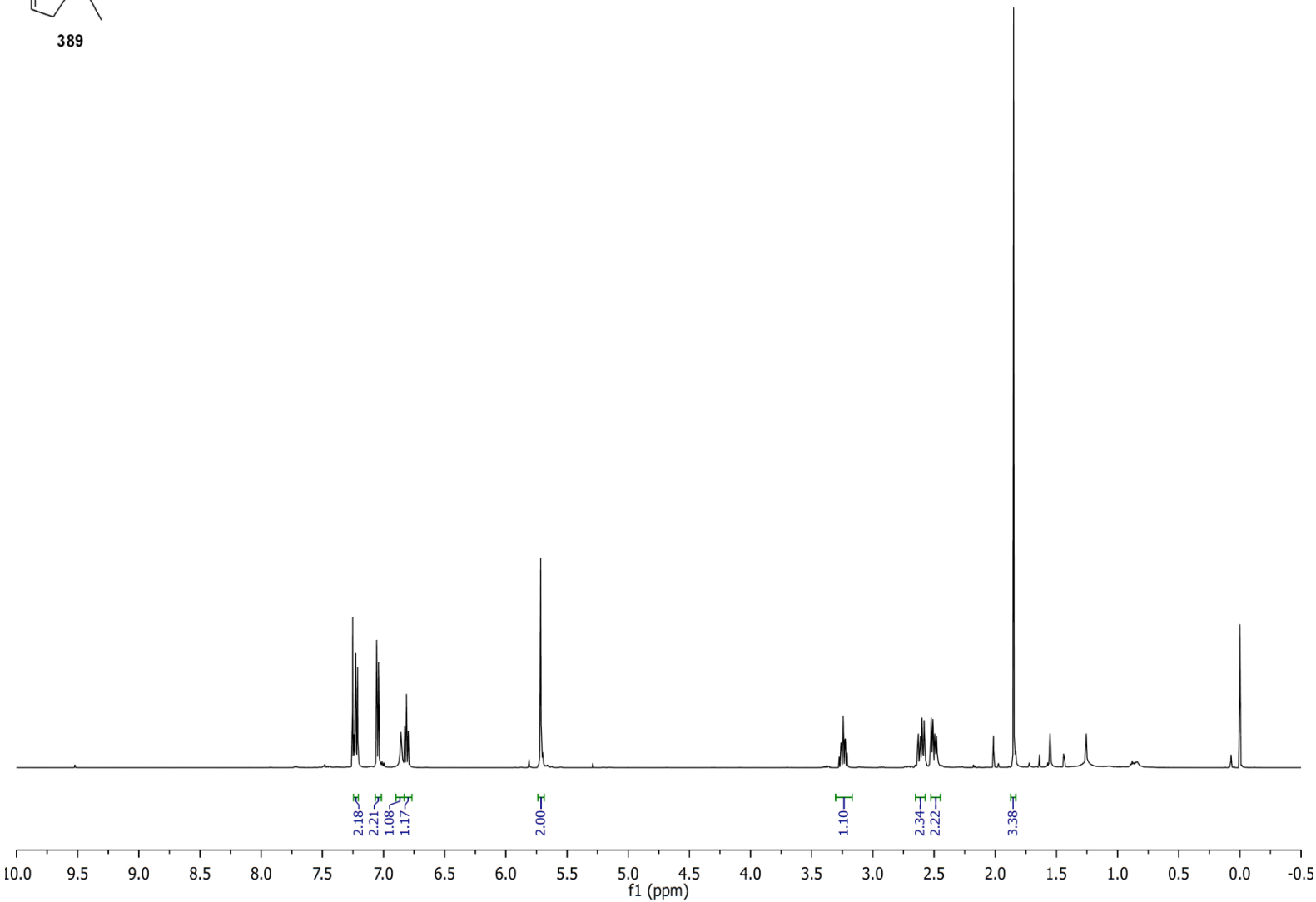

Ph
⊕
N
N
⊖OTf
Ph
253
Ph
⊕
N
N
⊖OTf
Ph
254
1.00
0.95
0.30
f1 (ppm)

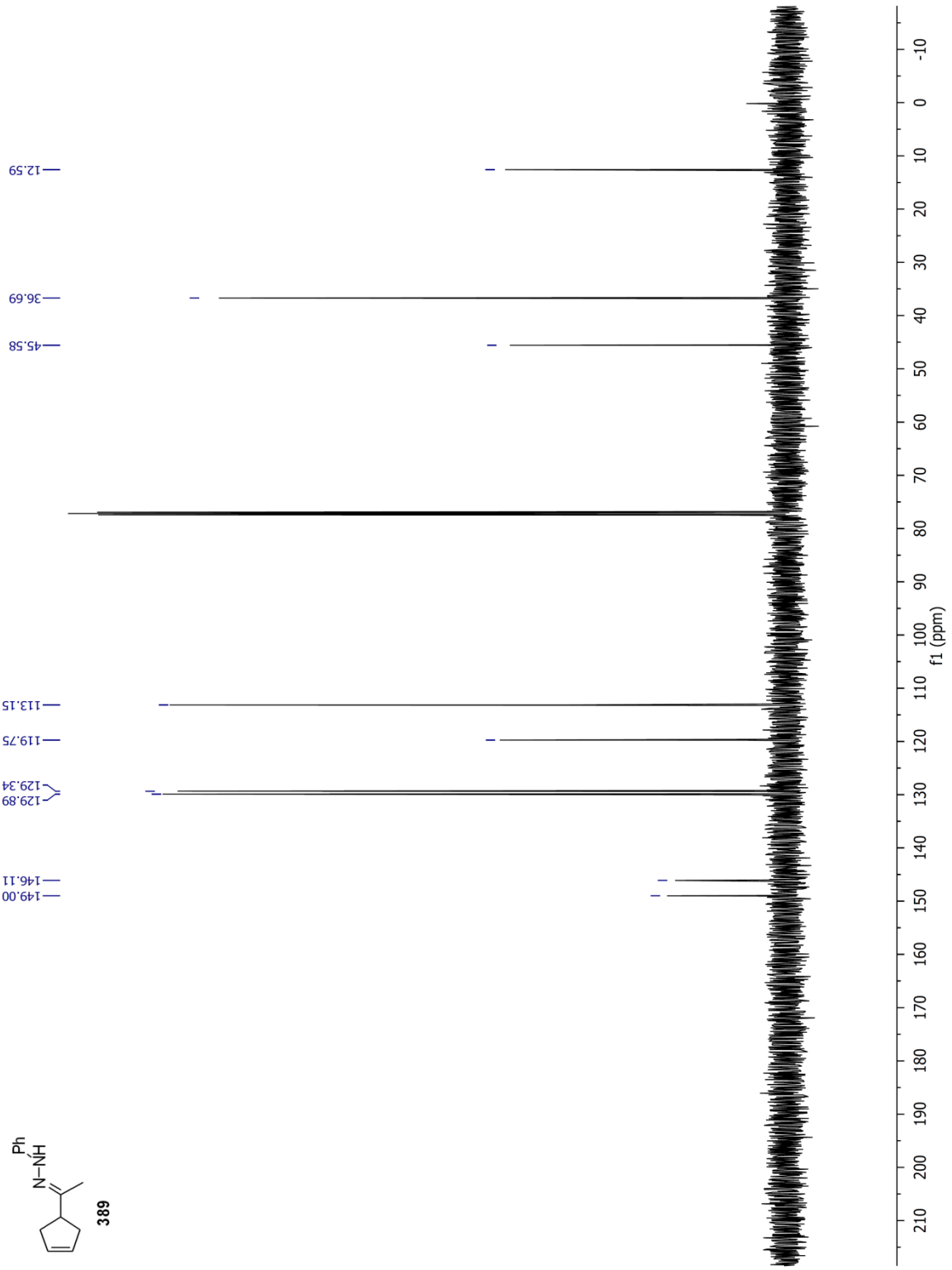

259
1.37
3.11
1.00
f1 (ppm)

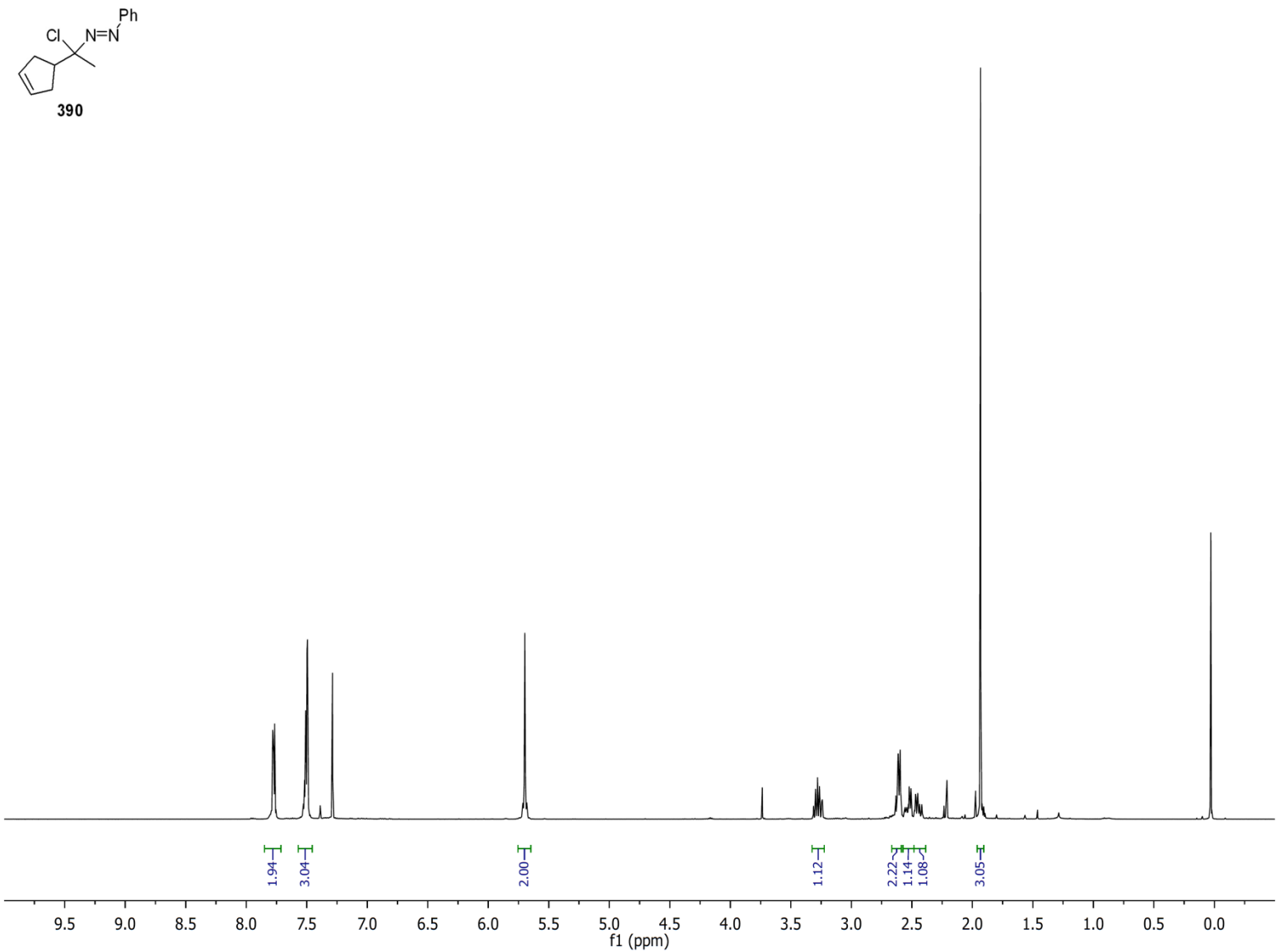

OTf
Ph
N=N
264
265
0.78
1.01
1.00
f1 (ppm)

