Derivatization of Azomethine Imines into β-Aminocarbonyl Motifs

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Abstract

β-Aminocarbonyl motifs are a privileged substructures in medicinal chemistry and peptidomimetics. As part of our efforts toward metal free aminations, we developed a method for intermolecular amino-carbonylation of alkenes using hydrazones. This method provides access to cyclic azomethine imines containing a β-aminocarbonyl motif. Conceptually, these dipoles can be derivatized into many bioactive compounds, such as 1,3-diamines, β-amino amides and β-amino acids.

The first part of this thesis will present the results on the derivatization of our aminocarbonylation products into various nitrogen-containing molecules, such as β-amino amides, β-amino acids and pyrazolones. More specifically, a short, chromatography-free derivatization of azomethine imines into *N*-Boc-β-amino amides will be presented.

Following these results, the next chapter will focus on attempts at develop novel aminocarbonylation reactivity between 1,2-diacylhydrazines and alkenes followed by results from our reductive N-N bond cleavage experiments on our cyclic hydrazides.

Acknowledgements

A master's degree is more than just academics. It's a collection of learning experiences that left me with knowledge that is beyond what I had ever expected. For that, I have André to thank. Not just for giving me the chance to complete this master's degree in a way that leaves me proud and content regardless of all the craziness that has happened, but for being the most supportive, patient, and considerate supervisor one could ever have chosen. Anyone would be lucky to have you as their supervisor.

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I also have my parents and sister to thank. I always looked up to my sister Caro, your persistence in your own chemistry master's motivated me to succeed at this same chapter in my life.

Je veux surtout remercier ma mère. Tu es toujours prête à prendre soins de moi dans n'importe quelle situation. C'est ton amour inconditionnel et ton support continuel qui m'a permis de finir d'écrire cette thèse. Alors avec tout mon cœur et toute ma joie, c'est à toi que j'aimerais la dédier.

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"I have learned that success is to be measured not so much by the position that one has reached in life as by the obstacles which one has overcome while trying to succeed." — Booker T. Washington

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List of Abbreviations

Δ – reflux

Δ*S* – difference in entropy

°C – degrees Celsius

α – alpha

[M] – mass of compound

Ac – acetyl

anti – apart, opposite side

β – beta

Bn – benzyl

Boc – *tert*-butyloxycarbonyl

Boc_2O – di-*tert*-butyl dicarbonate

br – broad signal

Bz – Benzoyl

calcd – calculated

Cbz – carboxybenzyl

cm – centimeter

COOH – carboxylic acid

COOMe – methyl ester

CNS – central nervous system

CSI – chlorosulfonyl isocyanate

d – doublet

DABCO – 1,4-diazabicyclo[2.2.2]octane

DBU – 1,8-Diazabicyclo-undec-7-ene

DCC – *N*,*N'*-dicyclohexylcarbodiimide

DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

d.e. – diastereometic excess

DFT – discrete Fourier transform

diox. – 1,4-dioxane

DMAP – 4-dimethylaminopyridine

DMF – *N*,*N*-dimethyl formamide

DMSO – dimethyl sulfoxide

dr – diastereomeric ratio

EDG – electron-donating group

ee – enantiomeric excess

eq – stoichiometric equivalent

Equiv. – stoichiometric equivalent

ESI – electrospray ionization

Et – ethyl

EtOAc – ethylacetate

EtOH – ethanol

EWG – electron-withdrawing group

Flu – fluorenyl

Fmoc – Fluorenylmethyloxycarbonyl chloride

FTIR – Fourier transform infrared

g – gram

h – hour

HMPA – hexamethylphosphoramide

HRMS – Hight-resolution mass spectroscopy

Hz – Hertz

i-Pr – *iso*-propyl

IR – infrared

J – coupling constant

L – generic ligand

L – litre

LG – generic leaving group

LRMS – Low-resolution mass spectroscopy

m – multiplet

M – molar

Me – methyl

MeCN - acetonitrile

MeOH – methanol

MHz – mega hertz

mins – minutes

mL – milliliter

mmol – milimole

mol – mole

n-Bu – *n*-butyl

NMP – *N*-methyl-2-pyrrolidone

NMR – nuclear magnetic resonance

n-Pr – *n*-propyl

Nuc – nucleophile

o – *ortho*

O.N. – overnight

p – para

PG – protecting group

Ph – phenyl

PMP – *para*-methoxyphenyl

ppm – parts per million

pyr – pyridine

q – quartet

R – generic group

R – Latin, rectus

Ra-Ni – Raney-Nickel

RED-OX – reduction/oxidation reaction

R*f* – retention factor

ROH – Alcohol

rt – room temperature

s – singlet

S – Latin, sinister

SM – starting material

SPRIX – spiro bis(isoxazoline)

syn – together, same side

t – triplet

T° – temperature

TADDOL – α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanols

t-Bu – *tert*-butyl

t-BuOH – *tert*-butanol

temp. – temperature

Tf – triflate

TFA – trifluoroacetic acid

TIPBA – 2,4,6-triisopropylbenzenesulfonic acid

THF – tetrahydrofuran

TLC – thin layer chromatography

TMS – trimethylsilane

X – generic halide, generic heteroatom or generic leaving group

δ – chemical shift in parts per million

μm – micrometer

μW – microwave

1

Introduction

1.1 β-Aminocarbonyl Motif: Nitrogen Containing Molecules

Nitrogen containing molecules are found in many products including pharmaceuticals, agrochemicals, biochemical building blocks, cosmetics, and everyday household products. While approximately 90% of all pharmaceuticals contain at least one nitrogen atom in their structure, 15% of those require a carbon-nitrogen bond formation. This is represented in Figure 1.1, along with a comparison to other reactions used in the pharmaceutical industry.[1] With the increasing need of new pharmaceuticals, there still remain challenges in the synthesis of difficult C-N bonds.

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

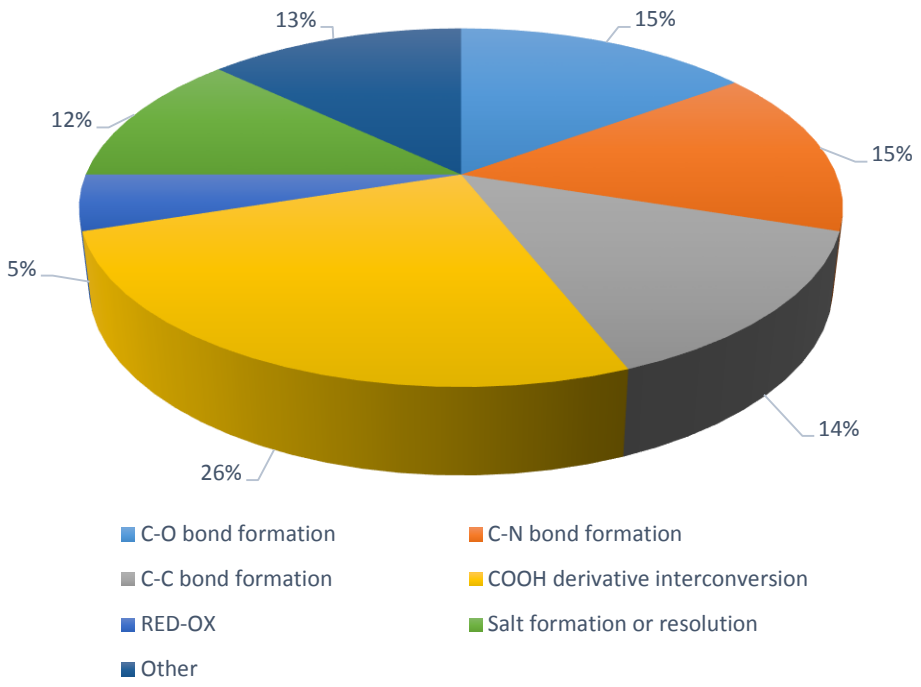


Figure 1.1 Bulk reactions performed in industry between 1985 and 2002.

A significant portion of these nitrogen containing molecules that contain C-N bonds have a β–aminocarbonyl motif, most commonly β-amino acids and peptides. This motif is often incorporated in bacterial, plant, and fungal metabolites as potent biologically active compounds for their survival.[2] Many natural products were isolated from these organisms and used to treat mammalian diseases.[3] The importance and widespread use of this motif is illustrated in Figure 1.2.[4] As shown below, some natural products like Penicillin antibiotics found in bacteria and the anti-cancer drug Taxol found

[2] a) von Nussbaum, F.; Spiteller, P.; β-Amino Acids in Nature. In: Schmuck, C.; Wennemers, H. editors. *Highlights in Bioorganic Chemistry: Methods and Applications*. Weinheim: Wiley-VCH. 2004, 63. b) Buchwaldt, L.; Green, H. *Plant Pathol*.**1992**, *41*, 55. c) Engel, S.; Jensen, P. R.; Fenical, W. *J. Chem. Ecol*. **2002**, *28*, 1971.
[3] Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M. I. *Curr. Med. Chem*. **2002**, *9*, 811.
[4] a) Czernecki, S.; Franco, S.; Valery, J-M. *J. Org. Chem*. **1997**, *62*, 4845. b) Hill; Mio; Prince; Hughes; Moore *Chem. Rev*. **2001**, *101*, 3893. c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev*. **2001**, *101*, 3219. d) Gademann, K.; Kimmerlin, T.; Hoyer, H.; Seebach, D. *J. Med. Chem*. **2001**, *44*, 2460.

in a plant possess a β–aminocarbonyl scaffold.[5] These natural products suggest the significance of this motif and its high stability in biologically active compounds. Through the years, medicinal chemists started adding this motif to new therapeutics. We can find it in popular drugs like the antiemetic Ondansetron and the CNS stimulant Ritalin. Although we have now seen that the β–aminocarbonyl motif is often found in but not limited to β–amino acids, this section will focus on the importance of β–amino acids and their derivatives, followed by the currents methods to synthesize them in an enantiopure fashion.

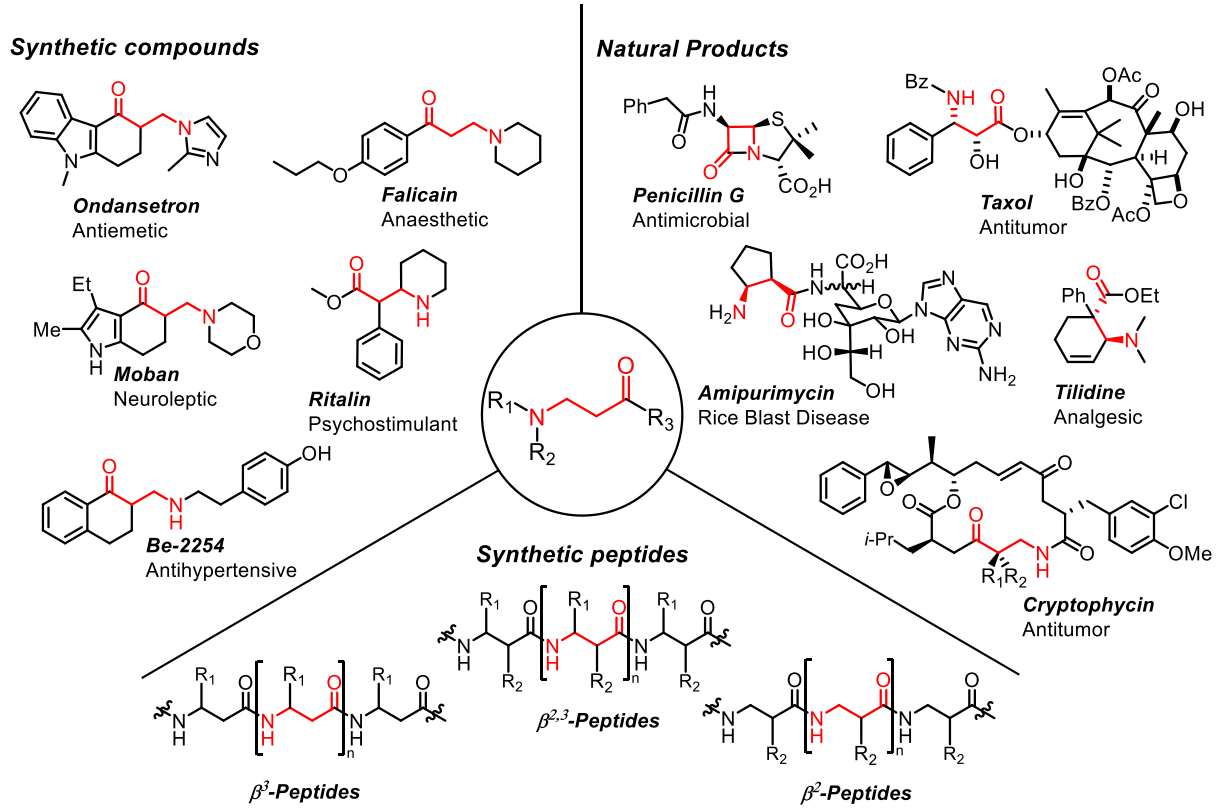


Figure 1.2 Synthetic and natural products containing the β-aminocarbonyl motif

[5] a) Garrod, L. P. *Brit. Med. J*. **1960**, *2*, 1695. b) Hall, N. *Chem. Commun*. **2003**, *6*, 661.

1.2 Applications and Advantages of β–Amino Acids

Although mammalian proteins are built from α-amino acids, nature is comprised of more proteinogenic β-amino acids than α-amino acids.[6] As we can see in Figure 1.3, β–amino acids have a much higher functionalization density than α–amino acids.[6] This is due to its added methylene unit, which increases the possibility of substitutions and configurations.

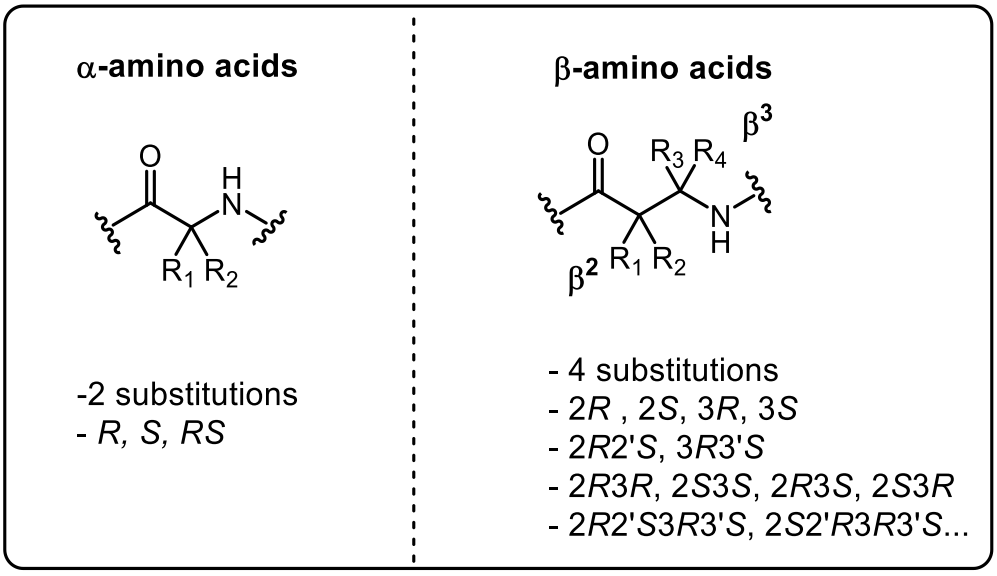


Figure 1.3 Structural diversity of β-amino acids vs. α-amino acids

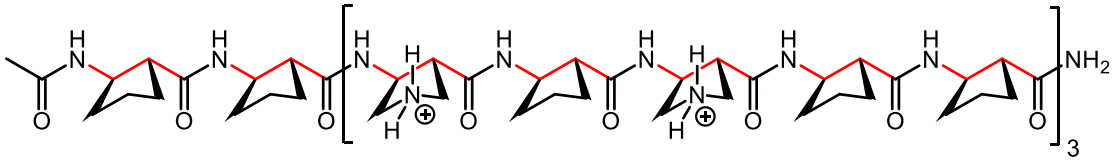
One of the most important aspect of β–amino acids in comparison to α–amino acids are their stability against mammalian enzymes. The slow rate of mammalian

[6] Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodivers*. **2004**, *1*, 1111.

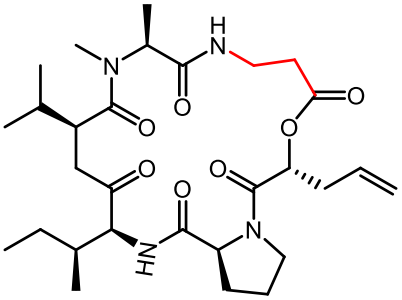
hydrolytic enzymes to cleave the α–β and β–β peptide link make these linkages stable to degradation over a prolonged period of time compared to the α–α linkage.[7] This characteristic, in addition to the possibility of mimicking α–peptide biological activities, make the addition of β–amino acids into α–peptides or even as pure β–peptides an interesting application in medicinal chemistry and peptidomimetics.[6]

Resistance to degradation isn't the only advantage of adding β–amino acids in therapeutic peptides. β–Peptides can fold into more secondary structures than α–peptides due to their numerous conformations and substitutions, with less units and less restrictions to their backbone rotations.[8] A few examples of β–peptides and α,β–peptides as therapeutics are shown in Figure 1.4.[9]

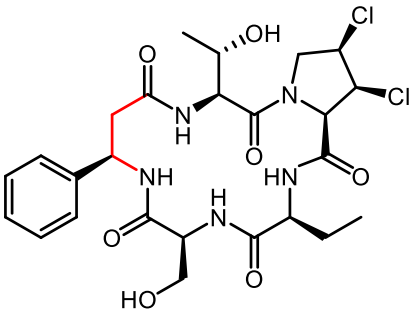
[7] a) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M. I. *Curr. Med. Chem*. **2002**, *9*, 811. b) Pegova, A.; Abe, H.; Boldyrev, A. *Comp. Biochem. Physiol. B*. **2000**, *127*, 443.
[8] Seebach, D.; Gardiner, J. *Acc. Chem. Res*. **2008**, *41*, 1366.
[9] a) Porter, E. A.; Wang, X.; Lee, H-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565. b) Morita, H.; Nagashima, S.; Uchumi, Y.; Kuroki, O.; Taketa, K.; Itokawa, H. *Chem Pharm. Bull*. **1996**, *44*, 1026. c) Pedras, M. S. C.; Zaharia, L. I.; Ward, D. E. *Phytochemistry* **2002**, *59*, 579.



β-17 : Antimicrobial activity



Destruxin A : Insecticide



Astin A : Antitumor

Figure 1.4 Therapeutic β-peptides and α,β-peptides

An interesting area of research linked to β-peptide and α,β-peptide therapeutics are protein-peptide and protein-protein interactions to treat autoimmune disorders such as arthritis.[8,9] Another interesting area of research involving the possibility of β–peptides as therapeutics is peptidic inhibition of proteins to reduce cholesterol accumulation.[10] β–Peptides have also shown activity as antimicrobials for mammalian immune systems, which is of interesting due to the current increase in antibiotic resistant infectious bacteria.[11]

[10] Werder, M.; Hauser, H.; Abele, S.; Seebach, D. *Helvetica Chimica Acta*. **1999**, *82*, 1774.
[11] Arvidsson, P. I.; Ryder, N. S.; Weiss, H. M.; Hook, D. F.; Escalante, J.; Seebach, D. *Chem. Biodivers*. **2005**, *2*, 401.

1.3 Current Ways to Synthesize β-Amino Acids and Derivatives

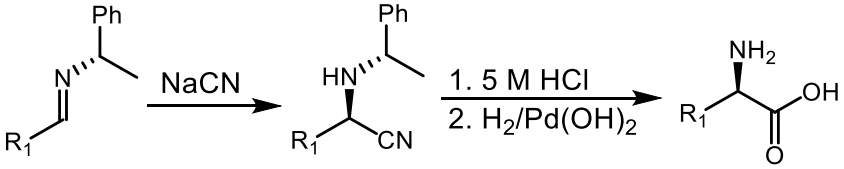
In the previous section, the importance and applications of the β–aminocarbonyl motif was presented. Although this scaffold is of interest and very useful in medicinal chemistry, its synthesis can still be challenging. Due to increased necessity of a variety of natural and unnatural β–amino acids, the development of new methodologies towards these molecules is important and encouraged in organic chemistry. In this section we will review some of the most popular and general methods to synthesize β–amino acids. Examples shown will be general, focused on asymmetric methods and will not be comprehensive.

1.3.1 Homologation of β-Amino Acids: Arndt-Eistert

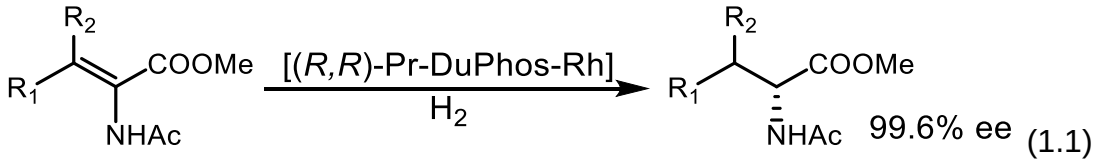
Many methods towards stereoselective synthesis of α–amino acids have been studied and published. Among the most popular is the Strecker reaction, involving the conversion of aldehydes into aminonitriles, which are then hydrolyzed to α–amino acids (Scheme 1.1).[12] This reaction has grown increasingly popular over the years due to the variety of natural and unnatural α–amino acids that can be synthesized.

[12] Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947.

Scheme 1.1 Asymmetric Strecker Reaction



Another popular method towards enantioenriched α-amino acids is asymmetric hydrogenation of α,β-unsaturated α-amino esters. A popular example of this method is the hydrogenation of these esters in a hydrogen atmosphere with a chiral rhodium catalyst (Equation 1.1).[13]



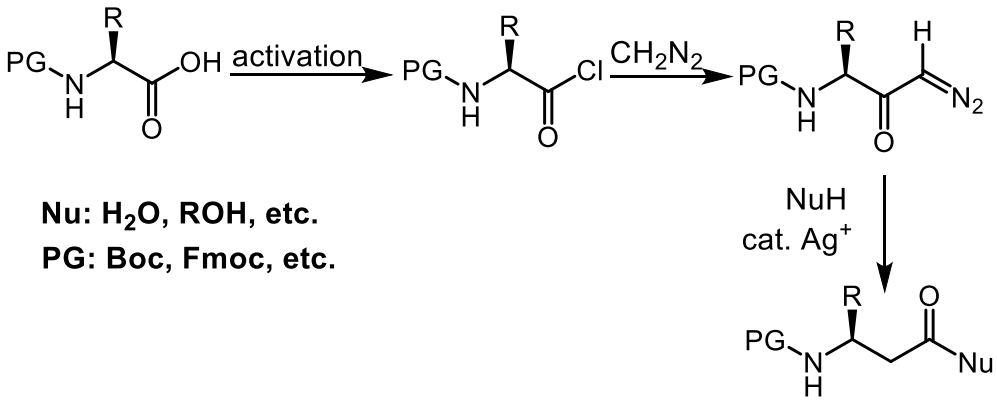
The homologation of α–amino acids is one of the most popular and general methods for the synthesis of enantioenriched β–amino acids. Reasons for this are the well-known literature on the synthesis of enantioenriched α–amino acids and their availability from commercial suppliers. A successful method for the homologation of α–amino acids into β–amino acids is the Arndt-Eistert synthesis.[14]

This synthesis consists of the reaction between an activated carboxylic acid and a diazomethane to form a diazoketone. This is followed by a Wolff rearrangement in

[13] Chi,Y.; Tang, W.; Zhang, X. Rhodium-catalyzed asymmetric hydrogenation. In: Evans, P. A., editor. *Modern rhodium-catalyzed organic reactions.* Weinheim: Wiley-VCH: 2005 pp 1-31.
[14] Ye. T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

presence of a protic nucleophile and loss of nitrogen gas to form a β-amino acid (Scheme 1.2).[15]

Scheme 1.2 General Arndt-Eistert homologation



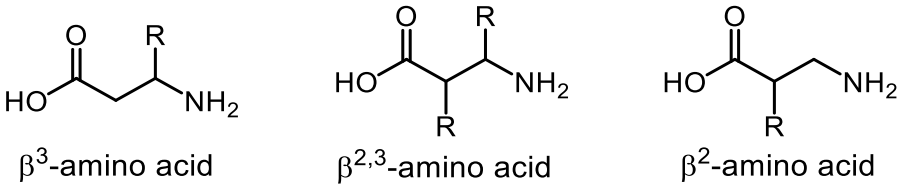
Although this reaction is easily accessible with a catalytic silver (I) salt, photochemical and thermal conditions have also been established.[16 a)] This reaction is tolerant to diverse substituents, which makes it a general approach. However, it also has limitations. For instance, the scope of products is restricted to linear β^3-amino acids along with the chance of starting material racemization, such as for phenylglycine.[16b] Also, due to constant presence of small amounts of water in ethereal diazomethane solutions, α–amino ester byproducts are often formed from the hydrolysis of activated amino acids.[17] Another important drawback of this synthesis is the requirement of

[15] a) Penke, B.; Czombos, J.; Balaspiri, L.; Petres, J.; Kocacs, K. *Helv. Chim. Acta* **1970**, *53*, 1057. b) Balaspiri, L.; Penke, B.; Papp, G.; Dombi, G.; Kovacs, K. *Helv. Chim. Acta* **1975**, *58*, 969.
[16] a) Kirmse, W. *Eur. J. Org. Chem.* **2002**, *14*, 2193. b) Podlech, J.; Seebach, D. *Angew. Chem*. **1995**, *107*, 507.
[17] Plucinska, K.; Liberek, B. *Tetrahedron* **1987**, *43*, 3509.

diazomethane, which is a hazardous reagent, making it inappropriate when scaling up for industrial purposes.[18]

1.3.2 Conjugate Addition to α,β-Unsaturated Carbonyl Compounds

Another popular method to synthesize β^2, β^3 and β^2,β^3-aminoacids, which are presented in Figure 1.5, is the nucleophilic amine conjugate addition to functionalized α,β-unsaturated carbonyl derivatives, or hetero-Michael addition.



β^3-amino acid $\beta^{2,3}$-amino acid β^2-amino acid

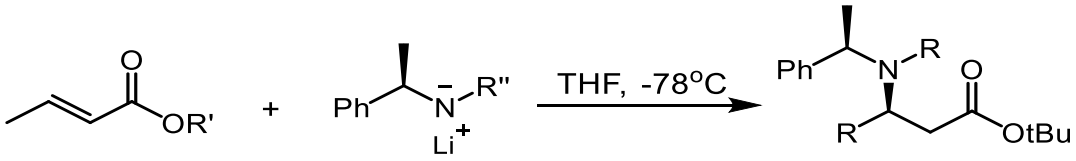
Figure 1.5 A few possible substitutions on β-aminocarbonyls

This reaction is defined by the nucleophilic addition of amines to α,β-unsaturated carbonyls. Although this method has been known for many years, we now have reports of a few asymmetric variants. The first involves the diastereoselective addition of a chiral nitrogen nucleophile to a non-chiral Michael acceptor. The second involves the diastereoselective addition of an achiral nucleophile to a chiral Michael acceptor.

[18] Gutsche, C. D. *Org. React.* **1954**, *8*, 391.

Finally, the last option is the asymmetric catalysis of conjugate additions between nitrogen or carbon nucleophiles and achiral acceptors.

The first method usually involves lithiated α-benzylamine derivatives reacting with an α,β-unsaturated ester in THF at -78 °C. A lithiated amine is chosen to increase nucleophilic reactivity and to reduce the possibility of reversibility from nucleophilic addition (Equation 1.2). It generally produces high yields and is highly diastereoselective.[19]



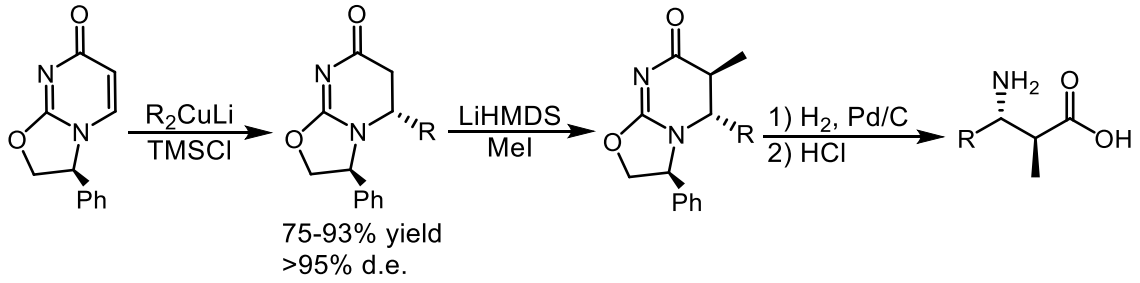
Yield: 23-88%
>95% d.e.

(1.2)

Dechoux's group has developed an interesting general procedure following the second method, the diastereoselective addition of an achiral nucleophile to a chiral Michael acceptor. In this method, various cuprates are added to a pyrimidone derivative. This product is then methylated alpha to the amide, reduced, and hydrolyzed to give various chiral β^2,β^3-amino acids (Scheme 1.3).[20]

[19] a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183. b) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.
[20] a) Agami, C.; Cheramy, S.; Dechoux, L.; Melaimi, M. *Tetrahedron* **2001**, *57*, 195. b) Agami, C.; Cheramy, S.; Dechoux, L.; Kadouri-Puchot, C. *Synlett* **1999**, *6*, 727. c) Agami, C.; Cheramy, S.; Dechoux, L. *Synlett* **1999**, *11*, 1938.

Scheme 1.3 Diastereoselective cuprate addition to a pyrimidone β-amino acid derivative

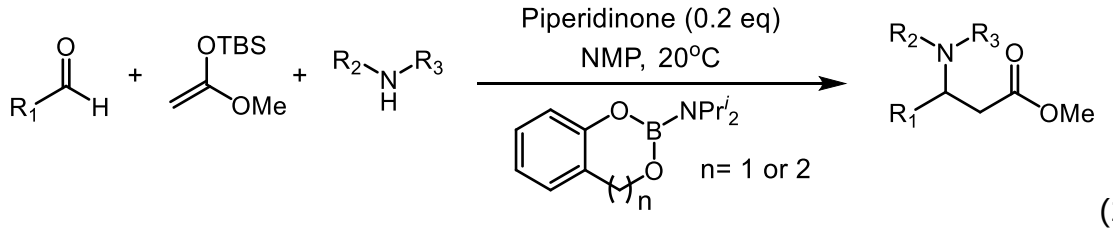


Using these methods is very advantageous due to high product diastereoselectivity. The catalyzed asymmetric α,β–conjugate addition is the most advantageous due to the easily accessible achiral starting materials. However, limitations still exist due to low reactivity of certain Michael acceptors caused by electron donating substitutions.

1.3.3 Mannich Reactions

In the past two decades, the Mannich reaction has become increasingly interesting as a general method to synthesize β–amino acids. This reaction is defined by nucleophilic addition of an enolate to an imine to form the β-aminocarbonyl motif. As Mannich reactions used to be disregarded due to their harsh conditions that limited the

scope, a new and improved method has been introduced.[21] An interesting method reported by Murakami in 2004 employs aminoborane mediation towards easier iminium ion generation in milder conditions that allow acid sensitive functional groups on β-aminocarbonyl products (Equation 1.3).[20]

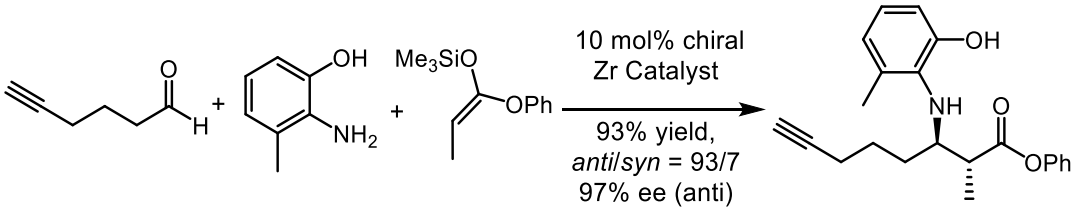


(1.3)

Asymmetric Mannich reactions have also been developed. Two popular strategies have been reported. The first one is comprised of chiral imines and the second one includes chiral enolate nucleophiles.[22] Unfortunately, these procedures contained a chiral auxiliary that needs to be removed, which was reported as a difficult step.[23] In 1991, Corey et al. reported a new and improved method towards the asymmetric Mannich reaction towards β–amino acids using asymmetric catalysis.[24] The first syntheses used up large amounts of catalysts, until improvements brought different types of catalyst to light: chiral Lewis acids using metal enolates and organocatalysis. Enantioselective Mannich reactions forming β–amino acid derivatives can usually be

[21] Suginome, M.; Uehlin, L.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 13196.
[22] Juristi, E.; Soloshonok, V. Catalytic Enantioselective Mannich Reactions. In: Hoboken, N. J.; Soloshonok, V. A. editors. *Enantioselective synthesis of β-amino acids.* Wiley. 2005, 139.
[23] a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. b) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev*. **1996**, 117. c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1044.
[24] Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.

regrouped in three different categories. The first is through chiral Lewis acids. A successful diasterio- and enantio-selective high yielding example of a chiral Lewis acid catalyzed Mannich reaction is with a zirconium catalyst (Equation 1.4).[25] In this example, an α-alkoxy silyl enol ether reacts with an aniline derived imine. The product can then be hydrolyzed into an ester using potassium carbonate in methanol and the amine can be deprotected with ceric ammonium nitrate.

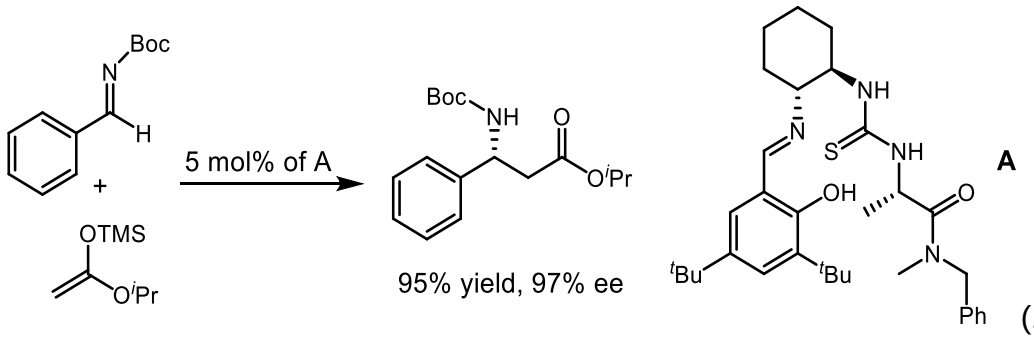


(1.4)

The second approach to achieve this enantioselective Mannich reaction is through a similar process as Equation 1.4, replacing the Lewis acid is by metal enolates such as lithium and palladium species.[26]

Finally, the third method is an asymmetric Mannich reaction with organocatalysis. A wide variety of catalysts have shown moderate to excellent results.[27] A few examples are amino acids, short peptides, ureas and benzoquinone derivatives. In Equation 1.5, we can see a successful example of urea catalyzed synthesis of Boc protected β–amino acids through the enantioselective addition of silyl ketene acetals to *N*-Boc-aldimines.[26]

[25] Kobayashi, S.; Kobayashi, J.; Ishitani, H. Ueno, M. *Chem. Eur. J.* **2002**, *8*, 4185.
[26] Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060.
[27] a) Wenzel, A. G.; Jacobsen, E. N. *J. Am, Chem. Soc.* **2002**, *124*, 12964. b) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919.

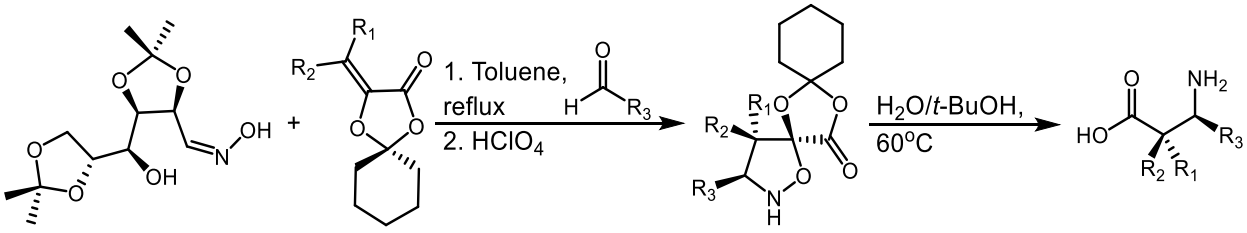


(1.5)

1.3.4 Cycloaddition towards β-Amino Carbonyls

Cycloaddition reactions are prevalent for the synthesis of β-amino acids. Recently, Bode published an efficient chromatography free synthesis of enantioenriched β-amino acids through [3+2] nitrone cycloadditions with acrylates (Scheme 1.4).[28]

Scheme 1.4 Diastereoselective [3+2] cycloadditions towards β-amino acids



[28] 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.

