

# **Synthesis of beta-Aminocarbonyl Compounds and Hydrazine Derivatives Using Amino- and Imino-Isocyanates**

by

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

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## Abstract

Over the past recent years,  $\beta$ -aminocarbonyls have been of great interest to medicinal chemists. As a practical method to obtain these moieties, alkene aminocarbonylation, accounting for the formation of a C-N and a C-C bond, has been the subject of limited research efforts (very specific intramolecular metal-catalyzed variants have been reported). Direct aminocarbonylation of alkenes constitutes a challenging and an important potential innovation in the synthesis of  $\beta$ -aminocarbonyls such as  $\beta$ -amino acids. The research efforts described in the present thesis have been primarily directed towards the development of concerted pathways for the amination of alkenes using hydrazine derivatives as bifunctional reagents. Building on our previous report on the reactivity of hydrazides, progress on the aminocarbonylation of alkenes along with the synthetic scope of this reactivity are herein provided.

Therefore, the first part of the present thesis (Chapter 2) focuses primarily on the development of thermolytic conditions for the intramolecular aminocarbonylation of alkenes using amino-isocyanates. Alongside, development of imino-isocyanates have provided complementary synthetic tools for aminocarbonylation. The second part (Chapter 3) describes the work accomplished towards intermolecular aminocarbonylation of alkenes and the synthesis of complex azomethine imine products (Chapter 3).

Finally, the last part of the discussion (Chapter 4) will be on the development of new hydrazide reagents for the intramolecular Cope-type hydroamination of alkenes. In doing so, description of the synthetic utility of amino-isocyanates as amphoteric reagents for cascade reactions and heterocyclic synthesis will be provided.

## Acknowledgements

I remember vividly, as a teenager, when a high school teacher explained to me the importance for young people to find a mentor at some point in their life. I know for a fact that few supervisors are as dedicated to their students as André has been for me. Thank you for giving me the chance to fail and to thrive: I could not have asked for a better experience.

Since I joined the Beauchemin group, many people have contributed directly and indirectly to the present thesis. I must thank Isabelle who has been a dear friend; Ashley, my first laboratory partner; Peter, my conference buddy and Francis for picking me up during the bus strike and for the late nights in the lab. Thanks to Amy, my first undergraduate student, who played a significant role in the early stages of these projects. Thanks to Wei, who has been a real chemistry machine and to Tom for the good times in the lab. I must also acknowledge the students who have continually been developing new ideas from our *N*-substituted isocyanate technology: Thanks to Amanda for making this chemistry useful and to Jean-François for incessantly bringing his creative mind to the table. Obviously, I've had the chance to work with many more members of the Beauchemin group. To all of you, I wish the utmost success in all of your future endeavors.

Finally, this thesis could not have come into being without the constant support of my family. To my father Jeannot, my mother Suzanne, my partner Mathieu and my sister Véronic, I am eternally grateful for your unconditional love and encouragements.

“Stubborn pursuit of a goal is often praised as a virtue, and sometimes leads to success.

However, accidental observations can disclose new horizons, far off the original target and sometimes more valuable. The luck chance might lurk just outside the experimenter’s door, but the door is not always open. Opening it brings serendipity – acceptance of Fortuna’s gift. ”

– Rolf Huisgen



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## List of Abbreviations

[M] – generic metal

[O] – generic oxidant

$[\alpha]_d^{20}$  – specific rotation at 20°C and 589 nm

°C – degrees Celsius

Å – angstrom

Ac – acetyl

Ala – alanine

Ar – generic aryl

B3LYP – Becke-3-Lee-Yang-Parr

BINOL – 1,1'-bi-2-naphthol

Bn – benzyl

Boc – *tert*-butyloxycarbonyl

Bz – Benzoyl

C – carbon

calcd - calculated

CDI – carbonyl diimidazole

cm – centimeter

COD – cyclooctadiene

CSI – chlorosulfonyl isocyanate

Cy – cyclohexyl

DCC – *N,N'*-dicyclohexylcarbodiimide

DCE – 1,2-dichloroethane

DFT – density functional theory

DMAP – 4-dimethylaminopyridine

DMF – *N,N*-dimethylformamide

DMSO – dimethyl sulfoxide

dr – diastereomeric ratio

E – generic electrophile

*E* – *Ger.*, entgegen

E<sub>1</sub>cB – elimination unimolecular conjugate base

E<sub>act</sub> – energy of activation

EDG – electron-donating group

ee – enantiomeric excess

EI – electron impact

equiv – stoichiometric equivalent

Et – ethyl

EWG – electron-withdrawing group

FTIR – Fourier transform infrared

FVT – flash vacuum thermolysis

g – gram

h – hour

HA – hydroamination

HRMS – high-resolution mass spectroscopy

Hz – Hertz

hν – light; electromagnetic radiation

*i*-Pr – isopropyl

IR – infrared

*J* – coupling constant

K – Kelvin

kcal – kilocalorie

L – generic ligand

L – litre, levorotatory

LG – generic leaving group

Lys – lysine

*m* – meta

M – molar

Me – methyl

mins – minutes

mmol – milimole

mol – mole

MOM – methoxymethyl

*n*-Bu – *n*-butyl

NMR – nuclear magnetic resonance

NOE – nuclear Overhauser effect

*n*-Pr – *n*-propyl

Ns – 2-nitrobenzenesulphonyl

Nuc – nucleophile

*o* – *ortho*

*p* – para

PG – protecting group

Ph – phenyl

Phe – phenylalanine

PLP – pyridoxal-5'-phosphate

PMP – *para*-methoxyphenyl

ppm – parts per million

PPP - hydroxyphenyl-*N*-1-propylpiperidine

pyr – pyridine

R – generic group

*R* – *Latin, rectus*

Ra-Ni – Raney-Nickel

R<sub>f</sub> – retention factor

rt – room temperature

*S* – *Latin, sinister*

SPRIX - spiro bis(isoxazoline)

*syn* – together, same side

*t*-Bu – *tert*-butyl

*t*-BuOH – *tert*-butanol

temp. – temperature

Tf – trifluoromethanesulfonyl

TFA – trifluoroacetic acid

THF – tetrahydrofuran



Thr – threonine

TIPBA - 2,4,6-triisopropylbenzenesulfonic acid

TLC – thin-layer chromatography

Trp – tryptophan

Ts – *para*-toluenesulfonyl

TS – transition state

UV – ultraviolet

vac – vacuum

X – generic halide, generic leaving group

X – heteroatom or pseudohalide

Y – generic leaving group

Z – *Ger.*, zusammen

$\Delta$  – thermolysis

$\delta$  – chemical shift in parts per million

$\mu\text{m}$  – micrometer

$\mu\text{W}$  – microwave

# Chapter

# 1 Introduction

## 1.1 Introduction

Since the advent of the first reported synthesis of urea by Friedrich Wöhler in 1828,<sup>1</sup> organic chemistry has undergone incessant evolution and lived through profound advances.<sup>2</sup> Progress has allowed synthetic chemistry to accomplish molecular assemblage of remarkable complexity. Given the sheer number of regularly published examples of total syntheses, the question has risen whether there remains synthetic targets still unattainable by modern methodologies. In answering this question, one must recognize that today, synthetic chemists are facing an ever-increasing number of challenges. For example, the large-scale production of commodity pharmaceuticals still relies heavily on semi-synthetic routes using natural chemical sources, which often restricts drug development. Thus, in

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<sup>1</sup> Wöhler, F. *Ann. Phys. Chem.* **1828**, 12, 253.

<sup>2</sup> Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, 39, 44.

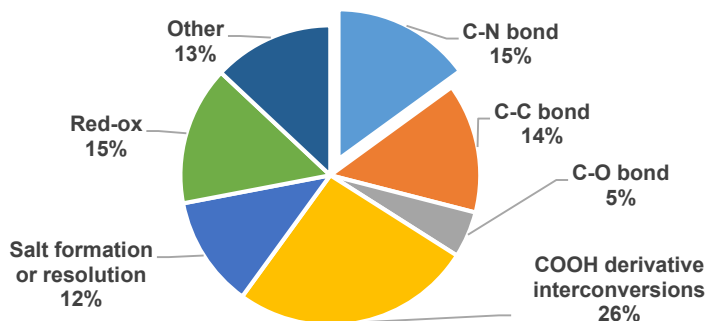
response to the needs of the modern world, research efforts have consistently been shifting away from traditional synthetic objectives towards the added demands of developing reliable, practical, environmentally sound, economically viable and safe chemical processes.

Despite a plethora of synthetic tools available to medicinal chemists, certain types of bond-formations are especially important because of their biological relevance. This is in part due to the fact that nature is often biased in using certain functionalities for achieving its biological functions. As such, nitrogen-containing molecules play a distinctive role. Incorporation of nitrogen to organic frameworks has for long been at the center of intensive research efforts, encompassing some of the most important synthetic challenges facing chemists. Despite these difficulties, the prevalence of C-N bonds in biological systems has continuously fueled the development of new methodologies yielding highly chemo-, regio- and stereoselective bond formations. In view of this, these reactions represent 15% of the overall chemical transformations performed by the pharmaceutical industry (Figure 1.1).<sup>3</sup> From these, C-N bond formation still heavily relies on the use of alkylating agents, adding the risk for the presence of genotoxic impurities in drug products.<sup>4</sup> Consequently, answering the need for improved C-N bond generating processes is of vital importance.

---

<sup>3</sup> Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, 9, 253.

<sup>4</sup> Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, 4, 2337.



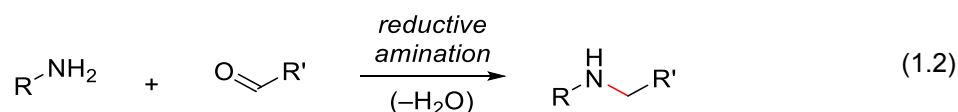
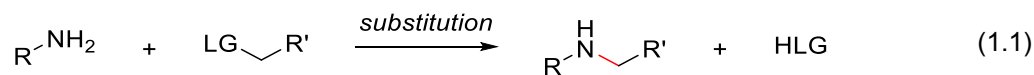
**Figure 1.1** Distribution of reactions performed in the pharmaceutical industry by chemical transformation, surveyed from 1985 to 2002 <sup>3</sup>

## 1.2 Amination Reactions

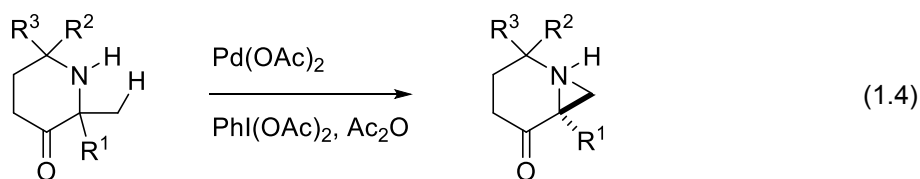
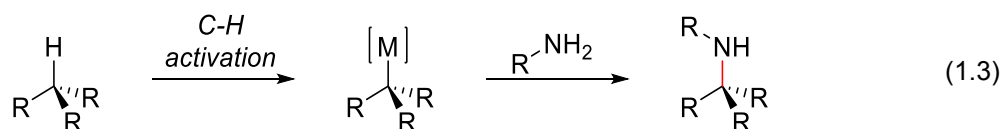
### 1.2.1 Common Methods of Generating C-N Bonds

While nitrogen is present in a variety of functionalities ranging from heteroaromatic cycles, carbonyls, imines and nitriles, amines are especially difficult to generate given the added stereochemical considerations associated with  $sp^3$  carbons. Amines are important motifs, with for example  $\alpha$ -amino acids acting as subunits of enzymes, protein polymers and constituting a major nitrogen building blocks in alkaloid natural product biosyntheses. Hence, amination reactions, the introduction of amine moieties to organic molecules, are valuable synthetic tools.

For the most part, carbon amination processes make use of nitrogen nucleophiles. As previously mentioned, substitution reactions of amines with alkylating agents (equation 1.1) are common methods for the C-N bond formation of amines. Alternatively, reductive aminations are also frequently used transformations (equation 1.2). Even though these reactions are widespread, they suffer from important chemoselectivity issues in addition to presenting poor atom economy.



Instead, reactions through direct carbon functionalization are much more desirable. Notably, strategies involving C-H activation of  $sp^3$  carbons represent major advancements for the synthesis of amines (equation 1.3).<sup>5</sup>

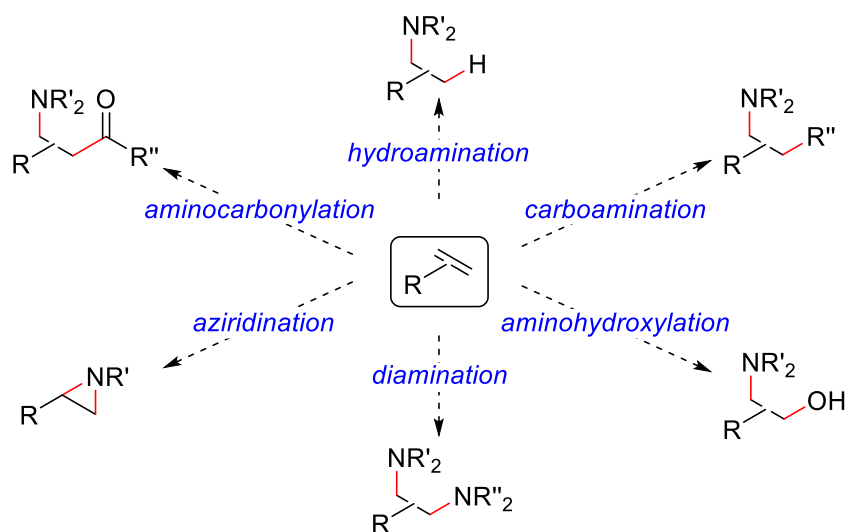


Despite significant progress (equation 1.4), aminations by C-H activation still suffer from important limitations such as the stoichiometric use of oxidant and requirements for intramolecular directing groups. In addition, transition-metal catalyzed processes are often unamenable to late stage derivatization of pharmaceutical products because of the added risk for the presence of metal impurities. Nonetheless, amination through C-H functionalization is rapidly evolving and solutions to these problems are continuously being reported.

<sup>5</sup> For a recent review of C-H bond activation for intramolecular C-N bond formation, see: Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, 44, 1778.

### 1.2.2 Amination of Alkenes

Alternatively, functionalization of  $sp^2$  carbons, specifically carbon-carbon  $\pi$ -bonds, to  $sp^3$  products has been subject to intense research efforts. Alkenes, many derived from petroleum feedstock, are widely available and inexpensive starting materials. Therefore, reactions generating C-N bonds from olefins may offer attractive and cost-efficient methodologies for the synthesis of value-added products such as amines. In turn, amine functionalities are numerous and varied. Important alkene amination processes have been reported over the years (Figure 1.2). From these, aminations can be combined with other bond formations of relevance to biological systems.

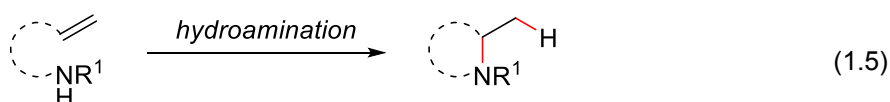


**Figure 1.2** Methods for amination of alkenes

The examples provided correspond only to a general overview of methodologies allowing C-N bond formations from alkenes. Despite the importance of these transformations, few have found solutions to the direct conversion from alkenes and most suffer from important synthetic limitations. However, mechanistic parallels may be drawn between them. This chapter is meant to propose trends and considerations for the

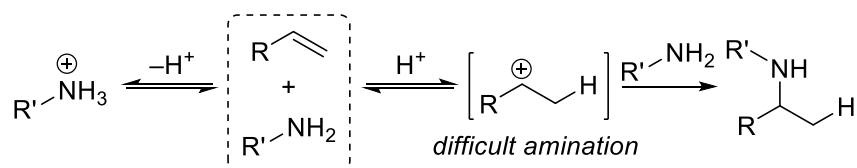
development of amination methodologies involving alkenes. While it is understood that detailed nuances exist, the following discussion is not meant to provide an exhaustive survey of amination reactions. However, the conclusions to be drawn here will lead us to discuss new strategies and development of reagents for some of these transformations.

### 1.2.3 Amination of Alkenes: Considerations and Limitations



The formal addition of N-H bonds across olefins, namely hydroamination, has is a powerful tool for the synthesis of nitrogen-containing molecules. Given its complete atom-economy, alkene hydroamination has become especially attractive for the synthesis of bulk chemicals and has found major relevance within industrial processes. As such, alkene hydroamination represents a greener alternative to direct amine alkylation. Although this simple bond formation is a highly attractive transformation, reactions between amines and unactivated alkenes is inherently difficult given that both reactants are electron-rich. Consequently, electrostatic repulsion between reagents imposes a high energy barrier to C-N bond formation. Therefore, hydroamination of olefins requires substrate activation and is often difficult even at elevated temperature. However, strategies for catalytic activations have been put forward. For example, in reactions involving Brønsted acids, activation occurs via protonation of alkene, as represented in Scheme 1.3. However, such reactions are rendered difficult by the presence basic nitrogen nucleophiles which competes with the alkene protonation (Scheme 1.3). Consequently, this reactivity generally involves to nitrogen nucleophiles with minimal basicity (e.g. amides, sulfonamides, etc.).

Additionally, Brønsted acid catalyzed hydroaminations are typically performed under elevated temperatures involving lengthy reaction times.



**Figure 1.3** Chemoselectivity issues associated with Brønsted acid catalyzed hydroamination

In turn, transition-metals have provided some control over these chemoselectivity issues.<sup>6</sup> Thus far, most intermolecular examples of alkene hydroamination are restricted to strained-olefins,<sup>7</sup> dienes,<sup>8</sup> and styrenes.<sup>9</sup> In turn, the amine scope generally suffers from substrate specificity given the necessity for amine bearing electron-withdrawing substituents. This is essential as amines generally exhibit strong affinity for metal catalysts such as palladium; therefore, chemical differentiation between amine and alkenes is again, as with Brønsted acids, an important limitation to hydroamination. Arguably, such chemoselectivity issues may similarly affect development of other olefin amination methods.

<sup>6</sup> For selected reviews, see: (a) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795 and reviews cited therein. (b) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (c) Hultsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (d) Nobis, M.; Holscher-Driebed, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3983. (e) Müller, E. T.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

<sup>7</sup> Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

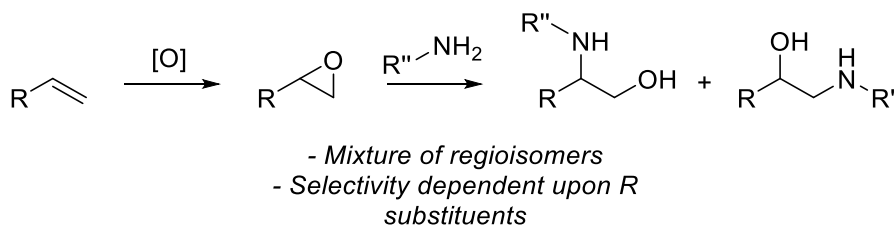
<sup>8</sup> Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.

<sup>9</sup> (a) Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051. (b) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.



### 1.2.4 Chemoselectivity: A Stepwise Approach

Over the years, various methods of alkene activations have been put forward. A common strategy involves oxidation of alkenes to haloniums or epoxides that permits C-N bond formation with nucleophilic amines. However, as with hydroamination reactions, reagent compatibility can be problematic (e.g.: amine oxidation). Therefore, to bypass these chemoselectivity issues, stepwise activation-amination approaches have been reported. For example, epoxidation of olefins followed by aminolysis affords vicinal amino alcohols, a common structural motif found in many biologically active compounds (Figure 1.4).



**Figure 1.4** Synthesis of 1,2-aminoalcohols by epoxide aminolysis

Unfortunately, addition of amines to epoxides can be poorly regioselective and highly dependent on substitution of both nucleophilic and electrophilic components.<sup>10</sup> These are impractical sequences, given requirements for additional purifications, while oxidation of olefins may lack functional group tolerance. Therefore, combination of such oxidative activation and aminolysis into a single step is desirable transformation and would provide an alternative method to the synthesis of important amine functionalities.

<sup>10</sup> (a) Bonollo, S.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2006**, 8, 960. (b) Azizi, N.; Saidi, M. R. *Org. Lett.* **2005**, 7, 3649.

### 1.2.5 Concerted Approach to the Aminohydroxylation of Alkenes



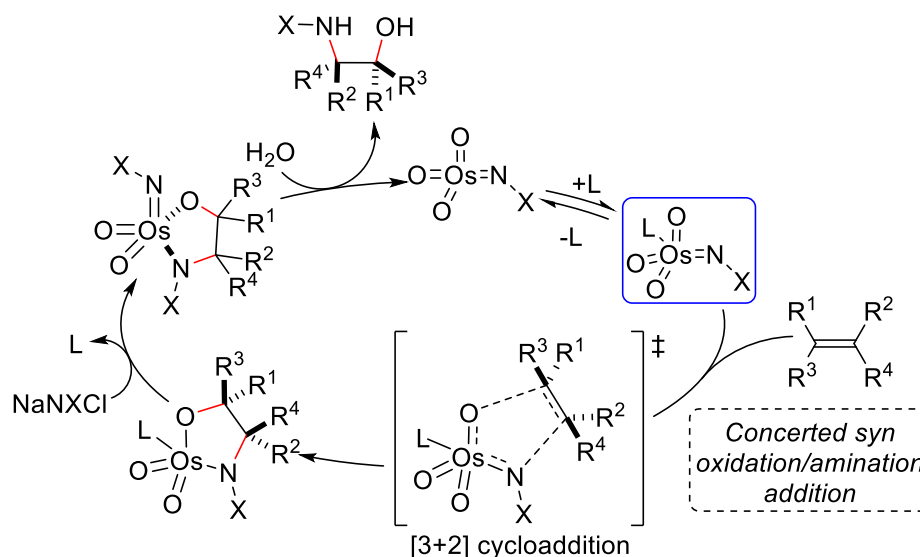
During the 1970's, Sharpless reported a solution to this synthetic problem. Following the discovery of osmium tetroxide catalyzed dihydroxylation, report came of the development of a nitrogen variant of this reaction.<sup>11</sup> Illustrated in Figure 1.5, Sharpless proposes the use of reactive imidotrioxoosmium, which in the presence of a suitable ligand performs aminohydroxylation of olefins. Following oxidation and catalyst turnover, this addition effectively affords vicinal amino alcohols. The process was later made enantioselective by use of chiral alkaloid ligands, providing a leap forward in the synthesis of these important moieties.<sup>12</sup> Of interest to the present discussion is the ability of the amination reagent to perform bond formation with retention of stereochemical information from the alkene, *E* versus *Z*, which is strongly indicative of a concerted *syn* addition. The C-N bond formation is suggested to occur via five-membered transition state as a [3+2] dipolar cycloaddition. However, evidence for a [2+2] cycloaddition has also been put forward but has recently lost some support.<sup>13</sup>

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<sup>11</sup> Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544.

<sup>12</sup> Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1997**, *35*, 2813.

<sup>13</sup> Munz, D.; Strassner, T. *J. Org. Chem.* **2010**, *75*, 1491, and references cited therein.



**Figure 1.5** The Sharpless asymmetric osmium catalyzed alkene aminohydroxylation

As discussed in section 1.1.3, thermodynamic factors and static repulsion between reagents may adversely affect nitrogen addition to alkenes. Therefore, we described the requirement for pre-activation of the olefin prior to C-N bond formation. For this purpose, we described the utility of transition metal and Brønsted acid catalysts while denoting the chemoselective challenges associated with olefin activation, namely a difficult differentiation between reagents. In this view, the mechanistic proposition and reactive intermediate put forward by Sharpless for aminohydroxylation is particularly interesting.

During the cycloaddition step, imidotrioxoosmium simultaneously generates C-O and C-N bond. In this process, the alkene moiety undergoes oxidation. In analogy to the necessity for previously discussed olefin pre-activation, we may suggest that alkene amination is initiated via oxidative C-O bond formation by osmium oxide. In other words, the imidotrioxoosmium reagent has the dual ability to oxidatively activate alkenes and simultaneously facilitate nitrogen addition. To support this hypothesis, we would expect generation of C-O bond with olefin to precede C-N bond formation. Indeed, recent DFT

calculations reveals a shorter C-O versus C-N bond in the transition state, supporting a concerted yet asynchronous mechanism where bond formation is initiated via interaction between carbon and oxygen.<sup>14</sup> As such, Sharpless' aminohydroxylation reagent combines an activating and an aminating function. While this description of the mechanistic outcome remains speculative, it denotes an important feature of the proposed amination reagent, namely its bifunctional character.

The importance of the concerted nature of this mechanism must be emphasized. Pre-activation of alkenes typically involves generation of high energy intermediates for which control of the reactive outcome, as demonstrated with aminolysis of epoxides (Figure 1.4), might be difficult to predict. Therefore, the advantage of such bifunctional reagent in aminations of olefins is to perform substrate activation while avoiding these intermediates, which may result in a lower energy process. The reaction therefore provides control over the chemoselective and stereoselective outcome.

The Sharpless aminohydroxylation is a powerful amination method for the functionalization of alkenes. Involvement of a concerted *syn* addition allows diastereocontrol demonstrating the value of 1,3-dipolar cycloaddition in C-N bond formations. While many factors are known to affect the regioselectivity of this transformation, it has nonetheless become a valuable method for the synthesis of chiral vicinal amino alcohols. Therefore, lessons from the bifunctional reactivity of imidoosmium reagent ought to be learned and applied to the development of other bifunctional amination reagents.

### 1.2.6 Dipoles as Reagents for C-N Bond Formation

As it appears with Sharpless's aminohydroxylation, the bifunctionality of the reagent may appear key to the C-N bond formation. Recognizing the importance of concerted additions for the efficiency and selectivity of these transformations, the reaction is not unlike that of 1,3-dipole reagents. As such, dipoles have an amphoteric character, thus possessing both an electrophilic (electron-poor) and nucleophilic (electron-rich) functionality, which also allows them undergo dipolar cycloadditions with olefins.

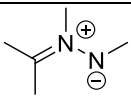
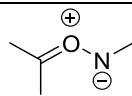
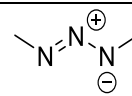
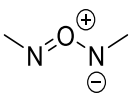
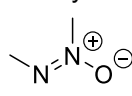
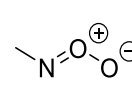
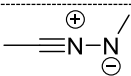
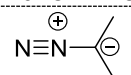
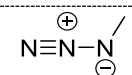
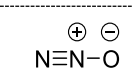
The premise for dipolar cycloadditions was established by Huisgen in the 1960s. Provided then were arguments for the reactivity potential of many dipole moieties which, as postulated by Huisgen, could undergo 6- $\pi$  electron bond formation as [3+2] cycloadditions.<sup>14</sup> Over the years, many were experimentally confirmed to cyclize with  $\pi$ -bonds. Hence, dipolar cycloadditions have become vital synthetic tools for the generation of a numerous heterocycles. In turn, these have opened the door to molecular ligation methods for which the importance has echoed in various fields, from material science to chemical biology.<sup>15</sup> Illustrated in Table 1.1 are dipole reagents allowing C-N bond formations, as predicted by Huisgen.

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<sup>14</sup> For a general overview of dipolar cycloadditions, see: (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, 2, 633. (b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, 2, 565.

<sup>15</sup> For a recent review of reactions for bioconjugation, see: Debets, M. F.; Van Berkel, S. S.; Dommerholt, J.; Dirks, A. J.; Rutjied, F. P. J. T.; Van Delft, F. L. *Acc. Chem. Res.* **2011**, 44, 805.

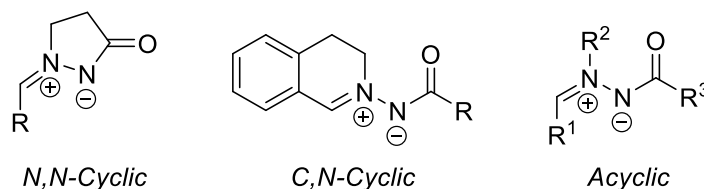
**Table 1.1** 1,3-Dipole reagents for dipolar cycloadditions predicted by Huisgen for C-N bond formation

|                   |                                                                                                                                           |                                                                                                      |                                                                                                      |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
|                   | $\begin{array}{c} a=b-c \\     \\ R \end{array} \longrightarrow \begin{array}{c} a \quad b=c \\ \diagdown \quad \diagup \\ R \end{array}$ |                                                                                                      |                                                                                                      |
| Allyl-type        | <br>Azomethine imines                                    | <br>Carbonyl imine | <br>Azimine       |
|                   | <br>Nitrosimines                                         | <br>Azoxides       | <br>Nitrosoxides  |
|                   | <br>Nitrile imine                                        |                                                                                                      |                                                                                                      |
| Nitrilium betaine |                                                                                                                                           |                                                                                                      |                                                                                                      |
| Diazolium betaine | <br>Diazoalkane                                          | <br>Azide          | <br>Nitrous oxide |
|                   |                                                                                                                                           |                                                                                                      |                                                                                                      |
|                   |                                                                                                                                           |                                                                                                      |                                                                                                      |

Huisgen also categorized 1,3-dipoles according to their geometry. Allyl- and propargyl-type dipoles are today the most commonly used moieties for dipolar cycloadditions. These reagents have found many more applications with alkynes than alkenes, as triple bonds are more reactive, given the lower activation energy requirements associated with such  $\pi$ -systems. Therefore, dipolar cycloadditions with alkenes are comparably more challenging as, in opposition to triple bonds, they cannot afford aromatic compounds (with the resulting thermodynamic driving force). Such transformations are nonetheless synthetically useful. As it pertains to the present discussion, the following section will survey recent examples of dipolar cycloadditions of alkenes encompassing C-N bond formation.

### 1.2.6.1 Azomethine Imines

Most dipole reagents are synthesized in-situ and hardly isolable. Their dipolar character makes them challenging to characterize and sometimes difficult to observe. However, this highly reactive nature makes them attractive reagents for notoriously difficult transformations such as alkene functionalization, especially when involving C-N bond formation. Therefore, applications of reagents such as azomethine imines have had a significant impact on the synthesis of nitrogen containing molecules. More so, in opposition to other dipoles, many azomethine imines are stable enough to be isolated which has facilitated development of their reactivity. Perhaps, this might explain why azomethine imines have received much attention.



**Figure 1.6** Reported azomethine imine motifs

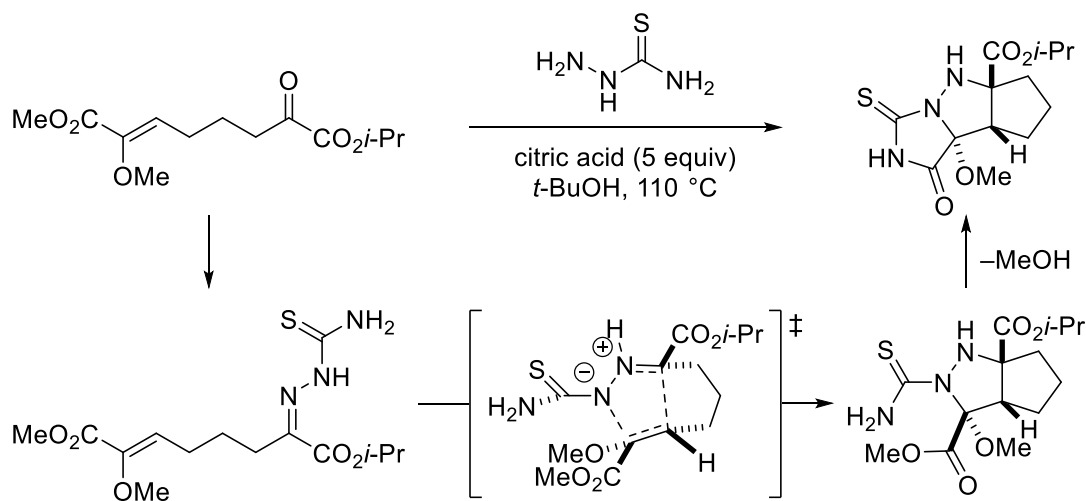
Azomethine imines can exist in different forms, of which three major categories emerge, all sharing an allylic dipolar C=N<sup>+</sup>-N<sup>-</sup> character (Figure 1.6).<sup>16</sup> While each type features various levels of reactivity, reactions of azomethine imines with alkenes have found widespread applications in heterocyclic synthesis.<sup>17</sup> Particular attention must be provided for their ability to introduce N-N functionalities within cyclic core. Intramolecular cycloadditions are especially important because of their ability to generate polycyclic

<sup>16</sup> Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, 3, 642.

<sup>17</sup> For a review of the reactivity of azomethine imines, see: Schantl, J.G. *Azomethine Imines, Science of Synthesis* **2004**, 27, 731.

molecules with important biological applications and therapeutic potential.<sup>18</sup> A great example was recently published by Overman and coworkers for the preparation of a potential precursor of the alkaloid Palau'amine.<sup>19</sup>

**Scheme 1.1** Diastereoselective synthesis of *cis*-cyclopenapyrazolidine by intramolecular 1,3-dipolar cycloaddition with azomethine imine



In this reaction sequence, the thiosemicarbazone is generated by in-situ condensation of thiosemicarbazide with a  $\alpha$ -keto ester. Under acidic conditions, an azomethine imine dipole is generated and effectively cyclizes with a vinyl ether moiety with good diastereoselectivity. Following this, intramolecular transesterification effectively produces a polycyclic pyrazolidine.

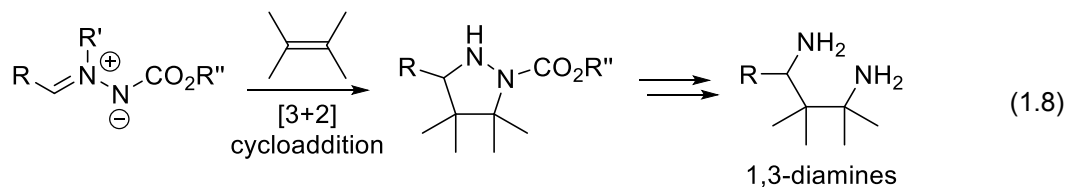
However, as C-N bond formation reagents, intermolecular reactions of azomethine imines are very useful. In the 1980's, Kanemasa and coworkers proposed to use pyrazolidine products resulting from dipolar cycloadditions between azomethine imines

<sup>18</sup> Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 10.

<sup>19</sup> Gergely, J.; Morgan, J. B.; Overman, L. E. *J. Org. Chem.* **2006**, 71, 9144.

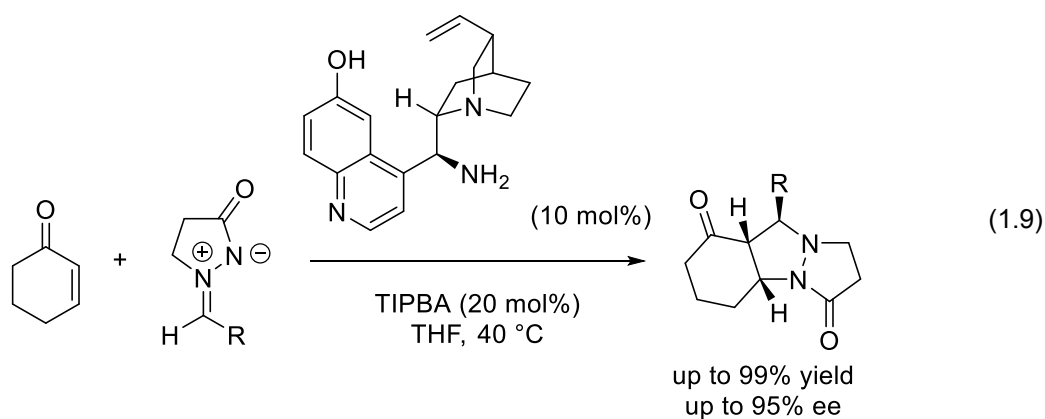


and alkenes as precursors to functionalized 1,3-diamines, a common feature of alkaloid natural products (equation 1.8).<sup>20</sup>



The advantage of using alkenes as dipolarophiles is the potential to generate stereocenters. Yet, such transformation remains very challenging. Thankfully, reports of enantioselective additions are now emerging: Presented herein are selected examples using various catalytic strategies.

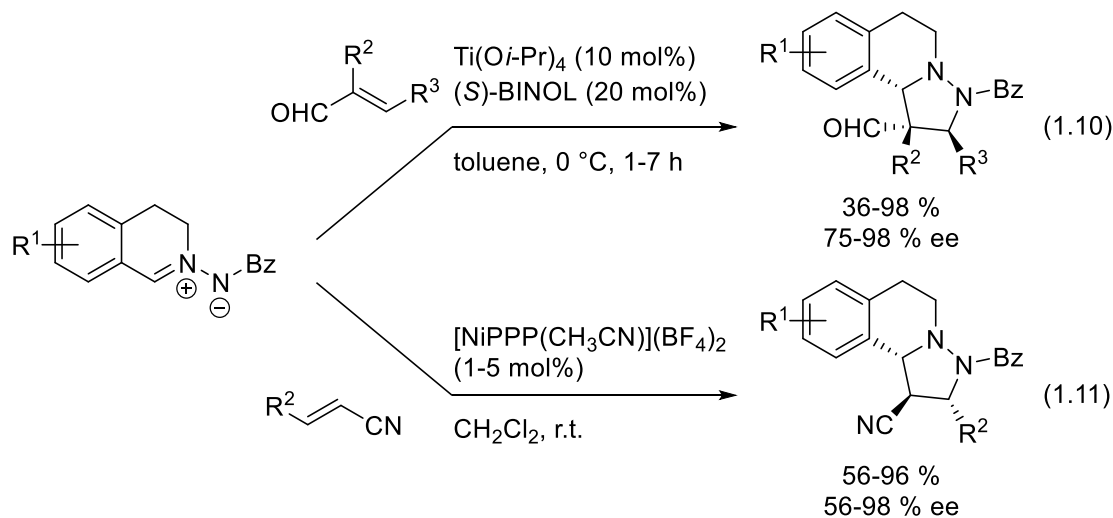
Recently, Chen and coworkers proposed the use of a chiral cinchona alkaloid in an iminium catalyzed addition of *N,N*-cyclic azomethine imine to enones.<sup>21</sup> The reaction proved efficient, resulting in excellent yield for the desired cycloaddition product. Very good levels of enantioselectivity were also obtained, which the authors attribute to a tight catalyst and substrate binding, due to H-bonding.



<sup>20</sup> Kanemasa, S.; Tomoshige, N.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, 62, 3944.

<sup>21</sup> Chen, W.; Du, Wei; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2007**, 46, 7667.

In addition, the Maruoka group recently reported a titanium catalyzed process with (*S*)-binol as a chiral ligand for the cycloaddition with an unsaturated aldehyde (equation 1.10).<sup>22</sup> Later, Togni and coworkers extended on the reactivity and made use of a chiral nickel catalyst in the presence of acrylonitrile, which resulted in nitrile substituted pyrazolidine products (equation 1.11).<sup>23</sup>



While good yields and stereoselectivity are achieved, the methodologies here presented suffer from important synthetic limitations. For one, cycloaddition is amenable only with electron poor olefins onto which substitution allows moderate retention of diastereoselectivity.

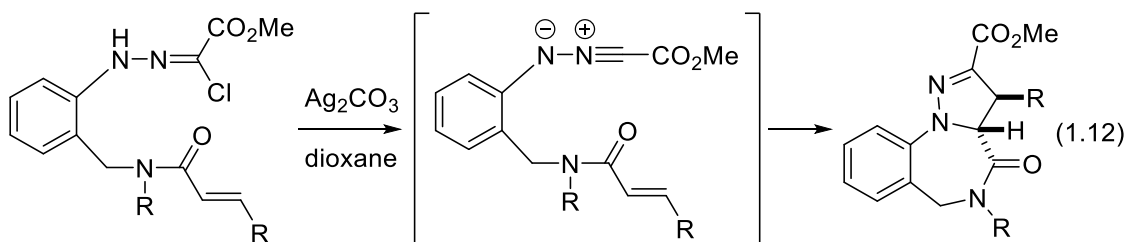
#### 1.2.6.2 Nitrilimines

Alternatively to azomethine imines, nitrilimines also have N-N functionality but possess an extra level oxidation. Therefore, these dipoles depict a propargylic character, as

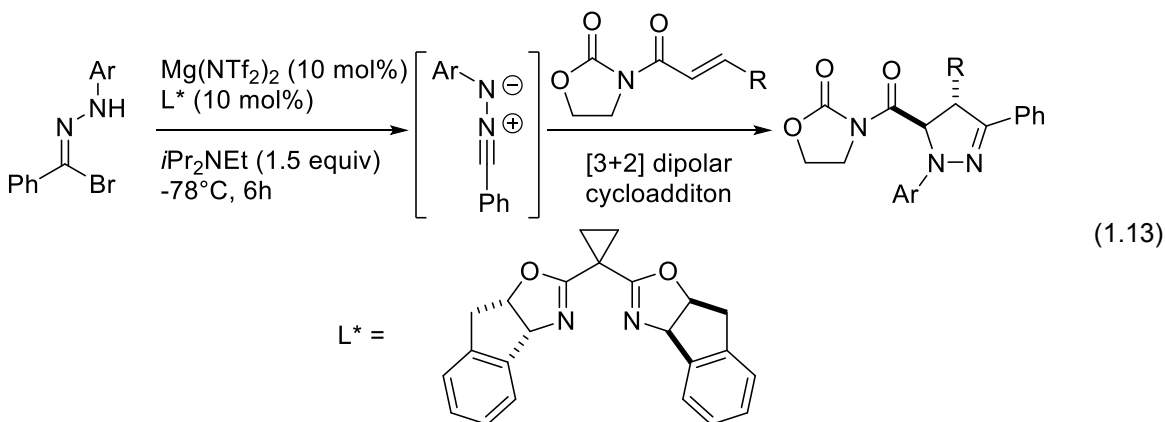
<sup>22</sup> Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076.

<sup>23</sup> Milosevic, S.; Togni, A. *J. Org. Chem.* **2013**, *78*, 9638.

described by Huisgen. Contrary to azomethine imines, these must be generated in-situ, for which multiple strategies have been put forward. The most common precursors to nitrilimines are acyl-halohydrazone, which in the presence of a suitable reagent, such as silver carbonate depicted in equation 1.12, decomposes to the corresponding dipole.



These are also amenable to intramolecular dipolar cycloadditions and have proved useful for the synthesis of polycyclic molecules. Recently, Sibi and coworkers reported an intermolecular enantioselective magnesium catalyzed dipolar cycloaddition with unsaturated carbonyls.<sup>24,25</sup> However, stereocontrol is limited to substrates bearing oxazolidones (equation 1.13).



<sup>24</sup> Sibi, M. P.; Stanley, L. M.; Soeta, T. *Adv. Synth. Catal.* **2006**, *348*, 2371.

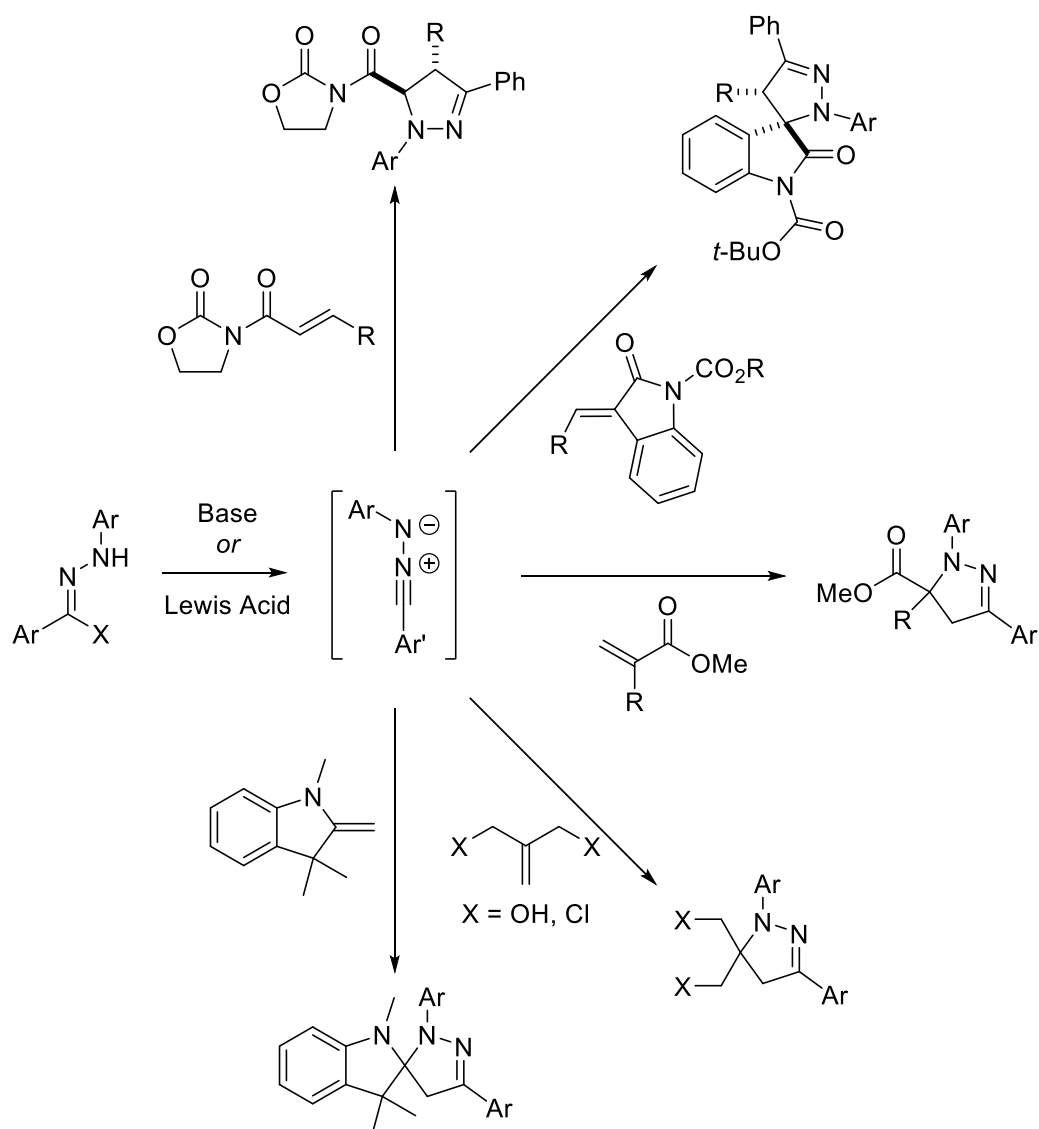
<sup>25</sup> For similar reactivity, see also: (a) Wang, G.; Liu, X.; Huang, T.; Kuang, Y.; Lin, L.; Feng, X. *Org. Lett.* **2013**, *15*, 76. (b) Gerten, A. L.; Slade, M. C.; Pugh, K. M.; Stanley, L. M. *Org. Biomol. Chem.*, **2013**, *11*, 7834. (c) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971.

Other examples of intermolecular reactivity have been reported. However, scope and thus synthetic utility of nitrileimines dipoles are still limited to activated alkenes (electron-rich and electron-poor) (Scheme 1.2).<sup>26</sup> Accounts of similar reactivity with non-conjugated alkenes are rare.

**Scheme 1.2** Synthetic scope of intermolecular 1,3-dipolar cycloaddition with alkenes

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<sup>26</sup> Dadiboyena, S.; Hamme II, A. T. *Eur. J. Org. Chem.* **2013**, 7567.



### 1.2.6.3 Summary of 1,3-Dipolar Cycloaddition with Alkenes

While the reactivity surveyed in this section is by no means representative of all dipolar cycloadditions, our attention has been focused on dipole reagents that were successfully applied to the C-N functionalization of alkenes. Additional emphasis has been put on dipoles reagents bearing hydrazine moieties, as these functions will pertain to coming chapters. Relevance of dipoles to the present discussion on amination reagents relies in their ability to generate C-N bonds with alkenes a concerted manner. This has

significant implications for the development of bifunctional reagents as previously described. Therefore, it begs to question whether the combination of aminating functionalities with different activator groups, in a single reagent, could enable the design of other C-N bond formation processes.

### 1.3 Bifunctional Reagents

The term “multifunctional” has been broadly used to designate several types of reagents. The loose usage of the term has often been associated with reagents or catalysts providing various transformations or bond formations, sometimes in a single step. Bifunctional reagents typically provide combinations of two reactive functionalities of either electrophilic or nucleophilic character and have found applications for diverse purposes such as molecular bioconjugation,<sup>27</sup> multi-component and cascade reactions<sup>28,29</sup> and catalysis.<sup>30</sup>

In previous sections, we have drawn parallels between different methods for the amination of alkenes. As such, we have emphasized the bifunctional amphoteric character of these reagents and the importance of concerted additions for the efficiency and selectivity of these transformations. Importantly, we have described the ability of some

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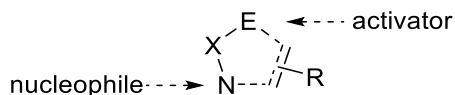
<sup>27</sup> (a) Ji, T. H. *Methods In Enzymology* **1983**, 91, 580. (b) Han, K. K.; Richard, C.; Delacourte, A. *Int. J. Biochem.* **1984**, 16, 129. (c) Fasold, H.; Klappenberger, J.; Meyer, C.; Remold, H. *Angew. Chem. Int. Ed.* **1971**, 10, 795.

<sup>28</sup> For recent applications of bifunctional reagents, see : (a) Campos, C. A.; Gianino, J. B.; Ashfeld, B. L. *Org. Lett.* **2013**, 15, 2656. (b) Scotti, N.; Ravaiso, N.; Zaccheria, F.; Psaro, R.; Evangelisti, C. *Chem. Commun.* **2013**, 49, 1957.

<sup>29</sup> For an interesting synthetic application of bifunctional reagent to bryostatins, see : Keck, G. E.; Yu, T.; McLaws, M. D. *J. Org. Chem.* **2005**, 70, 2543.

<sup>30</sup> For a recent example of multifunctional catalyst, see: Lee, J. S.; Kim, D.; Kong, S. B.; Han, H. *Chem. Eur. J.* **2013**, 19, 4135.

reagents to synergistically act on alkenes to activate  $\pi$ -bonds and selectively promote amine additions.

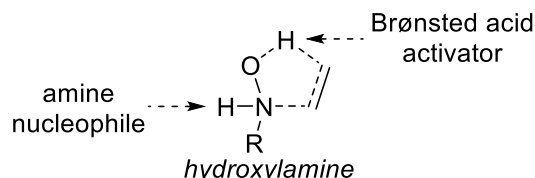


**Figure 1.7** Representation of bifunctional reagent for amination of alkenes

Of interest to the present discussion are bifunctional reagents bearing both an activator moiety (electrophile) and a reactive counterpart (nucleophile), specifically in the context of reactions with olefins. As it will be discussed, such bifunctional reagents are useful in the development of amination reactions, as these moieties are prone to act synergistically with olefins and undergo bond-formation in a concerted manner. In continuity with the previously discussed examples of amination reactions, this section will focus on the development of bifunctional reagents for the C-N functionalization of alkenes. More precisely, aim will be taken at describing recent contributions from the Beauchemin group towards the development of Cope-type hydroamination and further leading to the discovery of new reactivity.

### 1.3.1 Cope-type Hydroamination with Hydroxylamines

Hydroamination, has for long been limited to intramolecular reactivity and only few metal-free strategies are currently available. Additionally, stereoselective intermolecular hydroamination has proven particularly challenging.<sup>31</sup>



**Figure 1.8** Bifunctional character of hydroxylamines

Interestingly, early work reviewed by Cooper and Knight revealed the propensity of hydroxylamines to readily react with  $\pi$ -bonds in a reverse Cope-type hydroamination reaction (Scheme 1.3).<sup>32</sup> In this case, the use of hydroxylamines, as with previously described reagents, combines both an activator, in the form of an acidic hydrogen and a nucleophilic nitrogen, providing a bifunctional character (Figure 1.8). Thus, in line with our previous description of bifunctional reagents, hydroxylamines have both the ability to activate and aminate olefins simultaneously. Initial work by the Beauchemin group established the generality of Cope-type hydroamination with alkenes, expanding the scope to intermolecular substrates.<sup>34</sup> The group also demonstrated the importance of using protic

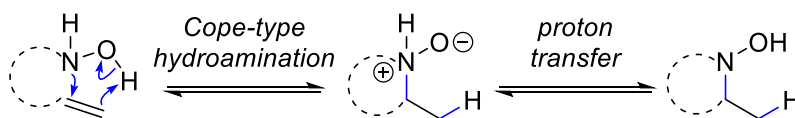
<sup>31</sup> For a recent and interesting example of stereoselective intermolecular hydroamination of unactivated alkenes, see : Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 3200.

<sup>32</sup> For a review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.



solvents to increase the efficiency of the overall process, potentially by providing stabilization of the dipole intermediate.<sup>33,34</sup>

**Scheme 1.3** Cope-type hydroamination of alkenes with hydroxylamines



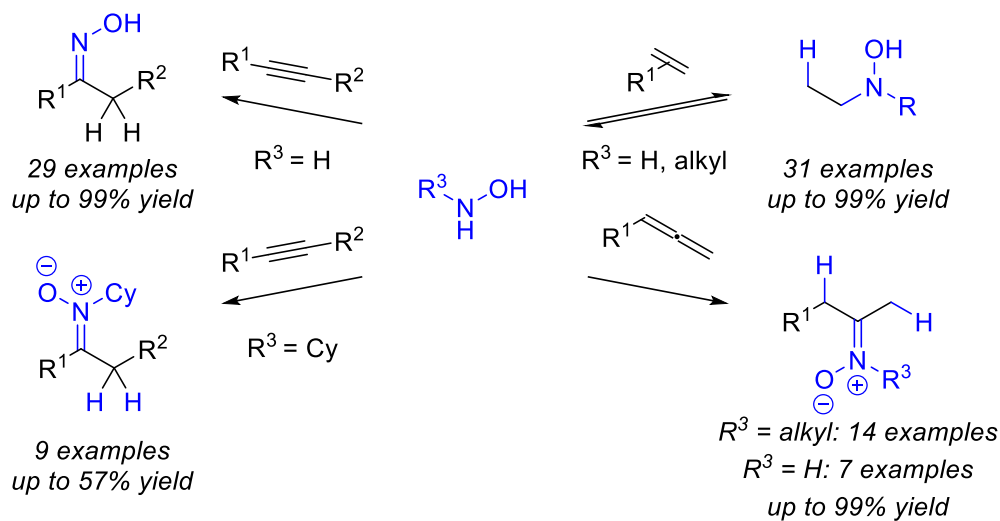
Hydroxylamines also proved to react well with alkynes and allenes affording ketonitrone and oximes (Scheme 1.4).<sup>33ab,35</sup> In turn, intermolecular hydroamination with alkenes is limited to strained and activated olefins.<sup>33a</sup> However, recent advances have demonstrated the ability of aldehydes to catalyze hydroamination of allylic amines through a catalytic tethering strategy.<sup>36</sup>

<sup>33</sup> (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893. (c) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874. (d) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1875.

<sup>34</sup> For a review and further discussion on the solvent effect on the Cope-type hydroamination of olefins using hydroxylamines, see: Beauchemin, A. M. *Org. Biomol. Chem.* **2013**, *11*, 7039.

<sup>35</sup> Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895.

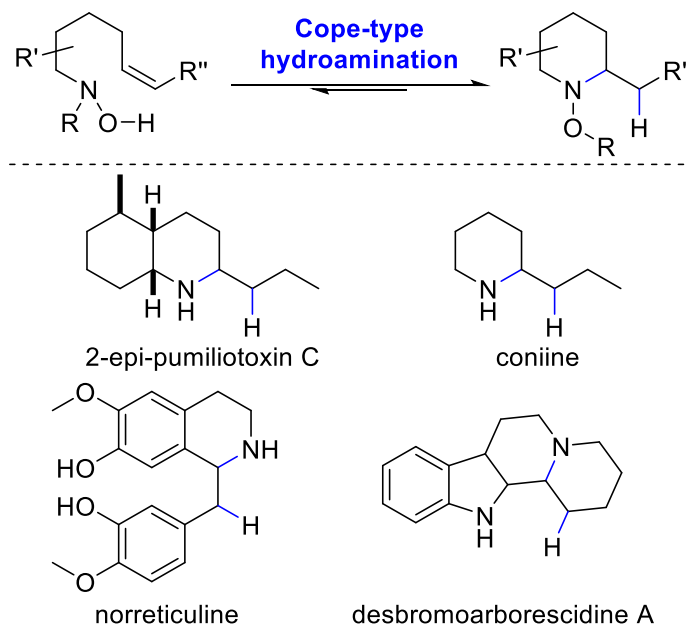
<sup>36</sup> (a) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100. (b) Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571.

**Scheme 1.4** Scope of intermolecular Cope-type hydroamination with hydroxylamines

Early investigation on intramolecular hydroamination with alkenes proved mostly limited to five-membered cycles given the poor thermal stability of hydroxylamines and the higher energy requirements necessary to the generation medium-sized ring systems. As such, synthesis of piperidine derivatives proved challenging. However, following optimization, six-membered rings could be generated and the method could be applied to the synthesis of several natural products (Scheme 1.5).<sup>37</sup>

<sup>37</sup> Dion, I.; Vincent-Rocan, J.-F.; Zhang, L.; Cebrowski, P.; Lebrun, M.-E.; Pfeiffer, J. Y.; Bédard, A.-C.; Beauchemin, A. M. *J. Org. Chem.* **2013**, 78, 12735.

**Scheme 1.5** Synthesis of piperidine natural products by intramolecular alkene hydroamination with hydroxylamines as bifunctional reagents



The aforementioned reactivity is remarkable as generation of six-membered rings from linear precursors is a well-known synthetic problem. The reactivity thus far presented demonstrates the power of bifunctional reagents, such as hydroxylamines, to undergo difficult transformations and provide synthesis of challenging molecules. Therefore, the Beauchemin group thrived at exploring the reactivity of other bifunctional moieties, which could provide solutions to inconveniences associated with hydroxylamines and enable the development of new synthetic tools.

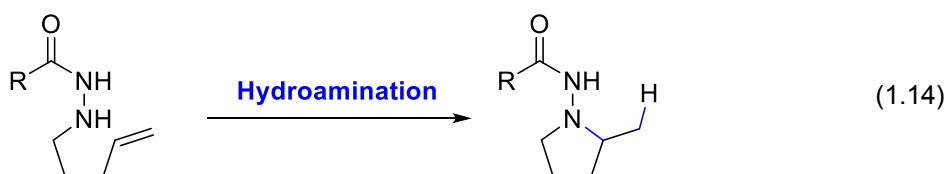
### 1.3.2 Cope-Type Hydroamination with Hydrazines

Following hydroxylamines, systems presenting similar characteristics were also investigated for their hydroamination potential. Hydrazines, as for hydroxylamines, presented poor reagent stability, and early investigation proved hydroamination to be

limited to aryl acetylenes.<sup>38</sup> Therefore, development of stable reagents became vital to further the applicability of Cope-type hydroamination. Fortunately, a breakthrough came with the study of *N*-acylhydrazines, namely hydrazides, which proved better hydroamination reagents than their hydrazine counterparts because of their added bench stability. Hydrazides were also hypothesized as improved hydroamination substrates given the greater N-H acidity and activation potential towards alkenes. They later proved resistant to harsher thermal conditions and less susceptible to oxidation than hydroxylamines. Given these advantages, the Beauchemin group embarked on a systematic study into the reactivity of these functionalities. In the next sections, we will describe work on the Cope-type hydroamination of alkenes with hydrazides.

### 1.3.3 Cope-Type Hydroamination with Hydrazides

Initial investigation into the reactivity of hydrazides was performed by Mr. Jean-Grégoire Roveda. This work provided important insights into the development of a first generation hydrohydrazidation system.<sup>39</sup>

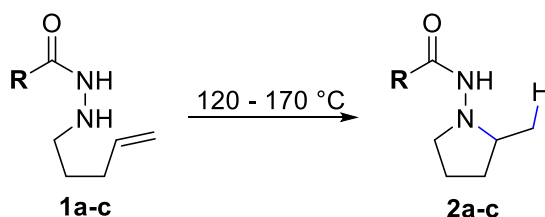


<sup>38</sup> Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492.

<sup>39</sup> Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

Initial survey of hydrazides revealed these substrates to cyclize well but proved less reactive than hydroxylamines towards hydroamination (Table 1.1). Optimization of the reactivity with benzoic hydrazide **1a** allowed establishment of the reactive conditions under which the desired hydroamination product **2a** could be produced. At 120 °C, *tert*-butyl and pyridinyl substrates (entry 2-3) could react but required higher temperature and reaction time than the closely related hydroxylamine system to achieve high yields.

**Table 1.2** Optimization of hydrohydrazidation reactivity



| entry | conditions <sup>a</sup> | R            | yield(s) (%) <sup>b</sup> |
|-------|-------------------------|--------------|---------------------------|
| 1     | 120 °C, 18h             | Ph           | 93 ( <b>2a</b> )          |
| 2     | 150 °C, 16h             | <i>t</i> -Bu | 66 ( <b>2b</b> )          |
| 3     | 170 °C, 42h             | 2-pyridyl    | 64 ( <b>2c</b> )          |

<sup>a</sup> Heating performed in PhCF<sub>3</sub> (0.05 M, sealed tube) unless indicated otherwise. <sup>b</sup> Isolated yield.

With the optimized benzoic hydrazide reagent in hand, Mr. Roveda, in collaboration with Mrs. Ashley Hunt, explored the synthetic scope of the reaction: Substrates bearing various alkenyl chains were synthesized (See Table 1.2). As a result, substitution on the alkenyl chain proved amenable to hydroamination allowing synthesis of five-membered pyrrolidine rings (**1b**). A *gem*-dimethylated substrate was synthesized and, in agreement with the Thorpe-Ingold effect, permitted cyclization at lower temperature with excellent yield (**1e**). Substitution at the alkene distal position could also be tolerated (**1c-d**) with *trans*- and *cis*-methyl alkenyl benzoic hydrazides providing, respectively, the (*E*) and (*Z*) hydroamination products with good yield despite the requirement for higher cyclization temperature (175 °C). Likewise, a six-membered

piperidine rings (**1g**) could be efficiently obtained under harsher conditions. Similar yields were obtained with morpholine and *N*-tosylated piperazine (**1h-i**). The reaction could also tolerate substitution at the alkene proximal position as demonstrated by the good yield of piperazine product **1j** (entry 9). Pushing the reactivity further, ethyl substitution was added at the alkene distal position of the piperidine precursor. As a result, both *cis*- and *trans*-alkenes provided the corresponding hydroamination product with moderate yield (**1k-l**).

**Table 1.3** Scope of intramolecular hydrohydrazidation reactivity <sup>a</sup>

|                           |                                                                                                                                                    |                                                                                                              |                                        |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------------------------------------|
|                           |                                                                                                                                                    |                                                                                                              |                                        |
|                           |                                                                                                                                                    |                                                                                                              |                                        |
| 120 °C, 93% ( <b>1a</b> ) | 120 °C, 98% ( <b>1b</b> ) <sup>c</sup>                                                                                                             | 175 °C, <i>cis</i> , 61% ( <b>1c</b> )<br>175 °C, <i>trans</i> , 75% ( <b>1d</b> )                           | 85 °C, 96% ( <b>1e</b> )               |
|                           |                                                                                                                                                    |                                                                                                              |                                        |
| 200 °C, 90% ( <b>1g</b> ) | 200 °C<br>R <sup>1</sup> =H, X=O, 75% ( <b>1h</b> )<br>R <sup>1</sup> =H, X=NTs, 81% ( <b>1i</b> )<br>R <sup>1</sup> =Me, X=NTs, 84% ( <b>1j</b> ) | 220 °C, <i>cis</i> , 51% ( <b>1k</b> ) <sup>d</sup><br>220 °C, <i>trans</i> , 47% ( <b>1l</b> ) <sup>d</sup> | 235 °C, 39% ( <b>1m</b> ) <sup>d</sup> |

<sup>a</sup> Conditions: Heating performed in PhCF<sub>3</sub> (0.05 M), in sealed tubes (**1a-e**) or microwave irradiation (**1g-m**). <sup>b</sup> Isolated yield. <sup>c</sup> 2.4:1 dr. <sup>d</sup> NMR yield using 1,4-dimethoxybenzene as an internal standard.

These two examples are noteworthy since most reported examples of piperidine ring formation via hydroamination have been reported for terminal alkenes. The obtained ring system corresponds to a (±)-coniine precursor, previously synthesized in the group

from hydroxylamines (see Figure 1.5), further establishing the utility of this strategy. A challenging, medium sized seven-membered ring could also be obtained despite moderate yield (**1m**).

#### 1.3.4 Summary of the Initial Investigations on Cope-Type Hydroamination

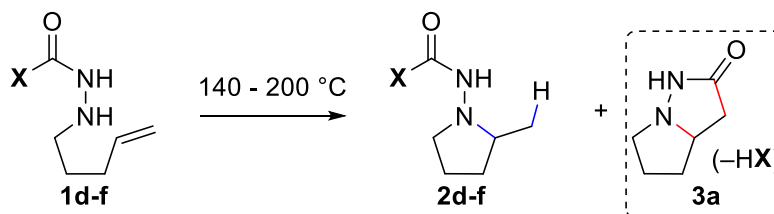
With this initial investigation, demonstration was made that hydrazides are useful bifunctional hydroamination reagents. The reagent proved very stable under thermal conditions which made the reaction amenable for the synthesis of various heterocycles. Initial calculations support a concerted mechanism while demonstrating participation of the carbonyl in facilitating proton transfer step.<sup>39</sup> It is of note that similar reactivity of has recently been reported.<sup>40</sup> With these new insights, improvement of the reaction conditions and scope appeared attainable. Further discussion on recent developments on hydrohydrazidation will be provided in Chapter 4.

#### 1.3.5 Discovery of New Aminocarbonylation Reactivity

During initial optimization of the described hydroamination reactivity hydrazides, interesting results were obtained with carbazates bearing *O*-alkyl substituents. Mr. Christopher Whipp found that thermolysis of such compounds resulted in the generation of a new product. The compound could later identified as aminocarbonylation product **3a** resulting from formation of a C-N and C-C bond across the olefin from an unknown intermediate. From this result, Mr. Jean-Grégoire Roveda optimized the reaction and found that higher temperature resulted in greater yields of product **3a**, especially with substrates bearing bulky alkoxy leaving groups (*O**t*-Bu, **1e**).

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<sup>40</sup> Baxter Vu, J. M.; Leighton, J. L. *Org. Lett.* **2011**, 13, 4056.

**Table 1.4** Optimization of hydroamination/aminocarbonylation reactivity

| entry | conditions <sup>a</sup> | X                    | yield(s) (%) <sup>b</sup>      |
|-------|-------------------------|----------------------|--------------------------------|
| 1     | 140 °C, 16h             | OEt (1d)             | 25 (2d) + 6 (3a)               |
| 2     | 200 °C (μW), 5 h        | OEt (1d)             | 13 (2d) + 46 (3a)              |
| 3     | 200 °C (μW), 5 h        | Ot-Bu (1e)           | 0 (2e) + 71 (3a)               |
| 4     | 150 °C (μW), 5 h        | NH <sub>2</sub> (1f) | 50 (2f) + 20 (3a) <sup>c</sup> |
| 5     | 200 °C (μW), 15 min     | NH <sub>2</sub> (1f) | 10 (2f) + 85 (3a) <sup>c</sup> |

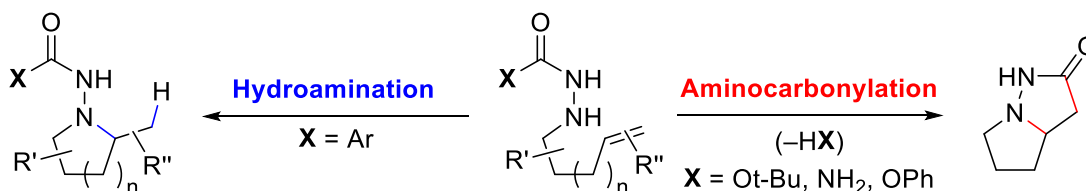
<sup>a</sup> Heating performed in PhCF<sub>3</sub> (0.05 M, sealed tube) unless indicated otherwise. <sup>b</sup> Isolated yield.

<sup>c</sup> NMR yield using 1,4-dimethoxybenzene as an internal standard.

Further investigating the nature of the leaving group lead to synthesis of semicarbazide **1f**, which upon thermolysis produced ammonia. This lead to increased substrate stability and improved aminocarbonylation. It further demonstrated that aminocarbonylation was not limited to oxygen-substituted precursors, thus indicating the involvement of a common reactive intermediate for which further discussion will be provided in Chapter 2.

### 1.3.6 Summary of Hydrazide Reactivity.

The reactivity herein described is remarkable given that simple thermal control allows divergent hydrazide reactivity and leads to valuable alkene functionalization (Scheme 1.6).

**Scheme 1.6** Divergent alkene hydroamination and aminocarbonylation from hydrazides



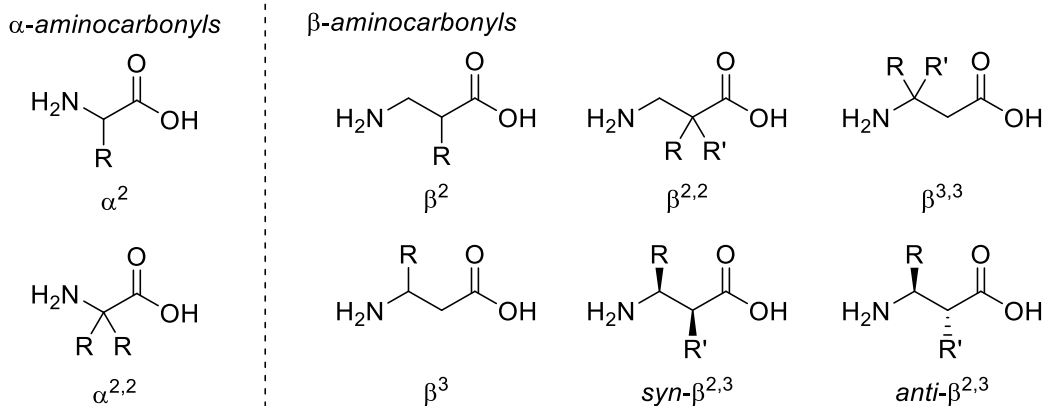
Further insights into the development Cope-type hydroamination with hydrazides will be the topic of later chapters (Chapter 4). The present thesis will essentially focus on the development of aminocarbonylation reactivity. In Chapter 2, we will discuss research efforts towards the development of intramolecular aminocarbonylation. In turn, Chapter 3 will focus on intermolecular reactivity and the derivatization of aminocarbonylation products to  $\beta$ -aminocarbonyl compounds. For now, we will end the present chapter with a discussion of the importance of  $\beta$ -aminocarbonyl moieties.

#### ***1.4 Biological Relevance of $\beta$ -Aminocarbonyls***

Alkene aminocarbonylation is an interesting type of alkene functionalization, and generation of the resulting  $\beta$ -aminocarbonyl functionality makes this transformation especially important. Prior to further exploring this new reactivity, it was necessary to establish the synthetic relevance. Therefore, this section will focus on the relevance of  $\beta$ -aminocarbonyls for synthetic and medicinal chemistry. Discussion of current methods for the synthesis of  $\beta$ -aminocarbonyl compounds and their limitations will follow in section 1.5.

##### ***1.4.1 Occurrence of $\beta$ -Aminocarbonyl Motifs***

In comparison to native  $\alpha$ -aminocarbonyl subunits, the backbone of  $\beta$ -aminocarbonyls possesses a second methylene subunit, thus providing an added position for substitution. Therefore, natural and unnatural monomeric  $\beta$ -amino acids can be found with larger degrees of variation than the parent  $\alpha$ -substituted aminocarbonyl (Figure 1.9).



**Figure 1.9** Mono- and bis-substituted  $\beta$ -amino acids and concurring nomenclature

### 1.4.2 $\beta$ -Aminocarbonyl Therapeutics

The ability of  $\beta$ -aminocarbonyls to emulate native  $\alpha$ -amino acids while remaining structurally distinct confers them unique features while providing, amid other advantages, resistance to proteolytic degradation.<sup>41</sup> In natural peptide oligomers, replacement of only one  $\alpha$ -amino acid subunit with its corresponding  $\beta$ -amino acid appears to protect against peptide degradation.<sup>42</sup> As currently standing, the fact that nature has not yet developed the capability to fully assimilate  $\beta$ -aminocarbonyls motifs, consequently offers opportunities for the development of new lines of drug therapeutics. Nonetheless, some organisms have evolved to exploit the improved pharmacokinetic properties of  $\beta$ -aminocarbonyls to produce highly potent natural products (Figure 1.10). For example,  $\beta$ -amino acid

<sup>41</sup> (a) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, 79, 913. (b) Hintermann, T.; Seebach, D. *Chimia* **1997**, 51, 244. (c) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, 52, 734.

<sup>42</sup> Steer, D. L.; Lew, R. A.; Perimutter, P.; Smith, A. I.; Aguilar, M. I. *Curr. Med. Chem.* **2002**, 9, 811.

containing molecules such as cryptophycins,<sup>43</sup> found in cyanobacteria, have promising antitumoral activity while paclitaxel, isolated from plants, is widely utilized for cancer treatment. In turn,  $\beta$ -lactams, such as cyclic  $\beta$ -aminocarbonyls, constitute some of the most important classes of antibiotics available to date while amipurimycins display impressive antifungal activity.<sup>44</sup> SAR studies have confirmed the importance of  $\beta$ -amino acid subunits to the activity of several of these natural products. Surprisingly, cispentacin, a  $\beta$ -aminocarbonyl subunit of amipurimycins, was found to also display biological activity, which is comparatively atypical of  $\alpha$ -amino acid monomers and thus further demonstrates the therapeutic potential of such functionalities.<sup>45</sup>

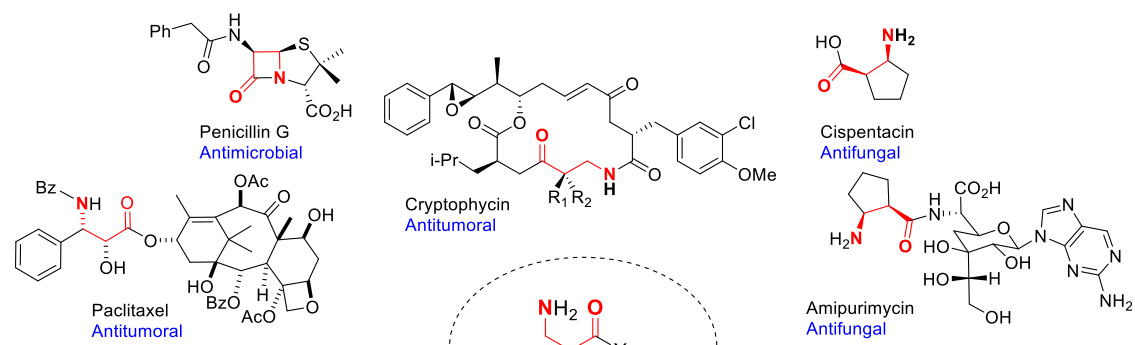
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<sup>43</sup> Eggen, M.; Georg, G. I. *Med. Res. Rev.* **2002**, 22, 85.

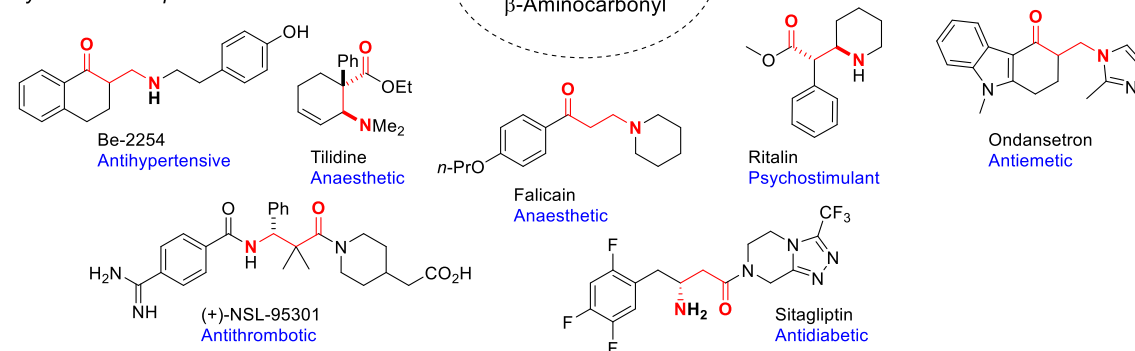
<sup>44</sup> Stauffer, C. S.; Datta, A. *J. Org. Chem.* **2008**, 73, 4166.

<sup>45</sup> Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibio.* **1989**, 62, 1749.

## Natural Products &amp; Therapeutics



## Synthetic Therapeutics



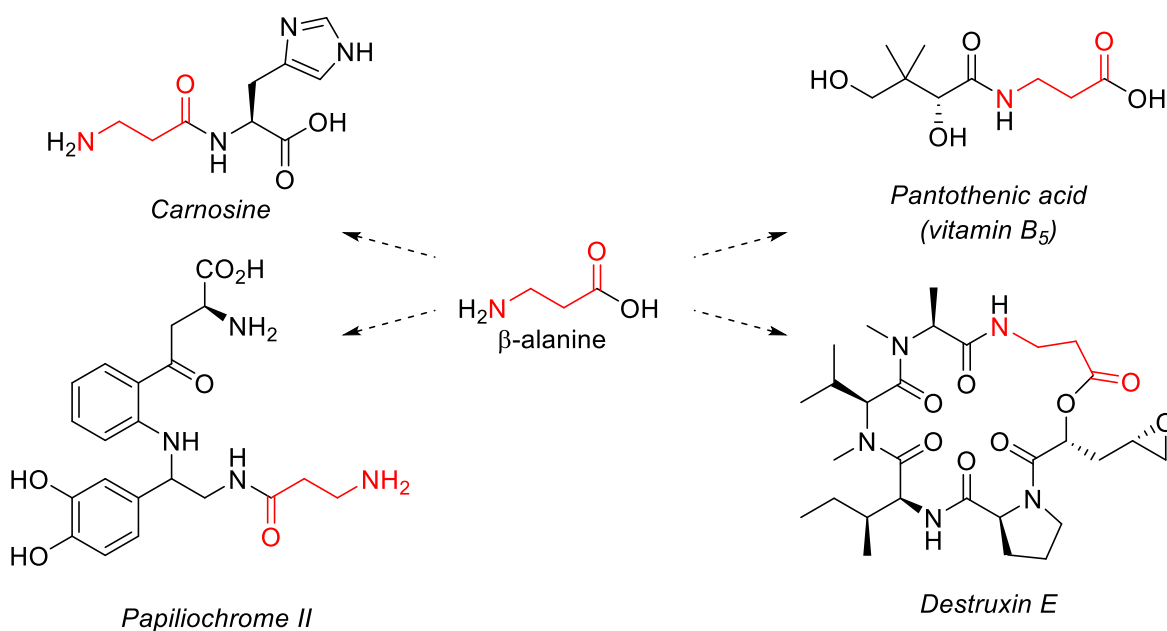
**Figure 1.10** Pharmaceuticals containing  $\beta$ -aminocarbonyl motifs

Today,  $\beta$ -aminocarbonyl motifs are also present in many synthetic pharmaceuticals used for treatment of various medical conditions. Notable examples are methylphenidate (Ritalin) for treatment of ADHD, Falicaia, a local anaesthetic; Ondansetron, an important antiemetic used to control vomiting and nausea in chemotherapy patients. Sitagliptin (Januvia), an antihyperglycemic drug, is used in combination therapy with methformin for treatment of diabetes mellitus of type 2.

### 1.4.3 Proteinogenic Derived $\beta$ -Amino Acids

Whether these motifs are unnatural or derivatives of native peptides subunits,  $\beta$ -aminocarbonyls display unique structural characteristics.  $\beta$ -Amino acids have been isolated in their monomeric forms from various natural sources. For example,  $\beta$ -alanine ( $\beta$ -

aminopropionic acid) is a non-proteinogenic  $\beta$ -amino acid found in humans. Interestingly, it is generated through catalytic degradation of dihydrouracils. Even though its function is still unclear,  $\beta$ -alanine is thought to play a role as a GABA uptake inhibitor within neuron synapses.<sup>46</sup> It is also commonly taken as a food supplement as it is involved in the synthesis of muscular carnosine and anserine antioxidants and thought to provide resistance to muscular fatigue.<sup>47</sup>



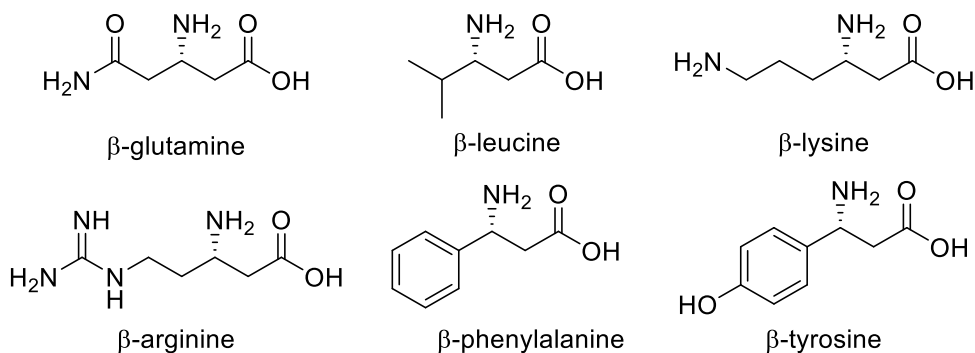
**Figure 1.11**  $\beta$ -Alanine and derivatives as metabolites of living systems

<sup>46</sup> Sunol, C.; Babot, Z.; Cristofol, R.; Sonnewald, U.; Waagepetersen; Schousboe, A. *Neurochem. Res.* **2010**, 35, 1384.

<sup>47</sup> Hill, C. A.; Harris, R. C.; Kim, H. J.; Harris, B. D.; Sale, C.; Boobis, L. H.; Kim, C. K.; Wise, J. A. *Amino Acids* **2007**, 32, 225.

In other living organisms,  $\beta$ -alanine is an essential precursor to multiple biologically active compounds such as vitamin B<sub>3</sub> and B<sub>5</sub>.<sup>48</sup> It is the simplest and most widespread  $\beta$ -amino acid monomer and as such, is commonly integrated within the primary and secondary metabolism of living systems. It is a component of natural products such as destruxins,<sup>49</sup> leucinostatins,<sup>50</sup> papiliochrome II (Figure 1.11)<sup>51</sup> and yanucamides.<sup>52</sup>

Other  $\beta$ -amino acids related to proteinogenic  $\alpha$ -amino acids can be isolated in their monomeric forms and are present in a large array of natural products. Selected examples of  $\beta$ -amino acids isolated from natural sources are shown in Figure 1.12.



**Figure 1.12** Selected  $\beta$ -amino acids derived from proteinogenic  $\alpha$ -amino acids

<sup>48</sup> For an exhaustive discussion of  $\beta$ -amino acids and their synthesis, see Juaristi, E.; Soloshonok, V.A. *Enantioselective Synthesis of  $\beta$ -Amino Acids*, Second Edition (2005), John Wiley & Sons, 634 pages and the references cited therein.

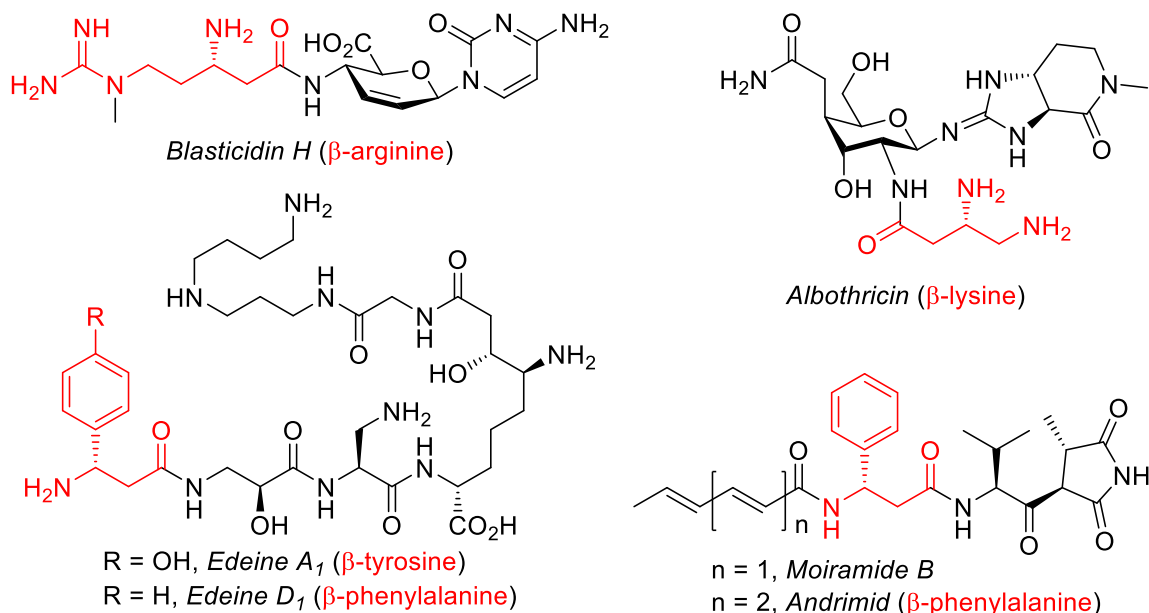
<sup>49</sup> Pedras, M. S. C.; Zaharia, L. I.; Ward, D. E. *Phytochemistry* **2002**, 59, 579.

<sup>50</sup> (a) Cerrini, S.; Lamba, D.; Scatturin, A.; Rossi, C.; Ughetto, G. *Biopolymers* **1989**, 28, 409. (b) Kuwata, S.; Nakanishi, A.; Yamada, T.; Miyazawa, T. *Tetrahedron Lett.* **1992**, 33, 6995.

<sup>51</sup> Rembold, H.; Umebachi, Y. The Structure of Papiliochrome II, the Yellow Wing Pigment of the Papilionid Butterflies, in *Progress in Tryptophan and Serotonin Research*, H. G. Schlossberger, Ed., Degruyter, Berling, **1984**, pp. 743-746.

<sup>52</sup> Sitachitta, N.; Williamson, R. T.; Gerwick, W. H. *J. Nat. Prod.* **2000**, 63, 197.

$\beta$ -Amino acids result from various biosynthetic pathways. Recently,  $\beta$ -leucine was suggested to originate from  $\alpha$ -leucine. However, clear mechanistic details for this transformation remain to be provided.<sup>53,54</sup>



**Figure 1.13** Selected natural products containing  $\beta$ -amino acids derived from proteinogenic  $\alpha$ -amino acids

Similarly,  $\beta$ -lysine is generated from 2,3-aminomutase converting enzyme from native  $\alpha$ -lysine.  $\beta$ -Lysine is a constituent of many natural products such as albothricin (and other streptothricin related antibiotics),<sup>55</sup> capreomycins (antituberculosis)<sup>56</sup> and viomycin

<sup>53</sup> Aberhart, D. J. *Anal. Biochem.* **1988**, 169, 350.

<sup>54</sup> Rosenblatt, D. S.; Cooper, B. A.; Pottier, A.; Lue-Shing, H.; Matiaszuk, N.; Grauer, K. *J. Clin. Invest.* **1984**, 74, 2149.

<sup>55</sup> Goo, Y. M.; Kim, O. Y.; Joe, Y. A.; Lee, Y. B.; Ju, J.; Kim, B. T.; Lee, Y. Y. *Arch. Pharm. Res.* **1996**, 19, 153.

<sup>56</sup> Johansen, S. K.; Maus, C. E.; Plikaytic, B. B.; Douthwaite, S. *Mol. Cell.* **2006**, 23, 173.

(antituberculosis)<sup>57</sup> to name a few (Figure 1.12). In turn,  $\beta$ -arginine is present in the core structure of blasticidins, peptidyl nucleosides isolated from *Streptomyces griseochromogenes*. These compounds are employed in the agrochemical industry as protective antifungal agents against *Pyricularia oryzae*, the cause of rice blast disease.<sup>58</sup>

Since  $\beta$ -phenylalanine and  $\beta$ -tyrosine residues are functionally very close, it is common to find derivatives of both residues the same families of molecules (tyrosine possessing an added phenolic moiety) and as such are constituents of many known natural products. Interestingly,  $\beta$ -phenylalanine is found in short peptides with  $\beta$ -alanine subunit in  $\gamma$ -L-Glu-L- $\beta$ -Phe- $\beta$ -Ala isolated from *Phaseolus angularis* (Adzuki beans).<sup>59</sup> It is also a structural feature of pseudopeptide pyrrolidinedione antibiotics such as andrimids and moiramides (Figure 1.12), which have been identified as effective acetyl coenzyme A carboxylase (ACC) inhibitors in bacteria.<sup>60</sup> Linear peptides of the edeine family, having potent antibiotic properties, have been found to contain a  $\beta$ -phenylalanine or  $\beta$ -tyrosine residues. Given their biologically active nature, these compounds are now seen as potential new lines of broad spectrum antibiotics.

In addition, some unusual cyclic peptides, isolated from plants, also possess both  $\beta$ -phenylalanine and  $\beta$ -tyrosine subunits. Verbascenine and periphylline are isolated from

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<sup>57</sup> Kitagawa, T.; Miura, T.; Fujiwara, K.; Taniyama, H. *Chem. Pharm. Bull.* **1972**, 20, 2215.

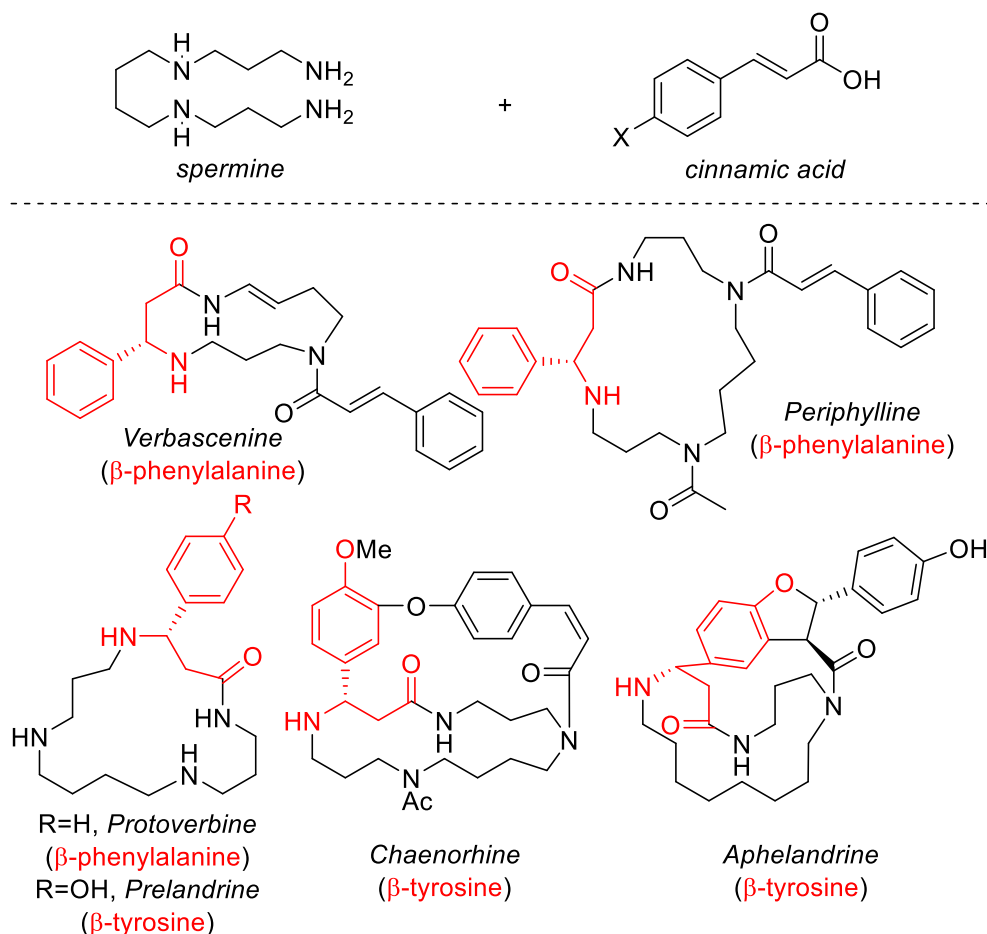
<sup>58</sup> Yamaguchi, H.; Tanaka, N. *J. Biochem.* **1966**, 60, 632.

<sup>59</sup> Koyama, M; Obata, Y. *Agric. Biol. Chem.* **1966**, 30, 472.

<sup>60</sup> Freiberg, C.; Pohlmann, J.; Nell, P. G.; Endermann, R.; Schuhmacher, J.; Newton, B.; Otteneder, M.; Lampe, T.; Habich, D.; Ziegelbauer, K. *Antimicrob. Agents Chemother.* **2006**, 50, 2707.



*Peripterygis marginata*<sup>61,62</sup> and aphelandrine is derived from spermine (Figure 1.13). It is hypothesized that these products are not made through peptide coupling of  $\beta$ -amino acids, but rather from conjugate addition of the polyamine, to cinnamic acid residues.<sup>63</sup>



**Figure 1.14**  $\beta$ -Phenylalanine and  $\beta$ -tyrosine containing spermine alkaloids

<sup>61</sup> Hocquemiller, R.; Cavé, A.; Husson, H.-P. *Tetrahedron* **1977**, 33, 645.

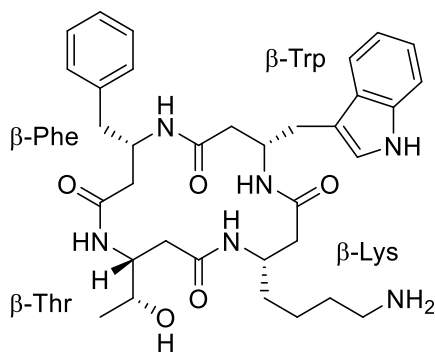
<sup>62</sup> Cordell, G. A. Natural Polamine Derivatives, in *The Alkaloids: Chemistry and Biology*, Academic Press, **1998**, pp. 243.

<sup>63</sup> Nezbedova, L.; Hesse, M.; Drandarov, K.; Werner, C. *Helv. Chim. Acta* **2001**, 84, 172.



observation, analogous  $\beta$ -peptides have been synthesized. Accordingly, similar biological activity could be observed. Remarkably, certain conformationally restricted  $\beta$ -peptides have the ability to fold into helical secondary structure with as few as four <sup>67</sup> to six <sup>68</sup> monomeric subunits. In comparison, certain native proteinogenic  $\alpha$ -peptides require fifteen to twenty residues.

Additionally, cyclic peptides are receiving much attention for their therapeutic properties. As such, recent studies have shown small cyclic tetra- $\beta$ -peptides scaffolds (Figure 1.15) to structurally mimic somatostatin, a human hormone.<sup>69</sup> It is also conformationally similar to pharmaceutical octreotide, a  $\alpha$ -peptide somatostatin inhibitor.



**Figure 1.16** Cyclic tetra-β-peptide analogue of octreotide somatostatin inhibitor

<sup>67</sup> Appela, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206.

<sup>68</sup> (a) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, 79, 913. (b) Appela, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, 121, 7574.

<sup>69</sup> Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D.; *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 1223.

### 1.4.5 $\beta^2$ -Amino Acids

It is noteworthy to consider that many  $\beta$ -peptide products described in the literature contain  $\beta^3$ -aminocarbonyl moieties. Therefore  $\beta^2$ -aminocarbonyls are relatively underrepresented in the realm of peptidomimetics due to the lack of preparative synthetic methodologies. This is unfortunate, as pointed by Seebach, since oligomers of  $\beta^2$ -aminoacids provide greater conformational rigidity compared to  $\beta^3$  subunits.<sup>70</sup> Future synthetic efforts should focus on these moieties.

### 1.4.6 Summary

Thus far, we have described how  $\beta$ -aminocarbonyls represent important structural motifs of natural products and therapeutics. By their distinct characteristics, they have been shown to provide significant benefits to the properties of many biomolecules. As such, oligomers of  $\beta$ -amino acids have great untapped therapeutic potential. As recently noted by Gellman, development of  $\beta$ -peptide therapeutics is directly dependant on the ability to rapidly and effectively generate the necessary monomers in a cost-effective manner.<sup>64</sup> It is therefore essential to provide these research efforts with viable synthetic tools to enable further exploration of peptidomimetic compounds.

## 1.5 Synthesis of $\beta$ -Aminocarbonyl Motifs

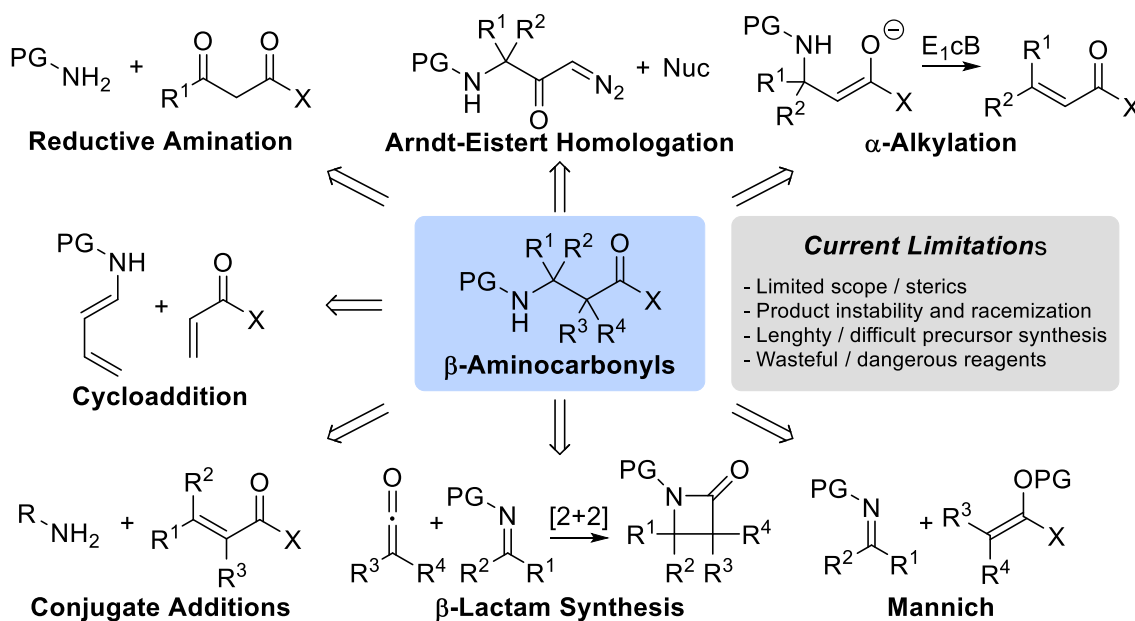
### 1.5.1 General Methods

Various methods have been reported for the modification and synthesis of  $\alpha$ -amino acids. As such, the Strecker reaction has provided tremendous opportunities for the

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<sup>70</sup> Lelais, G.; Seebach, D. *Biopolymers (Peptide Science)* **2004**, 76, 206.

enantioselective synthesis of amino acid building blocks.<sup>71</sup> Additionally, recent development of chiral Brønsted acid and asymmetric phase transfer<sup>72</sup> catalyzed alkylations has provided impressive tools for the direct conversion of glycinate into various optically active  $\alpha$ -aminocarbonyls. In the previous section, we have established the biological importance of  $\beta$ -aminocarbonyl moieties. Unfortunately, synthesis of  $\beta$ -aminocarbonyl compounds, and in particular  $\beta$ -amino acid building blocks remains challenging. Summarized in Figure 1.16 are successful retrosynthetic strategies. This section will provide a brief overview of the most successful methodologies applied to the synthesis of  $\beta$ -aminocarbonyls. However, several examples of these variants have been published.<sup>48</sup>

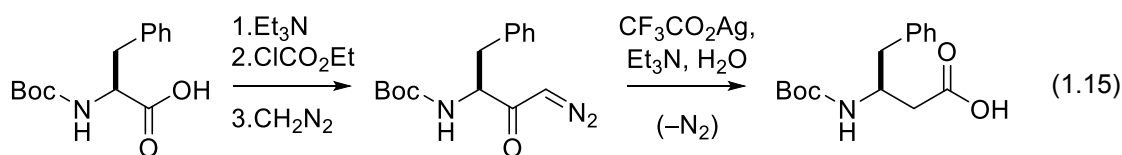


**Figure 1.17** Methods for the synthesis of  $\beta$ -aminocarbonyl compounds

<sup>71</sup> Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

<sup>72</sup> (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (b) For leading review of asymmetric phase-transfer catalysis, see: Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 422.

Contrary to  $\alpha$ -glycinates,  $\beta$ -alanine does not easily undergo  $\alpha$ -alkylations given the propensity of enols and enolates to undergo E1cB-type eliminations. However, the Arndt-Eistert homologation provides conversion of native  $\alpha$ -amino acids to  $\beta$ -amino acids by means of diazoketone formation and subsequent Wolff rearrangement in the presence of a nucleophile (equation 1.15). This approach was used extensively by the Seebach group in their pioneering studies on  $\beta$ -peptides.



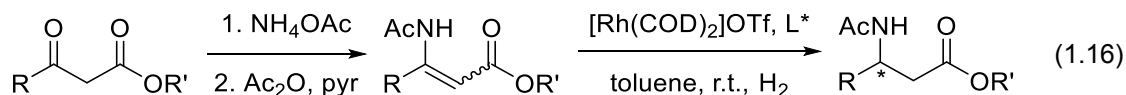
The method is lengthy and wasteful as it involves carbonyl activation. Addition of toxic diazomethane is also problematic given its highly unstable nature; the reaction is hardly amenable to large-scale synthesis, thus making industrial applications very difficult and unsafe. Furthermore, scope is limited as certain substrates, and those such as aryl glycines, will readily racemize under standard conditions.<sup>73</sup>

Methods of reductive aminations have been applied to the synthesis of  $\beta$ -aminocarbonyls with limited success given that the required keto-esters are not always readily available: Their modification requires additional synthetic steps. Moreover, acidity of the  $\alpha$ -hydrogens causes the corresponding imine condensation product to tautomerize easily, making these substrates unstable and the method vulnerable to undesirable side

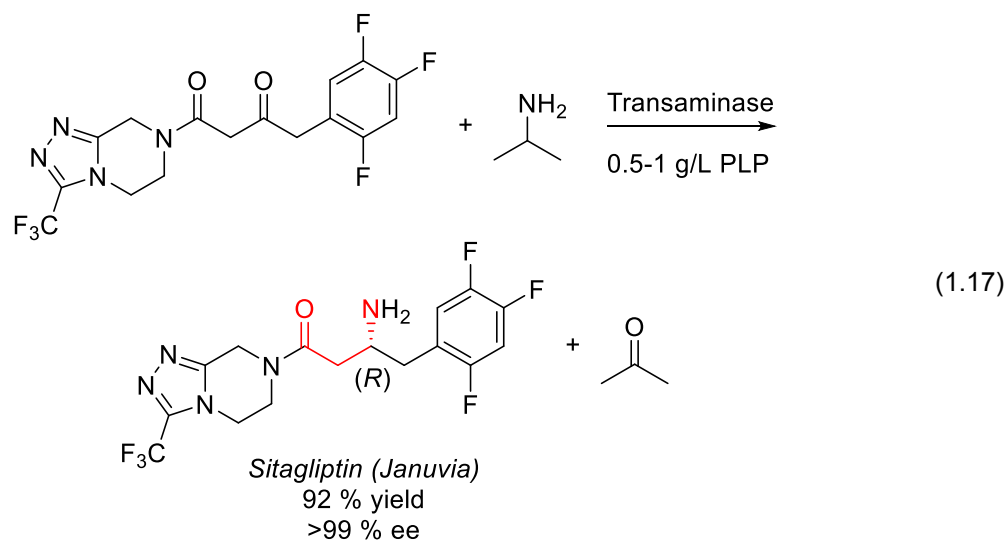
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<sup>73</sup> Podlech, J.; Seebach, D. *Angew. Chem. Int. Ed.* **1995**, *34*, 471.

reactions. However, hydrogenation of the corresponding enamine has been readily performed with good enantioselectivity.<sup>74</sup>



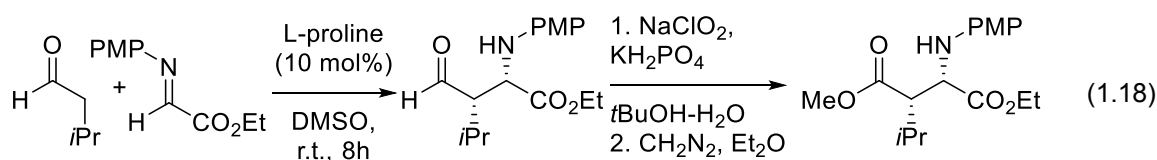
Recently, a biocatalytic asymmetric process has been developed by Codexis and Merck Process Research for the industrial production of antidiabetic drug Sitagliptin.<sup>75</sup> The process involves direct amination of prositagliptin ketone using transaminase enzyme and isopropylamine in the presence of PLP co-factor (equation 1.17). The reaction is very effective and highly enantioselective: The authors report no detectable traces of the (*S*) isomer.



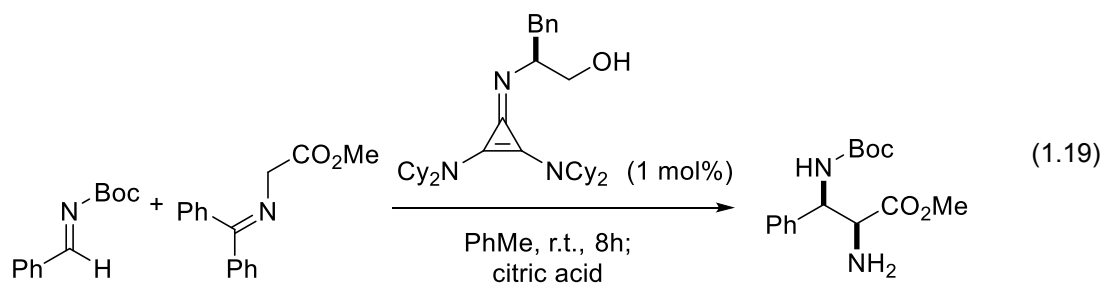
<sup>74</sup> Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, 12, 6907.

<sup>75</sup> Saville, C. K.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Science* **2010**, 329, 305.

Amongst the most successfully applied methodologies to the formation of  $\beta$ -aminocarbonyls is the Mannich reaction. Multiple examples have been performed with respectable enantio- and diastereoselectivity. However, the reaction may suffer from limited scope because of reagents' steric hindrance and sometimes poor stability of imine precursors. However, Zhu and coworkers have recently published a synthetic sequence involving a proline catalyzed addition to *N*-protected imine esters (equation 1.18).



Another notable example has recently published by Lambert and coworkers (equation 1.19).<sup>76</sup> The method exploits chiral cyclopropenimine to catalyze glycinate addition to *N*-Boc-imines.

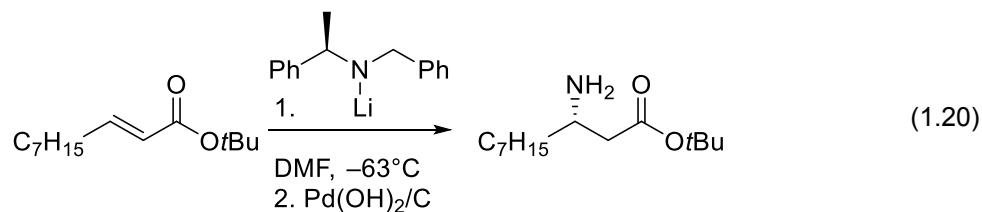


Comparably, conjugate additions of amines to  $\alpha,\beta$ -unsaturated carbonyls have also been achieved with good stereocontrol. Because the basicity of these conditions may favour a thermodynamic equilibrium, reactions are typically performed with strong nucleophiles. Therefore, addition of metalated amines, such as lithiated amides, to unsaturated carbonyl

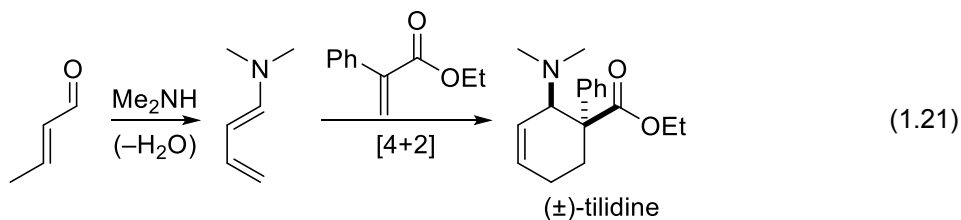
<sup>76</sup> Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799.



results in good conversion to the desired product. To achieve stereocontrol, chiral nitrogen nucleophiles have been used (equation 1.20).<sup>77</sup>



Cycloaddition reactions have been especially useful for the synthesis of a cyclic  $\beta$ -amino acids. The Diels-Alder reaction of aminodienes with  $\alpha,\beta$ -unsaturated carbonyls has been applied to the construction of six-membered carbocycles (equation 1.21).<sup>78</sup>

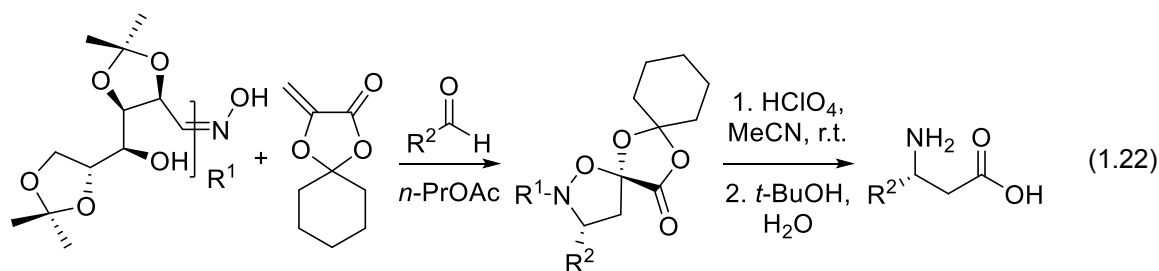


This method is used for the industrial production of synthetic opioid (±)-tilidine (see Figure 1.9).<sup>79</sup> However, aminodienes can be difficult to synthesize and prone to polymerization.

<sup>77</sup> Davies, S. G.; Mulvaney, A. W.; Russell, A. J.; Smith, A. D. *Tetrahedron Asym.* **2007**, *18*, 1554.

<sup>78</sup> (a) Sustmann, R.; Rogge, M.; Nuchter, U.; Bandmann, H. *Chem. Ber.* **1992**, *125*, 1647. (b) Snowden, R. L.; Brauchli, R.; Wust, M.; *Helv. Chim. Acta.* **1990**, *73*, 640.

<sup>79</sup> Satzinger, G. Substituted Cyclohexenes, Derivatives Thereof and Processes for Obtaining Same, US patent 3557127, January 19<sup>th</sup>, 1971.



Recently, Bode and coworkers reported an interesting strategy involving [3+2] cycloaddition of nitrones to acrylates. Stereocontrol is achieved by use of chiral auxiliary D-gluconic acid-1,4-lactone (equation 1.22).<sup>80</sup> Despite a multistep synthetic sequence, the process is advantageous as it may be performed without chromatographic purifications.

### 1.6 Perspectives: Towards an Ideal Aminocarbonylation Reagent

There is no simple solution to the synthesis of  $\beta$ -aminocarbonyls; each of the examples described herein have their own innate inconveniences. However, a common drawback relies in the scarcity of the reagents: Access to some is either costly or requires multiple synthetic steps. Therefore, an ideal method would make use of a single reagent capable of converting readily available substrates into usable  $\beta$ -aminocarbonyl motifs. While discussion of such a reagent still needs to be provided, reactions of alkene aminocarbonylation would fit well into this description. Therefore, given our prior discussion of the thermal reactivity of hydrazides, it was concluded that the discovered aminocarbonylation reactivity discussed in previous sections deserved further attention. Investigation into the true nature of the reactive intermediate became a key aspect for the exploration of this unique aminocarbonylation reactivity. Before continuing with our

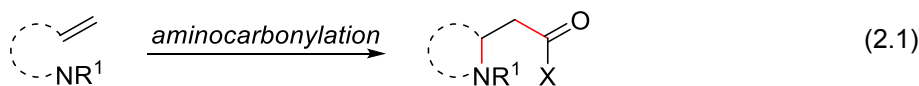
<sup>80</sup> (a) Yu, S.; Ishida, H.; Juarez-Garcia, M. E.; Bode, J. W. *Chem. Sci.* **2010**, *1*, 637. (b) Gerfaud, T.; Chiang, Y.-L.; Kreituss, I.; Russak, J.; Bode, J. W. *Org. Process Res. Dev.* **2012**, *16*, 687.

discussion on the reactivity of hydrazides, it is important to establish precedents of alkene aminocarbonylation, as it will be covered in Chapter 2.

# Chapter

# 2 Intramolecular Aminocarbonylation of Alkenes

## 2.1 Introduction



While various amination reactions have received much attention over the years, some alkene functionalization reactions have remained comparatively undeveloped. As previously described, alkene aminocarbonylation, the formal addition of a C-N and C-C bonds across olefins, is representative of such reactions. It is especially attractive as aminocarbonylation allows generation of important  $\beta$ -aminocarbonyl motifs such as  $\beta$ -amino acid derivatives. For now, we will focus on alkene aminocarbonylation and the approaches taken which permitted intramolecular alkene functionalization.

## 2.2 Palladium-Catalyzed Aminocarbonylation of Alkenes

In Chapter 1, a brief discussion of transition metal catalyzed amination reaction of alkenes was provided. As such, C-N bond formation with alkenes facilitated by palladium(II) complexes has been successfully applied to alkene hydroamination, despite its limitations. Wacker-type oxidative processes have also been applied to carboaminations of olefins, resulting in a C-N and C-C bond formation across an alkenes.<sup>1</sup> However, development of reactions combining processes of aminopalladation of an alkene with a carbonylative bond formation, in the form of an aminocarbonylation, is still limited.

Initial prospecting into this reactivity was conveyed by Hegedus and coworkers while investigating the insertion potential of unsaturations to  $\sigma$ -alkylpalladium complexes.<sup>2</sup> From previous study, intramolecular cyclization of ortho-anilines with alkenes assisted by alkylpalladium(II) specie served as a suitable system for the synthesis of alkylated indoles. From this reaction, aminopalladation product was thought to have sufficient lifetime to undergo insertion of carbon monoxide (Scheme 2.1). Therefore, under appropriate conditions, aminocarbonylation could be accomplished in good yields. However, in surveying optimal reaction conditions, Hegedus also denotes the requirements to accomplish the desired bond formation. First, the reaction must provide

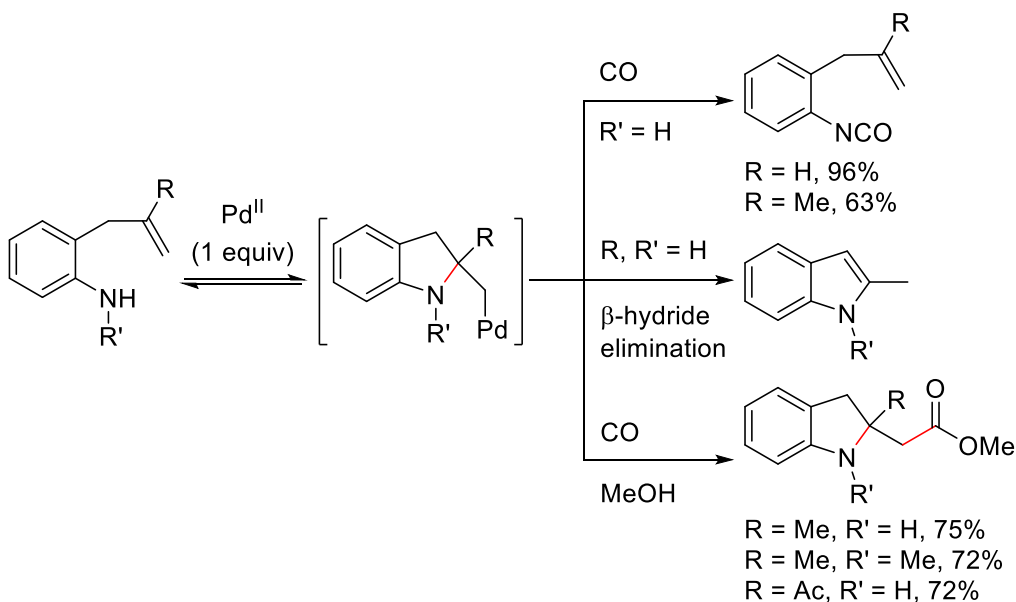
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<sup>1</sup> For a recent review, see: Wolfe, J. P. *Synlett* **2008**, 2913.

<sup>2</sup> Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.

the necessary conditions for aminopalladation to occur and, secondly, be mild enough to prevent competing  $\beta$ -hydride elimination prior to carbonylation. Additionally, carbonylation of the amine center with carbon monoxide must be avoided. To prevent isocyanate formation, *N*-substituted allylic anilines have been used. This observation is particularly interesting in the context of the present discussion, as it provides additional support to our previously stated general requirement for chemoselectivity with regard to reagents involved in amination of alkenes (Section 2.1).

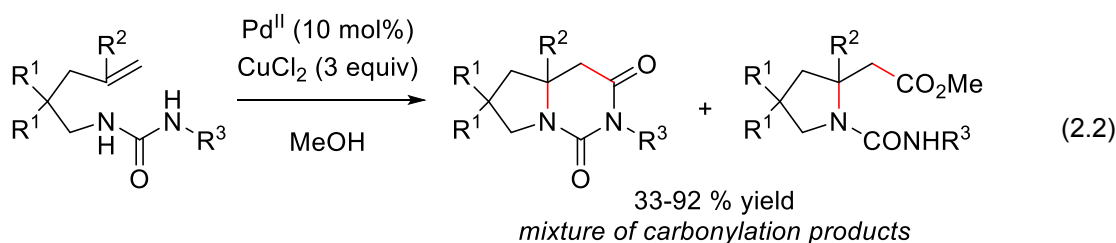
**Scheme 2.1** Intramolecular aminocarbonylation by amino-palladation/carbonylation sequence



However encouraging, these results shed light on the challenges associated with aminocarbonylation. For one, the reaction here proposed is limited to intramolecular reagents and favored by close proximity between nitrogen and alkene. Secondly, stoichiometric amount of palladium is used, making the overall process highly

impractical. Strikingly, all of these limitations are accountable to the same basic problem, the strong coordination of amines to palladium (II).

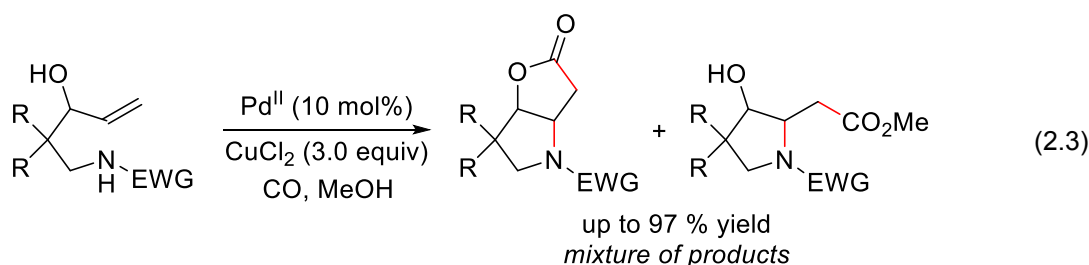
Almost a decade later, efforts towards development of an efficient aminocarbonylation process catalytic in palladium were prompted by Tamaru and coworkers.<sup>3</sup> In doing so, the group suggested addition of an external oxidant in a Wacker-type reaction to the conditions provided by Hegedus, while attempting cyclization using ureas as a nitrogen nucleophile (equation 2.2). However, it was understood that conditions were to prevent oxidation of the amine prior to cyclization. Following optimization, addition of copper (II) as an oxidant proved efficient.



A survey of the reactivity proved efficient as moderate to good yields were obtained for the amination products. However, despite complete conversion of the alkene, most reported examples were obtained as mixtures of aminocarbonylation products (equation 2.3). This is due to the fact that the reaction must be carried out in alcoholic solvent, such as methanol, which provides solvolysis of the final product to the

<sup>3</sup> Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1988**, *110*, 1994.

corresponding ester. To overcome this, solvent was replaced with acetic acid, for which better results were obtained for some substrates, as this solvent displays reduced nucleophilicity. Additionally, necessity for excess oxidant proved the reaction, again, impractical. The reaction nonetheless proved particularly interesting for the synthesis of nitrogen containing heterocyclic and polycyclic molecules. In a later report, Tamaru reported the intramolecular aminocarbonylation of allylic alcohol (equation 2.3).<sup>4</sup> The reaction could also be optimized to favor intramolecular solvolysis and synthesis of lactones.



In later reports, Tamaru described the reactivity of various endo and exo carbamates and ureas for intramolecular aminocarbonylation (Table 2.1).<sup>5</sup> Generally, endo substrates showed increased level of reactivity (entry 2 and 4) as compared to exo (entry 1 and 3). Substitution on the alkene can be tolerated, however, only in the proximal

<sup>4</sup> Tamaru, Y.; Hojo, M.; Yoshida, Z.-I. *J. Org. Chem.* **1988**, 53, 5731.

<sup>5</sup> (a) Tamaru, Y.; Tanigawa, H.; Itoh, S.; Kimura, M.; Tanaka, S.; Fugami, K. *Tetrahedron Lett.* **1992**, 33, 631. (b) Harayama, H.; Okuno, H.; Takahashi, Y.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1996**, 37, 7287. (c) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, 62, 2113.



position. In addition, improved cyclization is achieved when gem-dimethyl substituent is present on the alkenyl chain, in accordance with a Thorpe-Ingold effect.

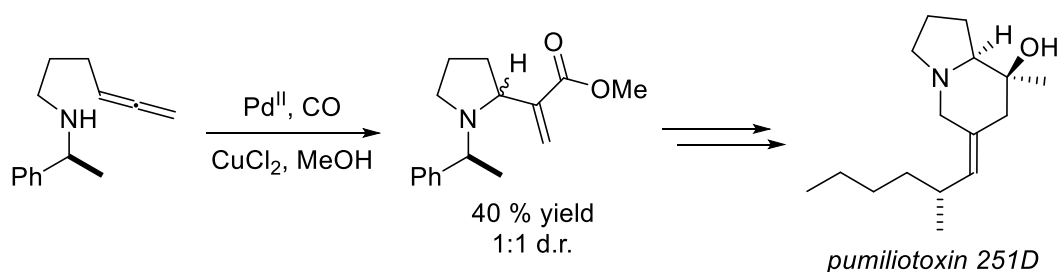
**Table 2.1** Selected intramolecular palladium catalyzed aminocarbonylation with *N*-acyl precursors

| entry | starting material | product | yield (%)       |
|-------|-------------------|---------|-----------------|
| 1     |                   |         | 79              |
| 2     |                   |         | 97              |
| 3     |                   |         | 88              |
| 4     |                   |         | 90 <sup>a</sup> |

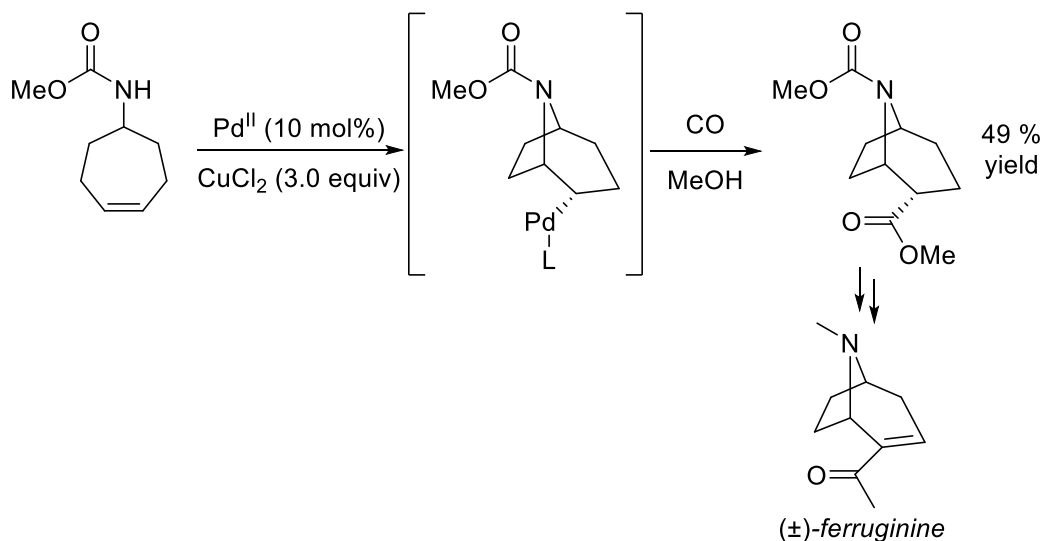
<sup>a</sup> Reaction performed with trimethyl orthoformate as an additive (18 equiv).

The reaction could also be applied to the total synthesis of natural products. As such, aminocarbonylation was employed for the generation of pyrrolidine ring precursor of pumiliotoxin 251D (Scheme 2.2).<sup>6</sup> However, it is to note that the cyclization was performed on an allene which, compared to alkenes, is generally more reactive.

<sup>6</sup> Fox, D. N. A.; Lathbury, D.; Mbon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652.

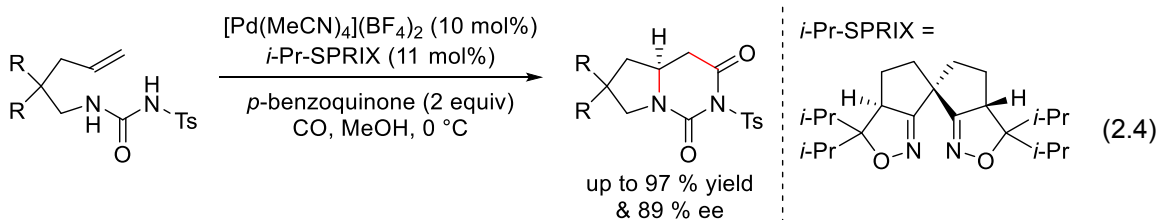
**Scheme 2.2** Synthesis of pumiliotoxin 251D using aminocarbonylation of alkene

It could also be applied to the formal synthesis of ( $\pm$ )-ferruginine, a tropane alkaloid (Scheme 2.3).<sup>7</sup> Interestingly, aminocarbonylation could be applied for the synthesis of such bridged bicyclic substrate, showing the versatility of the method.

**Scheme 2.3** Formal synthesis of ( $\pm$ )-ferruginine by alkene aminocarbonylation

<sup>7</sup> Ham, W.-H.; Jung, Y. H.; Lee, K.; Oh, C.-Y.; Lee, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 3247.

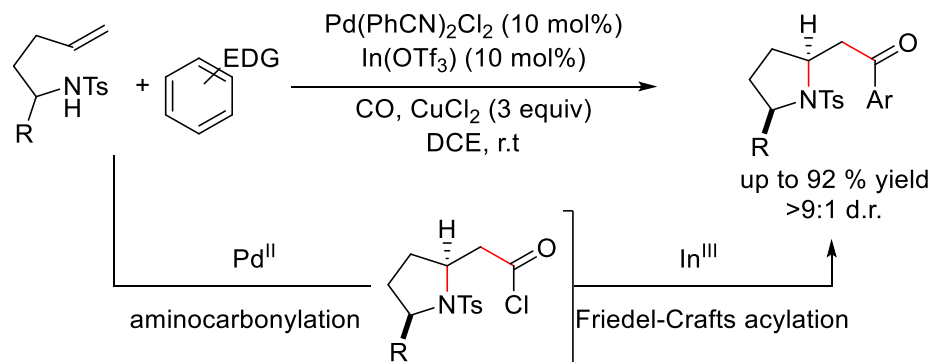
Given the biological importance and therapeutic potential of  $\beta$ -aminocarbonyls, generation of these products in an optically active represents a crucial objective to the applicability of aminocarbonylation reactivity. In a recent article by Sasai and coworkers, report is made of such enantioselective intramolecular aminocarbonylation of alkenylureas (equation 2.4).<sup>8</sup>



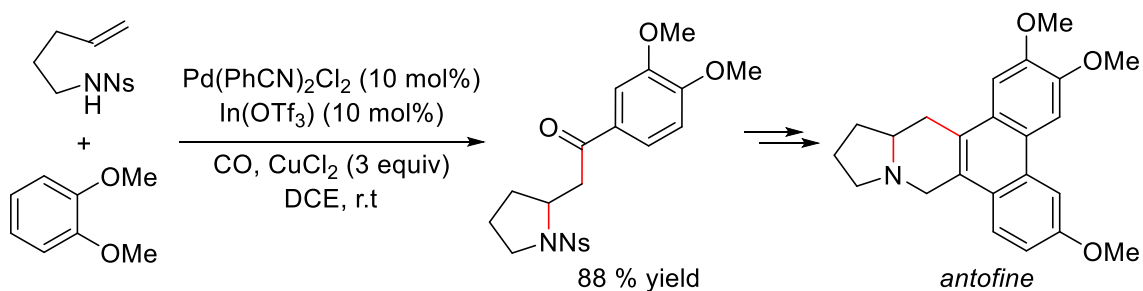
In their mechanistic proposal, enantio-induction occurs at the aminopalladation step. It is also interesting to notice, that the  $\sigma$ -palladium(II) complex's reactivity only results in carbonylation with carbon monoxide. Indeed, presence of fairly acidic N-H bond positioned on adjacent urea could act as a proton source and react with the palladium complex. Formation of diamination side-products could also be expected.<sup>9</sup>

<sup>8</sup> Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, *74*, 9275.

<sup>9</sup> For an example of intramolecular diamination of alkenes with ureas, see: Streuf, J.; Hövelmann, C. H.; Nieger, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586.

**Scheme 2.4** Cascade aminochlorocarbonylation / Friedel-Crafts acylation

Recently, Lambert and coworkers expanded the scope of this reaction. Building onto previous methodology, aminocarbonylation could be combined with Friedel-Crafts acylation using sequential palladium(II) and indium(III) catalysis.<sup>10</sup> The methodology was also applied to the synthesis of antofine, a tylophora alkaloid (Scheme 2.5).<sup>11</sup>

**Scheme 2.5** Synthesis of antofine by alkene aminocarbonylation / Friedel-Crafts acylation

<sup>10</sup> (a) Cernak, T.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124. (b) Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H. *Synthesis* **2010**, 870.

<sup>11</sup> Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H. *Tetrahedron Lett.* **2010**, *51*, 4882.