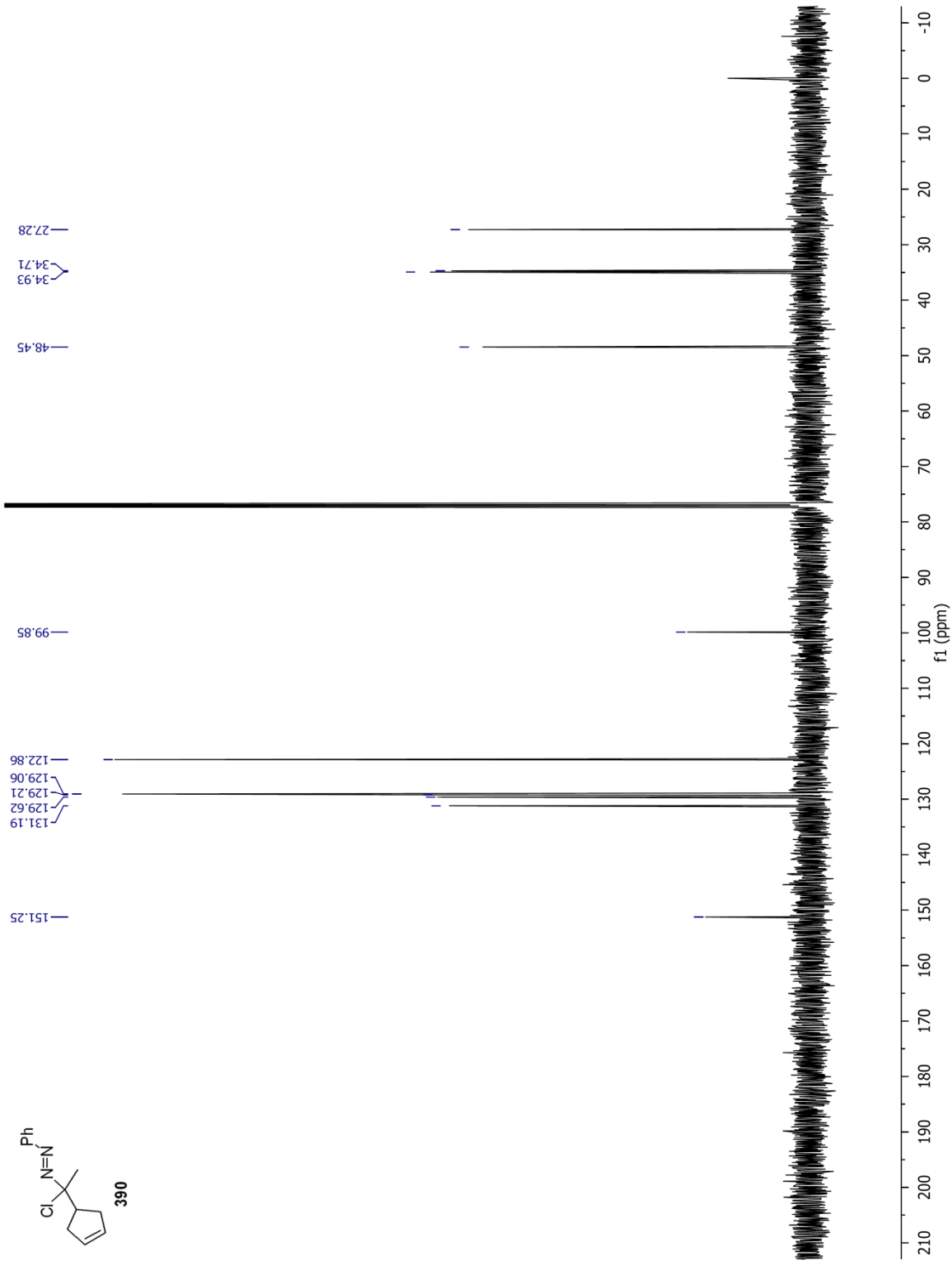

Ph
N–NH

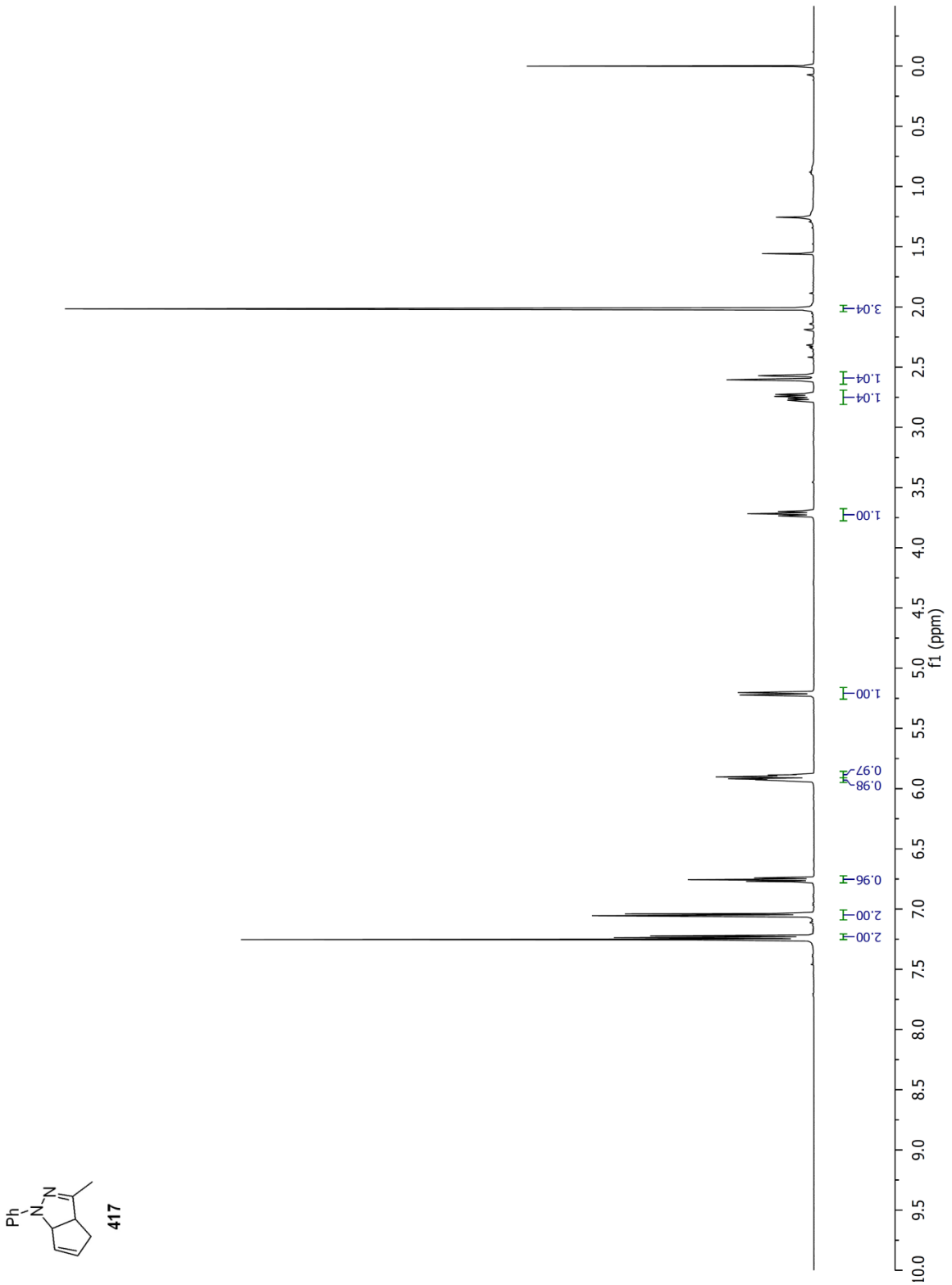
389

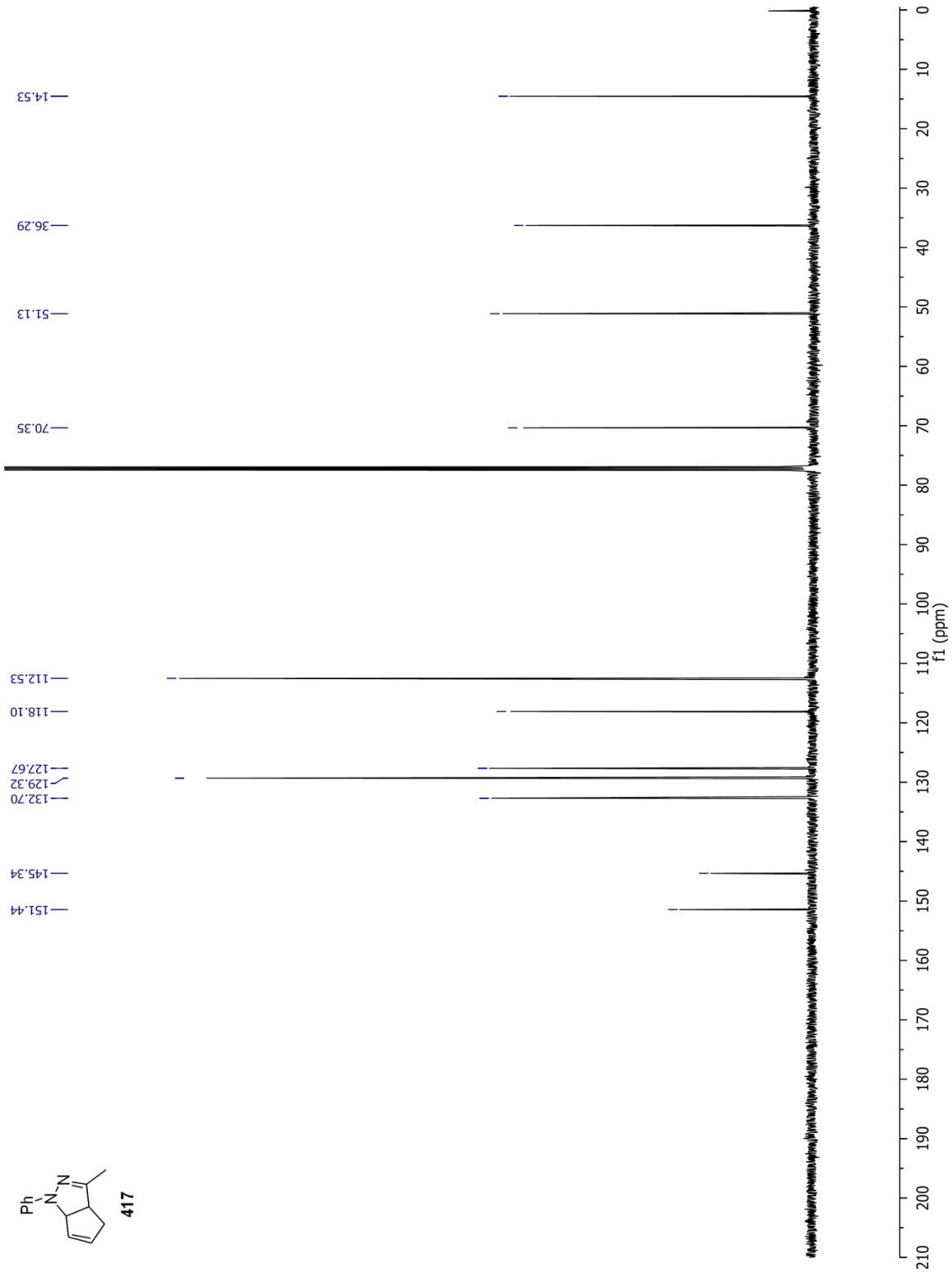

2.18
2.21
1.08
1.17
2.00
1.10
2.34
2.22
3.38
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

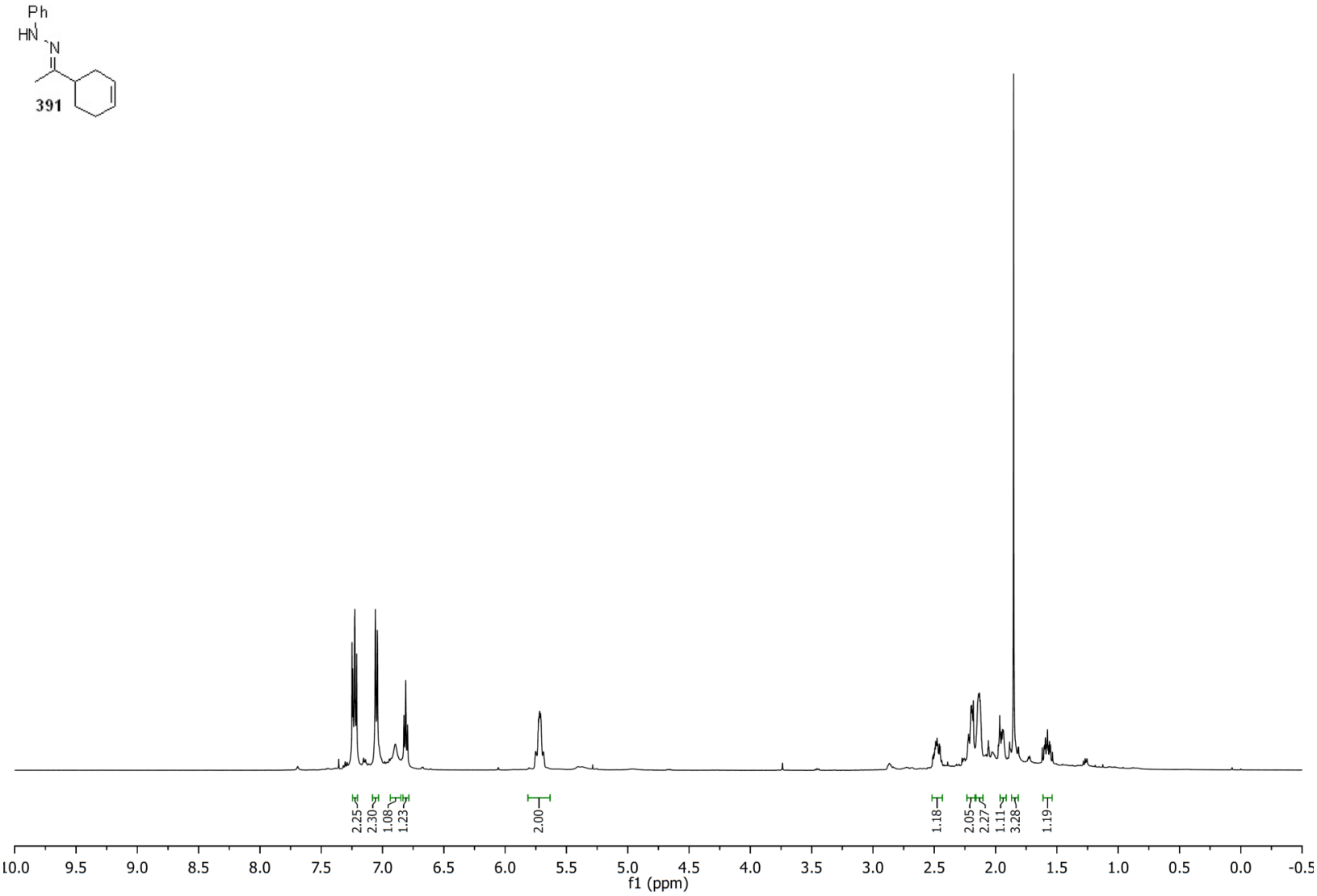

Ph
HN
N
389
149.00
146.11
129.89
129.34
119.75
113.15
45.58
36.69
12.59
f1 (ppm)

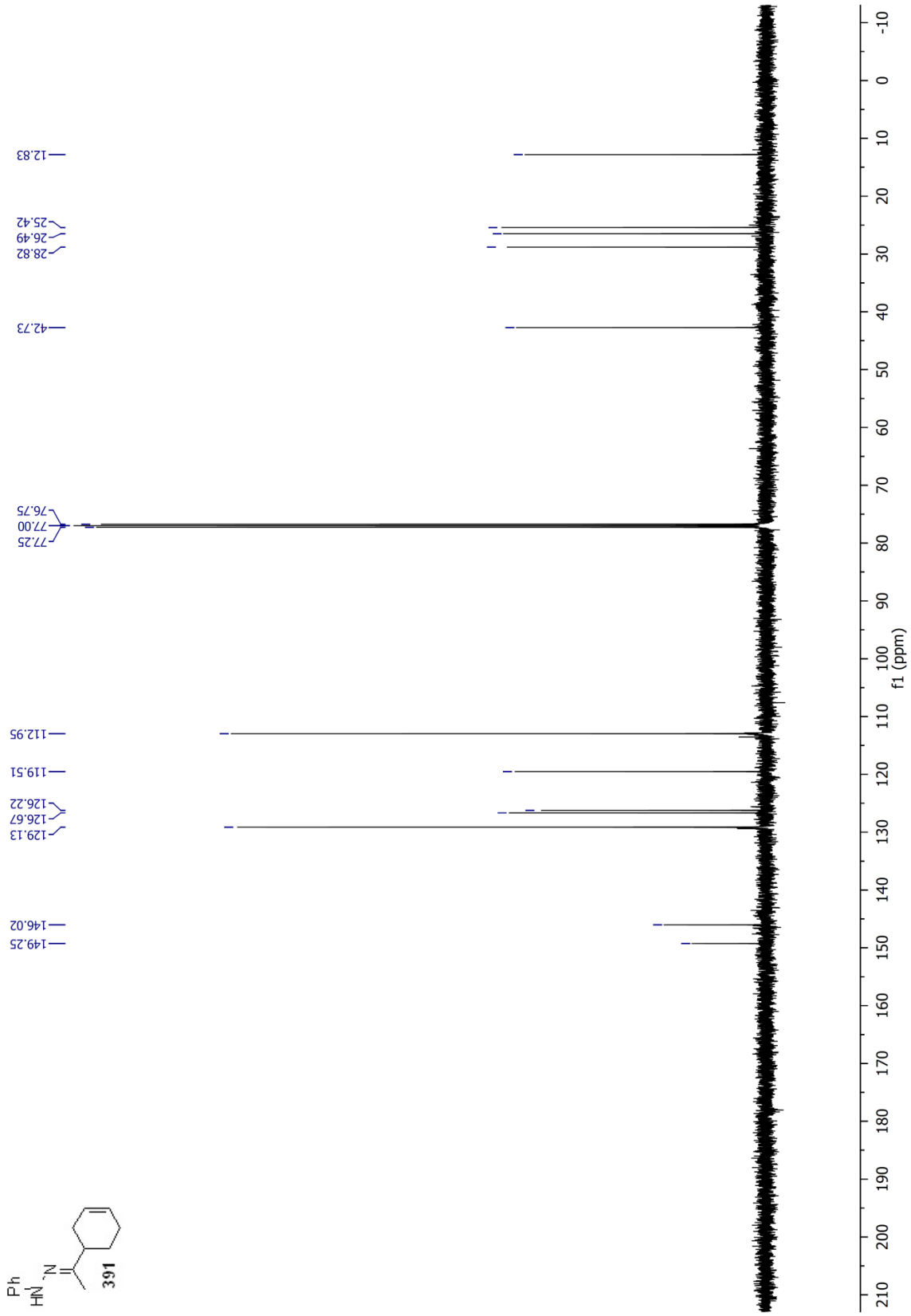

Cl
N=N
Ph
390
1.94
3.04
2.00
1.12
2.22
1.14
1.08
3.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

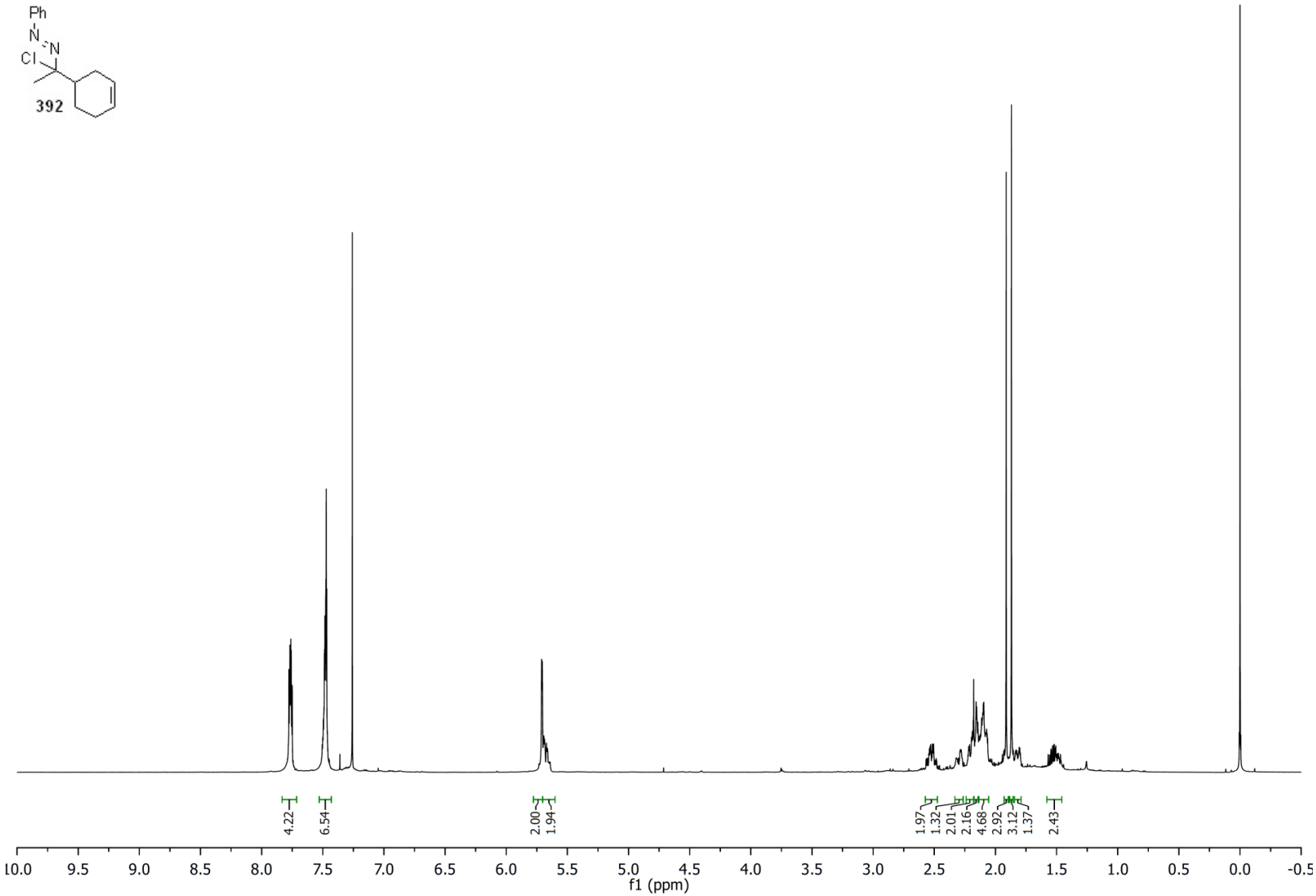

Ph
N=N
Cl
390
151.25
131.19
129.62
129.21
129.06
122.86
99.85
48.45
34.93
34.71
27.28
f1 (ppm)

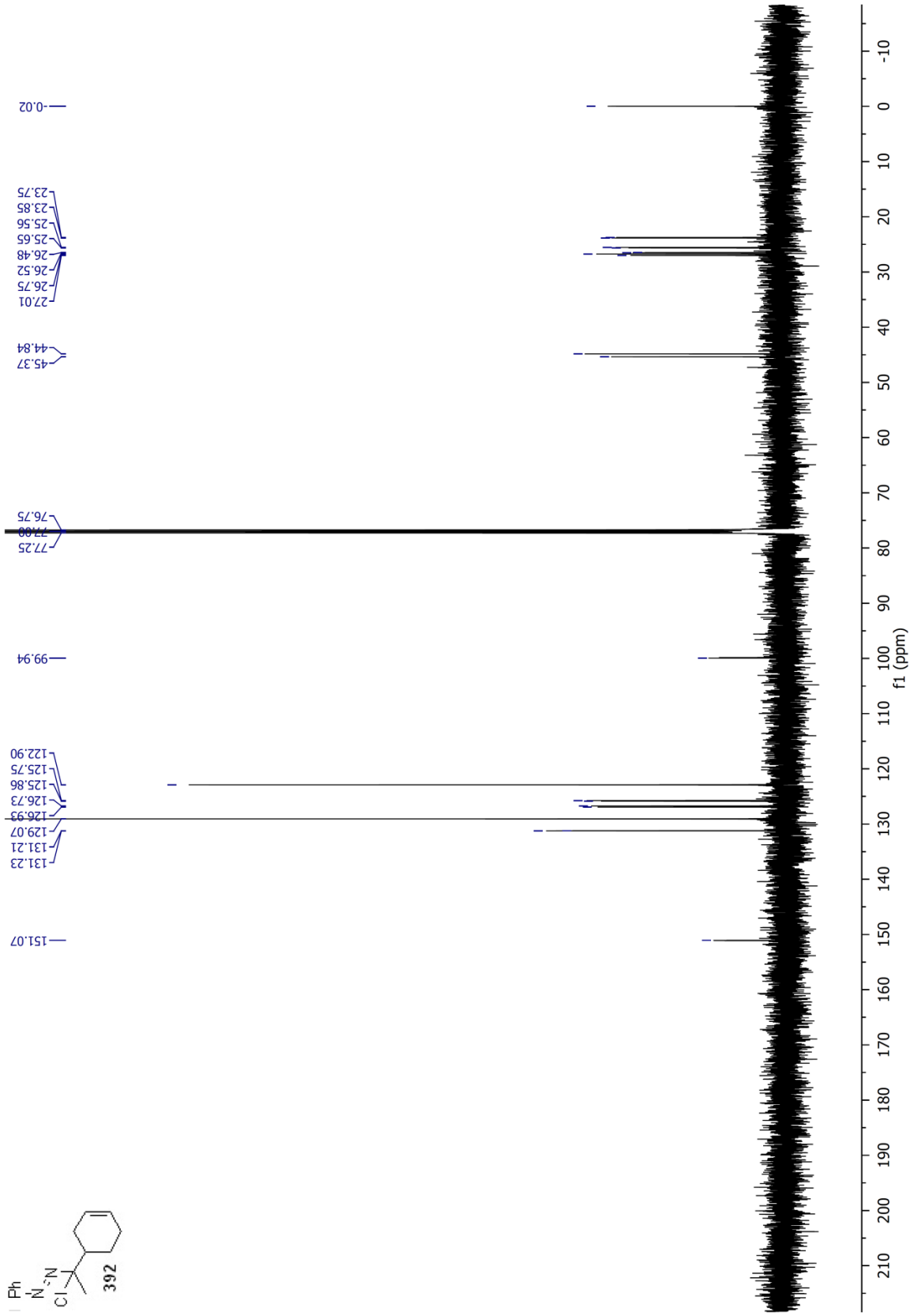

Ph
N
N
417
3.04
1.04
1.04
1.00
1.00
0.98
0.97
0.96
2.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

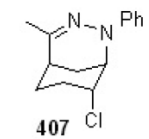

Ph
N
N
417
151.44
145.34
132.70
129.32
127.67
118.10
112.53
70.35
51.13
36.29
14.53
f1 (ppm)


Ph
HN
N
391
2.25
2.30
1.08
1.23
2.00
1.18
2.05
2.27
1.11
3.28
1.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


391
12.83
25.42
26.49
28.82
42.73
76.75
77.00
77.25
112.95
119.51
126.22
126.67
129.13
146.02
149.25
f1 (ppm)