This reaction finds its enantiocontrol through chiral auxiliary mediation. The resulting product is then cleaved of its chiral auxiliary and fragmented in a water/*tert*-butanol heated mixture to yield enantiopure β-amino acids.[27]

Cycloaddition chemistry can also be used towards the synthesis of cyclic β–amino acids. Although their synthesis is still a challenge, these compounds have many potential applications and are becoming important in medicinal chemistry. An example of a cyclic β–amino acid that exists in its free form is Cispentacin (Figure 1.6), a natural β–amino acid used as an antifungal antibiotic.[29] It is also part of the rice blast disease antibiotic, amipurimycin (Figure 1.6).[30] These cyclic β–aminocarbonyl compounds can also be of use as total synthesis building blocks or as chiral auxiliaries.[31]

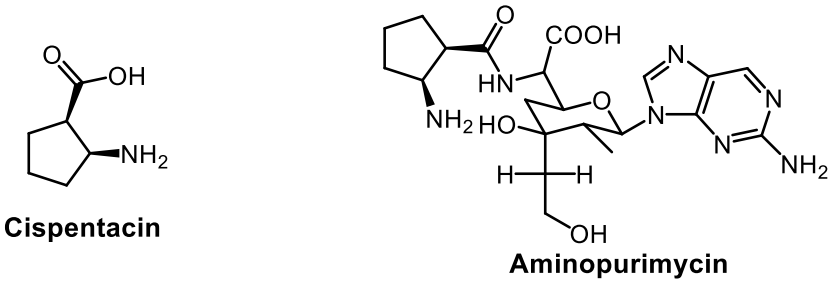
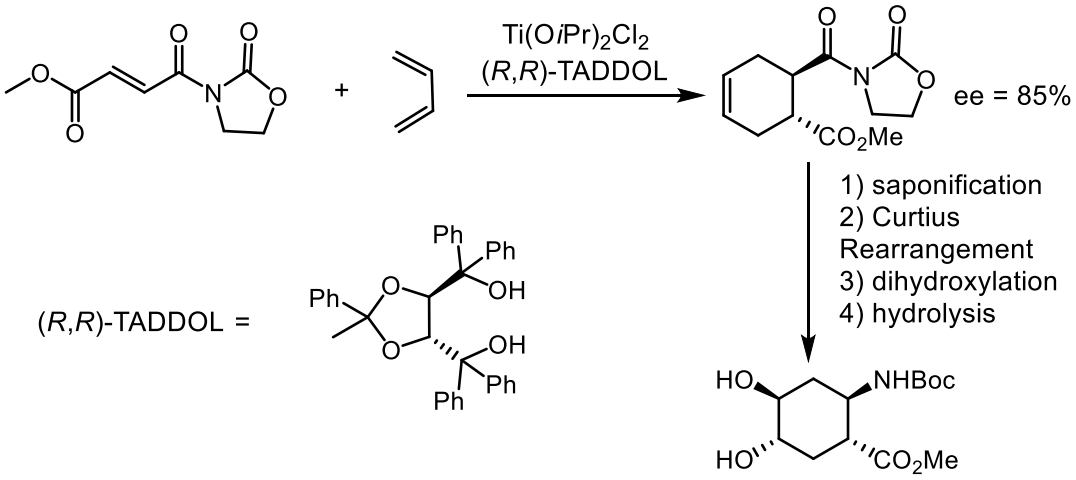


Figure 1.6 Examples of biologically active cyclic β-amino acids

[29] Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawagushi, H. *J. Antibio*. **1989**, *42*, 1749.
[30] a) Goto, T.; Toya, Y.; Ohgi, T.; Kondo, T. *Tetrahedron Lett*. **1982**, *23*, 1271. b) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859.
[31] Fulop, F. *Chem. Rev*. **2001**, *101*, 2181.

One of the least explored strategies used to make enantiopure cyclic β–amino acids is by Diels-Alder cycloaddition with chiral catalysts. Although very few examples have been published, many cyclic derivatives can be synthesized such as cyclopentanes, cyclohexenes, bicycles and heterocycles.[32] Nonetheless, strategies relying on the Diels-Alder reaction requiring 5-6 steps, including a Curtius rearrangement to produce the amino acids (Scheme 1.5).[33]

Scheme 1.5 Titanium-catalyzed Diels-Alder reaction toward cyclic β-amino acids



While there are many ways to synthesize β–amino acids, general and metal free methods with fewer steps are still of interest in synthetic and medicinal chemistry. In this next section, we will review the literature on aminocarbonylation methods including a method introduced by the Beauchemin group. This method will lead us towards β-

[32] a) Furuta, K.; Hayashi, S.; Miwa, Y.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 5841. b) Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett*. **1994**, *35*, 4419. c) Konoshu, T.; Oida, S. *Chem. Pharm. Bull*. **1993**, *41*, 1012. d) Hanselmann, R.; Zhou, J.; Ma, P.; Confalone, P. N. *J. Org. Chem*. **2003**, *68*, 8739.
[33] Wipf, P.; Wang, X. *Tetrahedron Lett.* **2000**, *41*, 8747.

aminocarbonyl containing azomethine imines, which will be introduced as precursors for their derivatization into β-aminocarbonyl compounds.

1.4 Aminocarbonylation methods

Functionalization of alkenes to sp^3 carbons have been of interest for quite a while due to their variety, availability and affordability. The amination of alkenes to make new C-N bonds are especially relevant due to the prevalence of nitrogen containing molecules found in pharmaceuticals and natural products. Figure 1.7 illustrates different methods of aminations of alkenes forming new C-N bonds, yielding nitrogen-containing molecules.[34] These reactions are often paired with another simultaneous bond formation making complex products from simple starting materials.

[34] a) Hydroamination: a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. b) Aminohydroxylation: Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1997**, *35*, 2813. c) Diamination: de Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067. d) Aziridination: Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115* , 5326. e) Oxidative amination: Obora, Y.; Ishii, Y. *Catalysts* **2013**, *3*, 794.

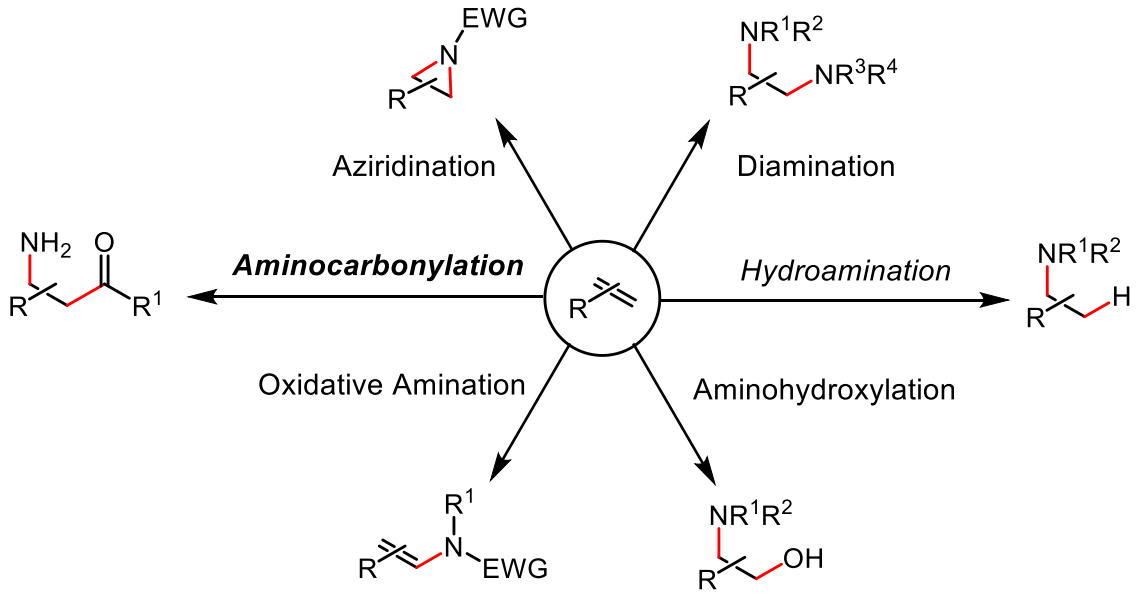


Figure 1.7 Known methods for amination of alkenes towards new C-N bonds

While some of these reactions are extensively studied, alkene aminocarbonylation is one of many reactions that has yet to be fully developed. This reaction is defined by the simultaneous formation of both a C-N and C-(C=O) bond from an olefin. The products obtained contain the β-aminocarbonyl motif, and can be derivatized into interesting nitrogen containing molecules such as unnatural β–amino acids derivatives. As discussed earlier, there are limitations to the synthesis of these scaffolds, and aminocarbonylation is a complementary approach to these moieties. It has the potential of being less expensive and attractive due to diversity of available alkenes. We will first overview metal catalyzed intramolecular aminocarbonylation, followed by reactions of chlorosulfonyl isocyanate, to finally discuss the discovery of new aminocarbonylation reactivity from the Beauchemin group.

1.4.1 Metal Catalyzed Intramolecular Aminocarbonylation of Alkenes

In 1980, Hegedus introduced the first palladium (II) catalyzed aminocarbonylation of *N*-substituted ortho-allylanilines towards functionalized indolines (Figure 1.8).[35] It was proposed that the mechanism was step-wise and started with the formation of σ-alkylpalladium (II) complex intermediate followed by carbon monoxide insertion. Although promising, this reaction had many side reactions, including the insertion of carbon monoxide onto the amine to form an isocyanate in the case where the nitrogen was unsubstituted. Another observed side reaction is a β–hydride elimination that competes with the carbon monoxide insertion (Figure 1.8).

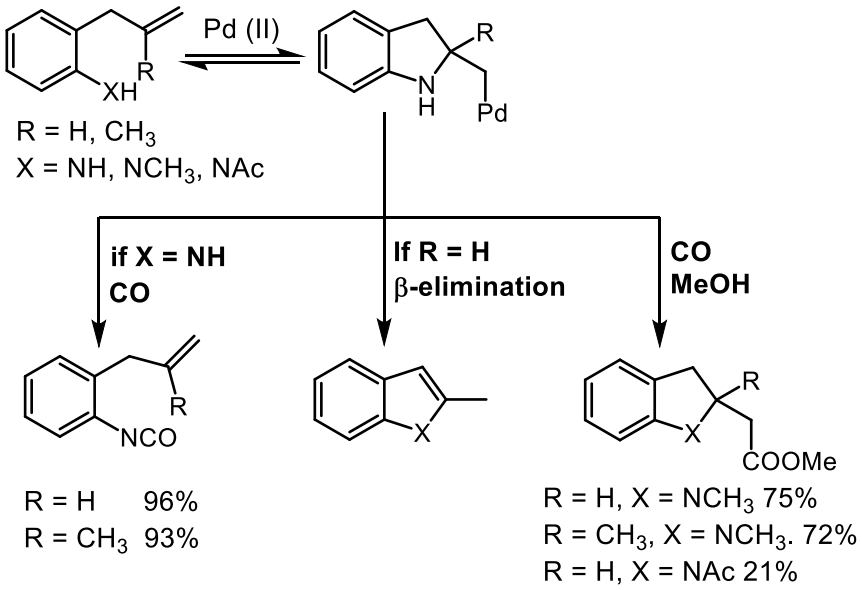
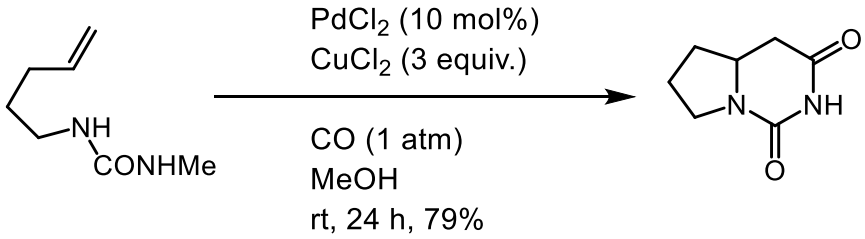


Figure 1.8 Pd(II) assisted intramolecular aminocarbonylation of *o*-allylanilines

[35] Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.

Although Hegedus and coworkers were able to achieve aminocarbonylation in moderate to good yields, the scope was limited to *N*-substituted anilines and temperatures had to be maintained below -25 °C to prevent β-hydride elimination. This type of aminocarbonylation was also restricted to intramolecular systems and stoichiometric amounts of Pd(II) due to strong coordination of the amine.[34] Progress was made by the Tamaru group, through improvement of Hegedus' conditions, towards intramolecular aminocarbonylation of *exo* and *endo* *N*-alkenylureas (Equation 1.6). Their strategy was to add copper (II) as an external oxidant in order to minimize oxidation of the unsubstituted ureas and facilitate oxidation of the reduced palladium species. This enabled them to use catalytic palladium (II) species.[36]

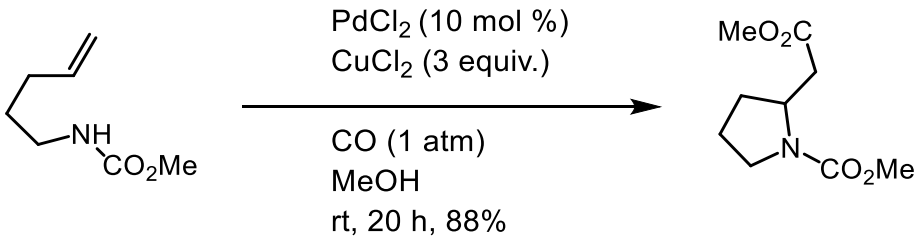


(1.6)

In later studies, Tamaru and Yoshida introduced Palladium catalyzed intramolecular aminocarbonylation of exo and endo carbamates. While exo carbamates are favoured under the same acidic conditions as the ureas (equation 1.7), Tamaru and

[36] a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1988**, *110*, 1994. b) Tamaru, Y.; Tanigawa, H.; Itoh, S.; Kimura, M.; Tanaka, S.; Fugami, K.; Sekivama, T.; Yoshida, Z.-I. *Tetrahedron Lett.* **1992**, *33*, 631. c) Harayama, H.; Okuno, H.; Takahashi, Y.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1996**, *37*, 7287. d) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113.

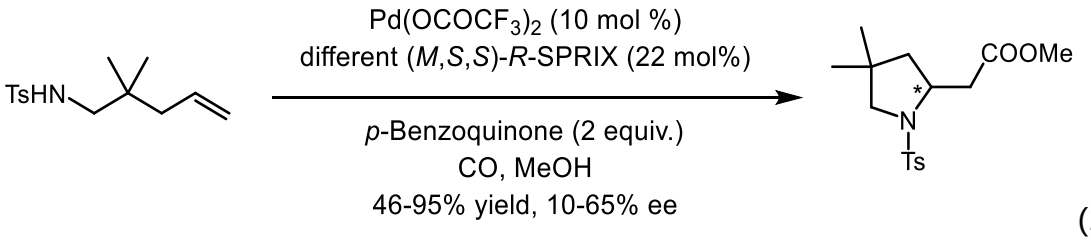
Yoshida have shown that endo carbamates give higher yields under buffered conditions.[36d] Although this reaction is high yielding, the reaction still requires stoichiometric amounts of oxidant while the scope is limited to intramolecular alkenyl ureas and carbamates.



(1.7)

As we saw earlier, aminocarbonylation can lead to interesting β–aminocarbonyl motifs, which we could otherwise not attain with other methods in such high yields and few steps. However, there still is the challenge of enantioselectivity to overcome. In 2003, Sasai and coworkers published the first enantioselective intramolecular alkene aminocarbonylation, achieved with a chiral Pd(II)-SPRIX catalyst. [37] Sasai's reaction conditions were similar to Tamaru's conditions, with an external oxidizing agent in stoichiometric amounts and carbon monoxide atmosphere in methanol (Equation 1.8).

[37] a) Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711. b) Dohanosova, J.; Gracza, T. *Molecules* **2013**, *18*, 6173.



(1.8)

Since these findings were published, Sasai introduced more examples of asymmetric metal catalyzed aminocarbonylation of different reagents such as alkenylureas.[38] As we have observed, metal-catalyzed aminocarbonylation is emerging as a valuable method for the synthesis of nitrogen containing molecules. The possibility of obtaining enantioenriched products makes this area of research very promising. Unfortunately, reaction conditions still include stoichiometric amounts of oxidizing agents and very few asymmetric reactions have been developed to this day.

1.4.2 Intermolecular Aminocarbonylation with Chlorosulfonyl Isocyanates

Nucleophilic additions of alkenes onto electrophiles to form C-N bonds are desirable due to the possibilities of forming rare nitrogen containing products. However, the low nucleophilic reactivity of alkenes has limited these reactions to the use of activated olefins, which contain electron donating groups, and/or very strong electrophiles.

[38] Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, *74*, 9275.

In the 1950's, Graf discovered chlorosulfonyl isocyanate (CSI), an extremely reactive electrophile.[39] For a few years he studied CSI thoroughly to establish three different types of reactivity of this molecule, which he classified according to the final products. Type I is a nucleophilic attack onto the carbonyl motif, Type II is a cycloaddition to the C=N bond, and Type III is a nucleophilic attack onto the sulfonyl group. This is illustrated in Figure 1.9.[40]

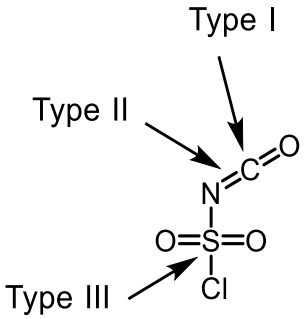


Figure 1.9 Chlorosulfonyl Isocyanate and reactivity sites

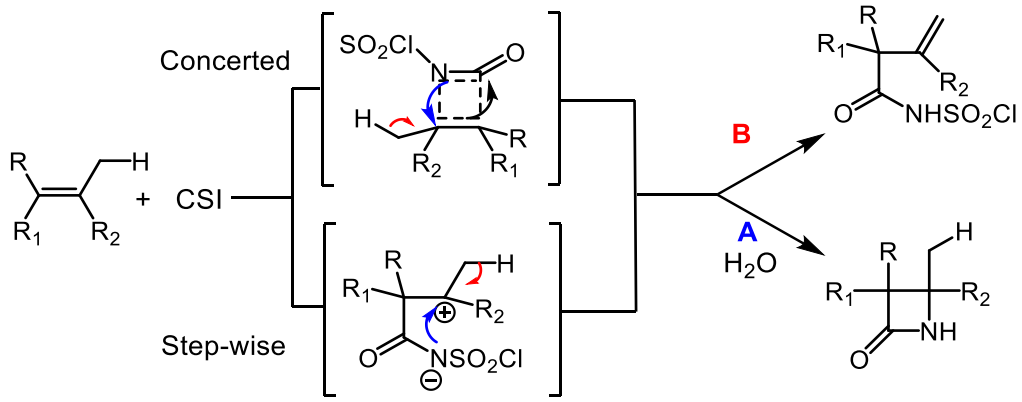
Although reactions of Type I and III have been well assessed, those of Type II are interesting in regards to alkene aminocarbonylation. Arguably, this has also been the most used in the literature. In Type II reactions, CSI undergoes a [2+2] cycloaddition with olefins to form β–lactams in a regioselective manner (Scheme 1.6, path A).[41] While both stepwise and concerted mechanisms have been proposed for this reaction, Shellhamer *et al.* brought evidence that it takes place via a concerted mechanism, with

[39] a) Graf, R. *Chem. Ber.* **1956**, *89*, 1071. b) Graf, R. *Liebigs Ann. Chem.* **1963**, *661*, 111. c) Moriconi, E. J.; Crawford, W. D. *J. Org. Chem.* **1968**, *33*, 370. d) Barrett, A. G. M.; Betts, M. J.; Fenwick, A.; *J. Org. Chem.* **1966**, *31*, 1372.

[40] Miller, M. J.; Ghosh, M.; Guzzo, P. R.; Vogt, P. F.; Hu, J. E. (2005) Chlorosulfonyl Isocyanate. In *e-Encyclopedia of Reagents for Organic Synthesis.* Retrieved from http://onlinelibrary.wiley.com.proxy.bib.uottawa.ca/doi/10.1002/047084289X.rc149.pub2/full

the transition state possessing an asynchronous character.[41] The regiochemistry observed is Markovnikov.[41]

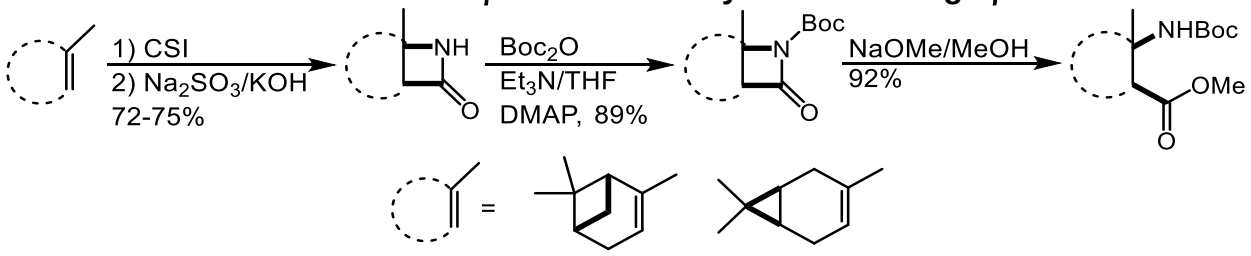
Scheme 1.6 Reactivity and by-products from CSI and alkene reactions



A limitation of the cycloaddition of CSI with olefins is the possible formation of a by-product from a competing elimination reaction shown in red as path B in Scheme 1.6. The ratio of β–lactam to the by-product is dependent on the substitution on the alkene and its electronic character.[40,42] CSI is known to react well with strained olefins that are highly electron donating to produce β–lactams as demonstrated in Scheme 1.7. These β–lactam products can be readily converted into β–amino carbonyls, such as esters and carboxylic acids, in 2-3 steps.[43]

[41] a) Cossio, F. P.; Lecea, B.; Lopez, X.; Roa, G.; Arrieta, A.; Ugalde, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1450. b) Shellhamer, D. F.; Davenport, K. J.; Hassler, D. M.; Hickle, K. R.; Thorpe, J. J.; Vandenbroek, D. J.; Heasley, V. L.; Boatz, J. A.; Reingold, A. L.; Moore, C. E. *J. Org. Chem.* **2010**, *75*, 7913.
[42] Kaluza, Z.; Abramski, W.; Belzecki, C.; Grodner, J.; Mostowicz, D.; Urbanski, R.; Chmielewski, M. *Synlett* **1994**, 539.
[43] Szakonyi, Z.; Fülöp, F. *Amino Acids* **2011**, *41*, 597.

Scheme 1.7 CSI derived β-amino carbonyl motifs through β-lactams



As it was discussed, β–lactam synthesis from CSI can form cyclic and linear β–aminocarbonyls through their derivatization.[43] Products from this reaction are often found in great yields. Unfortunately, CSI is an unstable, toxic reagent that must be stored with precaution due to its reactive nature, notably when it comes in contact with water. This reactivity also limits its tolerance to many types of functional groups and therefore reduces the diversity in product scope.

1.4.3 Alkene Aminocarbonylation Forming Azomethine Imines

Cyclic azomethine imines are also interesting heterocyclic compounds that contain the β-aminocarbonyl motifs. A few azomethine imine scaffolds are known and three of them are often seen in the literature: *N*,*N'*-cyclic, acyclic, and *C,N*-cyclic (Figure 1.10).[44]

[44] a) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nature Chem*. **2011**, *3*, 642. b) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc*. **2010**, *132*, 4076.

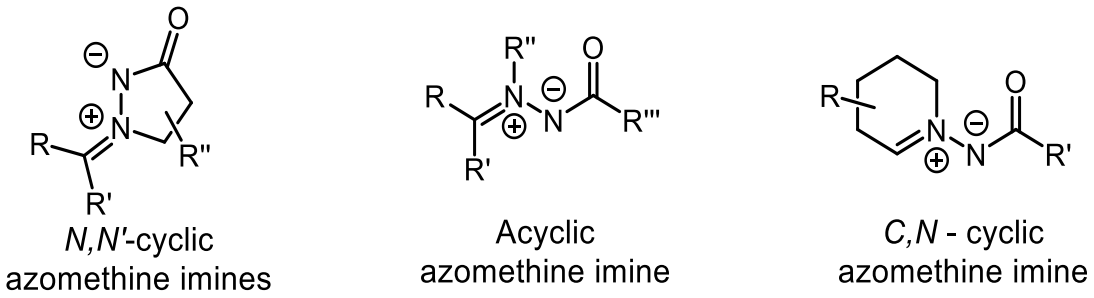
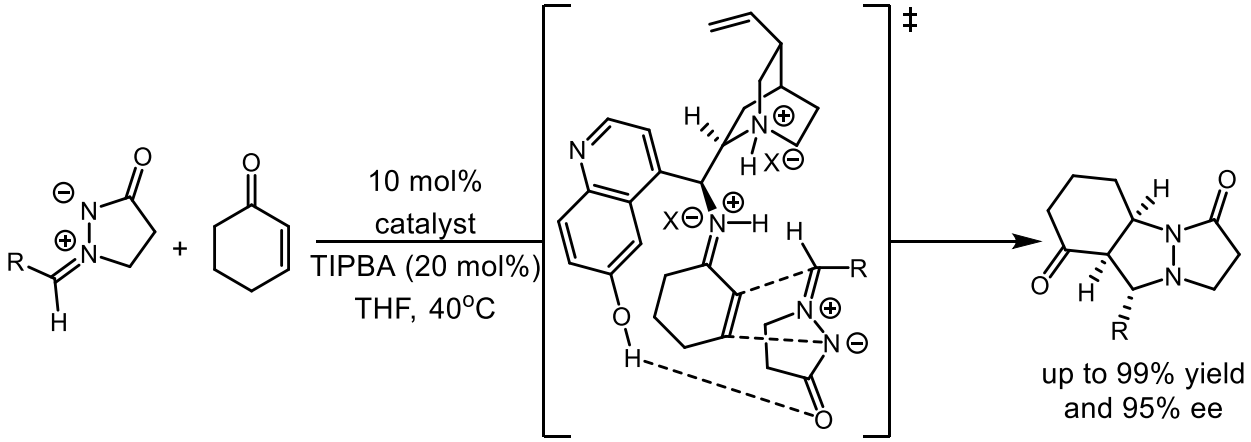


Figure 1.10 Known azomethine imine scaffolds

These substrates are commonly used for 1,3-dipolar cycloadditions. Asymmetric variants have been developed. Although the three azomethine imine scaffolds in Figure 1.10 have been relatively well studied, we will focus our attention on *N,N*'-cyclic azomethine imines. A great example of cycloaddition reaction of azomethine imines is the recent work by Chen where cyclic azomethine imines were developed as precursors to an asymmetric cycloaddition. This reaction proceeds by reacting azomethine imines with enones in the presence of chiral catalyst derived from cinchona alkaloids (Scheme 1.8).[45] This catalysis is obtained by Schiff base formation between the enone and the free amine of the catalyst. As demonstrated in the proposed transition state model, enantiocontrol is found through hydrogen bonding between the hydroxyl and the carbonyl group of the azomethine imine.

[45] Chen, W.; Du, Wei; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 7667.

Scheme 1.8 Asymmetric cycloaddition of *N,N*-cyclic azomethine imines

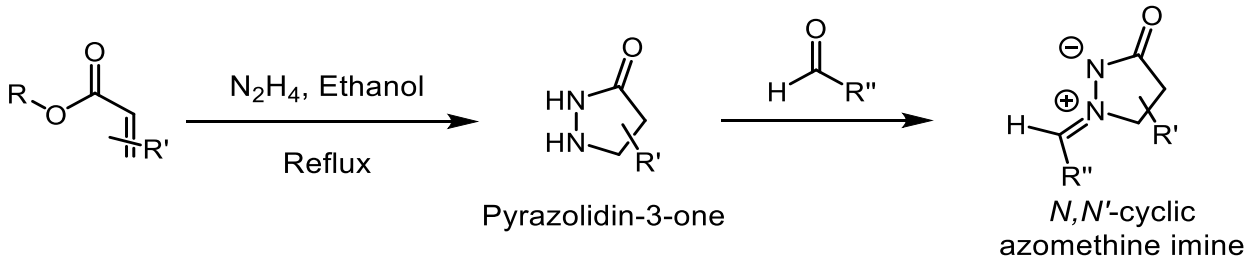


As it was previously stated, these cyclic azomethine imines are also interesting due to their inclusion of β-aminocarbonyl motif, and can be derivatized into β-amino acids by cleavage of the N-N bond. A few different procedures are known in the literature for the synthesis of these *N,N'*-cyclic azomethine imines.[46]

In 1968, Dorn and Otto introduced what became the most standard and general method to form these molecules. It consists of the synthesis of pyrazolidinones from hydrazines and α,β-unsaturated esters, followed by the condensation of aldehydes (Scheme 1.9).[47] This reaction is very convenient as it is tolerant of various substituents in order to build a diverse scope in high yields. Difficulties around this reaction are found in the condensation of unactivated carbonyls. This makes carbonyl derived *N,N*'-cyclic azomethine imines extremely rare. No other general and high yielding reactions are known for the synthesis of these molecules.[48]

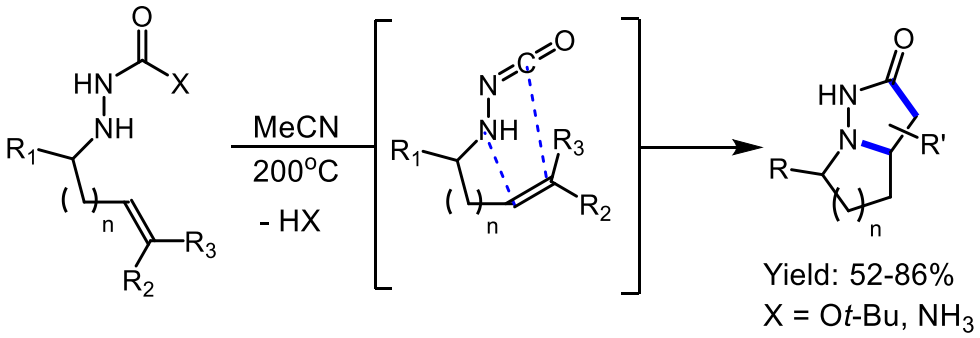
[46] Shintani, R.; Hayashi, T. *J. Am. Chem. Soc*. **2006**, *128*, 6330.
[47] Dorn, H.; Otto, A. *Chem. Ber.* **1968**, *101*, 3287.
[48] a) Perri, S. T.; Slater, S. C.; Toske, S. G.; White, J. D. *J. Org. Chem*. **1990**, *55*, 6037. b) Stetter, H.; Findeisen, K. *Chem. Ber.* **1965**, *98*, 3228., c) Struckwisch, C. G. *Synthesis* **1973**, 469

Scheme 1.9 Azomethine imine synthesis from pyrazolidinones and aldehydes



In 2009, the Beauchemin group reported thermal intramolecular aminocarbonylation of alkenes with hydrazides through amino-isocyanate intermediates.[49] This type of metal free approach to aminocarbonylation allows a C-N and C-C bond formation through easily accessible and affordable starting materials, towards a wide variety of polycyclic products. Findings through the development of that project led towards high yielding results with several hydrazides and semicarbazides (Scheme 1.10).

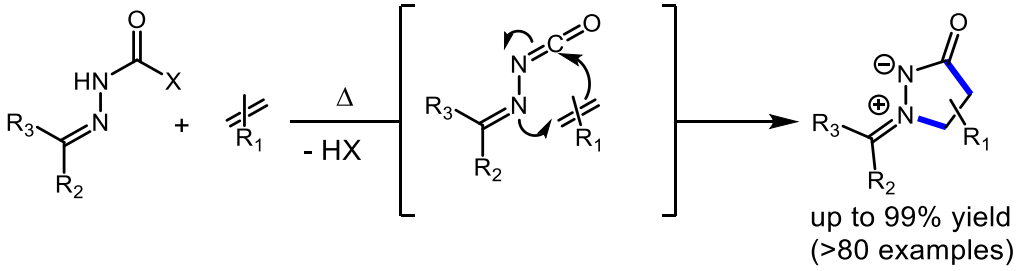
Scheme 1.10 Intramolecular aminocarbonylation of hydrazides



[49] Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, S. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

As we can see in Scheme 1.10, the intramolecular aminocarbonylation of hydrazides likely involve a reactive amino-isocyanate intermediate generated by thermal extrusion of the leaving group. Following these results, we focused our attention on thermal intermolecular aminocarbonylation between hydrazones and alkenes. The use of hydrazones was chosen over hydrazides to reduce the possibility of forming isocyanate dimers, and to form azomethine imine products. This reaction allowed milder reaction conditions and displayed a broader scope. The intermolecular aminocarbonylation of alkenes goes through the thermal loss of the leaving group to generate a reactive imino-isocyanate species, which undergoes [3+2] cycloaddition with an alkene to form structurally complex *N,N'*-cyclic azomethine imine (Scheme 1.11).[50]

Scheme 1.11 Intermolecular aminocarbonylation of hydrazones and alkenes



[50] a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A. B.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111. b) Gan, W.; Moon, P. J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett*. **2013**, *15*, 1890.

This reaction was thoroughly studied. Results showed that yields were dependent upon many variables, such as the nature of leaving group, which affected the kinetics of imino-isocyanate formation.[51] Since the reaction can form by-products, such as dimers from imino-isocyanate intermediates and additional 1,3-dipolar cycloaddition of the azomethine imines, higher steric hindrance in hydrazones was found to increase yields due to dipole shielding (thus preventing further reactions of the products).[50] Also, higher yields were typically observed with electron rich and sterically strained alkenes, due to higher reactivity and lower by-product formation.[50]

Intermolecular alkene aminocarbonylation has proven to be a successful method to synthesize azomethine imines and allows a large scope with high diversity and substitutions. This new reactivity allows formation of azomethine imines through a one-step reaction from readily available and inexpensive starting materials. In contrast with the classic method, these products can easily be made with hydrazones derived from both aldehyde and ketone groups rather than being limited to aldehydes.

With the diverse scope of *N,N*-cyclic azomethine imines that we can synthesize through this reaction, there is a great opportunity for derivatizing them into several interesting compounds with varying substitutions including 1,3-diamines, cyclic hydrazines, pyrazolones and cyclic hydrazides (Figure 1.11).

[51] Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, M. *Org. Lett*. **2013**, *15*, 4074.

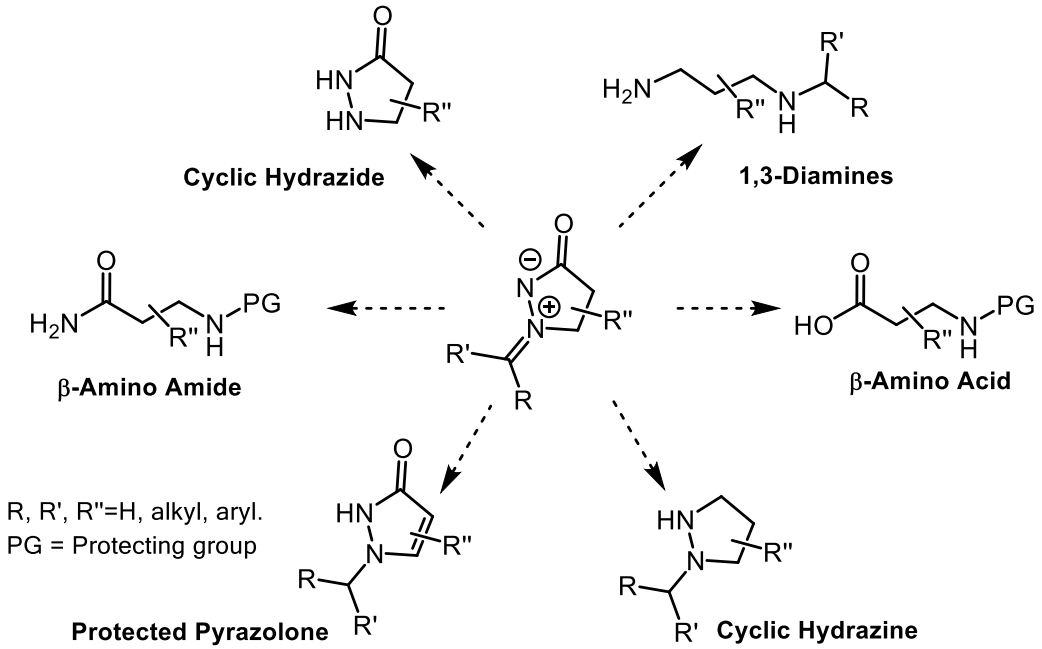


Figure 1.11 Possible derivatization objectives of *N,N*-Cyclic azomethine imines

As we can see in this Figure 1.11, we could also derivatize these azomethine imines into biologically active β-aminocarbonyl compounds. Since this method allows us to make a more diverse scope of azomethine imines than any method in the literature, there are countless possibilities for the structures of β-aminocarbonyl compounds, including natural and unnatural β-amino acids.

1.5 Objectives of the Project

As it was discussed in section 1.4.3, *N,N'*-cyclic azomethine imines formed through the Beauchemin group's intermolecular aminocarbonylation are molecules with excellent potential for derivatization due to their β–aminocarbonyl motif. The first

generation derivatization of these molecules, which we will review in Chapter 2, had used harsh conditions and required difficult purification methods.

The goal of my project was to develop a short and high yielding derivatization method towards β–amino amides from the azomethine imines formed in the Beauchemin Group (Figure 1.12). This derivatization would include the cleavage of the N-N bond along with the cleavage of the iminium substituent and protection of the final primary amine product with easily removable protecting groups towards stable β-amino amides.

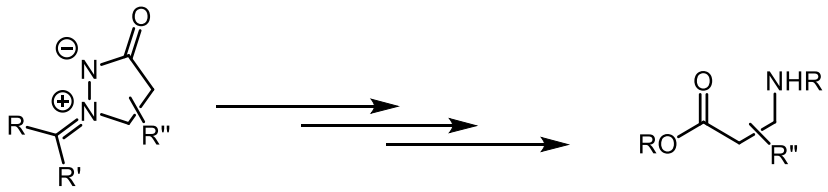


Figure 1.12 Derivatization of *N,N*-cyclic azomethine imines into *N*-protected-β-amino amides

In addition, the amide products of this derivatization were of interest towards their use as starting materials to develop the aldehyde-catalyzed hydrolysis of β-amino amides. This would give us access to unnatural β–amino acids through fewer derivatization and purification steps.