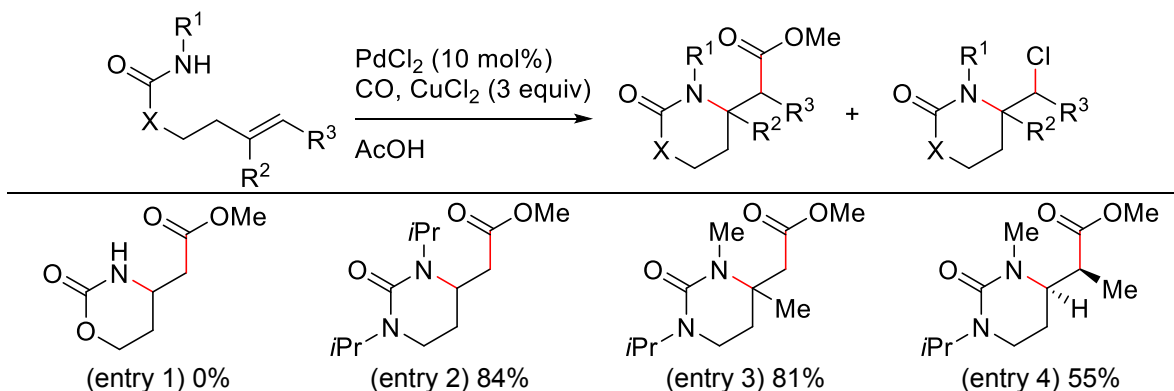
### 2.2.1 Synthesis of Six-Membered Rings with Alkene Aminocarbonylation

All of the aminocarbonylation examples thus far provided have been for the formation of pyrrolidine ring systems. However, little attention has been provided to the parent  $\beta$ -aminocarbonyl six-membered cycles. As discussed in previous sections, generation of medium-sized rings from linear precursors represents important synthetic challenges. Therefore, application of intramolecular cyclization to the generation of piperidines (or larger) rings represents an important extension of aminocarbonylation.

In 1988, Tamaru and coworkers reported their efforts towards solving this synthetic problem.<sup>12</sup> However, they quickly found that previously standardized aminocarbonylation conditions could not be applied to these new substrates. Initially, the reaction proved optimal in protic solvents and improved in acetic acid. Hence, acidic conditions proved most beneficial to the transformation, probably as to minimize strong amine coordination to palladium. Presented in Table 2.2 are selected examples of the reactivity.

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<sup>12</sup> Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1988**, *110*, 3994.

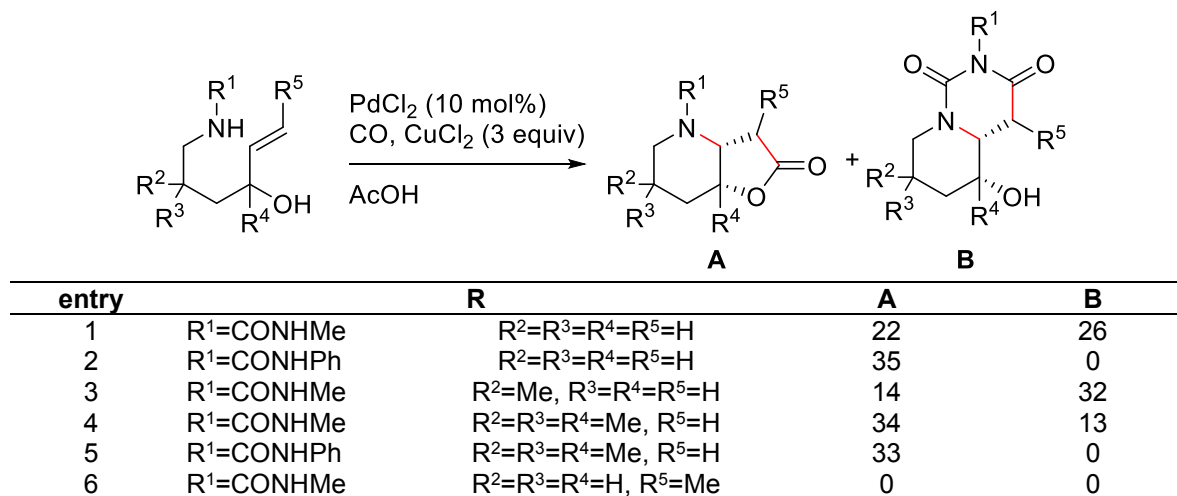
**Table 2.2** Selected examples of intramolecular amidocarbonylation of alkene for the formation of six-membered urea ring cycles <sup>a</sup>

<sup>a</sup> Conditions: heated at 0 - 60 °C for 2 - 36 h in MeOH.

Surprisingly and despite much efforts, hexenylcarbamate could not provide the desired cyclization (entry 1). However, hexenylureas proved amenable to the transformation (entry 2), arguably due to the added nucleophilicity of the concerned nitrogen atom and the urea's conformational effects favoring cyclization. The reaction showed tolerance to substitution both on the proximal (entry 3) and distal (entry 4) alkene position.

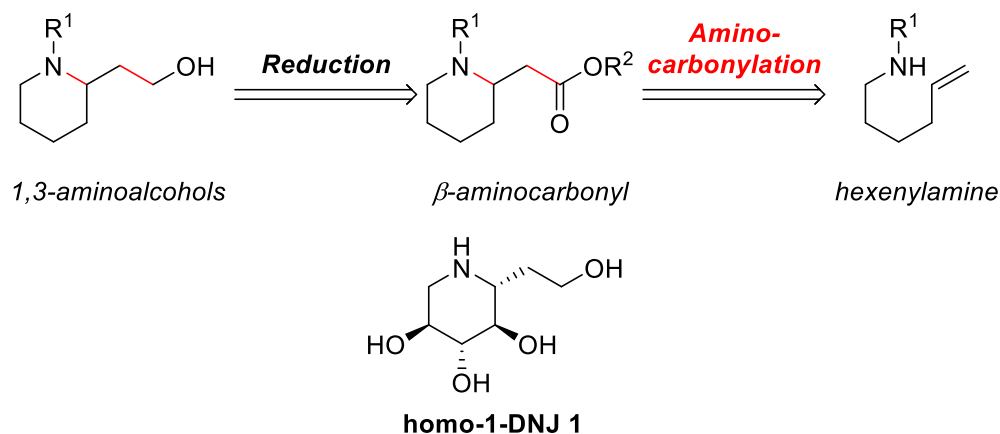
Improved conditions were to be found in order to access more challenging substrates. Therefore, Tamaru and coworkers developed an amidocarbonylation/intramolecular lactonization cascade specifically for the generation of piperidine-lactones (Table 2.3).<sup>12</sup> The method is attractive as it provides access to highly valuable alkaloid products.

**Table 2.3** Amidocarbonylation/lactonization cascade reaction of hexenolamines for the

formation of six-membered piperidine products <sup>a</sup><sup>a</sup> Conditions: heated at 0 - 60 °C for 2 to 3 days in acetic acid (0.2 M).

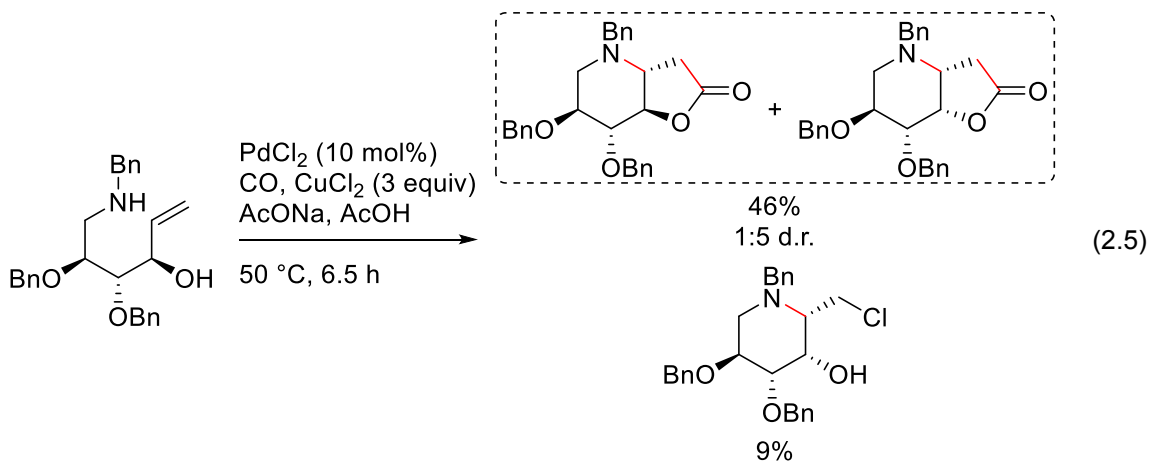
More so, the reaction can tolerate substitution on the alkene's internal position, but not at the distal position (entry 4-6). A phenyl-urea protective group was found to favor formation of piperidine-lactone products (entry 2 & 5). However, the reaction was poorly selective and aminocarbonylation was obtained as a mixture of products. Furthermore, although Tamura reports quantitative conversions, significant amounts of aminochlorination and other unidentified by-products were observed. Overall, the reaction is specific to amine protecting groups.

It is interesting to note that despite these poor results, aminocarbonylation was still perceived as a powerful method for the synthesis of 1,3-aminoalcohols and specifically, as precursors of homo-aza glycosides (see Figure 2.1).



**Figure 2.1** Retrosynthetic analysis of piperidine 1,3-aminoalcohol involving intramolecular alkene aminocarbonylation

Thus, Grazca and coworkers applied palladium(II) catalyzed aminocarbonylation to the synthesis of homologues of 1-deoxynojirimycins (equation 2.5).<sup>13</sup>



Results presented in equation 2.5 revealed aminocarbonylation to be obtained as a mixture of diastereomers. Again, an aminochlorination by-product produced in

<sup>13</sup> Szolcsanyi, P.; Gracza, T.; Koman, M.; Pronayova, D.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2579.



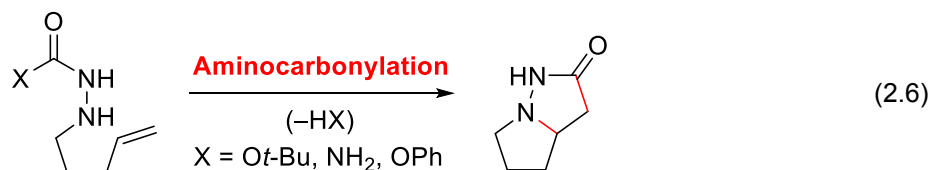
significant amount. Remarkably, the reaction could proceed without use of N-acyl protective groups (*N*-benzyl instead of *N*-carbamoyl).

### 2.2.2 Summary of Intramolecular Alkene Aminocarbonylation

We've thus far demonstrated the utility of intramolecular aminocarbonylation for the synthesis of  $\beta$ -homo-proline derivatives. Since the initial studies by Hegedus, palladium-catalyzed processes have improved and the work of Tamaru and coworkers established the basis for this important reactivity. However, reactions are still dependent on stoichiometric use of oxidant from which significant amounts of by-products are produced. Synthetically, standard aminocarbonylation conditions are amenable but still not ideal for the formation of six-membered rings. Access to larger rings still needs to be provided. Furthermore, no examples of intermolecular reactivity has thus far been reported. Overall, development of palladium-catalyzed aminocarbonylation remains limited despite important advancements in terms of enantioselective reactivity. Therefore, much effort is still required in order to turn alkene aminocarbonylation into a readily accessible synthetic tool.

## 2.3 Aminocarbonylation of Alkenes with Hydrazides

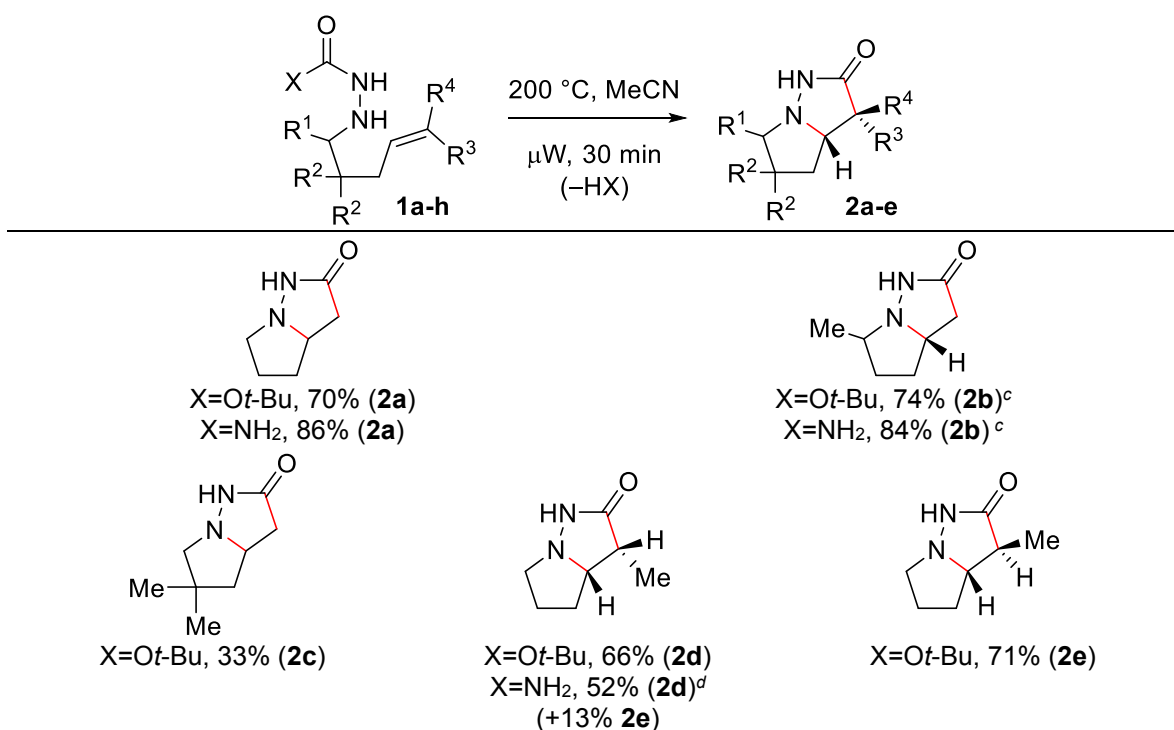
### 2.3.1 Substrate Scope



In continuation with our initial discovery of alkene aminocarbonylation with hydrazides, we attempted to further explore the synthetic scope to gain insights into this newly reactivity of hydrazides. As such, two substrates with distinct leaving groups were surveyed: Carbazates ( $X = Ot\text{-}Bu$ ) and semicarbazides ( $X = NH_2$ ). While aminocarbonylation conditions could be performed under very high temperatures (200 °C), it appeared that semicarbazides provided greater stability and thus, better yields than the parent *tert*-butylcarbazate. The same trend could be observed with generation of 2-methyl substituted pyrrolidine product **2b**. To improve the cyclization, we also attempted to use a Thorpe-Ingold effect. Accordingly, addition of steric hindrance to a linear cyclization precursor is known to increase the rate of the reaction. For example, rotational restrictions imposed by benzene substituents and quaternary carbon centers have been shown to help difficult cyclizations. However, gem-dimethylated substrate **1c** resulted in the increased rate of formation of the competing hydroamination pathway instead of aminocarbonylation, which explains the low yield obtained of product **2c**. Finally, the reaction has shown been to tolerate substitution at the alkene distal position (product **2d-e**) with slight epimerization of product **2d** given the basicity of ammonia ( $NH_3$ ) generated

from semicarbazide thermolysis. Interestingly, stereochemical information of the provided *cis*- and *trans*-substituted alkene, was transferred to the resulting aminocarbonylation product. This observation is important as it provides insights towards the mechanism involved in the transformation. As such, retention of the alkene's stereochemical information is reminiscent of a concerted (*syn*) addition that would later offer important evidence for the intermediate involved in the transformation.

**Table 2.4** Scope of Intramolecular Aminocarbonylation Reactivity <sup>a</sup>

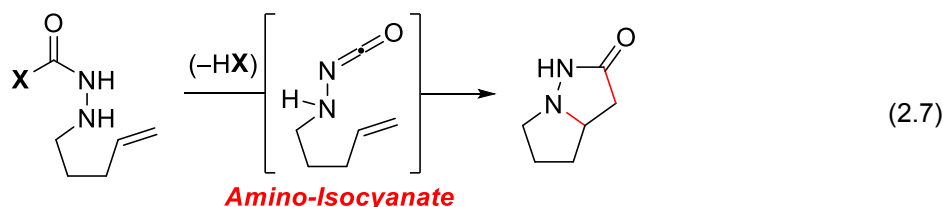


<sup>a</sup> Conditions: Heating performed in MeCN (200 °C, 30 min, 0.05 M, microwave reactor). <sup>b</sup> Isolated yield. <sup>c</sup> 2:1 dr. <sup>d</sup> NMR yield using 1,4-dimethoxybenzene as an internal standard.

In summary, two conclusion could be drawn from this initial survey. First, semicarbazides and *tert*-butyl carbazate substrates likely share a common aminocarbonylation intermediates. Secondly, this intermediate's addition to the alkene is concerted.

### 2.3.2 Aminocarbonylation with Amino-Isocyanates

In lieu of these insights, it became imperative to identify the active species involved in the transformation. As such, an *amino-isocyanate* was suggested as a reasonable aminocarbonylation precursor (equation 2.5).<sup>14</sup>

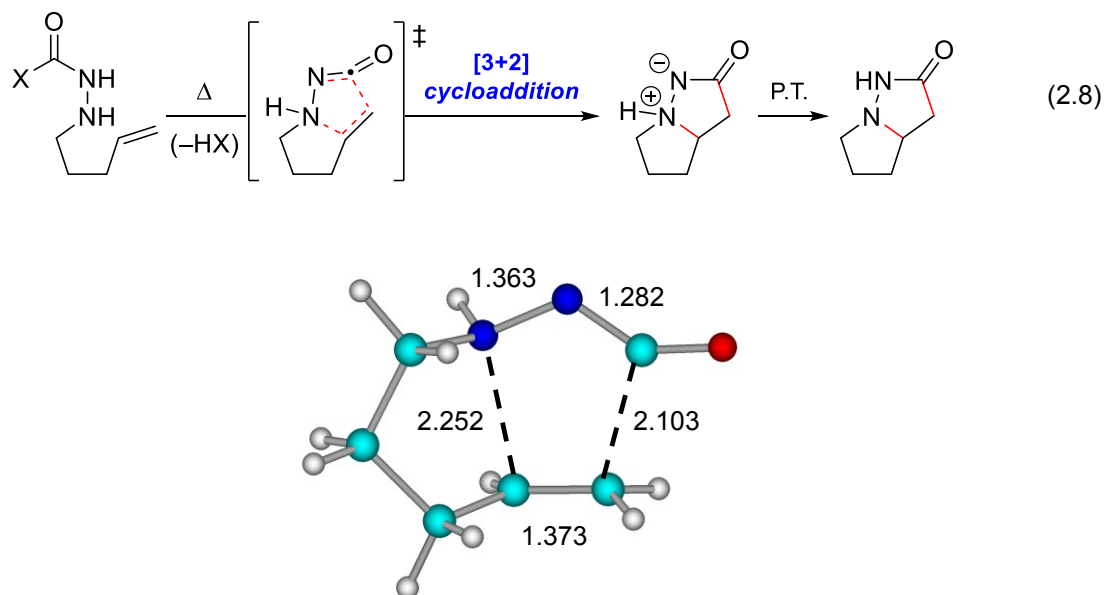


To account for the observed stereocontrol of the bond-formation, addition of amino-isocyanate to alkene was suggested to undergo a [3+2] cycloaddition (equation 2.8). We thus subjected this hypothesis to DFT (Figure 2.3). In collaboration with Serge I. Gorelsky, the reaction could be confirmed as concerted but with asynchronous bond formation and activation energy requirements of  $E_{\text{act}} = 19.1$  kcal/mol. From amino-isocyanate, the overall process was found to be thermodynamically favorable by  $\Delta G^{\circ} = -17.6$  kcal/mol. However, calculations also revealed a difficult proton transfer step from the resulting aminocarbonylation dipole intermediate ( $\Delta G^{\ddagger} = 33.3$  kcal/mol). Concurrently, despite the necessity for harsh thermal conditions (up to 200 °C), the calculated energetic requirements for the transformation suggested that the cyclization of

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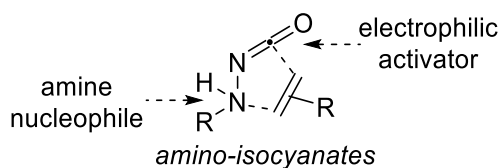
<sup>14</sup> Clavette, C. *A Metal-Free Aminocarbonylation of Alkenes; Honour's Thesis, University of Ottawa*, 2009, 100 pages.

amino-isocyanate with alkenes was conceivable at room temperature. Therefore, it was suggested that the generation of amino-isocyanate was rate-determining to the transformation.



**Figure 2.2** Transition state structure for the intramolecular aminocarbonylation. Internuclear distances (Å) are shown for relevant chemical bonds.

### 2.3.3 Amino-Isocyanates as Bifunctional Reagents.



**Figure 2.3** Amino-isocyanates as bifunctional reagents

In line with our previous description of alkene amination reagents, amino-isocyanates, as for hydroxylamines and hydrazides, also portray an amphoteric character (Figure 2.4). However, prior examples of amino-isocyanates are quite scarce and their reactivity is even less described. Nonetheless, it became imperative to the development of our newly found aminocarbonylation system to survey prior work on these elusive moieties.

## 2.4 Precedents on Amino-Isocyanates

Reactivity of *N*-substituted isocyanates bearing electron-withdrawing moieties such as sulfonyls, chlorosulfonyls, phosphorus and carbonyls have been the subject of significant research efforts and the topic of upcoming sections.<sup>15</sup> However, the synthetic potential of *N*-substituted isocyanates bearing nucleophiles has not yet been fully

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<sup>15</sup> (a) Ulrich, H. *Chem. Rev.* **1965**, 65, 369; Onodera, N. *Kagaku (Kyoto)* **1964**, 19, 1240. (b) Graf, R. *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 172. (c) Derkatsch, G. I. *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 421. (d) Tsuge, O. *Kagaku To Kogyo (Tokyo)* **1969**, 22, 770.

exploited. Oxygen-, sulfur-, <sup>16</sup> and in particular nitrogen-substituted heteroallenes, such as amino-isocyanates, have in the past created several unique synthetic opportunities but consideration into their reactive potential is still deficient.<sup>17</sup> As the focus of this section, several methods towards the synthesis of amino-isocyanates will be presented along with discussion of their reactive behavior.

#### 2.4.1 Generation of Amino-Isocyanates

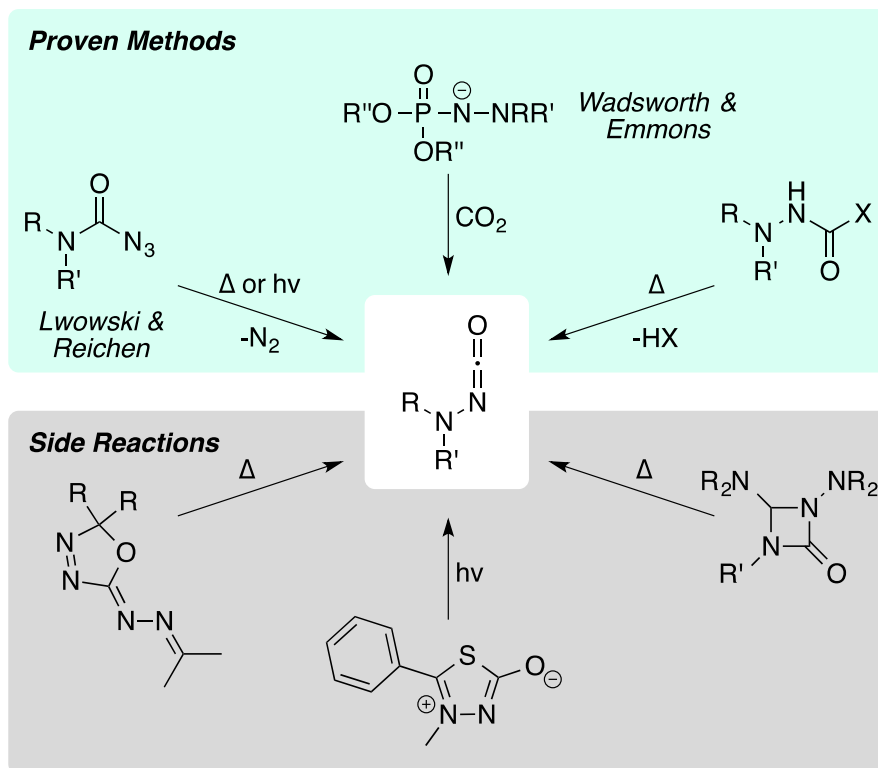
As reviewed by Reichen in 1978, few methods have proven efficient towards the synthesis of amino-isocyanates.<sup>32</sup> Presented in Scheme 2.6 are reactions that have resulted in generation of amino-isocyanates.<sup>18</sup> Amino-isocyanate moieties have hardly been observed in nature and in rare occasions have they been analyzed as single entities. Therefore, present discussion will essentially focus on proven methods presented in Scheme 2.6.

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<sup>16</sup> For recent examples of heteroatom-substituted isocyanates, see : Koch, R.; Finnerty, J. J.; Wentrup, C. *J. Org. Chem.* **2011**, *15*, 6024.

<sup>17</sup> For a review on the formation and reactivity of amino-isocyanates, see: (a) Reichen W. *Chem. Rev.* **1978**, *78*, 569. (b) Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem.* **2011**, *15*, 1745.

<sup>18</sup> Amino-isocyanates have also been observed as by-products of the thermal degradation of polyurethanes: Karlsson, D.; Dahlin, J.; Skarping, G.; Dalene, M. *J. Environ. Monit.* **2002**, *4*, 216.

**Scheme 2.6** Reported methods for the synthesis of amino-isocyanates

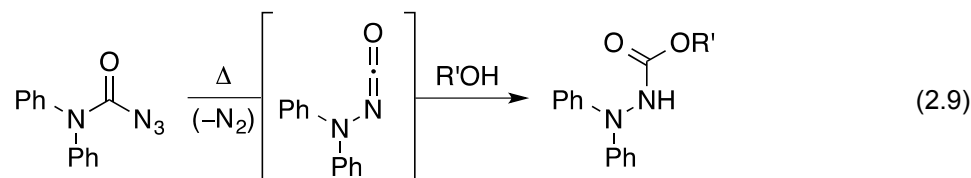
#### 2.4.1.1 Curtius Degradation of Carbamoyl Azides

Following the discovery the Curtius rearrangement of acyl azides in 1914,<sup>19</sup> various azides were tested for this particular rearrangement. Carbamoyl azides, originally considered as rigid forms of azides (in other words, azides that hardly undergo rearrangement), are now known to readily rearrange to amino isocyanates under photolysis or thermolysis as demonstrated by Stollé in the 1920's. Diphenylcarbamoyl

<sup>19</sup> Curtius, Z. T. *Angew. Chem.* **1914**, 27, 213.



azide (equation 2.9), upon heating, readily generated diphenyl amino-isocyanate, which could be trapped upon solvolysis by running the reaction in alcoholic solvent.<sup>20</sup>



The mechanism behind the thermal decomposition of carbamoyl azides has been debated over the years. Whether it involved a concerted S<sub>N</sub>2-type displacement or formation of a nitrene intermediate remained elusive.<sup>21</sup> During the 1960's, Lwowski and coworkers demonstrated that a nitrene intermediate had no involvement in the transformation.<sup>22,23,24</sup> However, exceptional cases have proven otherwise.<sup>25</sup>

While later, very few examples of amino-isocyanates had been reported, Lwowski and coworkers aimed at exploring the ability of previously deemed unreactive rigid-azides. Expanding on Stollé's results, photolysis of carbamoyl azides in alcoholic

<sup>20</sup> (a) R. Stollé, *J. Prakt. Chem.* **1927**, 116, 192. (b) R. Stollé, *J. Prakt. Chem.* **1928**, 117, 185.

<sup>21</sup> Stieglits, *J. Am. Chem. J.* **1896**, 18, 751.

<sup>22</sup> (a) Linke, S.; Tisue, T.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, 89, 6308. (b) Koga, N.; Koga, G.; Anselme, J.-P. *Tetrahedron* **1972**, 28, 4515.

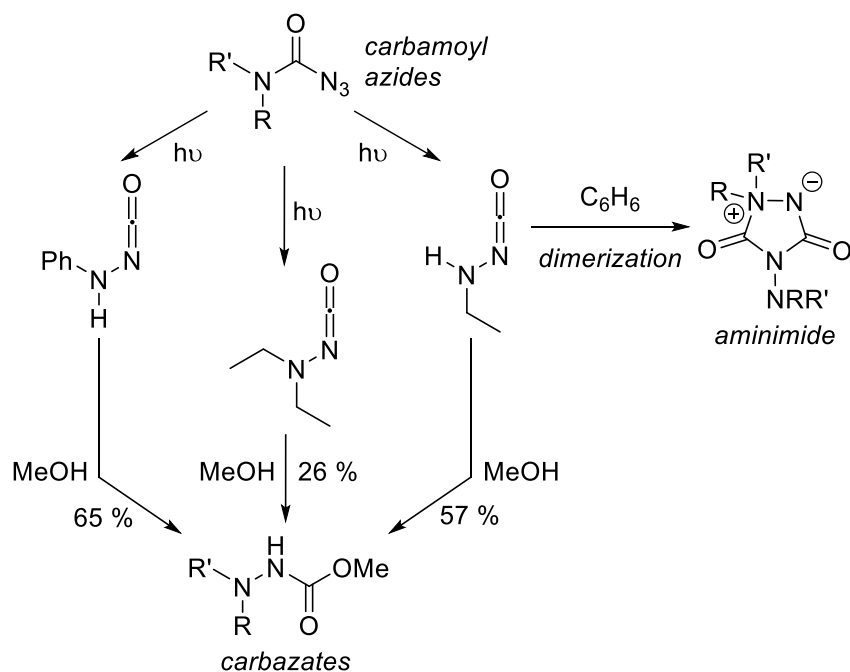
<sup>23</sup> For the thermolysis of carbamoyl azides and a Cu catalyzed variant see: (a) Reichen, W. *Hel. Chim. Acta* **1976**, 59, 2601. (b) Reichen, W. *Hevl. Chim. Acta* **1977**, 60, 498.

<sup>24</sup> Lwowski, W. ; de Mauriac, R. A. ; Thompson, M. *J. Org. Chem.* **1975**, 40, 2608.

<sup>25</sup> Patai, S.; Lwowski, W. *The Chemistry of the Azido Group*, Ed. Inter-science, New York, N.Y., 1971, p. 425.

solvents resulted in isolation of carbazates generated from solvolysis of the corresponding amino-isocyanate product.<sup>26</sup> Lwowski thus demonstrated the reactivity to be amenable to various *N*-aryl and *N*-alkyl carbamoyl azides.

**Scheme 2.7** Lwowski's initial experiments on *N*-alkyl and *N*-aryl amino-isocyanates

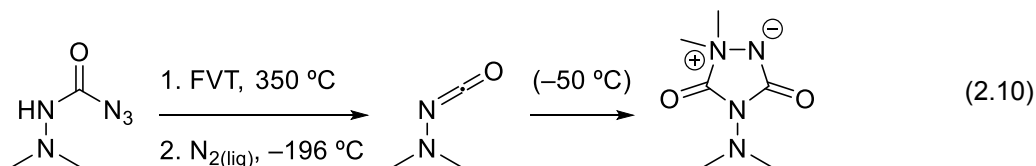


Comparably, irradiation of mono-aryl, mono-alkyl and dialkyl carbamoyl azides in non-nucleophilic solvents (cyclohexane, cyclohexene, benzene) yielded high molecular weight compounds presenting no traces of groups derived from the solvent. These were later found to correspond to aminimide products, resulting from dimerization of amino-

<sup>26</sup> Lwowski, W. ; De Mauriac, R. ; Mattingly, T. W. Jr. ; Scheiffele, E. *Tetrahedron Lett.* **1964**, 3285.

isocyanates (Scheme 2.7). Thus, chemical environment was found to play an important role for the existence of previously claimed barriers between “rigid” and “non-rigid” azides. Trapping of isocyanate with nucleophilic solvents provides thermodynamically stable products (carbazates), thus favouring amino-isocyanate formation.<sup>27</sup>

For some time, no direct observation of amino-isocyanates could be made. However, analysis of the thermolytic degradation of carbamoyl azides could be performed using flash-vacuum thermolysis (FVT, equation 2.10).<sup>28</sup>



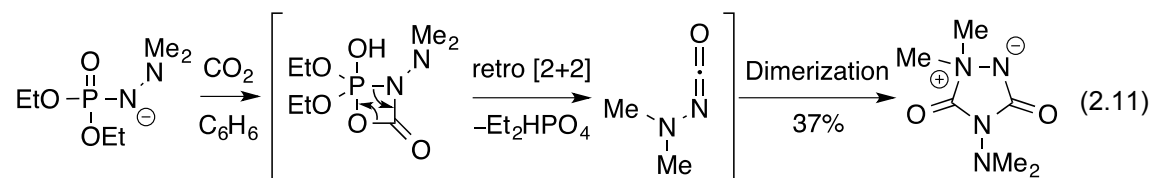
Upon heating *N,N*-dimethyl carbamoyl azide, the corresponding *N,N*-dimethyl amino-isocyanate could be isolated in liquid nitrogen (−196 °C) and analyzed as is. IR spectroscopy revealed a band at 2215 cm<sup>−1</sup>, that is typical of an isocyanate. Interestingly, amino-isocyanate proved unstable at higher temperatures and readily converted to aminimide at temperatures above −50 °C as observed by Lwowski. Thus, this result demonstrates the facility with which amino-isocyanate dimerization can proceed.

<sup>27</sup> (a) Lwowski, W.; DeMauriac, R.; Mattingly, T. W. Jr.; Scheiffele, E. *Tetrahedron Lett.* **1964**, 5, 3285. (b) Lwowski, W.; DeMauriac, R.; Murray, R.; Lunow, L. *Tetrahedron Lett.* **1971**, 12, 425.

<sup>28</sup> Lukosch, A. *Thermisches Verhalten von-Halogenethioethern, Carbamoy-laziden und 3-Methylenpyrrol-2-ones*. Diploma Thesis, Universität Marburg: Marburg, Germany, **1981**.

## 2.4.1.2 Carboxylation of Phosphoramidate Anions

Discovered by Wadsworth and Emmons, the reaction of phosphoramidate anions is a convenient method towards the synthesis of nitrogen-containing unsaturated compounds. In 1967, they reported formation of amino-isocyanate from the reaction of *N,N*-dimethyl phosphohydrazidate with carbon dioxide (equation 2.11). The reaction resulted in amino-isocyanate dimerization from which the product could be isolated in moderate yield.<sup>29</sup>



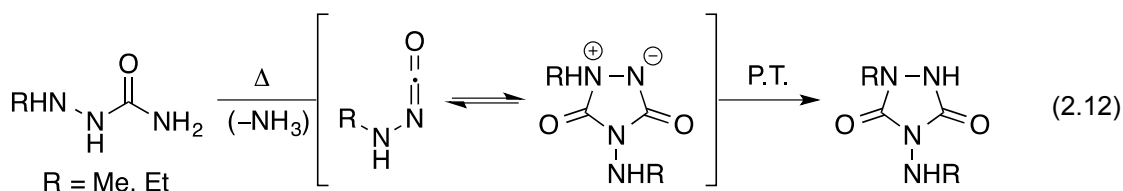
As reported, *N,N*-dialkylamino-isocyanates could not be observed in their monomeric form. Dimerization could be avoided by trapping of the amino-isocyanate, as previously reported, with alcoholic solvents. However, *n*-butyl- and *n*-octyl-isocyanates yielded 62 % and 71 % respectively of the corresponding dimer products. Although providing a source of amino-isocyanate under mild conditions, this method lacks convenience due to the complexity of the experimental procedure. As a matter of fact, this methodology is limited in its substrate scope. However, the process is nonetheless

<sup>29</sup> Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1967**, 32, 1279.

interesting and presents synthetic potential amenable to improvements and future developments.

#### 2.4.1.3 Thermal Degradation of Semicarbazides

Arguably, a simpler method to generate amino-isocyanates involves thermal degradation of hydrazide precursors.<sup>30</sup> Under such conditions, Busch demonstrated formation of amino-isocyanate dimers from the degradation of *N*-alkylsemicarbazides by production of an equivalent of ammonia (equation 2.12). These results were later confirmed by the work of Wadsworth and Emmons.<sup>16</sup>

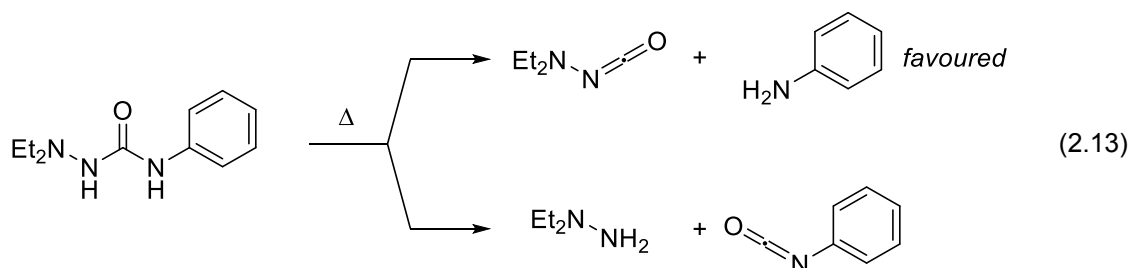


Surprisingly, semicarbazides showed preference for expulsion of NH<sub>2</sub> leaving group over the hydrazine moiety. Later, Larsen and coworkers submitted *N,N*-diethyl-*N'*-phenylsemicarbazide to similar conditions and demonstrated that two possible fragmentation patterns occurred. Both *N,N*-diethyl amino-isocyanate and phenyl-isocyanate were obtained. Mass analysis suggests that the latter is being formed in lesser proportion (equation 2.13), demonstrating preference for generation of amino-isocyanate.

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<sup>30</sup> (a) Busch, M. *J. Chem. Soc* **1901**, 80, 488. (b) Pinner, G. *Ber.* **1908**, 21, 1225.

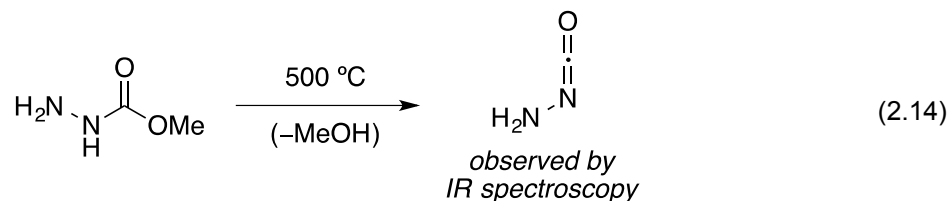
<sup>31</sup> This might be attributed to the enhanced leaving group behavior of aniline compared to *N,N*-diethylhydrazine.



#### 2.4.1.4 Thermal Degradation of Carbazates

Following the work of Meier and Teles, pyrolysis of *O*-methoxycarbazate and subsequent rapid cooling led to rare observation of amino-isocyanate (equation 2.14).<sup>32</sup>

The monomer could be analyzed and characterized accordingly.

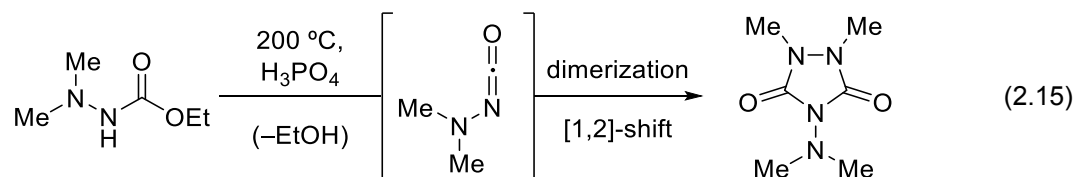


Along with these results, Wadsworth and Emmons also explored the reactivity of carbazates upon thermolysis as an independent synthetic method from their phosphoramidate methodology, in an attempt to generate amino-isocyanates. As such,

<sup>31</sup> Larsen, C.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1969**, 23, 322.

<sup>32</sup> Maier, G.; Teles, H. *Chem. Ber.* **1989**, 122, 745.

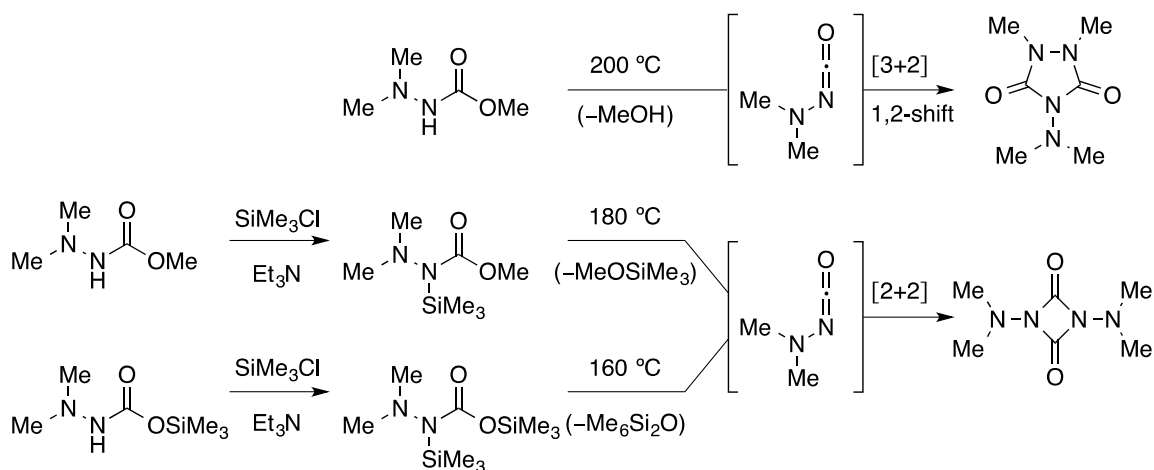
thermolysis of dialkyl *O*-ethoxy-carbazate in the presence of phosphoric acid (presumably acting as Brønsted catalyst) at 200°C resulted in production of amino-isocyanate dimer in limited yield (equation 2.15).



Kirilin and coworkers propose the formation of amino-isocyanates under slightly milder conditions. In accordance with Wadsworth and Emmons, *O*-methoxy carbazate presented in Scheme 2.8, silylated carbazates decomposed at lower temperature: 160 °C and 180 °C respectively.<sup>33</sup>

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<sup>33</sup> Kirilin, A. D.; Dokuchayev, A. A.; Sokova, N. B.; Chernyshev, E. A. *Russ. Chem. Bull.* **1999**, 48, 169.

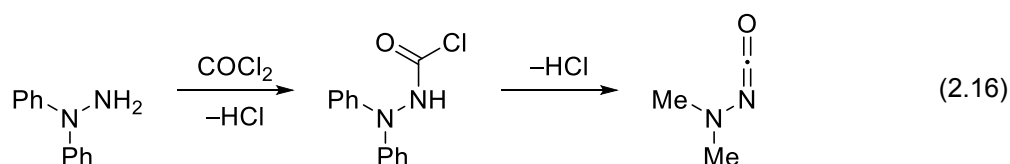
**Scheme 2.8** Thermolysis of dialkyl silylcarbazates and dimerization of amino-isocyanates

In comparison to Wadsworth and Emmons, two dimers of amino-isocyanates were suggested. The first, resulting from previously observed self-dimerization by [3+2] cycloaddition. The second, resulting from a [2+2] cycloaddition between two isocyanates; a typical side-reaction of isocyanate thermolysis. However, generation of the later product lacks experimental support and, despite Kirilin and coworkers' claims for a thermal control over dimer formation, previous reports on dimer formation supports aminimide formation. Effect of silyl substituents on the substrates' ability to generate amino-isocyanates is also unclear.



### 2.4.1.5 Phosgenation of Hydrazines

In 1903, Acree provided one of the first observation of an amino-isocyanate.<sup>34</sup> Treatment of diphenylhydrazine with phosgene and decomposition of the resulting *N,N*-diphenylhydrazidic acid chloride, ensued development of a strong ammonia-like odour, typical of isocyanates (equation 2.16).

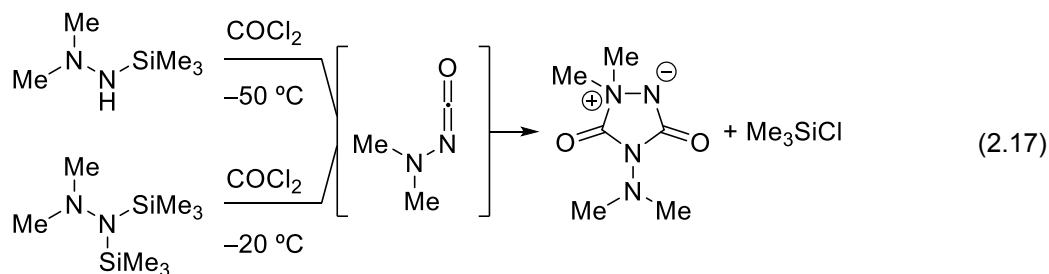


Later, following the work of Kirlin, mono- and bis-silylated dimethylhydrazines were treated with phosgene at temperatures of -50 and -20 °C respectively. Both were found to effectively generate dimethyl amino-isocyanate that was attempted to be isolated with no success. In the process, the previously reported [3+2] cycloaddition dimer was observed.<sup>33</sup>

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<sup>34</sup> Acree, S.F. *Ber. Deut. Chem. Ges.* **1903**, 36, 3154-3158.

**Scheme 2.8** Reactivity of hydrazines with phosgene and formation of triazoles from the dimerization of aminoisocyanates



Phosgene is well known to easily undergo transacylation reactions and to generate isocyanates from primary amines. We've thus far demonstrated that reaction with hydrazines can lead without surprise to amino-isocyanates. However, phosgene, as a gas, is toxic and inherently difficult to work with. Therefore, it is to be expected that phosgene equivalents, such a carbonyl diimidazole (CDI) may provide an interesting alternative to the synthesis of amino-isocyanates. More on the reactivity of transacylation agents with hydrazines will be covered in upcoming sections.

#### 2.4.2 Generation of Amino-Isothiocyanates

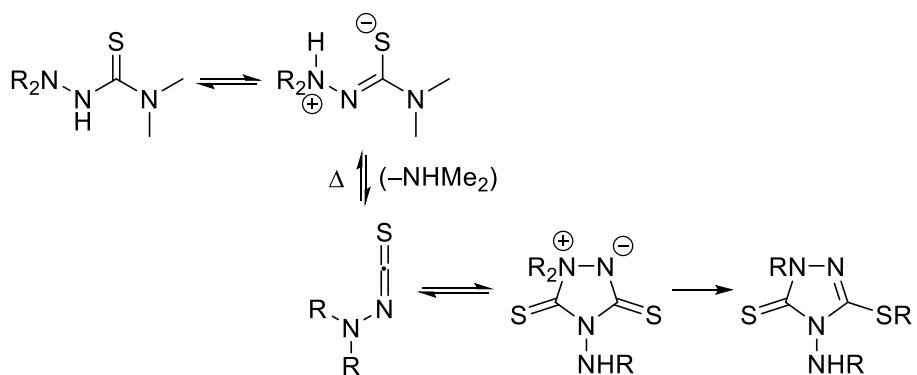
During the 1960s, Larsen and coworkers performed a thorough investigation of the thermal stability of various thiohydrazides and their propensity to decompose into amino-isothiocyanates.<sup>35</sup> It is worth considering these results as they provide insightful

<sup>35</sup> For an overview of the reactivity of amino-isothiocyanates, see: Jensen, K. A.; Anthoni, U.; Kägi, B.; Larsen, C.; Pedersen, C. T. *Acta Chem. Scand.* **1968**, 22, 1.

information on the reactive behaviour of *N*-substituted isocyanate species pertaining to the present discussion.

Early on, Larsen explored the reactivity of thiosemicarbazides. As presented in Scheme 2.10, thermolysis of *N,N*-dialkyl thiosemicarbazide resulted in expulsion of dimethylamine and nearly quantitative conversion to dimeric amino-isothiocyanate.<sup>36</sup>

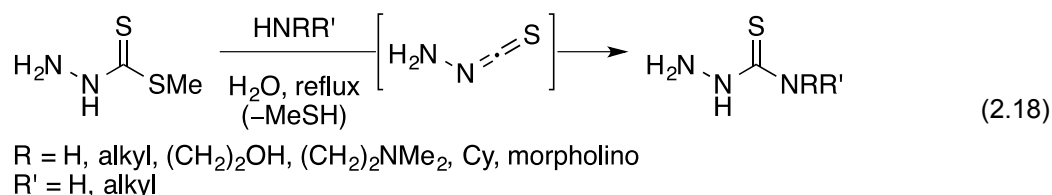
**Scheme 2.9** Thermal degradation of thiosemicarbazide and synthesis of amino-thiocyanates



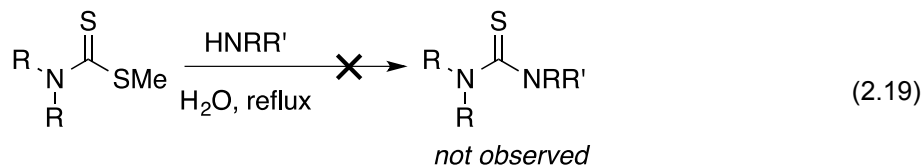
For this reaction, Larsen proposed thiosemicarbazide to be in equilibrium with its tautomeric form owing to the high polarizability of thiocarbonyl moiety. Arguably, such species could act as amino-isothiocyanate precursor. This proposition is interesting as it may also apply to the formation of (oxo)-isocyanates.

<sup>36</sup> (a) Larsen, C.; Binderup, E. *Acta Chem. Scand.* **1967**, 21, 1984. (b) Larsen, C.; Anthoni, U.; Nielsen, P. H. *Acta Chem. Scand.* **1969**, 23, 320.

Furthermore, Larsen explored the thermal reactivity of carbazate thioesters. As such, trapping of amino-isothiocyanates was devised by means of amine nucleophiles. As presented in equation 2.18, substitution proved useful to the synthesis of a variety of thiosemicarbazides.<sup>37</sup> It is interesting to note that amino-isothiocyanate, in this case, can tolerate aqueous conditions, even at reflux.



Support for an amino-isothiocyanate intermediate was provided based on the comparably difficult aminolysis of *N,N*-dialkylamino dithiomethyl esters with amines under the same conditions (equation 2.19).<sup>38</sup> In this case, no exchange product (thiourea) is observed.

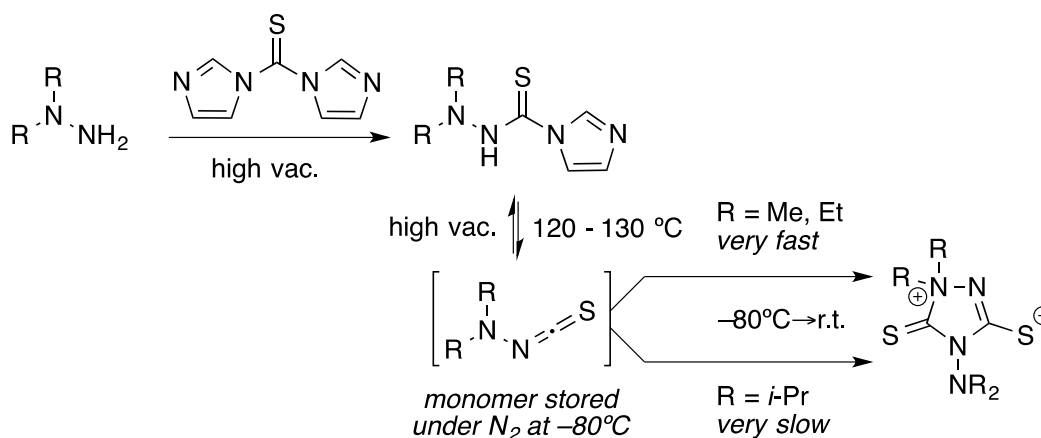


<sup>37</sup> McElhinney, R. S. *J. Chem. Soc. (C)* **1966**, 950.

<sup>38</sup> (a) Delépine, M. *Bull. Soc. Chim. France* **1902**, 27, 816. (b) Delépine, M.; Schving, P. *Bull. Soc. Chim. France* **1910**, 7, 896. (c) Aubert, P.; Knott, E. B.; Williams, L. A. *J. Chem. Soc.* **1951**, 2188. (d) Knott, E. B. *J. Chem. Soc.* **1956**, 1644.

In another study, formation of aminoisothiocyanates from transacylation of thiocarbonyl diimidazole and unsymmetrical dialkylhydrazines was investigated (Scheme 2.11).<sup>39</sup>

**Scheme 2.10** Reactivity of dialkyl hydrazides with thiocarbonyl diimidazole and thermolysis of imidazo thiosemicarbazide

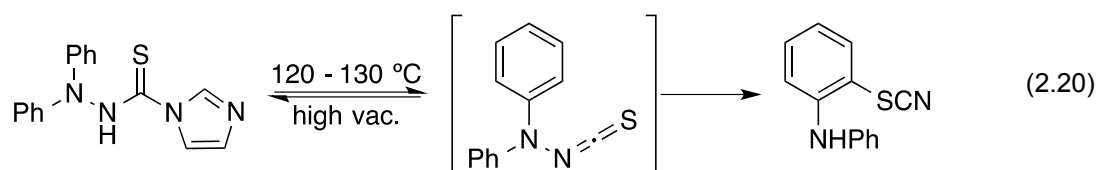


From this study, Anthony and coworkers isolated and stored the amino-thioisocyanates at  $-80^\circ C$ . In doing so, amino-isothiocyanate's rate of dimerization could be compared on the basis of  $N,N$ -substitution. Once heated to room temperature,  $N,N$ -dimethyl- and  $N,N$ -diethyl-amino-isothiocyanates were found to rapidly dimerize. In stark contrast, diisopropyl-amino-isothiocyanate was proven stable at room temperature and produced

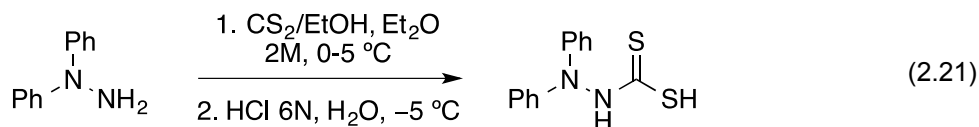
<sup>39</sup> Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1966**, 20, 1714.

little dimer after several days. These results revealed importance of steric hindrance over the reactivity of amino-isothiocyanate.<sup>40</sup>

Following this, attempt was made at the generation of *N,N*-diphenyl-amino-isothiocyanate (equation 2.20). However, observation of amino-isothiocyanate monomer or dimer proved unsuccessful. Instead, obtained was thiocyanatodiphenylamine product resulting, as argued, from amino-isothiocyanate rearrangement.<sup>41</sup>



Larsen also proposed an alternative to the synthesis of *N,N*-diphenyl amino-isothiocyanate. As such, treatment of diphenylhydrazine with carbon disulfide produced diphenyldithiocarbazic acid according to equation 2.21.<sup>42</sup>



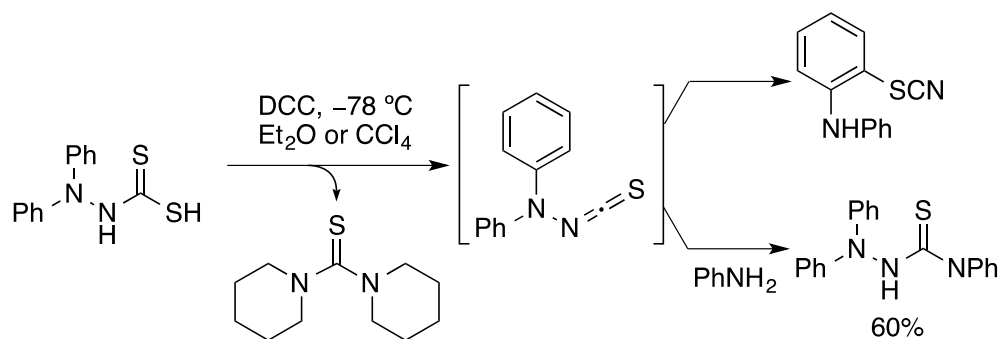
<sup>40</sup> Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1967**, 21, 2061.

<sup>41</sup> Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1967**, 21, 1201.

<sup>42</sup> Anthoni, U. *Acta Chem. Scand.* **1966**, 20, 2742.

Thiocarbazic acid was then reacted with dicyclohexyl carbodiimide (DCC) for three days at  $-80\text{ }^{\circ}\text{C}$  in ether or  $\text{CCl}_4$ . Unfortunately, the corresponding diphenyl isothiocyanate monomer, or its dimer, could not be isolated and again, a rearrangement product would be obtained. However, the production of amino-thioisocyanate could be confirmed by aminolysis with aniline and subsequent yielding of the corresponding thiosemicarbazide in good yield.

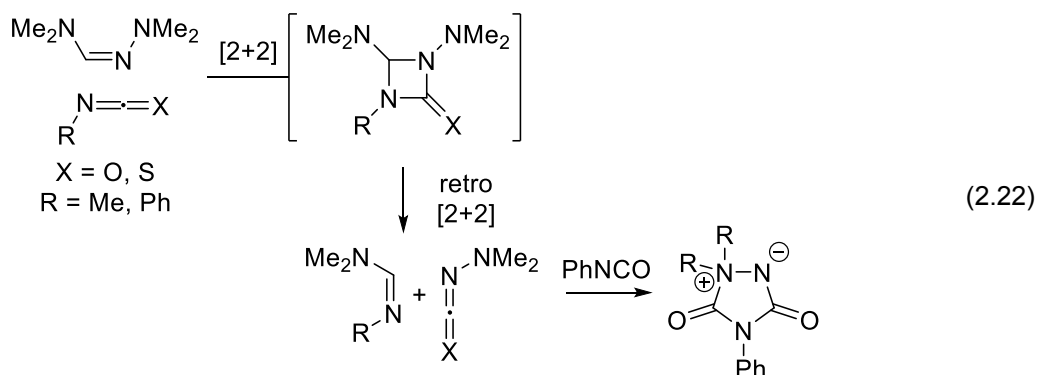
**Scheme 2.11** Reactivity of dithiocarbazic acid with dicyclohexyl carbodiimide



### 2.4.3 Cycloaddition and Cycloreversion

An alternative method towards the synthesis of amino-isocyanates involves the [2+2] cycloaddition/cycloreversion of aminimide derivatives. As presented in equation

2.22, thermal degradation of dimethylaminoformamidine leads to formation of an amino-isocyanate.<sup>43,44</sup>

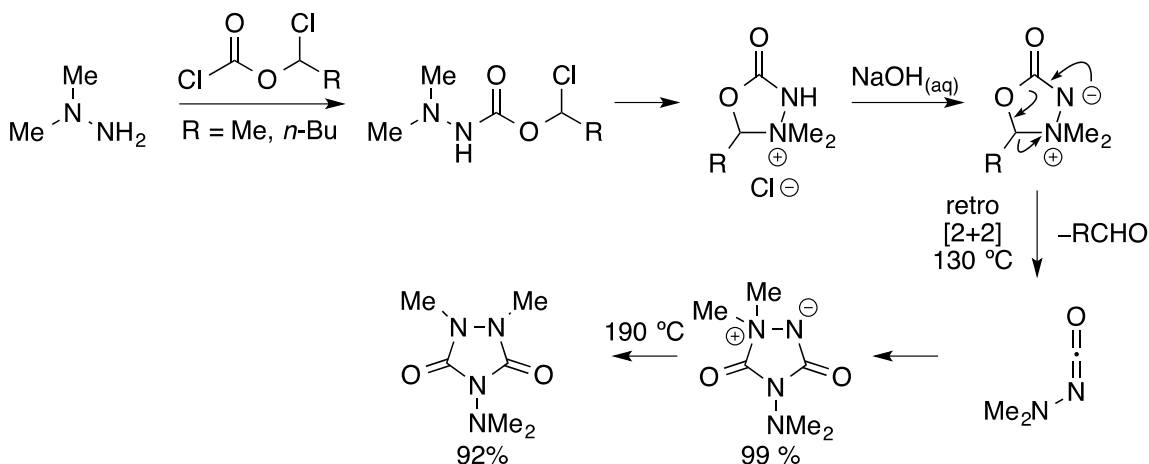


In 1986, Senet and coworkers described a multistep synthesis of amino-isocyanate involving a [3+2] cycloreversion process. Dimethyl-hydrazine is treated with a chloroformate which undergoes intramolecular S<sub>N</sub>2 displacement. The resulting salt is then treated with base to generate aminimide ylide. Upon thermolysis, ensued cycloreversion leads to dimethyl-amino-isocyanate and the corresponding aldehyde.

<sup>43</sup> Seckinger, K. *Helv. Chim. Acta.* **1973**, 56, 2061.

<sup>44</sup> For a similar example involving tetrazene and ketene, see: Kerber, R. C.; Ryan, T. J. *J. Org. Chem.* **1971**, 36, 1566.



**Scheme 2.12** Synthesis, thermolysis and decomposition of cyclic carbalkoxy aminimides

Aminoisocyanate dimer was obtained in nearly quantitative yields at temperatures of  $-40^\circ\text{C}$  and the subsequent thermolysis effectively provided 1,2-alkyl shift in excellent yield.<sup>45</sup> Amino-isocyanate could also be trapped in the presence of nucleophiles. Interestingly, authors also report dimerization of dimethyl amino-isocyanate.

As seen, self-dimerization of amino-isocyanates appears as an energetically favorable process for most species described herein. However, no discussion of the reversibility of this process as thus far been provided.

In search of a practical solution to the generation of amino-isocyanates, milder conditions than the previously explored photo-catalyzed carbamoyl azide decomposition

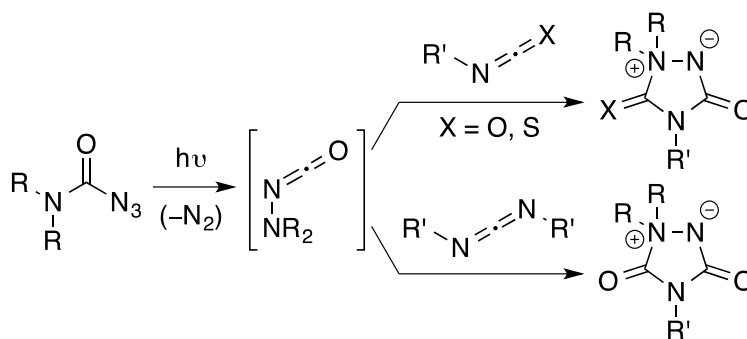
<sup>45</sup> Senet, J.-P.; Vergne, G.; Wooden, G. P. *Tetrahedron Lett.* **1986**, 27, 6319.

was envisioned. As such, Lwowski and coworkers explored the ability of zwitterionic dimers to cycloreverse and thus act as amino-isocyanate precursors.

## 2.5 Reactivity of Amino-Isocyanates

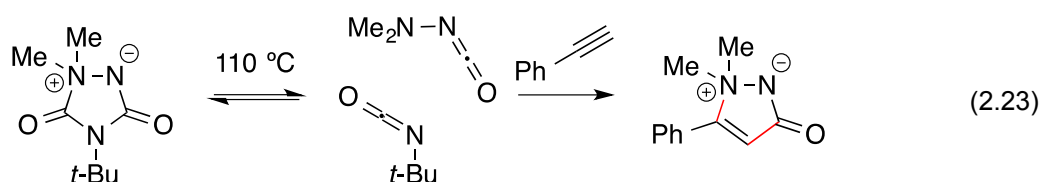
While the topic of the present discussion involves primarily generation of amino-isocyanates, we have thus far discussed some reactive behavior of the aforementioned species such as self-dimerization and solvolysis. However, Lwowski and coworkers also demonstrated the versatility of amino-isocyanates to react with  $\pi$ -bonds. As such, heterocumulenes such as isocyanates and carbodiimides were found to readily undergo cycloaddition (Scheme 2.14).

**Scheme 2.13** Reactivity of amino-isocyanates with heterocumulenes

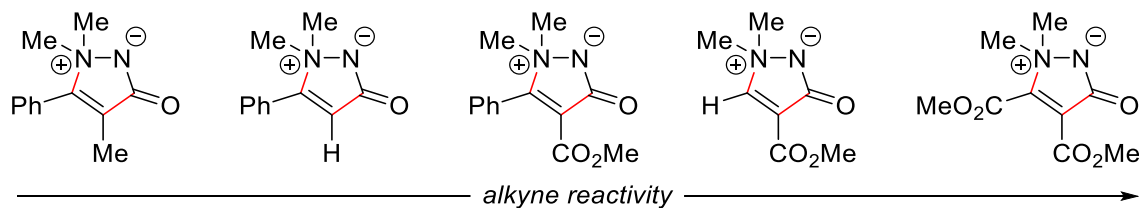


More so, Lwowski demonstrated the utility of such species in acting as amino-isocyanate precursors. As such, thermolysis of either dimers or isocyanate-derived cycloaddition products (Scheme 2.14) resulted in cycloreversion (equation 2.23). This was particularly useful in providing reliable source of amino-isocyanates to explore additional cyclizations with other  $\pi$ -bonds.

Interestingly, amino-isocyanates were found to cyclize with alkynes (equation 2.23).<sup>46</sup> Reaction is performed in conditions into which aminimide is poorly soluble. Therefore, concentration of amino-isocyaante is kept low which allows control over rate of self-dimerization thus permitting reaction with phenyl acetylene.



A qualitative assessment of acetylene reactivity was performed (Figure 2.4). Electron-poor alkynes proved most reactive whereas phenyl acetylene showed some level of reactivity. In contrast, unactivated aliphatic alkyne showed no sign of reactivity. Although Lwowski's exploitation of the reactivity of alkynes was limited, it nonetheless represented the first example of aminocarbonylation of a C-C  $\pi$ -bond with an amino-isocyanates.

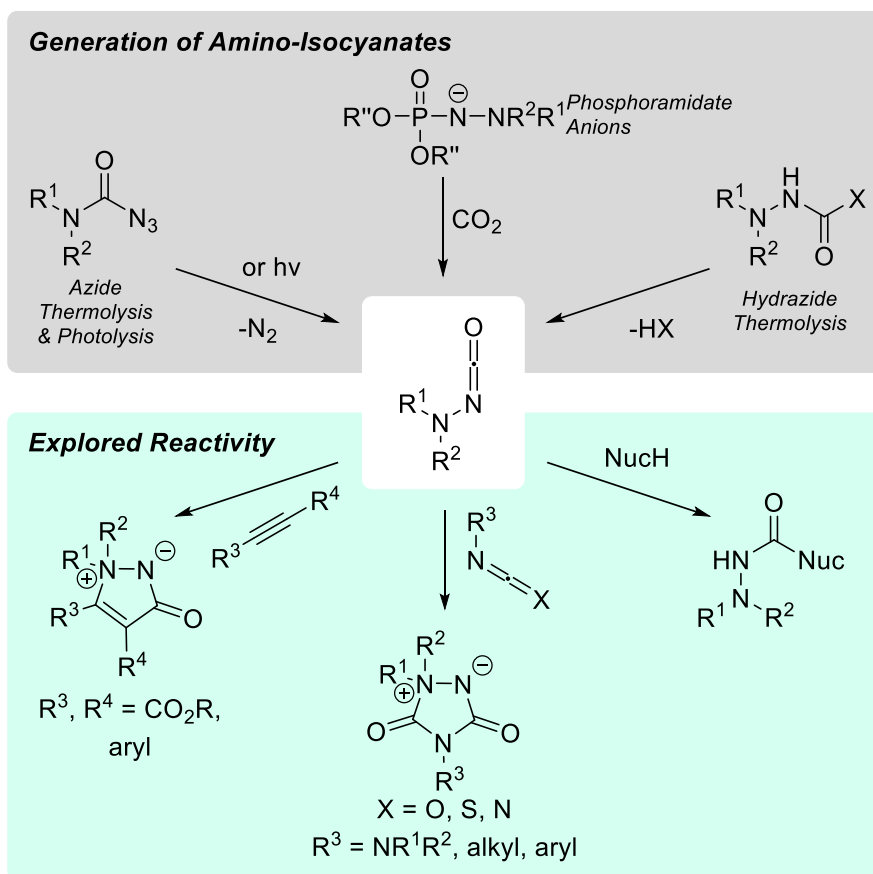


**Figure 2.4** Acetylene assessment of amino-isocyanate reactivity

<sup>46</sup> Lockley, W. J. S. ; Lwowski, W. *Tetrahedron Lett.* **1974**, 48, 4263.

### 2.5.1 Summary of the Reactivity of Amino-Isocyanates

From this literature survey, amino-isocyanates may be generated using various synthetic methods. However, it was soon recognized that hydrazide thermolysis, despite the harsh conditions sometimes necessary to isocyanate formation, offered a simple and tunable method for amino-isocyanate generation. Overall, enough examples had been reported to provide indirect but conclusive evidence for the existence and involvement of amino-isocyanates in the aforementioned alkene aminocarbonylation reaction. However, to develop this reactivity further, it became important to highlight the general affinity of amino-isocyanates for activated  $\pi$ -bonds, and their inclination towards self-dimerization. Therefore, it was essential to consider whether amino-isocyanate dimerization could compete with the desired aminocarbonylation reactivity. In establishing these considerations, steps were taken towards development of a second generation aminocarbonylation reagent.

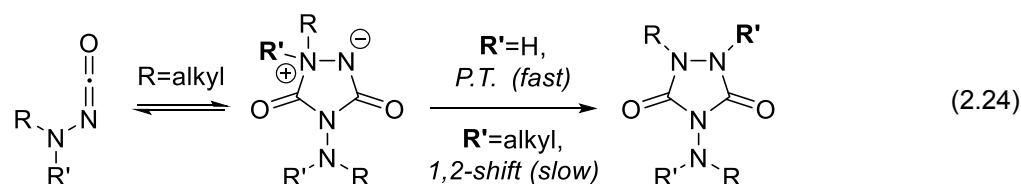
**Scheme 2.14** Summary of the generation and reactivity of amino-isocyanates

## 2.6 Towards an Improved Method for Alkene Aminocarbonylation

With the combined insights gained from DFT calculations (Figure 2.3) and conclusions from prior work done on the generation of amino-isocyanates, two objectives were established towards an improved aminocarbonylation process: First, efforts would be put towards the development of improved substrates under the previously optimized thermolytic conditions. Secondly, these substrates would lead to further optimization of the reaction conditions and possibly, to aminocarbonylation at room temperature.

Because of the possibility for reagent's competing self-dimerization, we rationalized that minimizing this side reaction could be beneficial to aminocarbonylation. In doing so, initial investigation focused on the nature of *N*-alkyl substitution of amino-isocyanates. It was hypothesized that the added steric hindrance of dialkyl amino-isocyanate over mono-alkyl substrates, as previously explored, could slow down dimerization.

Additionally, assessment of Lwowski's work suggests that dimers of *N,N*-dialkyl-amino-isocyanates are capable of undergoing cycloreversion more easily than *N*-monoalkyl-substrates, thus resulting in increased concentration of amino-isocyanate. This makes sense when considering the readiness with which we may assume proton transfer occurs in comparison to 1,2-alkyl shift (equation 2.24).



### 2.6.1 Intramolecular Aminocarbonylation with *N,N*-bis-Alkyl Amino-Isocyanates.

We envisioned the use of *N,N*-dialkyl hydrazides substrates as improved amino-isocyanate precursors. It was argued that, in addition to minimized dimer formation, the added alkyl substituent could make the amine's nitrogen more nucleophilic and thus, result in a more reactive aminocarbonylation reagent. Furthermore, substituting a hydrogen for an alkyl group, zwitterionic aminimide generated from amino-isocyanate cyclization was intended to undergo a 1,2-alkyl-shift. Benzyl substituents were chosen for this purpose, given their ability to undergo a Stevens rearrangement under thermal conditions, comparable to that of our aminocarbonylation process.<sup>47</sup>

Presented in Table 2.5 are comparison between the reactivity of mono-alkyl carbazate (R=H) and that of benzylated dialkenyl carbazates (R=Bn). Under standard aminocarbonylation conditions (200 °C), mono-alkenyl carbazate **1a** provided good yield of the aminocarbonylation product (Table 2.4, entry 1). In turn, preliminary results from benzylated alkenyl carbazate **3a** provided comparable yield for aminocarbonylation as the shifted product (**5a**). While attempting to optimize the conditions for this reactions, substrate **3a** was heated at 150 °C. Analysis of the crude solution revealed the presence of what was identified as a mixture of shifted (**5a**) and unshifted (**4a**) aminocarbonylation products.

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<sup>47</sup> (a) Benecke, H. P.; Wikel, J. H. *Tetrahedron Lett.* **1971**, 3479. (b) Chantrapromma, K.; Ollix, D. W.; Sutherland, I. O. *J. Chem. Soc. Perkin Trans. I* **1983**, 1029. For a review of rearrangements of aminimides, see: McKillip, W. J.; Sedon, E. A.; Culbertson, B. M.; Wawzonek, S. *Chem. Rev.* **1973**, 73, 255.

**Table 2.5** Intramolecular aminocarbonylation of alkenes using alkyl hydrazides <sup>a</sup>

| entry | LG              | R                | temp.<br>(°C)    | product & yield<br>(%)        |                               |
|-------|-----------------|------------------|------------------|-------------------------------|-------------------------------|
|       |                 |                  |                  |                               |                               |
| 1     | O <i>t</i> -Bu  | H ( <b>1a</b> )  | 200              | 0 ( <b>4a</b> )               | 76 ( <b>2a</b> )              |
| 2     | O <i>t</i> -Bu  | Bn ( <b>3a</b> ) | 200              | 0 ( <b>4b</b> )               | 74 ( <b>5a</b> )              |
| 3     | O <i>t</i> -Bu  | Bn ( <b>3a</b> ) | 150 <sup>c</sup> | 49 ( <b>4b</b> ) <sup>b</sup> | 24 ( <b>5a</b> ) <sup>b</sup> |
|       |                 |                  |                  |                               |                               |
| 4     | O <i>t</i> -Bu  | H ( <b>3b</b> )  | 200              | 0 ( <b>4c</b> )               | 0 ( <b>5b</b> )               |
| 5     | NH <sub>2</sub> | H ( <b>3c</b> )  | 200              | 0 ( <b>4c</b> )               | 0 ( <b>5b</b> )               |
| 6     | O <i>t</i> -Bu  | Bn ( <b>3d</b> ) | 200              | 0 ( <b>4d</b> )               | 99 ( <b>5c</b> )              |
| 7     | O <i>t</i> -Bu  | Bn ( <b>3d</b> ) | 150 <sup>c</sup> | 0 ( <b>4d</b> ) <sup>b</sup>  | 66 ( <b>5c</b> ) <sup>b</sup> |

<sup>a</sup> Conditions: Heating performed in PhCF<sub>3</sub> in a sealed tube (0.05 M) using a microwave reactor for 30 mins unless indicated otherwise.<sup>48</sup> <sup>b</sup> NMR yield using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Conditions: Heated for 3 hours.

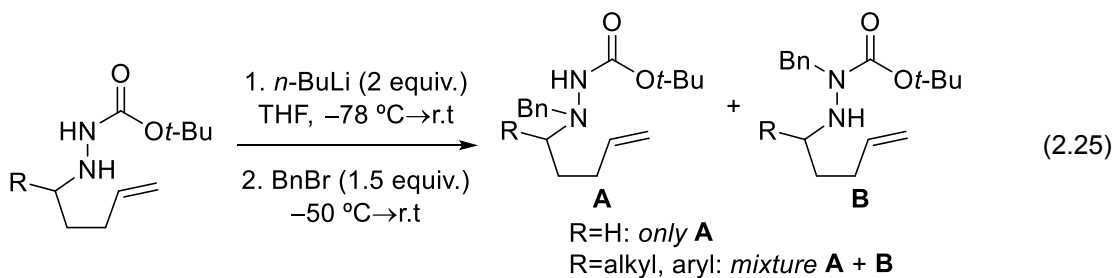
Given these encouraging results, we questioned whether these aminocarbonylation substrates could enable the synthesis of more challenging products. In a prior survey, steps were made towards the synthesis of piperidine ring systems. Unfortunately, mono-

<sup>48</sup> (a) The choice of PhCF<sub>3</sub> as the solvent to conduct this study is based on a previous survey and optimization of alkene aminocarbonylation and hydroamination using hydrazides; see: Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, 131, 8740. (b) For further information on the usefulness of PhCF<sub>3</sub> and other benzotrifluorides as alternative solvents to dichloromethane, see: Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, 62, 450.



alkenyl carbazates and semicarbazides (entry 4 & 5) could not provide the desired piperidine product. In stark contrast, benzylated six-membered ring precursor cyclized in nearly quantitative yield to the desired aminocarbonylation product (entry 6). We also attempted to optimize the reaction conditions and lower the temperature for aminocarbonylation (entry 3 & 7). At 150 °C, five-membered alkenyl precursor **3b** provided a mixture of non-shifted and shifted aminocarbonylation products. In contrast, only the shifted piperidine product was obtained for six-membered ring precursor, with no traces of the unshifted product indicating a more facile 1,2-shift or an energetically higher dipole intermediate.

With anticipation, we decided to further explore the scope of the reaction. Unfortunately, the methodology used for the benzylation of carbazates proved limited (equation 2.25).



Based on the procedure developed by Maeorg and coworkers,<sup>49</sup> carbazates bearing substitution on the alkenyl chain resulted in a mixture of *N*-proximal and *N*-distal alkylation products and poor yields.

Nonetheless, exploration of the reactivity was expanded to new aminocarbonylation substrates. Summarized in Table 2.6 are additional entries. Starting with mono-alkyl carbazates, 2-phenyl pyrrolidine product **5e** could be obtained in good yield as a mixture of diastereomers. Comparably, benzylidene substrate **3f** could provide the corresponding aminocarbonylation (entry 2). Benzylated *cis* and *trans* methyl-alkenyl carbazates (entry 3 & 4) cyclized moderately albeit lower yields than the parent mono-alkenyl substrate (entry 5 & 6, Table 2.4). In these cases, *bis*-alkylation is detrimental to the aminocarbonylation process, which may be due to the added steric hindrance between the benzyl group and alkene substituent. We also expanded the synthesis of six-membered ring substrates to morpholine derivative **5h** (entry 5). Surprisingly, product generation proved optimal at lower temperature (150 °C) and could be obtained in nearly quantitative yield (entry 6).

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<sup>49</sup> (a) Bredihhin, A.; Groth, U. M.; Maeorg, U. *Org. Lett.* **2007**, 9, 1097. (b) Bredihhin, A.; Maeorg, U. *Org. Lett.* **2007**, 9, 4975.

**Table 2.6** Additional scope of intramolecular alkene aminocarbonylation with hydrazides <sup>a</sup>

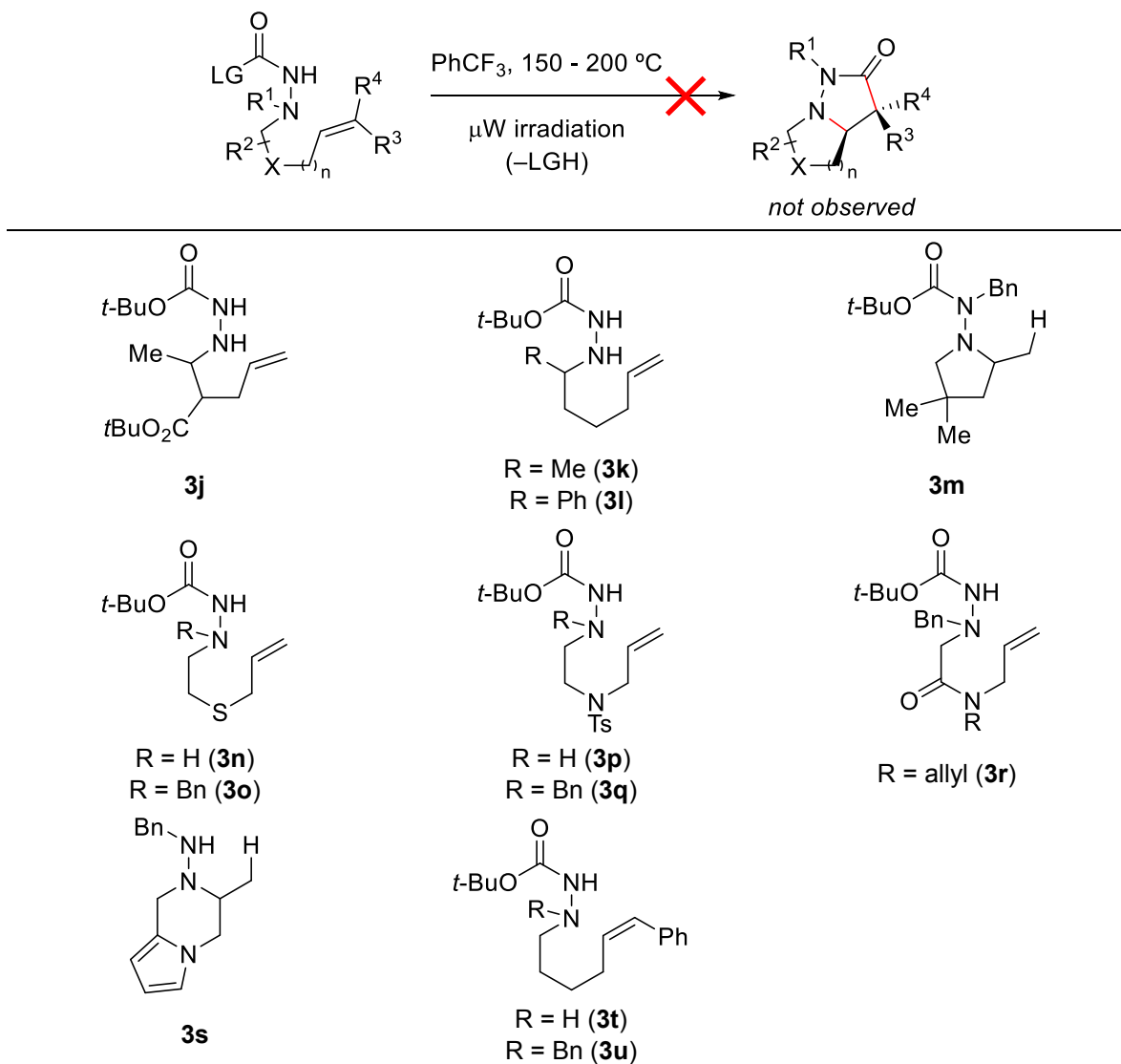
$\text{PhCF}_3, 150 - 200\text{ }^\circ\text{C}$   
 $\mu\text{W irradiation}$   
 $(-\text{LGH})$

| entry | substrate     | temperature (°C) | product       | yield (%)       |
|-------|---------------|------------------|---------------|-----------------|
| 1     | <br><b>3e</b> | 200              | <br><b>5d</b> | 76 <sup>d</sup> |
| 2     | <br><b>3f</b> | 200              | <br><b>5e</b> | 60              |
| 3     | <br><b>3g</b> | 200              | <br><b>5f</b> | 44 <sup>b</sup> |
| 4     | <br><b>3h</b> | 200              | <br><b>5g</b> | 43 <sup>b</sup> |
| 5     | <br><b>3i</b> | 200              | <br><b>5h</b> | 82              |
| 6     | <b>3i</b>     | 150 <sup>c</sup> | <b>5h</b>     | 98              |

<sup>a</sup> Condition: Heating performed in PhCF<sub>3</sub> in a sealed tube (0.05 M) using a microwave reactor for 30 mins unless indicated otherwise. <sup>b</sup> NMR yield using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Heated for 6 hours. <sup>d</sup> Obtained as a mixture of diastereomers (3:2 d.r.).

with Jean-François Vincent-Rocan, Amy Toderian and Ryan Ivanovich

Although *bis*-alkyl substrates provided access to challenging aminocarbonylation reactivity, the method suffers from relatively poor substrate scope. Presented in Table 2.7 are substrates which failed to provide the desired aminocarbonylation reactivity. In some cases, amino-isocyanate dimerization seems to be a significant problem. In other cases such as for substrates **3m** and **3s**, competing hydroamination is preferred over aminocarbonylation. Steric hindrance and conformational restrictions may explain the difficult cyclization associated the reactivity of substrates **3n-r**, however, further investigation would be necessary to obtain conclusive evidence. As it should have been expected from the poor yield obtained with *cis*- and *trans*- substituted alkenyl substrates **3g** and **3h**, the reaction did not sustain cyclization with more challenging aminocarbonylation precursors such as **3u**.

**Table 2.7** Substrates that failed to cyclize under standard aminocarbonylation conditions

<sup>a</sup> Condition: Heated in PhCF<sub>3</sub> in a sealed tube (0.05 M) using a microwave reactor.

with Jean-François Vincent-Rocan, Amy Toderian, Ryan Ivanovich and Nimrat Obhi

### 2.6.2 Towards a Mild Aminocarbonylation with *bis-Alkyl Amino-Isocyanates*

To further our exploration of aminocarbonylation, the search for milder conditions lead us to consider other methods of isocyanate formation. As such, phosgenation of hydrazine was attractive given that many transacylation reagents decompose to isocyanates at room-temperature. Unfortunately, as it is often the case with hydrazine synthesis, nitrogen selectivity can be an issue. However, Boc-deprotection of our newly accessed dialkylated carbazates provided unsymmetrical hydrazines which in turn could be treated with phosgene equivalents. These substrates, in opposition to mono-alkenyl hydrazines, provided the necessary selectivity to allow amino-isocyanate formation under mild conditions. Results from this survey are presented in Table 2.8.

**Table 2.8** Intramolecular aminocarbonylation by transacylation of unsymmetrical *bis*-alkyl hydrazine

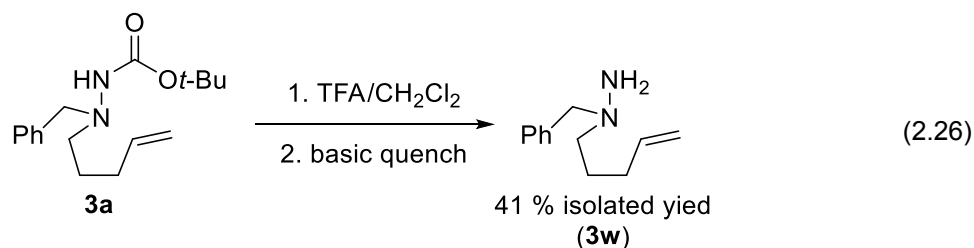
| entry | reagent | time (h) | temp. (°C) | NMR Yield (%) <sup>a</sup> |
|-------|---------|----------|------------|----------------------------|
| 1     |         | 1        | 25         | 32                         |
| 2     |         | 1        | 25         | 0                          |
| 3     |         | 12       | 25         | 81                         |
| 4     |         | 12       | 40         | 62                         |
| 5     |         | 3        | 60         | 16                         |
| 6     |         | 1        | 25         | 93 <sup>b</sup>            |

<sup>a</sup> Determined using 1,3,5-trimethoxybenzene as internal standard. <sup>b</sup> *N,N*-Dimethyl-4-aminopyridine was added as an additive (10 equiv).

As predicted, the resulting amino-isocyanate provided the desired aminocarbonylation reactivity. Aminocarbonylation was obtained in the form of zwitterionic dipole **4b**, as observed in prior study from the thermolysis of *tert*-butyl carbazate **3b** (Table 2.8). Oxalyl chloride provided moderate yield of the desired aminocarbonylation (entry 1) whereas no product could be observed from treatment of *bis*-alkyl hydrazine with *p*-nitrobenzene chloroformate (entry 2). Phosgene equivalent reacted more effectively. Carbonyl diimidazole (CDI) resulted in excellent yield of the product at room temperature (entry 3). Compared to other acylating agents, CDI was slower to decompose. To overcome long reaction time, temperature was increased,

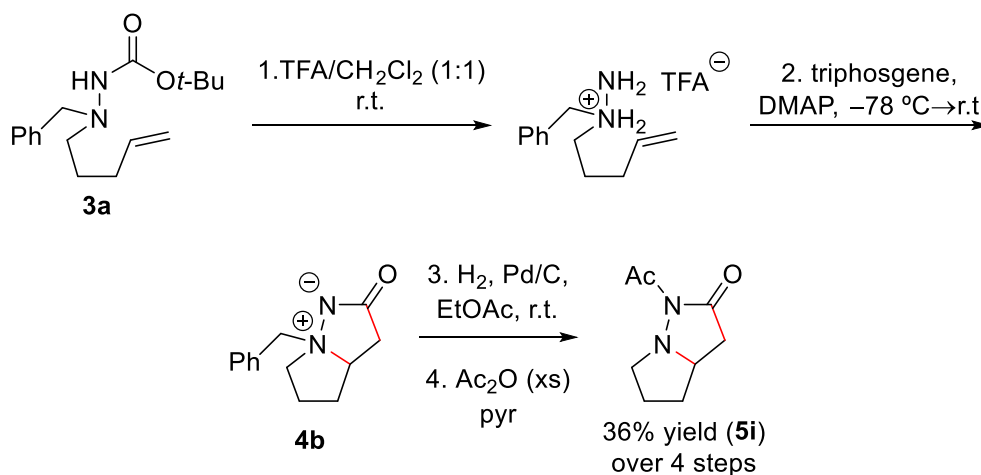
resulting in lower yield (entry 4 & 5). This negative effect could be explained either by a reversible aminocarbonylation reaction or the higher amino-isocyanate concentration that would facilitate the competing dimerization. Triphosgene provided excellent yield of the desired product (entry 6). Excess 4-dimethylaminopyridine was used both as a base, given phosgene's equimolar production of HCl, and as a nucleophilic catalyst to promote the reagent's transacylation.

Unfortunately the method used to obtain the results herein described is generally inconvenient. For one, Boc-deprotection with TFA is difficult to control given the resulting product's ability to undergo side reactions (such as acid catalyzed hydroamination). As seen in equation 2.26, TFA deprotection followed by basic quench of the reaction could only provide moderate yield of the corresponding free hydrazine (**3w**).



Additionally, the resulting dipole product from our aminocarbonylation sequence could not be isolated by standard chromatographic method. Therefore, a new reactive sequence was designed to overcome these issues.



**Scheme 2.15** Synthetic sequence for the intramolecular aminocarbonylation of alkene at room temperature

Treatment of *tert*-butyl carbazate **3b** with TFA followed by reaction with triphosgene provided the desired aminocarbonylation product **4b**. However, given the dipolar nature of the product, benzyl removal was performed using standard hydrogenation conditions. Following *N*-acyl protection provided the desired product (**5h**) in 36 % yield over four steps from the starting Boc-carbazate. These results also provide support to the intramolecular reactivity described in this section. Further optimization of this reactivity should be provided in due course.

### 2.6.3 Summary of Intramolecular Aminocarbonylation with Amino-Isocyanates

The objectives initially established for intramolecular aminocarbonylation of alkenes have been answered. Dialkyl amino-isocyanates have proven more reactive than their mono-alkyl counterparts under termolysis. They have also confirmed the ability of amino-isocyanates to undergo aminocarbonylation under mild conditions. With the

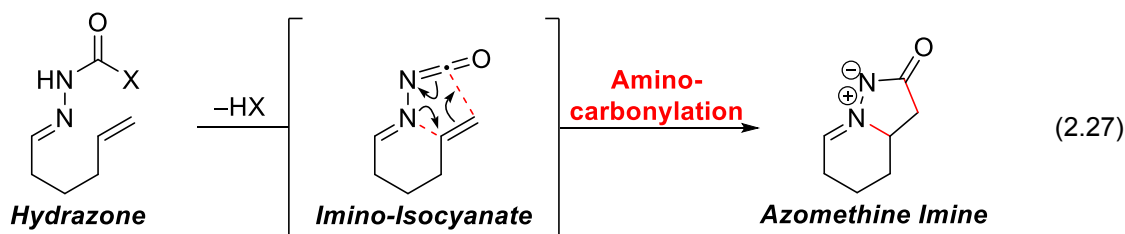
investigation, development of an effective synthesis of piperidine-rings by alkene aminocarbonylation is a significant achievement. Hence, we have demonstrated that amino-isocyanate can be useful tools for the synthesis of nitrogen heterocycles.

However, multiple factors are detrimental to the development of aminocarbonylation. For one, amino-isocyanates' self-dimerization is still problematic. Synthesis of *bis*-alkyl amino-isocyanates is also difficult, poor yielding and limited to Boc-protected hydrazines and despite much effort, the scope of this intramolecular reaction is still very narrow. Therefore, development of new and improved aminocarbonylation conditions and formation of amino-isocyanates under catalytic conditions is important and currently ongoing. Additionally, insights gained from the reaction performed at room temperature are encouraging and should provide an excellent starting point for future investigations.

## 2.7 Development of New Reagents for Alkene Aminocarbonylation

Following our investigation of the intramolecular reactivity of amino-isocyanates, we became interested in exploring the reactivity of other aminocarbonylation reagents. For one, we hypothesized that hydrazones, as synthetic precursors to hydrazides, had the propensity, under thermolysis, to generate new *N*-substituted isocyanates under the form of imino-isocyanates (equation 2.27).

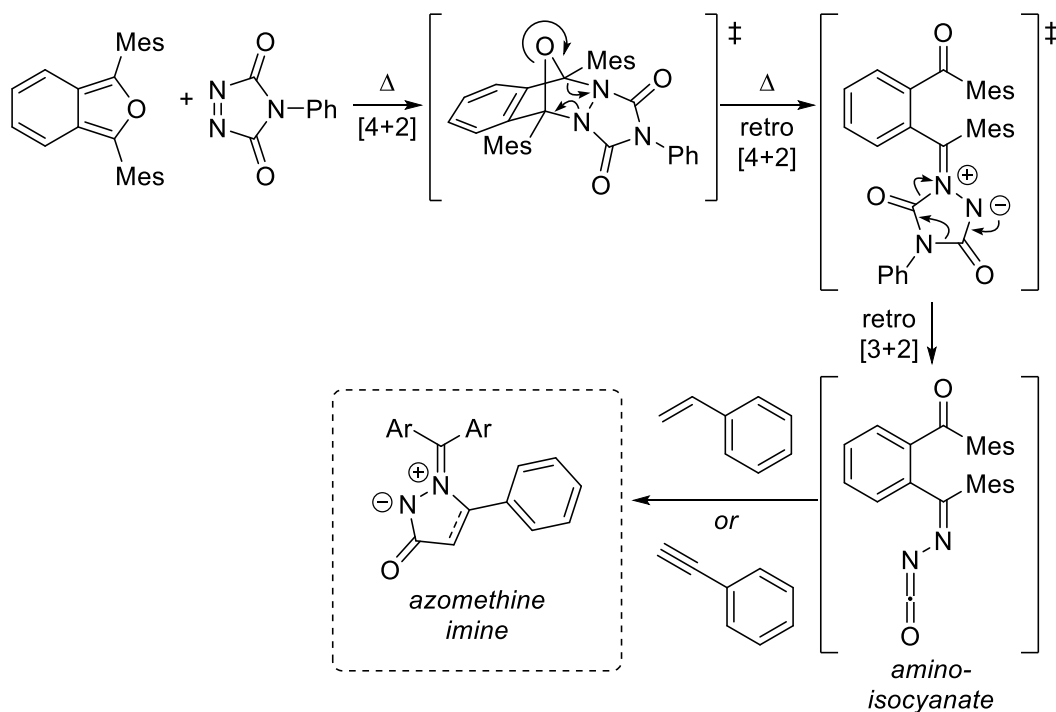
As discussed in previous section, the mechanism for aminocarbonylation with amino-isocyanates likely involves a [3+2] cycloaddition with the  $\pi$ -bond of the alkene and the generation of a hydrazinium ylide intermediate. When applying the same mechanism, but this time with a  $sp^2$  hybridized nitrogen reagent, this aminocarbonylation reaction was thought to result in the generation of a  $\beta$ -aminocarbonyl motif under the form of an azomethine-imine product (equation 2.27).



As previously mentioned, azomethine imines are well-known dipolar adducts (see section 1.2.6.1). Therefore, it was thought that such reaction would provide a useful methodology to the synthesis of  $\beta$ -aminocarbonyls and complex azomethine imines. Hence we asked whether imino-isocyanates had previously been encountered in the scientific literature. In 1982, Jones and coworkers claim the observation of an imino-

isocyanate generated in-situ by a cascade cycloaddition/retro-cycloaddition reaction.<sup>50</sup> Interestingly, Jones reacted the ensuing imino-isocyanate intermediate using phenyl acetylene and styrene (Scheme 2.16), in a similar fashion as the herein described aminocarbonylation process.

**Scheme 2.16** Comparison of potential aminocarbonylation reactivity of imino-isocyanates and amino-isocyanates



While the efficiency of this approach and the likelihood of generating imino-isocyanates upon thermolysis of simple hydrazone precursors remained to be

<sup>50</sup> (a) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1982**, 766. For reviews, see: (b) Reichen, W. *Chem. Rev.* **1978**, 78, 569. (c) Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem.* **2011**, 15, 1745.

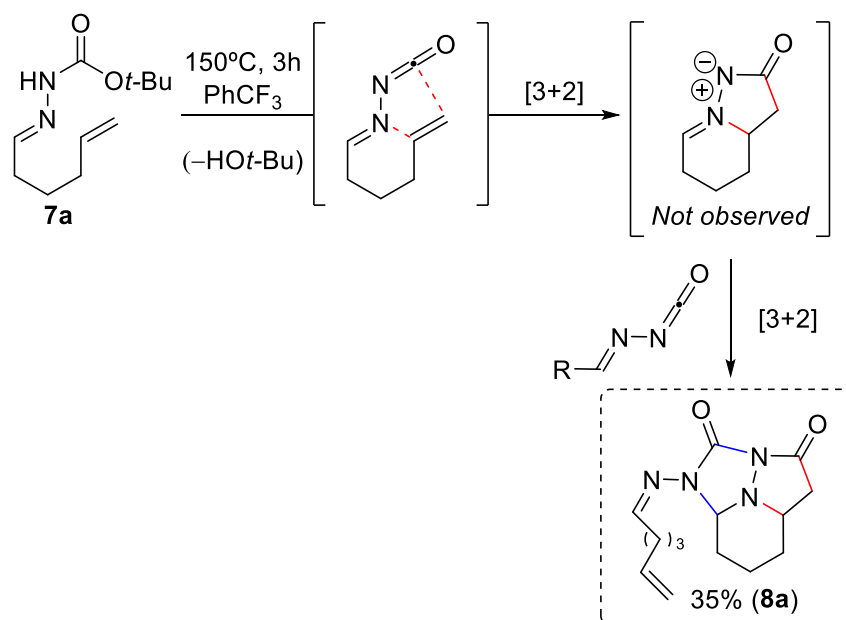
demonstrated, results from Jones provided the necessary support for our aminocarbonylation hypothesis and encouraged further exploration of this system.

## 2.8 Intramolecular Aminocarbonylation with Imino-Isocyanates

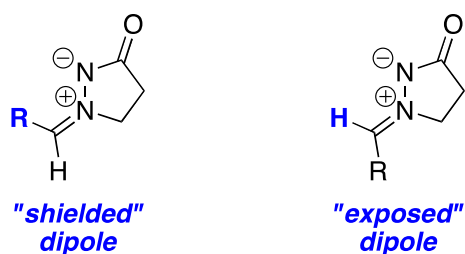
### 2.8.1 Preliminary Investigation

Initially in our investigation, attempt was made at designing the simplest testable system for the postulated imino-isocyanate hypothesis. Contrary to amino-isocyanates, molecular modeling analysis revealed generation of six-membered ring products to be more favorable than five-membered given the ring-strain associated with the latter azomethine imine cycle. Additionally, based on our previous study of amino-isocyanates, *tert*-butyl carbamoyl hydrazone was chosen as the isocyanate precursor. From this, aldohydrazone **7a** was subjected to microwave irradiation under matching set of conditions to previously optimized aminocarbonylation reactions.

Presented in Scheme 2.17, the desired azomethine imine product was not observed. However, we found strong indication of its existence following isolation and identification of tricyclic product **8a** from the crude mixture. From our analysis, we concluded the resulting compound to most logically derive from formation of the desired intramolecular azomethine imine which then underwent a dipolar cycloaddition reaction with the most reactive  $\pi$ -bond present, a second imino-isocyanate moiety. While these results remained preliminary, it provided support to our early assumptions that (1) carbamoyl hydrazones can act as precursors of imino-isocyanates and (2) imino-isocyanates, as amino-isocyanates do, may act as reagents for the aminocarbonylation of alkenes.

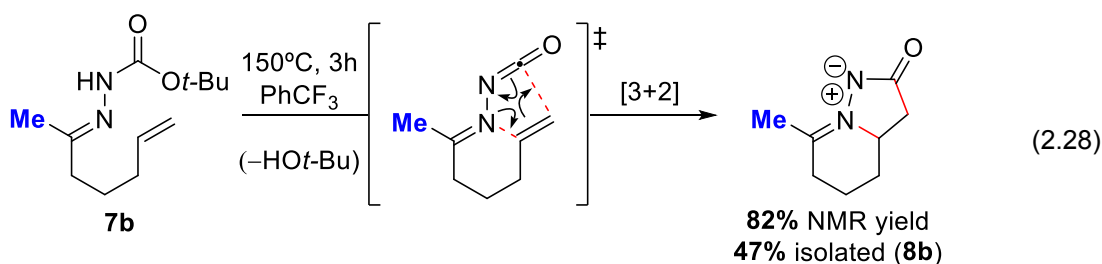
**Scheme 2.17** Preliminary intramolecular reactivity of aldehydrazone

Generation of product **8a** leads to the conclusion that the desired azomethine imine dipole, derived from aldehydrazones, is highly reactive. Hence, we attributed the limited yields of the present experiment to the relative instability of the desired azomethine imine.

**Figure 2.5** Isomers of azomethine imine dipoles

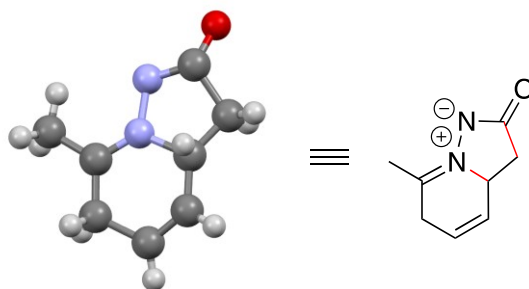
We thus pursued a strategy that would permit control of the reactive outcome by stabilizing the resulting azomethine imine. Survey of previously reported aldehyde derived azomethine imines discloses the predisposition of such dipoles, as presented in figure 2.4, to favor “shielded” isomers in opposition to the “exposed” forms. To the best of our analysis, two reasons for this may be put forward. First, presence of unfavorable 1,4 steric interactions between the alkyl group of the keto moiety with the pyrazolidinone promotes isomerization to the shielded product. Secondly, steric shielding from iminium’s alkyl or aryl substituent limits exposure of the dipole moiety.

In the present intramolecular system, rotational restrictions imposed by the bicyclic structure of the azomethine imine product may only result in the azomethine imine shown. Therefore, to ensure proper shielding of the azomethine imine, we proposed the use of a ketohydrazones as dipole precursor to aminocarbonylation. As such, we synthesized methyl ketohydrazone **7b** and subjected it to our standard aminocarbonylation conditions (equation 2.29).



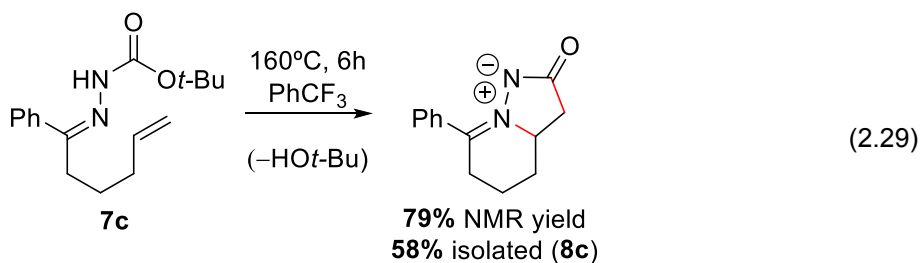
To our delight, the strategy was successful. Azomethine imine product **8b** was obtained in good yield and proved stable enough to be purified by column chromatography. In addition, the product is solid and could be subjected to recrystallization. As presented in Figure 2.6, this allowed X-ray crystallographic analysis

which provided conclusive support for our proposed aminocarbonylation reactivity with imino-isocyanates.



**Figure 2.6** X-ray analysis of intramolecular aminocarbonylation product **8b**

However, confusion remains regarding the exact structure obtained for product **8b**. Strangely, C4 and C5 positions were identified as  $sp^2$  hybridized. While other characterization data strongly confirms the proposed structure as correct (see S.I.), it is believed that the structural discrepancy between the X-ray analysis and the proposed compound is attributable to the poor quality of the crystal sample. Nonetheless, the azomethine imine moiety is clearly observed and demonstrates the ability of imino-isocyanate to undergo aminocarbonylation with alkenes and generate  $\beta$ -aminocarbonyl compounds.

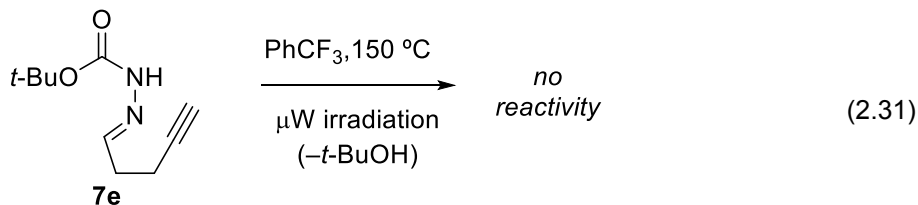
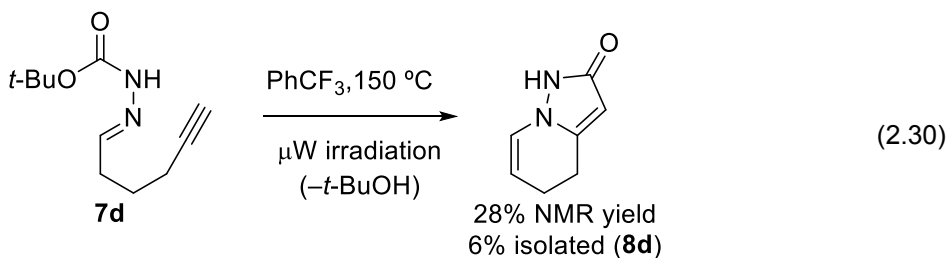




Another attempt at exploring this reactivity was made by Mrs. Nimrat Obhi with her synthesis of phenyl-ketohydrazone **7c** (equation 2.29), for which the corresponding aminocarbonylation product **8c** was obtained in comparable yield to that of methyl ketohydrazone substrate **7b** (equation 2.28), although slightly higher temperature and longer reaction time were required.

### 2.8.2 Intramolecular Aminocarbonylation of Alkynes

During the course of our exploration of imino-isocyanates, the intramolecular aminocarbonylation of alkynes was also considered. As such, Mrs. Amy Toderian subjected alkynyl aldohydrazone **7d** to standard aminocarbonylation conditions (equation 2.30). However, the crude mixture did not show presence of an azomethine imine product but instead, compound **8d** was obtained in moderate yield. It is suggested that **8d** results from the tautomerization of an azomethine imine intermediate, driven by the aromatic character of the resulting pyrazolone product.



Further attempts were made to expand the scope of this reactivity to five-membered rings (equation 2.31). Unfortunately, substrate **7e** failed to provide the desired

aminocarbonylation reactivity. It is suggested that presence of imine within the cyclic core of the desired product is too strained and high in energy transition state.

### 2.8.3 Summary of Intramolecular Aminocarbonylation with Imino-Isocyanates

Conditions for aminocarbonylation with carbamoyl hydrazones are comparable to that of *bis*-alkyl carbazates (section 2.5.1). As previously discussed, the synthesis of six-membered cycles are knowingly difficult. Amino-isocyanates have proven not only limited in reactivity but precursors have been difficult to synthesize. Comparably, use of ketone derived imino-isocyanates has allowed generation of six-membered rings which can easily be converted to piperidines by subsequent reduction.

As previously shown, intramolecular aminocarbonylation with amino-isocyanates had failed to generate 2-substituted piperidines. Therefore, the reactivity herein described is the first to allow such substitution. Combined with the relative easiness with which ketohydrazones can be synthesized, these substrates provide much advantage over previously described aminocarbonylation methods. Therefore, it is felt that imino-isocyanates are important reagents for alkene aminocarbonylation and provide useful methods for the synthesis  $\beta$ -proline analogs. As such, it is believed that this reactivity deserves further attention and developments that should be reported in due course.

## 2.9 Conclusions and Perspectives on the Intramolecular Aminocarbonylation of Alkenes

The developments of aminocarbonylation reagents discussed herein are significant as they provide improved alternatives to palladium-catalyzed methodologies and a solution to some limitations of previously reported examples. However, the implications of this reactivity are arguably much broader than initially anticipated. For one, the fact that amino- and imino-isocyanates have rarely been observed and even less so utilized suggests that much exploration remains to be done to fully grasp the synthetic potential of these reagents. Although the synthesis of  $\beta$ -aminocarbonyl compounds is a desirable achievement, amino- and imino-isocyanates should also be recognized for their ability to introduce N-N functionalities to molecular structures and to generate polycyclic ring systems. Therefore, efforts are currently underway to find improved conditions for intramolecular aminocarbonylation and gain additional insights into the reactivity of amino- and imino-isocyanates. However, with the insights gained from intramolecular aminocarbonylation, a greater challenge was undertaken as we started our exploration of intermolecular aminocarbonylation.

# Chapter

# 3

## Intermolecular Aminocarbonylation of Alkenes

### 3.1 Introduction

In Chapter 2, we have demonstrated the utility of aminocarbonylation for the generation of nitrogen heterocycles. Two synthetic tools were put forward, relying on amino- and imino-isocyanates. However, the scope of alkene aminocarbonylation has until now been limited to intramolecular substrates, and thus, for the synthesis of  $\beta$ -homo-proline derivatives. Although the importance of such motifs to the development of  $\beta$ -peptides cannot be overstated,  $\beta$ -amino acids are much more diverse. Therefore, a general method to convert cheap and widely available alkenes into  $\beta$ -aminocarbonyls would represent a powerful synthetic strategy for the synthesis of  $\beta$ -amino acids. Hence, the underlying objective of our investigation has been the development of effective methods for intermolecular alkene aminocarbonylation. During the course of this chapter, we will discuss efforts made towards this goal. However, in continuation with our

discussion, precedents of intermolecular alkene aminocarbonylation must be briefly summarized.

### 3.1.1 $\beta$ -Lactam Synthesis from Alkene Aminocarbonylation with CSI

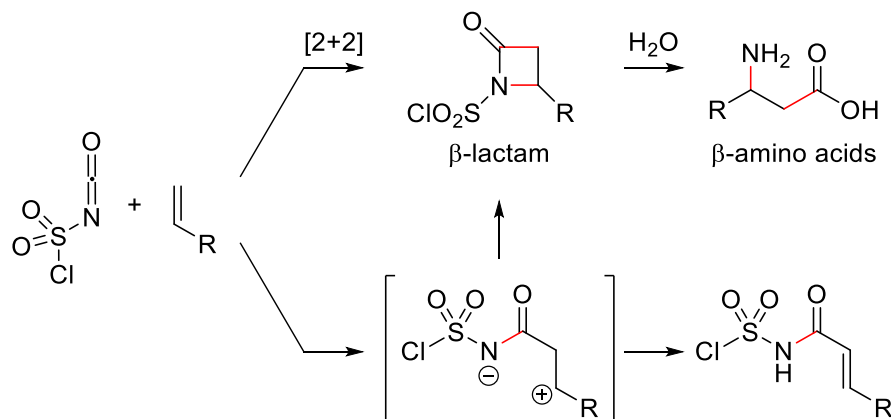
The synthesis of  $\beta$ -lactams by the [2+2] cycloaddition between alkenes and isocyanates has been known for quite some time.<sup>1</sup> Amongst the studied reagents, chlorosulfonyl isocyanate (CSI) has proved to be most useful and is today one of the only reagents utilized for intermolecular aminocarbonylation of alkenes.<sup>2</sup> Concerted and non-concerted mechanisms have been suggested to account for this transformation (Scheme 3.1).<sup>3</sup>

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<sup>1</sup> (a) Graf, R. *Chem. Ber.* **1956**, 89, 1071. (b) Graf, R. *Liebigs Ann. Chem.* **1963**, 661, 111. (c) Moriconi, E. J.; Kelly, J. F. *Tetrahedron Lett.* **1968**, 1463. (d) Moriconi, E. J.; Crawford, W. D. *J. Org. Chem.* **1968**, 33, 370. (e) Barrett, A. G. M.; Betts, M. J.; Fenwick, A.; *J. Org. Chem.* **1966**, 31, 1372. (f) Rasmussen, J. R.; Hassner, A. *Chem. Rev.* **1976**, 76, 389. (a) Barrett, A. B. M.; Fenwick, A.; Betts, M. J. *J. Chem. Soc., Chem. Commun.* **1983**, 300. (b) Chan, J. H.; Hall, S. S. *J. Org. Chem.* **1984**, 49, 15. (c) Barrett, A. G. M. *J. Org. Chem.* **1985**, 50, 169.

<sup>2</sup> For reviews on the reactivity of CSI, see: Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, 76, 389. (b) Graf, R. *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 172. (c) Szabo, W. A. *Aldrichim. Acta* **1977**, 10, 116. (d) Dhar, D. N.; Keshava Murthy, K. S. *Synthesis* **1986**, 473.

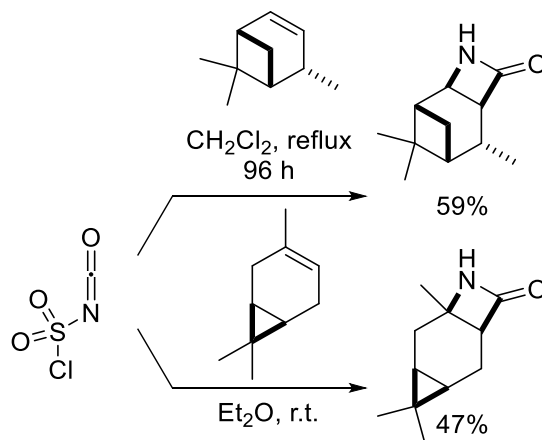
<sup>3</sup> (a) Moriconi, E. J.; Meyer, W. C. *J. Org. Chem.* **1971**, 36, 2841. (b) Cossio, F. P.; Lecea, B.; Lopez, X.; Roa, G.; Arrieta, A.; Ugalde, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1450. (c) Furman, B.; Borsuk, K.; Kaluza, Z.; Lysek, R.; Chmielewski, M. *Curr. Org. Chem.* **2004**, 8, 463.

**Scheme 3.1** Reactivity of chlorosulfonyl isocyanate and alkenes

However, the reaction between CSI and alkenes often results in the formation of unsaturated amide by-products. Additionally, because of its highly reactive nature, CSI has poor functional group tolerance, thus often negatively affecting the scope of the reaction.

The synthesis of  $\beta$ -lactams from the treatment of alkenes with CSI is generally most effective with strained and/or electron-rich conjugated alkenes. Recently the synthesis of monoterpene-based chiral  $\beta$ -lactams has been reported (Scheme 3.2). The resulting products could subsequently be converted to  $\beta$ -amino acids.<sup>4</sup>

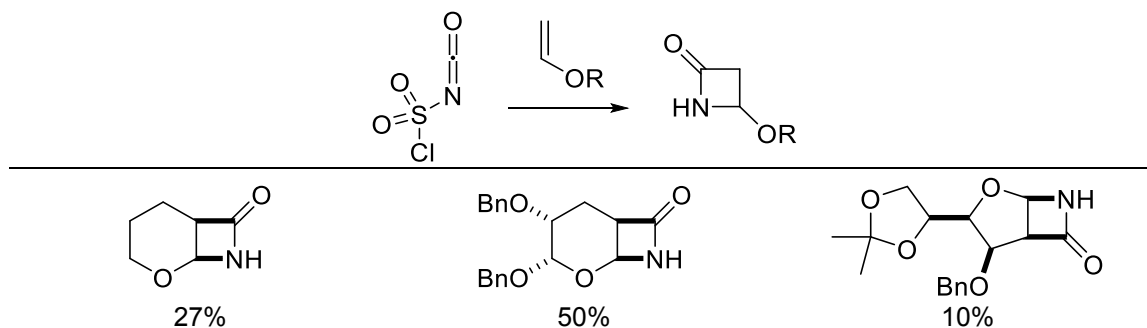
<sup>4</sup> Szakonyi, Z.; Fülöp, F. *Amino Acids* **2011**, 41, 597.

**Scheme 3.2** Synthesis of monoterpene-based  $\beta$ -lactams using CSI

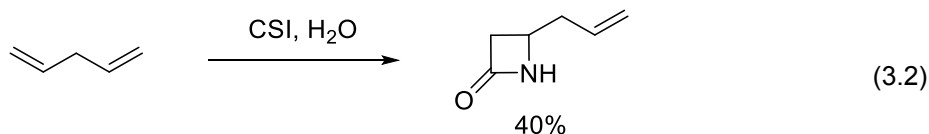
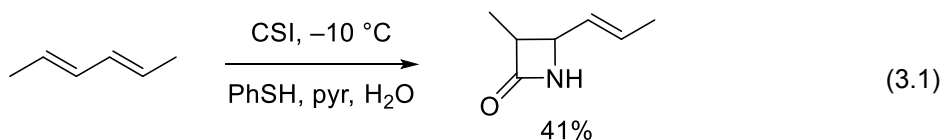
Additionally, vinyl ethers have proved generally versatile reagents for the synthesis of  $\beta$ -lactams. In Table 3.1, selected examples of glucals and other saccharide-derived vinyl ethers are presented.<sup>5</sup> Interestingly, the [2+2] cycloaddition reactivity of CSI could not be performed with less reactive *N*-substituted isocyanates: The authors report that *N*-trichloroacetyl and *N*-tosyl isocyanate displayed comparably no reactivity towards the alkene substrates. It must be also noted, that cycloadducts are generally isolated in moderate yields and that significant amounts of unsaturated amide by-products are produced.<sup>6</sup>

<sup>5</sup> Kaluza, Z.; Abramski, W.; Belzecki, C.; Grodner, J.; Mostowicz, D.; Urbanski, R.; Chmielewski, M. *Synlett* **1994**, 539.

<sup>6</sup> For other examples of reactions of vinyl ethers with CSI, see: (a) Chitwood, J. L.; Gott, G. P.; Martin, J. C. *J. Org. Chem.* **1971**, *36*, 2228. (b) Hall, R. H.; Jordann, A.; Lourens, G. J. *J. Chem. Soc. Perkin I* **1973**, 38. (c) Hall, R. H.; Jordann, A.; de Villiers, O. G. *J. Chem. Soc. Perkin I* **1975**, 626. (d) Furman, B.; Borsuk, K.; Kaluza, Z.; Lysek, R.; Chmielewski, M. *Curr. Org. Chem.* **2004**, *8*, 463.

**Table 3.1** CSI reactivity with selected vinyl ethers

The reactivity has also proved amenable to other electron-rich conjugated alkenes: Treatment of 1,3-dienes with CSI followed by hydrolysis has led to the generation of 2-azetidinones (equation 3.1).<sup>3a,7</sup> In addition, 1,4-dienes could also react and be converted to  $\beta$ -lactams (equation 3.2).<sup>8</sup>



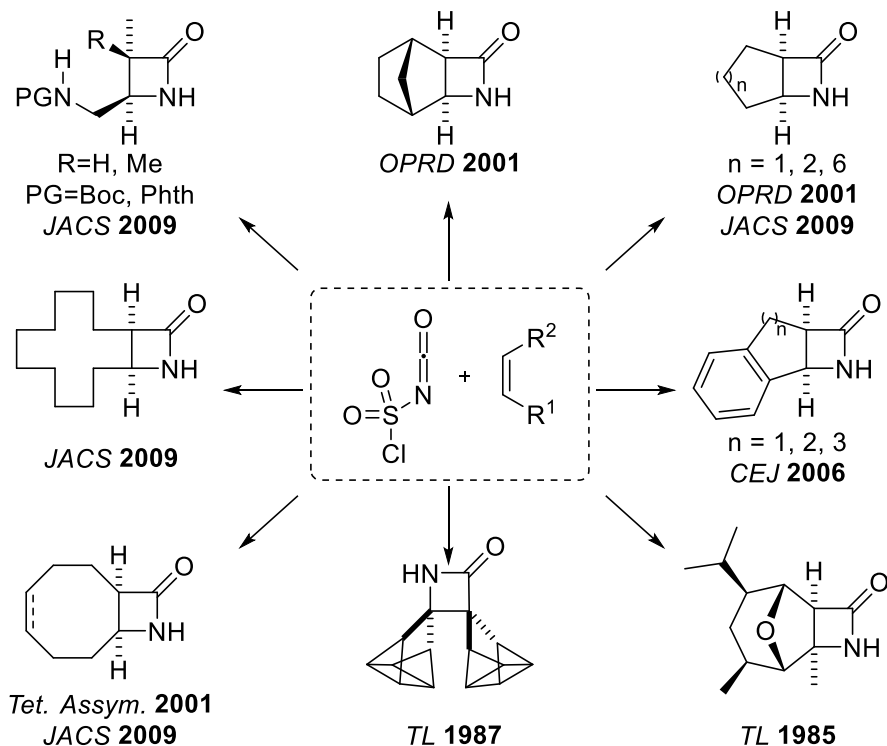
Furthermore, as presented in Figure 3.1, CSI has been used for the conversion of various olefins to  $\beta$ -lactams,<sup>9</sup> and in particular has proven useful to the synthesis of cispentacin derivatives from the treatment of cyclic alkenes (see Figure 1.10).<sup>9c,g</sup>

<sup>7</sup> For additional examples of the reactivity of CSI with conjugated 1,3-dienes, see: (a) Goebel, P.; Clauß, K. *Justus Liebigs Ann. Chem.* **1969**, 36, 2841. (b) Malpass, J. R.; Twedde, N. J. *J. Chem. Soc., Chem. Commun.* **1972**, 1247.

<sup>8</sup> Baxter, A. J. G.; Kickinson, K. H. *J. Chem. Soc., Chem. Commun.* **1979**, 236.

<sup>9</sup> (a) Mann, J.; Overton, H. J. *Tetrahedron Lett.* **1985**, 26, 6133. (b) Trah, S.; Weidmann, K.; Fritz, H.; Prinzbach, H. *Tetrahedron Lett.* **1987**, 28, 4399. (c) Dener, J. M.; Fantauzzi, P. P.; Kshirsagar,





**Figure 3.1** Alkene scope of reported  $\beta$ -lactam syntheses using CSI <sup>9</sup>

### 3.1.2 Perspectives on the Synthetic Utility of CSI

As presented, CSI has been widely utilized for the synthesis of  $\beta$ -lactams: Its ability to provide rapid access to  $\beta$ -amino acids from alkenes makes it a useful reagent. However, CSI's lack of practicality, poor functional group tolerance and unpredictable reactive outcome calls for the development of new reagents. The discussion provided in this section has been intended to shed light on some of the limitations of CSI with regards to alkene aminocarbonylation. Much development remains to be achieved for a truly

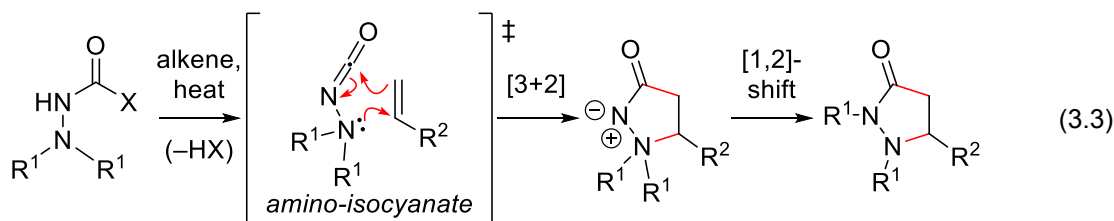
T. A.; Kelly, D. E.; Wolfe, A. B. *Org. Process Res. Dev.* **2001**, 5, 445. (d) Gyarmati, Z. C.; Liljeblad, A.; Argay, G.; Kalman, A.; Bernath, G.; Kanerva, L. T. *Adv. Synth. Catal.* **2004**, 346, 566. (e) Fulop, F.; Foro, E.; Toth, G. K. *Org. Lett.* **2004**, 6, 4239. (f) Bakshi, R. K.; Hong, Q.; Olson, J. T.; Ye, Z.; Sebat, I. K.; Weinberg, D. H.; MacNeil, T.; Kalyani, R. N.; Tang, R.; Martin, W. J.; Strack, A.; McGowan, E.; Tamvakopoulos, C.; Miller, R. R.; Stearns, R. A.; Tang, W.; MacIntyre, D. E.; van der Ploeg, L. H. T.; Patchett, A. A.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2005**, 15, 3430. (g) Forro, E.; Fulop, F. *Chem. Eur. J.* **2006**, 12, 2587. (h) Zhang, J.; Kissounko, D. A.; Lee, S. E.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, 131, 1589.

versatile intermolecular reaction to be unveiled. In the next section we will propose an alternative to CSI.

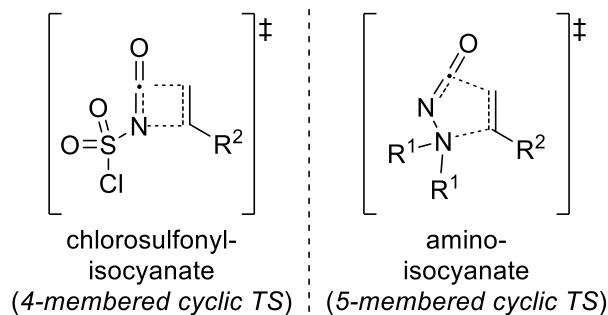
## 3.2 Intermolecular Aminocarbonylation with Amino-isocyanates

### 3.2.1 Comparing the Reactivity of Amino-Isocyanates and CSI

Our efforts towards intermolecular aminocarbonylation focused initially on the reactivity of amino-isocyanates. Proposed were conditions for the thermolysis of *bis*-alkyl carbazates in the presence of alkenes, as described for intramolecular aminocarbonylation. As represented in equation 3.3, the mechanistic sequence envisioned for the reaction involves an intermolecular 3+2 cycloaddition of amino-isocyanate and alkene.



Obvious links may be drawn between CSI and amino-isocyanates: Both are bifunctional reagents for which the carbonylative moieties are an isocyanate. But important differences also arise when considering the reagent's ability to perform cycloadditions with alkenes (Figure 3.2).



**Figure 3.2** Transition state comparison between CSI and amino-isocyanates for the aminocarbonylation of alkenes

The outcomes of the reactivity of CSI, whether dictated by a concerted or stepwise mechanism, appears to be limited by high energy barriers that would be expected from the advent of a four-membered cyclic transition state. In contrast, the aminating moiety of amino-isocyanate is one atom further away from the carbonyl center. Arguably, the resulting five-membered transition state could allow for a more favorable concerted addition, and as such, could be expected to provide more control over the reactivity compared to CSI. Therefore, we were able to contrast the advantages offered by amino-isocyanates. As such, amino-isocyanates appeared as likely reagents for the development of intermolecular aminocarbonylation.

### 3.2.2 Intermolecular Aminocarbonylation of Alkenes Using Carbazates

As an entry point into intermolecular aminocarbonylation, we subjected *bis*-benzyl carbazate **1a** (Table 3.2) to previously optimized conditions for intramolecular aminocarbonylation. Thankfully, at 150 °C (entry 1), the amino-isocyanate reacted with norbornene with the envisioned aminocarbonylation reactivity, despite moderate yield. Longer reaction time and higher temperature each resulted in improved yield.

**Table 3.2** Optimization of intermolecular aminocarbonylation with norbornene <sup>a</sup>

| entry | temperature (°C) | time | yield (%) <sup>b</sup> |
|-------|------------------|------|------------------------|
| 1     | 150              | 6    | 28                     |
| 2     | 150              | 18   | 55                     |
| 3     | 180              | 6    | 43                     |

<sup>a</sup> Conditions: Entries are made on a 70 – 80 mg scale of hydrazide. The reactions were run under microwave irradiation with the hydrazide dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.05 M), for the specified time and temperature. <sup>b</sup> NMR yield taken with 1,4-dimethoxybenzene as an internal standard.

The search for a widely applicable aminocarbonylation reagent thus required alkene screening with the *bis-N,N*-benzyl amino-isocyanate precursor. Unfortunately, only norbornene has provided the desired reactivity. Presented in Table 3.3 are olefins that did not undergo aminocarbonylation.

**Table 3.3** Screened alkenes for the intermolecular aminocarbonylation with amino-isocyanates that failed to provide the desired reactivity <sup>a</sup>

|  |  |  |  |
|--|--|--|--|
|  |  |  |  |
|  |  |  |  |

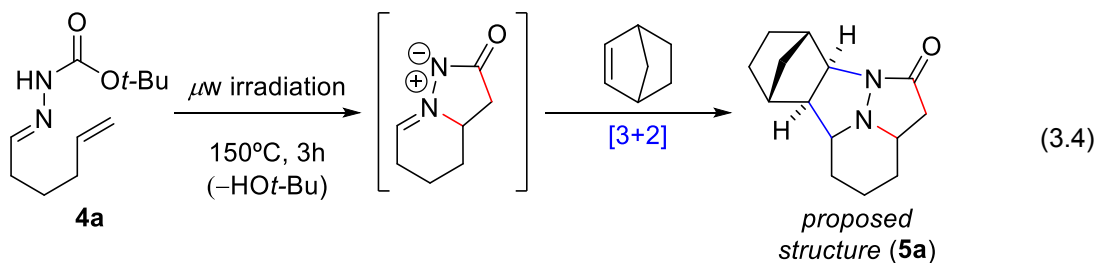
<sup>a</sup> Conditions: Entries are made on a 70 – 80 mg scale of hydrazide. The reactions were run under  $\mu W$  irradiation with hydrazide dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.05 M) for three hours.

Although the sample reactivity thus far provided is rather small, additional scope of amino-isocyanate precursors would be necessary to provide a thorough overview of the present reactivity. It is also possible that milder conditions, such as those provided for intramolecular aminocarbonylation using hydrazine transacylation at room temperature may result in control over dimerization and improved conditions. Therefore, discussion of such work will be left to future research efforts, as we must move on with our discussion of intermolecular aminocarbonylation.

### 3.3 Intermolecular Aminocarbonylation of Alkenes with Imino-Isocyanates

#### 3.3.1 Preliminary Results

In continuation with our preliminary results obtained with aldehydrazones on the intramolecular aminocarbonylation of alkenes with imino-isocyanates and the results reported by Jones and coworkers,<sup>10</sup> we put forward the possibility of exploiting the reactive nature of azomethine imines towards dipolar cycloadditions. We explored the possibility of trapping the postulated aldehyde derived azomethine imine with alkenes (equation 3.4).

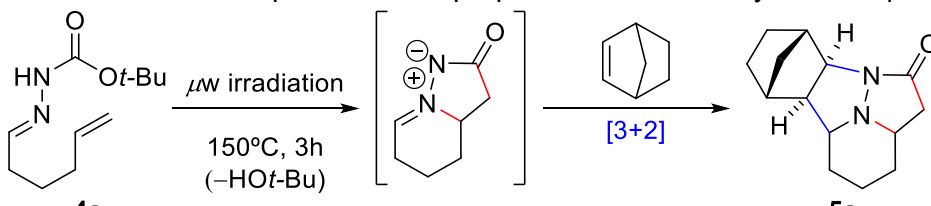


For this purpose, norbornene was chosen as the dipolarophile. Gratifyingly, from our initial result (Table 3.4, entry 1) a 68% NMR yield of what was proposed as the

<sup>10</sup> Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1982**, 766.

desired aminocarbonylation product **5a** was obtained. Surprisingly, shorter reaction time resulted in a higher yield (entry 2). Unfortunately, yields proved difficult to improve beyond these results (entry 3-7) despite the fact that reactivity could be observed at temperatures as low as 100 °C with significantly longer reaction time (entry 8).