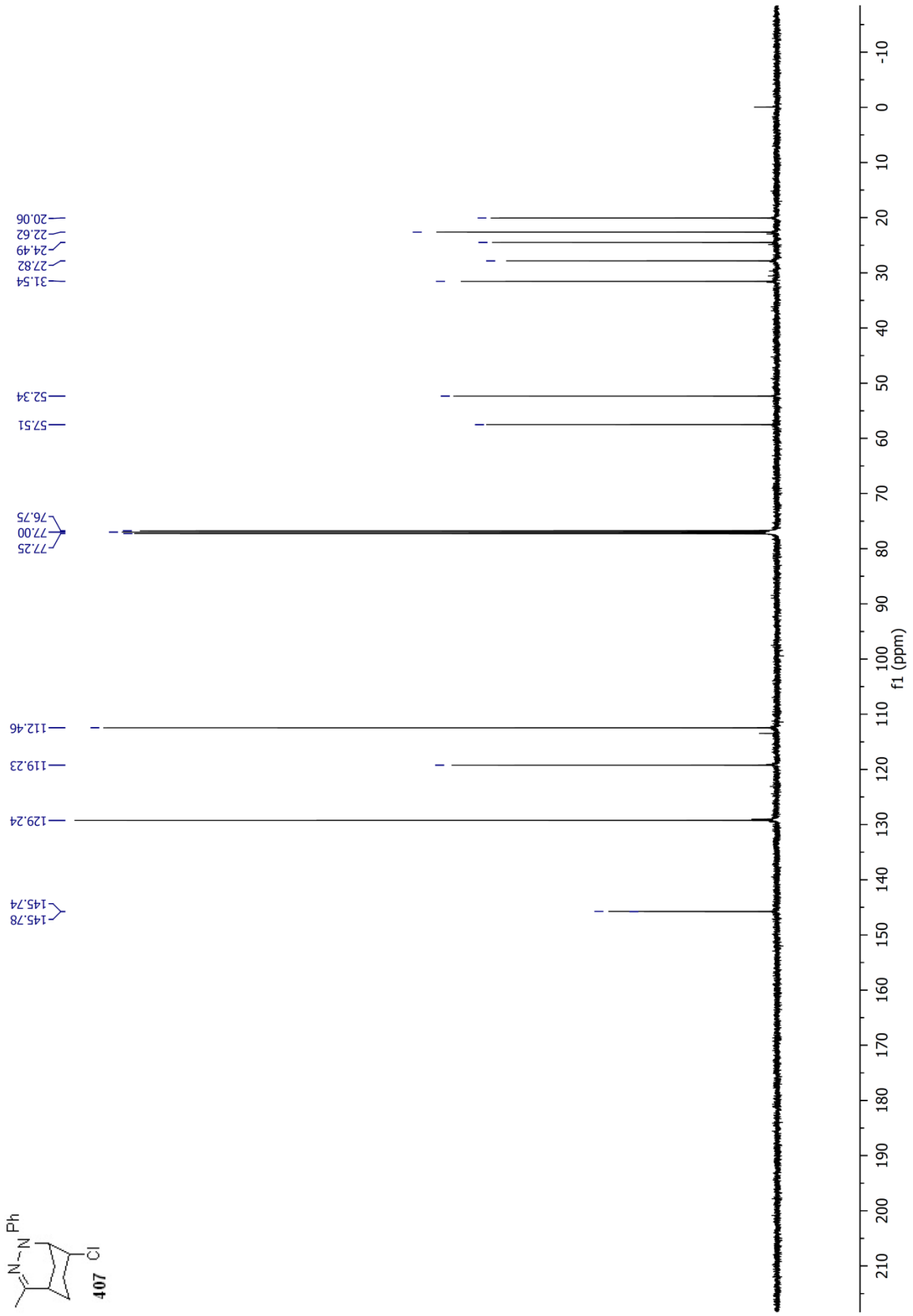

Ph
N
N
Cl
392
4.22
6.54
2.00
1.94
1.97
1.32
2.01
2.16
4.68
2.92
3.12
1.37
2.43
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

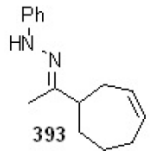

Ph
N
N
Cl
392
-0.02
23.75
23.85
25.56
25.65
26.48
26.52
26.75
27.01
44.84
45.37
76.75
77.00
77.25
99.94
122.90
125.75
125.86
126.73
126.93
129.07
131.21
131.23
151.07
f1 (ppm)

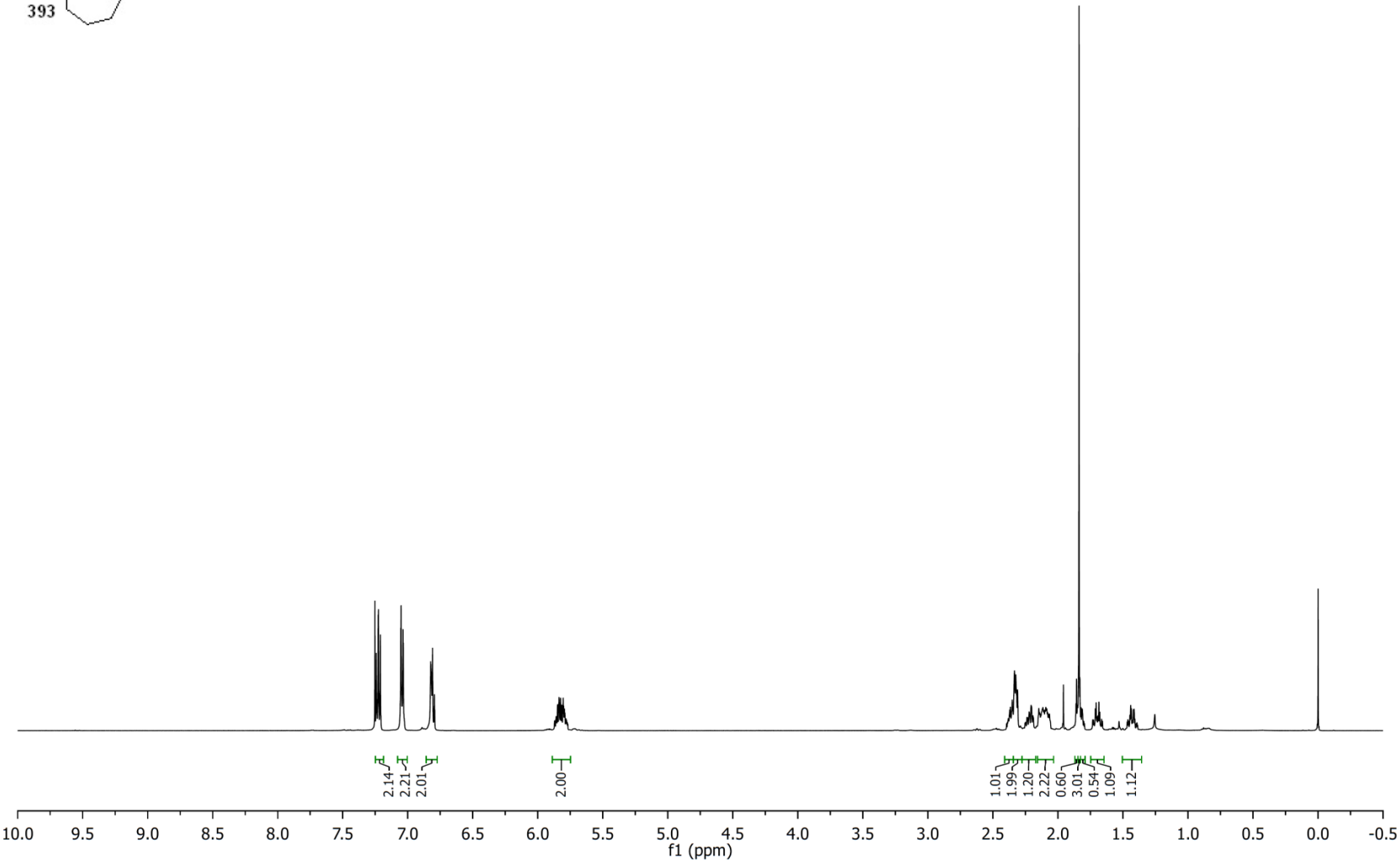

N
N
Ph
Cl

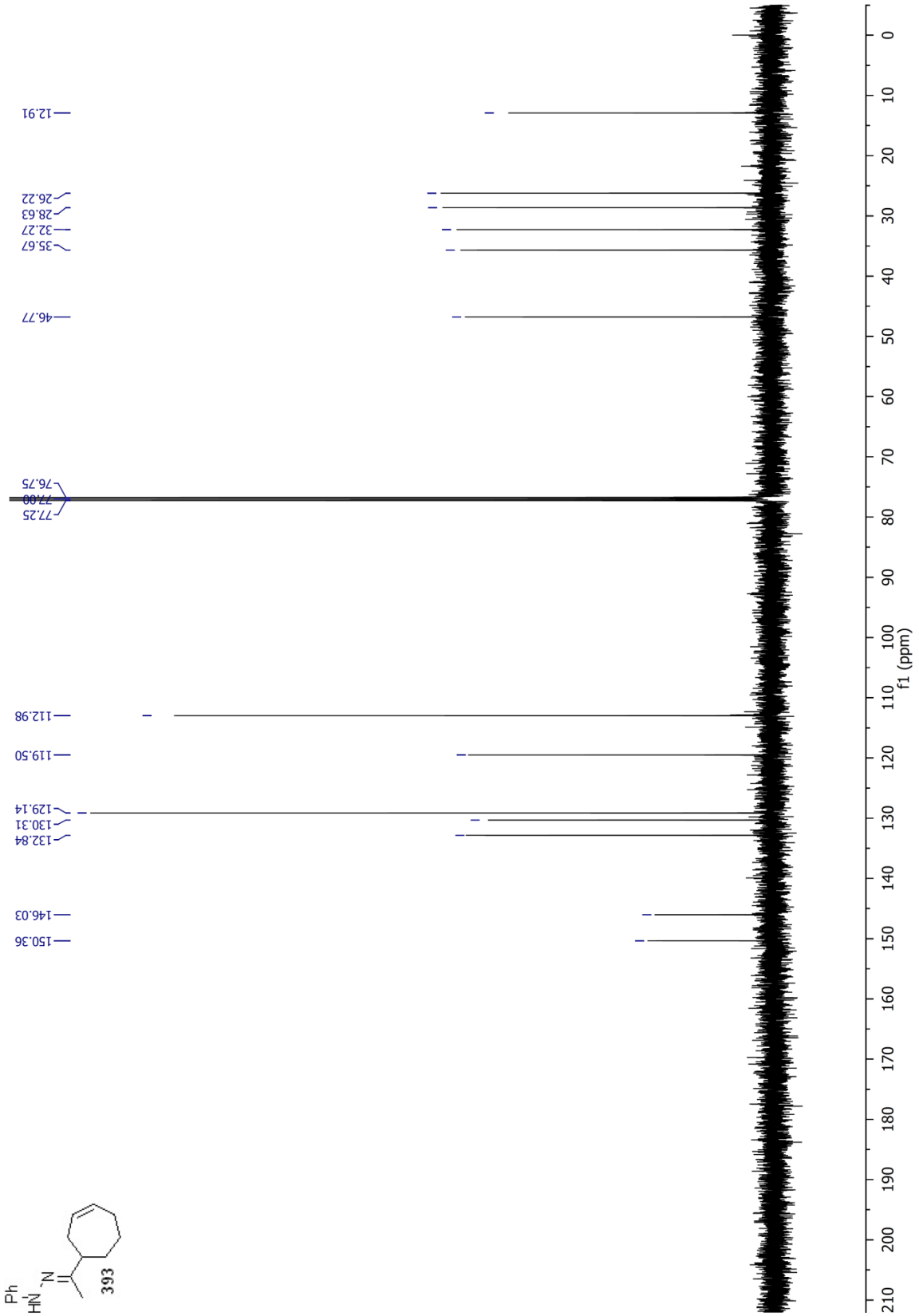
407

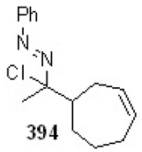
2.36
2.08
1.01
1.00
1.01
1.12
1.11
0.76
2.94
0.38
1.35
2.09
1.32
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


145.78
145.74
129.24
119.23
112.46
77.25
77.00
76.75
57.51
52.34
31.54
27.82
24.49
22.62
20.06
f1 (ppm)
Ph
N
N
Cl
407

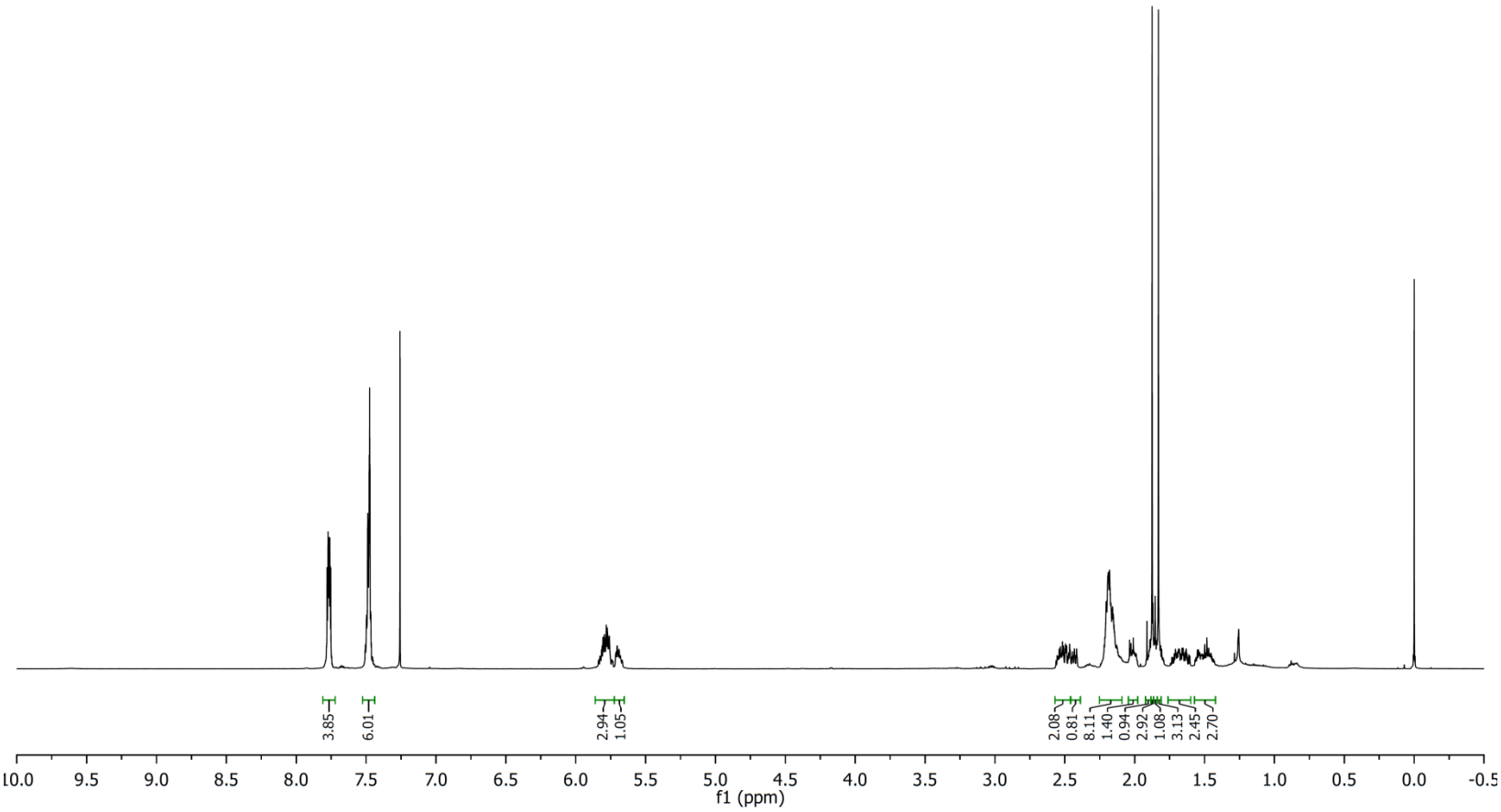

Ph
HN
N
393

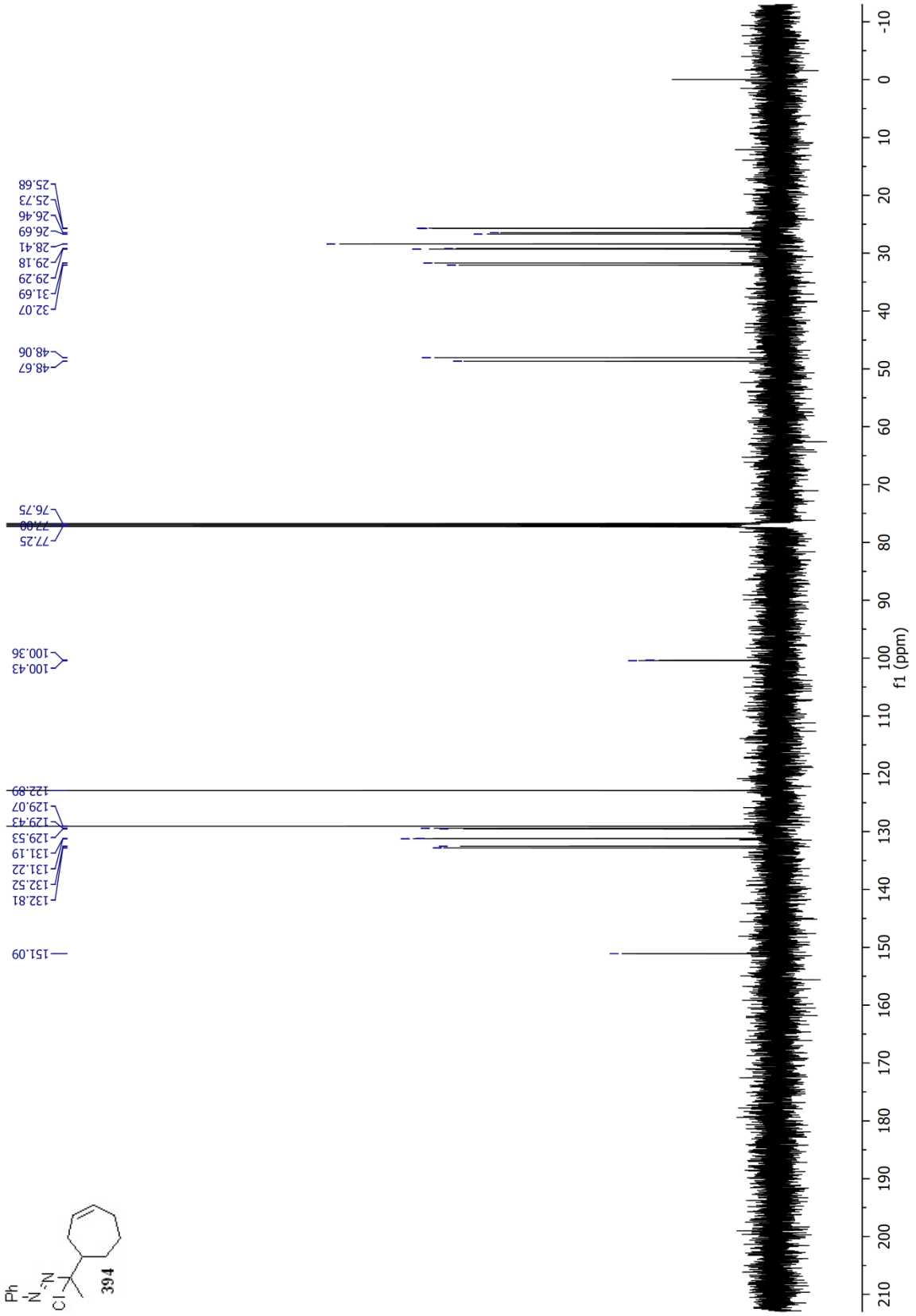

2.14
2.21
2.01
2.00
1.01
1.99
1.20
2.22
0.60
3.01
0.54
1.09
1.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

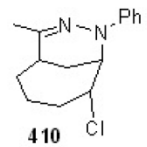

12.91
26.22
28.63
32.27
35.67
46.77
76.75
77.00
77.25
112.98
119.50
129.14
130.31
132.84
146.03
150.36
f1 (ppm)
393