2

Derivatization of Azomethine Imines into *N*-Boc-β-amino Amides

2.1 Introduction

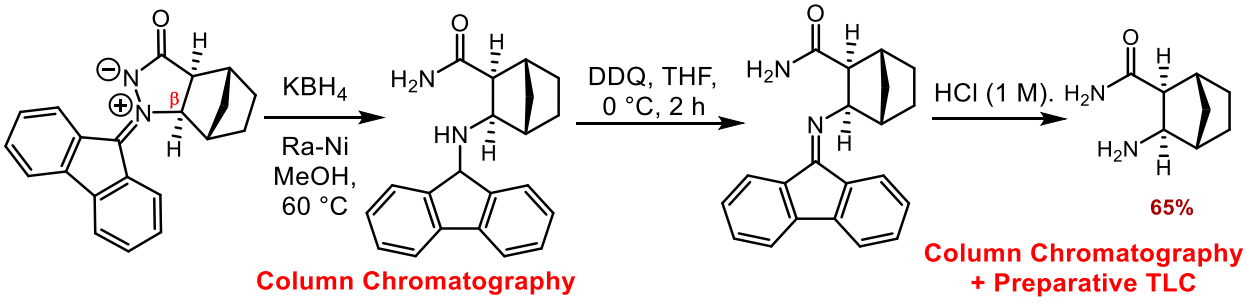
The focus of this chapter will be on the derivatization of azomethine imines synthesized using intermolecular aminocarbonylation, developed in the Beauchemin group, starting from simple alkenes and hydrazones. They also have the potential to be converted into various β–aminocarbonyl compounds, which are valuable due to their inclusion in many synthetic compounds and β–peptide targets as seen in Chapter 1.

This chapter will begin with a focus on the derivatization of azomethine imines into β–aminocarbonyls. First, we will review the first generation derivatization of these compounds into fluorenyl protected β–amino amides. Challenges and limitations of this method, along with successful and unsuccessful work towards new methods for efficient derivatization will be discussed. Synthesis of pyrazolones from the derivatization of azomethine imines will also be discussed.

2.2 First Generation: Derivatization of Azomethine Imines

In the first attempt to derivatize azomethine imines into β-amino amides, two different approaches were used. As both methods failed to reduce the N-N bond on azomethine imines derived from diisopropylketohydrazone due to steric hindrance, only fluorenone-derived azomethine imines were derivatized. The first method, which used protocols adapted from the literature, was the reduction of the iminium with sodium borohydride followed by a reductive cleavage of the N-N bond using Raney-Nickel. [52,50a] This amine was then re-oxidized to the imine using DDQ followed by acidic hydrolysis of the fluorenone-derived imine using HCl.[53] As can be seen in Scheme 2.1, only one compound was synthesized through this method and obtained in a moderate yield of 65%.

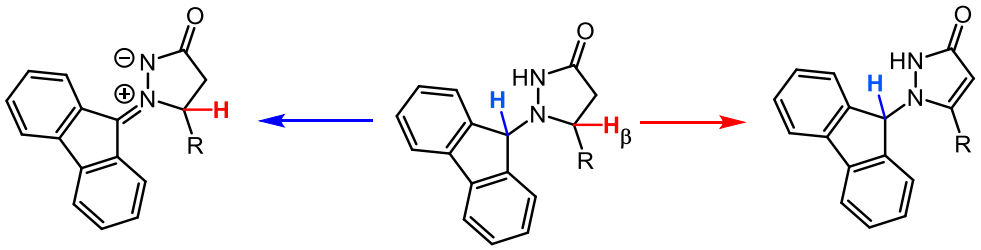
Scheme 2.1 First generation derivatization of azomethine imines



[52] Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625.
[53] Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2000** *39*, 1650.

The first limitation of this method is related to the reductive cleavage with KBH_4, which is restricted to certain compounds due to its reductive properties and inherent functional group tolerance. In addition, we observed a more favorable isomerization through an azomethine ylide intermediate when an electron withdrawing group is present at the β position making the proton more acidic and labile (β proton shown in Scheme 2.2). The second limitation of this methodology is the deprotection of β-amino amides. The oxidizing properties of DDQ can create by-products that are dependent of the substitutions on the azomethine imine. This problem could arise with, but is not limited to electron-rich aromatics, and ether substituents. DDQ is known to rearomatize compounds that have acidic protons and this could create by-products such as pyrazolones (Scheme 2.2).[54] Another drawback to this method is the purification requiring two flash silica columns and a preparative thin layer chromatography following the DDQ deprotection conditions.

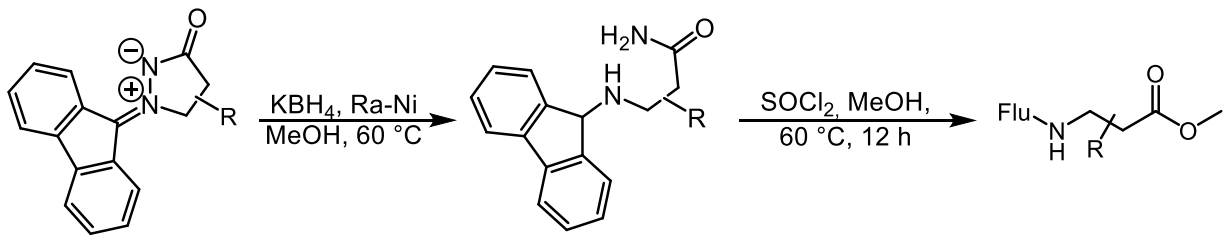
Scheme 2.2 DDQ oxidation products depending on R group electronic properties

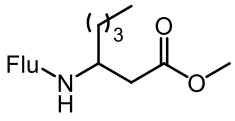


[54] a) Ahluwalia, V. K.; Jolly, R. S. *Synlett* **1982**, *74*, 3. b) Brown, W.; Turner, A. B. *J. Chem. Soc. C.* **1971**, 2566. c) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153. d) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915.

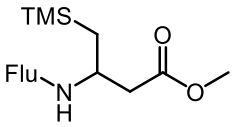
The second strategy towards the derivatization of azomethine imines began with the same reductive cleavage of the N-N bond using basic conditions. The β-amino amide was then converted into a β-amino ester with protocols in the literature using thionyl chloride and methanol to generally give moderate to good yields of 49 – 64% for **1b** to **1e** and 89% for **1a** (Table 2.1).[55]

Table 2.1 First generation derivatization of azomethine Imines

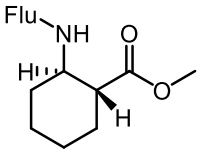




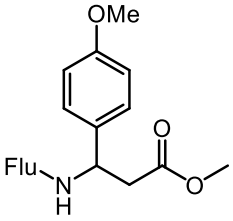
89%, **1a**



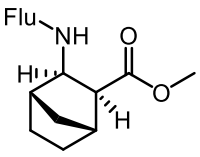
64%, **1b**



50%, **1c**



60%, **1d**



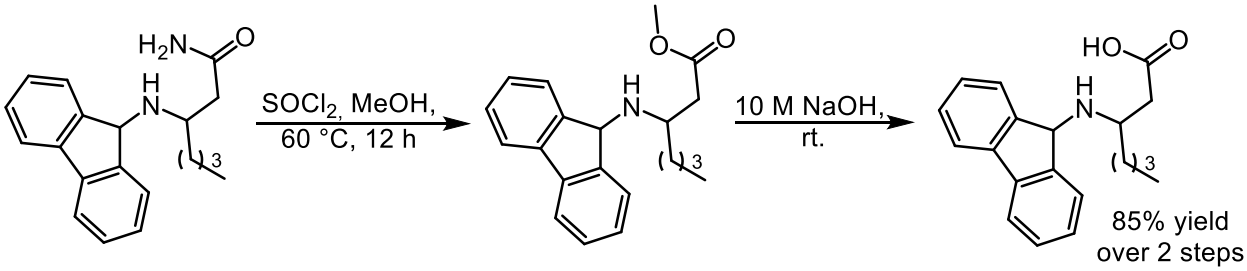
49%, **1e**

Flu = Fluorenyl.

[55] Li, L.-C.; Ren, J.; Liao, T.-G. ; Jiang, J.-X.; Zhu, H.-J. *Eur. J. Org. Chem.* **2007**, 1026.

As ester **1a** gave the highest yield, it was then subjected to saponification conditions to obtain fluorenyl protected β–amino acid in 85% yield over two steps (Scheme 2.3).[50]

Scheme 2.3 Conversion of β-amino amide to β-amino acid



This method requires the same reductive N-N bond cleavage with poor functional group tolerance as the first method. Once cleaved, the β-amino acid can be obtained over two steps using the same reaction conditions as in Scheme 2.3. These products would also have to be deprotected by DDQ and HCl to be used as β–amino acids, which would require the same difficult purification as the first example.

A restriction surrounding these two derivatization methodologies is the limitation in starting materials. These derivatization methods were developed for fluorenone protected azomethine imines due to steric hindrance on diisopropyl derivatives. As these derivatization methods are not general, it does not portray the novelty behind various high yielding azomethine imines formed from the Beauchemin group alkene aminocarbonylation, which was extended to symmetrical and unsymmetrical ketone and aldehyde derived hydrazones.

For the second generation of the azomethine imine derivatization, the goals were to reduce the number of steps, find a general method to remove any N^{β}-substituents before the N-N bond cleavage and simplify the purification process. As the yields of the first generation derivatization were decreased due to difficult purification steps, simple purification methods were also of interest in the second generation derivatization. We were also interested in adding easily removable amine protecting groups to our final β-amino amide to increase their synthetic utility.

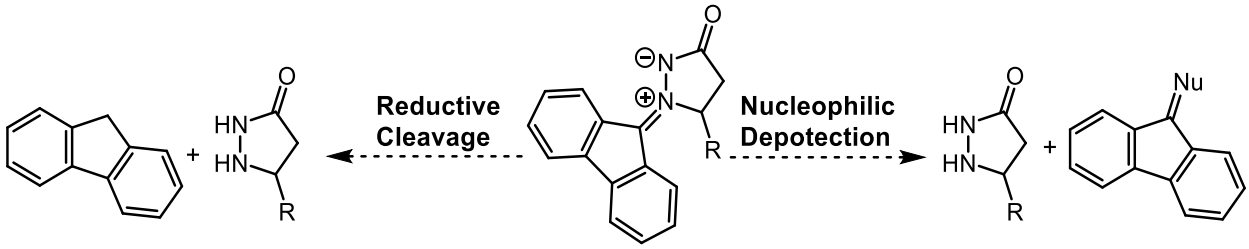
2.3 Second Generation: Derivatization of Azomethine Imines

The first step taken towards achieving the goals of this project was to develop a method for the deprotection of nitrogen substituents on azomethine imines. The objective was to access an *N*-unsubstituted cyclic hydrazide by cleaving any iminium substituent on azomethine imines. After this deprotection, cleavage of the N-N bond should be easily accomplished. In order to have efficient handling and long term storage of β-amino amides, nitrogen protecting groups, such as Boc or Fmoc, could then be added.

2.3.1 Deprotection of Azomethine Imines

Although azomethine imines were formed from many symmetrical and unsymmetrical ketone and aldehyde hydrazones, a large scope of fluorenone derivatives were synthesized from various alkenes. Consequently, these fluorenone derivatives were chosen to start this deprotection project. Two main strategies towards deprotection of fluorenone azomethine imines were taken. The first was the reductive cleavage of the fluorenone group and the second was the nucleophilic deprotection through formation of a Schiff base (Scheme 2.4).

Scheme 2.4 Strategies towards azomethine imine deprotection

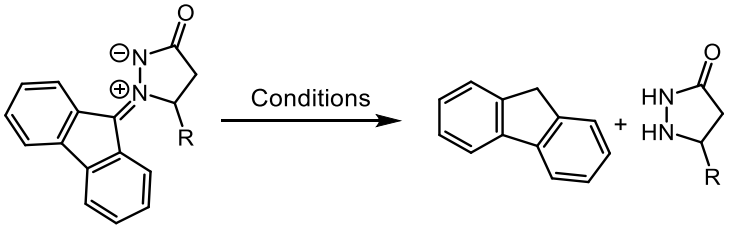


We first focused our attention on the reductive cleavage of the fluorenone group. As a starting point, palladium on carbon under hydrogen atmosphere was tested to remove the fluorenone group from azomethine imines as these conditions were known to reduce imines to amines and cleave benzyl amines.[56] Consequently, it was hypothesized that palladium on carbon could possibly reduce the iminium of the

[56] a) Ram, S.; Spicer, L. *Synth. Commun*. **1987**, *17*, 415. b) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem. Int. Ed*. **2006**, *45*, 3832.

azomethine imine followed by deprotection of the fluorenyl group which has a benzylic proton. Unfortunately, this would mean that these conditions could potentially not tolerate all substituents on azomethine imines, such as the phenyl derivative. This azomethine imine would be benzylic at the β-position, which could cause reduction at that position. Therefore, to observe the effect of the R-group during a palladium reduction of azomethine imines, starting materials with both butyl and phenyl R groups were chosen.

Table 2.2 Reductive conditions towards deprotection of fluorenone

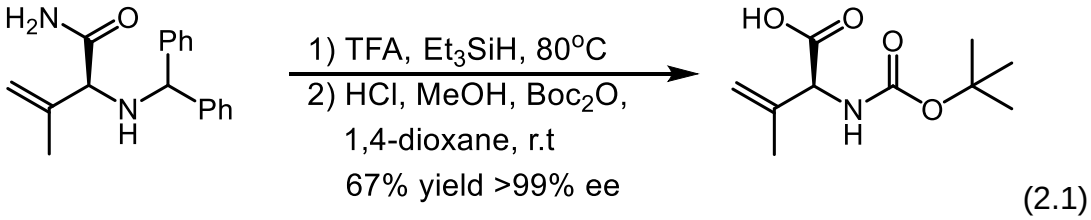


Entry	R	Reducing Conditions*	Time	Temp.	Products
1	*n*-Bu	Pd/C (20 mol%), H_2, EtOH	2 h	r.t	Mix of 3 reduced products + fluorenyl
2	*n*-Bu	Pd/C (20 mol%), H_2, EtOH	1 h	r.t	Mix of 3 reduced products + fluorenyl
3	Ph	Pd/C (20 mol%), H_2, EtOH	24 h	r.t	Mix of 3 reduced products + fluorenyl
4	*n*-Bu	Et_3SiH (6 eq.) TFA (4 eq.), Ar, CH_2Cl_2	3.5 h	0-40°C	SM
5	*n*-Bu	Et_3SiH (18 eq.) TFA (60 eq.), Ar, CH_2Cl_2	48 h	40°C – r.t	SM + trace fluorenyl + 2 reduced products

*These experiments were performed at atmospheric pressure.

As it was determined through experimentation and by NMR, palladium on carbon did remove the fluorenyl group (entry 1-3, Table 2.2). Regardless of the nature of the R group, a mixture of three co-eluting polar products were observed, which challenged the efficacy of this method. Due to product mixture obtained from palladium on carbon conditions and these conditions being specific to fluorenone derived azomethine imines, experimentations with these conditions were not pursued any further.

The second reductive method chosen was the treatment of fluorenone derived azomethine imines with triethylsilane and trifluoroacetic acid. These conditions have previously been published for imine reduction and cleavage of the diphenylmethyl amine protecting group.[57] An example published by Hoveyda is shown in Equation 2.1. In this example, a diphenylmethyl nitrogen protected α-amino acid is deprotected and hydrolyzed, followed by *tert*-butyloxycarbonyl protection of the resulting free amine.[58a)]



(2.1)

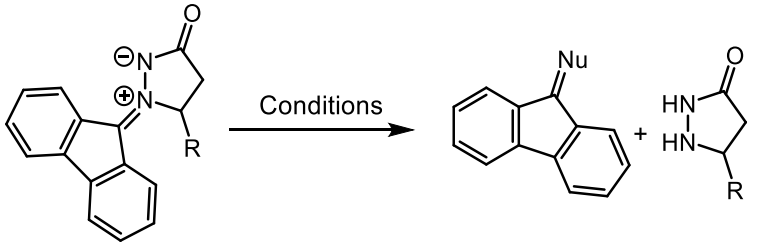
As experiments were conducted, when equivalents of triethylsilane and trifluoroacetic acid were increased, reactivity towards fluorenone deprotection was

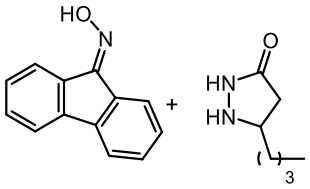
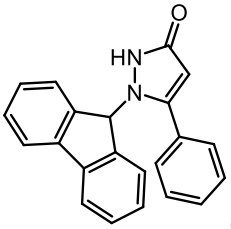
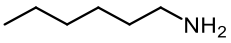
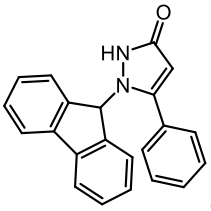
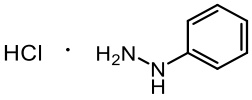
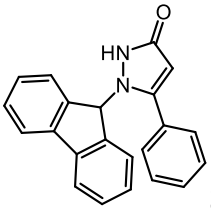
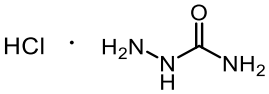
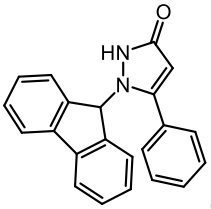
[57] a) Porter, J. R.; Wirschun, W. G; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657. b) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, *2*, 3921.

detected (entry 4 and 5, Table 2.2). Although unreactive butyl derived azomethine imine was used, these conditions also produced a mixture of products from the triethylsilane conditions and very little reactivity over a long period of time. As nucleophilic deprotection proved to be more promising, attempts to achieve cleavage under reducing conditions were not pursued any further.

Our second hypothesis was that treating ketone and aldehyde derived azomethine imines with a nucleophile could lead to the deprotection of their N^{β}-substituents through the formation of a Schiff base between the carbonyl group and an amine nucleophile. The nucleophile had to be strong with only mildly basic properties to avoid deprotonation of acidic protons.

Table 2.3 Nucleophilic deprotection of fluorenone-derived azomethine imines

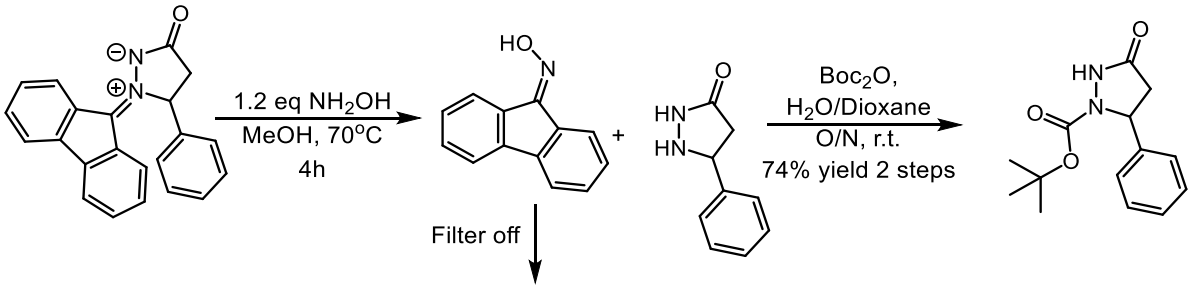


Entry	R group	Nucleophile	Conditions	Product	NMR Yield
1	*n*-Bu	aq. NH_2OH	MeOH, r.t 2 h		96%
2	Ph	$MeNH_2$	MeOH, 70°C 24 h	 **3a**	91%
3	Ph		MeOH, 70°C 24 h	 **3a**	93%
4	Ph		MeOH, 70°C 24 h	 **3a**	80%
5	Ph		MeOH, 70°C 24 h	 **3a**	83%

The first nucleophile tested on azomethine imines was aqueous hydroxylamine, which produced the desired cyclic hydrazide along with the fluorenone oxime by-product in 96% NMR yield. As we can see in Table 2.3, other nucleophiles such as amines, hydrazines and hydrazides reacted with azomethine imines as bases to form a by-product that was identified as a pyrazolone (**3a**) in 80-93% NMR yield (entry 2-5). These nucleophiles are slightly basic and therefore it was hypothesized that deprotonation of acidic protons, forming an azomethine ylide intermediate, followed by rearomatization lead to the formation of pyrazolones. We will review these compounds in Chapter 3.

Although hydroxylamine demonstrated 96% NMR yield, the product was lost during purification due to its miscibility with water and high polarity. Nevertheless, it was a potential general deprotection method and the purification was then optimized by simple trituration of the byproduct with a solution of 20% methanol in water. Finally, this hydroxylamine deprotection method was used and optimized on the phenyl-β-substituted fluorenone-derived azomethine imine (**5d**), which was readily protected with a Boc group to yield 74% of product over two steps (Scheme 2.5). The reaction on the phenyl group required four hours and the temperature was increased to 70 °C due to solubility issues caused by the fluorenone substituent. The *N*$^{\beta}$-Boc-protected cyclic hydrazide product generated herein could then be part of the N-N bond cleavage procedure studies which will be discussed in chapter 3.

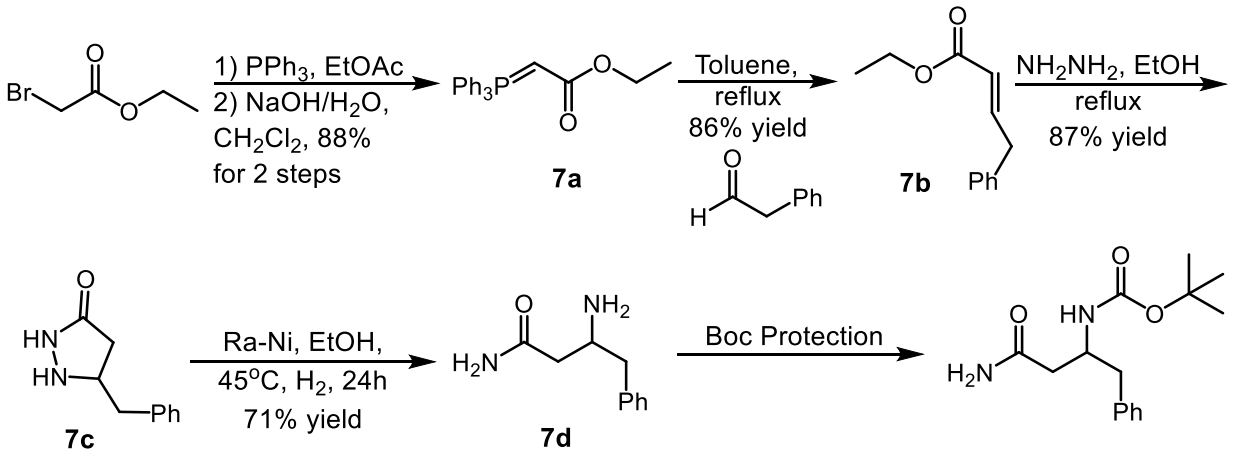
Scheme 2.5 Derivatization to *N-tert*-butyloxycarbonyl protected cyclic hydrazides



2.3.2 Optimization of *tert*-Butyloxycarbonyl β–Amino Amide Protection

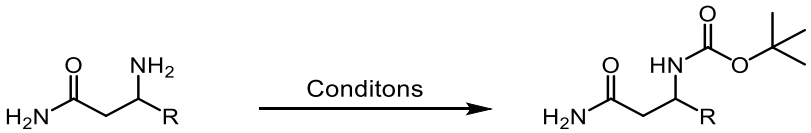
Efforts were then focused on the optimization of β-amino amides protection with *tert*-butyloxycarbonyl. Starting material for this optimization was synthesized through the conversion of ethyl bromo acetate into benzyl α,β-unsaturated ethyl ester using a Wittig reaction, which was then reacted with hydrazine to form a cyclic hydrazide.[47] The N-N bond was then cleaved by reductive Raney-Nickel conditions, that were optimized by Dr. Nicolas DasNeves from the Beauchemin group, to obtain unprotected β–amino amides (Scheme 2.6). Once the deprotection with hydroxylamine from the previous section was developed and optimized, starting materials with a variety of R-groups were used in the Boc protection optimization that will be presented shortly.

Scheme 2.6 β-amino amide protection optimization from cyclic hydrazine



As we can see in table 2.4, many conditions were tested towards tert-butyloxycarbonyl protection of β–amino amides. When dichloromethane was used as a solvent, desired product was observed, however the β-amino amide was not fully soluble which lead to low yields of 33% (entry 1). In contrast, water as a solvent showed limited reactivity due to the poor solubility of di-*tert*-butyl dicarbonate to give 28% yield (entry 2). Consequently a solvent which had a higher polarity than dichloromethane and lower polarity than water was used, such as *tert*-butanol. Although *tert*-butanol did solubilize the starting materials, no products were isolated when high concentration of sodium hydroxide were used (entry 3). Consequently, Boc protection in *tert*-butanol was tested on two different starting materials with catalytic amounts of sodium hydroxide to yield 67-73% of product (entry 4 and 5).

Table 2.4 Optimization of the *tert*-butyloxicarbonyl β–amino amide protection



Entry	R	Boc_2O	Solvent	Additive	Temp.	Time	Yield
1	Benzyl	1 eq	CH_2Cl_2	Et_3N 2 eq.	45°C - rt	19h	33%
2	Benzyl	1.1 eq	H_2O	---	35°C	16h	28%
3	PMP	3 eq	*t*-BuOH	NaOH, 3 eq.	rt	16h	0%
4	Phenyl	2	*t*-BuOH	NaOH, 0.2 eq.	rt - 60°C	24h	67%
5	PMP	2	*t*-BuOH	NaOH, 0.2 eq.	rt	12h	73%

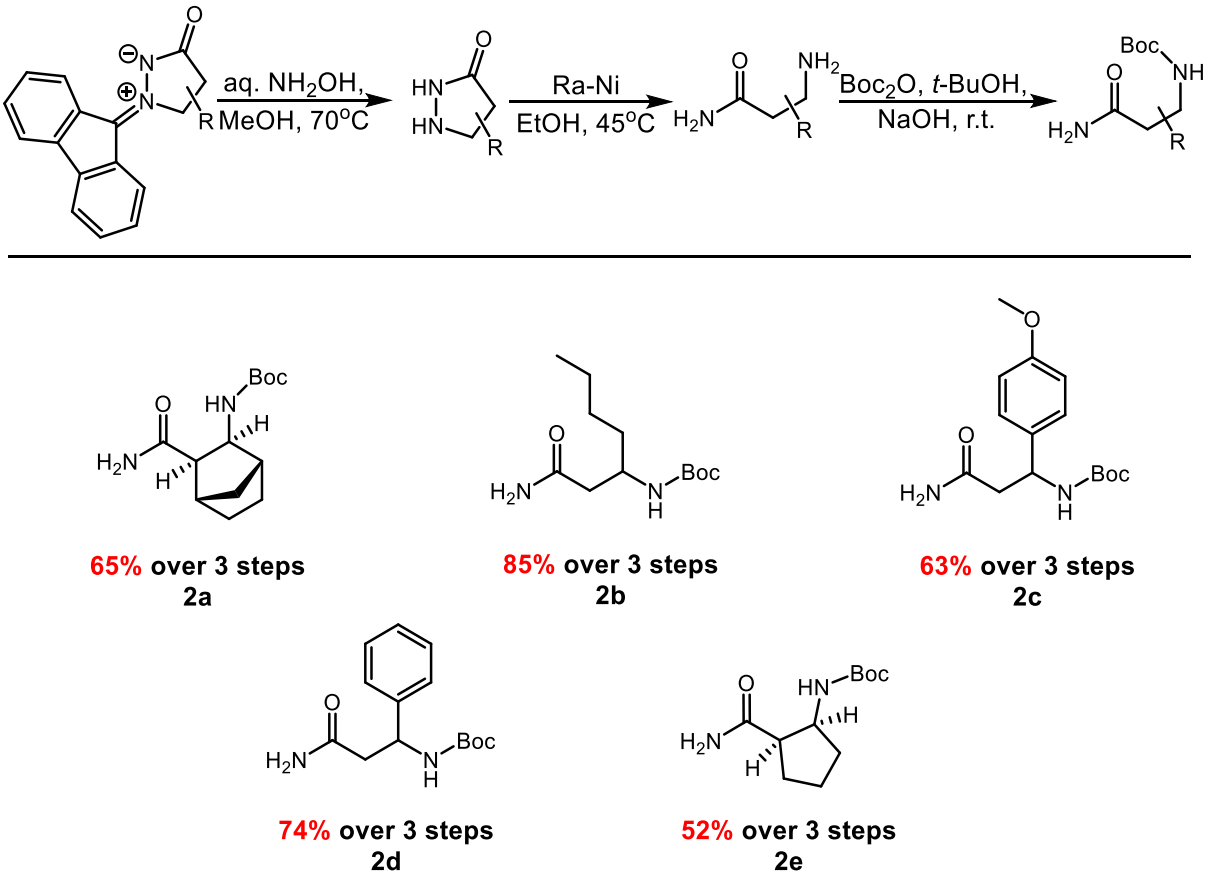
For the protection of β-amino amides, challenges were found during the purification step and most importantly in the characterization. In many cases, the products were lost during the extraction and could not be recovered due to solubility issues. Similarly, characterization of the products was difficult due to poor solubility. It was found that high temperature NMR over long periods of time provided satisfactory results by reducing large signals caused by rotamers. These NMR samples also had to be stirred in deuterated solvents for long periods of time to reduce H-bonding which caused poor solubility and weak NMR signals.

2.3.3 Derivatization of Azomethine Imines into *N*-Boc-β-Amino Amides

Once the hydroxylamine-induced deprotection of fluorenone-derived azomethine imines and the *tert*-butyloxycarbonyl protection of β–amino amides were optimized, the project was steered towards a high yielding and purification free derivatization of azomethine imines into *N*-Boc-β-amino amides.

First, the separation of products by filtration was optimized on the phenyl-substituted substrate, followed by the Raney-Nickel N-N bond reduction, which was previously optimized by Dr. Nicolas Das Neves. Finally these resulting β-amino amides were subjected to optimized *tert*-butyloxycarbonyl protection conditions. Once this derivatization was optimized for fluorenone-derived azomethine imines, the scope of the procedure was extended and results are shown in Table 2.5.

Table 2.5 Azomethine imine derivatization into *N*-Boc-β-amino amides



As shown above, cyclic derivatives such as **2a** and **2e,** which are more sterically hindered, have a combined yield over three steps that is lower than linear compounds such as **2b** (52% and 65% vs. 85% yield, respectively). This could be due to slower reactions due to steric hindrance. Fortunately, the yields of these cyclic derivatives were still acceptable over three steps. Aromatic substituents such as in **2c** and **2d** gave moderate to good yields over three steps with 63% and 74% yield respectively. The strongest asset of this derivatization compared to the first generation derivatization is the lack of chromatographic purification steps which are replaced by simple filtration. After the deprotection of fluorenone, the oxime by-product is triturated off and the filtrate

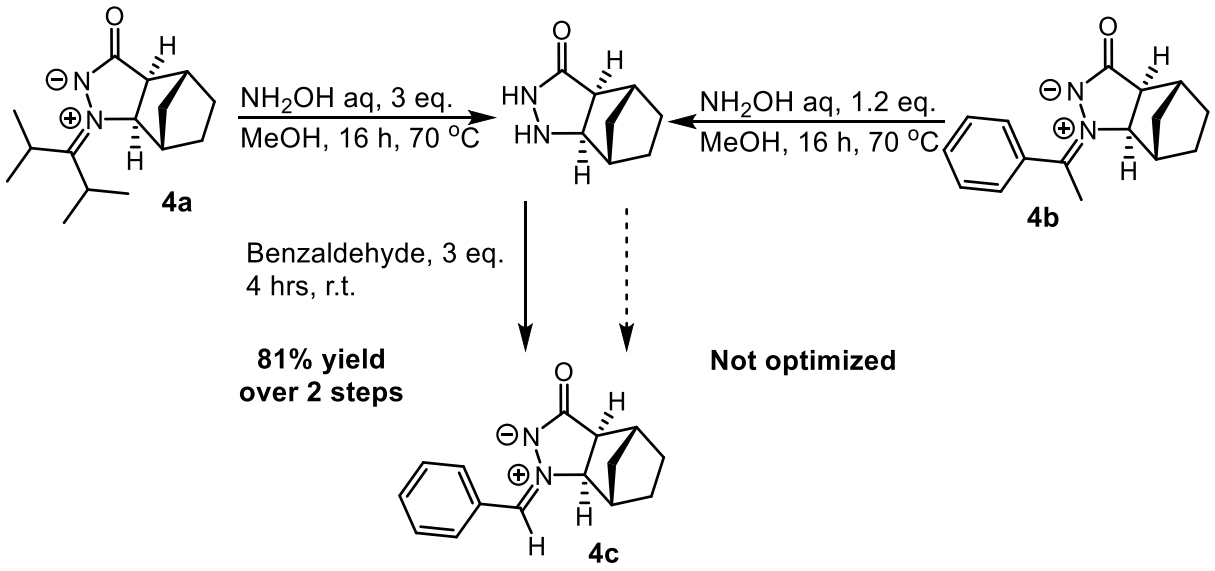
is concentrated and subjected to reducing conditions with Raney-Nickel. This mixture is then filtered through celite and concentrated to yield an unprotected β-amino amide. This mixture is then subjected to Boc protection conditions and the product precipitated out as a white powder, which was filtered and washed to yield the desired *N*-Boc-β-amino amides.

Although this procedure was useful in the derivatization of fluorenone-derived azomethine imines, which have been the main focus in the Beauchemin laboratory, the ultimate goal was the derivatization of azomethine imines with any carbonyl protecting groups. The first generation of intermolecular alkene aminocarbonylation with imino-isocyanates involved a diisopropylketone-derived azomethine imine, which caused steric hindrance. This steric hindrance restrained the N-N bond from successful cleavage. Consequently, the first generation derivatization could not be used towards derivatizing these azomethine imines into β-amino amides.

Thus, this second generation methodology of azomethine imine deprotection was tested on a diisopropylketone-derived azomethine imine (**4a**) along with an azomethine imine derived from an unsymmetrical ketone. Fortunately, the use of hydroxylamine in higher concentration also demonstrated reactivity towards deprotection of the diisopropylketone-derived azomethine imine. Once the deprotection was achieved with this new method, the resulting cyclic hydrazide was reacted with benzaldehyde and purified to yield product **4c** in 81% yield over 2 steps (Scheme 2.7). Hydroxylamine also allowed derivatization of an azomethine imine synthesized with unsymmetrical hydrazone derived from acetophenone (**4b**). Unfortunately products could not be recovered after the deprotection and these results were not optimized. While the

reaction with benzaldehyde was used to facilitate purification and allow assessment of the efficiency of the deprotection method, the cyclic hydrazide obtained after the deprotection step could also be derivatized into *N*-Boc-β-amino amides.

Scheme 2.7 Carbonyl deprotection and aldehyde protection of azomethine imines



While a broadly applicable method towards deprotection of several types of azomethine imine N^{β}-substituent groups was finally within reach and protected β–amino amides were produced in a few high yielding steps, the use of the new procedure helped other projects in the Beauchemin Group advance at higher rates. It was taken up by Amanda Bongers as a purification free route towards various aldehyde-protected azomethine imines for her kinetic resolution project. Fortunately, this method can be used to synthesize aldehyde-derived azomethine imines, which are difficult to synthesize through the Beauchemin Group aminocarbonylation reactivity, from easily synthesized fluorenone azomethine imines.