**Table 3.4** Conditions optimization of proposed aminocarbonylation sequence



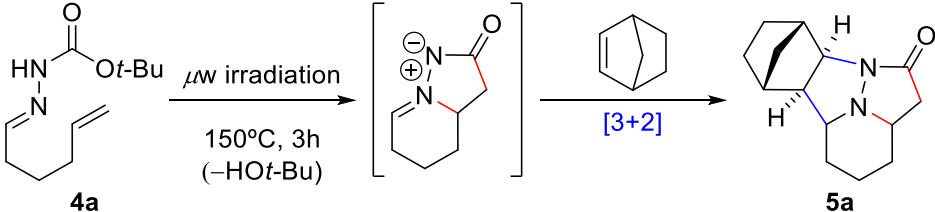
| entry <sup>a</sup> | temperature (°C) | time (h) | yield (%) <sup>b</sup> |
|--------------------|------------------|----------|------------------------|
| 1                  | 150              | 10       | 68                     |
| 2                  | 150              | 3        | 76                     |
| 3                  | 145              | 15       | 64                     |
| 4                  | 135              | 15       | 67                     |
| 5                  | 135              | 10       | 69                     |
| 6                  | 135              | 5        | 66                     |
| 7                  | 120              | 15       | 55                     |
| 8                  | 100              | 24       | 11                     |

<sup>a</sup> Entries are made on a 40 – 60 mg scale. The reactions were run in the  $\mu w$  with the hydrazone dissolved in  $\alpha, \alpha, \alpha$ -trifluorotoluene, for the specified time and temperature, at 0.05 M. <sup>b</sup> NMR yield taken with 0.5 equiv of dimethoxybenzene as an internal standard.

We further attempted to optimize the conditions by surveying solvents (Table 3.5). Initially chosen trifluorotoluene provided the best yields (entry 1) while other aromatic solvents such as chlorobenzene and toluene gave comparable results (entry 2-3). Polar aprotic solvents, acetonitrile and tetrahydrofuran, could only provide moderate yields (entry 4 & 5). We also tried a pyridine/trifluorotoluene mixture as a solvent and concluded it was detrimental to the reactivity. In turn, *tert*-butanol did not allow observation of any of the desired product, probably due to its interference with the imino-isocyanate generation, reverting the reaction to the hydrazone. While we were unable to improve upon the results of our initial reaction conditions, we could not account for the

loss of mass observed under our optimized conditions (76% NMR yield) even though full conversion of the starting material was being observed.

**Table 3.5** Solvent optimization of proposed aminocarbonylation sequence



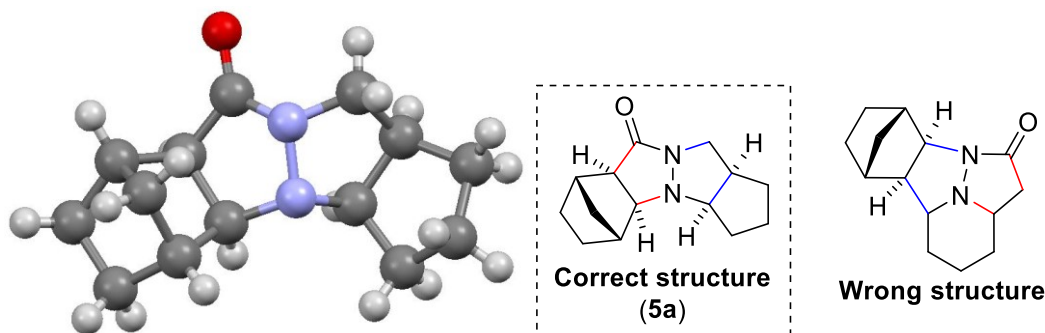
| entry <sup>a</sup> | solvent                      | yield (%) <sup>b</sup> |
|--------------------|------------------------------|------------------------|
| 1                  | PhCF <sub>3</sub>            | 76                     |
| 2                  | PhCl                         | 73                     |
| 3                  | Toluene                      | 62                     |
| 4                  | MeCN                         | 46                     |
| 5                  | THF                          | 40                     |
| 6                  | PhCF <sub>3</sub> :Pyr (1:1) | 28                     |
| 7                  | Pyridine                     | 5                      |
| 8                  | <i>t</i> -BuOH               | 0                      |

<sup>a</sup> Entries are made on a 40 – 60 mg scale. The reactions were run in the  $\mu$ w with the hydrazone dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene, for the specified time and temperature, at 0.05 M. <sup>b</sup> NMR yield taken with 0.5 equiv. of 1,4-dimethoxybenzene as an internal standard.

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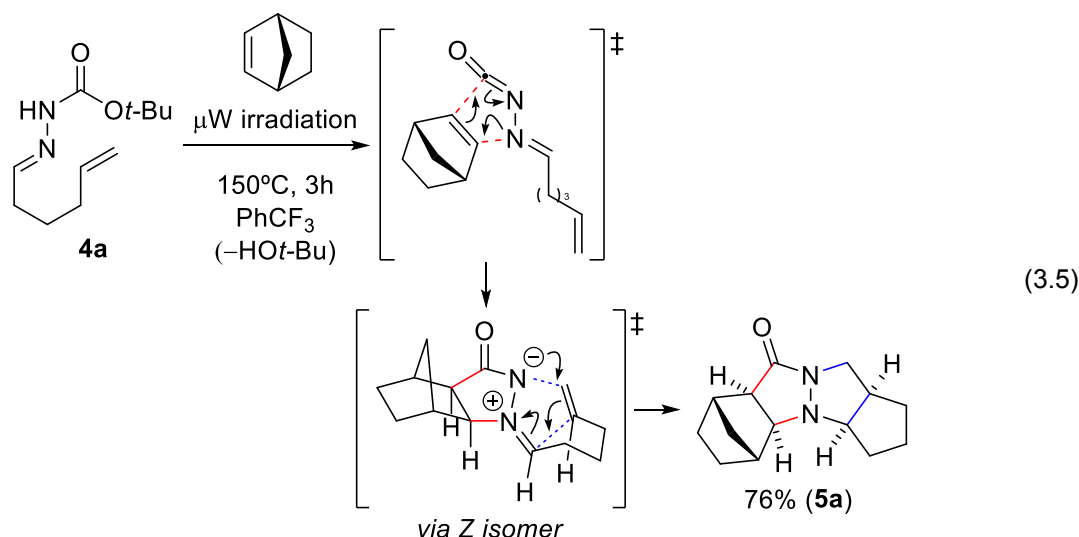
### 3.3.2 Additional Analytical Insights into Azomethine Imine Trapping

Meanwhile, in an attempt to gain further insights of the diastereomeric features of our product, compound **5a** was subjected to X-ray crystallographic analysis. To our amazement, we found that product **5a** had originally been miss-assigned (Figure 3.2).



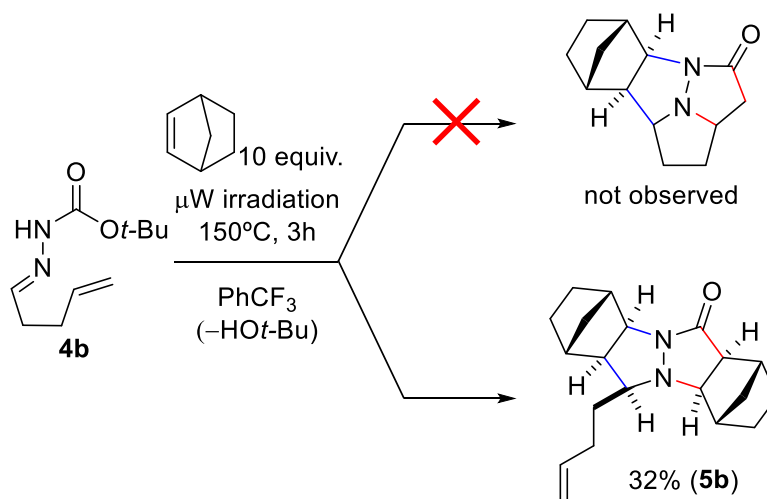
**Figure 3.3** X-ray analysis of product **5a** and correct structure

From our analysis, the generated tricyclic structure confirmed by X-ray was suggested to have resulted from an intermolecular aminocarbonylation of the imino-isocyanate with norbornene, followed by an intramolecular cyclization of the azomethine imine and alkenyl side-chain (equation 3.5).



In the meantime, we also attempted to perform a similar cascade aminocarbonylation reaction using an aldohydrazone precursor **4b** (Scheme 3.3). However, the desired product could not be obtained. Despite this, the crude mixture was purified and compound **5b** was isolated in 32% yield.



**Scheme 3.3** Reactivity of hydrazone **4b** in the presence of excess norbornene

As for product **5a**, formation of compound **5b** resulted from the initial intermolecular cycloaddition of imino-isocyanate to norbornene followed by a dipolar cycloaddition of azomethine imine with a second norbornene molecule. This second intermolecular addition was clearly preferred over an intramolecular cyclization which would have result in generation of an unstable four-membered cycle.

Despite not resulting in the desired intramolecular reactivity, the outcome of the experiments depicted in this section resulted in even more remarkable reactivity than anticipated: The inclination of imino-isocyanates towards intermolecular aminocarbonylation of alkenes. Given our interest into the functionalization of alkenes, we chose to further explore this intermolecular reactivity.

### 3.4 Intermolecular Aminocarbonylation Using Imino-Isocyanates

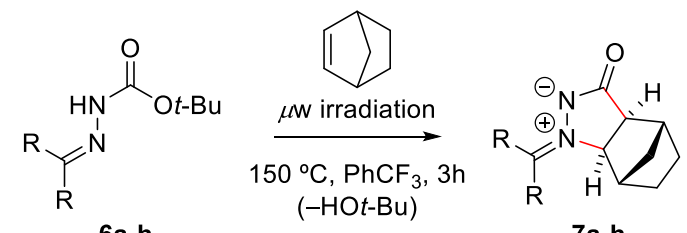
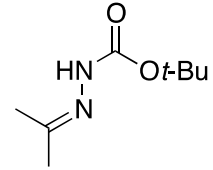
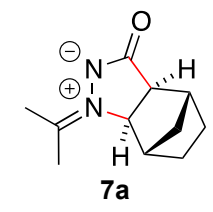
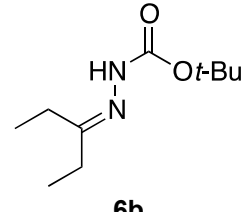
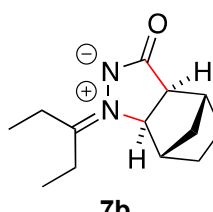
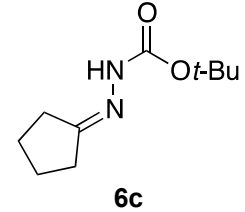
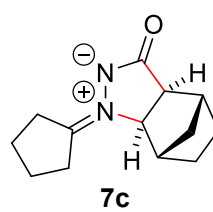
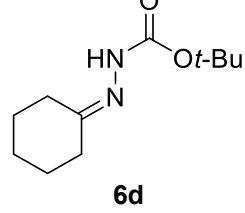
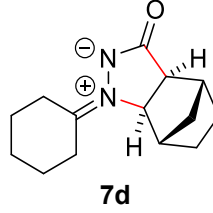
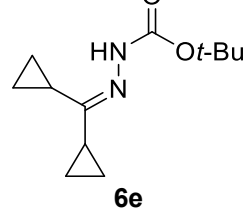
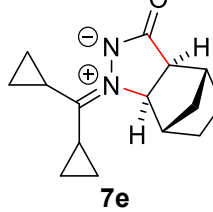
With insights gained from our previous investigation, we designed our initial study of intermolecular aminocarbonylation with imino-isocyanates based on two observations. First, ketohydrazones proved better reagents for intramolecular

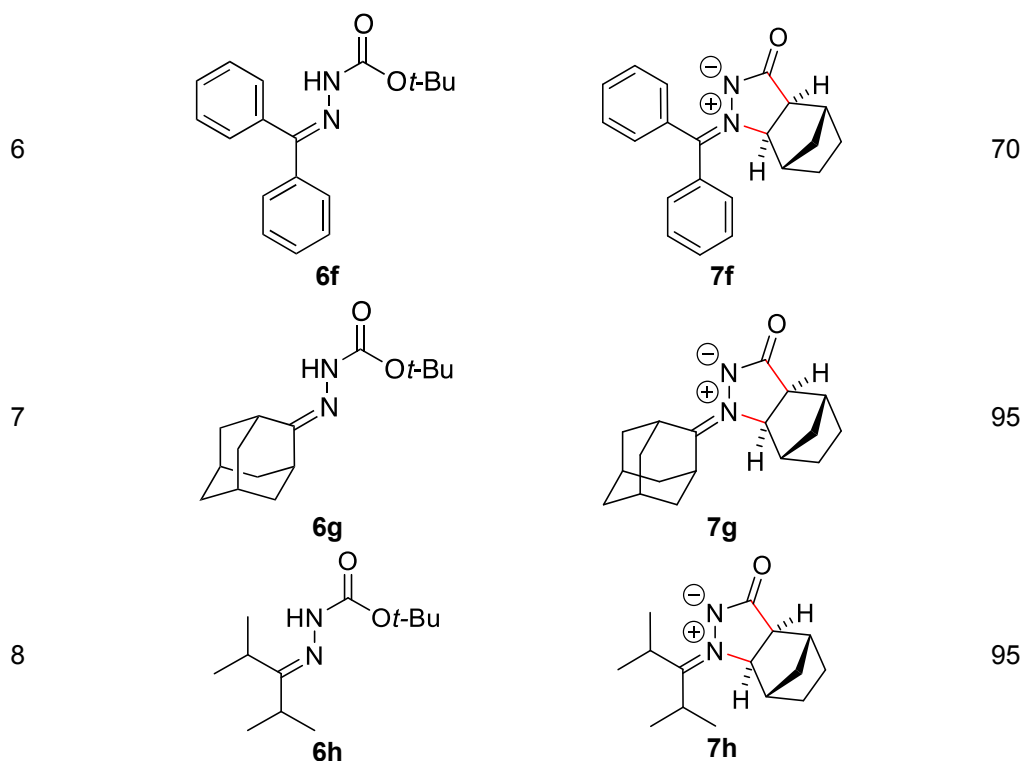
aminocarbonylation than aldohydrazones. To simplify our analysis, we initially focussed on symmetrical ketones, since unsymmetrical substrates would result in mixtures of isomeric products (see section 6.2). Secondly, norbornene was chosen as the testing alkene since it had already proved successful at providing the desired intermolecular aminocarbonylation reactivity.

#### *3.4.1 Development of a First Generation Aminocarbonylation Reagent*

We began our investigation by evaluating the reactive profile of various ketohydrazones. Conditions were chosen on the basis of those developed for prior investigation of intramolecular aminocarbonylation. For the sake of simplicity, dimethyl ketohydrazone served as the starting point for the design of our initial imino-isocyanate precursor. As presented in Table 3.6, hydrazone **6a** was synthesized and submitted to our reaction conditions (entry 1). To our delight, this substrate successfully provided the corresponding azomethine imine **7a** in good yield. To further improve the reactivity, we proposed that further shielding of the dipole moiety would increase the stability of the ensuing product. Diethyl and cyclopentyl carbamoyl hydrazones (**6b** & **6c**) provided no significant improvement in yield (entry 2-3). Lower yields were obtained for cyclohexyl and dicyclopropyl substrates **6d** and **6e**. We chose to further increase the steric bulk by synthesizing benzophenone carbamoyl hydrazone **6f** (entry 6), which did not provide improved aminocarbonylation reactivity.

**Table 3.6** Development of ketohydrazone aminocarbonylation reagent <sup>a</sup>

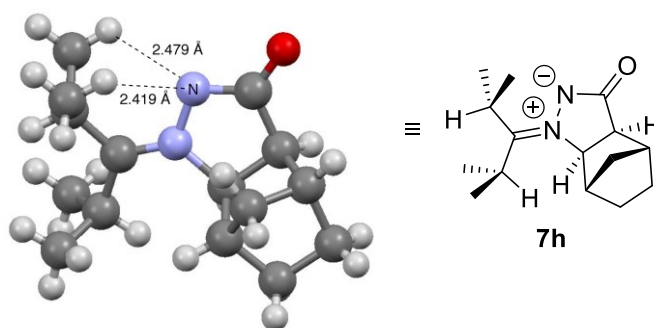
| <div style="text-align: center;">  <p>6a-h</p> <p>7a-h</p> </div> |                                                                                               |                                                                                                |                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------|
| entry                                                                                                                                               | hydrazone                                                                                     | product                                                                                        | yield (%) <sup>b</sup> |
| 1                                                                                                                                                   |  <p>6a</p>   |  <p>7a</p>   | 70 <sup>c</sup>        |
| 2                                                                                                                                                   |  <p>6b</p>   |  <p>7b</p>   | 67 <sup>d</sup>        |
| 3                                                                                                                                                   |  <p>6c</p>  |  <p>7c</p>  | 70                     |
| 4                                                                                                                                                   |  <p>6d</p> |  <p>7d</p> | 46 <sup>e</sup>        |
| 5                                                                                                                                                   |  <p>6e</p> |  <p>7e</p> | 54 <sup>e</sup>        |



<sup>a</sup> Conditions: hydrazone (1 equiv), alkene (10 equiv) in PhCF<sub>3</sub> (0.05 M) heated in a sealed vial (microwave reactor, 150 °C, 3 h). <sup>b</sup> Isolated yield. <sup>c</sup> Reaction at 120 °C. <sup>d</sup> 15 equiv of C<sub>7</sub>H<sub>10</sub>. <sup>e</sup> NMR yield using 1,4-dimethoxybenzene as an internal standard.

It was argued that rotation of the alkyl substituents could be detrimental to proper shielding of the desired dipole. Therefore, we hypothesized that bulky *and* conformationally constrained ketones could favour the desired outcome of our reactions. Consequently, we tested the reactivity of such ketoimino-isocyanate precursors with adamantanone hydrazone **6g** (entry 7). To our delight, this substrate resulted in excellent conversion to the desired product. However, despite its relative ease of purification, the product proved unstable over time, probably due to the hydrolysis of the iminium functionality. Therefore, requirements for the design of a bench stable aminocarbonylation product lead us to the synthesis of *bis*-isopropyl ketohydrazone **6h**. Gratifyingly, this precursor provided product **7h** in excellent yield (entry 7) and became the foundation for our first generation aminocarbonylation reagent.

The resulting azomethine imine was easy to purify, highly stable and crystalline. Therefore, to obtain the proof of concept for the herein described aminocarbonylation reactivity, we submitted compound **6h** to X-ray crystallographic analysis (Figure 3.4).



**Figure 3.4** X-ray crystal structure of azomethine imine **7h**

Analysis of the crystal structure suggested that conformational restrictions from isopropyl substituents were beneficial for steric shielding, likely playing a role in stabilizing the azomethine imine dipole. This likely prevented undesirable competing side-reactions. For examples, for hydrazone substrates bearing smaller substituents, [3+2] cycloaddition from the azomethine imine could be observed. Therefore, *bis*-isopropyl ketohydrazone **6h** proved ideal as a first generation substrate.

### 3.4.2 Optimization of Intermolecular Aminocarbonylation

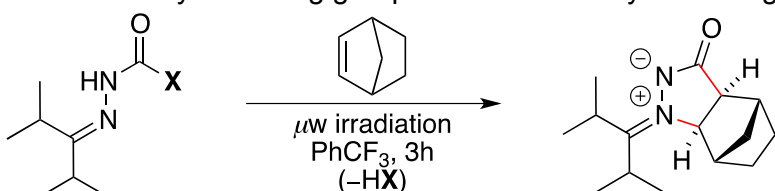
In an attempt to optimize the reactivity of *bis*-isopropyl hydrazone **6h**, we attempted to optimize the reaction temperature. In the meantime, we also synthesized new carbamoyl hydrazones bearing different leaving groups. This allowed us to survey various substrates for imino-isocyanate generation and evaluate the overall efficiency of imino-isocyanates to undergo aminocarbonylation at several temperatures (Table 3.7).

Overall, excellent yields were obtained with all hydrazones at 150 °C. More so, some leaving groups could provide the desired reactivity at or below 100 °C. As expected, the use of better oxygen and sulfur leaving groups led to increased yields at lower temperatures.

The reaction temperature of ethanolic hydrazone **8a** could not be lowered without significant loss in yields (entry 2). However, electron withdrawing substituents, such as trifluoroethanolic hydrazone **8b** resulted in traces of reactivity at temperatures as low as 80 °C (entry 3). In turn, we observed comparable level of reactivity with thioethanol as leaving group **8c** (entry 4). Satisfyingly, the use of phenolic and thiophenolic hydrazones **8d** and **8e** also provided aminocarbonylation reactivity at 80 °C. In agreement with recent work by Booker-Milburn, Lloyd-Jones et al.,<sup>11</sup> we observed that sterically hindered amine leaving group of semicarbazide **8f** also led to mild generation of the desired isocyanate.

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<sup>11</sup> Hutchby, M.; Houlden, C. E.; Haddow, M. F.; Tyler, S. N. G.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2009**, *48*, 8721.

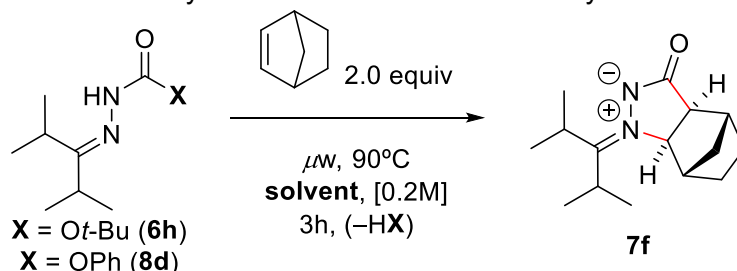
**Table 3.7** Survey of leaving groups for aminocarbonylation reagent


| Entry <sup>a</sup> | X                                              | Yield (%) |       |       |      |
|--------------------|------------------------------------------------|-----------|-------|-------|------|
|                    |                                                | 150°C     | 120°C | 100°C | 80°C |
| 1                  | <i>tert</i> -Bu ( <b>6h</b> )                  | 99        | 69    | 23    | 7    |
| 2                  | OEt ( <b>8a</b> )                              | 99        | 8     | 0     | 0    |
| 3                  | OCH <sub>2</sub> CF <sub>3</sub> ( <b>8b</b> ) | 82        | 55    | 30    | 9    |
| 4                  | SEt ( <b>8c</b> )                              | 98        | 64    | 46    | 11   |
| 5                  | OPh ( <b>8d</b> )                              | 92        | 85    | 84    | 38   |
| 6                  | SPh ( <b>8e</b> )                              | 90        | 69    | 60    | 31   |
| 7                  | N( <i>i</i> -Pr) <sub>2</sub> ( <b>8f</b> )    | 90        | 69    | 46    | 13   |

<sup>a</sup> Conditions: hydrazone (1 equiv.), alkene (10 equiv.) in PhCF<sub>3</sub> (0.05 M) heated in a sealed vial (microwave reactor). <sup>b</sup> NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

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Despite our initial results that demonstrated  $\alpha,\alpha,\alpha$ -trifluorotoluene as the optimal solvent for our intramolecular system, we attempted to optimize the newly found intermolecular reactivity by surveying solvents (Table 3.8). Performed by Mr. Thomas Markiewicz, polar aromatic and aprotic solvents provide the best results. In addition to  $\alpha,\alpha,\alpha$ -trifluorotoluene, chlorobenzene, *ortho*-dichlorobenzene and toluene provided comparable yields (entry 1-4). Limited reactivity was achieved in pyridine (entry 5). Polar aprotic solvents, dioxane and dimethylformamide, provided average and poor yields respectively. In turn, reactions in protic solvents such as *tert*-butanol and water did not yield any trace of the desired product in neither of the two systems. Surprisingly, reactions performed free of solvent resulted in increased yield when using hydrazone **8d**.

**Table 3.8** Survey of of solvents for amiocarbonylation reaction

| Entry <sup>a</sup> | Solvent                                                 | X = O <i>t</i> -Bu<br>NMR yield (%) <sup>b</sup> | X = OPh NMR yield<br>(%) <sup>b</sup> |
|--------------------|---------------------------------------------------------|--------------------------------------------------|---------------------------------------|
| 1                  | PhCF <sub>3</sub>                                       | 6                                                | 63                                    |
| 2                  | PhCl                                                    | 8                                                | 69                                    |
| 3                  | <i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 10                                               | 71                                    |
| 4                  | PhMe                                                    | 6                                                | 70                                    |
| 5                  | Pyr                                                     | 3                                                | 26                                    |
| 6                  | Dioxane                                                 | 1                                                | 41                                    |
| 7                  | DMF                                                     | 1                                                | 13                                    |
| 8                  | <i>t</i> -BuOH                                          | 0                                                | 0                                     |
| 9                  | H <sub>2</sub> O                                        | 0                                                | 0                                     |
| 10                 | neat                                                    | 1                                                | 74                                    |

<sup>a</sup> Conditions: To a flame dried screw cap vial, *tert*-butyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate **6h** (0.2 mmol, 1 equiv.) and norbornene (0.4 mmol, 2 equiv.) in the solvent (1 mL). The reaction was heated at  $90^\circ\text{C}$  for three hours. <sup>b</sup> NMR yields taken with 0.5 equiv of 1,3,5-trimethoxybenzene as an internal standard.

### 3.4.3 Initial Alkene Scope for Aminocarbonylation with Imino-Isocyanates

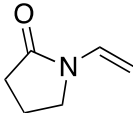
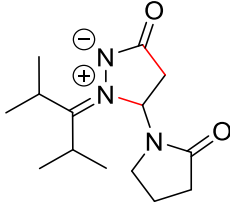
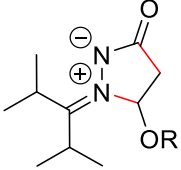
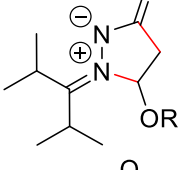
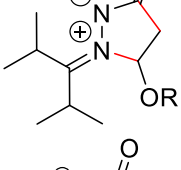
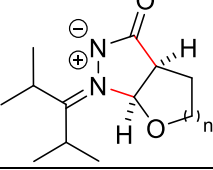
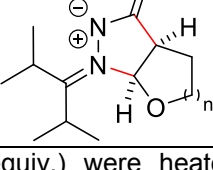
With our optimized conditions at hand, and our two reagents **6h** (O-*t*Bu) and **8d** (OPh) we explored the scope of intermolecular aminocarbonylation with various alkenes (Table 3.9). We were pleased to observe that unactivated alkenes such as 1-hexene and allyl-trimethylsilane (entry 1 & 2) could react and provide moderate to good yields of the desired azomethine imine. We also found that strained and conjugated dienes tend to react favorably with imino-isocyanates. Norbonadiene and 1,5-cyclooctadiene (entry 3 & 4), were able to undergo aminocarbonylation in a 78% and 33% yield respectively. Addition to 1,3-cyclohexadiene (entry 5) could also be performed efficiently and resulted as a mixture of regioisomers. Despite moderate yields, vinyl anisole (entry 6) could be



converted to the desired azomethine imine. Overall, electron-rich alkenes reacted well with imino-isocyanates. As such, heteroconjugated alkenes provided excellent reactivity (entry 7-12). *N*-Vinyl-pyrrolidinone (entry 7) provided the desired azomethine imine in good yield. However, improved results were obtained with vinyl ethers: Linear (entry 8-10) and cyclic (entry 11-12) substrates lead to aminocarbonylation with excellent yields.

**Table 3.9** Alkene scope of first generation aminocarbonylation reagent

| entry          | alkene | conditions                 | product | yield (%) <sup>b</sup> |           |
|----------------|--------|----------------------------|---------|------------------------|-----------|
| 1              |        | X = O- <i>t</i> Bu, 150 °C |         | 66 <sup>c</sup>        | <b>9a</b> |
| 2              |        | X = O- <i>t</i> Bu, 150 °C |         | 40                     | <b>9b</b> |
| 3              |        | X = OPh, 80 °C             |         | 78                     | <b>9c</b> |
| 4 <sup>d</sup> |        | X = O- <i>t</i> Bu, 150 °C |         | 33                     | <b>9d</b> |
| 5              |        | X = OPh, 120 °C            |         | 60 <sup>c</sup>        | <b>9e</b> |
| 6              |        | X = OPh, 120 °C            |         | 43                     | <b>9f</b> |

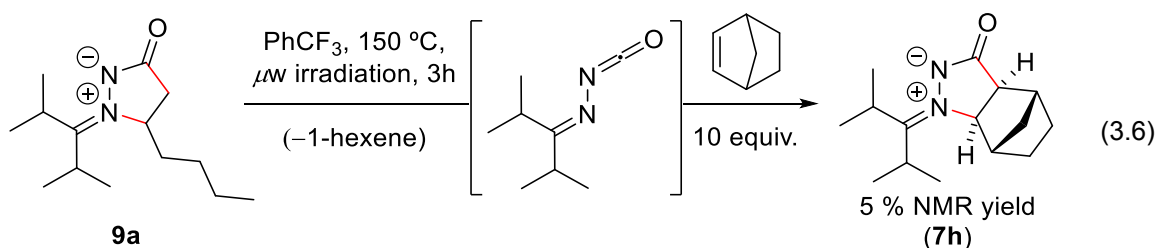
|    |                                                                                   |                |                                                                                    |           |    |
|----|-----------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------------------|-----------|----|
| 7  |  | X = OPh, 80 °C |  | <b>9g</b> | 77 |
| 8  | $R=n\text{-Bu}$                                                                   | X = OPh, 80 °C |  | <b>9h</b> | 49 |
| 9  | $R=\text{Cy}$                                                                     | X = OPh, 80 °C |  | <b>9i</b> | 81 |
| 10 | $R=t\text{-Bu}$                                                                   | X = OPh, 80 °C |  | <b>9j</b> | 89 |
| 11 | $n = 1$                                                                           | X = OPh, 80 °C |  | <b>9k</b> | 99 |
| 12 | $n = 2$                                                                           | X = OPh, 80 °C |  | <b>9l</b> | 70 |

<sup>a</sup> Conditions: hydrazone (1.0 equiv.), alkene (10 equiv.) were heated in a sealed vial (microwave reactor). <sup>b</sup> Isolated yield. <sup>c</sup> Isolated as regioisomeric mixtures [7:1 (**9a**) & 7:1 (**9e**)].

<sup>d</sup> In PhCF<sub>3</sub> (0.05 M).

### 3.4.4 Cycloreversion Experiment

From the alkene survey presented in Table 3.9, it was concluded that unactivated alkenes are less reactive towards imino-isocyanates than strained or conjugated alkenes. Therefore, we suggested that the possible reversibility of the azomethine imine formation might account for the lower yields obtained with aliphatic alkenes. To test this hypothesis, we devised a cycloreversion experiment using aminocarbonylation product **9a** (equation 3.6).

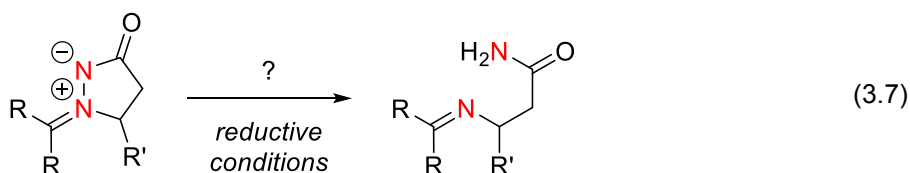


The product was subjected to standard aminocarbonylation conditions in the presence of a large excess of norbornene. From this experiment, traces amount of

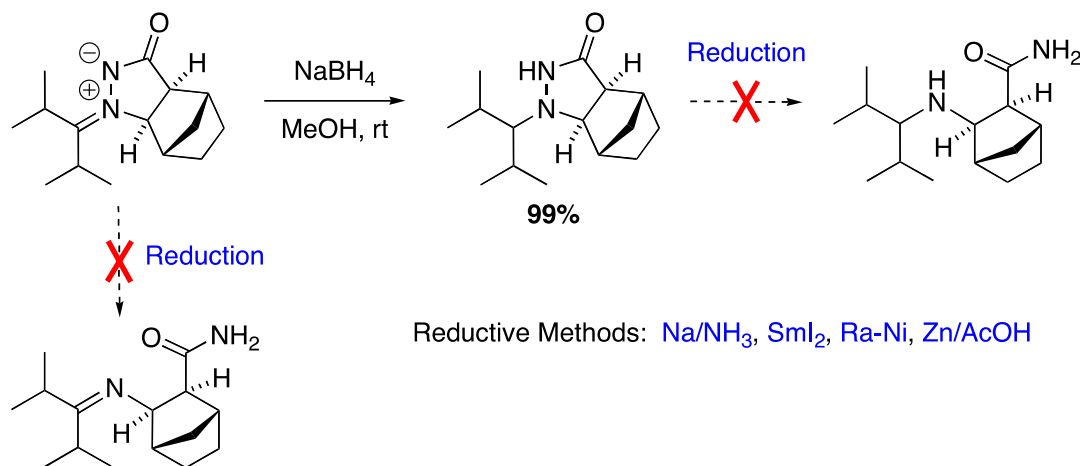
aminocarbonylation product **7h** could be identified. This provided suitable evidence, as we suggested, to support that azomethine imine could cycloreverse to the azomethine imine intermediate. This observation could account for a loss of mass and therefore, lower yields of unactivated alkene substrates.

### 3.4.5 Derivatization of Azomethine Imines to $\beta$ -Aminocarbonyl Compounds

One of the most interesting aspects of the present reactivity is that it allows straightforward access to  $\beta$ -aminocarbonyl motifs from readily available alkenes. However, to make such a process useful,  $\beta$ -aminocarbonyls allow functionalization and/or effective inclusion into synthetic sequences, especially for the synthesis of  $\beta$ -peptides. Therefore, it became imperative to find a straightforward method to convert azomethine imines into  $\beta$ -aminocarbonyl compounds (equation 3.7).



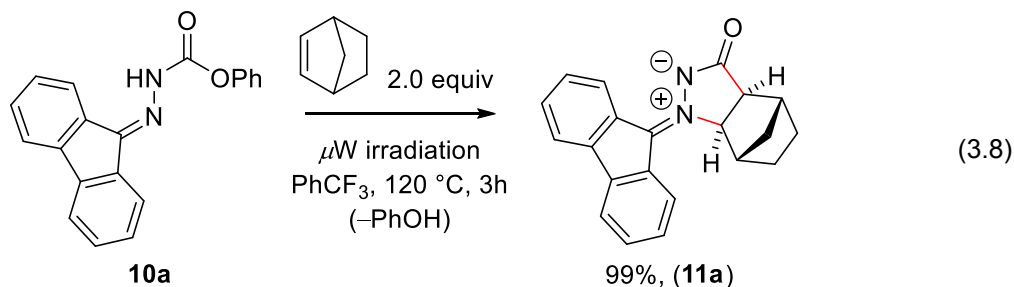
Consequently, we had to find a reliable N-N bond cleavage from azomethine imines. Unfortunately, various reductive methods proved unsuccessful with our *bis*-isopropyl ketone-derived substrates (Scheme 3.4). However, treatment of azomethine imine with sodium borohydride resulted in excellent conversion to the corresponding pyrrazolidinone. Unfortunately, N-N cleavage could not be performed with this product.

**Scheme 3.4** Attempted derivatization of *bis*-isopropyl azomethine imines

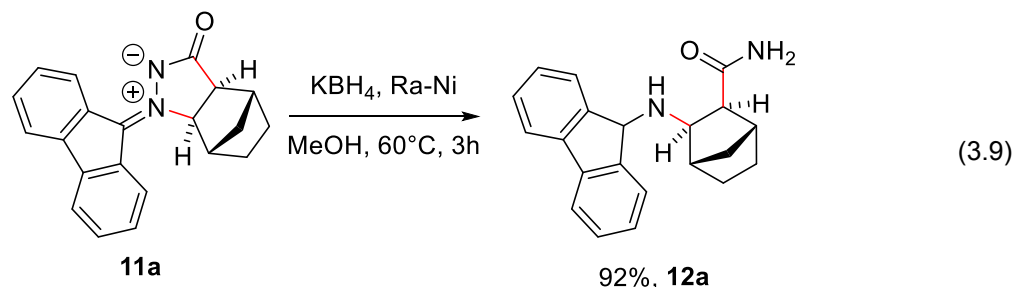
Although we argued that steric shielding was beneficial to the stability of the azomethine imine, aminocarbonylation product **7h** was too hindered to be effectively derivatized. We realized that the optimized substrate **6h** could not be effectively utilized for the synthesis of  $\beta$ -aminocarbonyl compounds, despite its effectiveness to undergo aminocarbonylation. This led us to explore alternative aminocarbonylation reagents which prompted the development of a second generation substrate.

### 3.4.6 Development of Second Generation Aminocarbonylation Reagent

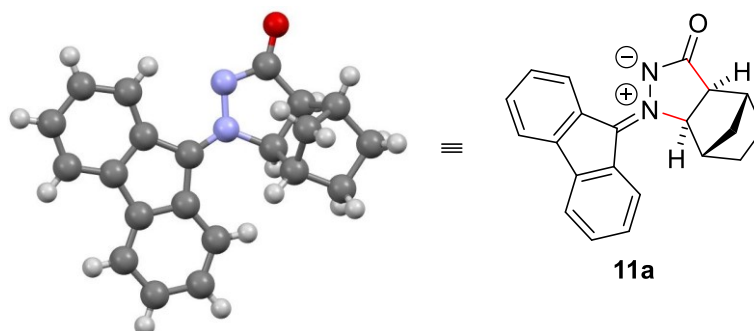
A breakthrough came from the synthesis of fluorenone-derived hydrazone substrate **10a**. *O*-Phenyl leaving group was also utilized since it allowed generation of imino-isocyanate under milder conditions. In the presence of norbornene, azomethine imine product **11a** was generated in quantitative yield (equation 3.8).



In contrast with *bis*-isopropyl ketone-derived aminocarbonylation product **7h**, a derivatization of azomethine imine was developed by Dr. Wei Gan and provided direct access to  $\beta$ -aminocarbonyl compound **11a**. This one-pot process involves reduction of the iminium moiety with potassium borohydride, followed by N-N cleavage with Raney-Nickel under dihydrogen atmosphere (equation 3.9).



Additionally, aminocarbonylation product **6a** could be submitted to X-ray crystallographic analysis (Figure 3.5).



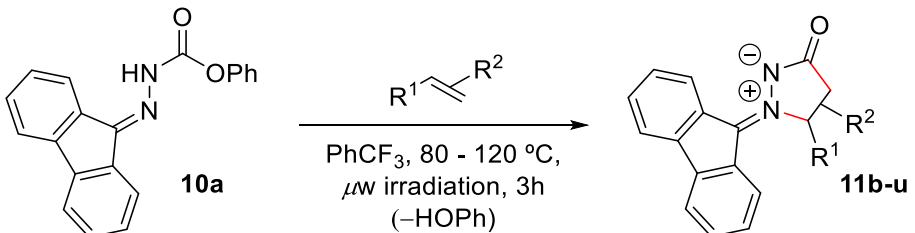
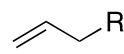
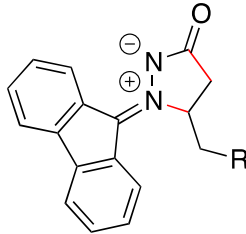
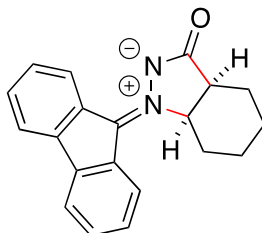
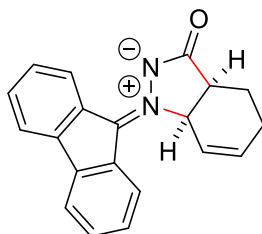
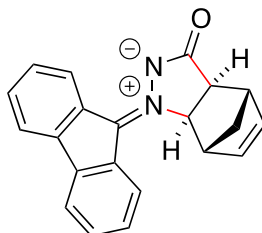
**Figure 3.5** X-ray crystallographic analysis of azomethine imine product **11a**

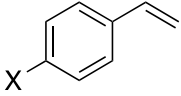
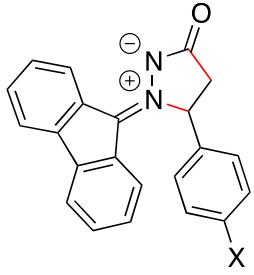
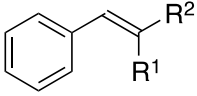
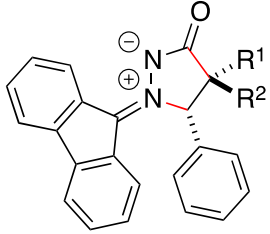
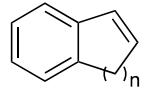
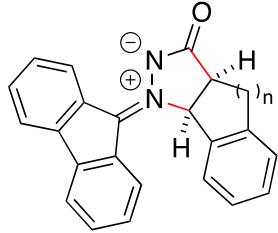
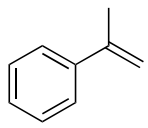
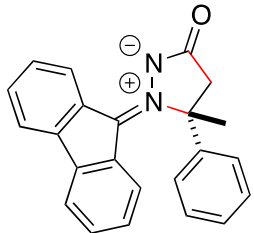
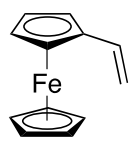
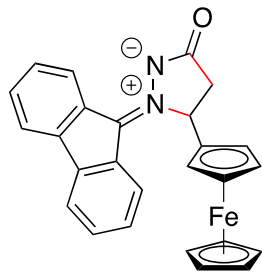
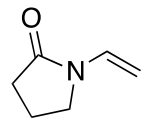
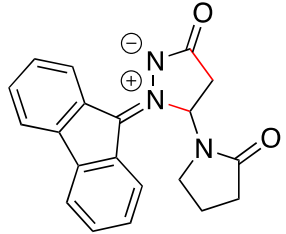
With our new fluorenone-derived hydrazone reagent in hand (**10a**), we surveyed the reactivity profile of various classes of alkenes (Table 3.10). An important trend is the recurring Markovnikov selectivity present for all substrates. Similar to results observed in bis-isopropyl ketohydrazones, terminal alkenes such as 1-hexene and allyltrimethylsilane reacted in good yields (entries 1 & 2). The same was observed for allyl benzyl ether, despite lower yields, affording aminocarbonylation product **11d** which corresponds to a  $\beta$ -amino acid derivative of homo-serine. Cyclohexene (entry 4) and cyclohexadiene (entry 5) provided the desired adducts in modest to very good yields. As with previous strained alkenes, norbornadiene produced aminocarbonylated product **11g** in good yield (entry 6).

We were also encouraged by the results obtained for vinyl arenes (entries 7-14). Styrene provided good yields of the azomethine imine product (entry 7), same as for 4-fluorostyrene and vinyl anisole (entries 8-9). We also found the reaction to tolerate substitution at the alkene distal position. *Cis*- and *trans*- $\beta$ -methyl styrene (entries 10-11) could yield the desired azomethine imines as a mixture of regioisomers favouring generation of the Markovnikov product. Additionally, NMR analysis demonstrated that products **11n** and **11o** were structurally distinct, thus indicating retention of stereochemical information of the alkene. This observation strongly suggested a concerted *syn* addition of the imino-isocyanate to the alkene. We were also delighted to observe reactivity, despite poor yields, of *trans*-stilbene (entry 12). Indene and dihydronaphthalene (entries 13-14) also reacted well and were isolated, again, as a mixture of regioisomers. In addition, substitution could also be tolerated at the alkene

proximal position, where  $\alpha$ -methyl styrene (entry 15) could afford the corresponding azomethine imine product in moderate yield.

**Table 3.10** Alkene scope of first generation aminocarbonylation reagent

| <div style="text-align: center;">  </div> |                                                                                     |            |                                                                                      |                        |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------|--------------------------------------------------------------------------------------|------------------------|
| entry                                                                                                                       | alkene                                                                              | conditions | product                                                                              | yield (%) <sup>b</sup> |
|                                                                                                                             |    |            |    |                        |
| 1                                                                                                                           | R= <i>n</i> -Bu                                                                     | 150 °C     | <b>11b</b>                                                                           | 73 <sup>c</sup>        |
| 2                                                                                                                           | R=TMS                                                                               | 150 °C     | <b>11c</b>                                                                           | 81                     |
| 3                                                                                                                           | R=CH <sub>2</sub> OBn                                                               | 150 °C     | <b>11d</b>                                                                           | 52                     |
| 4                                                                                                                           |  | 150 °C     |   | <b>11e</b><br>49       |
| 5                                                                                                                           |  | 120 °C     |  | <b>11f</b><br>52       |
| 6                                                                                                                           |  | 80 °C      |  | <b>11g</b><br>86       |

|                |                                                                                                                                                                                                              |        |                                                                                      |                                        |                                    |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|--------------------------------------------------------------------------------------|----------------------------------------|------------------------------------|
| 7<br>8<br>9    | <br>X=H<br>X=F<br>X=OMe                                                                                                     | 120 °C |    | <b>11h</b><br><b>11i</b><br><b>11j</b> | 64<br>54<br>74                     |
| 10<br>11<br>12 | <br>R <sup>1</sup> =Me, R <sup>2</sup> =H<br>R <sup>1</sup> =H, R <sup>2</sup> =Me<br>R <sup>1</sup> =H, R <sup>2</sup> =Ph | 120 °C |    | <b>11k</b><br><b>11l</b><br><b>11m</b> | 24<br>52 <sup>c</sup><br>33        |
| 13<br>14       | <br>n=1<br>n=2                                                                                                              | 120 °C |    | <b>11n</b><br><b>11o</b>               | 41 <sup>c</sup><br>51 <sup>c</sup> |
| 15             |                                                                                                                           | 120 °C |   | <b>11p</b>                             | 19                                 |
| 16             |                                                                                                                           | 80 °C  |  | <b>11q</b>                             | 93                                 |
| 17             |                                                                                                                           | 80 °C  |  | <b>11r</b>                             | 40                                 |



|    |                 |       |            |    |
|----|-----------------|-------|------------|----|
|    |                 |       |            |    |
| 18 | R= <i>n</i> -Bu | 80 °C | <b>11s</b> | 75 |
| 19 | R=Cy            |       | <b>11t</b> | 68 |
|    |                 |       |            |    |
| 20 | n = 1           | 80 °C | <b>11u</b> | 57 |
| 21 | n = 2           |       | <b>11v</b> | 77 |

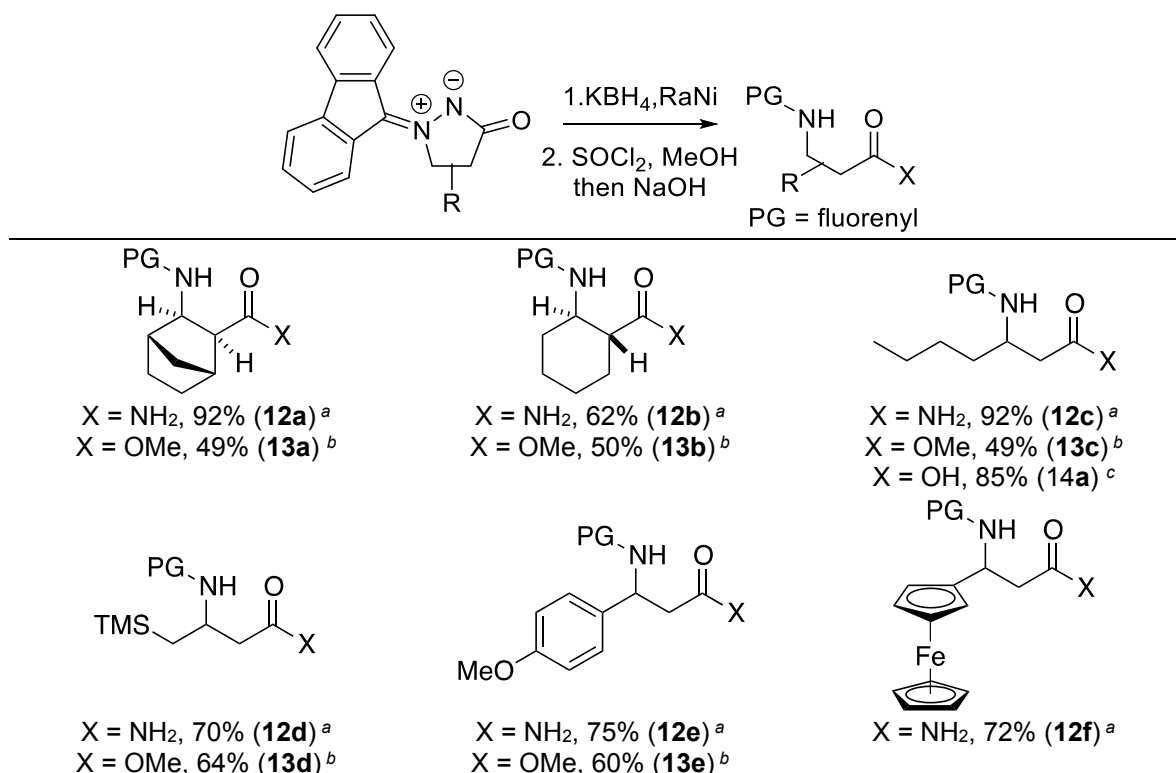
<sup>a</sup> Conditions: hydrazone (1.0 equiv.), alkene (10 equiv.) were heated in a sealed vial (microwave reactor). <sup>b</sup> Isolated yield. <sup>c</sup> Isolated as regioisomeric mixtures [7:1 (**11b**), 7:1 (**11f**), 1:1 (**11l**), 6:1 (**11n**), 3:2 (**11o**)]. <sup>d</sup> In PhCF<sub>3</sub> (0.05 M).

with Wei Gan, Amanda Bongers & Thomas Markiewicz

In contrast, electron-rich alkenes such as vinylferrocene reacted with excellent yields at 80 °C (entry 16, **11q**). In comparison to other substrates, the quantity of vinyl ferrocene could be reduced to only one equivalent, supporting our assumption regarding the strong affinity of imino-isocyanates for electron-rich alkenes. As such, alkenes conjugated to electron-donating substituents also proved quite reactive. *N*-vinylpyrrolidinone (entry 17) as well as linear and cyclic vinyl ethers (entry 17-21) effectively provided the corresponding azomethine imine.

### 3.4.7 Derivatization of Fluorenone-Derived Azomethine Imines

In addition to our previously discussed norbornyl adduct, we also applied our derivatization method to other azomethine imine products. Gratifyingly, we observed that various aminocarbonylation products provided  $\beta$ -amino acid derivatives upon reductive treatment with potassium borohydride in the presence of Raney-Nickel (Table 3.11).

**Table 3.11** Derivatization of azomethine imines to  $\beta$ -aminocarbonyl compounds <sup>a</sup>

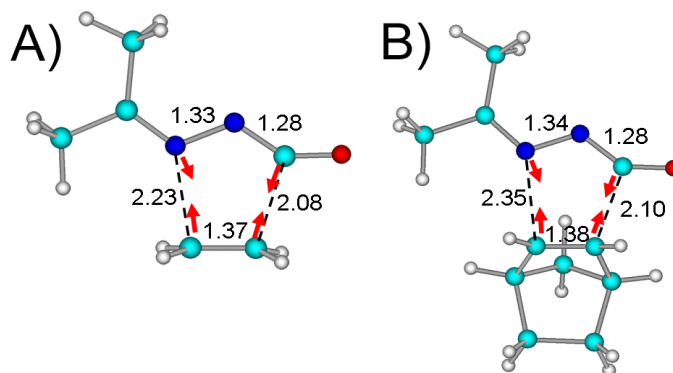
<sup>a</sup> Conditions: KBH<sub>4</sub>, Ra-Ni, MeOH, 60 °C, 3 h. <sup>b</sup> SOCl<sub>2</sub>, MeOH, 60 °C, 12 h. <sup>c</sup> SOCl<sub>2</sub>, MeOH, 60 °C, 12 h; then 10 M NaOH, rt.

with Wei Gan and Amanda Bongers

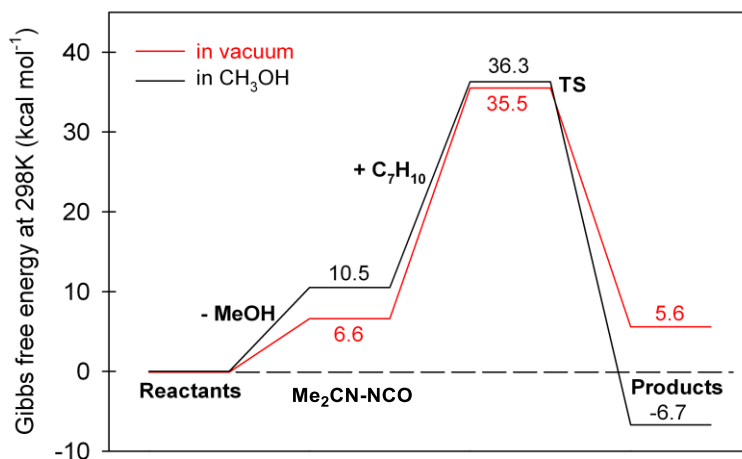
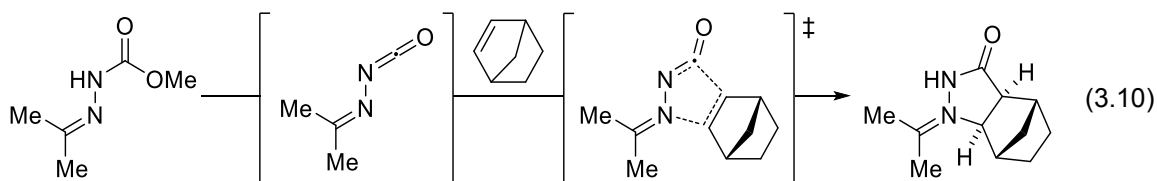
Substrates bearing cyclic (cyclohexane) and linear alkyl substituents (*n*-butyl, methylene trimethylsilane) were easily converted to  $\beta$ -aminocarbonyl amides (**12b-d**). It must be noted that cyclohexane product **12b**, under our conditions, was converted to the *trans* diastereomer. In addition, aminocarbonylation products with *p*-methoxy benzene and ferrocene (**12e-f**), could be derivatized with equal effectiveness. The conversion of amide functionalities to methyl esters upon treatment with thionyl chloride and methanol afforded moderate to good yields of the desired products (**13a-e**). Using the same methodology, we could derivatize amides to carboxylic acids by treatment with water (**14a**).

### 3.4.8 DFT Calculations and Mechanistic Details

To obtain additional insight on the mechanism of the transformation, DFT calculations were performed by Dr. Serge Gorelsky in an effort to probe the pathway involving *bis*-methyl imino-isocyanate (Figure 3.6). The potential energy surface has been calculated for the reaction with ethylene and norbornene.



**Figure 3.6** Transition state structures for the intermolecular aminocarbonylation of A) ethylene and B) norbornene ( $C_7H_{10}$ ) using dimethyliminoisocyanate in vacuum. Relevant bond distances (Å) are shown. Red arrows indicate the atomic movements which correspond to the imaginary normal mode.

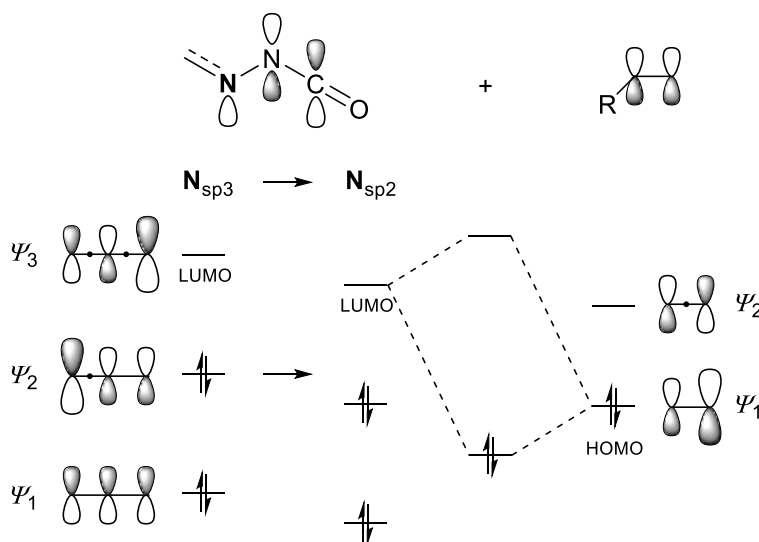


**Figure 3.7** Gibbs free energies (in kcal/mol, 298 K) for the aminocarbonylation of norbornene ( $C_7H_{10}$ ) using dimethyliminoisocyanate in vacuum (red line) and in methanol (black line)

In equation 3.10 is presented the transition state structure determined for the reaction between dimethyl imino-isocyanate and ethylene and norbornene respectively. Gibbs free energies of activation ( $\Delta G^\ddagger_{298K}$ ) for concerted processes in the gas phase were calculated to be 36.1 kcal/mol for ethylene and 35.5 kcal/mol for norbornene (Figure 3.7), which is consistent with a reaction requiring heat to proceed. These barriers remain fairly unchanged when concerted aminocarbonylation occurs in solvent ( $\Delta G^\ddagger_{298K}$  is 36.3 kcal/mol for the reaction with norbornene in MeOH). The asynchronous transition state is also in line with the high Markovnikov selectivity observed experimentally.

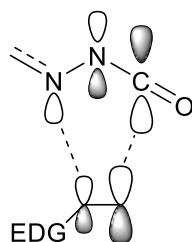
In order to support the likeliness of the proposed mechanism, analysis of the atomic orbitals involved in the transformation may be put forward. As such we may qualitatively assess the cycloaddition by using frontier molecular orbital theory (FMO)

and to explain some experimental observations. Represented in figure 3.8 is the HOMO-LUMO interactions proposed to take place between amino- ( $N_{sp^3}$ ) and imino-isocyanates ( $N_{sp^2}$ ) and alkenes.



**Figure 3.8** HOMO-LUMO interaction of amino- and imino-isocyanates with olefins

Experimental evidence suggests that electron-rich alkenes have an increased propensity towards aminocarbonylation. It is therefore arguable that the HOMO of the alkene reacts with the LUMO of the  $N$ -substituted isocyanate. If so, this might explain why better reactivity is observed with imino-isocyanates compared to amino-isocyanates. As such, the LUMO of the  $sp^2$  nitrogen (imino-) compared to the  $sp^3$  nitrogen of an amino-isocyanate, should be lower in energy. In turn, an electron-rich alkenes should have a HOMO that is higher in energy than unactivated alkenes. Together, these suggestions would provide a lower energy difference between the HOMO and the LUMO, thus resulting in a better orbital overlap (see Figure 3.9) when imino-isocyanates are involved.



**Figure 3.9** Proposed orbital overlap for the aminocarbonylation of alkenes with amino- and imino-isocyanates

Additionally, by considering the electronic characters each counterparts, the lobe of the distal carbon (HOMO) found on the alkene and that of the electrophilic carbon of the isocyanate (LUMO) should be larger. Given that interactions between large lobes should be favourable (closer in energy), this may provide justification for the high Markovnikov selectivity observed with aminocarbonylation.

While this analysis remains speculative, it nonetheless sheds some light over alkene aminocarbonylation and should uphold future development of the reactivity. However, a detailed comparison between amino- and imino-isocyanates, potentially involving additional DFT calculations, would be required to fully address the questions pertaining to the exact orbital interactions and mechanisms.

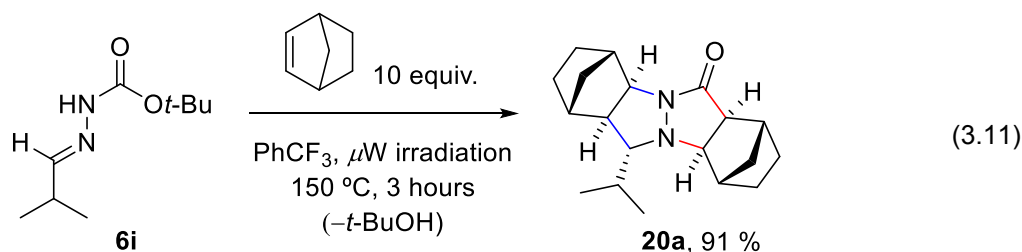
### 3.5 Generation of Unsymmetrical Azomethine Imines

Thus far, we have demonstrated the versatility of *symmetrical* hydrazones as imino-isocyanate precursors for the synthesis of azomethine imine and further derivatization to  $\beta$ -aminocarbonyl compounds. However, as seen in Section 1.1.6.1, azomethine imines are not only useful as 1,3-dipole reagents but have recently emerged

as valuable adducts for asymmetric synthesis.<sup>12</sup> As such, most azomethine imines are typically synthesized from the reaction between pyrazolidinones and aldehydes,<sup>13</sup> whereas access to keto-derived azomethine imines is much more limited. Consequently, the reactivity of ketone derived azomethine imines has rarely been studied.<sup>14</sup> In answer to this synthetic problem, we sought to investigate the intermolecular reactivity of *unsymmetrical* imino-isocyanates towards alkenes.

### 3.5.1 Alkene Aminocarbonylation with Unsymmetrical Aldohydrazones

Reactions of aldohydrazones proved challenging, as the use of *O**t*-Bu carbamoyl hydrazones under forcing conditions (up to 150 °C) resulted in the azomethine imine products reacting further through a [3+2] cycloaddition in the presence of excess alkene (equation 3.11). The stereochemistry of the product was by analogy to results obtained by Mr. Patrick Moon of the X-ray crystallographic analysis of a different product.



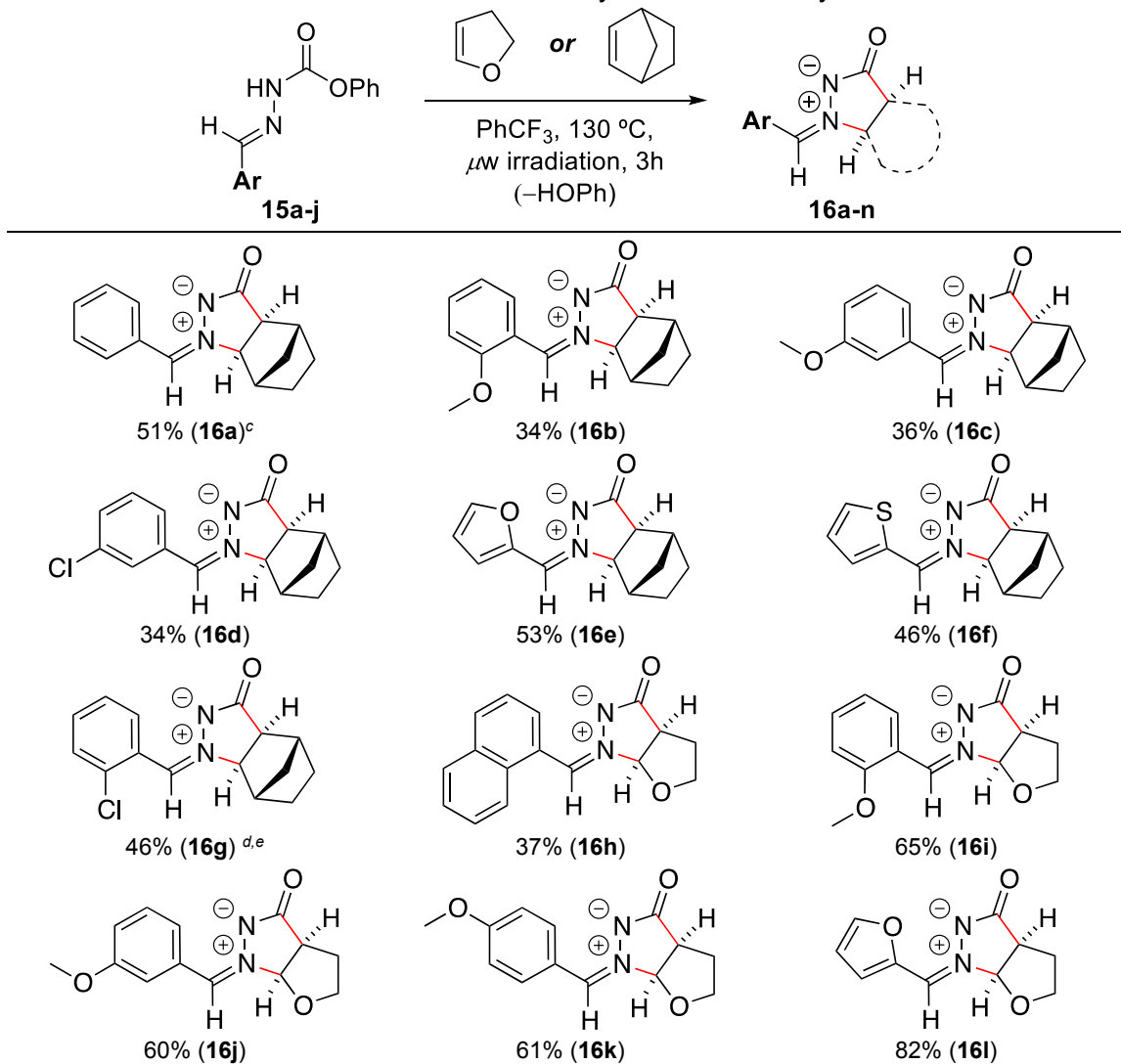
<sup>12</sup> For recent examples, see: (a) Suarez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, 127, 11244. (b) Chen, W.; Yuan, X. H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, 348, 1818. (c) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, 9, 97. (d) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, 46, 7667. (e) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, 10, 2971. (f) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, 132, 4076.

<sup>13</sup> Godfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1955**, 9, 1498.

<sup>14</sup> For a review, see section 1.1.6.1 and the references cited therein.

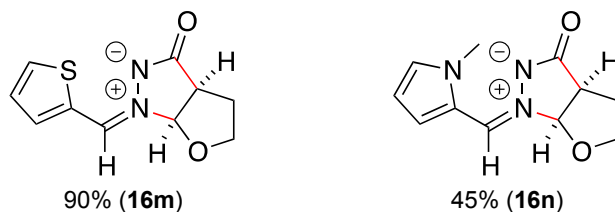
Fortunately, use of *O*-phenyl carbamoyl hydrazone allowed optimization of the temperature and ensuring control over competing double addition side-reaction. Performed primarily by Dr. Wei Gan and Mr. Patick Moon, the investigation was initiated with the survey carbamoyl aldohydrazone (Table 3.12).<sup>15</sup>

**Table 3.12** Alkene aminocarbonylation with aldehydes



<sup>15</sup> Gan, W.; Moon, P. J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890.





<sup>a</sup> Conditions: hydrazone (1 equiv.), alkene (1.2-10 equiv., see above) in PhCF<sub>3</sub> (0.05 M) heated in a sealed vial (microwave reactor, 130 °C, 1-3 h). Typical scale: 0.2 mmol of **15a-j**. <sup>b</sup> The identity of the major stereoisomer was secured by NOE experiments on **16e**. Stereochemistry of other dipoles was assigned by analogy. <sup>c</sup> 120 °C. <sup>d</sup> NMR yield. <sup>e</sup> 150 °C.

by Wei Gan and Patrick Moon

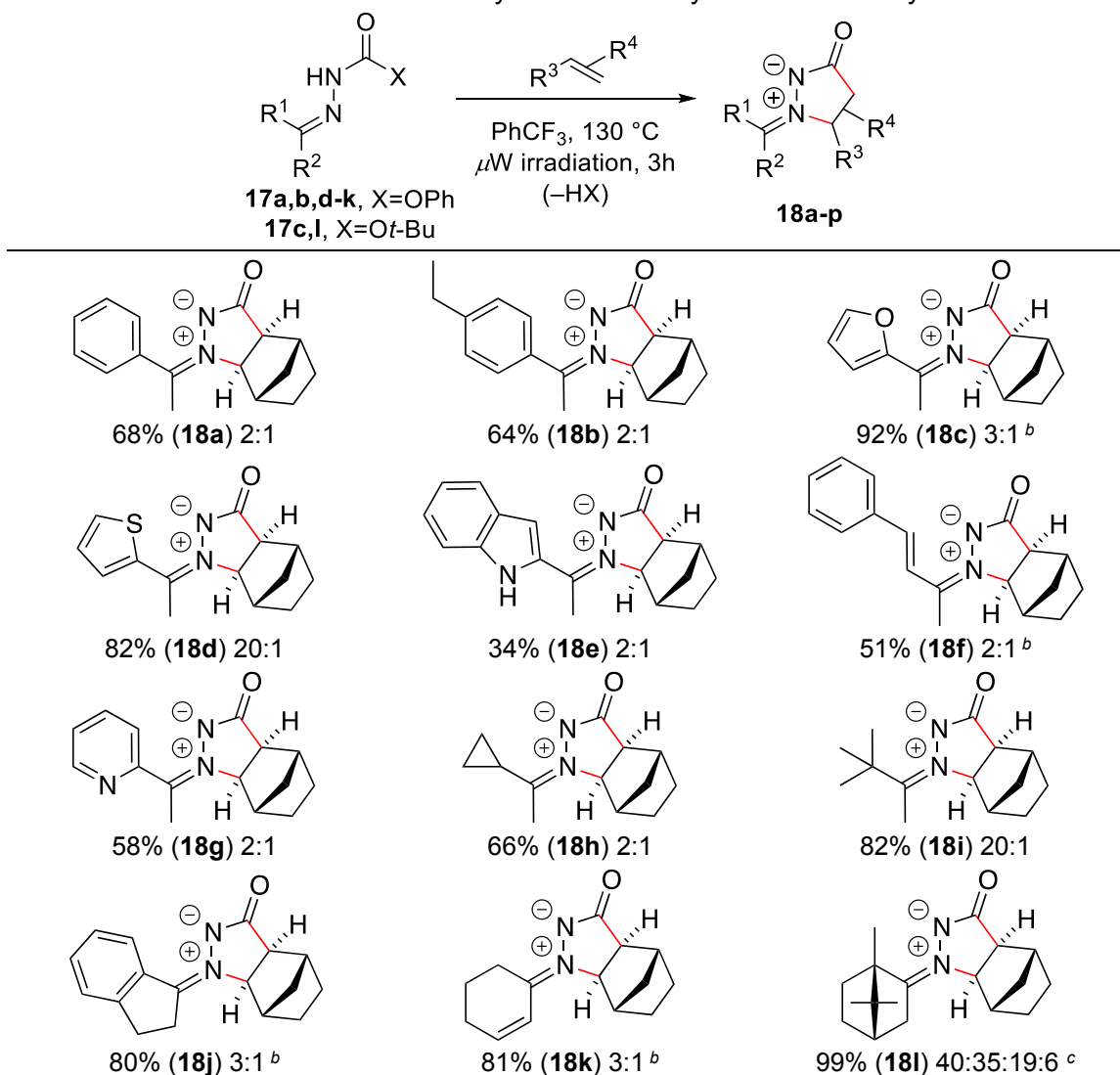
Norbornene and dihydrofuran were chosen as the initial alkenes for this investigation due to their good reactivity with imino-isocyanates. Reaction of aryl (**16a-d** & **16g-k**) and heteroaryl aldehydrazones (**16e-f** & **16l-n**) provided the desired azomethine imines in modest to good yields as a single stereoisomer for all cases.

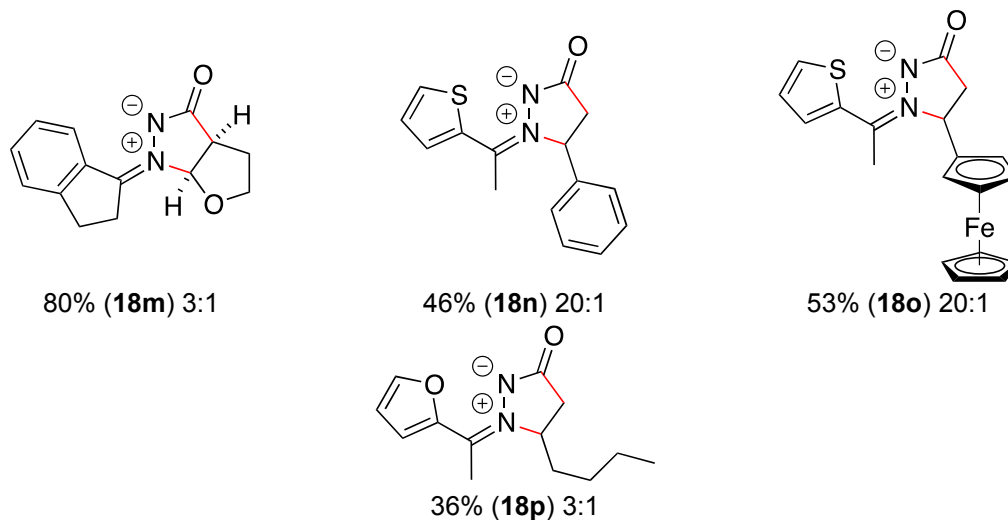
### 3.5.2 Alkene Aminocarbonylation with Unsymmetrical Ketohydrazones

We then surveyed the reactivity of unsymmetrical ketohydrazone reagents. Again, the substrate survey was achieved using norbornene and dihydrofuran which allowed us to compare the reactive outcome of multiple ketohydrazone reagents. Presented in Table 3.13, *O*-phenyl carbamoyl aryl (**18a-b**, **18j**) and heteroaryl (**18c-g**) react well under our conditions. In turn, alkenyl substrates (**18f** & **18k**) provided the desired substrate in good yields. These are especially important as 1,4-addition of pyrazolidinone to enone would be expected from a typical azomethine imine synthesis from a condensation. Furthermore, alkyl ketohydrazones (**18h-i**, **18l**) were subjected to aminocarbonylation conditions and resulted in yields ranging from moderate to good. Unfortunately, (*R*)-camphor provided poor diastereoselectivity. Importantly, in opposition to aldehydrazones reagents, ketohydrazones generally resulted in a mixture of regisomers. Notably, substrates bearing  $\pi$ -excessive heteroaryl substituents effectively reacted. It may be

argued that conjugation of the electron-rich aryl with the imine's nucleophilic nitrogen results in a more reactive imino-isocyanate species. To expand the scope of the reaction, furyl and thiophenyl derived ketohydrazone were reacted with styrene, vinyl ferrocene, and 1-hexene (products **18n-p**), for which the corresponding aminocarbonylation product could be isolated in moderate yields.

**Table 3.13** Alkene aminocarbonylation with unsymmetrical ketohydrazone<sup>a</sup>





<sup>a</sup> Conditions: hydrazone (1 equiv), alkene (10 equiv) in PhCF<sub>3</sub> (0.05 M) heated in a sealed vial (microwave reactor, 130 °C, 1-3 h). Typical scale: 0.2 mmol of **17a-l**. <sup>b</sup> The identity of the major stereoisomer was secured by NOE experiments on **18c**, **18f**, **18j**, and **18k** and by X-ray crystallographic analysis of **18c**. Stereochemistry of other dipoles was assigned by analogy. <sup>c</sup> *tert*-Bu substituted hydrazone was used at 150 °C.

with Wei Gan and Patrick Moon

### 3.5.3 Summary of Alkene Aminocarbonylation with Unsymmetrical Hydrazones

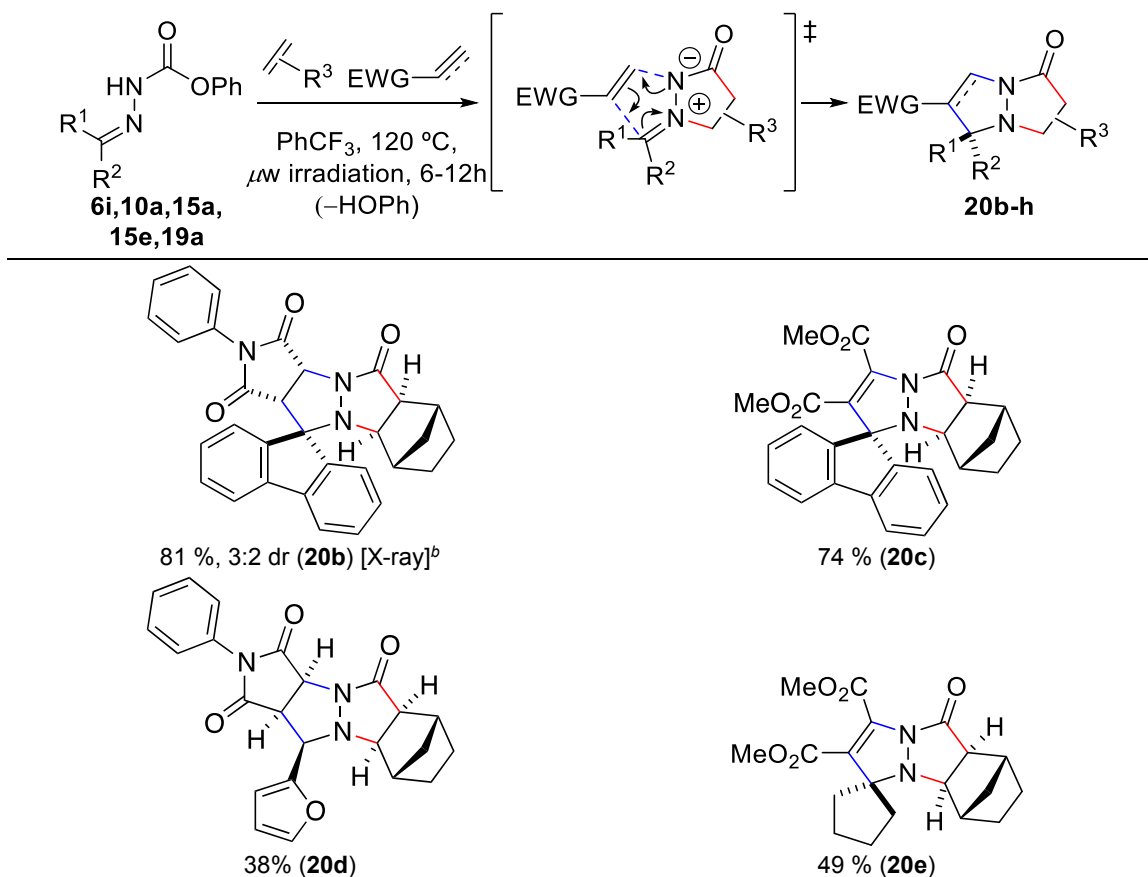
Overall, we have demonstrated that aminocarbonylation of alkenes with imino-isocyanates is not limited to symmetrical hydrazone reagents. We have thus shown that the reactivity is broadly applicable to the synthesis of a variety of azomethine imine products and especially useful for generating ketone-derived substrates and complex dipole reagents.

## 3.6 Cascade Aminocarbonylation / Dipolar Cycloaddition Sequence

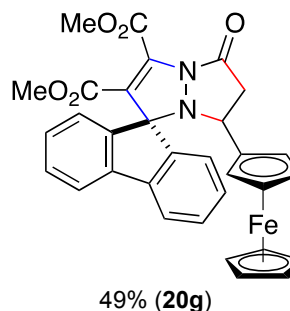
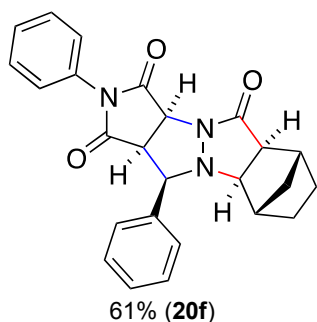
Throughout the investigation of the present aminocarbonylation reactivity, we found imino-isocyanates to preferably react with electron-rich and strained alkenes. Exploratory trials with electron-poor alkenes proved these  $\pi$ -bonds unreactive. In stark contrast, a literature survey revealed the preference of similar azomethine imines to our aminocarbonylation products to react well with conjugated electron-poor  $\pi$ -bonds in

dipolar cycloaddition reactions.<sup>16</sup> Therefore, we asked whether the chemoselective character for imino-isocyanates could be exploited. More precisely, we proposed a one pot cascade sequence where the imino-isocyanate would first react with either a strained or electron-rich alkene, followed by dipolar cycloaddition of the resulting azomethine imine with an electron-poor alkene. The scope of this cascade sequence is presented in Table 3.14.

**Table 3.14** Scope of aminocarbonylation / dipolar cycloaddition sequence



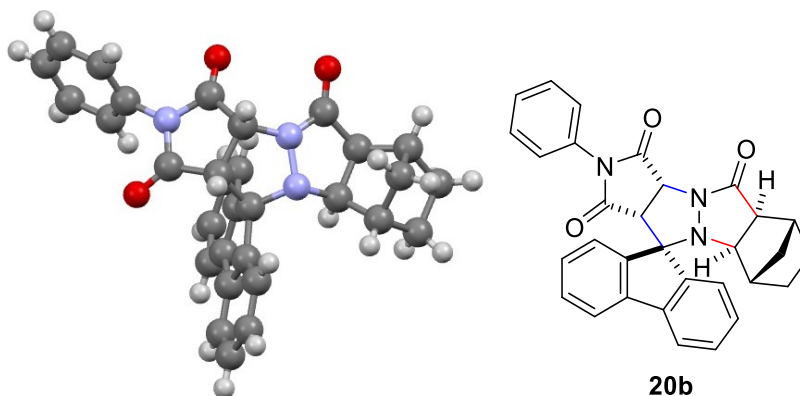
<sup>16</sup> (a) Dorn, H.; Otto, A. *Chem. Ber.* **1968**, *101*, 3287. (b) Pezdirc, L.; Gloselj, U.; Meden, A.; Stanovnik, B.; Svete, J. *J.Heterocycl.Chem.* **2008**, *45*, 181.



<sup>a</sup> Conditions: Hydrazone, alkene (10 equiv) and electron-poor alkene (10 equiv) are dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.3 M) in a sealed tube and heated under microwave irradiation for twelve hours. <sup>b</sup> See supporting information.

with Nicolas Das Neves

Four hydrazones were used for this survey, however, fluorenone-derived **10a** hydrazone provided higher yields of the cascade (products **20b-c**). From an initial reaction with norbornene, the resulting azomethine imine could efficiently cyclize with *N*-phenyl maleimide to form a mixture of diastereomers. Following X-ray crystallographic analysis, we identified the major product to correspond to the *trans* isomer (Figure 3.8). The cascade scope could be expanded to acetylene dicarboxylate, providing product in good yield (products **20c**). Dihydrofuran and vinyl ferrocene also reacted in cascade reaction despite lower yields (**20g**). Aldehyde derived hydrazone reagents could successfully cyclize sequentially with norbornene and *N*-phenyl maleimide. As such, furanyl, phenyl and isopropyl substitutions were tolerated despite lower yields (products **20d,f,h**).

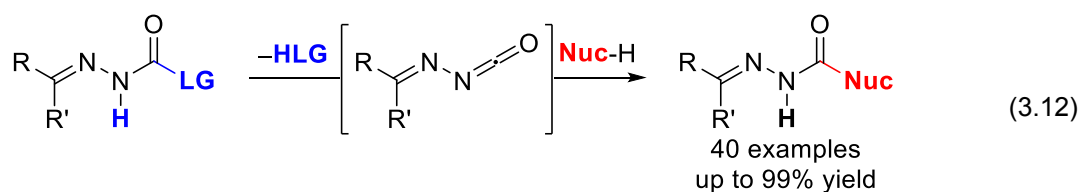


**Figure 3.10** X-ray crystallographic analysis of cascade aminocarbonylation/dipolar cycloaddition reaction

### 3.7 Conclusions and Perspectives on the Intermolecular Aminocarbonylation of Alkenes

Although amino-isocyanates have found limited applications for the synthesis of  $\beta$ -aminocarbonyl compounds, imino-isocyanates have comparatively emerged as valuable synthetic tools. We have demonstrated the versatility of fluorenone-derived *O*-phenyl hydrazone as a reagent for intermolecular aminocarbonylation. We have also found reliable conditions for the subsequent derivatization of azomethine imine products to useful  $\beta$ -aminocarbonyl compounds. As such, imino-isocyanates have been proven as useful alternatives to chlorosulfonyl isocyanate. Broad structural diversity is obtained since various alkenes were combined with unsymmetrical hydrazones, symmetrical and thus enabling the synthesis of a variety of azomethine imine products. In addition to those herein reported, over a hundred examples of azomethine imines have thus far been synthesized by the Beauchemin group. Efforts are now focused on the development of enantioselective kinetic resolutions and more effective methods for derivatization. Enantioselective aminocarbonylation is also being explored.

The versatility of the *N*-substituted isocyanates described goes beyond the functionalization of alkenes. As new classes of “blocked” isocyanates,<sup>17</sup> carbamoyl hydrazones have also been utilized to achieve substitution in the presence of nucleophiles. While initially, this reactivity was developed to generate new aminocarbonylation reagents, the Beauchemin group has found an effective method for the rapid generation of semicarbazones and hydrazone derivatives via imino-isocyanates (equation 3.12).<sup>18</sup> This method provides a useful alternative to the synthesis of hydrazones by condensation of the parent carbamoyl hydrazines with aldehydes or ketones.



Given the control provided over self-dimerization anticipated with amino-isocyanates, imino-isocyanates should find broad synthetic applications. However, even though applications of amino-isocyanates have been thus far rather limited, the next chapter will provide demonstration of their synthetic utility.

<sup>17</sup> (a) Wicks, D. A.; Wicks, Z. W. Jr. *Prog. Org. Coat.* **1999**, 36, 148. (b) Wicks, D. A.; Wicks, Z. W. Jr. *Prog. Org. Coat.* **2001**, 41, 1.

<sup>18</sup> Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, 15, 4074.

# Chapter

# 4 Amino-Isocyanates as Powerful Intermediates in Heterocyclic Chemistry

## 4.1 Introduction

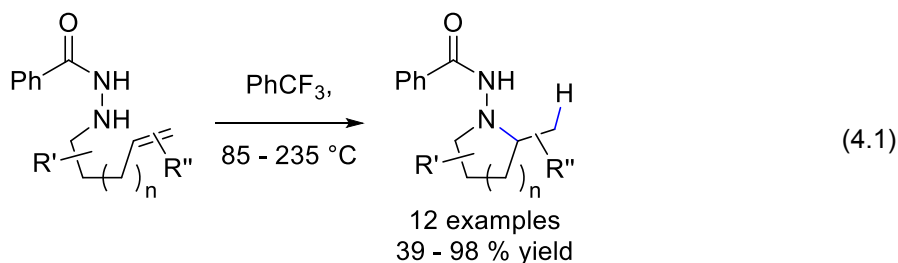
Improvement of current chemical processes and discovery efforts require efficient reactions with the ability to rapidly assemble complex molecules from simple starting materials. Development of novel pharmaceuticals relies on practical synthetic strategies offering step-economy and chemoselectivity. This consequently restricts the use of certain reagents bearing unique and interesting functionalities. For instance, hydrazines have inherent chemoselectivity issues because of the possibility that both nitrogen atoms could react. For example, regio- and chemoselective alkylation reactions are hardly achievable without the use of protecting groups. Despite this, the importance of hydrazine scaffolds has led to many recent reports. The goal of this chapter is to discuss new advances for the hydroamination of hydrazides and to demonstrate, for this purpose, the utility of N-



substituted isocyanates and in particular amino-isocyanates in providing highly chemoselective functionalization of hydrazines.

#### 4.1.1 Summary of Initial Hydrazone Hydroamination Substrates

In previous work, the Beauchemin group demonstrated the reactive potential of hydrazides to undergo hydroamination and their advantages over hydrazine and hydroxylamines in terms of stability and practicality. Initial investigation permitted development of a first generation system involving benzoic hydrazides as presented in equation 4.1.<sup>1</sup>



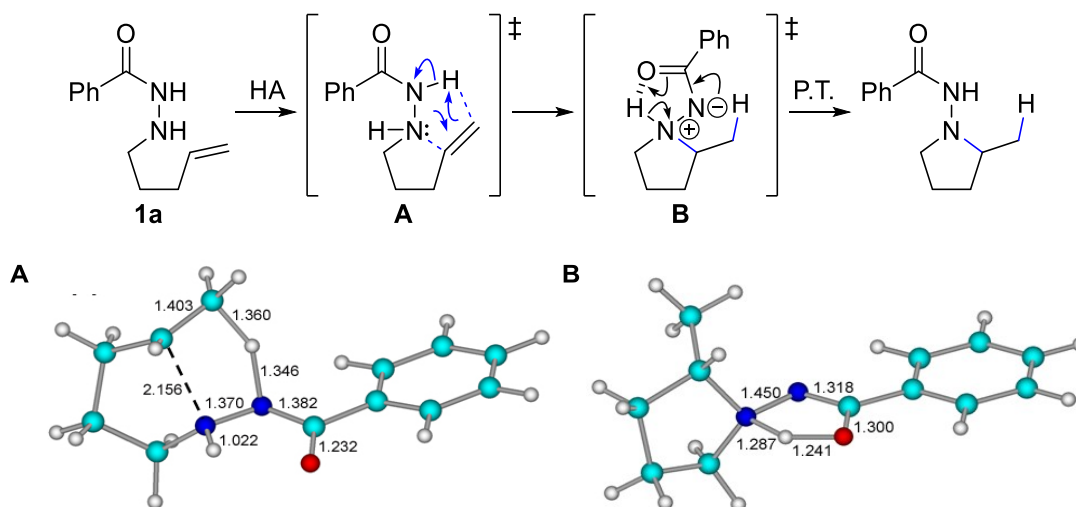
Following an initial survey of hydrazides, hydroamination was found to be preferred for substrates without the propensity of generating amino-isocyanates which can result in undesired side-reactions. Benzoic hydrazides proved very stable under thermal conditions which made the reaction amenable for the synthesis of various heterocycles. In continuation with this initial study, it became necessary to acquire further mechanistic details in order to orient future developments of the reactivity.

#### 4.1.2 Mechanistic Insights Into the Hydrohydrazidation of Alkenes

In efforts to better describe the hydroamination event, DFT calculations were performed on benzoic hydrazide **1a**. Activation energies ( $\Delta G_{\text{HA}}^\ddagger$ ) calculated for

<sup>1</sup> Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 9740.

hydrohydrazidation transition states were of 28.7 kcal/mol for five-membered transition state **A**. Attributed to this is the increased acidity of hydrazides' alpha proton, given the electron withdrawing effect of the carbonyl group. This is thought to promote the hydroamination event by facilitating the olefin protonation and stabilizing the resulting dipole (see TS **A**, Figure 4.1). In addition, calculations revealed the importance of the subsequent proton transfer step (**B**), which was found to be facilitated by the carbonyl moiety in a five-membered transition state ( $\Delta G_{PT}^\ddagger = 5.2$  kcal/mol).



**Figure 4.1** Transition state for the hydrohydrazidation of alkenes (**A**) and proton transfer of the dipolar intermediate (**B**)

## 4.2 Hydroamination of Alkenes with Hydrazides: Second Generation

Given the apparent importance of the alpha proton's acidity in the reaction mechanism, we sought to further enhance hydroamination by exploring the reactivity of new and untapped reagents. In collaboration with Mr. Francis Loiseau, a systematic survey of hydrazine derivatives was undertaken.

#### 4.2.1 Survey of New Hydrazides as Hydroamination Substrates

Expanding from our initial work on hydrohydrazidation, Table 4.1 includes hydrazides bearing various electron-withdrawing groups.<sup>2</sup> We started our investigation by evaluating the reactivity of thiosemicarbazide **2a**, which under our reaction conditions displayed very good reactivity at lower temperatures (entry 1, 100 °C) than the first generation benzoic hydrazides. Arguably, sulfur, given its polarizable nature, increases the acidity of the alpha proton, thus favoring hydroamination. Comparably to this result, the reactivity could be extended to phosphohydrazides, which despite the necessity for longer reaction time could afford hydroamination with excellent yields (entry 2-3). Building on previous work on benzoic hydrazides, attention was focused on substituted aromatic substrates. Gratifyingly, we saw increased reactivity with substrates possessing hydrogen bonding such as the hydroxy group (entry 4-5) and electron withdrawing substituents (entry 5-7). However, given the poor solubility of substrates bearing nitro groups, the (bis-trifluoromethyl)benzoic hydrazide reagent was chosen for further exploration of more challenging intramolecular reactions.

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<sup>2</sup> Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin A. M. *Chem. Commun.* **2011**, 47, 562.

**Table 4.1** Scope of intramolecular hydroamination using hydrazides

$$\text{EWG}-\text{NH}-\text{CH(R}^1\text{)}-\text{CH}_2-\text{CH=CH}_2 \xrightarrow[\text{conditions}^a]{70-170\text{ }^\circ\text{C}} \text{EWG}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH(R}^1\text{)}-\text{CH}_3$$

**1a-g** **2a-g**

| Entry | EWG                                   | R <sup>1</sup> | Temp. (°C) | Product   | Yield <sup>b</sup> (%) |
|-------|---------------------------------------|----------------|------------|-----------|------------------------|
| 1     | <p>X = S (<b>1a</b>)</p>              | H              | 100        | <b>2a</b> | 86                     |
| 2     | <p>R = Et (<b>1b</b>)</p>             | H              | 120        | <b>2b</b> | 98 <sup>c</sup>        |
| 3     | <p>R = Ph (<b>1c</b>)</p>             | H              | 110        | <b>2c</b> | 98 <sup>c</sup>        |
| 4     | <p>R = H (<b>1d</b>)</p>              | Me             | 90         | <b>2d</b> | 90 <sup>d</sup>        |
| 5     | <p>R = NO<sub>2</sub> (<b>1e</b>)</p> | Me             | 70         | <b>2e</b> | 88 <sup>d</sup>        |
| 6     | <p><b>1f</b></p>                      | Me             | 90         | <b>2f</b> | 91 <sup>d</sup>        |
| 7     | <p><b>1g</b></p>                      | H              | 95         | <b>2g</b> | 81                     |

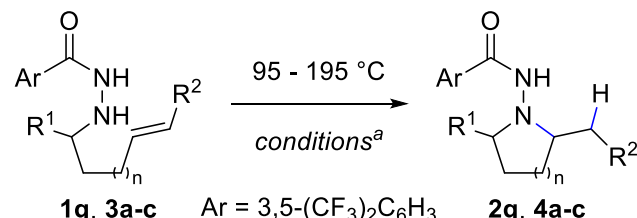
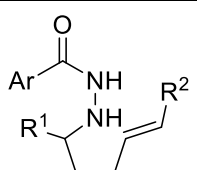
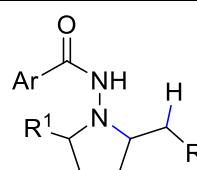
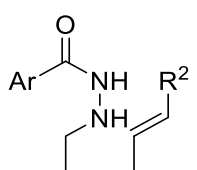
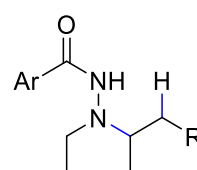
<sup>a</sup> Conditions: Heating performed in PhCF<sub>3</sub> (0.05 M), in sealed tubes (18–40 h) or in a microwave reactor (10–16 h). <sup>b</sup> Isolated yield. <sup>c</sup> NMR yield using 1,4-dimethoxybenzene as an internal standard. <sup>d</sup> Obtained as a mixture of diastereomers.

with Francis Loiseau

To compare the reactivity and improvement on the synthetic scope of the reaction, alkenyl hydrazide precursors were selected from our previous survey of benzoic hydrazides (see Table 1.6). Generally, the effect of *bis*-trifluoromethyl was positive on the outcome of the hydroamination event. In comparison to unsubstituted benzoic hydrazides (Table 4.2),

cyclization was possible at lower temperatures (Table 4.4). Again, substitution on the alkenyl chain and distal position of the alkene was tolerated and the cyclized products were obtained in good yields (entry 1-3). We also observed significant improvement for the formation of piperidine rings (entry 4 & 5).

**Table 4.2** Scope of 3,5-bis(bis(trifluoromethyl)benzylhydrazides hydroamination

|  |                                                                                     |               |                                                                                      |                           |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------|--------------------------------------------------------------------------------------|---------------------------|
| entry                                                                              | substrate                                                                           | temp.<br>(°C) | product                                                                              | yield <sup>b</sup><br>(%) |
|                                                                                    |   |               |   |                           |
| 1                                                                                  | R <sup>1</sup> =H, R <sup>2</sup> =H ( <b>1g</b> )                                  | 95            | <b>2g</b>                                                                            | 81                        |
| 2                                                                                  | R <sup>1</sup> =Me, R <sup>2</sup> =H ( <b>3a</b> )                                 | 95            | <b>4a</b>                                                                            | 85 <sup>c</sup>           |
| 3                                                                                  | R <sup>1</sup> =H, R <sup>2</sup> =Me ( <b>3b</b> )                                 | 150           | <b>4b</b>                                                                            | 91                        |
|                                                                                    |  |               |  |                           |
| 4                                                                                  | R <sup>2</sup> =H ( <b>3c</b> )                                                     | 175           | <b>4c</b>                                                                            | 82                        |
| 5                                                                                  | R <sup>2</sup> =Et ( <b>3d</b> )                                                    | 195           | <b>4d</b>                                                                            | 53                        |

<sup>a</sup> Conditions: Heating performed in PhCF<sub>3</sub> (0.05 M), in sealed tubes (10-24 h) or in a microwave reactor (10-16 h). <sup>b</sup> Isolated yield. <sup>c</sup> NMR yield using 1,4-dimethoxybenzene as an internal standard.

#### 4.2.2 Summary of Improved of Cope-type Hydroamination

In addition to the intramolecular reactivity herein presented, Mr. Loiseau and colleagues further expanded the use of bis-(trifluoromethyl) hydrazide reagents towards the development of intermolecular hydrohydrazidation.<sup>8</sup> While further details into this

inquiry are reported in Mr. Loiseau's thesis,<sup>3</sup> development of improved benzoic hydrazide derivatives for hydroamination nonetheless proved challenging. Solubility issues and difficulties in characterizing substrates shed light on some of the inconveniences associated with this Cope-type hydroamination approach. However, this investigation revealed the generalizability of hydroamination to different carbamoyl hydrazide precursors and confirmed, as predicted, the effect of increasing the alpha nitrogens' acidic character which resulted in better yields and milder hydroamination conditions.

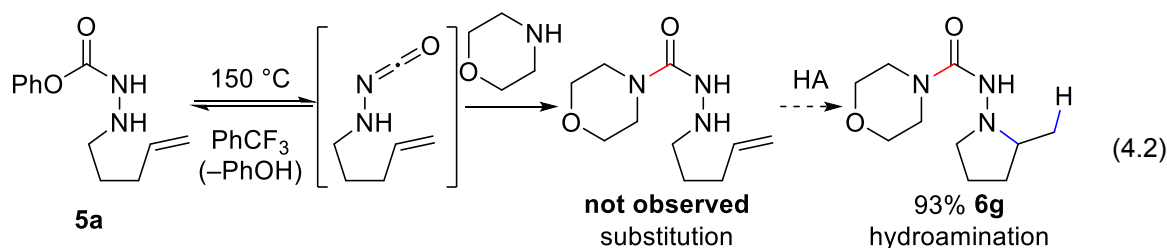
### 4.3 Amino-Isocyanates Reagents for the Hydroamination of Alkenes

#### 4.3.1 Preliminary Results

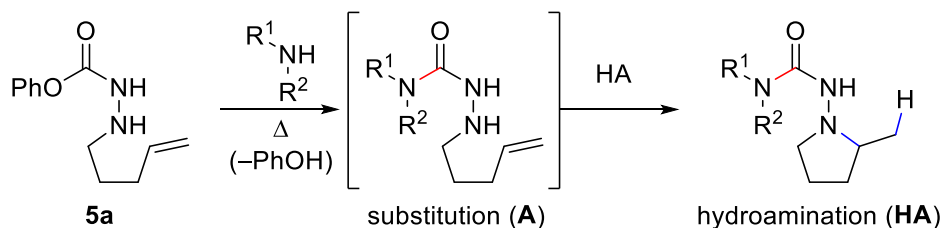
While reagent screening is an important part of the study of new reactions, efforts towards the development of hydrazine reagents is sometimes slowed by the limited diversity of available derivatives. In our efforts towards optimization of previously described aminocarbonylation reaction, it was understood that further insights in the generation of amino-isocyanates would require screening for the reactivity of carbazates bearing different leaving groups. As a solution, we sought to make use of our previously developed conditions for the generation of amino-isocyanates and expose these intermediates to various nucleophiles. For instance, we submitted *O*-phenyl hydrazide **5a** to standard amino-isocyanate generating conditions (150 °C) in the presence of an amine nucleophile (equation 4.2) with the hopes of exchanging the corresponding leaving group. While we did observe the desired reaction, we also isolated hydroamination product **6g** in excellent yield.

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<sup>3</sup> Loiseau, F. *Cope-Type Hydroamination of Alkenes with Hydroxylamines and Hydrazines – Scope and Mechanism*. Ph. D. Thesis, 2012, University of Ottawa.



Although this surprising result revived our interest in a potentially new kind of synthetic sequence for Cope-type hydroamination, questions remained as to which species performed the cyclization. Two possibilities emerged: The first, corresponding to the exchange/hydroamination sequence of equation 4.2. The second involving direct hydroamination of carbamate **6a** followed by substitution of leaving group. To discriminate between these two possibilities, we attempted to optimize the substitution reaction as to minimize the hydroamination event then isolate the corresponding semicarbazide and submit it to standard hydroamination conditions. Results are presented in Table 4.3. Entries performed with morpholine were difficult since hydroamination proved facile (entry 1-5). Lower temperature and shorter reaction time did not provide optimum conditions for generation of the semicarbazide, traces of hydroamination would often be observed and difficult to separate. Therefore, we instead used pyrrolidine as the amine nucleophile. Initially, reaction in pyrrolidine as a solvent proved promising for substitution while minimizing formation of the hydroamination product. Thus, temperature could be lowered from 150 °C to 80 °C (entry 8-12). However, because the use of large excess of amine was impractical, we also explored if the amount of nucleophile could be reduced. To our delight, we were able to optimize the amine loading by lowering the equivalents of pyrrolidine to a small excess (1.1 equivalent) and increasing the reaction concentration (entry 13-14). In addition, at 80 °C the substitution reaction proved essentially complete after only 10 minutes with no apparent traces of hydroamination (entry 14).

**Table 4.3** Optimization of amine substitution with O-phenyl carbazate

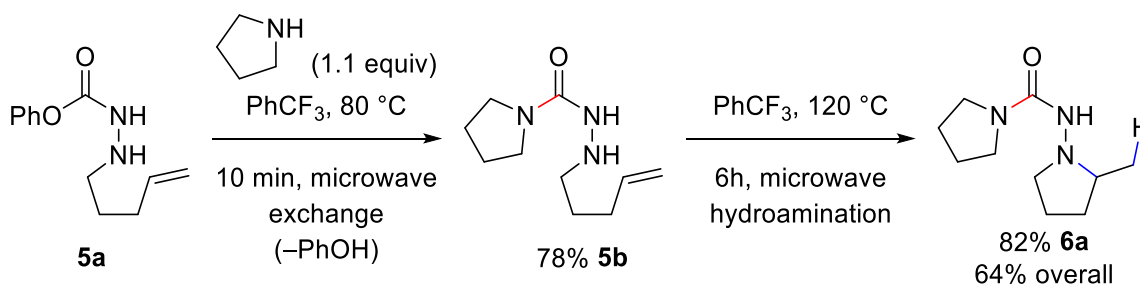
| entry | amine | equiv. | solvent           | conc.<br>(M) | temp.<br>(°C) | time<br>(h) | yield (%) <sup>a</sup> |                 |     |
|-------|-------|--------|-------------------|--------------|---------------|-------------|------------------------|-----------------|-----|
|       |       |        |                   |              |               |             | 10a                    | A               | HA  |
| 1     |       | 2.0    | PhCF <sub>3</sub> | 0.3          | 150           | 0.5         | < 1                    | 0               | 93  |
| 2     |       | 2.0    | PhCF <sub>3</sub> | 0.3          | 150           | 1           | 0                      | 0               | 99  |
| 3     |       | 1.0    | PhCF <sub>3</sub> | 0.3          | 150           | 1           | 0                      | 0               | 88  |
| 4     |       | 2.0    | PhCF <sub>3</sub> | 0.3          | 120           | 1           | 0                      | 37              | 73  |
| 5     |       | 2.0    | PhCF <sub>3</sub> | 0.3          | 80            | 1           | 96                     | 0               | 3   |
| 6     |       | 1.1    | PhCF <sub>3</sub> | 0.3          | 80            | 10 min      | 99                     | 0               | 0   |
| 7     |       | 1.0    | neat              | 0.1          | 120           | 1           | 0                      | 42              | 55  |
| 8     |       | 1.0    | neat              | 0.1          | 150           | 3 min       | 0                      | -               | < 1 |
| 9     |       | 1.0    | neat              | 0.1          | 150           | 1 min       | 0                      | -               | < 1 |
| 10    |       | 1.0    | neat              | 0.1          | 120           | 10 min      | 0                      | -               | < 1 |
| 11    |       | 1.0    | neat              | 0.1          | 120           | 1 min       | 0                      | -               | < 1 |
| 12    |       | 1.0    | neat              | 0.1          | 100           | 1 min       | 0                      | -               | < 1 |
| 13    |       | 1.0    | PhCF <sub>3</sub> | 0.3          | 80            | 0.5         | 0                      | 82              | < 1 |
| 14    |       | 1.1    | PhCF <sub>3</sub> | 0.3          | 80            | 10 min      | 0                      | 99 <sup>b</sup> | 0   |

<sup>a</sup> Yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. <sup>b</sup> Isolated yield.

Fortunately, the substitution product **5b** could be isolated and subsequently submitted to our previously described hydroamination conditions (Scheme 4.1). As a result, product **6a** was isolated in excellent yield, thus confirming semicarbazide **5b** as the hydroamination precursor.<sup>4</sup>

<sup>4</sup> Clavette, C.‡; Vincent-Rocan, J. F.‡; Beauchemin A. M. *Angew. Chem. Int. Ed.* **2013**, 52, 12705.

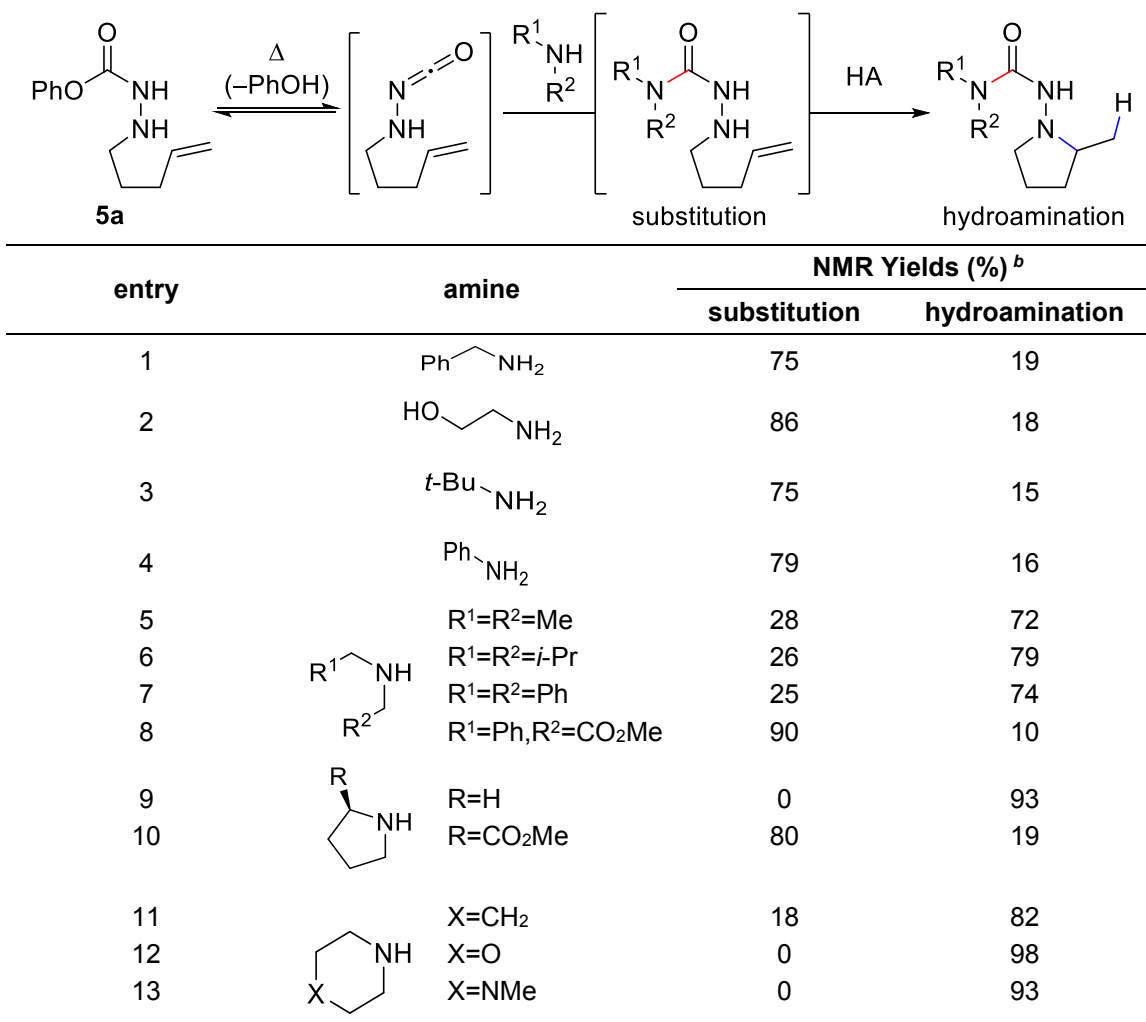


**Scheme 4.1** Stepwise exchange / hydroamination sequence

Assuming amine substitution to readily take place under our hydroamination conditions, we sought to combine these reactions in a one-pot substitution/hydroamination cascade. Therefore, we surveyed the scope of amines to identify the most suitable semicarbazide species for hydroamination (Table 4.4). Results of this survey served as a qualitative assessment of the reactivity and a guide to subsequent development efforts. Fortunately, the reactions herein described revealed no apparent traces of starting material leftover, thus implying full conversion. While all amines effectively provided substitution products, discernment towards the propensity of these semicarbazides for hydroamination could be drawn. As such, primary amines were found to cyclize in poor yields (entry 1-4). Interestingly, use of ethanolamine (entry 2) provided only substitution from the amine moiety, thus demonstrating the greater propensity of amines, in opposition to alcohols, to react with isocyanates. Hindered nucleophiles such as *tert*-butylamine could also react, whereas aniline provided comparable yield (entry 3-4). Overall, adducts of secondary amines proved to be superior hydroamination precursors. Symmetrical acyclic amines provided hydroamination products in good yield (entry 5-7) whereas benzyl methylglycinate showed lower levels of reactivity (entry 8). In comparison to the stepwise sequence described in Scheme 4.2, the one pot procedure with pyrrolidine (entry 9) provided superior yield for hydroamination. Interestingly, as with the glycinate derivative

(entry 8), methyl prolinates did not cyclize appropriately. Insights into the reactivity of amino esters will be provided in further discussion (Section 4.3.2). In turn, as demonstrated previously with morpholine, substitution with six-membered cyclic amines underwent hydroamination with very good yields (entry 12-13).

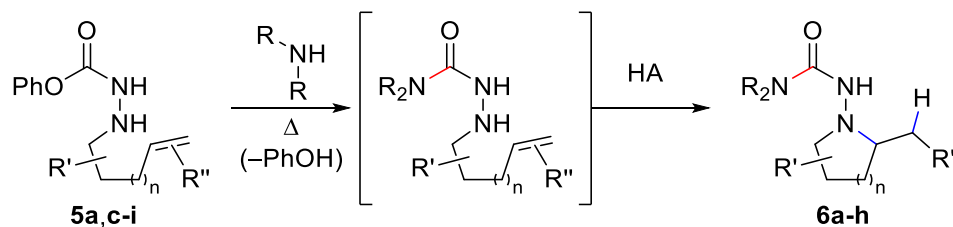
**Table 4.4** Optimization of amines for substitution/hydroamination sequence <sup>a</sup>



<sup>a</sup> Conditions: carbazate (1 equiv), amine (1.1 equiv) in PhCF<sub>3</sub> (0.3M) heated in a sealed vial (microwave reactor, 120 °C, 6h). <sup>b</sup> Yield determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

We then embarked on a study to determine if this cascade reaction could provide access to various heterocyclic hydrazides: the results obtained are shown in Table 4.5. As

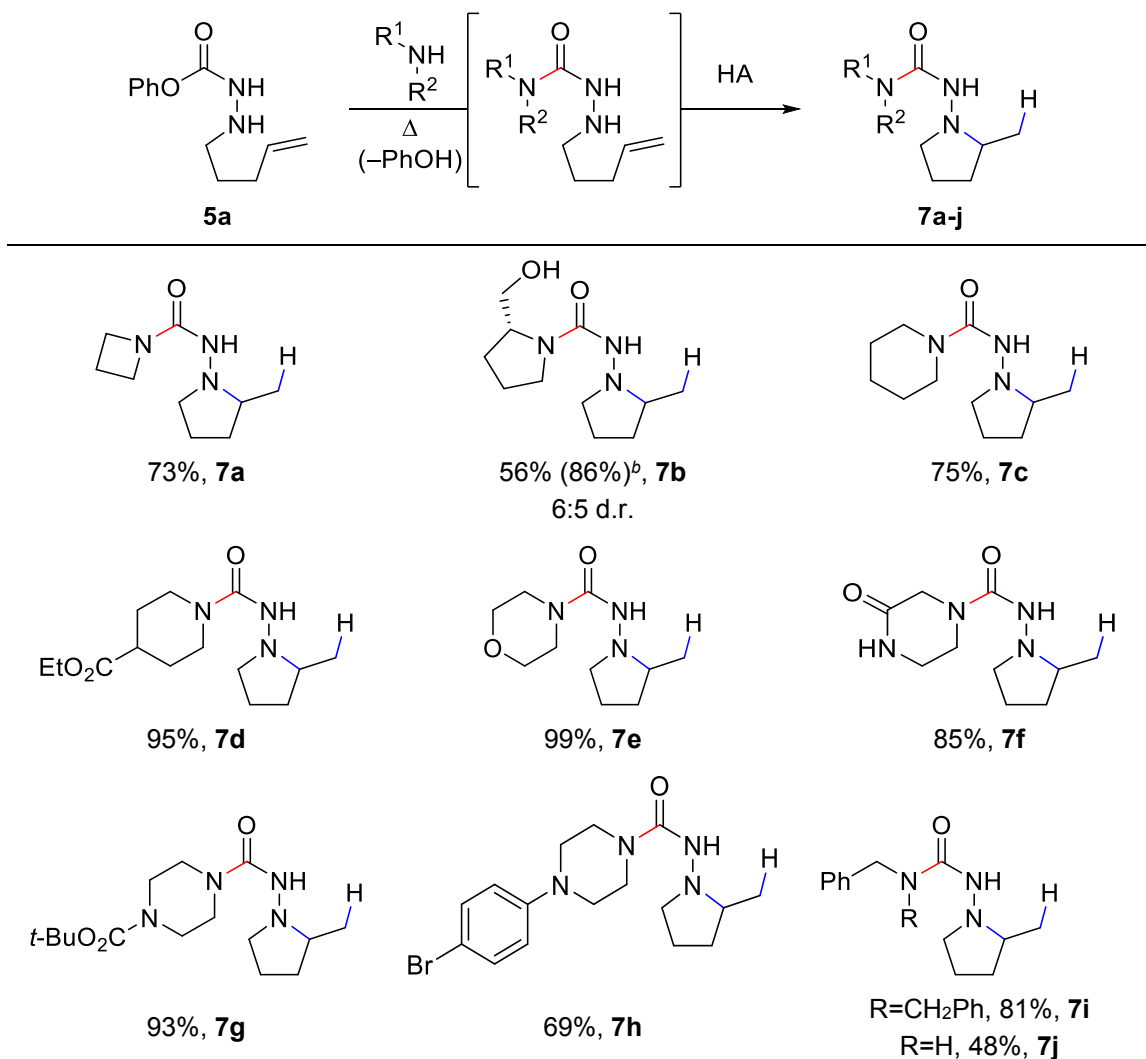
expected, the gem-dimethylated substrate **10c** cyclized under milder reaction conditions (80 °C) because of a favorable Thorpe-Ingold effect (entry 2). Substitution was also tolerated on the distal position of the alkene but slightly higher temperatures were required to achieve the parent sequence on both *cis* and *trans* alkenes (entry 3-4). The sequence also proved versatile to form six-membered-ring systems and led to the formation of piperidine and piperazine motifs (entries 6-8).

**Table 4.5** Substitution/hydroamination sequence using carbazates <sup>a</sup>

| entry | alkenyl carbazate                      | temp.<br>(°C) | time<br>(h) | product   | yield <sup>b</sup><br>(%) |
|-------|----------------------------------------|---------------|-------------|-----------|---------------------------|
|       |                                        |               |             |           |                           |
| 1     | $R^1=R^2=R^3=H$ ( <b>5a</b> )          | 120           | 6           | <b>6a</b> | 88                        |
| 2     | $R^1=R^2=Me$ , $R^3=H$ ( <b>5c</b> )   | 80            | 6           | <b>6b</b> | 99                        |
| 3     | $R^1=R^2=H$ , $R^3=Me$ ( <b>5d</b> )   | 175           | 6           | <b>6c</b> | 86                        |
|       |                                        |               |             |           |                           |
| 4     | $R^1=H$ , $R^2=CH_2OMOM$ ( <b>5e</b> ) | 175           | 6           | <b>6d</b> | 74                        |
| 5     | $R^1=Me$ , $R^2=H$ ( <b>5f</b> )       | 120           | 6           | <b>6e</b> | 94                        |
|       |                                        |               |             |           |                           |
| 6     | $X=CH_2$ ( <b>5g</b> )                 | 175           | 16          | <b>6f</b> | 79                        |
| 7     | $X=NTs$ ( <b>5h</b> )                  | 175           | 6           | <b>6g</b> | 86                        |
| 8     | $X=C(CH_3)_2$ ( <b>5i</b> )            | 150           | 12          | <b>6h</b> | 82                        |

<sup>a</sup> Conditions: carbazate (1 equiv), amine (1.1 equiv) in  $PhCF_3$  (0.3M) heated in a sealed vial (microwave reactor). <sup>b</sup> Yield of the isolated product. <sup>c</sup> 1:1 d.r. MOM = methoxymethyl, Ts = 4-toluenesulfonyl.

As part of ongoing work on Cope-type hydroaminations, we often faced the issue that intramolecular alkene hydroaminations are generally not amenable to rapid generation of molecular complexity. Indeed, synthesis of the precursors typically requires several steps, and cyclization can only form one product. In efforts to demonstrate the synthetic advantages of the present cascade reaction, we further refined our survey of amine nucleophiles. As shown in Table 4.6, ten different hydroamination products were isolated using the same precursor, **5a**.

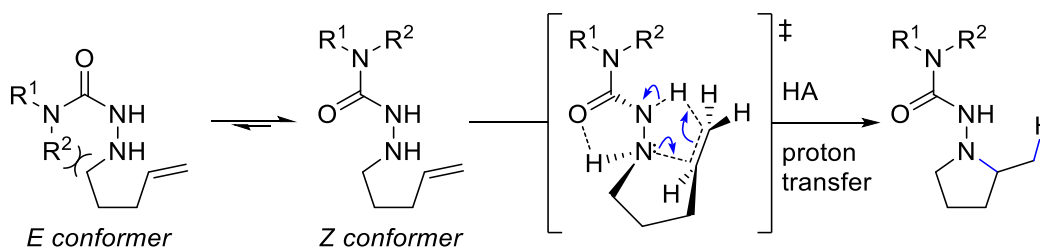
**Table 4.6** Amine scope of substitution/hydroamination cascade

<sup>a</sup> Conditions: carbamate (1 equiv), amine (1.1 equiv) in PhCF<sub>3</sub> (0.3M) heated in a sealed vial (microwave reactor, 120 °C, 6h). Yields reported are those of the isolated products. <sup>b</sup> Yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Again, both cyclic and acyclic secondary amines proved to be competent nucleophiles. For cyclic amines, four-, five- and six-membered amines led to the desired hydroamination products. (*S*)-Prolinol also reacted well as a nucleophile and provided hydroamination in good yield, but only showed modest diastereoselectivity under the reaction conditions (1.2:1 d.r.). Piperidine derivatives, proved efficient reagents. Other nitrogen heterocycles such as morpholine and piperazines, including the medically

relevant 2-oxopiperazine motif, underwent the reaction sequence to provide the hydroamination products in good to excellent yields. We then compared the reactivity of cyclic versus acyclic secondary amines. *N,N*-Dibenzylamine provided the hydroamination product **7i** in good yield but proved less reactive than cyclic derivatives. In contrast, primary amines such as benzylamine only gave a moderate yield of the hydroamination product **7j**. We explain this difference in hydroamination reactivity between adducts of the primary and secondary amines by the increased population of the *Z* conformer present in the hydroamination substrate (Scheme 4.2).

**Scheme 4.2** Cope-type hydroamination transition state with semicarbazide



Arguably, secondary amine moieties provide increased steric hindrance between substituents and N-N bond of the *E* conformer normally favored by hydrazides because of dipole minimization. This hindrance could be further accentuated with cyclic amines given the rotational restriction imposed by a cyclic functionality. As supported by previous DFT calculations (see section 4.1), the *Z* conformer is in the appropriate conformation to react via the proposed concerted transition-state. Reasons for this conformational requirement remain unclear, however it is arguable that hydrogen bonding between the carbonyl and amine nucleophile could provide significant stabilization for the hydrazides' developing zwitterionic character (see transition state, Scheme 4.2), an interaction not possible with the *E* conformer. In addition, while yields and conditions here obtained are comparable to

hydroaminations with benzoic hydrazides, effect of an added electron donating nitrogen as with the herein discussed semicarbazides should have for effect of reducing the acidity of adjacent N-H bond, not increasing it. Therefore, these results suggest that the efficiency of the hydroamination event is not completely dependent on the acidity of the reagent's protonating moiety but that conformational effects play an significant role as well.

#### *4.3.2 Summary of the Intramolecular Hydroamination of Alkenes with Hydrazides.*

During our study of the reactivity of hydrazides, we had initially found carbazates to be unsuitable for hydroamination given their ability to generate amino-isocyanates under thermal conditions. However, amino-isocyanates have given us the possibility to obtain untapped molecular complexity and allowed further insights into Cope-type hydroamination reactivity. As a unique feature of the described hydroamination sequence, amino-isocyanates have provided the possibility to obtaining rapid and effective modification of hydroamination substrates, to allow as we have demonstrated a diversity of new and easily accessible semicarbazide products. These new results have encouraged us to further improve the reactivity of hydrazides through catalytic and/or enantioselective variants. For example, the semicarbazides' urea moiety could provide a handle for activation with Brønsted or Lewis acids. Further investigations are currently underway to develop these reactions.



## 4.4 Cascade Substitution / Cyclization with Amino-Isocyanates.

### 4.4.1 Synthesis of Aza-Peptoids

Having demonstrated the versatility of sequential reactions involving amino isocyanates in the context of hydroamination, we then focused on the synthesis of other important and medically relevant hydrazine subunits. We thus sought to demonstrate that this substitution reactivity could provide access to various azadipeptide subunits.<sup>5,6</sup> Indeed, azapeptides and peptoids are part of the rapidly expanding repertoire of amino acid mimics which are used in peptidomimetics.<sup>11</sup> The increased metabolic stability of the resulting unnatural oligomers is well-established. However, a notable advantage of azapeptides is that their subunits lack stereochemical information in contrast to  $\alpha$ ,  $\beta$ , and  $\gamma$ -amino acids derived peptides, which require the use of enantiopure unnatural amino acids. Consequently, we felt that simple substitution reactivity would provide a useful tool in peptidomimetics, and decided to perform exploratory studies with *N*-benzyl azapeptoid building block **5j** (Table 4.7).

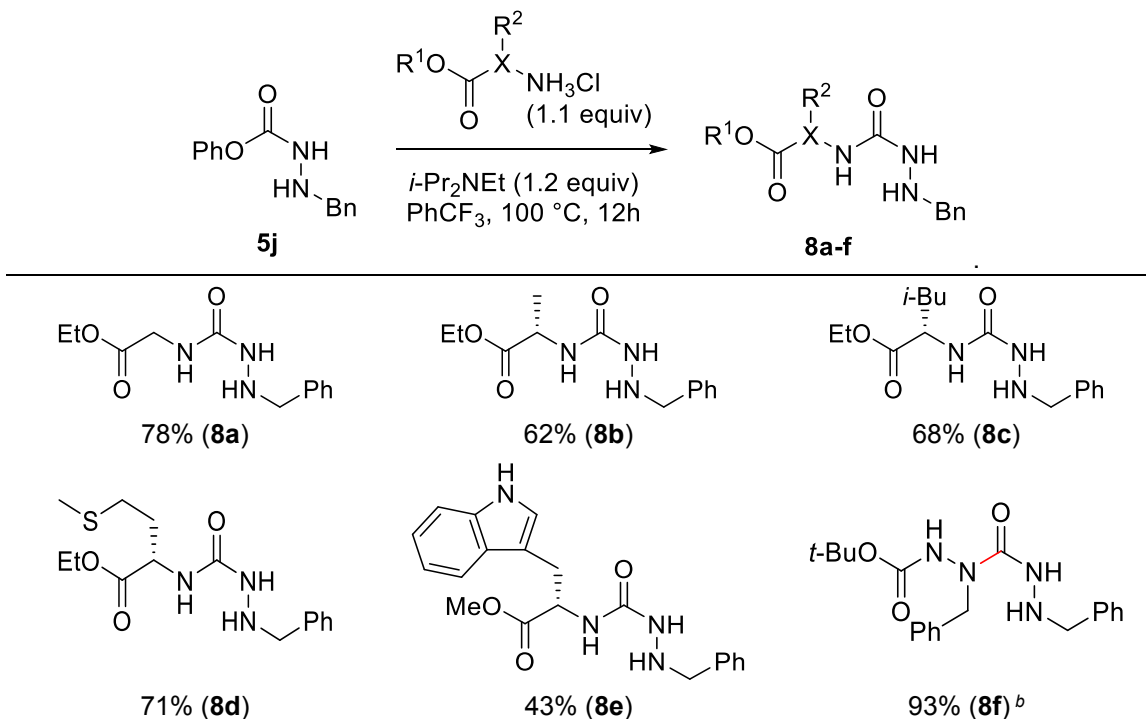
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<sup>5</sup> Azapeptides: a) C. B. Bourguet, C. Proulx, S. Kloczek, D. Sabatino, W. D. Lubell, *J. Pept. Sci.* **2010**, *16*, 284; b) C. Gibson, S. L. Goodman, D. Hahn, G. Holzemann, H. Kessler, *J. Org. Chem.* **1999**, *64*, 7388; c) E. Wiczerzak, E. Jankowska, S. Rodziejewicz-Motowidlo, A. Geldon, J. Lagiewka, Z. Grzonka, M. Abrahamson, A. Grubb, D. Bromme, *J. Pept. Res.* **2006**, *66*, 1; d) E. Wiczerzak, S. Rodziejewicz-Motowidlo, E. Jankowska, A. Geldon, J. Ciarkowski, *J. Pept. Sci.* **2007**, *13*, 536; e) H.-J. Lee, J.-W. Song, Y.-S. Choi, H.-M. Park, K.-B. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 11881; f) N. S. Freeman, Y. Tal-Gan, S. Klein, A. Levitzki, C. Gilon, *J. Org. Chem.* **2011**, *76*, 3078; azatides: g) H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, *118*, 2539; h) Y. Han, J. Yoon, K. D. Janda *Bioorg. Med. Chem. Lett.* **1998**, *8*, 117;

<sup>6</sup> (Hydrazino azapeptoids: a) A. Aubin, B. Martin, J.-G. Delcros, Y. Arlot-Bonnemains, M. Baudy-Floc'h, *J. Med. Chem.* **2005**, *48*, 330; For selected reviews, see: b) C. Proulx, D. Sabatino, R. Hopewell, J. Spiegel, Y. Garcia Ramos, W. D. Lubell, *Future Med. Chem.* **2011**, *3*, 1139; b) J. Gante, *Angew. Chem.* **1994**, *106*, 1780. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699; d) A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244.

Encouragingly, the use of commercially available  $\alpha$ -aminoester ethyl glycinate (HCl salt) provided the azadipeptide subunit **8a** in 78% yield. A similar result was obtained with L-alanine ethyl ester to form **8b**, and we ensured that racemization did not occur under the reaction conditions (see supporting information). Several encouraging results were also obtained with enantiopure  $\alpha$ -aminoesters (**8c-e**). Seeking to form the parent nitrogen analogue (an azatide subunit), *tert*-butylbenzylcarbazate was able to undergo an efficient substitution with **8j** despite a much slower reaction (**8f**, 93% yield). We explain this observation by the reduced nucleophilicity of *tert*-butyl-*N*-benzylcarbazate relative to primary and secondary amines.

**Table 4.7** Synthesis of dipeptide analogues using substitution reaction <sup>a</sup>

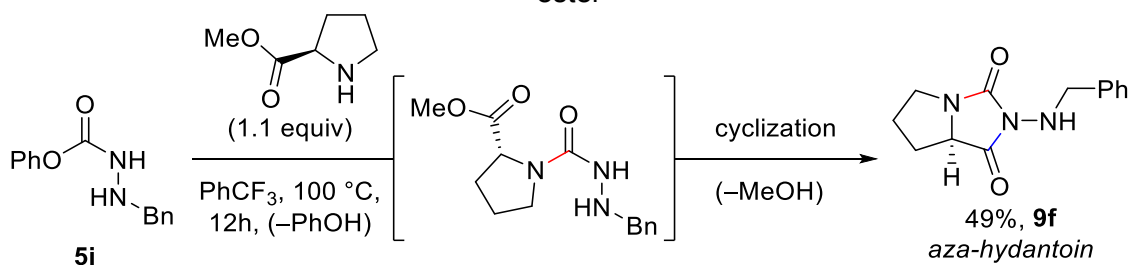


<sup>a</sup> Conditions: carbazate (1 equiv), amine (1.1 equiv), *i*-Pr<sub>2</sub>NEt (1.2 equiv) in PhCF<sub>3</sub> (0.3 M) heated in a sealed vial (100 °C, 12 h). Yields shown are those of the isolated product. <sup>b</sup> Conditions: similar, except: *tert*-butyl-*N*-benzylcarbazate (10 equiv), heated in oil bath.

#### 4.4.2 New Aza-Hydantoin Synthesis

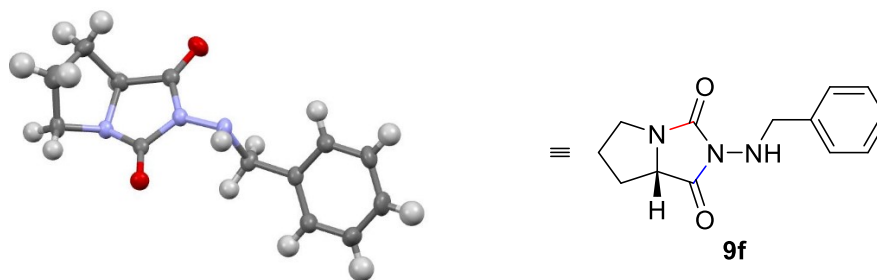
Additionally, it is important to note that yields of products herein presented are dependent on the nature of the amino ester nucleophile. Indeed, we found primary amino esters to provide improved yields of the desired aza-dipeptides while the generation of a second product was observed when secondary amines were used. Indeed, with proline methyl ester, under our optimized conditions, we found ourselves incapable of efficiently generating the corresponding dipeptide. Interestingly, we instead isolated cyclization product **9g** (Scheme 4.3). Mass analysis also revealed the product to be lacking a methanolic moiety, suggesting an intramolecular transformation involving the ester.