Ph
N
N
Cl

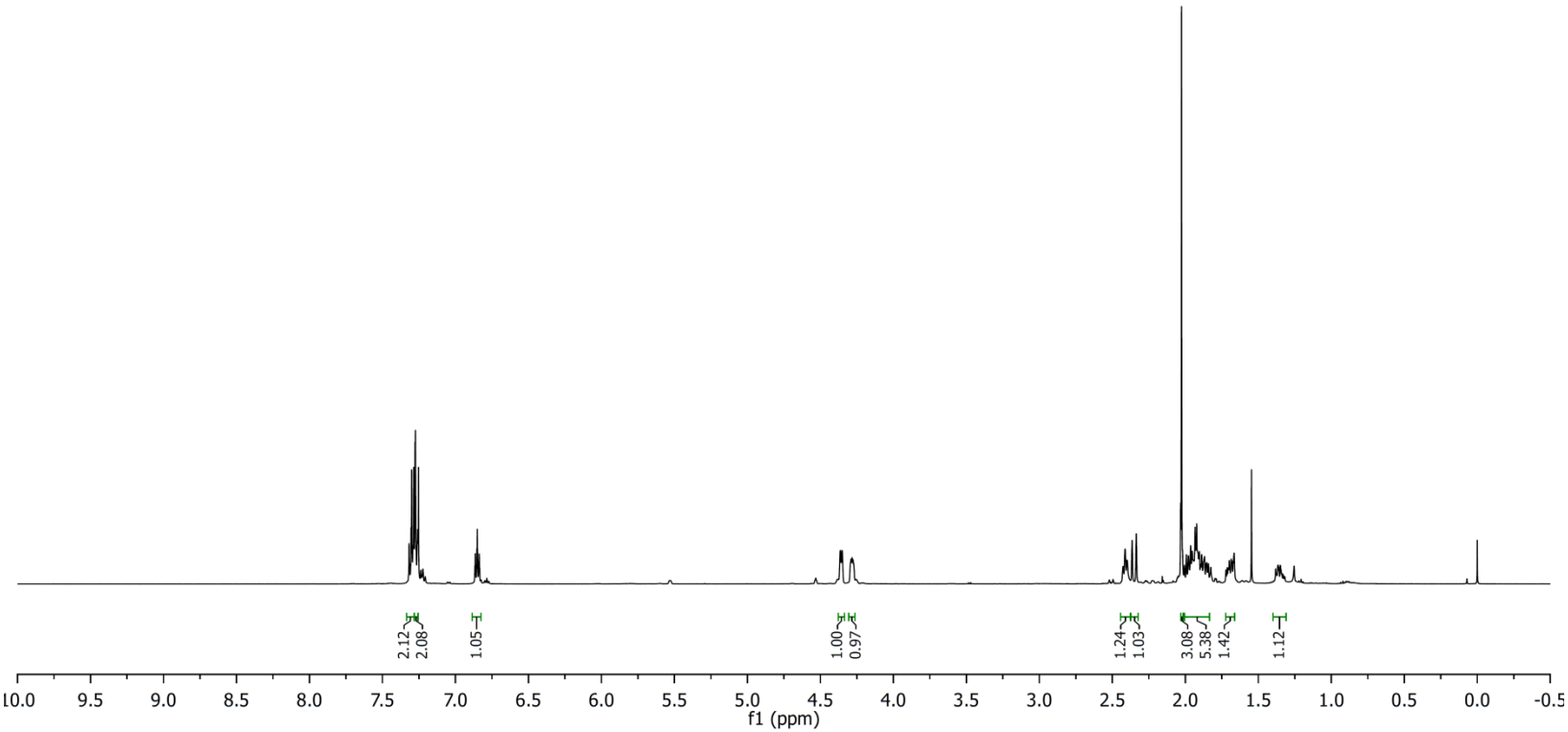
394

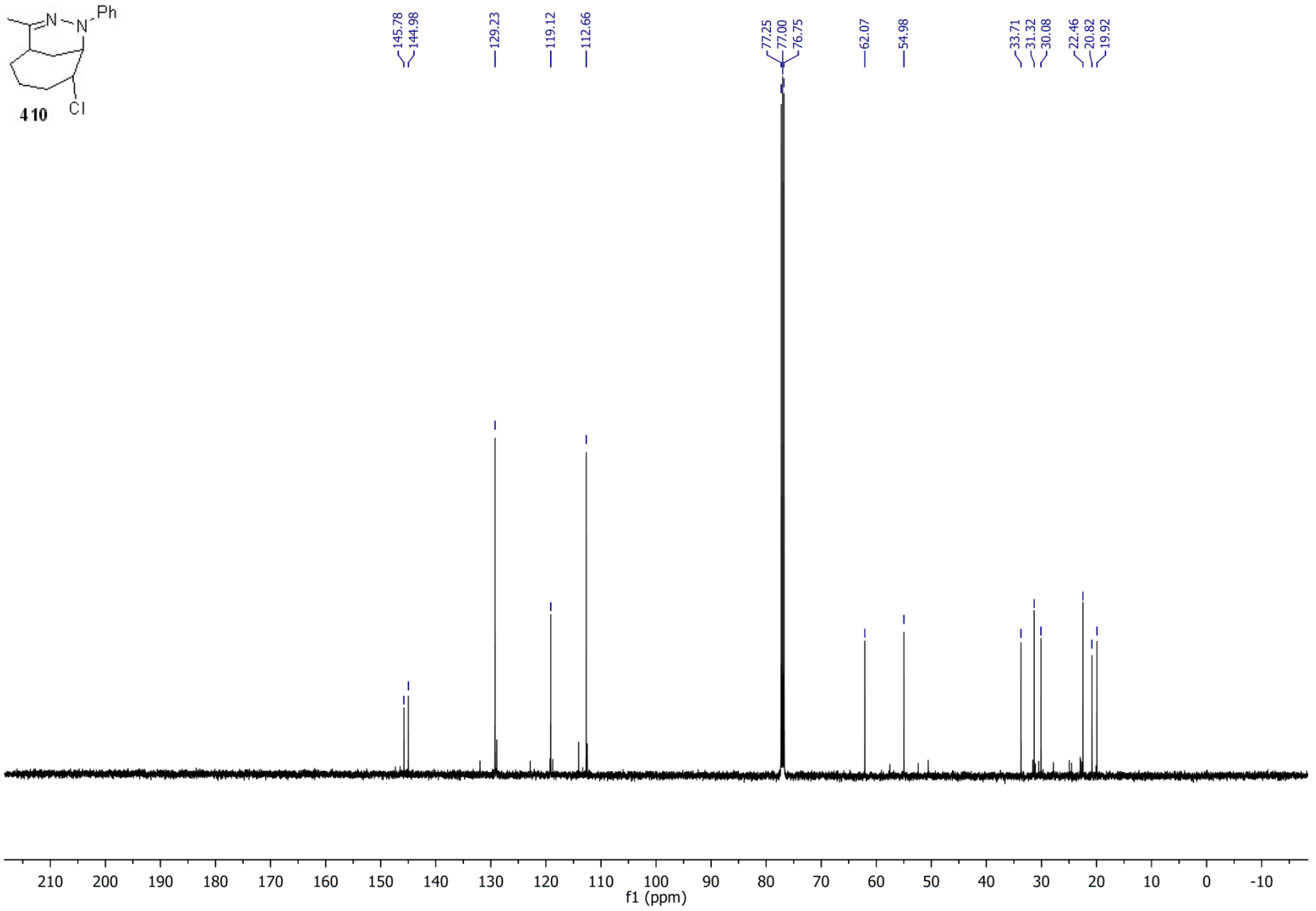

3.85
6.01
2.94
1.05
2.08
0.81
8.11
1.40
0.94
2.92
1.08
3.13
2.45
2.70
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

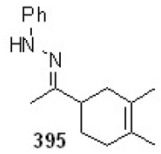

25.68
25.73
26.46
26.69
28.41
29.18
29.29
31.69
32.07
48.06
48.67
76.75
77.08
77.25
100.36
100.43
122.89
129.07
129.43
129.53
131.19
131.22
132.52
132.81
151.09
Ph
N
N
Cl
394
f1 (ppm)

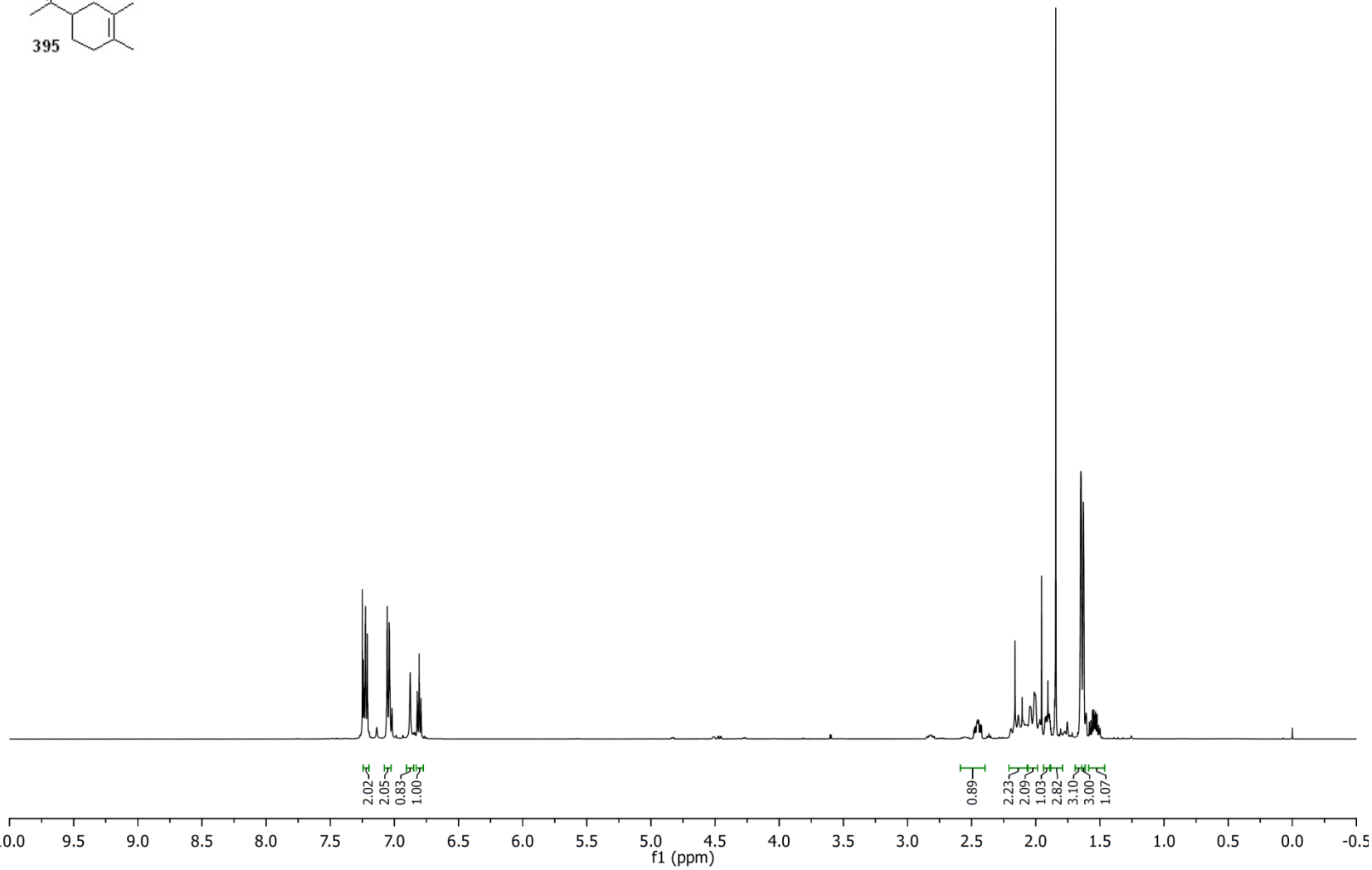

N
N
Ph
Cl

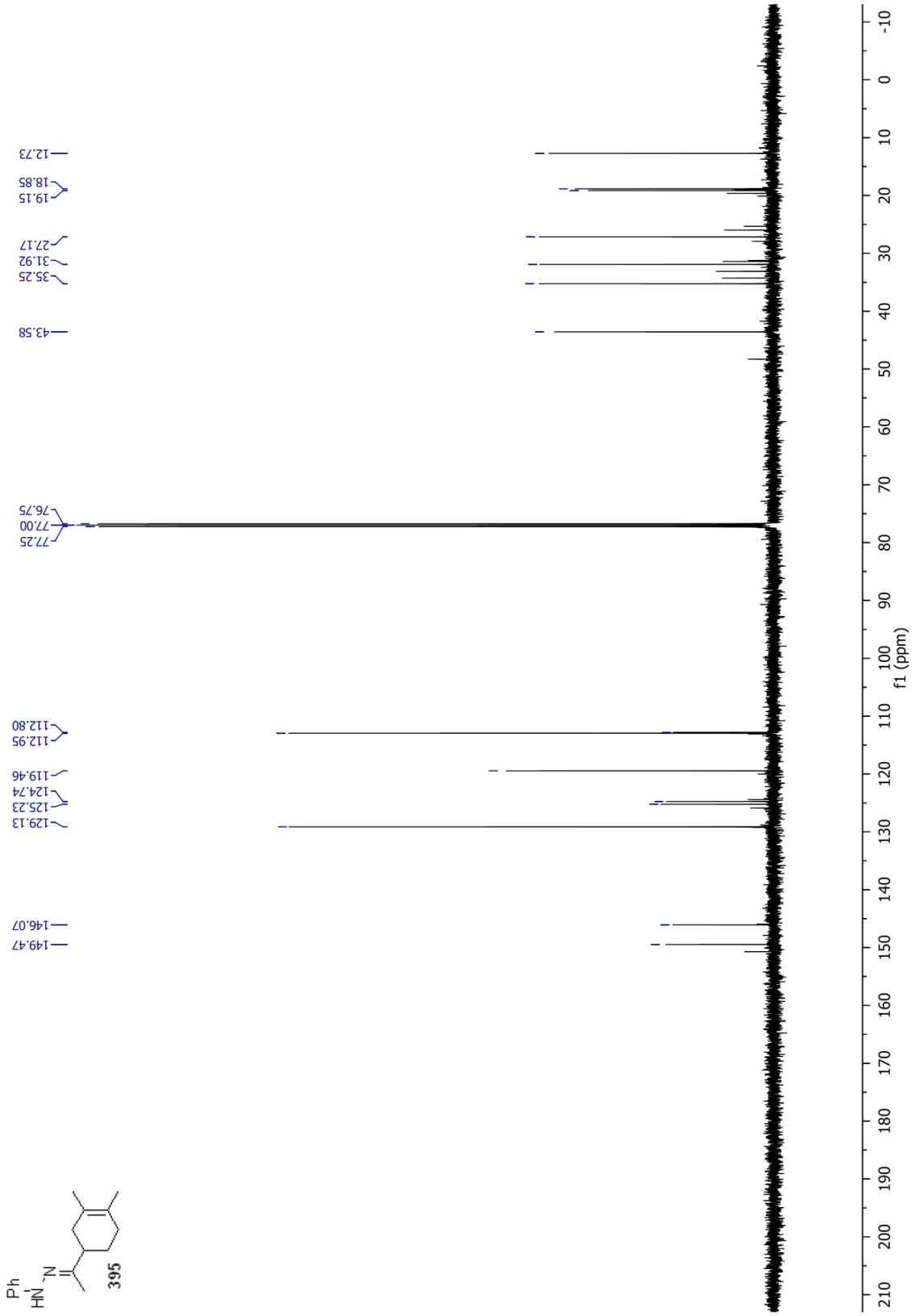
4 10

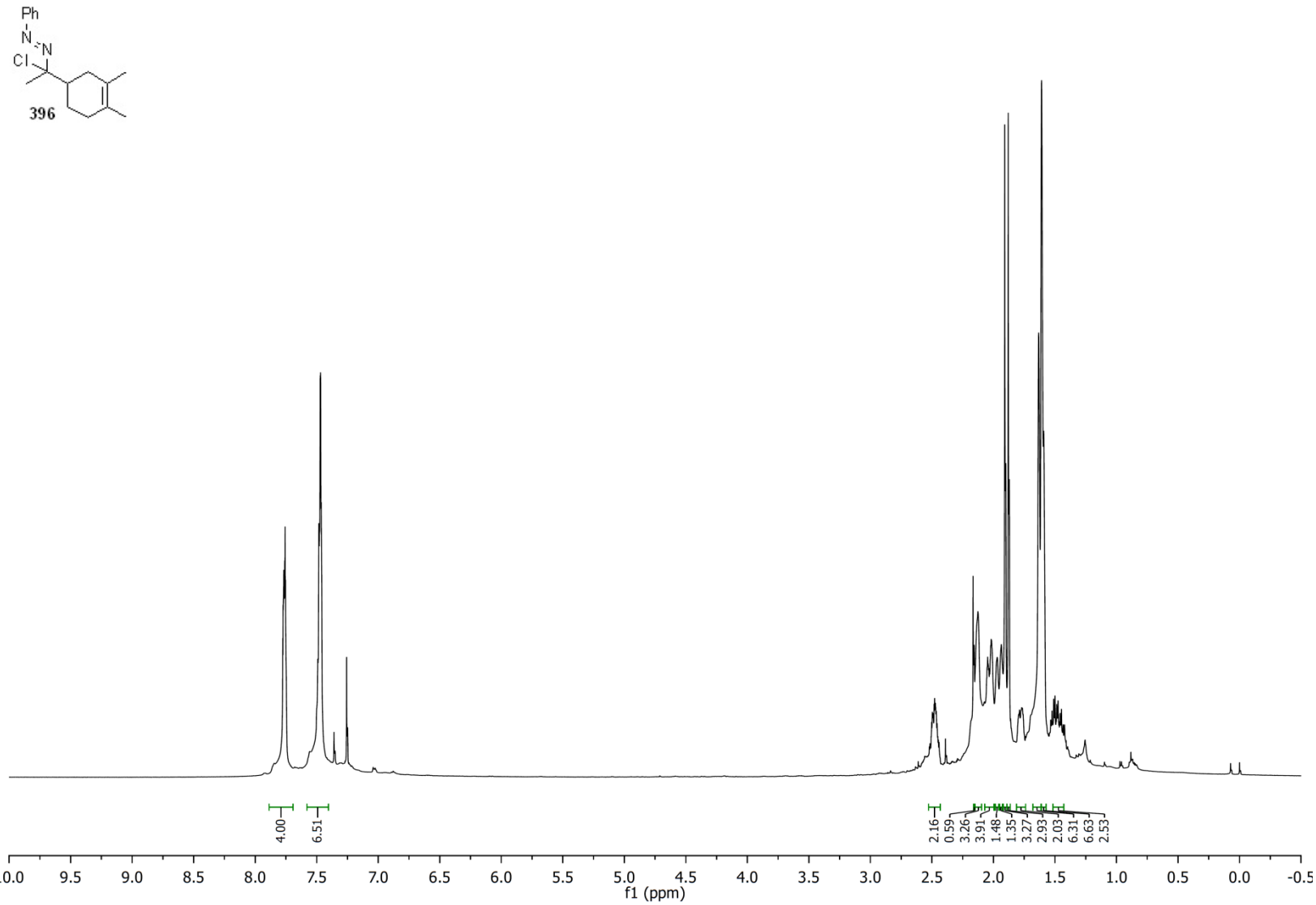

2.12
2.08
1.05
1.00
0.97
1.24
1.03
3.08
5.38
1.42
1.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