2.4 Pyrazolones

In the late 1800's interesting aromatic heterocycles were discovered and became an important part of many chemistry related industries. These pyrazolones are found in three different classes shown in Figure 2.1. They were first discovered as part of the dye industry and grew to be important pharmaceuticals and agrochemicals.[58] In Figure 2.2 we can observe examples of important pyrazolones: a herbicide named Armezon, an analgesic named Dipyrone and Pigment Yellow 10.[59]

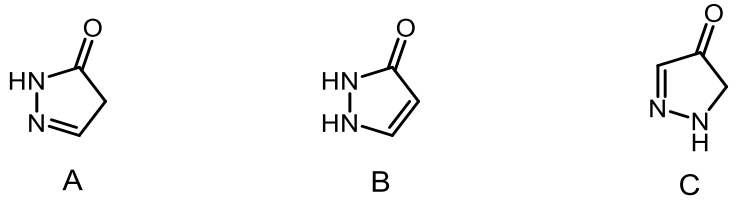


Figure 2.1 Known classes of pyrazolones

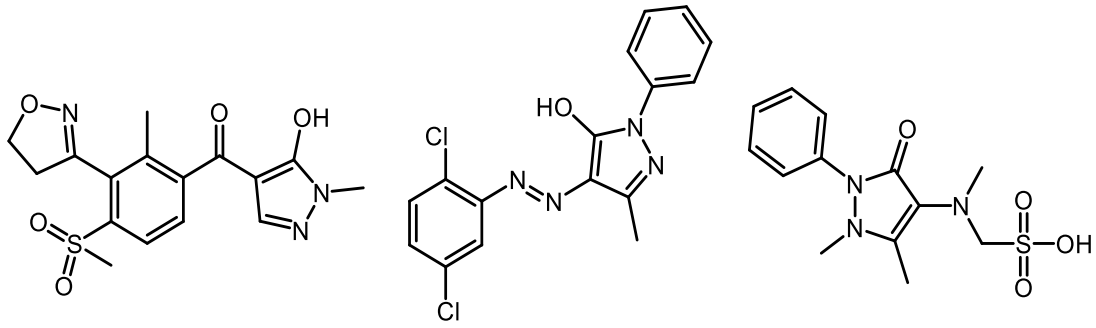
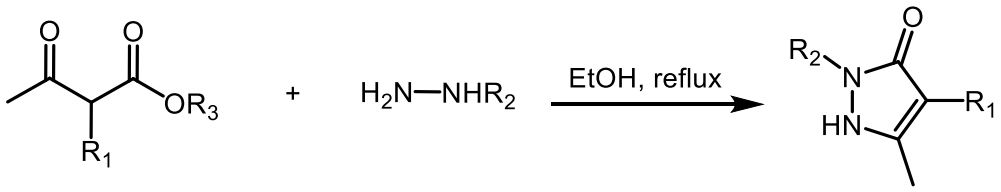


Figure 2.2 Pyrazolones in agrochemical, pharmaceutical and dye industries

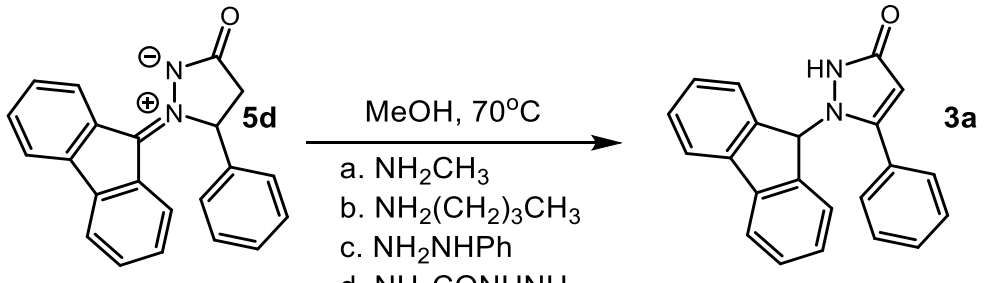
[58] Metwally, M. A.; Bondock, S. A.; El-Desouky, S. I.; Abdou, M. M. *Inter. J. Mod. Org. Chem.* **2012**, *1*, 19.
[59] a) Brogden, R. N. *Drugs* **1986**, *32*, 60. b) Rahman, A.; Dowsett, C. A.; Trolove, M. R.; James, T. K. *New Zealand Plant Protection* **2014**, *67*, 298. c) Whitaker, A. *J. Soc. Dyers and Colourists* **1987**, *103*, 270.

The most effective and popular way to synthesize these compounds is through the condensation of substituted hydrazines and β–keto esters (Equation 2.2).[60] This is a well-studied reaction that is reliable for the synthesis of a wide variety of pyrazolones yet requires the synthesis of various β-keto esters.



(2.2)

As discussed in Chapter 1, β–amino amides are not the only interesting products that could be derived from azomethine imines. Through developing methodology towards deprotection of these molecules, a few side reactions were detected. As shown in Equation 2.3, by-product **3a** was produced when azomethine imine **5d** was subjected to primary amines, hydrazides and hydrazines (Table 2.3 from section 2.3.2).



(2.3)

[60] Varvounis, G. Pyrazol-3-ones: Part IV: Synthesis and Applications. In: A. R. Katritzky., editor. *Advances in Heterocyclic Chemistry* Elsevier. **2009,** 98, pp. 1-328.

In this reaction, it was hypothesized that in the presence of an electron-withdrawing group at the β position, a key azomethine ylide-like intermediate can be formed and stabilized by an aromatic anion. First, there is a deprotonation at the β position which is favoured by the stabilization through conjugation with the phenyl group. This is followed by an isomerization due to the stabilization provided by the aromaticity of the fluorenyl anion, which is then neutralized by protonation. Finally, the reaction is driven towards formation of the more stable 2-pyrazolin-5-one by aromatization and protonation (Figure 2.3).

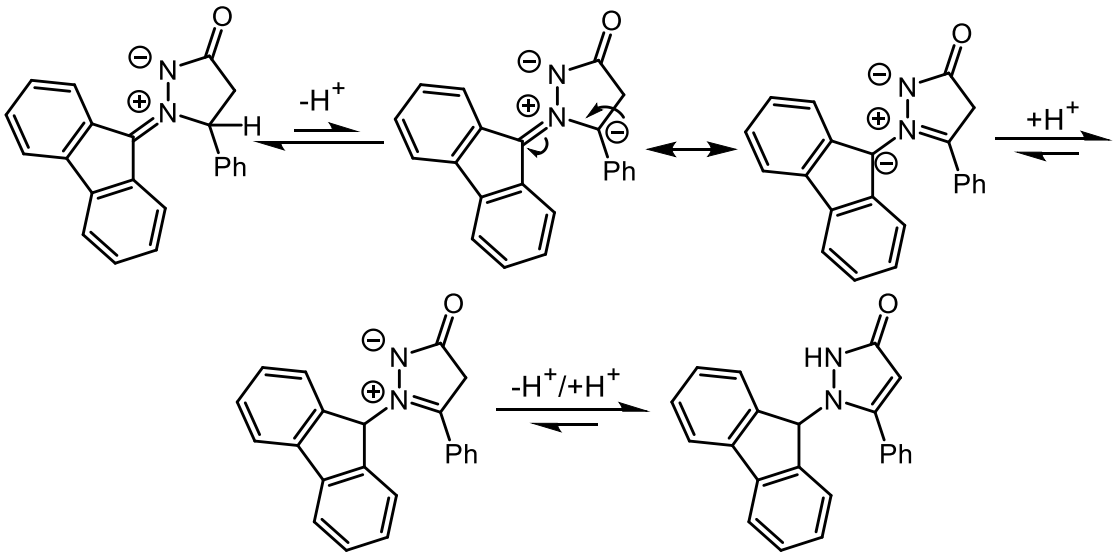
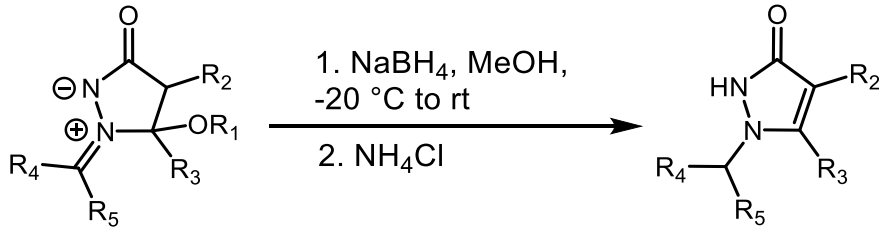


Figure 2.3 Proposed mechanism for the pyrazolone formation

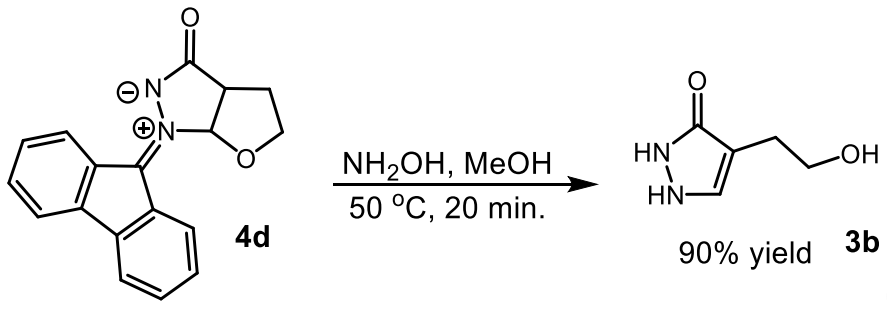
Coincidentally in the following months, Kaitlyn Lavergne also discovered reductive conditions to form pyrazolones from azomethine imines. She then built a

scope of fluorenyl-*N*-protected pyrazolones through subjecting azomethine imines synthesized from enol ethers to sodium borohydride. The reaction is shown in Equation 2.4.



(2.4)

While this work was ongoing, it was discovered that when azomethine imines synthesized from enol ethers were subjected to hydroxylamine deprotecting conditions, unprotected pyrazolones, such as **3b,** could be formed in high yields (Equation 2.5). This simple reaction introduces new opportunities towards possible pyrazolone targets. Many different substituents can be added to unprotected pyrazolones to form new products.



(2.5)

2.5 Summary and Future Directions

As it was presented, the primary goal towards a general method for the derivatization of azomethine imines derived from various carbonyl substituents was successfully developed, and relied on the use of hydroxylamine. This methodology allows the deprotection of azomethine imines which can be protected with aldehydes to result in products that are difficult to synthesize through the Beauchemin alkene intramolecular aminocarbonylation reactivity with imino-isocyanates. The resulting products from the deprotection were then derivatized into a variety of high yielding *N*-Boc-β-amino amides. Finally, an interesting reactivity converting azomethine imines into fluorenyl protected or unprotected pyrazolones was discovered along this project. The following chapter is an extension of this derivatization project towards milder conditions for N-N bond cleavage.

3

New Methods towards N-N Bond Cleavage

3.1 Introduction

For many years now Raney-Nickel has been one of the most reliable methods towards the cleavage of N-N bonds. For our group, it has been uniquely effective in cleaving our protected and unprotected cyclic hydrazides into β-amino amides.[50] Nonetheless, it comes with a few drawbacks such as the necessity for many equivalents and heating in alcoholic solvents over a long period of time to obtain good yields. A milder and quicker method to cleave N-N bonds would be of great value. In the Beauchemin group, we have been interested to find different and milder ways to cleave N-N bonds from derivatized azomethine imine products. In this next section, experiments towards the cleavage of the N-N bond from the Boc protected cyclic hydrazides that were introduced in Chapter 2 will be presented. We will start with reviewing efforts towards synthesizing Boc or Fmoc protected cyclic hydrazides directly using new aminocarbonylation reagents. We will then proceed to a review of the literature for N-N bond cleaving methods, followed by experimental methodologies tested onto our compounds.

3.2 Exploration of the Aminocarbonylation Reactivity of 1,2-Hydrazines Dicarboxylates

Previously, Boc and Fmoc N^{β}-protected cyclic hydrazides could be attained by the deprotection of our azomethine imines followed by the protection with a Boc or Fmoc group (Path A, Figure 3.1), or by the condensation of hydrazine onto an α,β-unsaturated ester, which would then be protected with Boc or Fmoc (Path B, Figure 3.1).[47] A third potential way towards the synthesis of these compounds was through new, direct alkene aminocarbonylation reactivity, in one short step (Path C, Figure 3.1).

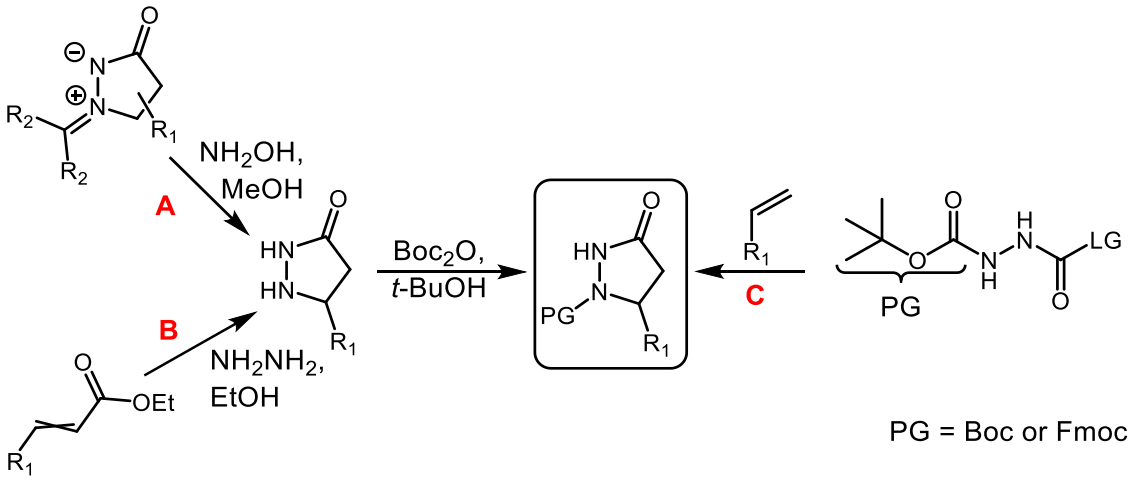
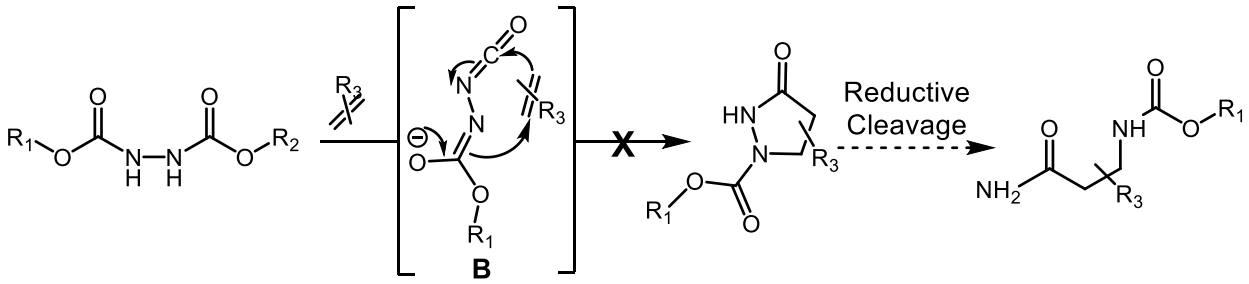


Figure 3.1 Various synthesis of N^{β}-protected cyclic hydrazides

The hypothesis behind this new reactivity was that 1,2-hydrazine dicarboxylates and alkenes would react through intermolecular aminocarbonylation to form cyclic hydrazides. These hydrazines were synthesized through an adaptation of known

procedures and then subjected to aminocarbonylation conditions.[61] In the targeted reaction, the enolate imino-isocyanate (**B**) would undergo aminocarbonylation with an alkene as shown in Scheme 3.1. This was based on the hypothesis that under aminocarbonylation conditions, the hydrazine could form an imino-isocyanate which contained an enolate (**B**). This enolate was required since the reaction would be dependent on the nucleophilic attack from its imine towards the alkene (Scheme 3.1).

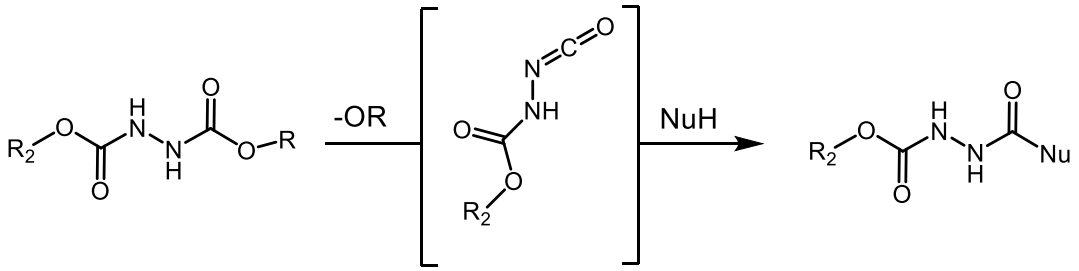
Scheme 3.1 Aminocarbonylation of carbamate isocyanate and alkenes

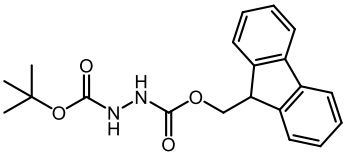
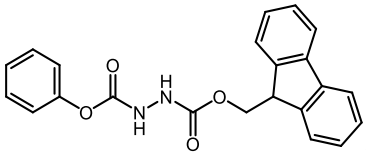
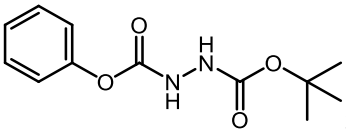


The first experiments carried on these 1,2-hydrazine dicarboxylates was substitution chemistry, which was used to detect the formation of imino-isocyanates. This reactivity was taken from a Beauchemin group project by Keira Garland.[52] Based on this reactivity, if the nucleophile was to be exchanged with a leaving group, this would show evidence of imino-isocyanate formation. This reaction along with the experiments are presented in Table 3.1.

[61] a) Dufau, L.; Ressurreiçaao, A. S. M.; Fanelli, R.; Kihal, N.; Vidu, A.; Milcent, T.; Soulier, J.-L.; Rodrigo, J.; Desvergne, A.; Leblanc, K.; Bernadat, G.; Crousse, B.; Reboud-Ravaux, M.; Ongeri, S. *J. Med. Chem.* **2012**, *55*, 6762. b) Weber, D.; Kessler, H.; Berger, C.; Antel, J.; Heinrich, T. (2003) Non-peptidic BRS-3 agonists. German Patent WO2003104196 A1. Retrieved from Patentscope.

Table 3.1 Isocyanate formation studies from substitution chemistry



Entry	Starting Material	Conditions	Product
1		Hexylamine, 120 °C, 10 min[1]	Fmoc deprotection
2	 **3c**	Benzyl alcohol, 150 °C, 25 min[1]	SM
3		Benzyl alcohol, 80 °C, 25 min[1]	SM
4	 **3d**	Benzyl alcohol, 150 °C, 25 min[1]	SM
5		Hexylamine, rt, 48 h[2]	SM
6	 **3e**	Hexylamine, 100 °C, 45 min[1]	Substitution product

[1] 0.1 M $PhCF_3$, microwave reaction. [2] 0.1 M $PhCF_3$, oil bath or room temperature reaction.

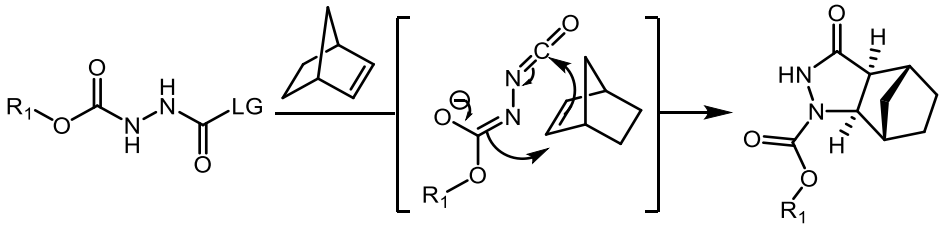
Although hexylamine was previously shown to be a great nucleophile for substitution chemistry by Keira Garland, when it was added to hydrazide **3c**, the Fmoc group was deprotected due to its basic properties (entry 1).[51] Following that result, a non-basic nucleophile had to be used. Substitution chemistry was then tested on this same hydrazine with benzyl alcohol. We observed that at 150 °C, only starting material

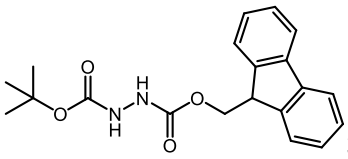
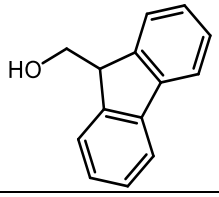
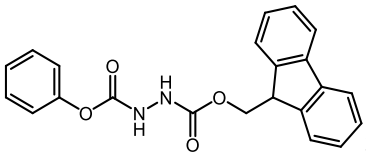
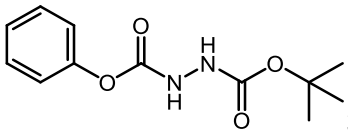
was recovered (entry 2). As *tert*-butanol was expected not to be removed from the molecule below 150 °C based on previous results, 9-fluorenemethanol was intended to be the leaving group. Since this group could also sustain high temperatures with nucleophile benzyl alcohol, hydrazine **3d** was synthesized with phenol as a leaving group. As Ms. Garland had previously demonstrated, phenol was easily removed to form imino-isocyanates.[51] We then proceeded to the reaction of hydrazine **3d** with benzyl alcohol, as it still required a non-basic nucleophile (entry 3 and 4). Only starting material was recovered at both 80 °C and 150 °C.

This prompted us to synthesize hydrazine **3e**, which included both a more robust *tert*-butanol leaving group and the phenol leaving group which was shown to form isocyanate with lower energy of activation.[51] Since this hydrazine had groups that could sustain basic conditions, it was tested for substitution chemistry with hexylamine, which had previously shown higher reactivity than benzyl alcohol in substitution chemistry.[51] Although the reaction of hydrazine **3e** with hexylamine produced only starting material at room temperature (entry 5), the exchange product was found when the temperature was increased to 100 °C (entry 6). This was the confirmation that this starting material was able to form an imino-isocyanate.

Once this was demonstrated aminocarbonylation reactions were tested on these starting materials (Table 3.2). Norbornene was chosen as the alkene of choice towards aminocarbonylation tests due to its high reactivity with imino-isocyanates as observed in our intermolecular aminocarbonylation.[50] The three hydrazine starting materials were tested as precursors of *N*-substituted isocyanates.

Table 3.2 Aminocarbonylation reactivity from 1,2-hydrazine dicarboxylates



Entry	Starting Material	Conditions	Product
1	 **3c**	Norbornene, 150 °C, 6 h[1]	SM
2		Norbornene, 200 °C, 2.5 h[1]	
3	 **3d**	Norbornene, 150 °C, 3 h[1]	SM
4		Norbornene, DABCO, 120 °C, 3 h[1]	Inconclusive
5	 **3e**	Norbornene, DBU, 100 °C, 16 h[2]	Inconclusive
6		Norbornene, Et_3N, 100 °C, 2 h[1]	Phenol + SM
7		TMS-Cl, Et_3N, 35 °C, 3 h[3]	SM
8		TMS-Cl, Et_3N, 100 °C, 3 h[2]	Phenol + decomposed SM

[1] 0.1M $PhCF_3$, microwave reaction. [2] 0.1M $PhCF_3$, oil bath. [3] 0.1M CH_2Cl_2, oil bath reaction.

Although hydrazine **3c** and **3d** did not show any imino-isocyanate formation during the substitution chemistry experiments, they were both tested in aminocarbonylation conditions with norbornene. When hydrazine **3c** was subjected to aminocarbonylation conditions at 150 °C for 6 hours no reactivity was observed (entry 1). If an isocyanate was to form from the Fmoc group of hydrazine **3c**, which we hypothesized to be the most labile between the two carbamates, it would release 9-fluorenmethanol by-product as a result. As the temperature was increased to 200 °C, we observed this by-product which suggested isocyanate formation (entry 2). We had probably not seen these results in the substitution experiments because the highest temperature tested was 150 °C. When aminocarbonylation with norbornene was conducted on hydrazine **3d**, only recovered starting material was observed (entry 3).

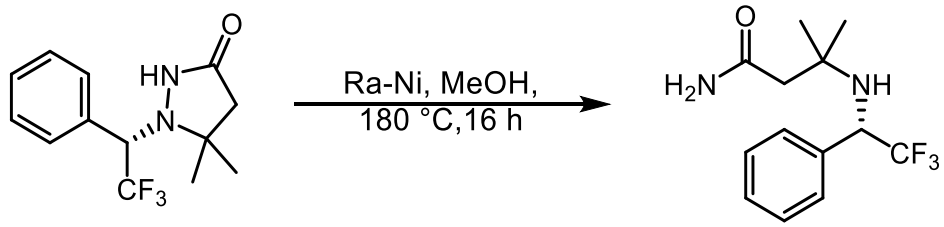
While this project was advancing, Kaitlyn Lavergne was working on base catalysis to render imino-isocyanate formation more efficient. This proved to be successful when isocyanate formation was the rate determining step of the aminocarbonylation chemistry. Once substitution chemistry had shown reactivity on hydrazine **3e**, base catalyzed aminocarbonylation with norbornene was tested. Although aminocarbonylation experiments with 1,4-diazabicyclo-octane (DABCO) and 1,8-Diazabicyclo-undec-7-ene (DBU) bases did not give the expected products or exchange chemistry products, triethylamine proved to help formation of imino-isocyanates through isolation of phenol (entry 4-6). It was hypothesized that the lack of aminocarbonylation product was due to the deficiency of enolate formation of the starting material. Consequently, we tried adding trimethylsilane to the starting material

to trap the enolate which would then be tested under aminocarbonylation conditions (entry 12 and 13).

Because of the lack of reactivity, this strategy was left aside and focus was set onto different ways to form the amine protected cyclic hydrazide starting material for reductive N-N bond cleavage.

3.3 Strategies towards New N-N Bond Cleavage Reactivity

In 1954 Ainsworth introduced Raney-Nickel as an excellent catalyst towards hydrazide N-N bond cleavage, forming ammonia and an amide.[62] Following that discovery, many have exploited Raney-Nickel as an N-N bond reducing agent. In 2009, Shibata published conditions towards reducing alkyl substituted N-N bonds from a cyclic hydrazide under Raney-Nickel conditions at high temperature without hydrogen gas (Equation 3.1).[63] This system is closely related to our cyclic hydrazides.



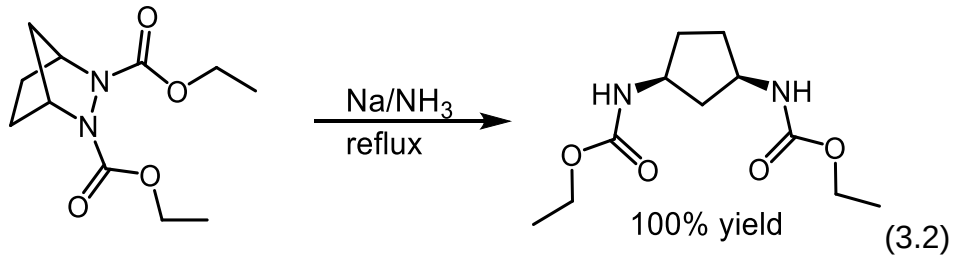
(3.1)

[62] Ainsworth, C. *J. Am. Chem. Soc*. **1954**, *76*, 5774.
[63] Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6324.

The limitations of Raney-Nickel are the harsh conditions, need of pressure or hydrogen gas and its spontaneous combustion under dry environments. Nonetheless, due to known reactivity and need of acyclic β-aminocarbonyl motifs, methods with Raney-Nickel to cleave cyclic hydrazides from our azomethine imines have been optimized in the Beauchemin Group. In the first generation derivatization, the fluorenone-derived azomethine imine was set under conditions of reductive $NaBH_4$ and Raney-Nickel in methanol at 60 °C.[50] In the second generation derivatization, the azomethine imine was reacted with hydroxylamine to form the cyclic hydrazide and an oxime by-product, followed by a reduction with Raney-Nickel in ethanol, under hydrogen gas at 45 °C. These last reducing conditions were optimized by Dr. DasNeves.

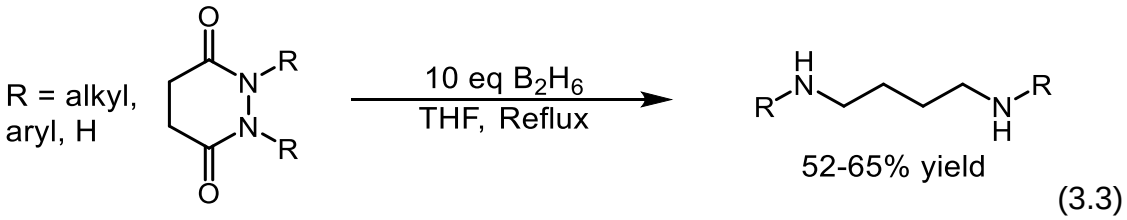
Raney-Nickel is not the only reducing agent that has been published to cleave N-N bonds. Other known method towards reducing N-N bonds of *N*,*N′*-alkyl/aryl, *N,N′*-monoacyl, diacyl, and triacyl derivatives include Na/NH_3, PtO_2, Li/NH_3, SmI_2, B_2H_6 and $TiCl_3$.[64] In Equation 3.2, a reduction of *N*,*N′*-dialkyl-diacyl N-N bond with excellent yield is shown using sodium in liquid ammonia in refluxing conditions.[65] The limitation of these conditions are the side reactions with many aromatic substituents, such as the Birch reaction which converts aromatic rings into 1,4-cyclohexadienes, and the danger behind sodium's explosive nature when in contact with water.

[64] Magnus, P.; Garizi, N.; Seibert, K. A.; Ornholt, A. *Org. Lett*. **2009**, *11*, 5646.
[65] Mellor, J. M.; Smith, N. M. *J. Chem. Soc. Perkin. Trans*. *1* **1984**, 2927.



(3.2)

As we can observe in Equation 3.3, treatment of cyclic *N*,*N'*-diacyl compounds with excess diborane results in the reduction of both the carbonyl groups and the N-N bond.[66]

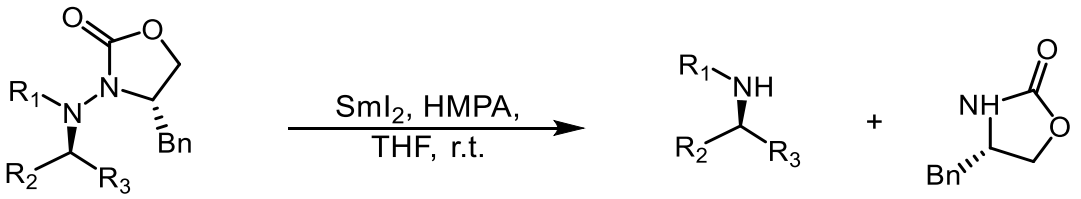


(3.3)

Another well-known reagent to cleave N-N bonds is samarium diiodide. Friestad established optimized conditions towards this reductive cleavage and demonstrated the need of benzoyl *N*-protection (Equation 3.4).[67] He demonstrated that samarium (II) iodide does not reduce the N-N bond of hydrazines that contains two carbamoyl groups (C or D) but it is very effective at the cleavage of N-N bonds with a carbamoyl and acyl group protecting the nitrogens. Additionally, samarium (II) iodide is known to be

[66] Feuer, H.; Brown, J. F. *J. Org. Chem.* **1970**, *35*, 1468.
[67] Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

compatible with many substituents and reactions can be done at ambient temperature and pressure.



A: R_1 = H, R_2, R_3 = alkyl, aryl, alkene
B: R_1 = PhCO, R_2, R_3 = alkyl, aryl, alkene
C: R_1 = CBz, R_2, R_3 = alkyl, aryl, alkene
D: R_1 = MeOCO, R_2, R_3 = alkyl, aryl, alkene

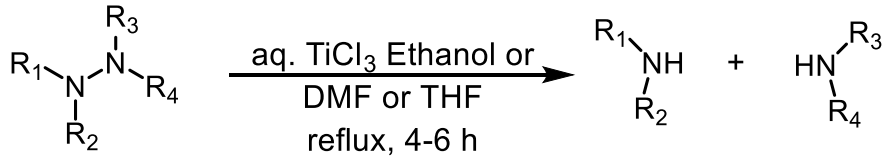
A: No reaction
B: 96% yield
C: No reaction
D: No reaction

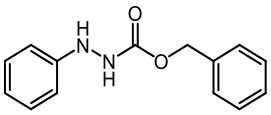
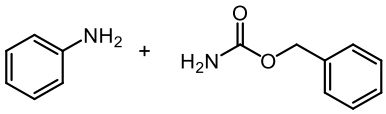
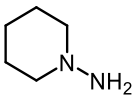
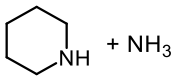
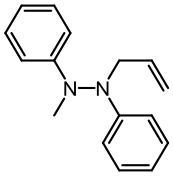
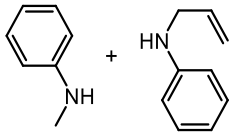
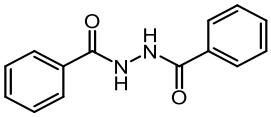
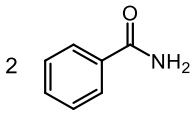
(3.4)

Titanium (III) can also be used for N-N bond cleavage. In 2011, Luo and coworkers published a study on N-N bond cleavage of diverse substituted hydrazines and hydrazides using $TiCl_3$ solution in a range of pH from acidic to basic.[68] In Table 3.3, a selection of examples that have similarities to our compounds are presented. Using this methodology, they were able to cleave a wide variety of hydrazides.

[68] Zhang, Y.; Tang, Q.; Luo, M. *Org. Biomol. Chem*. **2011**, *9*, 4977.

Table 3.3 Reductive N-N bond cleavage with $TiCl_3$ solution at different pH[68]

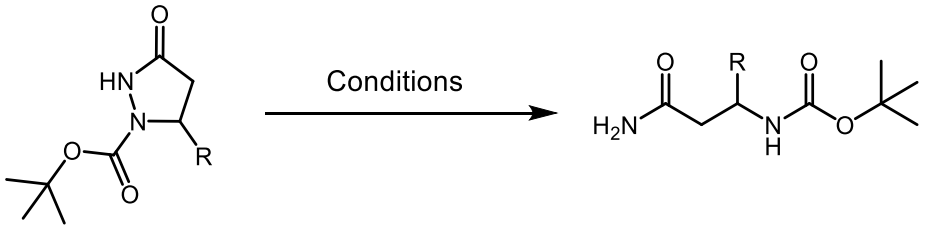


Entry	SM	Product	Yield (3% HCl)	Yield (pH 7)	Yield (pH 10)
1			74%	76%	75%
2			74%	73%	75%
3			79%	79%	81%
4			75%	80%	77%

In section 2.3.2., fluorenone deprotection of azomethine imines followed by addition of *tert*-butyloxycarbonyl protecting group on cyclic hydrazides, as well as

investigation into N-N bond cleavage of these cyclic *N*-Boc protected hydrazides were discussed. The Boc group was chosen as the nitrogen protecting group since it would reduce the steps towards Boc protected β-amino amides. Consequently, a few experiments with different reaction times were tested. Unfortunately, Raney-Nickel did not show any reduction of the N-N bond and starting material was recovered (Table 3.4, entry 1,).

Table 3.4 Conditions tested to reduce N-N bond of cyclic hydrazide



Entry	Conditions	Product
1	Raney-Nickel, MeOH, rt - reflux, H_2, 4-24 h	SM
2	SmI_2 in THF, MeOH, rt, 5 min - 48 h	SM
3	$TiCl_3$ in THF, Acidic, reflux, 4 - 6 h	Removal of Boc
4	$TiCl_3$ in THF, pH<10, reflux, 4 - 6 h	SM + Boc removal
5	$TiCl_3$ in THF, pH = 7, reflux, 4 - 6 h	SM + Boc removal

As discussed earlier, samarium (II) iodide is a good N-N reducing agent and has shown great potential to reduce hydrazines. It was hypothesized by Friestad that

benzoyl groups were essential to render this cleavage possible.[67] Regardless, similar reaction conditions to Friestad's conditions (Equation 3.4) were tested onto our cyclic Boc protected hydrazide. These reactions were done and monitored from 5 minutes to 48 hours (entry 2). Due to continuous starting material isolation, conclusions made by Friestad about the importance of the radical stabilization by resonance from the benzoyl group for the samarium iodide to perform its reducing reactivity was confirmed.

Finally, as titanium (III) trichloride demonstrated such interesting reactivity towards N-N bond reduction, these conditions were tested onto our Boc protected cyclic hydrazides. Although in acidic environment only deprotected cyclic hydrazide was recovered, a mixture of starting material and this same deprotected product was found under neutral and basic conditions with no recovery of desired product (entry 3-5).

3.4 Summary and Future Directions

While a few methods to reduce the N-N bond of N^{β}-Boc protected cyclic hydrazides were tested, mostly Boc deprotection was observed. In all of these methods, the newest titanium (III) trichloride is the most interesting and promising due to the variety of hydrazines that were reduced in high yields in Luo's publications.[68] Testing these conditions on the unprotected cyclic hydrazides, along with testing all previously presented N-N bond cleaving methods on a N^{β}-Cbz protected cyclic hydrazide would be of interest for future experiments. The resulting *N*-Cbz-β-amino amide would be stable and easily deprotected to yield the free amide.

As we have seen in this chapter, there are still challenges in finding milder conditions to cleave the N-N bond of cyclic hydrazides and azomethine imines. In this next Chapter, a summary of the new derivatization of azomethine imines will be presented along with future directions of this project.

4

Conclusions

4.1 Summary and Future Work

As it was presented in Chapter 1, azomethine imines resulting from the Beauchemin group's intermolecular aminocarbonylation reaction between alkenes and hydrazones possess the increasingly popular β-aminocarbonyl motif. Due to the lack of general procedures to remove various substitution groups on the N^{β} position of these azomethine imines, this project's focus was to introduce their efficient derivatization into β-aminocarbonyls, such as β-amino amides. A summary of the recent derivatization of azomethine imines is presented in Figure 4.1.