**Scheme 4.3** Substitution cyclization reactivity of *O*-phenyl carbazate with proline methyl ester



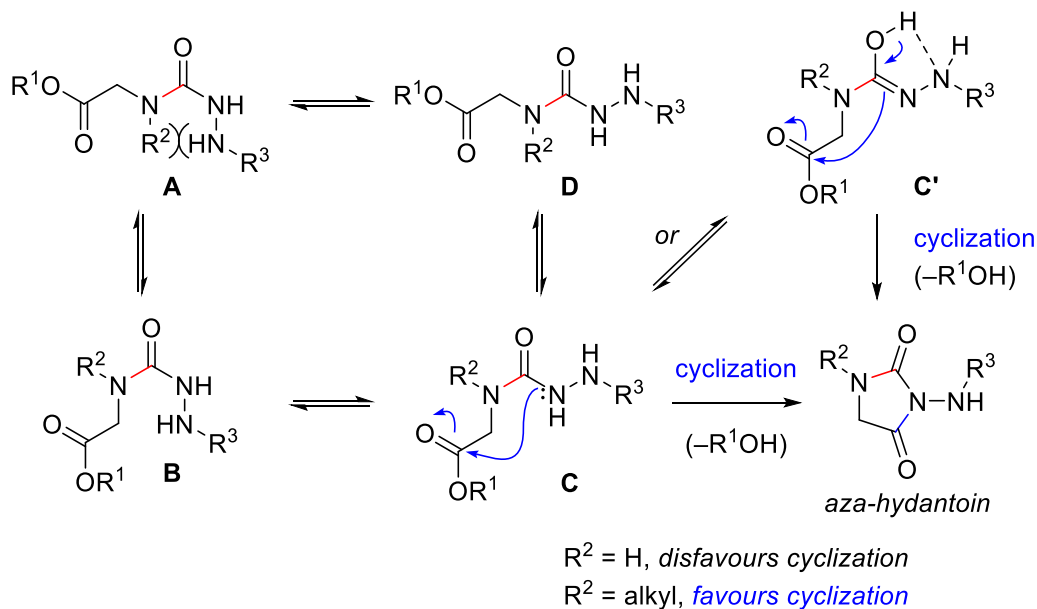
We therefore submitted product **9g** for X-ray crystallographic analysis and were able to confirm the structure as an aza-hydantoin (Figure 4.2). Following the exchange of the *O*-phenyl leaving group for the amine moiety, we proposed the nucleophilic attack of the hydrazide's alpha nitrogen on the ester to take place, as pictured in Scheme 4.4.<sup>7</sup>

<sup>7</sup> Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A. M. *manuscript in preparation*.



**Figure 4.2** X-ray crystallographic structure of aza-hydantoin product **9f**

Attempts at providing a mechanistic explanation for the formation of the observed aza-hydantoin product lead us to wonder about the various conformations adoptable by our aza-dipeptoid subunits. To start with, experimental evidence suggests the preference of the hydrazide moiety for the *E* conformation as presented by conformers **A** and **B** (Scheme 4.4). However, as suggested by our work on hydroamination, the resulting semicarbazide, from the leaving group exchange with a secondary amine is thought to adopt the *Z* conformation (conformers C and D) due to increased steric hindrance between the N-N moiety and the amine's alkyl group. In addition, it is envisioned that an equilibrium exists between conformations around the amine moiety (conformers A and B). Therefore, considering of these factors, conformer C was suggested as the most favorable intermediate for intramolecular cyclization.

**Scheme 4.4** Possible conformers intermediates in the formation of aza-dipeptoids and aza-hydantoin

With this description, we were also able to account for the fact that substrates derived from primary amines ( $R^2 = H$ ) prefer to adopt a *Z* conformation (conformer A). Additionally, this reactivity allowed us to explain the reasons behind the poor yields obtained in the previously described exchange/hydroamination cascade. In this case, competition between hydroamination and hydantoin formation occurs, disfavoring the formerly desired product (Table 4.4, entry 8 & 10).

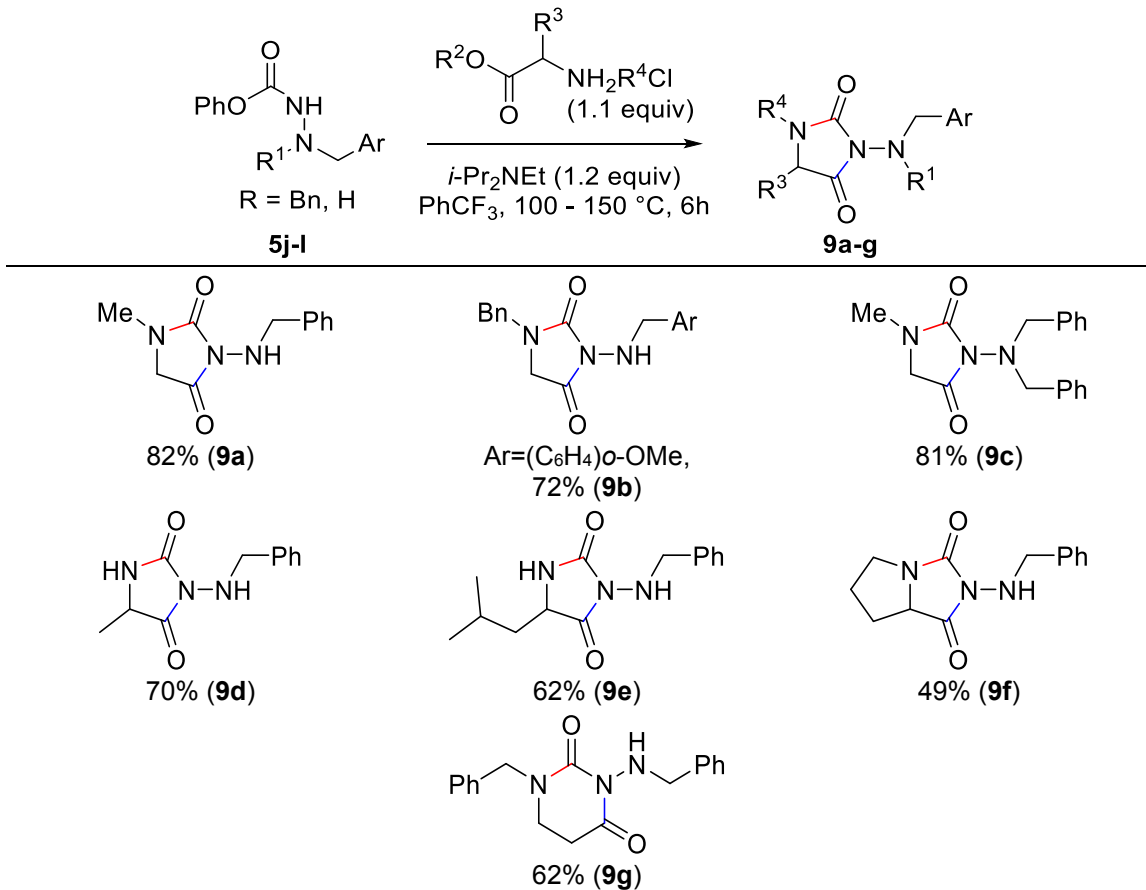
### 4.3.3 Exchange/Cyclization Cascade for the Synthesis of Aza-Hydantoins

Following a literature survey, the synthetic value of the discovered reactivity was soon recognized, given the limited number of reported examples of aza-hydantoins and the medicinal importance of hydantoin motifs.<sup>8,9</sup> We therefore surveyed the synthetic scope of this cascade reaction starting with various amino esters and benzyl carbazates. As presented in Table 4.8, various derivatives of *N*-methyl glycinate methyl ester could be obtained with benzyl, *ortho*-methoxy benzyl and dibenzyl phenylcarbazate for which the corresponding aza-hydantoin product could be isolated in good yields (**9a-c**). Increased temperature and longer reaction time also allowed for the use of primary aminoesters derived from alanine and valine (**9d-e**), despite a more difficult cyclization as reflected by the obtained yields.

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<sup>8</sup> For a recent review on hydantoin and their synthesis see: M. Meusel, M. Gütschow, *Org. Prep. Proced. Int.* **2004**, 36, 391 and references cited therein.

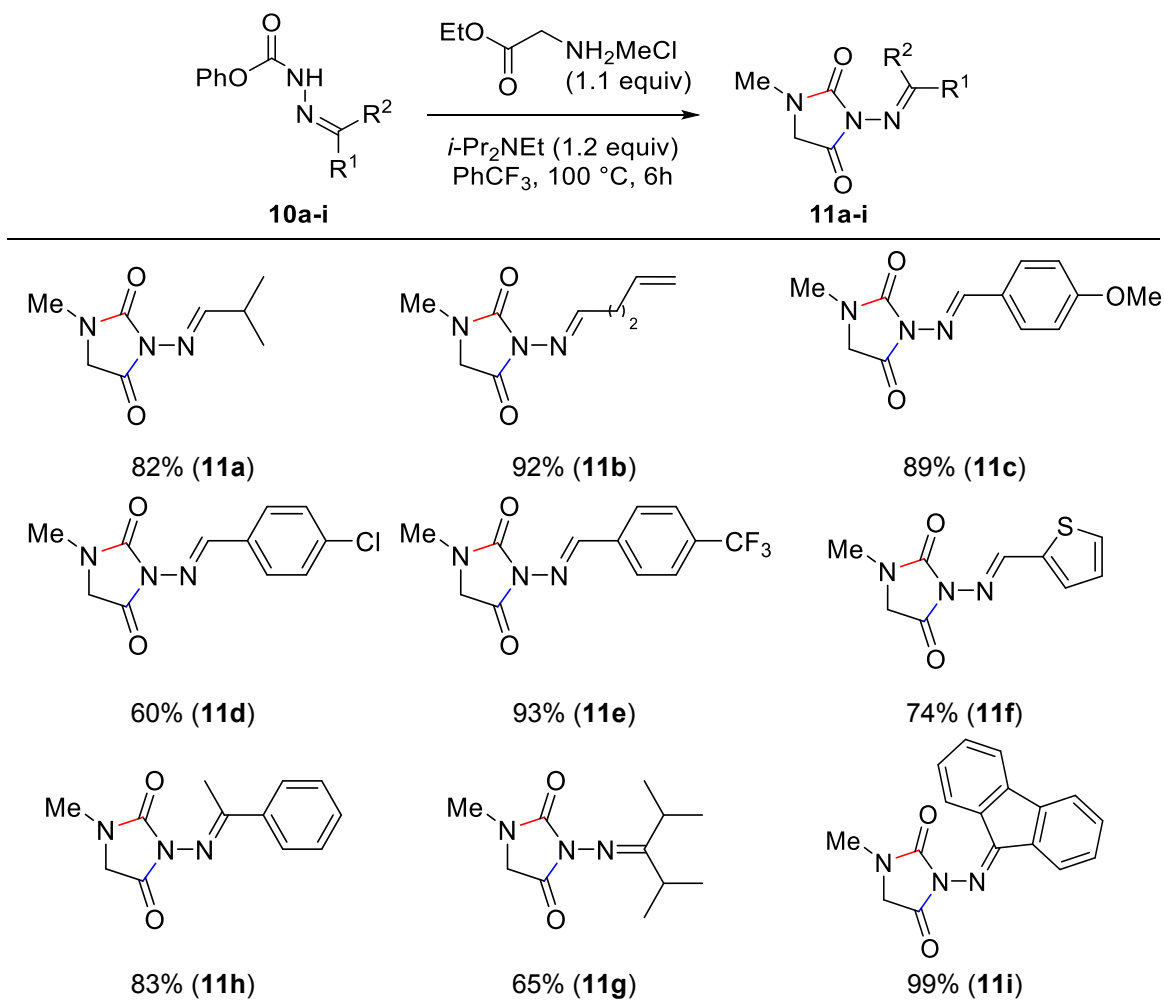
<sup>9</sup> For recent synthesis of hydantoin see: (a) F. Olimpieri, A. Volonterio, M. Zanda, *Synlett* **2008**, 3016. (b) O. A. Attanasi, L. De Crescentini, G. Favi, S. Nicolini, F. R. Perrulli, S. Santeusano, *Org. Lett.* **2011**, 13, 353. (c) T. Miura, Y. Mikano, M. Murakami, *Org. Lett.* **2011**, 13, 3560. (d) K. Dhara, G. C. Mydya, J. Dash, *J. Org. Chem.* **2012**, 77, 8071. (e) S.M. Dumbis, D. J. Díaz, L. McElwee-White, *J. Org. Chem.* **2009**, 74, 8862. (f) Y. Kuninobu, K. Kikuchi, K. Takai, *Chem. Lett.* **2008**, 37, 740. (g) J.M. Iganico, S. Macho, S. Marcaccini, R. Pepino, T. Torroba, *Synlett* **2005**, 3051. (h) A. Volonterio, C. Ramirez de Arellano, M. Zanda, *J. Org. Chem.* **2005**, 70, 2161. (i) S. Gore, K. Chinthapally, S. Baskaran, B. König, *Chem. Commun.* **2013**, 49, 5052. (j) F. Olimpieri, M. C. Bellucci, T. Marcelli, A. Volonterio, *Org. Biomol. Chem.* **2012**, 10, 9538.

**Table 4.8** Initial scope using benzyl O-phenyl carbazate and natural amino acid derivatives

with Jean-François Vincent-Rocan

In addition to previously described proline methyl ester derived hydantoin **9f**, excitingly, we found  $\beta$ -amino ester could also undergo the cascade reaction, resulting in a six-membered aza-dihydrouracil derivative (**9g**).

While leaving group substitution with amines had previously been demonstrated with imino-isocyanates, Mr. Jean-François Vincent-Rocan and Mr. Kyle Leckett also used this cascade reaction to generate hydrazone derivatives of hydantoins (Table 4.9).

**Table 4.9** Initial scope of aza-hydantoin synthesis with hydrazones

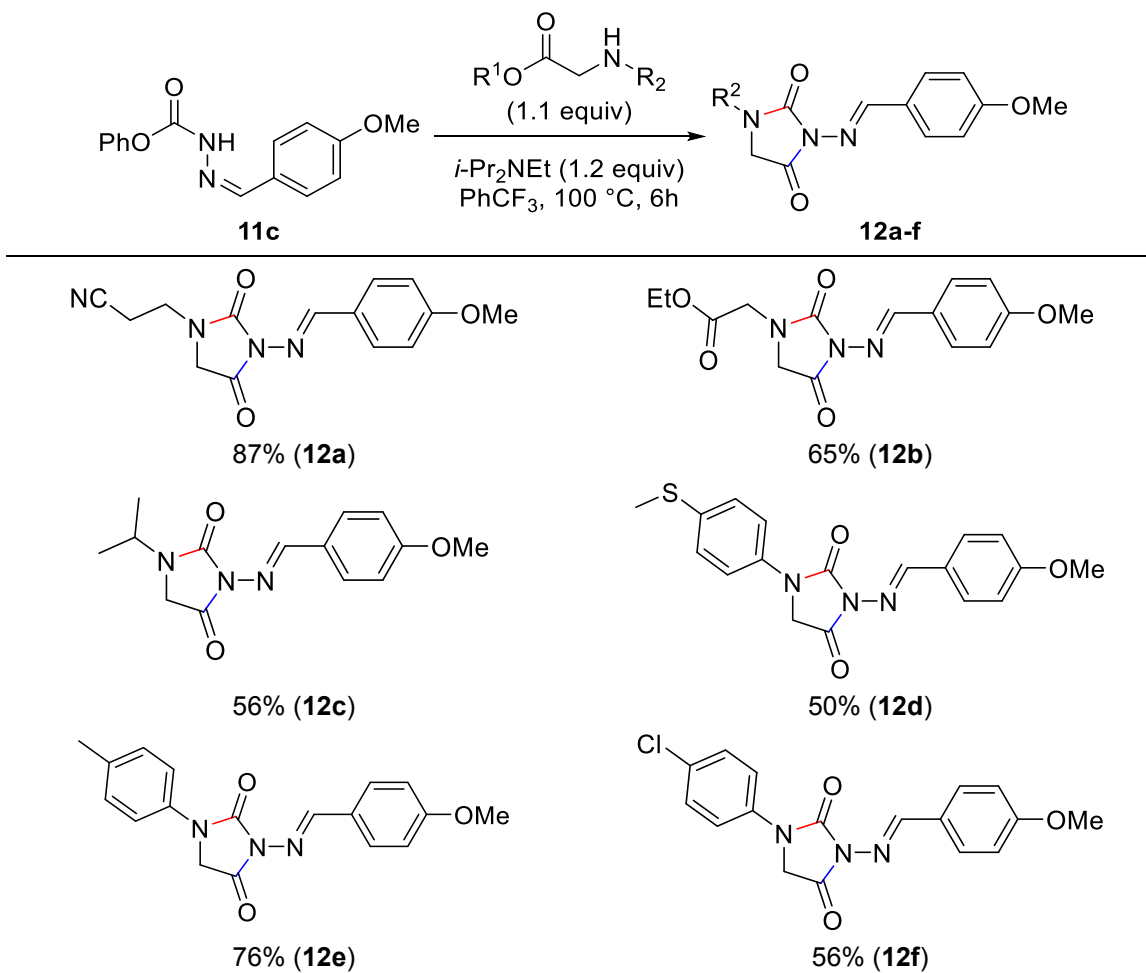
by Jean-François Vincent-Rocan & Kyle Leckett

Starting with *N*-methyl ethyl glycinate, aldo- and ketohydrazones were surveyed. Aliphatic derived hydrazones reacted well under the reaction conditions (**11a-b**) while benzaldehydes bearing electron donating and withdrawing substituents provided excellent yields (**11c-e**). Thiophene carboxaldehyde derived hydrazone could also undergo efficient cyclization (**11f**). The cyclization was also performed using asymmetrical (**11h**) and symmetrical ketohydrazones (**11g-i**). The expected products were obtained in excellent yields.



In addition, the reaction was found to tolerate various functional groups at the amino ester side chain (Table 4.10). Reaction with *ortho*-methoxy benzene derived hydrazone allowed us to synthesize hydantoin products bearing propionitrile, ester and alkyl substituents (**12a-c**). Interestingly, aniline derivatives could also undergo the reaction and provide medicinally relevant substrates (**12d-f**).

**Table 4.10** Scope of secondary amino-esters with hydrazones



by Jean-François Vincent-Rocan & Kyle Leckett

#### 4.4 Summary and Outlook

In this chapter, we have demonstrated the versatility of amino-isocyanates as amphoteric reagents for new hydroamination sequences, peptidomimetic and heterocyclic synthesis. No other reported method enables rapid substrate modification as part of a hydroamination sequence. Amino-isocyanates have thus emerged as unique synthetic tools for the introduction of N-N functionalities to the core structure of important heterocyclic compounds. Additional efforts are currently underway for the development of new reaction sequences involving amino- and imino-isocyanates and should be reported in due course.

# **Chapter**

# **5**

## **Supporting Information**

## Supporting Information

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## **General Information**

Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63  $\mu\text{m}$ ), unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum, cut to size. Visualization was accomplished with UV light followed by staining with a potassium permanganate solution and heating.

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker AVANCE 300 MHz and 400 MHz spectrometers at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm using solvent as the reference ( $\text{CDCl}_3$  at 7.26 ppm,  $\text{C}_6\text{D}_6$  at 7.15 ppm or  $\text{DMSO}-d_6$  at 2.50 ppm for  $^1\text{H}$  NMR and  $\text{CDCl}_3$  at 77.0 ppm or  $\text{DMSO}-d_6$  at 39.43 for  $^{13}\text{C}$  NMR).  $^1\text{H}$  NMR data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sext. = sextuplet, sept = septuplet, m = multiplet), integration and coupling constant(s) in Hz. Infrared (IR) spectra were obtained with neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). High-resolution mass spectrometry (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV. Low-resolution mass spectrometry (LRMS) was performed on a Micromass Q-TOF 1 and Accurate Mass ESI LC-MS. All mass spectrometry were performed at the Ottawa-Carleton Mass Spectrometry Centre.

## **Materials**

Unless otherwise noted, all commercially available materials were purchased from commercial sources and used without further purification.

## **Chapter 2: Intramolecular Aminocarbonylation of Alkenes**

## **Intramolecular Aminocarbonylation of Alkenes with Amino-Isocyanates**

### **General Procedures for the Synthesis of Substrates**

#### **Procedure A: Synthesis of Hydrazones**

*Oxidation of Alcohol to Aldehyde or Ketone:* According to the procedure published by the Mukai group.<sup>1</sup> To a dry round bottom flask, the alkenyl alcohol was dissolved in dichloromethane (0.33 M) to which triethylamine (3.0 equiv.) was added. The mixture was stirred under argon and cooled in an ice bath. In a separate flask, pyridinium trisulfoxide complex (3.0 equiv.) was dissolved in dry dimethyl sulfoxide (0.33 M) and added dropwise to the alkenylalcohol solution. Solution was stirred under argon and allowed to gradually warm up to room temperature. After three hours, solution was cooled in an ice bath and saturated solution of ammonium chloride was added. Solution was extracted three times with dichloromethane and dimethyl sulfoxide was washed out of solution five times with a 1:1 brine/water solution. The combined organic layer was dried with sodium sulfate and solvent was evaporated in vacuo.

*Condensation to hydrazone:* The crude aldehyde was dissolved in dry methanol (0.2 M) to which the carbazate or semicarbazide (1.1 equiv.) was added. The reaction was stirred under argon until consumption of the aldehyde or ketone was judged complete by TLC (30% EtOAc/hexanes). The solution was dried with sodium sulfate, filtered and solvents were removed *in vacuo*. The crude hydrazone was purified by column chromatography using 20-30 % EtOAc/hexanes.

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<sup>1</sup> Mukai, C.; Nomura, I.; Katagaki, S. *J. Org. Chem.* **2003**, 68, 1376.

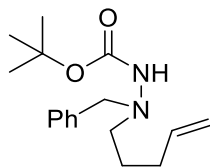


**Procedure B: Synthesis of mono-alkenyl hydrazides**

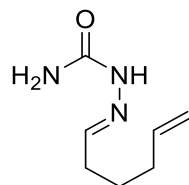
To a dry round bottom flask, hydrazone was dissolved in methanol (0.2 M) to which sodium cyanoborohydride (3.0 equiv.) and a pinch of methyl orange was added and stirred under argon at room temperature for thirty minutes. Acetic acid was then added until pH turns acidic and reaction was stirred for an additional two hours. Volatiles were then evaporated *in-vacuo* and remaining solution was quenched with a saturated solution of sodium bicarbonate and solution was gradually basified with 25% NaOH to pH of 8. Solution was extracted three times with dichloromethane, dried with sodium sulfate, filtered and evaporated *in-vacuo*. Crude hydrazide was then purified by column chromatography with 30% EtOAc/hexanes unless indicated otherwise.

**Procedure C: Alkylation of *tert*-butyl alkenyl carbazates.**

To a flame-dried round bottom flask, hydrazide was dissolved in tetrahydrofuran (0.2M) and cooled to  $-78^{\circ}\text{C}$  under argon. After stirring for fifteen minutes, a solution of *n*-butyl lithium in hexanes (1.1 equiv.) was added dropwise and stirred under argon for thirty minutes. Benzyl bromide was then added dropwise (1.0 equiv.). Solution was warmed to  $-50^{\circ}\text{C}$  and stirred under argon for thirty minutes after which a second portion of benzyl bromide was added (0.5 equiv.). Reaction was then allowed to warm up to room temperature and was then quenched with methanol and water. Volatiles were evaporated and solution was extracted three times with dichloromethane, dried with sodium sulfate, filtered and volatiles were again removed *in-vacuo*. Crude product was purified by column chromatography with 10% EtOAc/hexanes.

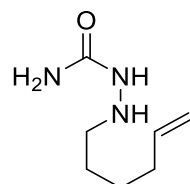


**tert-Butyl 2-benzyl-2-(pent-4-enyl)hydrazinecarboxylate (Table 2.5, 3a).** Synthesized according to general procedure C using *tert*-butyl 2-(pent-4-enyl)hydrazinecarboxylate (1.50 g, 7.15 mmol) and benzyl bromide (1.83 g, 10.7 mmol). The reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash chromatography using 10% EtOAc/hexanes. The title compound was obtained as a clear oil (1.27 g, 4.39 mmol, 61% yield). TLC  $R_f$  = 0.38 in 10 % EtOAc/hexanes;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.22 - 7.34 (m, 5 H) 5.77 (d,  $J$ =6.7 Hz, 1 H) 5.34 - 5.52 (m, 1 H) 4.88 - 5.02 (m, 2 H) 3.94 (s, 2 H) 2.74 (s, 2 H) 2.11 (d,  $J$ =7.0 Hz, 2 H) 1.59 (t,  $J$  = 7.3 Hz, 2 H) 1.37 (s, 9 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 154.8 (C), 138.5 (CH), 137.0 (CH), 129.4 (CH), 128.2 (CH), 127.3 (CH), 114.6 ( $\text{CH}_2$ ), 79.4 (C), 61.5 ( $\text{CH}_2$ ) 55.6 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_2$ ), 28.27 ( $\text{CH}_3$ ), 26.4 ( $\text{CH}_2$ ); IR (film,) 3291, 2975, 2930, 2850, 1698, 1366, 1169, 911, 698  $\text{cm}^{-1}$  ; LRMS  $m/z$  (relative intensity) 91.1, (100%), 57.1 (34%), 101.1 (16%), 135.1 (12%), 179.1 (10%).

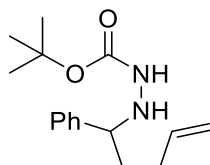


**2-(hex-5-en-1-ylidene)hydrazinecarboxamide.** Synthesized according to procedure A using 5-hexen-1-ol (2.50 g, 24.8 mmol) and semicarbazide hydrochloride (1.71 g, 15.3 mmol). The crude solution was purified by column chromatography using 100% EtOAc and The title compound was isolated as a white solid (1.38 g, 65% yield). TLC  $R_f$  = 0.3 in 100% EtOAc;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) \* denotes minor traces of isomers  $\delta$  ppm 8.97 (br. s, 1 H) \*8.14 (br. s, 1 H) 7.10 (t,  $J$ =5.3

Hz, 1 H) \*6.48 (t,  $J=5.3$  Hz, 1 H) 5.69 - 5.91 (m, 1 H) 4.93 - 5.13 (m, 2 H) 2.01 - 2.32 (m, 4 H) 1.63 (sext,  $J=7.1$  Hz, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 157.6 (C), 145.0 (CH), 138.0 ( $\text{CH}_2$ ), 115.2 (CH), 33.1 ( $\text{CH}_2$ ), 31.5 ( $\text{CH}_2$ ), 25.6 ( $\text{CH}_2$ ). IR (film) 3454, 3274, 3072, 2936, 2854, 1666, 1576, 1428, 906, 870, 773  $\text{cm}^{-1}$ ; LRMS  $m/z$  (relative intensity): 57.1 (100%), 59.1 (63%), 103.1 (52%), 41.0 (44%), 158.1 (24%), 55.1 (19%), 39.0 (18%), 29.0 (15%).

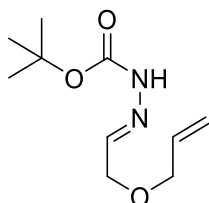


**2-(hex-5-en-1-yl)hydrazinecarboxamide (Table 2.5, 3c).** Synthesized according to procedure **B** using 2-(hex-5-en-1-ylidene)hydrazinecarboxamide (0.0485 g, 3.13 mmol). The title compound was obtained as a clear yellow oil (0.291 g, 1.85 mmol, 59% isolated yield). TLC  $R_f$  = 0.38 in 8% MeOH/ $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm 6.24 (br. s, 1 H) 5.79 (ddt,  $J=17.0$ , 10.3, 6.7, 6.7 Hz, 1 H) 5.46 (br. s, 2 H) 4.85 - 5.08 (m, 2 H) 3.68 (br. s, 1 H) 2.81 (t,  $J=6.7$  Hz, 2 H) 1.96 - 2.14 (m, 2 H) 1.34 - 1.57 (m, 4 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 160.90 (C) 138.34 (CH) 114.79 ( $\text{CH}_2$ ) 52.45 ( $\text{CH}_2$ ), 33.45 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ); LRMS  $m/z$  (relative intensity): 45.0 (100%), 88.1 (46%), 41.0 (35%), 98.1 (25%), 44.0 (24%), 39.0 (20%), 55.1 (16%), 32.0 (15%), 27.0 (15%), 28.0 (11%), 30.0 (10%).

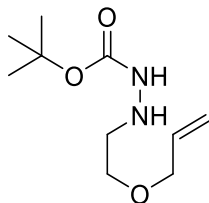


**tert-Butyl 2-(1-phenylpent-4-en-1-yl)hydrazinecarboxylate (Table 2.6, 3e).** Synthesized according to procedure **B** from the corresponding hydrazone (2.15 g, 7.86 mmol). The crude mixture was purified by column chromatography using 10 % EtOAc/hexanes. The title compound

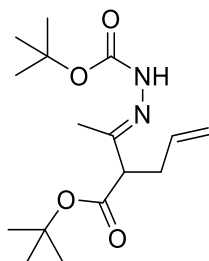
was obtained as a clear oil (1.243 g, 4.50 mmol, 57 % isolated yield). TLC  $R_f$  = 0.46 in 20% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 7.19 - 7.42 (m, 5 H) 5.96 (br. s, 1 H) 5.68 - 5.87 (m, 1 H) 4.87 - 5.04 (m, 2 H) 4.04 (br. s, 1 H) 3.47 - 3.97 (m, 1 H) 1.62 - 2.04 (m, 4 H) 1.44 (s, 9 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 156.6 (C), 141.6 (CH), 138.0 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 114.8 ( $\text{CH}_2$ ), 80.4 (C), 64.4 (CH), 34.1 ( $\text{CH}_2$ ), 30.1 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_3$ ); LRMS  $m/z$  (relative intensity): 69.0 (100%), 91.1 (35%), 145.1 (24%), 106.1 (16%).



***tert*-Butyl-2-(2-(allyloxy)ethylidene)hydrazinecarboxylate.** Synthesized according to procedure A using 2-(allyloxy)ethanol (2.25 g, 22.03 mmol) and *tert*-butyl carbazate (3.20 g, 22.03 mmol). The title compound was obtained as a clear oil (0.8818 g, 4.12 mmol, 19 % isolated yield). TLC  $R_f$  = 0.44 in 30% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz) \*denotes presence of minor isomer  $\delta$  ppm \*9.36 (s, br, 1H), 8.39 (s, br, 1H), 7.24 (t,  $J$  = 3.4, 1H), \*6.57 (t,  $J$  = 3.2), 5.82 (dt,  $J$  = 13.1, 6.9, 1H), 5.25-5.11 (m, 2H), 4.12 (m, 2H), 3.98-3.93 (m, 2H), 1.44 (d,  $J$  = 4.9, 9H) ;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz) denotes presence minor isomer  $\delta$  ppm 152.7 (C), 143.3 (CH), \*139.4 (CH), 134.1 (CH), \*133.1 (CH), \*118.5 ( $\text{CH}_2$ ), 117.5 ( $\text{CH}_2$ ), 81.2 (C), \*72.1 ( $\text{CH}_2$ ), 71.5 ( $\text{CH}_2$ ), 69.3 ( $\text{CH}_2$ ), \*66.9( $\text{CH}_2$ ), 28.0 ( $\text{CH}_3$ ); IR (film); 3257, 2979, 2854, 1729, 1542, 1082, 930, 846, 771  $\text{cm}^{-1}$  ; LRMS  $m/z$  (relative intensity): 57.07 (100%), 41.0389 (40%), 102.04 (18%), 158.07 (12%), 29.0391 (12%).

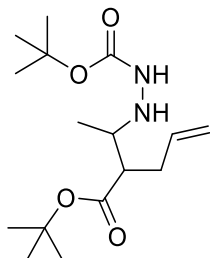


**tert-butyl-2-(2-(allyloxy)ethyl)hydrazinecarboxylate.** Synthesized according to procedure **B** using *tert*-butyl-2-(2-(allyloxy)ethylidene)hydrazinecarboxylate (0.8818 g, 4.12 mmol). The title compound was obtained as a clear yellow oil (0.6223 g, 2.87 mmol, 70% isolated yield). TLC  $R_f$  = 0.43 50% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm 6.60 (s, br, 1H), 5.74 (dt,  $J$  = 12.9, 6.9, 1H), 5.14-4.99 (m, 2H), 4.24 (s, br, 1H), 3.84 (dd,  $J$  = 4.4, 1.2, 2H), 3.39 (t,  $J$  = 5.3, 2H), 2.89 (t,  $J$  = 5.3, 2H), 1.31 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 156.6 (C), 134.6 (CH), 116.8 ( $\text{CH}_2$ ), 80.0 (C), 71.8 ( $\text{CH}_2$ ), 67.7 ( $\text{CH}_2$ ), 51.1( $\text{CH}_2$ ), 28.2 ( $\text{CH}_3$ ); IR (film): 3257, 2979, 2854, 1729, 1542, 1082, 930, 846, 771  $\text{cm}^{-1}$ ; LRMS  $m/z$  (relative intensity): 57.07 (100%), 41.0381 (52%), 49.05 (43%), 89.04 (17%), 29.04 (16%), 39.02 (12%), 160.08 (12%).



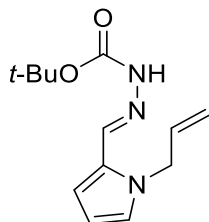
**tert-butyl-2-(3-(tert-butoxycarbonyl)hex-5-en-2-ylidene)hydrazinecarboxylate.** Synthesized according to procedure **A** using the corresponding allyl-ketoester (0.622 g, 3.14 mmol) and *tert*-butyl carbazate (0.456 g, 3.45 mmol). The title compound was obtained as white crystals (0.750 g, 2.39 mmol, 24 % isolated yield). TLC  $R_f$  = 0.25 in 10% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm 7.47 (br. s, 1 H) 5.76 (d,  $J$ =6.9 Hz, 1 H) 4.90 - 5.15 (m, 2 H) 3.45 (t,  $J$ =7.6 Hz, 1 H) 2.63 (d,  $J$ =6.9 Hz, 1 H) 2.28 - 2.52 (m, 1 H) 1.80 (s, 3 H) 1.51 (s, 9 H) 1.23 - 1.46 (m, 9 H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 171.0 (C), 148.6 (C), 135.0 (CH), 116.9 ( $\text{CH}_2$ ), 81.3 (C), 81.1 (C), 54.5 (CH), 33.9 ( $\text{CH}_2$ ), 28.24 ( $\text{CH}_3$ ), 28.0 ( $\text{CH}_3$ ), 12.7 ( $\text{CH}_3$ ). HRMS (EI): Exact mass calcd for  $\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_4$   $[\text{M}]^+$ : 312.2049. Found: 312.2049.



**tert-butyl 2-(3-(tert-butoxycarbonyl)hex-5-en-2-yl)hydrazinecarboxylate (Table 2.7, 3j).**

Synthesized according to procedure **B** using the corresponding hydrazone (0.0406 g, 1.30 mmol). Crude mixture was purified by column chromatography using 8% EtOAc/hexanes. The title compound was obtained as white crystals (0.407 g, 1.29 mmol, 99 % isolated yield). TLC  $R_f$  = 0.12 in 20% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm 5.99 - 6.63 (m, 1 H) 5.63 - 5.84 (m, 1 H) 4.94 - 5.16 (m, 2 H) 3.54 - 4.48 (m, 1 H) 3.04 - 3.30 (m, 1 H) 2.41 (br. s, 3 H) 1.30 - 1.60 (m, 18 H) 1.08 (d,  $J=6.5$  Hz, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 173.3 (C), 172.7 (C), 135.7 (CH), 116.5 ( $\text{CH}_2$ ), 80.8 (C), 57.1 (CH), 48.8 (CH), 32.8 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_3$ ), 28.1 ( $\text{CH}_3$ ), 15.7 ( $\text{CH}_3$ ), 15.0 ( $\text{CH}_3$ ). LRMS  $m/z$  (relative intensity): 103.0 (100%), 57.1 (94%), 202.1 (62%), 59.1 (49%), 99.9 (42%), 41.0 (31%), 31.0 (17%), 162.0 (16%), 143.0 (15%), 28.0 (14%), 29.0 (13%), 85.1 (12%).

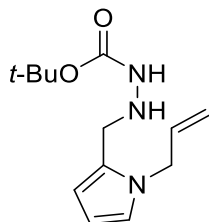


***tert*-Butyl-2-(((1-allyl-1H-pyrrol-2-yl)methylene)amino)acetate.**

***N*-allyl-**

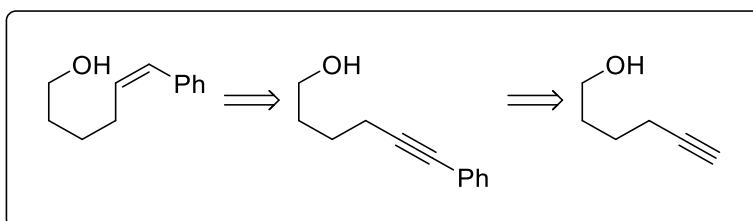
**pyrrolecarbaldehyde.** Synthesized according to the procedure by Albano and coworkers.<sup>2</sup> To a solution of 1,4-dioxane (111 mL) was added 2-pyrrolecarbaldehyde (5.27 g, 55.4 mmol), allyl bromide (7.38 g, 61.0 mmol) and potassium carbonate (8.42 g, 61.0 mmol). The reaction was stirred and refluxed for 8 hours then cooled to room temperature. Hexanes (111 mL) was added and the resulting precipitate was removed by filtration over celite. Volatiles were evaporated and crude mixture was purified by column chromatography using 10% in EtOAc/hexanes (6.85 g, 50.7 mmol, 92% yield). Hydrazone was synthesized according to procedure A using *N*-allyl-pyrrolecarbaldehyde (1.322 g, 9.79 mmol) and *tert*-butyl carbazate (1.42 g, 10.8 mmol) in MeOH (19.6 mL). Crude mixture was purified by column chromatography using 100% CH<sub>2</sub>Cl<sub>2</sub> and then 10% EtOAc/hexanes. The title compound was obtained as a clear colorless oil (1.77 g, 7.08 mmol, 72% isolated yield). TLC R<sub>f</sub> = 0.32 in 10% EtOAc/hexanes. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ ppm 8.94 (br, s, 1 H) 7.83 (br, s, 1 H) 6.56 - 6.73 (m, 1 H) 6.38 (dd, *J*=3.8, 1.6 Hz, 1 H) 6.09 (dd, *J*=3.6, 2.8 Hz, 1 H) 5.75 - 5.99 (m, 1 H) 4.76 - 5.12 (m, 4 H) 1.50 (s, 9 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) 152.8 (C), 136.7 (CH), 134.3 (CH), 126.5 (CH), 125.7 (CH), 116.1 (CH<sub>2</sub>), 114.4 (CH), 108.1 (CH), 80.0 (C), 50.4 (CH<sub>2</sub>), 28.0 (CH<sub>3</sub>). HRMS (EI): Exact mass calcd for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> [M]<sup>+</sup>: 249.1477. Found 249.1466.

<sup>2</sup> Albano, G. V.; Gualandi, A.; Monari, M.; Savoia, D. *J. Org. Chem.* **2008**, 73, 8376.

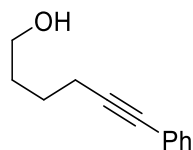


***tert*-Butyl 2-((1-allyl-1H-pyrrol-2-yl)methyl)hydrazinecarboxylate (Table 2.7, 3s).**

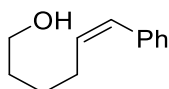
Synthesized according to procedure **B** using *tert*-butyl-2-(((1-allyl-1H-pyrrol-2-yl)methylene)amino)acetate (6.01 g, 24.01 mmol). Crude mixture was purified by column chromatography using 15% EtOAc/hexanes. The title compound was obtained as a dark red oil (2.134 g, 8.49 mmol, 32% isolated yield). TLC  $R_f$  = 0.43 in 20 % EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 6.61 (d,  $J$ =2.0 Hz, 1 H) 5.79 - 6.18 (m, 4 H) 5.13 (dd,  $J$ =10.2, 1.0 Hz, 1 H) 4.94 (dd,  $J$ =17.0, 1.1 Hz, 1 H) 4.58 (d,  $J$ =5.0 Hz, 2 H) 3.93 (br. s, 3 H) 1.45 (s, 9 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 156.6 (C), 135.0 (CH), 127.9 (C), 122.0 (CH), 116.0 ( $\text{CH}_2$ ), 110.0 (CH), 107.0 ( $\text{CH}_2$ ), 80.4 (C), 49.1 ( $\text{CH}_2$ ), 47.1 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_3$ ); HRMS (EI): Exact mass calcd for  $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_2$   $[\text{M}]^+$ : 251.1634. Found: 251.1648.





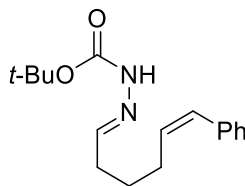


**6-Phenylhex-5-yn-1-ol.** Synthesized according to procedure by Petrignet and coworkers.<sup>3</sup> To a flame-dried round bottom flask, hexyn-1-ol (2.53 g, 25.8 mmol), iodobenzene (5.26 g, 25.8 mmol), copper iodide (0.098 g, 0.516 mmol) and palladium-tetrakis(triphenylphosphine) (0.2981 g, 0.258 mmol) were dissolved in triethylamine (51.6 mL). Solution was stirred overnight under argon. Crude mixture was then filtered over celite and volatiles were evaporated. Crude mixture was purified by column chromatography using 20% EtOAc/hexanes (3.73 g, 21.4 mmol, 85 % isolated yield) TLC  $R_f$  = 0.31 in 20% EtOAc/hexanes. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 7.27 - 7.36 (m, 2 H) 7.13 - 7.24 (m, 3 H) 3.64 (t,  $J$ =6.1 Hz, 2 H) 2.20 - 2.55 (m, 2 H) 1.55 - 1.77 (m, 4 H).

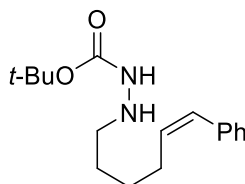


**(Z)-6-Phenylhex-5-en-1-ol.** To a flame-dried round bottom flask, nickel bis-acetate tetrahydrate (0.329 g, 1.32 mmol) and sodium borohydride (0.049 g, 1.32 mmol) were dissolved in ethanol (22.0 mL) and put under dihydrogen atmosphere. Solution of 6-phenylhexyn-1-ol (1.15 g, 6.60 mmol) and ethyldiamine (0.283, 4.71 mmol) in ethanol was prepared separately, then added to the mixture and stirred overnight at room temperature. Solvent was then evaporated and residue purified by filtration followed by column chromatography using Et<sub>2</sub>O. The title compound was obtained as a clear oil (0.998 g, 5.67 mmol, 86 % isolated yield).

<sup>3</sup> Petrignet, J.; Boudhar, A.; Blond, G.; Suffert, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3285.

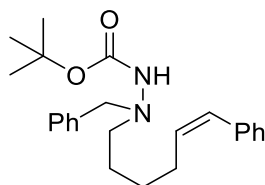


***tert*-Butyl-2-((*Z*)-6-phenylhex-5-en-1-ylidene)hydrazinecarboxylate.** Synthesized according to procedure **A** using (*Z*)-6-phenylhex-5-en-1-ol (0.998 g, 5.67 mmol) and *tert*-butyl carbazate (1.42 g, 10.8 mmol) in MeOH (19.6 mL). Crude mixture was purified by column chromatography using 100% CH<sub>2</sub>Cl<sub>2</sub> and then 10% EtOAc/hexanes. The title compound was obtained as a clear colorless oil (1.77 g, 7.08 mmol, 72% isolated yield). TLC R<sub>f</sub> = 0.32 in 10% EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 8.94 (br. s., 1 H) 7.83 (br. s., 1 H) 6.56 - 6.73 (m, 1 H) 6.38 (dd, *J*=3.8, 1.6 Hz, 1 H) 6.09 (dd, *J*=3.6, 2.8 Hz, 1 H) 5.75 - 5.99 (m, 1 H) 4.76 - 5.12 (m, 4 H) 1.50 (s, 9 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) 152.8 (C), 136.7 (CH), 134.3 (CH), 126.5 (CH), 125.7 (CH), 116.1 (CH<sub>2</sub>), 114.4 (CH), 108.1 (CH), 80.0 (C), 50.4 (CH<sub>2</sub>), 28.0 (CH<sub>3</sub>).



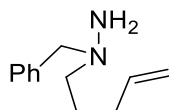
**(*Z*)-*tert*-Butyl-2-(6-phenylhex-5-en-1-yl)hydrazinecarboxylate (Table 2.7, 3t).** Synthesized according to procedure **B** using *tert*-butyl-2-((*Z*)-6-phenylhex-5-en-1-ylidene)hydrazinecarboxylate (0.905 g, 3.14 mmol). Crude mixture was purified by column chromatography using 20 % EtOAc/hexanes. The title compound was obtained as a clear oil (0.630 g, 2.17 mmol, 69% isolated yield). TLC R<sub>f</sub> = 0.62 in 50 % EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 7.09 - 7.40 (m, 6 H) 6.40 (d, *J*=11.6 Hz, 2 H) 5.52 - 5.73 (m, 1 H) 3.62 - 3.99 (m, 1 H) 2.69 - 2.91 (m, 2 H) 2.22 - 2.43 (m, 2 H) 1.32 - 1.63 (m, 13 H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)

$\delta$  ppm 156.6 (C), 137.5 (C), 132.5 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 126.4 (CH), 80.2 (C), 62.4 (CH<sub>2</sub>), 51.7 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 27.28 (CH<sub>2</sub>).



**(Z)-tert-butyl 2-benzyl-2-(6-phenylhex-5-en-1-yl)hydrazinecarboxylate (Table 2.7, 3u).**

Synthesized according to general procedure C using (Z)-tert-Butyl-2-(6-phenylhex-5-en-1-yl)hydrazinecarboxylate (0.283 g, 0.973 mmol) and benzyl bromide (0.183 g, 1.07 mmol). The reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash chromatography using 10% EtOAc/hexanes. The title compound was obtained as a clear oil (0.062 g, 0.163 mmol, 17% yield). TLC  $R_f$  = 0.3 in 10 % EtOAc/hexanes; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 7.09 - 7.42 (10 H, m) 6.39 (1 H, d,  $J$ =11.7 Hz) 5.64 (1 H, d,  $J$ =11.7 Hz) 4.83 - 5.54 (1 H, m) 3.94 (2 H, br. s) 2.73 (2 H, br. s) 2.31 (2 H, d,  $J$ =5.8 Hz) 1.52 (4 H, br. s) 1.37 (9 H, s); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) \*denotes minor traces of isomers  $\delta$  ppm 154.8 (C), 137.7 (C), 136.8 (C), 132.9 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.17 (CH), 128.1 (CH), 127.3 (CH), 126.4 (CH), 79.8 (C), \*63.2 (CH<sub>2</sub>), 61.4 (CH<sub>2</sub>), \*57.2 (CH<sub>2</sub>), 56.0 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 27.3 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>). ; IR (film) 3298, 2934, 2861, 1957, 1880, 1804, 1717, 1993, 1455, 1246 cm<sup>-1</sup>; LRMS  $m/z$  (relative intensity): 91.1, (100%), 57.1 (18%), 117.1 (11%), 135.1 (9%), 29.0 (9%).



**1-benzyl-1-(pent-4-en-1-yl)hydrazine (equation 2.26, 3w).** To a flame-dried round bottom flask, *tert*-butyl 2-benzyl-2-(pent-4-enyl)hydrazinecarboxylate (0.638 g, 2.20 mmol) was dissolved in dry dichloromethane (5 mL) to which was added TFA (5 mL). Solution was stirred for an hour under argon atmosphere. Solvent was then evaporated and hydrazine-TFA salt was then quench with saturated sodium bicarbonate solution and extracted with dichloromethane. Crude mixture was purified by column chromatography using 60% Et<sub>2</sub>O/pentane treated with 1% triethylamine. The title compound was obtained as a clear oil (0.170 g, 0.893 mmol, 41 % isolated yield). TLC R<sub>f</sub> = 0.5 in 80% Et<sub>2</sub>O/pentane. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 7.16 - 7.47 (6 H, m) 5.84 (1 H, ddt, *J*=17.0, 10.3, 6.6, 6.6 Hz) 4.85 - 5.12 (2 H, m) 3.68 (2 H, s) 2.81 (2 H, br. s) 2.47 - 2.64 (2 H, m) 2.14 (2 H, q, *J*=7.0 Hz) 1.72 (2 H, quin, *J*=7.3 Hz). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>) δ 138.6 (CH), 137.9 (CH), 129.2 (CH), 128.4 (CH), 127.3 (CH), 114.6 (CH<sub>2</sub>), 66.31 (CH<sub>2</sub>), 60.0 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>). IR (film): 3344, 3062, 3032, 2928, 2852, 1953, 1877, 1806, 1588, 1561, 1495, 1452, 913, 754, 732, 694 cm<sup>-1</sup>. LRMS *m/z* (relative intensity): 91.1 (100%), 41.0 (23%), 82.9 (15%).

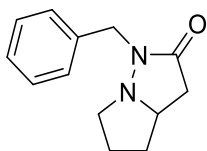
## General Procedures for the Intramolecular Aminocarbonylation of Alkenes

### Procedure A: Microwave Conditions

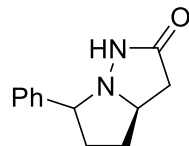
A 5 mL μw tube equipped with a stir bar was flame-dried and purged with argon and an outlet for five minutes. The alkenyl hydrazide (1.00 equiv.) and trifluorotoluene (0.05 M) were added to the sealed tube, and kept under argon atmosphere. The septum was replaced with a microwave cap, sealed, and heated for 0.5 hours at 200<sup>o</sup>C. The reaction mixture was cooled to ambient temperature, concentrated under reduced pressure and analyzed by <sup>1</sup>H NMR using 1,4-dimethoxybenzene (0.50 equiv.) as an internal standard. The reaction mixture was again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product.

### Procedure B: Room Temperature Conditions

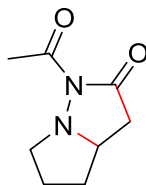
To a flame-dried round bottom flask, bis-alkyl carbazate was dissolved in dry dichloromethane (5 mL) to which was added TFA (5 mL). Solution was stirred for an hour under argon atmosphere. Solvent was then evaporated and deprotected hydrazine salt was used as it and dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.05M) to which pyridine or 4-dimethylaminopyridine were added (10 equiv.). Acylating reagent was then added and reaction stirred under argon according to the specified amount of time.



**1-Benzylhexahydropyrazolo[1,4-a]pyrrolo[2,1-b]pyridin-2(1H)-one** (Table 2.5, 5a). Synthesized according to the procedure A from *tert*-butyl 2-benzyl-2-(pent-4-enyl)hydrazinecarboxylate (0.076 g, 0.261 mmol). The reaction mixture was concentrated under reduced pressure and the product was isolated using flash chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The title compound was obtained as a colourless oil (0.042 g, 0.193 mmol, 74 % isolated yield). TLC R<sub>f</sub> = 0.39 in 5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 7.18 - 7.37 (5 H, m) 4.59 - 4.71 (1 H, m) 4.44 - 4.58 (1 H, m) 3.87 - 4.02 (1 H, m) 2.89 - 3.06 (1 H, m) 2.60 - 2.73 (2 H, m) 2.43 - 2.59 (1 H, m) 1.98 - 2.13 (1 H, m) 1.82 - 1.97 (1 H, m) 1.59 - 1.81 (2 H, m); <sup>13</sup>C NMR (300 MHz, DMSO)  $\delta$  ppm 170.8 (C), 136.7 (C), 128.5 (CH), 128.1 (CH), 127.5 (CH), 59.4 (CH), 55.2 (CH<sub>2</sub>), 47.7 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 23.7 (CH<sub>2</sub>); HRMS (EI): Exact mass calcd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O [M]<sup>+</sup>: 216.1263. Found 216.1261.



**6-phenyltetrahydro-1H-pyrrolo[1,2-b]pyrazol-2(3H)-one** (Table 2.6, 5d). Synthesized according to procedure A from *tert*-butyl 2-(1-phenylpent-4-en-1-yl)hydrazinecarboxylate (0.276 g, 1.00 mmol). Crude mixture was purified by column chromatography using 20 % to 100 % EtOAc/hexanes. The title compound was obtained as a white solid and a mixture of diastereomers (73 % NMR yield, 5:2 d.r.). TLC  $R_f$  = 0.46 in 20% EtOAc/hexanes;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.23 - 7.41 (m, 5 H) 6.53 - 7.20 (m, 1 H) 4.12 - 4.40 (m, 1 H) 3.70 - 4.00 (m, 1 H) 2.58 (d,  $J$ =9.8 Hz, 2 H) 2.16 - 2.44 (m, 2 H) 1.65 - 2.01 (m, 2 H);  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 175.0 (C), 140.0 (C), 128.6 (CH), 127.8 (CH), 127.2 (CH), 72.7 ( $\text{CH}_2$ ), 62.0 ( $\text{CH}_2$ ), 38.0 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_2$ ), 30.0 ( $\text{CH}_2$ ).; HRMS (EI): Exact mass calcd for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$   $[\text{M}]^+$ :202.1106. Found: 202.1117.

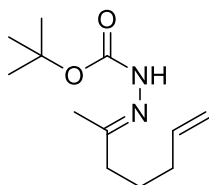


**1-acetyltetrahydro-1H-pyrrolo[1,2-b]pyrazol-2(3H)-one** (Scheme 2.17, 5i). Synthesized according to procedure B using *tert*-butyl 2-benzyl-2-(pent-4-enyl)hydrazinecarboxylate (0.3060 g, 1.05 mmol). The crude mixture was purified by column chromatography using 50% EtOAc/hexanes. The title compound was obtained as a white solid (0.0612 g, 0.360 mmol, 34% isolated yield over four steps). TLC  $R_f$  = 0.31 50% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm 4.00 (dtd,  $J$  = 10.7, 7.8, 3.1 Hz, 1H), 3.66 (ddd,  $J$  = 10.5, 6.6, 4.1 Hz, 1H), 2.80 (dd,  $J$  = 17.9, 8.4 Hz, 1H), 2.71-2.56 (m, 2H), 2.46 (s, 3H), 2.17 (dtd,  $J$  = 13.1, 8.0, 5.1 Hz, 1H), 2.05-1.92

(m, 2H), 1.80-1.69 (m, 1H).;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz) 173.1 (C), 167.0 (C), 57.5 ( $\text{CH}_3$ ), 55.6 ( $\text{CH}_2$ ), 38.9 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 24.4 ( $\text{CH}_3$ ), 23.4 ( $\text{CH}_2$ ); LRMS  $m/z$  (relative intensity): 126.1 (100%), 91.1 (53%), 41.0 (39%), 41.04 (35%), 170.11 (21%).

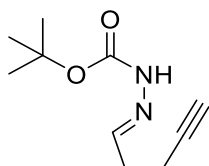
### **Intramolecular Aminocarbonylation with Imino-Isocyanates**

#### **General Procedures for the Synthesis of Substrates**



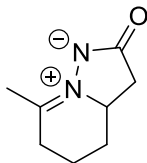
***tert*-Butyl 2-(hept-6-en-2-ylidene)hydrazinecarboxylate (equation 2.29, 7b).** To a round bottom flask, *tert*-butyl-acetoacetate (4.44 g, 28.1 mmol) was dissolved in dry THF (141 mL) stirred under argon and cooled to 0 °C. Potassium *tert*-butoxide (3.15 g, 28.1 mmol) was then added in small portions and then stirred for 1 hour after which sodium iodide was added (2.11 g, 14.1 mmol). 4-Bromobutene (3.80 g, 28.1 mmol) was then added dropwise over fifteen minutes. The solution was then allowed to warm up to room temperature followed by reflux for twenty hours. The reaction was allowed to cool and then quenched with a saturated ammonium chloride solution and water. The organic layer was extracted three times with ether, dried with sodium sulphate and volatiles were removed. The crude mixture was then dissolved in a 1:1:1 mixture of concentrated HCl, water and methanol (30 mL) and then refluxed for 1 hour. Reaction was quenched with 10% aq. NaOH and extracted three times with diethylether. Following this, *tert*-butyl carbazate (4.08 g, 30.9 mmol) was then treated the crude mixture of hept-6-en-2-one following general procedure A in methanol (34.3 mL). The product was purified by column chromatography using 4%  $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ . The title compound was obtained as a white solid (1.82

g, 8.06 mmol, 29% isolated yield over three steps). TLC  $R_f$  = 0.33 in 40% EtOAc/*n*-hexanes.  $^1\text{H}$ -NMR (300 MHz;  $\text{CDCl}_3$ ): \*denotes minor traces of isomers  $\delta$  ppm 7.38 (d,  $J$  = 39.1 Hz, 1H), 5.78 (ddt,  $J$  = 17.0, 10.3, 6.7 Hz, 1H), 5.09-4.92 (m, 2H), 2.30 (dd,  $J$  = 8.9, 6.9 Hz, 2H), 2.08 (m, 2H), 1.78 (s, 3H), 1.64 (m, 2H), 1.50 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm \*152.9 (C), 152.9 (C), \*152.7 (C), 152.7 (C), 138.3 (CH), \*116.1 ( $\text{CH}_2$ ), 115.0 ( $\text{CH}_2$ ), 80.9 (C), 38.5 ( $\text{CH}_2$ ), 33.4 ( $\text{CH}_3$ ), \*33.3 ( $\text{CH}_3$ ), \*28.9 ( $\text{CH}_3$ ), 28.3 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_2$ ), \*24.3 ( $\text{CH}_2$ ), \*23.4 (CH), 14.7 ( $\text{CH}_2$ ). LRMS  $m/z$  (relative intensity): 57.07 (100%), 116.06 (43%), 72.07 (39%), 41.04 (35%), 170.11 (21%).

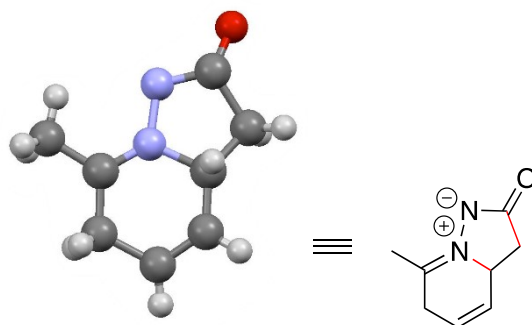


**(E)-tert-butyl 2-(pent-4-yn-1-ylidene)hydrazinecarboxylate (equation 2.32, 7e).** Synthesized according to procedure A using pentyn-1-ol (2.51 g, 29.8 mmol) and *tert*-butyl carbazate (3.59 g, 27.1 mmol). The crude mixture was purified by column chromatography using 25% EtOAc/hexanes. The title compound was obtained as white amorphous crystals (1.83 g, 9.32 mmol, 34 % isolated yield). TLC  $R_f$  = 0.3 in 20 % EtOAc/hexanes.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.07 (1 H, br. s) 6.53 - 7.43 (1 H, m) 2.47 (2 H, t,  $J$  = 5.8 Hz) 2.31 - 2.42 (2 H, m) 1.96 (1 H, t,  $J$  = 2.5 Hz) 1.40 - 1.53 (9 H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm \*denotes traces of isomers 152.6 (C), 144.9 (CH), \*144.0 (CH), 82.7 (CH), \*82.0 (CH), 81.0 (C), \*70.0 (C), 69.4 (C), 31.0 ( $\text{CH}_2$ ), 28.2 ( $\text{CH}_3$ ), \*25.6 ( $\text{CH}_2$ ), 16.1 ( $\text{CH}_2$ ), 15.5 ( $\text{CH}_2$ ). IR(film): 3610, 3196, 1981, 2113, 1699, 1536, 1368, 1164, 1023, 771  $\text{cm}^{-1}$ . LRMS  $m/z$  (relative intensity): 29.0 (100%), 27.0 (89%), 57.1 (71%), 29.1 (34%), 28.0 (23%), 28.0 (22%), 26.0 (18%), 41.0 (16%), 140.1 (16%).





**7-Methyl-2-oxo-2,3,3a,4,5,6-hexahydropyrazolo[1,5-a]pyridin-8-ium-1-ide** (equation 2.29, **8b**). Synthesized according to general procedure C using *tert*-butyl 2-(hept-6-en-2-ylidene)hydrazinecarboxylate (59.6 mg, 0.264 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (5.0 mL) and heating at 150 °C for three hours under microwave irradiation. The crude mixture was purified by column chromatography using 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a white solid (19.3 mg, 0.127 mmol, 48% isolated yield, 82% NMR yield using 1,4-dimethoxybenzene as an internal standard). TLC R<sub>f</sub> = 0.35 in 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.19 (q,  $J$  = 8.6, 1H), 2.79 (dd,  $J$  = 15.6, 8.4, 1H), 2.70-2.52 (m, 3H), 2.34 (s, 1H), 2.28 (t,  $J$  = 0.9, 3H), 1.99 (t,  $J$  = 10.6, 1H), 1.84-1.66 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 180.5 (C), 149.9 (C), 64.6 (CH), 37.6 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 20.9 (CH<sub>3</sub>), 18.3 (CH<sub>2</sub>); IR (film); 2916.9, 2849.9, 1679.4, 1582.1, 1380.9, 1340.6, 1085.7 cm<sup>-1</sup>; LRMS  $m/z$  (relative intensity): Exact mass calcd for C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>1</sub> [M]<sup>+</sup>: 152.0944; found: 152.0955.

**X-ray Crystallographic Data****Figure 5.1** Crystal structure of product **8b** (equation 2.29)**Table 5.1** Crystal data and structure refinement for product **8b** (equation 2.29)

|                                   |                                                                                                                         |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Identification code               | ab005_5                                                                                                                 |
| Empirical formula                 | C <sub>15</sub> H <sub>15</sub> N <sub>2</sub> O                                                                        |
| Formula weight                    | 239.29                                                                                                                  |
| Temperature                       | 200(2) K                                                                                                                |
| Wavelength                        | 0.71073 Å                                                                                                               |
| Crystal system, space group       | Monoclinic, P2(1)                                                                                                       |
| Unit cell dimensions              | a = 8.3332(19) Å    alpha = 90 deg.<br>b = 7.6263(18) Å    beta = 100.738(7) deg.<br>c = 10.555(2) Å    gamma = 90 deg. |
| Volume                            | 659.1(3) Å <sup>3</sup>                                                                                                 |
| Z, Calculated density             | 2, 1.206 Mg/m <sup>3</sup>                                                                                              |
| Absorption coefficient            | 0.077 mm <sup>-1</sup>                                                                                                  |
| F(000)                            | 254                                                                                                                     |
| Crystal size                      | 0.20 x 0.15 x 0.12 mm                                                                                                   |
| Theta range for data collection   | 1.96 to 18.84 deg.                                                                                                      |
| Limiting indices                  | -7 ≤ h ≤ 7, 0 ≤ k ≤ 6, 0 ≤ l ≤ 9                                                                                        |
| Reflections collected / unique    | 458 / 530 [R(int) = 0.0000]                                                                                             |
| Completeness to theta = 28.31     | 82.7 %                                                                                                                  |
| Absorption correction             | Semi-empirical from equivalents                                                                                         |
| Max. and min. transmission        | 0.9908 and 0.9848                                                                                                       |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                                             |
| Data / restraints / parameters    | 530 / 102 / 113                                                                                                         |
| Goodness-of-fit on F <sup>2</sup> | 1.158                                                                                                                   |
| Final R indices [I > 2sigma(I)]   | R1 = 0.1028, wR2 = 0.2534                                                                                               |
| R indices (all data)              | R1 = 0.1097, wR2 = 0.2610                                                                                               |
| Absolute structure parameter      | -5(10)                                                                                                                  |
| Largest diff. peak and hole       | 0.293 and -0.391 e.Å <sup>-3</sup>                                                                                      |

**Table 5.2** Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) of product **8b** (equation 2.29) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|       | x          | y         | z          | U (eq) |
|-------|------------|-----------|------------|--------|
| N (1) | 1300 (20)  | 4620 (40) | 5739 (12)  | 51 (4) |
| N (2) | 90 (20)    | 4750 (40) | 4600 (13)  | 52 (5) |
| O (1) | -2593 (19) | 5080 (40) | 4144 (14)  | 95 (9) |
| C (1) | -1360 (30) | 4420 (50) | 4899 (18)  | 64 (7) |
| C (2) | -1230 (30) | 4850 (60) | 6359 (17)  | 77 (7) |
| C (3) | 440 (30)   | 4460 (70) | 6862 (18)  | 79 (4) |
| C (4) | 1540 (30)  | 4460 (60) | 8069 (18)  | 79 (4) |
| C (5) | 3150 (30)  | 4940 (50) | 8230 (20)  | 79 (4) |
| C (6) | 3960 (30)  | 4750 (60) | 7047 (16)  | 64 (4) |
| C (7) | 2870 (30)  | 4600 (60) | 5808 (18)  | 64 (4) |
| C (8) | 3520 (30)  | 4690 (60) | 4617 (15)  | 64 (4) |
| O (2) | 7595 (14)  | 4580 (40) | 10135 (10) | 42 (3) |
| O (3) | 400 (17)   | 4660 (30) | 1932 (11)  | 52 (4) |
| O (4) | 7270 (20)  | 1871 (18) | 8600 (20)  | 55 (3) |
| O (5) | 5459 (17)  | 4630 (40) | 1819 (11)  | 55 (3) |
| O (6) | 7020 (20)  | 7330 (20) | 8450 (20)  | 55 (3) |

**Table 5.3** Bond lengths [Å] and angles [deg] for product **8b** (equation 2.29)

---

|                |           |
|----------------|-----------|
| N(1)-C(7)      | 1.29(3)   |
| N(1)-N(2)      | 1.43(2)   |
| N(1)-C(3)      | 1.50(2)   |
| N(2)-C(1)      | 1.32(3)   |
| O(1)-C(1)      | 1.28(3)   |
| C(1)-C(2)      | 1.56(3)   |
| C(2)-C(3)      | 1.42(3)   |
| C(3)-C(4)      | 1.43(3)   |
| C(4)-C(5)      | 1.37(3)   |
| C(5)-C(6)      | 1.53(3)   |
| C(6)-C(7)      | 1.45(3)   |
| C(7)-C(8)      | 1.46(3)   |
|                |           |
| C(7)-N(1)-N(2) | 126.9(15) |
| C(7)-N(1)-C(3) | 125.6(16) |
| N(2)-N(1)-C(3) | 107.5(15) |
| C(1)-N(2)-N(1) | 108.6(14) |
| N(2)-C(1)-O(1) | 116(2)    |
| N(2)-C(1)-C(2) | 107.4(19) |
| O(1)-C(1)-C(2) | 115(3)    |
| C(3)-C(2)-C(1) | 102(2)    |
| C(4)-C(3)-C(2) | 139(3)    |
| C(4)-C(3)-N(1) | 112.3(18) |
| C(2)-C(3)-N(1) | 105.5(16) |
| C(5)-C(4)-C(3) | 125(2)    |
| C(4)-C(5)-C(6) | 116(2)    |
| C(7)-C(6)-C(5) | 117(2)    |
| N(1)-C(7)-C(6) | 120(2)    |
| N(1)-C(7)-C(8) | 118.9(18) |
| C(6)-C(7)-C(8) | 120(2)    |

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Symmetry transformations used to generate equivalent atoms:

**Table 5.4** Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) of product **8b** (equation 2.29). The anisotropic displacement factor exponent takes the form:  $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

|      | U <sub>11</sub> | U <sub>22</sub> | U <sub>33</sub> | U <sub>23</sub> | U <sub>13</sub> | U <sub>12</sub> |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| N(1) | 44 (6)          | 84 (10)         | 26 (6)          | 1 (15)          | 6 (5)           | -3 (15)         |
| N(2) | 36 (7)          | 86 (12)         | 32 (7)          | 32 (15)         | 7 (5)           | 6 (14)          |
| O(1) | 29 (8)          | 200 (30)        | 48 (8)          | 15 (16)         | -21 (8)         | -24 (13)        |
| C(1) | 43 (8)          | 110 (17)        | 39 (8)          | 51 (14)         | 5 (7)           | -25 (14)        |
| C(2) | 42 (8)          | 160 (20)        | 36 (7)          | 63 (16)         | 12 (6)          | -32 (17)        |
| C(3) | 42 (6)          | 158 (12)        | 37 (4)          | 37 (12)         | 6 (4)           | -45 (11)        |
| C(4) | 42 (6)          | 158 (12)        | 37 (4)          | 37 (12)         | 6 (4)           | -45 (11)        |
| C(5) | 42 (6)          | 158 (12)        | 37 (4)          | 37 (12)         | 6 (4)           | -45 (11)        |
| C(6) | 41 (5)          | 104 (9)         | 45 (5)          | 18 (11)         | 7 (4)           | -47 (11)        |
| C(7) | 41 (5)          | 104 (9)         | 45 (5)          | 18 (11)         | 7 (4)           | -47 (11)        |
| C(8) | 41 (5)          | 104 (9)         | 45 (5)          | 18 (11)         | 7 (4)           | -47 (11)        |
| O(2) | 23 (8)          | 66 (7)          | 41 (7)          | 14 (13)         | 16 (6)          | 7 (11)          |
| O(3) | 36 (8)          | 72 (8)          | 46 (8)          | 31 (15)         | 1 (7)           | -10 (13)        |
| O(4) | 35 (6)          | 77 (5)          | 55 (5)          | 4 (9)           | 14 (5)          | -1 (7)          |
| O(5) | 35 (6)          | 77 (5)          | 55 (5)          | 4 (9)           | 14 (5)          | -1 (7)          |
| O(6) | 35 (6)          | 77 (5)          | 55 (5)          | 4 (9)           | 14 (5)          | -1 (7)          |

**Table 5.5** Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) of product **8b** (equation 2.29)

|        | x     | y    | z     | U (eq) |
|--------|-------|------|-------|--------|
| H (2A) | -1481 | 6100 | 6491  | 93     |
| H (2B) | -1974 | 4104 | 6755  | 93     |
| H (3A) | 303   | 3158 | 6807  | 95     |
| H (4A) | 1134  | 4098 | 8810  | 95     |
| H (5A) | 3734  | 5361 | 9034  | 95     |
| H (6A) | 4670  | 5781 | 7014  | 76     |
| H (6B) | 4667  | 3700 | 7168  | 76     |
| H (8A) | 2617  | 4607 | 3875  | 95     |
| H (8B) | 4277  | 3712 | 4593  | 95     |
| H (8C) | 4093  | 5801 | 4585  | 95     |
| H (2C) | 7851  | 5159 | 9395  | 63     |
| H (2D) | 8204  | 5135 | 10946 | 63     |
| H (3B) | 131   | 4514 | 2767  | 78     |
| H (3C) | -621  | 4788 | 1262  | 78     |
| H (4B) | 7502  | 2100 | 9508  | 82     |
| H (4C) | 8289  | 1469 | 8304  | 82     |
| H (5C) | 6360  | 4619 | 2526  | 82     |
| H (5D) | 4968  | 5830 | 1695  | 82     |
| H (6C) | 8040  | 7427 | 8158  | 82     |
| H (6D) | 7204  | 7336 | 9413  | 82     |

**Table 5.6** Torsion angles [deg] of product **8b** (equation 2.29)

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|                            |          |
|----------------------------|----------|
| C (7) -N (1) -N (2) -C (1) | 169 (4)  |
| C (3) -N (1) -N (2) -C (1) | -10 (4)  |
| N (1) -N (2) -C (1) -O (1) | 156 (3)  |
| N (1) -N (2) -C (1) -C (2) | 25 (4)   |
| N (2) -C (1) -C (2) -C (3) | -31 (4)  |
| O (1) -C (1) -C (2) -C (3) | -162 (3) |
| C (1) -C (2) -C (3) -C (4) | -179 (5) |
| C (1) -C (2) -C (3) -N (1) | 24 (4)   |
| C (7) -N (1) -C (3) -C (4) | 6 (6)    |
| N (2) -N (1) -C (3) -C (4) | -175 (4) |
| C (7) -N (1) -C (3) -C (2) | 170 (4)  |
| N (2) -N (1) -C (3) -C (2) | -11 (4)  |
| C (2) -C (3) -C (4) -C (5) | -142 (5) |
| N (1) -C (3) -C (4) -C (5) | 14 (6)   |
| C (3) -C (4) -C (5) -C (6) | -25 (6)  |
| C (4) -C (5) -C (6) -C (7) | 18 (6)   |
| N (2) -N (1) -C (7) -C (6) | 170 (4)  |
| C (3) -N (1) -C (7) -C (6) | -12 (7)  |
| N (2) -N (1) -C (7) -C (8) | -1 (7)   |
| C (3) -N (1) -C (7) -C (8) | 177 (4)  |
| C (5) -C (6) -C (7) -N (1) | 0 (6)    |
| C (5) -C (6) -C (7) -C (8) | 171 (4)  |

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Symmetry transformations used to generate equivalent atoms:

**Table S7** Hydrogen bonds of product **8b** (equation 2.29) [Å and deg.]

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| D-H...A | d (D-H) | d (H...A) | d (D...A) | < (DHA) |
|---------|---------|-----------|-----------|---------|
|---------|---------|-----------|-----------|---------|

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### **Chapter 3: Intermolecular Aminocarbonylation of Alkenes**



## **Intermolecular Aminocarbonylation of Alkenes with Amino-Isocyanates**

### **General Procedures for the Synthesis of Substrates**

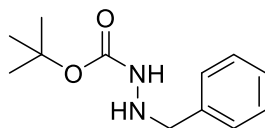
#### **Procedure A:** *Synthesis of mono-alkenyl carbazates*

Aldehyde (2.0 equiv.) was dissolved in dry methanol (0.2 M) to which *tert*-butyl carbazate (1.0 equiv.) was added. The reaction was stirred under argon until consumption of the aldehyde was judged complete by TLC (30% EtOAc/hexanes). Solution was dried with sodium sulfate, filtered and dried in vacuo. Crude hydrazone was purified by column chromatography with 20-30% EtOAc/hexanes. To a dry round bottom flask, hydrazone was then dissolved in methanol (0.2M) to which sodium cyanoborohydride (3.0 equiv.) and a pinch of methyl orange was added and stirred under argon at room temperature for thirty minutes. Acetic acid was then added until pH turns acidic and reaction was stirred for an additional two hours. Volatiles were then evaporated in-vacuo and remaining solution was quenched with a saturated solution of sodium bicarbonate and solution was gradually basified with 25% NaOH to pH of 8. Solution was extracted three times with dichloromethane, dried with sodium sulfate, filtered and evaporated in-vacuo. Crude hydrazide was then purified by column chromatography with 30% EtOAc/hexanes.

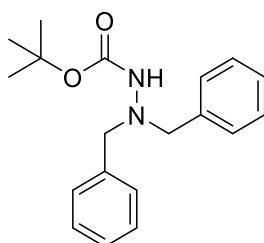
#### **Procedure B:** *Alkylation of tert-butyl alkenyl carbazates*

To a flame-dried round bottom flask, hydrazide was dissolved in tetrahydrofuran (0.2 M) and cooled to -78°C under argon. After stirring for fifteen minutes, a solution of *n*-butyl lithium in hexanes (1.1 equiv.) was added dropwise and stirred under argon for thirty minutes. Benzyl bromide was then added dropwise (1.0 equiv.). Solution was warmed to -50°C and stirred under argon for thirty minutes after which a second portion of benzyl bromide was added (0.5 equiv.). Reaction was then allowed to warm up to room temperature and was then quenched with methanol

and water. Volatiles were evaporated and solution was extracted three times with dichloromethane, dried with sodium sulfate, filtered and volatiles were again removed in-vacuo. Crude product was purified by column chromatography with 10% EtOAc/hexanes.



**tert-Butyl 2-benzylhydrazinecarboxylate.** Synthesized according to procedure **A** using *tert*-butyl carbazate (7.51 g, 56.8 mmol) and benzaldehyde (12.04 g, 113.6 mmol). Crude mixture was purified by column chromatography using 30% EtOAc/hexanes.  $R_f = 0.53$  in 30% EtOAc/hexanes. Product was obtained as white crystals (7.35 g, 33.1 mmol, 58% isolated yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.18 - 7.48 (m, 5 H) 6.06 - 6.45 (m, 1 H) 3.97 - 4.06 (m, 2 H) 3.78 - 3.94 (m, 1 H) 1.47 (s, 9 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 156.6 (C), 137.6 (C), 129.0 (CH), 128.4 (CH), 127.4 (CH), 80.5 (C), 55.7 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_3$ ). IR (film) 3409, 3340, 2979, 2937, 2861, 2439, 2284, 2151, 1953, 1701, 1520, 873,  $\text{cm}^{-1}$ ; LRMS  $m/z$  (relative intensity): 91.1 (100%), 57.1 (75%), 166.1 (29%), 122.1 (20%), 41.0 (19%), 106.1 (15%), 92.1 (13%), 167.0 (10%)



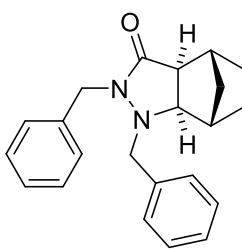
**tert-Butyl 2,2-dibenzylhydrazinecarboxylate (Table 3.2, 1a).** Synthesized according to the procedure by Maeorg and coworkers,<sup>4</sup> using *tert*-butyl 2-benzylhydrazinecarboxylate (7.35 g, 33.1 mmol) and benzyl bromide (6.21 g, 36.3 mmol). The crude mixture was purified by column

<sup>4</sup> Bedihhin, A.; Groth, U. M.; Maeorg, U. *Org. Lett.* **2007**, *9*, 1097.

chromatography using 12% Et<sub>2</sub>O/pentane. Title compound was obtained as white crystals (5.06 g, 15.5 mmol, 47 % isolated yield).  $R_f = 0.7$  in 30% EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 7.40 (d,  $J=7.2$  Hz, 14 H) 7.19 - 7.33 (m, 6 H) 3.89 (s, 4 H) 1.24 (s, 9 H). <sup>13</sup>C NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 157.5, 139.0 (C), 130.7 (CH), 129.2 (CH), 62.4 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>).

### General Procedures for the Intermolecular Aminocarbonylation of Alkenes

A 5 mL  $\mu$ w tube equipped with a stir bar was flame-dried and purged with argon and an outlet for five minutes. The *bis*-alkyl carbazate (1.0 equiv.), norbornene (10.0 equiv.) and trifluorotoluene (0.05 M) were added to the sealed tube, and kept under argon atmosphere. The septum was replaced with a microwave cap, sealed, and heated under microwave irradiation. The reaction mixture was cooled to ambient temperature, concentrated under reduced pressure and analyzed by <sup>1</sup>H NMR using 1,4-dimethoxybenzene (0.5 equiv.) as an internal standard. The reaction mixture was again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product.



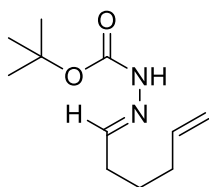
**1,2-Dibenzylhexahydro-1H-4,7-methanoindazol-3(2H)-one (Table 3.2, 2a).** Synthesized according to the general procedure using *tert*-butyl 2,2-dibenzylhydrazinecarboxylate (0.080 g, 0.257 mmol), norbornene (0.942 g, 10.0 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (5.0 mL). The solution was heated in a sealed tube under microwave irradiation for six hours. The crude mixture was purified by column chromatography using 3 % *i*-PrOH/CH<sub>2</sub>Cl<sub>2</sub> (0.0113 g, 0.034 mmol, 43% NMR yield, 13% isolated yield).  $R_f = 0.3$  in 3% *i*-PrOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  ppm

7.06 - 7.44 (m, 10 H) 4.84 (d,  $J=14.8$  Hz, 1 H) 4.02 - 4.44 (m, 2 H) 3.48 (d,  $J=12.8$  Hz, 1 H) 2.89 (d,  $J=8.1$  Hz, 1 H) 2.49 - 2.73 (m, 2 H) 1.81 (d,  $J=3.9$  Hz, 1 H) 1.32 - 1.54 (m, 2 H) 0.95 - 1.26 (m, 4 H) 0.62 - 0.93 (m, 2 H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 171.7 (C), 136.7 (C), 136.2 (C), 129.2 (CH), 128.41 (CH), 128.36 (CH), 127.6 (CH), 67.12 ( $\text{CH}_2$ ), 61.3 ( $\text{CH}_2$ ), 50.0 (CH), 47.0 ( $\text{CH}_2$ ), 43.6 (CH), 40.1 (CH), 33.1 ( $\text{CH}_2$ ), 27.6 (CH), 25.2 ( $\text{CH}_2$ ). HRMS(EI): Exact mass calcd for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}$   $[\text{M}]^+$ : 332.1889. Found: 332.1898.

### **Intermolecular Aminocarbonylation of Alkenes Using Imino-Isocyanates**

#### **General Procedures for the Preparation of Substrates:**

Procedure taken from Leighton and coworkers.<sup>5</sup> To a round-bottom flask were added the corresponding carbazate, ketone (2.0 equiv), methanol and a catalytic amount of acetic acid (5-15 mol%). The reaction solution was refluxed overnight (10-14 h), then cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography or direct recrystallization to give the corresponding hydrazones.

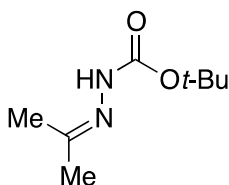


***tert*-Butyl 2-(hex-5-enylidene)hydrazinecarboxylate (equation 3.4, 4a).** 5-Hexen-1-ol was oxidized to hex-5-enal according to previously reported procedure by the Mukai group.<sup>6</sup> The title compound was synthesized according to general procedure using *tert*-butyl carbazate (1.015 g, 7.68 mmol) and crude mixture of hex-5-enal (9.98 mmol). Observed a mixture of *E* and *Z*

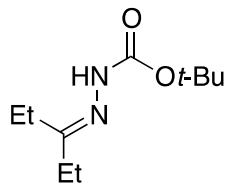
<sup>5</sup> Berger, R. ; Duff, K. ; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, 126, 5686.

<sup>6</sup> Mukai, C.; Nomura, I.; Katagaki, S. *J. Org. Chem.* **2003**, 68, 1376.

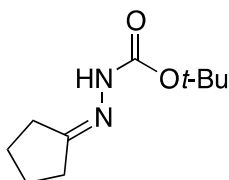
isomers in 3.6:1 ratio, respectively. The crude mixture was purified by column chromatography (30% EtOAc/*n*-hexanes) and isolated as a white solid (1.38 g, 65% yield). TLC  $R_f$  = 0.36 (30% EtOAc/hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) \*denotes minor isomer  $\delta$  ppm 7.69 (s, 1H), 7.14 (t,  $J$  = 5.2 Hz, 1H), \*6.61 (t,  $J$  = 5.2 Hz, 1H), 5.77 (tdd,  $J$  = 6.8 Hz, 13.2 Hz, 12.1 Hz, 1H), 5.04-4.92 (m, 2H), 2.29 (tdd,  $J$  = , 2H), 2.09-2.03 (m, 2H), \*1.66 (m,  $J$  = 7.2 Hz, 2H), 1.59 (m,  $J$  = 8.0 Hz, 2H), \*1.51 (s, 9H), 1.48 (s, 9H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 152.9 (C), 147.0 (C), \*146.0 (C), 137.9 (CH), \*137.3 (CH), \*115.9 ( $\text{CH}_2$ ), 115.1 ( $\text{CH}_2$ ), 81.0 (CH), 33.2 ( $\text{CH}_2$ ), \*33.0 ( $\text{CH}_2$ ), 31.6 ( $\text{CH}_2$ ), 28.2 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_2$ ), \*25.5 ( $\text{CH}_2$ ), \*25.0 ( $\text{CH}_2$ ); IR (film) 3241, 3078, 2983, 2934, 2865, 1710, 1641, 1539, 1360, 1254, 1166, 1048, 1017, 904, 866, 763  $\text{cm}^{-1}$ ; LRMS  $m/z$  (relative intensity): 57.07 (100%), 41.04 (23.9%), 29.04 (17.7%), 58.05 (12.7%), 39.02 (9.2%).



***tert*-Butyl 2-(propan-2-ylidene)hydrazinecarboxylate (Table 3.6, 6a).** Synthesized according to general procedure using *tert*-butyl carbazate (0.50 g, 3.8 mmol), acetone (15 mL, as reagent and solvent) and acetic acid (0.20 mL). The reaction mixture was concentrated under reduced pressure and the product was isolated by silica gel flash chromatography (30% EtOAc/hexanes). The title compound was obtained as a white solid (0.52 g, 79% yield). TLC  $R_f$  = 0.29 in 30% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.76 (s, 1H), 1.46 (s, 9H), 1.05 (d,  $J$  = 6.9, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 152.9 (C), 149.9 (C), 80.9 (C), 31.4 ( $\text{CH}_3$ ), 28.4 ( $\text{CH}_3$ ), 20.0 ( $\text{CH}_3$ ); IR (film); 3207, 2967, 2329, 1755, 1680  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calcd for  $\text{C}_9\text{H}_{18}\text{N}_2\text{O}_2[\text{M}]^+$ : 186.1368; found: 186.1325.

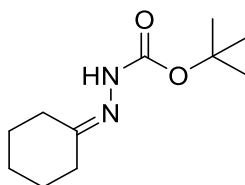


***tert*-Butyl 2-(diethyl)hydrazinecarboxylate (Table 3.6, 6b).** Synthesized according to general procedure using *tert*-butyl carbazate (5.09 g, 38.5 mmol), pentan-3-one (10 mL) and acetic acid (0.20 mL) in methanol (193 mL). The reaction mixture was concentrated under reduced pressure and the product was isolated by silica gel flash chromatography (30% EtOAc/hexanes). The title compound was obtained as a white solid (3.45 g, 45% yield). m.p.: 134-135 °C. TLC  $R_f$  = 0.49 in 20% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.50 (br. s, 1H), 2.30 (q,  $J$  = 7.5 Hz, 2H), 2.17 (q,  $J$  = 7.7 Hz, 2H), 1.49 (s, 9H), 1.09 (td,  $J$  = 7.6, 5.5 Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  158.1 (C), 153.0 (C), 80.7 (C), 29.9 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_3$ ), 21.4 ( $\text{CH}_2$ ), 10.9 ( $\text{CH}_3$ ), 9.6 ( $\text{CH}_3$ ); IR (film); 3207, 3048, 2979, 1728, 1694, 1542, 1364, 1181  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calcd for  $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_2[\text{M}]^+$ : 200.1525; found: 200.1482.



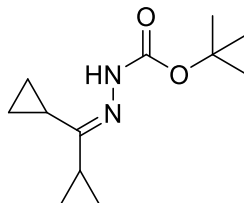
***tert*-Butyl 2-cyclopentylidenehydrazinecarboxylate (Table 3.6, 6c).** Synthesized according to general procedure using *tert*-butyl carbazate (10.5 g, 79.1 mmol), cyclopentanone (7.31 g, 87.0 mmol) and acetic acid (0.20 mL) in methanol (396 mL). The title compound was obtained as a white solid and recrystallized from hexanes (13.03 g, 83% yield). m.p.: 129-130 °C. TLC  $R_f$  = 0.39 in 40% EtOAc/hexanes. The spectral data corresponds to that of a previous literature report by

Ghali and coworkers.<sup>7</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.17 (br. s, 1H), 2.45 (t,  $J$  = 7.2 Hz, 2H), 2.16 (t,  $J$  = 7.1 Hz, 2H), 1.84 (quint,  $J$  = 7.1 Hz, 2H), 1.73 (quint,  $J$  = 7.0 Hz, 2H), 1.50 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 162.3 (C), 153.0 (C), 33.5 (CH<sub>2</sub>), 28.4 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 24.9 (CH<sub>2</sub>), 24.9 (CH<sub>2</sub>).



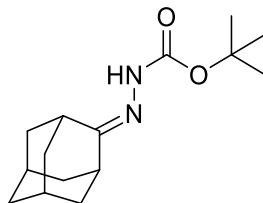
***tert*-Butyl 2-cyclohexylidenehydrazinecarboxylate (Table 3.6, 6d).** Synthesized according to general procedure using *tert*-butyl carbazate (5.54 g, 42.8 mmol), cyclohexanone (4.62g, 47.1 mmol) and acetic acid (0.20 mL). Crude mixture was purified by column chromatography using 20% EtOAc/hexanes. TLC  $R_f$  = 0.33 in 20% EtOAc/hexanes. The title compound was obtained as a white (7.82 g, 88 % isolated yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 7.33 - 8.25 (m, 1 H) 2.28 (t,  $J$ =6.1 Hz, 2 H) 2.17 (t,  $J$ =5.8 Hz, 2 H) 1.49 - 1.69 (m, 6 H) 1.35 - 1.49 (m, 9 H) . <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 155.9 (C), 153.1 (C), 80.5 (C), 35.2 (CH<sub>2</sub>), 28.1 (CH<sub>3</sub>), 26.6 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>). IR (film); 3246, 2977, 2933, 2858, 1723, 1515, 1391, 1366, 1165, 1045, 881 cm<sup>-1</sup>. HRMS (EI): Exact mass calcd for C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>[M]<sup>+</sup>: 212.1525; found: 212.1522.

<sup>7</sup> Ghali, N. I.; Venton, D. L.; Hung, S. C.; Le Breton, G. C. *J. Org. Chem.* **1981**, *46*, 5413.

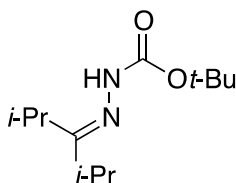


***tert*-Butyl-2-(dicyclopropylmethylene)hydrazinecarboxylate (Table 3.6, 6e).** Synthesized according to general procedure using *tert*-butyl carbazate (5.18 g, 39.3 mmol), dicyclopropylketon (4.76 g, 43.19 mmol) and acetic acid (0.20 mL). Crude mixture was purified by column chromatography using 30% Et<sub>2</sub>O/pentane. The title compound was obtained as a white solid and recrystallized from hexanes (1.16 g, 5.17 mmol, 13% yield). TLC R<sub>f</sub> = 0.31 in 20% EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 7.93 (br. s, 1 H) 1.49 (s, 9 H) 1.37 - 1.46 (m, 1 H) 1.25 - 1.36 (m, 1 H) 0.86 - 0.97 (m, 2 H) 0.75 - 0.85 (m, 4 H) 0.58 - 0.68 (m, 2 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 155.5 (C), 152.7 (C), 80.6 (C), 28.3 (CH<sub>3</sub>), 13.6 (CH), 10.3 (CH), 6.1 (CH<sub>2</sub>), 4.9 (CH<sub>2</sub>). IR (film); 3207, 3013, 2979, 1698, 1534, 1360, 1245, 1174, 1056 cm<sup>-1</sup>. HRMS (EI): Exact mass calcd for C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>[M]<sup>+</sup>: 224.1525; found: 224.1516.



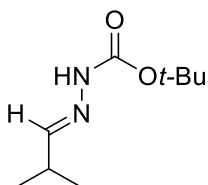


***tert*-Butyl-2-Adamantanylidenehydrazinecarboxylate (Table 3.6, 6g).** Synthesized according to general procedure using *tert*-butyl carbazate (5.01 g, 37.9 mmol), 2-admantanone (6.26 g, 41.7 mmol) in hexanes (200 mL). Product was directly recrystallized from crude mixture and dried in vacuo. The title compound was obtained as white crystalline needles (9.62 g, 96% yield). m.p.: 183-184 °C. TLC  $R_f$  = 0.5 in 40% EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.54 (d,  $J$  = 0.2 Hz, 1H), 2.90 (s, 1H), 2.69 (s, 1H), 1.97-1.74 (m, 12H), 1.47 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 162.7 (C), 153.4 (C), 80.7 (C), 39.4 (CH), 37.6 ( $\text{CH}_2$ ), 36.4 ( $\text{CH}_2$ ), 30.7 (CH), 28.4 ( $\text{CH}_3$ ), 27.8 (CH); IR (film); 3210, 2979, 2914, 2853, 1728, 1702, 1534  $\text{cm}^{-1}$ ; MS  $m/z$  (relative intensity): 57.0710 (100%), 41.0392 (33%), 79.0554 (17.3%), 81.0698 (16.3%), 39.0238 (16.2%).

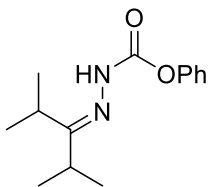


***tert*-Butyl-2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (Table 3.6, 6h).** Synthesized according to general procedure using *tert*-butyl carbazate (10 g, 76 mmol), 2,4-dimethylpentan-3-one (22.0 mL, 152 mmol, 2.00 equiv), acetic acid (0.50 mL, 8.7 mmol) and methanol (250 mL). The target compound was directly recrystallized from hexanes and obtained as a white solid (15 g, 87% yield). m.p.: 144-145 °C. TLC  $R_f$  = 0.71 in 20% EtOAc/hexanes.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (br. s, 1H), 2.73 (sept,  $J$  = 7.04 Hz, 1H), 2.59 (sept,  $J$  = 6.81 Hz, 1H), 1.47 (s, 9H), 1.12 (d,  $J$  = 7.03 Hz, 6H), 1.10 (d,  $J$  = 6.08 Hz, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100

MHz)  $\delta$  163.4 (C), 153.0 (C), 80.7 (C), 31.6 (CH), 28.4 (CH<sub>3</sub>), 27.8 (CH), 21.5 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>). IR (film) 3208, 2973, 2934, 1736, 1703, 1528, 1369, 1251, 1179, 1047 cm<sup>-1</sup>. LRMS  $m/z$  (relative intensity): 57.0719 (100%), 41.0397 (50.8%), 172.1176 (29.6%), 43.0559 (27.5%), 27.9977 (27.3%), 55.0569 (23.8%), 85.0754 (21.3%).

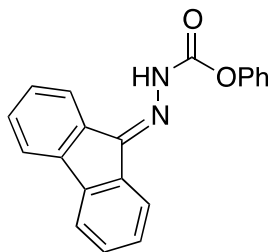


**(*E*)-tert-butyl 2-(2-methylpropylidene)hydrazinecarboxylate (equation 3.11, 6i).** Synthesized according to general procedure using 2-methylpropionaldehyde (25.3 g, 35.1 mmol), *tert*-butyl carbazate (5.18 g, 39.2 mmol). Crude mixture was purified by column chromatography using 20% EtOAc/hexanes. The title compound was obtained as white clear crystals (6.67 g, 35.8 mmol, 91% yield). TLC  $R_f$  = 0.5 in 20% EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 7.77 (br. s, 1 H) 7.03 (d,  $J$ =5.5 Hz, 1 H) 2.36 - 2.69 (m, 1 H) 1.47 (s, 9 H) 1.06 (d,  $J$ =6.9 Hz, 6 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  169.9 (C), 152.3 (CH), 80.9 (C), 31.4 (CH), 28.4 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>). IR (film); 3350, 2968, 1620, 867. cm<sup>-1</sup>. HRMS(EI): Exact mass calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> [M]<sup>+</sup>: 186.1368. Found: 186.1326.

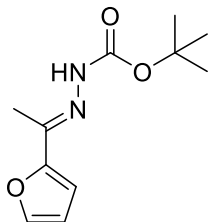


**Phenyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (Table 3.7, 8d).** Synthesized according to general procedure. To a 10-20 mL  $\mu$ w sealed tube was added phenyl carbazate (1.3 g, 9.0 mmol), 2,4-dimethylpentan-3-one (2.5 mL, 18 mmol). Product was recrystallized from 20%

EtOAc in hexanes to give target compound as a white solid (1.1 g, 4.4 mmol, 50% yield). mp: 90-91 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.08 (s, br, 1H), 7.38-7.31 (m, 2H), 7.22-7.15 (m, 3H), 2.82 (sept.,  $J = 7.02$  Hz, 1H), 2.65 (sept.,  $J = 6.75$  Hz, 1H), 1.19-1.12 (m, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 166.2 (C), 156.3 (C), 150.8 (C), 129.3 (CH), 125.5 (CH), 121.5 (CH), 31.6 (CH), 27.9 (CH), 21.5 ( $\text{CH}_3$ ), 18.9 ( $\text{CH}_3$ ); IR 3214, 3028, 2963, 2930, 2872, 1723, 1529, 1492, 1246, 1038, 1000, 737, 704, 683  $\text{cm}^{-1}$ ; HRMS(EI): Exact mass calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$   $[\text{M}]^+$ : 248.1519. Found: 248.1495.

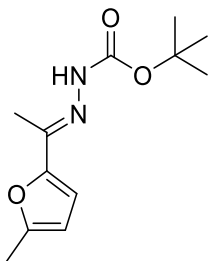


**Phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (equation 3.8, 10a).** Synthesized according to general procedure using phenyl carbazate (2.43 g, 16.0 mmol), fluoren-9-one (2.90 g, 16.0 mmol) and AcOH (0.20 mL) in MeOH (35 mL). Product was directly recrystallized from crude mixture and dried in vacuo. The title compound was obtained as yellow solid (4.0 g, 80% yield). m.p.: 178-180 °C. TLC  $R_f = 0.31$  in 20% EtOAc/hexanes.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.18 (s, 1H), 7.91 (d,  $J = 7.48$  Hz, 1H), 7.82 (d,  $J = 7.63$  Hz, 1H), 7.66 (d,  $J = 7.51$  Hz, 1H), 7.56 (d,  $J = 7.43$  Hz, 1H), 7.47-7.21 (m, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.1(C), 150.6 (C), 142.6 (C), 139.5 (C), 136.8 (C), 131.4 (CH), 130.3 (CH), 129.7 (C), 129.6 (CH), 128.4 (CH), 128.1 (CH), 126.0 (CH), 125.6 (CH), 122.6 (CH), 121.5 (CH), 121.0 (CH), 119.7 (CH). IR (film) 1716, 1735, 1490, 1471, 1219, 1171, 772  $\text{cm}^{-1}$ ; HRMS(EI): Exact mass calcd for  $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_2$   $[\text{M}]^+$ : 314.1050. Found: 314.1056.



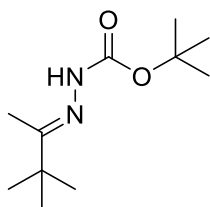
**(Z)-tert-butyl 2-(1-(5-methylfuran-2-yl)ethylidene)hydrazinecarboxylate (Table 3.13, 17c).**

Synthesized according to general procedure using *tert*-butyl carbazate (6.18 g, 56.2 mmol), 2-acetylfuran (2.90 g, 16.0 mmol). Crude mixture was recrystallized from EtOAc and hexanes. The title compound was obtained as white clear crystals (3.10 g, 13.8 mmol, 25% yield). TLC  $R_f$  = 0.51 in 50% EtOAc/hexanes.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.62 - 7.99 (m, 1 H) 7.44 (s, 1 H) 6.74 (d,  $J$ =3.3 Hz, 1 H) 6.42 (dd,  $J$ =3.3, 1.7 Hz, 1 H) 2.14 (s, 3 H) 1.31 - 1.65 (m, 9 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.8 (C), 143.4 (C), 111.5 (CH), 109.5 (CH), 104.5 (CH), 81.4 (C), 28.2 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>). IR (film); 3214, 2983, 2918, 2853, 1728, 1705, 1531, 1250, 1151 1048, 732  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_3$   $[\text{M}]^+$ : 224.1161. Found: 224.1152.



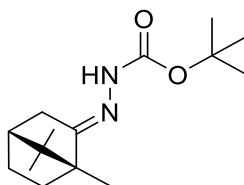
**(Z)-tert-butyl 2-(1-(furan-2-yl)ethylidene)hydrazinecarboxylate.** Synthesized according to general procedure using *tert*-butyl carbazate (3.03 g, 22.9 mmol), 5-methyl-2-acetylfuran (2.85 g, 22.9 mmol). Crude mixture was purified by column chromatography using 50% EtOAc/hexanes. The title compound was obtained as white clear crystals (3.81 g, 16.0 mmol, 70% yield). TLC  $R_f$  = 0.31 in 50% EtOAc/hexanes.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.50 - 8.50 (m, 1 H) 6.53 (d,  $J$ =3.1 Hz, 1 H) 5.95 (d,  $J$ =2.7 Hz, 1 H) 2.26 (s, 3 H) 2.06 (s, 3 H) 1.48 (s, 9 H).  $^{13}\text{C}$  NMR (100

MHz, CDCl<sub>3</sub>)  $\delta$  153.8, 152.6 (C), 150.0 (C), 140.0 (C), 111.1 (CH), 107.5 (CH), 81.0 (C), 28.0 (CH<sub>3</sub>), 13.6 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>). IR (film); 3245, 2975, 2930, 1710, 1546, 1516, 1366, 1268, 1248, 1152, 1049, 1023, 786 cm<sup>-1</sup>. HRMS(EI): Exact mass calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> [M]<sup>+</sup>: 238.1317. Found: 238.1314.



**(*E*)-tert-Butyl 2-(3,3-dimethylbutan-2-ylidene)hydrazinecarboxylate (Table 3.13, 17i).**

Synthesized according to general procedure using *tert*-butyl carbazate (5.11 g, 38.7 mmol), 3,3-dimethylbutan-2-one (7.74 g, 77.3 mmol) and acetic acid (1 mL) in methanol. Crude mixture was purified by column chromatography using 20 % EtOAc/hexanes. The title compound was obtained as a white solid (2.56 g, 12.0 mmol). TLC R<sub>f</sub> = 0.47 in 20% EtOAc/hexanes. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.37 (s, 1H), 1.74 (s, 3H), 1.48 (s, 9H), 1.12 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 158.0 (C), 153.0 (C), 80.7 (C), 38.7 (C), 28.4 (CH<sub>3</sub>), 27.6 (CH<sub>3</sub>), 11.1 (CH<sub>3</sub>); IR (film); 3210, 2953, 1748, 1734, 1684 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>11</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> [M]<sup>+</sup>: 214.1681; found: 214.1619.



***tert*-Butyl-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinecarboxylate (Table**

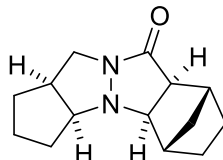
**3.13, 17c).** Synthesized according to general procedure using camphor (0.568 g, 5.70 mmol), *tert*-butyl carbazate (0.829, 6.27 mmol) and acetic acid (1 mL) in ethanol (30 mL). Crude mixture was

purified by column chromatography using 20% EtOAc/hexanes. Title compound was obtained as white crystals (0.869 g, 3.27 mmol, 57% isolated yield). TLC  $R_f$  = 0.48 in 20 % EtOAc/hexanes.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.17 (bs, 1H), 2.28 (dt,  $J$  = 16.4, 3.7 Hz, 1H), 1.95 (t,  $J$  = 4.4 Hz, 1H), 1.89-1.60 (m, 3H), 1.46 (s, 9H), 1.46-1.37 (m, 1H), 1.20-1.08 (m, 1H), 1.04 (s, 3H), 0.89 (s, 3H), 0.71 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 165.3 (C), 152.8 (C), 80.6 (C), 52.6 (C), 48.0 (C), 44.0 ( $\text{CH}_3$ ), 33.3 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 28.4 ( $3\text{CH}_3$ ), 27.4 ( $\text{CH}_2$ ), 19.6 ( $\text{CH}_3$ ), 18.7 (CH), 11.2 ( $\text{CH}_3$ ). IR (film); 3051, 2968, 2873, 2075, 1721, 1542, 1268, 1778  $\text{cm}^{-1}$ . LRMS  $m/z$  (relative intensity): 57.1 (100%), 93.1 (74%), 41.0 (54%), 134.1 (53%), 41.0 (48%), 39.0 (47%), 166.1 (46%), 210.1, (45%), 44.0 (26%), 123.1 (32%), 55.1 (29%), 56.1 (28%), 79.1 (23%), 54.0 (23%), 67.1 (21%), 109.1 (19%), 151.1 (18%), 91.1 (18%), 121.1 (16%).

### **Cascade Aminocarbonylation / Intramolecular [3+2] Cycloaddition**

#### **General Procedure**

To a 10-20 mL microwave vial were added the hydrazone (1 equiv), the corresponding alkene (10 equiv), the corresponding dipolarophile (10 equiv) and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.05 M). The vial was then purged under argon and quickly sealed and heated in a microwave reactor for 6 hours at 120  $^\circ\text{C}$ . The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by  $^1\text{H}$  NMR using 1,3,5-trimethoxybenzene as an internal standard. The corresponding product was then purified using silica gel chromatography.



**1,9-Diaza[7, 6, 1<sup>4,7</sup>, 0<sup>3,8</sup>, 0<sup>10,14</sup>, 0]tetrdecan-2-one (Figure 3.2, equation 3.5, 5a).** Synthesized from general procedure C using *tert*-Butyl 2-(hex-5-enylidene)hydrazinecarboxylate (0.053 g, 0.25

mmol) and norbornene (235 g, 25 mmol). The reaction time was three hours. The title compound was obtained as a white solid and a single diastereoisomer (0.036 g, 0.16 mmol, 76% NMR yield, 62% isolated yield). TLC  $R_f$  = 0.30 in 100% EtOAc.  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ ):  $\delta$  ppm 4.08 (dd,  $J$  = 11.6, 9.3 Hz, 1H), 3.03 (d,  $J$  = 7.9 Hz, 2H), 2.79 (td,  $J$  = 8.3, 4.6 Hz, 1H), 2.72 (d,  $J$  = 7.9 Hz, 1H), 2.63 (dd,  $J$  = 11.6, 5.8 Hz, 1H), 2.56 (d,  $J$  = 2.1 Hz, 1H), 2.31 (d,  $J$  = 3.6 Hz, 1H), 1.81-1.43 (m, 9H), 1.22-1.07 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 171.1 (C), 73.8 (CH), 68.7 (CH), 53.8 ( $\text{CH}_2$ ), 46.9 ( $\text{CH}_2$ ), 44.2 (CH), 43.9(CH), 39.4 ( $\text{CH}_2$ ), 33.7 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 24.6 ( $\text{CH}_2$ ). IR (film) 3428, 1656, 1097  $\text{cm}^{-1}$ ; HRMS(EI): Exact mass calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_1$   $[\text{M}]^+$ : 232.1576. Found: 232.1565.

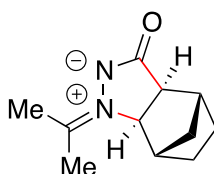
### **General Procedures for the Intermolecular Aminocarbonylation of Alkenes**

**General procedure A:** An oven or flame dried 2-5 mL  $\mu\text{w}$  vial with a stir bar was capped with a septum and purged with argon for 5 minutes. The acyl hydrazone, the corresponding alkene (1 to 10 equiv) and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.5 to 0.05 M) were added to the vial. The septum was removed and the vial was then quickly sealed with a microwave cap and heated in a microwave reactor for 2-6 hours at 80-150  $^\circ\text{C}$ . The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by  $^1\text{H}$  NMR using 1,4-dimethoxybenzene or 1,3,5-trimethoxybenzene as an internal standard. The corresponding product was purified using silica gel chromatography (using dichloromethane then EtOAc to elute the by-products first, then using 10-20% MeOH in EtOAc or 10% MeOH in  $\text{CH}_2\text{Cl}_2$  to elute the target compound), unless noted otherwise.

**General procedure B (neat reaction):** To a 0.2-0.5 mL  $\mu\text{w}$  vial were added the acyl hydrazone and corresponding alkene (1 to 10 equiv). The vial was then sealed with a microwave cap and heated in a microwave reactor for 3 hours at 80-150  $^\circ\text{C}$ . The reaction solution was cooled to

ambient temperature, concentrated under reduced pressure and analyzed by  $^1\text{H}$  NMR using 1,4-dimethoxybenzene or 1,3,5-trimethoxybenzene as an internal standard. The corresponding product was purified using silica gel chromatography (using EtOAc to elute by-products first, then using 10-20% methanol in EtOAc to elute the target compound), unless noted otherwise.

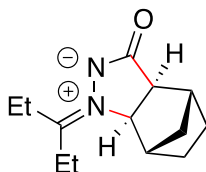
**General procedure C (gram-scale reaction):** The acyl hydrazone and alkene (5 equiv) were dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.05 M) in a dry round-bottom flask. The flask was equipped with a reflux condenser and stirred under argon. The mixture was heated to 100 °C in an oil bath for six hours. The mixture was then cooled to room temperature, the stir bar removed, and solvent was evaporated to give a dark residue. The crude mixture was purified by passing through a silica plug, eluting first with 1/4 : EtOAc/ $\text{CH}_2\text{Cl}_2$  to remove excess alkene and a purple by-product, then then 9/1 : EtOAc/MeOH to elute the product. Solvent was removed by evaporation to give the product.



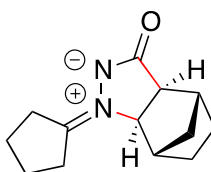
(±)-*exo*-2-(Propan-2-ylidene)-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.6, 7a). Synthesized according to general procedure A using *tert*-butyl 2-(propan-2-ylidene)hydrazinecarboxylate **2b** (0.034 g, 0.20 mmol) and norbornene (0.19 g, 2.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL). The reaction was heated at 150 °C for three hours. The title compound was obtained as yellow oil (0.029 g, 70% yield). TLC  $R_f$  = 0.29 in 20% MeOH/EtOAc.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.17 (d,  $J$  = 7.13 Hz, 1H), 2.75 (d,  $J$  = 7.09 Hz, 1H), 2.70 (s, 1H), 2.52 (s, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 1.65-1.52 (m, 2H), 1.45-1.38 (m, 1H), 1.29-1.11 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.3 (C), 147.6 (C), 71.5 (CH), 52.7 (CH),



41.8 (CH), 39.0 (CH), 32.3 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 22.8 (CH<sub>3</sub>), 21.4 (CH<sub>3</sub>). HRMS(EI): Exact mass calcd for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O [M]<sup>+</sup>: 192.1257. Found: 192.1239.

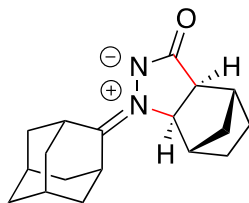


**(±)-exo-2-(Butan-3-ylidene)-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.6, 7b).** Synthesized according to general procedure A using *tert*-butyl 2-(diethyl)hydrazinecarboxylate **2c** (0.034 g, 0.20 mmol) and norbornene (0.293 g, 3.11 mmol, 15 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL). The reaction was heated at 150 °C for three hours. The title compound was purified by silica gel chromatography (50% *i*-PrOH/toluene) and obtained as yellow oil (70% NMR yield, 0.030 g, 67% isolated yield). TLC R<sub>f</sub> = 0.34 in 50% *i*-PrOH/toluene. <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  3.96 (d, *J* = 7.1 Hz, 1H), 2.78 (d, *J* = 2.7 Hz, 1H), 2.63-2.51 (m, 2H), 2.38 (t, *J* = 6.4 Hz, 1H), 2.05 (td, *J* = 13.4, 6.3 Hz, 3H), 1.43-1.00 (m, 8H), 0.81 (q, *J* = 7.3 Hz, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  182.8 (C), 152.9 (C), 70.8 (CH), 52.6 (CH), 43.0 (CH), 39.6 (CH), 32.5 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 10.9 (CH<sub>3</sub>), 9.0 (CH<sub>3</sub>). IR (film); 2968, 2873, 1649, 1577, 1467, 1399, 1274, 743 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O [M]<sup>+</sup>: 220.1576. Found: 220.1573.

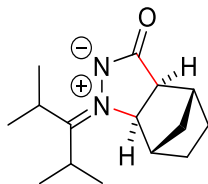


**(±)-exo-2-Cyclopentanylidene-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.6, 7c).** Synthesized according to general procedure A using *tert*-butyl 2-cyclopentanylidenehydrazinecarboxylate **2f** (0.040 g, 0.20 mmol) and norbornene (0.19 g, 2.0

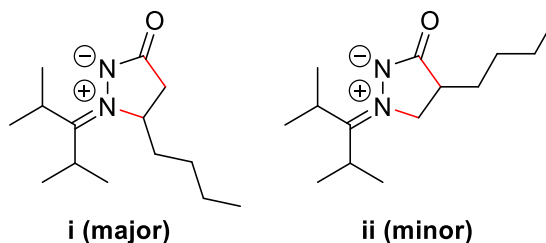
mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL). The reaction was heated at 150 °C for three hours. The title compound was obtained as a white solid (71% NMR yield, 0.0306 g, 70% isolated yield). m.p.: 133-135 °C. TLC  $R_f$  = 0.47 in 7.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.15 (d,  $J$  = 6.9, 1H), 2.66 (m, 7H), 1.93 (m, 4H), 1.60-1.43 (m, 3H), 1.25-1.18 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm , 183.4 (C), 160.4 (C), 72.4 (CH), 52.6 (CH), 40.7 (CH), 39.1 (CH), 33.9 (CH<sub>2</sub>), 32.4 (CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 24.4 (CH<sub>2</sub>); IR (film); 2971, 2918, 2850, 1664, 1569, 1405 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>1</sub> [M]<sup>+</sup>: 218.1414; found: 218.1429.



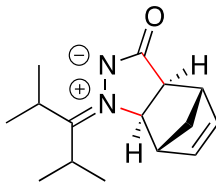
**(±)-*exo*-2-(2-Admantanylidene)-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide** (Table 3.6, 7g). Synthesized according to general procedure A using *tert*-butyl 2-(adamantan-2-ylidene)hydrazinecarboxylate **2g** (0.134 g, 0.510 mmol) and norbornene (0.480 g, 5.10 mmol, 10.0 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (10 mL). The reaction was heated at 150 °C for three hours. The title compound was obtained as a white solid (99% NMR yield, 0.138 g, 95% isolated yield). m.p.: 288-290 °C. TLC  $R_f$  = 0.30 in 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.12 (d,  $J$  = 7.2 Hz, 1H), 3.85 (s, 1H), 2.93 (s, 1H), 2.67 (d,  $J$  = 8.5 Hz, 2H), 2.32 (s, 1H), 2.09-1.80 (m, 12H), 1.52-1.40 (m, 3H), 1.13-1.08 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  182.6 (C), 161.4 (C), 70.3 (CH), 51.7 (CH), 42.5 (CH), 38.6 (CH), 38.6 (CH<sub>2</sub>), 38.5 (CH<sub>2</sub>), 37.5 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 35.3 (CH), 34.8 (CH), 34.4 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 26.7 (CH), 26.6 (CH<sub>2</sub>), 26.6 (CH), 24.9 (CH<sub>2</sub>); IR (film); 2964, 2924, 2855, 1656, 1596, 1342, 1320, 1279 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O<sub>1</sub> [M]<sup>+</sup>: 284.1883; found: 284.1877.



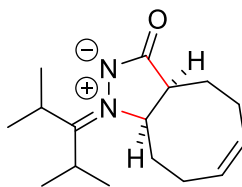
**(±)-*exo*-2-(2,4-Dimethylpentan-3-ylidene)-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.6, 7h).** Synthesized according to general procedure A using *tert*-butyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate **1a** (0.050 g, 0.20 mmol) and norbornene (0.19 g, 2.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL). The reaction was heated at 150 °C for three hours. The title compound was obtained as a white solid (99% NMR yield, 0.047 g, 95% isolated yield). The product was recrystallized from dichloromethane/hexanes and crystals were submitted for X-ray crystallographic analysis. m.p.: 189-190 °C. TLC  $R_f$  = 0.54 in 15% MeOH in EtOAc.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.18 (d,  $J$  = 7.17 Hz, 1H), 3.00 (sept.,  $J$  = 6.50 Hz, 1H), 2.85-2.71 (m, 2H), 2.63 (d,  $J$  = 7.10 Hz, 1H), 2.39 (s, 1H), 1.66-1.53 (m, 2H), 1.39 (d,  $J$  = 10.79 Hz, 1H), 1.33 (t,  $J$  = 6.95, 6.95 Hz, 6H), 1.31-1.23 (m, 2H), 1.21 (d,  $J$  = 6.72 Hz, 3H), 1.18-1.12 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.3, 161.2, 72.6 (CH), 51.0 (CH), 43.1 (CH), 39.1 (CH), 32.7 (CH), 32.2 ( $\text{CH}_2$ ), 29.9 (CH), 27.1 ( $\text{CH}_2$ ), 25.4 ( $\text{CH}_2$ ), 19.0 ( $\text{CH}_3$ ), 18.9 ( $\text{CH}_3$ ), 16.9 ( $\text{CH}_3$ ), 16.5 ( $\text{CH}_3$ ). IR (film); 2959, 2879, 1652, 1582, 1362, 1020  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calcd for  $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_1$   $[\text{M}]^+$ : 248.1889; found: 248.1905. **Gram scale reaction:** To a flame-dried sealed tube, *tert*-butyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate **2g** (1.7125 g, 7.5 mmol) and norbornene (7.06 g, 75 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (75 mL). The reaction was heated at 150 °C in an oil bath for three hours. The title compound was obtained as a white solid (1.13 g, 4.55 mmol, 61% isolated yield) with recovered starting material.



**1-(2,4-Dimethylpentan-3-ylidene)- 5-*n*-pentanyl -3-oxopyrazolidine-1-ium-2-ide (Table 3.9, 9a).** Synthesized according to general procedure **B** using *tert*-butyl 2-(2,4-dimethylpentan-2-ylidene)hydrazinecarboxylate (46 mg, 0.20 mmol) and 1-hexene (4 mL) as the solvent. The reaction was heated in a sealed tube at 150 °C for 3 hours. The title compound was obtained as a 7:1 mixture of regioisomers (**i** and **i**) as a yellow oil (31 mg, 66%) with product **i** as the major regioisomer. TLC  $R_f$  = 0.34 in 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Regioisomer **i**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.59 (t,  $J$  = 9.0 Hz, 1H), 2.99-2.75 (m, 3H), 2.37 (dd,  $J$  = 16.1, 1.8 Hz, 1H), 1.78-1.55 (m, 2H), 1.38-1.18 (m, 16H), 0.88 (t,  $J$  = 7.0 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 181.4 (C), 161.8 (C), 66.1 (CH), 36.1 (CH<sub>2</sub>), 35.0 (CH<sub>2</sub>), 32.3 (CH), 30.2 (CH), 26.6 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 19.3 (CH<sub>3</sub>), 19.1 (CH<sub>3</sub>), 17.0 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>). IR (film); 2915, 2846, 1656, 1622, 1086 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>14</sub>H<sub>26</sub>N<sub>2</sub>O<sub>1</sub> [M]<sup>+</sup>: 238.2045; found: 238.2093. Regioisomer **ii**: Synthesized according to general procedure **B** using *tert*-butyl 2-(2,4-dimethylpentan-2-ylidene)hydrazinecarboxylate (282.7 mg, 1.2381 mmol) and 1-hexene (20 mL) as the solvent. The reaction was heated in a sealed tube at 150 °C for 3 hours. The title compound (22.0 mg, 7.4 % isolated yield) was obtained as yellow oil. TLC  $R_f$  = 0.5 in 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.35 (dd,  $J$  = 12.8, 9.6 Hz, 1H), 3.85 (dd,  $J$  = 12.8, 6.2, 1H), 3.04-2.92 (m, 2H), 2.82-2.72 (m, 1H), 2.08-1.97 (m, 1H), 1.53-1.32 (m, 11H), 1.21 (dd,  $J$  = 6.8, 1.4, 6H), 0.90 (t,  $J$  = 6.9, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  ppm 184.6 (C), 160.7 (C), 59.1 (CH<sub>2</sub>), 41.1 (CH), 32.2 (CH), 31.2 (CH<sub>2</sub>), 30.1 (CH), 30.0 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 18.8 (2CH<sub>3</sub>), 17.1 (CH<sub>3</sub>), 17.0 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>).

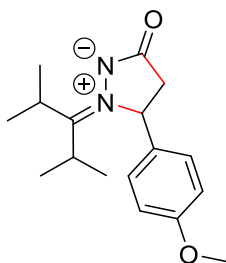


**(±)-*exo*-2-(2,3-Dimethylpentan-3-ylidene)-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.9, 9c).** Synthesized according to general procedure **B** using phenyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (0.050 g, 0.20 mmol) and norbornadiene (0.20 mL, 2.0 mmol, 10 equiv). The reaction was heated at 80 °C for three hours. The title compound was obtained as a red solid (0.039 g, 78% yield). TLC  $R_f$  = 0.39 in 5% MeOH/ $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.43 (dd,  $J$  = 5.67, 3.00 Hz, 1H), 6.08 (dd,  $J$  = 5.64, 3.11 Hz, 1H), 4.44 (d,  $J$  = 7.08 Hz, 1H), 3.31 (s, 1H), 3.11 (sept.,  $J$  = 6.73 Hz, 1H), 3.03 (s, 1H), 2.92 (d,  $J$  = 6.96 Hz, 1H), 2.83 (sept.,  $J$  = 6.96 Hz, 1H), 1.72-1.56 (m, 2H), 1.37 (t,  $J$  = 6.80 Hz, 6H), 1.29-1.17 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 181.8 (C), 162.0 (C), 142.5 ( $\text{CH}_1$ ), 133.5 (CH), 74.1 (CH), 51.0 (CH), 49.0 (CH), 44.7 (CH), 43.2 ( $\text{CH}_2$ ), 32.7 (CH), 30.0 (CH), 19.1 ( $\text{CH}_3$ ), 19.0 ( $\text{CH}_3$ ), 16.9 ( $\text{CH}_3$ ), 16.8 ( $\text{CH}_3$ ). IR (film); 2968, 2927, 1645, 1580, 1455, 1394, 1323, 1241, 1020, 906, 730  $\text{cm}^{-1}$ ; HRMS(EI): Exact mass calcd for  $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_1$   $[\text{M}]^+$ : 246.1727. Found: 246.1712.



**(±)-*cis*-(Z)-1-(2,4-Dimethylpentan-3-ylidene)-3-oxo-1,3,3a,4,5,8,9,9a-octahydrocycloocta[c]-pyrazol-1-ium-2-ide (Table 3.9, 9d).** Synthesized according to general procedure **A** using *tert*-butyl 2-(2,4-dimethylpentan-2-ylidene)hydrazinecarboxylate (46 mg, 0.2 mmol) 1,5-cyclooctadiene (0.25 mL, 2.0 mmol) in *aaa*-trifluorotoluene (4 mL). The reaction was heated in a sealed tube at 150 °C for 3 hours. The title compound (18 mg, 33%) was obtained as a yellow oil.

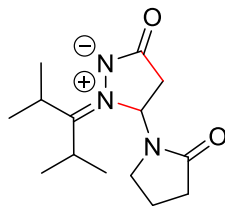
TLC  $R_f$  0.23 in 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H-NMR (400 MHz; CDCl<sub>3</sub>):  $\delta$  ppm 5.81-5.74 (m, 1H), 5.59 (ddt,  $J$  = 8.6, 8.4, 3.1 Hz, 1H), 4.90-4.82 (m, 1H), 2.87 (sept.,  $J$  = 6.8 Hz, 1H), 2.85 (sept.,  $J$  = 6.8 Hz, 1H), 2.81-2.65 (m, 2H), 2.56 (d,  $J$  = 16.5 Hz, 1H), 2.45-2.37 (m, 1H), 2.31-2.02 (m, 4H), 1.89-1.77 (m, 1H), 1.39 (d,  $J$  = 7.0 Hz, 3H), 1.35 (d,  $J$  = 7.0 Hz, 3H), 1.25 (d,  $J$  = 6.7 Hz, 3H), 1.21 (d,  $J$  = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 183.0 (C), 161.4 (C), 133.3 (CH<sub>1</sub>), 125.7 (CH<sub>1</sub>), 68.6 (CH<sub>1</sub>), 47.4 (CH<sub>1</sub>), 32.7 (CH<sub>1</sub>), 30.2 (CH<sub>1</sub>), 29.0 (CH<sub>2</sub>), 28.7 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 19.5 (CH<sub>3</sub>), 19.3 (CH<sub>3</sub>), 17.2 (CH<sub>3</sub>), 17.0 (CH<sub>3</sub>). IR (film); 2927, 2852, 1708, 1580, 1461, 1367, 912, 736 cm<sup>-1</sup>; HRMS(EI): Exact mass calcd for C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>O<sub>1</sub> [M]<sup>+</sup>: 262.2040. Found: 262.2029.



**1-(2,4-Dimethylpentan-3-ylidene)-5-(4-methoxyphenyl)-3-oxopyrazolidine-1-ium-2-ide**

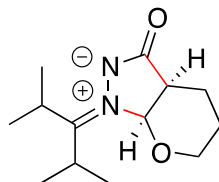
(Table 3.9, 9f). Synthesized according to general procedure B using phenyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (63.4 mg, 0.255 mmol) and 4-methoxystyrene (0.34 mL, 2.55 mmol) heated at 120°C for 3 hours. The title compound was obtained as a white solid (31.2 mg, 43% isolated yield and 54% NMR yield). TLC  $R_f$  = 0.26 in 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.13 (d,  $J$  = 8.8 Hz, 2H), 6.87 (d,  $J$  = 8.8 Hz, 2H), 5.53 (dd,  $J$  = 9.9, 2.8 Hz, 1H), 3.78 (s, 3H), 3.18 (dd,  $J$  = 16.4, 9.9 Hz, 1H), 2.89 (dt,  $J$  = 13.4, 6.7 Hz, 1H), 2.78 (dt,  $J$  = 13.9, 6.9 Hz, 1H), 2.49 (dd,  $J$  = 16.4, 2.8 Hz, 1H), 1.41 (d,  $J$  = 6.9 Hz, 6H), 1.13 (d,  $J$  = 6.8 Hz, 3H), 0.51 (d,  $J$  = 6.6 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 181.1 (C), 162.6 (C), 159.8 (C), 132.3 (C), 126.5 (CH), 115.0 (CH), 69.7 (CH), 55.5 (CH), 40.4 (CH<sub>2</sub>), 32.9 (CH), 30.3 (CH), 19.0

(CH<sub>3</sub>), 17.7 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>), 16.4 (CH<sub>3</sub>), ; IR (film); 2964, 2918, 2846, 2010, 1675, 1577, 1513, 1251, 1014 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> [M]<sup>+</sup>: 288.1838; found: 288.1823.



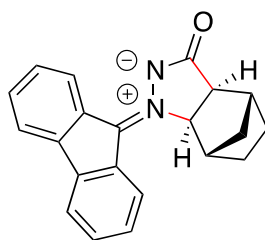
**1-(2,4-Dimethylpentan-3-ylidene)-3-oxo-5-(2-oxopyrrolidin-1-yl)pyrazolidin-1-ium-2-ide**

(Table 3.9, 9g). Synthesized according to general procedure B using phenyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (0.0654 g, 0.263 mmol) and 1-vinyl-2-pyrrolidinone (0.353 g, 3.18 mmol, 12 equiv). The reaction was heated at 80 °C for three hours. The title compound was obtained as a white solid (82% NMR yield, 0.0536 g, 77 % isolated yield) m.p.: 140-142 °C. TLC R<sub>f</sub> = 0.35 in EtOAc. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 6.58 (dd, *J* = 9.0, 1.7 Hz, 1H), 3.40 (ddd, *J* = 9.9, 8.4, 6.4 Hz, 1H), 3.07-2.80 (m, 4H), 2.50-2.27 (m, 3H), 2.16-1.89 (m, 2H), 1.35 (dd, *J* = 8.1, 7.0 Hz, 6H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 179.2 (C), 173.6 (C), 165.1 (C), 71.2 (CH), 41.3 (CH<sub>2</sub>), 33.9 (CH<sub>2</sub>), 31.9 (CH), 30.4 (CH<sub>2</sub>), 30.4 (CH), 18.9 (CH<sub>2</sub>), 18.7 (CH<sub>3</sub>), 17.8 (CH<sub>3</sub>), 16.7 (CH<sub>3</sub>), 16.4 (CH<sub>3</sub>); IR (film); 2972, 2930, 1691, 1645, 1579, 1417, 1265, 1014 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>14</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> [M]<sup>+</sup>: 265.1785; found: 265.1765.



(±)-*cis*-1-(2,4-Dimethylpentan-3-ylidene)-3-oxo-tetrahydro-2*H*-pyro[2,3-*c*]pyrazolidine-1-ium-2-ide (Table 3.9, 9I). Synthesized according to general procedure B using phenyl 2-(2,4-

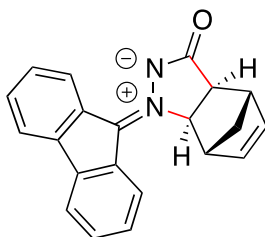
dimethylpentan-3-ylidene)hydrazinecarboxylate (0.0902 g, 0.363 mmol) and 3,4-dihydro-2H-pyran (0.331 mL, 3.63 mmol, 10.0 equiv). The reaction was heated at 80 °C for three hours. The title compound was obtained as a white solid (70 % NMR yield, 0.0608 g, 70 % isolated yield). TLC  $R_f$  = 0.30 in 5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.93 (d,  $J$  = 7.7 Hz, 1H), 3.63-3.44 (m, 2H), 3.14 (sept.,  $J$  = 6.7 Hz, 1H), 2.83 (sept.,  $J$  = 6.9 Hz, 1H), 2.67 (t,  $J$  = 3.7 Hz, 1H), 2.19 (d,  $J$  = 10.9 Hz, 1H), 1.72-1.58 (m, 3H), 1.28 (dd,  $J$  = 13.8, 7.0 Hz, 6H), 1.09 (d,  $J$  = 6.7 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  181.4 (C), 165.3 (C), 91.1 (CH), 61.1 (CH<sub>2</sub>), 37.9 (CH), 32.3 (CH), 30.0 (CH), 19.2 (CH<sub>2</sub>), 19.1 (CH<sub>3</sub>), 18.8 (CH<sub>3</sub>), 16.6 (CH<sub>3</sub>), 16.5 (CH<sub>3</sub>), 16.3 (CH<sub>2</sub>); IR (film); 2971, 2876, 1649, 1577, 1135, 1063, 1048, 1016 cm<sup>-1</sup>; MS  $m/z$  (relative intensity): 84.1 (100.0%), 55.1 (73.0%), 43.1 (63.3%), 97.0 (45.6%), 111.0 (36.9%), 195.1 (23.2%), 83.1 (21.6%), 56.1 (20.9%), 70.1 (19.4%), 124.1 (17.5%), 155.1 (17.2%), 83.1 (17.1%).