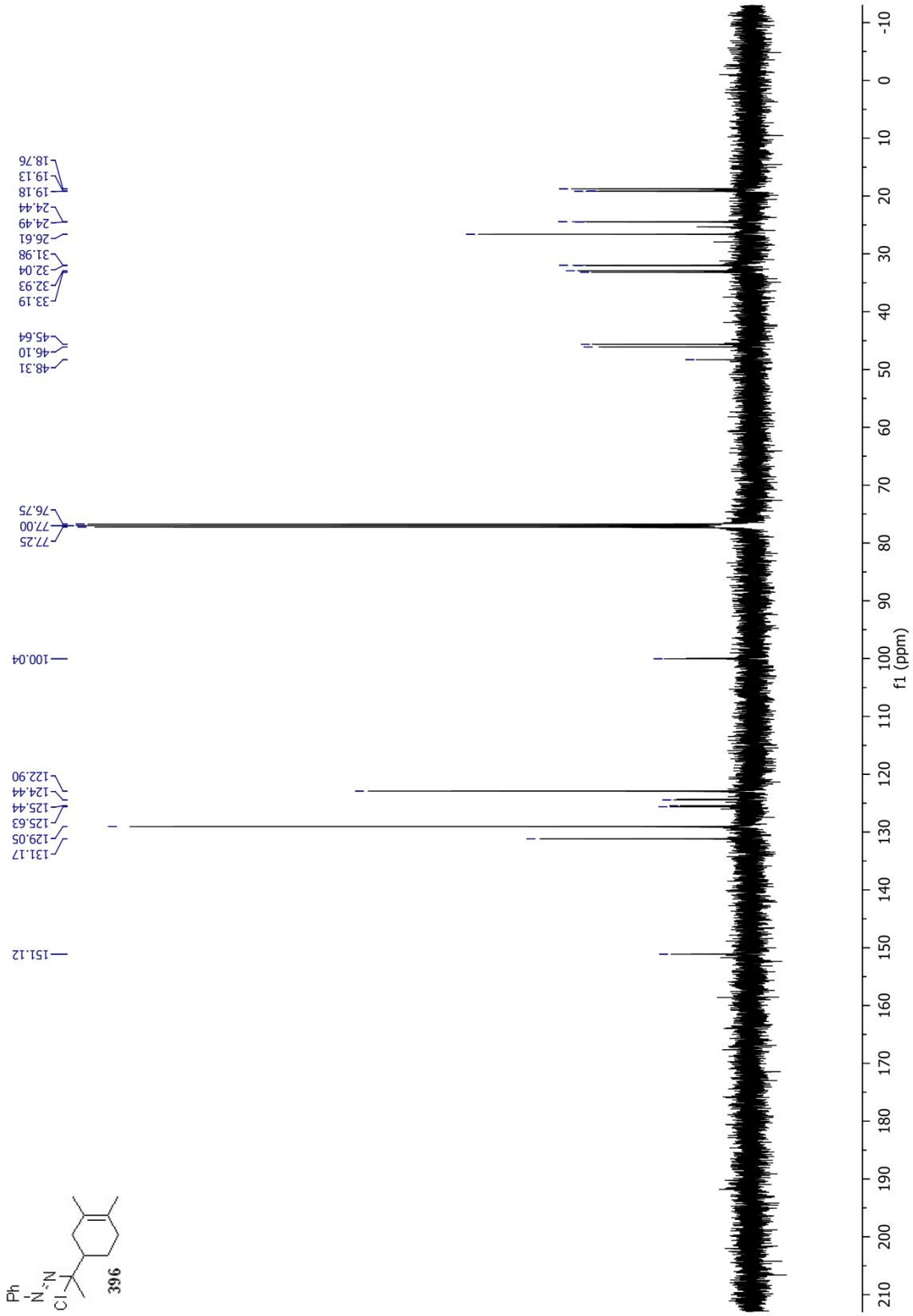

410
N
N
Ph
Cl
145.78
144.98
129.23
119.12
112.66
77.25
77.00
76.75
62.07
54.98
33.71
31.32
30.08
22.46
20.82
19.92
208
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

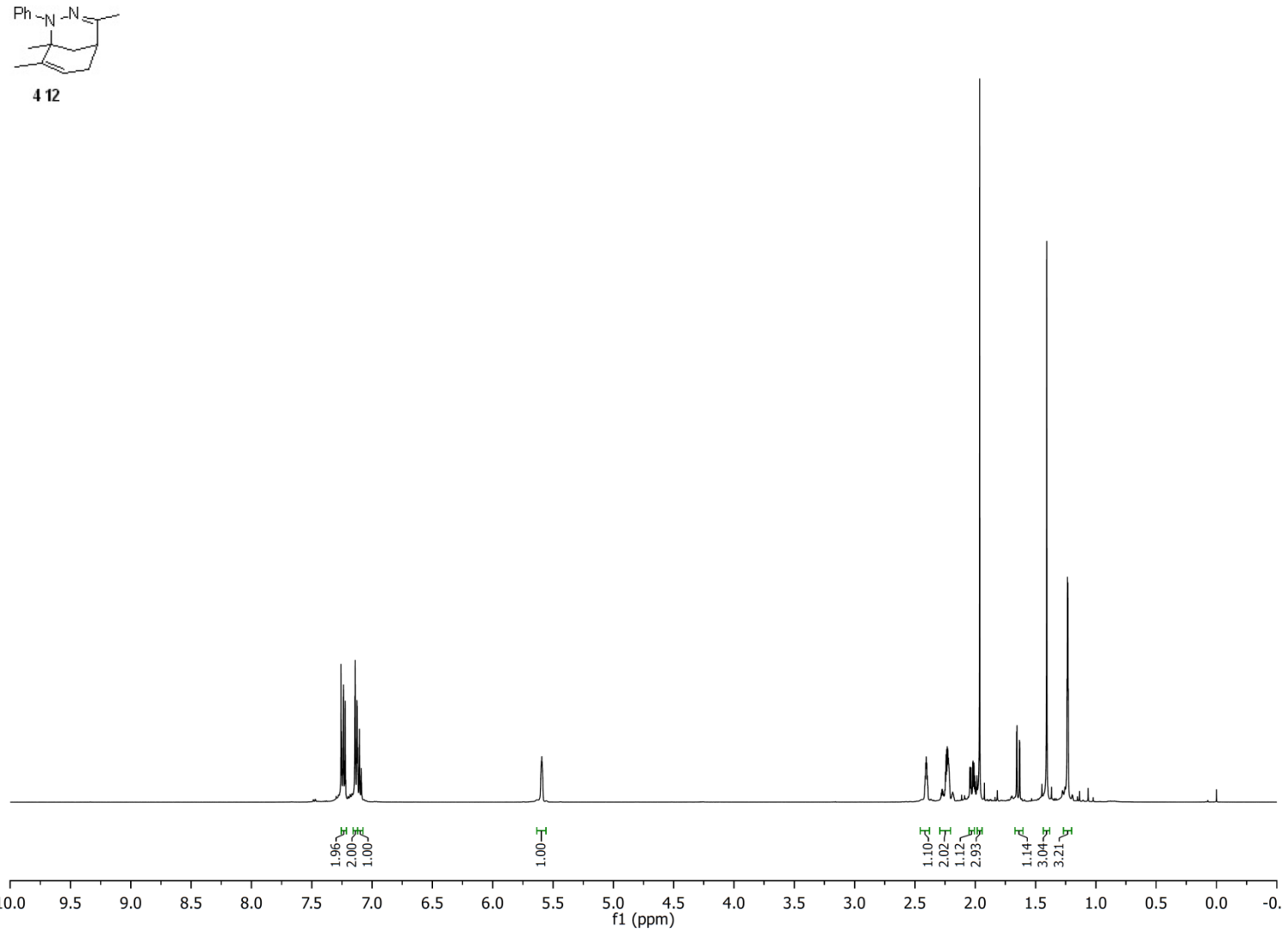

Ph
HN
N
395

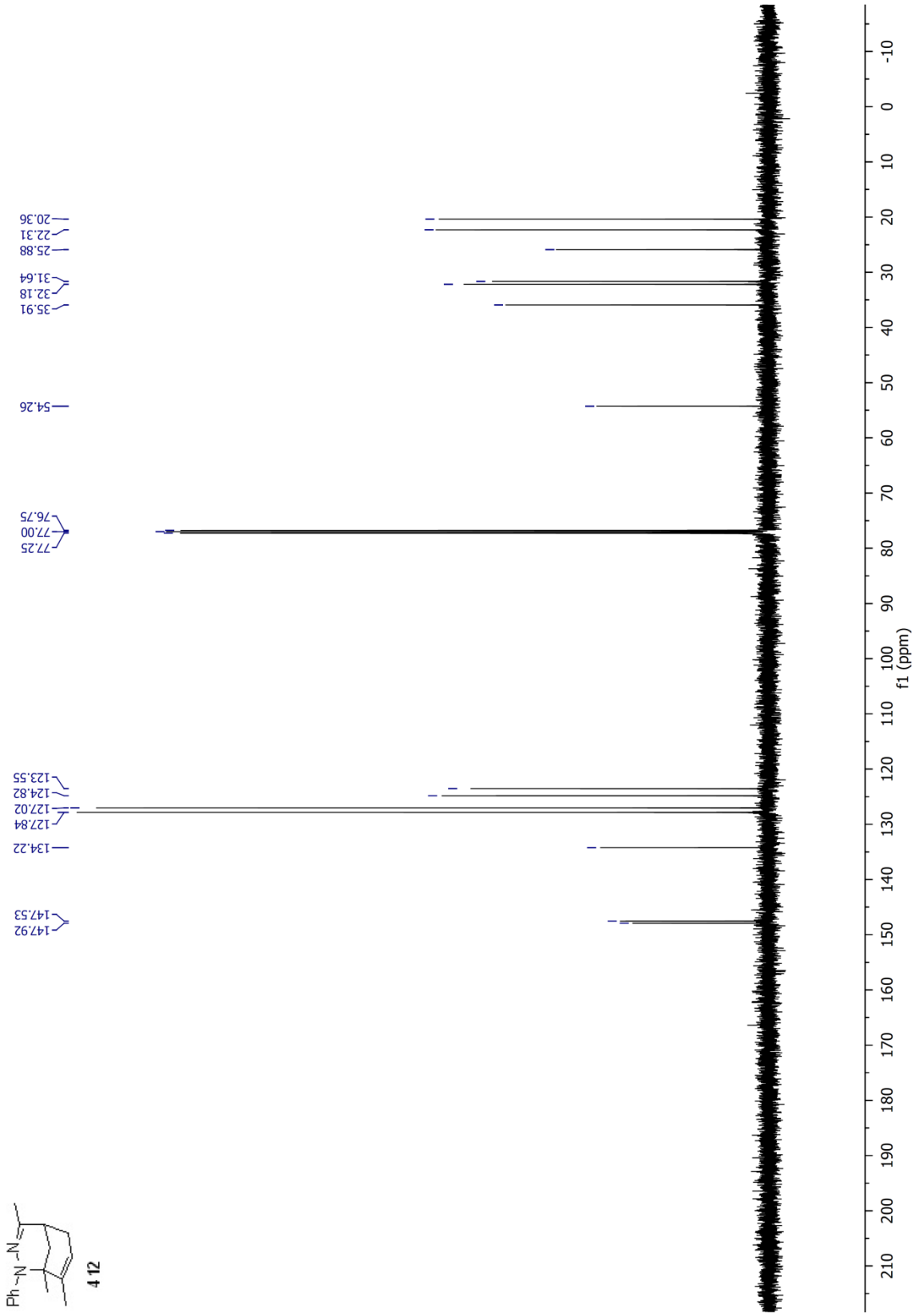

2.02
2.05
0.83
1.00
0.89
2.23
2.09
1.03
2.82
3.10
3.00
1.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

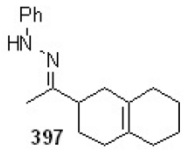

Ph
HN
N
395
12.73
18.85
19.15
27.17
31.92
35.25
43.58
76.75
77.00
77.25
112.80
112.95
119.46
124.74
125.23
129.13
146.07
149.47
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

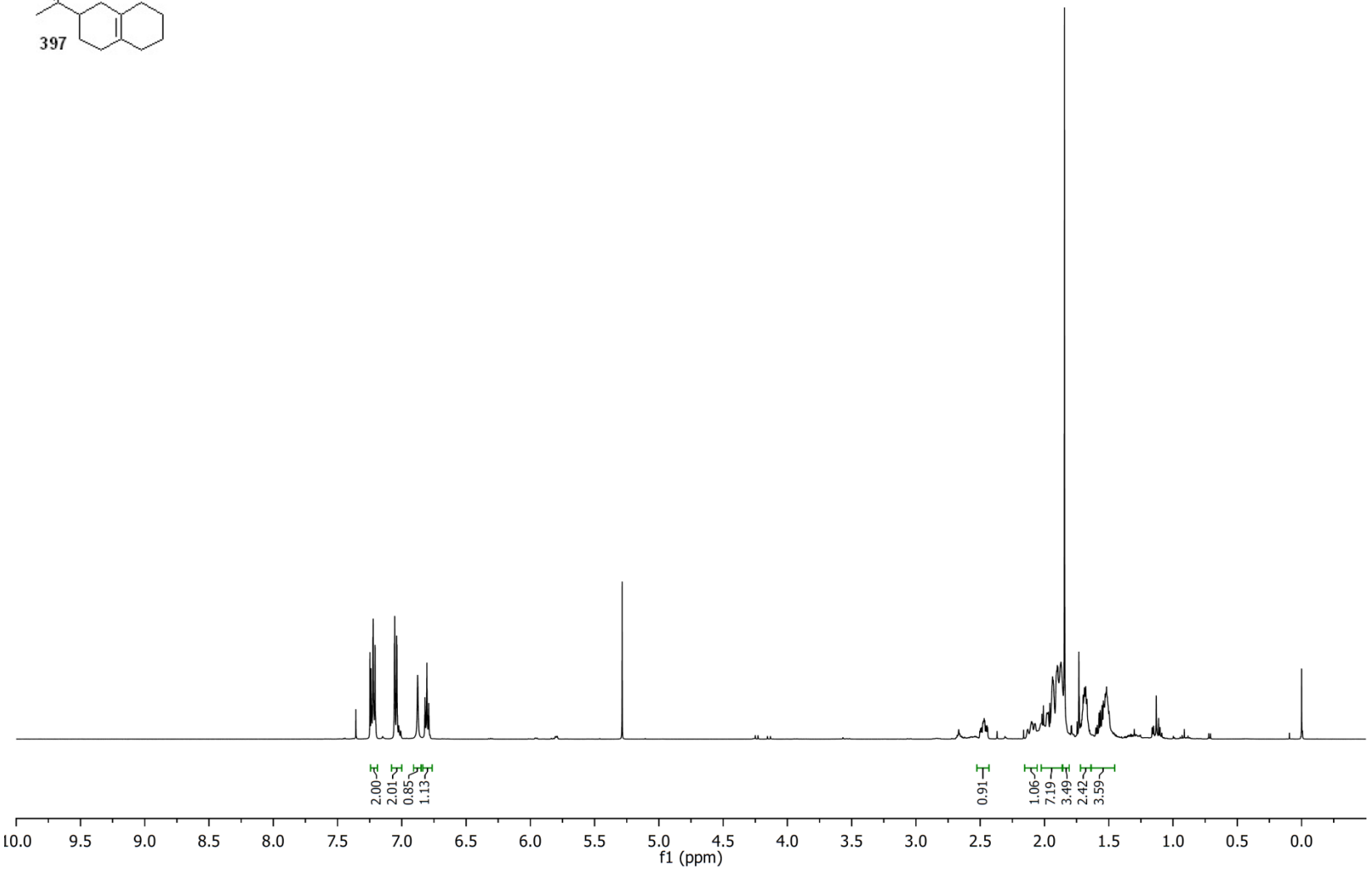

Ph
N
N
Cl
396
4.00
6.51
2.16
0.59
3.26
3.91
1.48
1.35
3.27
2.93
2.03
6.31
6.63
2.53
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

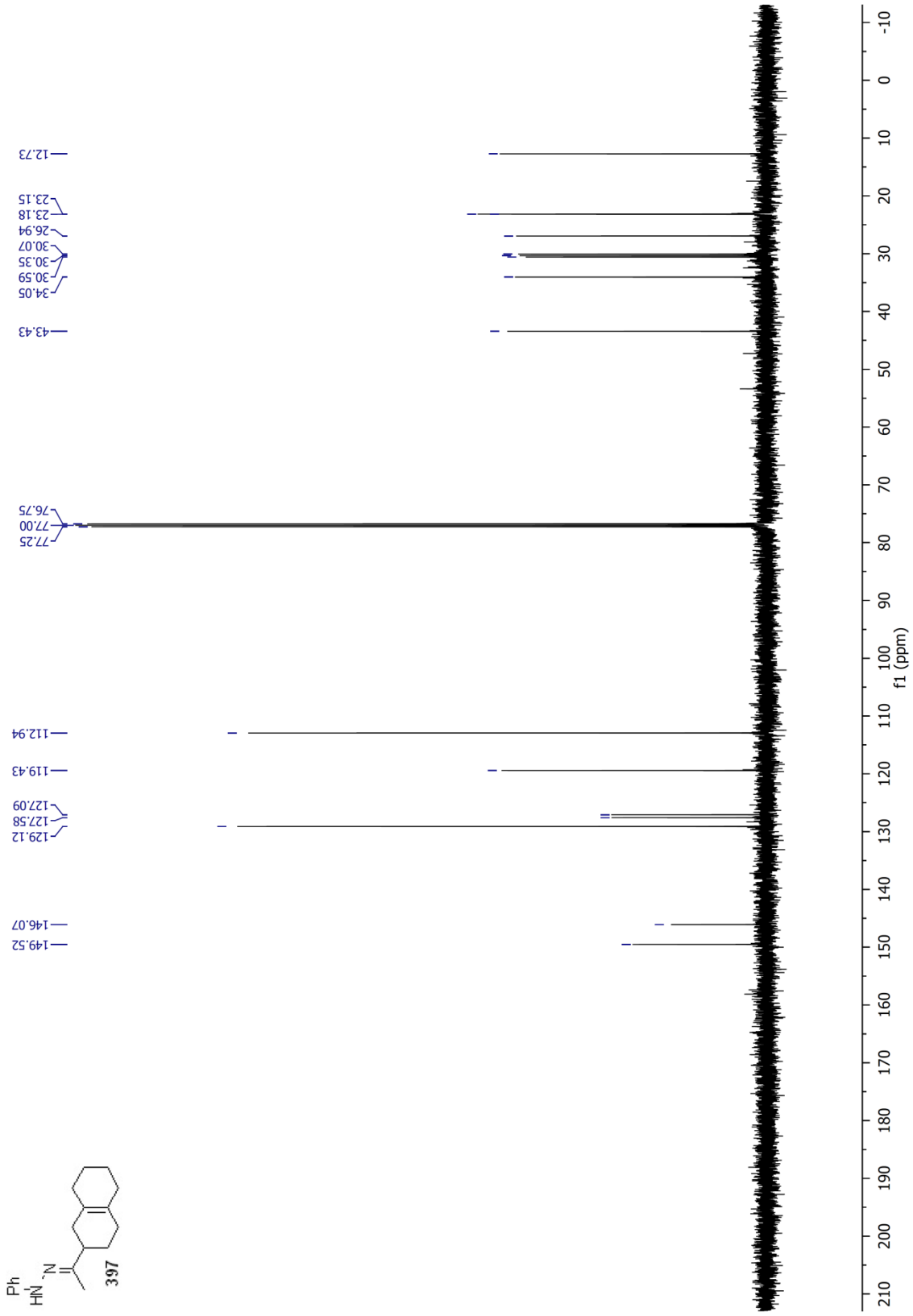

Ph
N
N
Cl
396
151.12
131.17
129.05
125.63
125.44
124.44
122.90
100.04
77.25
77.00
76.75
48.31
46.10
45.64
33.19
32.93
32.04
31.98
26.61
24.49
24.44
19.18
19.13
18.76
f1 (ppm)

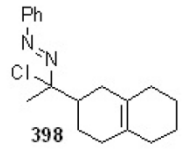

Ph
N
N
4 12
1.96
2.00
1.00
1.00
1.10
2.02
1.12
2.93
1.14
3.04
3.21
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)


Ph
N
N
4 12
20.36
22.31
25.88
31.64
32.18
35.91
54.26
76.75
77.00
77.25
123.55
124.82
127.02
127.84
134.22
147.53
147.92
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