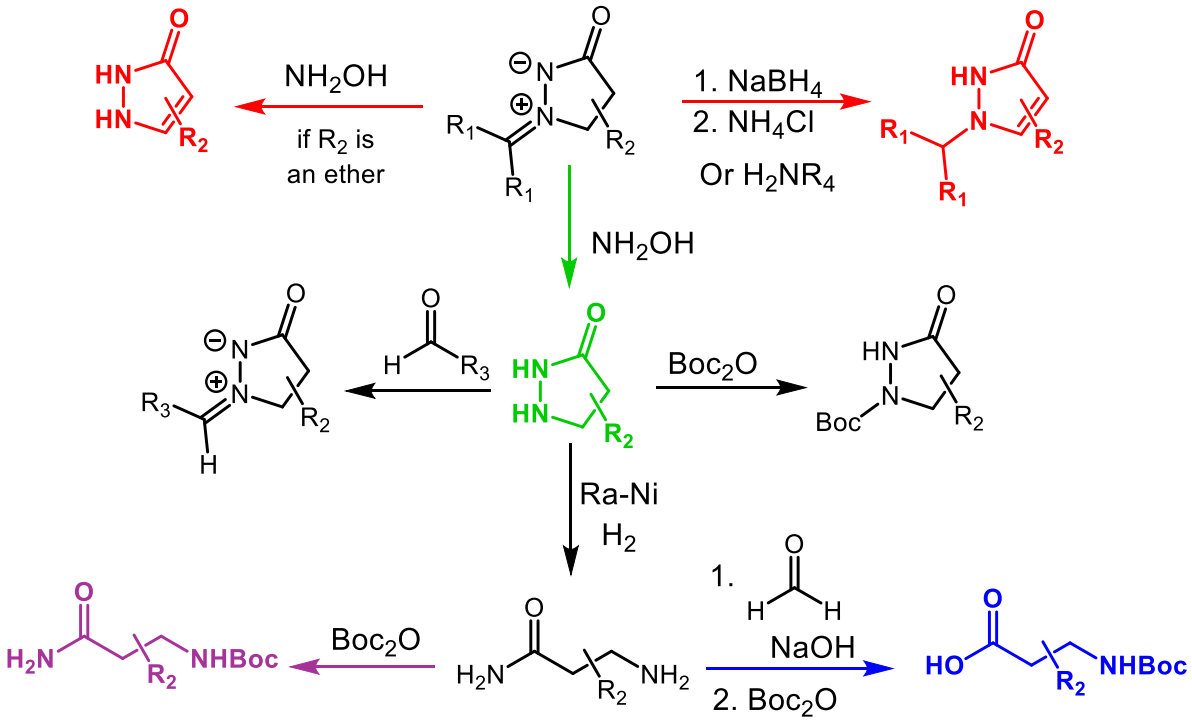


Figure 4.1 Second generation derivatization of azomethine Imines

The main issue in the first generation derivatization likely was the shielding of the N-N bond with sterically hindered groups on the N^{β}, which prohibited various azomethine imines from reductive cleavage of that bond. Thus we attempted to find a general procedure towards the deprotection of these groups. In Chapter 2, we presented a new procedure towards their nucleophilic deprotection, which affords free cyclic hydrazides through Schiff base formation from aqueous hydroxylamine (green on Figure 4.1). This new method proceeds under mild conditions which allow various labile substituents on starting materials. This method also exhibits high reactivity towards the deprotection of various ketone-derived azomethine imines, including sterically hindered and unsymmetrical ones.

Following that discovery, a simple three-step, chromatography-free derivatization of these azomethine imines towards *N*-Boc-β-amino amides was developed. The three simple steps are the nucleophilic deprotection of the N^{β}-substituent followed by a Raney-Nickel reduction of the N-N bond and Boc protection of the free amine (purple in Figure 4.1). During this project, we also discovered new methodologies towards the conversion of azomethine imines into substituted pyrazolones with basic amines and un-substituted pyrazolones with hydroxylamine (red in Figure 4.1). Future directions towards derivatization of azomethine imines would be to find a milder, metal free reaction towards cleaving the N-N bond and their derivatization into 1,3-diamines amongst other interesting motifs.

4.2 Claims to Original Research

1. Development of azomethine imine deprotection of various N^{β}-substutuents with hydroxylamine towards cyclic hydrazides.
2. Development of a three-step, chromatography free, derivatization of azomethine imines into *N*-Boc-β-amino amides.

4.3 Publications and Presentations from this Work

4.3.1 Manuscript in Preparation

1. Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, A. M. *Manuscript in preparation*.

4.3.2 Poster Presentations

1. Betit, L.; Clavette, C.; Bongers, A.; Chitale, S.; Beauchemin, A. M. Ottawa Carleton Chemistry Institute Day (OCCI Day) – Ottawa, May 23, 2014. Poster presentation.
2. Betit, L.; Clavette, C.; Bongers, A.; Tanveer, K.; Beauchemin, A. M. Quebec-Ontario Mini-Symposium on Bio-organic and Organic Chemistry – Sherbrook, November 8-10, 2013. Poster presentation.

5

Experimental

5.1 General Information

Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 µm) or by recrystallization using a variety of solvents, 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 or ninhydrin solution, and heating.

^{1}H NMR and ^{13}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 ($CDCl_3$ at 7.27 ppm, CD_3OD at 3.31 ppm, D_2O at 4.79 or DMSO-d_6 at 2.50 ppm for ^{1}H NMR and $CDCl_3$ at 77.16 ppm, CD_3OD at 49.00 ppm or DMSO-d_6 at 39.52 for ^{13}C NMR). ^{1}H NMR data was reported as: multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz.

Infrared (IR) spectra were obtained from compounds in solid form and were recorded on Cary 630 Fourier transform infrared spectrometer (FTIR) using Attenuated Total Reflection.

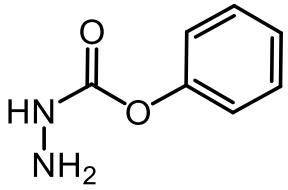
High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 ev at the Ottawa-Carleton Mass Spectrometry Centre.

Low resolution mass spectrometry (LRMS) was performed on a Micromass Quatro-LC Electrospray spectrometer with a pump rate of 20 µL/min using electrospray ionization (ESI).

Microwave reactions were performed using a Biotage Initiator Eight microwave reactor and Biotage microwave vials.

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

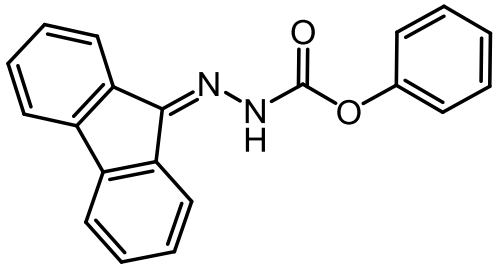
5.2 General Procedure towards Hydrazones (Chapter 2) Starting Materials



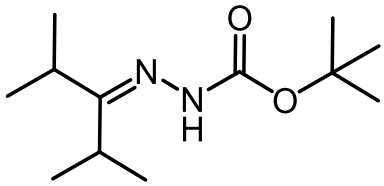
Phenyl carbazate (6a). To 1000 mL round bottom flask filled with 150 mL of dichloromethane and 28 mL (3 equiv.) of hydrazine monohydrate, was added a dropping funnel with 50 mL of dichloromethane and 23 mL (1 equiv.) of phenyl chloroformate. The round bottom flask was cooled to -7 °C with an ice and salt bath. The phenyl chloroformate mixture was added to the reaction one drop per second with vigorous stirring. Once fully added, the reaction was stirred at room temperature for 1-2 hours. Methanol was then added to the reaction until the hydrazine hydrochlorate salt crashed out, which was filtered. Purification by flash chromatography (1/1 ethyl acetate and hexanes, followed by 3/1 ethyl acetate and hexanes) afforded the desired product (22.0 g, 79% yield) as a white solid. R*f* 0.31 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, J = 6.0 Hz, 2 H), 7.23 (t, J = 9.0 Hz, 1 H), 7.14 (d, J = 9.0 Hz, 2 H), 6.63-6.44 (br, 1 H), 4.02-3.79 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 150.7, 129.4, 125.6, 121.4. IR (film): 3540, 3461, 3306, 3015, 1764, 1707, 1655, 1593, 1519, 1489, 1370, 1280, 1195, 1161, 1069, 1045, 1005, 940, 911, 834, 784, 714, 687 cm-1; HRMS (ESI): Exact mass calcd for $C_7H_8N_2O_2Na$ $[M+Na]^+$: 175.048. Found: 175.0862.

General hydrazone preparation: Procedure taken from Leighton and coworkers.[69] In a dried round bottom flask charged with a stirrer were added the corresponding carbazate, methanol, the corresponding carbonyl, and acetic acid. This reaction was refluxed, cooled to room temperature, and concentrated under reduced pressure. The crude was purified by filtration or recrystallization to yield the corresponding hydrazone.

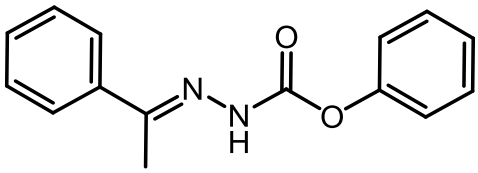
[69] Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc*. **2004**, *126*, 5686



Phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (6b). Synthesized according to the general hydrazone procedure, with minor modifications.[50,69] In an oven dried 100 mL round bottom flask was added phenyl carbazate (2.43 g, 16.0 mmol, 1 equiv.), methanol (35 mL, 0.5 M), followed by fluoren-9-one (2.90 g, 16.0 mmol, 1 equiv.). A 0.20 mL catalytic amount of acetic acid was added to the mixture, which was purged with argon and set to reflux for 6 hours. The reaction then formed a yellow precipitate and was stirred at room temperature overnight. The reaction mixture was filtered and washed with dichloromethane to keep the yellow precipitate. The product was dried under pressure and yielded a yellow powder (4.53 g, 90% yield). R*f* 0.31 (20% EtOAc in hexanes). Spectral data matches those reported in the literature.[50]



***tert*-Butyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (6c).** Synthesized according to the general hydrazone procedure, with minor modifications.[50,69] In an oven dried 250 mL round bottom flask was added *tert*-butyl carbazate (5.0 g, 38 mmol, 1 equiv.), methanol (125 mL, 0.3 M), followed by 2,4-dimethylpentan-3-one (10.7 mL, 75.8 mmol, 2 equiv.). A 0.33 mL catalytic amount of acetic acid was added to the mixture, which was purged with argon and set to reflux for 16 hours. The target compound was directly recrystallized from hexanes and obtained as a white solid (7.2 g, 85% yield). R*f* 0.65 (20% EtOAc in hexanes); Spectral data matches those reported in the literature.[50]

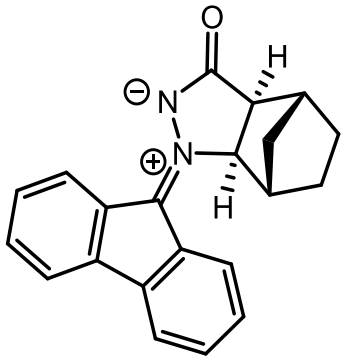


(*E and Z*)-Phenyl 2-(1-phenylethylidene)hydrazinecarboxylate (6d). Synthesized according to the general hydrazone procedure, with minor modifications.[50,69] In an oven dried 100 mL round bottom flask was added phenyl carbazate (1.0 g, 6.6 mmol, 1 equiv.), methanol (20 mL, 0.33 M), followed by acetophenone (0.77 mL, 6.6 mmol, 1 equiv.). A catalytic amount of acetic acid (6 drops) was added to the mixture, which was purged with argon and set to reflux for 16 hours. The target compound was directly recrystallized from hexanes and obtained as a white solid (1.24 g, 74% yield). R*f* 0.30 (20% EtOAc in hexanes); Spectral data matches those reported in the literature.[50]

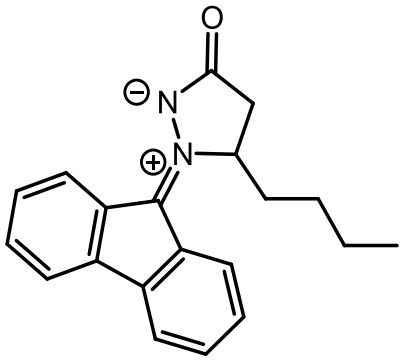
5.3 General Procedure for the Aminocarbonylation of Alkenes (Chapter 2)

General procedure A: An oven dried μW vial was purged with argon followed by addition of the stir bar, acyl hydrazone (1 equiv.) and 0.05 M α,α,α-trifluorotoluene. After the corresponding alkene (1-10 equiv.) was added to the vial, it was purged again with argon and sealed with a microwave cap. The reaction was heated in a microwave reactor for 1-8 hours at 80-150 ºC. Once the reaction was completed, it was cooled to room temperature and concentrated under reduced pressure. The product was isolated by recrystallization or silica gel flash chromatography by removing by-products and starting material with 1/4 ethyl acetate and dichloromethane followed by isolation with 1/9 methanol in dichloromethane. The product was obtained by concentration under reduced pressure.

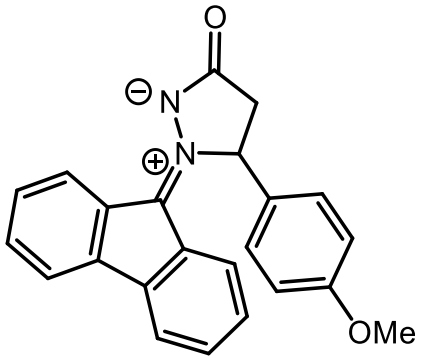
General procedure B: An oven dried round bottom flask was purged with argon followed by addition of the stir bar, acyl hydrazone (1 equiv.) and 0.05 M α,α,α-trifluorotoluene. After the corresponding alkene (1-10 equiv.) was added to the flask, it was purged again with argon followed by addition of a reflux condenser. The reaction was refluxed for 3-12 hours at 110 ºC. Once the reaction was completed, it was cooled to room temperature and concentrated under reduced pressure. The product was isolated by silica gel flash chromatography by removing by-products and starting material with 1/4 ethyl acetate and dichloromethane followed by isolation with 1/9 methanol in dichloromethane. The product was obtained by concentration under reduced pressure.



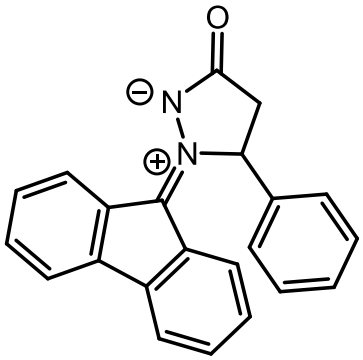
(±)-*exo*-2-[*N*-(9*H*-Fluoren-9-ylidene)]-4-oxo-2,3-diazatricyclo[4,3,16,9,0]decane-2-ium-3-ide (5a). Synthesized according to general procedure **B** with **6b** (2.00 g, 6.37 mmol, 1 equiv.) and norbornene (1.20 g, 12.7 mmol, 2 equiv.) in α,α,α-trifluorotoluene (127 mL, 0.05 M). The reaction was refluxed at 110 ºC for 1 hour to yield a yellow solid (1.91 g, 95% yield). R*f* 0.32 (5% MeOH in CH_2Cl_2); Spectral data matches those reported in the literature.[50]



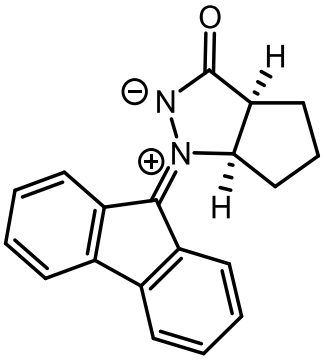
3-Butyl-2-(9H-fluoren-9-ylidene)-5-oxopyrazolidin-2-ium-1-ide (5b). Synthesized according to general procedure **B** with **6b** (2.0 g, 6.3 mmol, 1 equiv.) and 1-hexene (7.9 mL, 63 mmol, 10 equiv.) in α,α,α-trifluorotoluene (127 mL, 0.05 M). The reaction was heated at 110 °C for 5 hours in an oil bath. The compound was obtained as a yellow solid (1.35 g, 70% yield). R*f* 0.20 (EtOAc); Spectral data matches those reported in the literature.[50]



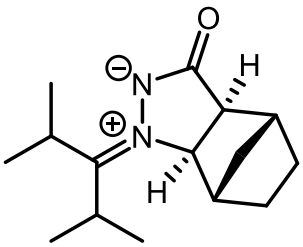
2-(9H-Fluoren-9-ylidene)-3-(4-methoxyphenyl)-5-oxopyrazolidin-2-ium-1-ide (5c). Synthesized according to general procedure **B** with **6b** (4.00 g, 12.7 mmol, 1 equiv.) and 4-methoxystyrene (8.46 mL, 63.7 mmol, 5 equiv.) in α,α,α-trifluorotoluene (250 mL, 0.05 M). The reaction was heated at 110 ºC for 4 hours. The product was obtained as yellow solid (3.3 g, 73% yield). R*f* 0.20 (7% MeOH in CH_2Cl_2); Spectral data matches those reported in the literature.[50]



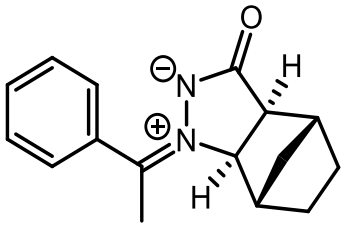
2-(9H-Fluoren-9-ylidene)-5-oxo-3-phenylpyrazolidin-2-ium-1-ide (5d). Synthesized according to general procedure **B** using **6b** (4.00 g, 12.7 mmol, 1 equiv.) and styrene (15.0 mL, 127 mmol, 10 equiv.) in α,α,α-trifluorotoluene (250 mL, 0.05 M). The reaction was heated at 110 ºC for 7 hours. The product was obtained as yellow solid (2.40 g, 58% yield). R*f* 0.25 (7% MeOH in CH_2Cl_2); Spectral data matches those reported in the literature.[50]



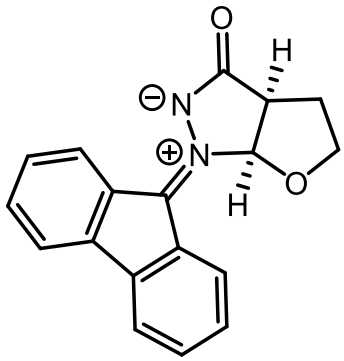
(±)-*exo*-2-[*N*-(9*H*-Fluoren-9-ylidene)]-4-oxo-2,3-diazacyclopentan-2-ium-3-ide (5e). Synthesized according to general procedure **B** using **6b** (2.00 g, 6.37 mmol, 1 equiv.) and cyclopentene (2.81 mL, 31.8 mmol, 5 equiv.) in α,α,α-trifluorotoluene (127 mL, 0.05 M). The reaction was heated at 110 ºC for 6 hours. The product was obtained as yellow solid (1.55 g, 85% yield). R*f* 0.35 (5% MeOH in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.93 (2, *J* = 9 MHz, 1 H), 7.70-7.51 (m, 3 H), 7.46-7.21 (m, 4 H), 5.54-5.43 (br, 1H), 3.42 (t, J = 9 MHz, 1 H), 2.54-2.41 (m, 1 H), 2.35-2.16 (m, 2 H), 1.96-1.74 (m, 2 H), 1.67-1.45 (m, 1 H).^{13}C NMR (75 MHz, $CDCl_3$) *δ* 186.5, 141.6, 139.6, 131.7, 131.0, 130.8, 130.0, 128.0, 125.0, 120.9, 119.6, 73.1, 47.3, 36.1, 30.4, 23.1. Characterized by Amanda Bongers.



(±)-*exo*-2-(2,4-Dimethylpentan-3-ylidene)-4-oxo-2,3-diazatricyclo[4,3,16,9,0]decane -2-ium-3-ide (4a). Synthesized according to general procedure **A** with **6c** (0.225 g, 0.985 mmol, 1 equiv.) and norbornene (0.927 g, 9.85 mmol, 10 equiv.) in α,α,α-trifluorotoluene (19 mL, 0.05 M). The reaction was heated in the microwave reactor at 150 ºC for 3 hours. The title compound was recrystallized with ether and yielded a white solid (0.207 g, 85% yield). R*f* 0.26 (7% MeOH in CH_2Cl_2); Spectral data matches those reported in the literature.[50]

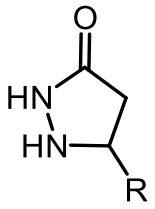


(±)-*exo*-(*E and Z*)-2-(1-Phenylethylidene)-4-oxo-2,3-diazatricyclo[4,3,16,9,0]decane-2-ium-3-ide (4b). Synthesized according to general procedure **B** with **6d** (0.254 g, 1.00 mmol, 1 equiv.), norbornene (0.941 g, 10.0 mmol, 10 equiv.). This mixture was heated in a microwave reactor for 2 hours. The compound was recrystallized with ether from the crude mixture to yield a beige solid (0.045 g, 18% yield) as a mixture of *E/Z* isomers (ratio = 2:1 *E/Z*). R*f* 0.23 (7% MeOH in CH_2Cl_2); Spectral data matches those reported in the literature.[50]

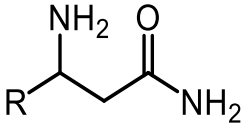


(±)-*cis*-1-[*N*'-(9*H*-Fluoren-9-ylidene)]-3-oxotetrahydro-1*H*-furo[2,3-*c*]pyrazolidine-1-ium-2-ide (4d). Synthesized according to general procedure **B**, with minor modifications. **6b** (2.19 g, 6.98 mmol, 1.55 equiv.) was mixted with α,α,α-trifluorotoluene (75 mL, 0.06 M), dihydrofuran (0.340mL, 4.50 mmol, 1 equiv.) and triethylamine (0.019 mL, 0.14 mmol, 0.03 equiv.) as a catalyst in a round bottom flask. The reaction was stirred at 70 °C for 2.5 hours and stirred at room temperature overnight to yield an orange powder (1.30 g, 99% yield). R*f* 0.25 (10% MeOH in EtOAc); Spectral data matches those reported in the literature.[50]

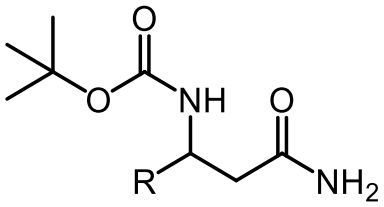
5.4 General procedures towards β-amino amides (Chapter 2)



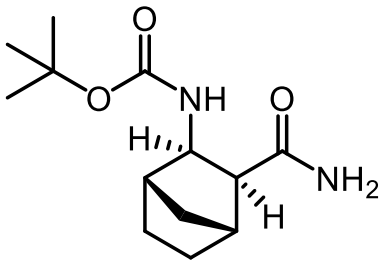
General procedure towards cleaving the azomethine imine substituent: To a 150 mL pressure flask were added fluoren-9-one protected azomethine imine (0.500 g, 1 equiv.), methanol (0.05 M), and aqueous hydroxylamine (50% weight in H_2O, 1-3 equiv.). The flask was sealed with a pressure cap and heated at 40-70 ºC over 3-16 hours. The reaction solution was cooled to room temperature and concentrated under reduced pressure. The resulting solid was triturated with 10-50% Methanol in water and added to a 25 mL round bottom flask. The liquid phase was concentrated under reduced pressure and subjected to the next step.



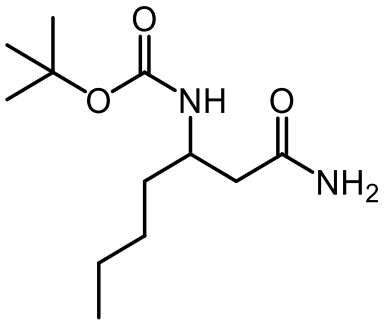
General procedure towards cleaving the N-N bond: The resulting crude from the previous deprotection was diluted in ethanol (0.1 M) and purged with hydrogen gas. A pipette full solution of Raney-Nickel was taken up and washed with ethanol three times before addition to the round bottom flask. The mixture was purged with hydrogen gas two more times and vigorously stirred at 45 °C overnight. Once completed, the reaction mixture was cooled to room temperature, filtered through celite and washed with methanol. The filtrate was concentrated under reduced pressure. The resulting mixture was then subject to Boc protection.



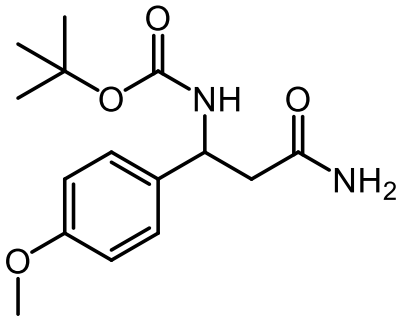
General procedure towards Boc protecting the β-amino amides: The crude was added to a round bottom flask, followed by *tert*-butanol (1 M), NaOH solution (0.2 equiv., 5 M), and *tert*-butyl anhydride (2 equiv.). The clear beige mixture was stirred overnight to reveal a white precipitate that was isolated by filtration and washed to yield the desired *N*-Boc-β-amino amide.



3-*tert*-Butyl-amino-3, 2-norbornenepropanamide (Table 2.5, 2a). Prepared according to previous general procedure using **5a** (0.50 g, 1.6 mmol, 1 equiv.), aqueous hydroxylamine (0.126 mL, 1.91 mmol, 1.20 equiv.) and methanol (32 mL, 0.05 M) in a pressure flask, heated for 16 hours at 60 °C. The concentrated mixture was triturated twice with 10 mL of 20% methanol in water. The concentrated crude was subjected to reductive cleavage with Raney-Nickel, in ethanol (3.18 mL, 0.5 M), under hydrogen atmosphere at 45 °C for 16 hours. Once this was filtered and the filtrate was concentrated, *tert*-butanol (1.6 mL, 1 M) was added, followed by *tert*-butyl anhydride (0.693 g, 3.18 mmol, 2 equivalents) and a catalytic solution of 5 M aqueous sodium hydroxide (0.064 mL, 0.318 mmol, 0.2 equiv.) and stirred at room temperature for 16 hours. The desired product was refluxed in 60% ethyl acetate in hexanes and filtered when hot to yield 65% of white powder. R*f* 0.35 (7% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) *δ* 3.85-3.70 (br d, J = 8.0 Hz, 1 H), 3.63-3.50 (br d, J = 8.0 Hz, 1 H), 2.33 (br, 1 H), 2.08 (br, 1 H), 1.99-1.87 (m, 1 H), 1.63-1.49 (m, 1 H), 1.41 (s, 9 H), 1.30-1.15 (m, 4 H).^{13}C NMR (100 MHz, CD_3OD) *δ* 176.5, 156.3, 78.9, 56.1, 51.9, 42.2, 40.5, 28.4, 27.3, 26.0. IR (film): 3411, 3300, 3215, 2967, 2930, 2867, 1676, 1654, 1624, 1550, 1360, 1308, 1281, 1251, 1063, 1022, 834, 703 cm-1. HRMS (ESI): Exact mass calcd for $C_{13}H_{22}N_2O_3Na$ $[M+Na]^+$: 277.152. Found: 277.1728.

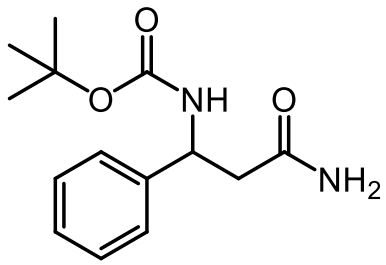


3-*tert*-Butyl-amino-3-butylpropanamide (Table 2.5, 2b). Prepared according to previous general procedure using **5b** (0.50 g, 1.64 mmol, 1 equiv.), aqueous hydroxylamine (0.13 mL, 1.97 mmol, 1.20 equiv.) and methanol (33 mL, 0.05 M) in a pressure flask, heated for 16 hours at 70 °C. The concentrated mixture was triturated with 10 mL of 30% methanol in water. The concentrated crude was subjected to reductive cleavage with Raney-Nickel, in ethanol (3.28 mL, 0.5 M), under hydrogen atmosphere at 45 °C for 16 hours. Once this was filtered and the filtrate was concentrated, *tert*-butanol (1.64 mL, 1 M) was added, followed by *tert*-butyl anhydride (0.715 g, 3.28 mmol, 2 equiv.) and a catalytic solution of 5 M aqueous sodium hydroxide (0.066 mL, 0.328 mmol, 0.2 equiv.) and stirred at room temperature for 16 hours. The desired product was filtered and yielded 86% of white powder. R*f* 0.33 (7% MeOH in CH_2Cl_2) ^{1}H NMR (300 MHz, CD_3OD) δ 3.90-3.80 (m, 1 H), 2.32 (m, 2 H), 1.59 – 1.25 (m, 6 H), 1.43 (s, 9 H), 0.91 (t, *J* = 6.0 Hz, 3 H).^{13}C NMR (75 MHz, CD_3OD) δ 175.2, 156.5, 78.5, 40.9, 34.2, 27.9, 27.4, 22.1, 13.0 IR (film): 3397, 3352, 3191, 2928, 2861, 1682, 1652, 1530, 1442, 1369, 1346, 1295, 1280, 1247, 1175, 1083, 1021, 861, 778, 698 cm-1. HRMS (ESI): Exact mass calcd for $C_{12}H_{24}N_2O_3Na$ $[M+Na]^+$: 267.168. Found: 267.1685.

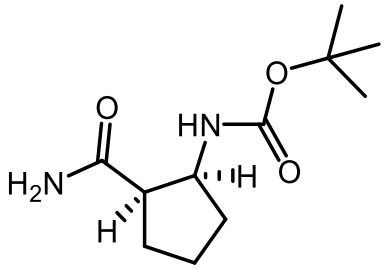


3-*tert*-Butyl-amino-4-methoxy-3-phenylpropanamide (Table 2.5, 2c). Prepared according to previous general procedure using **5c** (0.50 g, 1.41 mmol, 1 equiv.), aqueous hydroxylamine (0.131 mL, 1.97 mmol, 1.4 equiv.) and methanol (33 mL, 0.06

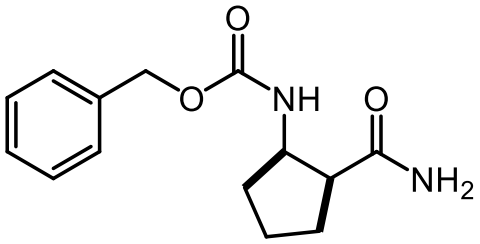
M) in a pressure flask, heated for 16hours at 60 °C. The concentrated mixture was triturated with 10 mL of 50% methanol in water. The concentrated crude was subjected to reductive cleavage with Raney-Nickel, in ethanol (3.28 mL, 0.43 M), under hydrogen atmosphere at 45 °C for 16 hours. Once this was filtered and the filtrate was concentrated, *tert*-butanol (1.41 mL, 1 M) was added, followed by *tert*-butyl anhydride (0.615 g, 2.82 mmol, 2 equiv.) and a catalytic solution of 5 M aqueous sodium hydroxide (0.056 mL, 0.282 mmol, 0.2 equiv.) and stirred at room temperature for 16 hours. The desired product was refluxed in 60% ethyl acetate in hexanes and filtered when hot to yield 63% of white powder. R*f* 0.23 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20 (d, J = 9.0 Hz, 2 H), 7.17-7.10 (br, 2 H), 6.84 (d, J = 9.0 Hz, 2 H), 6.69-6.54 (br, 1 H), 4.87-4.67 (m, 1 H), 3.73 (s, 3 H), 2.45 (t, J = 6.0 Hz, 2 H), 1.34 (s, 9 H).^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 158.6, 155.2, 136.2, 114.0, 78.2, 55.6, 51.5, 42.8, 28.7. IR (film): 3417, 3374, 3185, 2976, 2835, 1682, 1649, 1614, 1513, 1459, 1430, 1409, 1390, 1367, 1354, 1327, 1301, 1251, 1168, 1046, 1025, 914, 862, 840, 827, 777, 761, 731, 672 cm-1. HRMS (ESI): Exact mass calcd for $C_{15}H_{22}N_2O_4Na$ $[M+Na]^+$:: 317.147. Found: 317.1477.



3-*tert*-Butyl-amino-3-phenylpropanamide (Table 2.5, 2d). Prepared according to general procedure using **5d** (1.0 g, 3.1 mmol, 1 equiv.), aqueous hydroxylamine (0.246 mL, 3.72 mmol, 1.2 equiv.) and methanol (62 mL, 0.05 M) in a pressure flask, heated for 16 hours at 70 °C. The concentrated mixture was triturated with 10 mL of 30% methanol in water. The concentrated crude was subjected to reductive cleavage with Raney-Nickle, in ethanol (6.0 mL, 0.1 M), under hydrogen atmosphere at 45 °C for 16 hours. Once this was filtered and the filtrate was concentrated, *tert*-butanol (3 mL, 1 M) was added, followed by *tert*-butyl anhydride (1.29 g, 5.93 mmol, 2 equiv.) and a catalytic solution of 5 M aqueous sodium hydroxide (0.119 mL, 0.593 mmol, 0.2 equiv.) and stirred at room temperature for 16 hours. The desired product was filtered and yielded 74% of white powder. R*f* 0.20 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29-7.09 (m, 5 H), 3.96-3.80 (br, 1 H), 2.50-2.38 (m, 2 H), 1.31 (s, 9 H).^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 154.8, 142.5, 127.6, 125.6, 77.8, 51.1, 41.6, 27.1. IR (film): 3413, 3371, 3181, 2978, 1681, 1655, 1625, 1519, 1431, 1407, 1391, 1362, 1322, 1292, 1269, 1251, 1171, 1046, 1027, 909, 863, 837, 757, 705 cm-1 HRMS (ESI): Exact mass calcd for $C_{14}H_{20}N_2O_3Na$ $[M+Na]^+$: 287.314. Found: 287.1372.

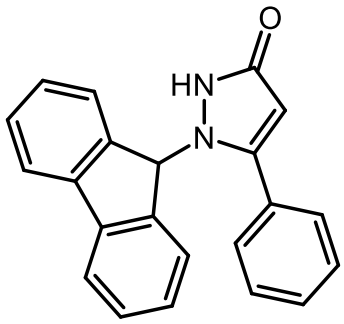


2-*tert*-Butyl-aminocyclopentane-carboxamide (Table 2.5, 2e). Prepared according to general procedure using **5e** (0.50 g, 1.73 mmol, 1 equiv.), aqueous hydroxylamine (0.137 mL, 2.08 mmol, 1.2 equiv.) and methanol (35 mL, 0.05 M) in a pressure flask, heated for 4 hours at 70 °C. The concentrated mixture was triturated with 10 mL of 20% methanol in water. The concentrated crude was subjected to reductive cleavage with Raney-Nickel, in ethanol (3.46 mL, 0.5 M), under hydrogen atmosphere at 45 °C for 16 hours. Once this was filtered and the filtrate was concentrated, *tert*-butanol (1.71 mL, 1 M) was added, followed by *tert*-butyl anhydride (0.745 g, 3.42 mmol, 2 equiv.) and a catalytic solution of 5 M aqueous sodium hydroxide (0.068 mL, 0.342 mmol, 0.2 equiv.) and stirred at room temperature for 16 hours. This was concentrated and re-subjected to protection conditions for 16 hours. The desired product was filtered and yielded 52% of white powder. R*f* 0.26 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) *δ* 4.16-4.05 (br, 1 H), 2.96-2.83 (br, 1 H), 2.02-1.52 (m, 6 H), 1.45 (s, 9 H). ^{13}C NMR (75 MHz, CD_3OD) *δ* 177.2, 156.2, 78.8, 54.1, 32.4, 27.7, 27.6, 22.2. IR (film): 3464, 1671, 1450, 1365, 1168, 1059, 991, 850, 836, 677 cm-1. HRMS (ESI): Exact mass calcd for $C_{11}H_{20}N_2O_3Na$ $[M+Na]^+$: 251.137. Found: 251.1372.

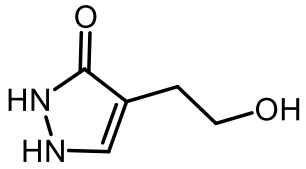


2-Cbz-Aminocyclopentane-1-carboxamide (2f). Prepared according to general procedure, with mild modifications. **5e** (0.500 g, 1.73 mmol, 1 equiv.), aqueous hydroxylamine (0.137 mL, 2.08 mmol, 1.2 equiv.) and methanol (35 mL, 0.05 M) were added to a pressure flask and heated for 4 hours at 70 °C. The concentrated mixture was triturated with 10 mL of 20% methanol in water. The concentrated crude was

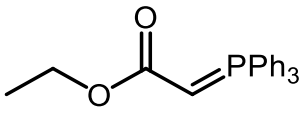
subjected to reductive cleavage with Raney-Nickel, in ethanol (3.46 mL, 0.5 M), under hydrogen atmosphere at 45 °C for 16 hours. The mixture was filtered through celite and added to a 25 mL round bottom flask equipped with a stir bar. An aqueous solution of NaOH (0.37 mL, 2 M) and tetrahydrofuran 0.74 mL) was added to the crude. The mixture was then cooled to 0 °C with an ice bath and benzylchloroformate (0.061 mL, 0.429 mmol, 1.1 equiv.) was slowly added. The reaction was stirred at 0 °C for 5 minutes and at room temperature for 1 hour. The mixture was extracted with ethyl acetate twice and washed with brine. The organic phase was concentrated under reduced pressure and the desired product was purified by recrystallization with ether to yield a white solid (0.085 g, 83% isolated yield). R*f* 0.17 (7% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) *δ* 7.43-7.22 (m, 5 H), 5.05 (s, 2 H), 4.19 (q, *J* = 6.0 Hz, 1 H), 2.92 (q, *J* = 6.0 Hz, 1 H), 2.04-1.51 (m, 6 H). ^{13}C NMR (75 MHz, CD_3OD) *δ* 177.3, 156.8, 136.8, 128.0, 127.5, 127.3, 66.1, 54.4, 32.1, 27.4, 22.8, 22.0. IR (film): 3331, 2954, 2865, 2578, 2478, 2409, 1668, 1634, 1541, 1468, 1443, 1349, 1283, 1252, 1188, 1057, 1023, 841, 774, 758, 721, 695 cm-1. HRMS (ESI): Exact mass calcd for $C_{14}H_{18}N_2O_3Na$ $[M+Na]^+$: 285.123. Found: 285.2116.