**(±)-*exo*-2-[*N*-(9*H*-Fluoren-9-ylidene)]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>]decane-2-ium-3-ide (equation 3.8, 11a):** Synthesized according to general procedure A using phenyl 2-[*N*-(9*H*-fluoren-9-ylidene)]hydrazinecarboxylate (0.063 g, 0.20 mmol) and norbornene (0.038 g, 0.40 mmol, 2.0 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL). The reaction was heated at 100 °C for two hours. The title compound was obtained as yellow solid (94% NMR yield, 0.058 g, 93% isolated yield). m.p.: 232-236 °C. TLC  $R_f$  = 0.16 in EtOAc. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.87 (d,  $J$  = 7.73 Hz, 1H), 7.58 (d,  $J$  = 7.43 Hz, 1H), 7.50 (d,  $J$  = 7.37 Hz, 1H), 7.45 (d,  $J$  = 7.87 Hz, 1H), 7.34 (t,  $J$  = 7.46 Hz, 2H), 7.28-7.22 (m, 2H), 4.80 (d,  $J$  = 6.77 Hz, 1H), 2.86 (d,  $J$  = 6.72 Hz, 1H), 2.81

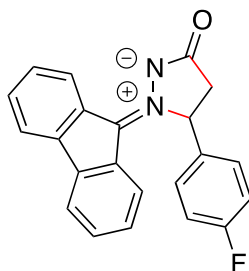


(s, 2H), 1.77-1.63 (m, 2H), 1.50 (d,  $J = 11.89$  Hz, 1H), 1.46-1.36 (m, 2H), 1.18 (d,  $J = 11.03$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  185.8 (C), 141.6 (C), 139.5 (C), 139.1 (C), 131.7 (CH), 131.6 (C), 131.0 (CH), 130.7 (CH), 129.9 (C), 129.0 (CH), 128.1 (CH), 125.2 (CH), 120.9 (CH), 119.6 (CH), 74.7 (CH), 50.8 (CH), 42.2 (CH), 40.0 (CH), 32.1 ( $\text{CH}_2$ ), 27.2 ( $\text{CH}_2$ ), 25.3 ( $\text{CH}_2$ ). IR (film); 2973, 2876, 1669, 1606, 1549, 1450, 1281, 1130, 1087, 727  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}$   $[\text{M}]^+$ : 314.1414. Found: 314.1414. **Gram Scale:** To a flame-dried sealed vial, *tert*-butyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (1.71 g, 7.50 mmol) and norbornene (7.06 g, 75.0 mmol, 10.0 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (75 mL). The reaction was heated at 150  $^\circ\text{C}$  in an oil bath for three hours. The title compound was obtained as a white solid (1.13 g, 61% yield) with recovered starting material.



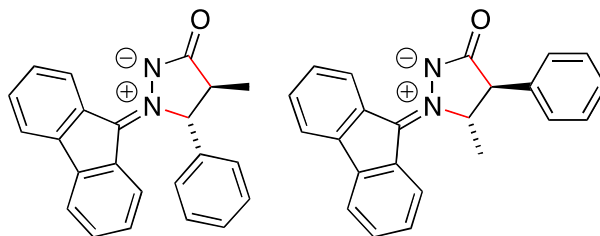
( $\pm$ )-*exo*-2-[*N'*-(9*H*-Fluoren-9-ylidene)]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]dec-7-ene-2-ium-3-ide (Table 3.10, 11g): Synthesized according to general procedure A using phenyl 2-[*N*-(9*H*-fluoren-9-ylidene)]hydrazinecarboxylate (0.063 g, 0.20 mmol) and norbornadiene (0.20 mL, 2.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL). The reaction was heated at 120  $^\circ\text{C}$  for one hour. The title compound was obtained as yellow solid (0.054 g, 86 % isolated yield) after silica gel chromatography using 10 % MeOH in  $\text{CH}_2\text{Cl}_2$  as eluent. m.p.: 238-240  $^\circ\text{C}$ . TLC  $R_f = 0.46$  in 10% MeOH in EtOAc.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.83 (d,  $J = 7.72$  Hz, 1H), 7.57 (d,  $J = 7.15$  Hz, 1H), 7.53-7.44 (m, 2H), 7.40-7.18 (m, 4H), 6.50 (dd,  $J = 5.43, 2.81$  Hz, 1H), 6.26 (dd,  $J = 5.30, 2.93$  Hz, 1H), 5.01 (d,  $J = 6.31$  Hz, 1H), 3.41 (s, 1H), 3.36 (s, 1H), 3.13 (d,  $J = 6.68$  Hz, 1H), 1.76

(d,  $J = 9.82$  Hz, 1H), 1.63 (d,  $J = 9.97$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  184.1 (C), 142.5 (CH), 141.8 (C), 139.7 (C), 139.4 (C), 133.5 (CH), 131.8 (CH), 131.5 (C), 131.3 (CH), 130.9 (CH), 129.9 (C), 129.0 (CH), 128.2 (CH), 125.4 (CH), 121.0 (CH), 119.6 (CH), 76.4 (CH), 51.0 (CH), 48.1 (CH), 45.3 (CH), 42.9 ( $\text{CH}_2$ ). IR (film) 7990, 1653, 1606, 1550, 1290, 1133, 775, 727  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$   $[\text{M}]^+$ : 314.1257. Found: 312.1269.

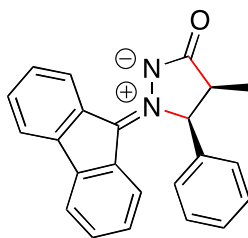


**2-(9H-Fluoren-9-ylidene)-3-(4-fluorophenyl)-5-oxopyrazolidin-2-ium-1-ide (Table 3.10, 11i).**

Synthesized according to general procedure A using phenyl 2-[*N*-(9*H*-fluoren-9-ylidene)]hydrazinecarboxylate (0.262 g, 0.834 mmol) and 4-fluorostyrene (1.02 g, 8.34 mmol, 10.0 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.7 mL). The reaction was heated at 120 °C for three hours. The title compound was obtained as yellow crystals (0.154 g, 54% yield). m.p.: 246-248 °C. TLC  $R_f$  = 0.63 in 10% MeOH/ $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  9.05 (d,  $J = 7.6$ , 1H), 7.53 (d,  $J = 7.5$ , 2H), 7.40-7.21 (m, 6H), 7.01 (t,  $J = 8.3$ , 3H), 6.33 (d,  $J = 8.9$ , 1H), 3.47 (dd,  $J = 16.3$ , 9.2, 1H), 2.67 (d,  $J = 16.1$ , 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  182.3, (C), 164.2 - 160.9 (d,  $J_{\text{C-F}} = 990$  Hz, C), 141.9 - 141.3 (d,  $J_{\text{C-F}} = 180$  Hz, CH), 140.3 (C), 133.9 (d,  $J_{\text{C-F}} = 990$  Hz, CH), 132.5 (CH), 131.7 - 131.6 (d,  $J_{\text{C-F}} = 30$  Hz, CH), 131.3 (CH), 129.3 (CH), 129.2 (CH), 128.1 (CH), 126.8 (CH), 126.7 (CH), 125.9 (CH), 121.0 (CH), 120.0 (CH), 117.1 (CH), 116.8 (CH), 71.6 (CH), 40.9 ( $\text{CH}_2$ ); IR (film); 3268, 2918, 2854, 2325, 1968, 1656, 1565, 1421, 1269, 733  $\text{cm}^{-1}$ . HRMS (EI): Exact mass calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_1$   $[\text{M}]^+$ : 342.1168; found: 342.1185.

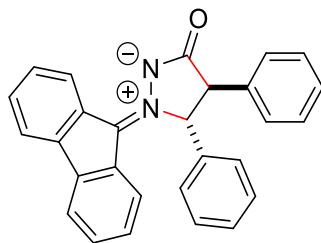


**2-(9H-Fluoren-9-ylidene)-5-oxo-*trans*-2-methyl-3-phenylpyrazolidin-2-ium-1-ide** (Table 3.10, 11l). Synthesized according to general procedure using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.0843 g, 0.268 mmol) and *trans*- $\beta$ -methylstyrene (0.35 mL, 2.68 mmol) dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene (5.37 mL, 0.05M). The target compound was obtained as a yellow solid (0.0475 g, 52%) and a 1:1 mixture of regioisomers. TLC  $R_f$  = 0.61 in 100% EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) ppm 9.18 (d,  $J$  = 7.3, 1H), 9.12 (d,  $J$  = 7.6, 1H), 7.64 (ddd,  $J$  = 30.5, 16.4, 7.2, 5H), 7.48-7.21 (m, 18H), 7.05 (s, 1H), 5.91 (s, 1H), 5.36 (q,  $J$  = 6.3, 1H), 3.79 (s, 1H), 2.83 (q,  $J$  = 7.1, 1H), 1.89 (d,  $J$  = 6.6, 3H), 1.60 (d,  $J$  = 7.4, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  ppm 186.2, 183.6, 142.3, 141.8, 140.3, 140.0, 138.2, 137.7, 132.3, 131.8, 131.8, 131.8, 131.6, 131.3, 131.1, 129.9, 129.6, 129.5, 129.4, 129.3, 128.8, 128.5, 128.0, 127.9, 127.1, 126.0, 125.5, 124.5, 121.3, 120.9, 119.8, 79.9, 72.5, 56.8, 48.1, 21.8, 18.4; HRMS(EI): Exact mass calcd for  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$   $[\text{M}]^+$ : 338.1419. Found: 338.1404.



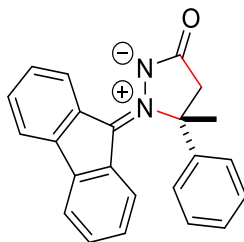
**2-(9H-Fluoren-9-ylidene)-5-oxo-*cis*-2-methyl-3-phenylpyrazolidin-2-ium-1-ide** (Table 3.10, 11k). Synthesized according to general procedure using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.105 g, 0.335 mmol) and *cis*- $\beta$ -methylstyrene (0.396 g, 3.35

mmol) dissolved in  $\alpha,\alpha,\alpha$ -trifluorotoluene (6.7 mL, 0.05M). The target compound was obtained as a yellow solid (0.0273 g, 24% yield) as a 10:1 mixture of the target compound and 2-(9H-Fluoren-9-ylidene)-5-oxo-*trans*-2-methyl-3-phenylpyrazolidin-2-ium-1-ide. TLC  $R_f$  = 0.41 in 100% EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 9.17 (d,  $J$  = 7.2, 1H), 7.58-7.55 (m, 2H), 7.47-7.25 (m, 9H), 7.07 (t,  $J$  = 7.5, 1H), 6.36 (d,  $J$  = 8.8, 1H), 3.43 (quintet,  $J$  = 7.6, 1H), 0.90 (d,  $J$  = 7.2, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  ppm ; 185.3 (C), 141.6 (C), 140.8 (C), 140.1 (C), 133.9 (C), 132.0, 131.8, 131.7, 130.8, 129.4, 129.4, 129.3, 129.1, 128.9, 127.8, 127.0, 127.0, 126.4, 125.9, 120.7, 119.6, 41.3, 11.4.



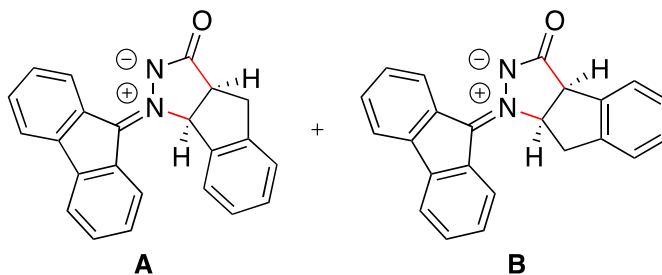
**(3S,4R)-2-(9H-fluoren-9-ylidene)-5-oxo-3,4-diphenylpyrazolidin-2-ium-1-ide (Table 3.10, 11m).** Synthesized according to general procedure A using phenyl 2-[*N*-(9H-fluoren-9-ylidene)]hydrazinecarboxylate 0.232 g, 0.740 mmol) and *trans*-stilbene (1.33 g, 7.40 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.5 mL). The reaction was heated at 120 °C for three hours. Crude mixture was purified by column chromatography using 100 % EtOAc. The title compound was obtained as yellow solid (0.093 g, 33 % isolated yield) TLC  $R_f$  = 0.65 in 100 % EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 9.29 (1 H, d,  $J$  = 7.5 Hz) 7.14 - 7.75 (18 H, m) 6.91 - 7.13 (1 H, m) 6.28 (1 H, s) 3.99 (1 H, d,  $J$  = 0.9 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz) 182.8 (C), 141.9 (C), 141.8 (C), 140.7 (C), 138.2 (C), 137.2 (C), 132.5 (C), 131.9 (C), 131.7 (CH), 131.2 (CH), 129.9 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.2 (CH), 126.0 (CH), 124.6 (CH),

120.9 (CH), 119.8 (CH), 80.5 (CH), 59.4 (CH). HRMS(ESI): Exact mass calcd for  $C_{28}H_{20}N_2O$   $[M]^+$ : 400.1576. Found: 400.1574.



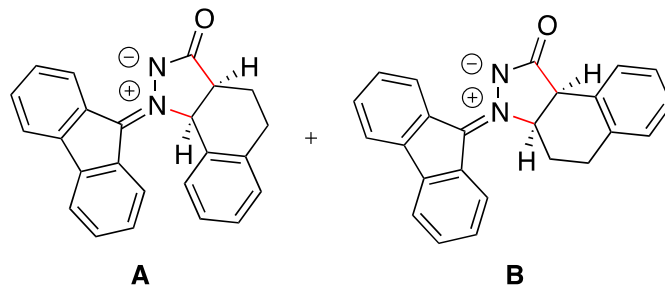
**2-(9H-fluoren-9-ylidene)-3-methyl-5-oxo-3-phenylpyrazolidin-2-ium-1-ide (Table 3.10, 11p).**

Synthesized according to general procedure A using phenyl 2-[*N*-(9*H*-fluoren-9-ylidene)]hydrazinecarboxylate (0.088 g, 0.280 mmol) and  $\alpha$ -methylstyrene (0.331 g, 2.80 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (5.6 mL). The reaction was heated at 120 °C for six hours. Crude mixture was purified by column chromatography using 100 % EtOAc. The title compound was obtained as yellow solid (0.0176 g, 19 % isolated yield) TLC  $R_f$  = 0.26 in 100 % EtOAc.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  ppm 9.31 (1 H, d,  $J$ =7.5 Hz) 7.58 (2 H, dd,  $J$ =14.0, 7.2 Hz) 7.30 - 7.51 (7 H, m) 7.21 (1 H, ddd,  $J$ =7.6, 5.0, 3.1 Hz) 6.67 - 6.89 (2 H, m) 2.95 - 3.29 (2 H, m) 2.35 (3 H, s).  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz) 181.0 (C), 142.2 (C), 141.5 (C), 141.2 (C), 140.1 (C), 133.2 (C), 132.6 (CH), 132.1 (CH), 130.6 (CH), 130.0 (CH), 129.3 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.1 (CH), 123.7 (CH), 122.1 (CH), 120.3 (CH), 119.3 (CH), 81.5 (C), 51.6 (CH<sub>2</sub>), 24.3 (CH<sub>3</sub>). HRMS(ESI): Exact mass calcd for  $C_{23}H_{18}N_2O$   $[M]^+$ : 338.1419. Found: 338.1415.



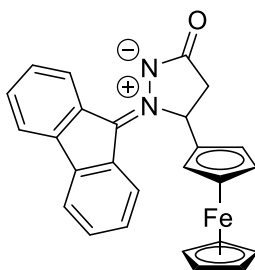
**1-(9*H*-Fluoren-9-ylidene)-3,3 $\alpha$ ,4,8 $\beta$ -tetrahydro-2*H*-indeno[2,1-*c*]-pyrazolidine-1-ium-2-ide**

**(Table 3.10, 11n):** Synthesized according to general procedure **A** using phenyl 2-[*N*-(9*H*-fluoren-9-ylidene)]hydrazinecarboxylate **2h** (0.063 g, 0.20 mmol) and 1*H*-indene (**4j**, 0.23 g, 2.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL). The reaction was heated at 120 °C for three hours. The title compound **A** and its regioisomer **B** was obtained as yellow solid (0.034 g, 51% yield) and a 6:1 mixture of regioisomers, respectively. m.p.: 267-268 °C. TLC  $R_f$  = 0.26 in EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.94 (d,  $J$  = 7.80 Hz, 1H), 7.99 (d,  $J$  = 7.95 Hz, 1H), 7.74 (d,  $J$  = 7.41 Hz, 1H), 7.64 (d,  $J$  = 7.48 Hz, 1H), 7.52-7.26 (m, 7H), 7.13-7.05 (m, 1H), 6.78 (d,  $J$  = 7.20 Hz, 1H), 3.74 (t,  $J$  = 7.53 Hz, 1H), 3.67 (d,  $J$  = 16.75 Hz, 1H), 3.34 (dd,  $J$  = 16.64, 8.44 Hz, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  185.8 (C), 143.4 (C), 142.3 (C), 140.1 (C), 137.1 (C), 132.2 (CH), 131.7 (C), 131.6 (CH), 131.4 (CH); 130.6 (C), 130.3 (CH), 129.2 (CH), 128.4 (CH), 127.5 (CH), 126.1 (CH), 125.5 (CH), 125.3 (CH), 121.3 (CH), 119.8 (CH), 76.0 (CH), 45.9 (CH), 33.3 ( $\text{CH}_2$ ). IR (film) 2981, 1670, 1606, 1546, 1282, 1120, 775, 728  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{23}\text{H}_{16}\text{N}_2\text{O}$   $[\text{M}]^+$ : 336.1257. Found: 336.1233.



**1-(9*H*-Fluoren-9-ylidene)-3-(1,2,3,4-tetrahydro-naphthalene)-pyrazolidine-1-ium-2-ide (Table 3.10, 11o).** Synthesized according to general procedure **A** using phenyl 2-[*N*-(9*H*-fluoren-9-ylidene)]hydrazinecarboxylate (0.235 g, 0.748 mmol) and dihydronaphthalene (0.913 g, 7.48 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.5 mL). The reaction was heated at 120 °C for three hours. Volatiles were removed and the crude product obtained as a mixture of regioisomers **A** and **B** (3:2, 51% NMR yield). The regioisomers were separated by silica gel chromatography with 100% CH<sub>2</sub>Cl<sub>2</sub>, then 50% EtOAc/*n*-hexanes gradually increased to 100% EtOAc. The major regioisomer **A** was obtained as yellow crystals (0.0819 g, 31% yield). m.p.: 246-247 °C. TLC R<sub>f</sub> = 0.30 in 100% EtOAc. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  9.10 (d,  $J$  = 7.4, 1H), 7.72 (dd,  $J$  = 14.7, 7.3, 2H), 7.44 (dq,  $J$  = 19.8, 9.9, 4H), 7.27 (d,  $J$  = 6.5, 2H), 7.20 (d,  $J$  = 7.7, 2H), 7.08 (t,  $J$  = 8.1, 1H), 6.26 (s, 1H), 3.69 (s, 1H), 2.98 (d,  $J$  = 13.6, 1H), 2.75 (t,  $J$  = 12.1, 1H), 2.42 (s, 1H), 2.02 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  185.4 (C), 142.4 (C), 142.3 (C), 140.3 (C), 139.9 (C), 132.5 (C), 132.0 (CH), 131.7 (CH), 131.5 (CH), 130.5 (C), 129.5 (CH), 129.3 (CH), 129.0 (C), 128.8 (CH), 128.5 (CH), 126.9 (CH), 126.0 (CH), 125.5 (CH), 121.2 (CH), 119.9 (CH), 69.8, 42.6, 28.5, 21.4; IR (film) 3059, 2914, 2850, 1672, 1603, 1550, 1451, 1257, 1132, 729 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>24</sub>H<sub>18</sub>N<sub>2</sub>O<sub>1</sub>[M]<sup>+</sup>: 350.1419; found: 350.1438. Minor regioisomer **B** was obtained as yellow crystals (0.0524 g, 20% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  9.05 (dd,  $J$  = 7.7, 0.5 Hz, 1H), 7.71 (dd,  $J$  = 7.5, 0.7 Hz, 1H), 7.65-7.57 (m, 3H), 7.44 (tt,  $J$  = 7.5, 1.2 Hz, 2H), 7.38-7.30 (m, 3H), 7.25-7.20 (m, 1H), 7.13 (d,  $J$  = 7.2 Hz, 1H), 5.68 (dt,  $J$  = 8.6, 5.7 Hz, 1H), 4.22 (d,  $J$  = 8.4 Hz, 1H),

2.85-2.69 (m, 2H), 2.34 (q,  $J = 6.0$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  182.1 (C), 142.0 (C), 139.8 (C), 139.4 (C), 136.4 (C), 132.1 (C), 131.7 (CH), 131.4 (CH), 131.1 (CH), 130.8 (CH), 130.6 (CH), 129.7 (C), 129.3 (CH), 128.4 (CH), 127.7 (CH), 127.3 (CH), 125.4 (CH), 121.3 (CH), 119.7 (CH), 68.0 (CH), 46.0 (CH), 29.6 ( $\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ ).



**2-(9H-Fluoren-9-ylidene)-3-(penta(ferrocenyl)cyclopentadienyl)-5-oxopyrazolidin-2-ium-1-ide (Table 3.10, 11q).** Synthesized according to general procedure **A** using phenyl 2-[*N*-(9H-fluoren-9-ylidene)]hydrazinecarboxylate (0.0800 g, 0.255 mmol) and vinyl-ferrocene (**4l**, 0.0541 g, 0.255 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.28 mL). The reaction was heated at 80 °C for three hours. Volatiles were removed and the crude product was isolated by column chromatography with 100%  $\text{CH}_2\text{Cl}_2$ , then 50% EtOAc/*n*-hexanes and gradually increased to 100% EtOAc. The title compound was obtained as dark red crystals (0.102 g, 93 % yield). m.p.: 181-183 °C. TLC  $R_f$  = 0.22 in EtOAc.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  8.90 (d,  $J = 7.6$ , 1H), 7.97 (dd,  $J = 7.1$ , 4.0, 2H), 7.62-7.48 (m, 4H), 7.30 (t,  $J = 7.5$ , 1H), 6.35-6.33 (m, 1H), 4.36 (d,  $J = 20.6$ , 2H), 4.15 (d,  $J = 0.3$ , 1H), 3.84 (s, 1H), 3.34-3.33 (m, 12H), 3.14 (d,  $J = 15.7$ , 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  184.3, 140.7, 139.9, 138.3, 132.2 (CH), 131.1 (CH), 130.3 (CH), 129.8 (C), 129.3 (CH), 128.6 (CH), 127.0 (CH), 121.5 (CH), 120.9 (CH), 89.2 (C), 69.5 (CH), 69.3 (CH), 67.8 (CH), 67.5 (CH), 67.4 (CH), 66.6 (CH), 40.4 ( $\text{CH}_2$ ); IR (film) 3086, 2975, 1664, 1546, 1273, 1120, 733  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calcd for  $\text{C}_{28}\text{H}_{26}\text{Fe}_1\text{N}_2\text{O}_1[\text{M}]^+$ : 432.0925; found: 432.0951. **Gram Scale:** Phenyl 2-[*N*-(9H-fluoren-9-ylidene)]hydrazinecarboxylate (1.04 g, 3.33 mmol), vinyl ferrocene (0.705 g,

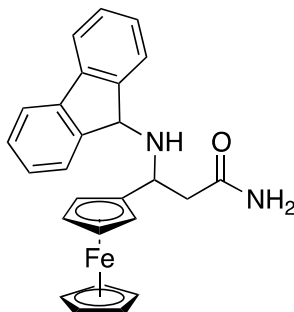


3.33 mmol, 1.00 equiv.), and  $\text{PhCF}_3$  (11.1 mL) were combined in a 100 mL round-bottom flask, equipped with a reflux condenser. The mixture was heated to 80 °C in an oil bath and stirred. After 48 hours the mixture was cooled to room temperature, the stir bar removed, and  $\text{PhCF}_3$  evaporated to give a dark crystals. This was purified by silica gel chromatography by flushing with dichloromethane followed by gradual addition of EtOAc up to 100%. Solvent was removed by evaporation to give the product as a dark red solid (1.09 g, 76% yield).

### **Derivatization of Azomethine Imines to $\beta$ -Aminocarbonyl Compounds**

#### **General Procedure:**

To a 150 mL screw-top flask were added azomethine imine (3.0 mmol), Raney-Nickel (1 mL, slurry in water) and  $\text{KBH}_4$  (10.0 equiv) and methanol (60 mL). Care must be taken in choosing size of the flask to allow a maximum volume of air to be present once sealed. The flask was sealed and the reaction mixture was stirred at 60 °C for 12 hours. The mixture was concentrated under reduced pressure and then quenched with saturated  $\text{NH}_4\text{Cl}$  (60 mL). The crude product was extracted with dichloromethane (50 mL  $\times$  3) and the combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. Purification by silica gel chromatography (using EtOAc) and recrystallization from EtOAc/hexanes gave the target compound.



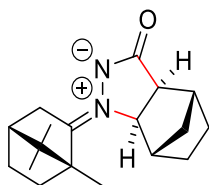
**3-((9H-Fluoren-9-yl)amino)-3-(penta(ferrocenyl)cyclopentadienyl)propanamide** (Table 3.11, 12f). Synthesized according the general procedure using **12f** (0.155 g, 0.358 mmol), Raney nickel (0.5 mL slurry in MeOH),  $\text{KBH}_4$  (0.116 g, 2.15 mmol, 6.00 equiv) and methanol (20 mL). The title compound was obtained as a yellow solid (0.113 g, 72% yield). TLC  $R_f$  = 0.46 in EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (d,  $J$  = 7.2, 2H), 7.65-7.62 (m, 1H), 7.54 (s, 1H), 7.47-7.29 (m, 5H), 6.92 (s, 1H), 4.97 (s, 1H), 4.32-4.26 (m, 2H), 4.23 (s, 1H), 4.19 (s, 1H), 4.15 (d,  $J$  = 8.4, 6H), 2.72 (dd,  $J$  = 14.7, 4.8, 1H), 2.60 (dd,  $J$  = 14.7, 7.9, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  174.3 (C), 148.2 (C), 148.0 (C), 140.6 (C), 140.4 (C), 128.7 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 126.1 (CH), 126.1 (CH), 120.8 (CH), 120.7 (CH), 93.6 (CH), 69.3 (5CH), 68.5 (CH), 68.3 (CH), 67.7 (CH), 67.1 (CH), 61.7 (CH), 53.1 (CH), 43.4 ( $\text{CH}_2$ ). IR (film); 3317, 3177, 1956, 1666, 1603, 1447, 1406, 1093, 740  $\text{cm}^{-1}$ ; MS  $m/z$  (relative intensity): 180.1 (100%), 255.0 (54%), 190.0 (48%), 69.0 (45%), 377.1 (34%), 165.1 (27%), 162.0 (27%).

### **Synthesis of Unsymmetrical Azomethine Imines by Alkene Aminocarbonylation**

**General procedure A:** An oven or flame dried 2-5 mL  $\mu\text{w}$  vial with a stir bar was capped with a septum and purged with argon for 5 minutes. The acyl hydrazone, the corresponding alkene (1 to 10 equiv) and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.5 to 0.05 M) were added to the vial. The septum was removed and the vial was then quickly sealed with a microwave cap and heated in a microwave reactor for 2-6 hours at 80-150  $^\circ\text{C}$ . The reaction solution was cooled to ambient temperature,

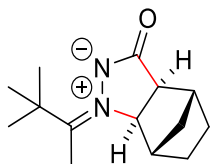
concentrated under reduced pressure and analyzed by  $^1\text{H}$  NMR using 1,4-dimethoxybenzene or 1,3,5-trimethoxybenzene as an internal standard. The corresponding product was purified using silica gel chromatography (using dichloromethane then EtOAc to elute the by-products first, then using 10-20% MeOH in EtOAc or 10% MeOH in  $\text{CH}_2\text{Cl}_2$  to elute the target compound), unless noted otherwise.

**General procedure B (neat reaction):** To a 0.2-0.5 mL  $\mu\text{w}$  vial were added the acyl hydrazone and corresponding alkene (1 to 10 equiv). The vial was then sealed with a microwave cap and heated in a microwave reactor for 3 hours at 80-150  $^\circ\text{C}$ . The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by  $^1\text{H}$  NMR using 1,4-dimethoxybenzene or 1,3,5-trimethoxybenzene as an internal standard. The corresponding product was purified using silica gel chromatography (using EtOAc to elute by-products first, then using 10-20% methanol in EtOAc to elute the target compound), unless noted otherwise.



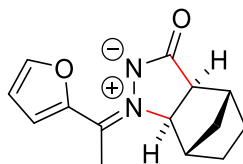
( $\pm$ )-*exo*-2-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)-4-oxo-2,3-diazatricyclo-[4,3,1<sup>6,9</sup>,0]-decane-2-ium-3-ide (Table 3.13, 18). Synthesized according to general procedure A using *tert*-butyl 2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinecarboxylate (69 mg, 0.26 mmol) and norbornene (245 mg, 2.6 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (5.0 mL). The reaction was heated at 150  $^\circ\text{C}$  for three hours. The title compound was obtained a mixture of diastereoisomers and isolated by column chromatography using 5% MeOH/ $\text{CH}_2\text{Cl}_2$  (99% NMR yield, 24:9:34:33 dr., 60 mg, 0.21 mmol, 80% isolated yield). TLC  $R_f$  = 0.49 in 10% MeOH/ $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz) \*mixture of four diastereoisomers  $\delta$  4.39-3.98 (m,

<sup>1</sup>H), 2.92-2.69 (m, 3H), 2.56-2.14 (m, 2H), 2.05-1.12 (m, 14H), 0.92-0.78 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) \*mixture of four diastereoisomers δppm 183.4 (C), 183.4 (C), 182.3 (C), 181.9 (C), 165.1 (C), 164.1 (C), 162.8 (C), 162.6 (C), 73.7 (CH), 72.9 (CH), 70.6 (CH), 70.1 (CH), 57.3, 56.8, 55.3, 54.6, 53.5, 52.8, 52.2, 51.5, 51.4, 51.4, 51.3, 50.7, 49.5, 46.4, 44.1, 43.8, 43.7, 43.3, 42.7, 41.5, 41.1, 40.6, 39.2, 39.2, 39.0, 38.8, 38.2, 37.5, 34.1, 33.0, 32.8, 32.4, 32.3, 32.3, 32.1, 31.3, 29.7 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 25.0 (CH<sub>2</sub>), 20.4 (CH<sub>2</sub>), 20.4 (CH<sub>2</sub>), 20.2 (CH<sub>2</sub>), 20.1 (CH<sub>2</sub>), 19.1 (CH<sub>2</sub>), 18.8 (CH<sub>2</sub>), 18.6 (CH<sub>2</sub>), 18.5 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>), 13.4 (CH<sub>3</sub>), 12.9 (CH<sub>3</sub>); IR (film); 2964, 2922, 2880, 1744, 1672, 1592, 1375, 1303, 790 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O [M]<sup>+</sup>: 286.2045; found: 286.2045. One of the four diastereoisomers was isolated by silica gel column chromatography using 40% *i*-PrOH/toluene. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.95 (d, *J* = 6.9, 1H), 2.77-2.57 (m, 4H), 2.27 (s, 1H), 2.05 (s, 1H), 1.62-1.53 (m, 4H), 1.47 (s, 3H), 1.28-1.14 (m, 6H), 0.93-0.80 (m, 7H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 183.3 (C), 161.3 (C), 72.9 (CH), 57.1 (C), 51.4 (CH), 49.4 (C), 43.8 (CH), 41.5 (CH<sub>2</sub>), 38.8 (CH), 37.3 (CH<sub>2</sub>), 32.2 (CH<sub>2</sub>), 29.7 (CH), 27.1 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 20.3 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>); HRMS (EI): Exact mass calcd for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>1</sub> [M]<sup>+</sup>: 286.2045; found: 286.2049.



**(±)-*exo*-(*Z*)-2-(3,3-dimethylbutan-2-ylidene)-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.13, 18i).** Synthesized according to general procedure **B** using using phenyl 2-(3,3-dimethylbutan-2-ylidene)hydrazinecarboxylate (44 mg, 0.20 mmol), norbornene (190 mg, 2.0

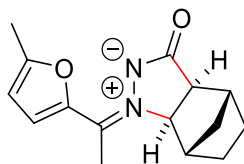
mmol). The reaction time was 1 hour. The title compound was obtained as a yellow oil (38 mg, 82%). TLC  $R_f$  0.13 in 5% methanol in dichloromethane.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 4.24 (d,  $J = 7.1$  Hz, 1H), 2.77 (s, 3H), 2.66 (d,  $J = 7.0$  Hz, 1H), 2.50 (s, 1H), 2.22 (s, 3H), 1.67-1.56 (m, 2H), 1.37 (s, 9H), 1.32-1.10 (m, 4H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 183.1 (C), 156.2 (C), 74.2 (CH), 50.9 (CH), 42.1 (CH), 39.4 (CH), 32.0 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 26.2 ( $\text{CH}_3$ ), 25.2 ( $\text{CH}_2$ ), 18.8 ( $\text{CH}_3$ ). IR (film) 3422, 2961, 2878, 1638, 1568, 1352, 1220, 772  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}$   $[\text{M}]^+$ : 234.1727. Found: 234.1733.



**(±)-*exo*-(*Z*)-2-[(1-Furan-2-yl)ethylidene]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide and (±)-*exo*-(*E*)-2-[(1-Furan-2-yl)ethylidene]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.13, 18c).**<sup>8</sup> Synthesized according to general procedure **B** using using phenyl 2-(1-(furan-2-yl)ethylidene)hydrazinecarboxylate (49 mg, 0.20 mmol), norbornene (190 mg, 2.0 mmol). The solution was heated using a microwave reactor for one hour at 120 °C for one hour. The *Z* isomer was obtained as yellow solid (31 mg, 69%). TLC  $R_f$  0.22 in 10% methanol in EtOAc.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.20 (d,  $J = 3.6$  Hz, 1H), 7.55 (s, 1H), 6.58 (dd,  $J = 3.6$  and 1.7 Hz, 1H), 4.33 (d,  $J = 7.0$  Hz, 1H), 2.79-2.74 (m, 2H), 2.64 (s, 1H), 2.56 (s, 3H), 1.72-1.54 (m, 2H), 1.44 (d,  $J = 11.0$  Hz, 1H), 1.37-1.24 (m, 2H), 1.17 (d,  $J = 11.0$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 184.5 (C), 147.2 (C), 145.4 (CH), 132.1 (C), 122.8 (CH), 113.5 (CH), 72.7 (CH), 51.3 (CH), 42.1 (CH), 39.2 (CH), 32.2 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 25.4 ( $\text{CH}_2$ ), 15.8 ( $\text{CH}_3$ ). IR (film) 2963, 2874, 1644, 1568, 1475, 1353, 1310, 1217, 1134, 771  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for

<sup>8</sup> The structure of the isomer was determined by X-ray crystallographic analysis (see Figure S4).

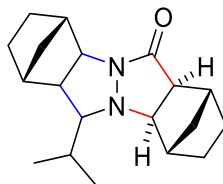
$C_{14}H_{16}N_2O_2$   $[M]^+$ : 244.1206. Found: 244.1193. The *E* isomer was obtained as yellow solid (11 mg, 23%). TLC  $R_f$  0.10 in 10% methanol in EtOAc.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 7.64 (d,  $J = 1.3$  Hz, 1H), 6.90 (d,  $J = 3.6$  Hz, 1H), 6.60 (dd,  $J = 3.6$  and 1.7 Hz, 1H), 4.85 (d,  $J = 7.1$  Hz, 1H), 2.79 (d,  $J = 7.1$  Hz, 1H), 2.72 (s, 1H), 2.56 (s, 1H), 2.43 (s, 3H), 1.67-1.53 (m, 2H), 1.43 (d,  $J = 10.8$  Hz, 1H), 1.36-1.26 (m, 2H), 1.10 (d,  $J = 11.0$  Hz, 1H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  ppm 183.6 (C), 146.4 (C), 145.8 (CH), 133.6 (C), 117.9 (CH), 113.0 (CH), 73.8 (CH), 52.2 (CH), 42.7 (CH), 39.4 (CH), 32.0 ( $CH_2$ ), 27.0 ( $CH_2$ ), 25.2 ( $CH_2$ ), 19.5 ( $CH_3$ ).



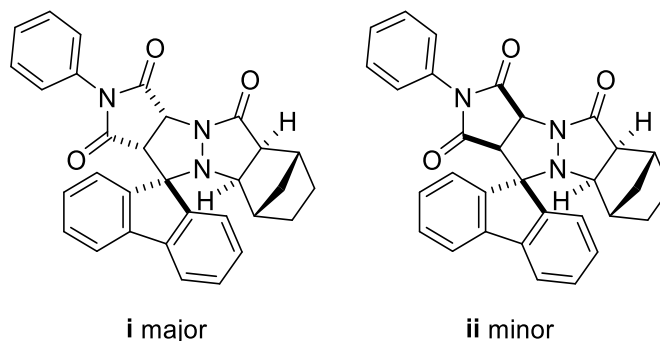
**(±)-*exo*-(*Z*)-2-[(1-Furan-2-yl)ethylidene]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide and (±)-*exo*-(*E*)-2-[(1-Furan-2-yl)ethylidene]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide.** Synthesized according to general procedure **B** using phenyl 2-(1-(furan-2-yl)ethylidene)hydrazinecarboxylate (49 mg, 0.20 mmol), norbornene (190 mg, 2.0 mmol). The solution was heated using a microwave reactor for one hour at 120 °C for one hour. The *Z* isomer was obtained as yellow solid (31 mg, 69%). TLC  $R_f$  0.22 in 10% methanol in EtOAc.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 8.20 (d,  $J = 3.6$  Hz, 1H), 7.55 (s, 1H), 6.58 (dd,  $J = 3.6$  and 1.7 Hz, 1H), 4.33 (d,  $J = 7.0$  Hz, 1H), 2.79-2.74 (m, 2H), 2.64 (s, 1H), 2.56 (s, 3H), 1.72-1.54 (m, 2H), 1.44 (d,  $J = 11.0$  Hz, 1H), 1.37-1.24 (m, 2H), 1.17 (d,  $J = 11.0$  Hz, 1H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  ppm 184.5 (C), 147.2 (C), 145.4 (CH), 132.1 (C), 122.8 (CH), 113.5 (CH), 72.7 (CH), 51.3 (CH), 42.1 (CH), 39.2 (CH), 32.2 ( $CH_2$ ), 27.0 ( $CH_2$ ), 25.4 ( $CH_2$ ), 15.8 ( $CH_3$ ). IR (film) 2963, 2874, 1644, 1568, 1475, 1353, 1310, 1217, 1134, 771  $cm^{-1}$ . HRMS(EI): Exact mass calcd for  $C_{14}H_{16}N_2O_2$   $[M]^+$ : 244.1206. Found: 244.1193. The *E* isomer was obtained as yellow solid (11 mg, 23%). TLC  $R_f$

0.10 in 10% methanol in EtOAc.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.64 (d,  $J = 1.3$  Hz, 1H), 6.90 (d,  $J = 3.6$  Hz, 1H), 6.60 (dd,  $J = 3.6$  and 1.7 Hz, 1H), 4.85 (d,  $J = 7.1$  Hz, 1H), 2.79 (d,  $J = 7.1$  Hz, 1H), 2.72 (s, 1H), 2.56 (s, 1H), 2.43 (s, 3H), 1.67-1.53 (m, 2H), 1.43 (d,  $J = 10.8$  Hz, 1H), 1.36-1.26 (m, 2H), 1.10 (d,  $J = 11.0$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 183.6 (C), 146.4 (C), 145.8 (CH), 133.6 (C), 117.9 (CH), 113.0 (CH), 73.8 (CH), 52.2 (CH), 42.7 (CH), 39.4 (CH), 32.0 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 19.5 ( $\text{CH}_3$ ).

### Cascade Aminocarbonylation / Intermolecular [3+2] Cycloaddition



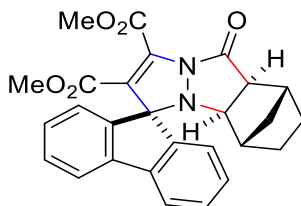
**12-Isopropyl-12,12-dihydro-1,4:7,10-dimethanoindazolo[2,1-a]indazol-6(1H)-one** (equation 3.11, 20a). Synthesized according to general procedure A using (*E*)-*tert*-butyl 2-(2-methylpropylidene)hydrazinecarboxylate (0.069 g, 0.30 mmol), norbornene (0.099 g, 0.531 mmol) and norbornene (0.500 g, 5.31 mmol) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (5.0 mL). The reaction was heated at 150 °C for 3 hours. Crude mixture was purified by column chromatography using 100% EtOAc. The title compound was obtained as a white solid (0.150 g, 94% isolated yield). TLC  $R_f = 0.3$  in 100% EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 3.33 (d,  $J=6.2$  Hz, 2 H) 2.78 - 3.02 (m, 2 H) 2.63 (br. s, 2 H) 2.48 (br. s, 1 H) 2.00 - 2.18 (m, 2 H) 1.88 (dd,  $J=11.7, 6.1$  Hz, 1 H) 1.68 (br. s, 1 H) 1.34 - 1.58 (m, 4 H) 0.71 - 1.31 (m, 13 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) 162.3 (C), 65.1 (CH), 60.6 (CH), 58.4 (CH), 57.4 (CH), 52.2 (CH), 40.1 (CH), 38.5 (CH), 37.9 (CH), 37.0 (CH), 34.0 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_2$ ), 28.3, 27.4 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 24.4 ( $\text{CH}_2$ ), 19.8 ( $\text{CH}_3$ ), 16.3 ( $\text{CH}_3$ ). IR (film) 3450, 2959, 2872, 1652, 1454, 751  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}$   $[\text{M}]^+$ : 300.2202. Found: 300.2199.



(*3aR,5aS,6R,9S,9aR,11aR*)-2-phenyl-5a,6,7,8,9,9a-hexahydrospiro[6,9-methanopyrrolo-[3',4':3,4]pyrazolo[1,2-*a*]indazole-11,9'-fluorene]-1,3,5(2*H*,3*aH*,11*aH*)-trione (Equation 2, **10a**) and (*3aS,5aS,6R,9S,9aR,11aS*)-2-phenyl-5a,6,7,8,9,9a-hexahydrospiro[6,9-methanopyrrolo[3',4':3,4]pyrazolo[1,2-*a*]indazole-11,9'-fluorene]-1,3,5(2*H*,3*aH*,11*aH*)-trione (Table 3.14, **20b**). An oven dried 5 mL  $\mu$ w vial with a stir bar was capped with a septum and purged with argon for 5 minutes. Phenyl 2-[*N*-(9*H*-fluoren-9-ylidene)]hydrazinecarboxylate (0.0802 g, 0.255 mmol), norbornene (0.240 g, 2.55 mmol) and *N*-phenyl maleimide (0.442 g, 2.55 mmol) were added to  $\alpha\alpha\alpha$ -trifluorotoluene (5.0 mL) and stirred under argon. The septum was removed and the vial was then quickly sealed with a microwave cap and heated for 12 hours at 120 °C. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by  $^1\text{H}$  NMR using 1,3,5-trimethoxybenzene as an internal standard (92 % NMR yield). The corresponding product was purified by silica gel chromatography using 40 % to 100 % EtOAc/*n*-hexanes. A mixture of diastereoisomers was obtained as a white solid (0.100 g, 0.2059 mmol, 81% isolated yield). Isomers were separated by column chromatography using 40% EtOAc/*n*-hexanes then 100% EtOAc. Major product **10a** was obtained as a white solid. Crystals for X-ray crystallography were collected from fractions of the column (40% EtOAc/*n*-hexanes). m.p.: 258-259 °C. TLC  $R_f$  = 0.24 in 50% EtOAc.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.78-7.65 (m, 3H), 7.51-7.41 (m, 3H), 7.39-7.30 (m, 4H), 7.26-7.21 (m, 1H), 6.98-6.95 (m, 1H), 5.17 (d,  $J$  = 8.8,

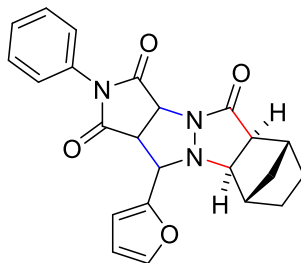


1H), 4.42 (d,  $J = 8.8$ , 1H), 2.70-2.65 (m, 2H), 2.41 (d,  $J = 8.4$ , 1H), 1.82-1.75 (m, 3H), 1.42 (tt,  $J = 12.1, 4.5$ , 1H), 1.27-1.16 (m, 2H), 1.02-0.93 (m, 1H), 0.67-0.58 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  170.2 (C), 167.2 (C), 166.4 (C), 142.3 (C), 141.9 (C), 140.8(C), 140.6 (C), 131.0 (C), 130.3 (CH), 130.2 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 127.9 (CH), 126.2 (CH), 124.6 (CH), 124.4 (CH), 121.2 (CH), 120.7 (CH), 74.8 (C), 61.7 (CH), 58.5 (CH), 57.0 (CH), 55.3 (CH), 43.5 (CH), 39.8 (CH), 34.5 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_2$ ), 24.0 ( $\text{CH}_2$ ). IR (film); 3059, 2964, 2873, 1789, 1728, 1683, 1492, 1451, 1375, 1196, 732  $\text{cm}^{-1}$ ; Exact mass calcd for  $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_3$   $[\text{M}]^+$ : 487.1896. Found: 487.1896. Minor product **10b** was obtained as a white solid. m.p.: 198-199 °C. TLC  $R_f$  = 0.51 in 50% EtOAc.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1-H NMR 7.75-7.69 (m, 2H), 7.54-7.39 (m, 7H), 7.35-7.25 (m, 3H), 7.13 (d,  $J = 7.6$ , 1H), 5.49 (d,  $J = 7.9$ , 1H), 3.73 (d,  $J = 7.9$ , 1H), 2.57 (d,  $J = 3.8$ , 1H), 2.36 (d,  $J = 7.7$ , 1H), 2.18 (d,  $J = 7.7$ , 1H), 1.89 (d,  $J = 4.4$ , 1H), 1.70 (d,  $J = 10.7$ , 1H), 1.41 (td,  $J = 9.1, 5.3$ , 1H), 1.22 (dt,  $J = 8.2, 4.2$ , 1H), 1.14 (dd,  $J = 9.4, 1.2$ , 1H), 0.96-0.91 (m, 1H), 0.65-0.59 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  172.8 (C), 172.0 (C), 171.1 (C), 144.3 (C), 141.0 (C), 140.8(C), 138.8 (C), 131.6 (C), 130.2 (CH), 129.9 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 127.2 (CH), 126.3 (CH), 124.0 (CH), 120.7 (CH), 120.2 (CH), 78.7 (C), 62.9 (CH), 55.0 (CH), 54.5 (CH), 54.2 (CH), 43.5 (CH), 39.9 (CH), 34.2 ( $\text{CH}_2$ ), 27.8 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ). IR (film); 3431, 2964, 2873, 2094, 1721, 1645, 1379, 1208, 748  $\text{cm}^{-1}$ ; Exact mass calcd for  $\text{C}_{31}\text{H}_{25}\text{N}_3\text{O}_3$   $[\text{M}]^+$ : 487.1896. Found: 487.1906.



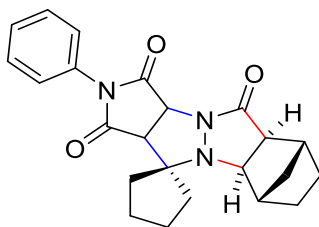
**Dimethyl 9-oxo-5,6,7,8,8a,9-hexahydro-4aH-spiro[5,8-methanopyrazolo[1,2-a]indazole-3,9'-fluorene]-1,2-dicarboxylate (Table 3.14, 20c).** Synthesized according to general procedure using

phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.094 g, 0.30 mmol), norbornene (0.28 g, 3.0mmol, 10 equiv) and dimethyl acetylenedicarboxylate (0.43 g, 3.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (6 mL). The reaction was heated at 120 °C for 6 hours. The title compound was obtained as yellow solid (0.101 g, 74% yield) after column chromatography (80:20 to 70:30 Hexane/EtOAc). TLC Rf = 0.32 in 30% EtOAc/hexanes.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 7.57 - 7.80 (m, 3 H) 7.20 - 7.57 (m, 5 H) 4.00 (s, 3 H) 3.37 (s, 3 H) 2.54 - 2.83 (m, 3 H) 1.85 (d,  $J=10.73$  Hz, 1 H) 1.70 (d,  $J=4.13$  Hz, 1 H) 1.33 - 1.56 (m, 1 H) 1.12 - 1.29 (m, 2 H) 0.93 - 1.11 (m, 1 H) 0.66 (br. s, 1 H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 168.4 (C) 161.8 (C) 159.8 (C) 144.9 (C) 141.3 (C) 140.6 (C) 140.2 (C) 134.9 (C) 130.2 (CH) 129.4 (CH) 128.1 (CH) 128.0 (CH) 125.3 (CH) 124.6 (CH) 120.9 (C) 120.5 (CH) 119.8 (CH) 80.7 (C) 62.1 (CH) 56.3 (CH) 53.5 ( $\text{CH}_3$ ) 51.7 ( $\text{CH}_3$ ) 43.4 (CH) 39.9 (CH) 34.3 ( $\text{CH}_2$ ) 28.2 ( $\text{CH}_2$ ) 23.5 ( $\text{CH}_2$ ). IR (film) 3064, 2955, 2875, 1736, 1611, 1422, 1394, 1338, 1257  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_5$   $[\text{M}]^+$ : 456.1685. Found: 456.16747.



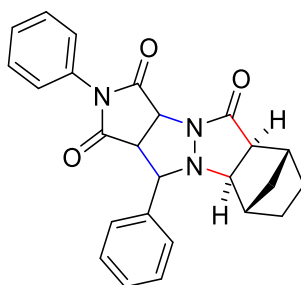
**11-(furan-2-yl)-2-phenyloctahydro-1H-6,9-methanopyrrolo[3',4':3,4]pyrazolo[1,2-a]indazole-1,3,5(2H,3aH)-trione (Table 3.14, 20d).** Synthesized according to general procedure using phenyl (Z)-phenyl 2-(furan-2-ylmethylene)hydrazinecarboxylate (0.069 g, 0.30 mmol), norbornene (0.28 g, 3.0mmol, 10 equiv) and *N*-phenyl maleimide (0.52 g, 3.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (6 mL). The reaction was heated at 120 °C for 6 hours. The title compound was obtained as beige solid (0.046 g, 38% yield) after column chromatography (40:60

Hexane/EtOAc). TLC R<sub>f</sub> = 0.22 in 60% EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 7.30 - 7.55 (m, 5 H) 6.38 - 6.44 (m, 1 H) 6.33 (d, *J*=3.16 Hz, 1 H) 5.26 (d, *J*=7.70 Hz, 1 H) 4.68 (s, 1 H) 3.78 (d, *J*=9.0 Hz, 1 H) 3.04 (d, *J*=6.0 Hz, 1 H) 2.49 (br. s, 1 H) 2.33 (br. s, 1 H) 2.25 (br. s, 1 H) 1.94 (d, *J*=7.57 Hz, 1 H) 1.76 (d, *J*=10.73 Hz, 1 H) 1.38 - 1.58 (m, 2 H) 1.15 (d, *J*=10.73 Hz, 1 H) 0.94 - 1.10 (m, 2 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 174.7 (C) 174.3 (C) 171.0 (C) 148.8 (C) 143.8 (CH) 131.3 (C) 129.2 (CH) 128.9 (CH) 126.4 (CH) 111.2 (CH) 111.0 (CH) 63.5 (CH) 61.9 (CH) 55.0 (CH) 52.5 (CH) 51.3 (CH) 39.4 (CH) 33.6 (CH<sub>2</sub>) 27.7 (CH<sub>2</sub>) 25.4 (CH<sub>2</sub>). IR (film) 2959, 2874, 2363, 2327, 1715, 1385, 1200, 1092 cm<sup>-1</sup>. HRMS(EI): Exact mass calcd for C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> [M]<sup>+</sup>: 403.1532. Found: 403.1537.



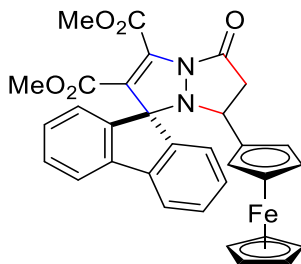
**Phenylhexahydrospiro[6,9-methanopyrrolo[3',4':3,4]pyrazolo[1,2-a]indazole-11,1'-cyclopentane]-1,3,5(2H,3aH,11aH)-trione (Table 3.14, 20e).** Synthesized according to general procedure using phenyl 2-cyclopentylidenehydrazinecarboxylate (0.059 g, 0.30 mmol), norbornene (0.282 g, 3.0mmol, 10 equiv) and *N*-phenyl maleimide (0.52 g, 3.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (6 mL). The reaction was heated at 120 °C for 6 hours. The title compound was obtained as brown solid (0.028 g, 24% yield) after column chromatography (70:30 to 80:20 Hexane/EtOAc). TLC R<sub>f</sub> = 0.37 in 20% EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 7.35 - 7.56 (m, 3 H) 7.26 - 7.35 (m, 2 H) 4.78 (d, *J*=8.80 Hz, 1 H) 3.88 (d, *J*=8.94 Hz, 1 H) 3.16 (d, *J*=8.67 Hz, 1 H) 2.91 (d, *J*=8.67 Hz, 1 H) 2.70 (br. s, 1 H) 2.24 (br. s, 1 H) 2.03 - 2.22 (m, 2 H) 1.09 - 2.03 (m, 14 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 172.3 (C) 167.6 (C) 165.2 (C) 130.9 (C) 129.2 (2 CH)

128.9 (CH) 126.3 (2 CH) 73.3 (C) 60.8 (CH) 59.0 (CH) 56.7 (CH) 54.4 (CH) 43.7 (CH) 39.5 (CH) 36.7 (CH<sub>2</sub>) 34.2 (CH<sub>2</sub>) 28.1 (CH<sub>2</sub>) 27.0 (CH<sub>2</sub>) 26.4 (CH<sub>2</sub>) 24.6 (CH<sub>2</sub>) 24.3 (CH<sub>2</sub>). IR (film) 2971, 2874, 2359, 2331, 1723, 1381, 1091 cm<sup>-1</sup>. HRMS(EI): Exact mass calcd for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub> [M]<sup>+</sup>:391.1896. Found: 391.1918



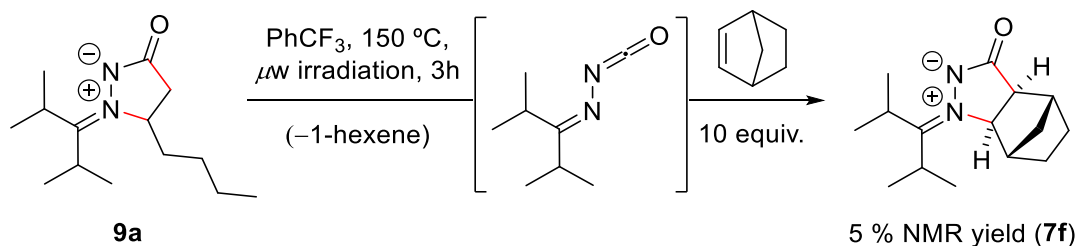
**1,9,13-Triaza-10,13-diphenyl[7, 6, 1<sup>4,7</sup>, 0<sup>3,8</sup>,0<sup>11,15</sup>,0]tetrdecane-2,12,14-trione (Table, 3.14, 20f).**

Synthesized according to general procedure using phenyl 2-benzylidenehydrazinecarboxylate (0.070 g, 0.290 mmol), norbornene (0.27 g, 2.9mmol, 10 equiv) and *N*-phenyl maleimide (0.50 g, 2.9 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (5.8 mL). The reaction was heated at 120 °C for 12 hours. The title compound was obtained as yellow solid and a single diastereomer (0.179 g, 61%, dr > 20). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.32-7.61 (m, 10H), 4.63 (d, *J* = 7.5 Hz, 1H), 3.91 (d, *J* = 6.7 Hz, 1H), 3.60 (t, *J* = 7.12 Hz, 1H), 3.08 (d, *J* = 7.64 Hz, 1H), 2.80 (d, *J* = 7.64 Hz, 1H), 2.64 (br. s, 1H), 2.32 (br. s, 1H), 1.85 (d, *J* = 10.62 Hz, 1H), 1.37-1.65 (m, 2H), 1.11-1.32 (m, 3H), 0.99 (d, *J* = 10.24 Hz, 1H), 0.87 (br. s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  173.7 (C), 172.7 (C), 167.7 (C), 137.0 (C), 131.3 (C), 129.1 (2CH), 129.0 (2CH), 128.8 (CH), 128.7 (CH), 127.5 (2CH), 126.4 (2CH), 73.2 (CH), 66.4 (CH), 57.1 (CH), 56.8 (CH), 52.7 (CH), 42.7 (CH), 39.7 (CH), 33.6 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>). IR (film) 3067, 2959, 2878, 2367, 2331, 178, 1699, 1373, 1184, 1095 cm<sup>-1</sup>.



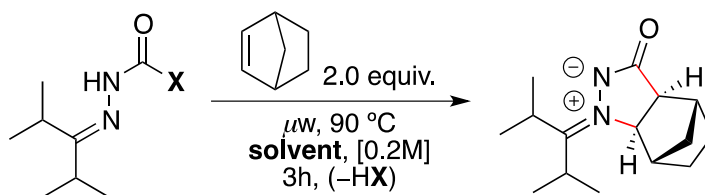
**Dimethyl-7'-ferrocenyl-5'-oxo-6',7'-dihydro-5'H-spiro[fluorene-9,1'-pyrazolo[1,2-a]pyrazole]-2',3'-dicarboxylate (Table 3.14, 20g).** Synthesized according to general procedure using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.094 g, 0.30 mmol), ferrocene (0.64 g, 0.3 mmol, 1 equiv) and dimethyl acetylenedicarboxylate (0.42 g, 3.0 mmol, 10 equiv) in  $\alpha,\alpha,\alpha$ -trifluorotoluene (6 mL). The reaction was heated at 120 °C for 6 hours. The title compound was obtained as brown solid (0.084 g, 49% yield) after column chromatography (70:30 Hexane/EtOAc). TLC  $R_f$  = 0.33 in 30% EtOAc/hexanes.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 7.70 (d,  $J=7.43$  Hz, 1 H) 7.42 - 7.53 (m, 4 H) 7.39 (d,  $J=7.43$  Hz, 1 H) 7.08 - 7.26 (m, 2 H) 4.08 - 4.20 (m, 1 H) 4.04 (s, 3 H) 3.92 (s, 5 H) 3.84 (d,  $J=7.29$  Hz, 2 H) 3.61 (br. s, 1 H) 3.35 (s, 3 H) 3.20 (d,  $J=11.97$  Hz, 1 H) 3.06 (d,  $J=7.43$  Hz, 1 H) 2.85 (s, 1 H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 162.4 (C) 161.7 (C) 159.6 (C) 145.3 (C) 140.8 (C) 140.0 (C) 139.4 (C) 133.8 (C) 130.2 (CH) 128.8 (CH) 127.7 (CH) 127.2 (CH) 125.7 (CH) 125.2 (CH) 120.6 (CH) 119.3 (CH) 118.5 (C) 81.7 (C) 78.4 (C) 68.9 (CH) 68.3 (CH) 68.2 (2  $\text{CH}_3$ ) 67.3 (CH) 65.2 (2 CH) 57.4 (CH) 53.6 (2 CH) 51.6 (2 CH) 42.7 ( $\text{CH}_2$ ). IR (film) 1751, 1714, 1606, 1429, 1348, 1260, 1219, 740, 427  $\text{cm}^{-1}$ . HRMS(ED): Exact mass calcd for  $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_4$   $[\text{M}]^+$ : 574.1191. Found: 574.11871.

## Cycloreversion Experiment



**General procedure:** An oven or flame dried 2-5 mL  $\mu\text{w}$  vial with a stir bar was capped with a septum and purged with argon for 5 minutes. The azomethine imine **9a** (0.2 mmol),  $\alpha,\alpha,\alpha$ -trifluorotoluene (4 mL) and norbornene (2 mmol, 10 equiv) were added to the sealed vial. The septum was removed and the vial was then quickly sealed with a microwave cap and heated for three hours at 150  $^\circ\text{C}$ . The reaction solution was cooled to ambient temperature, concentrated under reduced pressure. Analysis by  $^1\text{H}$  NMR using 1,4-dimethoxybenzene as an internal standard showed the product **7f** (5% NMR yield) and the starting azomethine imine **9a** (95% NMR yield). This supports the hypothesis that imino-isocyanate cycloreversion from the azomethine imine was possible under the presented conditions.

## Solvent Scan



**General Procedure for Solvent Scan (Table 3.8):** To a flame dried screw cap vial, *tert*-butyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (0.2 mmol, 1 equiv.) and norbornene (0.4 mmol, 2 equiv.) in the solvent (1 mL). The reaction was heated at 90 °C in an oil bath for three hours. Solvent was removed *in-vacuo* and the crude mixture was analyzed by  $^1\text{H}$  NMR with addition of 0.5 equivalent of 1,3,5-trimethoxybenzene as an internal standard.

## **Computational Details**

Density functional theory (DFT) calculations have been performed using the *Gaussian 09* program.<sup>9</sup> Optimized molecular geometries were calculated using the B3LYP<sup>10,11</sup> exchange-correlation functional in vacuum and in solution. The triple-zeta TZVP<sup>12</sup> basis set and tight SCF convergence criteria were used for calculations. Wave function stability calculations were performed to confirm that the calculated wave functions corresponded to the ground state. Harmonic frequency calculations were performed to ensure that the stationary points were true energy minima or transition states (TSs) and to calculate Gibbs free energies. The unscaled frequencies were used for calculating the Gibbs free energies of the species. Intrinsic reaction coordinate (IRC)<sup>13,14</sup> calculations were used to confirm the reaction pathways through the CMD transition states (TSs) for all reactants. Calculations in solution were performed using the SMD implicit solvation model<sup>15</sup> with methanol as a solvent.

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<sup>9</sup> Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc., Wallingford, CT, 2009.

<sup>10</sup> Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

<sup>11</sup> Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785.

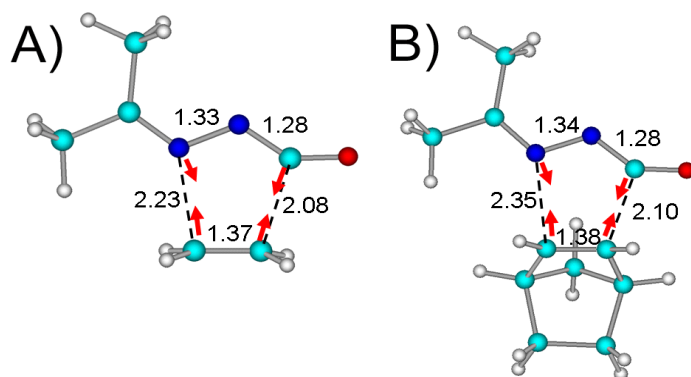
<sup>12</sup> Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.

<sup>13</sup> Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.

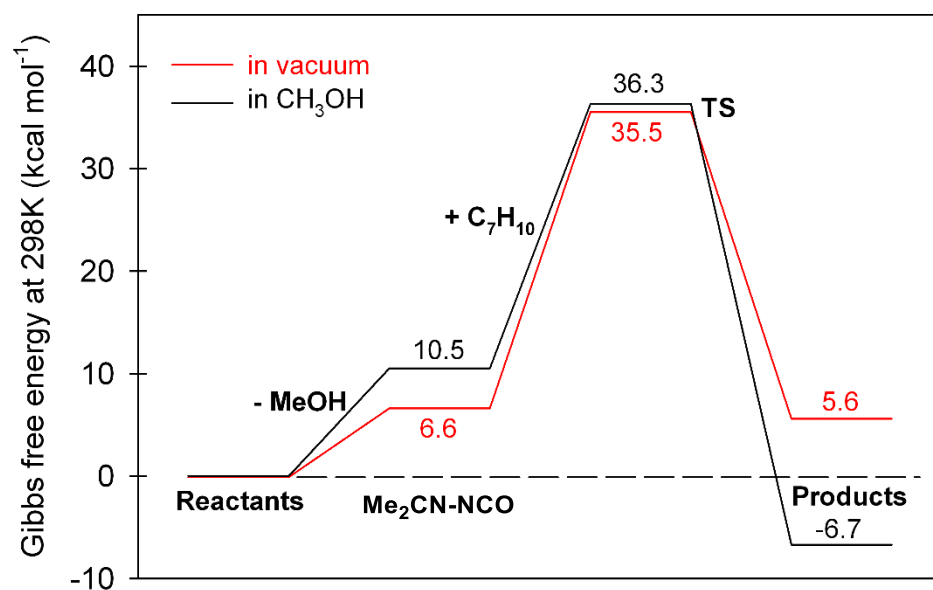
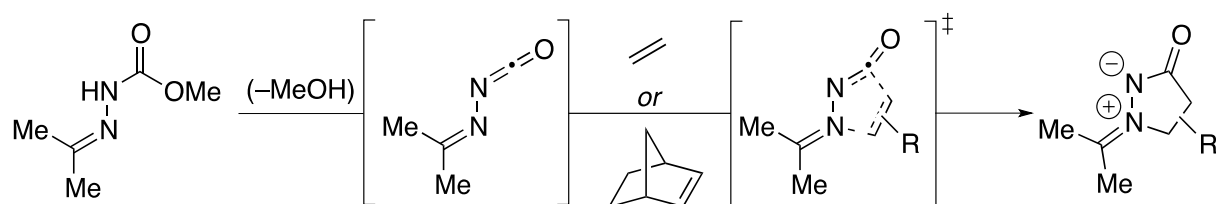
<sup>14</sup> Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

<sup>15</sup> Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.



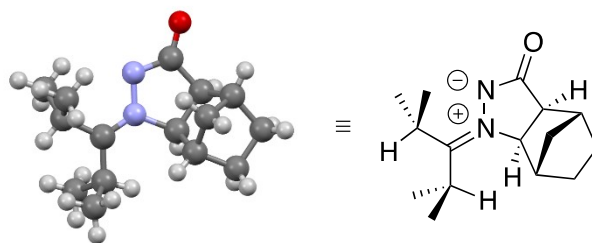


**Figure 5.1** Transition state structures for the intermolecular aminocarbonylation of A) ethylene and B) norbornene ( $C_7H_{10}$ ) using dimethyliminoisocyanate in vacuum. Relevant bond distances (Å) were shown. Red arrows indicate the atomic movements which correspond to the imaginary normal mode.



**Figure 5.2** Gibbs free energies (in kcal/mol, 298K) for the aminocarbonylation of norbornene ( $C_7H_{10}$ ) using dimethyliminoisocyanate in vacuum (red line) and in methanol (black line)

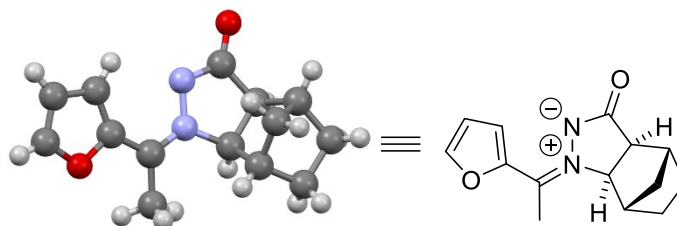
### X-ray Crystallographic Data



**Figure 5.3** Crystal structure of (±)-exo-2-(2,4-Dimethylpentan-3-ylidene)-4-oxo-2,3-diazatricyclo-[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.6, entry 8, **7h**)

**Table 5.8** Crystal data and structure refinement for (±)-exo-2-(2,4-dimethylpentan-3-ylidene)-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.6, entry 8, **7h**)

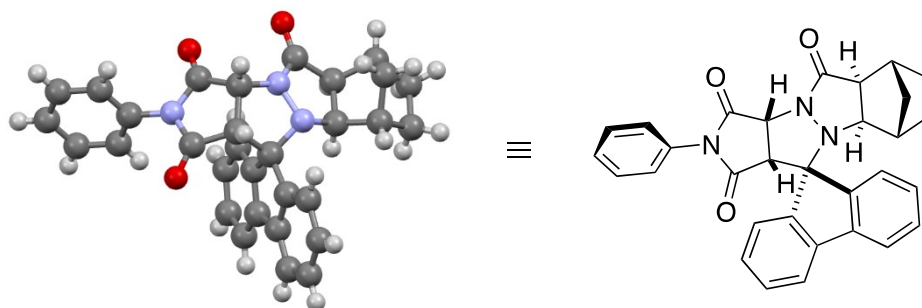
|                                   |                                                                                                                     |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Identification code               | ab003a                                                                                                              |
| Empirical formula                 | C <sub>15</sub> H <sub>24</sub> N <sub>2</sub> O                                                                    |
| Formula weight                    | 248.36                                                                                                              |
| Temperature                       | 296(2) K                                                                                                            |
| Wavelength                        | 0.71073 Å                                                                                                           |
| Crystal system, space group       | Orthorhombic, Pna2(1)                                                                                               |
| Unit cell dimensions              | a = 12.8722(2) Å    alpha = 90 deg.<br>b = 9.68850(10) Å    beta = 90 deg.<br>c = 11.38460(10) Å    gamma = 90 deg. |
| Volume                            | 1419.80(3) Å <sup>3</sup>                                                                                           |
| Z, Calculated density             | 4, 1.162 Mg/m <sup>3</sup>                                                                                          |
| Absorption coefficient            | 0.073 mm <sup>-1</sup>                                                                                              |
| F(000)                            | 544                                                                                                                 |
| Crystal size                      | 0.18 x 0.17 x 0.10 mm                                                                                               |
| Theta range for data collection   | 2.63 to 28.29 deg.                                                                                                  |
| Limiting indices                  | -15 ≤ h ≤ 17, -12 ≤ k ≤ 12, -15 ≤ l ≤ 15                                                                            |
| Reflections collected / unique    | 13919 / 3463 [R(int) = 0.0220]                                                                                      |
| Completeness to theta             | = 28.29    99.7 %                                                                                                   |
| Absorption correction             | Semi-empirical from equivalents                                                                                     |
| Max. and min. transmission        | 0.9927 and 0.9870                                                                                                   |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                                         |
| Data / restraints / parameters    | 3463 / 1 / 163                                                                                                      |
| Goodness-of-fit on F <sup>2</sup> | 1.023                                                                                                               |
| Final R indices [I > 2sigma(I)]   | R1 = 0.0346, wR2 = 0.0848                                                                                           |
| R indices (all data)              | R1 = 0.0416, wR2 = 0.0895                                                                                           |
| Absolute structure parameter      | 0.6(12)                                                                                                             |
| Largest diff. peak and hole       | 0.119 and -0.123 e.Å <sup>-3</sup>                                                                                  |



**Figure S4** Crystal structure of (±)-exo-(Z)-2-[(1-furan-2-yl)ethylidene]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.13, **18c**)

**Table S9** Crystal data and structure refinement for (±)-exo-(Z)-2-[(1-Furan-2-yl)ethylidene]-4-oxo-2,3-diazatricyclo[4,3,1<sup>6,9</sup>,0]decane-2-ium-3-ide (Table 3.13, **18c**)

|                                   |                                                                                                                    |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Identification code               | ab004                                                                                                              |
| Empirical formula                 | C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>                                                      |
| Formula weight                    | 244.29                                                                                                             |
| Temperature                       | 200(2) K                                                                                                           |
| Wavelength                        | 0.71073 Å                                                                                                          |
| Crystal system, space group       | Monoclinic, P2(1)/c                                                                                                |
| Unit cell dimensions              | a = 9.355(3) Å    alpha = 90 deg<br>b = 10.436(3) Å    beta = 102.117(17) deg<br>c = 12.314(4) Å    gamma = 90 deg |
| Volume                            | 1175.4(6) Å <sup>3</sup>                                                                                           |
| Z, Calculated density             | 4, 1.380 Mg/m <sup>3</sup>                                                                                         |
| Absorption coefficient            | 0.094 mm <sup>-1</sup>                                                                                             |
| F(000)                            | 520                                                                                                                |
| Crystal size                      | 0.28 x 0.21 x 0.17 mm                                                                                              |
| Theta range for data collection   | 2.23 to 28.66 deg.                                                                                                 |
| Limiting indices                  | -12 ≤ h ≤ 12, -14 ≤ k ≤ 11, -16 ≤ l ≤ 16                                                                           |
| Reflections collected / unique    | 17491 / 2929 [R(int) = 0.0351]                                                                                     |
| Completeness to theta = 28.66     | 96.9 %                                                                                                             |
| Absorption correction             | Semi-empirical from equivalents                                                                                    |
| Max. and min. transmission        | 0.9843 and 0.9743                                                                                                  |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                                        |
| Data / restraints / parameters    | 2929 / 0 / 164                                                                                                     |
| Goodness-of-fit on F <sup>2</sup> | 1.023                                                                                                              |
| Final R indices [I > 2sigma(I)]   | R1 = 0.0405, wR2 = 0.1052                                                                                          |
| R indices (all data)              | R1 = 0.0519, wR2 = 0.1148                                                                                          |
| Absolute structure parameter      |                                                                                                                    |
| Largest diff. peak and hole       | 0.289 and -0.201 e.Å <sup>-3</sup>                                                                                 |



**Figure S5** Crystal structure of (3 $\alpha$ R,5 $\alpha$ S,6R,9S,9 $\alpha$ R,11 $\alpha$ R)-2-phenyl-5 $\alpha$ ,6,7,8,9,9 $\alpha$ -hexahydro-drospiro[6,9-methanopyrrolo-[3',4':3,4]pyrazolo[1,2- $\alpha$ ]indazole-11,9'-fluorene]-1,3,5-(2H,3 $\alpha$ H,11 $\alpha$ H)-trione (Table 3.14, **20b**)

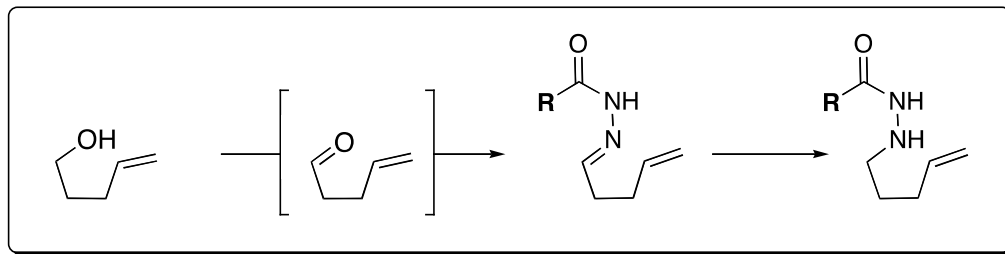
**Table S10** Crystal data and structure refinement for (3 $\alpha$ R,5 $\alpha$ S,6R,9S,9 $\alpha$ R,11 $\alpha$ R)-2-phenyl-5 $\alpha$ ,6,7,8,9,9 $\alpha$ -hexahydro-drospiro[6,9-methanopyrrolo-[3',4':3,4]pyrazolo[1,2- $\alpha$ ]indazole-11,9'-fluorene]-1,3,5-(2H,3 $\alpha$ H,11 $\alpha$ H)-trione (Table 3.14, **20b**)

|                                 |                                                                                                                                            |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Identification code             | ab013                                                                                                                                      |
| Empirical formula               | C <sub>31</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub>                                                                              |
| Formula weight                  | 487.54                                                                                                                                     |
| Temperature                     | 200(2) K                                                                                                                                   |
| Wavelength                      | 0.71073 Å                                                                                                                                  |
| Crystal system, space group     | Triclinic, P-1                                                                                                                             |
| Unit cell dimensions            | a = 9.9898(2) Å    alpha = 69.5350(10) deg.<br>b = 11.2967(3) Å    beta = 77.9570(10) deg.<br>c = 11.9851(3) Å    gamma = 87.4660(10) deg. |
| Volume                          | 1238.68(5) Å <sup>3</sup>                                                                                                                  |
| Z, Calculated density           | 2, 1.307 Mg/m <sup>3</sup>                                                                                                                 |
| Absorption coefficient          | 0.085 mm <sup>-1</sup>                                                                                                                     |
| F(000)                          | 512                                                                                                                                        |
| Crystal size                    | 0.35 x 0.14 x 0.12 mm                                                                                                                      |
| Theta range for data collection | 1.85 to 28.37 deg.                                                                                                                         |
| Limiting indices                | -13 ≤ h ≤ 13, -15 ≤ k ≤ 15, -15 ≤ l ≤ 16                                                                                                   |
| Reflections collected / unique  | 15079 / 6033 [R(int) = 0.0171]                                                                                                             |
| Completeness to theta = 28.37   | 97.3 %                                                                                                                                     |
| Absorption correction           | Semi-empirical from equivalents                                                                                                            |
| Max. and min. transmission      | 0.9898 and 0.9708                                                                                                                          |
| Identification code             | ab013                                                                                                                                      |
| Empirical formula               | C <sub>31</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub>                                                                              |

## **Chapter 4: Amino-Isocyanates as Powerful Intermediates in Heterocyclic Chemistry**

## Intramolecular Cope-type Hydroamination Using Hydrazides

### General Procedures for the Preparation of Substrates



**General Procedure A: Alcohol Oxidation:** Prepared according to the procedure by Mukai.<sup>16</sup> A flame-dried round bottom flask charged with a magnetic stir bar, alkenol, DMSO (3 equiv.) and Et<sub>3</sub>N (3 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> was added SO<sub>3</sub>•Pyr (3 equiv.) at 0°C. The reaction was monitored by TLC until completion. The reaction was quenched by addition of saturated aqueous ammonium chloride, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with water and brine. The crude mixture was evaporated *in-vacuo*, and used without further purification. *Carbazate Condensation:* Prepared according to the procedure from the Leighton group.<sup>17</sup> To the crude mixture was added the corresponding carbazate and acetic acid in methanol. The mixture was refluxed until consumption of the aldehyde or hydrazide was judged complete by TLC. Corresponding crude hydrazone was directly reduced without further purification.

**General Procedure B: Hydrazone Reduction:** Prepared from a modified procedure by Lane.<sup>18</sup> The corresponding hydrazone was combined with NaCNBH<sub>3</sub> (3 equiv.), a pinch of methyl orange and stirred in methanol. The solution was capped with a septum and purged for 5 minutes. Acetic

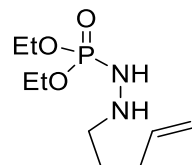
<sup>16</sup> C. Mukai, I. Nomura, S. Katagaki, *J. Org. Chem.* **2003**, 68, 1376.

<sup>17</sup> J. L. Leighton, R. Berger, K. Duff, *J. Am. Chem. Soc.* **2004**, 126, 5686.

<sup>18</sup> C. F. Lane, *Synthesis* **1975**, 135.

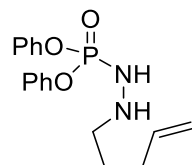
acid was added dropwise until the solution becomes acidic. The reaction mixture is stirred for 3 hours. Excess acetic acid was then evaporated and pH was increased with saturated sodium bicarbonate solution and then with 10% NaOH (aq) to reach a pH of 8. Solution was extracted three times with dichloromethane and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Volatiles were removed from the organic phase in-vacuo and crude product was purified by column chromatography.

**General Procedure C: Amine Substitution:** An oven dried 5 mL  $\mu$ W tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.0 equiv.), amine (1.1 equiv.), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for three hours at 80°C. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.

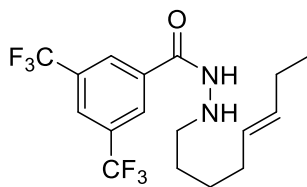


**bis-Ethoxyphospho-N'-(pent-4-enyl)-hydrazide (Table 4.1, 1b).** Synthesized following the general procedure **B**. The crude mixture was purified by column chromatography. The title compound was obtained as a yellow oil (1.49 g, 72% yield isolated yield). TLC R<sub>f</sub> 0.69 in 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  ppm 5.78 (tdd,  $J$  = 16.87, 10.17, 6.63Hz, 1H), 5.05-4.91 (m, 2H), 4.48 (d,  $J$  = 30.23 Hz, 1H), 4.17-4.02 (m, 4H), 3.24 (s, 1H), 2.83 (t,  $J$  = 7.18 Hz, 2H), 2.07 (dd,  $J$  = 14.65, 6.85 Hz, 2H), 1.63-1.51 (m, 2H), 1.32 (dt,  $J$  = 7.07, 7.06, 0.60 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 138.0, 114.9, 62.8, 62.7, 53.0, 53.0, 31.1, 26.6, 16.2,

16.2; IR (film); 3473, 3272, 2983, 2914, 2858  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calcd for  $\text{C}_9\text{H}_{21}\text{N}_2\text{O}_3\text{P}_1$   $[\text{M}]^+$ : 236.129; found: 236.129.



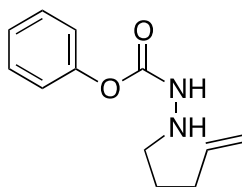
**bis-Phenoxyphospho-*N'*-(pent-4-enyl)-hydrazide (1d) - (Table 4.1, 1c).** Synthesized following the general procedure **B**. The crude mixture was purified by column chromatography. The title compound was obtained as a white solid (0.419g, 82% yield). TLC  $R_f$  0.34 in 20% EtOAc/hexanes).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz) 7.39-7.24 (m, 8H), 7.17 (t,  $J = 7.11$  Hz, 2H), 5.75 (tdd,  $J = 16.90, 10.29, 6.67$  Hz, 1H), 5.03-4.91 (m, 2H), 4.72 (d,  $J = 36.12$  Hz, 1H), 3.50-3.35 (m, 1H), 2.79 (dd,  $J = 10.82, 6.62$  Hz, 2H), 2.06 (q,  $J = 6.85, 6.72$  Hz, 2H), 1.60-1.49 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 138.1, 129.8, 125.1, 120.5, 120.5, 115.2, 53.1, 53.1, 31.1, 26.7; IR (film); 2918, 2850, 1580, 1542, 1470  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calcd for  $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}_3\text{P}$   $[\text{M}]^+$ : 332.129; found: 332.126.



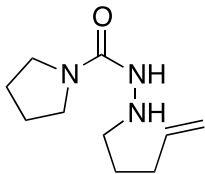
**1-Benzyl-tetrahydro-1H-pyrrolo[1,2-*b*]pyrazol-2(3H)-one (Table 4.2, 3d)** Synthesized according to general procedure **B**. The title compound was obtained as a white solid. The crude mixture was purified by column chromatography using 15 % EtOAc/hexanes. The title compound was obtained as a white solid (1.270 g, 3.32 mmol, 72 % isolated yield). TLC  $R_f = 0.39$  in 5% MeOH/ $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm 1H NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.24 (s, 2H), 8.02 (s, 1H), 5.33 (ddt,  $J = 17.80, 10.75, 6.98$  Hz, 2H), 2.97 (t,  $J = 6.95$  Hz, 2H), 2.10-1.95



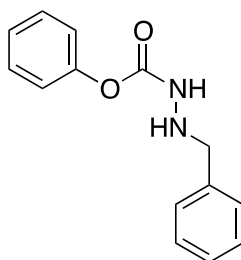
(m, 4H), 1.62-1.50 (m, 2H), 1.48-1.36 (m, 2H), 0.93 (t,  $J = 7.54$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm \*denotes minor traces of isomers 164.4 (C), 134.9 (C), 132.3 (q,  $J = 33.90$ , 33.84 Hz, 2C), 132.2 (CH), 128.4 (CH), 127.3 (CH), \*124.6 (C), 121.0 (C), 52.1 (CH), 27.5 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 26.8 ( $\text{CH}_2$ ), 20.5 ( $\text{CH}_2$ ), 14.3 ( $\text{CH}_3$ ); IR (film) 3443, 2097, 1653  $\text{cm}^{-1}$ ; HRMS (EI): Exact mass calcd for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_6[\text{M}]^+$ : 382.1480; found: 382.1488.



**Phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (equation 4.2, Table 4.3, 4.4, 4.6, Scheme 4.1, 5a).** Synthesized according to general procedure **A** using 4-pentenol (1.31 g, 15.2 mmol), Condensation of aldehyde with carbazate was then performed using phenyl hydrazinecarboxylate (2.10 g, 13.8 mmol) in MeOH (46.0 mL). Product was directly reduced according to general procedure **B**. The crude mixture was purified by column chromatography using 5% EtOAc/ $\text{CH}_2\text{Cl}_2$ . The title compound was obtained as a white solid (0.712 g, 3.23 mmol, 23% isolated yield). TLC  $R_f = 0.24$  in 5% EtOAc/ $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ )  $\delta$  7.37-7.10 (m, 5H), 6.60 (s, 1H), 5.83 (d,  $J = 10.2$  Hz, 1H), 5.06-4.99 (m, 2H), 3.82 (s, 1H), 2.94 (t,  $J = 7.2$  Hz, 2H), 2.16-2.09 (m, 2H), 1.61 (q,  $J = 7.3$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ) 155.6 (C), 150.8 (C), 138.2 (CH), 129.5 (CH), 125.7 (CH), 121.5 (CH), 115.1 ( $\text{CH}_2$ ), 51.4 ( $\text{CH}_2$ ), 31.3 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ); IR (film) 3276, 3081, 2926, 2850, 1900, 1715, 1476, 1266, 1214, 907  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2[\text{M}]^+$ : 220.1212. Found: 220.1219.

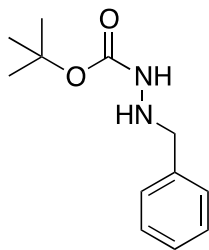


***N'*-(Pent-4-en-1-yl)pyrrolidine-1-carbohydrazide (Scheme 4.2, 5b).** Synthesized according to general procedure C using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (0.617 g, 2.80 mmol), pyrrolidine (0.219 g, 3.08 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (9.3 mL). Crude mixture was purified by silica gel column chromatography using 100% EtOAc. The title compound was obtained as a white solid (0.336 g, 61% yield). TLC  $R_f$  = 0.13 in 40% EtOAc/hexanes.  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ )  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ ):  $\delta$  5.89-5.75 (m, 1H), 5.89-5.75 (s, br, 1H), 5.06-4.93 (m, 2H), 3.62 (s, br, 1H), 3.32 (t,  $J$  = 6.7, 4H), 2.84 (t,  $J$  = 7.3, 2H), 2.15-2.07 (m, 2H), 1.94-1.86 (m, 4H), 1.59 (quintet,  $J$  = 7.4, 2H);  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ) 157.8 (C), 138.6 (CH), 114.8 ( $\text{CH}_2$ ), 52.6 ( $\text{CH}_2$ ), 45.5 ( $\text{CH}_2$ ), 31.5 ( $\text{CH}_2$ ), 27.3 ( $\text{CH}_2$ ), 25.5 ( $\text{CH}_2$ ); IR (film) 3500, 3238, 2980, 2872, 1653, 1546, 1402, 912, 759  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{10}\text{H}_{19}\text{N}_3\text{O}$   $[\text{M}]^+$ : 197.1528. Found: 197.1520.



**Phenyl 2-benzylhydrazinecarboxylate (Table 4.9, 5j).** Synthesized according to general procedure A using phenyl hydrazine carboxylate (0.512 g, 3.37 mmol), benzaldehyde (0.393 g, 3.7 mmol) MeOH (11.2 mL). Crude hydrazone was directly reduced using according to general procedure B. The crude mixture was purified by column chromatography using 5%

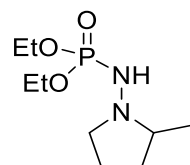
EtOAc/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a clear oil (2.485 g, 11.2 mmol, 43% yield). The title compound was obtained as a white solid (1.11 g, 4.59 mmol, 33% yield). TLC R<sub>f</sub> = 0.57 in 40% EtOAc/hexanes. <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>) δ 7.37-7.32 (m, 7H), 7.21 (s, 1H), 7.12 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.63 (s, 1H), 4.08 (s, 2H), 3.86 (s, 1H); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) 155.5 (C), 150.7 (C), 136.8 (C), 129.4 (CH), 129.1 (CH), 128.6 (CH), 127.8 (CH), 125.6 (CH), 121.4 (CH), 55.6 (CH<sub>2</sub>); IR (film) 3294, 3032, 2853, 1938, 1736, 1496, 1456, 1204, 746, 695 cm<sup>-1</sup>. HRMS(EI): Exact mass calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> [M]<sup>+</sup>: 242.1055. Found: 242.1034.



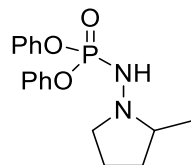
***tert*-Butyl 2-benzylhydrazinecarboxylate (Table 4.9, synthesis of 8f).** Synthesized according to general procedure A using *tert*-butyl carbazate (3.366 g, 25.5 mmol) and benzaldehyde (2.70 g, 25.4 mmol) in MeOH (77.0 mL). Crude hydrazone was directly reduced using sodium cyanoborohydride (5.27 g, 76.5 mmol) in MeOH (77.0 mL). Crude mixture was purified by column chromatography using 40% EtOAc/hexanes. The title compound was obtained as a clear oil (2.485 g, 11.2 mmol, 43% yield). TLC R<sub>f</sub> = 0.4 in 40% EtOAc/hexanes. <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 7.32-7.24 (m, 5H), 6.24 (s, 1H), 3.96 (s, 2H), 3.88 (s, 1H), 1.44 (s, 9H); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) 156.8 (C), 137.7 (C), 129.1 (CH), 128.6 (CH), 127.6 (CH), 80.6 (C), 55.9 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>); IR (film) 3409, 3340, 2979, 2937, 2861, 2439, 2284, 2151, 1953, 1700, 1520, 873 cm<sup>-1</sup>. <sup>1</sup>. HRMS(EI): Exact mass calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> [M]<sup>+</sup>: 222.1368. Found: 166.0748 (-*t*-Bu<sup>+</sup>).

## General Procedure for the Cope-type Intramolecular Hydrohydrazidation

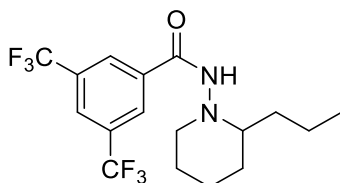
**General Procedure :** *Microwave:* The corresponding hydrazide and  $\alpha,\alpha,\alpha$ -trifluorotoluene (such that the concentration of the hydrazide was 0.05 M) were added to a microwave vial (0.5, 2, 5 or 20 mL), while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated in a Biotage Initiator microwave for 10-24 hours at 110 °C to 195 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and analyzed by  $^1\text{H}$  NMR using 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding hydrohydrazidation products.



**1-(2-methylpyrrolidin-1-yl)-bis-ethoxyphospho hydrazide (2c) - (Table 4.1, 2b).** Synthesized according to the general procedure using bisethoxyphospho-*N'*-(pent-4-enyl)-hydrazide (0.060 g, 0.252 mmol). The solution was heated under microwave irradiation at 120 °C for ten hours. Isolated (0.0584 g, 98% yield) as a yellow oil and purified over column chromatography (6% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). TLC R<sub>f</sub> 0.64 (7.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>).  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  ppm 4.24-4.00 (m, 4H), 3.58 (m, 1H), 3.39 (d,  $J$  = 2.97 Hz, 1H), 2.50-2.39 (m, 1H), 2.36 (m, 1H), 2.25 (s, 1H), 1.97-1.82 (m, 1H), 1.82-1.59 (m, 2H), 1.50-1.35 (m, 1H), 1.33 (t,  $J$  = 7.06 Hz, 6H), 1.15 (d,  $J$  = 6.08 Hz, 3H);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 63.8, 63.1, 63.0, 30.0, 19.9, 18.1, 16.4, 16.4, 16.4, 16.3; IR (film) 3488, 3184, 2976, 1645, 1444, 1394, 1231, 1036 cm<sup>-1</sup>; HRMS (EI): Exact mass calcd for C<sub>9</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>P[M]<sup>+</sup>: 236.1290; found: 236.1290.



**1-(2-Methylpyrrolidin-1-yl)-bis-phenoxyphospho hydrazide (Table 4.1, 2c).** Synthesized according to the general procedure using bisphenoxyphospho-*N'*-(pent-4-enyl)-hydrazide (0.083 g, 0.250 mmol). The solution was heated under microwave irradiation at 110 °C for 18 hours. Isolated (0.083 g, 0.250 mmol, 99% isolated yield) as a white solid. TLC  $R_f$  = 0.92 in 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz, 120 °C)  $\delta$  ppm 7.36-7.23 (m, 8H), 7.20-7.10 (m, 2H), 4.26 (s, 2H), 3.44-3.21 (m, 1H), 2.90-2.22 (m, 2H), 2.02-1.59 (m, 3H), 1.56-1.37 (m, 1H), 1.10 (d,  $J$  = 6.04 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 129.8, 129.7, 125.0, 124.9, 120.3, 64.1, 64.0, 58.5, 30.1, 20.0. Exact mass calculated for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>P [M]<sup>+</sup>: 332.1290. Found: 332.1297.



**3,5-bis-(Trifluoromethyl)-*N*-(2-propylpiperidin-1-yl)benzamide (Table 4.2, 4d).** Synthesized according to the general procedure (195 °C, 24h) using 3,5-bis(trifluoromethyl)-*N'*-((*Z*)-oct-5-enyl)benzohydrazide (0.0968 g, 0.2533 mmol). The solution was heated under microwave irradiation at 195 °C for 24 hours. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in hexanes). The title compound was obtained as brown crystal (0.0511 g, 53 % yield). TLC  $R_f$  0.63 (50% EtOAc/hexanes). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  ppm 9.28 (s, 1H), 8.38 (s, 2H), 8.12 (s, 1H), 3.10 (d,  $J$  = 10.29 Hz, 1H), 2.87 (m, 4H), 1.82-1.49 (m, 5H), 1.28 (m, 2H), 0.83 (t,  $J$  = 6.63 Hz, 3H), <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)

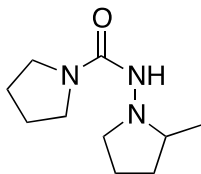
$\delta$  ppm \* *denotes traces of minor isomers* 161.5, 136.5, 129.85 (q,  $J = 33.78, 33.56$  Hz, 2CCF<sub>3</sub>), \*127.8, 122.50 (q,  $J = 272.91, 272.84$  Hz, 2 CF<sub>3</sub>) 127.4, 123.1, 62.0, 55.1, 34.2, 29.9, 24.5, 22.8, 17.2, 13.2. HRMS (EI): Exact mass calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>OF<sub>6</sub>[M]<sup>+</sup>: 382.148; found: 382.146.

### **Cascade Substitution / Hydroamination**

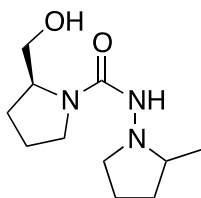
#### **General Procedure for the Substitution / Hydroamination**

**General Procedure A:** An oven dried 5 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for six hours at 120°C under microwave irradiation. The tube was cooled to ambient temperature, volatiles were removed under reduced pressure and crude product purified by silica gel chromatography.

**General Procedure B:** An oven dried 5 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.00 equiv.), amine (1.1 equiv.), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for six hours at 120 °C under microwave irradiation. The tube was cooled to ambient temperature, volatiles were removed under reduced pressure and crude product purified by silica gel chromatography.

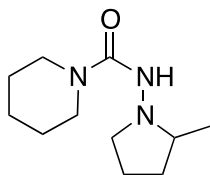


***N*-(2-Methylpyrrolidin-1-yl)pyrrolidine-1-carboxamide (Scheme 4.1, 6a).** Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (197 mg, 0.894 mmol), pyrrolidine (0.0699 g, 0.984 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (2.98 mL). The title compound was purified by column chromatography (4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) and obtained as a white solid (155 mg, 88% isolated yield, 88% NMR yield). TLC  $R_f$  = 0.25 in 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  4.90 (s, br, 1H), 3.39-3.25 (m, 5H), 2.67 (dq,  $J$  = 9.2, 6.4 Hz, 1H), 2.55 (q,  $J$  = 8.8 Hz, 1H), 1.96-1.64 (m, 7H), 1.44 (dddd,  $J$  = 12.1, 10.2, 9.4, 6.5 Hz, 1H), 1.11 (d,  $J$  = 6.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) 157.3, 62.1 (CH), 56.3 (CH<sub>2</sub>), 46.1 (CH<sub>2</sub>), 30.5 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 20.2 (CH<sub>2</sub>), 18.3 (CH<sub>3</sub>); IR (film) 3230, 2968, 2869, 1645, 1542, 1394 cm<sup>-1</sup>. Exact mass calcd for C<sub>10</sub>H<sub>19</sub>N<sub>3</sub>O [M]<sup>+</sup>: 196.1488; found: 196.0845.



**(2*S*)-2-(Hydroxymethyl)-*N*-(2-methylpyrrolidin-1-yl)pyrrolidine-1-carboxamide (Table 4.6, 7b).** Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (0.148 g, 0.669 mmol), (*S*)-(+)-prolinol (0.0745 g, 0.737 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (2.23 mL). The title compound was purified by column chromatography (4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) and obtained as a clear oil (84.9 mg, 56% isolated yield, 96% NMR yield).

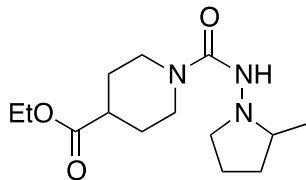
TLC  $R_f$  = 0.25 in 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H 1H-NMR (400 MHz; CDCl<sub>3</sub>) \*denotes presence of diastereoisomer  $\delta$  5.57 (t,  $J$  = 101.0 Hz, 2H), 4.04-3.94 (m, 1H), 3.56-3.44 (m, 2H), 3.41-3.21 (m, 3H), 2.67-2.47 (m, 2H), 1.96-1.60 (m, 6H), 1.54-1.36 (m, 2H), 1.06 (dd,  $J$  = 6.1, 1.7 Hz, 3H); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) 159.2 (C), \*159.0 (C), 67.5 (CH<sub>2</sub>), 67.5 (CH<sub>2</sub>), 62.2 (CH), \*61.8 (CH), 60.8 (CH), \*60.6 (CH), 56.2 (CH<sub>2</sub>), \*55.9 (CH<sub>2</sub>), 47.0 (CH<sub>2</sub>), \*46.8 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), \*30.2 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), \*28.5 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>), \*24.1 (CH<sub>2</sub>), 20.1 (CH<sub>2</sub>), \*20.1 (CH<sub>2</sub>), 18.2 (CH<sub>3</sub>), \*18.2 (CH<sub>3</sub>). IR (film) 3416, 3260, 2109, 1646, 703 cm<sup>-1</sup>. LRMS (EI): 84.1 (100%), 99.1 (48%), 55.1 (28%), 98.1 (19%), 70.1 (17%).



***N*-(2-Methylpyrrolidin-1-yl)piperidine-1-carboxamide (Table 4.6, 7c).** Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **1a** (0.0985 g, 0.447 mmol), piperidine (0.0419 g, 0.492 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.49 mL). Product was purified by column chromatography using 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a white solid (0.0704 g, 75% isolated yield, 95% NMR yield). TLC  $R_f$  = 0.17 in 40% EtOAc/*n*-hexanes. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) 1H-NMR (300 MHz; CDCl<sub>3</sub>):  $\delta$  5.05 (s, br, 1H), 3.32 (t,  $J$  = 4.9 Hz, 4H), 3.24 (td,  $J$  = 8.4, 3.4 Hz, 1H), 2.65-2.57 (m, 1H), 2.48 (q,  $J$  = 8.9 Hz, 1H), 1.87 (dddd,  $J$  = 12.0, 9.6, 7.2, 4.7 Hz, 1H), 1.76-1.64 (m, 2H), 1.57-1.33 (m, 7H), 1.06 (d,  $J$  = 6.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) 158.7 (C), 62.3 (CH), 56.0 (CH<sub>2</sub>), 45.5 (2CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 20.1 (CH<sub>2</sub>), 18.3 (CH<sub>3</sub>); IR (film) 3246, 3066, 2934, 2852, 1634, 1548,

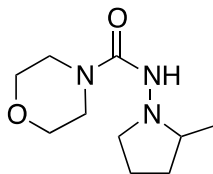


1404, 1092, 1089, 983  $\text{cm}^{-1}$ . TOF MS EI-: Exact mass calcd for  $\text{C}_{11}\text{H}_{21}\text{N}_3\text{O}$  [ $\text{M}^+$ ]: 210.1687; found ES [ $\text{M}$ ] $^-$ : 210.1113.

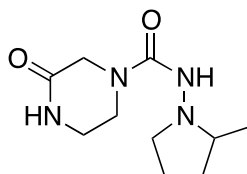


**Ethyl 1-((2-methylpyrrolidin-1-yl)carbamoyl)piperidine-4-carboxylate (Table 4.6, 7d).**

Synthesized according to general procedure **B** using 2-(pent-4-en-1-yl)hydrazinecarboxylate **1a** (0.0800 g, 0.363 mmol), ethyl piperidine-4-carboxylate (0.0628 g, 0.400 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.21 mL). Product was purified by column chromatography using 1% MeOH/ $\text{CH}_2\text{Cl}_2$ . The title compound was obtained as a white solid (0.0663 g, 0.234 mmol, 64% yield). TLC  $R_f$  = 0.38 in 5% MeOH/ $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ ) (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.99 (s, 1H), 4.08 (q,  $J$  = 7.1 Hz, 2H), 4.01-3.94 (m, 2H), 3.23 (td,  $J$  = 8.5, 3.2 Hz, 1H), 2.87-2.79 (m, 2H), 2.61-2.52 (m, 1H), 2.48-2.37 (m, 2H), 1.91-1.80 (m, 3H), 1.75-1.54 (m, 4H), 1.44-1.34 (m, 1H), 1.19 (t,  $J$  = 7.1 Hz, 3H), 1.06 (d,  $J$  = 6.1 Hz, 3H).;  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ) 174.6 (C), 158.8 (C), 62.4 (CH), 60.6 ( $\text{CH}_2$ ), 56.0 ( $\text{CH}_2$ ), 44.1 ( $\text{CH}_2$ ), 44.0 ( $\text{CH}_2$ ), 41.2 (CH), 30.4 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_2$ ), 27.9 ( $\text{CH}_2$ ), 20.0 ( $\text{CH}_2$ ), 18.3 ( $\text{CH}_3$ ), 14.2 ( $\text{CH}_3$ ); IR (film) 3386, 3315, 3074, 2967, 2853, 1730, 1699, 1535, 1364, 1173  $\text{cm}^{-1}$ . HRMS(EI): Exact mass calcd for  $\text{C}_{14}\text{H}_{25}\text{N}_3\text{O}_3$  [ $\text{M}$ ] $^+$ : 238.1896. Found: 238.1580 ( $-\text{C}_2\text{H}_5\text{O}$ ).

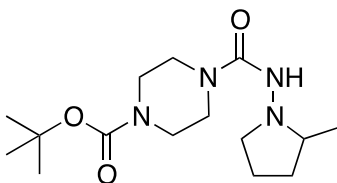


***N*-(2-Methylpyrrolidin-1-yl)morpholine-4-carboxamide** (Table 4.6, 7e). Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **1a** (0.0542 g, 0.246 mmol), morpholine (0.0236 g, 0.271 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.820 mL). Product was purified by column chromatography using 30% EtOAc/*n*-hexanes. The title compound was obtained as a white solid (0.0518 g, 0.243 mmol, 98% NMR yield, 99% isolated yield). TLC  $R_f$  = 0.23 in 100% EtOAc.  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ )  $\delta$  5.04 (s, 1H), 3.68-3.64 (m, 4H), 3.53-3.38 (m, 4H), 3.30-3.23 (m, 1H), 2.62 (qd,  $J$  = 6.4, 2.7 Hz, 1H), 2.50 (q,  $J$  = 8.9 Hz, 1H), 1.93 (dddd,  $J$  = 12.1, 9.5, 7.3, 4.9 Hz, 1H), 1.81-1.68 (m, 2H), 1.50-1.37 (m, 1H), 1.11 (d,  $J$  = 6.1 Hz, 3H).;  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ) 158.8 (C), 66.6 ( $\text{CH}_2$ ), 62.1 (CH), 55.7 ( $\text{CH}_2$ ), 44.8 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_2$ ), 20.0 ( $\text{CH}_2$ ), 18.2 ( $\text{CH}_3$ ); IR (film) 3430, 2975, 2867, 1846, 1555, 1264, 1098  $\text{cm}^{-1}$ . Exact mass calcd for  $\text{C}_{10}\text{H}_{19}\text{N}_3\text{O}_2$   $[\text{M}]^+$ : 213.1477. LRMS(EI): 84.1 (100%), 99.1 (68%), 70.0 (18%), 42.0 (14%), 162.0 (11%), 41.0 (11%), 56.1 (11%), 111.1 (11%).



***N*-(2-Methylpyrrolidin-1-yl)-3-oxopiperazine-1-carboxamide** (Table 4.6, 7f). Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **1a** (0.0799 g, 0.363 mmol), 2-oxopiperazine (0.0525 g, 0.499 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.21 mL). Product was purified by column chromatography using 10% MeOH/ $\text{CH}_2\text{Cl}_2$ . The title compound

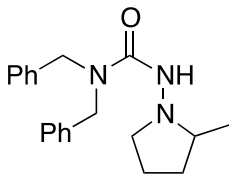
was obtained as a white solid (0.0698 g, 0.308 mmol, 85% isolated yield). TLC  $R_f$  = 0.35 in 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (300 MHz; DMSO-*d*<sub>6</sub>):  $\delta$  7.98 (s, br, 1H), 7.40 (s, br, 1H), 3.90-3.76 (m, 2H), 3.51-3.39 (m, 2H), 3.15 (td,  $J$  = 5.3, 2.5 Hz, 2H), 3.05 (q,  $J$  = 6.2 Hz, 1H), 2.89 (dq,  $J$  = 13.9, 6.7 Hz, 1H), 2.70 (q,  $J$  = 8.7 Hz, 1H), 1.87 (dq,  $J$  = 12.5, 6.5 Hz, 1H), 1.70-1.60 (m, 2H), 1.34-1.22 (m, 1H), 0.97 (d,  $J$  = 6.1 Hz, 3H).; <sup>13</sup>C NMR (100 MHz; DMSO-*d*<sub>6</sub>) 166.7 (C), 156.7 (C), 59.2 (CH), 53.9 (CH<sub>2</sub>), 47.6 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 19.9 (CH<sub>2</sub>), 18.4 (CH<sub>3</sub>); IR (film) 3386, 2256, 2129, 1662, 1052, 826 cm<sup>-1</sup>. HRMS (*m/z*): Exact mass calcd for C<sub>10</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub> [*M*<sup>+</sup>]: 226.1430; found: 226.1422.



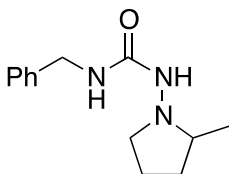
***tert*-Butyl-4-((2-methylpyrrolidin-1-yl)carbamoyl)piperazine-1-carboxylate (Table 4.6, 7g).**

Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **1a** (0.897 g, 0.407 mmol), *N*-*boc*-piperazine (0.0834 g, 0.448 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.36 mL). Product was purified by column chromatography using 1% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a white solid (116.7 mg, 0.373 mmol, 92% isolated yield, 85% NMR yield). TLC  $R_f$  = 0.3 in 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  5.19 (s, 1H), 3.43-3.34 (m, 8H), 3.22 (ddd,  $J$  = 8.8, 7.7, 3.6 Hz, 1H), 2.65-2.53 (m, 1H), 2.52-2.43 (m, 1H), 1.89 (dddd,  $J$  = 12.1, 9.4, 7.3, 4.9 Hz, 1H), 1.76-1.62 (m, 2H), 1.45-1.32 (m, 10H), 1.06 (d,  $J$  = 6.1 Hz, 3H).; <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) 158.8 (C), 154.6 (C), 80.0 (C), 62.3 (CH), 55.8 (CH<sub>2</sub>), 44.3 (CH<sub>2</sub>), 43.7 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 19.9 (CH<sub>2</sub>), 18.2 (CH<sub>3</sub>); IR (film)

3474, 3245, 2374, 2860, 1690, 1636, 1364, 1240, 769  $\text{cm}^{-1}$ . Exact mass calcd for  $\text{C}_{15}\text{H}_{28}\text{N}_4\text{O}_3$   $[\text{M}]^+$ : 311.2183; found: 311.2182.



**1,1-Dibenzyl-3-(2-methylpyrrolidin-1-yl)urea (Table 4.6, 7i).** Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **1a** (0.0488 g, 0.222 mmol), dibenzylamine (0.0482 g, 0.244 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.740 mL). Product was purified by column chromatography using 30% EtOAc/*n*-hexanes. The title compound was obtained as a white solid (0.0580 g, 81% isolated yield). TLC  $R_f$  = 0.31 in 40% EtOAc/*n*-hexanes.  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.34-7.22 (m, 10H), 5.02 (s, 1H), 4.48 (s, 4H), 3.21 (td,  $J$  = 8.4, 3.3 Hz, 1H), 2.59-2.48 (m, 1H), 2.41 (q,  $J$  = 8.8 Hz, 1H), 1.89-1.59 (m, 3H), 1.44-1.31 (m, 1H), 1.01 (d,  $J$  = 6.1 Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ) 158.6 (C), 137.8 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 61.8 (CH), 55.9 ( $\text{CH}_2$ ), 50.5 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_2$ ), 20.1 ( $\text{CH}_2$ ), 18.2 ( $\text{CH}_3$ ); IR (film) 3422, 2097, 1645, 1087  $\text{cm}^{-1}$ . LRMS(EI): 91.1 (100%), 84.1 (63%), 116.1 (0.4%), 99.1 (29%), 106.1 (29%).



**1-Benzyl-3-(2-methylpyrrolidin-1-yl)urea (Table 4.6, 7j).** Synthesized according to general procedure **B** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **1a** (0.0915 g, 0.415 mmol),

benzylamine (0.222 g, 2.08 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.38 mL). Product was purified by column chromatography using 70% EtOAc/hexanes. The title compound was obtained as a white solid (46.9 mg, 0.201 mmol, 48% isolated yield). TLC  $R_f$  = 0.3 in 80% EtOAc/*n*-hexanes.  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.35-7.22 (m, 5H), 6.35 (s, 1H), 5.23 (s, 1H), 4.52-4.37 (m, 2H), 3.23 (s, 1H), 2.50 (d,  $J$  = 20.3 Hz, 2H), 1.99-1.88 (m, 1H), 1.77-1.67 (m, 2H), 1.43-1.30 (m, 1H), 1.09 (d,  $J$  = 6.0 Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ) 158.6 (C), 137.8 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 61.8 (CH), 55.9 ( $\text{CH}_2$ ), 50.5 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_2$ ), 20.1 ( $\text{CH}_2$ ), 18.2 ( $\text{CH}_3$ ); IR (film) 3430, 3191, 3023, 2970, 2023, 1672, 1537  $\text{cm}^{-1}$ . LRMS(EI): 84.1 (100%), 85.08 (88%), 91.06 (66%), 41.04 (20%), 106.1 (19%).

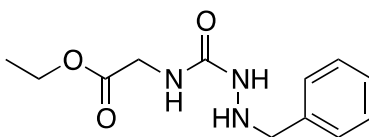
### **Synthesis of Aza-Dipeptides Using Amino-Isocyanates**

#### **General Procedure for the Synthesis of Aza-Dipeptides**

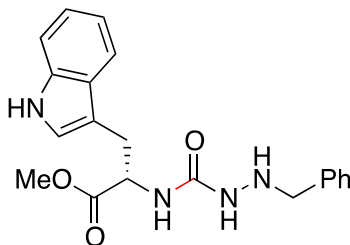
**General Procedure A: *Amine Substitution*:** An oven dried 5 mL  $\mu\text{W}$  tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.0 equiv.), amine (1.1 equiv.), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for three hours at 80°C. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.

**General Procedure B: *Amine Substitution with Amine Salt*:** An oven dried 5 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The carbazate (1.00 equiv), aminoester hydrochloride salt (1.1 equiv),

diisopropylethylamine (1.2 equiv) and  $\alpha,\alpha,\alpha$ -trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 12 hours at 100°C in an oil bath. The tube was cooled to ambient temperature, volatiles were removed under reduced pressure and crude product purified by silica gel chromatography.

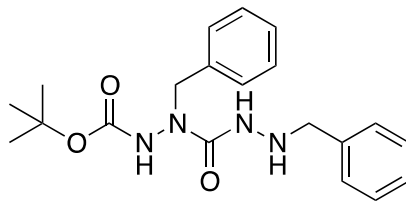


**Ethyl 2-(2-benzylhydrazinecarboxamido)acetate (Table 4.7, 8a).** Synthesized according to general procedure A (100°C) using phenyl 2-benzylhydrazinecarboxylate **5j** (0.120 g, 0.494 mmol), glycine ethyl ester hydrochloride (0.0758 g, 0.543 mmol), diisopropylethylamine (0.766 g, 0.593 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.65 mL). Crude mixture was purified by column chromatography 1% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a white solid (0.0972 g, 78% isolated yield). TLC R<sub>f</sub> = 0.46 in 100% EtOAc. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) \*denotes minor traces of isomer,  $\delta$  7.35-7.23 (m, 5H), 6.56-6.53 (m, 1H), 6.20 (s, br, 1H), 4.22-4.13 (m, 2H), 4.09-3.88 (m, 5H), 1.25 (t,  $J$  = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) 170.8 (C), 159.2 (C), 141.6 (C), 136.7 (CH), 129.6 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 126.8 (CH), 61.2 (CH<sub>2</sub>), 56.5 (CH<sub>2</sub>), \*41.7 (CH<sub>2</sub>), 41.5 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>); IR (film) 3344, 3283, 2983, 2941, 2857, 1748, 1653, 1542, 1212, 1181, 1037 cm<sup>-1</sup>. LRMS Exact mass calcd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub> ESI-[M]<sup>-</sup>: 251.1217; found: 251.0730.



**(S)-Methyl 2-(2-benzylhydrazinecarboxamido)-3-(1*H*-indol-3-yl)propanoate (Table 4.7, 8e).**

Synthesized according to general procedure C using phenyl 2-benzylhydrazinecarboxylate **5j** (0.0996 g, 0.411 mmol), (*S*)-methyl 2-amino-3-(1*H*-indol-3-yl)propanoate (0.1151 g, 0.452 mmol), diisopropylethylamine (0.0637 g, 0.493 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.37 mL). Crude mixture was purified by column chromatography 1% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a brown oil (0.0642 g, 0.180 mmol, 43% isolated yield).  $[\alpha]_D^{20} = +32.4$ , TLC R<sub>f</sub> = 0.24 in 40% EtOAc/hexanes. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  7.35-7.24 (m, 6H), 6.52-6.48 (m, 1H), 5.98 (s, br, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 2H), 3.44 (q, *J* = 6.2 Hz, 2H), 2.45 (t, *J* = 6.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) \*denotes traces of conformers  $\delta$  172.3 (C), \*171.2 (C), 157.5 (C), \*155.2 (C), 137.0 (C), \*136.7 (C), 135.9 (C), \*135.8 (C), 128.3, \*128.0, 127.7, \*127.5, 127.1, \*127.0, 126.7, \*126.6, 123.7, \*123.1, 120.5, \*120.4, 118.0, \*118.0, 117.9, \*117.6, 110.9, \*110.8, 108.9 (C), \*107.5 (C), 55.1, \*54.9, 52.8, \*52.7, 51.1, 27.5 (CH<sub>2</sub>), \*26.6 (CH<sub>2</sub>); IR (film) 3292, 1772, 1710, 1664, 1542, 1425, 1340 cm<sup>-1</sup>. LRMS(EI) *m/z*: 130.1 (100%), 91.1 (12.4%), 131.1 (9%), 162.0 (4%), 334.1 (4%).



***tert*-Butyl 2-benzyl-2-(2-benzylhydrazinecarbonyl)hydrazinecarboxylate (Table 4.7, 8f).**

Synthesized according to general procedure C using phenyl 2-benzylhydrazinecarboxylate **5j** (0.938 g, 0.387 mmol), *tert*-butyl 2-benzylhydrazinecarboxylate (0.861 g, 3.87 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.29 mL). Crude mixture was purified by column chromatography 40% EtOAc/hexanes. The title compound was obtained as a clear oil (132 mg, 0.357 mmol, 93% isolated yield). TLC  $R_f$  = 0.46 in 40% EtOAc/hexanes. \*denotes presence of minor isomer.  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ )  $\delta$  7.32-7.23 (m, 11H), 6.24 (s, 1H), 4.80 (s, 3H), 3.97 (s, 2H), \*1.41 (s, 9H), 1.38 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ )  $\delta$  158.5 (C), \*154.5 (C), 154.2 (C), \*45.3 (C), 137.3 (C), 135.9 (C), \*134.2 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH), \*128.6 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), \*127.4 (CH), 82.4 (C), 56.2 ( $\text{CH}_2$ ), 51.1 ( $\text{CH}_2$ ), \*28.4 ( $\text{CH}_3$ ), 28.2 ( $\text{CH}_3$ ).; IR (film) 3264, 2979, 2930, 1957, 1713, 1645, 1447, 1364, 684  $\text{cm}^{-1}$ . Exact mass calcd for  $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_3$  [ $\text{M}^+$ ]: 370.2005; Found [ $\text{M}^+$ ]: 370.2003.

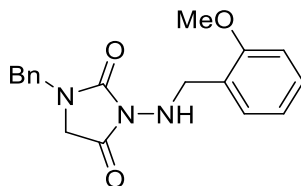
**Synthesis of Aza-Hydantoins and Aza-Dihydrouracil Using Amino-Isocyanates**

**General Procedure for the Synthesis of Aza-Hydantoins and Aza-Dihydrouracil**

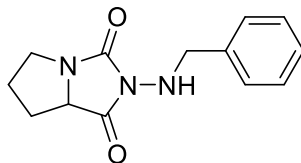
**General Procedure:** An oven dried  $\mu\text{W}$  tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The carbazate (1.0 equiv.), amino-ester hydrochloride salt (1.1 equiv.), diisopropylethylamine (1.2 equiv.) and  $\alpha,\alpha,\alpha$ -trifluorotoluene (acetonitrile) (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere.



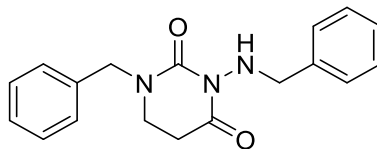
The septum was removed and the tube was then quickly sealed with a microwave cap and heated between three and six hours at 80-150°C. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



**4-Benzyl-1-(2-methoxybenzyl)-1,2,4-triazinane-3,6-dione (Table 4.8, 9b).** Synthesized according to general procedure using phenyl 2-(2-methoxybenzyl)hydrazinecarboxylate<sup>1</sup> (97.7 mg, 0.359 mmol), *N*-benzyl glycine ethylester (76.3 mg, 0.395 mmol), and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.20 mL). Crude mixture was purified by column chromatography 50% EtOAc/*n*-hexanes to which 10% dichloromethane was added for solubility. The title compound was obtained as a clear oil (83.8 mg, 72% isolated yield). TLC  $R_f$  = 0.21 in 40% EtOAc / *n*-hexanes. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  7.32 (m, 3H), 7.25 (dd,  $J$  = 7.7, 1.6 Hz, 1H), 7.17-7.14 (m, 1H), 7.10 (dd,  $J$  = 7.3, 1.8 Hz, 2H), 6.86-6.82 (m, 2H), 4.79 (s, br, 1H), 4.45 (s, 2H), 4.14 (s, 2H), 3.84 (s, 3H), 3.57 (s, 2H); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>)  $\delta$  166.9 (C), 158.3 (C), 155.3 (C), 135.2 (C), 130.9 (CH), 129.5 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 124.6 (CH), 120.3 (CH), 110.4 (CH), 55.4 (CH<sub>3</sub>), 50.3 (CH<sub>2</sub>), 47.5 (CH<sub>2</sub>), 46.8 (CH<sub>2</sub>); IR (film) 3061, 1774, 1709, 1493, 1450, 1244, 1027, 731, 642 cm<sup>-1</sup>. Exact mass calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub> [M]<sup>+</sup>: 272.1161. LRMS(EI): 91.1 (100%), 121.1 (96%), 136.1 (55%), 191.1 (32%), 69.0 (28%), 65.0 (14%), 92.1 (13%), 134.1 (13%), 122.1 (11%).

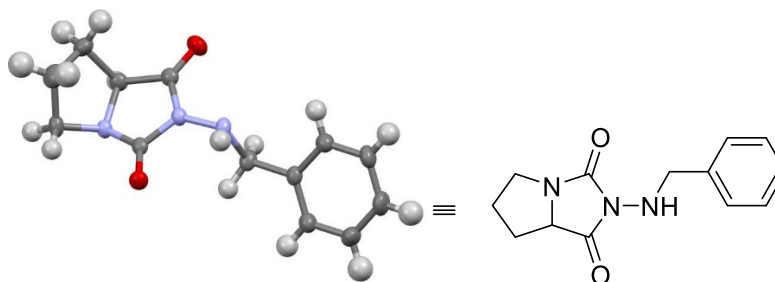


**2-benzylhexahydropyrrolo[1,2-*d*][1,2,4]triazine-1,4-dione (Scheme 4.3, Figure, 4.2, Table 4.8, 9f).** Synthesized according to general procedure using phenyl 2-benzylhydrazinecarboxylate<sup>1</sup> (99.0 mg, 0.409 mmol), L-proline ethyl ester hydrochloride (66.2 mg, 0.400 mmol), diisopropylethylamine (56.6 mg, 0.437 mmol) and  $\alpha,\alpha,\alpha$ -trifluorotoluene (1.21 mL). Crude mixture was purified by column chromatography 1% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a white solid (49.3 mg, 49% isolated yield). TLC R<sub>f</sub> = 0.46 in 20% EtOA/CH<sub>2</sub>Cl<sub>2</sub>. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  7.38-7.35 (m, 2H), 7.32-7.24 (m, 3H), 4.33 (s, 1H), 4.10 (s, 2H), 3.57 (dt, *J* = 11.2, 7.7 Hz, 1H), 3.19 (ddd, *J* = 11.2, 7.6, 5.2 Hz, 1H), 2.16 (dtd, *J* = 12.4, 7.1, 4.3 Hz, 1H), 2.01-1.91 (m, 2H), 1.49 (dq, *J* = 12.6, 9.0 Hz, 1H).; <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>)  $\delta$  171.7 (C), 159.2 (C), 135.7 (CH), 128.5 (CH), 128.1 (CH), 61.7 (CH), 54.5 (CH<sub>2</sub>), 45.7 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>); IR (film) 3276, 1774, 1713, 1493, 1456, 1404, 1219, 750, 698 cm<sup>-1</sup>. Exact mass calcd for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> [M]<sup>+</sup>: 245.1164. LRMS(EI): 70.1 (100%), 91.1 (97%), 141.1 (71%), 106.1 (66%), 65.4 (19%), 39.0 (11%), 245.1 (0.2%).



**1,4-dibenzyl-1,2,4-triazepane-3,7-dione (Table 4.8, 9g).** Synthesized according to general procedure using phenyl 2-benzylhydrazinecarboxylate<sup>1</sup> (188.1 mg, 0.777 mmol), ethyl 3-(benzylamino)propanoate (177.1 mg, 0.855 mmol) and  $\alpha,\alpha,\alpha$ -trifluorotoluene (2.59 mL). The

crude mixture was purified by column chromatography 40% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>. The title compound was obtained as a clear oil (149.2 mg, 0.482 mmol, 62% isolated yield). TLC R<sub>f</sub> = 0.25 in 40% EtOAc / *n*-hexanes. <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 7.41-7.26 (m, 8H), 7.16 (dd, *J* = 7.5, 1.9 Hz, 2H), 4.58 (s, 2H), 4.06 (s, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 6.8 Hz, 2H). <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>) δ 166.8 (C), 153.1 (C), 136.2 (C), 135.8 (C), 129.4 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 54.8 (CH<sub>2</sub>), 51.6 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 31.3 (CH<sub>2</sub>). IR (film) 3293, 3063, 3032, 2922, 2865, 2238, 1717, 1675, 1493, 1436, 1375, 745, 701 cm<sup>-1</sup>. HRMS(EI): Exact mass calcd for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> [M]<sup>+</sup>: 309.1477 Found: 310.152.

**X-Ray Crystallographic Data**

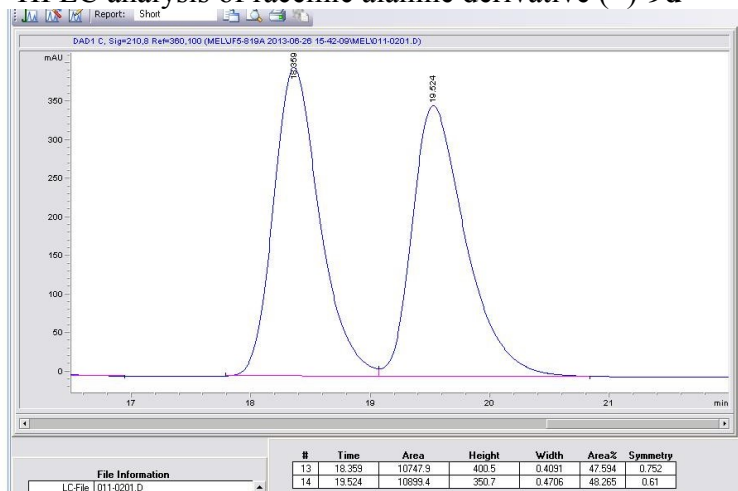
**Table 5.11** Crystal data and structure refinement for 2-(benzylamino)tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (Scheme 4.3, Figure, 4.2, Table 4.8, **9f**).

|                                   |                                                                                                                      |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------|
| Identification code               | ab020                                                                                                                |
| Empirical formula                 | C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>                                                        |
| Formula weight                    | 245.28                                                                                                               |
| Temperature                       | 200(2) K                                                                                                             |
| Wavelength                        | 0.71073 Å                                                                                                            |
| Crystal system, space group       | Monoclinic, P2(1)                                                                                                    |
| Unit cell dimensions              | a = 6.3017(3) Å    alpha = 90 deg<br>b = 7.8214(4) Å    beta = 92.031(3) deg.<br>c = 12.2241(6) Å    gamma = 90 deg. |
| Volume                            | 602.12(5) Å <sup>3</sup>                                                                                             |
| Z, Calculated density             | 2, 1.353 Mg/m <sup>3</sup>                                                                                           |
| Absorption coefficient            | 0.094 mm <sup>-1</sup>                                                                                               |
| F(000)                            | 260                                                                                                                  |
| Crystal size                      | 0.24 x 0.18 x 0.15 mm                                                                                                |
| Theta range for data collection   | 3.09 to 28.31 deg.                                                                                                   |
| Limiting indices                  | -8 ≤ h ≤ 8, -9 ≤ k ≤ 10, -15 ≤ l ≤ 16                                                                                |
| Reflections collected / unique    | 8578 / 2736 [R(int) = 0.0193]                                                                                        |
| Completeness to theta = 28.31     | 97.8 %                                                                                                               |
| Absorption correction             | Semi-empirical from equivalents                                                                                      |
| Max. and min. transmission        | 0.9861 and 0.9778                                                                                                    |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                                                          |
| Data / restraints / parameters    | 2736 / 1 / 163                                                                                                       |
| Goodness-of-fit on F <sup>2</sup> | 1.034                                                                                                                |
| Final R indices [I > 2sigma(I)]   | R1 = 0.0382, wR2 = 0.1022                                                                                            |
| R indices (all data)              | R1 = 0.0406, wR2 = 0.1057                                                                                            |
| Absolute structure parameter      | -0.4(11)                                                                                                             |
| Largest diff. peak and hole       | 0.497 and -0.281 e.Å <sup>-3</sup>                                                                                   |

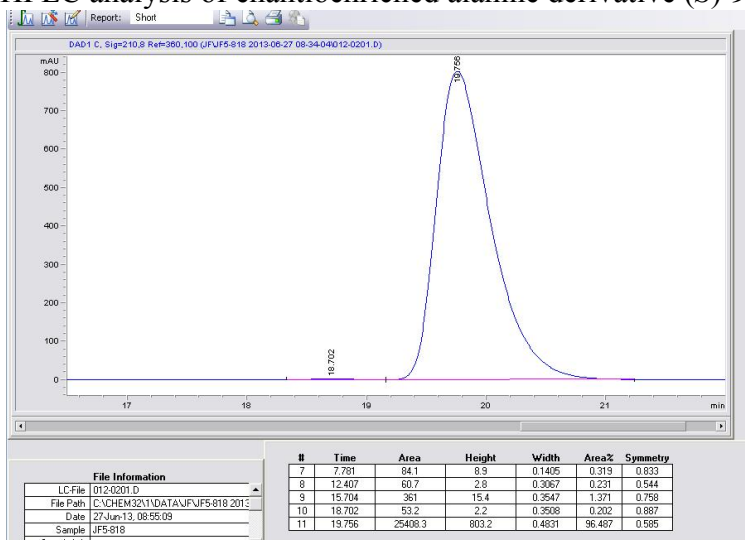
## Retention of Enantiopurity

The exchange reaction was performed with both racemic and enantiopure alanine ethyl ester to provide ( $\pm$ )-**9d** and (*S*)-**9d**.

### HPLC analysis of racemic alanine derivative ( $\pm$ )-**9d**



### HPLC analysis of enantioenriched alanine derivative (*S*)-**9d**



## **Appendix I**

## Claims to Original Research

1. Development of thermolytic conditions for the intramolecular aminocarbonylation of alkenes with amino-isocyanates.
2. Development of conditions for the intramolecular aminocarbonylation of alkenes with amino-isocyanates at room temperature.
3. Development of intramolecular alkene aminocarbonylation / Stevens rearrangement sequence.
4. Development of thermolytic conditions for the intra- and intermolecular aminocarbonylation of alkenes with imino-isocyanates.
5. Development of aminocarbonylation / [3+2] dipolar cycloaddition sequence.
6. Exploration of Cope-type hydroamination with phospho-hydrazides.
7. Development of cascade substitution / hydroamination reaction using amino-isocyanates.
8. Development of aza-dipeptide synthesis using amino-isocyanates.
9. Discovery and preliminary development of *N*-amino-hydantoin and *N*-amino-dihydrouracil synthesis.

## Publications from This Work

1. *A Cascade Synthesis of Amino-Hydantoins Using In Situ Generated N-Substituted-Isocyanates*; Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K. and Beauchemin, A. M. *Chem. Eur. J.* **2015**, *accepted for publication*.

2. *Diversity-Oriented Synthesis of Hydrazine-Derived Compounds from Amino-Isocyanates Generated In Situ*; Clavette, C.;<sup>†</sup> Vincent-Rocan, J.-F.;<sup>†</sup> Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2013**, 52, 12705. DOI: 10.1002/anie.201306379
3. *Synthesis and Reactivity of Unsymmetrical Azomethine Imines Formed Using Alkene Aminocarbonylation*; Gan, W.; Moon, P.; Clavette, C.; Das Neves, N.; Beauchemin, A. M. *Org. Lett.* **2013**, 15, 1890. DOI: 10.1021/ol400542b
4. *A Tunable Route for the Synthesis of Azomethine Imines and beta-Aminocarbonyl Compounds from Alkenes*; Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A. B.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, 134, 16111. DOI: 10.1021/ja305491t.
5. *Improved Cope-type Hydroamination Reactivity of Hydrazine Derivatives*, Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A. and Beauchemin A. M. *Chem. Commun.*, **2011**, 47, 562. DOI: 10.1039/c0cc02403a.

**Manuscripts in Preparation:**

6. *Intramolecular Alkene Aminocarbonylation Using Amino-Isocyanates*; Clavette, C.; Vincent-Rocan, J.-F.; Toderian, A.; Beauchemin, A. M. **2015**, *manuscript in preparation*.
7. *General Synthesis of Substituted Amino-Hydantoins from a Cascade Reaction Using Masked Amino-Isocyanates*; Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K. C.; Beauchemin, A. M. **2015**, *manuscript in preparation*.

**Patents and Copyrights:**

8. *Amphoteric Amino-Isocyanates for the Diversity-Oriented Synthesis of Nitrogen Heterocycles*. Inventors: Beauchemin, A. M.; Clavette, C.; Vincent-Rocan, J.-F.;



Provisionary Patent No.: TTBE.13.034

9. Process for the Synthesis of  $\beta$ -Aminocarbonyls. Inventors: Beauchemin, A. M.; Clavette, C.; Gan, W.; PCT/CA2012/050798.