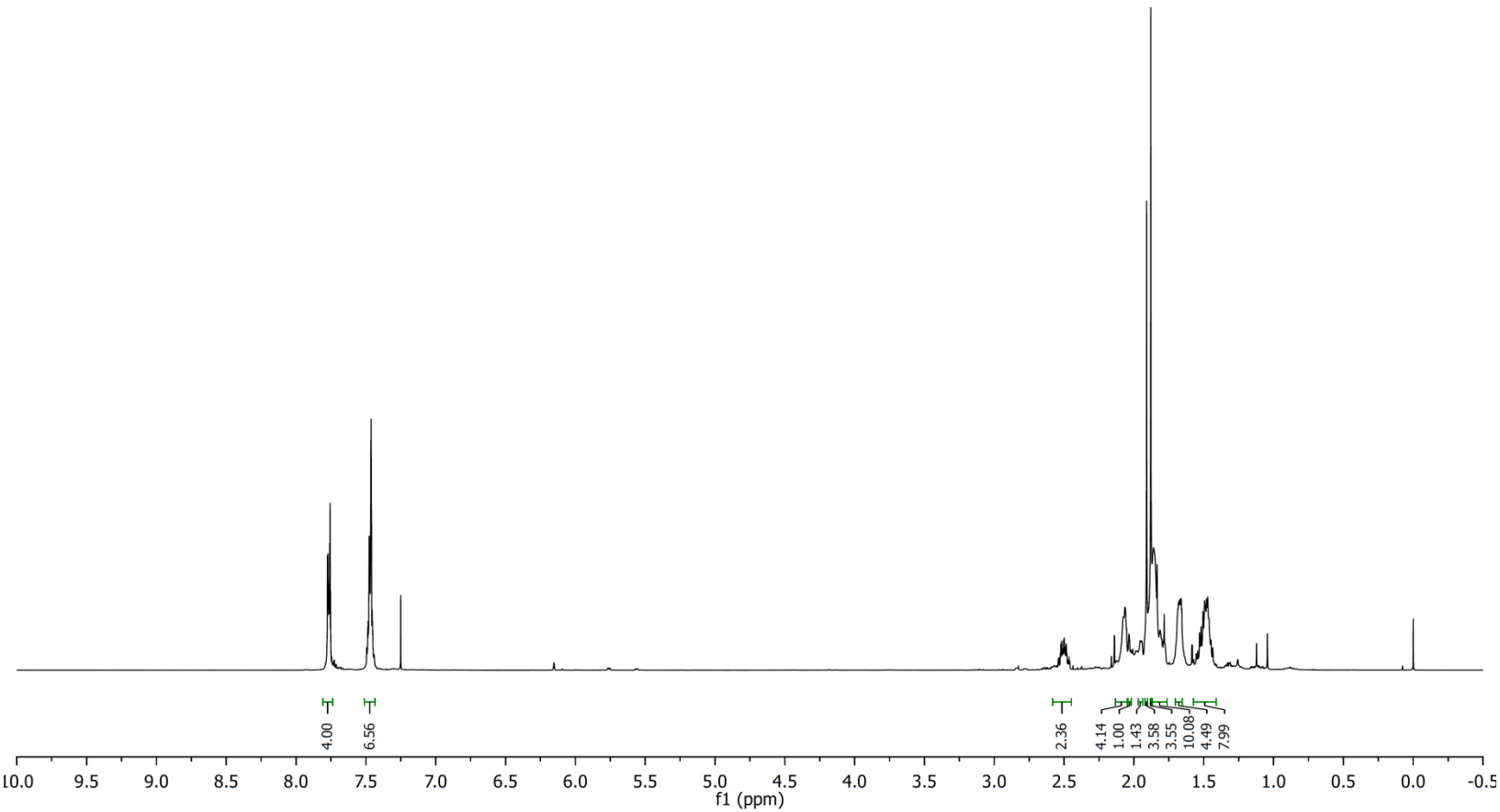

Ph
HN
N
397

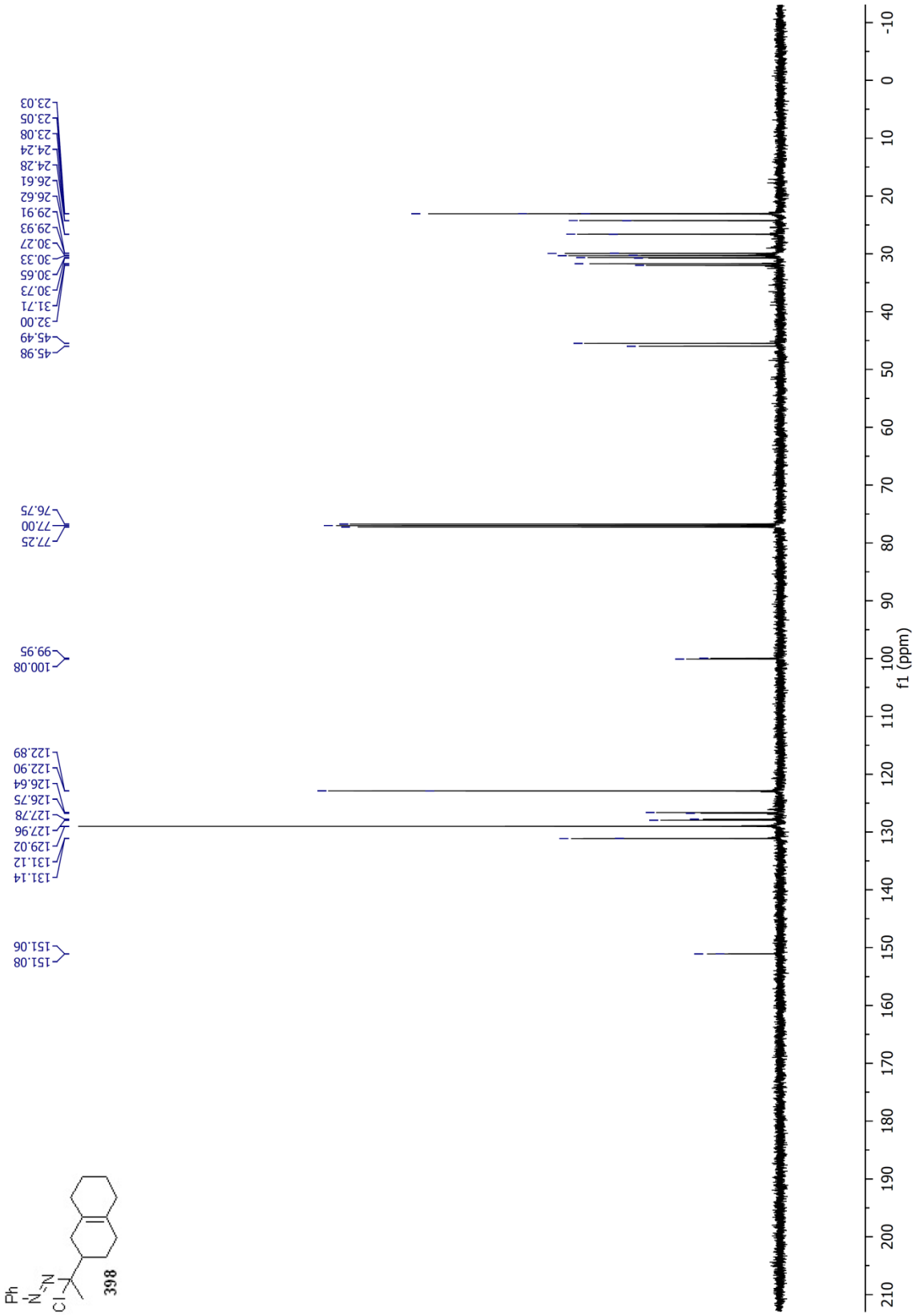

2.00
2.01
0.85
1.13
0.91
1.06
7.19
3.49
2.42
3.59
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

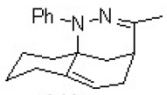

397
Ph
HN
N
12.73
23.15
23.18
26.94
30.07
30.35
30.59
34.05
43.43
76.75
77.00
77.25
112.94
119.43
127.09
127.58
129.12
146.07
149.52
f1 (ppm)


Ph
N
N
Cl

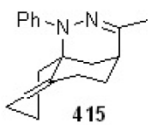
398


4.00
6.56
2.36
4.14
1.00
1.43
3.58
3.55
10.08
4.49
7.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


398
Ph
N
N
Cl
151.08
151.06
131.14
131.12
129.02
127.96
127.78
126.75
126.64
122.90
122.89
100.08
99.95
77.25
77.00
76.75
45.98
45.49
32.00
31.71
30.73
30.65
30.33
30.27
29.93
29.91
26.62
26.61
24.28
24.24
23.08
23.05
23.03
f1 (ppm)

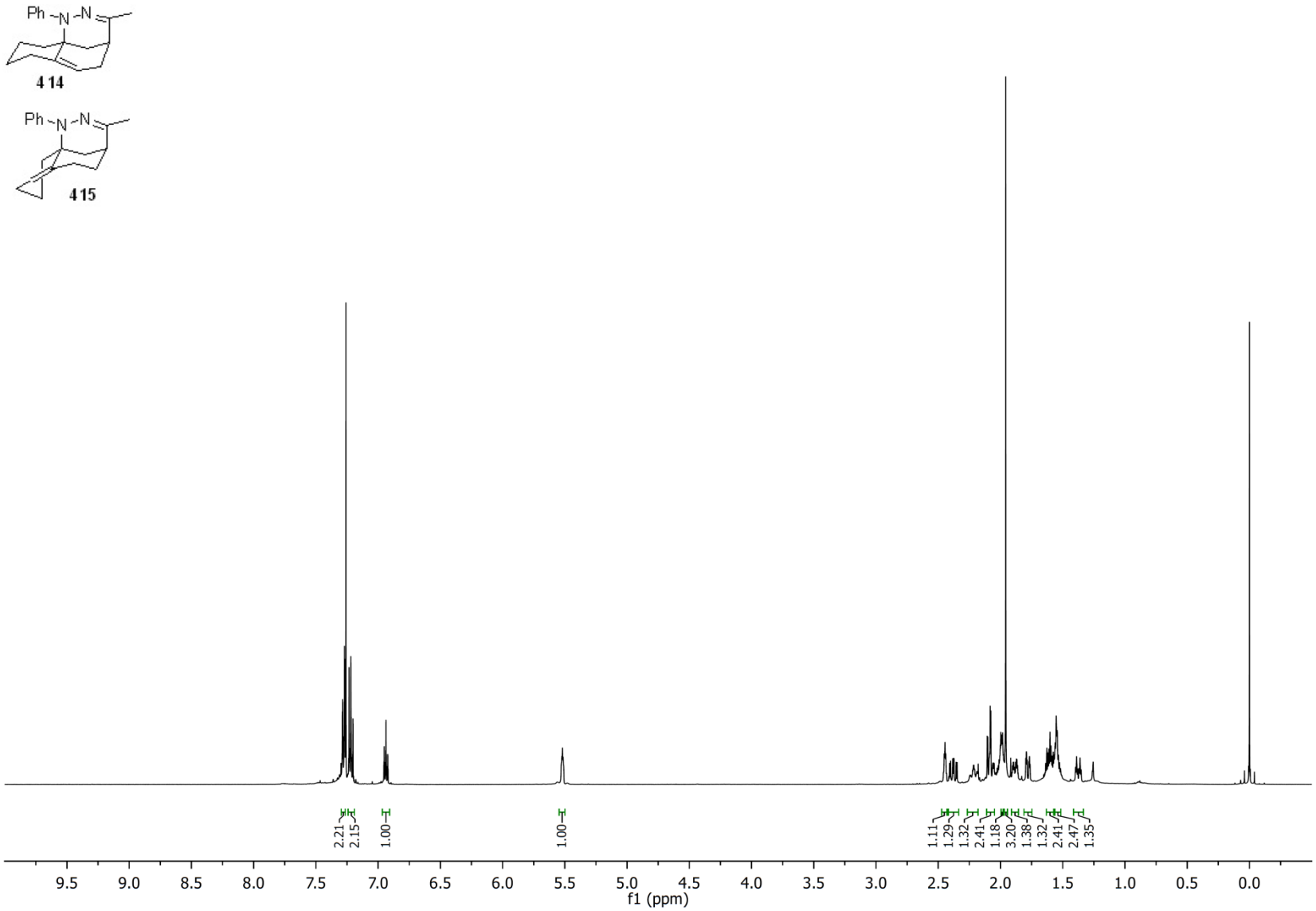

Ph
N
N

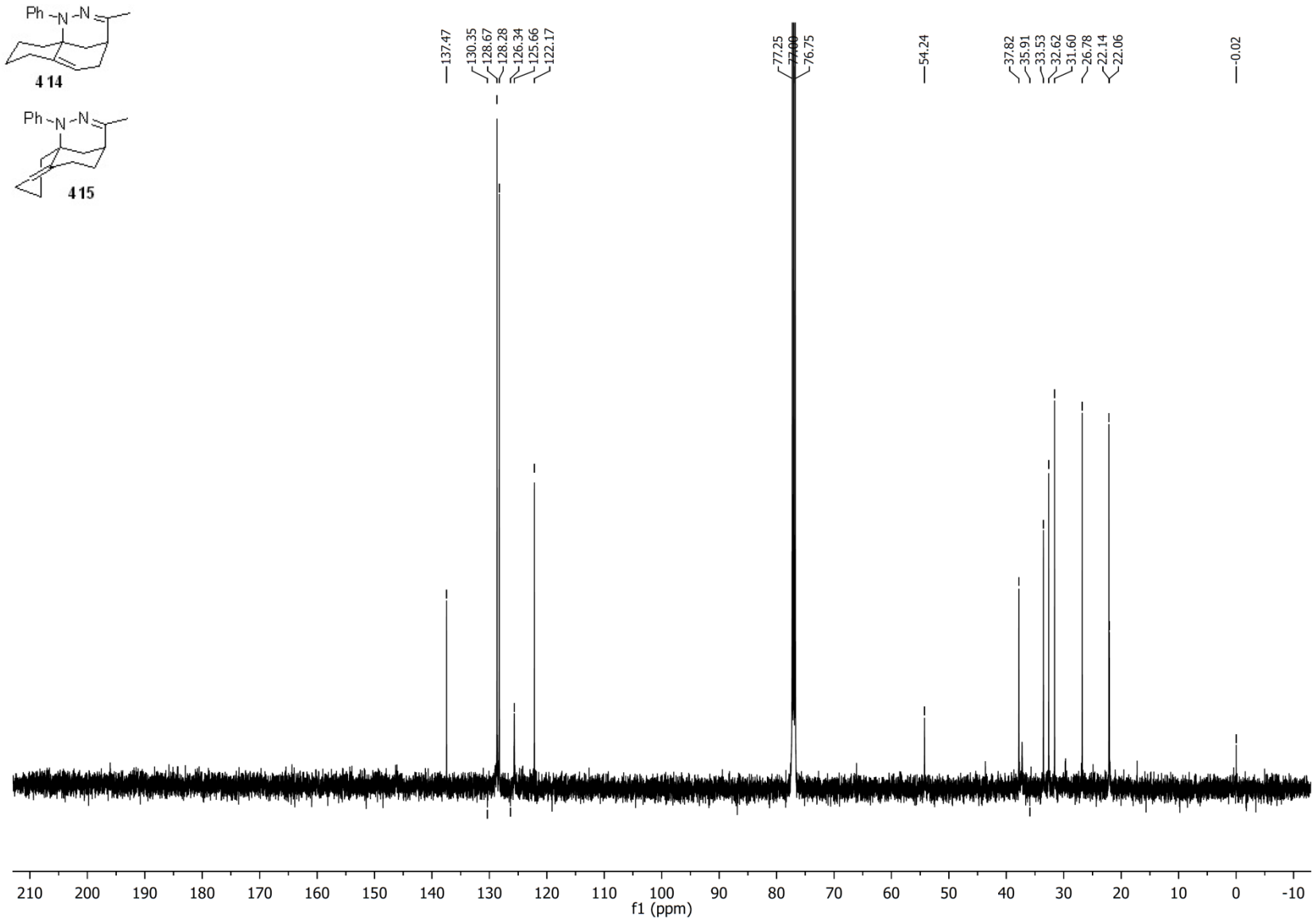
414

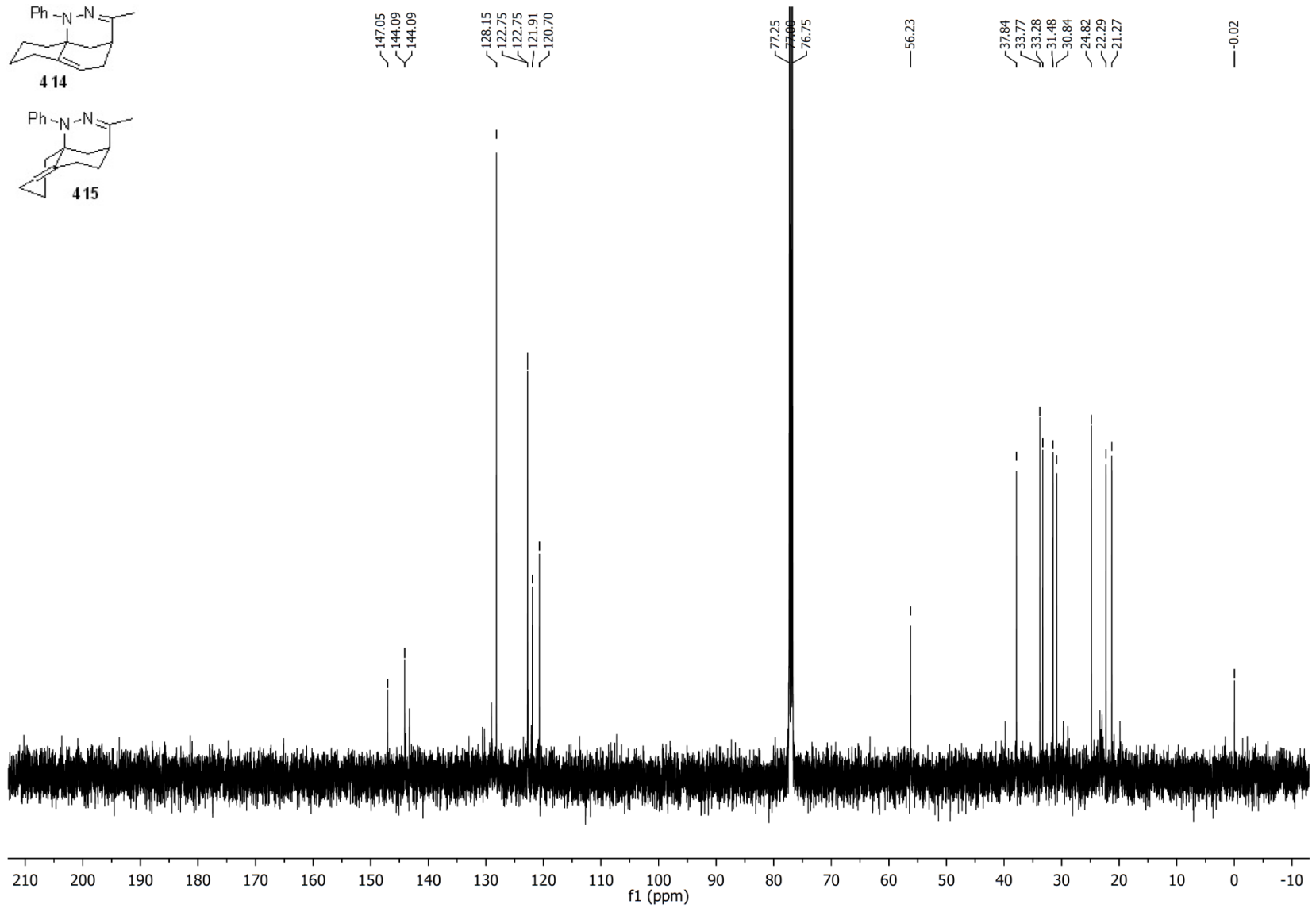

Ph
N
N

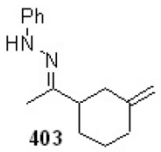
415

1.44
0.78
2.31
1.24
1.00
1.21
1.24
2.07
1.41
3.56
1.97
2.21
1.05
1.35
1.42
1.40
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