1-(9H-Fluoren-9-yl)-5-phenyl-1H-pyrazol-3(2H)-one (3a). To a 25 mL pressure flask was added **5d** (0.100 g, 0.309 mmol, 1 equiv.), methanol (6.00 mL, 0.05 M) and an amine (2 equiv.), which were stirred at 70 °C in an oil bath for 1 hour. The reaction was cooled to room temperature and filtered to yield a white solid (80-93% yield). R*f* 0.20 (10% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) *δ* 9.93 (s, 1 H), 7.81 (d, *J* = 6 Hz, 2 H), 7.73-7.65 (m, 2 H), 7.56-7.32 (m, 5 H), 7.31-7.20 (m, 4 H), 6.17 (s, 1 H), 5.73 (s, 1 H).^{13}C NMR (75 MHz, DMSO-d_6) *δ* 161.7, 147.3, 143.9, 140.5, 130.8, 129.5, 129.4, 129.3, 129.1, 128.0, 124.8, 120.8, 92.8, 62.7. IR (film): 3041, 2570, 2373, 1979, 1736, 1578, 1561, 1508, 1449, 1330, 1302, 1280, 1260, 1202, 1155, 1128, 1073, 1030, 1004, 995, 917, 876, 851, 778, 755, 741, 728, 698, 684 cm-1; LRMS (EI): Exact mass calcd for $C_{22}H_{16}N_2O$ [M]: 324.126. Found: 324.1.

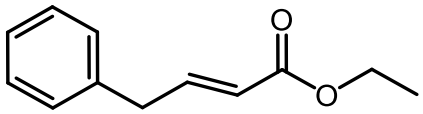


4-(2-Hydroxyethyl)-1H-pyrazol-3(2H)-one (3b). To a 25 mL pressure flask was added **4d** (0.200 g, 0.688 mmol, 1 equiv.), methanol (14.0 mL, 0.05 M) and an aqueous hydroxylamine solution (0.068 mL, 1.32 mmol, 1.5 equiv.), which were stirred at 50 °C in an oil bath. After 20 min, the reaction had turned from clear yellow to cloudy white. The reaction was cooled to room temperature, concentrated and triturated in 10 mL of 20% methanol in water. The filtrate was concentrated and yielded a pure white solid (0.079 g, 90% yield). R*f* 0.10 (10% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ 7.26 (s, 1 H), 3.69 (t, *J* = 6 Hz, 2 H), 2.58 (t, *J* = 6 Hz, 2 H). ^{13}C NMR (75 MHz, CD_3OD) δ 160.4, 130.1, 101.4, 61.8, 25.4. IR (film): 3400, 3099, 2928, 2859, 1597, 1515, 1471, 1351, 1306, 1250, 1195, 1083, 1041, 1014, 876, 841, 806, 744 cm-1; HRMS (ESI): Exact mass calcd for $C_5H_8N_2O_2$ [M]-: 127.1235. Found: 127.0508.

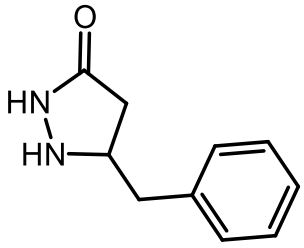


Ethyl-(triphenylphosphoranylidene)-acetate (7a). Procedure taken from Gainer and Grabiak with minor modifications.[70] With the use of an addition funnel, a solution of ethyl 2-bromoacetate in ethyl acetate (1.68 mL ethyl-2-bromoacetate in 10 mL ethyl acetate, 15.0 mmol, 1 equiv.) was slowly added to a solution of triphenylphosphine in ethyl acetate (4.06 g of PPh_3 in 10 mL of ethyl acetate, 15.5 mmol, 1 equiv.). Once fully added, the reaction was stirred overnight at room temperature. The white salt was filtered, washed with diethyl ether and dried under the high vacuum pump. The salt was then diluted in 50 mL of dichloromethane in a 250 mL round bottom flask. An equal volume of 1 M aqueous sodium hydroxide solution was added to the round bottom flask and stirred for 15 minutes at room temperature. The reaction was extracted three times with dichloromethane, concentrated under reduced pressure and dried under high vacuum to yield a white powder (4.7 g, 90% yield). R*f* 0.10 (10% EtOAc in hexane). Spectral data matches those reported in the literature.[70]

[70] Gainer, J. L.; Grabiak, R. C. (2004) *U.S. Patent No. US2004/14725*. Arlington, VA: U.S. Patent and Trademark Office.

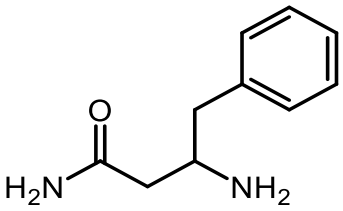


Ethyl-4-phenylbut-2-enoate (7b). Procedure taken from Tiekink and coworkers.[71] An oven dried 100 mL round bottom flask was purged with argon followed by the addition of freshly distilled phenylacetaldehyde (1.47 mL, 12.3 mmol, 1 equiv.), dry toluene (30 mL) and **7a** (4.7 g, 13 mmol, 1.1 equiv.). This reaction was purged with argon and refluxed overnight at 110 °C. The reaction was cooled to room temperature, triphenylphosphine oxide was precipitated with the addition of hexanes and filtered off. The filtrate was concentrated under reduced and the product was purified by silica gel column chromatography (4% ethyl acetate in hexanes) to yield a mixture of E and Z Ethyl-4-phenylbut-2-enoate as a colourless oil (2.00 g, 96% yield). R*f* 0.80 (20% hexane in ether). Spectral data matches those reported in the literature.[71]

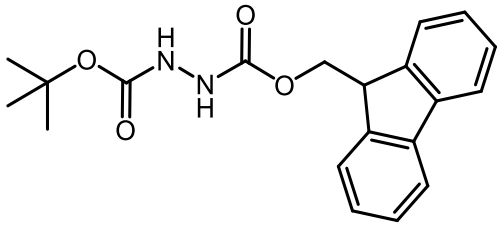


5-Benzylpyrazolidin-3-one (7c). Procedure taken from Witter and coworkers.[72] In a 50 mL round bottom flask was added **7b** (2.00 g, 10.5 mmol. 1 equiv.), ethanol (9.0 mL, 1.2 M) and hydrazine monohydrate (0.52 mL, 10.5 mmol, 1 equiv.). This mixture was refluxed at 80 °C for 20 hours. Once the reaction was cooled to room temperature, it was concentrate under reduced pressure and purified by silica gel column chromatography (1% ammonium hydroxide and 5% methanol in dichloromethane) to yield the desired product as a clear oil (1.4 g, 76% yield). R*f* 0.22 (7% MeOH in CH_2Cl_2). Spectral data matches those reported in the literature.[72]

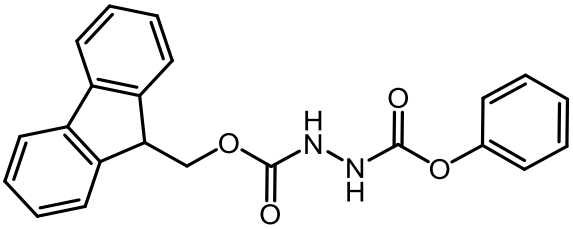
[71] Avery, T. D; Caiazza, D; Culbert, J. A; Taylor, D. K; Tiekink, E. R. T. *J. Org. Chem*. **2005**, *70*, 8344.
[72] Grimm, J. B; Wilson, K. J; Witter, D. J. *J. Org. Chem*. **2009**, *74*, 6390.



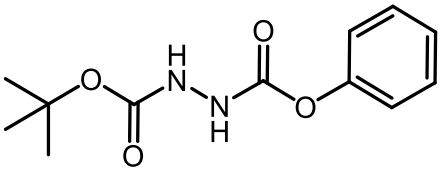
3-Amino-3-benzylpropanamide (7d). **7c** (1.4 g, 8.0 mmol) was diluted in ethanol (14.5 mL, 0.55 M) and purged with hydrogen gas. A pipette full of Raney-Nickel solution was taken up and washed with ethanol three times before addition to the round bottom flask. The mixture was purged with hydrogen gas two more times and vigorously stirred at 45 °C overnight. Once completed, the reaction mixture was cooled to room temperature, filtered through celite and washed with methanol. The filtrate was concentrated under reduced pressure and purified by silica column chromatography (50% isopropanol in toluene) to yield the desired product as pink crystals (0.998 g, 71% yield). R*f* 0.10 (7% MeOH in CH_2Cl_2).^{1}H NMR (300 MHz, CD_3OD) *δ* 7.26 (m, 5 H), 3.45-3.34 (m, 1H), 2.76 (dd, J_{AB} = 15, J_{AX} = 9 Hz, 1 H), 2.63 (dd, J_{AB} = 15, J_{BX} = 6 Hz, 1 H), 2.36 (dd, J_{AB} = 15, J_{AX} = 3 Hz, 1 H), 2.22 (dd, J_{AB} = 15, J_{BX} = 9 Hz, 1 H).^{13}C NMR (75 MHz, CD_3OD) *δ* 175.6, 138.5, 129.0, 128.2, 126.2, 49.7, 42.8, 41.1. IR (film): 3341, 3282, 3022, 2924, 2848, 1665, 1597, 1488, 1442, 1412, 1302, 1287, 1265, 1171, 1146, 1079, 1034, 996, 879, 847, 753, 699 cm-1. HRMS (ESI): Exact mass calcd for $C_{10}H_{14}N_2ONa$ $[M+Na]^+$: 201.100. Found: 201.1389.



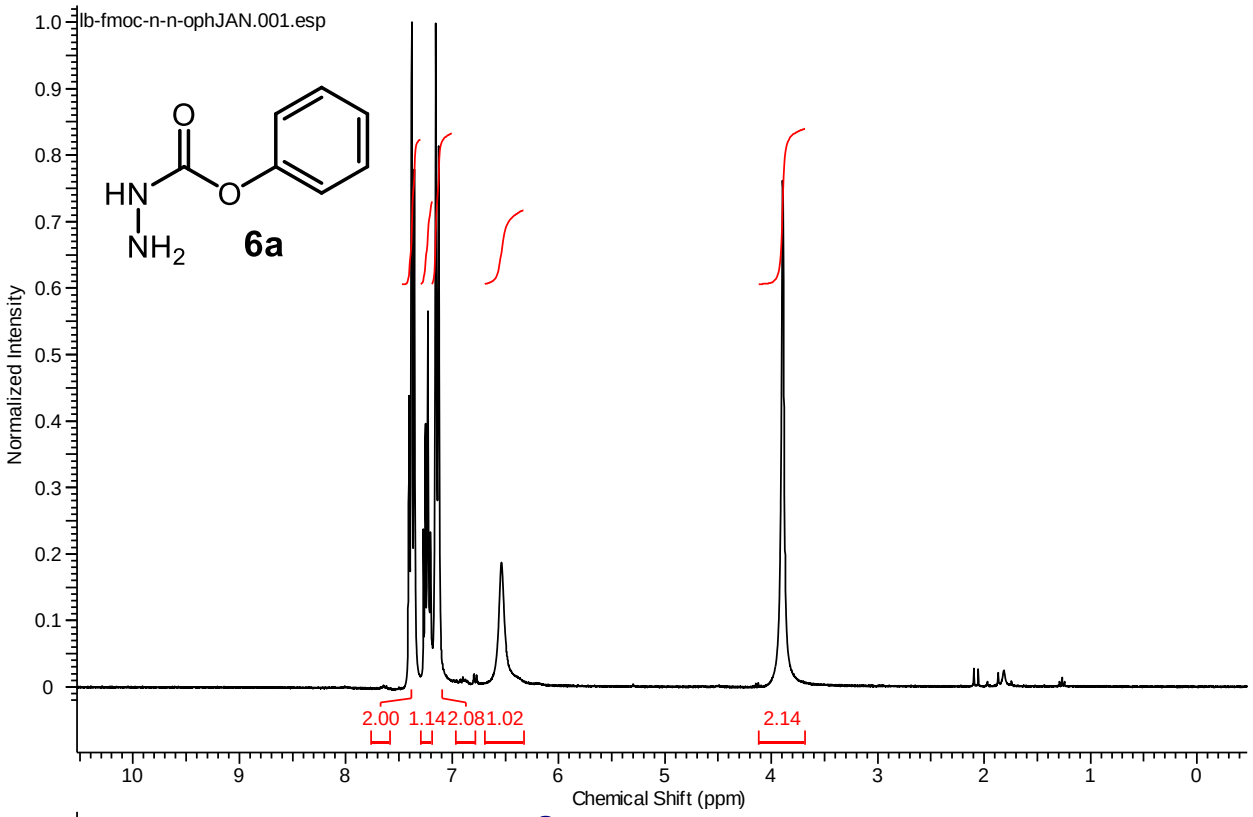
1-(*tert*-Butyloxycarbonyl)-2-fluorenylmethyloxycarbonyl-hydrazine (Table 3.1 and 3.2, 3c). Synthesized according to literature with mild modifications.[61b] In a 50 mL round bottom flask were added *tert*-butyl carbazate (0.100 g, 0.758 mmol, 1 equiv.), 1,4-Dioxane (6.5 mL, 0.12 M), sodium carbonate (0.095 g, 1.140 mmol, 1.5 equiv.) and fluorenylmethyloxycarbonyl chloride (0.195 g, 0.758 mmol, 1 equiv.). This reaction was stirred at room temperature for 3 hours, followed by an extraction with ether and brine. Once dried over magnesium sulphate, the organic layer was concentrated under reduced pressure and azeotroped with chloroform to yield the desired product as a white crystal (0.257 g, 96% yield). R*f* 0.70 (EtOAc). Spectral data matches those reported in the literature.[61b]



1-Phenyl-2-fluorenylmethyloxycarbonyl-hydrazine (Table 3.1 and 3.2, 3d). In a 50 mL round bottom flask were added phenyl carbazate (0.100 g, 0.658 mmol, 1 equiv.), 1,4- Dioxane (5.6 mL, 0.12 M), sodium carbonate (0.083 g, 0.90 mmol, 1.5 equiv.) and fluorenylmethyloxycarbonyl chloride (0.170 g, 0.658 mmol, 1 equiv.). This reaction was stirred at room temperature for 4 hours, followed by an extraction with ether and brine. Once dried over magnesium sulphate, the organic layer was concentrated under reduced pressure and azeotroped with chloroform to yield the desired product as a white crystal (0.175 g, 71% yield). R*f* 0.26 (20% EtOAc in Hexane). ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.77 (d, *J* = 6 Hz, 2 H), 7.60 (d, *J* = 6 Hz, 2 H), 7.45-7.10 (m, 9 H), 6.97-6.87 (m, 1 H), 6.83-6.72 (m, 1 H), 4.50 (d, *J* = 9 Hz, 2 H), 4.27 (t, *J* = 9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 150.4, 143.4, 141.3, 129.4, 127.9, 127.2, 126.0, 125.0, 121.3, 121.1, 120.0, 119.8, 68.3 46.9. IR (film): 3292, 2955, 1719, 1593, 1479, 1449, 1344, 1200, 1104, 1070, 1033, 963, 908, 758, 739, 689 cm-1. HRMS (ESI): Exact mass calcd for $C_{22}H_{18}N_2O_4Na$ $[M+Na]^+$: 397.116. Found: 397.2868.



1-(*tert*-Butyloxycarbonyl)-2-phenyloxycarbonyl-hydrazine (Table 3.1 and 3.2, 3e). Synthesized according to literature procedures with mild modifications.[61a] In a 50 mL round bottom flask was added *tert*-butyl carbazate (0.850 g, 6.40 mmol, 1.14 equiv.) and 1,4-dioxane (15.0 mL). Phenyl chloroformate (0.70ml, 5.6 mmol, 1 equiv.) was added slowly to the reaction, and the mixture was stirred at room temperature for 1 hour. The product was recrystallized from the crude with an ethyl acetate and hexane mixture, followed by a filtration to yield the desired product as white crystals (1.0 g, 71% yield). R*f* 0.35 (20% EtOAc in Hexane). Spectral data matches those reported in the literature.[61a]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O
NH2
6a
Normalized Intensity
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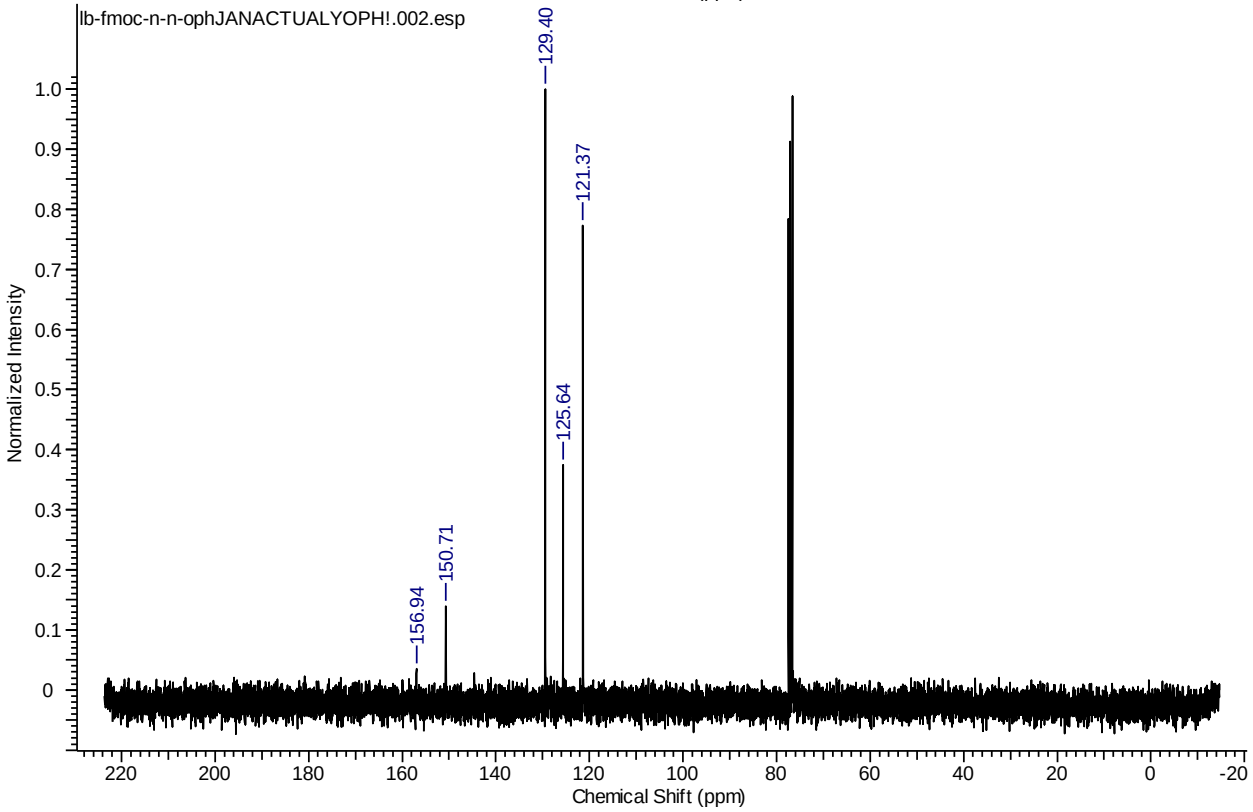
2.08
1.02
2.14
Chemical Shift (ppm)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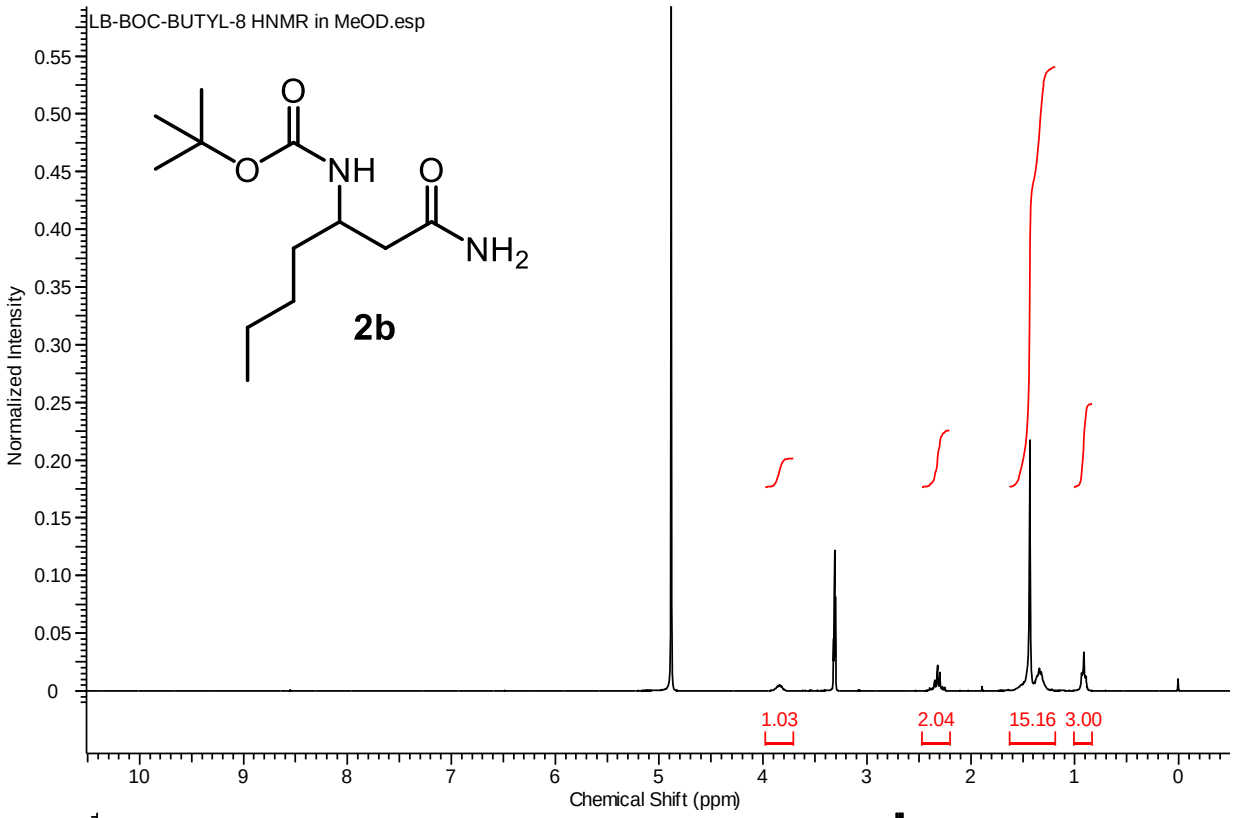
121.37
125.64
150.71
156.94
Normalized Intensity
Chemical Shift (ppm)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Normalized Intensity
Chemical Shift (ppm)
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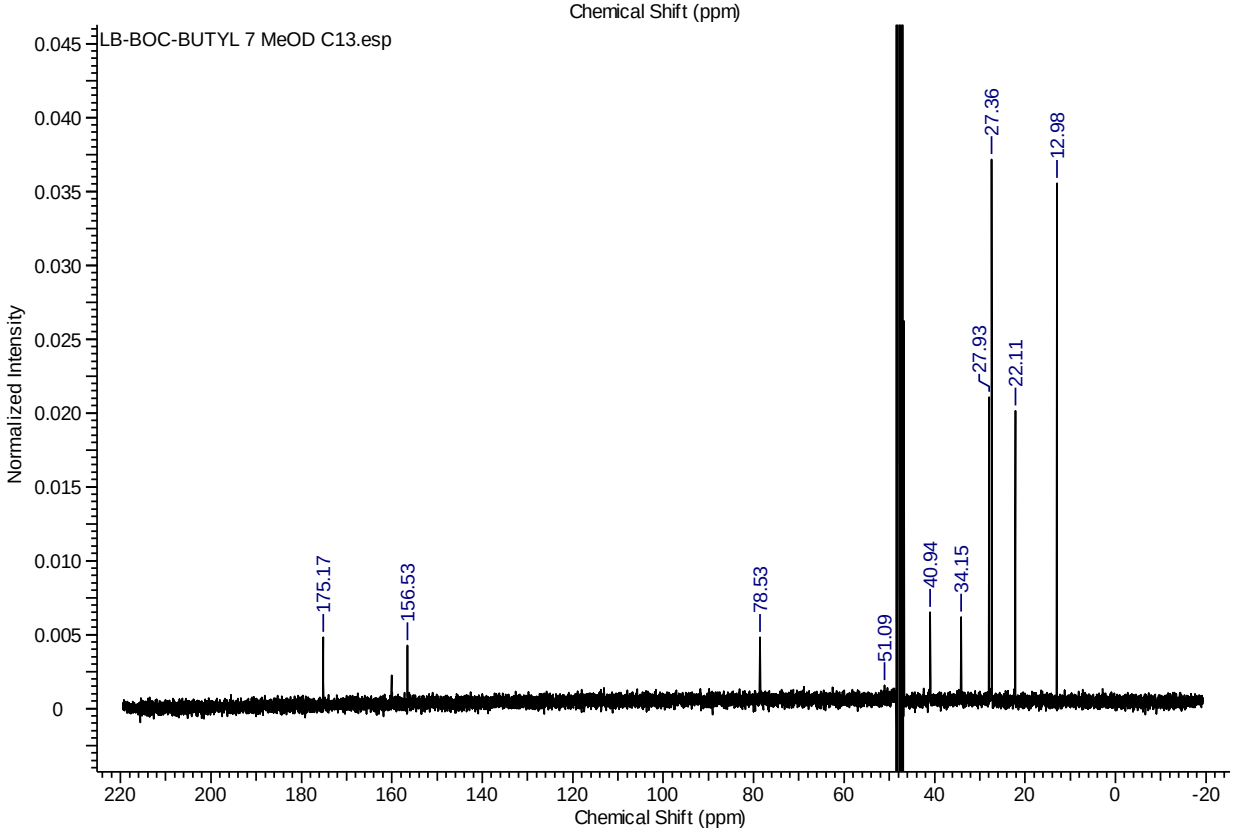
2.04
15.16
3.00
2b


LB-BOC-BUTYL 7 MeOD C13.esp
Normalized Intensity
Chemical Shift (ppm)
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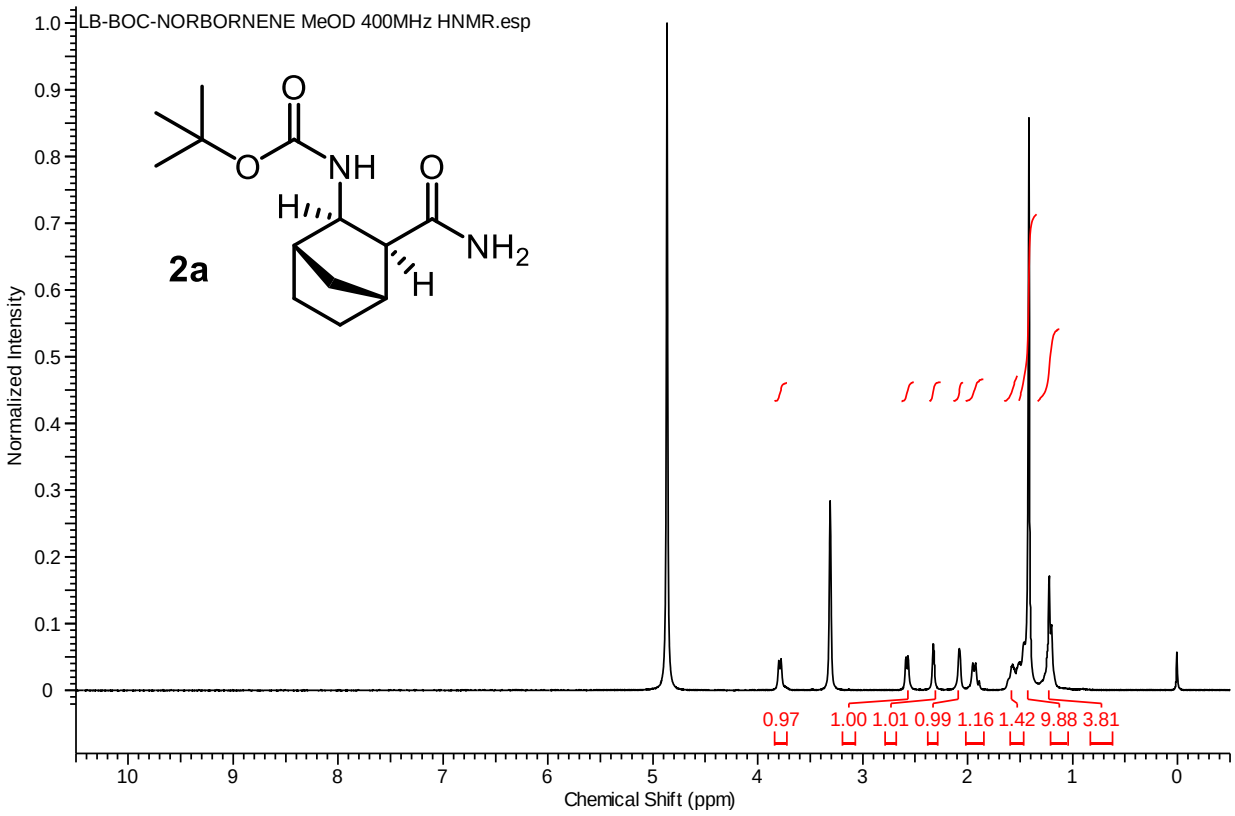
78.53
51.09
40.94
34.15
27.93
27.36
22.11
12.98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Chemical Shift (ppm)
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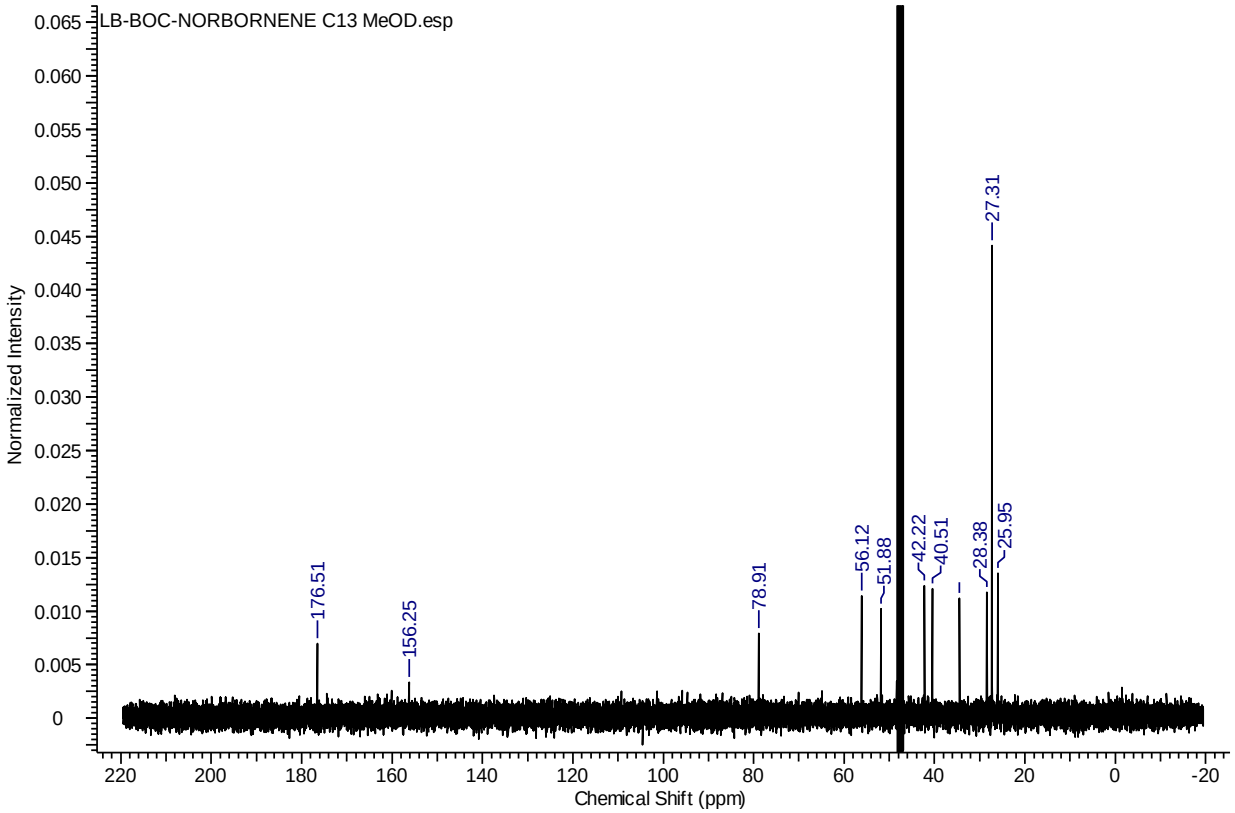
1.01
0.99
1.16
1.42
9.88
3.81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Normalized Intensity
Chemical Shift (ppm)
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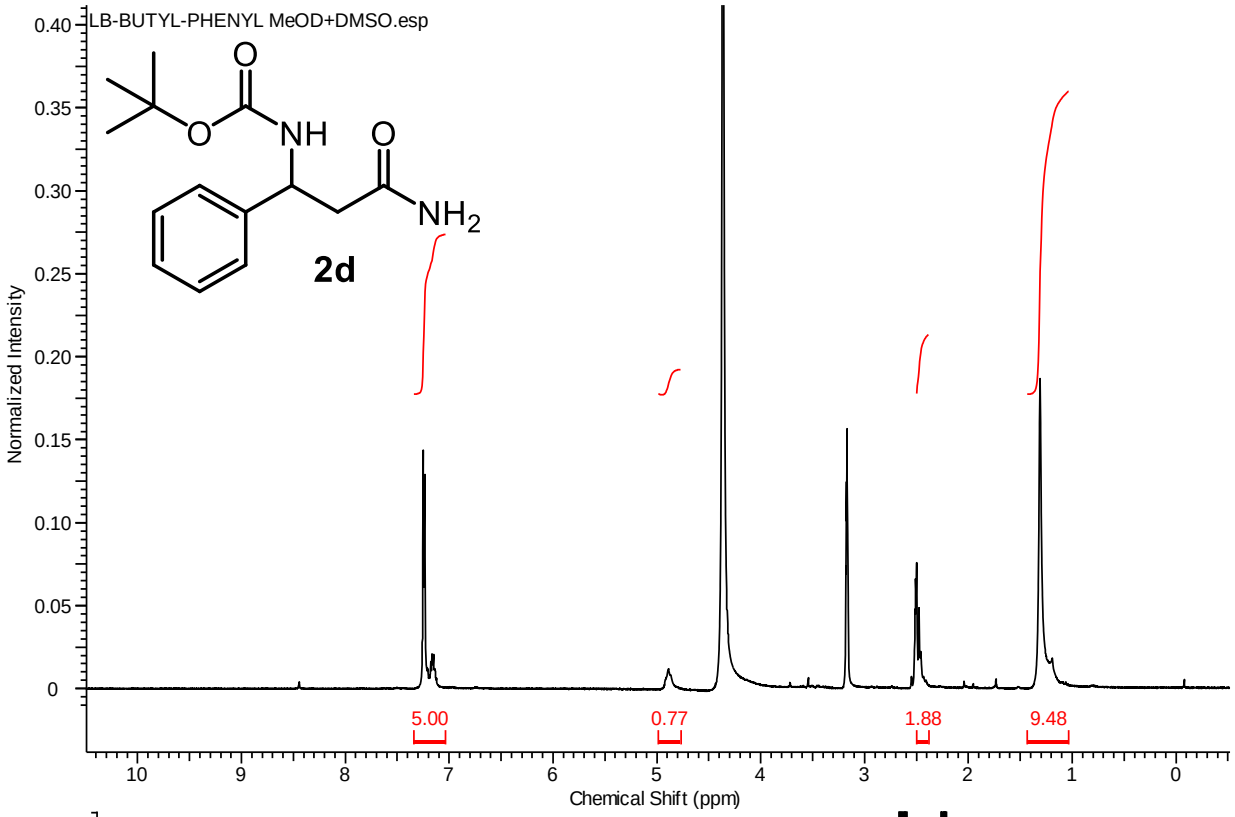
56.12
51.88
42.22
40.51
28.38
27.31
25.95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O
NH
O
NH2
2d
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0.30
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0.20
0.15
0.10
0.05
0
5.00
0.77
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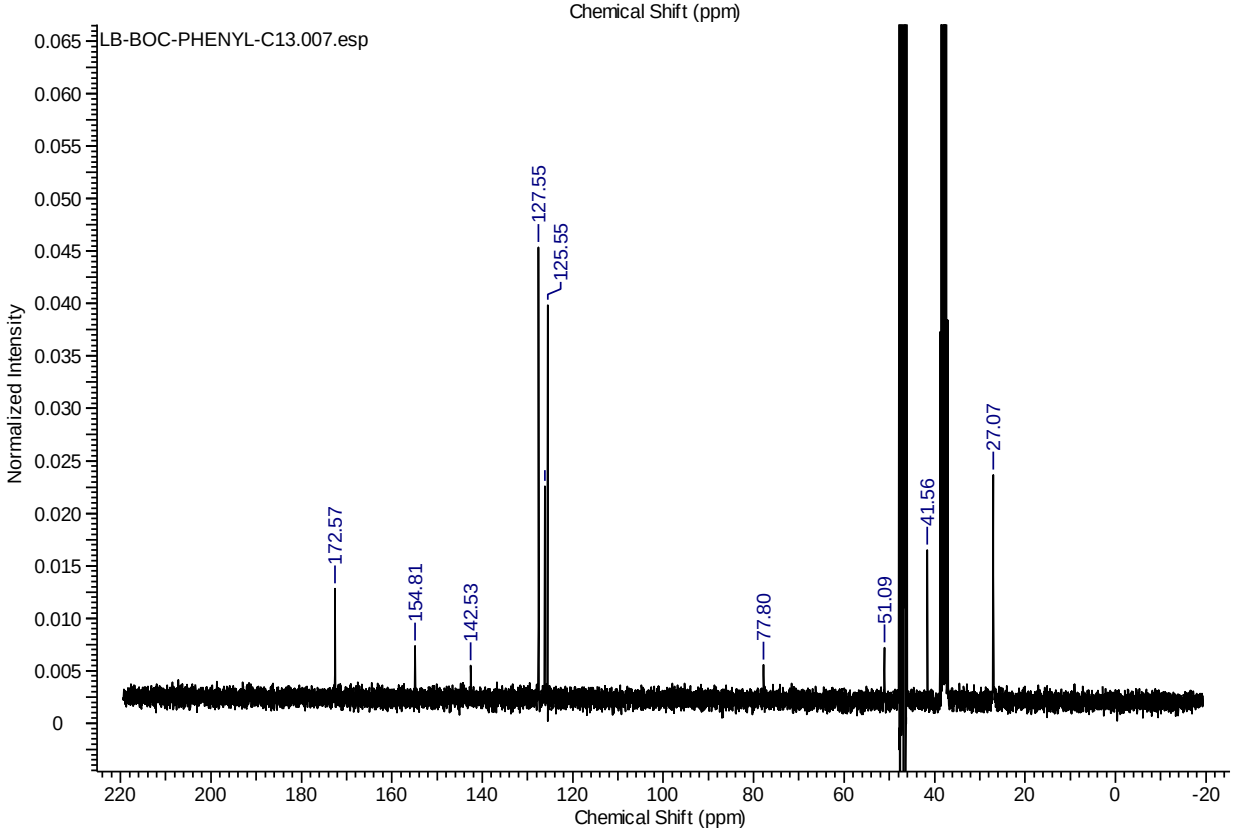
9.48
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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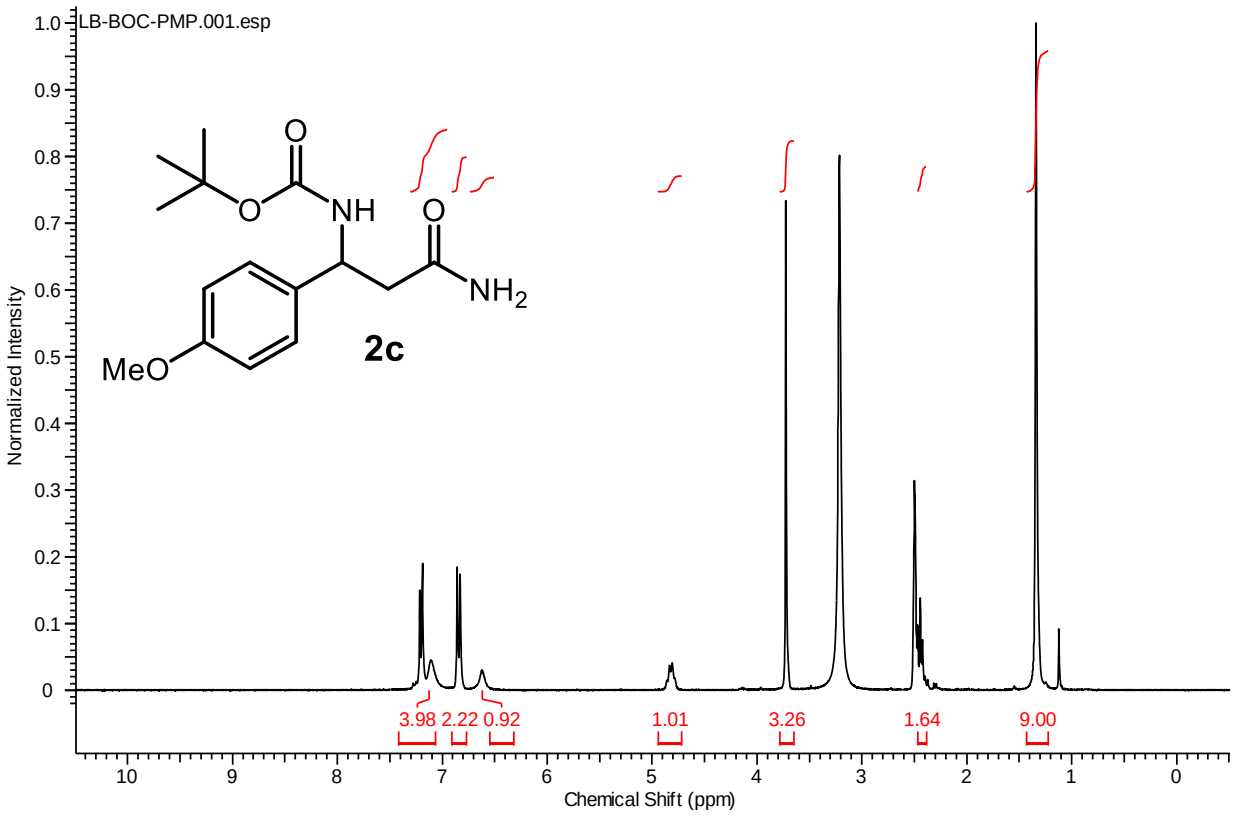
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
172.57
154.81
142.53
127.55
125.55
77.80
51.09
41.56
27.07
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