## **Presentations from This Work**

### *Oral Presentations:*

1. Christian Clavette, Jean-Grégoire Roveda, Christopher J. Whipp, Serge I. Gorelsky and André M. Beauchemin. *A Novel Metal-Free Aminocarbonylation of Alkenes*. 78<sup>e</sup> Congrès de l'Association canadienne-française pour l'avancement des sciences (ACFAS), Université de Montréal, Montréal, QC, May 2010.
2. Christian Clavette, Thomas Markiewicz, Wei Gan, Amy B. Toderian, Jean-Grégoire Roveda, Serge I. Gorelsky, A. M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Iminoisocyanates*. Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, Concordia University, Montreal, QC, November 2011. (*best oral presentation award*)
3. Christian Clavette, Wei Gan, Jean-François Vincent-Rocan, Amanda Bongers, Thomas Markiewicz, Amy B. Toderian and André M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isoycanates*. 96<sup>th</sup> Canadian Chemistry Conference & Exhibition, Québec, QC, May 2013.

### *Poster Presentations*

4. Christian Clavette, Jean-Grégoire Roveda, Christopher J. Whipp, Serge I. Gorelsky and André M. Beauchemin. *A Novel Metal-Free Aminocarbonylation of Alkenes*. Synthesis Day, University of Ottawa, Ottawa, ON, May 2009.

5. Christian Clavette, Jean-Grégoire Roveda, Christopher J. Whipp, Serge I. Gorelsky and André M. Beauchemin. *A Novel Metal-Free Aminocarbonylation of Alkenes*. CCRI Conference, University of Ottawa, Ottawa, ON, May 2009.
6. Christian Clavette, Jean-Grégoire Roveda, Christopher J. Whipp, Serge I. Gorelsky and André M. Beauchemin. *A Novel Metal-Free Aminocarbonylation of Alkenes*. 92<sup>nd</sup> Canadian Chemistry Conference & Exhibition, Hamilton, ON, May 2009.
7. Christian Clavette, Jean-Grégoire Roveda, Christopher J. Whipp, Serge I. Gorelsky and André M. Beauchemin. *A Novel Metal-Free Aminocarbonylation of Alkenes*. Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, Université Laval, Québec, QC, October 2009.
8. Christian Clavette, Jean-Grégoire Roveda, Serge I. Gorelsky and André M. Beauchemin. *Synthesis of  $\beta$ -Aminocarbonyl Groups from Aminocarbonylation of Alkenes with Amino-Isocyanates*. 93<sup>rd</sup> Canadian Chemistry Conference & Exhibition, Toronto, ON, May 2010.
9. Christian Clavette, Jean-Grégoire Roveda, Serge I. Gorelsky and André M. Beauchemin. *Synthesis of  $\beta$ -Aminocarbonyl Groups from Aminocarbonylation of Alkenes with Amino-Isocyanates*. CCRI Conference, Ottawa, ON, June 2010. (*best poster presentation award*)
10. Christian Clavette, Thomas Markiewicz, Wei Gan, Amy B. Toderian, Jean-Grégoire Roveda, Serge I. Gorelsky, A. M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Iminoisocyanates*. 3<sup>rd</sup> International IUPAC Green Chemistry Conference, Ottawa, ON, August 2010.
11. Christian Clavette, Thomas Markiewicz, Wei Gan, Amy B. Toderian, Jean-Grégoire Roveda, Serge I. Gorelsky, A. M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isocyanates*. Quebec-Ontario Mini-Symposium on

Bioorganic and Organic Chemistry, Brock University, Ste-Catharines, ON, October 2010.

*(best poster presentation award)*

12. Christian Clavette, Thomas Markiewicz, Wei Gan, Amy B. Toderian, Jean-Grégoire Roveda, Serge I. Gorelsky, A. M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isocyanates*. Pharmaqam 2011, UQAM, Montreal, QC, May 2011.
13. Christian Clavette, Thomas Markiewicz, Wei Gan, Amy B. Toderian, Jean-Grégoire Roveda, Serge I. Gorelsky, A. M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isocyanates*. International Sustainable Chemistry Summit, Kingston, ON, September 2011.
14. Christian Clavette, Wei Gan, Thomas Markiewicz, Amy B. Toderian, Jean-Grégoire Roveda, Serge I. Gorelsky and André M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isocyanates*. AstraZeneca Excellence in Chemistry Awards Symposium, AstraZeneca, Boston, MA, December 2011.
15. Christian Clavette, Jean-Grégoire Roveda, Christopher J. Whipp, Serge I. Gorelsky and André M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isocyanates*. CCRI Conference, University of Ottawa, Ottawa, ON, June 2012. *(best poster presentation award)*
16. Christian Clavette, Jean-Grégoire Roveda, Christopher J. Whipp, Serge I. Gorelsky and André M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isocyanates*. International Symposium on Medicinal Chemistry, Berlin, Germany, September 2012.

17. Christian Clavette, Wei Gan, Amanda Bongers, Thomas Markiewicz, Amy B. Toderian, Serge I. Gorelsky and André M. Beauchemin. *Synthesis of  $\beta$ -Aminocarbonyl Compounds Using Amino- and Imino-Isocyanates*. Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, University of Windsor, Windsor, ON, November 2012. (*best poster presentation award*)
18. Christian Clavette, Wei Gan, Jean-François Vincent-Rocan, Amanda Bongers, Nicolas Das Neves, Thomas Markiewicz, Amy B. Toderian, Jean-Grégoire Roveda, Serge I. Gorelsky and André M. Beauchemin. *A Simple Approach to  $\beta$ -Aminocarbonyl Motifs Using Amino- and Imino-Isocyanates*. Gordon Research Conferences - Organic Reactions and Processes, Bryant University, Smithfield, RI, United-States, July 2013.

## Appendix II

## Spectra

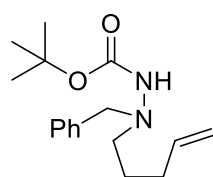
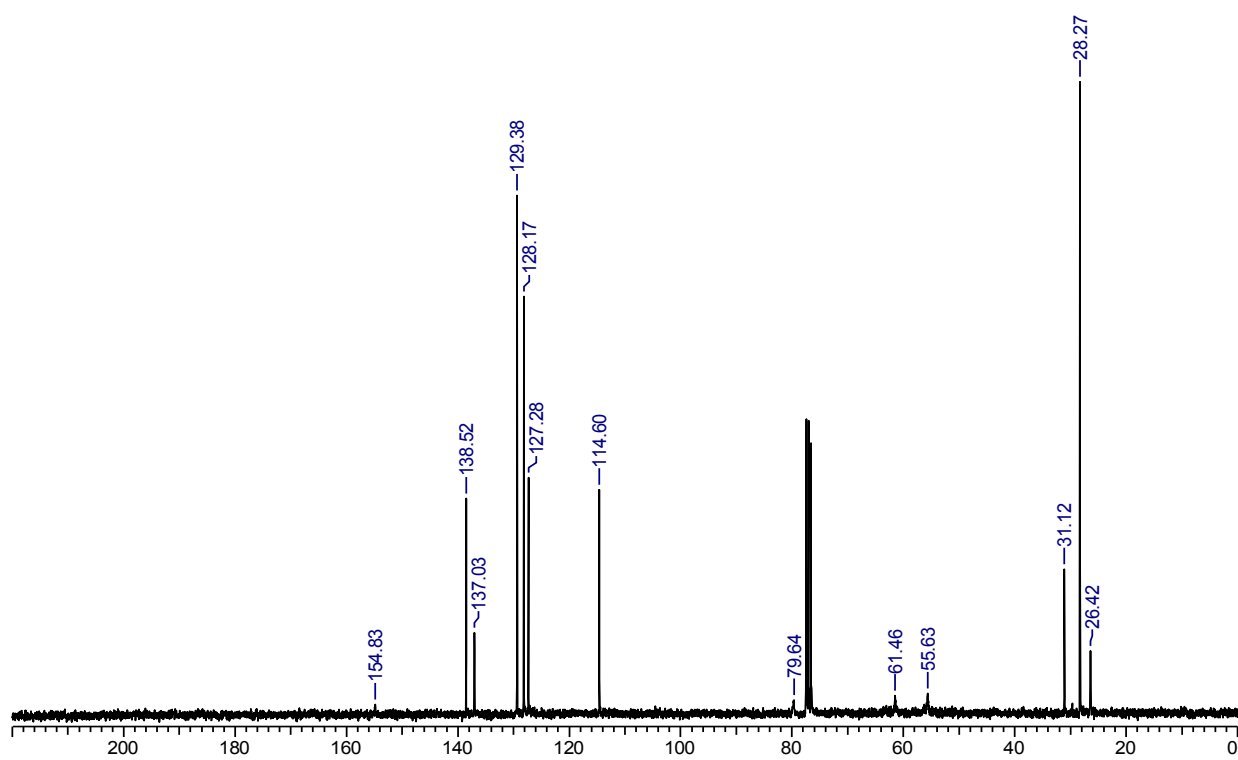
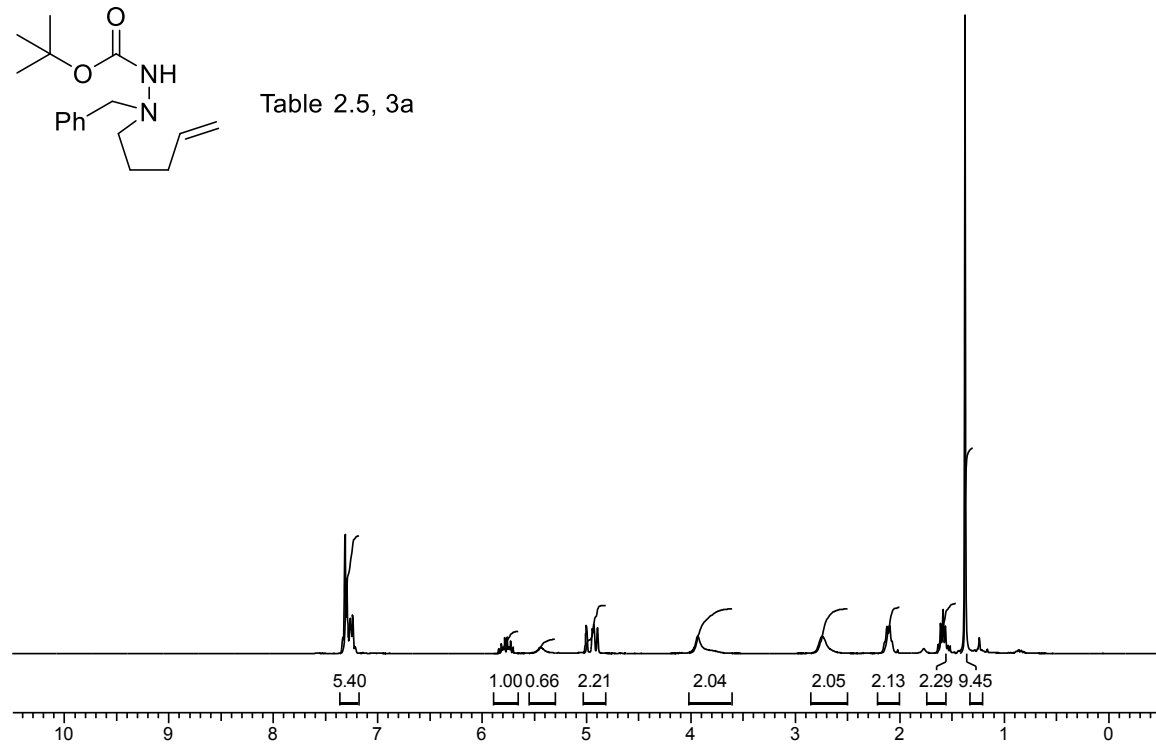
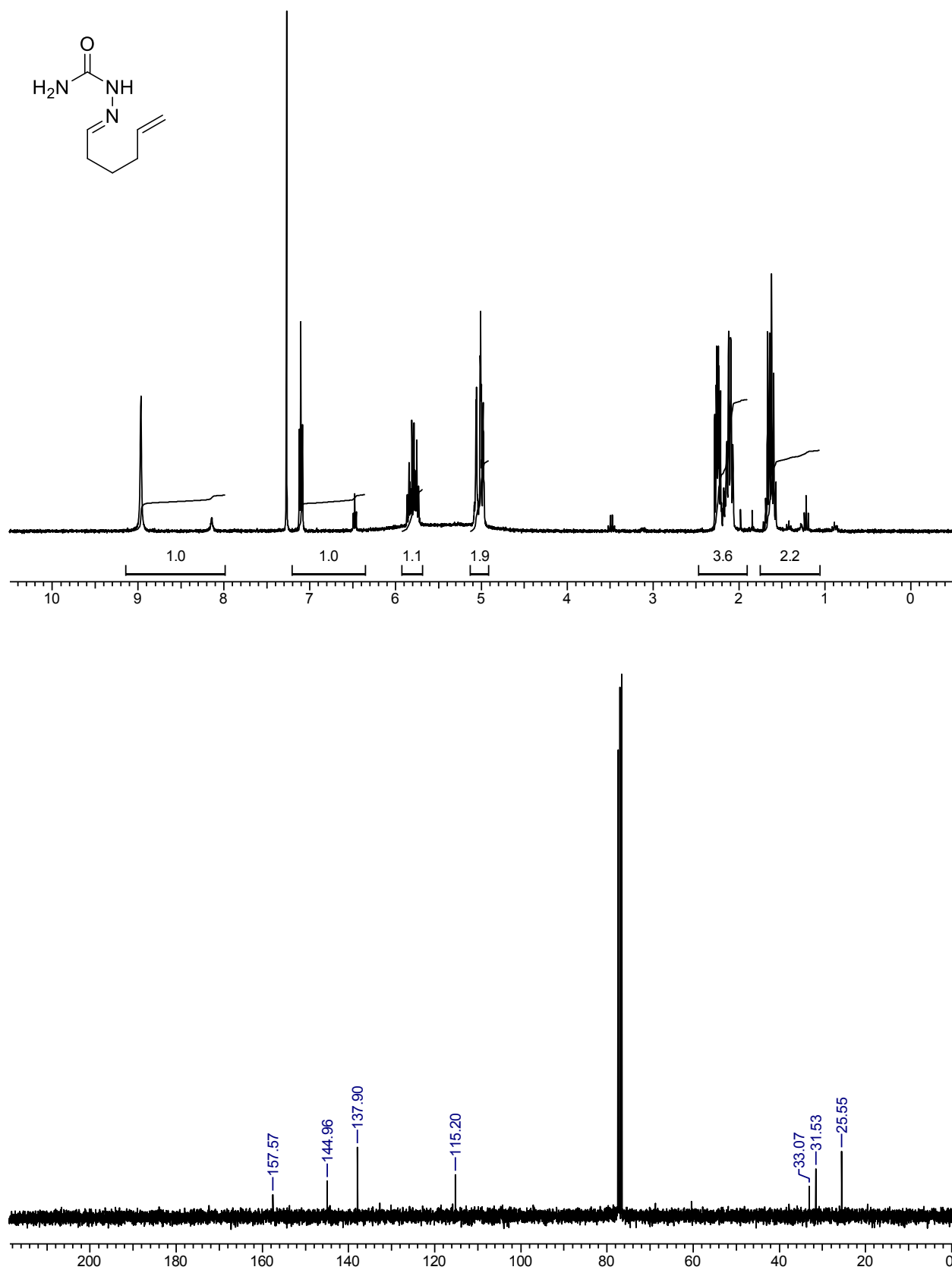


Table 2.5, 3a







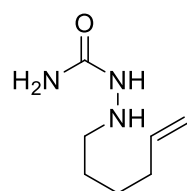
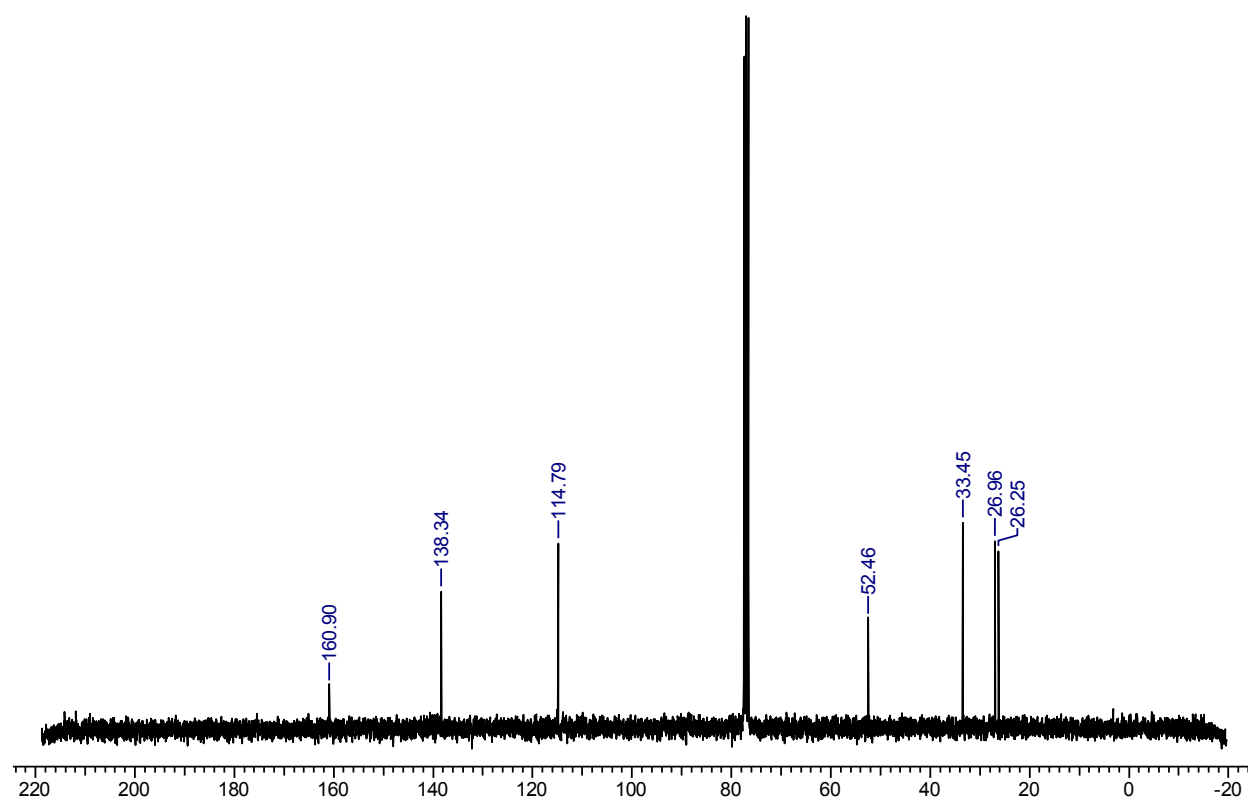
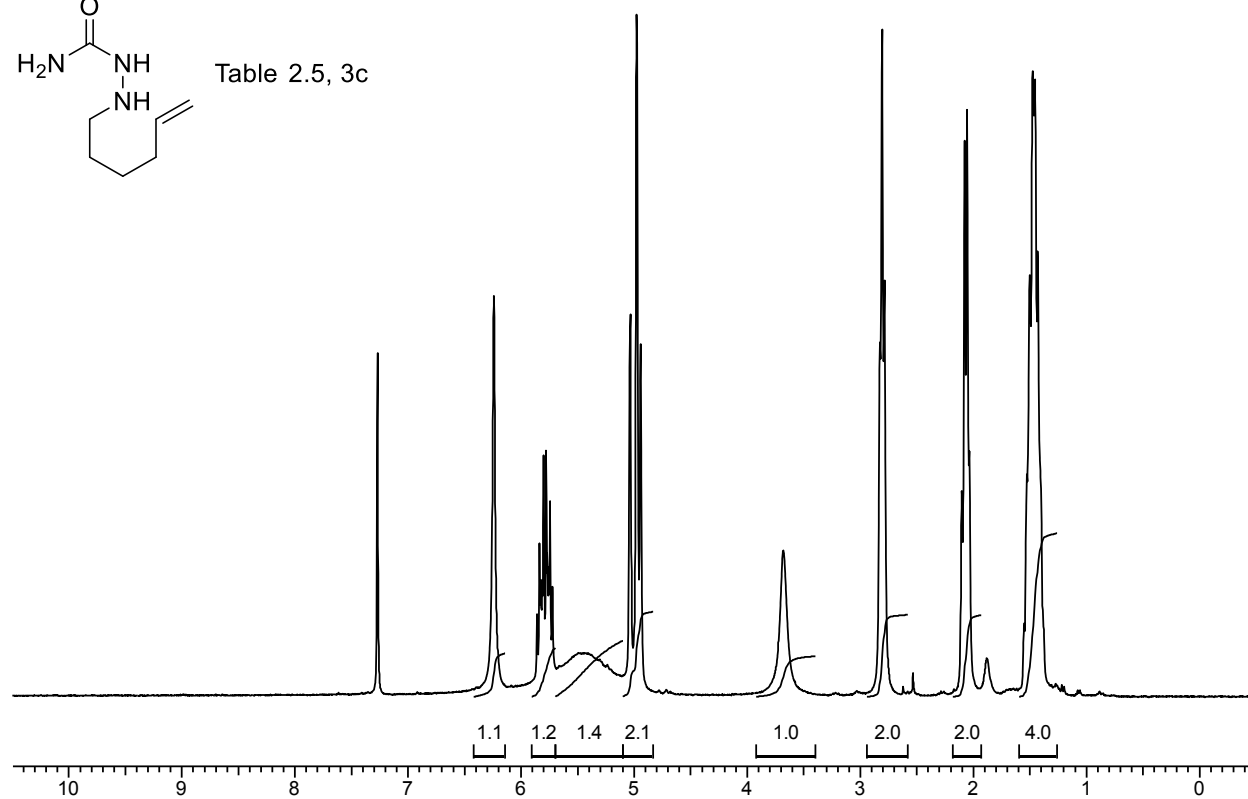


Table 2.5, 3c



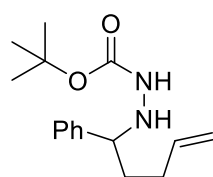
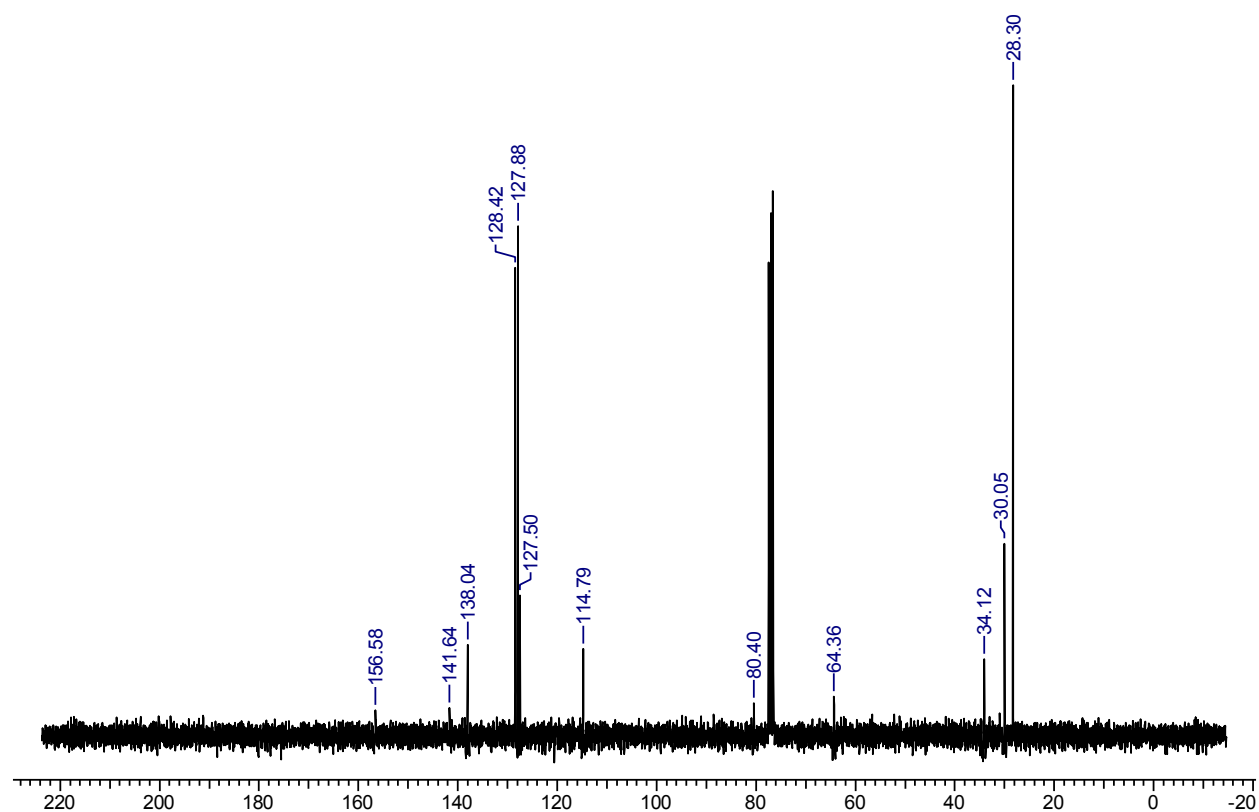
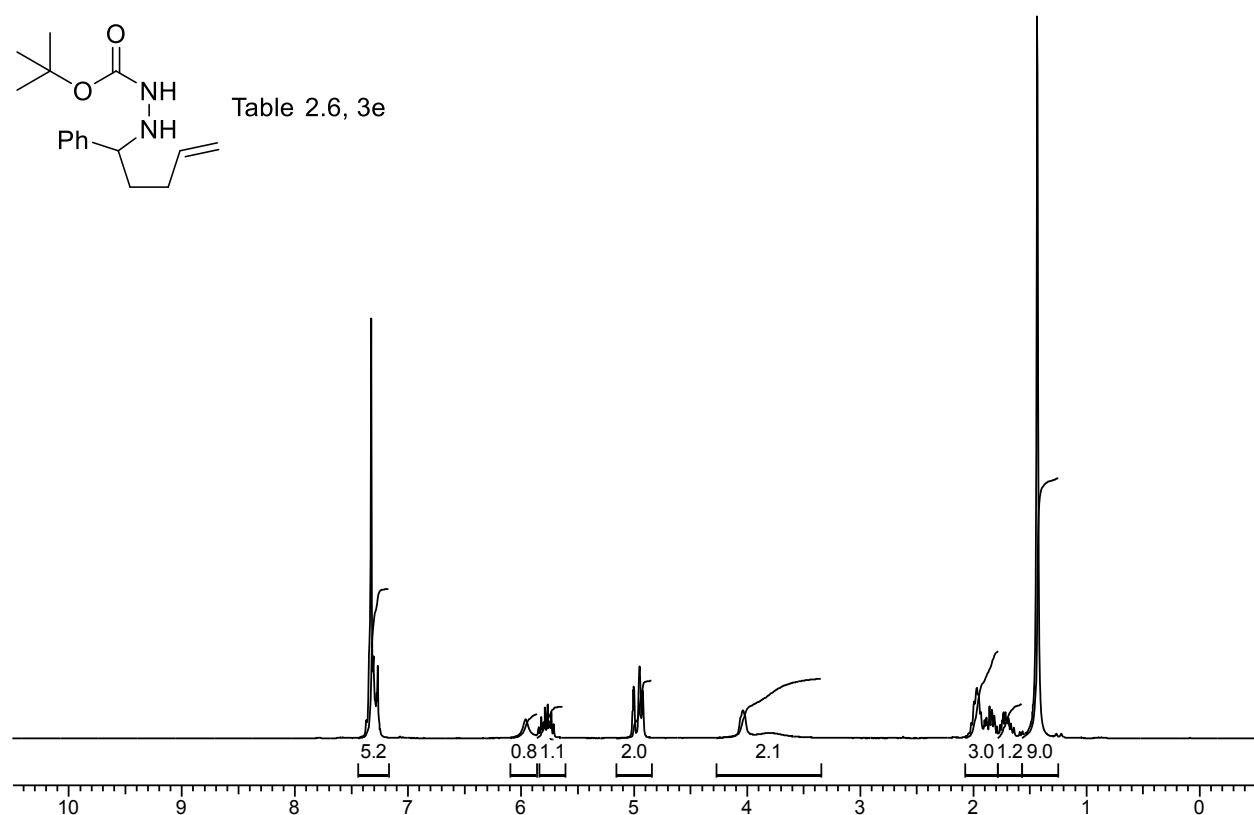
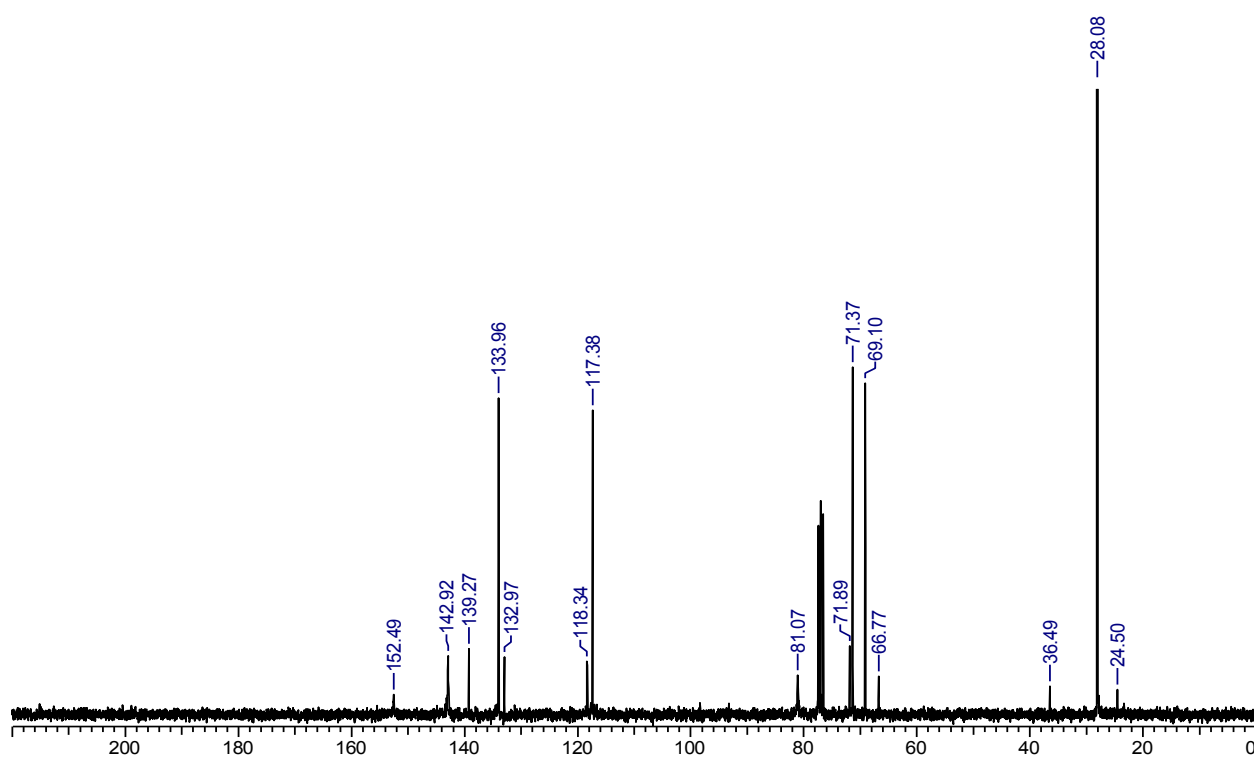
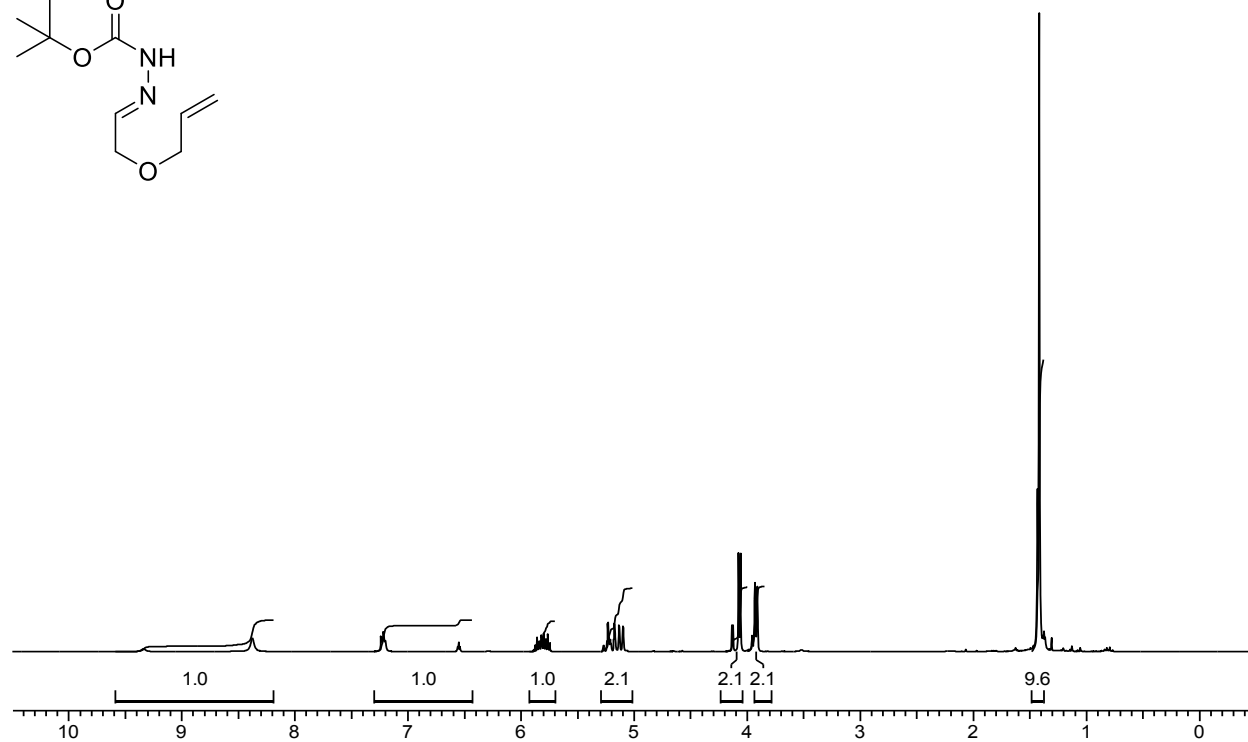
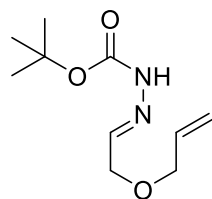
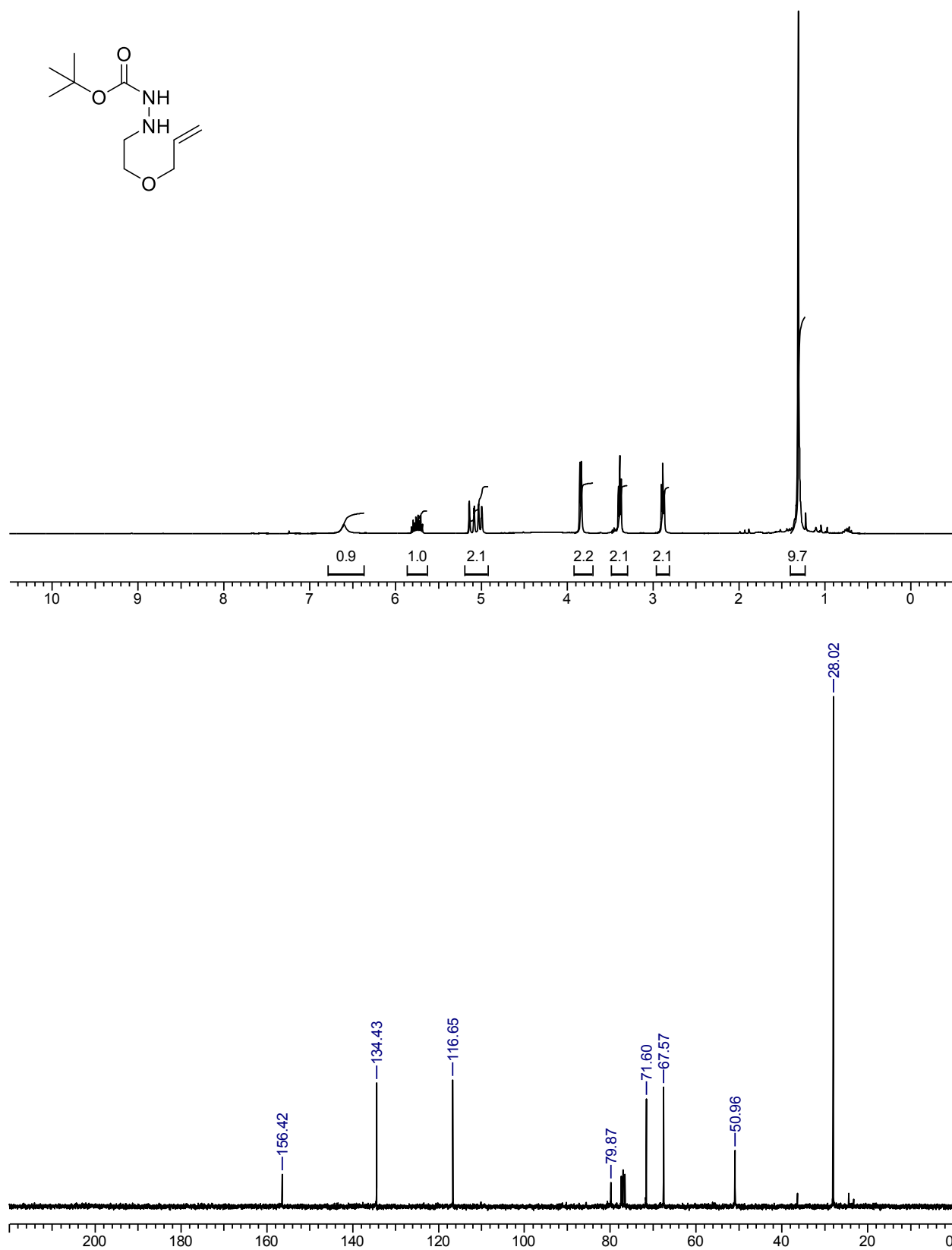
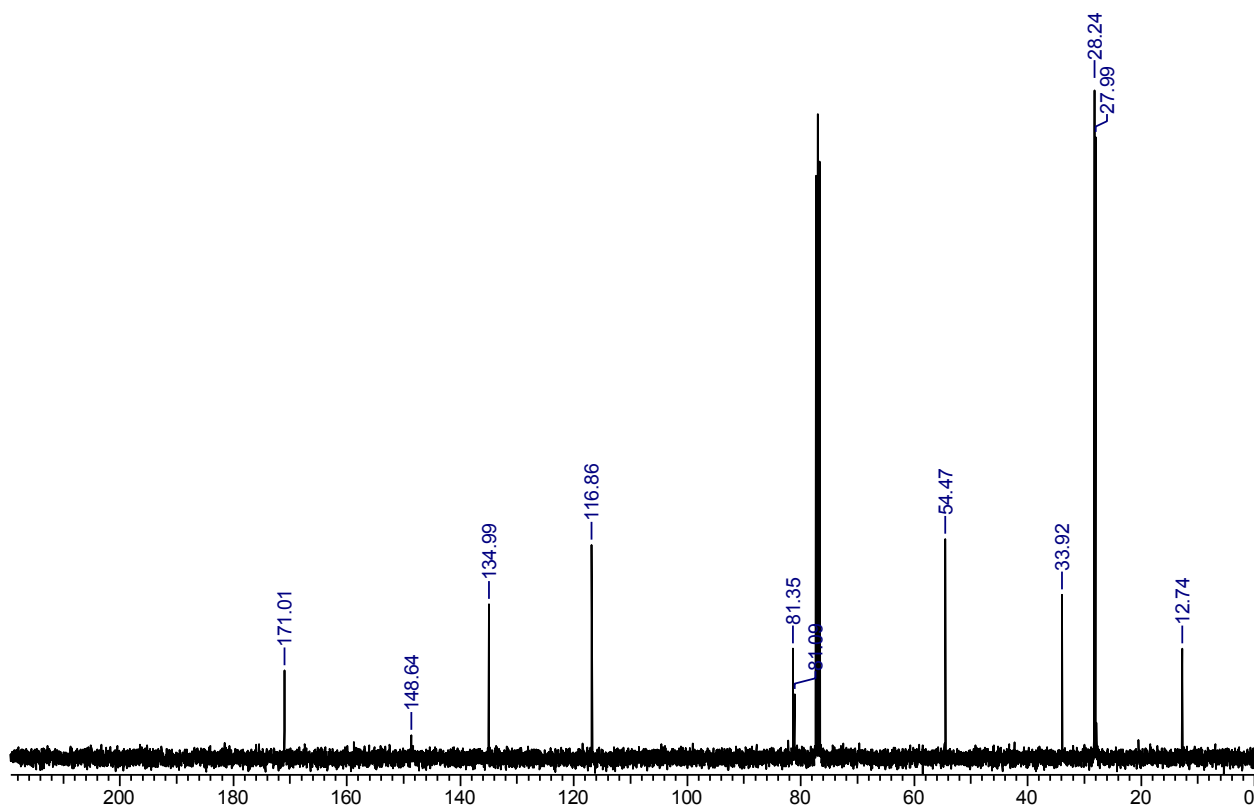
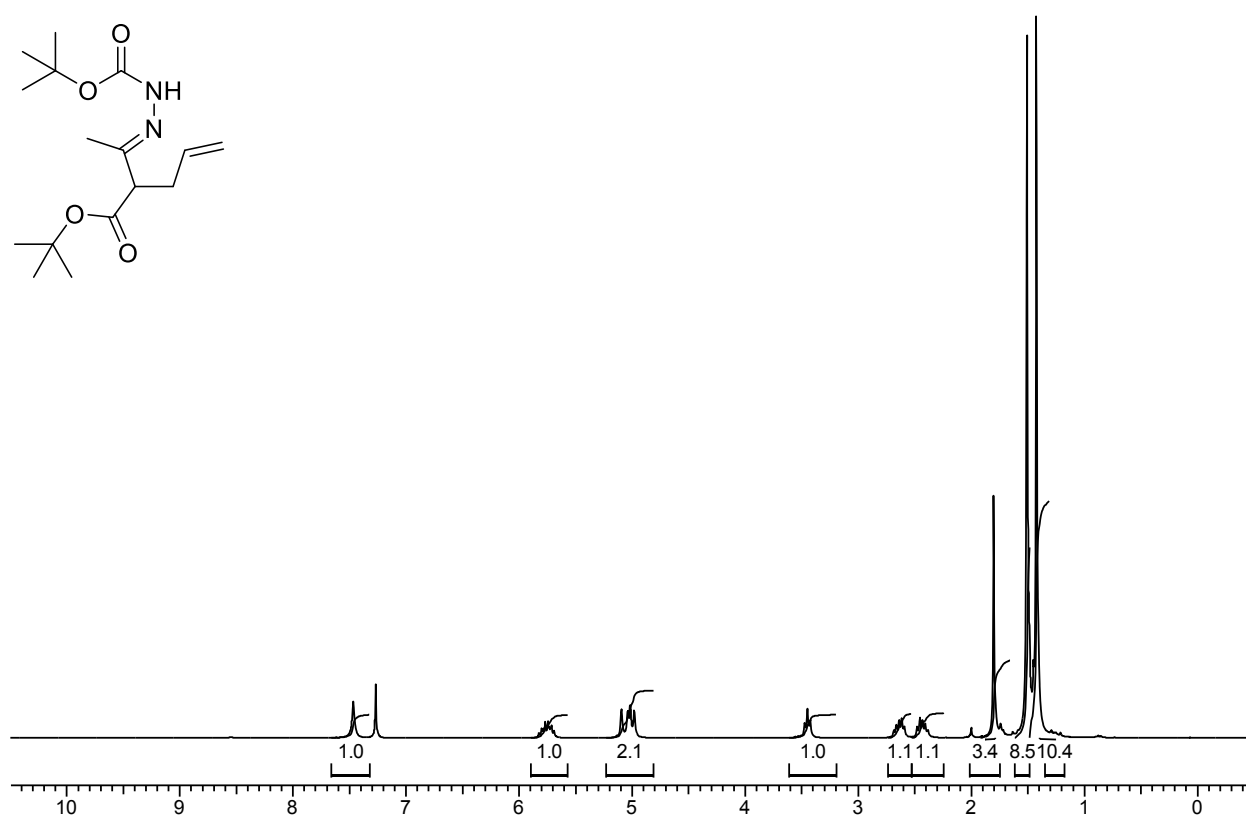
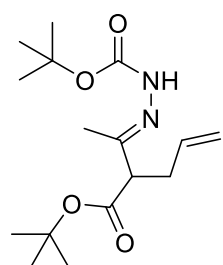


Table 2.6, 3e









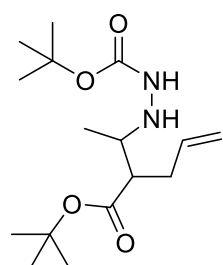
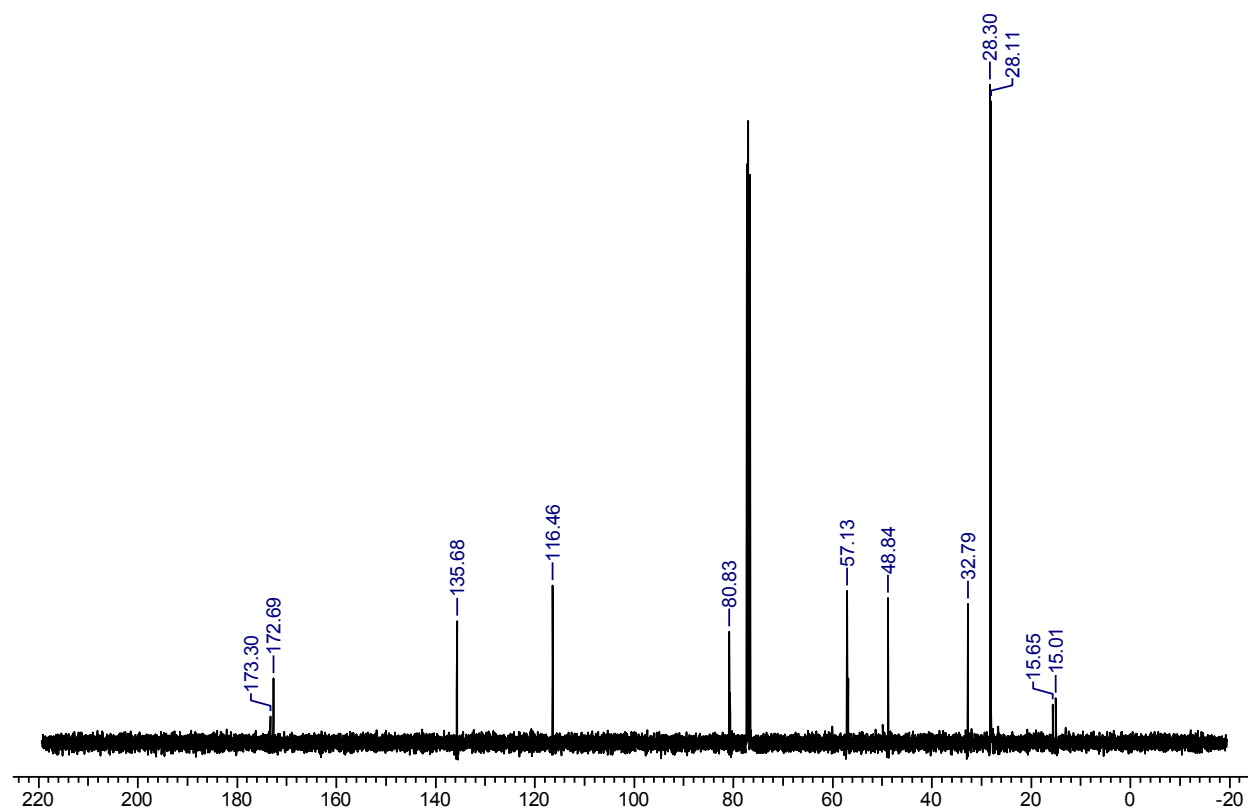
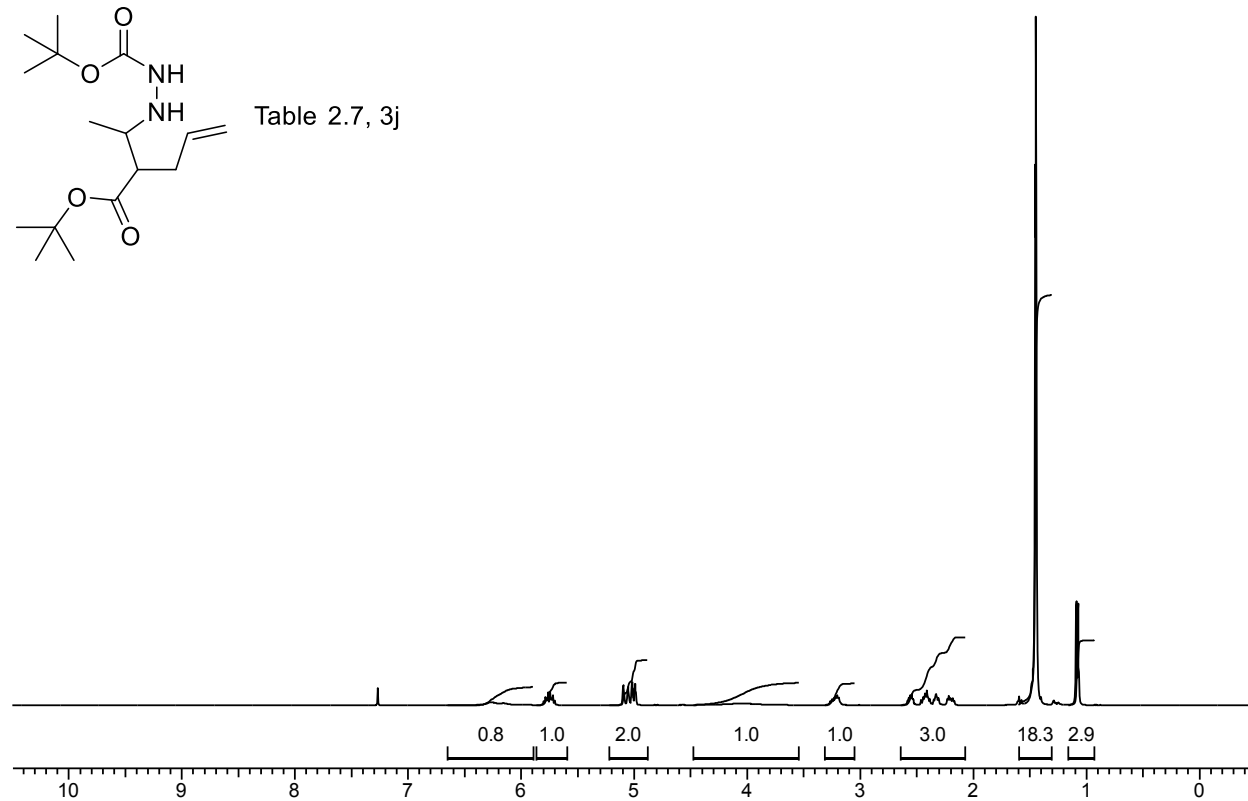
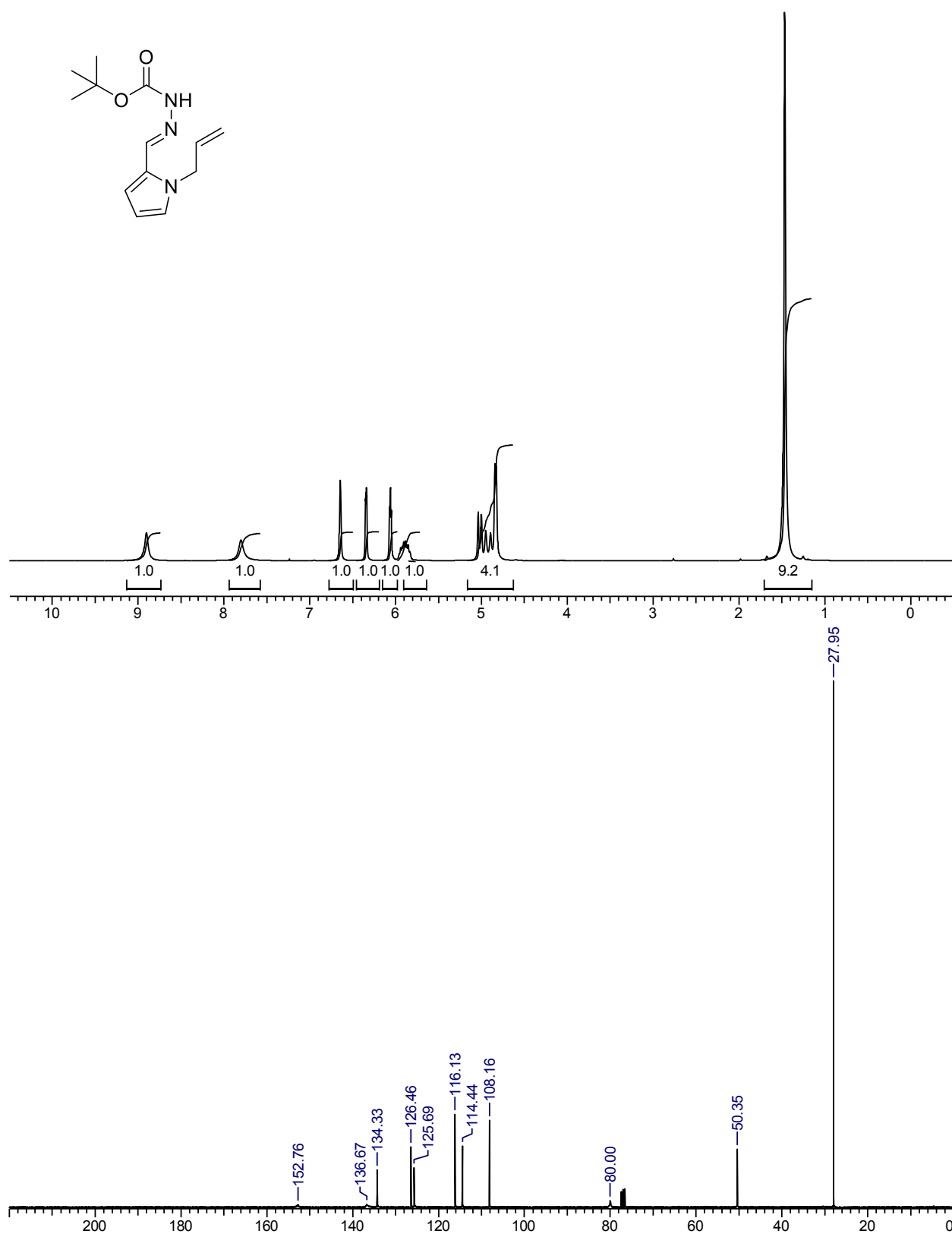
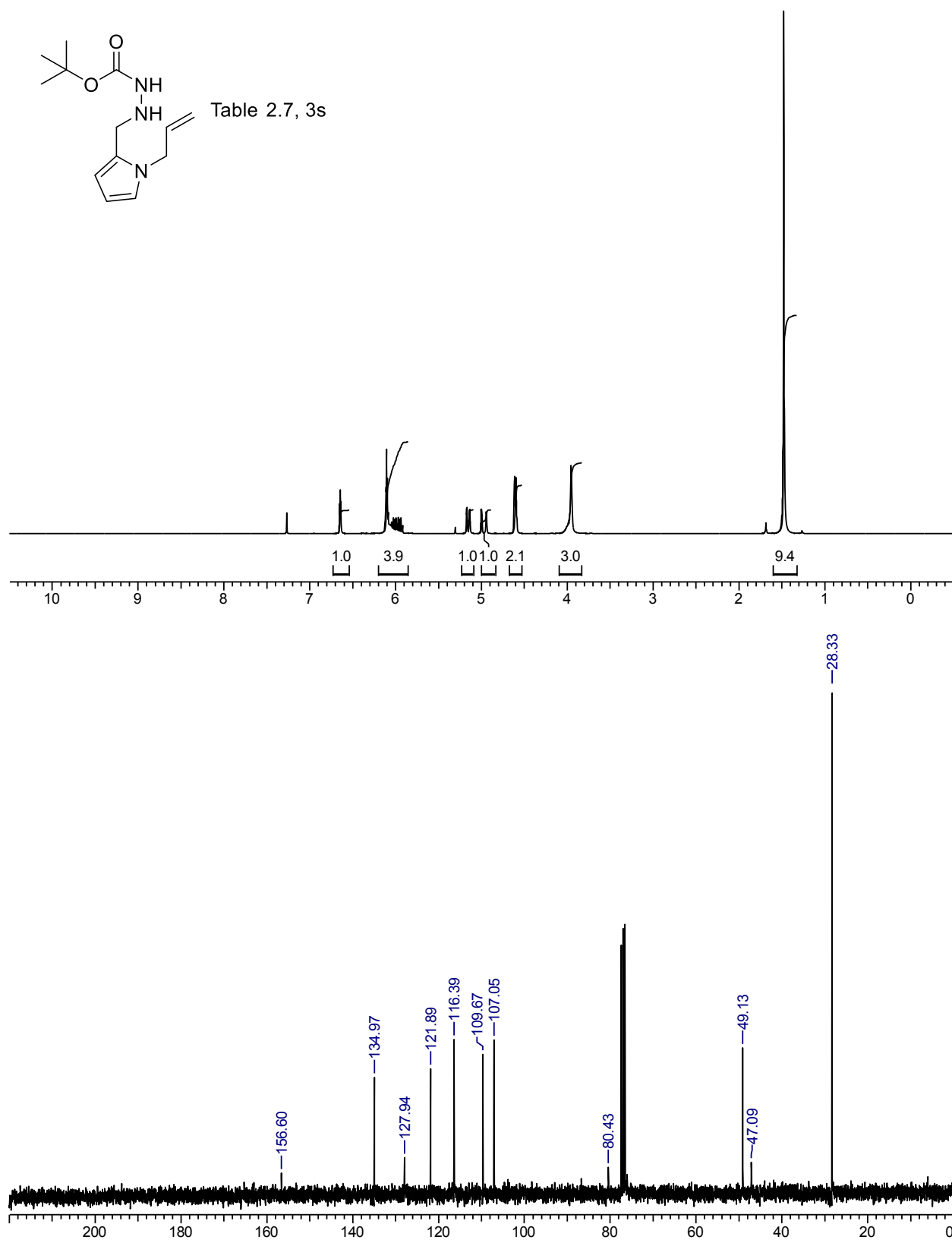


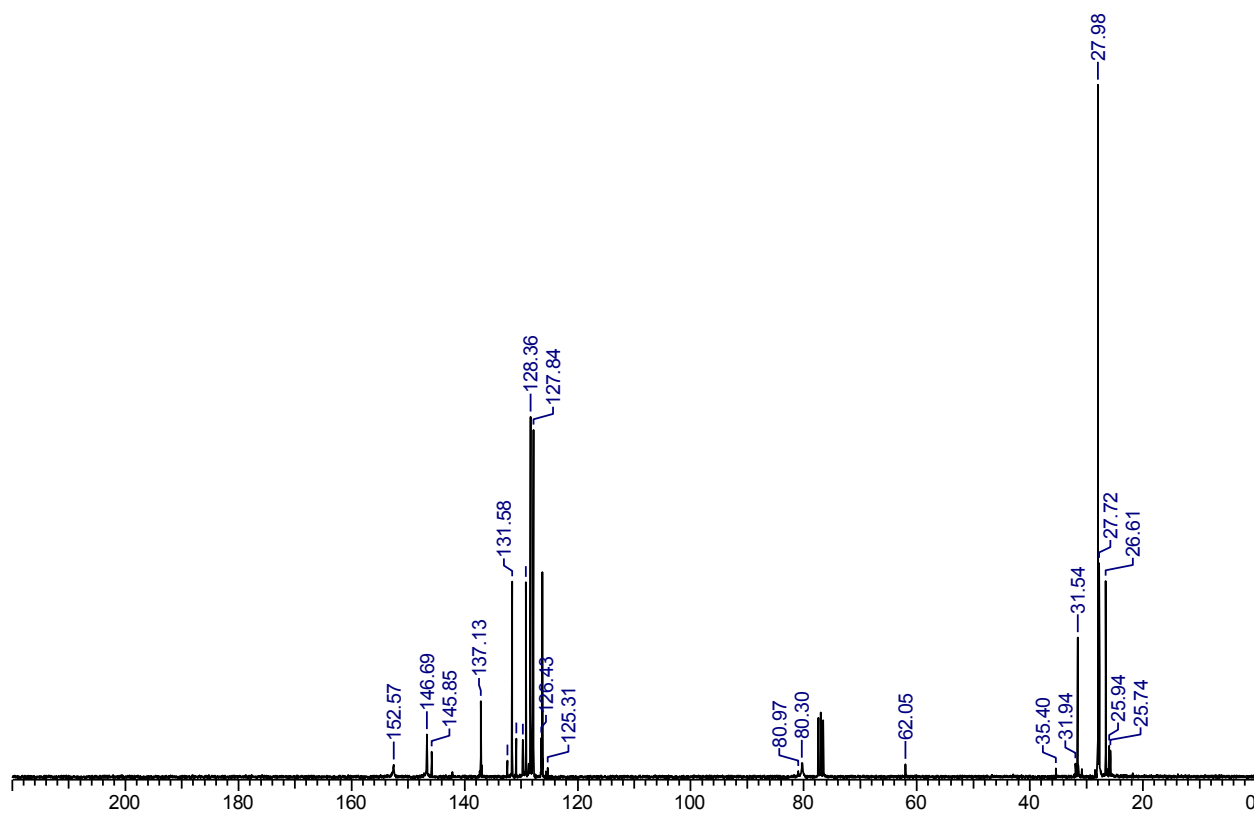
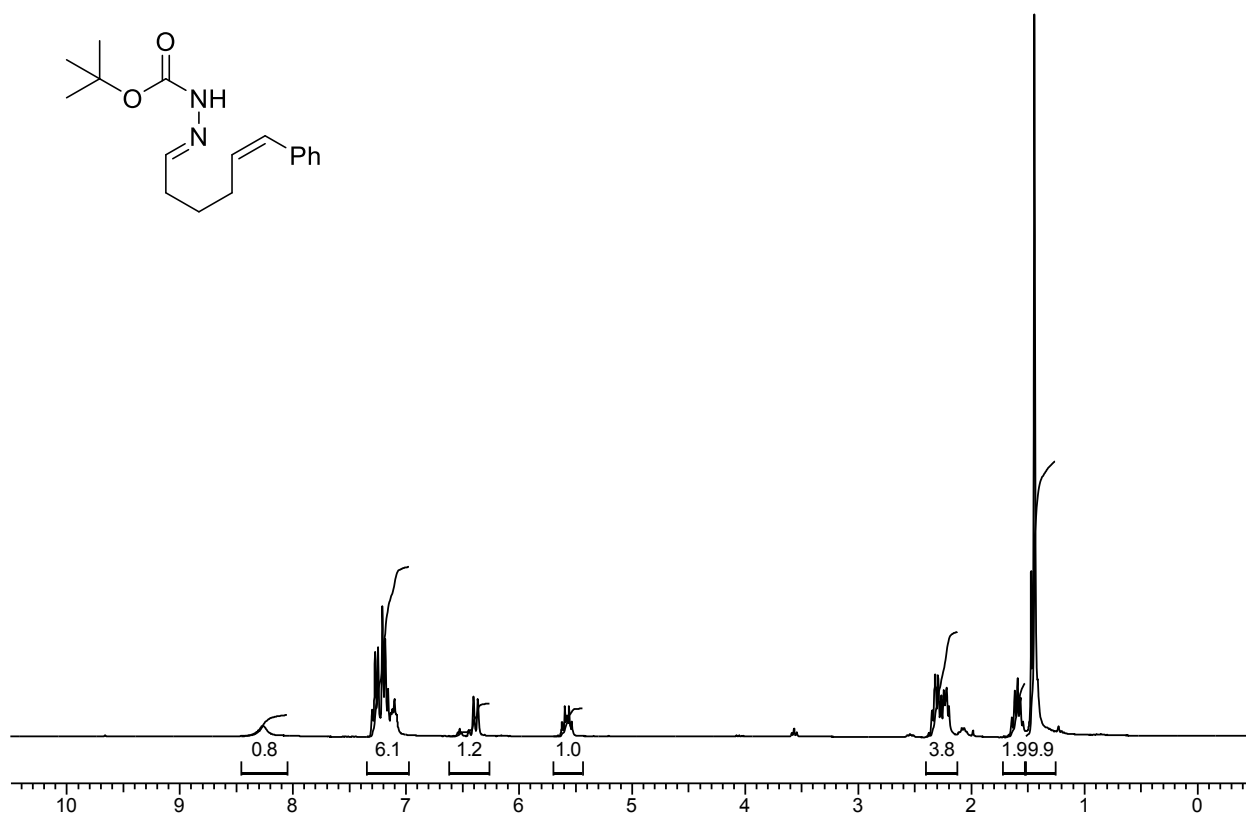
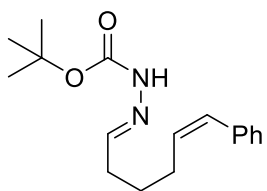
Table 2.7, 3j

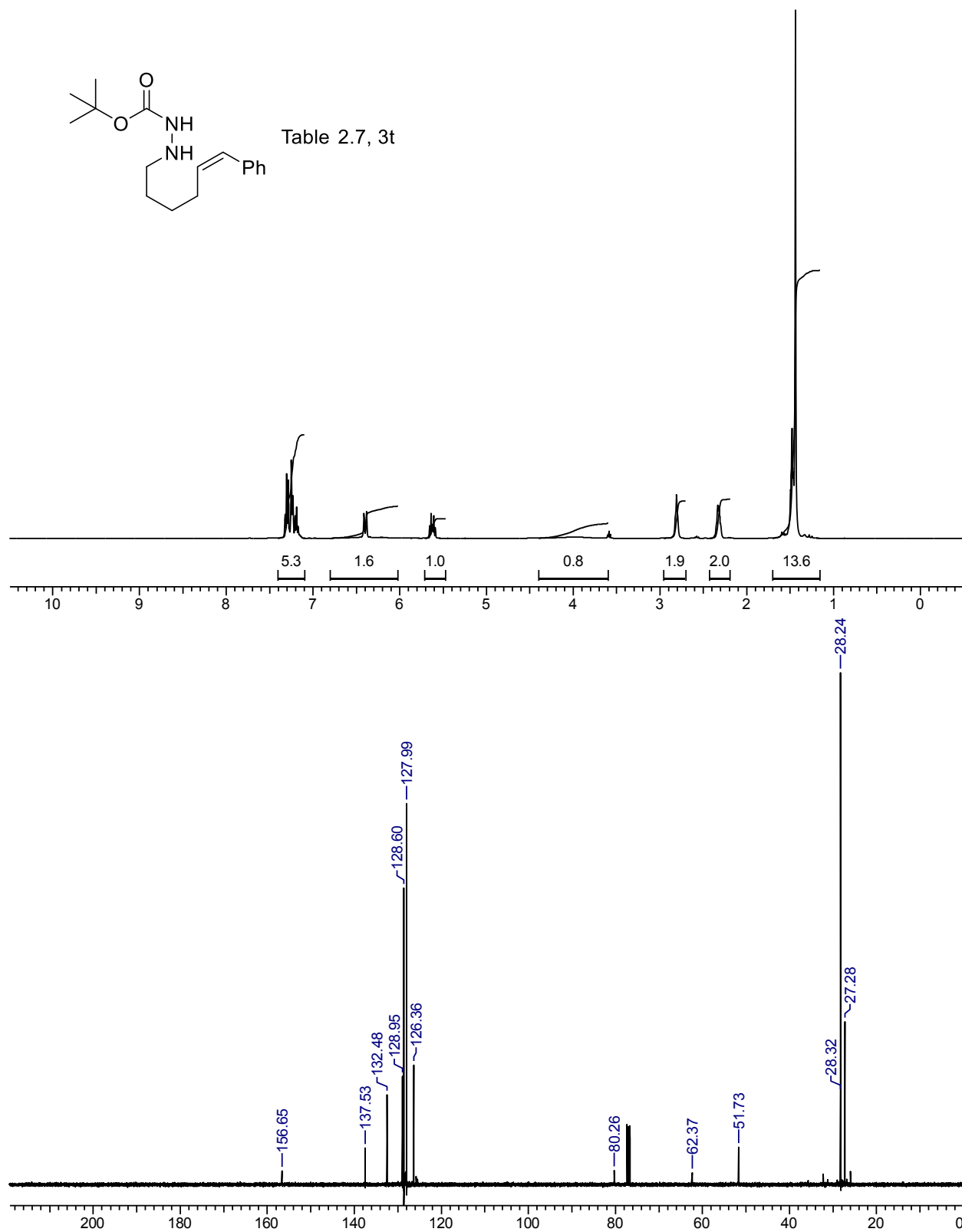


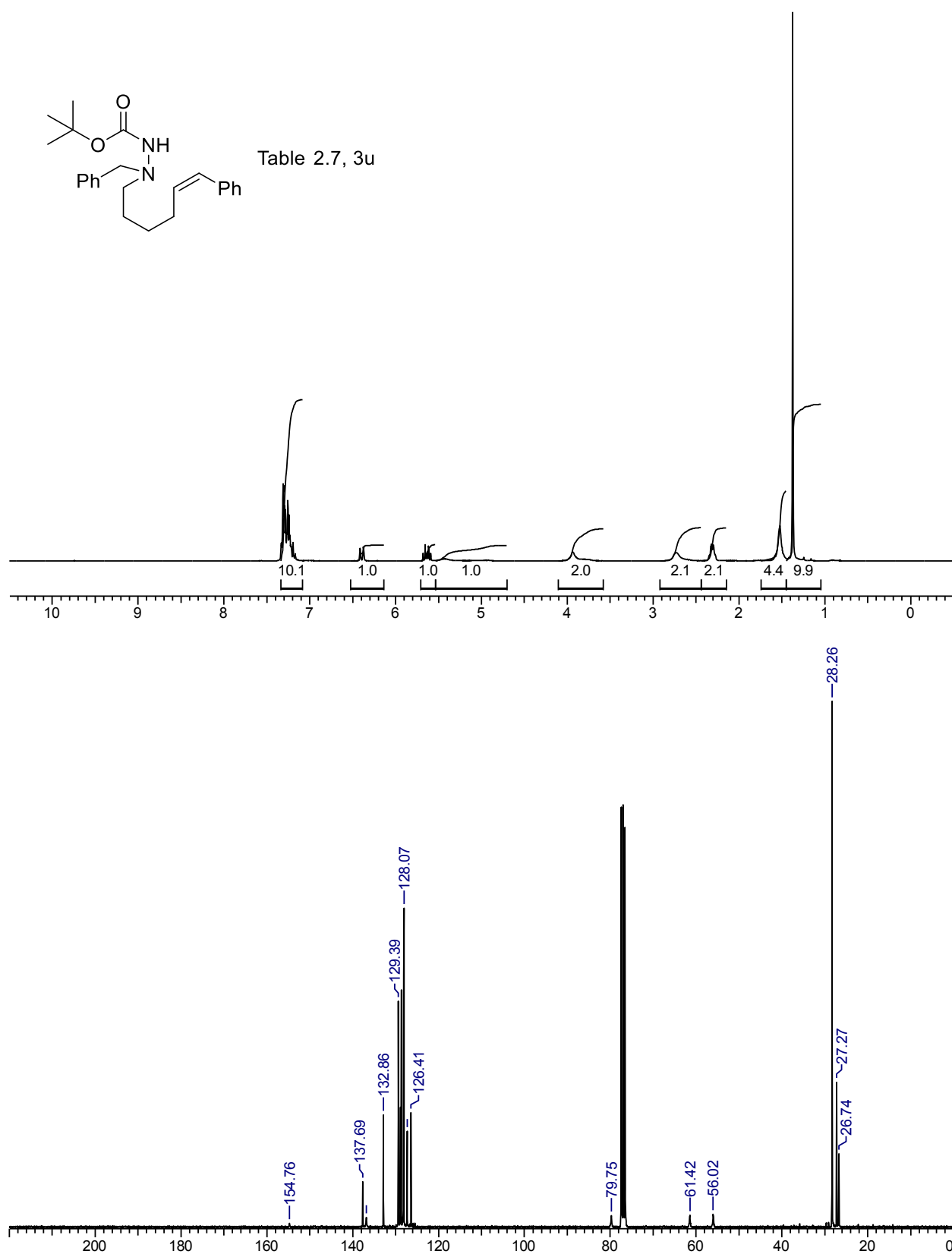


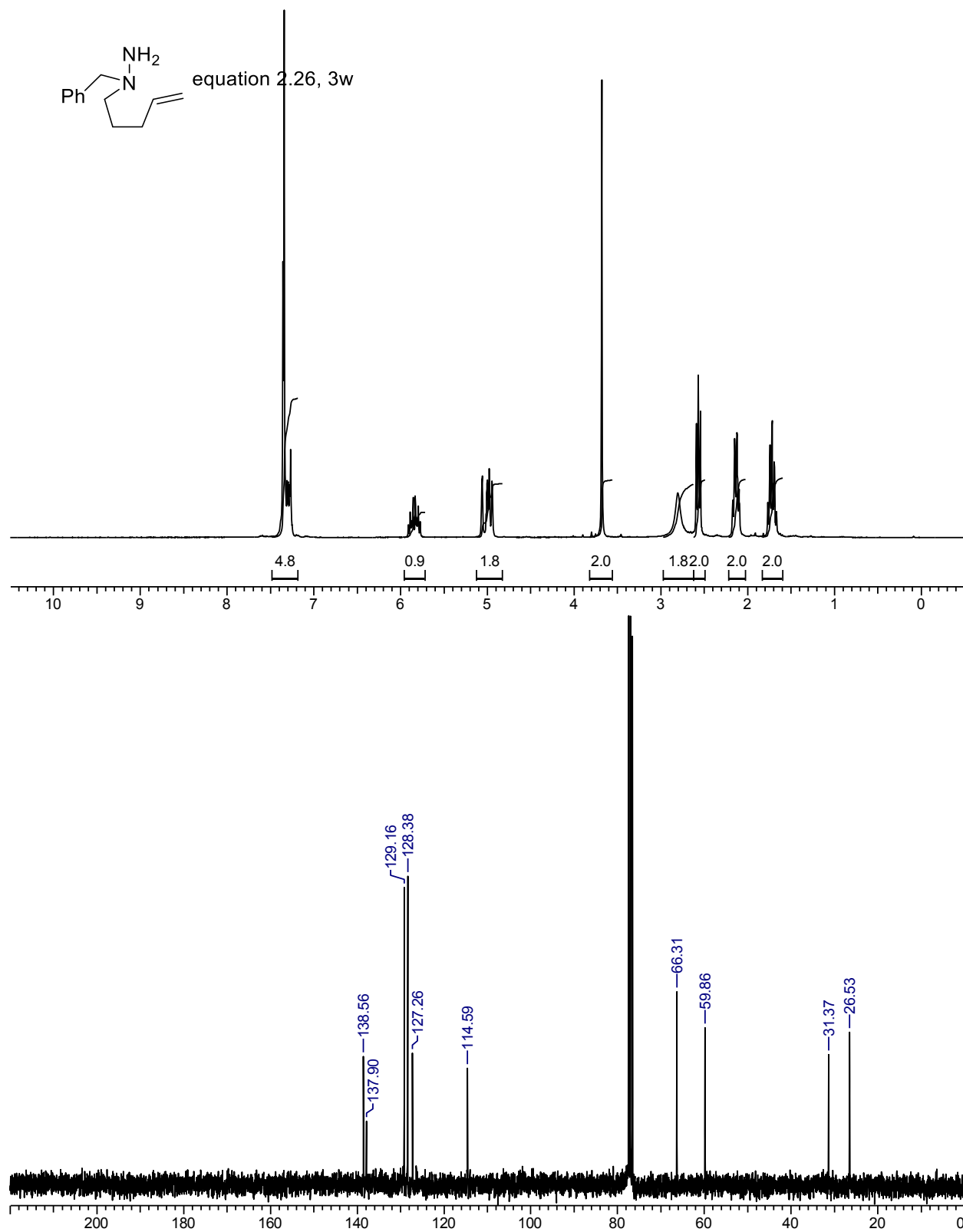


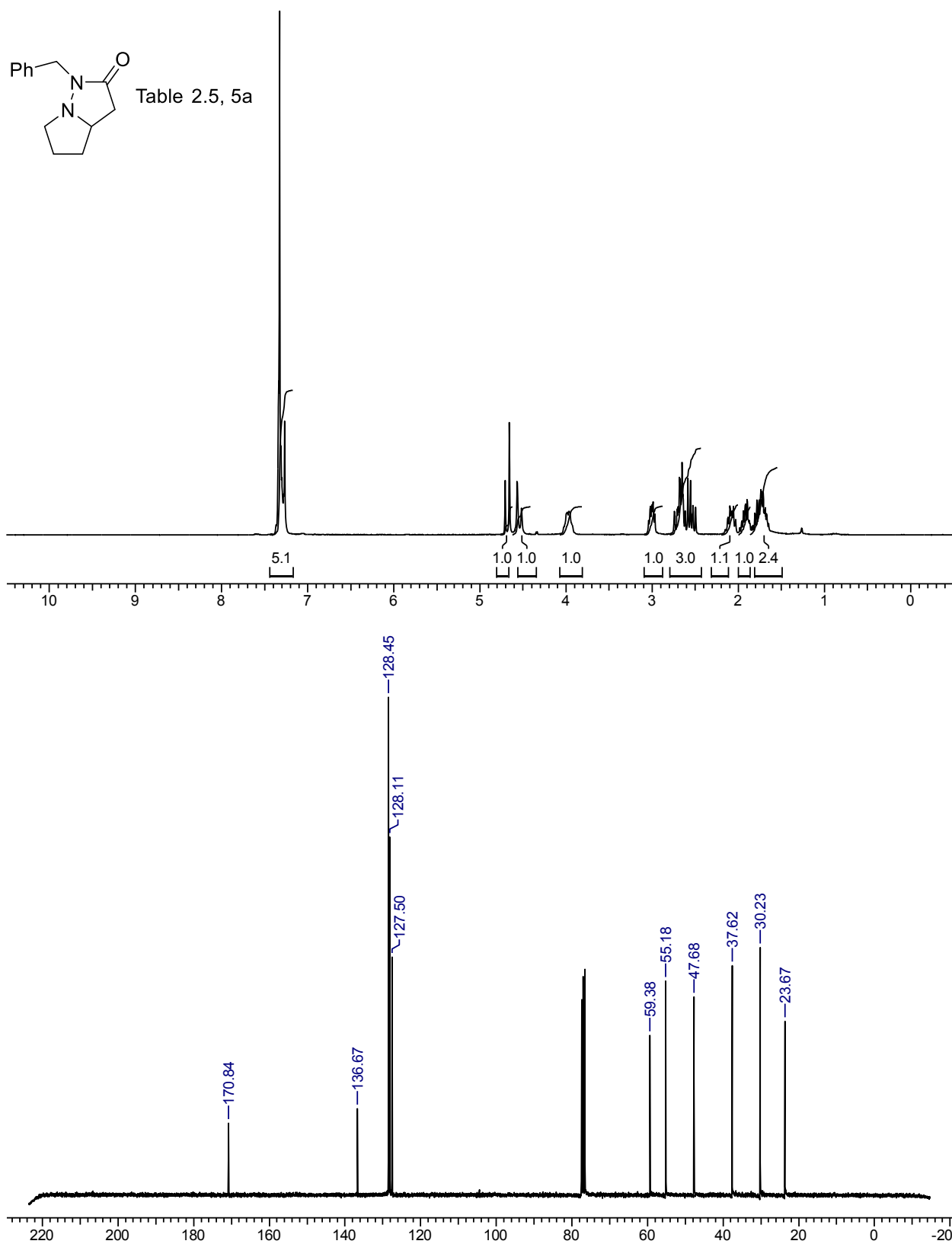


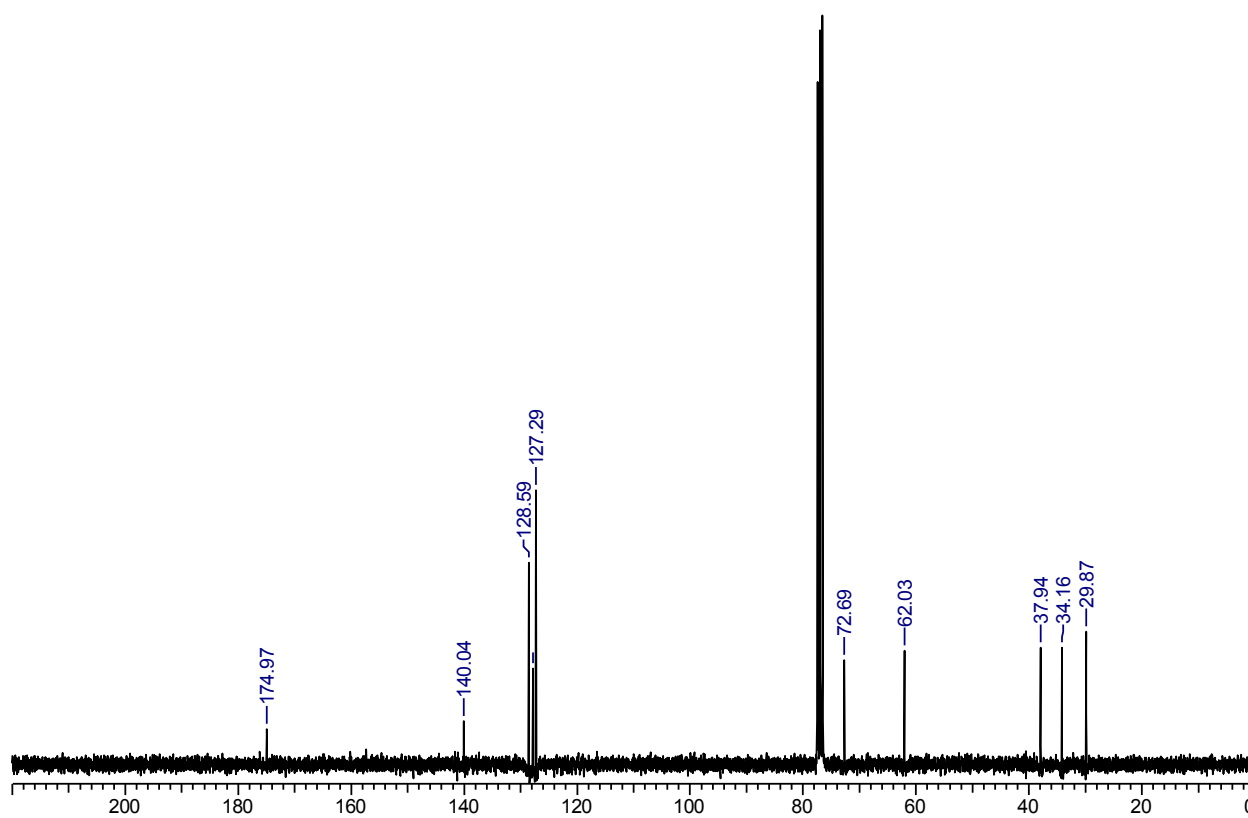
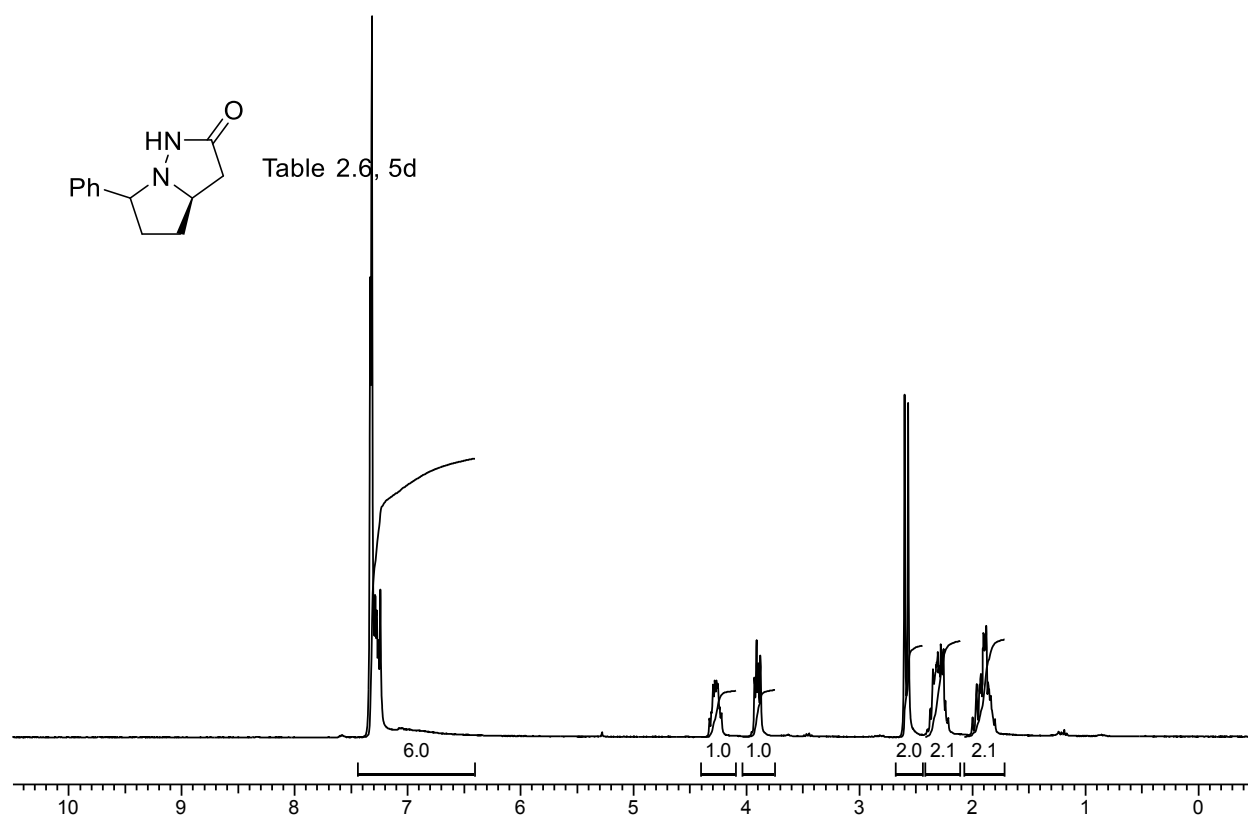


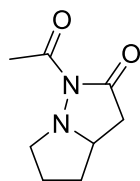




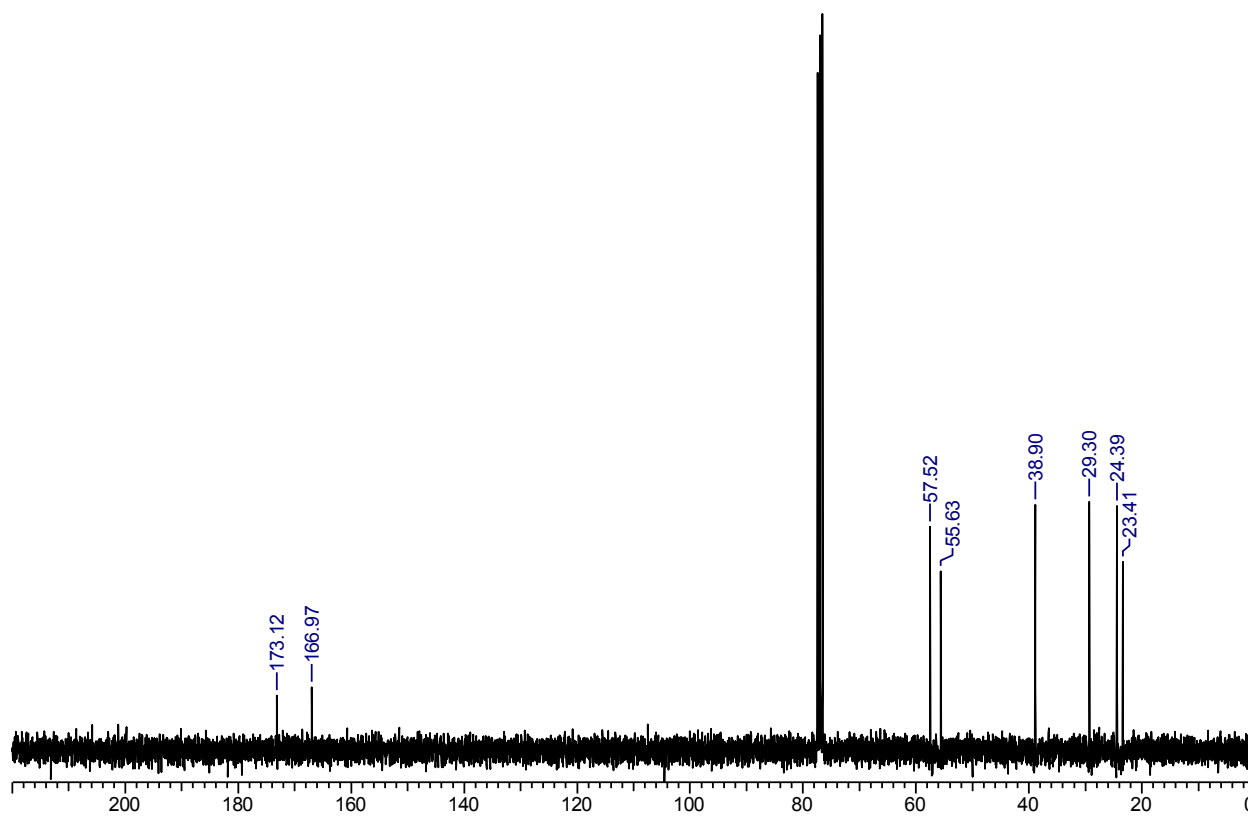
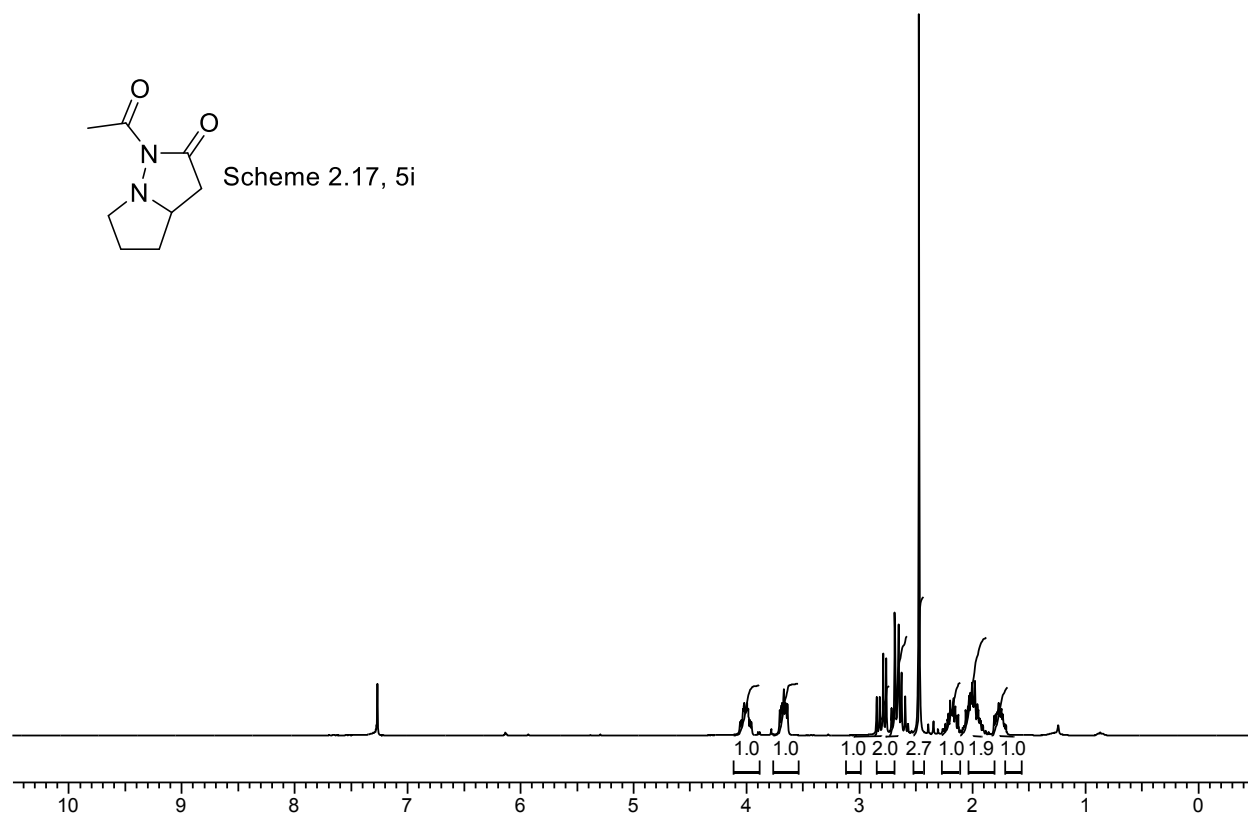


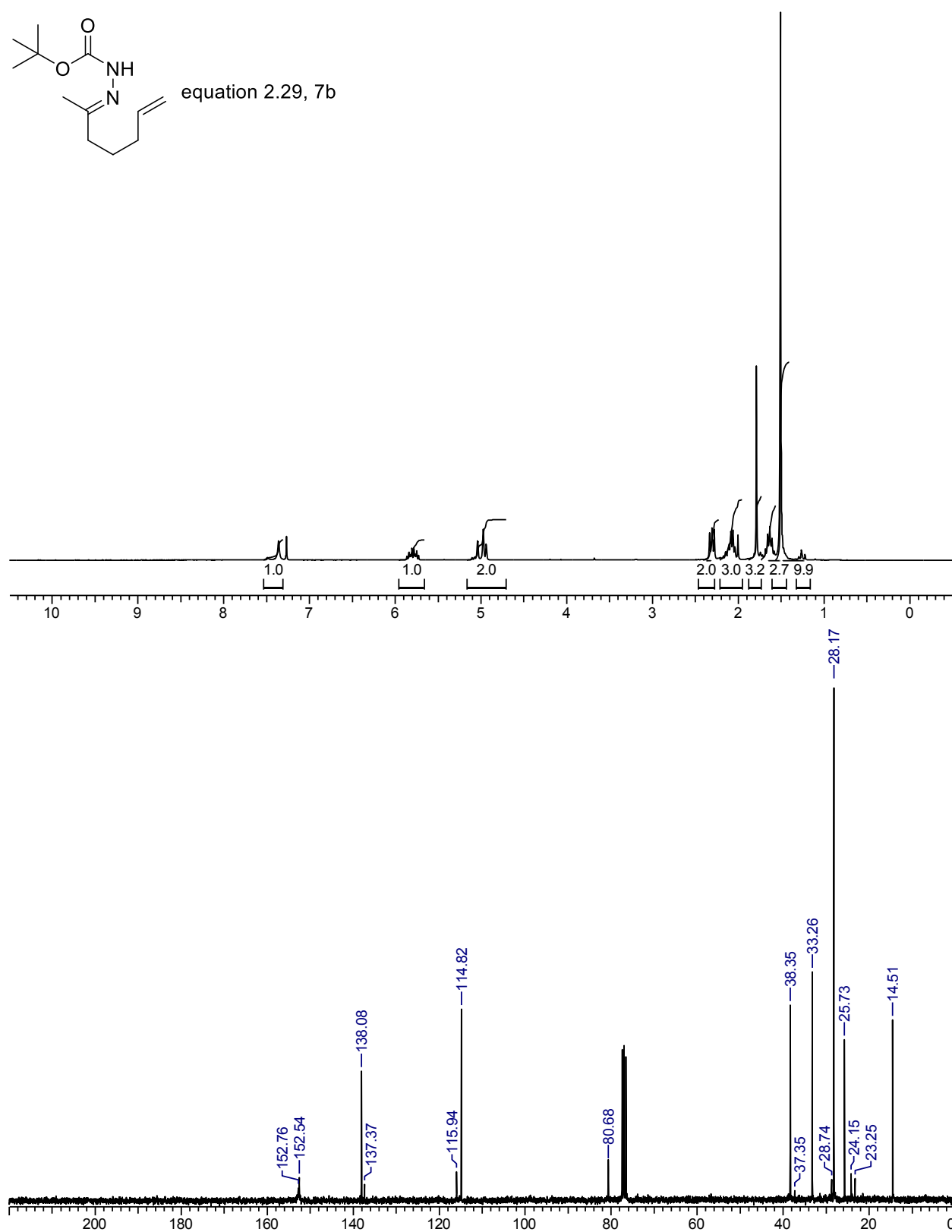
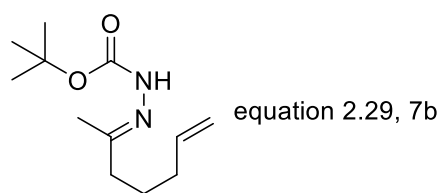




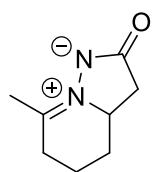


Scheme 2.17, 5i

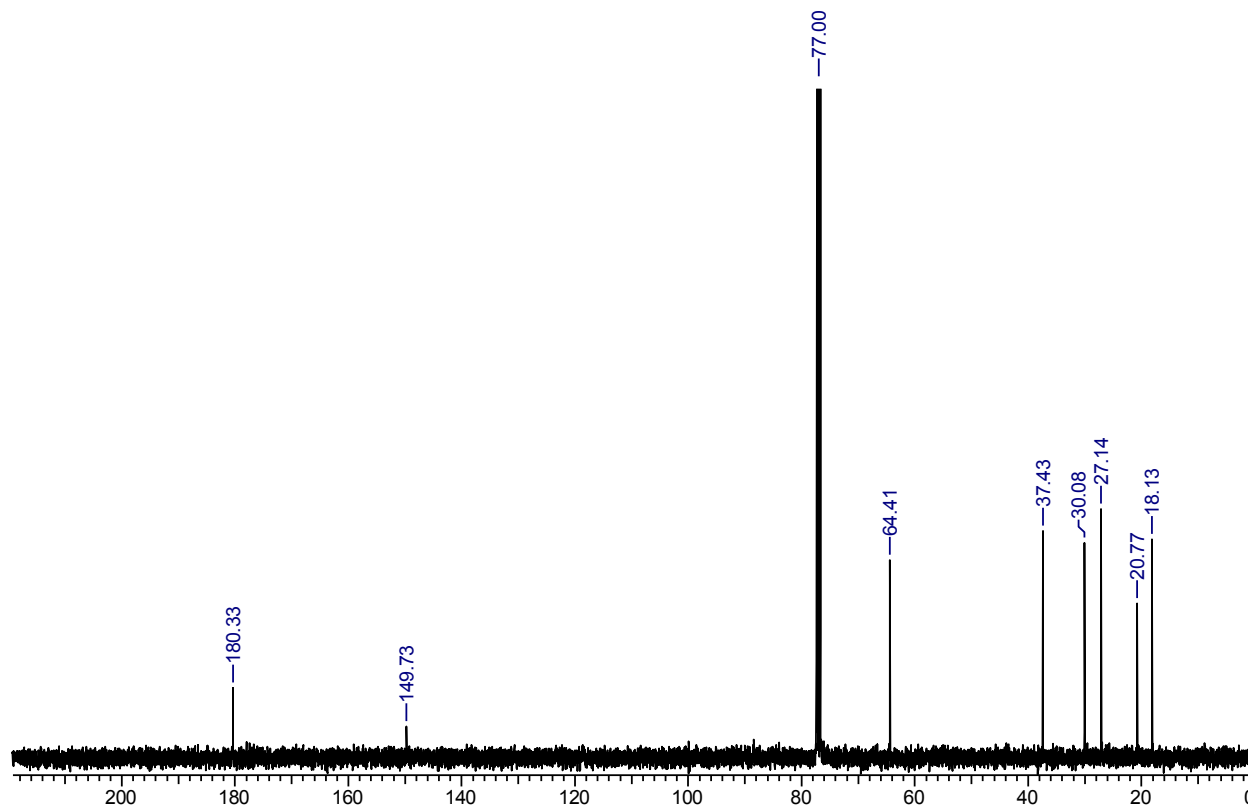
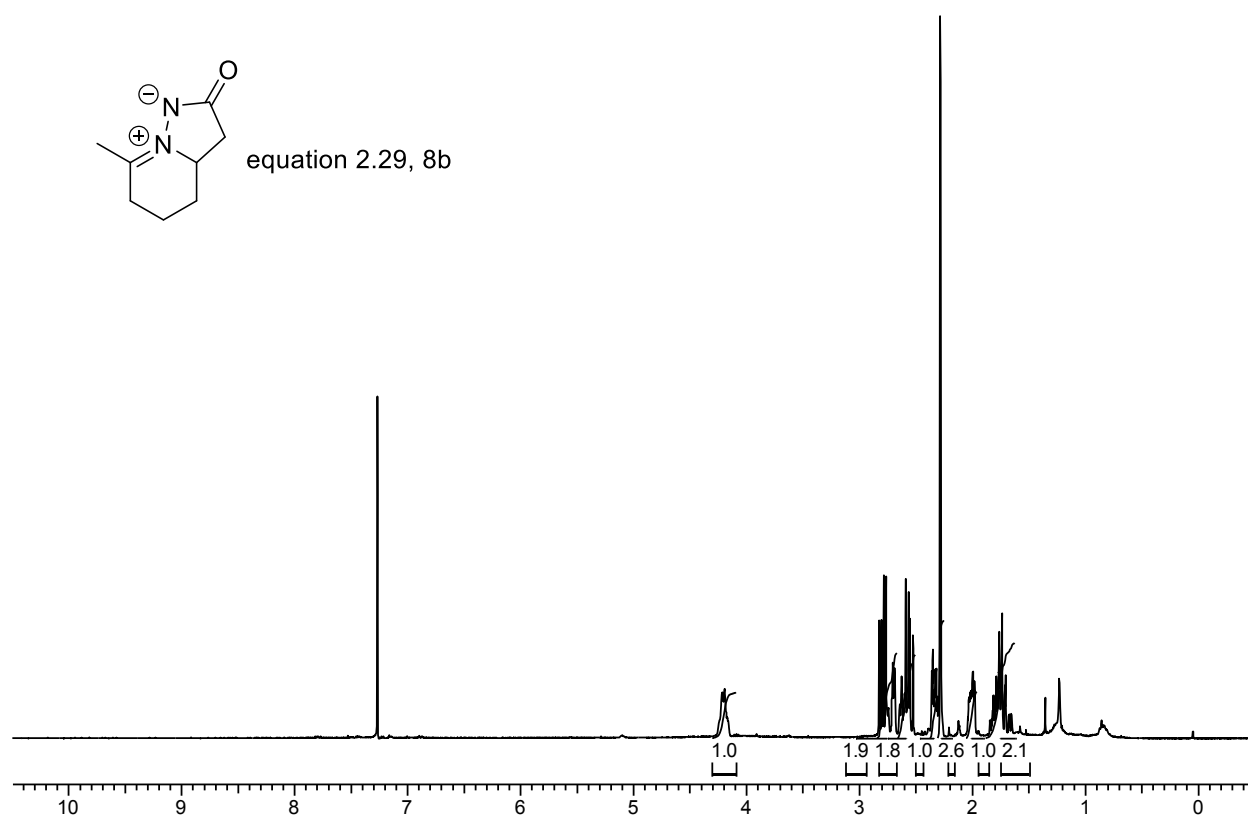


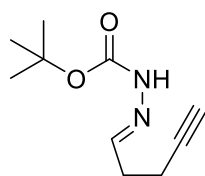




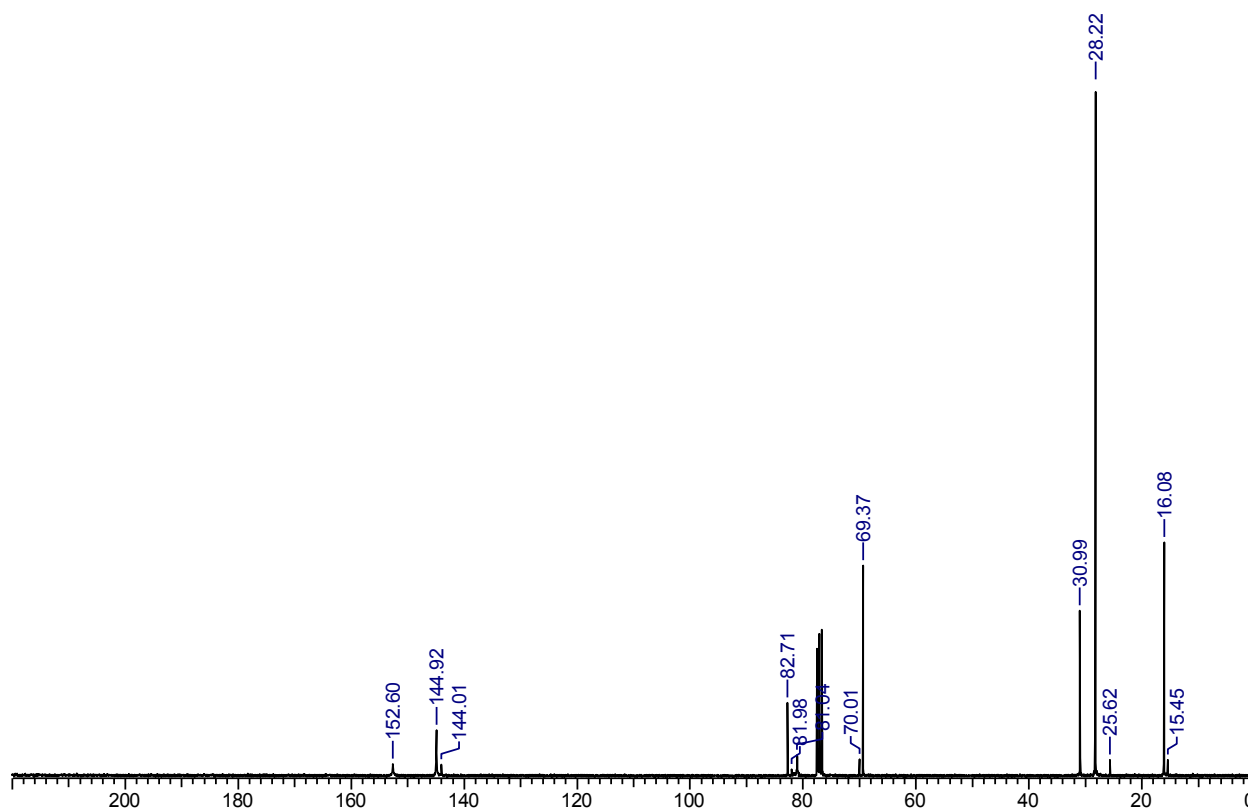
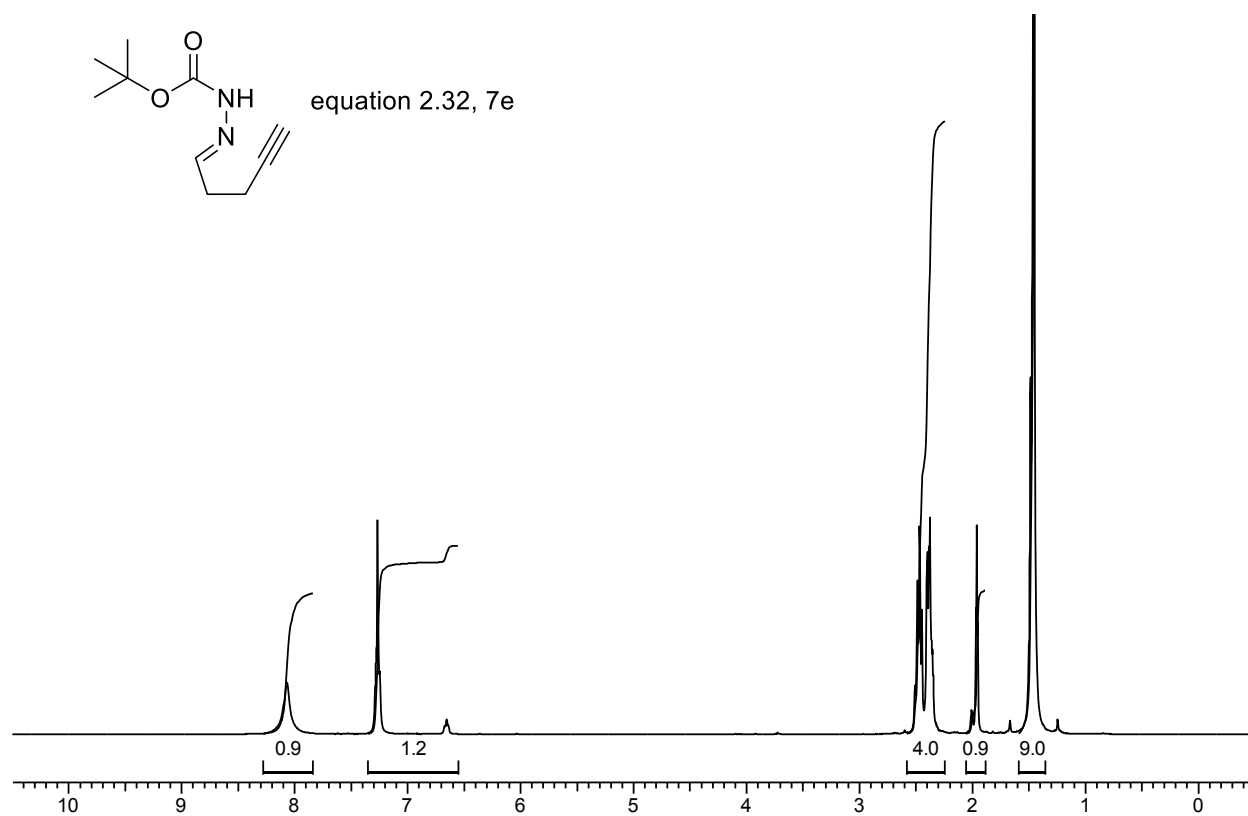


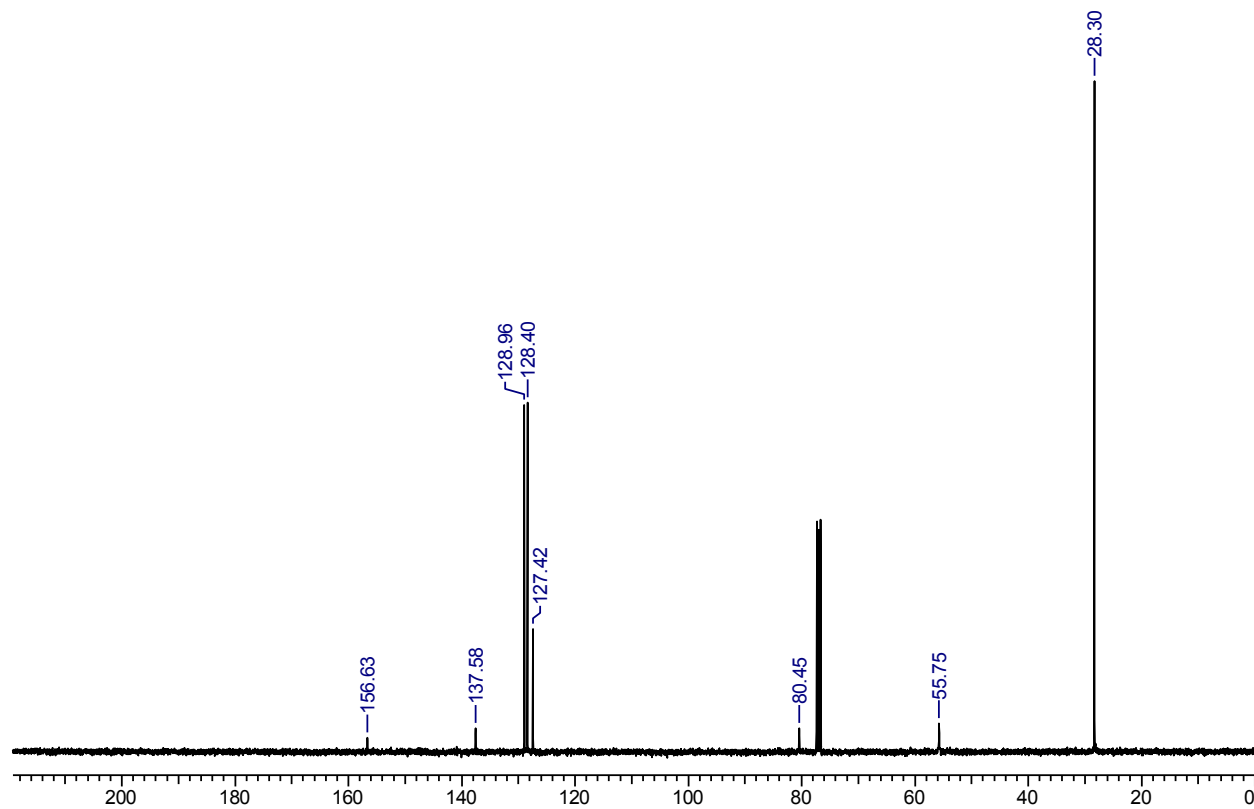
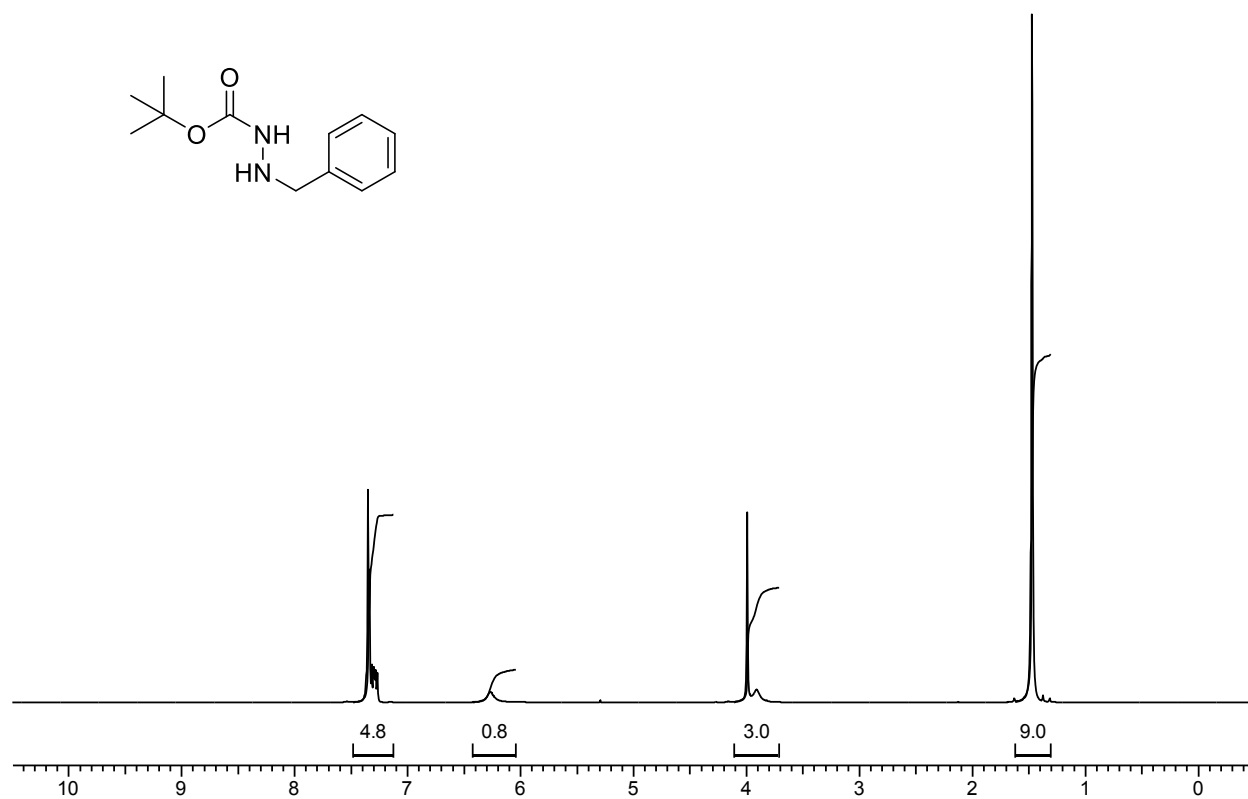
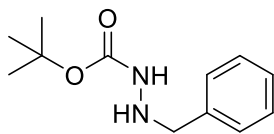
equation 2.29, 8b





equation 2.32, 7e





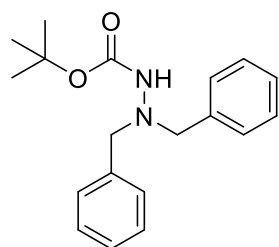
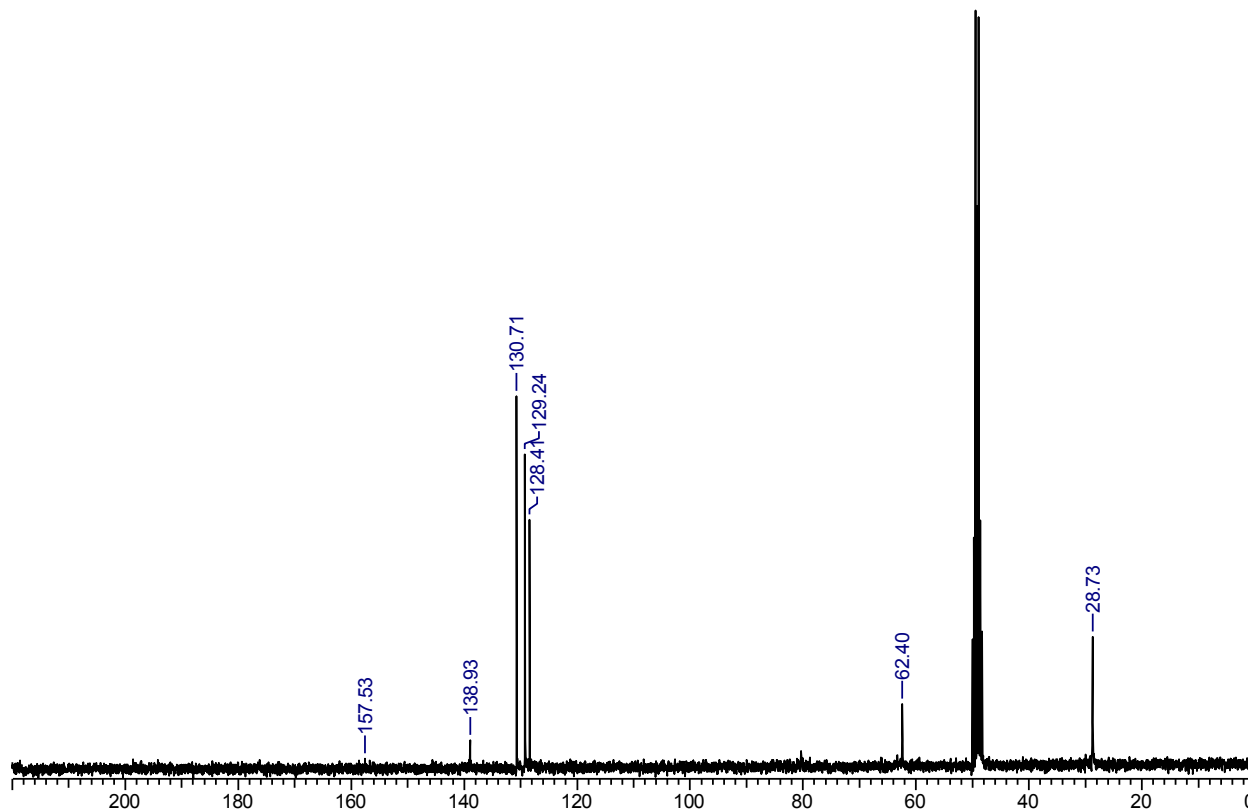
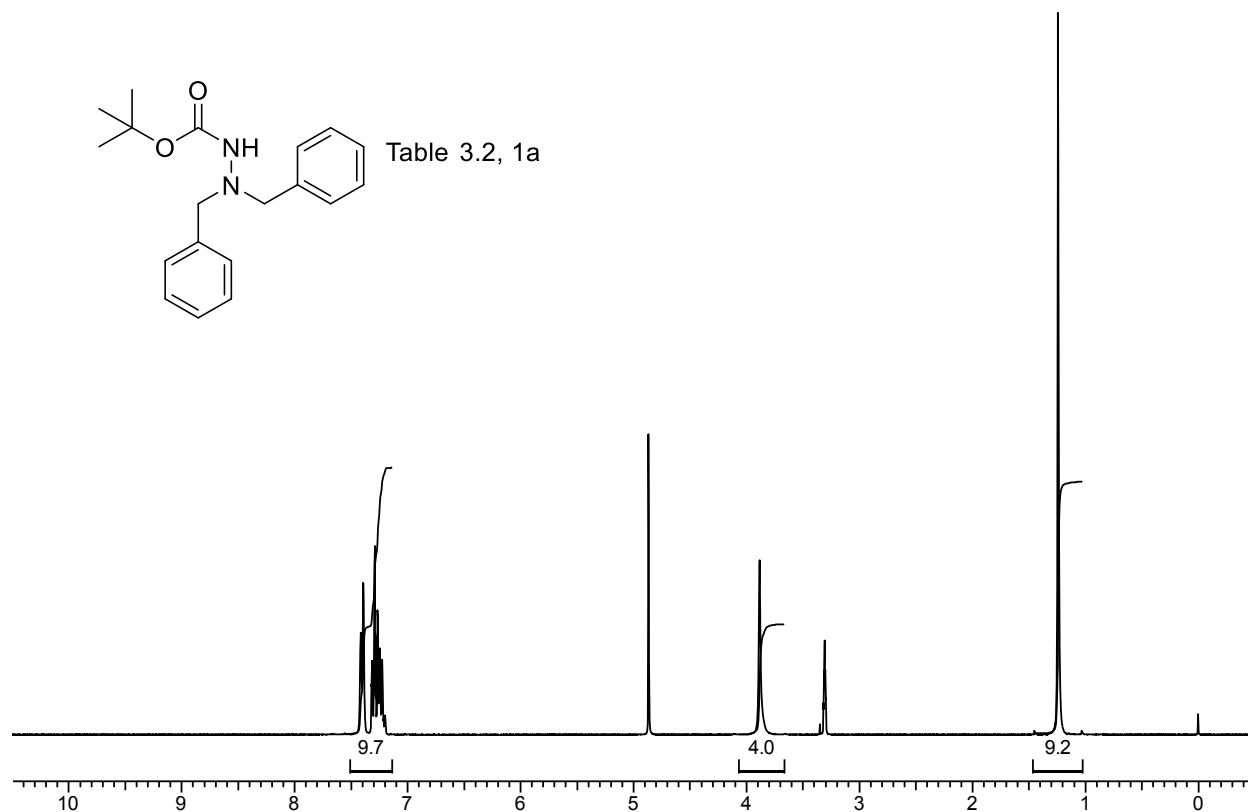
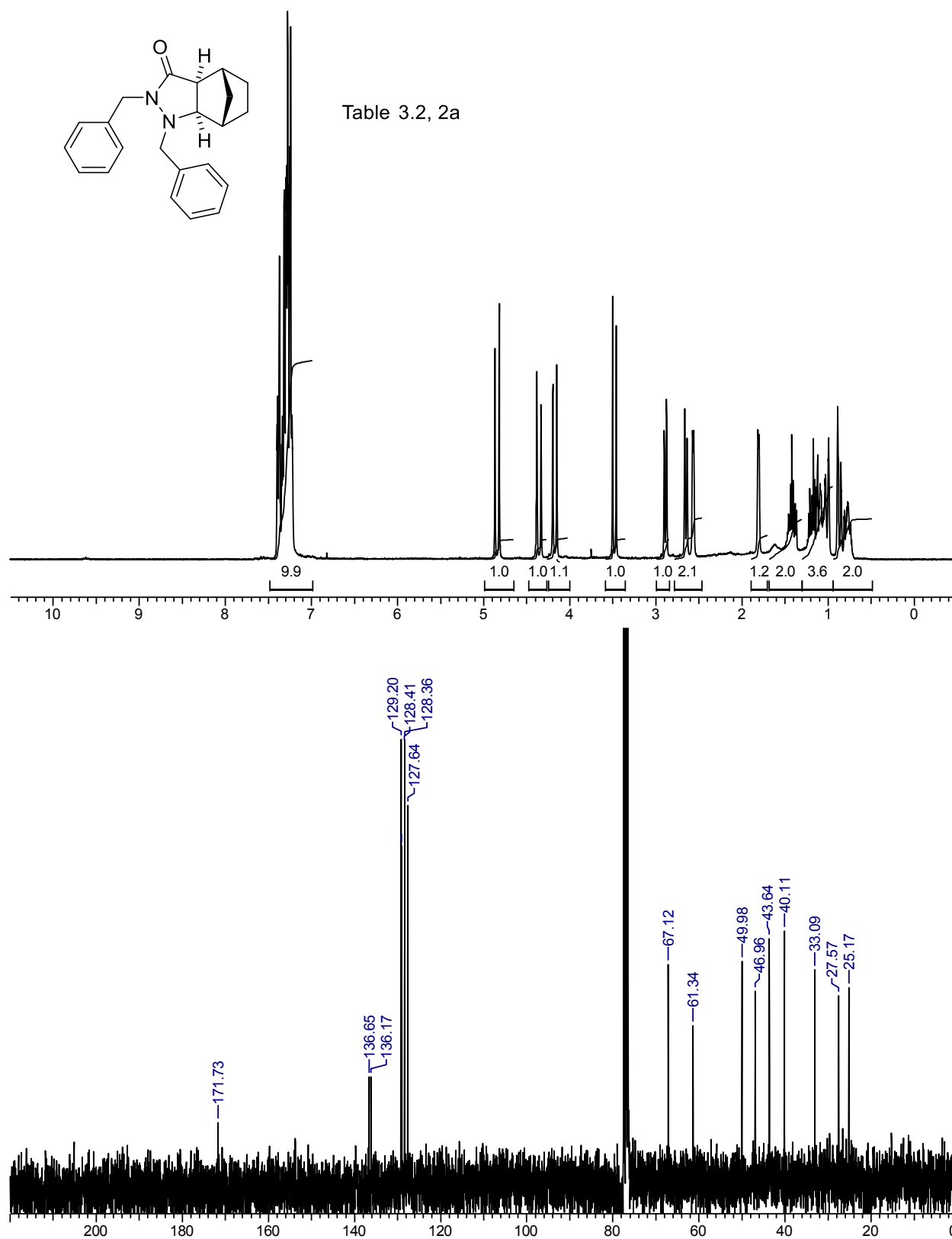


Table 3.2, 1a





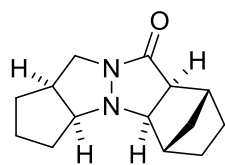
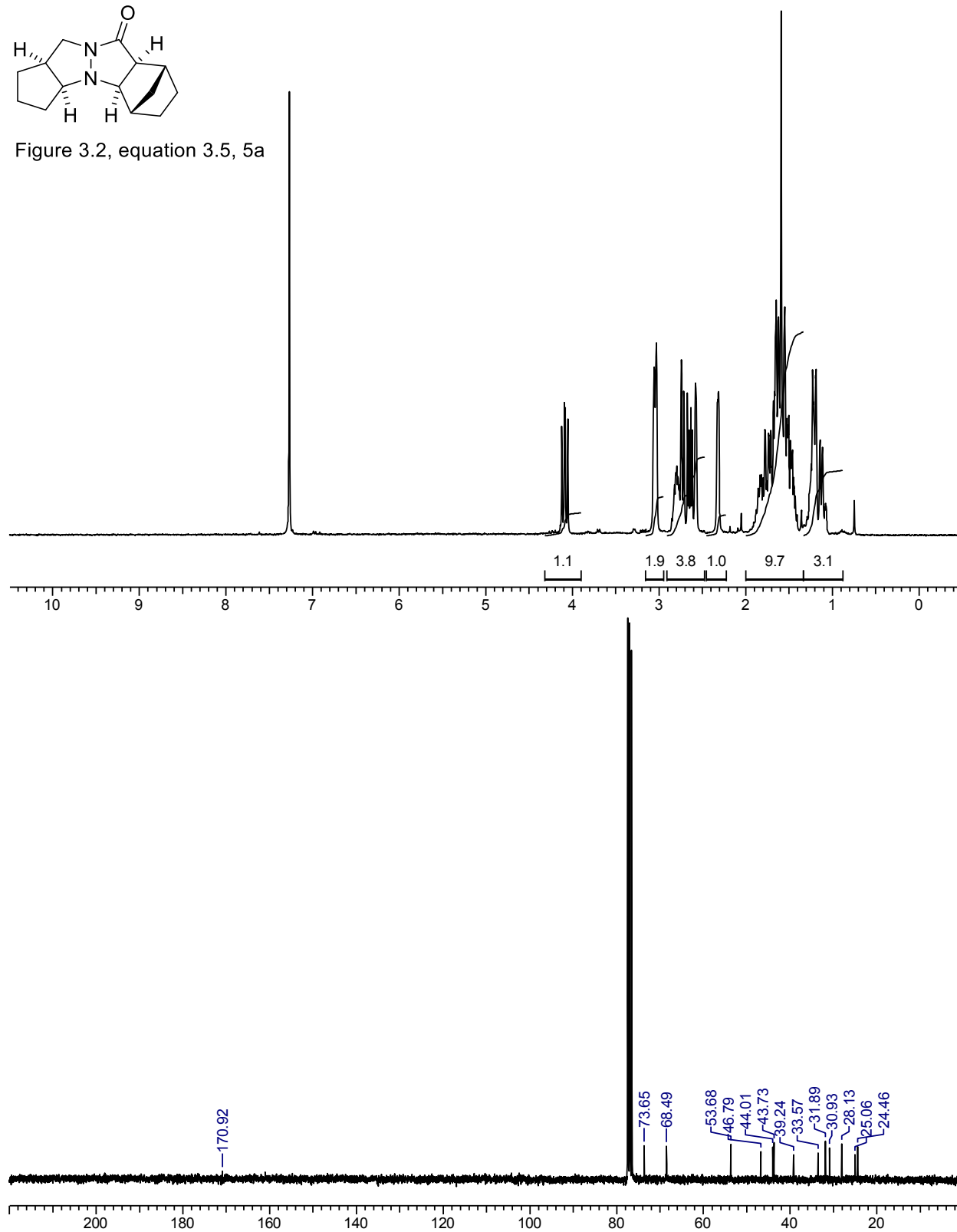
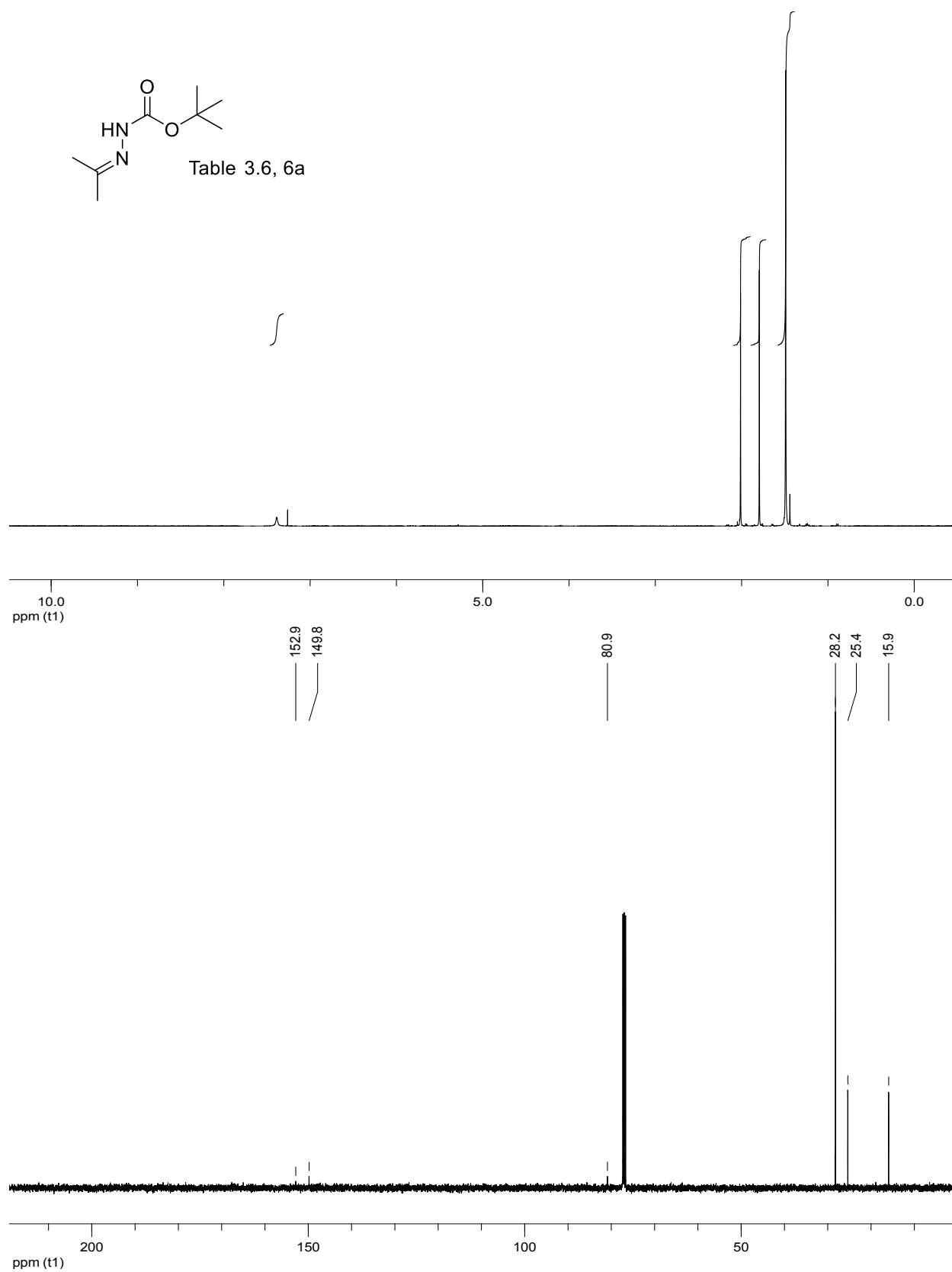