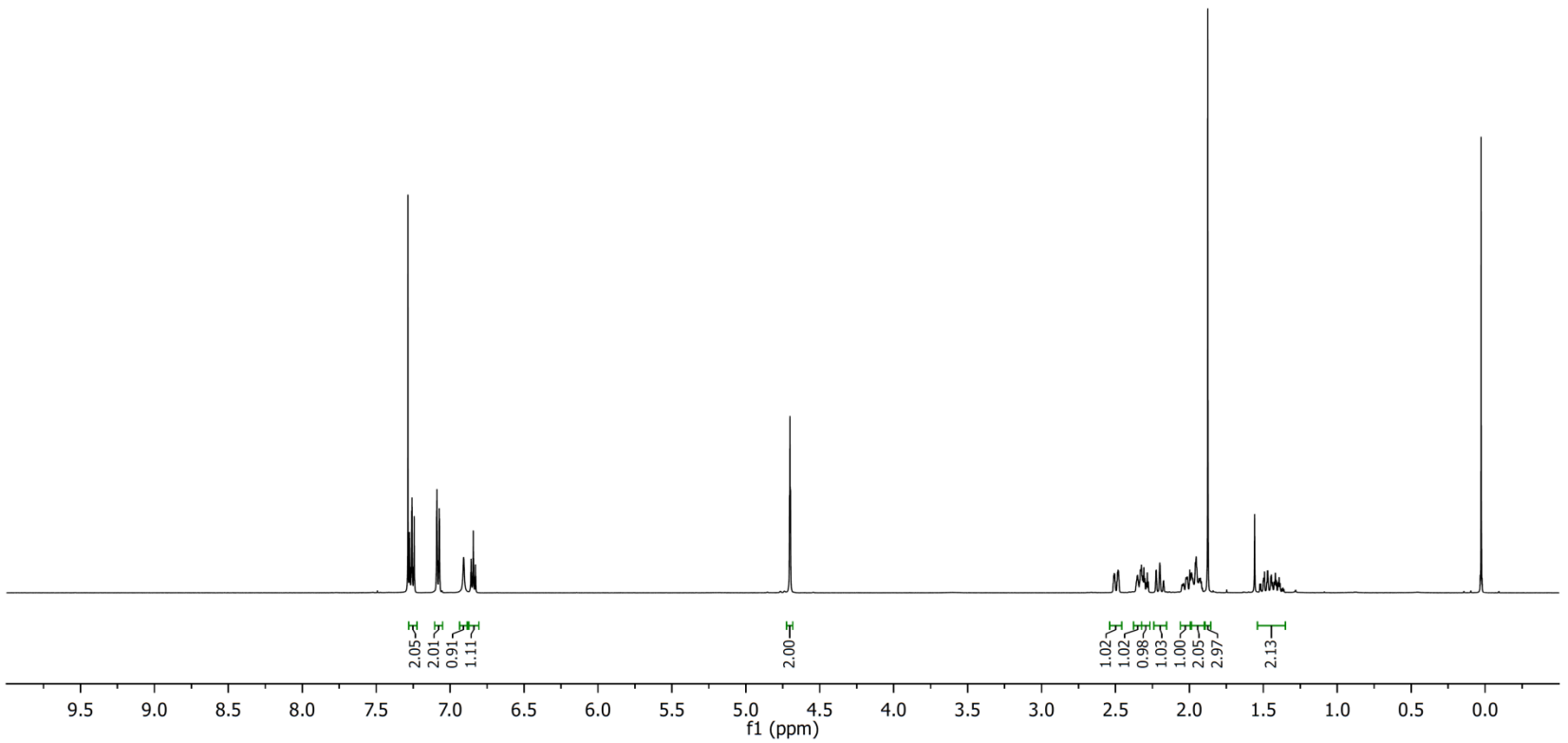

Ph
N
N
4 14
Ph
N
N
4 15
2.21
2.15
1.00
1.00
1.11
1.29
1.32
2.41
1.18
3.20
1.38
1.32
2.41
2.47
1.35
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

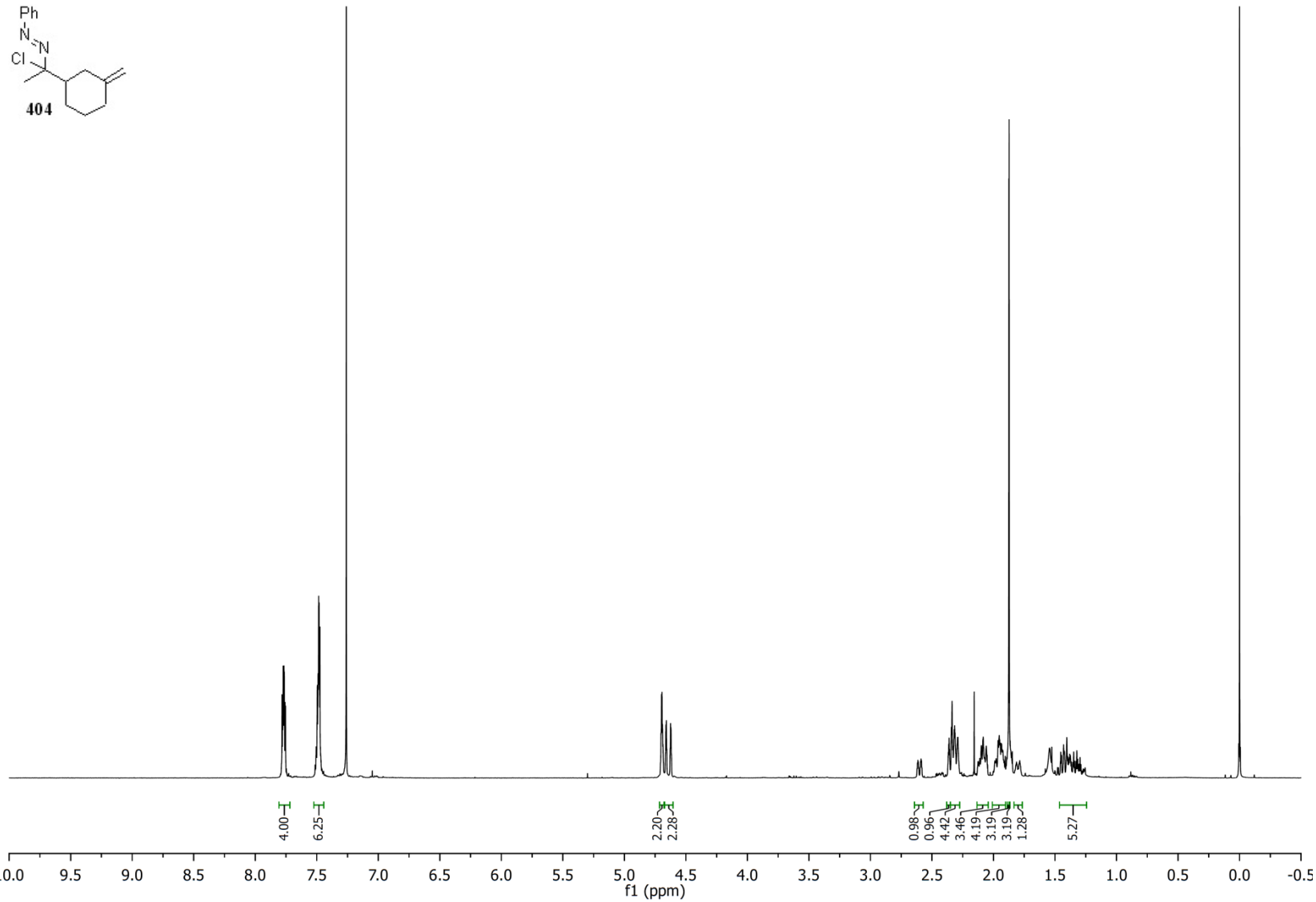

Ph
N
N
414
Ph
N
N
415
137.47
130.35
128.67
128.28
126.34
125.66
122.17
77.25
77.00
76.75
54.24
37.82
35.91
33.53
32.62
31.60
26.78
22.14
22.06
-0.02
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

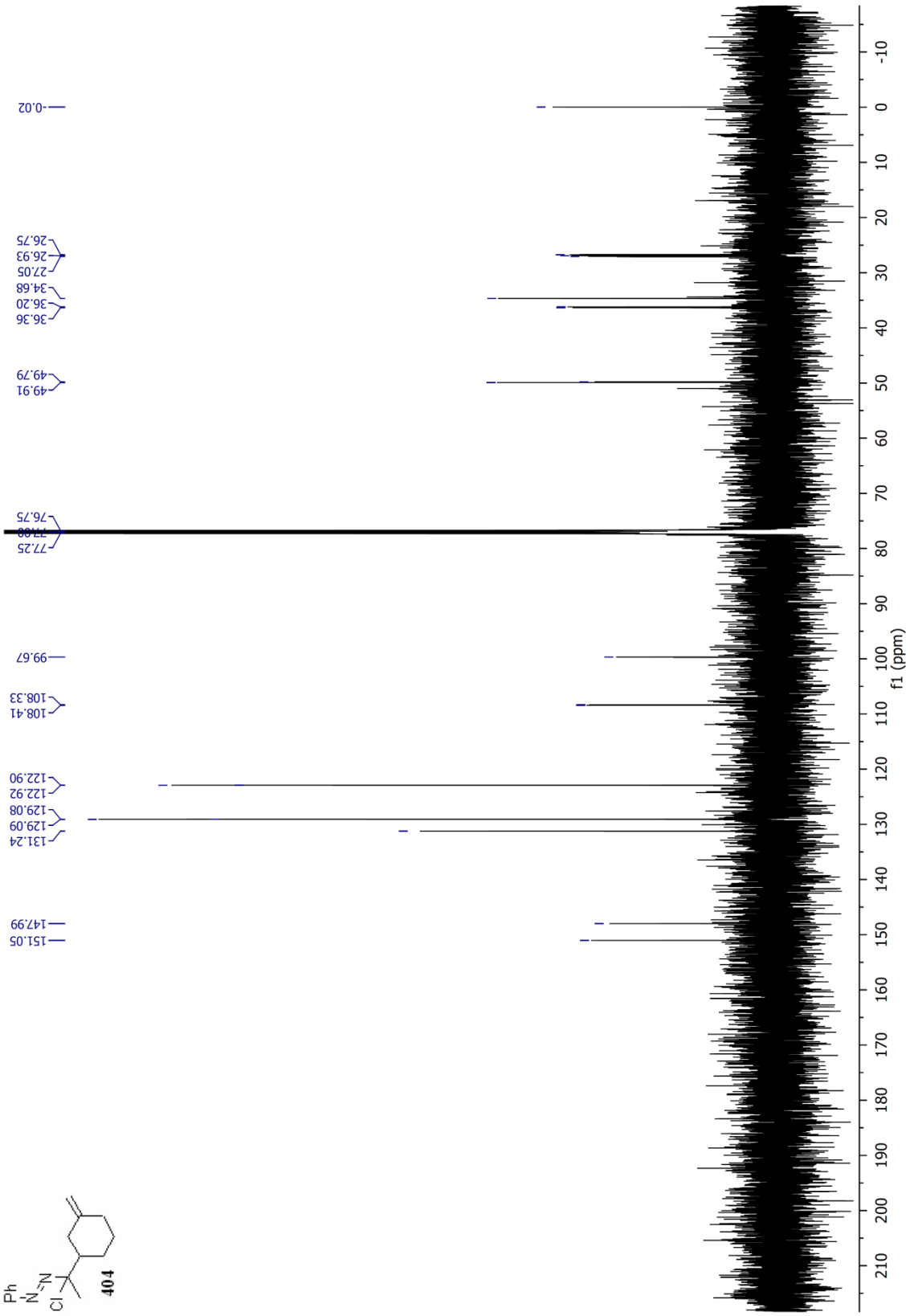

Ph
N
N
4 14
Ph
N
N
4 15
147.05
144.09
144.09
128.15
122.75
122.75
121.91
120.70
77.25
77.00
76.75
56.23
37.84
33.77
33.28
31.48
30.84
24.82
22.29
21.27
-0.02
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

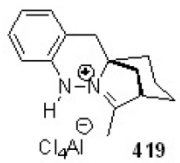

Ph
HN
N

403

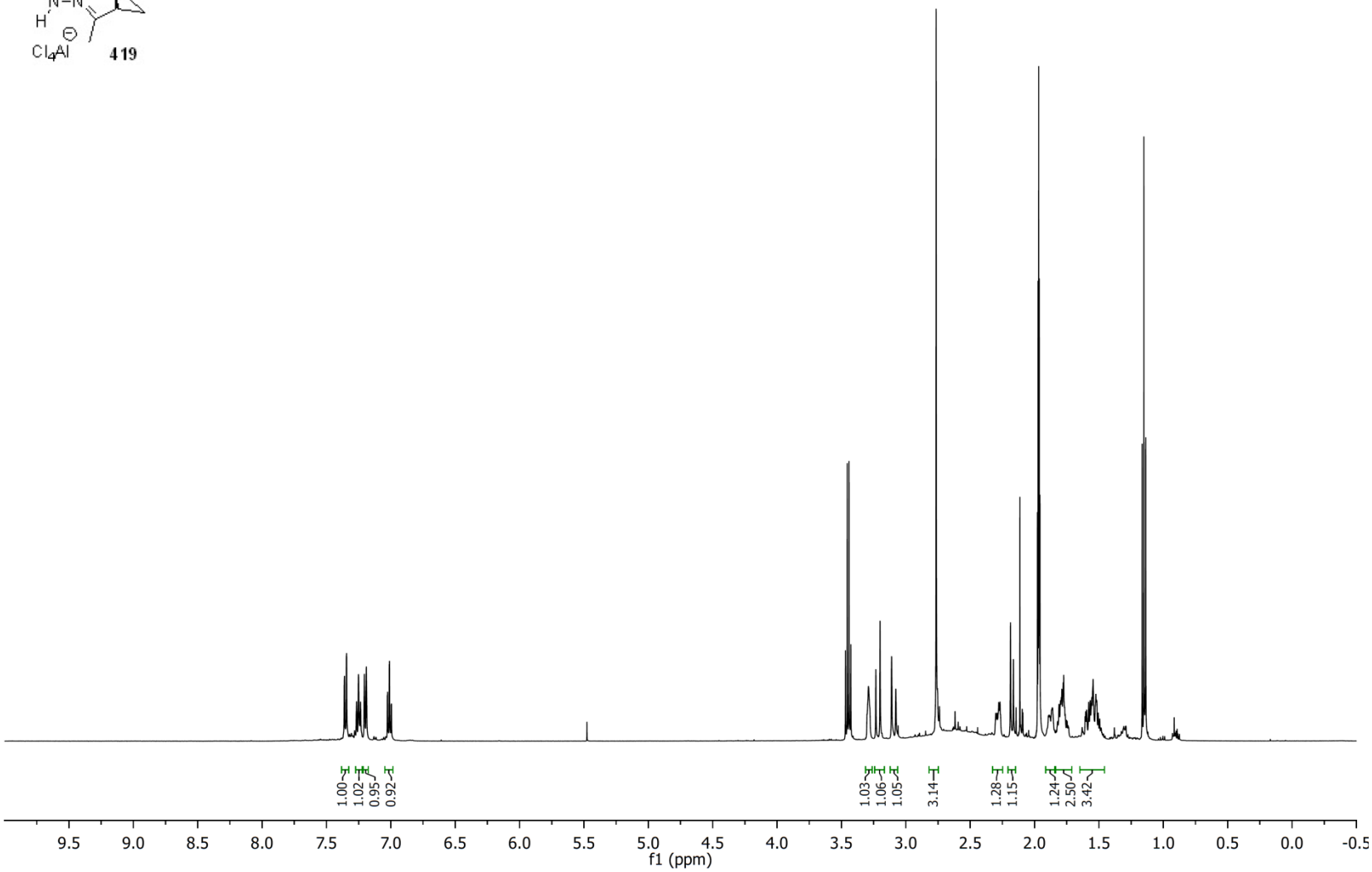

2.05
2.01
0.91
1.11
2.00
1.02
1.02
0.98
1.03
1.00
2.05
2.97
2.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

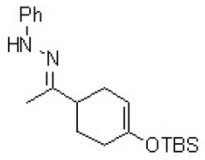

Ph
N
N
Cl
404
4.00
6.25
2.20
2.28
0.98
0.96
4.42
3.46
4.19
3.19
3.19
1.28
5.27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

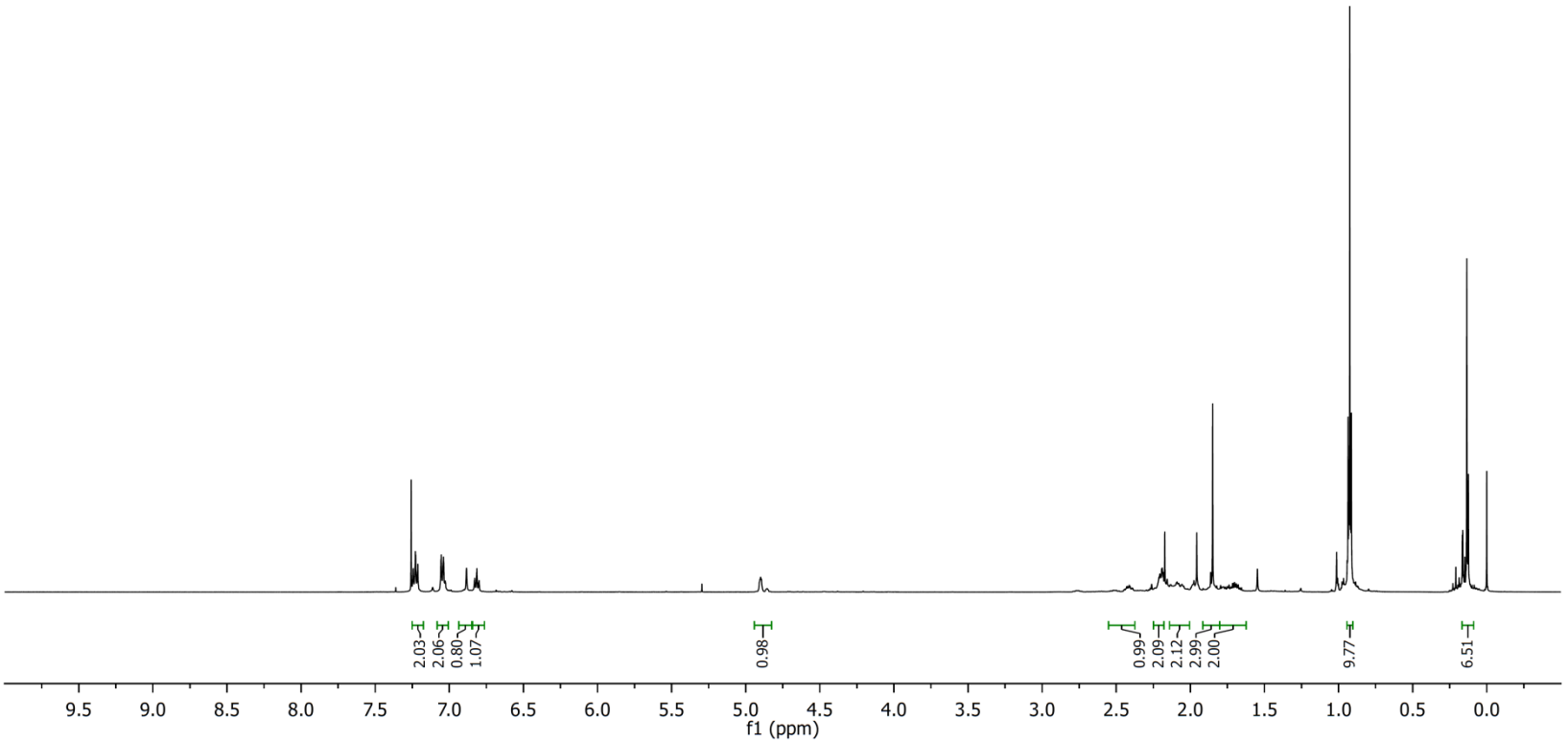

Ph
N
N
Cl
404
-0.02
26.75
26.93
27.05
34.68
36.20
36.36
49.79
49.91
76.75
77.08
77.25
99.67
108.33
108.41
122.90
122.92
129.08
129.09
131.24
147.99
151.05
f1 (ppm)