LB-BOC-PMP.001.esp
Normalized Intensity
Chemical Shift (ppm)
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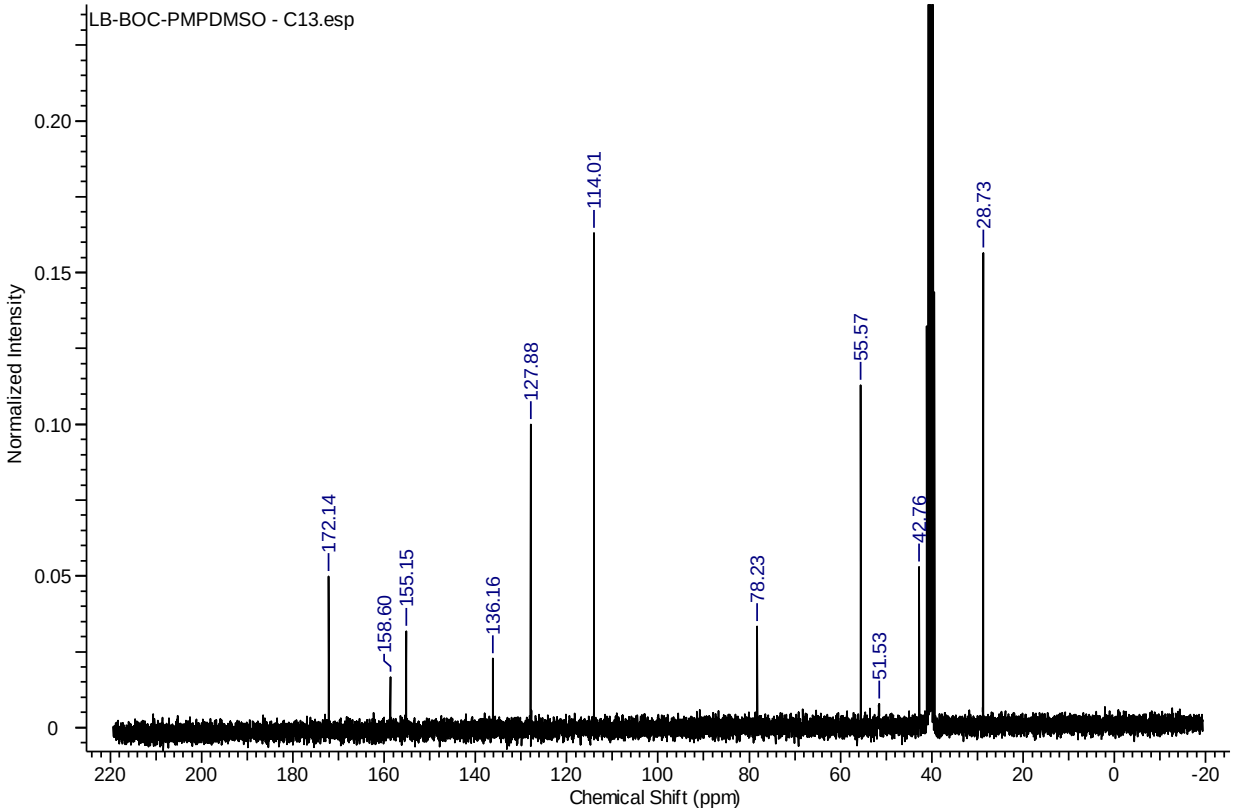
1.01
3.26
1.64
9.00
2c
MeO
NH
NH2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Normalized Intensity
Chemical Shift (ppm)
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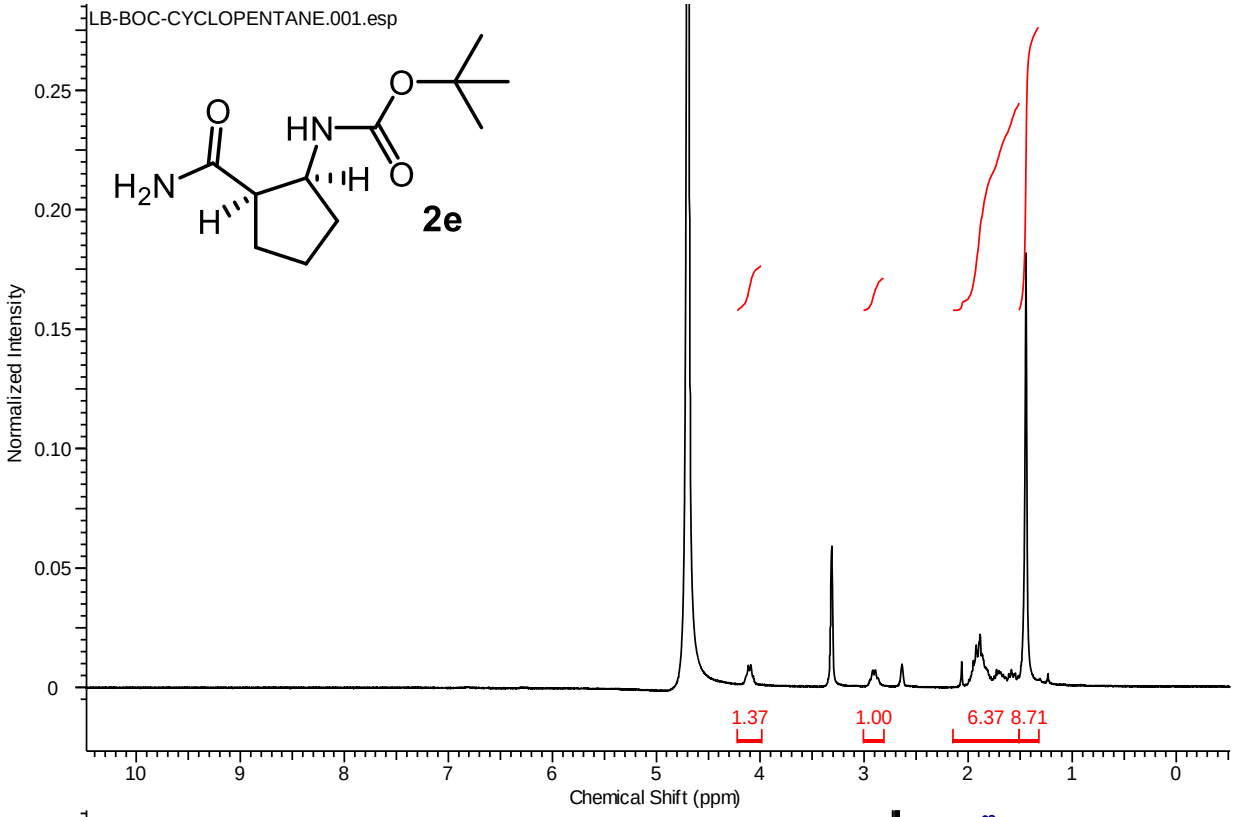
114.01
78.23
55.57
51.53
42.76
28.73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O
H_2N
H
H
O
2e
Normalized Intensity
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0.10
0.05
0
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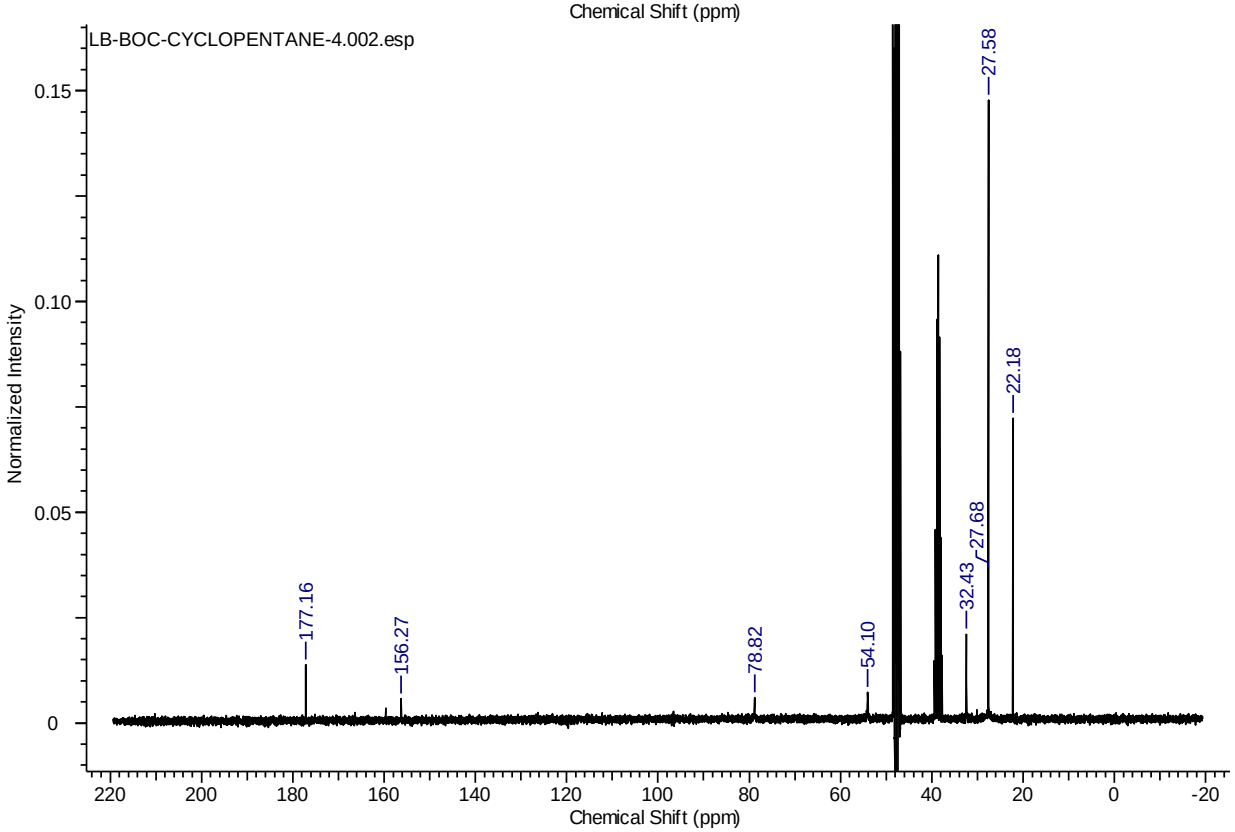
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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0
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54.10
32.43
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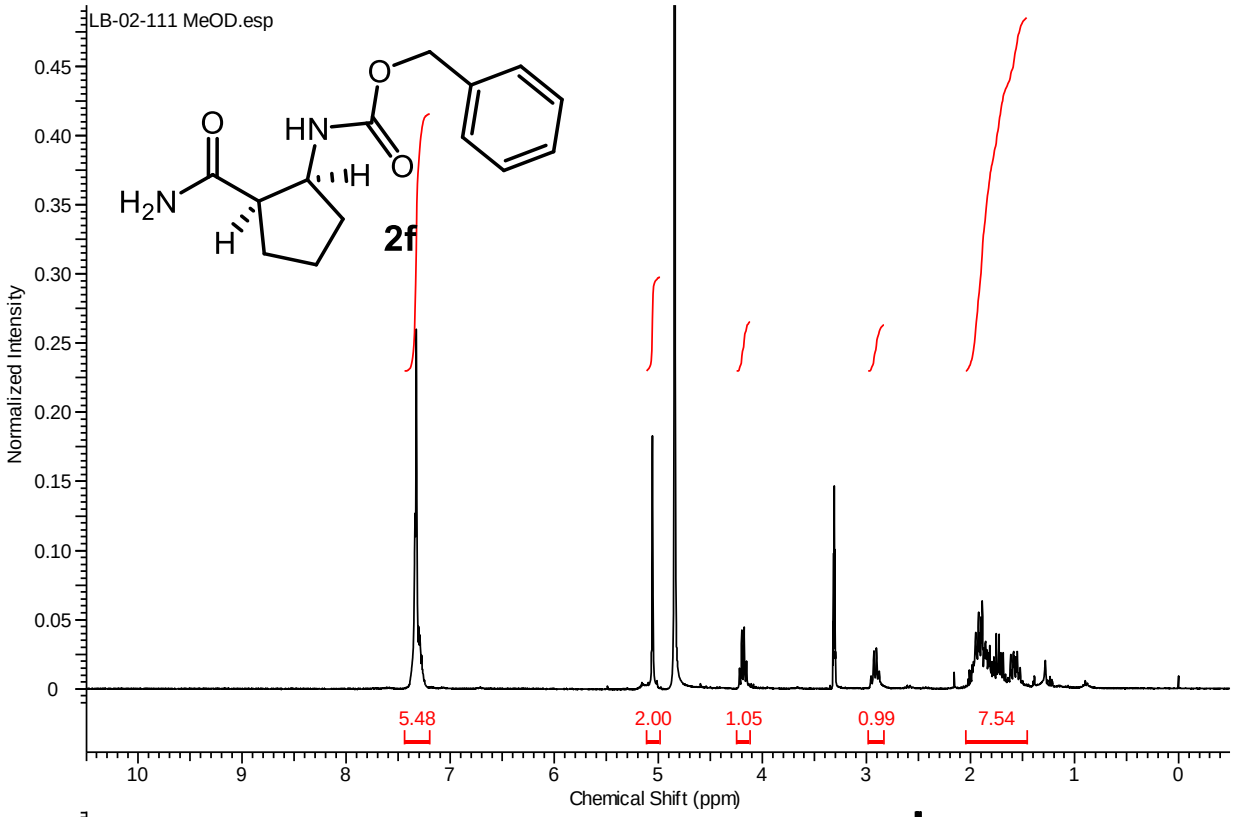
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)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Normalized Intensity
Chemical Shift (ppm)
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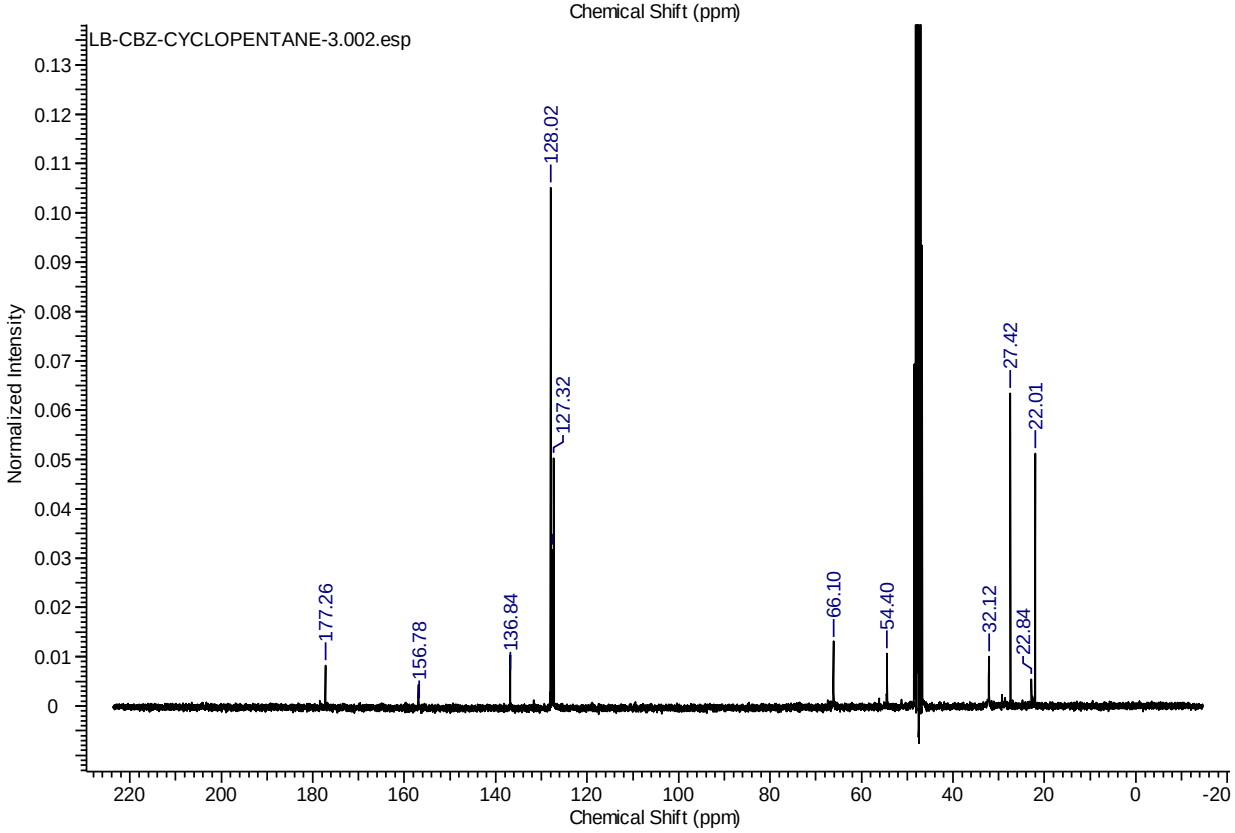
0.99
7.54
2f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Normalized Intensity
Chemical Shift (ppm)
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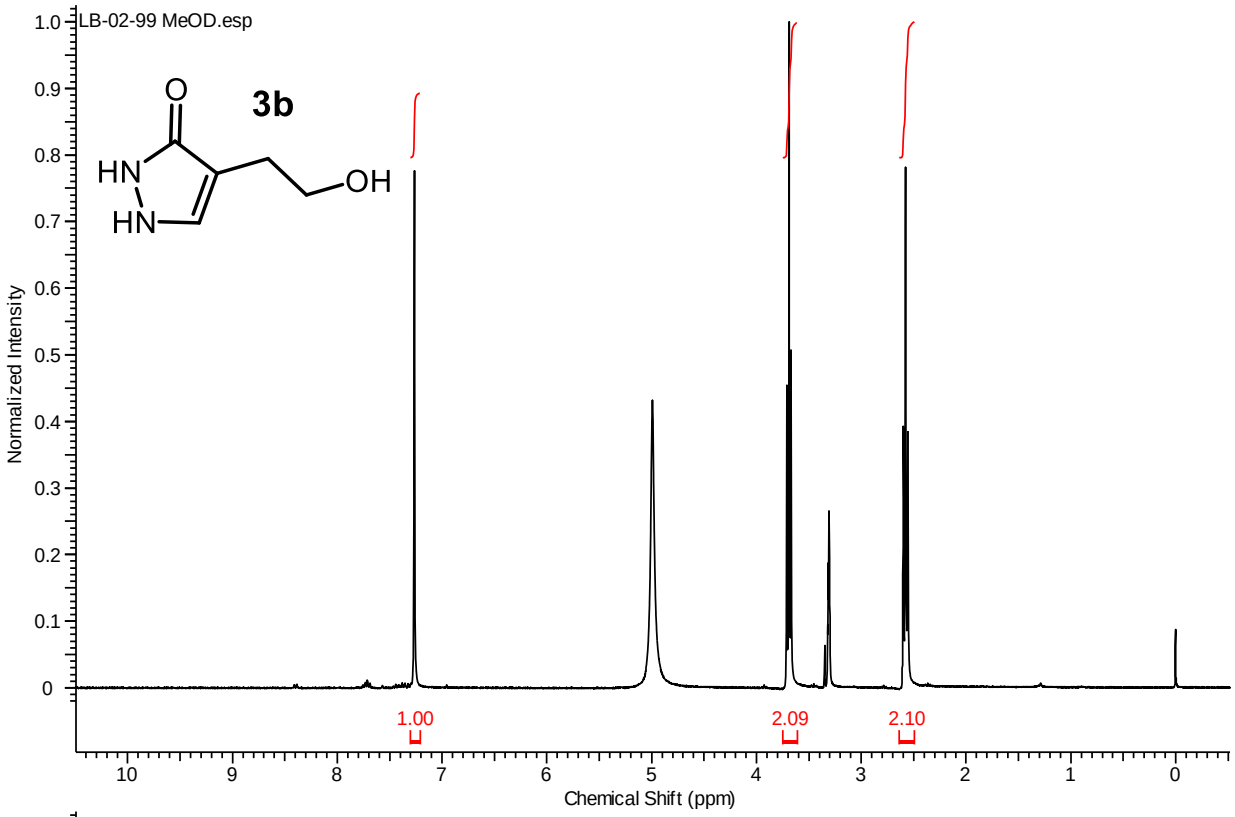
54.40
32.12
27.42
22.84
22.01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HN
HN
OH
Normalized Intensity
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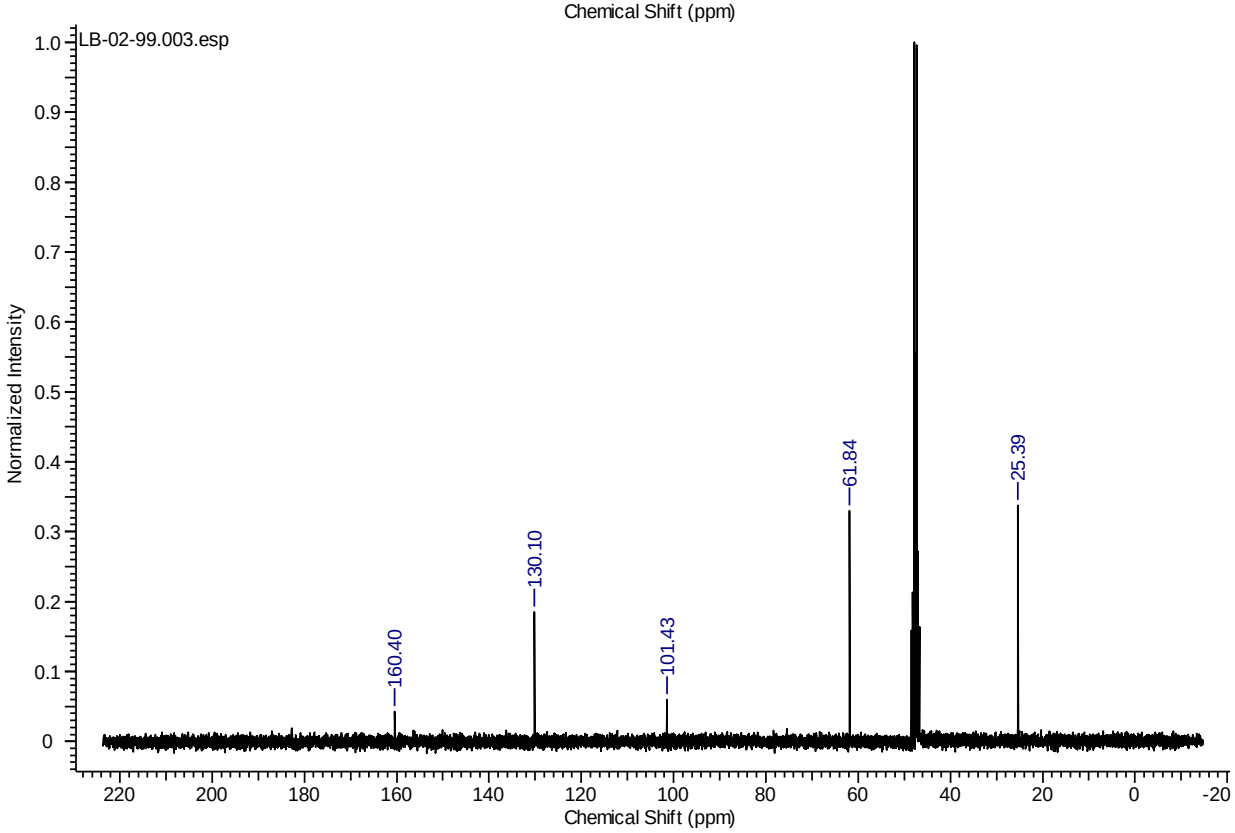
2.09
2.10
Chemical Shift (ppm)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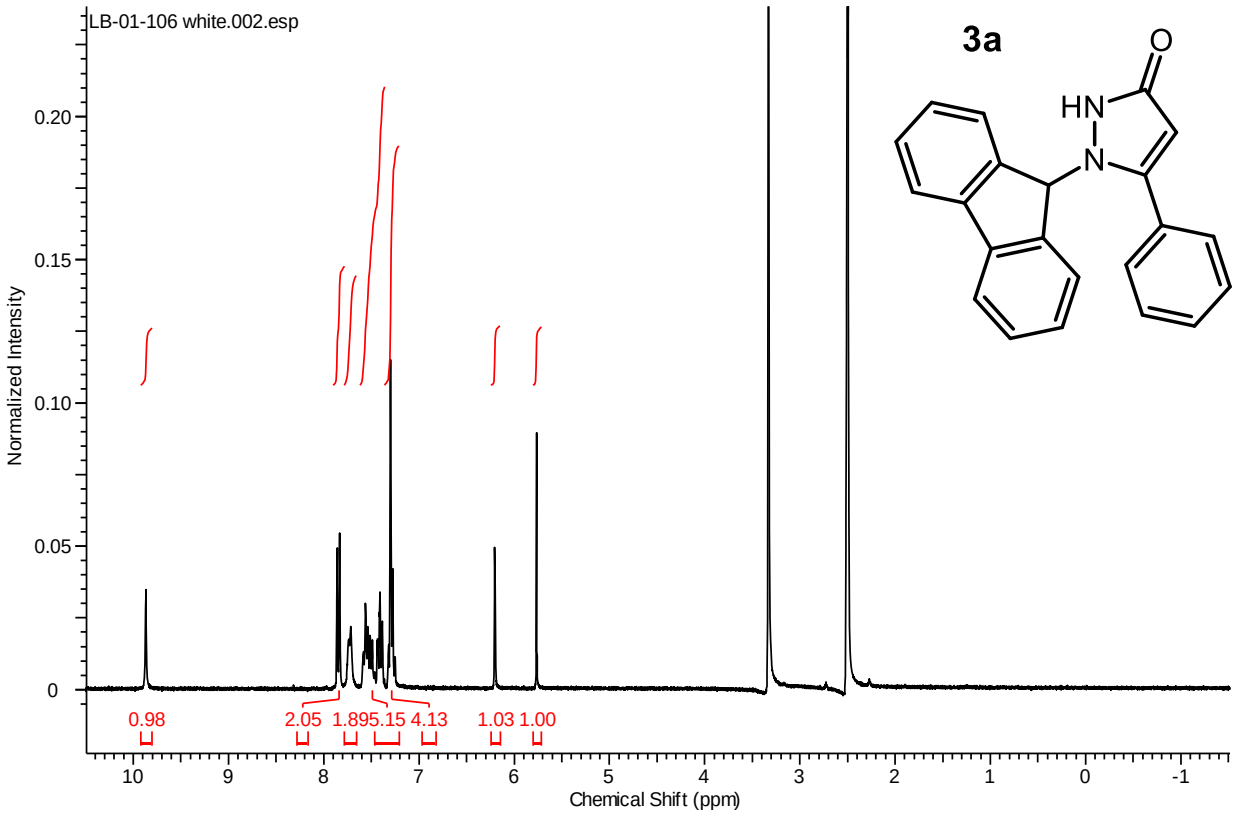
25.39
Chemical Shift (ppm)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3a
O
HN
N
Normalized Intensity
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0.05
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2.05
1.89
5.15
4.13
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1.00
10
9
8
7
6
5
4
3
2
1
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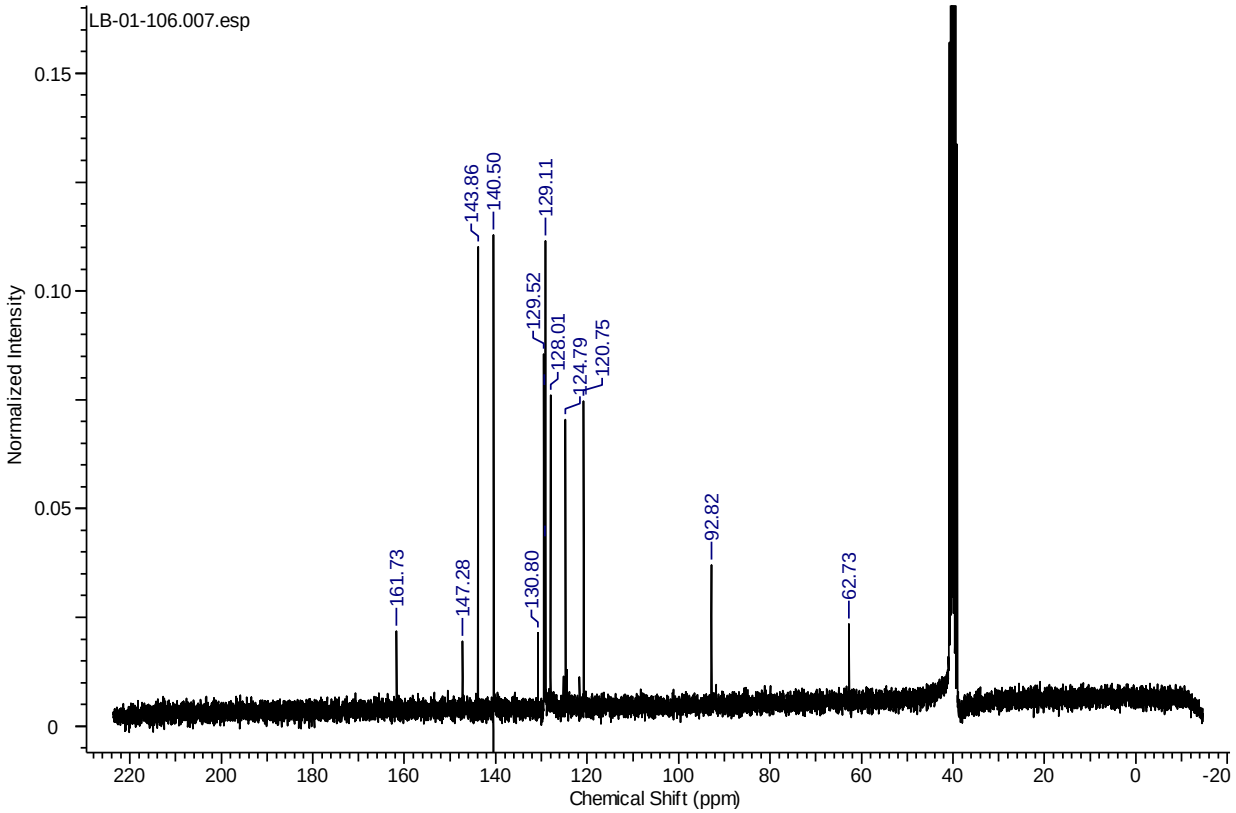
-1
Chemical Shift (ppm)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120.75
92.82
62.73
161.73
147.28
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200
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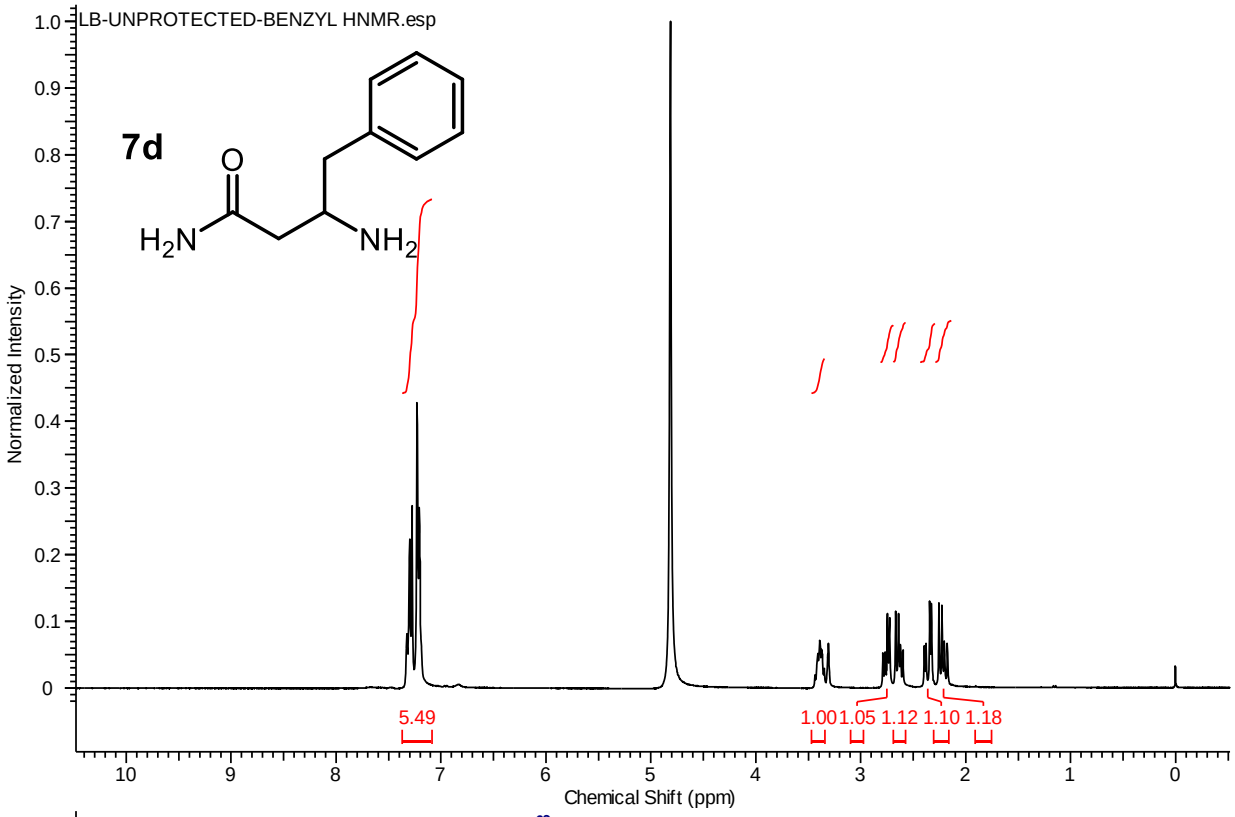
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)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H2N
NH2
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0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5.49
1.00
1.05
1.12
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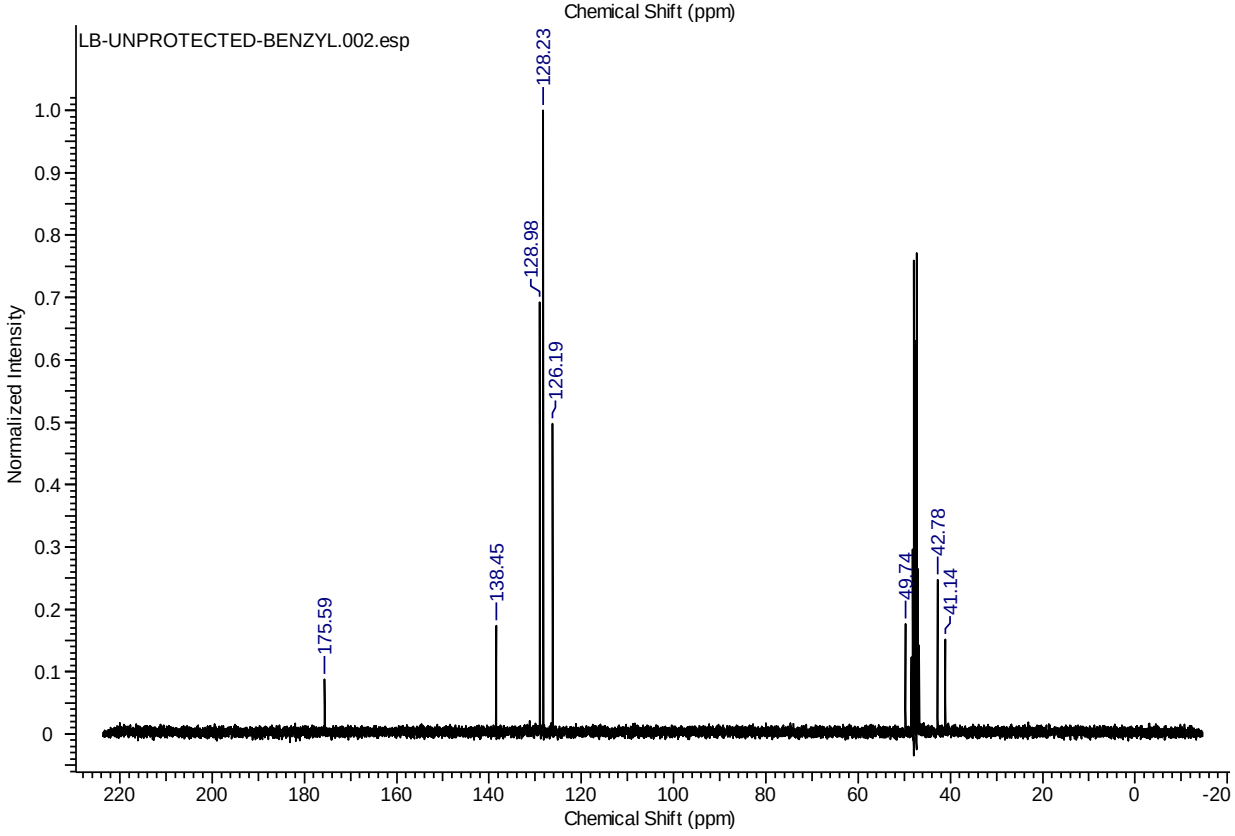
1.18
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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0.3
0.2
0.1
0
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128.98
126.19
175.59
138.45
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42.78
41.14
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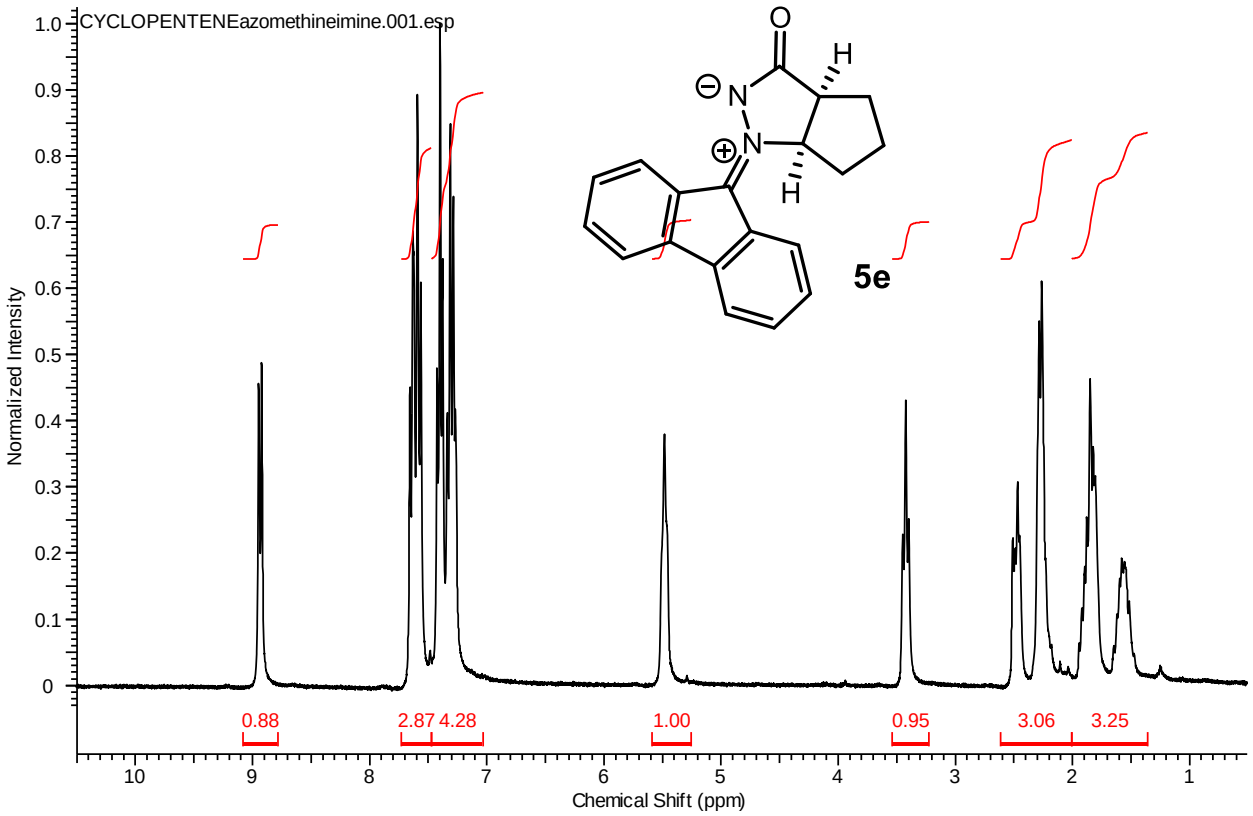
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)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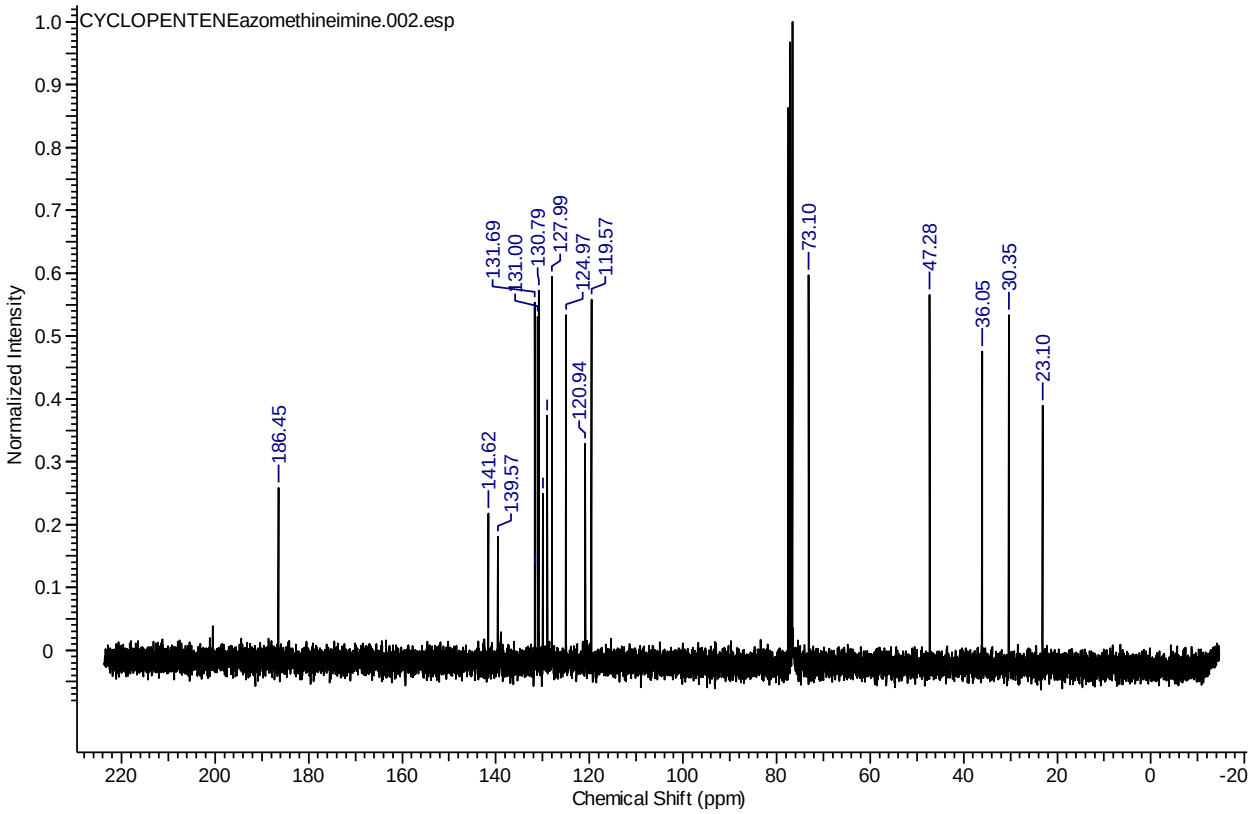
3.25
5e