Figure 3.2, equation 3.5, 5a





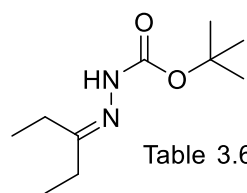
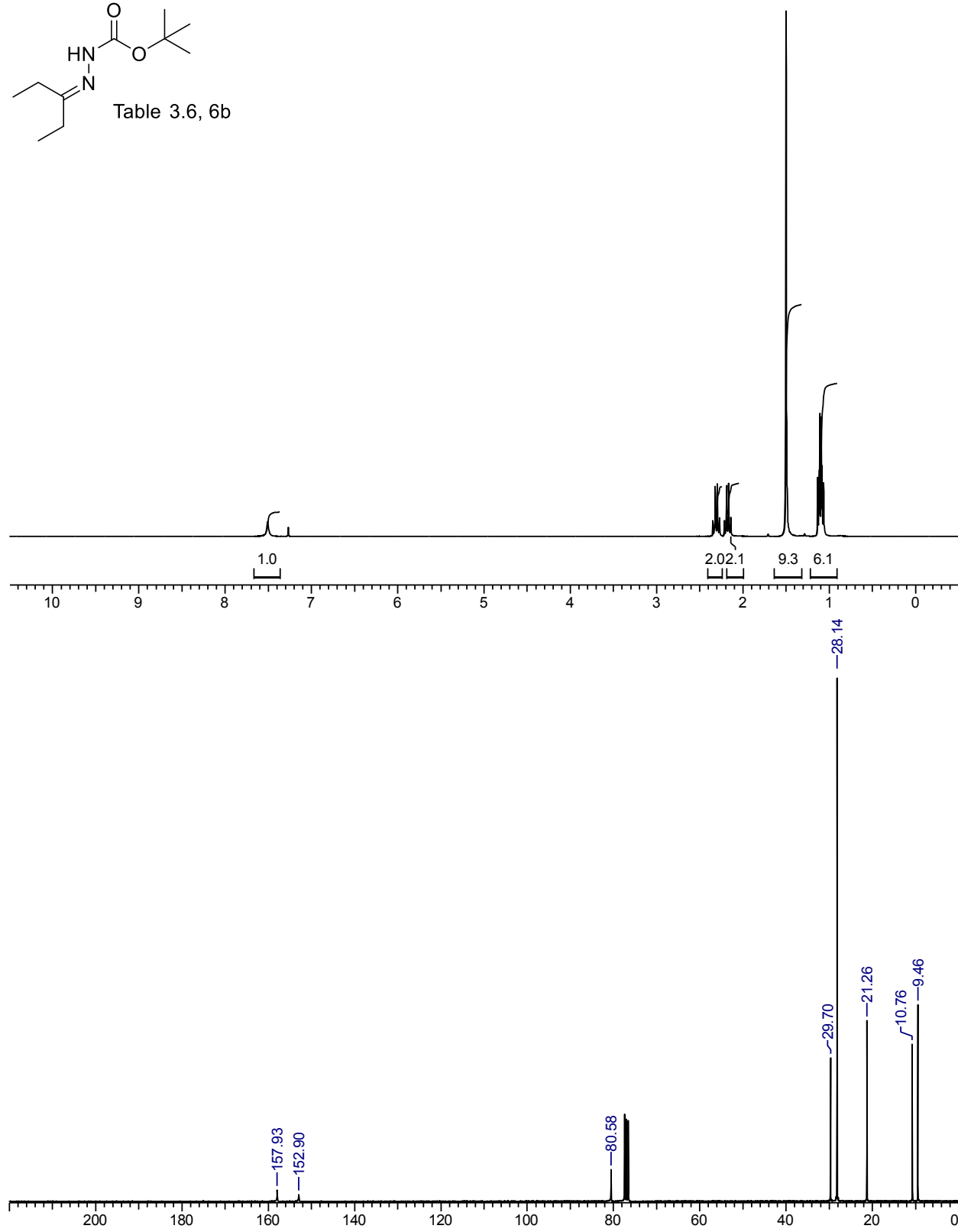


Table 3.6, 6b





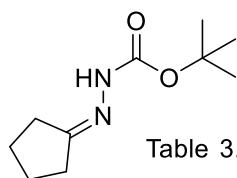
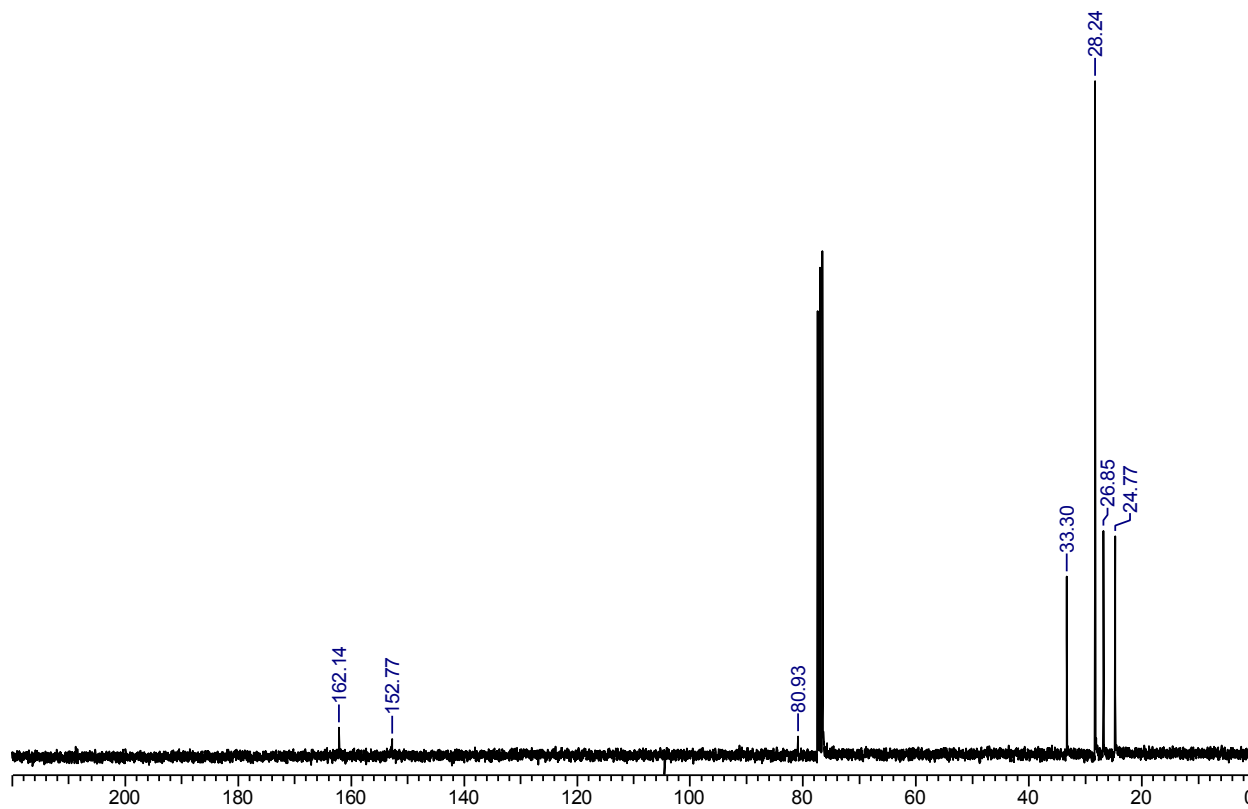
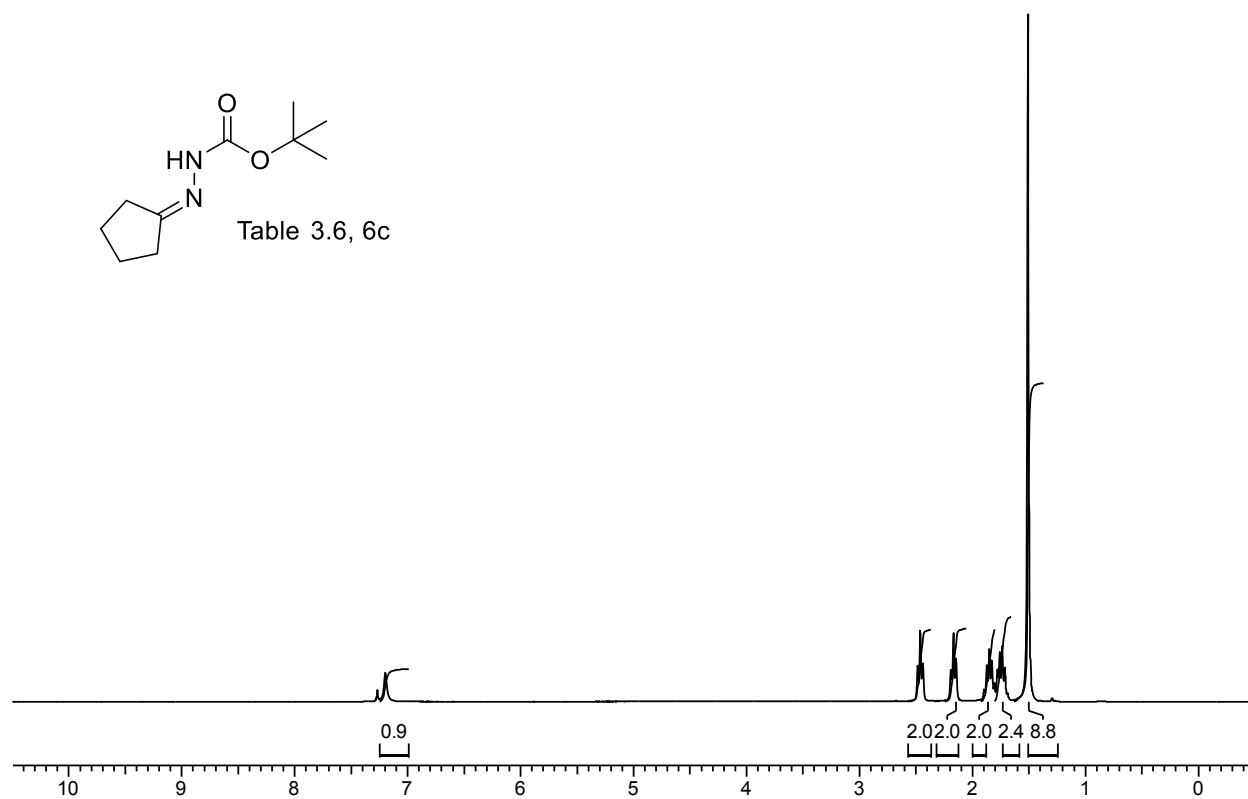


Table 3.6, 6c



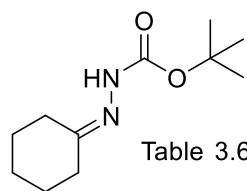
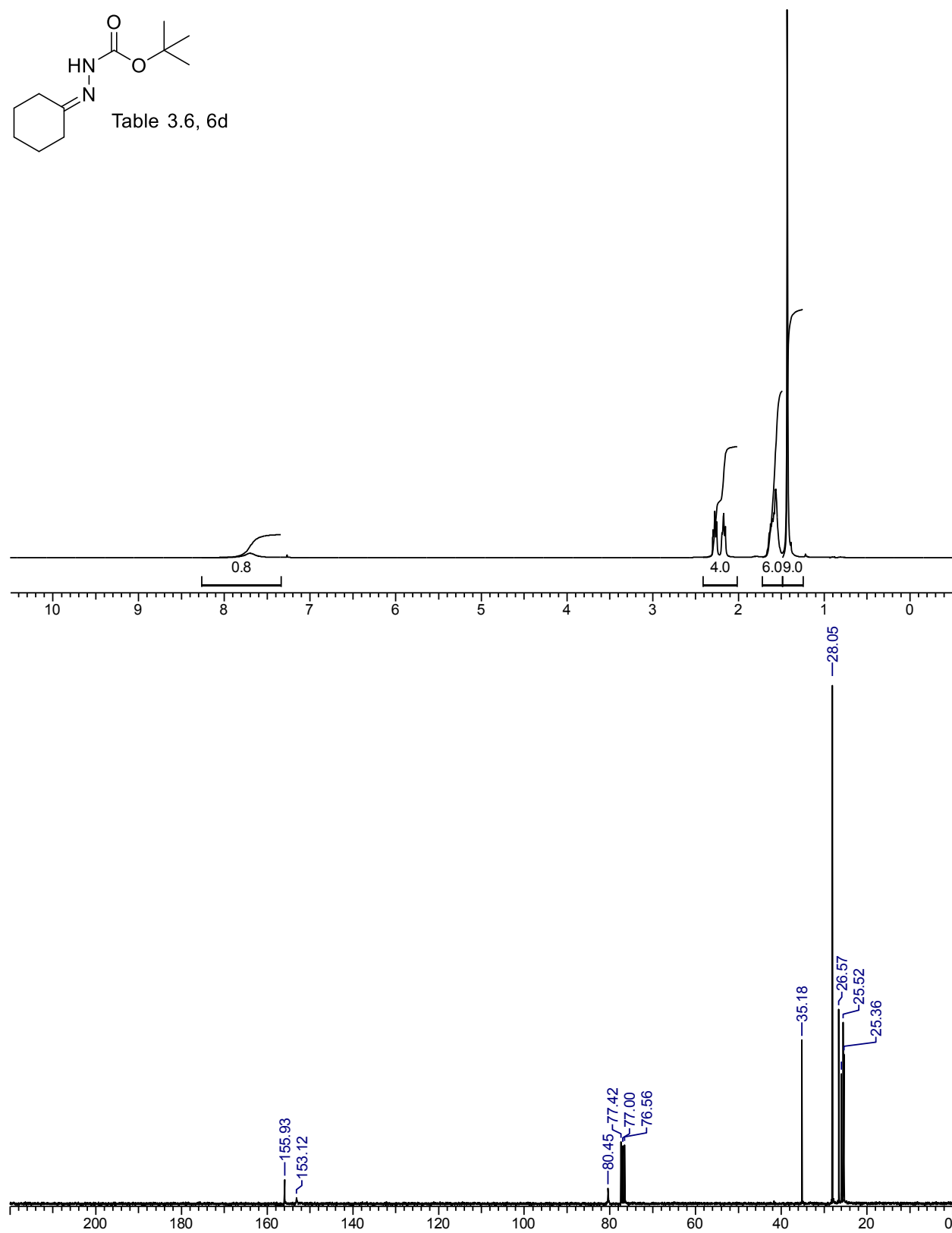


Table 3.6, 6d



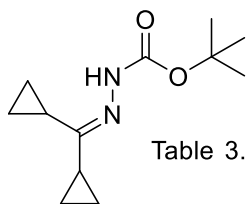
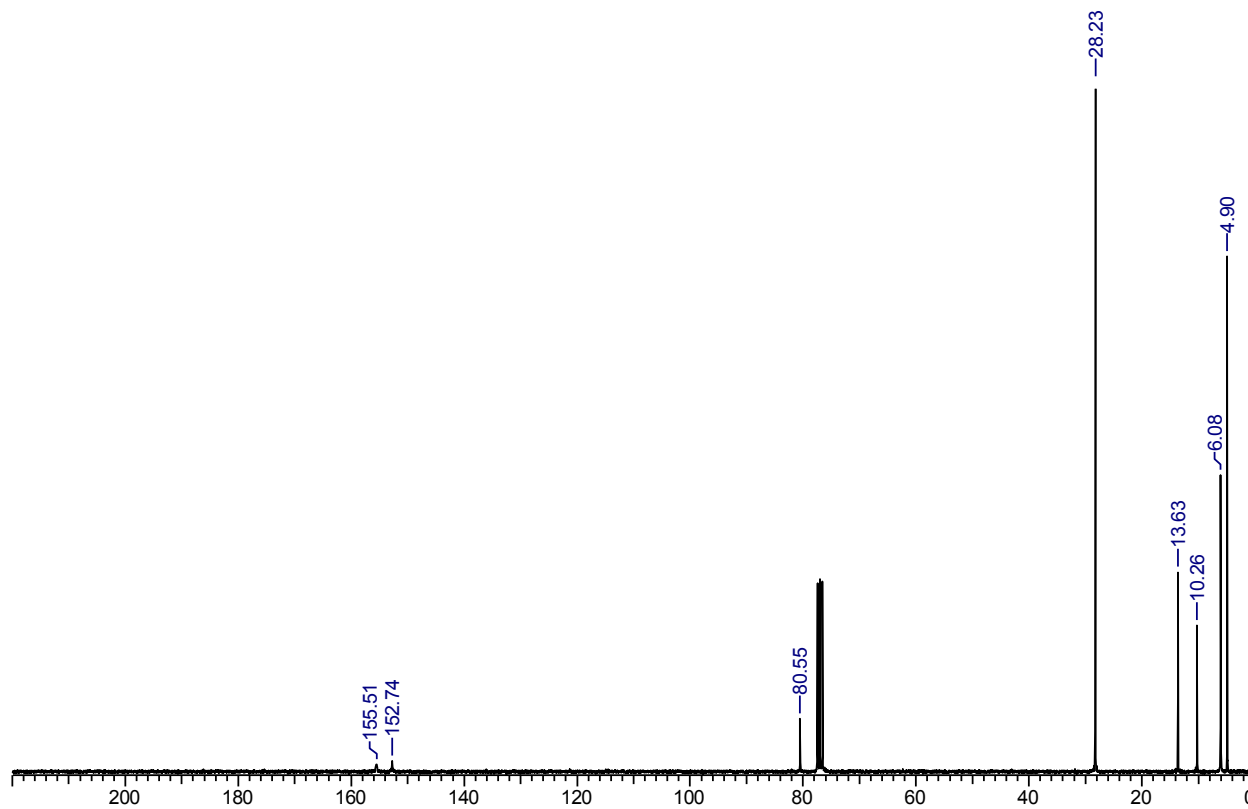
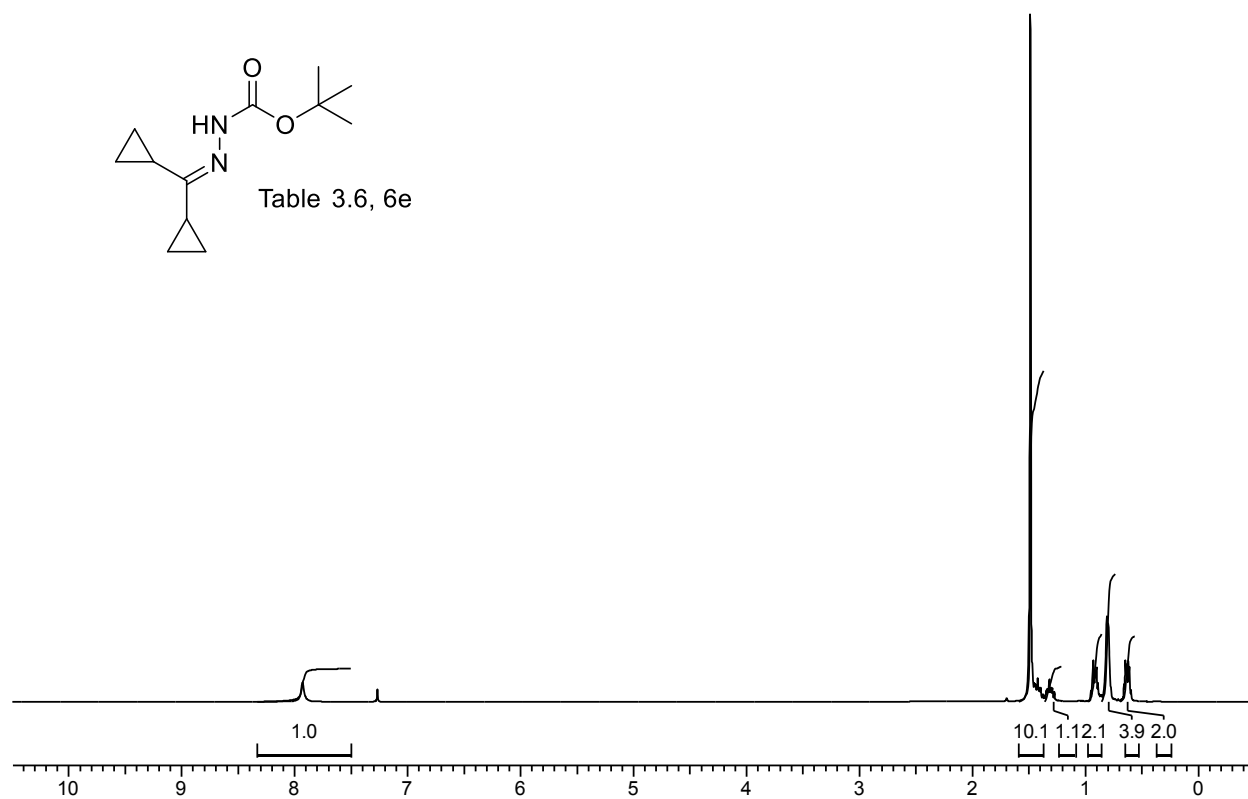


Table 3.6, 6e



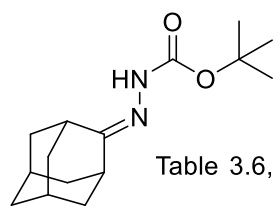
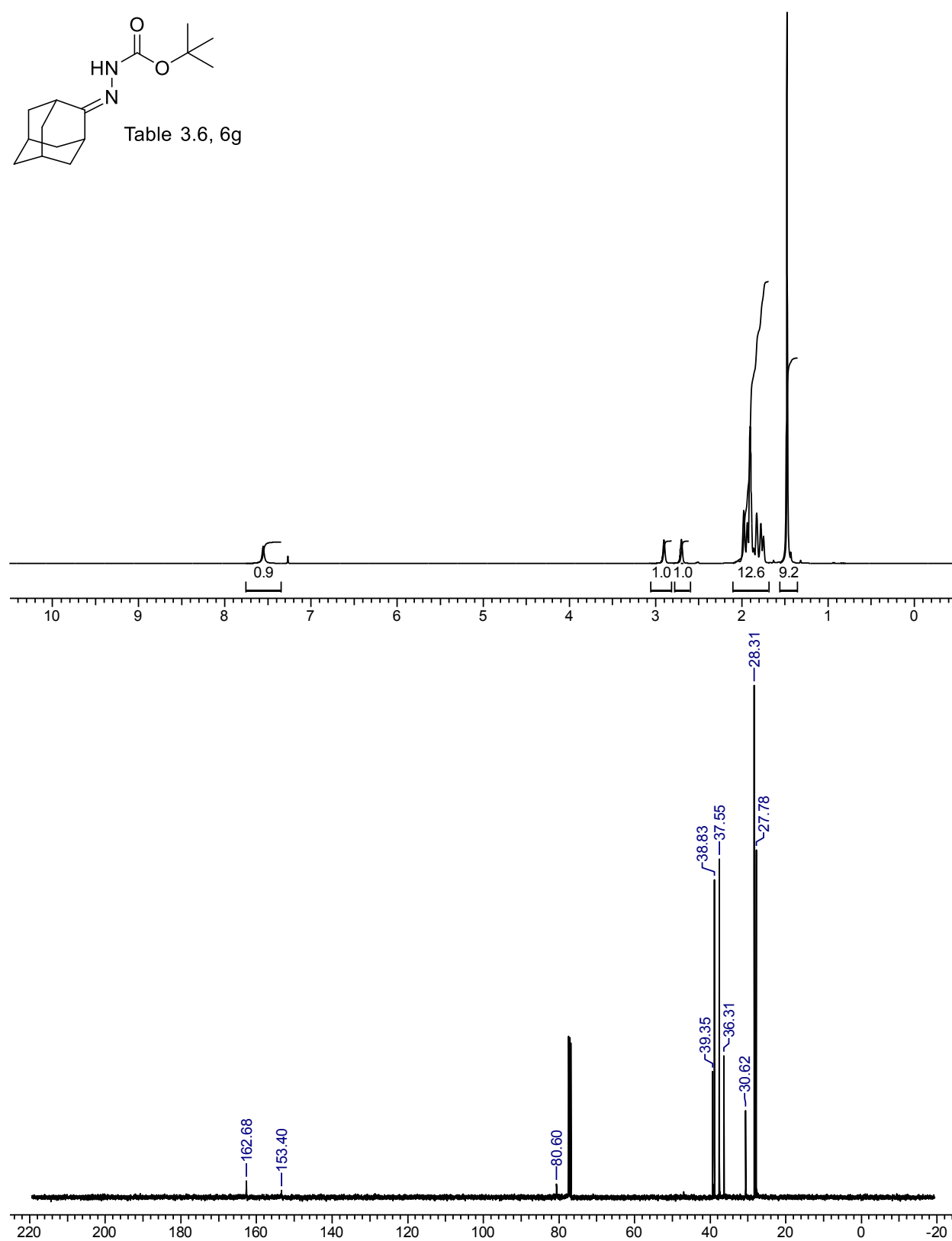


Table 3.6, 6g



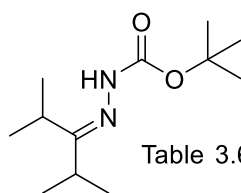
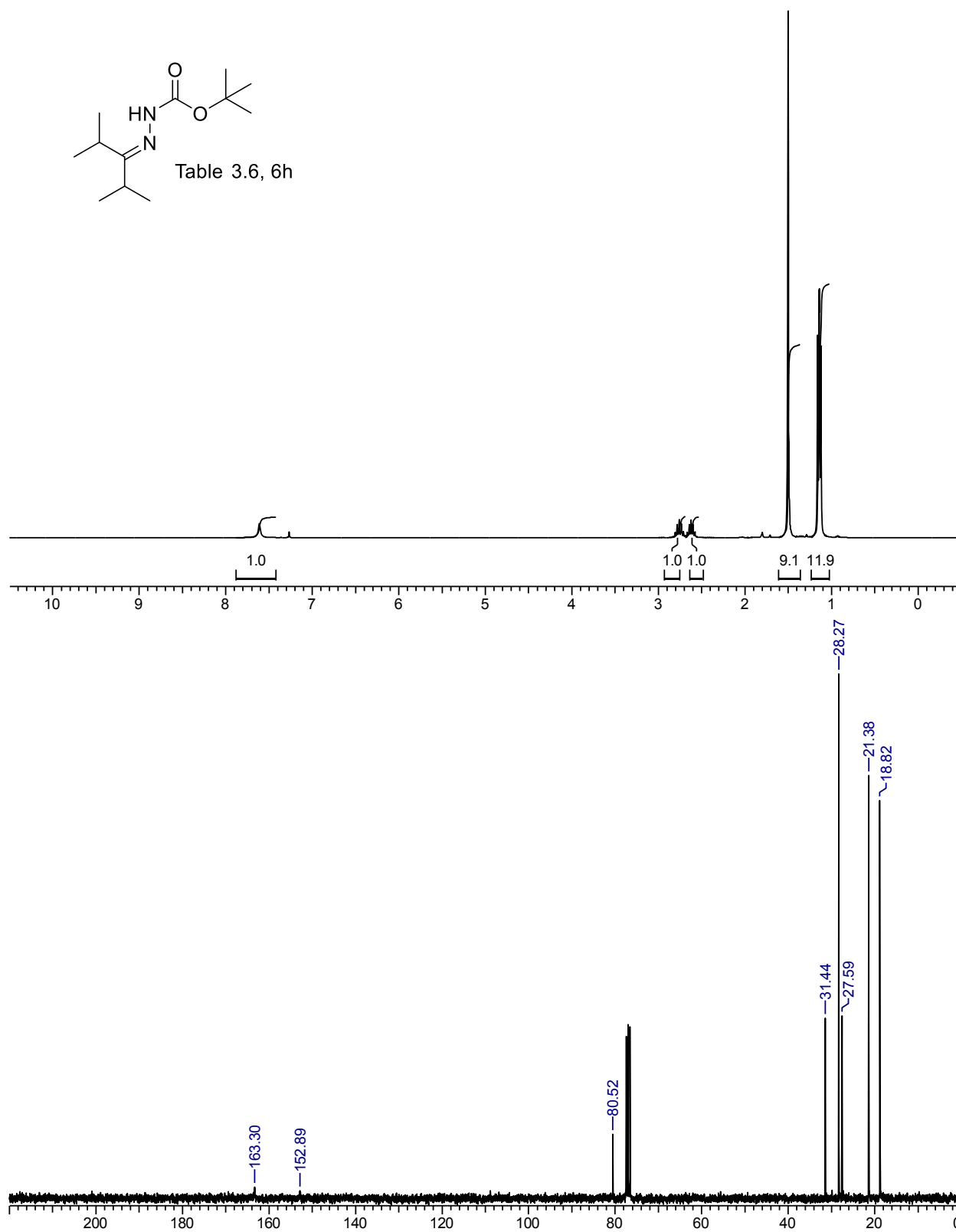


Table 3.6, 6h



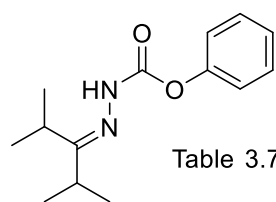
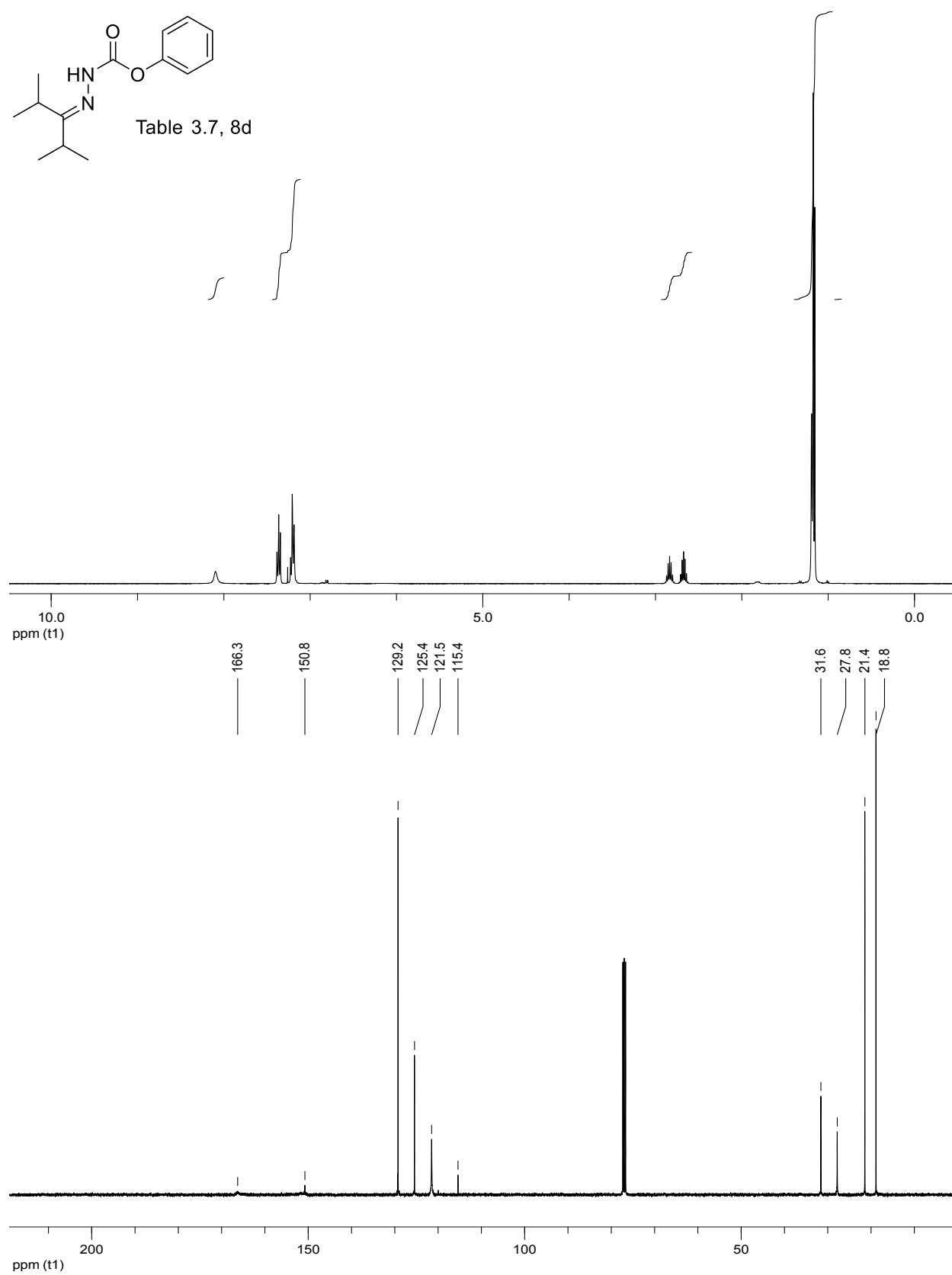
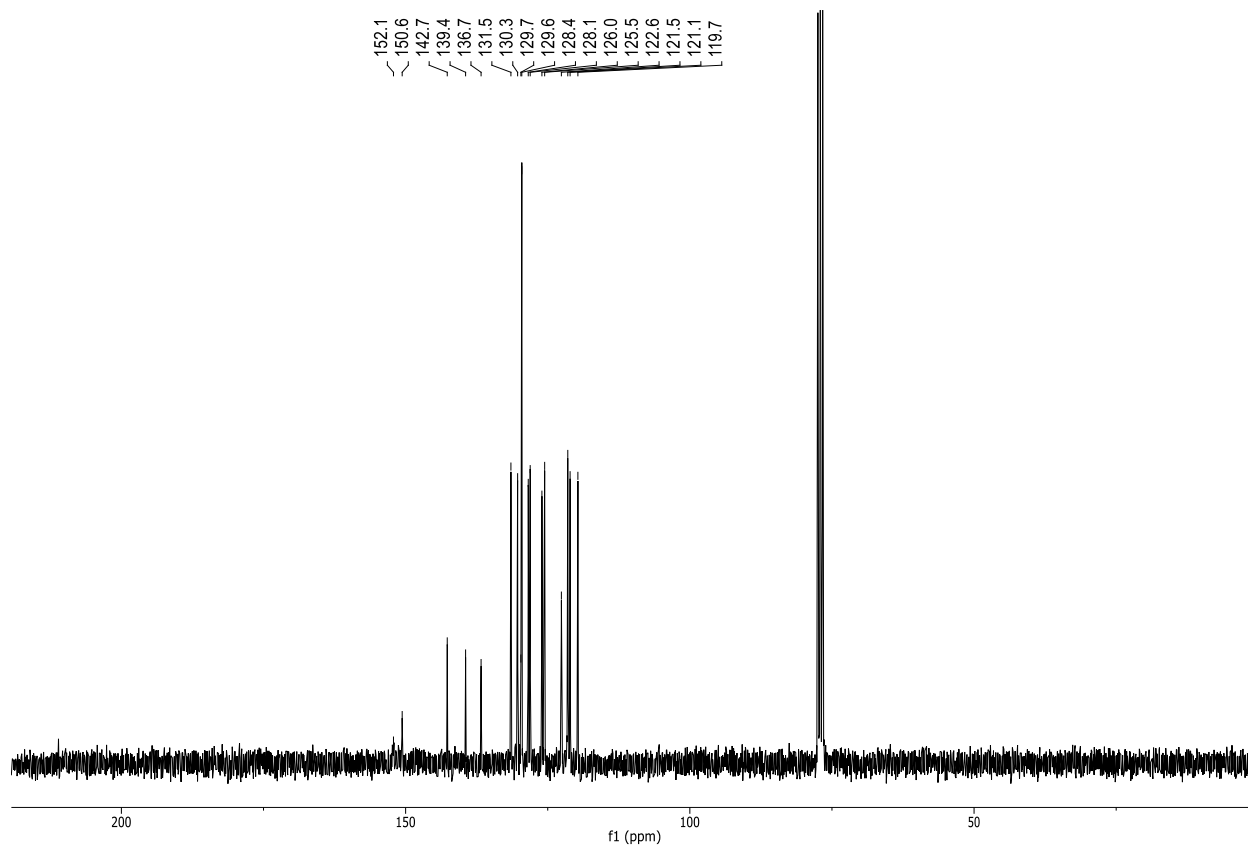
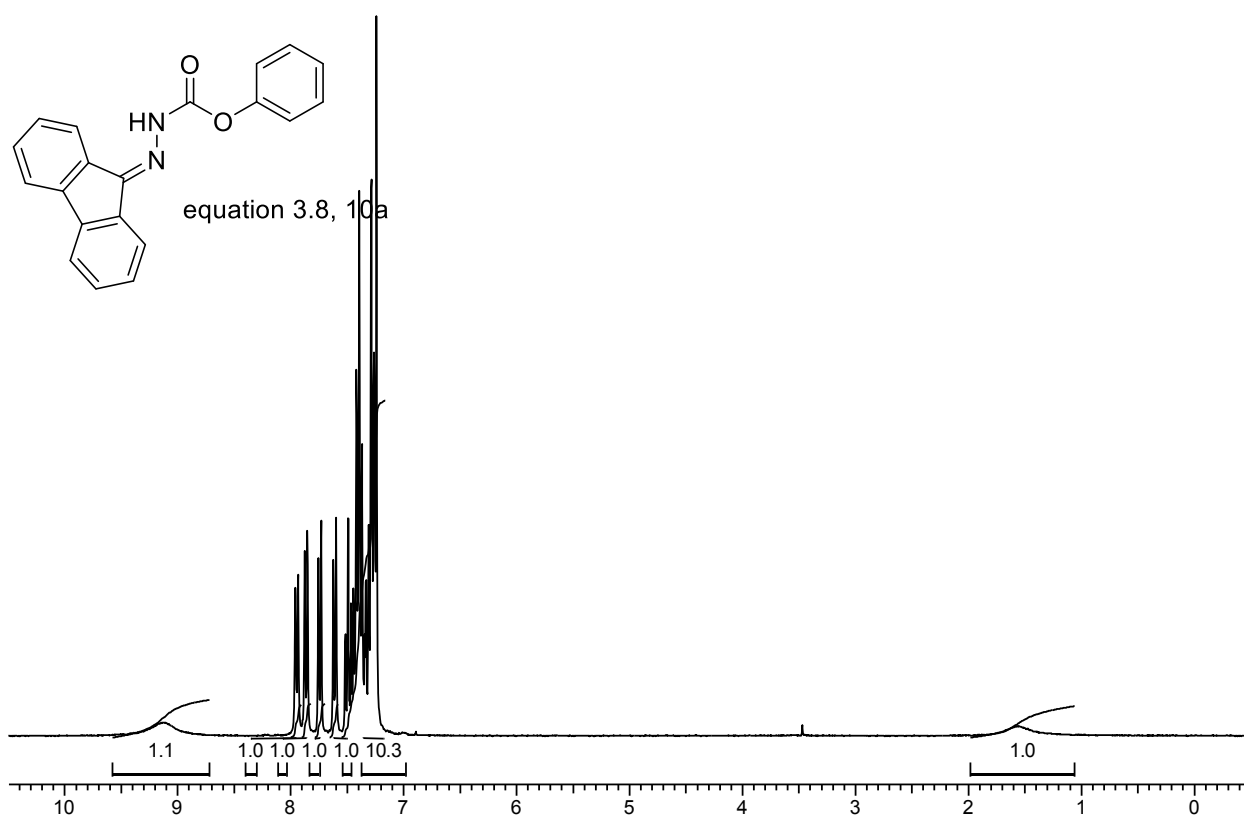


Table 3.7, 8d





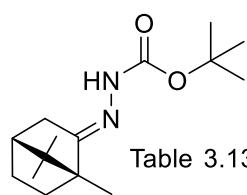
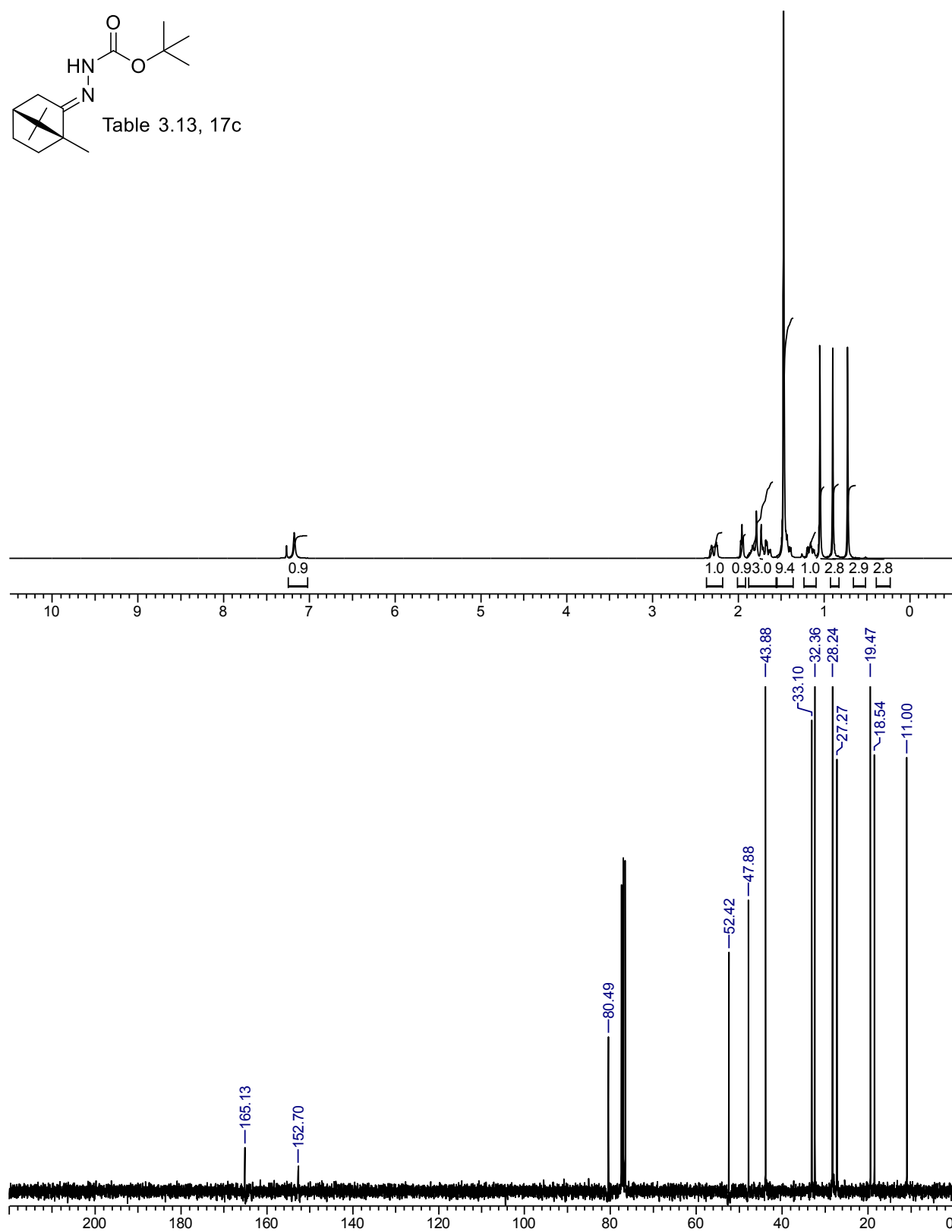


Table 3.13, 17c





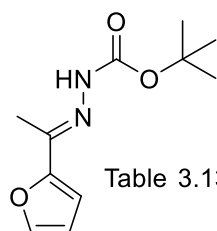
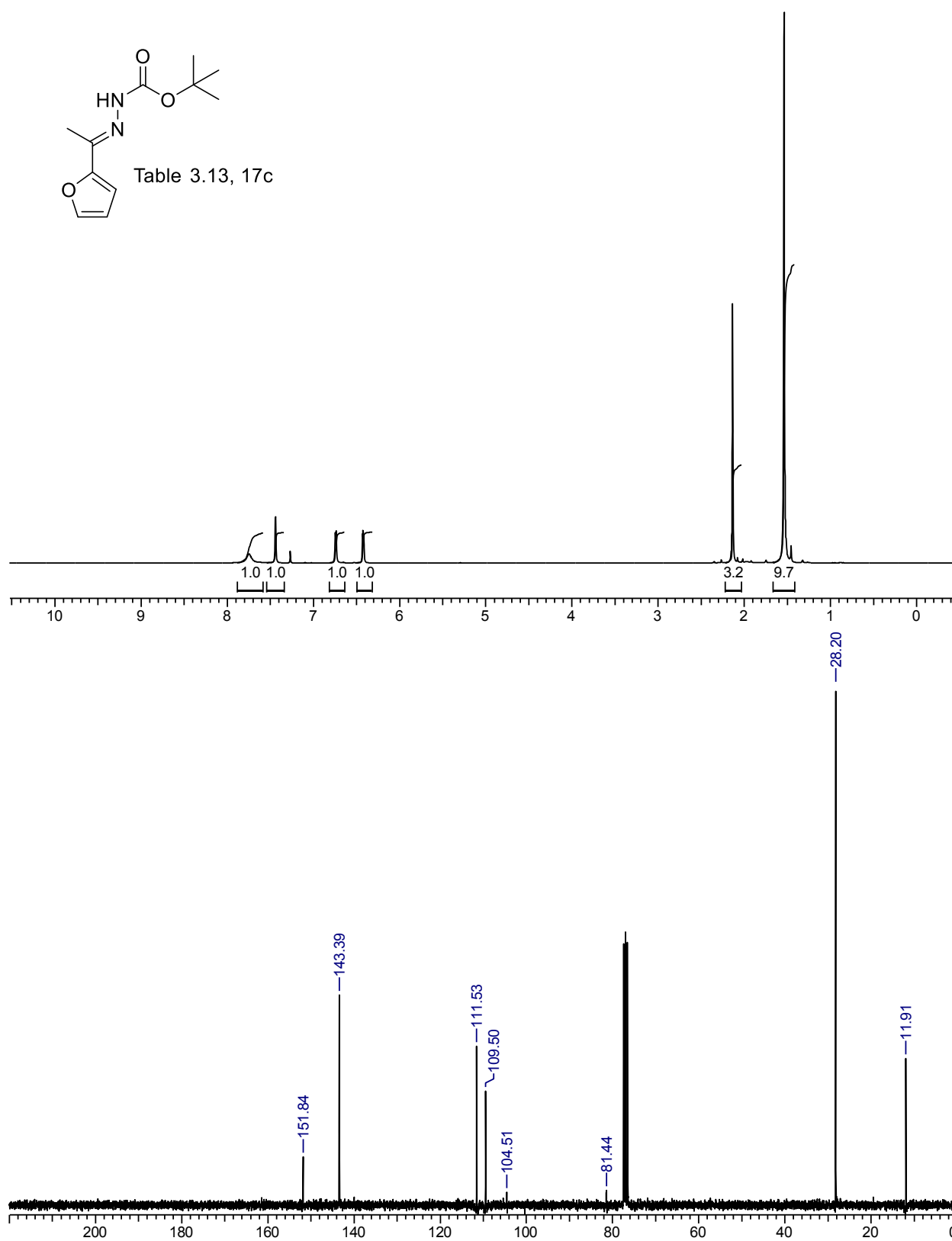
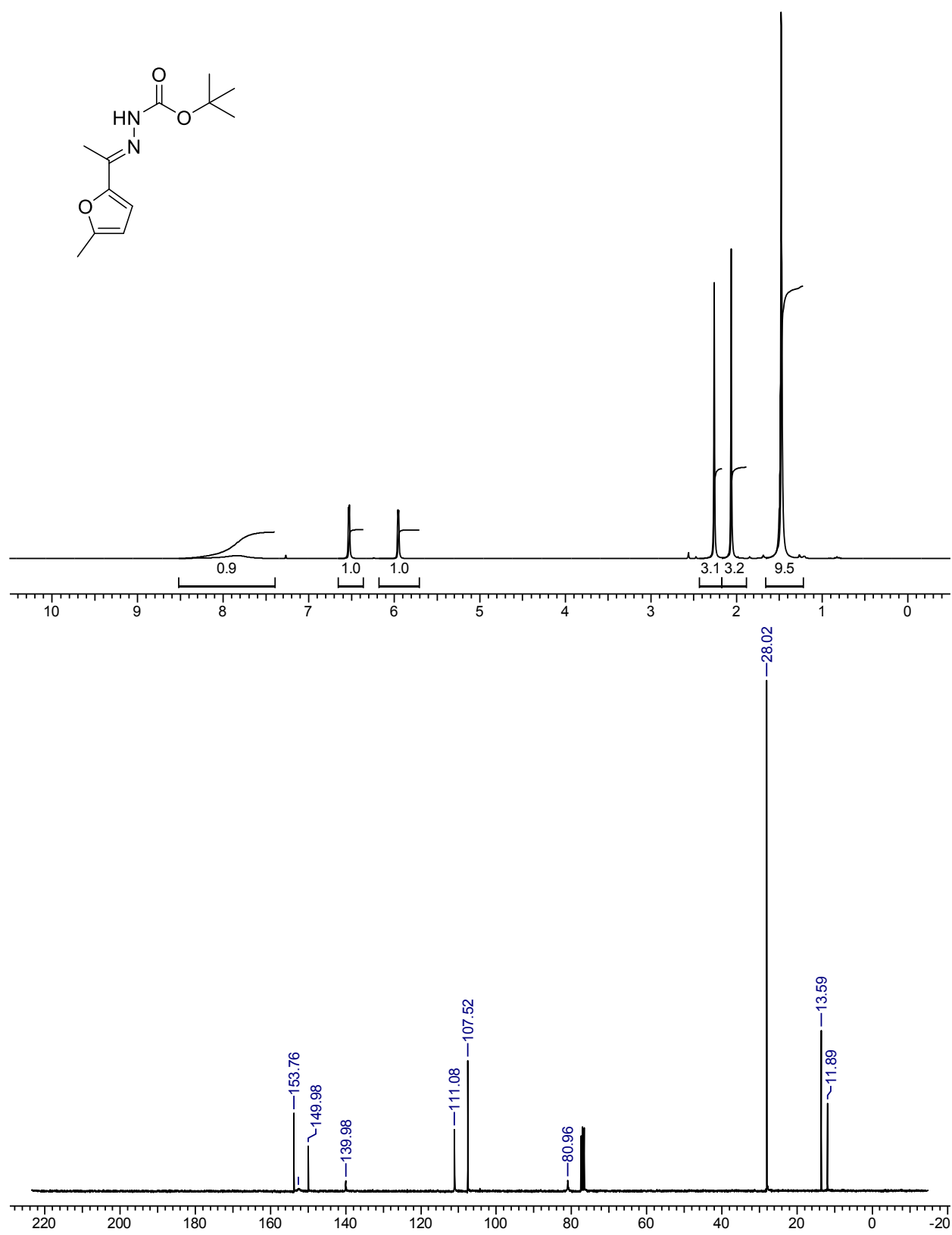


Table 3.13, 17c





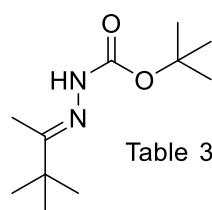
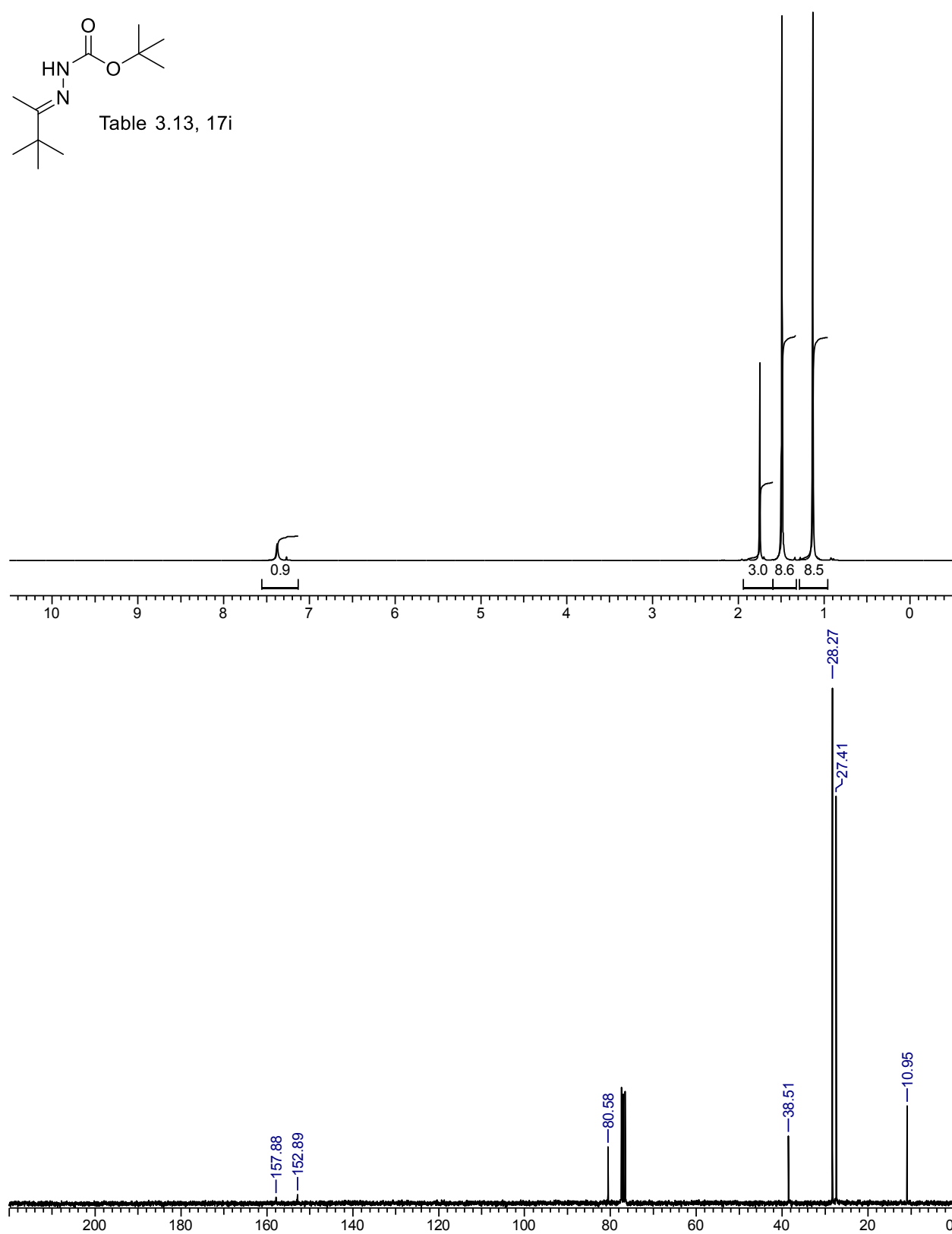
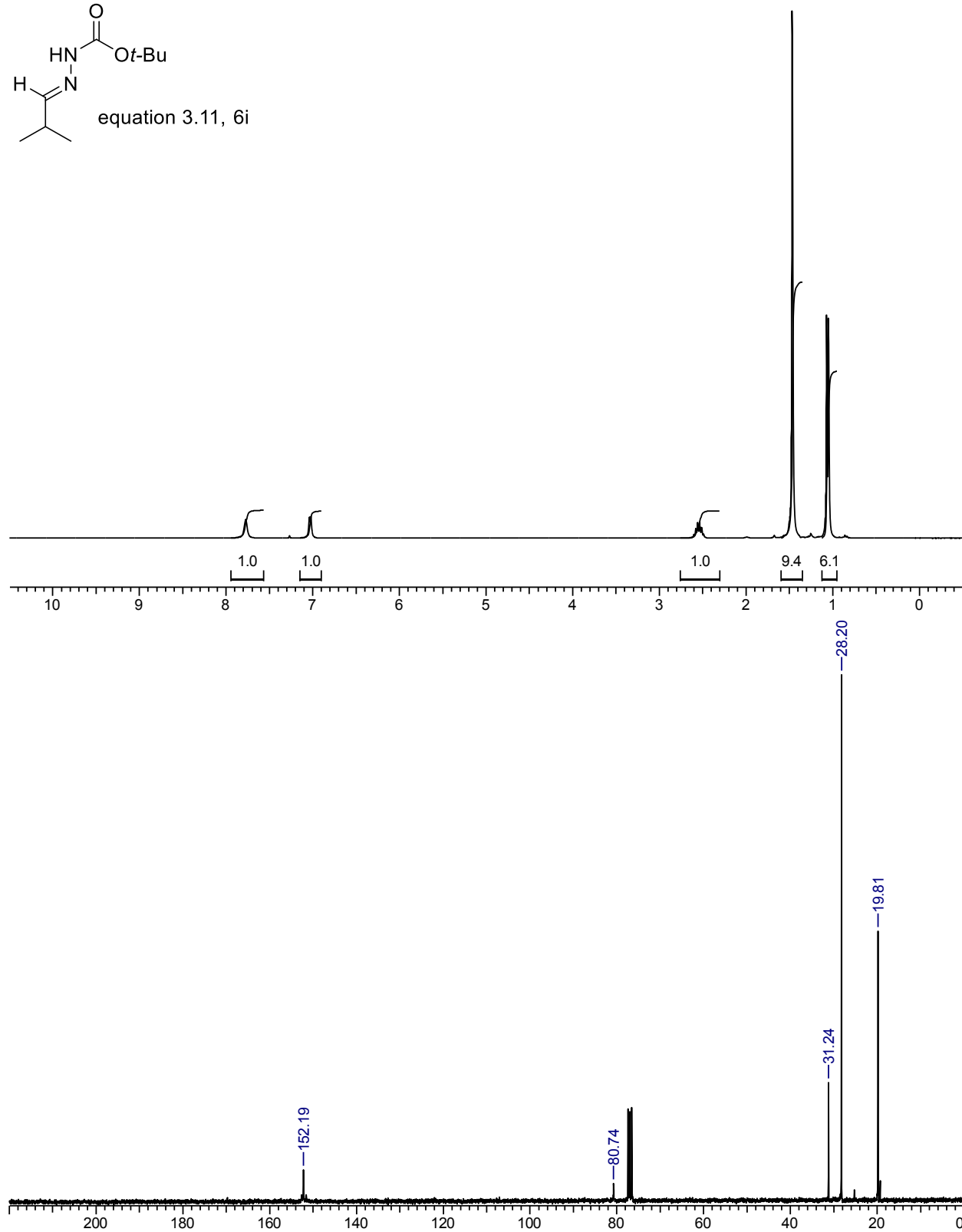
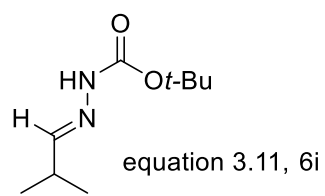
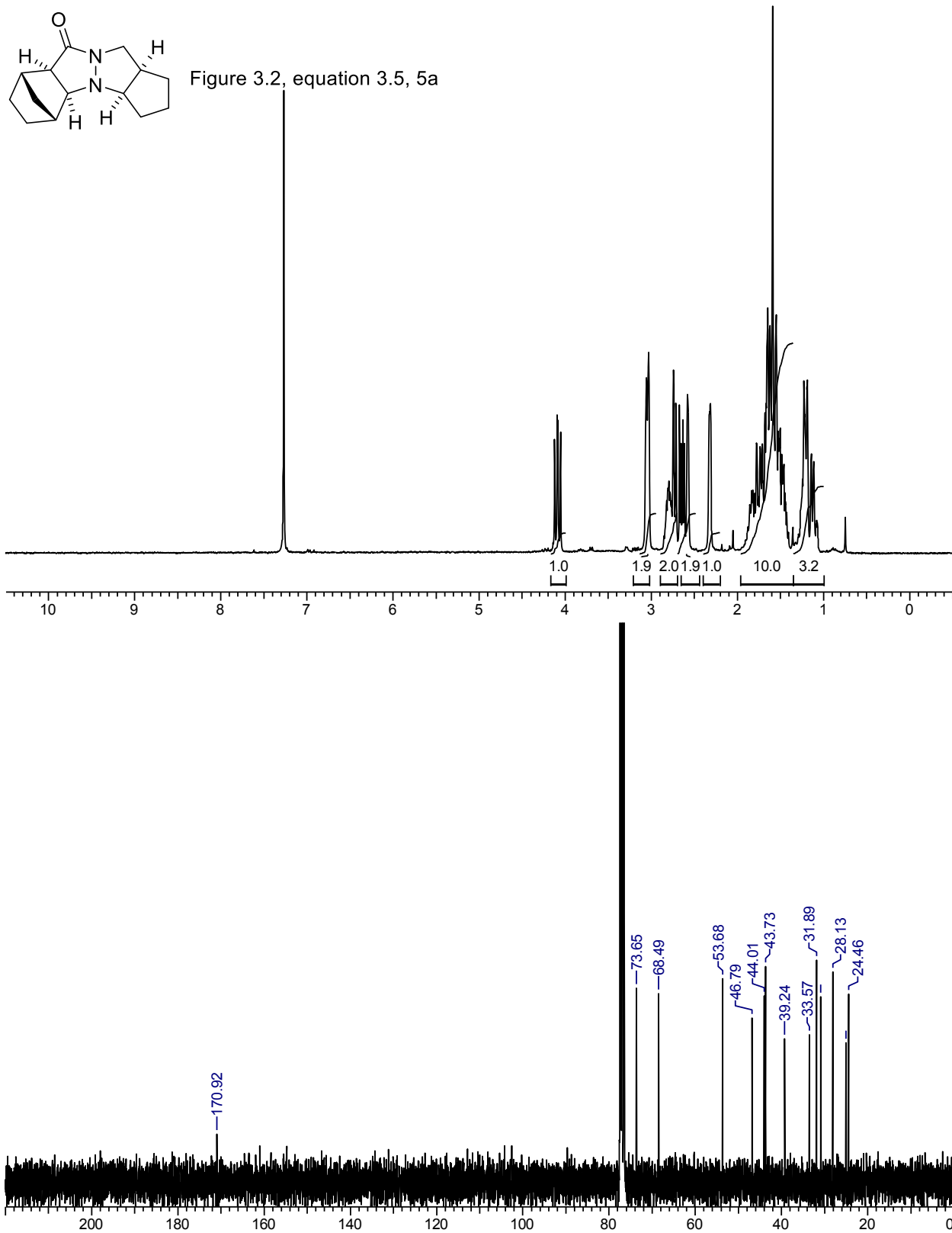
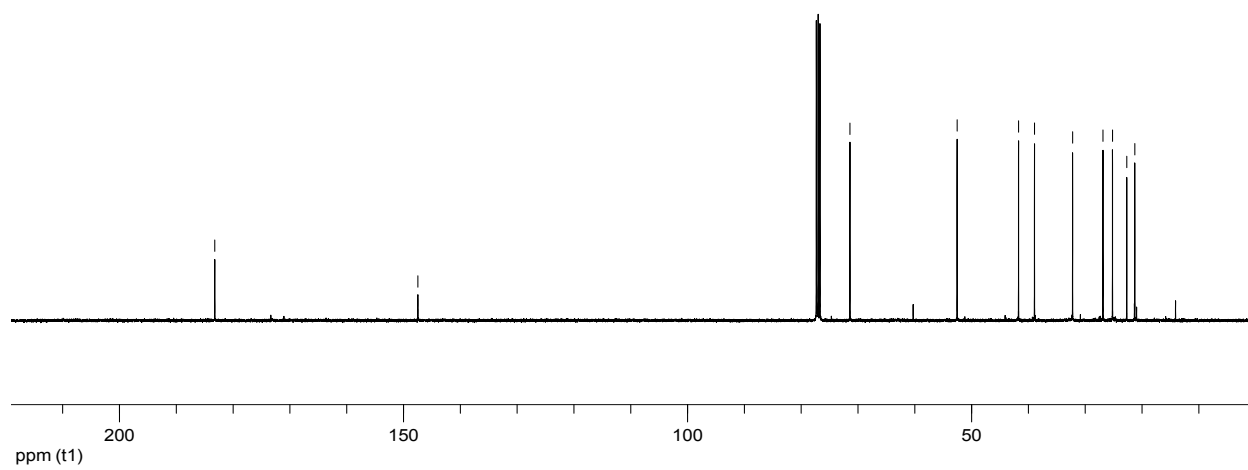
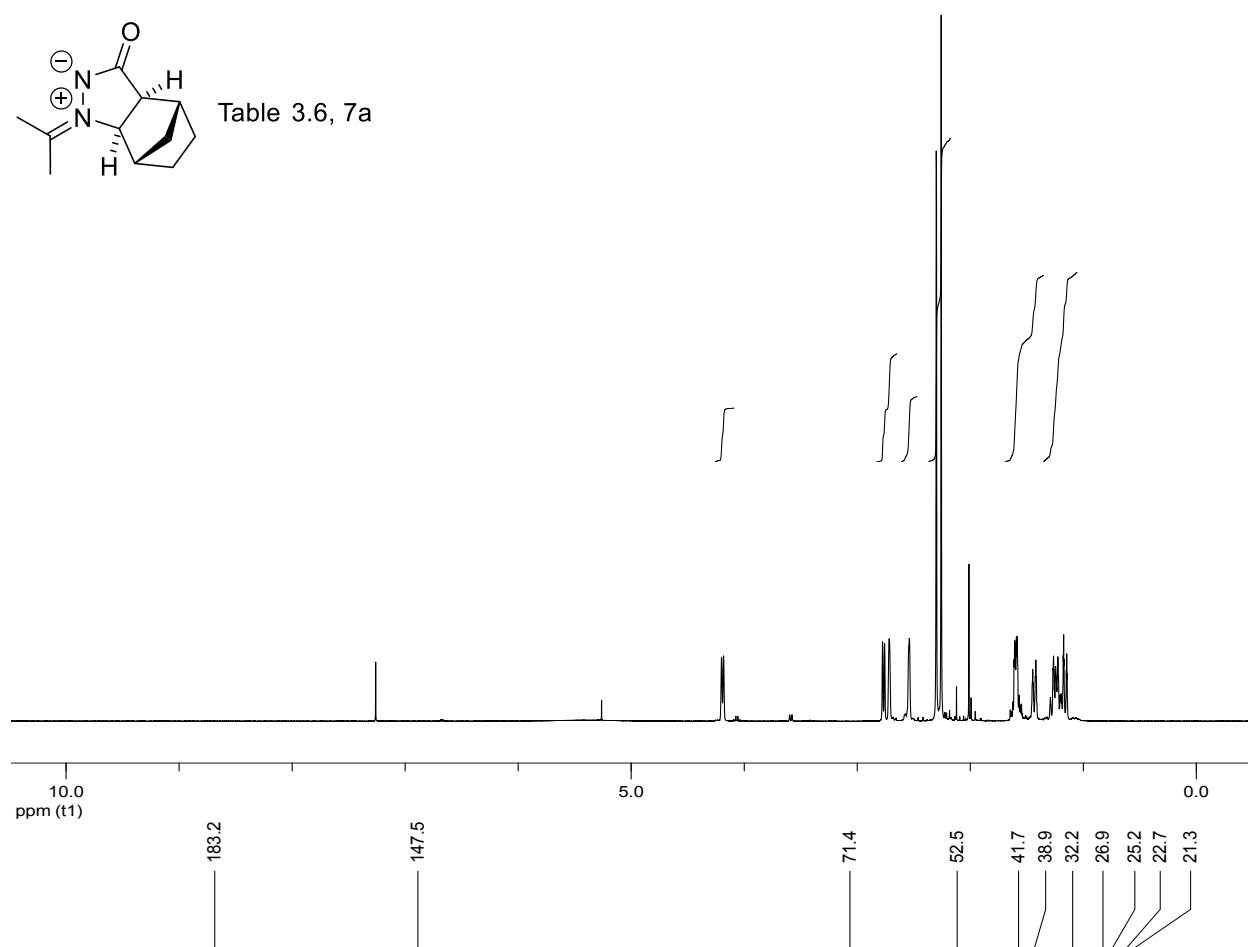
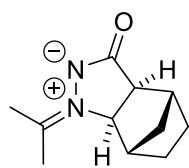


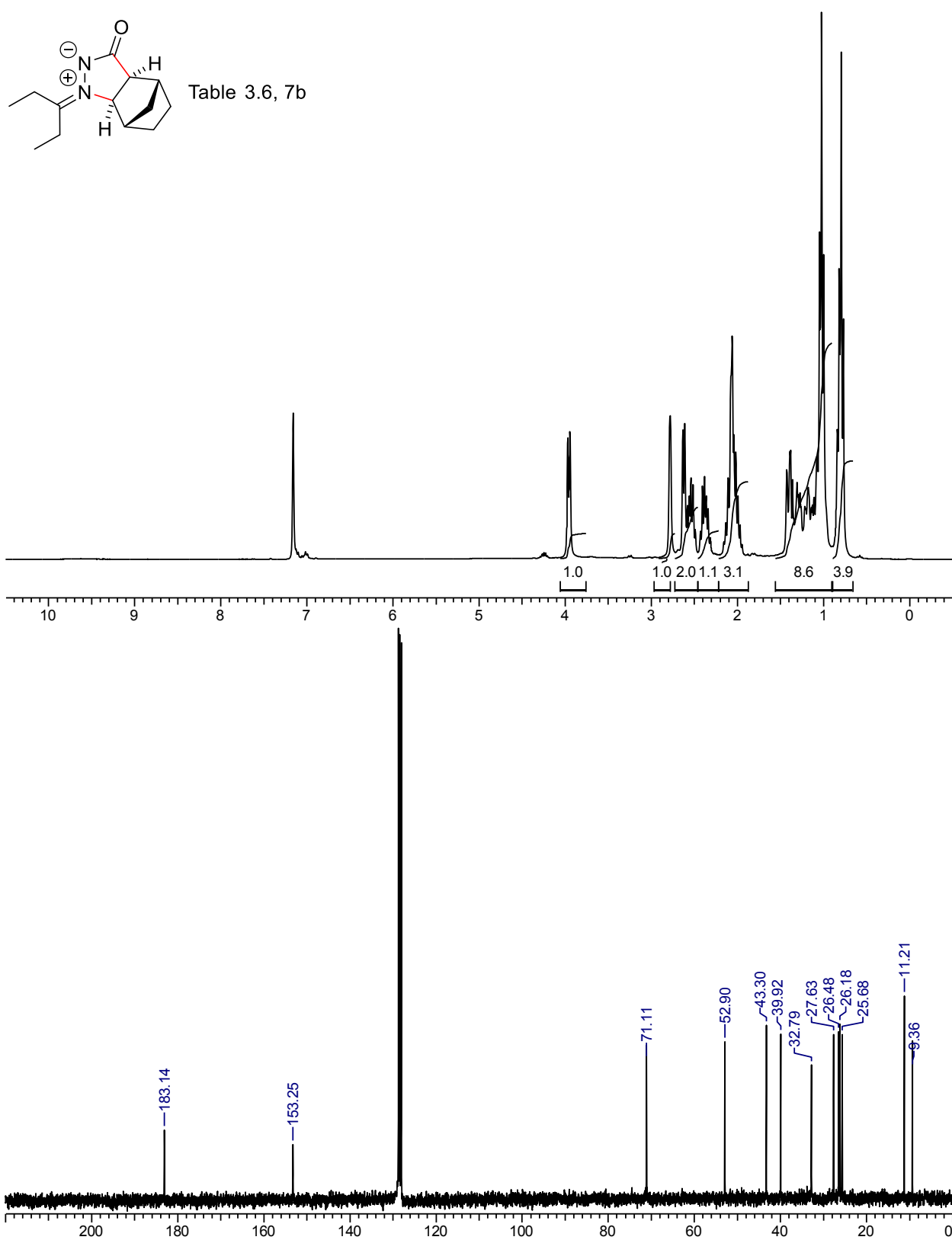
Table 3.13, 17i

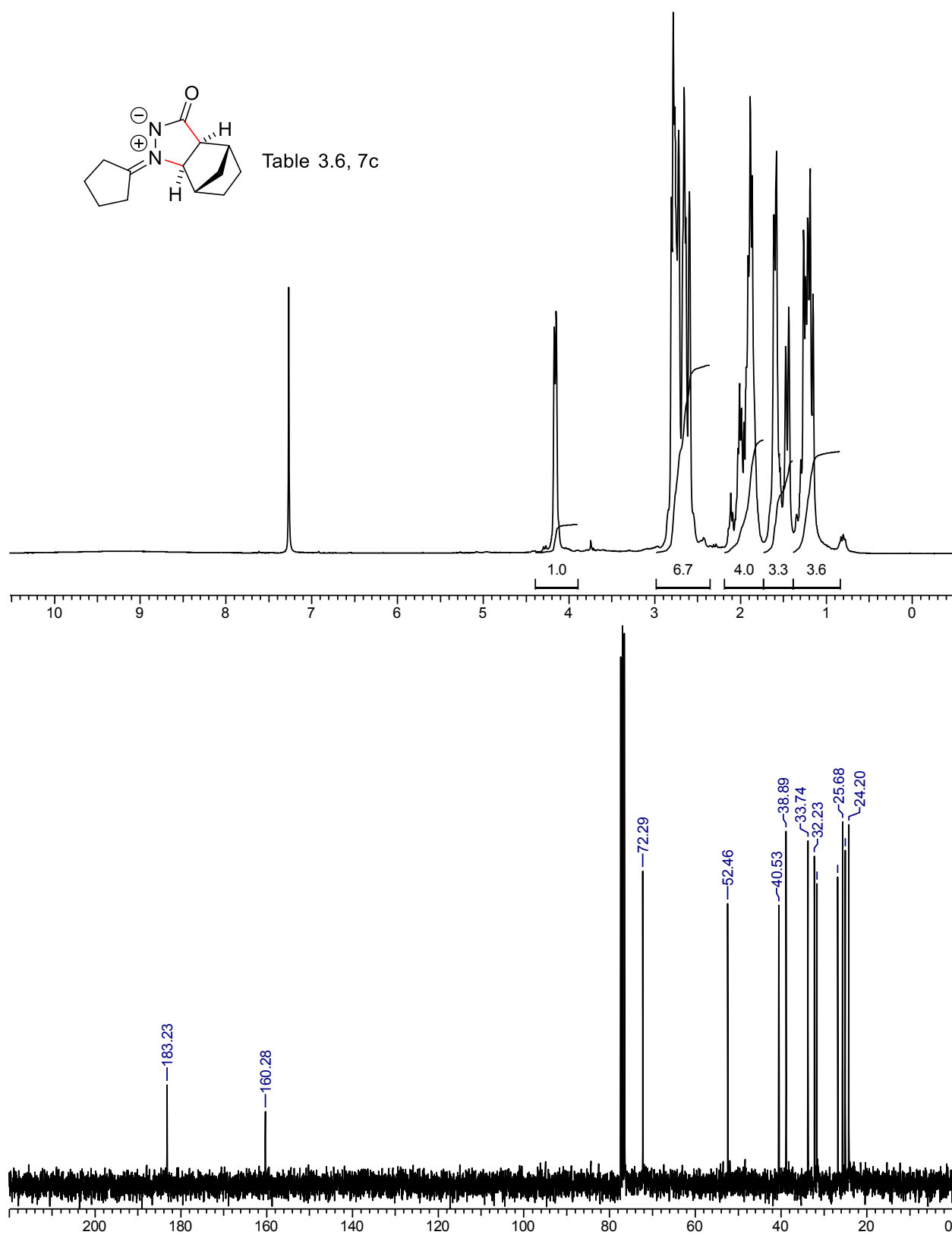














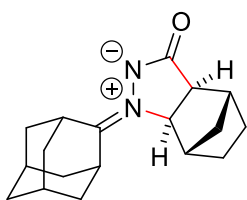
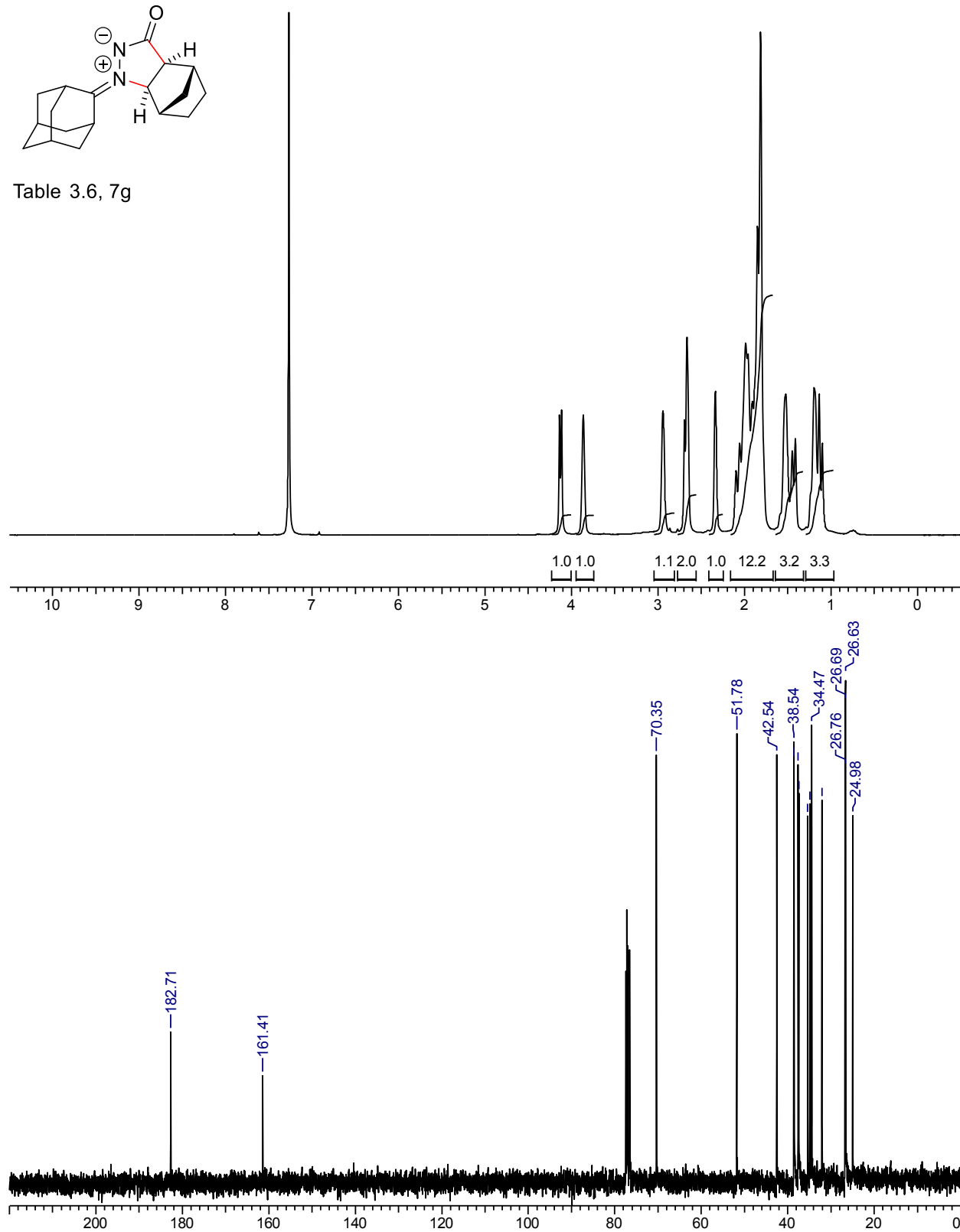


Table 3.6, 7g



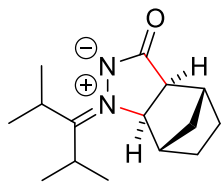
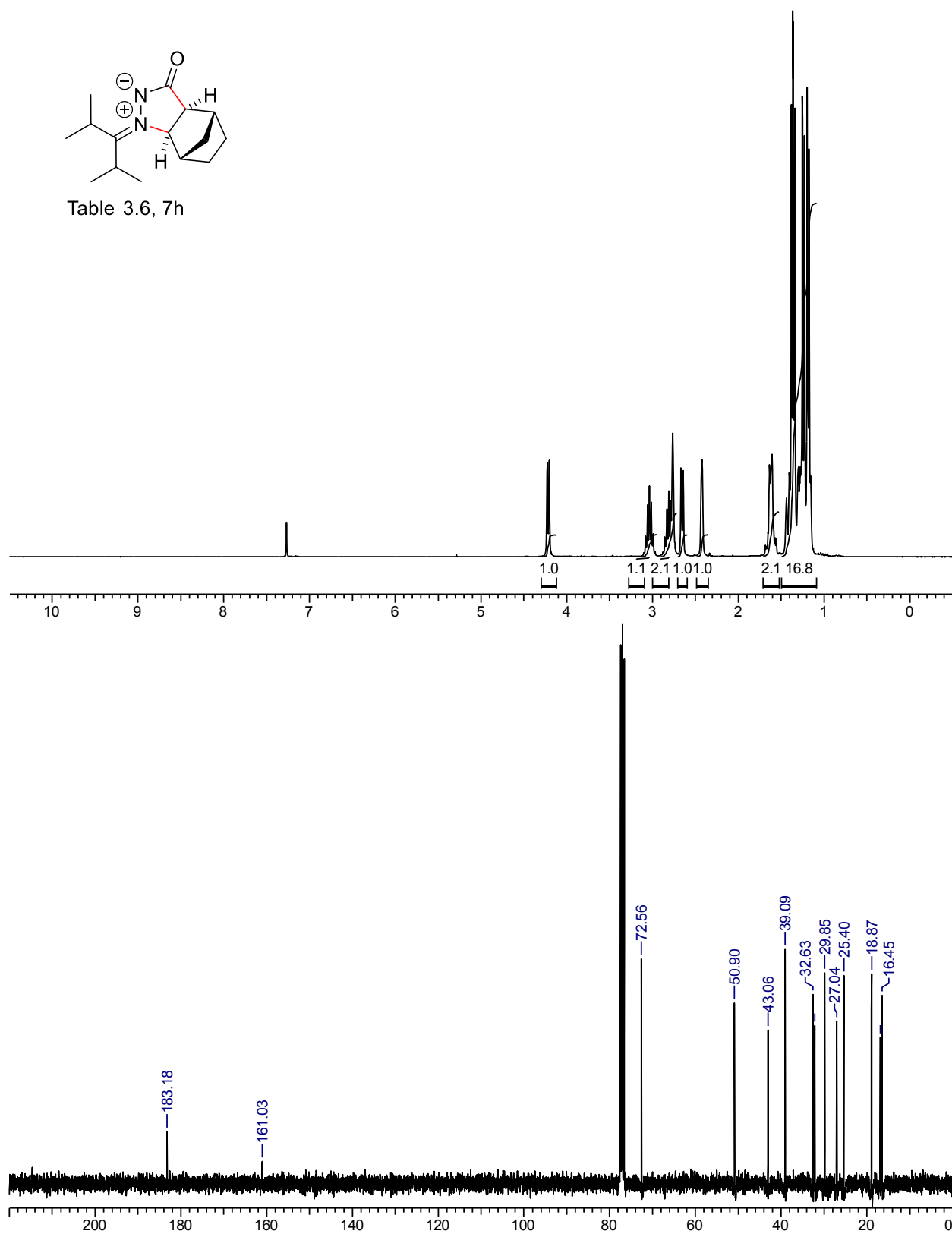
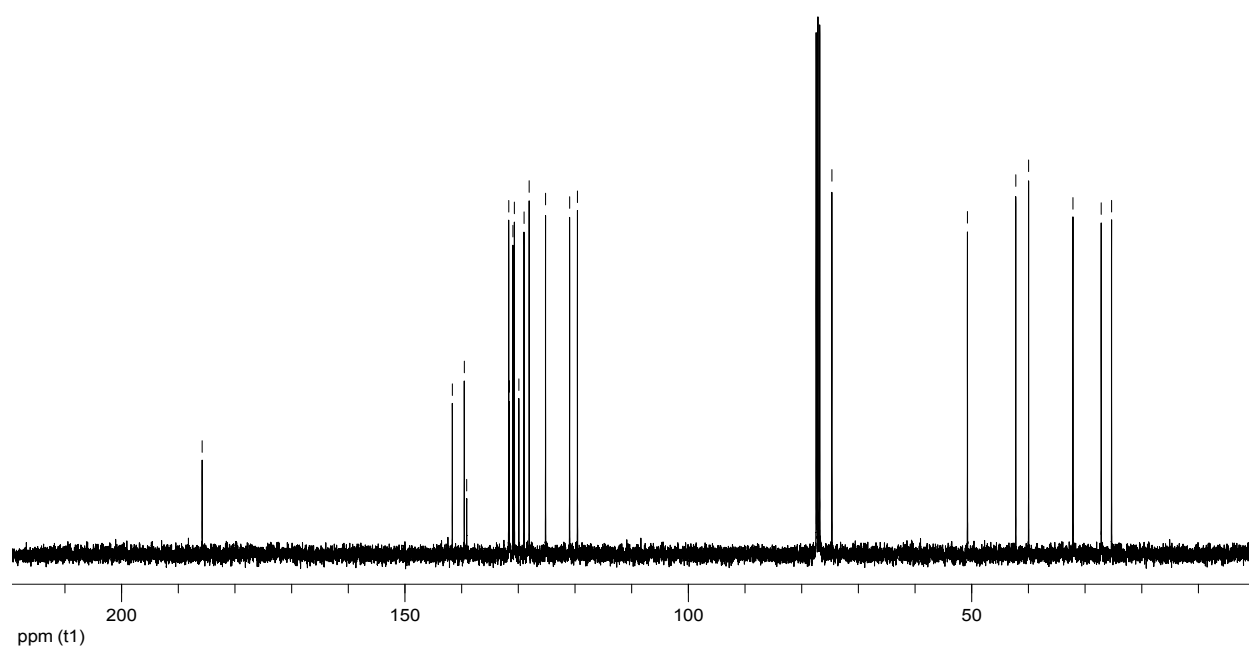
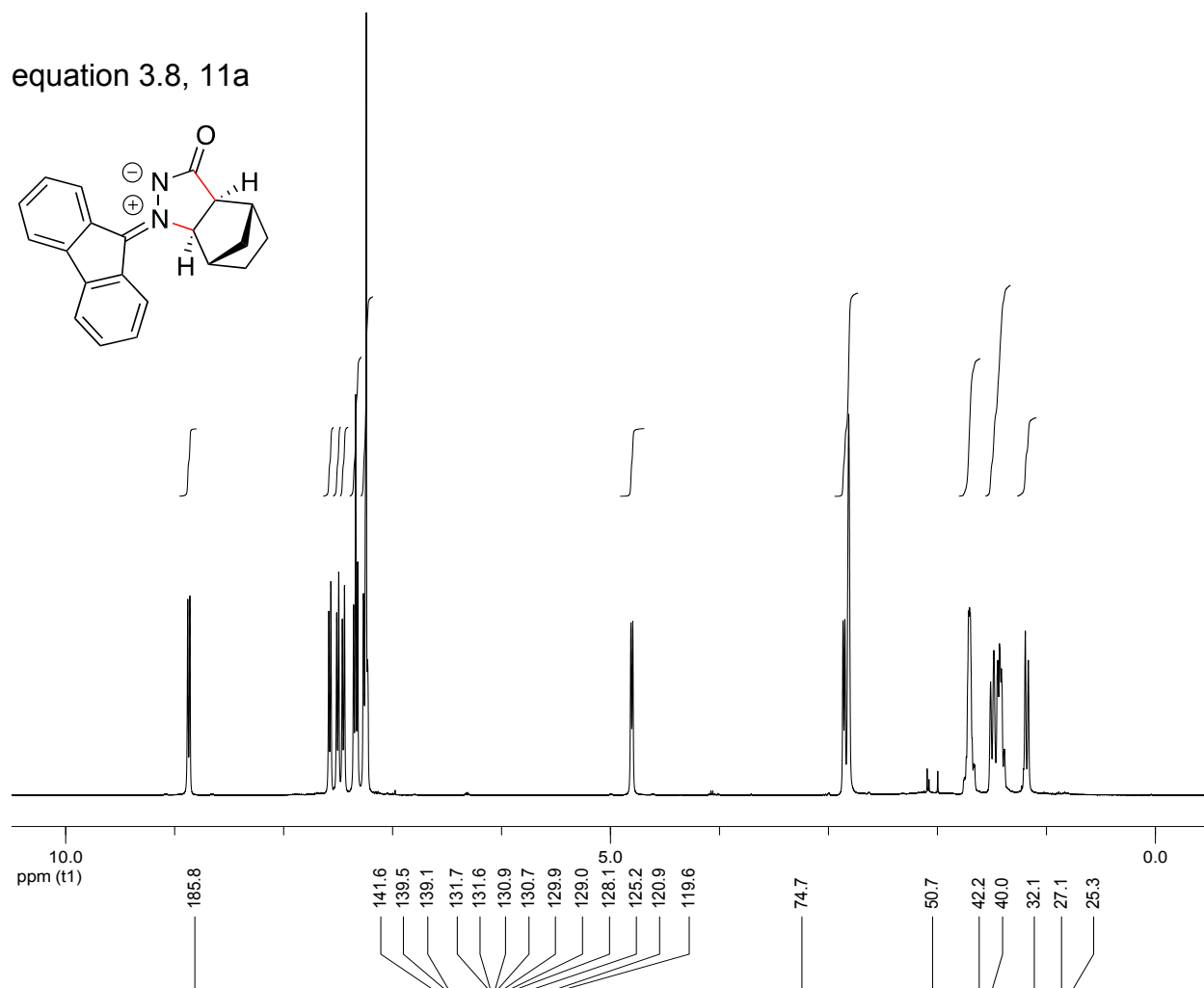
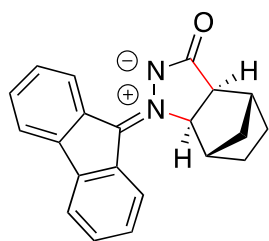
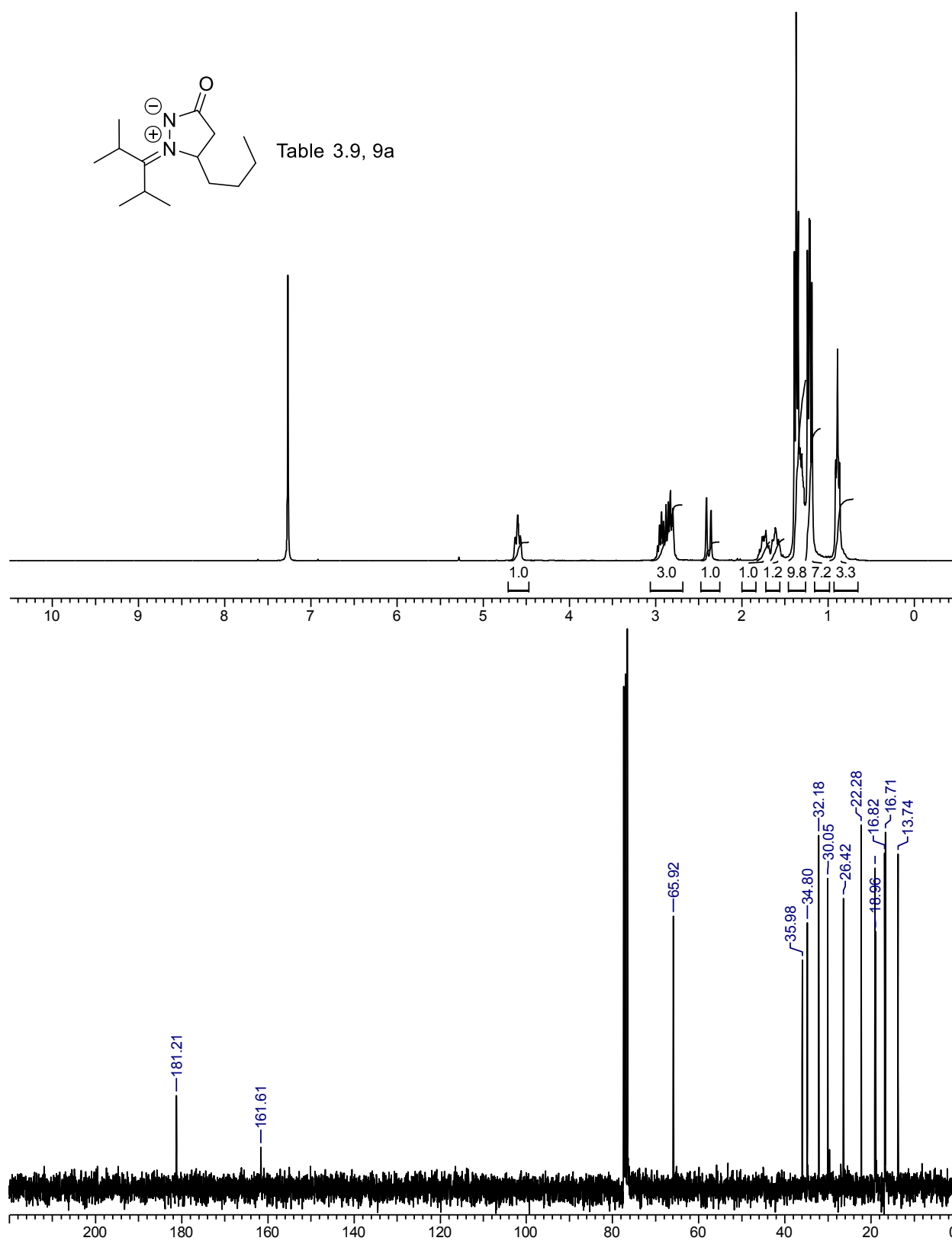


Table 3.6, 7h



equation 3.8, 11a





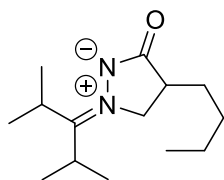
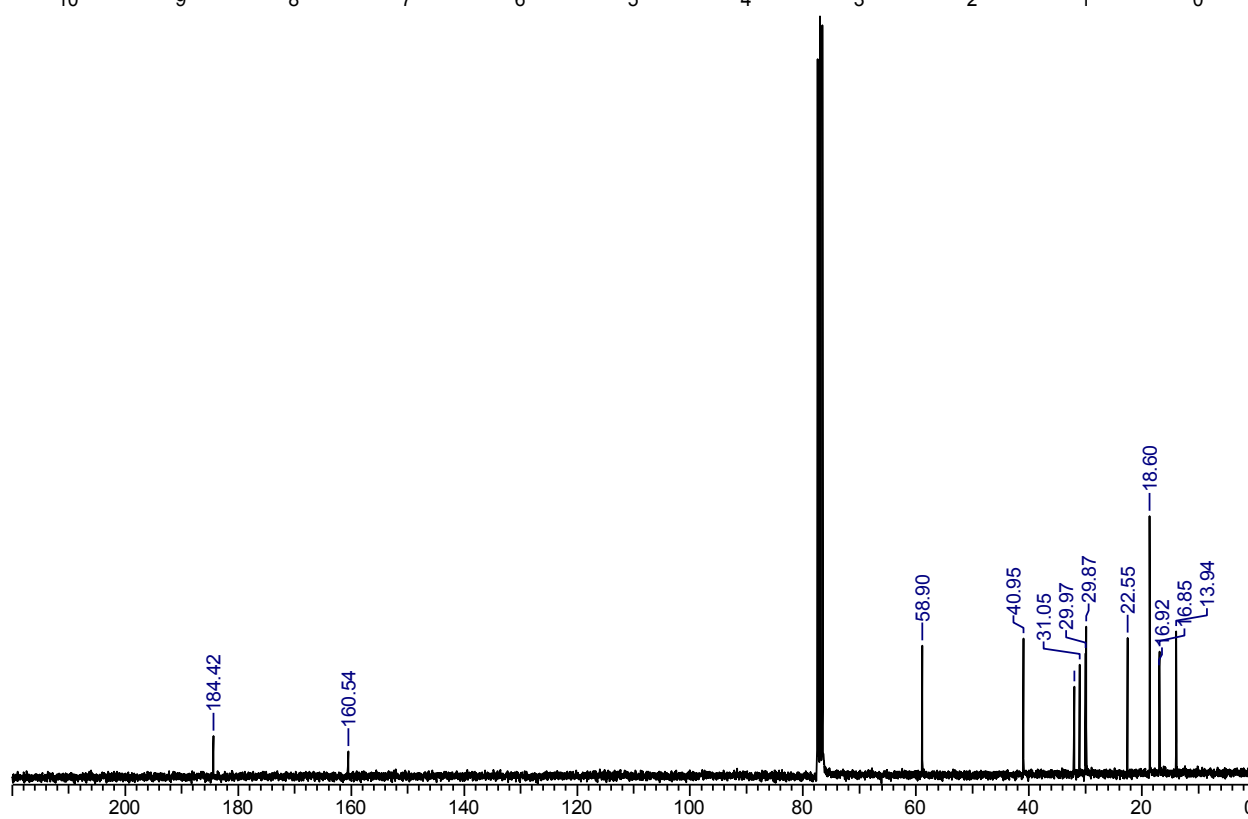
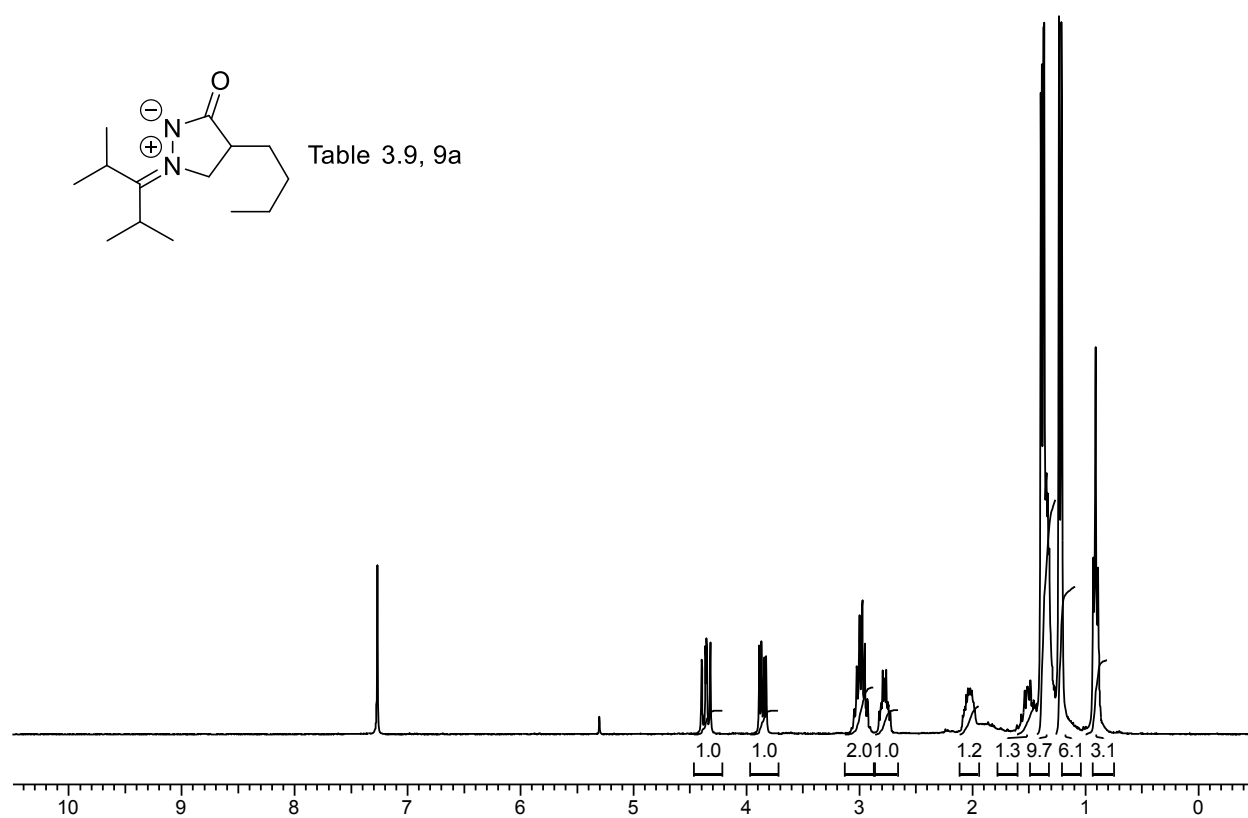
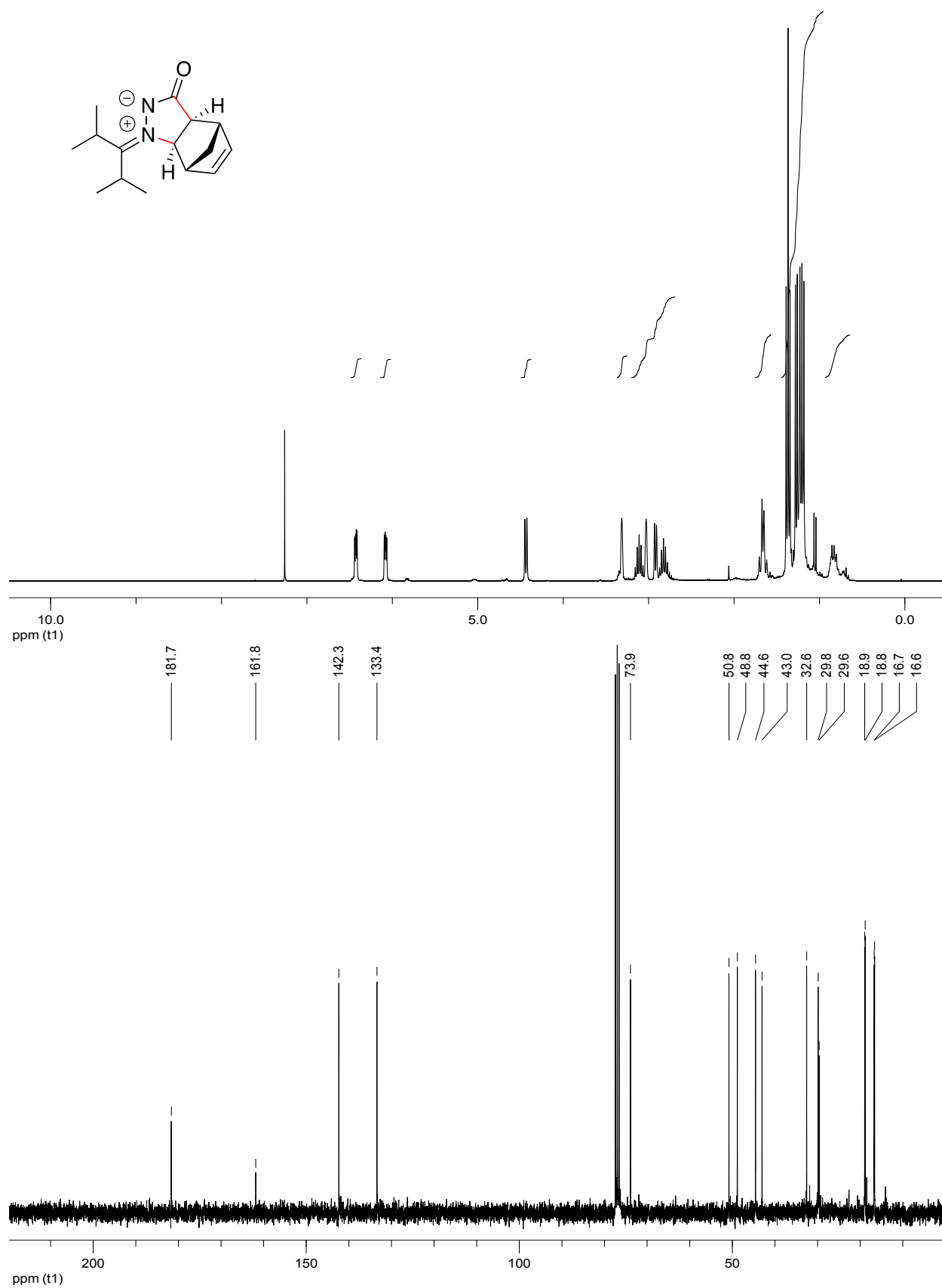
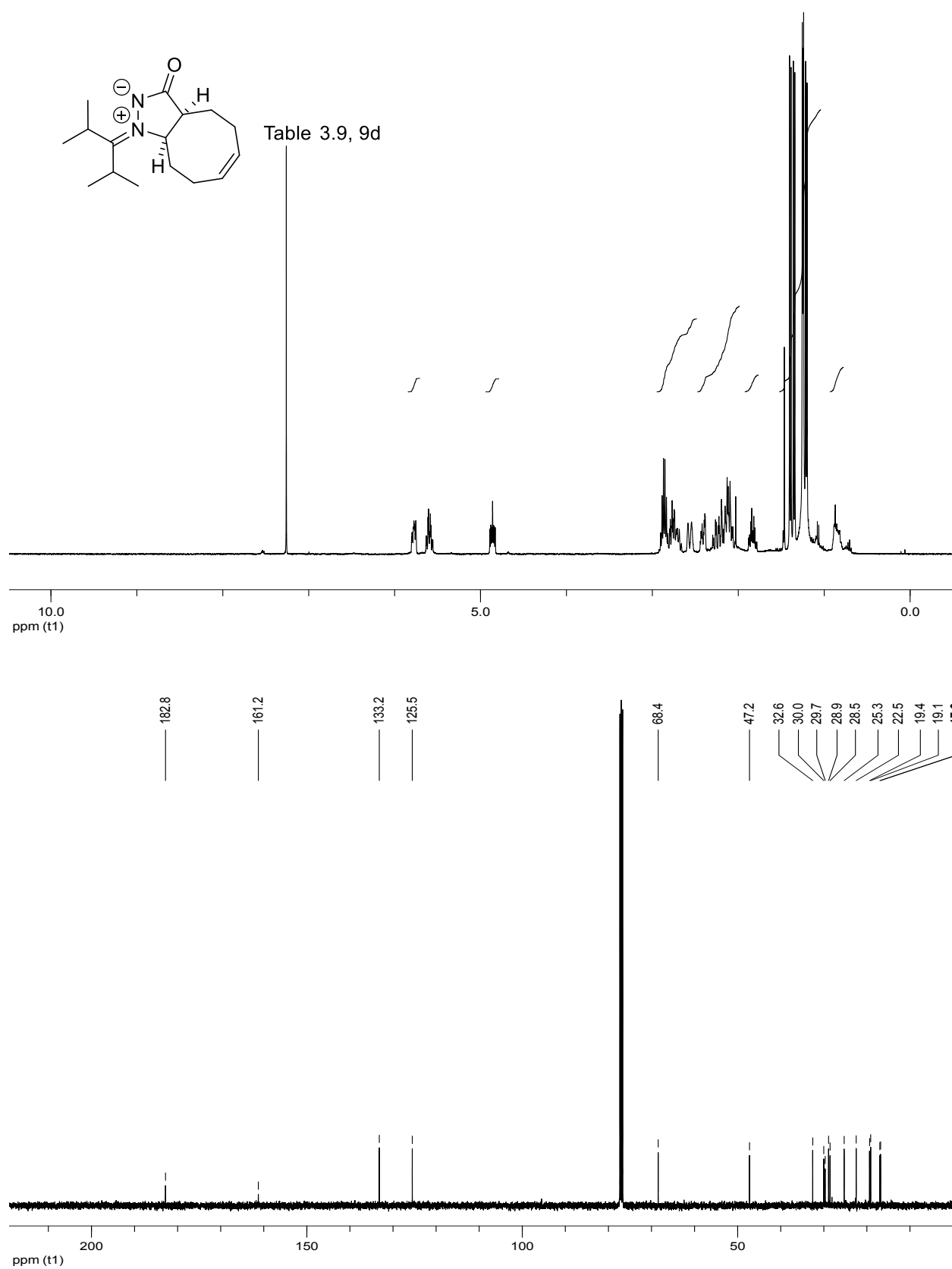
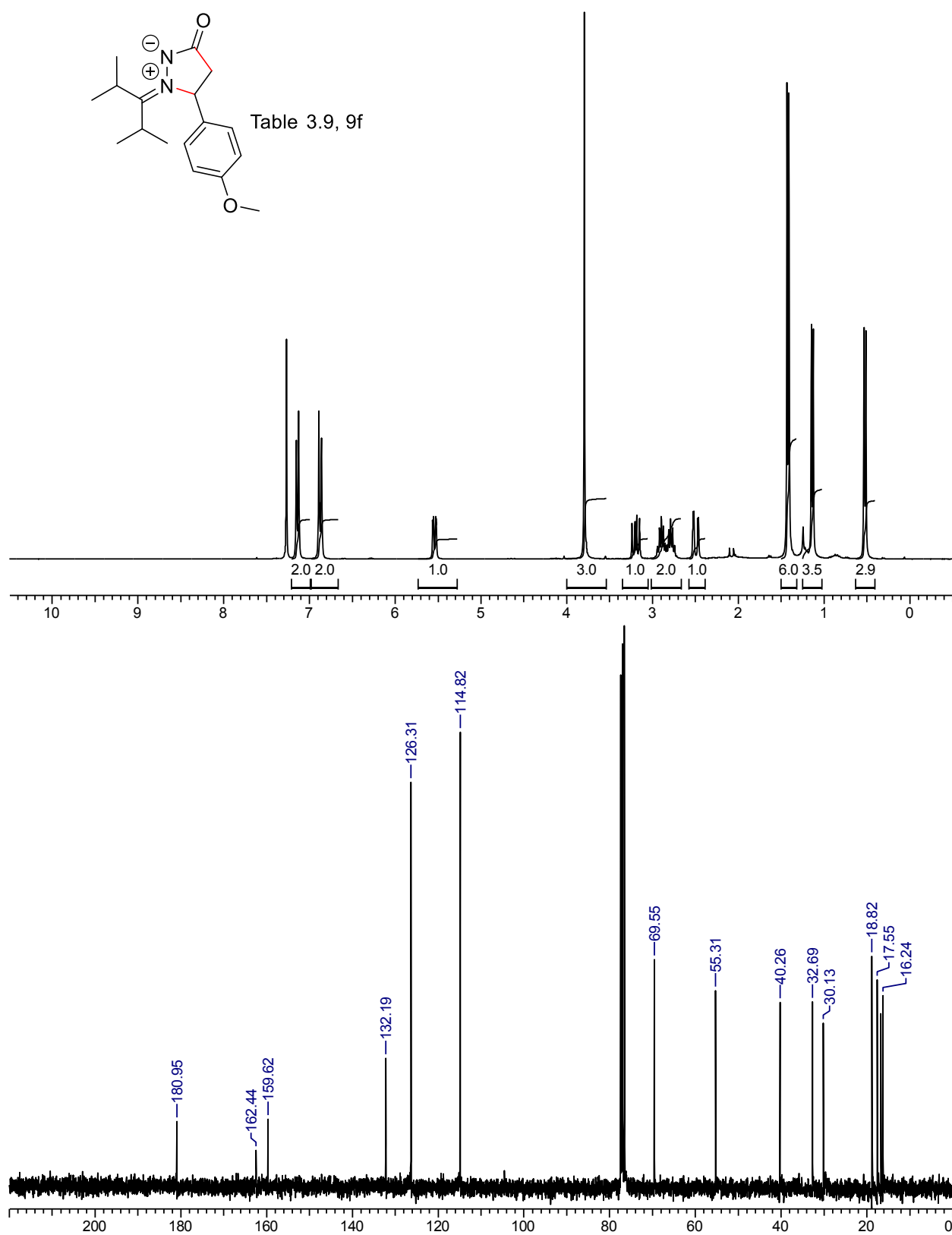


Table 3.9, 9a











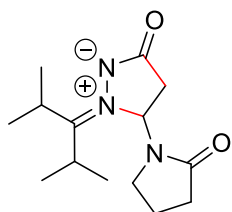
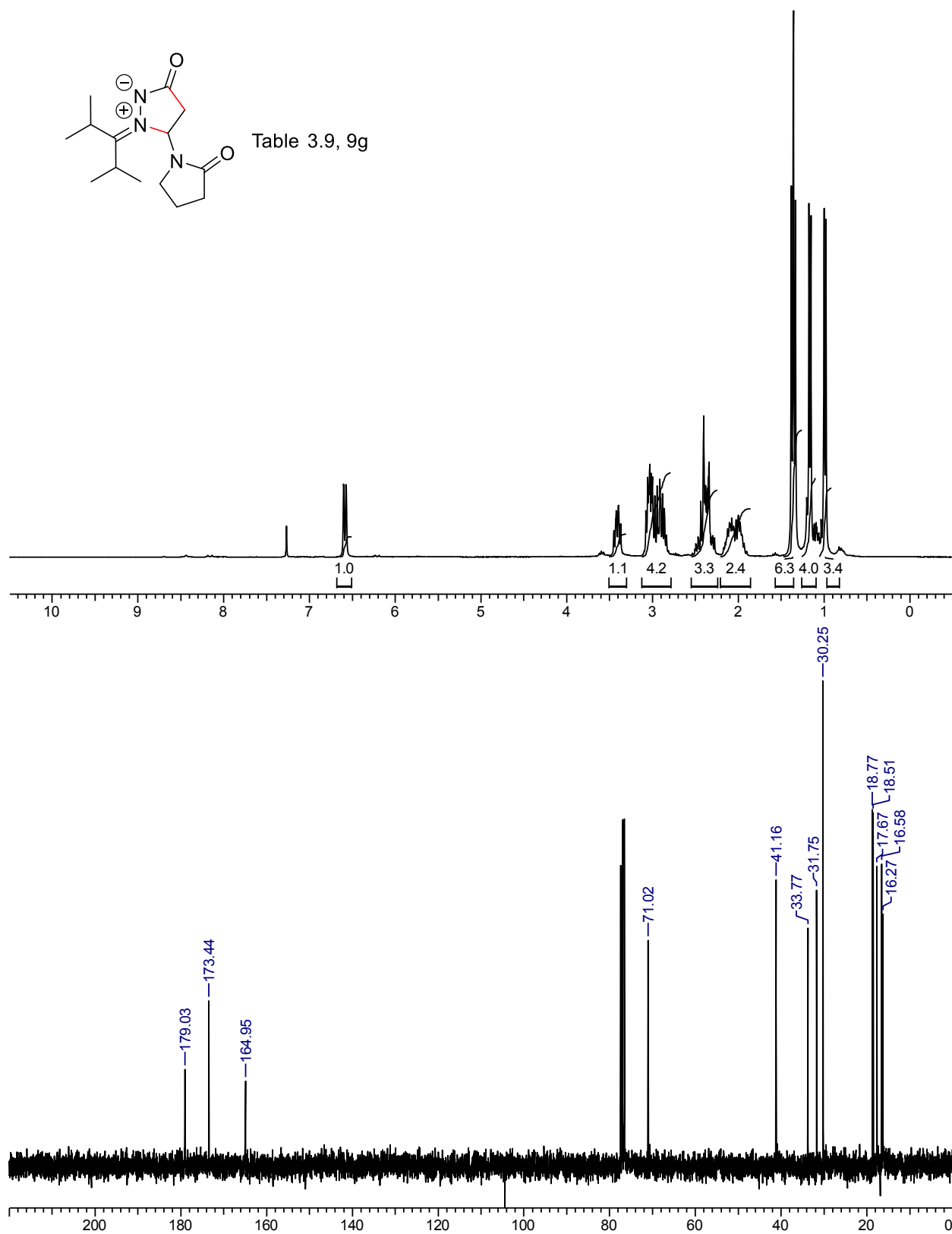


Table 3.9, 9g



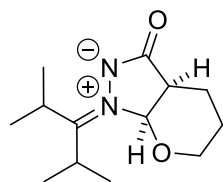
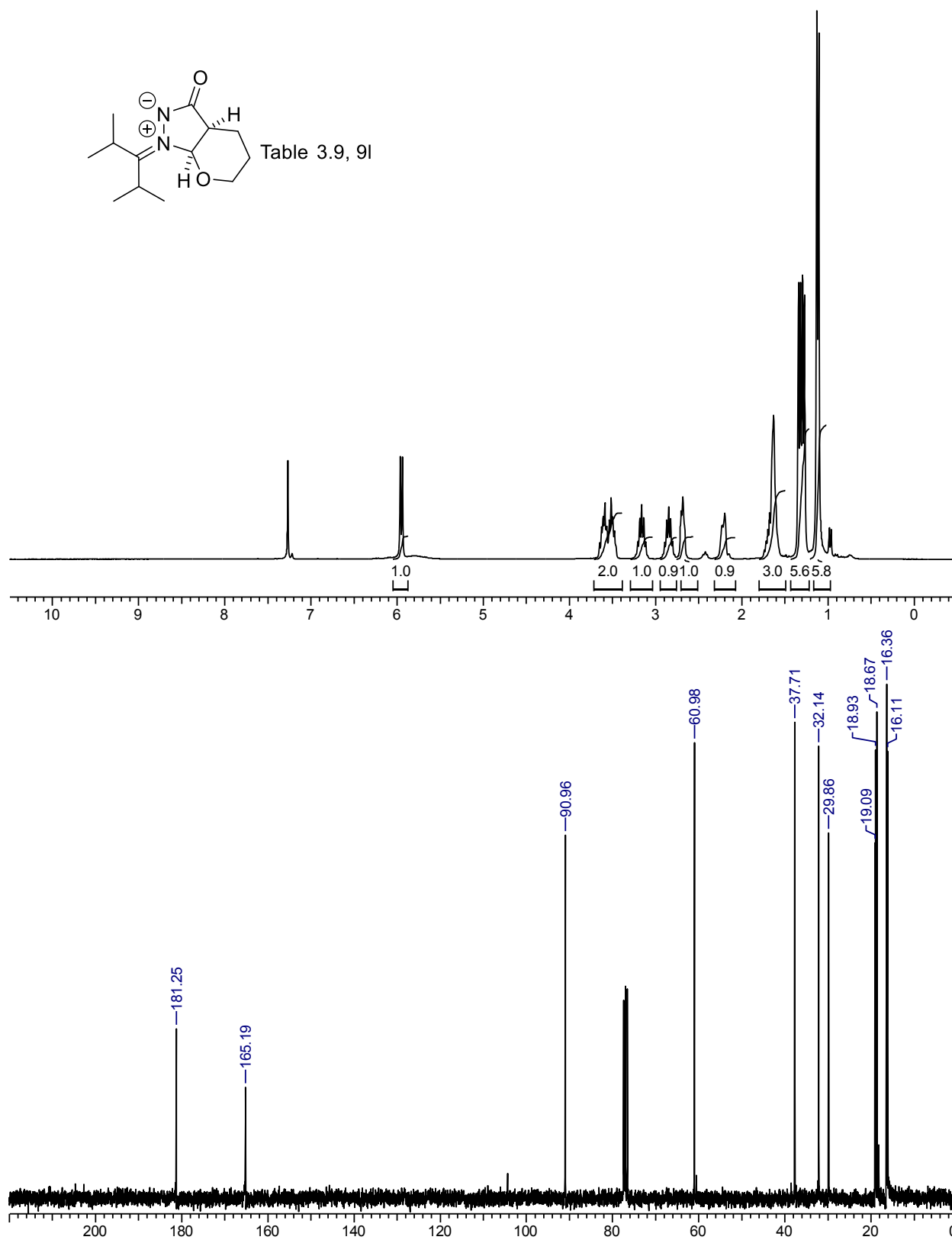