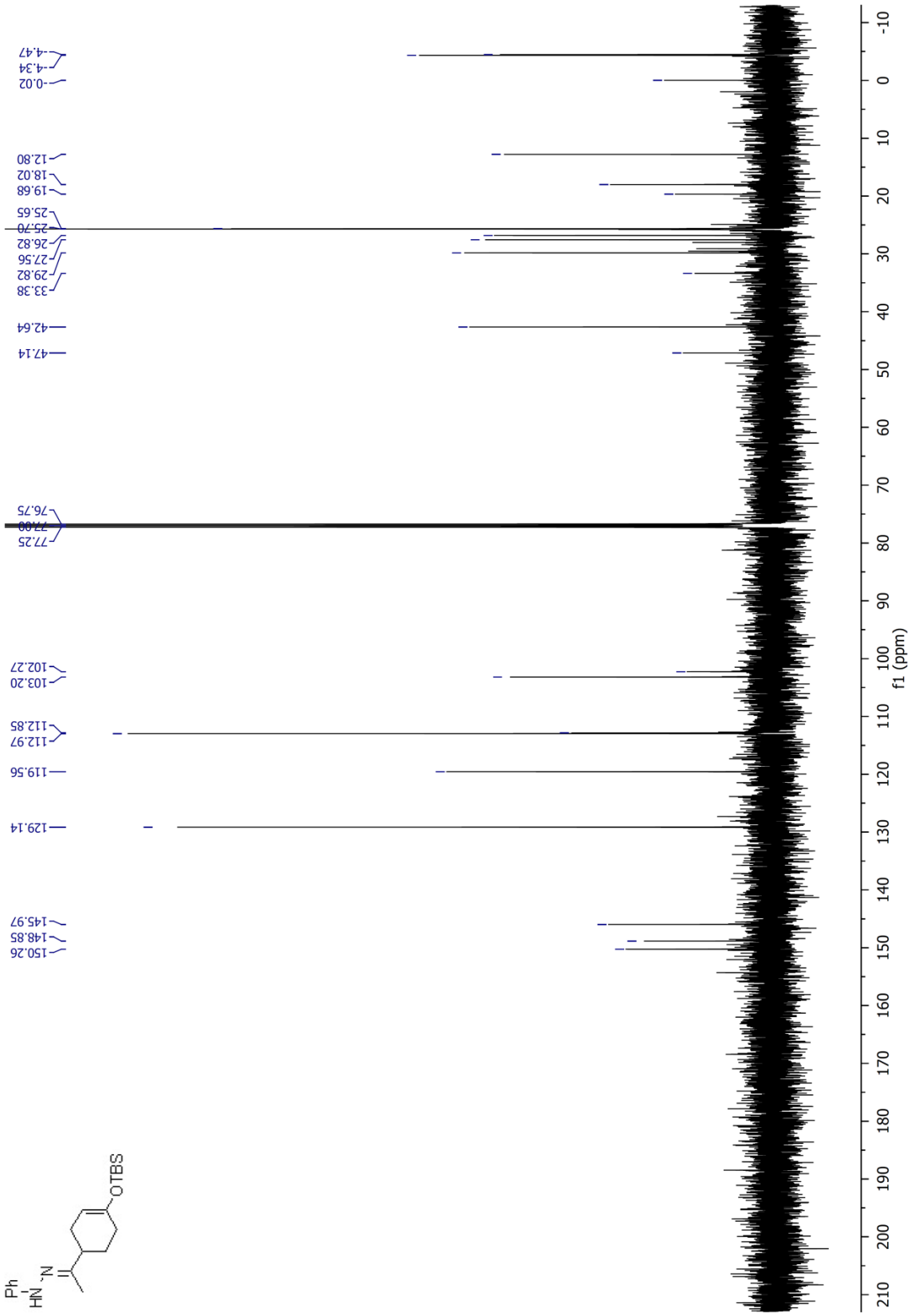

N
H
N
Cl4Al

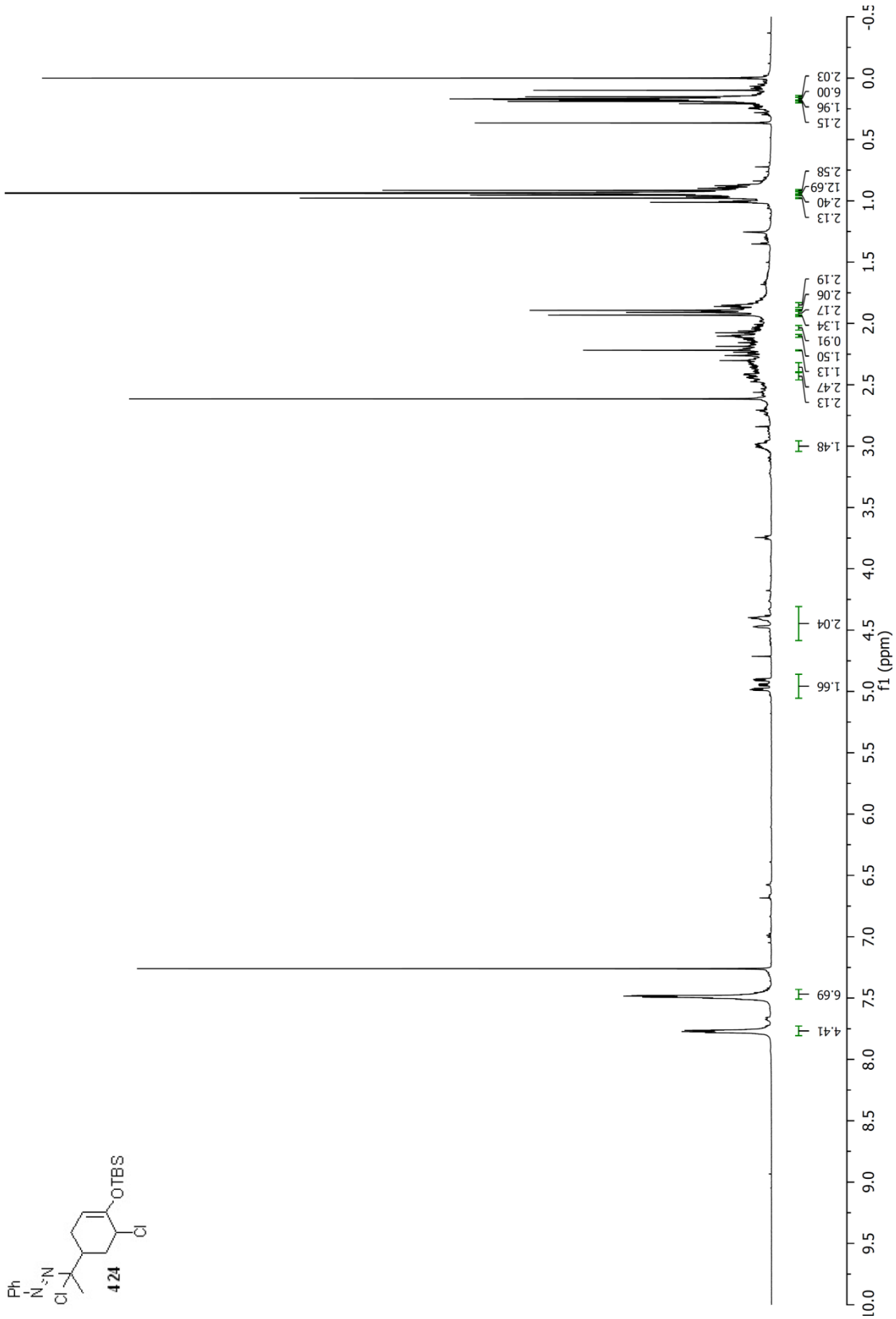
419

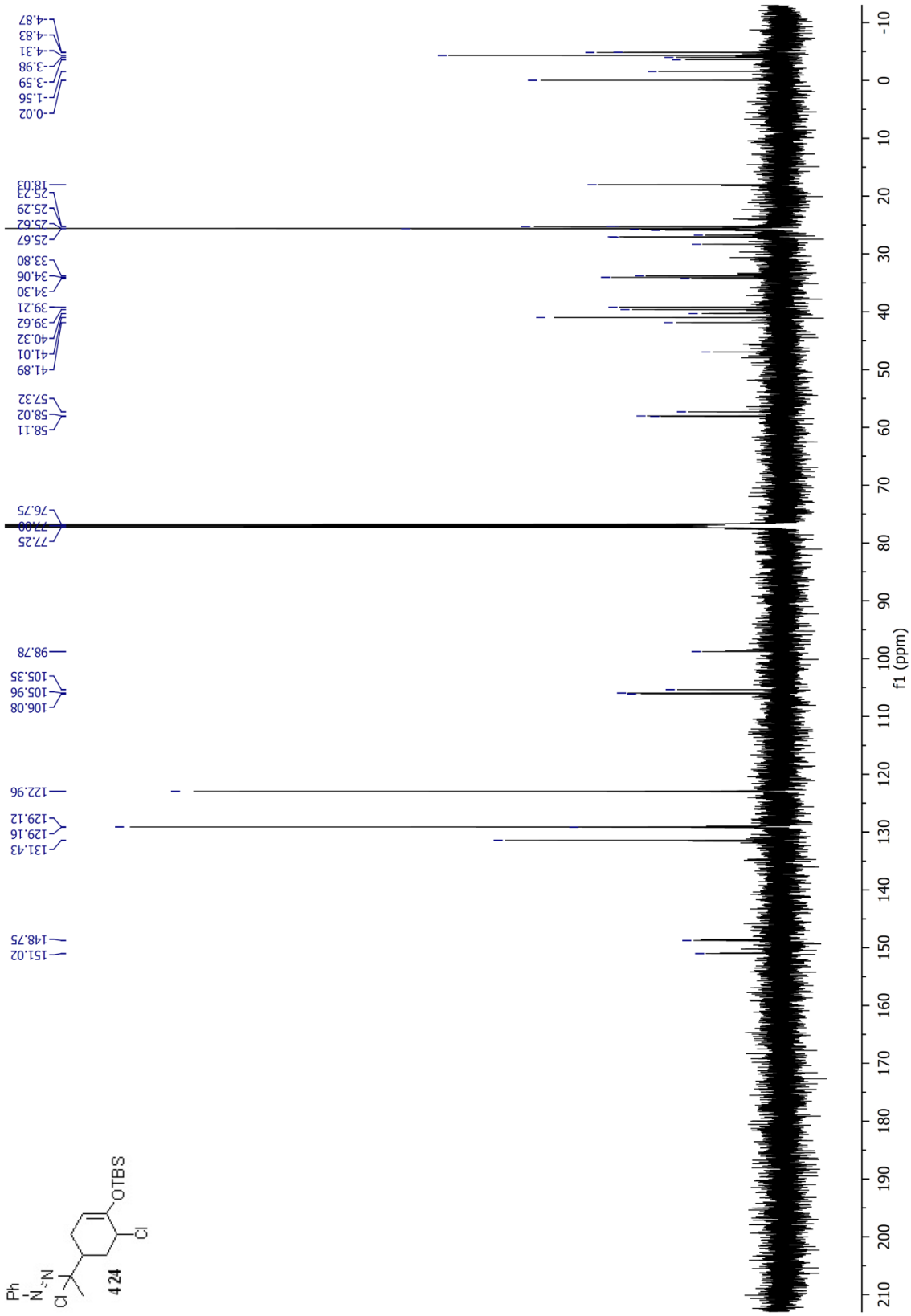

1.00
1.02
0.95
0.92
1.03
1.06
1.05
3.14
1.28
1.15
1.24
2.50
3.42
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

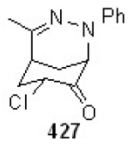

Ph
HN
N
OTBS


2.03
2.06
0.80
1.07
0.98
0.99
2.09
2.12
2.99
2.00
9.77
6.51
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

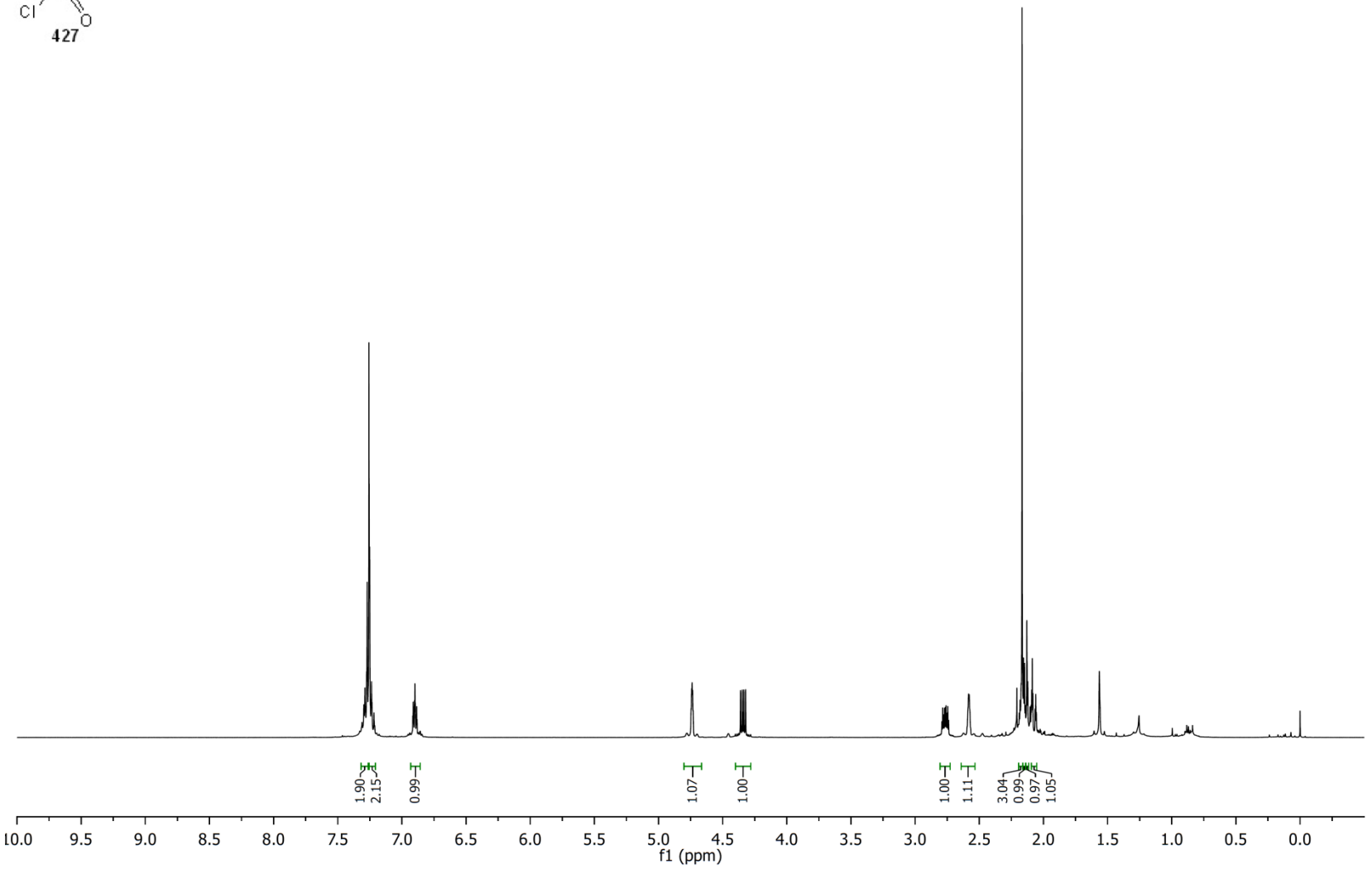

Ph
HN
N
OTBS
-4.47
-4.34
-0.02
12.80
18.02
19.68
25.65
25.70
26.82
27.56
29.82
33.38
42.64
47.14
76.75
77.00
77.25
102.27
103.20
112.85
112.97
119.56
129.14
145.97
148.85
150.26
f1 (ppm)

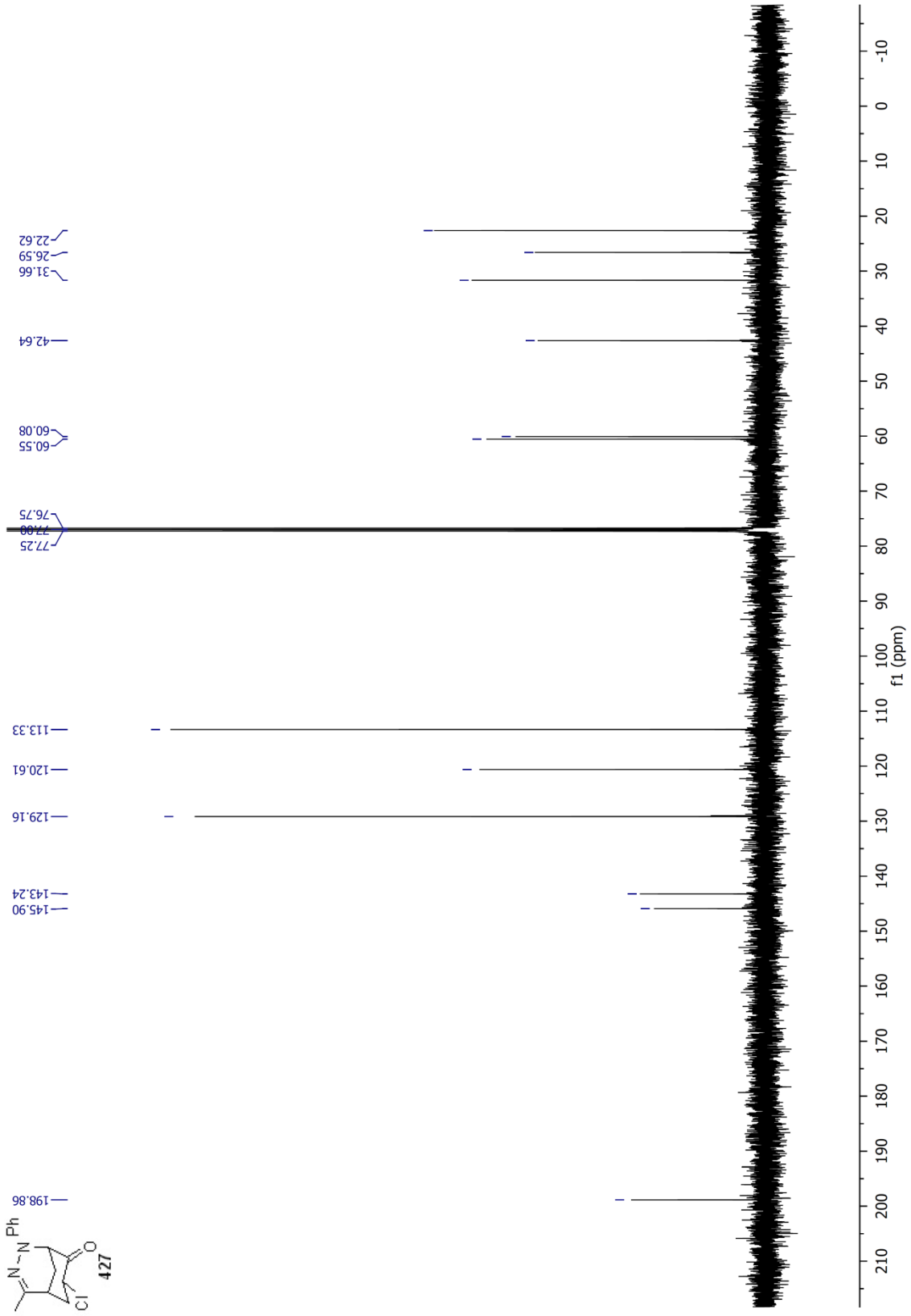

OTBS
Cl
Ph
N
N
Cl
424
f1 (ppm)


-4.87
-4.83
-4.31
-3.98
-3.59
-1.56
-0.02
18.03
25.23
25.29
25.62
25.67
33.80
34.06
34.30
39.21
39.62
40.32
41.01
41.89
57.32
58.02
58.11
76.75
77.08
77.25
98.78
105.35
105.96
106.08
122.96
129.12
129.16
131.43
148.75
151.02
OTBS
Cl
Cl
Ph
N
N
424
f1 (ppm)


N
N
Ph
Cl
O

427


1.90
2.15
0.99
1.07
1.00
1.00
1.11
3.04
0.99
0.97
1.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


198.86
145.90
143.24
129.16
120.61
113.33
77.25
77.00
76.75
60.55
60.08
42.64
31.66
26.59
22.62
f1 (ppm)
427