CYCLOPENTENEazomethineimine.002.esp
Normalized Intensity
Chemical Shift (ppm)
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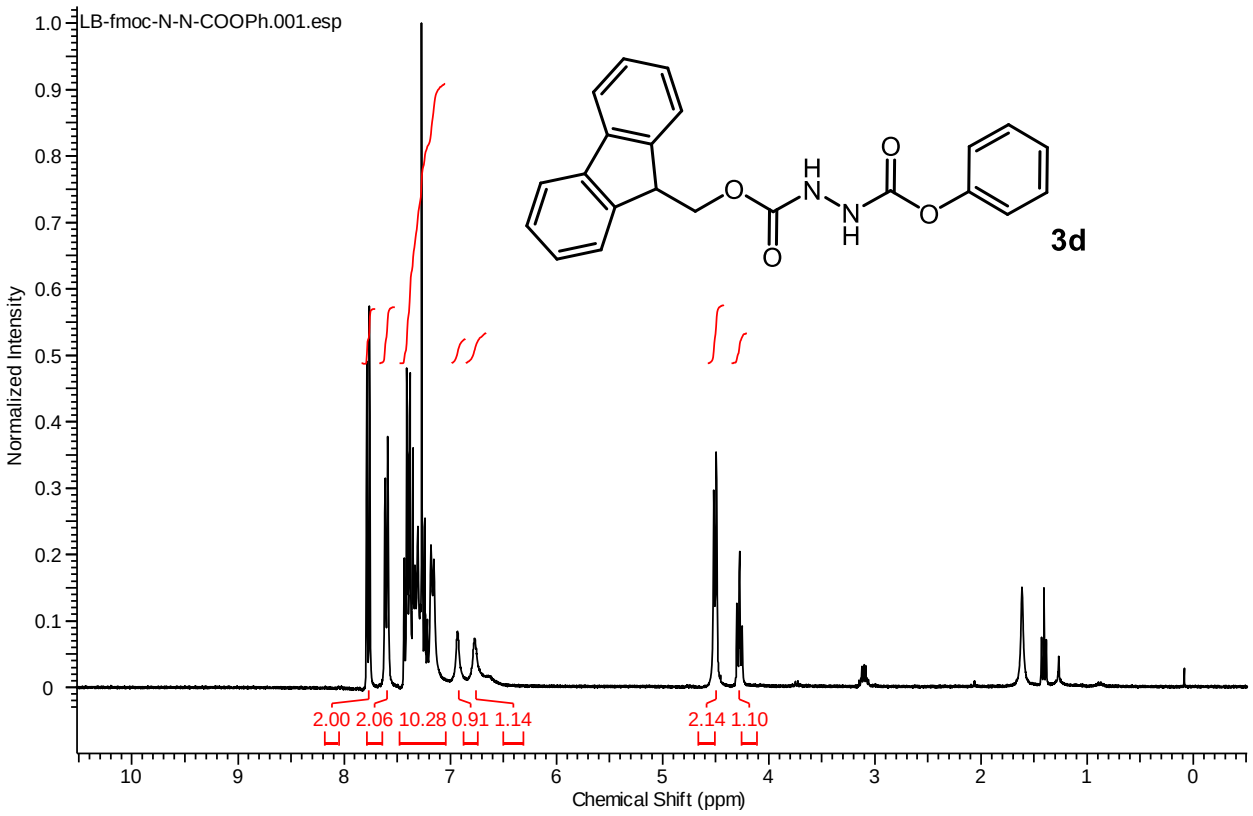
127.99
124.97
120.94
119.57
73.10
47.28
36.05
30.35
23.10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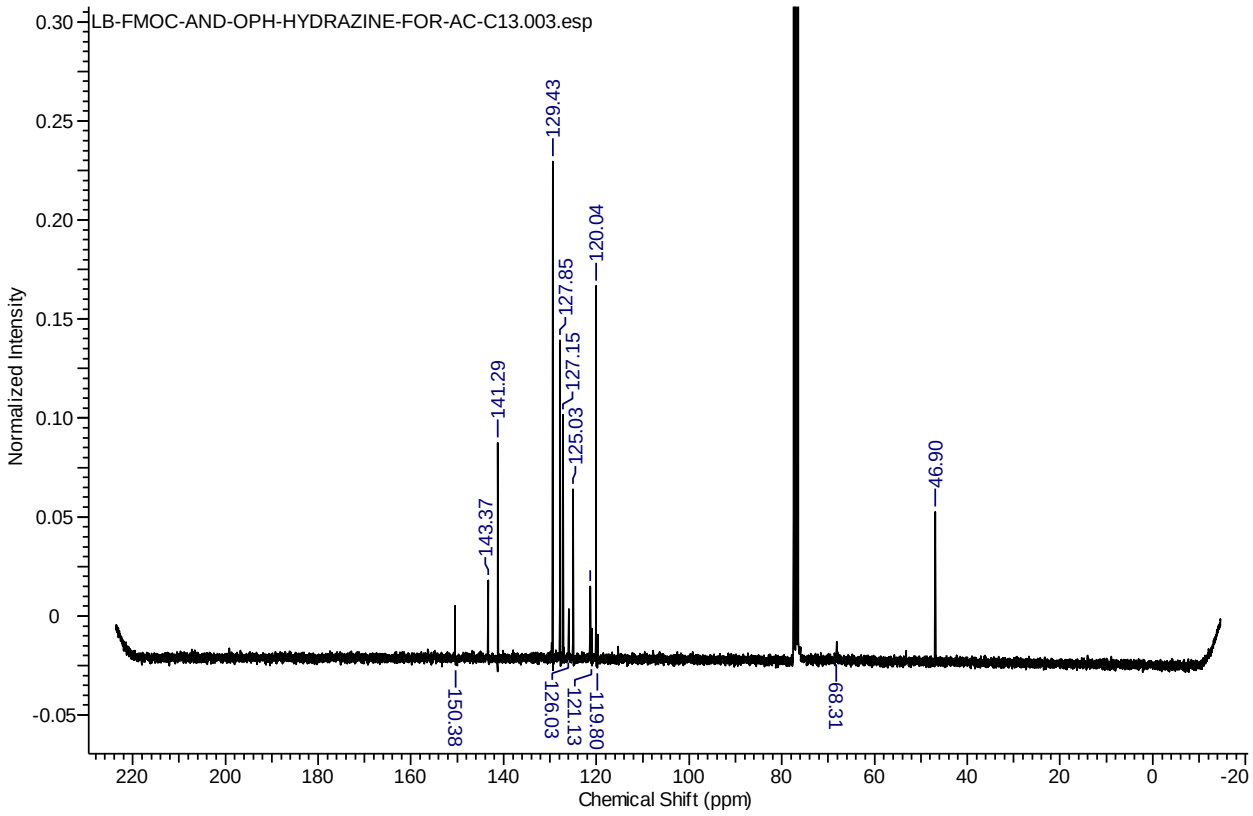
Normalized Intensity
Chemical Shift (ppm)
2.00 2.06 10.28 0.91 1.14
2.14 1.10
3d


LB-FMOC-AND-OPH-HYDRAZINE-FOR-AC-C13.003.esp
Normalized Intensity
Chemical Shift (ppm)
129.43
120.04
127.85
127.15
125.03
141.29
143.37
46.90
150.38
126.03
121.13
119.80
68.31

Appendix II: Aldehyde Catalyzed Hydrolysis

6.1 Introduction

In nature, hydrolysis is performed by hydrolase enzymes on many molecules in living organisms, such as DNA, proteins and lipids.[73] Although biological hydrolyses occur under mild conditions through enzymatic catalysis, in organic chemistry it often includes the use of strong acids that are not compatible with all functional groups, and cause racemization and other unwanted side reactions.

While the use of harsh conditions for difficult intermolecular reactions to proceed have been a problem in synthetic chemistry, the use of temporary tethers as a strategy to reduce the energy of activation has become quite popular.[74] This method is arguably a mimic of enzymatic mechanism through tethered reactions which transforms an intermolecular reaction into an intramolecular scenario.[75] The tethering catalysis lowers the energy of activation through increasing the energy of entropy as seen in Figure 6.1.

[73] Acton, A. Hydrolases. *Advances in Research and Application*. Scholarly editions: Georgia, Atlanta, USA, **2013**.
[74] a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307. b) Tan, K. L. *ACS Catalysis* **2011**, *1*, 877. c) Diederich, F.; Stang, P. J. Templated Organic Synthesis; Diederich, F.; Stang, P. J. editors. Wiley-VCH, 2000, pp 1-387. d) Cusak, *A. Chem. Eur. J.* **2012**, *18*, 5800. e) Bols, M.; Skrydstrup,T. *Chem. Rev*. **1995**, *95*, 1253. d) Bracegirdle, S.; Anderson, E. A. *Chem. Soc. Rev*. **2010**, *39*, 4114.
[75] a) Sammakia, T; Hurley, T. B. *J. Org. Chem*. **1999**, *64*, 5652. b) Sammakia, T.; Hurley, T. B. *J. Org. Chem*. **2000**, *65*, 974. c) Tan, K. L.; Sun, X.; Worthy, A. D. *Synlett* **2012**, *23*, 321.

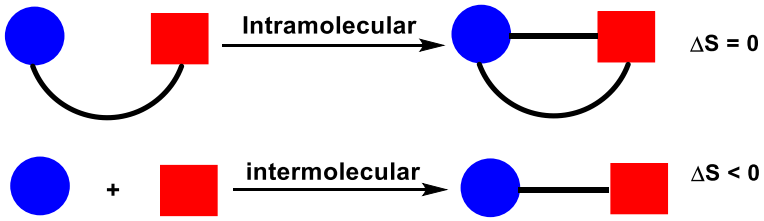
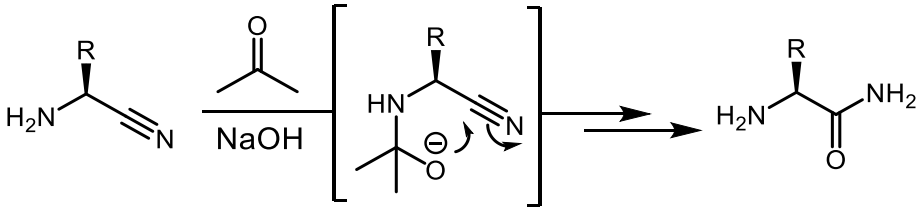


Figure 6.1. Decrease in energy of activation through tethering catalysis

In the 1970's, the Commeyras group introduced the first temporary intramolecular hydrolysis through tethering carbonyl catalysis. This work was focused on the hydrolysis of α-aminonitriles into α-amino amides and acids in stoichiometric conditions (Scheme 6.1).[76]

Scheme 6.1 Carbonyl catalyzed hydrolysis of α-aminonitriles

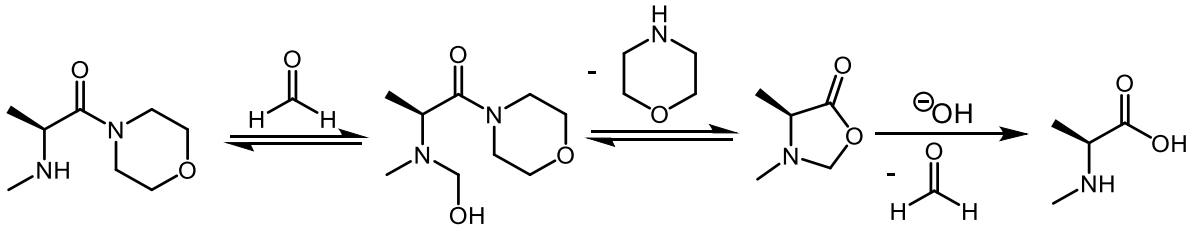


In this reaction, the primary amine of the α-aminonitrile condenses onto the acetone, which then attacks the carbon of the nitrile group. The hydrolysis mechanism of the oxazilidinone intermediate is debatable, however the high stoichiometric amounts of sodium hydroxide supports a nucleophilic attack of a tethered alkoxide anion. While

[76] a) Pascal, R.; Taillades, J.; Commeyras, A. *Bull. Soc. Chim. Fr. II* **1978**, *3-4*, 177. b) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1978**, *34*, 2275. c) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1980**, *36*, 2999. d) Pascal, R.; Marnier, M. L.; Rousset, A.; Commeyras, A.; Taillades, J.; Mion, L. (1981) US patent 4,243,814. Retrieved from IP Research and Communities.

the mechanism has been studied for a while, the scope of this reaction has only been explored. It is likely limited by the conditions which require excess base and stoichiometric amount of carbonyl compound. Following that discovery, Commeyras published findings for the formaldehyde-catalyzed hydrolysis of α-amino amides into α-amino acids under mild basic conditions with phosphate buffer (Scheme 6.2).[77]

Scheme 6.2 Formaldehyde catalysis of α-amino amides into α-amino acids



Here the amine condenses with formaldehyde and the oxygen from the hemi-aminal attacks the amide to form a 5-membered heterocycle. This intermediate is hydrolyzed by a hydroxide anion to generate a α-amino acid and potentially regenerate the formaldehyde catalyst. Unfortunately, the formation of 4-imidazolidinone (Figure 6.2) with primary amides limits the scope of this reaction.

[77] Pascal, R.; Lasperas, M.; Taillades, J.; Commeyras, A. *New. J. Chem.* **1987**, *11*, 235.

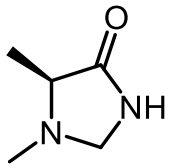
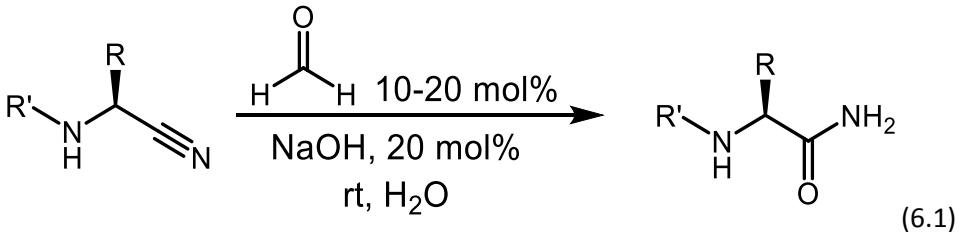


Figure 6.2 4-Imidazolidinone

6.2 Formaldehyde Catalyzed Hydrolysis of α-Aminonitriles

Due to the lack of efficient procedures to hydrolyze α-amino acids and amides through carbonyl-catalyzed hydrolysis, the Beauchemin group became interested in this area of research. We established a catalytic version of a formaldehyde hydrolysis of α-aminonitriles into α-amino amides and α-amino acids with milder conditions than Commeyras.

Dr. Sampada Chitale, Bashir Hussain and Kashif Tanveer have demonstrated over 30 examples of α-aminonitrile hydrolyses into α-amino amides with 10-20% formaldehyde as a catalyst and 10-20 mol% NaOH for the hydrolysis (Equation 6.1).[78]



(6.1)

[78] Chitale,S.; Hussain, B.; Tanveer, K.; Beauchemin, A. M. Manuscript in preperation.

They were also able to hydrolyze a few α-aminonitriles into α-amino acids. While developing this reaction, a cyclic side product was formed though aldehyde scavenging from the α-amino amide, which reduces the yield by causing catalyst inhibition (figure 6.3).

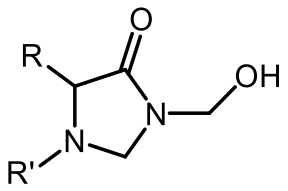
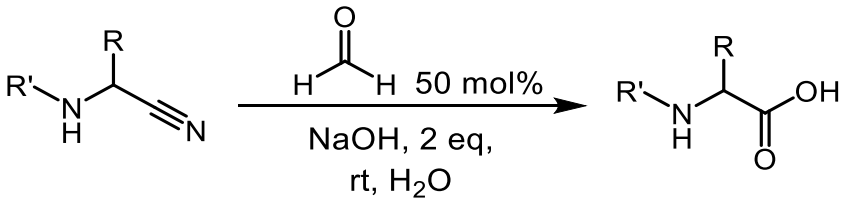


Figure 6.3 Cyclic by-product causing aldehyde scavenging

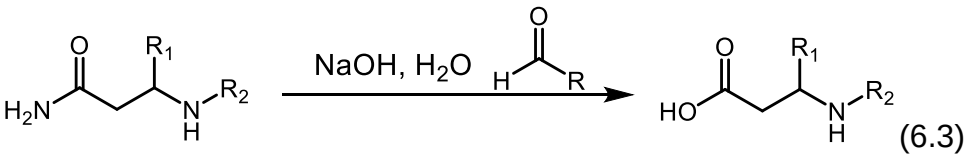
This problem was overcome by increasing catalyst loading to 50 mol% (Equation 6.2). The equivalents of base were also increased to 2 equivalents as one equivalent is used to form the carboxylate ion.



(6.2)

6.3 Formaldehyde Catalyzed Hydrolysis of β-Amino Amides

Once the aldehyde catalysis of α-aminonitriles towards α-amino acids was developed and optimized, interest arose towards hydrolysis of β–aminonitriles and β–amino amides into highly valued β–amino acids (Equation 6.3).



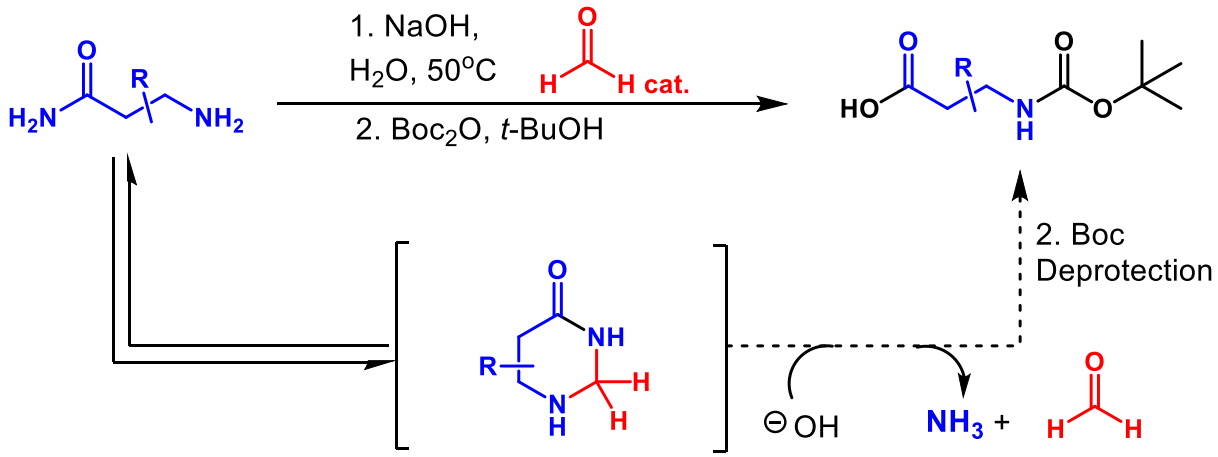
(6.3)

As we saw in a previous section, β–amino acids are very interesting targets and are part of many synthetic products including β–peptides. Currently, there's a high demand of β–amino acids that are cyclic or have unnatural side chains due to their challenging synthesis and new biological activities.[9a]

Exploratory studies were performed by Kashif Tanveer. He based his experiments on the α-amino amide formaldehyde catalyzed hydrolysis and optimized them towards β–amino amide hydrolysis. Similarly to the α-amino amide hydrolysis, a cyclic by-product was formed during the β–amino amide hydrolysis. Its structure is

shown in Scheme 6.3. This was not surprising since 4-imidazolidinones have been observed from the reaction of α-amino amides and carbonyls.[79]

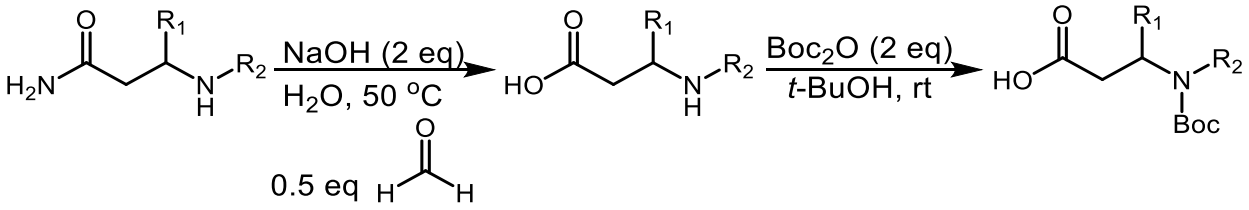
Scheme 6.3 By-product formation from β-amino amide aldehyde hydrolysis

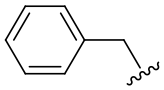
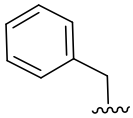
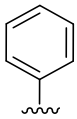


As this reaction was optimized towards lowering the amount of cyclic by-product, sodium hydroxide was increased to improve the rate of hydrolysis. Along with it, formaldehyde catalyst loading was decreased to reduce the amount of cyclic by-product. Once these tendencies were observed, Dr. Chitale went on optimizing results to have the best yields (combination of their work in Table 6.1). These experiments were run on β–amino amides with primary and secondary amines.

[79] a) Pascal, R.; Lasperas, M.; Taillades, J.; Commeyras, A.; Perez-rubalcaba, A. *Bull. Soc. Chim. Fr*. **1984**, 329. b) Zehavi, U.; Ben-Ishai, D. *J. Org. Chem.* **1961**, *26*, 1097.

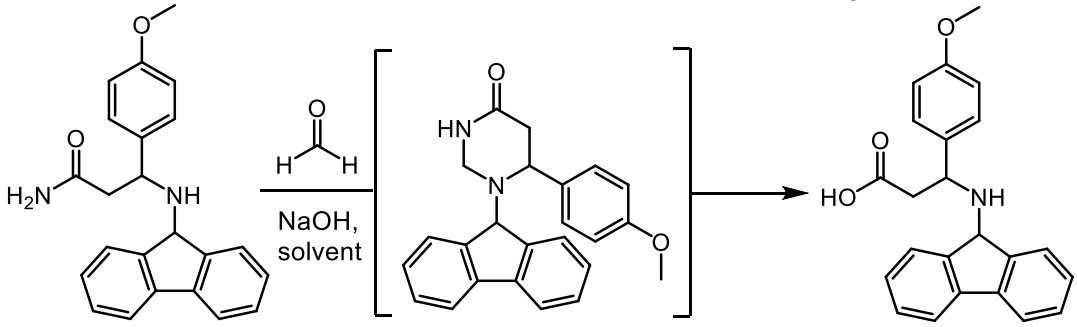
Table 6.1 Formaldehyde catalysis of β–amino amides towards β–amino acids



Entry	R_1	R_2	Yield (%)	Background Conversion (%)	Reaction Time of hydrolysis
1	H		85	55	9 h
2		H	86	≈ 25	23 h
3		H	76	-	O.N. or less

Although this project will be continued by Joshua Derasp on our scope of β–amino amides as primary and secondary amines, a side project concerning the first generation derivatization was revisited. Once it was determined that β–amino amides with secondary amines could be hydrolyzed by formaldehyde catalysis, the first generation derivatization product, fluorenyl protected β-amino amides, was tested under these conditions. If this hydrolysis would work, it would reduce the number of steps towards β–amino acids with the first generation derivatization and make it more efficient. Due to solubility problems caused by the fluorenyl group, a solvent scan for solubility and reactivity had to be performed, as presented in Table 6.2.

Table 6.2 Solvent scan for hydrolysis of fluorenyl protected β–amino amides



Entry	Solvent	Formaldehyde	NaOH	Temp.	Product
1	*t*-BuOH	0.2 eq	5 eq	rt	Not soluble
2	Acetonitrile	0.2 eq	5 eq	rt	Not soluble
3	1,4-Dioxane	0.2 eq	5 eq	rt	SM
4	THF	0.2 eq	5 eq	r.t	1:0.5 SM/ unknown Product
5	1,4-Dioxane	1.5 eq	1.5 eq	45 °C	SM
6	THF	1.5 eq	1.5 eq	45 °C	1:0.8 SM/unknown product
7	EtOH	1.5 eq	1.5 eq	50 °C	Side reaction with ethanol

As we were testing the formaldehyde catalyzed hydrolysis, we encountered solubility problems caused by the insoluble fluorenyl group of the starting material (entry 1 and 2). Although both tetrahydrofuran and 1,4-dioxane demonstrated solubility of these starting materials, the hydrolysis with 0.2 equivalents of formaldehyde and 5 equivalents of sodium hydroxide did not produce any desired compound (entry 3 and 4). Nonetheless, the reaction in tetrahydrofuran demonstrated an unknown secondary

product which could not be separated due to its similar R*f* to the starting material (entry 4). Following these results, we conducted reactions at higher temperature to increase reactivity (entry 5-7). These were also set with a higher catalyst loading (1.5 equiv.) and lower NaOH concentration (1.5 equiv.) to isolate the by-product, which seemed to be the cyclic product from NMR studies. The hydrolysis in 1,4-dioxane, following these conditions, still did not lead to any reactivity. When tetrahydrofuran was chosen as the solvent, we observed that the secondary product was formed in higher ratio compared to entry 4. Finally, ethanol, was also tested as a possible solvent but reacted with the product to form an unidentified side product.

As it was shown in this Chapter, preliminary results on aldehyde catalyzed hydrolysis of β-amino amides are promising. Mechanistic studies on the formation of cyclic intermediates would give more information on how to optimize this reaction. It would be interesting to visit possible asymmetric aldehyde catalyzed hydrolysis of these amides through chiral aldehydes. However, the use of fluorenyl protected β-amino amides requires further reaction optimization. The next step taken in this part of the project would be testing controls without NaOH to trap the cyclic product in THF at different temperatures. Background controls in THF with only NaOH and no catalyst at these temperatures should also be performed to determine the efficiency of the catalyzed hydrolysis.