Table 3.9, 9I



equation 3.8, 11a

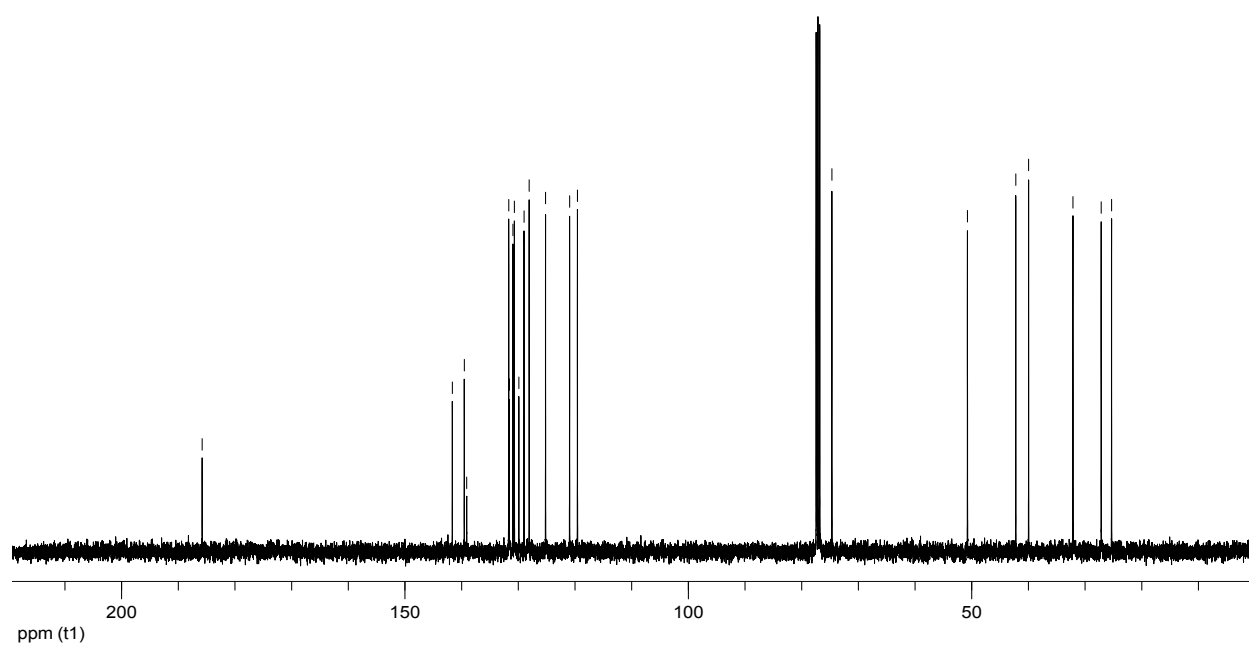
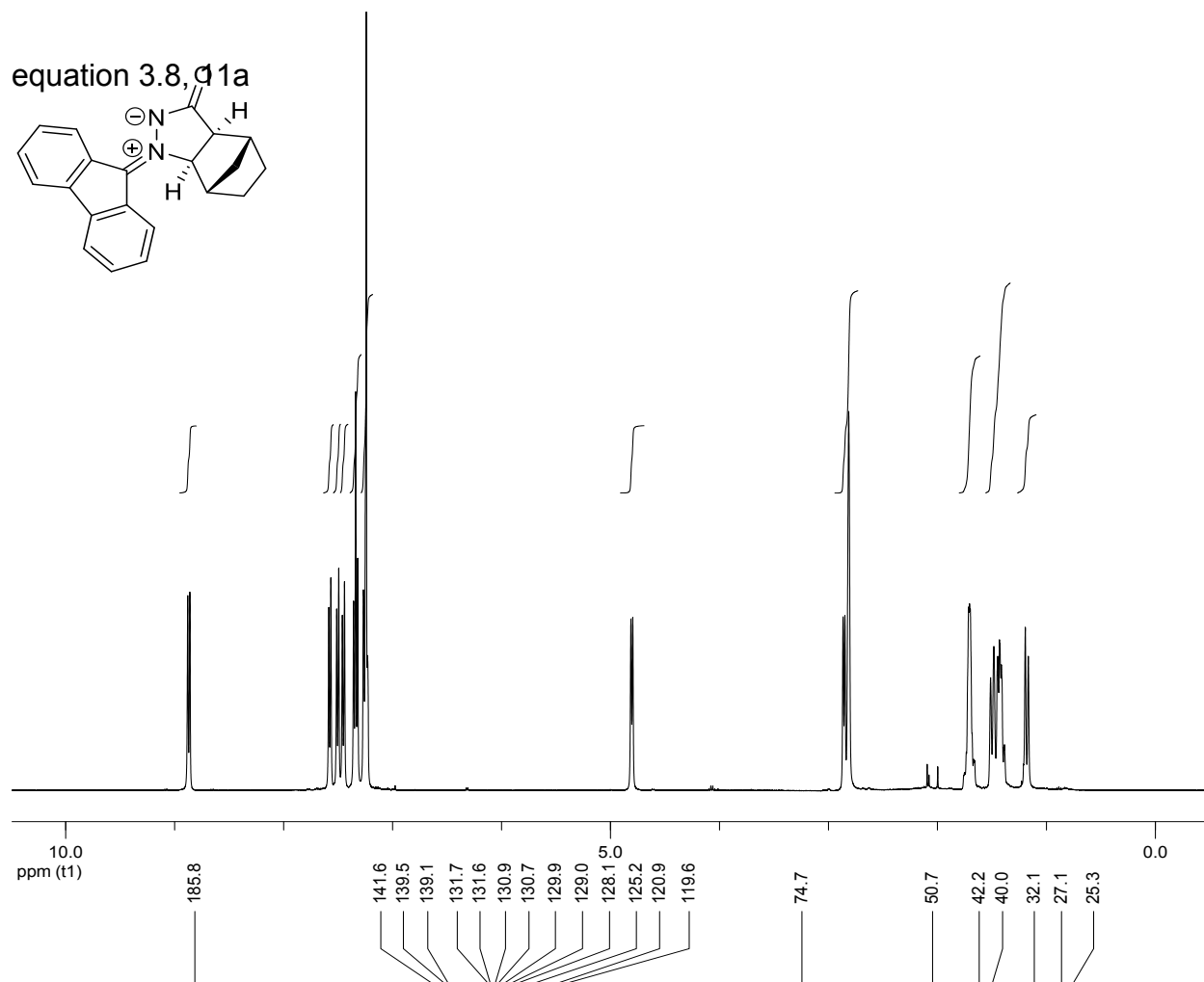
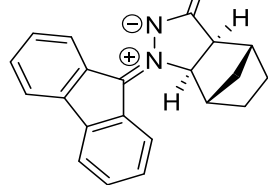
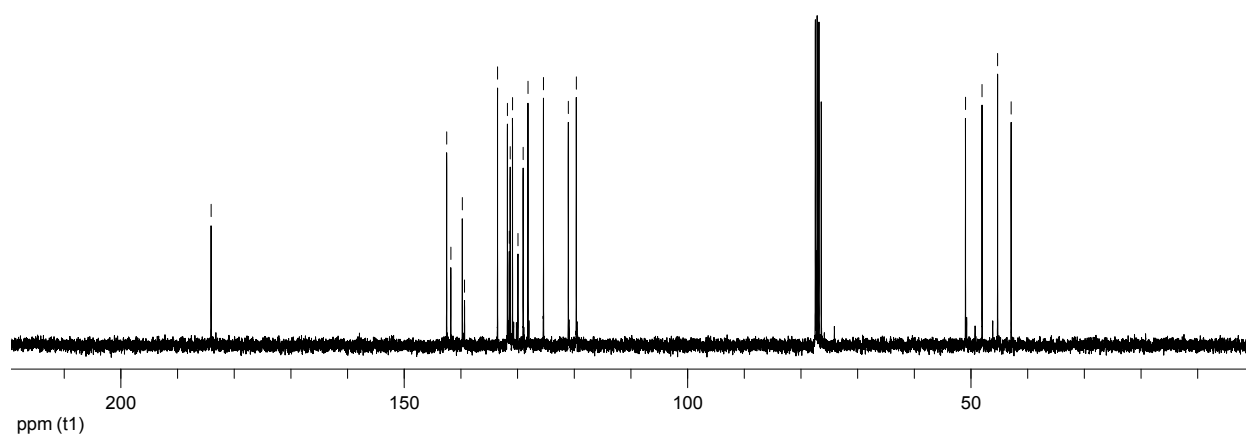
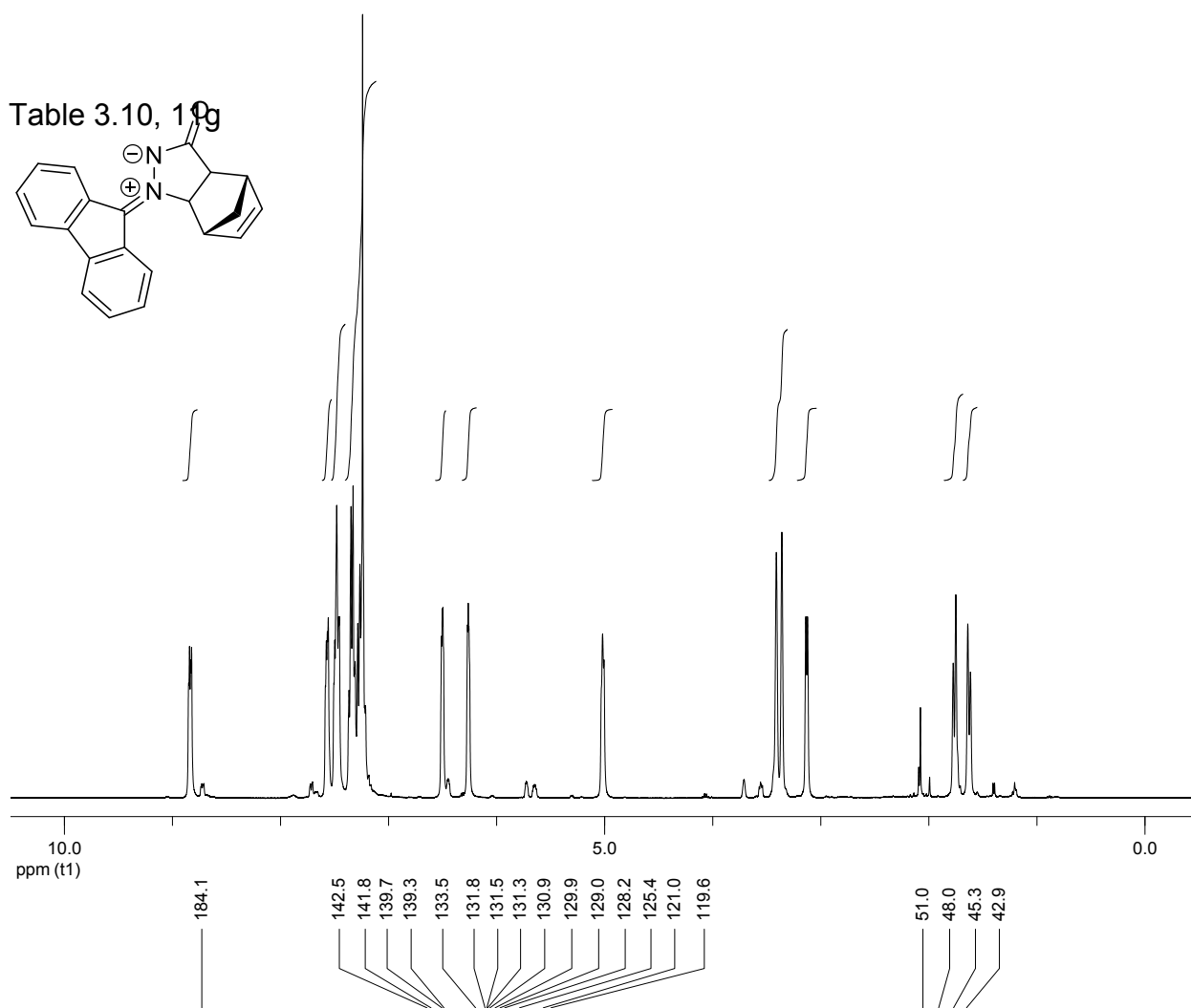
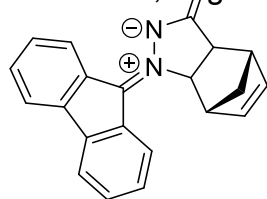
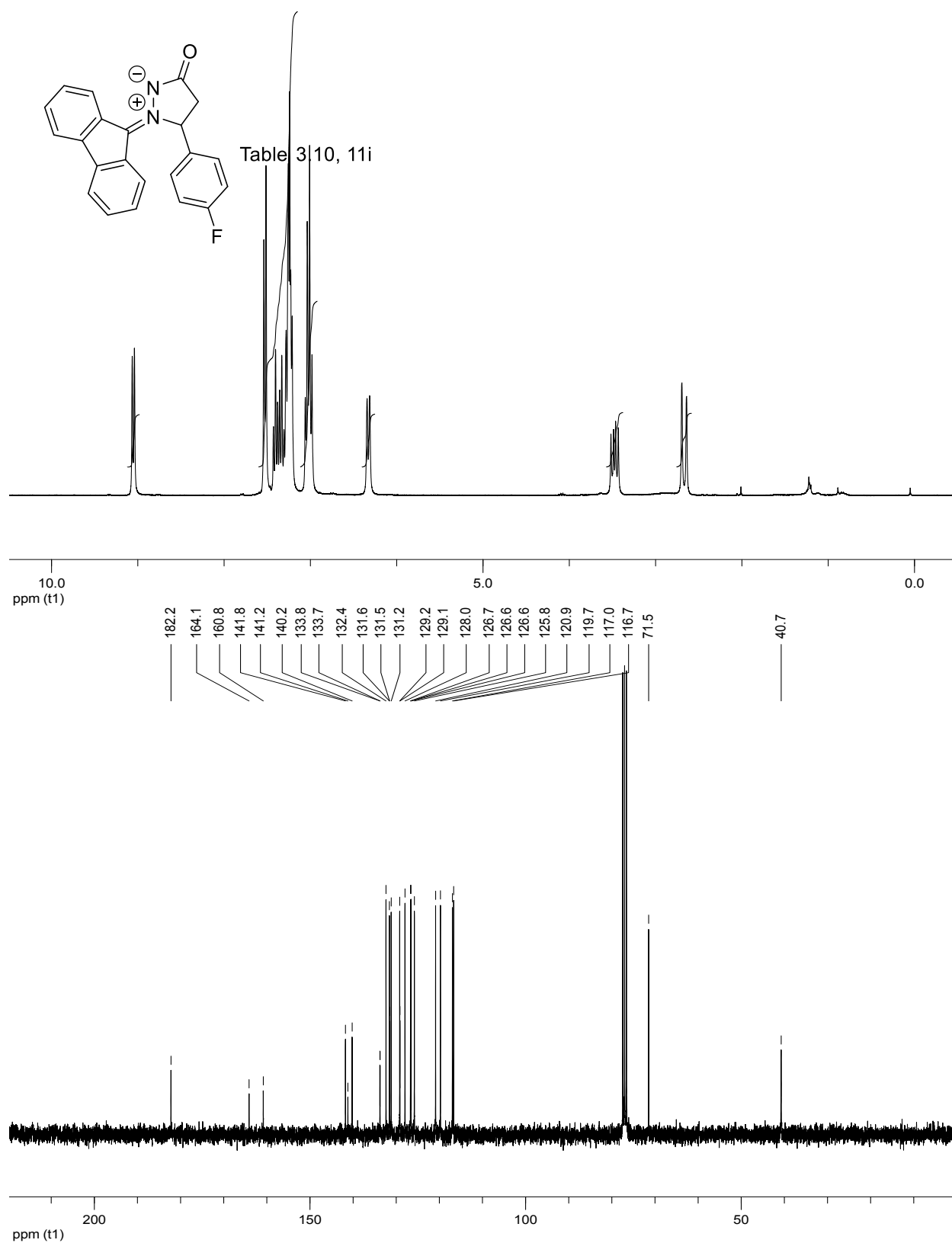
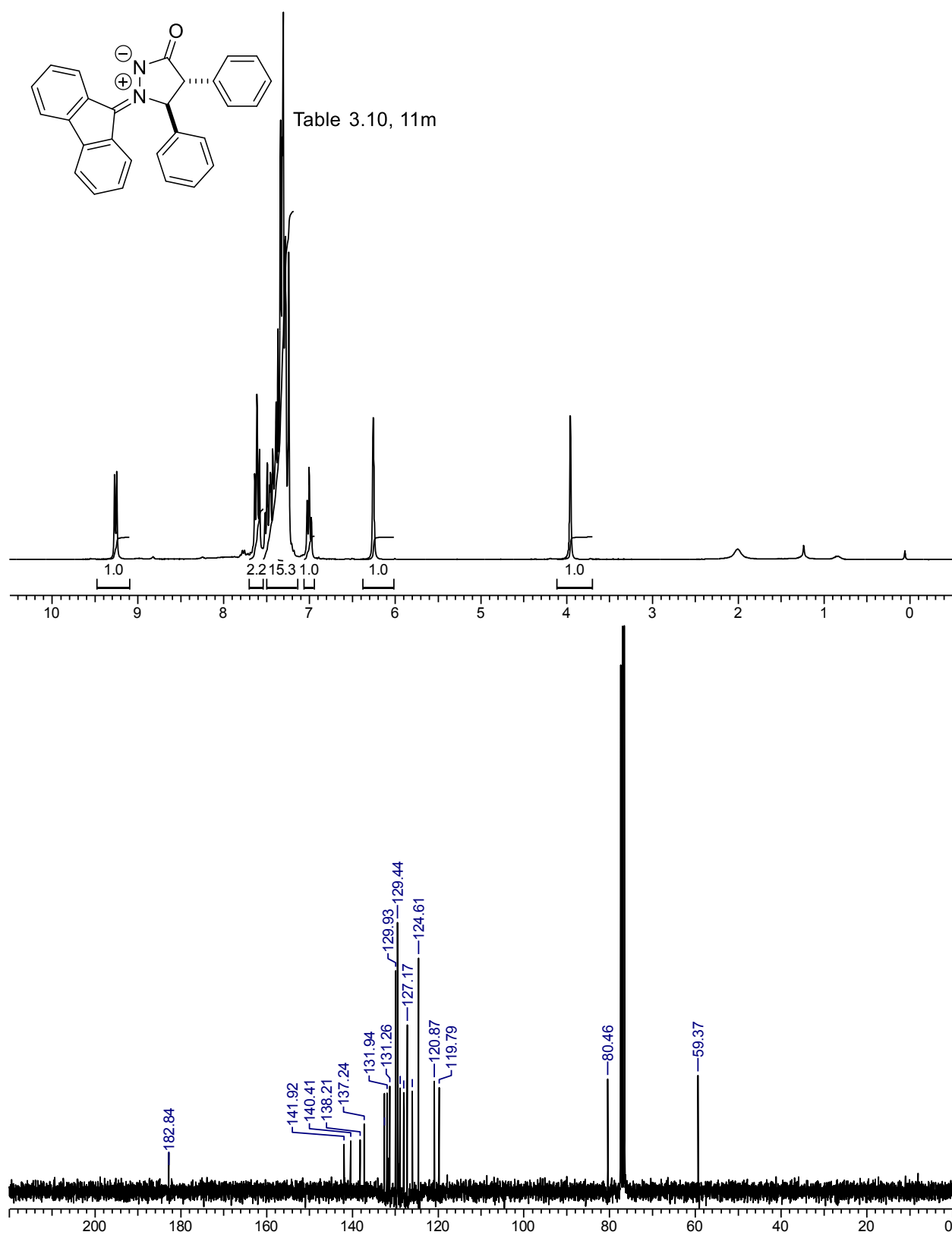
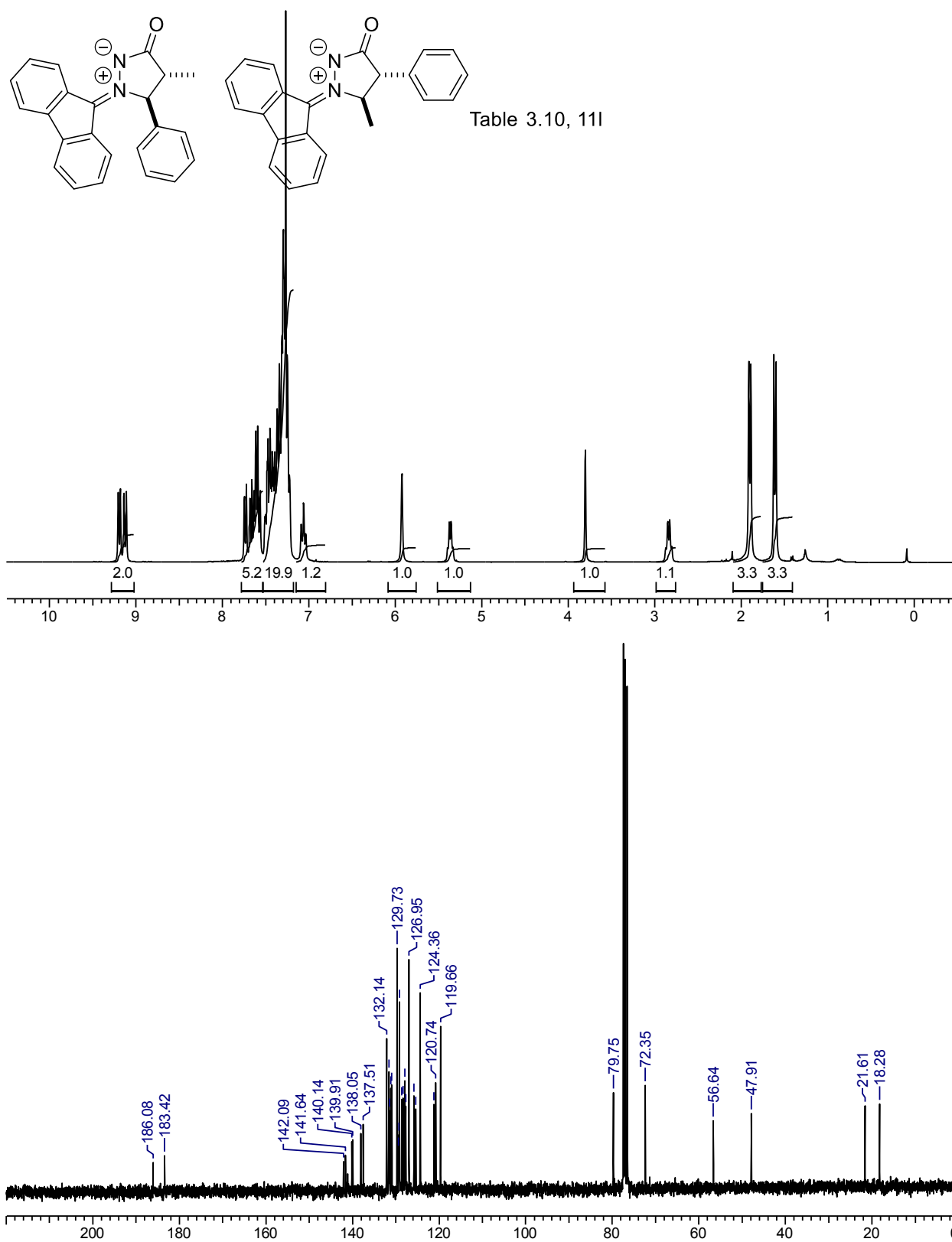


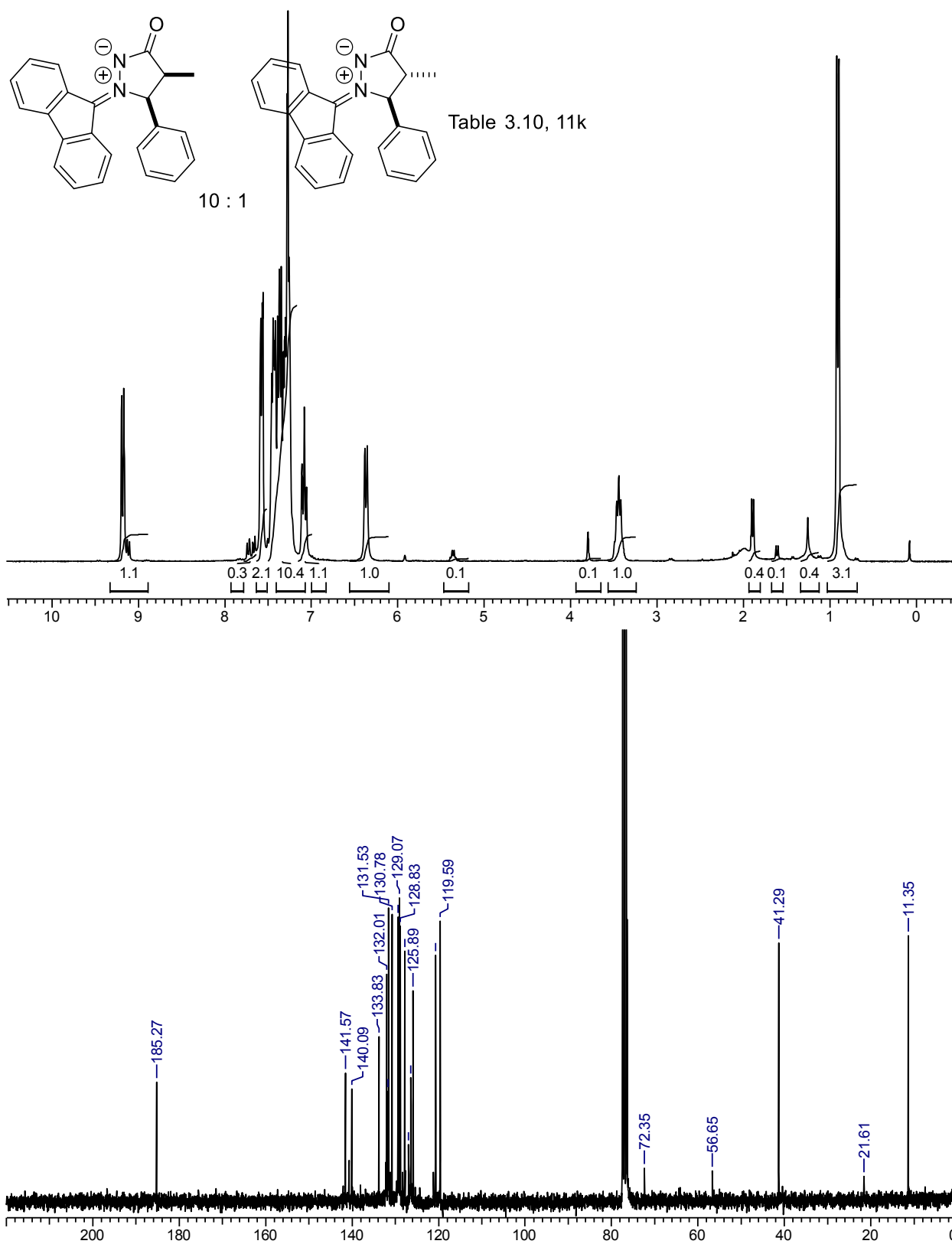
Table 3.10, 19g













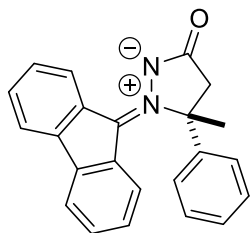
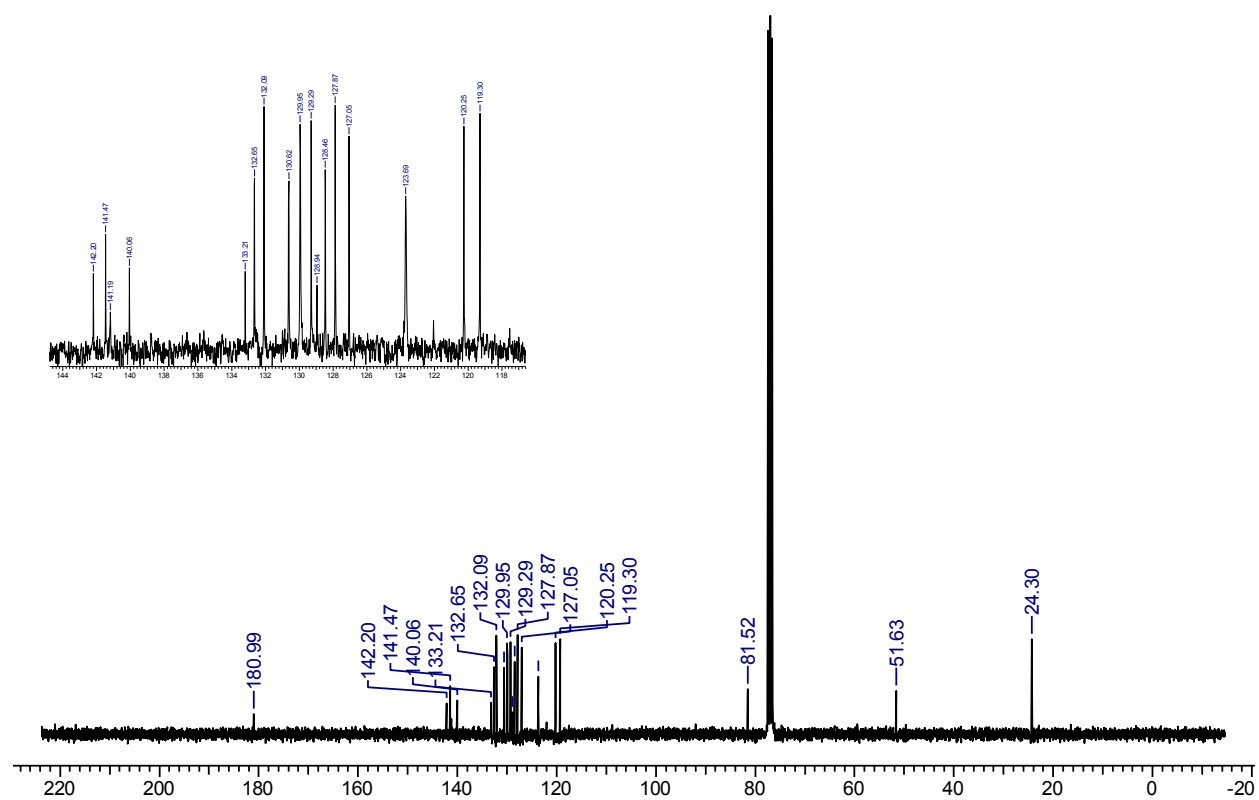
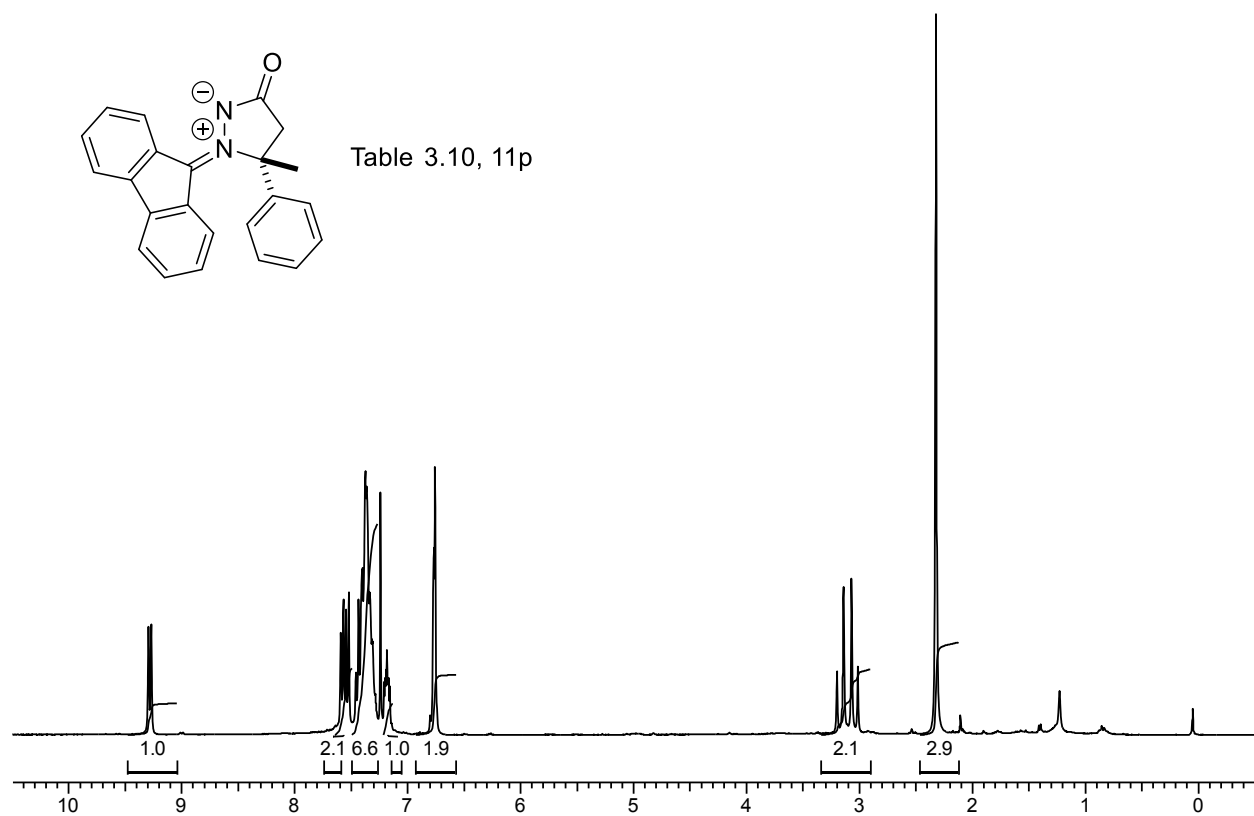
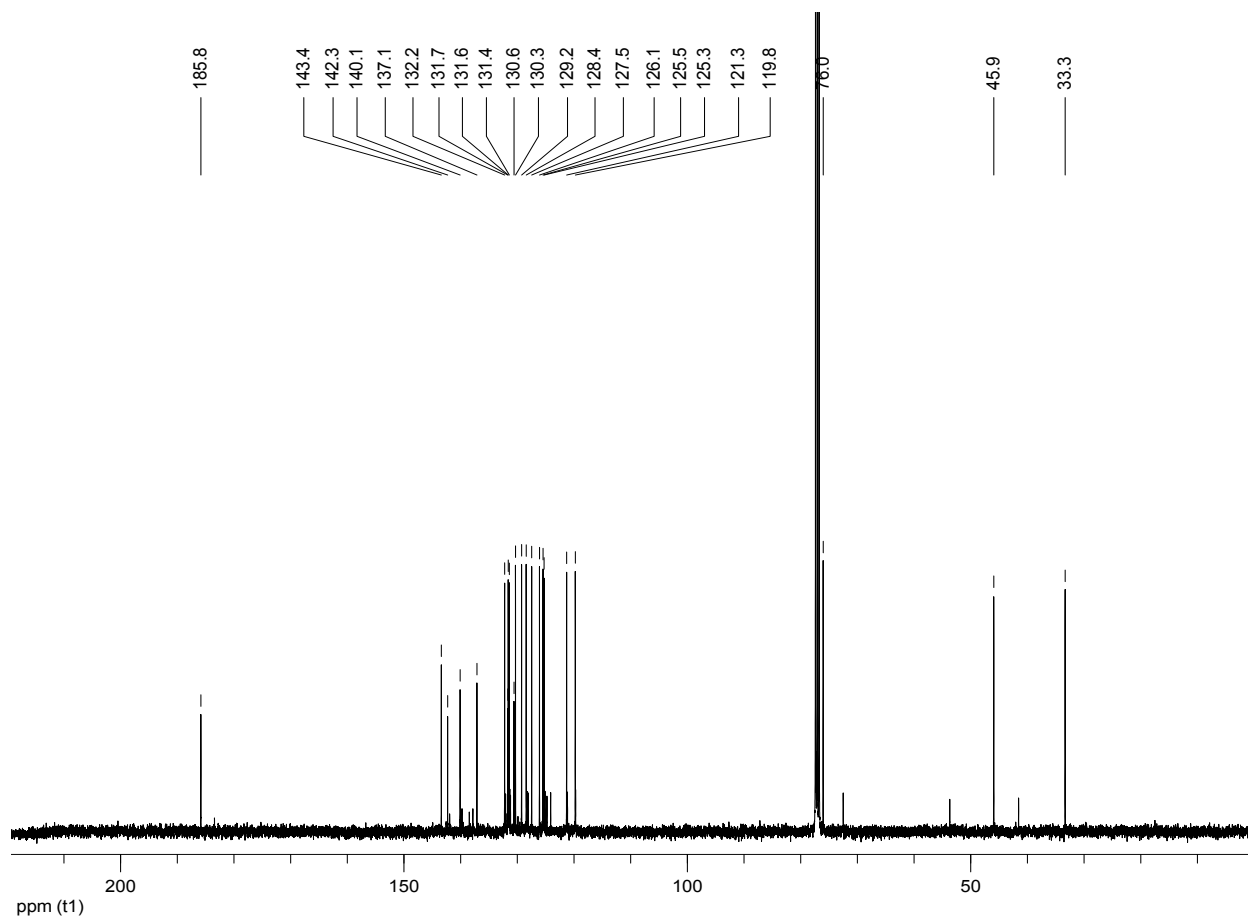
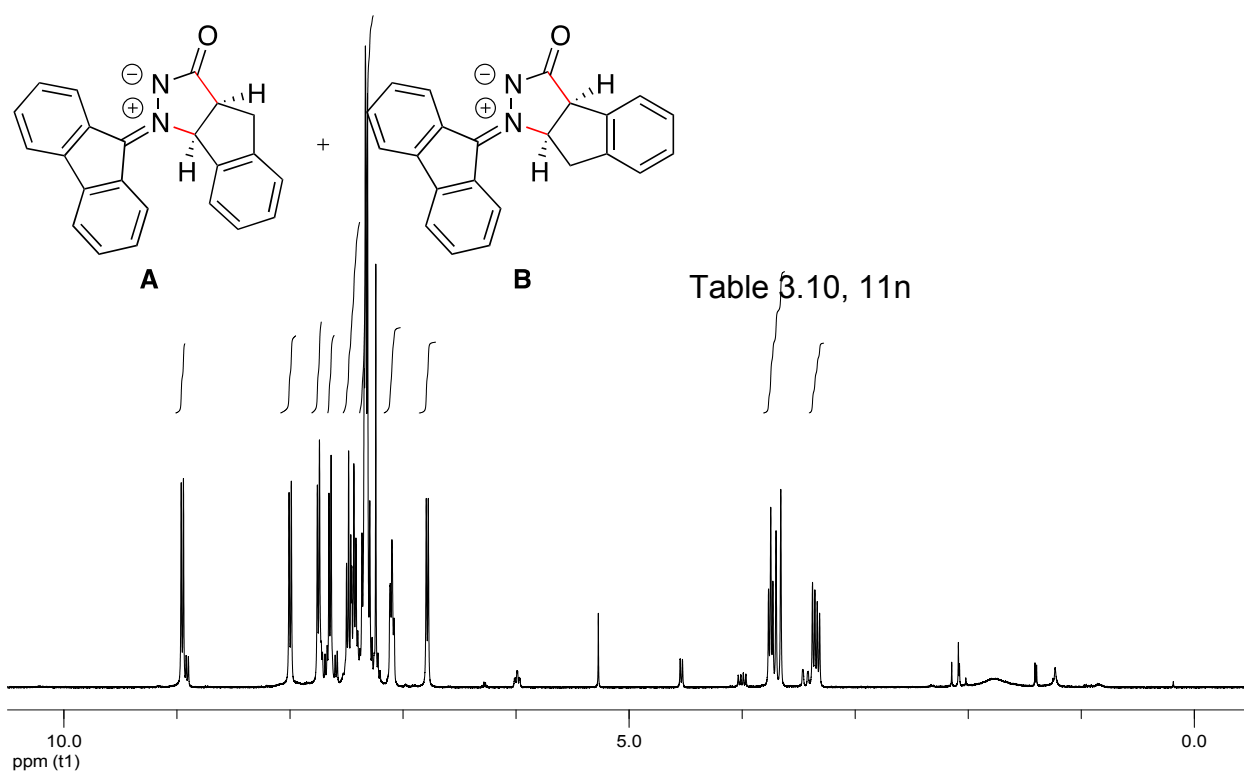
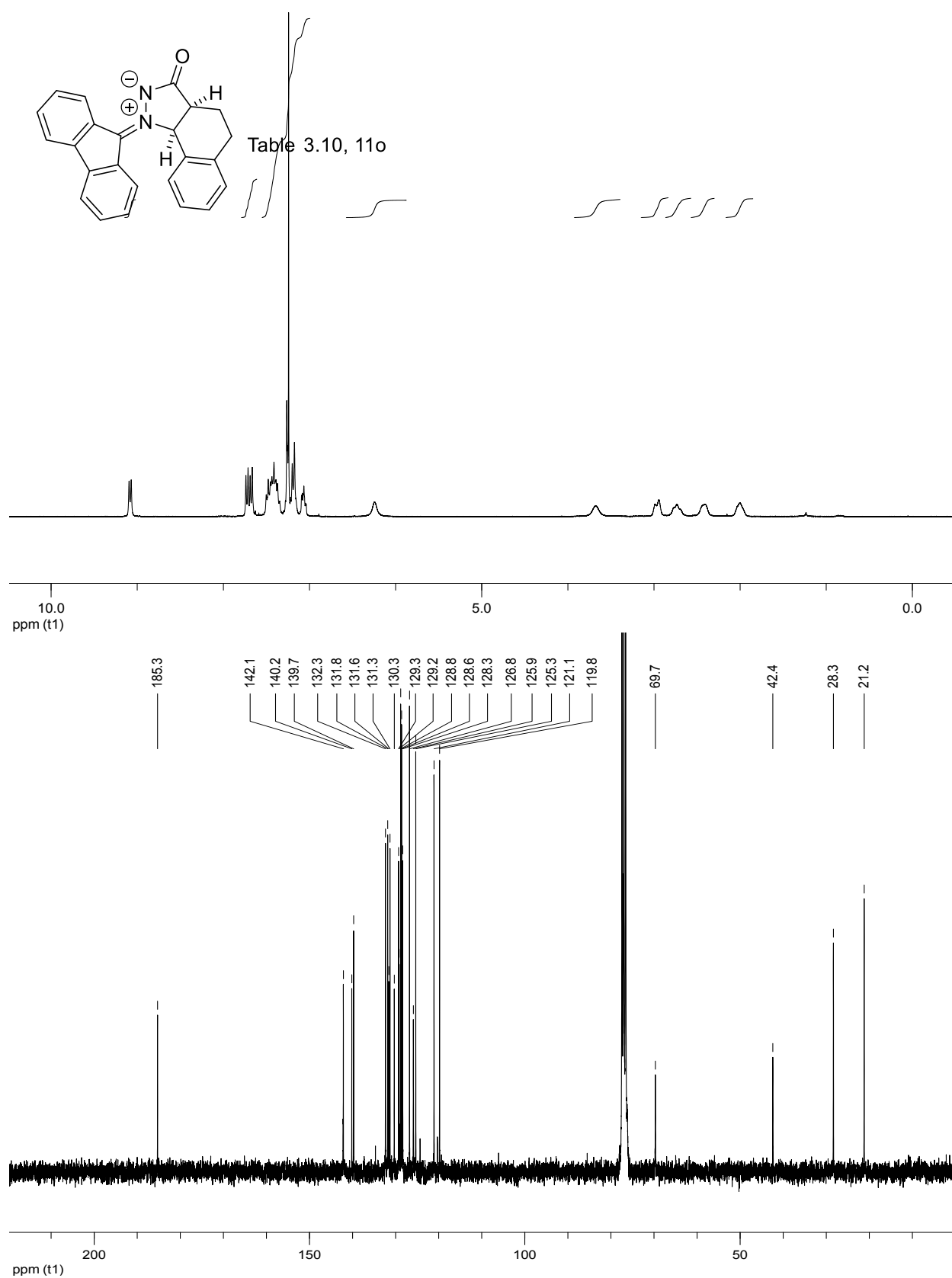
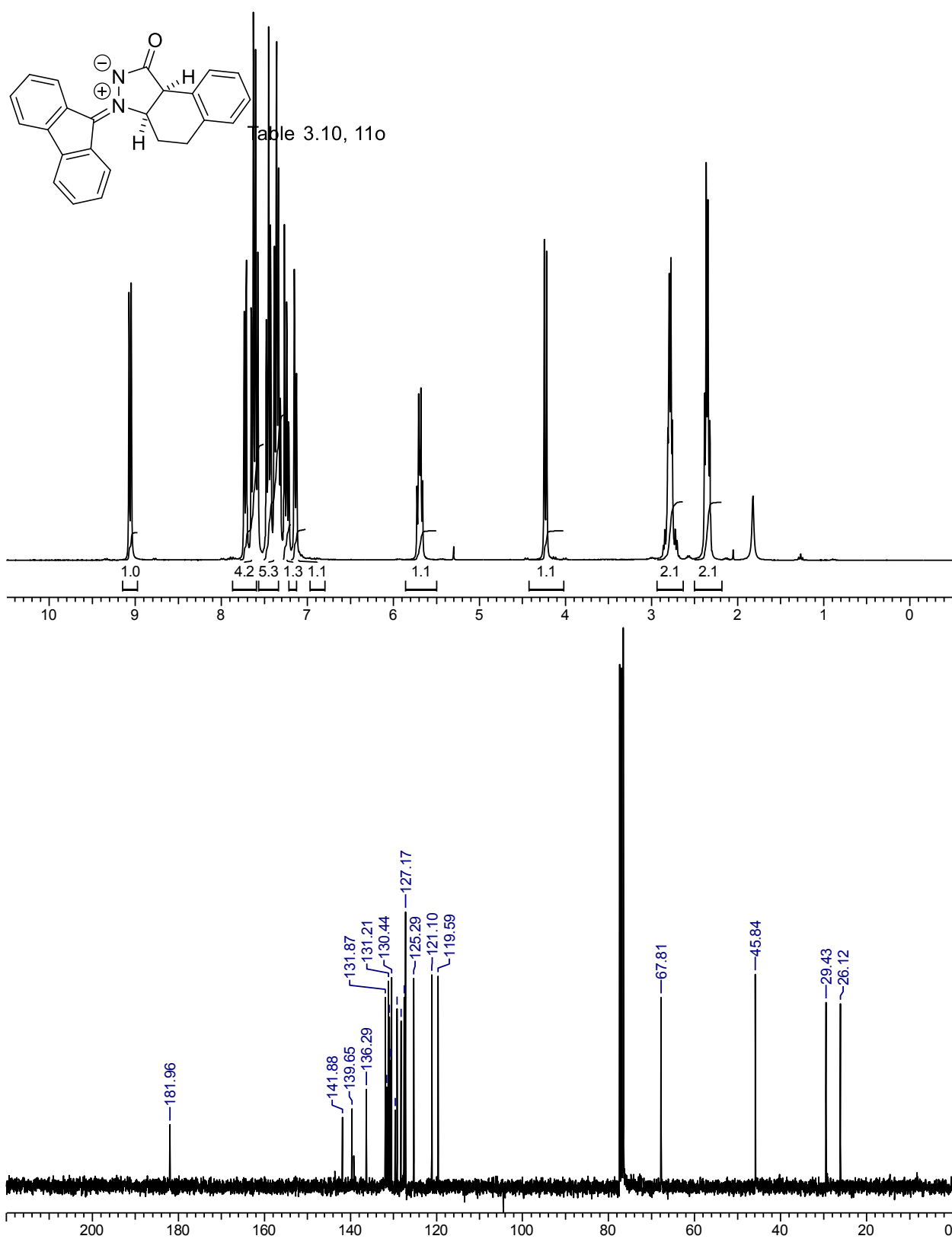


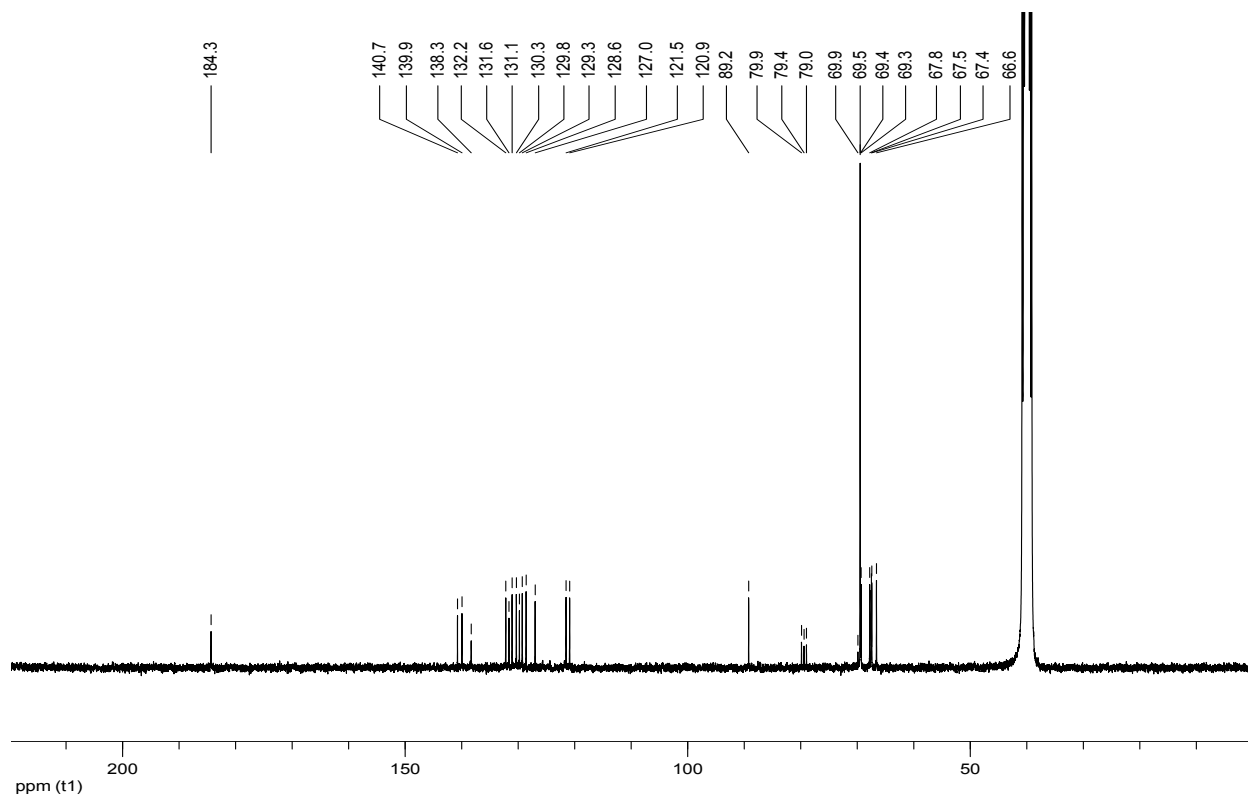
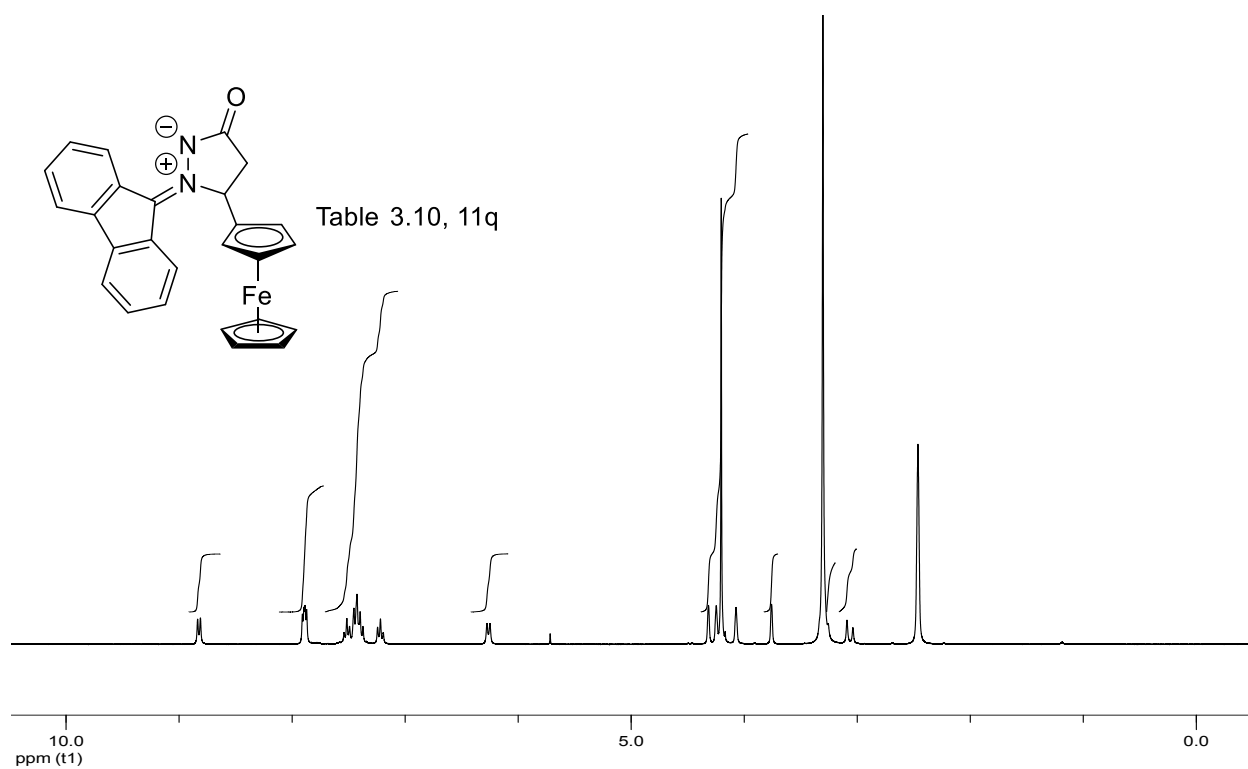
Table 3.10, 11p

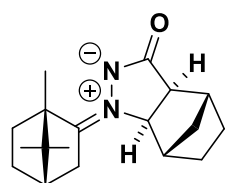






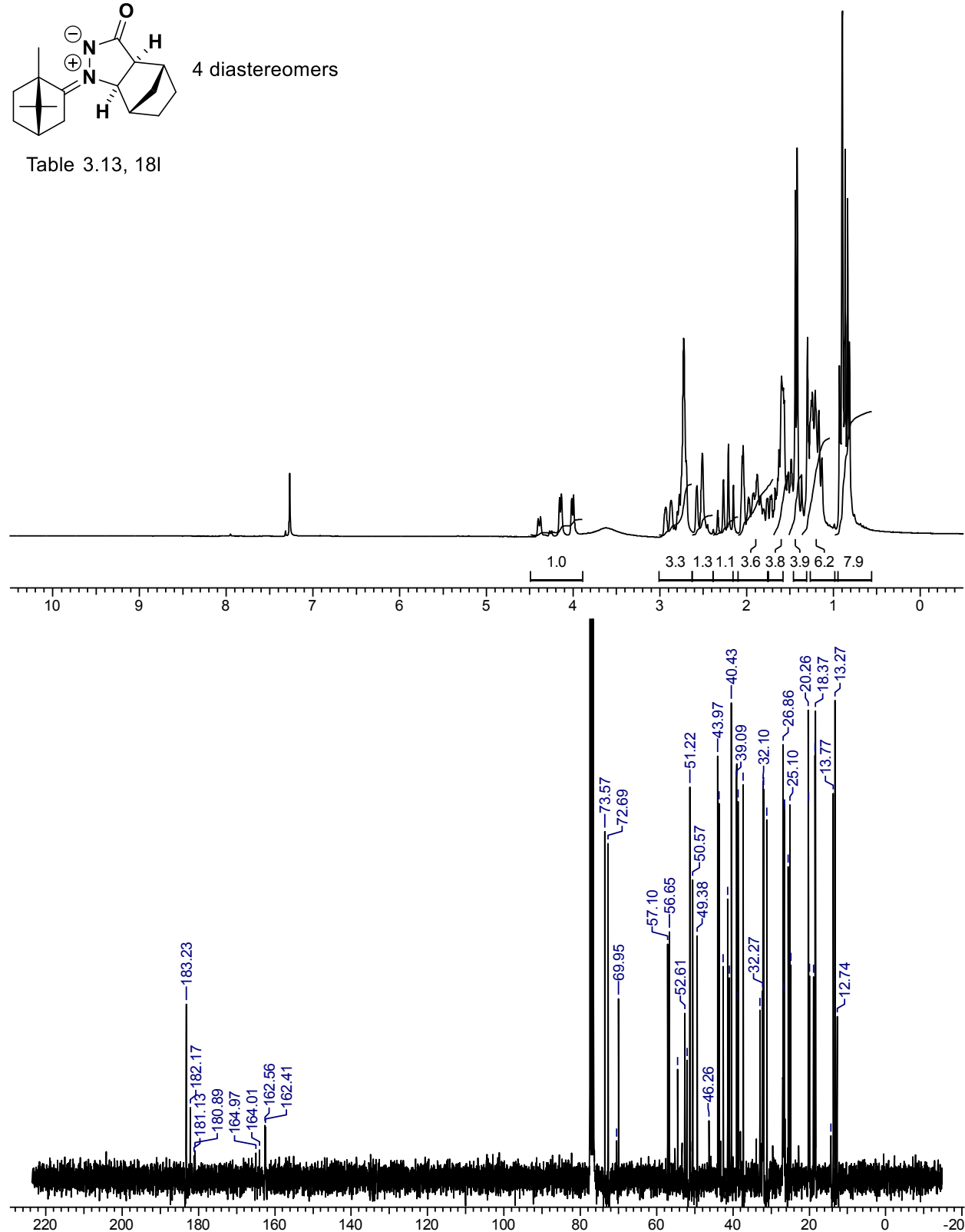






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Table 3.13, 18l



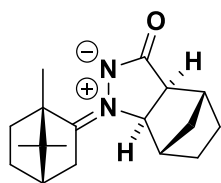
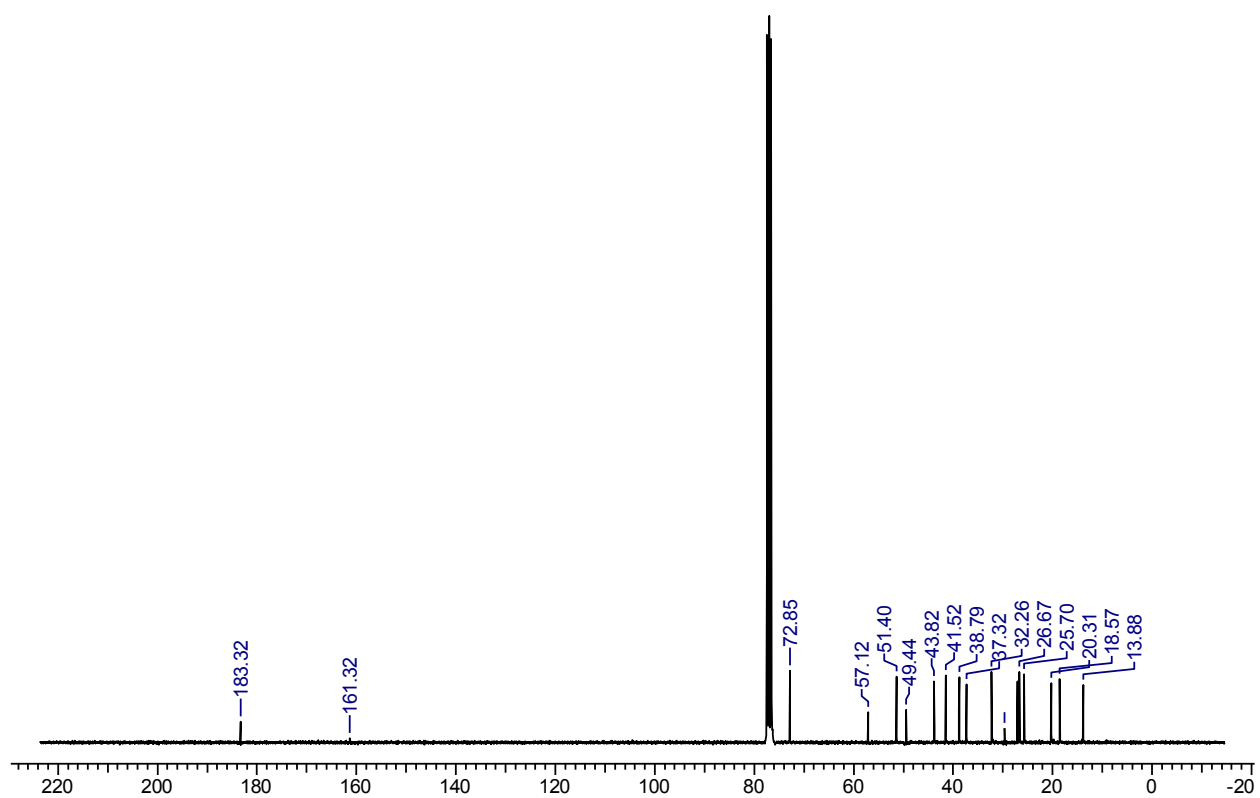
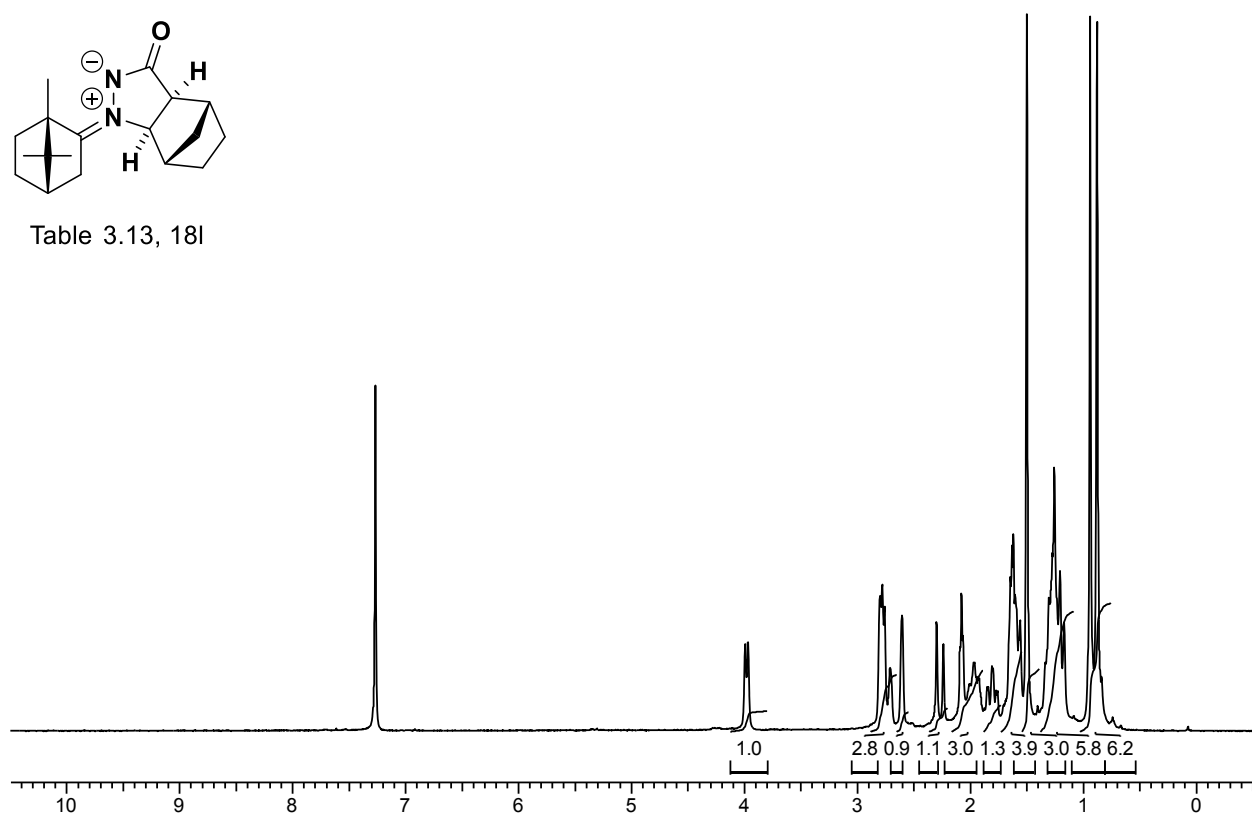


Table 3.13, 18l



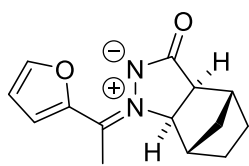
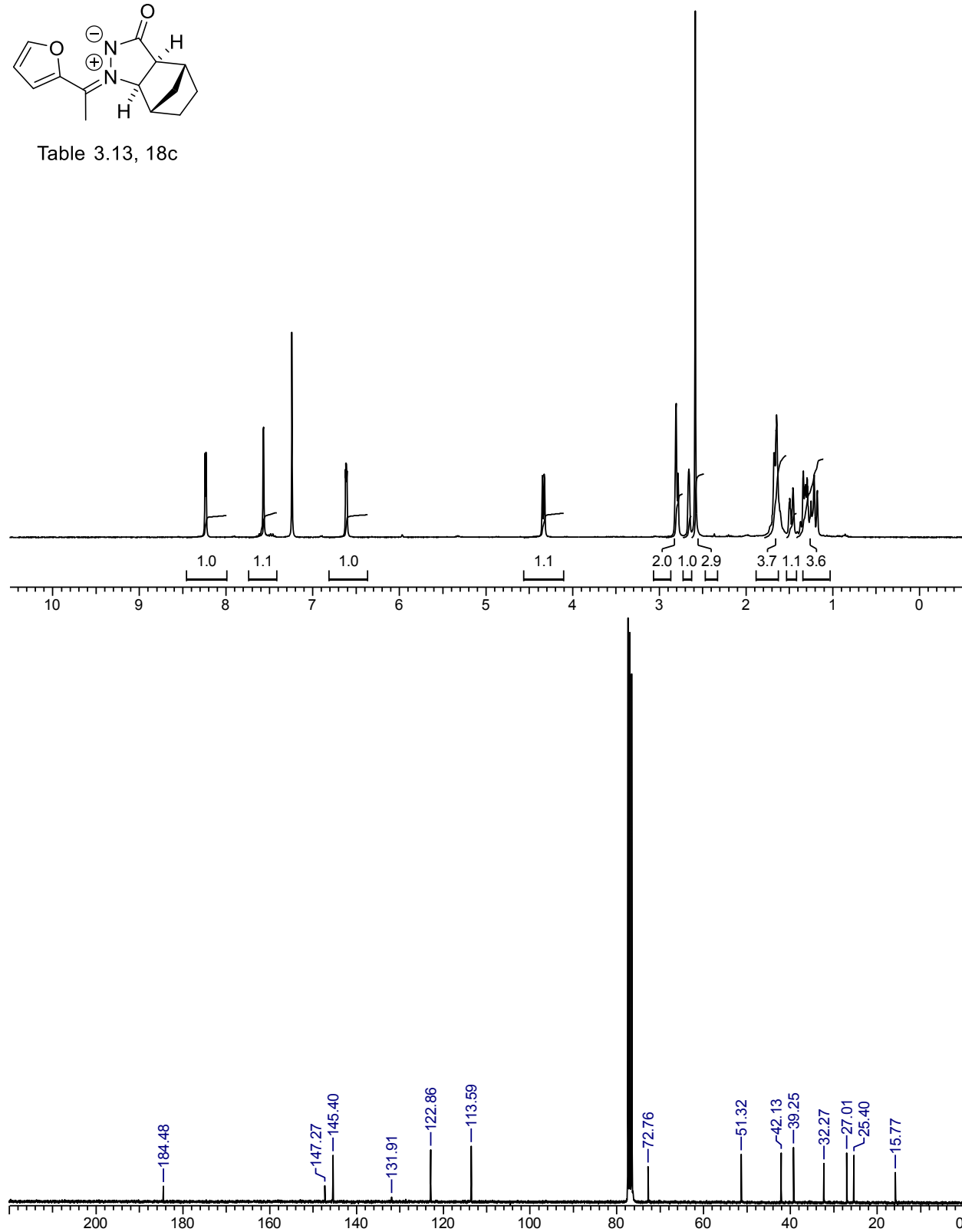
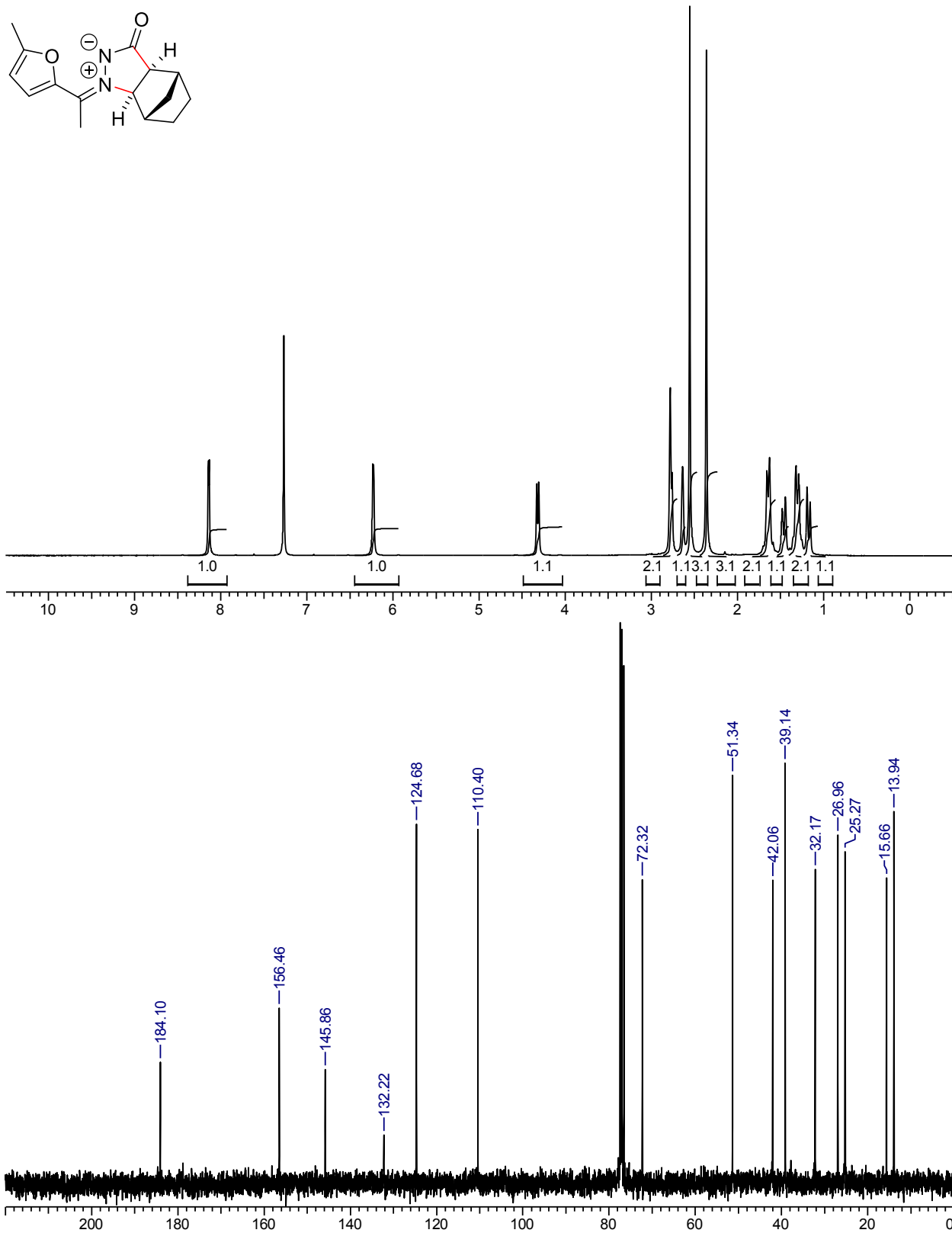


Table 3.13, 18c







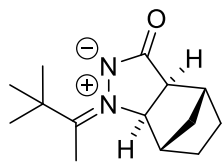
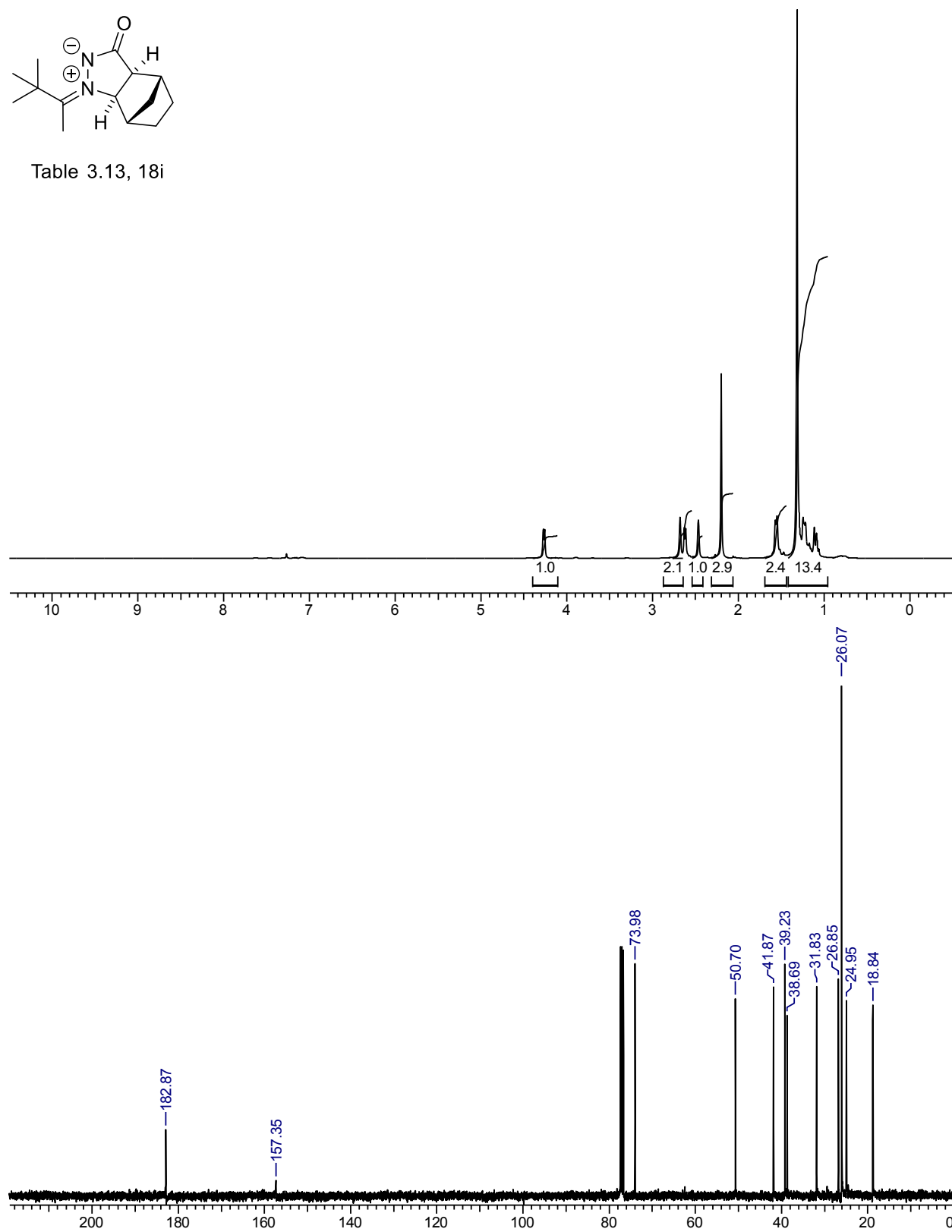
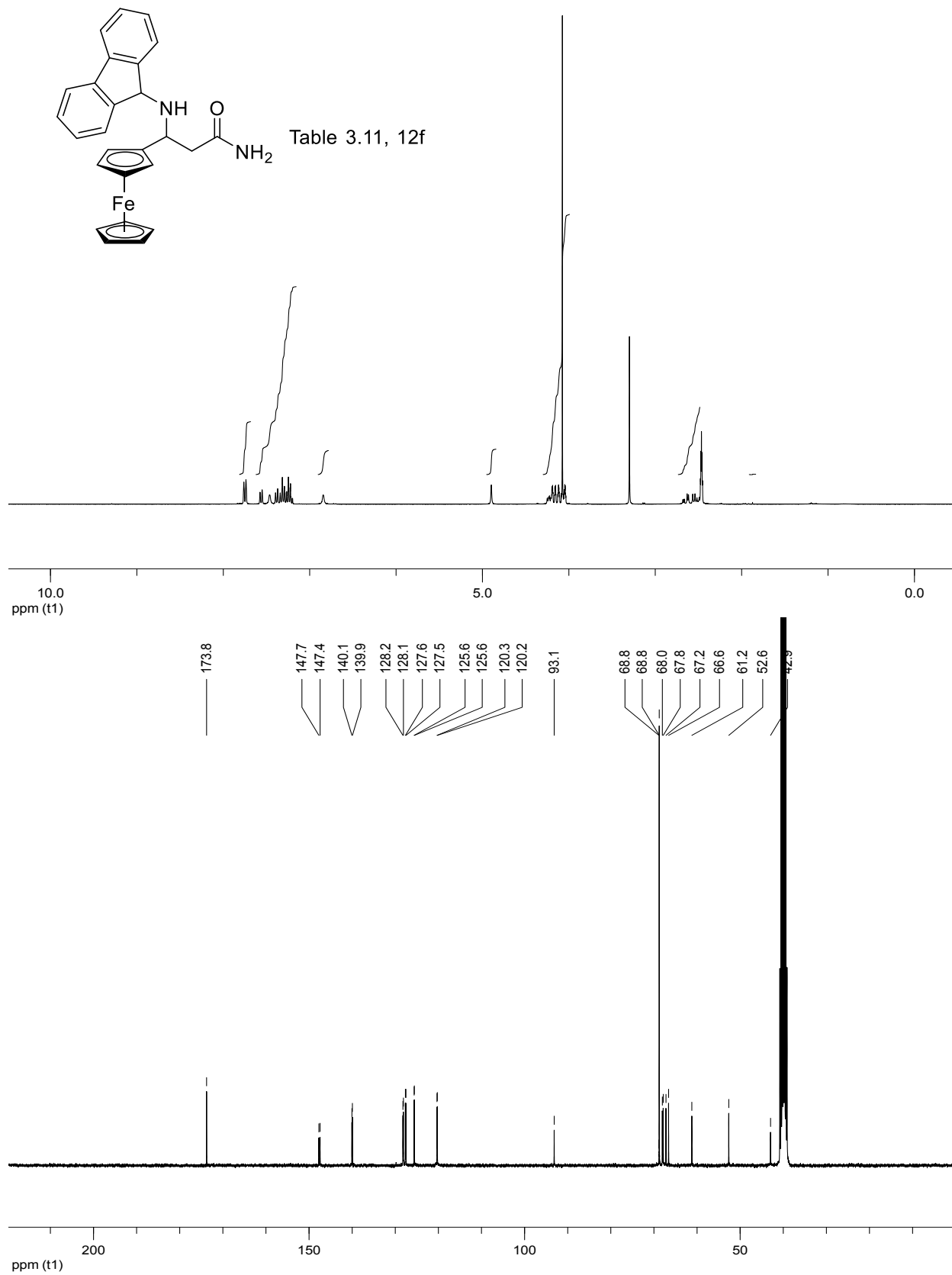
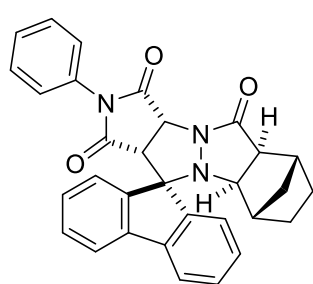


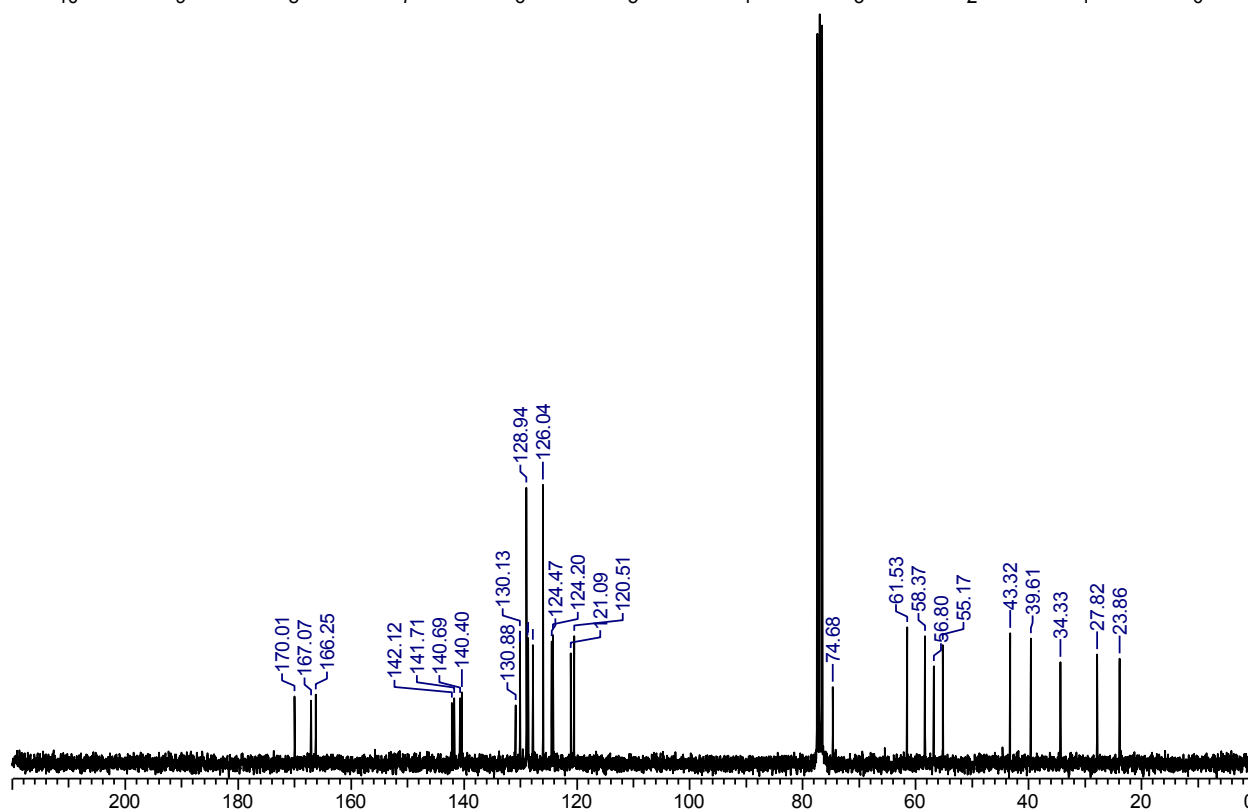
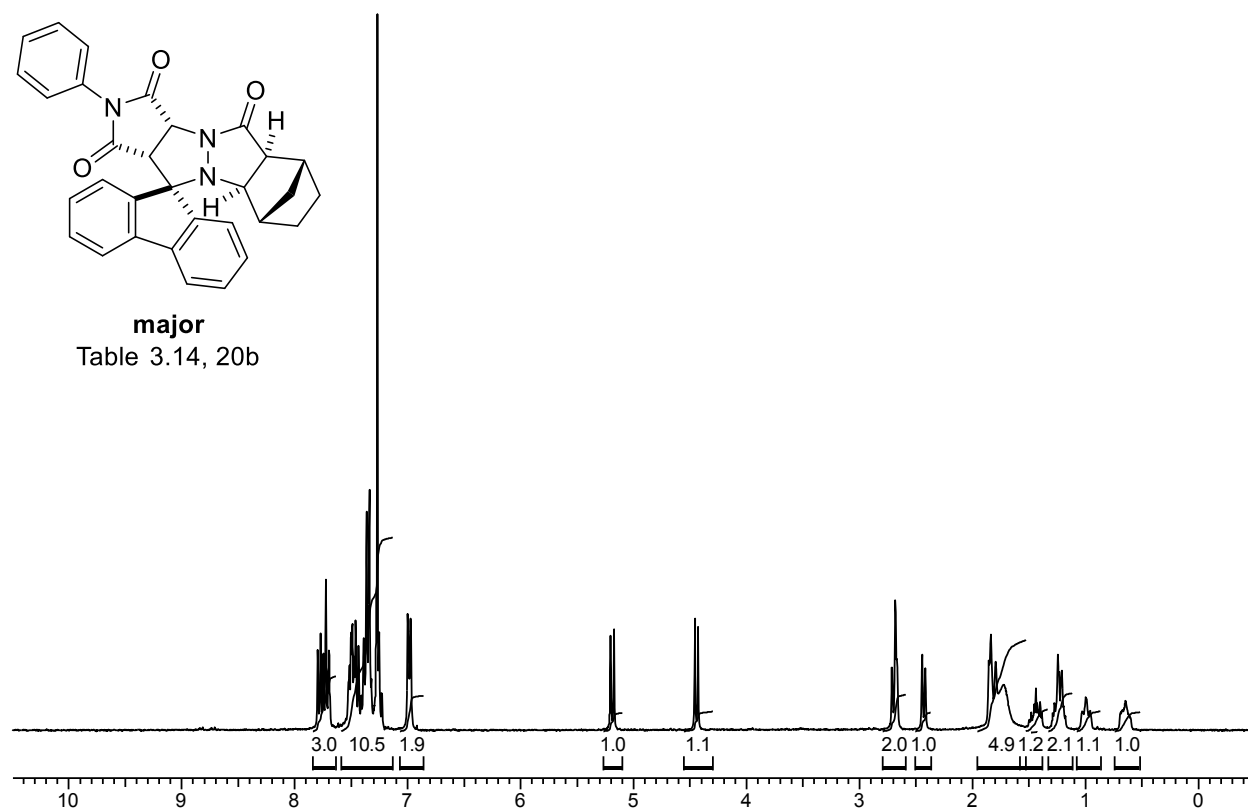
Table 3.13, 18i

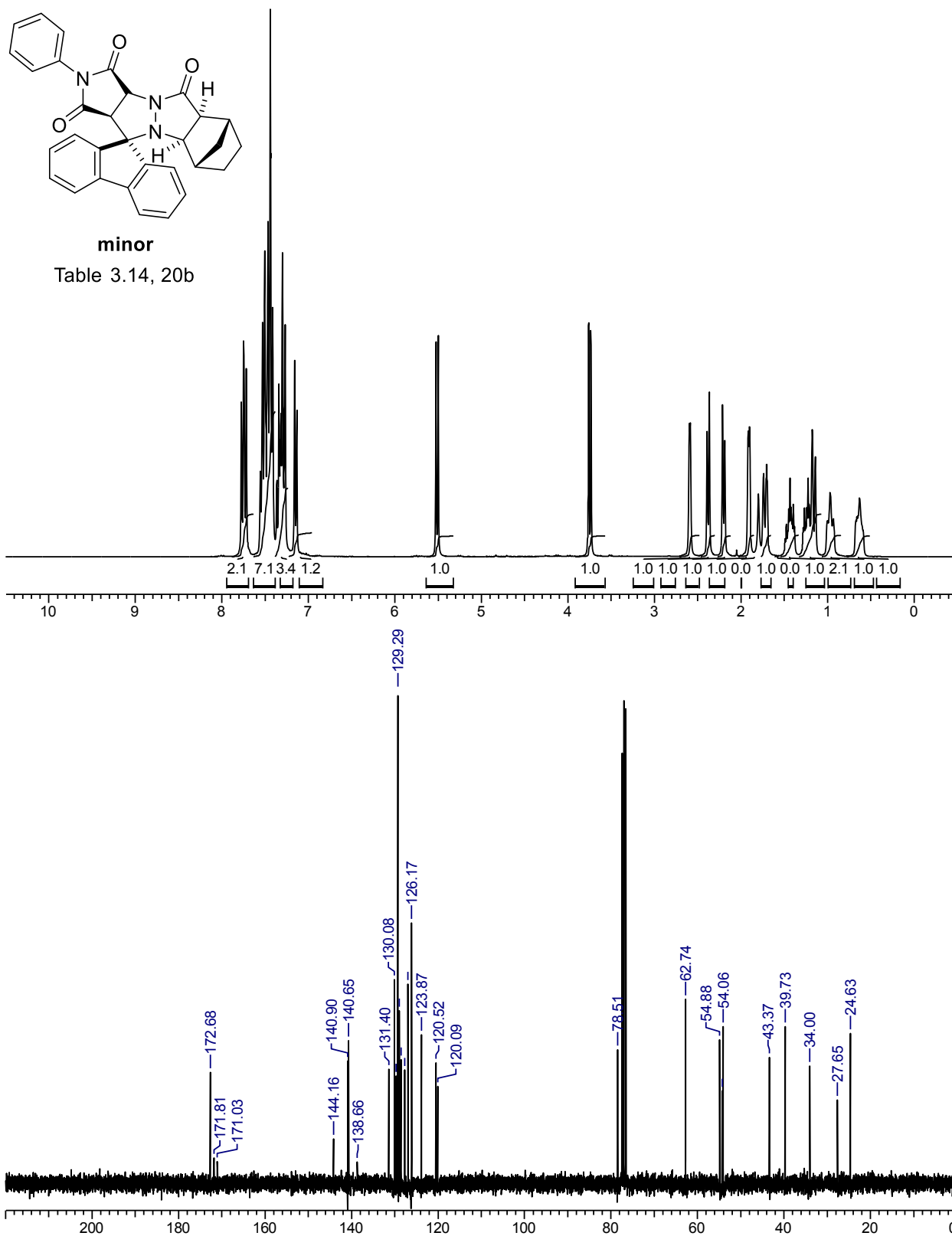






**major**  
Table 3.14, 20b





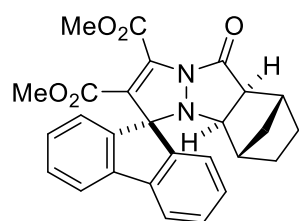
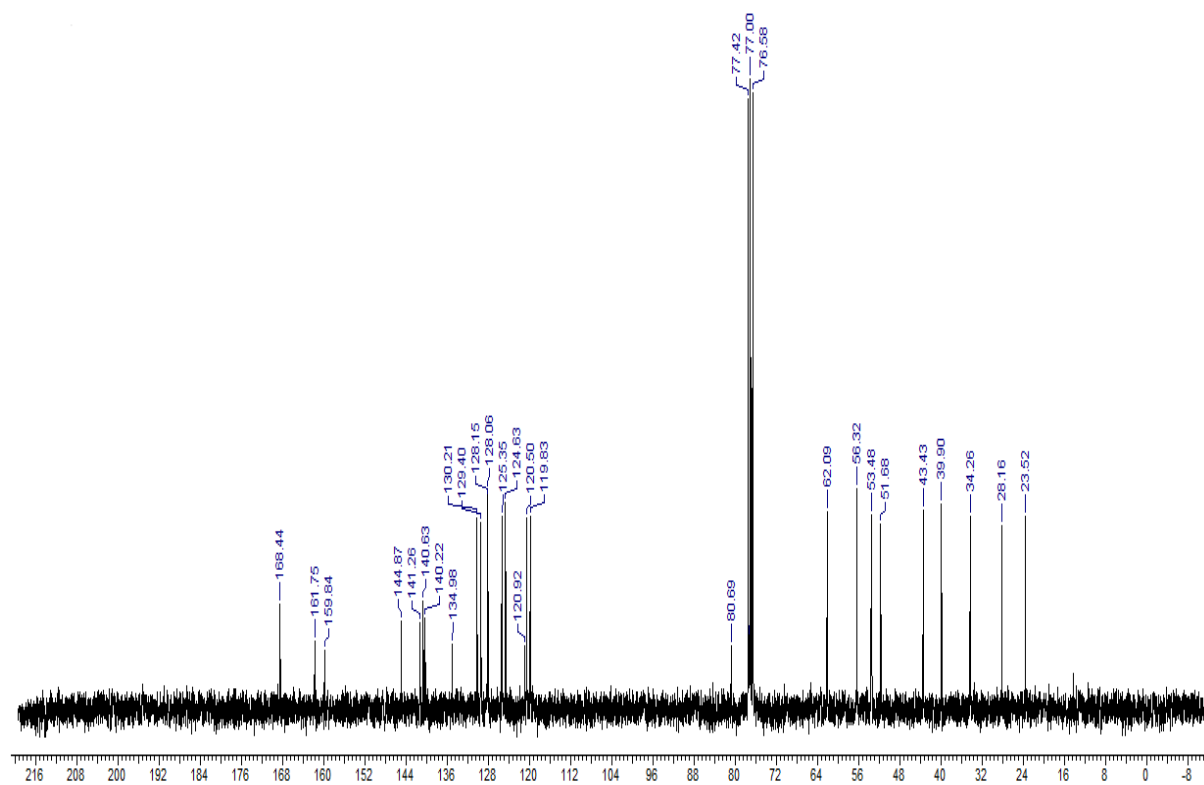
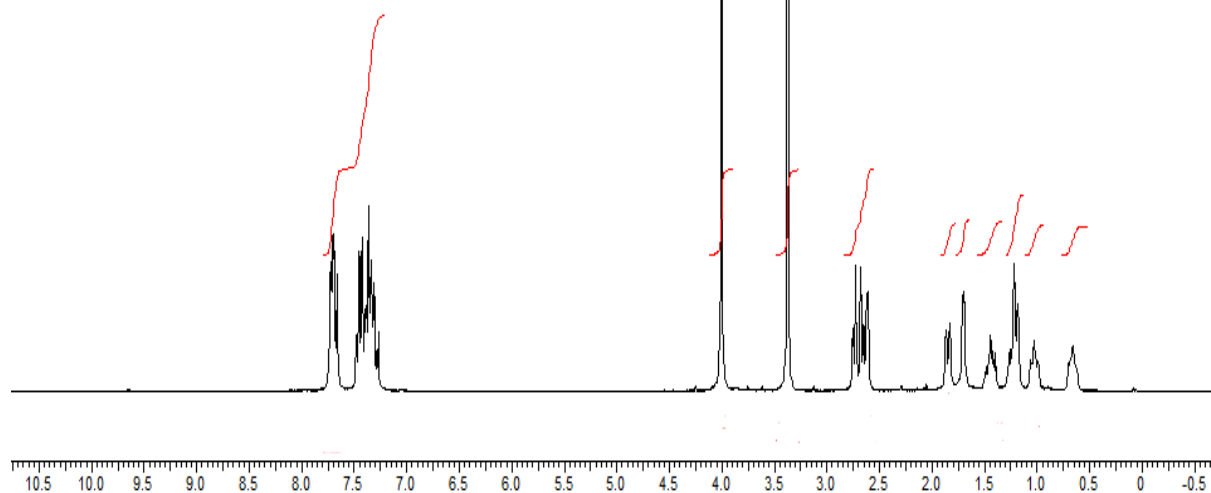
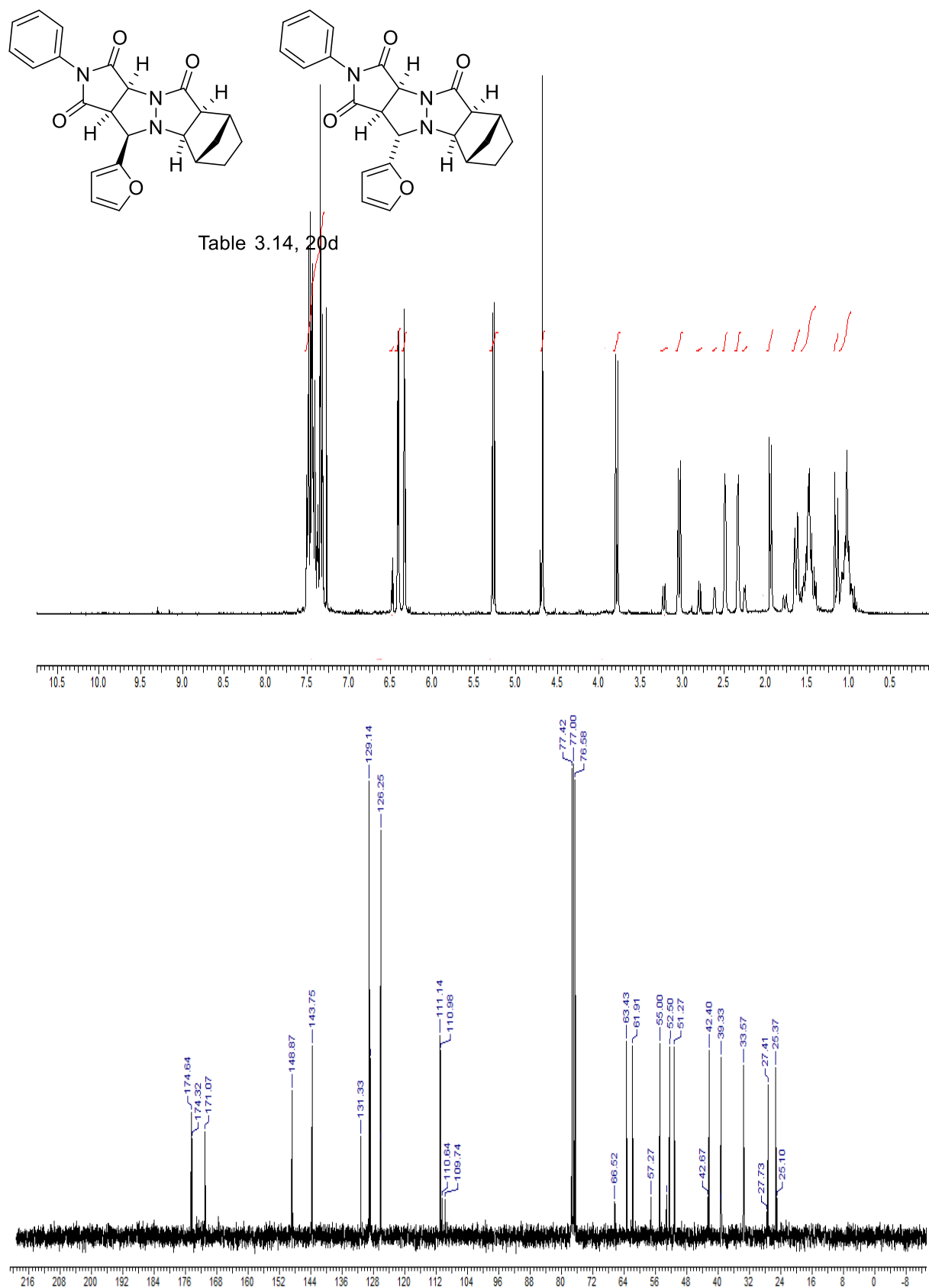
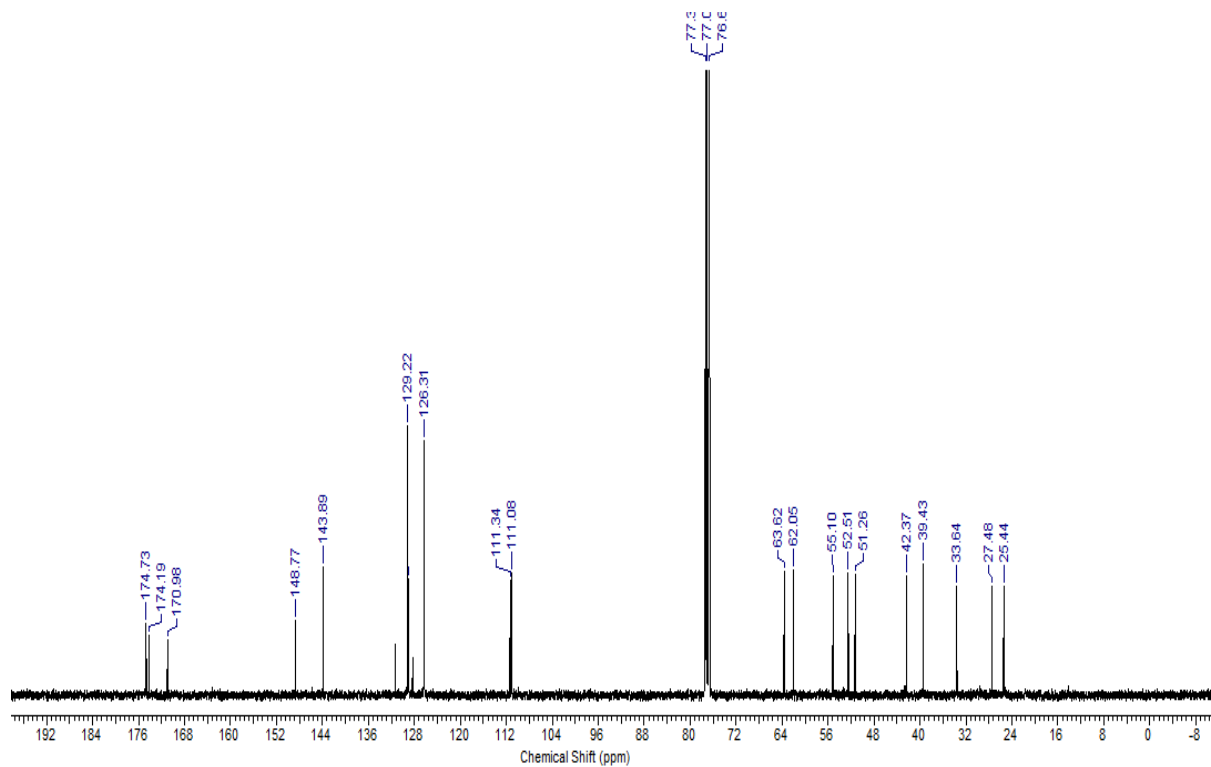
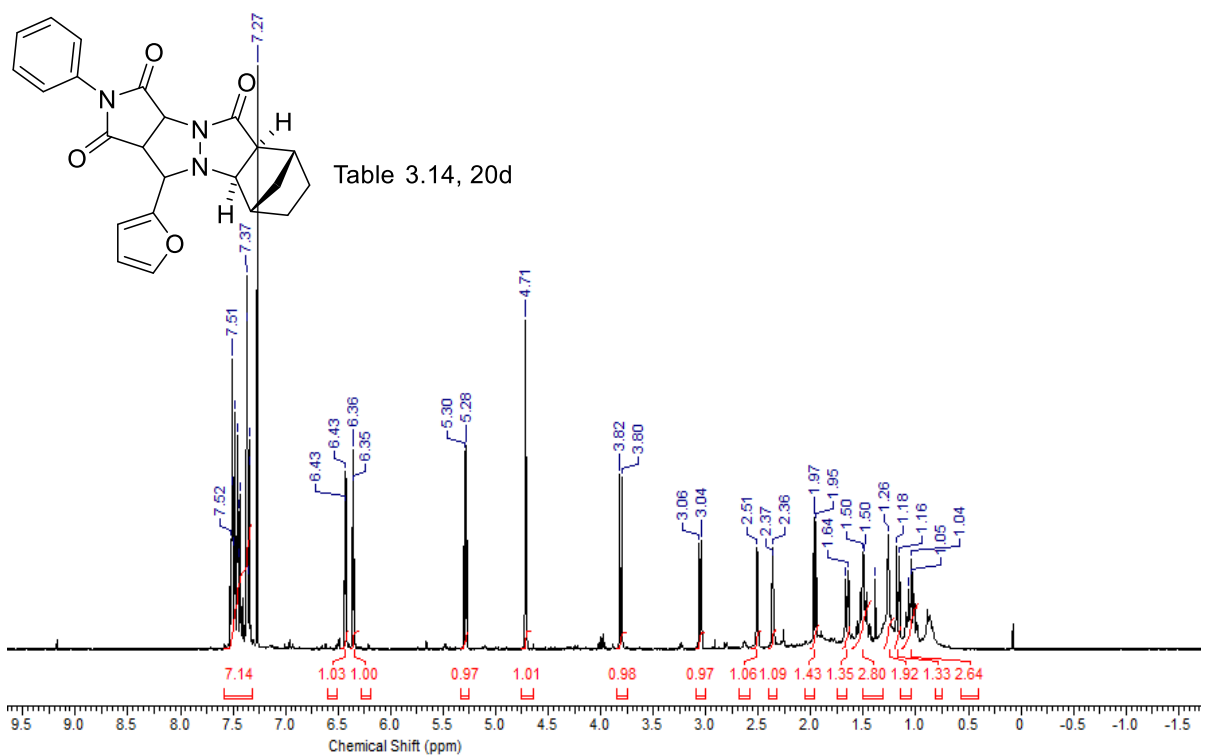


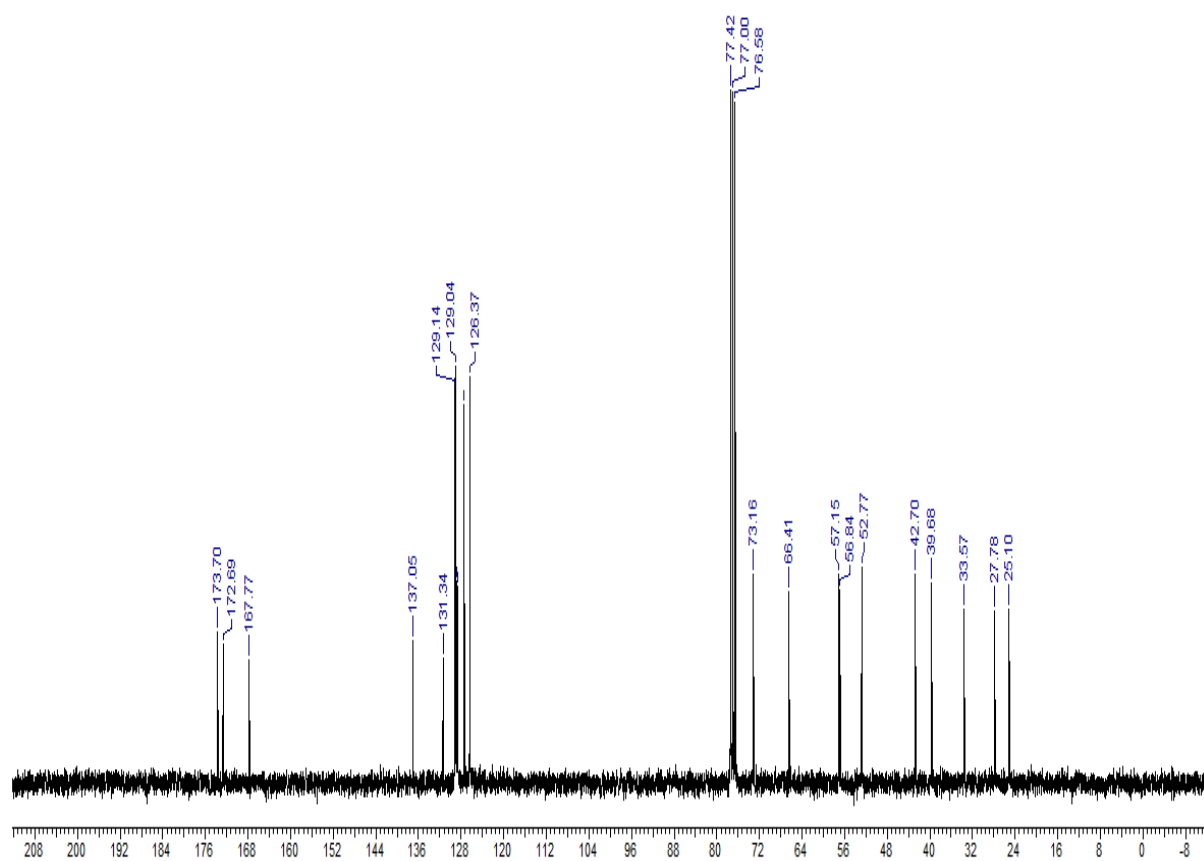
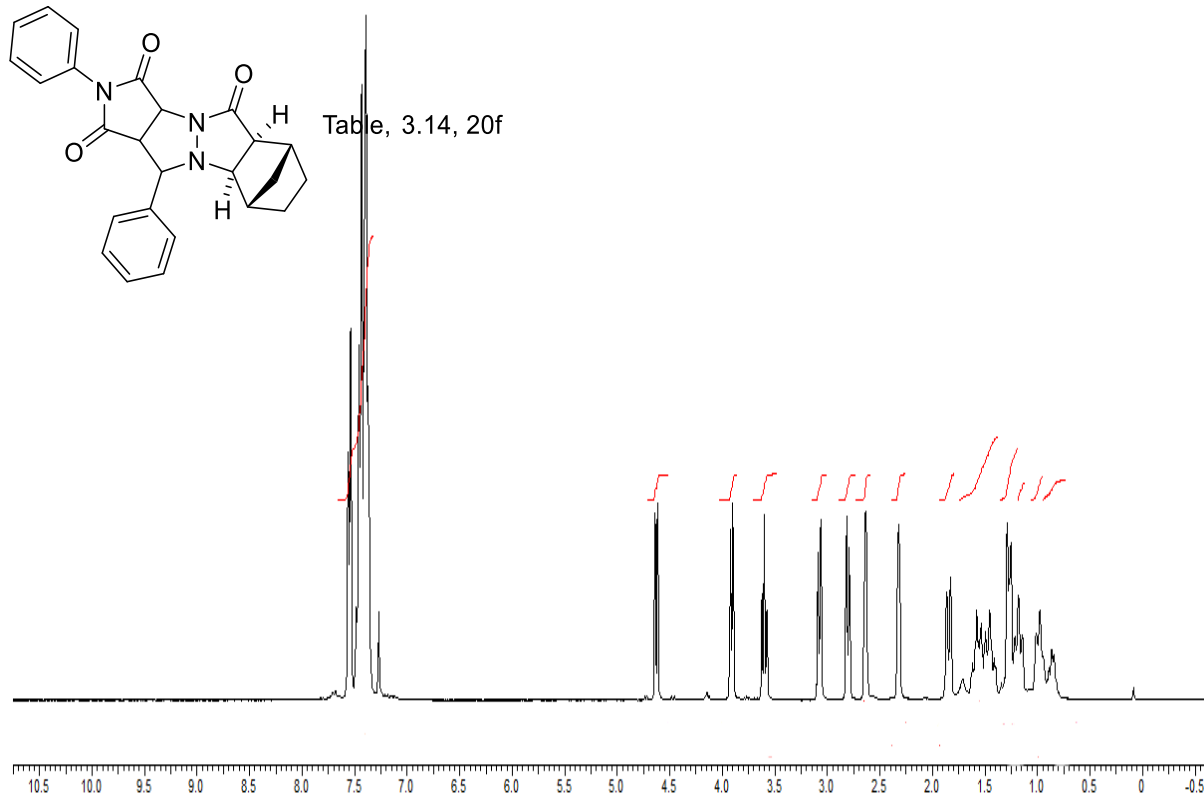
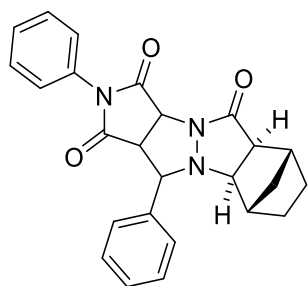
Table 3.14, 20c

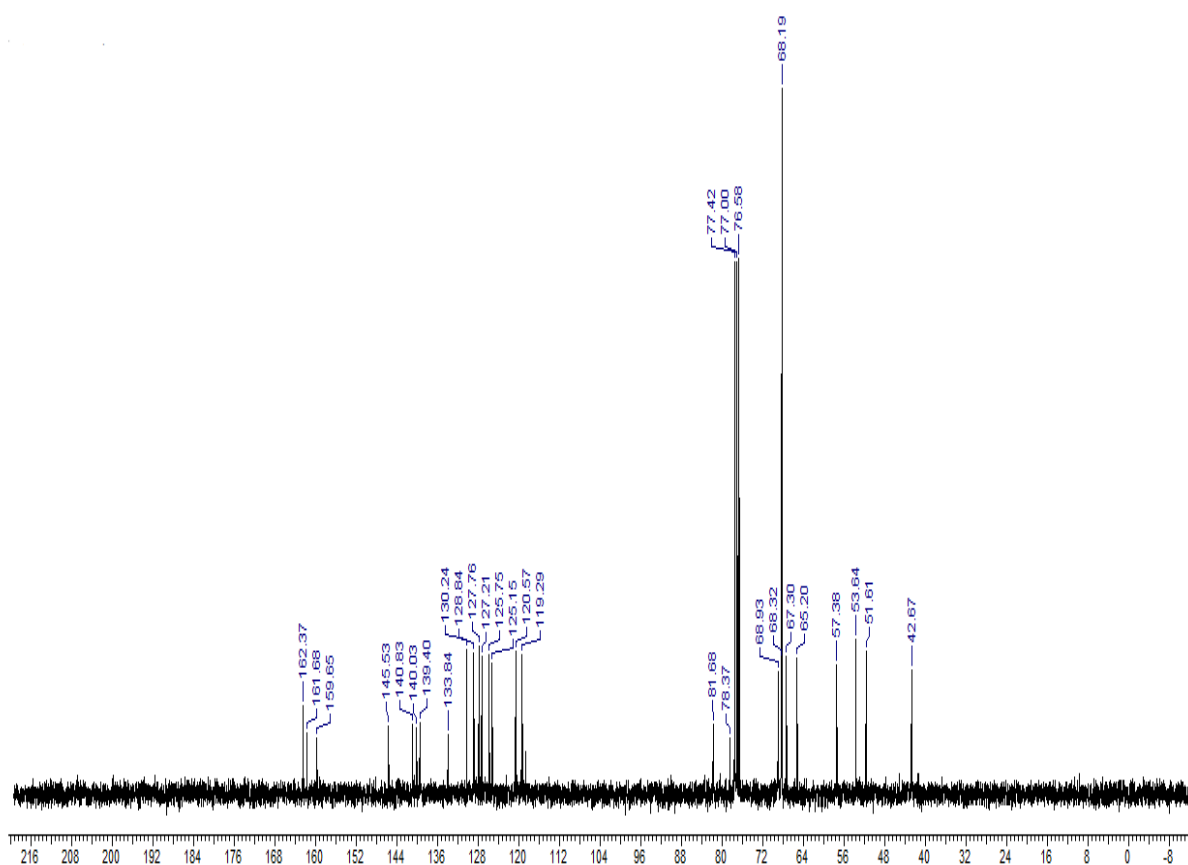
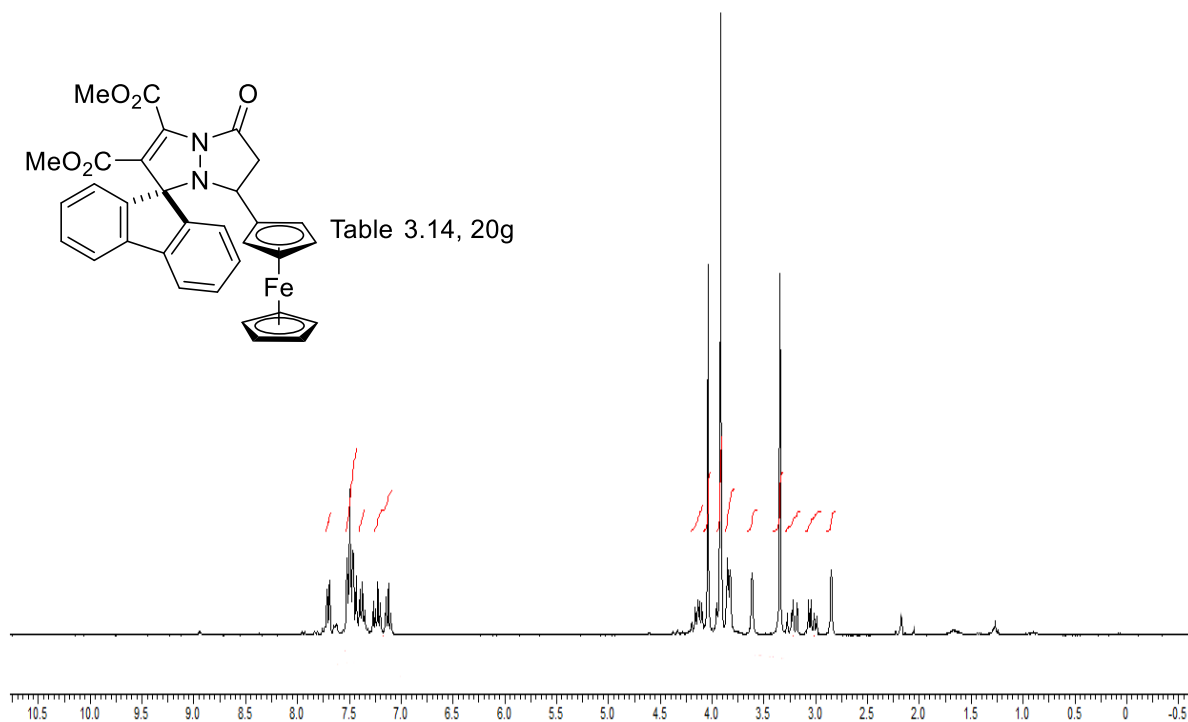












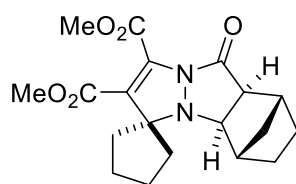
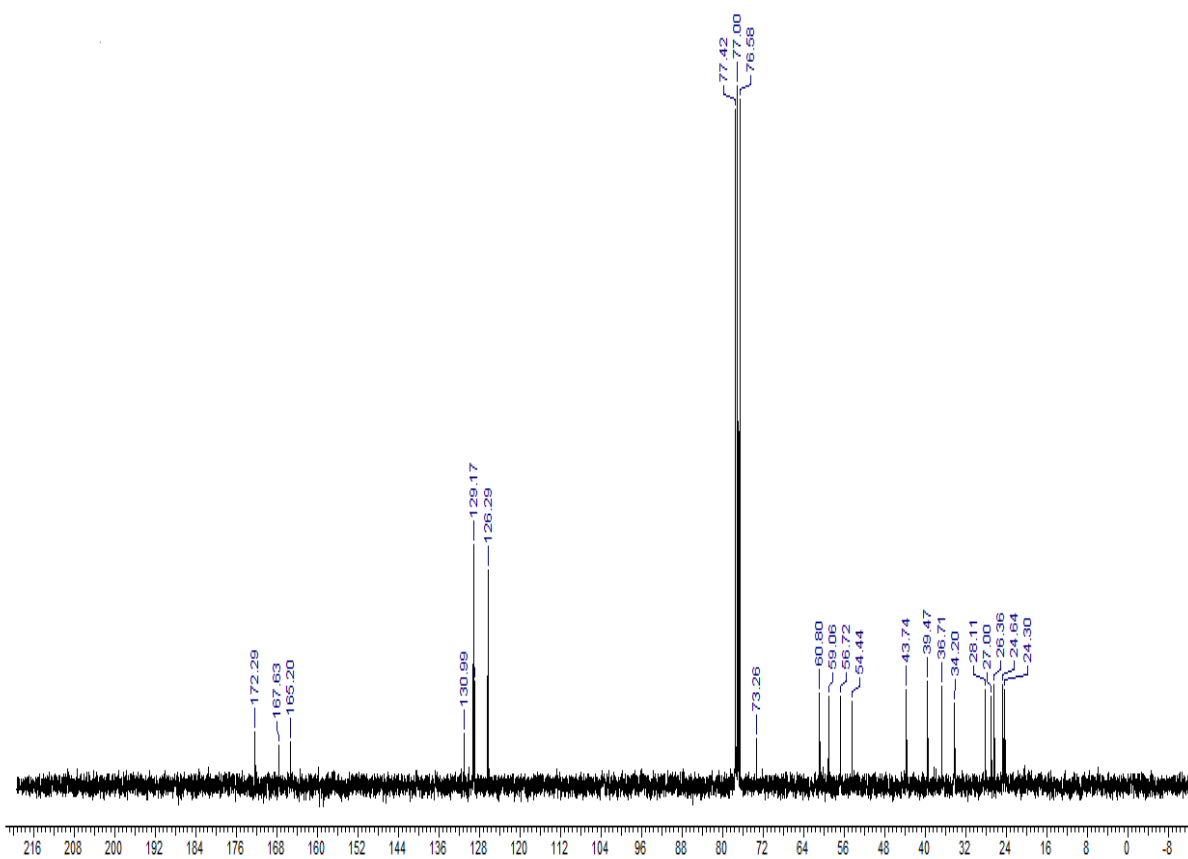
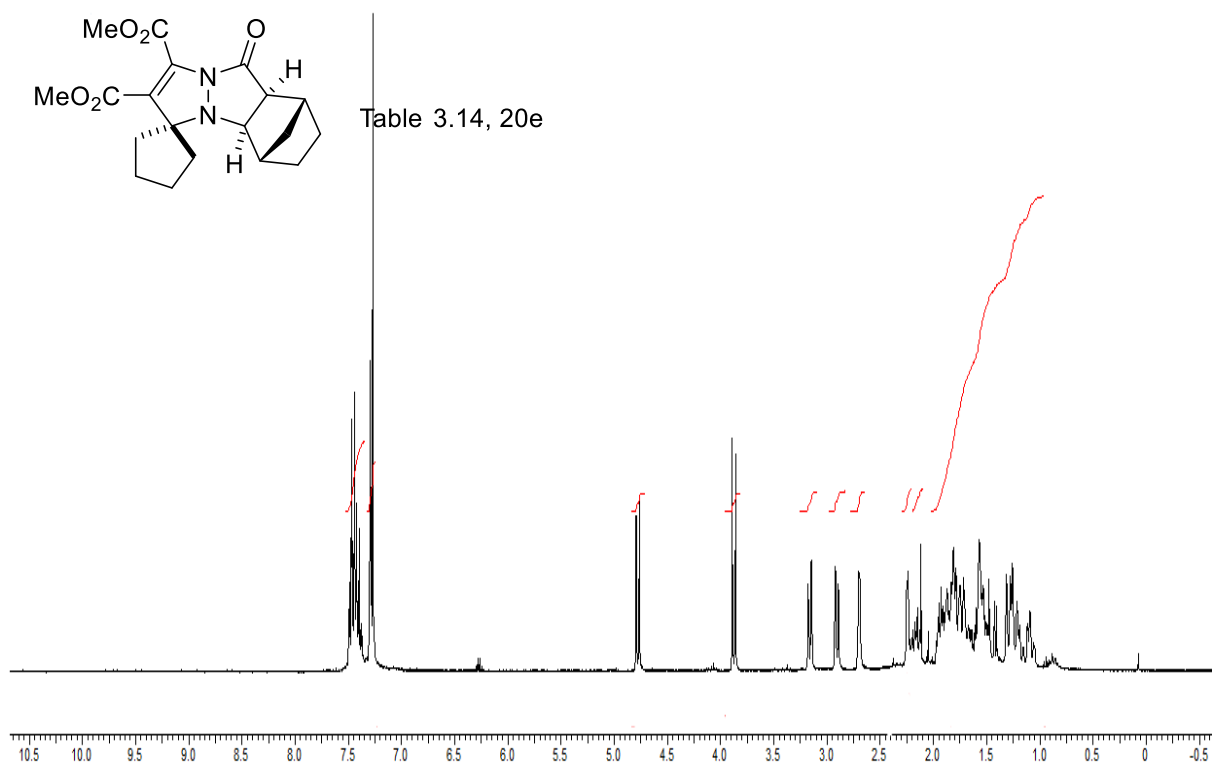
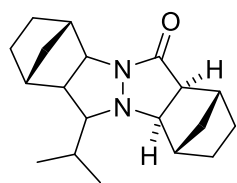
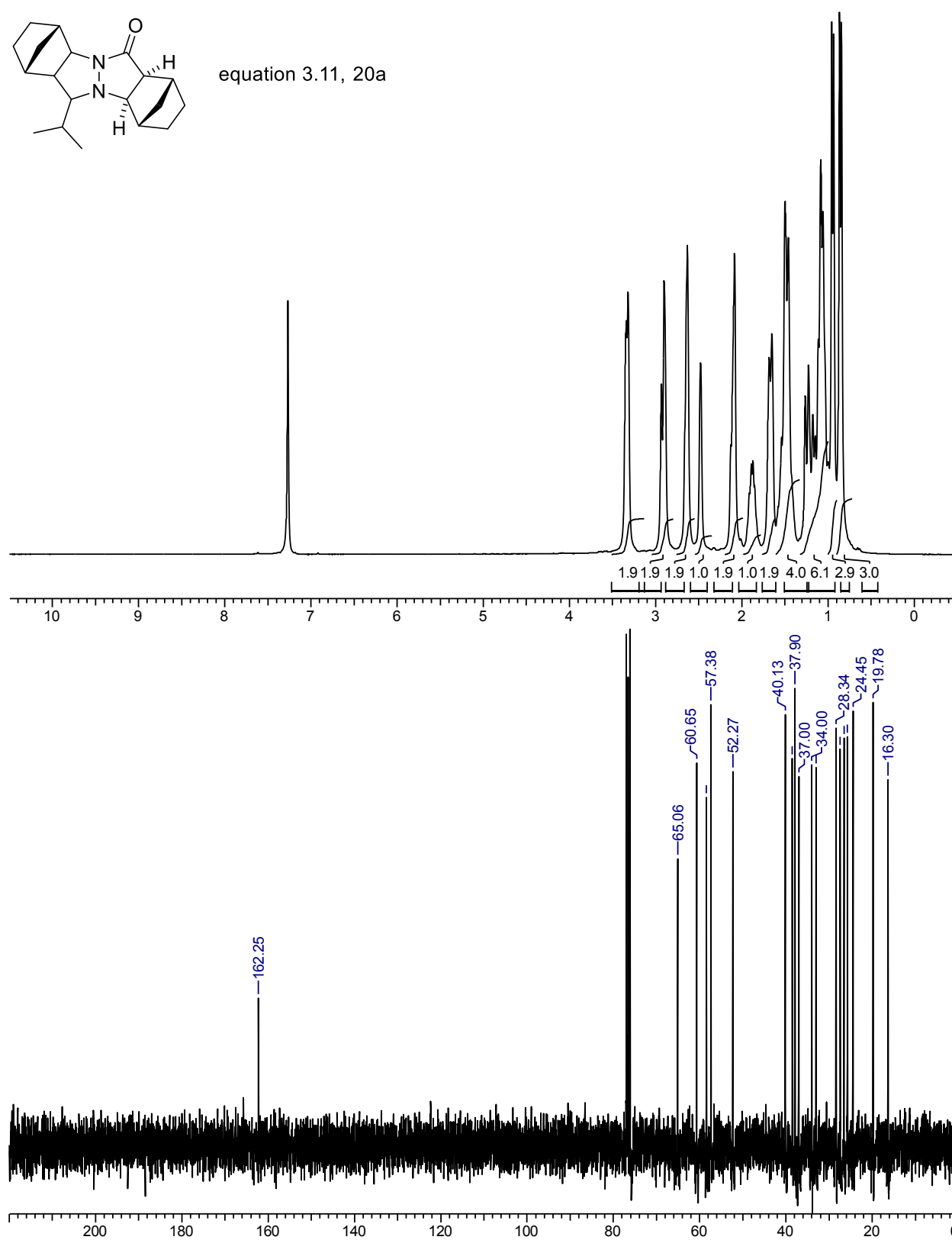


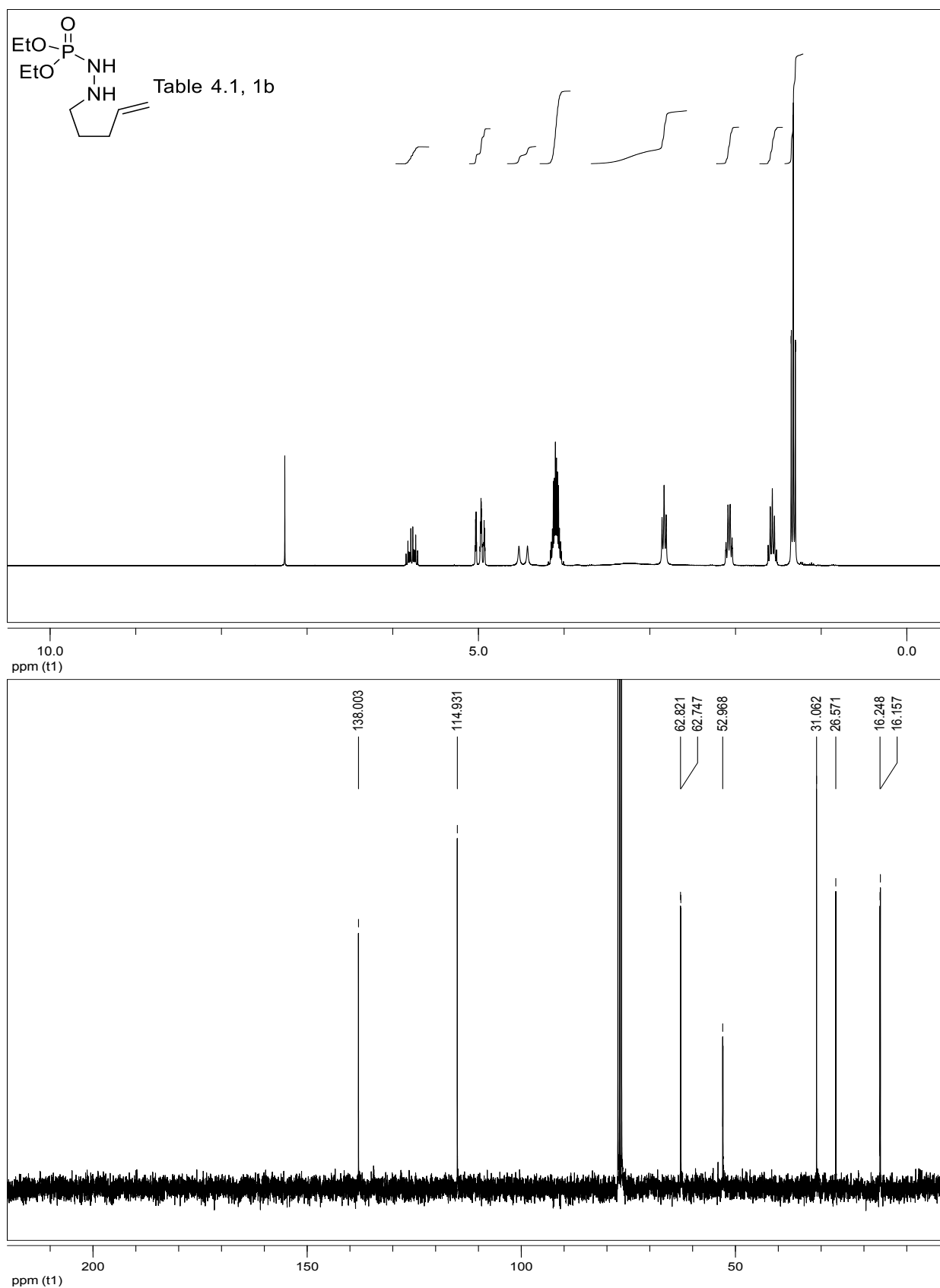
Table 3.14, 20e

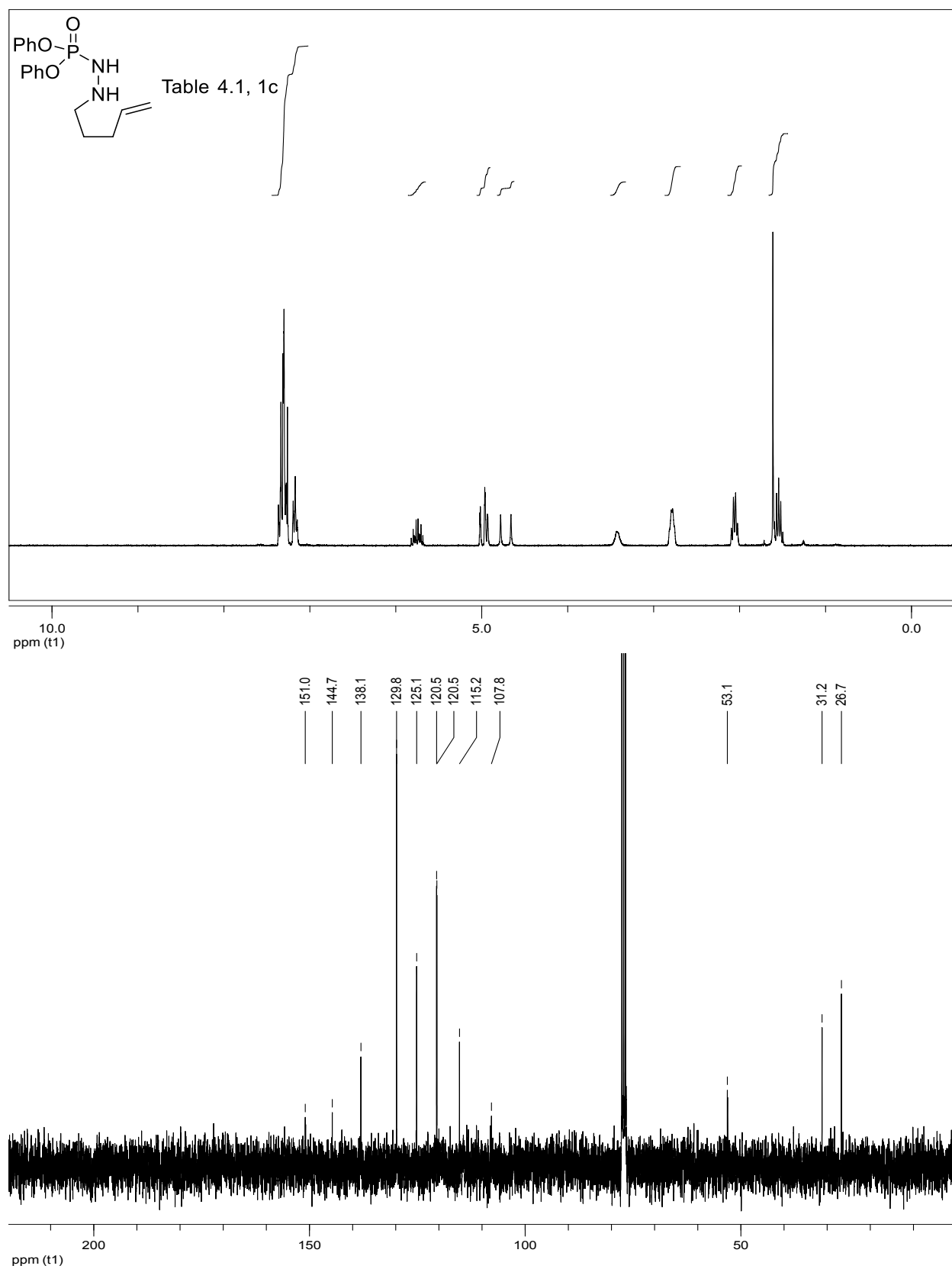


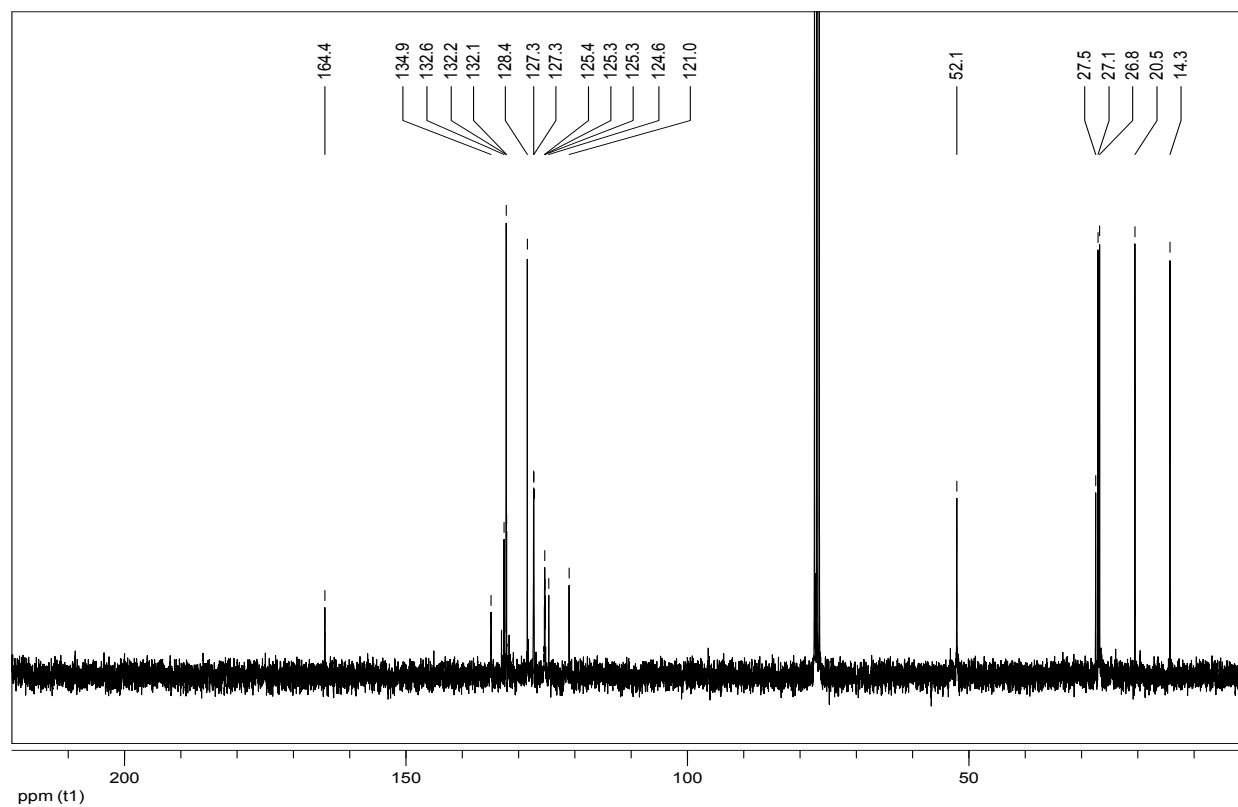
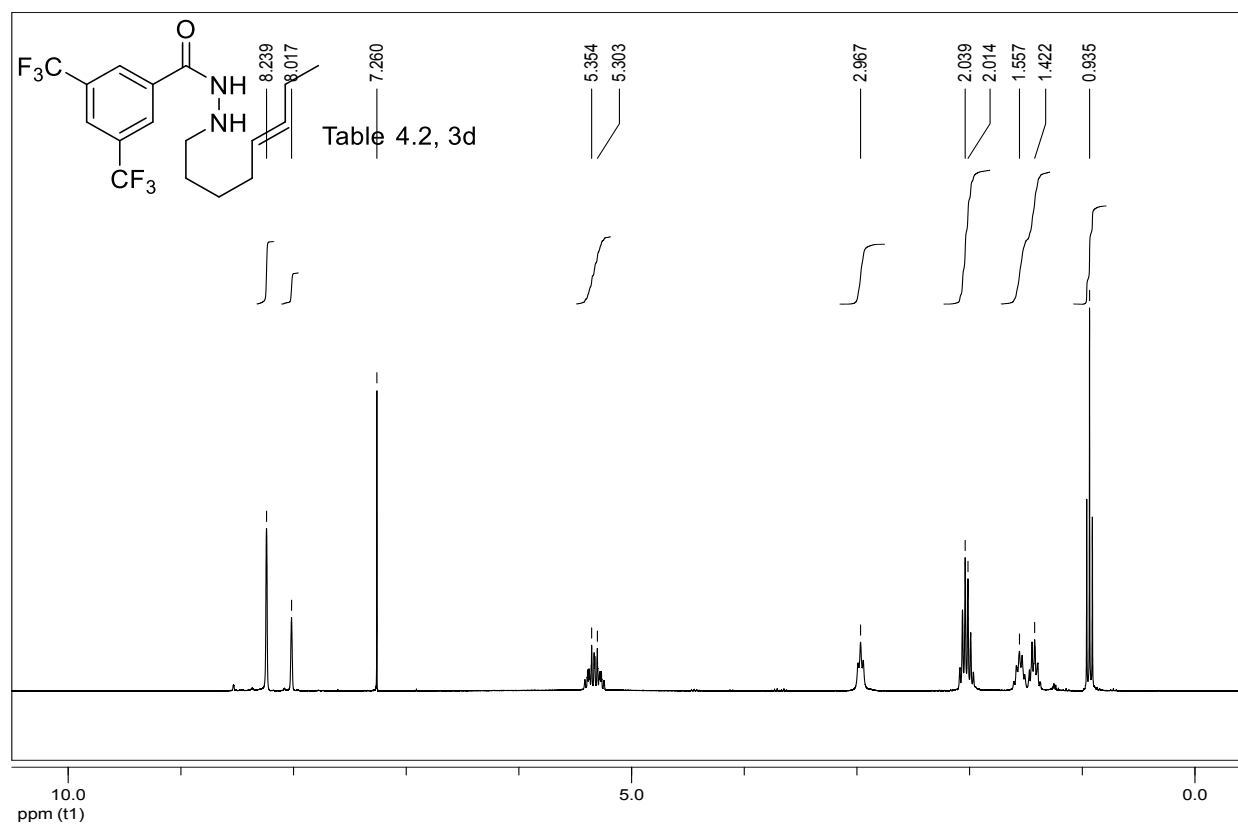


equation 3.11, 20a









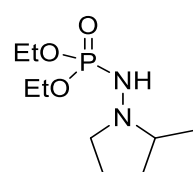


Table 4.1, 2b

